

Electrochemistry as a Sustainable Tool for the Synthesis of Heterocycles with a N,O-Moiety

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Declaration

The experimental work and written elaboration of this thesis was carried out from April 2022 to September 2024 at the Department of Chemistry (faculty of chemistry, pharmaceutical sciences, geography and geosciences) under supervision of [redacted]

Hereby, I, Johannes Winter declare that I wrote the submitted dissertation without any unauthorized assistance and used only sources acknowledged in this work. All textual passages, which were quoted verbatim or paraphrased from published work, as well as adapted figures or schemes are duly indicated and listed according to bibliographic rules.

Johannes Winter

“So long, and thanks for all the fish.”

[redacted],

The Hitchhiker’s Guide to the Galaxy

[redacted]

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Abstract

The aim of this dissertation was the electrochemical synthesis of various heterocycles featuring an endocyclic or exocyclic N,O-bond. The conventional synthesis of these motifs is usually carried out using equimolar amounts of redox-active and hazardous reagents via multistep processes, resulting in a poor atom economy and large amounts of waste. Organic electrosynthesis provides a modern methodology that can avoid the use of over-stoichiometric amounts of reagents and consequently diminish the amount of waste generated. Furthermore, the use of carbon-based electrodes and green solvents allows for a sustainable process design. Isoxazolines and isoxazoles were prepared from easily accessible aldoximes in a homogeneous or biphasic system. Conversion of the aldoximes to the corresponding nitrile oxides was achieved in-situ, either via direct anodic oxidation or by application of simple alkali halides as mediators. Subsequent (3+2) cycloaddition with a dipolarophile yields the targeted isoxazolines and isoxazoles. The sustainability of this methodology was demonstrated in the single-phase system by recovery of the solvent. The intrinsically sustainable nature of the biphasic system was demonstrated by a highly simplified purification procedure and the recovery of the dipolarophile used in excess.

The selective reduction of nitro arenes and subsequent cyclo-condensation allows for the selective synthesis of heterocycles with corresponding exocyclic N,O-bond. This method was used to synthesize quinoline *N*-oxides and 4-hydroxybenz-1,4-oxazinones. Furthermore, the 1-hydroxyquinazolin-4-ones and the 4-hydroxybenzo-1,2,4-thiadiazine-1,1-dioxides, which have not yet been reported in literature, were obtained analogously. The significance of this process was underlined by a broad scope. The applicability of this versatile tool in organic synthesis was demonstrated for each of these structural motifs on gram scale. Moreover, the reaction mechanism of the reduction of nitro arenes with subsequent cyclo-condensation was investigated using cyclic voltammetry. Compared to conventional reductions of nitro groups, neither stoichiometric amounts of reducing agents nor the use of precious transition metal catalysts were required. Moreover, the application of carbon-based electrodes and green solvents contributed further to fulfilling the principles of green chemistry.

Kurzzusammenfassung

Das Ziel der vorliegenden Dissertation war die elektrochemische Synthese verschiedenster Heterozyklen, welche über eine endozyklische oder exozyklische N,O-Bindung verfügen. Die konventionelle Synthese dieser Strukturmotive erfolgt zumeist unter Verwendung äquimolarer Mengen redox-aktiver und gefährlicher Reagenzien über mehrstufigen Prozesse, was in einer geringen Atomökonomie und großen Abfallmengen resultiert. Die organische Elektrosynthese liefert der modernen, organischen Chemie eine wichtige Methodik, welche die Nutzung überstöchiometrischer Mengen an Reagenzien vermeiden kann und in Folge die Abfallmengen verringert. Weiterhin erlaubt die Verwendung von kohlenstoffbasierten Elektroden und grünen Lösungsmitteln eine nachhaltige Prozessführung.

Isoxazoline und Isoxazole wurden im Zuge dessen ausgehend von leicht zugänglichen Aldoximen in einem einphasigen oder einem zweiphasigen Verfahren dargestellt. Die Umsetzung der Aldoxime zu den entsprechenden Nitriloxiden erfolgte *in situ*, entweder durch direkte anodische Oxidation oder durch Verwendung einfacher Alkalihalogenide als Mediatoren. Das Nitriloxid reagiert anschließend in einer (3+2) Cycloaddition mit einem Dipolarophil zu den entsprechenden Isoxazolinen und Isoxazolen. Die Nachhaltigkeit dieser Methodik wurde im einphasigen System mittels der Wiedergewinnung des Lösungsmittels gezeigt. Die intrinsisch nachhaltige Natur des zweiphasigen Systems wurde durch ein stark vereinfachtes Aufreinigungsverfahren und Wiedergewinnen des Dipolarophils demonstriert.

Die selektive Reduktion von Nitroaromaten und anschließende Cyclokondensation erlaubt die gezielte Synthese von Heterozyklen mit entsprechender exozyklischen N,O-Bindung. Diese Methodik wurde zur Synthese der literaturbekannten Chinolin-*N*-oxide und 4-Hydroxybenz-1,4-oxazinone genutzt. Weiterhin wurden die literaturunbekannten 1-Hydroxychinazolin-4-one und die 4-Hydroxybenzo-1,2,4-thiadiazin-1,1-dioxide analog erhalten. Die Vielseitigkeit dieses Verfahrens wurde durch ein breites Produktspektrum demonstriert. Die Anwendbarkeit als Werkzeug in der organischen Synthese wurde für jedes dieser Strukturmotive im Gramm-Maßstab gezeigt. Zudem wurden mechanistische Studien zur Reduktion von Nitroaromaten mit anschließender Cyclokondensation mit Hilfe der Cyclovoltammetrie durchgeführt. Verglichen mit herkömmlichen Reduktionen von Nitrogruppen, kamen weder stöchiometrische Mengen von Reduktionsmittel noch die Verwendung von kostenintensiven Übergangsmetall-katalysatoren zum Einsatz. Zudem zeichnen sich die entwickelten Synthesestrategien durch die Nutzung von kohlenstoffbasierten Elektroden und grünen Lösungsmitteln aus, wodurch weitere Aspekte der grünen Chemie erfüllt wurden.

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1 Introduction

1.1 Electrochemistry as a Sustainable Key Technology

As society is facing a global environmental crisis, sustainability became a crucial aspect and a major challenge for modern chemical process development.[1] To circumvent the use of hazardous chemicals, scarce resources, and inefficient processes the application of efficient and environmentally friendly technologies must be ensured. Furthermore, questionable supply chains in the manufacturing of everyday products must be avoided.[2,3] The goals of modern and sustainable chemistry have been summarized by *P. Anastas* and *N. Eghbali* as the 12 principles of *Green Chemistry*.[4]

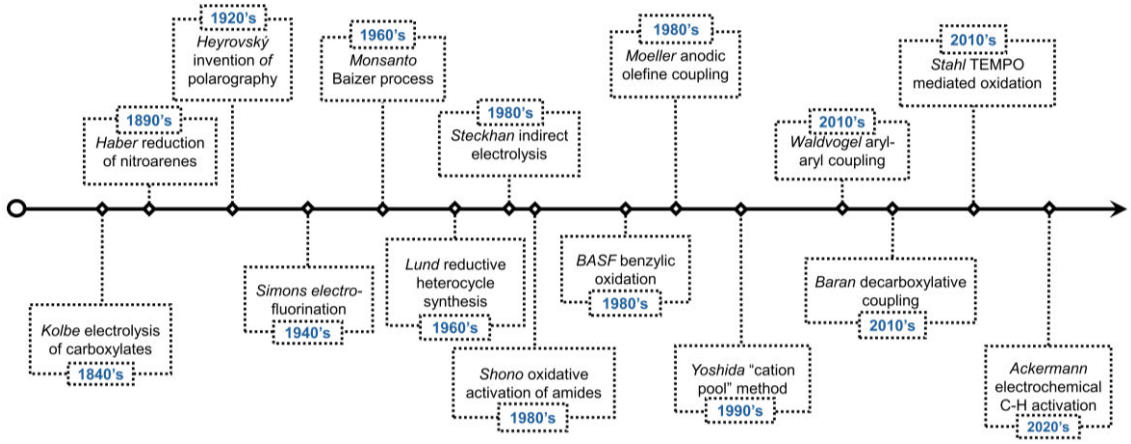


Figure 1: Contribution of electrochemistry to sustainable synthesis.

Electrochemical transformations fulfill aspects of these twelve principles and enable the development of innovative and sustainable supply chains to produce key chemicals (Figure 1).[5,6] Typically, traditional chemical processes use hazardous chemicals, equimolar amounts of redox-active reagents, and generate large amounts of waste.[7,8] In addition, these strategies often require multi-step processes. Electricity generated from renewable energy sources, as an inherently safe reagent, can serve as a surrogate for classical redox-active reagents, providing a clean alternative that avoids large amounts of waste and hazardous chemicals.[5,9–12] Moreover, electrochemistry can allow for synthetic shortcuts, enabling selective access to highly functionalized products.[13] Reactive intermediates are generated in-situ, bypassing their handling, and making the production of several products less harmful to humans and the environment. Therefore, electro-organic synthesis can be considered as an important tool for the design of modern and sustainable industrial processes.[14,15–17]

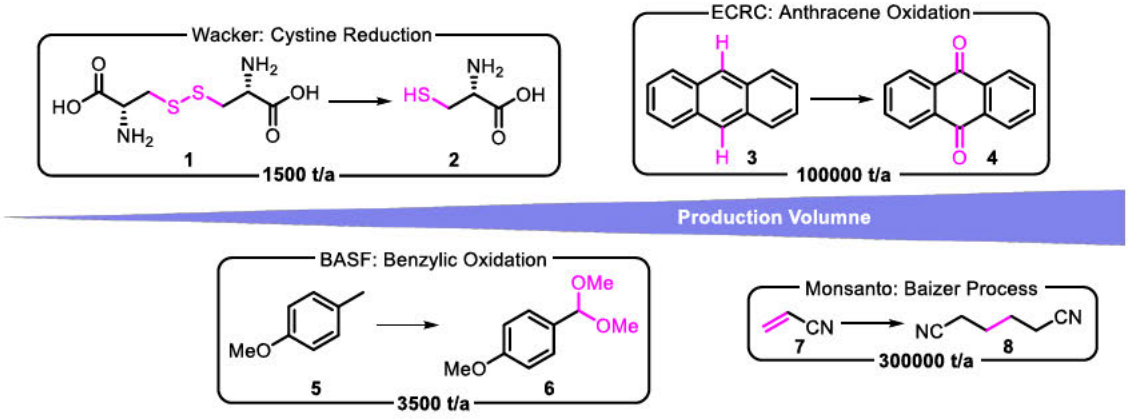
1.2 The History of Electro-organic Synthesis: From Lab-Scale to Industry

Electrochemical transformations have been investigated for several decades and the interest in the field of electro-organic synthesis continues growing (Scheme 1).[18] Organic electrosynthesis is based on the principles of electrolysis established by *M. Faraday* in 1834.[19] The first electro-organic synthesis was reported by *H. Kolbe* in 1848,[20] describing the decarboxylative coupling of alkali carboxylates to the corresponding alkanes by anodic oxidation.[21] In 1898, *F. Haber* established a simple protocol for the conversion of nitrobenzene to phenylhydroxylamine and related products.[22] The basis for the modern analysis of redox systems was developed by *J. Heyroský* during his research targeting the development of the polarography in 1922.[23]



Scheme 1: The history of the electro-organic synthesis. Adapted with permission from [24]. Copyright 2021 American Chemical Society.

J. H. Simons published the first fluorination of functionalized hydrocarbons in 1949 using hydrogen fluoride.[25] The reduction of nitro arenes by *H. Lund* resulted in the first electrochemical synthesis of quinoline *N*-oxides in 1969.[26] The anodic functionalization of amines was established by *T. Shono* in 1981 allowing for C–C bond formation in the α-position.[27] In 1986, *E. Steckhan* described the concept of indirect electro-organic synthesis, which uses a mediator acting as a redox-active platform in the transformation of compounds.[28] In the late 1980's the anodic oxidation of alkenes and subsequent cyclization was achieved by *Moeller et al.* and allowed for a direct C–C bond formation.[29] The oxidative generation of carbocations at low temperatures, first described in 1999 by *J. Yoshida*, represents a unique technique for the functionalization of amides.[30] The direct anodic arene coupling described by *S. R. Waldvogel* and the decarboxylative coupling using redox-active esters developed by *P. S. Baran* contributed to modern methods in the electrochemical C–C bond formation in the early 2010's.[31] The application of O-centered radicals like TEMPO in oxidations was further described by *S. Stahl* in the late 2010's.[32,33] Electrocatalytic C–H activation by transition metals established by *Ackermann et al.* is a rising field of interest and allows for a wide range of late-stage functionalization in complex molecules.[33]

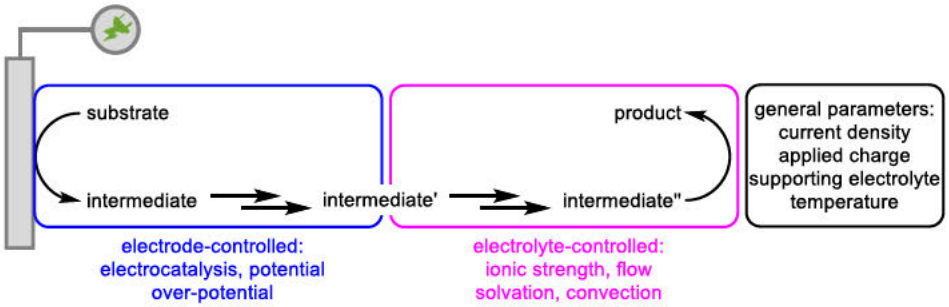


Scheme 2: Industrial scale electrosynthesis of bulk chemicals.[34]

Besides countless lab-scale protocols, various important industrial processes use highly efficient electrochemical transformations for sustainable access to common bulk chemicals.[35] L-Cysteine (Scheme 2, **2**), a semi-essential amino acid, is crucial in many biochemical processes and is commonly used as a food additive.[36] L-Cysteine is accessible by the electrochemical reduction of L-Cystine (Scheme 2, **1**) using different metals like lead, titan or stainless steel as cathode materials in an aqueous acid. A major drawback is the need to neutralize the reaction mixture to obtain the free amino acid, which can be avoided by performing the electrolysis in aqueous ammonia, simplifying downstream processing.[34] *p*-Anisaldehyde (Scheme 2, **6**) is a natural product obtained from star anise and a common chemical.[37] The industrial scale production of this chemical was established by *BASF* in 1960. 4-Methoxytoluene (Scheme 2, **5**) is oxidized in methanol resulting in the corresponding dimethylacetal, a precursor of *p*-anisaldehyde, in up to 3500 tons per year.[38] Moreover, the anodic oxidation of 4-*tert*-butyltoluene coupled with the cathodic hydrogenation of dimethyl phthalate results in a paired electrolysis protocol which was used by *BASF* in the production of both products in up to 4000 tons per year.[34] Anthraquinone (Scheme 2, **4**) and its derivatives are widely used in the paper industry and as natural dyes in food and cosmetics.[39] Anthracene (Scheme 2, **3**) can be oxidized using electrochemically generated cerium(IV) methanesulfonate to form anthraquinone. Alternatively, naphthalene is oxidized by oxygen resulting in naphthoquinone which reacts in a *Diels-Alder Reaction* with butadiene and subsequent oxidation to yield anthraquinone. Overall, 100000 tons of anthraquinone are produced by *ECRC* per year utilizing these methods.[35] One of the first, and most important electrochemical processes is the reductive electro-hydrodimerization of acrylonitrile (Scheme 2, **7**) to adiponitrile (Scheme 2, **8**) in the *Baizer Process*.[40] The adiponitrile produced at *Monsanto* by this process is used as a precursor for the synthesis of Nylon 6.6 an important polymer for everyday products.[35,41] The large-scale electrochemical synthesis of adiponitrile was developed by *M. Baizer* in 1964 and is still in use at *Monsanto* today.[42]

1.2.1 General Parameters of Electrochemical Transformations

The basic principle of organic electrosynthesis covers the anodic oxidation or cathodic reduction of the substrate during electrolysis and thereby the conversion into the desired product. This transfer of electrons is highly dependent on different electrolytic parameters (Scheme 3).[43]



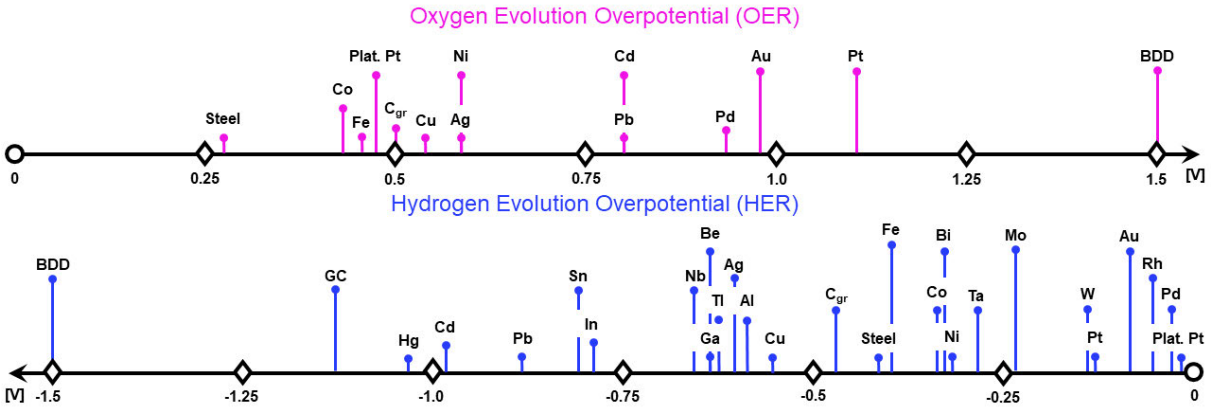
Scheme 3: Concept of electrochemical transformatiopns and common electrolytic paramters. Adapted with permission from [43]. Copyright 2020 American Chemical Society.

The amount of applied charge (Q/F) corresponds to the equivalents of redox-active reagent in conventional chemical conversions.[44] The electrode material serves as platform for the electron transfer and influences the reaction by its overpotential, interactions with intermediates, and its morphology.[43,45,46] The current density is comparable to the rate of substrate conversion during electrolysis.[43,44,46] The supporting electrolyte serves different roles in electrochemical reactions. Besides ensuring conductivity, it can protect the electrodes from corrosion, or take on a dual-role serving as redox-active mediator.[47] Furthermore, double layer formation on the electrode surface affects the diffusion of intermediates after electron transfer. The diffusion is further influenced by the solvent and the temperature during the electrolysis. Additionally, the solvation of the reactants and the ionic strength or buffering properties of the supporting electrolyte influence the reaction overall.[9,12,15,16,43] Despite the influence of the temperature on mass transport and conductivity, it is often a minor parameter in batch-type electrolysis on screening scale. However, when applying high current densities, the ohmic heating can cause a non-negligible temperature increase, necessitating external temperature control if the temperature influences the overall reaction.[5,10,15,43,44]

In general, reactions can be performed either by constant current electrolysis (CCE) or constant potential electrolysis (CPE). While CCE can be performed in a simple electrolytic set-up with two electrodes, CPE requires an additional reference electrode making the overall set-up more complex and challenging for scale-up. However, CPE is beneficial regarding the selectivity of the reaction by specifically applying the potential required for the electrochemical transformation.[5,10,15,43,44,46]

1.2.2 Electrode Materials and Modes of Operation

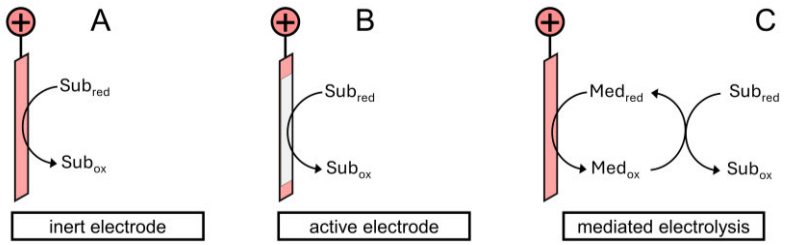
Overall, practicality is an important aspect to consider when choosing an electrode material. It should be easily accessible, inexpensive and ideally non-toxic to prevent product contamination with toxic residues. Furthermore, a suitable electrode material should enable highly selective and efficient synthetic transformations.[48,49]



Scheme 4: Electrode materials sorted by their potential for hydrogen evolution reaction or oxygen evolution reaction. Adapted from [49]; Copyright 2020 Wiley-VCH GmbH, Weinheim.

The overpotential of an electrochemical reaction describes the potential difference of the thermodynamic redox potential and the experimentally determined potential. This overpotential can be described as a sum of individual potentials of the microscopic and macroscopic reaction processes.[50] The electron transfer from/to the electrode to/from a substrate or mediator occurs as a heterogeneous process resulting in a large influence of the electrode material on the outcome of the reaction.[49] The electrode materials can be sorted according to their overpotential for oxygen evolution (OER) and hydrogen evolution (HER) (Scheme 4). For setting up an electrochemical reaction, it is crucial to select electrode materials that match with the targeted reactivities. For example, to perform an electrochemical reduction of a substrate, the employed cathode material should feature a high overpotential for HER. Considering the overpotential for hydrogen evolution, the most used electrode materials for reductive electrochemical reactions are carbon-based, such as glassy carbon or boron-doped diamond and metals like mercury or lead. The high overpotential for hydrogen evolution of lead or mercury as electrode material is often used for electrochemical reduction reactions or polarography.[51,52] Since mercury affects the environment negatively and is highly toxic, the use as electrode material must be avoided.[51,52] The slightly decreased toxicity and low price of lead makes it ideal for electrochemical reductions as shown in many examples.[53] The corrosion of lead electrodes could be inhibited by the addition of organic diammonium salts which also serve as supporting electrolyte.[54] The low mechanical stability of lead can be circumvented by using leaded bronzes which are commonly alloys of lead, copper and tin in different ratios.[55] The applicability of leaded bronzes as lead surrogate was demonstrated for example on electrochemical dehalogenation and carbon dioxide

reduction.[56,57] However, complete avoidance of trace metal contamination of the product should be considered when choosing a suitable electrode material.[49] Carbon-based electrode materials like graphite, glassy carbon (GC) or boron-doped diamond (BDD) allow for an omission of trace metal contamination enhancing the sustainability of electrochemical transformations.[58–60] The simplest carbon-based material is graphite. It features a wide potential window, is chemically nearly inert and low in cost.[58,61]. The carbon atoms in glassy carbon are almost all sp^2-hybridized, contributing to the unique properties of this material.[62] Additionally, the surface of glassy carbon can be further functionalized to modify the electrochemical properties.[63] Diamond is a carbon allotrope of high robustness, thermally conductive and an electrical insulator.[64] However, the electrical properties of diamond can be modified by doping with boron or nitrogen. The incorporation of boron results in boron-doped diamond (BDD), which exhibits excellent electrochemical properties and chemical resistance.[59] Based on these outstanding attributes of BDD it is used as electrode material in waste-water treatment and electro-organic synthesis.[65] Furthermore, boron-doped diamond electrodes are manufactured by chemical vapor deposition of methane and diborane on a support material like silicon, niobium or titanium.[59] Using methane generated from environmentally friendly sources like bio-gas contributes to the sustainability of BDD.



Scheme 5: Modes of operation of electrodes in organic electrosynthesis: **A** inert electrode, **B** active electrode or **C** mediated electrolysis.[43]

The choice of the ideal electrode material further depends on the mode of operation it is intended to be used in. The simplest mode of operation is the inert electrode, enabling a heterogeneous electron transfer to the substrate (Scheme 5, **A**). Therefore, the outcome of the reaction is solely dependent on the electrode potential.[10,43] The formation of an electro-catalytic layer on the surface of the electrode is described as an active electrode (Scheme 5, **B**).[43] The active species of this layer is formed and regenerated in-situ and is less dependent on the applied potential. Prominent examples of active electrodes are nickel oxide hydroxide on nickel in alkaline systems used in various oxidation reactions, molybdenum anodes in fluorinated alcohols for various aryl-aryl couplings and lead dioxide on lead in acidic media for the treatment of waste water.[66] Indirect electrolysis involves activation of a redox mediator at the electrode, which then reacts with the substrate (Scheme 5, **C**).[43] The mediator is regenerated at the electrode, enabling its use in catalytic amount. This method offers increased selectivity and milder electrolysis conditions by using narrower potential windows. Prominent examples are the TEMPO-mediated alcohol oxidations.[67]

1.2.3 Types of Electrolysis Cells

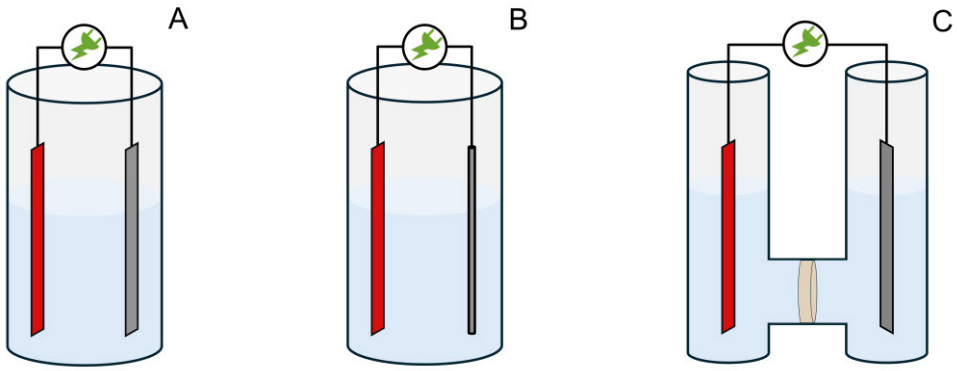


Figure 2: Different cell types used in organic electrosynthesis from left to right: undivided set-up (**A**), quasi-divided set-up (**B**) and divided set-up (**C**).[43,44,46,68]

Besides the impact of the electrode material on the overall reaction the cell set-up can be crucial for electrochemical transformations.[43] The undivided set-up represents the simplest electrolytic cell (Figure 2, **A**).[43,44,46,68] Anodic oxidation and cathodic reduction occur in one single compartment. In some cases, the missing separation of the anodic and cathodic reaction might result in undesired side reactions. This requires the separation of the anodic and cathodic reaction to suppress overoxidation or -reduction of the product. One possibility to circumvent side reactions while maintaining the undivided set-up is the quasi-divided approach (Figure 2, **B**).[43,44,46,68] Application of a wire or rod as counter electrode results in a tremendously decreased electrode surface area. Thus, the diffusion to the electrode, and therefore the conversion, is limited to highly mobile and concentrated species such as solvents.[16,43,44,46,68] Strict separation of anodic oxidation and the cathodic reduction can be achieved in a divided cell.[16,43,44,46,68] These electrolytic cells, often described as H-type cells, provide compartment separation by a separator material. The most common separators are porous ceramics and glass or polymeric and functionalized materials.[16,43,44,46,68] In general, porous materials made of glass or ceramics inhibit the mixing of the catholyte and the anolyte on a short time scale. However, the electrochemical reaction requires the transport of ions between the two compartments, causing the transfer of some substrate and product as a result of a concentration gradient.[16,43,44,46,68] The application of functionalized membrane materials like Nafion™ can bypass the undesired transfer of species due to their ion specific permeability.[16,43,44,46,68] A major drawback of the divided cell set-up is the higher complexity of the system and the increased cell voltage as a result of the higher resistance.[16,43,44,46,68]

1.2.4 Electrosynthesis in Biphasic Systems

Most electrochemical transformations are performed in a homogeneous system where all reactants are dissolved in a corresponding solvent (mixture). However, these reactions are lacking selectivity in some cases. Furthermore, the downstream processing of the reaction mixtures in organic electrosynthesis is a main challenge for developing sustainable methods.[3,5,7,12,13,17] As most of the electrochemical conversions involve the use of supporting electrolytes or other additives, an effective work-up procedure is mandatory for recycling the majority of components added to the reaction.[69] Performing electrolytic conversions in biphasic solvent systems can address these challenges of electrochemical synthesis in an elegant way.[70,71]

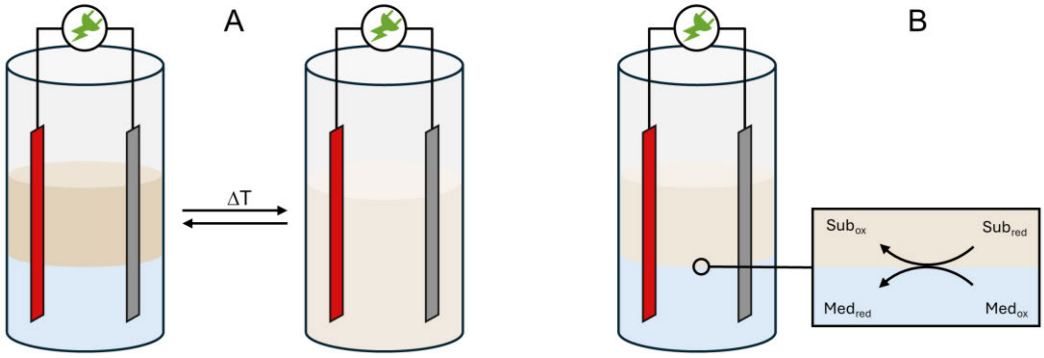
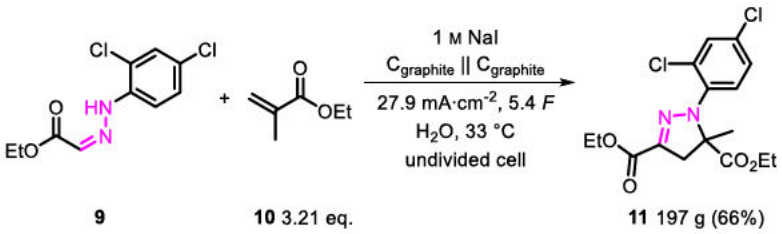


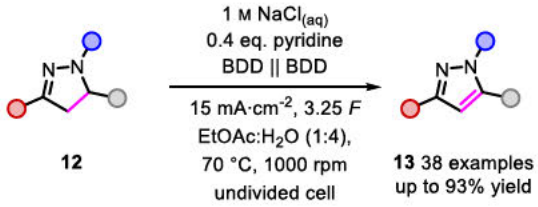
Figure 3: Principle of electrochemical reactions in a biphasic system: **A** thermo-responsive solvent mixture or **B** biphasic reaction at the interphase.[71–75,76,77,78]

One example of an efficient biphasic system involves the extraction of fluorinated products from the organic reaction mixture by application of highly fluorinated solvents.[79] This synthetic strategy was employed in several syntheses of heterocycles, their functionalization and amide coupling reactions.[80] However, due to the negative environmental impact of perfluorinated compounds their application is limited.[81] The thermo-responsive properties of an acetonitrile-cyclohexane mixture enables a unique technique which improves the downstream processing of several electrochemical reactions drastically (Figure 3, **A**).[82] While supporting electrolytes are commonly soluble in polar solvents like acetonitrile, apolar substrates or products exhibit an increased solubility in apolar solvents like cyclohexane. To increase the conductivity of this system, the reaction mixture is heated to form a homogeneous system. After the electrolysis, cooling results in phase separation. The product can be easily obtained from the cyclohexane layer while the polar acetonitrile layer can be recycled.[73] The applicability of this method was demonstrated on a broad variety of electrochemical synthesis like peptide couplings, oxidative carbon-carbon bond formations and sulfide modifications.[72,74,75,78] Furthermore, adapting this concept for the commonly used *Kolbe Electrolysis* could resolve some major issues like the passivation of the electrode surface or the low conductivity of non-aqueous reaction mixtures.[77]



Scheme 6: Electrochemical deca-gram scale synthesis of *Mefenpyr Diethyl* (**11**) in a biphasic system.[83,84]

Highly redox-sensitive compounds often undergo undesirable side reactions instead of conversion to the product. Sensitive alkenes such as styrene or acrylates for example, tend to undergo electrochemically initialized oligomerization.[85] To prevent adverse side reactions, the benefits of a mediated electrolysis can be combined with the biphasic electrochemical approach (Figure 3, **B**). In general, the substrates are dissolved in the organic layer while the supporting electrolyte and/or the mediator is dissolved in the aqueous layer. During the electrolysis the activated species of the mediator is formed and reacts with the substrate at the interphase to form the product. Since the organic layer lacks conductivity, the redox-sensitive components of the reaction are not subjected to a direct electron transfer. After electrolysis and a simple phase separation, the product can be obtained from the organic layer and the contents of the aqueous layer can be recycled.[83,84] The application of this simple and versatile approach was demonstrated on a variety of heterocycles. *Waldvogel et al.* demonstrated the broad applicability of this method as a modern synthetic tool by synthesis of various pyrazolines via (3+2) cycloaddition. The simplicity was underlined by using carbon-based electrodes, a simple ethyl acetate-water mixture as solvent and sodium iodide as mediator.[83,84] The scalability of this methodology was shown in the synthesis of the herbicide safener *Mefenpyr Diethyl* (**11**) in up to hecto-gram scale (Scheme 6).[83]

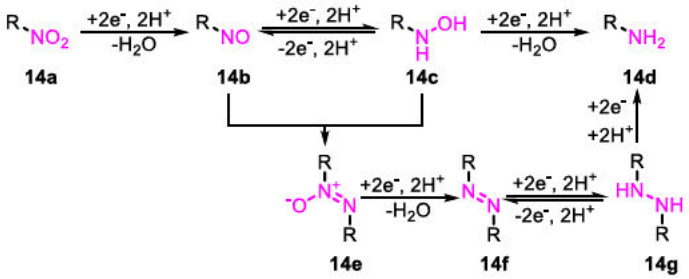


Scheme 7: Chloride-mediated electrochemical oxidation of pyrazolines **12** to pyrazoles **13** in a biphasic mixture of ethyl acetate and water.[86]

Besides the application in the direct construction of heterocycles, this technique can be used for the mediated oxidation of pyrazolines **12** to pyrazoles **13** (Scheme 7).[86]

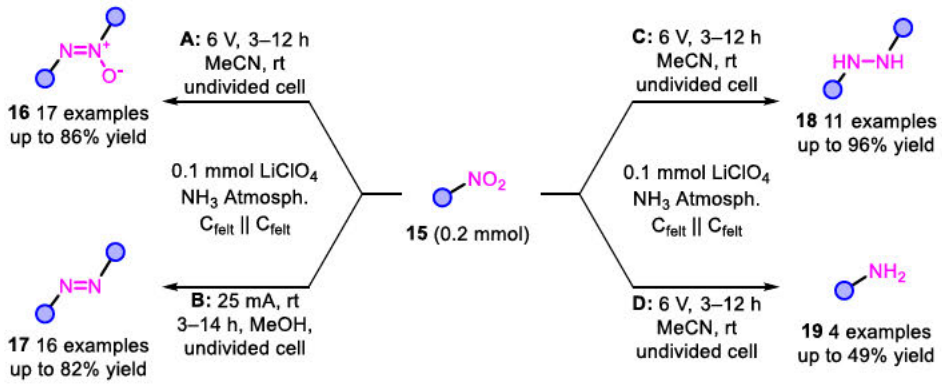
1.3 Cathodic Reduction of Nitro Arenes – A Versatile Tool in Heterocyclic Chemistry

The reduction of nitro groups is a versatile and powerful tool for accessing different nitrogen-containing functional groups or heterocycles.[87] Most of the conventional transformations are performed by catalytic hydrogenation using transition metal catalysis or equimolar amounts of reducing agents like zinc or iron dust in acidic media.[88]



Scheme 8: Mechanism of the electrochemical reduction of nitro arenes.[89]

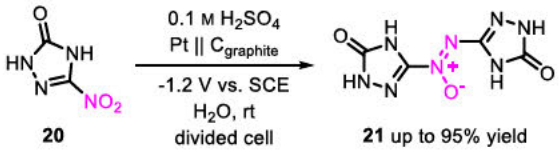
The electrochemical reduction of nitro groups **14a** is highly dependent on the employed solvent system and its pH (Scheme 8).[90] In protic solvents the nitro arene **14a** is reduced to the corresponding nitroso arene **14b**. The subsequent reduction of **14b** to the corresponding arylhydroxylamine **14c** is easily accomplished, proving the selective synthesis of nitroso arenes **14b** challenging. However, by selecting a specialized electrode material or by performing the reduction in a biphasic system using the nitro arene **14a** as the solvent, selectivity towards the nitroso arene **14b** is achieved.[91,92] Under highly acidic conditions, the arylhydroxylamine **14c** easily undergoes the final reduction to the corresponding aniline **14d**.[92] The intermediately formed nitroso arene **14b** can undergo a condensation reaction with the arylhydroxylamine **14c** to form azoxy- **14e**, azo- **14f** and hydrazobenzenes **14g**, which are further reduced to the corresponding anilines **14d**.[92,93]



Scheme 9: Electrochemical reduction of nitro arenes using ammonia as hydrogen source.[94]

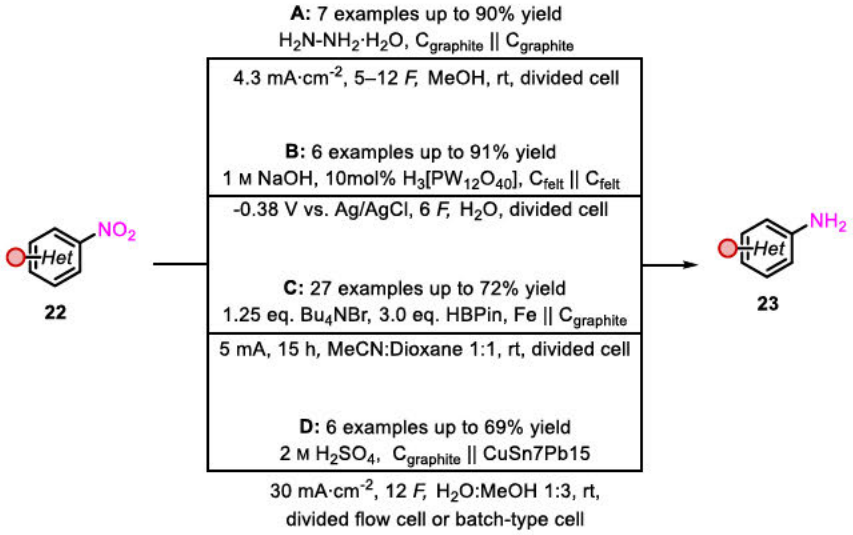
Cheng et al. (2021) demonstrated the use of ammonia as hydrogen source in the reduction of nitro arenes **15** to different value-added products (Scheme 9) by variation of the reaction conditions. Performing the electrolysis at 6 V (cell voltage) in acetonitrile using lithium perchlorate as supporting electrolyte yielded azoxybenzenes **16** selectively after three to twelve hours (Scheme 9, **A**). If the

electrolysis was carried out in methanol at 25 mA for three to fourteen hours (Scheme 9, **B**), azobenzenes **17** were selectively obtained. Further reduction (Scheme 9, **C**) resulted in different hydrazobenzenes **18**. Interestingly, nitro arenes featuring electron-donating groups formed the corresponding anilines **19** (Scheme 9, **D**).[94] However, the authors provided the electrochemical parameters insufficiently regarding scientific standards.



Scheme 10: Electrochemical reduction of a wastewater model containing NTO (**20**) for the synthesis of AZTO (**21**).[95]

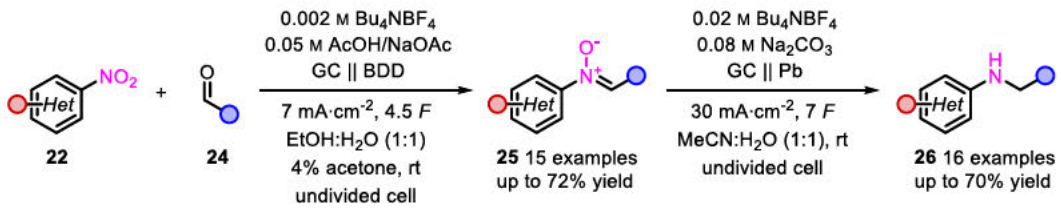
5-Nitro-1,2,4-triazol-3-one (**20**, NTO) is an insensitive explosive considered as a safer alternative for the commonly used hexogen (RDX). However, the good water solubility of NTO results in large quantities of NTO-contaminated waste water from its manufacturing. *Wallace et al.* developed a method for the preparation of azoxytriazolone (**21**, AZTO), a novel insensitive explosive, by electrochemical treatment of an aqueous solution of NTO (**20**, Scheme 10). The simple reduction of the nitro group and subsequent condensation of the derived nitroso- and hydroxylamine intermediates resulted in the selective formation of AZTO (**21**). This methodology represents a novel approach for the generation of a value-added product from wastewater.[95]



Scheme 11: Electrochemical reduction of nitro arenes **22** to anilines **23**.[96–99]

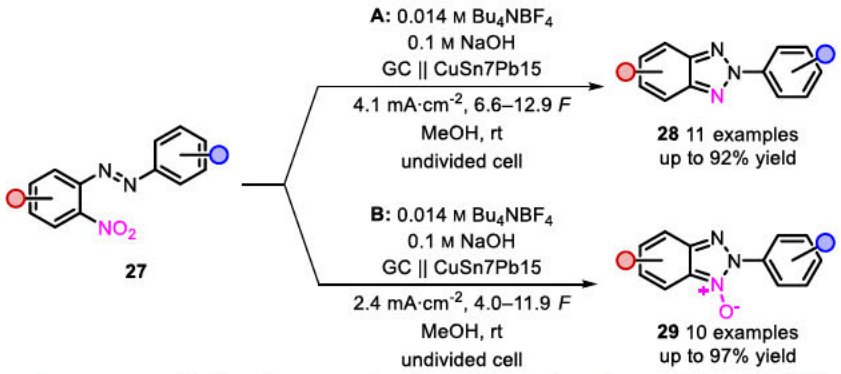
Lam et al. (Scheme 11, **A**) used hydrazine hydrate as hydrogen source in the reduction of nitro arenes **22** avoiding high pressure, molecular hydrogen and precious metal catalysts. Initially, hydrazine is oxidized to form diimine in-situ, the active reductant in this procedure which causes reduction of nitro arene **22** to the corresponding aniline **23**. Additionally, the reaction conditions enable the reduction of azides, alkenes and alkynes. However, this method requires large quantities of toxic hydrazine hydrate.[97] *Symes et al.* (Scheme 11, **B**) developed an electrocatalytic and potential-controlled approach for the selective and mild reduction of nitro arenes **22** to anilines **23**.[96] This mediated process involves

an initial reduction of the phosphotungstic acid and a subsequent electron transfer to nitrobenzene **22** results in the formation of anilines **23**. The scope of the reaction was demonstrated on a diverse selection of substrates showing a great functional group tolerance. *Shen et al.* (Scheme 11, **C**) avoided the use of hazardous hydrazine by application of non-toxic pinacolborane (HBPin) as hydrogen source. It was proposed that the sacrificial iron anode liberates Fe(III) cations catalyzing the hydrogen transfer from the pinacolborane. The protocol tolerates a wide range of functional groups and allows for the synthesis of anilines in up to gram-scale.[98] *Waldvogel et al.* (Scheme 11, **D**) could further simplify the reduction of nitro arenes **22** to anilines **23** in a divided batch-type or flow cell by avoiding mediators, metal catalyst and hazardous reagents. Sulfuric acid serves as additive promoting the reduction. Additionally, the employed acidic supporting electrolyte allows for simple isolation of the products via precipitation in form of the corresponding anilinium salts. The method's simplicity enables easy downstream processing and therefore contributes to its application potential on technically-relevant or industrial scale.[99]



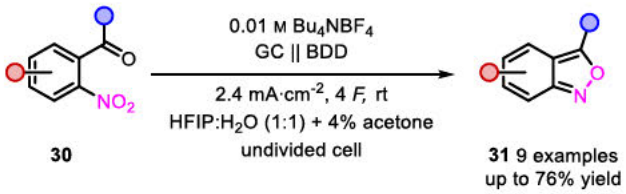
Scheme 12: Electrochemical reduction of nitro arenes **22** in the synthesis of nitrones **25** and subsequent reduction to secondary amines **26**.[100,101]

Selective reduction of nitro arenes **22** to arylhydroxylamines **14c** can be harnessed for the selective synthesis of complex molecules.[89] Nitrones are important building blocks, finding application in cycloaddition reactions or as precursors for the synthesis of various nitrogen containing functional groups.[102] *Waldvogel et al.* developed a simple synthetic strategy for the one-pot electrosynthesis of nitrones **25** from nitro arenes **22** and aldehydes **24**. This method gave access to a wide range of functionalized nitrones.[100] The reduction of nitrones **25** to the corresponding secondary amines **26** demonstrates the potential of **22** to server as platform for accessing several important motifs.[101]



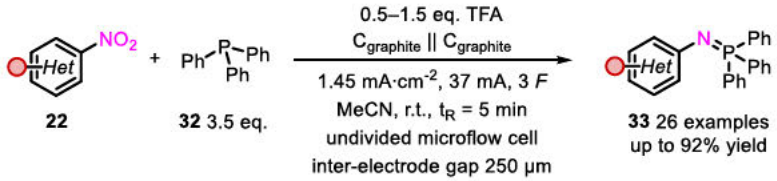
Scheme 13: Switchable selectivity in the electrochemical synthesis of **28** and **29**.[103]

Benzo-1,2,3-triazoles **28** and benzo-1,2,3-triazole-1-oxides **29** represent important motifs in drugs as well as functional materials.[104] A synthetic protocol by *Waldvogel et al.* enables selective reduction of nitroaryl azobenzenes **27** to the corresponding nitroso intermediates. Subsequent intramolecular cyclization yields either benzo-1,2,3-triazoles **28** or benzo-1,2,3-triazol-1-oxides **29**, depending on the employed current density. The easily switchable selectivity underlines the elegancy of the method in accessing two highly functional heterocyclic motifs.[103]



Scheme 14: Electrochemical synthesis of 2,1-benzisoxazoles **31** by cathodic reduction of 2-nitrobenzaldehydes **30**.[105]

A variety of natural products and potent drugs feature 2,1-benzisoxazoles **31** scaffolds.[106] *Waldvogel et al.* demonstrated the electrochemical synthesis of 2,1-benzisoxazoles **31** (Scheme 14) in a simple fashion starting from 2-nitrobenzaldehydes **30** in up to 76% yield. Moreover, this protocol could be adapted for the conversion of 2-nitrocinnamates to quinoline *N*-oxides.[105]



Scheme 15: Electrochemical synthesis of aryliminophosphoranes **33** in flow.[107]

Besides the synthesis of various heterocyclic compounds, the reduction of nitro arenes can be used in the synthesis of N–X bonds. Aryliminophosphoranes **33** function as essential intermediates in organic synthesis.[108] The protocol by *Noël et al*. enables access to several aryliminophosphoranes **33**, starting from widely available nitro arenes **22** and triphenylphosphine (**32**) (Scheme 15). This cooperative approach utilizes the anodic counterreaction for oxidation of triphenylphosphine, which reacts with the cathodically generated aniline. This synthetic strategy allows for efficient synthesis of a broad variety of aryliminophosphoranes **33** in an innovative flow set-up using carbon-based electrodes.

In summary, synthetic access to a wide range of important heterocycles and highly valuable functional groups can be granted via the reduction of nitro arenes. The simplicity of the underlying method starting from readily available nitro arenes contributes to its importance for the development of novel electrochemical strategies.

1.4 N,O-Heterocycles – Modern Scaffolds for Potent Compounds

Nitrogen containing heterocycles are building blocks in a broad variety of natural products, important drugs and agro-chemicals.[109,110] Heterocycles containing an endocyclic or exocyclic N,O-bond are a valuable class of compounds with unique reactivities or activities based on their structure.[110,111]

1.4.1 Isoxazol(in)es

Isoxazoles and isoxazolines are five-membered heterocycles bearing an endocyclic N,O-bond. They are featured in many highly potent drugs and effective herbicides or herbicide safeners as a core motif[112]

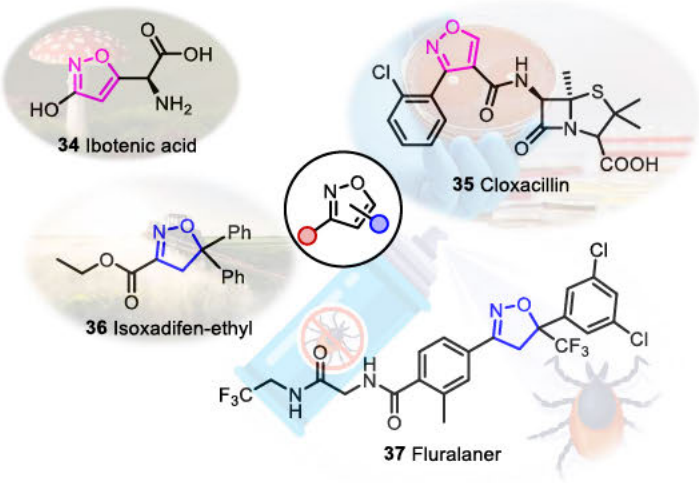
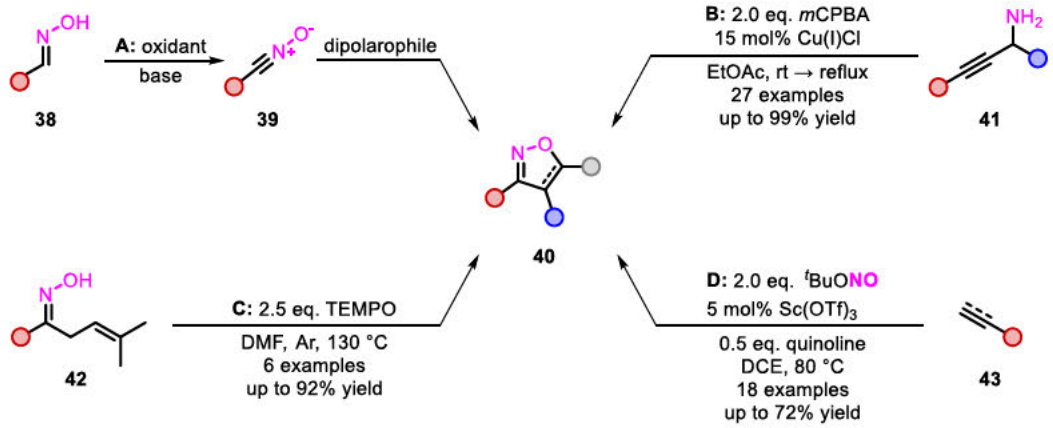


Figure 4: Examples of biologically active isoxazoles and isoxazolines.

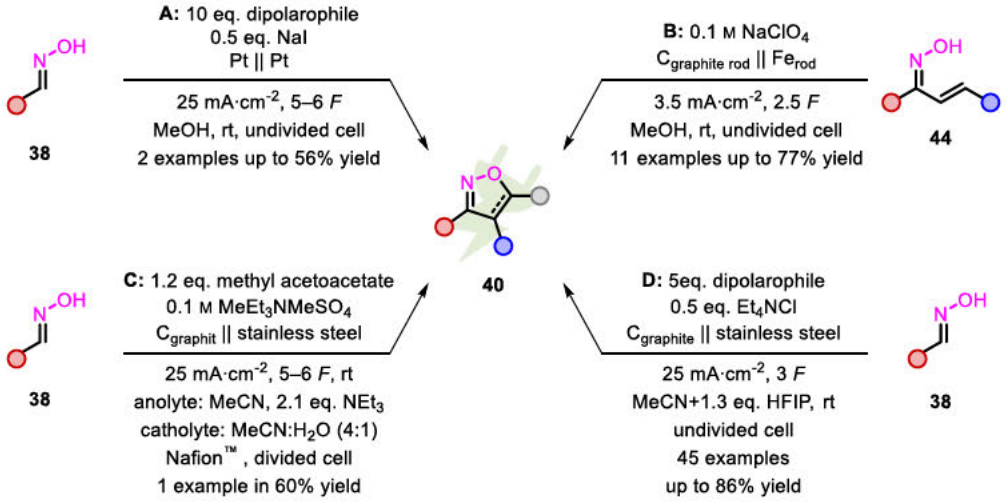
Ibotenic acid (Figure 4, **34**) is a prodrug to the psychoactive compound muscimol and commonly found in *Amanita muscaria* (fly argic).[113] The structural similarities of both compounds to glutamate, an important neurotransmitter, results in a stimulation of the corresponding glutamate receptor in the brain. This unique property of those compounds is further subject to the treatment of chronic pain.[114] Moreover, isoxazolines are found in a great number of highly potent antibiotics.[115] *Cloxacillin* (Figure 4, **35**) is a potent semi-synthetic antibiotic derived from 6-aminopenicillanic acid, listed as an essential drug by the WHO in 2019.[116] It is a commonly used highly oral bio available antibiotic, e.g. in the treatment of bacterial infections such as *Staphylococcus aureus.*[117] The herbicide safener *Isoxadifen-ethyl* (Figure 4, **36**) protects crops from the harmful effects of herbicides by accelerating the detoxification processes of the plant.[118] By applying herbicide safeners while treating crops with herbicides, the efficacy of the treatment can be tremendously increased.[119] The insecticide *Fluralaner* (Figure 4, **37**) is used against flee, ticks and mites in pets, especially in organisms with a resistance against certain insecticides such as dieldrin. The mechanism of action is based on a selective inhibition of ionotropic *γ*-aminobutyric acid (GABA) receptors in insects.[120]



Scheme 16: Conventional synthesis of isoxazol(in)es **40**.[121–129]

The most abundant synthetic approach for the synthesis of isoxazol(in)es **40** harnesses a highly reactive nitrile oxide **39** as 1,3-dipole, which is often formed in-situ (Scheme 16, **A**). The initial formation of the nitrile oxide is commonly achieved by oxidation of aldoximes **38**. A prominent approach includes conversion of **38** to the corresponding hydroximinoyl halide, by halogenation reagents such as *N*-chlorosuccinimide (NCS), hypochlorite or thionyl chloride. Afterwards, elimination of hydrogen halide by a base forms the nitrile oxide **39**, which undergoes 1,3-dipolar cycloaddition with a dipolarophile yielding the isoxazol(in)e **40**.[127–130] A major disadvantage is the use of equimolar amounts of highly hazardous halogenating agents which require safety precautions. A milder protocol involves the formation of the hydroxyminoyl halide by using a mixture of Oxone™ and sodium chloride for halogenation.[124] Hypervalent iodine species are also capable of yielding the nitrile oxide **39** directly and require only a catalytic amount of the corresponding iodo-arene, further decreasing the number of reagents required.[125] *Song et al.* provided a transition-metal catalyzed method using copper salts in the synthesis of various isoxazoles, starting from readily available propagylamines **41** (Scheme 16, **B**). Initially, the amine is oxidized by *meta*-chloroperoxybenzoic acid (*m*CPBA) to an α,β-acetyleneoxime. Activation of the alkyne moiety of the intermediate propargyloxime by a copper(I) salt results in an intramolecular cyclization to the desired isoxazole **40**.[123] Additionally, this cyclo-isomerization can be achieved by gold activation of α,β-acetyleneoximes or photo-redox activation of allylic oximes.[131,132] *Han et al.* established a metal-free and simple protocol involving an intramolecular cyclization of β,γ-unsaturated ketoximes **42** (Scheme 16, **C**). The cyclization is initiated by 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), forming an oxygen-centered radical. This radical undergoes a 5-*exo*-trig cyclization resulting in the formation of the isoxazolines **40**.[121] Besides the intramolecular cyclization of aldoximes the formation of isoxazol(in)es **40** can be achieved by intermolecular cyclization. *Patel et al.* established a simple multi-component protocol using quinoline as an inexpensive base, a scandium(III) triflate catalyst and *tert*-butyl nitrite as N,O-source (Scheme 16, **D**). The oxidation of the *tert*-butyl nitrite results in the formation of nitrosyl- and nitro radicals, leading to

intermediary formation of a nitroketone with the alkene or the alkyne. The scandium(III) triflate activates the unreacted alkene or alkyne to perform the cycloaddition to the final product **40**.[126]



Scheme 17: Electrochemical synthesis of isoxazol(in)es **40**.[133–136]

Electrochemical access to isoxazoles and isoxazolines **40** was first reported by *Shono et al.* while investigating the electrochemical transformation of aldoximes towards nitriles using alkali halides (Scheme 17, **A**). To proof the hypothesized halide-mediated oxidation of aldoximes to nitirile oxides in-situ, the latter was trapped as an isoxazoline by adding styrene to the reaction mixture.[134] The electrochemically initiated intramolecular cyclization of α,β-unsaturated ketoximines **44** offers the great advantage of avoiding hazardous oxidants and noble metals.[124,131,132] *Xiao et al.* established a simple protocol for the intramolecular formation of isoxazoles **40** from α,β-unsaturated ketoximines **44** (Scheme 17, **B**). The reaction is initiated by the anodic oxidation of the oxime moiety resulting in an oxygen centered radical. This radical undergoes cyclization to a radical intermediate. Which is further oxidized to the corresponding isoxazole **40** after protonation.[135] However, this method is limited to complex pre-functionalized substrates. *Zhang et al.* harnessed nitromethane as an inexpensive and widely accessible N,O-source directly using styrenes in a simple one-pot protocol. This approach generates furoxanes in-situ, accessing aldoxime isoxazoles after cycloaddition with styrenes.[137]

The direct anodic oxidation of aldoximes **38** without the use of mediators and external oxidants was initially developed by *Waldvogel et al.* as part of a domino oxidation-reduction sequence yielding a wide variety of nitriles.[138] As a proof of concept, the synthesis of a precursor for the widely used antibiotic dicloxacillin was demonstrated by adding triethylamine and methyl acetoacetate after electrolysis (Scheme 17, **C**). It was further observed, that sterically demanding aldoximes formed stable nitrile oxides which were detectable by gas chromatography.[133] Moreover, a protocol for the formation of stable betulin-derived nitrile oxides **39** was developed, for the synthesis of betulin-isoxazole conjugates by 1,3-dipolar cycloaddition.[139]

Reid et al. presented a homogeneous system for the chloride-mediated synthesis of various isoxazolines and investigated the mechanism of the reaction by cyclic voltammetry in combination with density

function theory (DFT) (Scheme 17, **D**). Application of a quaternary ammonium halide salt as mediator proved crucial for achieving satisfactory yield. Moreover, HFIP as additive promoted the reaction drastically due to its radical stabilizing properties.[136]

Overall, several protocols for the electrochemical synthesis of isoxazolines and isoxazoles have been established. However, most of these protocols use highly complex starting materials or could only be give access to a limited scope of isoxazolines or isoxazoles **40**. Furthermore, the downstream processing of a synthetic protocol needs to be taken into account for scale-up, necessitating improvement on the overall set-ups chosen to ensure applicability on technically-relevant scale.[140]

1.4.2 Quinoline *N*-oxides and Quinolines

Quinolines and quinoline *N*-oxides are prevalent motifs in a broad range of natural products and useful building blocks for organic compounds or potent drugs.[141] However, quinoline *N*-oxides are underexplored and mostly used as precursors in the synthesis of functionalized quinolines.[142]

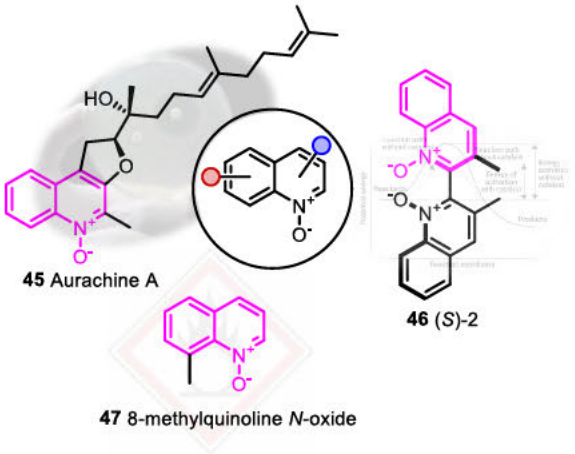
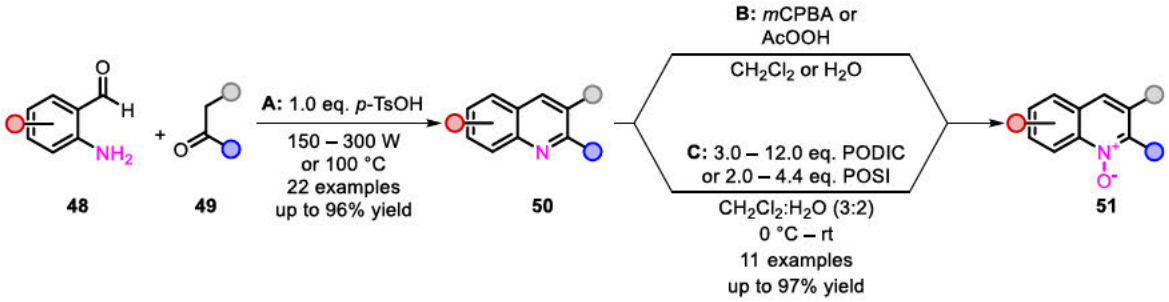


Figure 5: Naturally occurring quinoline *N*-oxides and important reagents bearing a quinoline *N*-oxides motif: Aurachine A (**45**), ligand (*S*)-2 (**46**) and 8-methylquinoline *N*-oxide (**47**).

Noteworthy, Aurachines are a family of naturally derived prenylated quinoline alkaloids found in the myxobacterium *Stigmatella aurantiaca*. *Aurachine A* (Figure 5, **45**) is one major product of the biosynthetic pathway of this microorganism and furthermore has shown antibiotic properties against certain strains of bacteria.[143] To counteract the rising number of antibiotic resistances, further investigations regarding this family of compounds are required to overcome the threatening shortage of effective drugs.[144]

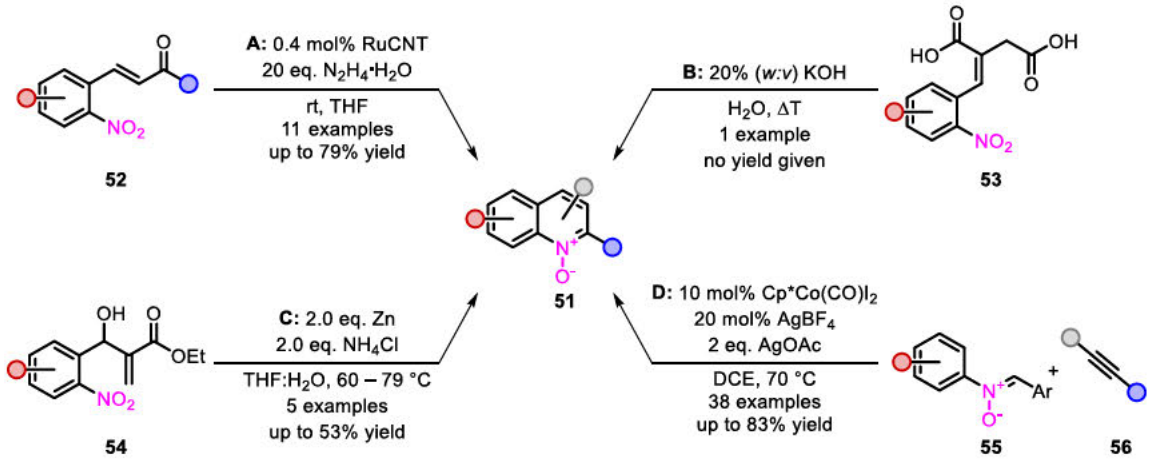
Due to the unique properties of the polarized N,O-bond, quinoline *N*-oxides function as precursors for the selective synthesis of functionalized quinolines or find application as ligands in asymmetric synthesis.[145] The N,O-bond of quinoline *N*-oxides has a high nucleophilicity towards silicon atoms. This property can be harnessed by using chiral quinoline *N*-oxide ligands as transfer agents in the enantioselective allylation of aldehydes (Figure 5, **46**).[146] In addition, the N,O-bond of quinoline *N*-oxides can serve as an oxygen-atom donor in transition metal catalyzed reactions of complex molecules.[147] For example, 8-methylquinoline *N*-oxides (**47**) are employed as an oxidant in the selective synthesis of cyclopentenones.[148] The application of inexpensive and simple quinoline *N*-oxides in this type of reaction avoids the use of highly hazardous diazo compounds, which are commonly applied in this type of reaction (Figure 5, **47**).[149]

The high demand for different quinolines and quinoline *N*-oxides has promoted the development of several methods for their construction.[150] Synthetic access to quinoline *N*-oxides is commonly provided by either oxidation of the corresponding quinoline or intramolecular cyclization of nitro arenes.[151,152]



Scheme 18: Synthesis of quinoline *N*-oxides **51** by initial condensation of 2-aminobenzaldehydes **48** with ketones **49** and subsequent oxidation of quinolines **50**; PODIC = peroxodicarbonate, POSI = phenoyloxy succinimide.[153–158]

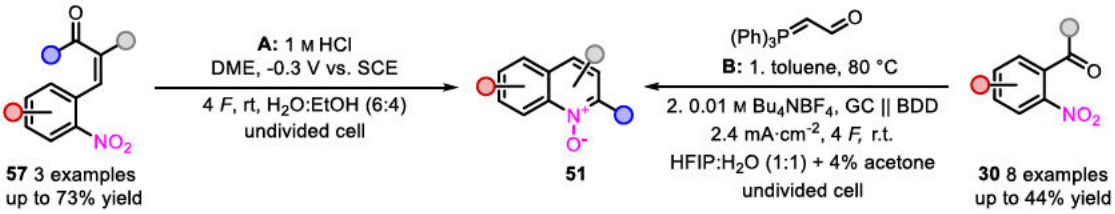
P. Friedländer first reported a simple protocol for accessing quinolines **50** by a simple two-fold condensation using readily available 2-aminobenzaldehydes **48** and substituted ketones **49**.[153,154] In recent years, a number of modern adaptations of this method have been developed, such as the solvent-free variant and the application of heat by microwave irradiation, which greatly reduces reaction times (Scheme 18, **A**).[159] The subsequent oxidation of the quinoline **50** to its quinoline *N*-oxide **51** is commonly performed using peroxy acids such as *m*CPBA and peroxyacetic acid (AcOOH) (Scheme 18, **B**).[157,158] However, these methods involve the use of equimolar amounts of hazardous peroxy acids which have to be handled with great caution.[160] The mild and electrochemically generated peroxodicarbonate (PODIC) offers a safe surrogate for several oxidation reactions (Scheme 18, **C**). *Waldvogel et al.* were able to demonstrate the great potential of this green platform oxidizer by developing a simple protocol for the synthesis of quinoline *N*-oxides **51**.[156]



Scheme 19: Conventional syntheses of quinoline *N*-oxides **51** by cyclization reactions.[161–164]

Besides by oxidation of the corresponding quinolines, quinoline *N*-oxides **51** can be obtained via different routes featuring reductive cyclization reactions starting from nitro arenes. The catalytic reduction of nitrochalcones **52** with hydrazine hydrate and ruthenium-carbon nano tubes (RuCNT) as catalyst allows for a mild synthesis of different quinoline *N*-oxides (Scheme 19, **A**).[164] A metal-free variant of this protocol proceeds at elevated temperature in the same fashion.[161] A major drawback of these protocols is the use of large quantities of hazardous hydrazine hydrate or noble metals. A simple and transition metal-free route involves the thermal treatment of 2-nitrobenzylidene-

substituted succinic acids **53** (Scheme 19, **B**). However, only one example was presented and no information about the yield or a mechanism has been provided by the authors.[151] The selective reduction of nitro arenes in a slightly acidic medium is a common technique for accessing different intermediates towards aniline-derivatives and can be harnessed for the synthesis of specific products.[165] The selective reduction of easily accessible *Baylis-Hillman* adducts **54** using zinc allows for the synthesis of various 4-hydroxyquinoline *N*-oxides **51** (Scheme 19, **C**).[163] However, the use of equimolar quantities of reducing agents results in large amounts of reagent waste. The transition metal-catalyzed synthesis of highly substituted quinoline *N*-oxides **51** can also be achieved by initial C-H activation of the corresponding nitrones **55** followed by cobalt-assisted cyclization (Scheme 19, **D**).[162] The use of excessive amounts of transition metals underscores the lack of sustainability of this method, making it only viable for laboratory-scale synthesis.



Scheme 20: Electrochemical synthesis of quinoline *N*-oxides **51** by cyclo-condensation.[26]

While establishing more sustainable synthetic routes to quinoline *N*-oxides, the application of electrochemical techniques supports overcoming certain challenges. The first electrochemical synthesis of quinoline *N*-oxides **51** was developed by *H. Lund* within polarographic studies regarding the synthesis of several N,O-heterocycles.[26] Under acidic conditions, the reduction of 2-nitrobenzylidene acetylacetones **57** using a dropping mercury electrode (DME) allowed for the direct synthesis of 2,3-disubtituted quinoline *N*-oxides **51** (Scheme 20, **A**). *A. Tallec* conducted comparable studies employing 2-nitrobenzoylacetylacetones, expanding the scope of this approach by the synthesis of various 4-hydroxyquinoline *N*-oxides.[166] However, both protocols involve a complex potential controlled set-up using toxic mercury as electrode material. Based on the electrochemical protocol for the synthesis of 2,1-benzisoxazoles, access to a range of quinoline *N*-oxides **51** in a simple current controlled, undivided set-up was granted by *Waldvogel et al.* (Scheme 20, **B**). The cinnamates required for this approach can be obtained in a single-step from widely available 2-nitrobenzaldehydes **30**. Previously employed toxic mercury electrodes could be substituted for carbon-based electrodes, which tremendously improved the sustainability of this synthetic strategy compared to the established methods.[105]

1.4.3 1*H*-1-Hydroxyquinazolin-4-ones & 1*H*-quinazolin-4-ones

Quinazolines and quinazolinones represent a common scaffold in highly biologically active compounds.[167] The motif occurs in potent drugs and natural products and is easily accessible by common synthetic routes.[168,169] Furthermore, various substitutions allow for the selective modification of the heterocyclic backbone towards the desired biological properties.[170,171]

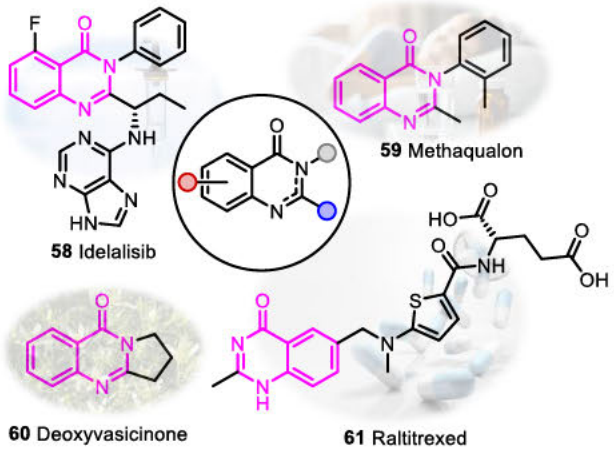
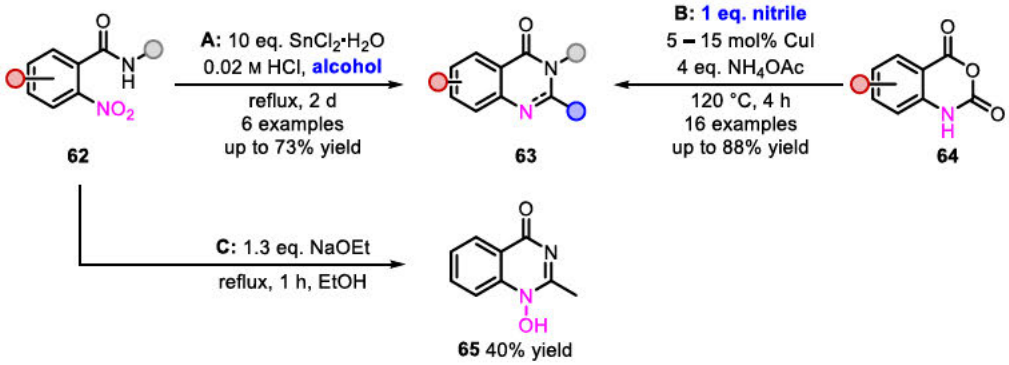


Figure 6: Potent chemotherapeutics, natural products and hypnotic drugs containing a quinazolin-3-one scaffold: *Idelalisib* (**58**), *Methaqualon* (**59**), *Deoxyvasicinone* (**60**) and *Raltitrexed* (**61**).

The treatment of cancer often requires cytostatic drugs non-specifically targeting rapidly dividing cells, which results in a number of unwanted side effects.[172] The selective inhibition of signal pathways in malicious cells prevents the unspecific cell death of non-cancer cells and consequently reduces the unwanted side effects.[173] *Idelalisib* (**58**, Figure 6) is a selective inhibitor of the phosphoinositide 3-kinase δ (PI3Kδ) which is hyperactivated only in cancer cells.[174,175] The targeted inhibition of this kinase solely in cancer cells reduces unfavorable side effects during chemotherapy.[176]

The established sedative-hypnotic drug *Methaqualon* (**59**, Figure 6) was initially developed as anti-malarial drug.[177] However, the high risk for drug abuse caused its withdrawal from the US market in 1985.[178] Today, *Methaqualone* (**59**) abuse is a widespread problem in several African countries.[179] The corresponding 1-oxide is accessible by oxidation with peracetic acid and represents one major metabolite of the drug in humans.[180,181] *Deoxyvasicinone* (**60**, Figure 6) and its derivatives are commonly found in the plant *Nitraria komarovii*.[182,183] These polycyclic alkaloids exhibit anti-inflammatory, antimicrobial and antidepressant properties. Furthermore, some derivatives of these pyrrolo[2,1-*b*]quinazoline alkaloids show high activity against certain types of cancer cells, and are therefore promising candidates for the development of novel anti-cancer agents.[184] Antifolates like *Raltitrexed* (**61**, Figure 6) interfere in the *de novo* biosynthesis of thymidine, a nucleoside required for the DNA synthesis in bacterial and mammalian cells.[185] They act as selective thymidylate synthase inhibitor and commonly used as a chemotherapeutic.[186,187]

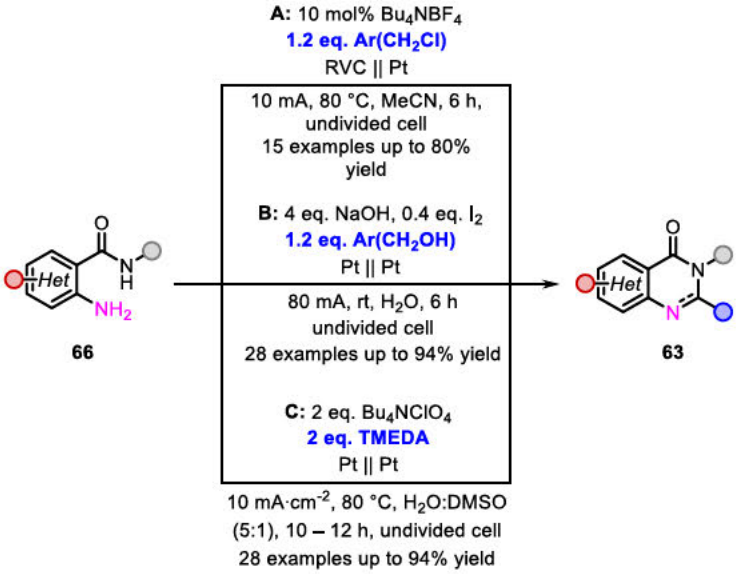
Despite some examples of 1-oxoquinazolin-3-one synthesis, little is known about 1-hydroxyquinazolin-3-ones **65**, highlighting the importance of their synthesis to make them common synthetic building blocks for modern pharmaceutical research.[188]



Scheme 21: Coventional synthesis of quinazolin-4-ones **63** and 1-hydroxyquinazolin-4-ones **65** by cyclization of 2-nitrobenzamides **62** and isatoic anhydride **64**.[188–192]

In general, a large number of synthetic protocols for the synthesis of quinazolin-4-ones **63** is described in literature.[189] The reduction of 2-nitrobenzamides **62** in an alcoholic solution of stannous chloride allows for a simple pathway towards several quinazolin-4-ones **63** without additional solvents (Scheme 21, **A**). The presence of air results in an in-situ oxidation of the employed alcohol, which subsequently undergoes cyclo-condensation with the 2-nitrobenzamide **62** after reduction by stannous chloride.[190] Comparable reactions are described using iron as reducing agent under acidic conditions.[157] Both protocols involve the use of excessive quantities of reductants generating tremendous amounts of waste. Furthermore, quinazolin-4-ones **63** can be obtained by direct condensation of 2-aminobenzamides with orthoesters .[193] Isatoic anhydrides **64** can serve as a platform compound for the synthesis of several heterocycles. The copper catalyzed ring-opening and condensation of isatoic anhydrides **64** results in the highly selective formation of quinazolin-4-ones **63** (Scheme 21, **B**).[192] Furthermore, a transition metal-free approach by simple one-pot condensation with an amine and aldehyde is reported.[194] However, isatoic anhydrides **64** are commonly produced using toxic phosgene.[195] Despite the variety of methods describing the synthesis of quinazolin-4-ones **63**, direct access to 1-hydroxyquinazolin-4-ones **65** remains underexplored. *Tennant et al.* described the direct synthesis of 1-hydroxyquinazolin-4-ones **65** under harsh and strongly alkaline conditions starting from *N*-substituted 2-nitrobenzamides **62** (Scheme 21, **C**). However, only a sole example is reported in poor yield .[188]

Besides the classical routes for obtaining quinazolin-4-ones **63**, several electrochemical approaches have been developed, most commonly starting from 2-aminobenzamides **62**.



Scheme 22: Electrochemical synthesis of quinazolin-3-ones **63** by cyclization of 2-aminobenzamides **66**.[196–198]

Chen et al. established a one-pot protocol using benzyl chlorides and substituted 2-aminobenzamides **66** to give various quinazolin-4-ones **63**. The key intermediate is a 2-(benzylamino)-*N*-methylbenzamide which undergoes benzylic oxidation and subsequent cyclization to form the product **63** (Scheme 22, **A**).[197] However, benzylchlorides exhibit lacrimating properties, which necessitates safety precautions while handling.[199] Therefore, a comparable approach was established employing benzylic alcohols instead. An iodide-catalyzed in-situ formation of the corresponding aldehydes yields product **63** after condensation with the amino group of the 2-aminobenzamides **66** (Scheme 22, **B**). The application of readily available benzyl alcohols and solely catalytic amounts of mediator ensures the applicability of this protocol. Furthermore, *Wang et al.* demonstrated the use of tetramethylethylenediamine (TMEDA) as a less toxic and easy to handle formaldehyde precursor. The in-situ generated formaldehyde can then be harnessed for the double condensation with the corresponding 2-aminobenzamides **66.** This allows for the simple and selective formation of 2-unsubstituted quinazolin-4-ones **63** without the need of handling carcinogenic formaldehyde (Scheme 22, **C**).[198]

In summary, several protocols have been developed for the synthesis of substituted quinazolin-4-ones **63**. However, these synthetic routes generally rely on large amounts of reagents and lack sustainability aspects.

1.4.4 Benzo[e]-1,2,4-thiadiazin-1,1-dioxides

Modern medicinal chemical research has gained an increasing interest in benzo[*e*]-1,2,4-thiadiazin 1,1-dioxides. This structural motif exhibits unique activities and is a promising candidate for the design of novel, highly potent drugs.[200,201,202] Regardless, the corresponding 4-hydroxy derivatives have yet not been reported in literature and are underexplored as possible scaffolds in medicinal chemistry.

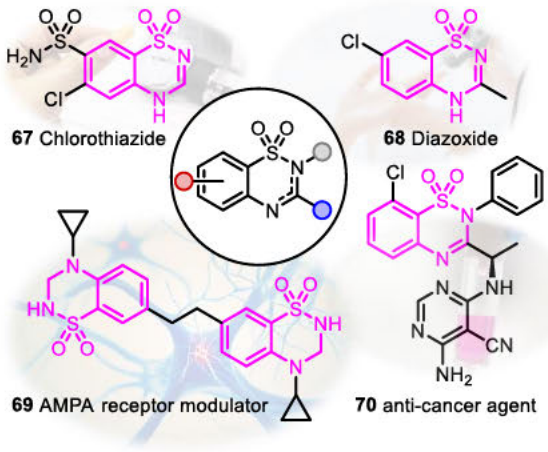
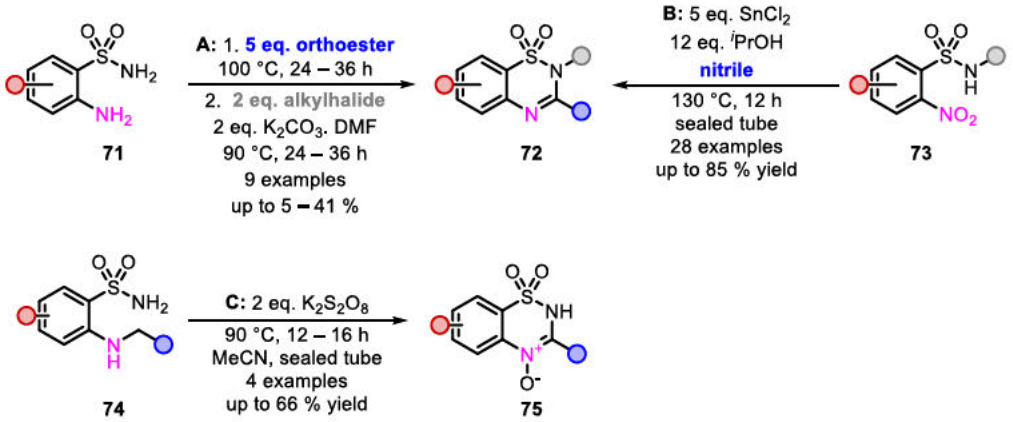


Figure 7: Biologically potent benzo[*e*]-1,2,4-thiadiazin-1,1-dioxides: *Chlorothiazide* (**67** anti-hypertensive), *Diazoxide* (**68** anti-diabetic), AMPA receptor modulator (**69**) and chemotherapeutic drug (**70**).[203]

Metabolic disorders like diabetes and several cardiovascular diseases are often a result of excessive sugar consumption related to unhealthy diets.[204] The sulfonyl urea derivative *Chlorothiazide* (**67**, Figure 7) causes selective inhibition of a sodium-chloride co-transporter in the kidney, resulting in an increased sodium chloride and water excretion.[205] As a result of the decreased sodium resorption, the blood pressure decreases, enabling an effective treatment of hypertension by *Chlorothiazide*.[206,207]

The mechanism of action of the related compound *Diazoxide* (**68**, Figure 7) differs from the one of *Chlorothiazide* by addressing β-cells in the pancreas.[208] As a result, the secretion of insulin is decreased.[209] Furthermore, it was observed that *Diazoxide* inhibits apoptosis of β-cells. By decreasing apoptosis of β-cells, the progression of diabetes in rats can be slowed down, making *Diazoxide* an important drug in the treatment of diabetes.[203] α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are a subgroup of glutamate receptors ubiquitously found in the central nervous system.[210] The regulation of these receptors plays a crucial role in addressing several psychological disorders like anxiety.[211] The experimental compound **69** (Figure 7) addresses both allosteric binding sites in the corresponding AMPA receptor selectively, hence showing high potency in modulating the activity of this receptor.[212] The common medicinal chemical technique of *scaffold hopping* targets further optimization of an activity by modulating the structure of the core motif.[213] This optimization is often carried out by variation of the heterocyclic core, called heterocyclic replacement.[214] This technique was employed to design the benzothiadiazine derivative **70** (Figure 7) and resulted in an increased potency against certain cancer cell lines.[215]

The numerous areas of applications of benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides **72** caused a demand for the development of simple and versatile synthetic routes towards these heterocycles.



Scheme 23: Conventional synthesis of benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides **72** and 4-oxo- benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides **75**.[216–218]

Easily accessible orthoesters can serve as both, solvent and reagent in the direct formation of 2-unsubstituted benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides **72** from 2-aminobenzenesulfonamides **71**. Further functionalization by subsequent nucleophilic substitution results in highly functionalized benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides **72** (Scheme 23, **A**).[216] However, rather poor yields of up to only 41% were achieved in total over two steps limiting the application potential of this protocol. A simple single-step protocol starting from readily available *N*-substituted 2-nitrosulfonamides **73** was presented by *Xia et al*. using stannous chloride as reductant (Scheme 23, **B**). Addition of alcohol to the reaction forms a reactive tin(IV) species, which promotes the condensation and deamination of the nitrile resulting in the desired benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides **72**. The major drawback of this method is the need for equimolar amount of reducing agents and consequently the generation of large amounts of waste.[217]

A single approach for the direct synthesis of 4-oxo-benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides **75** is reported by *Patel et al*. Therein, 2-benzylamino benzenesulfonamides **74** are converted using potassium persulfate as mild oxidant (Scheme 23, **C**). However, the proposed structure is lacking analytical evidence.[218]

Besides the conventional methods for preparing benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides **72** and their corresponding 4-oxo **75** species, no electrochemical synthetic protocols accessing these motifs are reported in literature. The conventional chemical approaches generate large amounts of waste by using stoichiometric quantities of reagents and are commonly performed under harsh reaction conditions. Thus, employing electro-organic strategies can contribute to the development of modern, efficient and more sustainable synthetic routes towards these underexplored heterocycles.

1.4.5 2*H*,4*H*-4-Hydroxybenz-1,4-oxazin-3-ones

Allelochemicals are a class of compounds isolated from terrestrial and aquatic plants.[219] Benzoxazinoids, for example, are cyclic hydroxamic acids released by plants as natural herbicides or pesticides.[220,221]

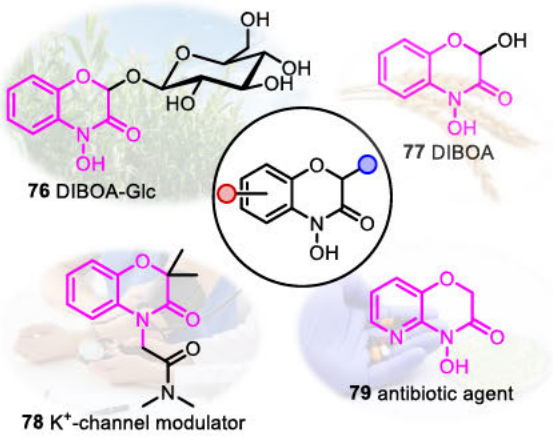
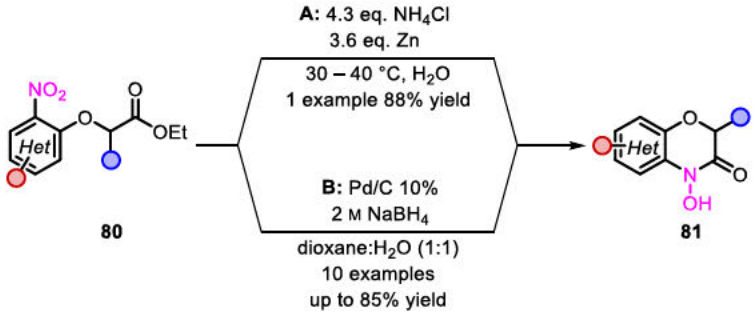


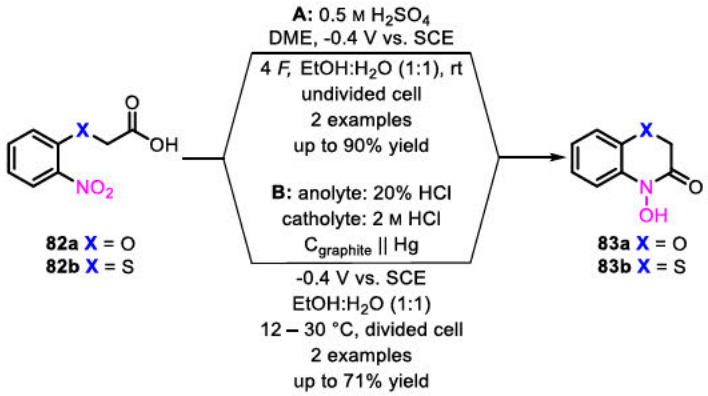
Figure 8: Benzoxazin-3-one derivatives exhibiting biological activity: DIBOA-Glc (**76**), DIBOA (**77**), K^+-channel modulator (**78**) and an experimental antibiotic (**79**).

Surprisingly, a variety of plants show resistance against triazine herbicides like *Atrazine*. This phenomenon and has been studied rigorously.[222] The benzoxazinoid 2-β-D-glucopyranosyloxy-4-hydroxy-1,4-benzoxazin-3-one (DIBOA-Glc, **76**, Figure 8) was observed to form a conjugate with herbicides, which might give an explanation for a main pathway of detoxification of plants.[223] Furthermore, upon an external attack, cleavage of the glucoside releases the corresponding 2*H*,4*H*-2,4-dihydroxy-1,4-benzoxazin-3-one (DIBOA, **77**, Figure 8) which shows activity against microbial and insecticidal pests.[224,225] In general, these compounds have been mostly extracted from natural sources. However, this method is considered rather laborious, since benzoxazinoids occur naturally in low concentrations.[226] Synthetic approaches have led to a variety of similar structures with appealing bioactive properties. Structure-activity studies led to benzoxazin-3-one **78** (Figure 8) which is capable of selectively addressing the corresponding cardiovascular potassium channels resulting in vasorelaxation.[227] Potassium channels play a crucial role in the function of different tissues like the smooth muscle or the cardiac muscle. Effecting these receptors can modulate their activity to address, e.g., cardiovascular diseases like hypertension. The potency of this potential drug can be further optimized to be used as an effective anti-hypertension drug. Studies on several bacteria and fungi confirmed antibiotic and antifungal properties of pyridoxazinones (**79**, Figure 8). Moreover, it was shown that the pyridine motif was the pharmacophoric scaffold increasing the activity against the tested strains. The pharmacological properties of these compounds boost an interest for the development of novel synthetic antibiotics.[228]



Scheme 24: Conventional synthesis of 2*H*,4*H*-4-hydroxy-1,4-benzoxazin-3-ones **81**.[228–230]

The demand of highly diverse 4-hydroxy-1,4-benzoxazin-3-ones **81** in modern research underlines the importance for multiple synthetic routes to access this family of compounds. Most commonly, these motifs are obtained by reduction of 2-nitrophenoxyacetic acid esters **80**. A versatile and simple protocol involves the reduction of the latter using zinc under slightly acidic conditions (Scheme 24, **A**).[229] However, besides the use of equimolar quantities of reducing agents, the free hydroxamic acid **81** has to be liberated from the zinc salt formed during this reaction. The milder reduction using palladium on carbon as catalyst and sodium borohydride as reductant allowed for the synthesis of various 4-hydroxy-1,4-benzoxazin-3-ones **81** (Scheme 24, **B**). Despite the mild reaction conditions, a major drawback can be found in the requirement of expensive noble metal catalysts.[228]



Scheme 25: Electrochemical synthesis of 2*H*,4*H*-4-hydroxy-1,4-benzoxazin-3-ones **83** (X=O) and 2*H*,4*H*-4-hydroxy-1,4-benzthiadiazin-3-ones **83** (X=S).

The first electrochemical synthesis of benzoxazin-3-ones **83a** and benzthiadiazin-3-ones **83b** was demonstrated by *Tallec et al.* in 1971. Easily accessible 2-nitrophenoxyacetic acids **82a** and 2-(nitrophenyl)thioacetic acids **82b** were employed as substrates using sulfuric acid as supporting electrolyte in a potential-controlled electrolysis. Toxic mercury electrodes were used to obtain the benzoxazin-3-ones **83a** and benzthiadiazin-3-ones **83b** in up to 90% yield (Scheme 25, **A**).[231,232] *Maschmeier et al.* investigated the mechanism of this synthesis further using a divided set-up using mercury electrodes. Instead of sulfuric acid as supporting electrolyte, diluted hydrochloric acid was used. The application of concentrated hydrochloric acid resulted in the formation of the chloro-substituted deoxygenated benzoxazin-3-ones **83a** and benzthiadiazin-3-ones **83b** which indicates a *Bamberger*-rearrangement under acidic conditions.[233]

2 Objectives

Heterocycles with endocyclic or exocyclic N,O-bonds represent important structural motifs in research and for the development of modern, novel pharmaceuticals or agrochemicals. The synthesis of these compounds commonly requires the use of equimolar amounts of redox-active reagents, toxic chemicals or complex multi-step routes with a consequently low atom economy.

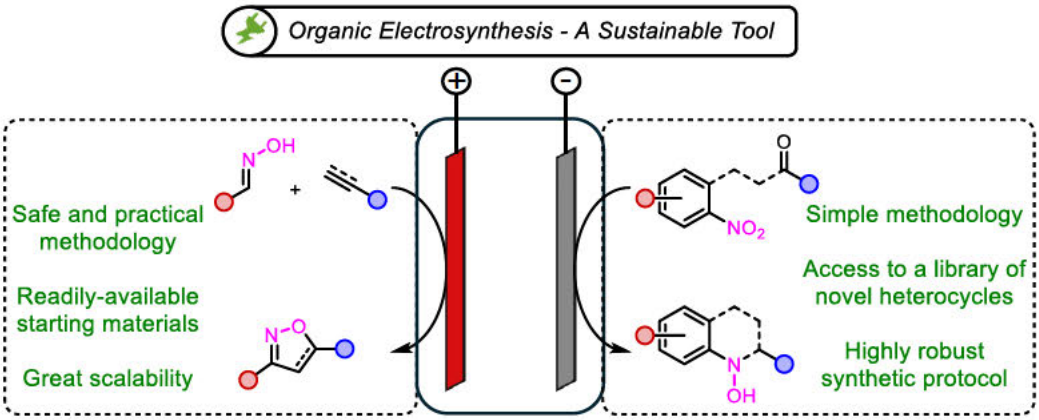


Figure 9: Electrochemistry allowing for the direct access of novel heterocycles bearing an endo- or exocyclic N,O-bond.

The aim of the presented work is to develop innovative, electrochemical routes for the sustainable synthesis of heterocycles containing an endo- or exocyclic N,O-bond. Electrosynthesis serves as the key technique, employing electric current as an inherently safe surrogate for harmful redox-active reagents. The direct electrochemical reduction of nitro arenes constitutes a highly adaptable and robust tool for obtaining various, to the best of our knowledge unreported heterocycles bearing an exocyclic N,O-bond. Aiming for the development of a versatile and sustainable methodology, the applicability of this protocol should be demonstrated in the synthesis of a wide range of highly functionalized heterocycles with a N,O-moiety. This should be underlined by replacing toxic metal electrodes used in most reported with carbon-based electrode materials such as BDD or glassy carbon. The construction of endocyclic N,O-bonds was envisioned via an intermolecular approach. Access to isoxazole(in)es should be granted through an electrochemically initiated (3+2) cycloaddition, starting from readily available aldoximes. Thus, the application of hazardous oxidizing agents could be avoided resulting in a more efficient, sustainable and synthetic method. In order to show the technical relevance of the established methodologies, appropriate scale-up to up to larger scales should be demonstrated. Hence, a synthetic toolbox should be established granting access to a variety of important N,O-heterocycles, from screening to preparative scale.

3 Results and Discussion

3.1 Electrochemically Initiated 1,3-Dipolar Cycloaddition for the Synthesis of Isoxazol(in)es

3.1.1 1,3-Dipolar Cycloaddition Initiated by Direct Anodic Oxidation of Aldoximes

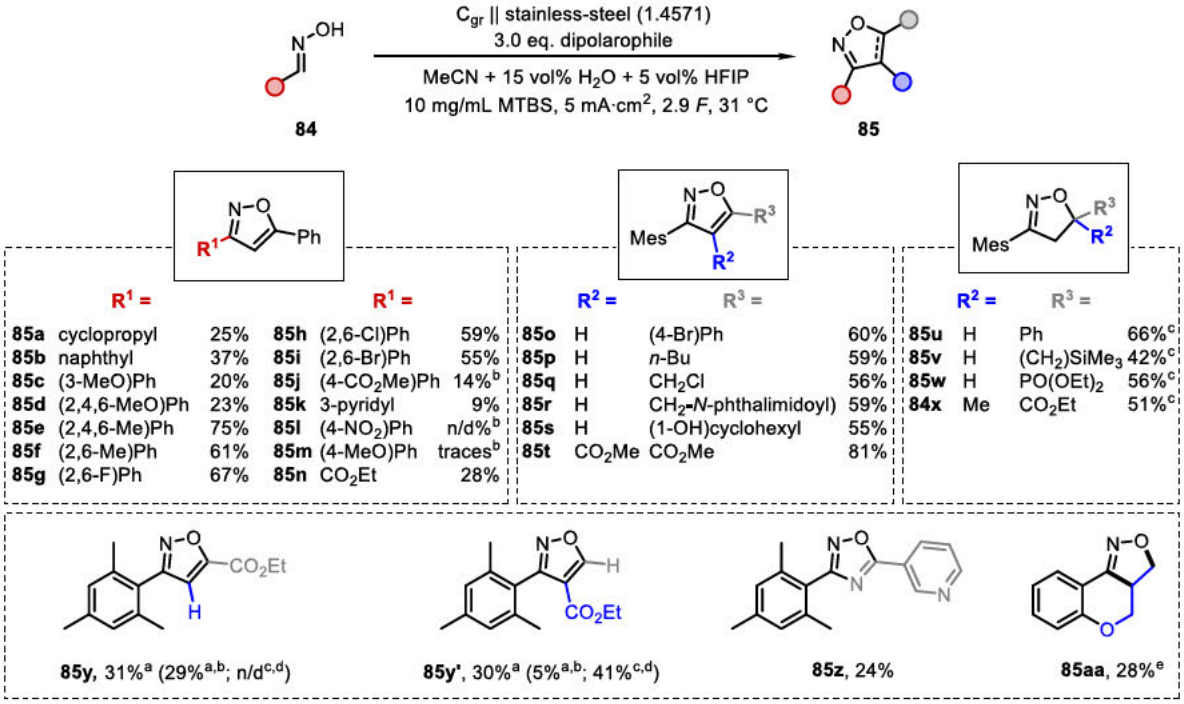
A manuscript was published on this chapter:

[redacted] *Electrochemical Synthesis of Isoxazoles and Isoxazolines via Anodic Oxidation of Oximes*, *ChemElectroChem* 2023, *10*, e202300434.

[redacted]

Isoxazolines and isoxazoles are widely found in herbicides, pharmaceuticals and functional materials.[112,118] Consequently, access to these compounds is of high interest in the field of modern organic chemistry. The conventional synthesis often involves a two-step process involving the conversion of easily accessible aldoximes to nitrile oxides and subsequent reaction with alkenes or alkynes to form the desired isoxazol(in)es. However, this approach uses equimolar amounts of hazardous reagents and often harsh reaction conditions.[121–132] Thus, a direct anodic oxidation of aldoximes followed by subsequent 1,3-dipolar cycloaddition was targeted based on previous reported results. *Shono et al.* demonstrated the halide-mediated synthesis of nitriles starting from aldoximes by anodic oxidation under constant current conditions. To proof the hypothesized formation of nitrile oxides as intermediates, styrene was added to the electrolysis as a trapping agent to obtain two isoxazolines in poor to moderate yields. Recently, *Reid et al*. utilized this approach and established a protocol for the chloride-mediated synthesis of isoxazolines. *Waldvogel et al.* developed a halide-free domino reaction sequence for the synthesis of nitriles starting from aldoximes.[133,138] Based on these results, an approach for the selective and synthesis of isoxazoles and isoxazolines via direct, anodic oxidation of aldoximes was envisioned.

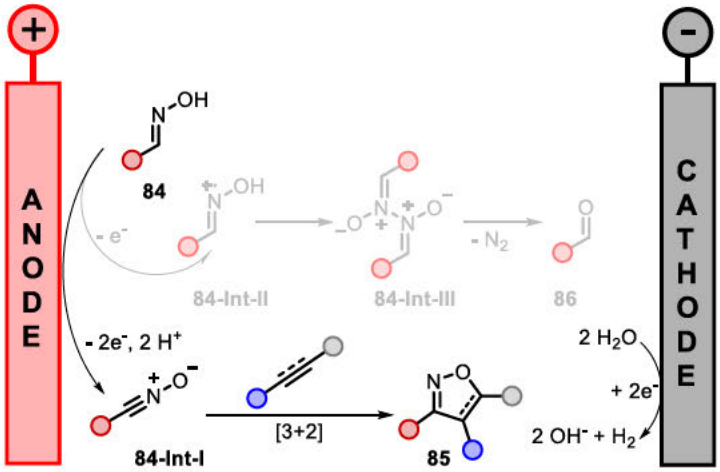
For the optimization of the electrolytic conditions, mesitylaldoxime (**83e**) was chosen as test substrate. The initial experiments were performed in a simple undivided set-up using a graphite anode and a stainless-steel cathode. Methyltributylammonium methylsulfate (MTBS) was chosen as supporting electrolyte dissolved in acetonitrile and 10 vol% water. Temperature, water content, substrate concentration, the amount of the dipolarophile, current density and amount of applied charge were subject to the optimization by *design of experiments* (DoE). Subsequently, the solvent system was further improved with regards to product yield by adding 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and increasing the water content, leading to a mixture of acetonitrile with 15 vol% water and 5 vol% HFIP. Starting from mesitylaldoxime (**84e**), 3-mesityl-5-phenylisoxazole (**85e**) was isolated in 75% yield. Subsequently, the scope of isoxazoles and isoxazolines was investigated applying the optimized reaction conditions (Scheme 26).



Scheme 26: Scope of the electrochemical synthesis of isoxazol(in)es by anodic oxidation and subsequent cycloaddition; Mes = 2,4,6-Trimethylphenyl; [a]regioisomers; [b]MeCN+15 vol% HFIP as solvent; [c]dipolarophile added post-electrolysis; [d]dipolarophile: ethyl (*E*)-3-(piperidin-1-yl)acrylate; [e] intramolecular cycloaddition, without phenylacetylene.

Initially, application of different benzaldoximes **84** was investigated using phenylacetylene as dipolarophile. Generally, 2,6-disubstituted aryl aldoximes **84f–g** were converted to the desired products in good yields up to 67%. This emphasized the impact of steric stabilization of the intermediary formed nitrile oxide. Thus, the conversion of 4-substituted aldoximes **84j, 84l** and **84m** was challenging. After adapting the solvent to a mixture of acetonitrile + 15 vol% HFIP, only **85j** could be obtained in 14% yield. The products of the corresponding 4-methoxy and 4-nitro derivatives were only obtained in traces or not at all, respectively, showing a limitation for 4-substituted aryl aldoximes. Contrarily, a great tolerance for functional groups was observed by variation of the alkynes. Especially, electron-deficient dipolarophiles were converted to the corresponding isoxazole **85o–t** in up to 81% yield.

Different olefines were converted in an ex-cell approach by adding the dipolarophile after electrolysis to prevent sensitive alkenes from undergoing side reactions. The success of this ex-cell variation was proven by obtaining even the phosphonic acid ester **85w** in 59% isolated yield. The use of propiolic acid esters resulted in the formation of the two regio-isomers **85y** and **85y'**. However, regio-selective formation of **85y'** in 41% yield was achieved by using ethyl (*E*)-3-(piperidin-1-yl)acrylate as dipolarophile. As a proof of concept, the applicability of nitriles as dipolarophiles was investigated in one example, enabling access to 1,2,4-oxadiazole **85z** 24% yield. Additionally, the scalability of the protocol was demonstrated in up to multi-gram scale, allowing for preparation of **85e** in 67% yield (3.53 g, 13.4 mmol). Furthermore, the solvent was recycled by a simple distillation and reused up to three times while maintaining a constant yield of 73–77% on a preparative 5 mmol-scale. Due to the potential negative impact of fluorinated chemicals on the environment, efficient recyclability thereof underlines the sustainability of the developed method.[81]



Scheme 27: Proposed mechanism of the direct electrochemical synthesis of isoxazoles by anodic oxidation of aldoximes.

The mechanism of the reaction was investigated via cyclic voltammetry (Scheme 27). Additionally, a mechanism was proposed based on previous reports by *Waldvogel et al.*.[138] The key intermediate is the nitrile oxide **84-Int-I** which is formed by a two electron oxidation of the aldoxime. Subsequent (3+2) cycloaddition of **84-Int-I** with the corresponding dipolarophile results in the formation of isoxazol(in)e **85**. Hydrogen evolution serves as cathodic counter reaction. The formation of a aldehyde **86** was described in literature and could be observed by GC-MS analysis as a side reaction.[138]

In summary the electrochemical synthesis of various isoxazol(in)es was achieved in a simple undivided set-up while using inexpensive and widely available electrode materials. Furthermore, the reaction's application potential was proven by a diverse scope as well as a 40-fold scale up in up to multi-gram scale. The recyclability of the solvent underlines the sustainability of the method.[234]

Special Collection

Electrochemical Synthesis of Isoxazoles and Isoxazolines via Anodic Oxidation of Oximes

Silja Hofmann,[a] Johannes Winter,[a] Tobias Prenzel,[a] María de Jesús Gálvez-Vázquez,[a] and Siegfried R. Waldvogel*[a, b]

Isoxazol(in)es are widely featured structural motifs in natural products, agrochemicals, and pharmaceuticals. The first intermolecular approach for a direct electrochemical synthesis from readily available aldoximes is reported. Isoxazoles and isoxazolines were obtained in yields up to 81%. The synthesis is carried out in an undivided cell as the simplest electrochemical set-up and requires only the use of electric current as traceless oxidizing agent. The application of inexpensive and widely available electrode materials in combination with recyclable supporting electrolytes and solvents paves the path for translation of the presented reaction onto preparative scale. This is underlined by successful scale-up to multi-gram runs.

Introduction

Five-membered heterocycles, especially isoxazoles and isoxazolines, are widely found in natural products and among important structural motifs in medicinal chemistry and agrochemistry (Figure 1). Ibotenic acid (**1**), for example, naturally occurring in *Amanita muscaria* (fly agaric), is a prodrug of psychoactive muscimol. The orthosteric agonist for $GABA_A$ receptors exhibits hallucinogenic and sedative-hypnotive psychoactivity.[1] Moreover, a variety of non-steroidal anti-inflammatory drugs,[2] antibiotics (e.g. cloxacillin, **2**),[3] as well as some promising candidates for immuno- and chemo-therapeutics feature isoxazol(in)es.[4] In the field of agrochemicals, isoxazoles and isoxazolines find frequently application as herbicides (fenoxasulfone, **3**),[5] fungicides (hymexazol, **4**),[6] and insecticides (fluxametamid, **5**).[7]

Conventionally, isoxazoles and isoxazolines can be accessed via intramolecular oxidative cyclization of allyl aldehyde oximes,[8] propargyl hydroxylamines[9] or propargyl aldehyde oximes.[10] In general, these methods require terminal oxidizers and eventually transition metal catalysts. Furthermore, commonly used methods start from easily accessible benzaldehyde oximes. Conversion to the desired isoxazol(in)es requires initial oxidation to their respective nitrile oxides and subsequent 1,3-dipolar cycloaddition with alkenes or alkynes. Therefore, hazardous and strong oxidizers such as *m*-CPBA in combination with iodobenzene,[11] hypervalent iodine reagents[12] or organo nitrites[13] need to be employed. Another route involves formation of *N*-hydroximidoyl halides which undergo base-promoted formation of nitrile oxides. These strategies require the use of hazardous halogenation reagents[14] and sometimes even additional use of transition metal catalysts,[15] resulting in significant amounts of reagent waste.

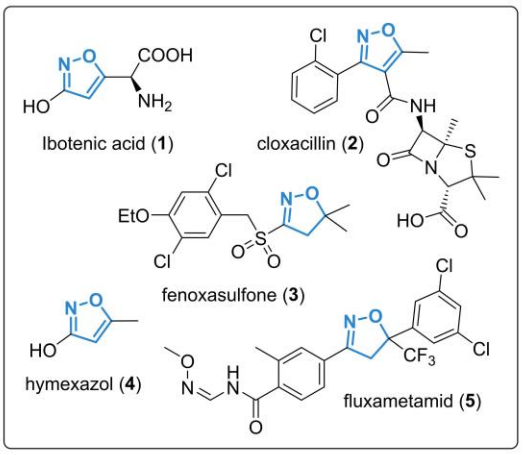


Figure 1. Important examples of isoxazoles and isoxazolines in natural products, pharmaceuticals, and agrochemicals.

As a greater awareness for sustainability of chemical processes is generated, modern chemical transformations aim for greener approaches. Electrochemistry fulfils many principles of green chemistry.[16] Hazardous redox reagents can be substituted with electric current and in combination with recyclable solvents and supporting electrolytes the generation of waste can be strongly diminished.[17] For translation of a synthetic protocol to a larger scale, the downstream processing must be considered, which is often costlier than the electrosynthetic step.[18] Moreover, electrochemical approaches in-

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An invited contribution to the Flavio Maran Festschrift.

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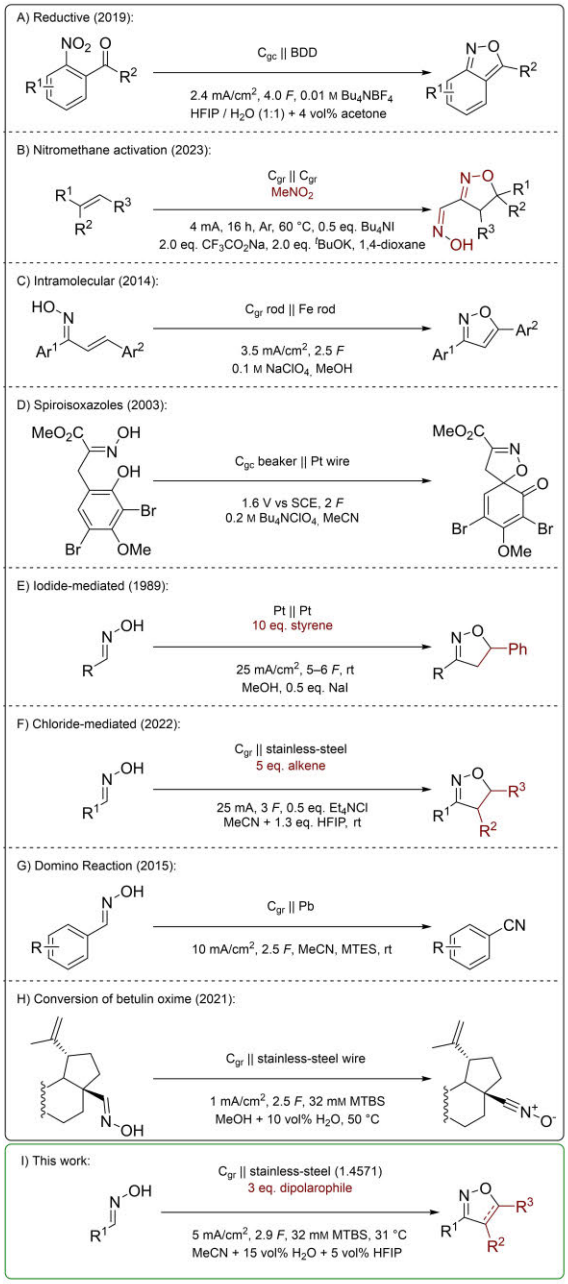
crease the safety of processes, as the constraint of the initial electron transfer to the electrode surface allows for precise reaction control.[19]

The synthesis of isoxazoles and isoxazolines as well as the generation of nitrile oxides has caught the interest of the electrochemical community for decades. Four examples granting access to isoxazole(in)es via intramolecular approaches are reported in literature. Synthesis of 2,1-benzoxazoles was enabled by reductive cyclization of *o*-nitrobenzaldehydes or -acetophenones (Scheme 1, A).[20] Noteworthy, such reductive conversions can be accompanied by cathodic corrosion making other approaches highly desired.[21] Recently, an electrochemical approach for the synthesis of isoxazoline aldoximes via nitromethane activation was established (Scheme 1, B).[22] Anodic oxidation of α,β-unsaturated oximes led to intramolecular cyclization, leading to 3,5-substituted isoxazoles (Scheme 1, C).[23] Furthermore, oxidation of phenols via constant potential electrolysis allowed for synthesis of spiroisoxazoles (Scheme 1, D).[24] Back in 1989, the first iodide-mediated synthesis of nitriles from aldoximes was reported (Scheme 1, E).[25] To prove the formation of nitrile oxides as intermediates, styrene was added as a trapping agent, yielding the corresponding isoxazoline. About 30 years later, a deeper mechanistic study of chloride-mediated aldoxime oxidation and subsequent isoxazoline formation was provided and a broad scope was presented (Scheme 1, F).[26] Furthermore, halide-free synthetic access to nitriles from aldoximes was achieved via a domino oxidation-reduction reaction (Scheme 1, G).[27] Thereby, anodic oxidation led to formation of nitrile oxides as intermediates, which were subsequently reduced to the corresponding nitrile at the counter-electrode. Recently, even highly lipophilic betulin oxime was successfully oxidized at a graphite anode in a quasi-divided set-up, resulting in the formation of stable nitrile oxides, while hydrogen evolution occurred at the cathode (Scheme 1, H).[28]

We developed an approach for the synthesis of isoxazoles and isoxazolines via direct anodic oxidation of aldoximes (Scheme 1, I). A simple undivided galvanostatic set-up with inexpensive graphite and stainless-steel electrodes was used. Using a solvent system of acetonitrile/water with HFIP as additive enabled the synthesis of isoxazol(in)es in moderate to very good yields. Moreover, the scalability of the reaction was demonstrated by multi-gram scale electrolysis. The recovery and reuse of electrolyte components supports the green nature of the approach.



Scheme 1. Electrochemical approaches for conversion of aldoximes to isoxazol(in)es.

Results and Discussion

Initially, the reaction was investigated in an undivided cell using 2,4,6-trimethylbenzaldehyde oxime (**6a**) as test substrate and phenylacetylene as dipolarophile. As the use of graphite anodes for successful oxidation of oximes has been thoroughly studied, graphite was chosen as anode and no further investigation was performed.[23,27–30] Based on previous results, acetonitrile and water with methyltributylammonium methylsulfate (MTBS) were chosen as supporting electrolyte.[27,29–30] First, different cathode materials suitable for hydrogen evolution as the desired counter reaction were screened (Table 1), since the counter electrode can have a significant impact on the overall performance of the electrolysis.[31]

Amongst the tested cathode materials, the metals proved superior to carbon-based cathodes. The latter allowed for synthesis of isoxazole **7a** in yields of 42–49%. Within the tested metals, nickel gave the lowest isoxazole **7a** yield of 56%, whereas platinum and stainless-steel provided comparable product yields of 60% and 59%, respectively. Thus, further reaction optimization was carried out using inexpensive and widely available stainless-steel as cathode.

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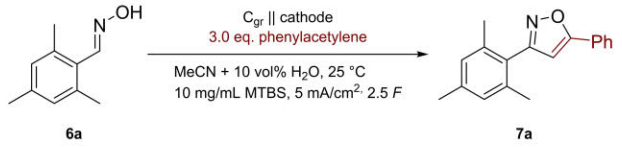
Table 1. Screening for different cathode materials.



6a 7a

Cathode	NMR yield[a]
Stainless-steel (1.4571)	59%
Platinum	60%
Nickel	56%
Graphite (C_{gr})	49%
Glassy carbon (C_{gc})	42%
Boron-doped diamond (BDD)	46%

Reaction was carried out using a 5 mL screening cell and 0.5 mmol oxime. [a] Quantification using ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

Reaction Optimization

A detailed evaluation and optimization of the targeted reaction was carried out using Design of Experiments (DoE).[32] Besides the electrochemical parameters such as current density (*j*) and amount of applied charge (*Q*), concentration of the starting material, equivalents of dipolarophile, amount of water as additive and reaction temperature were investigated. For investigation of those 6 parameters, a fractional factorial design was chosen (2^{6-2}, resolution IV with central point and rotatable axis points, each data point acquired twice). The observation of curvature within the main effects plot necessitated expansion to a response surface design (For detailed information see ESI, Table S2, Figure S1–2). Target optimization with regards to maximization of the isoxazole yield led to the following optimum reaction conditions: 5 mA/cm^2 as current density, an amount of applied charge of 2.9 *F*, 3 eq. of dipolarophile, 31 °C, 10 vol% water as additive in MeCN, and an optimum amount of aldoxime of 0.5 mmol.

Unfortunately, for the latter two parameters no clear optima were obtained. Thus, subsequent linear optimization (one variable at a time, OVAT) for the amount of water as additive as well as the starting material concentration was carried out. Decreasing the concentration of **6a** did not improve the yield of **7a**. However, the reaction proved stable in the range of 0.45 mmol–0.5 mmol starting material yielding 57% of isoxazole **7a**. Thus, a substrate concentration of 0.1 M (0.5 mmol) was chosen for further optimization.

Furthermore, the reaction time with regards to post-electrolysis stirring was investigated. Although generation of the 1,3-dipole is determined by the electrolysis time, the slower cycloaddition reaction might occur during the post-electrolysis stirring. For initial reaction optimization, a total reaction time of 24 h (19 h post-electrolysis stirring) was chosen in order to compensate for any potential effects of post-electrolysis stirring. This yielded isoxazole **7a** in 63% yield. Indeed, directly after the electrolysis isoxazole **7a** was obtained in only 45% yield, which gradually increased over time and the maximum of 63% was finally reached after 4 h of post-electrolysis stirring.

Last, the solvent system was investigated. First, the amount of water as an additive in acetonitrile was increased as indicated by the DoE results. The optimum was reached at 15 vol% water in MeCN, yielding 66% isolated yield of **7a**. Further increase to 20 vol% or 25 vol% water resulted in a drop in yield to 60%. As the anodic oxidation of aldoximes to nitrile oxides occurs overall via a two-electron transfer, the process could potentially benefit from a (radical) stabilizing additive. 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) is a well-known solvent and additive due to its unique physical and chemical properties and outstanding ability of engaging organic transformations.[33,34] HFIP exhibits high polarity,[35] a strong hydrogen-bond donor ability[36] and extraordinary (electro−)chemical stability.[37] Not only, but especially in electro-organic synthesis, HFIP is known for its potency of stabilizing ionic and radical intermediates and has proven to boost selectivity as well as yield for numerous reactions.[26,33,38] Indeed, addition of only 5 vol% HFIP to the solvent system of MeCN + 15 vol% H_2O led to an increase in yield, enabling access to product **7a** in a good isolated yield of 75%. Next, the scope of the reaction was investigated applying the following optimized conditions: graphite anode, stainless steel cathode, 0.1 M oxime, 10 mg/mL MTBS in MeCN + 15 vol% H_2O + 5 vol% HFIP, 5 mA/cm^2, 2.9 *F*, 3 eq. of dipolarophile, 31 °C (Scheme 2).

Scope and Limitations

First, the applicability of different dipolarophiles with 2,4,6-trimethylbenzaldehyde oxime (**7a**) as substrate was evaluated. 4-Bromophenylacetylene and 1-hexyne enabled access to products **7b** and **7c** in comparable yields of 60% and 59%, respectively. Interestingly, conversion of 1-hexyne allowed for a regioselective reaction. In contrast, ethyl propiolate gave a 1.03:1 mixture of the 3,5-disubstituted product **7d** (31%) and 3,4-disubstituted **7d'** (30%). Switching the solvent system to solely MeCN + 15 vol% HFIP allowed for an enhanced regioselective ratio of 5.8:1 (**7d**:**7d'**), yielding 29% of **7d** and only 5% of **7d'**. However, the combined yield of both isomers decreased from 61% to 34%. Nonetheless, a regioselective reaction yielding solely the 3,4-substituted derivative **7d'** (41%) was achieved when ethyl (*E*)-3-(piperidin-1-yl)acrylate was employed as dipolarophile. Thus, application of such acrylates could offer a general strategy for achieving a reversed regioselectivity within this electrochemical approach. To our delight, electron poor dimethyl acetylendicarboxylate yielded 3,4,5-trisubstituted product **7e** in a very good yield of 81%. Generally, a good functional group tolerance was observed at the propargylic position and yields of up to 59% were obtained for derivatives **7j**–**7m**. Noteworthy, even phthalimide-substituted **7l** (59%) and chloro-substituted derivate **7m** (56%) were obtained. Furthermore, 3-cyano-pyridine was successfully employed as dipolarophile, enabling access to oxadiazole **7k** in 24% yield. Moreover, the synthesis of various isoxazolines was achieved by application of different alkenes. To prevent sensitive alkenes

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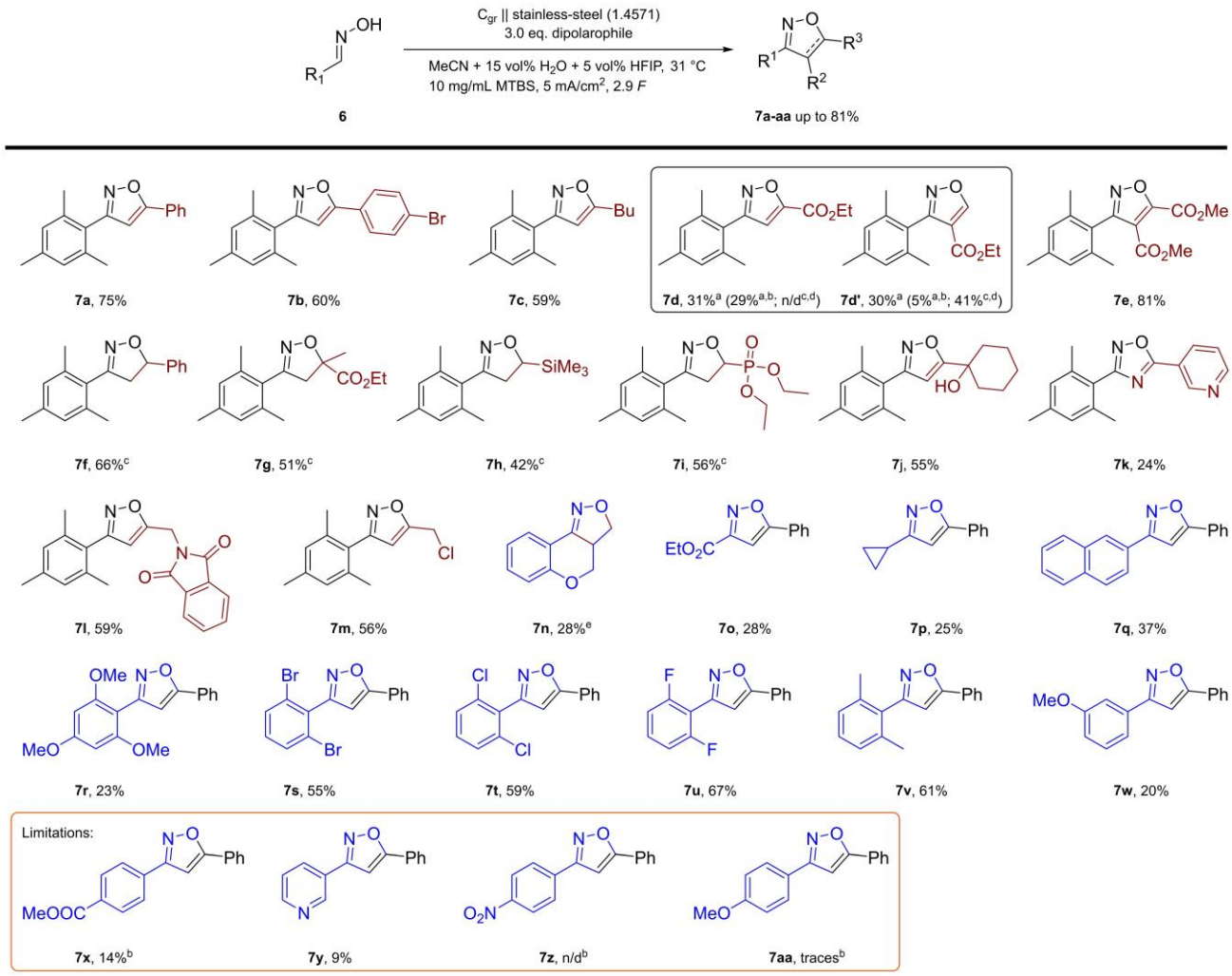

Scheme 2. Scope of isoxazoles and isoxazolines. 0.5 mmol scale, 4 h post-electrolysis stirring, isolated yields. [a] regioisomers. [b] MeCN + 15 vol% HFIP as solvent. [c] dipolarophile added after the electrolysis. [d] ethyl (*E*)-3-(piperidin-1-yl)acrylate as dipolarophile. [e] w/o phenylacetylene, intramolecular cyclization.

like styrene from undergoing side reactions, e.g. polymerizations, an ex-cell approach was established. Thus, the respective alkene was added after the electrolysis and the reaction mixture was stirred for 4 h. Derivatives **7f–l** were obtained in fair yields of up to 66%. Besides dipolarophiles like styrene (**7f**, 66%) and ethyl methacrylate (**7g**, 51%), even trimethyl vinylsilane (**7h**, 42%) and diethyl vinylphosphonate (**7i**, 56%) were successfully converted to the corresponding isoxazolines. Application of different oximes in the reaction proved that steric protection of the intermediary formed nitrile oxide is beneficial. Naphthyl- and ester-substituted derivatives **7q** and **7o** were obtained in moderate yields of 37% and 28%. Furthermore, conversion of cyclopropyl carbaldehyde oxime gave access to the corresponding isoxazole **7p** in a comparable yield of 25%. Thereby, no byproducts indicating ring-opening reactions of the cyclopropyl-ring were detected. Attempted synthesis of isoxazole **7y** from rather electron-deficient pyridine-3-carbaldehyde oxime resulted in a poor yield of 9%.

2,6-Disubstituted benzaldoximes were converted successfully due to steric protection of the intermediates (**7s–7v**, up to 67%). Within the halogen-substituted isoxazoles **7s–7u**, a trend of decrease in yield with decreasing electronegativity for higher homologues was observed (Br (55%) < Cl 59%) < F (67%)). An exception was found for conversion of electron-rich 2,4,6-trimethoxybenzaldoxim, yielding the corresponding isoxazole **7r** in a rather poor yield of 23%. Thus, successful conversion is most likely not only related to sufficient steric protection of the intermediary formed nitrile oxide, but also a matter of reactivity and electronic stabilization of any formed radical and ionic intermediates. Generally, synthesis of isoxazoles bearing electron-rich arenes in 2-position was restricted to *ortho*- and *meta*-substituted benzaldoximes in mediocre yields. Intramolecular cyclization of salicylaldehyde-derived oxime enabled synthesis of isoxazoline **7n** in 28% yield and *meta*-methoxy benzaldoxime yielded 20% of the corresponding isoxazole **7w**. However, after application of *para*-methoxybenzaldoxime only traces of the desired product **7aa** as well as the corresponding benzaldehyde were detected by GC-MS analysis (see Figure S6–S7, supporting information). Generally, application of *para*-substituted benzaldoximes in the reaction proved challenging.

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Para-nitro derivative **7z** could not be obtained, most likely due to the electrochemical sensitivity of the nitro-group tending to undergo electrochemical reduction.[39] Only *para*-(methoxycarbonyl) benz-aldoxime derived isoxazole **7x** was successfully isolated in a poor yield of 14%. However, a change of the solvent system to water-free MeCN + 15 vol% HFIP was required, as otherwise no product was obtained. Thus, the reaction was investigated using cyclic voltammetry (CV, Figure 2). No distinct oxidative peak could be observed for *para*-(methoxycarbonyl)benzaldoxime (**6x**) in the initially used aqueous solvent system.

However, the incipient oxidation is overlapping with the oxidative wave for the electrolyte. On the contrary, a clear oxidative peak for substrate **6x** was observed in the MeCN/HFIP-based solvent system, supporting the experimental findings. Furthermore, CV studies of test substrate **6a** in aqueous MeCN with and without HFIP as additive did not show any significant differences. Hence, these findings support the assumption that HFIP does not directly engage in the oxidation, but functions as a stabilizing agent for occurring intermediates. Therefore, application of HFIP as additive allows for higher yields of the target products due to protection of intermediates and thus promotes the desired subsequent cycloaddition reaction.

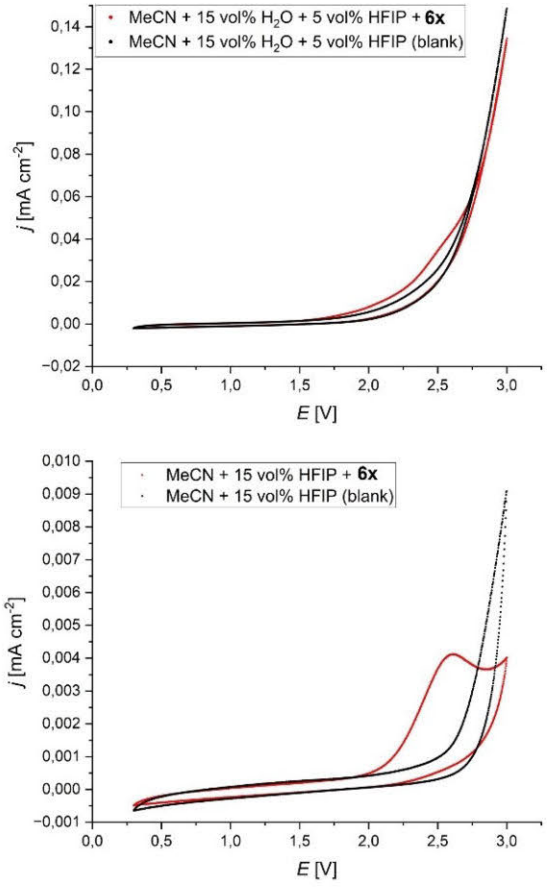
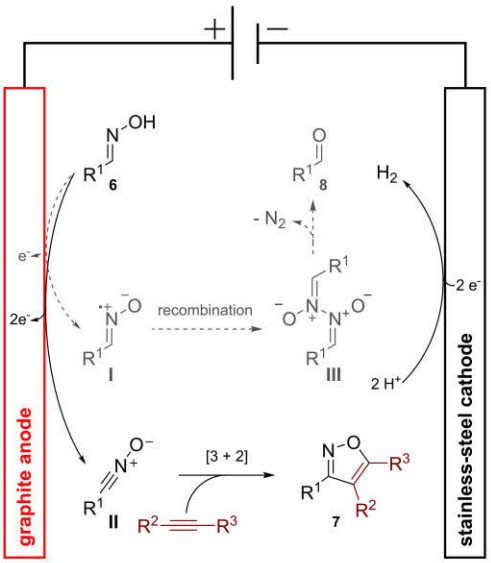


Figure 2. Cyclic voltammograms of *para*-(methoxycarbonyl)benzaldoxime (**6x**) in organic-aqueous (top) and organic (bottom) solvent systems. Working electrode: glassy carbon, counter electrode: Pt, reference electrode: Ag/AgCl in sat. LiCl/EtOH. Scan rate: 100 mV/s. Supporting electrolyte: 0.5 M MTBS; c(**6x**) = 5.0 mM.

Mechanistic Considerations

In accordance with literature and our experimental results, we propose anodic oxidation of the aldoximes followed by a conventional [3 + 2] dipolar cycloaddition (Scheme 3). Anodic oxidation of oxime **6** via two-electron transfer results in formation of nitrile oxide **II**. Coinciding with cathodic hydrogen evolution base is generated, which might engage in the deprotonation occurring in this step. Nitrile oxide **II** undergoes subsequent cycloaddition reaction with the added dipolarophile, resulting in formation of the desired isoxazole **7**. For 2,6-disubstituted aryl aldoximes, the corresponding nitrile oxide is sterically protected. Thus, the nitrile oxide of test substrate **6a** was detected by GC-MS (see Figure S8–S9, supporting information), supporting the hypothesis of isoxazole synthesis via conventional [3 + 2] cycloaddition. Formation of corresponding benzaldehydes as byproducts can be explained via initial one-electron oxidation of the aldoxime. According to literature, formation of iminoxyl-radicals (**I**) occurs which rapidly undergo recombination to intermediate (**III**).[27,40] Elimination of nitrogen finally yields the corresponding aldehyde **8**.

The nitrile oxides of *para*-substituted benzaldehyde oximes could not be observed by any analytical method. This could simply be a result of their lack of steric protection resulting in greater reactivity. However, DFT calculations and experimental findings indicate a radical mechanism for a chloride-mediated intermolecular electrochemical synthesis of isoxazolines according to literature.[25] Thus, in case of sterically non-protected aldoximes a radical reaction pathway might need to be considered alternatively to the conventional [3 + 2] cycloaddition as well. As no nitrile formation was observed in any case,



Scheme 3. Proposed reaction mechanism for formation of isoxazoles (black, plain) and aldehydes as potential byproducts (grey, dashed).

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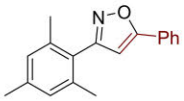
Table 2. Scale-up of the synthesis of **7a**.

Product				
 7a	75%[a] 0.33 mmol 87 mg	 72%[a] 1.81 mmol 476 mg	 73–77%[a, b] 3.64–3.88 mmol 961 mg–1.02 g	 67%[a] 13.4 mmol 3.53 g

[a] Isolated yields given. Reaction conditions: graphite anode, stainless-steel (1.4571) cathode, 10 mg/mL MTBS in MeCN + 15 vol% H_2O + 5 vol% HFIP, 31 °C, 5 mA/cm^2, 2.9 *F*, 3.0 eq. phenylacetylene, 4 h post-electrolysis stirring. [b] results obtained from solvent recycling; experiment replicated twice.

we propose solely hydrogen evolution serves as the cathodic counter reaction.

Scale-up and Solvent Recycling

Last, the scalability of the reaction was investigated using test substrate **6a** (Table 2). Initially, the reaction was transferred from screening-scale to a batch-type electrolysis via 5-fold scale-up. To our delight, isoxazole **7a** was obtained in 72% with almost no loss in yield. This could be maintained on 5.00 mmol-scale (815 mg **6a**), yielding 73% of isoxazole **7a**. Usually, the exemplary reuse of the supporting electrolyte is chosen to prove the sustainability of a process and its resource efficiency. Thus, the recyclability of tetraalkylammonium-based supporting electrolytes via extraction and recrystallization is widely demonstrated in literature.[41] As the application of HFIP as additive might be seen as a limiting factor of this procedure in particular, the recyclability of the employed mixed solvent system (MeCN + 15 vol% H_2O + 5 vol% HFIP) was investigated (Figure 3). Therefore, the solvent mixture was distilled under reduced pressure during work-up, which allowed for quantitative recycling, and reused for a second run. The targeted product **7a** was obtained without any loss in yield (73%). Even a third run with the recycled solvent mixture could be achieved without affecting the course of the reaction, yielding 77% of product **7a**. Hence, the recyclability of the used solvent mixture by simple vacuum distillation was proven. Moreover, the option of multiple reuses contributes to the sustainability of the established reaction, as the amount of solvent waste can be minimized. Thus, the use of small quantities of HFIP to improve the reaction's performance, which might appear to be a disadvantage at first, can be justified.

Last, a multi-gram scale electrolysis was performed. In a 40-fold scale-up, the desired product could still be obtained in a comparable yield of 67%, demonstrating the general translation of this electrosynthetic method to a preparative-relevant scale.

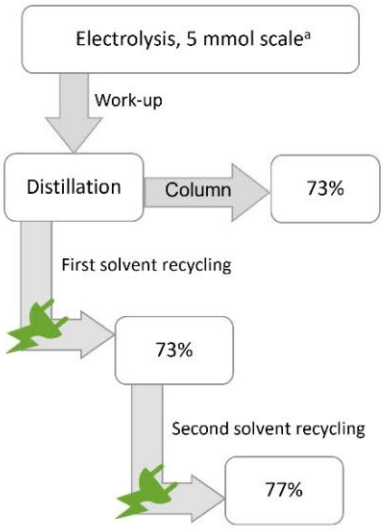


Figure 3. Demonstration of solvent recyclability.

Conclusions

An electrochemical method for the synthesis of isoxazoles and isoxazolines from readily available aldoximes in up to 81% yield was established. Constant current electrolysis was carried out in the simplest set-up in an undivided cell. Direct anodic oxidation of aldoximes in up to multi-gram scale with solely electric current as traceless oxidant minimizes reagent waste. Moreover, application of inexpensive and widely available electrode materials and the recyclability of solvents and supporting electrolyte contribute to an environmentally benign method that still captivates with cost-efficiency. The possibility of variation as an in-cell or ex-cell process allowed for application of a broad variety of alkynes and alkenes, highlighting a significant functional group tolerance. Furthermore, the applicability of heteroatomic dipolarophiles was demonstrated by exemplary synthesis of an oxadiazole. Thus, further development of the presented method might enable greener access to a broad variety of heterocyclic compounds in the future.

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Experimental Section

General Procedure for the Synthesis of Isoxazoles

The respective oxime (0.5 mmol, 1 eq.) and dipolarophile (1.5 mmol, 3 eq.) were placed in a 5 mL PTFE cell and dissolved in 5 mL of tributylmethylammonium methylsulfate (MTBS, 10 mg/mL) in acetonitrile + 15 vol% water + 5 vol% 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). The mixture was subjected to galvanostatic electrolysis at 31 °C under moderate stirring (magnetic stirrer set to approx. 500 rpm) using a current density of 5 mA/cm^2, a graphite anode and a stainless-steel (1.4571) cathode with a relevant surface area of 1.5 cm^2 (surface: 70 mm×10 mm, immersion depth of 1.5 cm), until an amount of charge of 2.9 *F* (142.3 C) was applied. The reaction mixture was stirred at 31 °C until the cycloaddition-reaction was completed (approx. 4 h). The mixture was transferred to a flask and evaporated to dryness under reduced pressure. The crude product was purified by recrystallisation or flash column chromatography.

General Procedure for the Synthesis of Isoxazolines

The respective oxime (0.5 mmol, 1 eq.) was placed in a 5 mL PTFE cell and dissolved in 5 mL of MTBS (10 mg/mL) in acetonitrile + 15 vol% water + 5 vol% HFIP. The mixture was subjected to galvanostatic electrolysis at 31 °C under moderate stirring (magnetic stirrer set to approx. 500 rpm) using a current density of 5 mA/cm^2, a graphite anode and a stainless-steel (1.4571) cathode with a relevant surface area of 1.5 cm^2 (surface: 70 mm×10 mm, immersion depth of 1.5 cm), until an amount of charge of 2.9 *F* (142.3 C) was applied. The respective dipolarophile (1.5 mmol, 3 eq.) was added and the mixture was stirred at 31 °C until the cycloaddition-reaction was completed (approx. 4 h). The mixture was transferred to a flask and evaporated to dryness under reduced pressure. The crude product was purified by recrystallisation or flash column chromatography.

General Procedure for Scale-up

The respective oxime (2.00 mmol or 5.00 mmol, 1 eq.) and dipolarophile (6.00 mmol or 15.00 mmol, 3 eq.) was placed in a 50 mL jacketed beaker-type cell, equipped with a cross-shaped stirring bar and dissolved in 25 mL or 50 mL of tributylmethylammonium methylsulfate (MTBS, 10 mg/mL) in acetonitrile + 15 vol% water + 5 vol% 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). The mixture was subjected to galvanostatic electrolysis at 31 °C under moderate stirring (magnetic stirrer set to approx. 500 rpm) using a current density of 5 mA/cm^2, a graphite anode and a stainless-steel (1.4571) cathode with a relevant surface area of 5 cm^2 (surface: 25 mm×20 mm, immersion depth of 2.5 cm) or 7 cm^2 (surface: 35 mm×20 mm, immersion depth of 3.5 cm), until an amount of charge of 2.9 *F* was applied. The mixture was stirred at 31 °C until the cycloaddition-reaction was completed (approx. 4 h), transferred to a flask and evaporated to dryness under reduced pressure. The crude product was purified by recrystallisation or flash column chromatography.

Supporting Information

Further experimental details and CV studies as well as data regarding the characterization of products is included in the Supporting Information of this article. The authors have cited additional references within the Supporting Information.[42–59]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: electrosynthesis · cycloaddition · anodic oxidation · oximes · isoxazoles

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3.1.2 Iodide-mediated Synthesis of Isoxazol(in)e carboxylates in a Biphasic System

A manuscript was published on this chapter:

[redacted] *Biphasic Electrosynthesis of 2-Isoxazol(in)e-3-carboxylates: Reaction Optimization from Milli- to Hectogram-Scale*, *ACS Sustainable Chem. Eng.* 2024, *12*, 11369–11376.

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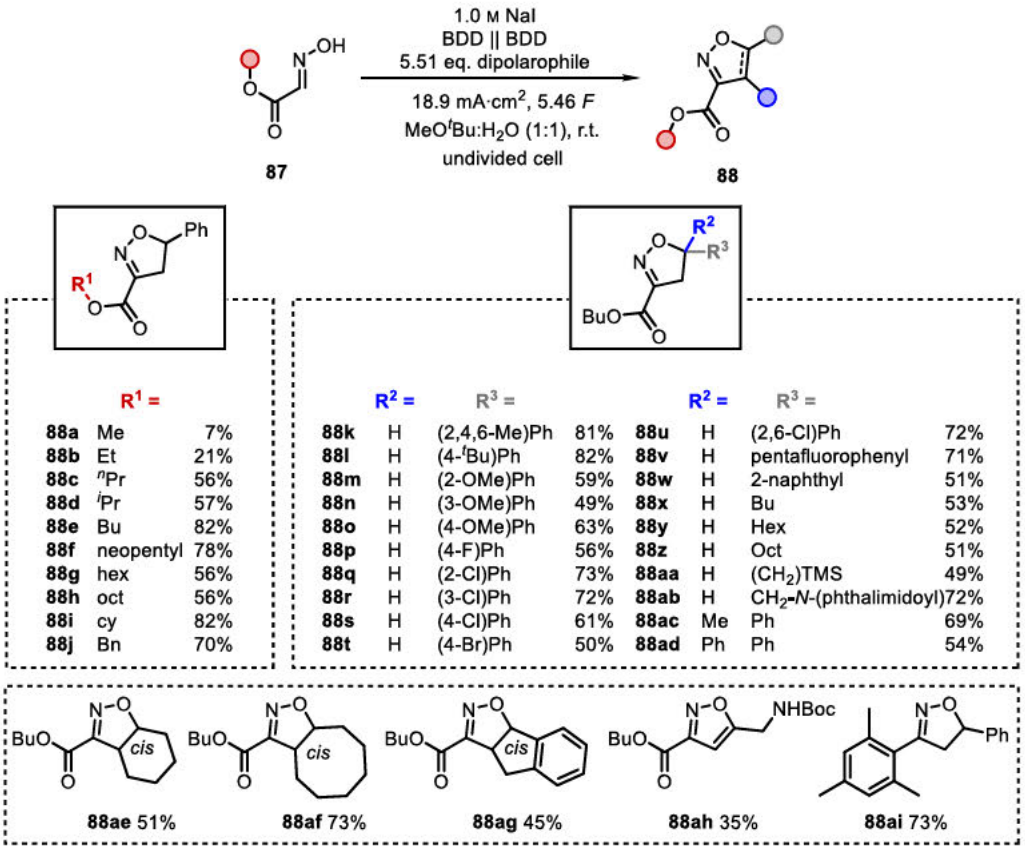
‡The authors contributed equally.

The direct electrolytic protocol for the synthesis of isoxazolines was challenging, as only an ex-cell approach worked out due to side reactions of the alkenes during electrolysis. To circumvent this problem, a biphasic and halide-mediated approach was chosen. This method was previously successfully employed in the synthesis of pyrazolines, allowing for application of even highly sensitive alkenes in the electrolysis. It was envisioned to extend the protocol to the synthesis of various isoxazoline-3-carboxylates, since they are a well-established scaffold in agro-chemicals such as *Isoxadifen-Ethyl*.[112,118] The initial optimization was performed by using ethyl 2-(hydroxyimino)acetate **87b** as test substrate and styrene as dipolarophile in an ethyl acetate:water mixture. Sodium iodide was used as mediator in combination with inexpensive and readily available graphite electrodes. The current density, the amount of applied charge and the equivalents of dipolarophile were subject to optimization by *DoE*. However, the yield of the corresponding isoxazoline **88b** did not exceed 31%. The low lipophilicity of the ethyl ester **87b** potentially caused diffusion of the intermediary formed nitrile oxide into the aqueous layer. The decreased interaction of the nitrile oxide with the styrene in the organic layer resulted in degradation of the starting material and the observed unsatisfactory yield. By employing butyl 2-(hydroxyimino)acetate **87e** under the optimized electrolytic conditions the corresponding isoxazoline **88e** was obtained in 51%. Afterwards the formation of **88e** was subject to further optimization. Initially, the influence of the solvent system, electrode materials and the halide source were re-investigated. This resulted in a 1:1 mixture of methyl-*tert*-butylether and water as solvent system, BDD as electrode material and sodium iodide as halide source. The second optimization

by *DoE* investigated the influence of the current density, the amount of applied charge and the equivalents of dipolarophile. Subsequently, product **88e** was isolated in a satisfactory yield of 82%.



Scheme 28: Scope of the halide-mediated electrochemical synthesis of isoxazol(in)es by anodic oxidation and subsequent cycloaddition.

After optimization the scope of the reaction was explored (Scheme 28). Different esters **87** were accessed in a simple and sustainable two-step synthesis starting from tartaric acid and the respective alcohol. The variation of the ester revealed the drastic influence of its lipophilicity on the formation of the isoxazoles **88a–j**. The yield of the products **88a–d** increases with the corresponding alkyl chain length of the ester from 7–57% yield. The butyl- and the cyclohexyl isoxazoline carboxylates **88e** and **88i** gave comparable yields of 82%. The hexyl- and octyl esters **88g** and **88h** were obtained in 56% yield. Interestingly, the yield of the isoxazoline correlates with the log *P* value of the associated alcohol. A maximum yield was observed at a log *P* value of 1. A variation of the alcohol and consequently of the log *P* value resulted in a decreased yield. This emphasized, that the polarity of the substrate needs to be considered a crucial parameter in this biphasic system. Afterwards, different dipolarophiles were tested. A great functional group tolerance was observed and a broad variety of isoxazolines was obtained. The electron-rich isoxazoline-3-carboxylates **88k–o** were obtained in up to 82% yield. Furthermore, the electron-deficient halo-substituted derivatives **88p–v** were isolated in up to 73%. The applicability of this method was underlined by the synthesis of *Isoxadifen-Butyl* (**88ad**, 54%), a variation of the common herbicide safener *Isoxadifen-Ethyl*. Furthermore, cyclic alkenes were employed to obtain the bicyclic isoxazoline-3-carboxylates **88ae–ag** in good yields up to 73%. Afterwards, the

scalability of the reaction was investigated using test substrate **88e**. The scale up of the reaction was investigated on 25 g scale. However, this proofed challenging and yielded 40% yield **88e** in the first attempt using a bipolar set-up. Surprisingly, complete conversion of the substrate was already observed after a reduced amount of applied charge of 2.5 *F*. In addition, changing the set-up to alternatingly polarized electrodes and increasing the inter-electrode gap to 10 mm yielded 82% of the product **88e**. This corresponds well to the results obtained on 3.44 mmol scale. The majority of unconverted styrene could be recovered by a simple distillation, contributing to the method's efficiency. Scale-up to hecto-gram scale was achieved in a continuously stirred tank reactor (CSTR) allowing for the synthesis of up to 195 g (53%) of the product **88e**. The decreased yield in the deca-gram scale could be a result of a less efficient emulsification of both layers. Thus, degradation of the starting materials might occur as a consequence of inefficient interaction between the organic and the aqueous phase.

Overall, the developed method enabled access to a broad scope of highly functionalized and novel isoxazoline-3-carboxylates **88** in a simple and efficient biphasic system. The sustainability of the method was demonstrated by recovering the unconverted styrene from the reaction mixture. The technical relevance of the protocol was shown on up to hecto-gram scale. The crude product already exhibited high purity after a simple work-up and was further purified by a simple silica filtration.[235]

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Research Article

Biphasic Electrosynthesis of 2-Isoxazol(in)e-3-carboxylates: Reaction Optimization from Milligram to Hectogram Scale

Yuto Nakamura,[⊥] Martin Linden,[⊥] Johannes Winter,[⊥] Silja Hofmann, Naoki Shida, Mahito Atobe, and Siegfried R. Waldvogel*

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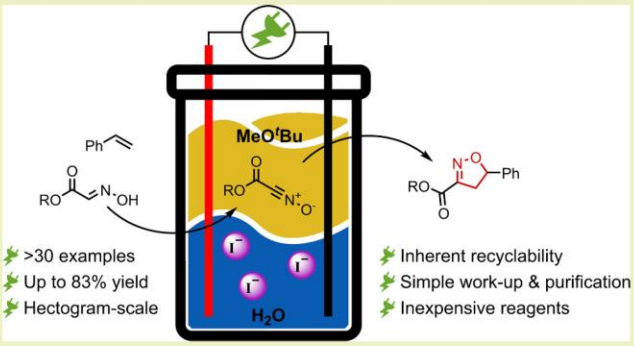
ABSTRACT: An electrochemical synthesis of isoxazol(in)e-3-carboxylates in a biphasic system allowing the direct access to technically relevant motifs in good yields has been established. The versatility of this protocol was demonstrated by >30 highly functionalized and diverse examples. Furthermore, a derivative of isoxadifen-ethyl was synthesized in a more sustainable approach, avoiding hazardous reagents and the generation of large amounts of waste. A nitrile oxide as the key intermediate is formed without addition of strong bases or oxidizers and directly undergoes the desired cycloaddition. The technical relevance of the established method was underlined by hectogram-scale synthesis while purifying the crude product by simple silica filtration. By simple distillation, nonconverted styrene was largely recovered, demonstrating the sustainability of this method.

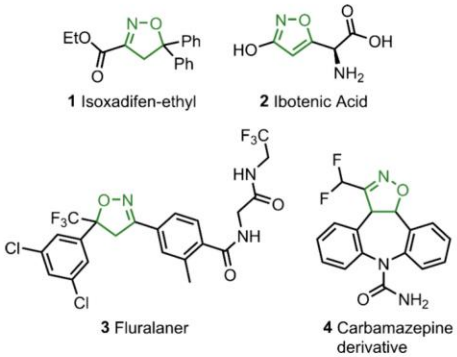


KEYWORDS: *electrosynthesis, dipolar cycloaddition, iodide-mediated, herbicide, scale-up*

1. INTRODUCTION

Isoxazol(in)es represent important structural motifs among biologically potent substances. They are found in various natural compounds, pharmaceuticals, and agrochemicals.[1] Isoxadifen-ethyl (Scheme 1, **1**), for example, is widely used as an herbicide safener to protect crops against several herbicides and thus enhances the efficiency of the treatment.[2−4] Furthermore, ibotenic acid (**2**) and fluralaner (**3**) represent pharmaceutically active isoxazol(in)es. Ibotenic acid (**2**) is a well-known, naturally occurring isoxazole with psychoactive properties found in *Amanita muscaria* (fly agaric).[5,6] Fluralaner (**3**) is a potent commercial antiparasitic drug for the therapy of cats and dogs infested with flea or ticks.[7] In addition, **4** is an isoxazoline derived from the anticonvulsant carbamazepine, demonstrating the application of dipolar cycloadditions in the late-stage functionalization of pharmaceuticals.[8,9]

Scheme 1. Biologically Active Isoxazolines Found as Naturally Occurring Products, Herbicide Safeners, or Pharmaceuticals



Common synthetic routes for accessing isoxazolines and isoxazoles involve the in situ formation of highly reactive nitrile oxides from *N*-hydroximidoyl halides followed by their 1,3-dipolar cycloaddition.[10,11] The major drawback of this synthetic protocol is the necessity for equimolar amounts of oxidants, large quantities of hazardous halogenating agents, and harsh reaction conditions.

While facing the climate crisis, the demand for more sustainable processes and synthetic protocols represents a main challenge for the modern organic chemist.[12−16] Electrochemistry as a synthetic tool can fulfill many points of green chemistry.[17−23] Electrical current as an inherently safe

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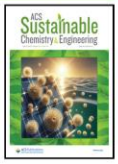

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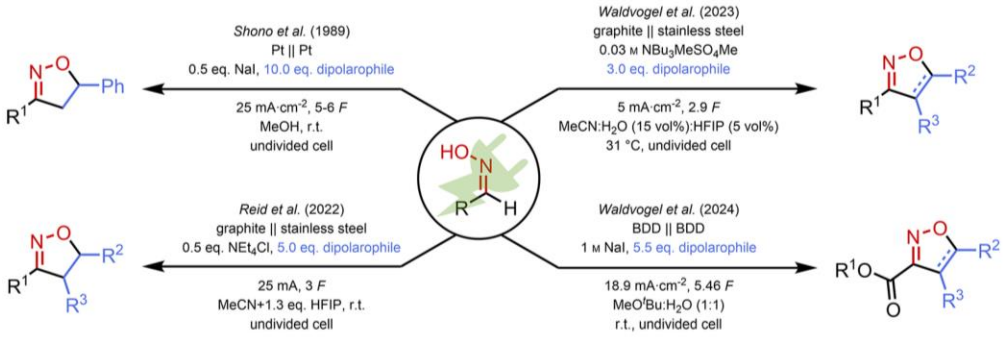
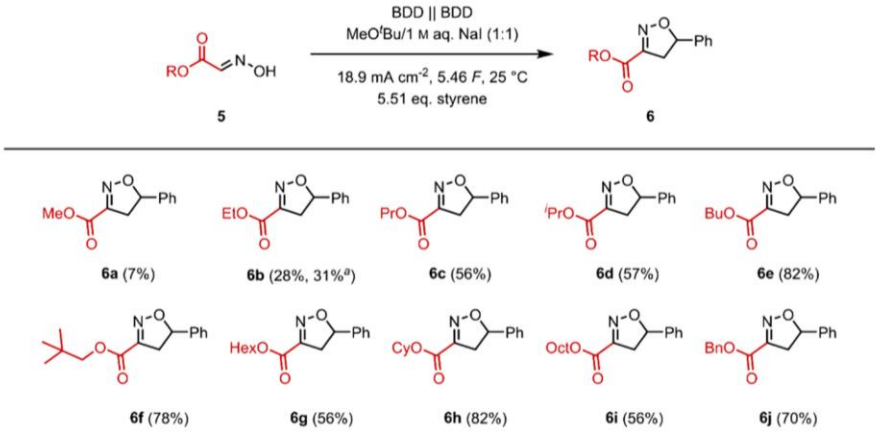
Scheme 2. Electrochemical Access to Isoxazolines and Isoxazoles



Scheme 3. Variation of the Ester Chain for the Electrochemical Synthesis of Isoxazolines[a]



[a]Isolated yields, 3.44 mmol scale. Superscript *a* in scheme: 4.27 mmol, 4.41 equiv of styrene, graphite||graphite, EtOAc/1 M aq. NaI (1:4), 18 mA cm^{-2}, 4.14 *F*, 25 °C.

surrogate for equimolar quantities of oxidants and recyclable solvents can be employed, avoiding large amounts of waste.[24−27] Additionally, the downstream processing of chemical reactions plays a crucial role, which should be considered in the design of industrial processes.[22]

The electrochemical synthesis of isoxazolines and isoxazoles is of great interest to the electro-organic community. Several methods have been reported based on halide-mediated electrochemical oxidation (Scheme 2). The earliest by Shono et al. used sodium iodide in methanol to gain access to several 3,5-disubstituted isoxazolines by trapping the intermediately formed nitrile oxide with a large excess of styrene.[28] Reid et al. presented a chloride-mediated homogeneous method.[29] The mechanism was further investigated, and the efficacy was shown on a larger scope. A mediator-free protocol was provided by Waldvogel et al. in a simple galvanostatic setup by direct anodic oxidation of several aldoximes.[30] The solvent system used in that method could be easily recycled by a simple distillation, minimizing fluorinated waste products.

Electrolysis in biphasic systems offers unique reactivity for the selective and efficient synthesis of various structural motifs like pyrazolines, oligosaccharides, and sophisticated cyclic hydrocarbons.[23,31−34] For large-scale processes, the recycling of both layers could be achieved by an easy separation and recovery and reuse of the organic solvent.

Here, we report an iodide-mediated approach for the synthesis of isoxazolines and isoxazoles in a biphasic system of methyl *tert*-butyl ether and water. Simple galvanostatic electrolytic conditions in an undivided setup and sustainable, carbon-based boron-doped diamond (BDD) electrodes[35−37] were used. Inexpensive and readily available sodium iodide as a supporting electrolyte was used, and the recyclability of styrene was demonstrated, underlining the green nature of this approach. To highlight the technical relevance of the established method, the scalability of the reaction was demonstrated by decagram- and hectogram-scale electrolysis.

2. RESULTS AND DISCUSSION

2.1. Optimization of the Electrolytic Conditions. The envisioned setup was based on methods for the electro-organic synthesis of pyrazolines and pyrazoles published by Waldvogel et al.[33,38,39] Starting from the reported conditions for the pyrazoline synthesis from glyoxylate hydrazones, a transfer on the conversion of ethyl 2-(hydroxyimino)acetate (Scheme 3, **5b**) and the reaction of the corresponding nitrile oxide with styrene was attempted. The appropriate supporting electrolyte, electrode material, and solvent were tested first (see Table S4). A biphasic system of ethyl acetate and a 1 M aqueous sodium iodide solution with isostatic graphite electrodes turned out to be the most feasible. In the following, further optimization of the amount of applied charge (Q), current density (j), and the equivalents of dipolarophile by Design of Experiment (DoE)[40−44] was performed. A 2^{3-1} fractional factorial design with a center point and rotatable axial points was chosen. The center point was acquired in triplicate. Additionally, ambient temperature and vigorous stirring turned out to be the most favorable conditions. However, the optimum conditions received from this optimization resulted only in an

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unsatisfactory yield of 31% for the corresponding isoxazoline **6b**.

Leakage of the highly polar nitrile oxide into the aqueous layer was accounted for the resulting low yields in the conversion of **5b**. Therefore, the test substrate was changed to butyl 2-(hydroxyimino)acetate (**5e**), which readily improved the yield to 51%, and the process was re-evaluated for the conversion of **5e**. Again, solvent, halide source, electrode material, and the ratio between organic and aqueous layers were tested first. This led to a 1:1 (v/v) system of methyl *tert*-butyl ether and 1 M aqueous sodium iodide with BDD as the anode and cathode. Further optimization was done in two DoE steps: first, the amount of applied charge, the current density, the equivalents of styrene, and the temperature were tested in a 2^{4-1} fractional factorial design (with a center point and rotatable axial points, every data point in triplicate). This revealed an optimal current density of 18.9 mA cm^{-2} independent from the other parameters. For *Q*, *T*, and the equivalents of styrene, the optimal settings were determined as their respective extreme settings. Thus, a second DoE included *Q*, *j*, and *T* with an adjusted range (2^{3-1} fractional factorial design with a center point and rotatable axial points, every data point in duplicate). The optimum conditions from both optimization steps were tested and revealed an optimal isolated yield of 82% at 18.9 mA cm^{-2}, 5.46 *F*, 25 °C, and 5.51 equiv of dipolarophile. Investigations on the substrate concentration finally revealed the initially chosen oxime concentration of 40 g/L (0.28 M) with respect to the organic layer as the optimum.

2.2. Scope. After optimization, the scope of the reaction was explored. First, the influence of the ester moiety was investigated. While only 7% of methyl ester **6a** could be isolated, the yield already increased to 28% (or 31% applying the conditions from the first optimization) for ethyl ester **6b**. Interestingly, propyl **6c** and *iso*-propyl ester **6d** were isolated in similar yields of 56 and 57%, respectively. The isoxazoline yield reached a maximum for butyl ester **6e** (82%), *neo*-pentyl ester **6f** (78%), and cyclohexyl ester **6h** (82%). For longer linear alkyl chains, the yield decreased again (**6g**, 56%; **6i** 56%). The observed trend very well corresponds to the log *P* values[45] of the corresponding alcohols with an optimum log *P* of ca. 1 (Figure 1). Merely the benzyl ester **6j** (70%) slightly deviates from this trend. The observed behavior indicates a well-balanced lipophilicity of the substrates **5** as a key factor for a successful conversion. A very hydrophilic oxime leads to the leakage of the oxime or the formed nitrile oxide into the aqueous layer, thus escaping the intended reaction. A very lipophilic oxime, on the other hand, does not accumulate in sufficient concentrations at the interphase where the oxidation takes place, or its surfactant-like properties may interfere with a smooth conversion.

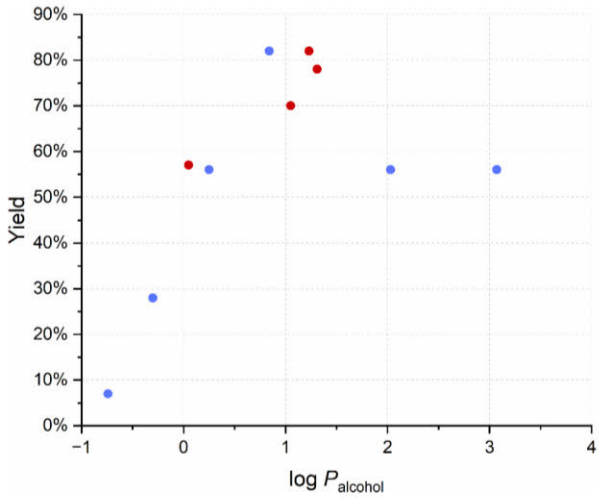

Figure 1. Correlation between the yields of isoxazolines with varying ester chains and the log *P* values[45] of the corresponding alcohols. Blue circle: linear esters; red circle: branched esters.

Second, the dipolarophile was varied (Scheme 4). A broad variety of isoxazolines bearing different functional groups was accessible in moderate to very good yields. In particular, for 5-aryl-substituted isoxazolines, appealing results were achieved (**6k**−**6z**). Among these, the 5-mesityl-substituted isoxazoline **6k** (81%) and the 5-(4-*tert*-butyl)phenyl-substituted isoxazoline **6l** (82%) gave the best results. Differently methoxylated styrenes were converted into the corresponding isoxazolines **6o**−**6q** in yields up to 63%. Furthermore, various halophenyl-substituted isoxazolines **6s**−**6y**, especially the 5-(chlorophenyl)isoxazolines **6s**−**6v**, were successfully obtained in up to 73% yield. The direct synthesis of diverse halo-substituted isoxazolines allows access to a broad variety of novel isoxazoline pesticides, as the halo substituents play a crucial role in the development of new pesticides.[46] 5,5-Disubstituted isoxazolines were accessible in moderate to good yields (**6n**, 69%; **6r**, 54%), emphasizing the influence of an increased steric demand on the cycloaddition. **6r** represents the butyl analogue of isoxadifen-ethyl, a commercial herbicide safener,[4,47] demonstrating the application potential of the established method.

Aliphatic alkenes were sufficiently tolerated. The butyl-substituted isoxazoline **6aa**, hexyl-substituted isoxazoline **6ab**, and the octyl-substituted isoxazoline **6ac** were accessed in moderate yields of 51−53% with almost no impact of the dipolarophile's periphery. Additionally, the trimethylsilyl-substituted isoxazoline **6ad** was obtained in 49% yield, allowing late-stage modifications by Hiyama cross-coupling reactions.[48] The cyclohexene-derived isoxazoline **6ae** and cyclooctene-derived isoxazoline **6af** were obtained in 51 and 73% yields, respectively. This is easily explained by the *cis*-configuration enforced by the cycloaddition reaction. For the cyclohexane ring of **6ae**, this results in a boat conformation introducing high ring strain. The cyclooctane ring of **6af**, on the other hand, can bypass this strain to a certain extent due to its higher degrees of freedom. Finally, the phthalimide-modified isoxazoline **6ag** was isolated in a good yield of 72%, enabling access to aminomethyl isoxazolines. In contrast, the Boc-protected isoxazole **6ah** was obtained in only 35% yield. The decreased yield is a result of the less reactive alkyne used as a dipolarophile.

Finally, the conversion of a nonglyoxylate-based oxime and the reaction of **5e** with phenylacetylene as dipolarophile were investigated. It was found that the herein presented method very well complements the recently described protocol[30] as it allows easy access to isoxazolines in an in-cell process. Isoxazoline **6ai** was thus obtained in an improved yield of 73% (instead of 66%, Scheme 5i). In contrast, isoxazoles were better accessible by the previously reported protocol (**6aj**/**ak**, Scheme 5ii). However, isoxazol(in)e-3-carboxylates remained scarcely available by electrochemical means. For the isoxazolines, this was readily circumvented by this new protocol.

2.3. Mechanistic Considerations. Based on the described findings and in accordance to previous reports,[28,33,39,49] the

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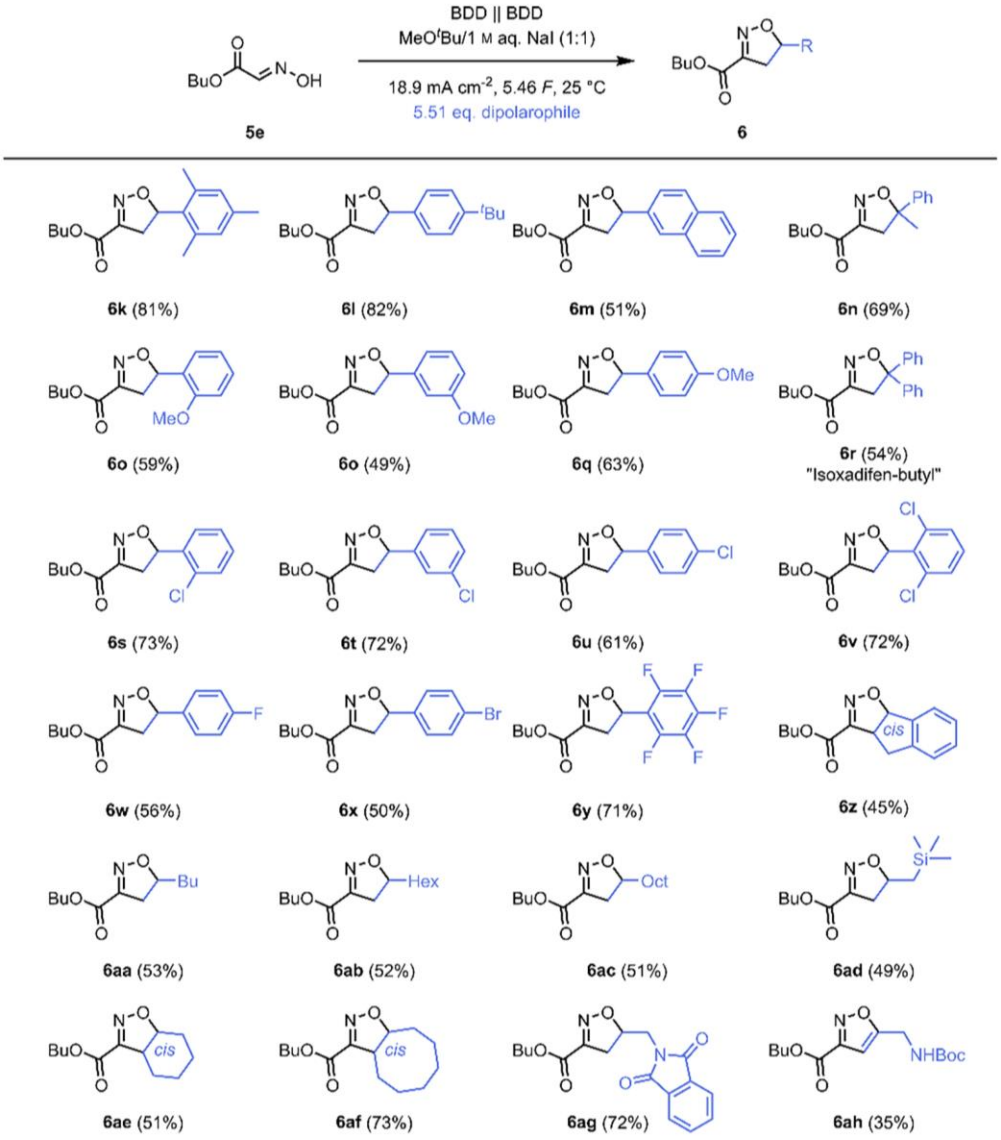
Scheme 4. Variation of the Dipolarophile in the Electrochemical Synthesis of Isoxazolines[a]



[a]Isolated yields, 3.44 mmol scale.

following mechanism is proposed (Scheme 6): Similar to the mechanism described by Shono et al.,[28] iodide is, in a first step, anodically oxidized to triiodide in the aqueous layer. At the phase boundary, oxime **5** is then oxidized by triiodide in analogy to the mechanism for the oxidation of oximes with NCS proposed by Togo and Kobayashi.[49] Upon deprotonation of the formed *N*-hydroxy-*N*-iodo iminium ion **5′** by electrogenerated hydroxide and elimination of iodide, nitrile oxide **5″** is released as the key intermediate. The latter then undergoes 1,3-dipolar cycloaddition to yield the desired isoxazol(in)e **6**.[28,49]

In general, the dipolarophile and the product **6** are less polar than the employed oxime **5** and the derived nitrile oxide **5″**. They are therefore located within the nonconductive organic layer (absence of an organo-soluble supporting electrolyte) rather than at the phase boundary. The spatial separation from the electrode reaction and the activated mediator species (triiodide) largely prevents side reactions or overoxidation. This significantly diminishes the required amount of dipolarophile compared to halide-mediated single phase systems. Moreover, a low impurity profile is achieved (see Figures S13−S15) that is advantageous for workup and further downstream processing.

2.4. Scale-up. To demonstrate the applicability of the newly developed method, scale-up to decagram and hectogram scale was envisioned. A first experiment under these conditions in a bipolar setup with 25.0 g (172 mmol) of oxime **5e**, however, revealed a severe drop in yield to only 40% **6e** (qNMR). Therefore, the reaction was reinvestigated on a 25 g scale (Table 1). This included variation of the electrode setup (polarization mode, interelectrode gap, and number of electrodes) and adjustment of the amount of applied charge. As a result, the electrolysis was performed at a sandwich setup of three alternatingly polarized BDD plates (polarization + − + , 10 mm interelectrode gap) with an amount of applied charge of 2.5 *F* (only 125% of the theoretical amount).

By distillation, 71.2 g (3.97 equiv) of styrene was recovered from the crude, indicating an overall dipolarophile con-

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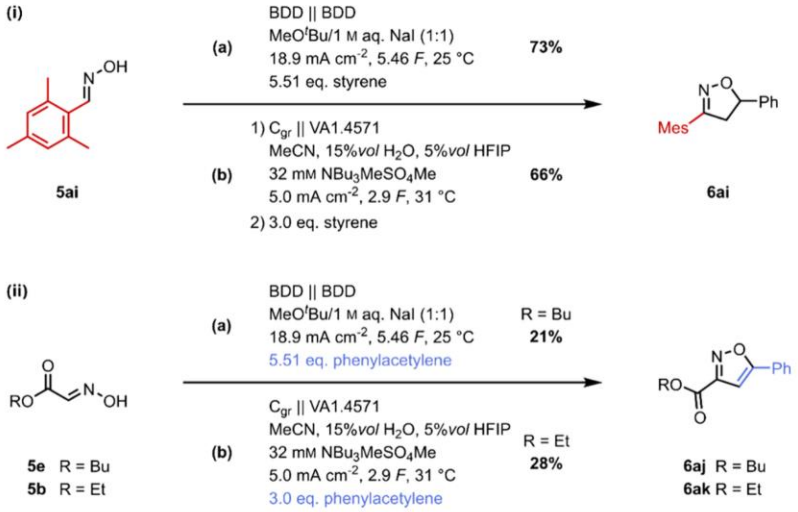
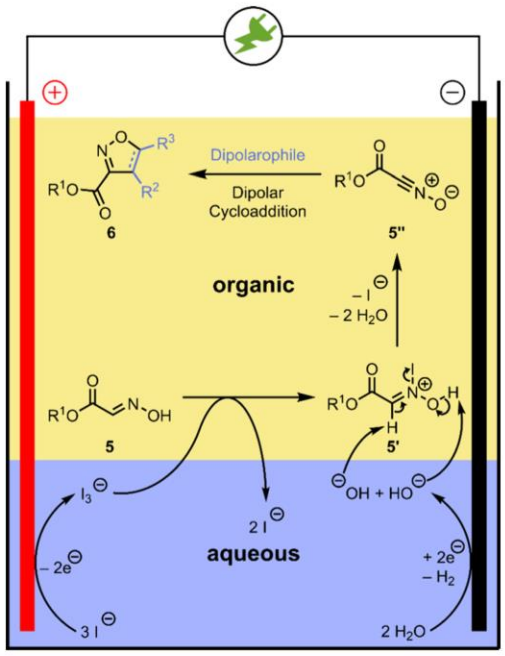
Scheme 5. Comparison between (a) the Newly Developed Method and (b) a Recently Presented[30] Electrochemical Isoxazol(in)e Synthesis for the Respective Test Substrates (i) Mesityl Aldoxime (5ai) and (ii) Alkyl 2-(Hydroxyimino)acetate 5e/b



Scheme 6. Mechanistic Proposal Based on the Observed Reactivity and Findings from Previous Publications[28,33,39,49]



sumption of only 1.54 equiv. Simple silica filtration of the distillation bottoms gave an isolated yield of 82% (35.0 g) of **6e**.

The relation between the interelectrode gap width and the decreased amount of applied charge is easily explained by the mechanism of electron transfer in the biphasic system. While the actual chemical transformation leading to the desired product occurs at the interphase and in the organic layer, the electrode reaction occurs in the aqueous layer. A small interelectrode gap may result in poor mixing in the interelectrode gap and, therefore, a small interphase area, leading to a low reaction rate for the desired conversion. This allows for electrochemical shortcutting of the cell by an iodine/iodide redox shuttle and, therefore, charge dissipation. A larger interelectrode gap facilitates better mixing in the gap and therefore diminishes the described charge dissipation. Similarly, every electrode represents an obstacle and, thus, their number may impact the fluid dynamics within the electrolyte. This in turn influences the size of the interphase area, which is crucial for a minimized charge dissipation and a high reaction rate of the desired conversion and, therefore, the yield.

In the following, the reaction was transferred to a continuously stirred batch tank reactor (CSTR). Without any further alterations, 218 g (1.50 mol) of oxime **5e** was converted, resulting in a yield of 53% (195 g, 0.789 mol) **6e** after silica filtration. On this scale, 3.20 equiv (500.5 g) of styrene could be recovered by distillation of the crude prior to the silica filtration.

It is to emphasize that the reaction was easily transferred to the hectogram scale (factor 436 compared to preparative scale) without larger variation of the conditions. On both scale-up stages, the crude product maintained a remarkably low impurity profile (see Figures S13–S15), facilitating a fast, low-effort workup and isolation. The decreased yield in the CSTR may result from a less efficient emulsification compared to the previous setup effecting the overall distribution of the two phases. Furthermore, evaporation of the organic phase was observed, resulting in an inconsistent concentration profile. As the substrate concentration was observed to influence the reaction outcome, this may very well explain the different results for the conventional batch-tank experiment (35.0 g **6e**, 82%) and the CSTR (195 g **6e**, 53%). Nevertheless, this proof-of-concept experiment showed the possibility to generate large quantities of this highly promising isoxazoline while combining well-known reactor concepts with electrolysis in biphasic reaction mixtures. Future developments will require a combination of ultramixing units between CSTR and the electrolyzer as demonstrated previously.[50,51]

3. CONCLUSIONS

A biphasic electrochemical access to 2-isoxazoline-3-carboxylates bearing a broad variety of functional groups via dipolar cycloaddition in up to 83% yield was established. The scope included the successful synthesis of the herbicide safener

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Table 1. Optimization of the Decagram-Scale Synthesis of Butyl 4,5-Dihydro-5-phenylisoxazole-3-carboxylate (6e)



entry	setup	no. of BDD electrodes (polarization)	interelectrode gap/mm	Q/F	post stirring	recovered styrene	yield
1	bipolar	6	5	5.46		n/d	40%[a]
2	bipolar	5	10	3.5		65.1 g (3.63 equiv)	56%[a]
3	bipolar	5	10	2.5		74.1 g (4.13 equiv)	57%[a]
4	bipolar	5	10	2.5	12 h	69.9 g (3.90 equiv)	56%[a]
5	alternatingly polarized	5 (+ − + − +)	10	2.75		74.5 g (4.15 equiv)	63%[a]
6	alternatingly polarized	3 (+ − +)	20	2.5		77.9 g (4.34 equiv)	63%[a]
7	alternatingly polarized	2 (+ −)	10	2.5		72.7 g (4.05 equiv)	83%[a]
8	alternatingly polarized	3 (+ − +)	10	2.5		71.2 g (3.97 equiv)	83%[a] (82%[b])

[a]Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. [b]Isolated via silica filtration (0% → 10% EA in CH).

analogue "Isoxadifen-butyl" (**6r**), demonstrating the application potential of the developed method. Furthermore, an interesting impact of the ester chain length on the yield was observed and could be very well correlated to the log *P* values of the corresponding alcohols. The process optimization for butyl 5-phenyl-2-isoxazoline-3-carboxylate (**6e**) over 5 orders of magnitude from screening (10^{-2} g) via decagram to hectogram scale was demonstrated. The excellent and robust scalability of this protocol was shown, resulting in 82% (35.0 g) yield on the decagram scale. Transfer to the hectogram scale demonstrated the large-scale applicability of the presented method, resulting in 53% (195 g) yield and including an easy-to-conduct workup and purification procedure. Therefore, this biphasic approach offers a simple, scalable, and sustainable tool for the electrochemical synthesis of isoxazolines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acssuschemeng.4c03621.

Experimental details and ^{1}H NMR spectra for all compounds (PDF)

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Author Contributions

⊥Y.N., M.L., and J.W. contributed equally to this work. Y.N., M.L., and S.H. performed the screening for the reaction conditions and analyzed the experimental data. Y.N., M.L., and J.W. synthesized the starting materials. Y.N., M.L., and J.W. conducted the scope and scale-up experiments. Y.N., M.L. J.W., N.S., M.A., and S.R.W. wrote the manuscript. All authors discussed the results and agreed to the manuscript.

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Notes

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3.2 Cathodic Reduction of Nitro Arenes for the Synthesis of Heterocycles with a N,O-Moiety

3.2.1 Selective Reduction of Nitroaryl-substituted β-Ketoesters for the Synthesis of Quinoline *N*-Oxides

A manuscript was published on this chapter:

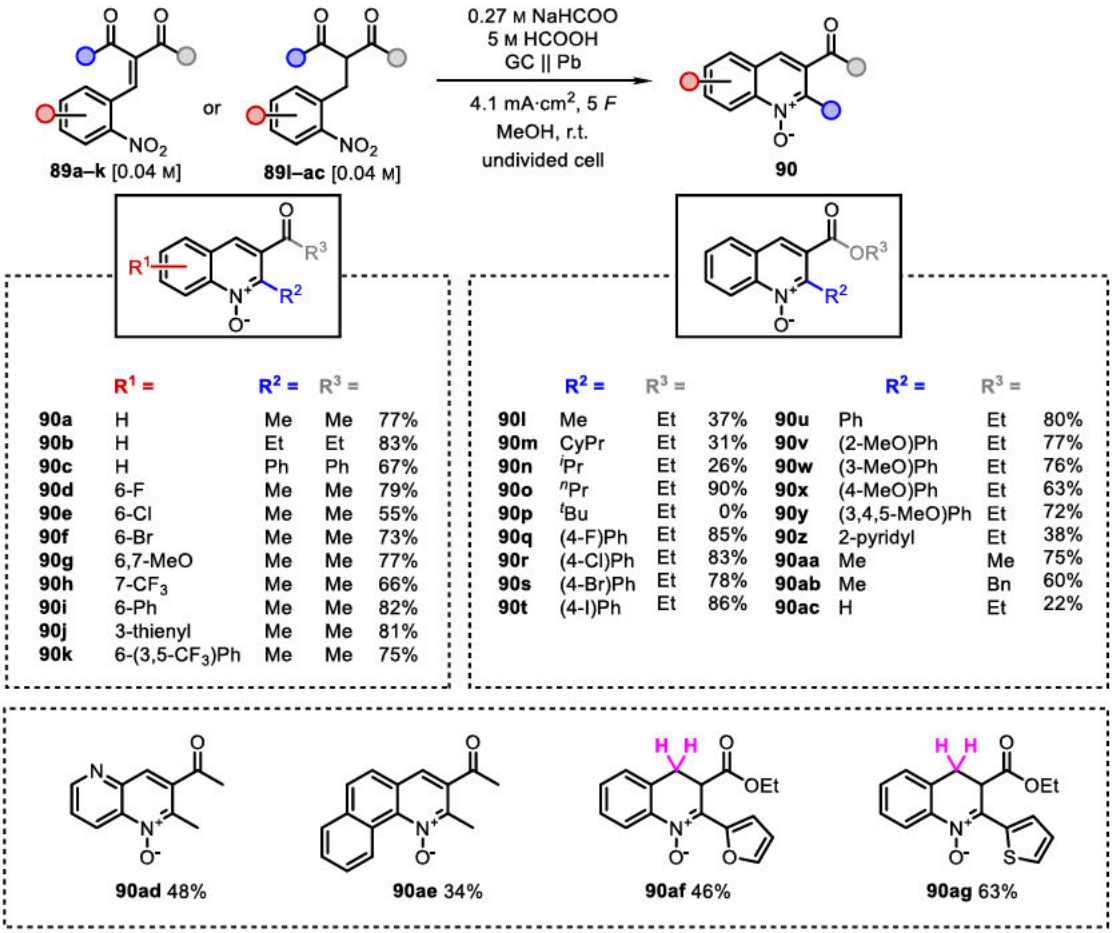
[redacted],
Direct Electrochemical Synthesis of 2,3-Disubstituted Quinoline N-oxides by Cathodic Reduction of Nitro Arenes, *Chem.Eur. J.* 2023, *29*, e202203319.

[redacted]

Quinolines and quinoline *N*-oxides are common and important scaffold in natural products, pharmaceuticals, and catalysts. The synthesis of quinoline *N*-oxides often involves a two-step reaction sequence by condensation and subsequent oxidation of the obtained quinoline.[150,152–154,158] However, this process involves the use of equimolar quantities of redox-active reagents and generates large amounts of waste. *Lund et al.* presented the first potential-controlled protocol for the direct electrochemical synthesis of quinoline *N*-oxides starting from 2-nitrobenzylidene β-ketocarbonyls.[26] However the complex electrolysis set-up and the limited scope restricts this protocol's application in modern organic synthesis. *Waldvogel et al.* developed the first constant current electrosynthesis of quinoline *N*-oxides in a simple undivided set-up. Readily available 2-nitrocinnamaldehydes were used as substrates and the corresponding products were obtained in moderate yields.[105]

Based on these results, a protocol for highly substituted and diverse quinoline *N*-oxides was envisioned. The initial optimization was performed using ethyl (2-nitrobenzyl)acetoacetate (**89l**) which was obtained in a single step from 2-nitrobenzylbromide and ethyl acetoacetate. Based on previous work, BDD was chosen as cathode material due to its high overpotential for hydrogen evolution and glassy carbon was used as anode.[49,89,100,101,103,105] Sulfuric acid as additive was employed in a dual role as supporting electrolyte and catalyst for promoting the cyclo-condensation of the intermediate. A current density of 4.1 $mA \cdot cm^{-2}$ and methanol as solvent were chosen and the electrolysis was carried out in a simple undivided electrolysis set-up. However, a product mixture of the desired quinoline *N*-

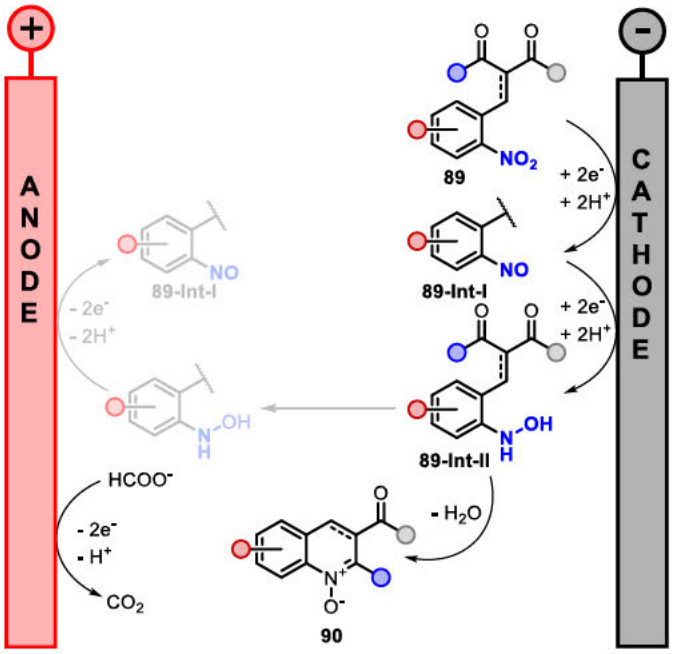
oxide **90l** and the deoxygenated quinoline was obtained. By applying a 5.27 M formate buffer in methanol as supporting electrolyte and using a lead cathode, the selectivity for the quinoline *N*-oxide was drastically improved and solely the desired product **90l** was isolated in 37% yield. Moreover, quinoline *N*-oxide **90a** was synthesized in 77% yield from 2-(2-nitrobenzylidene)acetacetone (**89a**).



Scheme 29: Scope of the direct electrochemical synthesis of 2,3-disubstituted quinoline *N*-oxides.

The optimized conditions were applied for the synthesis of various 2,3-disubstituted quinoline *N*-oxides (Scheme 29). First, 2-(2-nitrobenzylidene)-3-oxoketones (**89a–k**) were employed as starting materials. Halogenated nitro arenes were well tolerated in yields up to 79% (**90d–f**) allowing for further functionalization. Additionally, the more complex heterocycles **90ad** and **90ae** were obtained in 48% and 34% yield, respectively. Afterwards, the conversion of 2-(2-nitrobenzyl)acetoacetates (**89l–ac**) were investigated. The 2-alkylsubstituted quinoline *N*-oxide carboxylates **90l–n** were obtained in 26%–37% yield. The 2-*tert*-butyl substituted quinoline *N*-oxide **90p** could not be obtained, and only the corresponding hydroxylamine was detected by LC-MS. This observation showed the influence of sterically demanding substituents in 2-position, inhibiting the cyclo-condensation after reduction of the nitro group. The 2-aryl substituted quinoline *N*-oxides **90q-z** were isolated in 38%–85% yield, showing the tolerance towards electron-rich and -deficient substituents. Interestingly, the 2-furyl and 2-thienyl-substituted ketoesters **89af** and **89ag** failed to undergo the final aromatization and the corresponding

3,4-dihydroquinoline *N*-oxides **90af** and **90ag** were isolated in 46% and 63% yield. After exploring the scope of the reaction, a scale-up of the synthesis of quinoline *N*-oxide **90a** was performed and the product was isolated in up to 80% yield (8.08 g). The concentration of starting material was increased without a loss in yield, while maintaining high selectivity. Furthermore, product purification was achieved by a simple filtration over silica. A potential lead contamination was analyzed by ICP-OES to study cathodic corrosion during electrolysis. ICP-OES analysis showed 18 ppm of lead immediately after electrolysis, dropping below detection limits after processing. These lead traces likely resulted from the dissolution of the natural lead oxide layer in acidic media.



Scheme 30: Proposed mechanism of the direct electrochemical synthesis of quinoline *N*-oxides **90**.

The reaction mechanism was investigated by cyclic voltammetry (Scheme 30). Reduction of 2-nitro arenes **89** to the corresponding hydroxylamine **89-Int-II** occurs in two steps via a nitroso intermediate **89-Int-I**. Hydroxylamine **89-Int-II** undergoes a subsequent intramolecular cyclo-condensation. An additional oxidation was observed for 2-(2-nitrobenzyl)acetoacetates leading to aromatization after cyclization. The cyclic voltammograms of **89af** and **89ag** correspond to the experimental observation lacking the final oxidative wave of the aromatization.

In conclusion, a simple and scalable protocol for the synthesis of various 2,3-disubstituted quinoline *N*-oxides **90** has been developed. The scope of the reaction showed a wide functional group tolerance, allowing even the synthesis of complex heterocycles and highly substituted derivatives. Scalability was demonstrated up to the multi-gram scale without loss of yield. Purification could simply be achieved by filtration over silica. In addition, despite the use of lead cathodes, no lead contamination was detected in the final product by ICP-OES measurements, demonstrating the applicability of the method.[236]

Direct Electrochemical Synthesis of 2,3-Disubstituted Quinoline *N*-oxides by Cathodic Reduction of Nitro Arenes

Johannes Winter,[a] Tobias Prenzel,[a] Tom Wirtanen,[a] Dieter Schollmeyer,[a] and Siegfried R. Waldvogel*[a, b]

Abstract: The use of electric current in synthetic organic chemistry offers a sustainable tool for the selective reductive synthesis of quinoline *N*-oxides starting from easily accessible nitro compounds. The reported method employs mild and reagent-free conditions, a simple undivided cell, and constant current electrolysis set-up which provides conversion with a high atom economy. The synthesis of 30 differently substituted quinoline *N*-oxides was successfully performed in up to 90% yield. Using CV studies, the mechanism of the selective formation of the quinoline *N*-oxides was elucidated. The technical relevance of the described reaction could be shown in a 50-fold scale-up reaction.

Introduction

Nitrogen- and oxygen-containing heterocyclic compounds are prevalent in nature and modern organic synthesis.[1] Quinoline *N*-oxides should be emphasized because of their unique chemical features of the N–O motif. They can be used as intermediates in organic synthesis for C2 functionalization of quinoline[2] or as ligands in asymmetric synthesis, like 3,3-dimethyl-2,2′-biquinoline *N,N′*-dioxides (**1**) (Figure 1, left).[3] In addition, 8-alkylated quinoline *N*-oxides (**2**) (Figure 1, center) have been applied as mild oxidizers in the formation of α-oxo gold carbenes which are used as safer surrogates for α-diazo carbonyl compounds.[4]

The structural motif of quinoline *N*-oxides is found in biomolecules such as Aurachin A (**3**) (Figure 1, right), an antimicrobial agent found in *Stigmatella aurantiaca*, a member of an emerging class of new antibiotics found in nature.[5] Novel antibiotics are needed to combat a growing number of drug-resistant bacteria.[6] Substances containing an N–O motif could potentially be a class of novel drugs.[7] The conventional synthesis of quinoline *N*-oxides can be approached by

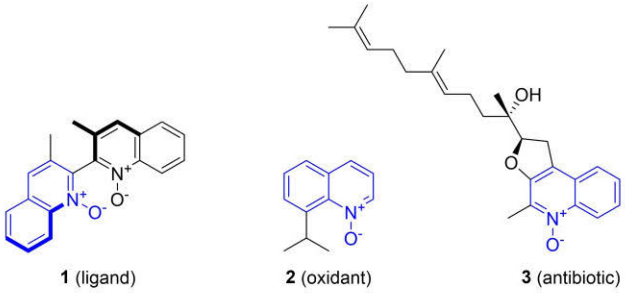


Figure 1. Ligand **1**, oxidizer **2**, and a biologically active quinoline *N*-oxide **3** bearing quinoline *N*-oxide motif.

Friedländer's quinoline synthesis starting from the corresponding 2-aminobenzaldehydes followed by their subsequent oxidation resulting in the desired quinoline *N*-oxide.[8] However, this process requires stoichiometric quantities of oxidizing agents, harsh reaction conditions, and generates large amounts of waste. A modern, biochemical approach involves bakers' yeast in the direct transformation of 2-nitrocinnamaldehydes under alkaline conditions to their respective quinoline *N*-oxides.[9] Despite the simple set-up, this reaction was only performed on a narrow scope with a low selectivity for the desired quinoline *N*-oxide. A direct metal-free approach by cyclization utilizes carcinogenic and highly toxic hydrazine under basic reaction conditions and therefore, does not represent a suitable alternative (Scheme 1).[10]

A potent tool in the preparation of various nitrogen-containing heterocycles is electro-organic synthesis.[11] The application of electric current as an inexpensive and traceless activator replaces the stoichiometric quantities of hazardous reagents.[12] Therefore, the amount of waste generated can be tremendously decreased and harmful reagents can be avoided.[13] For these reasons organic electrochemistry can be considered a green and modern synthetic tool.[14] Initial investigations into the electrochemical synthesis of quinoline *N*-oxides were conducted by *Lund* and *Feoktistov* in polarographic

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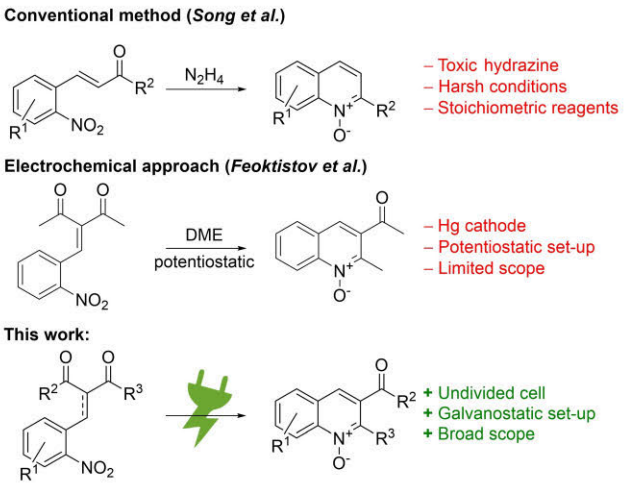


Scheme 1. Conventional and electrochemical approaches to quinoline *N*-oxides.

studies and gave the desired *N*-oxide. However, toxic mercury electrodes were applied in a sophisticated potentiostatic reaction set-up which only provided three derivatives on a very small scale.[15] The method described herein allows for the synthesis of a broad scope of quinoline *N*-oxides in high yields using a simple constant current set-up.

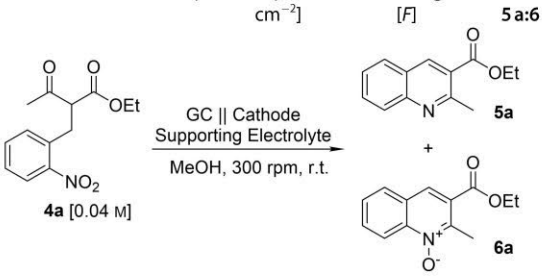
Results and Discussion

Nitro group containing compounds are easily accessible and inexpensive to obtain.[16] Based on previously reported results by the *Waldvogel* group the reduction of nitro groups provides a powerful tool for the direct synthesis of nitrogen containing heterocycles.[17] The direct electrochemical synthesis of N-heterocycles was demonstrated on different motifs in the past.[18] The retrosynthetic analysis of the quinoline *N*-oxide scaffold created the idea of partial reduction of the nitro group followed by a condensation reaction, resulting in the desired *N*-oxide motif. Initially, compound **4a** was chosen as a test substrate, which was easily synthesized in a single step by alkylation of the readily available ethyl acetoacetate with 2-nitrobenzyl bromide.[19] Based on conventional chemical considerations, sulfuric acid was chosen as an additive to promote cyclization after the reduction of the nitro group. The remaining electrolytic conditions were based on previously reported reductive reactions.[17,20] The screening of the electrosynthetic reaction was focused on all relevant parameters.[21–23] The yield of products **5a** and **6a** as well as the conversion of the substrate **4a** was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. Under the initially chosen electrolytic conditions (Table 1, Entry 1) quinoline **5a** was formed as the major product in 69% yield and only 19% of the quinoline *N*-oxide **6a** was observed. The molecular structure of **6a** was confirmed by X-ray analysis (CCDC: 2207689).

From these preliminary results, variation of different reaction parameters was conducted to further improve the selectivity of the reaction towards quinoline *N*-oxide **6a** and to increase its yield. Detailed information of each experiment is provided in the Supporting Information. To suppress a possible re-oxidation of the product a divided set-up was compared to the initially used undivided set-up (Table 1, Entry 2). The yield and selectivity decreased significantly in a divided cell, thus highlighting the importance of the counter reaction.[23]

Based on this, further experiments were carried out in undivided 5 mL Teflon® cells. As the supporting electrolyte can greatly influence the overall reaction, different electrolyte systems were tested.[22] A variation of the concentrations of sulfuric acid showed no improvement of selectivity, higher concentrations of sulfuric acid proved detrimental resulting in decomposition of the starting material (Supporting Information, Table S3). The selectivity was improved by using an acetate buffer (Table 1, Entry 3), suggesting weak acids were superior for the formation of the desired quinoline *N*-oxide **6a**. By using

Table 1. Initial screening of reaction conditions using dihydrocinnamate **4a**.



Entry	Cathode	Supporting electrolyte	Current Density [mA cm^{-2}]	Applied charge [*F*]	Yield[a] [%] **5a:6a**
1[b]	BDD	0.5 M H_2SO_4	4.1	6	69:19
2[c]	BDD	0.5 M H_2SO_4	4.1	6	24:3
3[b]	BDD	5 M AcOH 0.45 M NaOAc	4.1	6	4:20
4[b]	BDD	5 M HCOOH 0.27 M NaHCOO	4.1	6	3:27
5[b]	**Pb**	**5 M HCOOH 0.27 M NaHCOO**	**4.1**	**5**	**0:38**
6[b]	CuSn7Pb15	5 M HCOOH 0.27 M NaHCOO	4.1	5	0:14
7[b]	Pb	5 M HCOOH 0.27 M NaHCOO	2.4	5	0:35
8[b]	Pb	5 M HCOOH 0.27 M NaHCOO	4.1	4	0:37

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] Undivided 5 mL Teflon® cell; [c] Divided reaction set up, separator: glass frit; GC = glassy carbon, BDD = boron doped diamond.

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a formate buffer as supporting electrolyte (Table 1, Entry 4) the yield of **6a** was increased to 27%.

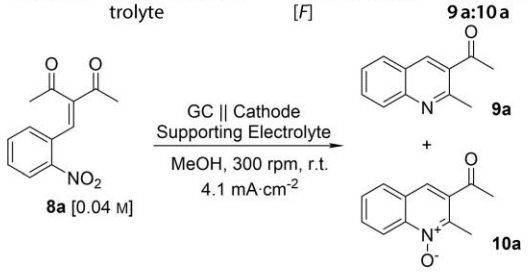
By applying lead as cathode material, which showed excellent results in previous studies for selective deoxygenation and has a high overpotential for hydrogen evolution, the yield increased up to 38% (Table 1, Entry 5).[24] Leaded bronze as a novel cathode material and a substitute for lead decreased the yield significantly (Table 1, Entry 6), which is why lead was used as cathode material in future experiments.[25] To reduce possible degradation of both the starting material and the product a lower current density was investigated (Table 1, Entry 7). Since no significant change in yield was observed this suggests the current density has a marginal influence on the overall reaction. As a total amount of applied charge of 4 *F* (Table 1, Entry 8) resulted in 92% conversion of the starting material, 5 *F* were used in further experiments resulting in 100% conversion of **4a**.

Considering the keto-enol tautomerism of the test substrate **4a** may have a significant influence on the overall reaction, a cinnamate test substrate **8a** was compared to the previously obtained results. Theoretically, a 1,3-diketo compound is more reactive compared to a β-ketoester as the opportunity for condensation is doubled with 2 keto groups.

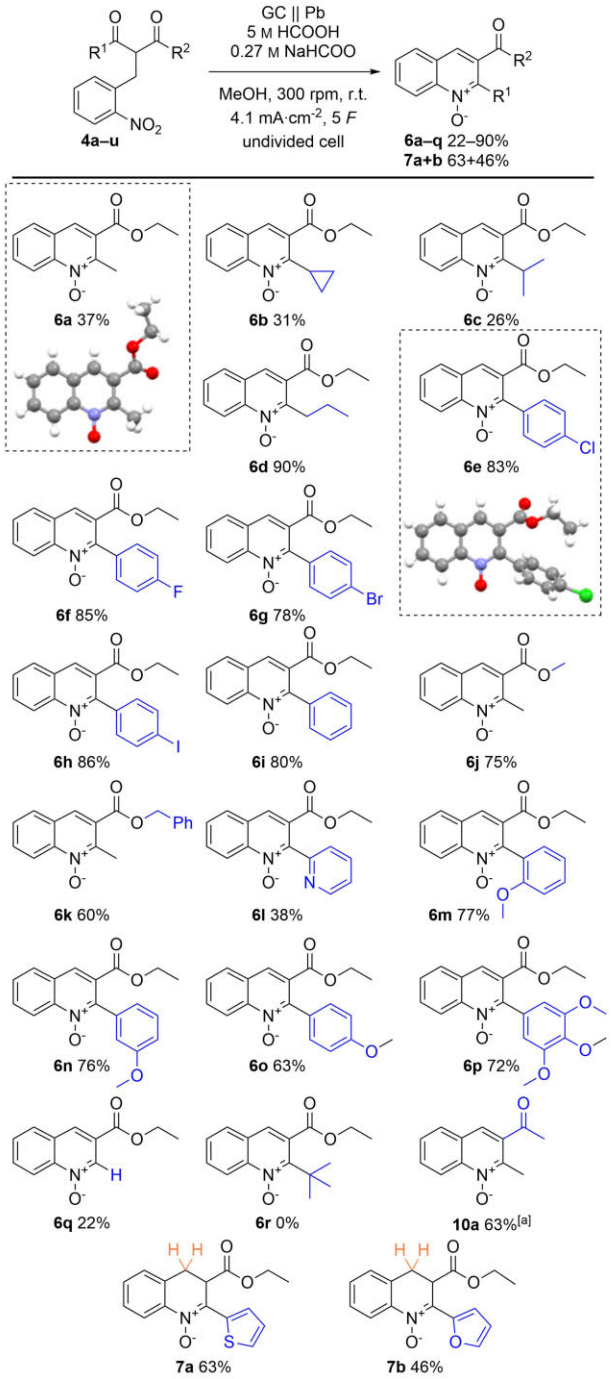
The cinnamyl methyl ketone **8a** as conjugated test substrate was obtained by *Knoevenagel* condensation of 2-nitro benzaldehyde with acetylacetone.[26] By utilizing the previously optimized reaction conditions the corresponding quinoline *N*-oxide **10a** was obtained in 80% yield (Table 2, Entry 3) revealing a significant influence of the keto-enol tautomerism and the more reactive 1,3-diketo substitution pattern of substrate **8a**. BDD as cathode material did not seem to be beneficial in neither the optimized formate buffer as electrolyte nor the sulfuric acid (Table 2, Entries 1 and 2). Finally, other carbon-based cathode materials were tested, resulting in a remarkable decrease in both yield and selectivity (Table 2, Entries 4 and 5). For scientific control, no electric current was applied, resulting in no conversion of the starting material **8a**.

After optimizing the reaction conditions the scope of the reaction was explored. Initially the scope of different 2-nitrobenzyl β-ketoesters was investigated (Scheme 2). Variation of the aliphatic substituent at position 2 revealed the effect of increasing steric demand of the substituent. Comparing **6b** to

Table 2. Screening of reaction conditions using cinnamyl ketone **8a**.

Entry	Cathode	Supporting electrolyte	Applied charge [*F*]	Yield[a] [%] **9a**:**10a**
				
	8a [0.04 M]	GC || Cathode Supporting Electrolyte MeOH, 300 rpm, r.t. 4.1 mA·cm^{-2}		**9a** + **10a**
1	BDD	0.5 M H_2SO_4	6	1:11
2	BDD	5 M HCOOH 0.27 M NaHCOO	5	5:49
3	Pb	5 M HCOOH 0.27 M NaHCOO	5	0:80(77[b])
4	GC	5 M HCOOH 0.27 M NaHCOO	5	19:38
5	RVC	5 M HCOOH 0.27 M NaHCOO	5	1:67
6[c]	Pb	5 M HCOOH 0.27 M NaHCOO	5	0:0

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] isolated yield; [c] No electricity was applied; GC = glassy carbon, BDD = boron doped diamond; RVC = reticulated vitreous carbon.



Scheme 2. Reaction scope of the 2-nitrobenzyl β ketoesters **4a–u**. [a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

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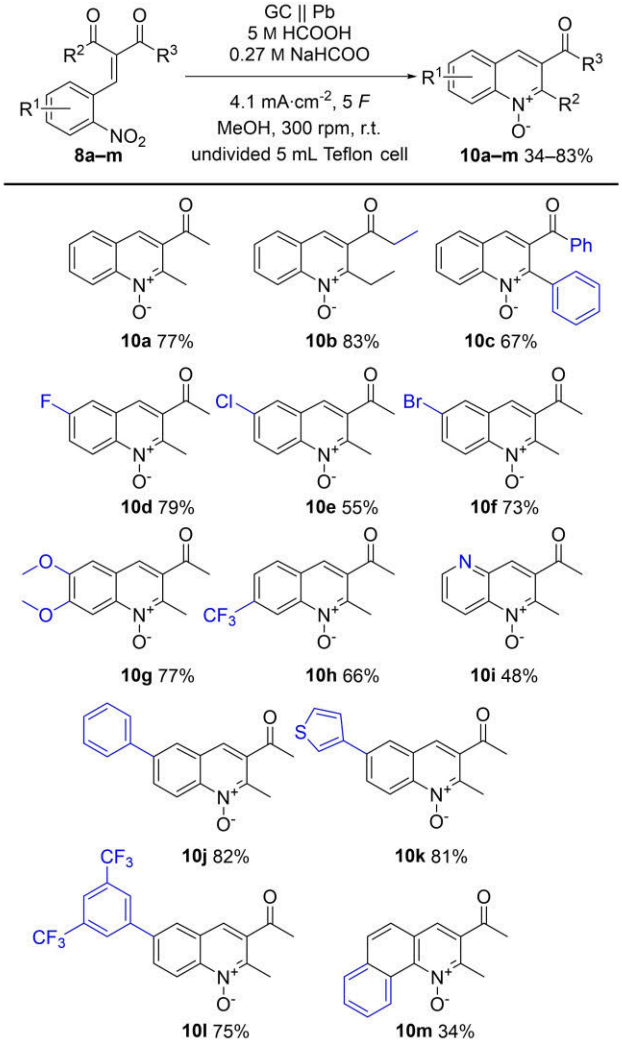
6c, a higher degree of freedom results in a lower yield of 26% for **6c** compared to 31% of **6b**. Following this trend, the *tert*-butyl derivative **6r** could not be isolated due to the complete reduction of the corresponding substrate to its aniline analogue, confirmed by LC–MS. In this case, the hydroxylamine intermediate was further reduced without cyclisation by condensation with the carbonyl group. Interestingly the *n*-butyl derivative **6d** was isolated in excellent yield of 90%. The *p*-halo aryl substituted quinoline *N*-oxides **6e**–**6h** were isolated in up to 86% yield. The high yield of the iodo derivative **6h** is particularly interesting as dehalogenation was suppressed in this electrochemical protocol, which occurred as side reaction in previous studies.[27] These halo derivatives **6e**–**6h** allow for further functionalization, unlocking a variety of novel scaffolds. The molecular structure of the *p*-chlorophenyl substituted derivative **6e** was confirmed by X-ray analysis (CCDC: 2207689). The phenyl substituted derivative **6i** could also be obtained in 80% yield, suggesting that phenyl substrates undergo the cyclization more easily based on the more reactive keto function resulting in better yields. Next, different carboxylic esters were tested. The methyl ester **6j** was obtained in good yield up to 75%. The benzyl ester gave 60% of the desired product **6k**. Next heterocyclic substituents were investigated and **6l** was obtained with 38% yield showing tolerance of additional nitrogen heterocycles which might be oxidized as side reaction.

The electron-rich aryl-substituted derivatives **6m**–**6p** were obtained in up to 77% yield. The non-substituted quinoline *N*-oxide in position 2 **6q** was isolated in 22% yield and opens up the possibility of further modifications in 2-position.

Substrate **4t** and **4u** formed compounds **7a** and **7b** in moderate yields of 63% and 46%, and did not result in the expected quinoline *N*-oxide by missing out the final oxidation revealing interesting insights in the mechanistic considerations.

The β-diketone **4s** gave a 63% yield by ^{1}H NMR of the desired quinoline *N*-oxide **10a** revealing the beneficial effect of the additional, more reactive keto function towards the cyclization compared to test substrate **4a**. Compared to the electroreduction of the cinnamyl methyl ketone **8a** with 77% yield, the effect of conjugation dominated.

The optimized reaction conditions were then applied to the 2-nitro cinnamyl ketones **8a**–**m** (Scheme 3). Initially, the substituent at positions 2 and 3 were varied. **10b** was isolated in very good yield of 83%. Derivative **10c** gave only 67% yield, possibly due to the high steric demand of both aryl groups. Next, the nitro benzylidene core of each substrate was modified. The halo substituted derivatives **10d**–**10f** were obtained in good yields of up to 79%, enabling further functionalization of the corresponding quinoline *N*-oxides. The trifluoromethyl group, which is considered as important functional group in medicinal chemistry, was tolerated to a moderate yield of 66% of **10h**.[28] The electron deficient derivative **10i** was selectively formed in 48% yield suggesting no secondary oxidation of the additional nitrogen atom occurred as previously observed by substrate **4l**. The electron-rich derivative **10g** was obtained in 77% yield. Substrate **8j** was converted to the resulting quinoline *N*-oxide **10j** in 82% yield



Scheme 3. Reaction scope of 2-nitro cinnamyl ketones and analogues **8a**–**m**.

bearing an additional phenyl substituent. The heterocycle containing derivative **10k** was isolated in 81% yield indicating a good tolerance for electron-rich heterocyclic substituents. The electron deficient derivative **10l** could also be obtained in 75% yield. Transformation of substrate **8m** gave the corresponding quinoline *N*-oxide **10m** in 34% yield enabling access to polycyclic aromatic quinoline *N*-oxide derivatives.

Following the investigation of the scope of this electrochemical protocol and based on results of earlier work on the reduction of nitro groups, mechanistic studies were conducted by cyclic voltammetry measurements (Scheme 4).[27] Test substrates **4a** and **8a**, as well as the substrate of the 3,4 dihydroquinoline *N*-oxide **4m**, and the quinoline *N*-oxide **6a** were investigated (for detailed information see Supporting Information: Figures S3–S7). Anodic corrosion of lead in the electrolyte containing formic acid results in the passivation of the electrode surface.[29] Therefore, glassy carbon was used as working electrode in CV studies. By recording substrate **4a** two broad reductive and two oxidative waves were observed, suggesting the mechanistic considerations shown in Scheme 4.

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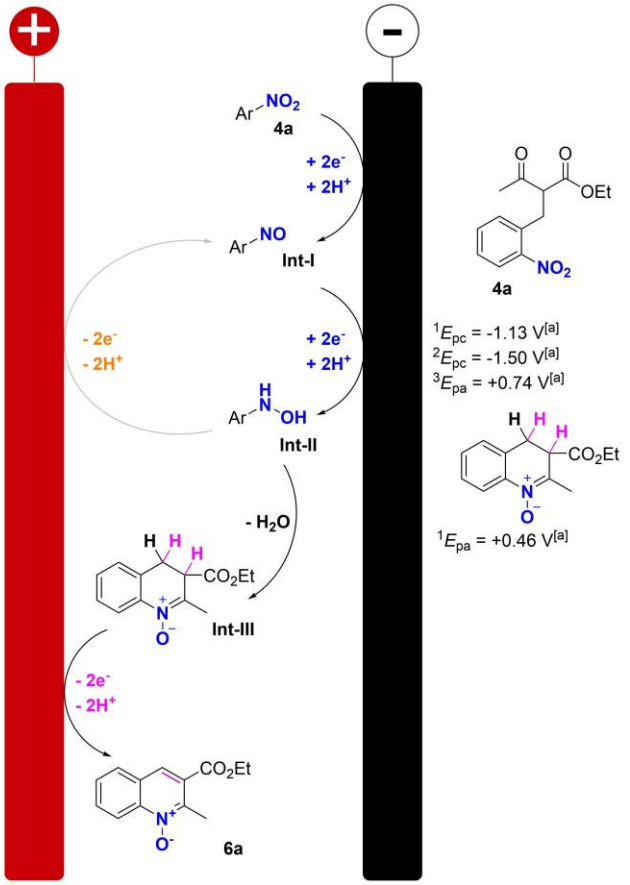


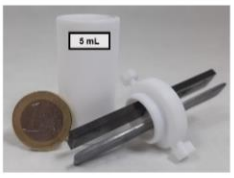
Scheme 4. Proposed mechanism of the electrochemical formation of quinoline *N*-oxides; [a] vs. FcH/FcH$^+$.

The first wave at −1.13 V corresponds to the reduction of the substrate **4a** to the nitroso intermediate **Int-I** by addition of 2e$^-$/2H$^+$, followed by the subsequent reduction at −1.50 V to hydroxylamine **Int-II** by addition of 2e$^-$/2H$^+$.[27] After condensation of the hydroxylamine **Int-II** resulting in the 1-oxy-3,4-dihydroquinoline **Int-III** the final oxidation at +0.46 V by the loss of 2e$^-$/2H$^+$ was observed resulting in the final quinoline *N*-oxide **6a** matching the suggested mechanistic considerations. A second oxidative wave at +0.74 V relates to the reoxidation of the hydroxylamine **Int-II** to the corresponding nitroso intermediate **Int-I** by the loss of 2e$^-$/2H$^+$. In contrast, the substrate **8a** lacks the characteristic oxidative wave at +0.46 V which corresponds to the final oxidation of the 1-hydroxy-1,4-dihydroquinoline in agreement with the proposed mechanism. Interestingly, this oxidation was not observed in the measurement of substrate **4m** matching the isolated 3,4-dihydroquinoline *N*-oxide products **7a** and **7b**. When measuring **6a** a weak reductive wave at −0.83 V was detected matching the decreased selectivity forming **5a** by subsequent reduction of **6a**.

The scale-up of the reaction was performed on test substrate **8a** (Table 3). Quinoline *N*-oxide **10a** was isolated in very good yields of up to 80% in a multi-gram scale set-up with a simple work-up procedure by filtration through silica which shows the high potential of the applied reaction conditions for technical purposes.

ICP-OES measurements revealed 0.86 ppm of lead in the crude product and 0.15 ppm in the final product which highlights the safe use of this method. The measured lead content in the electrolyte of 20 ppm is most likely due to the dissolution of the natural lead oxide layer of the electrode upon immersion

Table 3. Scale-up of the syntheses of **10a** from screening to multigram scale.[b]

Cell	*n*(Substrate) [mmol]	Yield[a] of **10a** [g]
	0.2	0.031 (77%)
	5	0.804 (80%)
	15	2.726 (91%)
	50	8.081 (80%)

[a] Isolated yield; [b] Anode: glassy carbon, cathode: lead, supporting electrolyte: 5 M HCOOH/0.27 M NaHCOO in methanol; j = 4.1 mA cm^{-2}, 5 *F*, 300 rpm, r.t., undivided batch-type cells.

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into the electrolyte and could be completely removed by the work-up procedure (Table 4).

Conclusion

In summary, the reported method provides a simple tool for the preparation of quinoline *N*-oxides by an electro-organic synthesis, with inexpensive reactants and a broad variety of tolerated functional groups. The optimized reaction conditions utilize a simple undivided reaction set up with inexpensive and easily accessible electrode materials. In addition, a sustainable buffer system was applied as supporting electrolyte keeping the cathode stable. The broad scope of the reaction was demonstrated by 30 examples in yields up to 90%. The diversity of the different substrates reveals the high robustness of the reaction conditions and allows for further functionalization of the different products. The technical relevance of the electrolysis conditions was shown on a multi-gram scale of the reaction. Mechanistic studies utilizing CV measurements revealed the selective reduction of the nitro group to the corresponding hydroxylamine, leading to the selective formation of the desired quinoline *N*-oxides.

Experimental Section

General protocol for the electrochemical synthesis of quinoline *N*-oxides: The electrolyte was prepared by dissolving 0.50 mol formic acid and 0.027 mol sodium formate in 100 mL methanol. The corresponding substrate was dissolved in 5 mL of the electrolyte in a 5 mL undivided Teflon® screening cell equipped with a stirring bar. The electrolysis was performed under constant current conditions (current density of 4.1 mA cm^{-2} for 96.5 C (5 *F*)). After 24 h the reaction mixture was dissolved in dichloromethane and washed once with saturated Na_2CO_3 solution (5 mL) and water (5 mL). The aqueous layer was extracted with dichloromethane (3× 10 mL), the combined organic fractions were washed once with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and 0.1 mmol 1,3,5-trimethoxybenzene was added as internal standard for quantification by ^{1}H NMR. Purification was performed using reversed phase flash column chromatography using acetonitrile and water (0.1% v/v formic acid) as eluents.

General protocol for the scale-up of electrochemical synthesis of 10a: The corresponding substrate was dissolved in the electrolyte (5 M formic acid/0.27 M sodium formate in methanol) in the different undivided batch-type cells (50 mL, 100 mL and 250 mL) equipped with a stirring bar. The electrolysis was performed under constant current conditions (current density of 4.1 mA × cm^{-2}, charge applied: 5 *F*). After completion of the electrolysis the reaction mixture was dissolved in dichloromethane and washed once with saturated Na_2CO_3 solution (25 mL) and water (25 mL). The aqueous layer was extracted with dichloromethane (3×50 mL). The combined organic layers were washed once with brine (50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Purification was performed by filtration through silica using cyclohexane:ethyl acetate 2:1 (v:v) to remove impurities. The product was eluted with ethyl acetate:methanol 95:5 (v:v) and obtained by removing the solvent under reduced pressure.

Table 4. ICP-OES measurements of the scale-up electrolysis.

Sample	Work-Up	Pb-contamination
Electrolyte	None	18 ppm
Crude Product	Extraction	0.86 ppm
Product	Filtration through Silica	0.15 ppm

Deposition Number(s) 2207689 (for 6a), 2207689 (for 6e) contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Supporting Information

The Supporting Information (PDF) including detailed optimization studies, experimental procedures, mechanistic studies, crystallographic data and copies of NMR spectra is available in the Supporting materials of this article.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: cyclization · electro-organic synthesis · nitrogen heterocycles · *N*-oxides · reduction

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3.2.2 Direct Reduction of *N*-Acylbenzamides for the Synthesis of 1-Hydroxyquinazolin-4-ones

A manuscript was published on this chapter:

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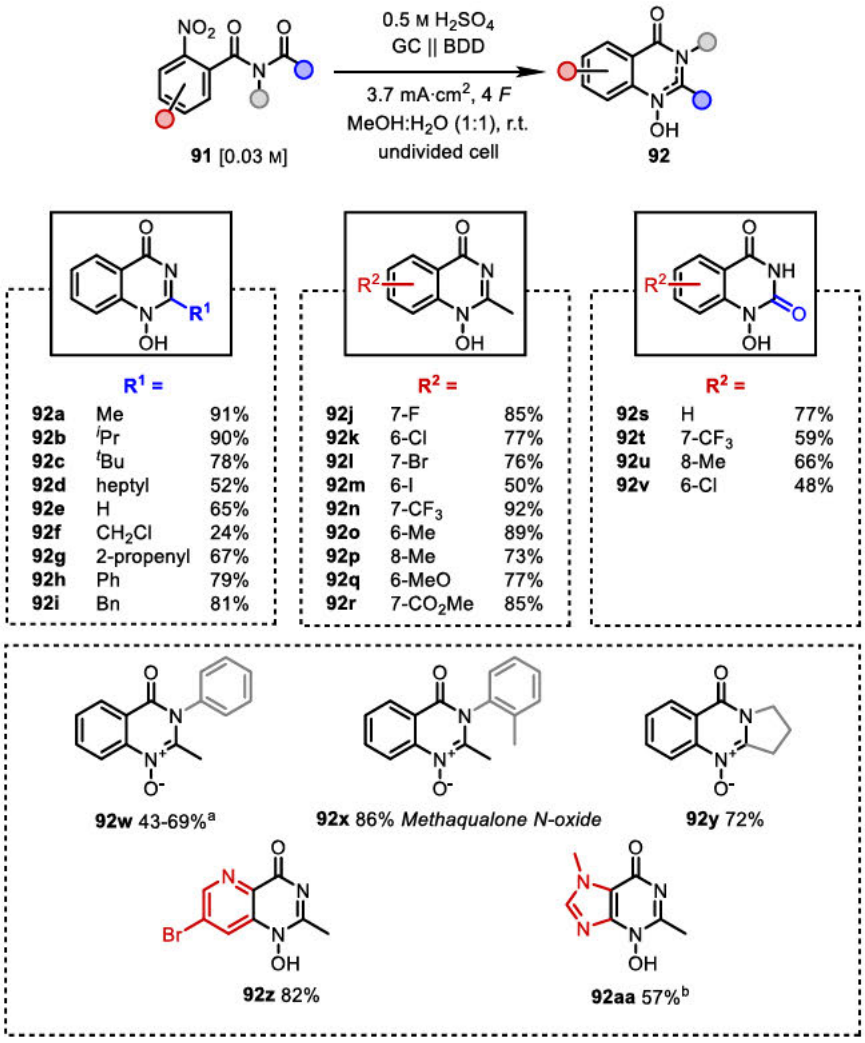
Quinazolin-4-ones are a promising scaffold found in natural products and various drugs like the blockbuster API *Idelalisib* or the hypnotic sedative *Methaqualone*.[167,169–171,173,174,179,180,183,184,187] However, the corresponding 1-hydroxyquinazolin-4-ones have been an unexplored class of N,O-heterocycles so far, that might exhibit similarly interesting pharmaceutical properties. Furthermore, no efficient synthetic route for their selective synthesis has been described in literature. Based on previous work, it was envisioned that 1-hydroxyquinazolin-3-ones could be obtained via direct cathodic reduction of *N*-acyl-2-nitrobenzamides. Reaction optimization was performed using *N*-acetyl-2-nitrobenzamide (**91a**) which is easily accessible in a single step from 2-nitrobenzamide. Based on previous work, the following reaction conditions were chosen for initial investigation: a glassy carbon anode and a BDD cathode were used. The application of carbon-based electrodes instead of metal electrodes avoids contamination of the final products with trace metal impurities. As reported before, sulfuric acid was used in a double role as supporting electrolyte and additive. The solvent system consisted of an environmentally benign mixture of methanol and water. The electrolysis was carried out in a simple undivided set-up under constant current conditions. The amount of applied charge of 4 *F* was based on the theoretically required amount and the current density of 3.7 $mA \cdot cm^{-2}$ was used. To our delight, product **92a** was already isolated in a very good yield of 91% prior to reaction optimization. However, attempts to optimize the reaction further, e. g. variation of the supporting electrolyte, the solvent or the electrode materials, failed and no improvement could be achieved with regards to yield. Nonetheless, glassy carbon as cathode material gave a comparable yield of 90% which

enhances the applicability of the method as glassy carbon is less expensive and more accessible. By increasing the concentration of the substrate **91a** from 0.03 M to 0.10 M the yield dropped to 73%, underlining the importance of low substrate concentrations for the intramolecular cyclization.



Scheme 31: Scope of the direct synthesis of 1-hydroxyquinazolin-4-ones **92** by cathodic reduction of *N*-acetyl-2-nitrobenzamides **91**; [a]variation in yield with repeated electrolysis; [b]isolated yield referring to the acetate adduct.

Whilst exploring the scope of the reaction, it was found that the yield of 1-hydroxyquinazolin-3-ones decreased with an increasing steric demand of the acyl substituent (**92a–d,** 52%–91%). The 1-hydroxyquinazolin-3-ones **92j–n** were obtained in up to 92% yield. Halo-substituents were tolerated well, despite being prone to undergo electrochemical dehalogenation as a common side reaction.[57] The electron-rich derivatives **92o–92q** were obtained in 73%–89% yield. Interestingly, even the 1-hydroxyquinazolin-2,4-diones **92s–92v** could be obtained in yields of up to 77%, underlining the broad applicability of the protocol described. Additionally, the corresponding 1-oxides **92w–y** were obtained by the reduction of *N,N*-disubstituted 2-nitrobenzamides **91w–y**. This allowed for the synthesis of the corresponding *N*-oxide of *Methaqualone*, a drug which is used as a hypnotic sedative (**92x**, 86%). The scalability of the reaction was demonstrated for the synthesis of **92a**. On 7.50 mmol scale the product was obtained in 86% yield (1.13 g) when using the standard concentration of the substrate **91a** of

0.03 M. Surprisingly, doubling the concentration of **91a** to 0.06 M affected the yield of **92a** only slightly (83%, 2.19 g). Furthermore, it was demonstrated that the use of a less expensive glassy carbon cathode on 0.75 mmol scale resulted in a yield of 89% (118 mg) of the desired product **92a** compared to 91% yield (120 mg) when using a BDD cathode. This allows for an easier scalability of the reaction due to the greater availability of glassy carbon compared to BDD. CV studies were conducted to give insides into the mechanism of this reaction. The cyclic voltammetry studies supported the hypothesized mechanism of a stepwise reduction of the nitro arene, which was also observed for the previous electrochemical synthesis of quinoline *N*-oxides.

In summary, a simple yet selective protocol for the synthesis of 1-hydroxyquinazolin-4-ones **92** was developed. The simplest electrochemical set-up was used in combination with carbon-based electrode materials and environmentally benign solvents. The synthesis showed excellent scalability in up to multi-gram scale and a broad scope of 27 examples in up to 92% yield was presented. Furthermore, the method's application potential was demonstrated by the synthesis of drug- and natural product derivatives.[237]

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Simple and scalable electrosynthesis of 1*H*-1-hydroxy-quinazolin-4-ones†

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Cathodic synthesis provides sustainable access to 1-hydroxy- and 1-oxy-quinazolin-4-ones from easily accessible nitro starting materials. Mild reaction conditions, inexpensive and reusable carbon-based electrode materials, an undivided electrochemical setup, and constant current conditions characterise this method. Sulphuric acid is used as a simple supporting electrolyte as well as a catalyst for cyclisation. The broad applicability of this protocol is demonstrated in 27 differently substituted derivatives in high yields of up to 92%. Moreover, mechanistic studies based on cyclic voltammetry measurements highlight a selective reduction of the nitro substrate to hydroxylamine as a key step. The relevance for preparative applications is demonstrated by a 100-fold scale-up for gram-scale electrolysis.

Introduction

Nitrogen containing heterocycles are ubiquitous in pharmaceuticals[1] and biomolecules as core motifs.[2] One particular example is quinazolin-4-ones. Derivatives are present in a variety of drugs and biomolecules with anticancer, diuretic, anti-inflammatory, anticonvulsant, and antihypertensive properties.[3]

Methaqualone (**1**) (Chart 1), known by its brand name Quaalude, is a hypnotic sedative that increases $GABA_A$ receptor activity.[4] The drug was withdrawn from the U.S. market in 1985, primarily because of its psychologically addictive potential, widespread abuse, and illicit recreational use.[5] The medication idelalisib (**2**) (Chart 1) is used to treat certain types of blood cancer and acts as a phosphoinositide 3-kinase inhibitor.[6] This drug alone amounted to a $72 million annual revenue for Gilead Sciences, Inc.[7] The naturally occurring plant alkaloid tryptanthrine (**3**) exhibits a broad spectrum of biological and pharmaceutical activity including antimicrobial, antiviral, anticancer, and antiparasitic properties.[8] In addition, the AstraZeneca anti-metabolite and cytotoxic drug raltitrexed (**4**) is used in chemotherapy treatments. The folic acid analogue acts as a selective inhibitor of thymidylate synthase.[9] Notably, *N*-oxides and *N*-hydroxy derivatives of these pharmaceuticals were found to be metabolites of these drugs.[10,11] However, the therapeutic effects of endocyclic *N*-hydroxy and *N*-oxy compounds have not been researched to the same degree. Considering their metabolic stability and the unique features of the N–O bond, this class of novel compounds are the subject of current pharmaceutical research.[12]

The synthesis of *N*-oxides and *N*-hydroxy derivatives of quinazolin-4-ones is scarce in the literature and the few published examples present various challenges. The synthesis of 1-oxy-2-alkylquinazolin-4-ones was described by Tennant starting from *N*-(1-cyano-alkyl)-2-nitro benzamides (Scheme 1, top).[13] Its base-catalysed cyclisation approach does not require additional

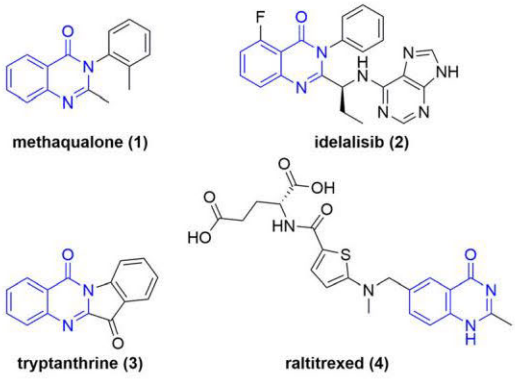

Chart 1 Important biologically active substances with quinazolin-4-one motif.

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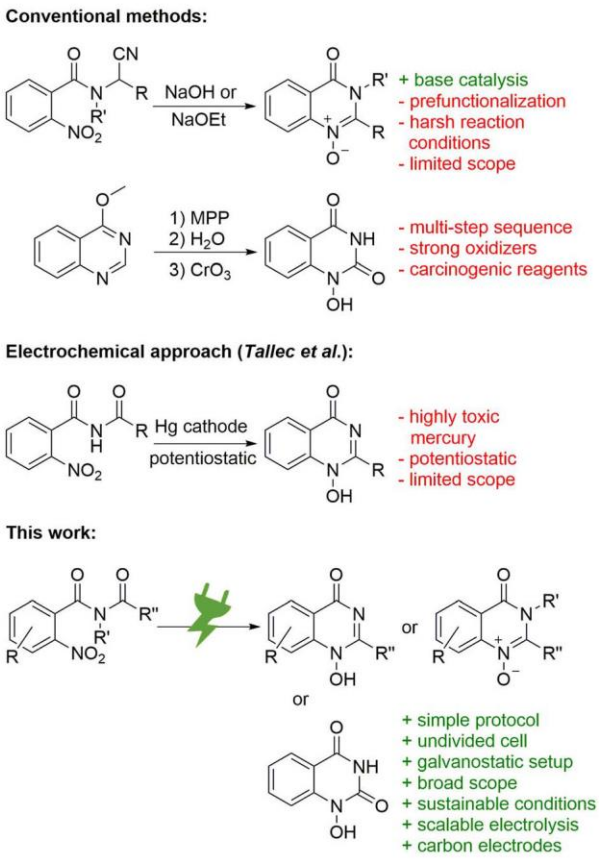


Scheme 1 Synthetic approaches to 1*H*-1-hydroxy-quinazolin-4-ones. MPP = monoperoxyphthalate.

reagents, but does use harsh reaction conditions.[13] The synthesis of 1-hydroxyquinazoline-2,4-diones by Yamanaka comprises a multi-step sequence from 4-methoxyquinazoles and involves two oxidizers: hazardous monoperoxyphthalate for the generation of the 1-oxide and highly toxic chromium(VI) oxide for the oxidation of the C-2 (Scheme 1, top).[14] Reductive cyclisation of nitro precursors is also known, typically *via* hydrogenation with expensive palladium catalysts.[15] In addition, Tallec described an electrochemical synthesis within polarographic studies (Scheme 1, middle). However, highly toxic mercury electrodes were required in a sophisticated potentiostatic reaction setup that was run on a small scale with a limited scope.[16]

Herein, a versatile, scalable, and high-yielding electrochemical reductive cyclisation of widely available, easy to prepare, and inexpensive nitro arenes[17] into 1-hydroxyquinazolin-4-ones is presented. The method uses a simple constant current setup and applies conditions that consider sustainable and environmental aspects (Scheme 1, bottom). In particular, this methodology can easily pay off for high value-added products.[18] The field of electrosynthesis is experiencing a renaissance as an alternative to conventional synthesis protocols[19–21] and is emerging as a key discipline for future synthetic applications.[22] The use of electric current as a reagent enables inherently safe processes by precise control of the reaction. Practically, turning off the electricity immediately stops the conversion and, unlike with traditional reagents, thermal runaway reactions are not possible. The absence of toxic and hazardous reagents and the use of sustainable electricity makes these methods almost waste- and pollutant-free, especially when solvents and supporting electrolytes are reused.[23,24] However, several parameters and counter reactions seem to play a crucial role for success.[25,26] Carbon-based electrode materials such as graphite, glassy carbon (GC), and boron-doped diamond (BDD) are sustainable and widely available.[27] In particular, these are superior in the synthesis of pharmaceuticals or APIs where trace metal impurities must be avoided.[22,28]

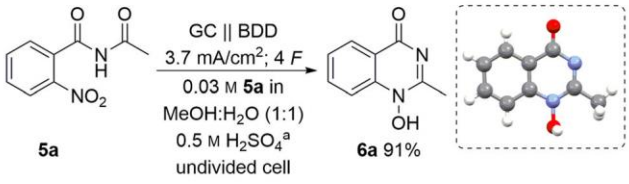
Results and discussion

Optimisation of the electrolysis conditions

Benzamide **5a** was chosen as a test substrate for cathodic reduction of a nitro group, and it was easily synthesised in a single step from commercially available 2-nitrobenzamide by treatment with acetic anhydride in a microwave-assisted acylation reaction or in a pressured vessel approach, both in high yields (see ESI† for detailed description).[29] Based on previous work by the Waldvogel lab, a foundation for the electrochemical conditions for nitro reduction were initially tested (Table 1, entry 1).[30–32]

The starting conditions used a water–methanol mixture (1 : 1 (v/v)) as a green solvent capable of dissolving the nitro compound **5a**. A moderate concentration of sulphuric acid (0.5

Table 1 Screening of electrolysis parameters for the optimisation of the synthesis of 1*H*-1-hydroxy-2-methyl-quinazolin-4-one (**6a**)



Entry	Deviation from standard conditions	Yield **6a**[b]/%
1	None	91% (91%)[c]
2	2.7 mA cm^{-2}	78%
3	5.7 mA cm^{-2}	78%
4	EtOH instead of MeOH	84%
5	MeCN instead of MeOH	71%
6	0.5 M acetate buffer[d]	66%
7	Pb cathode	27%
8	CuSn7Pb15 cathode	0%
9	Pt cathode	0%
10	Graphite cathode	84%
11	GC cathode	90%
12	0.06 M **5a**	85%
13	0.10 M **5a**	73%

[a] Concentration of sulphuric acid in the electrolyte, obtained by using methanol and 1 M aqueous sulphuric acid (1 : 1 (v/v)). [b] Yield of **6a** was determined by ^{1}H NMR spectroscopy using 2,2-dimethylmalonic acid as internal standard. [c] Isolated yield. [d] 0.5 M AcOH/AcONa was prepared with 90 mmol acetic acid and 10 mmol sodium acetate in 100 mL of distilled water and 100 mL methanol. BDD = boron-doped diamond; GC = glassy carbon.

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M) was used as the supporting electrolyte based on previous investigations into the concentration effect of the acidic component on the electrochemical reduction.[16,33] Moreover, it was envisioned that sulphuric acid may play a dual role in the reaction since acidic media should be beneficial for cyclisation after a nitro group reduction. Taking this into account, we examined constant current electrolysis (3.7 mA cm $^{-2}$ current density) of benzamide **5a** in an undivided cell in water–methanol media, using a glassy carbon anode and a boron-doped diamond (BDD) cathode. BDD as a carbon-based material offers unique reactivity towards electrochemical conversion of a multitude of substrates and can be manufactured in a sustainable manner by utilizing methane as carbon source.[34]

To our delight, the desired 1-hydroxyquinazolinone **6a** was isolated in 91% yield. Furthermore, the theoretical amount of charge required for this process (4 *F*) was applied and the high yield obtained shows that this process has a high current efficiency (Table 1, entry 1). The molecular structure of heterocycle **6a** was confirmed by X-ray analysis of a suitable single crystal.

Deviation from the starting electrolysis conditions obtained by electrosynthetic screening resulted in lower yields.[20,21,24,35] Both lower or higher current densities led to a decreased yield of 1-hydroxyquinazolinone **6a** to 78% (Table 1, entries 2 and 3). Replacement of methanol with other solvents such as ethanol and acetonitrile (Table 1, entries 4 and 5) afforded the desired heterocycle **6a** in slightly lower yields of 84% and 71%, respectively. Acetate buffer (Table 1, entry 6) was used as a weaker and biogenic alternative to sulphuric acid; however, the yield of **6a** decreased to 66%. Substitution of BDD as cathode material for lead significantly decreased the yield of **6a** to 27% (Table 1, entry 7). Furthermore, cathodic corrosion was observed resulting in the precipitation of lead salts.

More stable alternatives to lead cathodes such as leaded bronzes[36] (Table 1, entry 8) failed entirely in the formation of **6a**. Platinum was equally unsuccessful as cathode material (Table 1, entry 9), completely avoiding the desired reaction likely due its low overpotential for the hydrogen evolution side-reaction.[37]

Besides BDD, other carbon-based cathode materials such as graphite and glassy carbon provided product **6a** in comparable yields of 84% and 90% (Table 1, entries 10 and 11). Nevertheless, we decided to proceed with BDD due to its sustainability and chemical durability.[38] Electrolysis at higher benzamide **5a** concentrations resulted in lowered yields by up to nearly 20% (Table 1, entries 12 and 13). It is likely that higher concentrations of starting material result in the formation of high molecular weight side products which were observed as a brown plaque after the electrolysis was finished.

Scope of the reductive cyclisation

The broad applicability of the optimised reaction conditions was demonstrated on a versatile scope of substrates (Chart 2). First, we explored the effect of substitution pattern at the C-2 position of quinazolin-4-ones **6b–i** (Chart 2, top). The influence of primary, secondary, and tertiary alkyl substitutions was investigated in the synthesis of heterocycles **6a–c**, resulting in good yields of 78–91%. Here, the *tert*-butyl derivative **6c** with its sterically demanding substituent gave the lowest yield. Furthermore, 1*H*-2-heptyl-1-hydroxy-quinazolin-4-one (**6d**) with a hydrophobic chain was obtained in a moderate yield of 52%.

Both the 2-unsubstituted quinazolin-4-one **6e** and the 2-phenyl analogue **6h** were obtained in moderate to good yields (65% and 79%, respectively). Alkene as well as a benzylic moieties, usually prone to anodic oxidation, were well tolerated in the electrochemical reduction, and the desired heterocycles **6g** and **6i** were obtained in 67% and 81% yield. Interestingly, even the 2-chloromethyl substituted product **6f** was isolated in 24% yield despite its inherent instability.

Next, various functional groups in the aromatic subunit of 1-hydroxyquinazolin-4-ones **6j–r** were tested (Chart 2, middle). In all cases, the products were obtained in good to excellent yields regardless of the substituent's electronic nature. Benzamides with an electron-donating methoxy group and an electron-withdrawing ester moiety afforded the corresponding heterocycles **6q** and **6r** in comparable yields (77% and 85%, respectively). Likewise, the trifluoromethyl derivative **6n** and methyl quinazolin-4-ones **6o** and **6p** were obtained in 73–92% yield.

The 6-methyl derivative **6o** is an *N*-hydroxy analogue of a precursor to raltitrexed (**4**), thus its successful formation adds industrial relevance to this transformation.[39] Halides are redox-active groups in electrochemical reactions. To our delight, fluoro-, chloro- and bromo-substituted quinazolin-4-ones **6j–l** were obtained in 76–85% yield. Moreover, the developed electrochemical method also afforded the iodo-substituted product **6m**, albeit in moderate yield (50%) likely due to its susceptibility to oxidation.

It is noteworthy that heteroaromatic amides such as those derived from pyridines and imidazoles are applicable with the developed conditions (Chart 2, middle left). The pyrido pyrimidinone **6s** was obtained in 82% yield and the bromo substituent offers availability for a variety of post-functionalization reactions. Even the *N*-hydroxy purine **6t** was obtained in a good yield of 57%.

Furthermore, *N*-acetyl-*N*-aryl benzamides were converted into the corresponding *N*-oxy-quinazolin-4-ones **7a** and **7b** in moderate yields, likely due to their tendency to rearrangement reactions (Chart 2, middle right).[40] Interestingly, **7b** is a reported metabolite of methaqualone (**1**).[10] Furthermore, tertiary amides are also suitable as substrates as exemplified by the synthesis of pyrrolidone-based *N*-oxy-quinazolin-4-one **7c** (72%).

Finally, the presented methodology has also been applied to the synthesis of 1-hydroxy-quinazoline-2,4-diones **8a–d** by electrochemical reduction of methyl-(2-nitrobenzoyl)carbamates, which gave up to 77% yield (Chart 2, bottom). Here, the unsubstituted derivative **8a** had the best yield of 77%. The electron-withdrawing trifluoromethyl- and chloro-substituted products **8b** and **8d** were isolated in 59% and 48% yield. The methyl-substituted derivative **8c** was obtained in moderate yield of 66%.

Scale-up of electrolysis

To demonstrate the synthetic utility and scalability of the developed method, the synthesis of 1*H*-1-hydroxy-2-methyl-

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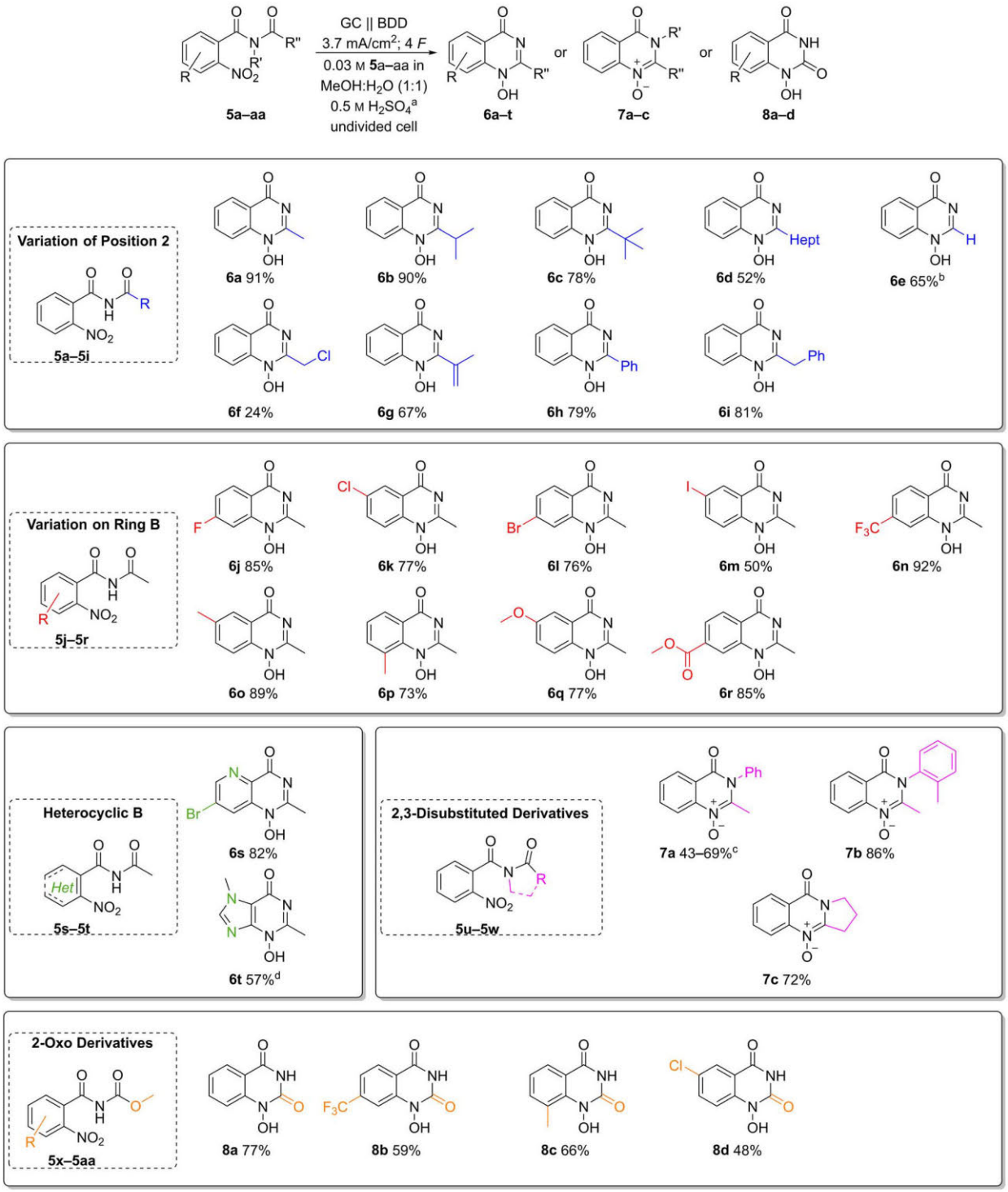

Chart 2 Scope of electrochemical reductive cyclisation and isolated yields. [a] Concentration of sulphuric acid in the electrolyte, obtained by using 12.5 mL methanol and 12.5 mL 1 M aqueous sulphuric acid (1 : 1 (v:v)), undivided 25 mL beaker-type glass cell; [b] isolated yield as formate adduct; [c] variation in yield with repeated electrolysis; [d] isolated yield as acetate adduct.

quinazolin-4-one (**6a**) was successfully scaled up to 15 mmol in a single electrolysis batch (Table 2). The 5-fold scale-up was performed with BDD and GC cathodes to demonstrate the robustness and applicability of the described method. Encouragingly, 20-fold scale-up (3.00 mmol) in a 100 mL electrolysis cell afforded the desired product **6a** without loss in yield or faradaic efficiency. Gram-scale electrolysis was also performed at 7.5 mmol and 15.0 mmol loading in a 250 mL electrolysis cell, affording 1.13 g and 2.19 g of the desired 1-hydroxy-quinazolin-2-one **6a**, respectively. The trend of decreased yield at higher

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Table 2 Scale-up of the electroreduction of 1*H*-1-hydroxy-2-methyl-quinazolin-4-one (**6a**)[a]

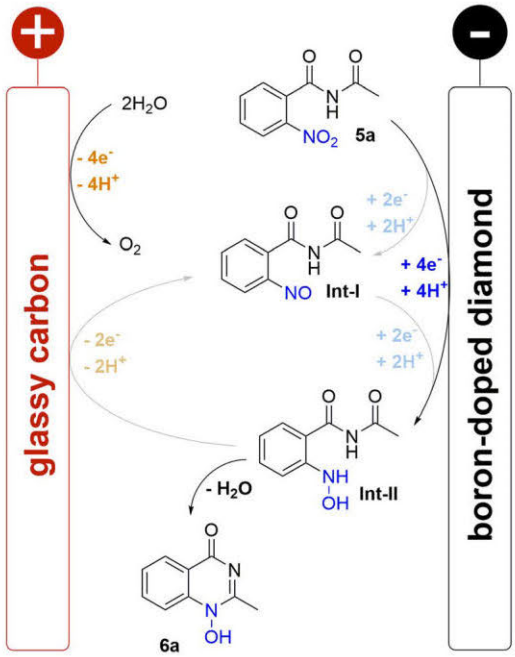
Electrolysis cell	Scale/mmol	Current (electrolysis time)	Yield **6a**
	0.15	5.6 mA (2.9 h)	24 mg (91%)
	0.75 0.75[b]	22.2 mA (3.6 h)	120 mg (91%) 118 mg (89%)
	3.00	22.2 mA (14.5 h)	481 mg (91%)
	7.50 15.0[c]	109.9 mA (7.3 h) 109.9 mA (14.6 h)	1.13 g (86%) 2.19 g (83%)

[a] Constant current conditions; surface areas of the electrodes: 5 mL Teflon™ cell (1.5 cm ^{2}), 25 mL and 100 mL glass cell (6.0 cm^2), 250 mL glass cell (29.7 cm^2). [b] GC cathode. [c] 0.06 M **5a**.

concentrations was also observed in the optimisation results (Table 1, entries 12 & 13).

Mechanistic studies

A plausible mechanism for the electrochemical cyclisation sequence is proposed based on earlier nitro reduction studies and cyclic voltammetry (CV) measurements of benzamide **5a** (Scheme 2; for detailed information see ESI†).[16,31–33] Accordingly, the reactions starts with the reduction of the nitro group on the BDD cathode which is evidenced by a single broad, irreversible wave (−0.94 V *vs.* FcH/FcH$^+$) corresponding to the 4e$^-$/4H$^+$ reduction to the hydroxylamine. It has been previously suggested that the reaction proceeds with two 2e$^-$ steps *via* intermediates **Int-I** and **Int-II**. However, because only one broad wave was observed rather than two distinct or overlapping waves, this suggests one reduction event occurs and that **5a** is reduced directly to **Int-II** The irreversible reduction to **Int-II** indicates a fast cyclisation step as no corresponding oxidative wave was observed. Further reduction of the *N*-hydroxy moiety was not observed for non-cyclised **Int-II** or the product **6a**. The impact of the counter reaction on the electrochemical conversion must also be considered; the oxidation of water at the glassy carbon anode is possibly the main counter reaction.[25] The corrosion of the glassy carbon anode was not observed after electrolysis. There was no indication of the oxidation of methanol, which was only observed under harsh basic conditions in previous studies.[41] Overall, the high performance of the reported method was enabled by the electrochemical stability of the product, the selective reduction to the hydroxylamine, and the fast cyclisation process.



Scheme 2 Proposed mechanism for the reductive cyclisation.

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Conclusions

In summary, the established method provides simple, direct, and sustainable electrochemical access to *N*-hydroxy- and *N*-oxyquinazolin-4-ones by a cathodic reduction sequence. The electrolytic conditions allow for a reproducible transformation in commercially available experimental setups. The simplest undivided cell was operated under constant current with widely available and sustainable carbon-based electrodes and a water–methanol mixture as an environmentally benign solvent. The sulphuric acid additive served a dual role as supporting electrolyte and acidic catalyst. The broad applicability of this method was demonstrated by 27 examples with up to 92% isolated yield. The electrolysis tolerates various functional groups, including electron-withdrawing and -donating, sterically demanding, and redox labile moieties such as bromides and iodides. The *N*-hydroxy analogue precursor of the cytotoxic drug raltitrexed was obtained in 89% yield. Selective nitro reduction to the hydroxylamine was confirmed by CV measurements to be a key step in the mechanism. The scalability of this electrochemical protocol was demonstrated by multigram-scale electrolysis.

Data availability

The ESI is available and contains experimental and analytical data.

Author contributions

O. K., T. P. and J. W. contributed equally. T. P. and S. W. conceived the idea of the research. O. K., T. P., J. W. and T. H. designed and carried out the batch electrolysis experiments and analysed the data. M. G. and T. P. designed and analysed the cyclic voltammetry measurements. D. S. performed the X-ray analysis and structural elucidation of the synthesised test substrate. T. P., O. K., J. W., and S. W. wrote the manuscript. S. W. supervised the project and E. S. and S. I. reviewed and edited the manuscript. All authors discussed the results and agreed to the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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3.2.3 Selective and Scalable Synthesis of the Novel Class of 4*H*-4-Hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxides

A manuscript was published on this chapter:

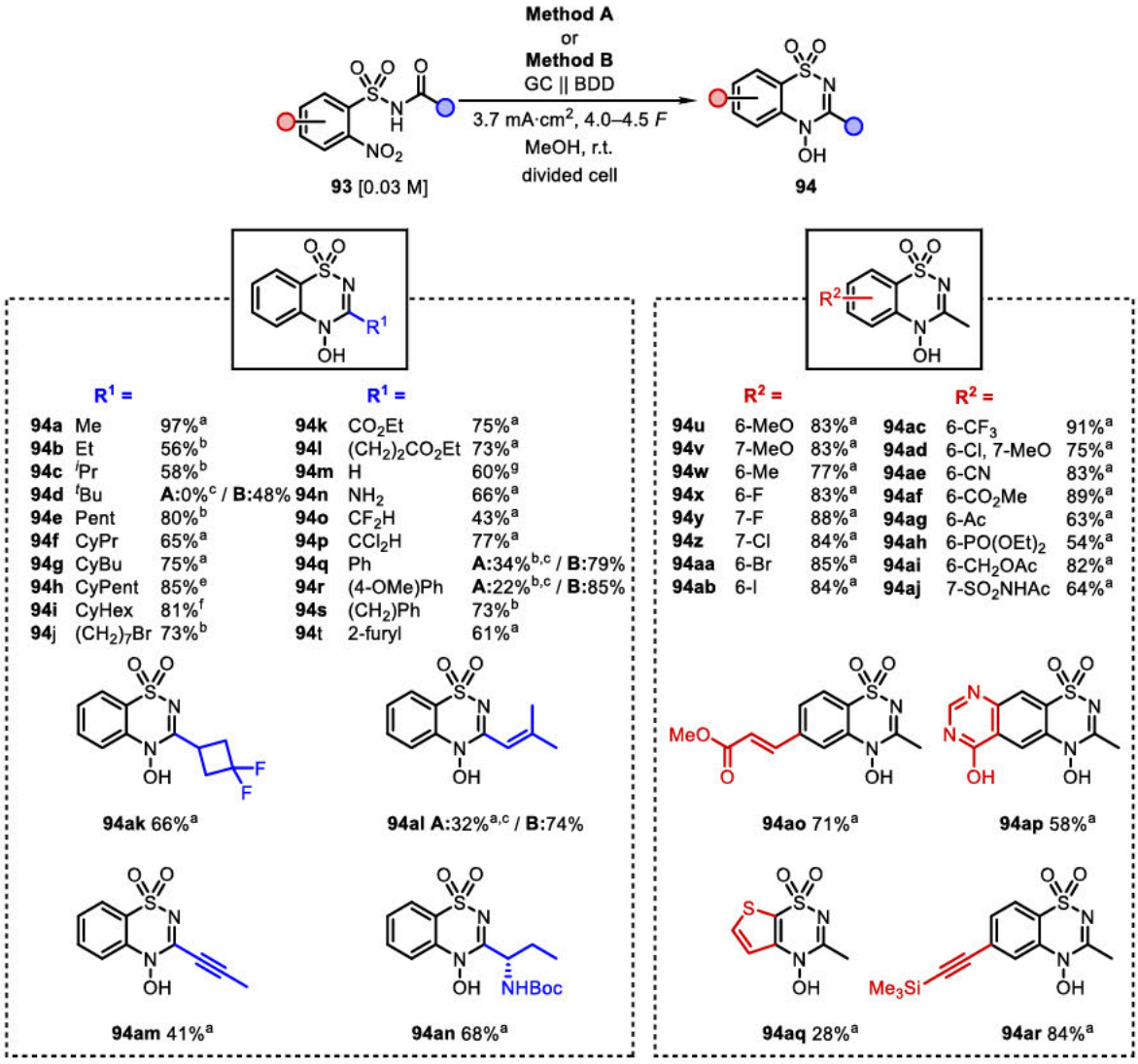
[redacted], *Highly Selective, Scalable Electrosynthesis of 4H-4-Hydroxybenzo[e]-1,2,4-thiadiazine-1,1-dioxides*, *Cell Rep. Phys. Sci.* **2024**, *5*, 101927.

[redacted]

[redacted]

[‡]The authors contributed equally.

Following the synthesis of 1-hydroxyquinazolin-3-ones, it was envisioned that 4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxides could be obtained in a similar manner. The corresponding deoxygenated benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides are an established motif found in blockbuster pharmaceuticals and drug candidates.[200,201,203,205,206,210,215] However, the 4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxides have so far been described only once as a side product.[218] As previously reported, the electrochemical reduction of easily accessible nitro arenes offers a sustainable and simple synthetic strategy for access to these compounds. The optimization was performed using *N*-acyl-2-nitrobenzenesulfonamide **93a** in a concentration of 0.03 M, using methanol as solvent and sulfuric acid as supporting electrolyte. Based on previous studies, the following initial reaction conditions were chosen: A glassy carbon anode and a BDD cathode, a current density of 8.2 mA·cm^{-2} and the theoretical amount of applied charge of 4 *F*. Hence, product **94a** was obtained in a yield of 36%. The most significant increase in yield was achieved while performing the electrolysis in a divided cell, using a simple glass frit as separator. Product **94a** was obtained in yields of in 71–78% yield at current densities of 2.0–10.4 mA·cm^{-2}. Finally, by using 0.5 M ammonium formate as supporting electrolyte and 1.0 M trifluoroacetic acid (TFA) as additive in the cathode compartment, the product **94a** was obtained in an isolated yield of 97% using a current density of 3.7 mA·cm^{-2}. The addition of TFA proved crucial for promoting the cyclo-condensation, since otherwise solely the intermediary formed hydroxylamine was detected by LC-MS. After optimization of the electrolytic conditions, the scope of the reaction was investigated (Scheme 32).



Scheme 32: Scope of 4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxides **94** by cathodic reduction of *N*-acetyl-2-nitrobenzenesulfonamides **93** on 5 mL (0.15 mmol) scale; [a] 1 M TFA, 4.0 *F*; [b] 2 M TFA, 4.0 *F*, [c] 4 *F*; [d] microwave-assisted cyclo-condensation (50 W, 10 min, 100 °C); [e] 2 M TFA, 4.5 *F*; [f] 2.5 M TFA, 4.0 *F*; [g] 0.4 mL TFA added after electrolysis, 4.0 *F*; method **A:** supporting electrolyte 0.5 M NH_4HCOO+1.0–2.5 M TFA; method **B:** supporting electrolyte 0.5 M H_2SO_4.

First, the acyl motif of the *N*-acyl-2-nitrobenzenesulfonamide (**93a–t, 93ak–an**) was varied. The ethyl and isopropyl-substituted products (**94b** and **94c**) were obtained in 56% and 58% yield, respectively. However, the *tert*-butyl substituted compound **94d** could not be obtained applying the optimized conditions (electrolytic protocol A), as only the hydroxylamine intermediate was detected by LC-MS. However, switching the supporting electrolyte to 0.5 M sulfuric acid in methanol proved to be sufficient for achieving the cyclization, granting access to **94d** in 48% yield (electrolytic protocol B). The increasing steric demand of the acyl group highly influences the cyclo-condensation, necessitating the use of stronger acids or higher TFA concentrations to enforce the cyclization. Surprisingly, the cycloalkyl-substituted derivatives **94f–i** were obtained in up to 85% yield. Even the corresponding 3-unsubstituted compound **94m** was obtained in 60% yield by adding the TFA after electrolysis to avoid deformylation during electrolysis. Moreover, the established route enables access to medicinally relevant structural

motifs. An example is difluoromethyl-substituted **94o** which was isolated in 43% yield. The low yield can be explained by formation of the deacetylated sulfonamide which was detected as the only byproduct via LC-MS. When applying conditions **A**, aryl-substituted derivatives **94q** and **94r** were only converted to the corresponding only hydroxylamines. Nonetheless, the cyclization could be enforced by adding 2.0 M TFA to the electrolysis and treating the reaction mixture with microwave radiation post-electrolysis to obtain the corresponding products **94q** and **94r** in 34% and 22% yield, respectively. However, by applying the electrolytic protocol B using 0.5 M sulfuric acid as supporting electrolyte, the products **94q** and **94r** were isolated in 79% and 85% yield. Access to the corresponding 3-(2-furyl) derivative **94t** was achieved in the same manner (61% yield), while this compound was not accessible by the electrolytic protocol A. Even **94an,** bearing a stereocenter was isolated in 68% yield and no racemization was observed despite the acidic reaction conditions.

Next, the impact of the variation of the nitro arene was investigated. The electron-rich derivatives **94u**–**w** were isolated in 77%–83% yield. Furthermore, the electron-poor halo-substituted compounds **94x**–**ad** could be obtained in up to 91% yield. Additionally, carbonyl functions **94ae–ag**, phosponic acid esters **94ah**, heterocycles **94ap** and **94aq** and *N*-acylsulfonamides **94aj** were tolerated and isolated in yields of up to 89%, underlining the high selectivity of this electrolytic protocol. **94a** and **94z** were used for studying the scalability towards technically relevant scale. To our delight both products were obtained in 92% (**94a**, 1.76 g) and 91% (**94z**, 2.01 g) yield. The purification of the crude products was achieved by a simple crystallization. To our delight, the outstanding yields could be maintained over a wide concentration range from 0.03 M – 0.06 M for the synthesis of **94a**, underlining the reaction's robustness.

A reaction mechanism was proposed based on previous considerations as well as CV-studies. Additionally, the effects of different TFA concentrations were investigated, demonstrating a shift towards increased positive redox potentials with increasing TFA concentrations promoting the reduction of the nitro motif. The corresponding products showed no oxidation or reduction under the reaction conditions. A comparison of electrolytic conditions A and B for the synthesis of **94q** showed that sulfuric acid results in increased positive reduction potentials compared to TFA, which further enhances the reduction of the nitro group.

In summary, a simple and selective electrolytic protocol was developed, granting direct access to the novel class of 4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1 dioxides. The method featured a great functional group tolerance and allowed for the synthesis of these compounds in up to multi-gram scale. Thus, this synthetic protocol could pave the path for the direct electrochemical synthesis of medicinally-relevant compounds.[238]

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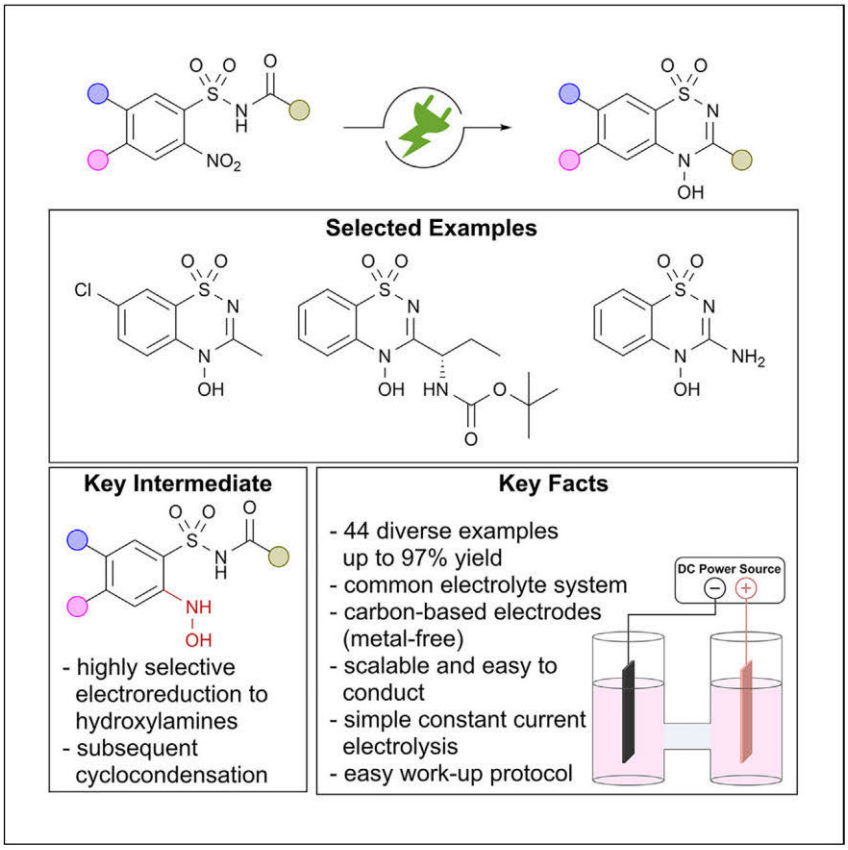
Highly selective scalable electrosynthesis of 4-hydroxybenzo[e]-1,2,4-thiadiazine-1,1-dioxides



Winter et al. report a versatile electrosynthesis for 4-hydroxybenzo[e]-1,2,4-thiadiazine-1,1-dioxides starting from easily accessible nitrobenzene sulfonamides. The electro-synthetic protocol is demonstrated on more than 40 diverse examples in up to 97% yield, and its practicability and technical relevance are underlined by multi-gram-scale synthesis of potential drug metabolites.

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Highlights

Electrochemical synthesis of 44 examples with up to 97% yield

Potential API metabolites involving *N*-hydroxyl modification

Selective reduction to hydroxylamines and acid-catalyzed cyclization as key steps

Technical relevance demonstrated by scalability and simple work-up protocol

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Highly selective scalable electrosynthesis of 4-hydroxybenzo[e]-1,2,4-thiadiazine-1,1-dioxides

Johannes Winter,[1,4] Tobias Prenzel,[1,4] Tom Wirtanen,[1,4] María de Jesús Gálvez-Vázquez,[1] Kamil Hofman,[1] Dieter Schollmeyer,[1] and Siegfried R. Waldvogel[1,2,3,4,5,*]

SUMMARY

4*H*-4-Hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxides are based on a widely found structural motif for pharmaceutical applications, having an additional unique exocyclic N–O bond that is not accessible by conventional synthetic routes. Electrochemistry offers a sustainable tool for the direct synthesis of these heterocyclic structures containing this *N*-hydroxy modification. Here, we report a highly selective synthesis of 4*H*-4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxides by direct reduction of widely available nitro arenes in almost quantitative yields. The electro-synthetic protocol is applied to more than 40 diverse examples, highlighting the versatility of this method. Furthermore, the technical relevance is demonstrated by two multi-gram-scale syntheses.

INTRODUCTION

Nitrogen-containing heterocycles play a crucial role in a broad variety of drugs and natural products.[1] Benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides resemble an evolving motif of modern blockbuster pharmaceuticals. They are found in candidates for new anti-cancer and anti-parasitic drugs and medications of neurodegenerative diseases. *Diazoxide* (Figure 1, **1**) is widely used in the therapy of hypoglycemia and is listed as an essential medicine by the World Health Organization since 2019.[2,3] Metabolic diseases are a major challenge in modern societies. Hence their treatment is a significant topic of the pharmaceutical industry.[4] Furthermore, benzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (Figure 1, **2**) has been investigated as potential drug against *Leishmania major*, which causes severe parasitic diseases in tropical countries. The narrow therapeutic window of most anti-leishmanial drugs used results by avoiding adverse side effects during treatment with established drugs.[5] Therefore, fast synthetic approaches to analogs are desperately required. By modulating glutamate receptors with a series of new benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides (Figure 1, **3**) the improved activity offers an innovative treatment of Alzheimer's disease and epilepsy.[6] Studies on the effectiveness of benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides (Figure 1, **4**) as anti-cancer agents related to *Idelalisib* shows promising results in the selective inhibition of the phosphoinositide 3-kinase δ in the treatment of leukemia.[7] The high affinity of benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides to glutamate receptors is further used in new radioligands by ^{11}C labeling for the detection of Alzheimer's disease (Figure 1, **5**).[8] In contrast to the importance of nitrogen-containing heterocycles in drug development, only little is known about the synthesis and biological properties of their corresponding *N*-hydroxy derivatives. The high stability of these compounds and the unique features of the N–O bond result in exclusive properties for this novel class of heterocycles,[9] which are assumed to be comparable to those of quinolines,[10] quinolones,[11,12] quinazolines,[13] indoles,[14] and benzoxazinones.[15] In

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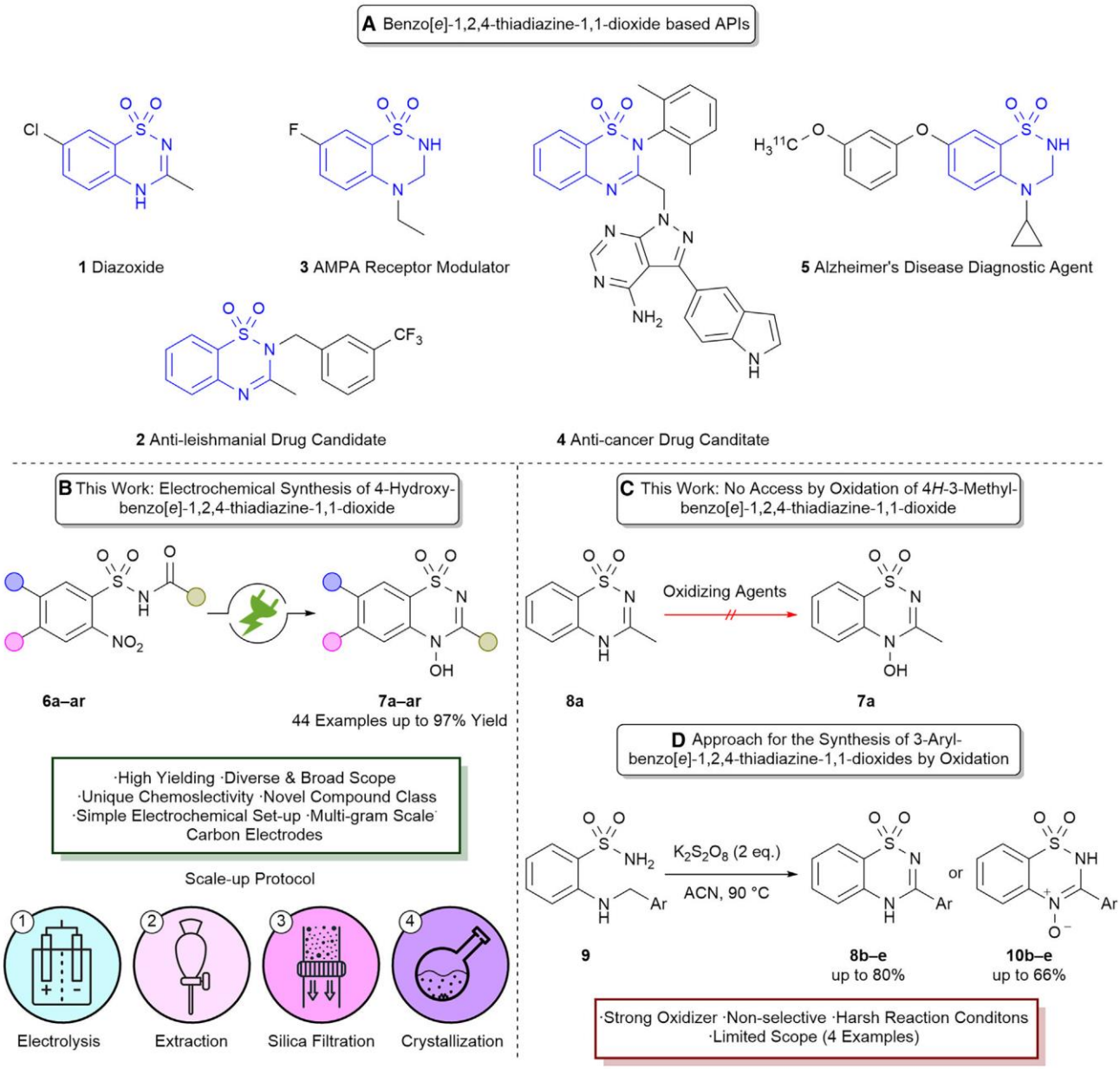


Figure 1. Overview of benzo[e]-1,2,4-thiadiazine-1,1-dioxides

(A) Examples for benzo[e]-1,2,4-thiadiazine-1,1-dioxide-based drug candidates.

(B) Electrochemical synthesis of 4H-4-hydroxybenzo[e]-1,2,4-thiadiazine-1,1-dioxides.

(C) Approaches for the oxidation of 3-methylbenzo[e]-1,2,4-thiadiazine-1,1-dioxide by common oxidants.

(D) Oxidation of 2-(benzylamino)benzenesulfonamides to 2H3 arylbenzo[e]-1,2,4-thiadiazine-1,1,4-trioxides.

addition, *N*-oxy heterocycles are often found as the main metabolites of such drugs. These metabolites can show a higher biological activity toward the target, which underlines the importance of exploring these compounds.

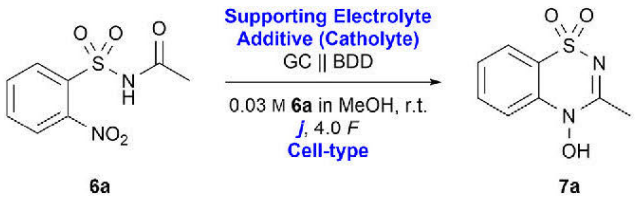
Currently, there is no protocol established for the selective synthesis of 4-hydroxy-benzo[e]-1,2,4-thiadiazine-1,1-dioxides. Common synthetic strategies for the synthesis of heterocycles containing exocyclic N–O bonds involve the selective reduction of

the corresponding nitro arenes using palladium catalysts or equimolar amounts of metals as reducing agents.[16] Additionally, a conventional route for accessing *N*-oxy heterocycles employs the late-stage functionalization of the heterocycle by equimolar amounts of oxidizer. However, none of these strategies is reported for benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides **8**. Furthermore, conventional approaches involve large amounts of reagents and harsh reaction conditions and generate huge quantities of reagent waste.[17–19] Patel et al. describe the formation of 2*H*-3-aryl-benzo[*e*]-1,2,4-thiadiazine-1,1,4-trioxides by the oxidation of 2-(benzylamino)-benzenesulfonamides using potassium peroxosulfate.[20] The reported method reports access to benzo[*e*]-1,2,4-thiadiazine-1,1,4-trioxides (4 examples, **10b–e**) as well as benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides (4 examples, **8b–e**) under the same conditions providing no rationale for the unselective oxidation.[20] As the environmental crisis is a major challenge for the chemical industry, electrochemistry is experiencing a renaissance.[21–29] By using electric current as an inherently safe reagent, electrochemical processes can be precisely controlled.[30] The reaction can be stopped by switching off the electricity, preventing a thermal runaway of the reaction. Furthermore, hazardous reagents and the generation of large amounts of reagent waste can be avoided. In fact, by using electric current from sustainable sources, electrochemical methods can be considered almost free from waste and pollutant.[31] The precise control by electrochemical parameters results in an exceptional selectivity toward the synthesis of several nitrogen heterocycles containing exocyclic N–O bonds.[32–35] Consequently, electrosynthesis is considered as a key discipline in the modern chemist's toolset. A simple, versatile, and scalable method for the high-yielding, selective synthesis of 4*H*-4-hydroxy-benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides has been established by the reductive cyclocondensation of widely available nitro arenes. This offers an easy and direct access to this novel class of compounds for further investigations on their biological activity as possible drug candidates.[34–39] By using constant current conditions, the simplicity of the method is highlighted. The utilization of heavy metal electrodes, which are often used in cathodic reduction due to their high overvoltage for the hydrogen evolution reaction, is avoided, preventing toxic contamination by cathodic corrosion.[40] Carbon-based electrode materials are used, which are known to be sustainable and environmentally friendly and allow the application in the late-stage production of pharmaceuticals.[41–44]

RESULTS AND DISCUSSION

Optimization of the electrolytic conditions

N-Acetyl-2-nitrobenzenesulfonamide **6a** was synthesized in a single step starting from commercially available 2-nitrobenzenesulfonamide (up to 97% yield; see General protocols; Schemes S1–S5 in the supplemental information) and was chosen as the test substrate for optimization (for further details see Optimization of the electrolytic conditions; Tables S2 and S3 in the supplemental information). The initial electrolytic conditions (Scheme 1; Table 1) were taken from previous results of the *Waldvogel lab*.[32] 0.5 M sulfuric acid serves in a dual role as supporting electrolyte for the electrolysis and as catalyst for the subsequent cyclocondensation, yielding the desired product **7a**. The undivided cell and constant current mode provide the simplest electrolytic reaction setup. Glassy carbon was chosen as the anode material, while boron-doped diamond (BDD) was used as cathode material. BDD as an innovative carbon-based electrode material exhibits a unique reactivity and selectivity toward the reduction of various nitro arenes.[42,45,46] The manufacturing of BDD electrodes fulfills several aspects of sustainability by using methane as renewable carbon source. Methanol as a green solvent was used. The theoretical amount of applied charge (4 *F*) for reduction of the nitro arene to the corresponding hydroxylamine was used.



Scheme 1. Optimization of the electrolytic conditions of the synthesis of 7a

The current density of 8.2 mA·cm ^{2} was chosen based on previous work (Table 1, entry 1). By applying these conditions, the desired product was detected in 36% yield (qNMR, Table 1, entry 1). The product was isolated, and the structure was unequivocally confirmed by X-ray analysis of a suitable single crystal. This molecular structure as 4*H*-4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxides **7a** is in conflict with the tautomeric 2*H*-3-arylbenzo-1,2,4-thiadiazine-1,1,4-trioxides **10b–e** reported by Patel et al.[47] The molecular structure determined with X-ray analysis clearly shows that **7a** is the preferred tautomer. Furthermore, the bond lengths and dihedral angle match well with DFT-optimized geometry (PBE0/def2-TZVP/C-PCM(methanol)) of **7a** and disagree with the alternative tautomer **10**. In addition, ΔG differences of 10.9 kcal mol ^{1} further indicate that **7a** is the preferred tautomer (see Computational methods and analysis in the supplemental information).

The electrolytic conditions were optimized by linear screening. A divided setup prevents oxidative side reactions of intermediates by separating the cathodic from the anodic compartment with a simple glass frit. Additionally, a lower current density of 5.2 mA·cm ^{2} was chosen to suppress the formation of the fully reduced 4*H*-3-methyl-benzo[*e*]-1,2,4-thiadiazine-1,1-dioxide. To our delight, these varied conditions (Table 1, entry 4) increased the yield dramatically to 76%. The yield could not be increased significantly by lowering (Table 1, entries 2 and 3) or increasing the current density (Table 1, entry 5). Moreover, by applying a higher current density, an increased formation of the fully reduced product was observed by liquid chromatography-mass spectrometry (LC-MS) analysis. Formate as supporting electrolyte gave excellent results in previous works.[33] 0.5 M ammonium formate in methanol served as supporting electrolyte in both compartments of the electrolysis cell, and 1.0 M trifluoroacetic acid (TFA) was added to the cathodic compartment to promote the cyclocondensation of the intermediate generated. The combination of formate as supporting electrolyte and TFA as additive gave 85% of the product (Table 1, entry 6). By lowering the current density to 3.7 mA·cm ^{2}, the desired product **7a** was isolated in 97% yield (Table 1, entry 7). Higher current densities result not only in a lower yield but also led to a decrease in selectivity of the nitro reduction, which ultimately results in a complex impurity profile due to undesired side reactions of intermediates occurring in the reduction.[48] When increasing the concentration to 0.06 M, the yield dropped to 62% (Table 1, entry 8). Intramolecular cyclocondensation is promoted at lower concentrations and suppresses possible intermolecular side reactions. If no TFA was added in the catholyte, no cyclocondensation occurred, and no product was detected (Table 1, entry 9). Lowering the supporting electrolyte concentration to 0.4 M decreased the yield to 88% (Table 1, entry 10). Methanesulfonic acid was tested as an alternative to TFA, which can be obtained by electrochemical methods directly by reacting methane and oleum.[49] Furthermore, mesylates are often found in approved drugs to modulate their physiochemical properties.[50] However, addition of methanesulfonic acid to promote the cyclocondensation resulted in a significant drop of the yield to <70% (Table 1, entries 11 and 12). Further alternatives, such as acetic acid or formic acid, did not catalyze

Table 1. Optimization of the electrolytic conditions

Entry	Supporting electrolyte	Additive (catholyte)	Cell type[a]	Current density [mA•cm^{-2}]	Yield[b] [%]
1	0.5 M H_2SO_4	–	undivided	8.2	36
2	0.5 M H_2SO_4	–	divided	2.0	71
3	0.5 M H_2SO_4	–	divided	3.7	52
4	0.5 M H_2SO_4	–	divided	5.2	76
5	0.5 M H_2SO_4	–	divided	10.4	78
6	0.5 M NH_4HCOO	1.0 M TFA	divided	5.2	85
7	0.5 M NH_4HCOO	1.0 M TFA	divided	3.7	97[b]
8	0.5 M NH_4HCOO	1.0 M TFA	divided	3.7	65[c]
9	0.5 M NH_4HCOO	–	divided	5.2	0
10	0.4 M NH_4HCOO	1.0 M TFA	divided	3.7	88
11	0.5 M NH_4HCOO	1.0 M MSA	divided	3.7	64
12	0.4 M NH_4HCOO	1.0 M MSA	divided	3.7	65

[a]Yield determined by ^{1}H NMR analysis (internal standard: 1,3,5-trimethoxybenzene).
[b]Isolated yield.
[c]Substrate concentration: 0.06 M; GC = glassy carbon; BDD = boron-doped diamond; TFA = trifluoroacetic acid; MSA = methanesulfonic acid.

the cyclocondensation of the hydroxylamine with the carbonyl moiety of the *N*-acylated sulfonamide. This is consistent with literature reports considering the importance of TFA in condensation reactions mostly reasoned by its pk_a.[51,52]

Scope of the reductive cyclocondensation

The optimal conditions were used to explore the applicability of the reaction regarding functional group tolerance.

Initially, the acyl moiety of the sulfonamides was varied to investigate the influence of the electronic and steric effects on the selective formation of the desired 4*H*-4-hydroxy-benzo[e]-1,2,4-thiadiazine-1,1-dioxides (Figure 2). The corresponding ethyl derivative **7b** was obtained in 56% yield. The sterically more demanding isopropyl derivative **7c** was obtained in 58% yield. The bulky *tert*-butyl derivative **7d** was initially not obtained following the general protocol of the electrochemical synthesis GP-A. Furthermore, only the intermediately formed hydroxylamine was detected via LC-MS, and its cyclocondensation could not be enforced by treating the catholyte by microwave irradiation. Following general protocol general protocol of the electrochemical synthesis (GP-B), the desired product **7d** was finally obtained in 48% yield, allowing the access to bulky functional groups by this method. This indicates the importance of the used acid in the cyclocondensation of the intermediate. The 3-(2-methyl-prop-1-en-1-yl)-substituted **7e** was at first isolated in 32% yield after treatment by microwave irradiation for cyclocondensation. If the conditions of GP-B were applied, the yield increased to 74%, which highlights the tolerance of alkenes that commonly undergo polymerization reactions if not stabilized. The pentyl-substituted **7f** was obtained in 80% yield. The cycloalkyl-substituted **7g** and **7h** were isolated in 65% and 75% yield. **7i** bearing a *gem*-difluorocyclobutane substituent was obtained in 66% yield. 3,3-Difluorocyclobutane substituents are used as bioisosteres for cyclohexyl motifs and are widely used in medicinal chemistry.[53,54] Surprisingly, the bulky cyclohexyl- and cyclopentyl-substituted **7j** and **7k** were obtained in 85% and 81% yield. With increasing sterically requirements of the corresponding substituents, higher TFA concentrations were required for the completion of the cyclocondensation. **7l** having a 7-bromoheptyl substitution was obtained in 73% yield. Usually, alkyl bromides are sensitive to hydrolysis and substitution, which was not observed in this case, highlighting the versatility of the method for labile groups.

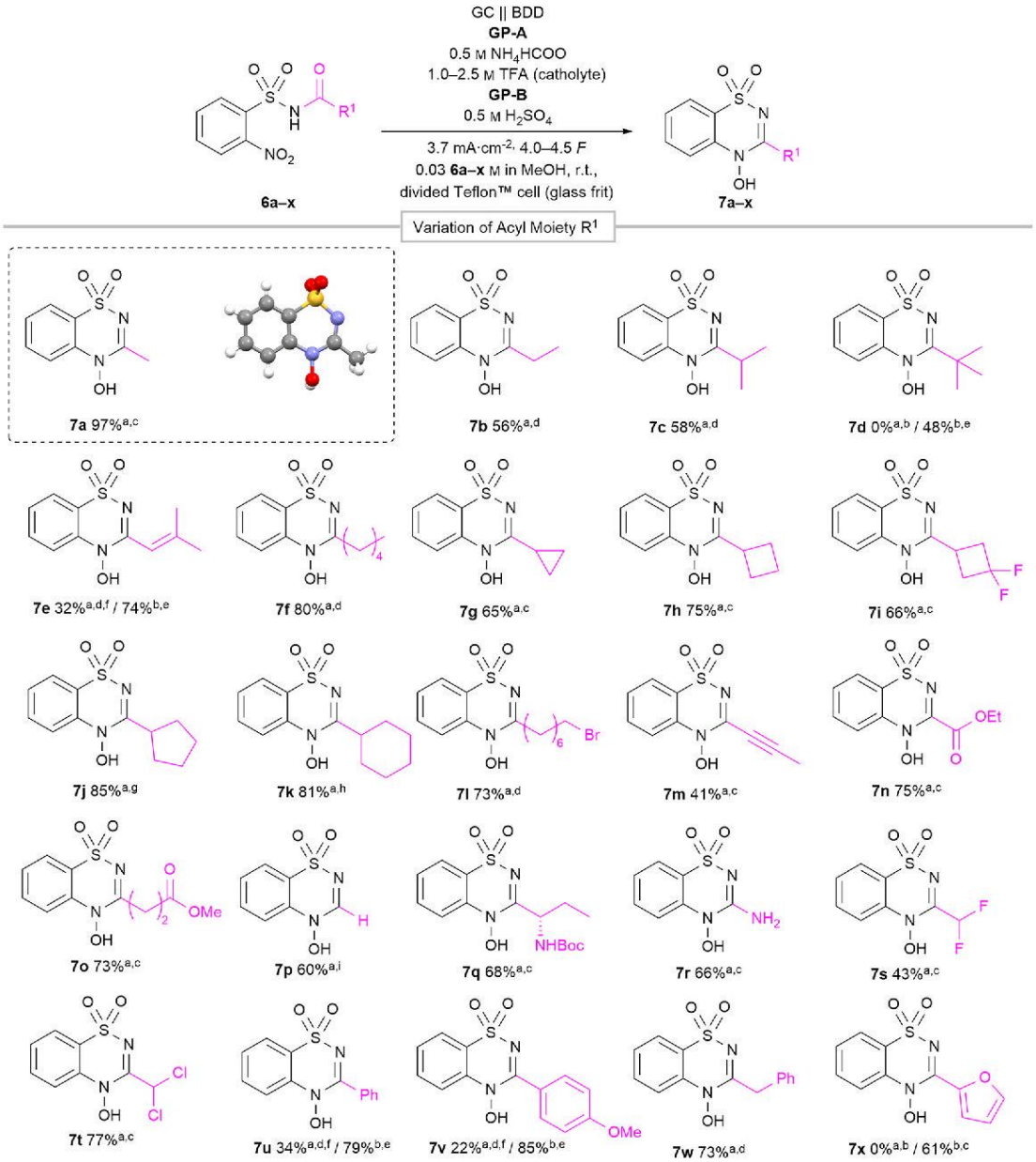


Figure 2. Scope of electrochemical reductive cyclocondensation of *N*-acylbenzenesulfonamides by diverse variation of the acyl motif

(A) Isolated yield using electrolysis method GP-A.

(B) Isolated yield using electrolysis method GP-B.

(C) 1 M TFA, 4.0 *F*.

(D) 2 M TFA, 4.0 *F*.

(E) 4 *F*.

(F) Microwave-assisted cyclocondensation (50 W, 10 min, 100°C).

(G) 2 M TFA, 4.5 *F*.

(H) 2.5 M TFA, 4.0 *F*.

(I) 4.0 *F*, TFA (0.4 mL) added after electrolysis.

Alkynes show a special reactivity toward cycloadditions, for example, in the synthesis of isoxazoles and triazoles.[55] **7m** bearing a prop-2-yne was isolated in 41% yield and allows further functionalization toward five-membered heterocycles. The esters **7n**

and **7o** were isolated in 75% and 73% yield. The non-substituted **7p** was obtained in 60% yield; however, the TFA must be added after electrolysis to suppress the hydrolysis of the starting material. The Boc-protected **7q** was isolated in 68% yield containing an unnatural amino acid. Additionally, no deprotection of the amino function and only the (*S*)-enantiomer were detected, underlining the selectivity of this method toward functionalized heterocycles with bioactive moieties. Cyclocondensation with a carbamimidic azide resulted in the amino-substituted **7r** that was isolated in 66% yield. The cyclocondensations with carbonyl analogs demonstrate the versatility of this method by extending the substrate spectrum with incorporation of heteroatoms in position 3. Difluoromethyl motifs are widely used in medicinal chemistry as lipophilic hydrogen donors. **7s** was isolated in 43% yield bearing a difluoromethyl moiety.[56] The analog dichloromethyl **7t** was isolated in 77% yield. The decreased yield of **7s** was a result of the hydrolysis of the starting material, which was detected via LC-MS. The phenyl-substituted **7u** was isolated in 34% yield by the general protocol GP-A and treatment of the catholyte in the microwave. By using sulfuric acid as supporting electrolyte according to GP-B, the yield was increased to 79%. According to this strategy, compound **7v** was isolated in 85% yield by GP-B compared to 22% by protocol GP-A and subsequent treatment of the catholyte in the microwave. The benzyl-substituted **7w** was isolated in 73% yield. The product formation occurred without the use of the microwave, which indicates a higher reactivity of non-conjugated carbonyl functions. Even the heterocyclic-substituted **7x** was isolated in 61% yield by applying the general protocol GP-B. This feature of the methodology highlights the high functional group tolerance. Overall, the substitution pattern in position α to the carbonyl moiety has the largest influence on cyclocondensation of the intermediately formed hydroxylamine. By varying the acid concentration or strength, a large variety of substituents in position 3 were installed.

After exploring the impact of the acyl motif, the arene core (Figure 3) was varied to investigate the functional group tolerance and electronic effects onto reduction of the nitro group. Both electron rich, **7y** and **7z** having a methoxy group and the methyl-substituted **7aa** gave very good yields of 83% (**7y** and **7z**) and a good yield of 77% (**7aa**). **7ab** being equipped with a TMS-acetylene unit was obtained in good yield of 84% allowing further functionalization, e.g., by cycloaddition or reduction.[57] Trifluoromethyl groups are widely found in established drugs to modulate their physiochemical properties.[58] The corresponding derivative bearing a trifluoromethyl group **7ac** was isolated in excellent yield of 91%. The fluoro-substituted **7ad** and **7ae** were isolated in splendid yields of 83% and 88%. Fluorinated arenes are widely used in nucleophilic aromatic substitutions to install further functional groups.[59] Haloarenes are generally used in metal-catalyzed coupling reactions.

Hence, halo-substituted compounds can be further modified to access more complex structures in the development of modern pharmaceuticals or agrochemicals. Usually, halo compounds are prone to electrochemical dehalogenation, limiting the functional group tolerance of cathodic reactions.[60–63] In contrast, the chloro-, bromo-, and iodo-substituted **7af–7ah** were isolated in very good yields of 84%–85%. Additionally, no dehalogenation was observed, underlining the great selectivity of this methodology. Therefore, the 4-hydroxy analog of the drug *Diazoxide* **1** could be synthesized as **7af**. **7ai** bearing a chloro and methoxy substituent was isolated in a good yield of 75%. Carbonyl functions allow a wide variety of further modifications.[64,65] Cyano-substituted **7aj** was isolated in a good yield of 83%. The corresponding methyl ester **7ak** was isolated in very good yield of 89%. The acetyl-substituted **7al** was obtained in a satisfying yield of 63%. The lower yield compared to the other carbonyl derivatives may be assigned to the more reactive keto function forming different side products by

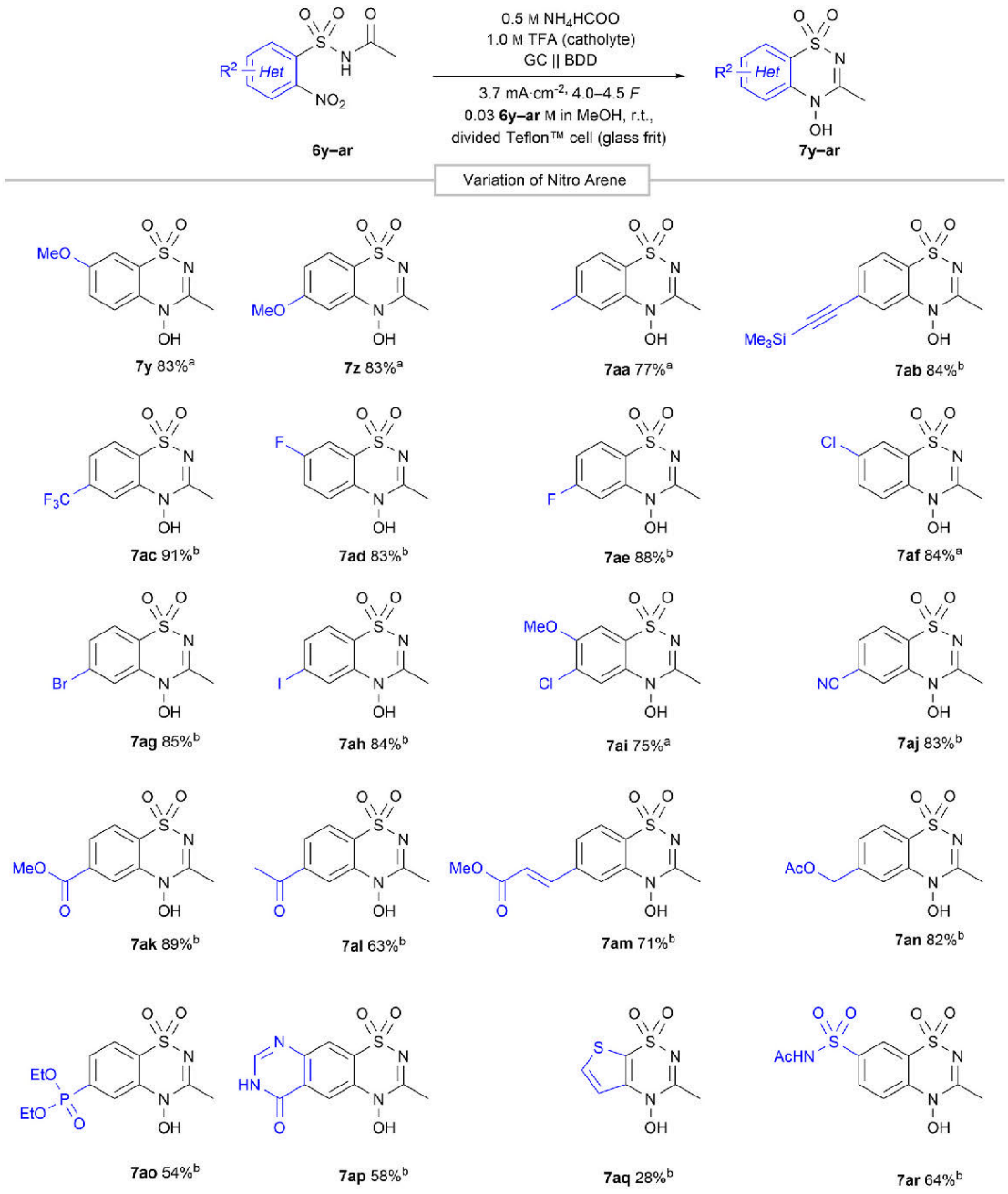


Figure 3. Scope of electrochemical reductive cyclocondensation of *N*-acylbenzenesulfonamides by diverse variation of the nitro arene subunit

Isolated yields are as follows.

(A) 4.5 *F*.

(B) 4.0 *F*.

condensation with intermediates of the nitro reduction. The nitro cinnamate-based **7am** was isolated in 71% yield. **7an** was isolated in a very good yield of 82%. Acetyl modified benzylic alcohols are known to be easily hydrolyzed, demonstrating the conservation labile functional groups in the described method.[66] Phosphonates are well established in common pharmaceuticals as isosteric replacements of phosphates modulating their interaction with enzymes.[67] The phosphonate involving **7ao** was

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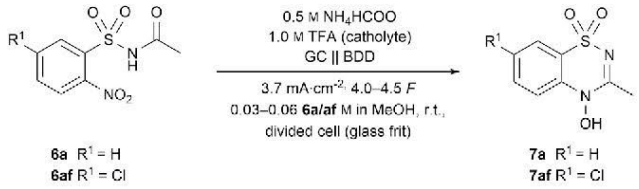


Scheme 2. Scale-up of the reductive cyclocondensation to 7a and 7af

obtained in a moderate yield of 54%. This shows the applicability of this method to modern small molecules drug design. Even annulated heterocyclic core motifs are tolerated, which was shown by yield of 58% for **7ap**. The incorporation of a redox labile thiophene (Figure 3, **7aq**) was successfully achieved in 28% yield.[68] The synthesis of a derivative of well-established drugs like *Chlorothiazid*, **7ar**, was shown in 64% yield.[69] Overall a wide functional group tolerance was shown on the synthesis of a broad scope of diversely and highly functionalized 4*H*-4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxides in up to 97% yield (for further synthetic details see General protocols in the supplemental information).

Scale-up of the reductive cyclocondensation

After exploring the scope of the reaction, the syntheses of 4-hydroxy-benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides **7** was tested on a multi-gram scale. In addition to **7a**, **7af** was synthesized on a multi-gram scale as an analog to the well-established drug *Diazoxide* **1** (Scheme 2; Table 2).

Initially, glassy carbon was tested as cathode material as an alternative to BDD in the synthesis of **7a**. To underline the simplicity of the method, glassy carbon as well resulted in a very good yield of 90% on a 0.15-mmol scale. On a 0.30-mmol scale, both BDD and glassy carbon as cathode material led to very good yields of 95% and 93%, respectively. On a 2.4-mmol scale, **7a** was obtained in 92% yield (0.469 g). **7af** was synthesized in 83% yield (0.493 g). The further scalability was shown on a 9.0-mmol scale using the same work-up protocol as described in the GP-A by reversed-phase column chromatography. Initially, the scale-up resulted in a decreased yield of 90% (1.720 g) for **7a**. A strong yellow discoloration of the electrolyte was associated with the presence of oxygen within the electrolyte leading to some decomposition. Therefore, the electrolyte was primarily purged with argon. Then, **7a** was isolated in 96% yield (1.830 g), which is comparable to the yield on a 0.15-mmol scale. Changing the work-up to a technically applicable protocol by simple filtration over silica and crystallization gave **7a** in 92% yield (1.760 g). **7af** could be isolated in 91% yield (2.008 g). Furthermore, by doubling of the substrate concentration, **7a** was isolated in 90% yield (3.420 g). By adding the substrate in portions and electrolyzing the reaction mixture stepwise, a similar yield of 90% (3.450 g) could be isolated (for further synthetic details see, Table S5; Figure S4 in the supplemental information).

Mechanistic studies

The mechanism of the reduction of nitro groups and their subsequent cyclocondensation was previously described.[32–36,38,70] The mechanism in electrosynthesis of 4-hydroxy-benzo[*e*]-1,2,4-thiadiazine-1,1-dioxides was further investigated by cyclic voltammetry (CV) of **7a** and its corresponding starting material **6a**, as well as the 7-chloro-substituted derivative **7af** and its starting material **6af** (Figure 4). To investigate the inhibited cyclocondensation of the aryl-substituted derivatives, **6u** was subject to mechanistic studies (see CV studies; Figures S5–S17 in the supplemental information).

Table 2. Scale-up of the reductive cyclocondensation to 7a and 7af

Electrolysis cell	Scale [mmol]	Work-up	Reaction time (amount of applied charge)	Yield 7a[a]	Yield 7af[a]
7 mL Teflon cell	0.15	A	2.4–2.7 h (4.0–4.5 *F*)	30.9 mg 97%	31.1 mg 84%
7 mL Teflon cell	0.15[b]	A	2.4–2.7 h (4.0–4.5 *F*)	28.6 mg 90%	–
10 mL glass cell	0.30	A	3.5 h (4.1 *F*)	60.6 mg 95%	–
10 mL glass cell	0.30[b]	A	3.5 h (4.1 *F*)	59.3 mg 93%	–
80 mL divided glass cell	2.4	A	9.8 h (4.5 *F*)	469 mg 92%	493 mg 83%
300 mL glass cell	9.0	A	9.2 h (4.5 *F*)	1.720 g 90%	–
300 mL glass cell	9.0[c]	A	8.6 h (4.2 *F*)	1.830 g 96%	–
300 mL glass cell	9.0[c]	B	8.6 h (4.2 *F*)	1.760 g 92%	2.008 g 91%
300 mL glass cell	18.0[c]	B	17.2 h (4.2 *F*)	3.420 g 90%	–
300 mL glass cell	18.0[c,d]	B	17.2 h (4.2 *F*)	3.450 g 90%	–

A = purification by reverse phase column chromatography; B = purification by filtration over silica and crystallization.
[a]Isolated yield.
[b]Glassy carbon was used as cathode instead of boron-doped diamond.
[c]Initial purging of electrolyte with argon.
[d]Substrate was added in portions.

First, the behavior of **6a** was investigated without the addition of 1.0 M TFA. Initially, **6a** is reduced by 4e /4H$^+$ at the BDD cathode to the hydroxylamine **Int-II** proven by a single broad wave (−1.44 V vs. FcH/FcH$^+$). The intermediately formed hydroxylamine is further detected by LC-MS analysis directly after the electrolysis. Hydroxylamine **Int-II** afterward undergoes a cyclocondensation by condensing with the acetyl-moiety of the sulfonamide forming the desired **7a**. A broad oxidative wave (+0.20 V vs. FcH/FcH$^+$) resulting from the re-oxidation of the hydroxylamine **Int-II** to the nitroso arene intermediate **Int-I** can be observed, which is also well known in the literature.[35,39,70] This underlines the requirement for the use of a divided cell. Interestingly, by adding 1.0 M TFA to the system, two distinct reductive waves were observed. The first wave is assigned to the 2e /2H$^+$ reduction of the nitro arene **6a** to the nitroso arene **Int-I** (−0.74 V vs. FcH/FcH$^+$). Afterward, a second 2e /2H$^+$ reduction of the nitroso arene **Int-I** to the hydroxylamine **Int-II** occurs. The addition of TFA results in an easier reduction of the nitro arene **6a** and subsequently the nitroso arene **Int-I** indicated by the higher reduction potential. Moreover, the addition favors the cyclocondensation to form the product. **7a** was subject to CV studies to investigate the stability of the compound under electrolytic conditions. The CV data show no reductive or oxidative wave of **7a** whether TFA was added or not. This indicates no degradation of product formed during the electrolysis. The cyclocondensation of benzoyl-substituted sulfonamides needed post-electrolysis treatment by microwave irradiation. To investigate whether the electrochemical reduction or the final cyclocondensation is inhibited for these compounds, benzoyl sulfonamide **6u** was subject to CV studies. Without the addition of TFA, the first 2e /2H$^+$ reduction (−0.84 V vs. FcH/FcH$^+$) indicated the formation of the nitroso arene **Int-I**. The second 2e /2H$^+$ reduction (−1.43 V vs. FcH/FcH$^+$) was observed forming the hydroxylamine **Int-II**. A broad oxidative wave was observed (+0.19 V vs.

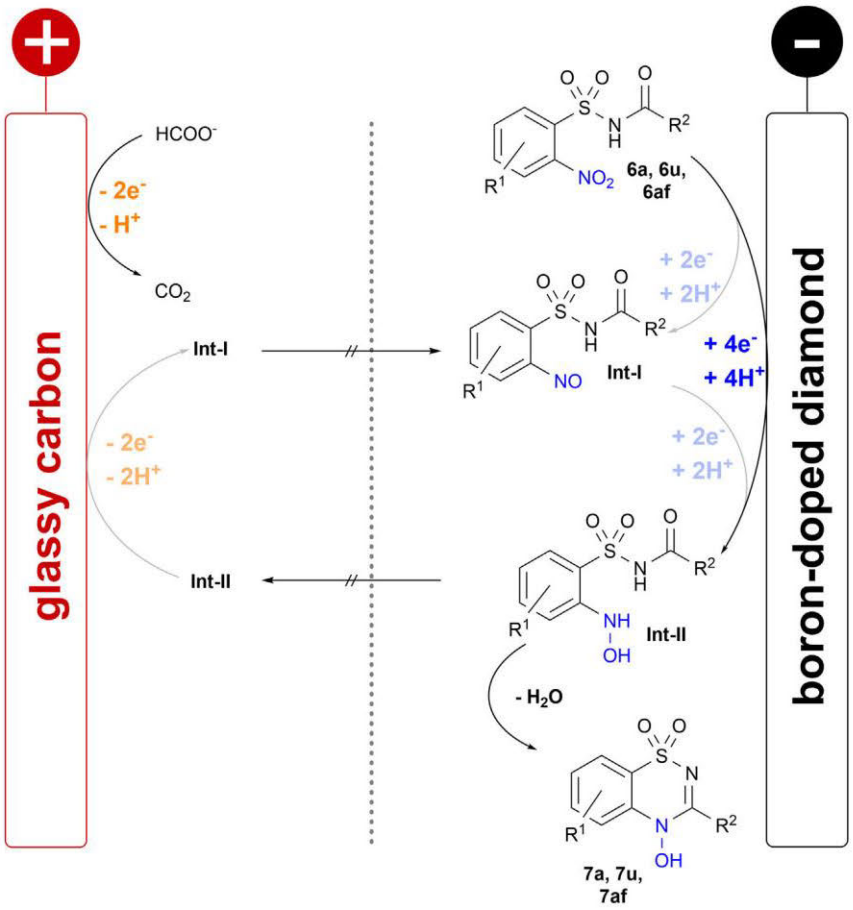
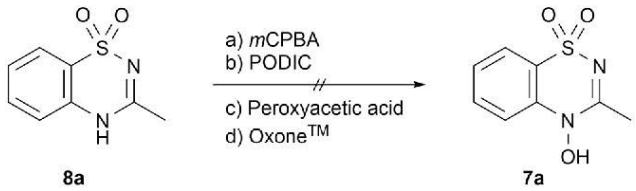


Figure 4. Proposed mechanism of the electrochemical reductive cyclocondensation
The nitro group of nitro arenes **6a**, **6u**, and **6f** is electrochemically reduced to Int-II, which subsequently undergoes the cyclocondensation to form the products **7a**, **7u**, and **7af** (see CV studies; Figures S5–S17 in the supplemental information).

FcH/FcH^+) corresponding to the re-oxidation of the hydroxylamine **Int-II** to the nitroso arene **Int-I**, which is also observed for the standard substrate **6a**. By increasing the TFA concentration, the reduction potentials shift to more positive potentials. When using 2.50 M TFA, the first $2e^-/2H^+$ reduction of the nitro arene **6u** to the nitroso arene **Int-I** shows a small reductive wave (−0.64 V vs. FcH/FcH^+) followed by a large reductive wave (−1.15 V vs. FcH/FcH^+) forming the hydroxylamine **Int-II**. Moreover, when using 0.5 M sulfuric acid as supporting electrolyte, the reductive potentials are even more shifted. The first $2e^-/2H^+$ reduction occurs at −0.62 V (vs. FcH/FcH^+), and the second $2e^-/2H^+$ reduction takes place at −1.07 V (vs. FcH/FcH^+). While the reduction of the nitro arene is favored at higher TFA concentrations and with sulfuric acid, the final cyclocondensation is hindered while using TFA. This is consistent with the requirement for microwave treatment to form the product in this case. When using sulfuric acid only, the product but no hydroxylamine was detected after electrolysis, indicating a favored cyclocondensation by sulfuric acid. Based on these studies, the final cyclocondensation appears to be dependent on pK_a of the acid used. Aliphatic acylated sulfonamides only need TFA for complete product formation, whereas aromatic acylated sulfonamides require the stronger sulfuric acid.



Scheme 3. Attempted oxidation of 4*H*-3-methylbenzo[e]-1,2,4-thiadiazine-1,1-dioxide (8a)

Oxidation of 4*H*-benzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (8a)

The oxidative hydroxylation reaction of 4*H*-3-methylbenzo[e]-1,2,4-thiadiazine-1,1-dioxide (**8a**) to enable an alternative access to of 4*H*-4-hydroxy-3-methylbenzo[e]-1,2,4-thiadiazine-1,1-dioxide (**7a**) using conventional oxidizers was investigated (Scheme 3). Furthermore, this oxidative approach should have been compared to the described electrochemical reduction method in terms of efficiency, selectivity, applicability, and sustainability aspects.[71–73]

Therefore, *meta*-chloroperbenzoic acid (*m*CPBA), electrochemically generated peroxodicarbonate (PODIC), peroxyacetic acid, and oxone were utilized as oxidizer under literature-known conditions for similar applications (see Studies on the conventional oxidation of 4H-3-methylbenzo[e]-1,2,4-thiadiazine-1,1- dioxide using literature known procedures; Table S4 in the supplemental information). However, no formation of the 4*H*-4-hydroxy-3-methyl-benzo[e]-1,2,4-thiadiazine-1,1-dioxide (**7a**) was observed at all.[17–19,74]

In conclusion, an easily scalable and high-yielding electrochemical method for the direct access to 4*H*-4-hydroxy-benzo[e]-1,2,4-thiadiazine-1,1-dioxides by reduction of nitro arenes was established. The simplicity of this method and the widely available nitro arenes as starting materials underline the significance of this green synthetic access. 4*H*-4-Hydroxy-benzo[e]-1,2,4-thiadiazine-1,1-dioxides feature a unique N–O bond that is not accessible by common synthetic routes. Furthermore, the selective electrochemical reduction offers a sustainable protocol for this type of reaction compared to conventional routes relying on chemical reducing agents. Methanol as green solvent and electric current as reagent underline the sustainability of this method. Additionally, the electrochemical protocol shows a very high functional group tolerance allowing its application in the synthesis of complex molecules. The scalability of the reaction was demonstrated by multi-gram-scale synthesis, highlighting the relevance for technical applications. CV studies gave a deeper understanding of the underlying mechanism. Overall, the described electrochemical methodology significantly enlarges the toolbox of the modern organic chemist working in medicinal chemistry or process development.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Siegfried R. Waldvogel (siegfried.waldvogel@cec.mpg.de).

Materials availability

Experimental details, general protocols, optimization studies of the electrolytic procedures, full experimental data for the scale-up reactions, CV studies, analytical data for all compounds including HRMS data, melting points, and ^{1}H NMR, ^{13}C NMR, ^{19}F

NMR, and ^{31}P NMR spectra are available in the supplemental information. All materials generated in this study are available from the lead contact without restriction.

Data and code availability

The datasets generated during this study are available in the manuscript and the supplemental information. Crystallographic data of **7a** and **7aj** are available from the Cambridge Crystallographic Data Center (CCDC): 2294500 (**7a**) and 2294499 (**7aj**).

General protocol of the electrochemical synthesis (GP)

GP-A: 0.15 mmol of the starting material was dissolved in 5 mL of 0.5 M ammonium formate solution in methanol in the cathodic compartment of a 7 mL divided Teflon screening cell, and 0.4–1.0 mL trifluoroacetic acid was added. The anodic chamber was equipped with 5.4–6.0 mL of 0.5 M ammonium formate solution in methanol. The anodic chamber was separated by a glass frit (Robu Por. 4, ROBU Glasfilter-Geräte GmbH, Hattert, Germany). The electrolysis was performed under constant current conditions (current density 3.7 mA·cm ^{2}) until a charge of 65.1 C (4.5 *F*) was applied. If the cyclocondensation of the hydroxylamine intermediate was incomplete, the reaction mixture was further stirred at room temperature until completion (LC-MS). If necessary, an additional 7.2 C (0.5 *F*) was applied for full conversion of the starting material. If no cyclocondensation was observed, the catholyte was treated in the microwave at 100°C for 10 min (50 W) to complete the product formation. The solvent was removed under reduced pressure. To remove residual trifluoroacetic acid, the crude product was co-evaporated with toluene once. The crude products were purified with column chromatography (SiO_2) or reverse phase column chromatography (C_{18}).

GP-B: 0.15 mmol of the starting material was dissolved in 5.0 mL of 0.5 M sulfuric acid solution in methanol in the cathodic chamber of a 7 mL divided Teflon screening cell. The anodic chamber was equipped with 5.0 mL of 0.5 M sulfuric acid solution in methanol. The anodic chamber was separated by a glass frit (Robu Por. 4, ROBU Glasfilter-Geräte GmbH, Hattert, Germany). The electrolysis was performed under constant current conditions (current density 3.7 mA·cm ^{2}) until a charge of 65.1 C (4.5 *F*) was applied. If the cyclocondensation of the hydroxylamine intermediate was incomplete, the reaction mixture was further stirred at room temperature until completion (LC-MS). If necessary, an additional 7.2 C (0.5 *F*) was applied for full conversion of the starting material. The reaction mixture was then diluted with 10 mL of water. The aqueous layer was extracted twice with 20 mL of ethyl acetate. The organic layer was washed once with 15 mL brine, dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude products were purified with column chromatography (SiO_2) or reverse phase column chromatography (C_{18}).

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xcrp.2024.101927.

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AUTHOR CONTRIBUTIONS

J.W., T.P., and T.W. contributed equally. J.W., T.P., and T.W. conceived the project. J.W., T.P., T.W., K.H., and M.d.J.G.-V. conducted the experiments and analyzed and interpreted the results. D.S. performed the X-ray analysis and structural elucidation of the synthesized compounds. J.W., T.P., and S.R.W. wrote and reviewed the manuscript. S. R.W. supervised the project. All authors discussed the results and agreed to the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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3.2.4 Cathodic Reduction of Nitro Phenoxyacetic Acids for the Synthesis of 2*H*,4*H*-4-Hydroxybenzo[*b*]-1,4-oxazin-3-ones

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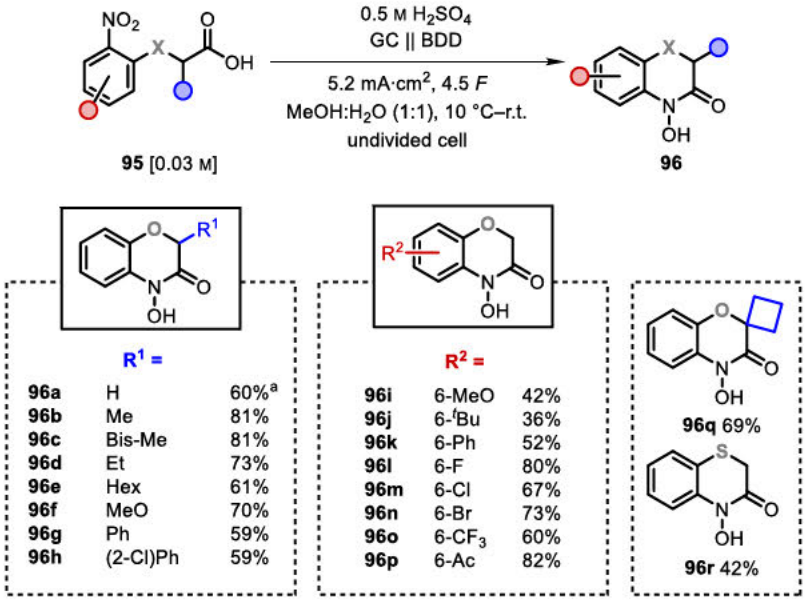
[redacted], *Simple electrochemical synthesis of cyclic hydroxamic acids by reduction of nitroarenes*, *Chem. Commun.* 2024, *60,* 7065-7068.

[redacted]

2*H*,4*H*-4-Hydroxybenzo[*b*]-1,4-oxazin-3-ones are widely found in several plants as natural herbicides and exhibit antibiotic and herbicidal properties.[167,219,221–227]Their common synthesis involves the use of noble metals or equimolar amounts of reactants for the reduction of (2-nitrophenoxy)acetic acids, resulting in large amounts of waste. *Tallec et al.* described the synthesis of two exemplary compounds in a constant potential electrolysis, requiring a complex set-up with a toxic mercury cathode.[231,232] However, the toxicity of mercury electrodes poses a danger to humans and the environment. Overall, this protocol cannot be translated to a preparative technique and large-scale production of highly active compounds. Based on sustainable considerations, a simple, electrochemical approach was envisioned for the direct and scalable synthesis of 2*H*,4*H*-4-hydroxybenzo[*b*]-1,4-oxazin-3-ones. Solely electrical current should be employed as an inherently safe and sustainable reducing agent. Initially, methyl (2-nitrophenoxy)acetate was chosen as standard substrate which is easily accessible in one step from inexpensive 2-nitrophenol and methyl 2-bromoacetate. The reaction conditions were chosen based on previous work: a current density of 3.7 mA·cm^{-2}, the theoretical amount of applied charge of 4 *F*, 0.5 M sulfuric acid in methanol as solvent and supporting electrolyte and a substrate concentration of 0.04 M. The electrolysis was carried out under constant current conditions in a simple undivided set-up at room temperature and the product **96a** was obtained in a yield of 31%. By increasing the current density to 5.2 mA·cm^{-2} the yield was further increased to 51%. Surprisingly, using the less electrophilic (2-nitrophenoxy)acetic acid **95a** instead of the corresponding methyl ester as substrate, yielded 47% of **96a** at a current density of 3.7 mA·cm^{-2}. The yield was further increased to 70% NMR yield of **96a** by lowering the substrate concentration to 0.03 M and decreasing the temperature to 10 °C to inhibit side reactions during electrolysis. **96a** was subsequently isolated in 60% yield.



Scheme 33: Scope of the direct synthesis of 2*H*,4*H*-4-hydroxybenzo-1,4-oxazin-3-ones and 2*H*,4*H*-4-hydroxybenzo-1,4-thiazin-3-ones **96** by cathodic reduction of (2-nitrophenoxy)acetic acids/2-((2-nitrophenyl)thio)acetic acids **95** 5 mL (0.15 mmol) scale; isolated yields; [a]temperature = 10 °C.

With the optimized conditions, the scope of the reaction was explored (Scheme 33). The methyl- **96b** and dimethyl- **96c** substituted derivatives were obtained in 81% yield. The increase in yield can be attributed to the *Thorpe-Ingold Effect*, promoting the cyclo-condensation.[239] However, increasing the length of the alkyl chain caused a decrease in yield to 73% for **96d** and 61% for **96e**. The corresponding methoxy substituted compound **96f**, representing an methylated derivative of naturally occurring DIBOA (**77**), was isolated in 70% yield.[221] The electron-rich derivatives **96i** and **96j** were isolated in 42% and 36% yield, respectively. Halo-substituents were tolerated well and resulted in yields of up to 80% (**96l**–**o**). Interestingly, the corresponding 2*H*,4*H*-4-hydroxybenzo[*b*]-1,4-thiazin-3-one **96r** was obtained in 42% yield, despite the sensitivity of sulfur regarding anodic oxidation. After the scope of the reaction was explored, a scale-up of the synthesis of **96c** was performed. On gram-scale, product **96c** was obtained in a satisfactory yield of 88% (1.27 g), underlining the scalability of the method. Furthermore, the crude product was purified by a simple recrystallisation, showing the potential for application on a technically relevant scale. Moreover, the mechanism was investigated using cyclic voltammetry. In general, the reduction of the nitro moiety was observed in accordance with previous reports. The nitro group gets selectively reduces to the hydroxylamine intermediate which subsequently undergoes cyclo-condensation. Additionally, two distinct oxidations were observed for the products **96a** and **96c**. It was hypothesized that these correspond to the literature known formation of an O centered radical, which is subjected to further oxidation.[240] In summary, a simple and easily scalable electrochemical protocol was developed for the synthesis of a broad scope of 18 highly interesting 4-hydroxybenzoxazinones in up to 81% yield. The scalability was demonstrated on up to gram-scale. Mechanistic studies by CV underlined the application potential of these compounds.

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Simple electrochemical synthesis of cyclic hydroxamic acids by reduction of nitroarenes†

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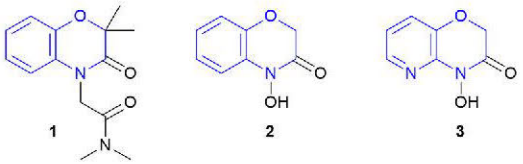
The electrochemical reduction of nitroarenes allows direct access to manifold nitrogen containing heterocycles. This work reports the simple and direct electro-organic synthesis of 18 different examples of 2*H*,4*H*-4-hydroxy-1,4-benzoxazin-3-ones in up to 81% yield. The scalability of the method was demonstrated on a gram-scale.

Nitrogen containing heterocycles are found in the majority of highly potent APIs and natural products.[1] In particular, exocyclic N–O heterocycles are often highly bioactive key motifs in naturally occurring products.[2] Thus, their synthesis plays a crucial role in modern organic chemistry by developing novel synthetic approaches to these compounds. 2*H*,4*H*-4-Hydroxy-1,4-benzoxazin-3-ones and their derivatives are found in natural products having herbicidal, fungicidal and therapeutic properties.[3]

1,4-Benzoxazin-3-ones are investigated as promising motifs in novel potassium channel modulators for treating high blood pressure (Schemes 1, **1**).[4] D-DIBOA (**2**) is naturally found in plants and has shown herbicidal and fungicidal activity and therefore could find application in agrochemistry.[5] Furthermore, the corresponding pyridine derivative showed activity against a variety of bacterial strains leading to potential agents for treating bacterial infections (**3**).[6] Additionally, the various activities against a broad range of pests highlights the significance as a highly promising motif for modern pharmaceutical and agrochemical research.[7]

A common and widely used strategy for the synthesis of N–O heterocycles is the selective reduction of nitroarenes, followed by cyclo-condensation. However, achieving a selective reduction remains quite challenging. The conventional approach for the selective synthesis of 2*H*,4*H*-4-hydroxy-1,4-benzoxazin-3-one requires the use of palladium catalysts (Scheme 2, **A**) or equimolar amounts of reducing agents (**B**).[8] *Tallec et al.* investigated the first potential controlled electro-synthesis in a divided cell using a mercury cathode (**C**).[9] In addition, the electrolysis has only been demonstrated on a milli-gram-scale and no further scale-up was attempted. This approach is severely limited for the practical synthesis in modern laboratories. Modern research faces the challenge of meeting the growing need for innovative, sustainable methods to synthesize highly functional compounds. Organic electrochemistry is experiencing a renaissance as it fulfils several aspects of the principles of green chemistry.[10,11] The use of electric current instead of hazardous redox reagents contributes to process safety. Moreover, the electrochemical reaction can be stopped by turning off the electrical current, preventing runaway reactions and enhancing the overall process safety.[12] This method is in particular attractive when a suitable drown-stream processing is combined.[13] Therefore, reduction and intramolecular cyclo-condensation of easily accessible and inexpensive nitroarenes offers a simple synthetic strategy for a large number of valuable fine chemicals and possible drug candidates.[14,15] Based on previous work on the direct electrochemical reductive synthesis of N–O heterocycles, a synthetic protocol for the selective and scalable synthesis of 2*H*,4*H*-4-hydroxy-1,



Scheme 1 Important examples of 1,4-benzoxazin-3-ones: possible K^+ channel modulator (**1**) D-DIBOA (natural product, **2**) and a possible antibiotic (**3**).

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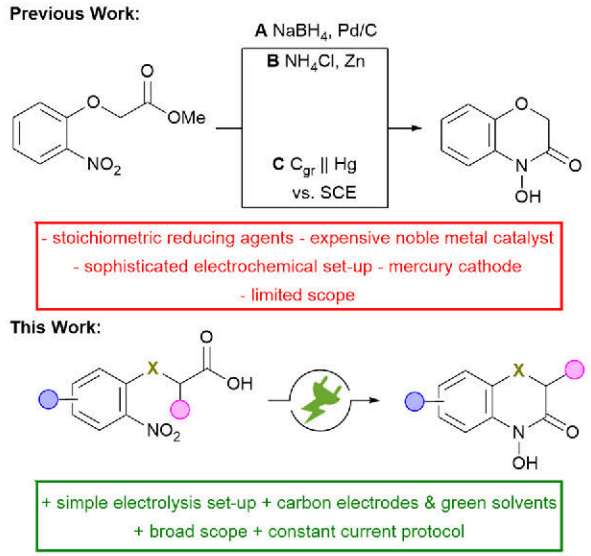
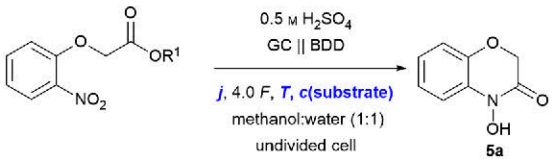
† Electronic supplementary information (ESI) available: Detailed experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra. CCDC 2349053. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4cc02118e



Scheme 2 Conventional and electrochemical reduction of nitroarenes for the synthesis of *2H,4H*-4-hydroxy-1,4-benzoxazin-3-ones; C_{gr} = graphite.

Table 1 Optimisation of the electrochemical synthesis of *2H,4H*-4-hydroxy-1,4-benzoxazin-3-one (**5a**) under constant current conditions



Entry	R^1	j/mA cm^{-2}	c(substrate)	T/°C	Yield[a] (%)
1	**6a**, Me	3.7	0.04 M	rt	31
2	**6a**, Me	5.2	0.04 M	rt	51
3	**4a**, H	3.7	0.04 M	rt	47
4	**4a**, H	3.7	0.04 M	50	22
5	**4a**, H	5.2	0.03 M	rt	60
6	**4a**, H	5.2	0.08 M	rt	26
7	**4a**, H	5.2	0.03 M	10	70 (60)[b]
8	**6t**, ^{t}Bu	5.2	0.03 M	10	0

[a] Yield determined by ^{1}H NMR; 1,3,5-trimethoxybenzene as internal standard. [b] Isolated yield; BDD = boron-doped diamond; GC = glassy carbon.

4-benzoxazin-3-ones was established, providing direct access to this highly promising class of compounds.[16–19]

For the optimisation of the electrolytic conditions, methyl 2-(2-nitrophenoxy)acetate (**6a**) was prepared in a single step. The initial electrolytic conditions were chosen based on previous reductions.[16,18] Sulphuric acid serves a dual role as a supporting electrolyte and catalyst in the cyclo-condensation by protonation.[20] The best yields and selectivity were obtained using methanol and water as green solvents. Boron-doped diamond (BDD) has a high overpotential for the hydrogen evolution reaction, providing selectivity for the reduction of the nitro group, and shows no cathodic corrosion.[11,21]

Glassy carbon was chosen as the anode material as the counter reaction plays an important role in electrochemical transformations.[22] The initial optimisation was performed using the theoretical amount of applied charge (4.0 *F*) and a current density of 3.7 mA cm^{-2}. Initially, **5a** was obtained in 31% NMR yield (Table 1, entry 1). The structure of the targeted **5a** was confirmed by NMR spectroscopy and mass spectrometry after isolation. Additionally, the deoxygenated 1,4-benzoxazin-3-one **5s** was prepared for comparison and verification of the analytical data used for NMR quantification (see ESI† for details). Alternatively, **5s** can be prepared by Yoshida amination reaction.[23]

By increasing the current density (j) to 5.2 mA cm^{-2}, the yield increased up to 51% (entry 2). To our delight, the less electrophilic carboxylic acid **4a** gave the product in 47% (Table 1, entry 3) yield by applying 3.7 mA cm^{-2}. Moreover, the influence of the reaction temperature was investigated. It was hypothesized that elevated temperatures could accelerate the cyclo-condensation by promoting water elimination. However, increasing the reaction temperature from rt to 50 °C resulted in a significant drop of the yield to 22% (entry 4), while no starting material was detected after electrolysis. As expected for intramolecular cyclisations, the substrate concentration was found to be crucial, since lower concentrations can suppress intermolecular side reactions. An optimum substrate concentration of 0.03 M in combination with the increased current density of 5.2 mA cm^{-2} yielded 60% of the desired **5a** (entry 5), whilst the yield dropped drastically to 26% (entry 6) when higher substrate concentrations of 0.08 M were used. On the contrary, through decreasing the temperature to 10 °C during electrolysis, the yield of **5a** was further increased to 70% NMR yield (60% isolated yield, entry 7). *tert*-Butyl esters are known to hydrolyse easily under acidic conditions, which might be beneficial for the cyclo-condensation. However, no product was obtained when using *tert*-butyl ester **6t** as a substrate and solely degradation of the substrate was observed (entry 8). Further variation of the electrode materials and additives did not increase the yield of **5a** (see ESI† for further details).

The scope of the reaction was investigated with the following optimised conditions: glassy carbon (anode) and BDD (cathode) were used. 0.5 M sulphuric acid in a methanol : water (1 : 1) mixture was used as an electrolyte while applying a current density of 5.2 mA cm^{-2} in an undivided cell (Scheme 3).

Despite the fact that reaction optimisation using test substrate **4a** indicated an optimum reaction temperature of 10 °C, most of the nitro-derivatives applied for investigation of the scope showed limited solubility under these conditions. Since this resulted in side-reactions significantly lowering the product yield, carrying out these syntheses at room temperature proved beneficial due to tremendously increased solubility. Furthermore, an amount of applied charge of 4.5 *F* was used to ensure full conversion of all substrates. First, the effect of a substitution in position 3 was studied. The 3-methyl substituted **5b** and **5c** were isolated in 81% yield. The corresponding ethyl substituted **5d** was obtained in 73% yield. The increased yield compared to the standard product is a result of the *Thorpe–Ingold* effect promoting the cyclisation, which is a key-step of the overall reaction.[24] Even spiro derivative **5e** was obtained in 69% yield. The *n*-hexyl modified compound **5f** was isolated in 61% yield. The sterical demand of long alkyl

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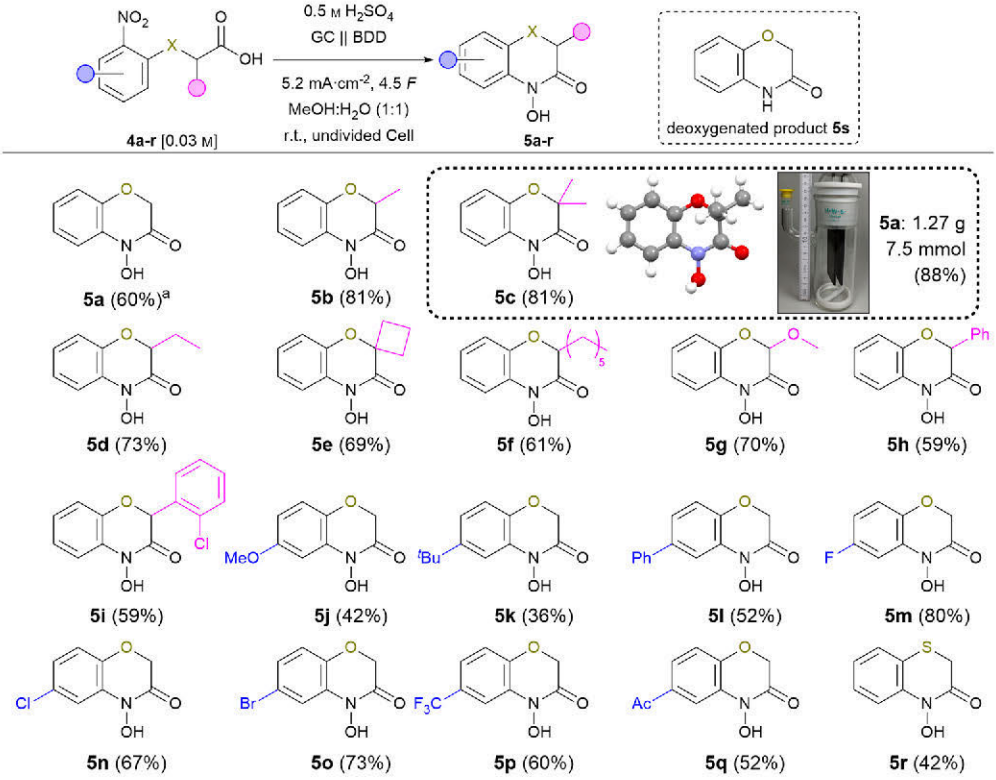


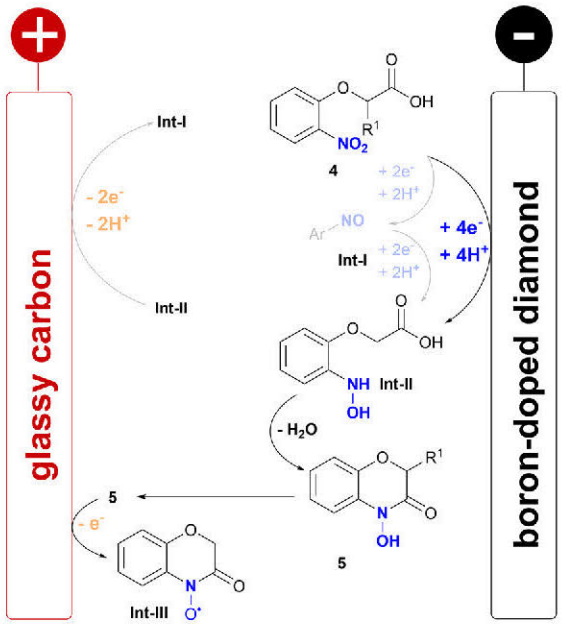
Scheme 3 Scope of the electrochemical synthesis of 2*H*,4*H*-4-hydroxy-1,4-benzoxazin-3-ones, isolated yields. [a] Temperature: 10 °C.

chains might counter the *Thorpe–Ingold* effect previously observed inhibiting the cyclisation. **5g** represents a methoxylated variant of the natural compound D-DIBOA (**2**) and was isolated in 70% yield avoiding the use of noble metals.[25] Derivatives **5h** and **5i** bearing an aryl-substituent were isolated in 59% yield each. The slightly decreased yields are most likely a result of steric effects as seen for the alkyl derivatives (**5b**–**5f**) yield. Afterwards, variation of the nitroarene was investigated. The electron-rich **5j** and **5k** were obtained in 41% and 36% yield, respectively. Generally, the reduction of electron-rich arenes is less favoured. The phenyl substituted derivative **5l** was obtained in 52% yield.

A great tolerance for halogens was observed and **5m**–**o** were isolated in up to 80% yield (F: 80% > Br: 73% > Cl: 67%).[26] To underline the method's application potential, trifluoromethyl-substituted derivative **5p** was isolated in 60% yield. The presence of trifluoromethyl groups in modern pharmaceuticals highlights the importance of tolerating this functional group during electrolysis.[27] The electron-deficient derivative **5q** with an acetyl group was isolated in 52% yield. Notably, no byproducts from intermolecular condensation were observed, highlighting the selectivity for the intramolecular product. Implementation of sulphur atoms in electrochemical reactions is a challenge due to their sensitivity of undergoing oxidation. To our delight, even 4-hydroxybenzo-1,4-thiazin-3-one (**5r**) was successfully obtained in 40% yield in an undivided cell. No oxidation of the sulphur could be observed, which emphasises that the methodology also tolerates oxidation-sensitive functional groups. Last, the scalability of the reaction was demonstrated employing derivative **5c**. On gram-scale, the product was obtained in an outstanding yield of 88% (6.6 mmol, 1.27 g), using an undivided beaker-type electrolysis cell as the simplest set-up. Moreover, product purification was achieved solely *via* simple crystallisation. This underlines the application potential of this method as it allows for efficient product isolation and downstream processing. Furthermore, the molecular structure of this compound was verified by X-ray analysis (CCDC: 2349053†).

Mechanistic studies of the acids **4a** and **4c** and the corresponding 4-hydroxy-1,4-benzoxazin-3-ones **5a** and **5c** by cyclic voltammetry (CV) were conducted (for details see ESI†). The acids **4a** and **4c** showed a broad reductive wave (−1.00 V *vs.* FcH/FcH^+) relating to the 4e /4H^+ reduction of the nitroarene to the intermediary formed hydroxylamine, which is reported in the literature (Scheme 4).[15,17,18] Interestingly, only **4a** showed a weak oxidative wave (+0.41 V *vs.* FcH/FcH^+) related to the reoxidation of the hydroxylamine to the nitroso arene. The 4-hydroxy-1,4-benzoxazin-3-ones **5a** and **5c** both showed two oxidative waves, which correspond to a N–O radical formed, which might later be oxidized to a cation.[9,28] This literature-known step might be the major side reaction resulting in methoxylated side products when applying higher current densities, which were observed during optimisation by LC-MS. However, this might give rise to another field of application, as the N–O radical formed could potentially be used as a mediator, similar to nitroxyl compounds such as TEMPO.[29]

In summary, a simple and easily scalable electrochemical protocol has been established, enabling direct access to a wide range of highly functionalised 2*H*,4*H*-4-hydroxy-1,4-benzoxazin-3-ones. The simplicity of the protocol was underlined by using



Scheme 4 Proposed mechanism of the electrochemical synthesis of 4-hydroxybenzoxazinones.

widely available 2-nitrophenols as inexpensive starting materials. Compared to the established electrochemical protocols, simple constant current conditions were applied instead of complex constant potential conditions where an additional reference electrode is needed. The toxic mercury electrodes were avoided and a broad scope of 18 examples was prepared in up to 81% yield, tolerating electrochemically sensitive functional groups.

Moreover, the scalability was demonstrated in up to gram-scale, without any loss in yield, and the product was purified by a simple crystallisation. Compared to classical methods, equimolar amounts of reductants were avoided diminishing the amount of generated waste.

J. W. conceived the project together with S. R. W., J. W., K. H., S. L., M. G. and T. P. conducted the experiments and interpreted and analysed the results. D. S. performed the X-ray analysis. J. W., S. L. and S. R. W. wrote and reviewed the manuscript. S. R. W. supervised the project. All authors discussed the results and agreed to the manuscript.

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Conflicts of interest

There are no conflicts to declare.

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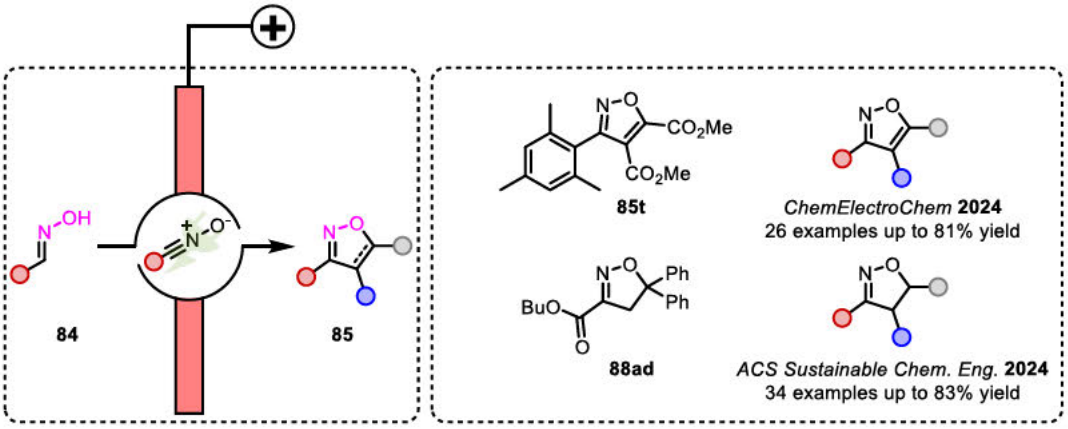
4 Conclusion

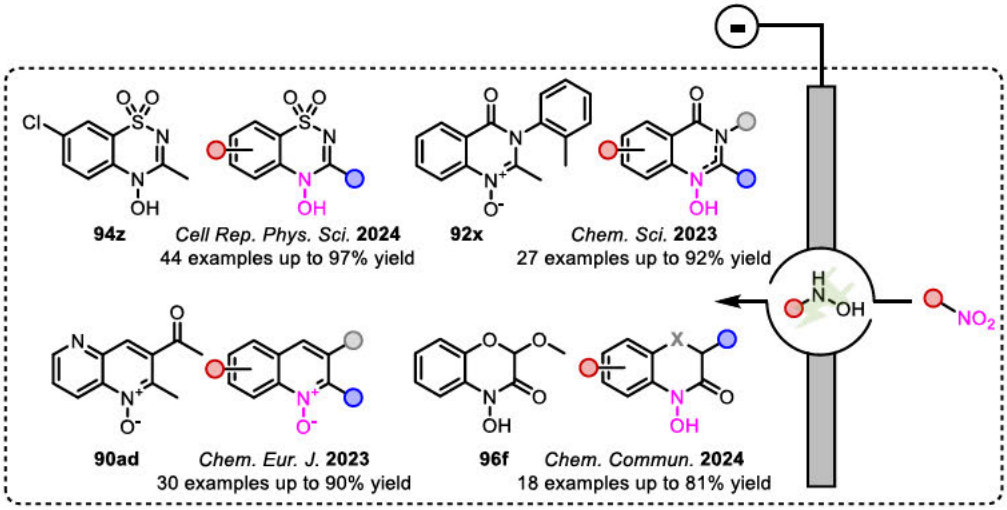
Within this work, a collection of novel electrochemical routes for the synthesis of heterocycles involving an endo- or exocyclic N,O-moiety was presented based on two key reactions: the anodic oxidation of aldoximes (Scheme 34) and the cathodic reduction of nitro arenes (Scheme 35).



Scheme 34: Electrochemical access to heterocycles with endo N,O-bond by anodic oxidation of aldoximes.

Electrochemical strategies for the synthesis of isoxazoles and isoxazolines was developed. Nitrile oxides were generated in-situ by direct anodic oxidation of aldoximes and converted into isoxazolines and isoxazoles **85** through (3+2) cycloaddition, yielding up to 81%. Efficient Solvent recycling during scale-up contributed further to improving the reaction's sustainability. Adapting the protocol to a biphasic, iodide-mediated approach allowed for synthesis of isoxazole(in)e-3-carboxylates **88**, whereby 34 examples were obtained in up to 82% yield. The method's technical relevance was underlined by product synthesis on hecto-gram scale in a continuously stirred tank reactor.

The direct electrochemical synthesis of 2,3-disubstituted quinoline *N*-oxides **90** was achieved via cathodic reduction of nitro arenes, circumventing the conventional use of equimolar amounts of reducing agents. A robust and efficient method was developed, allowing even for an increase of the starting material concentration upon scale-up. The reaction's versatility was shown on 30 examples, proving a great functional group tolerance. Transferring the knowledge of cathodic nitro reductions to *N*-acyl-2-nitrobenzamides allowed for the synthesis of 1-hydroxyquinazolin-4-ones **92**. A simple and sustainable solvent system of methanol-water using sulfuric acid as the supporting in combination with carbon-based electrodes highlighted the approach's sustainability. The method's versatility was demonstrated on 27 examples in up to 92% yield. Scale-up was achieved using either BDD or cost-effective glassy carbon cathodes, showcasing the protocol's adaptability. Moreover, the novel class of 4-hydroxybenzo-1,2,4-thiadiazine-1,1-dioxides **94**, inaccessible by common methods, was synthesized utilizing direct cathodic reduction of nitro arenes as a toolbox. Electrochemistry proved superior and highly selective, yielding 44 diverse examples in up to 97%. Scalability was demonstrated on up to multi-gram scale, enhancing the technical relevance of this method for accessing this new motif.

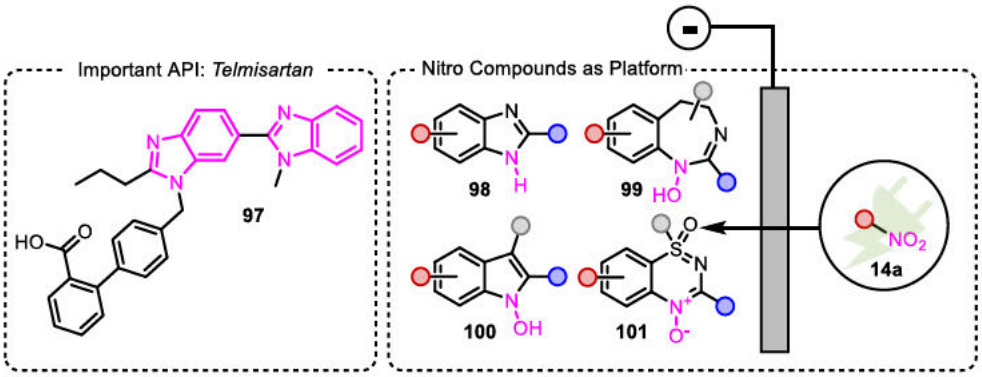


Scheme 35: Electrochemical access to heterocycles with exocyclic N,O-bonds by cathodic reduction of nitro arenes.

In a similar fashion, the naturally occurring class of 4-hydroxybenz-1,4-oxazin-3-ones **96** was accessed via the reduction of easily accessible 2-(nitrophenoxy)acetic acids under simple constant current conditions. A broad scope of 18 examples of these cyclic hydroxamic acids was prepared in a satisfying yield of up to 82%. Moreover, CV studies revealed the application potential of these compounds as mediators, due to their ability of forming O-centered radicals upon oxidation. Thus, the herein developed electrochemical synthetic protocol might enable access to a novel class of redox-active mediators.

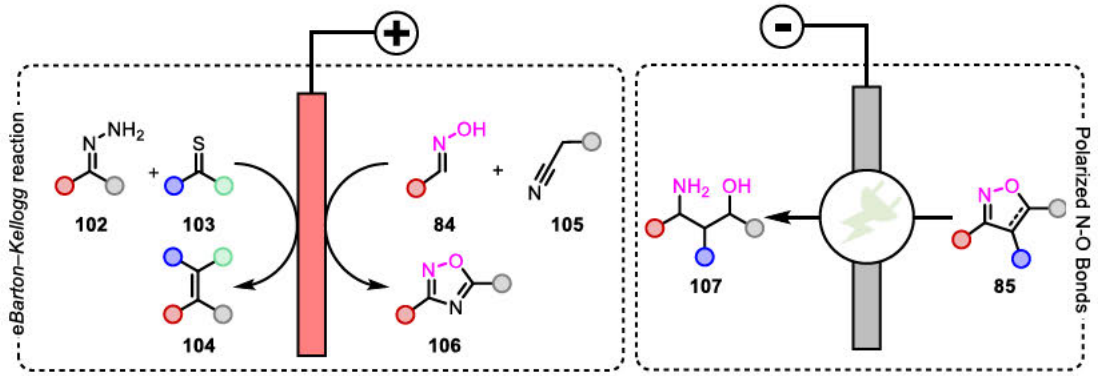
5 Outlook

In the field of heterocyclic chemistry, electro-organic synthesis offers diverse strategies for accessing bioactive heterocyclic motifs and their derivatives.



Scheme 36: Electrochemical conversion of nitro arenes into various nitrogen containing heterocycles.

In medicinal chemistry, editing of the pharmacophore scaffold is a commonly used technique. Hence, the cathodic reduction of nitro arenes can act as a platform technique enabling access to a library of novel N,O-heterocycles (Scheme 36). This includes motifs with a potentially high biological activity and represents unique synthetic pathways to an exocyclic N,O-bond. For example, the family of benzodiazepines is widely described as highly potent drugs.[241] So far, research focusses mostly on the biological activities of benzo-1,4-diazepines, whereas the group of benzo-1,3-diazepines **99** remains underexplored and their synthetic access is scarcely reported in literature.[242] The compound family of benzimidazoles is a widely found motif in established drugs like *Telmisartan* (**97**).[243] The key route towards benzimidazoles (**98**) involves the reduction of nitro arenes followed by a cyclo-condensation.[244] Utilizing electrochemistry, compounds like *Telmisartan* (**97**) could be accessed in a single step from the corresponding nitro arene, avoiding the use of expensive metal catalysts and hydrogen as reducing agent. Thus, an inexpensive and safer process design could be envisioned. Expanding the scope of the reduction of nitro arenes allows for the direct access to *N*-hydroxy indoles (**100**) an underexplored class of compounds. So far, only one example for their electrochemical synthesis is reported utilizing toxic mercury electrodes in a potentiostatic set-up.[232] Thus, establishing a methodology using carbon-based electrode materials in a galvanostatic set-up could allow for more efficient and sustainable synthetic access to these compounds. Benzo-1,2,4-thiadiazine-1-oxides (**101**) are a novel class of heterocycles currently under investigation in various drugs.[245] However, the corresponding 4-oxo-benzo-1,2,4-benzothiadiazine-1-oxides are not yet literature known and no synthetic protocol has been established for their synthesis. The selective reduction of nitro arenes provides a simple and selective methodology to gain access to this class of heterocycles.



Scheme 37: Electrochemical synthesis of γ-amino alcohols from isoxazolines, 1,2,4-oxadiazoles from aldoximes and olefines from hydrazones and thiokentones.

Besides the general construction of N,O-heterocycles, the specific reactivity of the N,O-bond can be harnessed in the cathodic reduction towards potent motifs such as γ-amino alcohols **107** and related compounds (Scheme 37). The latter was previously described as a spasmolytic drug and the synthesis of these compounds, especially asymmetric approaches, are of high interest.[246] Generally, the reduction of isoxazol(in)es **85** is performed using equimolar quantities of hazardous reducing agents.[247] Reported electrochemical methods involve toxic mercury electrodes or a complex constant potential set-up lacking applicability for technical scale.[248] While investigating the synthesis of isoxazoles, it was demonstrated in one example that the application of nitriles as dipolarophiles can yield the corresponding 1,2,4-oxadiazole **106**.[234] Further optimization of this approach allows for a simple access to these interesting heterocycles often found in modern API's.[249] The electrochemical synthesis of stabilized diazo compounds was demonstrated by *Lam et al.* (2022).[250] Adapting this protocol to a biphasic system might allow for the synthesis of non-stabilized diazo compounds from hydrazones **102** which subsequently react with thioketones **103** in an olefination reaction.[251] This approach avoids the direct handling of diazo compounds by generating them in-situ and directly convert them into the corresponding alkenes **104**.

The modern organic electrosynthesis fulfils several aspects of *green chemistry* by avoiding toxic metal electrodes or large amounts of hazardous redox-active reagents. The reduction of nitro compounds and the anodic oxidation of aldoximes or related compounds allows for the sustainable synthesis of heterocycles currently investigated as highly promising drugs.

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7 Publications and Other Contributions

7.1 Publications

[redacted] *Electrochemical heterocyclic ring-formation reactions by making C–N and N–N bonds* in *Construction and Functionalization of Heterocycles by Electrochemistry. Topics in Heterocyclic Chemistry*, Volume 61, Springer Nature, Cham., 2024 – accepted, *Reproduced with permission from Springer Nature*.

[redacted], *Biphasic Electrosynthesis of 2-Isoxazol(in)e-3-carboxylates: Reaction Optimization from Milli- to Hectogram-Scale*, *ACS Sustainable Chem. Eng.* 2024, *12*, 11369−11376.

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[redacted], *Self-standing Metal Foam Catalysts for Cathodic Electro-organic Synthesis*, *Adv. Mater.* 2024, *36*, 2307461.

[redacted], *Electrochemical Synthesis of Isoxazoles and Isoxazolines via Anodic Oxidation of Oximes*, *ChemElectroChem* 2023, e202300434.

[redacted], *Simple and Scalable Electrosynthesis of 1H-1-Hydroxy-quinazolin-4-ones*, *Chem. Sci.* 2023, *14*, 2669-2675.

[redacted], *Direct Electrochemical Synthesis of 2,3-Disubstituted Quinoline N-oxides by Cathodic Reduction of Nitro Arenes*, *Chem. – Eur. J.* 2023, *29*, e202203319.

[redacted], *Electrochemical Synthesis of N,N'-Disubstituted Indazolin-3-ones via Intramolecular Anodic Dehydrogenative N-N Coupling Reaction*, *Chem. Sci.* 2022, *13*, 8180–8186.

‡The authors contributed equally to this publication.

7.2 Conference Contributions

Poster Presentation at the 244th ECS Meeting (Gothenburg, Sweden, 2023) *Direct Electrochemical Reductive Synthesis - A Tool for Novel Classes of N–Oxy Heterocycles*.

Oral Presentation at the 10th German-Japanese Symposium on Electrosynthesis (Yokohama, Japan, 2023) *Direct Electrochemical Reductive Synthesis - A Tool for Accessing Novel Compound Classes of N–Oxy Heterocycles.*

7.3 Supervision of Research Work

[redacted]

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A-1 List of Abbreviations

A	Ampere
A	Active anode surface
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
API	Active pharmaceutical ingredient
aq.	aqueous
Ar	Aryl
ATP	Adenosine triphosphate
BDD	Boron-doped diamond
c	Concentration
CCE	Constant current electrolysis
$C_{graphite}$	Graphite
CH	Cyclohexane
CPE	Constant potential electrolysis
CSTR	Continuous stirred-tank reactor
Cy	Cyclohexyl
DME	Dropping mercury electrode
DoE	Design of Experiments
DSA	Dimensionally stable anode
Et	Ethyl
eq.	Equivalent
F	Faraday constant
GC	Glassy carbon
g	Gram
GABA	γ-Aminobutyric acid
h	Hour(s)
HER	Hydrogen evolution reaction
HFIP	1,1,1,3,3,3-Hexafluoro isopropanol
Hz	Hertz
I	Current
ICP-OES	Inductively coupled plasma atomic emission spectroscopy
J	Coupling constant
j	Current density
L	Liter
LC	Liquid chromatography
M	Molar
M	Mass
mA	Milliampere
m-CPBA	*meta*-Chlorperbenzoic acid
Me	Methyl
Med	Mediator
MeO^{t}Bu/MTBE	Methyl *tert.*-butyl ether
MHz	Megahertz
min	Minutes
mL	Milliliter
mmol	Millimole
n	Amount of Substance
NBS	*N*-bromo succinimid
NCS	*N*-Chloro succinimid
NMR	Nuclear Magnetic Resonance
OMe	Methoxy
OER	Oxygen evolution reaction
Ph	Phenyl
PODIC	Peroxodicarbonate
POSI	Phenoyloxy succinimide
ppm	Parts per million
NMR	Nuclear Magnetic Resonance
Q	Amount of applied charge
R_F	Retentionsfaktor
rt	Room temperature
SET	Single Electron Transfer
T	Temperature
TEMPO	2,2,6,6-Tetramethylpiperidinyloxyl
TMEDA	Tetramethylethylendiamin
TFA	Trifluoroacetic acid
Q	Amount of applied charge
t_R	Retention time
Ts	Tosyl
V	Potential
VA 1.4571	Stainless-steel type
vol%	Volume Percent
wt%	Weight percent
X^-	Halide
t_R	Retention time
ppm	Parts per million
NMR	Nuclear Magnetic Resonance
Q	Amount of applied charge

A-2 Supporting Information

A-2.1 Supporting Information: Electrochemical Synthesis of Isoxazoles and Isoxazolines via Anodic Oxidation of Oximes

ChemElectroChem

Supporting Information

Electrochemical Synthesis of Isoxazoles and Isoxazolines via Anodic Oxidation of Oximes

Silja Hofmann, Johannes Winter, Tobias Prenzel, María de Jesús Gálvez-Vázquez, and Siegfried R. Waldvogel*

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1. General Information

Unless otherwise stated, all chemicals were purchased and used without further purification. Anhydrous solvents were either purchased or dried over standard drying agents and freshly distilled prior to use. Reactions were monitored by TLC (Silica gel 60 F254, Merck KGaA, Darmstadt, Germany), GC (GC-2025, Shimadzu, Kyoto, Japan with quartz capillary column HP-5MS, Agilent Technologies, Santa Clara, California, USA) and GC-MS (GCMS-QP2010, Shimadzu, Kyoto, Japan with quartz capillary column HP-5MS, Agilent Technologies, Santa Clara, California, USA). The used method "*medium*" starts a 50 °C with a heating rate of 15 °C/min up to 310 °C. Flash column chromatography was performed on Silica Gel 60 M (40–63 µm, Machery-Nagel GmbH & Co., Düren, Germany) with a Büchi Sepacore system with Büchi Control Unit C-620, Büchi UV photometer C-635, Büchi fraction collector C-660 and two Büchi Pump Modules C-605 (Büchi-Labortechnik GmbH, Essen, Germany) or on a pre-packed PURIFLASH C18-HP 30 UM F0080 flash column (Interchim, Montluçon Cedex, France) with a Büchi Sepacore system in the same setup as described before. ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were acquired on a Bruker Avance III HD 300, Avance II 400, Avance III HD 400 or Avance III 600 (Bruker, Karlsruhe, Germany) in $CDCl_3$, CD_3CN at 25 °C with the solvent residual peaks as internal reference for ^{1}H and ^{13}C NMR spectra. Mass spectra via electrospray-ionization (ESI+/-) or atmospheric pressure chemical ionization (APCI+/-) mass spectrometry were recorded using an Agilent 6545 QTOF-MS (*Agilent*, Santa Clara (CA), USA). Parameter screenings of the electrolytic conditions were performed using an IKA Screening System Package (IKA-Werke GmbH & Co. KG, Staufen, Germany, Figure S1 left and center) with electrodes the size of 70 mm × 10 mm × 3 mm. The apparatus and detailed construction information is reported in literature.[1] The electrode surfaces were cleaned prior use. Isostatic graphite (C_{gr}, Sigrafine™ V2100, SGL Carbon, Bonn, Germany) was wet-polished with sandpaper (grade 1000 + 1200, Bosch, Stuttgart, Germany), rinsed with acetone and the abrasion was wiped off with a paper towel until the latter was not stained anymore. Platinum (OEGUSSA, Vienna, Austria), stainless-steel (1.4571) and nickel (*IKA Werke GmbH & Co. KG*, Staufen) were rinsed with water, acetone and acetonitrile. Glassy carbon (C_{gl}, SIGRADUR™ G, *HTW*, Thierhaupten, Germany), were rinsed with several solvents and wiped with a paper towel. Boron-doped diamond (BDD, DIACHEM™, 15 µm diamond layer on silicon support, CONDIAS GmbH, Itzehoe, Germany) was conditioned by electrolyzing as anode in 20% aqueous sulfuric acid (10 C/cm², 10 mA/cm²) and subsequently rinsed with water. Design of Experiments and statistical evaluation of the obtained data was performed with the software Minitab 19 (*Minitab GmbH*, Munich, Germany). Cyclic voltammetry was performed using a Metrohm 663 VA Stand equipped with a Autolab type III potentiostat (Metrohm AG, Herisau, Switzerland). Constant current electrolyses for scope and scale-up experiments were carried out in beaker-type cells (SynLectro™, *Merck KGaA*, Darmstadt, Germany) using TDK-Lambda Z+ series *(TDK-Lambda UK Limited*, Devon, UK) or multichannel power supply HMP4040 (*Rohde & Schwarz*, München, Germany) as power sources (Figure S1, right).



Figure S1: Schematic illustration of a screening block with undivided cells (left); Undivided teflon screening cell (center); jacketed beaker-type cells (2.00 – 5.00 mmol scale, 25 – 50 mL reaction volume) and beaker-type cell (20.0 mmol scale, 200 ml reaction volume) for scale-up (right).

2. Standard Operating Protocols

SOP 1: Screening for Suitable Electrolytic Conditions

In 5 mL PTFE cells, the respective oxime, alkyne and tributylmethylammonium methylsulfate (MTBS, 10 mg/mL) were dissolved in a mixture of acetonitrile and water at a given temperature under moderate stirring (magnetic stirrer set to approx. 500 rpm). The mixture was subjected to galvanostatic electrolysis using electrodes with a relevant surface area of 1.5 cm^2 (surface: 70 mm x 10 mm, immersion depth of 1.5 cm). The mixture was transferred to a flask and evaporated to dryness under reduced pressure. 1,3,5-Trimethoxybenzene (0.1 mmol, 16.8 mg) was added as internal standard and the mixture was dissolved in 0.3 mL $CDCl_3$. The solution was transferred to an NMR tube and the flask was rinsed with 0.2 mL $CDCl_3$, which were also added into the NMR tube. ^1H NMR spectra were acquired for quantification, whereby the aromatic protons of 1,3,5-trimethoxybenzene (6.05 ppm, s, 1H) and the proton in position 4 of the corresponding isoxazole (6.44 ppm, s, 1H) were used for integration.

SOP2: Electrochemical Synthesis of Isoxazoles A

The respective oxime (0.5 mmol, 1 eq.) and dipolarophile (1.5 mmol, 3 eq.) were placed in 5 mL PTFE cells and dissolved in 5 mL of tributylmethylammonium methylsulfate (MTBS, 10 mg/mL) in acetonitrile + 15 vol% water + 5 vol% 1,1,1,3,3,3-hexafluoroisopropanol (HFIP)). The mixture was subjected to galvanostatic electrolysis at 31 °C under moderate stirring (magnetic stirrer set to approx. 500 rpm) using a current density of 5 mA/cm^2, a graphite anode and a stainless-steel (1.4571) cathode with a relevant surface area of 1.5 cm^2 (surface: 70 mm x 10 mm, immersion depth of 1.5 cm), until an amount of charge of 2.9 *F* (142.3 C) was applied. In case full conversion of the starting material was not achieved (reaction control using TLC or GC-analysis), galvanostatic electrolysis was continued until the starting material was no longer detected. The reaction mixture was stirred at 31 °C until the cycloaddition-reaction was completed (approx. 4 h). The mixture was transferred to a flask and evaporated to dryness under reduced pressure. The crude product was purified by recrystallization or flash column chromatography.

SOP3: Electrochemical Synthesis of Isoxazoles B

The respective oxime (0.5 mmol, 1 eq.) and dipolarophile (1.5 mmol, 3 eq.) were placed in 5 mL PTFE cells and dissolved in 5 mL of tributylmethylammonium methylsulfate (MTBS, 10 mg/mL) in acetonitrile + 15 vol% HFIP. The mixture was subjected to galvanostatic electrolysis at 31 °C under moderate stirring (magnetic stirrer set to approx. 500 rpm) using a current density of 5 mA/cm^2, a graphite anode and a stainless-steel (1.4571) cathode with a relevant surface area of 1.5 cm^2 (surface: 70 mm x 10 mm, immersion depth of 1.5 cm), until an amount of charge of 2.9 *F* (142.3 C) was applied. The reaction mixture was stirred at 31 °C until the cycloaddition-reaction was completed (approx. 4 h). The mixture was transferred to a flask and evaporated to dryness under reduced pressure. The crude product was purified by recrystallization or flash column chromatography.

SOP4: Electrochemical Synthesis of Isoxazoles C

The respective oxime (0.5 mmol, 1 eq.) was placed in 5 mL PTFE cells and dissolved in 5 mL of tributylmethylammonium methylsulfate (MTBS, 10 mg/mL) in acetonitrile + 15 vol% water + 5 vol% HFIP. The mixture was subjected to galvanostatic electrolysis at 31 °C under moderate stirring (magnetic stirrer set to approx. 500 rpm) using a current density of 5 mA/cm^2, a graphite anode and a stainless-steel (1.4571) cathode with a relevant surface area of 1.5 cm^2 (surface: 70 mm x 10 mm, immersion depth of 1.5 cm), until an amount of charge of 2.9 *F* (142.3 C) was applied. The respective dipolarophile (1.5 mmol, 3 eq.) was added and the mixture was stirred at 31 °C until the cycloaddition-reaction was completed (approx. 4 h). The mixture was transferred to a flask and evaporated to dryness under reduced pressure. The crude product was purified by recrystallization or flash column chromatography.

SOP5: Electrochemical Synthesis of Isoxazoles D

The respective oxime (2.50 mmol or 5.00 mmol, 1 eq.) and dipolarophile (7.50 mmol or 15.00 mmol, 3 eq.) was placed in a 50 mL jacketed beaker-type cell, equipped with a cross-shaped stirring bar and dissolved in 25 mL or 50 mL of tributylmethylammonium methylsulfate (MTBS, 10 mg/mL) in acetonitrile + 15 vol% water + 5 vol% 1,1,1,3,3,3-hexafluoroisopropanol (HFIP). The mixture was subjected to galvanostatic electrolysis at 31 °C under moderate stirring (magnetic stirrer set to approx. 500 rpm) using a current density of 5 mA/cm^2, a graphite anode and a stainless-steel (1.4571) cathode with a relevant surface area of 5 cm^2 (surface: 25 mm x 20 mm, immersion depth of 2.5 cm) or 7 cm^2 (surface: 35 mm x 20 mm, immersion of 3.5 cm), until an amount of charge of 2.9 *F* (699.5 C or 1399.0 C) was applied. The mixture was stirred at 31 °C until the cycloaddition-reaction was completed (approx. 4 h), transferred to a flask and evaporated to dryness under reduced pressure. The crude product was purified by recrystallization or flash column chromatography.

SOP6: Synthesis of Oximes

The respective aldehyde was dissolved in ethanol and pyridine (1.8 eq.) at room temperature. Hydroxylamine hydrochloride (1.4 – 2.0 eq.) was added in portions and the resulting solution was stirred until completion of the reaction. The solvent of the reaction mixture was removed under reduced pressure and ethyl acetate was added. The organic layer was washed once with water, twice with 1 m hydrochloric acid, once with saturated sodium bicarbonate solution and once with brine. The organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude products were purified by recrystallisation or flash column chromatography.

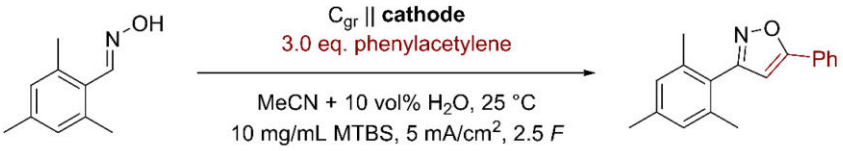
3. Screening for Suitable Electrolytic Conditions

Screening reactions were carried out according to SOP1 using 2,4,6-trimethylbenzaldehyde oxime (**6a**) as test substrate and phenylacetylene as dipolarophile. Unless stated otherwise, yields were determined using ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

3.1. Screening of Cathode Materials

Anode material, solvent system and supporting electrolyte were chosen based on previous publications. Thus, graphite was used as anode material, as it showed excellent performance in the formation of nitrile oxide intermediates.[2,3] MTBS was chosen as supporting electrolyte, acetonitrile was employed as organic solvent with water as additive to enable hydrogen evolution as cathodic counter reaction.[4] The investigated cathode materials were chosen based on their suitability for hydrogen evolution as the desired counter reaction (platinum, stainless-steel, nickel). Additionally, carbon-based electrode materials were tested as cathodes, as they showed poor performance in the electrochemical reduction of nitrile oxides to the corresponding nitriles (BDD, glassy carbon, gra-phite).[2] Amongst the tested materials, the nickel, stainless-steel (1.4571) and platinum proved superior to the carbon-based cathodes. As stainless-steel and platinum gave comparable results, inexpensive and abundant stainless-steel was used for further reaction optimization (Table S1).

Table S1: Screening for cathode materials using 2,4,6-trimethylbenzaldehyde oxime (**6a**) as test substrate.



anode	cathode	yield[a]
graphite	stainless-steel (1.4571)	59%
graphite	platinum	60%
graphite	nickel	56%
graphite	graphite	49%
graphite	glassy carbon	42%
graphite	BDD	46%

Reaction conditions: 0.5 mmol substrate, 3 eq. phenylacetylene, MeCN + 10 vol% H_2O (5 mL), 10 mg/mL MTBS, 25 °C

[a] Quantification using ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

3.2. Reaction Optimization via Design of Experiments

Reaction optimization with regards to current density, amount of applied charge, substrate concentration, amount of dipolarophile, temperature and amount of water as additive was performed using design of experiments (DoE). For investigation of those 6 parameters, a fractional factorial design was chosen (2^{6-2}, resolution IV with central point and rotatable axis points). Reactions were carried out according to SOP1, each data point, including the central point, was acquired twice (Table S2, entry 1 – 16). For expansion to a response surface design, star points were acquired once (Table S2, entry 17 – 28).

Table S2: DoE optimisation for the conversion of aldoxime 6a using phenylacetylene as alkyne.

Experiment	Run	*T* / °C	*j* / mA/cm²	*Q* / *F*	Vol% H_2O	*n*(substrate)	eq. alkyne	yield[a]
1	1	25	7.5	2	10	0.500	4	41%
	2	25	7.5	2	10	0.500	4	41%
2	3	25	2.5	2	10	0.750	4	45%
	4	25	2.5	2	10	0.750	4	46%
3	5	25	2.5	4	1.0	0.750	4	42%
	6	25	2.5	4	1.0	0.750	4	48%
4	7	25	7.5	2	1.0	0.750	2	50%
	8	25	7.5	2	1.0	0.750	2	49%
5	9	25	2.5	2	1.0	0.500	2	48%
	10	25	2.5	2	1.0	0.500	2	45%
6	11	25	7.5	4	10	0.750	2	43%
	12	25	7.5	4	10	0.750	2	45%
7	13	25	7.5	4	1.0	0.500	4	47%
	14	25	7.5	4	1.0	0.500	4	49%
8	15	25	2.5	4	10	0.500	2	42%
	16	25	2.5	4	10	0.500	2	45%
9	17	37.5	4.5	3	5.5	0.625	3	59%
	18	37.5	4.5	3	5.5	0.625	3	59%
10	19	50	7.5	2	1.0	0.750	4	46%
	20	50	7.5	2	1.0	0.750	4	44%
11	21	50	2.5	2	1.0	0.500	4	39%
	22	50	2.5	2	1.0	0.500	4	41%
12	23	50	2.5	2	10	0.750	2	37%
	24	50	2.5	2	10	0.750	2	36%
13	25	50	2.5	4	10	0.500	4	47%
	26	50	2.5	4	10	0.500	4	49%
14	27	50	7.5	4	10	0.750	4	50%
	28	50	7.5	4	10	0.750	4	49%
15	29	50	7.5	2	10	0.500	2	52%
	30	50	7.5	2	10	0.500	2	54%
16	31	50	7.5	4	1.0	0.500	2	44%
	32	50	7.5	4	1.0	0.500	2	44%

17	33	37.5	2.5	3	5.5	0.625	3	63%
18	34	37.5	7.5	3	5.5	0.625	3	54%
19	35	37.5	5.0	2	5.5	0.625	3	60%
20	36	37.5	5.0	4	5.5	0.625	3	56%
21	37	37.5	5.0	3	1.0	0.625	3	61%
22	38	37.5	5.0	3	10	0.625	3	64%
23	39	25	5.0	3	5.5	0.625	3	68%
24	40	50	5.0	3	5.5	0.625	3	53%
25	41	37.5	5.0	3	5.5	0.500	3	61%
26	42	37.5	5.0	3	5.5	0.750	3	61%
27	43	37.5	5.0	3	5.5	0.625	2	54%
28	44	37.5	5.0	3	5.5	0.625	4	55%

Reaction conditions: 5 mL PTFE cells, solvent: MeCN + H_2O as additive, 10 mg/mL MTBS as supporting electrolyte, magnetic stirrer set to approx. 500 rpm. Reaction duration: 24 h.
[a] Yield determined using ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.

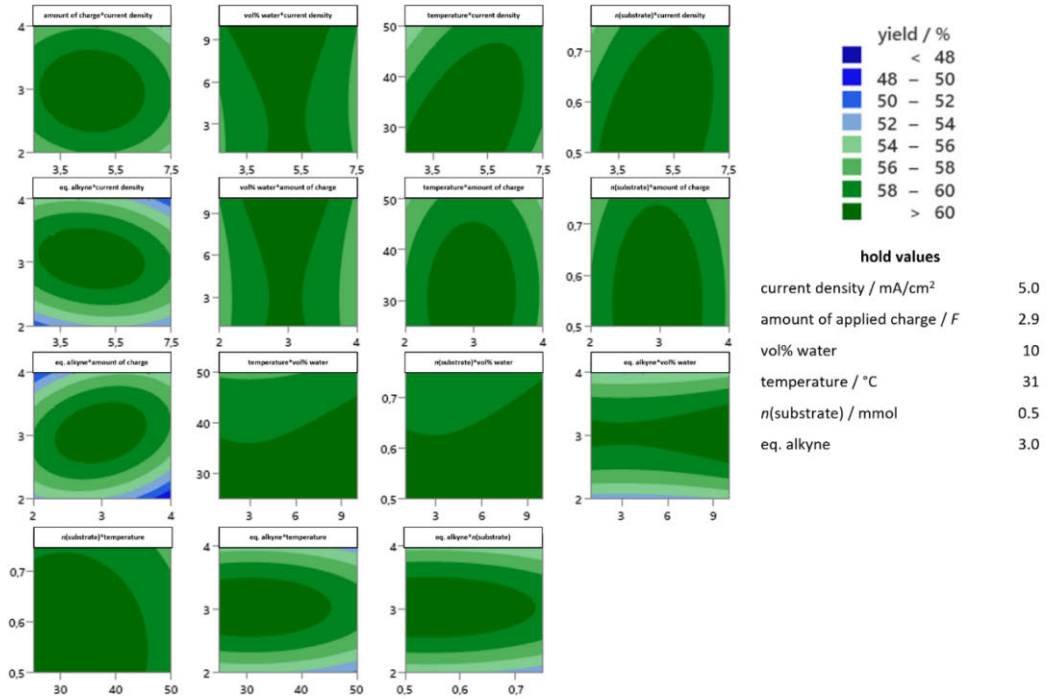


Figure S2: Contour plots of yield for the DoE-based optimization of current density (mA/cm^2), amount of applied charge (*F*), water as additive (vol% in MeCN as solvent), temperature (°C), amount of substrate (mmol) and equivalents of alkyne. Hold values set according to the predicted optimum conditions.

parameter setting	current density / mA/cm²	amount of appl. charge / *F*	vol% water	*T* / °C	*n*(oxime) / mmol	eq. alkyne
highest	7.5	4.0	10	50	0.75	4.0
lowest	2.5	2.0	1.0	25	0.50	2.0
predicted optimum	**5.0**	**2.9**	**10**	**31**	**0.50**	**3.0**

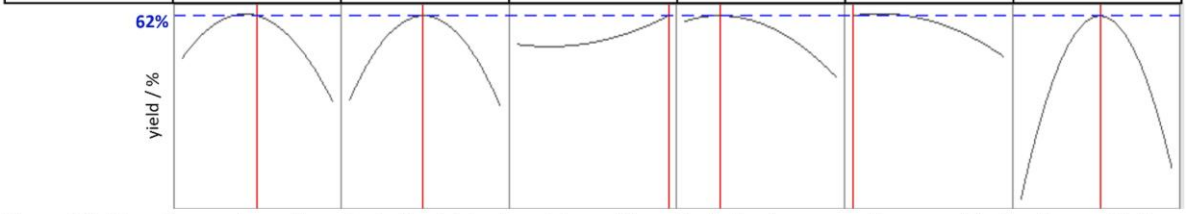


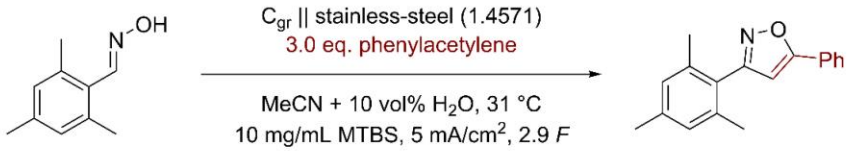
Figure S3: Top: Parameter settings including highest and lowest investigated values as well as predicted optimum. Bottom: Main effects plot for current density (mA/cm²), amount of applied charge (*F*), water as additive (vol% water in MeCN as solvent), temperature (°C), amount of substrate (mmol) and equivalents of alkyne with regards to yield; Predicted optimum marked with red line, predicted maximum yield highlighted in blue.

Maxima were obtained for current density, amount of charge, temperature and alkyne equivalents. Thus, values for these parameters were set as obtained by target optimization. However, amount of water as additive as well as the concentration of the starting material did not reach an optimum within the parameter settings chosen for DoE and further optimization was performed using a linear screening approach.

3.3. Screening for Optimum Starting Material Concentration, Reaction Time and Amount of Additive

Screening reactions were carried out according to SOP1 using 2,4,6-trimethylbenzaldehyde oxime (**6a**) as test substrate and phenylacetylene as dipolarophile. Unless stated otherwise, yields were determined using ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.
Screening for optimum starting material concentration was performed with regards to the results obtained using DoE. Thus, current density, amount of charge, temperature, amount of water as additive and equivalents of alkyne were set according to target optimization conditions. To verify the obtained optimum starting material concentration, lower concentrations were investigated (Table S3).

Table S3: Screening for starting material concentration.



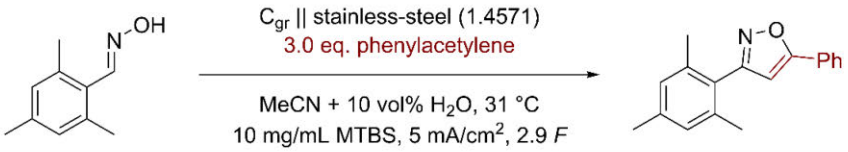
***c* (oxime) / mol/L**	***n* (oxime) / mmol**	**yield[a]**
0.10	0.50	57%
0.09	0.45	57%
0.08	0.40	45%
0.07	0.35	54%
0.06	0.30	49%
0.05	0.25	46%

Reaction conditions: 5 mL PTFE cells, magnetic stirrer set to approx. 500 rpm. Work-up after 3 h post electrolysis stirring.
[a] Quantification using ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

The reaction proceeded smoothly for starting material concentrations of 0.1 and 0.9 M. For lower concentration a drop in yield was obtained. Thus, further optimization was performed with oxime concentrations of 1.0 M.

Besides substrate oxidation, the cycloaddition rate of intermediary formed nitrile *N*-oxide and dipolarophile must be considered. As full conversion of the substrate was achieved within the electrolysis time, the influence of the overall reaction time including post electrolysis stirring was investigated (Table S4).

Table S4: Screening for reaction time (post electrolysis stirring).

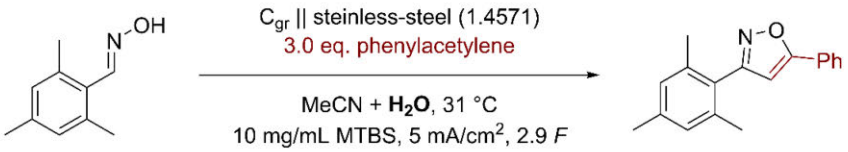


***t*(electrolysis)**	**post electrolysis stirring**	**overall reaction time**	**yield[a]**
5 h	0 h	5 h	45%
5 h	2 h	7 h	52%
5 h	4 h	9 h	63%
5 h	6 h	11 h	63%
5 h	19 h	24 h	63%

Reaction conditions: 5 mL PTFE cells, *n*(oxime) = 0.5 mmol, magnetic stirrer set to approx. 500 rpm.
[a] Quantification using ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.

After 4 h of post-electrolysis stirring, the maximum yield of 63% of isoxazole **7a** was reached. No further increase was noticeable after longer post-electrolysis stirring.
To investigate, whether the reaction of interest benefits from higher amounts of protic additives as indicated by DoE, a linear screening was performed (Table S5).

Table S5: Screening for optimum amount of protic additive.



amount of protic additive	**yield**
10 vol% H_2O	63%[a]
15 vol% H_2O	64%[a] (66%[b])
20 vol% H_2O	60%[a]
25 vol% H_2O	60%[a]
15 vol% H_2O + 5 vol% HFIP	75%[b]

Reaction conditions: 5 mL PTFE cells, magnetic stirrer set to approx. 500 rpm, *n*(oxime) = 0.5 mmol Reaction time: 24 h.
[a] Quantification using ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.
[b] Isolated yield.

4. Cyclic Voltammograms

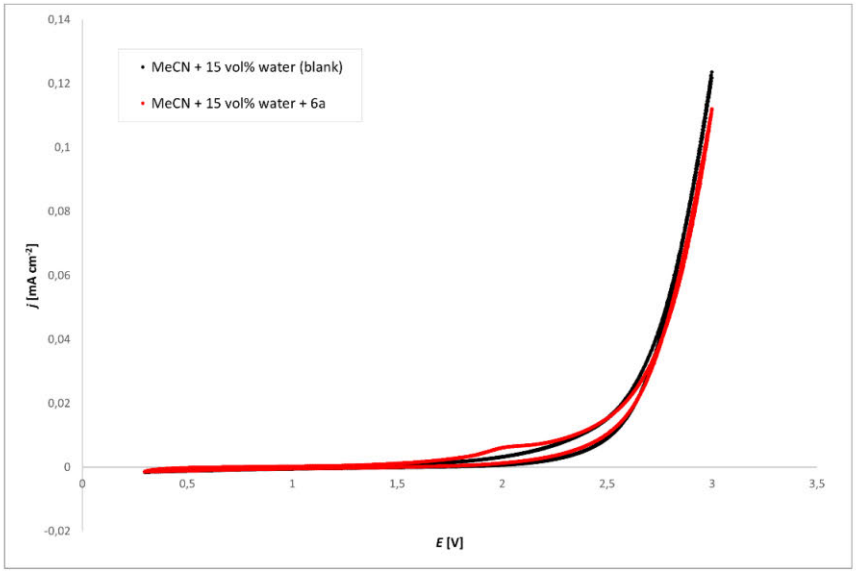


Figure S4: Cyclic voltammograms of mesitylaldoxime (6a) in MeCN + 15 vol% water as solvent.
Working electrode: glassy carbon, counter electrode: Pt, reference electrode: Ag/AgCl in sat. LiCl/EtOH. Scan rate: 100 mV/s.
Supporting electrolyte: 0.5 M MTBS; *c*(**6a**) = 5.0 m M.

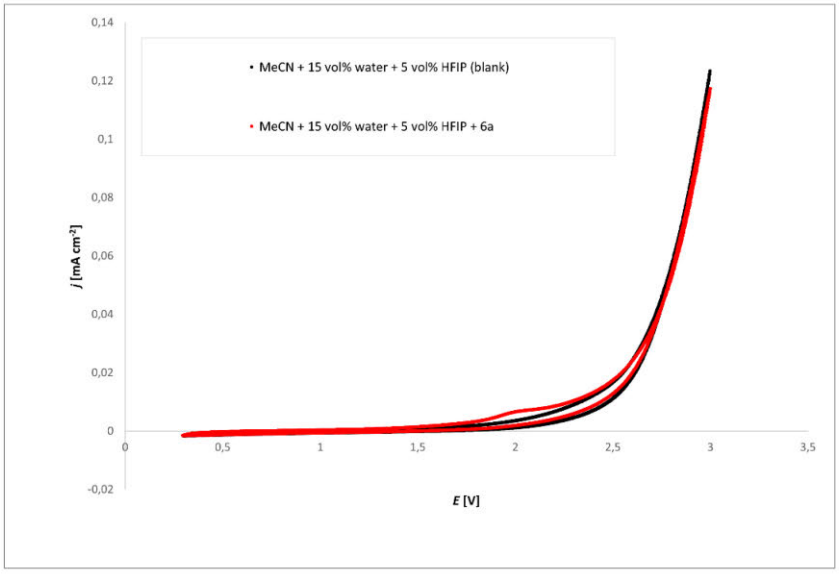
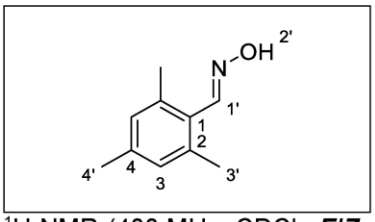


Figure S5: Cyclic voltammograms of mesitylaldoxime (6a) in MeCN + 15 vol% water + 5 vol% HFIP as solvent.
Working electrode: glassy carbon, counter electrode: Pt, reference electrode: Ag/AgCl in sat. LiCl/EtOH. Scan rate: 100 mV/s.
Supporting electrolyte: 0.5 M MTBS; *c*(**6a**) = 5.0 mM.

5. Synthesized Oximes, Isoxazoles, Isoxazolines and Oxadiazoles

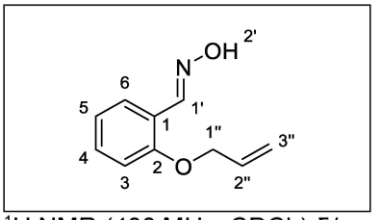
2,4,6-Trimethylbenzaldehyde oxime (6a)



The synthesis was carried out according to SOP6 using mesitylaldehyde (**0.175 mol, 25.91 g, 1.0 eq.**), hydroxylamine hydrochloride (**0.245 mol, 17.03 g, 1.4 eq.**), pyridine (**0.315 mol, 25 mL, 1.8 eq.**) and 150 mL ethanol. The product was obtained after work-up without further purification as a beige solid (**0.167 mol**, **27.30 g, 95%**).

^{1}H NMR (400 MHz, $CDCl_3$, ***E*/*Z* oxime**) δ/ppm: 8.86 (s, 1H, *H*-2'), 8.46 (s, 1H, *H*-1'), 7.68 (s, 1H, *H*-1'), 6.92 (s, 2H, *H*-3), 2.42 (s, 6H, *H*-3'), 2.33 (s, 3H, *H*-4'), 2.29 (s, 3H, *H*-4').
^{13}C NMR (101 MHz, $CDCl_3$, ***E*/*Z* oxime**) δ/ppm: 149.8, 148.7, 139.0. 138.8, 137.5, 135.9, 129.4, 128.2, 127.6, 126.5, 21.2, 21.2, 21.1, 19.9.
GC-MS (EI): t_R = 9.543 min (method „*medium*"); *m*/*z* = 163.
Known compound, spectroscopic data corresponds to literature.[5]

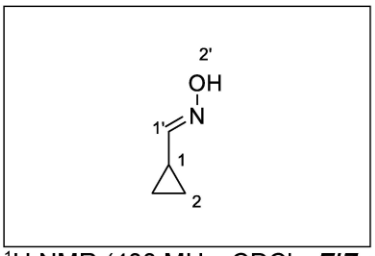
2-Allyloxybenzaldehyde oxime (6n)



The synthesis was carried out according to SOP6 using 2-allyloxybenzaldehyde (**0.010 mol, 1.62 g, 1.0 eq.**), hydroxylamine hydrochloride (**0.014 mol, 1.04 g, 1.4 eq.**), pyridine (**0.012 mol, 0.94 g, 1.2 eq.**) and 20 mL ethanol. The product was obtained without further purification as a colourless oil (**0.096 mol**, **1.70 g, 96%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.58 (s, 1H, *H*-2'), 8.61 (s, 1H, *H*-1'), 7.75 (dd, *J* = 7.7, 1.7 Hz, 1H, *H*-6), 7.34 (ddd, *J* = 8.4, 7.4, 1.7 Hz, 1H, *H*-4), 7.01 – 6.96 (m, 1H, *H*-5), 6.91 (d, *J* = 9.5 Hz, 1H, *H*-3), 6.07 (ddt, *J* = 17.3, 10.4, 5.2 Hz, 1H, *H*-2''), 5.45 – 5.40 (m, 1H, *H*-(3'')'), 5.33 – 5.29 (m, 1H, *H*-(3'')''), 4.59 (dt, *J* = 5.2, 1.6 Hz, 2H, *H*-1'').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 156.7, 146.6, 132.9, 131.3, 127.0, 121.0, 120.8, 117.8, 112.6, 69.2.
HRMS (ESI+), *m*/*z*: calculated for $C_{10}H_{11}NO_2$ + H^+ 178.0863 $[M+H]^+$, found 178.0854.
Known compound, spectroscopic data corresponds to literature.[6]

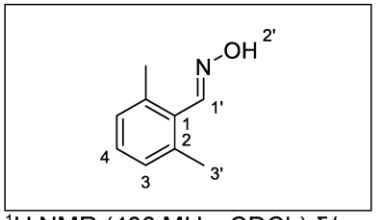
Cyclopropanecarbaldehyde oxime (6p)



The synthesis was carried out according to SOP6 using cyclopropyl carbaldehyde (**0.048 mol, 3.39 g, 1.0 eq.**), hydroxylamine hydrochloride (**0.067 mol, 4.66 g, 1.4 eq.**), pyridine (**0.086 mol, 6.80 g, 1.8 eq.**) and 50 mL ethanol. The product was obtained after recrystallisation (cyclohexane:ethanol 9:1 (*v*/*v*), 30 mL, crystallisation at 35 °C) as a colourless solid (**0.041 mol**, **3.49 g, 85%**).Decomposition of the oxime was observed during the final vacuum filtration.

^{1}H NMR (400 MHz, $CDCl_3$, ***E*/*Z* oxime**) δ/ppm: 8.67 (s, 1H, *H*-2'), 6.91 (d, *J* = 8.4 Hz, 1H, *H*-1'), 6.02 (d, *J* = 8.8 Hz, 1H, *H*-1'), 2.27 (qt, *J* = 8.4, 4.8 Hz, 1H, *H*-1), 1.61 (qt, J = 8.8, 4.8 Hz, 1H, *H*-1)), 0.98 – 0.91 (m, 1H, *H*-2), 0.89 – 0.82 (m, 1H, *H*-2), 0.64 – 0.59 (m, 2H, *H*-2).
^{13}C NMR (101 MHz, $CDCl_3$, ***E*/*Z* oxime**) δ/ppm: 155.5, 155.4, 11.0, 7.3, 6.1, 5.6.
HRMS (ESI+), *m*/*z*: calculated for C_4H_7NO + H^+ 86.0600 $[M+H]^+$, found 86.0599.
Known compound, spectroscopic data corresponds to literature.[7]

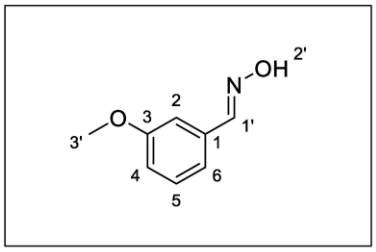
2,6-Dimethylbenzaldehyde oxime (6v)



The synthesis was carried out according to SOP6 using 2,6-dimethylbenzaldehyde (**0.008 mol, 1.06 g, 1.0 eq.**), hydroxylamine hydrochloride (**0.011 mol, 0.77 g, 1.4 eq.**), pyridine (**0.014 mol, 1.12 g, 1.8 eq.**) and 15 mL ethanol. The product was obtained after work-up without further purification as a beige solid (**0.0057 mol**, **0.85 g, 71%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.24 (s, 1H, *H*-2'), 8.50 (s, 1H, *H*-1'), 7.22 (t, *J* = 7.6 Hz 1H, *H*-4), 7.12 (d, *J* = 7.6 Hz, 2H, *H*-3), 2.47 (s, 6H, *H*-3').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 149.7, 137.5, 129.4, 129.1, 128.5, 21.1.
GC-MS (EI): t_R = 8.950 min (method „*medium*"); *m*/*z* = 149.
Known compound, spectroscopic data corresponds to literature.[8]

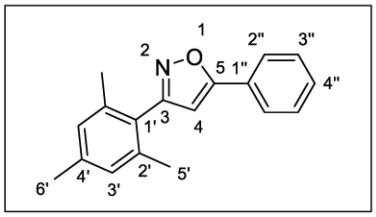
3-Methoxybenzaldehyde oxime (6w)



The synthesis was carried out according to SOP6 using 3-methoxybenzaldehyde (**0.025 mol, 3.41 g, 1.0 eq.**), hydroxylamine hydrochloride (**0.050 mol, 3.91 g, 2.0 eq.**), pyridine (**0.045 mol, 3.56 g, 1.8 eq.**) and 50 mL ethanol. The product was obtained after flash column chromatography (SiO_2, cyclohexane:ethyl acetate; 0% → 10% EtOAc) as a colourless oil (**0.0215 mol**, **3.25 g, 86%**).

^{1}H NMR (400 MHz, $CDCl_3$, ***E*/*Z* oxime**) δ/ppm: 9.45 (s, 1H, *H*-2'), 8.18 (s, 1H, *H*-1'), 7.65 (dd, *J* = 2.7, 1.5 Hz, 1H, *H*-2), 7.50 – 7.46 (m, 1H, *H*-5), 7.36 (t, *J* = 8.0 Hz, 1H, *H*-6), 7.31 (t, *J* = 7.9 Hz, 1H, *H*-5), 7.20 (dd, *J* = 2.7, 1.5 Hz, 1H, *H*-2), 7.16 – 7.14 (m, 1H, *H*-6), 7.01 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H, *H*-4), 6.96 (ddd, *J* = 8.3, 2.7, 1.0 Hz, 1H, *H*-4), 3.82 (s, 3H, *H*-3').
^{13}C NMR (101 MHz, $CDCl_3$, ***E*/*Z* oxime**) δ/ppm: 159.9, 159.5, 150.5, 146.6, 133.2, 131.0, 129.9, 129.6, 123.9, 120.3, 117.0, 116.6, 116.2, 111.3, 55.4.
HRMS (ESI+), *m*/*z*: calculated for $C_8H_9NO_2$ + H^+ 152.0706 $[M+H]^+$, found 152.0705.
Known compound, spectroscopic data corresponds to literature.[9]

3-Mesityl-5-phenylisoxazole (7a)



The synthesis was carried out according to SOP2 using mesitylaldoxime (**6a**, **0.50 mmol**, **82 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a light-yellow solid (**0.33 mmol**, **87 mg**, **75%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.87 (s, 2H, *H*-2''), 7.55 – 7.42 (m, 3H, *H*-3''), 6.98 (s, 2H, *H*-3'), 6.49 (s, 1H. *H*-4), 2.36 (s, 3H, *H*-6'), 2.22 (s, 6H, *H*-5').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 169.8, 162.9, 138.9, 137.3, 130.2, 129.1, 128.5, 127.7, 126.3, 125.9, 101.0, 21.2, 20.4.
HRMS (ESI+), *m*/*z*: calculated for $C_{18}H_{17}NO$ + H^+ 264.1383 $[M+H]^+$, found 264.1384.

Scale-up (2.50 mmol):

The synthesis was carried out according to SOP5 using mesitylaldoxime (**6a**, **2.50 mmol**, **408 mg**, **1 eq.**) and phenylacetylene (**7.50 mmol**, **765 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a light-yellow solid (**1.81 mmol**, **476 mg**, **72%**).

Scale-up (5.00 mmol) and solvent-recycling:

A) The synthesis was carried out according to SOP5. Mesitylaldoxime (**6a**, **5.00 mmol**, **815 mg**, **1 eq.**) and phenylacetylene (**15 mmol**, **1.53 mg**, **3 eq.**) were placed in a 50 mL jacketed beaker-type cell, equipped with a cross-shaped magnetic stirring bar. 50 mL of 10 mg/mL MTBS in acetonitrile + 15 vol% water + 5 vol% HFIP were added. The mixture was subjected to galvanostatic electrolysis at 31 °C under moderate stirring (magnetic stirrer set to approx. 500 rpm) using a current density of 5 mA/cm^2, a graphite anode and a stainless-steel (1.4571) cathode with a relevant surface area of 7 cm^2 (surface: 35 mm x 20 mm, immersion depth of 3.5 cm), until an amount of charge of 2.9 *F* (699.5 C) was applied. The mixture was stirred at 31 °C until the cycloaddition-reaction was completed (approx. 4 h), transferred to a flask and the solvent mixture distilled at 60 °C under reduced pressure (300 mbar → 100 mbar). The receiver flask was immersed in liquid nitrogen and the solvent mixture kept for reuse. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a light-yellow solid (**3.65 mmol**, **964 mg**, **73%**).

B) For investigation of solvent-mixture recyclability, mesitylaldoxime (**6a**, **5.00 mmol**, **815 mg**, **1 eq.**), phenylacetylene (**15 mmol**, **1.53 g**, **3 eq.**) and 500 mg MTBS were placed in a 50 mL jacketed beaker-type cell. The solvent mixture obtained by distillation (from A) was added and the mixture subjected to galvanostatic electrolysis as described above. The solvent mixture was again distilled from the crude reaction mixture and the product obtained after column chromatography as a light-yellow solid (**3.64 mmol**, **961 mg**, **73%**).

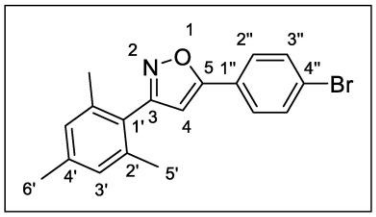
C) The solvent mixture obtained by distillation (from B) was reused a second time, following the procedure described above. The product was obtained after column chromatography as a light-yellow solid (**3.88 mmol**, **1.03 g**, **77%**).

Scale-up (20.0 mmol):

The synthesis was carried out according to SOP5. Mesitylaldoxime (**6a**, **20.0 mmol**, **3.26 g**, **1 eq.**) and phenylacetylene (**60.0 mmol**, **6.12 g**, **3 eq.**) were placed in a 200 mL beaker-type cell. 200 mL of 10 mg/mL MTBS in acetonitrile + 15 vol% water + 5 vol% HFIP were added. The mixture was subjected to galvanostatic electrolysis under moderate stirring (magnetic stirrer set to approx. 500 rpm) using a current density of 5 mA/cm^2, a graphite anode and a stainless-steel (1.4571) cathode with a relevant surface area of 28 cm^2 (surface: 80 mm x 40 mm, immersion depth of 7.0 cm), until an amount of charge of 2.9 *F* (5596.1 C) was applied The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a light-yellow solid (**13.4 mmol**, **3.53 g**, **67%**).

Known compound, spectroscopic data corresponds to literature.[10]

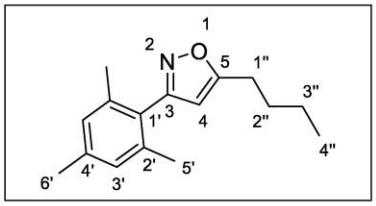
5-(4-Bromophenyl)-3-mesitylisoxazole (7b)



The synthesis was carried out according to SOP2 using mesitylaldoxime (**0.50 mmol**, **82 mg**, **1 eq.**) and 4-bromphenylacetylen (**1.50 mmol**, **271 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a pale-yellow solid (**0.29 mmol**, **102 mg**, **60%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.71 (s, 2H, *H*-2''), 7.65 – 7.59 (m, 2H, *H*-3''), 6.97 (s, 2H, *H*-3'), 6.48 (s, 1H, *H*-4), 2.34 (s, 3H, *H*-6'), 2.19 (s, 6H, *H*-5').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 168.8, 163.0, 139.1, 137.3, 132.4, 128.5, 127.4, 126.6, 126.0, 124.6, 101.5, 21.3, 20.4.
HRMS (ESI+), *m/z*: calculated for $C_{18}H_{16}{}^{79}BrNO + H^+$ 342.0488 $[M+H]^+$, found 342.0483; calculated for $C_{18}H_{16}{}^{81}BrNO + H^+$ 344.0469 $[M+H]^+$, found 344.0465.

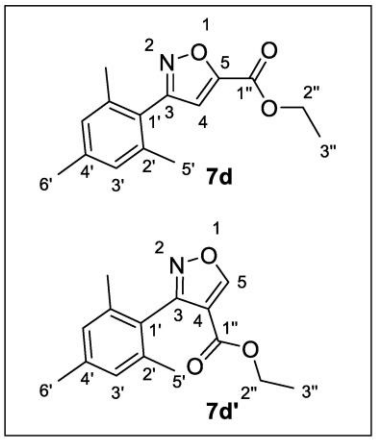
5-Butyl-3-mesitylisoxazole (7c)



The synthesis was carried out according to SOP2 using mesitylaldoxime (**0.50 mmol**, **82 mg**, **1 eq.**) and 1-hexyne (**1.50 mmol**, **123 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a colourless oil (**0.24 mmol**, **59 mg**, **49%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.93 (s, 2H, *H*-3'), 5.91 (s, 1H, *H*-4), 2.87 – 2.78 (m, 2H, *H*-1''), 2.32 (s, 3H,*H*-6'), 2.15 (s, 6H, *H*-5'), 1.81 – 1.70 (m, 2H, *H*-2''), 1.44 (h, *J* = 7.4 Hz, 2H, *H*-3''), 0.98 (t, *J* = 7.4 Hz, 3H, *H*-4'').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 173.6, 162.1, 138.7, 137.3, 128.4, 126.7, 102.3, 29.7, 26.6, 22.3, 21.2, 20.3, 13.8.
HRMS (ESI+), *m/z*: calculated for $C_{16}H_{21}NO + H^+$ 244.1696 $[M+H]^+$, found 244.1686.

Ethyl 3-mesitylisoxazole-5-carboxylate (7d) and ethyl 3-mesitylisoxazole-4-carboxylate (7d')

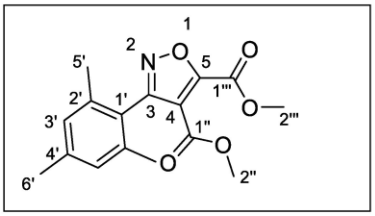


The synthesis was carried out according to SOP2 using mesitylaldoxime (**0.50 mmol**, **82 mg**, **1 eq.**) and ethyl propiolate (**1.50 mmol**, **147 mg**, **3 eq.**) as dipolarophile. Two regioisomers were obtained as products on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as colourless oils (**7d**, **0.15 mmol**, **40 mg**, **31%** and **7d'**, **0.15 mmol**, **39 mg**, **30%**).
If the synthesis was carried out according to SOP3, the regioisomers were obtained in the following ratio: **7d**, **0.14 mmol**, **37 mg**, **29%** and **7d'**, **0.02 mmol**, **7 mg**, **5%**.
If the synthesis was carried out according to SOP4 using ethyl (*E*)-3-(piperidin-1-yl)acrylate (**1.50 mmol, 275 mg, 3 eq.**) as dipolarophil only **7d'** (**0.21 mmol, 54 mg, 41%**) was obtained.

3-Mesitylisoxazole-5-carboxylate (7d):
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.95 (s, 2H, *H*-3'), 6.89 (s, 1H, *H*-4), 4.47 (q, *J* = 7.1 Hz, 2H, *H*-2''), 2.33 (s, 3H, *H*-6'), 2.13 (s, 6H, *H*-5'), 1.44 (t, *J* = 7.1 Hz, 3H, *H*-3'').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 162.9, 160.5, 157.1, 139.5, 137.3, 128.7, 125.0, 111.1, 62.5, 21.3, 20.4, 14.3.
HRMS (ESI+), *m/z*: calculated for $C_{15}H_{17}NO_3$ + H^+ 260.1281 $[M+H]^+$, found 260.1282.

3-Mesitylisoxazole-5-carboxylate (7d'):
^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.06 (s, 1H, *H*-5), 6.93 (s, 2H, *H*-3'), 4.17 (q, *J* = 7.1 Hz, 2H, *H*-2''), 2.32 (s, 3H, *H*-6'), 2.06 (s, 6H, *H*-5'), 1.16 (t, *J* = 7.1 Hz, 3H, *H*-3'').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 163.3, 161.0, 160.7, 139.1, 137.1, 128.2, 124.2, 114.4, 60.9, 21.3, 20.1, 14.0.
HRMS (ESI+), *m/z*: calculated for $C_{15}H_{17}NO_3$ + H^+ 260.1281 $[M+H]^+$, found 260.1282.

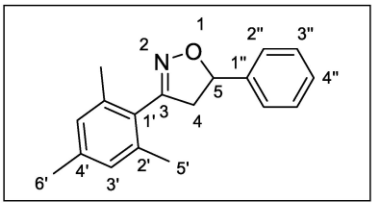
Dimethyl 3-mesitylisoxazole-4,5-dicarboxylate (7e)



The synthesis was carried out according to SOP2 using mesitylaldoxime (**0.50 mmol**, **82 mg**, **1 eq.**) and dimethyl acetylenedicarboxylate (**1.50 mmol**, **213 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica cyclohexane/ethyl acetate (0% → 15% EtOAc) as a colourless oil (**0.40 mmol**, **123 mg**, **81%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.92 (s, 2H, *H*-3'), 4.02 (s, 3H, *H*-2'''), 3.72 (s, 3H, *H*-2''), 2.31 (s, 3H, *H*-6'), 2.07 (s, 6H, *H*-5').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 162.1, 160.7, 160.2, 156.9, 139.6, 137.3, 128.3, 123.3, 116.4, 53.5, 52.7, 21.3, 20.0.
HRMS (ESI+), *m/z*: calculated for $C_{16}H_{17}NO_5$ + H^+ 304.1179 $[M+H]^+$, found 304.1176.
Known compound, spectroscopic data corresponds to literature.[11]

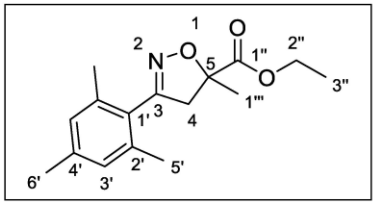
4,5-Dihydro-3-mesityl-5-phenylisoxazole (7f)



The synthesis was carried out according to SOP4 using mesitylaldoxime (**0.50 mmol**, **82 mg**, **1 eq.**) and styrene (**1.50 mmol**, **156 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a colourless oil (**0.39 mmol**, **101 mg**, **79%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.48 – 7.29 (m, 5H, *H*-2'', 3'', 4''), 6.90 (s, 2H, *H*-3'), 5.77 (dd, J = 10.9, 8.1 Hz, 1H, *H*-5), 3.61 (dd, J = 17.3, 10.9 Hz, 1H *H*-(4)'), 3.13 (dd, J = 17.3, 8.1 Hz, 1H, *H*-(4)''), 2.29 (s, 3H, *H*-6'), 2.23 (s, 6H, *H*-5').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 157.0, 141.3, 139.0, 136.7, 128.9, 128.6, 128.2, 126.1, 125.9, 81.9, 77.4, 47.4, 21.2, 19.9.
HRMS (ESI+), *m/z*: calculated for $C_{16}H_{19}NO$ + H^+ 266.1539 $[M+H]^+$, found 266.1544.
The compound is reported in literature.[12]

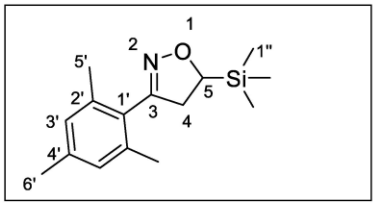
4,5-Dihydro-3-mesityl-5-phenylisoxazole (7g)



The synthesis was carried out according to SOP4 using mesitylaldoxime (**0.50 mmol**, **82 mg**, **1 eq.**) and ethyl methacrylate (**1.50 mmol**, **171 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a colourless oil (**0.25 mmol**, **70 mg**, **50%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.91 (s, 2H, *H*-3'), 4.29 (q, *J* = 7.2 Hz, 2H, *H*-2''), 3.67 (d, *J* = 17.6 Hz, 1H, *H*-(4)'), 3.03 (d, *J* = 17.6 Hz, 1H, *H*-(4)''), 2.29 (s, 3H, *H*-6'), 2.24 (s, 6H, *H*-5'), 1.73 (s, 3H, *H*-1'''), 1.34 (t, *J* = 7.1 Hz, 3H, *H*-3'').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 172.29, 157.31, 139.11, 136.75, 128.61, 125.70, 85.43, 62.16, 48.93, 23.57, 21.21, 19.70, 14.23.
HRMS (ESI+), *m/z*: calculated for $C_{16}H_{21}NO_3$ + Na^+ 298.1414 $[M+Na]^+$, found 298.1417.

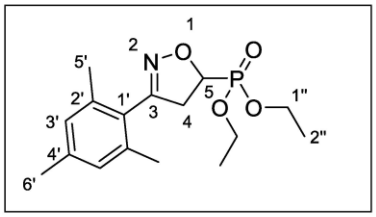
4,5-Dihydro-3-mesityl-5-(trimethylsilyl)-isoxazole (7h)



The synthesis was carried out according to SOP4 using mesitylaldoxime (**0.50 mmol**, **82 mg**, **1 eq.**) and trimethylvinylsilane (**1.50 mmol**, **222 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 2% EtOAc) as a colourless oil (**0.21 mmol**, **55 mg**, **42%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.90 (s, 2H, *H*-3'), 4.09 (dd, *J* = 16.2, 11.1 Hz, 1H, *H*-(4)'), 3.22 (dd, *J* = 16.6, 11.1 Hz, 1H, *H*-(4)''), 2.98 (t, *J* = 16.4 Hz, 1H, *H*-5), 2.29 (s, 3H, *H*-6'), 2.24 (s, 6H, *H*-5'), 0.19 (s, 9H, *H*-1'').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 157.2, 138.6, 136.5, 128.5, 126.9, 73.3, 42.2, 21.2, 19.8, -3.7.
HRMS (ESI+), *m/z*: calculated for $C_{15}H_{23}NOSi$ + H^+ 262.1622 $[M+H]^+$, found 262.1617.

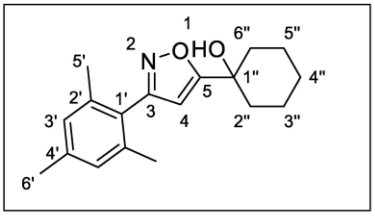
5-(Diethoxyphosphoryl)-4,5-dihydro-3-mesityl-isoxazole (7i)



The synthesis was carried out according to SOP4 using mesitylaldoxime (**0.50 mmol**, **82 mg**, **1 eq.**) and diethyl vinylphosphonate (**1.50 mmol**, **246 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a colourless oil (**0.28 mmol**, **91 mg**, **56%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.90 (s, 2H, *H*-3'), 4.87 (ddd, *J* = 12.2, 10.0, 2.3 Hz, 1H, *H*-5), 4.37 – 4.18 (m, 4H, *H*-1''), 3.61 – 3.36 (m, 2H, *H*-4), 2.29 (s, 3H, *H*-6'), 2.26 (s, 6H, *H*-5'), 1.38 (td, *J* = 7.1, 2.6 Hz, 6H, *H*-2'').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 157.2 (d, *J* = 6.6 Hz), 139.2, 136.8, 128.7, 125.0, 74.5 (d, *J* = 169.2 Hz), 63.6 (d, *J* = 7.2 Hz), 63.4 (d, *J* = 6.7 Hz), 41.7, 21.2, 19.8, 16.6 (d, *J* = 5.6 Hz).
^{31}P NMR (162 MHz, $CDCl_3$) δ/ppm: 18.9.
HRMS (ESI+), *m/z*: calculated for $C_{16}H_{24}NO_4P$ + H^+ 326.1516 $[M+H]^+$, found 326.1515.

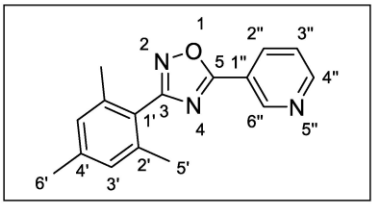
5-(1-Hydroxycyclohexyl)-3-mesitylisoxazole (7j)



The synthesis was carried out according to SOP2 using mesitylaldoxime (**0.50 mmol**, **82 mg**, **1 eq.**) and 1-ethynylcyclohexan-1-ol (**1.50 mmol**, **186 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on C_{18}-silica with water/acetonitrile (20% → 70% MeCN) as a colourless solid (**0.27 mmol**, **78 mg**, **55%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.91 (s, 2H, *H*-3'), 6.09 (s, 1H, *H*-4), 2.31 (s, 3H, *H*-6'), 2.13 (s, 6H, *H*-5'), 2.10 – 1.99 (m, 2H, *H*-(2'')', (6'')'), 1.98 – 1.88 (m, 2H, *H*-(2'')'', (6'')''), 1.86 – 1.70 (m, 2H, *H*-(3'')', (5'')'), 1.70 – 1.52 (m, 3H, *H*-(3'')'', (5'')'', (4'')'), 1.48 – 1.34 (m, 1H, *H*-(4'')'').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 177.8, 162.1, 138.9, 137.3, 128.5, 126.3, 101.3, 70.6, 36.8, 25.3, 21.8, 21.3, 20.4.
HRMS (ESI+), *m/z*: calculated for $C_{18}H_{23}NO_2$ + H^+ 286.1802 $[M+H]^+$, found 286.1802.

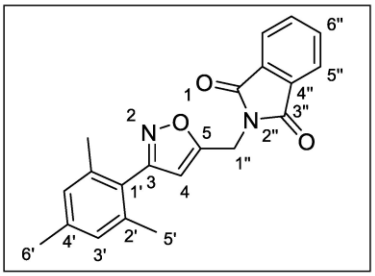
3-Mesityl-5-(pyridin-3-yl)-1,2,4-oxadiazole (7k)



The synthesis was carried out according to SOP2 using mesitylaldoxime (**0.50 mmol**, **82 mg**, **1 eq.**) and 3-cyanopyridine (**1.50 mmol**, **156 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a colourless solid (**0.33 mmol**, **87 mg**, **24%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 9.47 – 9.42 (m, 1H, *H*-6''), 8.84 (dd, *J* = 4.9, 1.7 Hz, 1H, *H*-4''), 8.48 (ddd, *J* = 8.0, 2.2, 1.8 Hz, 1H, *H*-2''), 7.52 (ddd, *J* = 8.0, 4.9, 0.9 Hz, 1H, *H*-3''), 7.00 – 6.95 (m, 2H, *H*-3'), 2.34 (s, 3H, *H*-6'), 2.34 – 2.21 (m, 6H, *H*-5').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 173.5, 169.2, 153.3, 149.2, 140.2, 137.9, 135.5, 128.8, 124.0, 123.5, 121.0, 21.4, 20.3.
HRMS (ESI+), *m/z*: calculated for $C_{16}H_{15}N_3O$ + H^+ 266.1288 $[M+H]^+$, found 266.1290.

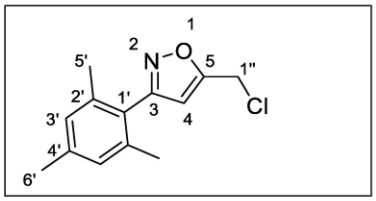
2-((3-Mesitylisoxazol-5-yl)methyl)isoindoline-1,3-dione (7l)



The synthesis was carried out according to SOP2 using mesitylaldoxime (**0.50 mmol**, **82 mg**, **1 eq.**) and *N*-propargylphthalimide (**1.50 mmol**, **277 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on C_{18}-silica with water/acetonitrile (20% → 80% MeCN) as a colourless solid (**0.29 mmol**, **102 mg**, **59%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.94 – 7.85 (m, 2H, *H*-5''), 7.80 – 7.71 (m, 2H, *H*-6''), 6.90 (s, 2H, *H*-3'), 6.20 (s, 1H, *H*-4), 5.10 – 5.00 (m, 2H, *H*-1''), 2.29 (s, 3H, *H*-6'), 2.10 (s, 6H, *H*-5').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 167.3, 166.2, 162.4, 138.9, 137.3, 134.5, 132.0, 128.4, 125.8, 123.8, 104.6, 33.4, 21.2, 20.4.
HRMS (ESI+), *m/z*: calculated for $C_{21}H_{18}N_2O_3$ + H^+ 347.1390 $[M+H]^+$, found 347.1394.

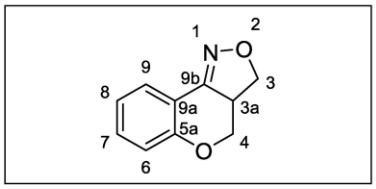
5-(Chloromethyl)-3-mesitylisoxazole (7m)



The synthesis was carried out according to SOP2 using mesitylaldoxime (**0.50 mmol**, **82 mg**, **1 eq.**) and propargyl chloride (**1.50 mmol**, **111 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on C_{18}-silica with water/acetonitrile (20% → 70% MeCN) as a colourless oil (**0.28 mmol**, **66 mg**, **56%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 6.95 (s, 2H, *H*-3'), 6.27 (s, 1H, *H*-4), 4.74 – 4.65 (d, *J* = 0.7 Hz, 2H, *H*-1''), 2.33 (s, 3H, *H*-6'), 2.15 (s, 6H, *H*-5').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 167.5, 162.5, 139.1, 137.3, 128.5, 125.7, 105.3, 34.7, 21.2, 20.4.
HRMS (ESI+), *m/z*: calculated for $C_{13}H_{14}{}^{35}ClNO + H^+$ 236.0837 $[M+H]^+$, found 236.0833; calculated for $C_{13}H_{14}{}^{37}ClNO + H^+$ 238.0810 $[M+H]^+$, found 238.0806.
The compound is reported in literature.[13]

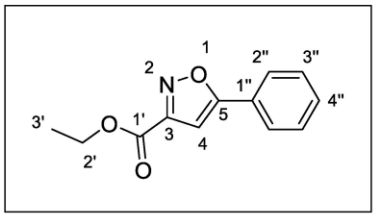
3a,4-Dihydro-3*H*-chromeno[4,3-c]isoxazole (7n)



The synthesis was carried out according to SOP2 using 2-(allyloxy)benzaldehyde oxime (**6n**, **0.50 mmol**, **89 mg**, **1 eq.**). The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) as a colourless oil (**0.14 mmol**, **25 mg**, **28%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.79 (dd, *J* = 7.8, 1.7 Hz, 1H, *H*-9), 7.33 (ddd, *J* = 8.4, 7.3, 1.7 Hz, 1H, *H*-7), 7.04 – 6.90 (m, 2H, *H*-6, 8), 4.78 – 4.62 (m, 2H, *H*-(3)', (3)''), 4.16 – 4.04 (m, 1H, *H*-3a), 3.98 – 3.88 (m, 2H, *H*-(4)', (4)'').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 155.7, 152.9, 132.6, 125.8, 122.0, 117.5, 113.2, 70.7, 69.4, 46.0.
HRMS (ESI+), *m/z*: calculated for $C_{10}H_9NO_2 + H^+$ 176.0706 $[M+H]^+$, found 176.0707.
Known compound, spectroscopic data corresponds to literature.[14]

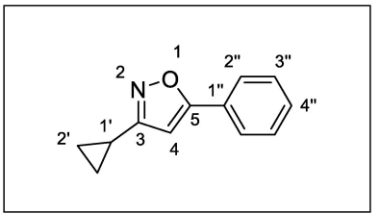
Ethyl 5-phenylisoxazole-3-carboxylate (7o)



The synthesis was carried out according to SOP2 using ethyl 2-(hydroxyimino)acetate (**0.50 mmol**, **59 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a light-yellow solid (**0.14 mmol**, **30 mg**, **28%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.85 – 7.75 (m, 2H, *H*-2''), 7.55 – 7.42 (m, 3H, *H*-3'', 4''), 6.92 (s, 1H, *H*-4), 4.47 (q, *J* = 7.1 Hz, 2H, *H*-2'), 1.44 (t, J = 7.1 Hz, 3H, *H*-3').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 171.8, 160.1, 157.1, 130.9, 129.2, 129.0, 126.7, 126.0, 100.0, 62.3, 14.3.
HRMS (ESI+), *m/z*: calculated for $C_{12}H_{11}NO_3 + H^+$ 218.0812 $[M+H]^+$, found 218.0808.
Known compound, spectroscopic data corresponds to literature.[15]

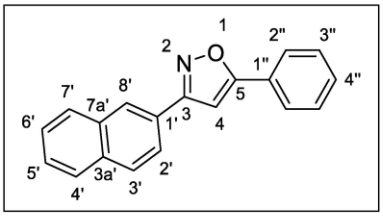
3-Cyclopropyl-5-phenylisoxazole (7p)



The synthesis was carried out according to SOP2 using cyclopropyl carboxaldehyde oxime (**6p**, **0.50 mmol**, **76 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a light-yellow oil (**0.12 mmol**, **23 mg**, **25%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.77 – 7.71 (m, 2H, *H*-2''), 7.48 – 7.40 (m, 3H, *H*-3'', 4''), 6.19 (s, 1H, *H*-4), 2.05 (tt, *J* = 8.3, 5.0 Hz, 1H, *H*-1'), 1.09 – 1.03 (m, 2H, *H*-(2')'), 0.92 – 0.86 (m, 2H, *H*-(2')'').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 169.7, 167.2, 130.1, 129.0, 127.7, 125.9, 97.0, 8.2, 7.6.
HRMS (ESI+), *m/z*: calculated for $C_{12}H_{11}NO + H^+$ 186.0913 $[M+H]^+$, found 186.0907.
Known compound, spectroscopic data corresponds to literature.[16]

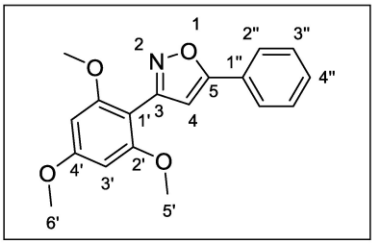
3-(Naphthalen-2-yl)-5-phenylisoxazole (7q)



The synthesis was carried out according to SOP2 using 2-naphthylaldehyde oxime (**0.50 mmol**, **86 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 3% EtOAc) as a light-yellow solid (**0.19 mmol**, **50 mg**, **37%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.50 – 8.40 (m, 1H, *H*-8'), 8.01 – 7.85 (m, 4H, *H*-3', 4', 6', 7'), 7.81 – 7.74 (m, 1H, *H*-2'), 7.65 – 7.43 (m, 6H, *H*-5', 2'', 3'', 4''), 6.85 (s, 1H, *H*-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 169.9, 163.3, 134.0, 131.2, 130.4, 130.4, 129.2, 128.6, 127.9, 127.6, 127.2, 127.1, 126.4, 126.0, 125.8, 125.3, 101.1.
HRMS (ESI+), *m/z*: calculated for $C_{19}H_{13}NO + H^+$ 272.1070 $[M+H]^+$, found 272.1073.
Known compound, spectroscopic data corresponds to literature.[17]

5-Phenyl-3-(2,4,6-trimethoxybenzyl)-isoxazole (7r)

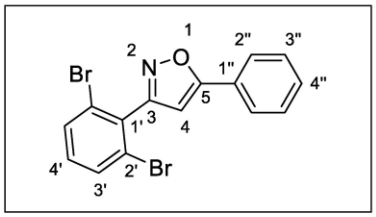


The synthesis was carried out according to SOP2 using 2,4,6-trimethoxy-benzaldehyde oxime (**0.50 mmol**, **106 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 25% EtOAc) as a light-yellow solid (**0.11 mmol**, **35 mg**, **23%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.86 – 7.78 (m, 2H, *H*-2''), 7.49 – 7.36 (m, 3H, *H*-3'',4''), 6.64 (s, 1H, *H*-4), 6.22 (s, 2H, *H*-3'), 3.86 (s, 3H, *H*-6'), 3.80 (s, 6H, *H*-5').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 168.6, 162.5, 159.7, 157.7, 129.8, 128.9, 128.1, 125.9, 102.7, 100.4, 90.9, 56.1, 55.5.
HRMS (ESI+), *m/z*: calculated for $C_{18}H_{17}NO_4 + H^+$ 312.1230 $[M+H]^+$, found 312.1235.

Known compound, spectroscopic data corresponds to literature.[18]

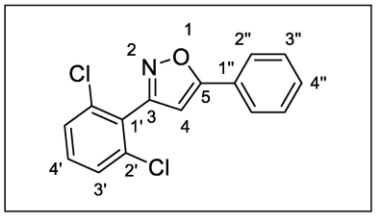
3-(2,6-Dibromophenyl)-5-phenylisoxazole (7s)



The synthesis was carried out according to SOP2 using 2,6-dibromobenzaldehyde oxime (**0.50 mmol**, **139 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) as a colourless solid (**0.27 mmol**, **104 mg**, **55%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.91 – 7.83 (m, 2H, *H*-2''), 7.66 (d, *J* = 8.1 Hz, 2H, *H*-3'), 7.54 – 7.42 (m, 3H, *H*-3'', 4''), 7.19 (t, *J* = 8.1 Hz, 1H, *H*-4'), 6.60 (s, 1H, *H*-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 170.4, 162.7, 132.2, 132.1, 131.9, 130.5, 129.2, 127.3, 126.0, 124.7, 100.8.
HRMS (ESI+), *m/z*: calculated for $C_{15}H_9{}^{79}Br_2NO + H^+$ 377.9124 $[M+H]^+$, found 377.9115; calculated for $C_{15}H_9{}^{79}Br^{81}BrNO + H^+$ 379.9104 $[M+H]^+$, found 379.9094; calculated for $C_{15}H_9{}^{81}Br_2NO + H^+$ 381.9085 $[M+H]^+$, found 381.9073.

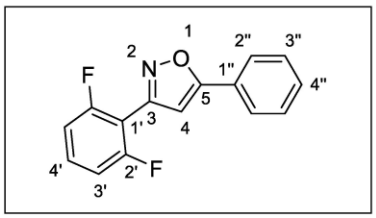
3-(2,6-Dichlorophenyl)-5-phenylisoxazole (7t)



The synthesis was carried out according to SOP2 using 2,6-dichlorobenzaldehyde oxime (**0.50 mmol**, **95 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) as a colourless solid (**0.29 mmol**, **86 mg**, **59%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.90 – 7.82 (m, 2H, *H*-2''), 7.55 – 7.40 (m, 5H, *H*-3', 3'', 4'), 7.34 (dd, J = 8.9, 7.2 Hz, 1H, *H*-4'), 6.63 (s, 1H, *H*-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 170.4, 159.5, 135.7, 131.2, 130.5, 129.2, 128.6, 128.4, 127.3, 126.0, 101.1.
HRMS (ESI+), *m/z*: calculated for $C_{15}H_9{}^{35}Cl_2NO + H^+$ 290.0134 $[M+H]^+$, found 290.0134; calculated for $C_{15}H_9{}^{37}Cl^{35}ClNO + H^+$ 292.0107 $[M+H]^+$, found 292.0103; calculated for $C_{15}H_9{}^{37}Cl_2NO + H^+$ 294.0083 $[M+H]^+$, found 294.0078.
Known compound, spectroscopic data corresponds to literature.[19]

3-(2,6-Difluorophenyl)-5-phenylisoxazole (7u)

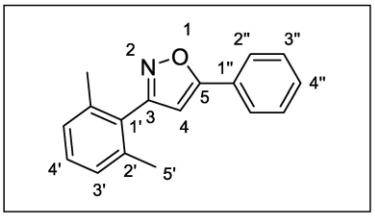


The synthesis was carried out according to SOP2 using 2,6-difluorobenzaldehyde oxime (**0.50 mmol**, **78 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) as a colourless solid (**0.33 mmol**, **86 mg**, **67%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.89 – 7.81 (m, 2H, *H*-2''), 7.53 – 7.37 (m, 4H, *H*-3', 3''), 7.11 – 7.01 (m, 2H, *H*-4', 4''), 6.87 (t, *J* = 1.7 Hz, 1H, *H*-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 170.1, 162.1 (d, *J* = 6.5 Hz), 160.4 – 153.7 (m), 131.5 (t, *J* = 10.6 Hz), 130.5, 129.2, 127.3, 126.0, 112.5 – 112.0 (m), 107.5 (d, *J* = 17.0 Hz), 101.1 (t, *J* = 3.7 Hz).
^{19}F NMR (376 MHz, $CDCl_3$) δ/ppm: -110.7 (ddd, *J* = 8.5, 6.3, 2.0 Hz).
HRMS (ESI+), *m/z*: calculated for $C_{15}H_9F_2NO$ + H^+ 258.0725 $[M+H]^+$, found 258.0721.

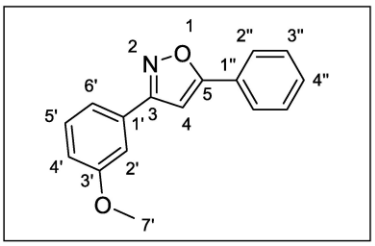
3-(2,6-Dimethylphenyl)-5-isoxazole (7v)



The synthesis was carried out according to SOP2 using 2,6-dimethylbenzaldehyde oxime (**6v**, **0.50 mmol**, **74 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) as a colourless solid (**0.31 mmol**, **76 mg**, **61%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.71 – 7.63 (m, 2H, *H*-2''), 7.33 – 7.25 (m, 3H, *H*-3'', 4''), 7.10 – 7.02 (m, 1H, *H*-4'), 6.98 – 6.89 (m, 2H, *H*-3'), 6.30 (s, 1H, *H*-4), 2.04 (s, 6H, *H*-5').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 170.0, 162.8, 137.5, 130.3, 129.2, 129.1, 127.7, 127.6, 126.2, 126.0, 100.8, 20.5.
HRMS (ESI+), *m/z*: calculated for $C_{17}H_{15}NO$ + H^+ 250.1226 $[M+H]^+$, found 250.1222.

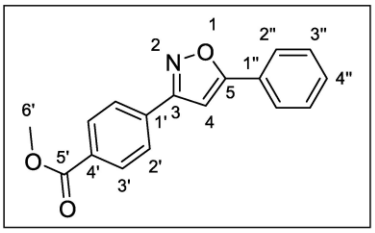
3-(3-Methoxyphenyl)-5-phenylisoxazole (7w)



The synthesis was carried out according to SOP2 using 4-methoxybenzaldehyde oxime (**6w**, **0.50 mmol**, **76 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) as a light-yellow solid (**0.10 mg**, **24 mg**, **20%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 7.87 – 7.83 (m, 2H, *H*-2''), 7.53 – 7.37 (m, 6H, *H*-2', 5', 6', 3'', 4''), 7.02 (ddd, *J* = 7.6, 2.6, 1.7 Hz, 1H, *H*-4'), 6.82 (s, 1H, *H*-4), 3.89 (s, 3H, *H*-7').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 170.6, 163.1, 160.1, 130.5, 130.4, 130.1, 129.2, 127.6, 126.0, 119.5, 116.3, 111.9, 97.7, 55.6.
HRMS (ESI+), *m/z*: calculated for $C_{16}H_{13}NO_2$ + H^+ 252.1019 $[M+H]^+$, found 252.1022.
Known compound, spectroscopic data corresponds to literature.[16]

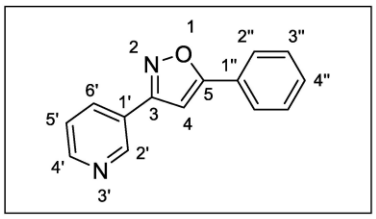
3-(4-Methoxycarbonyl)phenyl-5-phenylisoxazole (7x)



The synthesis was carried out according to SOP3 using 4-methoxycarbonylbenzaldehyde oxime (**0.50 mmol**, **80 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 3% EtOAc) as a light-yellow solid (**0.07 mmol**, **20 mg**, **14%**).

^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm: 8.20 – 8.12 (m, 2H, *H*-3'), 7.98 – 7.93 (m, 2H, *H*-2'), 7.88 – 7.82 (m, 2H, *H*-2''), 7.55 – 7.44 (m, 3H, *H*-3'', 4''), 6.88 (s, 1H, *H*-4), 3.96 (s, 3H, *H*-6').
^{13}C NMR (101 MHz, $CDCl_3$) δ/ppm: 171.1, 166.7, 162.3, 133.5, 131.6, 130.6, 130.4, 129.2, 127.4, 126.9, 126.0, 97.7, 52.5.
HRMS (ESI+), *m/z*: calculated for $C_{17}H_{13}NO_3$ + H^+ 280.0968 $[M+H]^+$, found 280.0963.
Known compound, spectroscopic data corresponds to literature.[17]

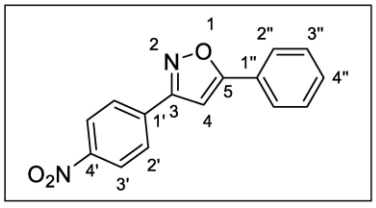
5-Phenyl-3-(3-pyridyl)isoxazole (7y)



The synthesis was carried out according to SOP2 using 2-naphthylaldehyde oxime (**0.50 mmol**, **86 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. The product was obtained after column chromatography on silica with cyclohexane/ethyl acetate (0% → 3% EtOAc) as a light-yellow solid (**0.05 mmol**, **10 mg**, **9%**).

^{1}H NMR (400 MHz, CD_3CN) δ/ppm: 9.09 (dd, *J* = 2.2, 0.9 Hz, 1H, *H*-2'), 8.69 (dd, *J* = 4.8, 1.7 Hz, 1H, *H*-4'), 8.24 (ddd, *J* = 7.9, 2.2, 1.7 Hz, 1H, *H*-6'), 7.93 – 7.89 (m, 2H, *H*-2''), 7.60 – 7.53 (m, 3H, *H*-3'', 4''), 7.50 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H, *H*-5'), 7.23 (s, 1H, *H*-4).
^{13}C NMR (101 MHz, CD_3CN) δ/ppm: 171.7, 161.9, 152.2, 148.7, 134.9, 131.6, 130.3, 128.1, 126.7, 126.1, 125.0, 99.0.
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{10}N_2O$ + H^+ 223.0866 $[M+H]^+$, found 223.0866.
Known compound, spectroscopic data corresponds to literature.[20]

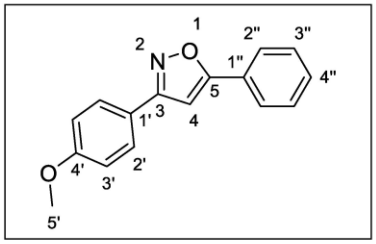
3-(4-Nitrophenyl)-5-phenylisoxazole (7z)



The synthesis was carried out according to SOP2 or SOP3 using 4-nitrobenzaldehyde oxime (**0.50 mmol**, **80 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **83 mg**, **3 eq.**) as dipolarophile. The product could not be obtained.

The compound is reported in literature.[21]

3-(4-Methoxyphenyl)-5-phenylisoxazole (7aa)



The synthesis was carried out according to SOP3 using 4-methoxybenzaldehyde oxime (**0.50 mmol**, **76 mg**, **1 eq.**) and phenylacetylene (**1.50 mmol**, **153 mg**, **3 eq.**) as dipolarophile. Traces of product were obtained according to GC-MS analysis (m/z = 251).

The compound is reported in literature.[17]

6. GC-MS

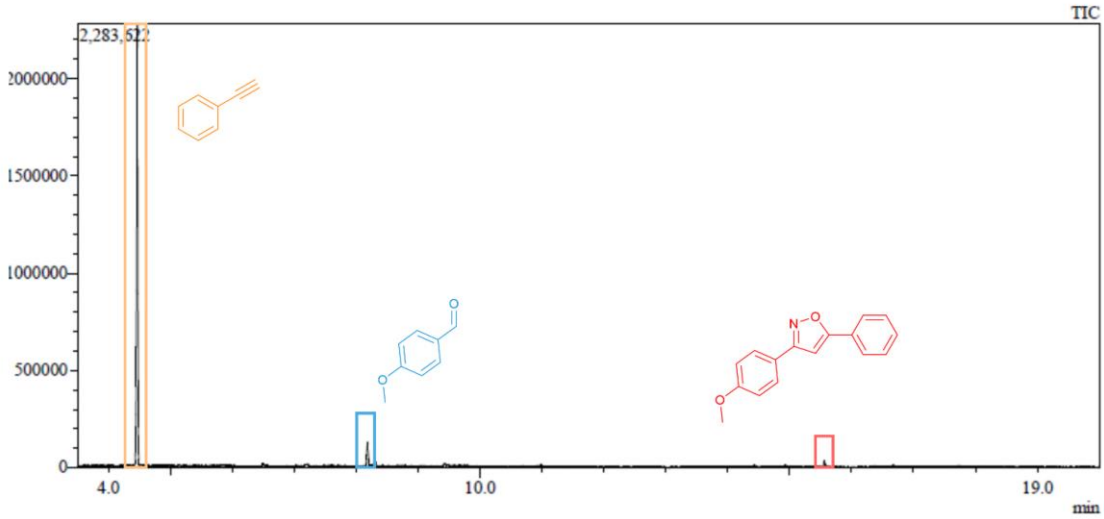


Figure S6: GC-MS of the crude reaction mixture of conversion of 4-methoxybenzaldoxime showing remaining phenylacetylene (orange), 4-methoxybenzaldehyde (blue) and traces of 3-(4-methoxybenzyl)-5-phenylisoxazole (**7aa**, red).

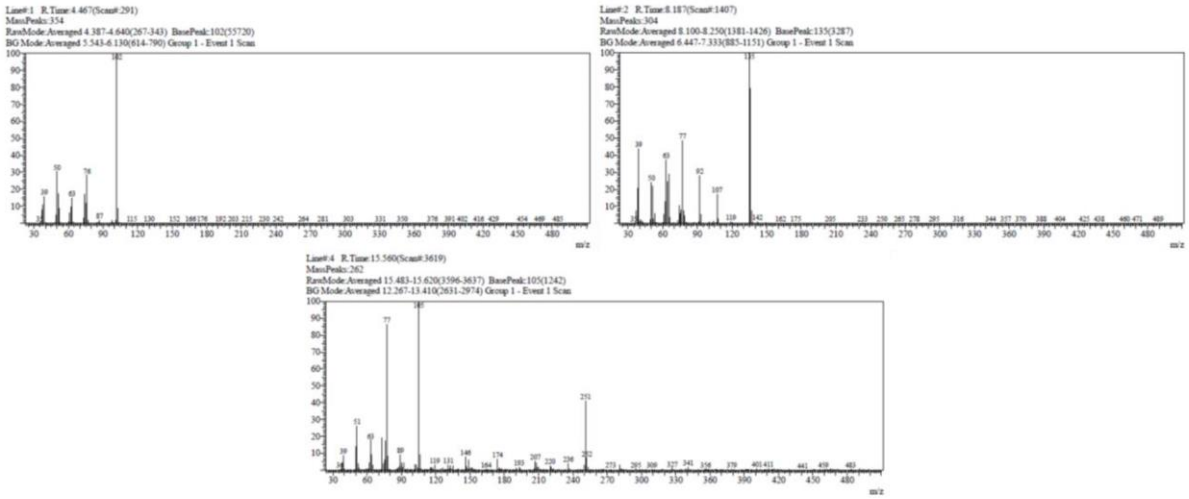


Figure S7: Mass spectra obtained by GC-MS analysis of the crude reaction mixture of conversion of 4-methoxybenzaldoxime. Top left: remaining phenylacetylene; top right: 4-methoxybenzaldehyde; bottom:3-(4-methoxybenzyl)-5-phenylisoxazole.

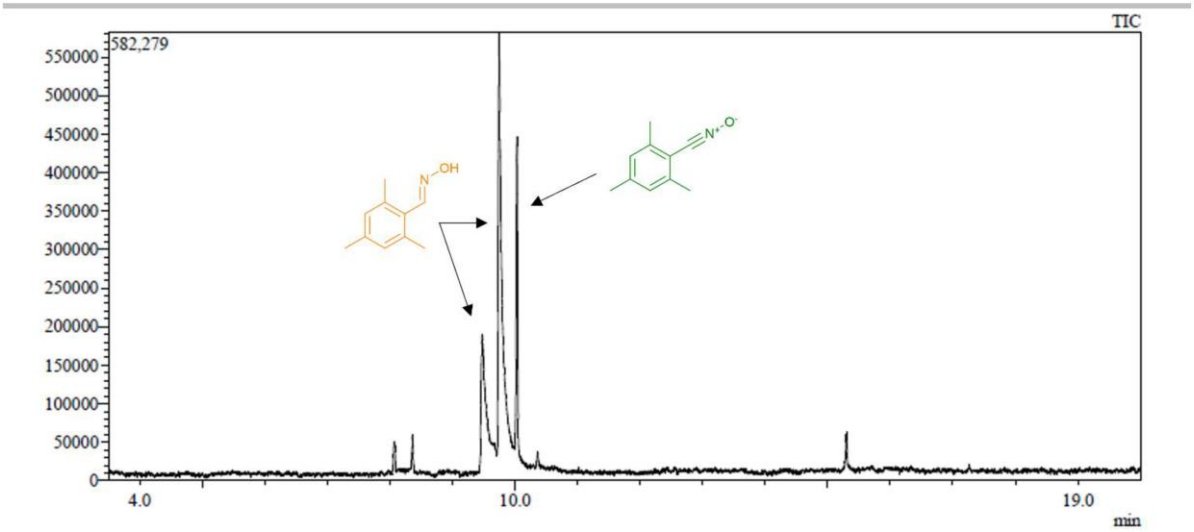


Figure S8: GC-MS analysis of the crude reaction mixture of conversion of mesitylaldoxim. Amount of applied charge: 0.9 *F*. Remaining mesitylaldoxim (orange, *E*/*Z* mixture), corresponding nitrile oxide (green).

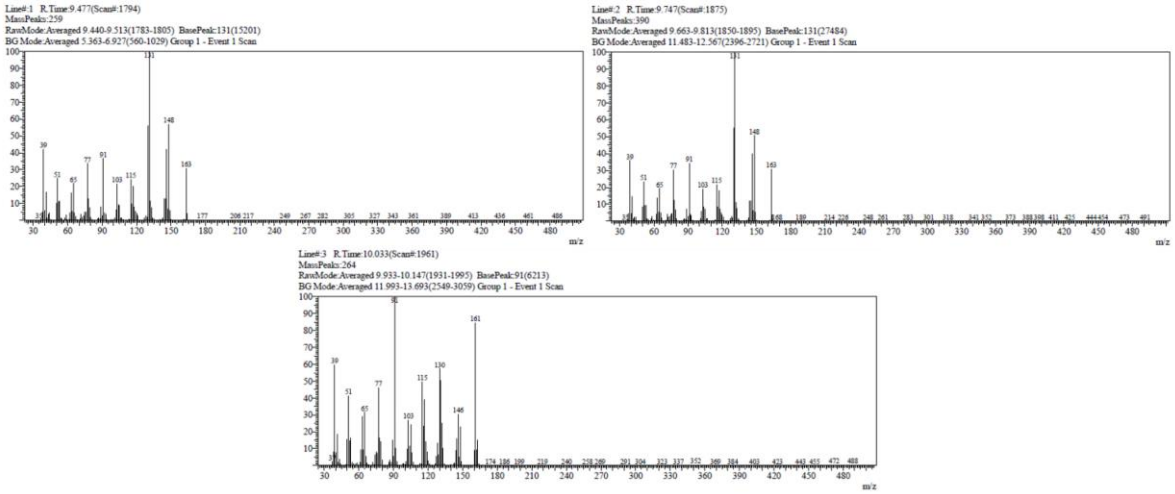


Figure S9: Mass spectra obtained by GC-MS analysis of the crude reaction mixture of conversion of mesitylaldoxim. Amount of applied charge: 0.9 *F*. Top: remaining mesitylaldoxim (*E*/*Z* mixture; m/z = 163); bottom: corresponding nitrile oxide (m/z = 161).

7. References

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8. NMR Spectra

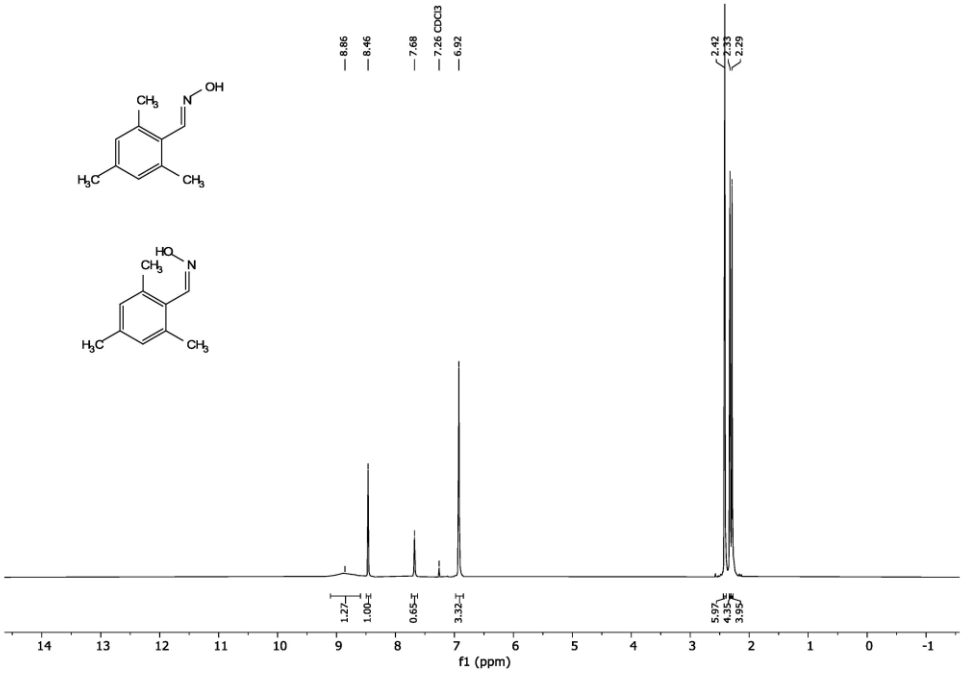

Figure S10: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6a**, mixture of *E*- and *Z*-oxime.

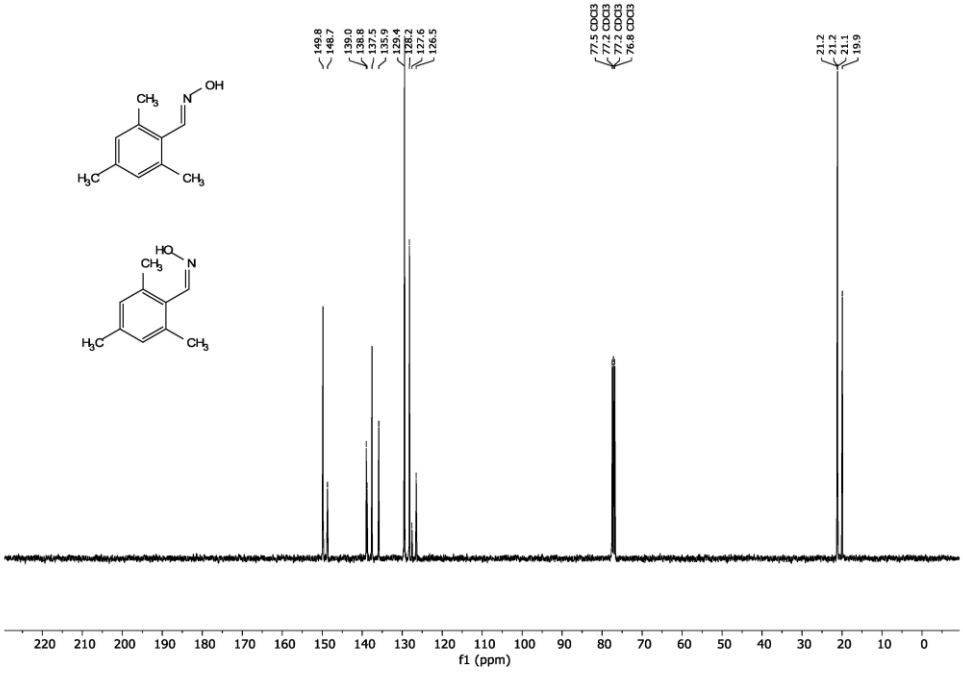

Figure S11: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6a**, mixture of *E*- and *Z*-oxime.

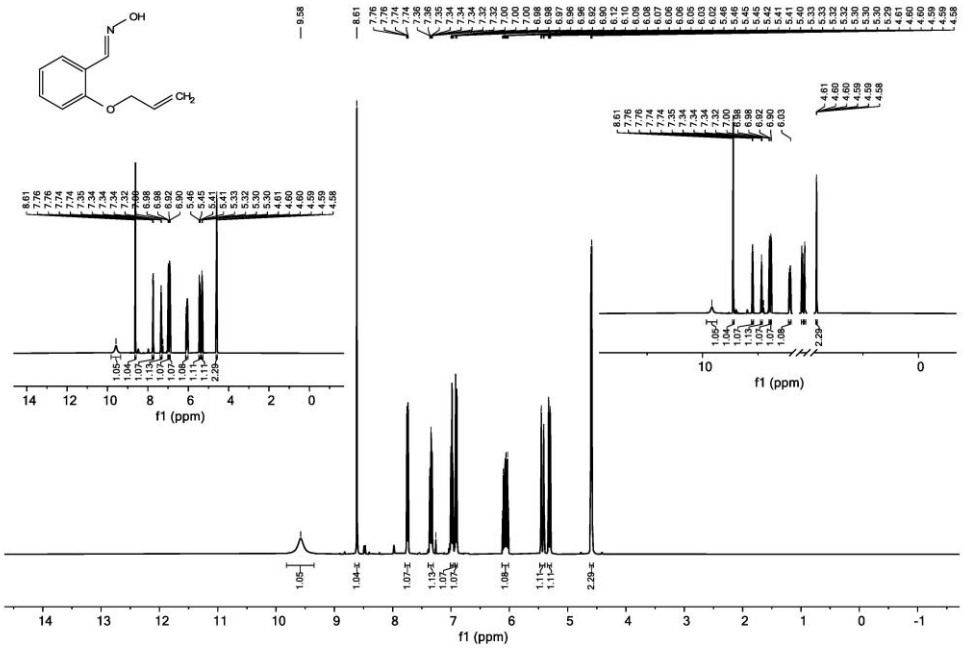

Figure S12: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6n**.

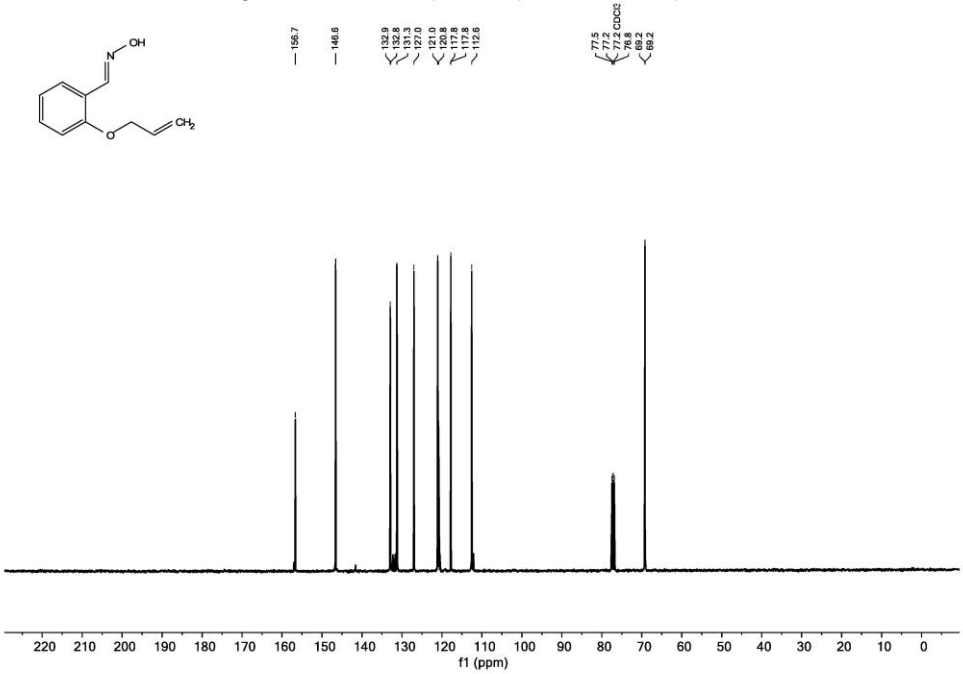

Figure S13: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6n**.

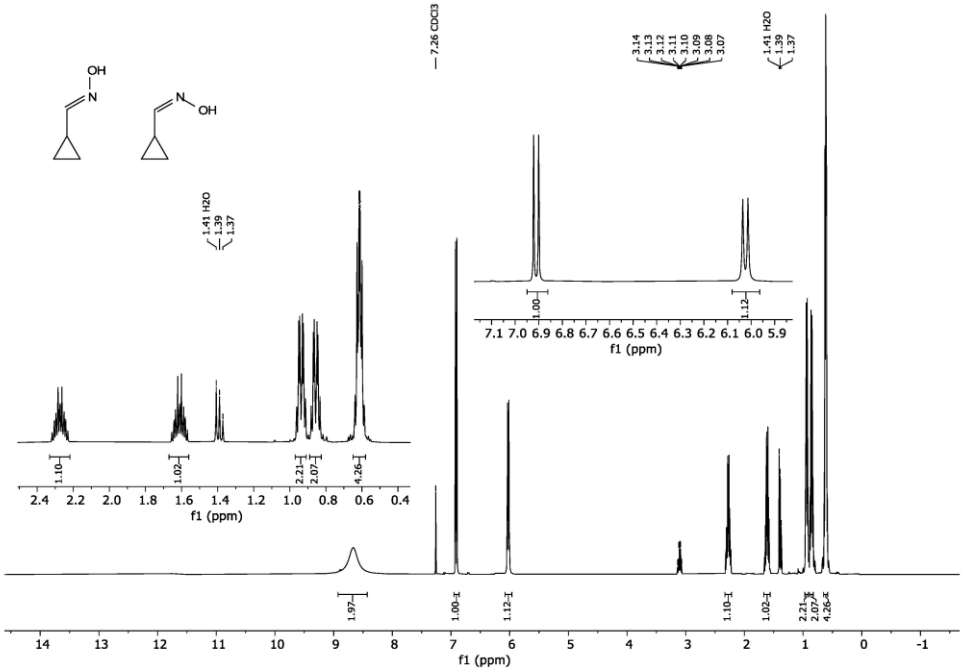

Figure S14: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6p**, mixture of *E*- and *Z*-oxime.

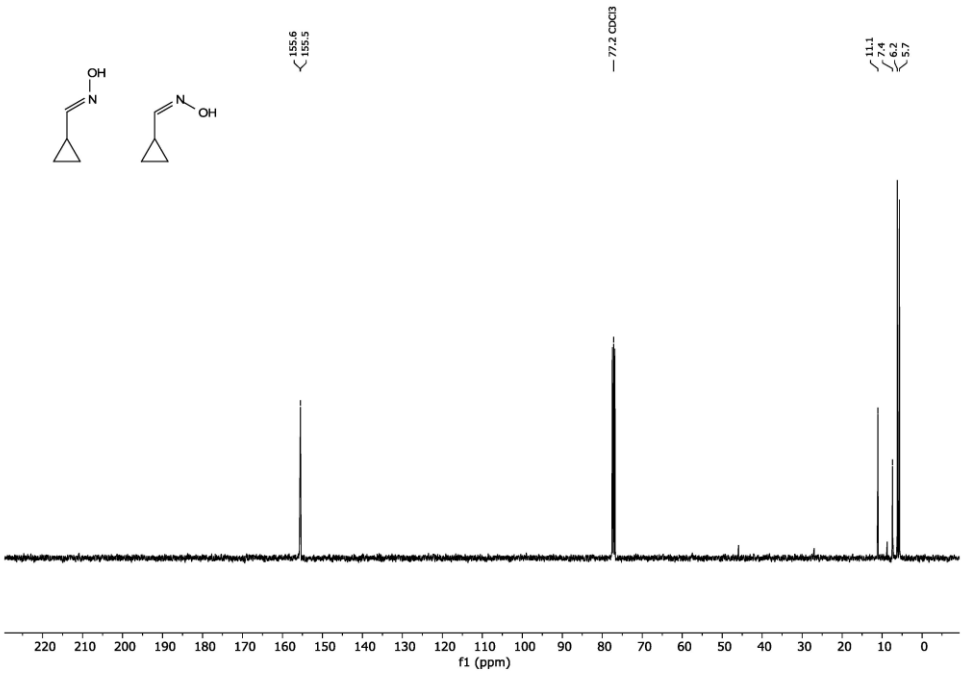

Figure S15: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6p**, mixture of *E*- and *Z*-oxime.

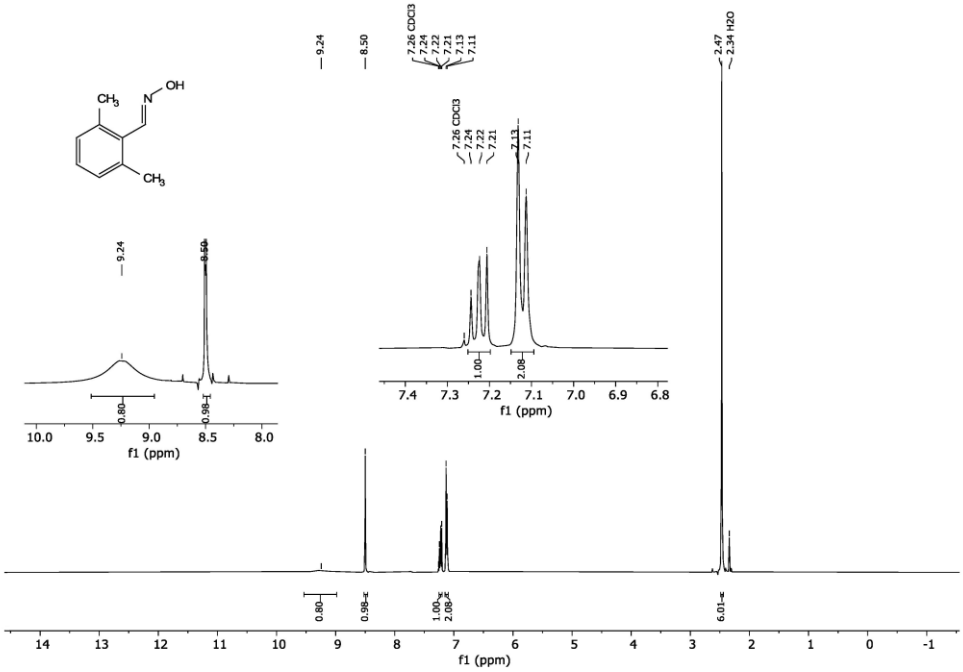

Figure S16:: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6v.**

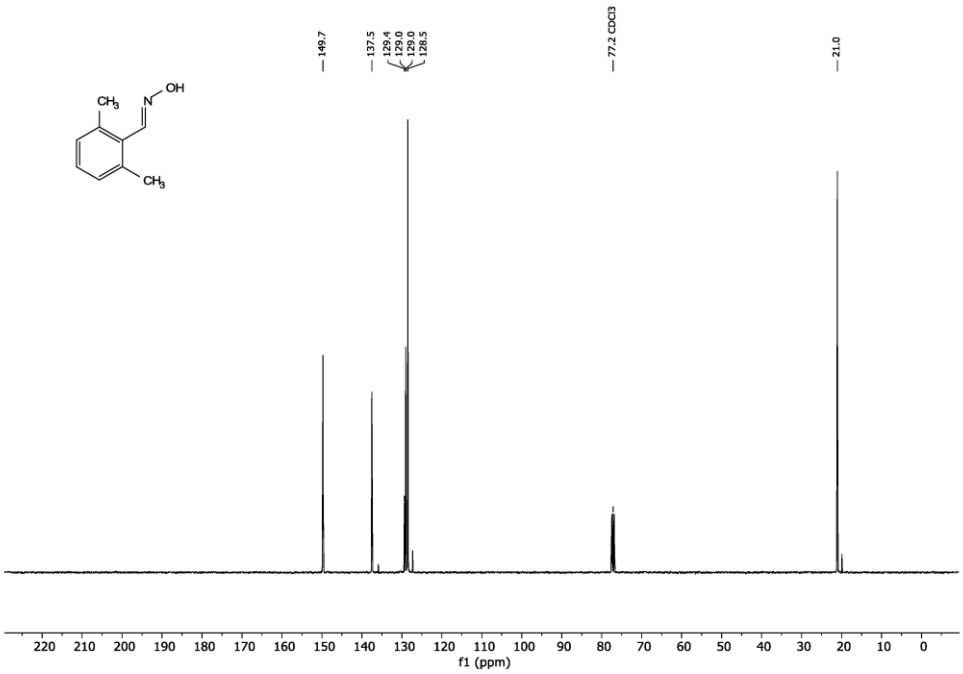

Figure S17: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6v.**

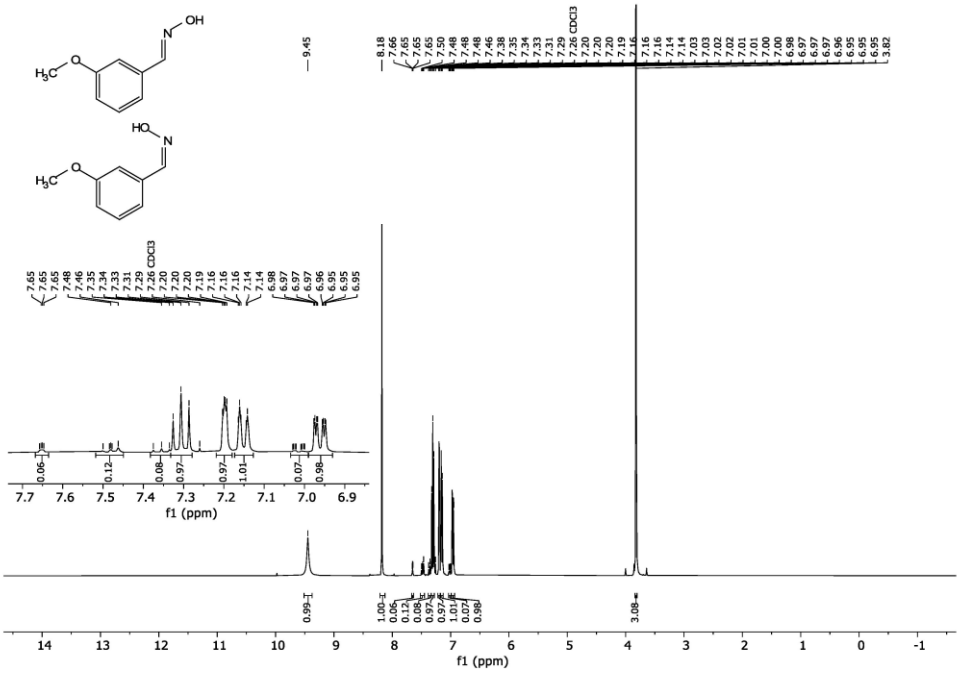

Figure S18: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6w**, mixture of *E*- and *Z*-oxime.

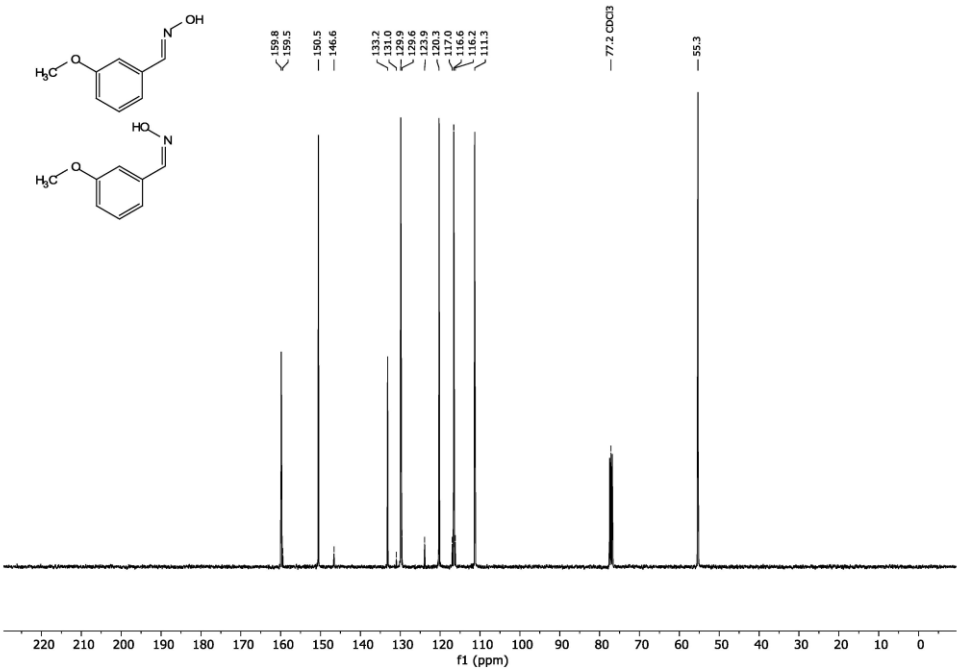

Figure S19: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6w**, mixture of *E*- and *Z*-oxime.

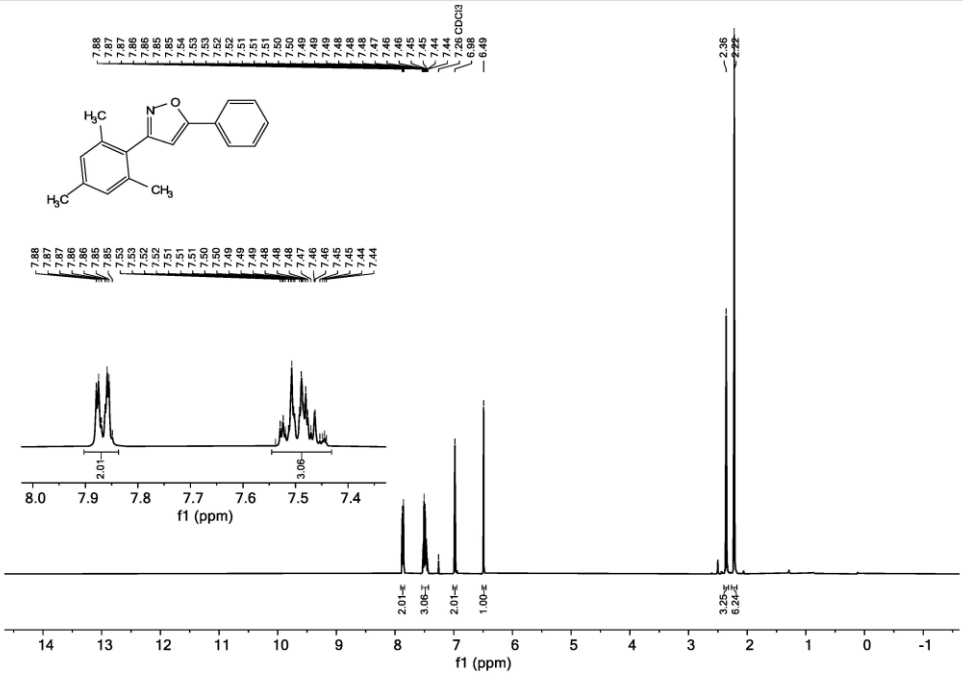

Figure S20: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7a**.

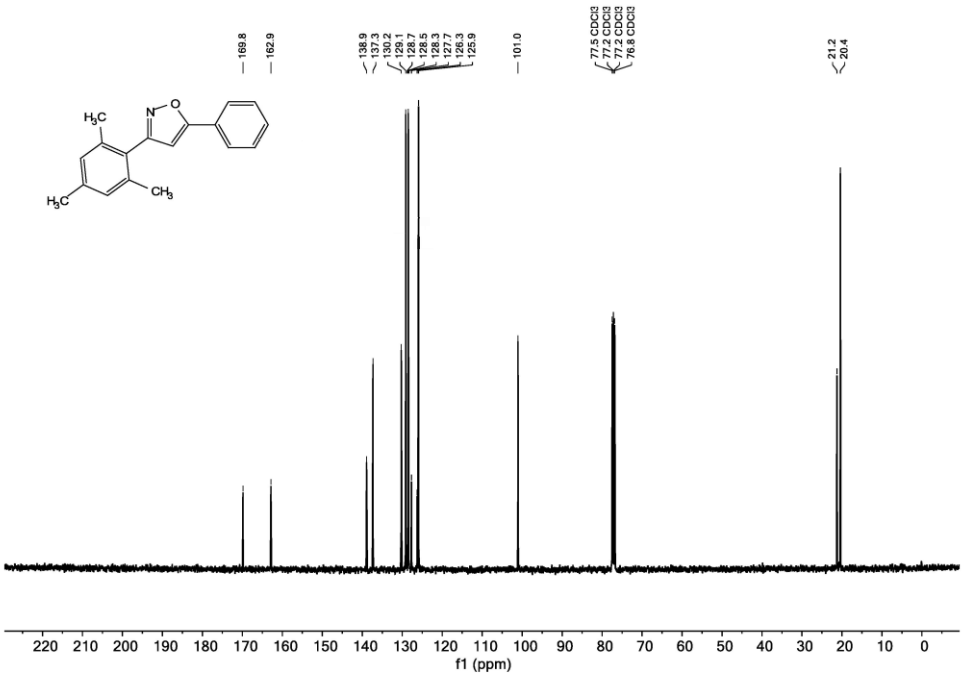

Figure S21: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7a**.

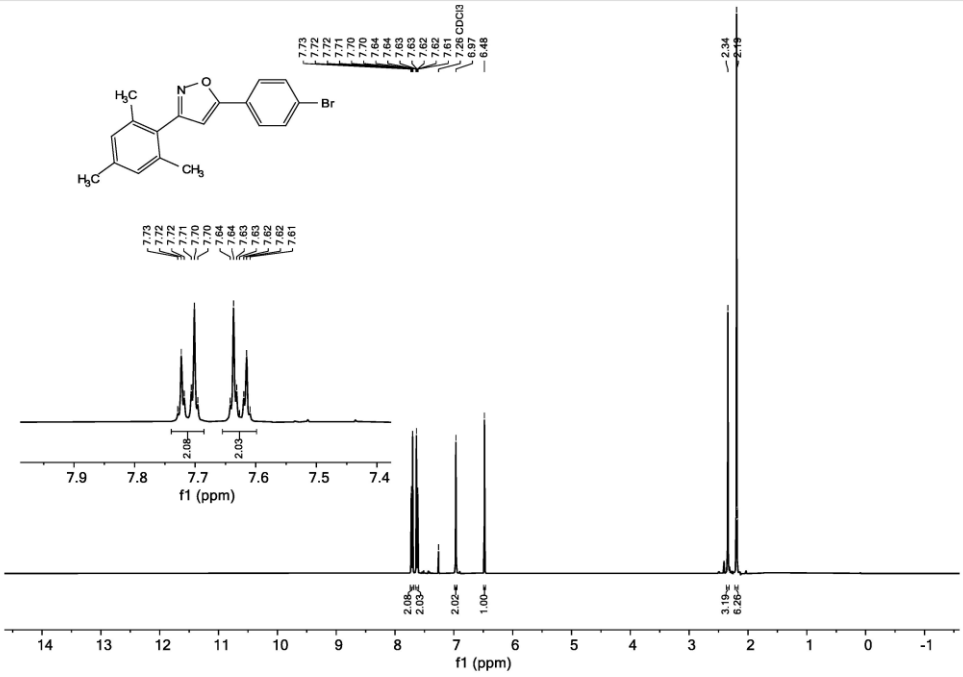

Figure S22: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7b**.

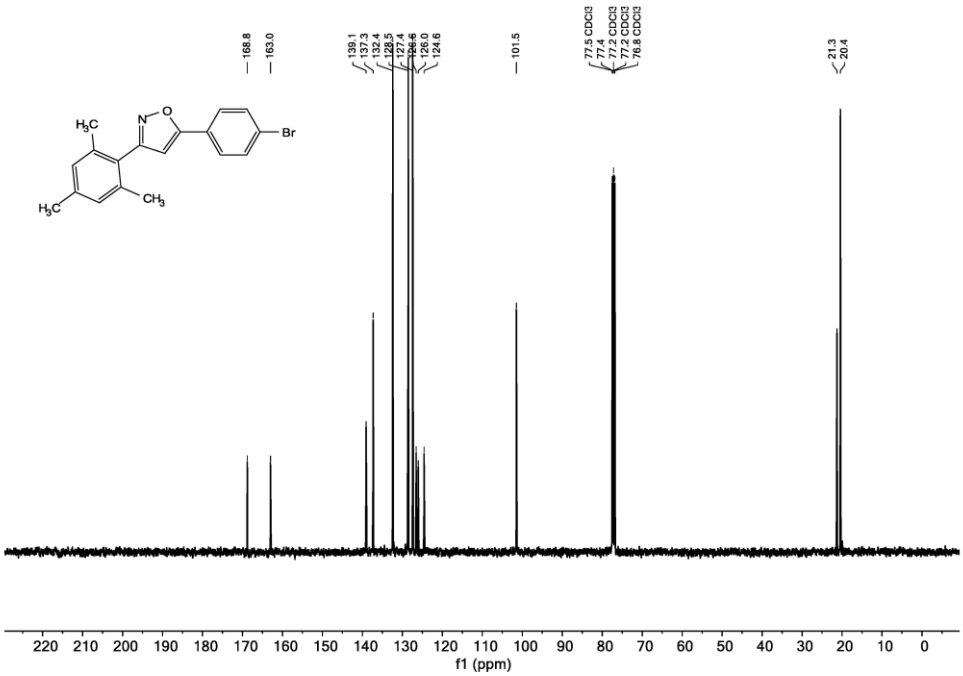

Figure S23: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7b**.

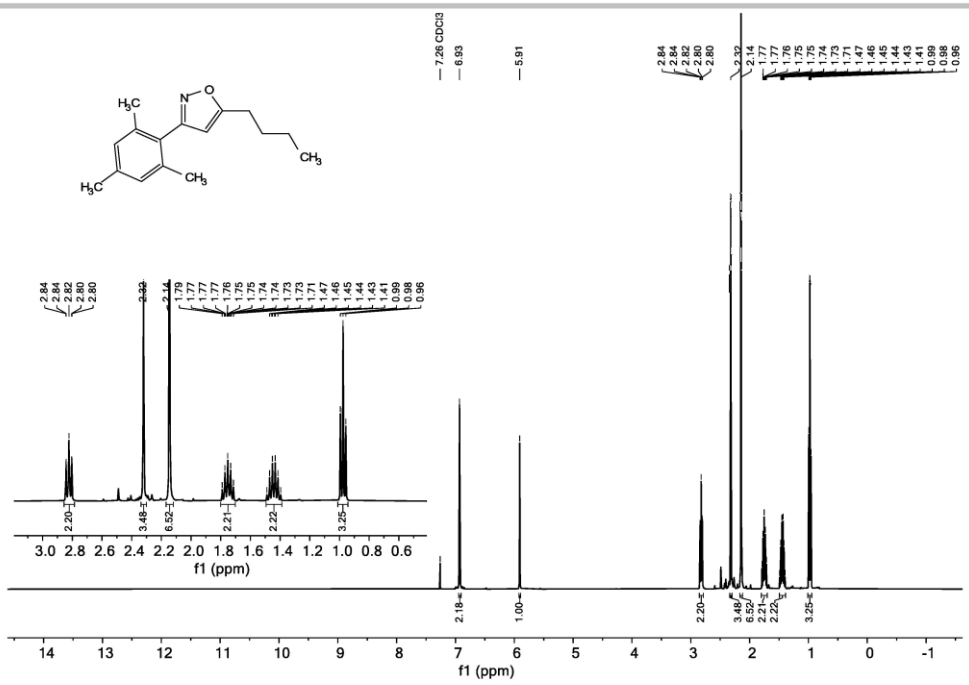

Figure S24: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7c**.

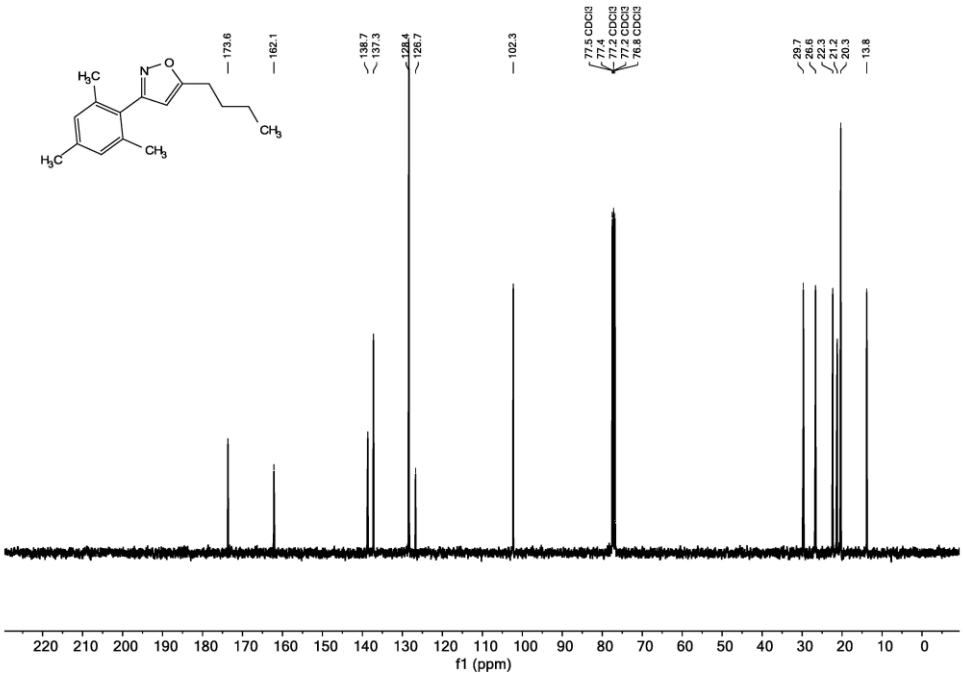

Figure S25: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7c**.

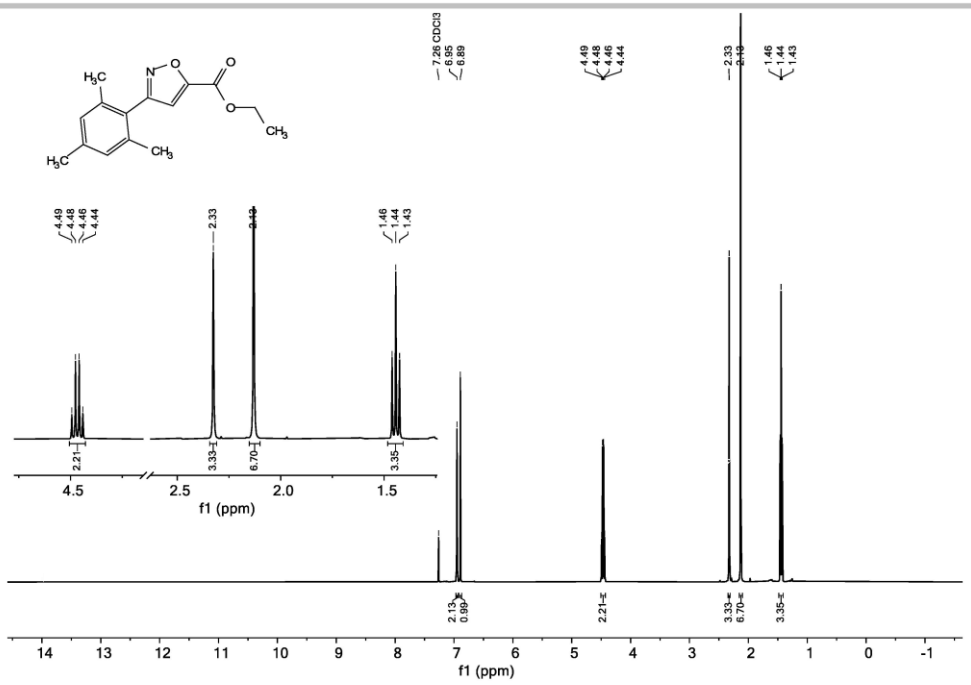

Figure S26: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7d**.

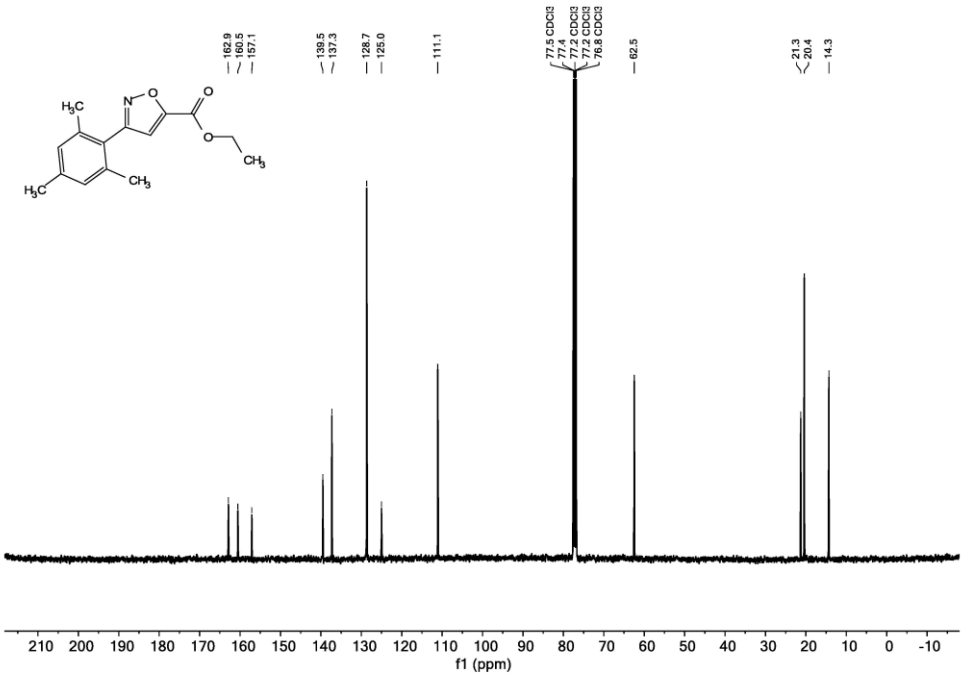

Figure S27: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7d**.

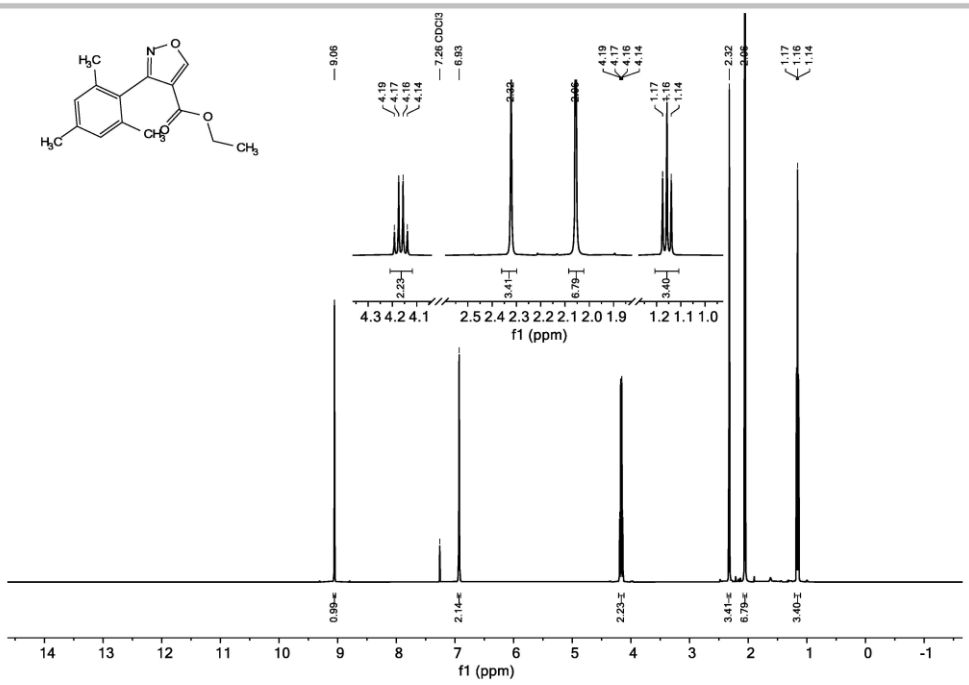

Figure S28: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7d'**.

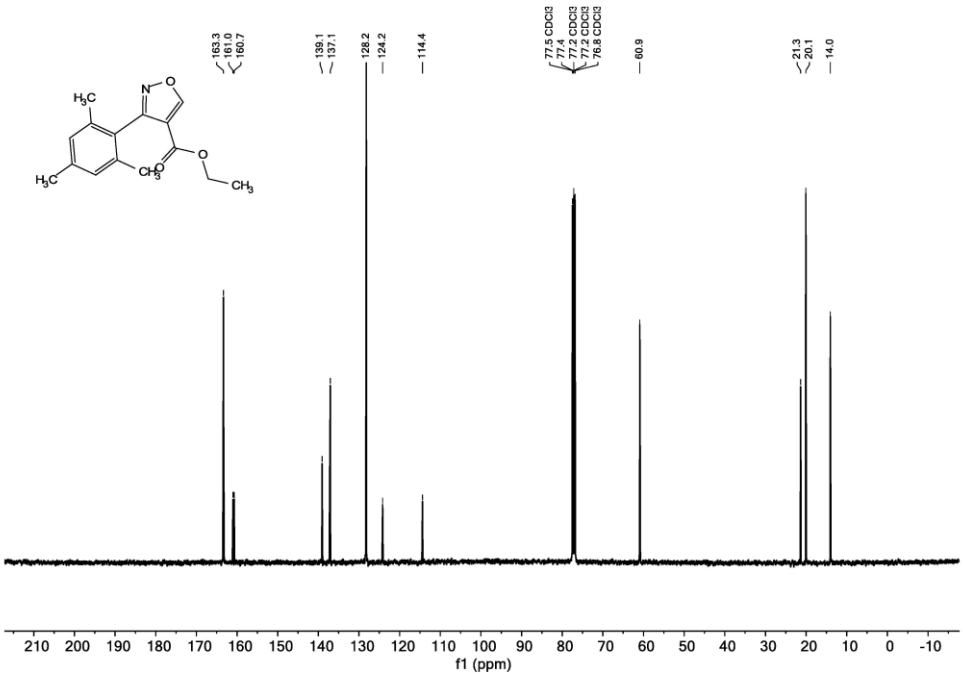

Figure S29: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7d'**.

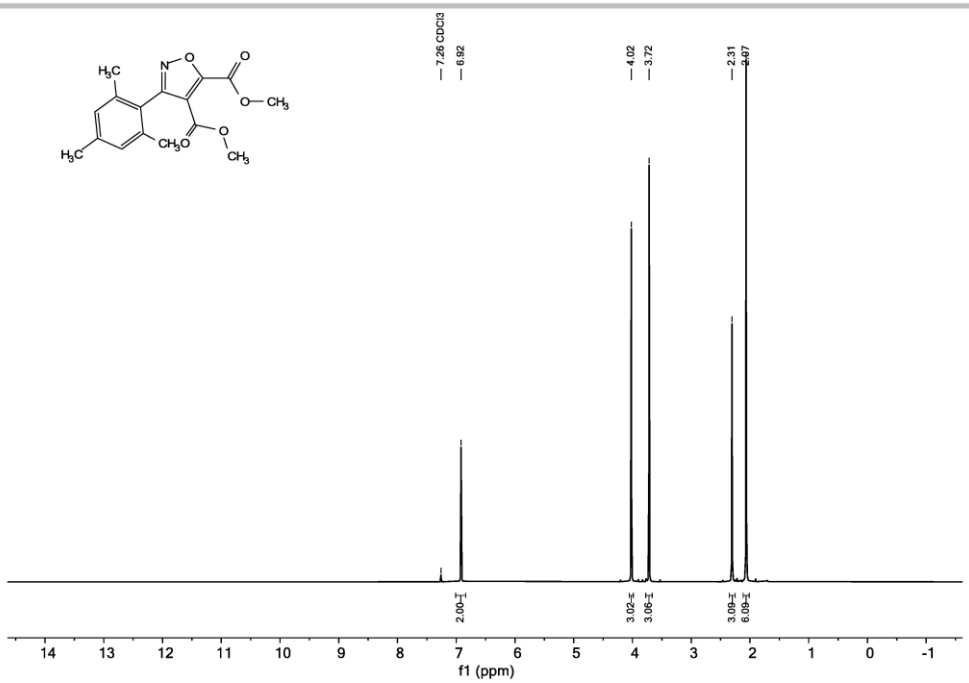

Figure S30: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7e**.

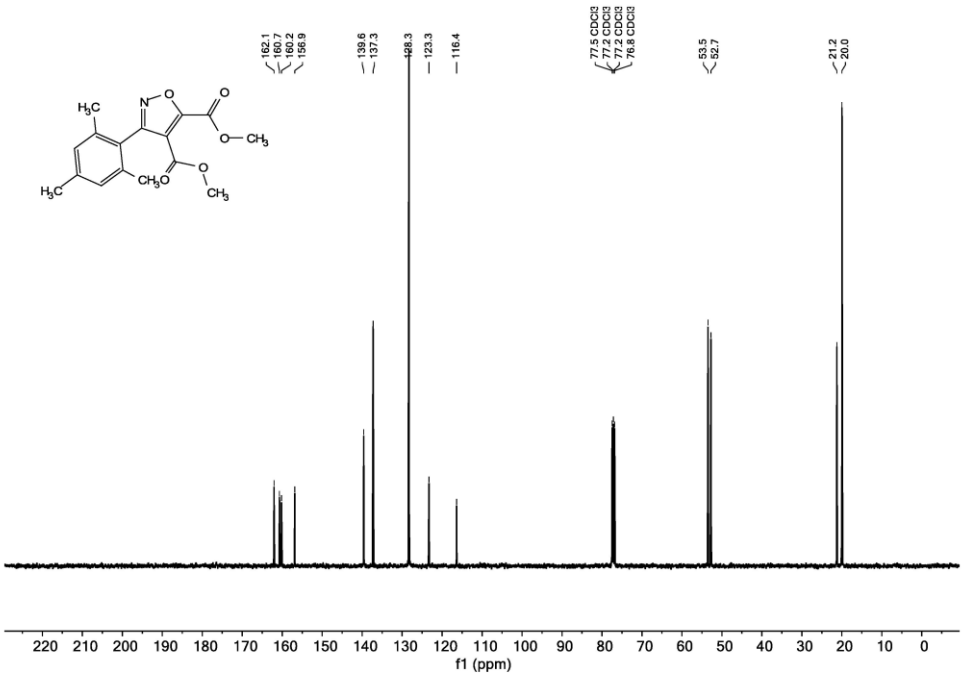

Figure S31: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7e**.

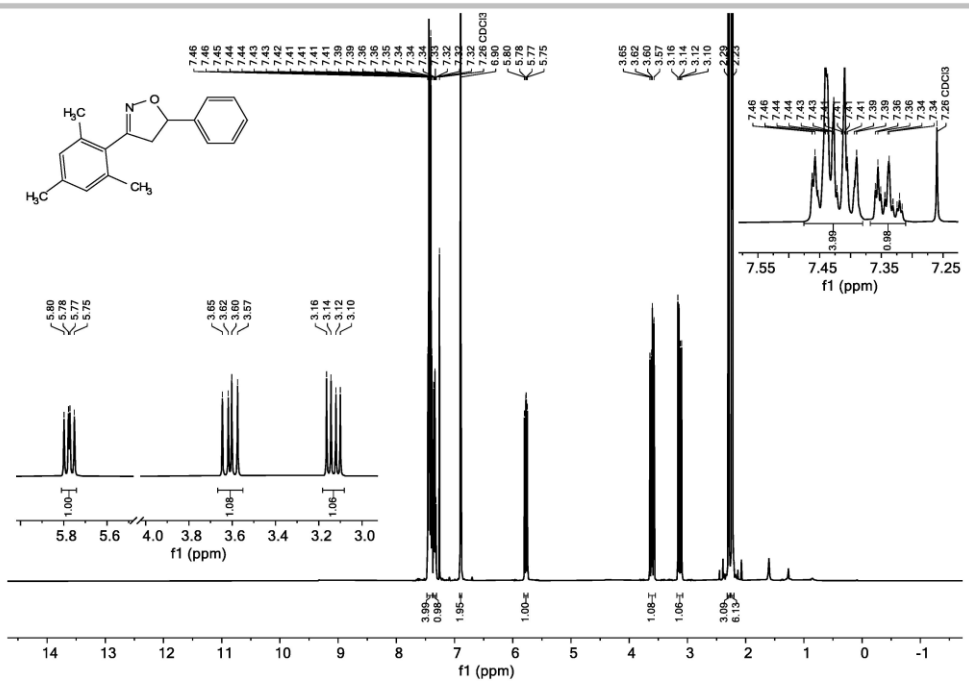

Figure S32: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7f**.

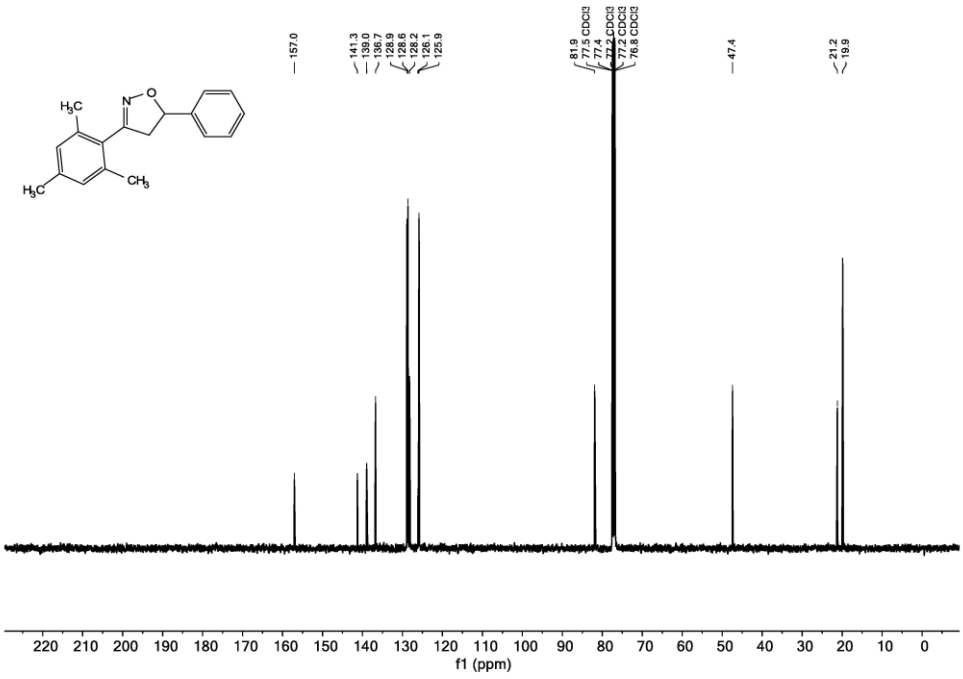

Figure S33: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7f**.

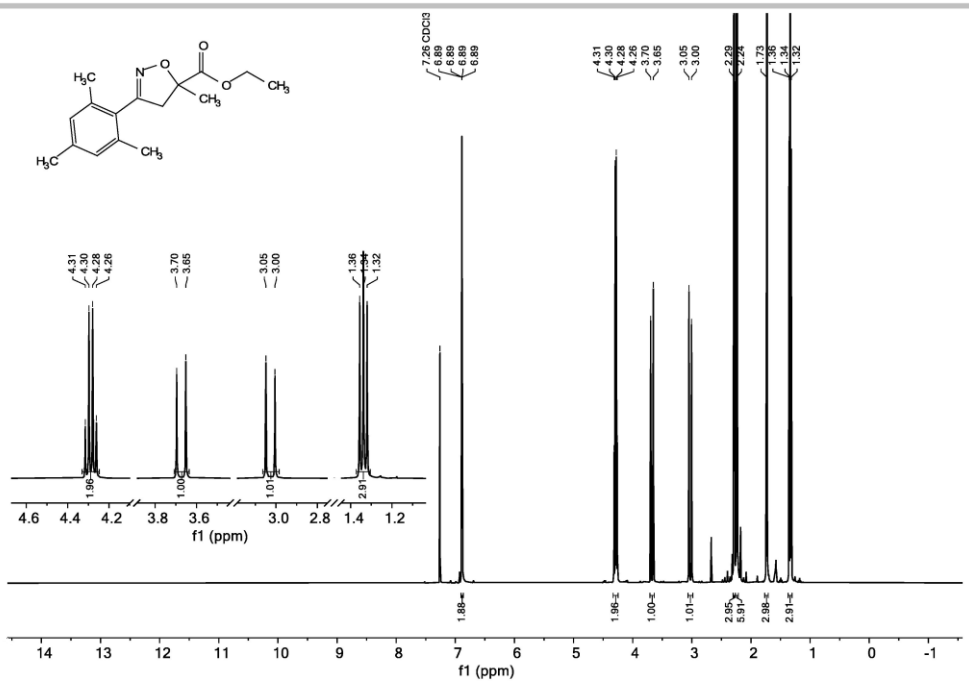

Figure S34: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7g**.

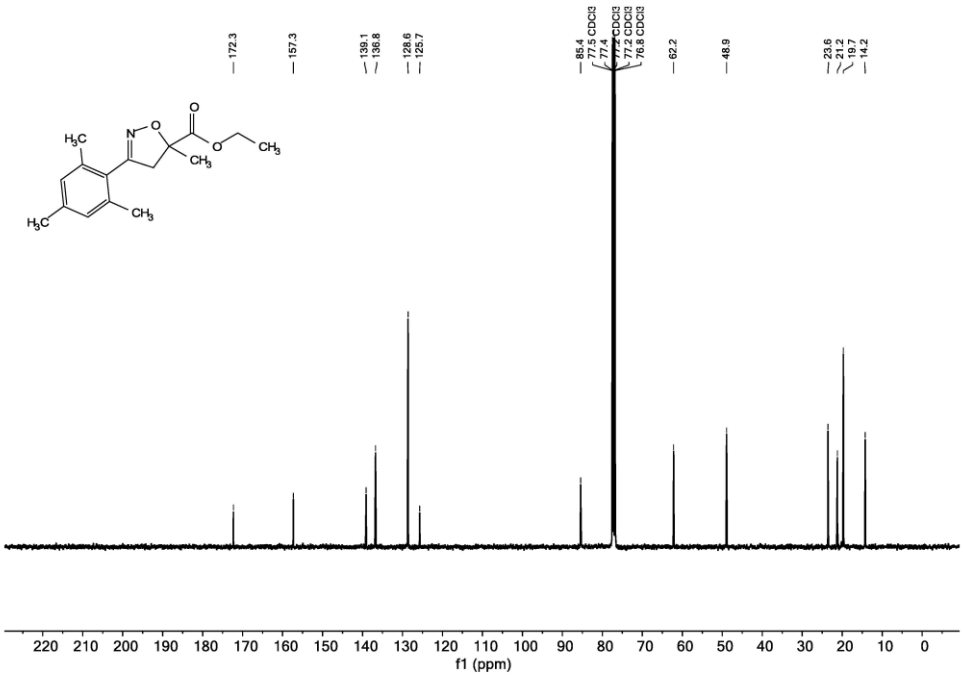

Figure S35: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7g**.

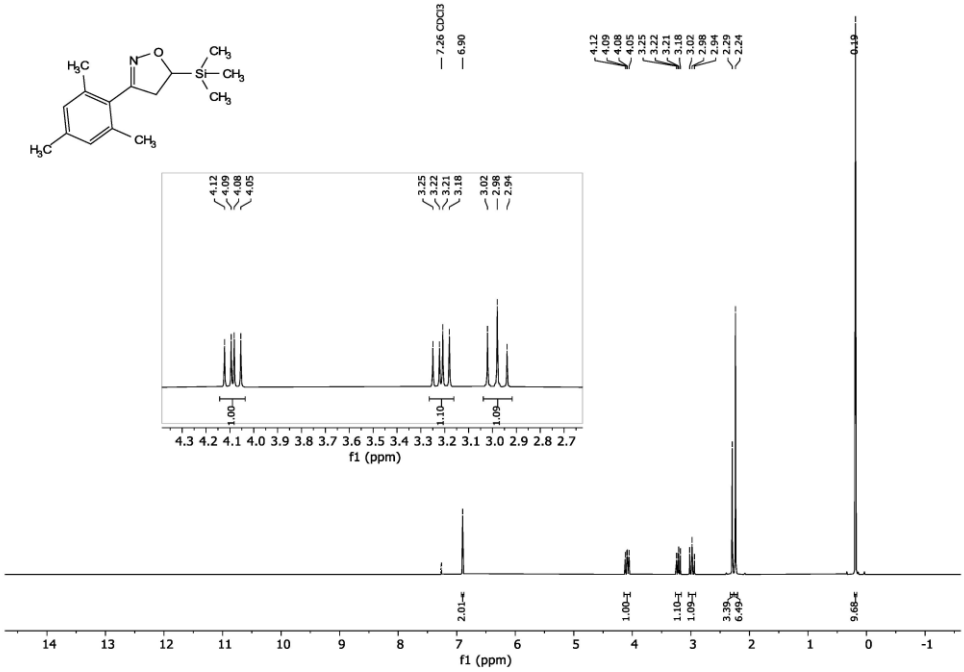

Figure S36: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7h**.

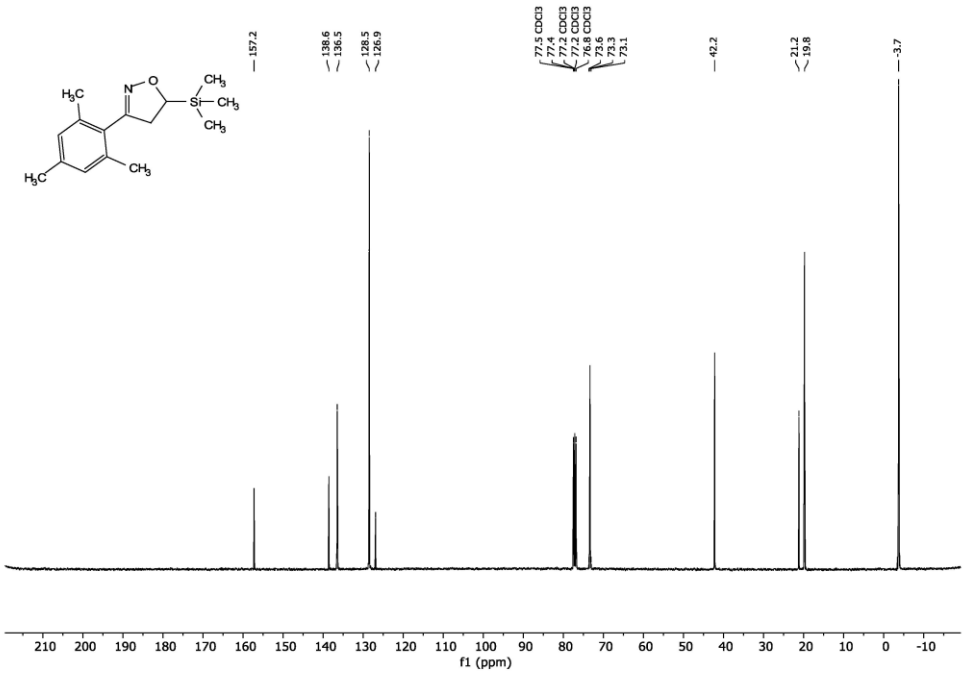

Figure S37: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7h**.

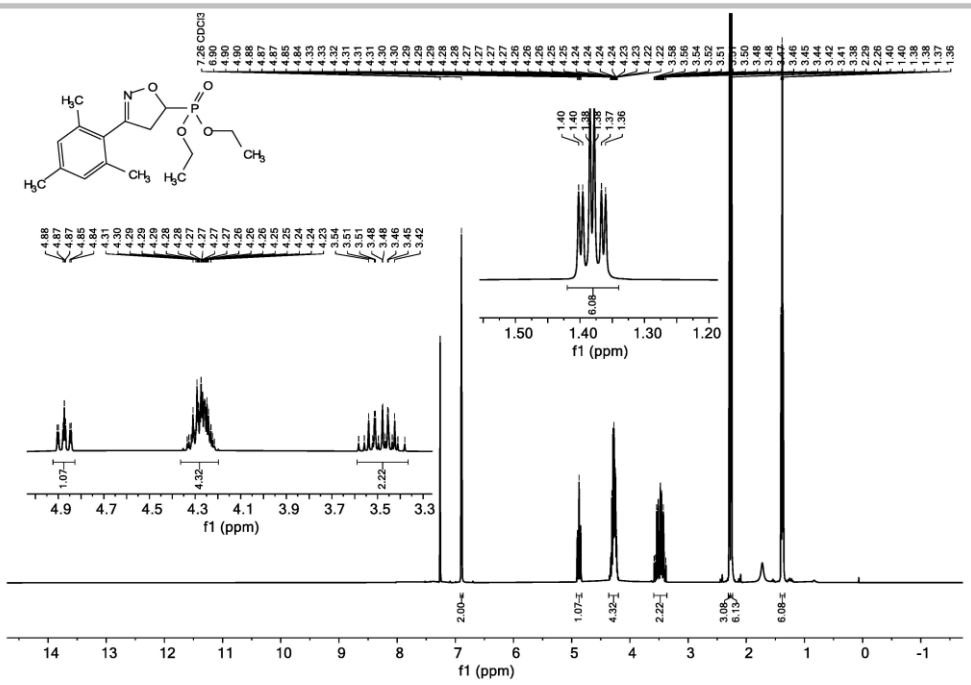

Figure S38: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7i**.

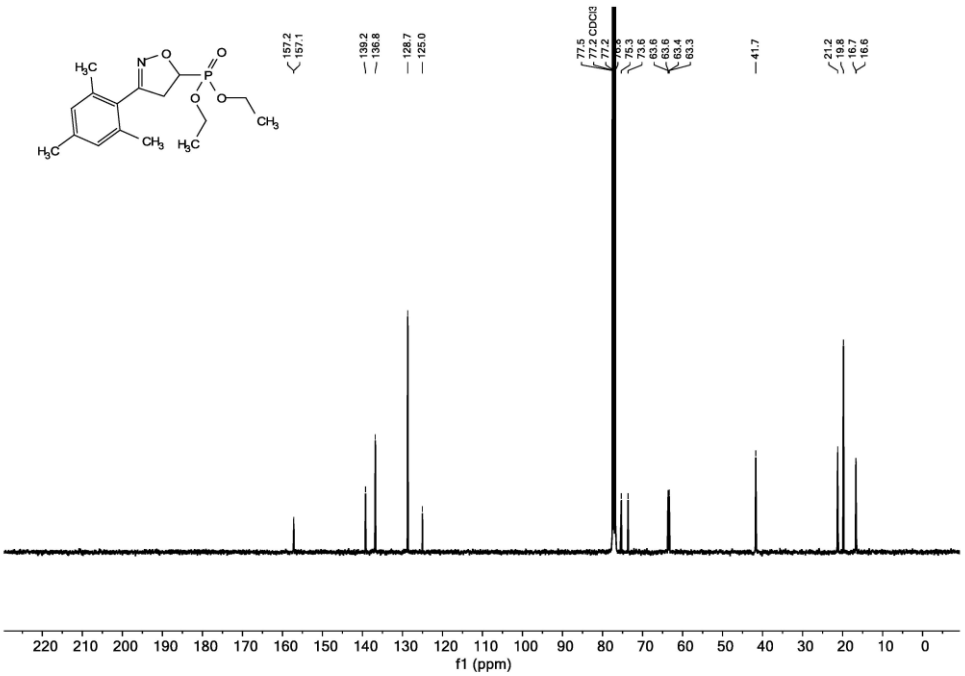

Figure S39: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7i**.

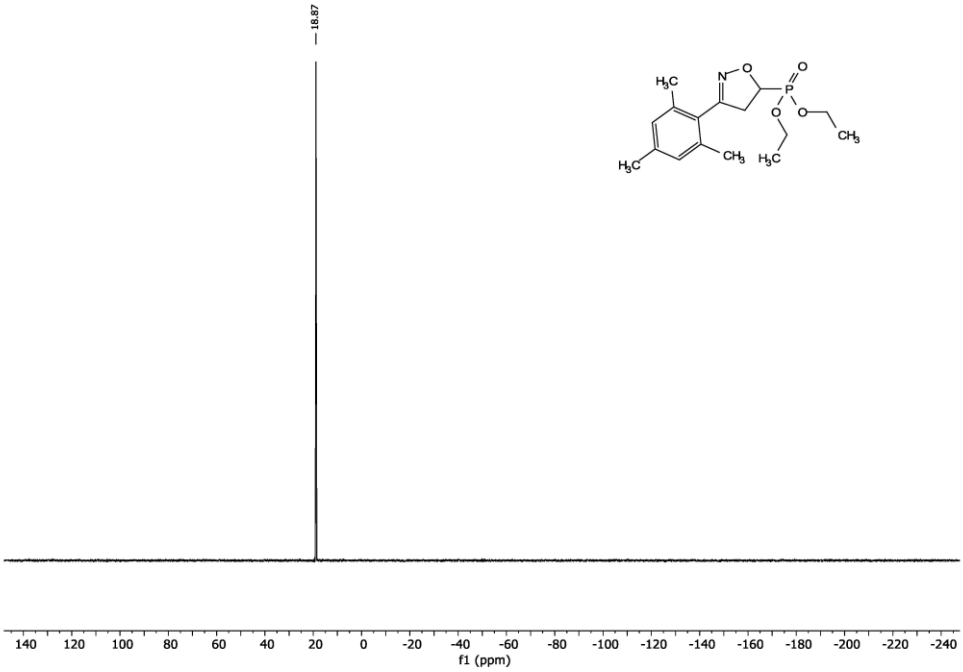

Figure S40: ^{31}P NMR spectrum (162 MHz, $CDCl_3$) of **7i**.

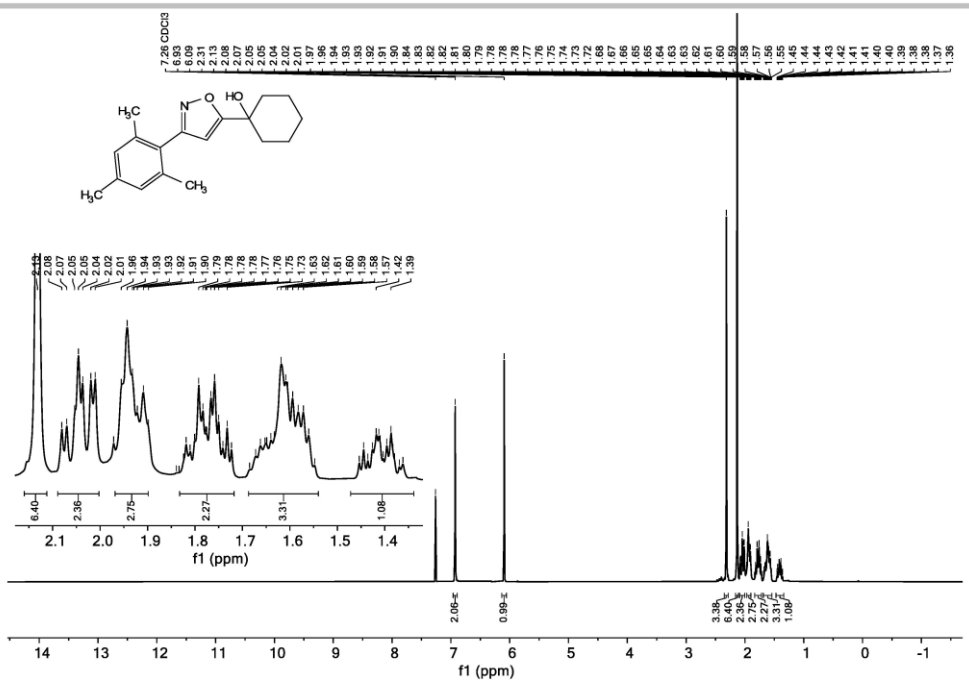

Figure S41: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7j**.

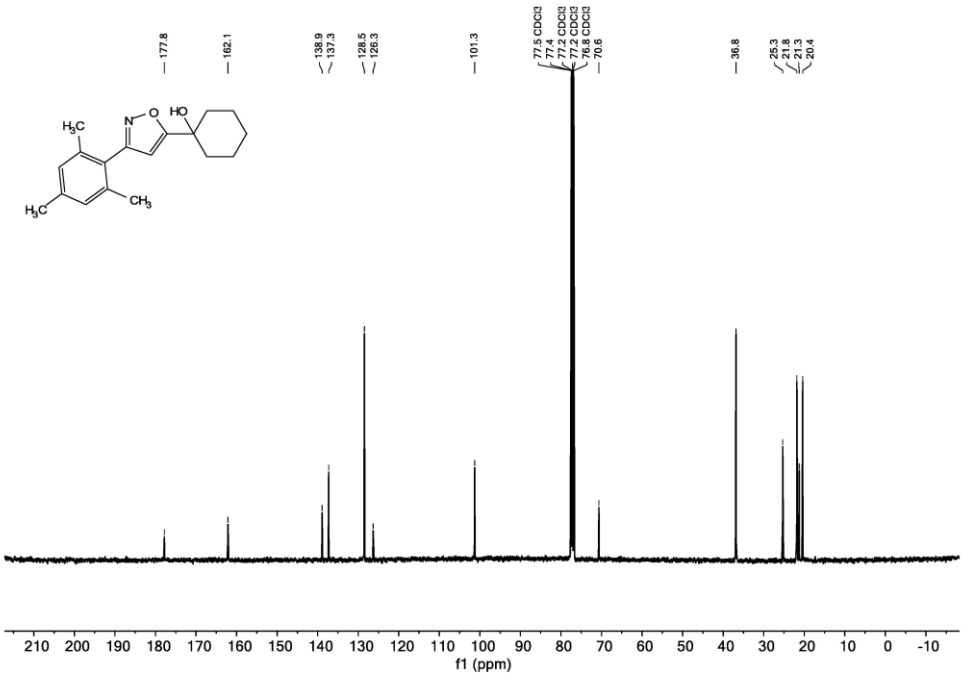

Figure S42: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7j**.

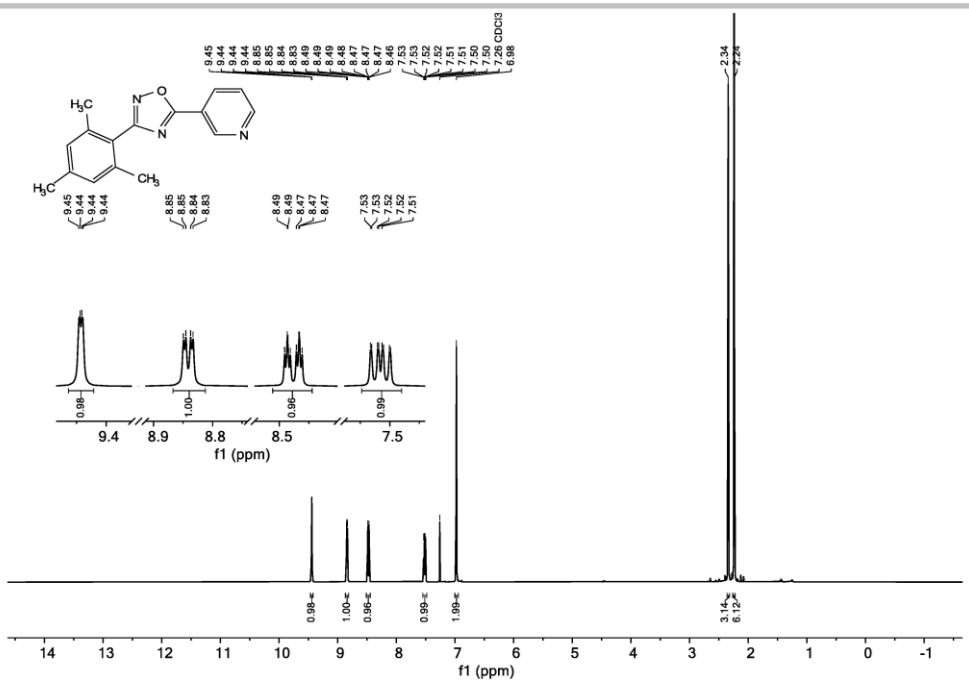

Figure S43: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7k**.

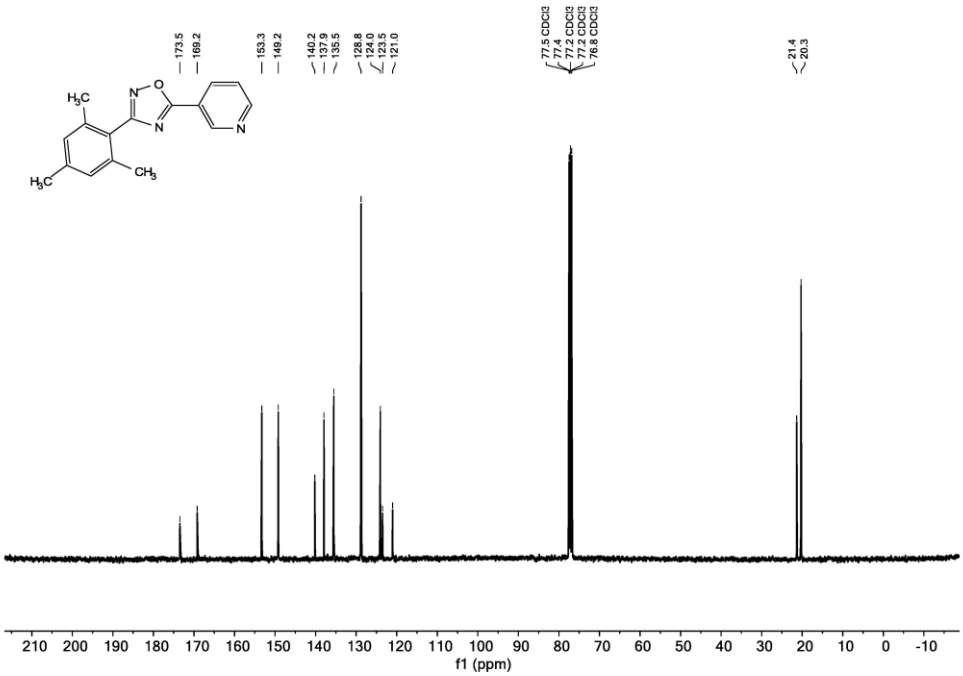

Figure S44: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7k**.

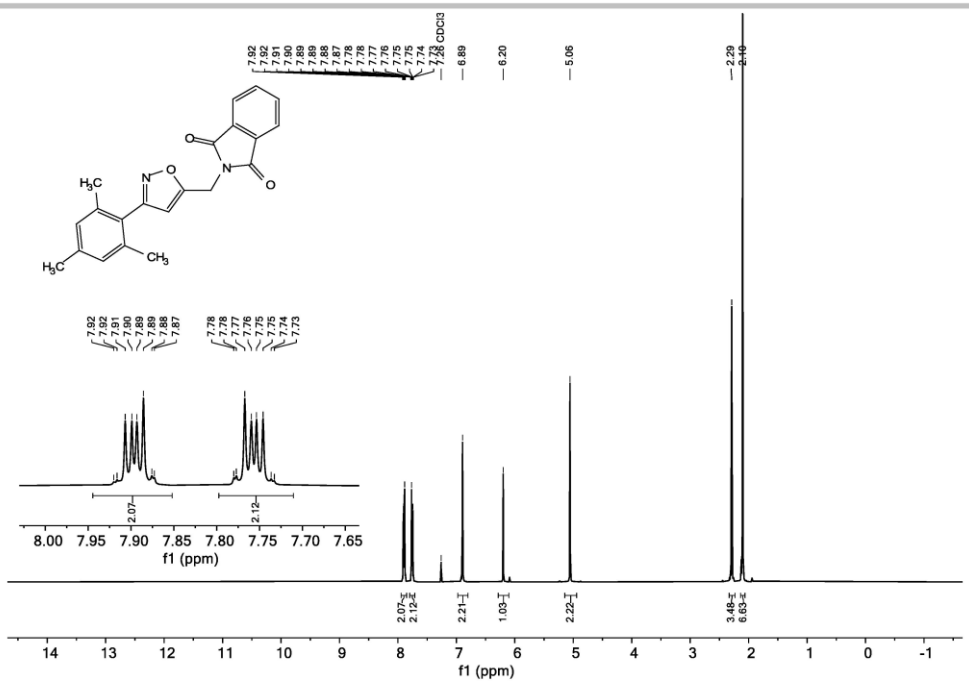

Figure S45: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7l**.

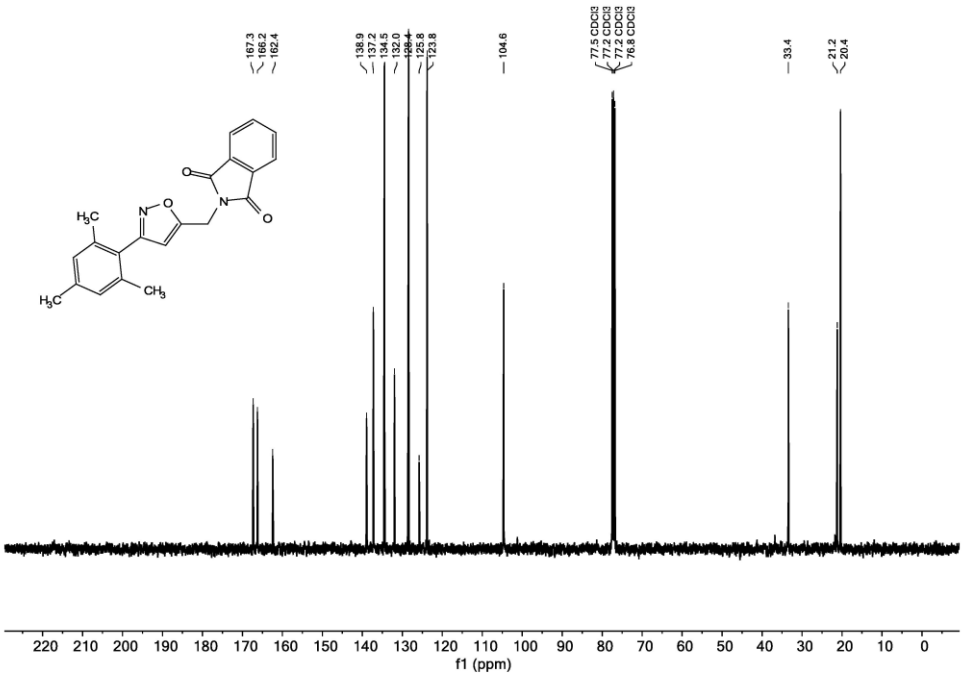

Figure S46: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7l**.

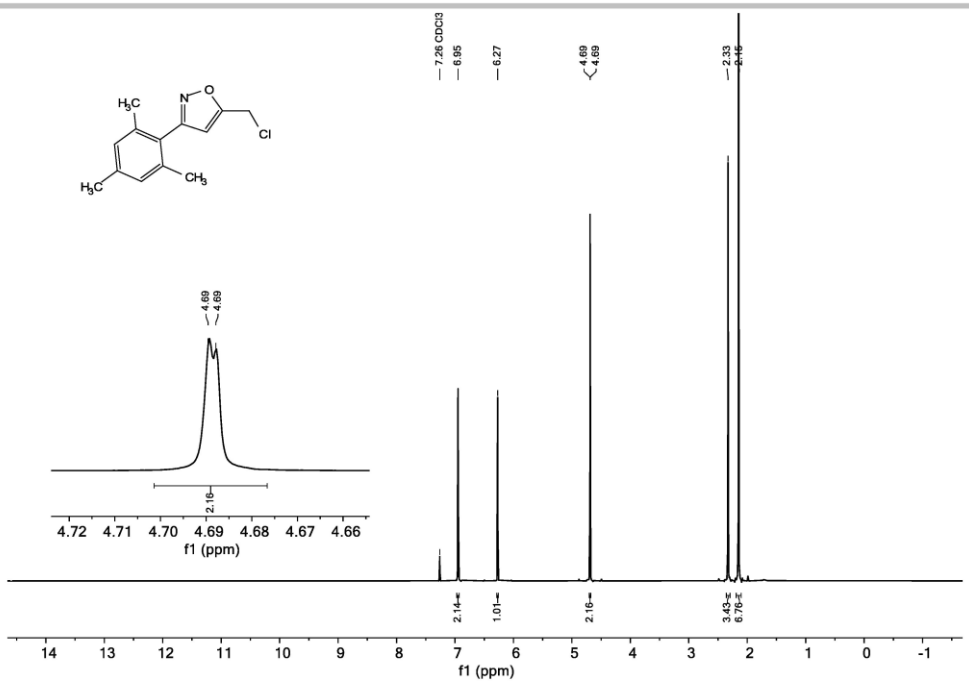

Figure S47: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7m**.

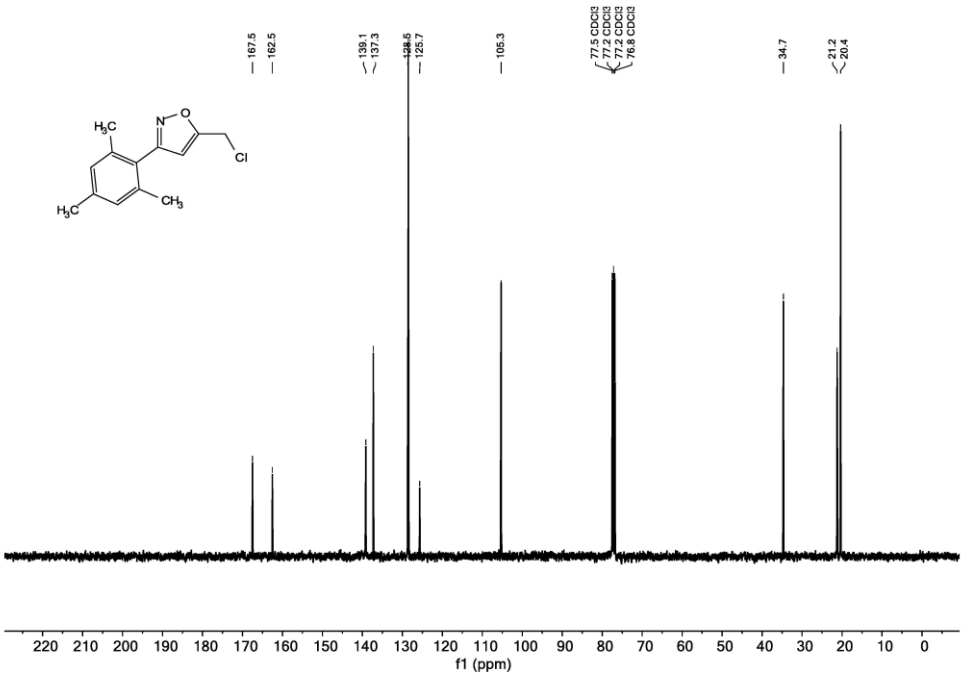

Figure S48: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7m**.

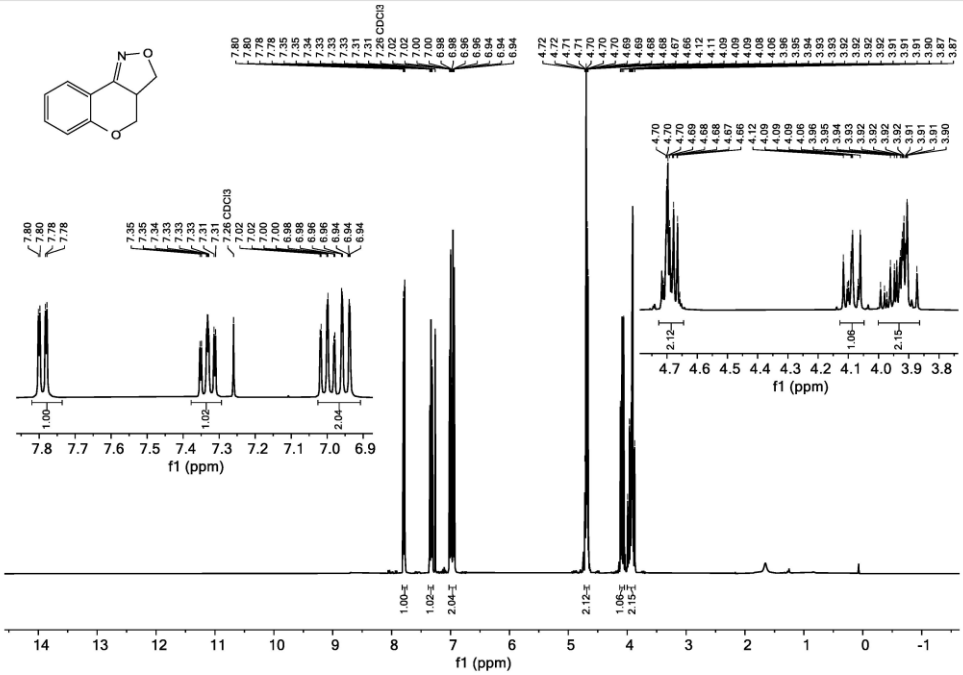

Figure S49: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7n**.

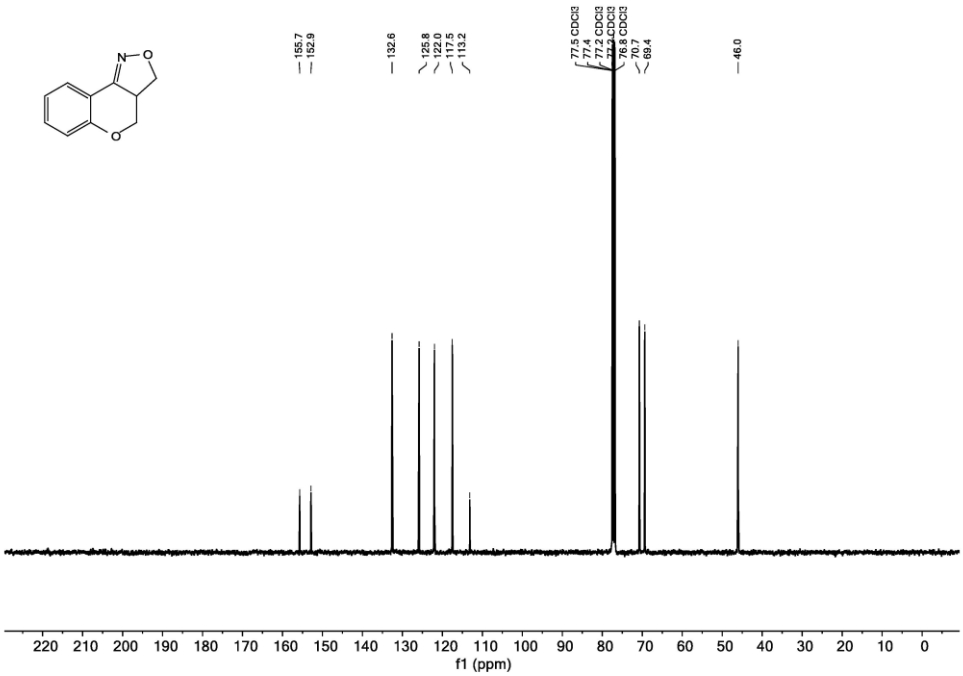

Figure S50: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7n.**

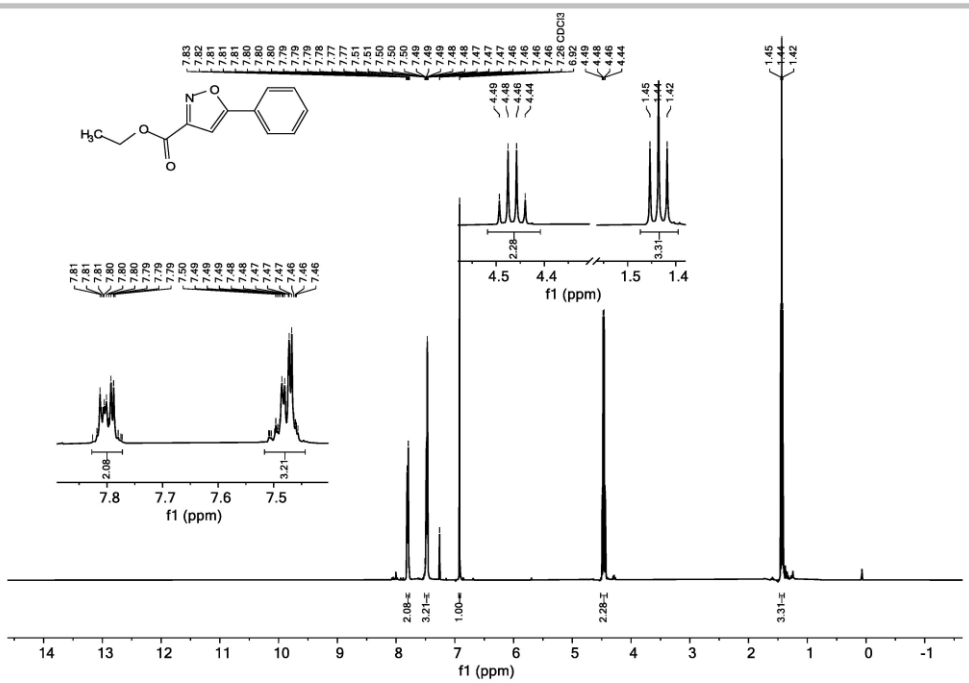

Figure S51: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7o**.

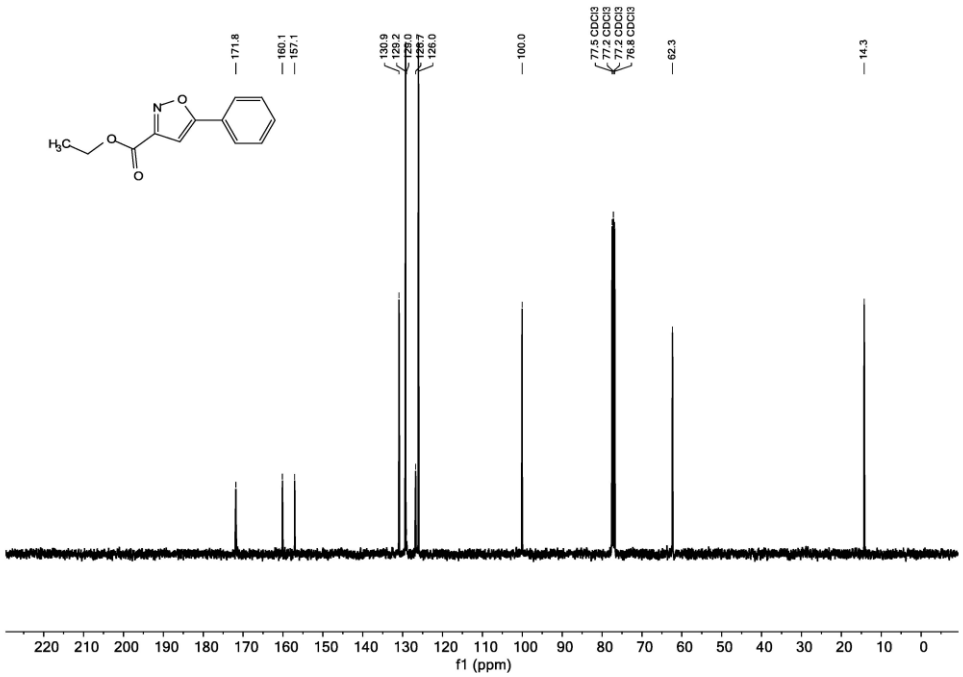

Figure S52: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7o**.

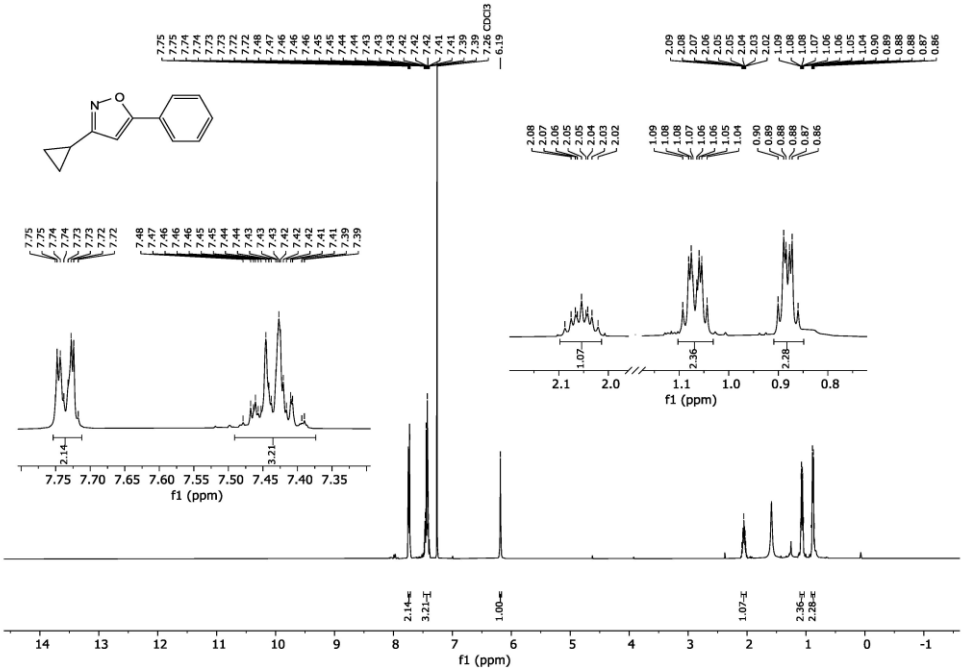

Figure S53: ^{1}H NMR spectrum (162 MHz, $CDCl_3$) of **7p**.

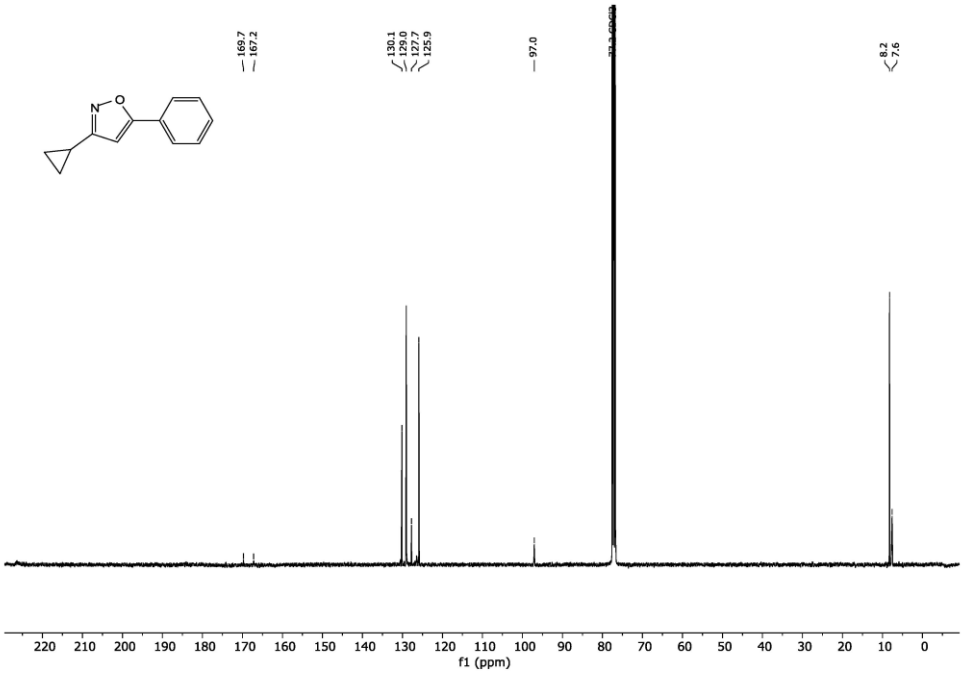

Figure S 54: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7p**.

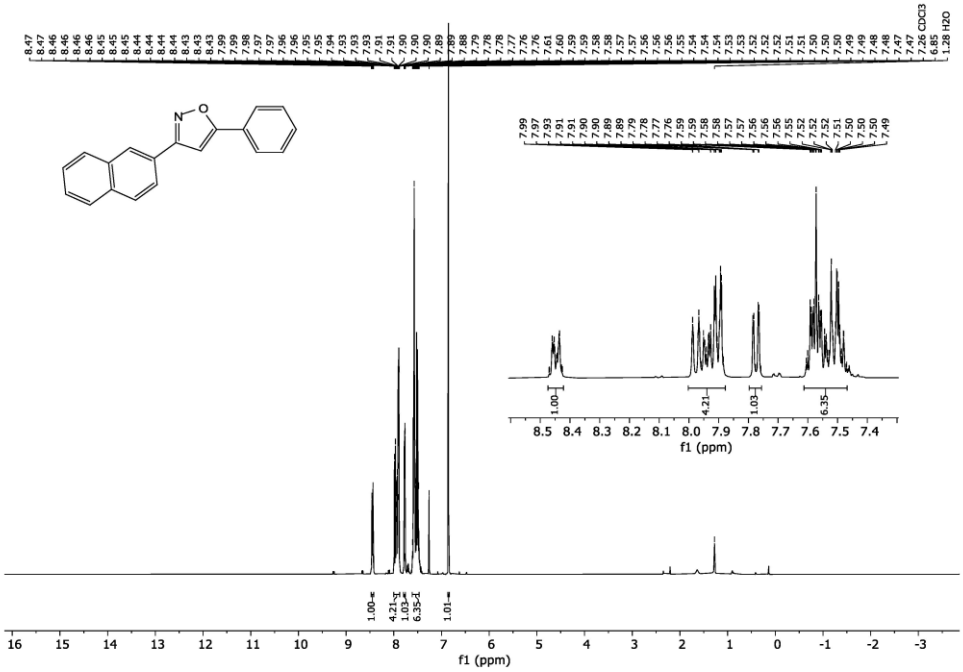

Figure S55: ^{1}H NMR spectrum (162 MHz, $CDCl_3$) of **7q**.

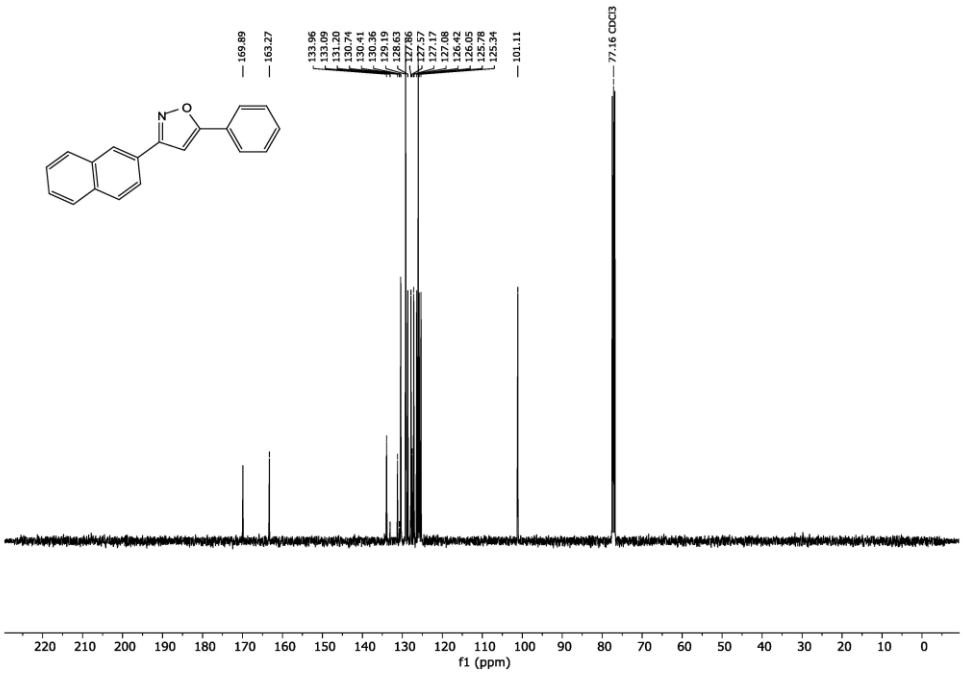

Figure S56: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7q**.

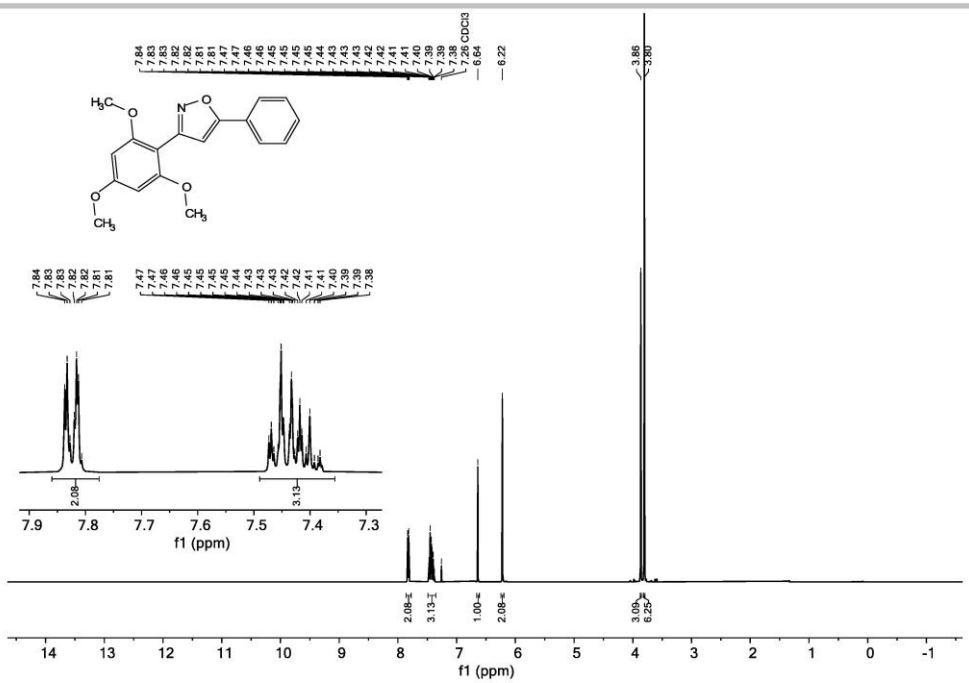

Figure S57: ^{1}H NMR spectrum (162 MHz, $CDCl_3$) of **7r**.

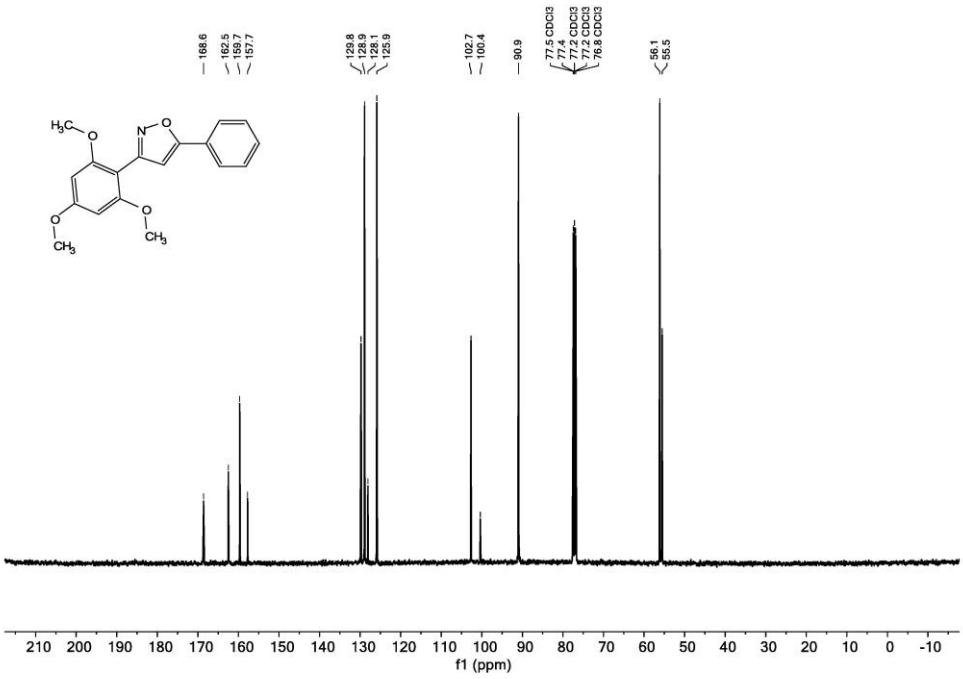

Figure S58: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7r**.

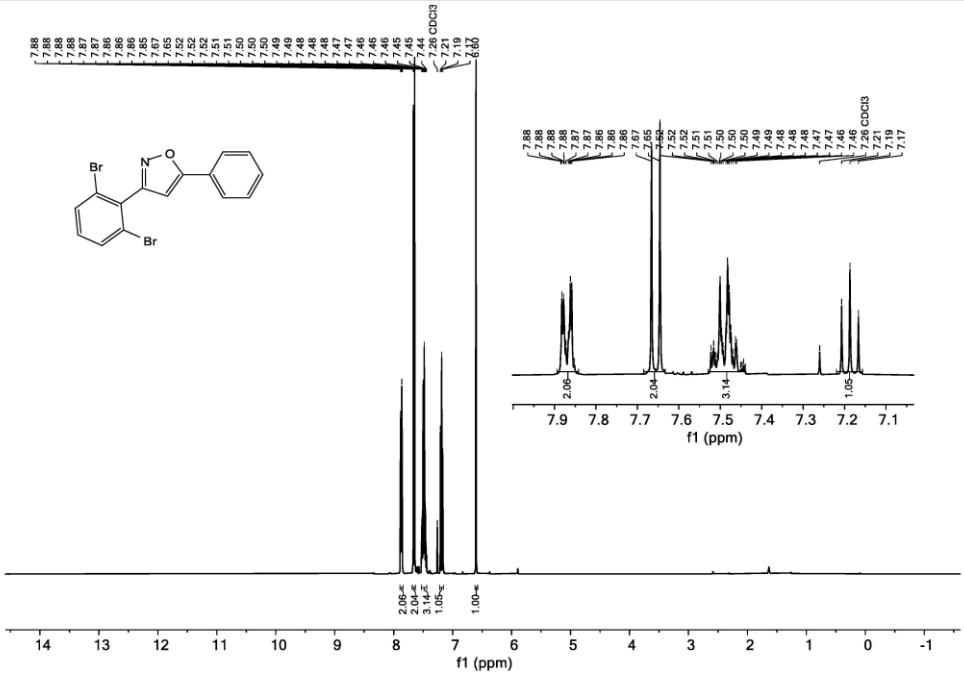

Figure S59: ^{1}H NMR spectrum (162 MHz, $CDCl_3$) of **7s**.

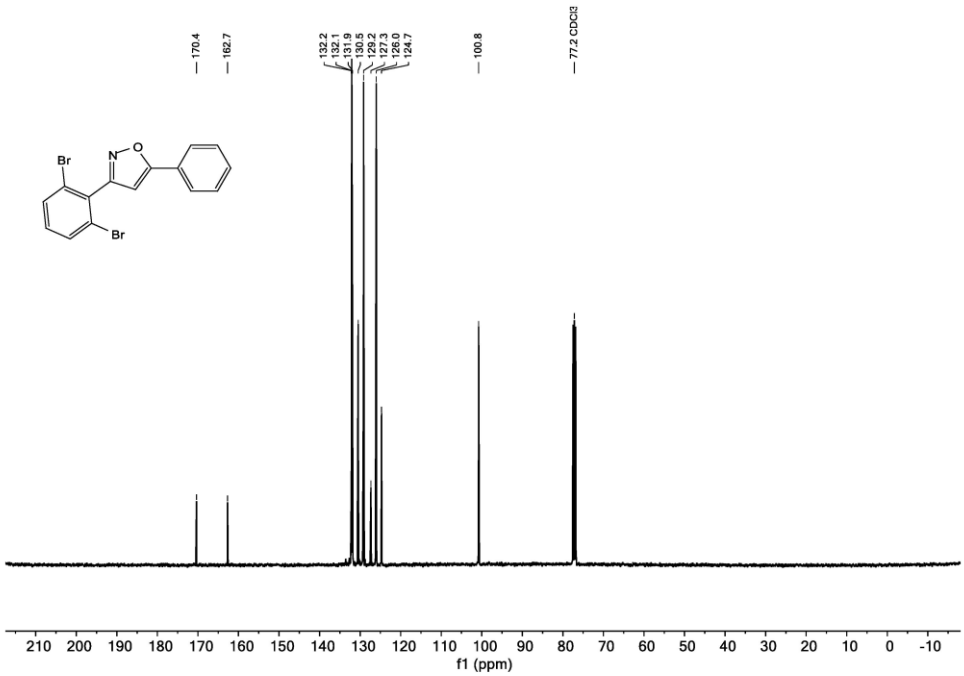

Figure S60: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7s**.

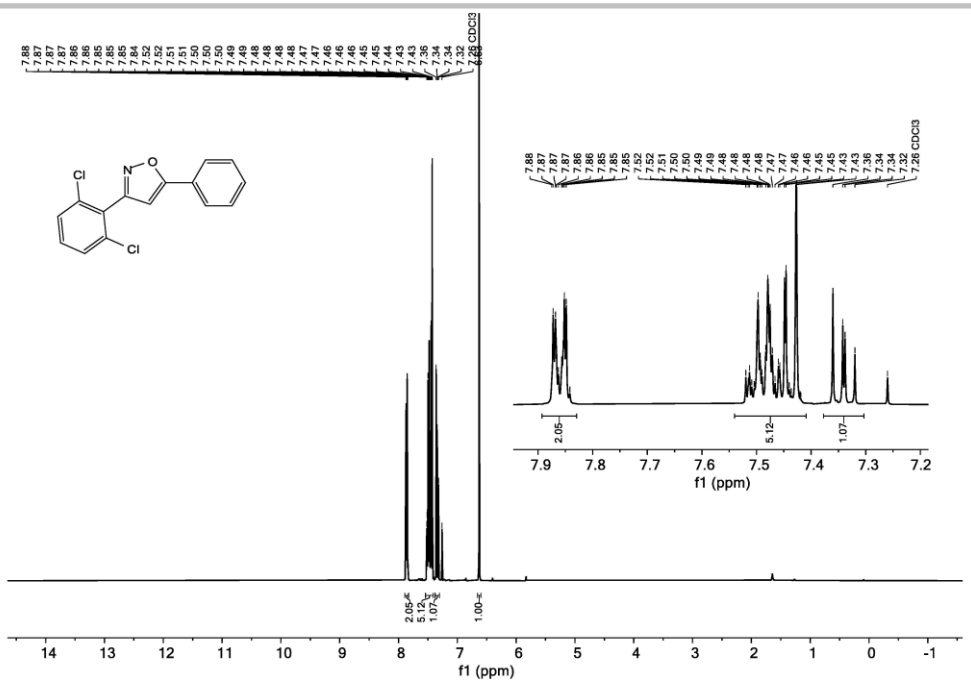

Figure S61: ^{1}H NMR spectrum (162 MHz, $CDCl_3$) of **7t**.

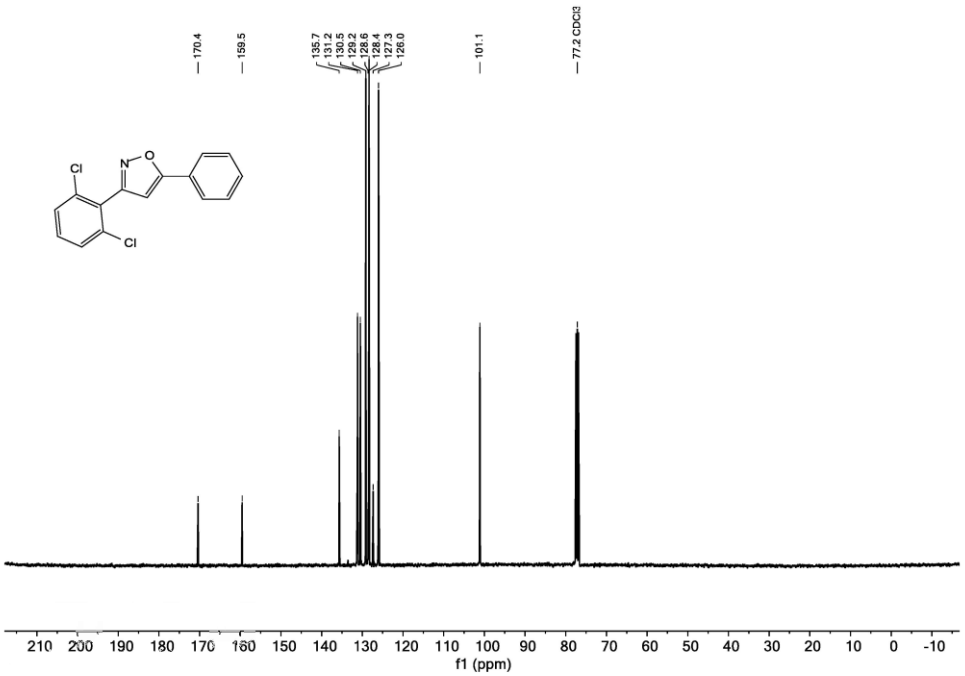

Figure S62: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7t**.

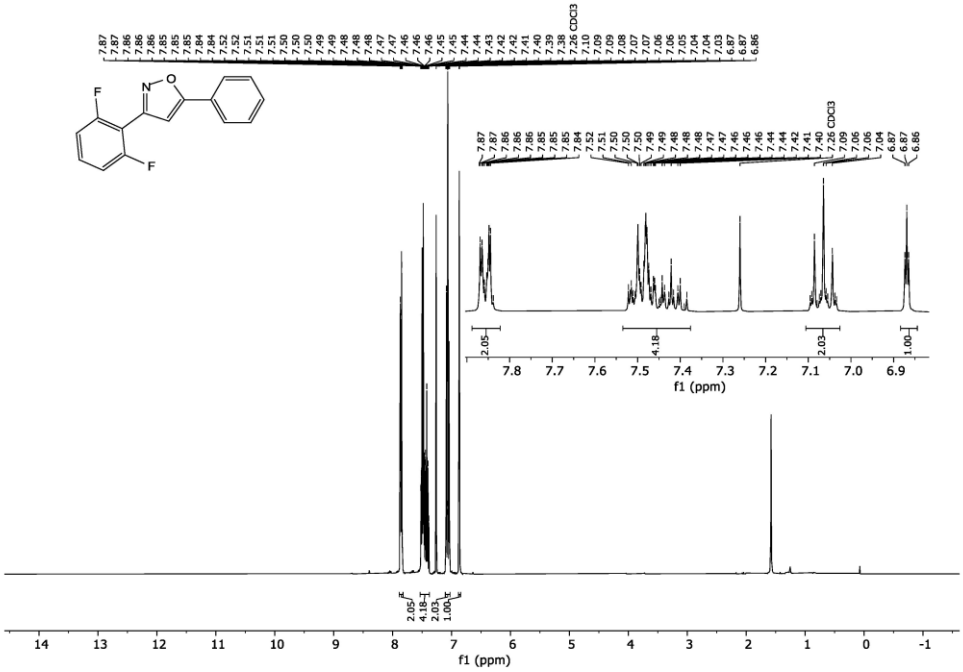

Figure S63: ^{1}H NMR spectrum (162 MHz, $CDCl_3$) of **7u**.

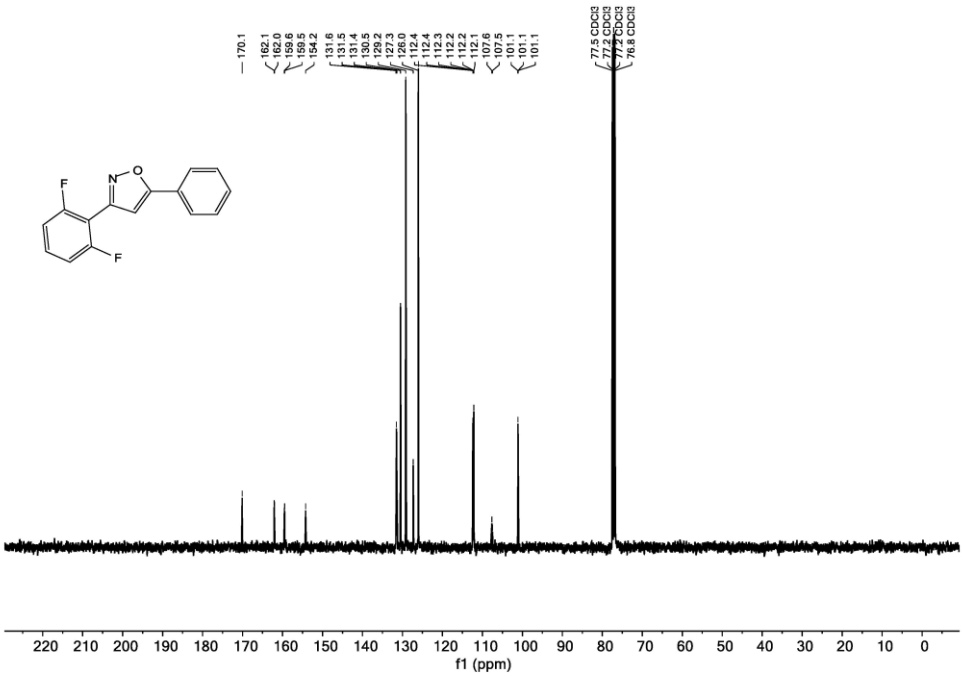

Figure S64: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7u**.

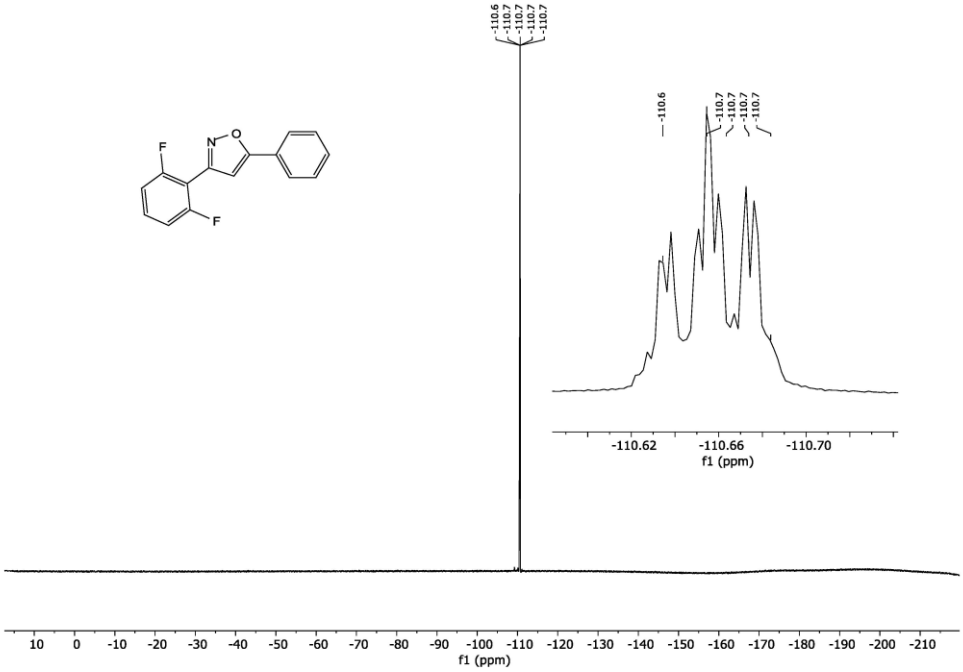

Figure S65: ^{13}C NMR spectrum (376 MHz, $CDCl_3$) of **7u**.

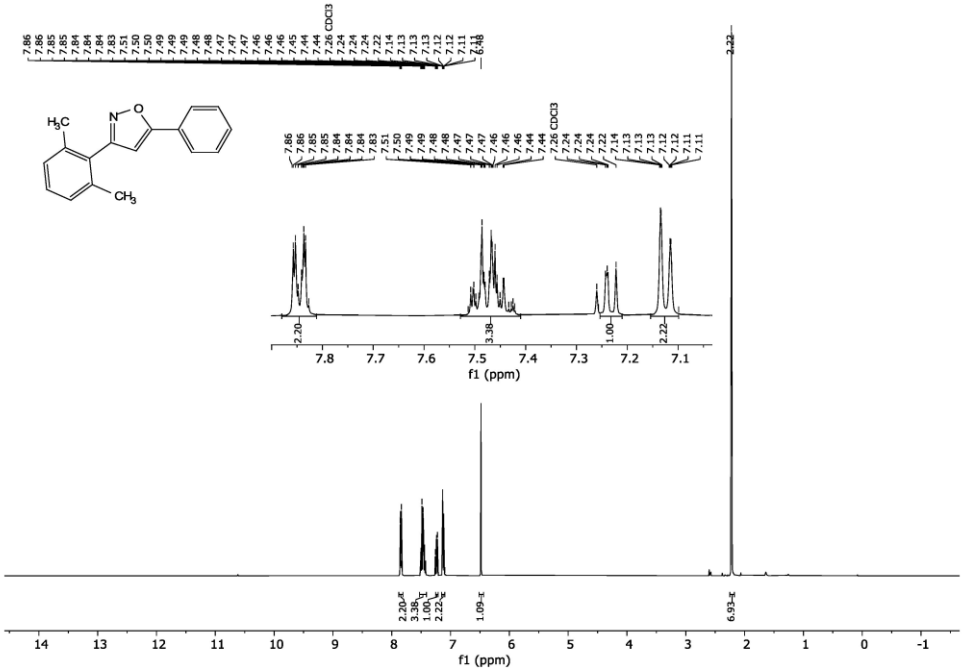

Figure S66: ^{1}H NMR spectrum (162 MHz, $CDCl_3$) of **7v**.

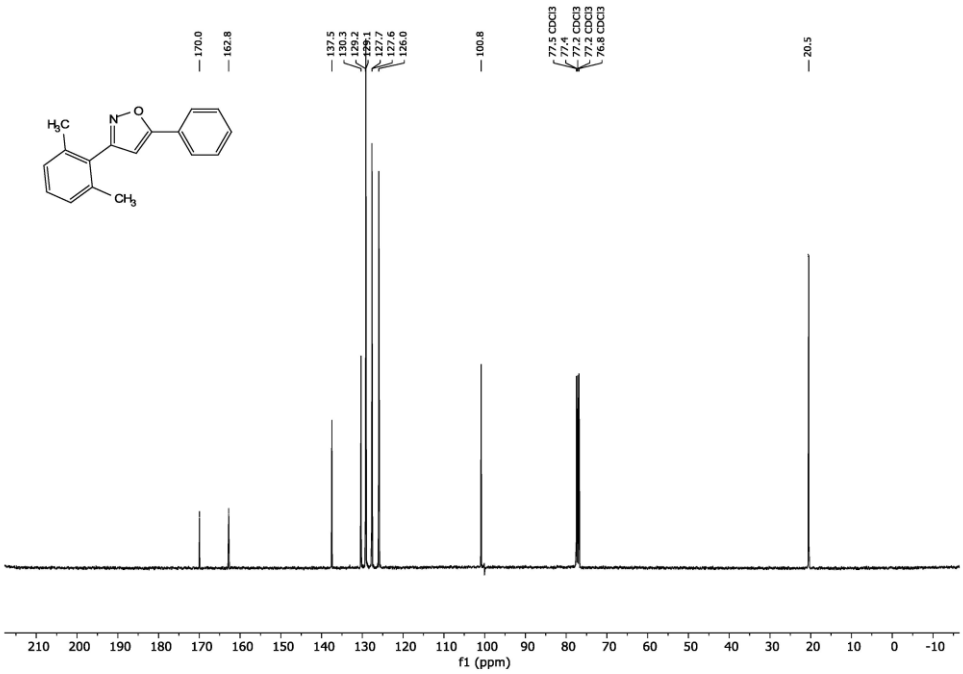

Figure S67: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7v**.

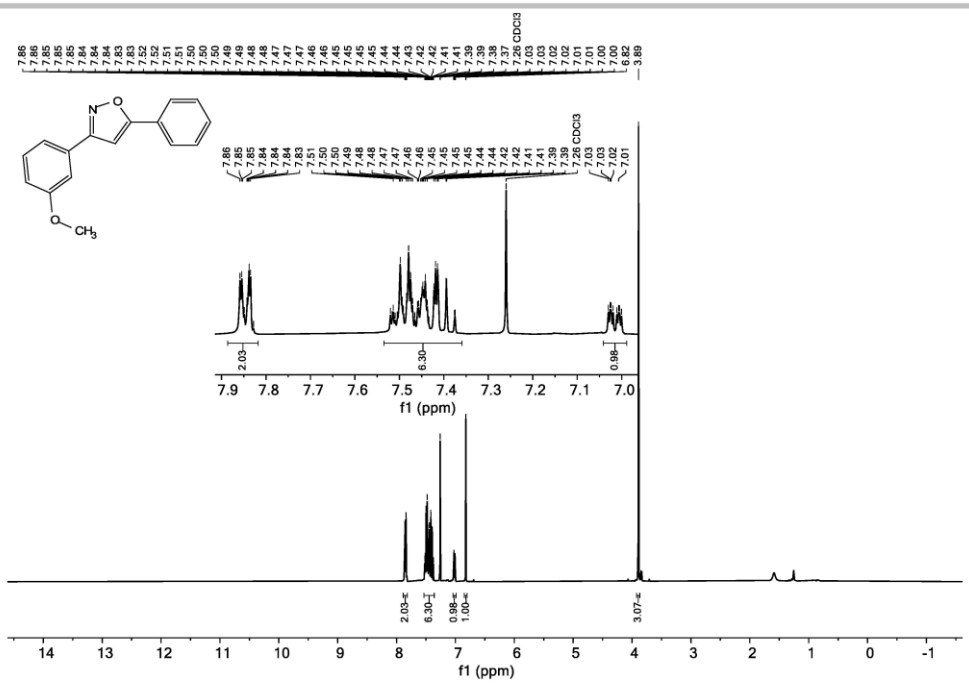

Figure S68: ^{1}H NMR spectrum (162 MHz, $CDCl_3$) of **7w**.

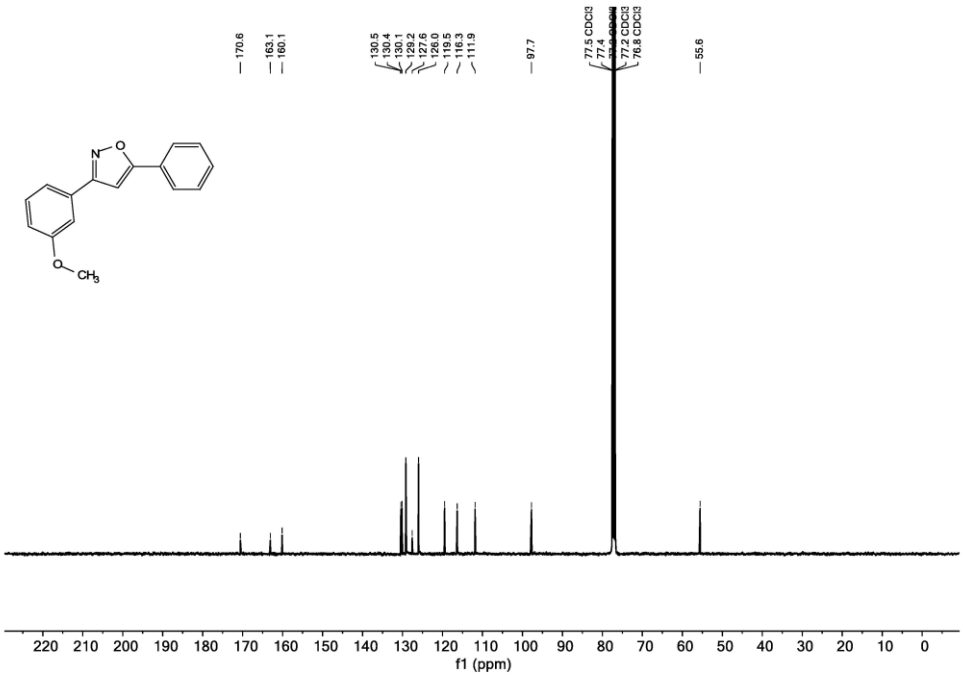

Figure S69: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7w**.

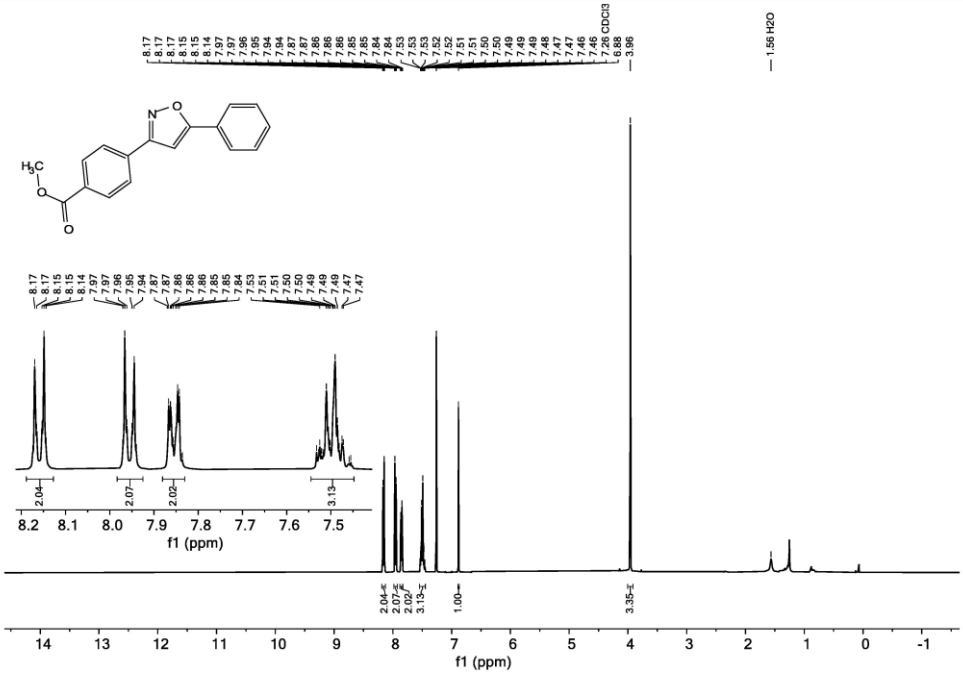

Figure S70: ^{1}H NMR spectrum (162 MHz, $CDCl_3$) of **7x**.

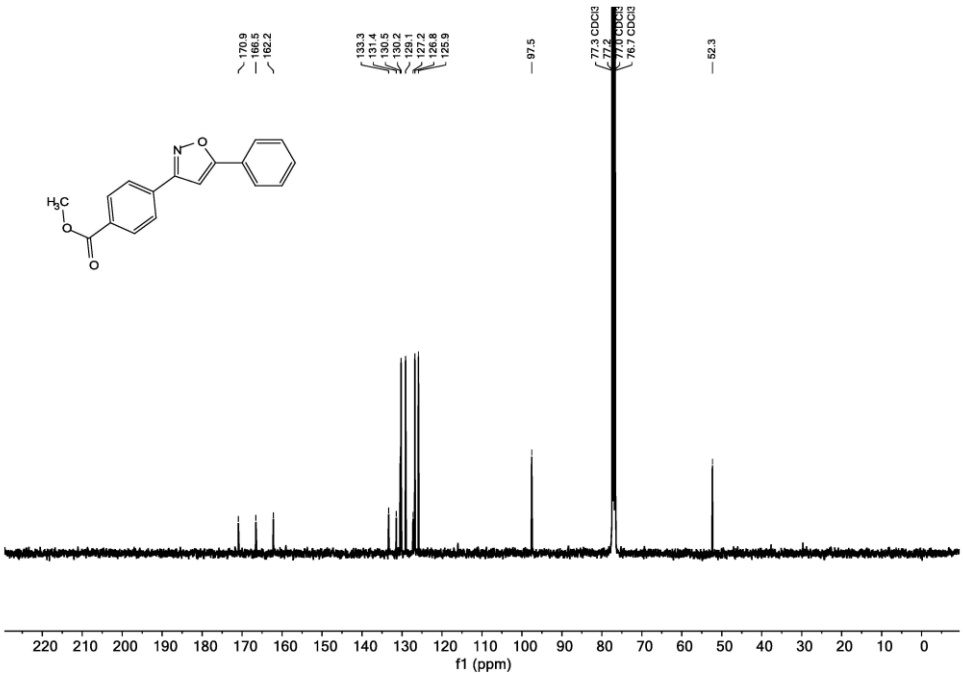

Figure S71: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7x**.

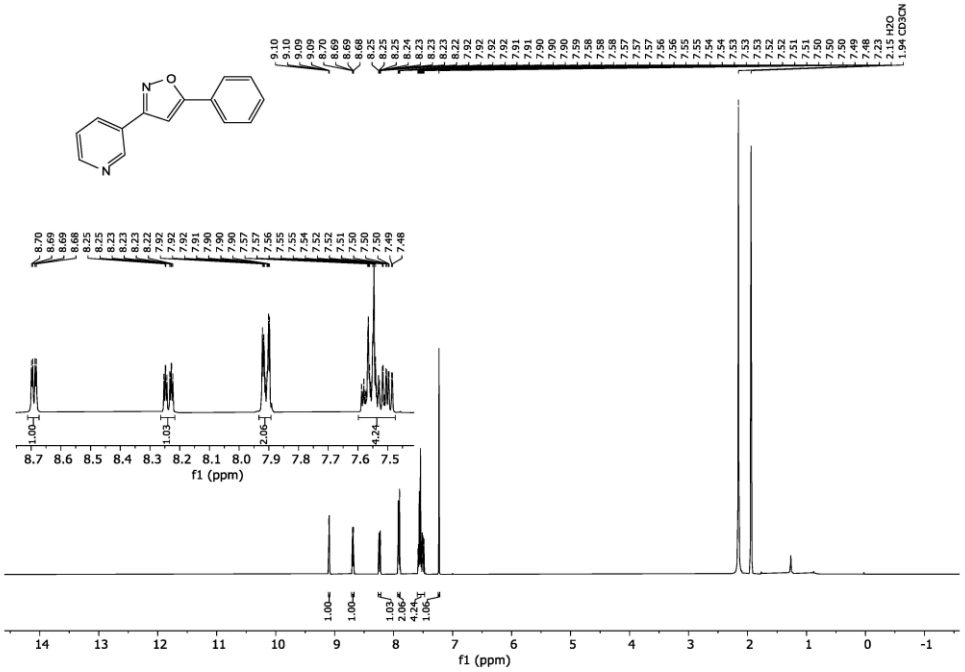

Figure S72: ^{1}H NMR spectrum (162 MHz, $CDCl_3$) of **7y**.

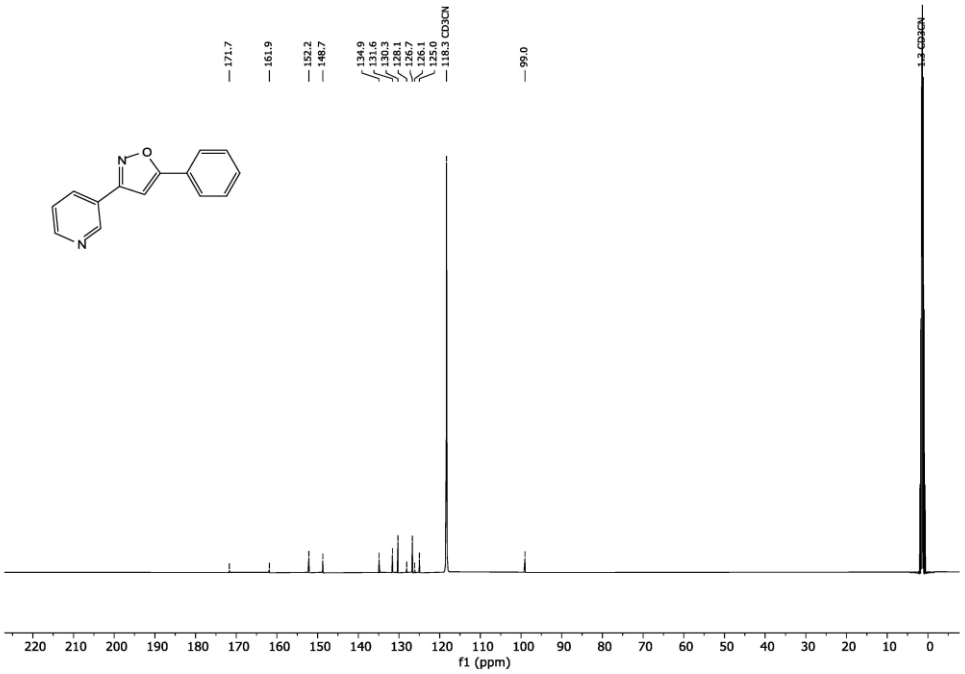

Figure S73: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7y**.

A-2.2 Supporting Information: Biphasic Electrochemical Hectogram Scale Synthesis of 2-Isoxazol(in)e-3-carboxylates

Supporting Information

Biphasic Electrochemical Hectogram Scale Synthesis of 2-Isoxazol(in)e-3-carboxylates

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S1. General Information

Unless otherwise stated, all chemicals were purchased and used without further purification. Anhydrous solvents were either purchased or dried over standard drying agents and freshly distilled prior to use. Mesitylaldoxime was prepared previously as described in the literature.[1]

GC (GC-2025, *Shimadzu*, Kyoto, Japan, quartz capillary column HP-5MS, *Agilent Technologies*, Santa Clara, California, USA), GC-MS (GCMS-QP2010, *Shimadzu*, Kyoto, Japan, quartz capillary column HP-5MS, *Agilent Technologies*, Santa Clara, California, USA) and HPLC-MS (LC-20A Prominence, *Shimadzu Deutschland GmbH*, Duisburg, Germany, UV/VIS-detector SPD-20A/AV (*Shimadzu Deutschland GmbH*, Duisburg, Germany), LCMS-2020 Single Quadrupole (*Shimadzu Deutschland GmbH*, Duisburg, Germany) and an Eurospher II 100-5 C-18-Trennsäule column (*Knauer Wissenschaftliche Geräte GmbH*, Berlin, Germany, length 150 mm, diameter 4 mm, pore size 100 Å, particle size 5 µm).

Reactions were monitored by TLC (Silica gel 60 F_{254}, *Merck KGaA*, Darmstadt, Germany). Preparative column chromatography was accomplished with a prepacked puriFlash® SI-HP silica PF-25SIHC-F0080 column (*Interchim SAS*, Montluçon Cedex, France) using a puriFlash® XS 520 Plus system (*Interchim SAS*, Montluçon Cedex, France).

^{1}H, ^{13}C, and 2D NMR spectra were acquired on a *Bruker* Avance III HD 300, Avance II 400 or Avance III HD 400 in $CDCl_3$, DMSO-d_6, CD_2Cl_2, at 25 °C with the residual solvent peaks as internal reference for ^{1}H and ^{13}C NMR spectra.

Mass spectra *via* electrospray-ionization (ESI+/-) mass spectrometry were recorded using an Agilent 6545 QTOF-MS (*Agilent*, Santa Clara (CA), USA).

Parameter screenings of the electrolytic conditions were performed using an *IKA* Screening System Package (*IKA-Werke GmbH & Co. KG*, Staufen, Germany, Figure S1 top) with electrodes the size of 70 mm × 10 mm × 3 mm. The apparatus and detailed construction information is reported in literature.[2]

The electrode surfaces were cleaned prior use. Isostatic graphite (C_{gr}, Sigrafine™ V2100, *SGL Carbon*, Bonn, Germany) was wet-polished with sandpaper (grade 1000 + 1200, Bosch, Stuttgart, Germany), rinsed with acetone and the abrasion was wiped off with a paper towel until the latter was not stained anymore. Glassy carbon electrodes (C_{gl}, SIGRADUR™ G, *HTW*, Thierhaupten, Germany) were rinsed with several solvents and wiped with a paper towel. Boron-doped diamond (BDD, DIACHEM™, 15 µm diamond layer on silicon support, *CONDIAS GmbH*, Itzehoe, Germany) was conditioned by electrolyzing as anode in 20% aqueous sulfuric acid (10 C cm², 10 mA cm²) and subsequently rinsed with water.

Constant current electrolyses for scale-up experiments were carried out in commercial (SynLectro™, *Merck KGaA*, Darmstadt, Germany, Figure S1, bottom left and middle)[3] or tailor-made (Figure S1, bottom, right)[4] beaker-type cells using TDK-Lambda Z+ series *(TDK-Lambda UK Limited*, Devon, UK) or multichannel power supply HMP4040 (*Rohde & Schwarz*, München, Germany) as power sources.



Figure S1: Top: schematic illustration of a screening block with undivided cells (left); undivided PTFE screening cell with BDD electrodes with a ruler for scale in cm (right). Bottom: jacketed beaker-type cell, up to 50 mL reaction volume (left); beaker-type cell, up to 250 ml reaction volume (middle); jacketed beaker-type cell with 6 electrodes in a bipolar or stacked set-up, up to 1.5 L reaction volume (right).

S2. Calibration of Yields by Gas Chromatography

The evaluation of the GC yields was achieved by external calibration with 1,3,5-trimethoxybenzene as internal standard. The calibration factors *k* for each substance were determined according to equation (*1*).

$$\frac{n_{\text{analyte}}}{n_{\text{standard}}} = k\frac{A_{\text{analyte}}}{A_{\text{standard}}} \qquad (1)$$

S2.1. Ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6b)

Stock solutions of 1,3,5-trimethoxybenzene, ethyl 2-(hydroxyimino)acetate (**5b**) and ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**) were prepared in ethyl acetate (Table S1). Different quantities of the stock solutions were transferred to GC vials (Table S2) and filled with acetonitrile to a total volume of 1.5 mL. Each vial was analyzed three times and for each substance the mean value of the peak areas *A* from these three runs was used as a calibration point. The calibration curve can be found in Figure S2. The calibration factors *k* for each substance are listed in Table S3.

Table S1: Stock solutions for external calibrations using gas chromatography.

#	Substance	*m* / mg	*n* / mmol	V_{solvent} / mL	*c* / mM
stock 1	1,3,5-trimethoxybenzene	3038	18.06	100	180.6
stock 2	ethyl 2-(hydroxyimino)acetate (**5b**)	19.8	0.169	10	16.9
stock 3	ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**)	38.6	0.176	5	35.2

Table S2: Calibration solutions for ethyl 2-(hydroxyimino)acetate (**5b**) and ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**), internal standard: 1,3,5-trimethoxybenzene.

#	$V_{\text{Stock 1}}$ / µL	$V_{\text{Stock 2}}$ / µL	$V_{\text{Stock 3}}$ / µL
cal. 1	10	60	30
cal. 2	10	120	60
cal. 3	10	180	90
cal. 4	10	240	120
cal. 5	10	300	150
cal. 6	10	360	180

#	$V_{\text{Stock 1}}$ / µL	$V_{\text{Stock 2}}$ / µL	$V_{\text{Stock 3}}$ / µL
cal. 7	10	430	215
cal. 8	10	500	250
cal. 9	10	600	300
cal. 10	10	700	350
cal. 11	10	800	400
cal. 12	10	900	450

Table S3: Calibration factors for ethyl 2-(hydroxyimino)acetate (**5b**) and ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**) used in the screening experiments.

substance	*k*
ethyl 2-(hydroxyimino)acetate (**5b**)	2.5547
ethyl 4,5dihydro-5-phenylisoxazole-3-carboxylate (**6b**)	0.6661

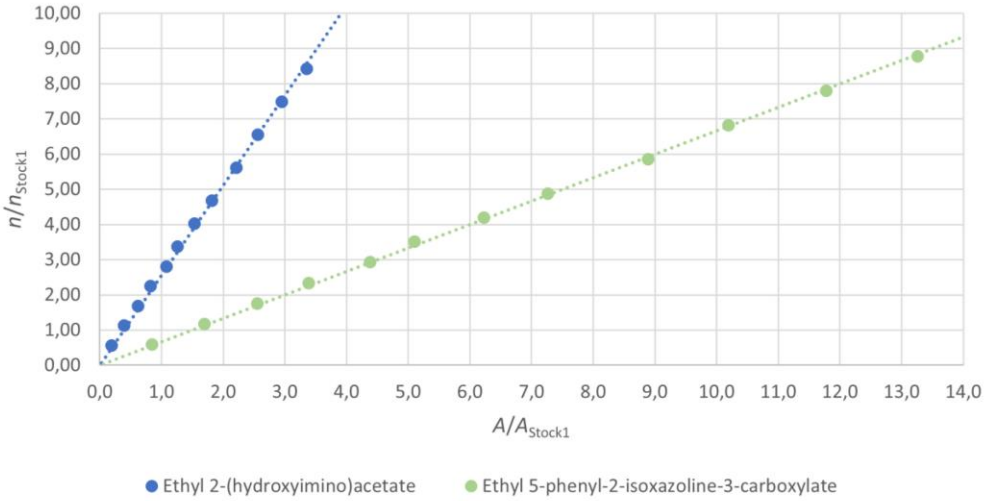


Figure S2: GC calibration for ethyl 2-(hydroxyimino)acetate (**5b**) and ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**) used in the screening experiments (internal standard: 1,3,5-trimethoxybenzene).

S2.2. Butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6e)

Stock solutions of 1,3,5-trimethoxybenzene, butyl 2-(hydroxyimino)acetate (**5e**) and butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**) were prepared in ethyl acetate (Table S4). Different quantities of the stock solutions were transferred to GC vials (Table S5) and filled with acetonitrile to a total volume of 1.5 mL. Each vial was analyzed three times and for each substance the mean value of the peak areas *A* from these three runs was used as a calibration point. The calibration curve can be found in Figure S3. The calibration factors *k* for each substance are listed in Table S6.

Table S4: Stock solutions for external calibrations using gas chromatography.

#	Substance	*m* / mg	*n* / mmol	$V_{solvent}$ / mL	*c* / mM
stock 1	1,3,5-trimethoxybenzene	2950	17.54	100	175.4
stock 2	butyl 2-(hydroxyimino)acetate (**5e**)	54.2	0.374	10	37.4
stock 3	butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**)	76.3	0.309	10	30.9

Table S5: Calibration solutions for butyl 2-(hydroxyimino)acetate (**5e**) and butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**), internal standard: 1,3,5-trimethoxybenzene.

#	$V_{Stock\ 1}$ / µL	$V_{Stock\ 2}$ / µL	$V_{Stock\ 3}$ / µL
cal. 1	10	30	30
cal. 2	10	60	60
cal. 3	10	90	90
cal. 4	10	120	120
cal. 5	10	150	150

#	$V_{Stock\ 1}$ / µL	$V_{Stock\ 2}$ / µL	$V_{Stock\ 3}$ / µL
cal. 6	10	190	190
cal. 7	10	225	225
cal. 8	10	260	260
cal. 9	10	300	300
cal. 10	10	350	350

Table S6: Calibration factors for butyl 2-(hydroxyimino)acetate (**5e**) and butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**) used in the screening experiments.

Substance	*k*
butyl 2-(hydroxyimino)acetate (**5e**)	1.4557
butyl 4,5dihydro-5-phenylisoxazole-3-carboxylate (**6e**)	0.4839

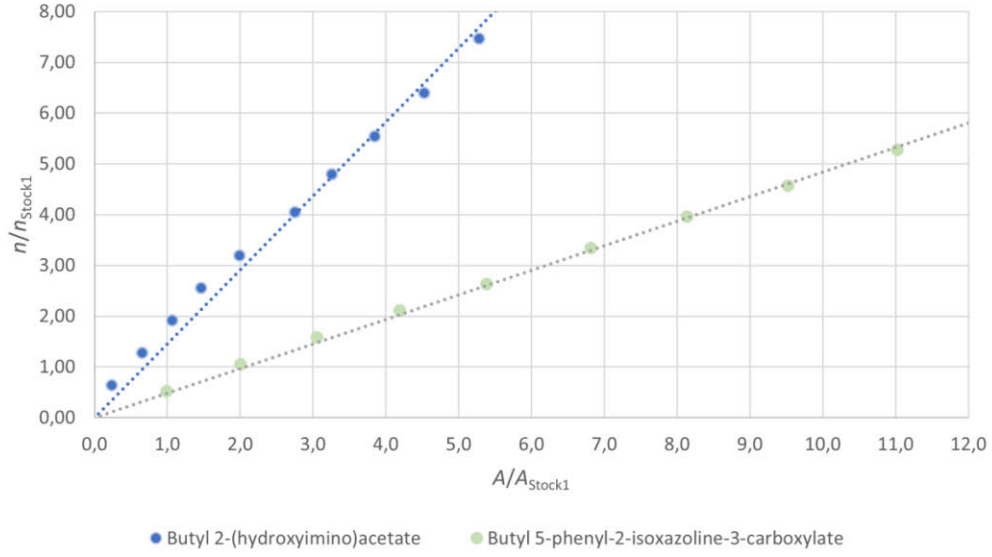


Figure S3: GC calibration for butyl 2-(hydroxyimino)acetate (**5e**) and butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**) used in the screening experiments (internal standard: 1,3,5-trimethoxybenzene).

S3. Standard Operating Protocols (SOP)

SOP1: Screening for Suitable Electrolytic Conditions

In 5 mL PTFE cells, the respective oxime and styrene were dissolved in 5 mL of a mixture of organic solvent and 1 M aqueous sodium halide solution at the given temperature under vigorous stirring (magnetic stirrer set to approx. 1000 rpm). The mixture was subjected to galvanostatic electrolysis on electrodes with a relevant surface area of 1.7 cm^2 (size: 70 × 10 × 3 mm, immersion depth 1.7 cm). The biphasic mixture was transferred to a separation funnel, and the cell was rinsed with ethyl acetate. 1 mL of a solution of 1,3,5-trimethoxybenzene (3.000 g/100 mL ethyl acetate) was added as internal standard and the mixture shaken briefly. After separation of the layers, the organic fraction was dried over anhydrous magnesium sulfate and filtered. An aliquot was filtered through silica and subjected to GC analysis for quantification.

SOP2: Preparative Electrolysis

In a 50 mL jacketed beaker-type glass cell, the respective oxime (**3.44 mmol, 1.0 eq.**) and the dipolarophile (**19.0 mmol, 5.51 eq.**) were dissolved a mixture of *tert*-butyl methyl ether (12.5 mL) and 1 M aqueous sodium iodide solution (12.5 mL) at 25 °C. The mixture was subjected to galvanostatic electrolysis under vigorous stirring (1000 rpm) on boron-doped diamond (BDD) electrodes with a relevant surface area of 6.0 cm^2 (size: 60 × 20 × 3 mm, immersion depth 3.0 cm) with a current density of 18.9 mA cm^{-2} until a charge of 5.46 *F* (1814.6 As) was applied. The biphasic mixture was transferred to a separation funnel, and the cell was rinsed with ethyl acetate. The layers were separated, and the aqueous layer was extracted once with ethyl acetate (30 mL). The combined organic fractions were dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography to obtain the pure product.

S4. Optimization of the Isoxazoline Syntheses

S4.1. Ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6b)

S4.1.1. Preliminary Optimization

Electrolysis was carried out according to SOP1 using ethyl 2-(hydroxyimino)acetate (**5b**, **0.85 mmol, 100 mg, 1.0 eq.**) and styrene (**3.42 mmol, 356 mg, 4.0 eq.**) in a mixture of organic solvent (1 mL) and 1 M aqueous sodium halide solution (4 mL). Constant current electrolysis was conducted at 25 °C under vigorous stirring (1000 rpm), with a current density of 25 mA cm^{-2} until a charge of 5.0 *F* (412.0 C) was applied. The results can be found in Table S7.

Table S7: Results of the preliminary screening for the synthesis of ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**).

#	Organic solvent	Electrode materials	Halide source	Yield (GC)[a]
1	CH_2Cl_2	C_{gr}||C_{gr}	NaCl	4%
2	CH_2Cl_2	C_{gr}||C_{gr}	NaBr	4%
3	CH_2Cl_2	C_{gr}||C_{gr}	NaI	15%
4	CH_2Cl_2	C_{gl}||C_{gl}	NaI	12%
5	CH_2Cl_2	BDD||BDD	NaI	5%
6	EtOAc	C_{gr}||C_{gr}	NaI	40%
7	MeO^{t}Bu	C_{gr}||C_{gr}	NaI	30%
8	PhCl	C_{gr}||C_{gr}	NaI	3%
9	PhMe	C_{gr}||C_{gr}	NaI	2%

[a] Determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.

S4.1.2. Optimization via Design of Experiments

Electrolysis was carried out according to SOP1 using ethyl 2-(hydroxyimino)acetate (**5b**, **0.85 mmol, 100 mg, 1.0 eq.**) and styrene. A mixture of ethyl acetate (1 mL) and 1 M aqueous sodium iodide solution (4 mL) was used. Electrolysis was performed at 25 °C on two isostatic graphite plates as anode and cathode under vigorous stirring (1000 rpm). The center point was acquired three times. The results can be found in Table S8.

Table S8: Optimization of the synthesis of ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**) *via* DoE.

#	m_{oxime} / mg	*T* / °C	*Q* / *F*	*j* / mA cm^2	eq. styrene	Yield (GC)[a]
1	100	25	2.38	25.0	3.00	37%
2	100	25	3.00	20.0	4.00	43%
3	100	25	3.00	30.0	2.00	34%
4	100	25	4.50	17.9	3.00	37%
5	100	25	4.50	25.0	1.59	29%
6a	100	25	4.50	25.0	3.00	38%
6b	100	25	4.50	25.0	3.00	38%
6c	100	25	4.50	25.0	3.00	38%
7	100	25	4.50	25.0	4.41	43%
8	100	25	4.50	32.1	3.00	37%
9	100	25	6.00	20.0	2.00	30%
10	100	25	6.00	30.0	4.00	39%
11	100	25	6.62	25.0	3.00	34%

[a] Determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.

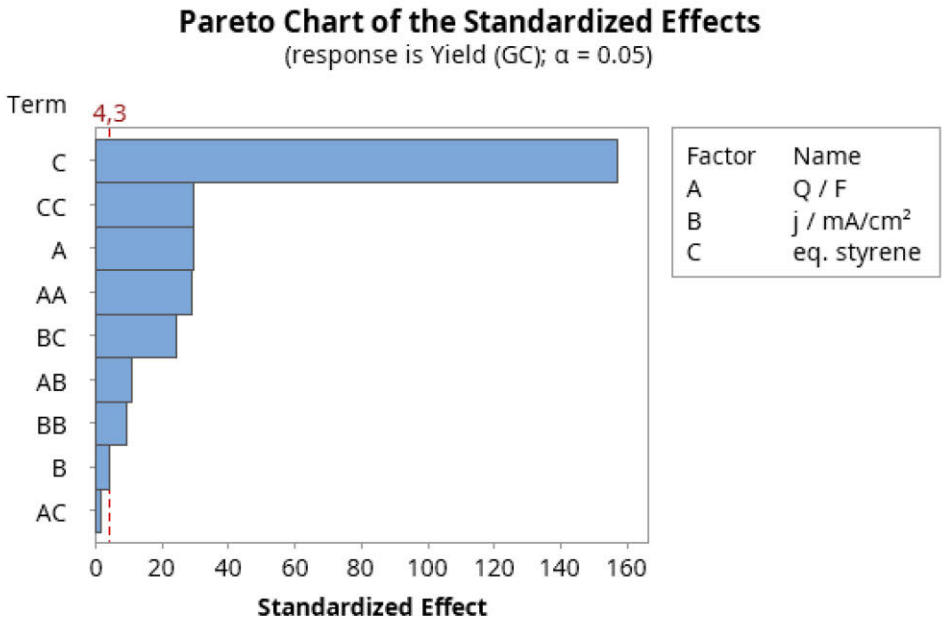


Figure S4: Pareto chart of the standardized effects for the optimization of the synthesis of ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**) *via* DoE.

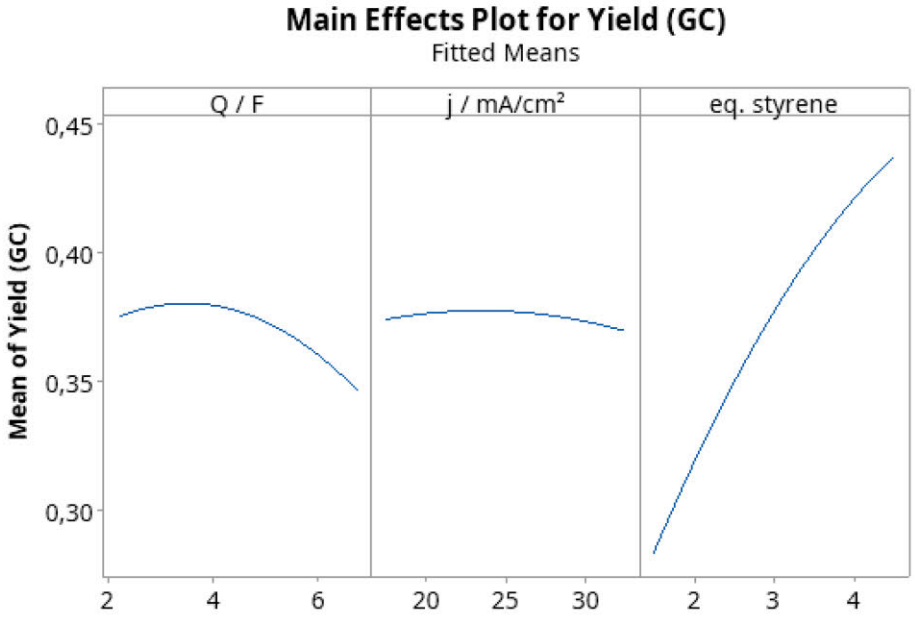


Figure S5: Main effects plot for the optimization of the synthesis of ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**) *via* DoE.

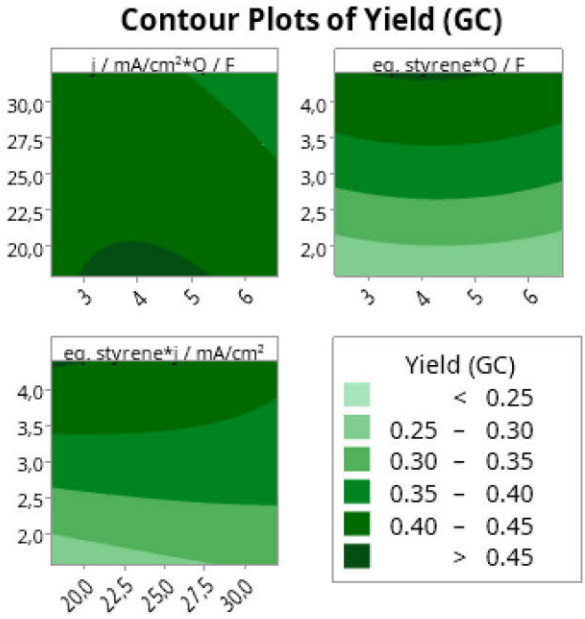


Figure S6: Contour plots for the optimization of the synthesis of ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**) *via* DoE.

S4.1.3. Impact of Reaction Temperatures and Stirring Speeds

Electrolysis was carried out according to SOP1 using ethyl 2-(hydroxyimino)acetate (**5b**, **0.85 mmol, 100 mg, 1.0 eq.**) and styrene (**2.56 mmol, 267 mg, 3.0 eq.**). A mixture of ethyl acetate (1 mL) and 1 M aqueous sodium iodide solution (4 mL) was used. Electrolysis was performed on two isostatic graphite plates as anode and cathode with a current density of 25 mA cm^{-2} until a charge of 4.5 *F* (370.8 As) was applied. The results can be found in Table S9.

Table S9: Investigation of the impacts of reaction temperature and stirring speed on the synthesis of ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**).

#	Stirring speed[a]	*T* / °C	Yield (GC)[b]
1	fast	25	39%
2	fast	38	39%
3	fast	50	33%

#	Stirring speed[a]	*T* / °C	Yield (GC)[b]
4	slow	25	7%
5	medium	25	26%

[a] Slow: stirring plate set to 100 rpm; medium: stirring plate set to 500 rpm; fast: stirring plate set to 1000 rpm.
[b] Determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.

S4.1.4. Test of the Predicted Optimum Conditions

Screening-Scale:

Electrolysis was carried out according to SOP1 using ethyl 2-(hydroxyimino)acetate (**5b**, **0.85 mmol, 100 mg, 1.0 eq.**) and styrene (**3.77 mmol, 392 mg, 4.41 eq.**). A mixture of ethyl acetate (1 mL) and 1 M aqueous sodium iodide solution (4 mL) was used. Electrolysis was performed at 25 °C on two isostatic graphite plates as anode and cathode with a current density of 18 mA cm^{-2} under vigorous stirring (1000 rpm) until a charge of 4.14 *F* (363.4 As) was applied.

Preparative Scale:

In 50 mL jacketed beaker-type glass cells, ethyl 2-(hydroxyimino)acetate (**5b**, **4.27 mmol, 500 mg, 1.0 eq.**) and styrene (**18.8 mmol, 1.96 g, 4.41 eq.**) were dissolved a mixture of ethyl acetate (5 mL) and 1 M aqueous sodium iodide solution (20 mL) at 25 °C. The mixture was subjected to galvanostatic electrolysis under vigorous stirring on isostatic graphite electrodes with a relevant surface area of 5.0 cm^2 (size: 60 × 20 × 3 mm, immersion depth 2.5 cm) with a current density of 18 mA cm^{-2} until a charge of 4.14 *F* (1705.6 As) was applied. The biphasic mixture was transferred to a separation funnel, and the cell was rinsed with ethyl acetate. The layers were separated, and the aqueous layer was extracted once with ethyl acetate (30 mL). The combined organic fractions were dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. Isoxazoline (**6b**) was obtained after flash column chromatography on silica (cyclohexane/ethyl acetate; 0% →10% EtOAc) as a yellow oil (**1.31 mmol, 287 mg, 31%**). The results can be found in Table S10.

Table S10: Test of the predicted optimum for the synthesis of ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**).

#	Scale	Yield
1	Screening (0.85 mmol)	45%[a]
2	Preparative (4.27 mmol)	31%[b]

[a] Yield determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.
[b] Isolated yield.

S4.1.5. Homogeneous System

In 5 mL PTFE cells, ethyl 2-(hydroxyimino)acetate (**5b**, **0.85 mmol, 100 mg, 1.0 eq.**) and tributylmethylammonium methylsulfate (**0.16 mmol, 50 mg**) were dissolved in a mixture of organic solvent (4.5 mL) and water (0.5 mL). Electrolysis was performed at the given temperature on an isostatic graphite plate with a relevant surface area of 1.7 cm^2 (size: 70 × 10 × 3 mm, immersion depth 1.7 cm) as anode and a stainless steel (VA1.4571) wire cathode under vigorous stirring (1000 rpm). The current density was set to 12.5 mA cm^{-2} until a charge of 3.0 *F* (247.2 As) was applied. Styrene (**3.42 mmol, 356 mg, 4.0 eq.**) was added and the mixture was stirred overnight while warming to room temperature The biphasic mixture was transferred to a separation funnel, the cell was rinsed with ethyl acetate and ethyl acetate (20 mL) and water (20 mL) were added. 1 mL of a solution of 1,3,5-trimethoxybenzene (3.000 g/100 mL ethyl acetate) was added as internal standard and the mixture shaken briefly. After separation of the layers, the organic fraction was dried over anhydrous magnesium sulfate and filtered. An aliquot was filtered through silica and subjected to GC analysis for quantification. The results can be found in Table S11.

Table S11: Screening for a homogenous system for the synthesis of ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6b**).

#	Solvent	$T_{electrolysis}$ / °C	Yield (GC)[a]
1	MeCN	25	*n/d*
2	MeCN	0	traces[b]
3	MeOH	0	*n/d*[b]

#	Solvent	$T_{electrolysis}$ / °C	Yield (GC)[a]
4	MeCN	-10	10%[b]
5	MeOH	-10	traces[b]

[a] Determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.
[b] Incomplete conversion.

An *ex-cell* approach was chosen due to the instability of styrene under electrolytic conditions. The increased yields with decreased temperature were assigned to thermal instability of the intermediary nitrile oxide. However, decreased temperatures led to significantly decreased substrate conversion.

S4.2. Butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6e)

S4.2.1. Initial Test

In 50 mL jacketed beaker-type glass cells, butyl 2-(hydroxyimino)acetate (**5e**, **4.34 mmol, 630 mg, 1.0 eq.**) and styrene (**19.1 mmol, 1.99 g, 4.41 eq.**) were dissolved a mixture of ethyl acetate (12.5 mL) and 1 M aqueous sodium iodide solution (12.5 mL) at 25 °C. The mixture was subjected to galvanostatic electrolysis under vigorous stirring on isostatic graphite electrodes with a relevant surface area of 5.0 cm^2 (size: 60 × 20 × 3 mm, immersion depth 2.5 cm) with a current density of 18 mA cm^{-2} until a charge of 4.14 *F* (1705.6 As) was applied. The biphasic mixture was transferred to a separation funnel, and the cell was rinsed with ethyl acetate. The layers were separated, and the aqueous layer was extracted once with ethyl acetate (30 mL). The combined organic fractions were dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. Isoxazoline (**6e**) was obtained after flash column chromatography on silica (cyclohexane/ethyl acetate; 0% →10% EtOAc) as a yellow oil (**2.20 mmol, 545 mg, 51%**).

S4.2.2. Preliminary Optimization

Electrolysis was carried out according to SOP1 using butyl 2-(hydroxyimino)acetate (**5e**, **0.69 mmol, 100 mg, 1.0 eq.**) and styrene (**2.90 mmol, 302 mg, 4.21 eq.**) in 5 mL of a mixture of organic solvent and 1 M aqueous sodium halide solution. Constant current electrolysis was conducted at 25 °C under vigorous stirring (1000 rpm), with a current density of 18 mA cm^{-2} until a charge of 4.14 *F* (275.2 C) was applied. The results can be found in Table S12.

Table S12: Results of the preliminary screening for the synthesis of butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**).

#	Organic solvent	Halide source	Volume ratio organic:aqueous	Electrode materials	Yield (GC)[a] Run 1	Run 2
1	EtOAc	NaCl	1:1	C_{gr}||C_{gr}	0%	2%
2	EtOAc	NaBr	1:1	C_{gr}||C_{gr}	2%	3%
3	EtOAc	NaI	1:1	C_{gr}||C_{gr}	39%	41%
4	PhMe	NaI	1:1	C_{gr}||C_{gr}	34%	31%
5	MeO^{t}Bu	NaI	1:1	C_{gr}||C_{gr}	56%	59%
6	PhCl	NaI	1:1	C_{gr}||C_{gr}	44%	40%
7	CH_2Cl_2	NaI	1:1	C_{gr}||C_{gr}	33%	29%
8	^{n}BuOAc	NaI	1:1	C_{gr}||C_{gr}	52%	50%
9	MeCN	NaI	1:1	C_{gr}||C_{gr}	5%	9%
10	EtOAc	NaI	1:4	C_{gr}||C_{gr}	19%	28%
11	EtOAc	NaI	2:3	C_{gr}||C_{gr}	23%	30%
12	EtOAc	NaI	3:2	C_{gr}||C_{gr}	41%	37%
13	EtOAc	NaI	4:1	C_{gr}||C_{gr}	26%	28%
14	EtOAc	NaI	1:1	BDD||BDD	50%	48%
15	EtOAc	NaI	1:1	C_{gl}||C_{gl}	41%	40%

[a] Yield determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.

S4.2.3. Optimization via Design of Experiments

Electrolysis was carried out according to SOP1 using butyl 2-(hydroxyimino)acetate (**5e**, **0.69 mmol, 100 mg, 1.0 eq.**) and styrene. A mixture of *tert*-butyl methyl ether (2.5 mL) and 1 M aqueous sodium iodide solution (2.5 mL) was used. Electrolysis was performed on two BDD-coated silicon plates as anode and cathode under vigorous stirring (1000 rpm). Each data point was acquired thrice. The results can be found in Table S13.

A second screening was done since the extreme settings were reached for all parameters in the predicted optimum. Electrolysis was carried out according to SOP1 using butyl 2-(hydroxyimino)acetate (**5e**, **0.69 mmol, 100 mg, 1.0 eq.**) and styrene. A mixture of *tert*-butyl methyl ether (2.5 mL) and 1 M aqueous sodium iodide solution (2.5 mL) was used. Electrolysis was performed on two BDD-coated silicon plates as anode and cathode under vigorous stirring (1000 rpm) with a current density of 18.9 mA cm^{-2}. Each data point was acquired three times. The results can be found in Table S13.

Table S13: First optimization of the synthesis of butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**) *via* DoE.

#	*Q* / *F*	*j* / mA cm^2	eq. styrene	*T* / °C	m_{oxime} / mg	Yield (GC)[a]
1a	4.25	20.0	4.25	18	100	71%
1b	4.25	20.0	4.25	18	100	72%
1c	4.25	20.0	4.25	18	100	76%
2a	3.50	15.0	3.50	25	100	66%
2b	3.50	15.0	3.50	25	100	65%
2c	3.50	15.0	3.50	25	100	61%
3a	5.00	15.0	5.00	25	100	85%
3b	5.00	15.0	5.00	25	100	76%
3c	5.00	15.0	5.00	25	100	80%
4a	3.50	25.0	5.00	25	100	72%
4b	3.50	25.0	5.00	25	100	77%
4c	3.50	25.0	5.00	25	100	70%
5a	5.00	25.0	3.50	25	100	69%
5b	5.00	25.0	3.50	25	100	75%
5c	5.00	25.0	3.50	25	100	72%
6a	4.25	11.6	4.25	35	100	77%
6b	4.25	11.6	4.25	35	100	83%
6c	4.25	11.6	4.25	35	100	81%
7a	2.99	20.0	4.25	35	100	73%
7b	2.99	20.0	4.25	35	100	64%
7c	2.99	20.0	4.25	35	100	69%
8a	4.25	20.0	2.99	35	100	69%
8b	4.25	20.0	2.99	35	100	69%
8c	4.25	20.0	2.99	35	100	66%
9a	4.25	20.0	4.25	35	100	81%
9b	4.25	20.0	4.25	35	100	81%
9c	4.25	20.0	4.25	35	100	76%
10a	4.25	20.0	5.51	35	100	78%
10b	4.25	20.0	5.51	35	100	79%
10c	4.25	20.0	5.51	35	100	78%
11a	5.51	20.0	4.25	35	100	80%
11b	5.51	20.0	4.25	35	100	77%
11c	5.51	20.0	4.25	35	100	76%
12a	4.25	28.4	4.25	35	100	71%
12b	4.25	28.4	4.25	35	100	72%
12c	4.25	28.4	4.25	35	100	64%

[a] Determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.

Table S13, continued.

#	*Q* / *F*	*j* / mA cm²	eq. styrene	*T* / °C	m_{oxime} / mg	Yield (GC)[a]
13a	3.50	15.0	5.00	45	100	62%
13b	3.50	15.0	5.00	45	100	73%
13c	3.50	15.0	5.00	45	100	72%
14a	5.00	15.0	3.50	45	100	72%
14b	5.00	15.0	3.50	45	100	70%
14c	5.00	15.0	3.50	45	100	66%
15a	3.50	25.0	3.50	45	100	71%
15b	3.50	25.0	3.50	45	100	70%
15c	3.50	25.0	3.50	45	100	73%
16a	5.00	25.0	5.00	45	100	66%
16b	5.00	25.0	5.00	45	100	65%
16c	5.00	25.0	5.00	45	100	58%
17a	4.25	20.0	4.25	52	100	61%
17b	4.25	20.0	4.25	52	100	67%
17c	4.25	20.0	4.25	52	100	67%

[a] Determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.

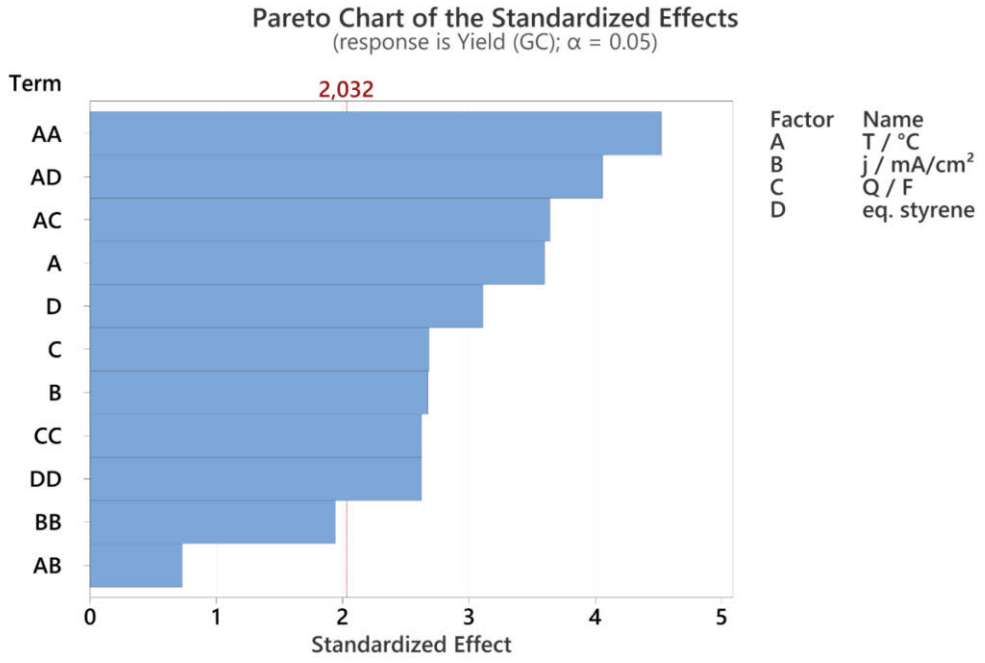


Figure S7: Pareto chart of the standardized effects for the first optimization of the synthesis of butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**) *via* DoE.

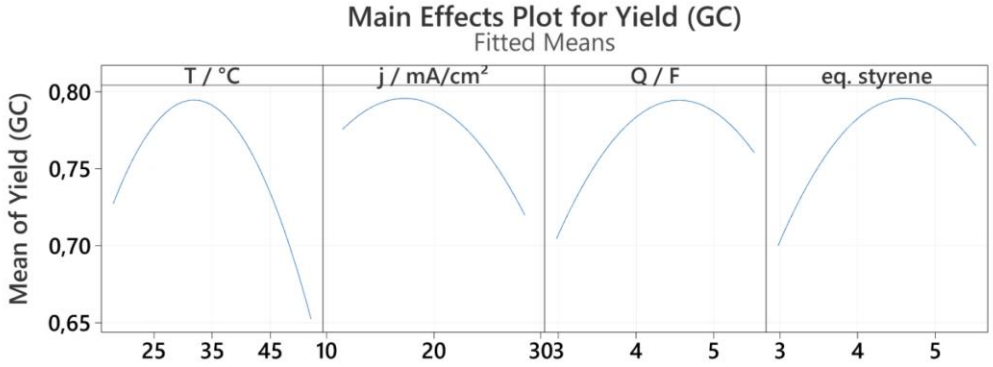


Figure S8: Main effects plot for the first optimization of the synthesis of butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**) *via* DoE.

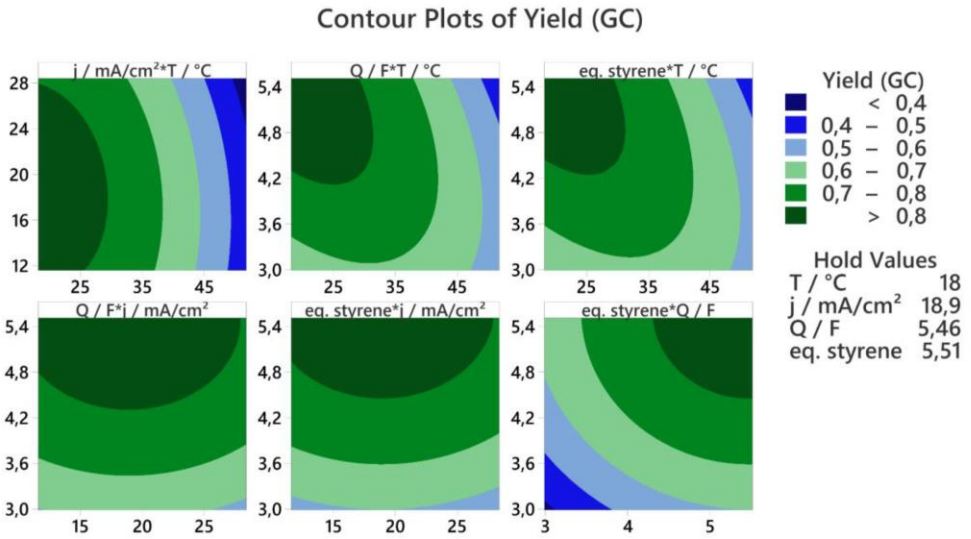


Figure S9: Contour plots for the first optimization of the synthesis of butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**) *via* DoE.

Table S14: Second optimization of the synthesis of butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**) *via* DoE.

#	*Q* / *F*	eq. styrene	*T* / °C	m_{oxime} / mg	Yield (GC)[a]
1a	5,50	5,50	14	100	61%
1b	5,50	5,50	14	100	63%
2a	5,00	6,00	15	100	58%
2b	5,00	6,00	15	100	60%
3a	6,00	5,00	15	100	52%
3b	6,00	5,00	15	100	55%
4a	4,79	5,50	18	100	60%
4b	4,79	5,50	18	100	59%
5a	5,50	4,79	18	100	59%
5b	5,50	4,79	18	100	63%

[a] Determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.

Table S14, continued.

#	*Q* / *F*	eq. styrene	*T* / °C	m_{oxime} / mg	Yield (GC)[a]
6a	5,50	5,50	18	100	63%
6b	5,50	5,50	18	100	63%
7a	5,50	6,21	18	100	62%
7b	5,50	6,21	18	100	65%
8a	6,21	5,50	18	100	61%
8b	6,21	5,50	18	100	61%
9a	5,00	5,00	20	100	77%
9b	5,00	5,00	20	100	78%
10a	6,00	6,00	20	100	62%
10b	6,00	6,00	20	100	59%
11a	5,50	5,50	21	100	65%
11b	5,50	5,50	21	100	65%

[a] Determined using GC analysis with external calibration; internal standard: 1,3,5-trimethoxybenzene.

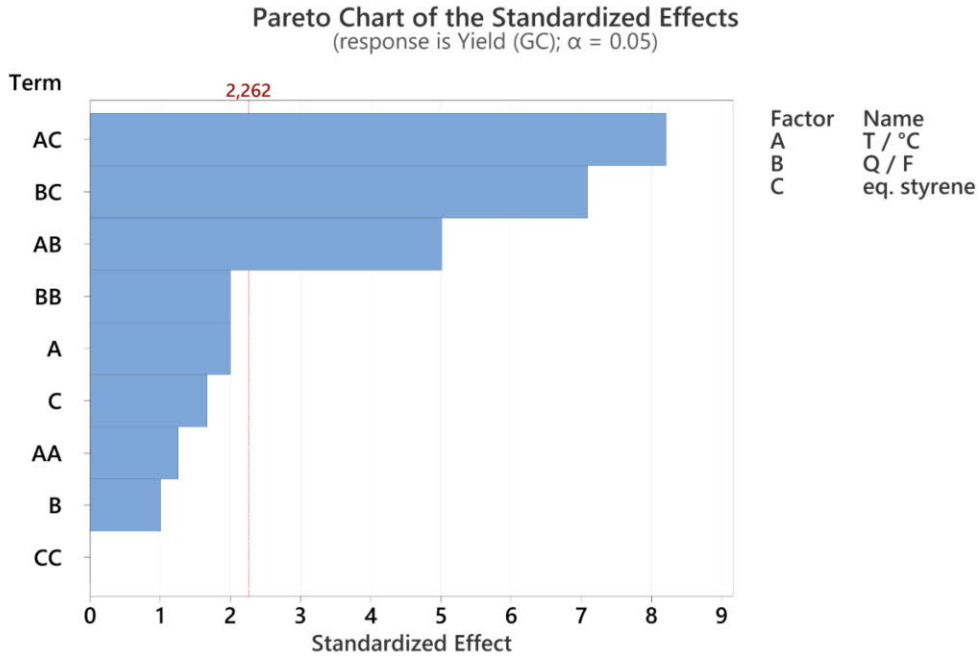


Figure S10: Pareto chart of the standardized effects for the second optimization of the synthesis of butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**) *via* DoE.

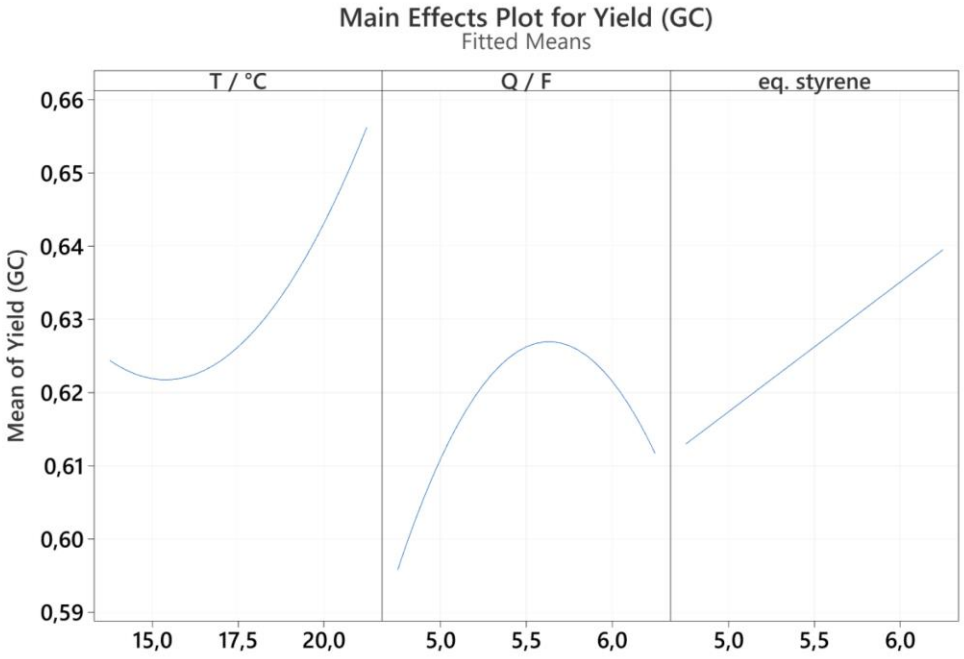


Figure S11: Main effects plot for the second optimization of the synthesis of butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**) *via* DoE.

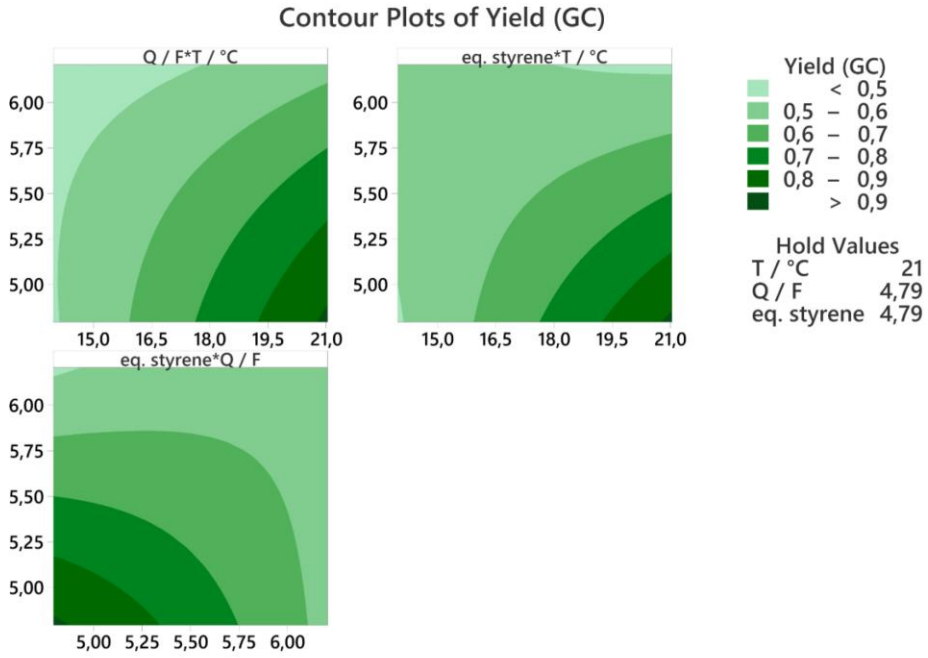


Figure S12: Contour plots for the second optimization of the synthesis of butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**) *via* DoE.

S4.2.4. Test of the Predicted Optimum Conditions

The optimum condition predicted from DoE and conditions derived thereof were tested in an additional step to determine the best conditions.

In 50 mL jacketed beaker-type glass cells, butyl 2-(hydroxyimino)acetate (**5e**, **3.44 mmol, 500 mg, 1.0 eq.**) and styrene were dissolved a mixture of *tert*-butyl methyl ether (12.5 mL) and 1 M aqueous sodium iodide solution (12.5 mL). The mixture was subjected to galvanostatic electrolysis under vigorous stirring on BDD electrodes with a relevant surface area of 5.0 cm^2 (size: 60 × 20 × 3 mm, immersion depth 2.5 cm). The biphasic mixture was transferred to a separation funnel, and the cell was rinsed with ethyl acetate. The layers were separated, and the aqueous layer was extracted once with ethyl acetate (30 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. Isoxazoline (**6e**) was obtained after flash column chromatography on silica (cyclohexane/ethyl acetate; 0% →10% EtOAc) as a yellow oil. The results can be found in Table S15.

Table S15: Test of the predicted optima for the synthesis of butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**).

#	eq. styrene	*Q* / *F*	*j* / mA cm^{-2}	*T* / °C	Yield[a]
1	6.21	6.21	18.9	14	35%
2	4.79	4.79	18.9	21	75%
3	5.51	5.46	18.9	18	65%
4	5.51	5.46	18.9	25	82%

[a] Isolated yield.

S4.2.5. Screening of the Concentration

In 50 mL jacketed beaker-type glass cells, butyl 2-(hydroxyimino)acetate (**5e**, **1.0 eq.**) and styrene (**5.51 eq.**) were dissolved a mixture of *tert*-butyl methyl ether (12.5 mL) and 1 M aqueous sodium iodide solution (12.5 mL) at 25 °C. The mixture was subjected to galvanostatic electrolysis under vigorous stirring on BDD electrodes with a relevant surface area of 5.0 cm^2 (size: 60 × 20 × 3 mm, immersion depth 2.5 cm) with a current density of 18.9 mA cm^{-2} until a charge of 5.46 *F* was applied. The biphasic mixture was transferred to a separation funnel, and the cell was rinsed with ethyl acetate. The layers were separated, and the aqueous layer was extracted once with ethyl acetate (30 mL). The organic fraction was dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. Isoxazoline (**6e**) was obtained after flash column chromatography on silica (cyclohexane/ethyl acetate; 0% → 10% EtOAc) as a yellow oil. The results can be found in Table S16.

Table S16: Screening of the substrate concentration for the synthesis of butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**).

#	m_{oxime} / g	$m_{styrene}$ / g	Yield[a]
1	0.25	0.99	64%
2	0.50	1.98	82%
3	1.00	3.95	75%
4	1.50	5.93	70%

#	m_{oxime} / g	$m_{styrene}$ / g	Yield[a]
5	2.00	7.91	59%
6	2.50	9.88	59%
7	3.00	11.9	48%

[a] Isolated yield.

S4.2.6. Optimization of the Scale-Up

To evaluate the optimum conditions on large scale, the reaction was re-investigated on 25 g-scale (0.172 mol).

In a 1.5 L jacketed beaker-type glass cell, butyl 2-(hydroxyimino)acetate (**5e, 0.172 mol, 25.0 g, 1.0 eq.**) and styrene (**0.949 mol, 98.8 g, 5.51 eq.**) were dissolved a mixture of *tert*-butyl methyl ether (625 mL) and 1 M aqueous sodium iodide solution (625 mL) at 25 °C. The mixture was subjected to galvanostatic electrolysis under vigorous stirring with a current density of 18.9 mA cm^{-2} on a stack of BDD-coated silicon plates. The biphasic mixture was transferred to a separation funnel, and the cell was rinsed with *tert*-butyl methyl ether. The layers were separated, and the aqueous layer was extracted with *tert*-butyl methyl ether (1 × 400 mL + 1 × 200 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered and the solvent was evaporated under reduced pressure (down to 150 mbar @ 50 °C). Subsequently, excessive styrene was recovered by vacuum distillation. An aliquot of the crude product was analyzed by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard to determine the yield. The results can be found in Table S17.

Table S17: Scale-up screening for the synthesis of butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (**6e**) on 25 g-scale.

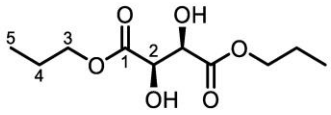
#	Setup	No. of BDD plates (polarization)	Interelectrode gap / mm	*Q* / *F*	Post stirring	Styrene recovery	Yield
1	Bipolar	6	5	5.46	-	*n/d*	40%[a]
2	Bipolar	5	10	3.5	-	65.1 g (3.63 eq.)	56%[a]
3	Bipolar	5	10	2.5	-	74.1 g (4.13 eq.)	57%[a]
4	Bipolar	5	10	2.5	12 h	69.9 g (3.90 eq.)	56%[a]
5	Alternatingly polarized	5 (+ – + – +)	10	2.75	-	74.5 g (4.15 eq.)	63%[a]
6	Alternatingly polarized	3 (+ – +)	20	2.5	-	77.9 g (4.34 eq.)	63%[a]
7	Alternatingly polarized	2 (+ –)	10	2.5	-	72.7 g (4.05 eq.)	83%[a]
8	Alternatingly polarized	3 (+ – +)	10	2.5	-	71.2 g (3.97 eq.)	83%[a] (82%[b])

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard.
[b] Isolated via filtration through silica (0% → 10% EA in CH); see section S6.

S5. Substrate Synthesis

S5.1. Tartrates (7c–7j)

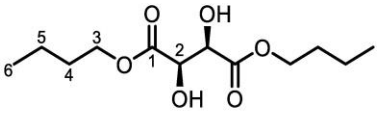
Dipropyl L-tartrate (7c)



In a 500 mL round bottom flask, L-tartaric acid (**0.10 mol, 15.0 g, 1.0 eq.**), propanol (**0.50 mol, 38 mL, 5.0 eq.**), and *p*-toluene sulfonic acid (**0.01 mol, 1.9 g, 0.1 eq.**) were dissolved in cyclohexane (150 mL). The mixture was refluxed at a Dean-Stark trap until full conversion of the tartaric acid was reached (control by TLC). The reaction mixture was transferred to a separation funnel and washed with saturated aqueous sodium bicarbonate (100 mL), water (100 mL) and brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The product was obtained as a colorless oil (**57 mmol, 13.4 g, 57%**).

^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 4.53 (s, 2H, *H*-2), 4.24 – 4.11 (m, 4H, *H*-3), 3.95 (s, 2H, 2-O*H*), 1.75 – 1.61 (m, 2H. *H*-4), 0.93 (t, *J* = 7.4 Hz, 6H, *H*-5).
^{13}C NMR (75 MHz, $CDCl_3$), δ/ppm: 171.8, 72.3, 67.9, 21.9, 10.3.
HRMS (ESI+), *m/z*: calculated for $C_{10}H_{18}O_6$ + H^+ 235.1176 $[M+H]^+$, found 235.1171.
Known compound and procedure, spectral data correspond to the literature.[5]

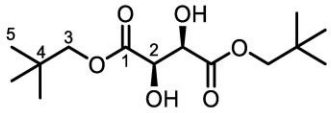
Dibutyl L-tartrate (7e)



In a 2 L round bottom flask, L-tartaric acid (**1.00 mol, 150 g, 1.0 eq.**), butanol (**5.00 mol, 371 g, 5.0 eq.**), and *p*-toluene sulfonic acid (**0.100 mol, 19.0 g, 0.1 eq.**) were dissolved in cyclohexane (750 mL). The mixture was refluxed at a Dean-Stark trap until full conversion of the tartaric acid was reached (control by TLC). The reaction mixture was transferred to a separation funnel and washed with saturated aqueous sodium bicarbonate (500 mL), water (500 mL) and brine (500 mL). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The product was obtained as a colorless oil (**0.96 mol, 252.3 g, 96%**).

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 4.49 (s, 2H, *H*-2), 4.27 – 4.14 (m, 4H, *H*-3), 3.37 (s, 2H, 2-O*H*), 1.68 – 1.56 (m, 4H, *H*-4), 1.41 – 1.29 (m, 4H, *H*-5), 0.90 (t, J = 7.4 Hz, 6H, *H*-6).
^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm: 171.7, 72.2, 66.2, 30.5, 19.0, 13.6.
HRMS (ESI+), *m/z*: calculated for $C_{12}H_{22}O_6$ + H^+ 263.1489 $[M+H]^+$, found 263.1490.
Known compound and procedure, spectral data correspond to the literature.[6]

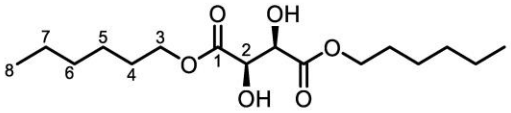
Dineopentyl L-tartrate (7f)



In a 500 mL round bottom flask, L-tartaric acid (**0.10 mol, 15.0 g, 1.0 eq.**), *neo*-pentanol (**0.50 mol, 44.1 g, 5.0 eq.**), and *p*-toluene sulfonic acid (**0.01 mol, 1.9 g, 0.1 eq.**) were dissolved in toluene (150 mL). The mixture was refluxed at a Dean-Stark trap until full conversion of the tartaric acid was reached (control by TLC). The reaction mixture was transferred to a separation funnel and washed with saturated aqueous sodium bicarbonate (100 mL), water (100 mL) and brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The product was obtained as a colorless solid (**89 mmol, 27.6 g, 89%**).

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 4.56 (s, 2H, *H*-2), 4.07 (d, *J* = 10.4 Hz, 2H, *H*-3), 3.89 (d, *J* = 10.4 Hz, 2H, *H*-3), 3.18 (s, 2H, 2-O*H*), 0.97 (s, 18H, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm: 171.8, 75.6, 72.3, 31.7, 26.4.
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{26}O_6$ + H^+ 291.1802 [*M*+H]$^+$, found 291.1794.
Known procedure to the literature.[5]

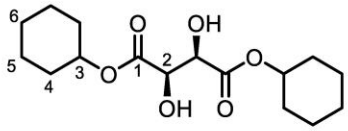
Dihexyl L-tartrate (7g)



In a 500 mL round bottom flask, L-tartaric acid (**0.10 mol, 15.0 g, 1.0 eq.**), hexanol (**0.50 mol, 63 mL, 5.0 eq.**), and *p*-toluene sulfonic acid (**0.01 mol, 1.9 g, 0.1 eq.**) were dissolved in toluene (150 mL). The mixture was refluxed at a Dean-Stark trap until full conversion of the tartaric acid was reached (control by TLC). The reaction mixture was transferred to a separation funnel and washed with saturated aqueous sodium bicarbonate (100 mL), water (100 mL) and brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The product was obtained as a colorless oil (**53 mmol, 17.0 g, 53%**).

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 4.52 (s, 2H, *H*-2), 4.32 – 4.18 (m, 4H, *H*-3), 2.78 (s, 2H, 2-O*H*), 1.73 – 1.62 (m, 4H, *H*-4), 1.41 – 1.23 (m, 12H, *H*-5, *H*-6, *H*-7), 0.91 – 0.85 (m, 6H, *H*-8).
^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm: 171.8, 72.2, 66.7, 31.5, 28.6, 25.5, 22.6, 14.1.
HRMS (ESI+), *m/z*: calculated for $C_{16}H_{30}O_6$ + H^+ 319.2115 [*M*+H]$^+$, found 319.2106.
Known procedure to the literature.[5]

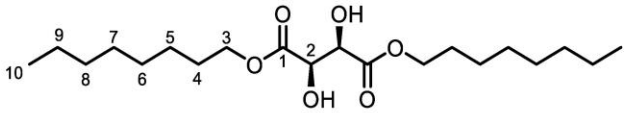
Dicyclohexyl L-tartrate (7h)



In a 2 L round bottom flask, L-tartaric acid (**0.10 mol, 15.0 g, 1.0 eq.**), cyclohexanol (**0.50 mol, 371 g, 5.0 eq.**), and sulfuric acid (**0.01 mol, 0.6 mL, 0.1 eq.**) were dissolved in cyclohexane (750 mL). The mixture was refluxed at a Dean-Stark trap until full conversion of the tartaric acid was reached (control by TLC). The reaction mixture was transferred to a separation funnel and washed with saturated aqueous sodium bicarbonate (100 mL), water (100 mL) and brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The product was obtained as a colorless oil by distillation at 1030 mbar, 170 °C (**88 mmol, 27.6 g, 88%**).

^{1}H NMR (300 MHz, $CDCl_3$), δ/ppm: 4.96 – 4.84 (m, 2H, *H*-3), 4.49 (s, 2H, *H*-2), 3.47 (s, 2H, 2-O*H*), 1.92 – 1.83 (m, 4H, *H*-4, *H*-5), 1.79 – 1.66 (m, 4H, *H*-4, *H*-5), 1.56 – 1.19 (m, 6H, *H*-4, *H*-5, *H*-6).
^{13}C NMR (75 MHz, $CDCl_3$), δ/ppm: 171.2, 75.2, 72.3, 31.5, 31.4, 25.3, 23.6, 23.6.
HRMS (ESI+), *m/z*: calculated for $C_{16}H_{26}O_6$ + H^+ 315.1802 [*M*+H]$^+$, found 315.1800.
Known compound and procedure, spectral data correspond to the literature.[7]

Dioctyl L-tartrate (7i)

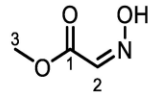


In a 500 mL round bottom flask, L-tartaric acid (**0.10 mol, 15.0 g, 1.0 eq.**), octan-1-ol (**0.50 mol, 65.1 g, 5.0 eq.**), and *p*-toluene sulfonic acid (**0.01 mol, 1.9 g, 0.1 eq.**) were dissolved in toluene (150 mL). The mixture was refluxed at a Dean-Stark trap until full conversion of the tartaric acid was reached (control by TLC). The reaction mixture was transferred to a separation funnel and washed with saturated aqueous sodium bicarbonate (100 mL), water (100 mL) and brine (100 mL). The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. The excess octan-1-ol was removed at 11 mbar, 78 °C. The product was obtained as a colorless oil (**58 mmol, 21.8 g, 58%**).

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 4.52 (s, 2H, *H*-2), 4.30 – 4.20 (m, 4H, *H*-3), 2.50 (s, 2H, 2-O*H*), 1.73 – 1.62 (m, 4H, *H*-4), 1.40 – 1.22 (m, 20H, *H*-5, *H*-6, *H*-7, *H*-8, *H*-9), 0.90 – 0.84 (m, 6H, *H*-10).
^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm: 171.8, 72.2, 66.8, 31.9, 28.6, 25.9, 22.8, 14.2.
HRMS (ESI+), *m/z*: calculated for $C_{20}H_{38}O_6$ + H^+ 375.2741 [*M*+H]$^+$, found 375.2733.
Known compound and procedure, spectral data correspond to the literature.[8,9]

S5.2. Oximes

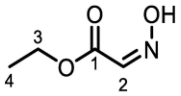
Methyl 2-(hydroxyimino)acetate (5a)



In a 500 mL three necked round bottom flask equipped with a mechanical stirrer and a dripping funnel dimethyl L-tartrate (**30 mmol, 5.30 g, 1.0 eq.**) was dissolved in acetonitrile (100 mL) and the mixture was cooled to 0 °C in an ice bath. Sodium *meta*-periodate (**33 mmol, 6.99 g, 1.1 eq.**) dissolved in water (150 mL) was added slowly under vigorous stirring while maintaining the temperature below 5 °C. Afterwards, the mixture was stirred overnight while warming to room temperature. Sodium chloride (15 g) was added, the mixture was briefly stirred and filtered, and the residue was washed with ethyl acetate (50 mL). The filtrate was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were dried over anhydrous sodium sulfate, toluene was added (20 mL), and ethyl acetate and acetonitrile were removed under reduced pressure (vacuum to 200 mbar@50 °C).
The residue was dissolved in acetonitrile (90 mL) and a solution of hydroxylamine hydrochloride (**104 mmol, 7.23 g, 3.0 eq.** respective to the tartrate) in water (50 mL) was added dropwise. The mixture was stirred overnight, transferred to a separatory funnel, and extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were washed with water (50 mL) once, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to yield the product as a colorless solid (**10 mmol, 1.03 g, 30%**).

^{1}H NMR (400 MHz, CD_2Cl_2), *δ*/ppm: 7.57 (s, 1H, *H*-2), 3.83 (s, 3H, *H*-3).
^{13}C NMR (101 MHz, CD_2Cl_2), *δ*/ppm: 163.2, 142.2, 52.9.
HRMS (ESI+), *m/z*: calculated for $C_3H_5NO_3$ + H^+ 104.0342 $[M+H]^+$, found 104.0342.

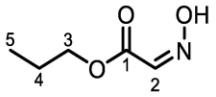
Ethyl 2-(hydroxyimino)acetate (5b)



In a 1 L three necked round bottom flask equipped with a mechanical stirrer ethyl glyoxalate (50% in toluene; **200 mmol, 40.84 g, 1.0 eq.**) was dissolved in ethanol (600 mL) and hydroxylamine hydrochloride (**300 mmol, 20.85 g, 1.5 eq.**) was added. The mixture was heated to reflux for 16 h. After completion of the reaction the mixture was cooled to room temperature and the solvent was removed under reduced pressure. The crude product was distilled *in vacuo* to yield the product as a colorless oil after filtration over silica (**193 mmol, 22.64 g, 97%**).

^{1}H NMR (400 MHz, CD_2Cl_2), *δ*/ppm: 10.50 (s, 1H, N-O*H*), 7.56 (s, 1H, *H*-2), 4.28 (q, *J* = 7.2 Hz, 2H, *H*-3), 1.29 (t, *J* = 7.2 Hz, 3H, *H*-4).
^{13}C NMR (101 MHz, CD_2Cl_2), *δ*/ppm: 163.3, 142.5, 62.5, 14.2.
HRMS (ESI+), *m/z*: calculated for $C_4H_7NO_3$ + H^+ 118.0499 $[M+H]^+$, found 118.0501.
b.p.: 72–79 °C @ 1 mbar.

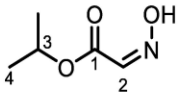
Propyl 2-(hydroxyimino)acetate (5c)



In a 500 mL three necked round bottom flask equipped with a mechanical stirrer and a dripping funnel dipropyl L-tartrate (**7c, 40 mmol, 9.37 g, 1.0 eq.**) was dissolved in acetonitrile (200 mL) and the mixture was cooled to 0 °C in an ice bath. Sodium *meta*-periodate (**44 mmol, 9.41 g, 1.1 eq.**) dissolved in water (150 mL) was added slowly under vigorous stirring while maintaining the temperature below 5 °C. Afterwards, the mixture was stirred overnight while warming to room temperature. Sodium chloride (15 g) was added, the mixture was briefly stirred and filtered, and the residue was washed with ethyl acetate (50 mL). The filtrate was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were dried over anhydrous sodium sulfate, toluene was added (20 mL), and ethyl acetate and acetonitrile were removed under reduced pressure (vacuum to 200 mbar@50 °C).
The residue was dissolved in acetonitrile (90 mL) and a solution of hydroxylamine hydrochloride (**120 mmol, 8.34 g, 3.0 eq.** respective to the tartrate) in water (50 mL) was added dropwise. The mixture was stirred overnight, transferred to a separatory funnel, and extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were washed with water (50 mL) once, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was distilled *in vacuo* to yield the product as a colorless oil (**59 mmol, 7.74 g, 74%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 10.39 (s, 1H, N-O*H*), 7.57 (s, 1H, *H*-2), 4.20 (t, *J* = 6.7 Hz, 2H, *H*-3), 1.76 – 1.66 (m, 2H, *H*-4), 0.95 (t, *J* = 7.5 Hz, 3H, *H*-5).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 163.1, 142.4, 67.8, 22.2, 10.4.
HRMS (ESI+), *m/z*: calculated for $C_5H_9NO_3$ + H^+ 154.0475 [*M*+Na]$^+$, found 154.0466.
b.p.: 102–115 °C @ 1 mbar.

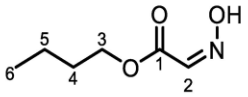
iso-Propyl 2-(hydroxyimino)acetate (5d)



In a 500 mL three necked round bottom flask equipped with a mechanical stirrer and a dripping funnel di-*iso*-propyl L-tartrate (**21 mmol, 5.00 g, 1.0 eq.**) was dissolved in acetonitrile (60 mL) and the mixture was cooled to 0 °C in an ice bath. Sodium *meta*-periodate (**23 mmol, 5.02 g, 1.1 eq.**) dissolved in water (150 mL) was added slowly under vigorous stirring while maintaining the temperature below 5 °C. Afterwards, the mixture was stirred overnight while warming to room temperature. Sodium chloride (15 g) was added, the mixture was briefly stirred and filtered, and the residue was washed with ethyl acetate (50 mL). The filtrate was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were dried over anhydrous sodium sulfate, toluene was added (20 mL), and ethyl acetate and acetonitrile were removed under reduced pressure (vacuum to 200 mbar@50 °C).
The residue was dissolved in acetonitrile (90 mL) and a solution of hydroxylamine hydrochloride (**63 mmol, 4.38 g, 3.0 eq.** respective to the tartrate) in water (50 mL) was added dropwise. The mixture was stirred overnight, transferred to a separatory funnel, and extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were washed with water (50 mL) once, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to yield the product as a colorless oil (**26 mmol, 3.34 g, 62%**).

^{1}H NMR (400 MHz, $DMSO_{d6}$), δ/ppm: 12.56 (s, 1H, N-O*H*), 7.50 (s, 1H, *H*-2), 5.01 (hept, *J* = 6.3 Hz, 1H. *H*-3), 1.23 (s, 3H, *H*-4), 1.22 (s, 3H, *H*-4).
^{13}C NMR (101 MHz, $DMSO_{d6}$), δ/ppm: 162.0, 141.3, 68.5, 21.6.
HRMS (ESI+), *m/z*: calculated for $C_5H_9NO_3$ + H^+ 154.0475 $[M+Na]^+$, found 154.0454.
Known compound, spectral data correspond to literature.[10]

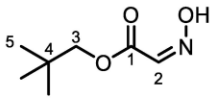
Butyl 2-(hydroxyimino)acetate (5e)



In a 6 L three necked round bottom flask equipped with a mechanical stirrer and a dripping funnel di-butyl L-tartrate (**7e, 0.500 mol, 131 g, 1.0 eq.**) was dissolved in acetonitrile (1.5 L) and the mixture was cooled to 0 °C in an ice bath. Sodium *meta*-periodate (**0.550 mol, 118 g, 1.1 eq.**) dissolved in water (3.5 L) was added slowly under vigorous stirring while maintaining the temperature below 5 °C. Afterwards, the mixture was stirred overnight while warming to room temperature. Sodium chloride (150 g) was added, the mixture was briefly stirred and filtered, and the residue was washed with ethyl acetate (500 mL). The filtrates were transferred to a separatory funnel in portions of ca. 1.5 L. For each portion, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 500 mL). The combined organic fractions were dried over anhydrous sodium sulfate, toluene was added (200 mL), and ethyl acetate and acetonitrile were removed under reduced pressure (vacuum to 200 mbar@50 °C).
The crude was dissolved in acetonitrile (750 mL) and a solution of hydroxylamine hydrochloride (**1.50 mol, 104 g, 3.0 eq.** respective to the tartrate) in water (1.5 L) was added dropwise. The mixture was stirred overnight, transferred to a separatory funnel in two portions. For each portion, ethyl acetate (500 mL) was added, the mixture was shaken, and the layers were separated. The aqueous layer was further extracted with ethyl acetate (2 × 500 mL), and the combined organic fractions were washed with water (500 mL) once. The combined organic extracts of both portions were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the crude was distilled *in vacuo* to yield the product as a colorless oil (**0.819 mol, 118.8 g, 82%**).

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.54 (s, 1H, *H*-2), 4.24 (t, *J* = 6.7 Hz, 2H, *H*-3), 1.66 (m, 2H, *H*-4), 1.43 – 1.32 (m, 2H, *H*-5), 0.91 (t, *J* = 7.4 Hz, 3H, *H*-6).
^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm: 162.6, 141.8, 65.8, 30.5, 19.1, 13.7.
HRMS (ESI+), *m/z*: calculated for $C_6H_{11}NO_3$ + H^+ 144.066 $[M+H]^+$, found 144.0662.
Known compound, spectral data correspond to literature.[11]
b.p.: 118–122 °C @ 12 mbar.

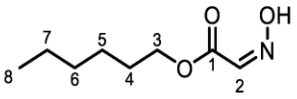
Neopentyl 2-(hydroxyimino)acetate (5f)



In a 500 mL three necked round bottom flask equipped with a mechanical stirrer and a dripping funnel di-*neo*-pentyl L-tartrate (**7f, 40 mmol, 11.61 g, 1.0 eq.**) was dissolved in acetonitrile (200 mL) and the mixture was cooled to 0 °C in an ice bath. Sodium *meta*-periodate (**44 mmol, 9.41 g, 1.1 eq.**) dissolved in water (150 mL) was added slowly under vigorous stirring while maintaining the temperature below 5 °C. Afterwards, the mixture was stirred overnight while warming to room temperature. Sodium chloride (15 g) was added, the mixture was briefly stirred and filtered, and the residue was washed with ethyl acetate (50 mL). The filtrate was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were dried over anhydrous sodium sulfate, toluene was added (20 mL), and ethyl acetate and acetonitrile were removed under reduced pressure (vacuum to 200 mbar@50 °C).
The residue was dissolved in acetonitrile (90 mL) and a solution of hydroxylamine hydrochloride (**120 mmol, 8.34 g, 3.0 eq.** respective to the tartrate) in water (50 mL) was added dropwise. The mixture was stirred overnight, transferred to a separatory funnel, and extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were washed with water (50 mL) once, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to yield the product as a colorless oil (**76 mmol, 12.11 g, 95%**).

^{1}H NMR (400 MHz, $CDCl_3$), *δ*/ppm: 7.59 (s, 1H, *H*-2), 3.95 (s, 2H, *H*-3), 0.96 (s, 9H, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$), *δ*/ppm: 162.6, 141.8, 75.1, 31.6, 26.5
HRMS (ESI+), *m/z*: calculated for $C_7H_{13}NO_3$ + H^+ 182.0788 [*M*+Na]$^+$, found 182.0780.

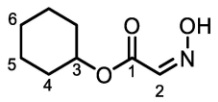
Hexyl 2-(hydroxyimino)acetate (5g)



In a 500 mL three necked round bottom flask equipped with a mechanical stirrer and a dripping funnel dihexyl L-tartrate (**7g, 40 mmol, 12.73 g, 1.0 eq.**) was dissolved in acetonitrile (200 mL) and the mixture was cooled to 0 °C in an ice bath. Sodium *meta*-periodate (**44 mmol, 9.41 g, 1.1 eq.**) dissolved in water (150 mL) was added slowly under vigorous stirring while maintaining the temperature below 5 °C. Afterwards, the mixture was stirred overnight while warming to room temperature. Sodium chloride (15 g) was added, the mixture was briefly stirred and filtered, and the residue was washed with ethyl acetate (50 mL). The filtrate was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were dried over anhydrous sodium sulfate, toluene was added (20 mL), and ethyl acetate and acetonitrile were removed under reduced pressure (vacuum to 200 mbar@50 °C).
The residue was dissolved in acetonitrile (90 mL) and a solution of hydroxylamine hydrochloride (**120 mmol, 8.34 g, 3.0 eq.** respective to the tartrate) in water (50 mL) was added dropwise. The mixture was stirred overnight, transferred to a separatory funnel, and extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were washed with water (50 mL) once, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to yield the product as a colorless oil (**75 mmol, 12.93 g, 94%**).

^{1}H NMR (300 MHz, $CDCl_3$), *δ*/ppm: 7.54 (s, 1H, *H*-2), 4.22 (t, *J* = 6.8 Hz, 2H, *H*-3), 1.73 – 1.62 (m, 2H, *H*-4), 1.37 – 1.24 (m, 6H, *H*-5, *H*-6, *H*-7), 0.89 – 0.82 (m, 3H, *H*-8).
^{13}C NMR (75 MHz, $CDCl_3$), *δ*/ppm: 162.7, 141.6, 66.1, 31.4, 28.4, 25.5, 22.6, 14.0.
HRMS (ESI+), *m/z*: calculated for $C_8H_{15}NO_3$ + H^+ 174.1125 [*M*+H]$^+$, found 174.1129.

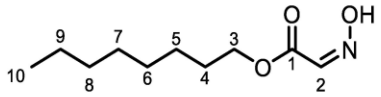
Cyclohexyl 2-(hydroxyimino)acetate (5h)



In a 500 mL three necked round bottom flask equipped with a mechanical stirrer and a dripping funnel dicyclohexyl L-tartrate (**7h, 40 mmol, 12.58 g, 1.0 eq.**) was dissolved in acetonitrile (200 mL) and the mixture was cooled to 0 °C in an ice bath. Sodium *meta*-periodate (**44 mmol, 9.41 g, 1.1 eq.**) dissolved in water (150 mL) was added slowly under vigorous stirring while maintaining the temperature below 5 °C. Afterwards, the mixture was stirred overnight while warming to room temperature. Sodium chloride (15 g) was added, the mixture was briefly stirred and filtered, and the residue was washed with ethyl acetate (50 mL). The filtrate was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were dried over anhydrous sodium sulfate, toluene was added (20 mL), and ethyl acetate and acetonitrile were removed under reduced pressure (vacuum to 200 mbar@50 °C).
The residue was dissolved in acetonitrile (90 mL) and a solution of hydroxylamine hydrochloride (**120 mmol, 8.34 g, 3.0 eq.** respective to the tartrate) in water (50 mL) was added dropwise. The mixture was stirred overnight, transferred to a separatory funnel, and extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were washed with water (50 mL) once, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to yield the product as a colorless solid after filtration over silica (**75 mmol, 12.79 g, 94%**).

^{1}H NMR (400 MHz, $CDCl_3$), *δ*/ppm: 10.35 (s, 1H, N-O*H*), 7.52 (s, 1H, *H*-2), 4.97 – 4.84 (m, 1H, *H*-3), 1.97 – 1.82 (m, 2H, *H*-4), 1.80 – 1.66 (m, 2H, *H*-4), 1.57 – 1.15 (m, 6H, *H*-5, *H*-6).
^{13}C NMR (101 MHz, $CDCl_3$), *δ*/ppm: 161.9, 142.2, 74.7, 31.5, 25.3, 23.7.
HRMS (ESI+), *m/z*: calculated for $C_8H_{13}NO_3$ + H^+ 172.0968 $[M+H]^+$, found 172.0969.

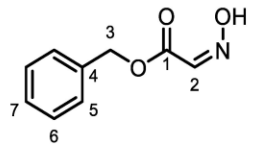
Octyl 2-(hydroxyimino)acetate (5i)



In a 500 mL three necked round bottom flask equipped with a mechanical stirrer and a dripping funnel dioctyl L-tartrate (**7i, 40 mmol, 14.98 g, 1.0 eq.**) was dissolved in acetonitrile (200 mL) and the mixture was cooled to 0 °C in an ice bath. Sodium *meta*-periodate (**44 mmol, 9.41 g, 1.1 eq.**) dissolved in water (150 mL) was added slowly under vigorous stirring while maintaining the temperature below 5 °C. Afterwards, the mixture was stirred overnight while warming to room temperature. Sodium chloride (15 g) was added, the mixture was briefly stirred and filtered, and the residue was washed with ethyl acetate (50 mL). The filtrate was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were dried over anhydrous sodium sulfate, toluene was added (20 mL), and ethyl acetate and acetonitrile were removed under reduced pressure (vacuum to 200 mbar@50 °C).
The residue was dissolved in acetonitrile (90 mL) and a solution of hydroxylamine hydrochloride (**120 mmol, 8.34 g, 3.0 eq.** respective to the tartrate) in water (50 mL) was added dropwise. The mixture was stirred overnight, transferred to a separatory funnel, and extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were washed with water (50 mL) once, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to yield the product as a colorless oil (**73 mmol, 14.72 g, 91%**).
^{1}H NMR (400 MHz, $CDCl_3$), *δ*/ppm: 7.55 (s, 1H, *H*-2), 4.23 (t, *J* = 6.8 Hz, 2H, *H*-3), 1.73 – 1.63 (m, 2H, *H*-4), 1.38 – 1.22 (m, 10H, *H*-5, *H*-6, *H*-7, *H*-8, *H*-9), 0.88 – 0.83 (m, 3H, *H*-10).
^{13}C NMR (101 MHz, $CDCl_3$), *δ*/ppm: 162.6, 141.7, 66.1, 31.8, 29.2, 29.2, 28.5, 25.9, 22.7, 14.2.

HRMS (ESI+), *m/z*: calculated for $C_{10}H_{19}NO_3$ + H^+ 202.1438 [*M*+H]$^+$, found 202.1433.

Benzyl 2-(hydroxyimino)acetate (5j)

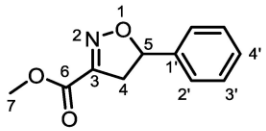


In a 500 mL three necked round bottom flask equipped with a mechanical stirrer and a dripping funnel dibenzyl L-tartrate (**30 mmol, 9.91 g, 1.0 eq.**) was dissolved in acetonitrile (100 mL) and the mixture was cooled to 0 °C in an ice bath. Sodium *meta*-periodate (**33 mmol, 7.06 g, 1.1 eq.**) dissolved in water (100 mL) was added slowly under vigorous stirring while maintaining the temperature below 5 °C. Afterwards, the mixture was stirred overnight while warming to room temperature. Sodium chloride (20 g) was added, the mixture was briefly stirred and filtered, and the residue was washed with ethyl acetate (2 × 100 mL). The filtrate was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 75 mL). The combined organic fractions were dried over anhydrous sodium sulfate, toluene was added (50 mL), and ethyl acetate and acetonitrile were removed under reduced pressure (vacuum to 200 mbar@50 °C).
The residue was dissolved in acetonitrile (100 mL) and a solution of hydroxylamine hydrochloride (**105 mmol, 7.30 g, 3.0 eq.** respective to the tartrate) in water (60 mL) was added dropwise. The mixture was stirred overnight, transferred to a separatory funnel, and extracted with ethyl acetate (3 × 50 mL). The combined organic fractions were washed with water (50 mL) once, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified via flash column chromatography on silica (cyclohexane/ethyl acetate; 0% →10% EtOAc) to yield the product as a colorless solid (**41 mmol, 7.38 g, 69%**).

^{1}H NMR (400 MHz, CD_2Cl_2), *δ*/ppm: 10.49 (s, 1H, N-O*H*), 7.66 (s, 1H, *H*-2), 7.48 – 7.39 (m, 5H, *H*-2', *H*-3', *H*-4'), 5.34 (s, 2H, *H*-3).
^{13}C NMR (101 MHz, CD_2Cl_2), *δ*/ppm: 162.8, 142.2, 135.4, 129.0, 128.9, 67.8.
HRMS (ESI-), *m/z*: calculated for $C_9H_9NO_3$ – H^- 178.0510 [*M*-H]$^-$, found 178.0510.

S6. Isoxazoline Synthesis

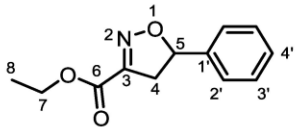
Methyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6a)



Product synthesis was carried out according to SOP2 using methyl 2-(hydroxyimino)acetate (**5a, 3.44 mmol, 355 mg, 1.0 eq.**) and styrene (**19.0 mmol, 1.98 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 13% EtOAc) the product was obtained as a yellow oil (**0.25 mmol, 51 mg, 7%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.44 – 7.30 (m, 5H, *H*-2', *H*-3', *H*-4'), 5.77 (dd, *J* = 11.6 Hz, 9.0 Hz, 1H, *H*-5), 3.87 (s, 3H, *H*-7), 3.63 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H, *H*-4), 3.20 (dd, *J* = 17.8 Hz, 9.0 Hz, 1H, *H*-4).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 161.3, 151.5, 140.0, 129.2, 129.0, 126.3, 85.4, 53.0, 41.8.
HRMS (ESI+), *m/z*: calculated for $C_{11}H_{11}NO_3$ + H^+ 206.0812 [*M*+H]$^+$, found 206.0807.

Ethyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6b)

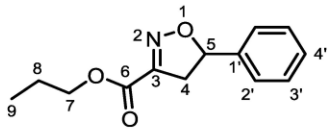


Protocol 1:
Product synthesis was carried out according to SOP2 using ethyl 2-(hydroxyimino)acetate (**5b, 3.44 mmol, 403 mg, 1.0 eq.**) and styrene (**19.0 mmol, 1.98 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) the product was obtained as a yellow oil (**0.98 mmol, 215 mg, 28%**).

Protocol 2:
In 50 mL jacketed beaker-type glass cells, ethyl 2-(hydroxyimino)acetate (**5b**, **4.27 mmol, 500 mg, 1.0 eq.**) and styrene (**18.8 mmol, 1.96 g, 4.41 eq.**) were dissolved a mixture of ethyl acetate (5 mL) and 1 M aqueous sodium iodide solution (20 mL) at 25 °C. The mixture was subjected to galvanostatic electrolysis under vigorous stirring on isostatic graphite electrodes with a relevant surface area of 5.0 cm^2 (size: 60 × 20 × 3 mm, immersion depth 2.5 cm) with a current density of 18 mA cm^{-2} until a charge of 4.14 *F* (1705.6 As) was applied. The biphasic mixture was transferred to a separation funnel, and the cell was rinsed with ethyl acetate. The layers were separated, and the aqueous layer was extracted once with ethyl acetate (30 mL). The combined organic fractions were dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated under reduced pressure. Isoxazoline (**6b**) was obtained after flash column chromatography on silica (cyclohexane/ethyl acetate; 0% →10% EtOAc) as a yellow oil (**1.31 mmol, 287 mg, 31%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.44 – 7.33 (m, 5H, *H*-2', *H*-3', *H*-4'), 5.77 (dd, *J* = 11.6 Hz, 9.0 Hz, 1H. *H*-5), 4.34 (q, *J* = 7.1 Hz, 2H, *H*-7), 3.64 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H, *H*-4), 3.21 (dd, *J* = 17.8 Hz, 9.0 Hz, 1H), 1.36 (t, J = 7.1 Hz, 3H, *H*-8).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 160.8, 151.7, 140.1, 129.1, 128.9, 126.3, 85.2, 62.3, 41.7, 14.2.
HRMS (ESI+), *m/z*: calculated for $C_{12}H_{13}NO_3$ + H^+ 220.0968 [*M*+H]$^+$, found 220.0959.

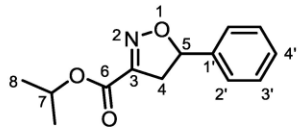
Propyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6c)



Product synthesis was carried out according to SOP2 using propyl 2-(hydroxyimino)acetate (**5c, 3.44 mmol, 451 mg, 1.0 eq.**) and styrene (**19.0 mmol, 1.99 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) the product was obtained as a yellow oil (**1.93 mmol, 450 mg, 56%**).

^{1}H NMR (400 MHz, CD_2Cl_2), *δ*/ppm: 7.45 – 7.34 (m, 5H, *H*-2', *H*-3', *H*-4'), 5.78 (dd, *J* = 11.6 Hz, 9.0 Hz, 1H, *H*-5), 4.25 (t, *J* = 6.8 Hz, 2H, *H*-7), 3.65 (dd, *J* = 17.8, 11.6 Hz, 1H, *H*-4), 3.21 (dd, *J* = 17.8, 9.0 Hz, 1H, *H*-4), 1.77 (dt, *J* = 7.5 Hz, 6.8 Hz, 2H, *H*-8), 1.01 (t, *J* = 7.5 Hz, 3H, *H*-9).
^{13}C NMR (101 MHz, CD_2Cl_2), *δ*/ppm: 161.0, 151.8, 140.3, 129.3, 129.0, 126.4, 85.4, 67.8, 41.9, 22.3, 10.6.
HRMS (ESI+), *m/z*: calculated for $C_{13}H_{15}NO_3$ + H^+ 234.1125 [*M*+H]$^+$, found 234.1118.

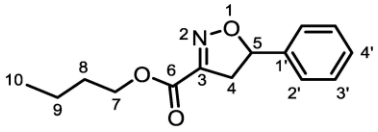
Iso-Propyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6d)



Product synthesis was carried out according to SOP2 using *iso*propyl 2-(hydroxyimino)acetate (**5d, 3.44 mmol, 500 mg, 1.0 eq.**) and styrene (**19.0 mmol, 1.98 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**1.97 mmol, 460 mg, 57%**).

^{1}H NMR (400 MHz, CD_2Cl_2), *δ*/ppm: 7.47 – 7.31 (m, 5H, *H*-2', *H*-3', *H*-4'), 5.76 (dd, *J* = 11.6 Hz, 9.0 Hz, 1H, *H*-5), 5.18 (hept, *J* = 6.3 Hz, 1H, *H*-7), 3.62 (dd, *J* = 17.8, 11.6 Hz, 1H, *H*-4), 3.19 (dd, *J* = 17.8 Hz, 9.0 Hz, 1H, *H*-4), 1.34 (dd, *J* = 6.3 Hz, 1.6 Hz, 6H, *H*-8).
^{13}C NMR (101 MHz, CD_2Cl_2), *δ*/ppm: 160.4, 152.0, 140.2, 129.2, 129.0, 126.3, 85.2, 70.3, 41.9, 21.8.
HRMS (ESI+), *m/z*: calculated for $C_{13}H_{15}NO_3$ + H^+ 234.1125 [*M*+H]$^+$, found 234.1115.

Butyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6e)



Preparative Scale:
Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 500 mg, 1.0 eq.**) and styrene (**19.0 mmol, 1.98 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**2.83 mmol, 700 mg, 82%**).

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.37 – 7.25 (m, 5H, *H*-2', *H*-3', *H*-4'), 5.74 (dd, *J* = 11.6 Hz, 8.9 Hz, 1H, *H*-5), 4.26 (t, *J* = 6.7 Hz, 2H, *H*-7), 3.60 (dd, *J* = 17.7 Hz, 11.6 Hz, 1H, *H*-4), 3.16 (dd, *J* = 17.7 Hz, 8.9 Hz, 1H, *H*-4), 1.74 – 1.64 (m, 2H, *H*-8), 1.46 – 1.35 (m, 2H, *H*-9), 0.93 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm: 160.5, 151.0, 139.5, 128.7, 128.5, 125.8, 84.8, 65.7, 41.4, 30.4, 18.9, 13.6.
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{17}NO_3$ + H^+ 248.1281 $[M+H]^+$, found 248.1271.

Decagram Scale:

In a 1.5 L jacketed beaker-type glass cell, butyl 2-(hydroxyimino)acetate (**XX, 172 mmol, 25.0 g, 1.0 eq.**) and styrene (**949 mmol, 98.8 g, 5.51 eq.**) were dissolved a mixture of *tert*-butyl methyl ether (625 mL) and 1 M aqueous sodium iodide solution (625 mL) at 25 °C. The mixture was subjected to galvanostatic electrolysis under vigorous stirring with a current density of 18.9 mA cm^{-2} until a charge of 2.5 *F* (41543 As) was applied. A stack of three alternatingly polarized (+ – +) BDD-coated silicon plates with a relevant surface area of 140 cm^2 (size: 200 × 70 × 3 mm, immersion depth 100 mm) and an interelectrode gap of 10 mm was used. The biphasic mixture was transferred to a separation funnel, and the cell was rinsed with *tert*-butyl methyl ether. The layers were separated, and the aqueous layer was extracted with *tert*-butyl methyl ether (1 × 400 mL + 1 × 200 mL). The combined organic fractions were dried over anhydrous sodium sulfate, filtered and the solvent was evaporated under reduced pressure (down to 150 mbar at 50 °C). Styrene was recovered by vacuum distillation (**684 mmol, 71.2 g, 3.97 eq.**). The crude product was purified by filtration through silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) to yield the product as an orange oil (**142 mmol, 35.0 g, 82%**).

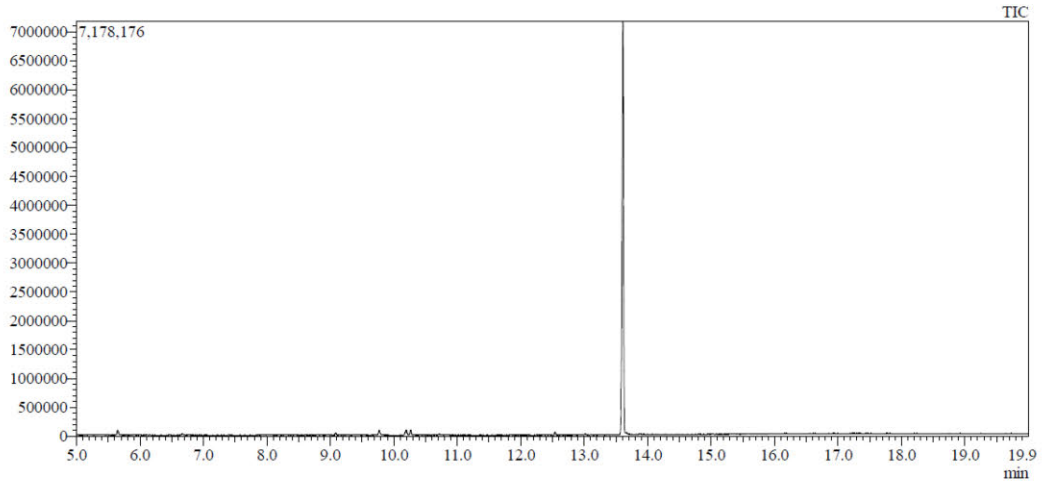


Figure S13: GC-MS chromatogram of the crude reaction mixture directly after electrolysis. Decagram scale. The styrene signal was cut off to avoid detector overload.

Hectogram Scale:

In a 12 L jacketed, stirred glass tank, butyl 2-(hydroxyimino)acetate (**5e, 1.5 mol, 218 g, 1.0 eq.**) and styrene (**8.74 mol, 910 g, 5.82 eq.**) were dissolved a mixture of *tert*-butyl methyl ether (5.45 L) and 1 M aqueous sodium iodide solution (5.45 L) at 25 °C. The mixture was vigorously stirred to produce a fine emulsion. The emulsion was continuously cycled through a 1.5 L jacketed beaker-type glass cell by a F01-700-2,5 pump (Fink Chem + Tec GmbH, Leinfelden-Echterdingen, Germany) with a flow rate of 25 L h^{-1}. In the cell, it was subjected to galvanostatic electrolysis under vigorous stirring with a current density of 18.9 mA cm^{-2} until a charge of 3.30 *F* (478251 As) was applied. A stack of three alternatingly polarized (+ – +) BDD-coated silicon plates with a relevant surface area of 196 cm^2 (size: 200 × 70 × 3 mm, immersion depth 140 mm) and an interelectrode gap of 10 mm was used. After

electrolysis, stirring was stopped and the layers were allowed to separate. The layers were drained into separate containers and the reactor was rinsed with *tert*-butyl methyl ether (4×1 L) and water (1 L). The combined aqueous layers were split in two portions (ca. 3 L each). Each portion was transferred into a 6 L three-necked round bottom flask equipped with a mechanical stirrer and extracted four times with *tert*-butyl methyl ether (1×1.5 L + 3×0.75 L) by vigorous stirring for 5 min. The layers were separated and combined organic fractions were dried over anhydrous sodium sulfate, filtered and the solvent was evaporated under reduced pressure (down to 150 mbar at 50 °C). Styrene was recovered by vacuum distillation (**4.81 mol, 500.5 g, 3.20 eq.**). The residue was incubated with 10%weigth of flash silica and stirred overnight. The mixture was filtered, and the silica purged with cyclohexane/ethyl acetate (4:1 *vol*/*vol*). The combined filtrates were washed with saturated sodium thiosulfate solution to remove remaining iodine, dried over anhydrous sodium sulfate, filtered and the solvent was evaporated under reduced pressure. The crude was purified by filtration through silica with cyclohexane/ethyl acetate (0% ⟶ 10% EtOAc) to yield isoxazoline **6e** as a colorless oil (**0.789 mol, 195.2 g, 53%**).

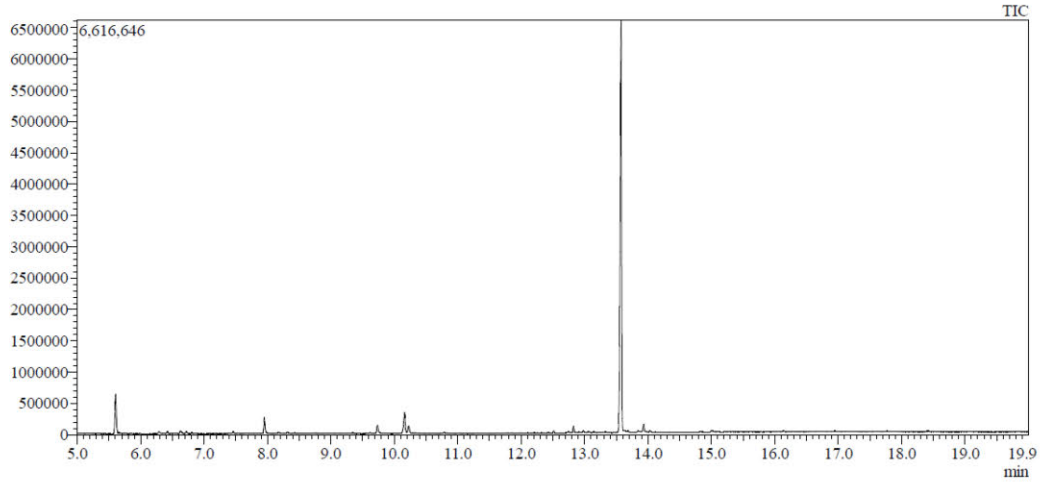


Figure S14: GC-MS chromatogram of the crude reaction mixture directly after electrolysis. Hectogram scale. Product signal at t_R = 13.5 min. The styrene signal was cut off to avoid detector overload.

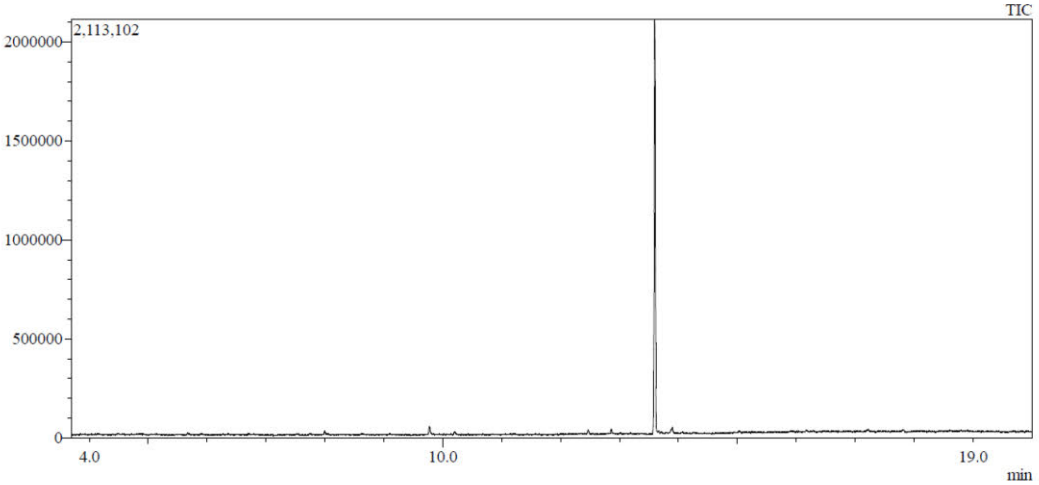
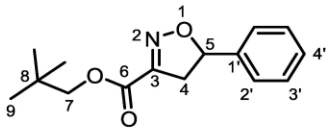


Figure S15: GC-MS chromatogram of the crude product after workup and distillation of excessive styrene. Hectogram scale.

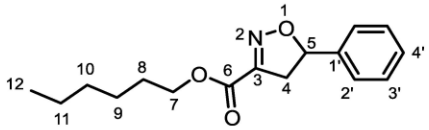
Neopentyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6f)



Product synthesis was carried out according to SOP2 using neopentyl 2-(hydroxyimino)acetate (**5f, 3.44 mmol, 550 mg, 1.0 eq.**) and styrene (**19.0 mmol, 1.98 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**2.68 mmol, 700 mg, 78%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.45 – 7.34 (m, 5H, *H*-2', *H*-3', *H*-4'), 5.79 (dd, *J* = 11.6 Hz, 9.1 Hz, 1H, *H*-5), 4.00 (s, 2H, *H*-7), 3.66 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H, *H*-4), 3.22 (dd, *J* = 17.8 Hz, 9.1 Hz, 1H, *H*-4), 1.03 (s, 6H, *H*-9).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 160.8, 151.7, 140.2, 129.2, 128.9, 126.3, 85.3, 75.2, 41.9, 31.7, 26.5.
HRMS (ESI+), *m/z*: calculated for $C_{15}H_{19}NO_3$ + H^+ 262.1438 $[M+H]^+$, found 262.1438.

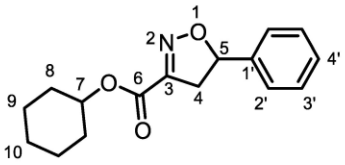
Hexyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6g)



Product synthesis was carried out according to SOP2 using hexyl 2-(hydroxyimino)acetate (**5g, 3.44 mmol, 598 mg, 1.0 eq.**) and styrene (**19.0 mmol, 1.99 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**1.93 mmol, 531 mg, 56%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.44 – 7.33 (m, 5H, *H*-2', *H*-3', *H*-4'), 5.78 (dd, *J* = 11.6 Hz, 9.0 Hz, 1H, *H*-5), 4.29 (t, *J* = 6.8 Hz, 2H, *H*-7), 3.64 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H, *H*-4), 3.21 (dd, *J* = 17.8, 9.0 Hz, 1H, *H*-4), 1.79 – 1.71 (m, 2H, *H*-8), 1.48 – 1.32 (m, 6H, *H*-9, *H*-10, *H*-11), 0.96 – 0.90 (m, 3H, *H*-12).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 160.8, 151.7, 140.2, 129.1, 128.9, 126.3, 85.2, 66.4, 41.8, 31.7, 28.8, 25.9, 22.9, 14.2.
HRMS (ESI+), *m/z*: calculated for $C_{16}H_{21}NO_3$ + H^+ 276.1594 $[M+H]^+$, found 276.1588.

Cyclohexyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6h)



Product synthesis was carried out according to SOP2 using cyclohexyl 2-(hydroxyimino)acetate (**5h, 3.44 mmol, 500 mg, 1.0 eq.**) and styrene (**19.0 mmol, 1.98 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**2.83 mmol, 700 mg, 82%**).

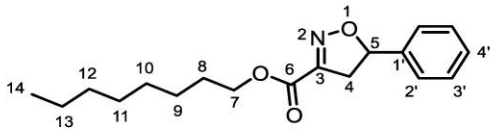
^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.44 – 7.31 (m, 5H, *H*-2', *H*-3', *H*-4'), 5.77 (dd, *J* = 11.6 Hz, 9.0 Hz, 1H, *H*-5), 4.96 (tt, *J* = 9.3 Hz, 3.9 Hz, 1H, *H*-7), 3.63 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H, *H*-4), 3.20 (dd, *J* =

17.8 Hz, 9.0 Hz, 1H, *H*-4), 1.98 – 1.90 (m, 2H, *H*-8), 1.80 – 1.73 (m, 2H, *H*-9), 1.61 – 1.50 (m, 3H, *H*-8, *H*-9), 1.48 – 1.26 (m, 3H, *H*-9, *H*-10).

^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 160.2, 152.0, 140.2, 129.1, 128.9, 126.3, 85.2, 75.0, 41.9, 31.8, 25.6, 24.0.

HRMS (ESI+), *m/z*: calculated for $C_{16}H_{19}NO_3$ + H^+ 274.1438 [*M*+H]$^+$, found 274.1431.

Octyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6i)



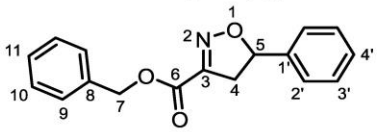
Product synthesis was carried out according to SOP2 using octyl 2-(hydroxyimino)acetate (**5i, 3.44 mmol, 694 mg, 1.0 eq.**) and styrene (**19.0 mmol, 1.99 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**1.92 mmol, 583 mg, 56%**).

^{1}H NMR (300 MHz, CD_2Cl_2), δ/ppm: 7.45 – 7.32 (m, 5H, *H*-2', *H*-3', *H*-4'), 5.78 (dd, *J* = 11.6 Hz, 9.0 Hz, 1H, *H*-5), 4.29 (t, *J* = 6.8 Hz, 1H, *H*-7), 3.65 (dd, *J* = 17.7 Hz, 11.6 Hz, 1H, *H*-4), 3.21 (dd, *J* = 17.7 Hz, 9.0 Hz, 1H, *H*-4), 1.82 – 1.69 (m, 2H, *H*-8), 1.51 – 1.25 (m, 10H, *H*-9, *H*-10, *H*-11, *H*-12, *H*-13), 1.01 – 0.86 (m, 3H, *H*-14).

^{13}C NMR (75 MHz, CD_2Cl_2), δ/ppm: 160.8, 151.7, 140.2, 129.1, 128.9, 126.3, 85.2, 66.3, 41.9, 32.2, 29.6, 29.5, 28.8, 26.2, 23.0, 14.3.

HRMS (ESI+), *m/z*: calculated for $C_{18}H_{25}NO_3$ + H^+ 304.1907 [*M*+H]$^+$, found 304.1901.

Benzyl 4,5-dihydro-5-phenylisoxazole-3-carboxylate (6j)



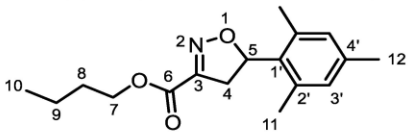
Product synthesis was carried out according to SOP2 using benzyl 2-(hydroxyimino)acetate (**5j, 3.44 mmol, 616 mg, 1.0 eq.**) and styrene (**19.0 mmol, 1.99 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) the product was obtained as a yellow solid (**2.41 mmol, 678 mg, 70%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.49 – 7.33 (m, 10H, *H*-2', *H*-3', *H*-4', *H*-9, *H*-10, *H*-11), 5.78 (dd, *J* = 11.6 Hz, 9.1 Hz, 1H), 5.33 (s, 2H, *H*-7), 3.65 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H), 3.23 (dd, *J* = 17.8 Hz, 9.1 Hz, 1H).

^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 160.8, 151.7, 140.2, 135.7, 129.4, 129.2, 129.1, 129.0, 126.5, 85.6, 68.0, 41.9.

HRMS (ESI+), *m/z*: calculated for $C_{17}H_{15}NO_3$ + H^+ 282.1125 [*M*+H]$^+$, found 282.1132.

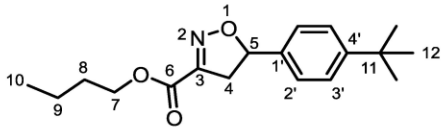
Butyl 4,5-dihydro-5-(2,4,6-trimethylphenyl)isoxazole-3-carboxylate (6k)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 500 mg, 1.0 eq.**) and 2,4,6-trimethylstyrene (**19.0 mmol, 2.78 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a colorless oil (**2.45 mmol, 709 mg, 81%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 6.89 (s, 2H, *H*-3'), 6.12 (t, *J* = 12.8 Hz, 1H, *H*-5), 4.38 – 4.24 (m, 2H, *H*-7), 3.50 (dd, *J* = 17.9 Hz, 12.8 Hz, 1H, *H*-4), 3.15 (dd, *J* = 17.9 Hz, 12.8 Hz, 1H, *H*-4), 2.32 – 2.26 (m, 9H, *H*-11, *H*-12), 1.79 – 1.70 (m, 2H, *H*-8), 1.52 – 1.40 (m, 2H, *H*-9), 0.99 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 161.3, 152.3, 138.7, 137.3, 131.4, 130.7, 83.2, 66.2, 39.6, 31.0, 21.1, 20.4, 19.7, 14.0.
HRMS (ESI+), *m/z*: calculated for $C_{17}H_{23}NO_3$ + H^+ 290.1751 [*M*+H]$^+$, found 290.1748.

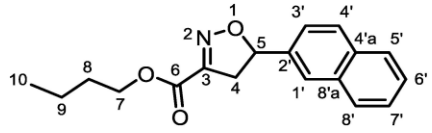
Butyl 5-(4-*tert*-butylphenyl)-4,5-dihydro-isoxazole-3-carboxylate (6l)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 498 mg, 1.0 eq.**) and 4*tert*-butylstyrene (**19.0 mmol, 2.56 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 7% EtOAc) the product was obtained as a yellow oil (**2.81 mmol, 851 mg, 82%**).

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.40 – 7.34 (m, 2H, *H*-2'), 7.27 – 7.20 (m, 2H, *H*-3'), 5.72 (dd, *J* = 11.6 Hz, 9.1 Hz, 1H, *H*-5), 4.26 (t, *J* = 6.7 Hz, 1H, *H*-7), 3.57 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H, *H*-4), 3.19 (dd, *J* = 17.8 Hz, 9.1 Hz, 1H, *H*-4), 1.74 – 1.65 (m, 2H, *H*-8), 1.45 – 1.35 (m, 2H, *H*-9), 1.28 (s, 9H, *H*-12), 0.92 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm: 160.8, 151.9, 151.2, 136.5, 125.9, 125.8, 85.0, 66.0, 41.3, 34.7, 31.4, 30.6, 19.2, 13.8.
HRMS (ESI+), *m/z*: calculated for $C_{18}H_{25}NO_3$ + H^+ 304.1907 [*M*+H]$^+$, found 304.1898.

Butyl 5-(naphthalen-2-yl)-4,5-dihydroisoxazole-3-carboxylate (6m)

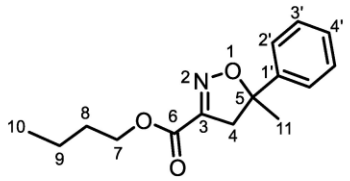


Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 498 mg, 1.0 eq.**) and 2-vinylnaphthalene (**19.0 mmol, 2.93 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a colorless oil (**1.75 mmol, 519 mg, 51%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.92 – 7.81 (m, 4H, *H*-1', *H*-4', *H*-5', *H*-8'), 7.56 – 7.50 (m, 2H, *H*-6', *H*-7'), 7.43 (dd, *J* = 8.5 Hz, 1.8 Hz, 1H, *H*-3'), 5.94 (dd, *J* = 11.6 Hz, 8.9 Hz, 1H, *H*-5), 4.30 (t, *J* = 6.7 Hz, 2H,

H-7), 3.70 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H, *H*-4), 3.29 (dd, *J* = 17.8 Hz, 8.9 Hz, 1H, *H*-4), 1.79 – 1.68 (m, 2H, *H*-8), 1.52 – 1.36 (m, 2H, *H*-9), 0.97 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, CD_2Cl_2), *δ*/ppm: 160.9, 151.8, 137.3, 133.7, 133.5, 129.3, 128.4, 128.1, 126.9, 126.9, 125.6, 123.7, 85.5, 66.2, 41.9, 30.9, 19.5, 13.8.
HRMS (ESI+), *m/z*: calculated for $C_{18}H_{19}NO_3$ + H^+ 298.1438 [*M*+H]$^+$, found 298.1434.

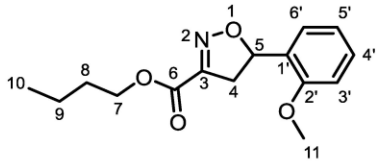
Butyl 4,5-dihydro-5-methyl-5-phenylisoxazole-3-carboxylate (6n)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 499 mg, 1.0 eq.**) and α-methylstyrene (**19.0 mmol, 2.28 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**2.36 mmol, 617 mg, 69%**).

^{1}H NMR (400 MHz, CD_2Cl_2), *δ*/ppm: 7.46 – 7.37 (m, 4H, *H*-2', *H*-3'), 7.34 – 7.29 (m, 1H, *H*-4'), 4.27 (t, *J* = 6.7 Hz, 2H, *H*-7), 3.45 – 3.31 (m, 2H, *H*-4), 1.77 (s, 3H, *H*-11), 1.76 – 1.67 (m, 2H, *H*-8), 1.50 – 1.39 (m, 2H, *H*-9), 0.98 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, CD_2Cl_2), *δ*/ppm: 161.2, 151.7, 145.0, 129.1, 128.2, 125.0, 91.5, 66.1, 47.6, 31.0, 28.4, 19.6, 14.0.
HRMS (ESI+), *m/z*: calculated for $C_{15}H_{19}NO_3$ + H^+ 262.1438 [*M*+H]$^+$, found 262.1426.

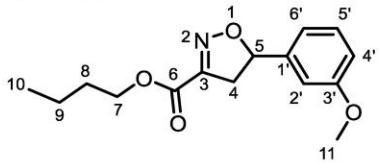
Butyl 4,5-dihydro-5-(2-methoxyphenyl)isoxazole-3-carboxylate (6o)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 499 mg, 1.0 eq.**) and 2-methoxystyrene (**19.0 mmol, 2.56 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**2.02 mmol, 561 mg, 59%**).

^{1}H NMR (400 MHz, CD_2Cl_2), *δ*/ppm: 7.40 – 7.20 (m, 2H, *H*-4', *H*-6'), 7.02 – 6.88 (m, 2H, *H*-3', *H*-5'), 5.98 (dd, *J* = 11.8 Hz, 8.1 Hz, 1H, *H*-5), 4.31 – 4.24 (m, 2H, *H*-7), 3.84 (s, 3H, *H*-11), 3.61 (dd, *J* = 17.8 Hz, 11.8 Hz, 1H, *H*-4), 3.10 (dd, *J* = 17.8 Hz, 8.4 Hz, 1H, *H*-4), 1.76 – 1.68 (m, 2H, *H*-8), 1.51 – 1.39 (m, 2H, *H*-9), 1.02 – 0.94 (m, 3H, *H*-10).
^{13}C NMR (101 MHz, CD_2Cl_2), *δ*/ppm: 161.1, 156.7, 152.0, 129.8, 128.5, 126.5, 120.9, 111.1, 81.3, 65.9, 55.7, 41.1, 30.9, 19.4, 13.8.
HRMS (ESI+), *m/z*: calculated for $C_{15}H_{19}NO_4$ + H^+ 278.1387 [*M*+H]$^+$, found 278.1381.

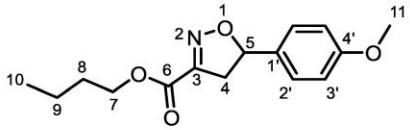
Butyl 4,5-dihydro-5-(3-methoxyphenyl)isoxazole-3-carboxylate (6p)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 499 mg, 1.0 eq.**) and 3-methoxystyrene (**19.0 mmol, 2.54 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**1.66 mmol, 459 mg, 49%**).

^{1}H NMR (400 MHz, CD_2Cl_2), *δ*/ppm: 7.34 – 7.27 (m, 1H, *H*-6'), 6.94 – 6.87 (m, 3H, *H*-2', *H*-4', *H*-5'), 5.74 (dd, *J* = 11.6 Hz, 9.0 Hz, 1H), 4.28 (t, *J* = 6.7 Hz, 2H, *H*-7), 3.80 (s, 3H, *H*-11), 3.62 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H, *H*-4), 3.20 (dd, *J* = 17.8 Hz, 9.0 Hz, 1H, *H*-4), 1.76 – 1.65 (m, 2H, *H*-8), 1.49 – 1.38 (m, 2H, *H*-9), 1.02 – 0.92 (m, 3H, *H*-10).
^{13}C NMR (101 MHz, CD_2Cl_2), *δ*/ppm: 160.8, 160.4, 151.7, 141.7, 130.2, 118.3, 114.3, 111.7, 85.1, 66.1, 55.5, 41.8, 30.8, 19.4, 13.8.
HRMS (ESI+), *m/z*: calculated for $C_{15}H_{19}NO_4$ + H^+ 278.1387 $[M+H]^+$, found 278.1381.

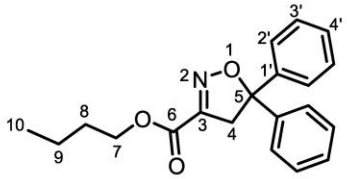
Butyl 4,5-dihydro-5-(4-methoxyphenyl)isoxazole-3-carboxylate (6q)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 499 mg, 1.0 eq.**) and 4-methoxystyrene (**19.0 mmol, 2.56 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a colorless oil (**2.16 mmol, 599 mg, 63%**).

^{1}H NMR (400 MHz, CD_2Cl_2), *δ*/ppm: 7.36 – 7.24 (m, 2H, *H*-2'), 7.00 – 6.91 (m, 2H, *H*-3'), 5.74 (dd, *J* = 11.5 Hz, 9.4 Hz, 1H, *H*-5), 4.32 (t, *J* = 6.7 Hz, 2H, *H*-7), 3.83 (s, 3H, *H*-11), 3.61 (dd, *J* = 17.8 Hz, 11.5 Hz, 1H, *H*-4), 3.23 (dd, *J* = 17.8 Hz, 9.4 Hz, 1H, *H*-4), 1.83 – 1.71 (m, 2H, *H*-8), 1.55 – 1.41 (m, 2H, *H*-9), 1.01 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, CD_2Cl_2), *δ*/ppm: 160.6, 160.0, 151.4, 131.6, 127.6, 114.2, 85.0, 65.7, 55.2, 41.1, 30.5, 19.1, 13.5.
HRMS (ESI+), *m/z*: calculated for $C_{15}H_{19}NO_4$ + H^+ 278.1387 $[M+H]^+$, found 278.1377.

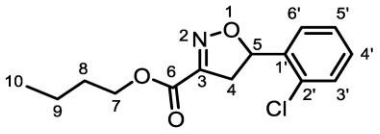
Butyl 4,5-dihydro-5,5-diphenylisoxazole-3-carboxylate (6r, *Isoxadifen-Butyl*)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 501 mg, 1.0 eq.**) and 1,1-diphenylethylene (**19.0 mmol, 3.44 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**1.86 mmol, 600 mg, 54%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.48 – 7.29 (m, 10H, *H*-2', *H*-3', *H*-4'), 4.33 – 4.25 (m, 2H, *H*-7), 3.92 – 3.86 (m, 2H, *H*-4), 1.77 – 1.68 (m, 2H, *H*-8), 1.51 – 1.39 (m, 2H, *H*-9), 1.01 – 0.95 (m, 3H, *H*-10).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 160.8, 151.8, 143.6, 128.9, 128.4, 126.2, 95.0, 66.2, 47.1, 30.8, 19.5, 13.9.
HRMS (ESI+), *m/z*: calculated for $C_{20}H_{21}NO_3$ + H^+ 324.1594 [*M*+H]$^+$, found 324.1593.

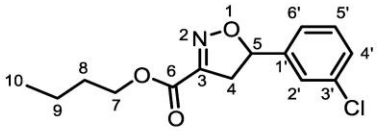
Butyl 5-(2-chlorophenyl)-4,5-dihydroisoxazole-3-carboxylate (6s)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 497 mg, 1.0 eq.**) and 2-chlorostyrene (**19.0 mmol, 2.632 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a slightly yellow oil (**2.52 mmol, 711 mg, 73%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.47 – 7.39 (m, 2H. *H*-3', *H*-6'), 7.35 – 7.26 (m, 2H, *H*-4', *H*-5'), 6.06 (dd, *J* = 11.8, 8.0 Hz, 1H), 4.26 (t, *J* = 6.7 Hz, 2H), 3.77 (dd, *J* = 17.9, 11.8 Hz, 1H), 3.08 (dd, *J* = 17.9, 7.9 Hz, 1H), 1.75 – 1.65 (m, 2H), 1.48 – 1.36 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 160.6, 151.8, 138.2, 131.6, 130.0, 129.9, 127.6, 126.8, 82.1, 66.2, 41.7, 30.8, 19.4, 13.8.
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{16}NO_3$ + H^+ 282.0891 [*M*+H]$^+$, found 282.0890.

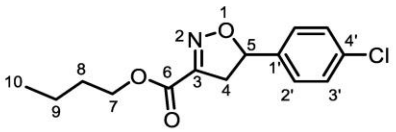
Butyl 5-(3-chlorophenyl)-4,5-dihydroisoxazole-3-carboxylate (6t)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 500 mg, 1.0 eq.**) and 3-chlorostyrene (**19.0 mmol, 2.65 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**2.49 mmol, 700 mg, 72%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.37 – 7.30 (m, 3H, *H*-2', *H*-4', *H*-6'), 7.26 – 7.21 (m, 1H, *H*-5'), 5.75 (dd, *J* = 11.6 Hz, 8.6 Hz, 1H, *H*-5), 4.27 (t, *J* = 6.7 Hz, 2H, *H*-7), 3.66 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H, *H*-4), 3.17 (dd, *J* = 17.8 Hz, 8.6 Hz, 1H, *H*-4), 1.77 – 1.65 (m, 2H, *H*-8), 1.48 – 1.35 (m, 2H, *H*-9), 0.96 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 160.7, 151.7, 142.4, 135.0, 130.6, 129.0, 126.3, 124.5, 84.3, 66.2, 42.0, 30.8, 19.4, 13.8.
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{16}{}^{35}ClNO_3$ + H^+ 282.0891 [*M*+H]$^+$, found 282.0883.

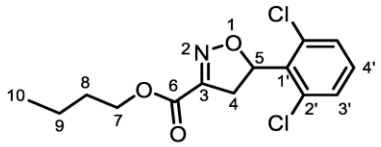
Butyl 5-(4-chlorophenyl)-4,5-dihydroisoxazole-3-carboxylate (6u)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 500 mg, 1.0 eq.**) and 4-chlorostyrene (**19.0 mmol, 2.63 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) the product was obtained as a yellow oil (**2.10 mmol, 593 mg, 61%**).

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.35 – 7.31 (m, 2H, *H*-2'), 7.27 – 7.22 (m, 2H, *H*-3'), 5.74 (dd, *J* = 11.6 Hz, 8.7 Hz, 1H, *H*-5), 4.28 (t, *J* = 6.7 Hz, 1H, *H*-7), 3.63 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H, *H*-4), 3.14 (dd, *J* = 17.8 Hz, 8.7 Hz, 1H, *H*-4), 1.75 – 1.65 (m, 2H, *H*-8), 1.46 – 1.35 (m, 2H, *H*-9), 0.93 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm: 160.5, 151.1, 138.1, 134.5, 129.1, 127.3, 84.1, 66.0, 41.6, 30.4, 19.1, 13.7.
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{16}{}^{35}ClNO_3$ + H^+ 282.0891 $[M+H]^+$, found 282.0887.

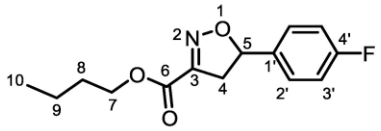
Butyl 5-(2,6-dichlorophenyl)-4,5-dihydroisoxazole-3-carboxylate (6v)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 503 mg, 1.0 eq.**) and 2,6-dichlorostyrene (**19.0 mmol, 3.29 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a colorless solid (**2.46 mmol, 777 mg, 72%**).

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.34 – 7.29 (m, 2H, *H*-3'), 7.23 – 7.17 (m, 1H, *H*-4'), 6.44 (dd, *J* = 12.7 Hz, 11.8 Hz, 1H, *H*-5), 4.34 – 4.22 (m, 2H, *H*-7), 3.57 – 3.37 (m, 2H, *H*-4), 1.75 – 1.64 (m, 2H, *H*-8), 1.48 – 1.33 (m, 2H, *H*-9), 0.92 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm: 160.6, 151.0, 135.7, 132.3, 130.5, 129.4, 81.1, 65.9, 38.7, 30.4, 19.0, 13.7.
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{15}{}^{35}ClNO_3$ + H^+ 316.0502 $[M+H]^+$, found 316.0492.

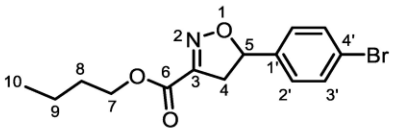
Butyl 4,5-dihydro-5-(4-fluorophenyl)isoxazole-3-carboxylate (6w)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 499 mg, 1.0 eq.**) and 4-fluorostyrene (**19.0 mmol, 2.34 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 10% EtOAc) the product was obtained as a slightly yellow oil (**1.93 mmol, 511 mg, 56%**).

^{1}H NMR (400 MHz, $CDCl_3$), δ/ppm: 7.34 – 7.24 (m, 2H, *H*-2'), 7.12 – 6.99 (m, 2H, *H*-3'), 5.75 (dd, *J* = 11.6 Hz, 8.9 Hz, 1H, *H*-5), 4.29 (t, *J* = 6.7 Hz, 2H, *H*-7), 3.62 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H, *H*-4), 3.17 (dd, *J* = 17.8 Hz, 8.9 Hz, 1H, *H*-4), 1.76 – 1.64 (m, 2H, *H*-8), 1.49 – 1.35 (m, 2H, *H*-9), 0.94 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, $CDCl_3$), δ/ppm: 164.1, 161.7, 160.7, 151.2, 135.4 (d, *J* = 3.1 Hz), 127.9 (d, *J* = 8.4 Hz), 115.9 (d, *J* = 21.9 Hz), 84.4, 66.1, 41.6, 30.6, 19.2, 13.8.
^{19}F NMR (376 MHz, $CDCl_3$), δ/ppm: -114.13 – -114.25 (m).
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{16}FNO_3$ + H^+ 266.1187 $[M+H]^+$, found 266.1183.

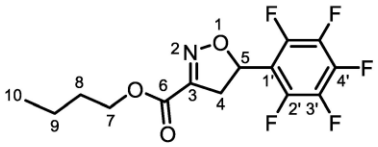
Butyl 5-(4-bromophenyl)-4,5-dihydroisoxazole-3-carboxylate (6x)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 499 mg, 1.0 eq.**) and 4-bromostyrene (**19.0 mmol, 3.48 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**1.71 mmol, 557 mg, 50%**).

^{1}H NMR (400 MHz, $CDCl_3$), *δ*/ppm: 7.48 – 7.43 (m, 2H, *H*-2'), 7.18 – 7.14 (m, 2H, *H*-3'), 5.70 (dd, *J* = 11.6 Hz, 8.7 Hz, 1H, *H*-5), 4.25 (t, *J* = 6.7 Hz, 2H, *H*-7), 3.61 (dd, *J* = 17.8 Hz, 11.6 Hz, 1H, *H*-4), 3.12 (dd, *J* = 17.8, 8.7 Hz, 1H, *H*-4), 1.71 – 1.63 (m, 2H, *H*-8), 1.43 – 1.34 (m, 2H, *H*-9), 0.91 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, $CDCl_3$), *δ*/ppm: 160.4, 151.1, 138.6, 131.9, 127.5, 122.5, 84.0, 66.0, 41.5, 30.4, 19.0, 13.6.
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{16}{}^{79}BrNO_3$ + H^+ 326.0386 [*M*+H]$^+$, found 326.0383.

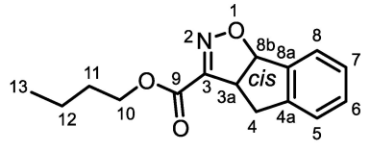
Butyl 4,5-dihydro-5-(perfluorophenyl)isoxazole-3-carboxylate (6y)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 498 mg, 1.0 eq.**) and 2,3,4,5,6-pentafluorostyrene (**19.0 mmol, 3.69 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a colorless solid (**2.45 mmol, 817 mg, 71%**).

^{1}H NMR (400 MHz, CD_2Cl_2), *δ*/ppm: 6.06 (dd, *J* = 12.5 Hz, 8.9 Hz, 1H, *H*-5), 4.29 (t, *J* = 6.7 Hz, 2H, *H*-7), 3.66 (dd, *J* = 18.0 Hz, 12.5 Hz, 1H, *H*-4), 3.35 (dd, *J* = 18.0 Hz, 8.9 Hz, 1H, *H*-4), 1.76 – 1.67 (m, 2H, *H*-8), 1.48 – 1.37 (m, 2H, *H*-9), 0.95 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, CD_2Cl_2), *δ*/ppm: 160.4, 151.5, 147.6 – 144.2 (m), 143.8 – 140.5 (m), 139.8 – 136.4 (m), 113.8 – 112.6 (m), 74.7, 66.5, 40.0, 30.8, 19.5, 13.8.
^{19}F NMR (376 MHz, CD_2Cl_2), *δ*/ppm: -143.72 – -143.85 (m), -154.25 – -154.49 (m), -163.09 – -163.36 (m).
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{12}F_5NO_3$ + H^+ 338.0810 [*M*+H]$^+$, found 338.0812.

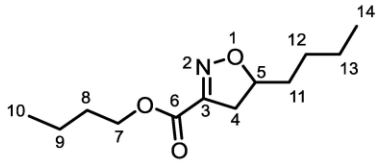
Butyl *cis*-4*H*-3a,8b-dihydroindeno[2,1-*d*]isoxazole-3-carboxylate (6z)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 500 mg, 1.0 eq.**) and 1*H*-indene (**19.0 mmol, 2.20 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**1.57 mmol, 406 mg, 46%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.52 – 7.49 (m, 1H, *H*-8), 7.41 – 7.27 (m, 3H, *H*-5, *H*-6, *H*-7), 6.25 (d, *J* = 9.6 Hz, 1H, *H*-8b), 4.36 – 4.23 (m, 3H, *H*-3a, *H*-10), 3.49 – 3.27 (m, 2H, *H*-4), 1.78 – 1.66 (m, 2H, *H*-11), 1.51 – 1.36 (m, 2H, *H*-12), 0.97 (t, *J* = 7.4 Hz, 3H, *H*-13).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 161.0, 153.9, 141.6, 140.0, 130.2, 127.9, 126.0, 125.4, 92.2, 66.0, 49.9, 36.5, 30.9, 19.5, 13.8.
HRMS (ESI+), *m/z*: calculated for $C_{15}H_{17}NO_3$ + H^+ 260.1281 [*M*+H]$^+$, found 260.1272.

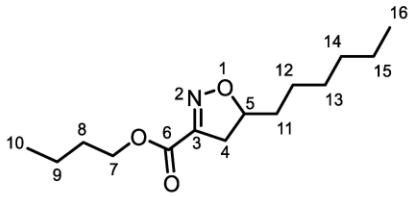
Butyl 5-butyl-4,5-dihydroisoxazole-3-carboxylate (6aa)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 499 mg, 1.0 eq.**) and hex-1-ene (**19.0 mmol, 1.60 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a yellow oil (**1.82 mmol, 414 mg, 53%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 4.74 (dddd, *J* = 10.9 Hz, 8.7 Hz, 6.9 Hz, 6.1 Hz, 1H, *H*-5), 4.23 (t, *J* = 6.7 Hz, 1H, *H*-7), 3.21 (dd, *J* = 17.5 Hz, 10.9 Hz, 1H, *H*-4), 2.80 (dd, *J* = 17.5 Hz, 8.7 Hz, 1H, *H*-4), 1.83 – 1.53 (m, 4H, *H*-8, *H*-11), 1.45 – 1.26 (m, 6H, *H*-9, *H*-12, *H*-13), 1.01 – 0.85 (m, 6H, *H*-10, *H*-14).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 161.2, 151.9, 84.5, 65.9, 38.8, 35.1, 30.9, 27.7, 22.8, 19.4, 14.1, 13.8.
HRMS (ESI+), *m/z*: calculated for $C_{12}H_{21}NO_3$ + H^+ 228.1594 [*M*+H]$^+$, found 228.1601.

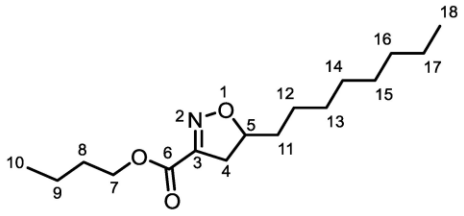
Butyl 4,5-dihydro-5-hexyl-isoxazole-3-carboxylate (6ab)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 501 mg, 1.0 eq.**) and oct-1-ene (**19.0 mmol, 2.14 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a colorless oil (**1.80 mmol, 458 mg, 52%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 4.75 (dddd, *J* = 10.9 Hz, 8.7 Hz, 6.8 Hz, 6.1 Hz, 1H, *H*-5), 4.23 (t, *J* = 6.7 Hz, 2H, *H*-7), 3.21 (dd, *J* = 17.5 Hz, 10.9 Hz, 1H, *H*-4), 2.80 (dd, *J* = 17.5 Hz, 8.7 Hz, 1H, *H*-4), 1.83 – 1.53 (m, 4H, *H*-8, *H*-11), 1.48 – 1.24 (m, 10H, *H*-9, *H*-12, *H*-13, *H*-14, *H*-15), 1.01 – 0.84 (m, 6H, *H*-10, *H*-16).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 161.2, 151.9, 84.5, 65.9, 38.8, 35.5, 32.1, 30.9, 29.4, 25.5, 22.9, 19.5, 14.2, 13.8.
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{25}NO_3$ + H^+ 256.1907 [*M*+H]$^+$, found 256.1911.

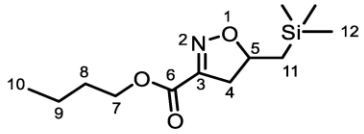
Butyl 4,5-dihydro-5-octyl-isoxazole-3-carboxylate (6ac)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 498 mg, 1.0 eq.**) and oct-1-ene (**19.0 mmol, 2.68 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a colorless oil (**1.78 mmol, 507 mg, 51%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 4.75 (dddd, *J* = 10.9 Hz, 8.7 Hz, 6.8 Hz, 6.1 Hz, 1H, *H*-5), 4.23 (t, *J* = 6.7 Hz, 2H, *H*-7), 3.21 (dd, *J* = 17.5 Hz, 10.9 Hz, 1H, *H*-4), 2.80 (dd, *J* = 17.5 Hz, 8.7 Hz, 1H, *H*-4), 1.81 – 1.56 (m, 4H, *H*-8, *H*-11), 1.51 – 1.22 (m, 14H, *H*-9, *H*-12, *H*-13, *H*-14, *H*-15, *H*-16, *H*-17), 1.00 – 0.85 (m, 6H, *H*-10, *H*-18).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 161.2, 151.9, 84.5, 65.9, 38.9, 35.5, 32.3, 30.9, 29.8, 29.8, 29.6, 25.6, 23.1, 19.5, 14.3, 13.9.
HRMS (ESI+), *m/z*: calculated for $C_{16}H_{29}NO_3$ + H^+ 284.2220 [*M*+H]$^+$, found 284.2220.

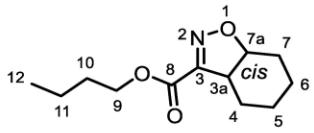
Butyl 5-((trimethylsilyl)methyl)-4,5-dihydroisoxazole-3-carboxylate (6ad)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 499 mg, 1.0 eq.**) and allyl-trimethyl-silane (**19.0 mmol, 2.18 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a colorless oil (**1.68 mmol, 431 mg, 49%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 4.93 – 4.79 (m, 1H, *H*-5), 4.23 (t, *J* = 6.7 Hz, 2H, *H*-7), 3.23 (dd, *J* = 17.2 Hz, 10.4 Hz, 1H, *H*-4), 2.71 (dd, *J* = 17.3 Hz, 9.5 Hz, 1H, *H*4), 1.73 – 1.64 (m, 2H, *H*-8), 1.46 – 1.35 (m, 2H, *H*-9), 1.25 (dd, *J* = 14.1 Hz, 5.9 Hz, 1H, *H*-11), 1.02 (dd, *J* = 14.1 Hz, 9.1 Hz, 1H, *H*-11), 0.94 (t, *J* = 7.4 Hz, 3H, *H*-10), 0.07 (s, 9H, *H*-12).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 161.3, 152.0, 83.4, 65.9, 40.9, 30.9, 24.6, 19.5, 13.9, -1.0.
HRMS (ESI+), *m/z*: calculated for $C_{12}H_{23}NO_3Si$ + H^+ 258.1520 [*M*+H]$^+$, found 258.1513.

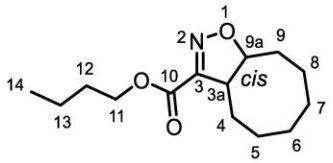
Butyl *cis*-3a,4,5,6,7,7a-hexahydrobenzo[*d*]isoxazole-3-carboxylate (6ae)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 500 mg, 1.0 eq.**) and cyclohex-1-ene (**19.0 mmol, 1.56 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a slightly yellow oil (**1.86 mmol, 420 mg, 54%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 4.54 – 4.49 (m, 1H, *H*-7a), 4.30 – 4.19 (m, 2H, *H*-9), 3.19 – 3.07 (m, 1H, *H*-3a), 2.14 – 2.04 (m, 1H, *H*-7), 2.00 – 1.89 (m, 3H, *H*-4, *H*-10), 1.81 – 1.18 (m, 6H, *H*-4, *H*-5, *H*-6, *H*-7, *H*-11), 0.94 (t, *J* = 7.4 Hz, 3H, *H*-12).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 161.4, 158.6, 83.1, 66.0, 44.1, 31.0, 26.0, 25.2, 21.9, 20.3, 19.6, 14.0.
HRMS (ESI+), *m/z*: calculated for $C_{12}H_{19}NO_3$ + H^+ 226.1438 [*M*+H]$^+$, found 226.1433.

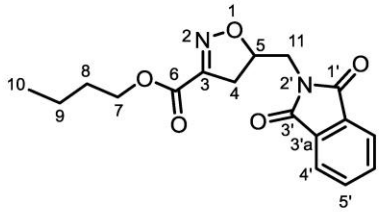
Butyl *cis*-3a,4,5,6,7,8,9,9a-octahydrocycloocta[*d*]isoxazole-3-carboxylate (6af)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 499 mg, 1.0 eq.**) and cyclooct-1-ene (**19.0 mmol, 2.14 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a colorless oil (**2.50 mmol, 633 mg, 73%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 4.56 – 4.48 (m, 1H, *H*-9a), 4.22 (tt, *J* = 7.4 Hz, 3.8 Hz, 2H, *H*-11), 3.25 (td, *J* = 9.9 Hz, 1.6 Hz, 1H, *H*-3a), 2.03 – 1.18 (m, 16H, *H*-4, *H*-5, *H*-6, *H*-7, *H*-8, *H*-9, *H*-12, *H*-13), 0.93 (t, *J* = 7.4 Hz, 3H, *H*-14).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 161.3, 156.9, 88.3, 65.8, 49.5, 31.0, 30.3, 26.0, 25.9, 25.6, 25.6, 25.1, 19.6, 14.0.
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{24}NO_3$ + H^+ 254.1751 [*M*+H]$^+$, found 254.1747.

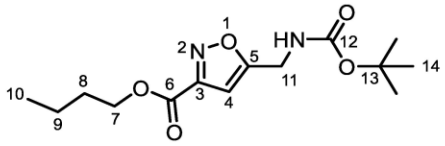
Butyl 5-((1,3-dioxoisoindolin-2-yl)methyl)-4,5-dihydroisoxazole-3-carboxylate (6ag)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 500 mg, 1.0 eq.**) and 2-allylisoindoline-1,3-dione (**19.0 mmol, 3.56 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 25% EtOAc) the product was obtained as a slightly orange oil (**2.46 mmol, 813 mg, 72%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.88 – 7.81 (m, 2H, *H*-4'), 7.81 – 7.69 (m, 2H, *H*-5'), 5.11 (dtd, *J* = 11.0 Hz, 7.1 Hz, 5.4 Hz, 1H), 4.28 – 4.19 (m, 2H, *H*-7), 3.93 (dd, *J* = 14.2 Hz, 7.2 Hz, 1H, *H*-11), 3.78 (dd, *J* = 14.2 Hz, 5.4 Hz, 1H, *H*-11), 3.30 (dd, *J* = 17.9 Hz, 11.0 Hz, 1H, *H*-4), 3.09 (dd, *J* = 17.9 Hz, 7.1 Hz, 1H, *H*-4), 1.73 – 1.63 (m, 2H, *H*-8), 1.46 – 1.34 (m, 2H, *H*-9), 0.96 – 0.90 (m, 3H, *H*-10).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 168.3, 160.6, 152.1, 134.6, 132.2, 123.7, 80.5, 66.2, 41.0, 37.6, 30.8, 19.4, 13.8.
HRMS (ESI+), *m/z*: calculated for $C_{17}H_{18}NO_3$ + H^+ 331.1288 [*M*+H]$^+$, found 331.1294.

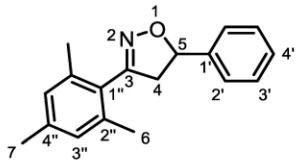
Butyl 5-(((*tert*-butoxycarbonyl)amino)methyl)isoxazole-3-carboxylate (6ah)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 501 mg, 1.0 eq.**) and *tert*-butyl prop-2-yn-1-ylcarbamate (**19.0 mmol, 2.96 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a colorless oil (**1.20 mmol, 360 mg, 35%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 6.54 (s, 1H, *H*-4), 5.41 (s, 1H, 11-N*H*), 4.44 (d, *J* = 6.3 Hz, 2H, *H*-11), 4.33 (t, *J* = 6.7 Hz, 2H, *H*-7), 1.77 – 1.68 (m, 2H, *H*-8), 1.49 – 1.38 (m, 11H, *H*-9, *H*-14), 0.95 (t, *J* = 7.4 Hz, 3H, *H*-10).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 172.8, 160.4, 157.1, 156.1, 102.7, 80.6, 66.4, 37.1, 31.0, 28.5, 19.6, 14.0.
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{22}N_2O_5$ + H^+ 299.1601 [*M*+H]$^+$, found 299.1595.

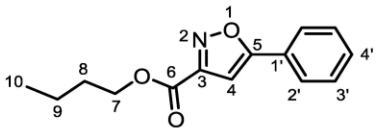
4,5-Dihydro-3-mesityl-5-phenylisoxazole (6ai)



Product synthesis was carried out according to SOP2 using 2,4,6-trimethylphenylaldoxime (**5e, 3.44 mmol, 562 mg, 1.0 eq.**) and styrene (**19.0 mmol, 1.98 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a slightly yellow oil (**2.51 mmol, 666 mg, 73%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.53 – 7.31 (m, 5H, *H*-2', *H*-3', *H*-4'), 6.94 (s, 2H, *H*-3''), 5.77 (dd, *J* = 10.9 Hz, 8.2 Hz, 1H, *H*-5), 3.63 (dd, *J* = 17.4 Hz, 10.9 Hz, 1H, *H*-4), 3.14 (dd, *J* = 17.4 Hz, 8.2 Hz, 1H, *H*-4), 2.32 (s, 3H, *H*-7), 2.25 (s, 6H, *H*-6).
^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 157.3, 141.8, 139.2, 136.9, 129.1, 128.8, 128.4, 126.5, 126.2, 82.2, 47.6, 21.2, 19.9.
HRMS (ESI+), *m/z*: calculated for $C_{18}H_{19}NO$ + H^+ 266.1539 [*M*+H]$^+$, found 266.1533.

Butyl 5-phenylisoxazole-3-carboxylate (6aj)



Product synthesis was carried out according to SOP2 using butyl 2-(hydroxyimino)acetate (**5e, 3.44 mmol, 511 mg, 1.0 eq.**) and phenylacetylen (**19.0 mmol, 2.96 g, 5.51 eq.**). After flash column chromatography over silica with cyclohexane/ethyl acetate (0% → 5% EtOAc) the product was obtained as a colorless solid (**0.73 mmol, 181 mg, 21%**).

^{1}H NMR (400 MHz, CD_2Cl_2), δ/ppm: 7.84 – 7.79 (m, 2H, *H*-2'), 7.54 – 7.47 (m, 3H, *H*-3', *H*-4'), 6.93 (s, 1H, *H*-4), 4.39 (t, *J* = 6.7 Hz, 2H, *H*-7), 1.83 – 1.73 (m, 2H, *H*-8), 1.53 – 1.42 (m, 2H, *H*-9), 0.99 (t, *J* = 7.4 Hz, 3H, *H*-10).

^{13}C NMR (101 MHz, CD_2Cl_2), δ/ppm: 172.1, 160.5, 157.6, 131.3, 129.7, 127.2, 126.4, 100.5, 66.5, 31.1, 19.7, 14.0.
HRMS (ESI+), *m/z*: calculated for $C_{14}H_{15}NO_3$ + H^+ 245.1052 $[M+H]^+$, found 245.1057.

S7. References

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S8. NMR Spectra

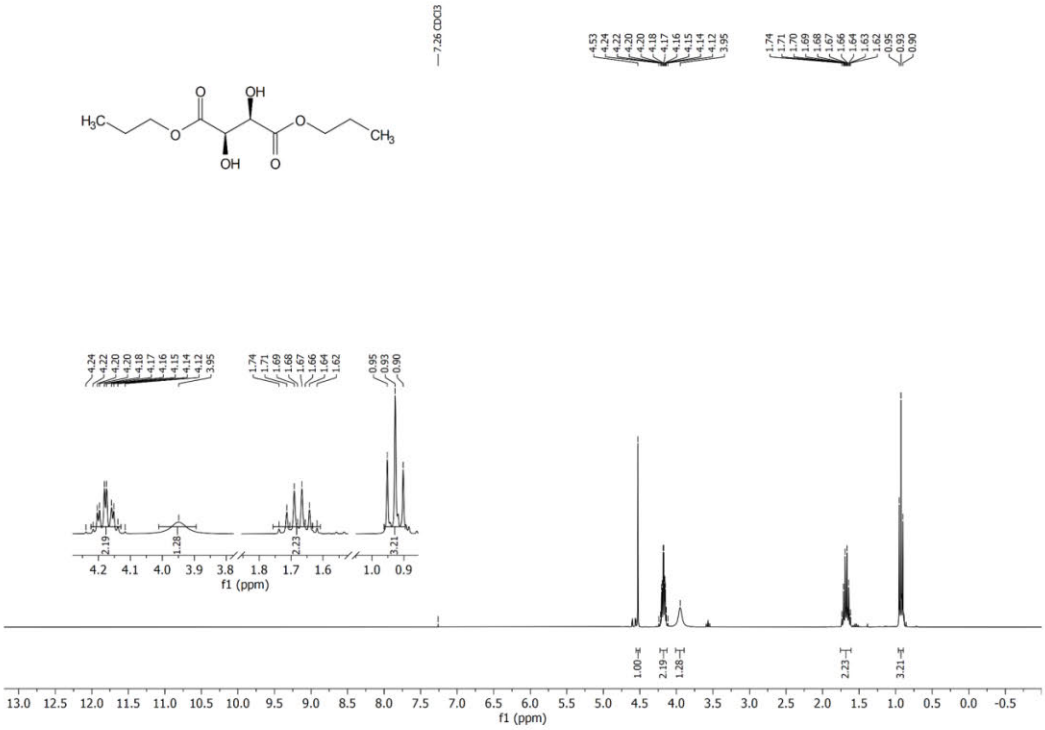

Figure S16: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7c**.

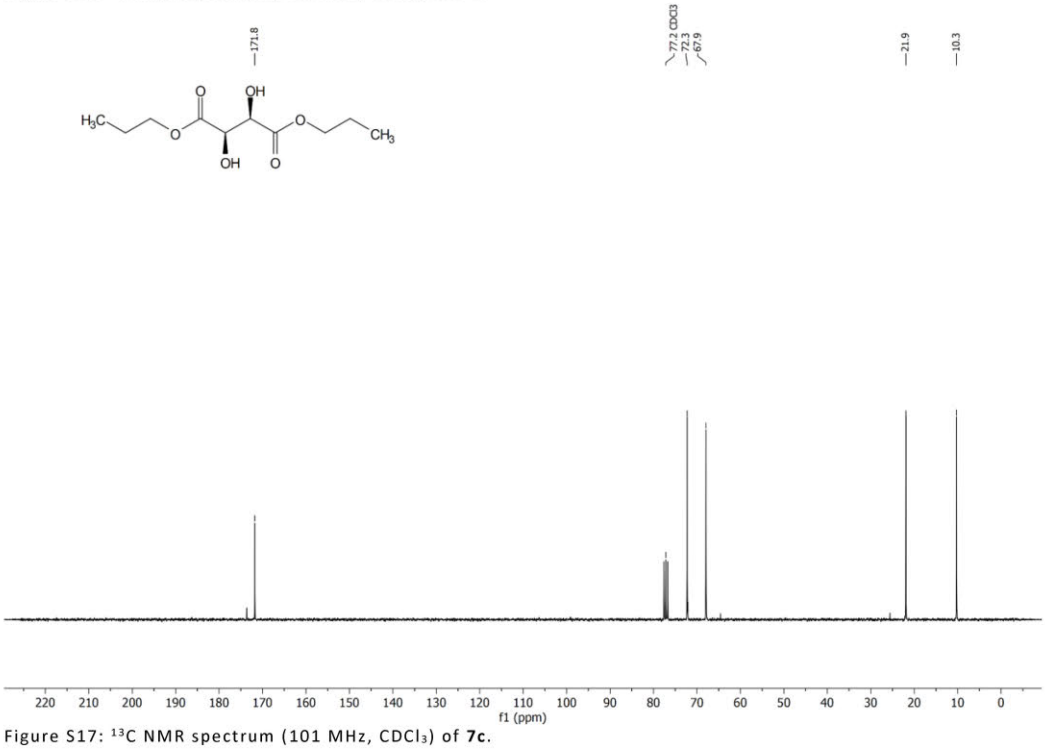

Figure S17: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7c**.

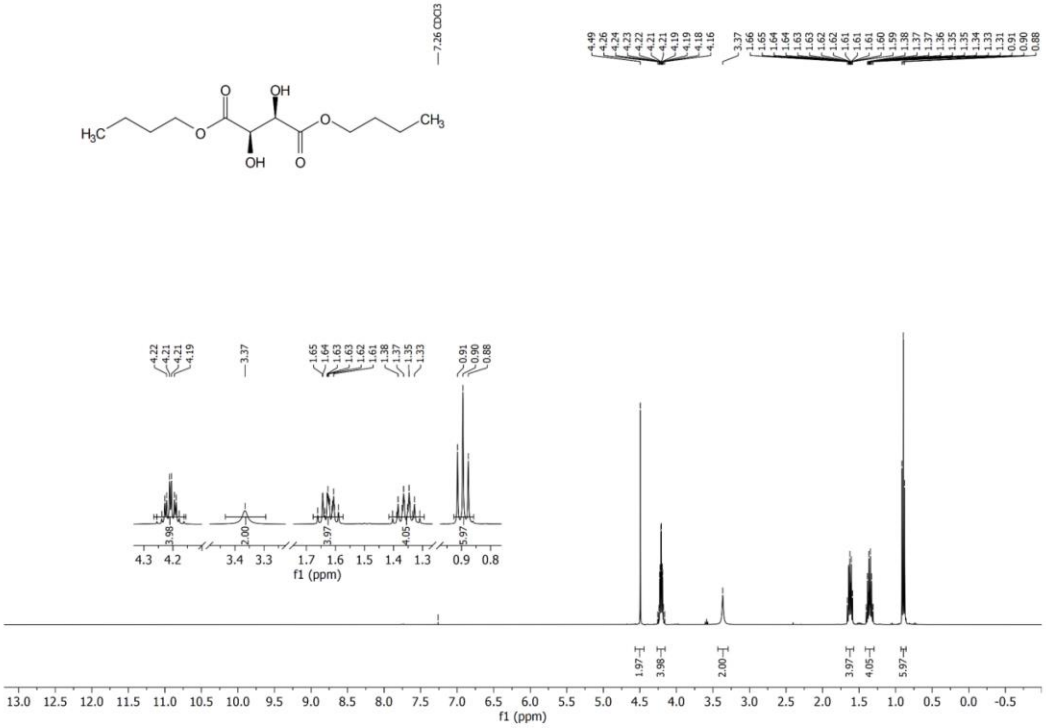

Figure S18: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7e**.

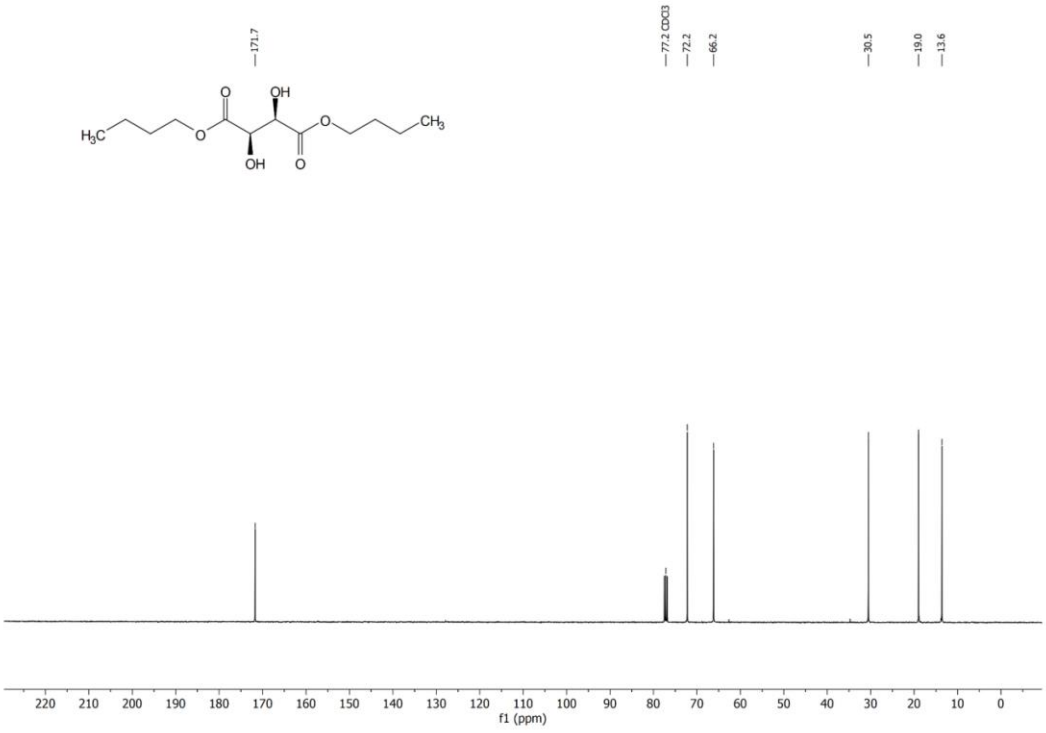

Figure S19: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7e**.

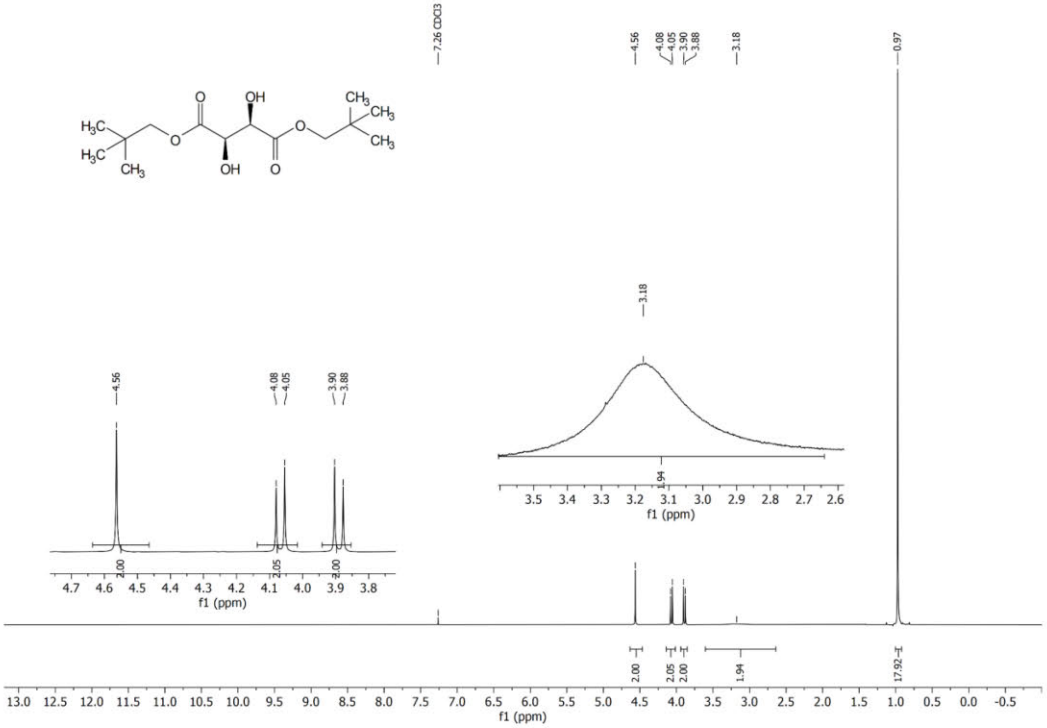

Figure S20: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7f**.

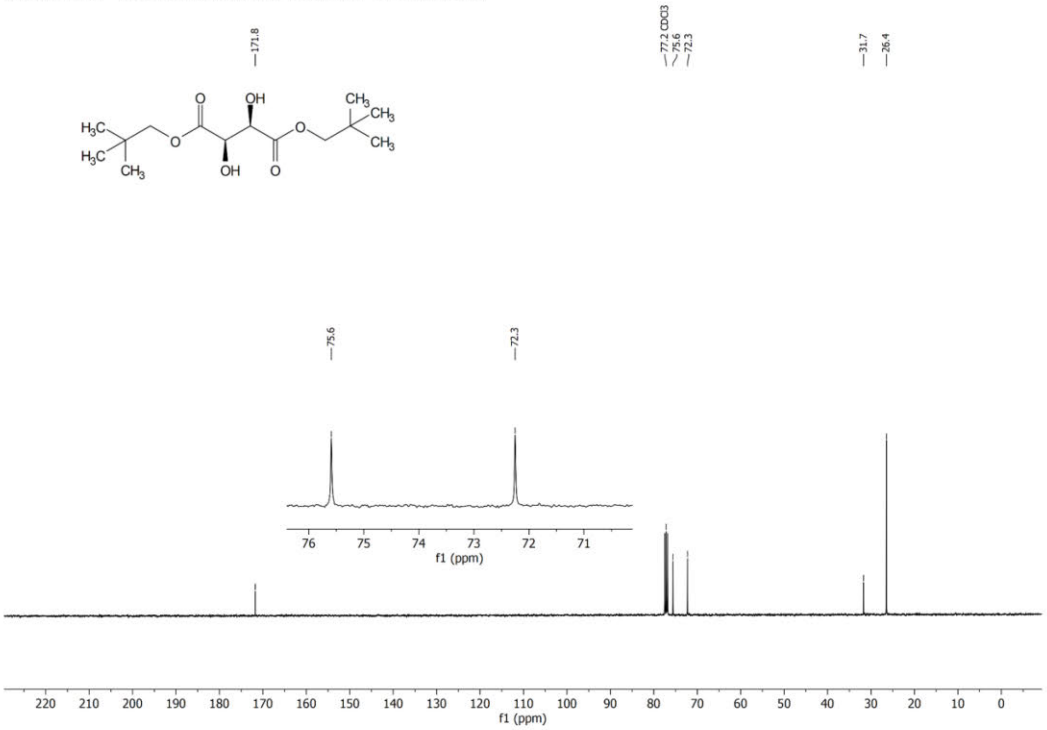

Figure S21: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7f**.

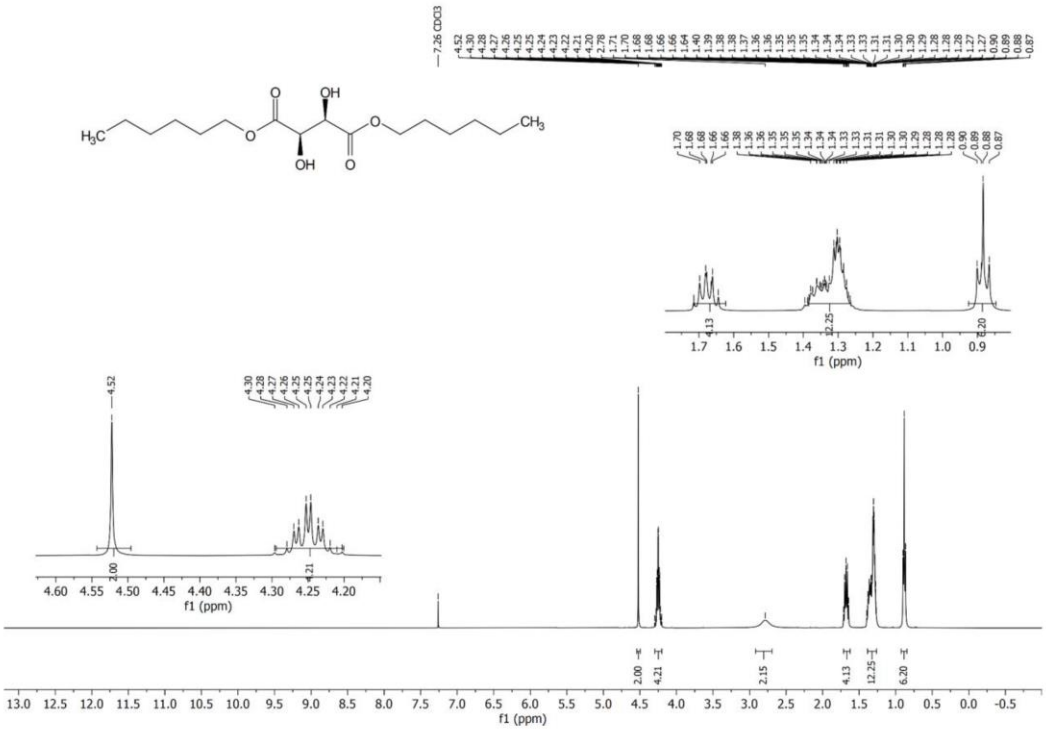

Figure S22: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7g**.

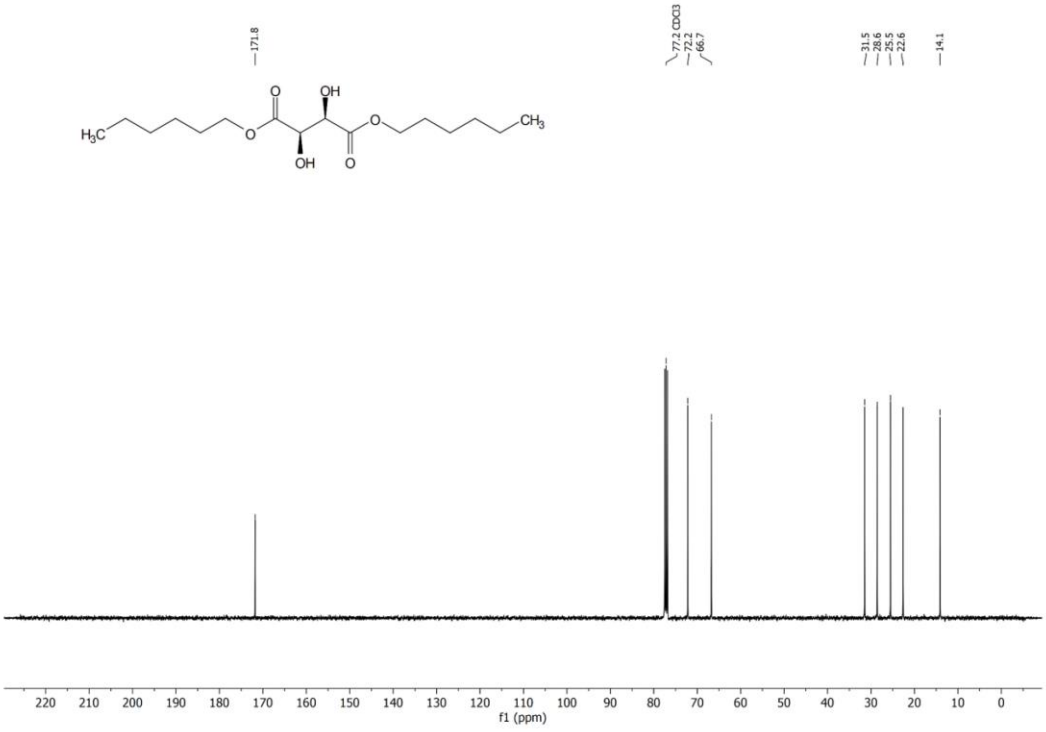

Figure S23: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7g**.

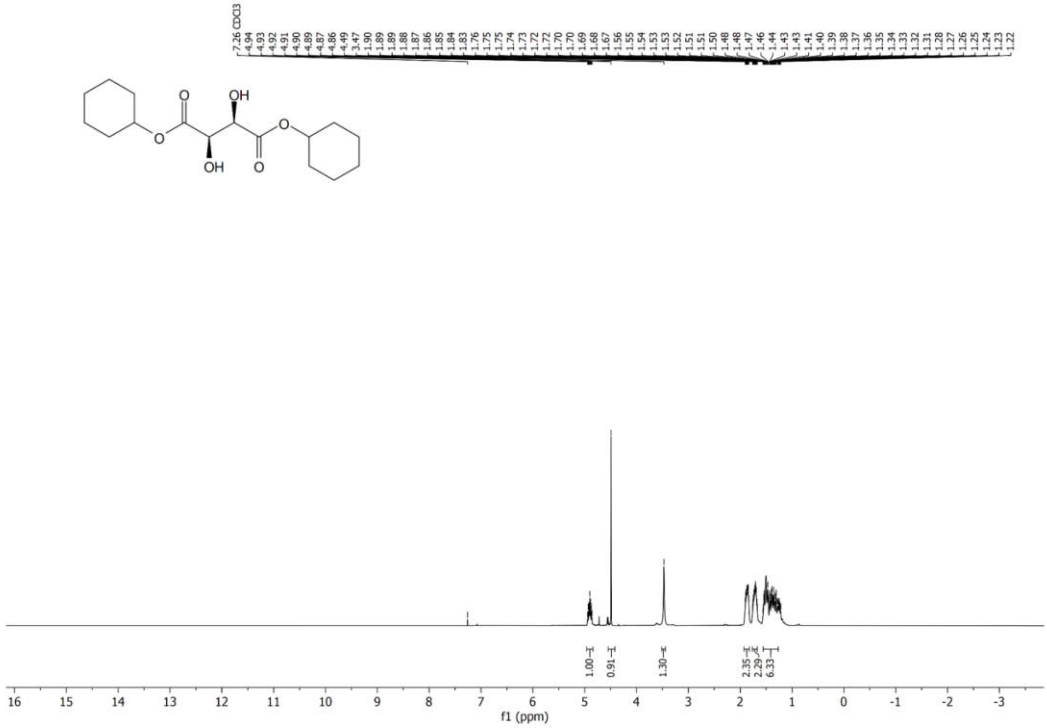

Figure S24: ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **7h**.

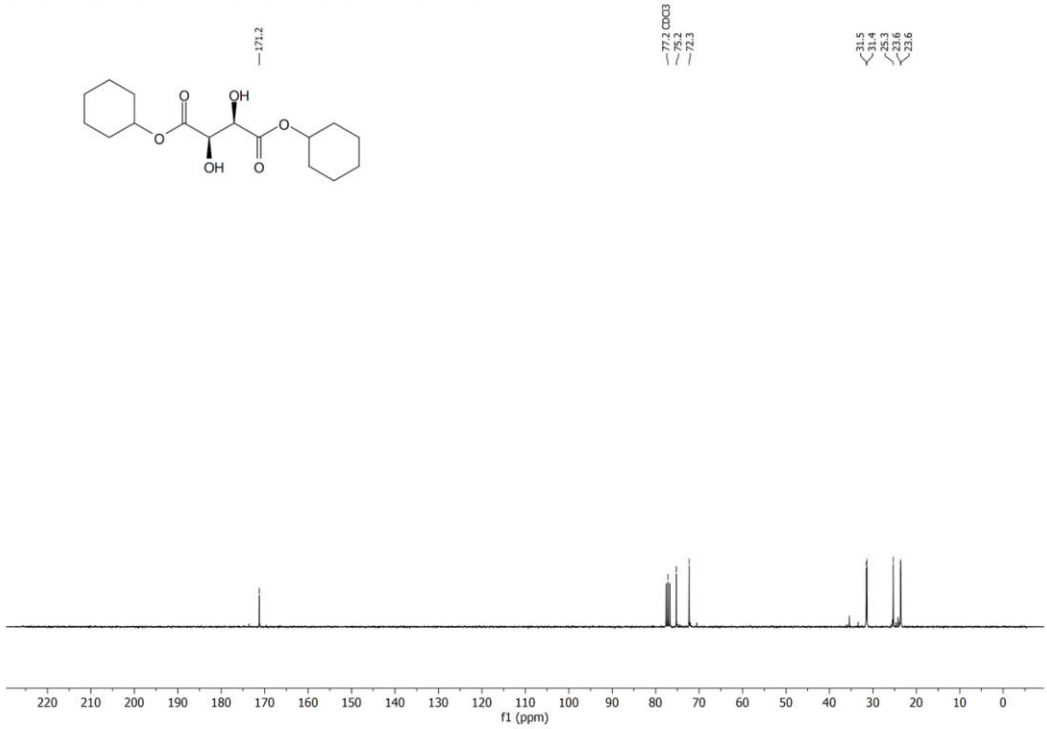

Figure S25: ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **7h**.

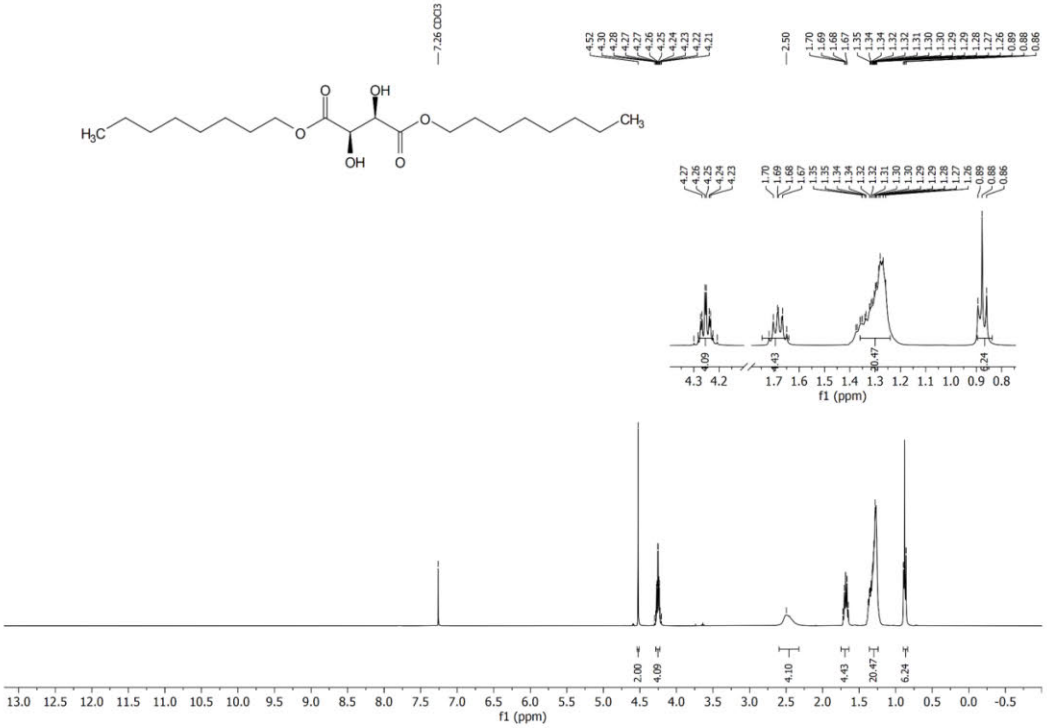

Figure S26: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **7i**.

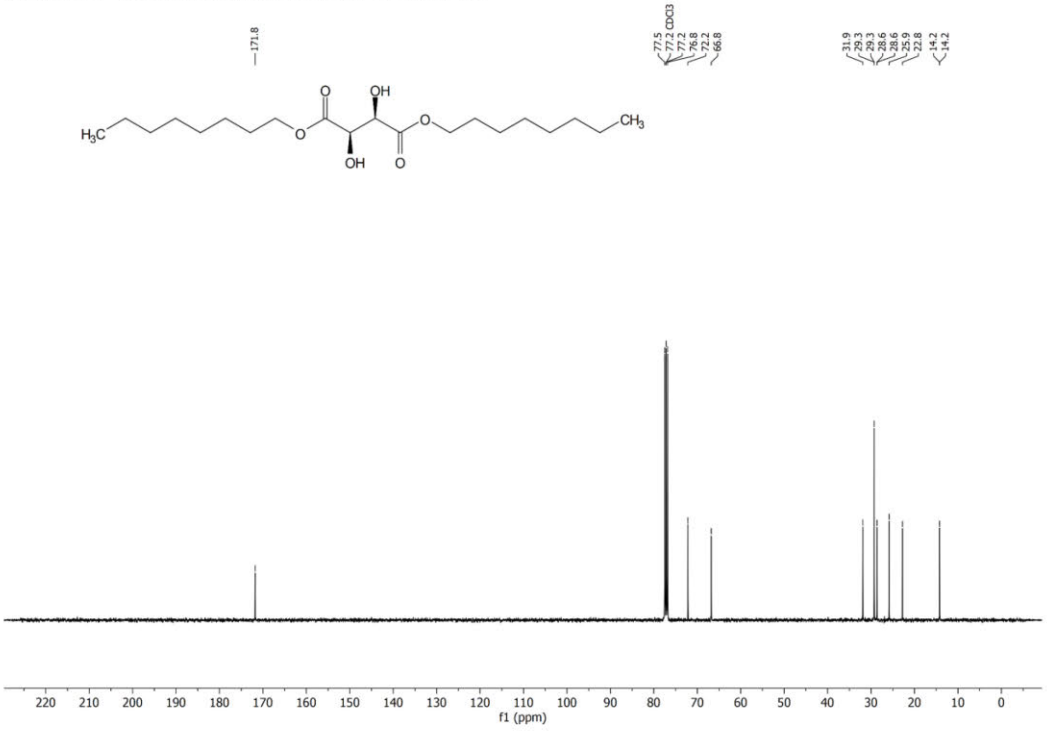

Figure S27: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **7i**.

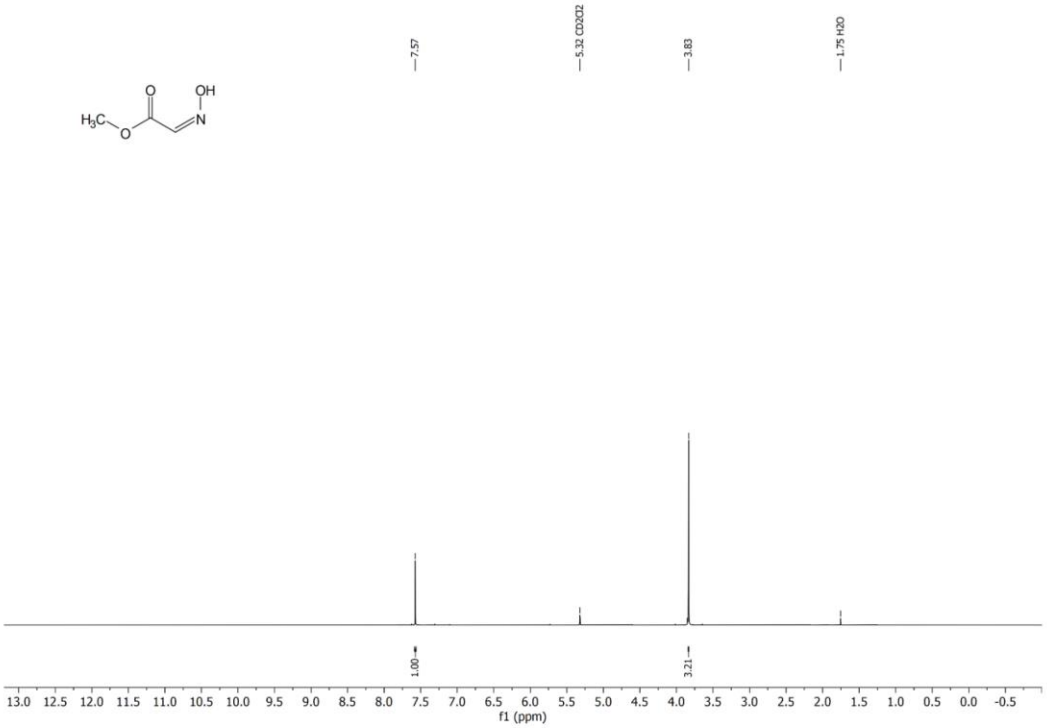

Figure S28: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **5a**.

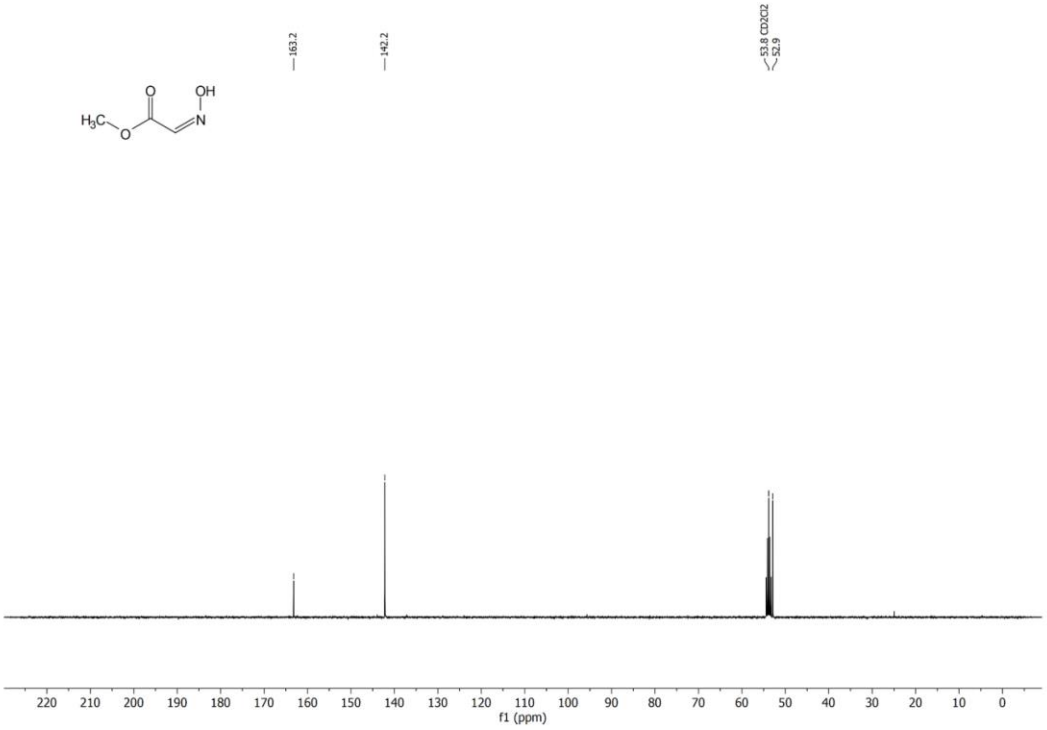

Figure S29: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **5a**.

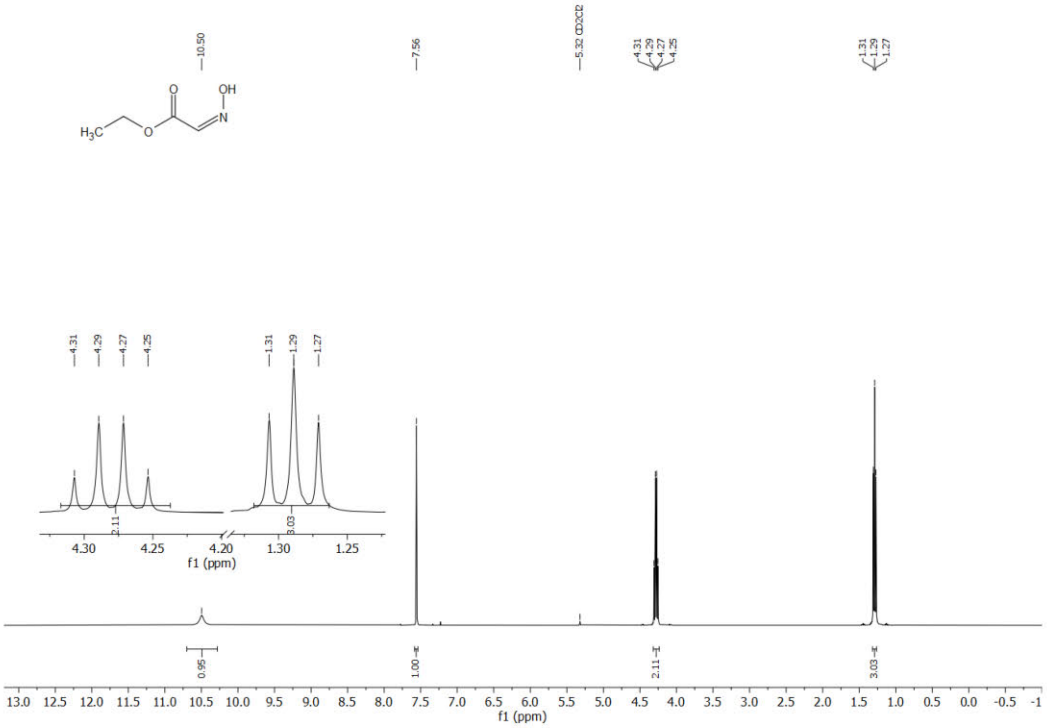

Figure S30: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **5b**.

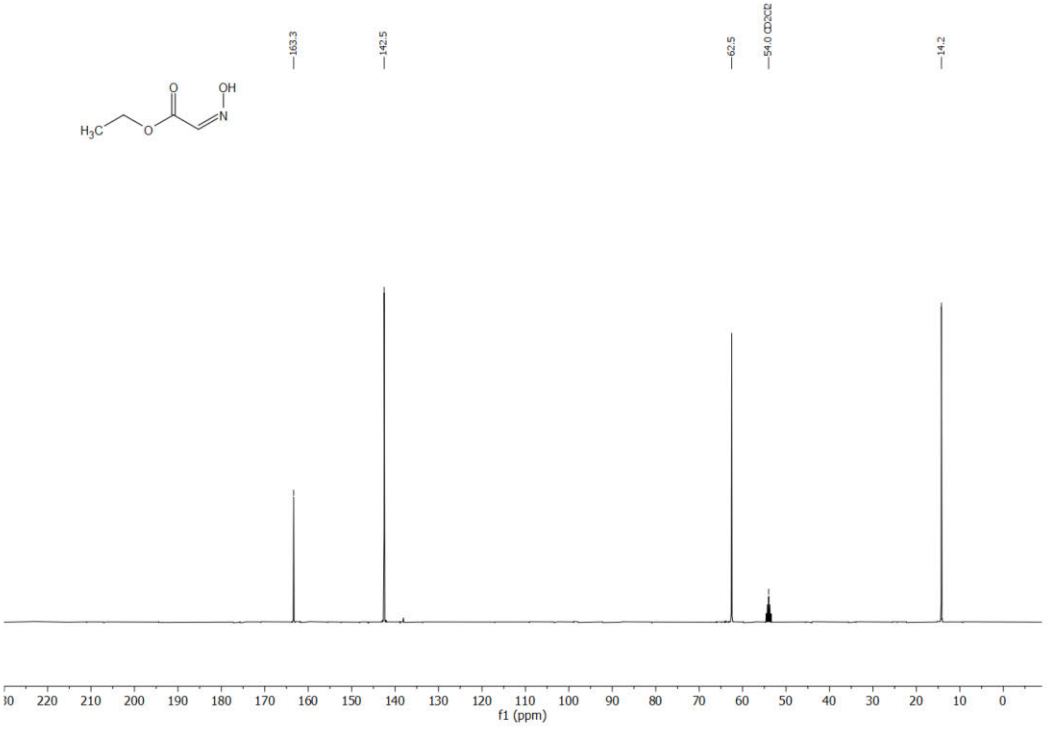

Figure S31: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **5b**.

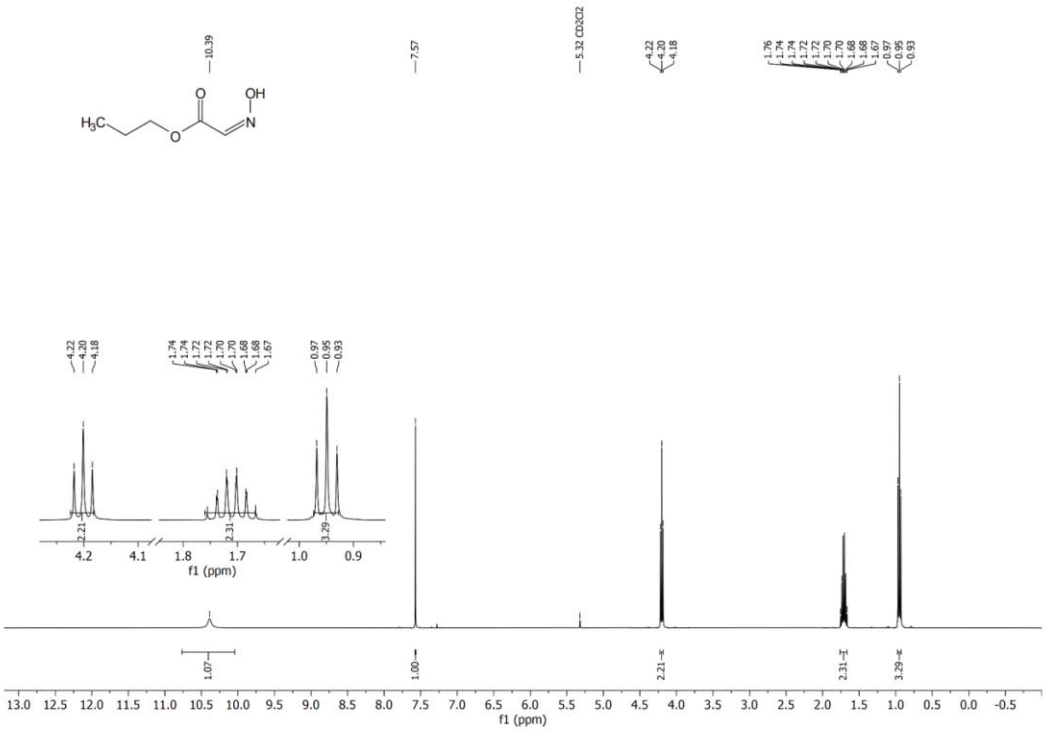

Figure S32: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **5c**.

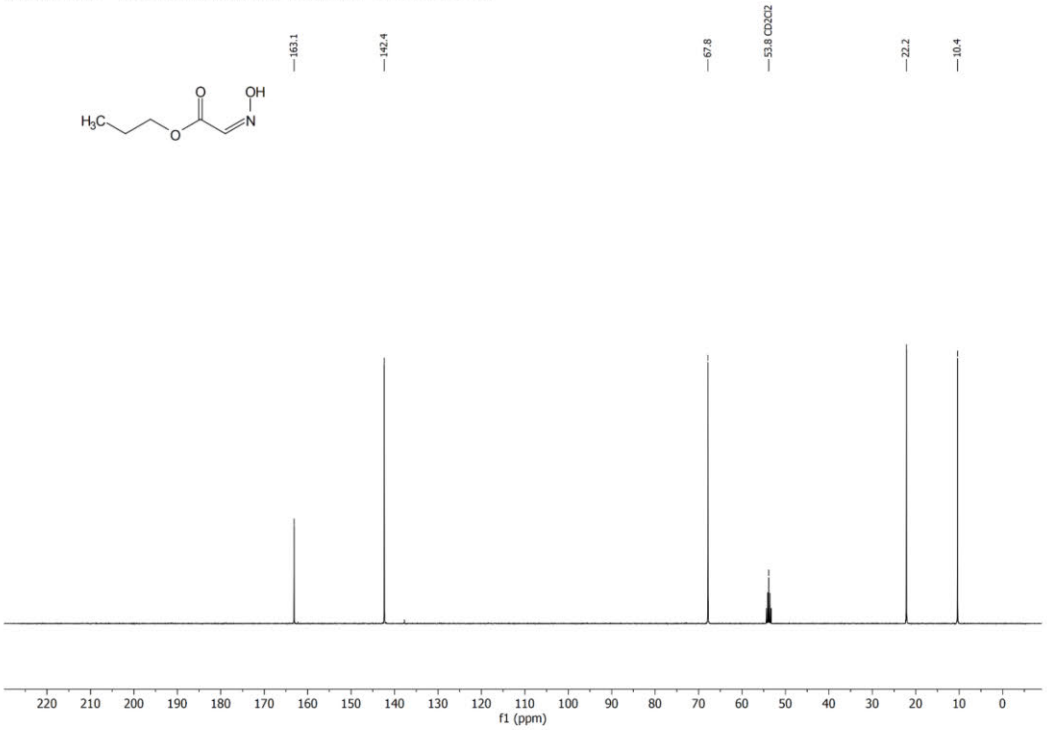

Figure S33: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **5c**.

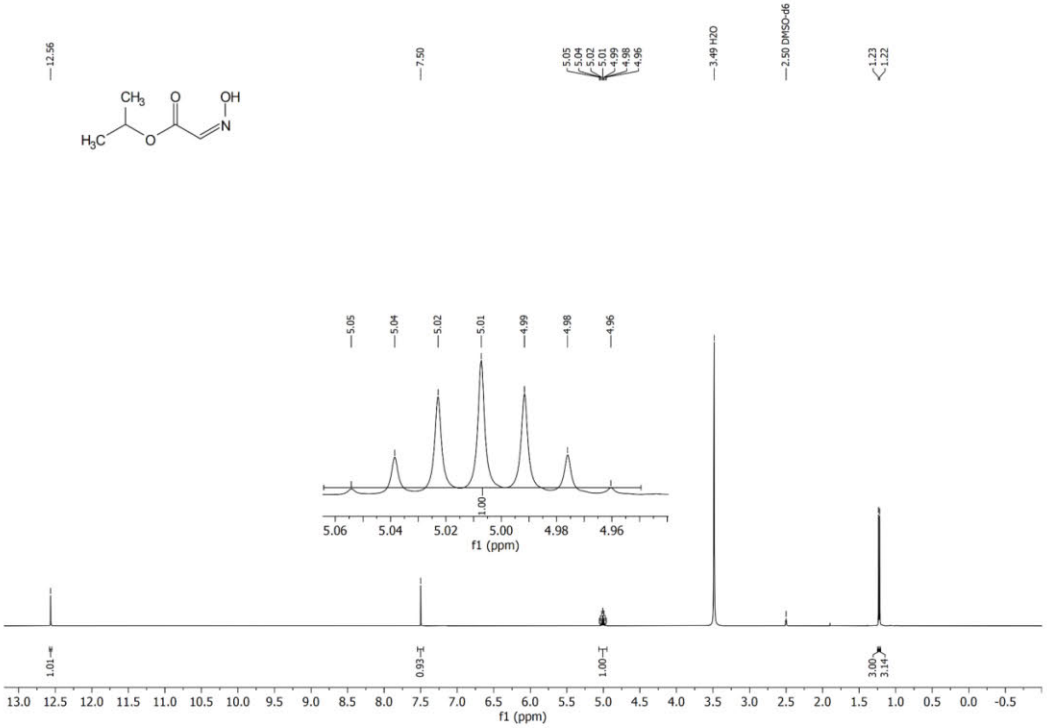

Figure S34: ^{1}H NMR spectrum (400 MHz, DMSO$_{d6}$) of **5d**.

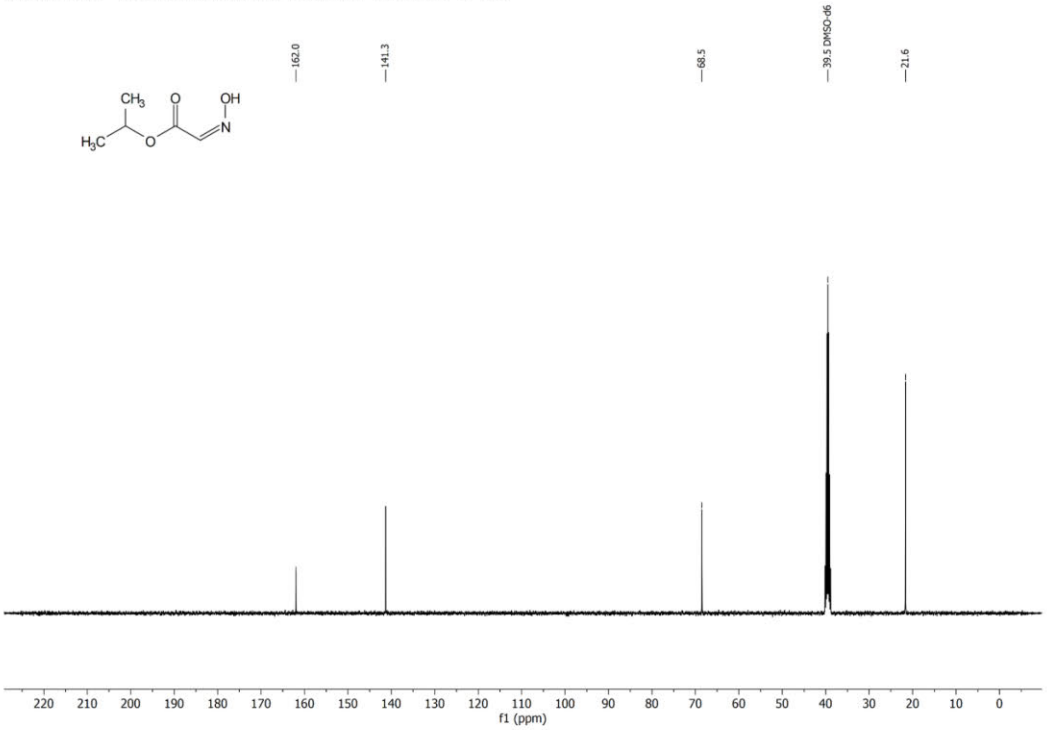

Figure S35: ^{13}C NMR spectrum (101 MHz, DMSO$_{d6}$) of **5d**.

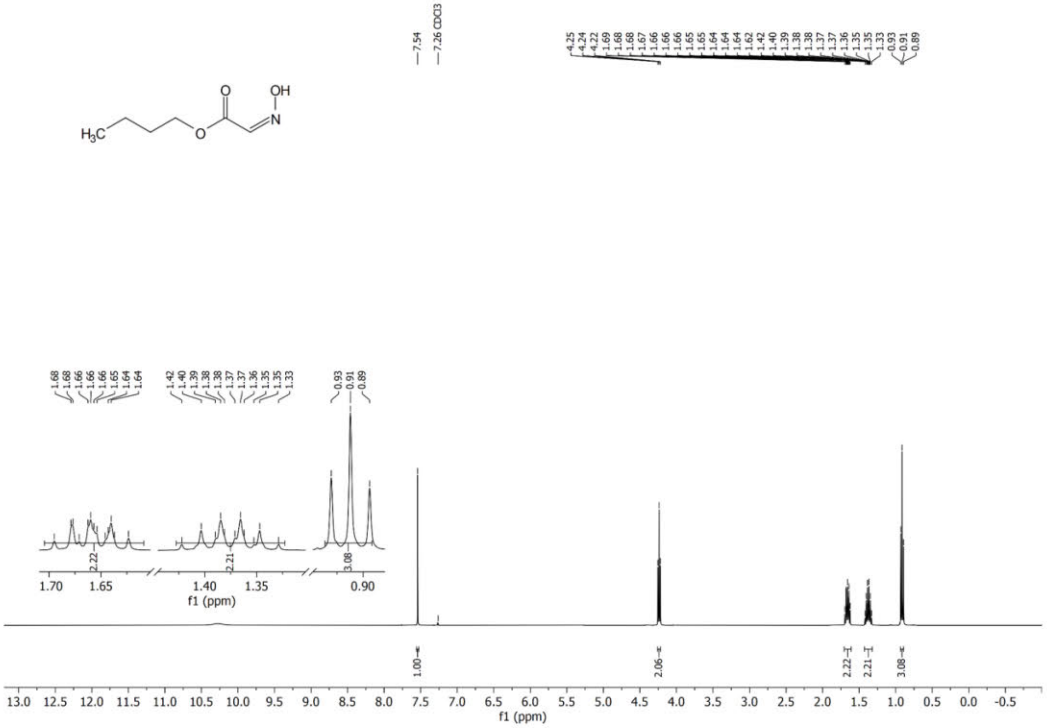

Figure S36: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5e**.

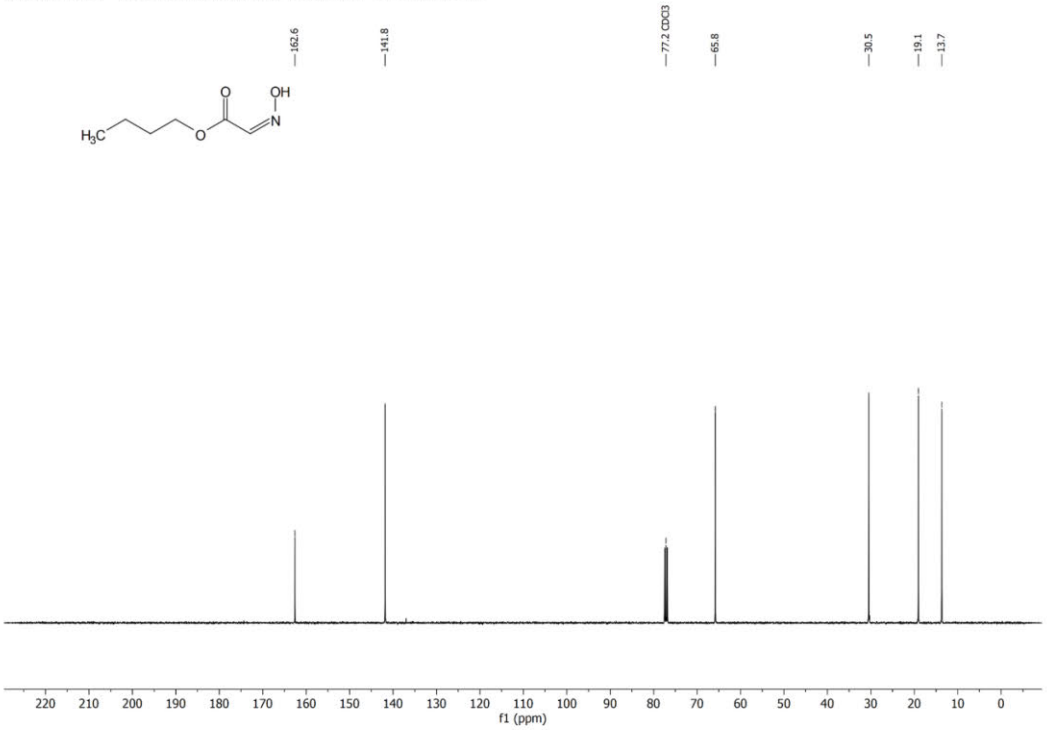

Figure S37: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **5e**.

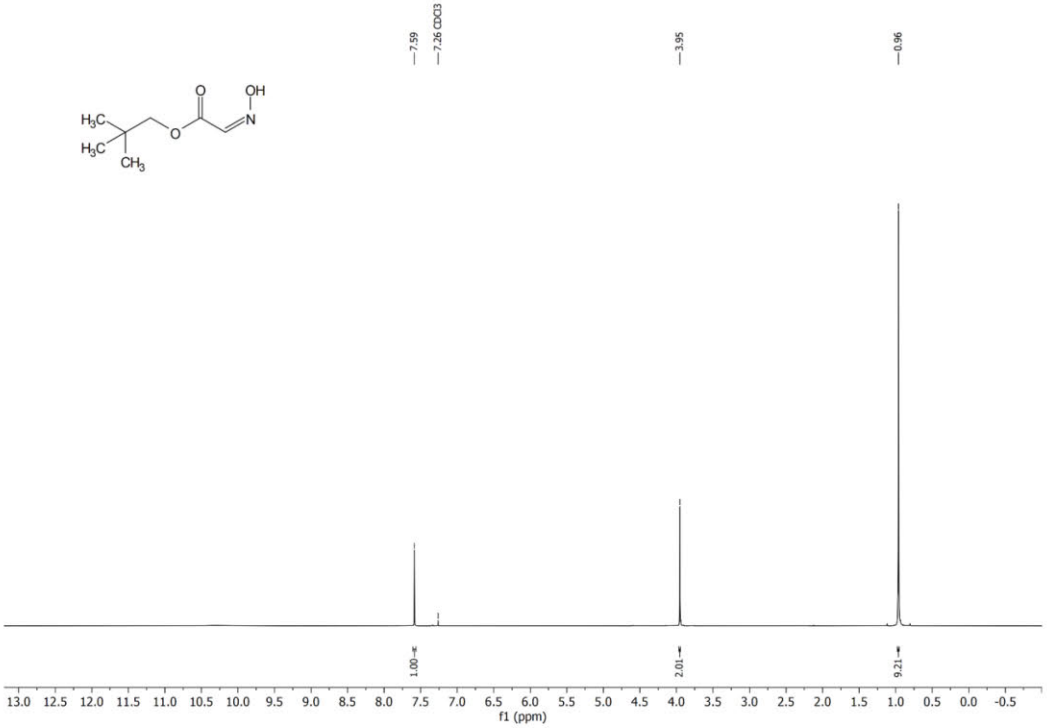

Figure S38: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5f**.

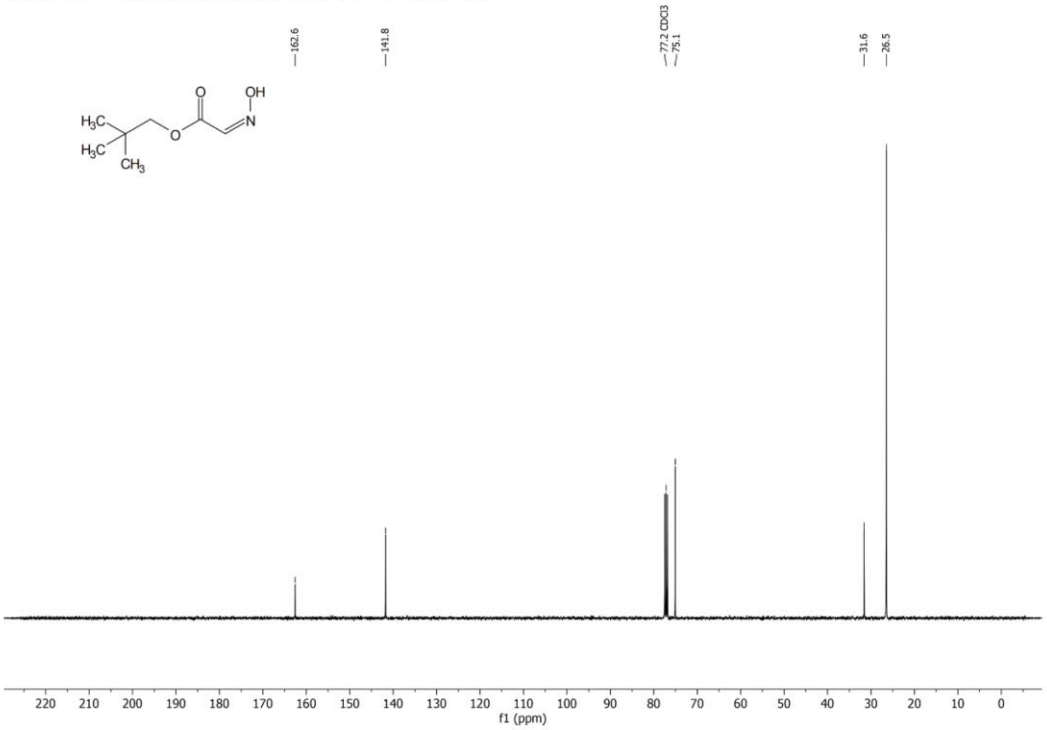

Figure S39: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **5f**.

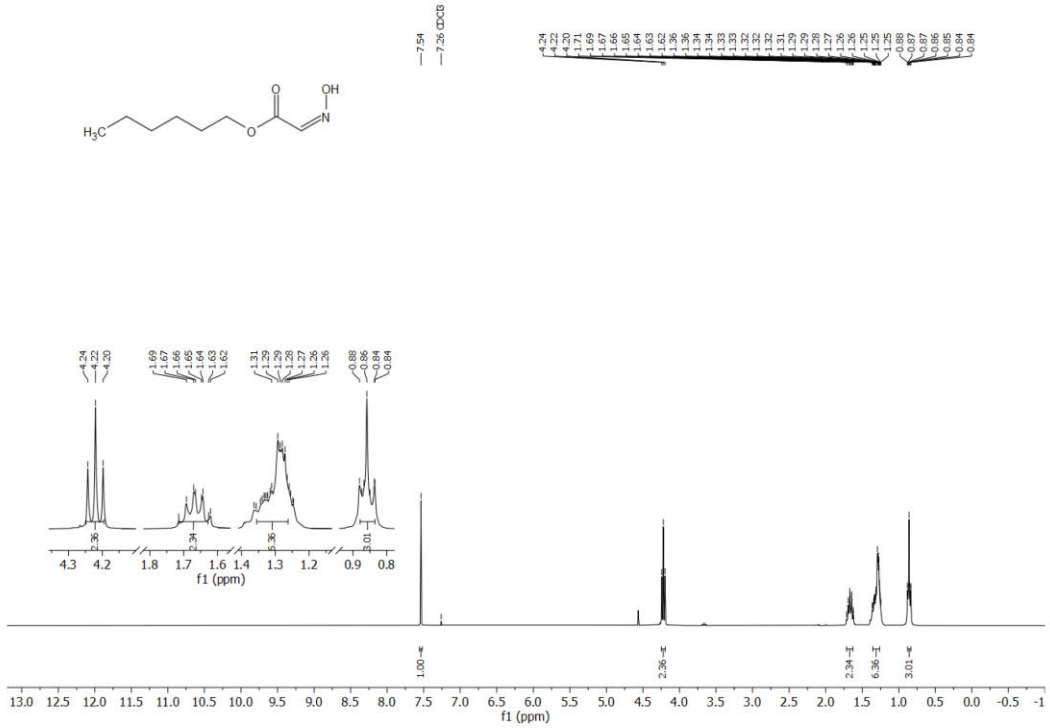

Figure S40: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5g**.

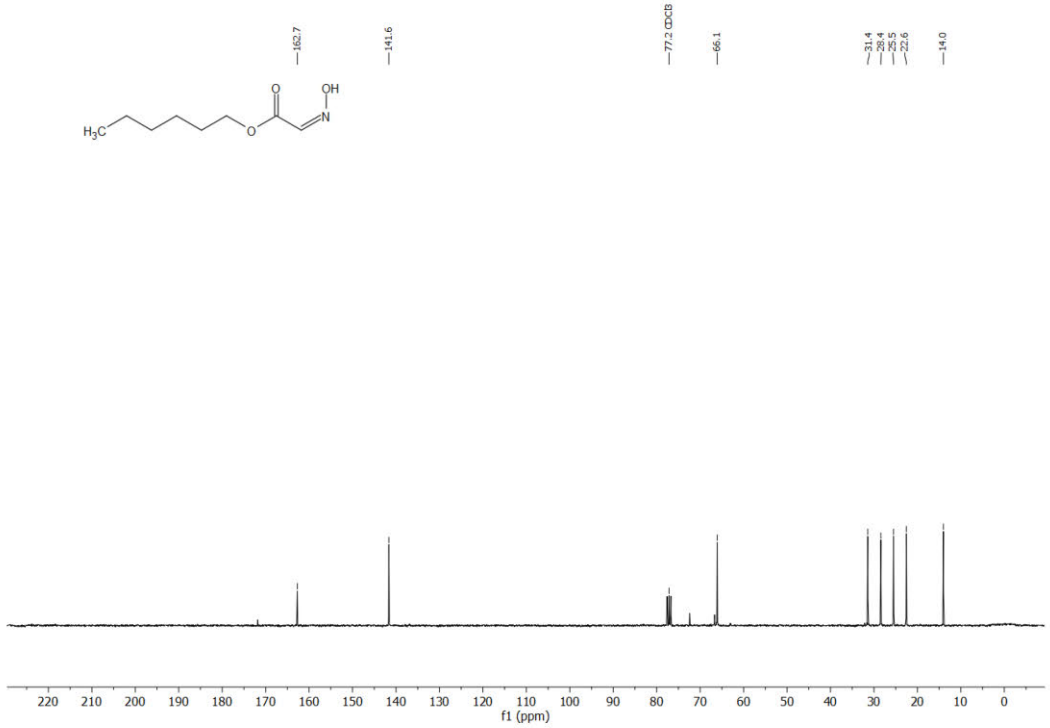

Figure S41: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **5g**.

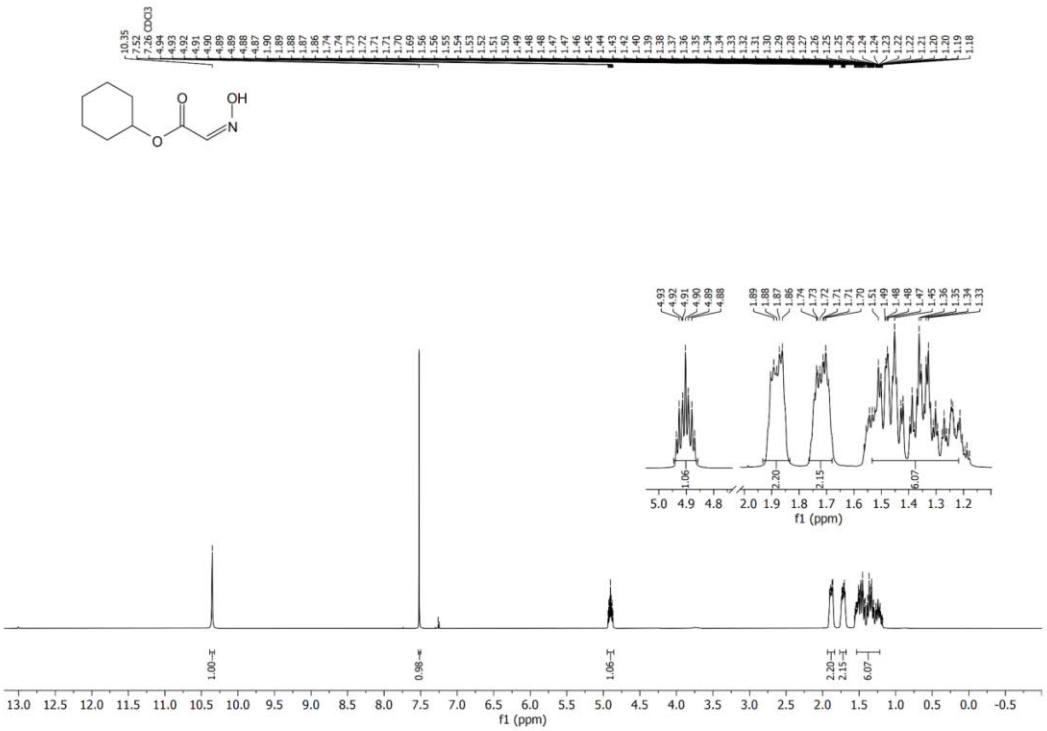

Figure S42: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5h**.

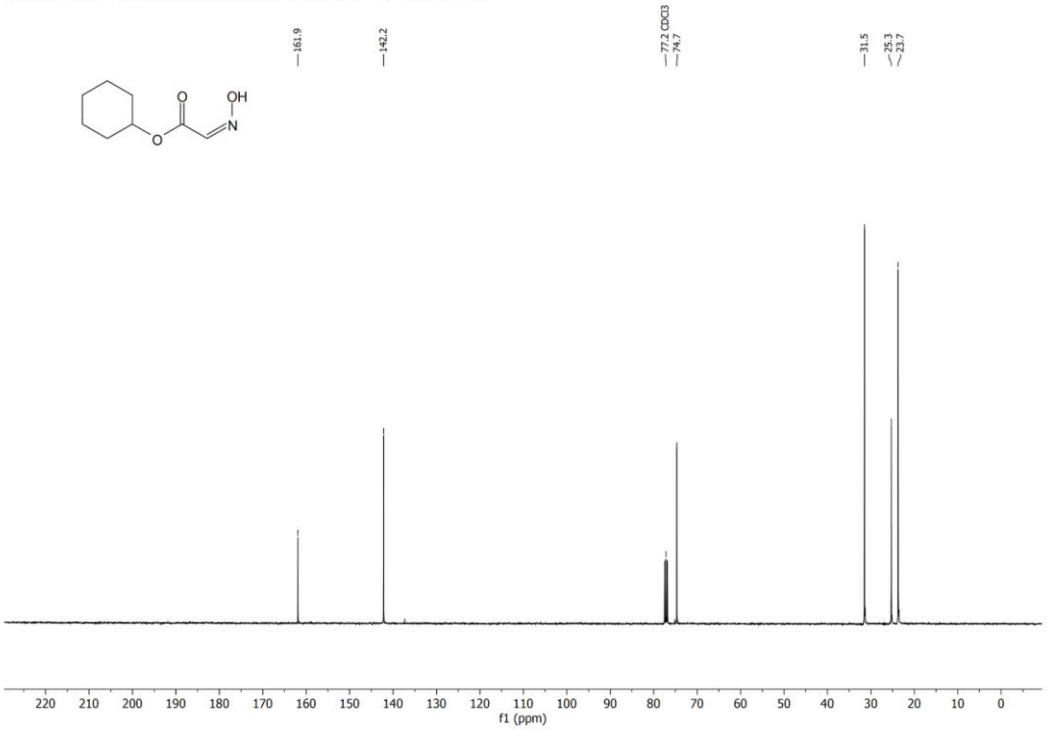

Figure S43: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **5h**.

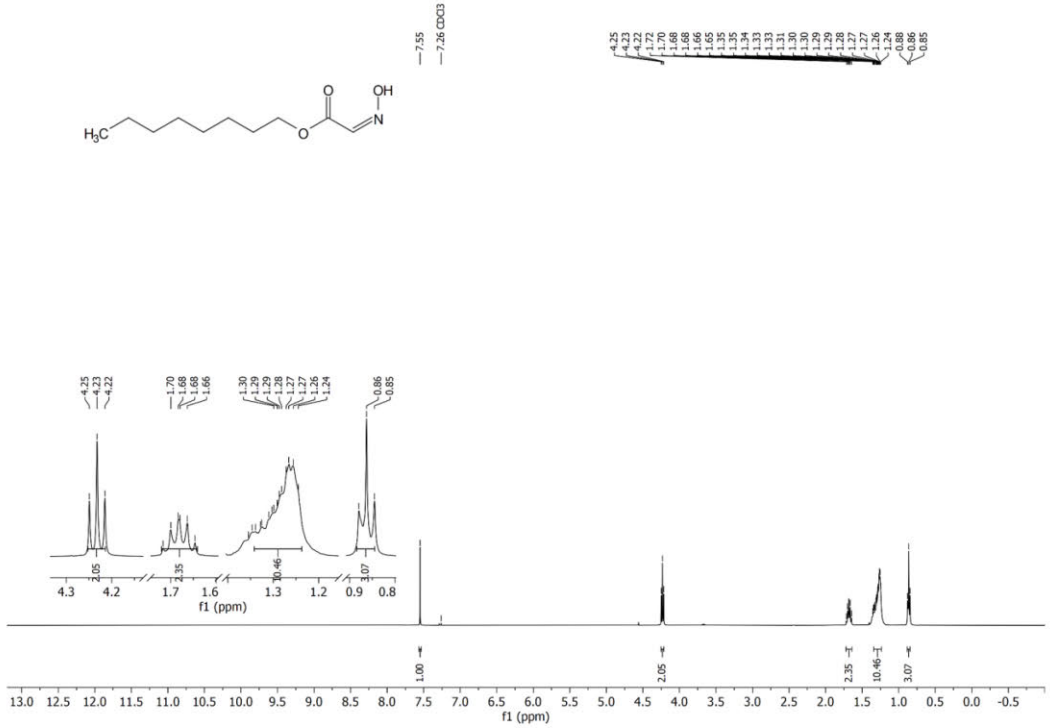

Figure S44: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **5i**.

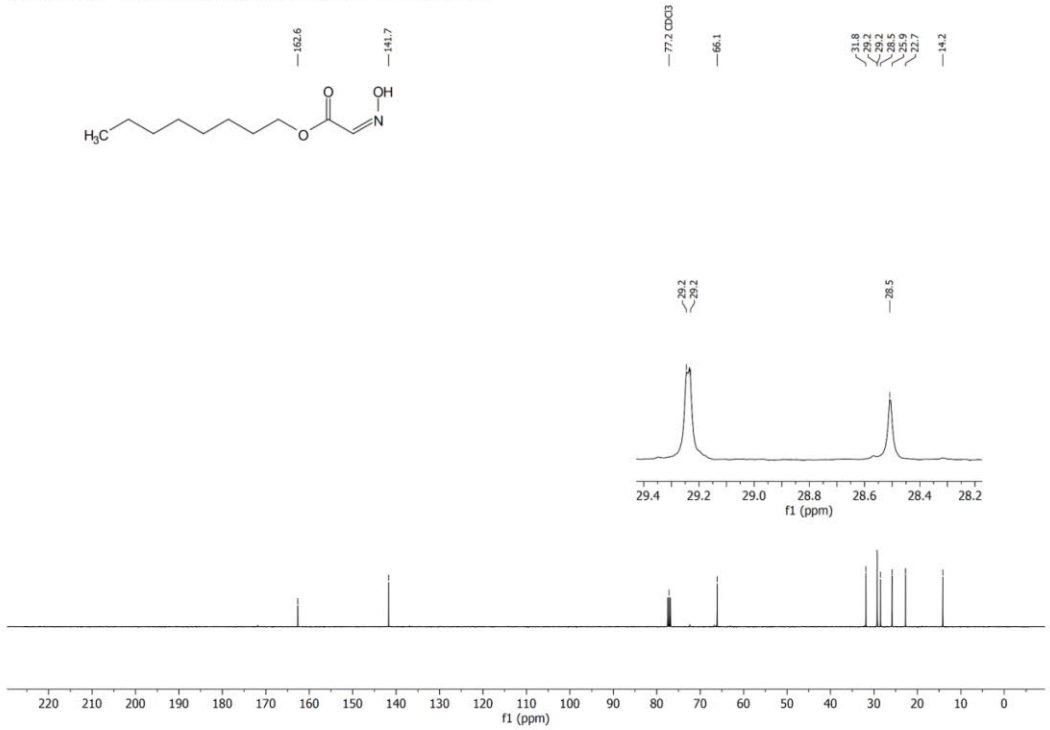

Figure S45: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **5i**.

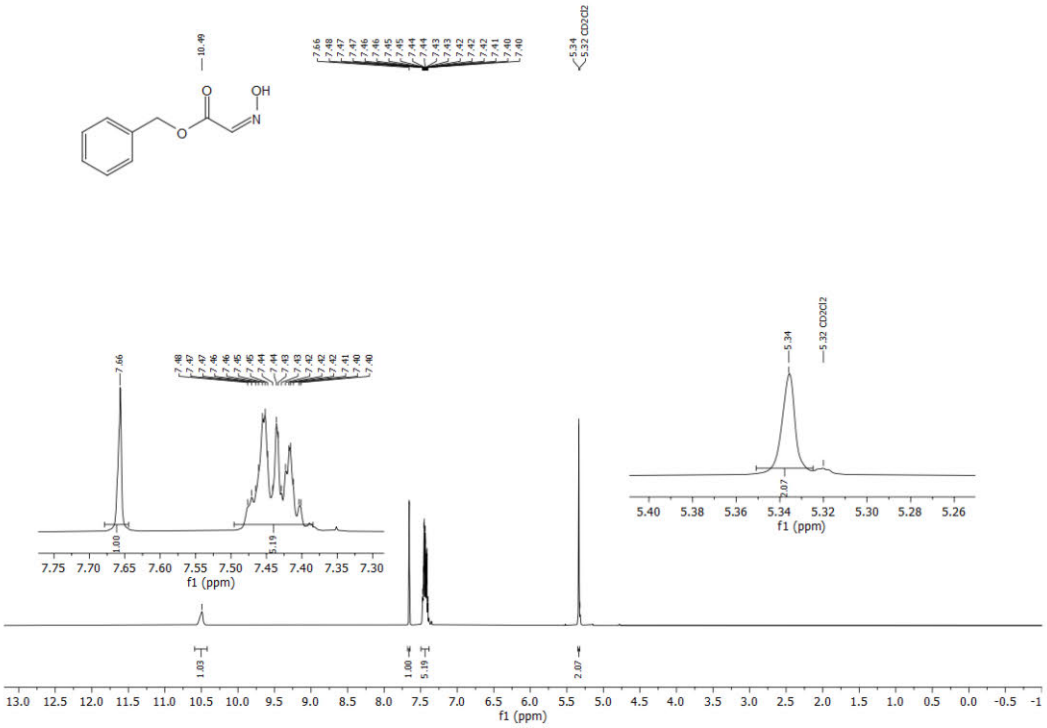

Figure S46: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **5j**.

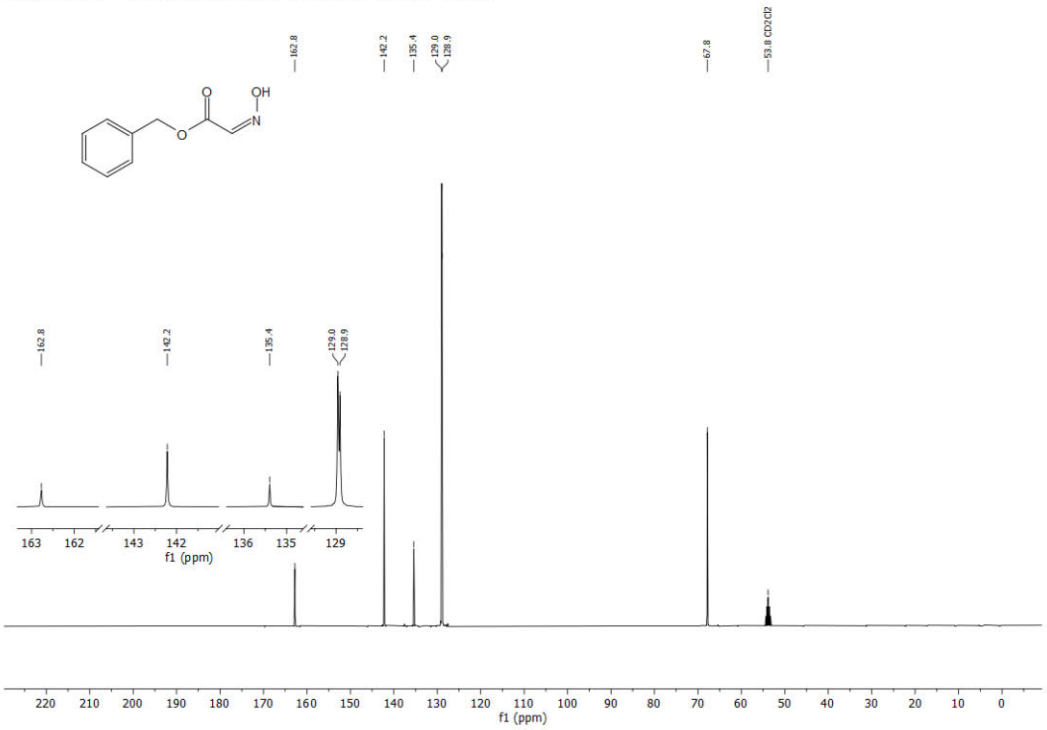

Figure S47: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **5j**.

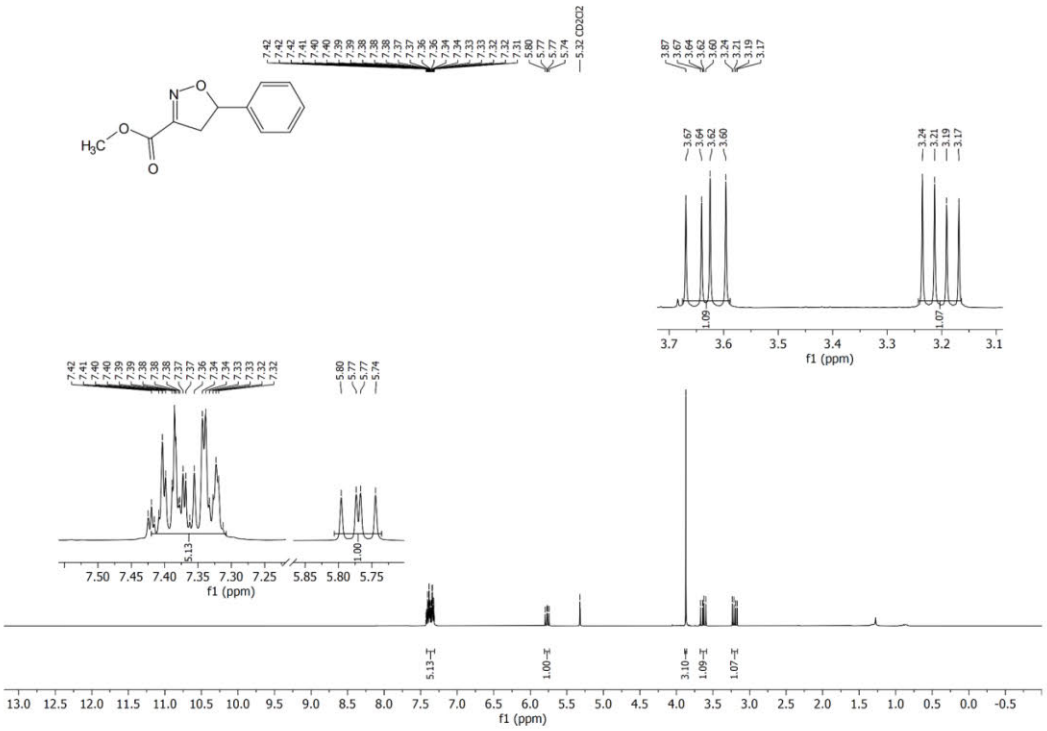

Figure S48: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6a**.

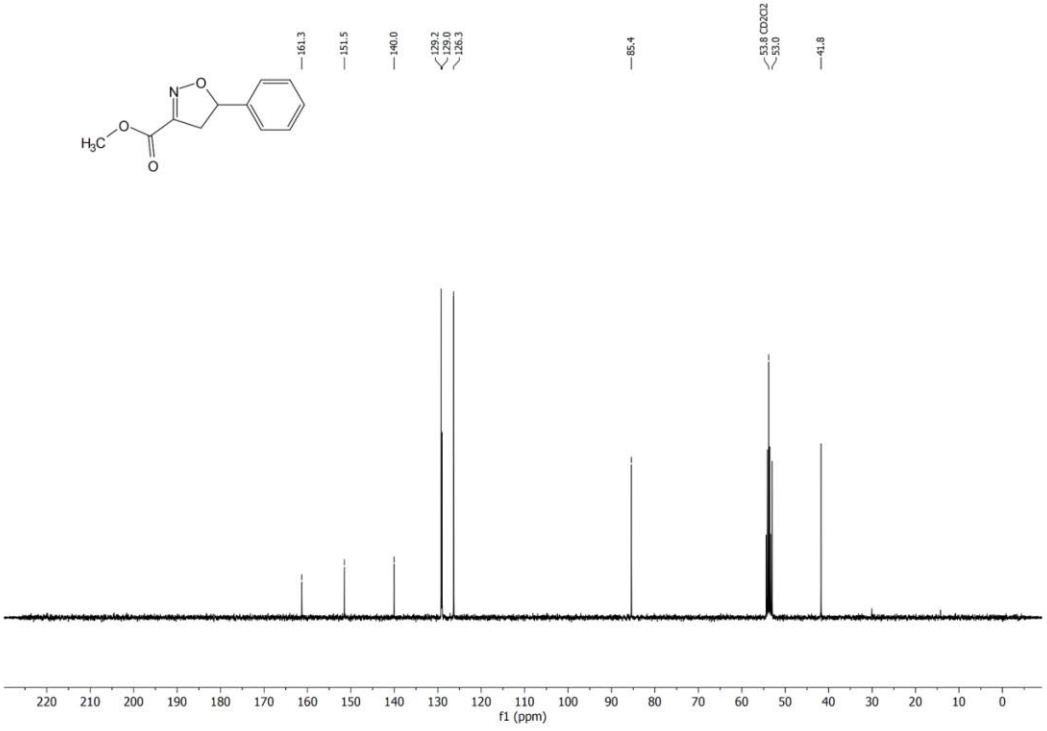

Figure S49: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6a**.

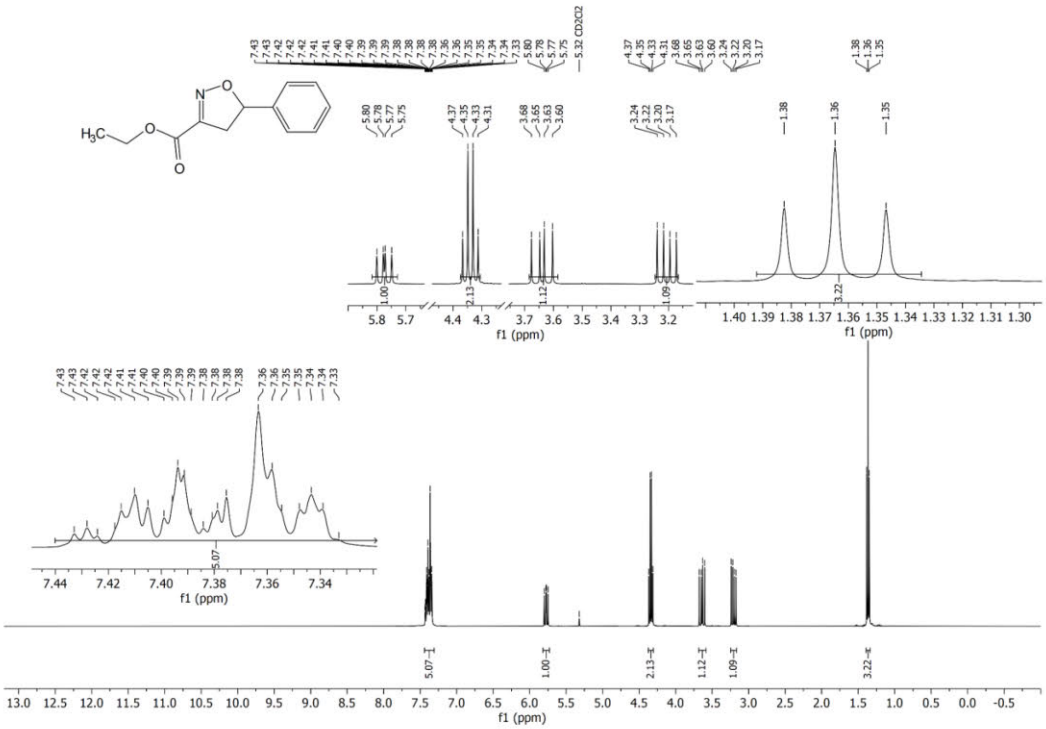

Figure S50: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6b**.

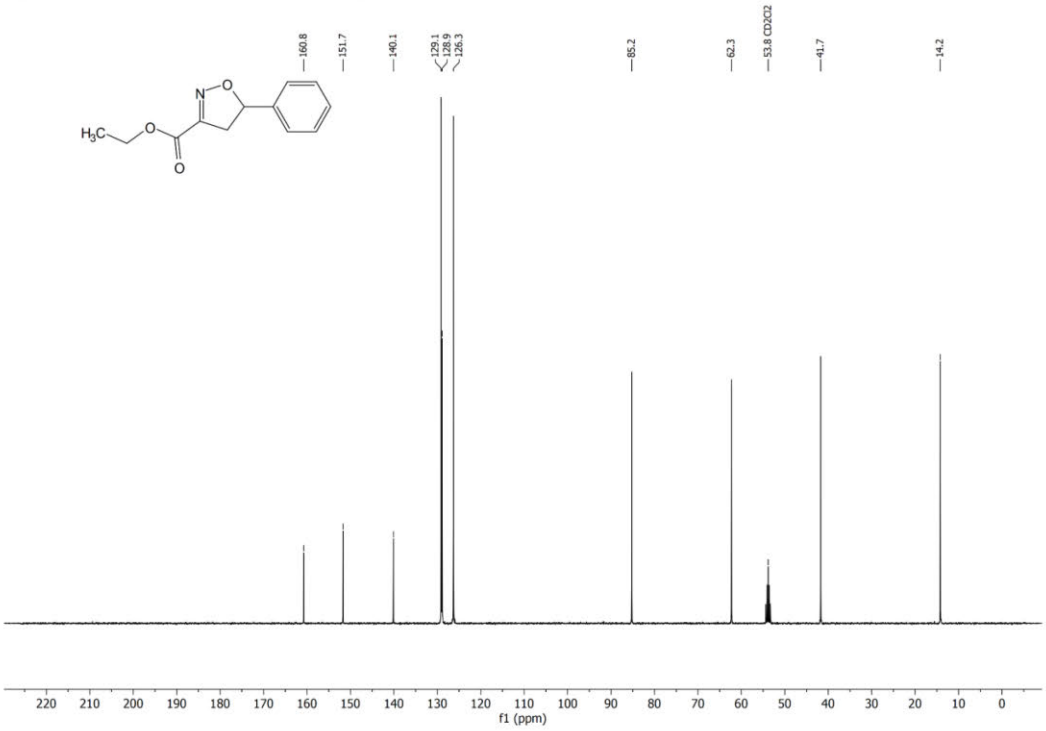

Figure S51: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6b**.

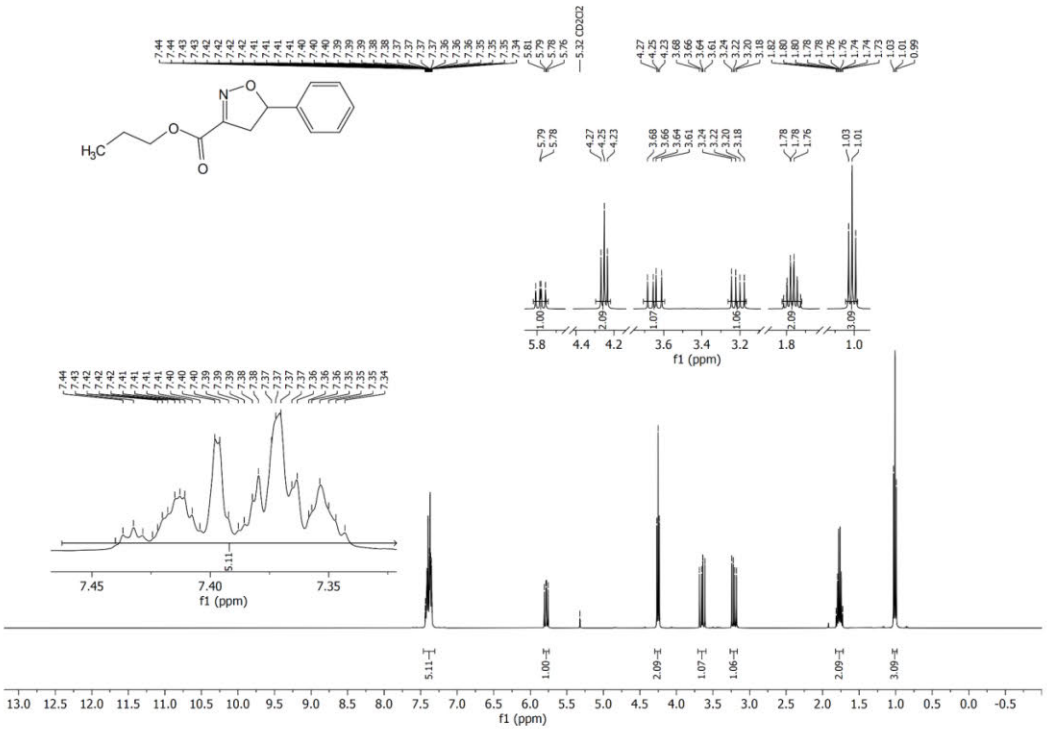

Figure S52: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6c**.

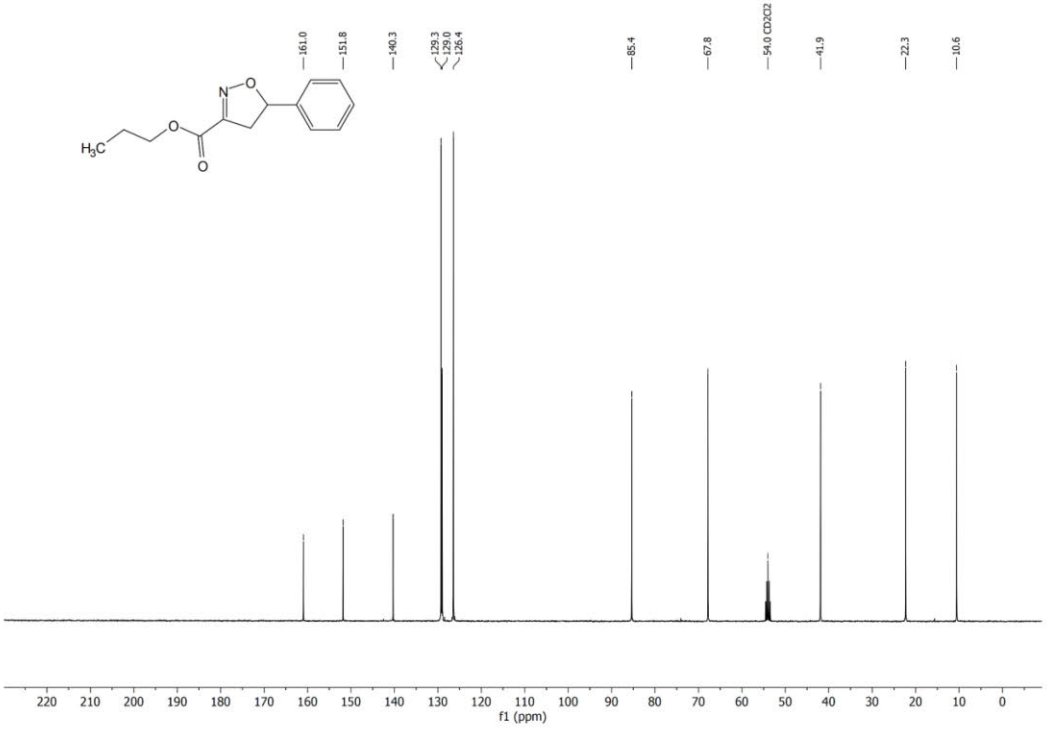

Figure S53: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6c**.

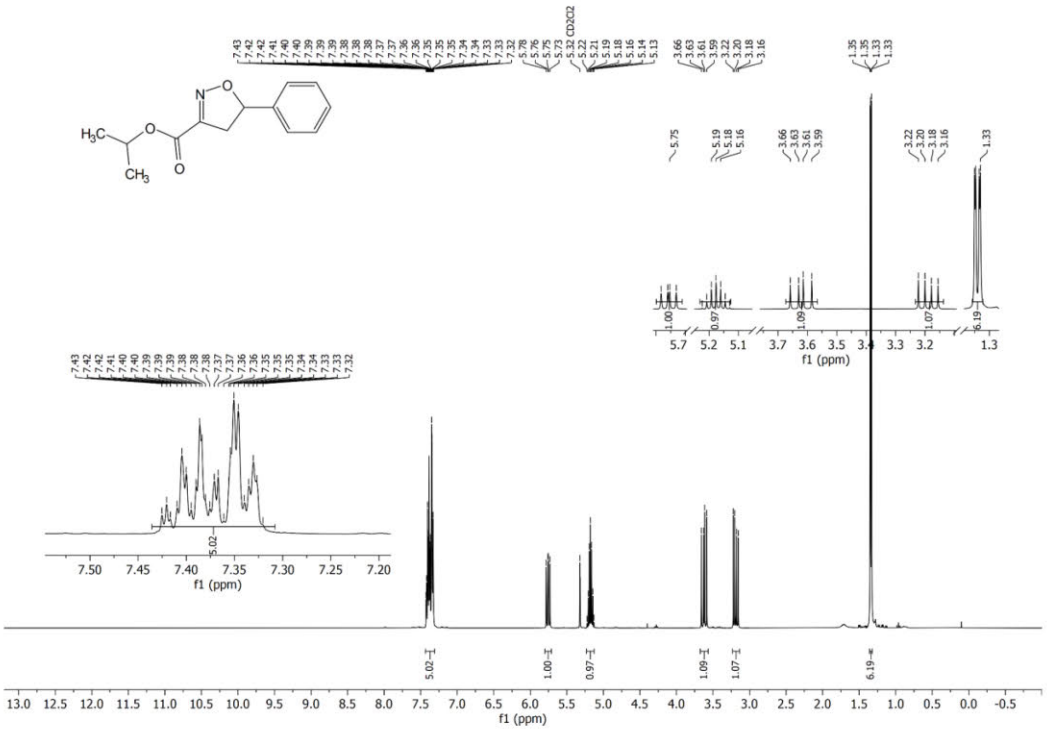

Figure S54: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6d**.

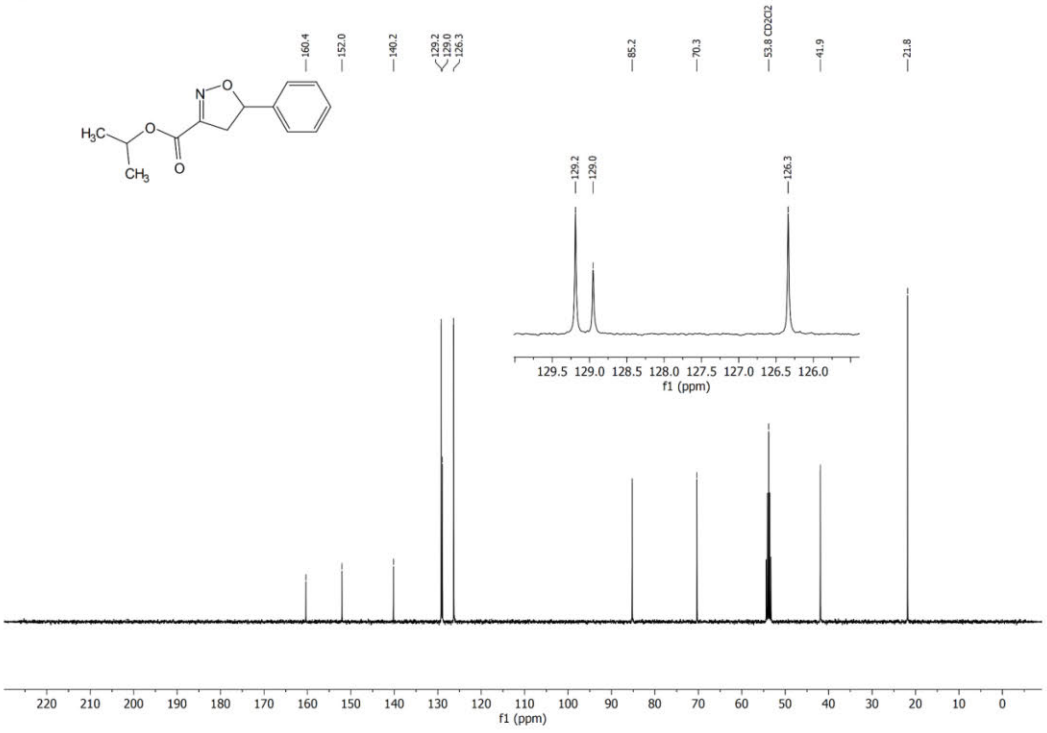

Figure S55: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6d**.

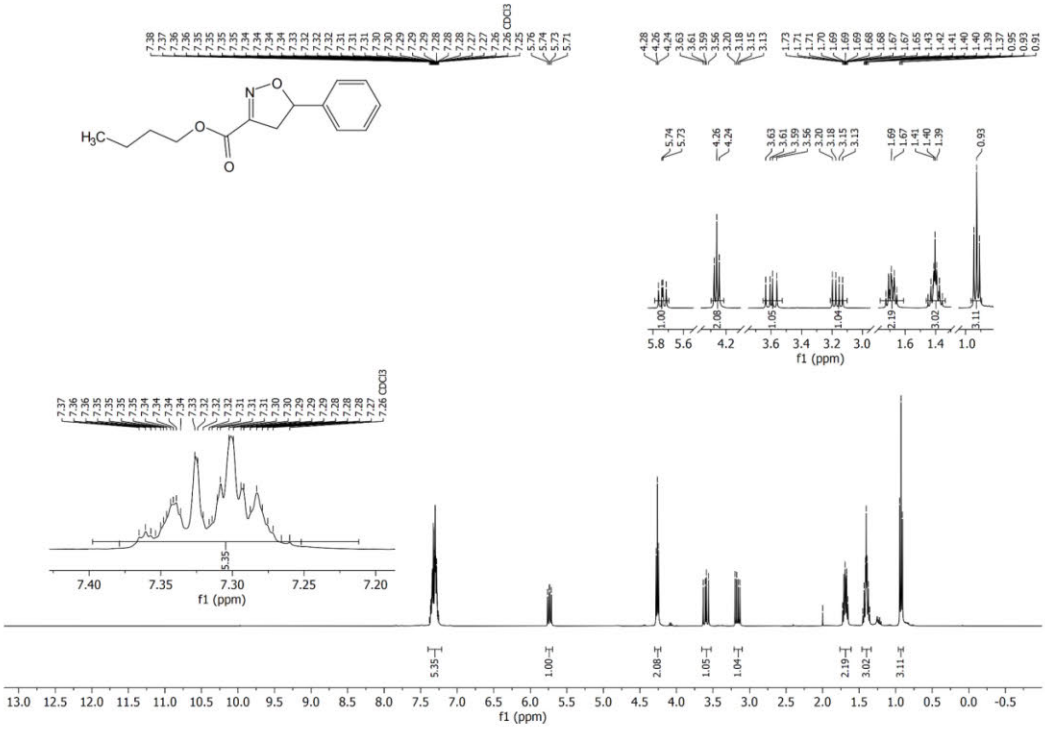

Figure S56: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6e**.

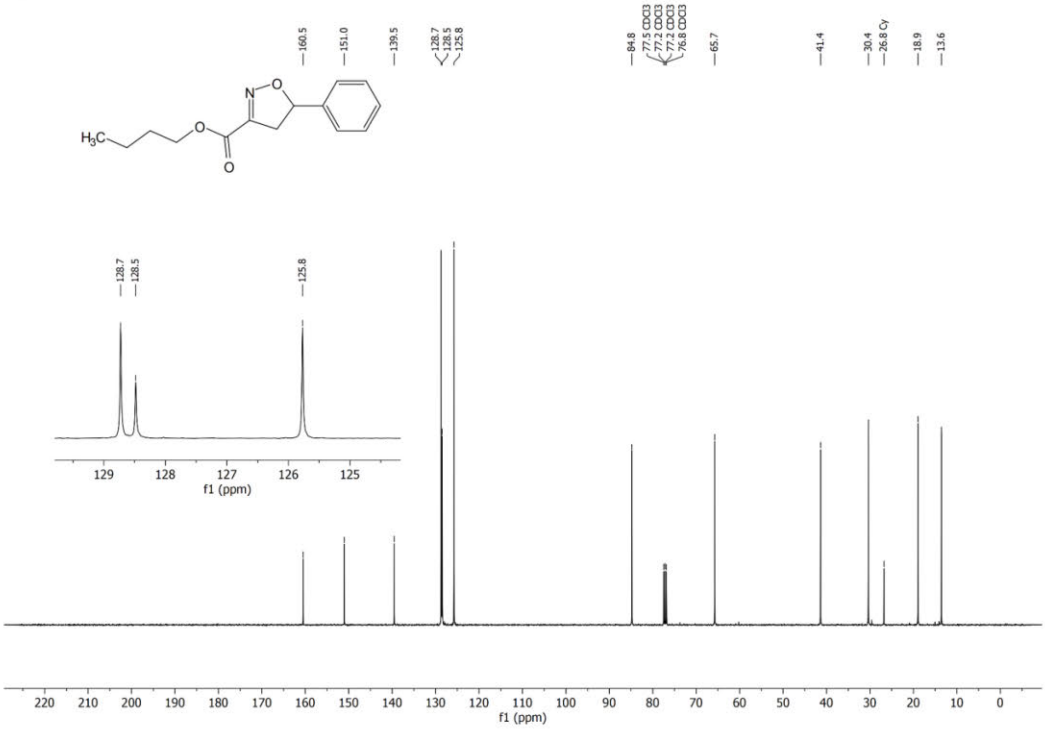

Figure S57: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6d**.

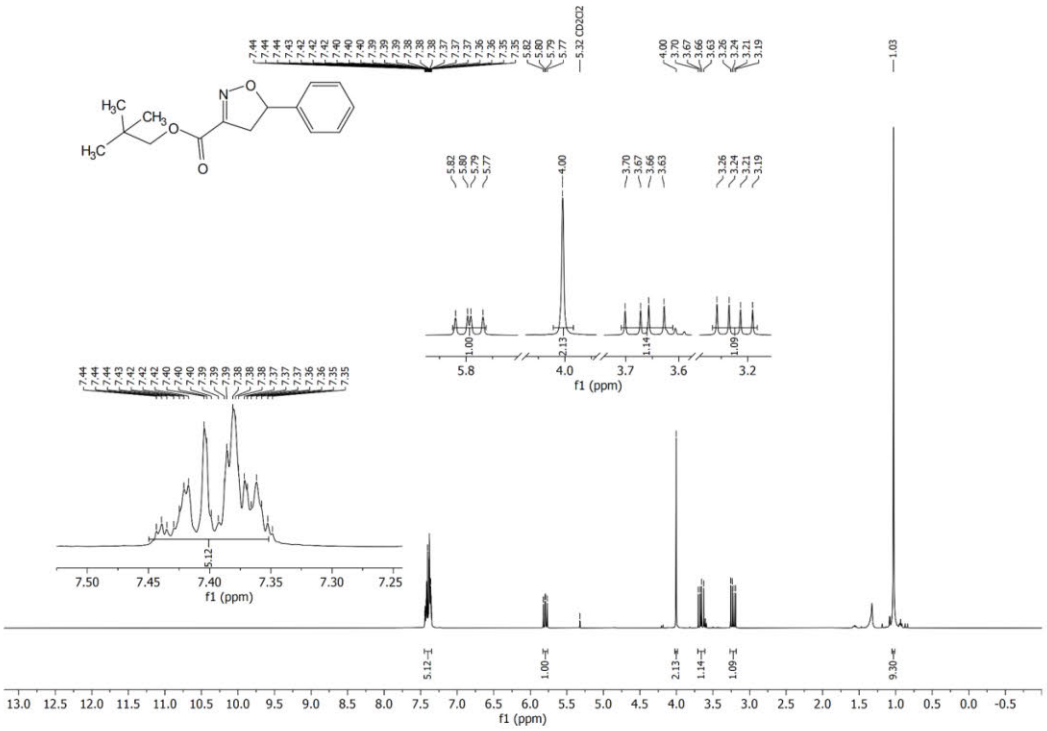

Figure S58: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6f**.

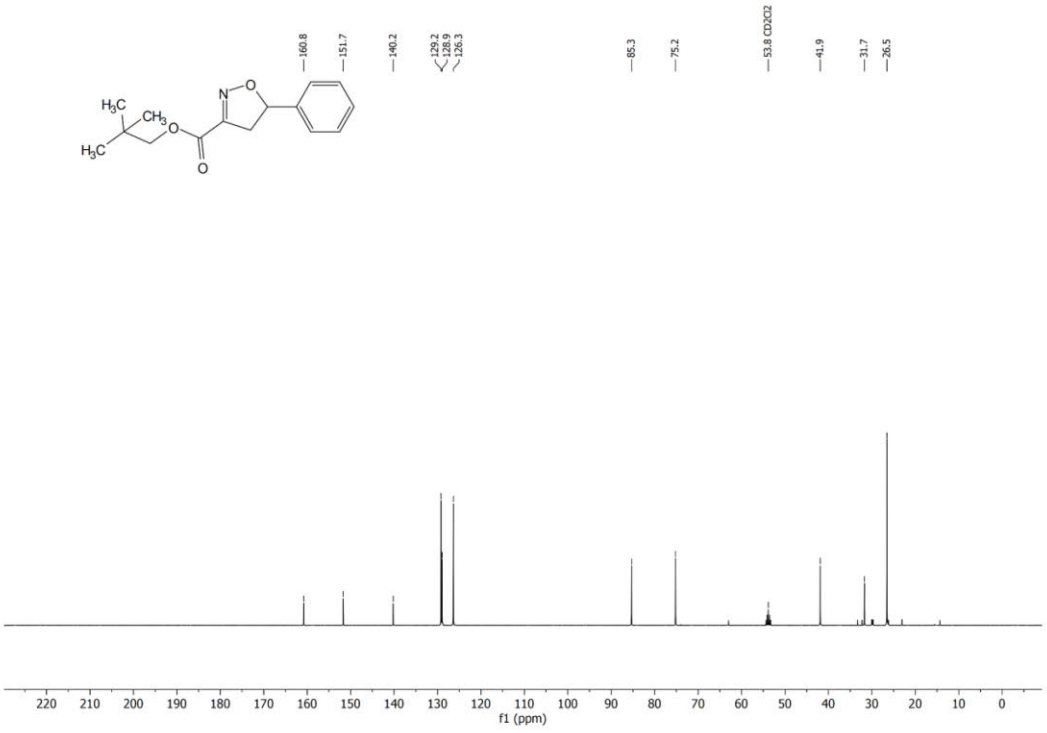

Figure S59: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6f**.

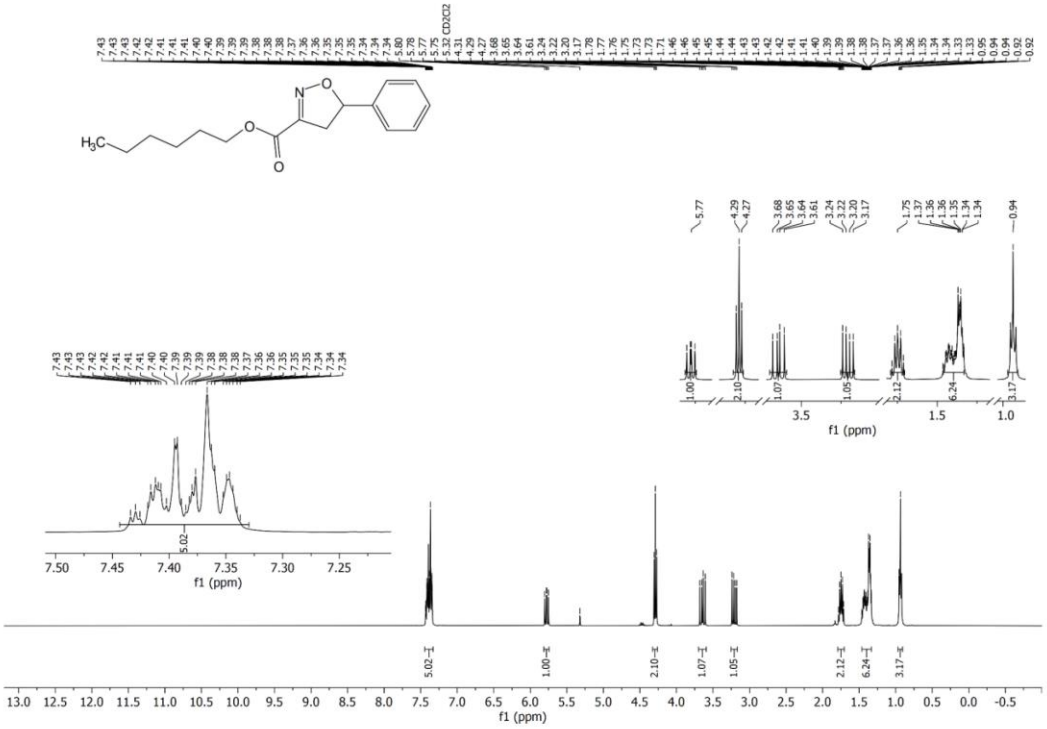

Figure S60: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6g**.

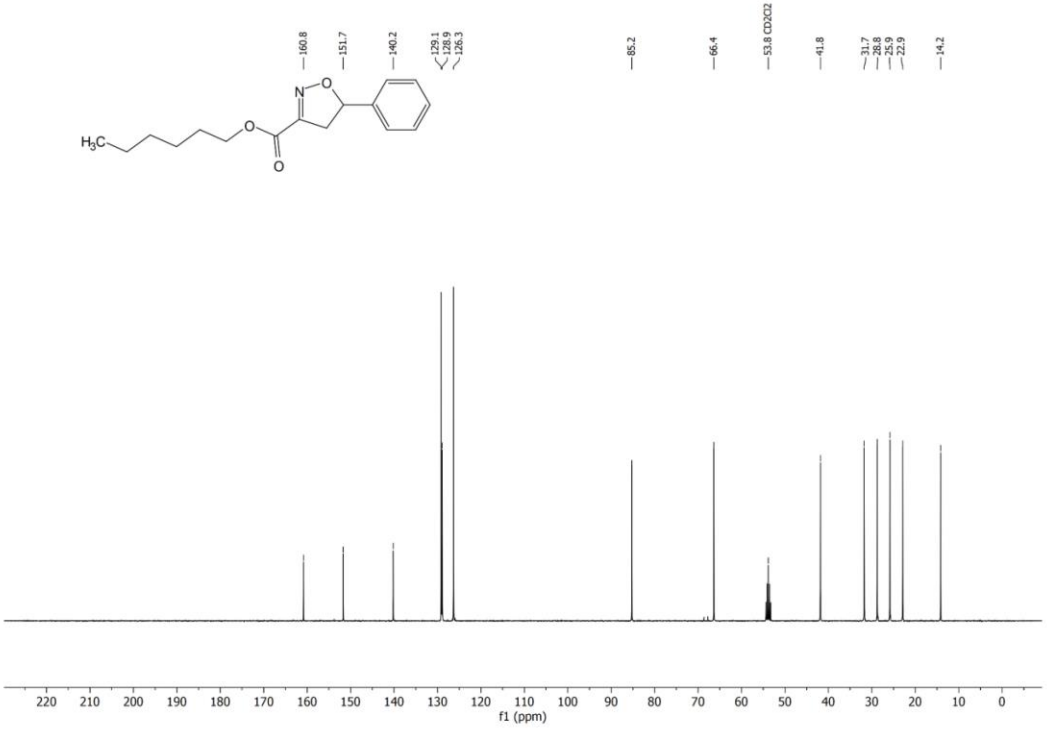

Figure S61: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6g**.

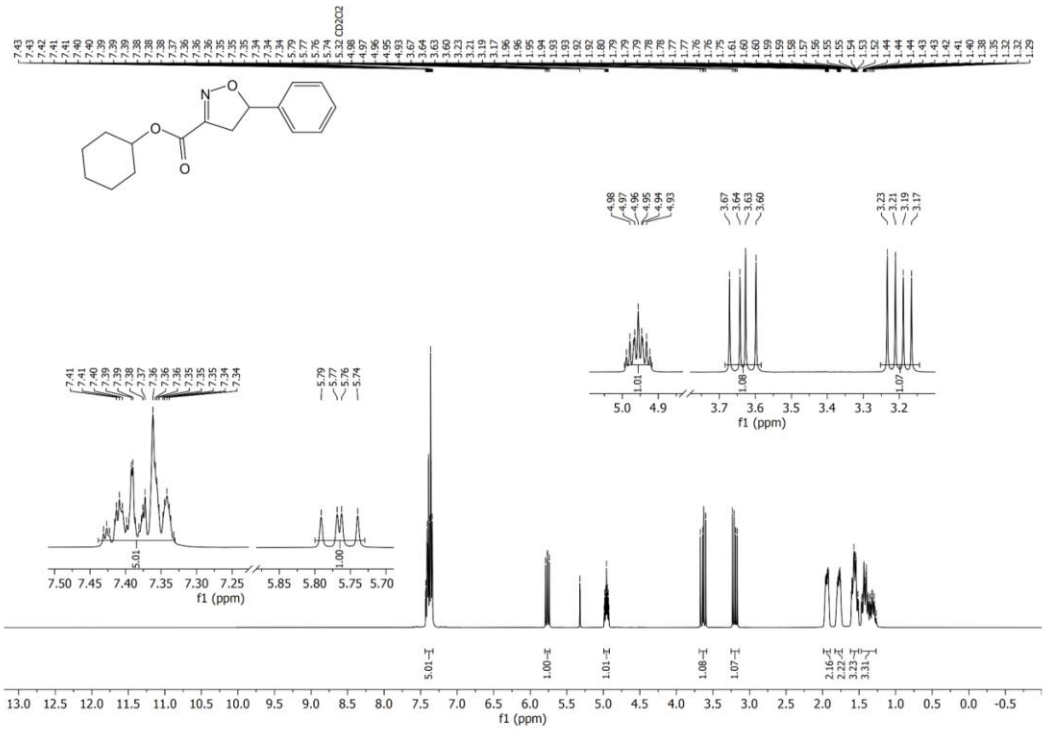

Figure S62: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6h**.

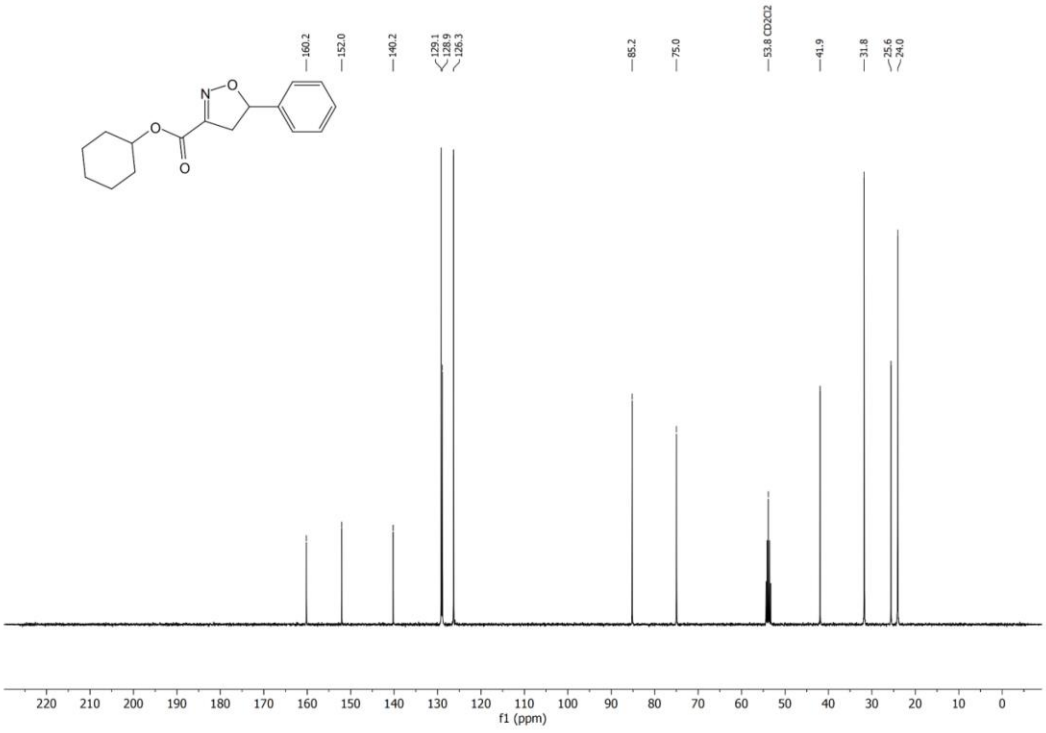

Figure S63: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6h**.

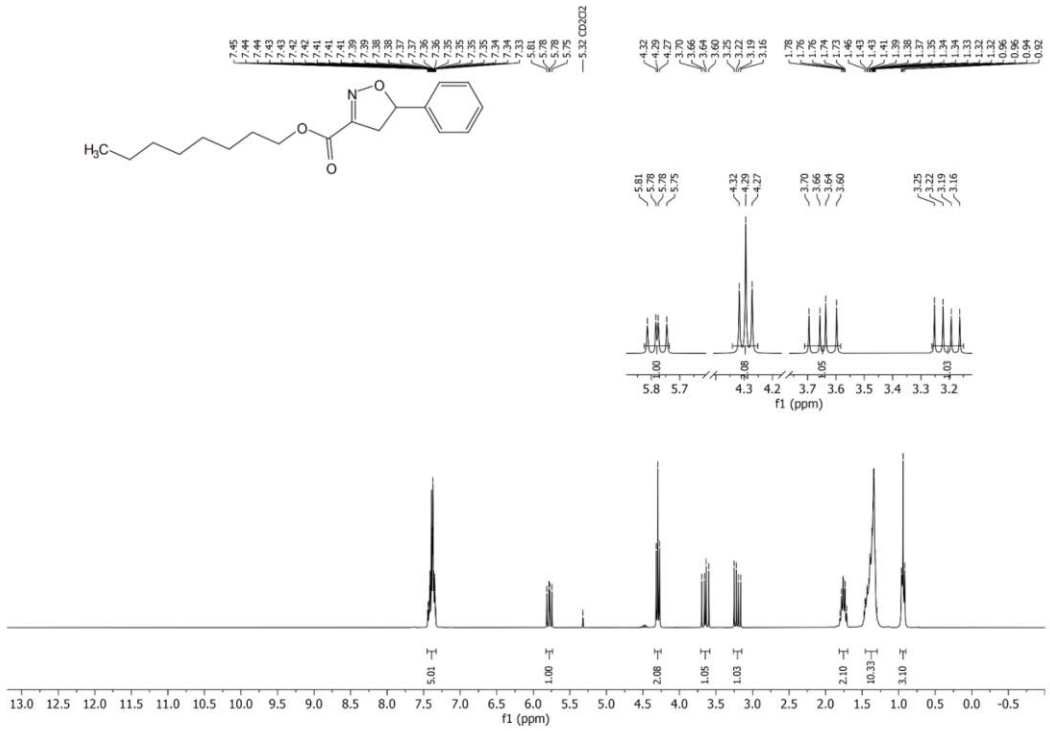

Figure S64: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6i**.

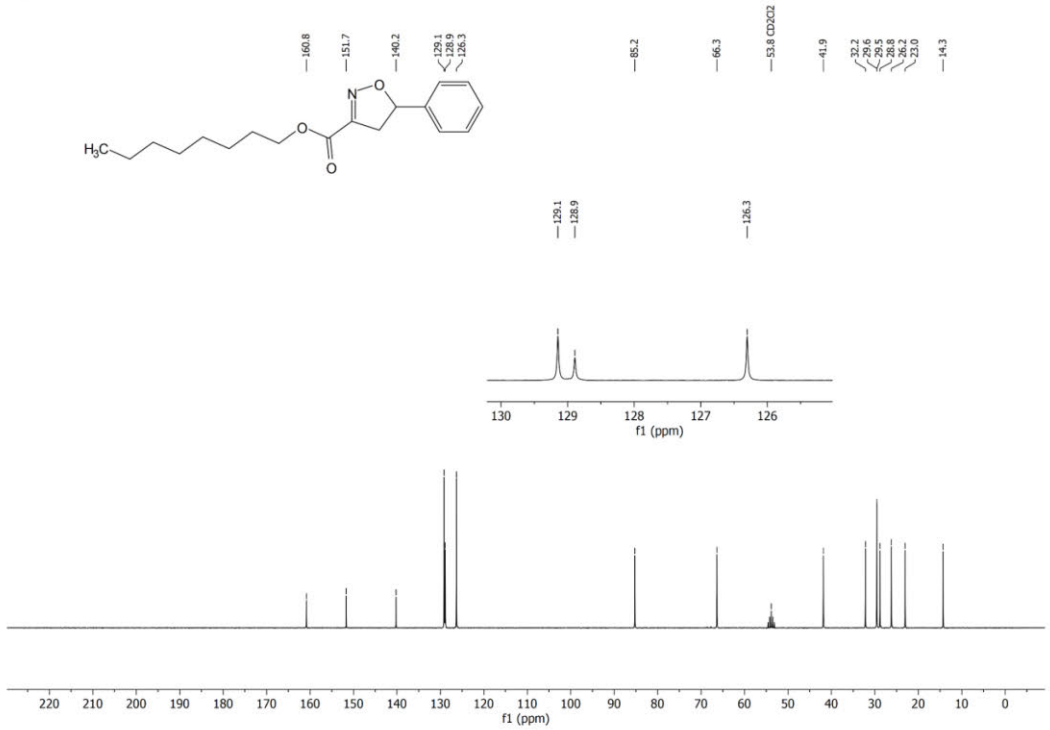

Figure S65: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6i**.

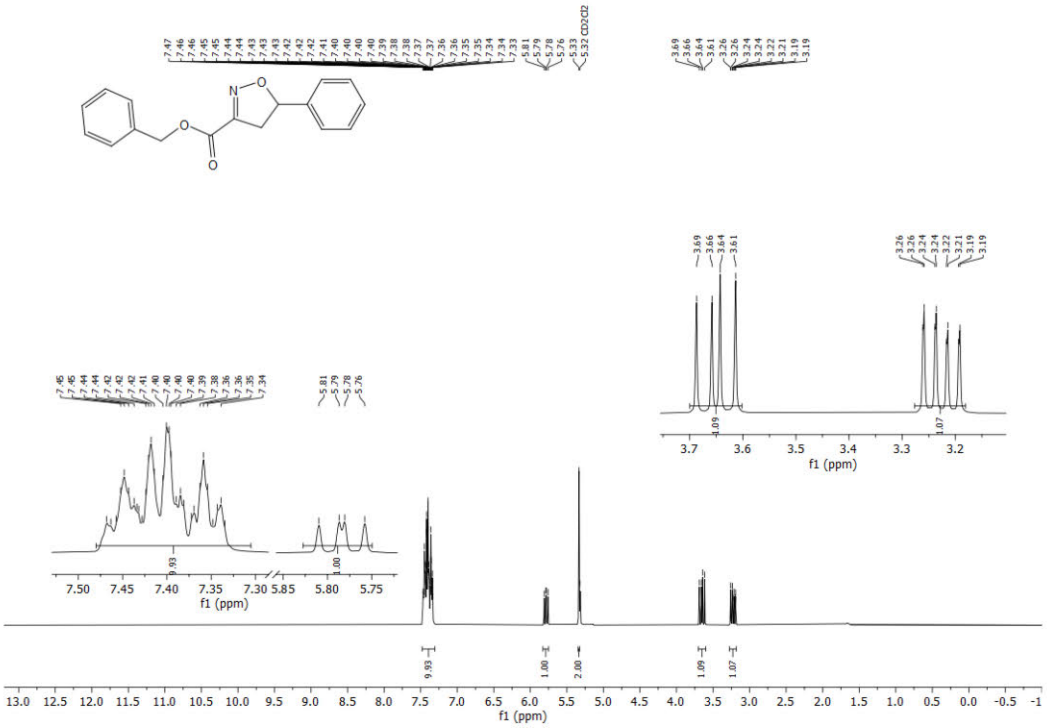

Figure S66: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6j**.

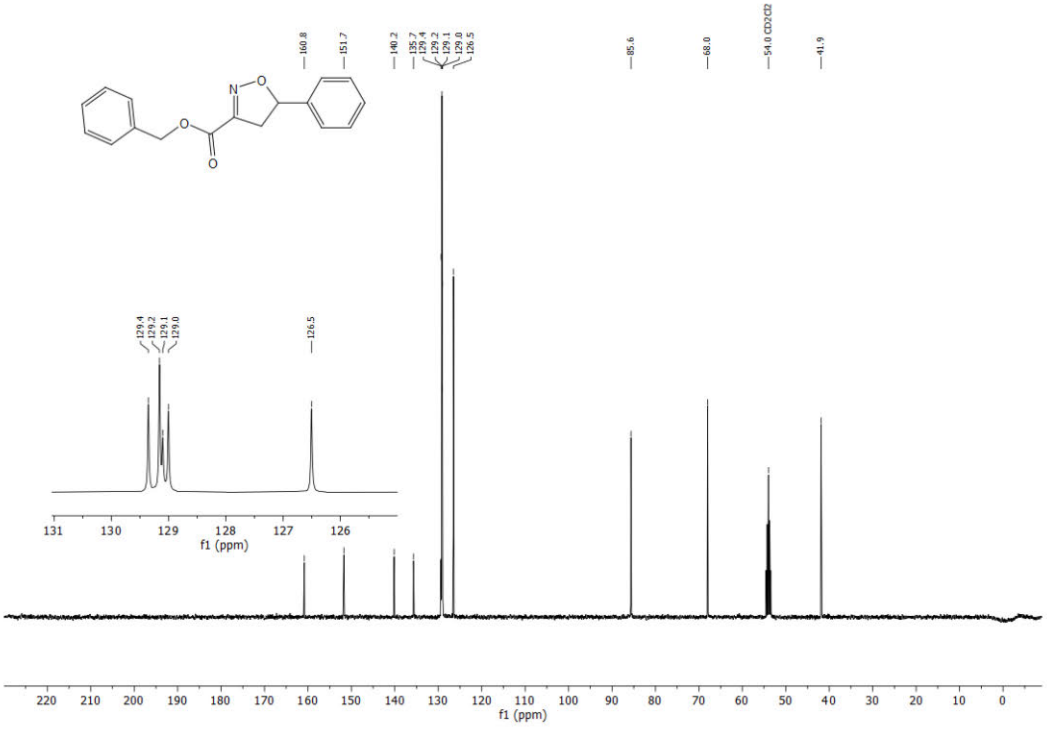

Figure S67: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6j**.

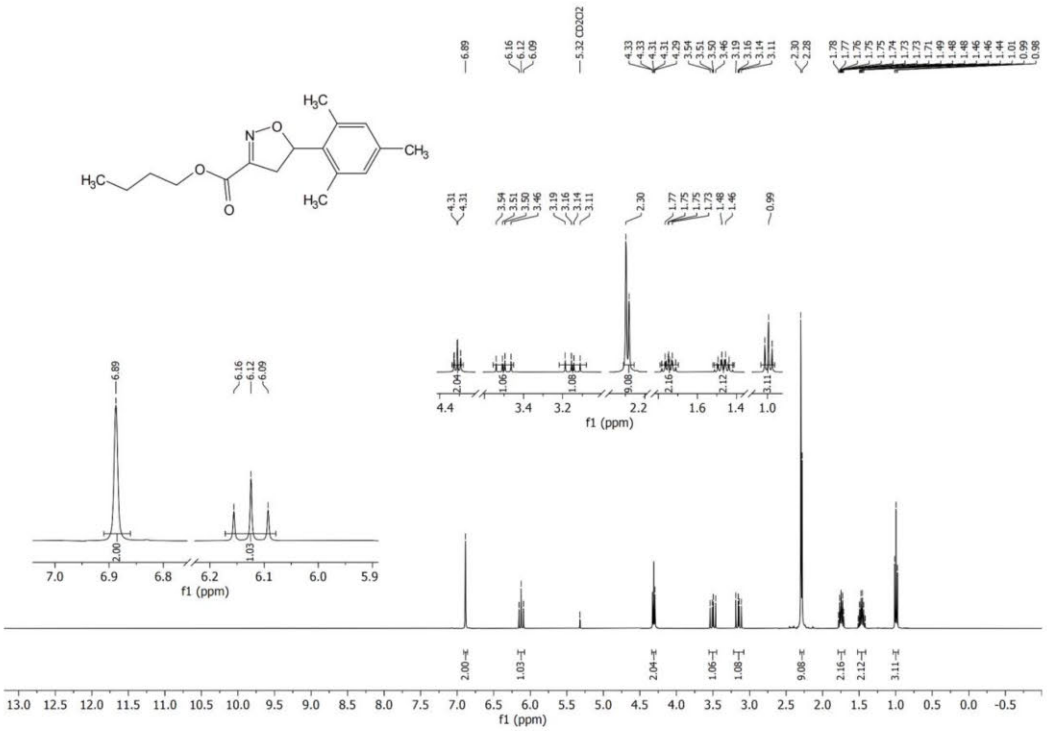

Figure S68: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6k**.

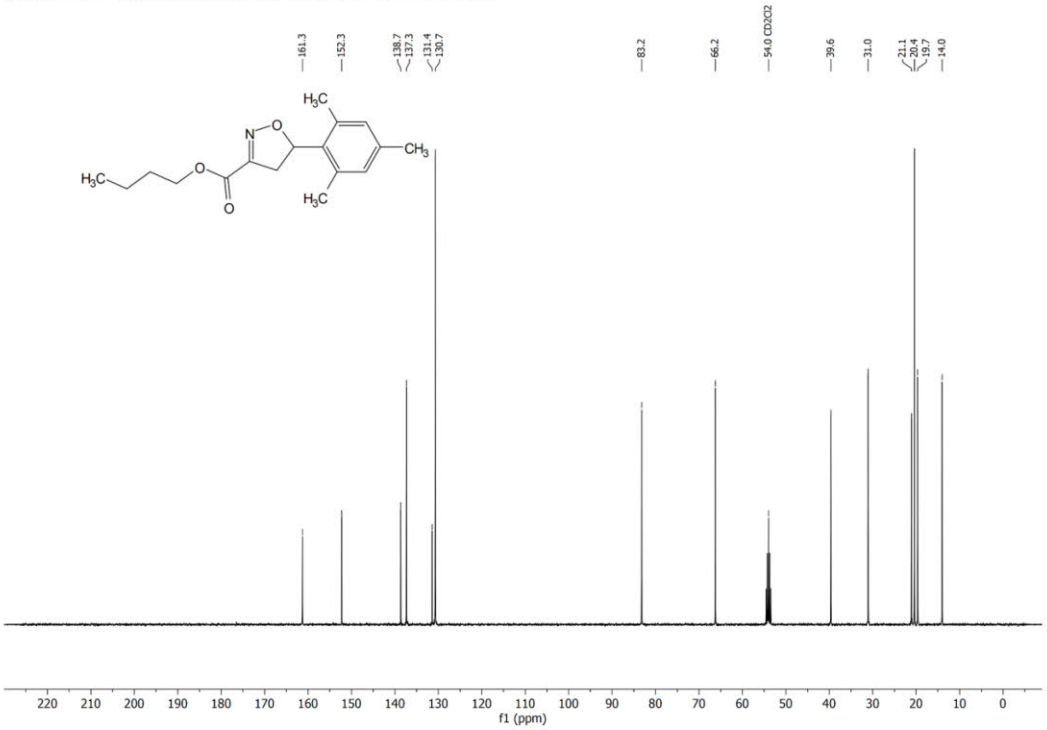

Figure S69: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6k**.

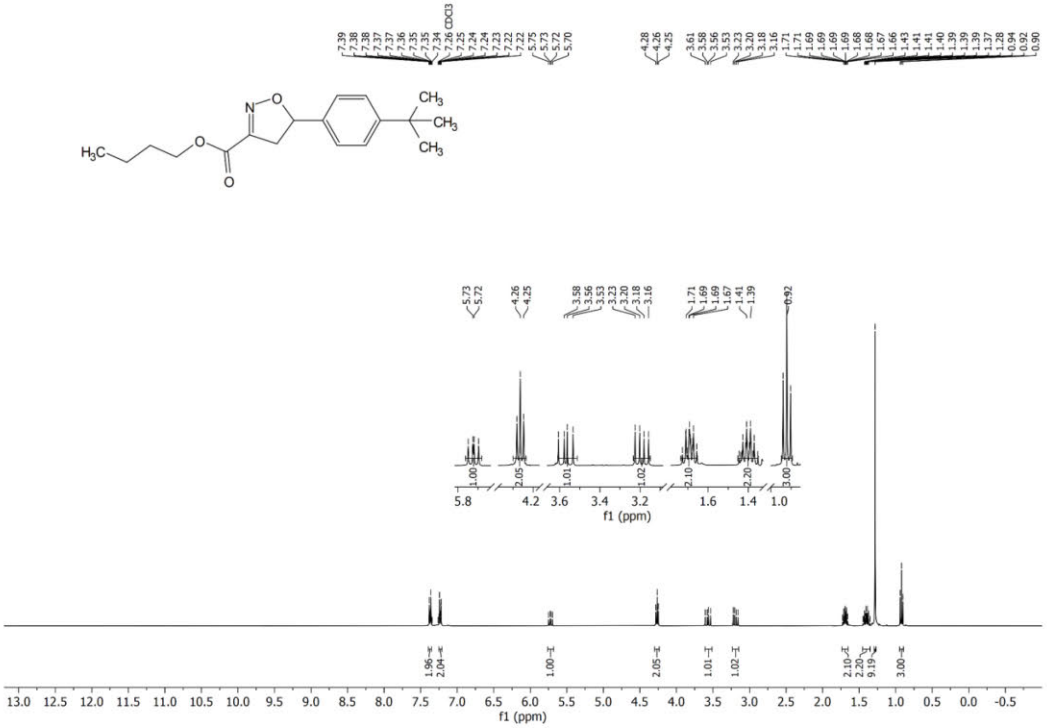

Figure S70: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6l**.

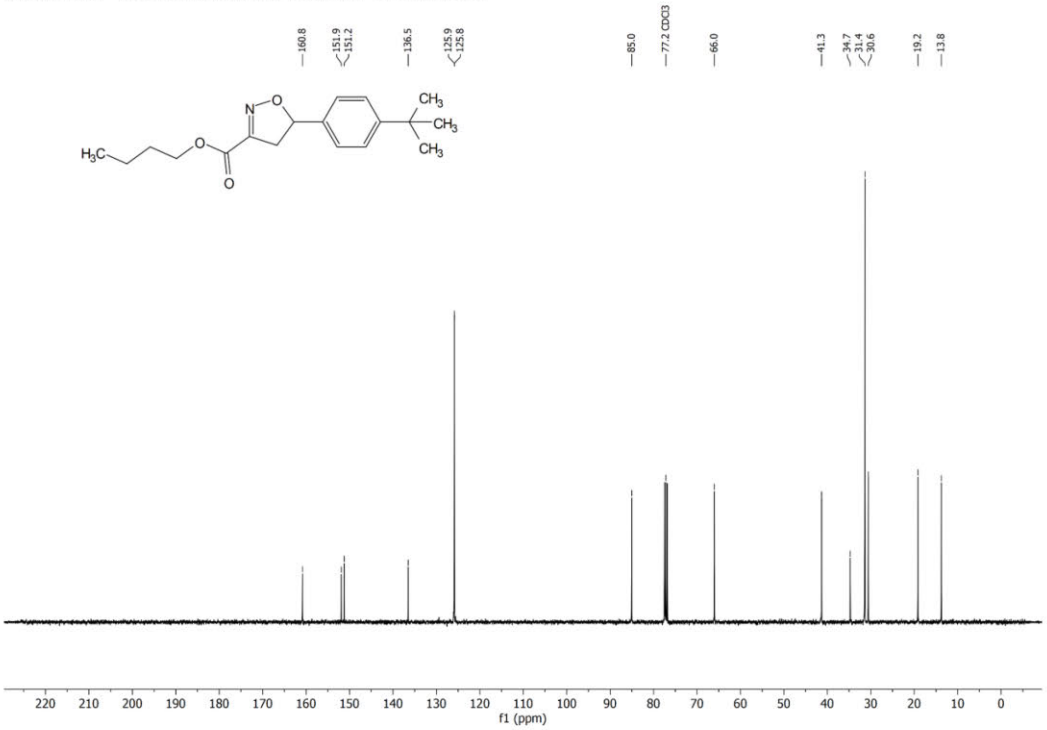

Figure S71: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6l**.

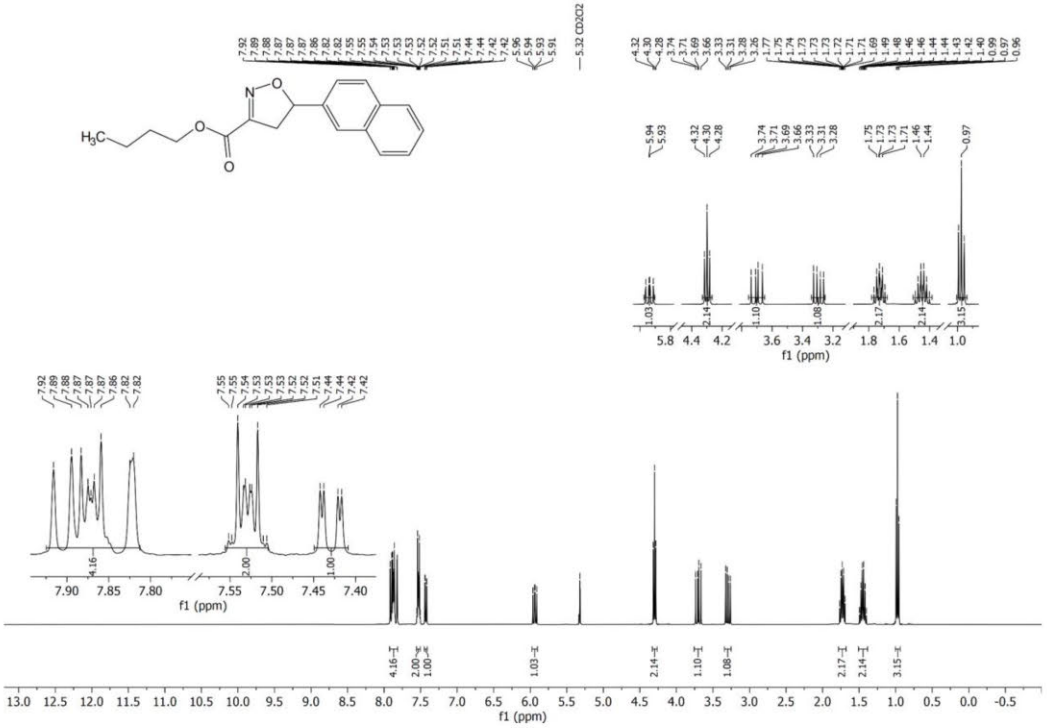

Figure S72: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6m**.

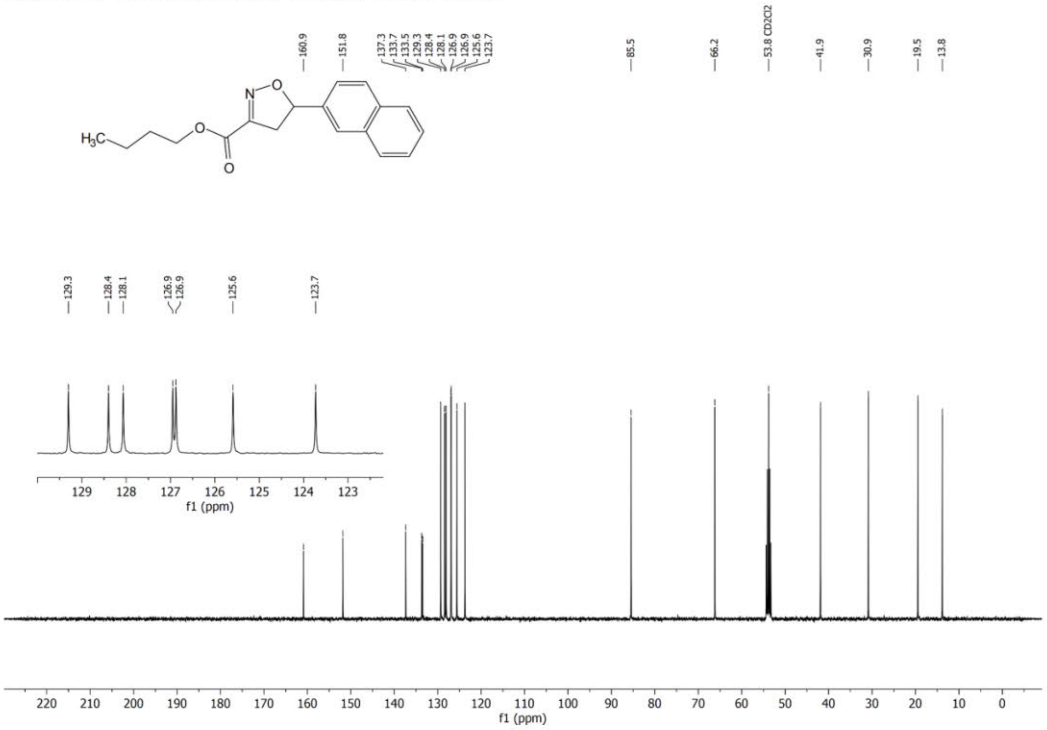

Figure S73: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6m**.

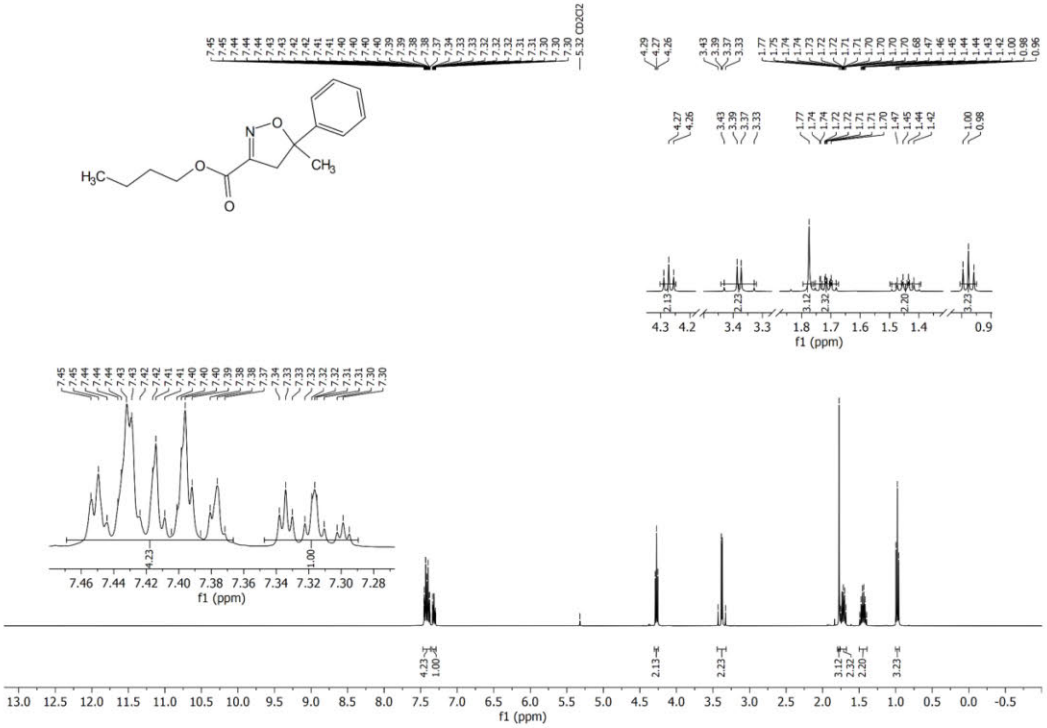

Figure S74: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6n**.

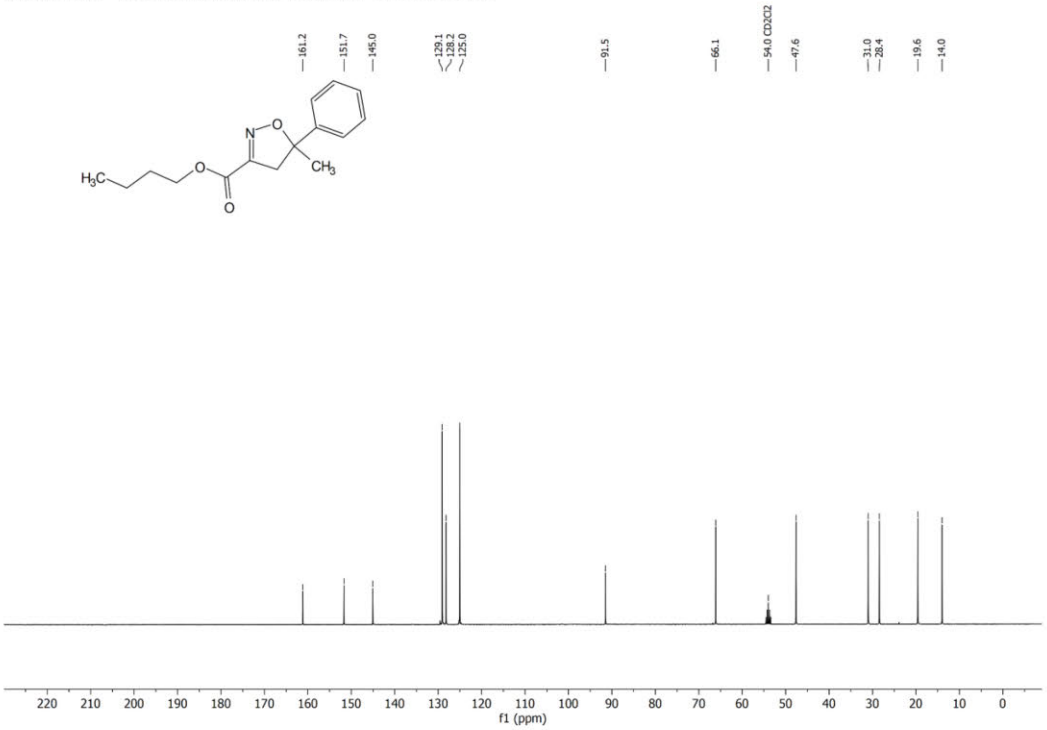

Figure S75: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6n**.

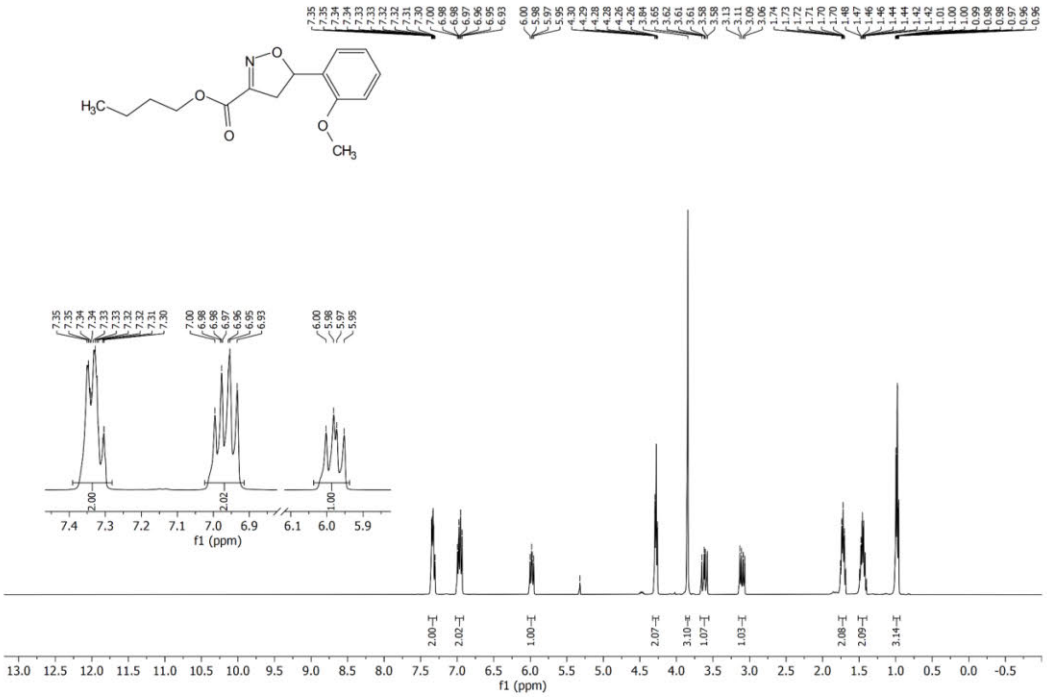

Figure S76: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6o**.

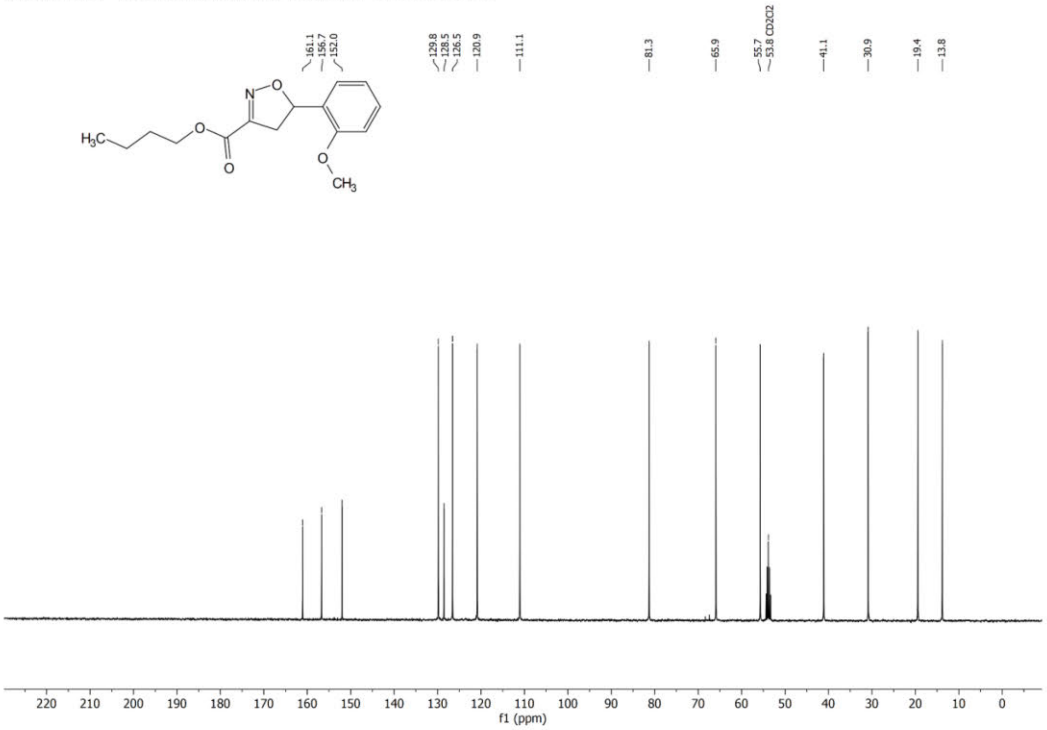

Figure S77: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6o**.

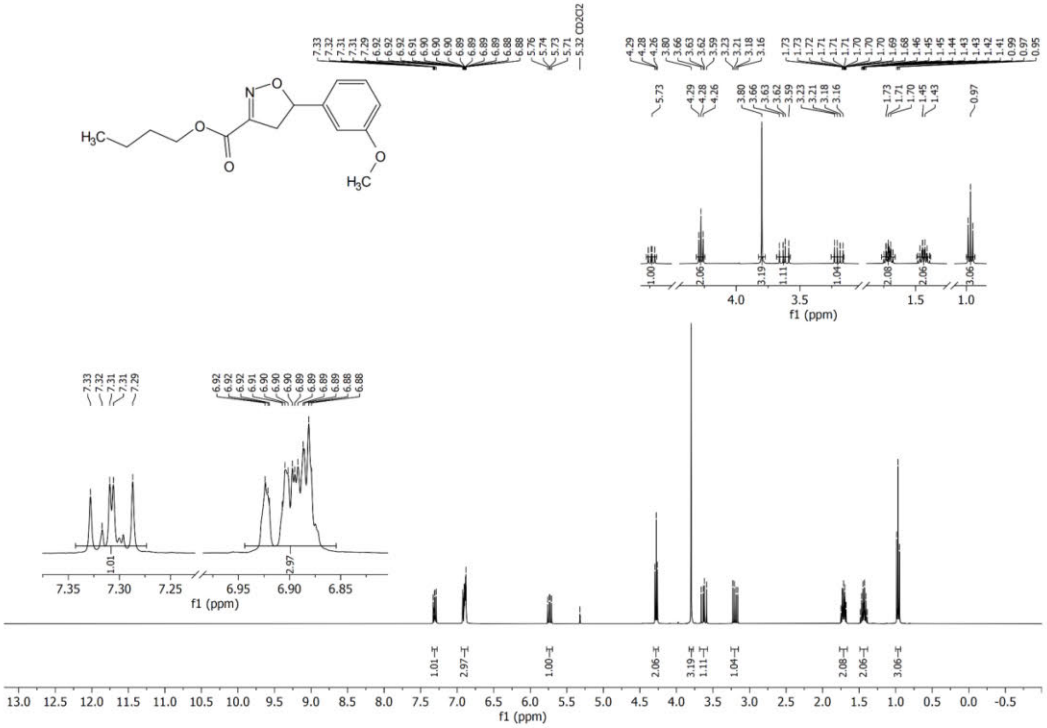

Figure S78: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6p**.

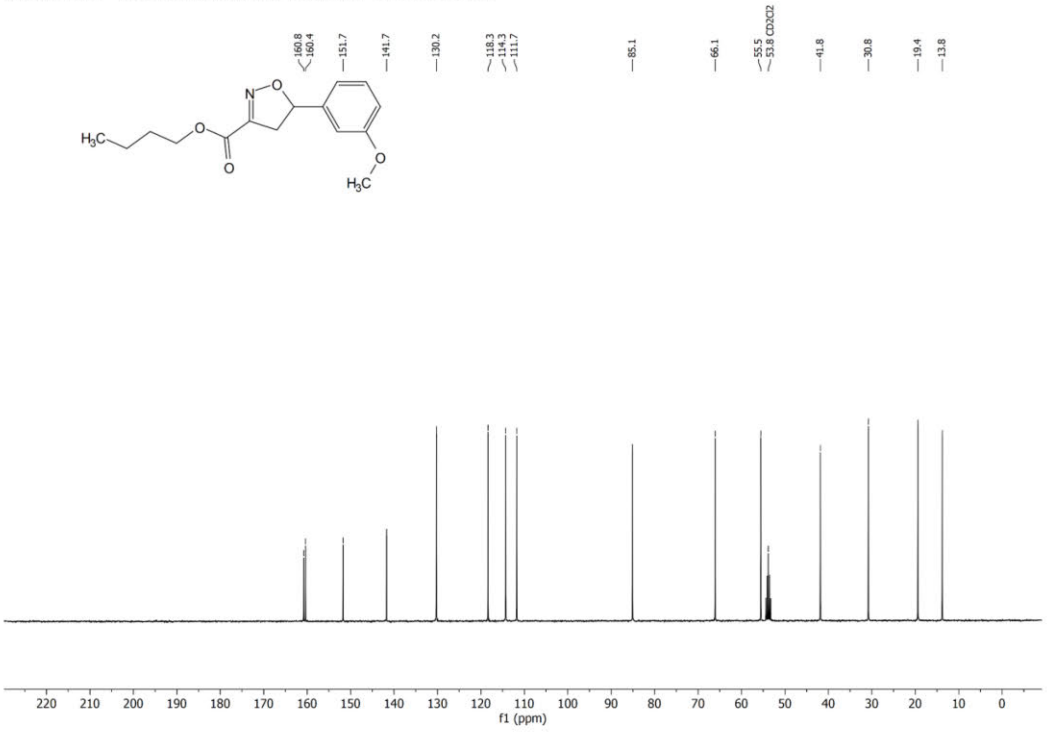

Figure S79: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6p**.

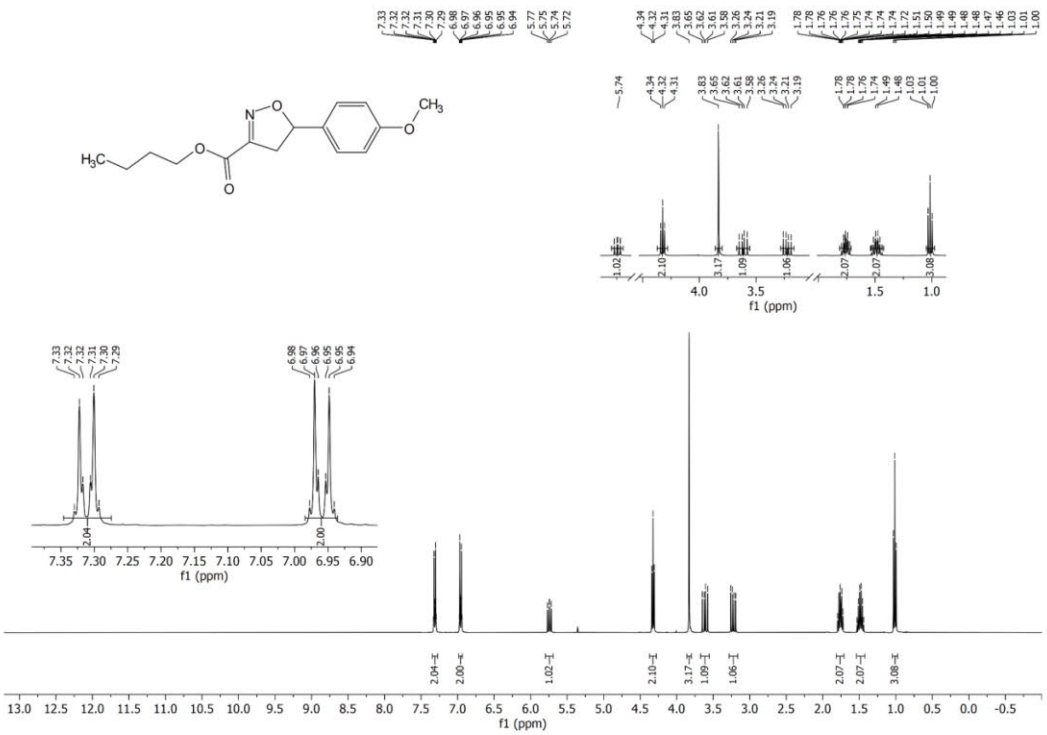

Figure S80: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6q**.

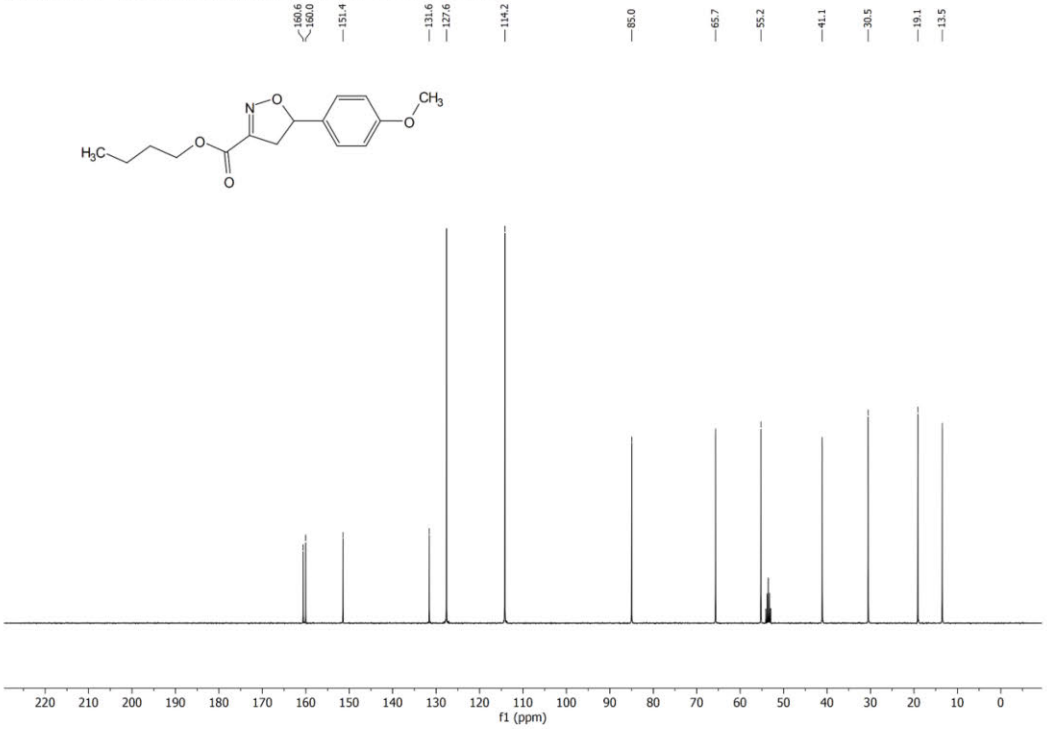

Figure S81: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6q**.

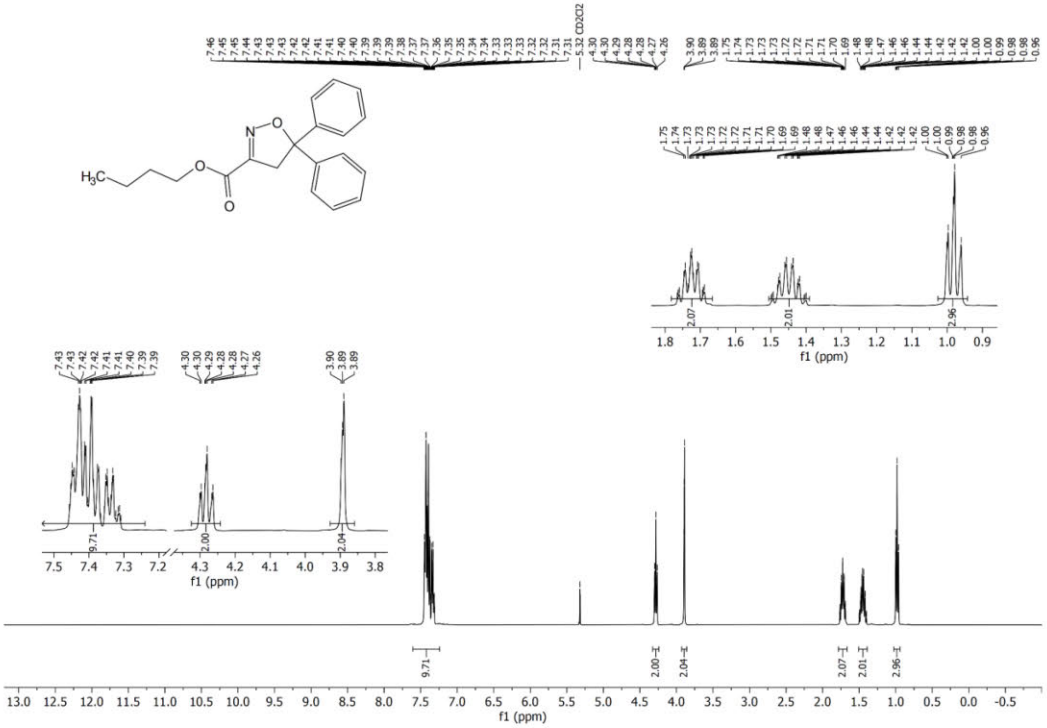

Figure S82: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6r**.

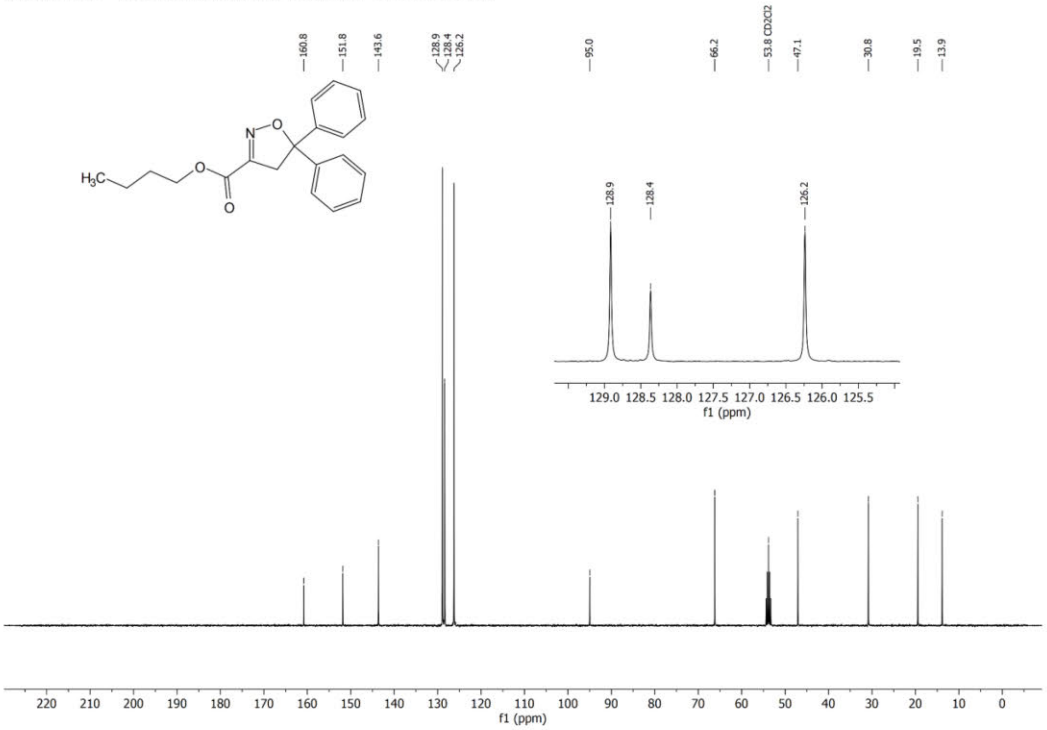

Figure S83: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6r**.

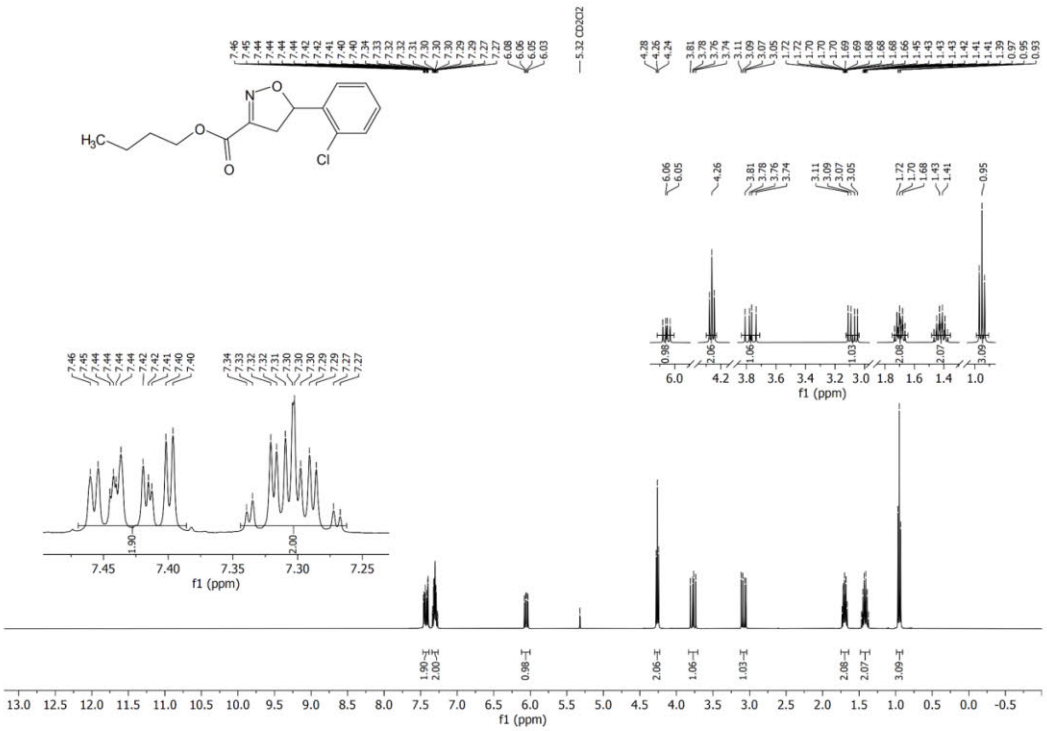

Figure S84: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6s**.

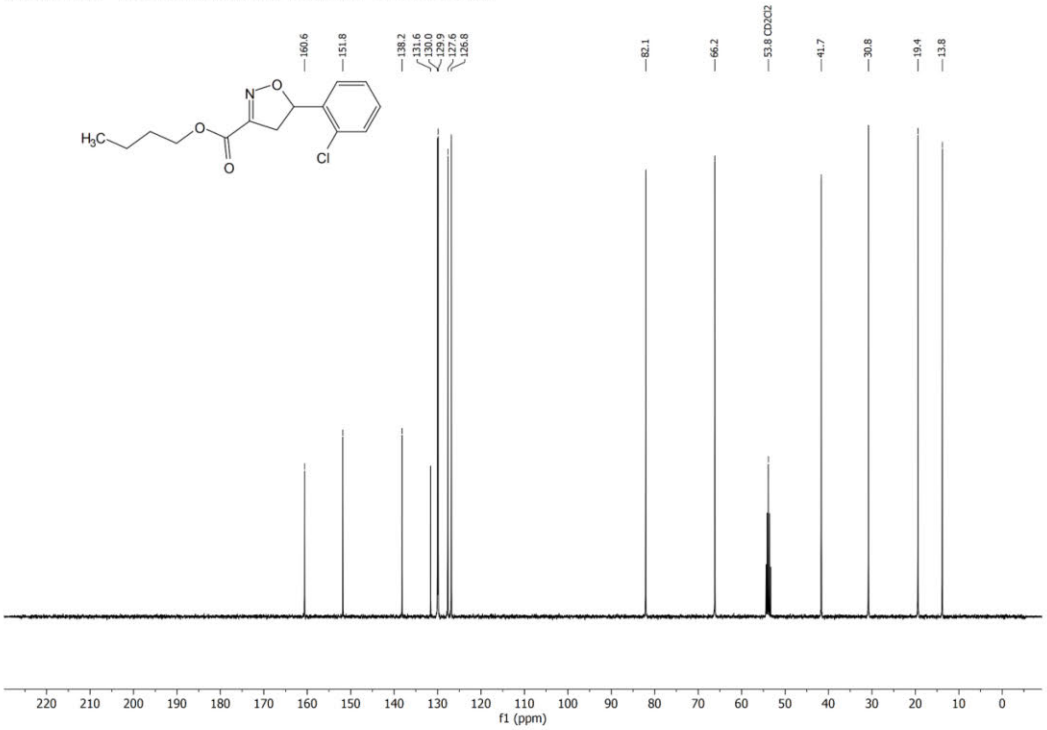

Figure S85: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6s**.

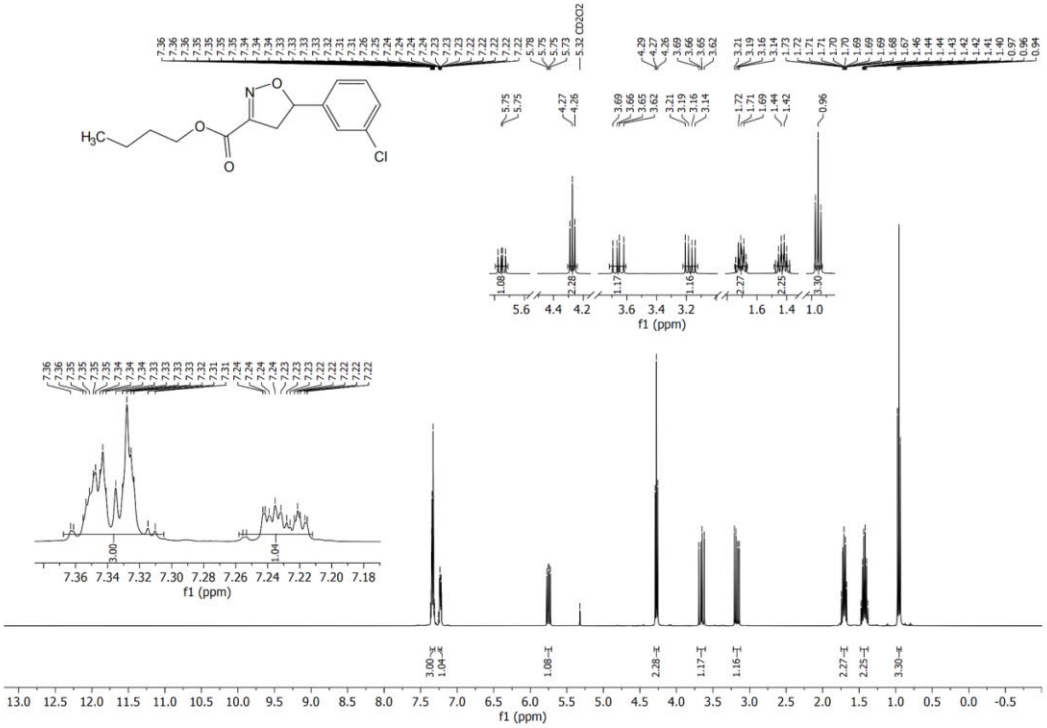

Figure S86: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6t**.

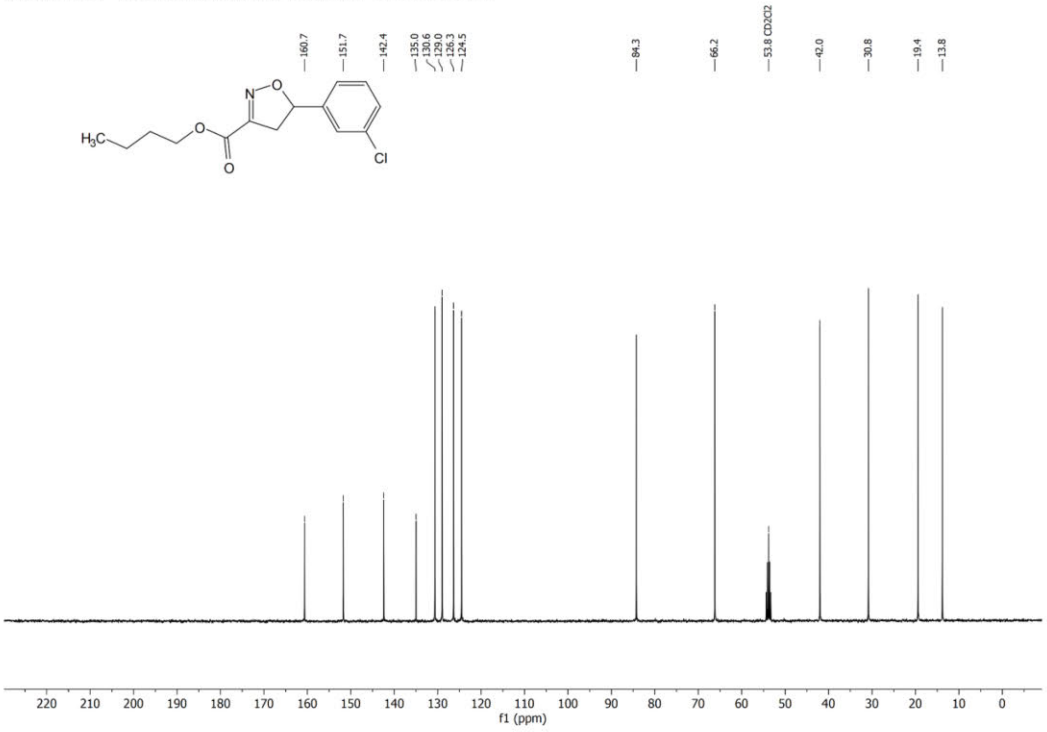

Figure S87: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6t**.

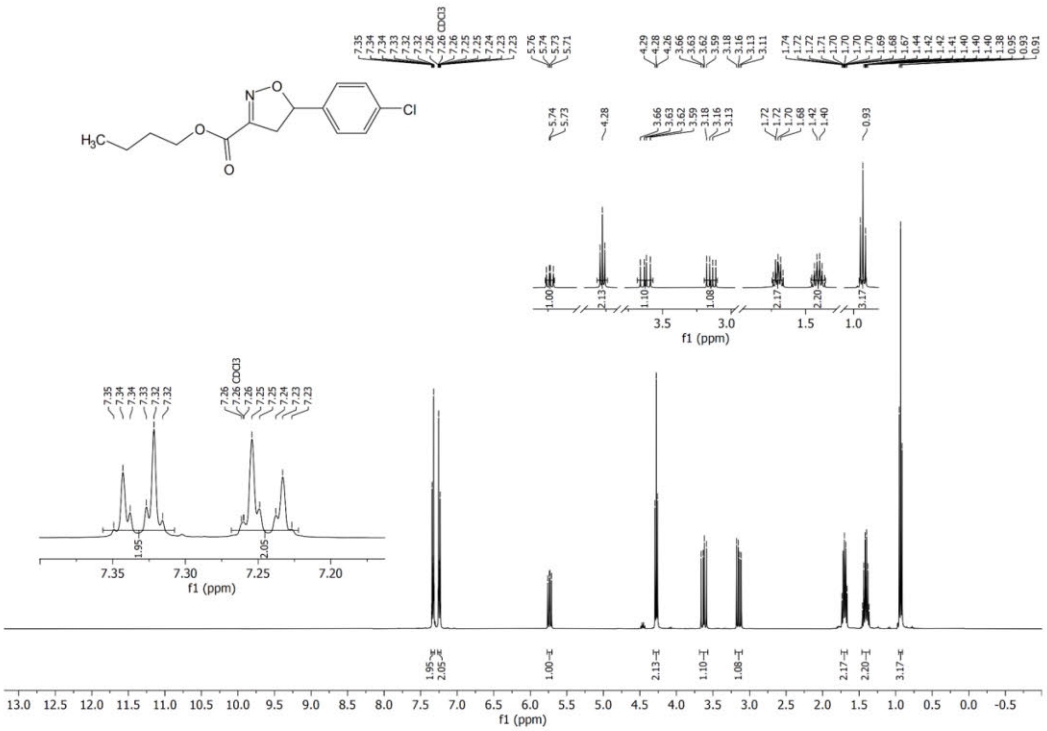

Figure S88: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6u**.

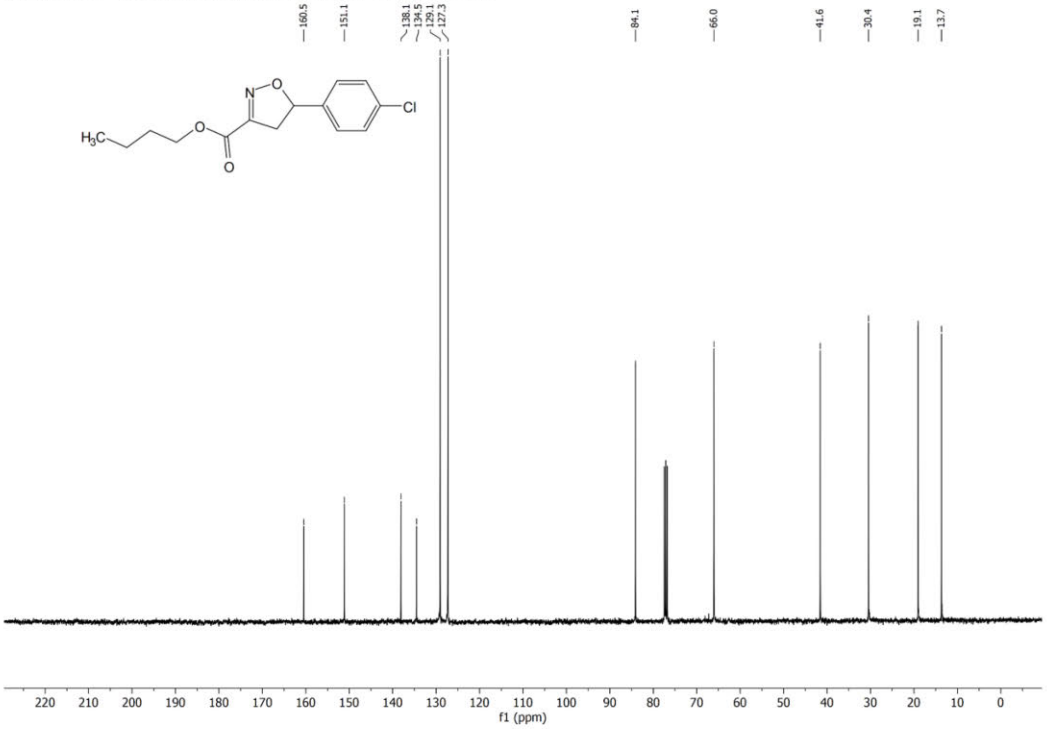

Figure S89: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6u**.

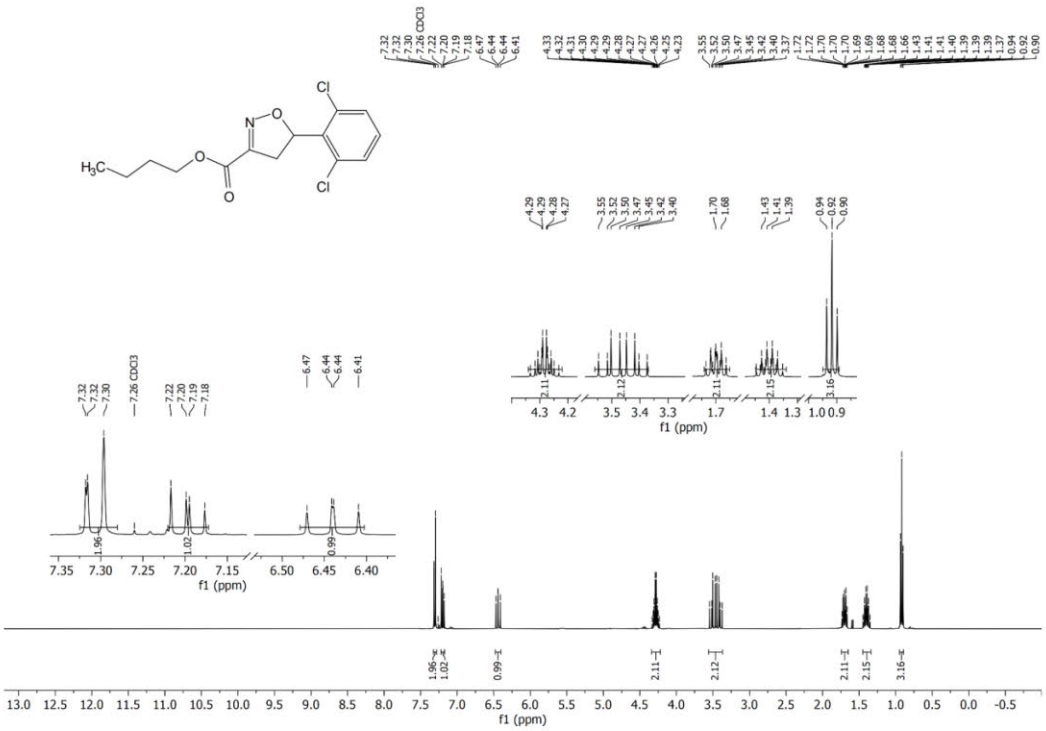

Figure S90: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6v**.

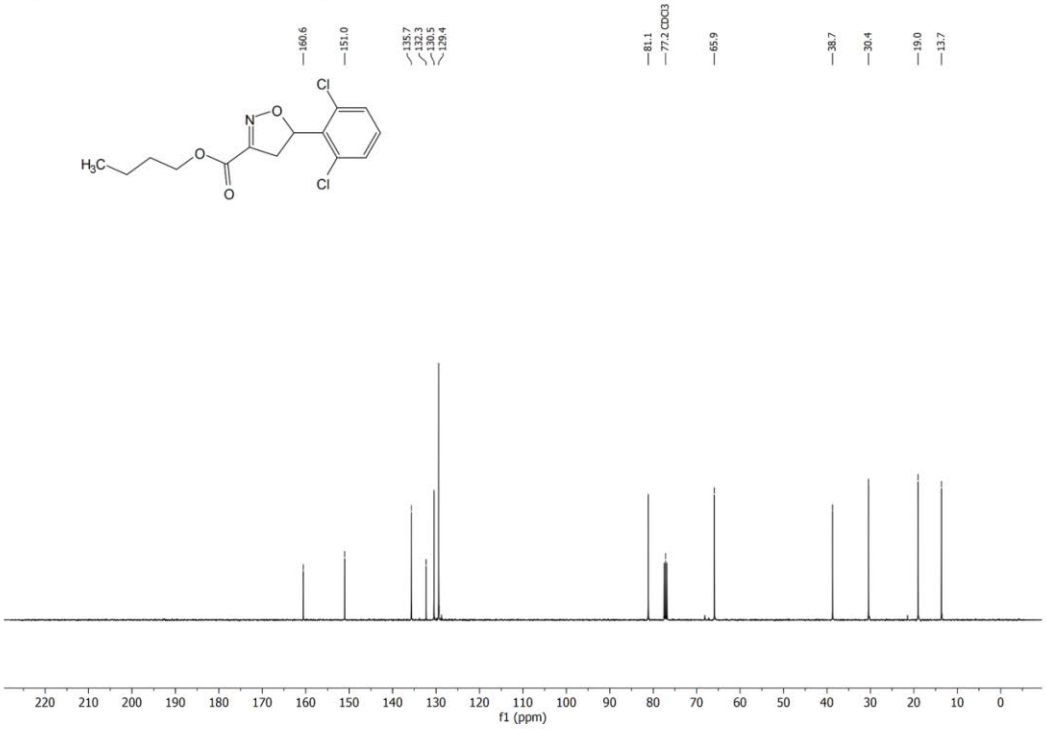

Figure S91: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6v**.

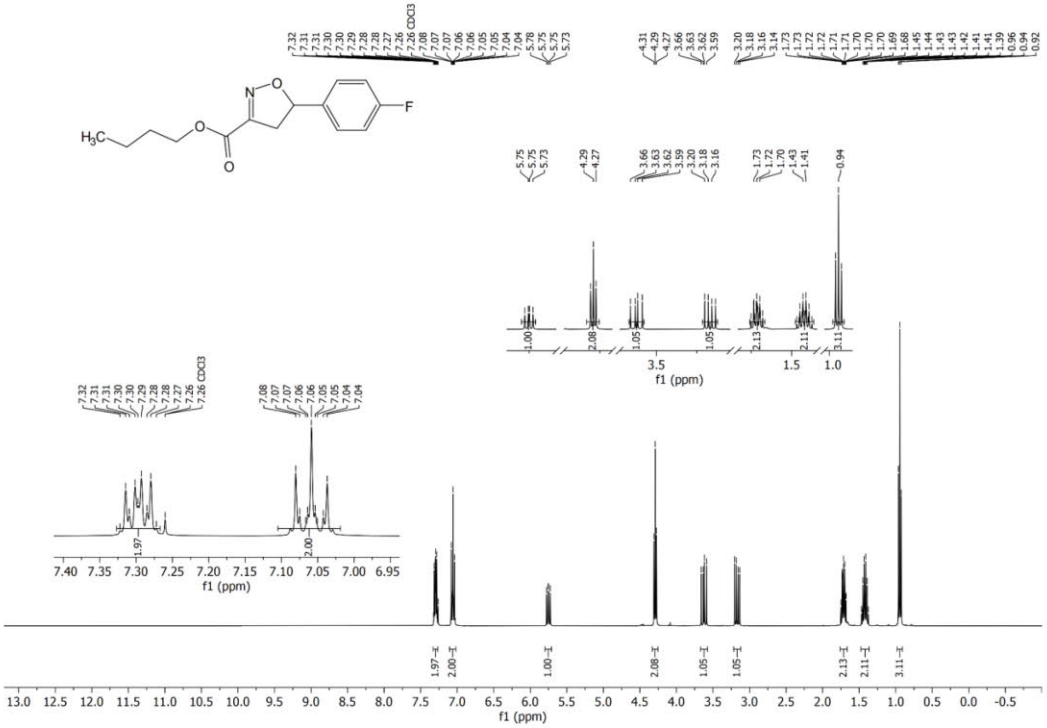

Figure S92: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6w**.

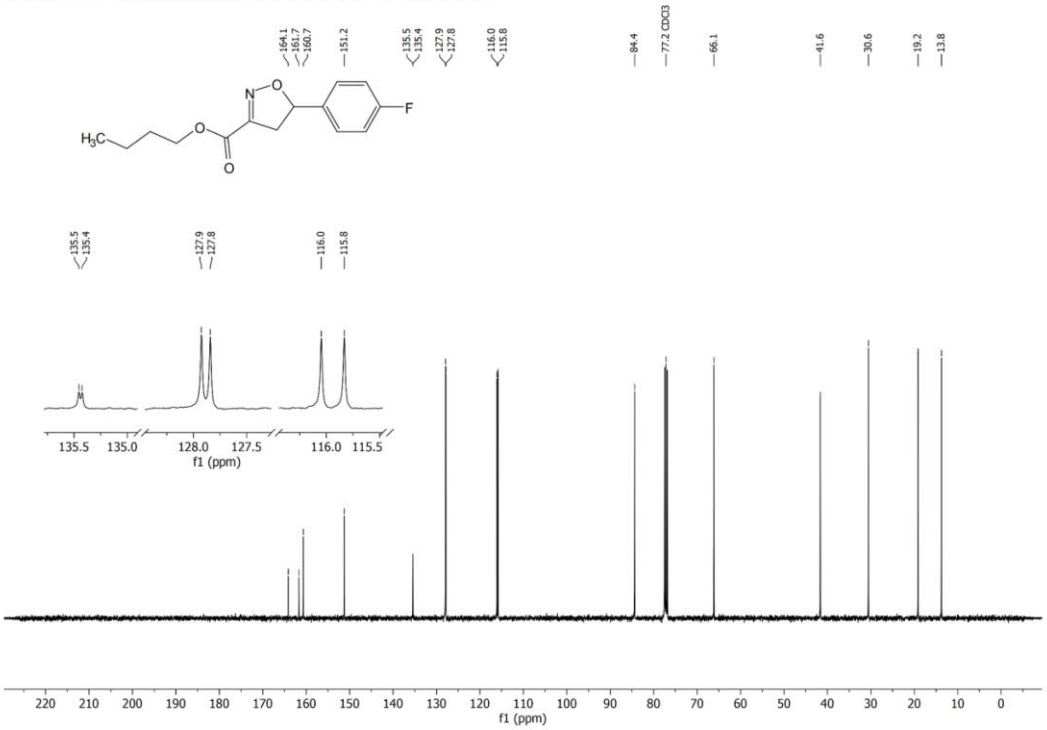

Figure S93: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6w**.

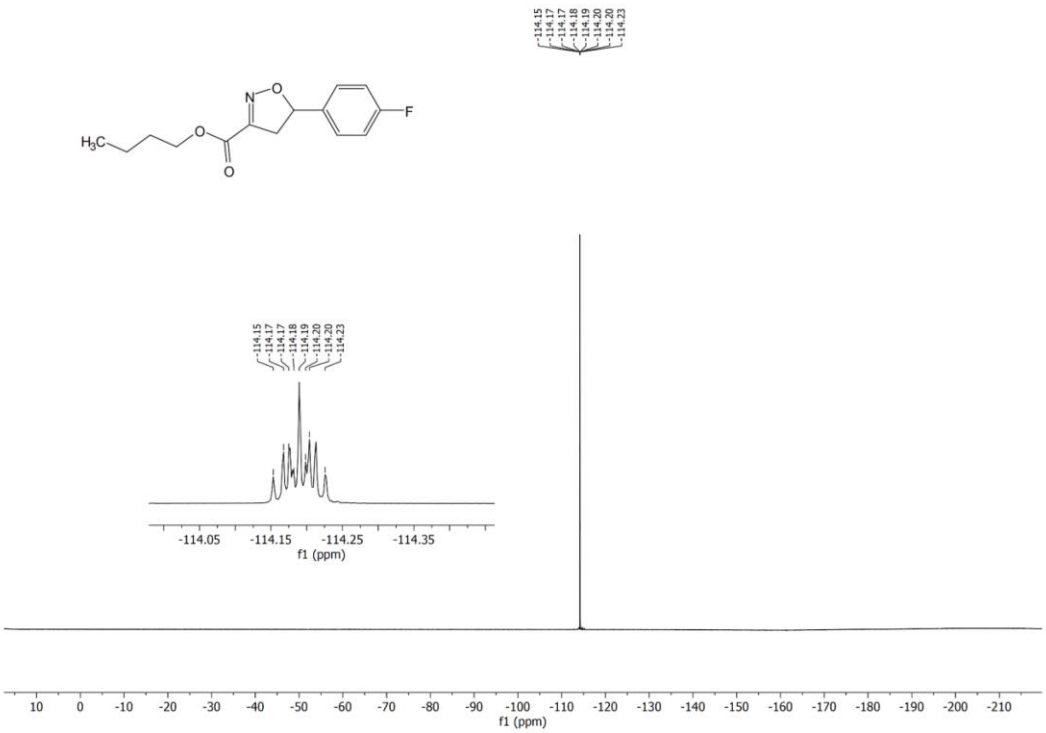

Figure S94: ^{19}F NMR spectrum (376 MHz, $CDCl_3$) of **6w**.

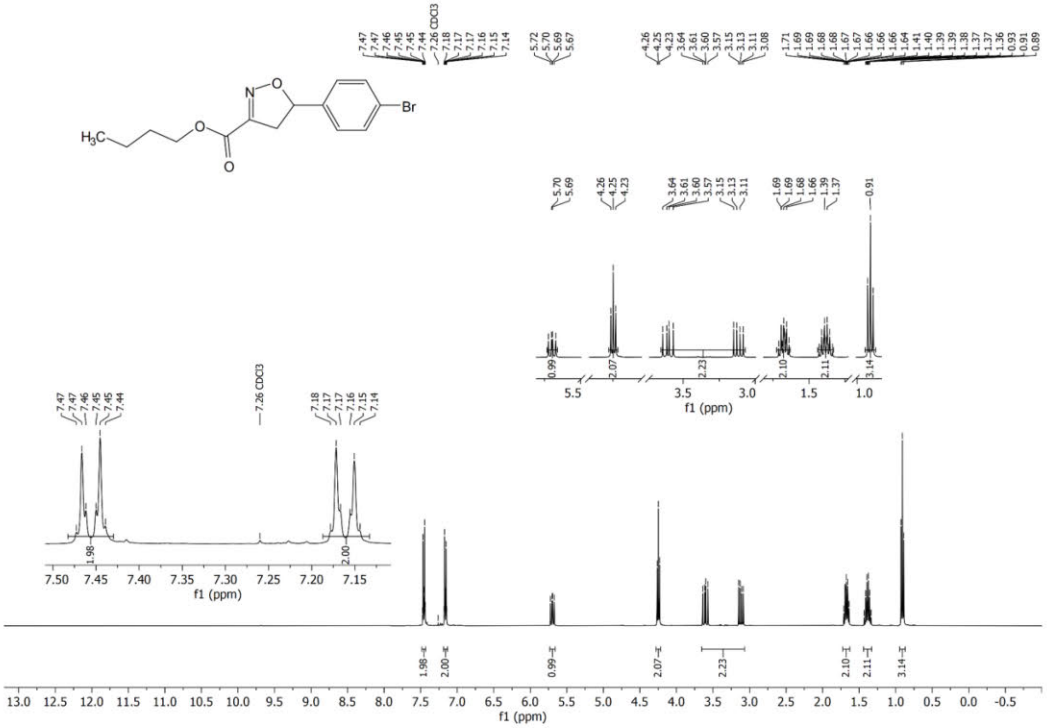

Figure S95: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6x**.

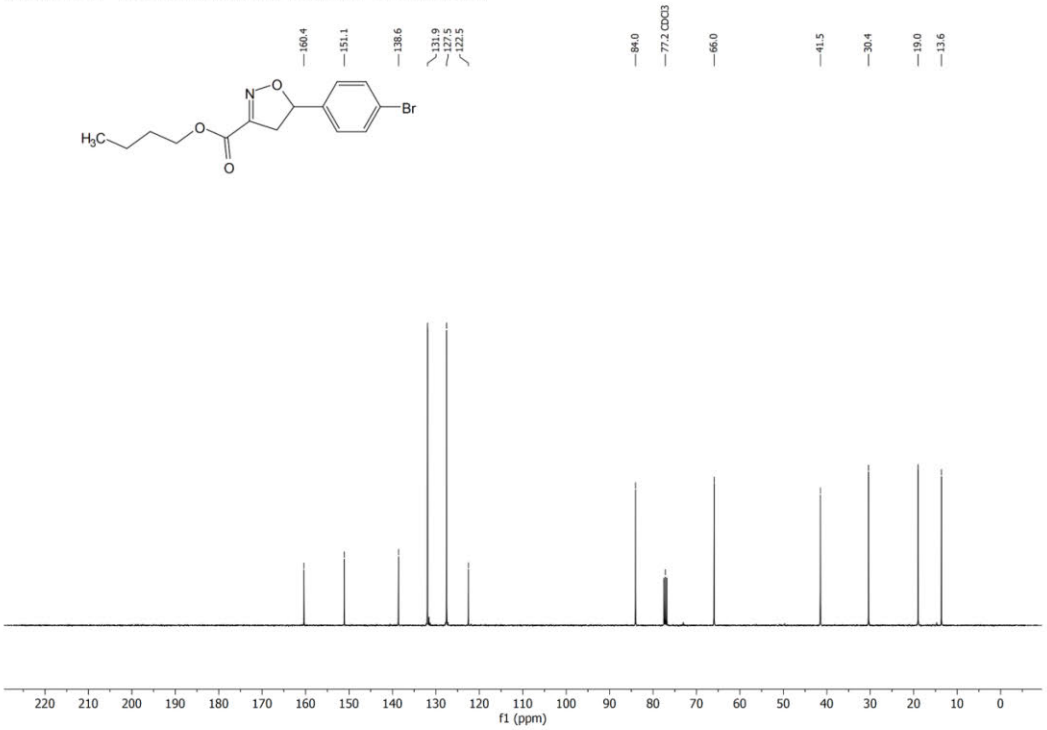

Figure S96: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6x**.

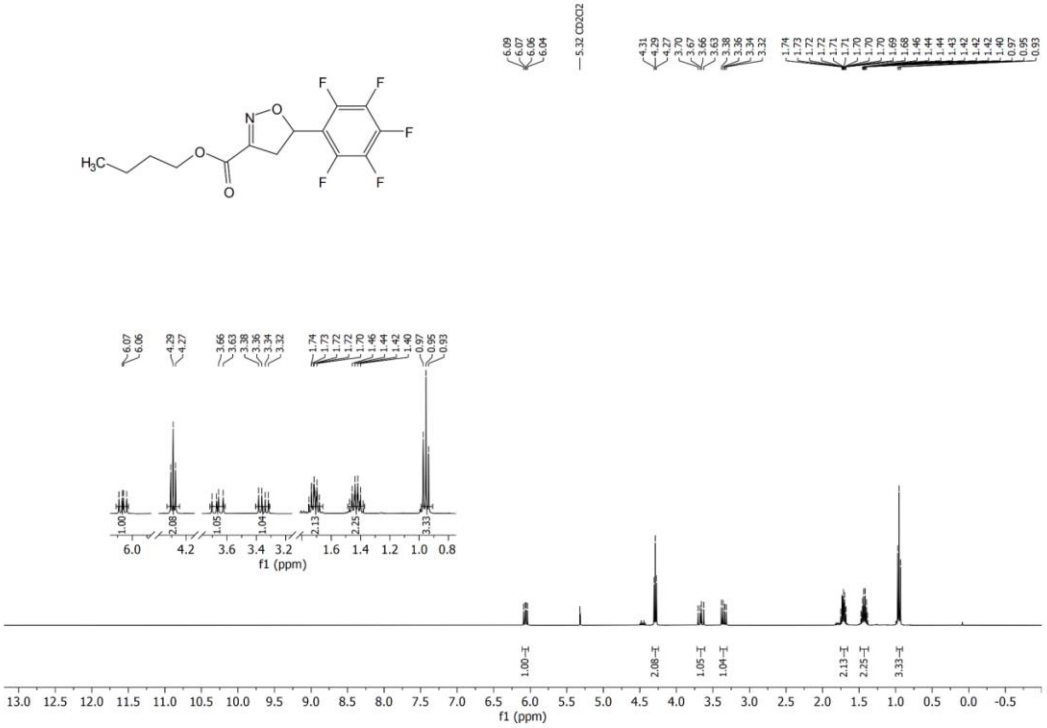

Figure S97: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6y**.

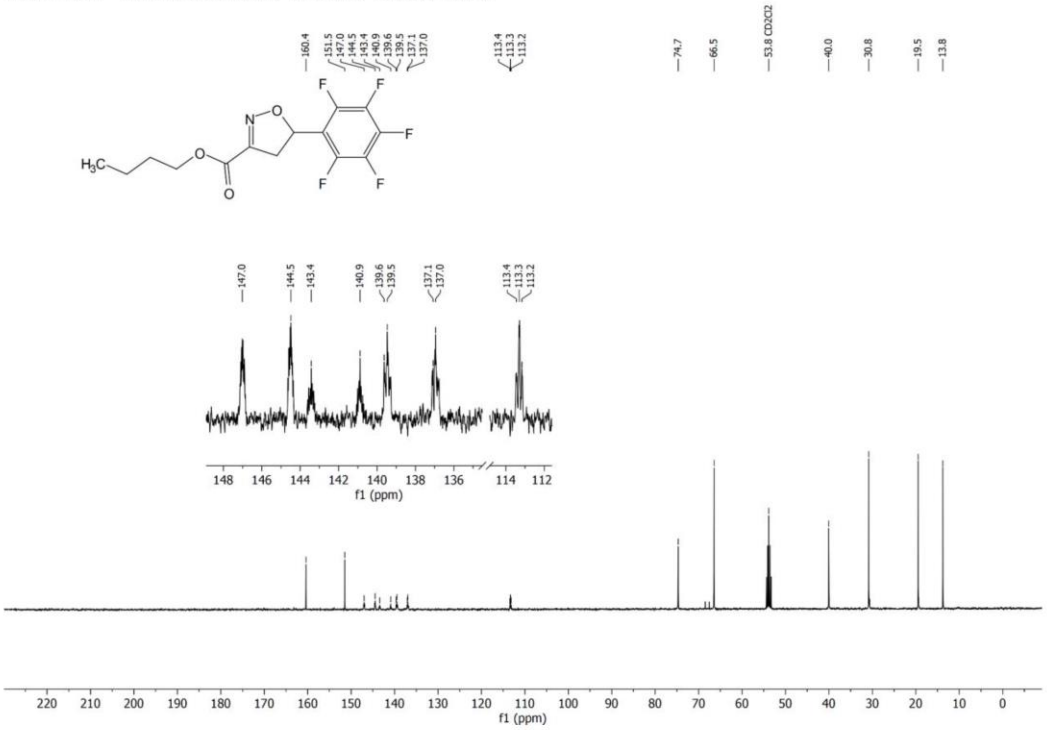

Figure S98: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6y**.

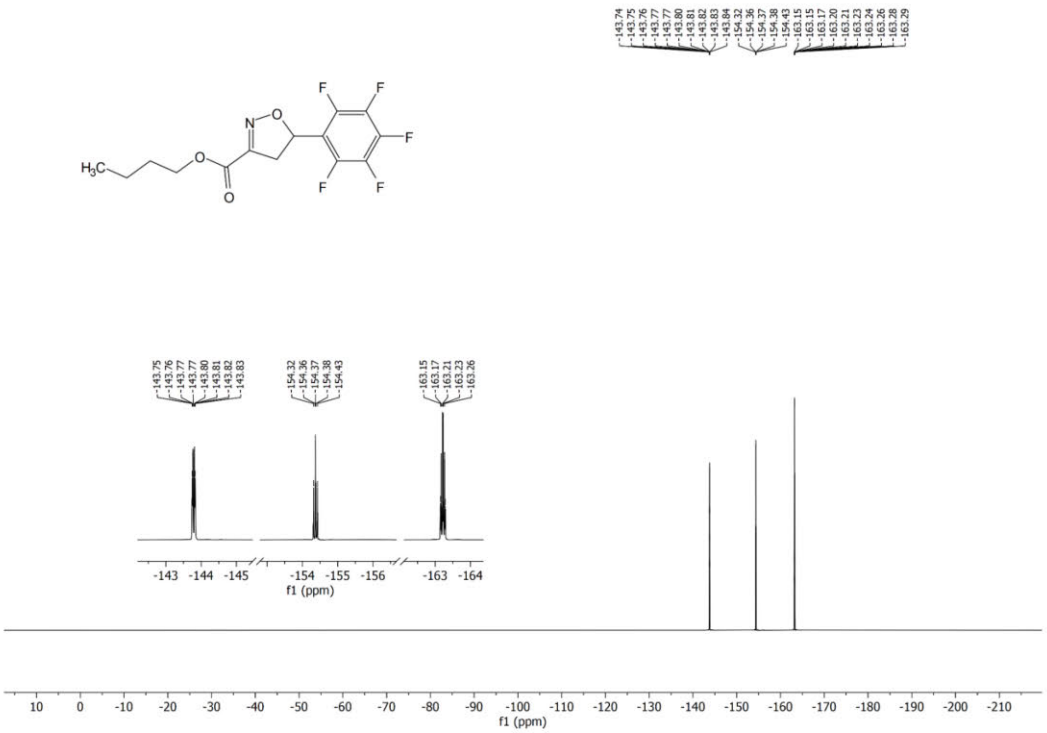

Figure S99: ^{19}F NMR spectrum (376 MHz, CD_2Cl_2) of **6y**.

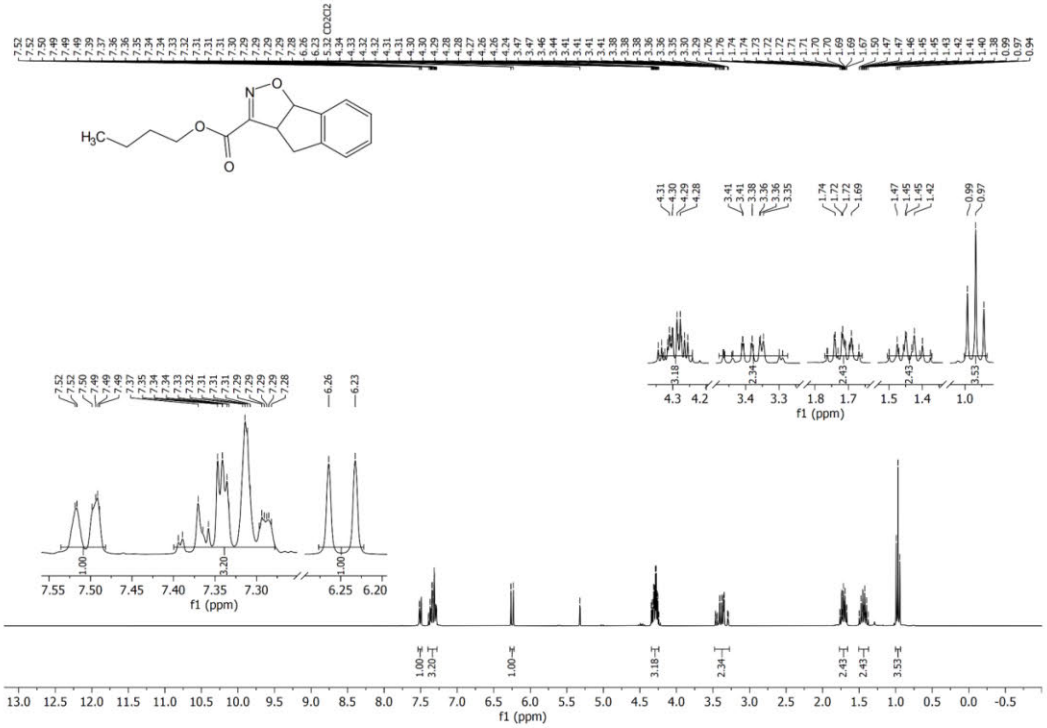

Figure S100: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6z**.

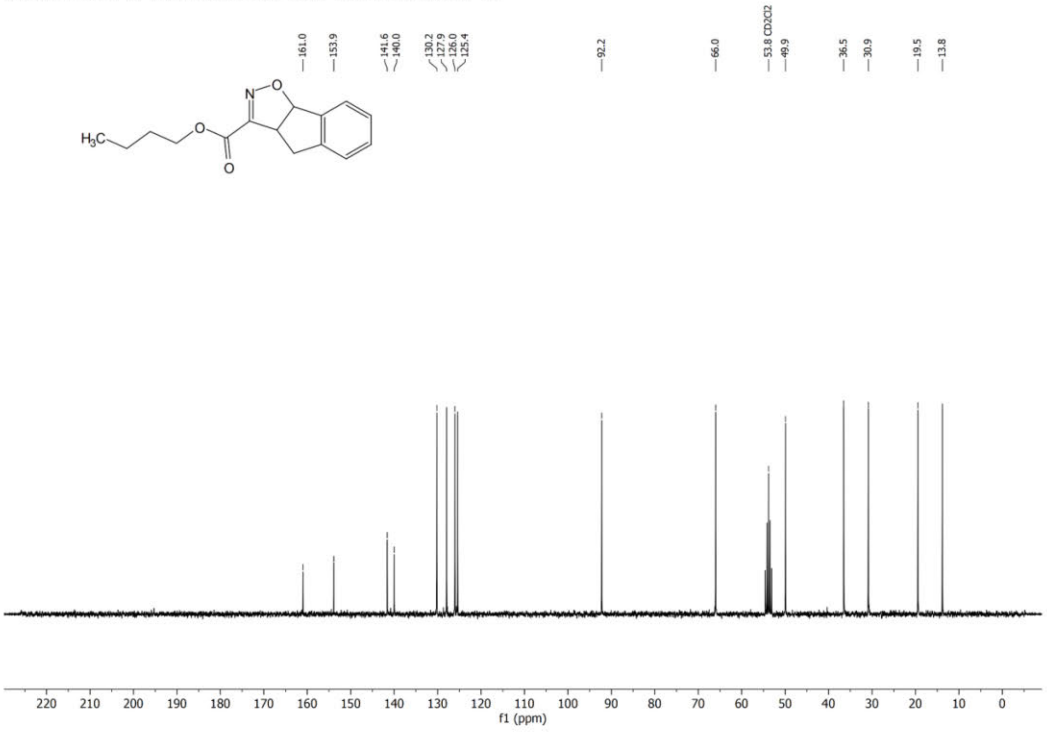

Figure S101: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6z**.

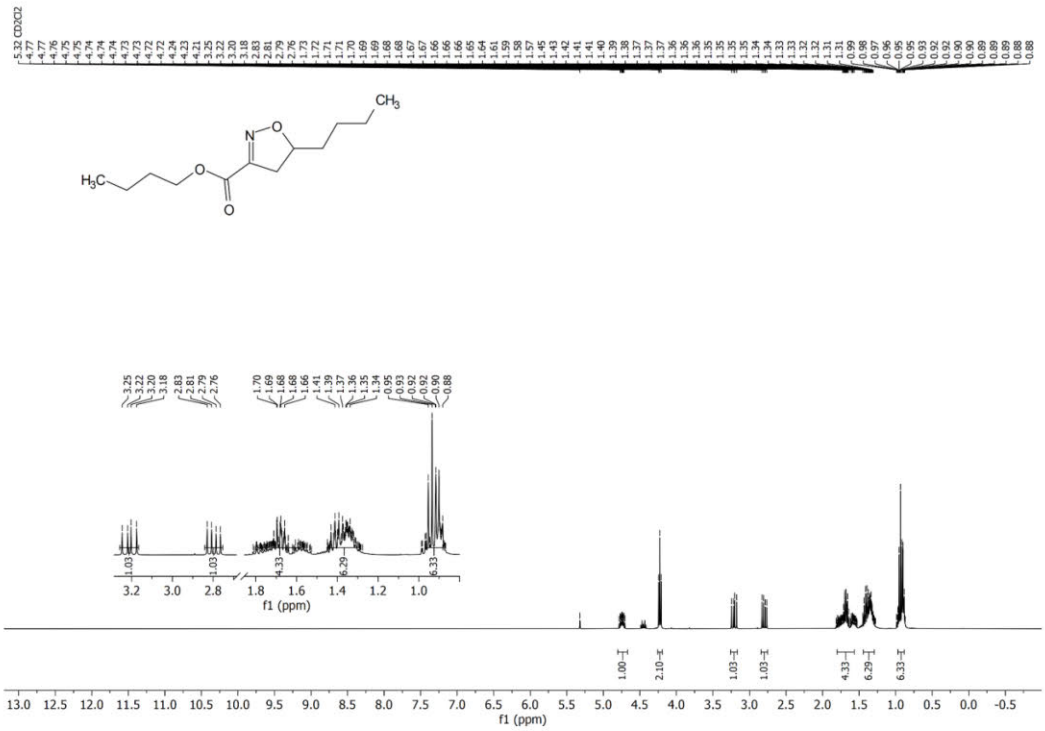

Figure S102: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6aa**.

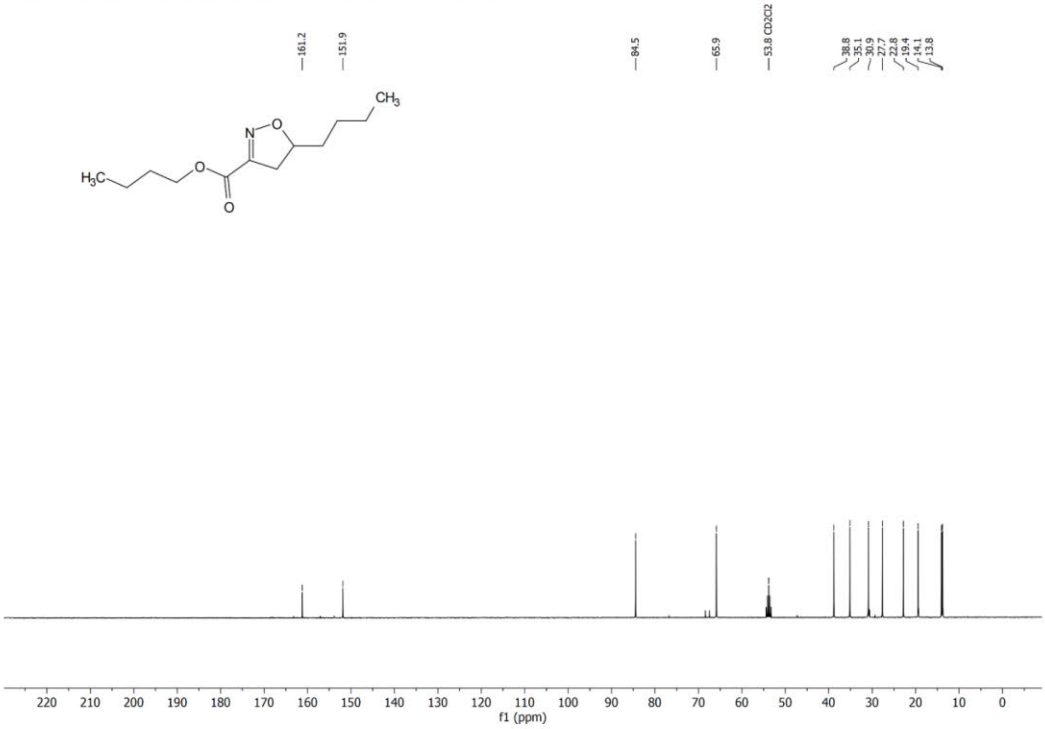

Figure S103: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6aa**.

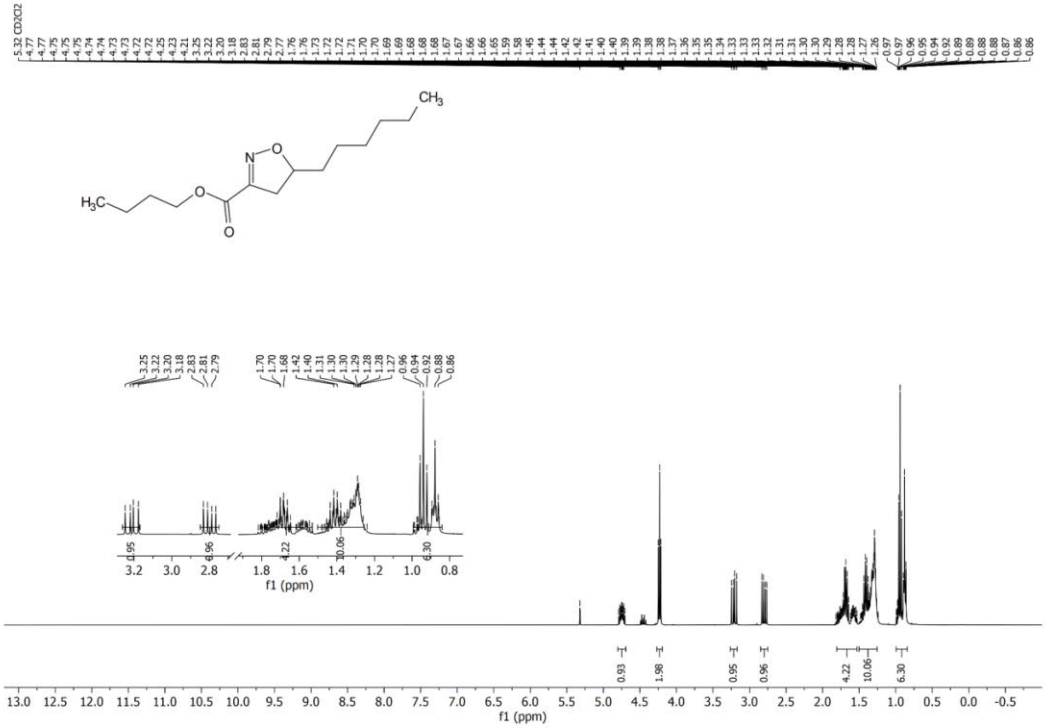

Figure S104: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6ab**.

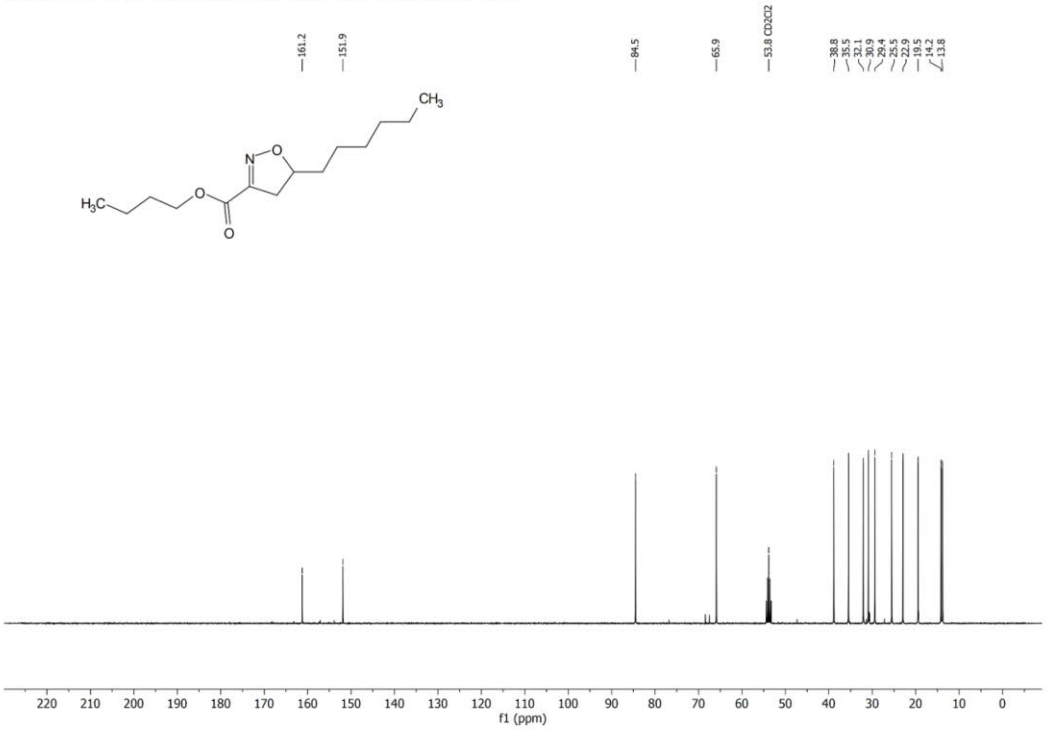

Figure S105: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6ab**.

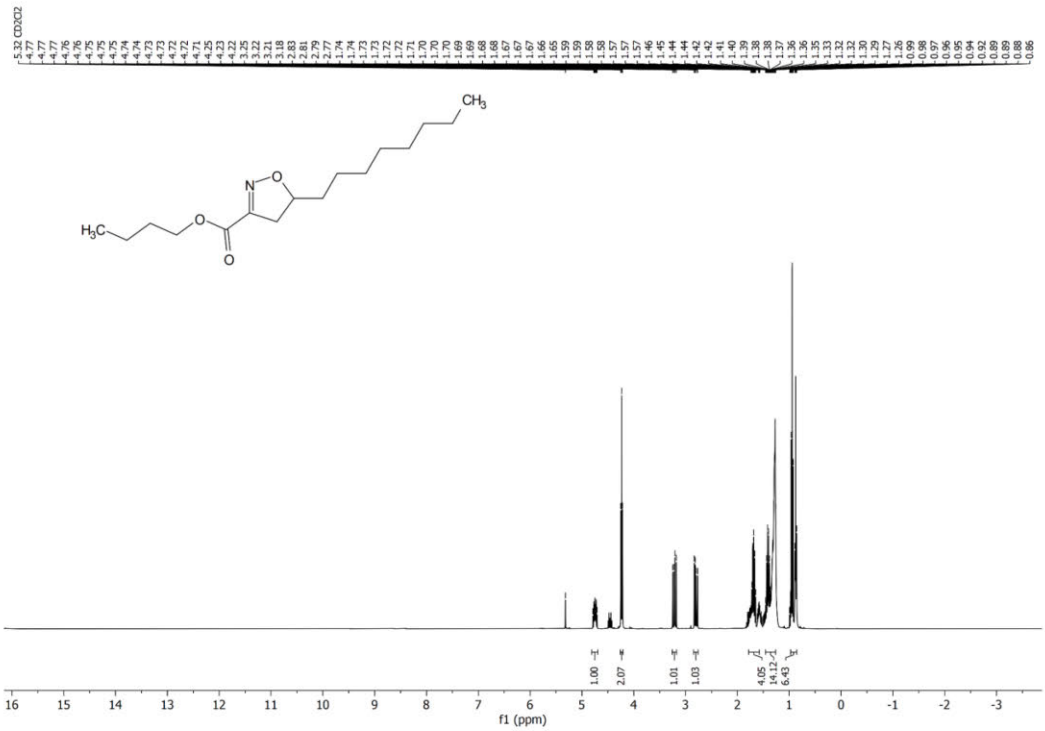

Figure S106: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6ac**.

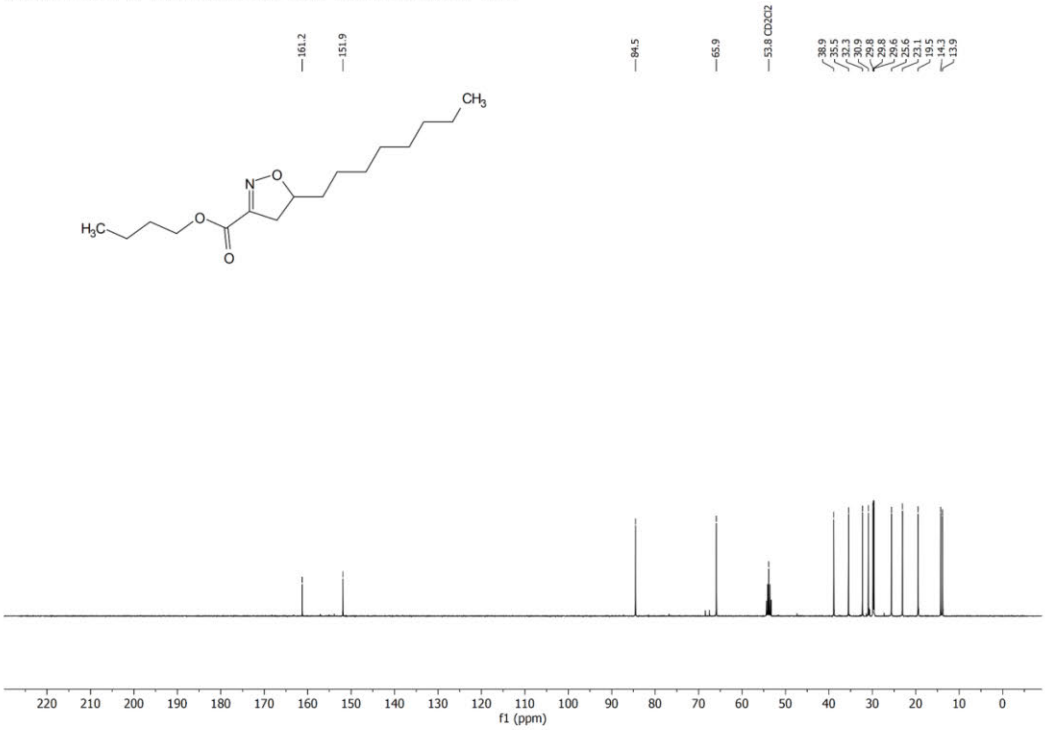

Figure S107: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6ac**.

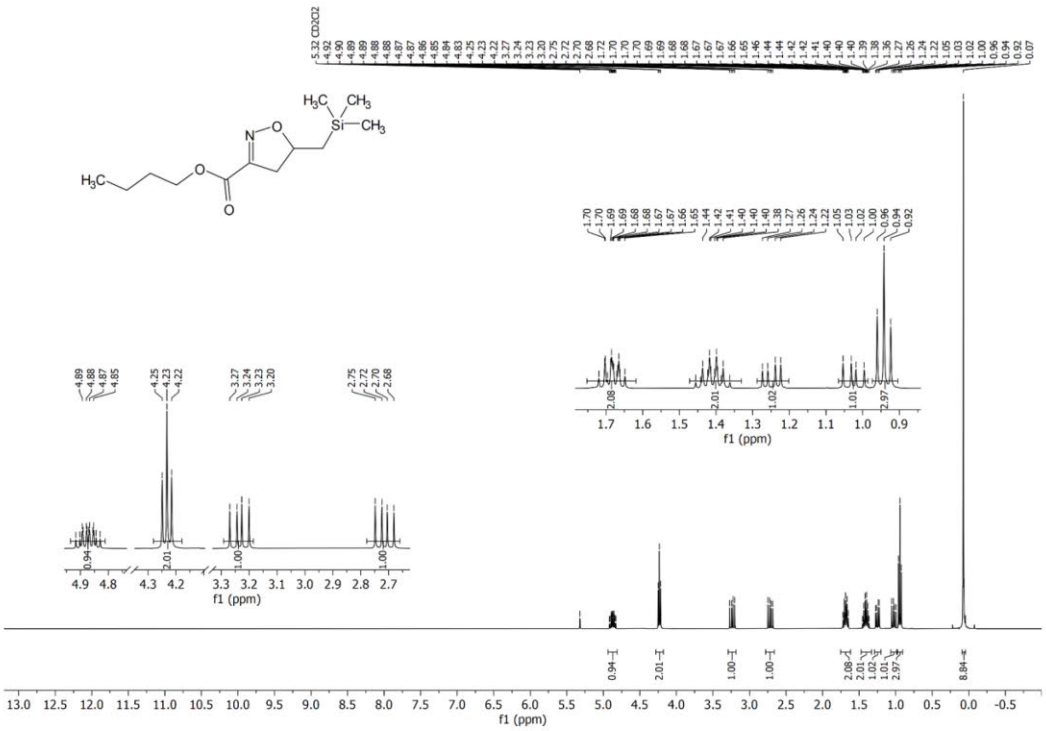

Figure S108: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6ad**.

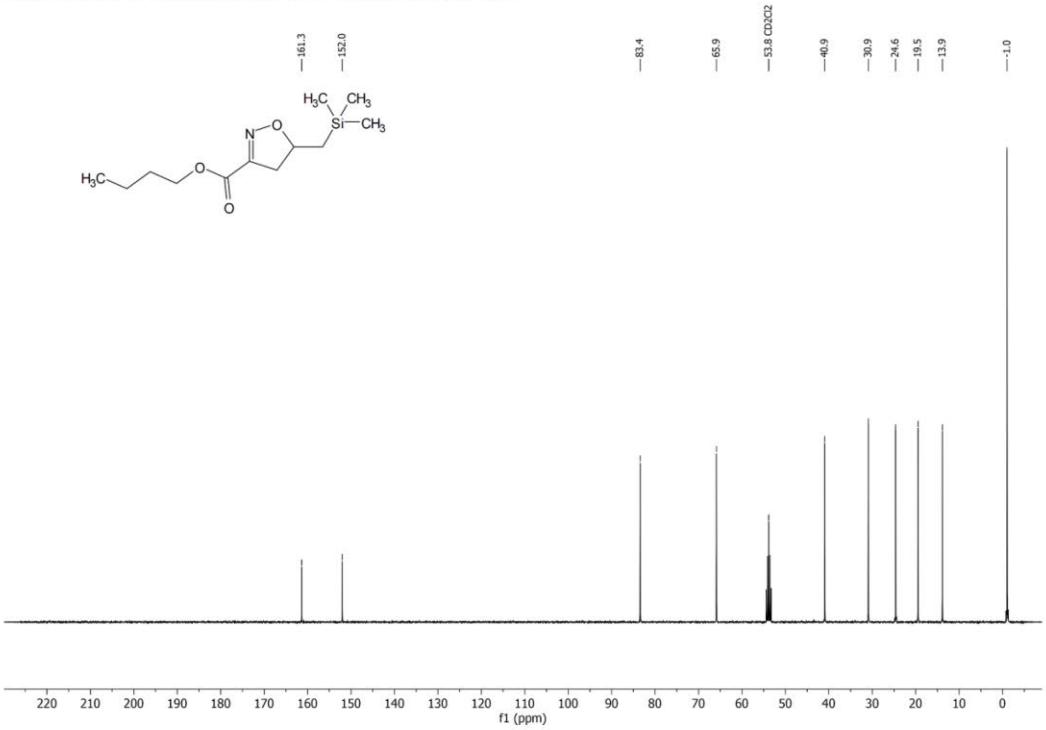

Figure S109: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6ad**.

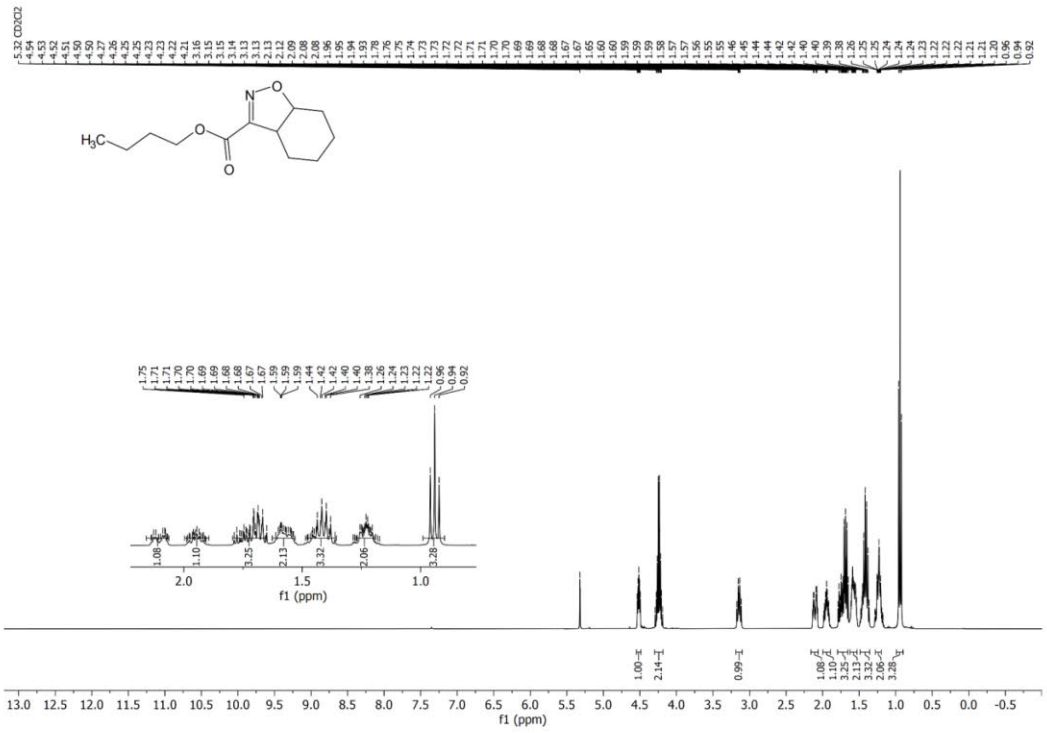

Figure S110: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6ae**.

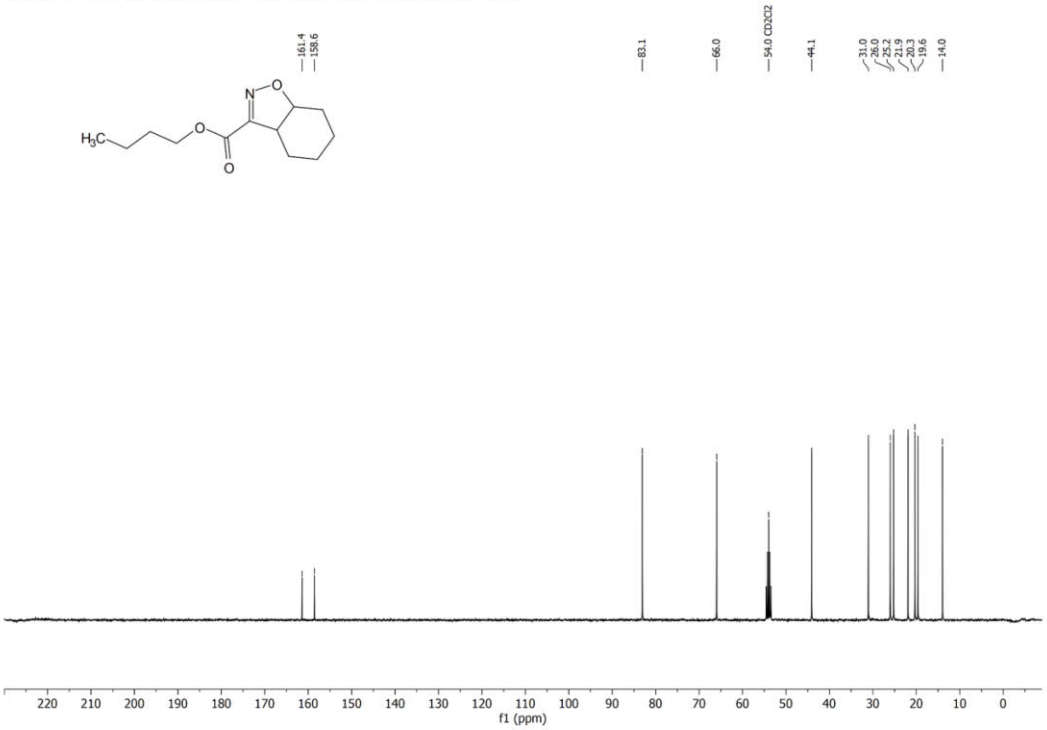

Figure S111: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6ae**.

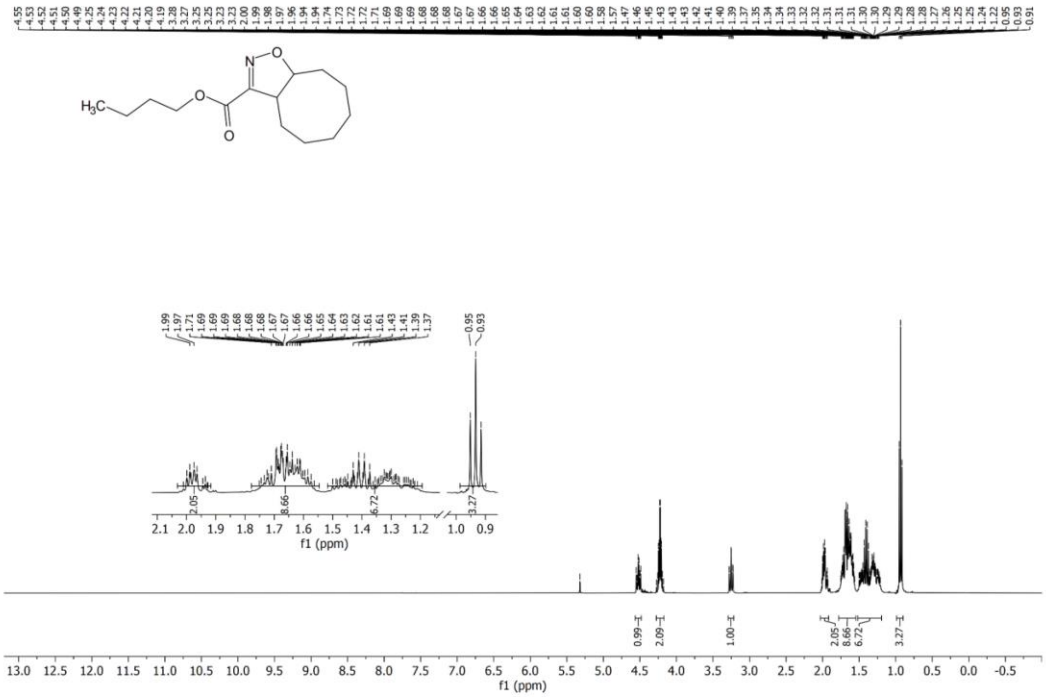

Figure S112: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6af**.

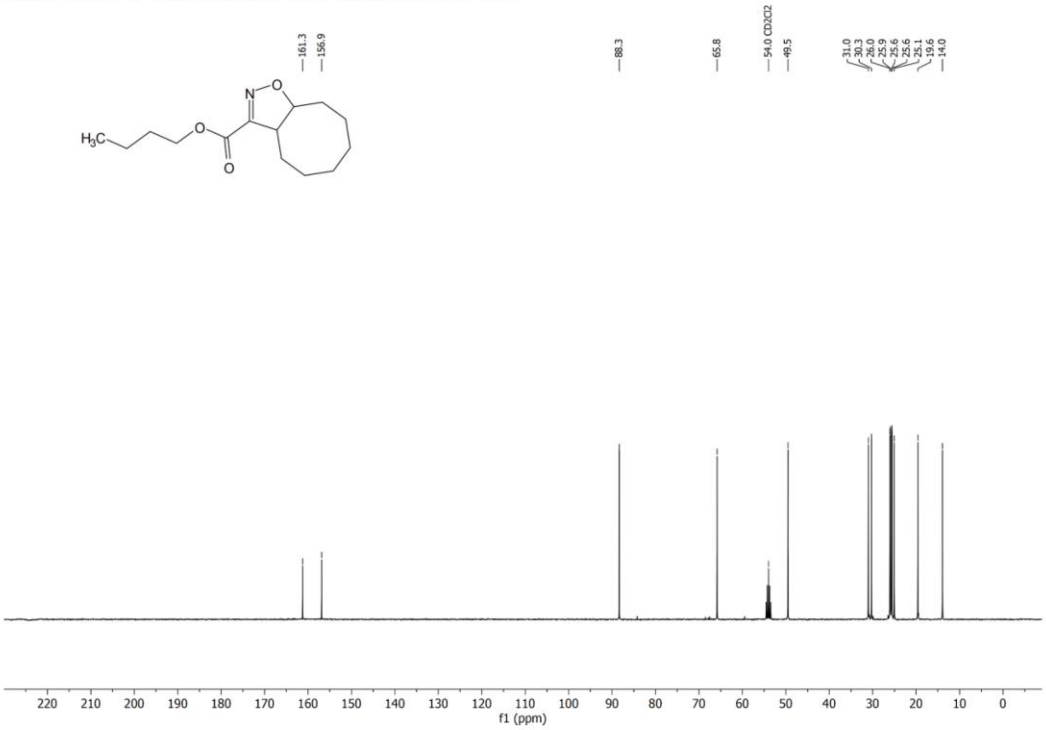

Figure S113: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6af**.

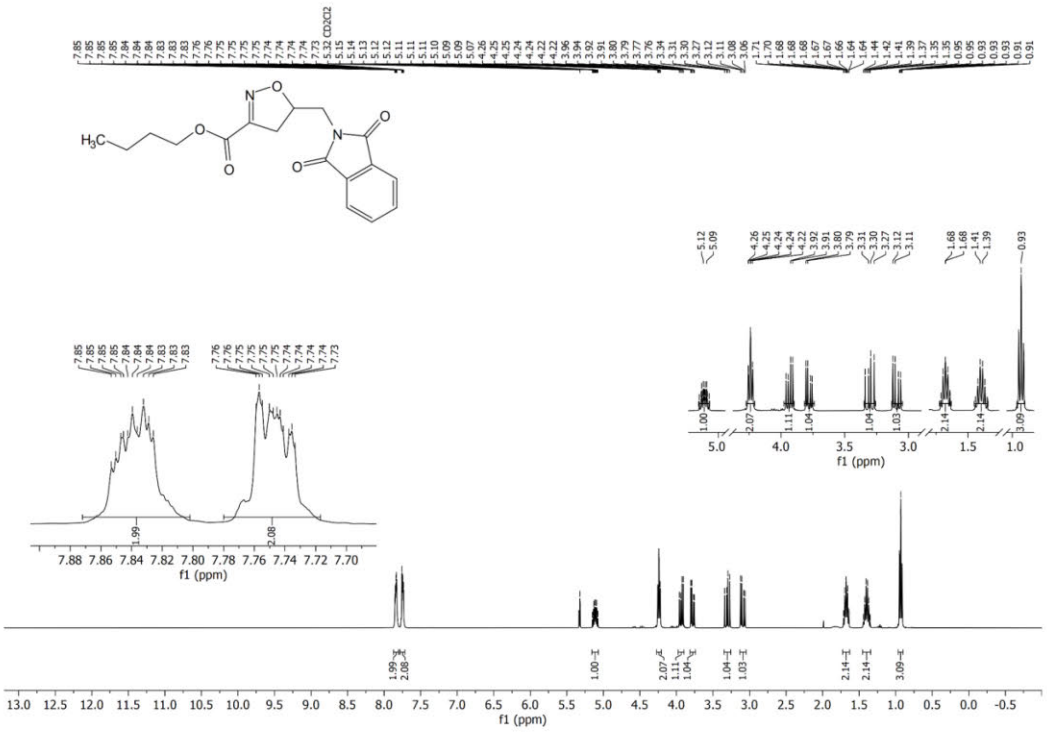

Figure S114: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6ag**.

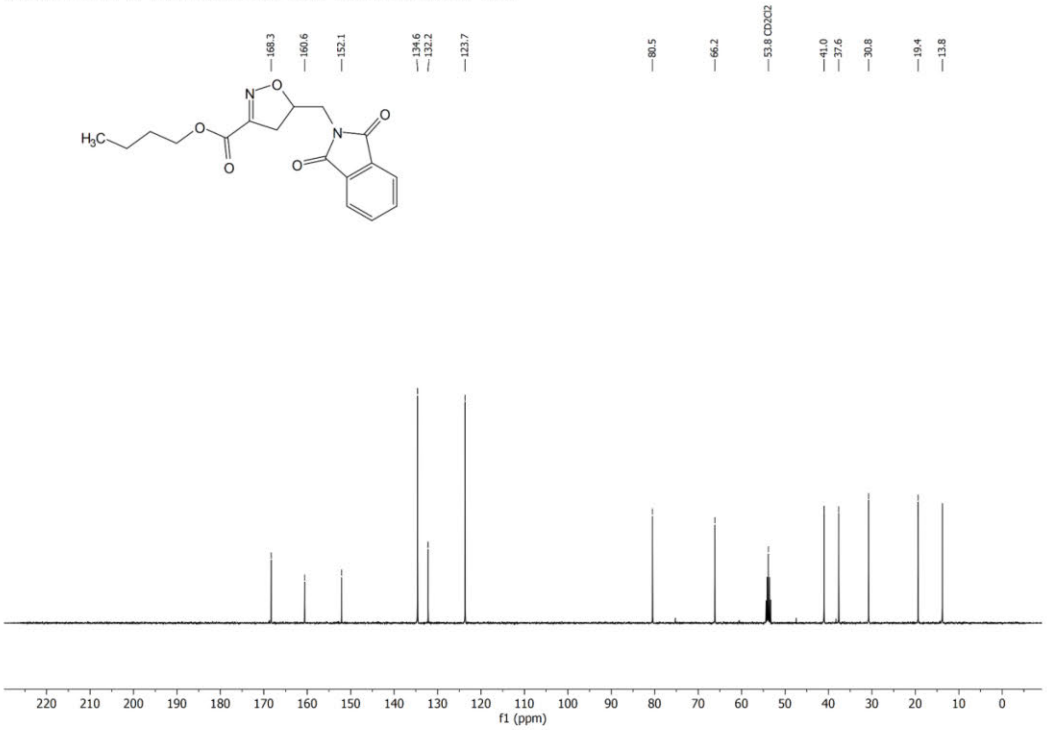

Figure S115: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6ag**.

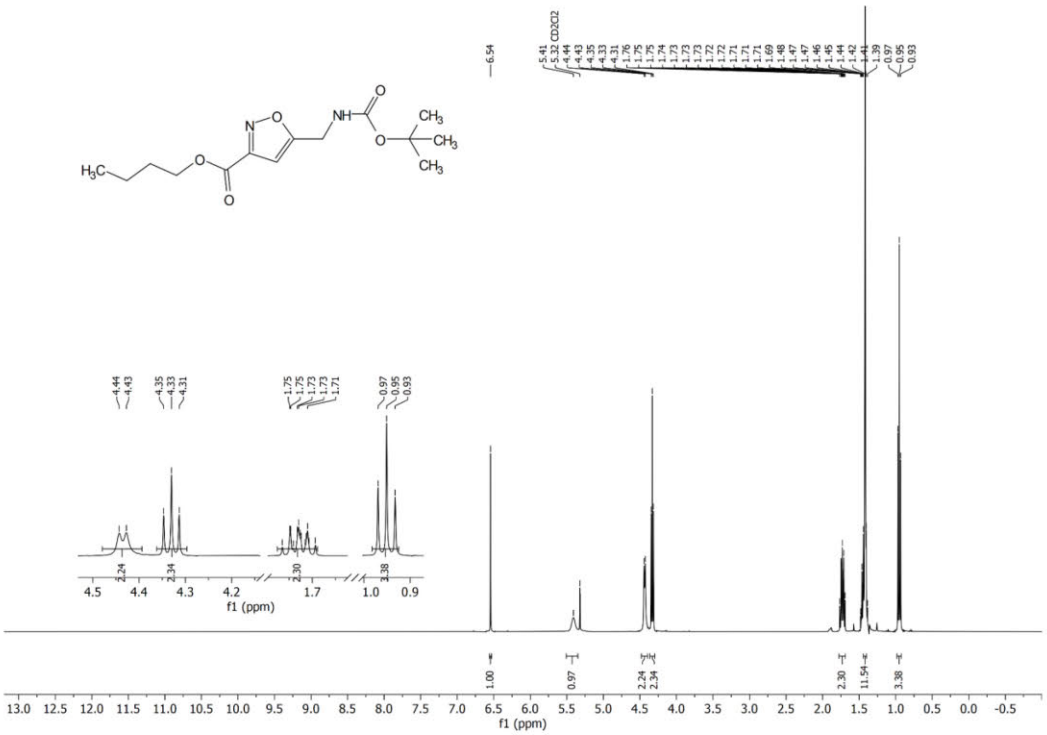

Figure S116: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6ah**.

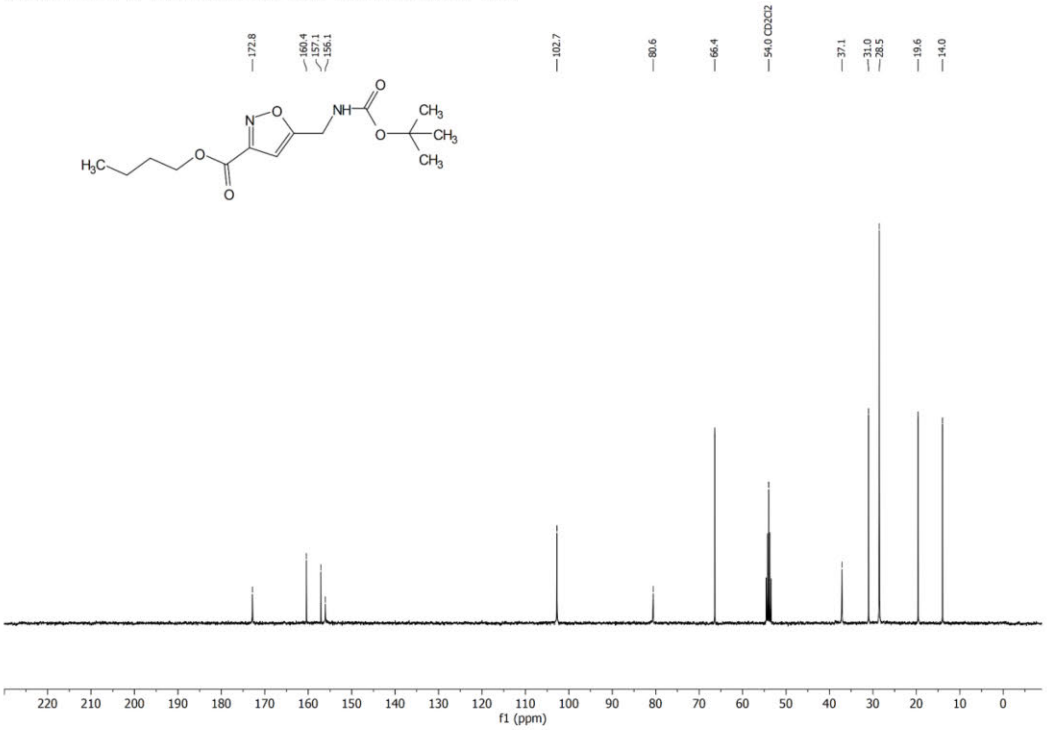

Figure S117: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6ah**.

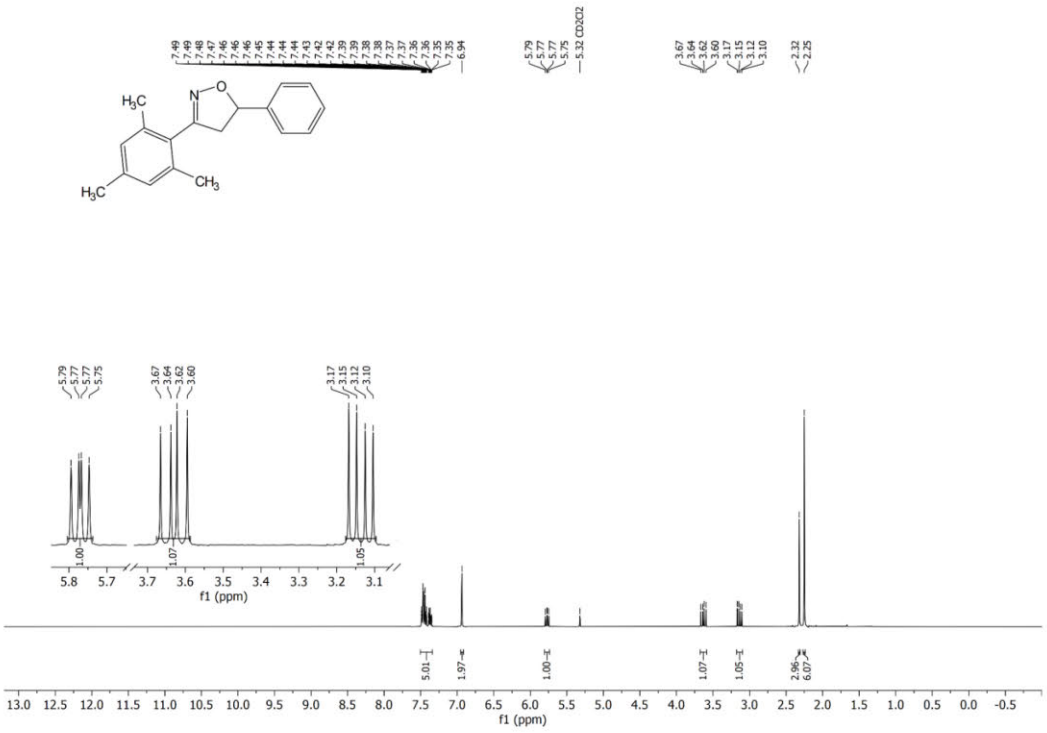

Figure S118: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6ai**.

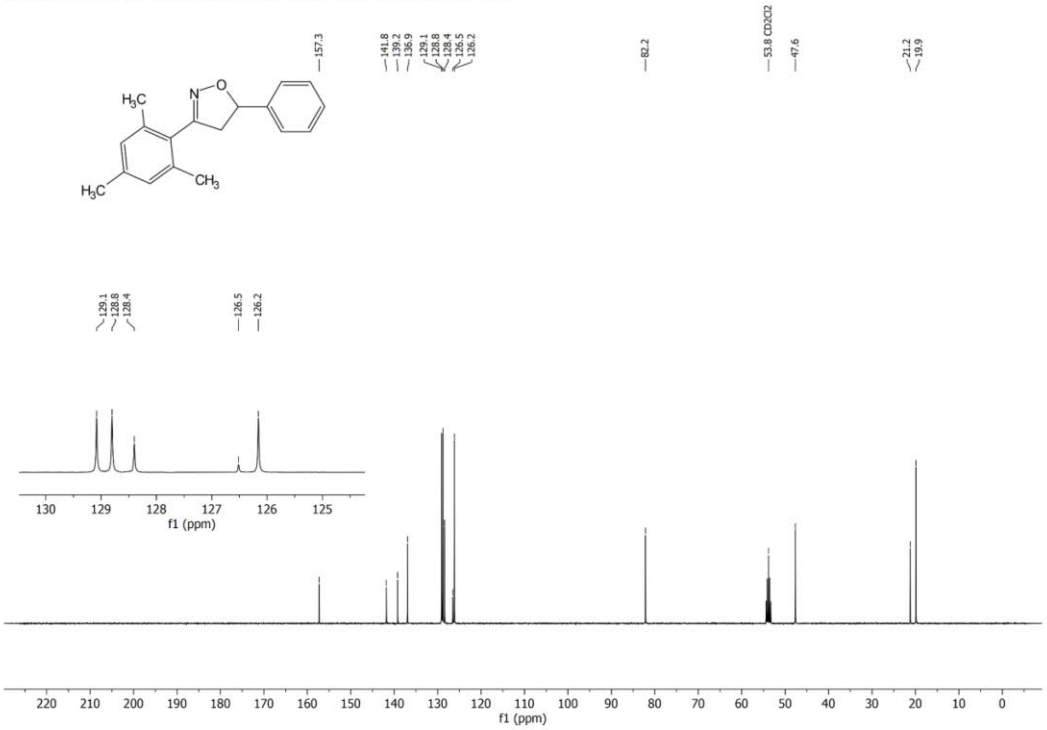

Figure S119: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6ai**.

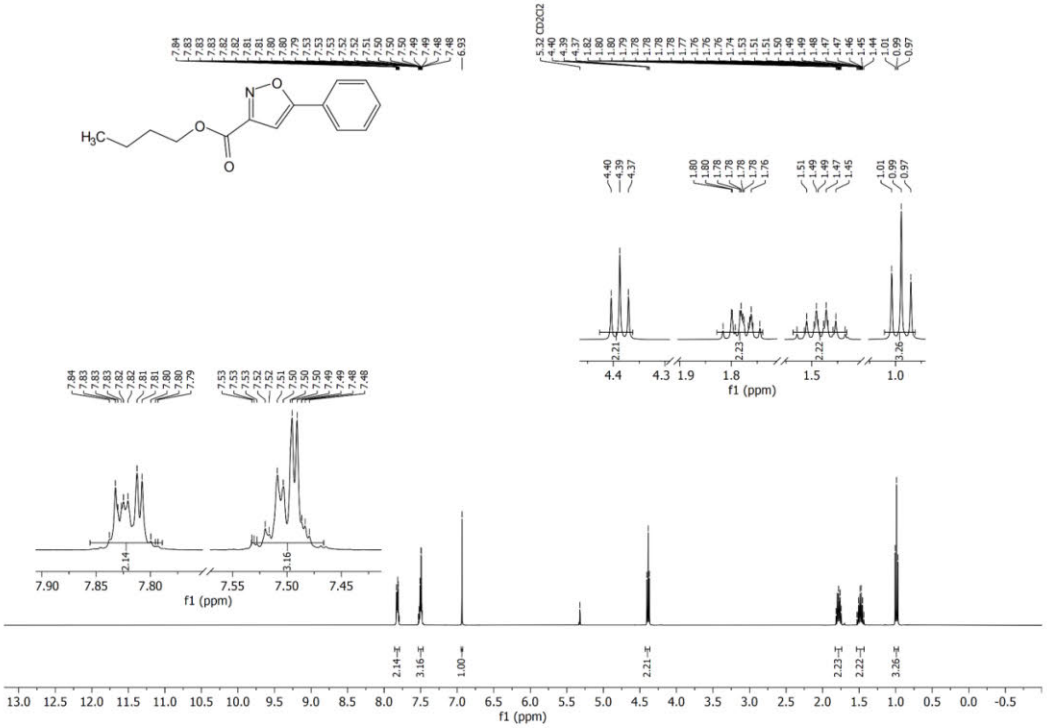

Figure S120: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6aj**.

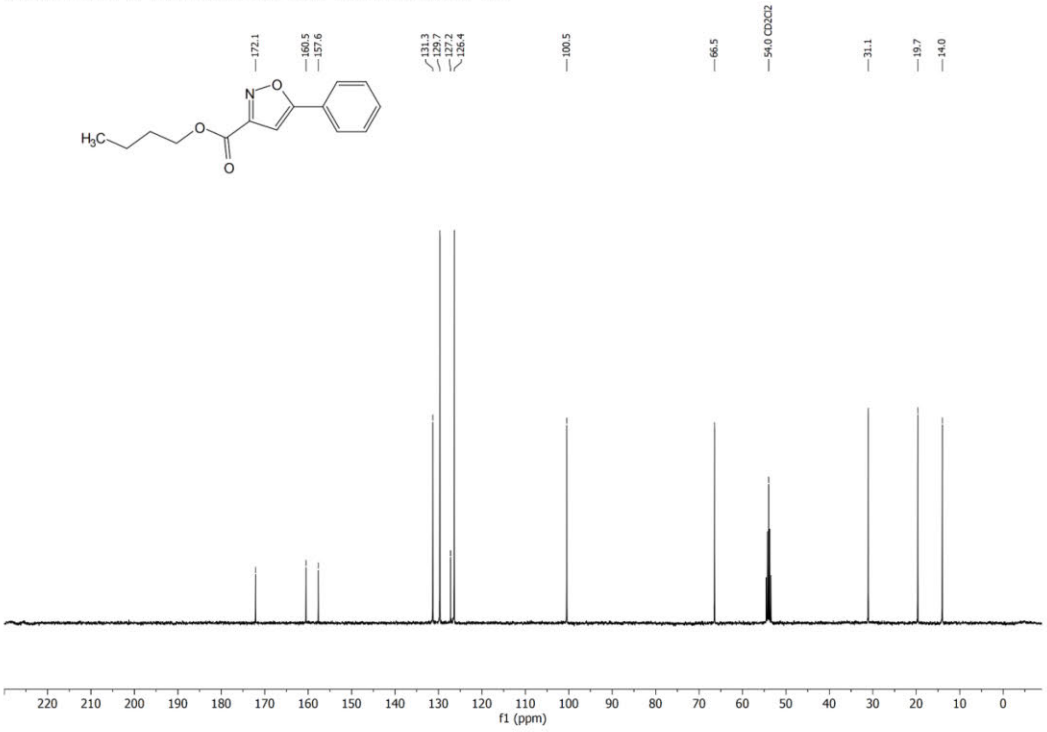

Figure S121: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6aj**.

A-2.3 Supporting Information: Direct Electrochemical Synthesis of 2,3-Disubstituted Quinoline *N*-oxides by Cathodic Reduction of Nitro Arenes

Chemistry—A European Journal

Supporting Information

Direct Electrochemical Synthesis of 2,3-Disubstituted Quinoline *N*-oxides by Cathodic Reduction of Nitro Arenes

Johannes Winter, Tobias Prenzel, Tom Wirtanen, Dieter Schollmeyer, and Siegfried R. Waldvogel*

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2. Experimental Procedures

General Information
If not stated otherwise, all reactions were performed under ambient conditions and chemicals in analytical grade were used as purchased without further purification. Cyclohexane and ethyl acetate were purchased in technical grade and purified by distillation under reduced pressure prior to use. Milli-Q® water was obtained using Simplicity® System (UV) (Merck KGaA, Darmstadt, Germany) for chromatography purposes. Anhydrous solvents were obtained from a solvent purification system SPS-5 (M. Braun Incorporated, Stratham, USA). Anhydrous acetone was obtained using molecular sieves 3 Å before application in reactions.

Instruments and Analytical Methods

Chromatography
Thin layer chromatography was performed using DC Kieselgel 60 F_{254} on aluminium plates (*Merck KGaA,* Darmstadt, Germany). A UV lamp (λ = 254 nm, NU-4 KL, *Benda*, Wiesloch, Germany) and 2,4-dinitrophenyl)hydrazine solution (1.0 g 2,4-DNPH in 250 mL 1M $HCL_{(aq.)}$) were used for substance detection. Preparative column chromatography was performed on silica gel 60 M (0.040–0.063 mm*, Macherey-Nagel GmbH & Co*, Düren, Germany) using a Sepacore® system with a Büchi Control Unit C-620, Büchi Pump Modules C-605, a UV detector Büchi UV photometer C-635, and Büchi Fraction Collector C-660 (*Büchi-Labortechnik GmbH*, Essen, Germany). The isolation of the different quinoline derivatives was conducted with reversed phase column chromatography on Sepacore® C18 (*Büchi-Labortechnik GmbH*, Essen, Germany) using different mixtures of water (0.1% formic acid) and acetonitrile as eluents.

High Resolution Mass Spectrometry
Mass spectra *via* electrospray-ionization (ESI+/ESI–) mass spectrometry was recorded using an Agilent 6545 QTOF-MS (*Agilent*, Santa Clara (CA), USA). Mass-charge ratios (*m*/*z*) were obtained for the characterized compounds.

X-ray Crystallography
The measurements of the crystal structures were carried out on a STOE IPDS-2T (*STOE & Cie GmbH*, Darmstadt, Germany) using a Mo source with graphite tube monochromator.

Gas Chromatography (GC)
Gas chromatography was performed using a GC-2010 (*Shimadzu*, Kyoto, Japan) equipped with a flame ionization detector (FID) and a quartz capillary column HI-5MS (*Avantor VWR*, Radnor, USA) with following specification: length of 30 m, inner diameter of 0.25 mm and a stationary phase ((5%-phenyl)-dimethylsiloxane) of 0.25 µm thickness. Hydrogen was used as carrier gas with a flow rate of 45.5 cm s^{-1}. Measurements were performed at an injector temperature of 250 °C and a detector temperature of 310 °C, starting at 50 °C and heating to 290 °C (holding for 2 min) with a temperature ramp of 15 °C/min (method: hart-18min).

High Performance Liquid Chromatography (HPLC)
Analysis of crude reaction mixtures and purified products was performed using a modular system LC-20A *Prominence* (*Shimadzu Deutschland GmbH*, Duisburg, Germany), UV/VIS-detector SPD-20A/AV (*Shimadzu Deutschland GmbH*, Duisburg, Germany), and LCMS-2020 Single Quadrupole (*Shimadzu Deutschland GmbH*, Duisburg, Germany). Analytical separation was performed using an Eurospher II 100-5 C-18-Trennsäule (*Knauer Wissenschaftliche Geräte GmbH*, Berlin, Germany) column (length of 150 mm, diameter of 4 mm, pore size of 100 Å, particle size 5 µm). As eluents, acetonitrile and water with 5% (*v*/*v*) acetonitrile and formic acid (1 mL L^{-1}) were used. Given retention times were obtained at λ = 254 nm.

Nuclear Magnetic Resonance (NMR) Spectroscopy
Nuclear magnetic resonance experiments were performed using a nuclear magnetic resonance spectrometer Avance III HD300 (*Bruker*, Karlsruhe, Germany) ^{1}H NMR (300 MHz), ^{19}F NMR (282 MHz), Avance II 400 (*Bruker*, Karlsruhe, Germany) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), and ^{19}F NMR (376 MHz), and Avance III 600 (*Bruker*, Karlsruhe, Germany) ^{1}H NMR (600 MHz), ^{13}C NMR (151 MHz). The spectra were recorded using deuterated solvents. To normalize the spectra obtained, reference was made to the existing solvent signal of non-deuterated fractions according to the data provided by *Fulmer et al.*[1]: $CDCl_3$ (^{1}H NMR: δ = 7.26 ppm, ^{13}C NMR: δ = 77.2 ppm), dichloromethane-d_2 (^{1}H NMR: δ = 5.32 ppm, ^{13}C NMR: δ =53.8 ppm), acetonitrile-d_3 (^{1}H NMR δ = 1.94 ppm, ^{13}C NMR: δ = 118.3 ppm) and acetone-d_6 (^{1}H NMR δ = 2.05 ppm, ^{13}C NMR: δ =29.8 ppm). Besides ^{1}H, ^{13}C and ^{19}F NMR experiments, the 2D techniques ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HSQC, ^{1}H,^{13}C-HMBC and ^{1}H,^{1}H-NOESY were used assisting to assign the signals. The following abbreviations were used to describe the signals: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), m (multiplet), q (quartet), sep (septet). The spectra obtained were evaluated with MestReNova 14.2.0-26256 (*Mestrelab Research S.L.*, Spain). ^{19}F NMR spectra were obtained with α-trifluorotoluene as external standard (δ = 63.9 ppm)[66] and recorded without ^{1}H decoupling.

Cyclic Voltammetry (CV) Measurements
Cyclic voltammetry was performed using a Metrohm 663 VA Stand equipped with a Autolab type III potentiostat (*Metrohm AG*, Herisau, Switzerland). WE: glassy carbon electrode tip, 2 mm in diameter; CE: glassy carbon rod; RE: Ag/AgCl (*vs.* FcH/FcH^+ = ferrocene). Scan rate=100 mV·s^{-1}. Electrolyte: 0.2 M formic acid/ 0.01 M sodium formate in methanol; *c*(substrate)=0.05 M.

SUPPORTING INFORMATION

Inductively Coupled Plasma Optical Emission Spectroscopy (ICP-OES)

ICP-OES measurements were performed with an ICP-OES 5800 VDV (Agilent Technologies Inc., Santa Clara, United States) and ICP multi-element standard solution IV Certipur® (Merck KGaA, Darmstadt, Germany) dissolved in 1% (m/v) nitric acid Suprapur® (Merck KGaA, Darmstadt, Germany). The calibration data was obtained using a dilution series of 0 ppb, 5 ppb, 50 ppb, 200 ppb, 600 ppb and 800 ppb. The measured concentration of lead was obtained by measuring at a wavelength of λ = 283.305 nm. The wavelength was chosen based on the lowest interference by other metals. All measurements were performed without matrix adaptation.

Electrochemical Set-Up

Electrochemical reactions were carried out using a multichannel galvanostat HMP4040 (*Rohde & Schwarz*, München, Germany). The different cells used for screening or batch reactions are described below.

Screening Reactions

Teflon® cells with a volume of 5 mL were used for the undivided set-up (figure S1, left). Divided Teflon® screening cells were equipped with a glass frit or Nafion® as separator material as shown (figure S1, right). Glass frits and Nafion® used as separator materials were pre-treated in the corresponding electrolyte prior to use. Stirring bars were used during electrolysis in each cell. The described screening systems are commercially available as IKA Screening System Package (*IKA® Werke GmbH & Co. KG*, Staufen, Germany).

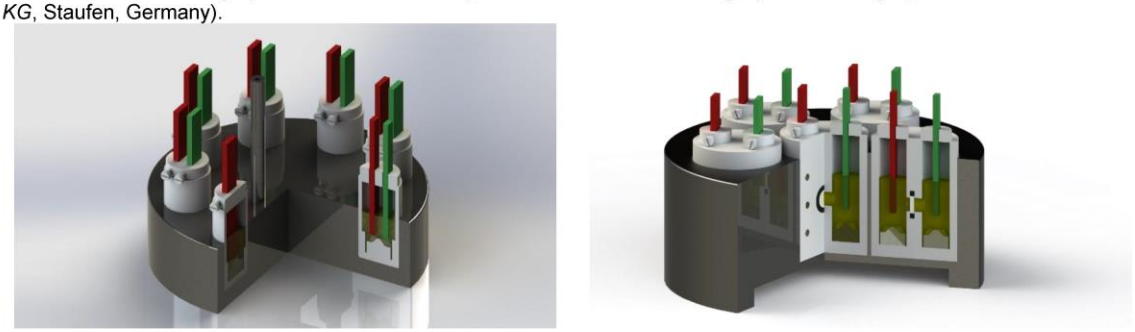


Figure S1: Undivided screening set-up (left) and divided screening set-up (right).[2]

The screening was carried out using various electrode materials (7 cm·1 cm). Metal and graphite electrodes were sanded using 600 grit followed by 1000 grit sandpaper and cleaned with methanol prior to use. Platinum foil electrodes were flame treated before use and fixed to Teflon® supports during electrolysis. BDD electrodes were electrochemically treated (j = 50 mA·cm^{-2}) in 20% (*v*/*v*) sulfuric acid for 30 min before use. In undivided cells, the electrodes were immersed 1.5 cm into the solution. This resulted in an electrode area of 1.5 cm^2 used for electrolysis. In divided cells, the electrodes were immersed 2.5 cm into the electrolyte. This resulted in an electrode area of 2.5 cm^2 used for electrolysis.

Electrode Materials

Table S1: Electrode materials, purity and their supplier.

Entry	Electrode Material	Purity	Supplier
1	Boron-doped diamond (DIACHEM®)	15 µm boron-doped diamond layer on silicon	*CONDIAS GmbH*, Itzehoe, Germany
2	Glassy carbon	-	*HTW*, Thierhaupten, Germany
3	Isostatic graphite	-	*SGL Carbon*, Bonn, Germany
4	Reticulated vitreous carbon (RVC, DUOCEL®)	1 ppi	*ERG Aerospace Corporation*, Oakland, CA, USA
5	Graphite felt (SIGRAFLEX®)	-	*SGL Carbon*, Meitingen, Germany
6	Platinum	>99%	*OEGUSSA*, Vienna, Austria
7	Nickel	-	*IKA®-Werke GmbH & CO. KG*, Staufen, Germany
8	Zinc	-	*Grillo-Werke AG*, Duisburg, Germany
9	Tin	-	*Goodfellow GmbH*, Hamburg, Germany
10	Lead	-	*Globus Fachmärkte GmbH & Co. KG*, Völklingen, Germany
11	Leaded bronze (CuSn7Pb15)	-	*Metallwerk Langenau GMBH*, Langenau, Germany

Scale-up experiments were performed in 50 mL, 100 mL, and 250 mL batch-type cells with a PTFE stopper and sleeve, electrodes and electrode holders used a TDK-Lambda Z+ series (*TDK-Lambda UK Limited*, Devon, United Kingdom) or a multichannel power supply HMP4040 (*Rohde & Schwarz*, München, Germany) as power sources. The batch-type cells of the scale-up experiments are commercially available as SynLectro™ Starter Kit (*Merck KGaA*, Darmstadt, Germany).[3]
In the 50 mL and 100 mL electrolysis set-up glassy carbon electrodes with dimensions of 6 cm·2 cm and lead electrodes of 7 cm·2 cm were used. In the 250 mL electrolysis set-up glassy carbon and lead electrodes with identical dimensions of 12 cm·4 cm were used.

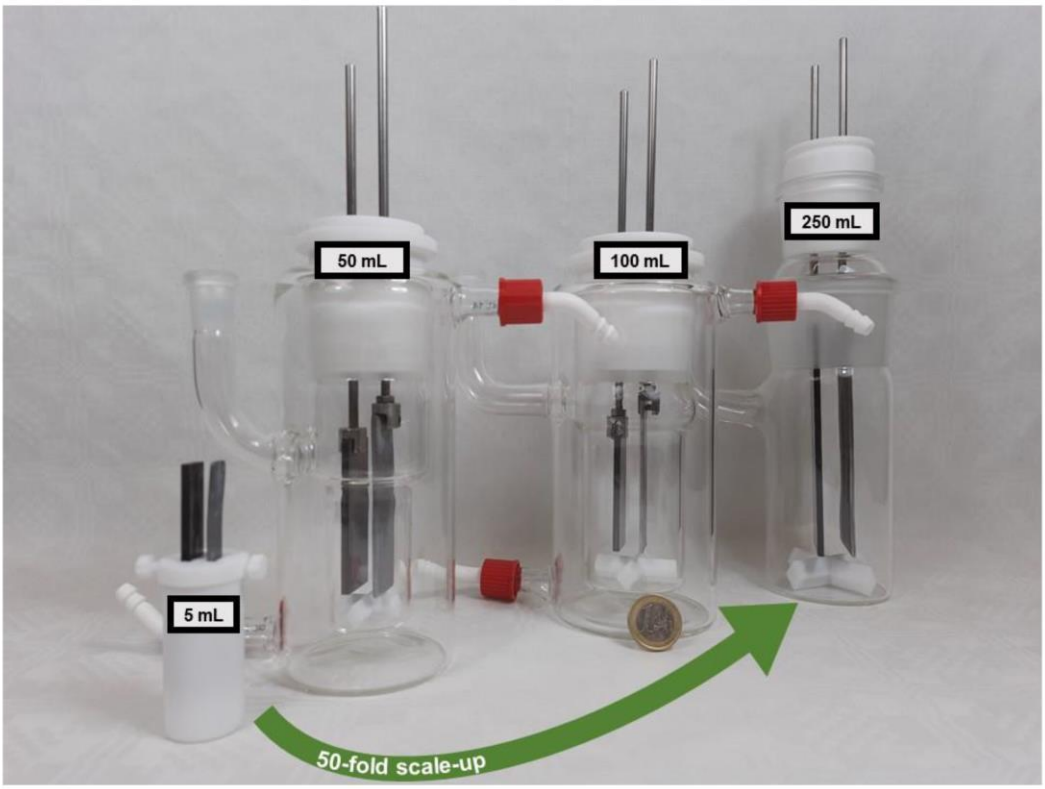


Figure S2: Different batch-type cells left to right: 5 mL Teflon® screening cell with glassy carbon and lead electrodes; 50 mL batch-type jacketed glass cell with glassy carbon and lead electrodes, Teflon® plug and electrode holders; 100 mL batch-type jacketed glass cell with glassy carbon and lead electrodes, Teflon® plug and electrode holders; 250 mL batch-type glass cell with glassy carbon and lead electrodes, Teflon® plug and electrode holders.

2.1. General Protocol for the Synthesis of α-Benzylated β-Ketoesters (GPI)

Under an argon atmosphere, potassium carbonate (6.0 eq.) was suspended in anhydrous acetone and chilled to 0 °C. The corresponding β-keto esters (3.0 - 4.0 eq.) and KI (0.05 eq.) were added, and the mixture was stirred for 30 minutes. 2-Nitrobenzyl bromide (1.0 eq.) was dissolved in anhydrous acetone, added dropwise, and the reaction mixture was stirred until completion of the reaction starting at 0 °C and slowly heating to room temperature. The solids were filtered off and the solvent was removed under reduced pressure. The residues were dissolved in ethyl acetate:water (1:1 *v*:*v*). The organic layer was washed twice with saturated sodium carbonate solution, once with brine, and dried over $MgSO_4$. The solvent was removed under reduced pressure. The desired α-benzylated β-keto esters were isolated by flash column chromatography using SiO_2 as stationary phase and cyclohexane:ethyl acetate as eluents.

2.2. General Protocol for the Synthesis of Benzylidene Diones (GPII)

2-Nitro benzaldehyde (1.0 eq.) and the corresponding dione (1.1 – 1.3 eq.) were dissolved in neat at 65 °C. Glacial acetic acid (0.1 mL) and piperidine were then added. The mixture was stirred at 65 °C until completion, diethyl ether was then added and the resulting solution was cooled to 0 °C. The precipitate formed was filtered and washed with cold diethyl ether. Where necessary, the crude product was recrystallized using the appropriate solvent to obtain the desired benzylidene dione.

2.3. General Protocol for the Synthesis of Benzylidene Diones (GPIII)

2-Nitro benzaldehyde (1.0 eq.) and the corresponding dione (1.1 – 1.3 eq.) were dissolved in acetonitrile. Piperidine (0.1 mL) was added and the mixture was stirred at 75 °C. After completion of the reaction the solvent was removed under reduced pressure and diethyl ether was added. The precipitate formed was filtered off and washed with cold diethyl ether. Where necessary, the crude product was recrystallized using the appropriate solvent to obtain the desired benzylidene dione.

2.4. General Protocol for the Electrochemical Synthesis of Quinoline *N*-oxides (GPIV)

The electrolyte was prepared by dissolving 0.50 mol formic acid and 0.027 mol sodium formate in 100 mL methanol. The corresponding substrate was dissolved in 5 mL of the electrolyte in a 5 mL undivided Teflon® screening cell equipped with a stirring bar. The electrolysis was performed under constant current conditions (current density of 4.1 $mA \cdot cm^{-2}$ for 96.5 C (5 *F*)). After 24 h the reaction mixture was dissolved in dichloromethane and washed once with saturated Na_2CO_3 solution (5 mL) and water (5 mL). The aqueous layer was extracted with dichloromethane (3 x 10 mL), the combined organic layers were washed once with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and 0.1 mmol 1,3,5-trimethoxybenzene was added as internal standard for quantification by ^1H NMR. Purification was performed using reversed phase flash column chromatography using acetonitrile and water (0.1% (*v*/*v*) formic acid) as eluents.

2.5. General Protocol for the Scale-Up of Electrochemical Synthesis of 10a (GPV)

The corresponding substrate was dissolved in 5 mL of the electrolyte (5 M formic acid/0.27 M sodium formate in methanol) in the different undivided batch-type cells (50 mL, 100 mL and 250 mL) equipped with a stirring bar. The electrolysis was performed under constant current conditions (current density of 4.1 $mA \cdot cm^{-2}$, charge applied:5 *F*). After completion of the electrolysis the reaction mixture was dissolved in dichloromethane and washed once with saturated Na_2CO_3 solution (25 mL) and water (25 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organic layers were washed once with brine (50 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure. Purification was performed by filtration through silica using cyclohexane:ethyl acetate 2:1 (*v*:*v*) to remove impurities. The product was eluted with ethyl acetate:methanol 95:5 (*v*:*v*) and obtained by removing the solvent under reduced pressure.

3. CV-Studies

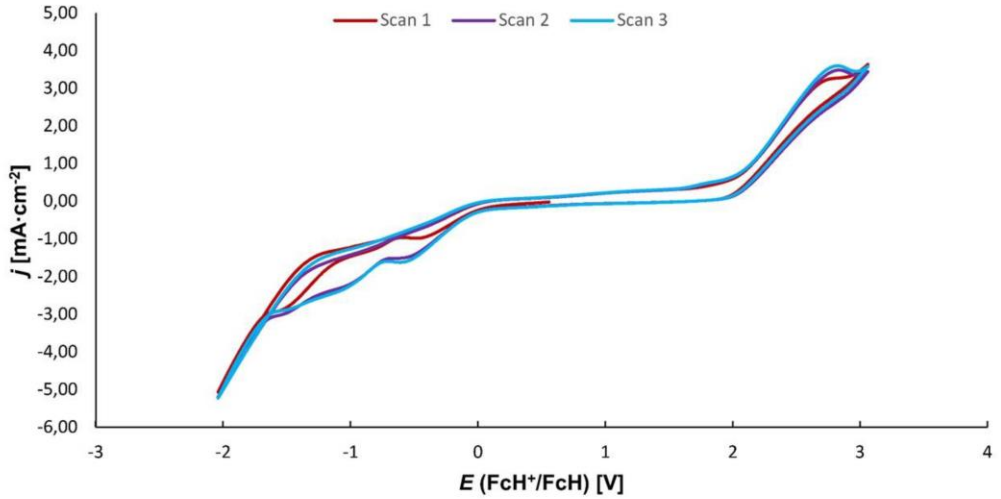


Figure S3: 0.2 M formic acid/ 0.01 M sodium formate in methanol; working electrode: glassy carbon; counter electrode: glassy carbon; reference electrode: Ag/AgCl in sat. LiCl/EtOH; Scan rate: 100 mV/s, 3 scans. Potential referenced vs. FcH/FcH^+ ($FcH = Fe(\eta^5\text{-}C_5H_5)_2$).

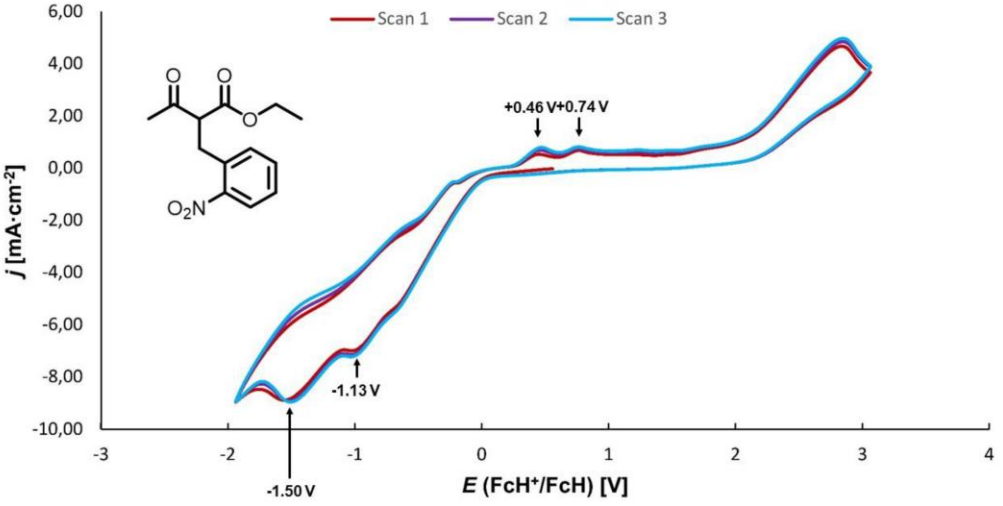


Figure S4: Compound **4a** *c*(substrate) = 0.025 M + 0.2 M formic acid/ 0.01 M sodium formate in methanol; working electrode: glassy carbon; counter electrode: glassy carbon; reference electrode: Ag/AgCl in sat. LiCl/EtOH; Scan rate: 100 mV/s, 3 scans. Potential referenced vs. FcH/FcH^+ ($FcH = Fe(\eta^5\text{-}C_5H_5)_2$).

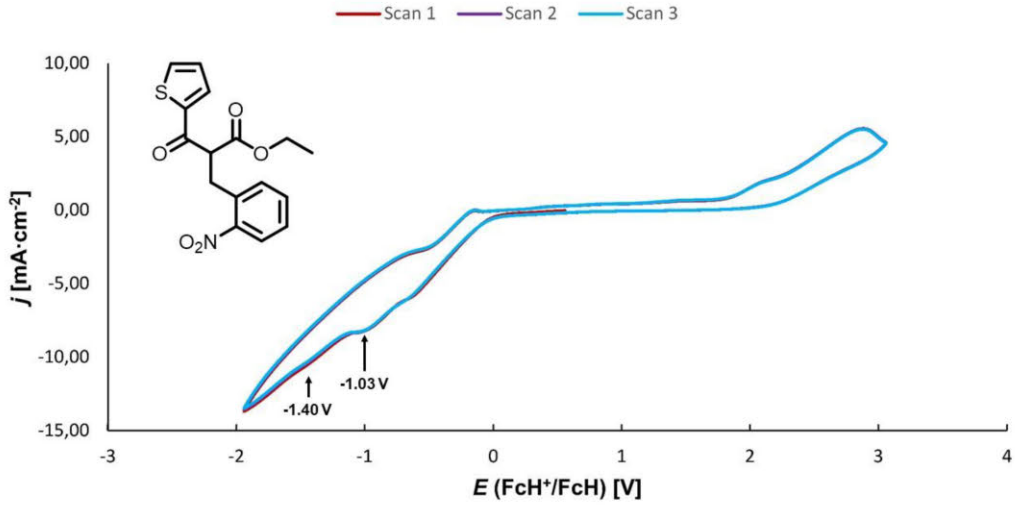


Figure S5: Compound **4m** *c*(substrate) = 0.025 M + 0.2 M formic acid/ 0.01 M sodium formate in methanol; working electrode: glassy carbon; counter electrode: glassy carbon; reference electrode: Ag/AgCl in sat. LiCl/EtOH; Scan rate: 100 mV/s, 3 scans. Potential referenced vs. FcH/FcH^+ ($FcH = Fe(\eta^5\text{-}C_5H_5)_2$).

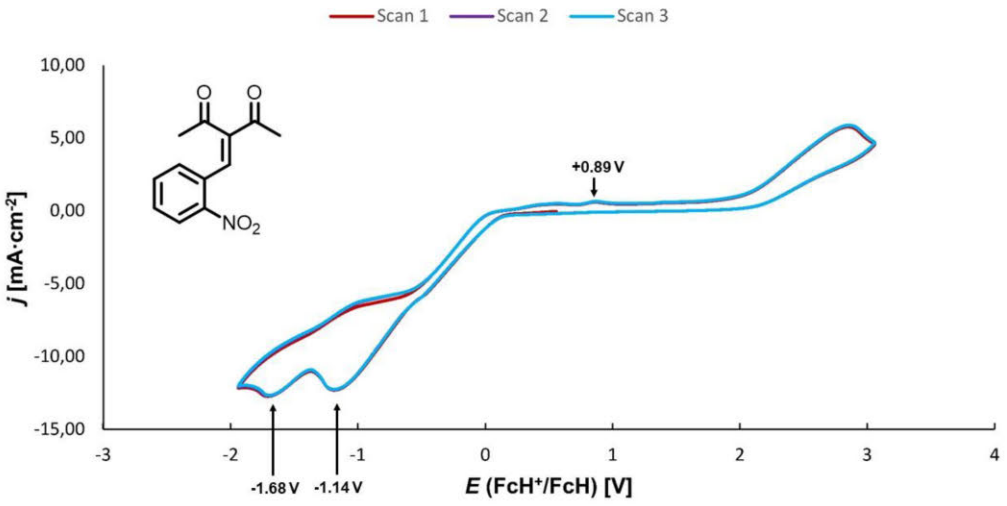


Figure S6: Compound **8a** *c*(substrate) = 0.025 M + 0.2 M formic acid/ 0.01 M sodium formate in methanol; working electrode: glassy carbon; counter electrode: glassy carbon; reference electrode: Ag/AgCl in sat. LiCl/EtOH; Scan rate: 100 mV/s, 3 scans. Potential referenced vs. FcH/FcH^+ ($FcH = Fe(\eta^5\text{-}C_5H_5)_2$).

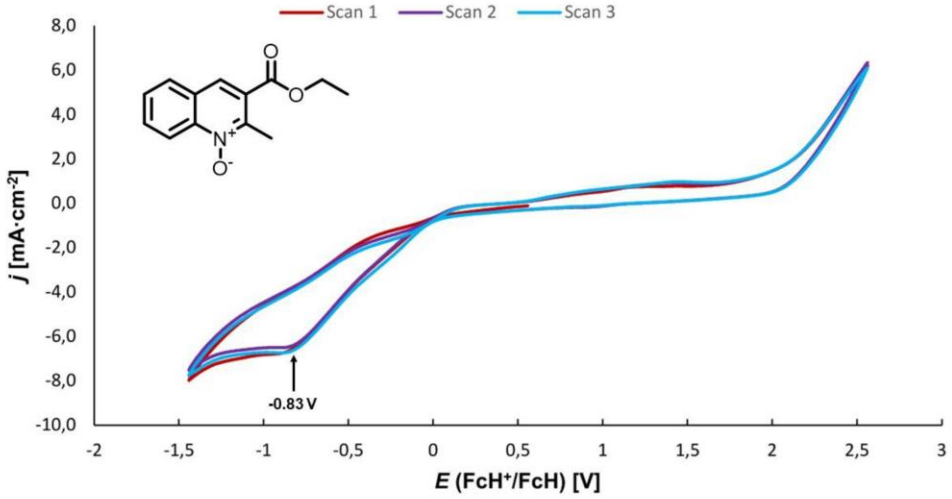
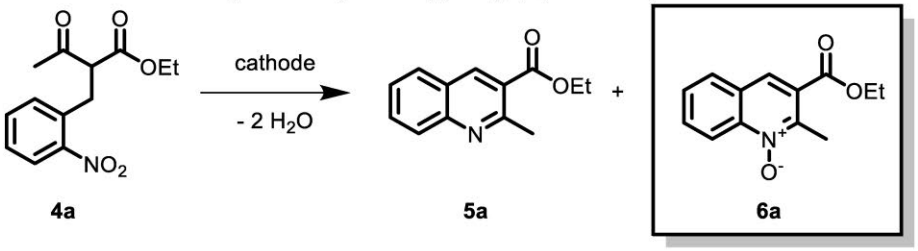


Figure S7: Compound **6a** *c*(substrate) = 0.025 M + 0.2 M formic acid/ 0.01 M sodium formate in methanol; working electrode: glassy carbon; counter electrode: glassy carbon; reference electrode: Ag/AgCl in sat. LiCl/EtOH; Scan rate: 100 mV/s, 3 scans. Potential referenced vs. FcH/FcH^+ ($FcH = Fe(\eta^5\text{-}C_5H_5)_2$).

Due to corrosion in the supporting electrolyte used, lead could not be used as the cathode material in the cyclovoltammetric measurements. Instead, glassy carbon was applied as the formation of **6a** could also be observed in the different screening experiments. The results of the different CV measurements match the proposed mechanism in the formation of the different quinoline *N*-oxides also showing the subsequent reduction of **6a** to form **5a**. The observed reduction of **6a** by using glassy carbon rather than lead as cathode material highlights the influence on the selectivity of the cathode material.

4. Optimization of electrolytic conditions

The optimization experiments of the electrolytic conditions in the selective formation of quinoline *N*-oxide **6a** were first conducted using substrate **4a** as standard substrate according to general protocol **GPIV**. The yield of the quinoline **5a** and quinoline *N*-oxide **6a** and conversion were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.



4a **5a** **6a**

Scheme S1: Electrochemical conversion of compound **4a** into the quinoline **5a** and quinoline *N*-oxide **6a**.

Table S2: Influence of the electrolysis setup.

Entry	Setup	Yield[a] of **5a** [%]	Yield[a] of **6a** [%]	Conversion[a][b] [%]
1	Undivided[c]	69	19	88
2	Divided; separator: glass frit[d]	24	3	96
3	Divided; separator: Nafion® [d]	0	7	100

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] Based on remaining starting material; [c] 0.04 M substrate, stirring velocity: 300 rpm, temperature: r.t., supporting electrolyte: 5 mL 0.5 M H_2SO_4 in methanol, j = 4.1 mA·cm^{-2}, charge applied: 6 F ; anode: glassy carbon, cathode, BDD; [d] 0.04 M substrate, 300 rpm stirring velocity, temperature: r.t., supporting electrolyte: 6 mL 0.5 M H_2SO_4 in methanol in each compartment, j = 4.1 mA·cm^{-2}, charge applied: 6 F ; anode: glassy carbon, cathode, BDD;

Table S3: Influence of the supporting electrolyte.[c]

Entry	Electrolyte	Yield[a] of **5a** [%]	Yield[a] of **6a** [%]	Conversion[a][b] [%]
1	0.5 M H_2SO_4 in methanol	69	19	88
2	1.0 M H_2SO_4 in methanol	17	8	87
3	2.0 M H_2SO_4 in methanol	21	6	95
4	0.05 M H_2SO_4 in methanol	45	4	98
5	0.5 M AcOH in methanol	7	23	98
6	0.5 M $MeSO_3H$ in methanol	20	5	96
7	0.05 M H_2SO_4 in methanol	45	4	98
8	5 M AcOH/0.028 M NaOAc in methanol	1	7	86
9	5 M AcOH/0.45 M NaOAc in methanol	4	20	99
10	0.01 M NBu_4BF_4 in methanol	3	13	98
11	5 M HCOOH/0.27 M NaHCOO in methanol	3	27	97
12	0.5 M NaOH in methanol	0	0	100
13	5% NMe_4OH in methanol (*w*/*v*)	0	0	100
14	0.01 M NBu_4BF_4 in HFIP	2	7	95
15	0.5 M NH_4HCOO in methanol:TFA 4:1 (*v*/*v*)	0	0	100

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] Based on remaining starting material; [c] 0.04 M substrate, stirring velocity: 300 rpm, temperature: r.t., j = 4.1 mA·cm^{-2}, charge applied: 6 F ; anode: glassy carbon, cathode, BDD, undivided 5 mL Teflon® cell.

Table S4: Influence of the cathode material.

Entry	Cathode	Yield[a] of **5a** [%]	Yield[a] of **6a** [%]	Conversion[a][b] [%]
1	BDD[c]	0	28	92
2	Lead[c]	0	37	92
3	CuSn7Pb15[c]	0	14	79
4	Lead[d]	0	38	100

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] Based on remaining starting material; [c] 0.04 M substrate, supporting electrolyte: 5 M HCOOH/0.27 M NaHCOO in methanol, stirring velocity: 300 rpm, temperature: r.t., j = 4.1 mA·cm^{-2}, charge applied: 4 F ; anode: glassy carbon, undivided 5 mL Teflon® cell; [d] 0.04 M substrate, supporting electrolyte: 5 M HCOOH/0.27 M NaHCOO in methanol, stirring velocity: 300 rpm, temperature: r.t., j = 4.1 mA·cm^{-2}, charge applied: 5 F ; anode: glassy carbon, undivided 5 mL Teflon® cell.

Table S5: Influence of the reaction time.

Entry	Time [h]	Yield[a] of **5a** [%]	Yield[a] of **6a** [%]	Conversion[a][b] [%]
1	24	0	38	100
2	48	0	41	100
3	72	0	40	100

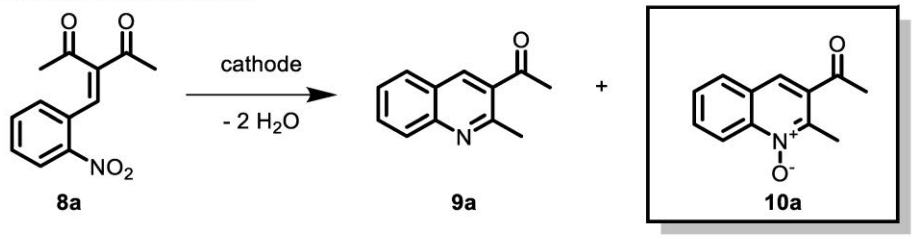
[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] Based on remaining starting material; [c] 0.04 M substrate, stirring velocity: 300 rpm, temperature: r.t., supporting electrolyte: 5 mL 0.5 M H_2SO_4 in methanol, j = 4.1 mA·cm^{-2}, charge applied: 5 F ; anode: glassy carbon, cathode, BDD; [d]] 0.04 M substrate, 300 rpm stirring velocity, temperature: r.t., supporting electrolyte: 5 M HCOOH/0.27 M NaHCOO in methanol, j = 4.1 mA·cm^{-2}, charge applied: 5 F ; anode: glassy carbon, cathode, lead, undivided 5 mL Teflon® cell.

Table S6: Influence of the current density.

Entry	J [mA·cm^{-2}]	Yield[a] of **5a** [%]	Yield[a] of **6a** [%]	Conversion[a][b] [%]
1	4.1	0	37	92
2	2.4	0	35	92

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] Based on remaining starting material; [c] 0.04 M substrate, stirring velocity: 300 rpm, temperature: r.t., supporting electrolyte: 5 mL 0.5 M H_2SO_4 in methanol, j = 4.1 mA·cm^{-2}, charge applied: 5 F ; anode: glassy carbon, cathode, BDD; [d]] 0.04 M substrate, 300 rpm stirring velocity, temperature: r.t., supporting electrolyte: 5 M HCOOH/0.27 M NaHCOO in methanol, j = 4.1 mA·cm^{-2}, charge applied: 5 F ; anode: glassy carbon, cathode, lead, undivided 5 mL Teflon® cell.

Further studies were conducted using substrate **8a** as standard substrate according to general protocol **GPIV** to observe further effects of the unsaturated motif on the selective formation of quinoline *N*-oxide **10a**. The yield of the quinoline **9a** and quinoline *N*-oxide **10a** and conversion of the starting material were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard.



Scheme S2: Electrochemical conversion of **8a** into the quinoline **9a** and quinoline *N*-oxide **9a**.

Table S7: Influence of the supporting electrolyte using BDD as cathode material.[c]

Entry	Electrolyte	Yield[a] of **9a** [%]	Yield[a] of **10a** [%]	Conversion[a][b] [%]
1	0.5 M H_2SO_4 in methanol[c]	1	11	100
2	5 M HCOOH/0.27 M NaHCOO in methanol[d]	5	49	100
3	1 M $HCl_{(aq.)}$:MeOH 3:2 (*v*:v)[d]	11	62	98

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] Based on remaining starting material; [c] 0.04 M substrate, stirring velocity: 300 rpm, temperature: r.t., j = 4.1 mA·cm^{-2}, charge applied: 6 F ; anode: glassy carbon, cathode, BDD, undivided 5 mL Teflon® cell; [d] 0.04 M substrate, stirring velocity: 300 rpm, temperature: r.t., j = 4.1 mA·cm^{-2}, charge applied: 5 F ; anode: glassy carbon, cathode, BDD, undivided 5 mL Teflon® cell.

Table S8: Control experiment without electricity.[c]

Entry	Electrolyte	Yield[a] of **9a** [%]	Yield[a] of **10a** [%]	Conversion[a][b] [%]
1	5 M HCOOH/0.27 M NaHCOO in methanol[c]	0	0	0

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] Based on remaining starting material; [c] 0.04 M substrate, stirring velocity: 300 rpm, temperature: r.t., anode: glassy carbon, cathode, lead, undivided 5 mL Teflon® cell.

Table S9: Influence of the cathode material.

Entry	Cathode	Yield[a] of **9a** [%]	Yield[a] of **10a** [%]	Conversion[a][b] [%]
1	BDD[c]	5	49	100
2	Lead[c]	0	57	81
3	Tin[d]	23	35	100
4	Zinc[d]	31	0	100
5	Glassy carbon[d]	19	38	100
6	RVC[d]	1	67	100
7	Nickel[d]	7	52	100
8	SIGRAFLEX®[d]	0	27	55
9	Lead[d]	0	80	98

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] Based on remaining starting material; [c] 0.04 M substrate, supporting electrolyte: 5 M HCOOH/0.27 M NaHCOO in methanol, stirring velocity: 300 rpm, temperature: r.t., j = 4.1 mA·cm^{-2}, charge applied: 4 F ; anode: glassy carbon, undivided 5 mL Teflon® cell; [d] 0.04 M substrate, supporting electrolyte: 5 M HCOOH/0.27 M NaHCOO in methanol, stirring velocity: 300 rpm, temperature: r.t., j = 4.1 mA·cm^{-2}, charge applied: 5 F ; anode: glassy carbon, undivided 5 mL Teflon® cell.

Table S10: Influence of the anode material.

Entry	Anode	Yield[a] of **9a** [%]	Yield[a] of **10a** [%]	Conversion[a][b] [%]
1	Isostatic graphite[c]	0	67	94
2	Glassy carbon[c]	0	80	98

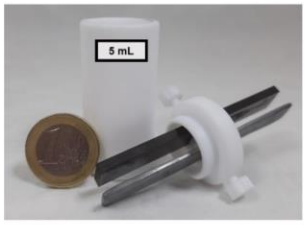
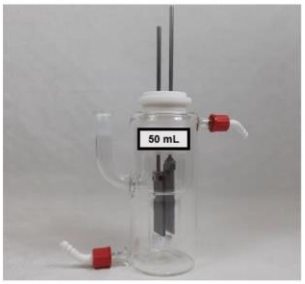
[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] Based on remaining starting material; [c] 0.04 M substrate, supporting electrolyte: 5 M HCOOH/0.27 M NaHCOO in methanol, stirring velocity: 300 rpm, temperature: r.t., j = 4.1 mA·cm^{-2}, charge applied: 5 F ; cathode: lead, undivided 5 mL Teflon® cell.

Table S11: Influence of the substrate concentration.[c]

Entry	*c*(Substrate)	Yield[a] of **9a** [%]	Yield[a] of **10a** [%]	Conversion[a][b] [%]
1	0.04 M	0	80	98
2	0.06 M	0	77	100
3	0.10 M	0	86	100
4	0.12 M	0	79	100
5	0.14 M	0	85	100
6	0.18 M	0	82	100
7	0.20 M	0	89	100
8	0.22 M	0	83	100
9	0.30 M	5	78	100
10	0.40 M	10	73	100
11	0.60 M	12	59	100

[a] Yield determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard; [b] Based on remaining starting material; [c] supporting electrolyte: 5 M HCOOH/0.27 M NaHCOO in methanol, stirring velocity: 300 rpm, temperature: r.t., j = 4.1 mA·cm^{-2}, charge applied: 5 F ; anode: glassy carbon, cathode: lead, undivided 5 mL Teflon® cell.

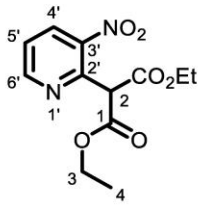
Table S12: Scale-up experiments on test substrate **8a**.[b]

Entry	Cell Type	*n*(Substrate) [mmol]	Yield[a] of **10a** [g]
1		0.2	0.031 (77%)
2		5	0.804 (80%)
3		15	2.726 (91%)
4		50	8.081 (80%)

[a] Isolated yield; [b] supporting electrolyte: 5 M HCOOH/0.27 M NaHCOO in methanol, stirring velocity: 300 rpm, temperature: r.t., j = 4.1 mA·cm^{-2}, charge applied: 5 F; anode: glassy carbon, cathode: lead.

5. Preparation of products and analytical data

Diethyl 2-(3-nitropyridin-2-yl)malonate (11)

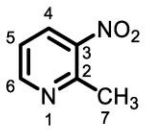


Diethyl malonate (6.13 g, 38 mmol, 1.2 eq.) and potassium carbonate (13.06 g, 95 mmol, 3.1 eq.) were stirred at room temperature for 15 min in 30 mL anhydrous acetone. 2-Chloro-3-nitropyridine (4.85 g, 31 mmol, 1.0 eq.) in 30 mL anhydrous acetone was added dropwise. After addition the reaction mixture was refluxed until completion of the reaction. The solids were filtered and the solvent was removed under reduced pressure. The crude product was dissolved in 50 mL ethyl acetate and washed once with 100 mL 6 M hydrochloric acid. The aqueous layer was extracted three times with 100 mL ethyl acetate. The combined organic layers were washed once with 50 mL water, once with 50 mL brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. 3.06 g (11.0 mmol, 35%) of the product was isolated as yellow oil by flash column chromatography (SiO_2; gradient 0 → 10% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.80 (dd, 1H, *J* = 4.7 Hz, 1.6 Hz, *H*-6'), 8.47 (dd, 1H, *J* = 8.3 Hz, 1.6 Hz, *H*-4'), 7.52 (dd, 1H, *J* = 8.3 Hz, 4.7 Hz, *H*-5'), 5.51 (s, 1H, *H*-2), 4.29 (q, 2H, *J* = 7.1 Hz, *H*-3), 1.28 (t, 3H, *J* = 7.1 Hz, *H*-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 166.6, 153.2, 149.2, 145.0, 133.4, 124.0, 62.3, 59.5, 14.1.
LC-MS: t_R = 8.005 min (method: 40% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* for $C_{12}H_{14}N_2O_6^+$, $[M+H]^+$ = 283.

The spectroscopic data are in accordance with those reported in the literature.[4]

2-Methyl-3-nitropyridine (12)

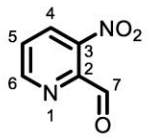


Diethyl 2-(3-nitropyridin-2-yl)malonate (2.93 g, 10 mmol, 1.0 eq.) was dissolved in 5 mL ethanol, 140 mL 6 M hydrochloric acid was added and the reaction mixture was heated under reflux until completion of the reaction. The reaction mixture was neutralized using potassium carbonate and extracted four times with 50 mL dichloromethane. The combined organic layers were washed once with 50 mL brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. 1.30 g (9.4 mmol, 94%) of the product was isolated as slightly brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.70 (dd, 1H, *J* = 4.8 Hz, 1.6 Hz, *H*-6), 8.25 (dd, 1H, *J* = 8.3 Hz, 1.6 Hz, *H*-4), 7.34 (dd, 1H, *J* = 8.3 Hz, 4.8 Hz, *H*-5), 2.84 (s, 3H, *H*-7).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 153.8, 152.9, 145.9, 132.6, 121.9, 23.9.
LC-MS: t_R = 5.153 min (method: 20% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* $C_6H_6N_2O_2^+$ $[M+H]^+$ = 139.

The spectroscopic data are in accordance with those reported in the literature.[5]

3-Nitropyridine-2-carbaldehyde (13)

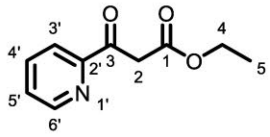


2-Methyl-3-nitropyridine (1.24 g, 9 mmol, 1.0 eq.) and selenium dioxide (1.28 g, 12 mmol, 1.3 eq.) were dissolved in 25 mL 1,4-dioxane and heated under reflux until completion of the reaction. The solids were filtered using Celite 535® and the solvent was removed under reduced pressure. 0.93 g (6.1 mmol, 67%) of the product was isolated as a yellow oil by flash column chromatography (SiO_2; gradient 0 → 25% ethyl acetate).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 10.19 (s, 1H, *H*-7), 8.96 (dd, 1H, *J* = 4.7 Hz, 1.4 Hz, *H*-6), 8.24 (dd, 1H, *J* = 8.3 Hz, 1.4 Hz, *H*-4), 7.75 (dd, 1H, *J* = 8.3 Hz, 4.7 Hz, *H*-5).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 188.8, 153.4, 146.3, 145.9, 132.2, 127.9.
HR-MS: *m/z* for $C_6H_{14}N_2O_3^+$, $[M+H]^+$ calculated: 153.0295; found: 153.0300.
LC-MS: t_R = 10.282 min (method: 15% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* $C_6H_4N_2O_3^+$ $[M+H]^+$ = 153.

The spectroscopic data are in accordance with those reported in the literature.[6]

Ethyl 3-oxo-3-(pyridin-2-yl)propanoate (14)

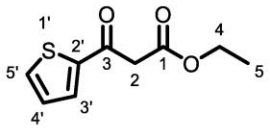


Under argon atmosphere 2-acetylpyridine (7.28 g, 60 mmol, 1.0 eq.) and sodium hydride 60% dispersion in mineral oil (10.74 g, 269 mmol, 4.5 eq.) were stirred at 0 °C for 15 min in 300 mL of anhydrous toluene. Diethyl carbonate (23.17 g, 196 mmol, 3.3 eq.) in 100 mL anhydrous toluene was added to the reaction mixture dropwise. After addition the reaction mixture was slowly heated to room temperature and stirred at room temperature until completion of the reaction. The reaction mixture was poured into 100 mL water:hydrochloric acid (1:1 *v*:*v*). The organic layer was separated and the aqueous layer was extracted three times using 75 mL of ethyl acetate. The combined organic layers were washed once with 75 mL brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. 1.38 g (7.1 mmol, 12%) of the product was isolated as pale yellow oil by flash column chromatography (SiO_2; gradient 0 → 5% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$, keto form) δ [ppm]: 8.66 (m, 1H, *H*-6'), 8.06 (m, 1H, *H*-3'), 7.84 (td, 1H, *J* = 7.7 Hz, 1.7 Hz, *H*-4'), 7.48 (ddd, 1H, *J* = 7.5 Hz, 4.8 Hz, 1.3 Hz, *H*-5'), 4.18 (m, 4H, *H*-2, *H*-4), 1.22 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ [ppm]: 12.39 (s, 1H, C3-O*H*), 8.62 (m, 1H, *H*-6'), 7.90 (m, 1H, *H*-3'), 7.78 (m, 1H, *H*-4'), 7.34 (ddd, 1H, *J* = 7.6 Hz, 4.7 Hz, 1.2 Hz, *H*-5'), 6.32 (s, 1H, *H*-2), 4.27 (q, 2H, *J* = 7.1 Hz, *H*-4), 1.32 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$, keto form) δ [ppm]: 194.8, 168.4, 152.5, 149.2, 137.1, 127.7, 122.2, 61.3, 45.0, 14.2.
^{13}C NMR (101 MHz, $CDCl_3$, enol form) δ [ppm]: 173.5, 168.9, 151.1, 149.5, 137.0, 125.6, 121.1, 89.5, 60.6, 14.4.
LC-MS: t_R = 5.826 min (method: 30% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* for $C_{10}H_{11}NO_3^+$, $[M+H]^+$ = 194.

The spectroscopic data are in accordance with those reported in the literature.[7]

Ethyl 3-oxo-3-(thien-2-yl)propanoate (15)

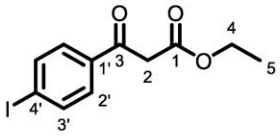


Under argon atmosphere 2-acetylthiophene (5.06 g, 40 mmol, 1.0 eq.) and sodium hydride 60% dispersion in mineral oil (7.23 g, 180 mmol, 4.5 eq.) were stirred at 0 °C for 15 min in 180 mL of anhydrous toluene. Diethyl carbonate (14.83 g, 126 mmol, 3.2 eq.) in 20 mL anhydrous toluene was added to the reaction mixture dropwise. After addition the reaction mixture was slowly heated to room temperature and stirred at room temperature until completion of the reaction. The reaction mixture was poured into 100 mL water:hydrochloric acid (1:1 *v*:*v*). The organic layer was separated and the aqueous layer was extracted three times using 75 mL of ethyl acetate. The combined organic layers were washed once with 75 mL brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. 5.97 g (30.1 mmol, 75%) of the product was isolated as brown oil by flash column chromatography (SiO_2; gradient 0 → 5% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$, keto form) δ [ppm]: 7.71 (d, 1H, *J* = 3.9 Hz, *H*-3'), 7.67 (d, 1H, *J* = 5.0 Hz, *H*-5'), 7.12 (dd, 1H, *J* = 5.0 Hz, 3.9 Hz, *H*-4'), 4.17 (q, 2H, *J* = 7.1 Hz, *H*-4), 3.89 (s, 2H, *H*-2), 1.23 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ [ppm]: 12.99 (s, 1H, C3-O*H*), 5.53 (s, 1H, C2-*H*), 1.29 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 185.0, 167.0, 143.2, 135.0, 133.3, 128.4, 61.6, 46.5, 14.1.
LC-MS: t_R = 5.253 min (method: 40% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* for $C_9H_{10}O_3S^+$, $[M+H]^+$ = 199.

The spectroscopic data are in accordance with those reported in the literature.[7]

Ethyl 3-(4-iodophenyl)-3-oxopropanoate (16)

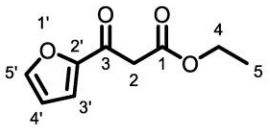


Under argon atmosphere 4'-iodoacetophenone (2.29 g, 9.3 mmol, 1.0 eq.) and sodium hydride 60% dispersion in mineral oil (1.60 g, 40 mmol, 4.3 eq.) were stirred at 0 °C for 15 min in 80 mL of anhydrous toluene. Diethyl carbonate (3.43 g, 29 mmol, 3.1 eq.) in 20 mL anhydrous toluene was added to the reaction mixture dropwise. After addition the reaction mixture was slowly heated to room temperature and stirred at room temperature until completion of the reaction. The reaction mixture was poured into 100 mL water:hydrochloric acid (1:1 *v*:*v*). The organic layer was separated and the aqueous layer was extracted three times using 50 mL of ethyl acetate. The combined organic layers were washed once with 50 mL brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. 1.94 g (6.1 mmol, 66%) of the product was isolated as beige oil by flash column chromatography (SiO_2; gradient 0 → 2% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN, keto form) δ [ppm]: 7.88 (m, 2H, *H*-3', *H*-5'), 7.65 (m, 2H, *H*-2', *H*-6'), 4.14 (q. 2H, *J* = 7.1 Hz, *H*-4), 3.98 (s, 2H, *H*-2), 1.20 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{1}H NMR (400 MHz, CD_3CN, enol form) δ [ppm]: 12.64 (s, 1H, C3-O*H*), 7.80 (m, 2H, *H*-3'), 7.53 (m, 2H, *H*-2'), 5.74 (s, 1H, *H*-2), 4.24 (q, 2H, *J* = 7.1 Hz, *H*-4), 1.28 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{13}C NMR (101 MHz, CD_3CN, keto form) δ [ppm]: 193.7, 168.4, 139.0, 136.4, 130.9, 102.2, 62.0, 46.5, 14.4.
^{13}C NMR (101 MHz, CD_3CN, enol form) δ [ppm]: 174.1, 171.1, 138.8, 133.7, 128.6, 98.6, 88.7, 61.6, 14.6.
LC-MS: t_R = 19.760 min (method: 40% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* for $C_{11}H_{11}IO_3^+$, $[M+H]^+$ = 319.

The spectroscopic data are in accordance with those reported in the literature.[8]

Ethyl 3-(furan-2-yl)-3-oxopropanoate (17)

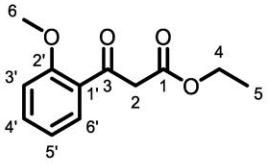


Under argon atmosphere 2-acetylfuran (2.21 g, 20 mmol, 1.0 eq.) and sodium hydride 60% dispersion in mineral oil (3.73 g, 93 mmol, 4.7 eq.) were stirred at 0 °C for 15 min in 120 mL of anhydrous toluene. Diethyl carbonate (7.10 g, 60 mmol, 3.0 eq.) in 30 mL anhydrous toluene was added to the reaction mixture dropwise. After addition the reaction mixture was slowly heated to room temperature and stirred at room temperature until completion of the reaction. The reaction mixture was poured into 100 mL water:hydrochloric acid (1:1 *v*:*v*). The organic layer was separated and the aqueous layer was extracted three times using 50 mL of ethyl acetate. The combined organic layers were washed once with 50 mL brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. 0.447 g (2.5 mmol, 13%) of the product was isolated as red oil by flash column chromatography (SiO_2; gradient 0 → 10% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$, keto form) δ [ppm]: 7.60 (dd, 1H, *J* = 1.7 Hz, 0.8 Hz, *H*-3'), 7.26 (dd, 1H, *J* = 3.6 Hz, 0.8 Hz, *H*-5'), 6.56 (dd, 1H, *J* = 3.6 Hz, 1.7 Hz, *H*-3'), 4.19 (q. 2H, *J* = 7.1 Hz, *H*-4), 3.83 (s, 2H, *H*-2), 1.24 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ [ppm]: 12.15 (s, 1H, C3-O*H*), 7.48 (dd, 1H, *J* = 1.8 Hz, 0.8 Hz, *H*-3'), 6.92 (dd, 1H, *J* = 3.5 Hz, 0.8 Hz, *H*-5'), 6.49 (dd, 1H, *J* = 3.5 Hz, 1.8 Hz, *H*-3'), 5.60 (s, 1H, *H*-2), 1.31 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$, keto form) δ [ppm]: 181.2, 167.1, 152.1, 147.1, 118.4, 112.8, 112.7, 61.6, 45.6, 14.2.
^{13}C NMR (101 MHz, $CDCl_3$, enol form) δ [ppm]: 145.0, 112.1, 86.4, 60.4, 14.4
LC-MS: t_R = 2.722 min (method: 50 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* for $C_9H_{10}IO_4^+$, $[M+H]^+$ = 183.

The spectroscopic data are in accordance with those reported in the literature.[9]

Ethyl 3-(2-methoxyphenyl)-3-oxopropanoate (18)

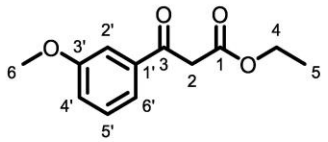


Under argon atmosphere 2'-methoxyacetophenone (6.01 g, 40 mmol, 1.0 eq.) and sodium hydride 60% dispersion in mineral oil (7.26 g, 182 mmol, 4.6 eq.) were stirred at 0 °C for 15 min in 180 mL of anhydrous toluene. Diethyl carbonate (14.33 g, 121 mmol, 3.0 eq.) in 20 mL anhydrous toluene was added to the reaction mixture dropwise. After addition the reaction mixture was slowly heated to room temperature and stirred at room temperature until completion of the reaction. The reaction mixture was poured into 100 mL water:hydrochloric acid (1:1 *v*:*v*). The organic layer was separated and the aqueous layer was extracted three times using 50 mL of ethyl acetate. The combined organic layers were washed once with 50 mL brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. 6.12 g (27.5 mmol, 69%) of the product was isolated as yellow oil by flash column chromatography (SiO_2; gradient 0 → 8% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN, keto form) δ [ppm]: 7.77 (dd, 1H, *J* = 7.7 Hz, 1.9 Hz, *H*-6'), 7.56 (ddd, 1H, *J* = 8.4 H, 7.2 Hz, 1.9 Hz, *H*-4'), 7.10 (dd, 1H, *J* = 8.4 Hz, 1.0 Hz, *H*-3'), 7.03 (m, 1H, *H*-5'), 4.13 (q, 2H, *J* = 7.1 Hz, *H*-4), 3.91 (s, 2H, *H*-2), 3.87 (s, 3H, *H*-6), 1.20 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{1}H NMR (400 MHz, CD_3CN, enol form) δ [ppm]: 12.77 (s, 1H, C3-O*H*), 7.45 (ddd, 1H, *J* = 8.4 Hz, 7.2 Hz, 1.8 Hz, *H*-4'), 6.01 (s, 1H, *H*-2), 4.24 (q, 2H, *J* = 7.1 Hz, *H*-4), 1.29 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{13}C NMR (101 MHz, CD_3CN, keto form) δ [ppm]: 194.2, 169.1, 160.3, 135.8, 131.3, 127.1, 121.6, 113.2, 61.6, 56.3, 51.2, 14.5.
^{13}C NMR (101 MHz, CD_3CN, enol form) δ [ppm]: 133.3, 130.0, 121.4, 112.9, 92.9, 61.3, 14.6.
LC-MS: t_R = 4.693 min (method: 50% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* for $C_{12}H_{14}IO_4^+$, $[M+H]^+$ = 223.

The spectroscopic data are in accordance with those reported in the literature.[10]

Ethyl 3-(3-methoxyphenyl)-3-oxopropanoate (19)

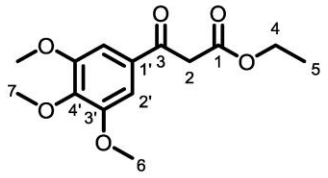


Under argon atmosphere 3'-methoxyacetophenone (6.01 g, 40 mmol, 1.0 eq.) and sodium hydride 60% dispersion in mineral oil (7.55 g, 188 mmol, 4.7 eq.) were stirred at 0 °C for 15 min in 150 mL of anhydrous toluene. Diethyl carbonate (17.33 g, 147 mmol, 3.7 eq.) in 50 mL anhydrous toluene was added to the reaction mixture dropwise. After addition the reaction mixture was slowly heated to room temperature and stirred at room temperature until completion of the reaction. The reaction mixture was poured into 100 mL water:hydrochloric acid (1:1 *v*:*v*). The organic layer was separated and the aqueous layer was extracted three times using 50 mL of ethyl acetate. The combined organic layers were washed once with 50 mL brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. 6.891 g (31.0 mmol, 78%) of the product was isolated as yellow oil by flash column chromatography (SiO_2; gradient 0 → 8% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN, keto form) δ [ppm]: 7.52 (m, 1H, *H*-6'), 7.43 (m, 2H, *H*-2', *H*-5'), 7.18 (m, 1H, *H*-4'), 4.15 (q, 2H, *J* = 7.1 Hz, *H*-4), 4.01 (s, 2H, *H*-2), 3.83 (s, 3H, *H*-6), 1.21 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{1}H NMR (400 MHz, CD_3CN, enol form) δ [ppm]: 12.69 (s, 1H, C3-O*H*), 7.35 (m, 3H, *H*-2', *H*-5', *H*-6'), 7.06 (m, 1H, *H*-4'), 5.76 (s, 1H, *H*-2), 4.24 (q, 2H, *J* = 7.1 Hz, *H*-4), 3.81 (s, 1H, *H*-6), 1.29 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{13}C NMR (101 MHz, CD_3CN, keto form) δ [ppm]: 194.0, 168.7, 160.9, 138.5, 130.9, 121.9, 120.7, 113.8, 62.0, 56.2, 46.8, 14.5.
^{13}C NMR (101 MHz, CD_3CN, enol form) δ [ppm]: 174.3, 172.1, 135.6, 130.8, 119.3, 112.1, 88.5, 61.5, 56.1, 14.6.
LC-MS: t_R = 4.938 min (method: 50% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* for $C_{12}H_{14}IO_4^+$, $[M+H]^+$ = 223.

The spectroscopic data are in accordance with those reported in the literature.[11]

Ethyl 3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (20)

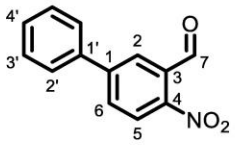


Under argon atmosphere 3',4',5'-trimethoxy-acetophenone (8.43 g, 40 mmol, 1.0 eq.) and sodium hydride 60% dispersion in mineral oil (7.33 g, 183 mmol, 4.6 eq.) were stirred at 0 °C for 15 min in 150 mL of anhydrous toluene. Diethyl carbonate (14,36 g, 122 mmol, 3.1 eq.) in 50 mL anhydrous toluene was added to the reaction mixture dropwise. After addition the reaction mixture was slowly heated to room temperature and stirred at room temperature until completion of the reaction. The reaction mixture was poured into 100 mL water:hydrochloric acid (1:1 *v*:*v*). The organic layer was separated and the aqueous layer was extracted three times using 50 mL of ethyl acetate. The combined organic layers were washed once with 50 mL brine and dried over magnesium sulfate. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO_2; gradient 0 → 16% ethyl acetate) and recrystallized using cyclohexane:propan-2-ol 9:1 (*v*:*v*) as solvent. 8.096 g (28.7 mmol, 72%) of the product was isolated as colorless solid.

^{1}H NMR (400 MHz, CD_3CN, keto form) δ [ppm]: 7.23 (s, 2H, *H*-2'), 4.15 (q, 2H, *J* = 7.1 Hz, *H*-4), 4.01 (s, 2H, *H*-2), 3.87 (s, 6H, *H*-6), 3.80 (s, 3H, *H*-7), 1.22 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{1}H NMR (400 MHz, CD_3CN, enol form) δ [ppm]: 12.75 (s, 1H, C3-O*H*), 7.08 (s, 2H, *H*-2'), 5.78 (s, 1H, *H*-2), 4.25 (q, 2H, *J* = 7.1 Hz, *H*-4), 3.85 (s, 6H, *H*-6), 3.77 (s, 3H, *H*-7), 1.29 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{13}C NMR (101 MHz, CD_3CN, keto form) δ [ppm]: 192.1, 167.9, 153.3, 142.9, 131.4, 106.1, 61.0, 60.0, 55.9, 45.6, 13.5.
LC-MS: t_R = 4.062 min (method: 50% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* for $C_{14}H_{18}IO_6^+$, $[M+H]^+$ = 283.

The spectroscopic data are in accordance with those reported in the literature.[10]

4-Nitro-(1,1'-biphenyl)-3-carbaldehyde (21)

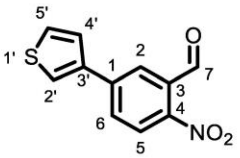


5-Bromo-2-nitrobenzaldehyde (1.15 g, 5.0 mmol, 1.0 eq.) and phenylboronic acid (0.68 g, 5.6 mmol, 1.1 eq.) were dissolved in 10 mL tetrahydrofuran. Potassium carbonate (1.53 g, 11 mmol, 2.2 eq.) in 20 mL water was added and the reaction mixture was degassed with argon for 15 min. Triphenylphosphine (84 mg, 0.32 mmol, 0.06 eq.) and palladium(II) acetate were added and the reaction mixture was heated at 65 °C until completion of the reaction under argon atmosphere. The mixture was filtered using Celite 545®, 20 mL ethyl acetate:water (1:1 *v*:*v*) was added and the organic layer was separated. The aqueous layer was extracted three times using 20 mL ethyl acetate. The combined organic layers were washed once with 50 mL brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. 1.00 g (4.40 mmol, 88%) of the product was isolated as beige solid by flash column chromatography (SiO_2; gradient 0 → 4% ethyl acetate).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 10.46 (s, 1H, *H*-7), 8.19 (d, 1H, *J* = 8.5 Hz, *H*-5), 8.11 (d, 1H, *J* = 2.1 Hz, *H*-2), 7.96 (dd, 1H, *J* = 8.5 Hz, 2.1 Hz, *H*-6), 7.68 (m, 2H, *H*-2'), 7.51 (m, 2H, *H*-3', *H*-4').
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 188.81, 148.43, 147.53, 137.99, 132.48, 131.95, 129.76, 129.63, 128.16, 127.74, 125.67.
LC-MS: t_R = 7.722 min (method: 60% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* for $C_{13}H_9NO_3^+$, $[M+H]^+$ = 228.

The spectroscopic data are in accordance with those reported in the literature.[12]

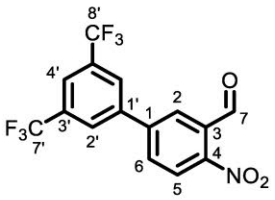
2-Nitro-5-(thien-3-yl)benzaldehyde (22)



5-Bromo-2-nitrobenzaldehyde (1.19 g, 5.2 mmol, 1.0 eq.) and thien-3-ylboronic acid (0.73 g, 5.7 mmol, 1.1 eq.) were dissolved in 10 mL tetrahydrofuran. Potassium carbonate (1.57 g, 11 mmol, 2.1 eq.) in 20 mL water was added and the reaction mixture was degassed with argon for 15 min. (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II) (76 mg, 0.1 mmol, 0.02 eq.) was added and the reaction mixture was heated at 65 °C until completion of the reaction under argon atmosphere. The mixture was filtered using Celite 545®, 20 mL ethyl acetate:water (1:1 *v*:*v*) was added and the organic layer was separated. The aqueous layer was extracted three times using 20 mL ethyl acetate. The combined organic layers were washed once with 20 mL brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. 1.10 g (4.72 mmol, 91%) of the product was isolated as a yellow solid by flash column chromatography (SiO_2; gradient 0 → 10% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 10.33 (s, 1H, *H*-7), 8.12 (d, 1H, *J* = 8.5 Hz, *H*-5), 8.06 (d, 1H, *J* = 2.0 Hz, *H*-2), 8.02, dd, 1H, *J* = 8.5 Hz, 2.0 Hz, *H*-6), 7.90 (dd, 1H, *J* = 2.5 Hz, 1.9 Hz, *H*-4'), 7.56 (m, 2H, *H*-2', *H*-5').
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 190.3, 148.4, 142.0, 139.7, 133.3, 131.5, 128.7, 127.6, 127.0, 126.3, 125.5.
HR-MS: *m/z* for $C_{11}H_7NO_3S^+$, $[M+Na]^+$ calculated: 256.0039; found: 256.0040.
LC-MS: t_R = 11.034 min (method: 40 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 234.

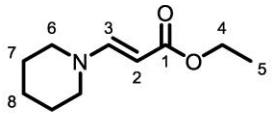
4-Nitro-3',5'-bis(trifluoromethyl)-(1,1'-biphenyl)-3-carbaldehyde (23)



5-Bromo-2-nitrobenzaldehyde (0.82 g, 3.6 mmol, 1.0 eq.) and (3,5-bis(trifluoromethyl)phenyl)boronic acid (1.00 g, 3.9 mmol, 1.1 eq.) were dissolved in 10 mL tetrahydrofuran. Potassium carbonate (1.09 g, 7.9 mmol, 2.2 eq.) in 20 mL water was added and the reaction mixture was degassed with argon for 15 min. (1,1'-bis(diphenylphosphino)ferrocene)dichloropalladium(II) (53 mg, 0.07 mmol, 0.002 eq.) was added and the reaction mixture was heated at 65 °C until completion of the reaction under argon atmosphere. The mixture was filtered using Celite 545®, 20 mL ethyl acetate:water (1:1 *v*:*v*) was added and the organic layer was separated. The aqueous layer was extracted three times using 20 mL ethyl acetate. The combined organic layers were washed once with 20 mL brine, dried over magnesium sulfate and the solvent was removed under reduced pressure. 1.05 g (2.89 mmol, 80%) of the product was isolated as beige solid by flash column chromatography (SiO_2; gradient 0 → 5% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 10.35 (s, 1H, *H*-7), 8.29 (s, 2H, *H*-2'), 8.22 (d, 1H, *J* = 8.5 Hz, *H*-5), 8.20 (d, 1H, *J* = 2.1 Hz, *H*-2), 8.14 (dd, 1H, *J* = 8.5 Hz, 2.1 Hz, *H*-6), 8.11 (s, 1H, *H*-4').
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 188.9, 149.1, 143.4, 140.1, 132.7, 132.3, 132.0, 131.9, 131.7, 131.4, 128.8, 128.4, 125.3, 124.8, 122.8, 122.1.
^{19}F NMR (282 MHz, CD_3CN) δ [ppm]: -63.32 (s).
HR-MS: *m/z* for $C_{16}H_8F_6NO_5^-$, $[M+HCOO]^-$ calculated: 408.0312; found: 408.297.
LC-MS: t_R = 13.704 min (method: 50 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI-) = 408.

Ethyl (*E*)-3-(piperidin-1-yl)acrylate (24)

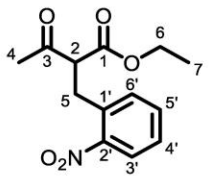


Under argon atmosphere ethyl propiolate (6.60 g, 67 mmol, 1.0 eq.) was dissolved in 150 mL acetonitrile. Piperidine (6.36 g, 75 mmol, 1.1 eq.) was added dropwise and the reaction mixture was stirred for 24 h at room temperature. The solvent was removed under reduced pressure. 9.11 g (48 mmol, 72%) of the product was isolated as slightly yellow oil by distillation (1.1 mbar, 110-113 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.30 (d, 1H, *J* = 13.1 Hz, *H*-2), 4.53 (d, 1H, *J* = 13.1 Hz, *H*-3), 4.03 (q, 2H, *J* = 7.1 Hz, *H*-4), 3.10 (t, 4H, *J* = 5.3 Hz, *H*-6), 1.52 (m, 6H, *H*-7, *H*-8), 1.17 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 170.0, 151.9, 83.6, 58.7, 25.3, 24.0, 14.6.
HR-MS: *m/z* for $C_{10}H_{17}NO_2^+$, $[M+H]^+$ calculated: 184.1332; found: 184.1332.

The spectroscopic data are in accordance with those reported in the literature.[13]

Ethyl 2-(2-nitrobenzyl)-3-oxobutanoate (4a)

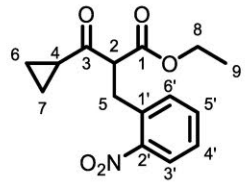


According to the general protocol **GPI** potassium carbonate (19.55 g, 140 mmol, 5.6 eq.), ethyl acetoacetate (13.19 g, 100 mmol, 4.0 eq.), potassium iodide (0.21 g, 1.3 mmol, 0.05 eq.) and 2-nitrobenzyl bromide (5.40 g, 25 mmol, 1.0 eq.) were reacted in 200 mL anhydrous acetone. 4.42 g (16.7 mmol; 67%) of the product were isolated as a pale yellow oil by flash column chromatography (SiO_2; gradient 0 → 5% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$, keto form) δ [ppm]: 7.98 (d, *J* = 8.59 Hz, 1H, *H*-3'), 7.51 (td, *J* = 7.35 Hz, 1.36 Hz, 1H, *H*-5'), 7.39 (m, 2H, *H*-4', *H*-6'), 4.12 (m, 2H, *H*-6), 3.98 (dd, *J* = 8.55 Hz, 5.75 Hz, 1H, *H*-2), 3.40 (m, 2H, *H*-5), 2.26 (s, 3H, *H*-4), 1.18 (t, *J* = 7.14 Hz, 3H, *H*-7).
^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ [ppm]: 12.99 (s, 1H, C3-O*H*), 7.86 (d, *J* = 8.05 Hz, 1.20 Hz, 1H, *H*-3'), 7.32 (t, *J* = 7.79 Hz, 1.40 Hz, 1H, *H*-4'), 7.24 (dd, *J* = 7.86 Hz, 1.26 Hz, 1H, *H*-6'), 3.85 (s, 2H, *H*-5), 2.01 (s, 3H, *H*-4), 1.06 (t, *J* = 7.09 Hz, 3H, *H*-7).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 201.9, 168.8, 149.1), 133,8, 133.5, 133.4, 128.2, 125.3, 61.7, 59.8, 31.4, 29.8, 14.1.
HR-MS: *m/z* for $C_{13}H_{15}NO_5Na^+$, $[M+Na]^+$ calculated: 288.0842; found: 288.0841.
LC-MS: t_R = 5.938 min (method: 50 → 100% acetonitrile in 20 min, 5 min at 100%), *m/z* (ESI+) = 266.

The spectroscopic data are in accordance with those reported in the literature.[14]

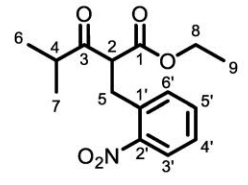
Ethyl 3-cyclopropyl-2-(2-nitrobenzyl)-3-oxopropanoate (4b)



According to the general protocol **GPI** potassium carbonate (2.07 g, 15 mmol, 6.0 eq.), ethyl 3-cyclopropyl-3-oxopropanoate (1.57 g, 10 mmol, 4.0 eq.), potassium iodide (0.057 g, 0.3 mmol, 0.1 eq.) and 2-nitrobenzyl bromide (0.54 g, 2.5 mmol, 1.0 eq.) were reacted in 100 mL acetone at room temperature for 4 h. The reaction mixture was dissolved in ether. 0.575 g (1.97 mmol; 79%) of the product were isolated as a slightly yellow oil by column chromatography (SiO_2; 0 → 5% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.00 (dd, *J* = 8.11 Hz, 1.39 Hz, 1H, *H*-3'), 7.51 (m, 1H, *H*-5'), 7.40 (m, 2H, *H*-4', *H*-6'), 4.16 (m, 3H, *H*-8, *H*-2), 3.45 (m, 2H, *H*-5), 2.12 (m, 1H, *H*-4), 1.20 (t, *J* = 7.11 Hz, 3H, *H*-9), 1.07 (m, 2H, *H*-6), 0.94 (m, 2H, *H*-7).
^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ [ppm]: 3.56 (s, 2H, *H*-5), 2.04 (m, 1H, *H*-4), 1.28 (t, *J* = 7.13 Hz, 3H, *H*-9).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 204.3, 168.9, 149.3, 133,9, 133.7, 133.4, 128.2, 125.3, 61.7, 60.0, 31.6, 20.6, 14.2, 12.2, 12.0.
HR-MS: *m/z* for $C_{15}H_{17}NO_5Na^+$, $[M+Na]^+$ calculated: 314.0999; found: 314.1001.
LC-MS: t_R = 8.035 min (method: 50 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 292.

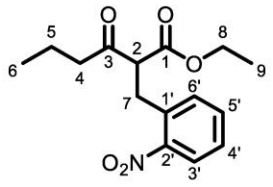
Ethyl 4-methyl-2-(2-nitrobenzyl)-3-oxopentanoate (4c)



According to the general protocol **GPI** potassium carbonate (1.57 g, 11 mmol, 5.8 eq.), ethyl 4-methyl-3-oxopentanoate (0.901 g, 5.7 mmol, 3.0 eq.), potassium iodide (0.020 g, 0.12 mmol, 0.06 eq.), tetrabutylammonium bromide (0.031 g, 0.10 mmol, 0.05 eq.) and 2-nitrobenzyl bromide (0.41 g, 1.9 mmol, 1.0 eq.) were reacted in 100 mL acetone at room temperature for 49 h. 0.463 g (1.58 mmol; 83%) of the product were isolated as a slightly yellow oil by flash column chromatography (SiO_2; 0 → 7% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.96 (m, 1H, *H*-3'), 7.49 (m, 1H, *H*-5'), 7.38 (m, 2H, *H*-4', *H*-6'), 4.20 (t, *J* = 7.12 Hz, 1H, *H*-2), 4.11 (m, 2H, *H*-8), 3.39 (m, 2H, *H*-5), 2.75 (sep, *J* = 6.84 Hz, 1H, *H*-4), 1.18 (t, *J* = 7.14 Hz, 3H, *H*-9), 1.06 (d, *J* = 6.76 Hz, 3H, *H*-6), 0.91 (d, *J* = 6.98 Hz, 3H, *H*-7).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 208.2, 168.7, 149.2, 133,8, 133.4, 128.2, 125.2, 61.6, 57.0, 41.3, 32.9, 17.9, 17.8, 14.1.
HR-MS: *m/z* for $C_{15}H_{19}NO_5^+$, $[M+Na]^+$ calculated: 316.1155; found: 316.1152.
LC-MS: t_R = 13.630 min (method: 50% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 294.

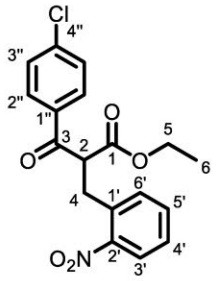
Ethyl 2-(2-nitrobenzyl)-3-oxohexanoate (4d)



According to the general protocol **GPI** potassium carbonate (8.31 g, 60 mmol, 6.0 eq.), methyl 3-oxohexanoate (4.75 g, 30 mmol, 3.0 eq.), potassium iodide (0.166 g, 1 mmol, 0.1 eq.) and 2-nitrobenzyl bromide (2.16 g, 10 mmol, 1.0 eq.) were reacted in 200 mL acetone at room temperature for 24 h. 2.03 g (6.92 mmol; 69%) of the product were isolated as a slightly yellow oil by flash column chromatography (SiO_2; 0 → 5% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$, keto form) δ [ppm]: 7.99 (m, 1H, *H*-3'), 7.51 (m, 1H, *H*-5'), 7.40 (m, 2H, *H*-4', *H*-6'), 4.13 (m, 2H, *H*-8), 3.62 (d, 1H, *J* = 2.5 Hz, *H*-2), 3.41 (m, 2H, *H*-7), 2.54 (m, 2H, *H*-4), 1.58 (m, 2H, *H*-5), 1.19 (t, 3h, *J* = 7.1 Hz, *H*-9), 0.87 (t, 3H, *J* = 7.4 Hz, *H*-6).**^{1}H NMR (400 MHz, $CDCl_3$, enol form)** δ [ppm]: 13.08 (s, 1H, C3-O*H*), 7.88 (dd, 1H, *J* = 8.2 Hz, 1.4 Hz, *H*-3'), 7.46 (m, 1H, *H*-5'), 7.40 (m, 1H, *H*-6'), 7.33 (m, 1H, *H*-4'), 4.01 (m, 4H, *H*-7, *H*-8), 2.37 (m, 2H, *H*-4), 1.51 (m, 2H, *H*-5), 1.04 (t, 3H, *J* = 7.2, *H*-9), 0.80 (t, 3H, *J* = 7.4 Hz, *H*-6).**^{13}C NMR (101 MHz, $CDCl_3$, keto form)** δ [ppm]: 204.4, 168.8, 149.2, 133.7, 133.4, 132.6, 128.2, 125.3, 61.7, 59.0, 44.8, 31.6, 17.0, 14.2, 13.6.
^{13}C NMR (101 MHz, $CDCl_3$, enol form) δ [ppm]: 206.6, 171.4, 150.4, 133.9, 133.2, 131.7, 128.2, 125.1, 64.6, 62.2, 42.6, 35.7, 17.4, 13.7.
HR-MS: *m/z* for $C_{15}H_{19}NO_5^+$, $[M+Na]^+$ calculated: 316.1155; found: 316.1153.
LC-MS: t_R = 5.596 min (method: 50% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 294.

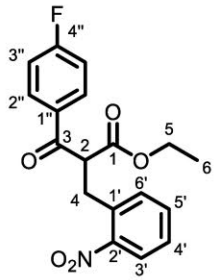
Ethyl 3-(4-chlorophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (4e)



According to the general protocol **GPI** potassium carbonate (6.01 g, 43 mmol, 6.0 eq.), ethyl 3-(4-chlorophenyl)-3-oxopropanoate (4.09 g, 18 mmol, 2.5 eq.), potassium iodide (0.058 g, 0.34 mmol, 0.05 eq.), tetrabutylammonium bromide (0.073 g, 0.23 mmol, 0.03 eq.) and 2-nitrobenzyl bromide (1.55 g, 7.2 mmol, 1.0 eq.) were reacted in 200 mL anhydrous acetone at room temperature for 1h. 2.35 g (6.50 mmol; 90%) of the product were isolated as slightly yellow oil by flash column chromatography (SiO_2; 0 → 3% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.99 (m, 3H, *H*-3', *H*-3'', *H*-5''), 7.51 (m, 1H, *H*-5'), 7.40 (m, 2H, *H*-4', *H*-6'), 7.14 (m, 2H, *H*-2'', *H*-6''), 4.84 (t, 1H, *J* = 6.8, *H*-2), 4.06 (q, *J* = 7.1 Hz, 1H, *H*-5), 3.54 (m, 2H, *H*-4), 1.08 (t, *J* = 7.1 Hz, 3H, *H*-6).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 193.2, 169.3, 167.9, 165.3, 149.8, 134.0, 133.8, 133.2, 132.0, 128.7, 125.6, 116.5, 116.2, 62.3, 54.9, 32.8, 14.2.
HR-MS: *m/z* for $C_{18}H_{16}{}^{35}ClNO_5^+$, $[M+Na]^+$ calculated: 384.0609; found: 384.0623.
LC-MS: t_R = 8.485 min (method: 65% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 362.

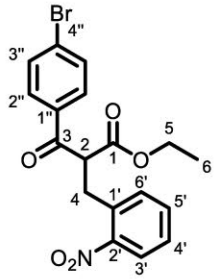
Ethyl 3-(4-fluorophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (4f)



According to the general protocol **GPI** potassium carbonate (6.93 g, 50 mmol, 7.6 eq.), ethyl 3-(4-fluorophenyl)-3-oxopropanoate (4.21 g, 20 mmol, 3.0 eq.), potassium iodide (0.069 g, 0.42 mmol, 0.06 eq.), tetrabutylammonium bromide (0.069 g, 0.21 mmol, 0.03 eq.) and 2-nitrobenzyl bromide (1.43 g, 6.6 mmol, 1.0 eq.) were reacted in 200 mL acetone at room temperature for 24 h. 2.14 g (6.20 mmol; 94%) of the product were isolated as slightly yellow oil by flash column chromatography (SiO_2; 0 → 3% ethyl acetate).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 7.99 (m, 3H, *H*-3', *H*-3''), 7.51 (m, 1H, *H*-5'), 7.40 (m, 2H, *H*-4', *H*-6'), 7.14 (m, 2H, *H*-2''), 4.84 (t, 1H, *J* = 6.8, *H*-2), 4.06 (q, *J* = 7.1 Hz, 1H, *H*-5), 3.54 (m, 2H, *H*-4), 1.08 (t, *J* = 7.1 Hz, 3H, *H*-6).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 193.2, 169.3, 167.9, 165.3, 149.8, 134.0, 133.8, 133.2, 132.0, 128.7, 125.6, 116.5, 116.2, 62.3, 54.9, 32.8, 14.2.
^{19}F NMR (282 MHz, CD_2Cl_2) δ [ppm]: -104.89 (m).
HR-MS: *m/z* for $C_{18}H_{16}FNO_5^+$, $[M+Na]^+$ calculated: 368.0905 found: 368.0905.
LC-MS: t_R = 5,938 min (method: 65% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 346.

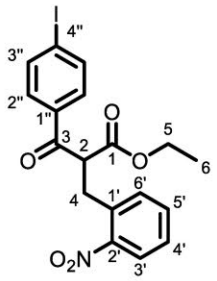
Ethyl 3-(4-bromophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (4g)



According to the general protocol **GPI** potassium carbonate (6.02 g, 44 mmol, 6.2 eq.), ethyl 3-(4-bromophenyl)-3-oxopropanoate (4.88 g, 18 mmol, 2.5 eq.), potassium iodide (0.057 g, 0.34 mmol, 0.05 eq.), tetrabutylammonium bromide (0.061 g, 0.19 mmol, 0.03 eq.) and 2-nitrobenzyl bromide (1.54 g, 7.1 mmol, 1.0 eq.) were reacted in 200 mL anhydrous acetone at room temperature for 24h. 2.59 g (6.39 mmol; 90%) of the product were isolated as slightly yellow oil by flash column chromatography (SiO_2; 0 → 3% ethyl acetate).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 7.97 (m, 1H, *H*-3'), 7.82 (m, 2H, *H*-3'', *H*-5''), 7.61 (m, 2H, *H*-2'', *H*-6''), 7.52 (m, 1H, *H*-5'), 7.40 (m, 2H, *H*-4', *H*-6'), 4.83 (t. 1H, *J* = 7.8 Hz, *H*-2), 4.05 (q, 2H, *J* = 7.1 Hz, *H*-5), 3.55 (m, 2H, *H*-4), 1.08 (t, 3H, *J* = 7.1 Hz, *H*-6).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 193.7, 169.0, 149.7, 135.3, 133.8, 133.7, 133.7, 132.4, 130.5, 129.3, 128.6, 125.4, 62.2, 54.7, 32.5, 14.1.
HR-MS: *m/z* for $C_{18}H_{16}{}^{79}BrNO_5^+$, $[M+Na]^+$ calculated: 428.0104; found: 428.0115.
LC-MS: t_R = 9.232 min (method: 65% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 406.

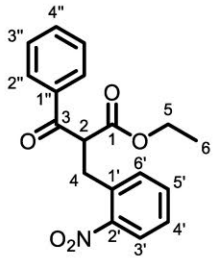
Ethyl 3-(4-iodophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (4h)



According to the general protocol **GPI** potassium carbonate (1.66 g, 12 mmol, 4.4 eq.), ethyl 3-(4-iodophenyl)-3-oxopropanoate (1.73 g, 5.4 mmol, 2.0 eq.), potassium iodide (0.019 g, 0.11 mmol, 0.04 eq.), tetrabutylammonium bromide (0.061 g, 0.05 mmol, 0.02 eq.) and 2-nitrobenzyl bromide (0.59 g, 2.7 mmol, 1.0 eq.) were reacted in 200 mL anhydrous acetone at room temperature for 24h. 0.849 g (1.87 mmol; 69%) of the product were isolated as slightly yellow oil by flash column chromatography (SiO_2; 0 → 3% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 7.93 (m, 1H, *H*-3'), 7.85 (m, 2H, *H*-3'', *H*-5''), 7.65 (m, 2H, *H*-2'', *H*-6''), 7.55 (m, 1H, *H*-5'), 7.42 (m, 2H, *H*-4', *H*-6'), 4.82 (t. 1H, *J* = 7.3 Hz, *H*-2), 4.01 (q, 2H, *J* = 7.1 Hz, *H*-5), 3.52 (d, 2H, *J* = 7.3 Hz, *H*-4), 1.02 (t, 3H, *J* = 7.1 Hz, *H*-6).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 195.1, 169.8, 150.4, 139.1, 136.4, 134.2, 134.1, 133.9, 130.9, 129.2, 125.8, 102.3, 62.6, 55.2, 32.2, 14.1.
HR-MS: *m/z* for $C_{18}H_{16}INO_5^+$, $[M+Na]^+$ calculated: 475.9965; found: 475.9970.
LC-MS: t_R = 10.034 min (method: 65% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 454.

Ethyl 2-(2-nitrobenzyl)-3-oxo-3-phenylpropanoate (4i)

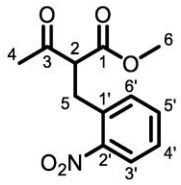


According to the general protocol **GPI** potassium carbonate (2.06 g, 15 mmol, 6.0 eq.), ethyl 3-oxo-3-phenylpropanoate (1.50 g, 7.8 mmol, 3.1 eq.), potassium iodide (0.024 g, 0.14 mmol, 0.06 eq.), tetrabutylammonium bromide (0.044 g, 0.14 mmol, 0.06 eq.) and 2-nitrobenzyl bromide (0.55 g, 2.5 mmol, 1.0 eq.) were reacted in 100 mL acetone at room temperature for 19 h. 0.735 g (2.25 mmol; 90%) of the product were isolated as slightly yellow oil by column chromatography (SiO_2; 0 → 7% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.97 (m, 3H, *H*-3', *H*-2''), 7.55 (m, 1H, *H*-4''), 7.46 (m, 4H, *H*-5', *H*-6', *H*-3''), 7.37 (m, 1H, *H*-4'), 4.91 (t, *J* = 7.86 Hz, 1H, *H*-2), 4.08 (m, 2H, *H*-5), 3.58 (m, 2H, *H*-4), 1.09 (t, *J* = 7.14 Hz, 3H, *H*-6).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 194.4, 169.0, 149.4, 136.2, 133.8, 133.7, 133.4, 128.9,128.3, 125.3, 61.8, 54.4, 32.6, 14.0.
LC-MS: t_R = 10.282 min (method: 50 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* for $C_{18}H_{17}NO_5^+$, $[M+H]^+$ = 328.

The spectroscopic data are in accordance with those reported in the literature.[15]

Methyl 2-(2-nitrobenzyl)-3-oxobutanoate (4j)

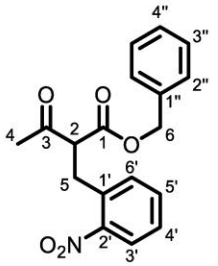


According to the general protocol **GPI** potassium carbonate (8,41 g, 61 mmol, 6.1 eq.), methyl 3-oxobutanoate (3.49 g, 30 mmol, 3.0 eq.), potassium iodide (0.087 g, 0.52 mmol, 0.05 eq.) and 2-nitrobenzyl bromide (2.16 g, 10 mmol, 1.0 eq.) were reacted in 200 mL acetone at room temperature for 24 h. 1.47 g (5.85 mmol; 59%) of the product were isolated as slightly yellow oil by flash column chromatography (SiO_2; 0 → 7% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$, keto form) δ [ppm]: 7.99 (m, 1H, *H*-3'), 7.52 (m, 1H, *H*-5'), 7.41 (m, 2H, *H*-4', *H*-6'), 4.02 (dd, 1H, *J* = 8.5 Hz, 5.8 Hz, *H*-2), 3.68 (s, 3H, *H*-6), 3.41 (m, 2H, *H*-5), 2.27 (s, 3H, *H*-4).
^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ [ppm]: 12.94 (s, 1H, C3-O*H*), 7.89 (m, 1H, *H*-3'), 7.52 (m, 1H, *H*-5'), 7.33 (m, 1H, *H*-4'), 7.23 (m, 1H, *H*-6'), 3.87 (s, 2H, *H*-5), 3.63 (s, 3H, *H*-6), 2.01 (s, 3H, *H*-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 201.9, 169.3, 149.1, 133.7, 133.5, 128.3, 125.3, 59.7, 52.7, 31.5, 29.9.
HR-MS: *m/z* for $C_{12}H_{13}NO_5^+$, $[M+H]^+$ calculated: 252.0866; found: 252.0870.
LC-MS: t_R = 4.628 min, 10.250 (method: 50% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 252.

The spectroscopic data are in accordance with those reported in the literature.[16]

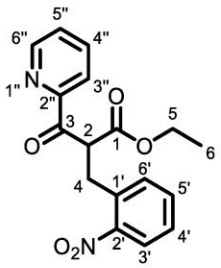
Benzyl 2-(2-nitrobenzyl)-3-oxobutanoate (4k)



According to the general protocol **GPI** potassium carbonate (8.36 g, 60 mmol, 6.0 eq.), benzyl 3-oxobutanoate (5.82 g, 30 mmol, 3.0 eq.), potassium iodide (0.099 g, 0.60 mmol, 0.06 eq.) 2-nitrobenzyl bromide (2.17 g, 10 mmol, 1.0 eq.) were reacted in 200 mL acetone at room temperature for 24 h. 1.74 g (5.31 mmol; 53%) of the product were isolated as slightly yellow oil by flash column chromatography (SiO_2; 0 → 4% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$, keto form) δ [ppm]: 7.98 (dd, 1H, *J* = 8.1 Hz, 1.5 Hz, *H*-3'), 7.44 (td, 1H, *J* = 7.5 Hz, 1.5 Hz, *H*-5'), 7.31 (m, 7H, *H*-4', *H*-6', *H*-2'', *H*-3'', *H*-4''), 5.09 (m, 2H, *H*-6), 4.06 (dd, 1H, *J* = 8.8 Hz, 5.6 Hz, *H*-2), 3.45 (m, 2H, *H*-5), 2.23 (s, 3H, *H*-4).
^{1}H NMR (400 MHz, $CDCl_3$, enol form) δ [ppm]: 12.92 (s, 1H, C3-O*H*), 7.82 (dd, 1H, *J* = 8.1 Hz, 1.5 Hz, *H*-3'), 7.31 (m, 9H, *H*-4', *H*-6', *H*-2'', *H*-3'', *H*-4'', *H*-5'', *H*-6''), 3.61 (d, 2H, *J* = 4.4 Hz, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 173.0, 167.4, 150.5, 134.6, 134.4, 134.0, 133.9, 133.2, 132.8, 129.7, 129.4, 126.1, 125.9, 125.5, 122.6, 94.2, 63.5, 62.2, 54.7, 50.4, 31.32, 30.93, 13.99, 13.91.
HR-MS: *m/z* for $C_{18}H_{17}NO_5^+$, $[M+Na]^+$ calculated: 350.0999; found: 350.1010.
LC-MS: t_R = 6.567 min, 13.002 min (method: 60% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 328.

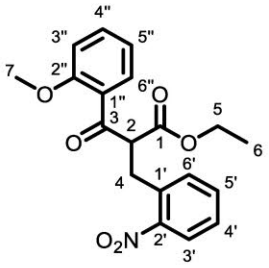
Ethyl 2-(2-nitrobenzyl)-3-oxo-3-(pyridin-2-yl)propanoate (4l)



According to the general protocol **GPI** potassium carbonate (3.14 g, 23 mmol, 4.9 eq.), ethyl 3-oxo-3-(pyridin-2-yl)propanoate (1.38 g, 7.1 mmol, 3.0 eq.), potassium iodide (0.039 g, 0.23 mmol, 0.05 eq.), tetrabutylammonium bromide (0.039 g, 0.12 mmol, 0.03 eq.) and 2-nitrobenzyl bromide (1.02 g, 4.7 mmol, 1.5 eq.) were reacted in 150 mL acetone at room temperature for 24 h. 0.807 g (2.46 mmol; 35%) of the product were isolated as slightly yellow oil by flash column chromatography (SiO_2; 0 → 10% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.59 (m, 1H, *H*-3''), 7.98 (m, 1H, *H*-3'), 7.91 (m, 2H, *H*-5', *H*-6'), 7.54 (m, 2H, *H*-4'', *H*-5''), 7.40 (m, 2H, *H*-4', *H*-6''), 5.05 (t, 3H, *J* = 7.6 Hz, *H*-2), 3.98 (m, 2H, *H*-5), 3.56 (m, 2H, *H*-4), 0.99 (t, 3H, *J* = 7.1 Hz, *H*-6).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 196.7, 170.5, 152.8, 150.5, 149.9, 138.5, 134.4, 134.1, 133.8, 129.0, 128.9, 125.7, 123.00, 62.0, 54.3, 32.0, 14.1.
HR-MS: *m/z* for $C_{17}H_{16}N_2O_5^+$, $[M+H]^+$ calculated: 329.1132; found: 329.1128.
LC-MS: t_R = 9.868 min (method: 50% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 329.

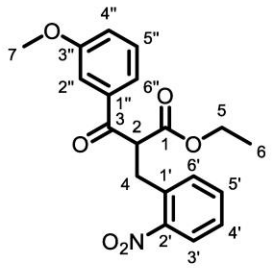
Ethyl 3-(2-methoxyphenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (4m)



According to the general protocol **GPI** potassium carbonate (5.74 g, 42 mmol, 4.2 eq.), ethyl 3-(2-methoxyphenyl)-3-oxopropanoate (2.22 g, 10 mmol, 1.0 eq.), potassium iodide (0.083 g, 0.50 mmol, 0.05 eq.), tetrabutylammonium bromide (0.083 g, 0.26 mmol, 0.03 eq.) and 2-nitrobenzyl bromide (2.17 g, 10 mmol, 1.0 eq.) were reacted in 200 mL anhydrous acetone at room temperature for 24 h. 1.048 g (2.93 mmol; 29%) of the product were isolated as yellow oil by flash column chromatography (SiO_2; 0 → 5% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN, keto form) δ [ppm]: 7.92 (dd, 1H*J* = 8.5 Hz, 1.4 Hz, *H*-3'), 7.59 (dd, 1H, *J* = 7.8 Hz, 1.8 Hz, *H*-6''), 7.53 (m, 2H, *H*-5', *H*-4''), 7.42 (m, 2H, *H*-4', *H*-6'), 7.02 (m, 2H, *H*-3'', *H*-5''), 4.77 (m, 1H, *H*-2), 3.99 (m, 2H, *H*-5), 3.77 (s, 3H, *H*-7), 3.49 (m, 2H, *H*-4), 1.02 (t, 3H, *J* = 7.1 Hz, *H*-6).**^{1}H NMR (400 MHz, CD_3CN, enol form)** δ [ppm]: 12.98 (s, 1H, C3-O*H*), 8.11 (dd, 1H, *J* = 8.2 Hz, 1.3 Hz, *H*-3''), 7.75 (dd, 1H, *J* = 8.0 Hz, 1.4 Hz, *H*-6''), 7.34 (m, 3H, *H*-4', *H*-5', *H*-5''), 7.25 (dd, 1H, *H*-6'), 4.11 (q, 2H, *J* = 7.1 Hz, *H*-5), 3.66 (s, 2H, *H*-4).
^{13}C NMR (101 MHz, CD_3CN, keto form) δ [ppm]: 196.8, 170.4, 159.5, 150.6, 135.4, 134.8, 134.1, 133.8, 131.4, 128.9, 127.7, 125.7, 121.7, 113.1, 62.0, 61.9, 59.5, 56.2, 32.1, 14.2, 14.2.
HR-MS: *m/z* for $C_{19}H_{19}NO_6^+$, $[M+H]^+$ calculated: 358.1285; found: 358.1274.
LC-MS: t_R = 9.777 min, 13.332 min (method: 50 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 358.

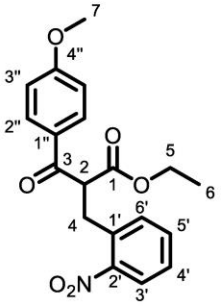
Ethyl 3-(3-methoxyphenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (4n)



According to the general protocol **GPI** potassium carbonate (5.71 g, 41 mmol, 4.1 eq.), ethyl 3-(3-methoxyphenyl)-3-oxopropanoate (2.22 g, 10 mmol, 1.0 eq.), potassium iodide (0.079 g, 0.50 mmol, 0.05 eq.), tetrabutylammonium bromide (0.081 g, 0.26 mmol, 0.03 eq.) and 2-nitrobenzyl bromide (2.59 g, 12 mmol, 1.2 eq.) were reacted in 200 mL anhydrous acetone at room temperature for 24 h. 2.808 g (7.86 mmol; 79%) of the product were isolated as yellow oil by flash column chromatography (SiO_2; 0 → 8% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 7.93 (dd, 1H, *J* = 8.2 Hz, 1.4 Hz, *H*-3'), 7.55 (td, 1H, *J* = 7.6 Hz, 1.4 Hz, *H*-5'), 7.51 (ddd, 1H, *J* = 7.7 Hz, 1.7 Hz, 1.0 Hz, *H*-2''), 7.42 (m, 4H, *H*-4', *H*-6', *H*-5'', *H*-6''), 7.16 (ddd, 1H, *H*-4''), 4.86 (m, 1H, *H*-2), 4.02 (qd, 2H, *J* = 7.1 Hz, 1.4 Hz, *H*-5), 3.80 (s, 3H, *H*-7), 3.52 (m, 2H, *H*-4), 1.03 (t, 3H, *J* = 7.1 Hz, *H*-6).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 195.4, 170.1, 160.9, 150.5, 138.5, 134.2, 133.9, 130.9, 129.2, 125.8, 121.9, 120.9, 113.8, 62.5, 56.2, 55.4, 32.4, 14.2.
HR-MS: *m/z* for $C_{19}H_{19}NO_6^+$, $[M+H]^+$ calculated: 358.1285; found: 358.1275.
LC-MS: t_R = 10.708 min, 12.565 min (method: 50 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 358.

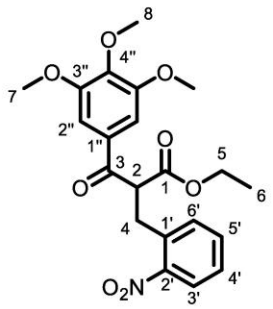
Ethyl 3-(4-methoxyphenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (4o)



According to the general protocol **GPI** potassium carbonate (5.64 g, 41 mmol, 4.1 eq.), ethyl 3-(4-methoxyphenyl)-3-oxopropanoate (3.35 g, 15 mmol, 1.5 eq.), potassium iodide (0.082 g, 0.50 mmol, 0.05 eq.), tetrabutylammonium bromide (0.071 g, 0.22 mmol, 0.02 eq.) and 2-nitrobenzyl bromide (2.16 g, 10 mmol, 1.0 eq.) were reacted in 200 mL anhydrous acetone at room temperature for 24 h. 2.497 g (6.99 mmol; 70%) of the product were isolated as yellow oil by flash column chromatography (SiO_2; 0 → 7% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 7.92 (m, 3H, *H*-3', *H*-2''), 7.54 (td, 1H, *J* = 7.5 Hz, 1.4 Hz, *H*-5'), 7.42 (m, 2H, *H*-4', *H*-6'), 6.96 (m, 2H, *H*-3''), 4.84 (t, 1H, *J* = 7.3 Hz, *H*-2), 4.02 (q, 2H, *J* = 7.1 Hz, *H*-5), 3.83 (s, 1H, *H*-7), 3.52 (d, 2H, *J* = 7.3 Hz, *H*-4), 1.04 (t, 3H, *J* = 7.1 Hz, *H*-6).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 193.8, 170.2, 165.1, 150.5, 134.4, 134.2, 133.9, 132.0, 129.9, 129.1, 125.8, 115.0, 62.4, 56.4, 54.8, 32.4, 14.2.
HR-MS: *m/z* for $C_{19}H_{19}NO_6^+$, $[M+H]^+$ calculated: 358.1285; found: 358.1277.
LC-MS: t_R = 10.198 min (method: 50 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 358.

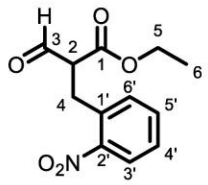
Ethyl 2-(2-nitrobenzyl)-3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (4p)



According to the general protocol **GPI** potassium carbonate (5.87 g, 42 mmol, 6.6 eq.), ethyl 3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (4.24 g, 15 mmol, 1.5 eq.), potassium iodide (0.079 g, 0.57 mmol, 0.06 eq.), tetrabutylammonium bromide (0.080 g, 0.25 mmol, 0.03 eq.) and 2-nitrobenzyl bromide (2.16 g, 10 mmol, 1.0 eq.) were reacted in 200 mL anhydrous acetone at room temperature for 24 h. 3.754 g (8.99 mmol; 90%) of the product were isolated as yellow oil by flash column chromatography (SiO_2; 0 → 10% ethyl acetate) followed by reversed phase flash column chromatography (40 → 50% acetonitrile).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 7.93 (dd, 1H, *J* = 8.1 Hz, 1.4 Hz, *H*-3'), 7.55 (m, 1H, *H*-5'), 7.43 (m, 2H, *H*-4', *H*-6'), 7.21 (s, 2H, *H*-2''), 4.87 (m, 1H, *H*-2), 4.05 (q, 2H, *J* = 7.1 Hz, *H*-5), 3.82 (s, 6H, *H*-7), 3.78 (s, 3H, *H*-8), 3.52 (m, 2H, *H*-4), 1.06 (t, 3H, *J* = 7.1 Hz, *H*-6).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 194.4, 170.3, 154.2, 150.5, 144.0, 134.3, 134.3, 134.0, 132.3, 129.2, 125.8, 107.1, 62.5, 61.0, 56.8, 55.1, 32.6, 14.3.
HR-MS: *m/z* for $C_{21}H_{23}NO_8^+$, $[M+Na]^+$ calculated: 440.1316; found: 440.1309.
LC-MS: t_R = 9.487 min (method: 50 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 418.

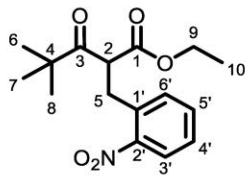
Ethyl 2-formyl-3-(2-nitrophenyl)propanoate (4q)



Under argon atmosphere ethyl (*E*)-3-(piperidin-1-yl)acrylate (1.87 g, 10 mmol, 1.0 eq.) was dissolved in acetonitrile. 2-nitrobenzyl bromide (2.17 g, 10 mmol, 1.0 eq.) was added dropwise. The reaction mixture was heated under reflux for 24 h. After completion of the reaction the reaction mixture was cooled to room temperature, 50 mL 1 M hydrochloric acid was added and the reaction mixture was stirred for 1 h. The solvent was removed under reduced pressure and the aqueous layer was extracted three times using 50 mL ethyl acetate. The combined organic layers were washed once with 50 mL water, once with 50 mL brine and dried over magnesium sulfate. 0.966 g (3.84 mmol, 38%) of the product was isolated as yellow oil by flash column chromatography (SiO_2; 0 → 13% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN, keto form) δ [ppm]: 9.70 (s, 1H, *H*-3), 7.97 (d, 1H, *J* = 8.1 Hz, *H*-3'), 7.81 (m, 1H, *H*-6'), 7.57 (m, 1H, *H*-5'), 7.41 (m, 1H, *H*-4'), 4.03 (q, 2H, *J* = 7.1 Hz, *H*-5), 3.86 (t, 1H, *J* = 8.4 Hz, *H*-2), 3.42 (m, 2H, *H*-4), 1.16 (t, 3H, *J* = 7.1 Hz, *H*-6).**^{1}H NMR (400 MHz, CD_3CN, enol form *E*+*Z*)** δ [ppm]: 11.45 (s, 2H, C3-O*H*), 7.81 (m, 2H, *H*-3'), 7.57 (m, 2H, *H*-5'), 7.41 (m, 4H, *H*-4', *H*-6'), 7.20 (s, 2H, *H*-3), 4.12 (qd, 2H, *J* = 7.1 Hz, 1.7 Hz, *H*-5), 4.08 (q, 2H, *J* = 7.1 Hz, *H*-5), 3.82 (s, 2H, *H*-4), 3.69 (s, 2H, *H*-4), 1.13 (t, 3H, *J* = 7.1 Hz, *H*-6), 1.06 (t, 3H, *J* = 7.1 Hz, *H*-6).
^{13}C NMR (101 MHz, CD_3CN, keto form & enol form *E*+*Z*) δ [ppm]: 196.4, 171.6, 168.3, 167.8, 162.7, 155.0, 150.0, 149.8, 135.0, 134.6, 133.4, 133.2, 132.8, 132.7, 132.7, 131.6, 130.4, 128.2, 127.4, 126.9, 124.9, 124.2, 123.9, 107.0, 102.8, 61.6, 60.6, 59.6, 58.9, 29.1, 28.3, 24.9, 13.6, 13.3, 13.2.
HR-MS: *m/z* for $C_{12}H_{13}NO_5H^-$, $[M-H]^-$ calculated: 250.0721; found: 250.0728.
LC-MS: t_R = 8.083 min (method: 40% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 252.

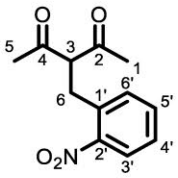
Ethyl 4,4-dimethyl-2-(2-nitrobenzyl)-3-oxopentanoate (4r)



According to the general protocol **GPI** potassium carbonate (2.08 g, 15 mmol, 6.0 eq.), ethyl 4,4-dimethyl-3-oxopentanoate (1.74 g, 10 mmol, 4.0 eq.), potassium iodide (0.057 g, 0.17 mmol, 0.07 eq.), tetrabutylammonium bromide (0.040 g, 0.12 mmol, 0.05 eq.) and 2-nitrobenzyl bromide (0.54 g, 2.5 mmol, 1.0 eq.) were reacted in 100 mL acetone at room temperature for 118 h. 0.616 g (2.00 mmol; 80%) of the product were isolated as slightly yellow oil by column chromatography (SiO_2; 0 → 2% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.96 (dd, *J* = 8.17 Hz, 1.37 Hz, 1H, *H*-3'), 7.49 (td, *J* = 7.51 Hz, 1.42 Hz 1H, *H*-5'), 7.38 (m, 1H, *H*-4'), 7.32 (dd, *J* = 7.68 Hz, 1.52 Hz 1H, *H*-6'), 4.48 (t, *J* = 7.51 Hz, 1H, *H*-2), 4.09 (m, 2H, *H*-9), 3.45 (m, 2H, *H*-5), 1.16 (t, *J* = 7.11 Hz, 3H, *H*-10), 1.00 (s, 9H, *H*-6, *H*-7, *H*-8).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 209.4, 168.8, 149.4, 133,9, 133.6, 133.3, 128.3, 125.2, 61.6, 52.8, 45.6, 33.7, 26.0, 14.1.
HR-MS: *m/z* for $C_{16}H_{21}NO_5Na^+$, $[M+Na]^+$ calculated: 330.1312; found: 330.1311.
LC-MS: t_R = 8.784 min (method: 60% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 308.

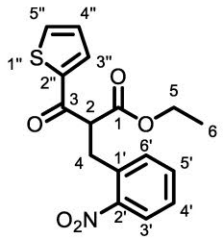
3-(2-Nitrobenzyl)pentane-2,4-dione (4s)



According to the general protocol **GPI** potassium carbonate (4.15 g, 30 mmol, 6.0 eq.), acetylacetone (2.02 g, 20 mmol, 4.0 eq.), potassium iodide (0.047 g, 0.28 mmol, 0.06 eq.) and 2-nitrobenzyl bromide (1.07 g, 5.0 mmol, 1.0 eq.) were reacted in 100 mL anhydrous acetone at room temperature for 16 h. 0.718 g (3.05 mmol; 61%) of the product were isolated as slightly yellow solid by flash column chromatography (SiO_2; 0 → 5% ethyl acetate).

^{1}H NMR (400 MHz, CD_2Cl_2, keto form) δ [ppm]: 7.98 (dt, *J* = 8.16 Hz, 1.89 Hz, 1H, *H*-3'), 7.58 (td, *J* = 7.61 Hz, 1.38 Hz, 1H, *H*-5'), 7.42 (m, 1H, *H*- 4'), 7.29 (m, 1H, *H*-6'), 3.97 (s, 2H, *H*-6), 2.00 (s, 6H, *H*-1, *H*-5).
^{1}H NMR (400 MHz, CD_2Cl_2, enol form) δ [ppm]: 4.20 (t, *J* = 6.85 Hz, 1H, *H*-3), 3.37 (d, *J* = 6.90 Hz, 2H, *H*-6), 2.17 (s, 6H, *H*-1, *H*-5).
^{13}C NMR (101 MHz, CD_2Cl_2, keto form) δ [ppm]: 193.0, 149.9, 135.1, 134.0, 129.5, 128.0, 125.5, 106.8, 30.2, 23.5.
^{13}C NMR (101 MHz, CD_2Cl_2, enol form) δ [ppm]: 203.3, 134.3, 134.0, 133.9, 128.7, 125.7, 68.1, 31.7, 30.6.
HR-MS: *m/z* for $C_{12}H_{13}NO_4Na^+$, $[M+Na]^+$ calculated: 258.0737; found: 258.0739.
LC-MS: t_R = 3.950 min; 7.642 min (method: 50% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 236.

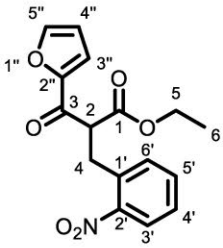
Ethyl 2-(2-nitrobenzyl)-3-oxo-3-(thien-2-yl)propanoate (4t)



According to the general protocol **GPI** potassium carbonate (5.65 g, 33 mmol, 6.6 eq.), ethyl 3-oxo-3-(thien-2-yl)propanoate (2.57 g, 13 mmol, 2.6 eq.), potassium iodide (0.042 g, 0.25 mmol, 0.05 eq.), tetrabutylammonium bromide (0.042 g, 0.13 mmol, 0.03 eq.) and 2-nitrobenzyl bromide (1.08 g, 5.0 mmol, 1.0 eq.) were reacted in 200 mL anhydrous acetone at room temperature for 24 h. 1.409 g (4.22 mmol; 84%) of the product were isolated as yellow oil by flash column chromatography (SiO_2; 0 → 5% ethyl acetate).

^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ [ppm]: 7.97 (m, 1H, *H*-3'), 7.93 (m, 2H, *H*-3'', *H*-5''), 7.61 (m, 1H, *H*-5'), 7.52 (m, 1H, *H*-6'), 7.48 (m, 1H, *H*-4'), 7.20 (dd, 1H, *J* = 5.0 Hz, 3.9 Hz, *H*-4''), 4.85 (t, 1H, *J* = 7.4 Hz, *H*-2), 4.08 (q, 2H, *J* = *7.1* Hz, *H*-5), 3.58 (m, 1H, *H*-4), 1.08 (t, 3H, *J* = 7.1 Hz, *H*-6).
^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ [ppm]: 187.6, 169.3, 150.5, 144.1, 136.6, 134.8, 134.0, 133.9, 133.8, 129.5, 129.1, 125.6, 62.2, 56.0, 32.2, 14.2.
HR-MS: *m/z* for $C_{16}H_{15}NO_5S^+$, $[M+Na]^+$ calculated: 356.0563; found: 356.0559.
LC-MS: t_R = 9.211 min (method: 50 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 334.

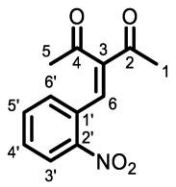
Ethyl 3-(furan-2-yl)-2-(2-nitrobenzyl)-3-oxopropanoate (4u)



According to the general protocol **GPI** potassium carbonate (0.51 g, 3.7 mmol, 3.1 eq.), ethyl 3-(furan-2-yl)-3-oxopropanoate (0.37 g, 2.0 mmol, 2.6 eq.), potassium iodide (0.007 g, 0.04 mmol, 0.03 eq.), tetrabutylammonium bromide (0.014 g, 0.04 mmol, 0.03 eq.) and 2-nitrobenzyl bromide (0.254 g, 1.2 mmol, 1.0 eq.) were reacted in 100 mL anhydrous acetone at room temperature for 24 h. 0.345 g (1.09 mmol; 93%) of the product were isolated as yellow oil by flash column chromatography (SiO_2; 0 → 10% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 7.94 (m, 1H, *H*-3'), 7.71 (d, 1H, *J* = 1.7 Hz, *H*-3''), 7:55 (m, 1H, *H*-5'), 7.42 (m, 2H, *H*-4', *H*-6'), 7.30 (d, 1H, *J* = 3.7 Hz, *H*-5''), 6.59 (dd, 1H, *J* = 3.7 Hz, *J* = 1.7 Hz, *H*-4''), 4.58 (t, 1H, *J* = 7.5 Hz, *H*-2), 4.06 (q, 2H, *J* = 7.1 Hz, *H*-5), 3.51 (m, 1H, *H*-4), 1.08 (t, 3H, *J* = 7.1 Hz, *H*-6).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 183.5, 169.7, 152.6, 150.5, 149.3, 134.3, 134.0, 133.9, 129.2, 125.9, 120.7, 113.7, 62.5, 55.4, 32.0, 14.2.
HR-MS: *m/z* for $C_{16}H_{15}NO_6^+$, $[M+Na]^+$ calculated: 340.0792; found: 340.0799.
LC-MS: t_R = 5.592 min (method: 55% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 318.

3-(2-Nitrobenzylidene)pentane-2,4-dione (8a)

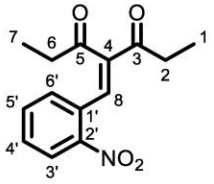


According to the general protocol **GPII** acetylacetone (1.13 g, 11 mmol, 1.1 eq.), 2-nitro benzaldehyde (1.52 g, 10 mmol, 1.0 eq.), glacial acetic acid and piperidine were reacted for 4 h. 1.544 g (6,6 mmol, 66%) of the product was obtained as beige solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.22 (dd, *J* = 8.09 Hz, 1.39 Hz, 1H, *H*-3'), 7.91 (s, 1H, *H*-6), 7.65 (td, *J* = 7.52 Hz, 1.41 Hz, 1H, *H*-5'), 7.59 (tdd, *J* = 7.55 Hz, 1.62 Hz, 1H, *H*-4'), 7.39 (dt, *J* = 7.52 Hz, 1.12 Hz, 1H, *H*-6'), 2.48 (s, 3H, *H*-1), 2.11 (s, 3H, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 202.9, 196.4, 147.1, 144.3, 137.9, 134.2, 131.3, 130.7, 130.1, 125.4, 31.9, 26.9.
LC-MS: t_R = 3.645 min (method: 50% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* for $C_{12}H_{11}NO_4^+$, $[M+H]^+$ = 234.

The spectroscopic data are in accordance with those reported in the literature.[17]

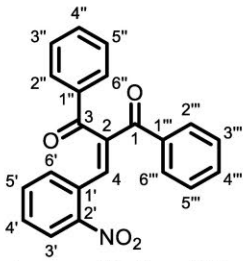
4-(2-Nitrobenzylidene)heptane-3,5-dione (8b)



According to the general protocol **GPII** heptane-3,5-dione (0.80 g, 6.2 mmol, 1.1 eq.), 2-nitro benzaldehyde (0.85 g, 5.6 mmol, 1.0 eq.), glacial acetic acid and piperidine were reacted for 17 h. 0.581 g (2.2 mmol, 39%) of the product were isolated as pale orange oil by flash column chromatography (SiO_2; 0 → 4% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.21 (dd, *J* = 8.10 Hz, 1.42 Hz, 1H, *H*-3'), 7.90 (s, 1H, *H*-5), 7.64 (td, *J* = 7.57 Hz, 1.48 Hz, 1H, *H*-5'), 7.57 (td, *J* = 7.47 Hz, 1.63 Hz, 1H, *H*-4'), 7.38 (dt, *J* = 7.60 Hz, 1.18 Hz, 1H, *H*-6'), 2.81 (q, *J* = 7.25 Hz, 2H, *H*-2), 2.11 (q, *J* = 7.19 Hz, 2H, *H*-6), 1.19 (t, *J* = 7.20 Hz, 3H, *H*-1), 0.90 (t, *J* = 7.24 Hz, 3H, *H*-7).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 206.5, 199.1, 147.3, 144.2, 136.1, 134.1, 131.5, 130.6, 130.2, 125.4, 37.8, 32.3, 8.1, 7.6.
HR-MS: *m/z* for $C_{14}H_{15}NO_4^+$, $[M+Na]^+$ calculated: 284.0893; found: 284.0888.
LC-MS: t_R = 9.793 min (method: 40 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 262.

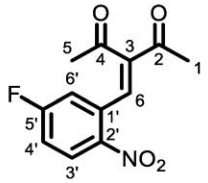
2-(2-Nitrobenzylidene)-1,3-diphenylpropane-1,3-dione (8c)



According to the general protocol **GPIII** 1,3-diphenylpropane-1,3-dione (2.76 g, 12 mmol, 1.2 eq.), 2-nitro benzaldehyde (1.52 g, 10 mmol, 1.0 eq.) and piperidine were reacted for 72 h. The crude product was recrystallized using ethanol. 1.787 g (5.0 mmol, 50%) of the product were isolated as yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.07 (dd, *J* = 8.04 Hz, 1.20 Hz, 1H, *H*-3'), 7.99 (m, 2H, *H*-2'', *H*-2'''), 7.95 (s, 1H, *H*-4), 7.88 (m, 2H, *H*-6'', *H*-6'''), 7.59 (m, 1H, *H*-5'), 7.48 (m, 6H, *H*-4', *H*-6', *H*-3'', *H*-4'', *H*-3''', *H*-4'''), 7.33 (m, 2H, *H*-5'', *H*-5''').
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 194.9, 193.7, 147.0, 141.5, 140.7, 136.8, 136.6, 134.1, 134.0, 133.2, 131.7, 130.5, 130.3, 129.8, 129.3, 128.9, 125.1.
HR-MS: *m/z* for $C_{22}H_{15}NO_4^+$, $[M+Na]^+$ calculated: 380.0893; found: 380.0905.
LC-MS: t_R = 10.410 min (method: 50 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 358.

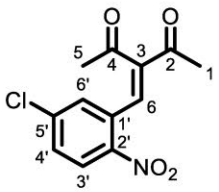
3-(5-Fluoro-2-nitrobenzylidene)pentane-2,4-dione (8d)



According to the general protocol **GPII** acetylacetone (1.21 g, 12 mmol, 1.2 eq.), 2-nitro benzaldehyde (1.69 g, 10 mmol, 1.0 eq.), glacial acetic acid and piperidine were reacted for 18 h. The crude product was recrystallized using water:propan-2-ol (9:1 *v/v)*. The crude product was 0.393 g (1.6 mmol, 16%) of the product were isolated as yellow solid.

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.32 (dd, *J* = 9.11 Hz, 1H, *H*-3'), 7.86 (s, 1H, *H*-6), 7.31 (td, *J* = 9.16 Hz, 2.81 Hz, 1H, *H*-4'), 7.12 (d, *J* = 2.76 Hz, 1H, *H*-6'), 2.51 (s, 3H, *H*-1), 2.17 (s, 3H, *H*-5).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 202.6, 196.9, 165.5, 145.1, 143.8, 137.3, 133.8, 128.7, 118.7 117.8, 32.1, 27.2.
^{19}F NMR (376 MHz, CD_2Cl_2) δ [ppm]: -103.09 (m).
HR-MS: *m/z* for $C_{12}H_{10}FNO_4^+$, $[M+Na]^+$ calculated: 274.0486; found: 274.0481.
LC-MS: t_R = 4.014 min (method: 50% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 252.

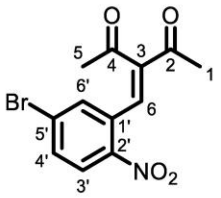
3-(5-Chloro-2-nitrobenzylidene)pentane-2,4-dione (8e)



According to the general protocol **GPII** acetylacetone (0.55 g, 5.5 mmol, 1.1 eq.), 2-nitro benzaldehyde (0.93 g, 5.0 mmol, 1.0 eq.), glacial acetic acid and piperidine were reacted for 2 h. The crude product was recrystallized using ethanol. 0.132 g (0.49 mmol, 10%) of the product were obtained as beige solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.19 (d, *J* = 8.80 Hz, 1H, *H*-3'), 7.82 (s, 1H, *H*-6), 7.54 (dd, *J* = 8.85 Hz, 2.23 Hz, 1H, *H*-4'), 7.37 (d, *J* = 2.31 Hz, 1H, *H*-6'), 2.49 (s, 3H, *H*-1), 2.18 (s, 3H, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 202.1 196.3, 145.4, 144.7, 140.9, 136.9, 131.9, 131.1, 130.5, 126.8, 31.9, 27.0.
HR-MS: *m/z* for $C_{12}H_{10}{}^{35}ClNO_4^+$, $[M+H]^+$ calculated: 268.0371; found: 268.0372.
LC-MS: t_R = 5.131 min (method: 50 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 268.

3-(5-Bromo-2-nitrobenzylidene)pentane-2,4-dione (8f)

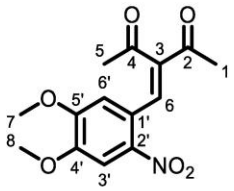


According to the general protocol **GPII** acetylacetone (1.42 g, 14 mmol, 1.4 eq.), 5-bromo-2-nitrobenzaldehyde (2.31 g, 10 mmol, 1.0 eq.), glacial acetic acid and piperidine were reacted for 15 h. The crude product was recrystallized using water:propan-2-ol (9:1 *v/v)* and filtered through SiO_2 using cyclohexane:ethyl acetate (9:1 *v/v*). 0.211 g (0.68 mmol, 7%) of the product were isolated as beige solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.09 (d, *J* = 8.76 Hz, 1H, *H*-3'), 7.80 (s, 1H, *H*-6), 7.73 (dd, *J* = 8.80 Hz, 2.19 Hz, 1H, *H*-4'), 7.52 (d, *J* = 2.15 Hz, 1H, *H*-6'), 2.46 (s, 3H, *H*-1), 2.14 (s, 3H, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 201.9, 196.3, 145.9, 144.6, 136.6, 133.6, 133.4, 131.9, 128.9, 126.6, 31.5, 26.6.
LC-MS: t_R = 8.867min (method: 40 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* for $C_{12}H_{10}{}^{79}BrNO_4{}^+$, $[M+H]^+$ = 312.

The spectroscopic data are in accordance with those reported in the literature.[18]

3-(4,5-Dimethoxy-2-nitrobenzylidene)pentane-2,4-dione (8g)

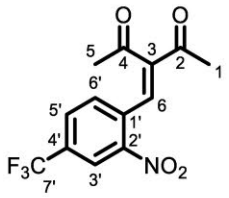


According to the general protocol **GPIII** acetylacetone (1.21 g, 12 mmol, 1.2 eq.), 2-nitro benzaldehyde (2.11 g, 10 mmol, 1.0 eq.) and piperidine were reacted for 192 h. The crude product was recrystallized using ethanol. 0.166 g (0.56 mmol, 6%) of the product were isolated as yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.93 (s, 1H, *H*-6), 7.76 (s, 1H, *H*-3'), 6.84 (s, 1H, *H*-6'), 3.98 (s, 3H, *H*-7), 3.93 (s, 3H, *H*-8), 2.47 (s, 3H, *H*-1), 2.10 (s, 3H, *H*-5).
^{13}C NMR (100 MHz, $CDCl_3$) δ [ppm]: 204.0, 196.6, 153.5, 149.8, 143.7, 139.9, 138.1, 124.1, 112.9, 108.1, 56.9, 56.7, 32.0, 26.7.
LC-MS: t_R = 8.831 min (method: 30 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* for $C_{14}H_{15}NO_6{}^+$, $[M+Na]^+$ = 294.

The spectroscopic data are in accordance with those reported in the literature.[18]

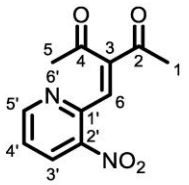
3-(2-Nitro-4-(trifluoromethyl)benzylidene)pentane-2,4-dione (8h)



According to the general protocol **GPIII** acetylacetone (0.98 g, 6.8 mmol, 1.3 eq.), 2-nitro-4-(trifluoromethyl)benzaldehyde (1.12 g, 5.1 mmol, 1.0 eq.) and piperidine were reacted for 48 h. 0.709 g (2.35 mmol, 46%) of the product were isolated red solid by flash column chromatography (SiO_2; 0 → 23% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.46 (s, 1H, *H*-3'), 7.90 (d, 1H, *J* = 8.0 Hz, *H*-5'), 7.85 (s, 1H, *H*-6), 7.54 (d, 1H, *J* = 8.0 Hz, *H*-6'), 2.50 (s, 3H, *H*-1), 2.15 (s, 3H, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 202.0, 196.3, 147.2, 145.1, 136.6, 133.7, 132.9 (d, *J* = 34.6 Hz), 132.3, 130.6, 122.54 (q, *J* = 273.1 Hz), 31.8, 26.9.
^{19}F NMR (282 MHz, $CDCl_3$) δ [ppm]: -63.12 (s).
HR-MS: *m/z* for $C_{13}H_{10}F_3NO_4^+$, $[M+Na]^+$ calculated: 324.0454; found: 324.0461.
LC-MS: t_R = 6.516 min (method: 50% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 302.

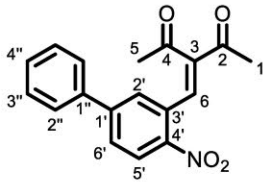
3-((3-Nitropyridin-2-yl)methylene)pentane-2,4-dione (8i)



According to the general protocol **GPIII** acetylacetone (0.711 g, 7.1 mmol, 1.2 eq.), 3-nitropicolinaldehyde (0.869 g, 5.7 mmol, 1.0 eq.) and piperidine were reacted for 24 h. 0.845 g (3.61 mmol, 63%) of the product were isolated beige solid by flash column chromatography (SiO_2; 0 → 20% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.77 (dd, 1H, *J* = 4.6 Hz, 1.5 Hz, *H*-5'), 8.39 (dd, 1H, *J* = 8.3 Hz, 1.5 Hz, *H*-3'), 7.95 (s, 1H, *H*-6), 7.50 (dd, 1H, *J* = 8.3 Hz, 4.6 Hz, *H*-4'), 2.49 (s, 2H, *H*-1), 2.45 (s, 3H, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 203.2, 196.9, 152.5, 148.4, 146.7, 145.5, 133.4, 131.8, 124.8, 31.6, 27.0.
HR-MS: *m/z* for $C_{11}H_{10}N_2O_4^+$, $[M+H]^+$ calculated: 235.0713; found: 235.0717.
LC-MS: t_R = 6.521 min (method: 15% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 235.

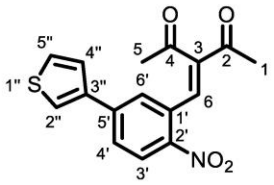
3-((4-Nitro-[1,1'-biphenyl]-3-yl)methylene)pentane-2,4-dione (8j)



According to the general protocol **GPIII** acetylacetone (0.581 g, 5.8 mmol, 1.5 eq.), 4-nitro-[1,1'-biphenyl]-3-carbaldehyde (0.906 g, 4.0 mmol, 1.0 eq.) and piperidine were reacted for 72 h. 0.383 g (1.24 mmol, 31%) of the product were isolated beige solid by flash column chromatography (SiO_2; 0 → 10% ethyl acetate).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.30 (d, 1H, *J* = 8.6 Hz, *H*-5'), 7.97 (s, 1H, *H*-6), 7.80 (dd, 1H, *J* = 8.6 Hz, 2.1 Hz, *H*-6'), 7.61 (m, 3H, *H*-2', *H*-2''), 7.50 (m, 3H, *H*-3'', *H*-4''), 2.49 (s, 3H, *H*-1), 2.13 (s, 3H, *H*-5).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 203.3, 197.0, 147.4, 146.2, 144.9, 138.7, 138.2, 131.2, 130.1, 129.9, 129.8, 129.1, 127.9, 126.4, 32.2, 27.2.
HR-MS: *m/z* for $C_{18}H_{15}NO_4^+$, $[M+Na]^+$ calculated: 332.0893; found: 332.0890.
LC-MS: t_R = 6.310 min (method: 60% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 310.

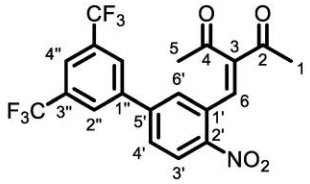
3-(2-Nitro-5-(thien-3-yl)benzylidene)pentane-2,4-dione (8k)



According to the general protocol **GPIII** acetylacetone (0.645 g, 6.4 mmol, 1.4 eq.), 2-nitro-5-(thien-3-yl)benzaldehyde (1.065 g, 4.6 mmol, 1.0 eq.) and piperidine were reacted for 48 h. 0.259 g (0.82 mmol, 18%) of the product were isolated yellow solid by flash column chromatography (SiO_2; 0 → 10% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.24 (d, 1H, *J* = 8.6 Hz, *H*-3'), 7.99 (s, 1H, *H*-6); 7.87 (dd, 1H, *J* = 8.6 Hz, 2.1 Hz, *H*-4'), 7.81 (dd, 1H, *J* = 2.9 Hz, 1.4 Hz, *H*-2''), 7.60 (d, 1H, *J* = 2.1 Hz, *H*-6'), 7.57 (dd, 1H, *J* = 5.1 Hz, 2.9 Hz, *H*-4''), 7.48 (dd, 1H, *J* = 5.1 Hz, 1.4 Hz, *H*-5''), 2.45 (s, 3H, *H*-1), 2.12 (s, 3H, *H*-5).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 204.1, 198.1, 146.3, 145.0, 141.8, 140.0, 139.8, 132.1, 129.0, 128.9, 128.4, 127.0, 126.9, 125.3, 31.9, 27.0.
HR-MS: *m/z* for $C_{16}H_{13}NO_4S^+$, $[M+Na]^+$ calculated: 338.0457; found: 338.0456.
LC-MS: t_R = 11.219 min (method: 40 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 316.

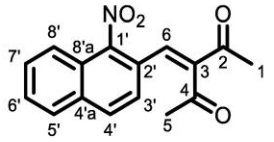
3-((4-Nitro-3',5'-bis(trifluoromethyl)-(1,1'-biphenyl)-3-yl)methylene)pentane-2,4-dione (8l)



According to the general protocol **GPIII** acetylacetone (0.355 g, 3.5 mmol, 1.3 eq.), 4-nitro-3',5'-bis(trifluoromethyl)-[1,1'-biphenyl]-3-carbaldehyde (0.992 g, 2.7 mmol, 1.0 eq.) and piperidine were reacted for 24 h. 0.506 g (1.14 mmol, 42%) of the product were isolated beige solid by flash column chromatography (SiO_2; 0 → 10% ethyl acetate).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.33 (d, 1H, *J* = 8.6 Hz, *H*-3'), 8.21 (s, 2H, *H*-2'', *H*-6''), 8.10 (s, 1H, *H*-4''), 8.00 (s, 1H, *H*-6), 7.97 (dd, 1H, *J* = 8.6 Hz, 2.1 Hz, *H*-4'), 7.70 (d, 1H, *J* = 2.1 Hz, *H*-6'), 2.47 (s, 3H, *H*-1), 2.13 (s, 3H, *H*-5).**^{13}C NMR (101 MHz, CD_3CN)** δ [ppm]: 203.9, 198.2, 148.0, 145.4, 144.1, 141.2, 139.5, 133.3, 133.0, 132.6, 132.1, 130.8, 130.1, 129.1, 126.9, 125.71, 123.7, 123.0, 31.9, 27.1.
^{19}F NMR (282 MHz, CD_3CN) δ [ppm]: -63.39 (s).
HR-MS: *m/z* for $C_{20}H_{13}F_6NO_4^+$, $[M+Na]^+$ calculated: 468.0641; found: 468.0634.
LC-MS: t_R = 9.106 min (method: 65% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 446.

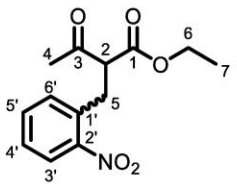
3-((1-Nitronaphthalen-2-yl)methylene)pentane-2,4-dione (8m)



According to the general protocol **GPIII** acetylacetone (0.608 g, 6.1 mmol, 1.3 eq.), 1-nitro-2-naphthaldehyde (0.974 g, 4.8 mmol, 1.0 eq.) and piperidine were reacted for 48 h. 0.394 g (1.39 mmol, 29%) of the product were isolated beige solid by flash column chromatography (SiO_2; 0 → 10% ethyl acetate).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.03 (d, 1H, *J* = 8.50 Hz, *H*-4'), 7.98 (d, 1H, *J* = 7.5 Hz, *H*-5'), 7.90 (d, 1H, *J* = 7.71 (m, 2H, *H*-6', *H*-7'), 7.61 (s, 1H, *H*-6), 7.41 (d, 1H, *H*-3'), 2.43 (s, 3H, *H*-1), 2.18 (s, 1H, *H*-5).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 203.5, 196.4, 147.6, 147.0, 134.7, 134.1, 132.1, 130.0, 129.0, 128.7, 125.4, 124.8, 124.71, 122.6, 32.0, 27.0.
HR-MS: *m/z* for $C_{16}H_{13}NO_4^+$, $[M+Na]^+$ calculated: 306.0737; found: 306.0749.
LC-MS: t_R = 8.160 min (method: 50% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 284.

Ethyl (2-nitrobenzylidene)-3-oxobutanoate (8n and 8o)



According to the general protocol **GPII** ethyl acetoacetate (1.44 g, 11 mmol, 1.1 eq.), 2-nitro benzaldehyde (1.51 g, 10 mmol, 1.0 eq.), glacial acetic acid and piperidine were reacted for 4 h. 0.779 g (3.0 mmol, 30%) of the *Z*-isomer **8o** as pale yellow oil and 0.166 g (0.63 mmol, 6%) of the *E*-isomer **8n** as beige solid were isolated by flash column chromatography (SiO_2; 0 → 10% ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$, *E*-isomer 8n) δ [ppm]: 8.18 (dd, *J* = 8.20 Hz, 1.37 Hz, 1H, *H*-3'), 8.01 (s, 1H, *H*-5), 7.65 (td, *J* = 7.57 Hz, 1.40 Hz, 1H, *H*-5'), 7.57 (td, *J* = 7.43 Hz, 1.56 Hz, 1H, *H*-4'), 7.34 (dt, *J* = 7.51 Hz, 1.22 Hz, 1H, *H*-6'), 4.32 (q, *J* = 7.13 Hz, 2H, *H*-6), 2.20 (s, 3H, *H*-4), 1.34 (t, *J* = 7.13 Hz, 3H, *H*-7).

^{13}C NMR (101 MHz, $CDCl_3$, *E*-isomer 8n) δ [ppm]: 200.9, 164.4, 147.8, 139.7, 136.9, 134.5, 131.4, 130.7, 125.5, 62.2, 31.6, 14.5.

^{1}H NMR (400 MHz, $CDCl_3$, *Z*-isomer 8o) δ [ppm]: 8.20 (dd, *J* = 8.20 Hz, 1.36 Hz, 1H, *H*-3'), 8.04 (s, 1H, *H*-5), 7.68 (td, *J* = 7.61 Hz, 1.38 Hz, 1H, *H*-5'), 7.60 (td, *J* = 8.06 Hz, 7.44 Hz, 1.54 Hz, 1H, *H*-4'), 7.43 (dt, *J* = 7.56 Hz, 1.22 Hz, 1H, *H*-6'), 4.04 (q, *J* = 7.13 Hz, 2H, *H*-6), 2.44 (s, 3H, *H*-4), 0.97 (t, *J* = 7.14 Hz, 3H, *H*-7).

^{13}C NMR (101 MHz, $CDCl_3$, *Z*-isomer 8o) δ [ppm]: 195.0, 166.2, 147.5, 140.8, 137.0, 134.5, 131.2, 130.8, 130.5, 125.4, 61.9, 27.5, 14.0.

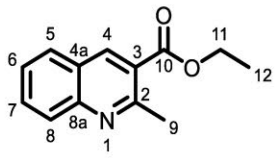
HR-MS (*E*-isomer 8n): *m/z* for $C_{13}H_{16}NO_5^+$, $[M+H]^+$ calculated: 286.0686; found: 286.0680.

LC-MS (*E*-isomer 8n): t_R = 8.825 min (method: 40 – 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 264.

HR-MS (*Z*-isomer 8o): *m/z* for $C_{13}H_{13}NO_5^+$, $[M+Na]^+$ calculated: 286.0686; found: 286.0681.

LC-MS (*Z*-isomer 8o): t_R = 7.372 min (method: 40 – 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 264.

3-(Ethoxycarbonyl)-2-methylquinoline (5a)

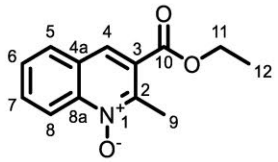


The title compound was prepared according **GPIV** using 53.1 mg (0.2 mmol) of 2-(2-nitrobenzyl)-3-oxobutanoate and 0.5 M H_2SO_4 as electrolyte. 15.1 mg (0.070 mmol, 35%) of the product were isolated as colorless solid by reversed phase column chromatography (C 18 silica gel, gradient: 0% acetonitrile → 10% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.70 (s, 1H, *H*-4), 8.01 (d, *J* = 8.49 Hz, 1H, *H*-8), 7.82 (dd, *J* = 8.12 Hz, 1.44 Hz, 1H, *H*-5), 7.74 (dt, *J* = 8.41 Hz, 1.55 Hz, 1H, *H*-7), 7.50 (dt, *J* = 8.02 Hz, 1.13 Hz, 1H, *H*-6), 4.42 (q, *J* = 7.12 Hz, 2H, *H*-11), 2.97 (s, 3H, *H*-9), 1.43 (t, *J* = 7.13 Hz, 3H, *H*-12).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]:166.6, 158.5, 148.7, 140.0, 131.7, 128.6, 128.5, 126.6, 125.8, 124.0, 61.5, 25.8, 14.4.
LC-MS: t_R = 7.106 min (method: 30% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) *m/z* for $C_{13}H_{13}NO_2^+$, $[M+H]^+$ = 216.

The spectroscopic data are in accordance with those reported in the literature.[19]

3-(Ethoxycarbonyl)-2-methylquinoline 1-oxide (6a)

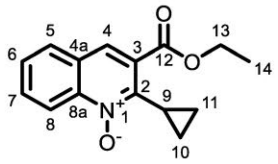


The title compound was prepared according **GPIV** using 52.8 mg (0.2 mmol) of 2-(2-nitrobenzyl)-3-oxobutanoate. 17.1 mg (0.074 mmol, 37%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 0% acetonitrile → 30% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.77 (d, *J* = 8.74 Hz, 1H, *H*-8), 8.25 (s, 1H, *H*-4), 7.91 (dd, *J* = 8.13 Hz, 1.31 Hz, 1H, *H*-5), 7.84 (dt, *J* = 8.53 Hz, 1.37 Hz, 1H, *H*-7), 7.65 (t, *J* = 7.50 Hz, 1H, *H*-6), 4.45 (q, *J* = 7.11 Hz, 2H, *H*-11), 2.98 (s, 3H, *H*-9), 1.45 (t, *J* = 7.15 Hz, 3H, *H*-12).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 165.4, 146.7, 142.6, 132.5, 129.2, 128.6, 128.0, 127.1, 126.2, 120.1, 62.2, 16.0, 14.4.
HR-MS: *m/z* for $C_{13}H_{13}NO_3^+$, $[M+H]^+$ calculated: 232.0968; found: 232.0970.
LC-MS: t_R = 6.937min (method: 25% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 232.

The spectroscopic data are in accordance with those reported in the literature.[20]

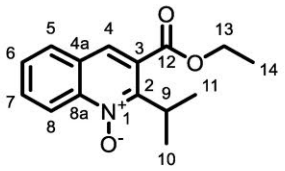
2-Cyclopropyl-3-(ethoxycarbonyl)quinoline 1-oxide (6b)



The title compound was prepared according **GPIV** using 58.3 mg (0.2 mmol) of ethyl 3-cyclopropyl-2-(2-nitrobenzyl)-3-oxopropanoate. 30.9 mg (0.061 mmol, 31%) of the product were isolated as pale yellow oil by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 30% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.75 (d, *J* = 8.75 Hz, 1H, *H*-8), 7.94 (s, 1H, *H*-4), 7.86 (dd, *J* = 8.08 Hz, 1.30 Hz, 1H, *H*-5), 7.80 (dt, *J* = 8.55 Hz, 1.37 Hz, 1H, *H*-7), 7.63 (t, *J* = 8.04 Hz, 1H, *H*-6), 4.45 (q, *J* = 7.16 Hz, 2H, *H*-13), 2.33 (sep, 1H, *H*-9), 1.44 (t, *J* = 7.14 Hz, 3H, *H*-14), 1.22 (m, 2H, *H*-10), 0.87 (m, 2H, *H*-11).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 166.3, 147.6, 142.6, 132.0, 129.2, 128.8, 127.6, 125.9, 119.9, 62.3, 14.4, 12.7, 7.7.
HR-MS: *m/z* for $C_{15}H_{15}NO_3^+$, $[M+H]^+$ calculated: 258.1125; found: 258.1134.
LC-MS: t_R = 8.760 min (method: 25% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 258.

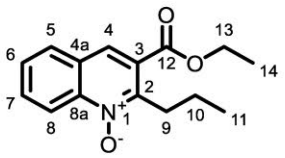
3-(Ethoxycarbonyl)-2-isopropylquinoline 1-oxide (6c)



The title compound was prepared according **GPIV** using 59.0 mg (0.2 mmol) of ethyl 4-methyl-2-(2-nitrobenzyl)-3-oxopentanoate. 19.8 mg (0.071 mmol, 26%) of the product were isolated as pale-yellow oil by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 30% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.76 (d, *J* = 8.95 Hz, 1H, *H*-8), 7.93 (s, 1H, *H*-4), 7.85 (d, *J* = 8.06 Hz, 1.37 Hz, 1H, *H*-5), 7.81 (dt, *J* = 8.52 Hz, 1.46 Hz, 1H, *H*-7), 7.63 (dt, *J* = 8.09 Hz, 1.15 Hz, 1H, *H*-6), 4.44 (q, *J* = 7.11 Hz, 2H, *H*-12), 3.99 (sep, *J* = 6.97 Hz, 1H, *H*-9), 1.56 (d, *J* = 6.93 Hz, 6H, *H*-10), 1.44 (t, *J* = 7.15 Hz, 3H, *H*-13).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 166.7, 151.4, 143.0, 132.0, 128.7, 128.2, 127.5, 126.3, 120.1, 62.4, 30.6, 17.5, 14.3.
HR-MS: *m/z* for $C_{13}H_{16}NO_5^+$, $[M+H]^+$ calculated: 260.1281; found: 260.1278.
LC-MS: t_R = 6.810 min (method: 40 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 260.

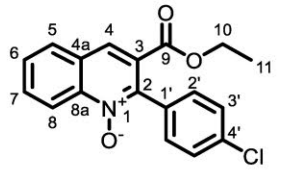
3-(Ethoxycarbonyl)-2-propylquinoline 1-oxide (6d)



The title compound was prepared according **GPIV** using 58.7 mg (0.2 mmol) of ethyl 2-(2-nitrobenzyl)-3-oxohexanoate. 46.3 mg (0.179 mmol, 90%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 35% acetonitrile).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.57 (m, 1H, *H*-8), 8.17 (s, 1H, *H*-4), 7.95 (m, 1H, *H*-5), 7.80 (m, 1H, *H*-7), 7.64 (m, 1H, *H*-6), 4.39 (q, 2H, *J* = 7.1 Hz, *H*-13), 3.26 (td, 2H, *J* = 7.8 Hz, 2.5 Hz, *H*-9), 1.72 (m, 2H, *H*-10), 1.39 (t, 3H, *J* = 7.1 Hz, *H*-14), 1.02 (t, 3H, *J* = 7.4 Hz, *H*-11).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 166.4, 149.3, 143.3, 133.0, 130.2, 129.4, 128.3, 127.5, 127.3, 120.3, 62.9, 31.4, 20.1, 14.7, 14.4.
HR-MS: *m/z* for $C_{15}H_{17}NO3^+$, $[M+H]^+$ calculated: 260.1281; found: 260.1286.
LC-MS: t_R = 8.839 min (method: 35% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 260.

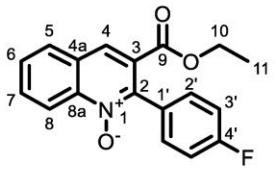
3-(Ethoxycarbonyl)-2-(4-chlorophenyl)quinoline 1-oxide (6e)



The title compound was prepared according **GPIV** using 72.3 mg (0.2 mmol) of 3-(4-chlorophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate. 54.0 mg (0.165 mmol, 83%) of the product were isolated as colorless solid by reversed phase column chromatography (C 18 silica gel, gradient: 15% acetonitrile → 40% acetonitrile).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.71 (d, 1H, *J* = 8.7 Hz, *H*-8), 8.24 (s, 1H, *H*-4), 8.01 (d, 1H, *J* = 8.1 Hz, *H*-5), 7.87 (td, 1H, *J* = 8.7 Hz, *H*-7), 7.74 (td, 1H, *J* = 8.1 Hz, *H*-6), 7.49 (m, 2H, *H*-2'), 7.43 (m, 2H, *H*-3'), 4.11 (q, 2H, *J* = 7.1 Hz, *H*-10), 1.06 (t, 3H, *J* = 7.1 Hz, *H*-11).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 165.5, 143.9, 143.4, 135.1, 132.6, 132.4, 131.4, 129.7, 129.6, 128.8, 128.7, 127.9, 126.8, 120.5, 62.3, 13.8.
HR-MS: *m/z* for $C_{18}H_{14}{}^{35}ClNO_3^+$, $[M+H]^+$ calculated: 328.0735; found: 328.0735.
LC-MS: t_R = 10.309 min (method: 40% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 328.

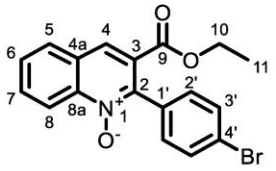
3-(Ethoxycarbonyl)-2-(4-fluorophenyl)quinoline 1-oxide (6f)



The title compound was prepared according **GPIV** using 68.9 mg (0.2 mmol) of ethyl 3-(4-fluorophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate. 52.7 mg (0.169 mmol, 85%) of the product were isolated as colorless solid by reversed phase column chromatography (C 18 silica gel, gradient: 15% acetonitrile → 40% acetonitrile).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.61 (d, 1H, *J* = 8.7 Hz, *H*-8), 8.24 (s, 1H, *H*-4), 8.07 (d, 1H, *J* = 8.2 Hz, *H*-5), 7.88 (td, 1H, *J* = 8.7 Hz, *H*-7), 7.76 (td, 1H, *J* = 8.2 Hz, *H*-6), 7.49 (m, 2H, *H*-2'), 7.23 (m, 2H, *H*-3'), 4.09 (q, 2H, *J* = 7.1 Hz, *H*-10), 1.03 (t, 3H, *J* = 7.1 Hz, *H*-11).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 166.3, 165.0, 162.6, 144.3, 143.8, 133.2, 132.8, 130.8, 130.7, 130.3 (d, *J* = 10.7 Hz), 129.5, 128.9, 126.9, 120.6, 116.0, 115.8, 62.7, 14.0.
^{19}F NMR (376 MHz, CD_3CN) δ [ppm]: -115.27 (m).
HR-MS: *m/z* for $C_{18}H_{14}FNO_3^+$, $[M+H]^+$ calculated: 312.1030; found: 312.1035.
LC-MS: t_R = 8.072 min (method: 35% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 312.

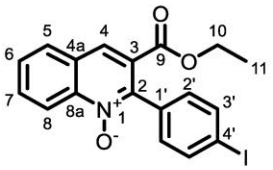
3-(Ethoxycarbonyl)-2-(4-bromophenyl)quinoline 1-oxide (6g)



The title compound was prepared according **GPIV** using 81.4 mg (0.2 mmol) of 3-(4-bromophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate. 58.0 mg (0.156 mmol, 78%) of the product were isolated as colorless solid by reversed phase column chromatography (C 18 silica gel, gradient: 15% acetonitrile → 42% acetonitrile).

^{1}H NMR (600 MHz, CD_3CN) δ [ppm]: 8.62 (d, 1H, *J* = 8.7 Hz, *H*-8), 8.30 (s, 1H, *H*-4), 8.11 (d, 1H, *J* = 8.2 Hz, *H*-5), 7.90 (td, 1H, *J* = 8.7 Hz, *H*-7), 7.78 (td, 1H, *J* = 8.1 Hz, *H*-6), 7.66 (m, 2H, *H*-2'), 7.39 (m, 2H, *H*-3'), 4.10 (q, 2H, *J* = 7.1 Hz, *H*-10), 1.04 (t, 3H, *J* = 7.1 Hz, *H*-11).
^{13}C NMR (151 MHz, CD_3CN) δ [ppm]: 166.1, 144.2, 143.8, 133.9, 133.3, 132.5, 132.1, 130.5, 130.4, 129.5, 128.6, 127.1, 123.3, 120.6, 62.7, 13.9.
HR-MS: *m/z* for $C_{18}H_{14}{}^{79}BrNO_3^+$, $[M+H]^+$ calculated: 372.0230; found: 372.0232.
LC-MS: t_R = 11.092 min (method: 40% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 372.

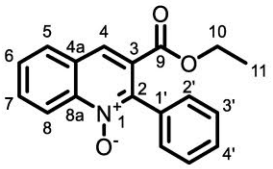
3-(Ethoxycarbonyl)-2-(4-iodophenyl)quinoline 1-oxide (6h)



The title compound was prepared according **GPIV** using 90.6 mg (0.2 mmol) of 3-(4-chlorophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate. 71.9 mg (0.172 mmol, 86%) of the product were isolated as colorless solid by reversed phase column chromatography (C 18 silica gel, gradient: 25% acetonitrile → 50% acetonitrile).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.70 (d, 1H, *J* = 8.7 Hz, *H*-8), 8.24 (s, 1H, *H*-4), 8.00 (d, 1H, *J* = 8.1 Hz, *H*-5), 7.86 (m, 3H, *H*-7, *H*-2', *H*-6'), 7.74 (t, 1H, *J* = 8.1 Hz, *H*-6), 7.24 (m, 2H, *H*-3', *H*-5'), 4.12 (q, 2H, *J* = 7.1 Hz, *H*-10), 1.06 (t, 3H, *J* = 7.1 Hz, *H*-11).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 165.4, 144.0, 143.3, 137.7, 133.5, 132.6, 131.7, 129.7, 129.6, 128.8, 127.7, 126.9, 120.5, 95.1, 62.3, 13.8.
HR-MS: *m/z* for $C_{18}H_{14}INO_3^+$, $[M+H]^+$ calculated: 420.0091; found: 420.0092.
LC-MS: t_R = 7.158 min (method: 35% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 420.

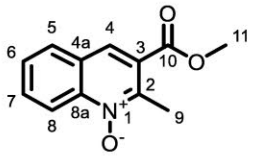
3-(Ethoxycarbonyl)-2-phenylquinoline 1-oxide (6i)



The title compound was prepared according **GPIV** using 65.5mg (0.2 mmol) of ethyl 2-(2-nitrobenzyl)-3-oxo-3-phenylpropanoate. 46.9 mg (0.160 mmol, 80%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 37% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.79 (d, *J* = 8.71 Hz, 1H, *H*-8), 8.22 (s, 1H, *H*-4), 7.96 (d, *J* = 8.07 Hz, 1H, *H*-5), 7.86 (dt, *J* = 8.39 Hz, *J* = 1.24 Hz, 1H, *H*-7), 7.71 (dt, *J* = 8.17 Hz, 1.13 Hz, 1H, *H*-6, 7.50 (m, 5H, *H*-2', *H*-3', *H*-4'), 4.07 (q, *J* = 7.14 Hz, 2H, *H*-10), 0.96 (t, *J* = 7.09 Hz, 3H, *H*-11).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 165.7, 145.1, 143.0, 133.1, 132.4, 129.3, 129.2, 129.1, 128.4, 127.9, 126.9, 120.6, 62.0, 13.6.
HR-MS: *m/z* for $C_{18}H_{15}NO_3^+$, $[M+H]^+$ calculated: 294.1125; found: 294.1120.
LC-MS: t_R = 8.991 min (method: 30 → 100% acetonitrile in 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 294.

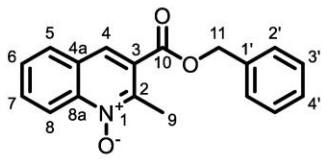
3-(Methoxycarbonyl)-2-methylquinoline 1-oxide (6j)



The title compound was prepared according **GPIV** using 50.3 mg (0.2 mmol) of methyl 2-(2-nitrobenzyl)-3-oxobutanoate. 32.3 mg (0.149 mmol, 75%) of the product were isolated as pale-yellow oil by reversed phase column chromatography (C 18 silica gel, gradient: 0% acetonitrile → 15% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.75 (d, *J* = 8.7 Hz, 1H, *H*-8), 8.25 (s, 1H, *H*-4), 7.88 (d, *J* = 8.1 Hz, 1H, *H*-5), 7.82 (dt, *J* = 8.7 Hz, 1.4 Hz, 1H, *H*-7), 7.63 (td, *J* = 7.5 Hz, 1H, *H*-6), 3.95 (s, 3H, *H*-11), 2.95 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 165.8, 146.5, 142.5, 132.5, 129.2, 128.6, 127.8, 127.1, 125.7, 120.1, 53.0, 16.0.
HR-MS: *m/z* for $C_{12}H_{11}NO_3^+$, $[M+H]^+$ calculated: 218.0812; found: 218.0814.
LC-MS: t_R = 11.155 min (method: 15% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 218.

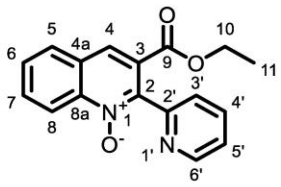
3-((Benzyloxy)carbonyl)-2-methylquinoline 1-oxide (6k)



The title compound was prepared according **GPIV** using 66.2 mg (0.2 mmol) of benzyl 2-(2-nitrobenzyl)-3-oxobutanoate. 35.1 mg (0.120 mmol, 60%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 30% acetonitrile).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.69 (d, 1H, *J* = 8.7 Hz, *H*-8), 8.26 (s, 1H, *H*-4), 7.92 (d, 1H, *J* = 8.0 Hz, *H*-5), 7.82 (td, 1H, *J* = 8.7 Hz, 6.9 Hz, *H*-7), 7.65 (td, 1H, *J* = 8.1 Hz, 6.9 Hz, *H*-6). 7.50 (m, 2H, *H*-2'), 7.42 (m, 3H, *H*-3', *H*-4'), 5.42 (s, 2H, *H*-11), 2.90 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 165.5, 146.3, 142.9, 135.9, 132.6, 129.6, 129.1, 128.9, 128.9, 128.8, 127.5, 127.4, 126.2, 120.0, 68.1, 16.0.
HR-MS: *m/z* for $C_{18}H_{15}NO_3^+$, $[M+H]^+$ calculated: 294.1125; found: 294.1133.
LC-MS: t_R = 8.408 min (method: 40% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 294.

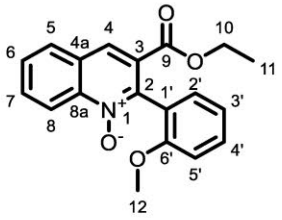
3-(Ethoxycarbonyl)-2-(pyridin-2-yl)quinoline 1-oxide (6l)



The title compound was prepared according **GPIV** using 65.6 mg (0.2 mmol) of ethyl 2-(2-nitrobenzyl)-3-oxo-3-(pyridin-2-yl)propanoate. 22.1 mg (0.0751 mmol, 38%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 0% acetonitrile → 20% acetonitrile).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.73 (d, 1H, *J* = 8.2 Hz, *H*-8), 8.68 (d, 1H, *J* = 4.9 Hz, *H*-6'), 8.21 (s, 1H, *H*-4), 8.10 (t, 1H, *J* = 8.0 Hz, *H*-4'), 8.00 (d, 1H, *J* = 8.1 Hz, *H*-5), 7.88 (m, 2H, *H*-7, *H*-3'), 7.74 (td, 1H, *J* = 8.1 Hz, 6.9 Hz, *H*-6), 7.38 (dd, 1H, *J* = 7.6 Hz, 4.9 Hz, *H*-5'), 4.09 (q, 2H, *J* = 7.2 Hz, *H*-10), 1.02 (t, 3H, *J* = 7.2 Hz, *H*-11).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 165.9, 151.9, 149.5, 143.5, 143.2, 136.1, 132.4, 129.9, 129.5, 129.0, 128.5, 126.9, 126.6, 124.0, 120.4, 62.1, 13.9.
HR-MS: *m/z* for $C_{17}H_{14}N_2O_3^+$, $[M+H]^+$ calculated: 295.1077; found: 295.1077.
LC-MS: t_R = 6.755 min (method: 20% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 295.

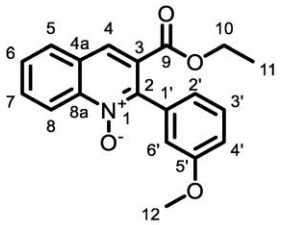
3-(Ethoxycarbonyl)-2-(2-methoxyphenyl)quinoline 1-oxide (6m)



The title compound was prepared according **GPIV** using 71.7 mg (0.2 mmol) of ethyl 3-(2-methoxyphenyl)-2-(2-nitrobenzyl)-3-oxopropanoate. 49.8 mg (0.154 mmol, 77%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 25% acetonitrile → 35% acetonitrile).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.72 (d, 1H, *J* = 7.7 Hz, *H*-8), 8.25 (s, 1H, *H*-4), 8.00 (d, 1H, *J* = 8.1 Hz, *H*-5), 7.85 (m, 1H, *H*-7), 7.72 (m, 1H, *H*-6), 7.40 (m, 1H, *H*-6'), 7.47 (m, 1H, *H*-4'), 7.35 (m, 1H, *H*-2'), 7.10 (m, 1H, *H*-4'), 7.04 (d, 1H, *J* = 8.1 Hz, *H*-5'), 4.10 (qd, 2H, *J* = 7.1 Hz, 1.3 Hz, *H*-10), 3.74 (s, 3H, *H*-12), 1.05 (t, 3H, *J* = 7.1 Hz, *H*-11).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 165.4, 157.6, 143.5, 143.0, 132.2, 130.8, 130.7, 129.5, 129.4, 128.8, 128.4, 126.3, 123.0, 120.8, 120.6, 111.2, 61.9, 55.9, 13.9.
HR-MS: *m/z* for $C_{19}H_{17}NO_4^+$, $[M+H]^+$ calculated: 324.1050; found: 324.1049.
LC-MS: t_R = 8.897 min (method: 30% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 324.

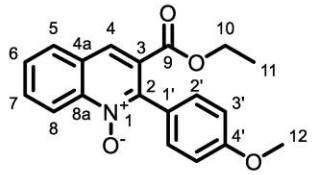
3-(Ethoxycarbonyl)-2-(3-methoxyphenyl)quinoline 1-oxide (6n)



The title compound was prepared according **GPIV** using 71.5 mg (0.2 mmol) of ethyl 3-(3-methoxyphenyl)-2-(2-nitrobenzyl)-3-oxopropanoate. 49.0 mg (0.152 mmol, 76%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 15% acetonitrile → 35% acetonitrile).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.61 (d, 1H, *J* = 7.9 Hz, *H*-8), 8.20 (s, 1H, *H*-4), 8.05 (d, 1H, *J* = 8.2 Hz, *H*-5), 7.86 (m, 1H, *H*-7), 7.74 (m, 1H, *H*-6), 7.40 (m, 1H, *H*-6'), 7.02 (m, 3H, *H*-2', *H*-3', *H*-4'), 4.07 (q, 2H, *J* = 7.1 Hz, *H*-10), 3.80 (s, 3H, *H*-12), 1.00 (t, 3H, *J* = 7.1 Hz, *H*-11).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 166.4, 160.4, 144.9, 143.7, 135.8, 133.1, 130.3, 130.2, 130.1, 129.4, 129.1, 126.6, 122.8, 120.6, 116.1, 115.3, 62.6, 56.0, 14.0.
HR-MS: *m/z* for $C_{19}H_{17}NO_4^+$, $[M+H]^+$ calculated: 324.1230; found: 324.1229.
LC-MS: t_R = 10.915 min (method: 30% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 324.

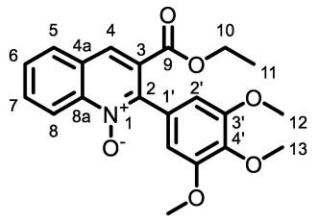
3-(Ethoxycarbonyl)-2-(4-methoxyphenyl)quinoline 1-oxide (6o)



The title compound was prepared according **GPIV** using 71.8 mg (0.2 mmol) of ethyl 3-(4-methoxyphenyl)-2-(2-nitrobenzyl)-3-oxopropanoate. 40.7 mg (0.126 mmol, 63%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 25% acetonitrile → 35% acetonitrile).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.63 (d, 1H, *J* = 8.8 Hz, *H*-8), 8.17 (s, 1H, *H*-4), 8.06 (d, 1H, *J* = 8.2 Hz, *H*-5), 7.87 (m, 1H, *H*-7), 7.74 (m, 1H, *H*-6), 7.44 (m, 2H, *H*-2'), 7.03 (m, 2H, *H*-3'), 4.09 (q, 2H, *J* = 7.1 Hz, *H*-10), 3.86 (s, 3H, *H*-12), 1.04 (t, 3H, *J* = 7.1 Hz, *H*-11).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 166.8, 161.2, 144.8, 143.7, 133.0, 132.2, 130.3, 130.1, 129.6, 129.4, 126.4, 120.6, 114.3, 62.6, 56.0, 14.1.
HR-MS: *m/z* for $C_{19}H_{17}NO_4^+$, $[M+H]^+$ calculated: 324.1230; found: 324.1222.
LC-MS: t_R = 13.022 min (method: 30% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 324.

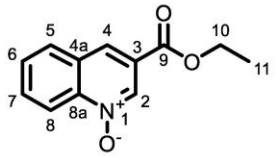
3-(Ethoxycarbonyl)-2-(3,4,5-trimethoxyphenyl)quinoline 1-oxide (6p)



The title compound was prepared according **GPIV** using 84.1 mg (0.2 mmol) of ethyl 2-(2-nitrobenzyl)-3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate. 55.1 mg (0.144 mmol, 72%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 15% acetonitrile → 30% acetonitrile).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.62 (d, 1H, *J* = 8.2 Hz, *H*-8), 8.17 (s, 1H, *H*-4), 8.06 (d, 1H, *J* = 6.8 Hz, *H*-5), 7.87 (m, 1H, *H*-7), 7.75 (m, 1H, *H*-6), 6.78 (s, 1H, *H*-2'), 4.09 (q, 2H, *J* = 7.1 Hz, *H*-10), 3.80 (s, 3H, *H*-13), 3.78 (s, 6H, *H*-12), 1.01 (t, 3H, *J* = 7.1 Hz, *H*-11).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 166.6, 154.2, 144.9, 143.7, 139.5, 133.1, 130.4, 130.2, 129.9, 129.4, 129.4, 126.4, 120.6, 108.3, 62.6, 61.0, 56.9, 14.1.
HR-MS: *m/z* for $C_{21}H_{21}NO_6^+$, $[M+H]^+$ calculated: 384.1442; found: 384.1434.
LC-MS: t_R = 8.430min (method: 30% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 384.

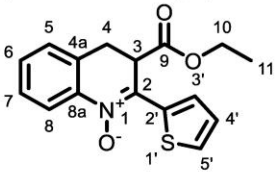
3-(Ethoxycarbonyl)quinoline 1-oxide (6q)



The title compound was prepared according **GPIV** using 50.2 mg (0.2 mmol) of ethyl 2-formyl-3-(2-nitrophenyl)propanoate. 9.6 mg (0.0441 mmol, 22%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 0% acetonitrile → 20% acetonitrile) and flash column chromatography (SiO_2, gradient 0% ethyl acetate → 30% ethyl acetate).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.97 (d, 1H, *J* = 1.4 Hz, *H*-2), 8.69 (d, 1H, *J* = 7.8 Hz, *H*-8), 8.38 (s, 1H, *H*-4), 8.02 (m, 1H, *H*-5), 7.87 (m, 1H, *H*-7), 7.73 (m, 1H, *H*-6), 4.44 (q, 2H, *J* = 7.1 Hz, *H*-10), 1.43 (t, 3H, *J* = 7.1 Hz, *H*-11).**^{13}C NMR (101 MHz, CD_2Cl_2)** δ [ppm]: 164.0, 143.7, 135.3, 132.8, 130.3, 130.0, 129.9, 127.6, 125.5, 120.2, 62.7, 14.6.
HR-MS: *m/z* for $C_{12}H_{11}NO_3^+$, $[M+H]^+$ calculated: 218.0812; found: 218.0814.
LC-MS: t_R = 3.867 min (method: 30% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 218.

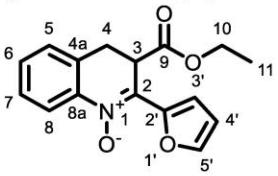
3-(Ethoxycarbonyl)-2-(thien-2-yl)-3,4-dihydroquinoline 1-oxide (7a)



The title compound was prepared according **GPIV** using 66.7 mg (0.2 mmol) of ethyl 2-(2-nitrobenzyl)-3-oxo-3-(thien-2-yl)propanoate. 37.8 mg (0.125 mmol, 63%) of the product were isolated as yellow oil by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 30% acetonitrile).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.12 (d, 1H, *J* = 8.0 Hz, *H*-8), 7.76 (d, 1H, *J* = 4.1 Hz, *H*-5'), 7.64 (d, 1H, *J* = 5.1 Hz, *H*-3'), 7.44 (t, 1H, *J* = 8.0 Hz, *H*-7), 7.38 (td, 1H, *J* = 7.4 Hz, 1.5 Hz, *H*-6), 7.32 (m, 1H, *H*-5), 7.27 (dd, 1H, *J* = 5.1 Hz, 4.1 Hz,*H*-4'), 4.64 (dd, 1H, *J* = 5.9 Hz, 2.9 Hz, *H*-3), 3.99 (q, 2H, *J* = 7.1 Hz, *H*-10), 3.41 (m, 2H, *H*-4), 1.01 (t, 3H, *J* = 7.1 Hz, *H*-11).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 170.2, 141.0, 134.6, 133.7, 131.0, 129.8, 129.3, 128.0, 127.9, 127.6, 126.9, 119.9, 61.6, 41.7, 26.9, 13.3.
HR-MS: *m/z* for $C_{16}H_{15}NO_3S^+$, $[M+H]^+$ calculated: 302.0845; found: 302.0853.
LC-MS: t_R = 6.408 min (method: 40% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 302.

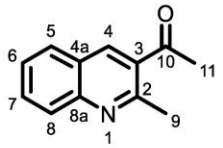
3-(Ethoxycarbonyl)-2-(furan-2-yl)-3,4-dihydroquinoline 1-oxide (7b)



The title compound was prepared according **GPIV** using 63.7 mg (0.2 mmol) of ethyl 3-(furan-2-yl)-2-(2-nitrobenzyl)-3-oxopropanoate. 26.0 mg (0.0911 mmol, 46%) of the product were isolated as brown oil by reversed phase column chromatography (C 18 silica gel, gradient: 0% acetonitrile → 30% acetonitrile).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.20 (d, 1H, *J* = 3.5 Hz, *H*-3'), 8.15 (d, 1H, *J* = 8.1 Hz, *H*-8), 7.63 (d, 1H, *J* = 1.8 Hz, *H*-5'), 7.41 (m, 1H, *H*-7), 7.34 (t, 1H, *J* = 7.4 Hz, *H*-6), 7.25 (d, 1H, *J* = 7.4 Hz, *H*-5), 6.68 (dd, 1H, *J* = 3.5 Hz, 1.8 Hz, *H*-4'), 4.58 (dd, 1H, *J* = 6.8 Hz, 2.2 Hz, *H*-3), 4.00 (q, 2H, *J* = 7.1 Hz, *H*-10), 3.36 (m, 2H, *H*-4), 1.02 (t, 3H, *J* = 7.1 Hz, *H*-11).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 170.4, 147.8, 144.8, 142.1, 131.2, 129.6, 128.5, 127.8, 127.8, 120.5, 117.8, 113.4, 62.1, 40.3, 27.4, 14.1.
HR-MS: *m/z* for $C_{16}H_{15}NO_4^+$, $[M+H]^+$ calculated: 286.1074; found: 286.1072.
LC-MS: t_R = 9.694 min (method: 30% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 286.

3-Acetyl-2-methylquinoline (9a)

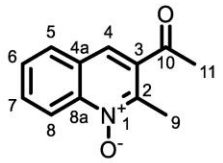


The title compound was prepared according **GPIV** using 46.5 mg (0.2 mmol) of 3-(2-nitrobenzylidene)pentane-2,4-dione and glassy carbon as cathode. 11.7 mg (0.063 mmol, 32%) of the product were isolated as colorless solid by reversed phase column chromatography (C 18 silica gel, gradient: 0% acetonitrile → 10% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.49 (s, 1H, *H*-4), 8.05 (d, *J* = 8.46 Hz, 1H, *H*-9), 7.86 (dd, *J* = 8.00 Hz, 1.48 Hz, 1H, *H*-6), 7.79 (dt, *J* = 8.41 Hz, 1.40 Hz, 1H, *H*-8), 7.56 (dt, *J* = 8.02 Hz, 1.07 Hz, 1H, *H*-7), 2.92 (s, 3H, *H*-11), 2.72 (s, 3H, *H*-13).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 200.0, 157.8, 148.3, 138.4, 132.0, 131.3, 128.7, 128.5, 126.9, 125.8, 29.4, 25.8.
LC-MS: t_R = 6.083 min (method: 10% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) *m/z* for $C_{12}H_{11}NO^+$, $[M+H]^+$ = 186.

The spectroscopic data are in accordance with those reported in the literature.[21]

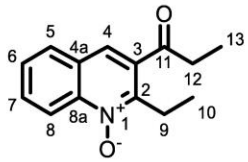
3-Acetyl-2-methylquinoline 1-oxide (10a)



The title compound was prepared according **GPIV** using 46.5 mg (0.2 mmol) of 3-(2-nitrobenzylidene)pentane-2,4-dione. 30.9 mg (0.153 mmol, 77%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 0% acetonitrile → 10% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.75 (d, *J* = 8.76 Hz, 1H, *H*-8), 7.98 (s, 1H, *H*-4), 7.89 (dd, *J* = 8.02 Hz, 1.31 Hz, 1H, *H*-5), 7.83 (dt, *J* = 8.57 Hz, 1.26 Hz, 1H, *H*-7), 7.65 (t, *J* = 8.15 Hz, 1H, *H*-6), 2.82 (s, 3H, *H*-9), 2.70 (s, 3H, *H*-11).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 198.7, 145.2, 142.2, 133.7, 132.4, 129.0, 128.7, 127.2, 125.5, 120.1, 29.8, 15.9.
HR-MS: *m/z* for $C_{12}H_{11}NO_2^+$, $[M+H]^+$ calculated: 202.0863; found: 202.0860.
LC-MS: t_R = 10.543 min (method: 10% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 202.

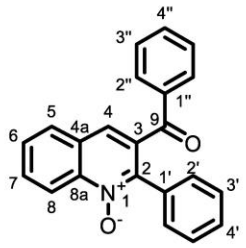
2-Ethyl-3-propionylquinoline 1-oxide (10b)



The title compound was prepared according **GPIV** using 52.2 mg (0.2 mmol) of 4-(2-nitrobenzylidene)heptane-3,5-dione. 37.9 mg (0.165 mmol, 83%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 30% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.76 (d, *J* = 8.68 Hz, 1H, *H*-8), 7.87 (m, 2H, *H*-4, *H*-5), 7.81 (dd, *J* = 8.46 Hz, 1.27 Hz, 1H, *H*-7), 7.68 (dt, *J* = 8.07 Hz, 1.08 Hz, 1H, *H*-6), 3.22 (q, *J* = 7.29 Hz, 2H, *H*-9), 3.02 (q, *J* = 7.20 Hz, 2H, *H*-12), 1.37 (t, *J* = 7.28 Hz, 3H, *H*-10), 1.26 (t, *J* = 7.25 Hz, 3H, *H*-13).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 202.4, 149.3, 142.2, 134.3, 132.1, 128.8, 128.7, 127.5, 124.3, 120.2, 35.6, 22.8, 10.8, 8.4.
HR-MS: *m/z* for $C_{14}H_{15}NO_2^+$, $[M+H]^+$ calculated: 230.1176; found: 230.1174.
LC-MS: t_R = 5.487min (method: 30% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 230.

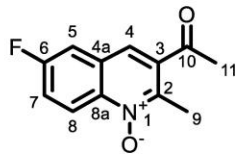
3-Benzoyl-2-phenylquinoline 1-oxide (10c)



The title compound was prepared according **GPIV** using 71.8 mg (0.2 mmol) of 2-(2-nitrobenzylidene)-1,3-diphenylpropane-1,3-dione. 43.5 mg (0.134 mmol, 67%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 55% acetonitrile).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.76 (d, *J* = 8.79 Hz, 1H, *H*-8), 7.97 (dd, *J* = 8.13 Hz, 1.36 Hz, 1H, *H*-5), 7.88 (dt, *J* = 8.57 Hz, 1.43 Hz, 1H, *H*-7), 7.83 (s, 1H, *H*-4), 7.75 (dt, *J* = 8.20 Hz, 1.37 Hz, 1H, *H*-6), 7.68 (m, 2H, *H*-2''), 7.52 (m, 1H, *H*-4''), 7.46 (m, 2H, *H*-2'), 7.36 (m, 2H, *H*-3''), 7.31 (m, 3H, *H*-3', *H*-4').
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 194.4, 144.1, 143.1, 137.1, 135.6, 134.1, 132.6, 132.1, 130.8, 130.3, 129.7, 129.4, 129.1, 129.0, 128.5, 124.6, 120.7.
HR-MS: *m/z* for $C_{22}H_{15}NO_2^+$, $[M+H]^+$ calculated: 326.1176; found: 326.1177.
LC-MS: t_R = 8.432 min (method: 40% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 326.

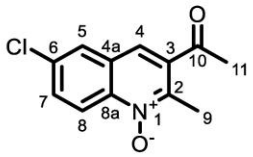
3-Acetyl-6-fluoro-2-methylquinoline 1-oxide (10d)



The title compound was prepared according **GPIV** using 50.2 mg (0.2 mmol) of 3-(5-fluoro-2-nitrobenzylidene)pentane-2,4-dione. 34.6 mg (0.157 mmol, 79%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 25% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.77 (dd, *J* = 9.50 Hz, 1H, *H*-8), 7.87 (s, 1H, *H*-4), 7.54 (m, 2H, *H*-5, *H*-7), 2.78 (s, 1H, *H*-9), 2.70 (s, 1H, *H*-11).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 198.6, 161.8, 144.4, 139.3, 135.1, 128.3, 124.0, 123.2, 121.9, 112.4, 29.8, 15.8.
^{19}F NMR (376 MHz, $CDCl_3$) δ [ppm]: -111.83 (m).
HR-MS: *m/z* for $C_{13}H_{16}NO_5^+$, $[M+H]^+$ calculated: 220.0768; found: 220.0769.
LC-MS: t_R = 4.114 min (method: 20% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 220.

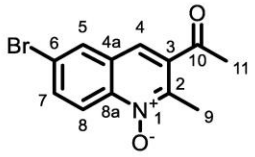
3-Acetyl-6-chloro-2-methylquinoline 1-oxide (10e)



The title compound was prepared according **GPIV** using 53.4 mg (0.2 mmol) of 3-(5-chloro-2-nitrobenzylidene)pentane-2,4-dione. 25.7 mg (0.109 mmol, 55%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 25% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.23 (d, *J* = 9.29 Hz, 1H, *H*-8), 7.42 (dd, *J* = 2.24 Hz, 1H, *H*-5), 7.40 (s, 1H, *H*-4), 7.27 (dd, *J* = 9.21 Hz, 2.17 Hz, 1H, *H*-7), 2.33 (s, 3H, *H*-9), 2.23 (s, 3H, *H*-11).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 198.5, 145.3, 140.6, 135.0, 134.9, 132.9, 128.0, 127.5, 123.9, 122.0, 29.8, 15.9.
HR-MS: *m/z* for $C_{12}H_{10}{}^{35}ClNO_2^+$, $[M+H]^+$ calculated: 236.0473; found: 236.0471.
LC-MS: t_R = 9.536 min (method: 20% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 236.

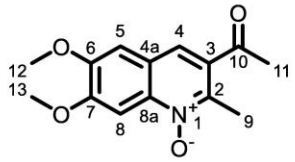
3-Acetyl-6-bromo-2-methylquinoline 1-oxide (10f)



The title compound was prepared according **GPIV** using 62.1 mg (0.2 mmol) of 3-(5-bromo-2-nitrobenzylidene)pentane-2,4-dione. 40.7 mg (0.145 mmol, 73%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 25% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.63 (d, *J* = 9.19 Hz, 1H, *H*-8), 8.06 (d, *J* = 2.03 Hz, 1H, *H*-5), 7.88 (dd, *J* = 9.29 Hz, 2.09 Hz, 1H, *H*-7), 7.86 (s, 1H, *H*-4), 2.79 (s, 1H, *H*-9), 2.70 (s, 1H, *H*-11).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 198.4, 145.5, 141.0, 135.6, 135.0, 130.8, 128.4, 123.8, 123.1, 122.1, 29.8, 15.9.
HR-MS: *m/z* for $C_{12}H_{10}{}^{79}BrNO_2^+$, $[M+H]^+$ calculated: 279.9968; found: 279.9969.
LC-MS: t_R = 9.082 min (method: 20% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 282.

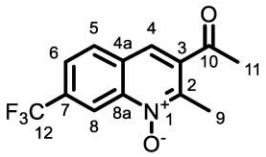
3-Acetyl-6,7-dimethoxy-2-methylquinoline 1-oxide (10g)



The title compound was prepared according **GPIV** using 58.8 mg (0.2 mmol) of 3-(4,5-dimethoxy-2-nitrobenzylidene)pentane-2,4-dione. 40.3 mg (0.154 mmol, 77%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 0% acetonitrile → 20% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.12 (s, *H*-8), 7.89 (s, 1H, *H*-4), 7.10 (s, 1H, *H*-5), 4.09 (s, 3H, *H*-12), 4.01 (s, 3H, *H*-13), 2.84 (s, 3H, *H*-9), 2.68 (s, 3H, *H*-11).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 198.6, 1551.2, 151.2, 144.1, 138.9, 131.5, 124.8, 122.4, 106.4, 99.7, 56.9, 56.4, 29.6, 15.8.
HR-MS: *m/z* for $C_{13}H_{16}NO_5^+$, $[M+H]^+$ calculated: 262.1074; found: 262.1077.
LC-MS: t_R = 8.671 min (method: 15% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 262.

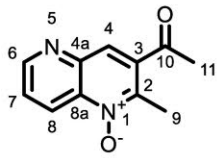
3-Acetyl-2-methyl-7-(trifluoromethyl)quinoline 1-oxide (10h)



The title compound was prepared according **GPIV** using 60.6 mg (0.2 mmol) of 3-(2-nitro-4-(trifluoromethyl)benzylidene)pentane-2,4-dione. 35.6 mg (0.132 mmol, 66%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 0% acetonitrile → 25% acetonitrile).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 9.02 (s, 1H, *H*-8), 8.08 (d, 1H, *J* = 8.5 Hz, *H*-5), 7.99 (s, 1H, *H*-4), 7.84 (dd, 1H, *J* = 8.5 Hz, 1.8 Hz, *H*-6), 2.75 (s, 3H, *H*-9), 2.71 (s, 3H, *H*-11).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 199.2, 146.3, 142.0, 136.4, 133.6 (q, *J* = 33.4 Hz), 130.9, 129.6, 124.8, 123.6 (p, *J* = 130.2 Hz), 30.2, 16.1.
^{19}F NMR (376 MHz, CD_2Cl_2) δ [ppm]: -64.22 (s).
HR-MS: *m/z* for $C_{13}H_{10}F_3NO_2^+$, $[M+H]^+$ calculated: 270.0736; found: 270.0737.
LC-MS: t_R = 7.328 min (method: 30% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 270.

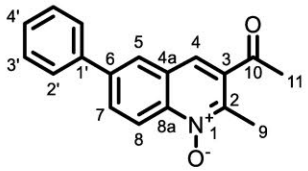
3-Acetyl-2-methyl-1,5-naphthyridine 1-oxide (10i)



The title compound was prepared according **GPIV** using 47.0 mg (0.2 mmol) of 3-((3-nitropyridin-2-yl)methylene)pentane-2,4-dione. 19.4 mg (0.0957 mmol, 48%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 0% acetonitrile → 5% acetonitrile).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 9.02 (dd, 1H, *J* = 4.2 Hz, 1.6 Hz, *H*-6), 8.98 (d, 1H, *J* = 8.8 Hz, *H*-8), 8.20 (s, 1H, *H*-4), 7.72 (dd. 1H, *J* = 8.8 Hz, 4.2 Hz, *H*-7), 2.74 (s, 3H, *H*-9), 2.72 (s, 3H, *H*-11).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 199.2, 153.0, 145.5, 143.3, 139.4, 136.9, 128.4, 126.3, 126.2, 30.0, 15.7.
HR-MS: *m/z* for $C_{11}H_{10}N_2O_2^+$, $[M+H]^+$ calculated: 203.0815; found: 203.0813.
LC-MS: t_R = 7.072 min (method: 5% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 203.

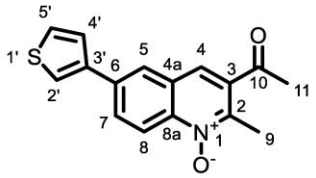
3-Acetyl-2-methyl-6-phenylquinoline 1-oxide (10j)



The title compound was prepared according **GPIV** using 62.4 mg (0.2 mmol) of 3-((4-nitro-(1,1'-biphenyl)-3-yl)methylene)pentane-2,4-dione. 45.1 mg (0.163 mmol, 82%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 35% acetonitrile).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.75 (d, 1H, *J* = 9.0 Hz, *H*-8), 8.10 (m, 2H, *H*-5, *H*-7), 8.04 (s, 1H, *H*-4), 7.74 (m, 2H, *H*-2'), 7.53 (m, 2H, *H*-3'), 7.46 (m, 1H, *H*-4'), 2.77 (s, 3H, *H*-9), 2.71 (s, 3H, *H*-11).**^{13}C NMR (101 MHz, CD_2Cl_2)** δ [ppm]: 199.3, 144.9, 141.8, 141.7, 139.5, 134.6, 131.9, 129.5, 128.8, 128.0, 127.8, 126.8, 125.2, 120.7, 29.9, 15.9.
HR-MS: *m/z* for $C_{18}H_{15}NO_2^+$, $[M+H]^+$ calculated: 278.1176; found: 278.1179.
LC-MS: t_R = 8.502 min (method: 35% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 278.

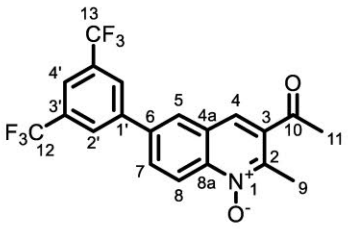
3-Acetyl-2-methyl-6-(thien-3-yl)quinoline 1-oxide (10k)



The title compound was prepared according **GPIV** using 63.5 mg (0.2 mmol) of 3-(2-nitro-5-(thien-3-yl)benzylidene)pentane-2,4-dione. 46.0 mg (0.162 mmol, 81%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 35% acetonitrile).

^{1}H NMR (600 MHz, CD_3CN) δ [ppm]: 8.61 (d, 1H, *J* = 9.0 Hz, *H*-8), 8.26 (s, 1H, *H*-4), 8.15 (m, 2H, *H*-5, *H*-7), 7.85 /m, 1H, *H*-2'), 7.60 (m, 2H, *H-4', H*-5'), 2.67 (s, 6H, *H*-9, *H*-11).
^{13}C NMR (151 MHz, CD_3CN) δ [ppm]: 200.5, 144.9, 141.8, 141.0, 136.3, 135.2, 131.4, 128.8, 128.4, 127.0, 126.4, 125.8, 123.5, 120.8, 30.0, 15.8.
HR-MS: *m/z* for $C_{16}H_{13}NO_2S^+$, $[M+H]^+$ calculated: 284.0740; found: 284.0742.
LC-MS: t_R = 9.463 min (method: 30% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 284.

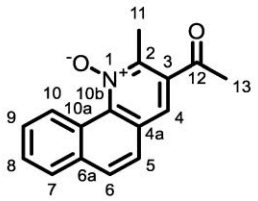
3-Acetyl-6-(3,5-bis(trifluoromethyl)phenyl)-2-methylquinoline 1-oxide (10l)



The title compound was prepared according **GPIV** using 89.1 mg (0.2 mmol) of 3-((4-nitro-3',5'-bis(trifluoromethyl)-(1,1'-biphenyl)-3-yl)methylene)pentane-2,4-dione. 61.8 mg (0.150 mmol, 75%) of the product were isolated as beige solid by reversed phase column chromatography (C 18 silica gel, gradient: 40% acetonitrile → 60% acetonitrile).

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.81 (d, 1H, *J* = 9.0 Hz, *H*-8), 8.19 (m, 3H, *H*-5, *H*-2'), 8.07 (m, 2H, *H*-4, *H*-7), 7.99 (s,1H, *H*-4'), 2.77 (s, 3H, *H*-9), 2.72 (s, 3H, *H*-11).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 199.1, 145.7, 142.3, 141.8, 138.6, 135.1, 132.7 (q, *J* = 33.4 Hz), 131.1, 128.1, 128.0, 127.8, 125.1, 124.9, 122.5, 121.5, 119.7, 29.9, 15.9.
^{19}F NMR (376 MHz, CD_3CN) δ [ppm]: -64.35 (m).
HR-MS: *m/z* for $C_{20}H_{13}F_6NO_2^+$, $[M+H]^+$ calculated: 414.0923; found: 414.0911.
LC-MS: t_R = 5.472 min (method: 65% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 414.

3-Acetyl-2-methylbenzo[h]quinoline 1-oxide (10m)



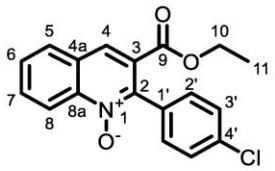
The title compound was prepared according **GPIV** using 56.7 mg (0.2 mmol) of 3-((1-nitronaphthalen-2-yl)methylene)pentane-2,4-dione. 16.8 mg (0.0669 mmol, 34%) of the product were isolated as pale-yellow oil by reversed phase column chromatography (C 18 silica gel, gradient: 10% acetonitrile → 35% acetonitrile).

^{1}H NMR (600 MHz, $CDCl_3$) δ [ppm]: 10.86 (m, 1H, *H*-10), 7.95 (m, 2H, *H*-8, *H*-4), 7.87 (m, 1H, *H*-6), 7.79 (m, 2H, *H*-7, *H*-9), 7.66 (m, 1H, *H*-5), 2.89 (1, 3H, *H*-11), 2.74 (m, 3H, *H*-13).
^{13}C NMR (151 MHz, $CDCl_3$) δ [ppm]: 199.2, 148.0, 139.5, 135.2, 133.4, 133.4, 130.7, 130.7, 129.7, 128.6, 128.6, 128.4, 128.1, 128.1, 127.9, 127.9, 125.9, 125.9, 125.3, 124.3, 30.1, 16.3.
HR-MS: *m/z* for $C_{16}H_{13}NO_2^+$, $[M+H]^+$ calculated: 252.1019; found: 252.1027.
LC-MS: t_R = 7.303 min (method: 35% acetonitrile isocratic 20 min, 5 min at 100% acetonitrile), *m/z* (ESI+) = 252.

SUPPORTING INFORMATION

Crystallographic Data

3-(Ethoxycarbonyl)-2-(4-chlorophenyl)quinoline 1-oxide (6f)



Crystallization was carried out by dissolving the compound in acetonitrile. Slow evaporating resulted in crystal formation.

Table S12: Crystal data and structure refinement for 6f.

CCDC Number	2207689
Empirical formular	$C_{18}H_{14}ClNO_3$
Moiety formular	$C_{18}H_{14}ClNO_3$
Formular weight	327.75 g mol^{-1}
Temperature	120(2) K
Wavelength, radiation type	0.71073Å, MoKα
Diffractometer	STOE IPDS 2T
Crystal system	Monoclinic
Space group name, number	P $2_1/n$, (14)
Unit cell dimensions	a = 11.1892(8) Å b = 10.6347(5) Å β = 112.470(5)° c = 13.6759(9) Å
Volume	1503.80(17) Å3
Number of reflections	16201
And range used for lattice parameters	2.98° <=Θ<= 28.23°
Z	4
Density (calculated)	1.448 g cm^{-3}
Absorption coefficient	0.229 mm^{-1}
Absorption correction	None
F(000)	680
Crystal size, colour and form	0.32·0.59·0.67 mm^3, colorless block
Theta range for data collection	2.984 – 27.843°
Index ranges	-14<=h<=14, -12<=k<=13, -17<=l<=14
Number of reflections:	
collected	7296
independent	3532 [R_{int} = 0.0157]
observed [I>2sigma(I)]	3284
Completeness to theta = 25.2°	98.8%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3532 / 0 / 261
Goodness-of-fit on F^2	1.055
Final R indices [I>2sigma(I)]	R1 = 0.0337, wR2 = 0.0889
R indices (all data)	R1 = 0.0367, wR2 = 0.0922
Largest diff. peak and hole	0.490 und -0.201 eÅ-3

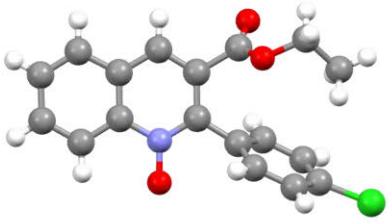


Figure S6: Molecular structure of compound 6f.

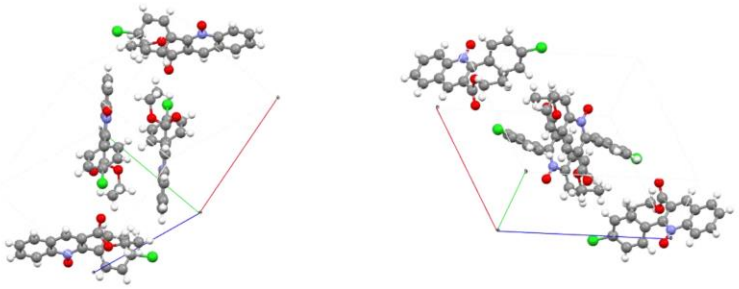
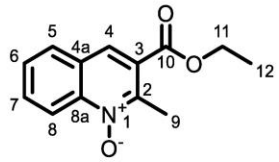


Figure S7: Packing of compound 6f.

3-(Ethoxycarbonyl)-2-methylquinoline 1-oxide



Crystallization was carried out by extraction after reversed phase column chromatography with ethyl acetate and slow evaporation.

Table S13: Crystal data and structure refinement for 6a.

CCDC Number	2207688
Empirical formular	$C_{14}H_{15}NO_5$
Moiety formular	$C_{13}H_{13}NO_3$, CH_2O_2
Formular weight	277.27 g mol^{-1}
Temperature	120(2) K
Wavelength, radiation type	0.71073 Å, MoKα
Diffractometer	STOE IPDS 2T
Crystal system	Monoclinic
Space group name, number	P 2_1/c, (14)
Unit cell dimensions	a = 15.6071(10) Å b = 10.2376(6) Å β = 92.961(5)° c = 8.3401(5) Å
Volume	1330.80(14) $Å^3$
Number of reflections	9170
And range used for lattice parameters	2.38° <=Θ<= 28.36°
Z	4
Density (calculated)	1.384 g cm^{-3}
Absorption coefficient	0.106 mm^{-1}
Absorption correction	None
F(000)	584
Crystal size, colour and form	0.16·0.25·0.76 mm^3, colorless block
Theta range for data collection	2.380 – 27.957°
Index ranges	-15<=h<=20, -11<=k<=13, -10<=l<=11
Number of reflections:	
collected	6037
independent	3118 [R_{int} = 0.0260]
observed [I>2sigma(I)]	2572
Completeness to theta = 25.2°	98.2%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3118 / 0 / 236
Goodness-of-fit on F^2	1.071
Final R indices [I>2sigma(I)]	R1 = 0.0460, wR2 = 0.1145
R indices (all data)	R1 = 0.0582, wR2 = 0.1267
Largest diff. peak and hole	0.292 und -0.206 e$Å^{-3}$

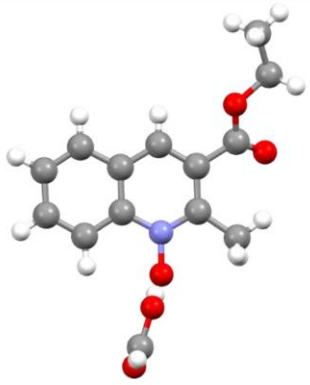


Figure S8: Molecular structure of compound 6a.

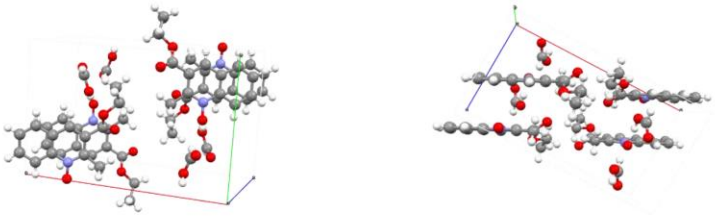
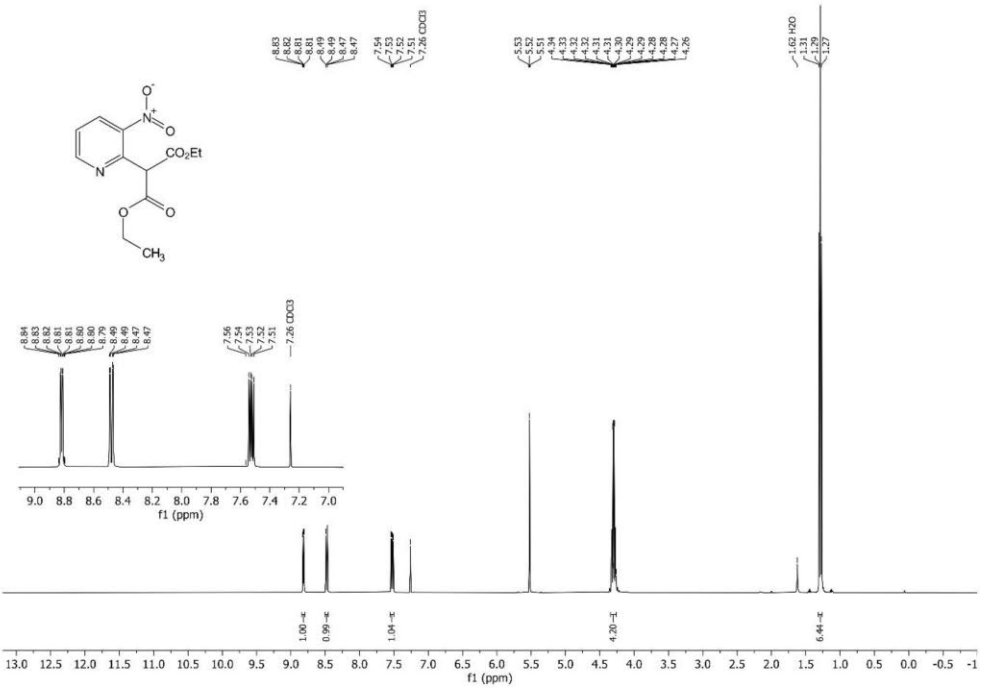
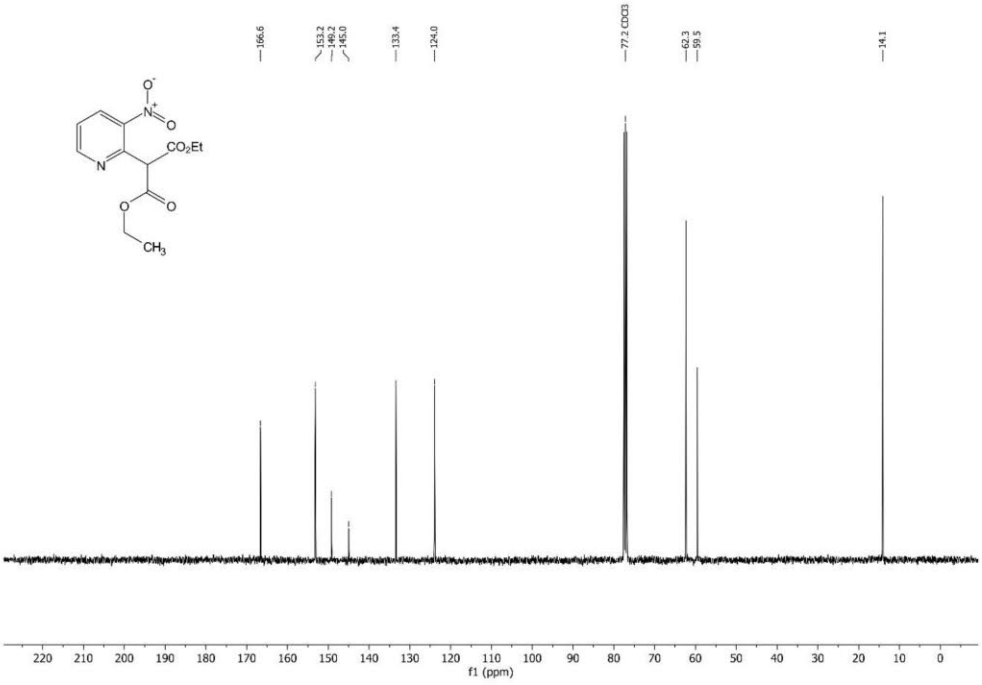


Figure S9: Packing of compound 6a.

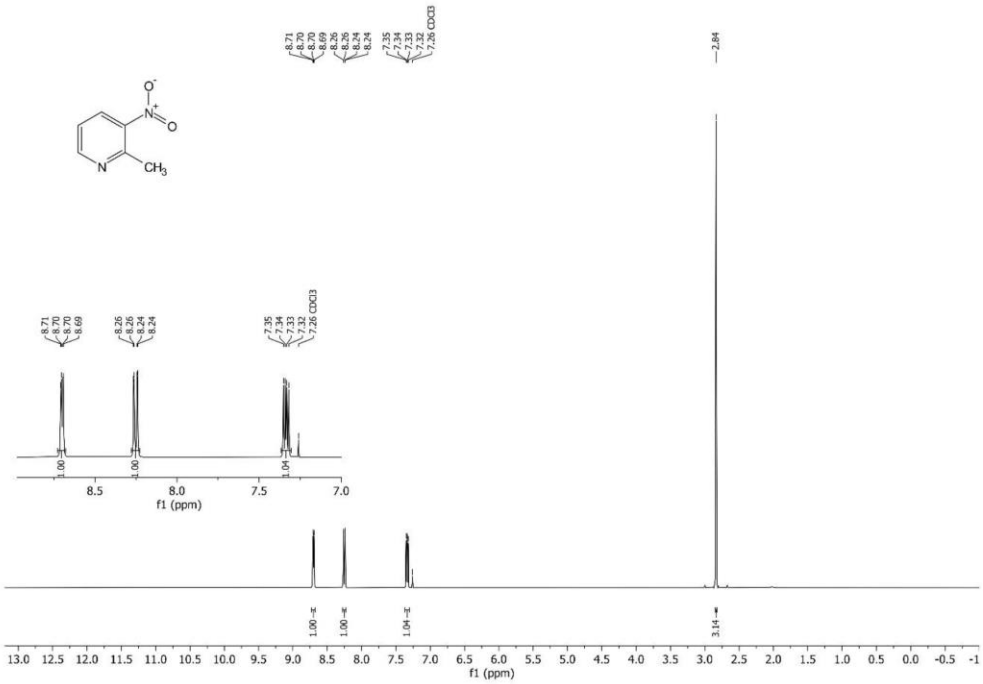
6. NMR Spectra



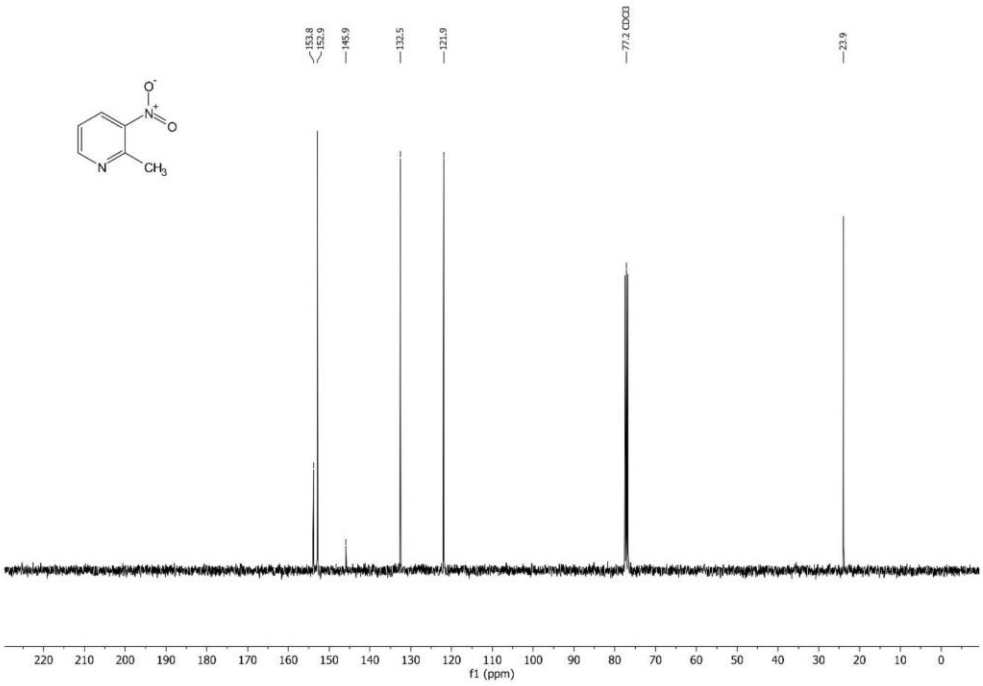
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of diethyl 2-(3-nitropyridin-2-yl)malonate (**11**).



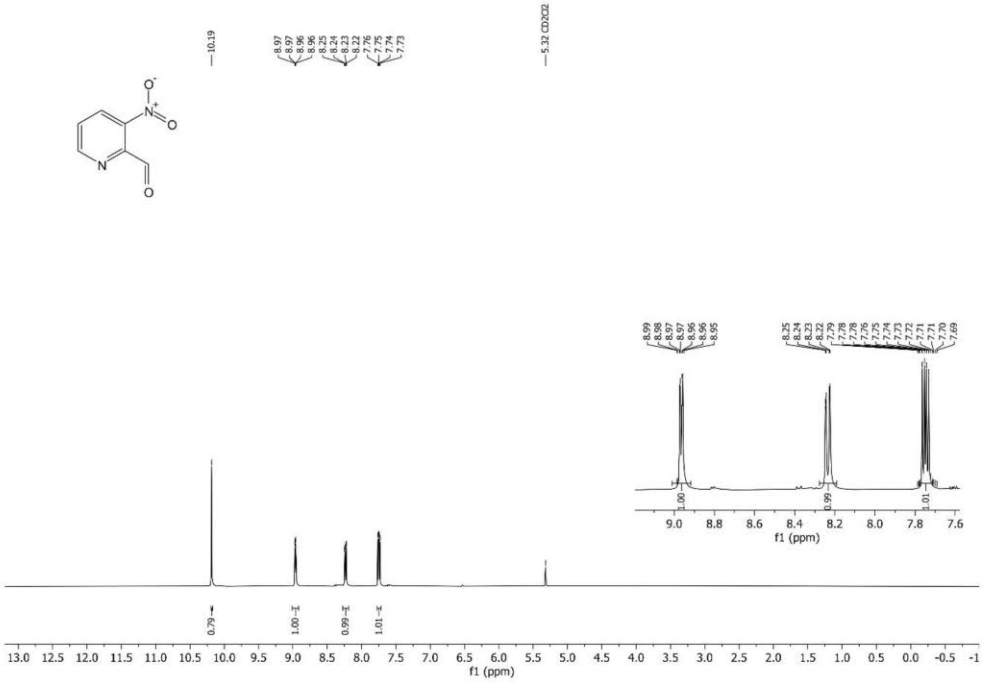
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of diethyl 2-(3-nitropyridin-2-yl)malonate (**11**).



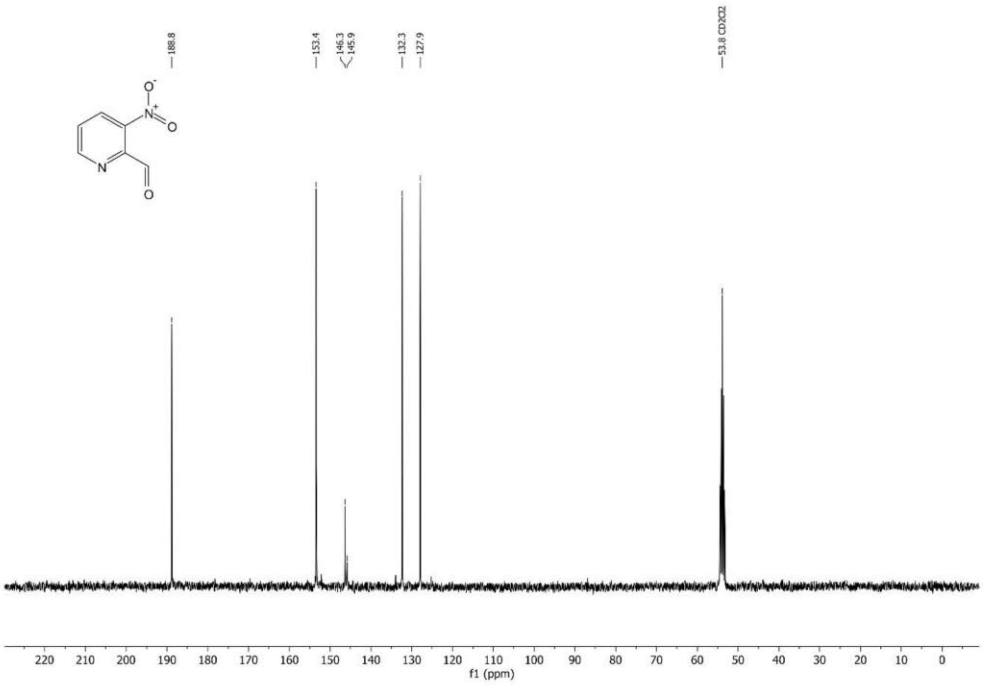
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-methyl-3-nitropyridine (**12**).



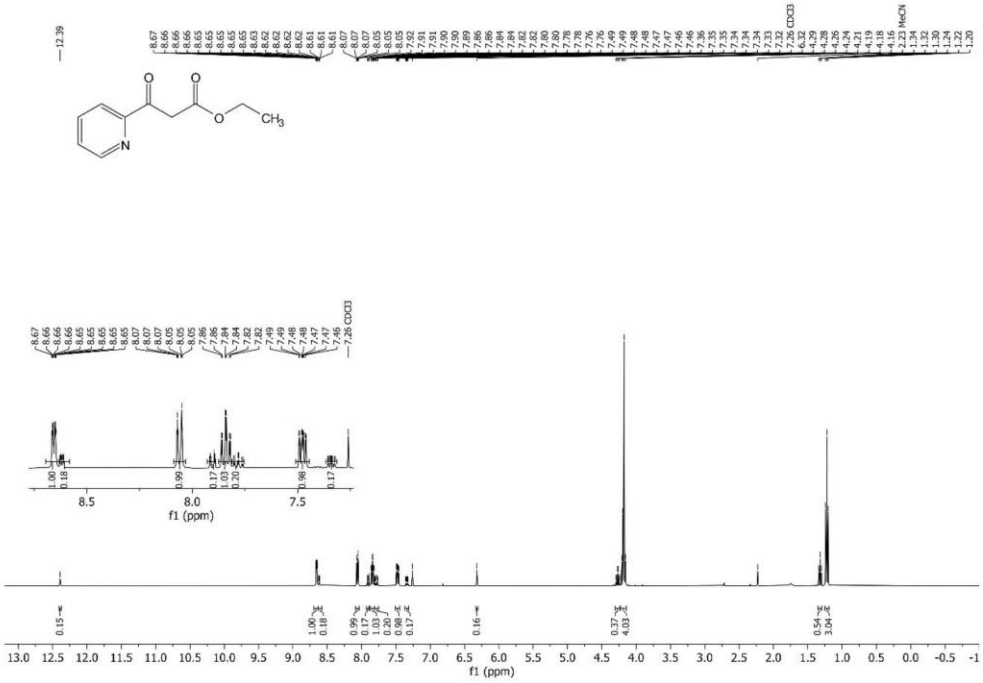
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 2-methyl-3-nitropyridine (**12**).



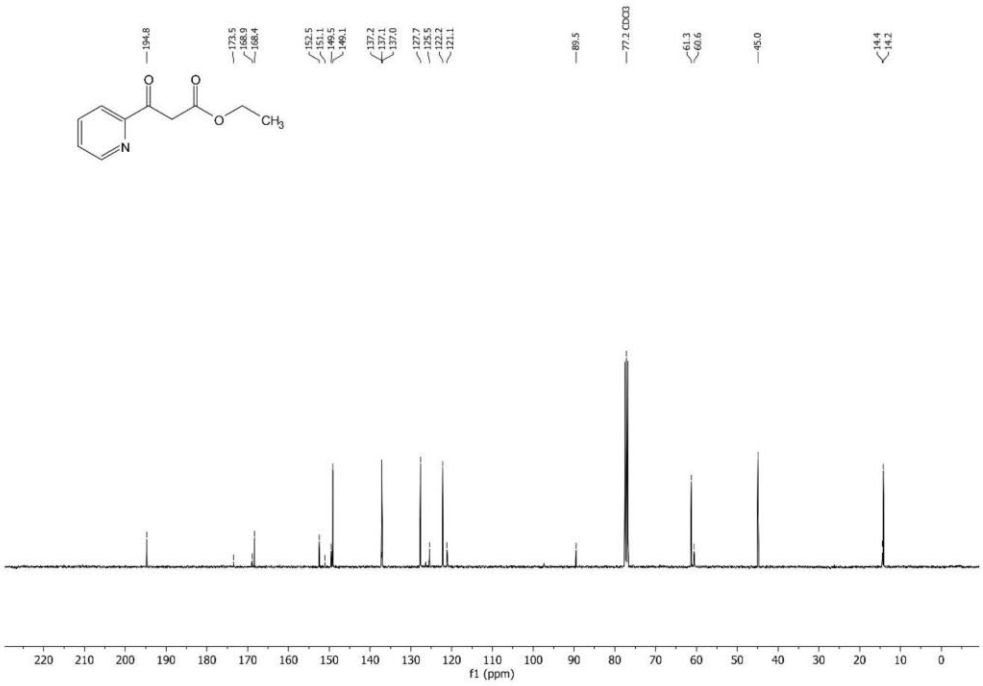
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-nitropyridine-2-carbaldehyde (**13**).



^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-nitropyridine-2-carbaldehyde (**13**).



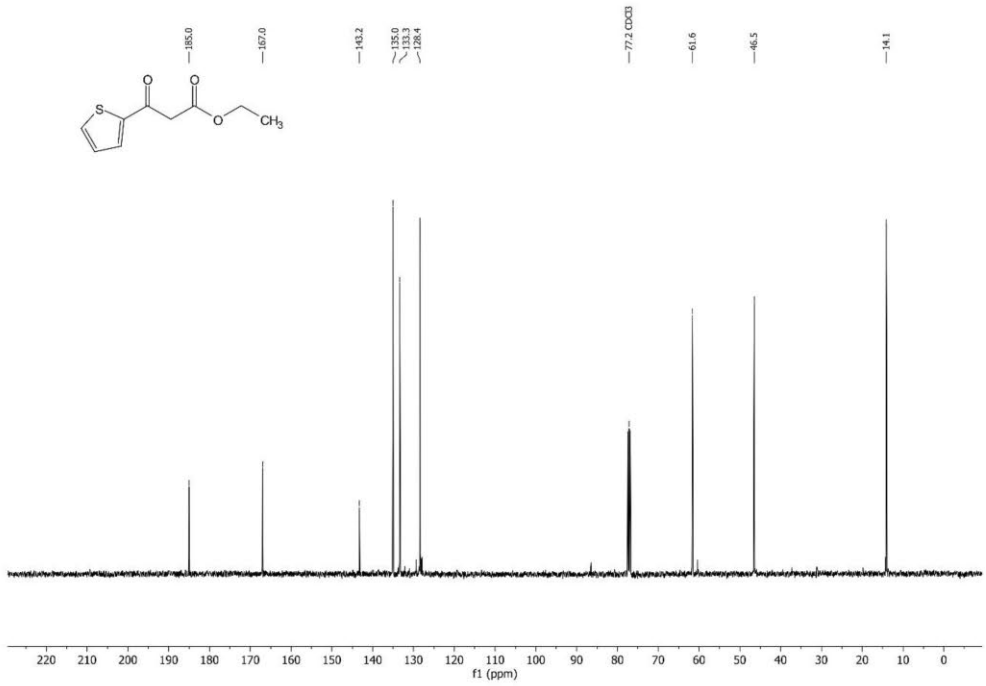
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 3-oxo-3-(pyridin-2-yl)propanoate (**14**).



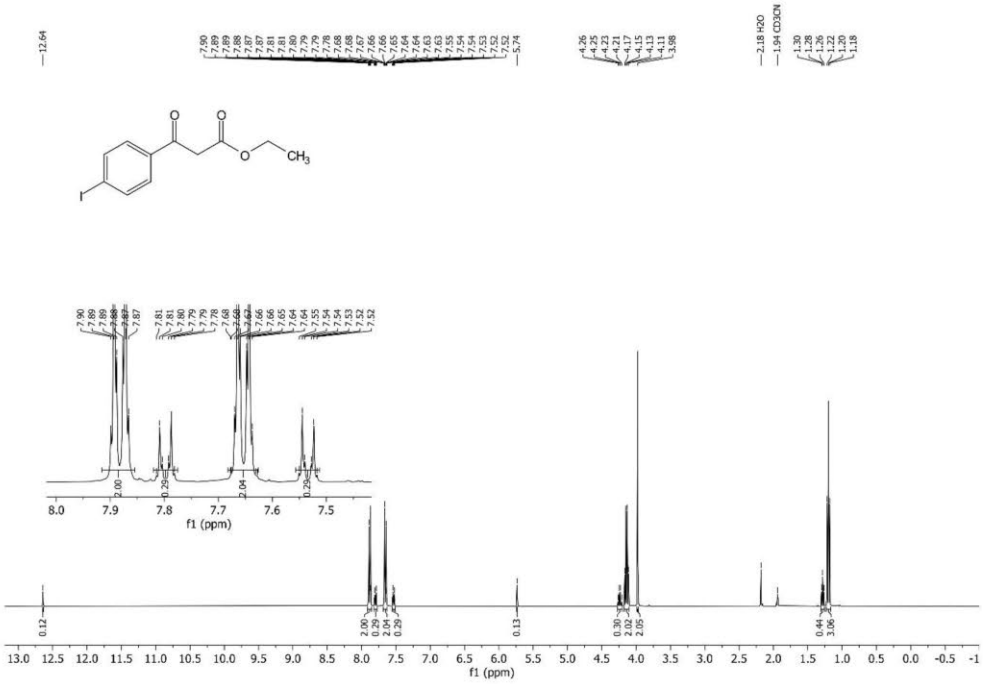
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of ethyl 3-oxo-3-(pyridin-2-yl)propanoate (**14**).



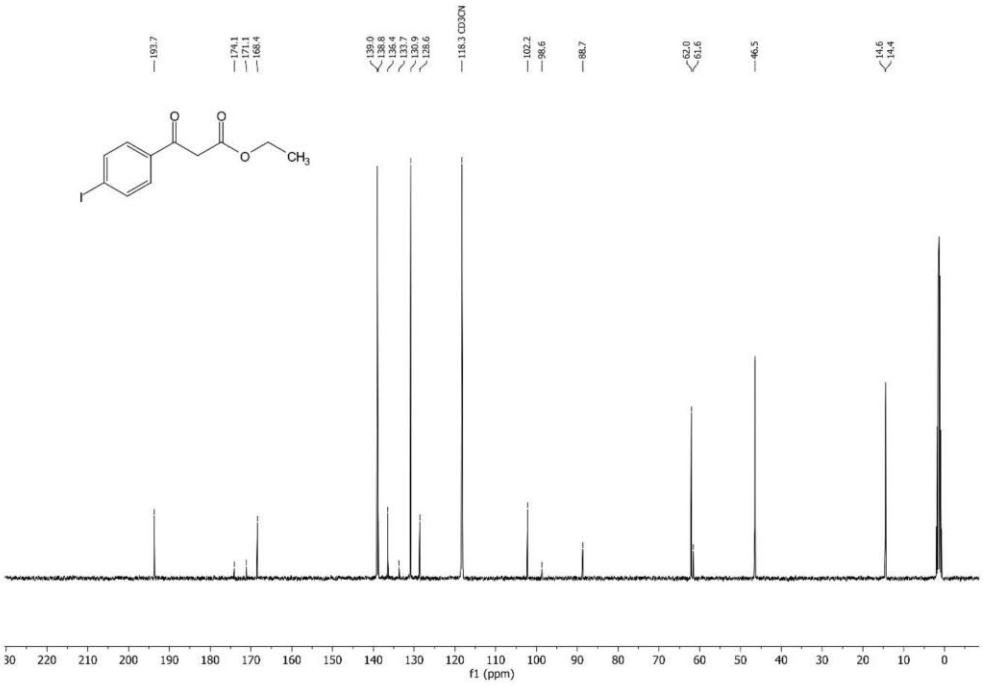
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 3-oxo-3-(thien-2-yl)propanoate (**15**).



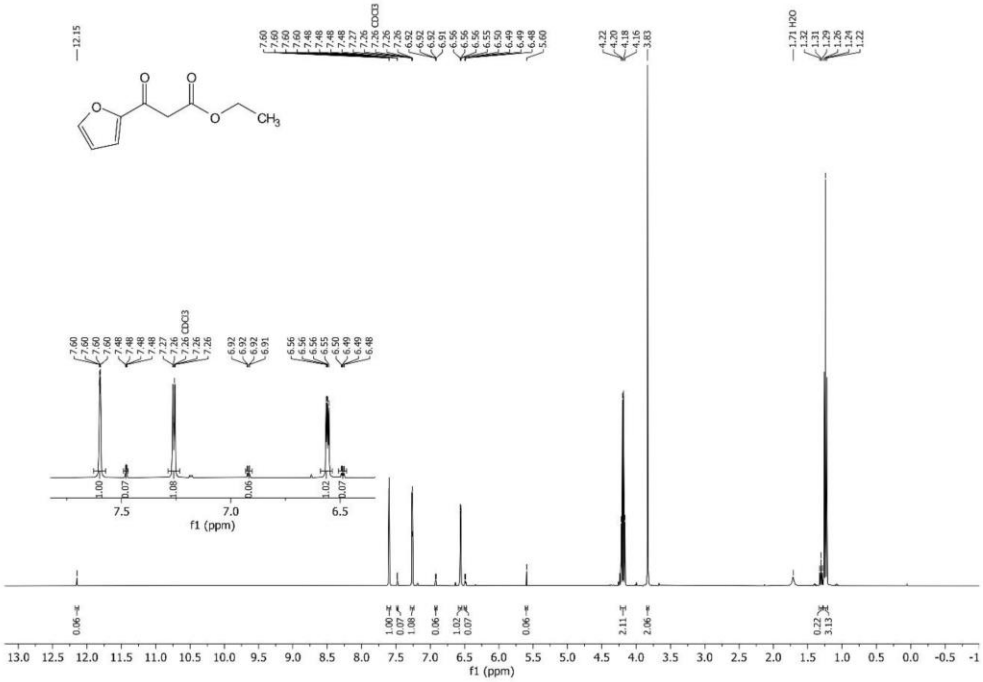
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of ethyl 3-oxo-3-(thien-2-yl)propanoate (**15**).



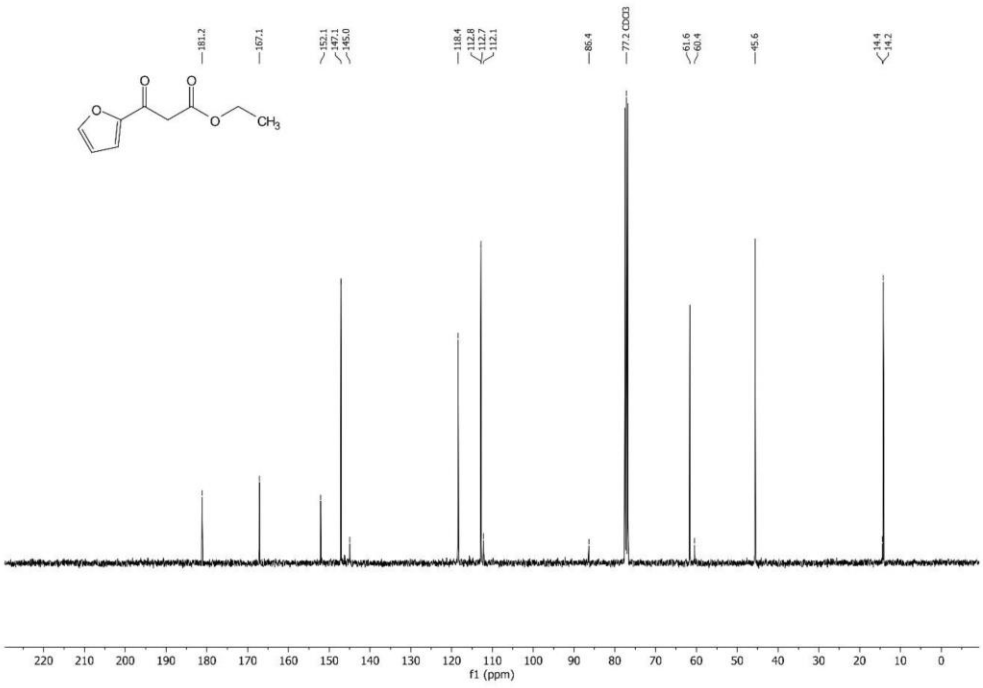
^{1}H NMR spectrum (400 MHz, CD_3CN) of ethyl 3-(4-iodophenyl)-3-oxopropanoate (**16**).



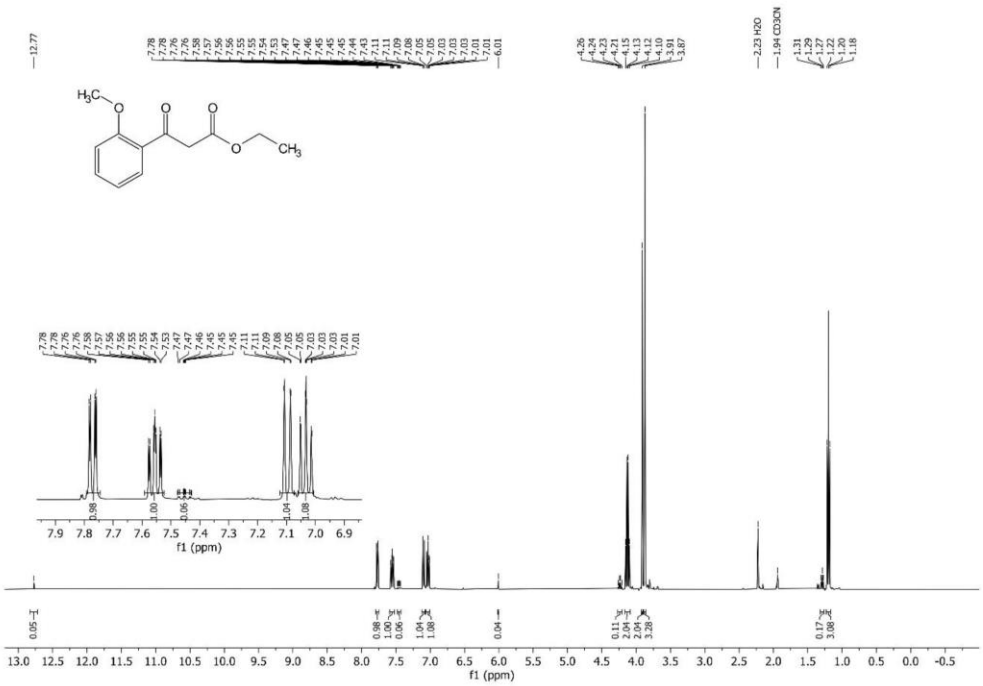
^{13}C NMR spectrum (101 MHz, CD_3CN) of ethyl 3-(4-iodophenyl)-3-oxopropanoate (**16**).



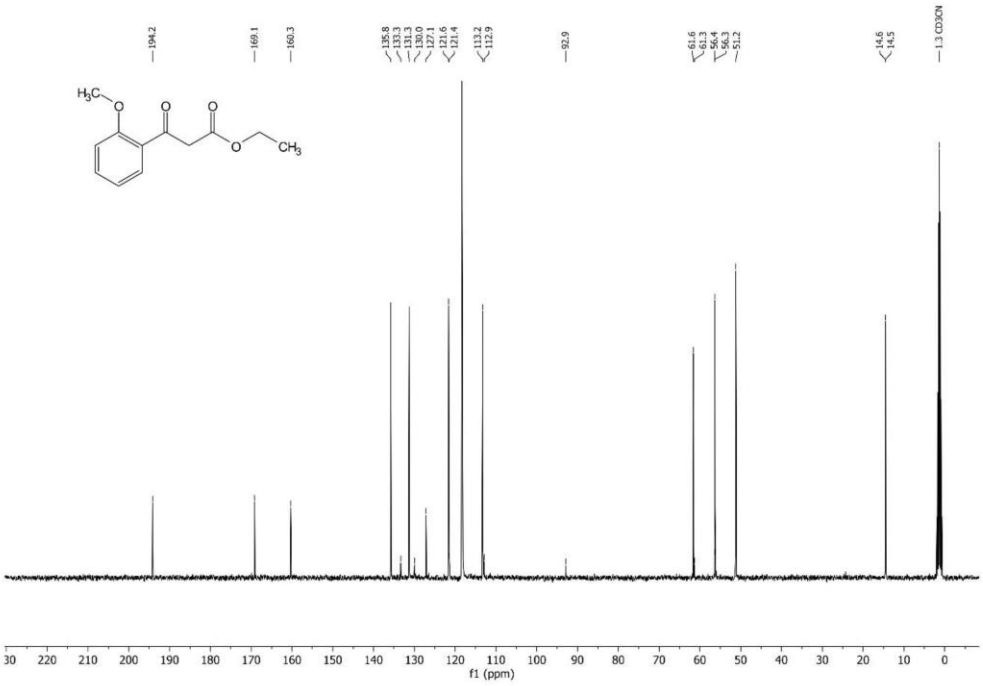
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 3-(furan-2-yl)-3-oxopropanoate (**17**).



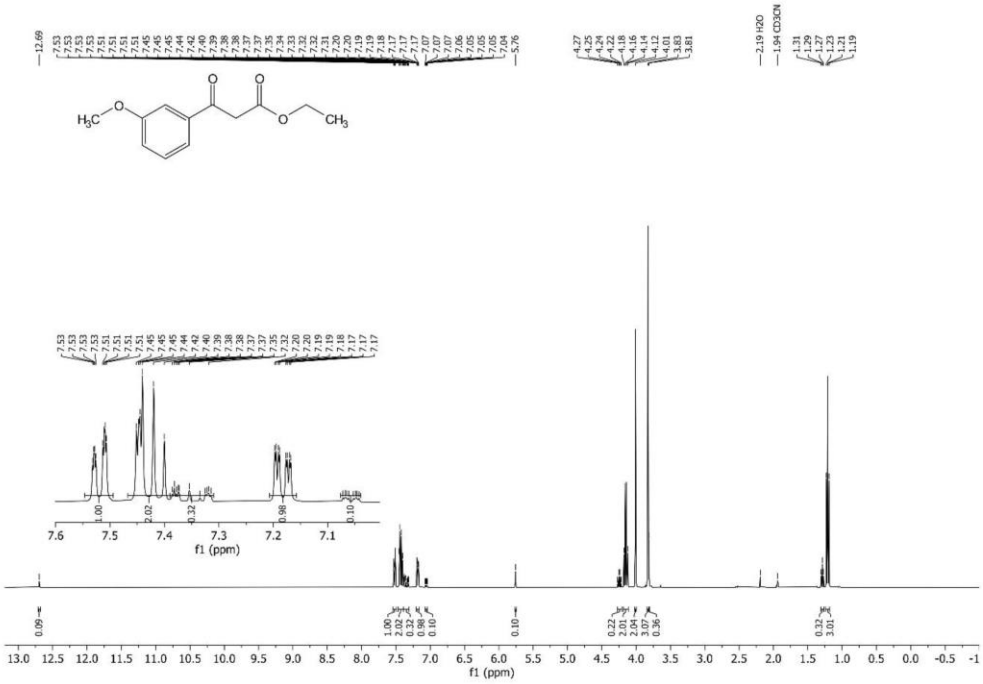
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of ethyl 3-(furan-2-yl)-3-oxopropanoate (**17**).



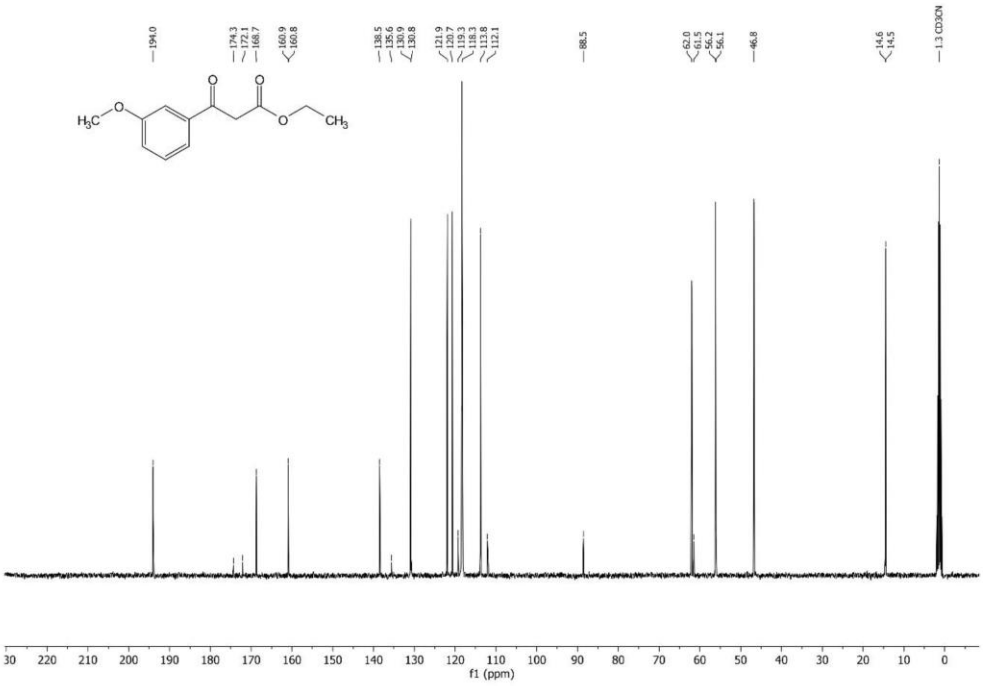
^{1}H NMR spectrum (400 MHz, CD_3CN) of ethyl 3-(2-methoxyphenyl)-3-oxopropanoate (**18**).



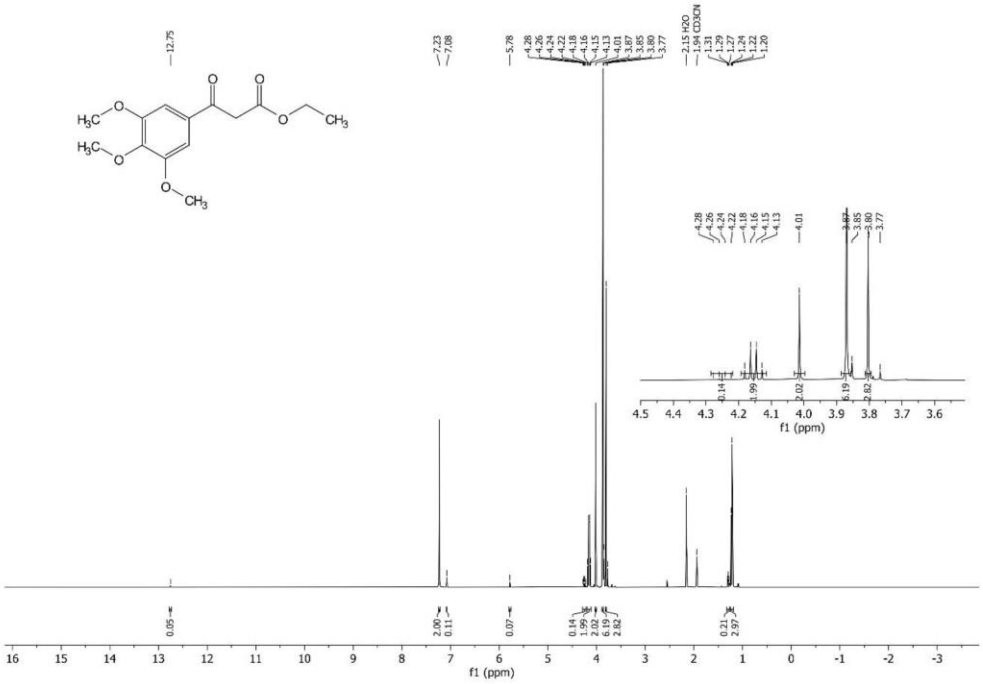
^{13}C NMR spectrum (101 MHz, CD_3CN) of ethyl 3-(2-methoxyphenyl)-3-oxopropanoate (**18**).



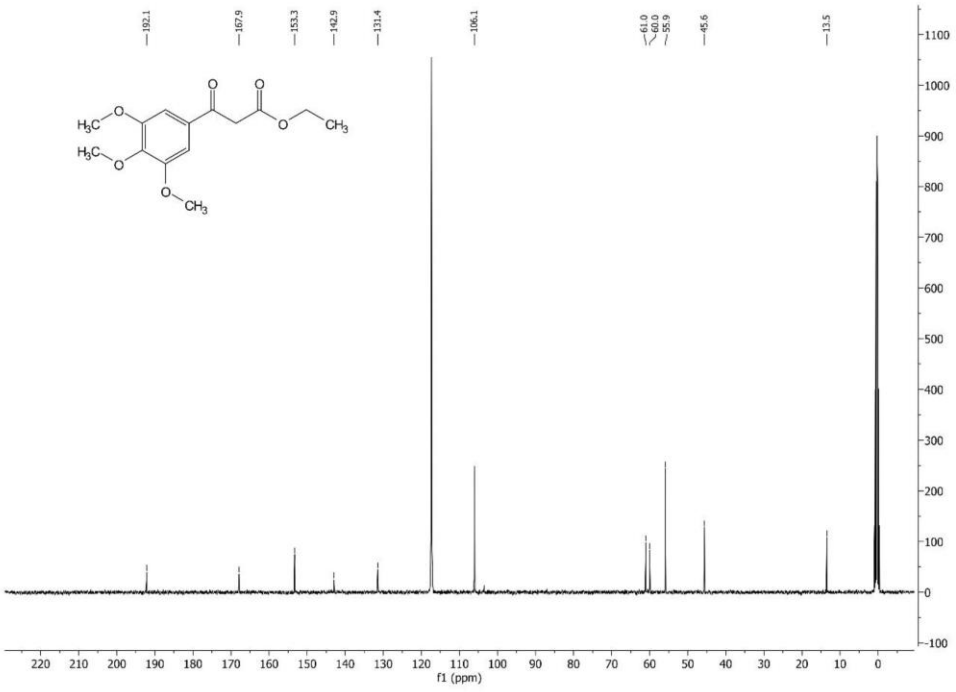
^{1}H NMR spectrum (400 MHz, CD_3CN) of ethyl 3-(3-methoxyphenyl)-3-oxopropanoate (**19**).



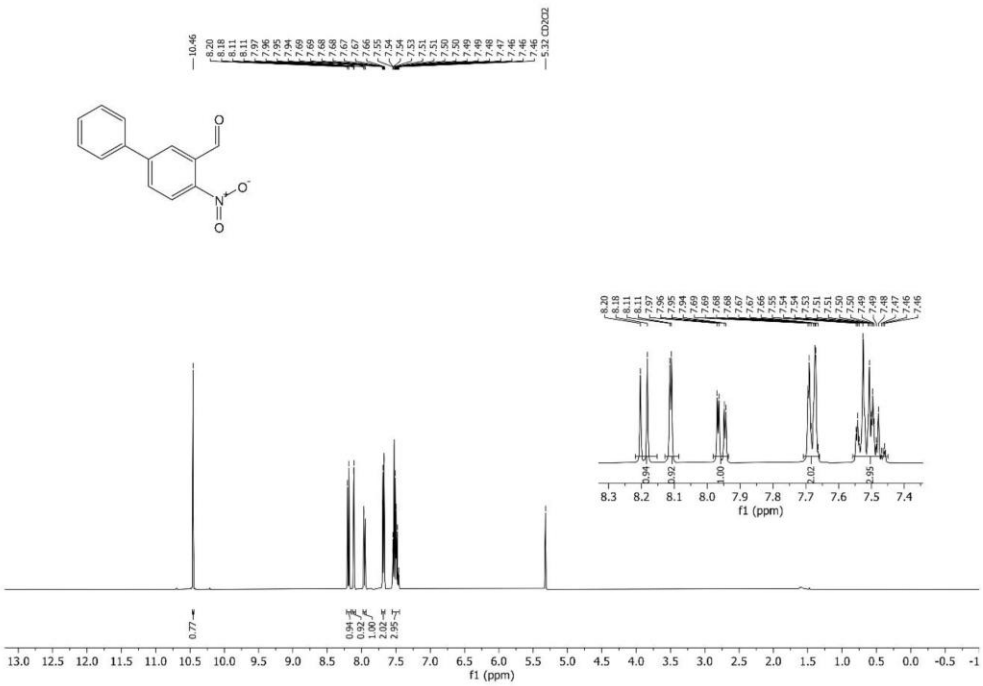
^{13}C NMR spectrum (101 MHz, CD_3CN) of ethyl 3-(3-methoxyphenyl)-3-oxopropanoate (**19**).



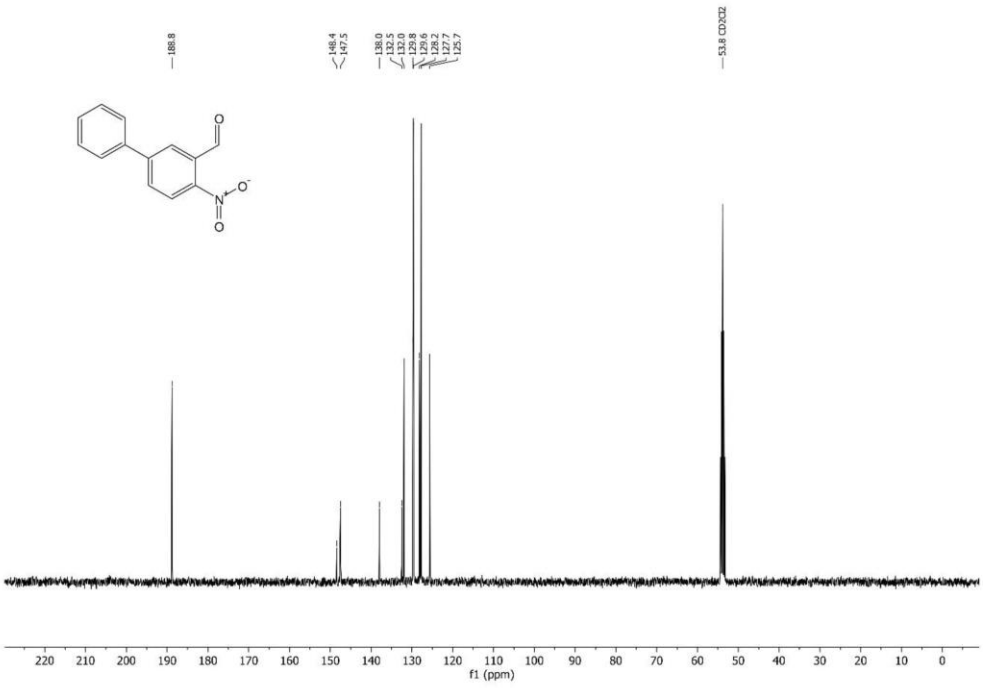
^{1}H NMR spectrum (400 MHz, CD_3CN) of ethyl 3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (**20**).



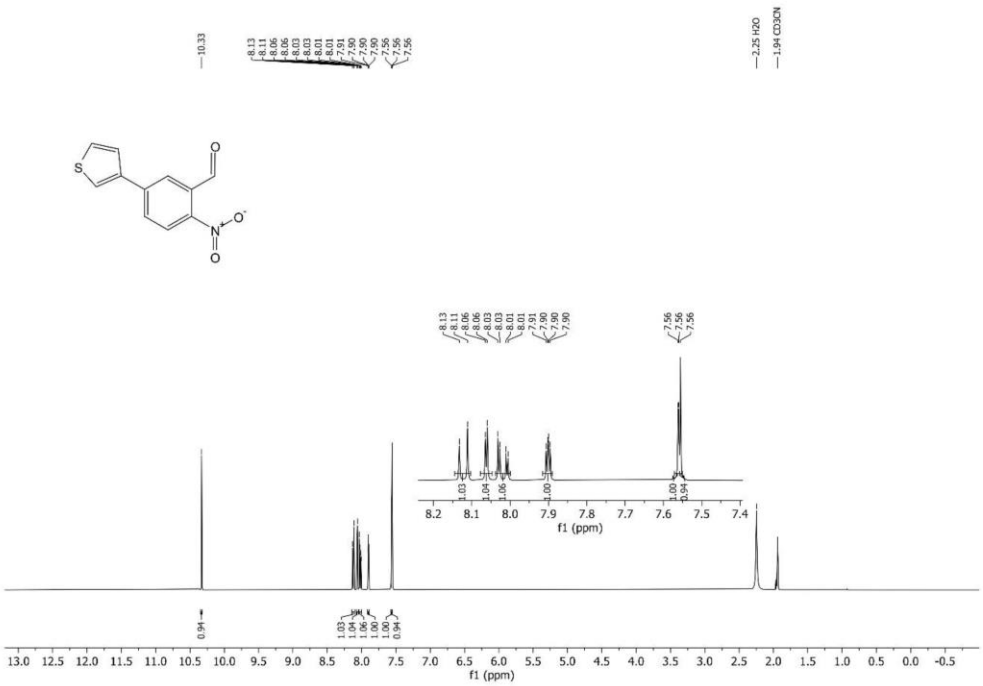
^{13}C NMR spectrum (101 MHz, CD_3CN) of ethyl 3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (**20**).



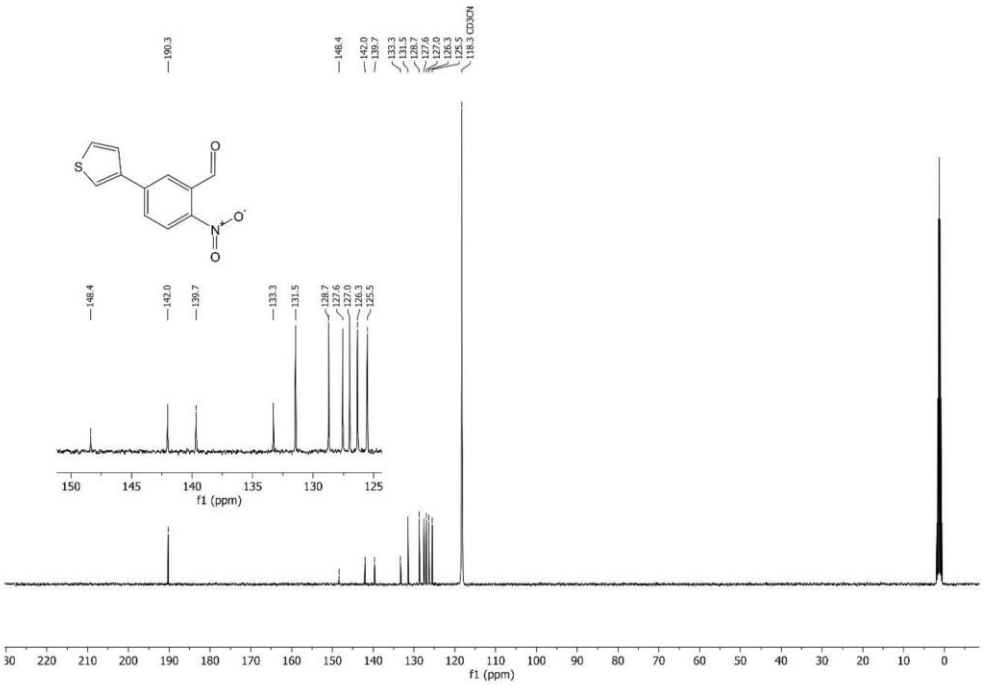
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 4-nitro-(1,1'-biphenyl)-3-carbaldehyde (**21**).



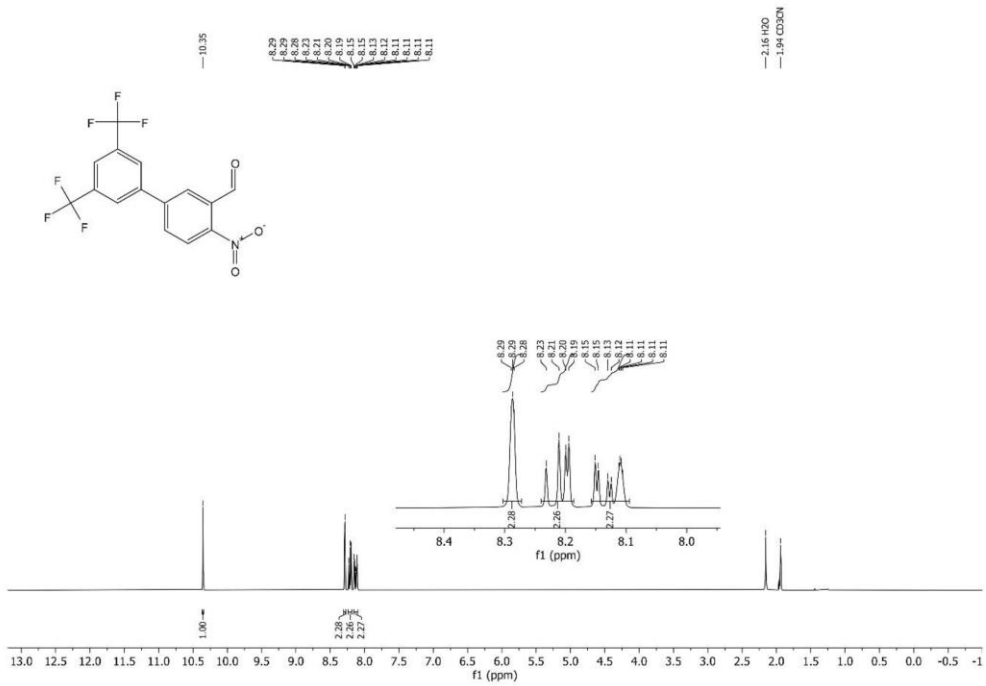
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 4-nitro-(1,1'-biphenyl)-3-carbaldehyde (**21**).



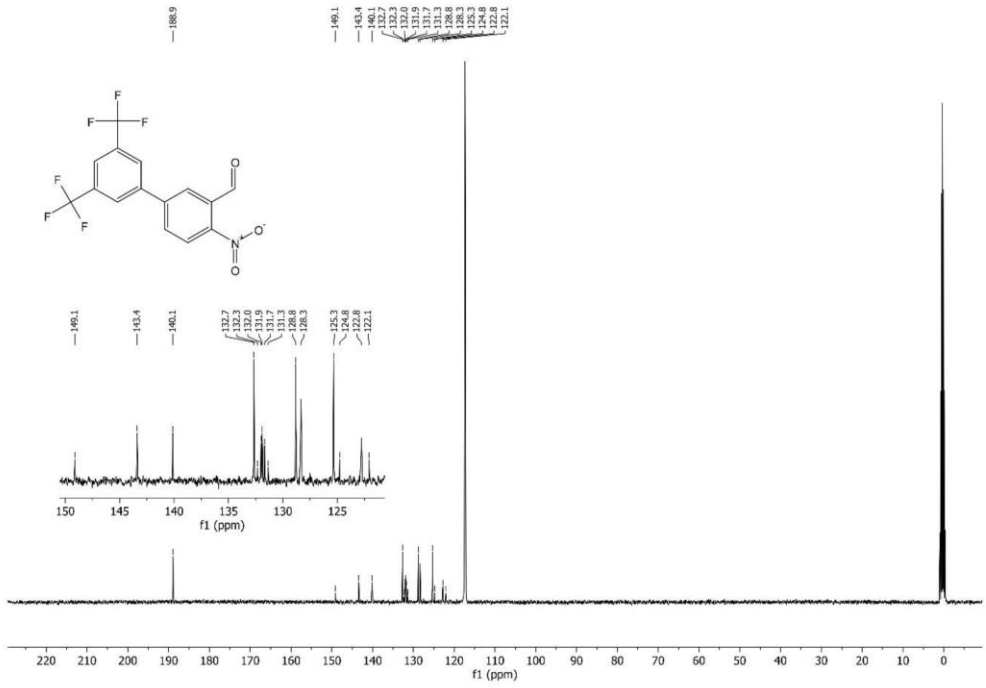
^{1}H NMR spectrum (400 MHz, CD_3CN) of 2-nitro-5-(thien-3-yl)benzaldehyde (**22**).



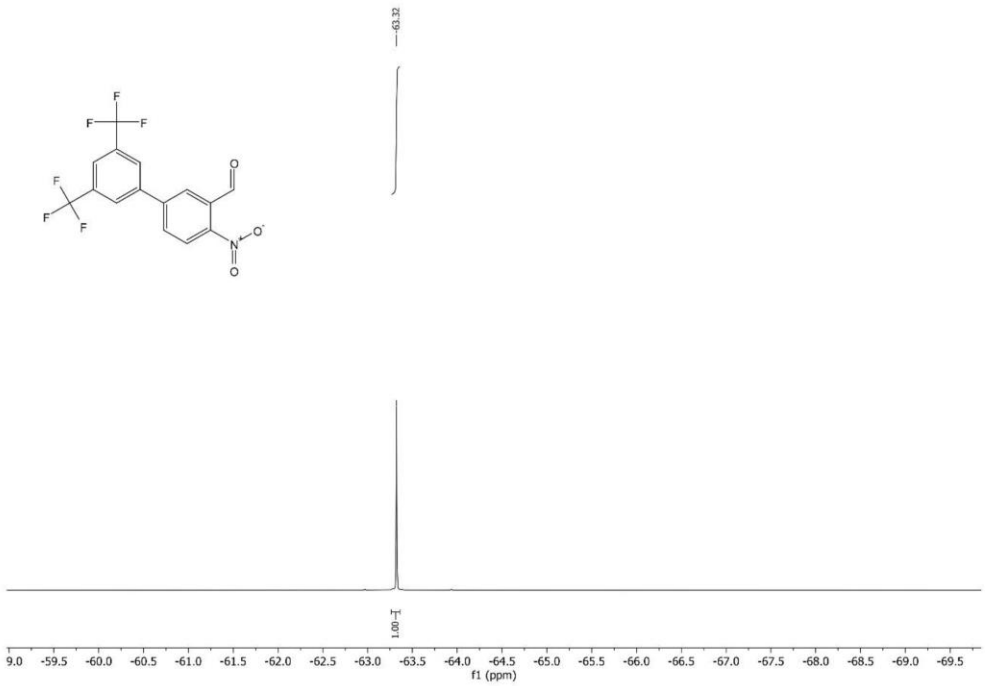
^{13}C NMR spectrum (101 MHz, CD_3CN) of 2-nitro-5-(thien-3-yl)benzaldehyde (**22**).



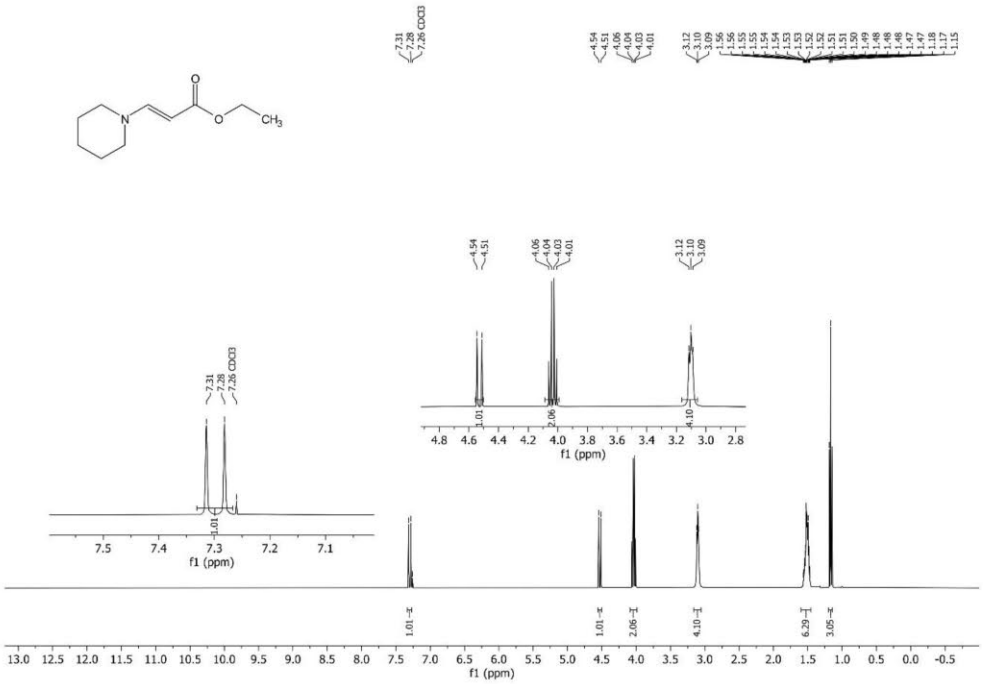
^{1}H NMR spectrum (400 MHz, CD_3CN) of 4-nitro-3',5'-bis(trifluoromethyl)-(1,1'-biphenyl)-3-carbaldehyde (**23**).



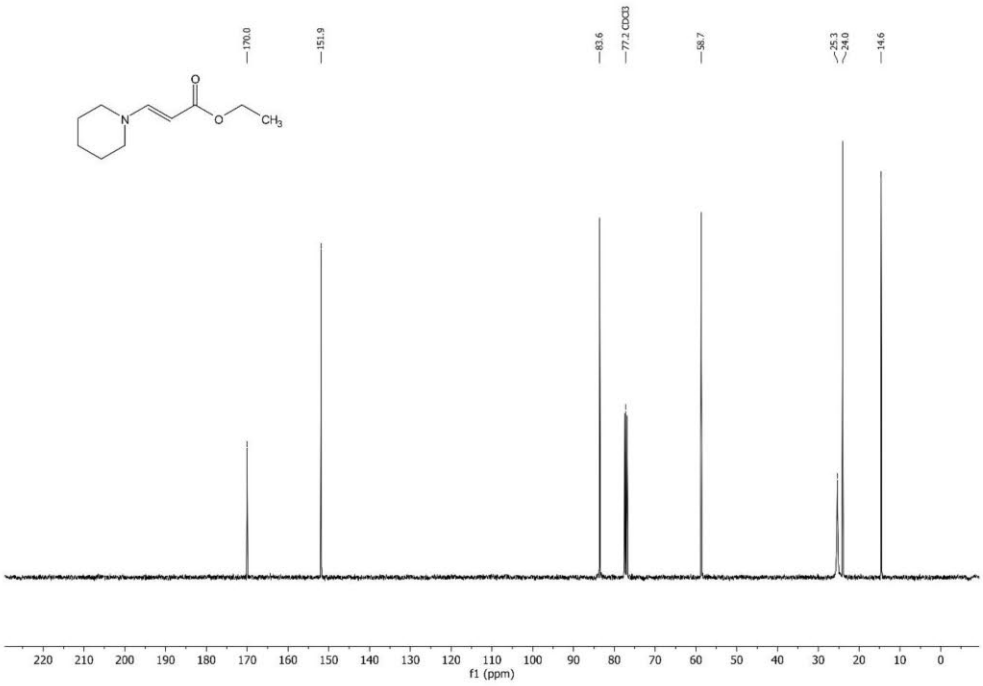
^{13}C NMR spectrum (101 MHz, CD_3CN) of 4-nitro-3',5'-bis(trifluoromethyl)-(1,1'-biphenyl)-3-carbaldehyde (**23**).



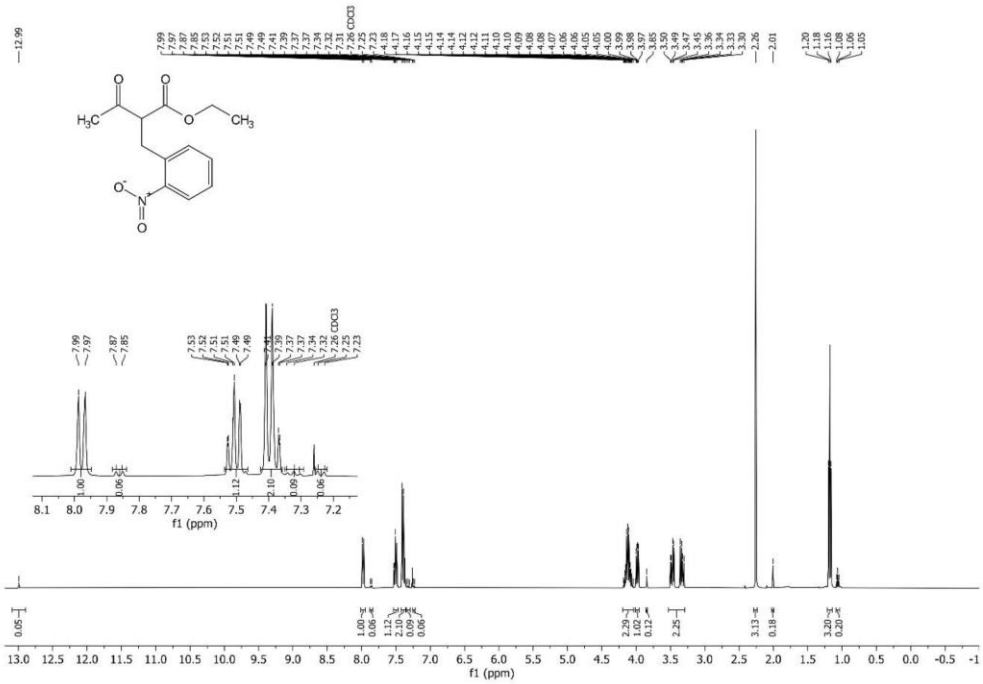
^{19}F NMR spectrum (282 MHz, CD_3CN) of 4-nitro-3',5'-bis(trifluoromethyl)-(1,1'-biphenyl)-3-carbaldehyde (**23**).



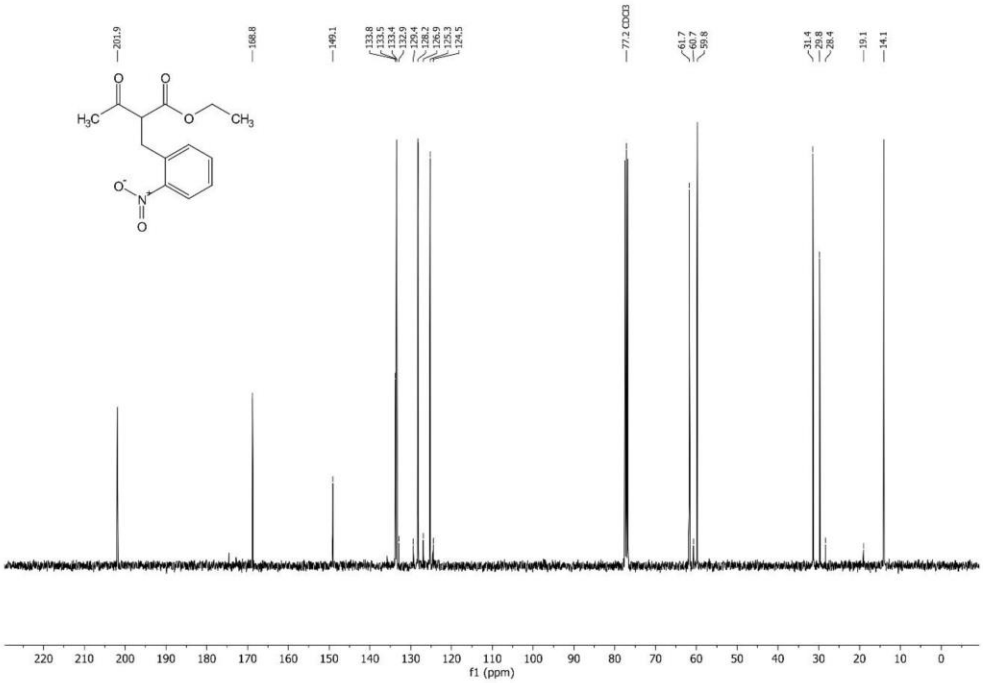
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl (*E*)-3-(piperidin-1-yl)acrylate (**24**).



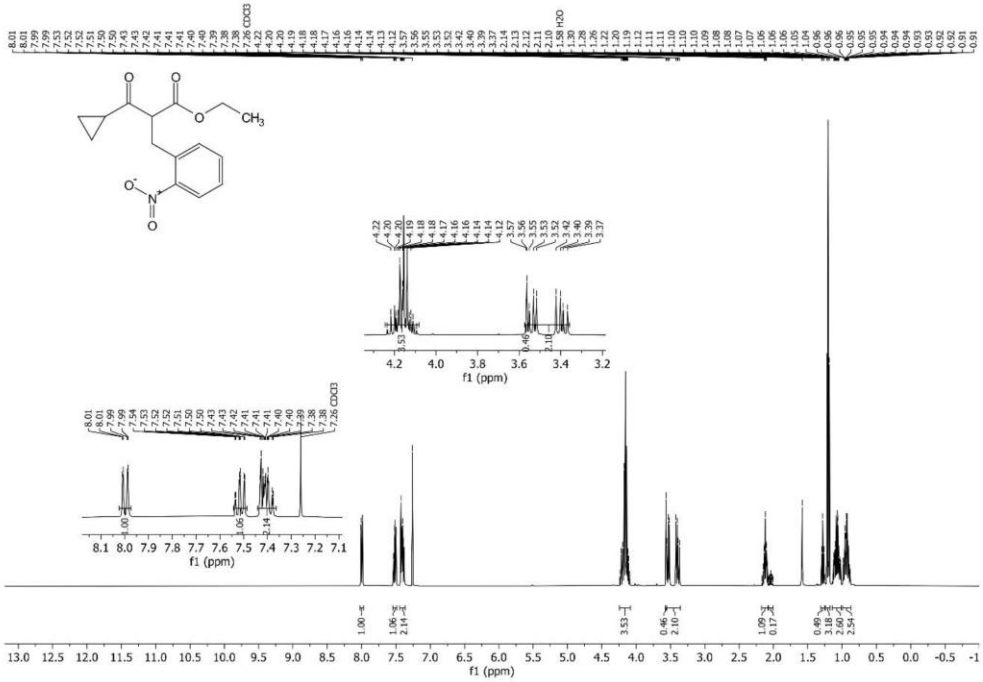
^{13}C NMR spectrum (101 MHz, CD_3CN) of $CDCl_3$) of ethyl (*E*)-3-(piperidin-1-yl)acrylate (**24**).



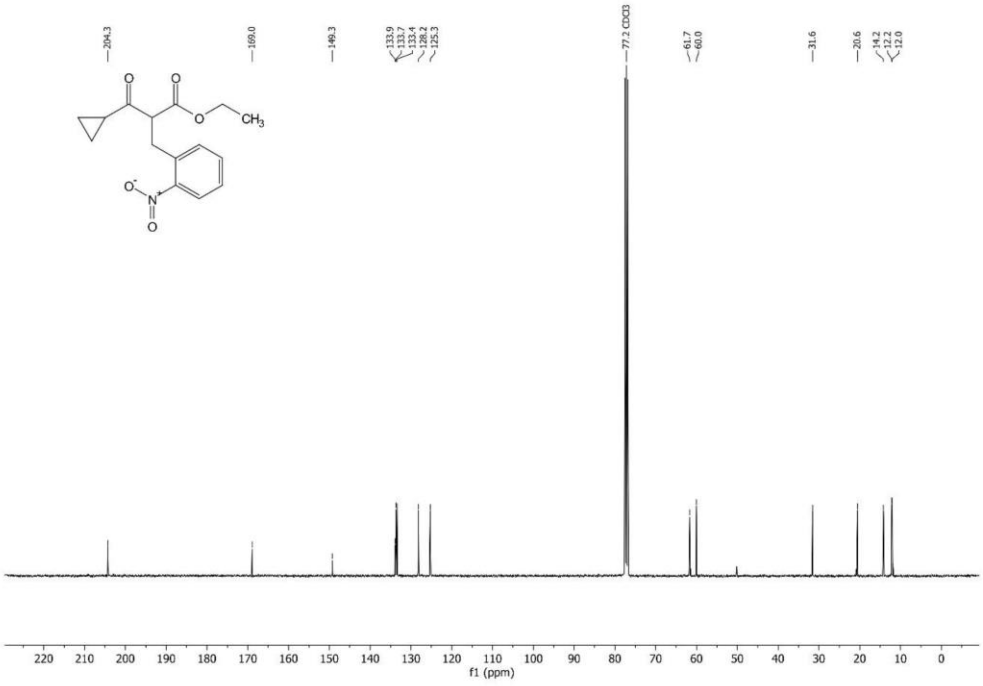
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 2-(2-nitrobenzyl)-3-oxobutanoate (**4a**).



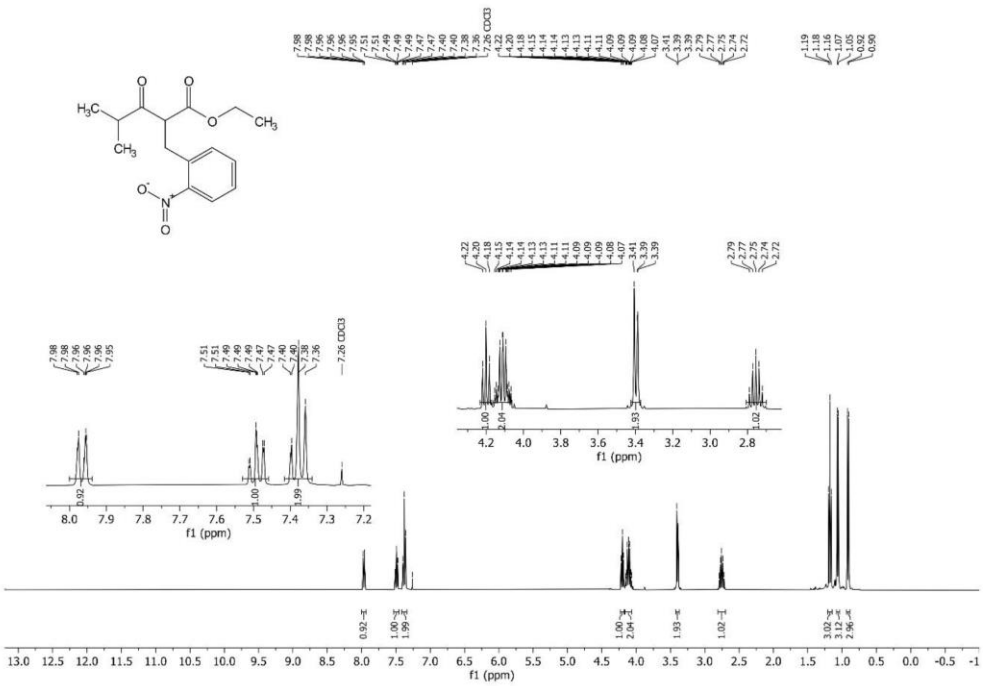
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of ethyl 2-(2-nitrobenzyl)-3-oxobutanoate (**4a**).



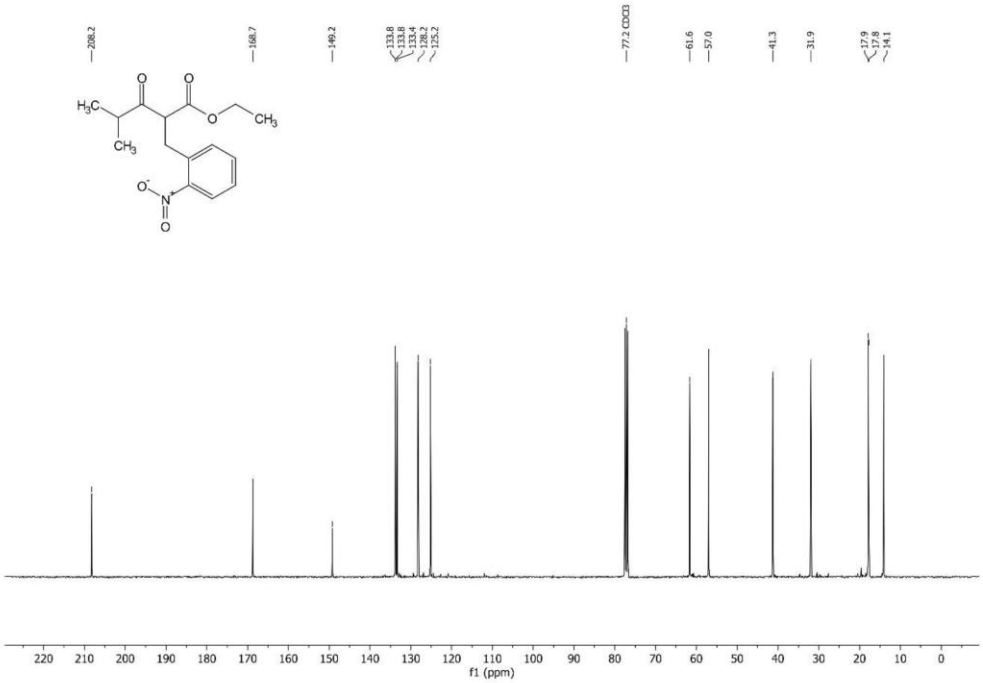
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 3-cyclopropyl-2-(2-nitrobenzyl)-3-oxopropanoate (**4b**).



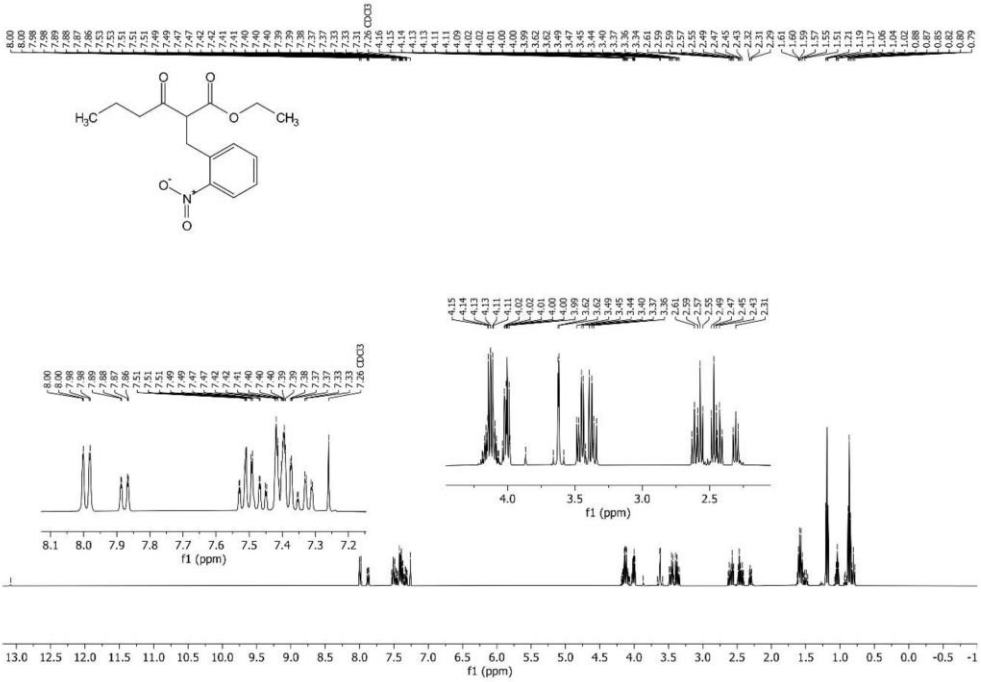
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of ethyl 3-cyclopropyl-2-(2-nitrobenzyl)-3-oxopropanoate (**4b**).



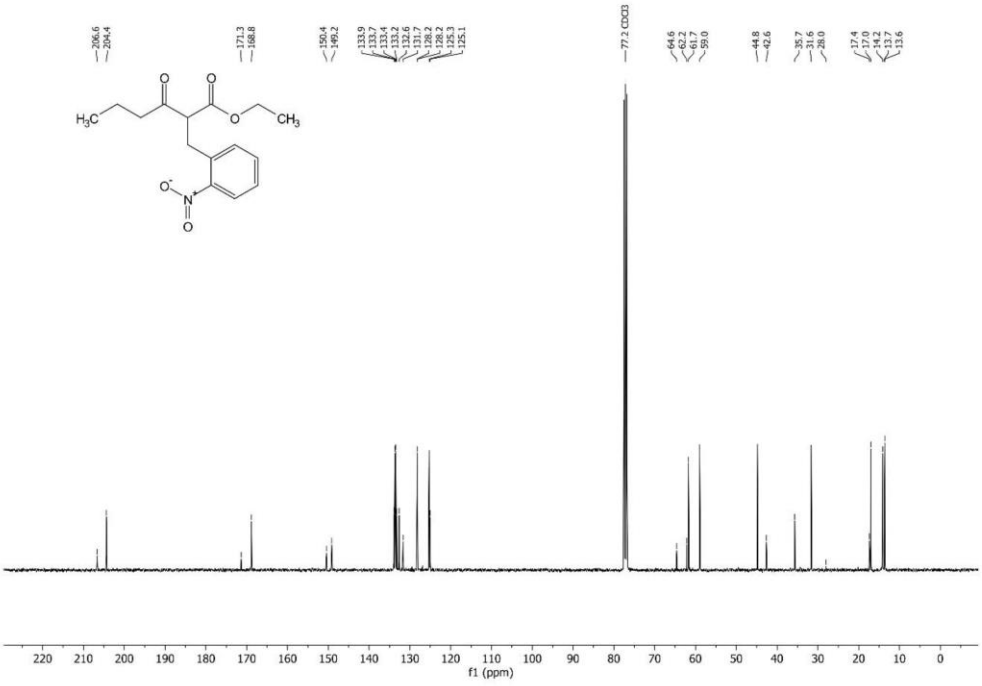
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 4-methyl-2-(2-nitrobenzyl)-3-oxopentanoate (**4c**).



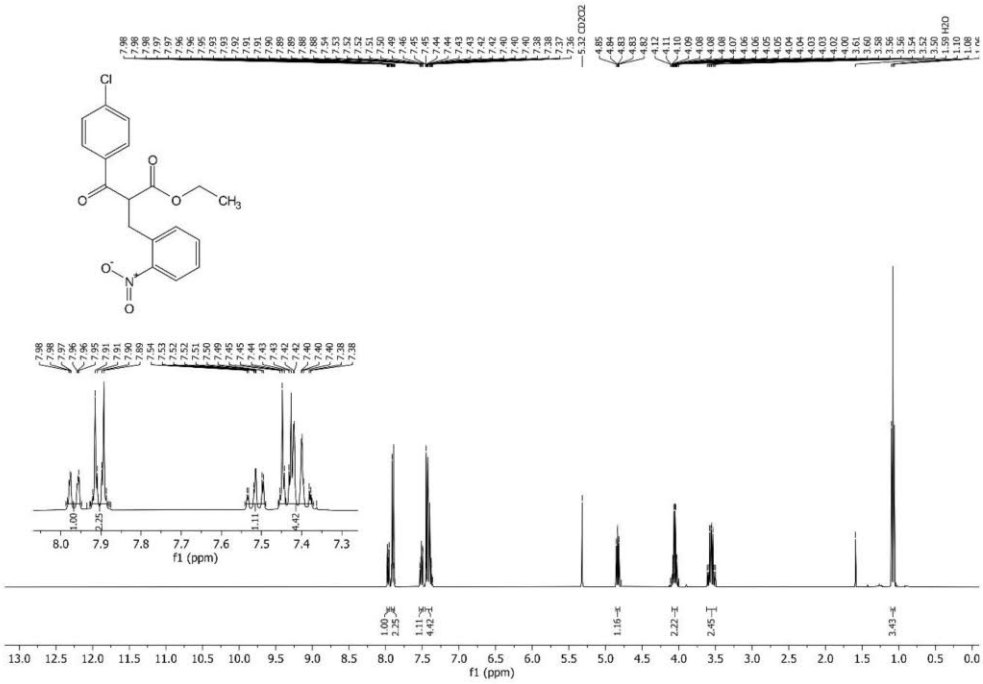
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of ethyl 4-methyl-2-(2-nitrobenzyl)-3-oxopentanoate (**4c**).



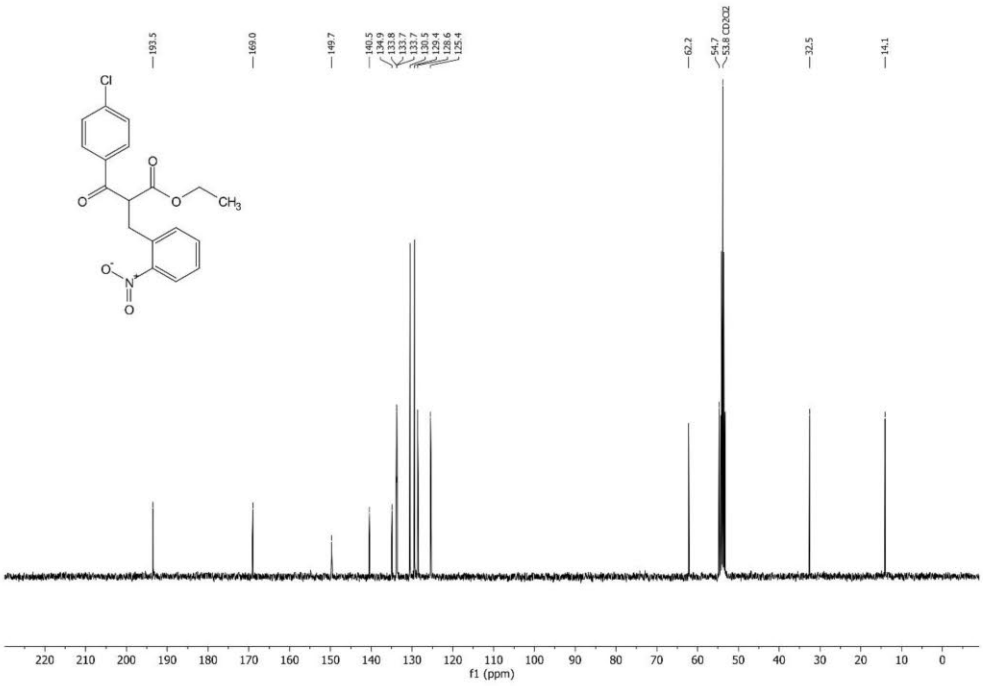
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 2-(2-nitrobenzyl)-3-oxohexanoate (**4d**).



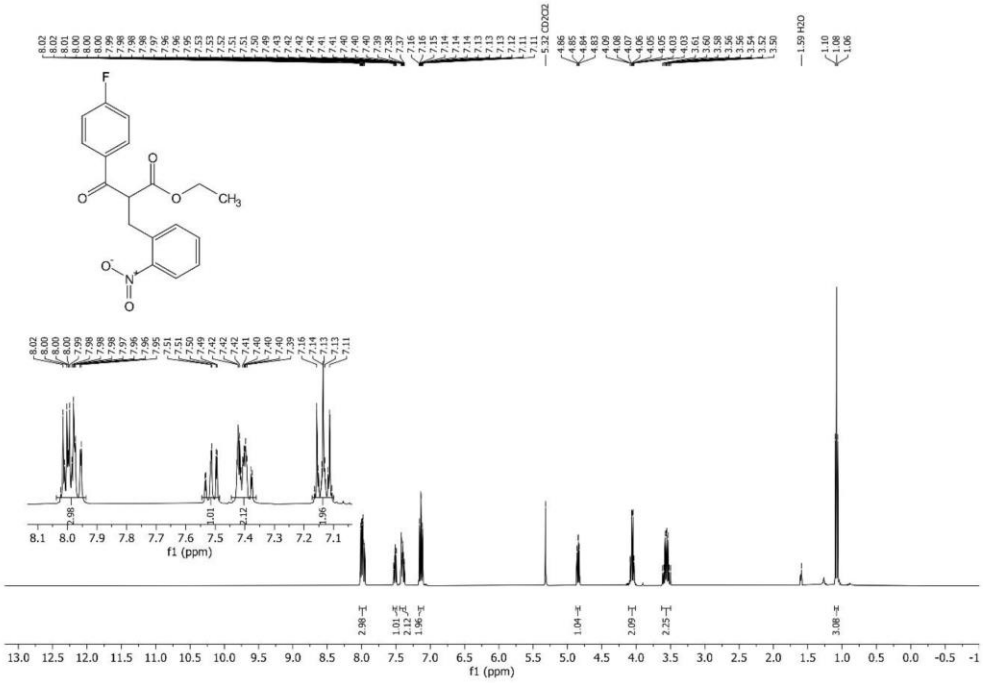
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of ethyl 2-(2-nitrobenzyl)-3-oxohexanoate (**4d**).



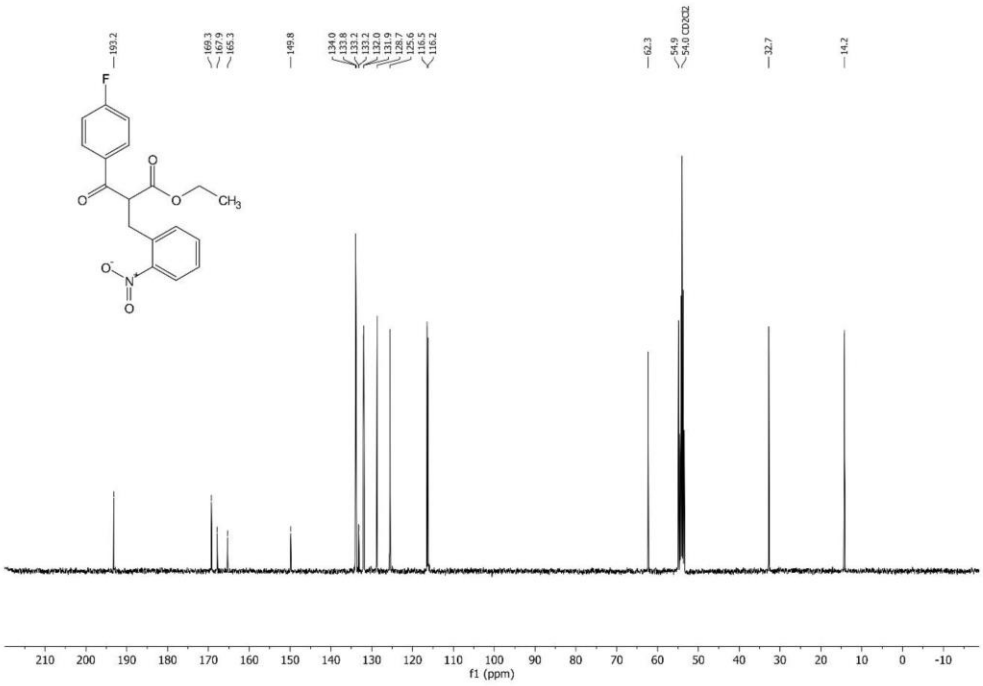
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of ethyl 3-(4-chlorophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4e**).



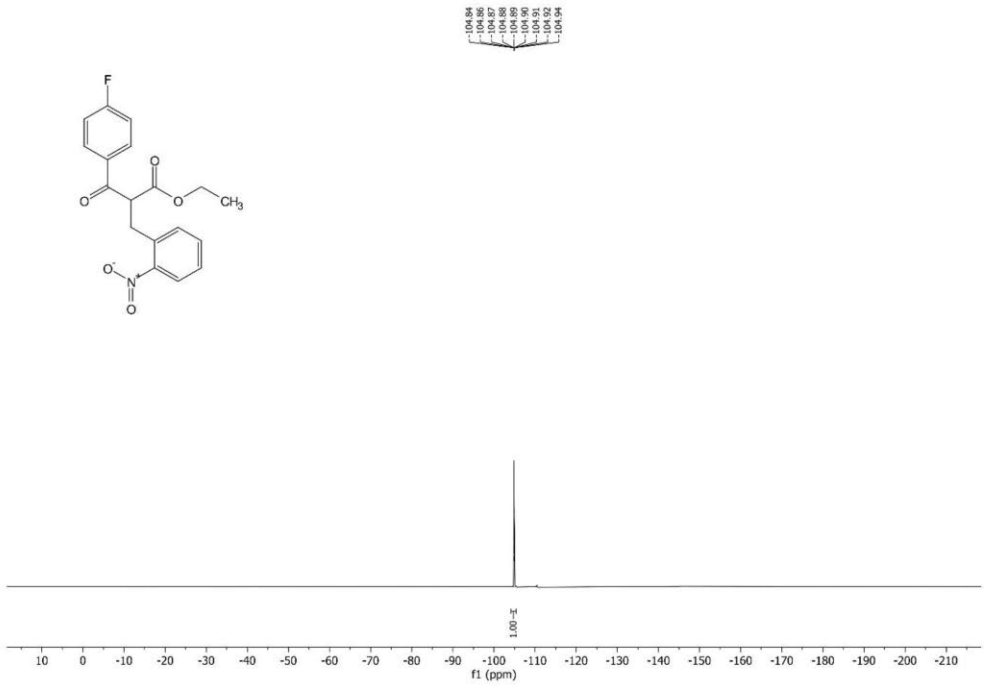
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of ethyl 3-(4-chlorophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4e**).



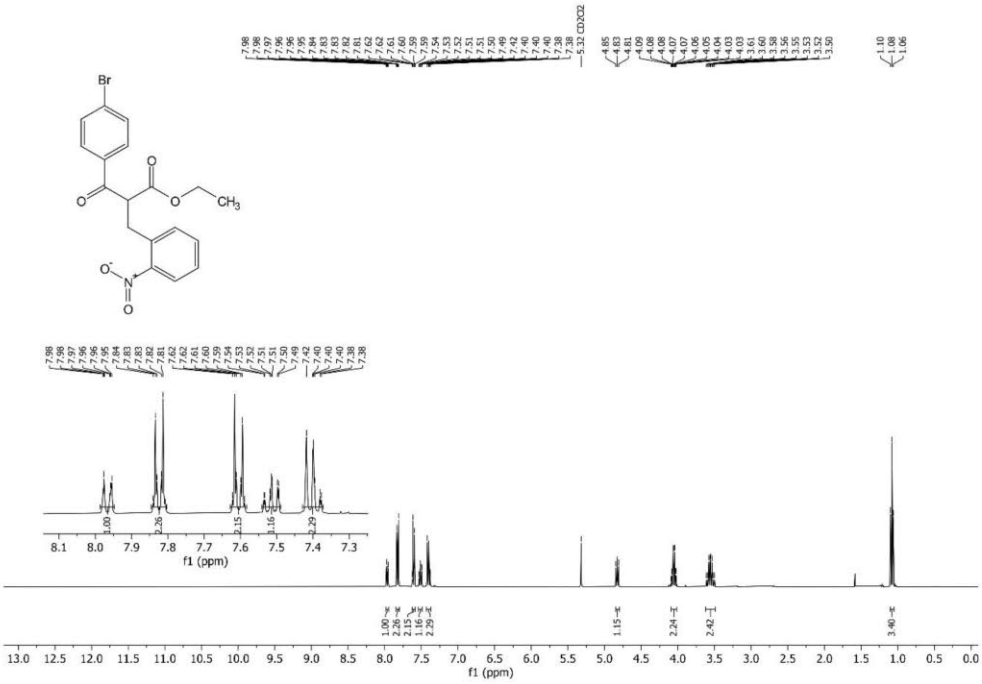
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of ethyl 3-(4-fluorophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4f**).



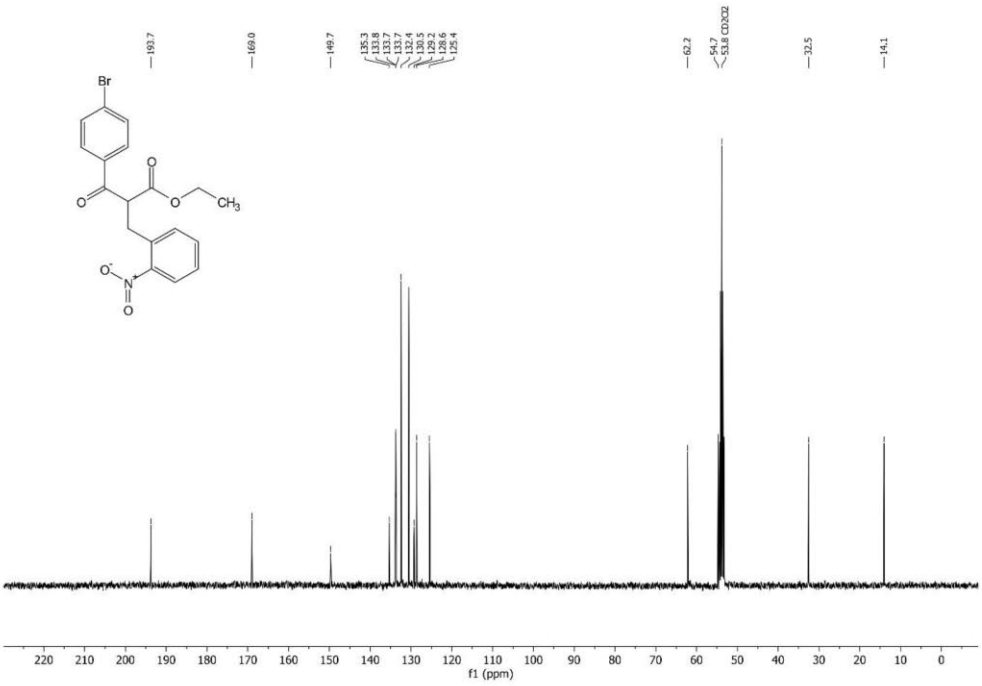
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of ethyl 3-(4-fluorophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4f**).



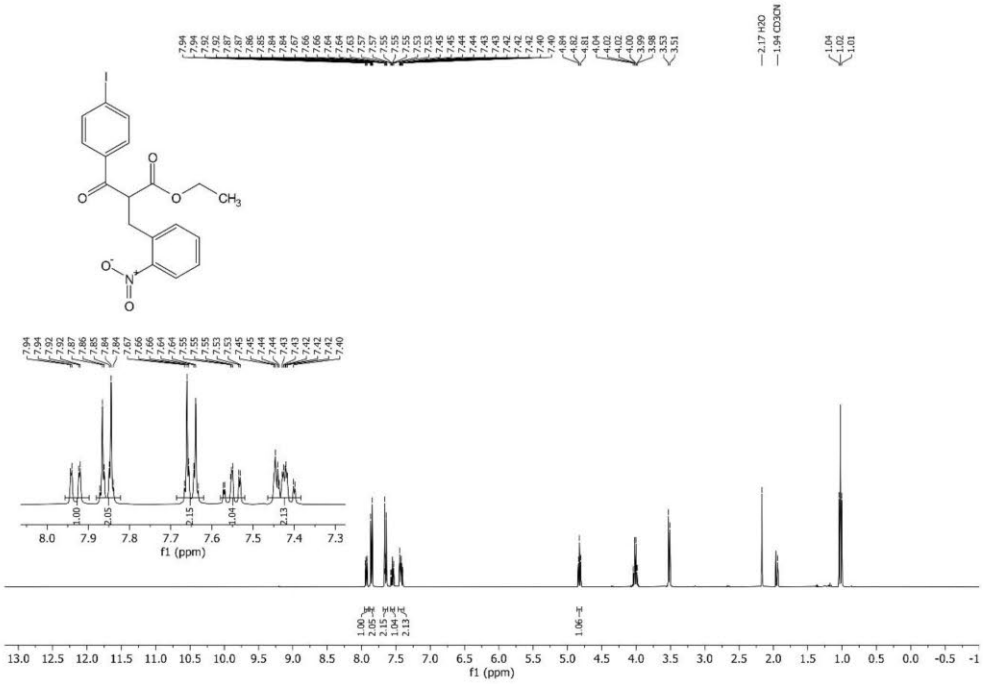
^{19}F NMR spectrum (282 MHz, CD_2Cl_2) of ethyl 3-(4-fluorophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4f**).



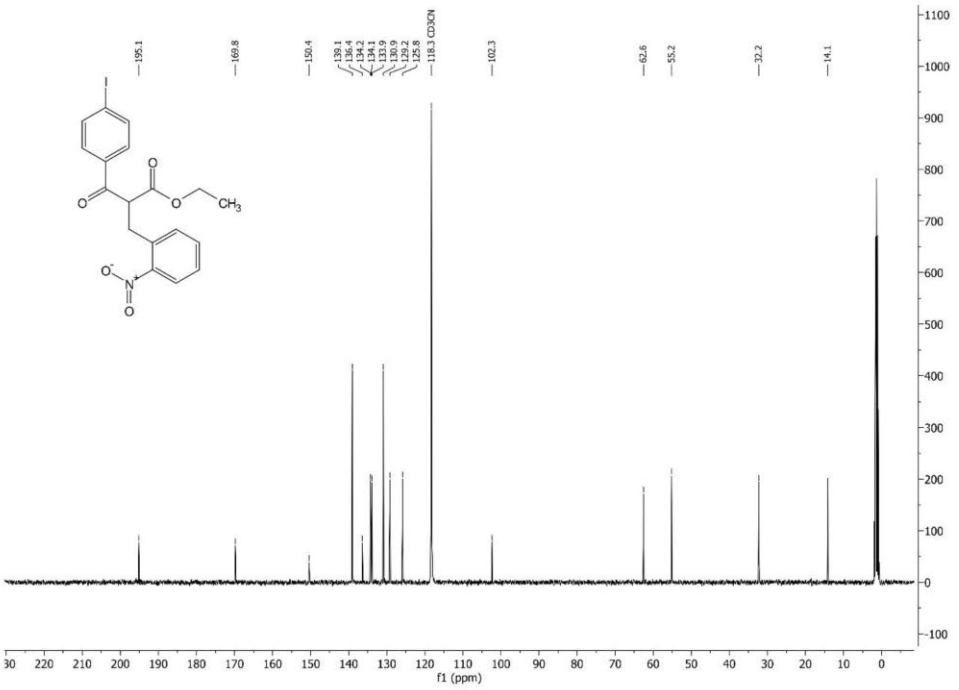
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of ethyl 3-(4-bromophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4g**).



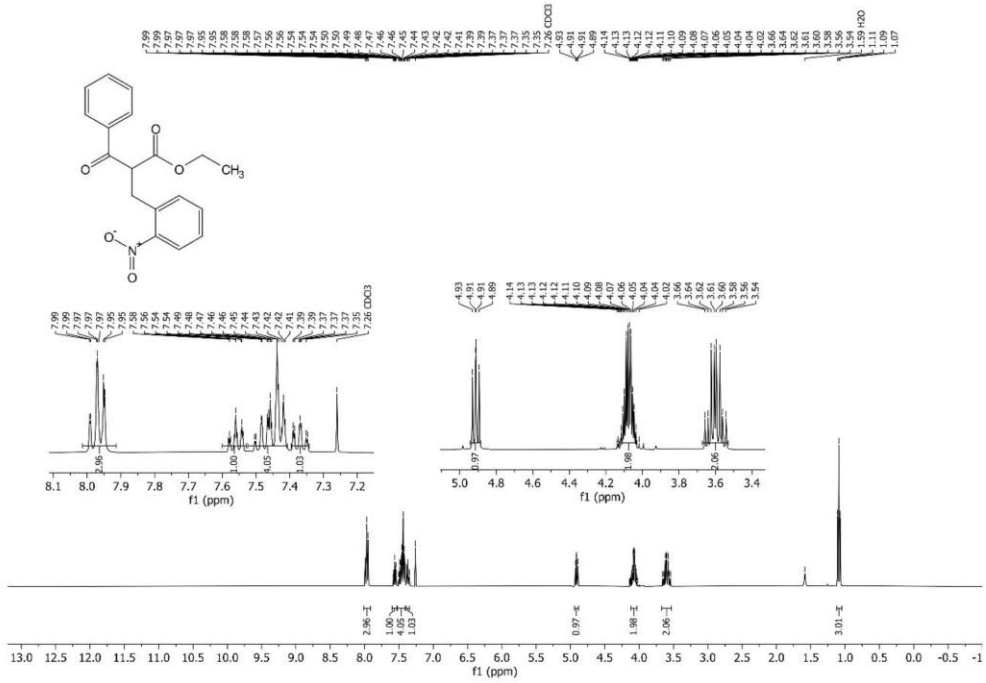
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of ethyl 3-(4-bromophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4g**).



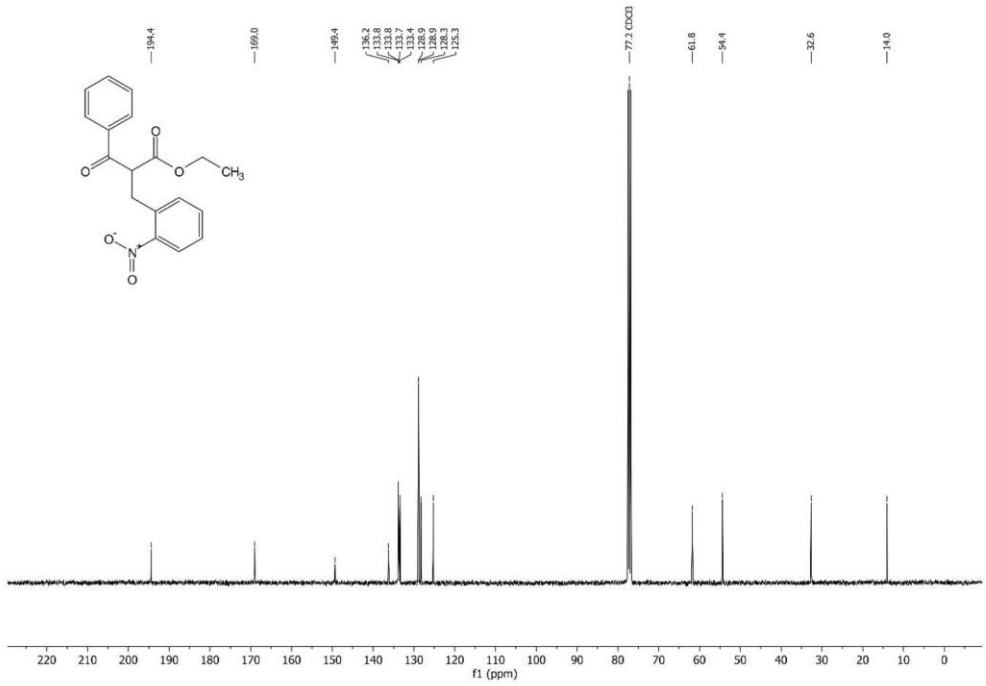
^{1}H NMR spectrum (400 MHz, CD_3CN) of ethyl 3-(4-iodophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4h**).



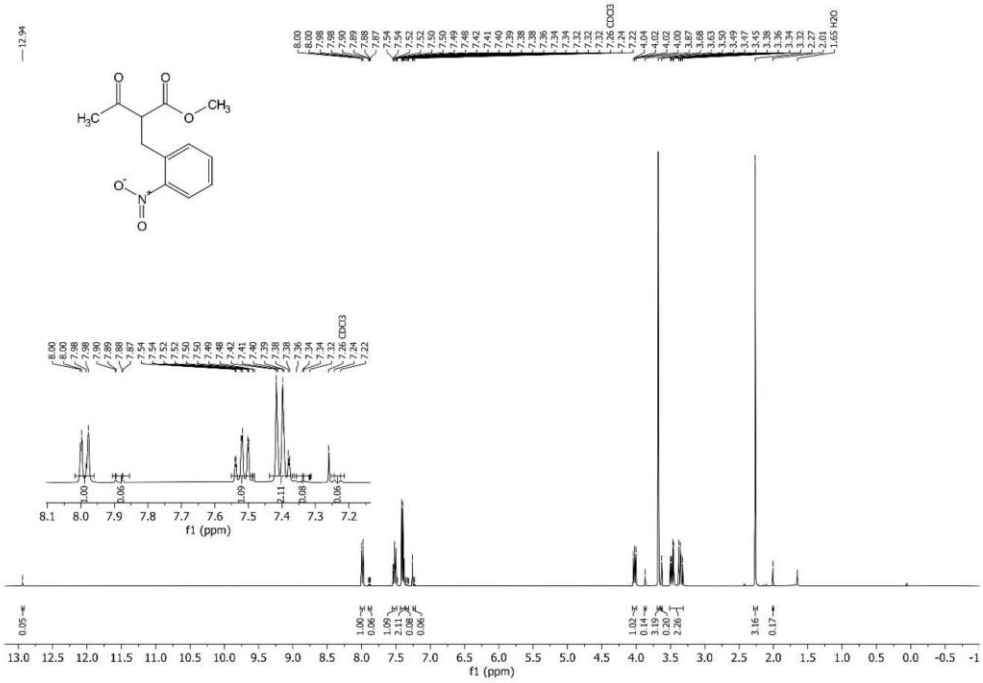
^{13}C NMR spectrum (101 MHz, CD_3CN) of ethyl 3-(4-iodophenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4h**).



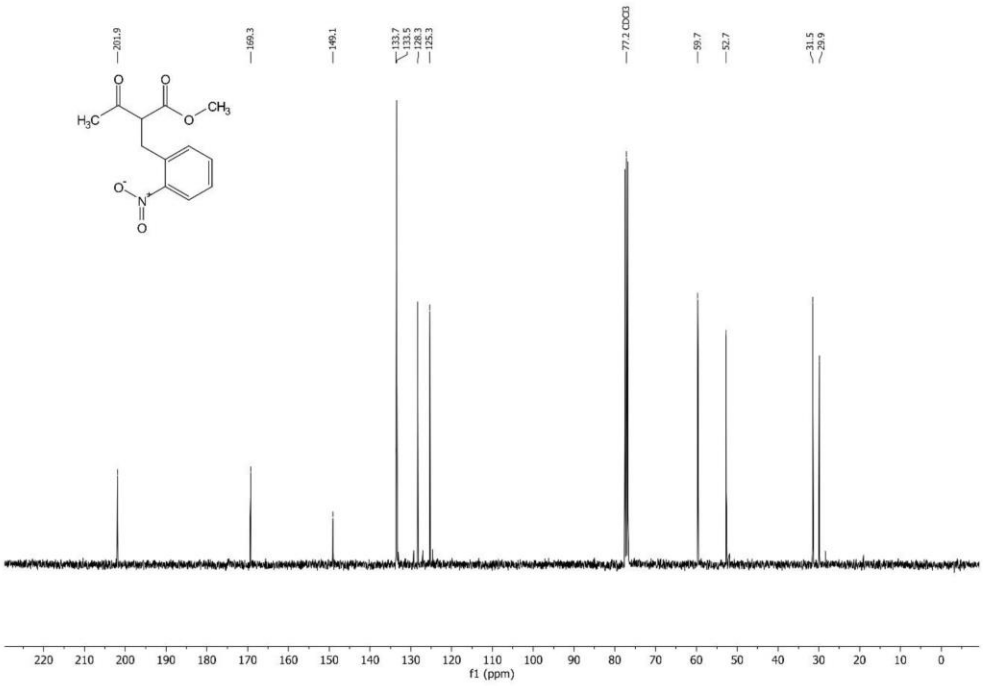
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 2-(2-nitrobenzyl)-3-oxo-3-phenylpropanoate (**4i**).



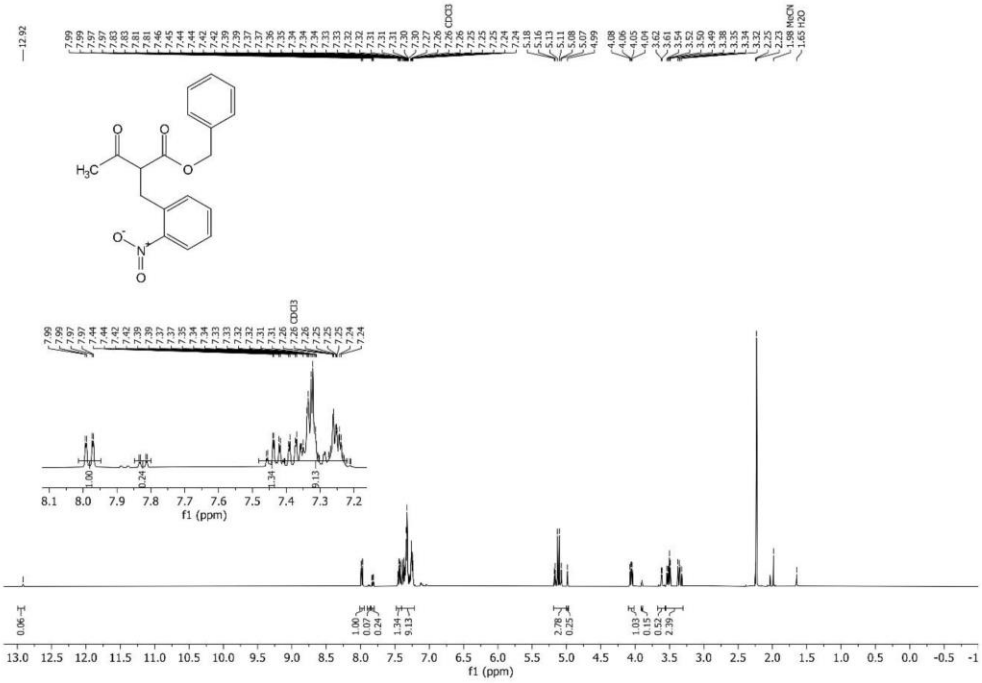
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of ethyl 2-(2-nitrobenzyl)-3-oxo-3-phenylpropanoate (**4i**).



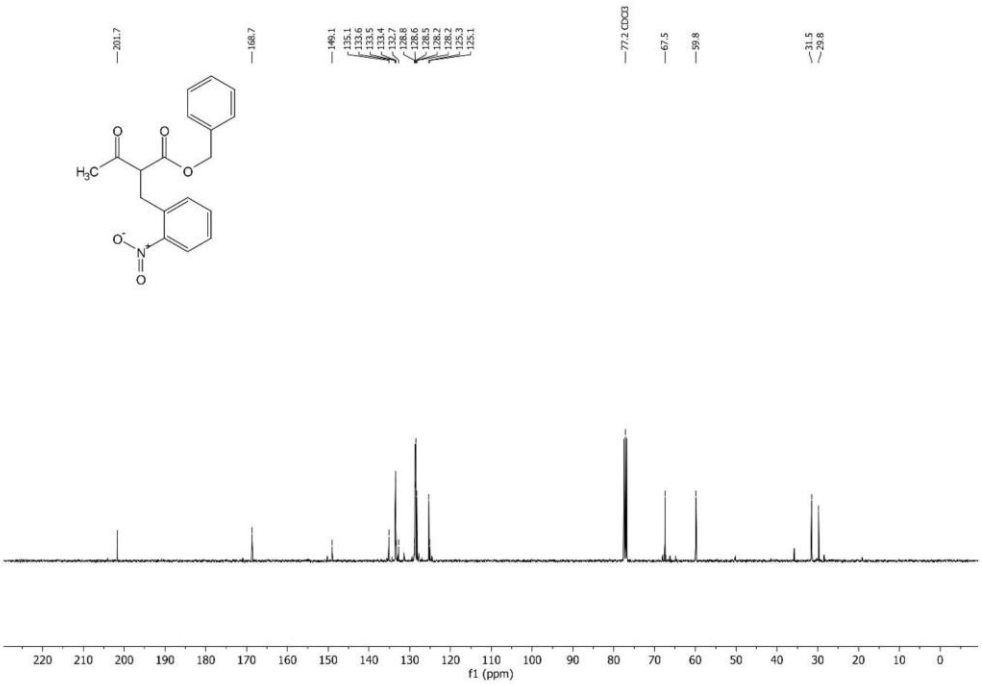
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of methyl 2-(2-nitrobenzyl)-3-oxobutanoate (**4j**).



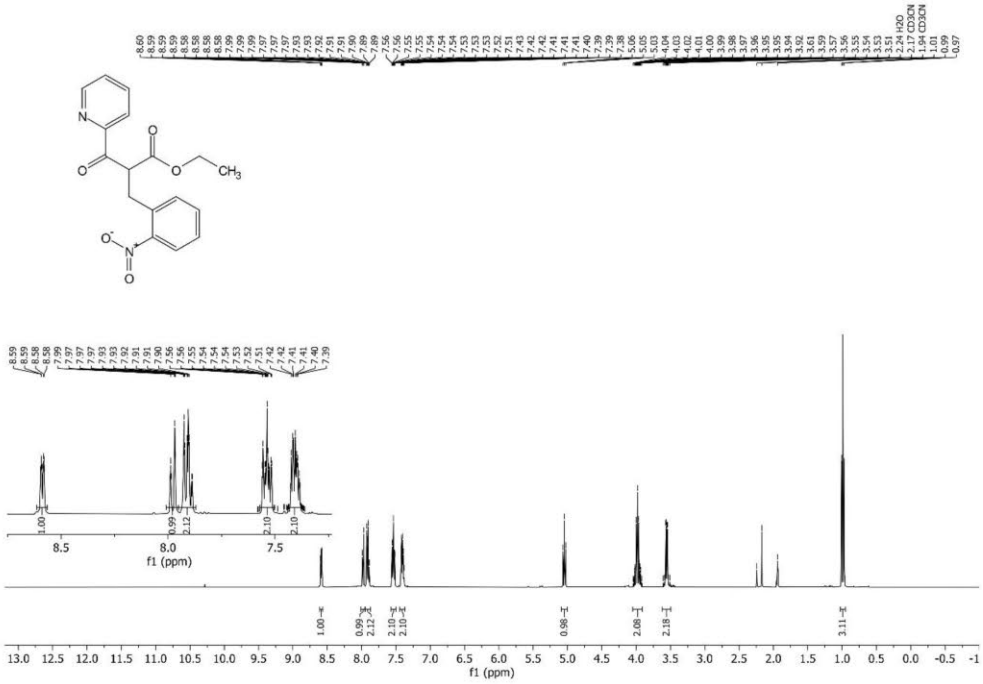
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of methyl 2-(2-nitrobenzyl)-3-oxobutanoate (**4j**).



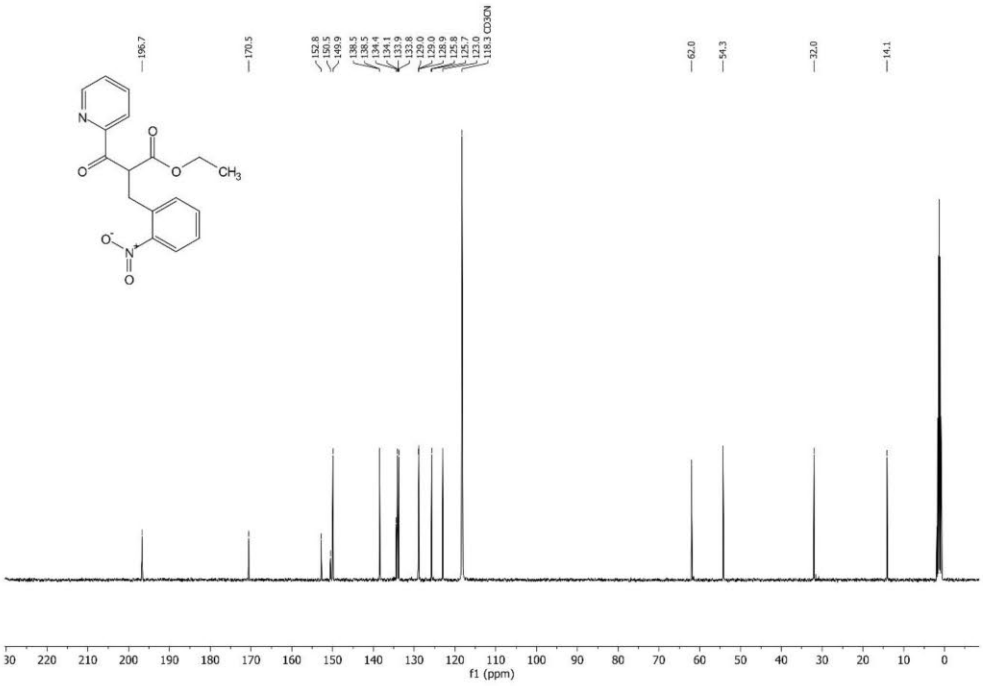
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of benzyl 2-(2-nitrobenzyl)-3-oxobutanoate (**4k**).



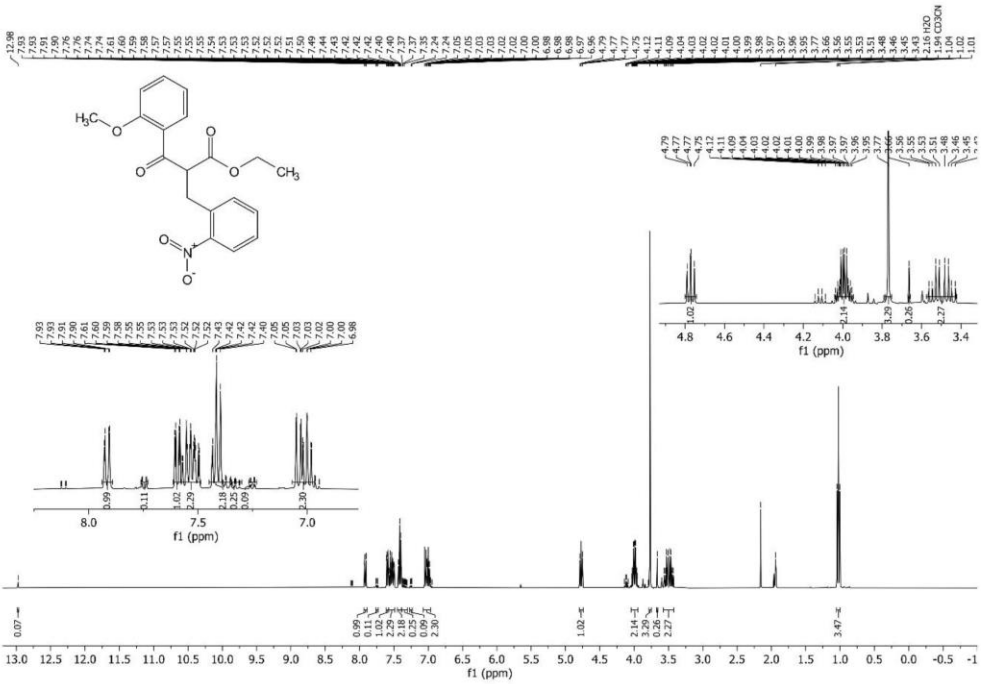
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of benzyl 2-(2-nitrobenzyl)-3-oxobutanoate (**4k**).



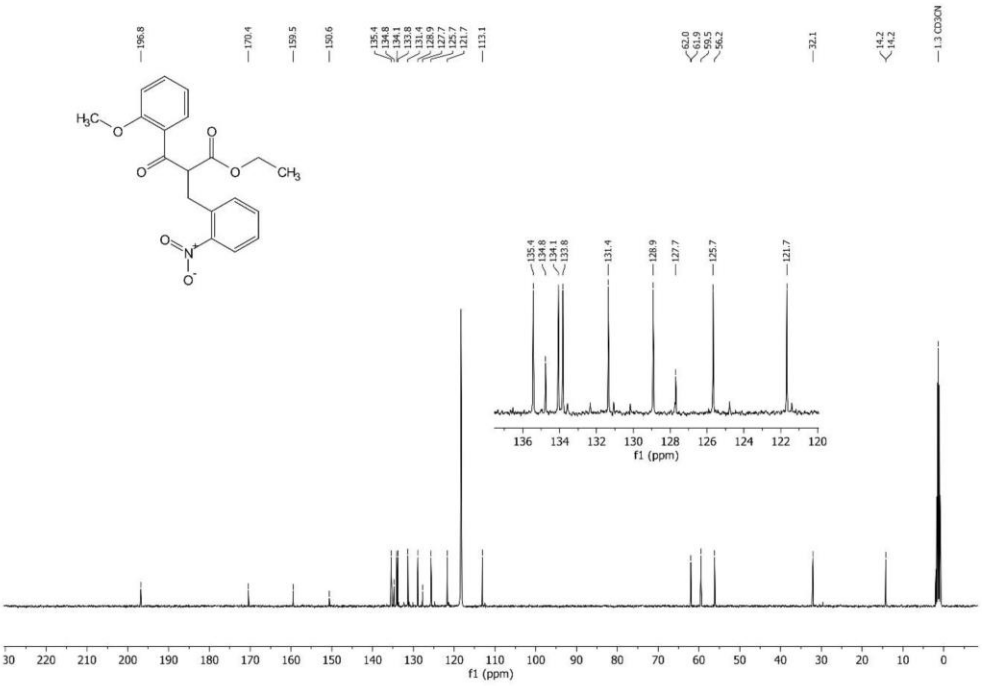
^{1}H NMR spectrum (400 MHz, CD_3CN) of ethyl 2-(2-nitrobenzyl)-3-oxo-3-(pyridin-2-yl)propanoate (**4l**).



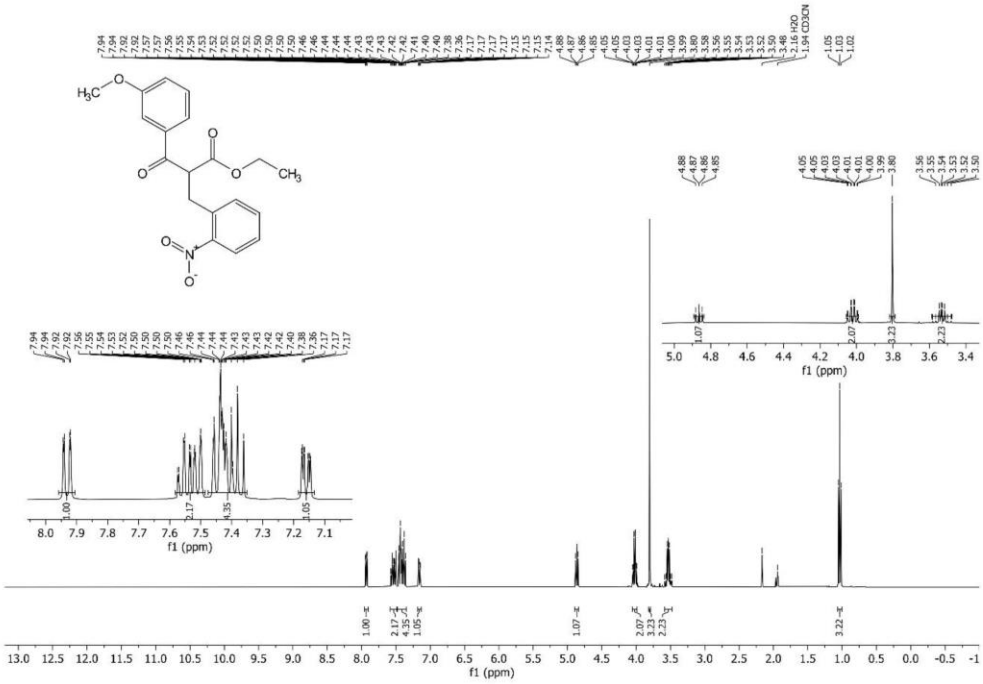
^{13}C NMR spectrum (101 MHz, CD_3CN) of ethyl 2-(2-nitrobenzyl)-3-oxo-3-(pyridin-2-yl)propanoate (**4l**).



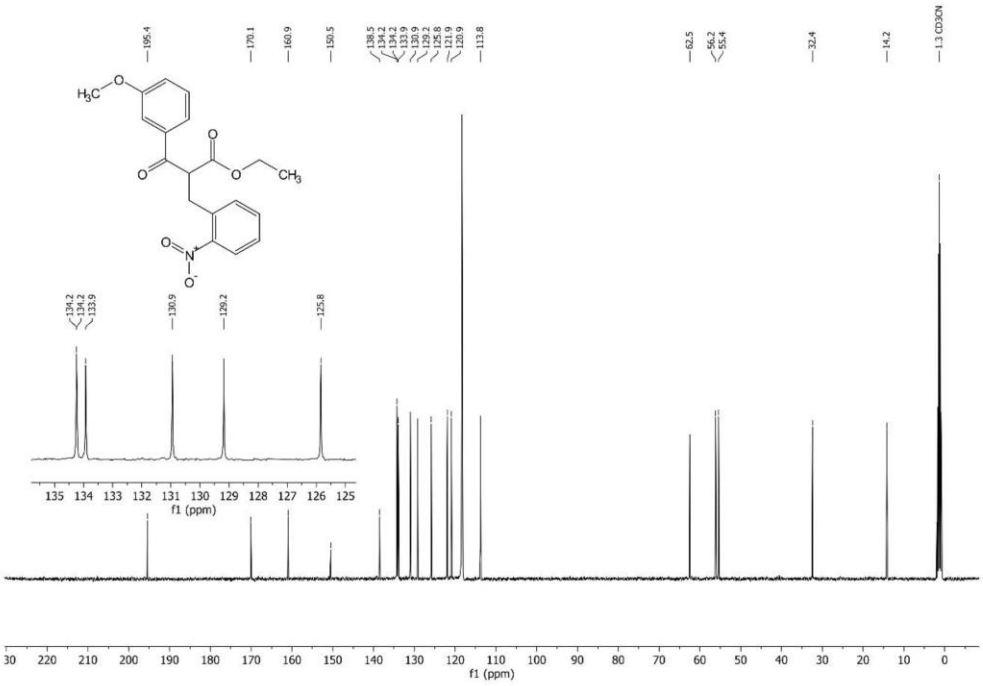
^{1}H NMR spectrum (400 MHz, CD_3CN) of ethyl 3-(2-methoxyphenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4m**).



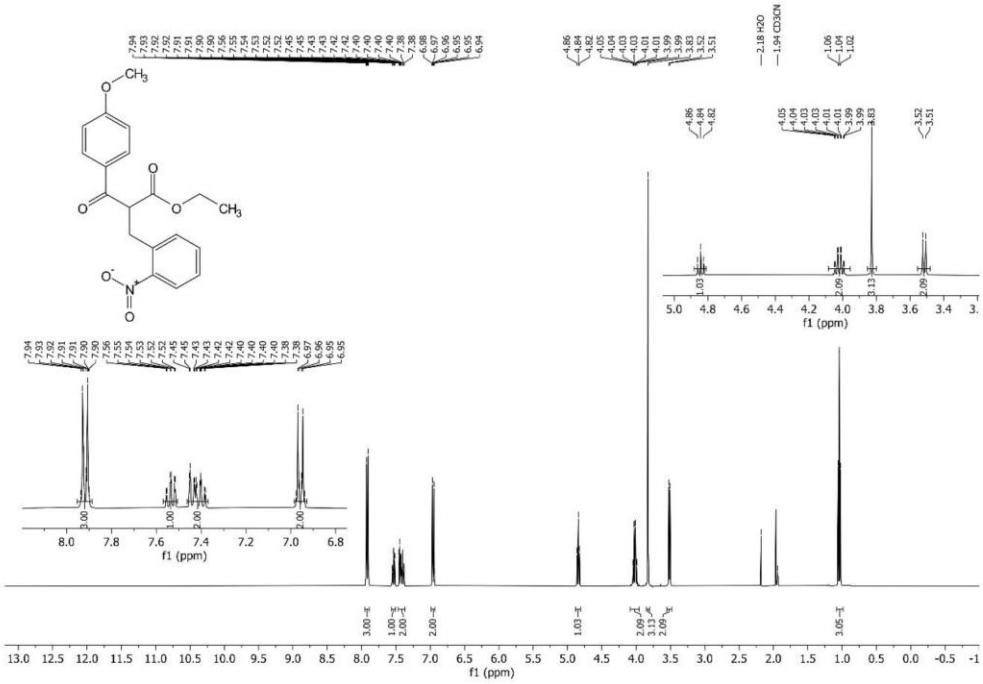
^{13}C NMR spectrum (101 MHz, CD_3CN) of ethyl 3-(2-methoxyphenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4m**).



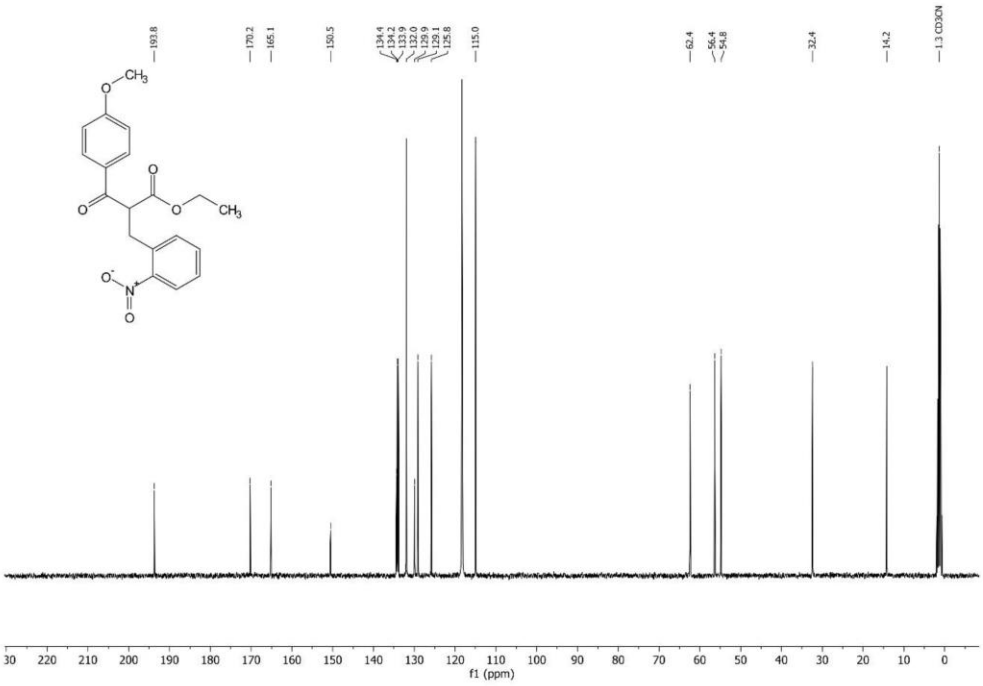
^{1}H NMR spectrum (400 MHz, CD_3CN) of ethyl 3-(3-methoxyphenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4n**).



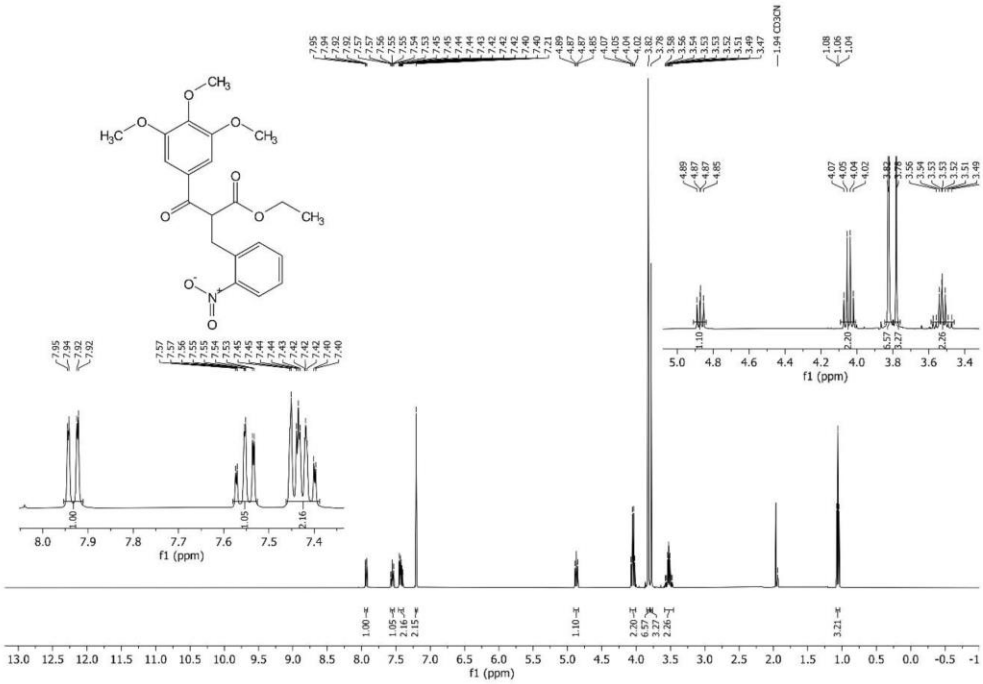
^{13}C NMR spectrum (101 MHz, CD_3CN) of ethyl 3-(3-methoxyphenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4n**).



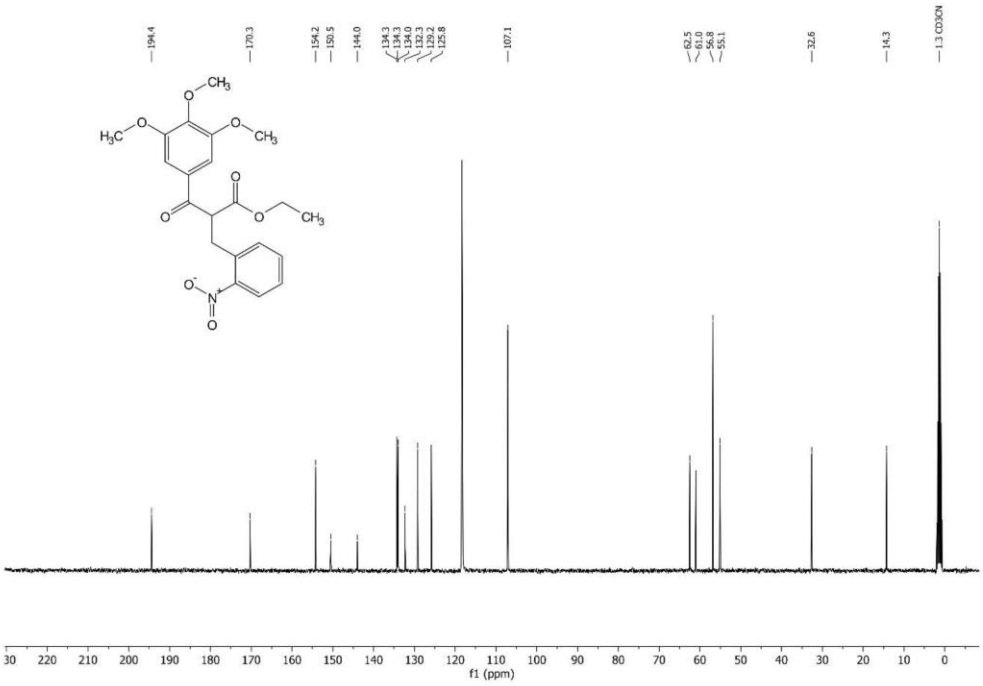
^{1}H NMR spectrum (400 MHz, CD_3CN) of ethyl 3-(4-methoxyphenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4o**).



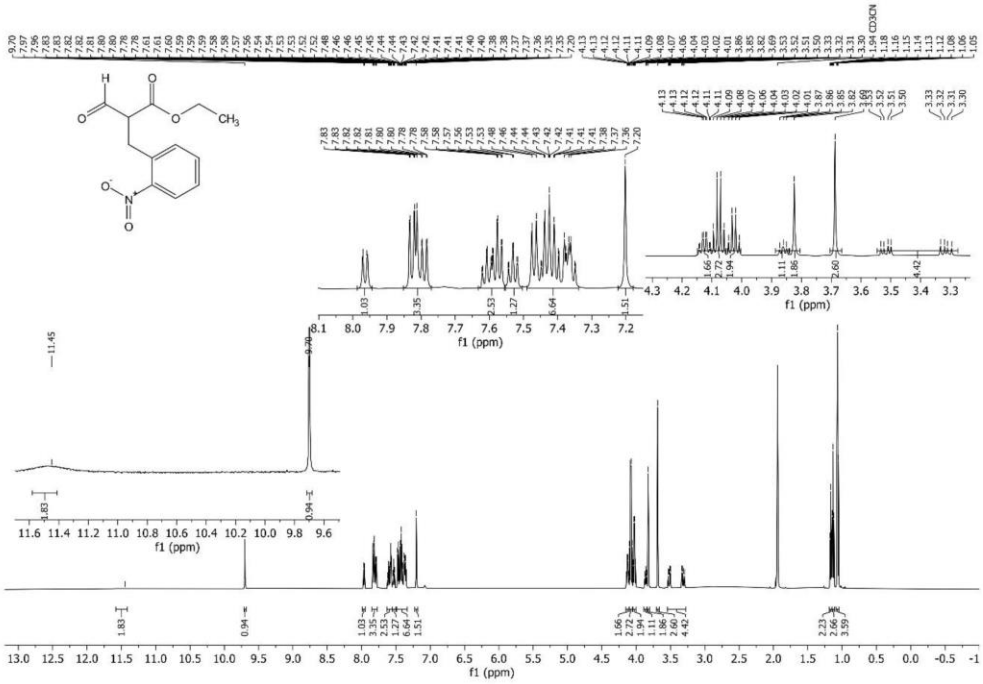
^{13}C NMR spectrum (101 MHz, CD_3CN) of ethyl 3-(4-methoxyphenyl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4o**).



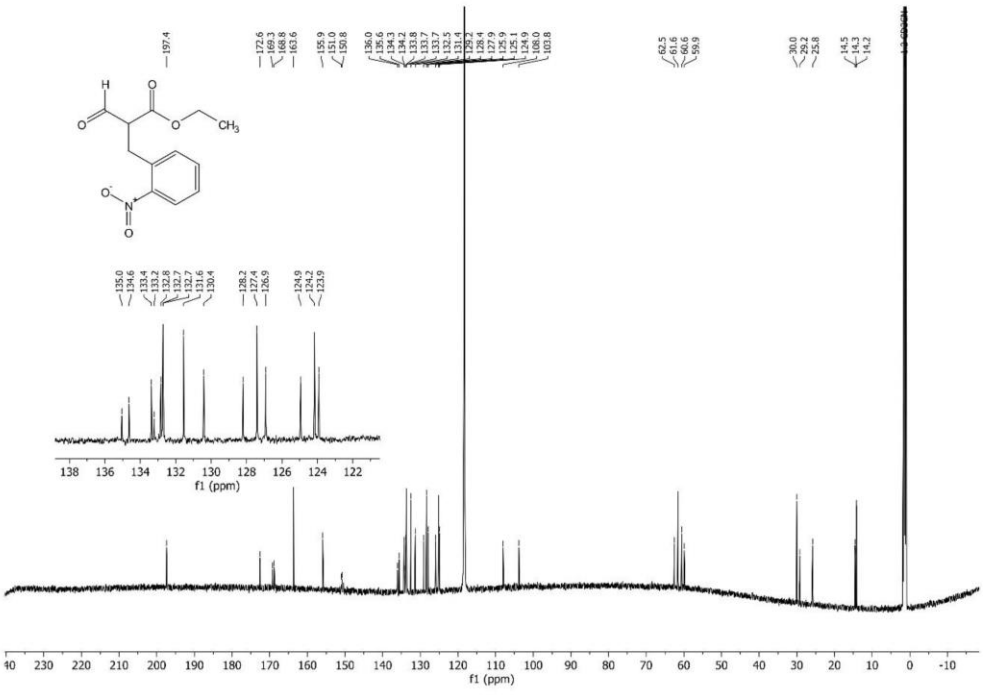
^{1}H NMR spectrum (400 MHz, CD_3CN) of ethyl 2-(2-nitrobenzyl)-3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (**4p**).



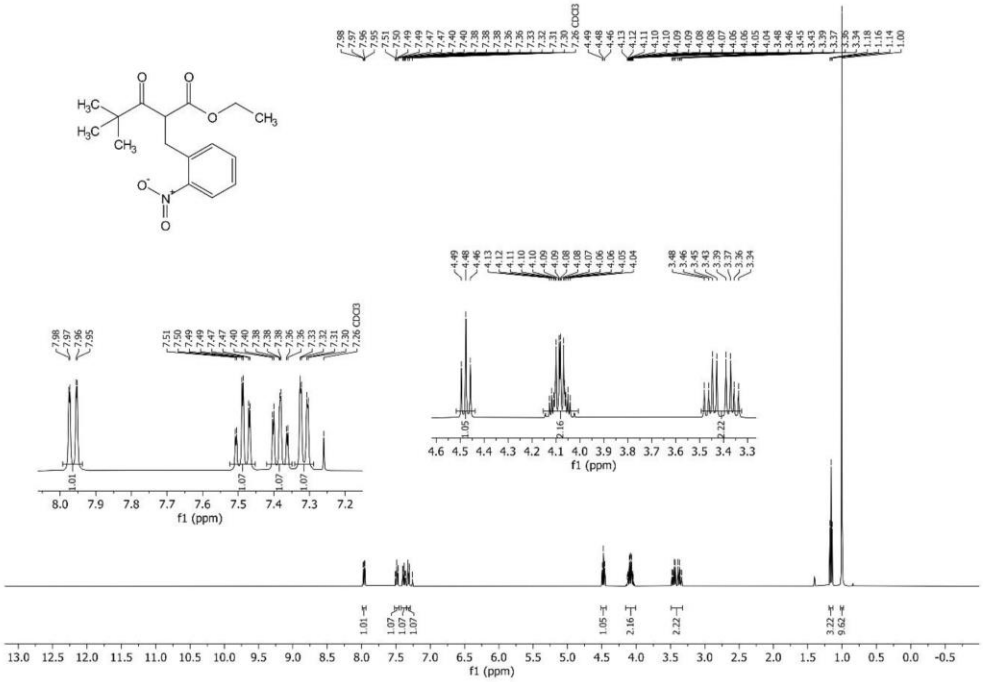
^{13}C NMR spectrum (101 MHz, CD_3CN) of ethyl 2-(2-nitrobenzyl)-3-oxo-3-(3,4,5-trimethoxyphenyl)propanoate (**4p**).



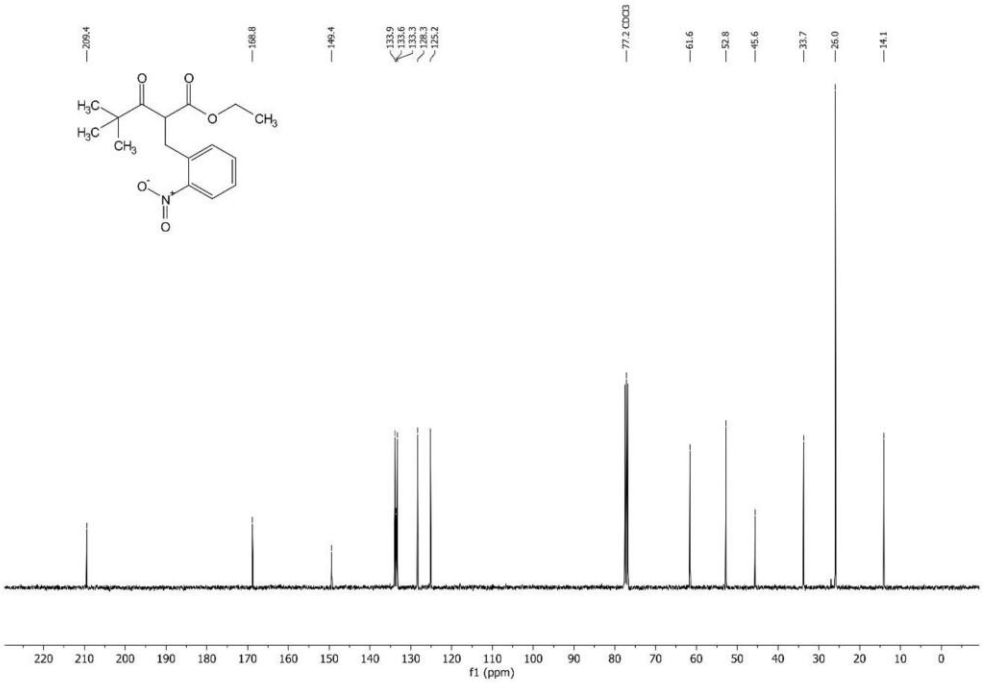
^{1}H NMR spectrum (400 MHz, CD_3CN) of ethyl 2-formyl-3-(2-nitrophenyl)propanoate (**4q**).



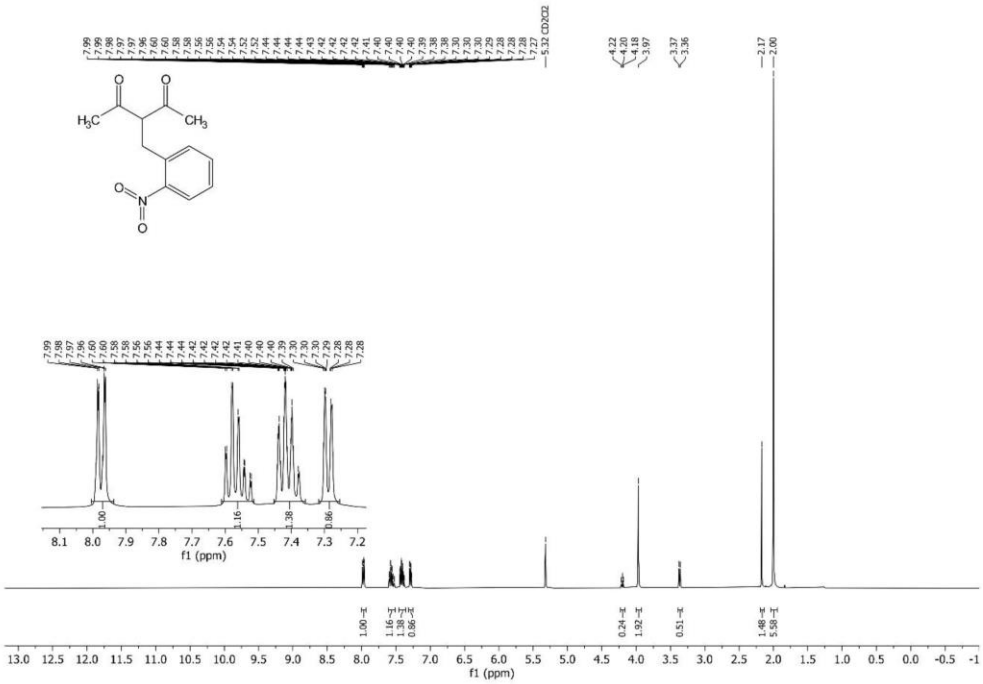
^{13}C NMR spectrum (101 MHz, CD_3CN) of ethyl 2-formyl-3-(2-nitrophenyl)propanoate (**4q**).



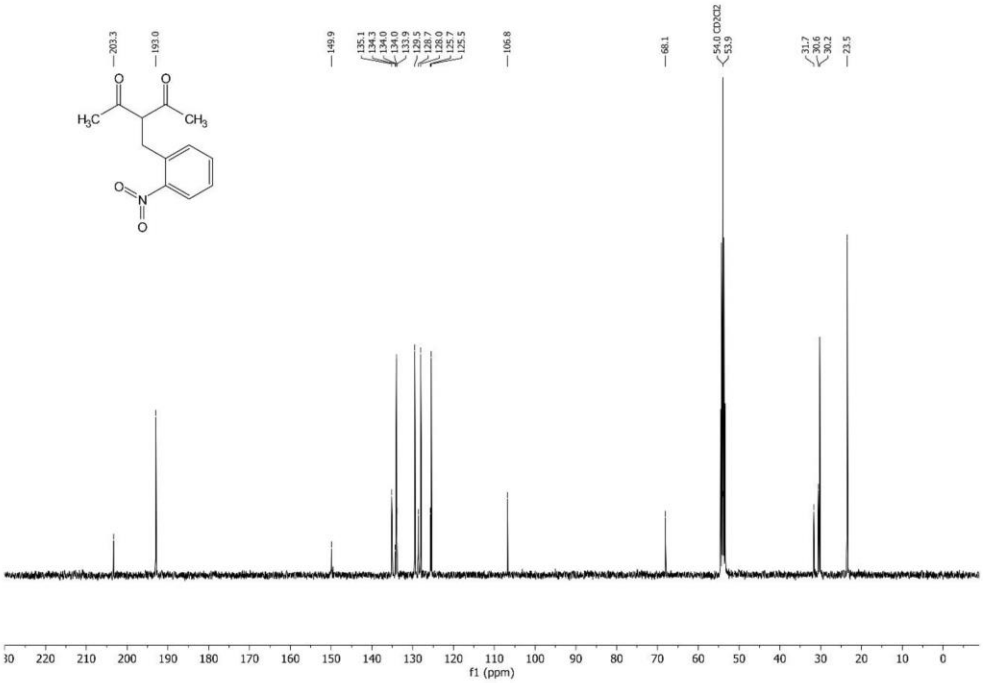
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 4,4-dimethyl-2-(2-nitrobenzyl)-3-oxopentanoate (**4r**).



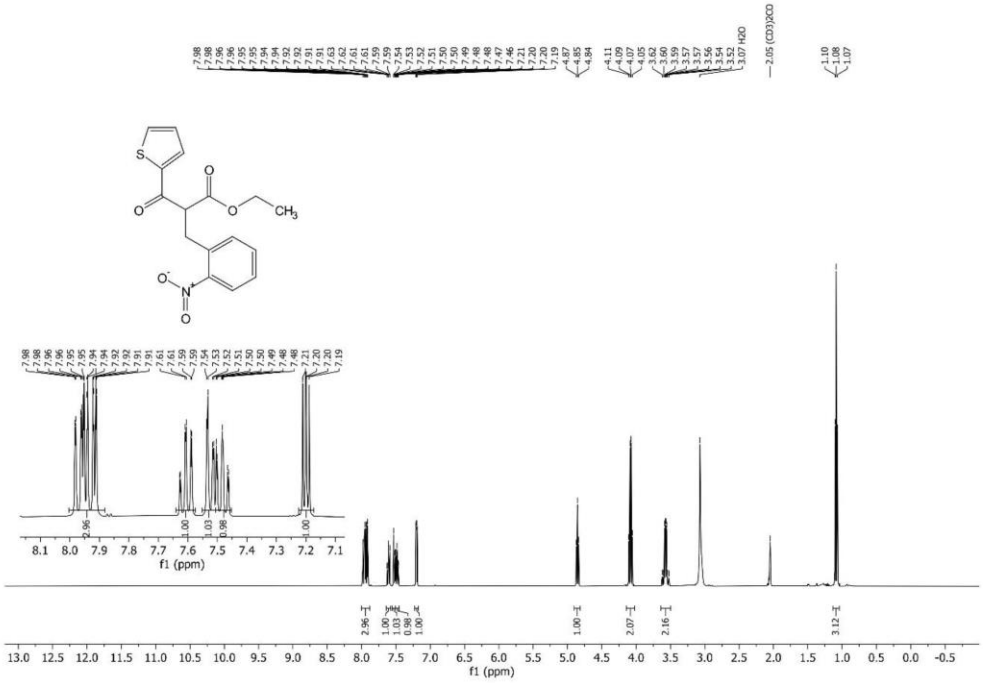
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of ethyl 4,4-dimethyl-2-(2-nitrobenzyl)-3-oxopentanoate (**4r**).



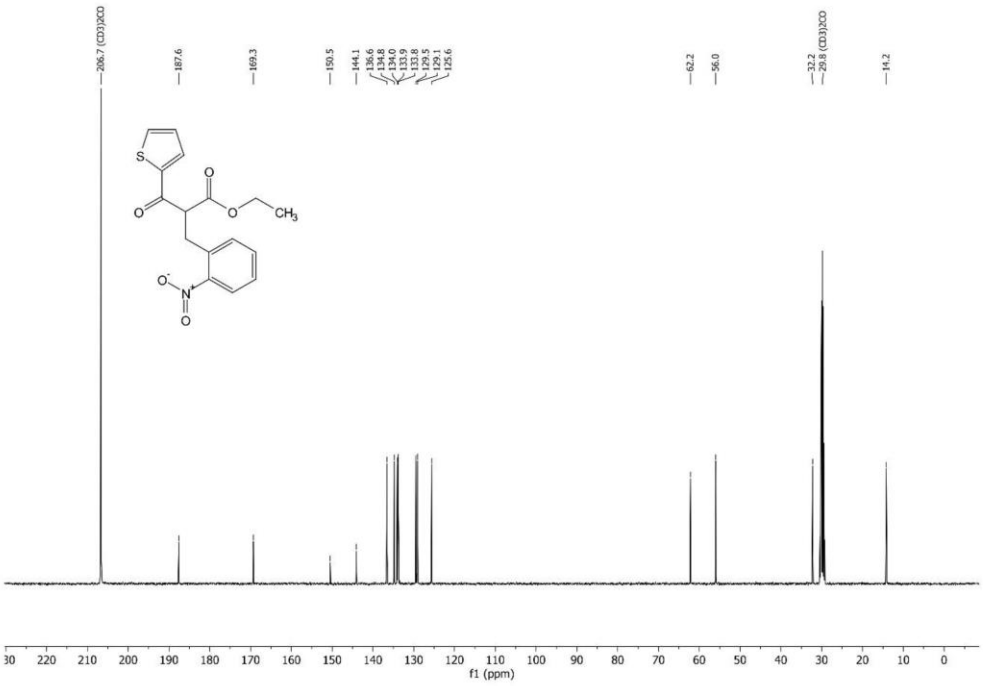
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-(2-nitrobenzyl)pentane-2,4-dione (**4s**).



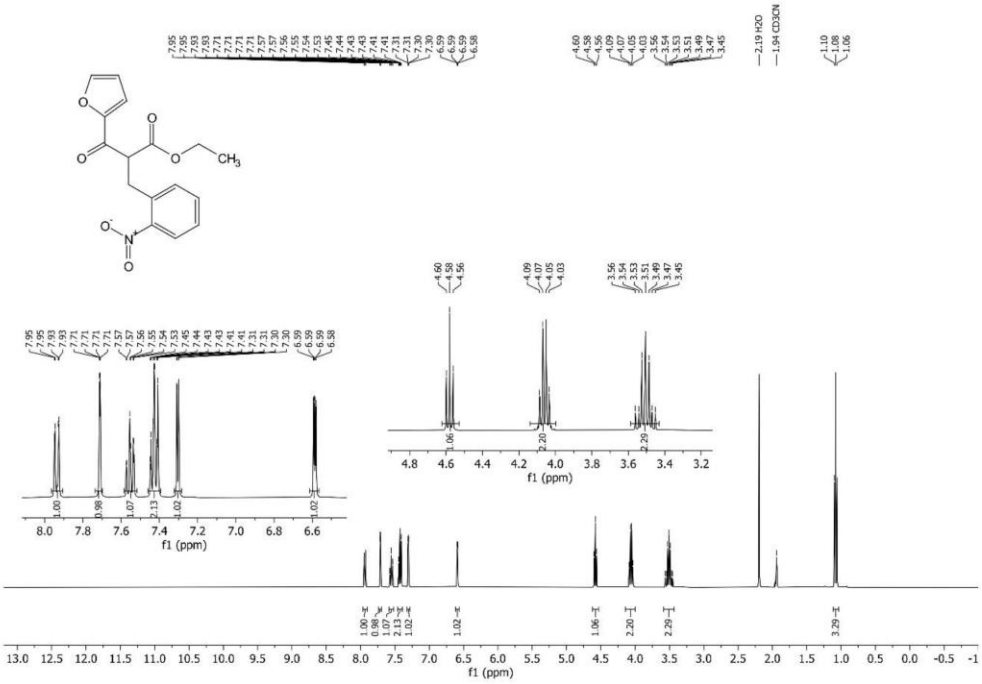
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-(2-nitrobenzyl)pentane-2,4-dione (**4s**).



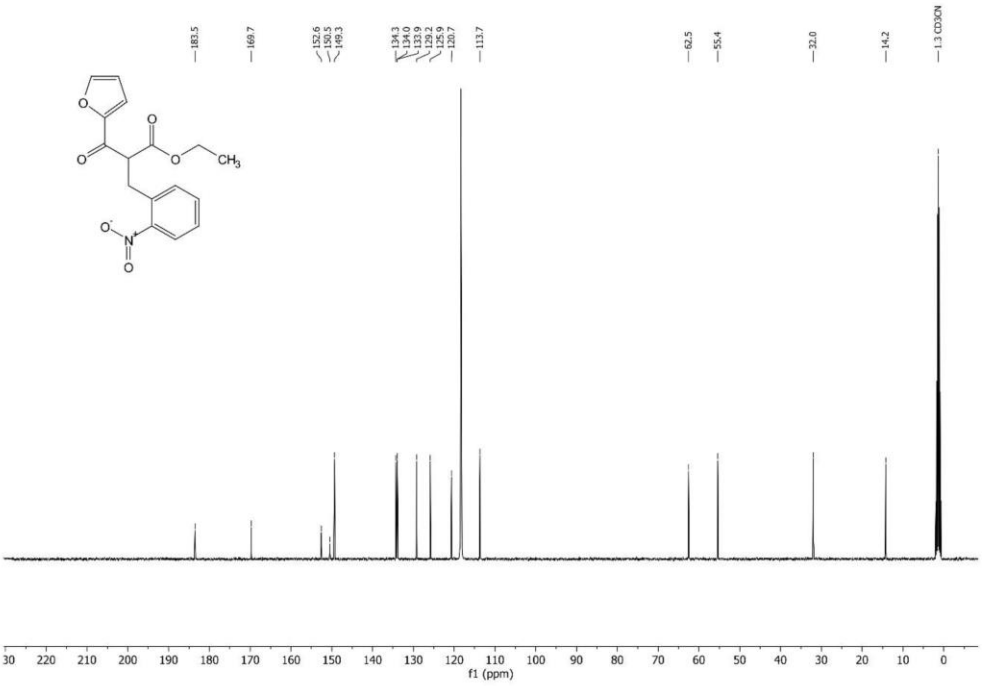
^{1}H NMR spectrum (400 MHz, $(CD_3)_2CO$) of ethyl 2-(2-nitrobenzyl)-3-oxo-3-(thien-2-yl)propanoate (**4t**).



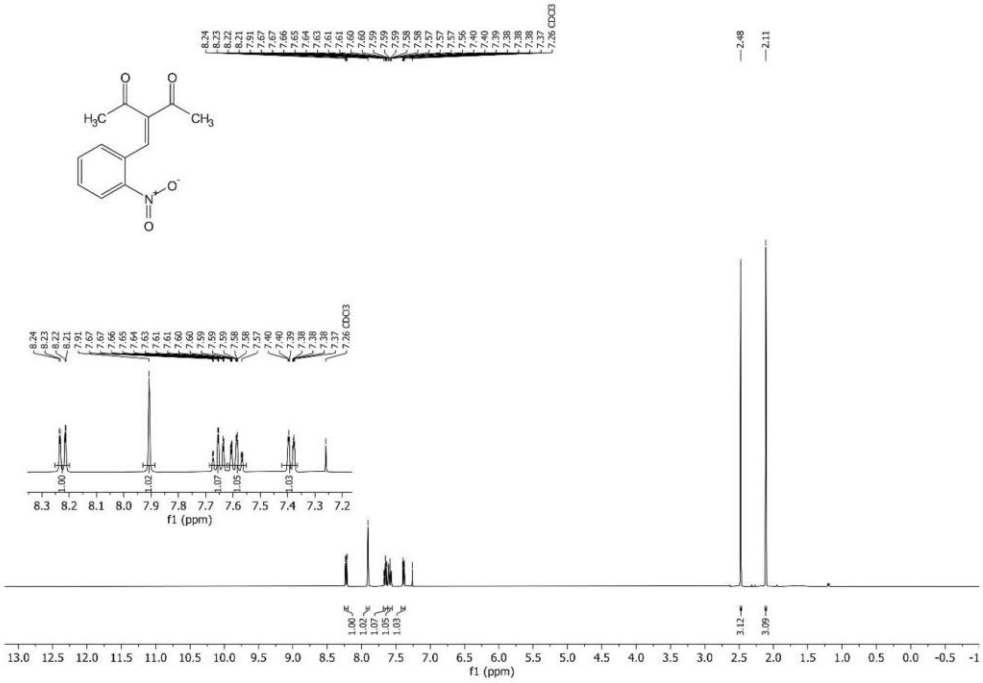
^{13}C NMR spectrum (101 MHz, $(CD_3)_2CO$) of ethyl 2-(2-nitrobenzyl)-3-oxo-3-(thien-2-yl)propanoate (**4t**).



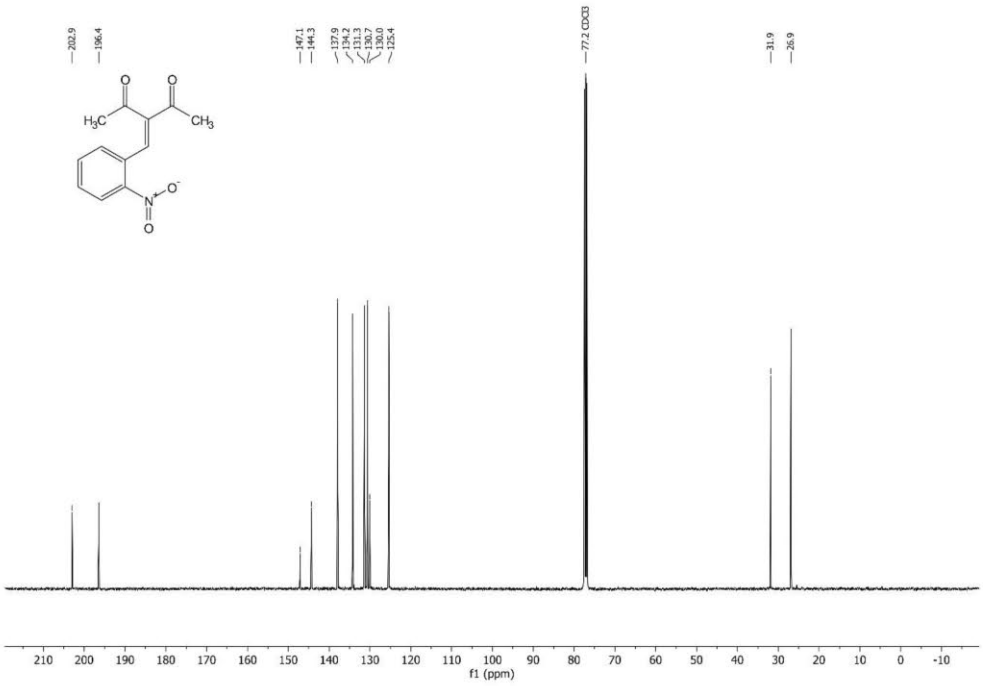
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of ethyl 3-(furan-2-yl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4u**).



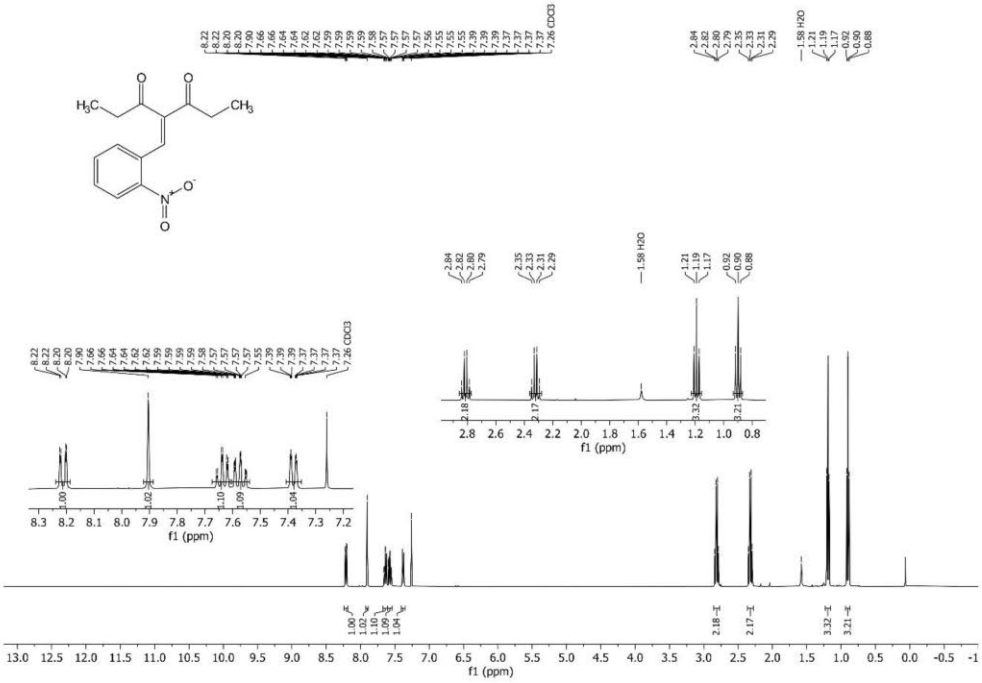
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of ethyl 3-(furan-2-yl)-2-(2-nitrobenzyl)-3-oxopropanoate (**4u**).



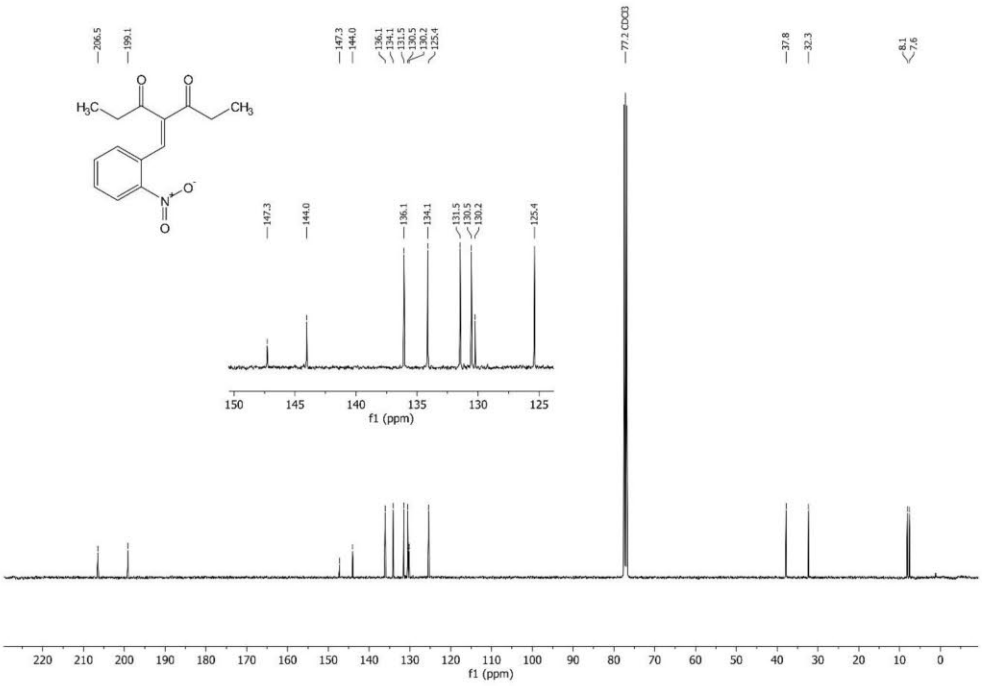
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-(2-nitrobenzylidene)pentane-2,4-dione (**8a**).



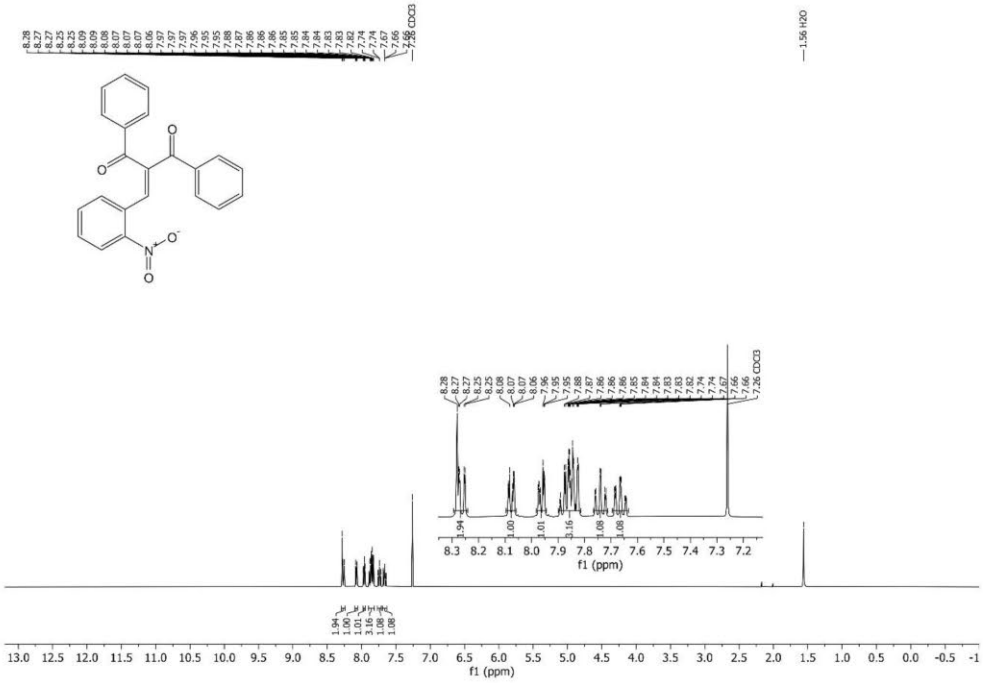
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-(2-nitrobenzylidene)pentane-2,4-dione (**8a**).



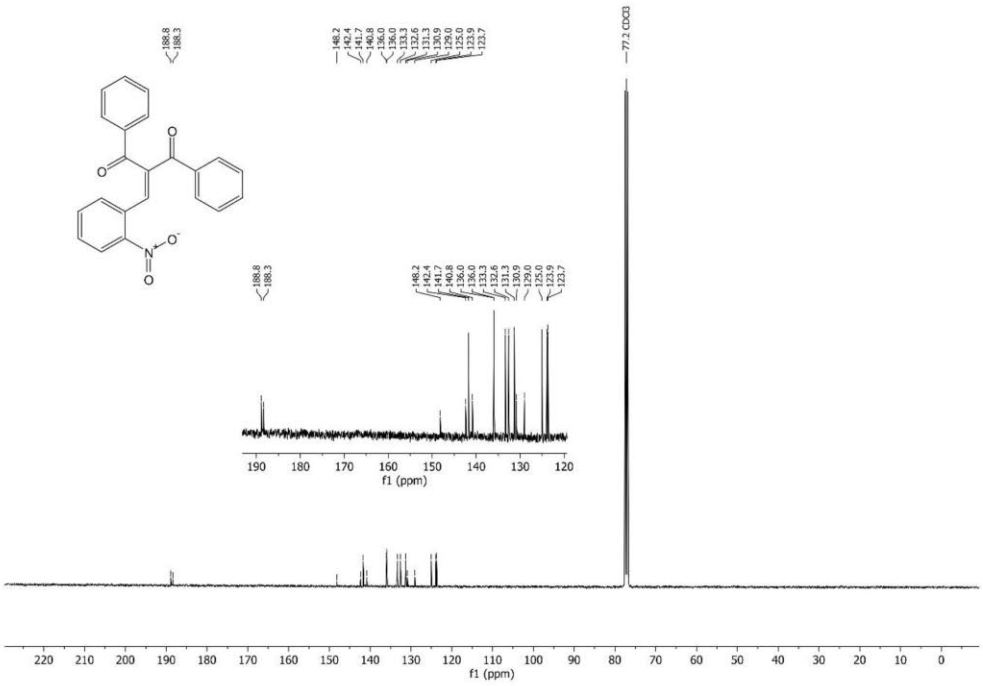
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 4-(2-nitrobenzylidene)heptane-3,5-dione (**8b**).



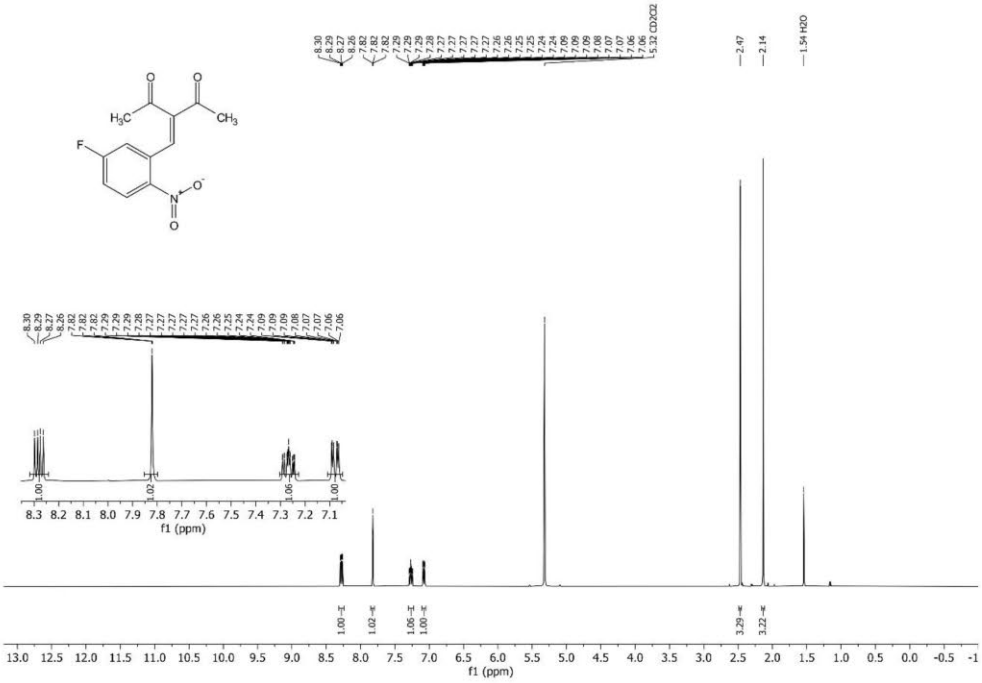
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 4-(2-nitrobenzylidene)heptane-3,5-dione (**8b**).



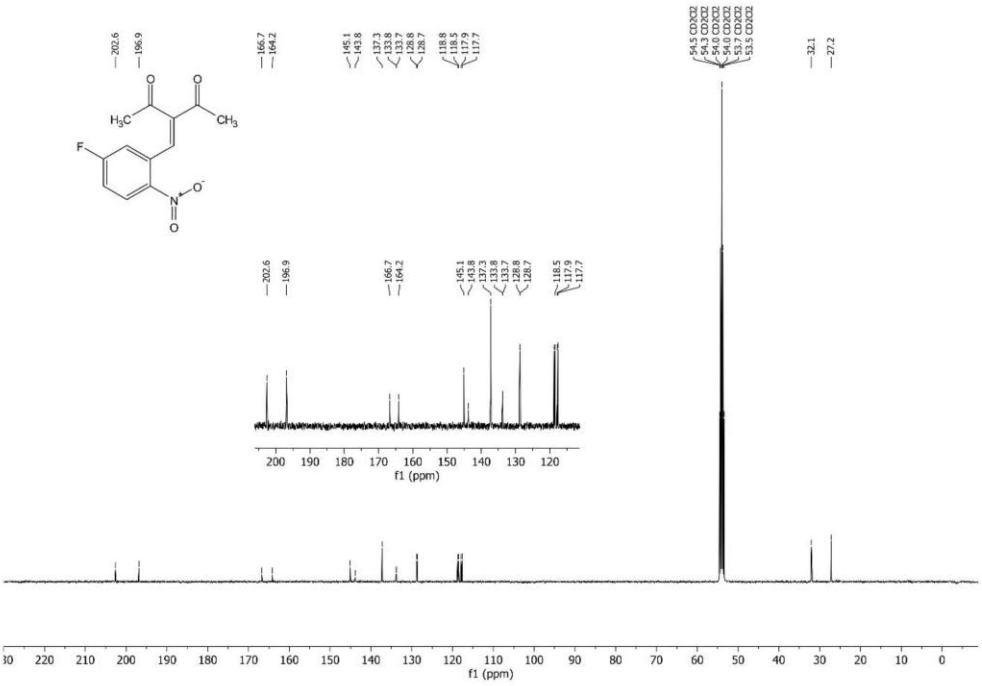
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-(2-nitrobenzylidene)-1,3-diphenylpropane-1,3-dione (**8c**).



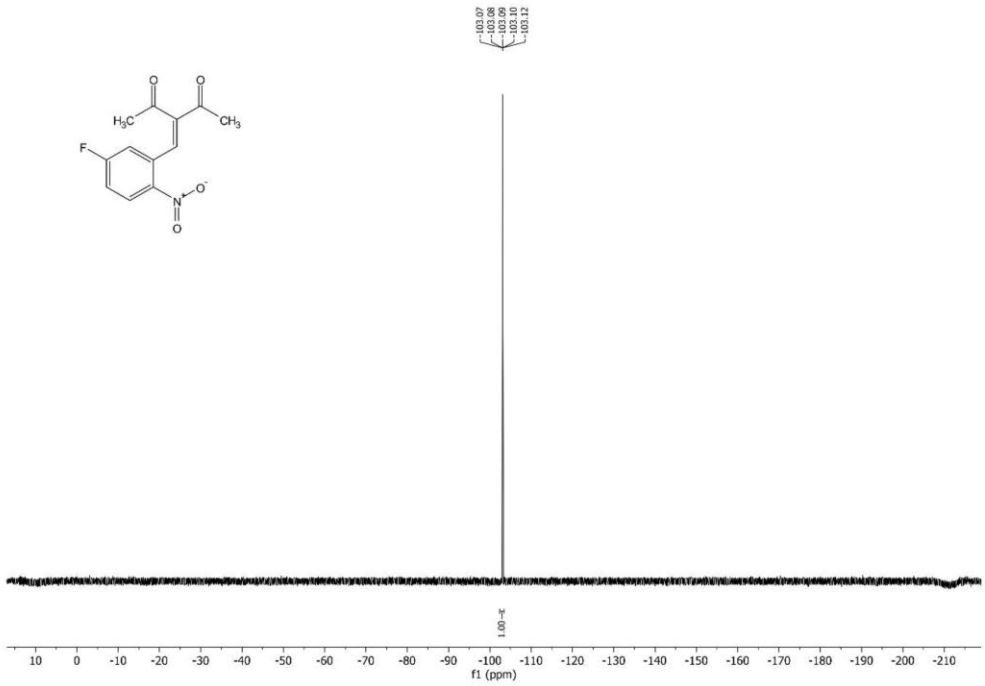
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 2-(2-nitrobenzylidene)-1,3-diphenylpropane-1,3-dione (**8c**).



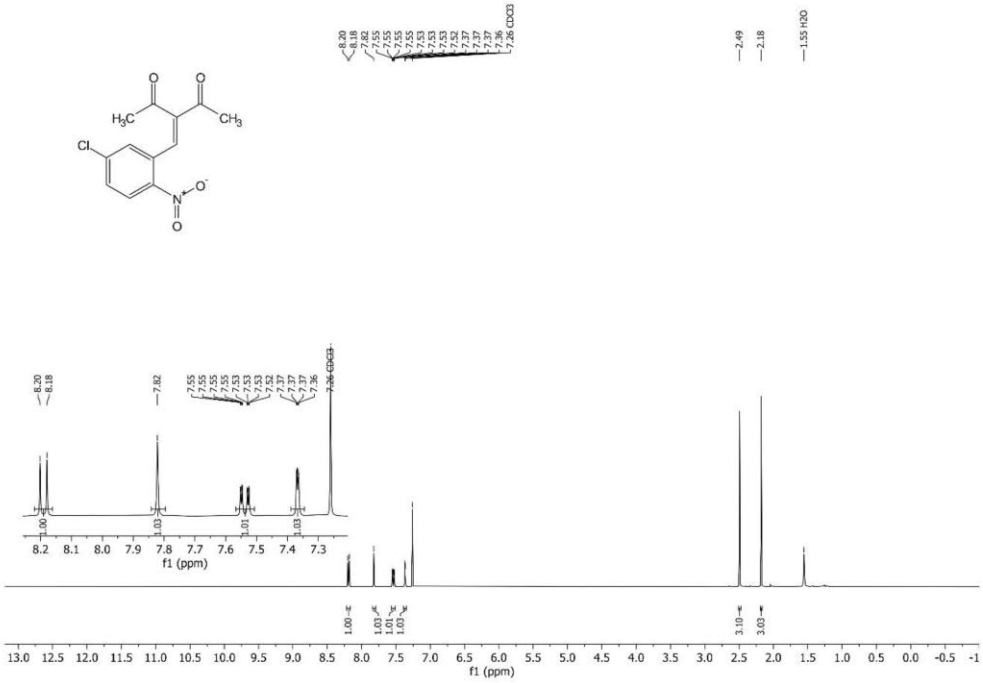
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-(5-fluoro-2-nitrobenzylidene)pentane-2,4-dione (**8d**).



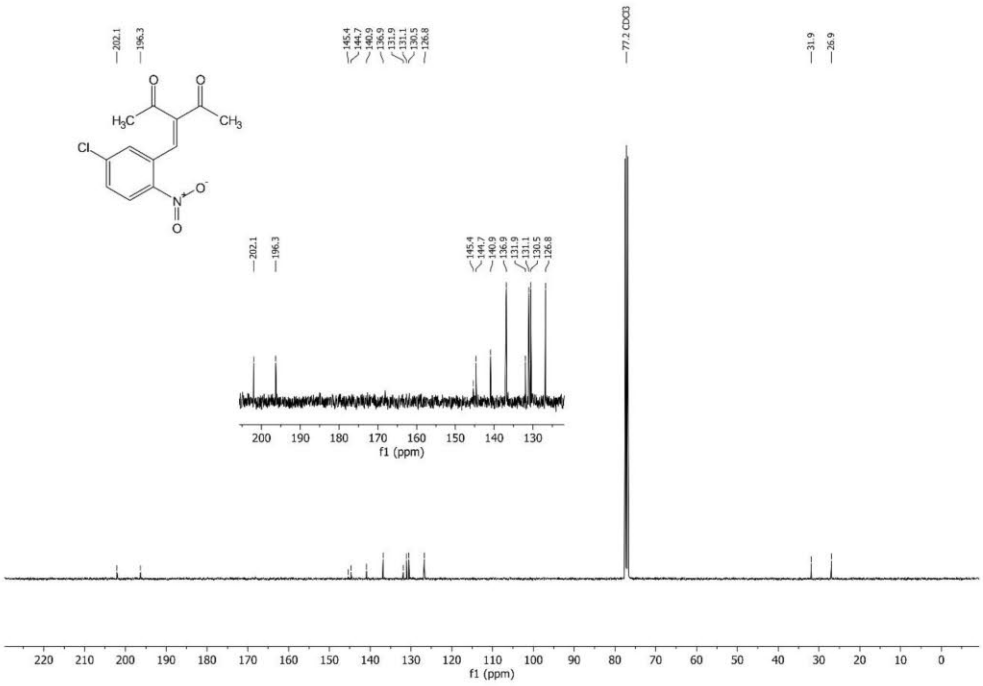
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-(5-fluoro-2-nitrobenzylidene)pentane-2,4-dione (**8d**).



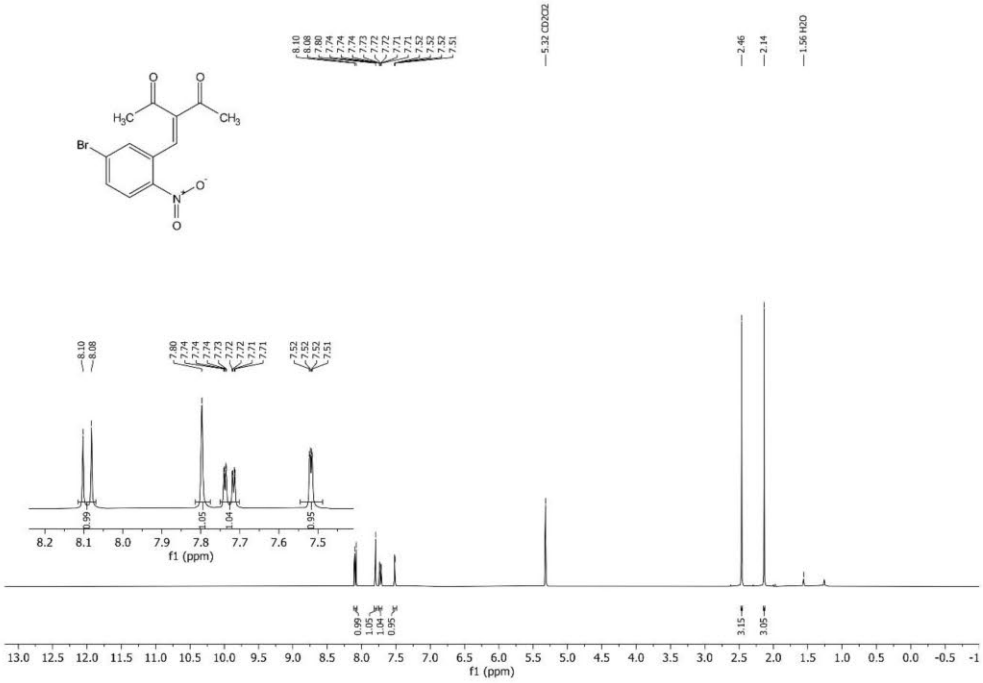
^{19}F NMR spectrum (376 MHz, CD_2Cl_2) of 3-(5-fluoro-2-nitrobenzylidene)pentane-2,4-dione (**8d**).



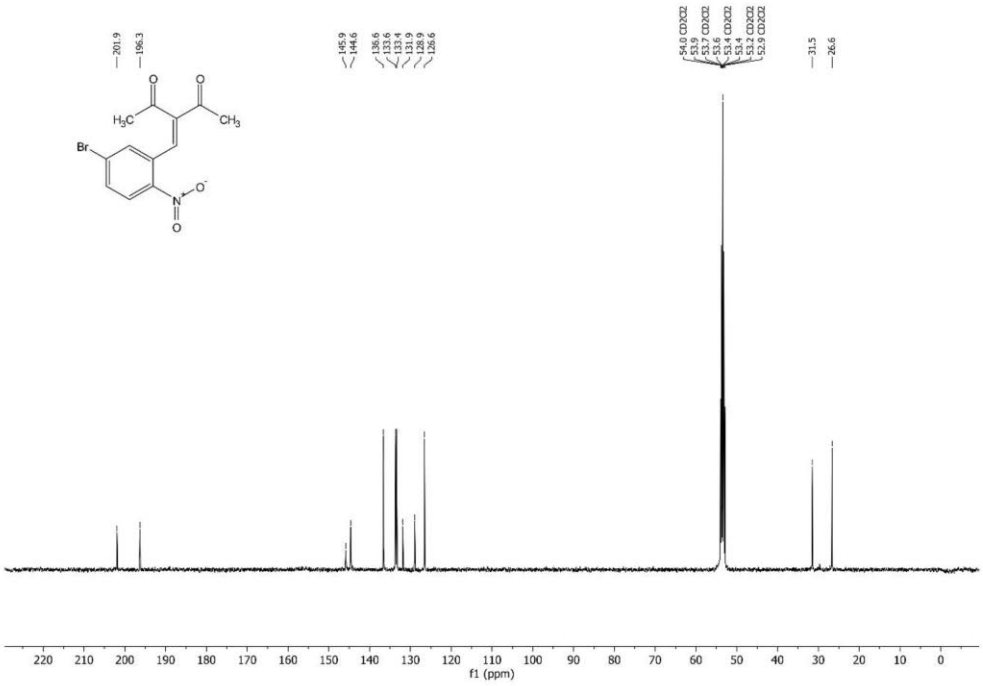
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-(5-chloro-2-nitrobenzylidene)pentane-2,4-dione (**8e**).



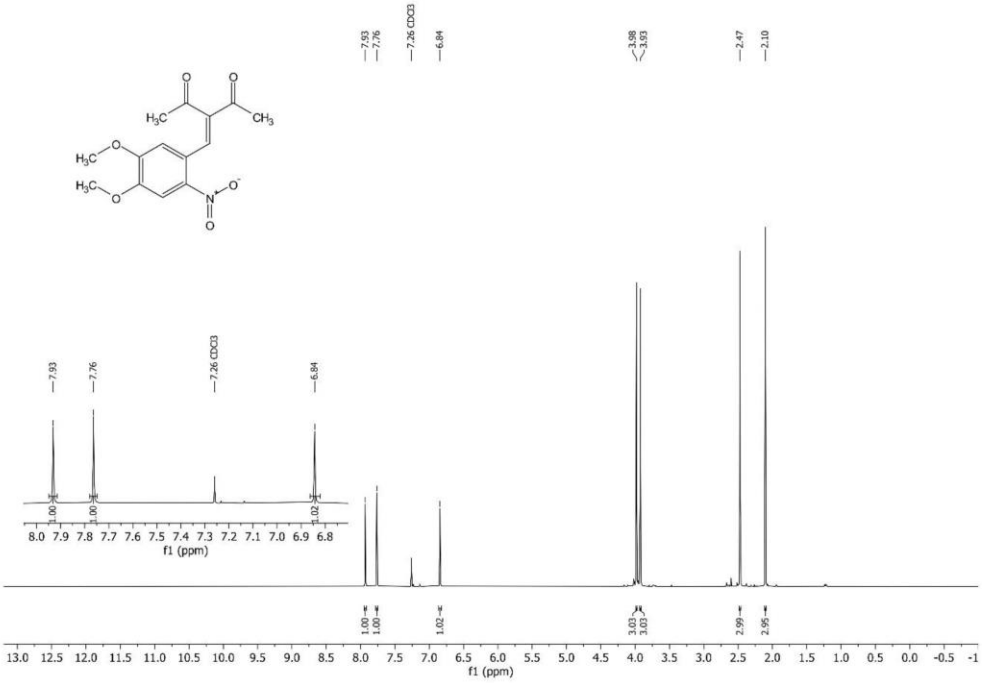
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-(5-chloro-2-nitrobenzylidene)pentane-2,4-dione (**8e**).



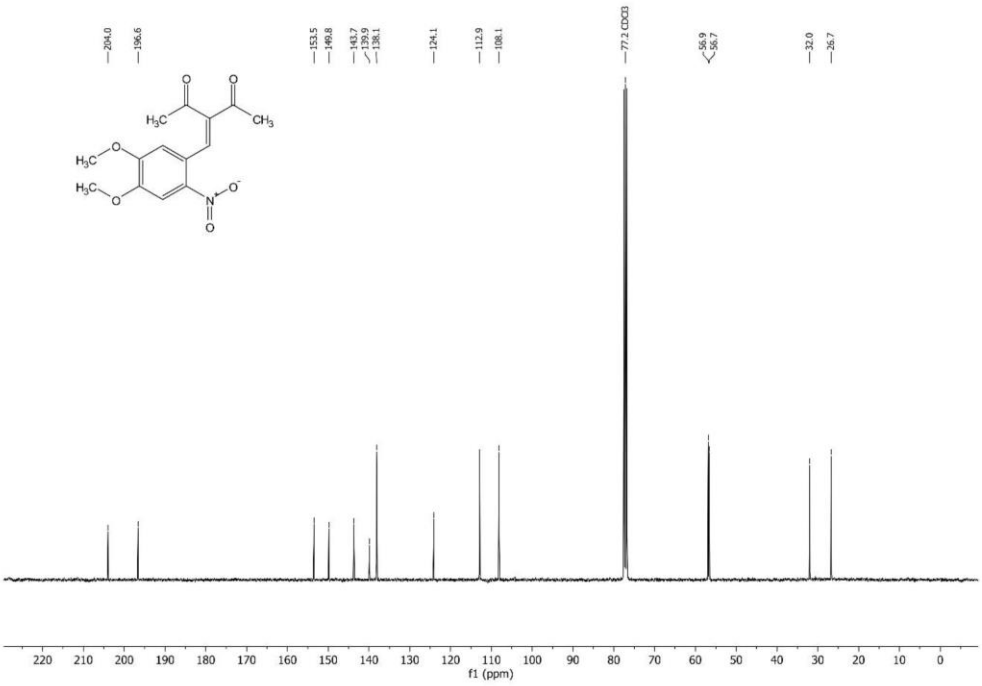
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-(5-bromo-2-nitrobenzylidene)pentane-2,4-dione (**8f**).



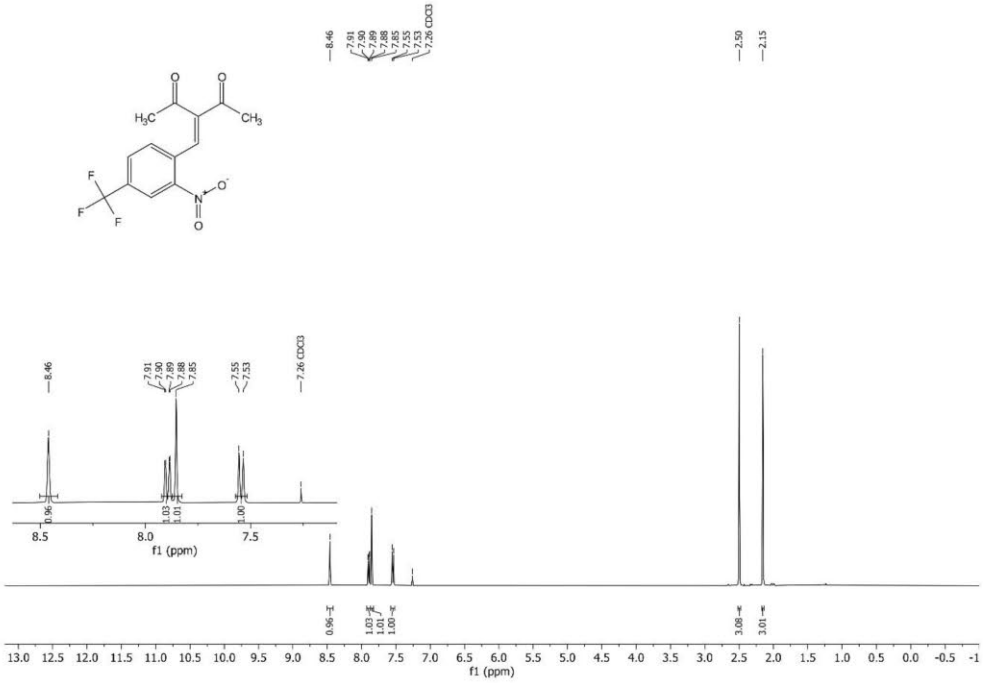
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-(5-bromo-2-nitrobenzylidene)pentane-2,4-dione (**8f**).



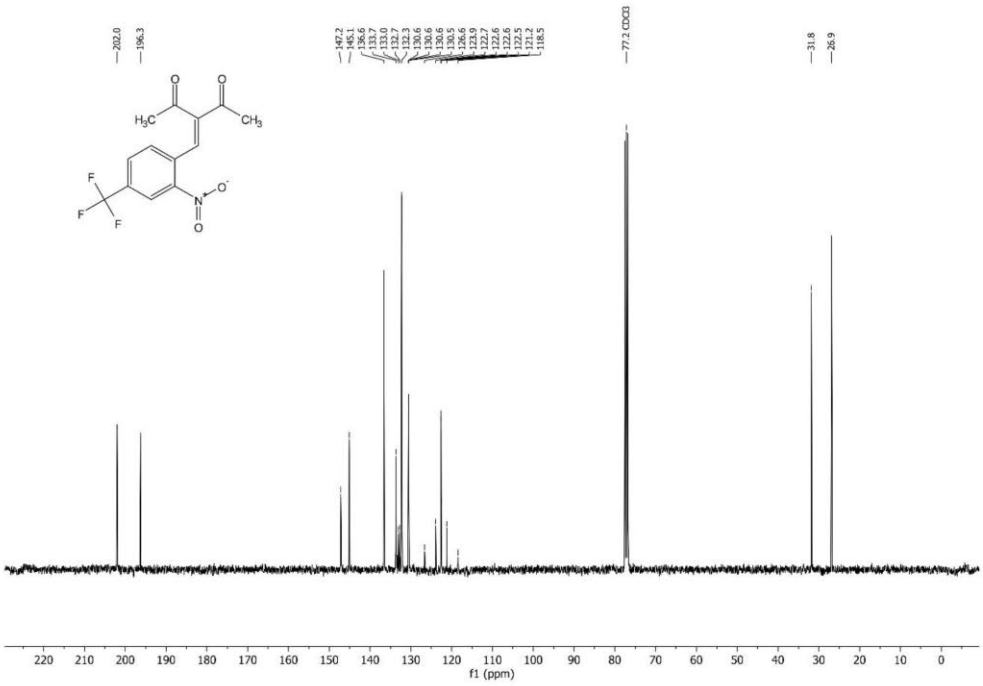
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-(4,5-dimethoxy-2-nitrobenzylidene)pentane-2,4-dione (**8g**).



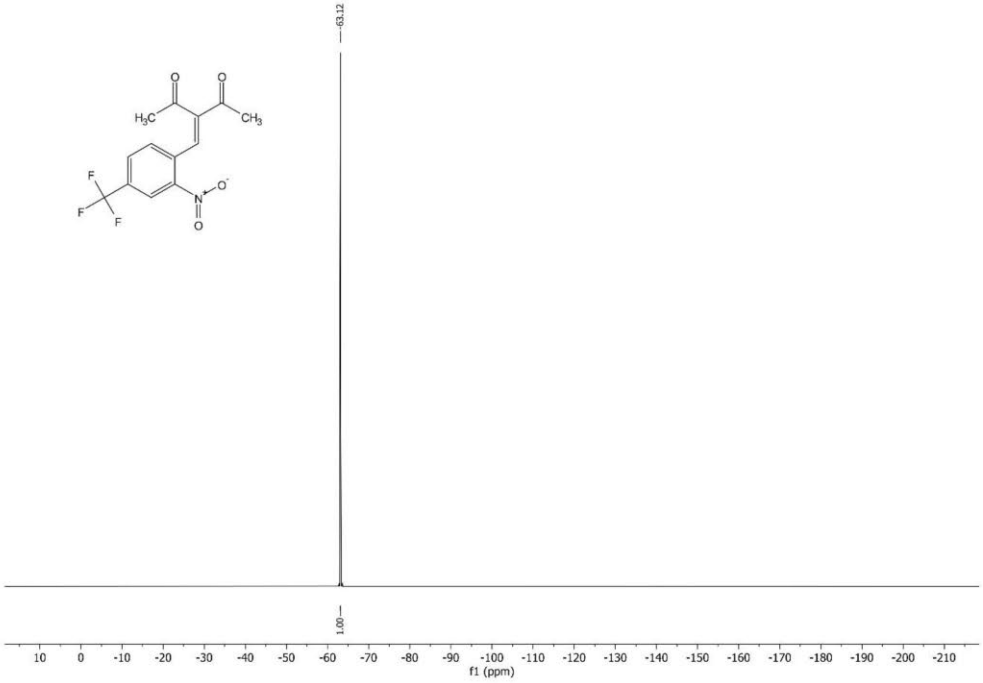
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-(4,5-dimethoxy-2-nitrobenzylidene)pentane-2,4-dione (**8g**).



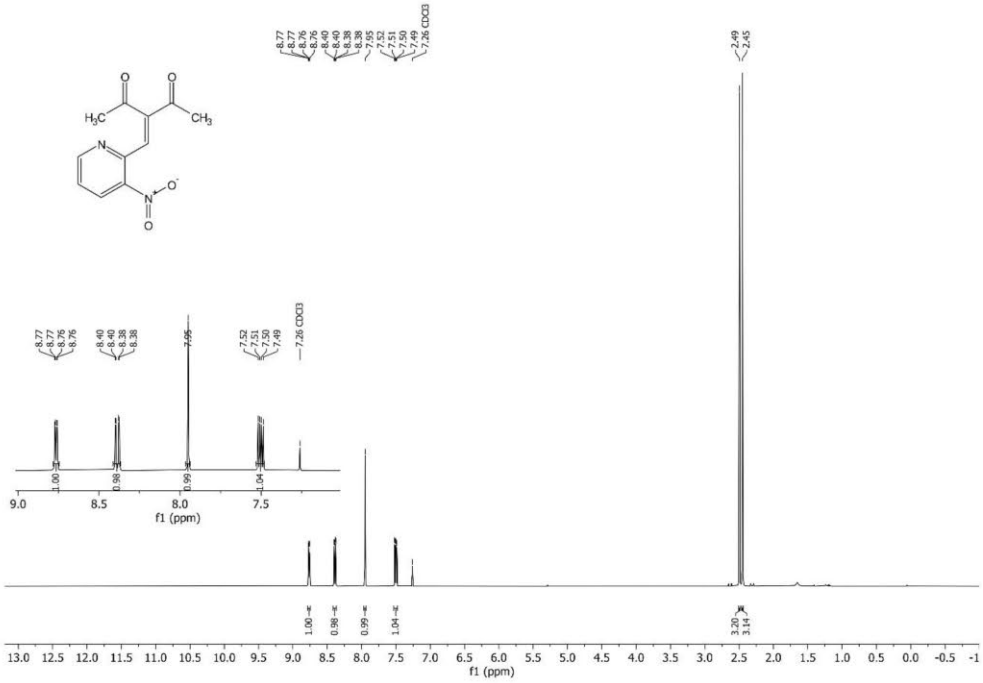
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-(2-nitro-4-(trifluoromethyl)benzylidene)pentane-2,4-dione (**8h**).



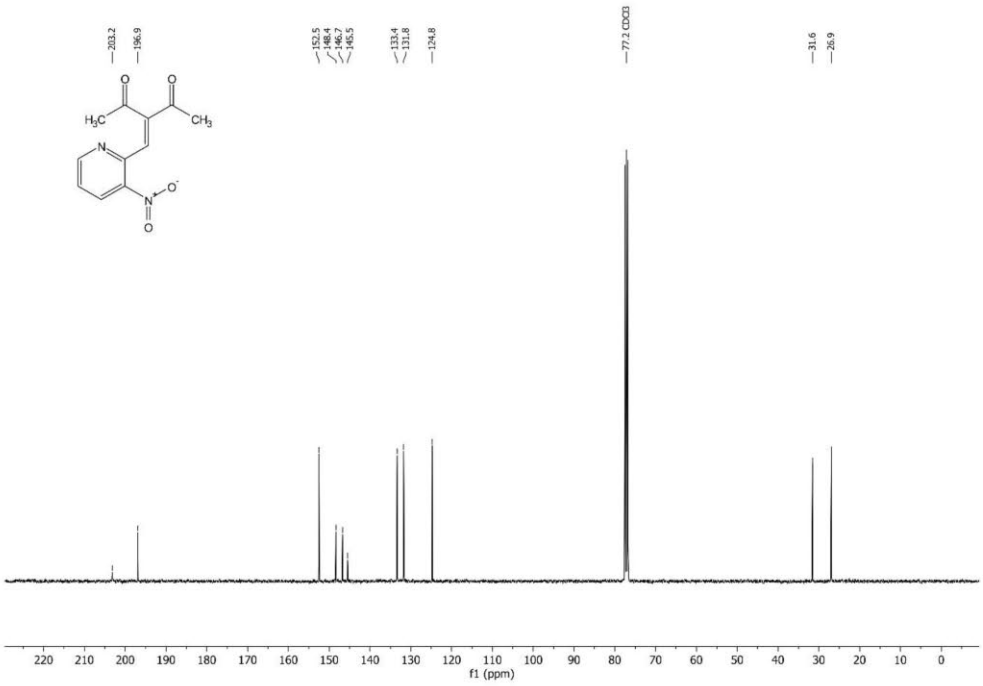
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-(2-nitro-4-(trifluoromethyl)benzylidene)pentane-2,4-dione (**8h**).



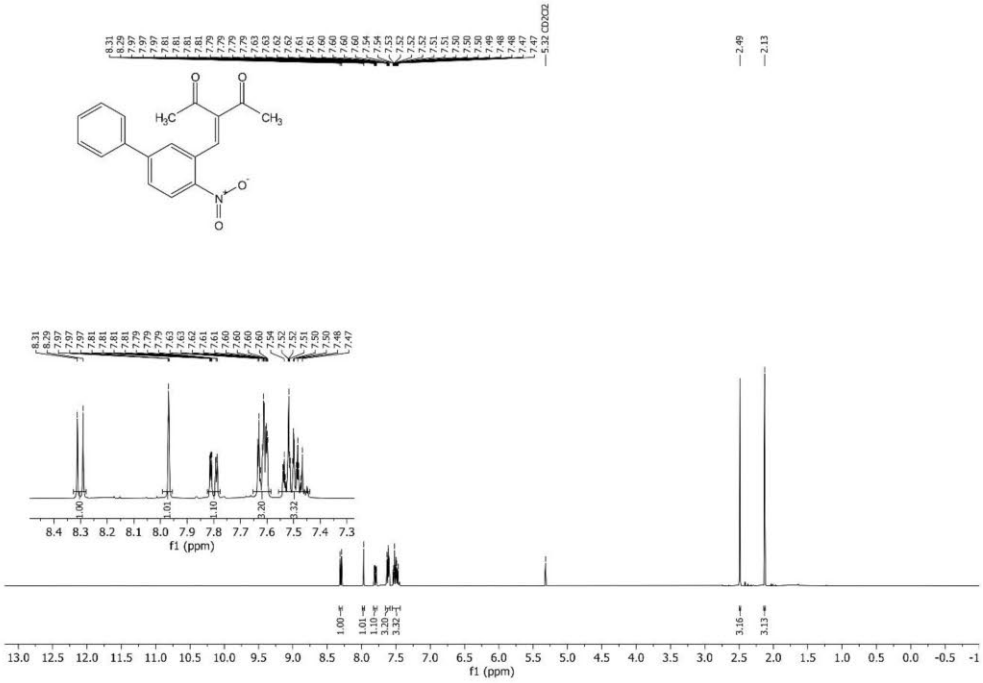
^{19}F NMR spectrum (282 MHz, $CDCl_3$) of 3-(2-nitro-4-(trifluoromethyl)benzylidene)pentane-2,4-dione (**8h**).



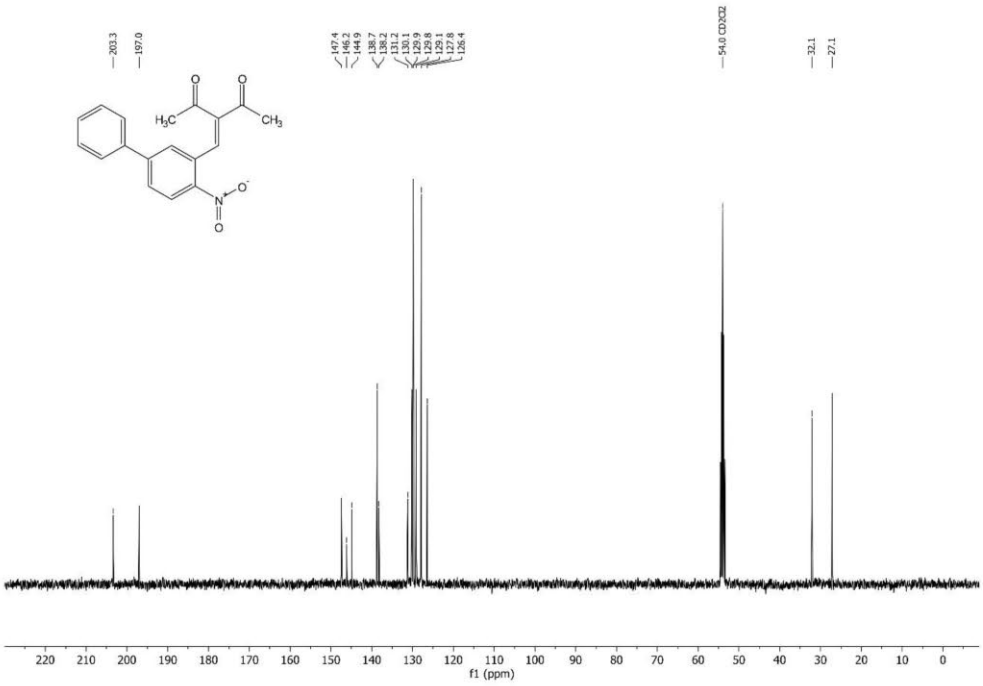
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-((3-nitropyridin-2-yl)methylene)pentane-2,4-dione (**8i**).



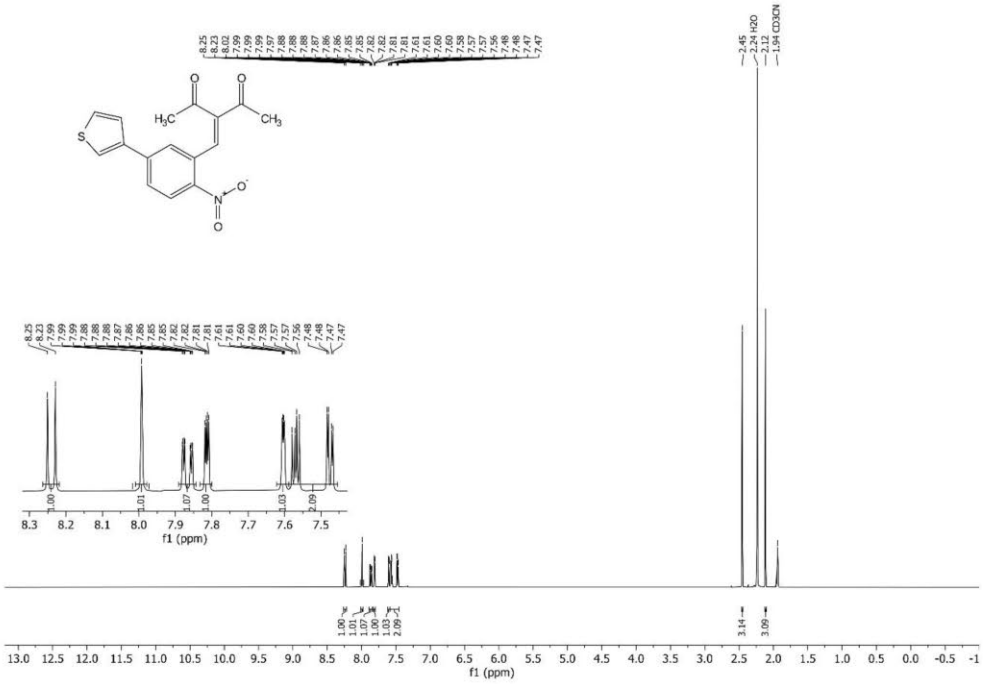
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-((3-nitropyridin-2-yl)methylene)pentane-2,4-dione (**8i**).



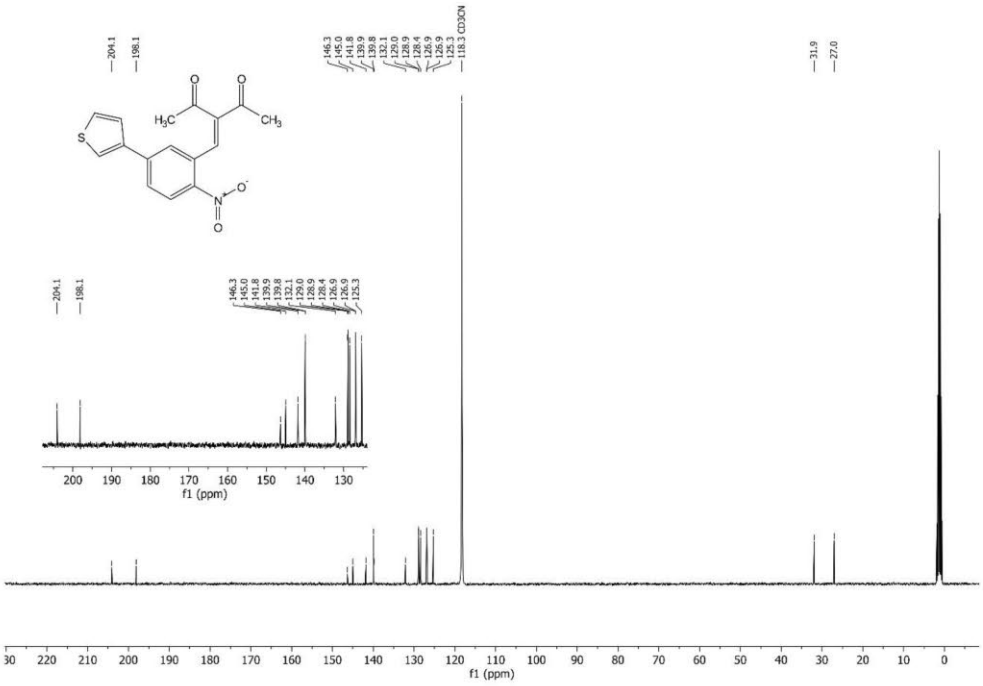
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-((4-nitro-(1,1'-biphenyl)-3-yl)methylene)pentane-2,4-dione (**8j**).



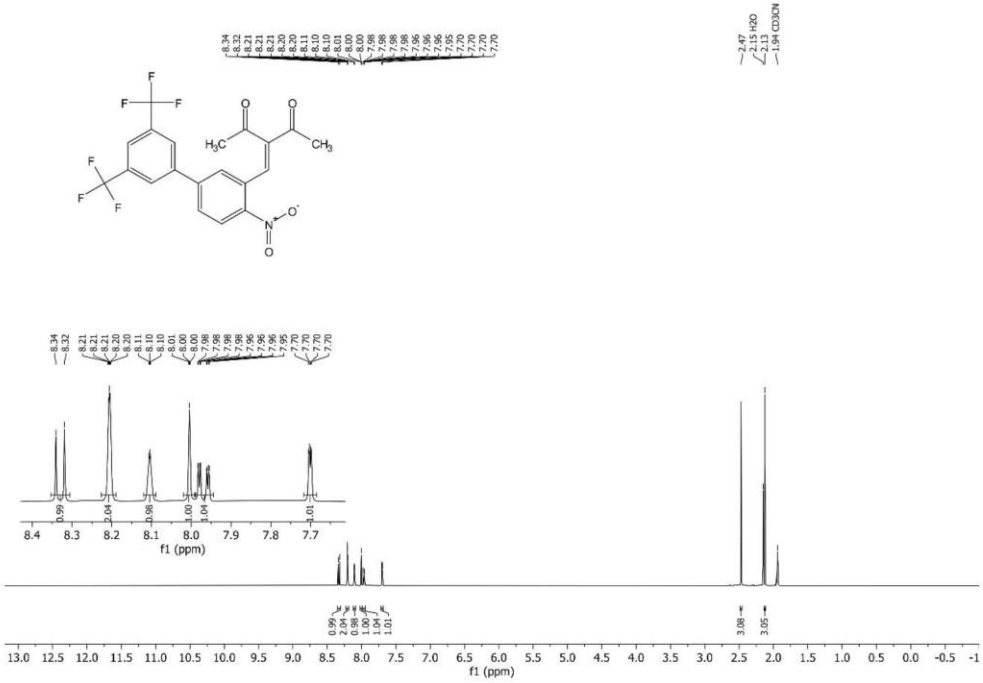
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-((4-nitro-(1,1'-biphenyl)-3-yl)methylene)pentane-2,4-dione (**8j**).



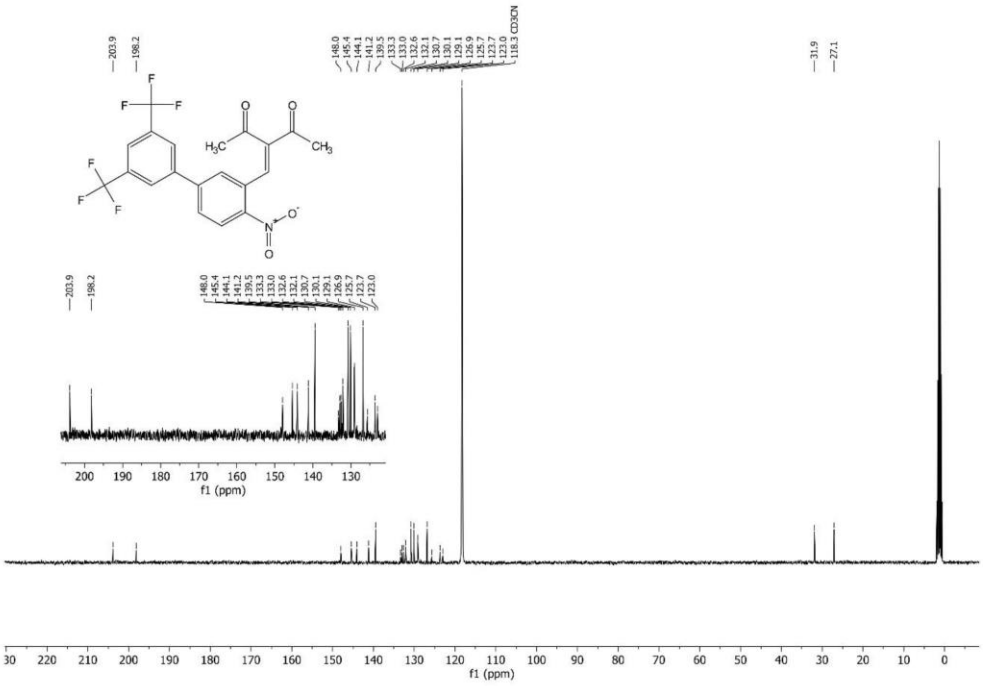
^{1}H NMR spectrum (400 MHz, CD_3CN) of 3-(2-nitro-5-(thien-3-yl)benzylidene)pentane-2,4-dione (**8k**).



^{13}C NMR spectrum (101 MHz, CD_3CN) of 3-(2-nitro-5-(thien-3-yl)benzylidene)pentane-2,4-dione (**8k**).



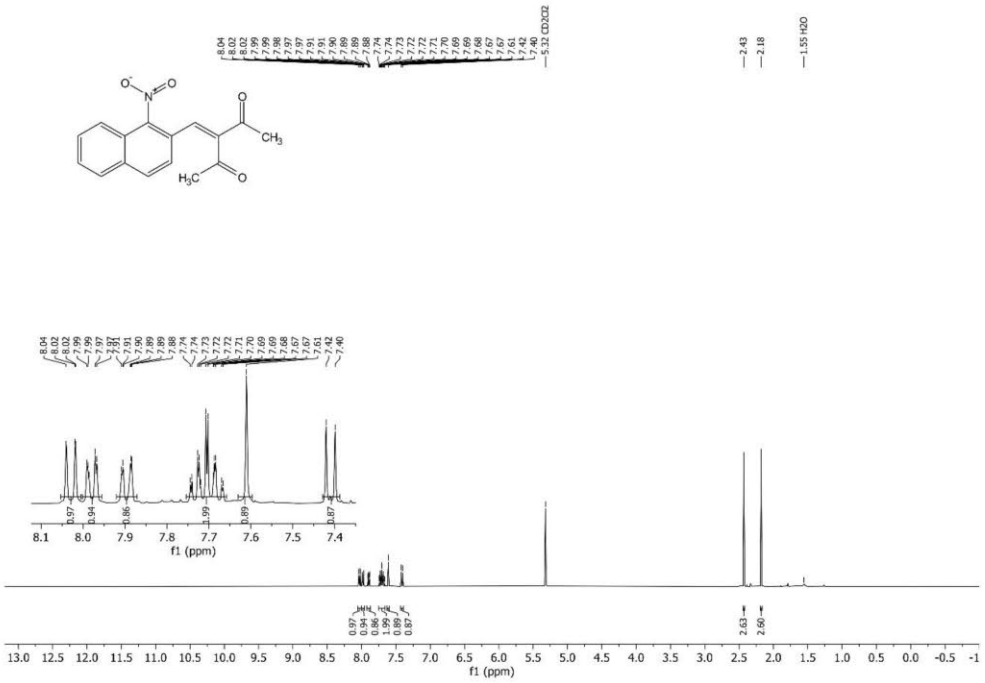
^{1}H NMR spectrum (400 MHz, CD_3CN) of 3-((4-nitro-3',5'-bis(trifluoromethyl)-(1,1'-biphenyl)-3-yl)methylene)pentane-2,4-dione (**8l**).



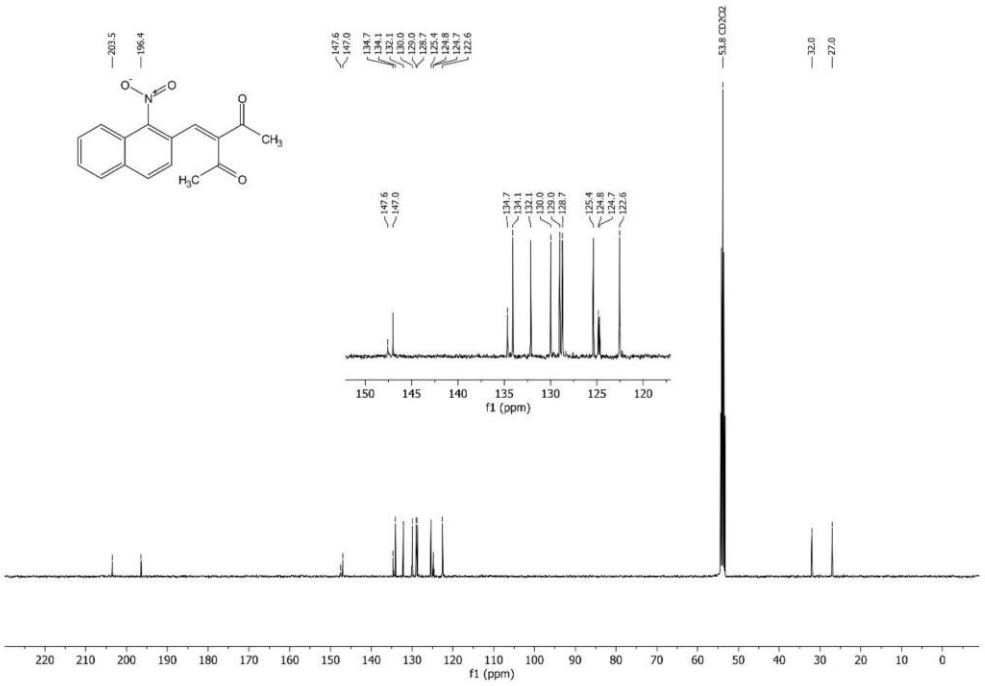
^{13}C NMR spectrum (101 MHz, CD_3CN) of 3-((4-nitro-3',5'-bis(trifluoromethyl)-(1,1'-biphenyl)-3-yl)methylene)pentane-2,4-dione (**8l**).



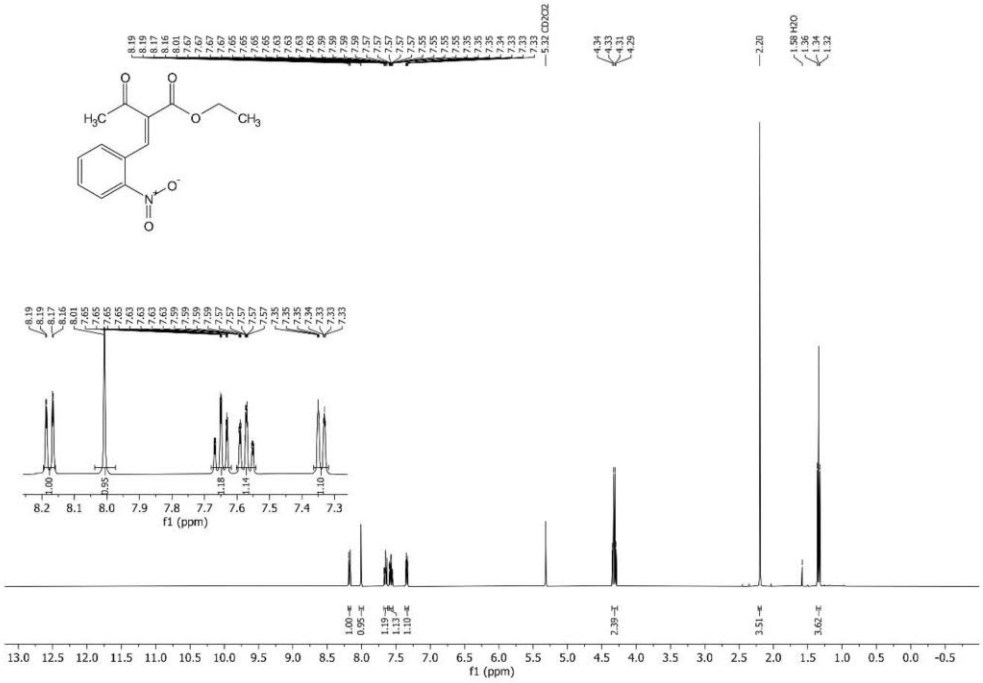
^{19}F NMR spectrum (282 MHz, CD_3CN) of 3-((4-nitro-3',5'-bis(trifluoromethyl)-(1,1'-biphenyl)-3-yl)methylene)pentane-2,4-dione (**8l**).



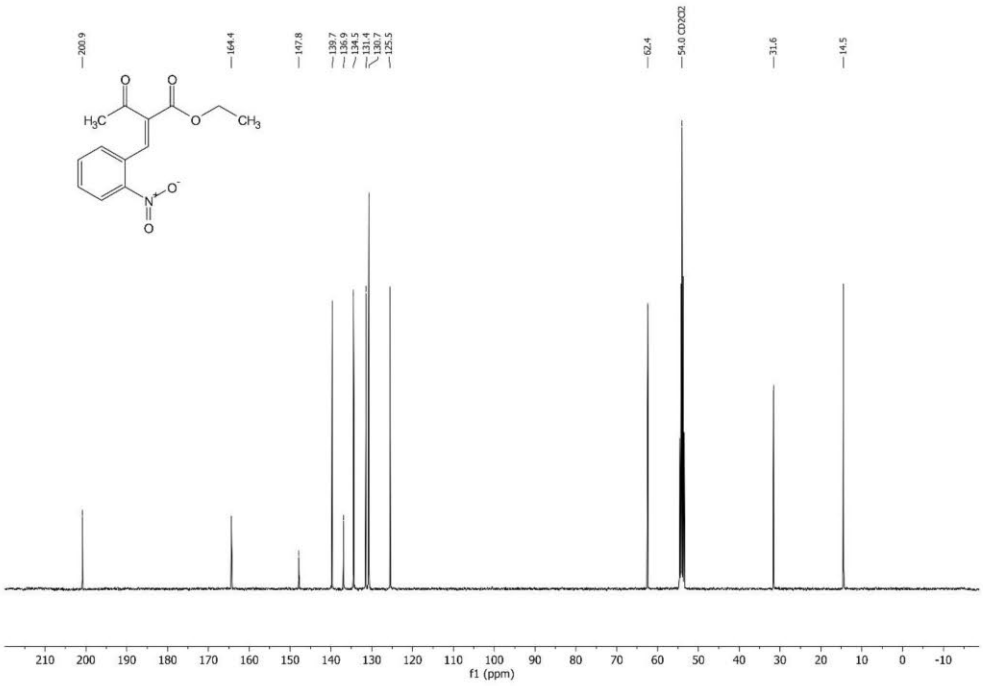
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-((1-nitronaphthalene-2-yl)methylene)pentane-2,4-dione (**8m**).



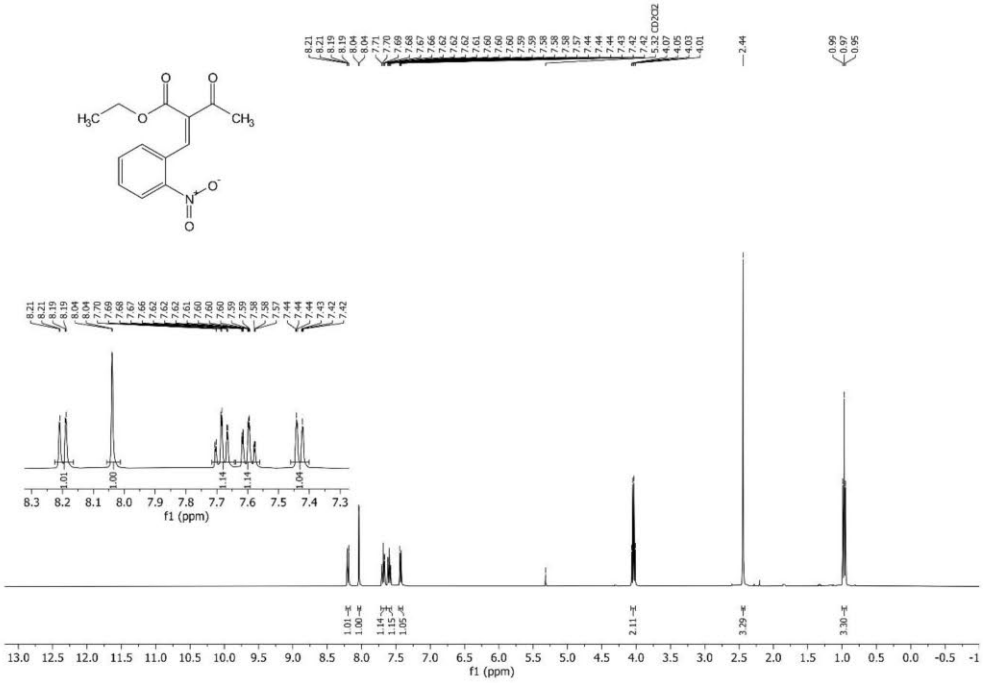
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-((1-nitronaphthalene-2-yl)methylene)pentane-2,4-dione (**8m**).



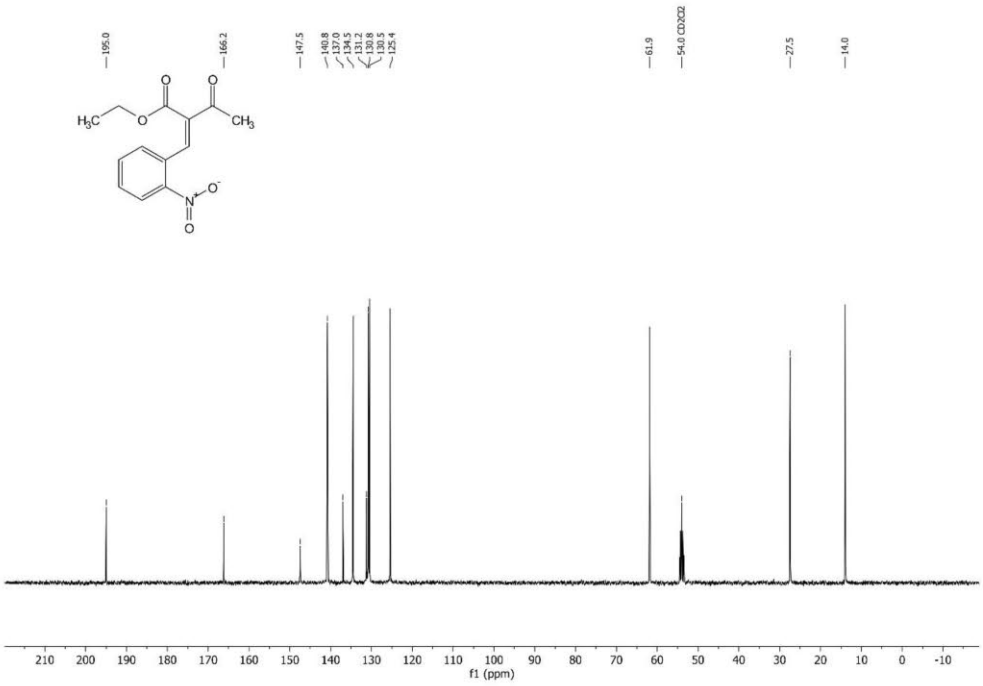
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of ethyl (*E*)-(2-nitrobenzylidene)-3-oxobutanoate (**8n**).



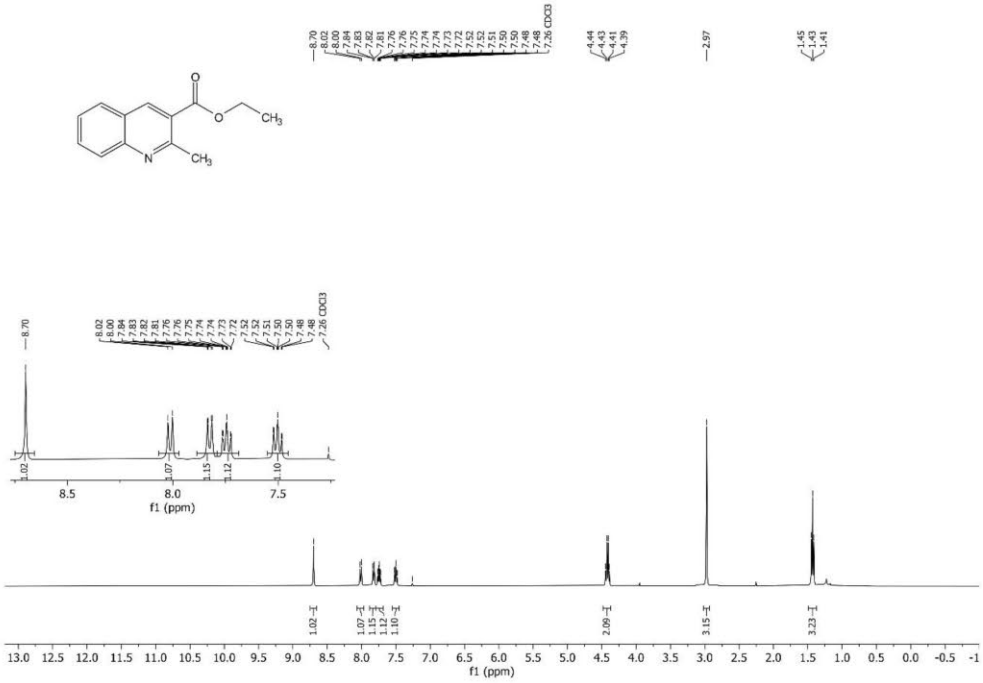
^{13}C NMR spectrum (101 MHz, CD_2Cl_2)) of ethyl (*E*)-(2-nitrobenzylidene)-3-oxobutanoate (**8n**).



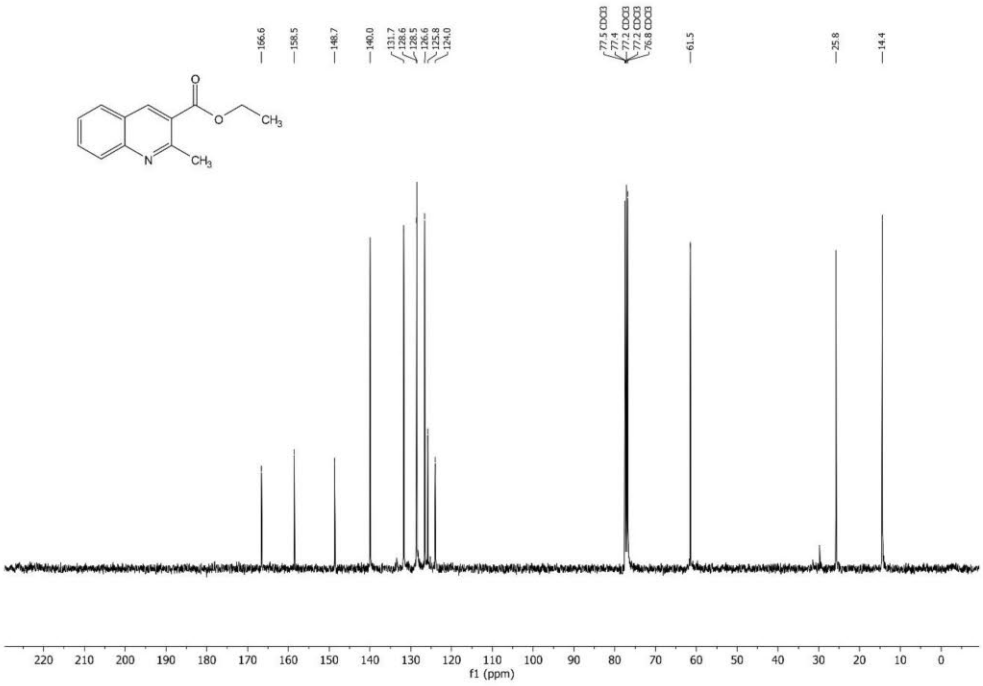
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of ethyl (*Z*)-(2-nitrobenzylidene)-3-oxobutanoate (**8o**).



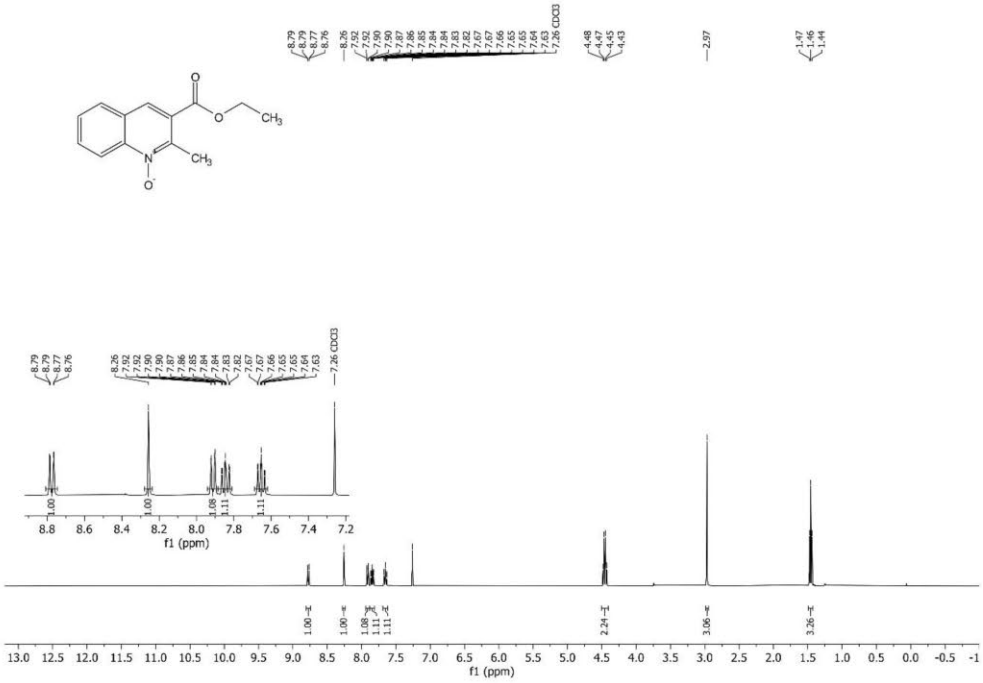
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of ethyl (*Z*)-(2-nitrobenzylidene)-3-oxobutanoate (**8o**).



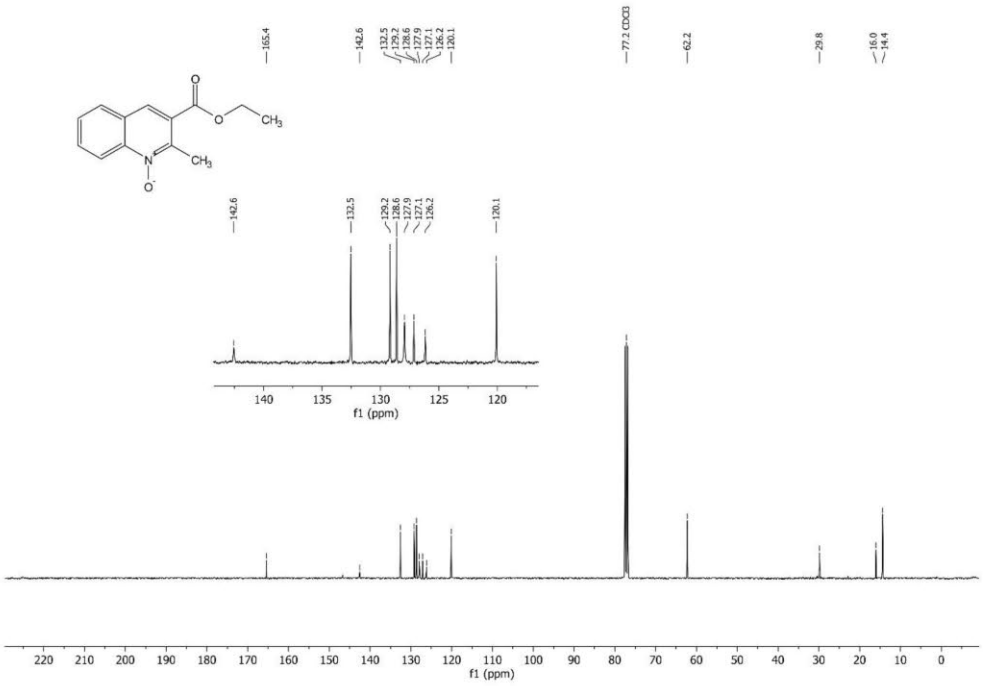
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-(ethoxycarbonyl)-2-methylquinoline (**5a**).



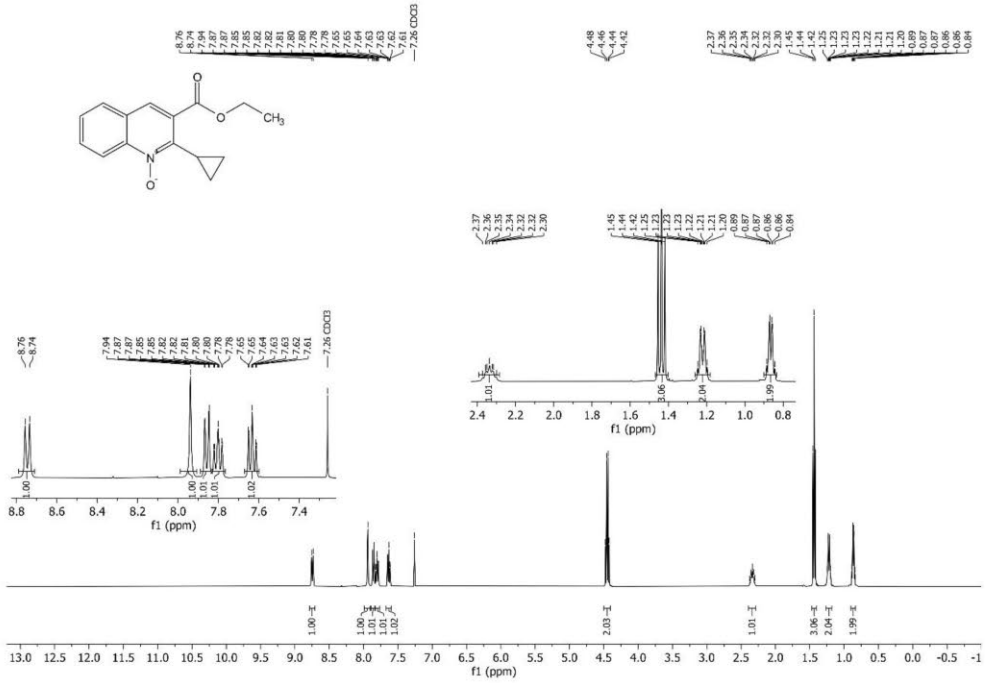
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-(ethoxycarbonyl)-2-methylquinoline (**5a**).



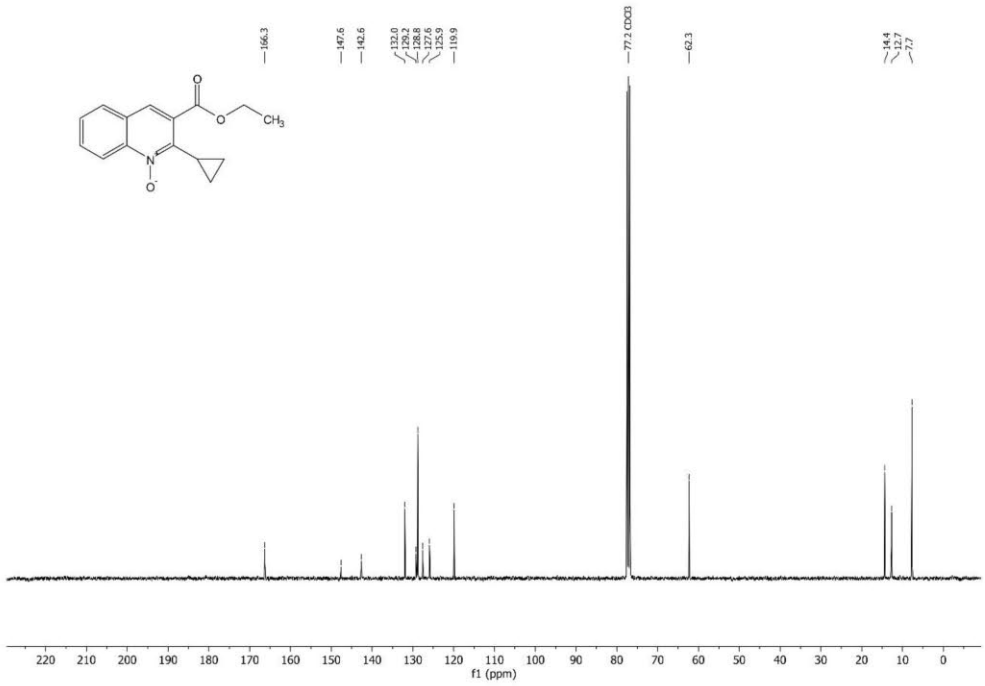
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-(ethoxycarbonyl)-2-methylquinoline 1-oxide (**6a**).



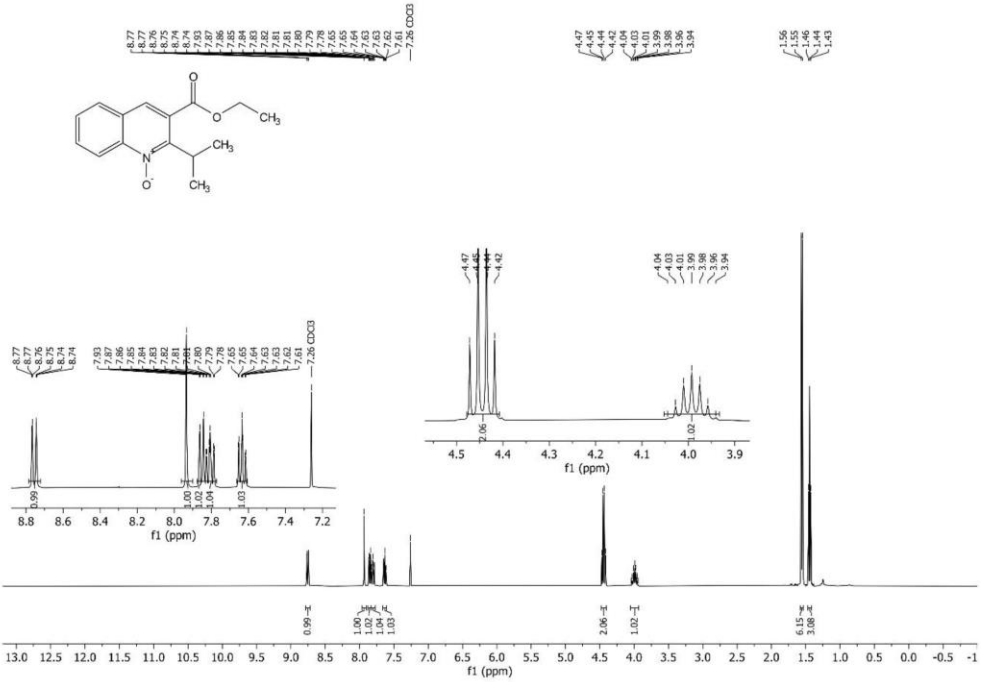
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-(ethoxycarbonyl)-2-methylquinoline 1-oxide (**6a**).



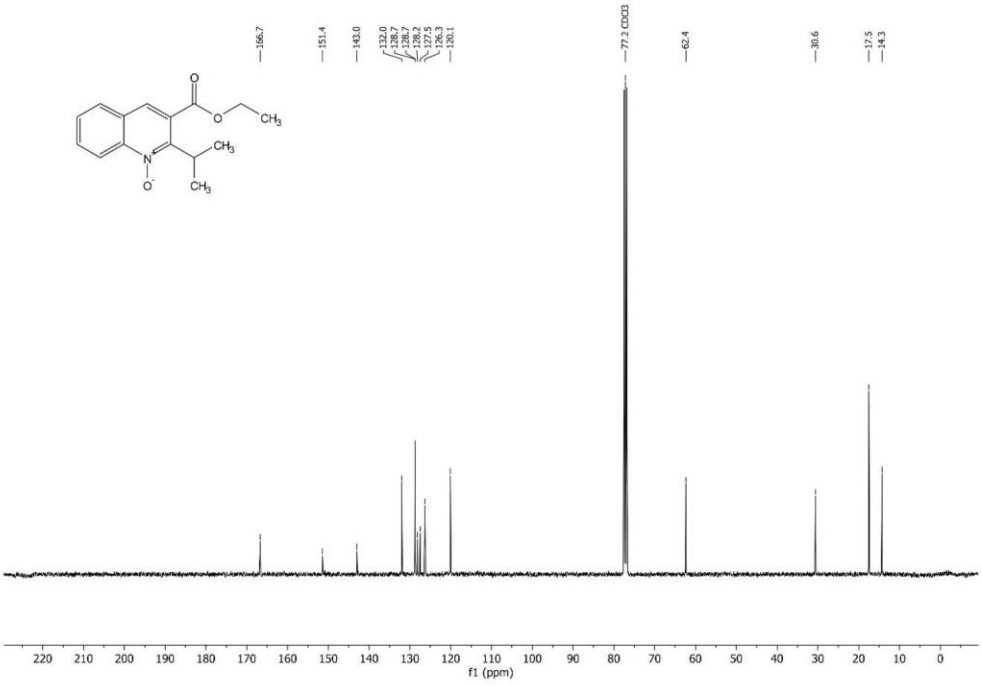
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-cyclopropyl-3-(ethoxycarbonyl)quinoline 1-oxide (**6b**).



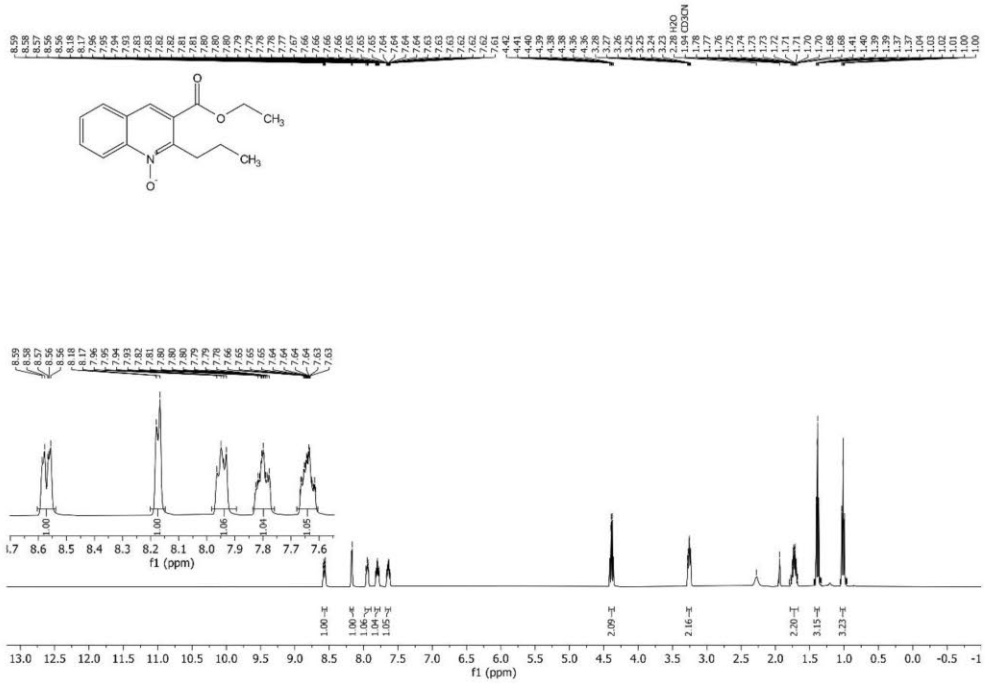
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 2-cyclopropyl-3-(ethoxycarbonyl)quinoline 1-oxide (**6b**).



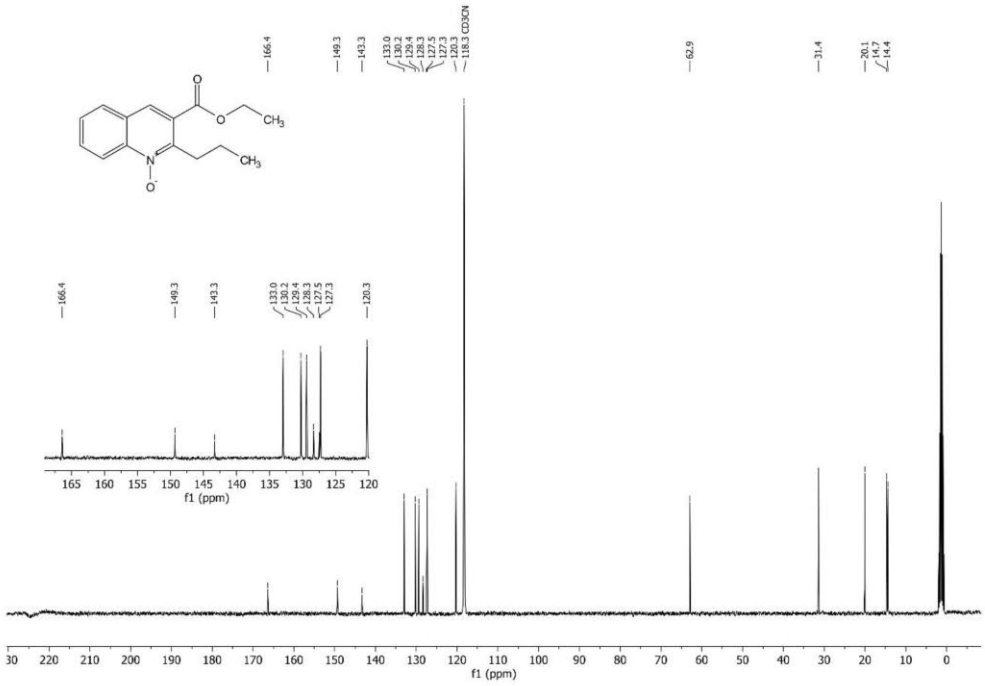
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-(ethoxycarbonyl)-2-isopropylquinoline 1-oxide (**6c**).



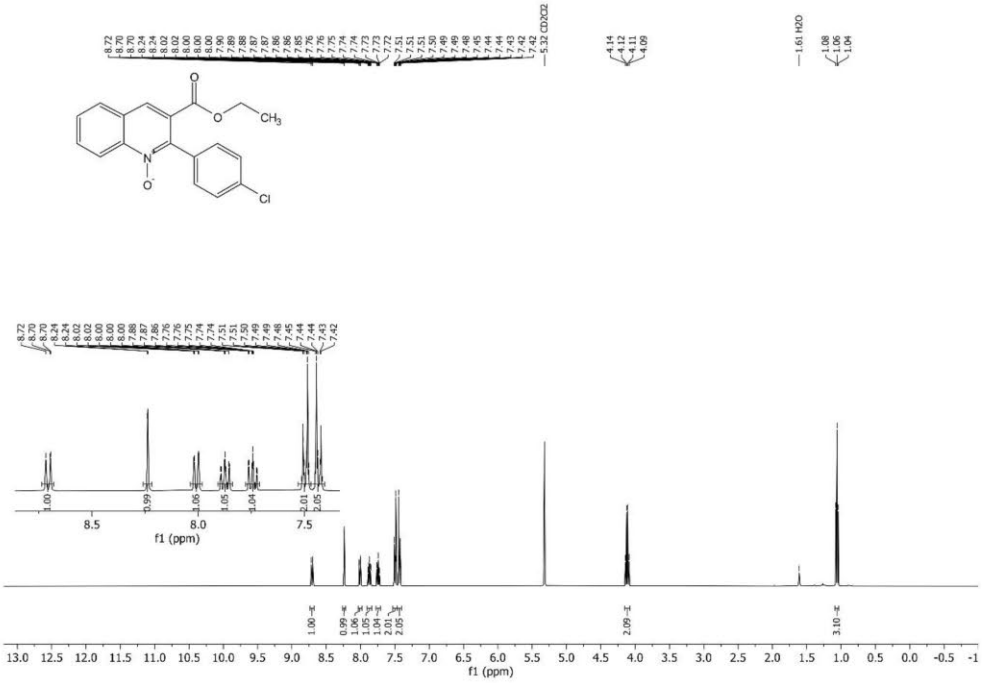
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-(ethoxycarbonyl)-2-isopropylquinoline 1-oxide (**6c**).



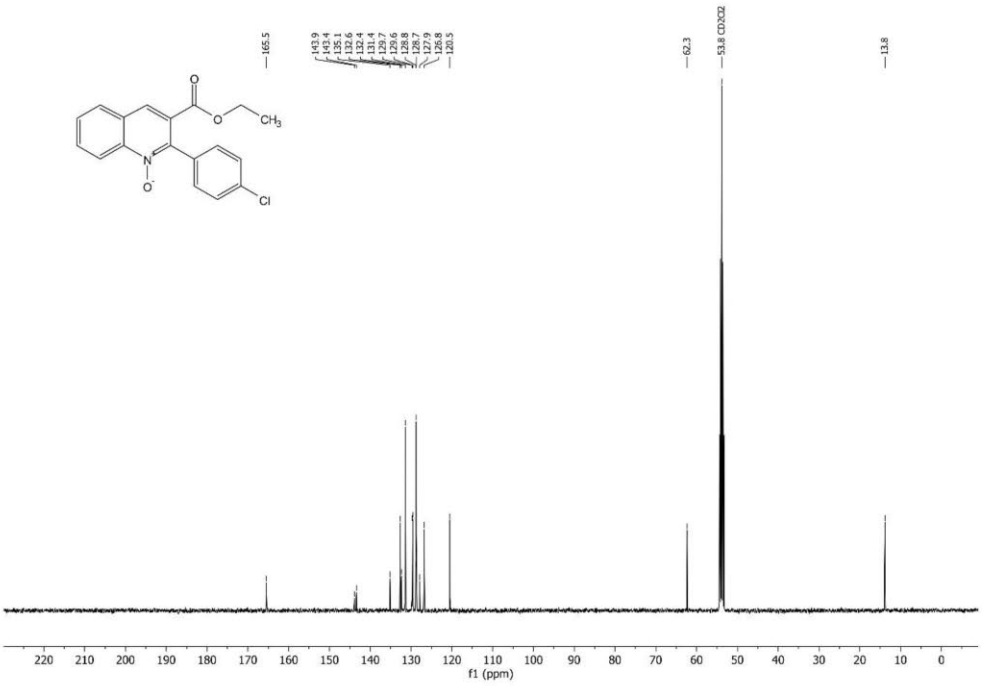
^{1}H NMR spectrum (400 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-propylquinoline 1-oxide (**6d**).



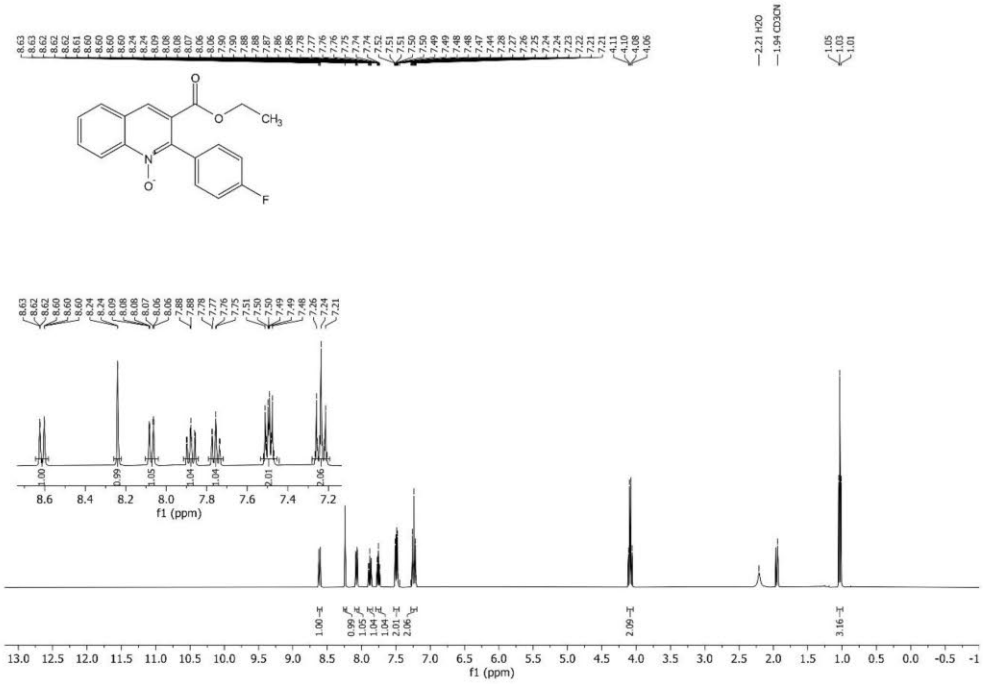
^{13}C NMR spectrum (101 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-propylquinoline 1-oxide (**6d**).



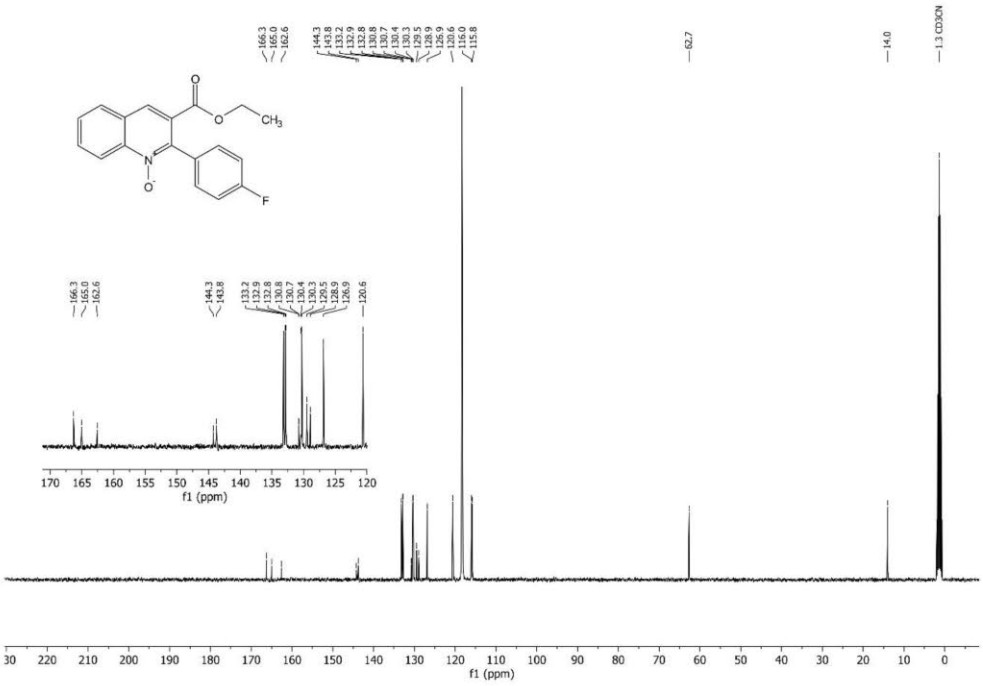
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-(ethoxycarbonyl)-2-(4-chlorophenyl)quinoline 1-oxide (**6e**).



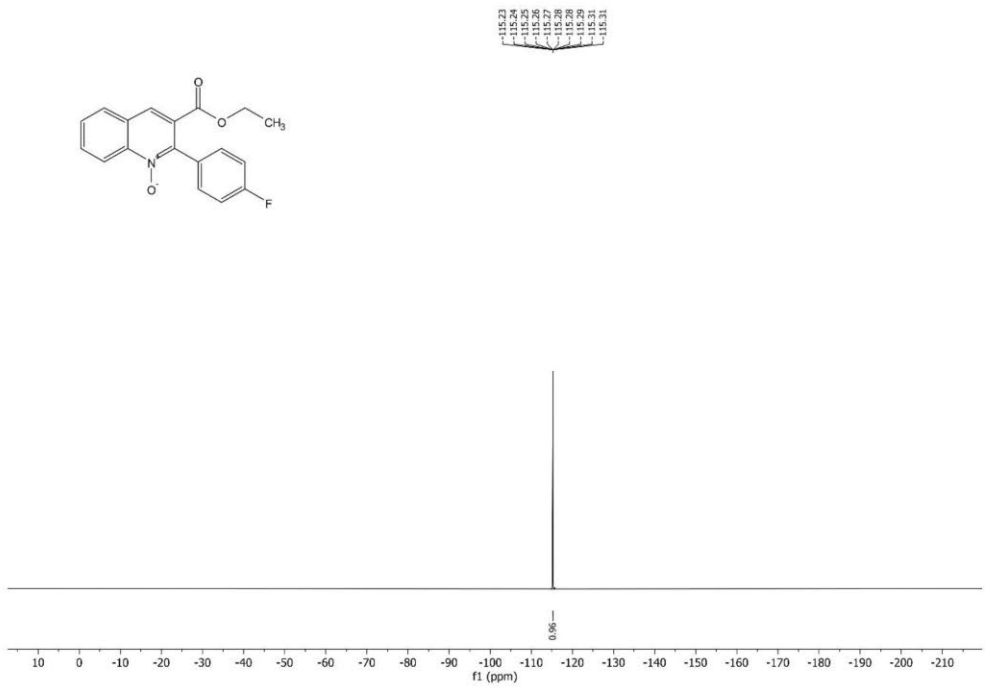
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-(ethoxycarbonyl)-2-(4-chlorophenyl)quinoline 1-oxide (**6e**).



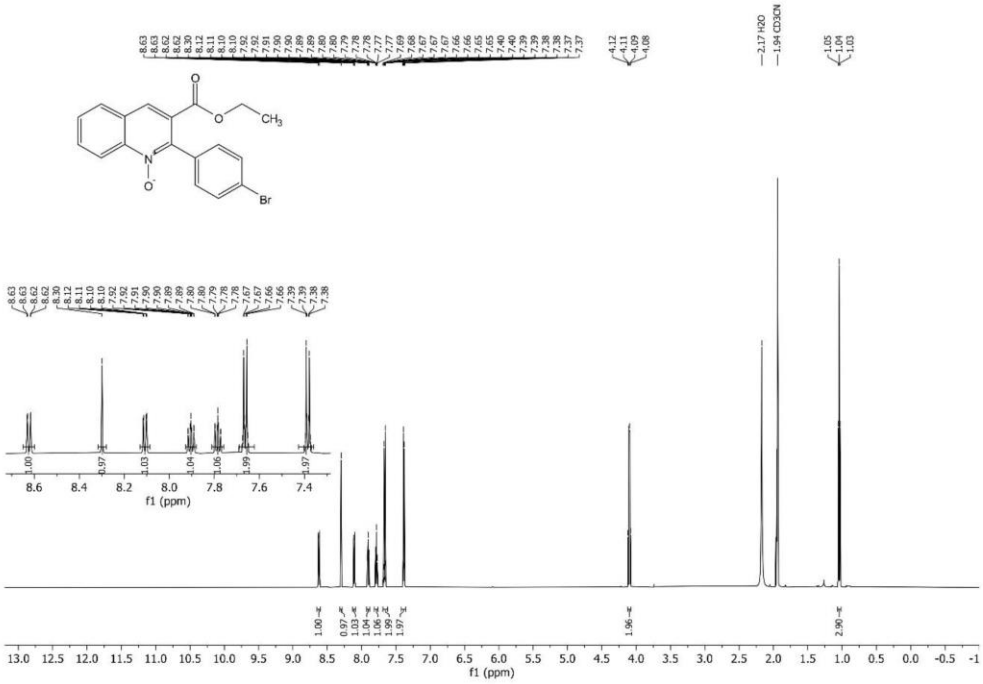
^{1}H NMR spectrum (400 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(4-fluorophenyl)quinoline 1-oxide (**6f**).



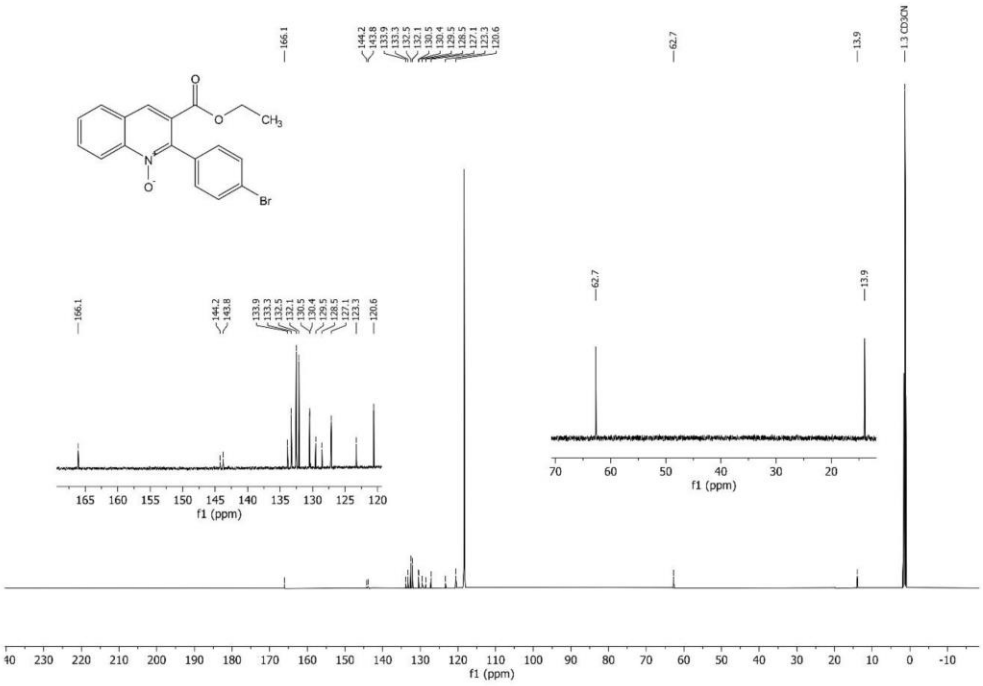
^{13}C NMR spectrum (101 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(4-fluorophenyl)quinoline 1-oxide (**6f**).



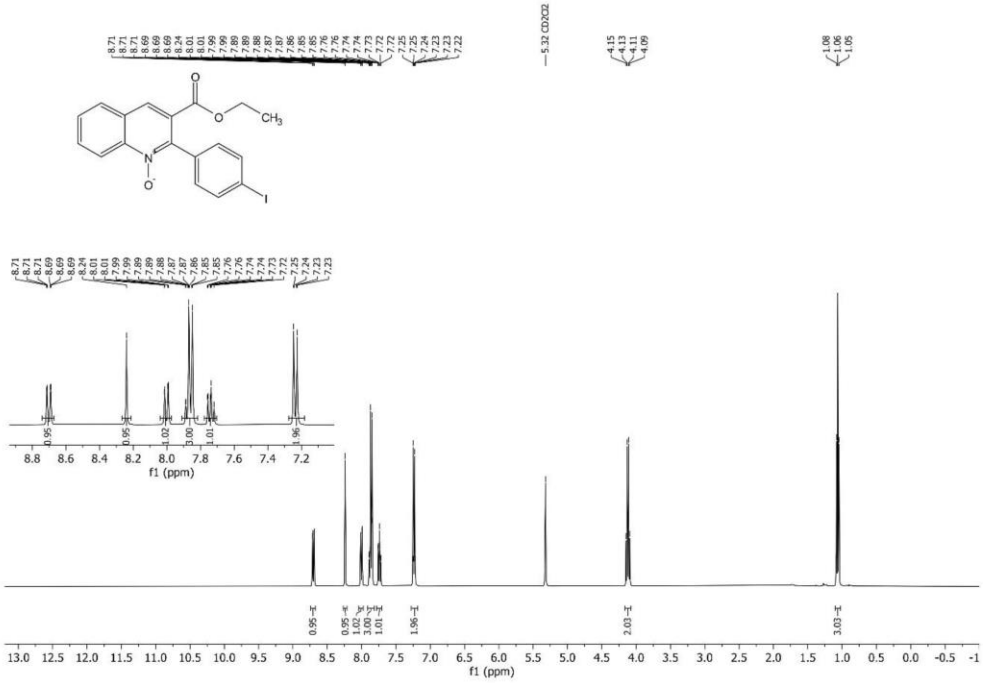
^{19}F NMR spectrum (376 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(4-fluorophenyl)quinoline 1-oxide (**6f**).



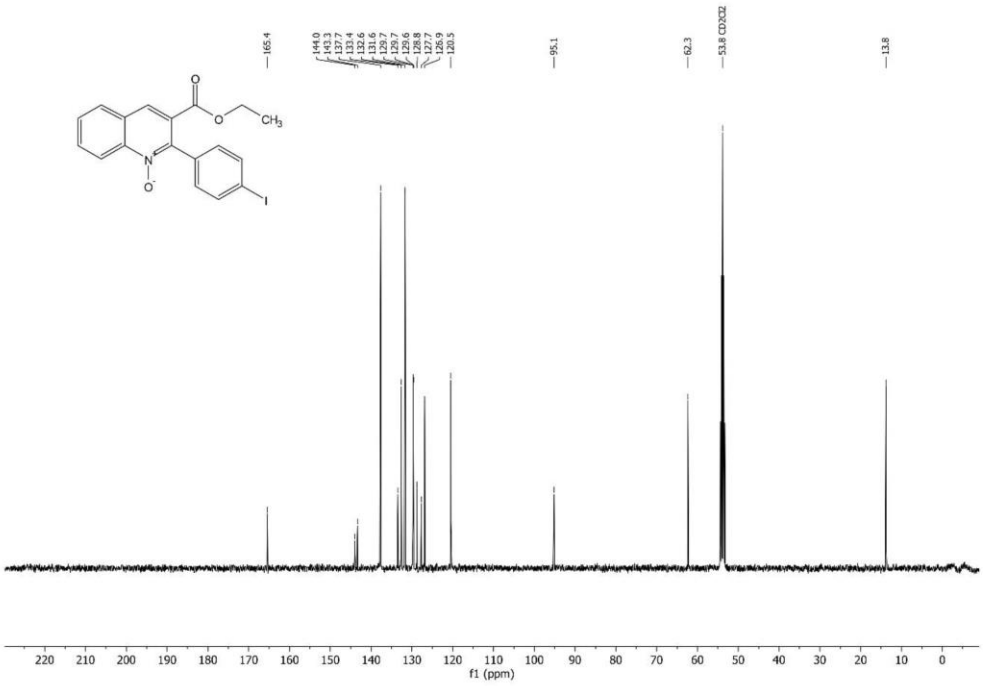
^{1}H NMR spectrum (600 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(4-bromophenyl)quinoline 1-oxide (**6g**).



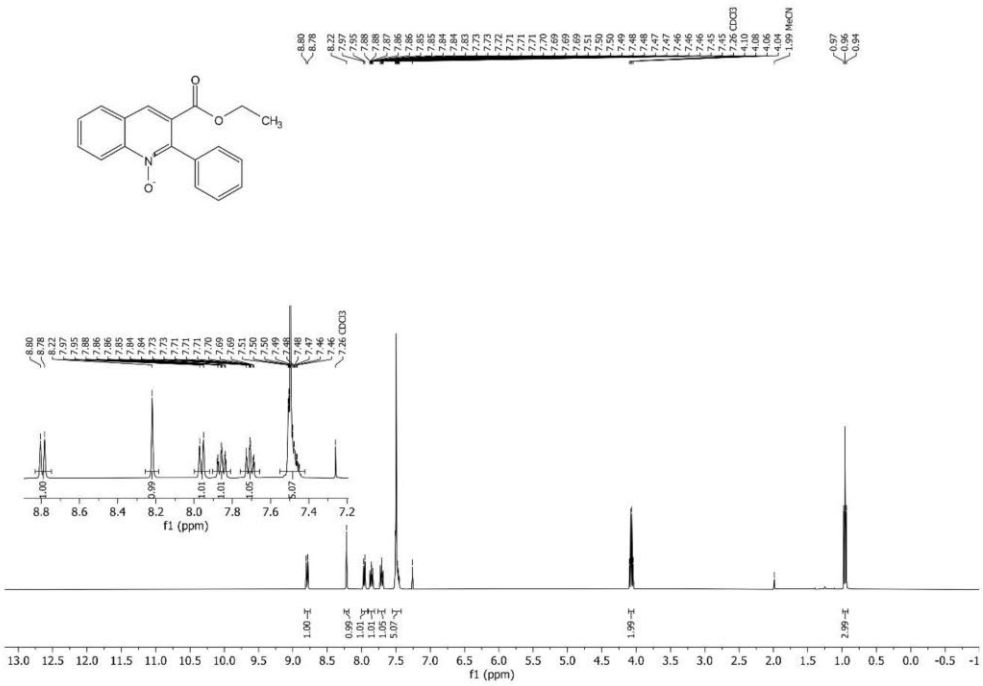
^{13}C NMR spectrum (151 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(4-bromophenyl)quinoline 1-oxide (**6g**).



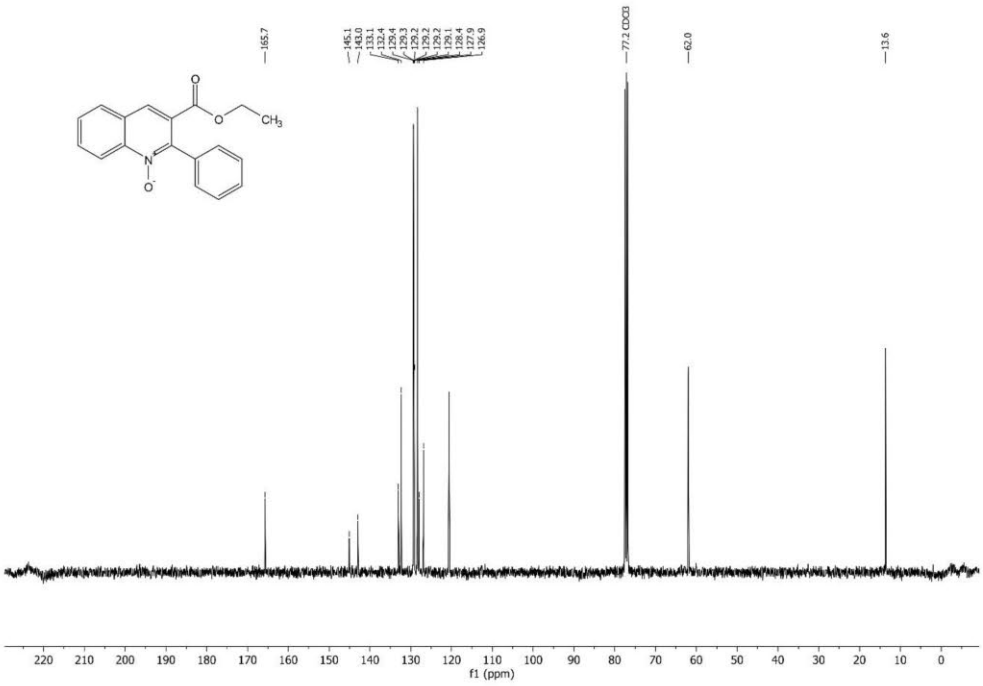
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-(ethoxycarbonyl)-2-(4-iodophenyl)quinoline 1-oxide (**6h**).



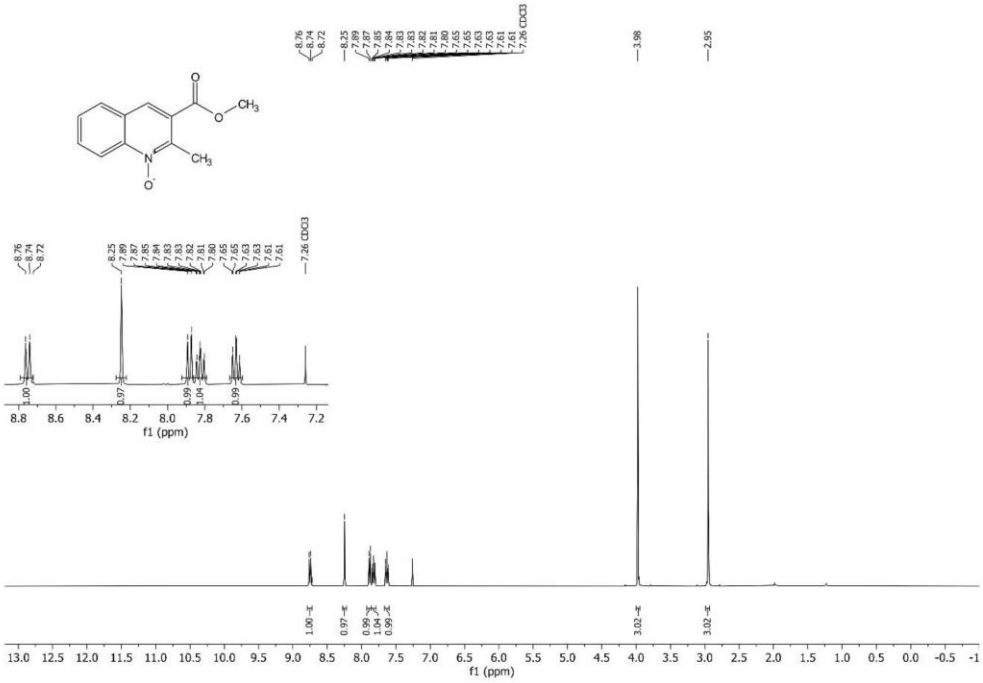
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-(ethoxycarbonyl)-2-(4-iodophenyl)quinoline 1-oxide (**6h**).



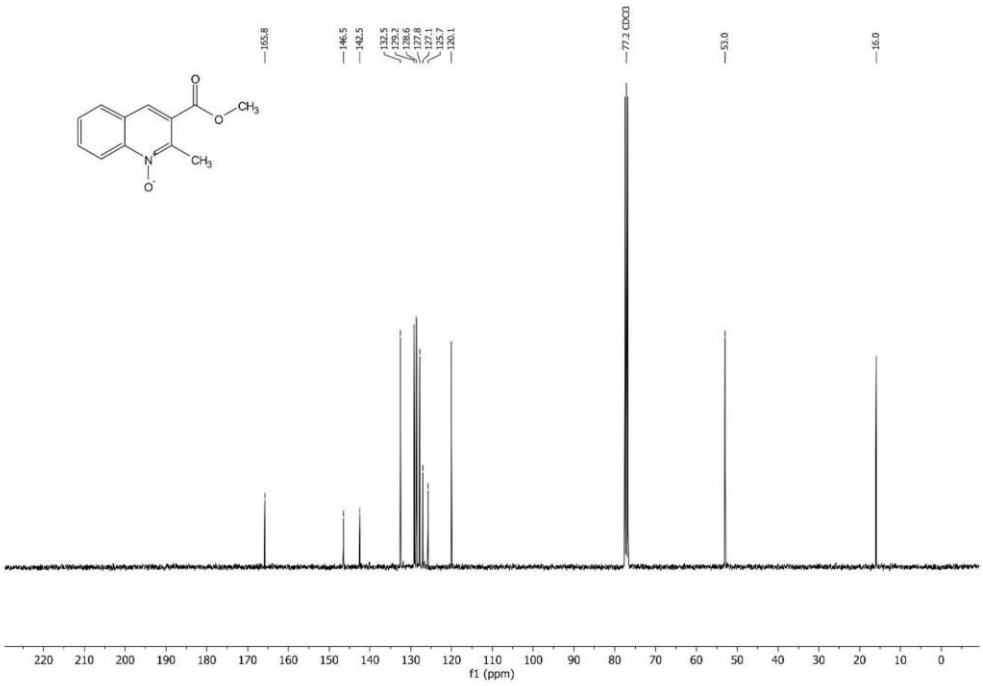
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-(ethoxycarbonyl)-2-phenylquinoline 1-oxide (**6i**).



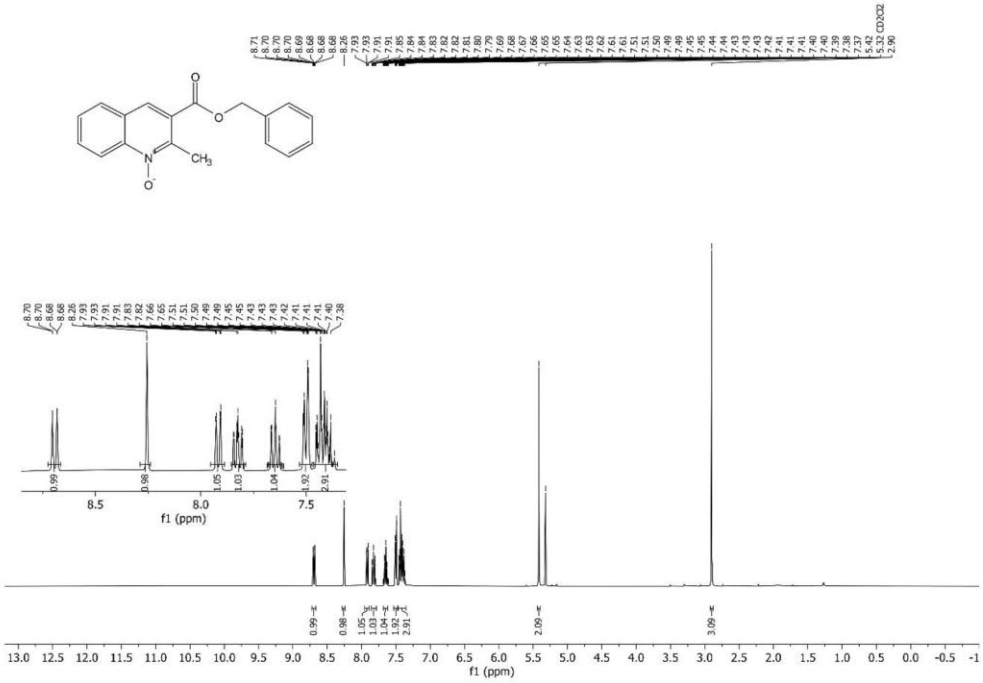
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-(ethoxycarbonyl)-2-phenylquinoline 1-oxide (**6i**).



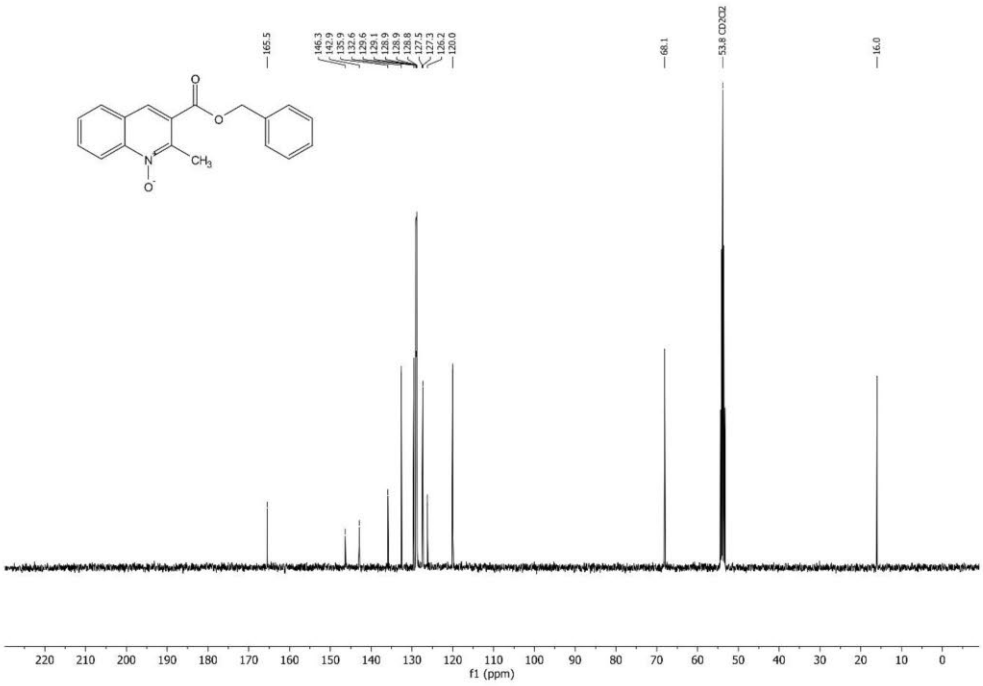
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-(methoxycarbonyl)-2-methylquinoline 1-oxide (**6j**).



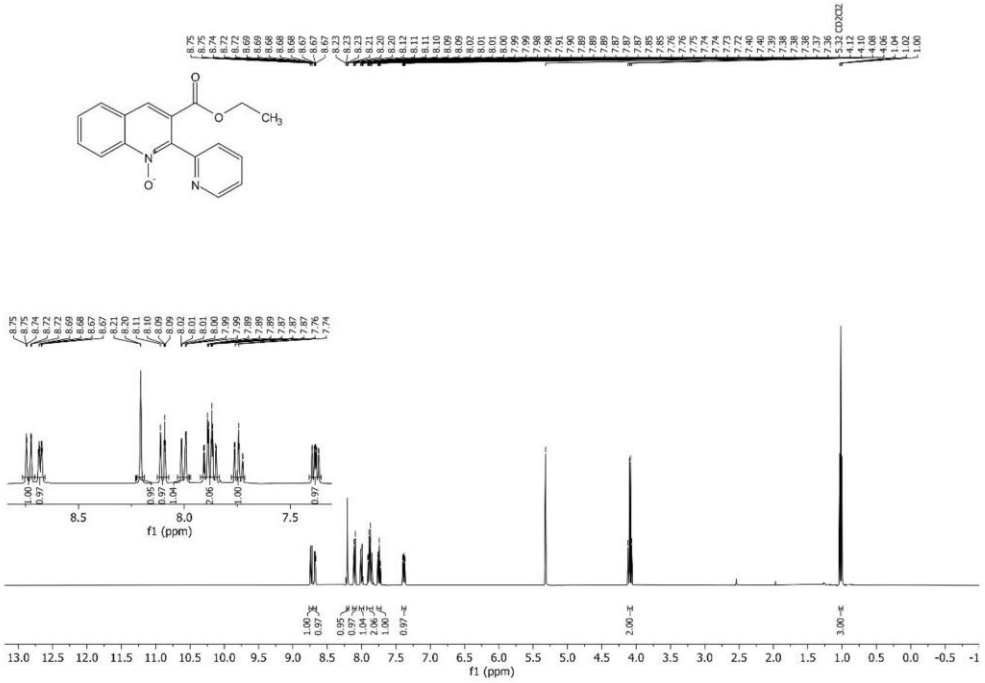
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-(methoxycarbonyl)-2-methylquinoline 1-oxide (**6j**).



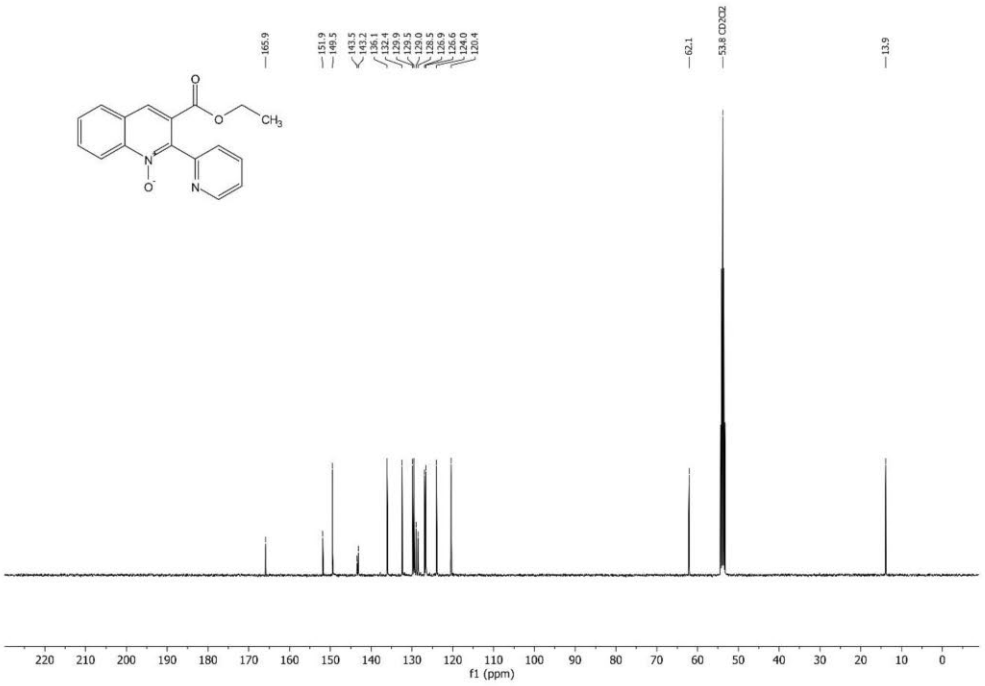
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-((benzyloxy)carbonyl)-2-methylquinoline 1-oxide (**6k**).



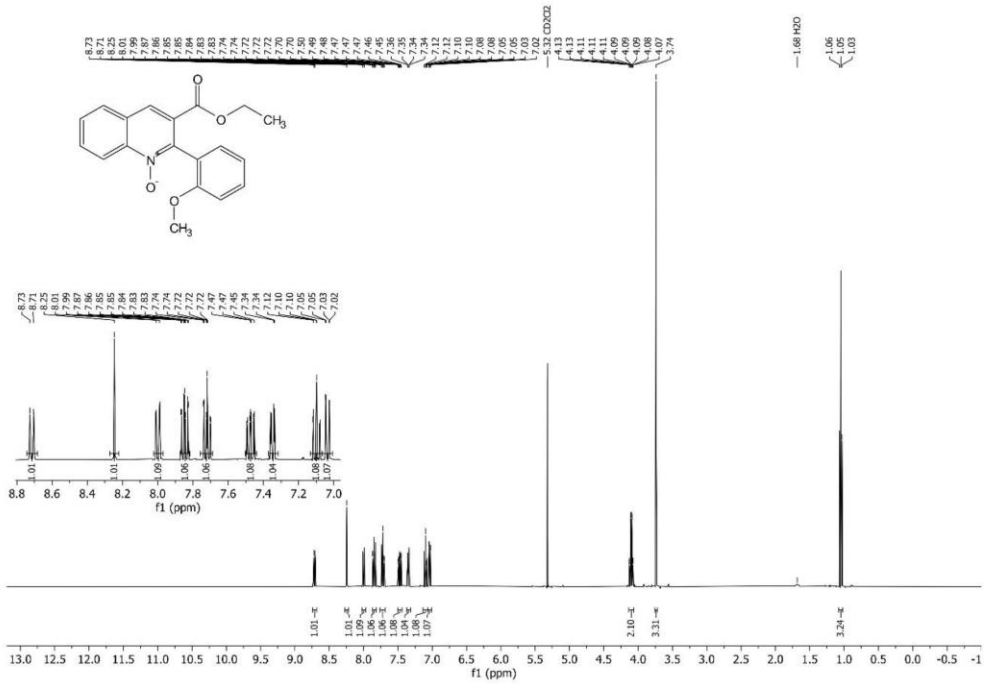
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-((benzyloxy)carbonyl)-2-methylquinoline 1-oxide (**6k**).



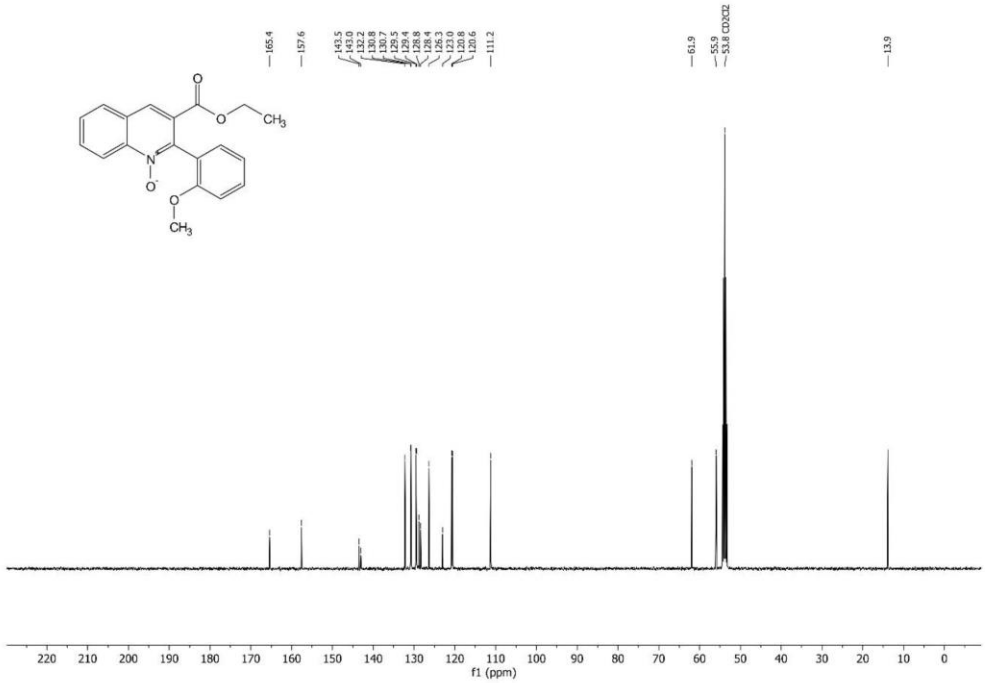
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-(ethoxycarbonyl)-2-(pyridin-2-yl)quinoline 1-oxide (**6l**).



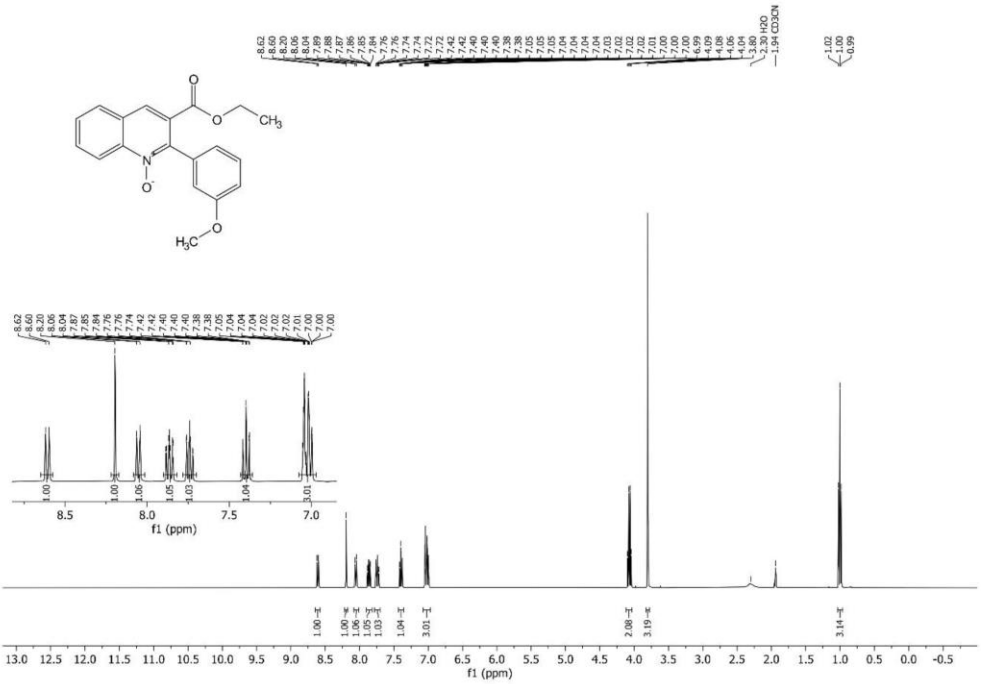
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-(ethoxycarbonyl)-2-(pyridin-2-yl)quinoline 1-oxide (**6l**).



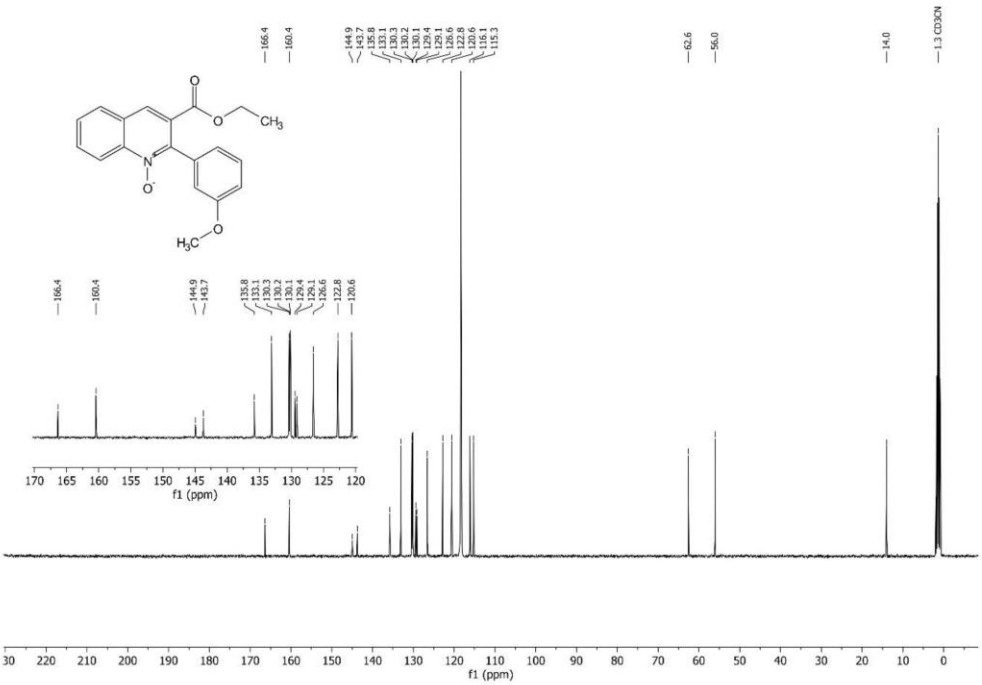
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-(ethoxycarbonyl)-2-(2-methoxyphenyl)quinoline 1-oxide (**6m**).



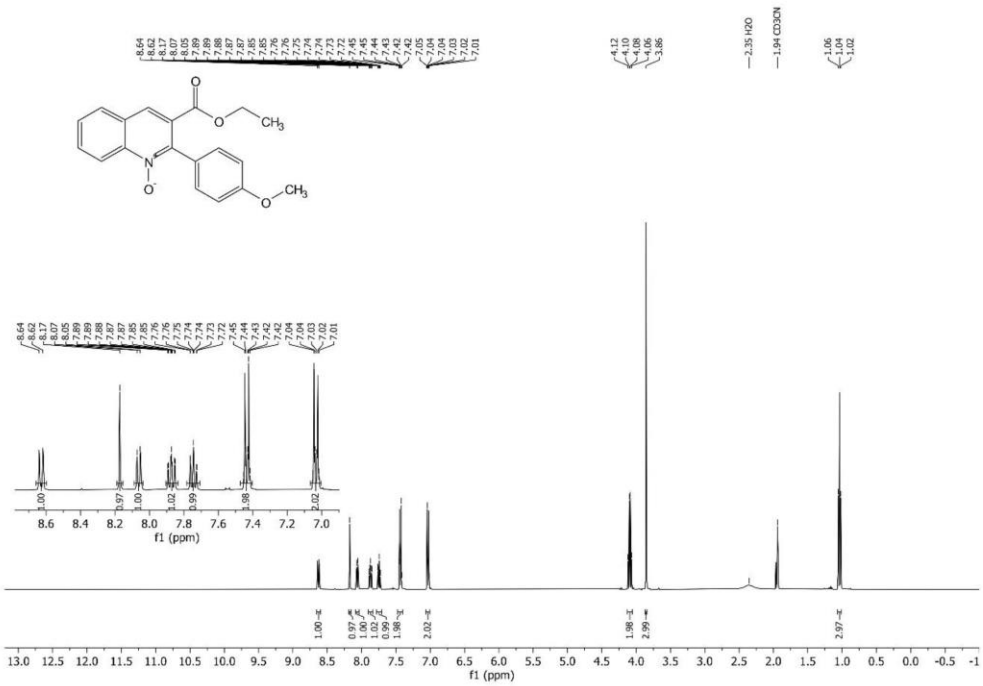
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-(ethoxycarbonyl)-2-(2-methoxyphenyl)quinoline 1-oxide (**6m**).



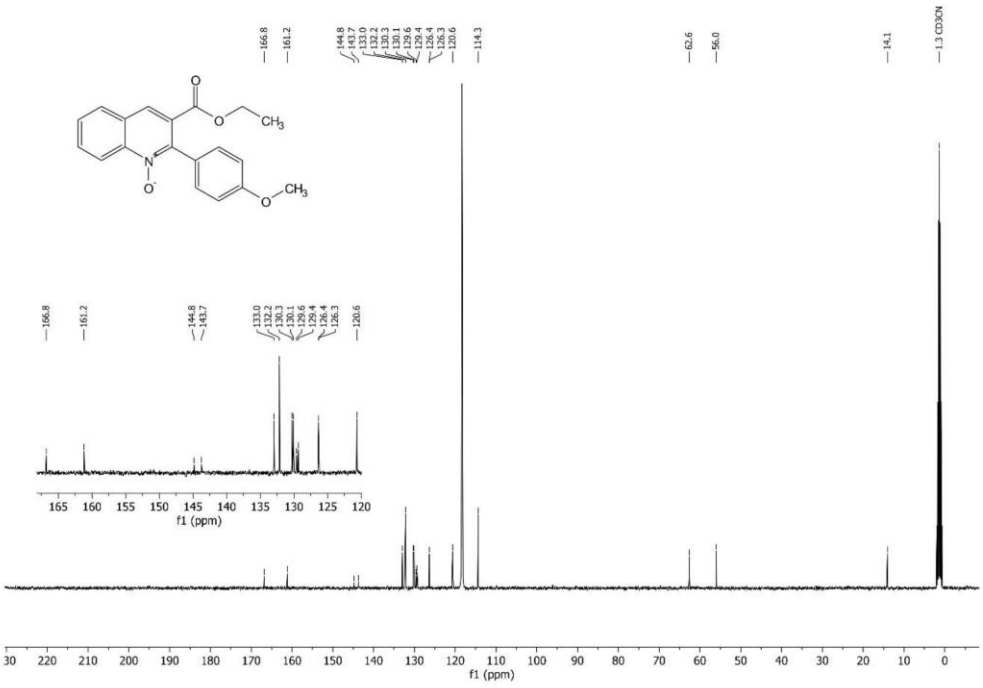
^{1}H NMR spectrum (400 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(3-methoxyphenyl)quinoline 1-oxide (**6n**).



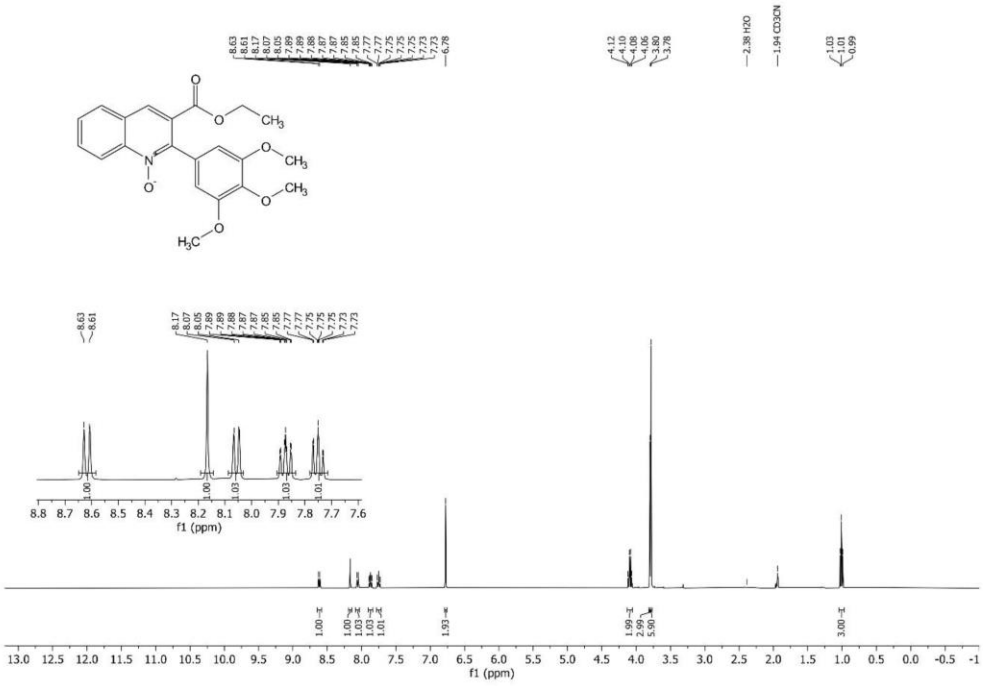
^{13}C NMR spectrum (101 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(3-methoxyphenyl)quinoline 1-oxide (**6n**).



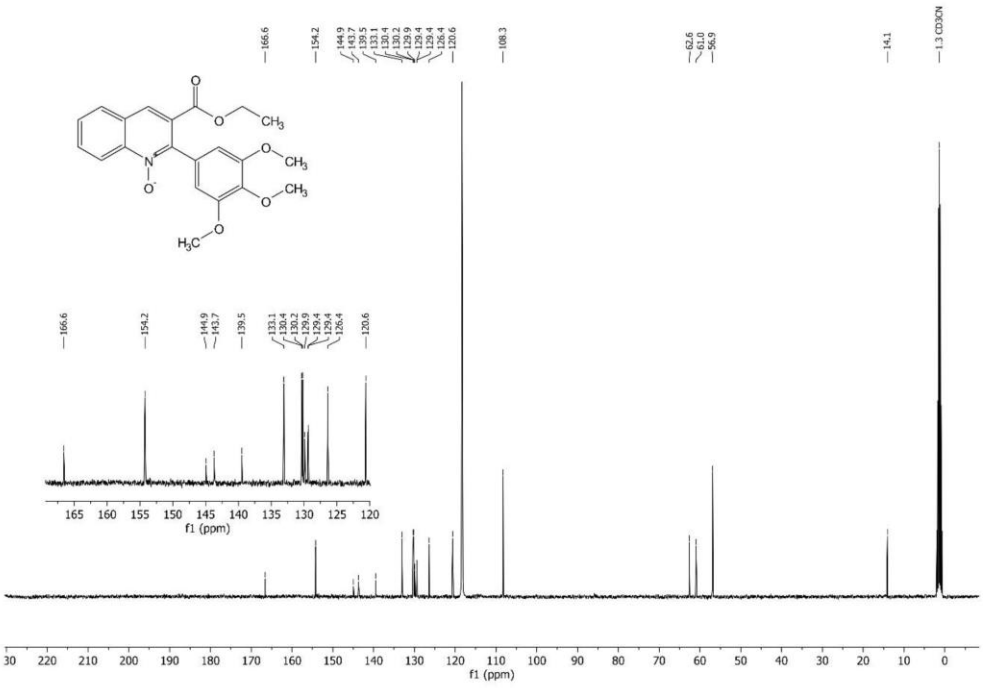
^{1}H NMR spectrum (400 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(4-methoxyphenyl)quinoline 1-oxide (**6o**).



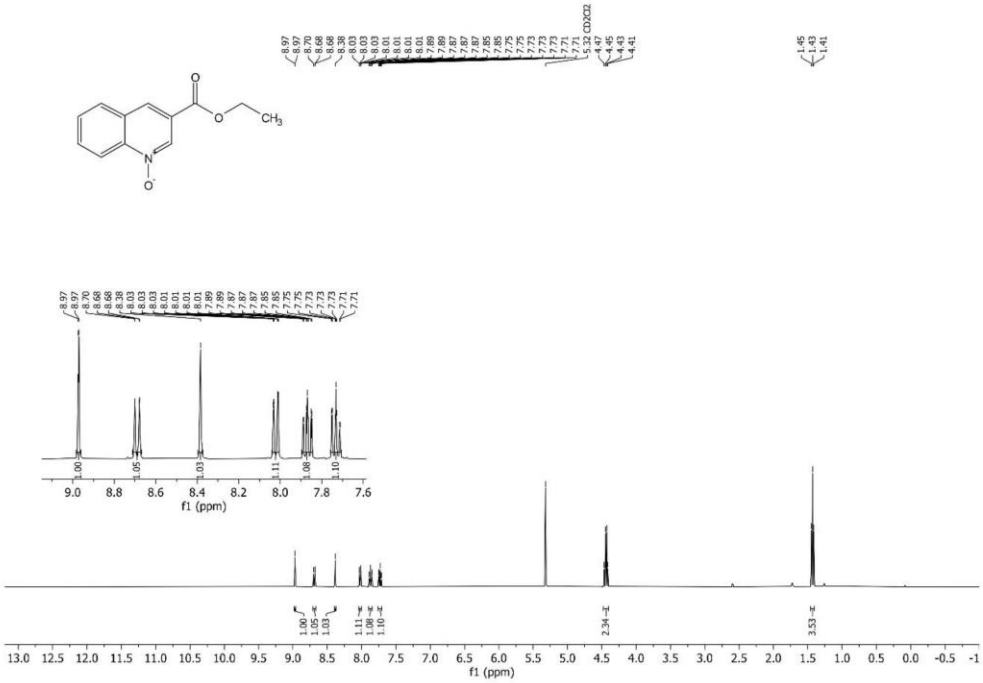
^{13}C NMR spectrum (101 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(4-methoxyphenyl)quinoline 1-oxide (**6o**).



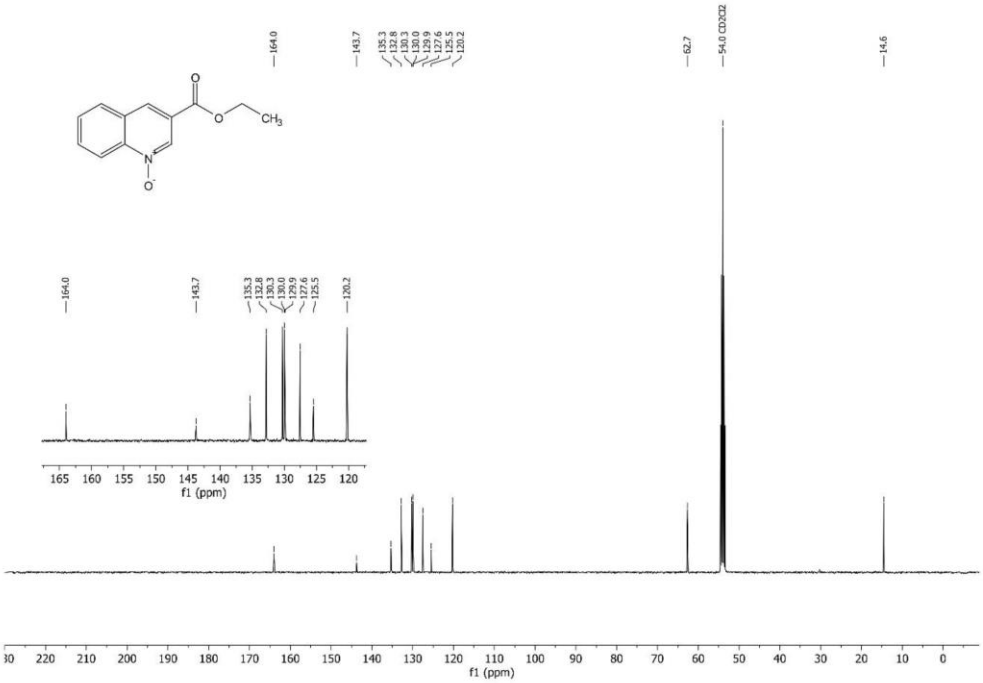
^{1}H NMR spectrum (400 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(3,4,5-trimethoxyphenyl)quinoline 1-oxide (**6p**).



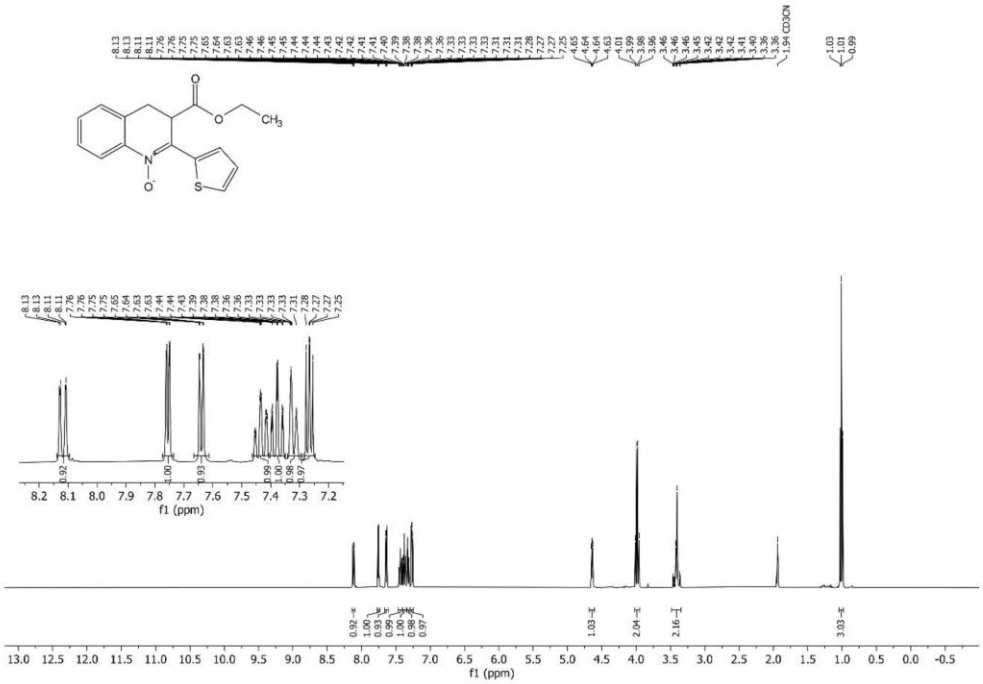
^{13}C NMR spectrum (101 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(3,4,5-trimethoxyphenyl)quinoline 1-oxide (**6p**).



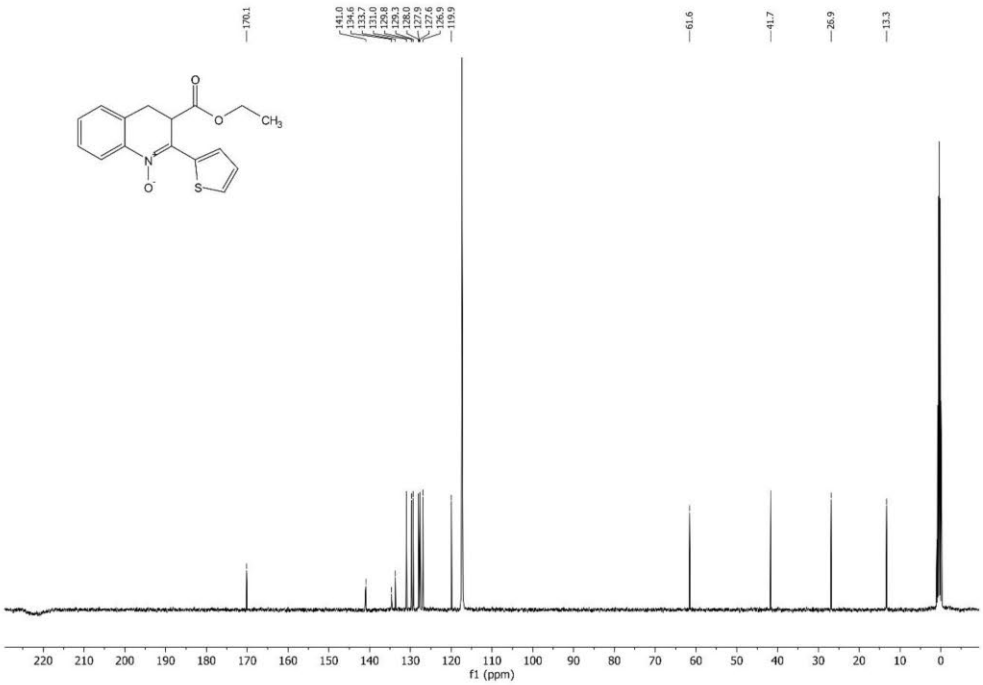
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-(ethoxycarbonyl)quinoline 1-oxide (**6q**).



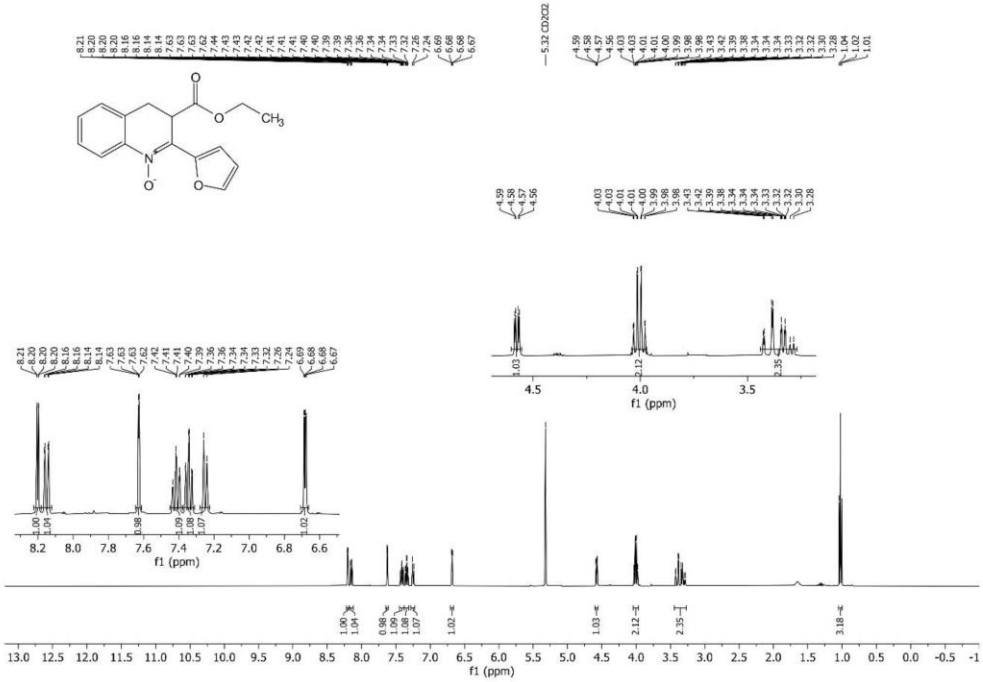
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-(ethoxycarbonyl)quinoline 1-oxide (**6q**).



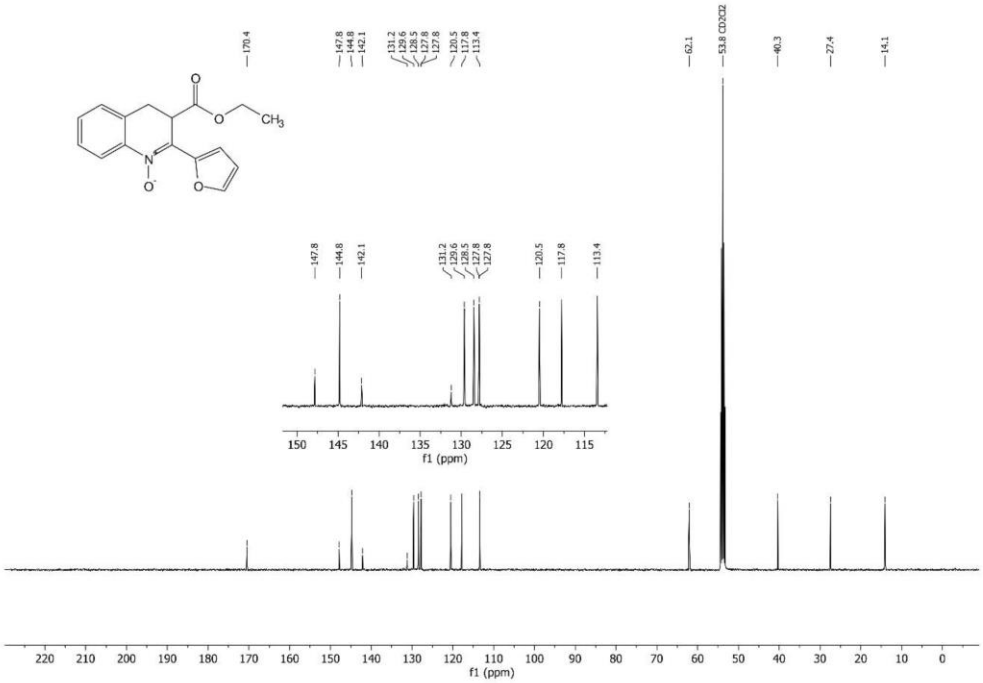
^{1}H NMR spectrum (400 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(thien-2-yl)-3,4-dihydroquinoline 1-oxide (**7a**).



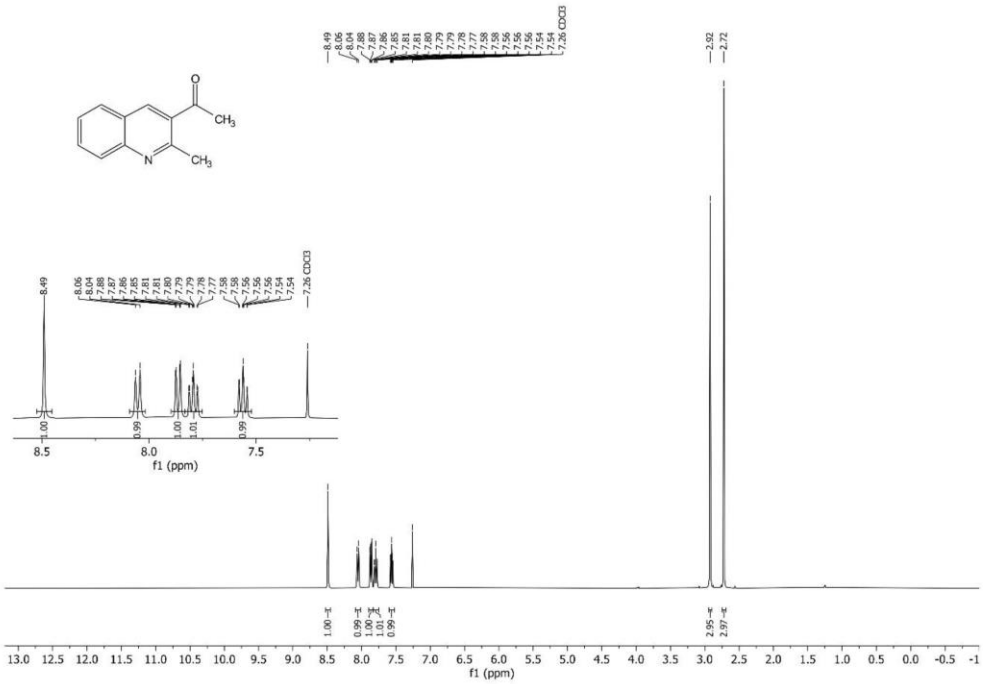
^{13}C NMR spectrum (101 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(thien-2-yl)-3,4-dihydroquinoline 1-oxide (**7a**).



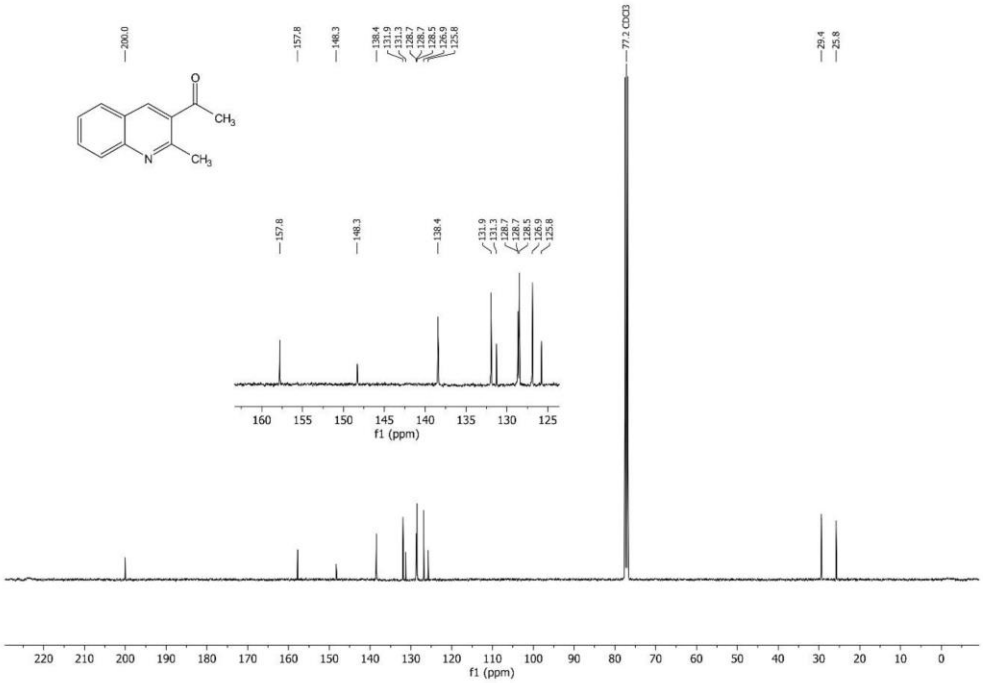
^{1}H NMR spectrum (400 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(furan-2-yl)-3,4-dihydroquinoline 1-oxide (**7b**).



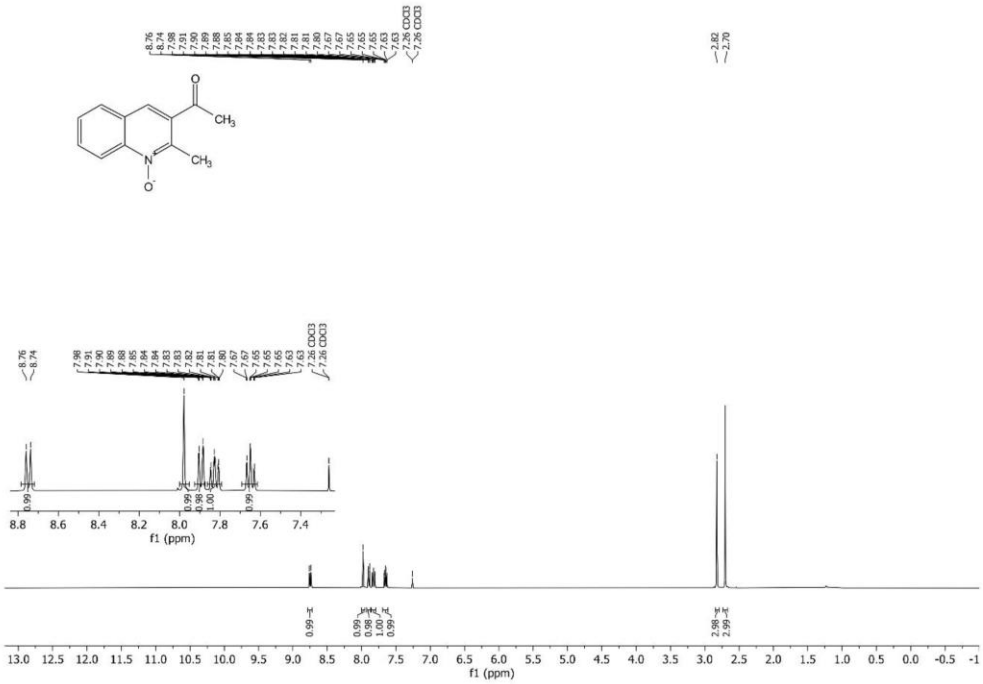
^{13}C NMR spectrum (101 MHz, CD_3CN) of 3-(ethoxycarbonyl)-2-(furan-2-yl)-3,4-dihydroquinoline 1-oxide (**7b**).



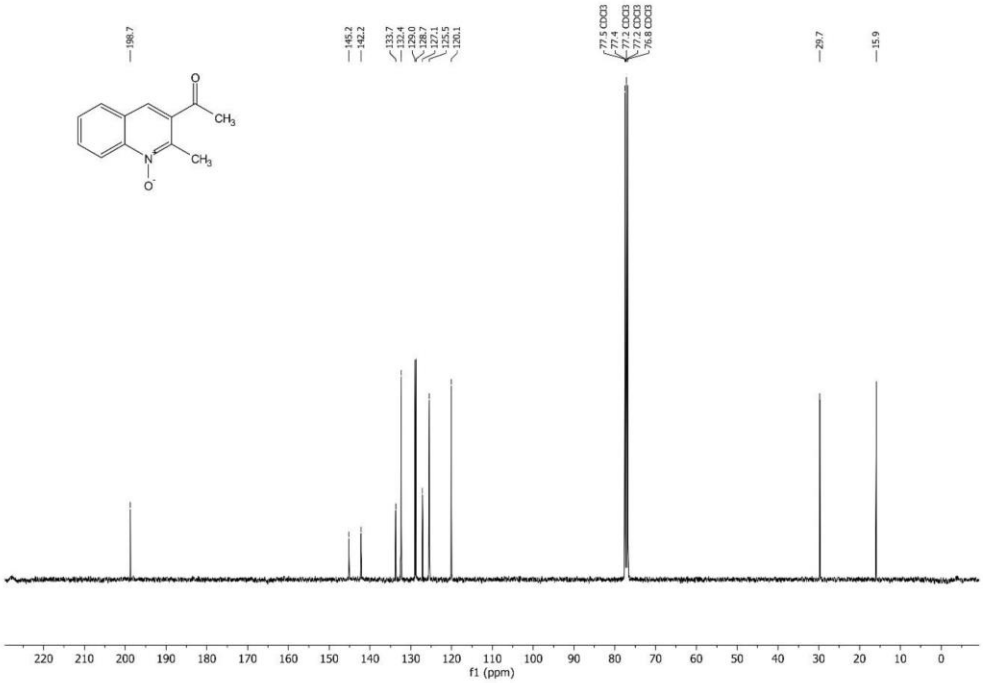
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-acetyl-2-methylquinoline (**9a**).



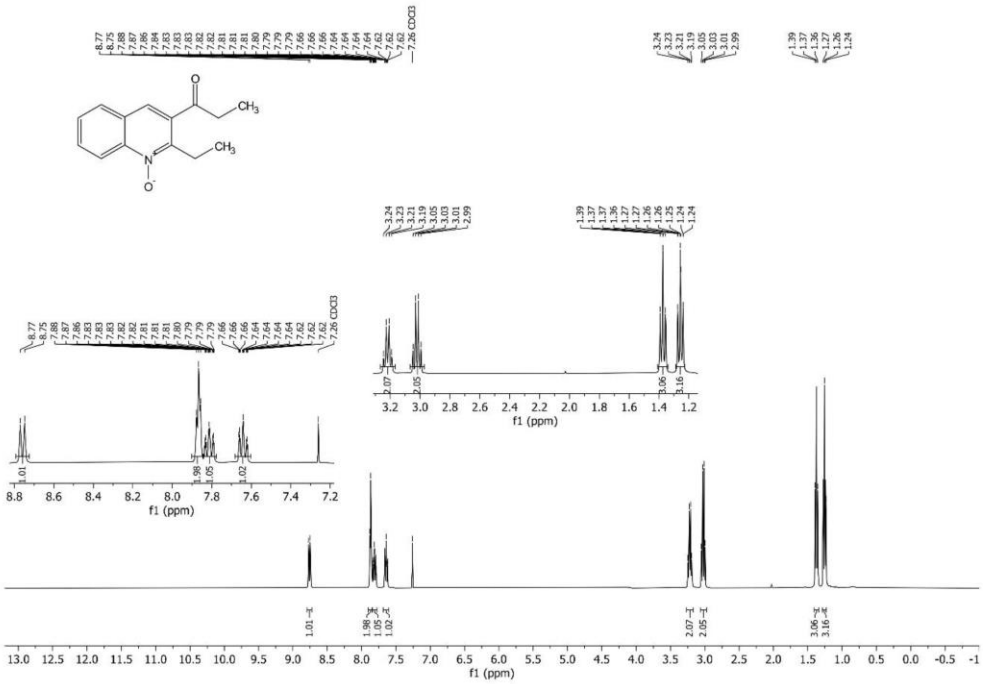
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-acetyl-2-methylquinoline (**9a**).



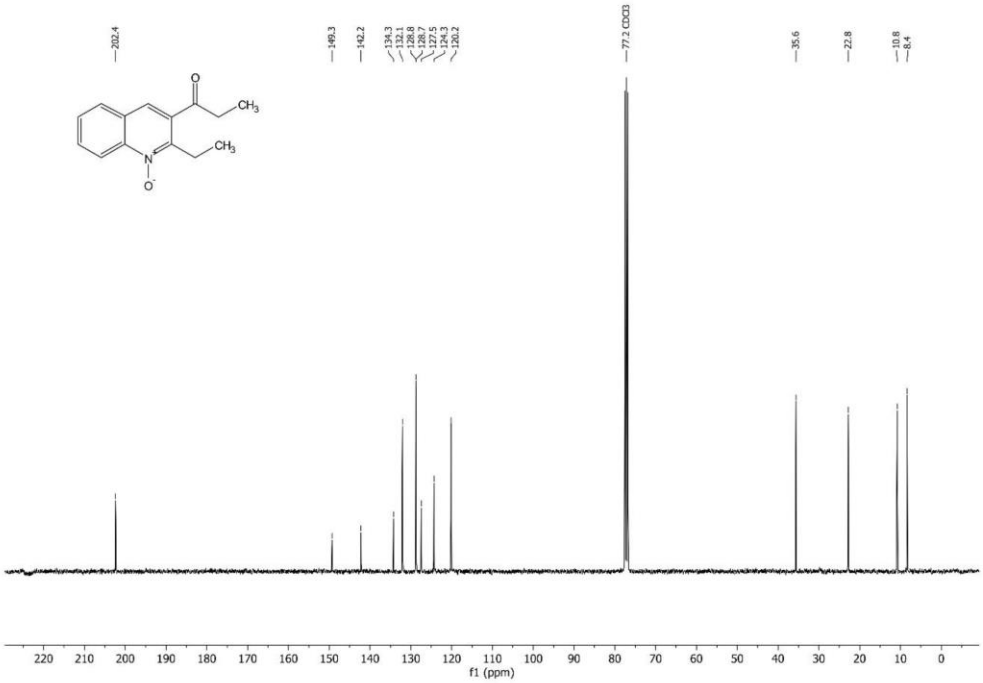
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-acetyl-2-methylquinoline 1-oxide (**10a**).



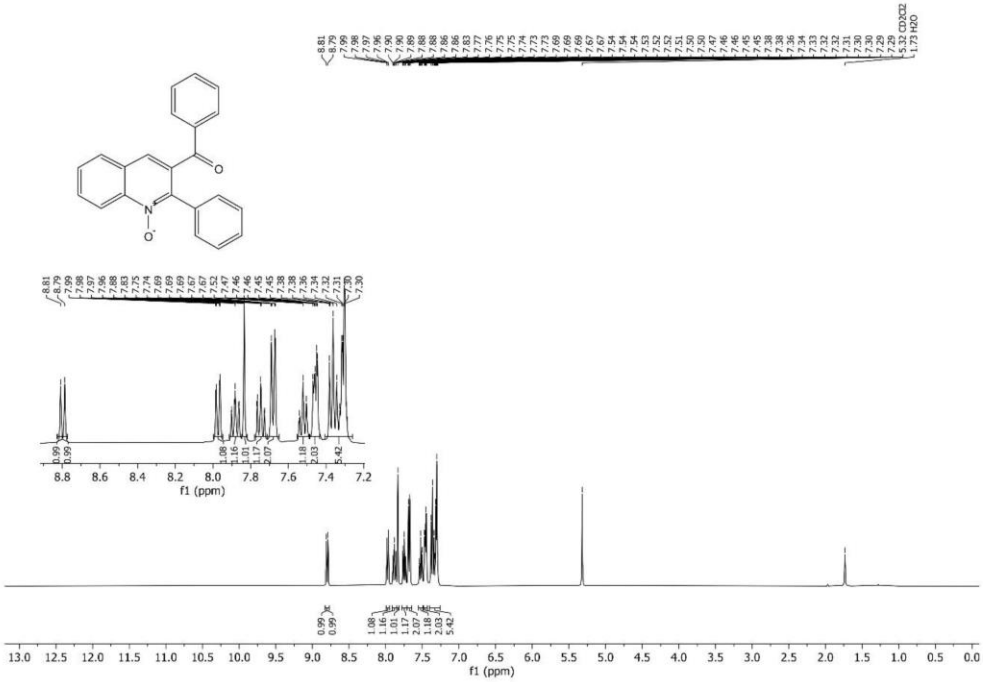
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-acetyl-2-methylquinoline 1-oxide (**10a**).



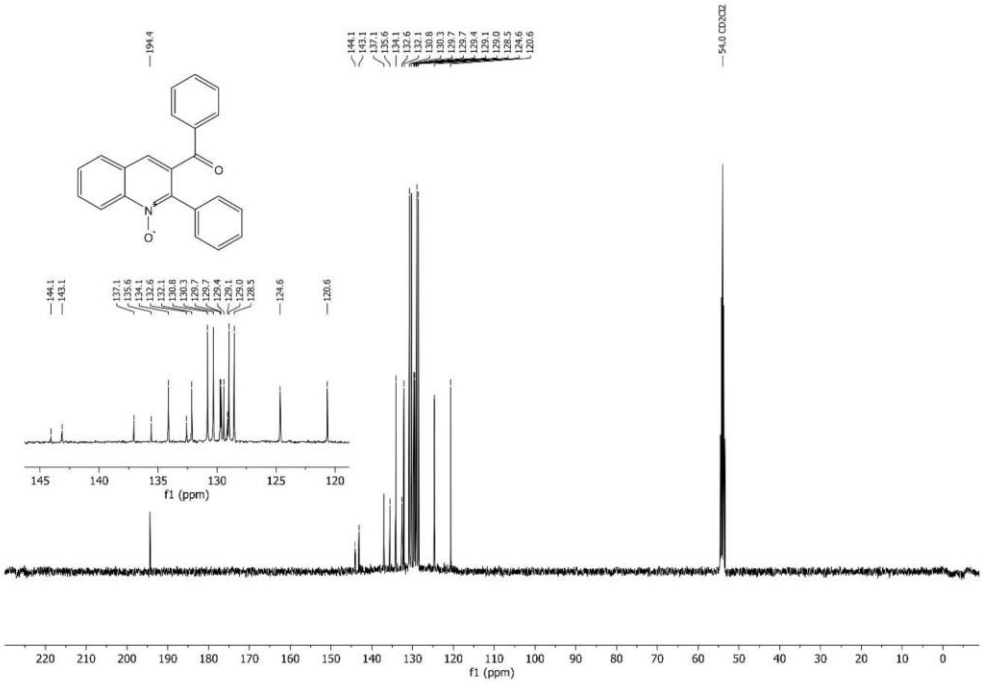
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 2-ethyl-3-propionylquinoline 1-oxide (**10b**).



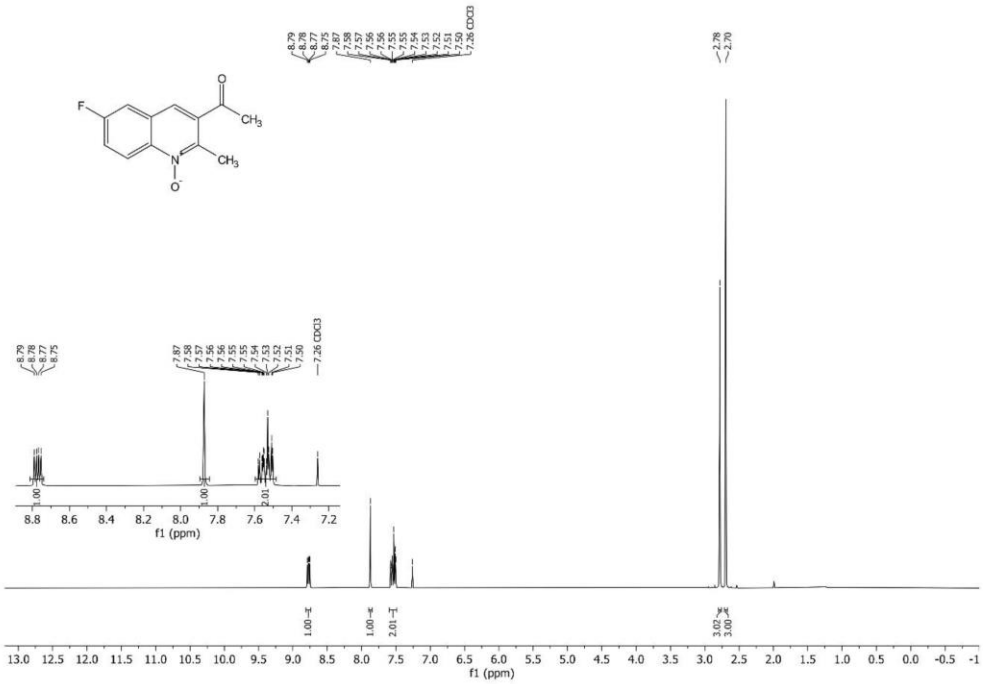
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 2-ethyl-3-propionylquinoline 1-oxide (**10b**).



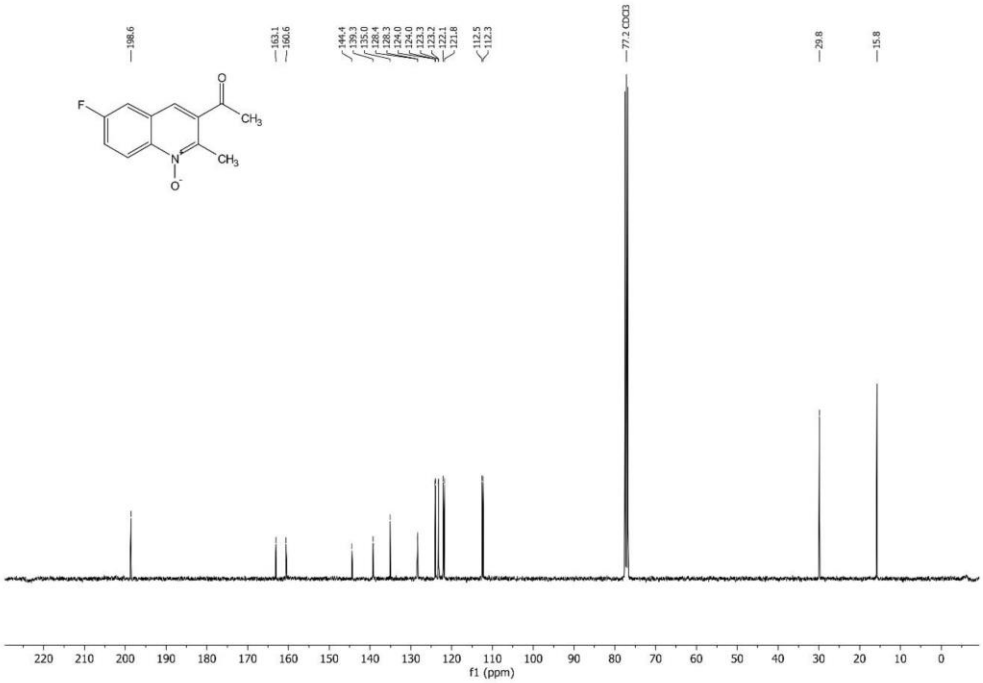
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-benzoyl-2-phenylquinoline 1-oxide (**10c**).



^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-benzoyl-2-phenylquinoline 1-oxide (**10c**).



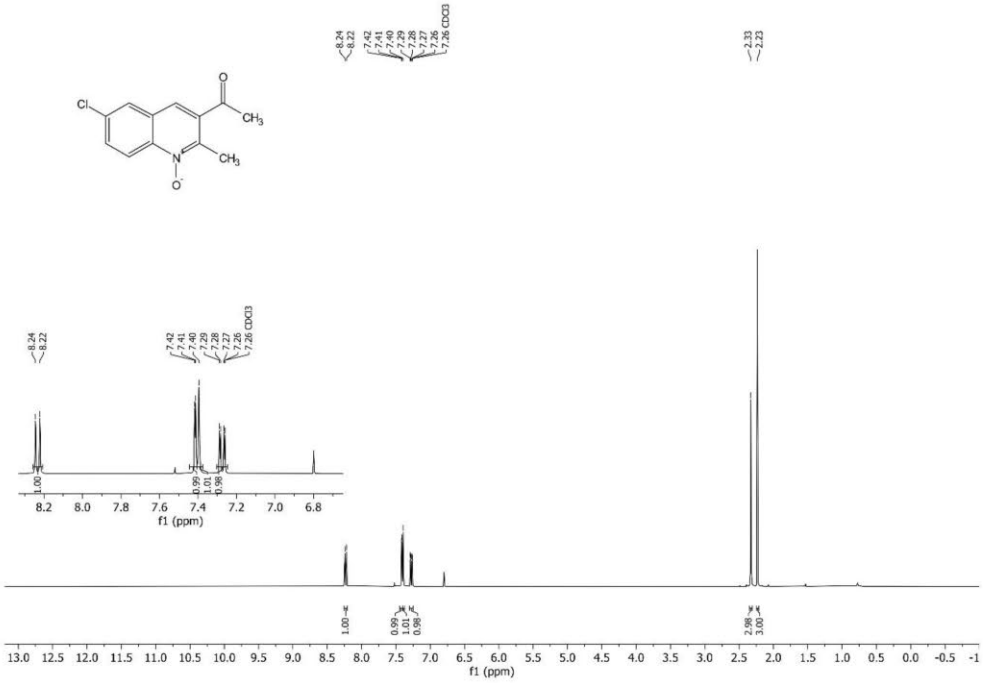
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-acetyl-6-fluoro-2-methylquinoline 1-oxide (**10d**).



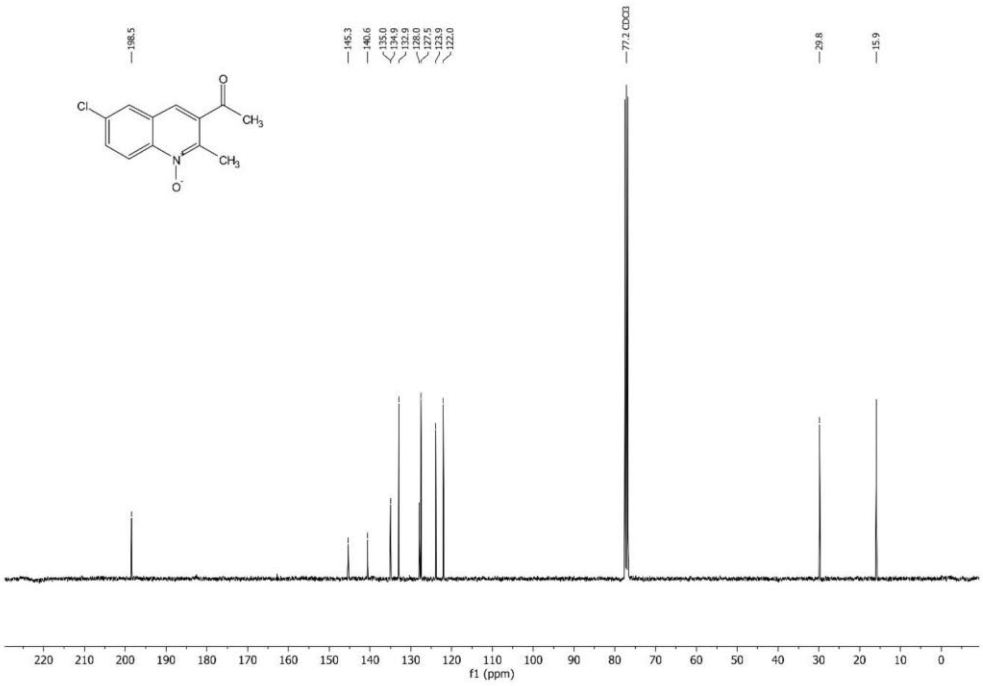
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-acetyl-6-fluoro-2-methylquinoline 1-oxide (**10d**).



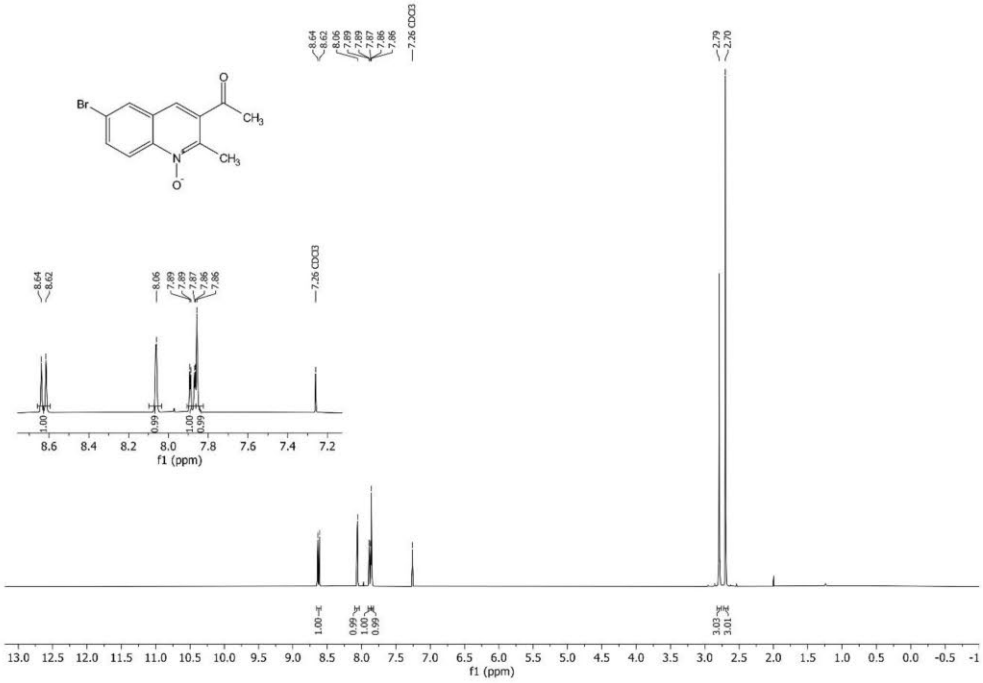
^{19}C NMR spectrum (376 MHz, $CDCl_3$) of 3-acetyl-6-fluoro-2-methylquinoline 1-oxide (**10d**).



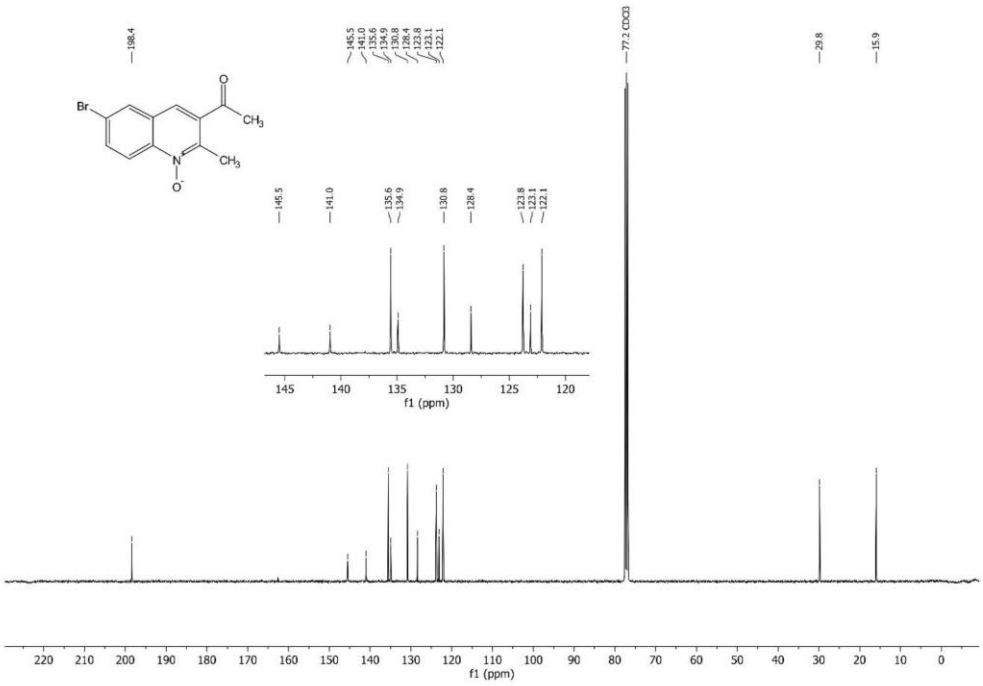
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-acetyl-6-chloro-2-methylquinoline 1-oxide (**10e**).



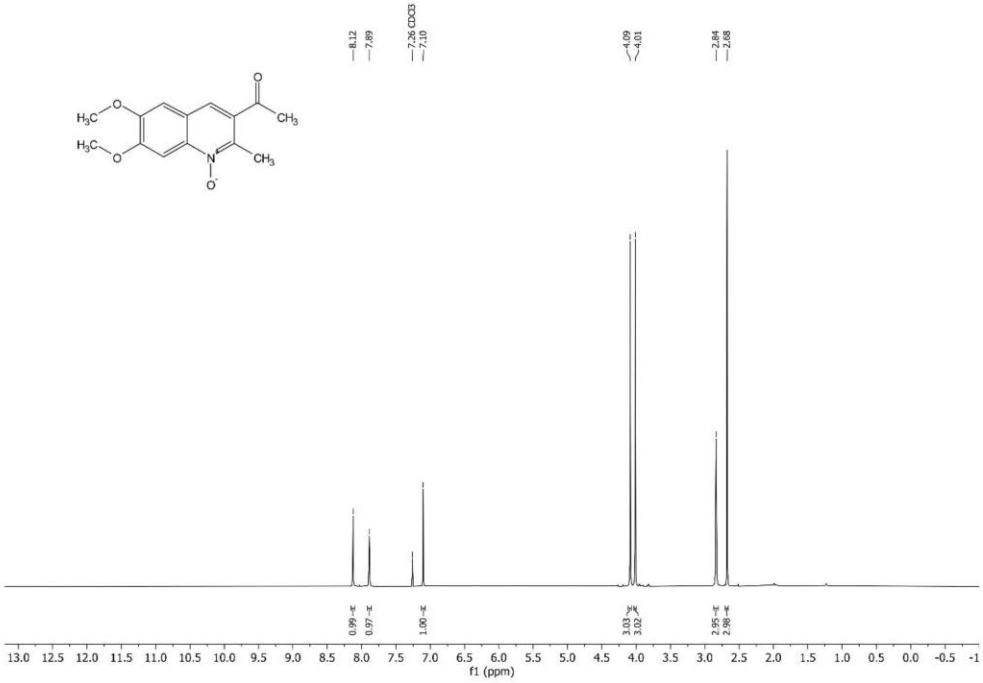
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-acetyl-6-chloro-2-methylquinoline 1-oxide (**10e**).



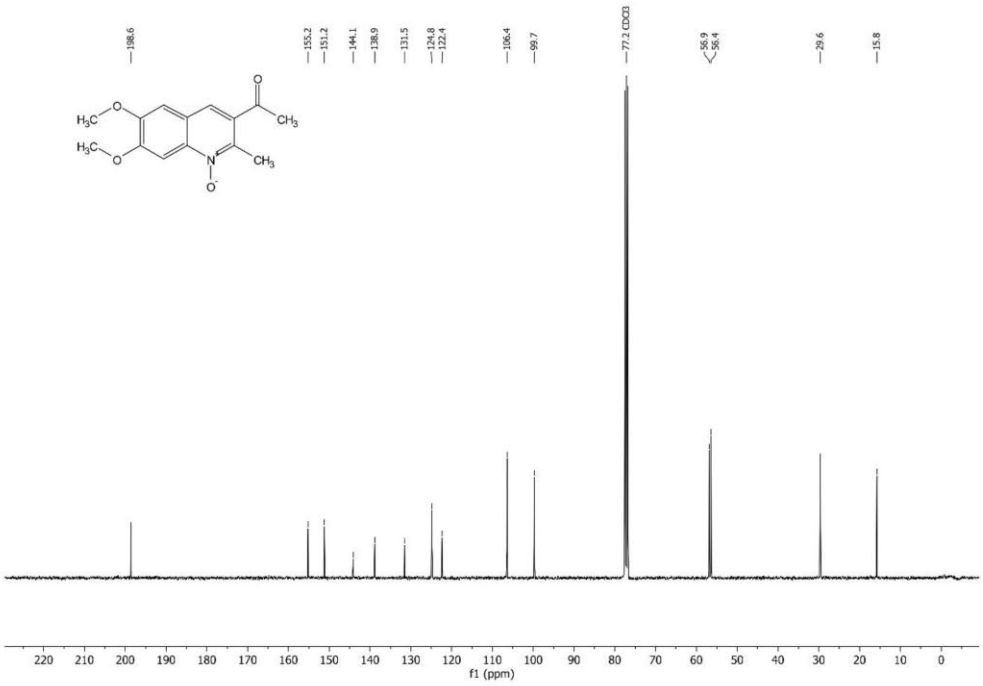
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-acetyl-6-bromo-2-methylquinoline 1-oxide (**10f**).



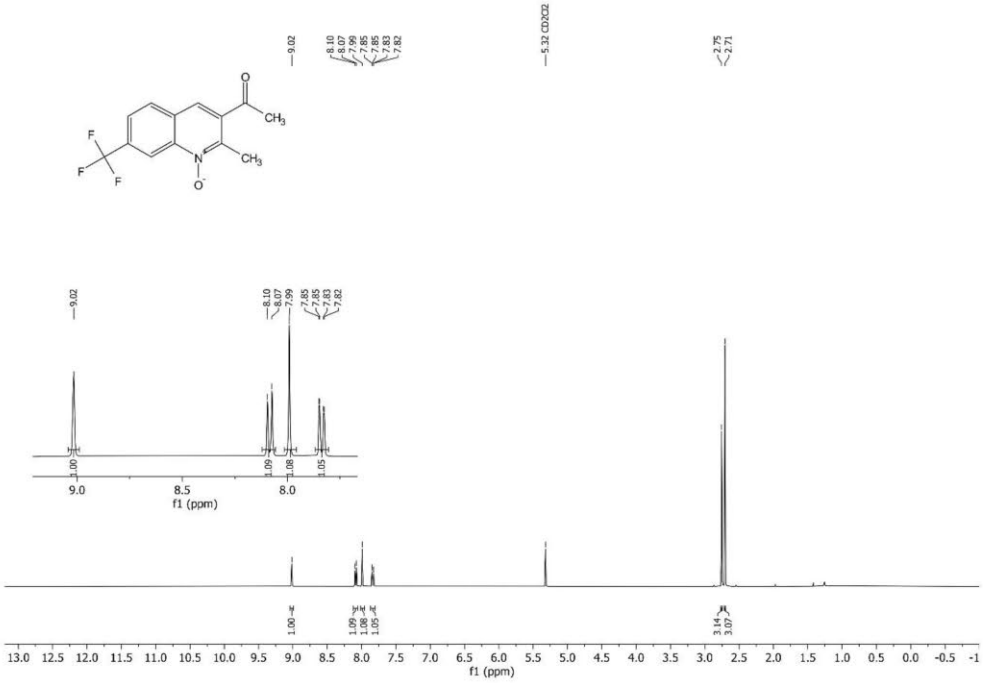
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-acetyl-6-bromo-2-methylquinoline 1-oxide (**10f**).



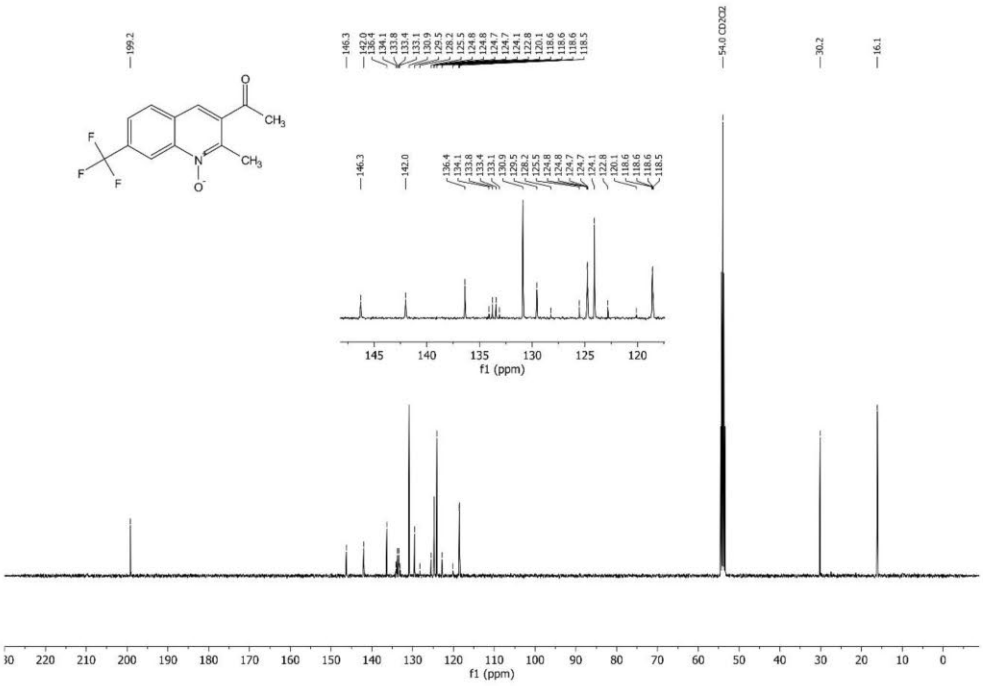
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of 3-acetyl-6,7-dimethoxy-2-methylquinoline 1-oxide (**10g**).



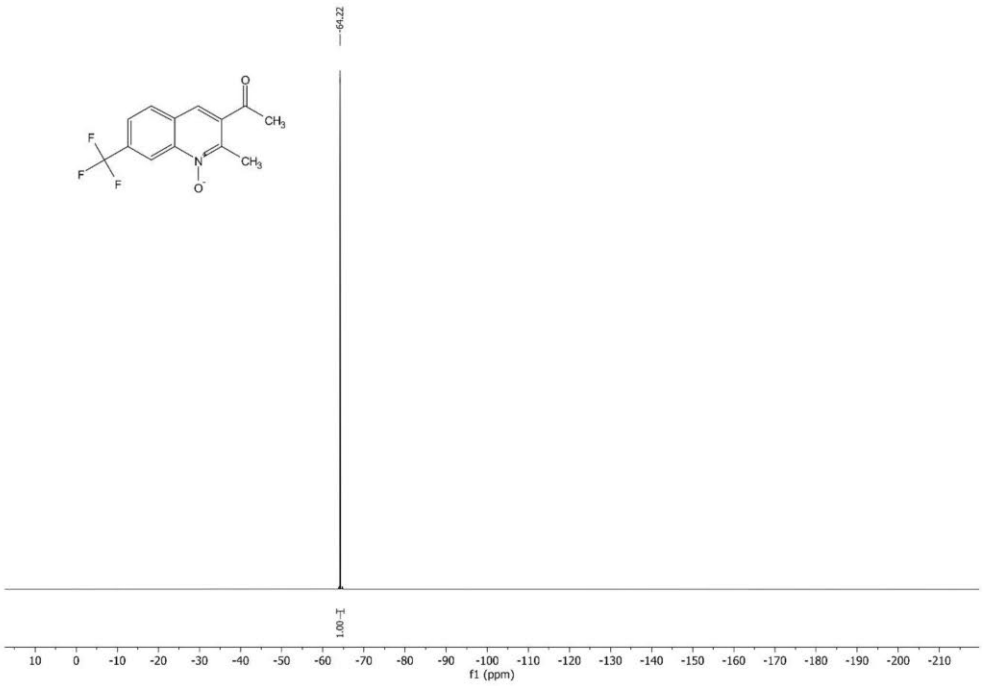
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of 3-acetyl-6,7-dimethoxy-2-methylquinoline 1-oxide (**10g**).



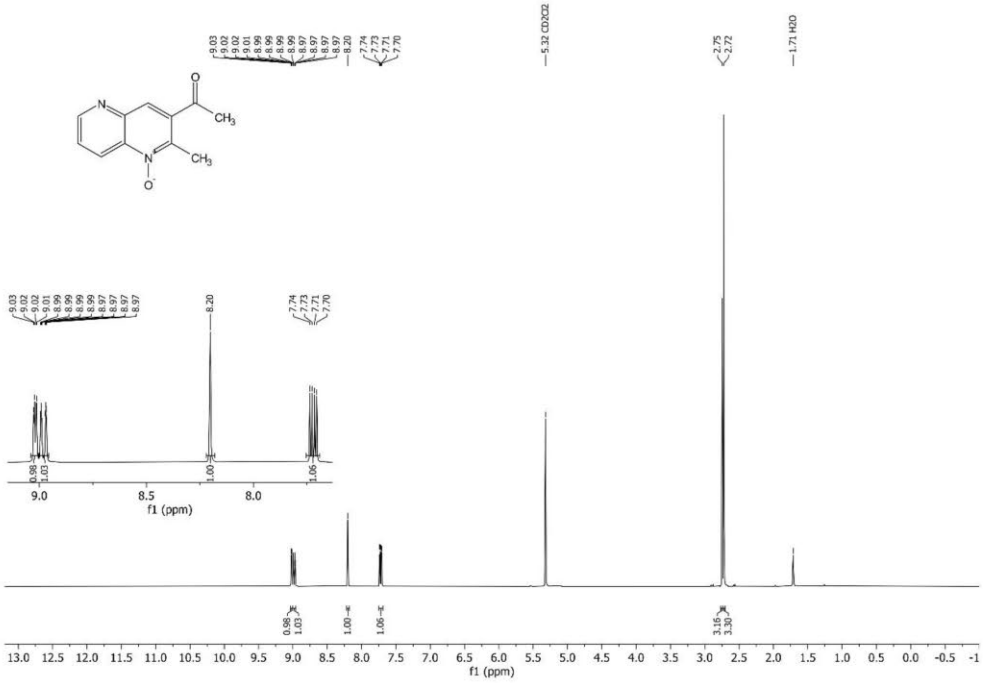
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-acetyl-2-methyl-7-(trifluoromethyl)quinoline 1-oxide (**10h**).



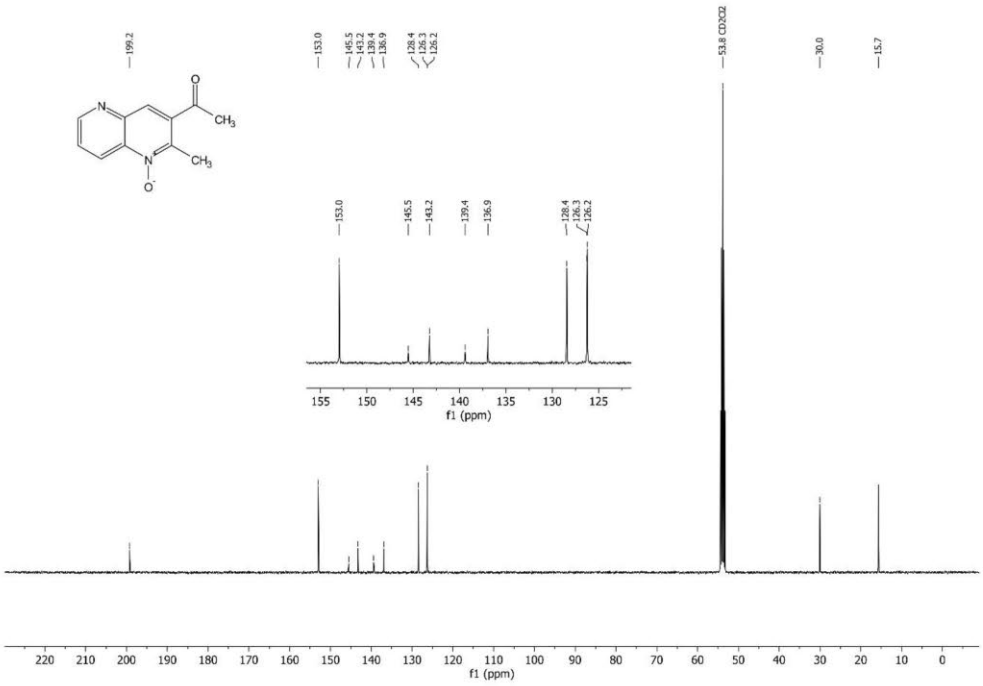
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-acetyl-2-methyl-7-(trifluoromethyl)quinoline 1-oxide (**10h**).



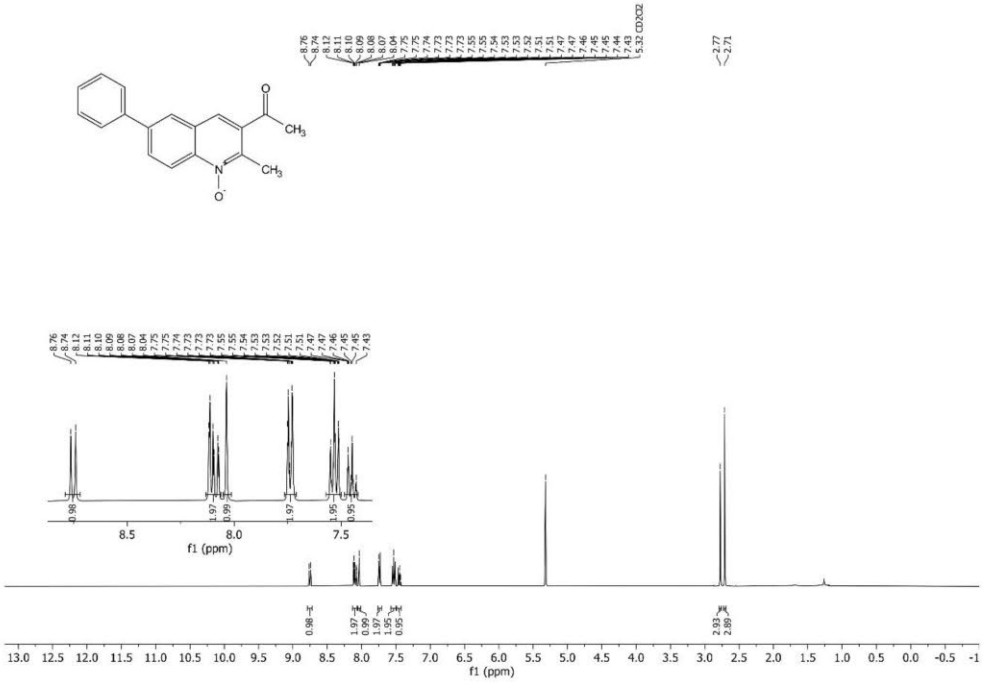
^{19}F NMR spectrum (376 MHz, CD_2Cl_2) of 3-acetyl-2-methyl-7-(trifluoromethyl)quinoline 1-oxide (**10h**).



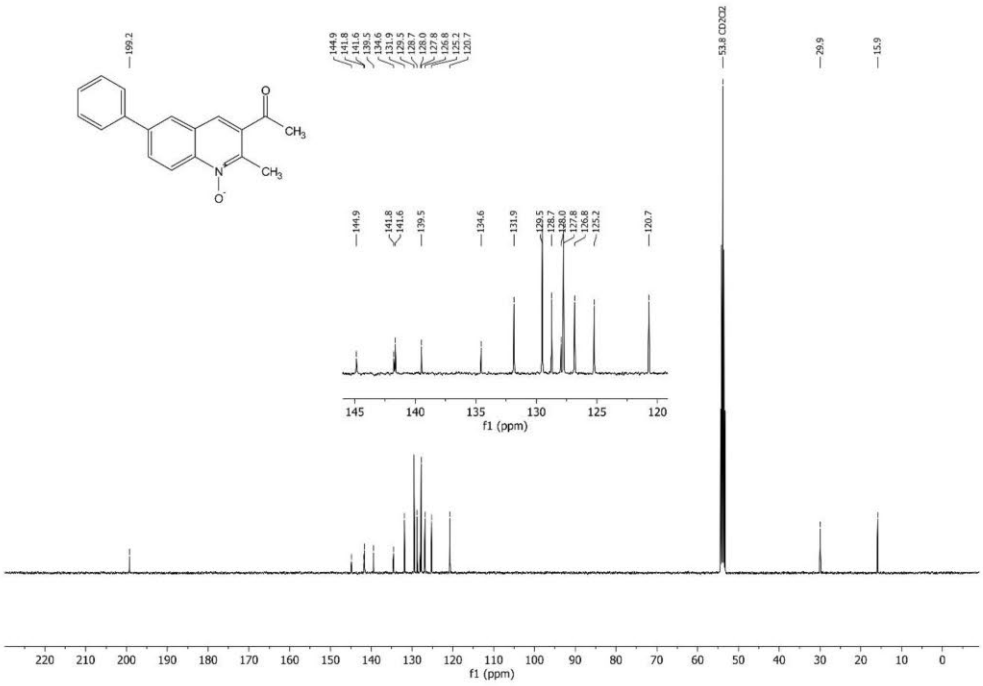
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-acetyl-2-methyl-1,5-naphthyridine 1-oxide (**10i**).



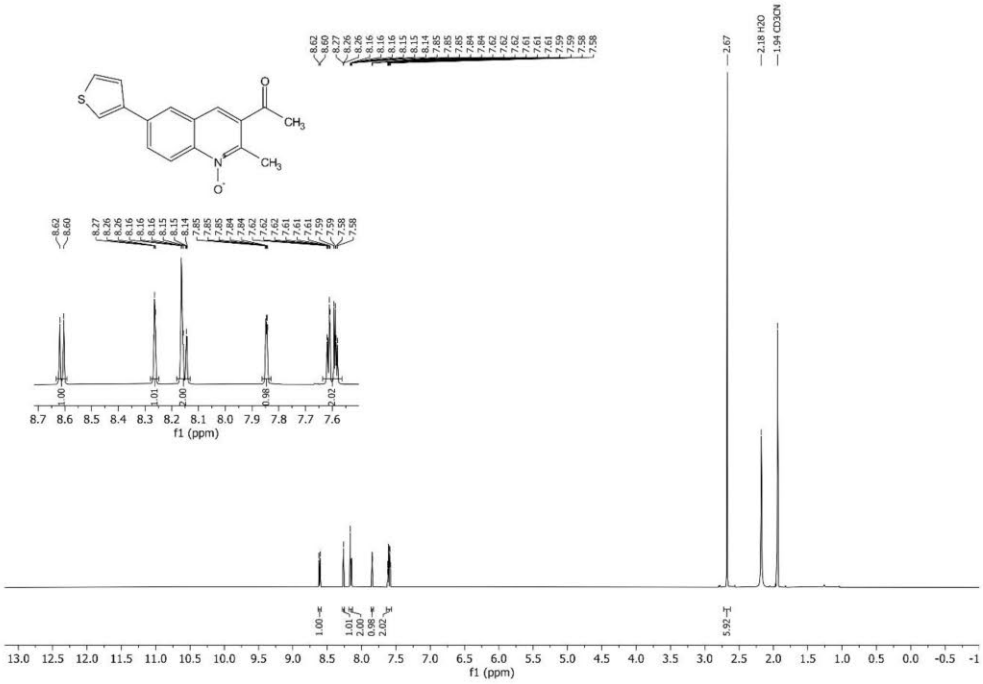
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-acetyl-2-methyl-1,5-naphthyridine 1-oxide (**10i**).



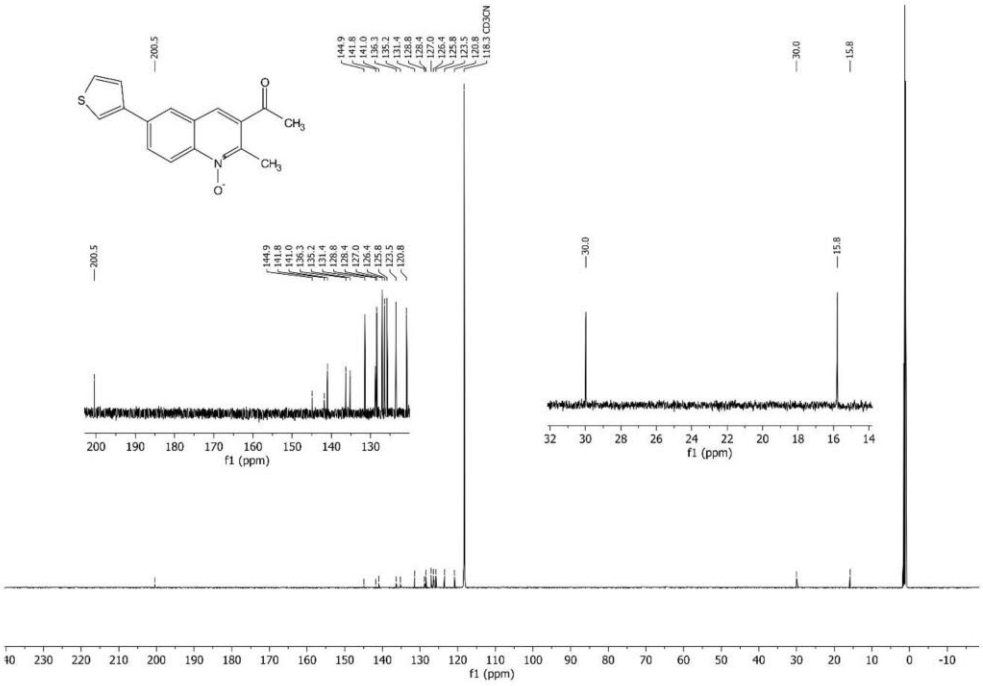
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-acetyl-2-methyl-6-phenylquinoline 1-oxide (**10j**).



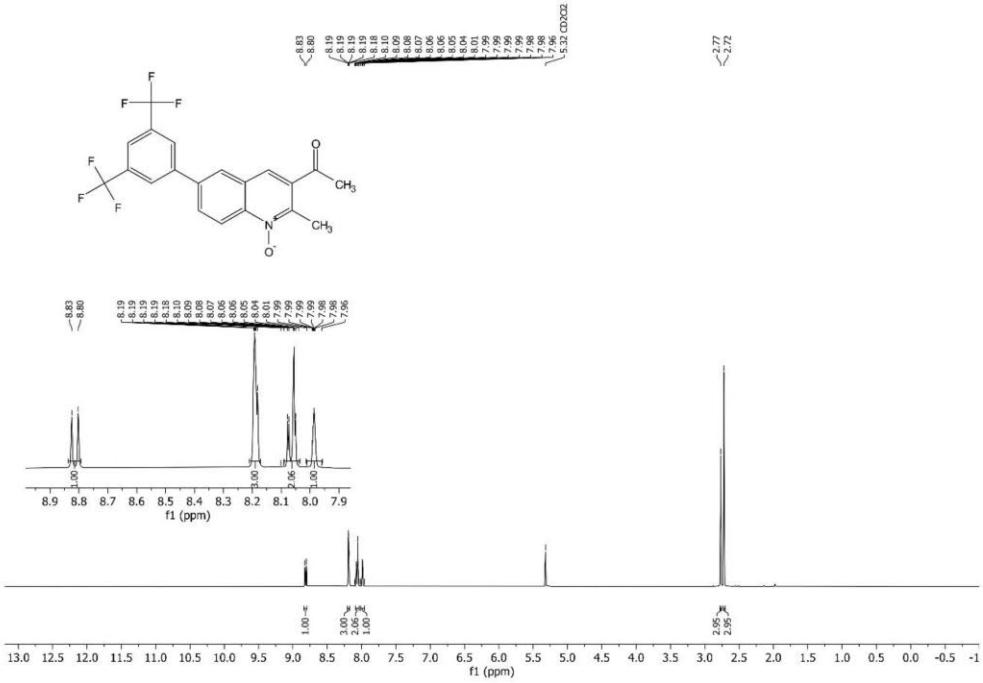
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-acetyl-2-methyl-6-phenylquinoline 1-oxide (**10j**).



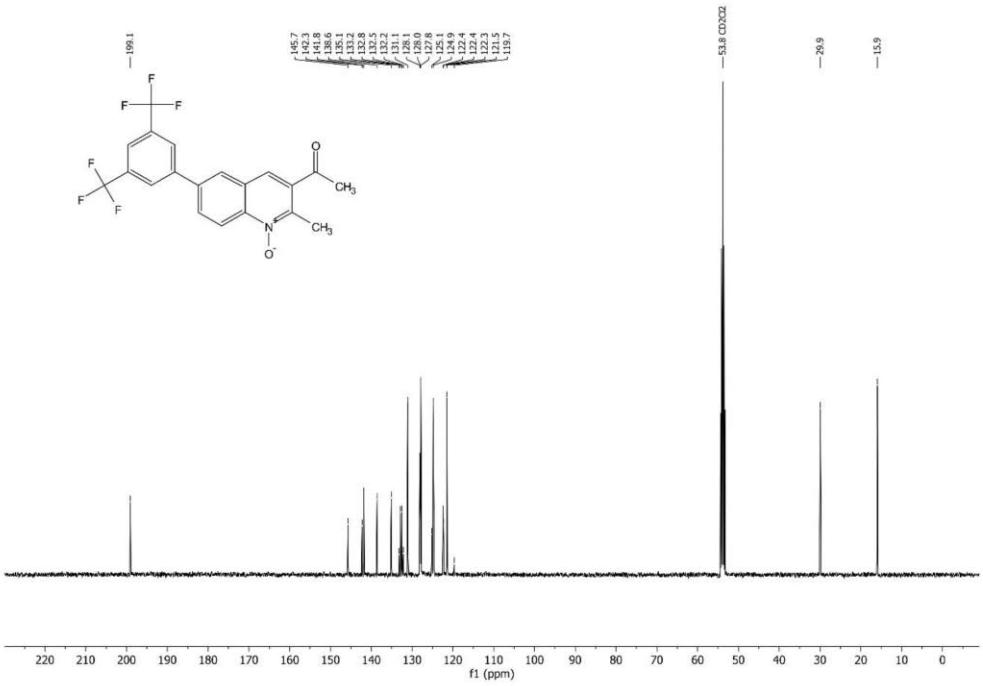
^{1}H NMR spectrum (600 MHz, CD_3CN) of 3-acetyl-2-methyl-6-(thien-3-yl)quinoline 1-oxide (**10k**).



^{13}C NMR spectrum (151 MHz, CD_3CN) of 3-acetyl-2-methyl-6-(thien-3-yl)quinoline 1-oxide (**10k**).



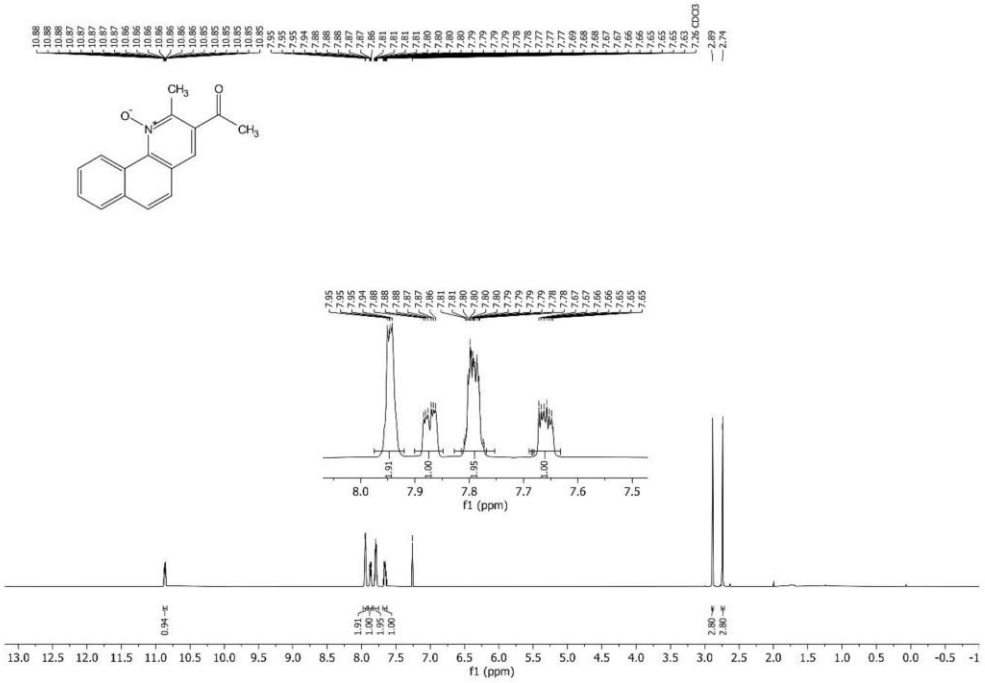
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of 3-acetyl-6-(3,5-bis(trifluoromethyl)phenyl)-2-methylquinoline 1-oxide (**10l**).



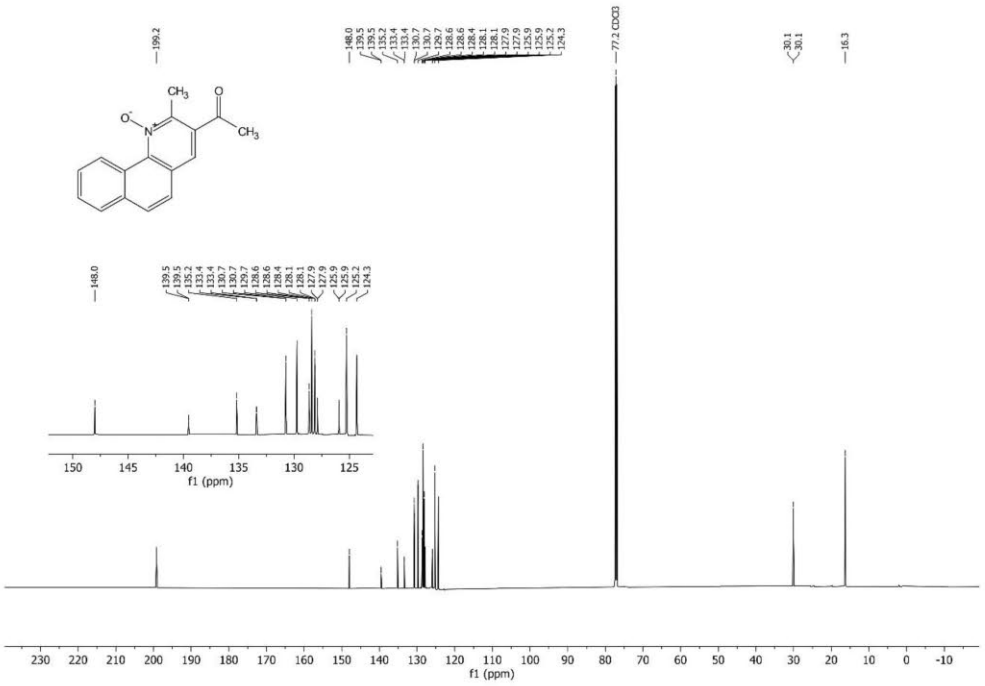
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of 3-acetyl-6-(3,5-bis(trifluoromethyl)phenyl)-2-methylquinoline 1-oxide (**10l**).



^{19}F NMR spectrum (376 MHz, CD_2Cl_2) of 3-acetyl-6-(3,5-bis(trifluoromethyl)phenyl)-2-methylquinoline 1-oxide (**10l**).



^{1}H NMR spectrum (600 MHz, $CDCl_3$) of 3-acetyl-2-methylbenzo[*h*]quinoline 1-oxide (**10m**).



^{13}C NMR spectrum (151 MHz, $CDCl_3$) of 3-acetyl-2-methylbenzo[*h*]quinoline 1-oxide (**10m**).

7. References

[1] G. R. Fulmer, A. J. M. Miller, N. H. Sherden, H. E. Gottlieb, A. Nudelman, B. M. Stoltz, J. E. Bercaw, K. I. Goldberg, *Organometallics* **2010**, *29*, 2176–2179.

[2] C. Gütz, B. Klöckner, S. R. Waldvogel, *Org. Process Res. Dev.* **2016**, *20*, 26–32.

[3] Merck KGaA, "SynLectro™ Electrolysis Platform", zu finden unter https://www.sigmaaldrich.com/DE/de/technical-documents/technical-article/chemistry-and-synthesis/organic-reaction-toolbox/synlectro-electrolysis-platform, **2022**.

[4] G. J. Atwell, B. M. Sykes, C. J. O'Connor, W. A. Denny, *J. Med. Chem.* **1994**, *37*, 371–380.

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8. Author Contributions

J. W: Conceptualization: Equal, Investigation Equal, Methodology: Equal, Data curation: Equal, Formal analysis: Equal, Writing the original draft: Equal.

T. P. Conceptualization: Supporting, Investigation: Supporting, Methodology: Supporting, Formal analysis: Supporting.

T. W. Conceptualization: Supporting, Investigation: Supporting, Methodology: Supporting, Formal analysis: Supporting.

D. S. Investigation: Supporting

S. R. W. Conceptualization: Equal, Funding acquisition, Project administration, Resources, Supervision, Writing the original draft: Equal

A-2.4 Supporting Information: Simple and Scalable Electrosynthesis of 1*H*—1-Hydroxyquinazolin-4-ones

Electronic Supplementary Material (ESI) for Chemical Science.
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Electronic Supporting Information (ESI)

Simple and Scalable Electrosynthesis of 1*H*-1-Hydroxyquinazolin-4-ones

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1. General Information

If not stated otherwise, all reactions were performed under ambient conditions and chemicals in analytical grade were used as purchased without further purification. Cyclohexane and ethyl acetate were purchased in technical grade and purified by distillation at reduced pressure prior to use. Milli-Q™ water was obtained using Simplicity™ System (UV) (*Merck KGaA*, Darmstadt, Germany) for chromatography purposes. Anhydrous solvents were obtained from a solvent purification system SPS-5 (*M. Braun Incorporated*, Stratham, USA).

Chromatography

Thin layer chromatography was performed using silica gel DC Kieselgel 60 F254 on aluminium plates (*Merck KGaA,* Darmstadt, Germany). A UV lamp (λ = 254 nm, NU-4 KL, *Benda*, Wiesloch, Germany). Preparative column chromatography was performed on silica gel 60 M (0.040–0.063 mm*, Macherey-Nagel GmbH & Co*, Düren, Germany) using a Sepacore™ system with a Büchi Control Unit C-620, Büchi Pump Modules C-605, a UV detector Büchi UV photometer C-635, and Büchi Fraction Collector C-660 (*Büchi- Labortechnik GmbH*, Essen, Germany). The isolation of the different quinoline derivatives was conducted with reversed phase column chromatography on Sepacore™ C18 (*Büchi-Labortechnik GmbH*, Essen, Germany) using different mixtures of water (0.1% formic acid) and acetonitrile as eluents.

High Resolution Mass Spectrometry

Mass spectra *via* electrospray-ionization (ESI+/ESI–) mass spectrometry were recorded using an Agilent 6545 QTOF-MS (*Agilent*, Santa Clara (CA), USA). Mass-charge ratios (*m*/*z*) were obtained for the characterized compounds.

X-ray Crystallography

The measurements of the crystal structures were carried out on a STOE IPDS-2T (*STOE & Cie GmbH*, Darmstadt, Germany) using a Mo source with graphite tube monochromator.

Gas Chromatography (GC)

Gas chromatography was performed using a GC-2010 (*Shimadzu*, Kyoto, Japan) equipped with a flame ionization detector (FID) and a quartz capillary column HI-5MS (*Avantor VWR*, Radnor, USA) with following specification: length of 30 m, inner diameter of 0.25 mm and a stationary phase ((5%-phenyl)-dimethylsiloxane) of 0.25 µm thickness. Hydrogen was used as carrier gas with a flow rate of 45.5 cm s-1. Measurements were performed at an injector temperature of 250 °C and a detector temperature of 310 °C, starting at 50 °C and heating to 290 °C (holding for 2 min) with a temperature ramp of 15 °C/min (method: hart-18min).

High Performance Liquid Chromatography (HPLC)

Analysis of crude reaction mixtures and purified products was performed using a modular system LC-20A *Prominence* (*Shimadzu Deutschland GmbH*, Duisburg, Germany), UV/VIS-detector SPD-20A/AV (*Shimadzu Deutschland GmbH*, Duisburg, Germany), and LCMS-2020 Single Quadrupole (*Shimadzu Deutschland GmbH*, Duisburg, Germany). Analytical separation was performed using an Eurospher II 100-5 C-18-Trennsäule (*Knauer Wissenschaftliche Geräte GmbH*, Berlin, Germany) column (length of 150 mm, diameter of 4 mm, pore size of 100 Å, particle size 5 µm). As eluents, acetonitrile and water with 5% (*v*/*v*) acetonitrile and formic acid (1 mL L^{-1}) were used. Given retention times were obtained at λ = 254 nm.

Microwave Synthesizer

Microwave reactions were performed using a Discover microwave reactor (*CEM Corporation*, Matthews (NC), USA) and 10 ml Pyrex Pressure Vessels (*CEM Corporation*, Matthews (NC), USA).

Nuclear Magnetic Resonance (NMR) Spectroscopy

Nuclear magnetic resonance experiments were performed using a nuclear magnetic resonance spectrometer Avance III HD300 (*Bruker*, Karlsruhe, Germany) ^{1}H NMR (300 MHz), ^{19}F NMR (282 MHz), Avance II 400 (*Bruker*, Karlsruhe, Germany) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), and ^{19}F NMR (376 MHz), and Avance III 600 (*Bruker*, Karlsruhe, Germany) ^{1}H NMR (600 MHz), ^{13}C NMR (151 MHz). The spectra were recorded using deuterated solvents. To normalize the spectra obtained, reference was made to the existing solvent signal of non-deuterated fractions according to the data provided by *Fulmer et al.*[1]: $CDCl_3$ (^{1}H NMR: δ = 7.26 ppm, ^{13}C NMR: δ = 77.2 ppm), dichloromethane-d_2 (^{1}H NMR: δ = 5.32 ppm, ^{13}C NMR: δ =53.8 ppm), methanol-d_4 (^{1}H NMR δ = 3.31 ppm, ^{13}C NMR: δ = 49.0 ppm) and water-d_2 (^{1}H NMR δ = 4.79 ppm) acetonitrile-d_3 (^{1}H NMR δ = 1.94 ppm, ^{13}C NMR: δ = 118.3 ppm) and. Besides ^{1}H, ^{13}C and ^{19}F NMR experiments, the 2D techniques ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HSQC, ^{1}H,^{13}C-HMBC and ^{1}H,^{1}H-NOESY were used assisting to assign the signals. The following abbreviations were used to describe the signals: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), m (multiplet), q (quartet), hep (heptet). The spectra obtained were evaluated with MestReNova 14.2.0-26256 (*Mestrelab Research S.L.*, Spain). ^{19}F NMR spectra were obtained with *α,α,α*-trifluorotoluene as external standard (δ = 63.9 ppm) and recorded without ^{1}H decoupling.

Cyclic Voltammetry (CV) Measurements

Cyclic voltammetry was performed using a Metrohm 663 VA Stand equipped with a Autolab type III potentiostat (*Metrohm AG*, Herisau, Switzerland). WE: boron-doped diamond tip, 2 mm in diameter; CE: glassy carbon rod; RE: Ag/AgCl (*vs.* FcH/FcH^{+} = ferrocene). Scan rate=100 mV·s^{-1}. Electrolyte: 0.5 M sulphuric acid in a 1:1 (*v*/*v*) water–methanol mixture; *c*(substrate)=0.05 M.

Electrochemical Set-Up

Electrochemical reactions were carried out using a multichannel galvanostat HMP4040 (*Rohde & Schwarz*, München, Germany) with a controllable DC output of 0-32 V and 0–10 A and a maximum power of 160 W per channel was used as power source. The different cells used for screening or batch reactions are described below.

Screening Reactions

Teflon™ cells with a volume of 5 mL were used for the undivided set-up (figure S1, left). Divided Teflon™ screening cells were equipped with a glass frit or Nafion™ as separator material as shown (figure S1, right). Glass frits and Nafion™ N324 membrane (DuPont, Wilmington, United States) used as separator materials were pre-treated in the corresponding electrolyte prior to use. Stirring bars were used during electrolysis in each cell. The described screening systems are commercially available as IKA Screening System Package (*IKA™ Werke GmbH & Co. KG*, Staufen, Germany).

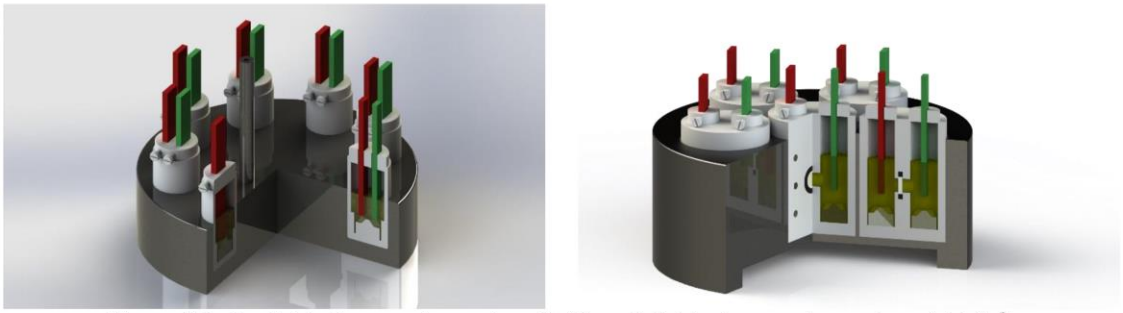


Figure S1: Undivided screening set-up (left) and divided screening set-up (right).[2]

Table S1: Electrode materials, purity and their supplier.

Entry	Electrode Material	Purity	Supplier
1	Boron-doped diamond (DIACHEM®)	15 µm boron-doped diamond layer on silicon	*CONDIAS GmbH*, Itzehoe, Germany
2	Glassy carbon	-	*HTW*, Thierhaupten, Germany
3	Isostatic graphite	-	*SGL Carbon*, Bonn, Germany
4	Lead	-	*Globus Fachmärkte GmbH & Co. KG*, Völklingen, Germany (home depot)
5	Platinum	>99%	*OEGUSSA*, Vienna, Austria
6	Leaded bronze (CuSn7Pb15)	-	*Metallwerk Langenau GMBH*, Langenau, Germany

Scale-up experiments were performed in 50 mL, 100 mL, and 250 mL batch-type cells with a PTFE stopper and sleeve, electrodes and electrode holders used a TDK-Lambda Z+ series (*TDK-Lambda UK Limited*, Devon, United Kingdom) or a multichannel power supply HMP4040 (*Rohde & Schwarz*, München, Germany) as power sources. The batch-type cells of the scale-up experiments are commercially available as SynLectro™ Starter Kit (*Merck KGaA*, Darmstadt, Germany).[3] In the 25 mL electrolysis set-up glassy carbon BDD electrodes with dimensions of 6 cm x 2 cm were used. In the 250 mL electrolysis set-up glassy carbon and BDD electrodes with identical dimensions of 12 cm x 4 cm were used.

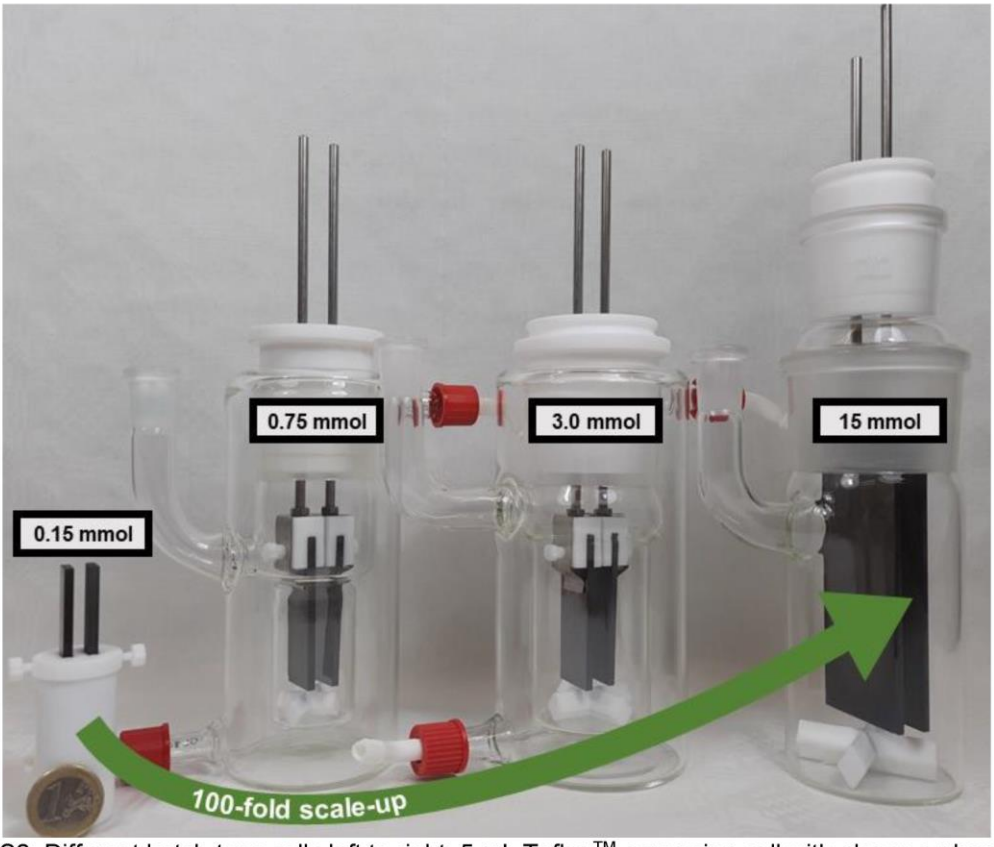
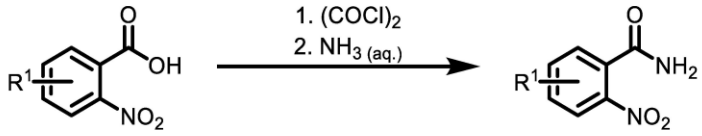


Figure S2: Different batch-type cells left to right: 5 mL Teflon™ screening cell with glassy carbon and BDD electrodes; 50 mL batch-type jacketed glass cell with glassy carbon and BDD electrodes, Teflon™ plug and electrode holders; 250 mL batch-type glass cell with glassy carbon and BDD electrodes, Teflon™ plug and electrode holders.

2. General Protocols

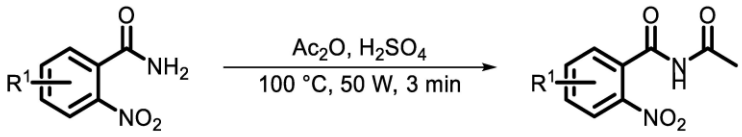
2.1. General Protocol for the Synthesis of Substituted 2-Nitrobenzamides (GPI)



Scheme S1: Synthesis of substituted 2-nitrobenzamides.

DMF (4 drops) was added to the 0.6 M solution of substituted 2-nitrobenzoic acid (1.0 eq.) in anhydrous THF or DCM. The reaction mixture was cooled to 0 °C and oxalyl chloride (1.1 – 2.0 eq.) was slowly added. The reaction solution was stirred at room temperature for 3 hours. After completion of the reaction the reaction mixture was added to aqueous ammonia (25% *w*/*v*, 10.0 eq) at 0 °C and stirred for 30 min at ambient temperature. The solvent was removed under reduced pressure. The precipitate formed was filtered off and washed with water. Residual water was removed by azeotropic distillation using toluene.

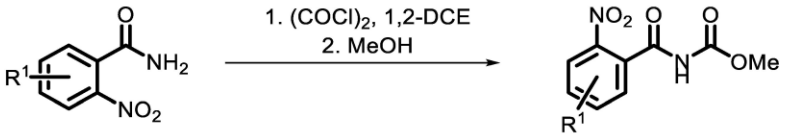
2.2. General Protocol for the Synthesis of Substituted *N*-Acyl-2-nitrobenzamides (GPII)



Scheme S2: Synthesis of substituted *N*-acyl-2-nitrobenzamides.

The reaction was performed in a microwave vial. Anhydride (3.0 – 10.0 eq.) was added to 2-nitrobenzamide (1.0 eq.) followed by the addition of 2 – 3 drops of 96% H_2SO_4. The reaction mixture was irradiated in a microwave for 3 min at 100 °C and 50 W with vigorous stirring. Then the reaction solution was diluted with 10 mL water and extracted three times with 10 mL ethyl acetate. The combined organic fractions were washed twice with 15 mL sat. aq. $NaHCO_3$, once with 15 mL brine and dried over anhydrous Na_2SO_4. The solvent was removed and the crude material was purified by column chromatography.

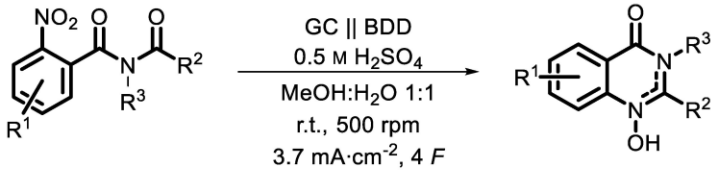
2.3. General Protocol for the Synthesis of Methyl (2-nitrobenzoyl)carbamates (GPIII)



Scheme S3: Electrochemical synthesis of substituted methyl (2-nitrobenzoyl)carbamates.

Oxalyl chloride (1.7 eq.) was added to a 0.4 M solution of 2-nitrobenzamide (1.0 eq.) in 1,2-dichloroethane. The solution was refluxed under argon atmosphere for 3 h. The reaction mixture was cooled to -10 °C, 4 mL of methanol:acetonitrile 1:1 (*v*:*v*) was added and stirred for 2 h. The solvent was removed and the product was precipitated by adding 10 mL of water. The solids were filtered off, washed once with water and dried.

2.4. General Protocol for the Electrochemical Synthesis of Substituted 1*H*-1-Hydroxyquinazolin-4-ones (GPIV)



Scheme S4: Electrochemical synthesis of substituted 1*H*-1-hydroxy-quinazolin-4-ones.

5 mL Teflon™ screening cell: 0.15 mmol of the corresponding substrate was dissolved in 2.5 mL methanol and diluted with 2.5 mL 1 M H_2SO_4 in a 5 mL Teflon™ screening cell equipped with a stirring bar. The glassy carbon anode and the BDD cathode were immersed into the solution (1.5 cm) resulting in a surface area of 1.5 cm^2. The electrolysis was performed under constant current conditions (current density j = 3.7 $mA \cdot cm^{-2}$ for 57.9 C (4 *F*)) with a stirring speed of 500 rpm. After completion of the reaction the pH value of the reaction mixture was adjusted to pH ≈ 8 with an aqueous solution of 1 M $NaHCO_3$. Na_2SO_4 was precipitated by adding 20 mL of methanol. The solids were removed by vacuum filtration and washed twice with 20 mL of methanol. The pH of the filtrate was adjusted to pH ≈ 4 – 5 with glacial acetic acid and the solvent was removed. The crude product was purified by reversed phase column chromatography using water with 0.1% formic acid (*v*/*v*) and acetonitrile.

25 mL glass cell: 0.75 mmol of the corresponding substrate was dissolved in 12.5 mL methanol and diluted with 12.5 mL 1 M H_2SO_4 in a 25 mL glass cell equipped with a stirring bar. The glassy carbon anode and the BDD cathode were immersed into the solution (3 cm) resulting in a surface area of 6 cm^2. The electrolysis was performed under constant current conditions (current density j = 3.7 $mA \cdot cm^{-2}$ for 289.5 C (4 *F*)) with a stirring velocity of 500 rpm. After completion of the reaction the pH value of the reaction mixture was adjusted to pH ≈ 8 with an aqueous solution of 1 M $NaHCO_3$. Na_2SO_4 was precipitated by adding 70 mL of methanol. The solids were removed by vacuum filtration and washed twice with 70 mL of methanol. The pH value of the filtrate was adjusted to pH ≈ 4 – 5 with glacial acetic acid and the solvent was removed. The crude product was purified by reversed phase column chromatography using water with 0.1% formic acid (*v*/*v*) and acetonitrile.

2.5. General Protocol for the Scale-Up of Electrochemical Synthesis of 6a (GPV)

The corresponding substrate was dissolved in methanol and 1 M $H_2SO_{4(aq.)}$ 1:1 (*v*:*v*) in a 100 mL or 250 mL glass cell equipped with a stirring bar. The glassy carbon anode and the BDD cathode were immersed into the solution (100 mL cell:3 cm and 25 mL cell: 7.4 cm) resulting in a surface area of 6 cm^2 (100 mL cell) or 29.7 cm^2 (250 mL cell). The electrolysis was performed under constant current conditions (current density j = 3.7 $mA \cdot cm^{-2}$, 4 *F*) with a stirring speed of 500 rpm. After completion of the reaction the pH of the reaction mixture was adjusted to pH ≈ 8 with an aqueous solution of 1 M $NaHCO_3$. Na_2SO_4 was precipitated by adding 120 mL of methanol. The solids were removed by vacuum filtration and washed twice with 120 mL of methanol. The pH value of the filtrate was adjusted to pH ≈ 4 – 5 with glacial acetic acid and the solvent was removed. The crude product was purified by reversed phase column chromatography using water with 0.1% formic acid (*v*/*v*) and acetonitrile.

3. Optimisation of the Electrolytic Reaction Conditions



Scheme S5: Initial conditions of the electrochemical conversion of compound **5a** into the 1*H*-1-hydroxy-2-methylquinazolin-4-one **6a**.

The optimization experiments of the electrolytic conditions in the reductive cyclisation to the 1*H*-1-hydroxy-2-methylquinazolin-4-one **6a** were conducted using substrate **5a** as standard substrate. The electroreduction were performed according to general procedure **GPIV** determining the yield with ^{1}H NMR spectroscopy using 2,2-dimethylmalonic acid as internal standard. Deviations from the standard electrolytic conditions are shown in table S1.

Table S1: Screening of electrolysis parameters by deviation from the standard conditions for the optimisation of the synthesis of 1*H*-1-hydroxy-2-methylquinazolin-4-one **6a.**

Entry	*j* / mA·cm^2	Solvent:Water 1:1 (*v:v*)	Supporting Electrolyte	Concentration **5a** / mol/L	Cathode	Yield[a] / %
1	-	-	-	-	-	91
2	1.7	-	-	-	-	65
3	2.7	-	-	-	-	78
3	5.7	-	-	-	-	78
4	-	EtOH	-	-	-	84
5	-	MeCN	-	-	-	71
6	-	DMF	-	-	-	89
7	-	MeOH[b]	NH_4HCOO	-	-	47
8	-	-	0.5 M acetate buffer[c]	-	-	66
9	-	-	-	0.02	-	88
10	-	-	-	0.06	-	85
11	-	-	-	0.10	-	73
12	-	-	-	-	Pt	0%
13	-	-	-	-	GC	90
14	-	-	-	-	Isostatic graphite	84
15	-	-	-	-	Pb	27
16	-	-	-	-	CuSn7Pb15	0%

a Yield of 6a was determined by 1H NMR spectroscopy using 2,2-dimethylmalonic acid as internal standard; b no water was used; c 0.5 M AcOH / AcONa was prepared with 90 mmol acetic acid and 10 mmol sodium acetate in 100 mL of distilled water and 100 mL methanol.

4. CV-Studies

Cyclic voltammetry (CV) measurements were carried out by using an Ag/AgCl in saturated EtOH as reference electrode and a glassy carbon rod as counter electrode, respectively. BDD were used as working electrodes. Prior to measurements, the solution in the cell was deaerated with an argon flow for 20–25 min. Argon was kept flowing over the electrolyte during the measurements. The CVs were measured starting from the open circuit potential (OCP) value towards cathodic potentials. Three cycles were recorded with a scan rate of 100 $mV \cdot s^{-1}$. The electrode potentials were converted to the reference redox system ferrocene/ferricenium ion (FcH^+/FcH). A blank measurement of the electrolyte is shown in figure S3. The CV measurement of the test substrate **5a** is depicted in figure S4. Hereby, a single broad reduction peak is observed at 0.94 V.

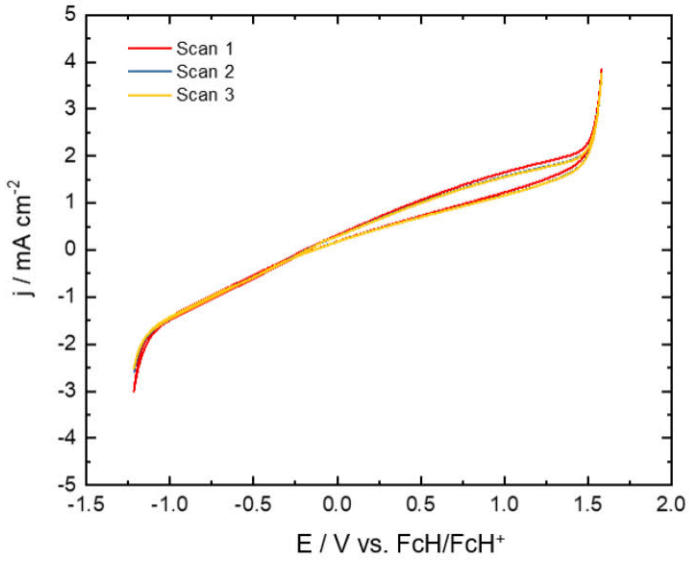


Figure S3: 0.5 M Sulphuric acid in a 1:1 (*v*:*v*) methanol–water mixture; working electrode: BDD; counter electrode: glassy carbon; reference electrode: Ag/AgCl in sat. LiCl/EtOH; Scan rate: 100 mV/s, 3 scans. Potential referenced vs. FcH/FcH^+ ($FcH = Fe(\eta^5\text{-}C_5H_5)_2$).

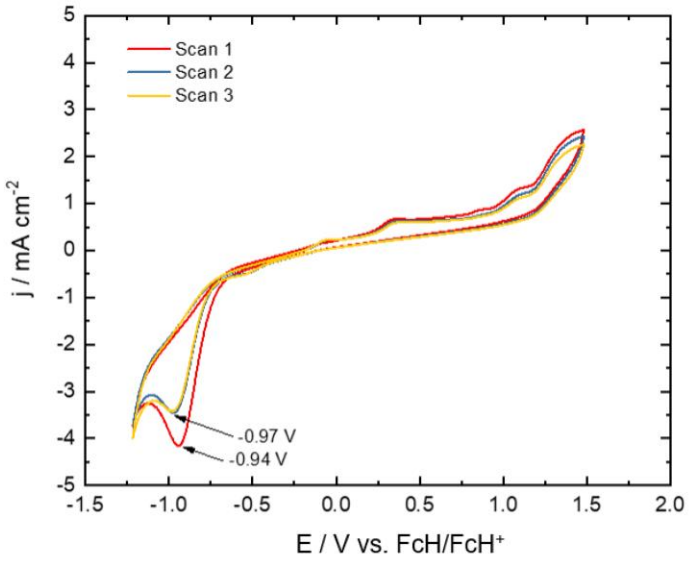
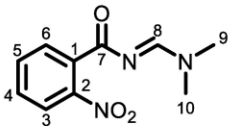


Figure S4: Test substrate **5a** *c*(substrate) = 5.0 mM + 0.5 M Sulphuric acid in a 1:1 (*v*:*v*) methanol–water mixture; working electrode: BDD; counter electrode: glassy carbon; reference electrode: Ag/AgCl in sat. LiCl/EtOH; Scan rate: 100 mV/s, 3 scans. Potential referenced vs. FcH/FcH^+($FcH = Fe(\eta^5\text{-}C_5H_5)_2$).

5. Preparation of Products and Analytical Data

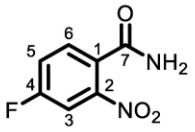
N-(2-(Dimethylamino)vinyl)-2-nitrobenzamide (9)



Under argon atmosphere 2-nitrobenzamide (2.49 g, 15 mmol, 1.0 eq.) and DMF-DMA (5.36 g, 45 mmol, 3.0 eq.) were dissolved in 50 mL anhydrous toluene and refluxed for 24 h. After cooling the reaction mixture to 8 °C 20 mL of cyclohexane was added. The precipitate formed was filtered off, washed twice with cold cyclohexane and twice with cold *n*-pentane. 2.863 g (12.9 mmol, 86%) of the product was isolated as colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.55 (s, 1H, *H*-8), 7.92–7.86 (m, 1H, *H*-3), 7.69–7.65 (m, 1H, *H*-6), 7.60–6.54 (m, 1H, *H*-4), 7.52–7.46 (m, 1H, *H*-5), 3.15 (s, 3H, *H*-9), 3.07 (s, 1H, *H*-10).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 176.2, 160.6, 149.6, 133.5, 131.9, 130.7, 130.4, 41.7, 35.6.
HR-MS: *m/z* for $C_{10}H_{11}N_3O_3+H^+$, $[M+H]^+$ calculated: 222.0873; found: 222.0873.
The spectroscopic data are in accordance with those reported in the literature.[4]

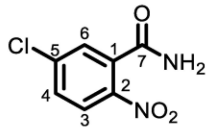
4-Fluoro-2-nitrobenzamide (10a)



According to general protocol I **GPI** 4-fluoro-2-nitrobenzoic acid (1.11 g, 6 mmol, 1.0 eq.) and 0.6 mL oxalyl chloride were reacted. The title compound was isolated as colourless amorphous solid (0.790 g, 4.3 mmol, 72%).

^{1}H NMR (300 MHz, DMSO-d_6) δ [ppm]: 8.17 (s, 1H, C7-NH_2), 7.98 (dd, 1H, *J* = 8.6 Hz, 2.4 Hz, *H*-3), 7.77–7.62 (m, 3H, *H*-5, *H*-6, C7-NH_2).
^{13}C NMR (75 MHz, DMSO-d_6) δ [ppm]: 166.1, 162.9, 160.4, 148.5 (d, *J* = 9.3 Hz), 131.1 (d, *J* = 8.8 Hz), 128.7 (d, *J* = 3.7 Hz), 120.1 (d, *J* = 21.4 Hz), 111.9 (d, J = 27.3 Hz).
^{19}F NMR (282 MHz, DMSO-d_6) δ [ppm]: -108.10 (td, *J* = 8.4 Hz, 5.6 Hz).
HR-MS: *m/z* for $C_7H_5FN_2O_3+H^+$, $[M+H]^+$ calculated: 185.0357; found: 185.0353.
The spectroscopic data are in accordance with those reported in the literature.[5]

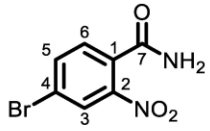
5-Chloro-2-nitrobenzamide (10b)



According to general protocol I **GPI** 5-chloro-2-nitrobenzoic acid (1.08 g, 5 mmol, 1.0 eq.) and 0.5 mL oxalyl chloride were reacted. The title compound was isolated as colourless amorphous solid (0.775 g, 3.9 mmol, 78%).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 8.21 (s, 1H, C7-NH_2), 8.05 (d, 1H, *J* = 8.6 Hz, *H*-6), 7.82 (s, 1H, C7-NH_2), 7.78–7.70 (m, 2H, *H*-3, *H*-4).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 165.7, 145.7, 137.9, 134.3, 130.4, 128.7, 126.1.
HR-MS: *m/z* for $C_7H_5{}^{35}ClN_2O_3+H^+$, $[M+H]^+$ calculated: 201.0061; found: 201.0059.

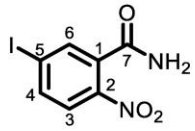
4-Bromo-2-nitrobenzamide (10c)



According to general protocol I **GPI** 4-bromo-2-nitrobenzoic acid (1.47 g, 6 mmol, 1.0 eq.) and 0.6 mL oxalyl chloride were reacted. The title compound was isolated as colourless amorphous solid (1.293 g, 5.3 mmol, 88%).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 8.24 (d, 1H, *J* = 1.9 Hz, *H*-3), 8.20 (s, 1H, C7-NH_2), 7.99 (dd, 1H, *J* = 8.2 Hz, 1.9 Hz, *H*-5), 7.77 (s, 1H, C7-NH_2), 7.59 (d, *J* = 8.2 Hz, *H*-6).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 166.2, 148.1, 135.9, 131.2, 130.6, 126.7, 122.8.
HR-MS: *m/z* for $C_7H_5{}^{79}BrN_2O_3+H^+$, $[M+H]^+$ calculated: 244.9556; found: 244.9552.

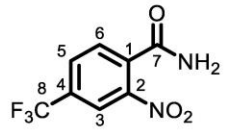
5-Iodo-2-nitrobenzamide (10d)



According to general protocol I **GPI** 5-iodo-2-nitrobenzoic acid (1.76 g, 6 mmol, 1.0 eq.) and 0.6 mL oxalyl chloride were reacted. The title compound was isolated as colourless amorphous solid (1.666 g, 5.7 mmol, 95%).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 8.18 (s, 1H, C7-NH_2), 8.05 (dd, 1H, *J* = 8.5 Hz, 1.9 Hz, *H*-4), 7.97 (d, 1H, *J* = 1.9 Hz, *H*-6), 7.81–7.72 (m, 2H, C7-NH_2, *H*-3).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 165.7, 146.7, 139.3, 137.1, 133.9, 125.6, 101.5.
HR-MS: *m/z* for $C_7H_5IN_2O_3$+H^+, $[M+H]^+$ calculated: 336.9327; found: 336.9326.

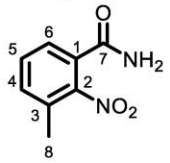
2-Nitro-4-(trifluoromethyl)benzamide (10e)



According to general protocol I **GPI** 2-nitro-4-(trifluoromethyl)benzoic acid (0.51 g, 2 mmol, 1.0 eq.) and 0.2 mL oxalyl chloride were reacted. The title compound was isolated as colourless amorphous solid (0.405 g, 1.7 mmol, 77%).

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]: 8.41 (d, 1H, *J* = 1.8 Hz, *H*-3), 8.31 (s, 1H, C7-NH_2), 8.19 (dd, 1H, *J* = 8.0 Hz, 1.0 Hz, *H*-5), 7.91 (s, 1H, C7-NH_2), 7.87 (d, 1H, *J* = 8.0 Hz, *H*-6).
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]: 166.1, 147.4, 136.1, 130.7 (q, *J* = 31.6 Hz), 130.4, 130.2 (q, *J* = 3.6 Hz), 122.8 (q, *J* = 272.8 Hz), 121.5.
^{19}F NMR (282 MHz, DMSO-d_6) δ [ppm]: -61.49.
HR-MS: *m/z* for $C_8H_5F_3N_2O_3$+H^+, $[M+H]^+$ calculated: 235.0325; found: 235.0329.

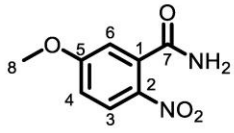
3-Methyl-2-nitrobenzamide (10f)



According to general protocol I **GPI** 3-methyl-2-nitrobenzoic acid (0.91 g, 5 mmol, 1.0 eq.) and 0.5 mL oxalyl chloride were reacted. The title compound was isolated as colourless amorphous solid (0.795 g, 4.4 mmol, 88%).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 8.19 (s, 1H, C7-NH_2), 7.68 (s, 1H, C7-NH_2), 7.62–7.49 (m, 1H, *H*-4, *H*-5, *H*-6), 2.28 (s, 3H, *H*-8).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 166.2, 149.2, 133.6, 130.4, 130.0, 129.5, 126.3, 16.7.
HR-MS: *m/z* for $C_8H_8N_2O_3$+H^+, $[M+H]^+$ calculated: 181.0608; found: 181.0608.
The spectroscopic data are in accordance with those reported in the literature.[6]

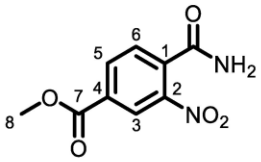
5-Methoxy-2-nitrobenzamide (10g)



According to general protocol I **GPI** 5-methoxy-2-nitrobenzoic acid (0.99 g, 5 mmol, 1.0 eq.) and 0.5 mL oxalyl chloride were reacted. The title compound was isolated as colourless amorphous solid (0.364 g, 1.9 mmol, 38%).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 8.09–7.99 (m, 2H, C7-NH_2, *H*-3), 7.66 (s, 1H, C7-NH_2), 7.14 (dd, 1H, *J* = 9.1 Hz, 2.8 Hz, *H*-4), 7.05 (d, 1H, *J* = 2.8 Hz, *H*-6), 3.90 (s, 3H, *H*-8).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 167.3, 162.9, 139.3, 135.9, 126.7, 114.7, 114.0, 56.4.
HR-MS: *m/z* for $C_8H_8N_2O_4$+Na^+, $[M+Na]^+$ calculated: 219.0376; found: 219.0374.

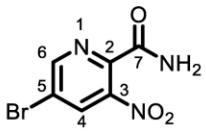
Methyl 4-carbamoyl-3-nitrobenzoate (10h)



According to general protocol I **GPI** 4-(methoxycarbonyl)-2-nitrobenzoic acid (0.90 g, 4 mmol, 1.0 eq.) and 0.4 mL oxalyl chloride were reacted. The title compound was isolated as colourless amorphous solid (0.759 g, 3.4 mmol, 85%).

^{1}H NMR (300 MHz, DMSO-d_6) δ [ppm]: 8.43 (d, 1H, *J* = 1.6 Hz, *H*-3), 8.31–8.25 (m, 2H, C7-NH_2, *H*-5), 7.86 (s, 1H, C7-NH_2), 7.78 (d, 1H, *J* = 8.0 Hz, *H*-6), 3.92 (s, 3H, *H*-8).
^{13}C NMR (75 MHz, DMSO-d_6) δ [ppm]: 166.5, 164.1, 147.0, 136.5, 133.7, 131.4, 129.7, 124.5, 53.0.
HR-MS: *m/z* for $C_9H_8N_2O_5$+H$^+$, [M+H]$^+$ calculated: 225.0506; found: 225.0506.
The spectroscopic data are in accordance with those reported in the literature.[7]

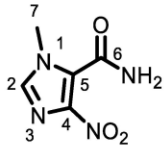
5-Bromo-3-nitropicolinamide (10i)



5-Bromo-3-nitropicolinonitrile (0.91 g, 4 mmol, 1.0 eq.) was dissolved in11 mL 96% sulphuric acid and heated at 70 °C for 6 h. After completion of the reaction the reaction mixture was cooled to room temperature and diluted with 50 mL cold water. The precipitates formed were filtered off and washed twice with water. Residual water was removed by azeotropic distillation with toluene. 0.922 g (3.8 mmol, 95%) of the product was isolated as colourless amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 9.03 (d, 1H, *J* = 2.0 Hz, *H*-4), 8.84 (d, 1H, *J* = 2.0 Hz, *H*-6), 8.32 (s, 1H, C7-NH_2), 8.01 (s, 1H, C7-NH_2).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 164.1, 152.5, 145.2, 144.0, 134.8, 121.8.
HR-MS: *m/z* for $C_6H_4{}^{79}BrN_3O_3$+H$^+$, [M+H]$^+$ calculated: 245.9509; found: 245.9509.

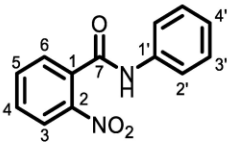
1*H*-1-Methyl-4-nitro-imidazole-5-carboxamide (10j)



1*H*-5-Chloro-1-methyl-4-nitro-imidazole (6.46 g, 40 mmol, 1.0 eq.) was suspended in 50 mL anhydrous ethanol. Potassium iodide (0.20 g, 1 mmol, 0.03 eq.) and potassium cyanide (5.21 g, 80 mmol, 2.0 eq.) were added and the reaction mixture was heated at reflux for 12 h. After completion 100 mL water was added. The aqueous layer was extracted three times with 100 mL dichloromethane. The organic fraction was washed twice with 100 mL water, once with 100 mL brine and dried over magnesium sulphate. The solvent was removed and the crude product was used without further purification.
The crude product was heated with 100 mL 90% sulphuric acid at 100°C. After completion the reaction mixture was cooled to room temperature and 100 mL water was added. The solution was neutralised with 1 M sodium bicarbonate. The precipitates formed were filtered off and washed twice with water and dried. 4.80 g (28mmol, 70%) of the product was isolated as colourless amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 8.34 (s, 1H, C7-NH_2), 8.16 (s, 1H, C7-NH_2), 7.84 (s, 1H, *H*-2), 7.84 (s, 1H, *H*-2), 3.69 (s, 1H, *H*-7).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 159.7, 143.1, 136.9, 127.7, 33.1.
HR-MS: *m/z* for $C_5H_6N_4O_3$+H$^+$, [M+H]$^+$ calculated: 171.0513; found: 171.0511.

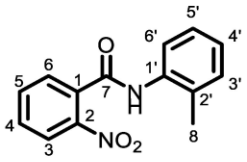
2-Nitro-*N*-phenylbenzamide (11a)



Aniline (5.10 g, 55 mmol, 1.8 eq.) and 6 mL pyridine was dissolved in 150 mL anhydrous THF. The reaction mixture was cooled to 0 °C and 2-nitrobenzoylchloride (5.56 g, 30 mmol, 1.0 eq.) in 50 mL anhydrous THF was added dropwise. After addition the reaction mixture was stirred for 24 h at room temperature. 30 mL of water was added and the THF was removed under reduced pressure. 50 mL of 1 M hydrochloric acid was added and the aqueous layer was extracted three times with 50 mL ethyl acetate. The combined organic fractions were washed four times with 50 mL 1 M hydrochloric acid, once with 50 mL brine and dried over magnesium sulphate. The solvent was removed and the crude product was recrystallised with ethanol. 5.447 g (22.5 mmol, 75%) of the product was obtained as colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.92 (s, 1H, C7-N*H*-), 8.06 (d, 1H, *J* = 8.34 Hz, *H*-3), 7.76–7.68 (m, 1H, *H*-5), 7.66–7.52 (m, 4H, *H*-4, *H*-6, *H*-2'), 7.42–7.33 (m, 2H, *H*-3'), 7.23–7.13 (m, 1H, *H*-4').
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 164.5, 146.4, 137.4, 134.1, 133.0, 130.9, 129.3, 128.7, 125.4, 124.9.
HR-MS: *m/z* for $C_{13}H_{10}N_2O_3$+H$^+$, [M+H]$^+$ calculated: 243.0764; found: 243.0764.
The spectroscopic data are in accordance with those reported in the literature.[8]

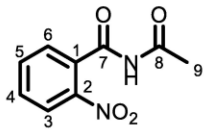
2-Nitro-*N*-(o-tolyl)benzamide (11b)



o-Toluidine (1.73 g, 15 mmol, 1.5 eq.) and 2 mL pyridine was dissolved in 50 mL anhydrous THF. The reaction mixture was cooled to 0 °C and 2-nitrobenzoylchloride (1.90 g, 10 mmol, 1.0 eq.) in 50 mL anhydrous THF was added dropwise. After addition the reaction mixture was stirred for 24 h at room temperature. 20 mL of water was added and the THF was removed under reduced pressure. 50 mL of 1 M hydrochloric acid was added and the aqueous layer was extracted three times with 50 mL ethyl acetate. The combined organic fractoions were washed four times with 50 mL 1 M hydrochloric acid, once with 50 mL brine and dried over magnesium sulphate. The solvent was removed and the crude product was recrystallised with ethanol. 1.139 g (4.4 mmol, 44%) of the product was obtained as colourless solid.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.39 (s, 1H, C7-N*H*-), 8.09 (dd, 1H, *J* = 8.2 Hz, 1.2 Hz, *H*-3), 7.81 (td, 1H, *J* = 7.5 Hz, 1.2 Hz, *H*-5), 7.75 (dd, 1H, *J* = 7.5 Hz, 1.6 Hz, *H*-6), 7.70 (td, 1H, *J* = 8.2 Hz, 1.6 Hz, *H*-4), 7.59 (d, 1H, *J* = 1.4 Hz, *H*-6'), 7.32–7.23 (m, 2H, *H*-3', *H*-4'), 7.18 (td, 1H, *J* = 7.4 Hz, 1.4 Hz, *H*-5'), 2.30 (s, 3H, *H*-8).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 164.9, 146.9, 135.4, 134.0, 132.9, 132.5, 130.9, 130.6, 129.1, 126.3, 126.3, 125.2, 124.4, 17.1.
HR-MS: *m/z* for $C_{14}H_{12}N_2O_3$+H$^+$, [M+H]$^+$ calculated: 257.0921; found: 257.0920.
The spectroscopic data are in accordance with those reported in the literature.[9]

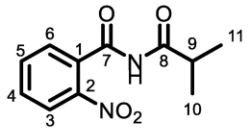
***N*-Acetyl-2-nitrobenzamide (5a)**



According to general protocol II **GPII** 2-nitrobenzamide (0.498 g, 3 mmol, 1.0 eq.) and anhydride (3 mL, 30 mmol, 10.0 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.587 g, 2.8 mmol, 94%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate = 1:1).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 11.42 (s, 1H, C7-N*H*-), 8.19 (dd, 1H, *J* = 8.2 Hz, 1.2 Hz, *H*-3), 7.85 (td, 1H, *J* = 7.5 Hz, 1.2 Hz, *H*-5), 7.72 (dd, 1H, *J* = 8.2 Hz, 7.5 Hz, 1.5 Hz, *H*-4), 7.61 (dd, 1H, *J* = 7.5 Hz, 1.5 Hz, *H*-6), 2.15 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 170.6, 167.0, 145.2, 134.7, 132.8, 130.7, 128.4, 124.0, 24.5.
HR-MS: *m/z* for $C_9H_8N_2O_4$+Na$^+$, [M+Na]$^+$ calculated: 231.0376; found: 231.0378.
The spectroscopic data are in accordance with those reported in the literature.[10]

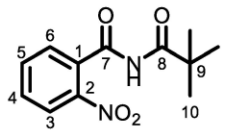
***N*-Isobutyryl-2-nitrobenzamide (5b)**



According to general protocol II **GPII** 2-nitrobenzamide (0.33 g, 2 mmol, 1.0 eq.) and anhydride (3 mL, 30 mmol, 15.0 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.431 g, 1.8 mmol, 90%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 9.28 (s, 1H, C7-N*H*-), 8.22 (dd, 1H, *J* = 8.2 Hz, 1.2 Hz, *H*-3), 7.74 (td, 1H, *J* = 7.5 Hz, 1.2 Hz, *H*-5), 7.62 (ddd, 1H, *J* = 8.2 Hz, 7.5 Hz, 1.5 Hz, *H*-4), 7.43 (dd, 1H, *J* = 7.5 Hz, 1.5 Hz, *H*-6), 2.73 (hept, 1H, *J* = 6.9 Hz, *H*-9), 1.18 (s, 3H, *H*-10), 1.15 (s, 3H, *H*-11).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 176.6, 168.8, 145.3, 134.5, 132.9, 130.5, 127.7, 124.4, 36.1, 18.7.
HR-MS: *m/z* for $C_{11}H_{12}N_2O_4$+Na$^+$, [M+Na]$^+$ calculated: 259.0689; found: 259.0695.

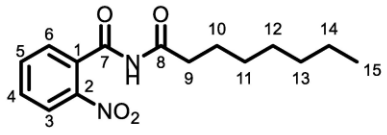
2-Nitro-*N*-pivaloylbenzamide (5c)



According to general protocol **GPII** 2-nitrobenzamide (0.33 g, 2 mmol, 1.0 eq.) and anhydride (4 mL, 20 mmol, 10.0 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.426 g, 1.7 mmol, 85%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate = 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.87 (s, 1H, C7-N*H*-), 8.24 (dd, 1H, *J* = 8.2 Hz, 1.2 Hz, *H*-3), 7.74 (td, 1H, *J* = 7.5 Hz, 1.2 Hz, *H*-5), 7.61 (ddd, 1H, *J* = 8.2 Hz, 7.5 Hz, 1.4 Hz, *H*-4), 7.40 (dd, 1H, *J* = 7.5 Hz, 1.4 Hz, *H*-6), 1.22 (s, 9H, *H*-10).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 177.0, 169.2, 145.0, 134.5, 133.3, 130.2, 127.5, 124.2, 40.1, 26.8.
HR-MS: *m/z* for $C_{12}H_{14}N_2O_4$+Na$^+$, [M+Na]$^+$ calculated: 273.0846; found: 273.0847.

2-Nitro-*N*-octanoylbenzamide (5d)

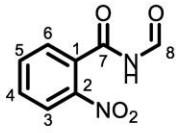


2-Nitrobenzamide (2.99 g, 18 mmol, 1.0 eq.) was suspended in nonanoic anhydride (16 mL, 54 mmol, 3.0 eq.) and 3 drops of sulphuric acid were added in a pressured vial. The reaction mixture was heated at 100 °C for 2 h. After completion of the reaction the solution was poured into 100 mL water and extracted three times with 150 mL ethyl acetate. The combined organic fractions were washed twice with 200 mL 1 M sodium bicarbonate solution, once with 200 mL brine and dried over sodium sulphate. The solvent was removed and the product was isolated as colourless amorphous solid (3.95 g, 13.5 mmol, 75%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 9.14 (s, 1H, C7-N*H*-), 8.20 (dd, 1H, *J* = 8.2 Hz, 1.2 Hz, *H*-3), 7.73 (td, 1H, *J* = 7.6 Hz, 1.2 Hz, *H*-5), 7.62 (ddd, 1H, *J* = 8.2 Hz, 7.5 Hz, 1.4 Hz, *H*-4),

7.40 (dd, 1H, *J* = 7.5 Hz, 1.4 Hz, *H*-6), 2.56 (t, 2H, *J* = 7.5 Hz, *H*-9), 1.61 (p, 2H, *J* = 8.3 Hz, *H*-10), 1.37–1.21 (m, 8H, *H*-11, *H*-12, *H*-13, *H*-14), 0.92–0.82 (m, 3H, *H*-15).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 173.5, 167.8, 145.5, 134.4, 132.6, 130.7, 127.8, 124.5, 37.3, 31.7, 29.1, 29.0, 24.2, 22.7, 14.2.
HR-MS: *m/z* for $C_{15}H_{20}N_2O_4$+Na^+, $[M+Na]^+$ calculated: 315.1315; found: 315.1315.

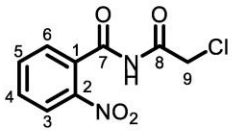
***N*-Formyl-2-nitrobenzamide (5e)**



N-(2-(Dimethylamino)vinyl)-2-nitrobenzamide (2.65 g, 12 mmol, 1.0 eq.) was suspended in 100 mL water. *p*-Toluenesulfonic acid (2.28 g, 12 mmol, 1.0 Eq.) in 20 mL water was added at room temperature. The resulting solution was stirred for 24 h. The precipitates formed were filtered, washed with water and residual dried by azeotropic distillation using toluene. 1.761 g (9.1 mmol, 76%) of the product were isolated as colourless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 9.12 (s, 1H, *H*-8), 8.81 (s, 1H, C7-N*H*-), 8.21 (dd, 1H, *J* = 8.1 Hz, 1.3 Hz, *H*-3), 7.81 (td, 1H, *J* = 7.5 Hz, 1.3 Hz, *H*-5), 7.73 (ddd, 1H, *J* = 8.2 Hz, 7.5 Hz, 1.5 Hz, *H*-4), 7.59 (dd, 1H, *J* = 7.5 Hz, 1.4 Hz, *H*-6).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 166.4, 162.2, 146.1, 134.6, 132.2, 130.1, 128.4, 125.2.
HR-MS: *m/z* for $C_8H_6N_2O_4$+Na^+, $[M+Na]^+$ calculated: 217.0220; found: 217.0217.
The spectroscopic data are in accordance with those reported in the literature.[11]

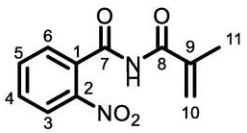
***N*-(2-Chloroacetyl)-2-nitrobenzamide (5f)**



2-Chloroacetyl chloride (0.8 mL, 4 mmol, 2.5 eq.) was added to 2-nitrobenzamide (0.66 mg, 4 mmol, 1.0 eq.). The suspension was stirred at 110 °C for 45 min. The reaction mixture was cooled down to room temperature and purified by flash column chromatography (SiO_2, cyclohexane:ethyl acetate 2:1). 0.793 g (3.2 mmol, 80%) of the product was isolated as colourless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 9.07 (s, 1H, C7-N*H*-), 8.24 (dd, 1H, *J* = 8.2 Hz, 1.2 Hz, *H*-3), 7.77 (td, 1H, *J* = 7.5 Hz, 1.2 Hz, *H*-5), 7.67 (ddd, 1H, *J* = 8.2 Hz, 7.5 Hz, 1.5 Hz, *H*-4), 7.46 (dd, 1H, *J* = 7.5 Hz, 1.5 Hz, *H*-6), 4.29 (s, 2H, *H*-9).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 166.8, 165.9, 145.5, 134.6, 131.7, 131.2, 127.8, 124.6, 43.4.
HR-MS: *m/z* for $C_9H_7{}^{35}ClN_2O_4$+Na^+, $[M+Na]^+$ calculated: 264.9987; found: 264.9983.

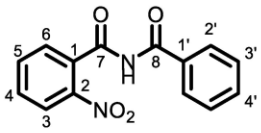
***N*-Methacryloyl-2-nitrobenzamide (5g)**



According to general protocol **GPII** 2-nitrobenzamide (0.50 g, 3 mmol, 1.0 eq.) and anhydride (1.3 mL, 9 mmol, 3.0 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.089 g, 0.4 mmol, 13%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate = 1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 9.16 (s, 1H, C7-N*H*-), 8.26 (dd, 1H, *J* = 8.2 Hz, 1.2 Hz, *H*-3), 7.75 (td, 1H, *J* = 7.5 Hz, 1.2 Hz, *H*-5), 7.62 (ddd, 1H, *J* = 8.2 Hz, 7.5 Hz, 1.5 Hz, *H*-4), 7.42 (dd, 1H, *J* = 7.5 Hz, 1.5 Hz, *H*-6), 5.95–5.65 (m, 2H, *H*-10, *H*-10'), 1.91 (s, 3H, *H*-11).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 169.1, 165.8, 145.2, 138.7, 134.5, 133.1, 130.3, 127.5, 124.3, 18.3.
HR-MS: *m/z* for $C_{11}H_{10}N_2O_4$+Na^+, $[M+Na]^+$ calculated: 257.0533; found: 257.0535.

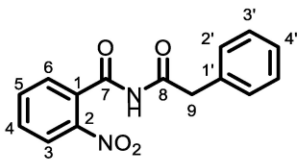
_N_-Benzoyl-2-nitrobenzamide (5h)



According to general protocol **GPII** 2-nitrobenzamide (0.50 g, 3 mmol, 1.0 eq.) and anhydride (2.4 mL, 9 mmol, 3.0 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.348 g, 1.3 mmol, 43%) after flash column chromatography (SiO_2, dichloromethane:methanol 50:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 9.43 (s, 1H, C7-N*H*-), 8.26 (dd, 1H, *J* = 8.3 Hz, 1.2 Hz, *H*-3), 7.87–7.82 (m, 2H, *H*-2'), 7.77 (td, 1H, *J* = 7.5 Hz, 1.2 Hz, *H*-5), 7.69–7.57 (m, 2H, *H*-4, *H*-6), 7.51–7.45 (m, 3H, *H*-3', *H*-4').
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 169.1, 165.0, 145.4, 134.5, 133.9, 133.1, 131.7, 130.4, 129.2, 128.1, 127.6, 124.3.
HR-MS: *m/z* for $C_{14}H_{10}N_2O_4$+Na^+, $[M+Na]^+$ calculated: 293.0533; found: 293.0535.

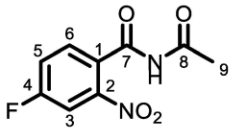
2-Nitro-_N_-(2-phenylacetyl)benzamide (5i)



Under argon atmosphere 2-Nitrobenzamide (0.66 g, 4 mmol, 1.0 eq.) was partially dissolved in 20 mL anhydrous THF. The reaction mixture was cooled to 0 °C, sodium hydride 60% dispersion on paraffin oil (*w*:*w*, 0.40 g, 10 mmol, 2.5 eq.) was added and the reaction was stirred at room temperature for 40 min. 2-Phenylacetyl chloride (1.2 mL, 9 mmol, 2.3 eq.) was slowly added and the reaction mixture was stirred at room temperature overnight. After completion of the reaction 20 mL saturated ammonium chloride solution was added. The aqueous layer was extracted three times with 15 mL ethyl acetate. The combined organic layers were washed once with 20 mL brine and dried over magnesium sulphate. The solvent was removed and the crude product was purified by flash column chromatography (SiO_2, cyclohexane:ethyl acetate 2:1). 0.282 g (1.0 mmol, 25%) of the product was isolated as colourless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.76 (s, 1H, C7-N*H*-), 8.20 (dd, 1H, *J* = 8.3 Hz, 1.2 Hz, *H*-3), 7.71 (td, 1H, *J* = 7.5 Hz, 1.2 Hz, *H*-5), 7.61 (ddd, 1H, *J* = 8.3 Hz, 7.5 Hz, 1.2 Hz, *H*-4), 7.43–7.29 (m, 4H, *H*-6, *H*-2', *H*-4'), 7.28–7.21 (m, 2H, *H*-3'), 3.82 (s, 2H, *H*-9).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 170.6, 167.7, 145.4, 132.6, 132.5, 130.7, 129.7, 129.3, 128.0, 127.7, 124.5, 44.2.
HR-MS: *m/z* for $C_{15}H_{11}N_2O_4$-H^+, $[M-H]^-$ calculated: 283.0726; found: 283.0724.

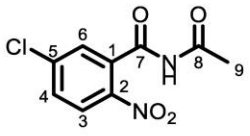
***N*-Acetyl-4-fluoro-2-nitrobenzamide (5j)**



According to general protocol **GPII** 4-fluoro-2-nitrobenzamide (0.37 g, 2 mmol, 1.0 eq.) and anhydride (1.9 mL, 20 mmol, 10.0 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.396 g, 1.8 mmol, 90%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 2:1).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 11.44 (s, 1H, C7-N*H*-), 8.12 (dd, 1H, *J* = 8.8 Hz, 2.4 Hz, *H*-3), 7.82–7.66 (m, 2H, *H*-5, *H*-6), 2.15 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 166.0, 161.7 (d, *J* = 250.8 Hz), 146.5 (d, *J* = 9.1 Hz), 130.7 (d, *J* = 8.9 Hz), 129.2, 121.7 (d, *J* = 21.8 Hz), 111.9 (d, *J* = 27.3 Hz).
^{19}F NMR (282 MHz, DMSO-d_6) δ [ppm]: -107.96 (q, *J* = 7.6 Hz).
HR-MS: *m/z* for $C_9H_7FN_2O_4$+Na^+, $[M+Na]^+$ calculated: 249.0282; found: 249.0281.

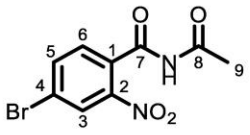
***N*-Acetyl-5-chloro-2-nitrobenzamide (5k)**



According to general protocol **GPII** 5-chloro-2-nitrobenzamide (0.30 g, 1.5 mmol, 1.0 eq.) and anhydride (1.4 mL, 15 mmol, 7.5 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.313 g, 1.3 mmol, 87%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 3:1).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 11.51 (s, 1H, C7-N*H*-), 8.22 (d, 1H, *J* = 8.5 Hz, *H*-3), 7.88–7.70 (m, 2H, *H*-4, *H*-6), 2.14 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 170.6, 165.5, 143.6, 139.6, 134.6, 130.4, 128.1, 126.1, 24.3.
HR-MS: *m/z* for $C_9H_7{}^{35}ClN_2O_4$+Na^+, $[M+Na]^+$ calculated: 264.9987; found: 264.9985.

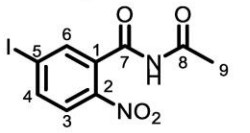
***N*-Acetyl-4-bromo-2-nitrobenzamide (5l)**



According to general protocol **GPII** 4-bromo-2-nitrobenzamide (0.49 g, 2 mmol, 1.0 eq.) and anhydride (1.9 mL, 20 mmol, 10.0 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.488 g, 1.7 mmol, 85%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 9.38 (s, 1H, C7-N*H*-), 8.20 (d, 1H, *J* = 1.9 Hz, *H*-3), 7.85 (dd, 1H, *J* = 8.1 Hz, 1.9 Hz, *H*-5), 7.33 (d, 1H, *J* = 8.1 Hz, 1.9 Hz, *H*-6), 2.33 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 171.0, 166.8, 146.1, 137.4, 131.0, 129.1, 127.7, 124.5, 24.9.
HR-MS: *m/z* for $C_9H_7{}^{79}BrN_2O_4$+Na^+, $[M+Na]^+$ calculated: 308.9481; found: 308.9494.

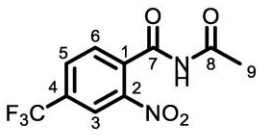
***N*-Acetyl-5-iodo-2-nitrobenzamide (5m)**



According to general protocol **GPII** 5-iodo-2-nitrobenzamide (0.58 g, 2 mmol, 1.0 eq.) and anhydride (1.9 mL, 20 mmol, 10.0 eq.) were reacted. The title compound was isolated as yellow amorphous solid (0.378 g, 1.1 mmol, 55%) after reverse phase flash column chromatography (0 → 100% acetonitrile).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 11.45 (s, 1H, C7-N*H*-), 8.10 (dd, 1H, *J* = 8.6 Hz, 1.9 Hz, *H*-4), 8.03 (d, 1H, *J* = 1.9 Hz, *H*-6), 7.93 (d, 1H, *J* = 1.9 Hz, *H*-3), 2.14 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 170.6, 165.5, 144.6, 139.4, 136.5, 134.0, 125.5, 103.6, 24.4.
HR-MS: *m/z* for $C_9H_7IN_2O_4$+Na^+, $[M+Na]^+$ calculated: 356.9343; found: 356.9337.

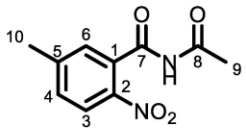
***N*-Acetyl-2-nitro-4-(trifluoromethyl)benzamide (5n)**



According to general protocol **GPII** 2-nitro-4-(trifluoromethyl)benzamide (0.25 g, 1 mmol, 1.0 eq.) and anhydride (1.0 mL, 11 mmol, 11.0 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.260 g, 0.9 mmol, 90%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 2:1).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 9.29 (s, 1H, C7-N*H*-), 8.47 (d, 1H, *J* = 1.7 Hz, *H*-3), 8.02–7.97 (m, 1H, *H*-5), 7.59 (d, 1H, *J* = 8.0 Hz, *H*-6), 2.30 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 170.4, 166.7, 145.5, 135.5, 133.3 (q, *J* = 34.6 Hz), 131.2 (q, *J* = 3.5 Hz), 128.8, 122.5 (q, *J* = 273.2 Hz), 121.9 (d, *J* = 3.8 Hz), 24.7.
^{19}F NMR (282 MHz, DMSO-d_6) δ [ppm]: -61.48.
HR-MS: *m/z* for $C_{10}H_7F_3N_2O_4$+Na^+, $[M+Na]^+$ calculated: 299.0250; found: 299.0249.

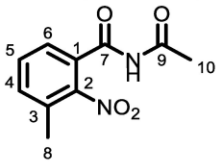
***N*-Acetyl-5-methyl-2-nitrobenzamide (5o)**



According to general protocol **GPII** 5-methyl-2-nitrobenzamide (1.00 g, 6 mmol, 1.0 eq.) and anhydride (6 mL, 56 mmol, 9.0 eq.) were reacted. The title compound was isolated as colourless amorphous solid (1.07 g, 4.8 mmol, 80%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 9.11 (s, 1H, C7-N*H*-), 8.07 (d, 1H, *J* = 8.4 Hz, *H*-3), 7.39 (ddd, 1H, *J* = 8.4 Hz, 1.9 Hz, 0.8 Hz, *H*-4), 7.24 (d, 1H, *J* = 1.9 Hz, *H*-6), 2.47 (s, 3H, *H*-10), 2.36 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 171.1, 167.5, 146.2, 143.3, 132.3, 131.4, 128.3, 124.7, 25.0, 21.6.
HR-MS: *m/z* for $C_{10}H_{10}N_2O_4$+Na^+, $[M+Na]^+$ calculated: 245.0533; found: 245.0532.

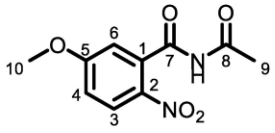
***N*-Acetyl-3-methyl-2-nitrobenzamide (5p)**



According to general protocol **GPII** 3-methyl-2-nitrobenzamide (0.13 g, 0.7 mmol, 1.0 eq.) and anhydride (0.7 mL, 7 mmol, 10.0 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.140 g, 0.63 mmol, 90%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.98 (s, 1H, C7-N*H*-), 7.57–7.43 (m, 3H, *H*-4, *H*-5, *H*-6), 2.49 (s, 3H, *H*-10), 2.44 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 172.8, 164.8, 149.2, 135.3, 132.6, 131.0, 129.1, 125.6, 25.5, 18.2.
HR-MS: *m/z* for $C_{10}H_{10}N_2O_4$+Na^+, $[M+Na]^+$ calculated: 245.0533; found: 245.0534.

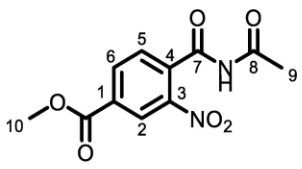
***N*-Acetyl-5-methoxy-2-nitrobenzamide (5q)**



According to general protocol **GPII** 5-methoxy-2-nitrobenzamide (0.25 g, 1.3 mmol, 1.0 eq.) and anhydride (1.2 mL, 13 mmol, 13.0 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.299 g, 1.3 mmol, quant.) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 9.09 (s, 1H, C7-N*H*-), 8.17 (d, 1H, *J* = 9.2 Hz, *H*-3), 7.01 (dd, 1H, *J* = 9.2 Hz, 2.7 Hz, *H*-4), 6.86 (d, 1H, *J* = 2.7 Hz, *H*-6), 3.91 (s, 3H, *H*-10), 2.36 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 171.1, 167.2, 164.3, 138.3, 134.7, 127.2, 115.3, 112.9, 56.4, 25.0.
HR-MS: *m/z* for $C_{10}H_{10}N_2O_5$+Na^+, $[M+Na]^+$ calculated: 261.0482; found: 261.0478.

Methyl 4-(acetylcarbamoyl)-3-nitrobenzoate (5r)

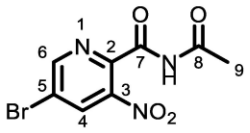


According to general protocol **GPII** methyl 4-carbamoyl-3-nitrobenzoate (0.67 g, 3 mmol, 1.0 eq.) and anhydride (2.8 mL, 30 mmol, 10 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.651 g, 2.5 mmol, 83%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 2:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 9.43 (s, 1H, C7-N*H*-), 8.79 (d, 1H, *J* = 1.5 Hz, *H*-2), 8.36 (dd, 1H, *J* = 7.9 Hz, 1.5 Hz, *H*-6), 7.52 (d, 1H, *J* = 7.9 Hz, *H*-5), 3.99 (s, 3H, *H*-10), 2.31 (s, 3H, *H*-9).

^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 170.8, 167.2, 164.4, 145.5, 135.8, 135.2, 132.8, 128.1, 125.6, 53.2, 24.8.
HR-MS: *m/z* for $C_{11}H_{10}N_2O_6$+Na^+, $[M+Na]^+$ calculated: 289.0431; found: 289.0428.

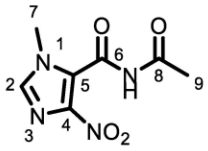
2-(Acetylcarbamoyl)-5-bromo-3-nitropyridine (5s)



According to general protocol **GPII** 5-bromo-3-nitropicolinamide (0.41 g, 2 mmol, 1.0 eq.) and anhydride (1.6 mL, 17 mmol, 8.5 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.374 g, 1.3 mmol, 65%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 2:1).

^{1}H NMR (600 MHz, DMSO-d_6) δ [ppm]: 11.73 (s, 1H, C7-N*H*-), 9.11 (d, 1H, *J* = 2.0 Hz, *H*-4), 8.98 (d, 1H, *J* = 2.0 Hz, *H*-6), 2.12 (s, 3H, *H*-9).
^{13}C NMR (151 MHz, DMSO-d_6) δ [ppm]: 170.9, 165.3, 154.9, 147.7, 141.5, 135.3, 120.4, 23.9.
HR-MS: *m/z* for $C_8H_6{}^{79}BrN_3O_4$-H^+, $[M-H]^-$ calculated: 284.9469; found: 284.9468.

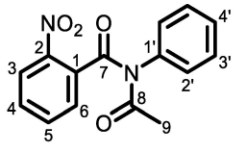
1*H*-*N*-Acetyl-1-methyl-4-nitro-1*H*-imidazole-5-carboxamide (5t)



According to general protocol **GPII** 1*H*-1-methyl-4-nitro-imidazole-5-carboxamide (2.99 g, 18 mmol, 1.0 eq.) and anhydride (16 mL, 54 mmol, 3.0 eq.) were reacted. The title compound was isolated as colourless amorphous solid (2.864 g, 13.5 mmol, 75%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 2:1).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 11.67 (s, C6-N*H*-), 7.91 (s, 1H, *H*-2), 3.70 (s, 3H, *H*-7), 2.22 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 170.8, 158.7, 143.7, 137.7, 126.1, 33.3, 24.8.
HR-MS: *m/z* for $C_8H_8N_4O_4$-H^+, $[M-H]^-$ calculated: 213.0618; found: 213.0616.

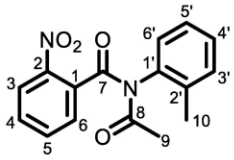
***N*-Acetyl-2-nitro-*N*-phenylbenzamide (5u)**



2-Nitro-*N*-phenylbenzamide (2.37 g, 10 mmol, 1.0 eq.) was dissolved in 50 mL anhydrous THF. 20 mL 1 M lithium bis(trimethylsilyl)amide (20 mmol, 2.0 eq.) was added at 0 °C and the reaction mixture was stirred for 15 min. Acetic anhydride (5 mL, 53 mmol, 5.3 eq.) was added dropwise, the reaction mixture was slowly allowed to warm to room temperature and stirred for additional 24 h. After completion the reaction mixture was poured into 50 mL water. The THF was removed and the aqueous layer was extracted three times with 50 mL ethyl acetate. The combined organic fractions were washed once with 50 mL brine, dried over magnesium sulphate and the solvent was removed. The title compound was isolated as beige amorphous solid (1.705 g, 6.0 mmol, 60%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 3:1).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.15 (dd, 1H, *J* = 8.2 Hz, 1.2 Hz, *H*-3), 7.76 (td, 1H, *J* = 7.6 Hz, 1.2 Hz, *H*-5), 7.62–7.52 (m, 2H, *H*-4, *H*-6), 7.51–7.36 (m, 5H, *H*-2', *H*-3', *H*-4'), 2.10 (s, 3H, *H*-9)
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 173.2, 169.5, 145.5, 139.4, 135.6, 135.5, 130.8, 130.6, 130.1, 130.1, 128.5, 125.0, 26.3.
HR-MS: *m/z* for $C_{15}H_{12}N_2O_4$+Na^+, $[M+Na]^+$ calculated: 307.0689; found: 307.0683.

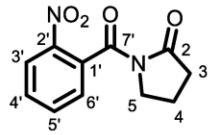
_N_-Acetyl-2-nitro-_N_-(o-tolyl)benzamide (5v)



2-Nitro-_N_-(o-tolyl)benzamide (0.48 g, 2 mmol, 1.0 eq.) was dissolved in 50 mL anhydrous THF. 5 mL 1 M lithium bis(trimethylsilyl)amide (4 mmol, 2.0 eq.) was added at 0 °C and the reaction mixture was stirred for 15 min. Acetic anhydride (1 mL, 6 mmol, 3.0 eq.) was added dropwise, the reaction mixture was slowly allowed to warm to room temperature and stirred for additional 24 h. After completion the reaction mixture was poured into 50 mL water. The THF was removed and the aqueous layer was extracted three times with 50 mL ethyl acetate. The combined organic fractions were washed once with 50 mL brine, dried over magnesium sulphate and the solvent was removed. The title compound was isolated as beige amorphous solid (0.258 g, 0.87 mmol, 44%) after flash column chromatography (SiO_2, cyclohexane:ethyl acetate 5:1).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.23 (dd, 1H, _J_ = 8.3 Hz, 1.2 Hz, _H_-3), 7.80 (td, 1H, _J_ = 7.6 Hz, 1.2 Hz, _H_-5), 7.64 (ddd, 1H, _J_ = 8.3 Hz, 7.5 Hz, 1.4 Hz, _H_-4), 7.52 (dd, 1H, _J_ = 7.6 Hz, 1.4 Hz, _H_-6), 7.44–7.33 (m, 4H, _H_-3', _H_-4', _H_-5', _H_-6'), 2.16 (s, 3H, _H_-9), 1.90 (s, 3H, _H_-10).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 173.0, 169.1, 138.3, 137.9, 136.0, 135.7, 132.4, 130.7, 130.6, 129.9, 128.5, 127.7, 125.1, 25.6, 17.7.
HR-MS: _m/z_ for $C_{16}H_{14}N_2O_4$+Na^+, $[M+Na]^+$ calculated: 299.1026; found: 299.1022.
The spectroscopic data are in accordance with those reported in the literature.[12]

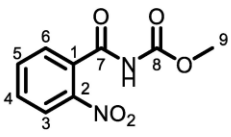
1-(2-Nitrobenzoyl)pyrrolidin-2-one (5w)



Under argon atmosphere pyrrolidin-2-one (0.643 g, 7.6 mmol, 1.5 eq.) was dissolved in 30 mL pyridine. 2-Nitrobenzoyl chloride (0.928, 5.0 mmol, 1.0 eq.) was added dropwise and the reaction mixture was heated at 60 °C for 24 h. 50 mL of water and 50 mL ethyl acetate was added and the organic layer was fractionated. The aqueous layer was extracted twice with 50 mL ethyl acetate. The combined organic fractions were washed four times with 50 mL 1 M hydrochloric, once with 50 mL brine and dried over magnesium sulphate. The solvent was removed and the crude product was further purified by flash column chromatography (SiO_2, cyclohexane:ethylacetate, 0 → 10% ethyl acetate). 0.268 g (1.1 mmol, 22%) of the product was isolated as colourless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.22 (dd, 1H, _J_ = 8.3 Hz, 1.2 Hz, _H_-3'), 7.72 (td, 1H, _J_ = 7.5 Hz, 1.2 Hz, _H_-5'), 7.60 (td, 1H, _J_ = 8.3 Hz, 1.5 Hz, _H_-4'), 7.36 (dd, 1H, _J_ = 7.5 Hz, 1.5 Hz, _H_-6'), 4.05 (t, 1H, _J_ = 7.0 Hz, _H_-5), 2.54 (t, 1H, _J_ = 8.0 Hz, _H_-3), 2.15 (p, 1H, _J_ = 8.0 Hz, _H_-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 174.9, 166.6, 145.3, 134.5, 133.2, 130.2, 128.0, 124.2, 45.5, 32.9, 17.5.
HR-MS: _m/z_ for $C_{11}H_{10}N_2O_4$+H^+, $[M+H]^+$ calculated: 235.0713; found: 235.0712.
The spectroscopic data are in accordance with those reported in the literature.[13]

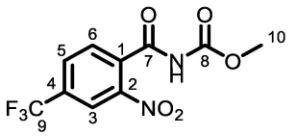
Methyl (2-nitrobenzoyl)carbamate (5x)



According to general protocol **GPIII** 2-nitrobenzamide (6.00 g, 36.1 mmol, 1.0 eq.) and oxalyl chloride (5.3 mL, 61 mmol, 1.7 eq.) were reacted. The title compound was isolated as colourless amorphous solid (7.48 g, 33.4 mmol, 92%) by filtration.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.37 (s, 1H, C7-N*H*-), 8.25 (dd, 1H, *J* = 8.3 Hz, 1.3 Hz, *H*-3), 7.75 (td, 1H, *J* = 7.5 Hz, 1.3 Hz, *H*-5), 7.63 (td, 1H, *J* = 8.4 Hz, 1.5 Hz, *H*-4), 7.45 (dd, 1H, *J* = 7.5 Hz, 1.5 Hz, *H*-6), 3.68 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 168.4, 152.0, 145.3, 134.5, 132.1, 130.6, 127.9, 124.3, 53.5.
HR-MS: *m/z* for $C_9H_8N_2O_5$+Na^+, $[M+Na]^+$ calculated: 247.0325; found: 247.0326.
The spectroscopic data are in accordance with those reported in the literature.[14]

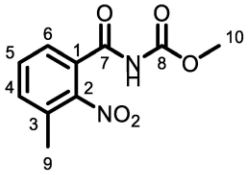
Methyl (2-nitro-4-(trifluoromethyl)benzoyl)carbamate (5y)



According to general protocol **GPIII** 2-nitro-4-(trifluoromethyl)benzamide (0.39 g, 1.7 mmol, 1.0 eq.) and oxalyl chloride (0.3 mL, 2.9 mmol, 1.7 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.441 g, 1.51 mmol, 89%) by filtration.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.55–8.42 (m, 1H, C7-N*H*-), 8.01 (dd, 1H, *J* = 8.0 Hz, 1.0 Hz, *H*-5), 7.60 (d, 1H, *J* = 8.0 Hz, *H*-6), 3.69 (s, 3H, *H*-10).zz
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 167.4, 152.1, 145.3, 135.3, 133.1 (q, *J* = 34.7 Hz), 131.2 (q, *J* = 3.5 Hz), 128.8, 122.6 (q, *J* = 273.0 Hz), 121.7 (q, *J* = 3.9 Hz), 53.7.
^{19}F NMR (282 MHz, $CDCl_3$) δ [ppm]: -63.05.
HR-MS: *m/z* for $C_9H_8N_2O_5$+Na^+, $[M+Na]^+$ calculated: 247.0325; found: 247.0326.
The spectroscopic data are in accordance with those reported in the literature.[14]

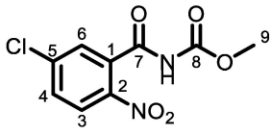
Methyl (3-methyl-2-nitrobenzoyl)carbamate (5z)



According to general protocol **GPIII** 3-methyl-2-nitrobenzamide (0.36 g, 2 mmol, 1.0 eq.) and oxalyl chloride (0.3 mL, 3 mmol, 1.7 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.444 g, 1.9 mmol, 95%) by filtration.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.25 (s, 1H, C7-N*H*-), 7.53–7.40 (m, 2H, *H*-4, *H*-5), 7.38–7.32 (m, 1H, *H*-6), 3.76 (s, 3H, *H*-10), 2.51 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 166.4, 151.8, 147.8, 134.6, 133.1, 131.6, 130.9, 125.8, 53.6, 19.4.
HR-MS: *m/z* for $C_{10}H_{10}N_2O_5$+Na^+, $[M+Na]^+$ calculated: 261.0482; found: 261.0477.
The spectroscopic data are in accordance with those reported in the literature.[14]

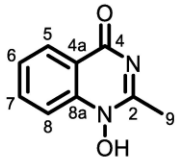
Methyl (5-chloro-2-nitrobenzoyl)carbamate (5aa)



According to general protocol **GPIII** 5-chloro-2-nitrobenzamide (0.40 g, 2 mmol, 1.0 eq.) and oxalyl chloride (0.3 mL, 3 mmol, 1.7 eq.) were reacted. The title compound was isolated as colourless amorphous solid (0.383 g, 1.5 mmol, 75%) by filtration.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.26 (s, 1H, C7-N*H*-), 8.20 (d, 1H, *J* = 8.8 Hz, *H*-3), 7.58 (dd, 1H, *J* = 8.8 Hz, 2.2 Hz, *H*-4), 7.41 (d, 1H, *J* = 2.2 Hz, *H*-3), 3.70 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 166.8, 151.9, 143.6, 141.4, 133.5, 130.6, 128.0, 125.7, 53.6.
HR-MS: *m/z* for $C_9H_7{}^{35}ClN_2O_5$+Na^+, $[M+Na]^+$ calculated: 280.9936; found: 280.9934.

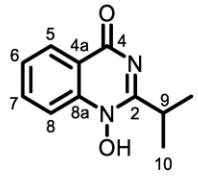
1*H*-1-Hydroxy-2-methylquinazolin-4-one (6a)



The title compound was prepared according to **GPIV** using 156 mg (0.75 mmol) of *N*-acetyl-2-nitrobenzamide. 120 mg (0.682 mmol, 91%) of the product were isolated as beige solid by flash column chromatography (silica gel, dichloromethane:methanol 6:1 + 0.5% acetic acid).

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 7.94–7.84 (m, 2H, *H*-6, *H*-8), 7.77–7.67 (m, 1H, *H*-7), 7.42–7.35 (m, 1H, *H*-5), 2.48 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 168.5, 156.4, 141.7, 134.1, 126.3, 126.0, 119.5, 116.1, 23.2.
HR-MS: *m/z* for $C_9H_8N_2O_2$+H^+, $[M+H]^+$ calculated: 177.0659; found: 177.0655.

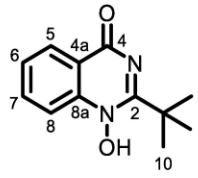
1*H*-1-Hydroxy-2-isopropylquinazolin-4-one (6b)



The title compound was prepared according to **GPIV** using 177 mg (0.75 mmol) of *N*-isobutyryl-2-nitrobenzamide. 138 mg (0.676 mmol, 90%) of the product were isolated as beige solid by flash column chromatography (silica gel, dichloromethane:methanol 20:1 + 0.5% acetic acid).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 12.04 (s, 1H, N-O*H*), 8.05–7.98 (m, 1H, *H*-8), 7.84 (ddd, 1H, *J* = 8.5 Hz, 7.0 Hz, 1.5 Hz, *H*-6), 7.77 (d, 1H, *J* = 8.5 Hz, *H*-5), 7.50 (ddd, 1H, *J* = 8.1 Hz, 7.0 Hz, 1.2 Hz, *H*-7), 3.52 (hept, 1H, *J* = 6.8 Hz, *H*-9), 1.23 (d, 6H, *J* = 6.8 Hz, *H*-10).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 166.5, 165.2, 140.6, 134.0, 127.0, 126.0, 119.4, 114.5, 29.3, 19.9.
HR-MS: *m/z* for $C_{11}H_{12}N_2O_2$+H^+, $[M+H]^+$ calculated: 205.0972; found: 205.0966.

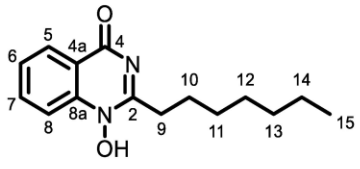
1*H*-2-(*tert*-Butyl)-1-hydroxyquinazolin-4-one (6c)



The title compound was prepared according to **GPIV** using 188 mg (0.75 mmol) of 2-nitro-*N*-pivaloylbenzamide. 128 mg (0.587 mmol, 78%) of the product were isolated as beige solid by flash column chromatography (silica gel, dichloromethane:methanol 20:1 + 0.5% acetic acid).

^{1}H NMR (400 MHz, D_2O) δ [ppm]: 8.10–8.03 (m, 1H, *H*-8), 7.98 (dd, 1H, *J* = 8.1 Hz, 1.5 Hz, *H*-5), 7.80 (ddd, 1H, *J* = 8.7 Hz, 7.1 Hz, 1.5 Hz, *H*-7), 7.48 (ddd, 1H, *J* = 8.1 Hz, 7.1 Hz, 1.1 Hz, *H*-6), 1.46 (s, 9H, *H*-10).
^{13}C NMR (101 MHz, D_2O) δ [ppm]: 168.9, 163.8, 143.7, 134.0, 126.4, 125.8, 119.2, 116.7, 38.1, 26.8.
HR-MS: *m/z* for $C_{12}H_{14}N_2O_2$+H^+, $[M+H]^+$ calculated: 219.1125; found: 219.1128.

1*H*-2-Heptyl-1-hydroxyquinazolin-4-one (6d)

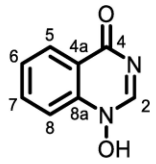


The title compound was prepared according to **GPIV** using 220 mg (0.75 mmol) of 2-nitro-*N*-octanoylbenzamide. 103 mg (0.396 mmol, 52%) of the product were isolated as beige solid by flash column

chromatography (reversed phase silica gel, water:acetonitrile 15% → 35% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.23 (dd, 1H, *J* = 7.9 Hz, 1.5 Hz, *H*-8), 8.15 (d, 1H, *J* = 8.4 Hz, *H*-5), 7.97 (ddd, 1H, *J* = 8.4 Hz, 7.2 Hz, 1.5 Hz, *H*-6), 7.67 (ddd, 1H, *J* = 7.9 Hz, 7.2 Hz, 1.1 Hz, *H*-6), 3.05–2.93 (m, 2H, *H*-9), 1.91–1.79 (m, 2H, *H*-10), 1.54–1.25 (m, 8H, *H*-11, *H*-12, *H*-13, *H*-14, *H*-15), 0.96–0.86 (m, 3H, *H*-15).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 156.2, 148.4, 143.1, 136.5, 129.2, 128.3, 121.6, 117.1, 114.7, 32.8, 31.8, 30.5, 30.0, 27.1, 23.7, 14.4.
HR-MS: *m/z* for $C_{15}H_{20}N_2O_2+H^+$, $[M+H]^+$ calculated: 261.1598; found: 261.1590.

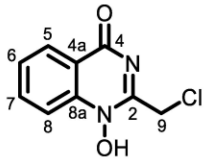
1*H*-1-Hydroxyquinazolin-4-one (6e)



The title compound was prepared according to **GPIV** using 145 mg (0.75 mmol) of 2-nitro-*N*-octanoylbenzamide. 128 mg (0.488 mmol, 65%) of the product were isolated as beige solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 10% acetonitrile) as formic acid adduct.

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 8.53 (s, 1H, *H*-2)8.03 (dd, 1H, *J* = 8.1 Hz, 1.4 Hz, *H*-8), 7.95 (dd, 1H, *J* = 8.5 Hz, 1.2 Hz, *H*-5), 7.88 (ddd, 1H, *J* = 8.5 Hz, 7.1 Hz, 1.4 Hz, *H*-6), 7.67 (ddd, 1H, *J* = 8.1 Hz, 7.1 Hz, 1.2 Hz, *H*-6).
^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 169.6, 145.9, 141.0, 134.4, 128.8, 126.4, 119.9, 116.2.
HR-MS: *m/z* for $C_8H_6N_2O_2+H^+$, $[M+H]^+$ calculated: 163.0502; found: 163.0501.

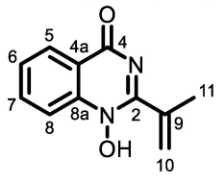
1*H*-2-(Chloromethyl)-1-hydroxyquinazolin-4-one (6f)



The title compound was prepared according to **GPIV** using 184 mg (0.75 mmol) of *N*-(2-chloroacetyl)-2-nitrobenzamide. 38 mg (0.181 mmol, 24%) of the product were isolated as beige solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 7.99 (d, 1H, *J* = 8.5 Hz, *H*-8), 7.90 (dd, 1H, *J* = 8.1 Hz, 1.4 Hz, *H*-5), 7.81–7.54 (m, 1H, *H*-6), 7.50–7.44 (m, 1H, *H*-7), 4.72 (s, 2H, *H*-9).
^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 168.5, 152.9, 141.8, 134.3, 127.4, 126.1, 120.2, 116.6, 40.7.
HR-MS: *m/z* for $C_9H_7{}^{35}ClN_2O_2-H^+$, $[M-H]^-$ calculated: 209.0123; found: 209.0124.

1*H*-1-Hydroxy-2-(prop-1-en-2-yl)quinazolin-4-one (6g)

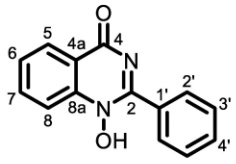


The title compound was prepared according to **GPIV** using 175 mg (0.75 mmol) of *N*-methacryloyl-2-nitrobenzamide. 102 mg (0.505 mmol, 67%) of the product were isolated as beige solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 8.24–8.18 (m, 1H, *H*-8), 8.12–8.07 (m, 1H, *H*-5), 7.98–7.92 (m, 1H, *H*-6), 7.66 (ddd, 1H, *J* = 8.1 Hz, 7.2 Hz, 1.4 Hz, *H*-7), 5.69–5.63 (m, 2H, *H*-10), 2.26 (s, 3H, *H*-11).
^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 166.7, 155.9, 143.1, 137.5, 136.4, 129.3, 128.3, 123.9, 121.7, 117.7, 20.2.

HR-MS: *m/z* for $C_{11}H_{10}N_2O_2$+H^+, $[M+H]^+$ calculated: 203.0815; found: 203.0809.

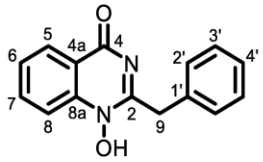
1*H*-1-Hydroxy-2-phenylquinazolin-4-one (6h)



The title compound was prepared according to **GPIV** using 149 mg (0.55 mmol due to the low solubility of the starting material) of *N*-benzoyl-2-nitrobenzamide. 103 mg (0.433 mmol, 79%) of the product were isolated as beige solid by flash column chromatography (silica gel, dichloromethane:methanol 20:1 + 0.5% acetic acid).

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 7.88-7.78 (m, 2H, *H*-8, H-*5*), 7.65–7.55 (m, 3H, *H*-6H, *H*-2'), 7.41–7.26 (m, 3H, *H*-3', *H*-4'), 7.29 (ddd, *J* = 8.1 Hz, 7.2 Hz, 1.1 Hz, *H*-7).
^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 168.4, 154.3, 142.0, 134.1, 133.2, 130.1, 128.8, 128.2, 126.9, 125.9, 119.8, 116.7.
HR-MS: *m/z* for $C_{14}H_{10}N_2O_2$+H^+, $[M+H]^+$ calculated: 239.0815; found: 239.0811.

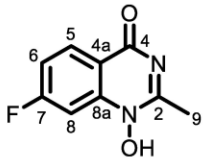
1*H*-2-Benzyl-1-hydroxyquinazolin-4-one (6i)



The title compound was prepared according to **GPIV** using 213 mg (0.75 mmol) of *N*-(2-phenylacetyl)-2-nitrobenzamide. 154 mg (0.611 mmol, 81%) of the product were isolated as beige solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 7.99–7.93 (m, 2H, *H*-5, *H*-8), 7.75–7.68 (m, 1H, *H*-6), 7.44–7.37 (m, 1H, *H*-7), 7.32–7.26 (m, 4H, *H*-2', *H*-3'), 7.26–7.18 (m, 1H, *H*-4'), 4.24 (s, 2H, *H*-9).
^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 168.7, 157.3, 142.0, 136.2, 134.1, 128.7, 128.6, 126.8, 126.7, 126.1, 119.7, 116.6.
HR-MS: *m/z* for $C_{15}H_{12}N_2O_2$+H^+, $[M+H]^+$ calculated: 253.0970; found: 253.0972.

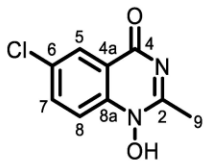
1*H*-7-Fluoro-1-hydroxy-2-methylquinazolin-4-one (6j)



The title compound was prepared according to **GPIV** using 170 mg (0.75 mmol) of *N*-acetyl-4-fluoro-2-nitrobenzamide. 107 mg (0.552 mmol, 74%) of the product were isolated as light yellow solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 7.62 (dd, 1H, *J* = 9.0 Hz, 5.9 Hz, *H*-6), 7.34 (dd, 1H, *J* = 10.3 Hz, 2.5 Hz, *H*-8), 6.85 (td, 1H, *J* = 8.7 Hz, 2.5 Hz, *H*-5), 2.36 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 167.4, 166.8, 164.3, 157.4, 143.1 (d, *J* = 12.3 Hz), 129.1 (d, *J* = 10.6 Hz), 116.0, 101.9 (d, *J* = 27.3 Hz), 18.9.
^{19}F NMR (282 MHz, D_2O+NaOD) δ [ppm]: -102.96.
HR-MS: *m/z* for $C_9H_7FN_2O_2$+H^+, $[M+H]^+$ calculated: 195.0564; found: 195.0563.

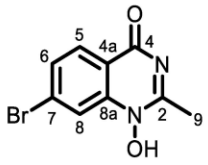
1*H*-6-Chloro-1-hydroxy-2-methylquinazolin-4-one (6k)



The title compound was prepared according to **GPIV** using 181 mg (0.75 mmol) of *N*-acetyl-5-chloro-2-nitrobenzamide. 121 mg (0.576 mmol, 77%) of the product were isolated as beige solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 7.80 (d, 1H, *J* = 9.0 Hz, *H*-8), 7.66 (d, 1H, *J* = 2.3 Hz, *H*-5), 7.54 (dd, 1H, *J* = 9.0 Hz, 2.3 Hz, *H*-7), 2.47 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 167.1, 156.7, 140.3, 134.0, 131.3, 125.0, 120.4, 118.3, 18.9.
HR-MS: *m/z* for $C_9H_7{}^{35}ClN_2O_2+H^+$, $[M+H]^+$ calculated: 211.0269; found: 211.0266.

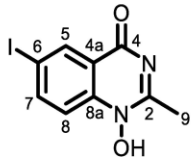
1*H*-7-Bromo-1-hydroxy-2-methylquinazolin-4-one (6l)



The title compound was prepared according to **GPIV** using 214 mg (0.75 mmol) of *N*-acetyl-4-bromo-2-nitrobenzamide. 158 mg (0.620 mmol, 83%) of the product were isolated as beige solid by flash column chromatography (reverse phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 8.05 (d, 1H, *J* = 1.9 Hz, *H*-8), 7.72 (d, 1H, *J* = 8.6 Hz, *H*-6), 7.44 (dd, 1H, *J* = 8.6 Hz, 1.9 Hz, *H*-6), 2.53 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 168.0, 157.5, 142.2, 129.4, 128.3, 127.9, 118.9, 118.3, 19.3.
HR-MS: *m/z* for $C_9H_7{}^{79}BrN_2O_2+H^+$, $[M+H]^+$ calculated: 254.9764; found: 254.9757.

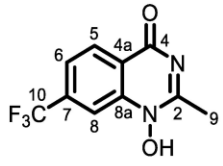
1*H*-1-Hydroxy-6-iodo-2-methylquinazolin-4-one (6m)



The title compound was prepared according to **GPIV** using 250 mg (0.75 mmol) of *N*-acetyl-5-iodo-2-nitrobenzamide. 113 mg (0.374 mmol, 50%) of the product were isolated as colourless solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 8.02 (d, 1H, *J* = 2.0 Hz, *H*-5), 7.84 (dd, 1H, *J* = 8.9 Hz, 2.0 Hz, *H*-7), 7.61 (d, 1H, *J* = 8.9 Hz, *H*-8), 2.51 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 166.8, 156.9, 142.3, 141.1, 134.7, 121.0, 118.2, 90.2, 19.5.
HR-MS: *m/z* for $C_9H_7IN_2O_2+H^+$, $[M+H]^+$ calculated: 302.9625; found: 302.9623.

1*H*-1-Hydroxy-2-methyl-7-(trifluoromethyl)quinazolin-4-one (6n)

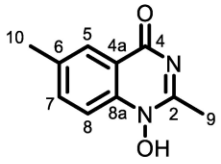


The title compound was prepared according to **GPIV** using 207 mg (0.75 mmol) of *N*-acetyl-2-nitro-4-(trifluoromethyl)benzamide. 169 mg (0.693 mmol, 92%) of the product were isolated as beige solid by flash column chromatography (silica gel, dichloromethane:methanol 20:1 + 0.5% acetic acid).

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 8.08 (d, 1H, *J* = 8.2 Hz, *H*-5), 7.77 (s, 1H, *H*-8), 7.62 (dd, 1H, *J* = 8.2 Hz, 1.7 Hz, *H*-6), 2.43 (s, 3H, *H*-9).

^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 165.0, 159.4, 140.9, 132.7 (q, *J* = 32.5 Hz), 128.7, 123.3 (q, *J* = 272.6 Hz), 121.8, 121.1, 111.8, 20.1.
^{19}F NMR (282 MHz, D_2O+NaOD) δ [ppm]: -64.06.
HR-MS: *m/z* for $C_{10}H_7F_3N_2O_2$+H^+, $[M+H]^+$ calculated: 245.0532; found: 245.0533.

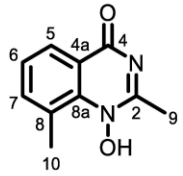
1*H*-1-Hydroxy-2,6-dimethylquinazolin-4-one (6o)



The title compound was prepared according to **GPIV** using 167 mg (0.75 mmol) of *N*-acetyl-5-methyl-2-nitrobenzamide. 128 mg (0.673 mmol, 89%) of the product were isolated as colourless solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 10% → 90% acetonitrile) as formate adduct.

^{1}H NMR (400 MHz, D_2O) δ [ppm]: 7.80 (d, 1H, *J* = 8.8 Hz, *H*-8), 7.63 (d, 1H, *J* = 2.0 Hz, *H*-5), 7.53 (dd, 1H, *J* = 8.8 Hz, 2.0 Hz, *H*-7), 2.52 (s, 3H, *H*-10), 2.34 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, D_2O) δ [ppm]: 168.1, 155.2, 139.8, 136.9, 135.4, 125.1, 119.4, 116.1, 20.3, 19.4.
HR-MS: *m/z* for $C_{10}H_{10}N_2O_2$+H^+, $[M+H]^+$ calculated:191.0815; found: 191.0814.

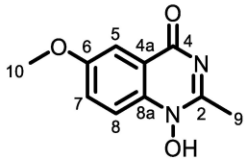
1*H*-1-Hydroxy-2,8-dimethylquinazolin-4-one (6p)



The title compound was prepared according to **GPIV** using 153 mg (0.69 mmol due to the low solubility of the starting material) of *N*-acetyl-2-methyl-6-nitrobenzamide. 96 mg (0.505 mmol, 73%) of the product were isolated as colourless solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, D_2O) δ [ppm]: 7.86 (dd, 1H, *J* = 7.5 Hz, 1.2 Hz, *H*-5), 7.50 (dd, 1H, *J* = 7.5 Hz, 1.2 Hz, *H*-7), 7.31 (t, 1H, *J* = 7.5 Hz, *H*-6), 2.85 (s, 3H, *H*-10), 2.50 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, D_2O) δ [ppm]: 168.7, 157.5, 140.9, 137.9, 129.4, 126.3, 124.5, 121.0, 23.0, 19.9
HR-MS: *m/z* for $C_{10}H_{10}N_2O_2$+H^+, $[M+H]^+$ calculated:191.0815; found: 191.0814.

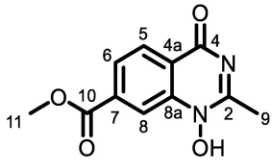
1*H*-1-Hydroxy-6-methoxy-2-methylquinazolin-4-one (6q)



The title compound was prepared according **GPIV** using 175 mg (0.75 mmol) of *N*-acetyl-5-methoxy-2-nitrobenzamide. 119 mg (0.578 mmol, 77%) of the product were isolated as colourless solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 7.80 (d, 1H, *J* = 9.3 Hz, *H*-8), 7.21 (dd, 1H, *J* = 9.3 Hz, 2.8 *H*-7), 7.14 (d, 1H, *J* = 2.8 Hz, *H*-5), 3.73 (s, 3H, *H*-10), 2.41 (s, 3H, *H*-9).Hz
^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 167.7, 157.0, 154.0, 136.7, 123.5, 120.6, 118.2, 105.7, 55.5, 18.7.
HR-MS: *m/z* for $C_{10}H_{10}N_2O_3$+H^+, $[M+H]^+$ calculated: 207.0764; found: 207.0762.

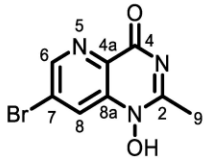
Methyl 1-hydroxy-2-methyl-4-oxo-1,4-dihydroquinazoline-7-carboxylate (6r)



The title compound was prepared according **GPIV** using 200 mg (0.75 mmol) of methyl 4-(acetylcarbamoyl)-3-nitrobenzoate. 150 mg (0.641 mmol, 85%) of the product were isolated as light yellow solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, D_2O+NaOD) δ [ppm]: 8.44 (d, 1H, *J* = 1.6 Hz, *H*-8), 8.06 (d, 1H, *J* = 8.3 Hz *H*-5), 7.89 (dd, 1H, *J* = 8.3 Hz, 1.6 Hz, *H*-7), 3.28 (s, 3H, *H*-11), 2.53 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, D_2O+NaOD) δ [ppm]: 174.0, 168.4, 157.2, 142.0, 141.9, 126.5, 126.2, 120.9, 116.7, 48.8.3, 19.2.
HR-MS: *m/z* for $C_{11}H_{10}N_2O_4$+H^+, $[M+H]^+$ calculated: 235.0713; found: 235.0708.

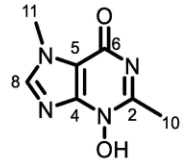
1*H*-7-Bromo-1-hydroxy-2-methylpyrido[3,2-*d*]pyrimidin-4-one (6s)



The title compound was prepared according to **GPIV** using 215 mg (0.75 mmol) of *N*-acetyl-6-bromo-3-nitropicolinamide. 157 mg (0.616 mmol, 82%) of the product were isolated as light yellow solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, D_2O) δ [ppm]: 8.61 (d, 1H, *J* = 2.1 Hz, *H*-8), 8.53 (dd, 1H, *J* = 2.1 Hz, 2.0 Hz, *H*-6), 2.50 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, D_2O) δ [ppm]: 167.1, 158.5, 149.6, 139.2, 132.8, 127.9, 125.0, 19.1.
HR-MS: *m/z* for $C_8H_6{}^{79}BrN_3O_2$+H^+, $[M+H]^+$ calculated: 255.9716; found: 255.9707.

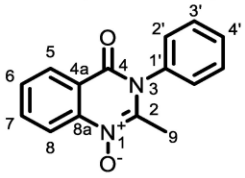
6*H*-3-Hydroxy-2,7-dimethyl-3,7-dihydropurin-6-one (6t)



The title compound was prepared according to **GPIV** using 159 mg (0.75 mmol) of 1*H*-*N*-Acetyl-1-methyl-4-nitro-imidazole-5-carboxamide. 196 mg (0.430 mmol, 57%) of the product were isolated as beige solid by flash column chromatography (silica gel, dichloromethane:methanol 50% → 100% methanol) as a acetate adduct.

^{1}H NMR (400 MHz, D_2O) δ [ppm]: 7.97 (s, 1H, *H*-8), 4.00 (s, 3H, *H*-11), 2.50 (s, 3H, *H*-10).
^{13}C NMR (101 MHz, D_2O) δ [ppm]: 158.2, 150.9, 146.3, 142.2, 113.9, 30.9, 15.7.
HR-MS: *m/z* for $C_7H_8N_4O_2$+H^+, $[M+H]^+$ calculated: 181.0720; found: 181.0714.

2-Methyl-4-oxo-3-phenyl-3,4-dihydroquinazoline 1-oxide (7a)

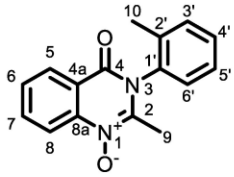


The title compound was prepared according to **GPIV** using 213 mg (0.75 mmol) of *N*-acetyl-2-nitro-*N*-phenylbenzamide. 81 mg (0.321 mmol, 43%) of the product were isolated as light yellow oil by flash column chromatography (reversed phase silica gel, water:acetonitrile 10% → 90% acetonitrile).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.43–8.36 (m, 1H, *H*-8), 8.24–8.17 (m, 1H, *H*-5), 8.01–7.92 (m, 1H, *H*-6), 7.52–7.74 (m, 4H, *H*-7, *H*-4', *H*-3'), 7.45–7.37 (m, 2H, *H*-2'), 2.38 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 164.5, 158.9, 150.5, 143.2, 138.0, 136.6, 131.0, 130.8, 130.0, 129.3, 128.2, 119.8, 17.7.

HR-MS: *m/z* for $C_{15}H_{12}N_2O_2+H^+$, $[M+H]^+$ calculated: 253.0972; found: 253.0966.

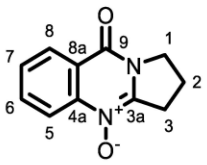
2-Methyl-4-oxo-3-(o-tolyl)-3,4-dihydroquinazoline 1-oxide (7b)



The title compound was prepared according to **GPIV** using 217 mg (0.75 mmol) of *N*-acetyl-2-nitro-*N*-(o-tolyl)benzamide. 172 mg (0.646 mmol, 86%) of the product were isolated as light yellow oil by flash column chromatography (reversed phase silica gel, water:acetonitrile 10% → 90% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.48–8.41 (m, 1H, *H*-8), 8.32–8.23 (m, 1H, *H*-5), 8.11–8.03 (m, 1H, *H*-6), 7.80–7.73 (m, 1H, *H*-5), 7.52–7.47 (m, 2H, *H*-6', *H*-4'), 7.46–7.39 (m, 1H, *H*-5'), 7.37–7.31 (m, 1H, *H*-3'), 3.35 (s, 3H, *H*-10), 2.14 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 164.7, 158.9, 151.9, 143.2, 137.3, 137.1, 136.9, 132.8, 131.5, 130.7, 129.4, 129.0, 128.8, 121.3, 119.8, 17.3.
HR-MS: *m/z* for $C_{16}H_{14}N_2O_2+H^+$, $[M+H]^+$ calculated: 267.1128; found: 267.1122.

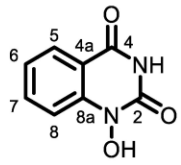
9-Oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline 4-oxide (7c)



The title compound was prepared according to **GPIV** using 161 mg (0.75 mmol) of 1-(2-Nitrobenzoyl)pyrrolidin-2-one. 109 mg (0.540 mmol, 72%) of the product were isolated as beige solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 5% → 10% acetonitrile).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.46 (dd, 1H, *J* = 7.3 Hz, 1.1 Hz, *H*-5), 7.63 (dd, 1H,, *J* = 8.0 Hz, 1.5 Hz, *H*-8), 7.95–7.87 (m, 1H, *H*-7), 7.68–7.59 (m, 1H, *H*-6), 4.39–4,27 (m, 2H, *H*-1), 3.59 (t, 2H, *H*-3), 2.48–2.32 (m, 2H, *H*-2).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 156.6, 150.1, 143.3, 135.3, 128.9, 127.3, 120.7, 118.8, 49.2, 29.6, 19.4.
HR-MS: *m/z* for $C_{11}H_{10}N_2O_2+H^+$, $[M+H]^+$ calculated: 203.0815; found: 203.0814.

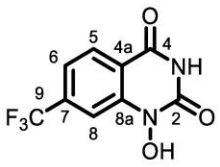
1*H*,3*H*-1-Hydroxyquinazoline-2,4-dione (8a)



The title compound was prepared according to **GPIV** using 168 mg (0.75 mmol) of methyl (2-nitrobenzoyl)carbamate. 103 mg (0.579 mmol, 77%) of the product were isolated as colourless solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 11.63 (s, 1H, *N*-H), 7.94 (dd, 1H, *J* = 7.9 Hz, 1.5 Hz, *H*-8), 7.80–7.72 (m, 1H, *H*-6), 7.52–7.43 (m, 1H, *J* = 8.4 Hz, 1.0 Hz, *H*-5), 7.21–7.20 (m, 1H, *H*-7), 4.92 (s, 1H, *O*-H).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 161.3, 148.2, 141.6, 135.5, 127.3, 122.7, 114.1, 112.5.
HR-MS: *m/z* for $C_8H_6N_2O_3+H^+$, $[M+H]^+$ calculated: 179.0451; found: 179.0451.
The spectroscopic data are in accordance with those reported in the literature.[15]

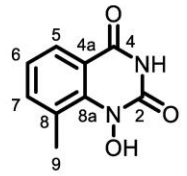
1*H*,3*H*-1-Hydroxy-7-(trifluoromethyl)quinazoline-2,4-dione (8b)



The title compound was prepared according to **GPIV** using 44 mg (0.15 mmol) of methyl (2-nitro-4-(trifluoromethyl)benzoyl)carbamate. 22 mg (0.0894 mmol, 59%) of the product were isolated as colourless solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 12.08–11.42 (m, 2H, *N*-H, *O*-H), 8.13 (d, 1H, *J* = 8.2 Hz, *H*-8), 7.67 (d, 1H, *J* = 1.7 Hz, *H*-5), 7.57 (dd, 1H, *J* = 8.2 Hz, 1.7 Hz, *H*-7), 2.52 (s, 3H, *H*-10), 2.34 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 160.5, 148.1, 142.0, 134.6 (q, *J* = 37.3 Hz), 129.0, 124.8, 122.1, 118.9 (q, *J* = 140.3 Hz), 117.2, 109.2 (q, *J* = 4.1 Hz).
^{19}F NMR (282 MHz, DMSO-d_6 δ [ppm]: -62.02.
HR-MS: *m/z* for $C_9H_5F_3N_2O_3$-H^+, $[M-H]^-$ calculated: 245.0180; found: 245.0179.

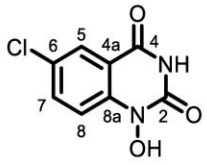
1*H*,3*H*-1-Hydroxy-8-methylquinazoline-2,4-dione (8c)



The title compound was prepared according to **GPIV** using 179 mg (0.75 mmol) of methyl (3-methyl-2-nitrobenzoyl)carbamate. 95 mg (0.495 mmol, 66%) of the product were isolated as colourless solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 11.67 (s, 1H, *N*-H), 10.86 (s, 1H, *O*-H), 7.83 (dd, 1H, *J* = 7.8 Hz, 1.7 Hz, *H*-5), 7.51 (dd, 1H, *J* = 7.3 Hz, 1.7 Hz, *H*-7), 7.13 (dd, 1H, *J* = 7.8 Hz, 7.3 Hz, *H*-6),2.62 (s, 3H, *H*-9),
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 161.4, 149.4, 140.2, 139.2, 125.8, 124.3, 122.9, 115.4, 22.6.
HR-MS: *m/z* for $C_9H_8N_2O_3$+H^+, $[M+H]^+$ calculated: 193.0608; found: 193.0607.

1*H*,3*H*-6-Chloro-1-hydroxyquinazoline-2,4-dione (8d)

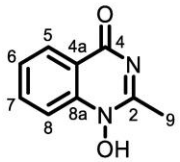


The title compound was prepared according to **GPIV** using 194 mg (0.75 mmol) of methyl (5-chloro-2-nitrobenzoyl)carbamate. 76 mg (0.358 mmol, 48%) of the product were isolated as colourless solid by flash column chromatography (reversed phase silica gel, water:acetonitrile 0% → 100% acetonitrile).

^{1}H NMR (400 MHz, DMSO-d_6) δ [ppm]: 11.78 (s, 1H, *N*-H), 11.21 (s, 1H, *O*-H), 7.82 (d, 1H, *J* = 8.8 Hz, *H*-8), 7.78 (dd, 1H, *J* = 8.8 Hz, 1.7 Hz, *H*-7), 7.48 (d, 1H, *J* = 2.5 Hz, 1.7 Hz, *H*-7).
^{13}C NMR (101 MHz, DMSO-d_6) δ [ppm]: 160.3, 148.0, 140.5, 135.2, 126.8, 126.2, 115.5, 114.8.
HR-MS: *m/z* for $C_8H_5{}^{35}ClN_2O_3$-H^+, $[M-H]^-$ calculated: 210.9916; found: 210.9914.

6. Crystallographic Data

1*H*-1-Hydroxy-2-methylquinazolin-4-one (6a)



Crystallization was carried out by dissolving the compound in acetonitrile. Slow evaporating resulted in crystal formation.

CCDC Number		
Empirical formular	$C_9H_8N_2O_2$	
Moiety formular	$C_9H_8N_2O_2$	
Formular weight	176.17 $g \cdot mol^{-1}$	
Temperature	120(2) K	
Wavelength, radiation type	0.71073 Å, MoKα	
Diffractometer	STOE IPDS 2T	
Crystal system	Monoclinic	
Space group name, number	P $2_1/n$, (14)	
Unit cell dimensions	a = 9.1643(7) Å	α = 90°
	b = 9.1814(7) Å	β = 115.381(6)°
	c = 10.4783(9) Å	γ = 90°
Volume	796.56(12) $Å^3$	
Number of reflections	3502	
And range used for lattice parameters	3.09° <=θ<= 28.33°	
Z	4	
Density (calculated)	1.469 mg/m^3	
Absorption coefficient	0.107 mm^{-1}	
Absorption correction	None	
F(000)	368	
Crystal size, colour and form	0.120·0.120·0.120 mm^3, colourless block	
Theta range for data collection	3.091 to 27.845°.	
Index ranges	-12<=h<=11, -12<=k<=12, -12<=l<=13	
Number of reflections:		
collected	4012	
independent	1883 [R(int) = 0.0409]	
observed [I>2sigma(I)]	1370	
Completeness to theta = 25.2°	99.9%	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1883 / 0 / 148	
Goodness-of-fit on F^2	1.123	
Final R indices [I>2sigma(I)]	R1 = 0.0645, wR2 = 0.1532	
R indices (all data)	R1 = 0.0961, wR2 = 0.1769	
Largest diff. peak and hole	0.382 and -0.388 $eÅ^{-3}$	

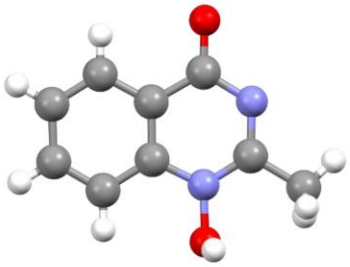


Figure S5: Molecular structure of compound 6a.

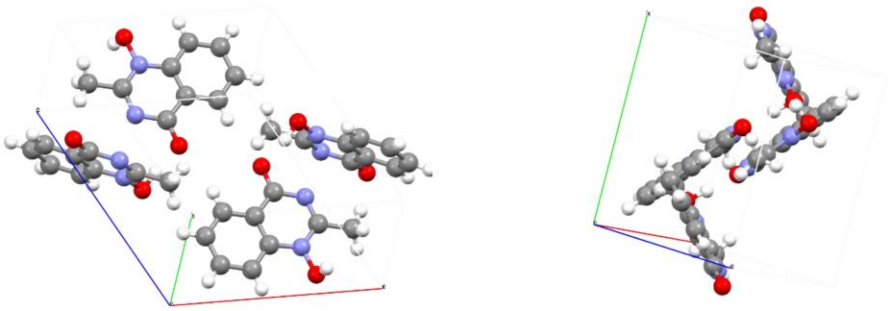
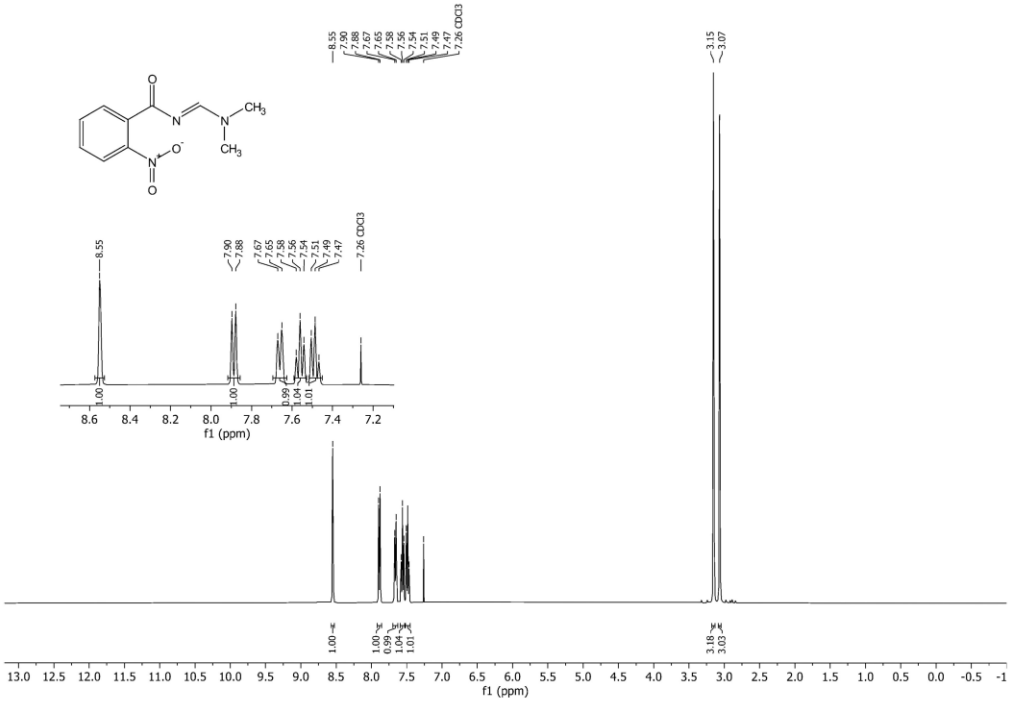
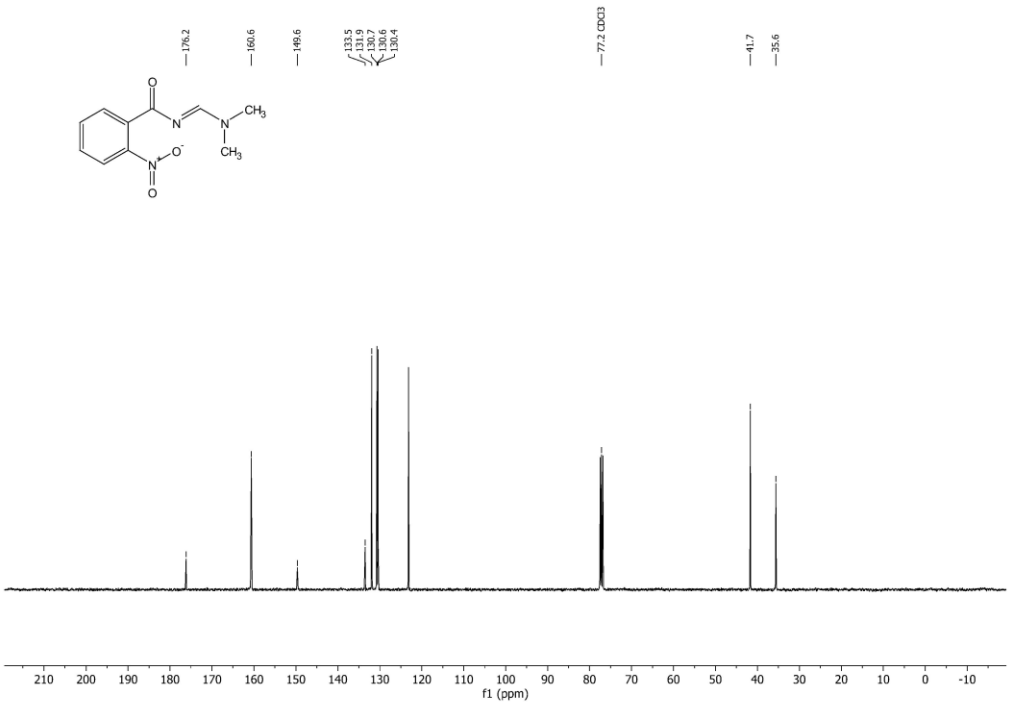


Figure Sb: Packing of compound 6a.

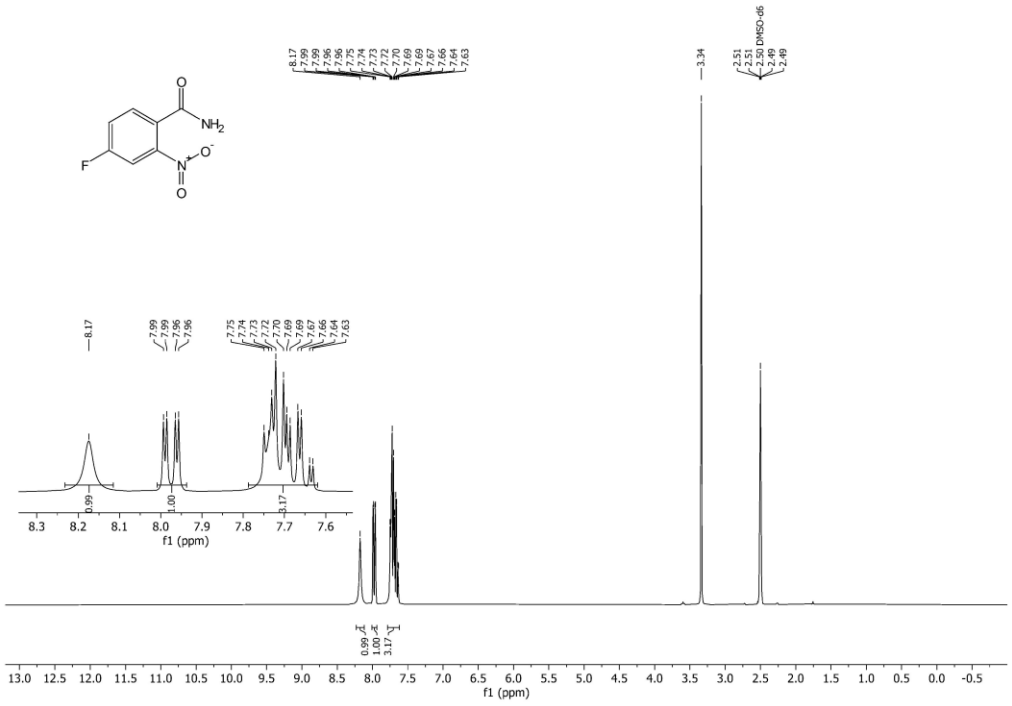
7. NMR Spectra

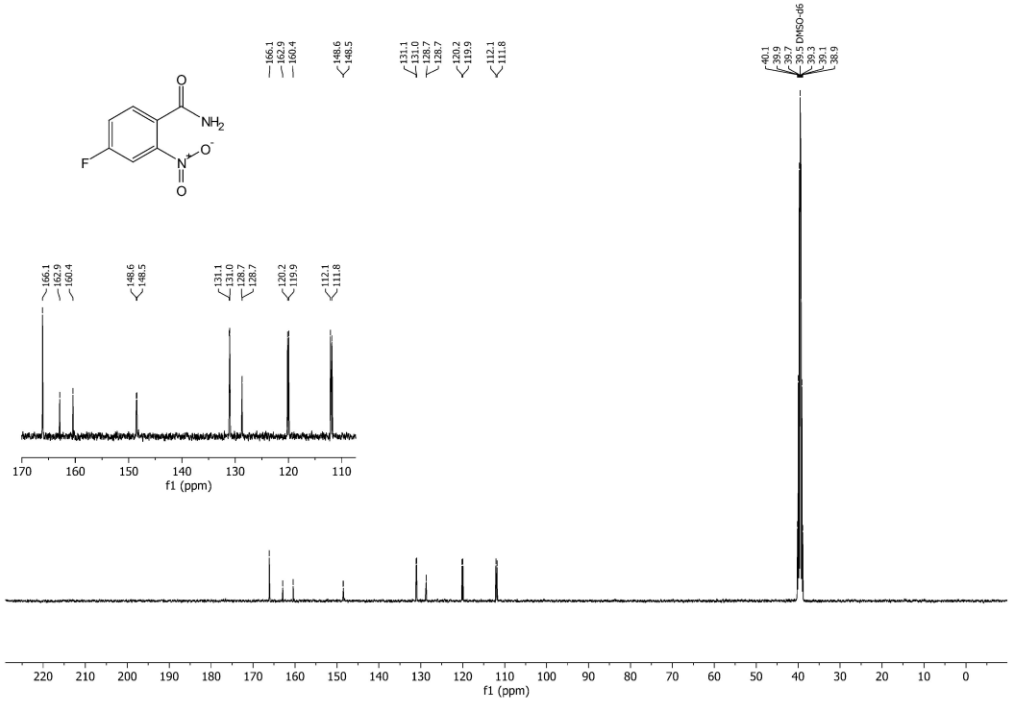
N-(2-(Dimethylamino)vinyl)-2-nitrobenzamide (9)

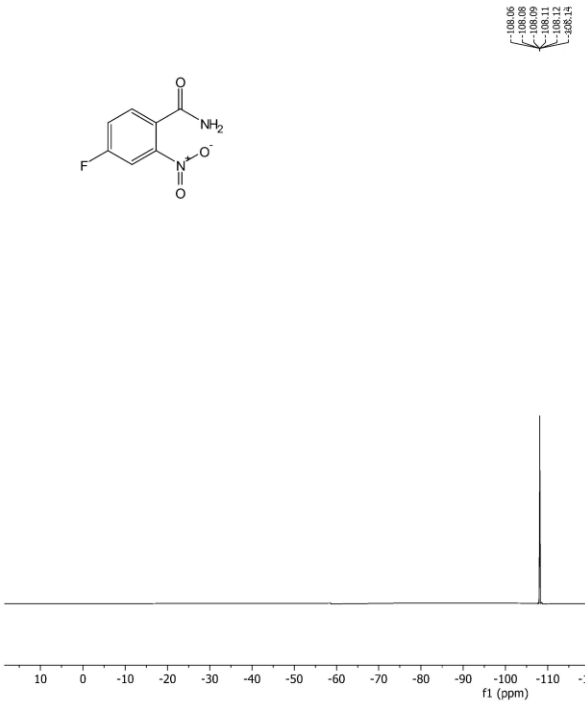




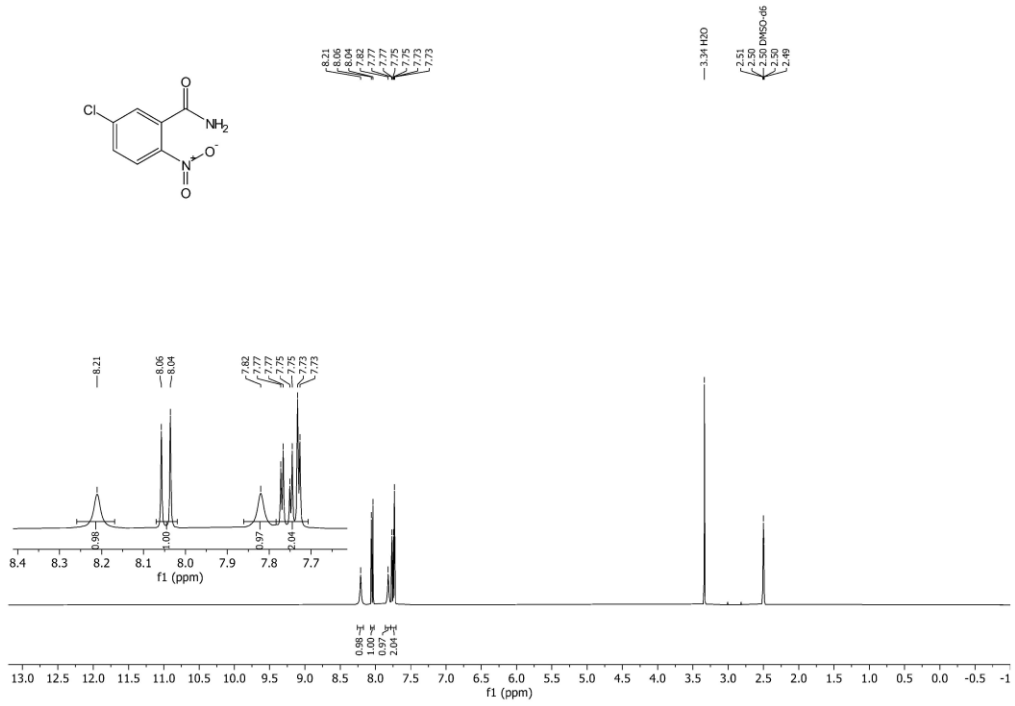
4-Fluoro-2-nitrobenzamide (10a)

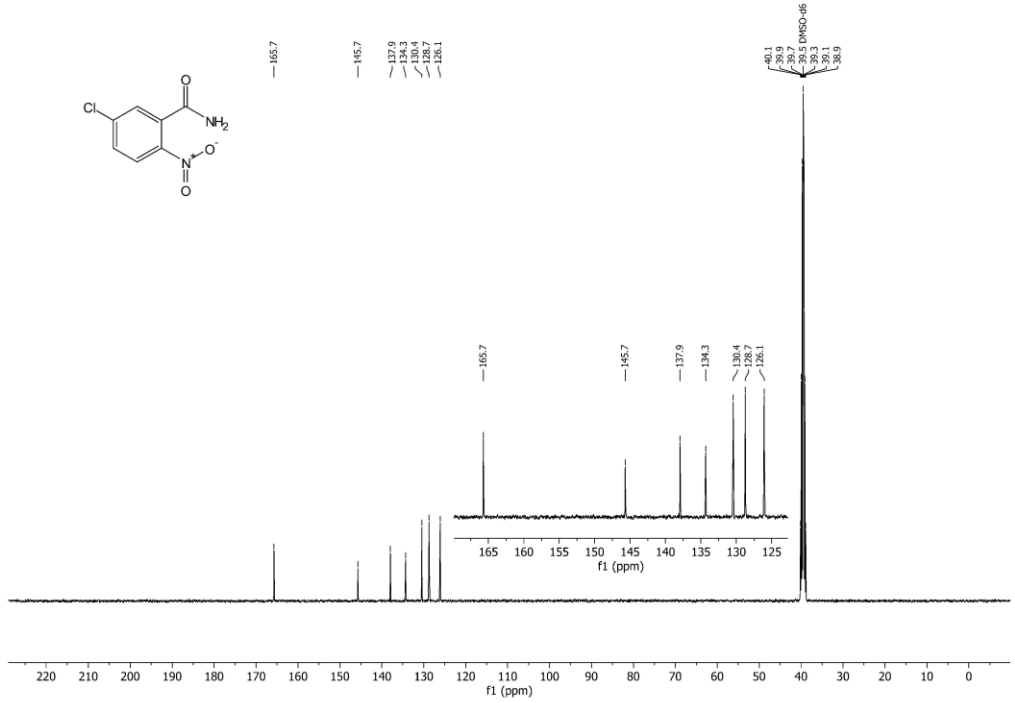




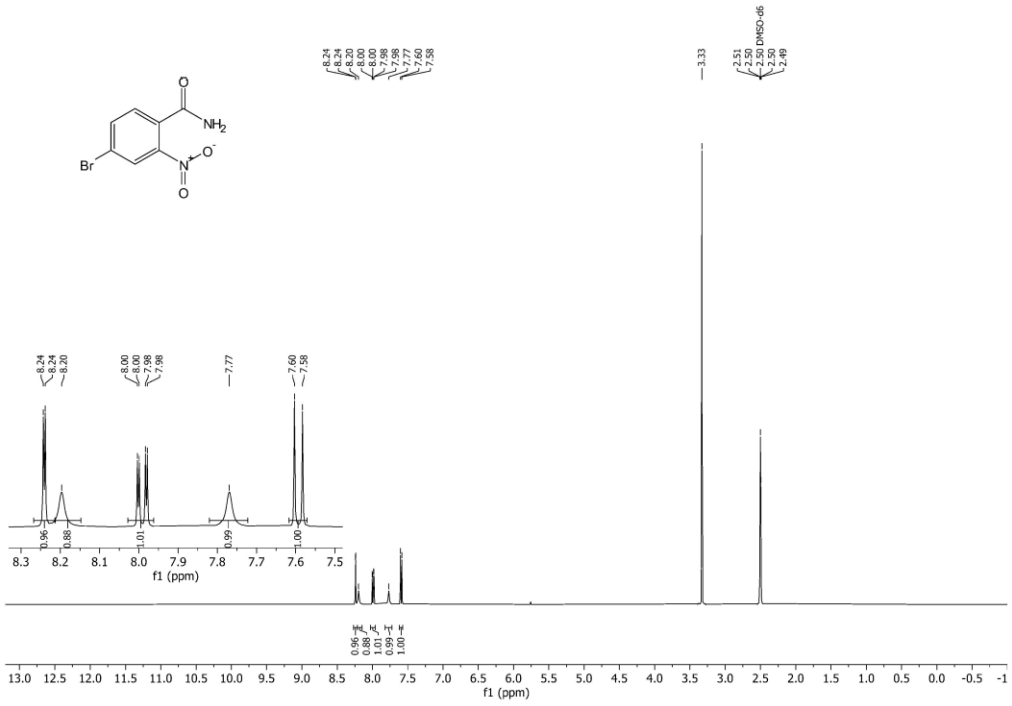

-108.06
-108.08
-108.09
-108.11
-108.12
-108.14
O
NH2
F
N+
O-
O
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

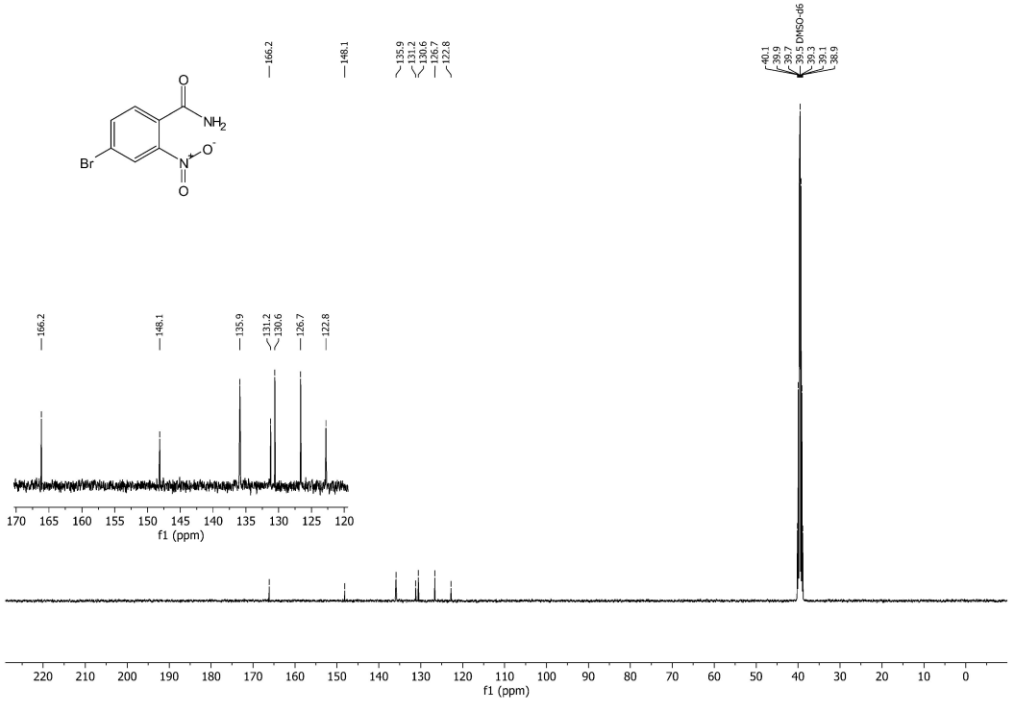
5-Chloro-2-nitrobenzamide (10b)



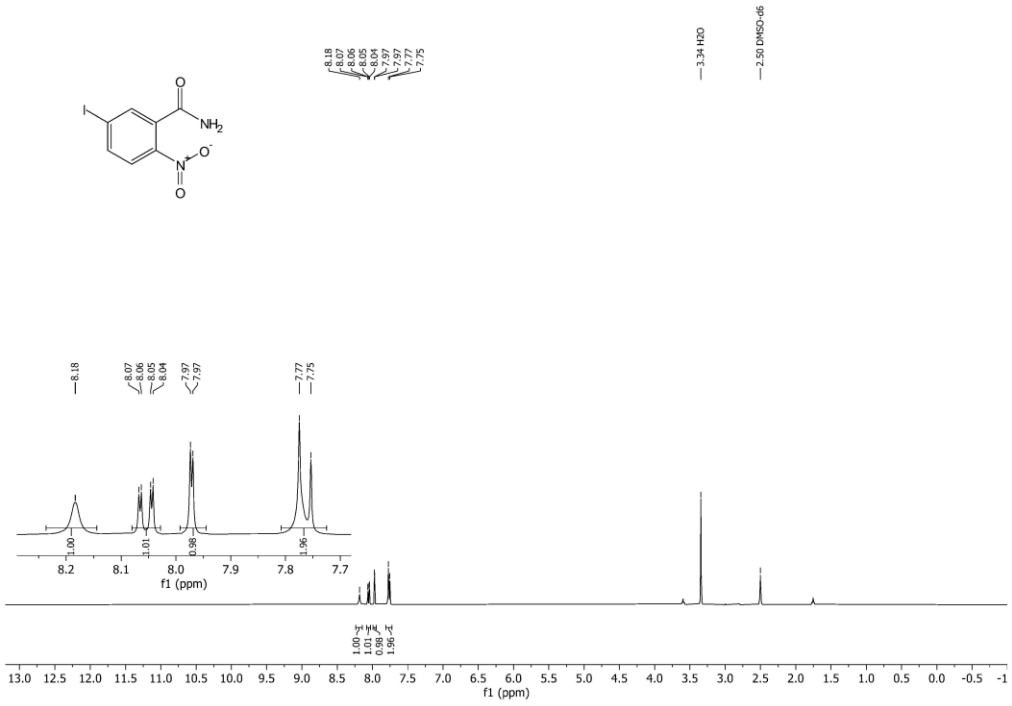


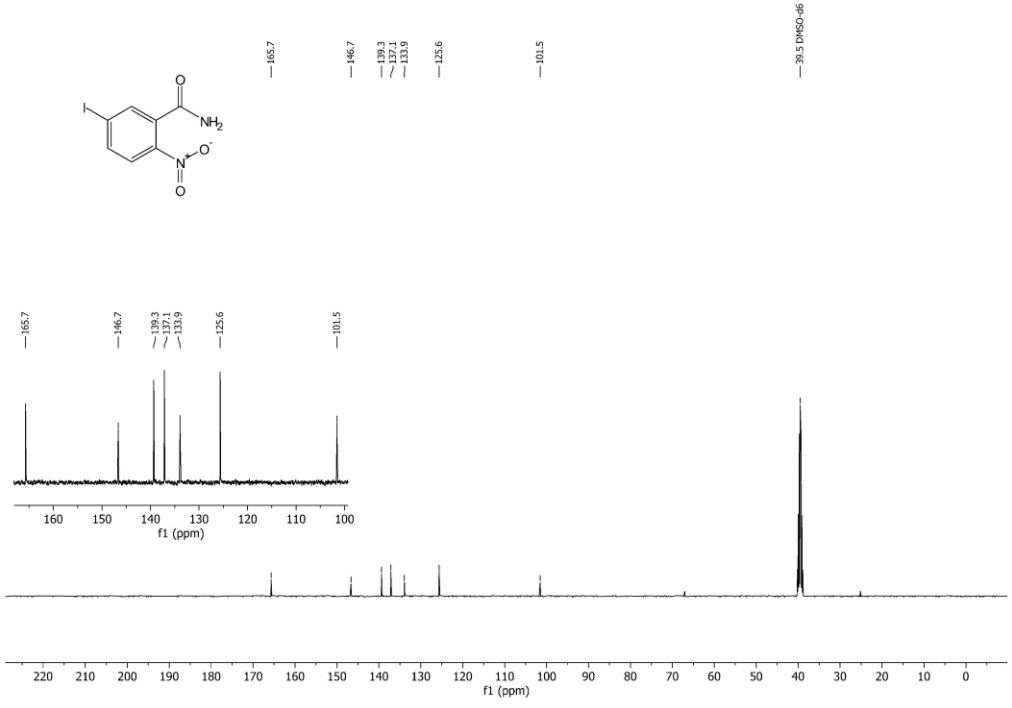
4-Bromo-2-nitrobenzamide (10c)



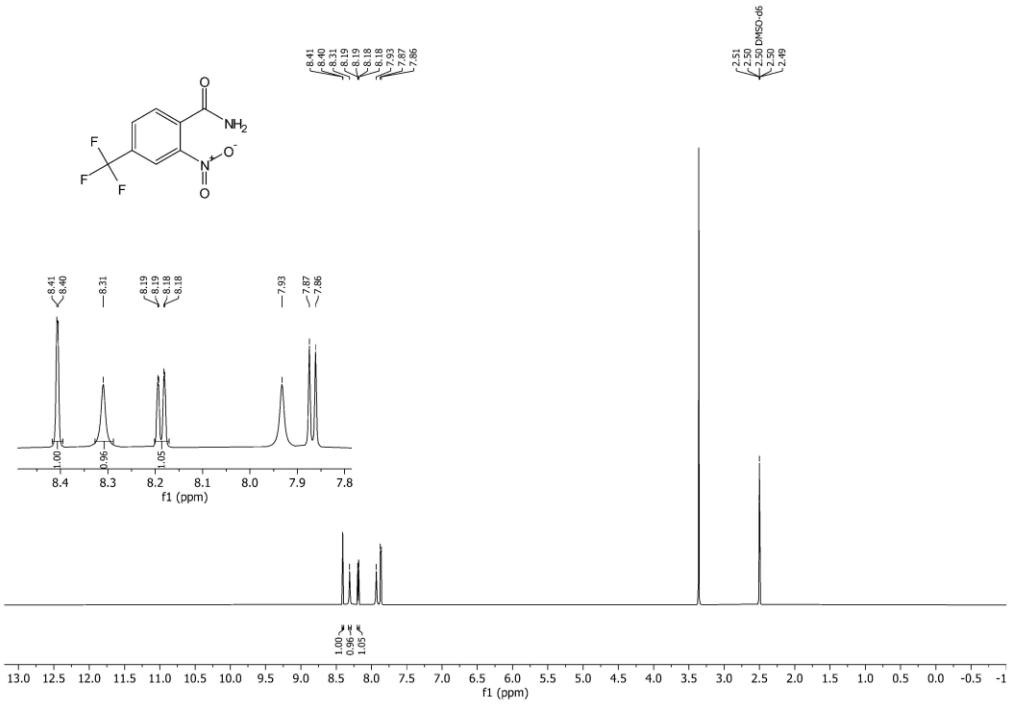


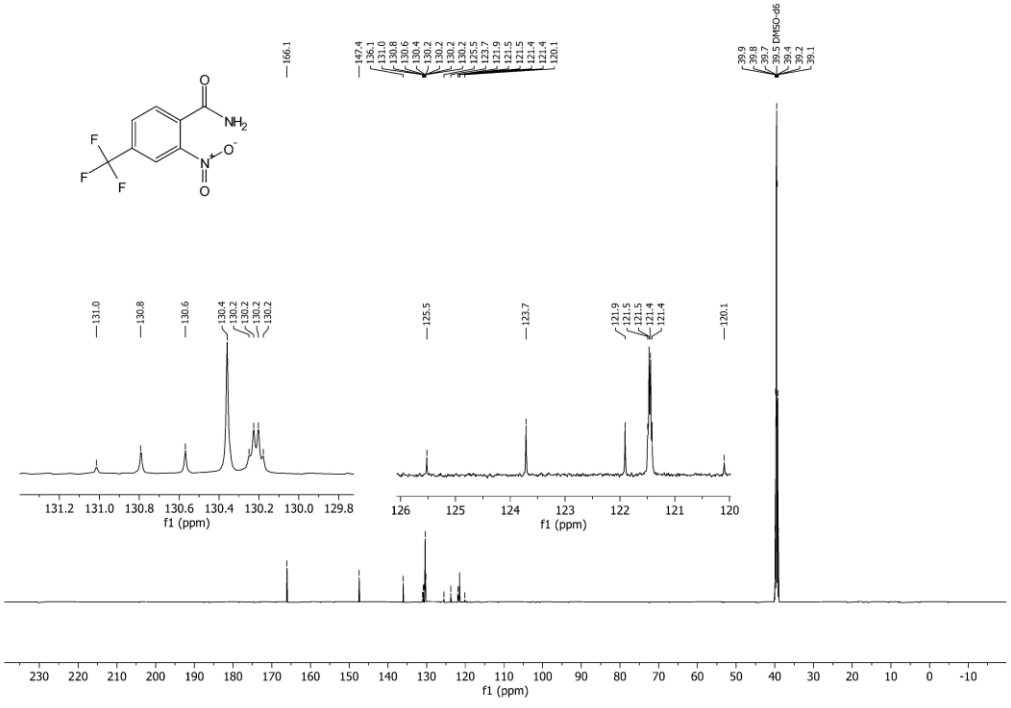
5-Iodo-2-nitrobenzamide (10d)

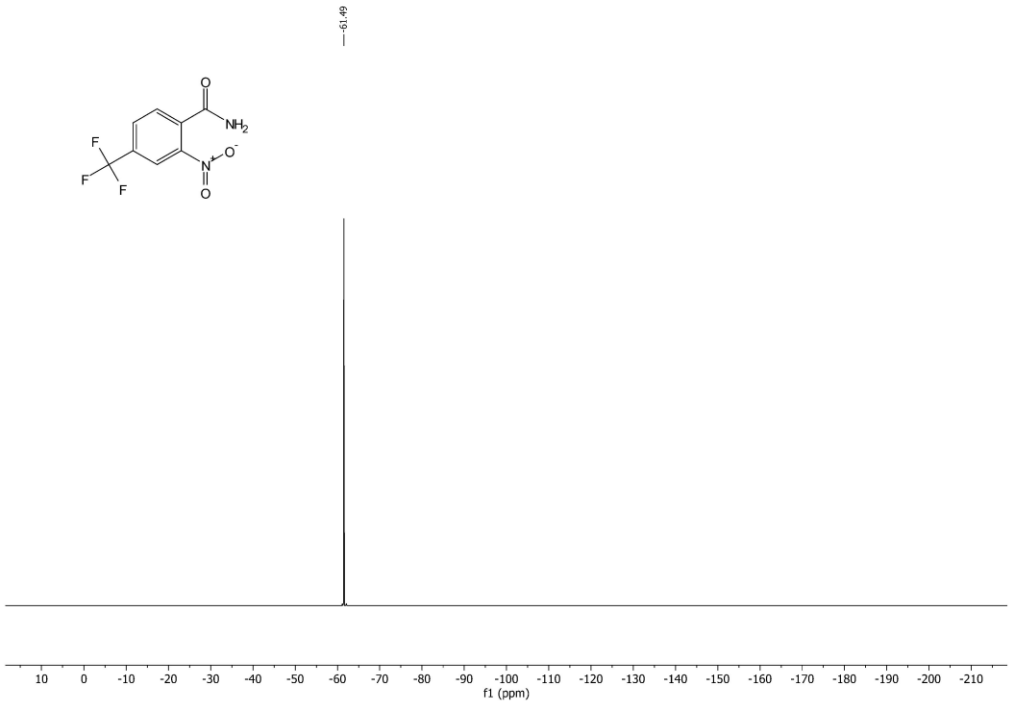




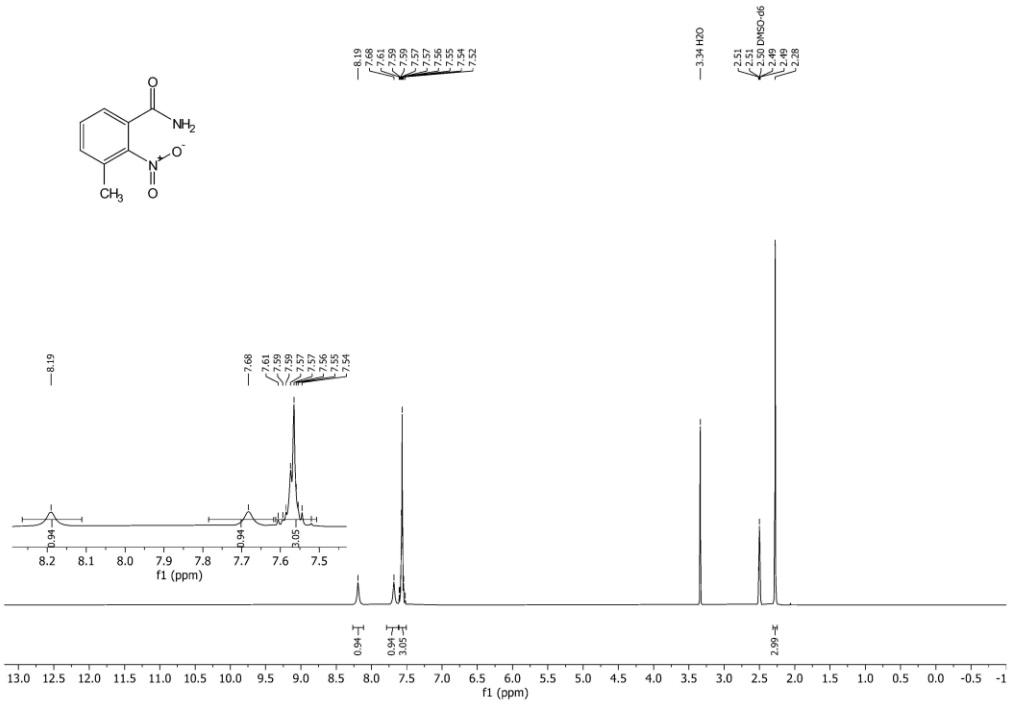
2-Nitro-4-(trifluoromethyl)benzamide (10e)

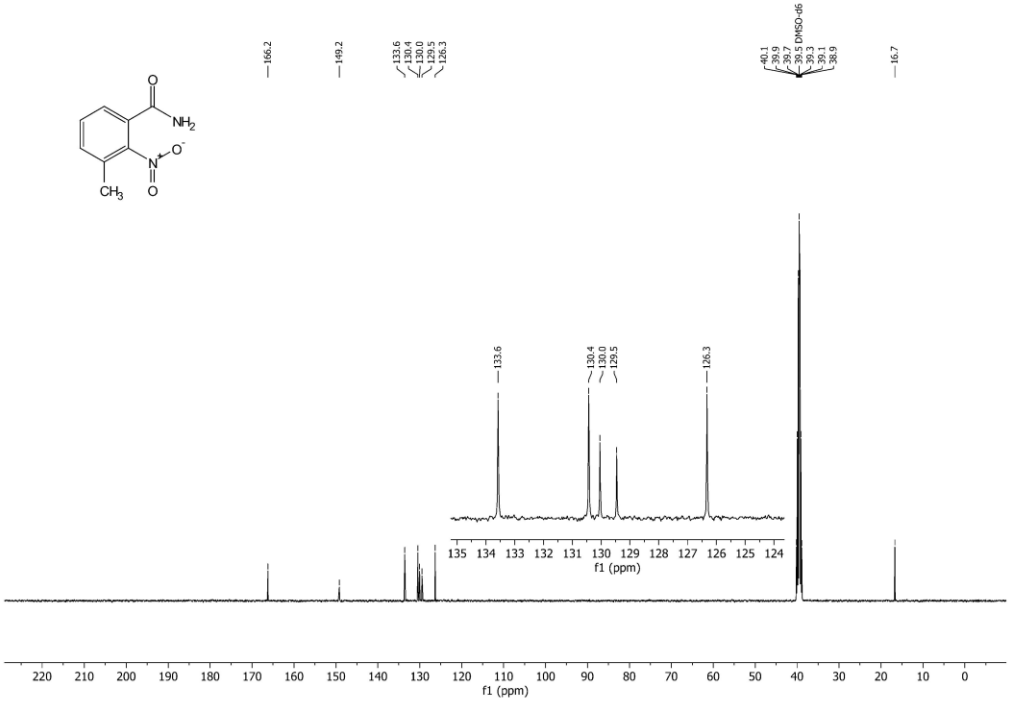




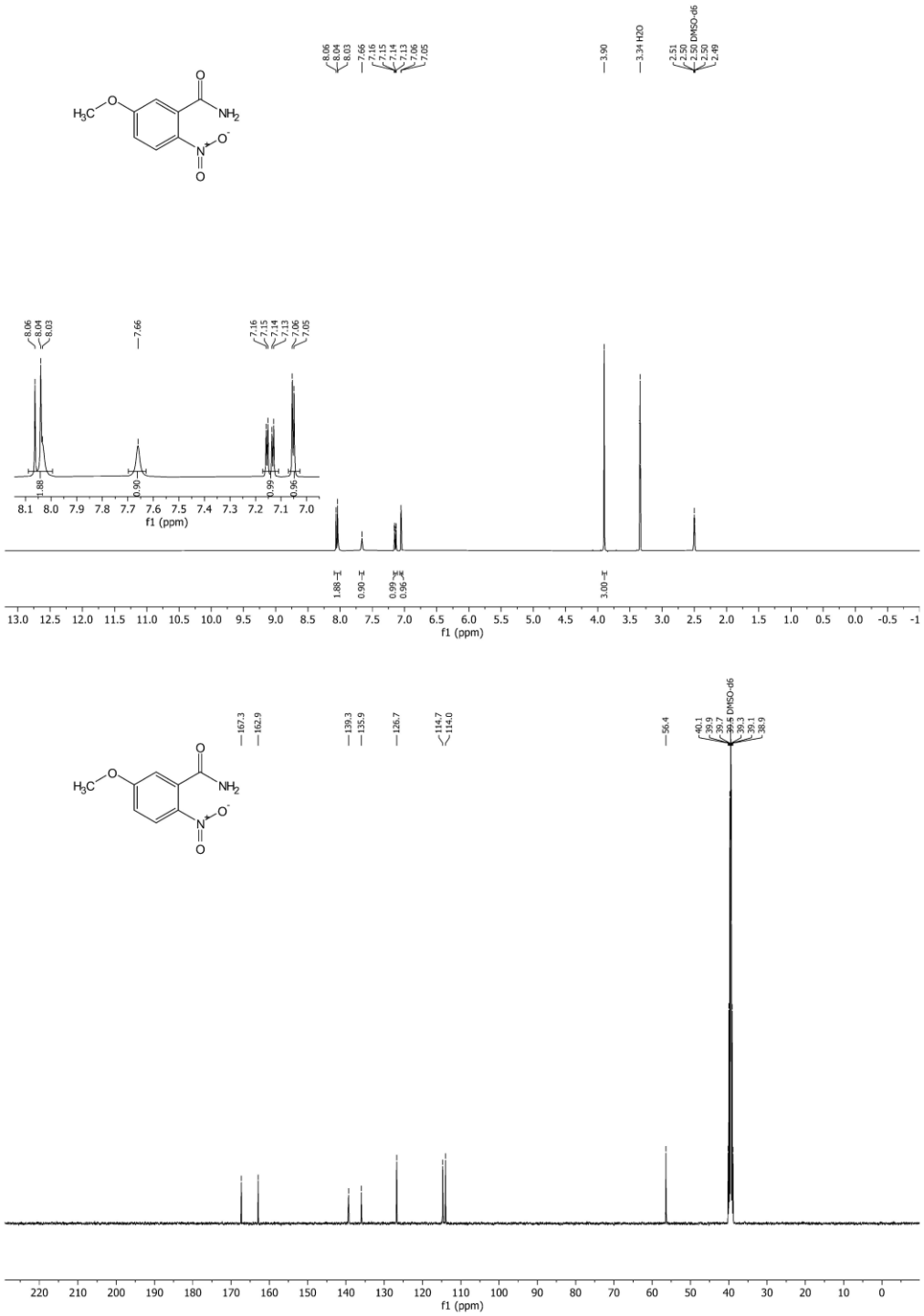

-61.49
O
NH2
F
F
F
N+
O-
O
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

3-Methyl-2-nitrobenzamide (10f)

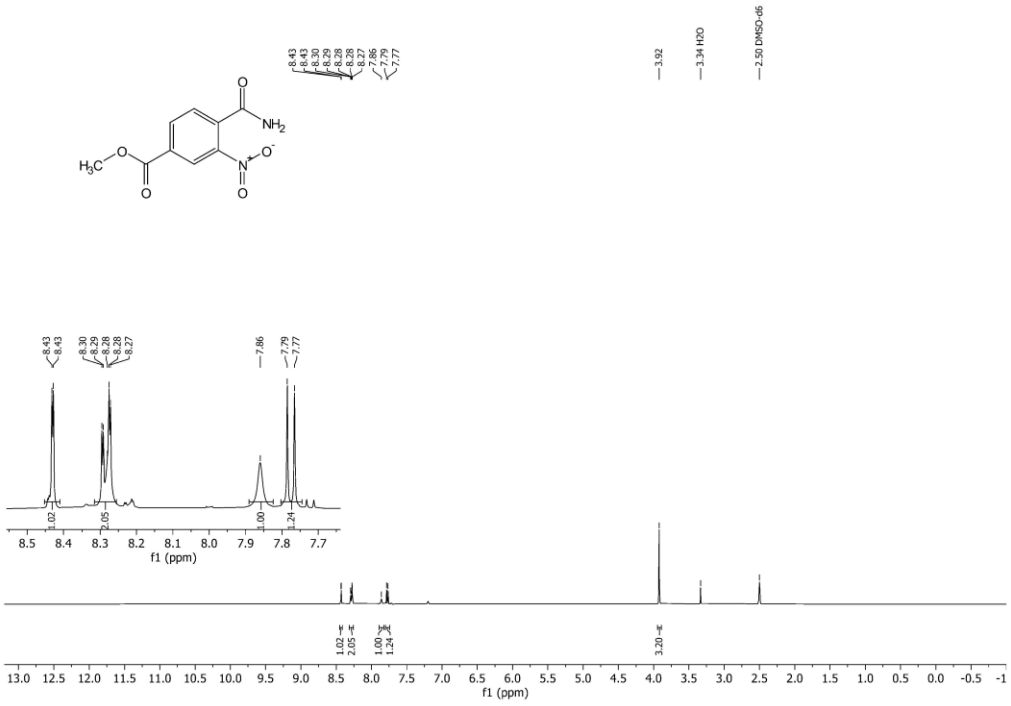


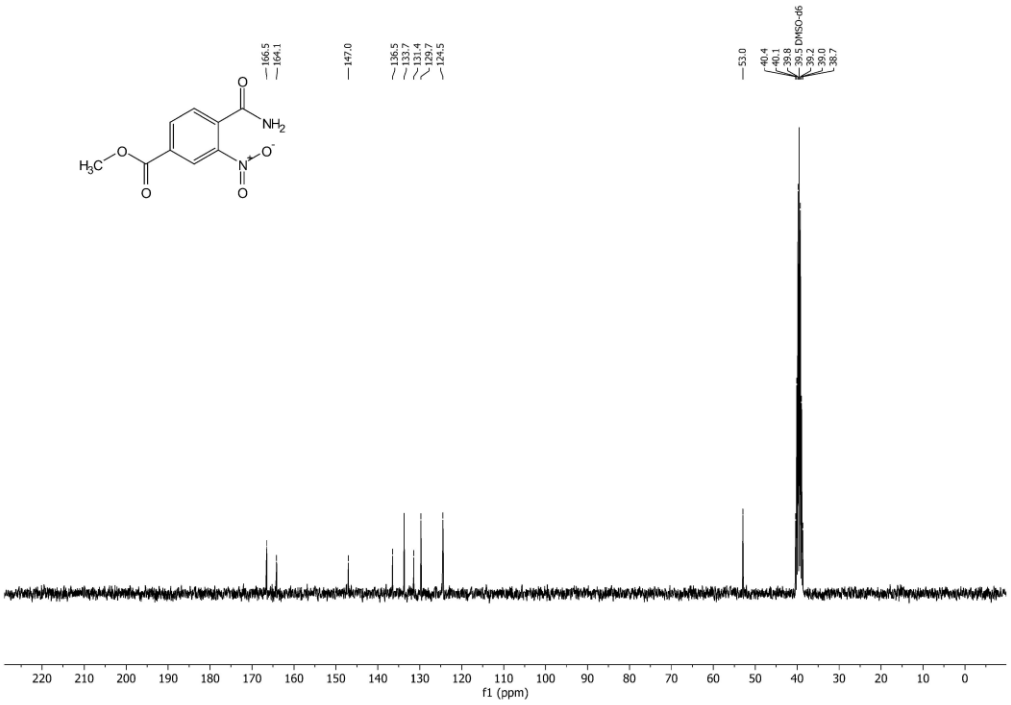


5-Methoxy-2-nitrobenzamide (10g)

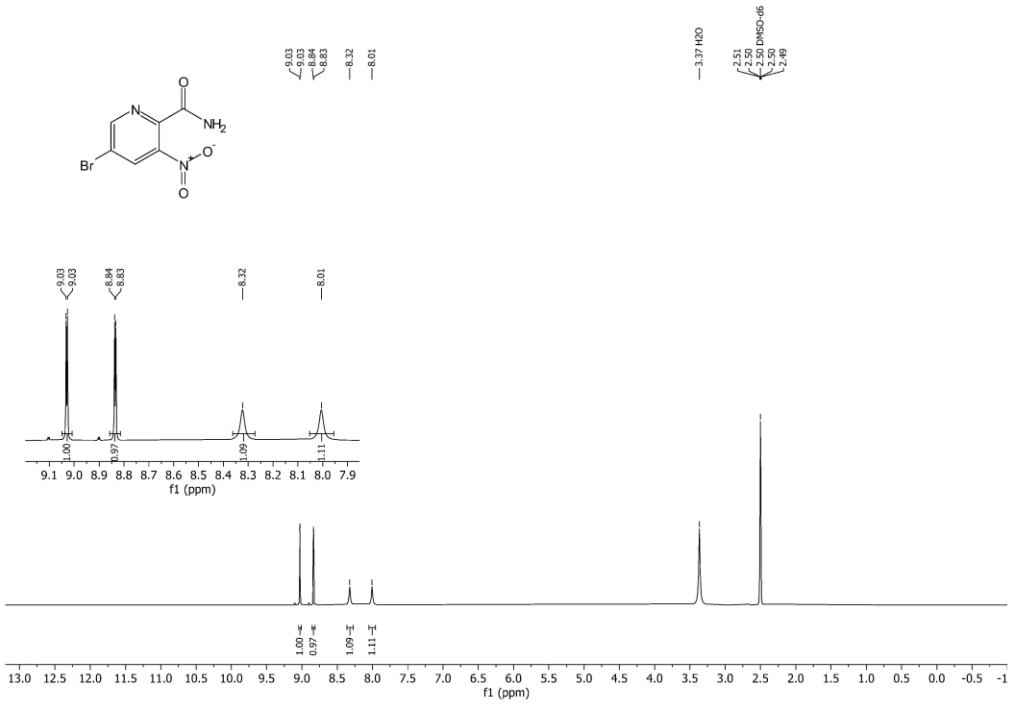


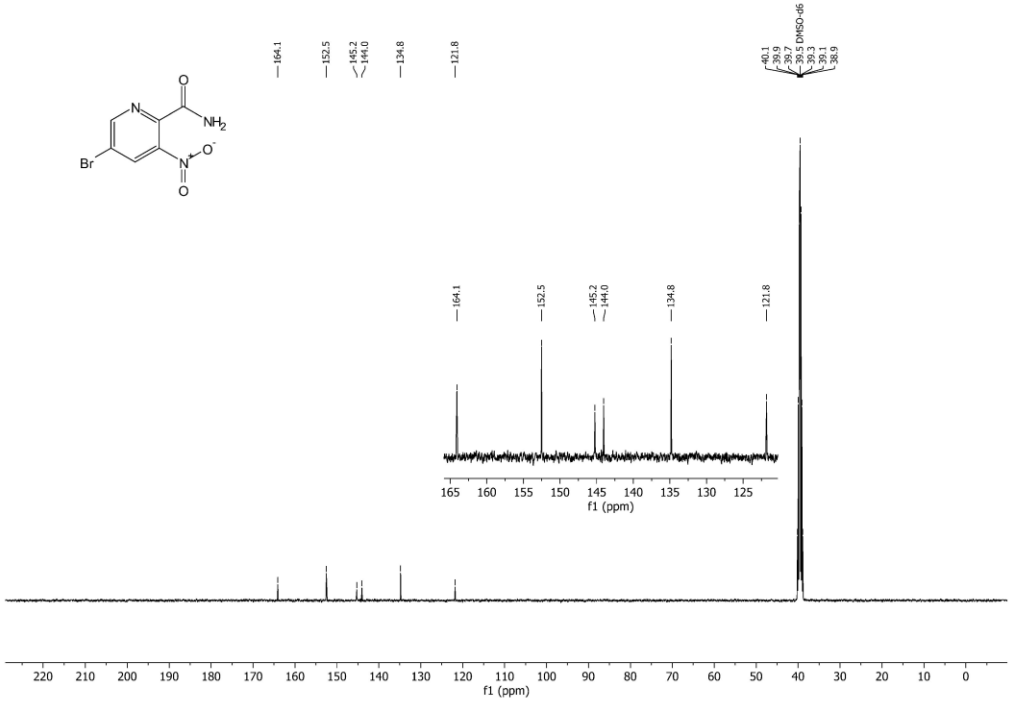
Methyl 4-carbamoyl-3-nitrobenzoate (10h)



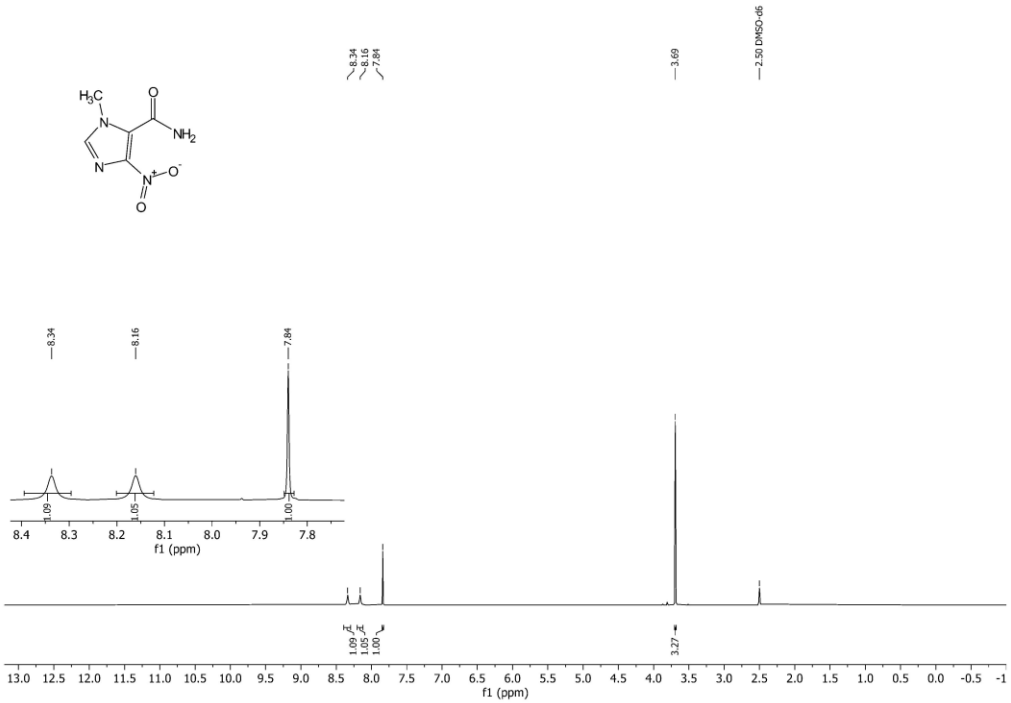


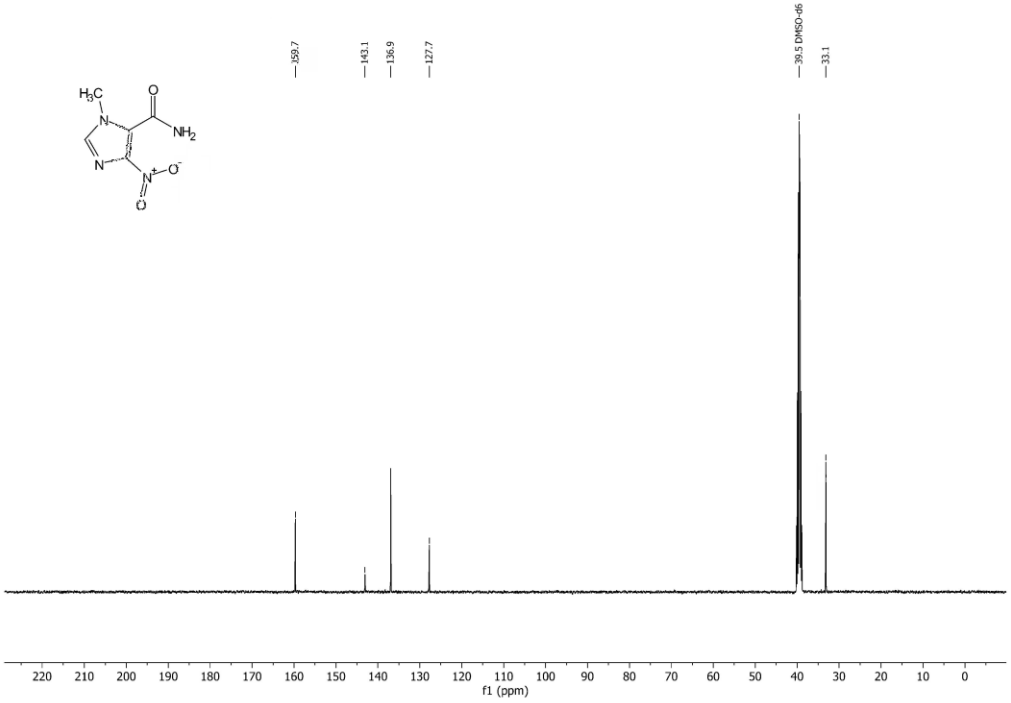
5-Bromo-3-nitropicolinamide (10i)



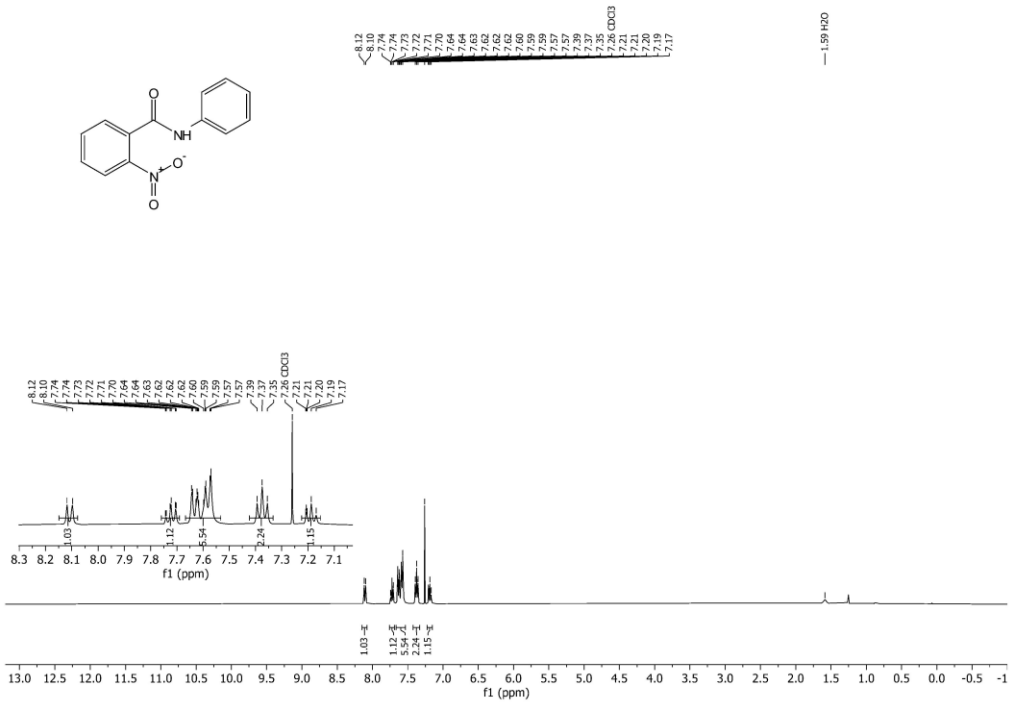


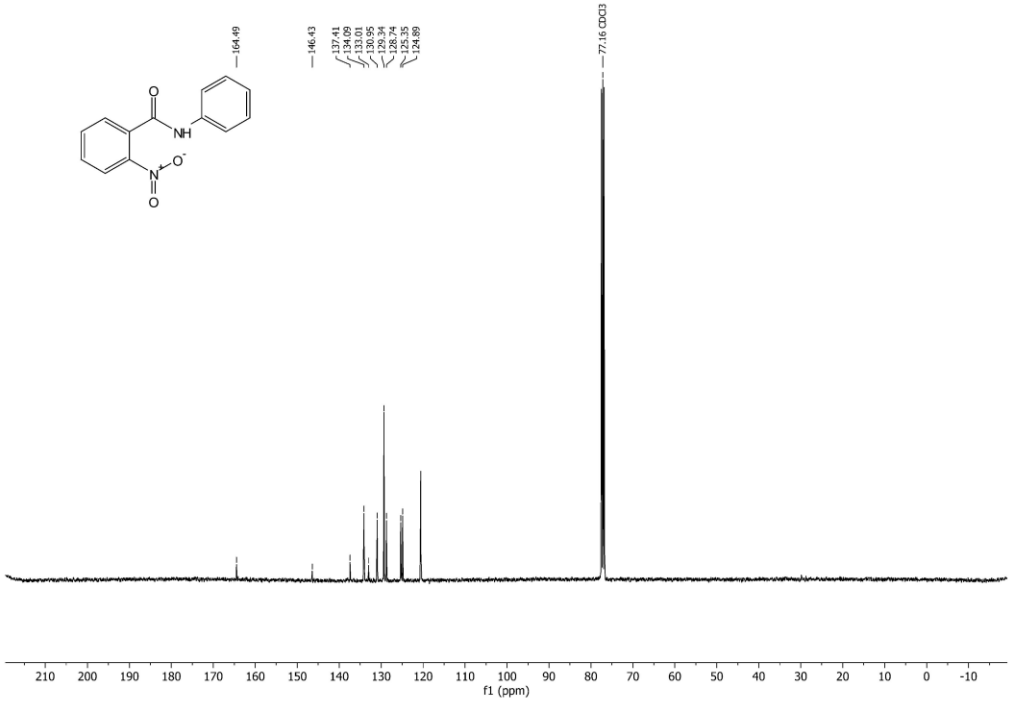
1*H*-1-Methyl-4-nitro-imidazole-5-carboxamide (10j)



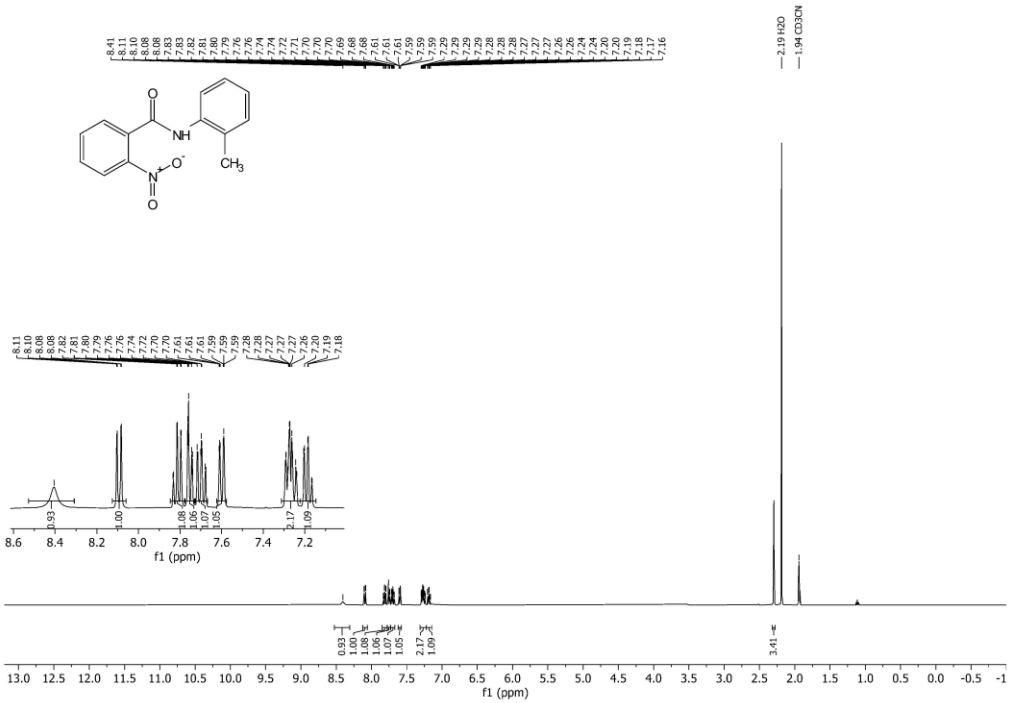


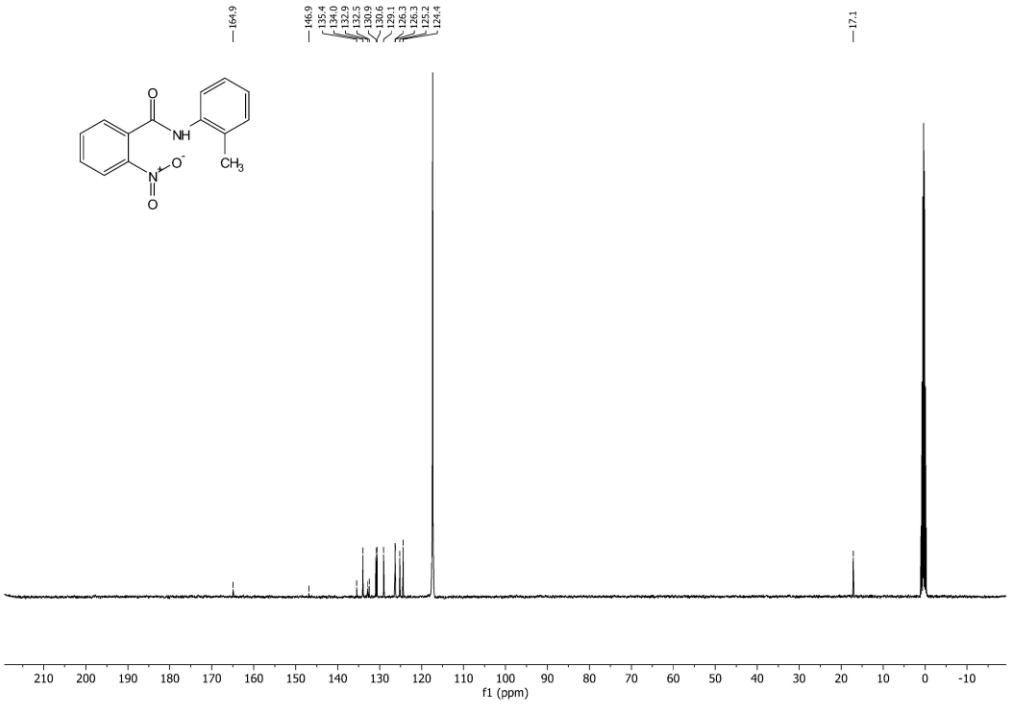
2-Nitro-*N*-phenylbenzamide (11a)



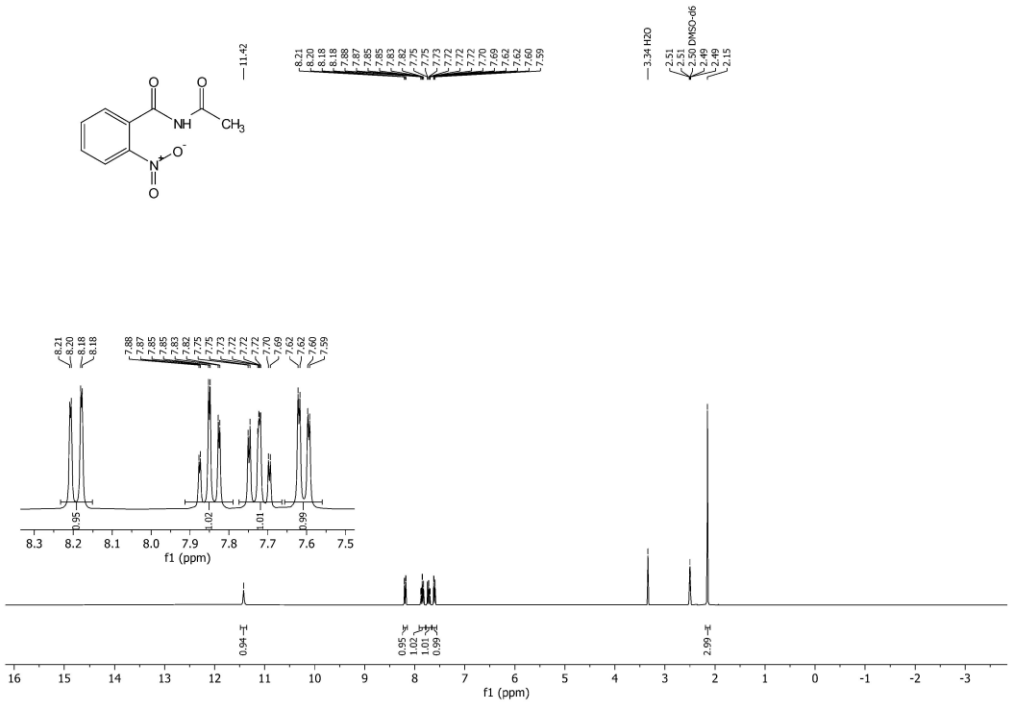


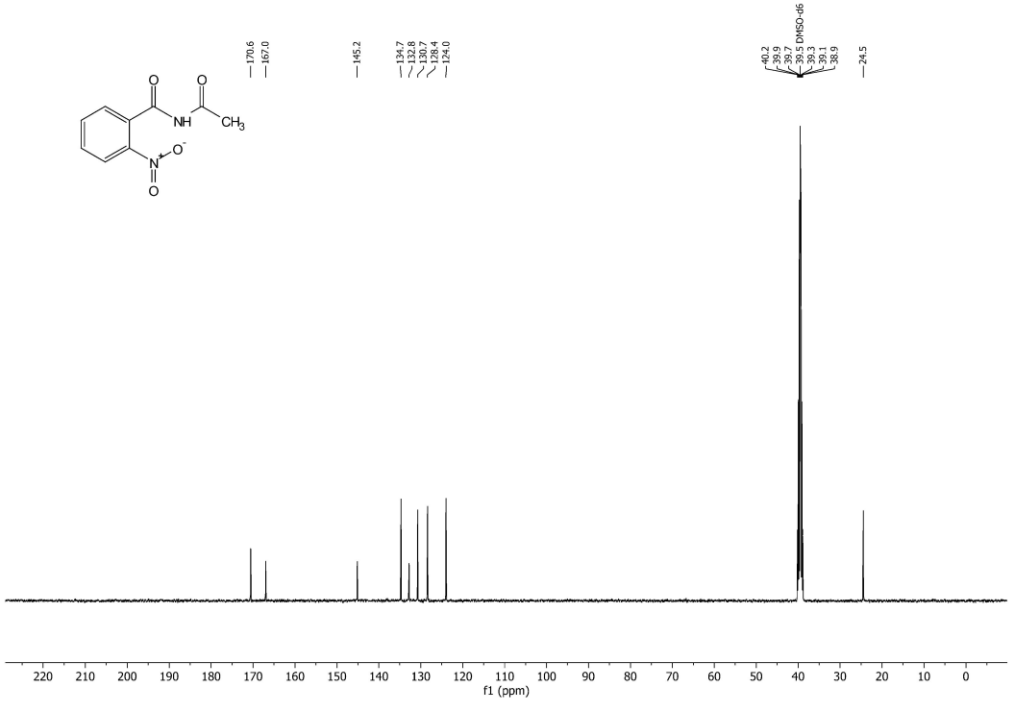
2-Nitro-*N*-(o-tolyl)benzamide (11b)



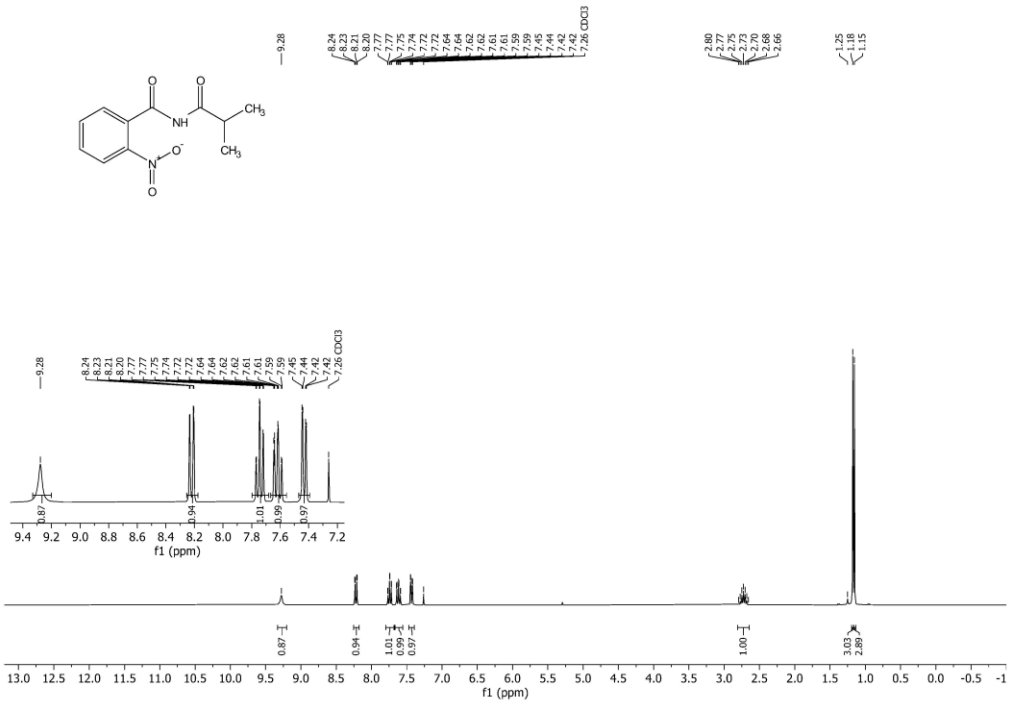


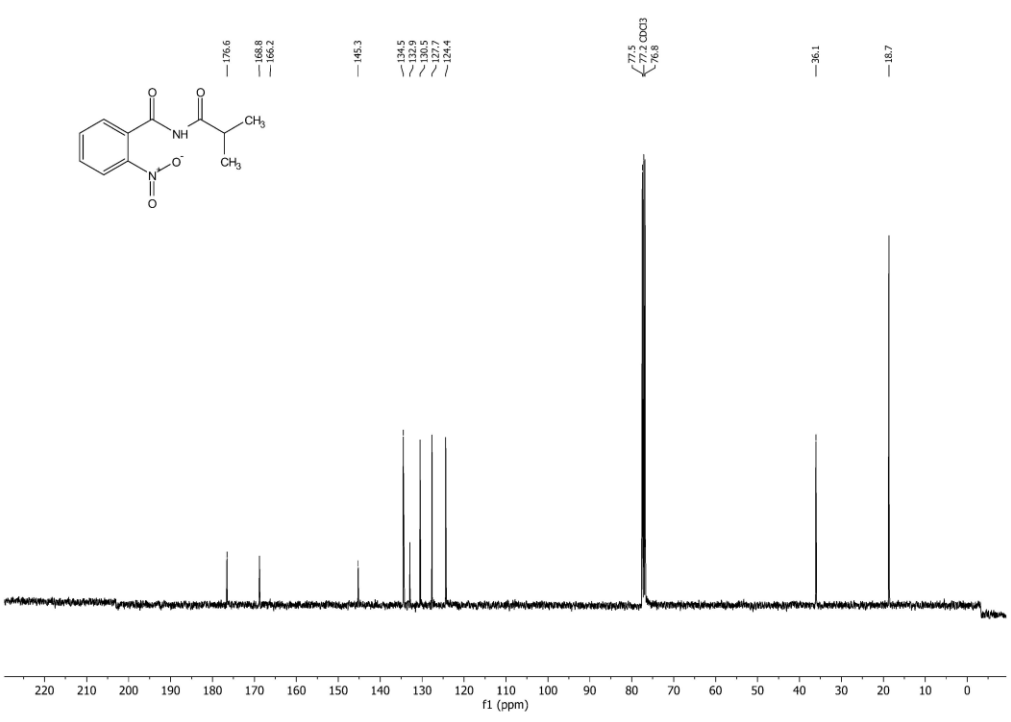
_N_-Acetyl-2-nitrobenzamide (5a)



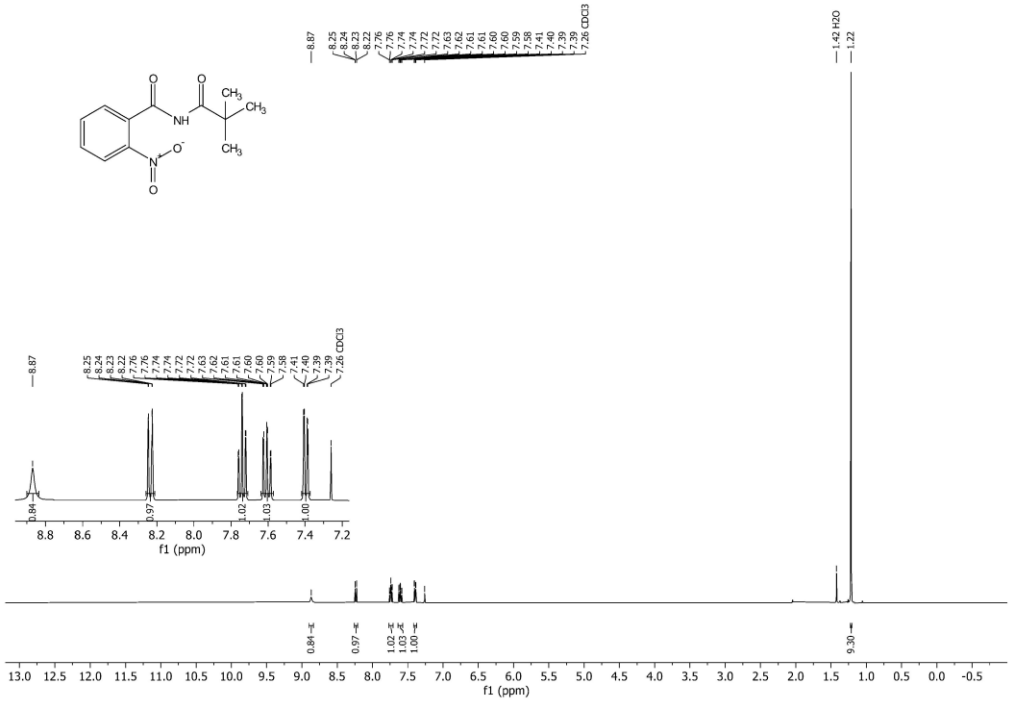


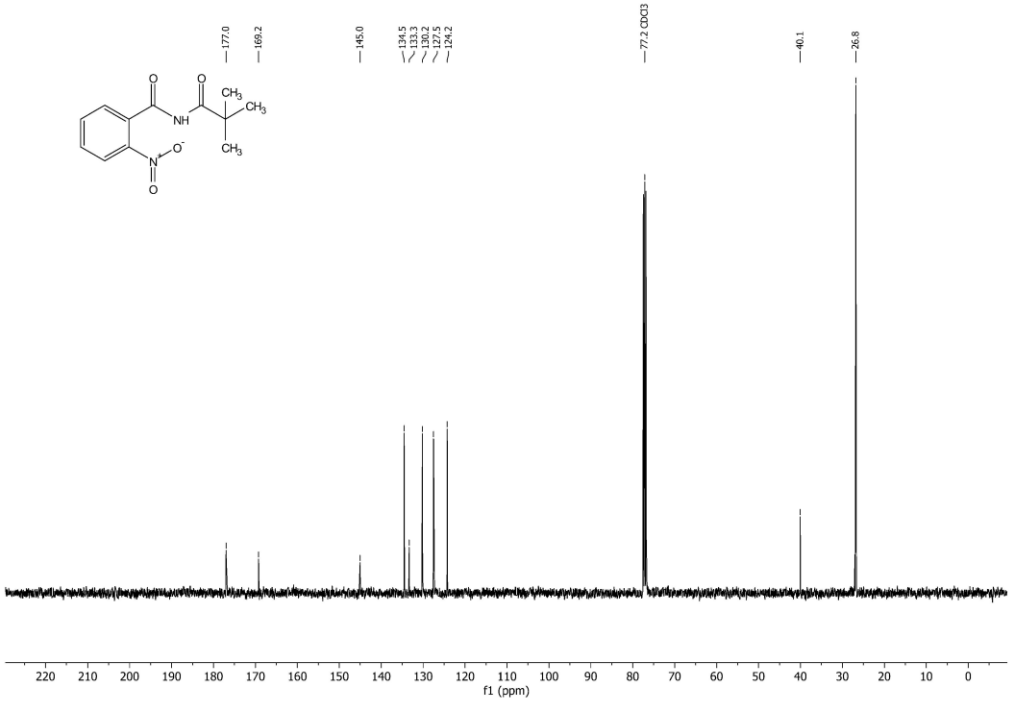
_N_-Isobutyryl-2-nitrobenzamide (5b)



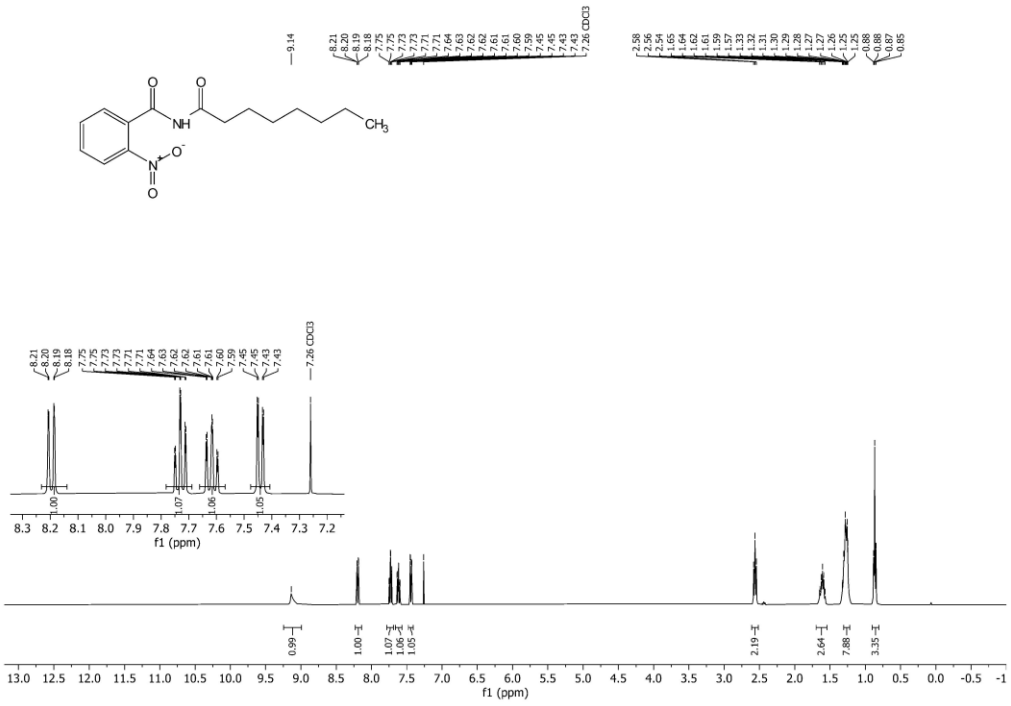


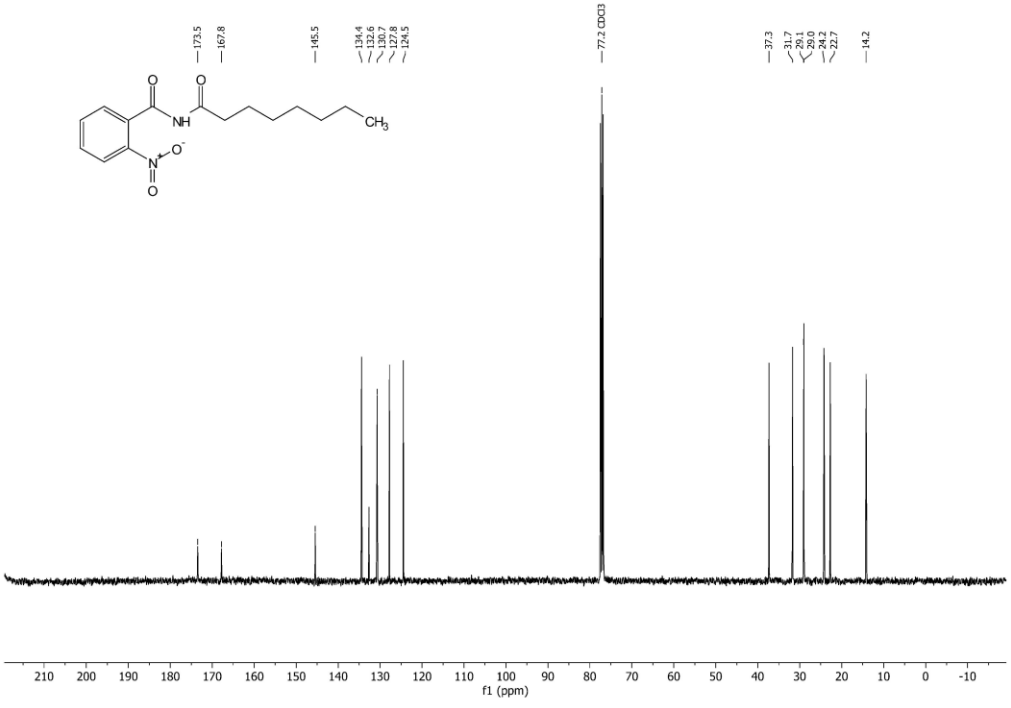
2-Nitro-*N*-pivaloylbenzamide (5c)



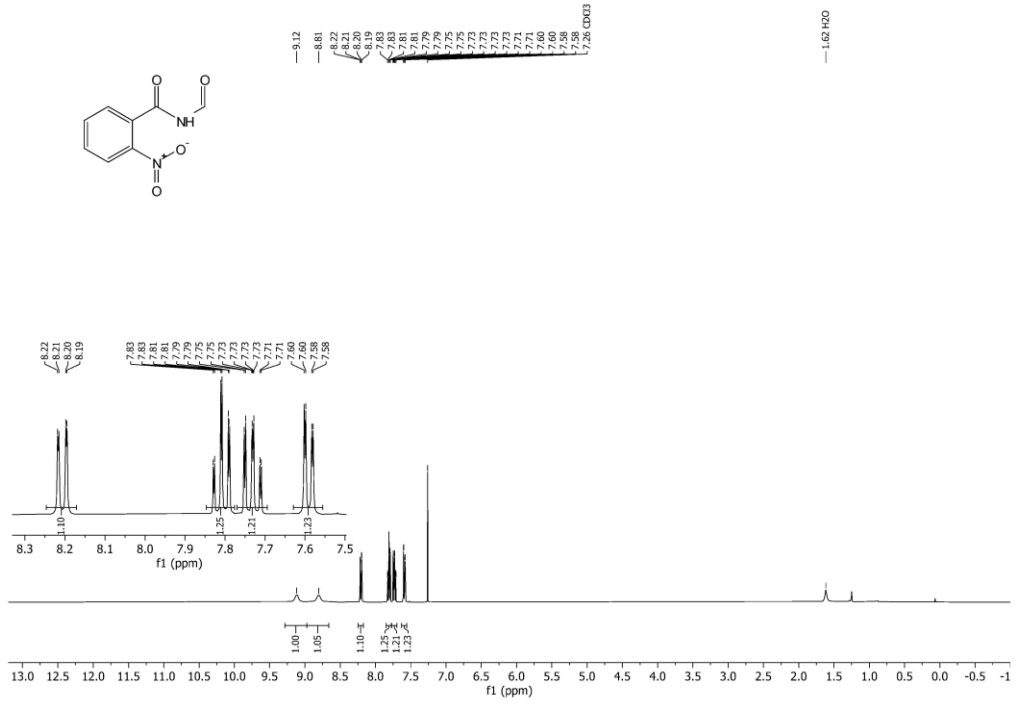


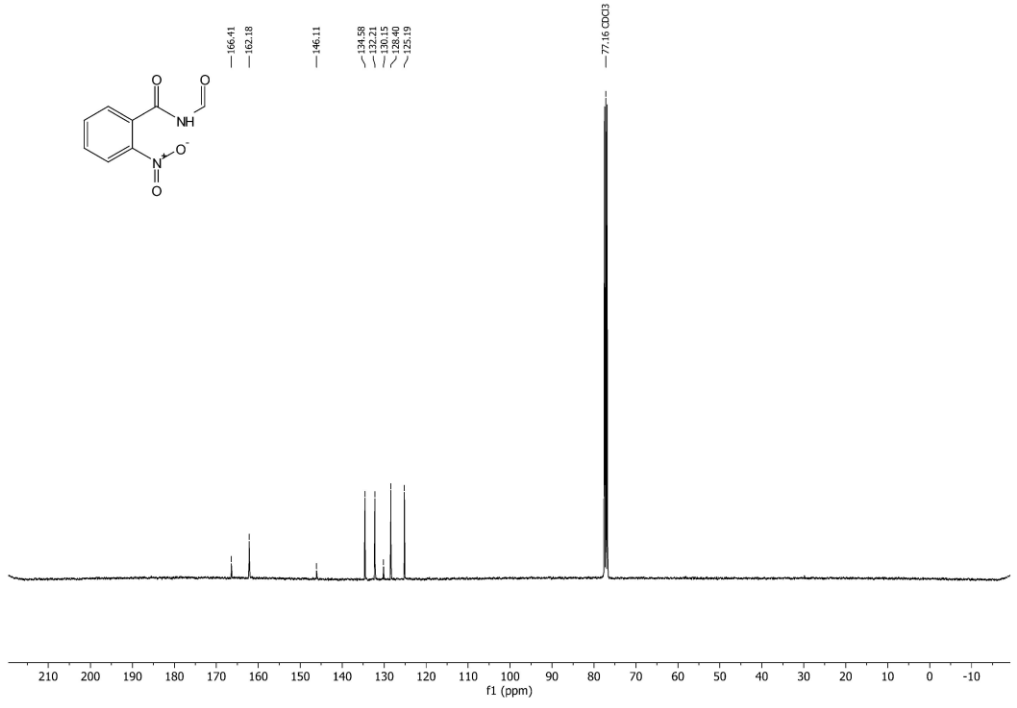
2-Nitro-*N*-octanoylbenzamide (5d)



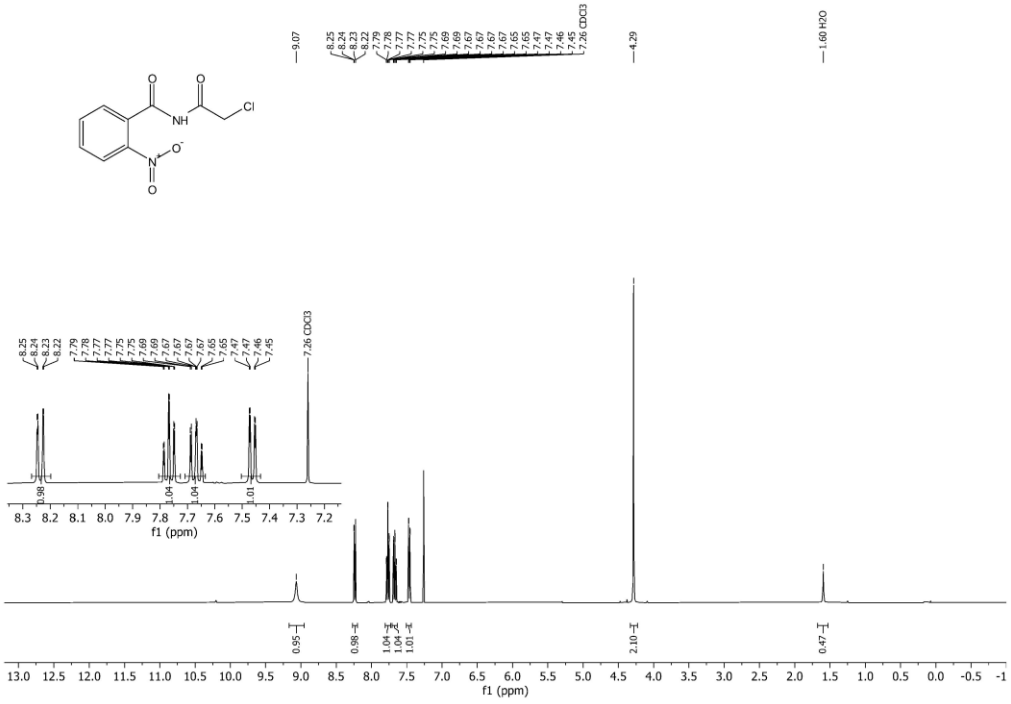


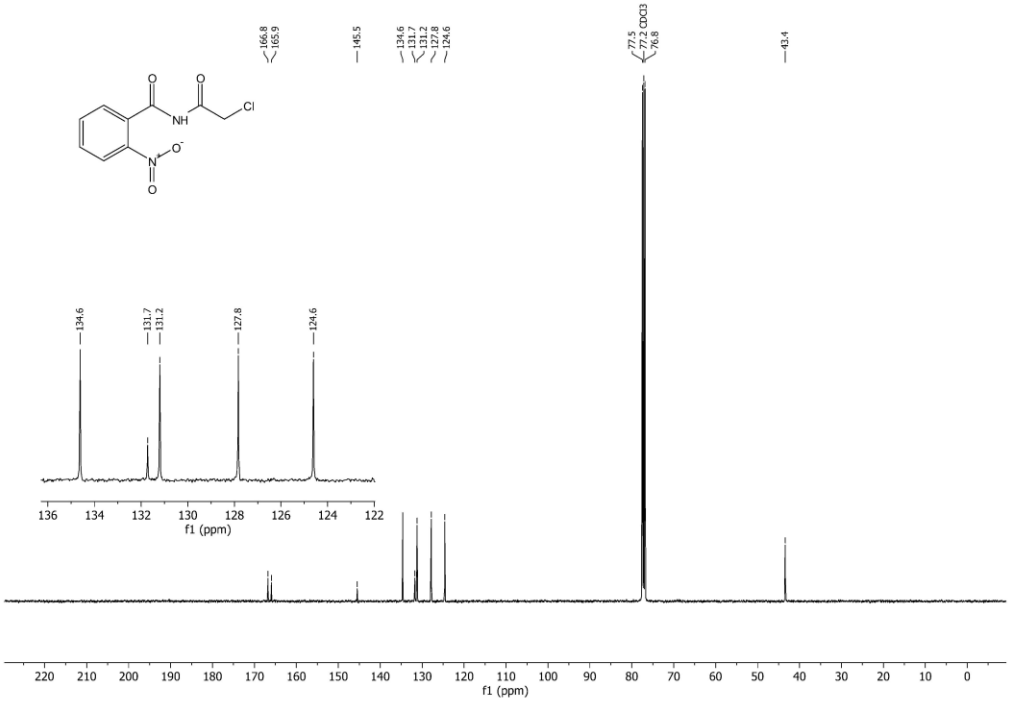
***N*-Formyl-2-nitrobenzamide (5e)**



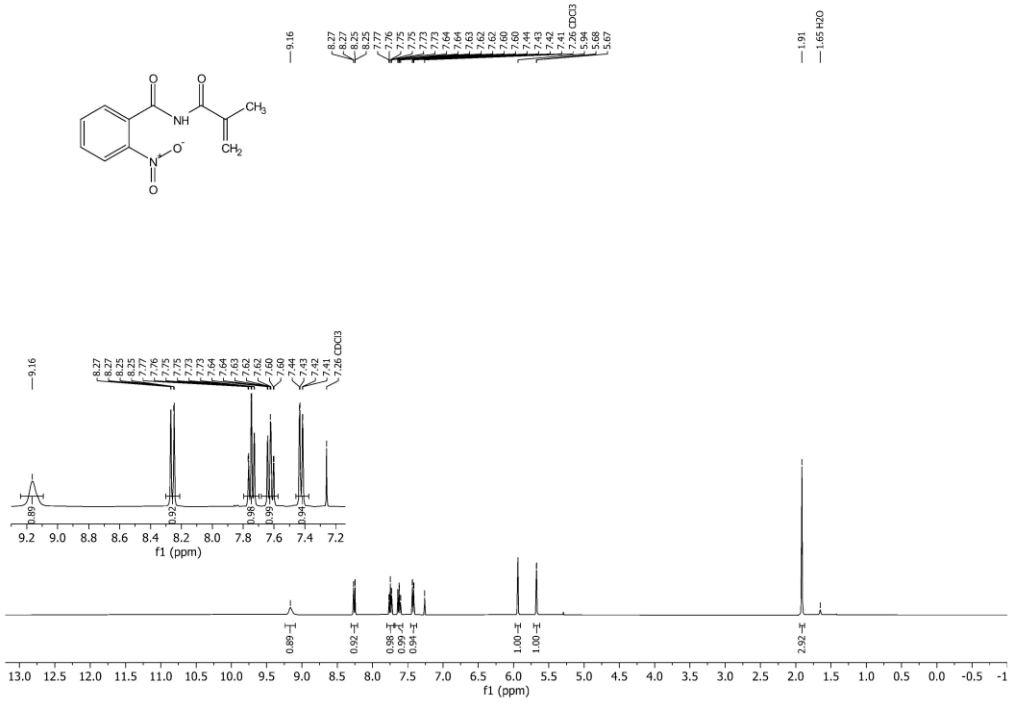


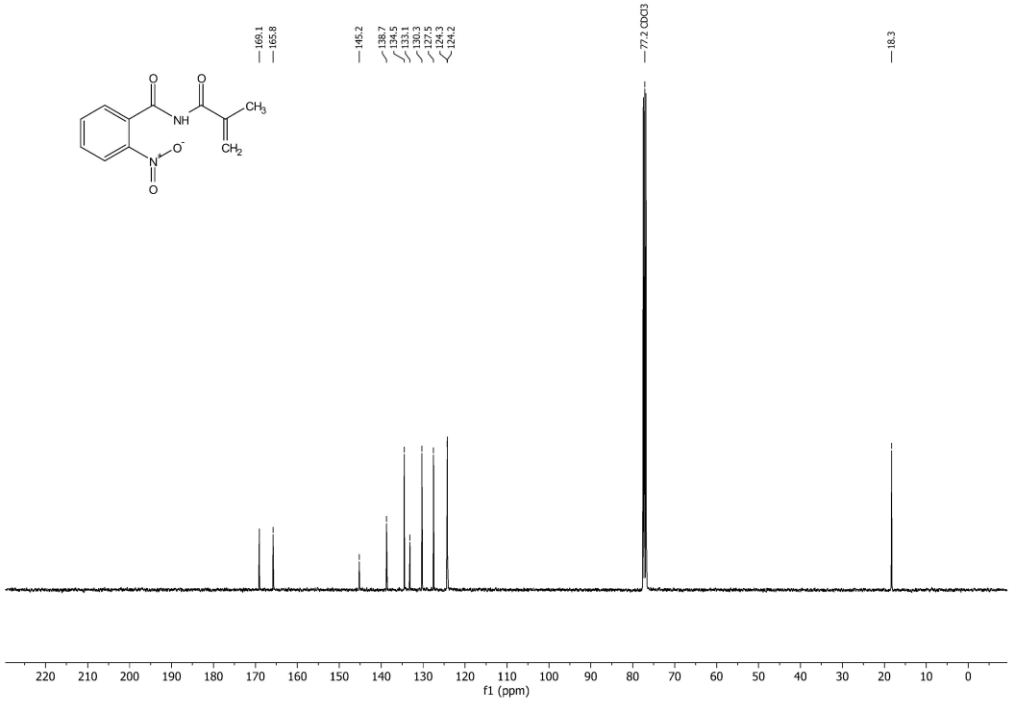
_N_-(2-Chloroacetyl)-2-nitrobenzamide (5f)



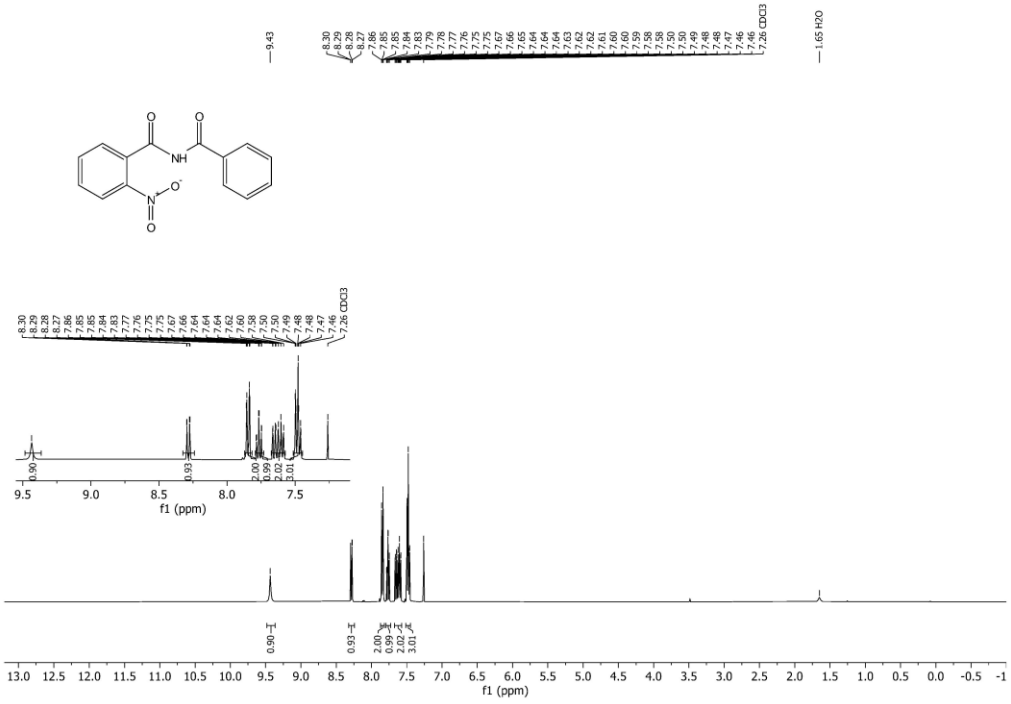


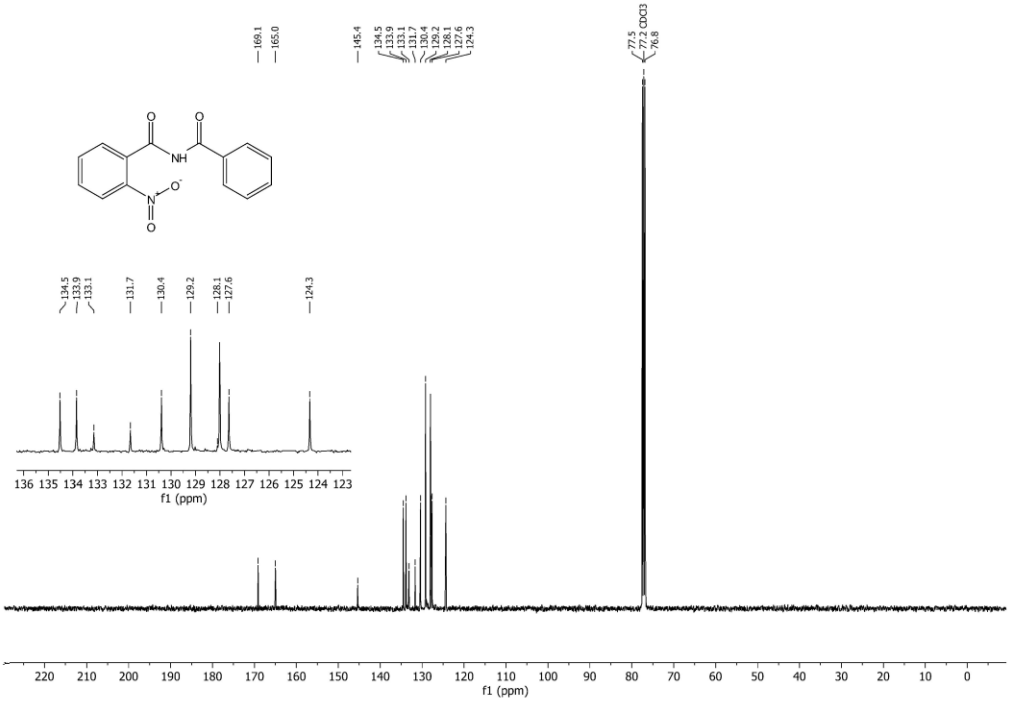
_N_-Methacryloyl-2-nitrobenzamide (5g)



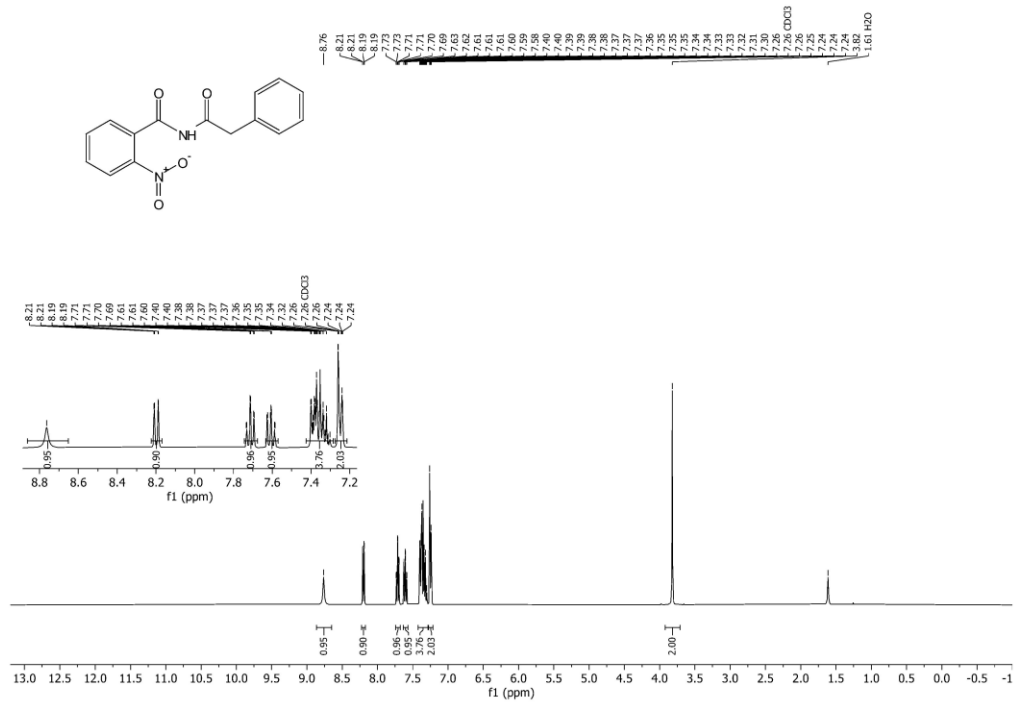


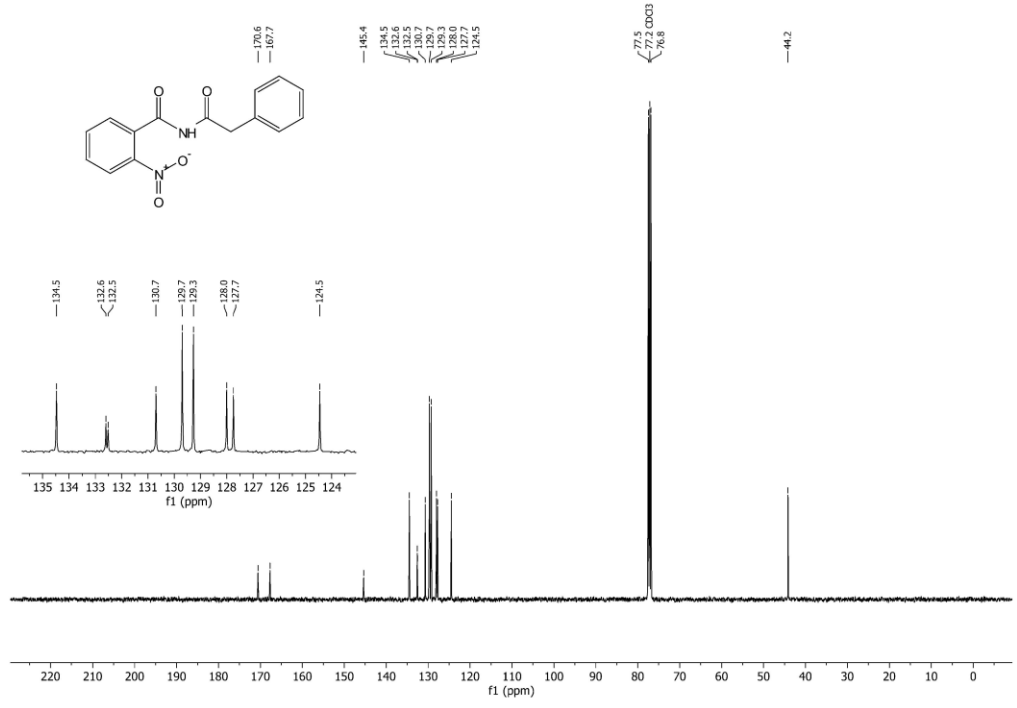
_N_-Benzoyl-2-nitrobenzamide (5h)



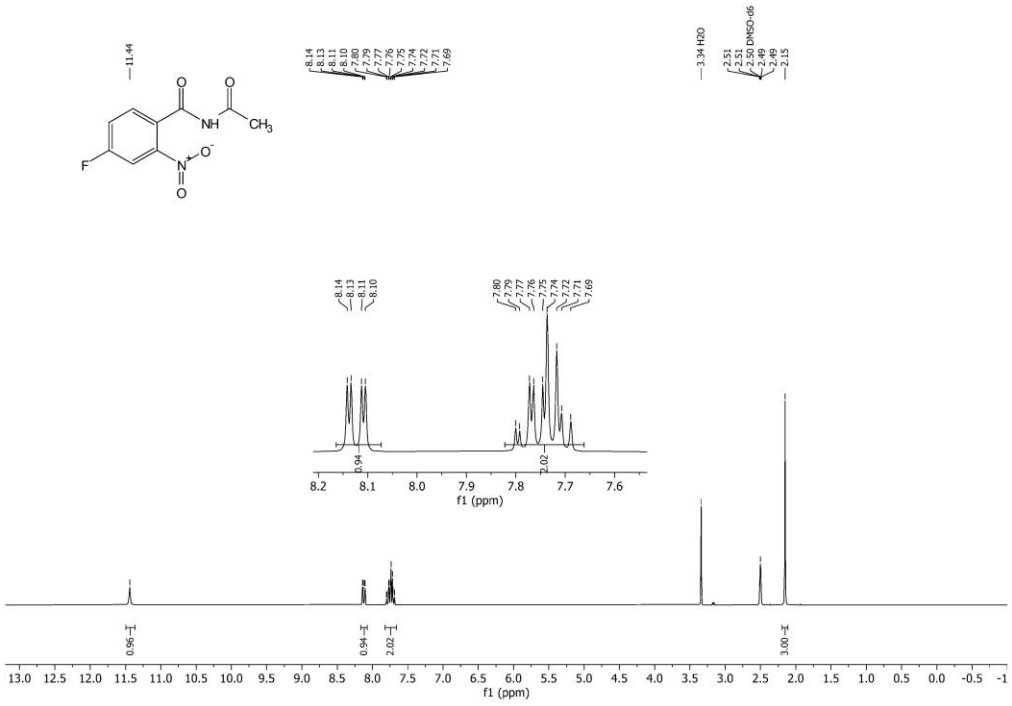


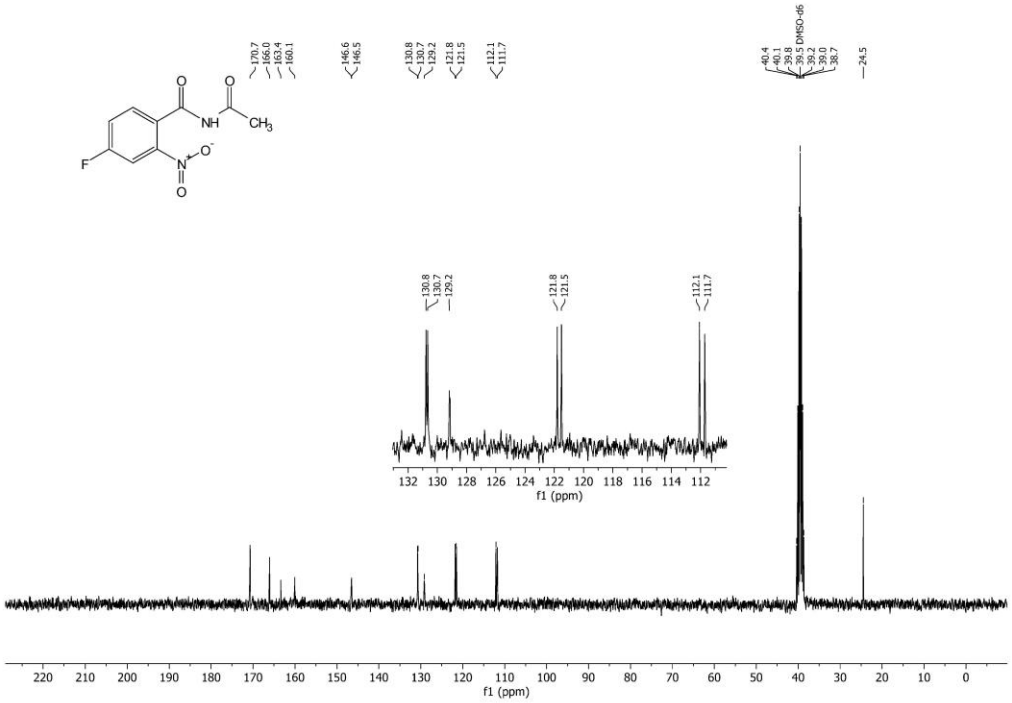
2-Nitro-*N*-(2-phenylacetyl)benzamide (5i)

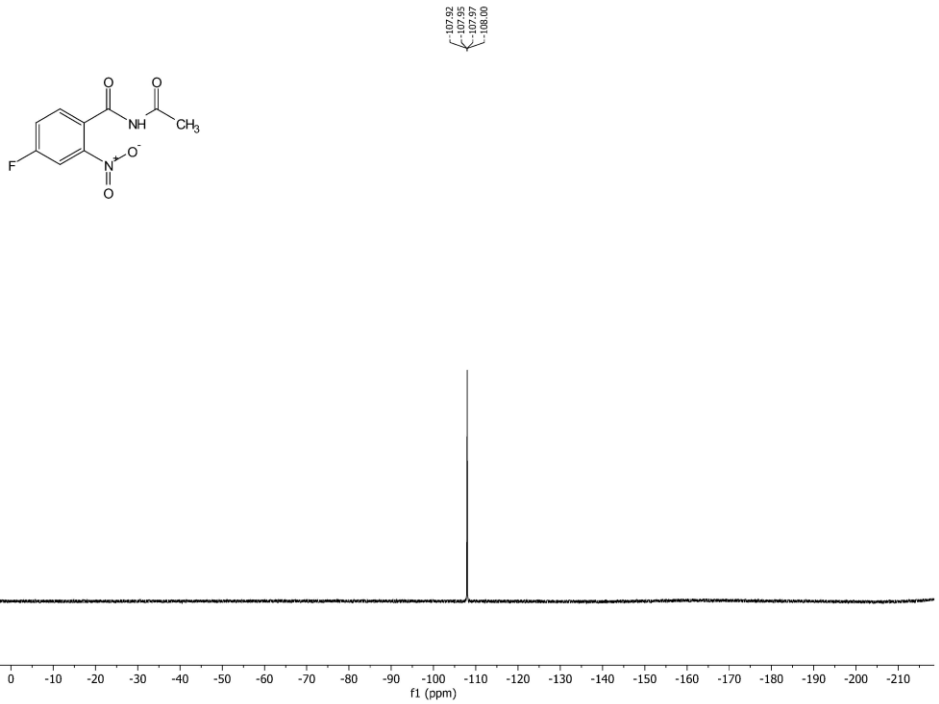




_N_-Acetyl-4-fluoro-2-nitrobenzamide (5j)



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-107.97
-108.00
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O
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CH3
F
N+
O-
O
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0
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-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
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-200
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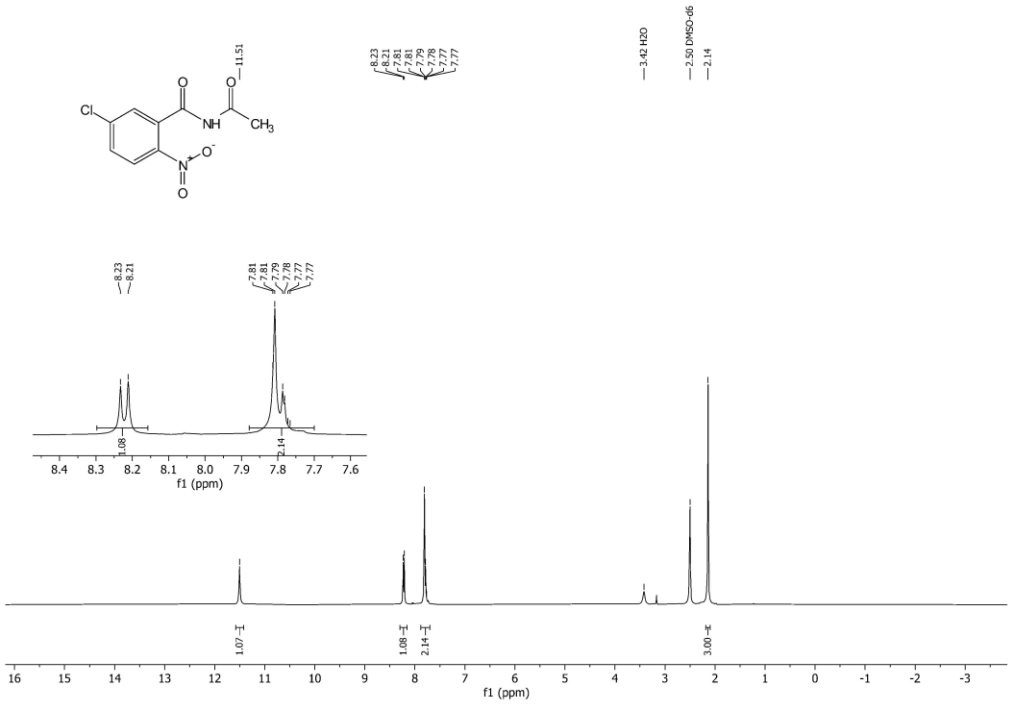
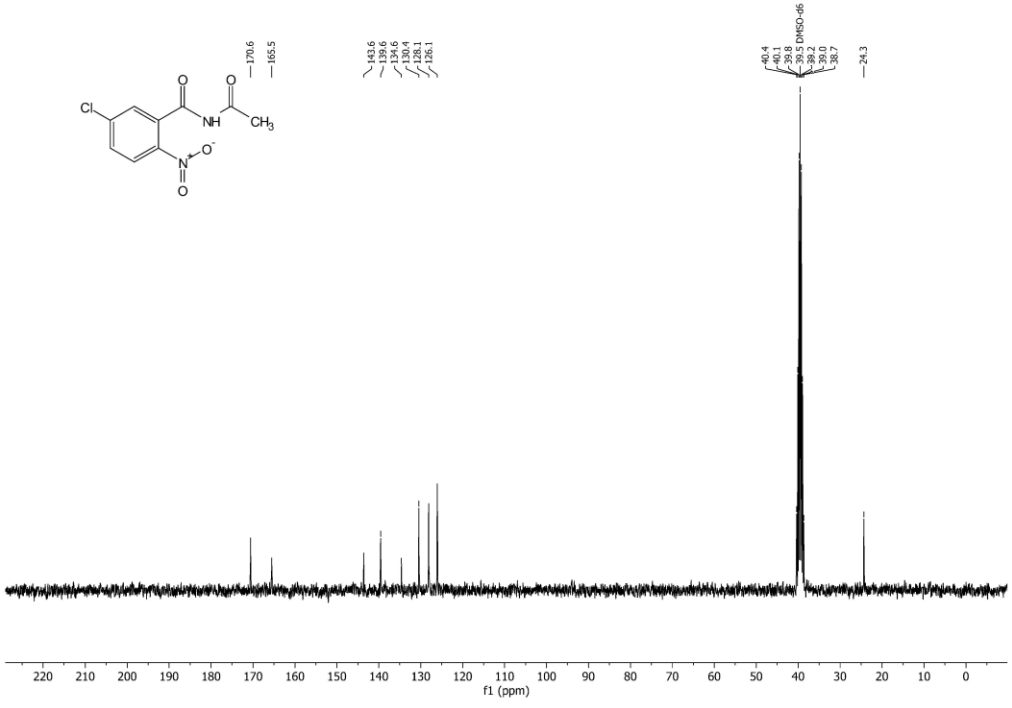
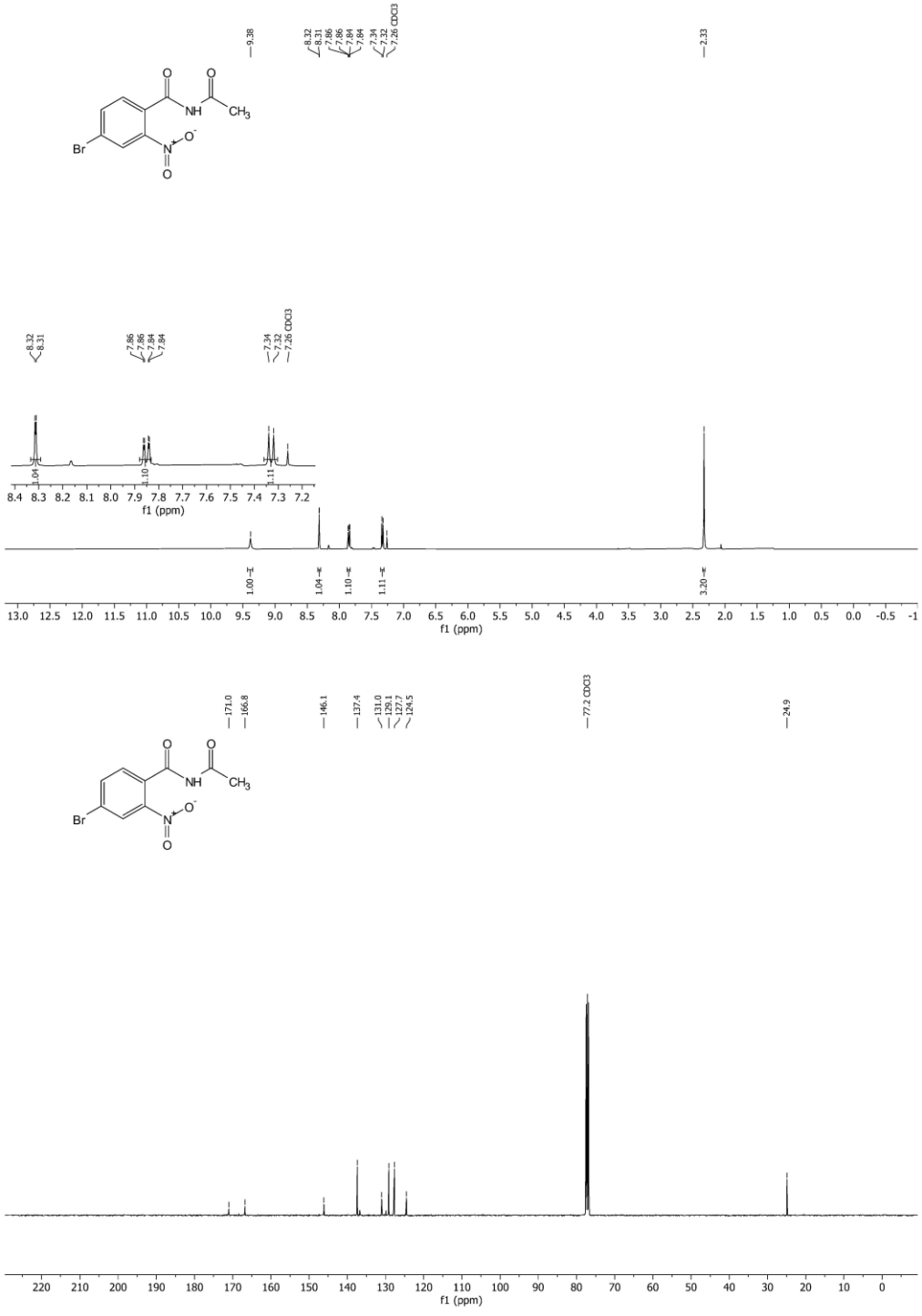
f1 (ppm)

_N_-Acetyl-5-chloro-2-nitrobenzamide (5k)

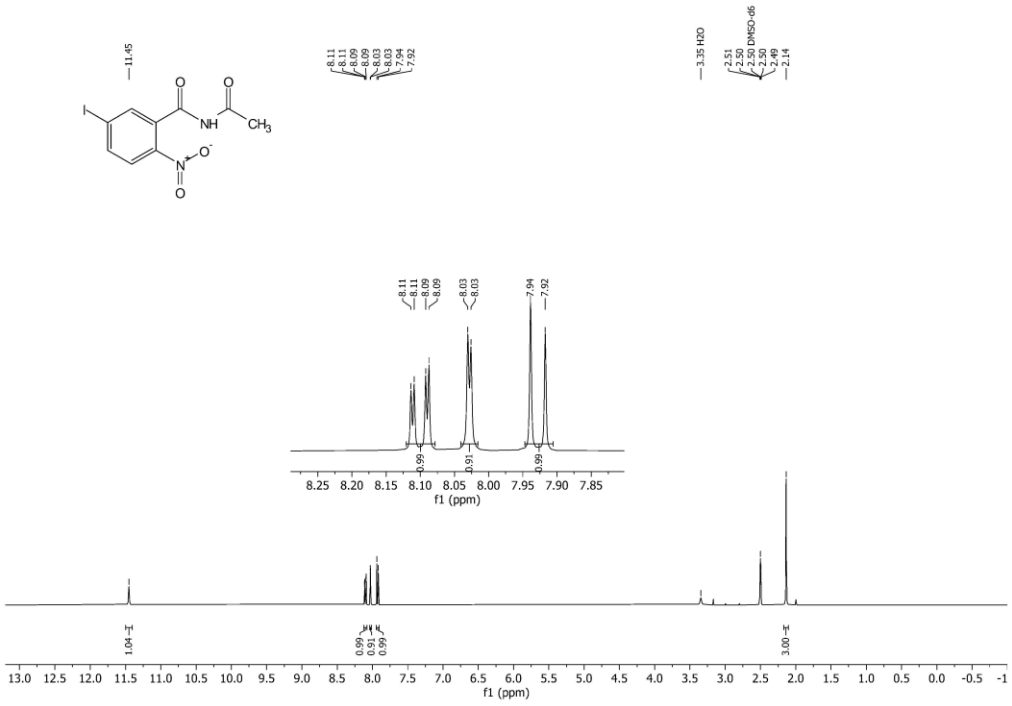


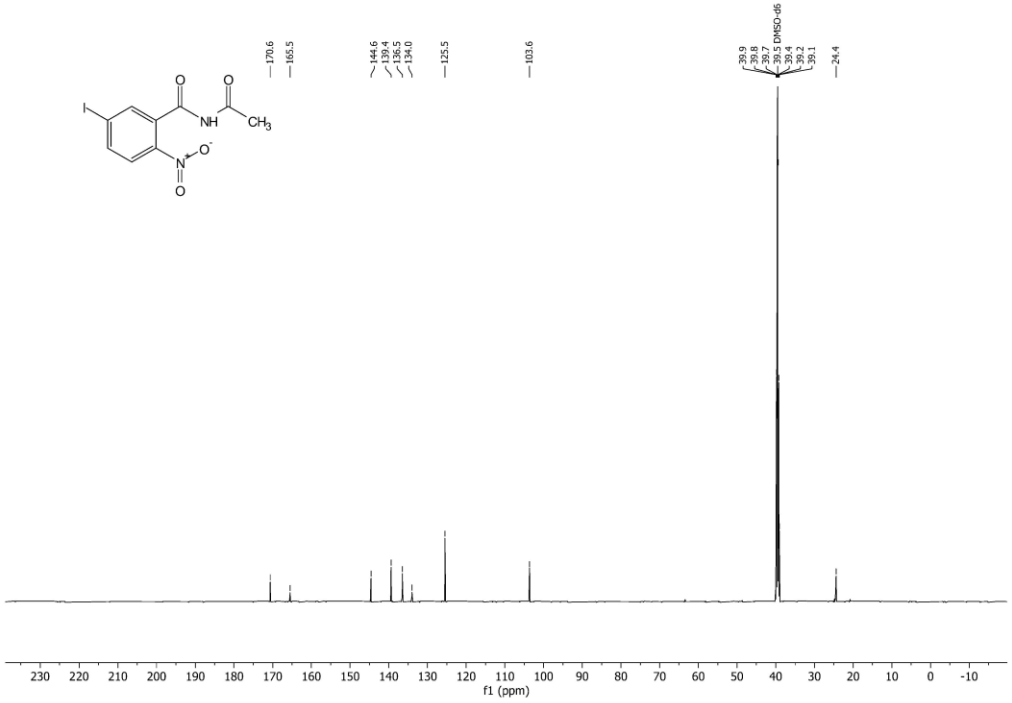


_N_-Acetyl-4-bromo-2-nitrobenzamide (5l)

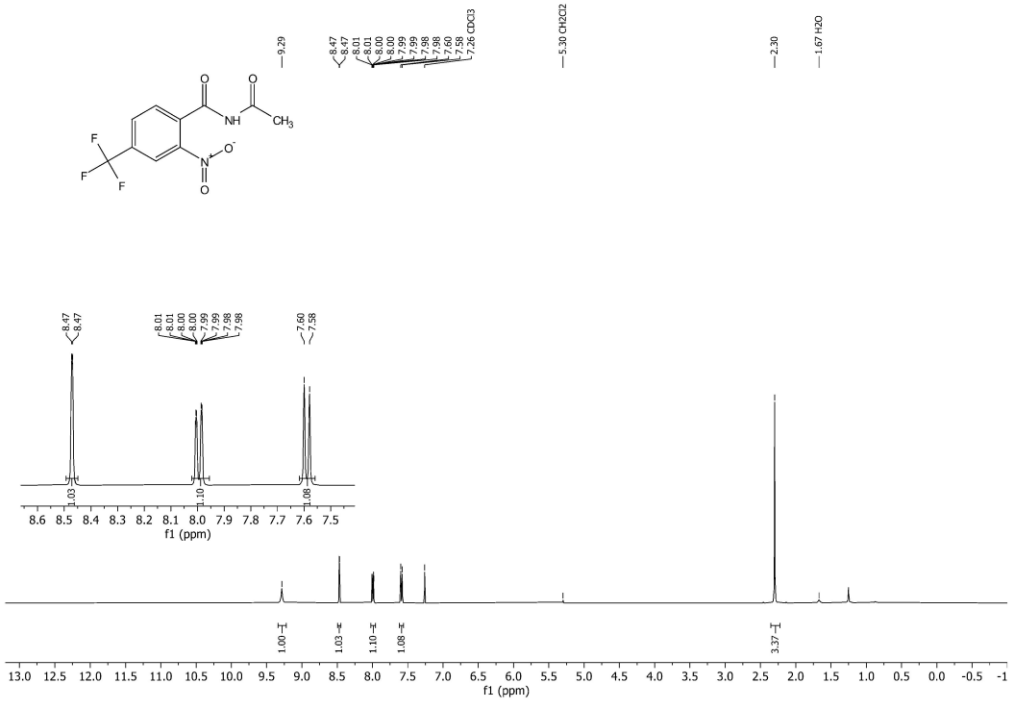


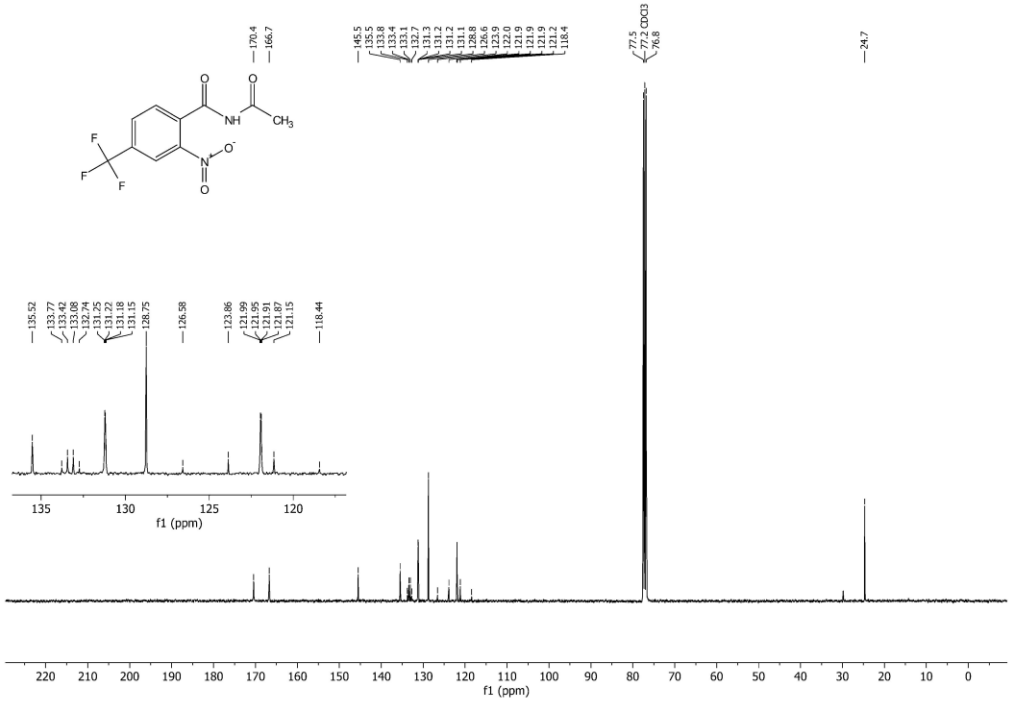
_N_-Acetyl-5-iodo-2-nitrobenzamide (5m)

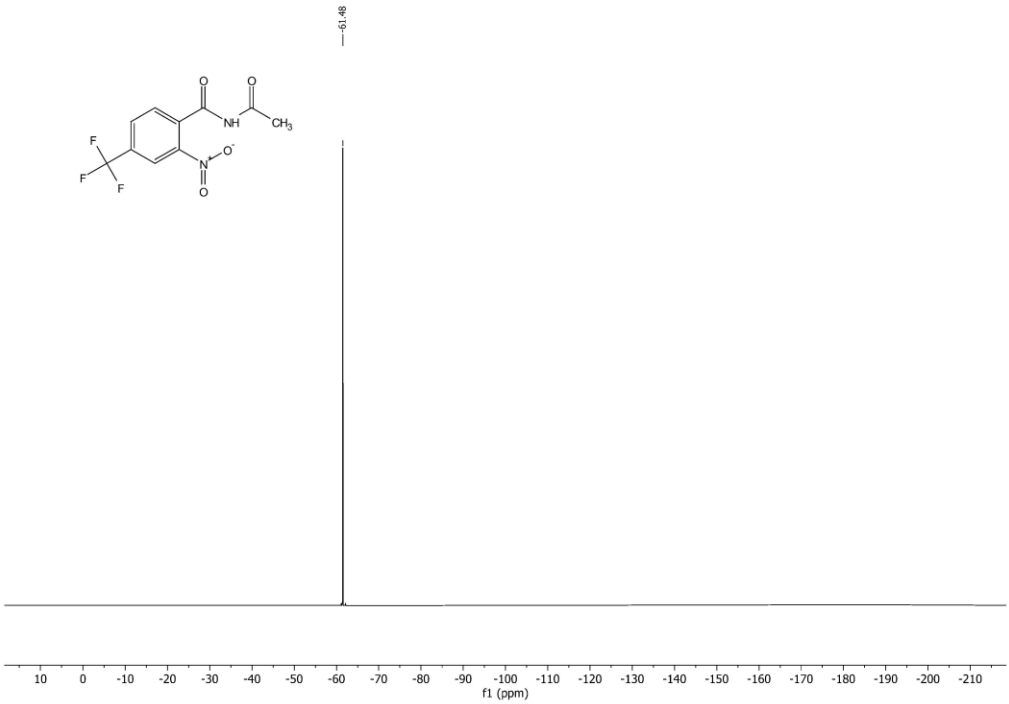




_N_-Acetyl-2-nitro-4-(trifluoromethyl)benzamide (5n)



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CH3
F
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N+
O-
O
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-80
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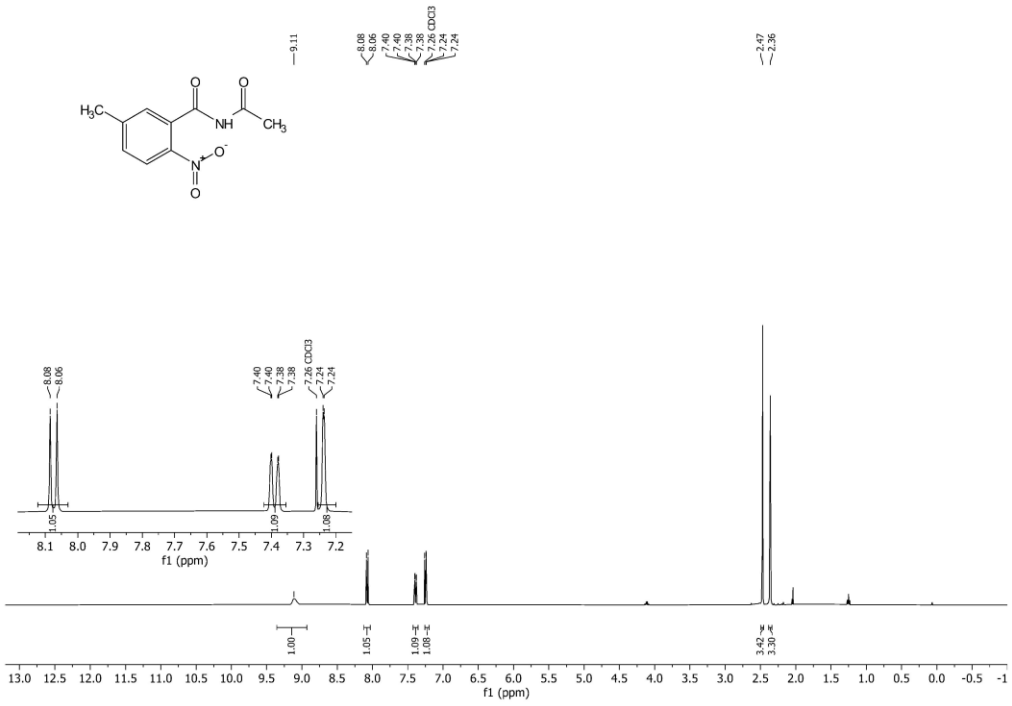
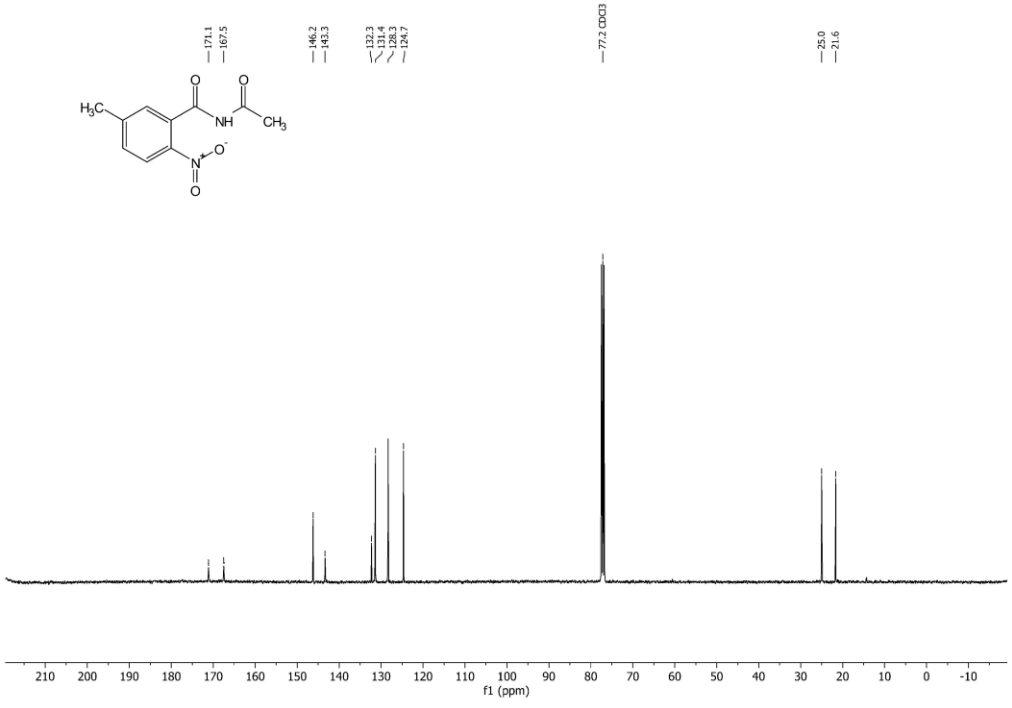
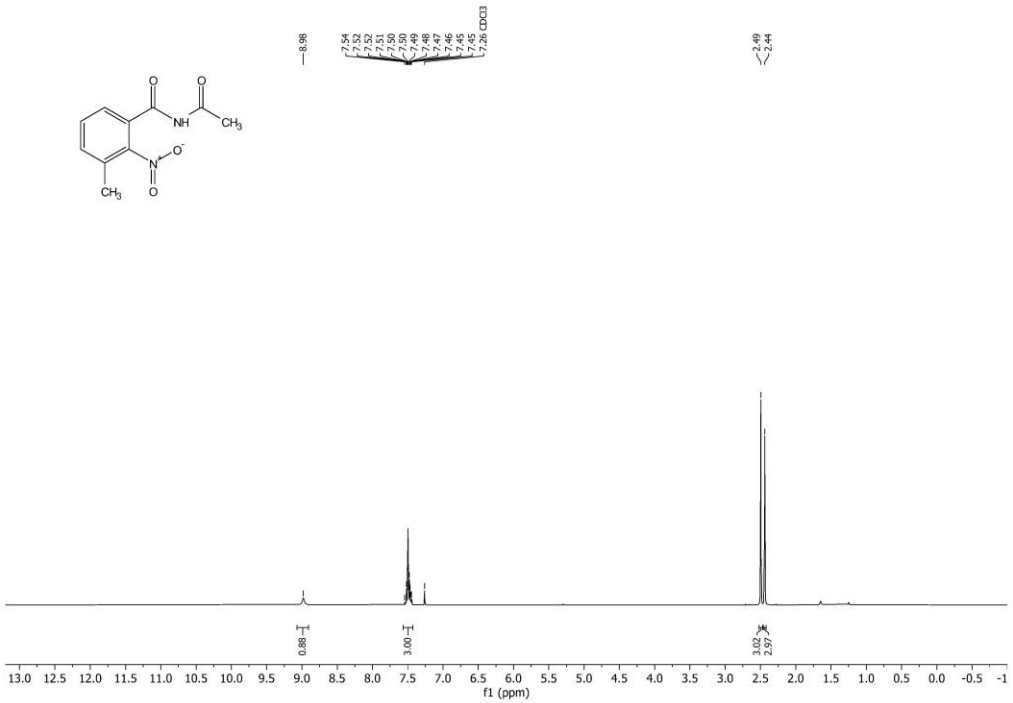
f1 (ppm)

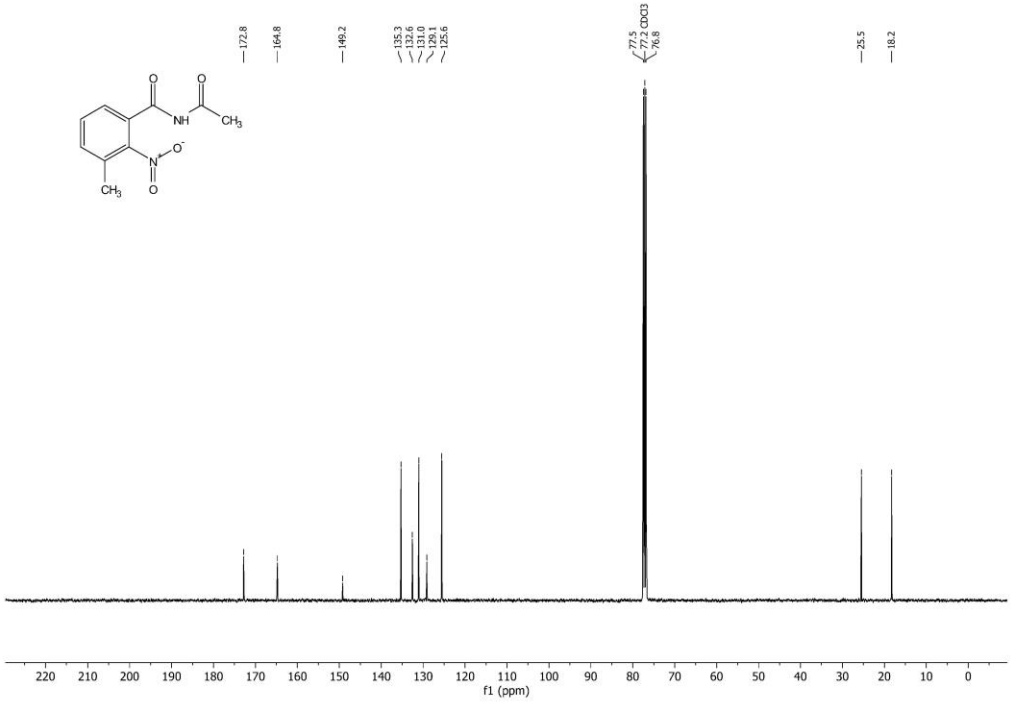
***N*-Acetyl-5-methyl-2-nitrobenzamide (5o)**



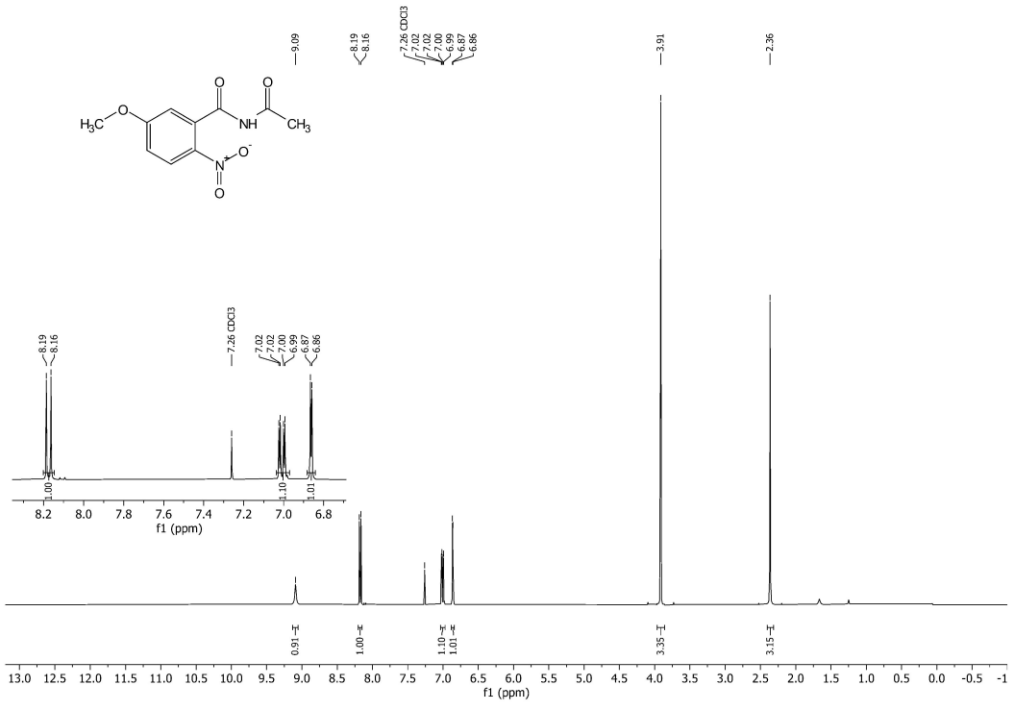


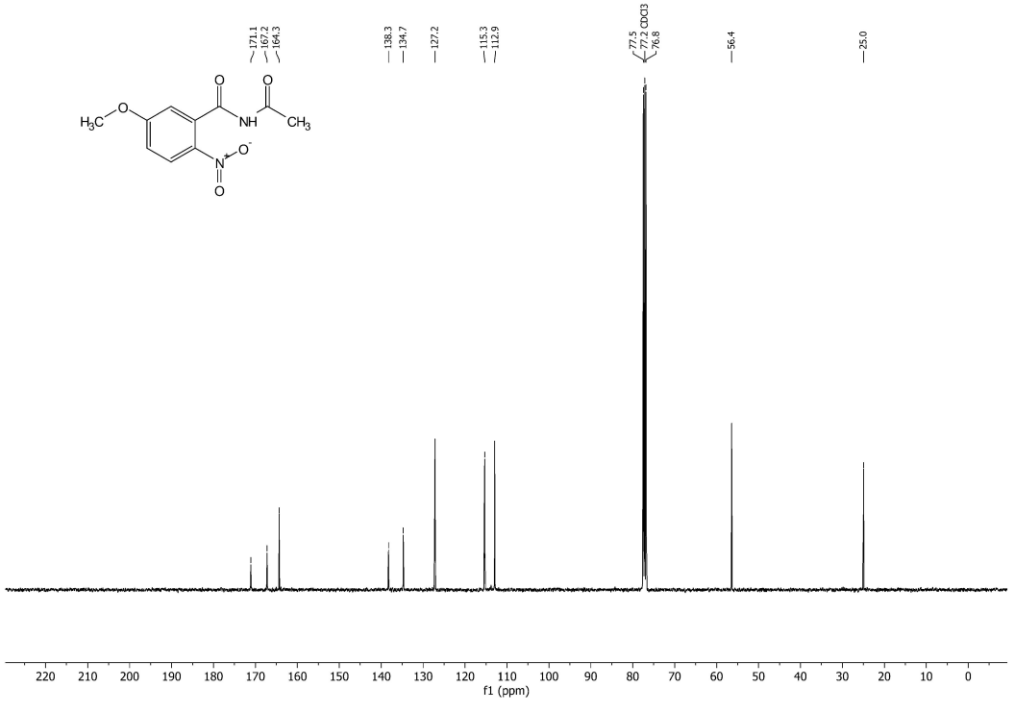
_N_-Acetyl-3-methyl-2-nitrobenzamide (5p)



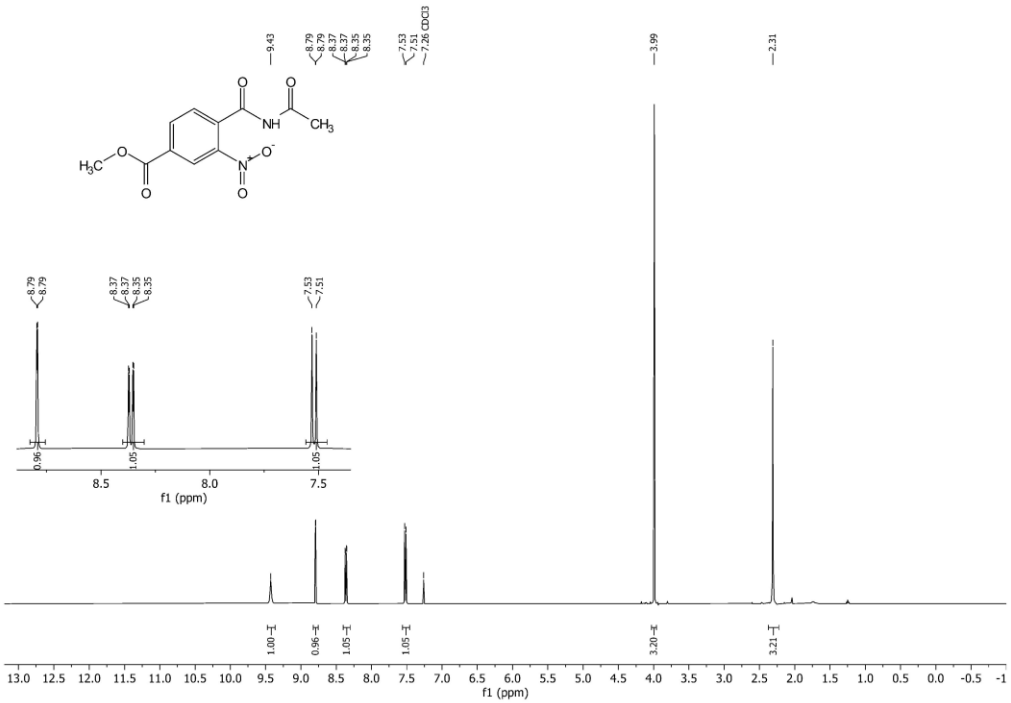


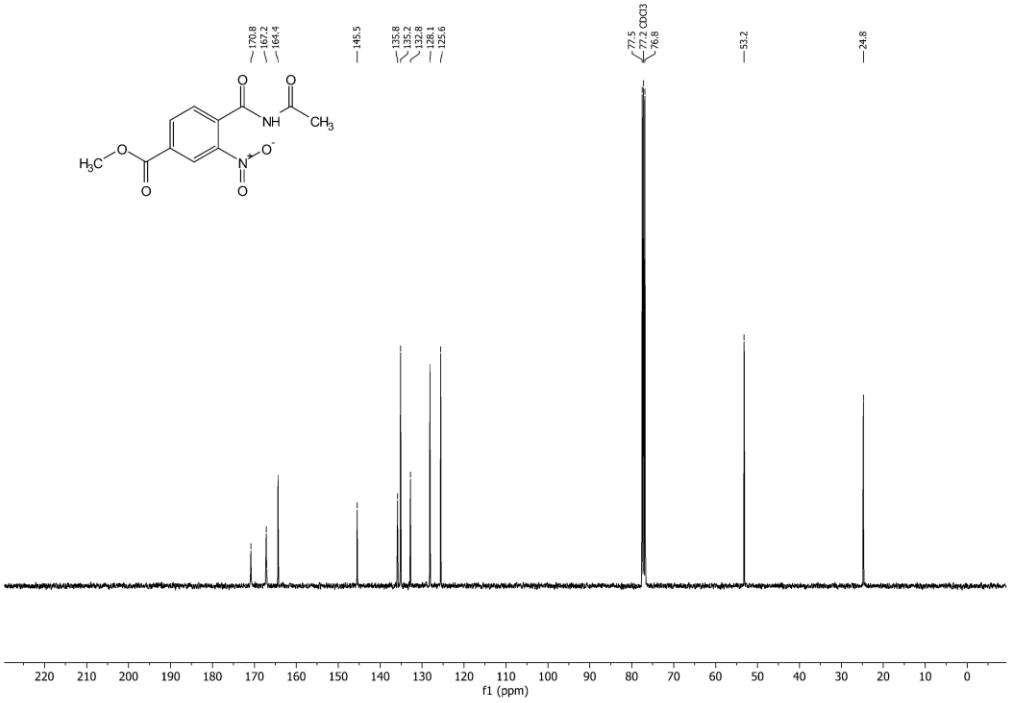
***N*-Acetyl-5-methoxy-2-nitrobenzamide (5q)**



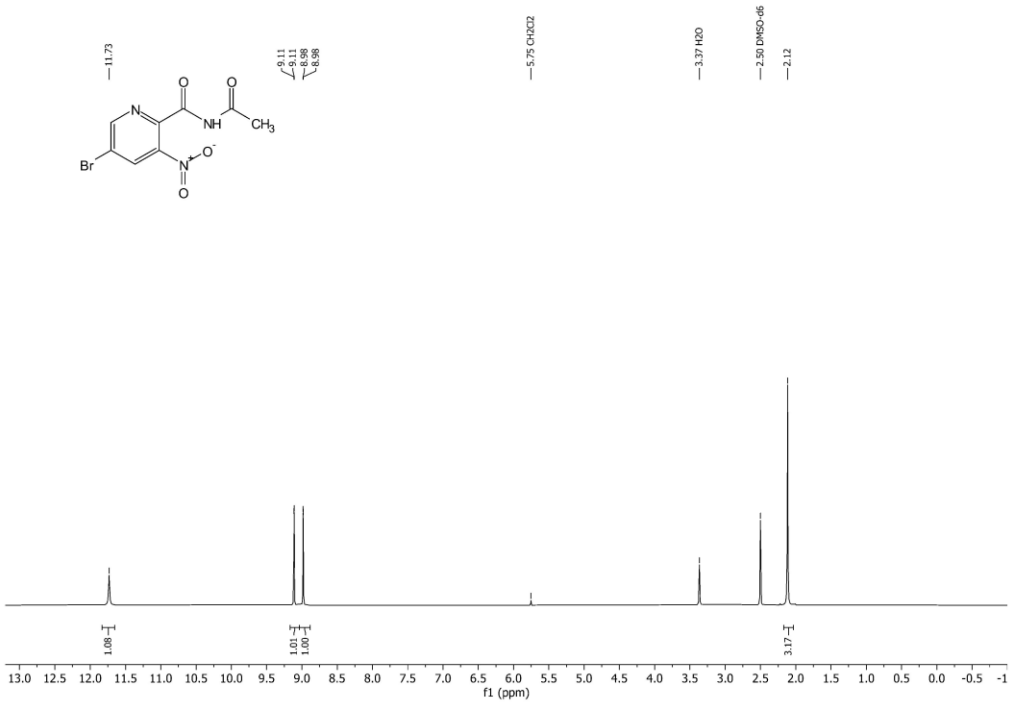


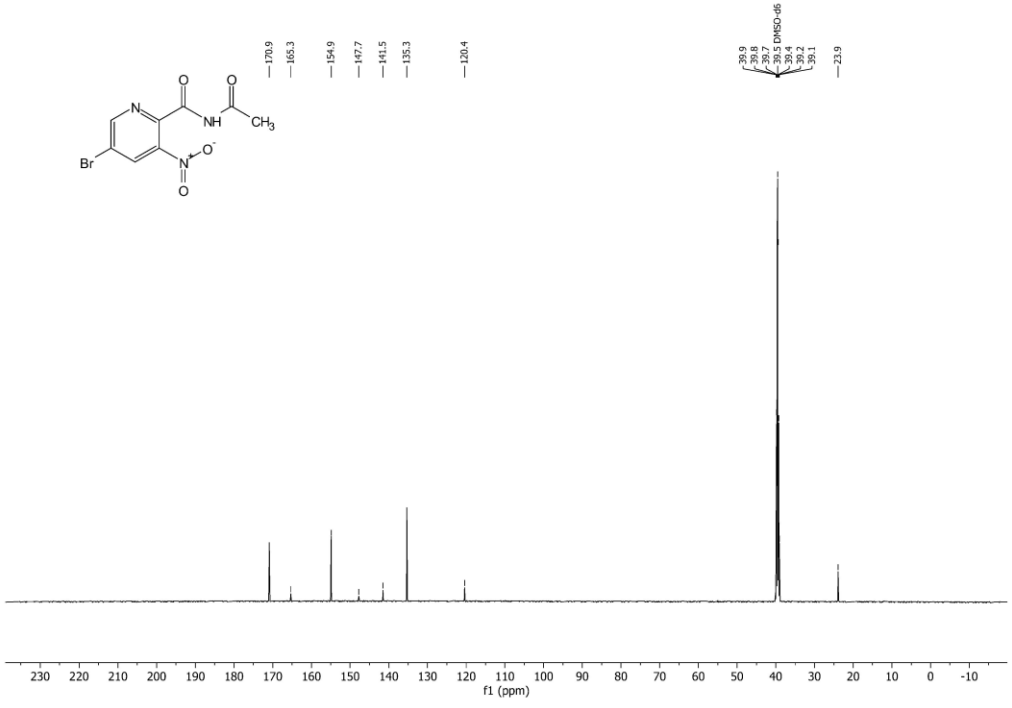
Methyl 4-(acetylcarbamoyl)-3-nitrobenzoate (5r)



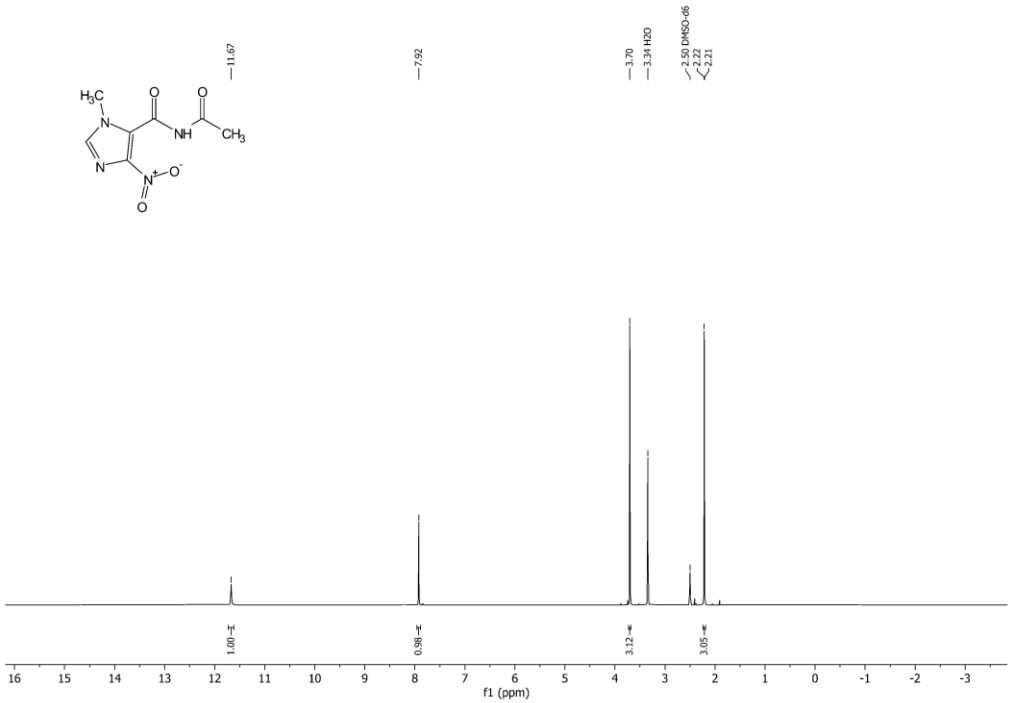


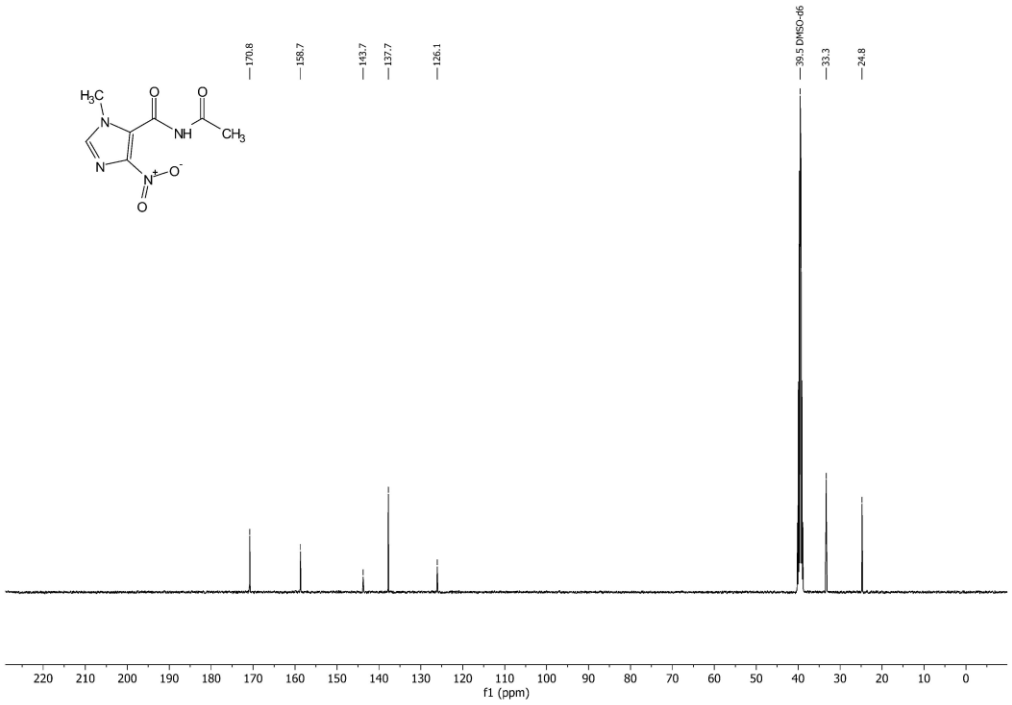
2-(Acetylcarbamoyl)-5-bromo-3-nitropyridine (5s)



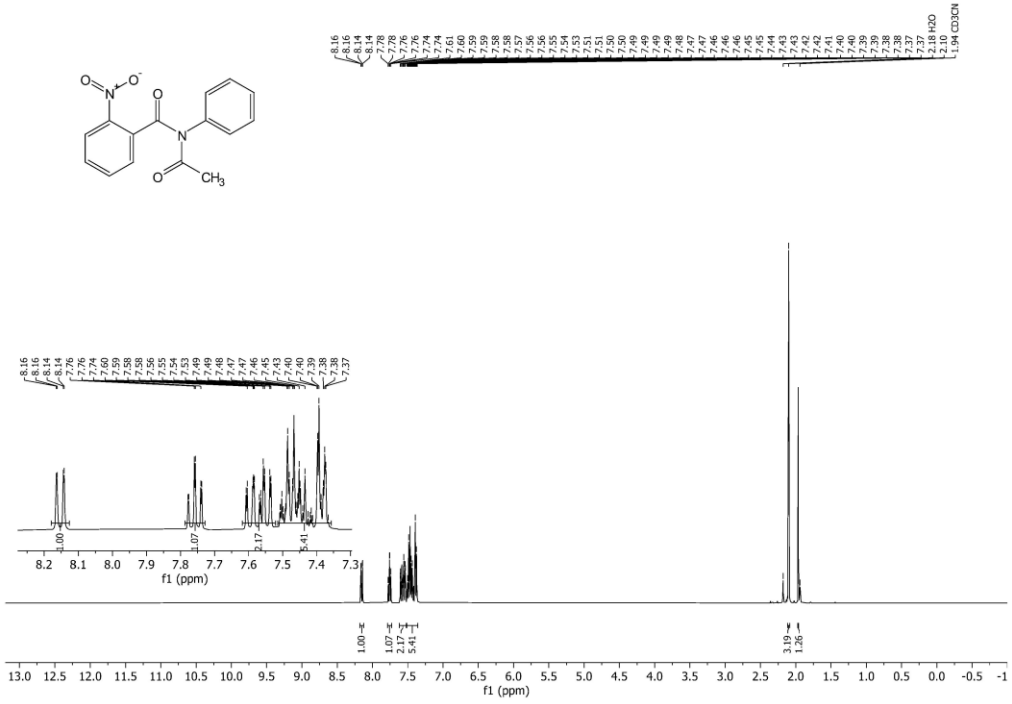


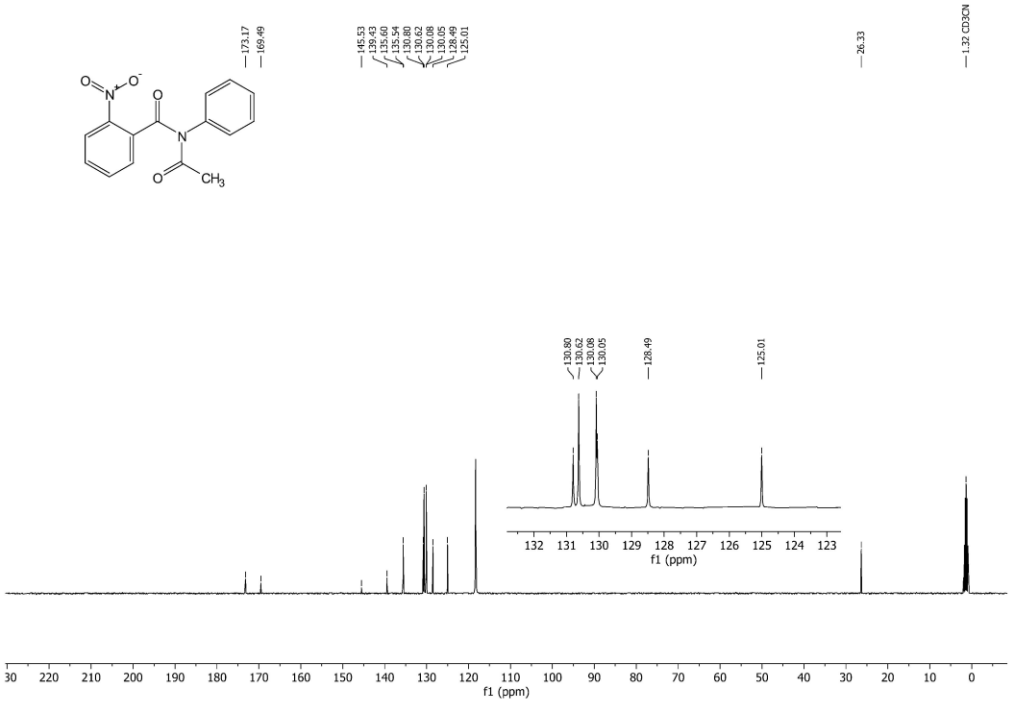
1*H*-*N*-Acetyl-1-methyl-4-nitro-1*H*-imidazole-5-carboxamide (5t)



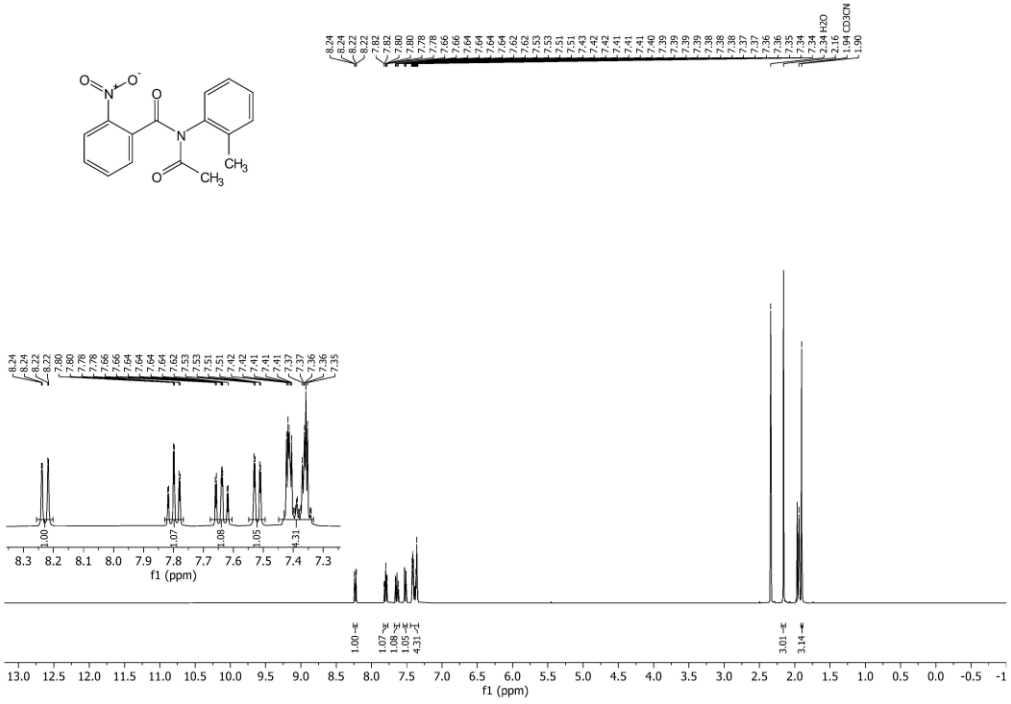


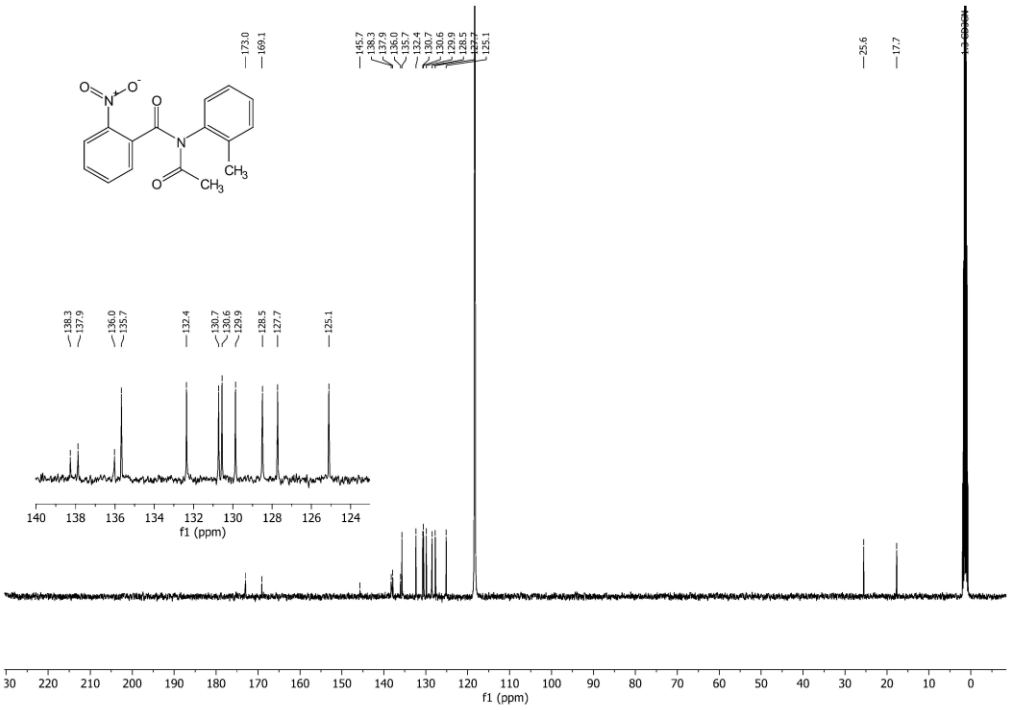
_N_-Acetyl-2-nitro-_N_-phenylbenzamide (5u)



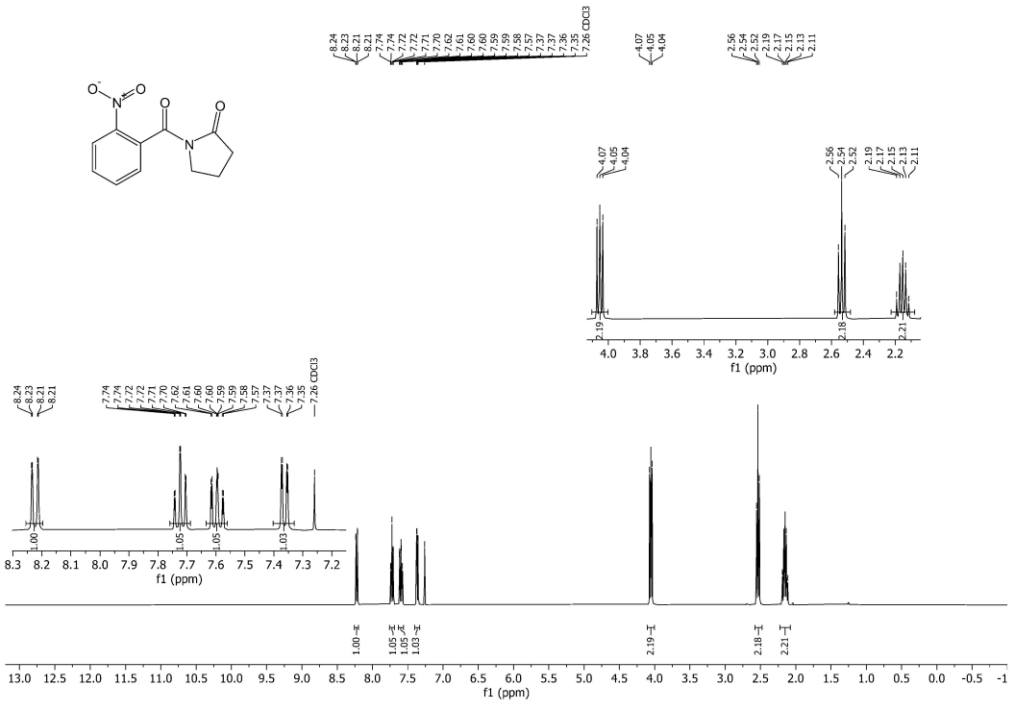


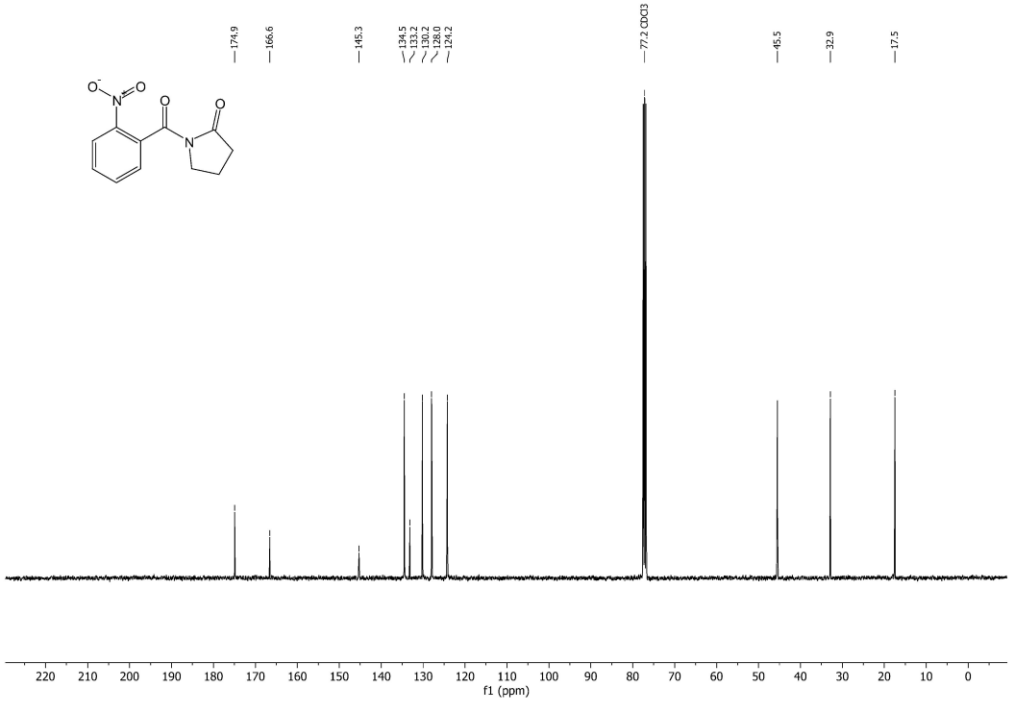
_N_-Acetyl-2-nitro-_N_-(o-tolyl)benzamide (5v)



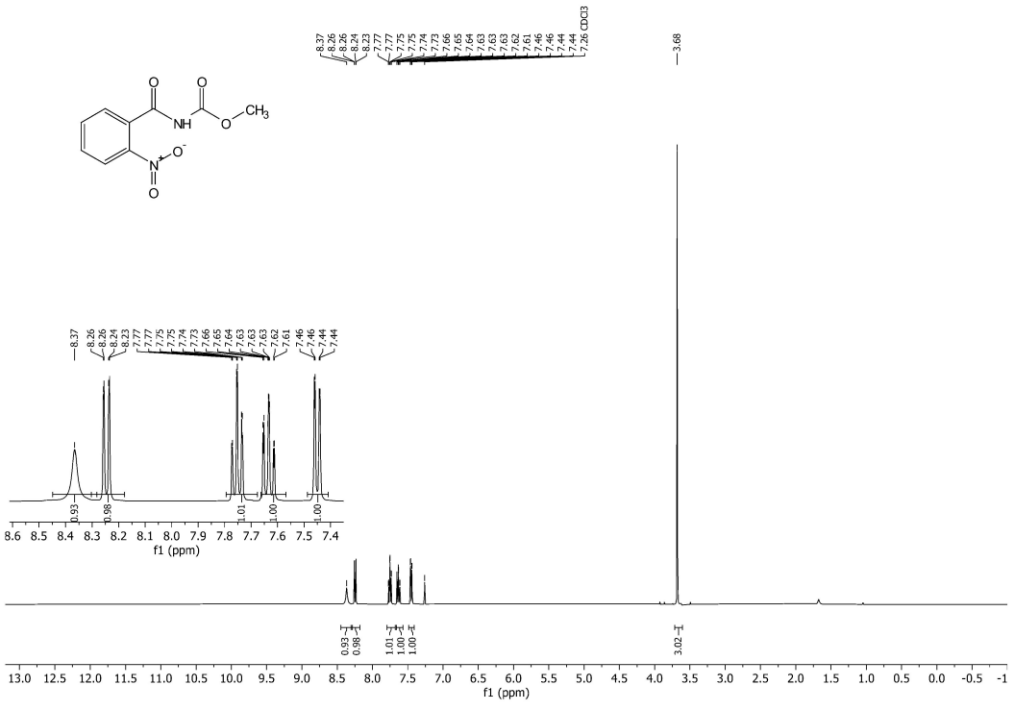


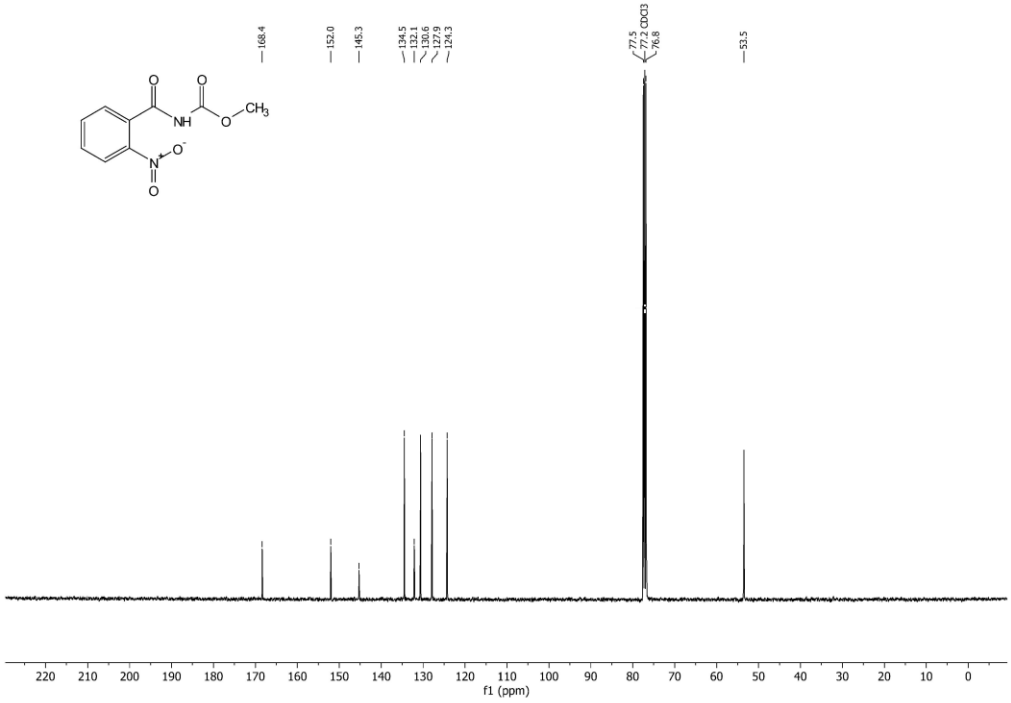
1-(2-Nitrobenzoyl)pyrrolidin-2-one (5w)



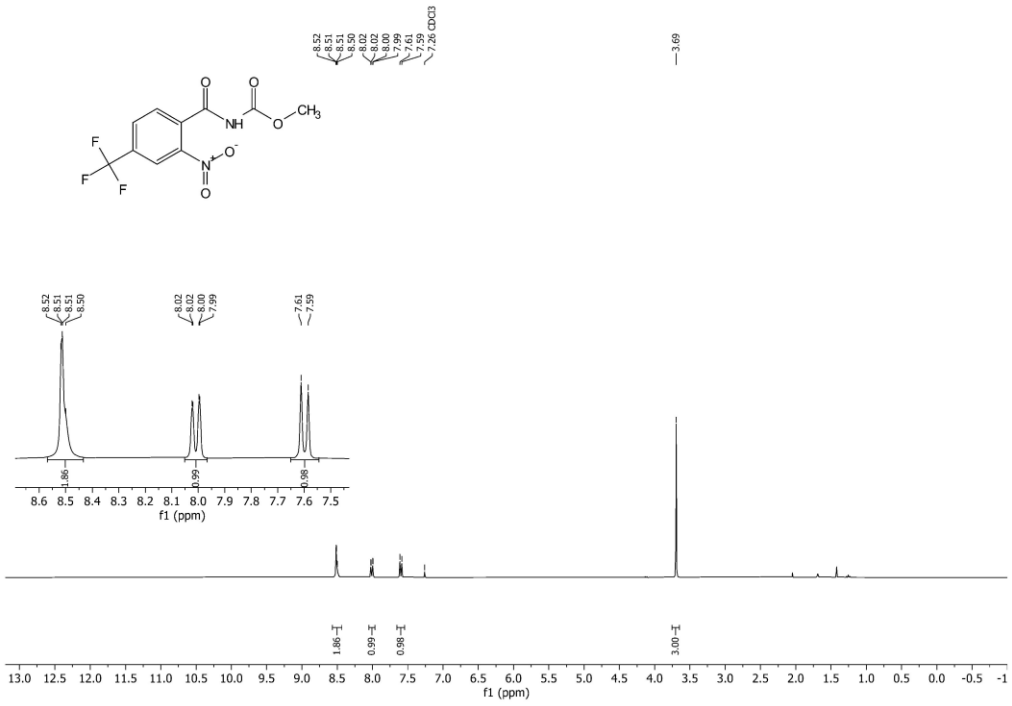


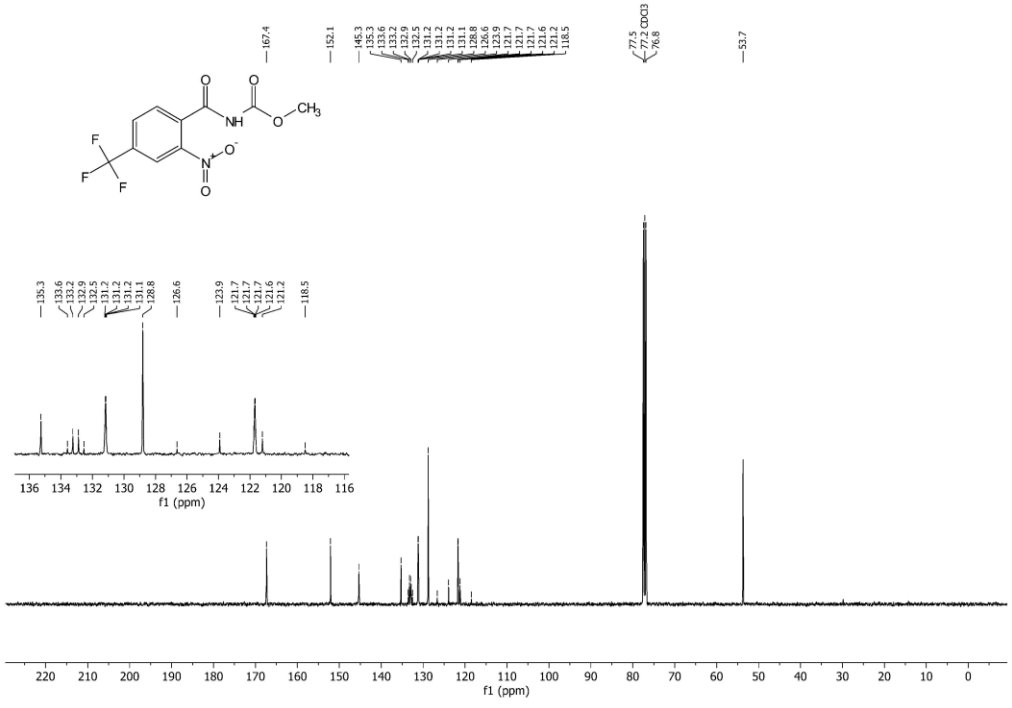
Methyl (2-nitrobenzoyl)carbamate (5x)

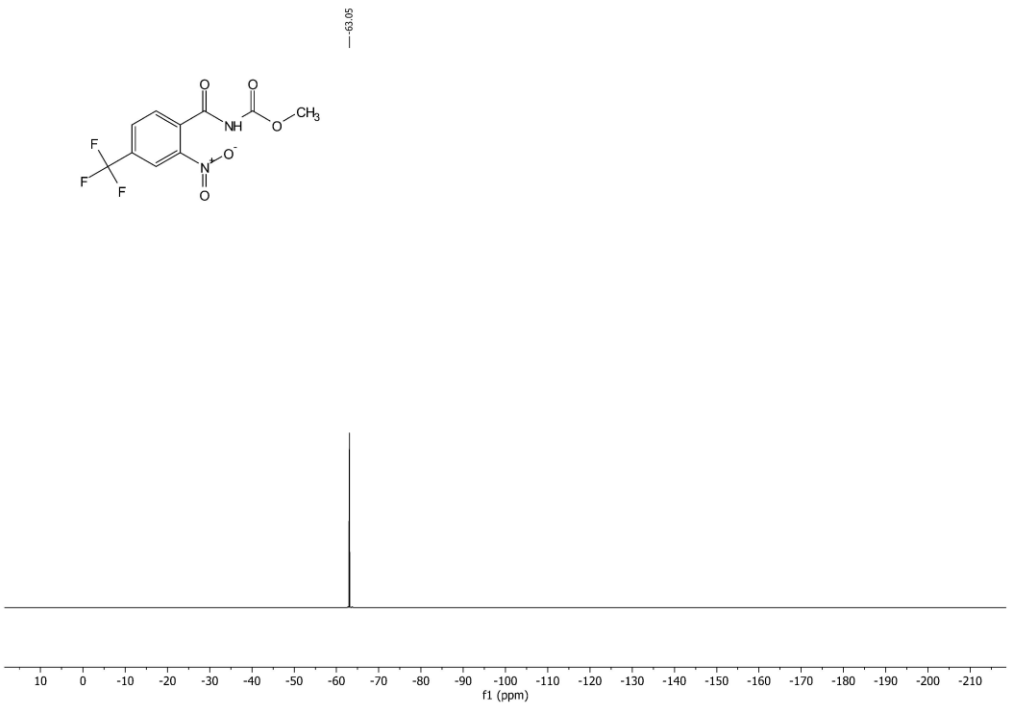




Methyl (2-nitro-4-(trifluoromethyl)benzoyl)carbamate (5y)






-63.05
O
O
NH
O
CH3
F
F
F
N+
O-
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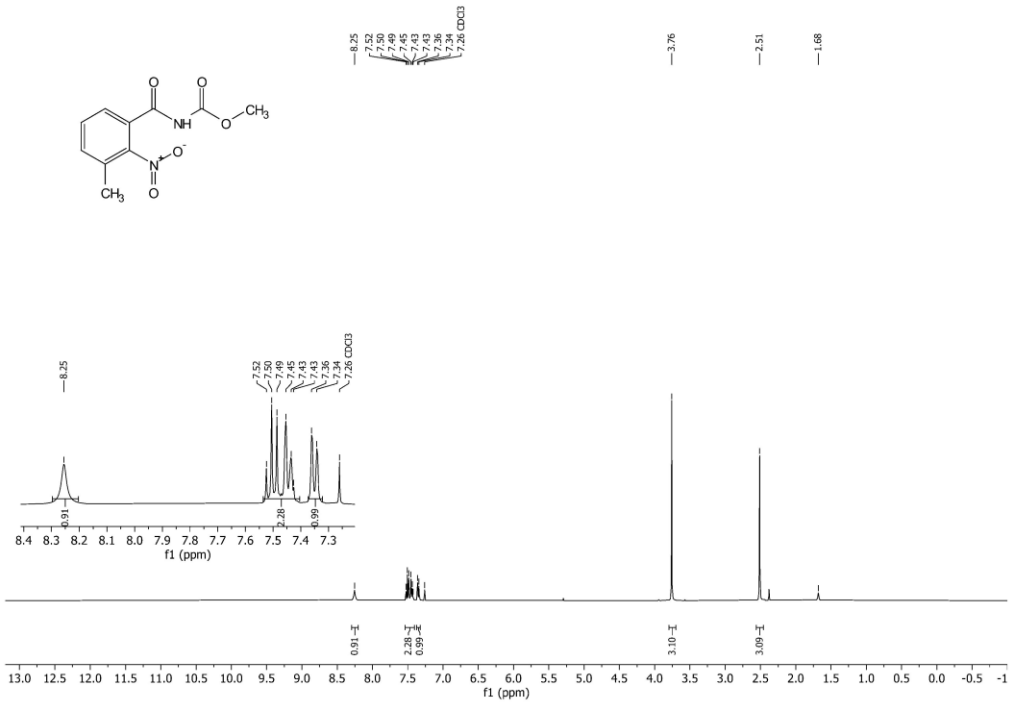
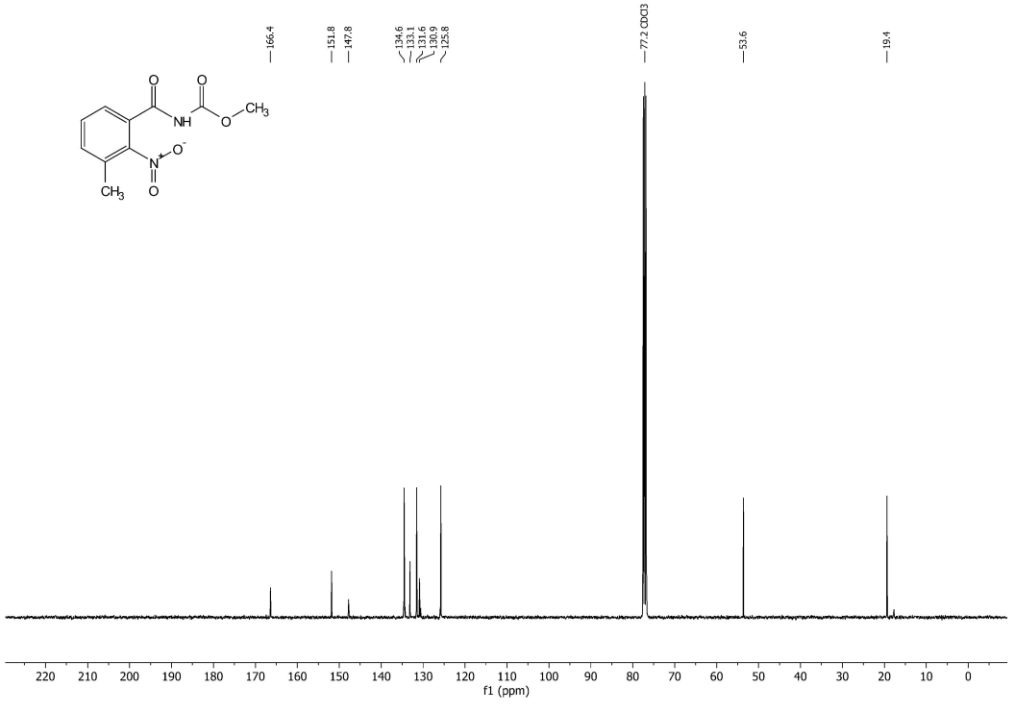
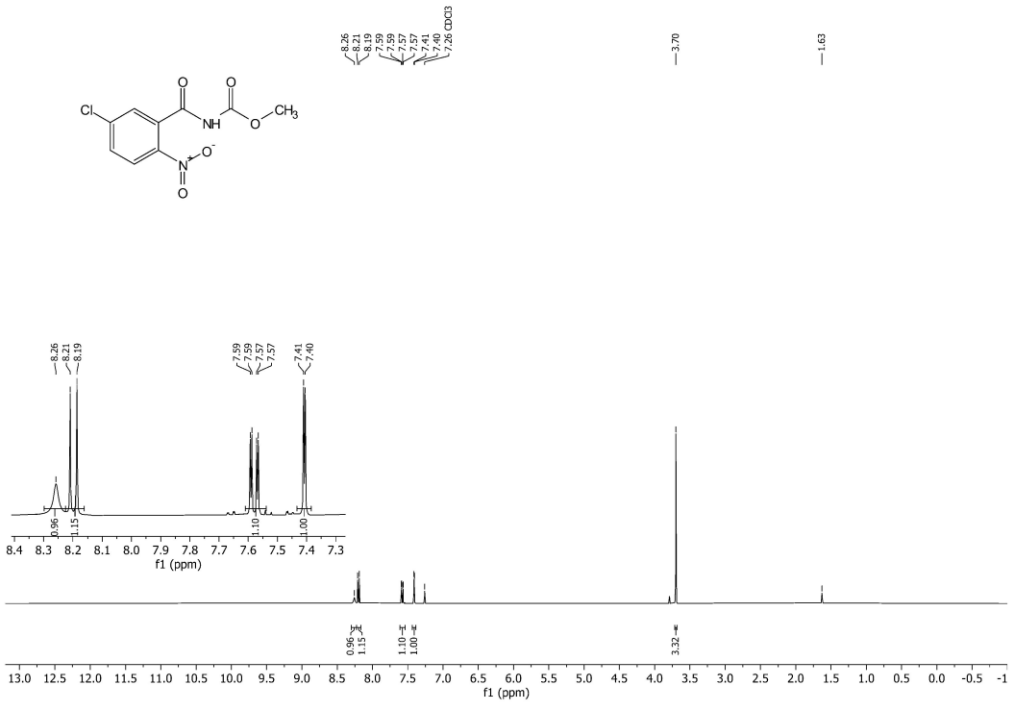
-210
f1 (ppm)

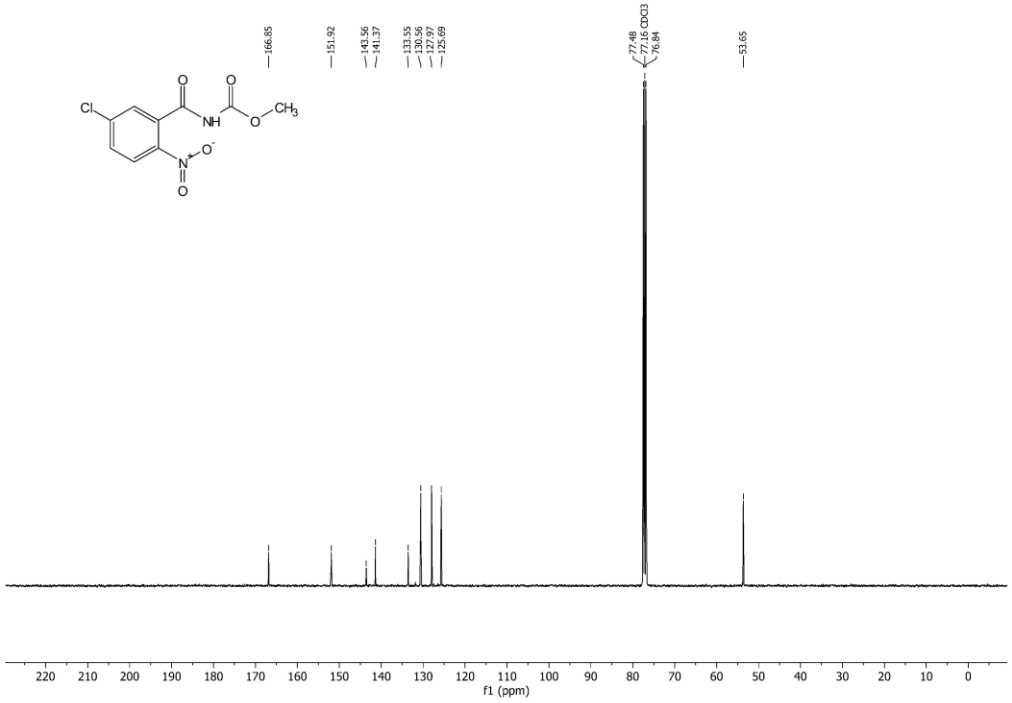
Methyl (3-methyl-2-nitrobenzoyl)carbamate (5z)



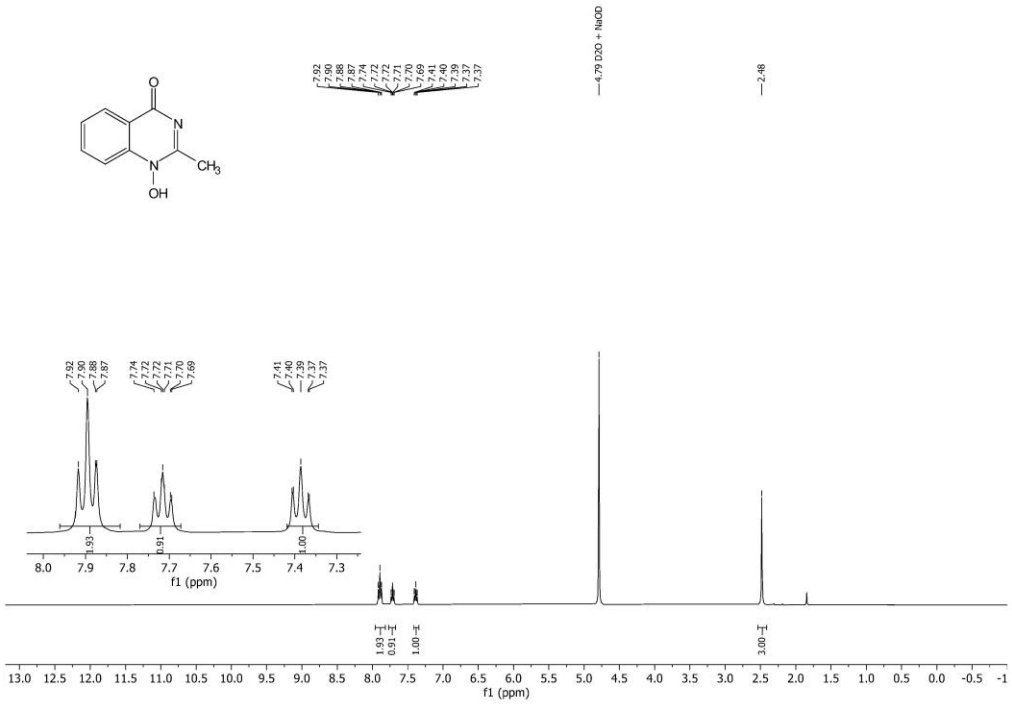


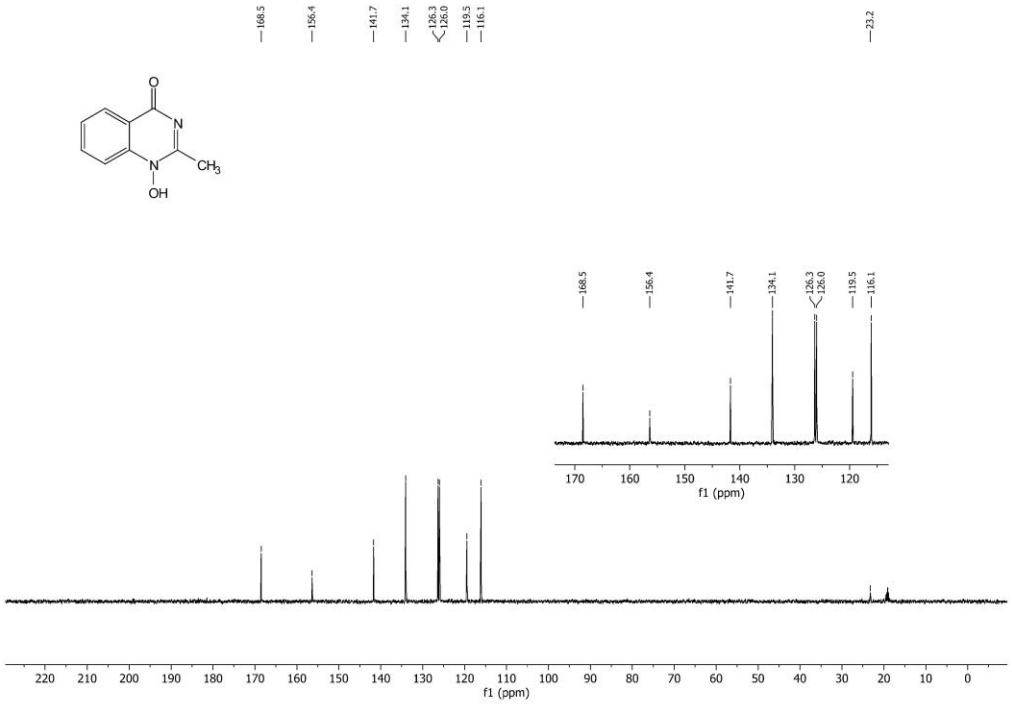
Methyl (5-chloro-2-nitrobenzoyl)carbamate (5aa)



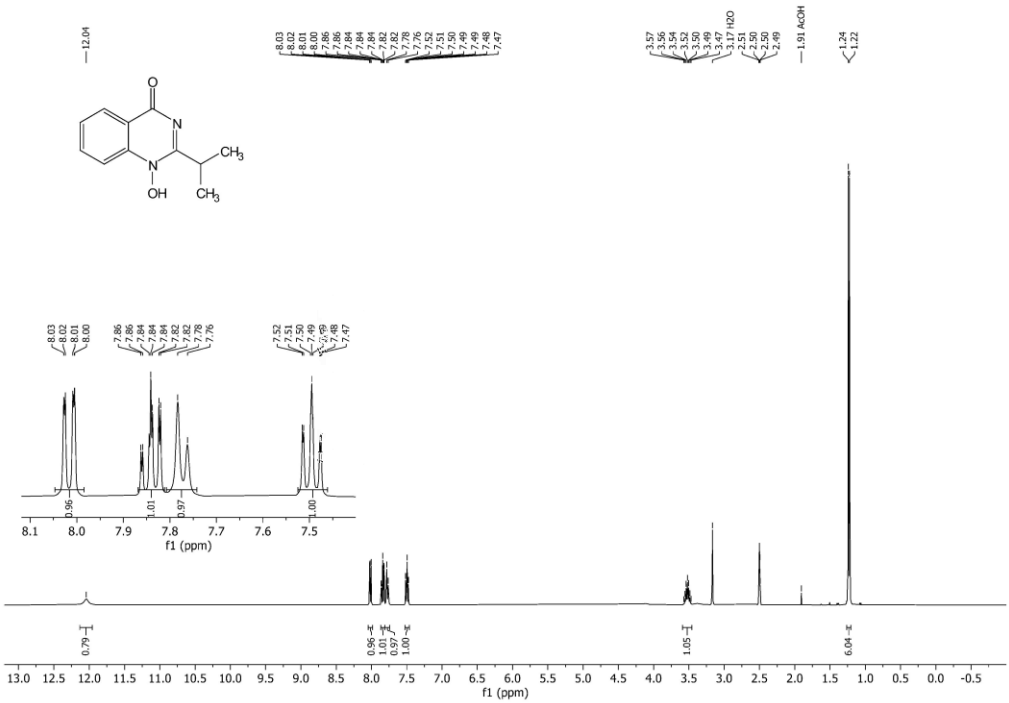


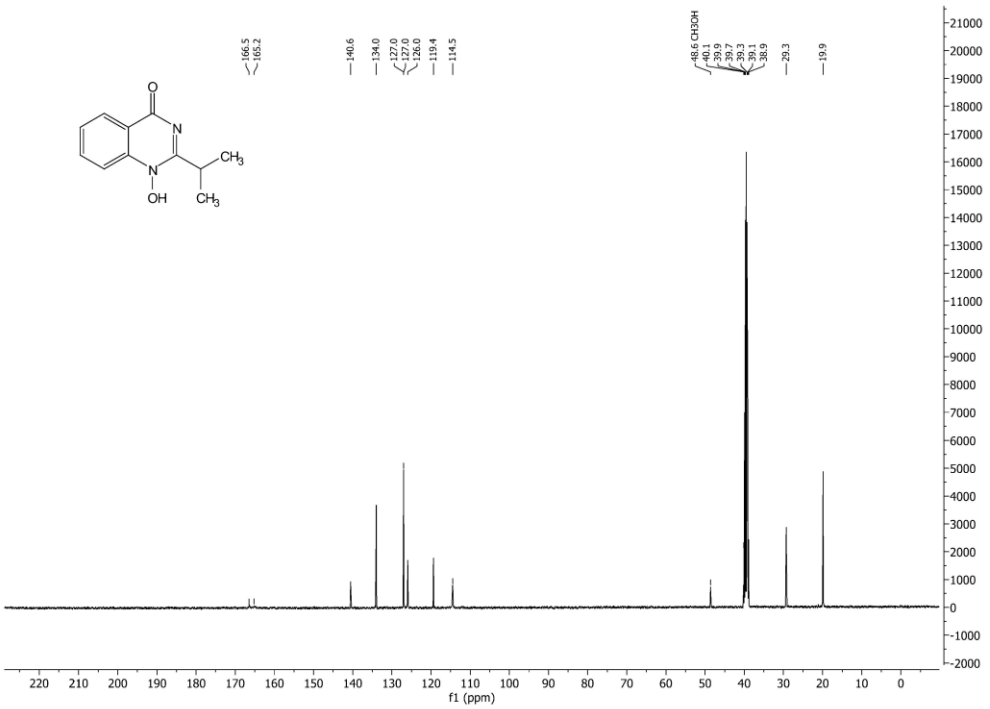
1*H*-1-Hydroxy-2-methylquinazolin-4-one (6a)



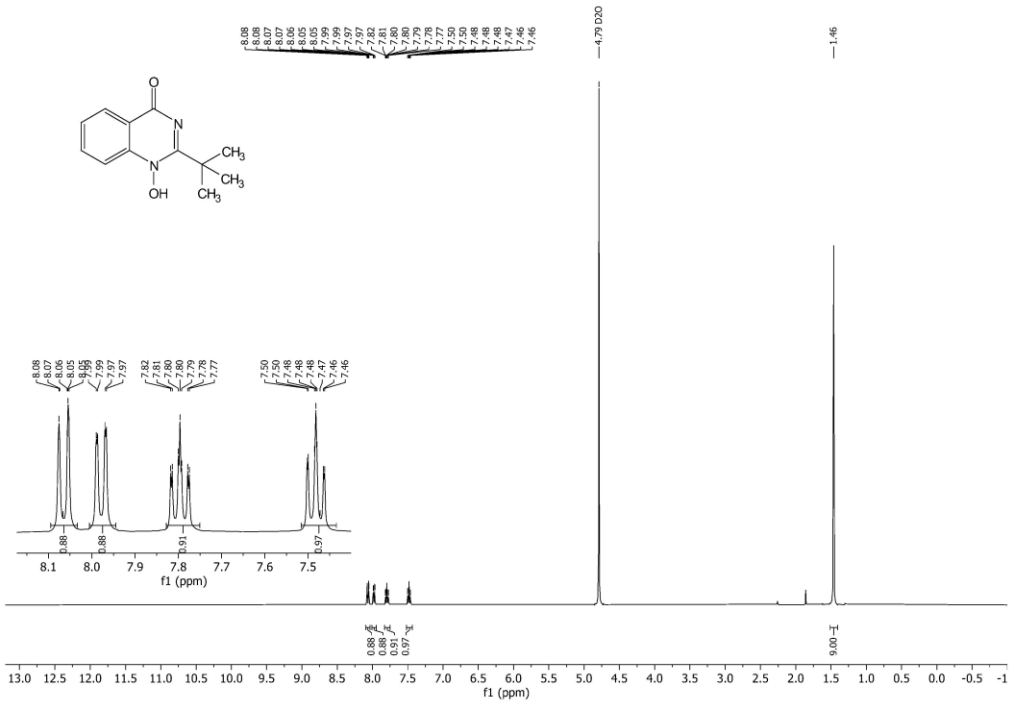


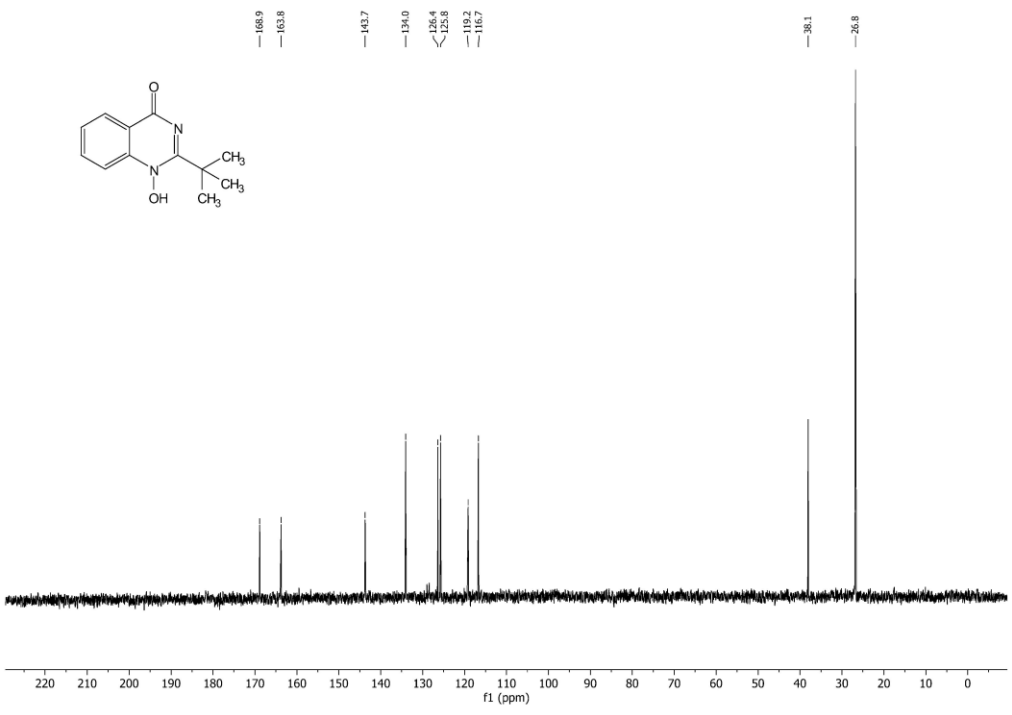
1*H*-1-Hydroxy-2-isopropylquinazolin-4-one (6b)



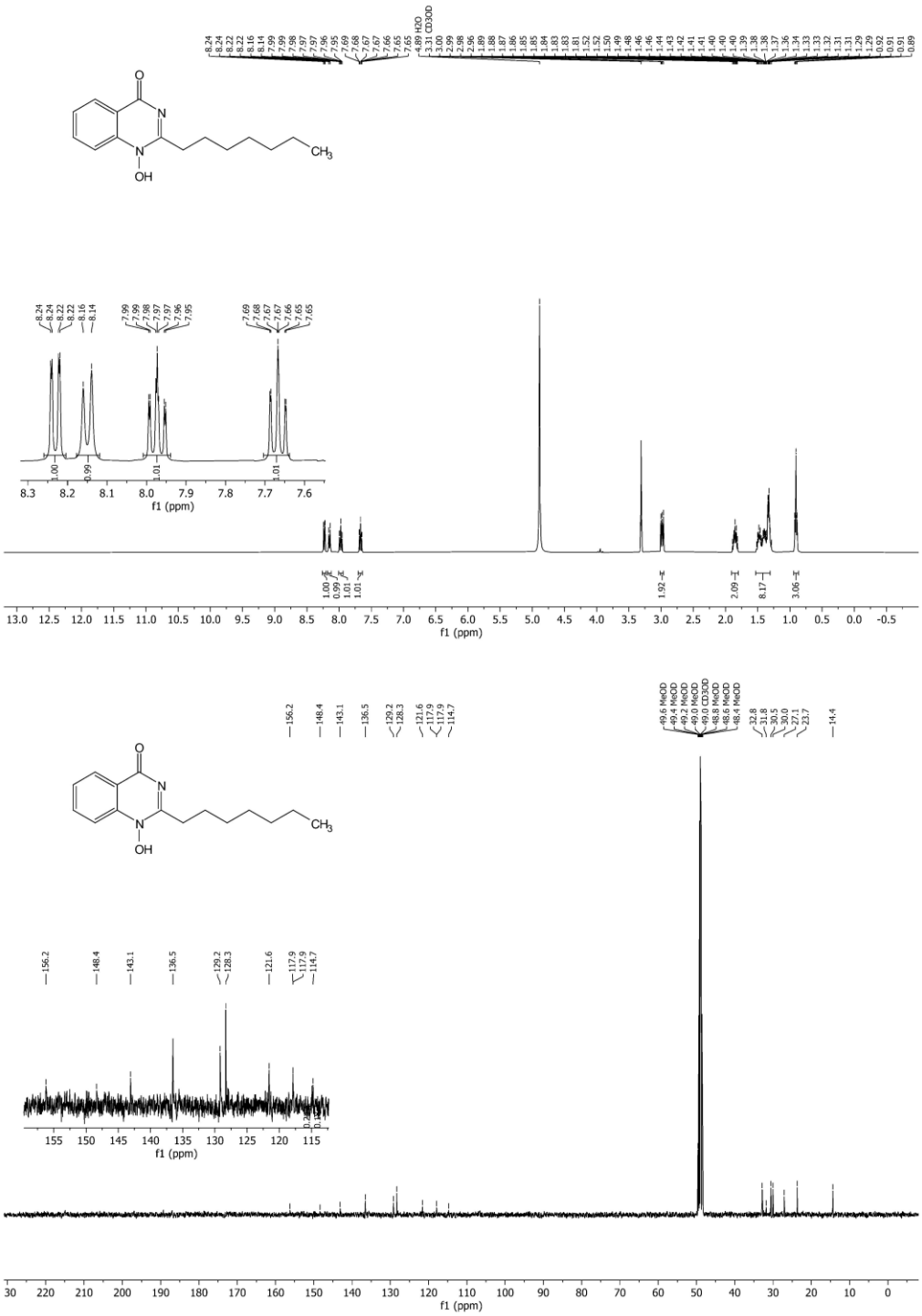


1*H*-2-(*tert*-Butyl)-1-hydroxyquinazolin-4-one (6c)

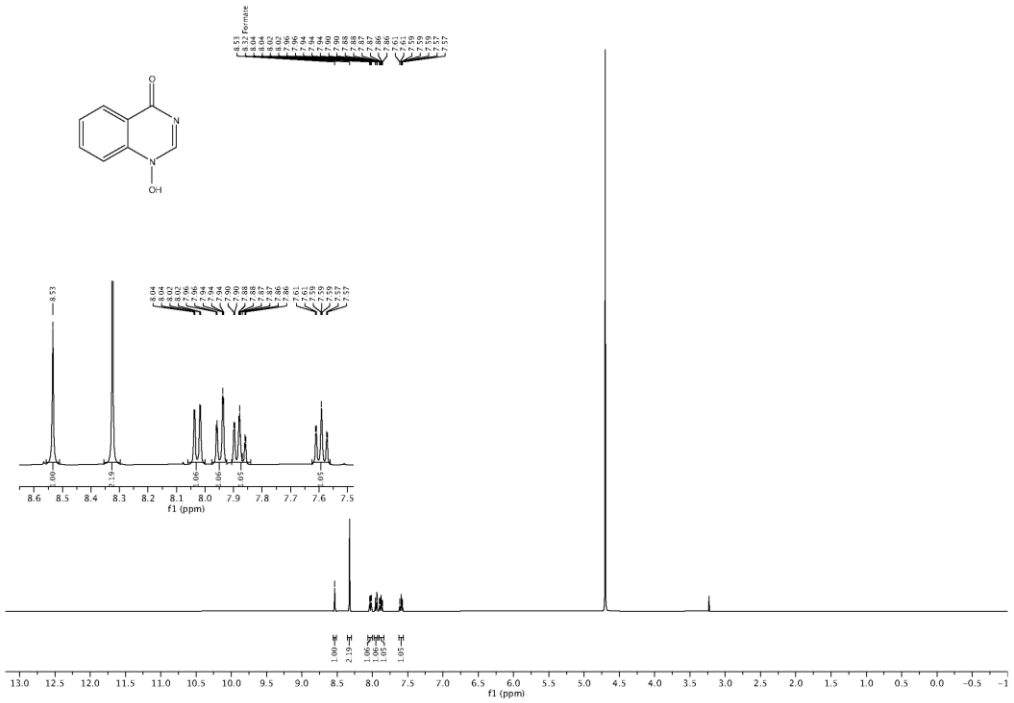


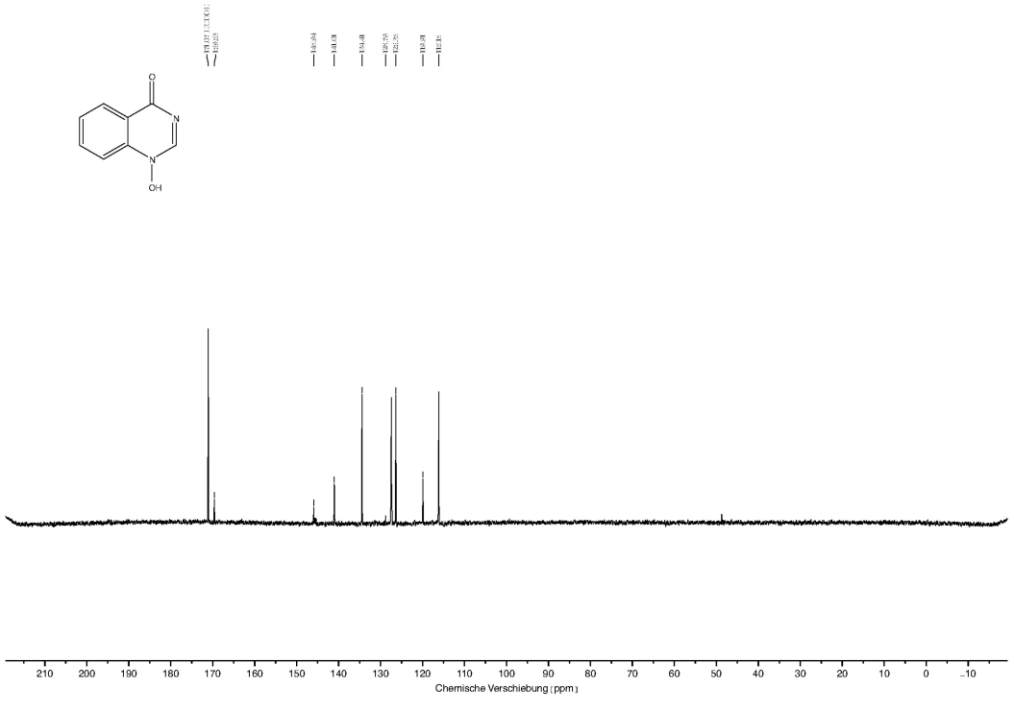


1*H*-2-Heptyl-1-hydroxyquinazolin-4-one (6d)

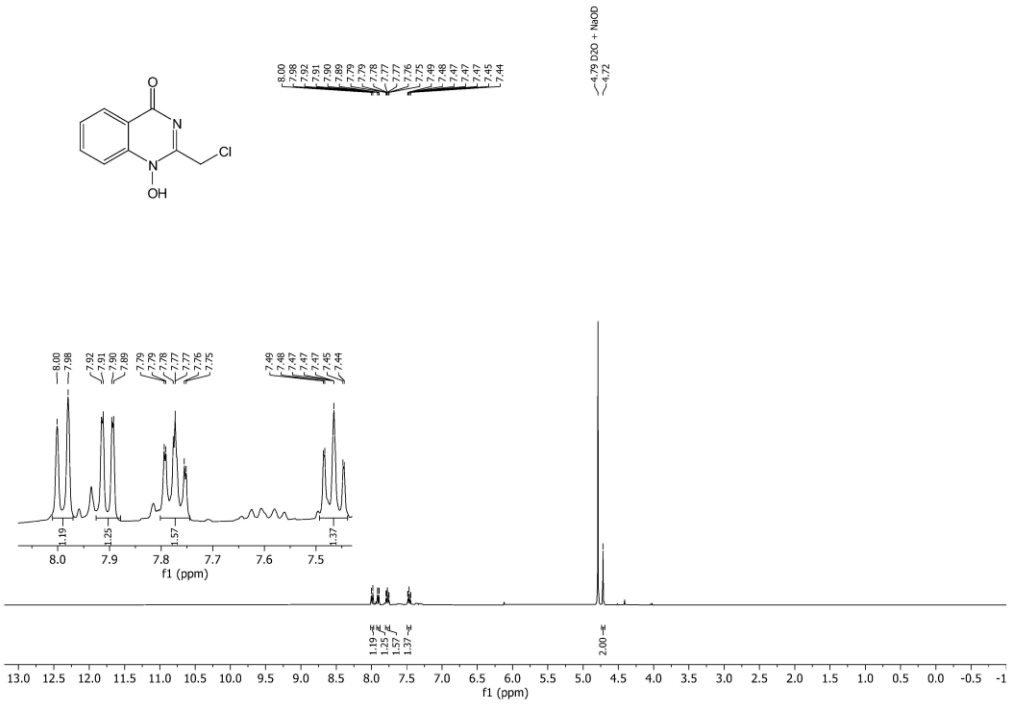


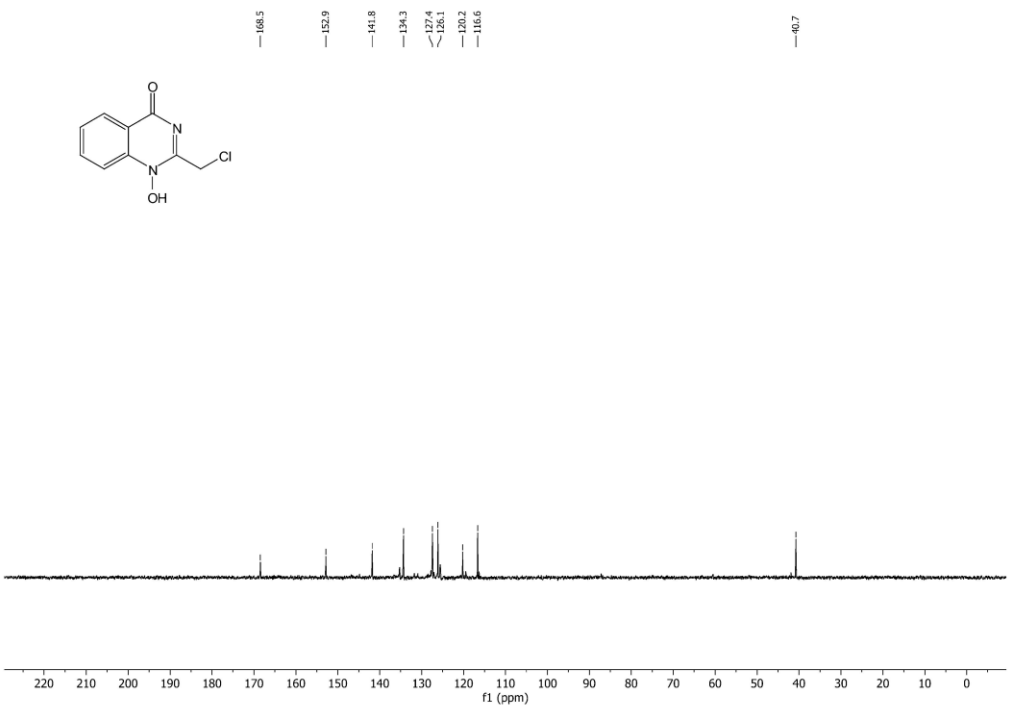
1*H*-1-Hydroxyquinazolin-4-one (6e)



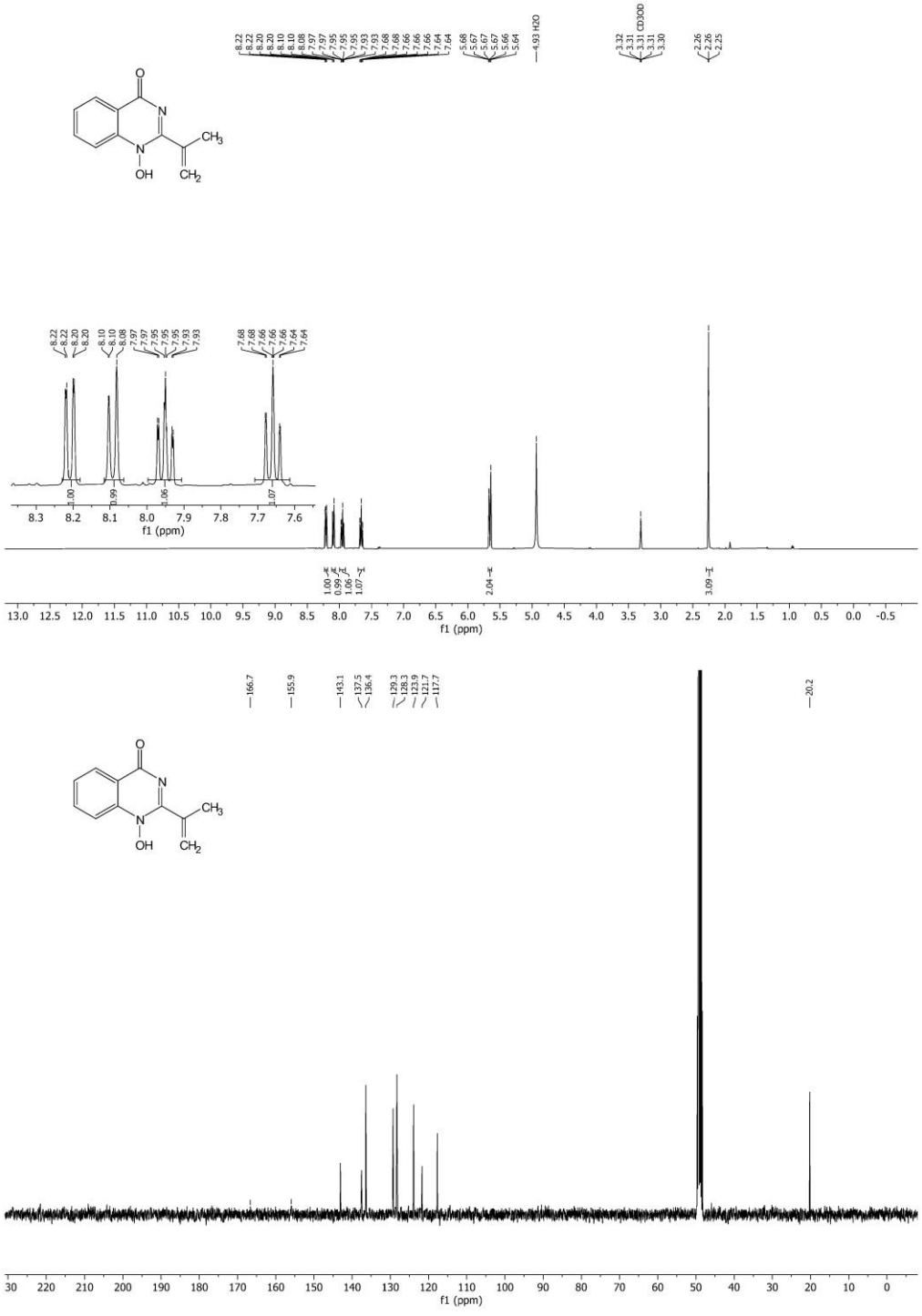


1*H*-2-(Chloromethyl)-1-hydroxyquinazolin-4-one (6f)

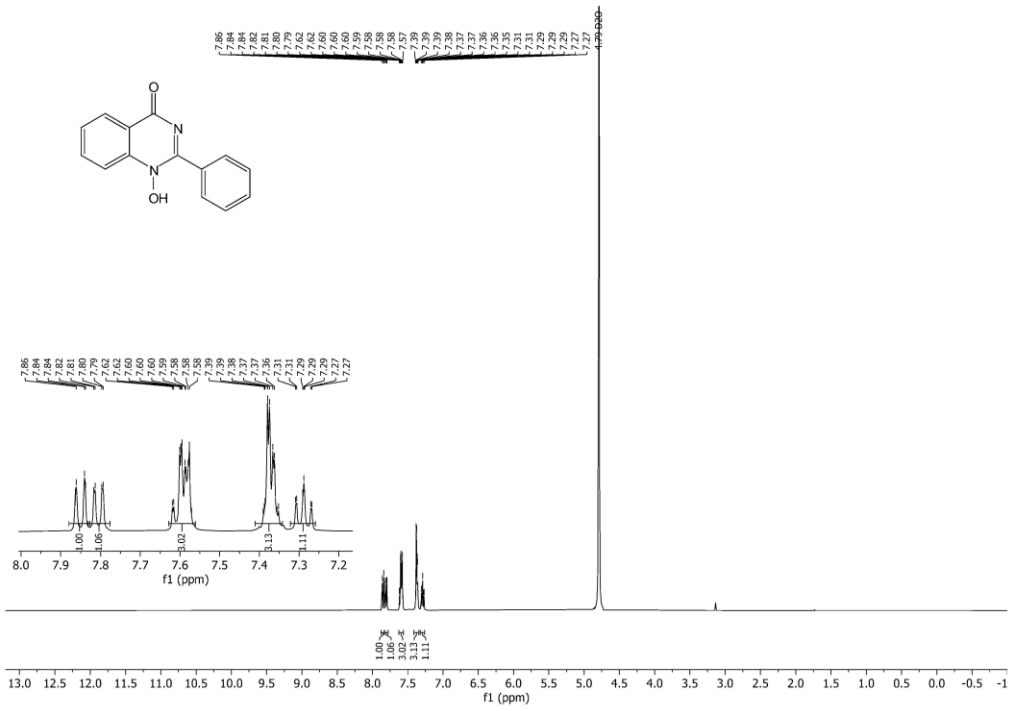


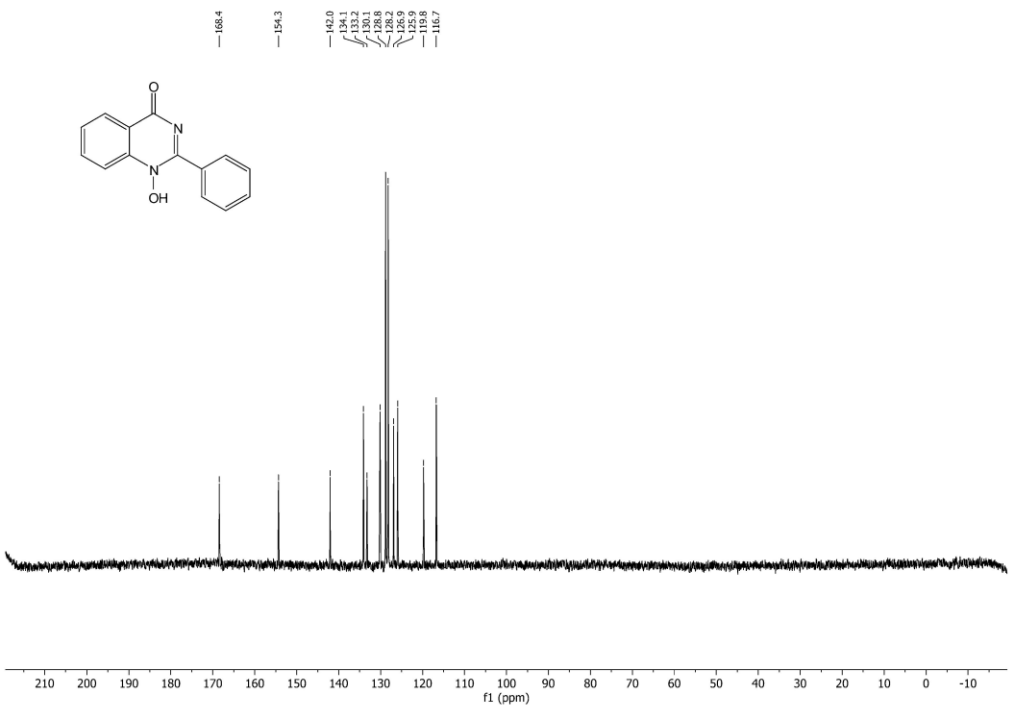


1*H*-1-Hydroxy-2-(prop-1-en-2-yl)quinazolin-4-one (6g)

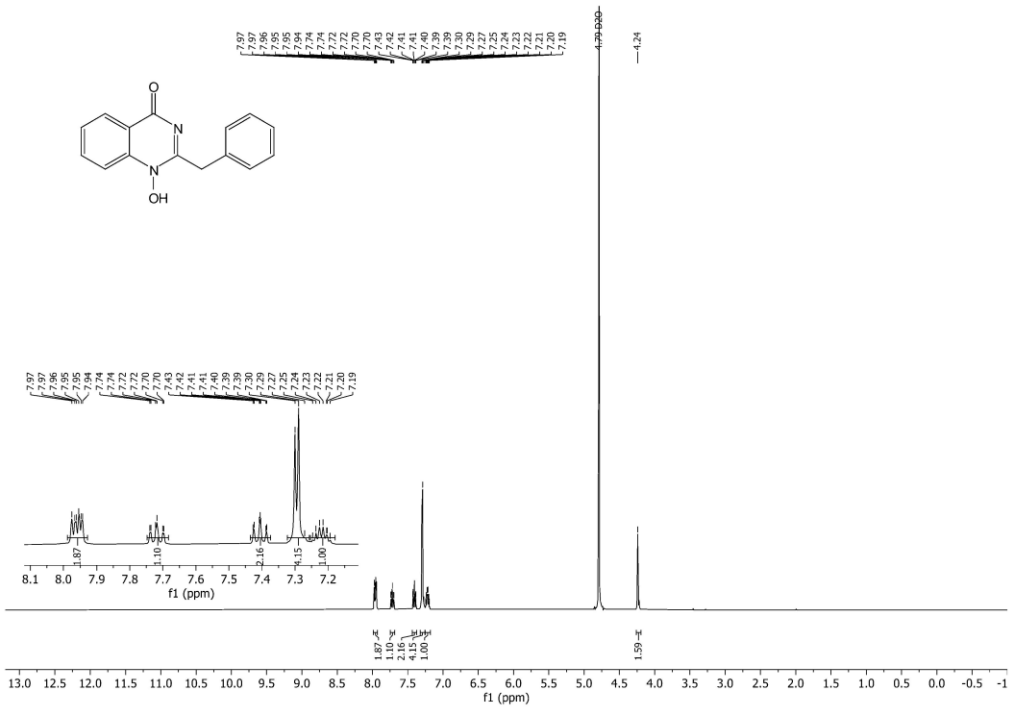


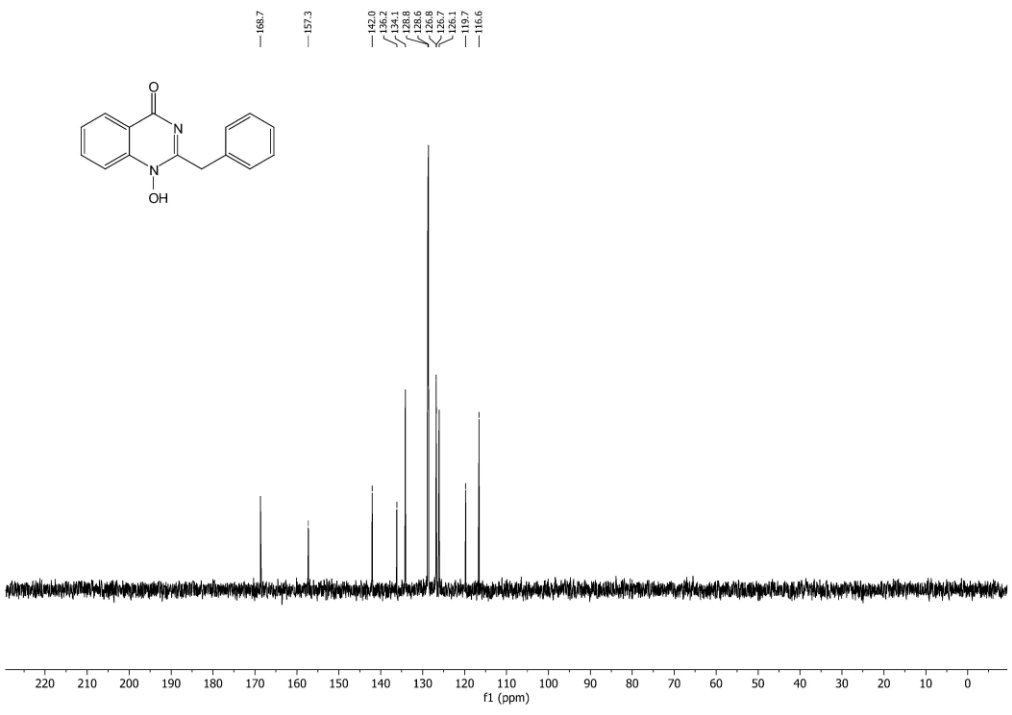
1*H*-1-Hydroxy-2-phenylquinazolin-4-one (6h)



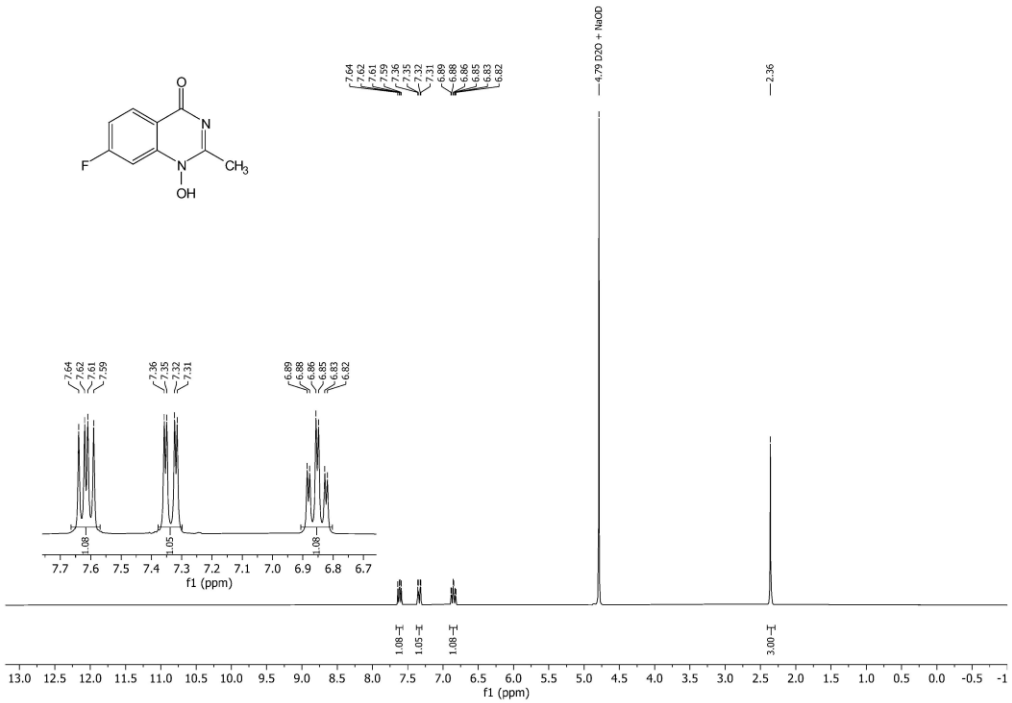


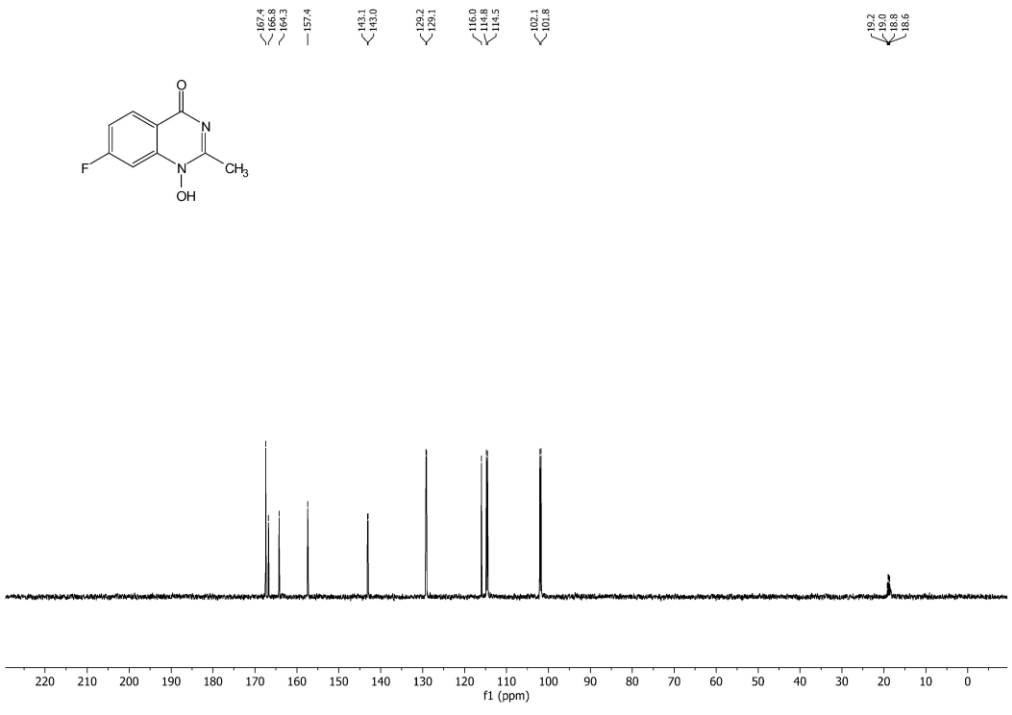
1*H*-2-Benzyl-1-hydroxyquinazolin-4-one (6i)

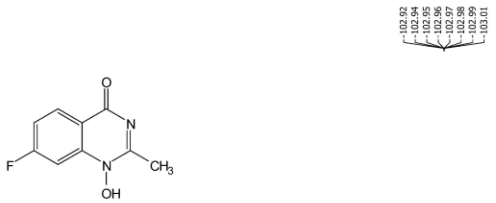




1*H*-7-Fluoro-1-hydroxy-2-methylquinazolin-4-one (6j)



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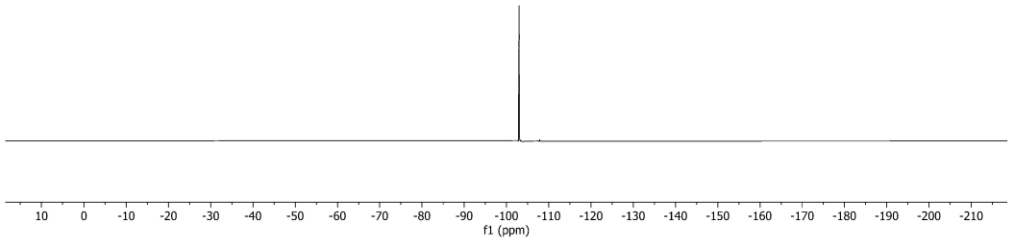
-102.99
-103.01
O
N
F
N
CH3
OH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-150
-160
-170
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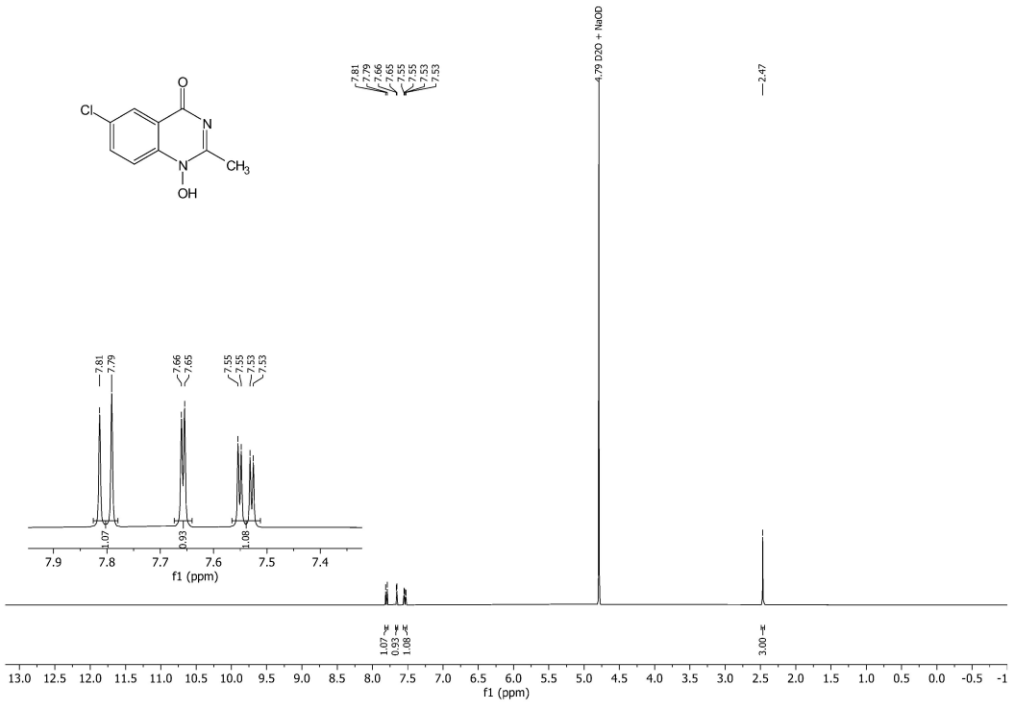
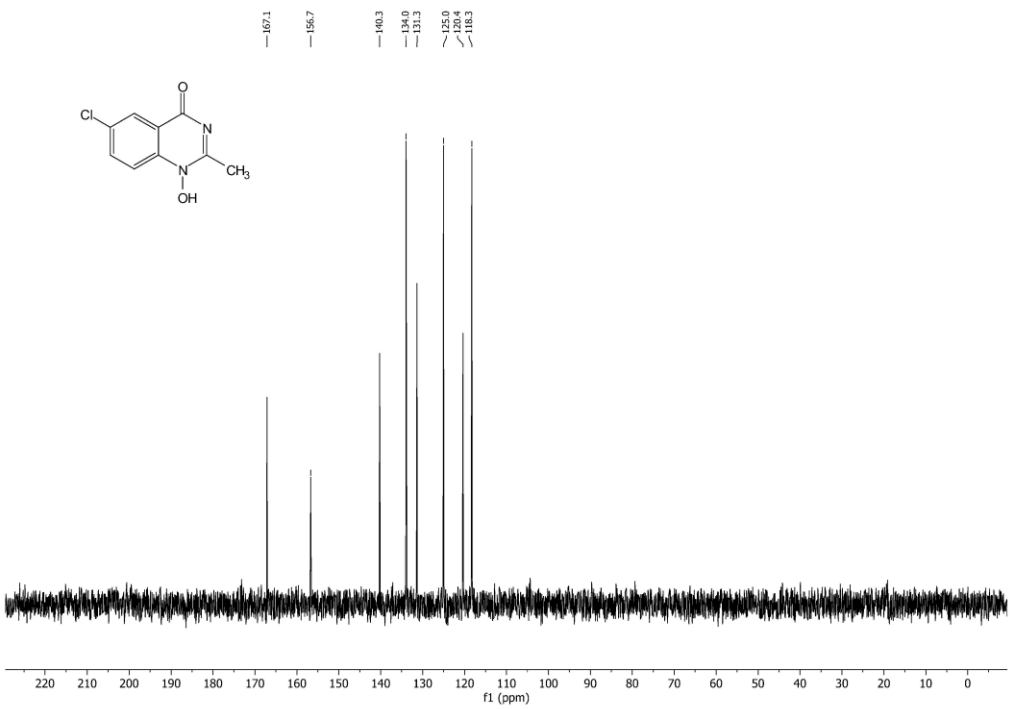
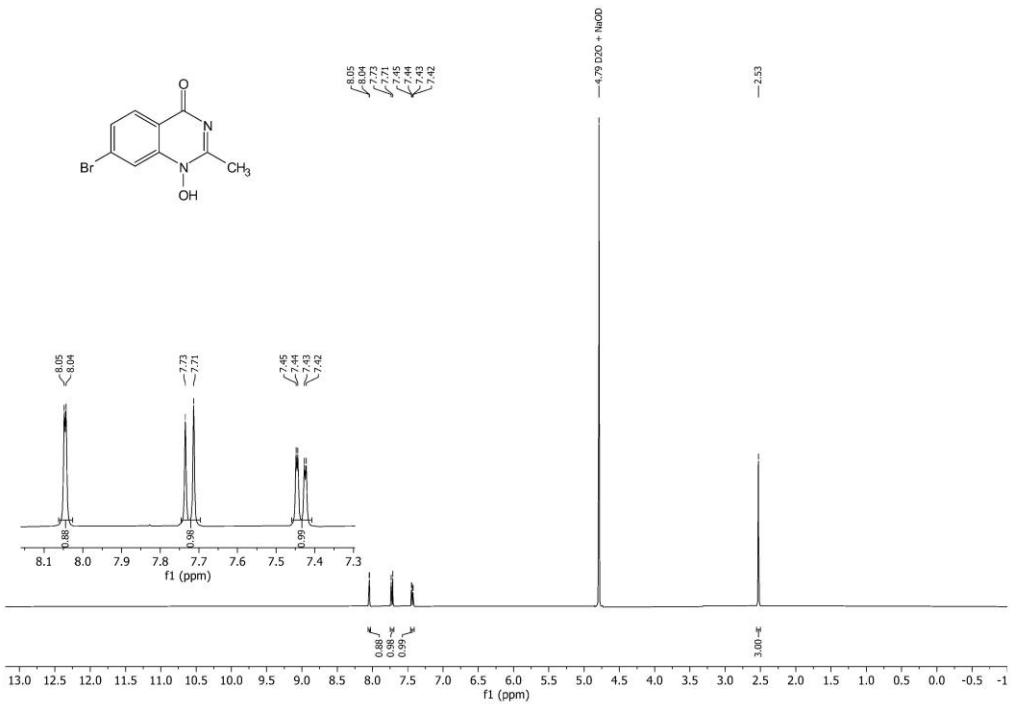
-190
-200
-210
f1 (ppm)

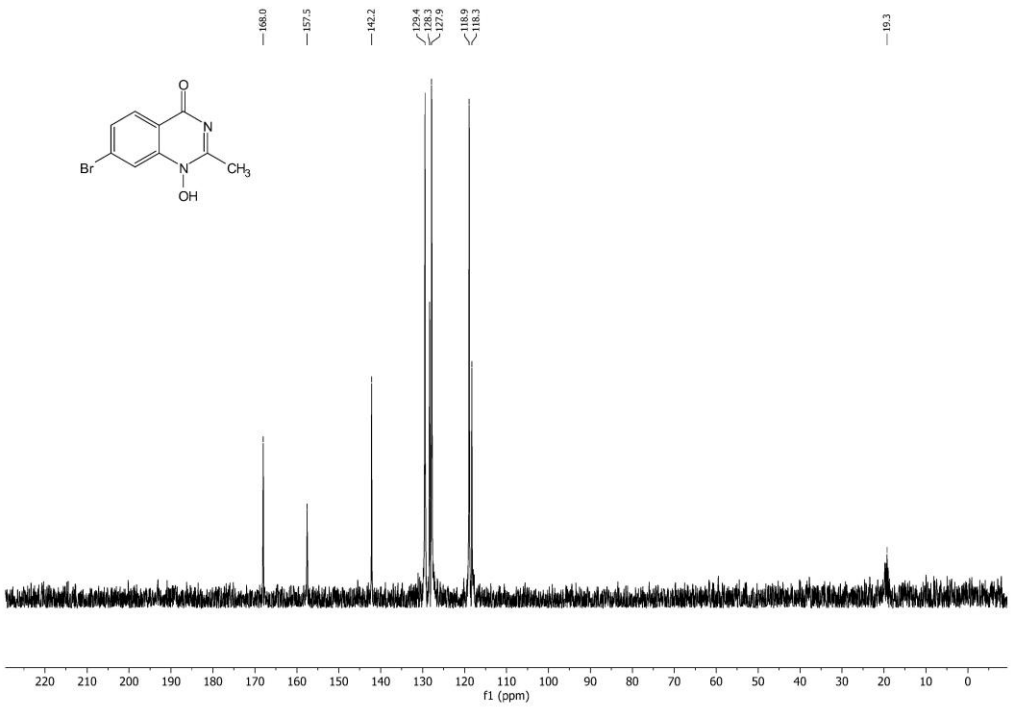
1*H*-6-Chloro-1-hydroxy-2-methylquinazolin-4-one (6k)



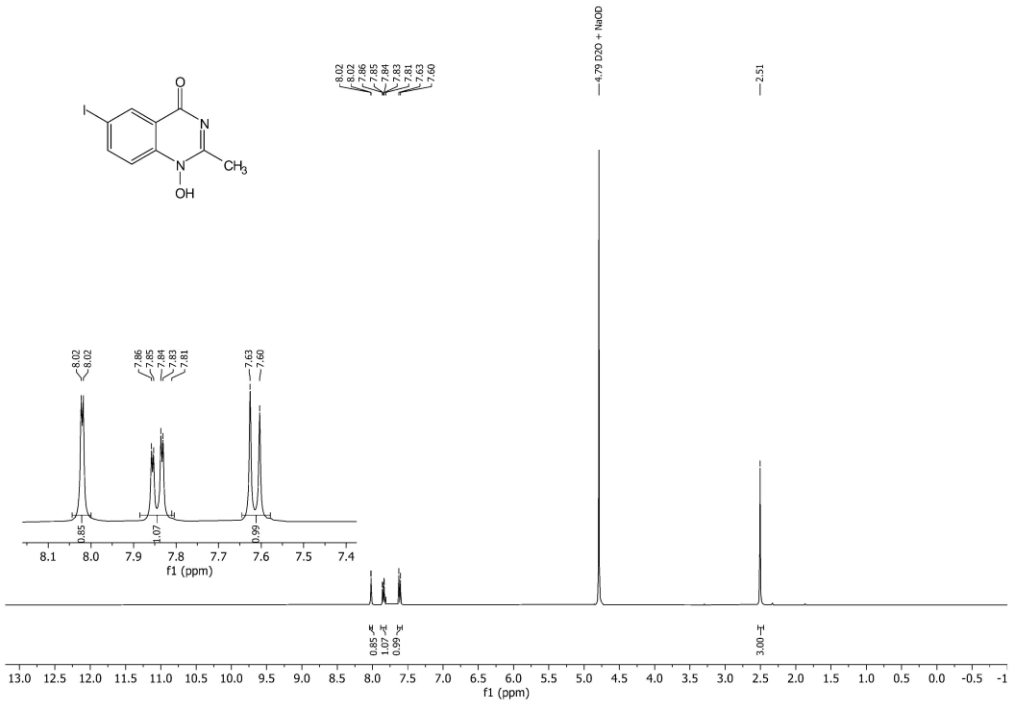


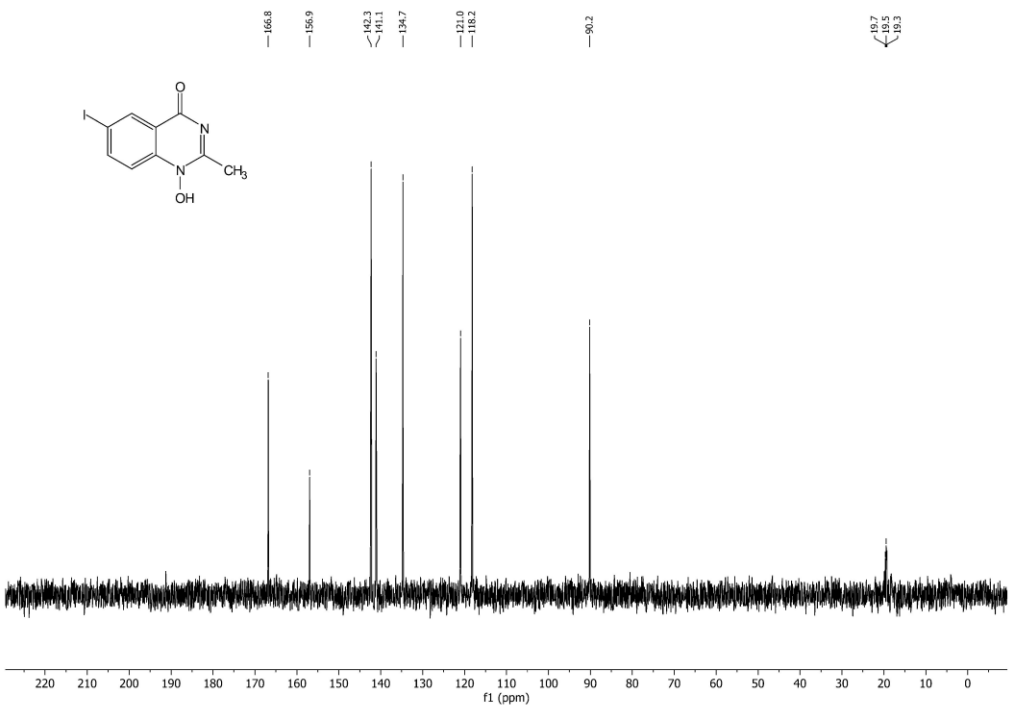
1*H*-7-Bromo-1-hydroxy-2-methylquinazolin-4-one (6l)



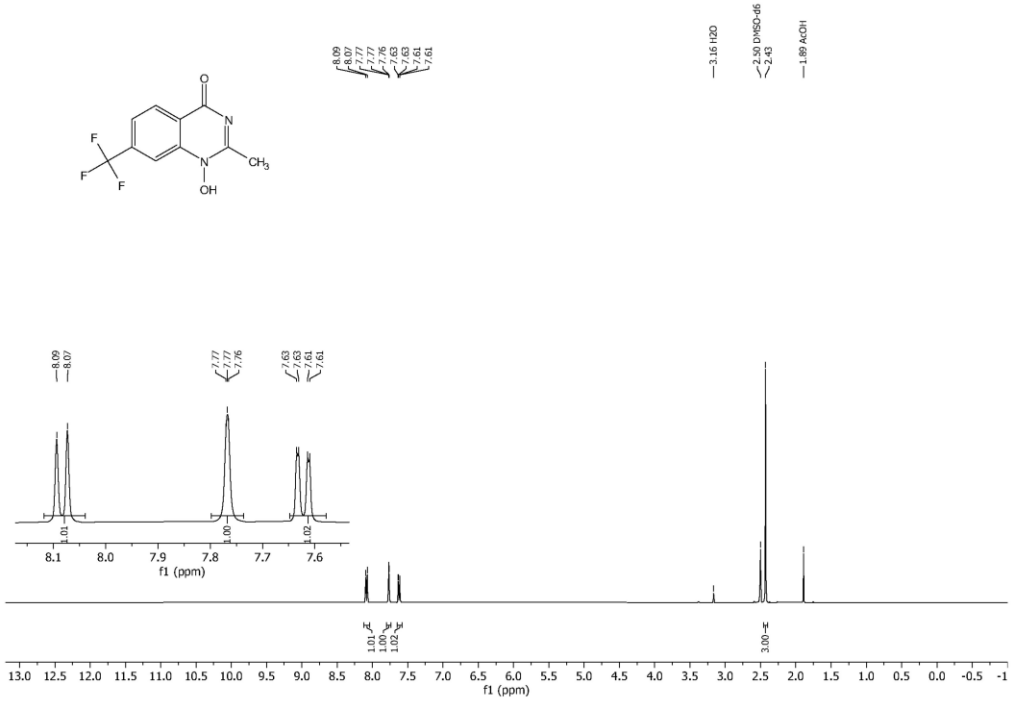


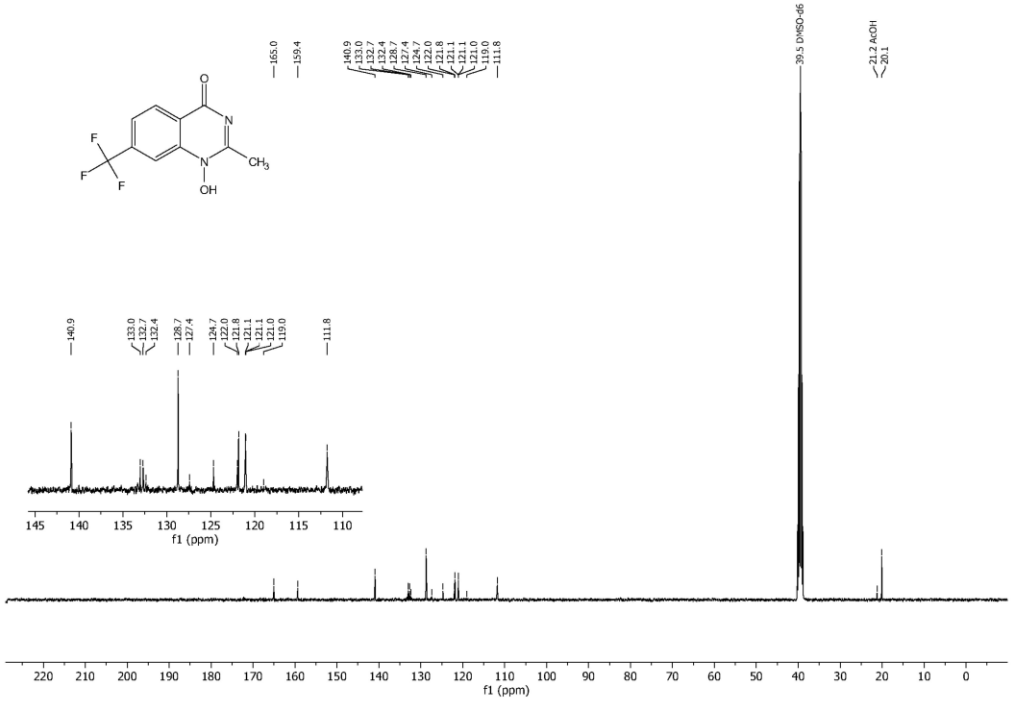
1*H*-1-Hydroxy-6-iodo-2-methylquinazolin-4-one (6m)

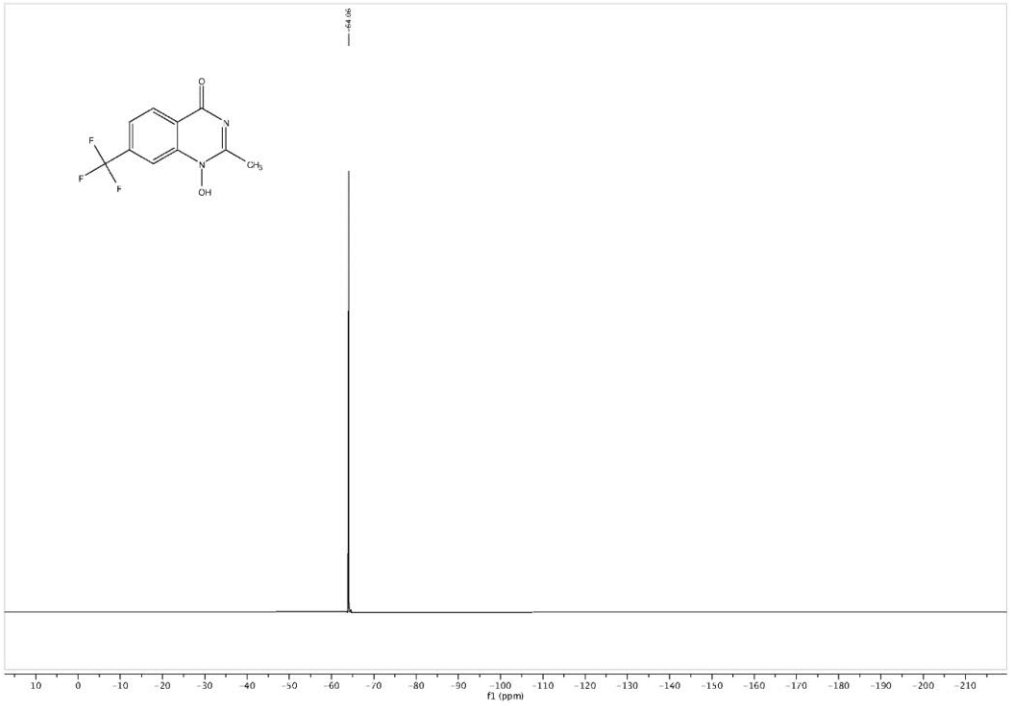




1*H*-1-Hydroxy-2-methyl-7-(trifluoromethyl)quinazolin-4-one (6n)



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F
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F
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CH3
OH
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-130
-140
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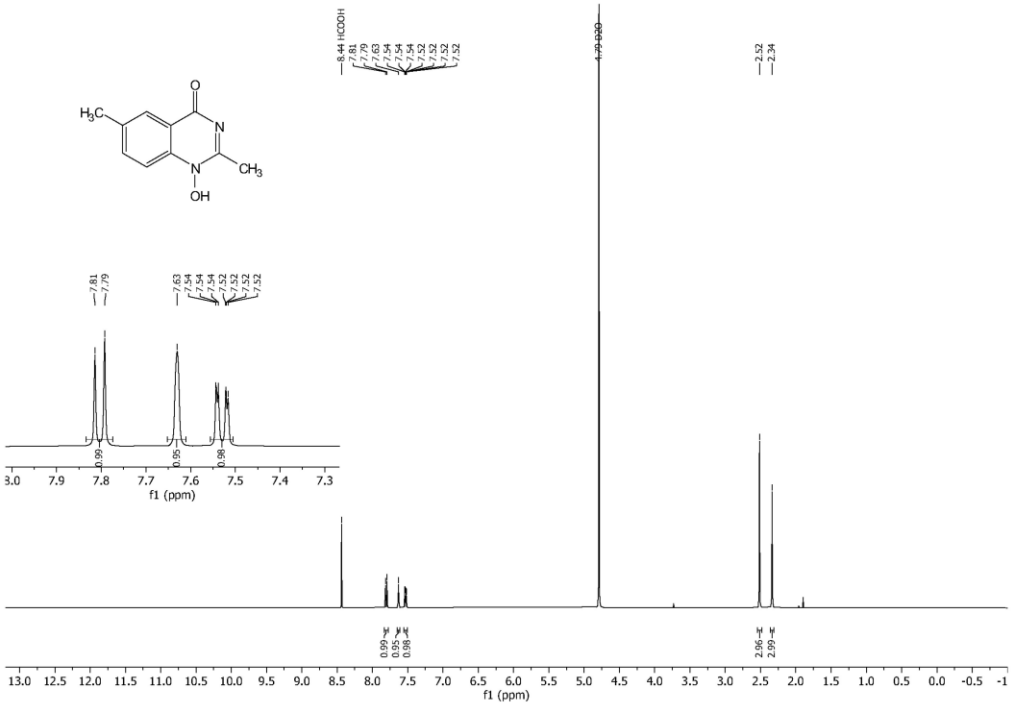
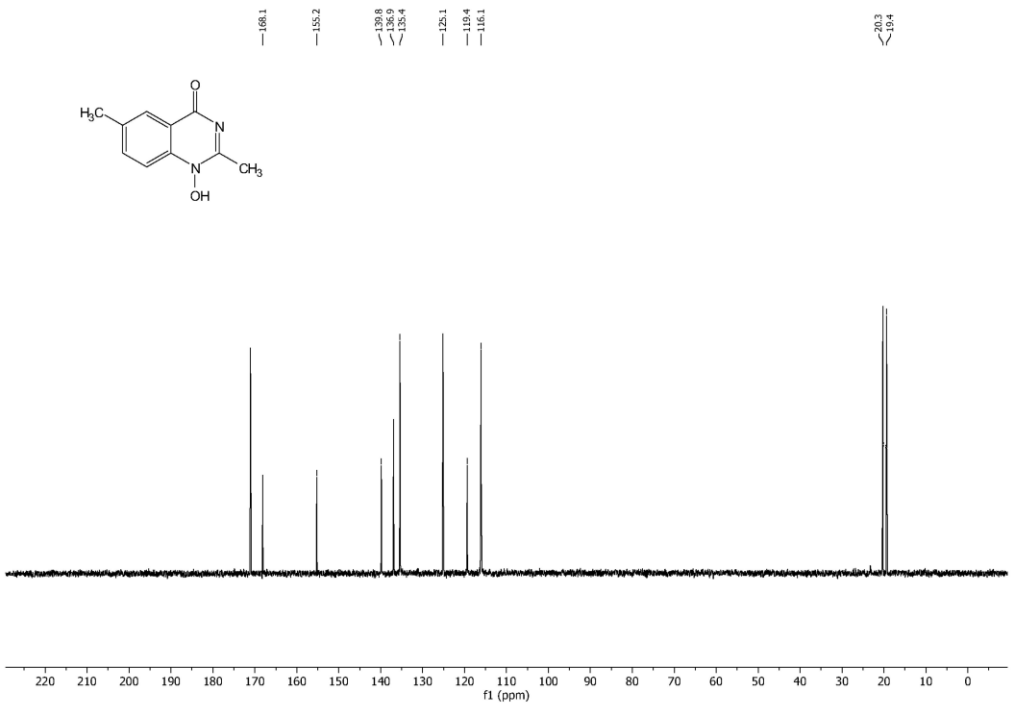
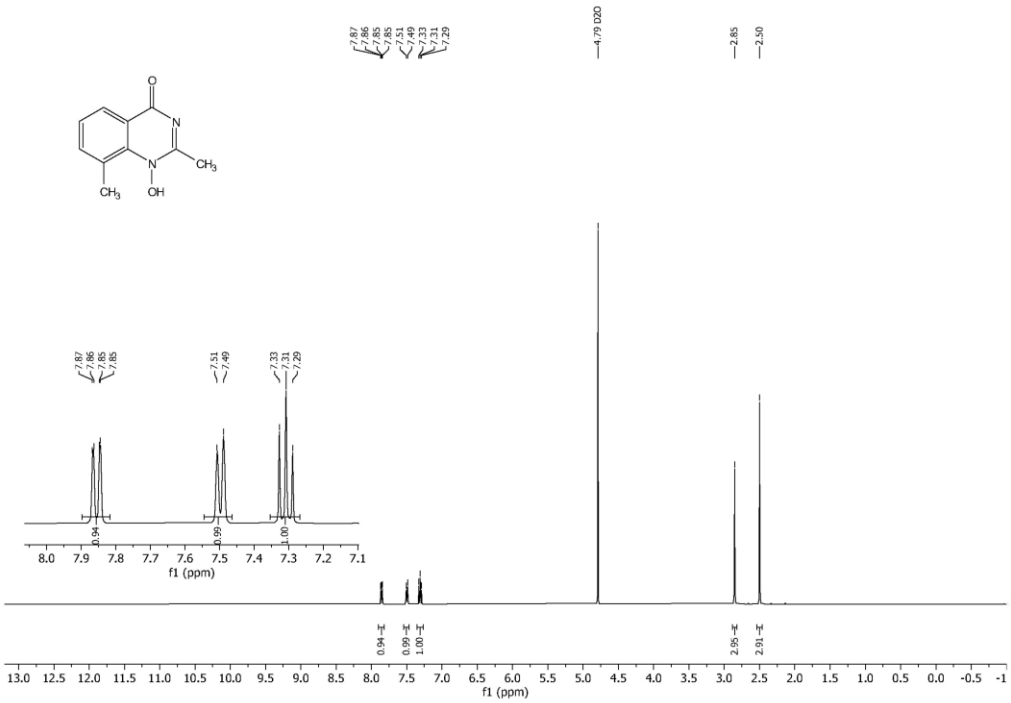
-210
f1 (ppm)

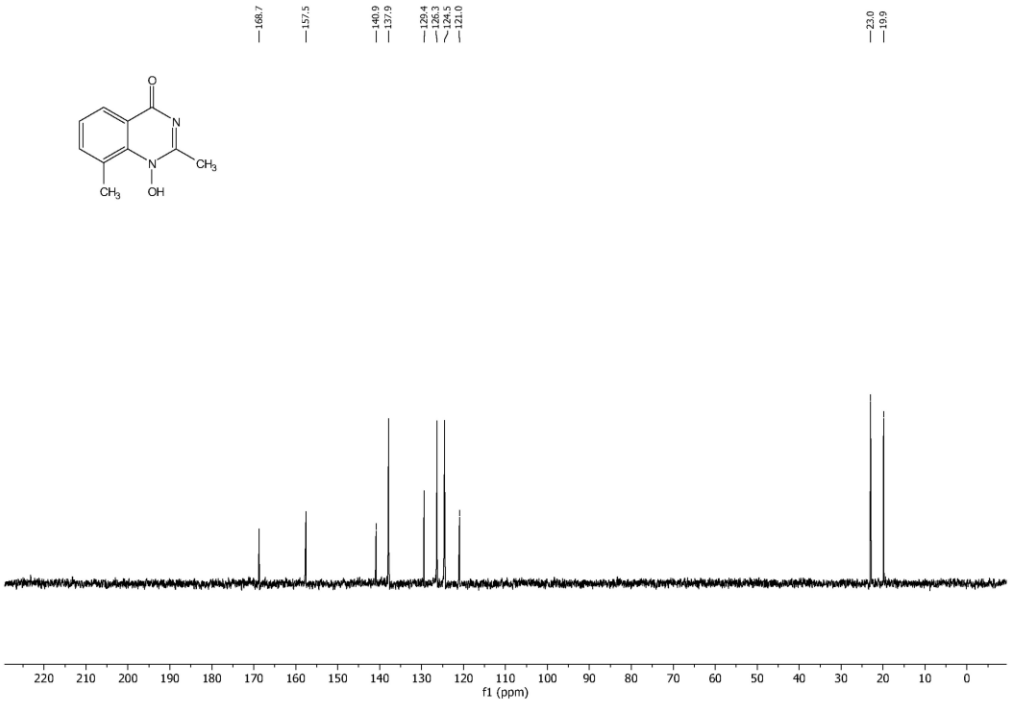
1*H*-1-Hydroxy-2,6-dimethylquinazolin-4-one (6o)



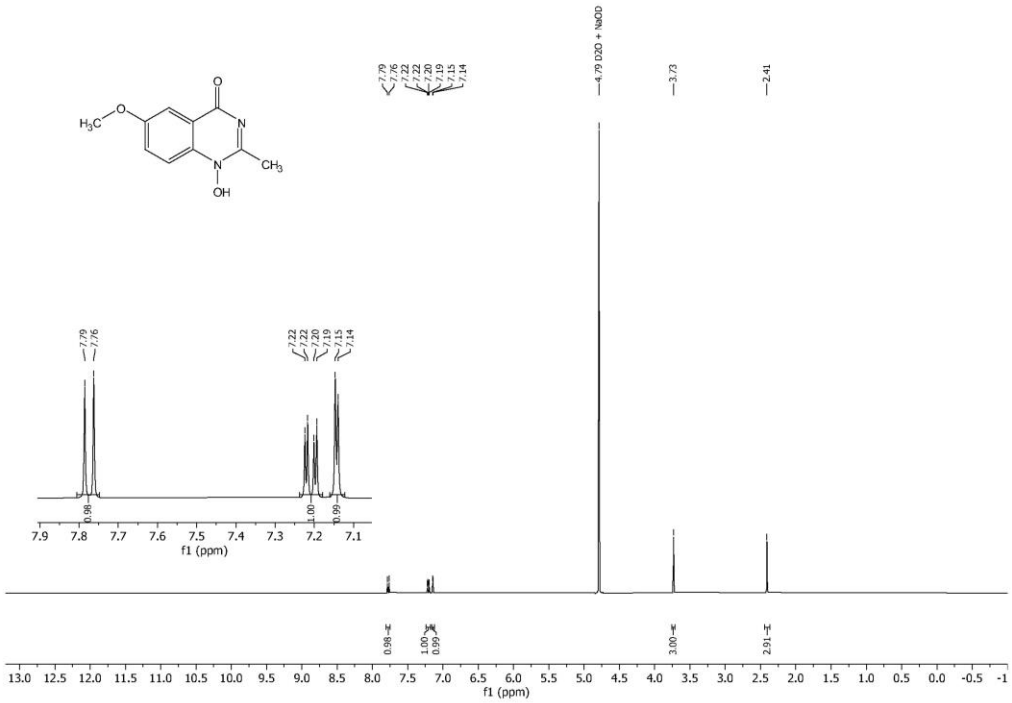


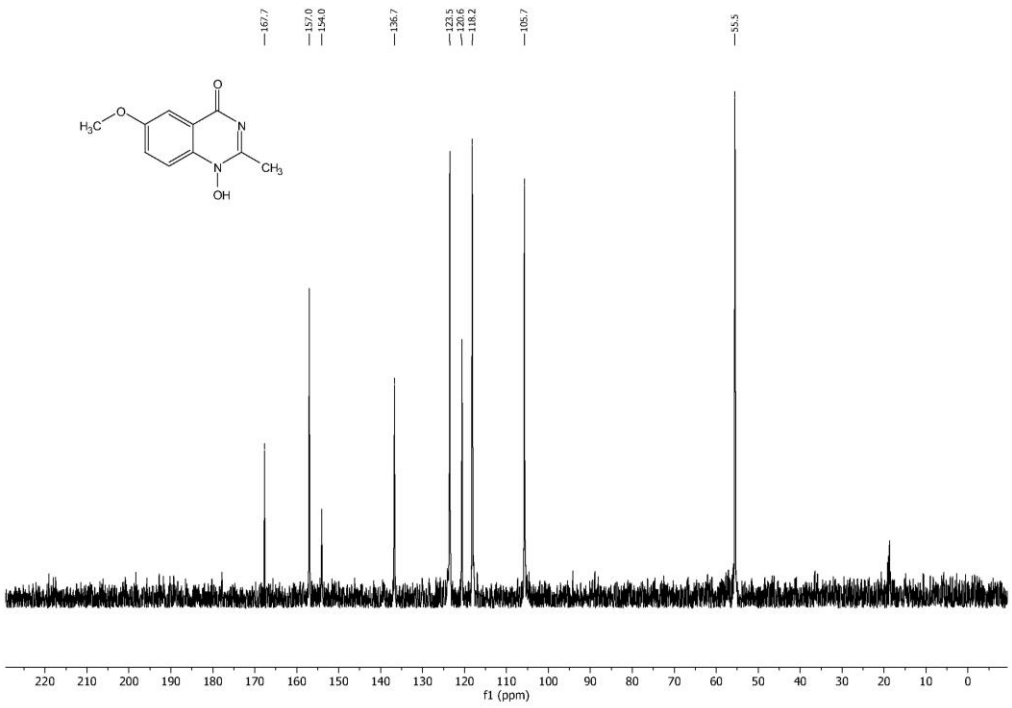
1*H*-1-Hydroxy-2,8-dimethylquinazolin-4-one (6p)



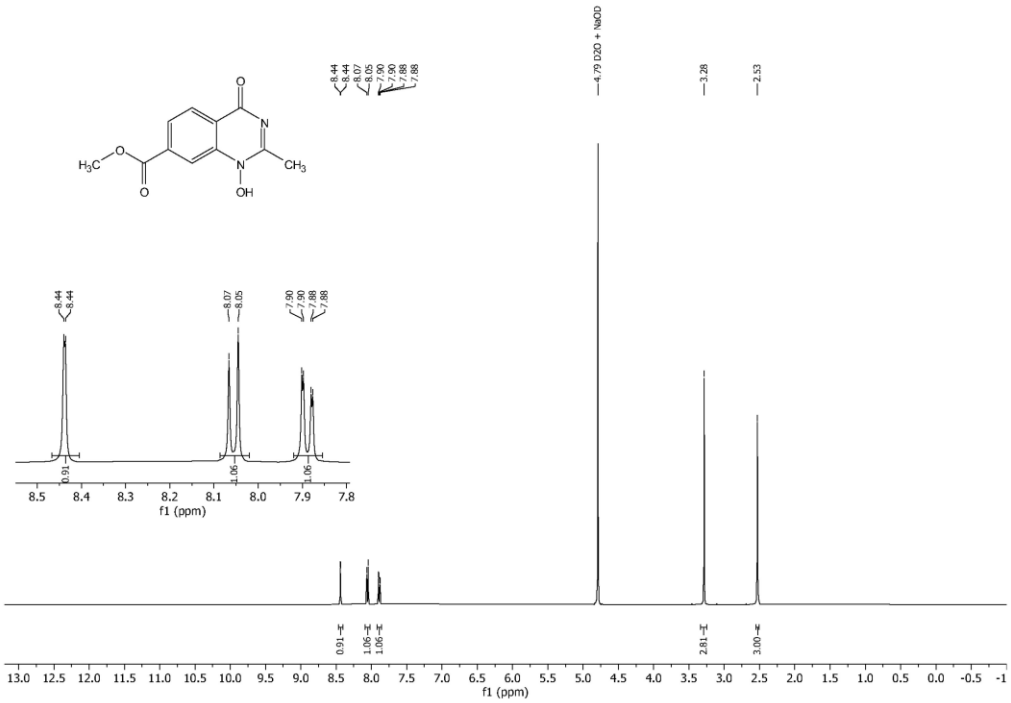


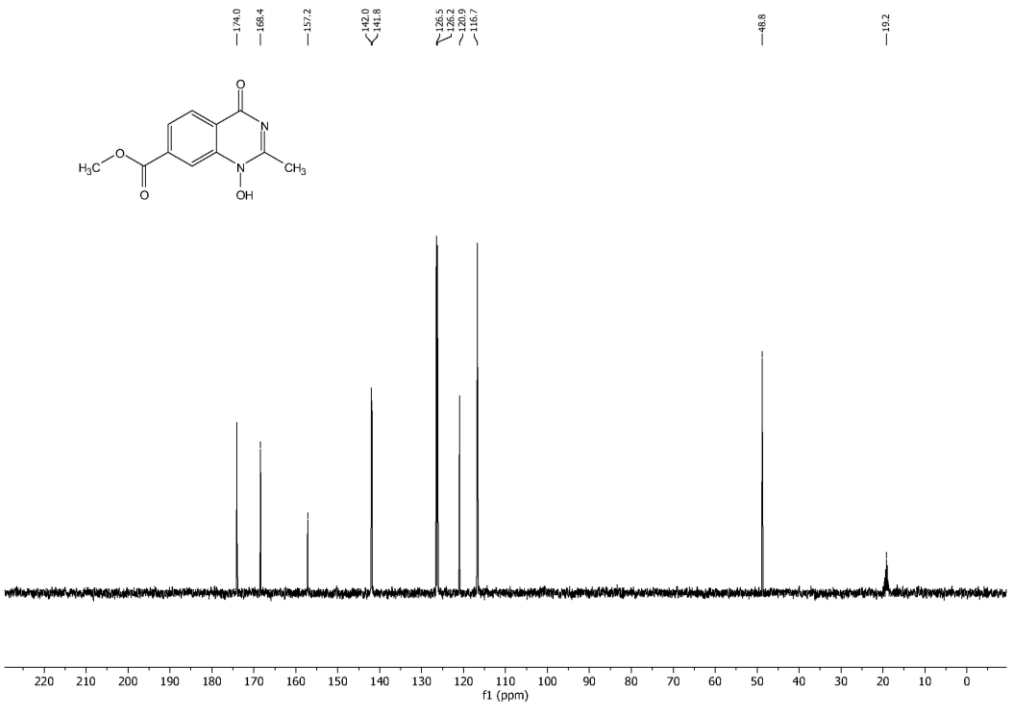
1*H*-1-Hydroxy-6-methoxy-2-methylquinazolin-4-one (6q)



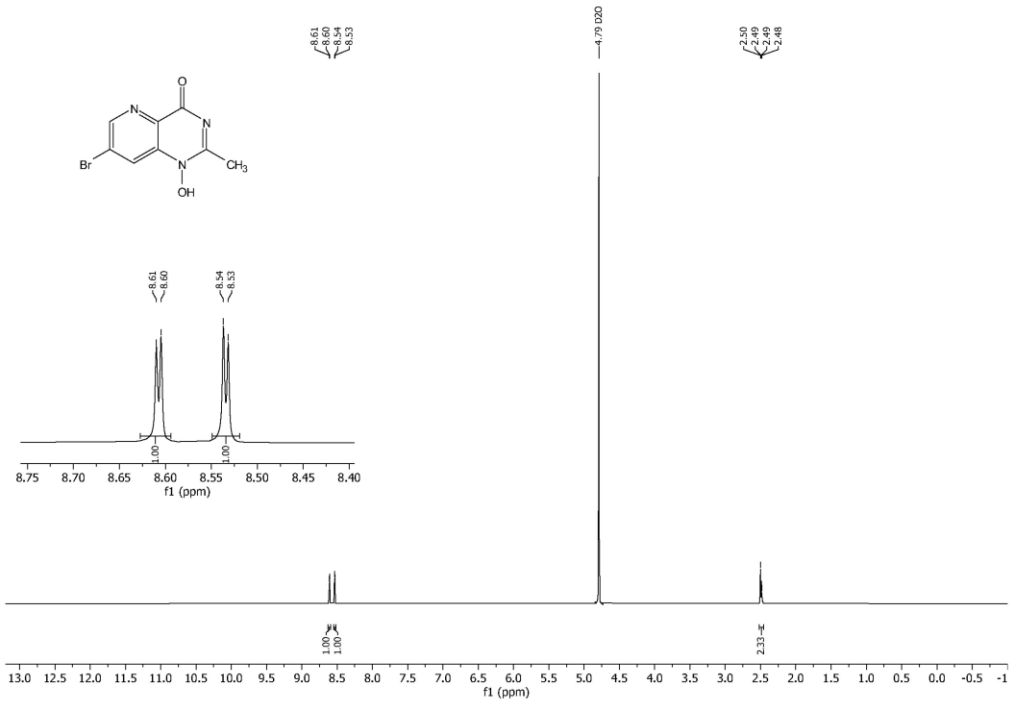


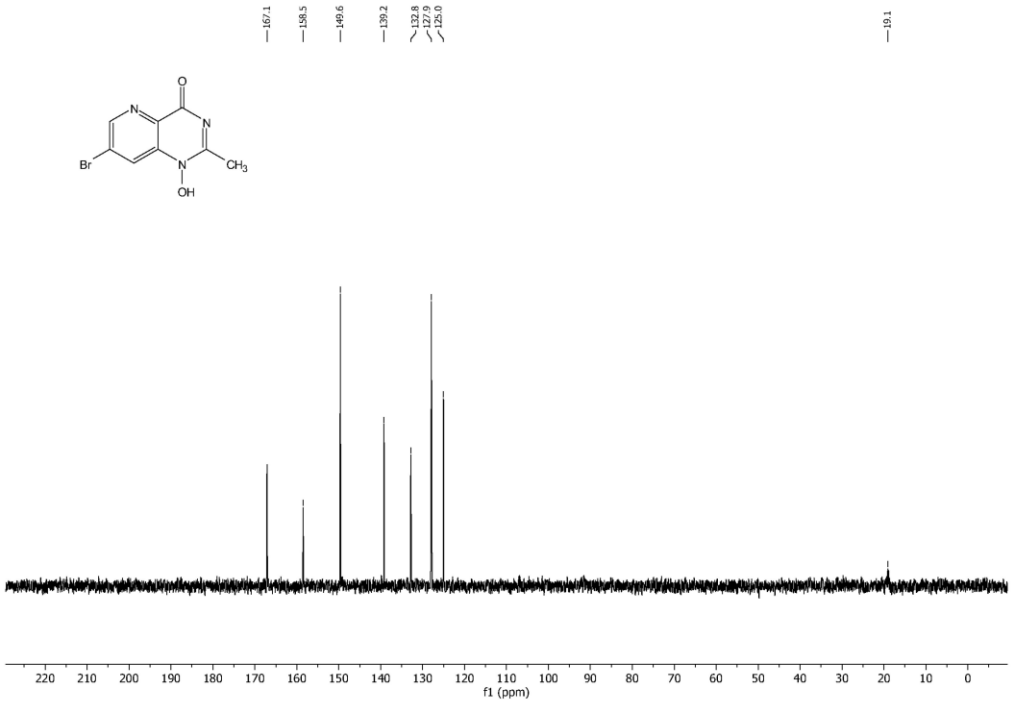
Methyl 1-hydroxy-2-methyl-4-oxo-1,4-dihydroquinazoline-7-carboxylate (6r)



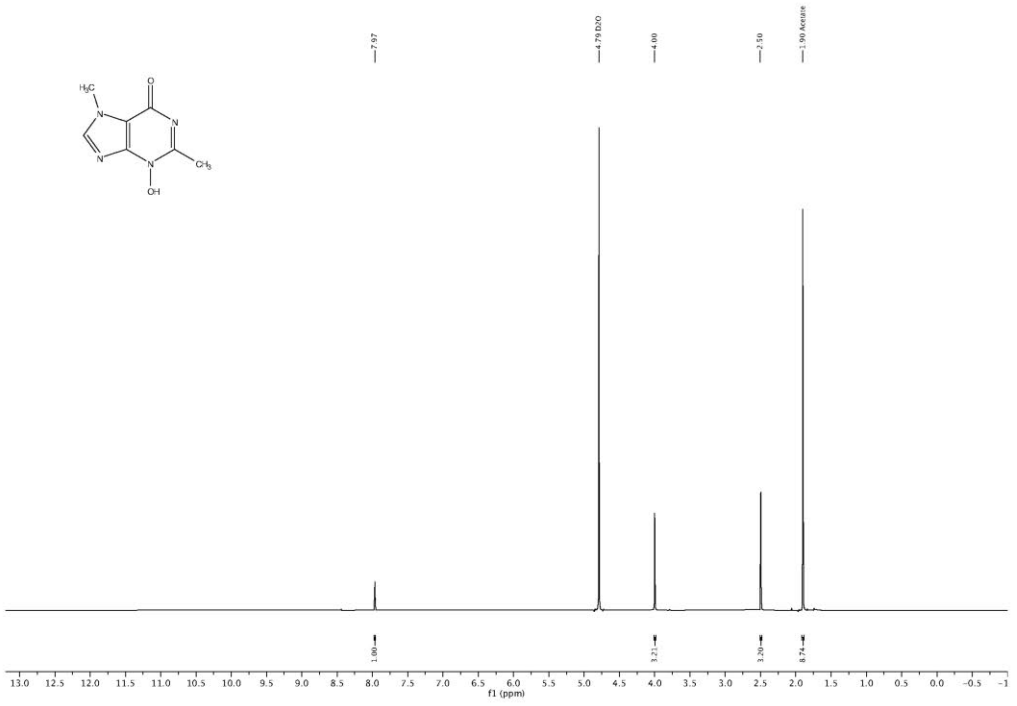


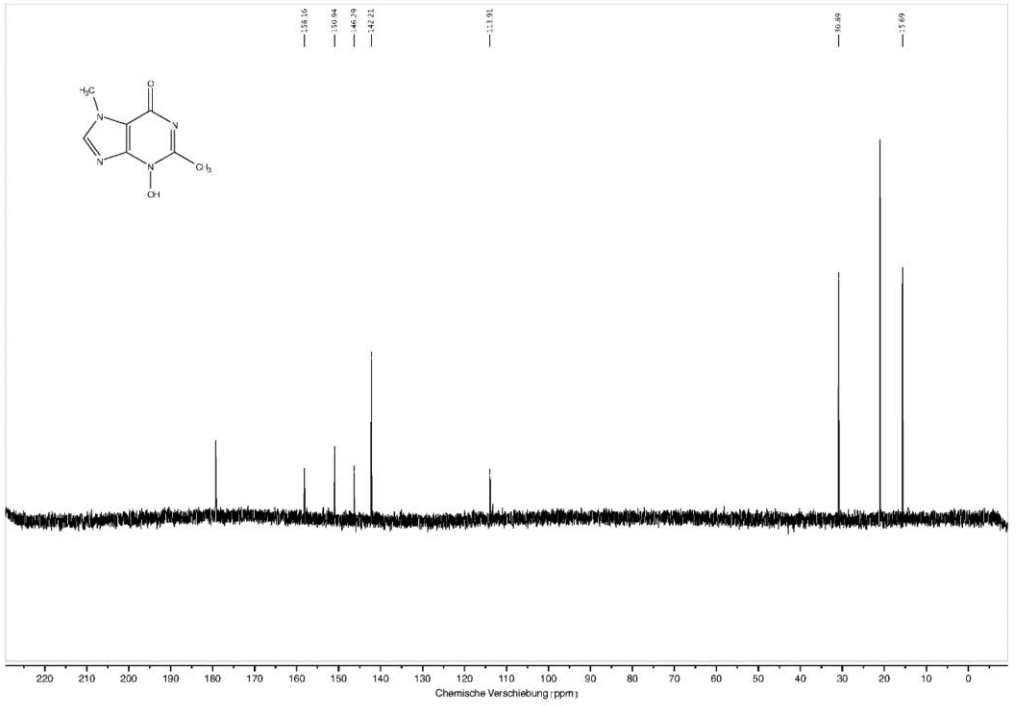
1*H*-7-Bromo-1-hydroxy-2-methylpyrido[3,2-*d*]pyrimidin-4-one (6s)



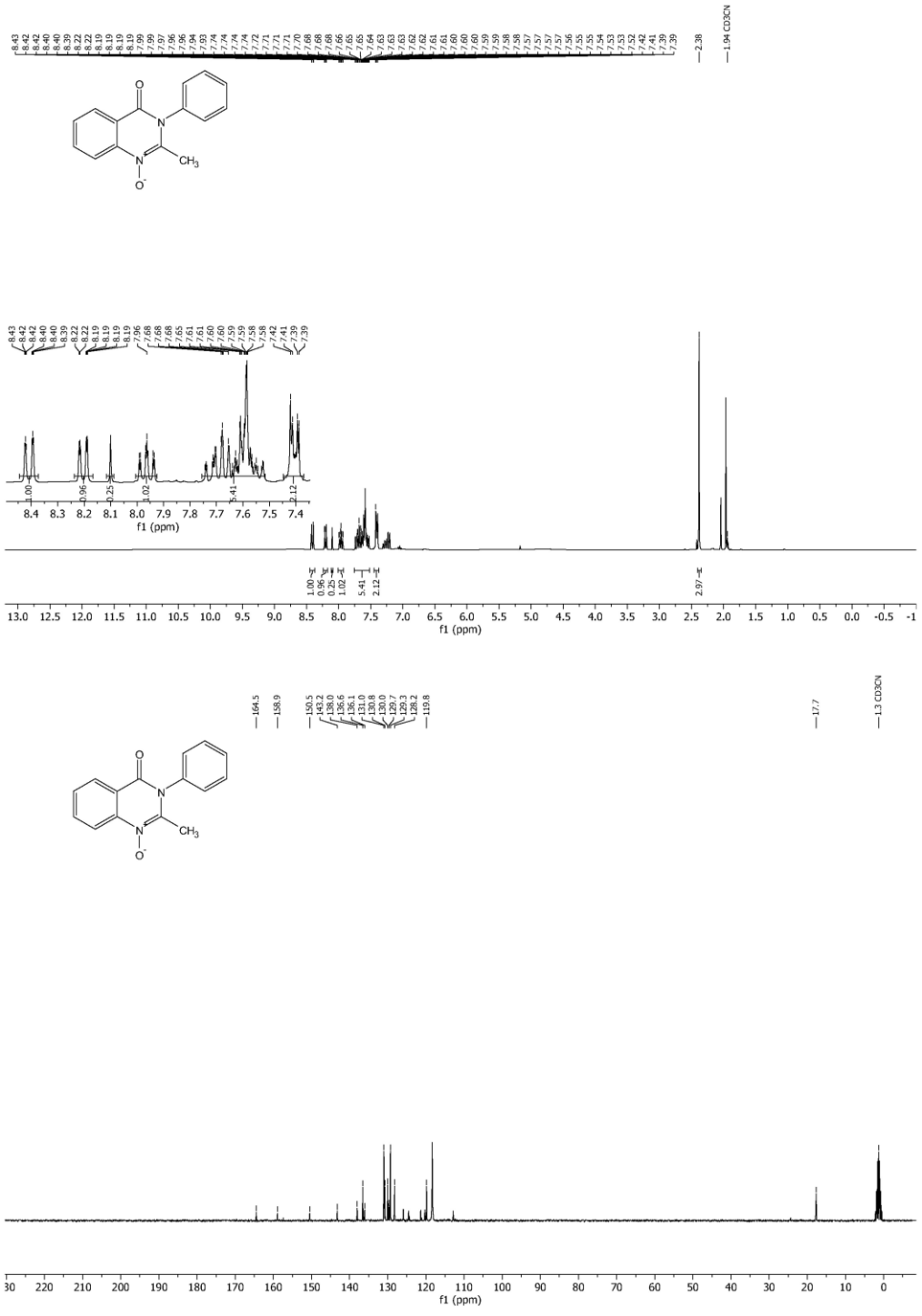


6*H*-3-Hydroxy-2,7-dimethyl-3,7-dihydropurin-6-one (6t)

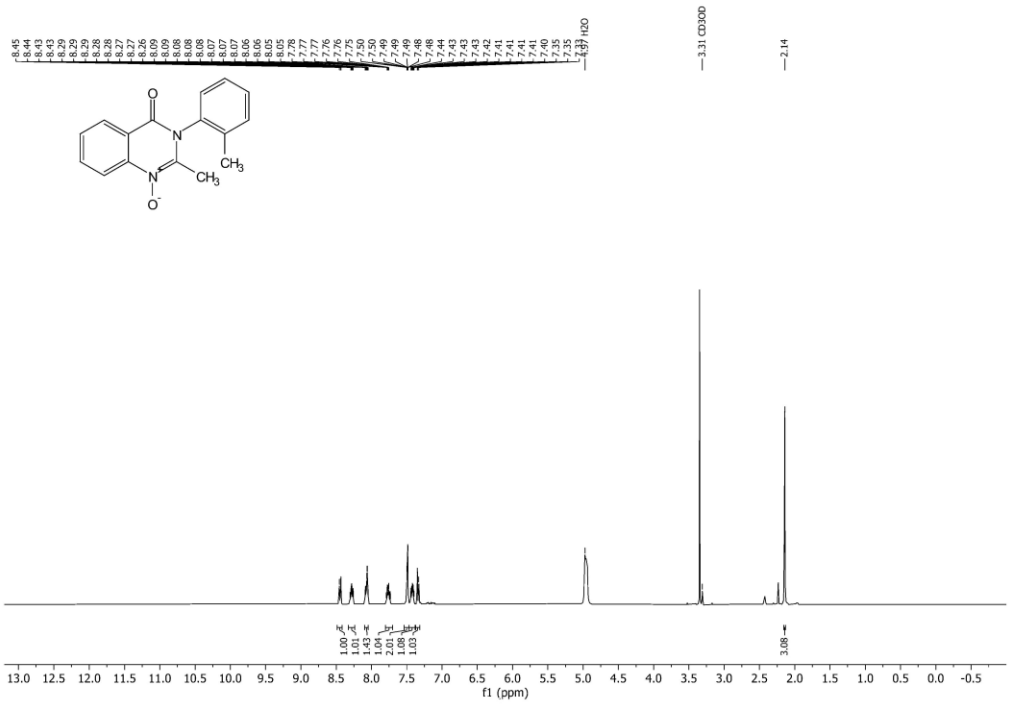


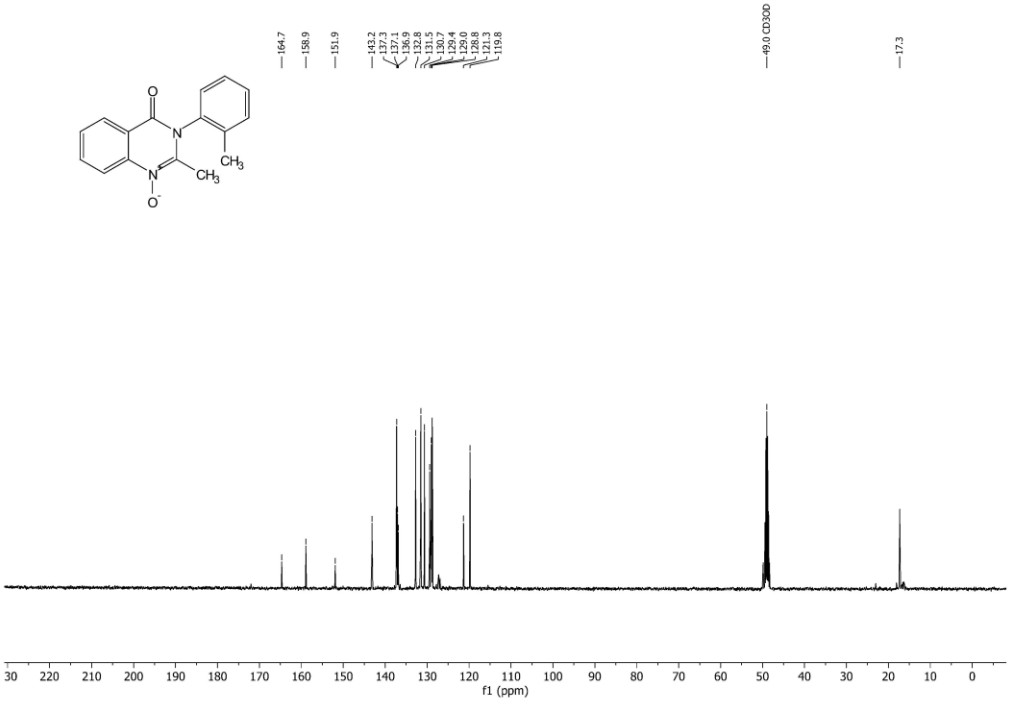


2-Methyl-4-oxo-3-phenyl-3,4-dihydroquinazoline 1-oxide (7a)

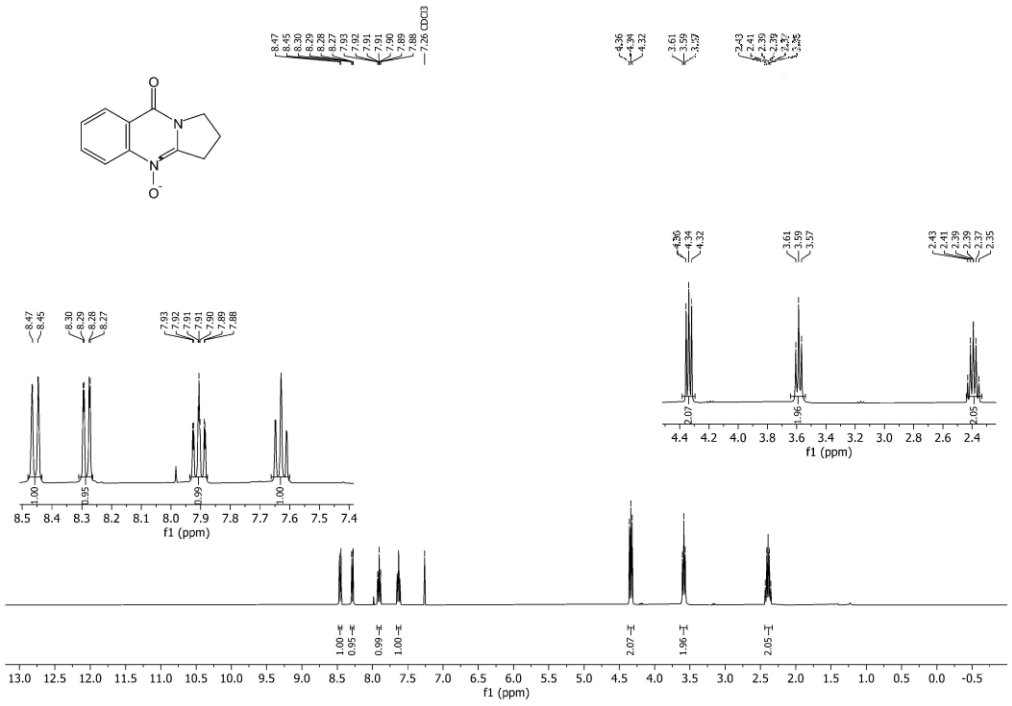


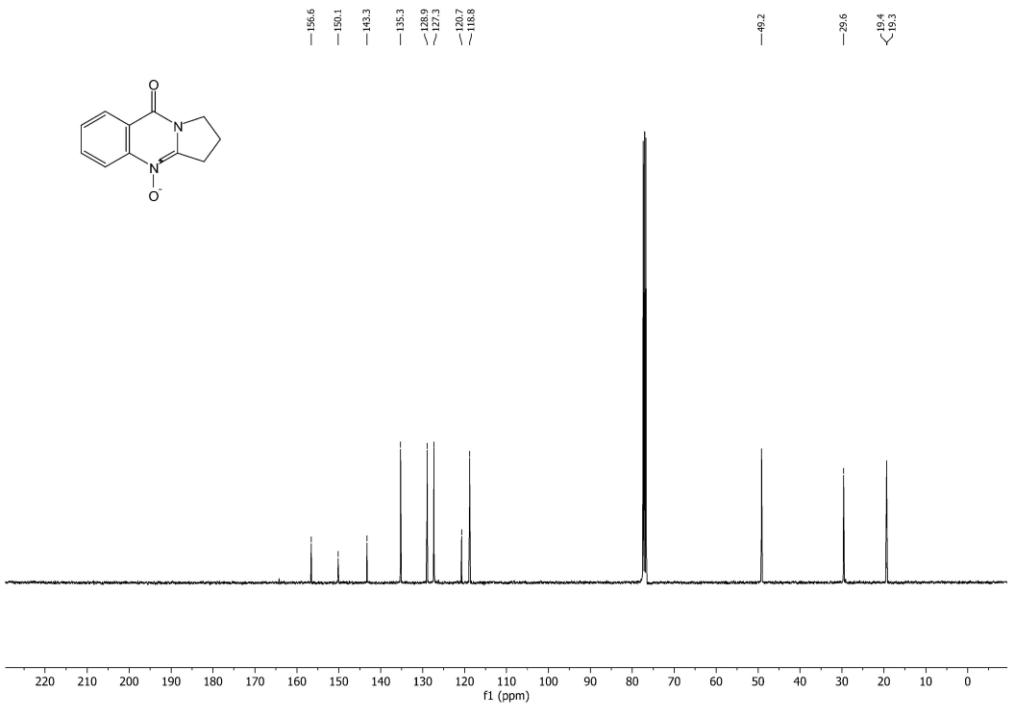
2-Methyl-4-oxo-3-(o-tolyl)-3,4-dihydroquinazoline 1-oxide (7b)



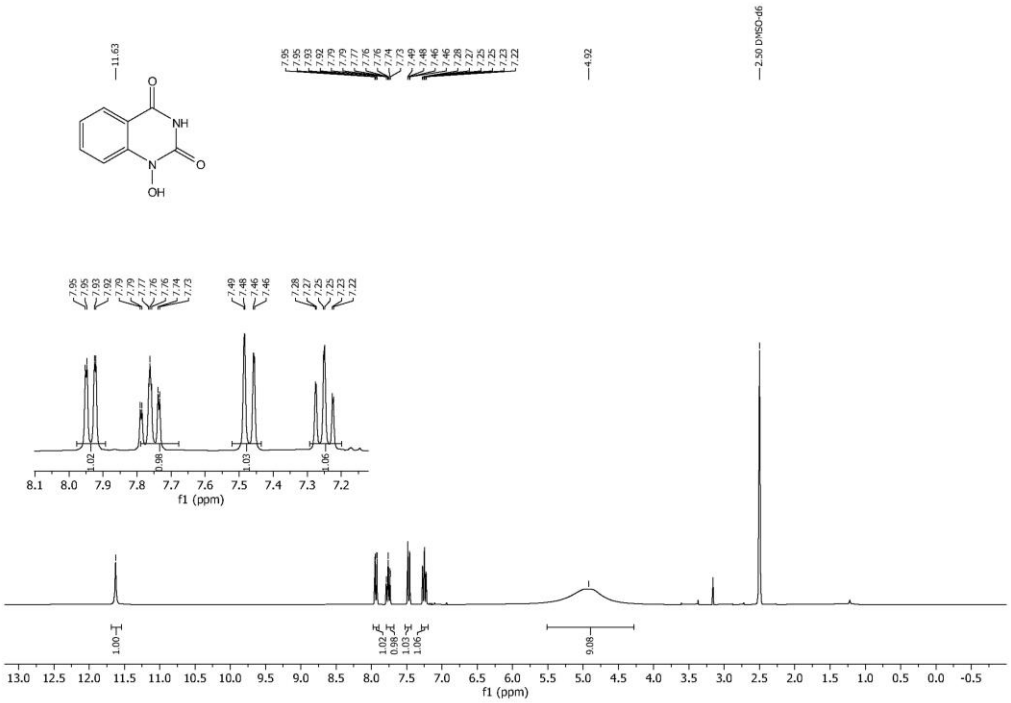


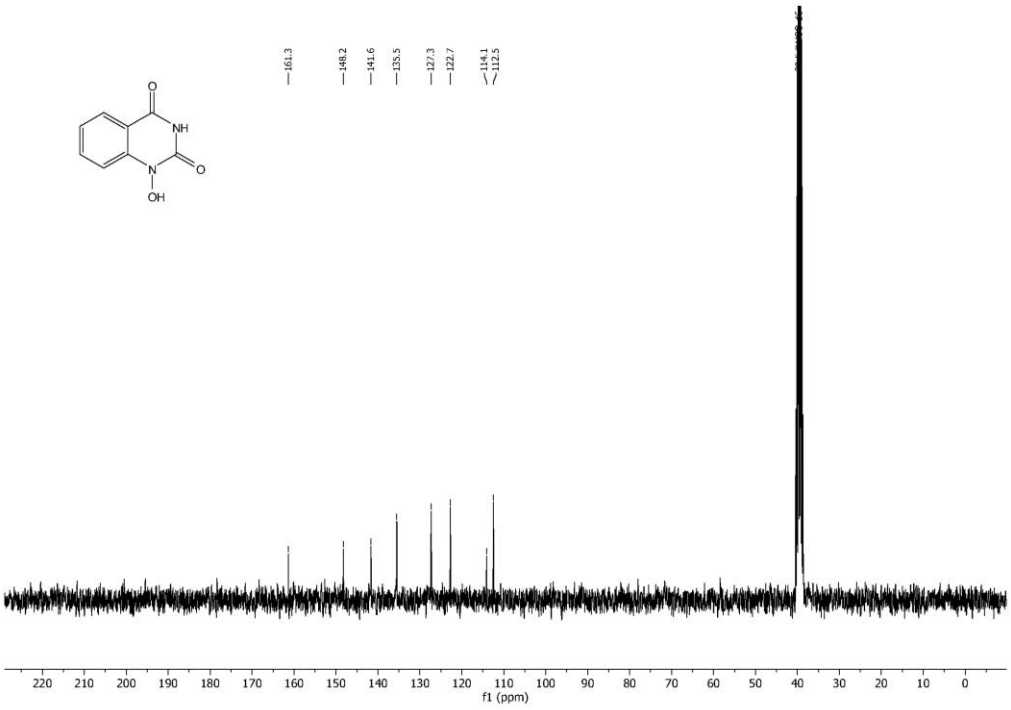
9-Oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline 4-oxide (7c)



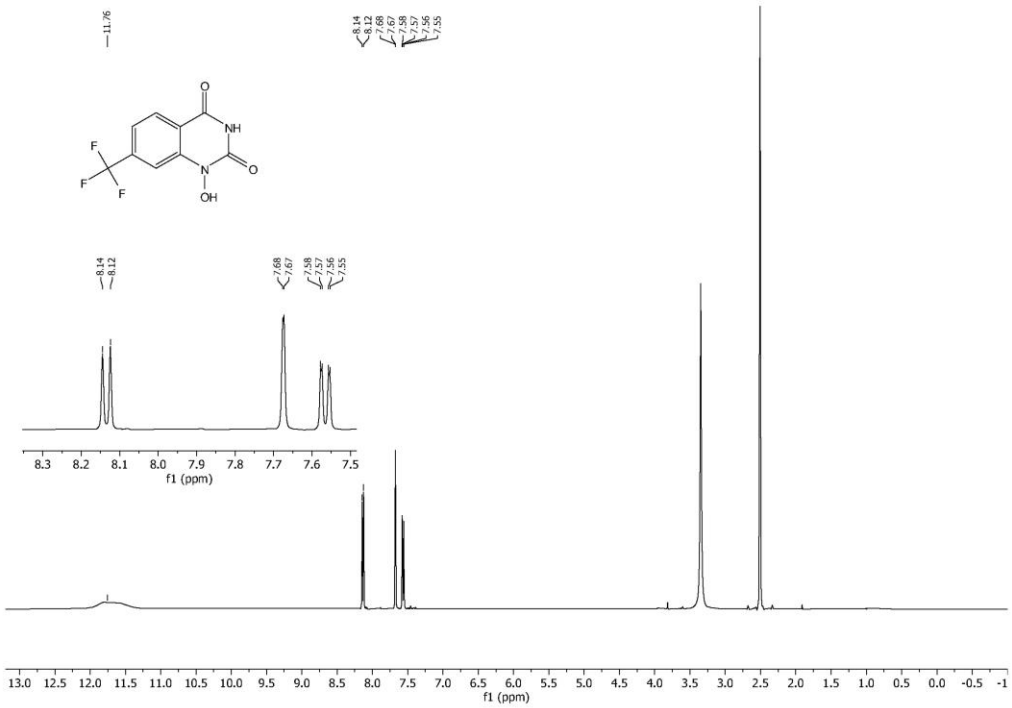


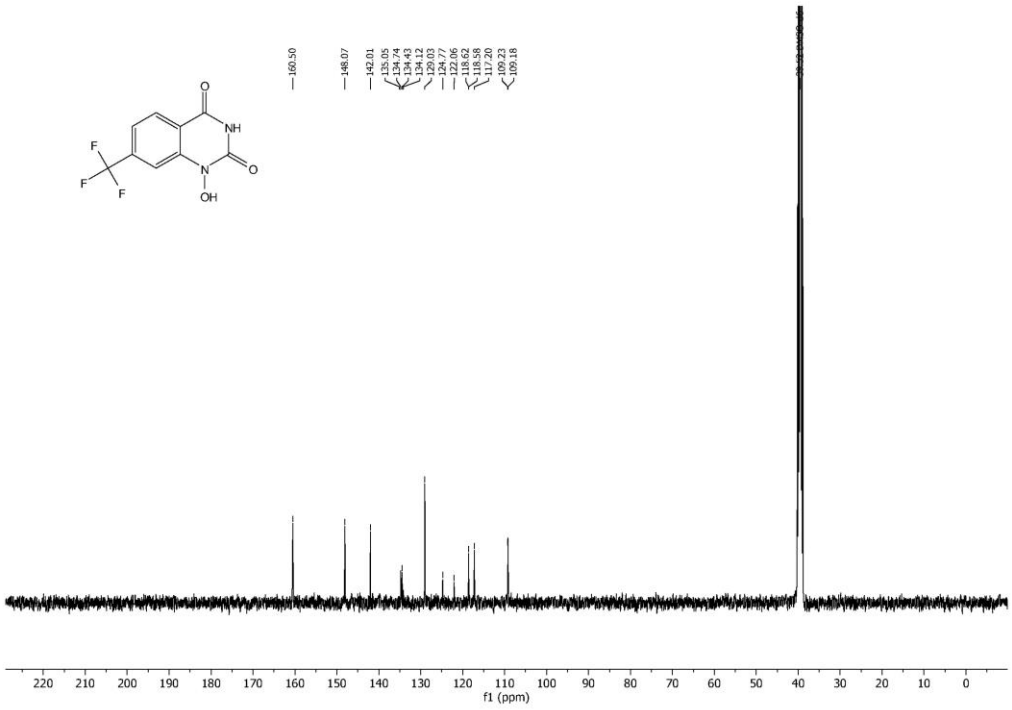
1*H*,3*H*-1-Hydroxyquinazoline-2,4-dione (8a)

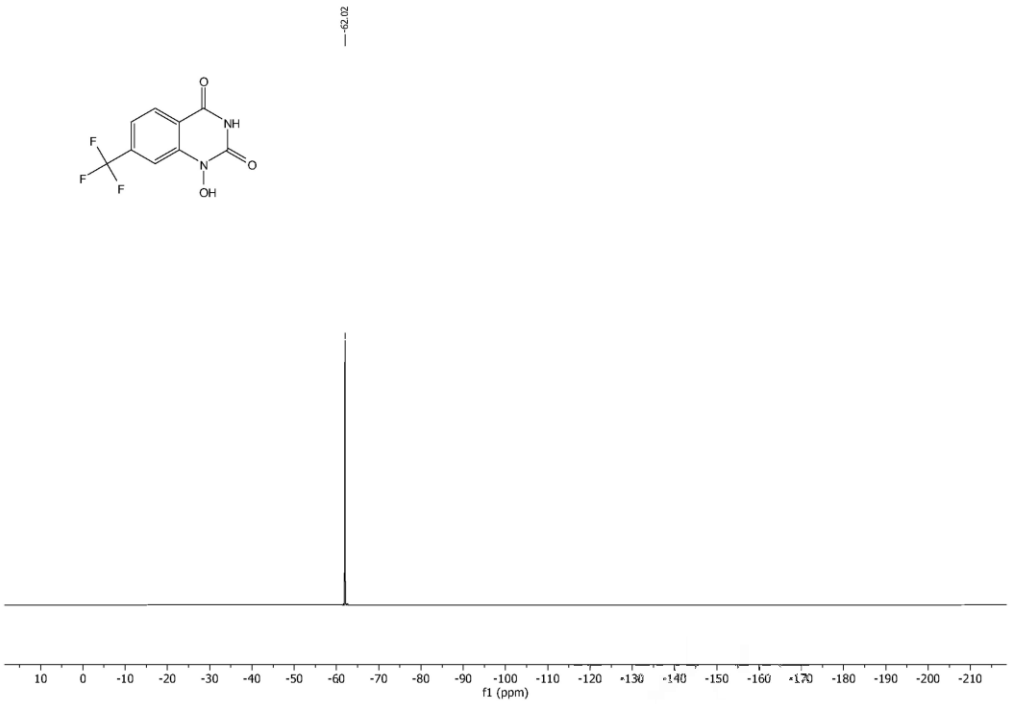




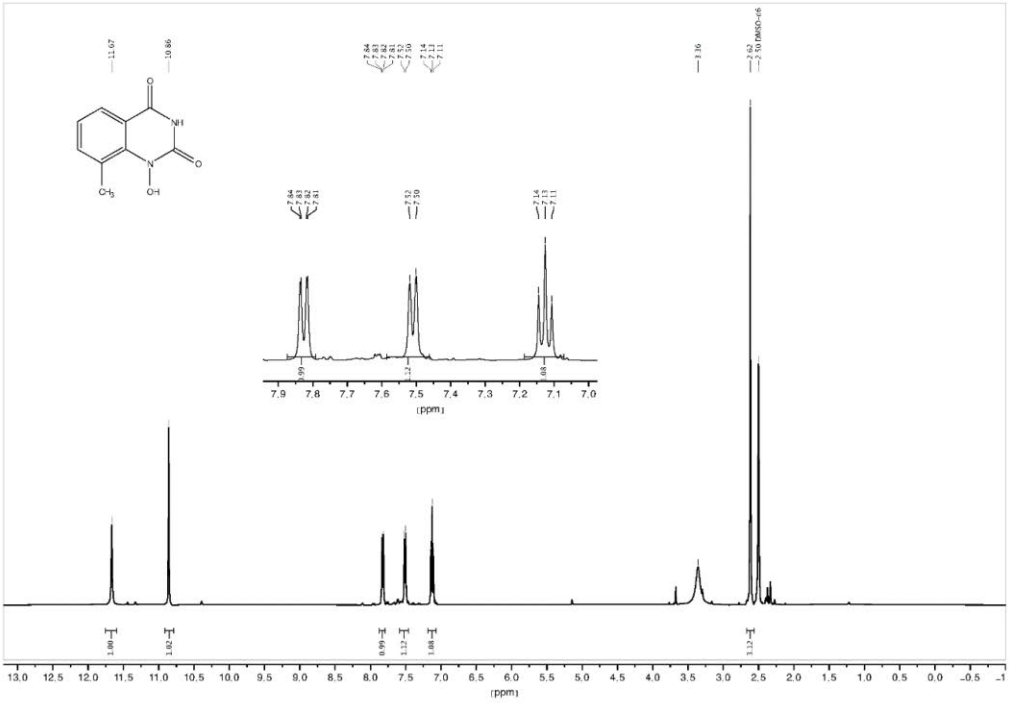
1*H*,3*H*-1-Hydroxy-7-(trifluoromethyl)quinazoline-2,4-dione (8b)

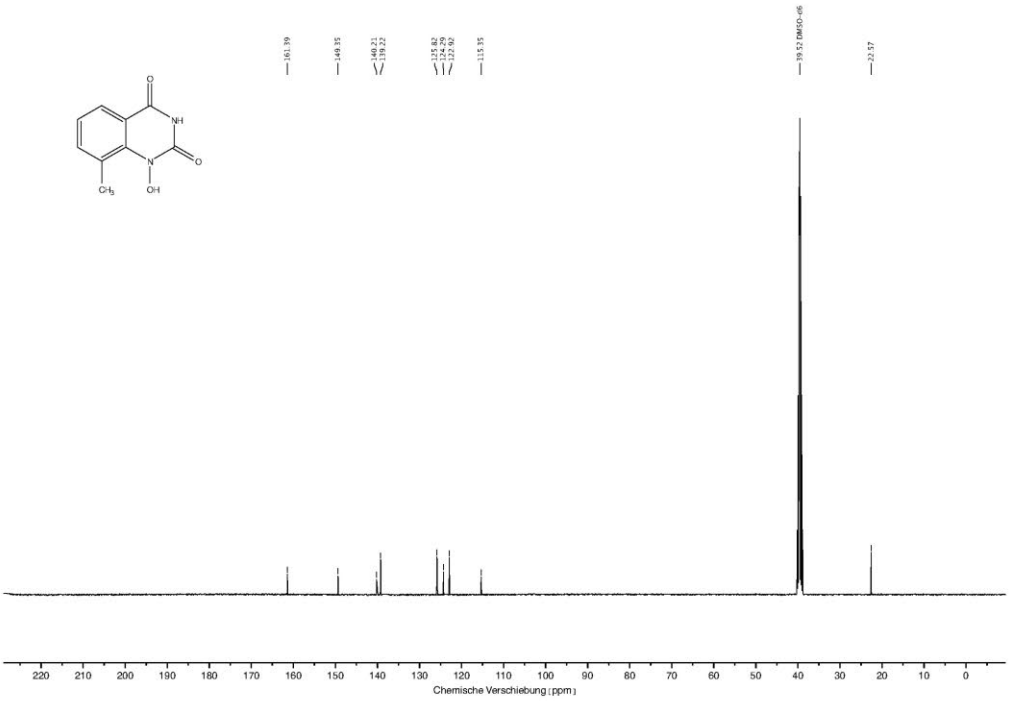




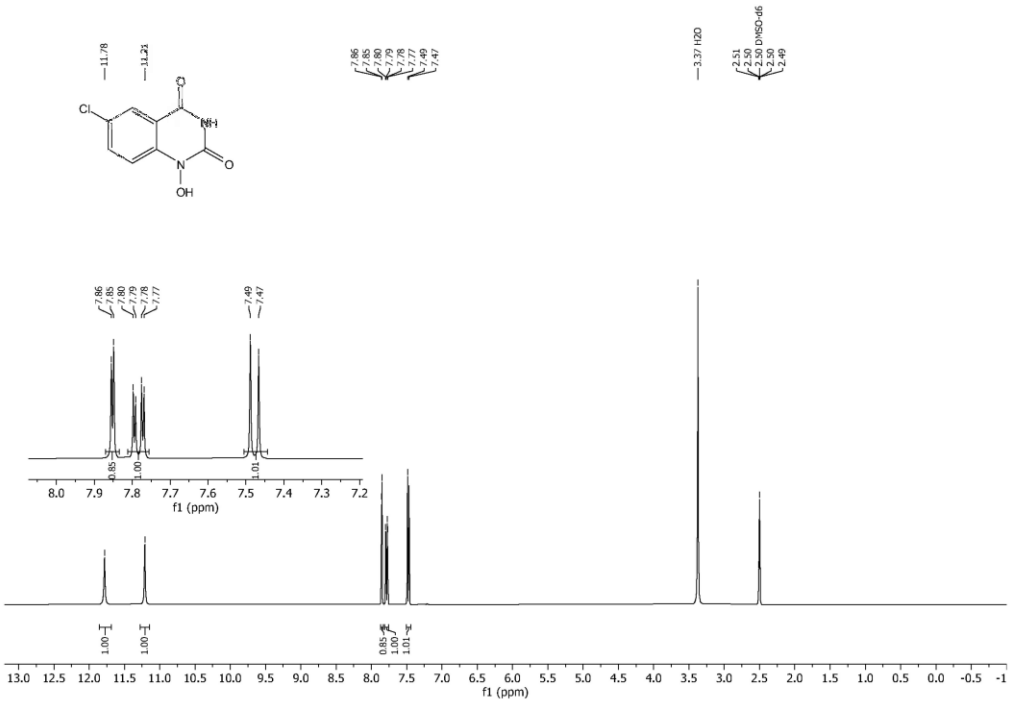

-62.02
O
NH
O
N
OH
F
F
F
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

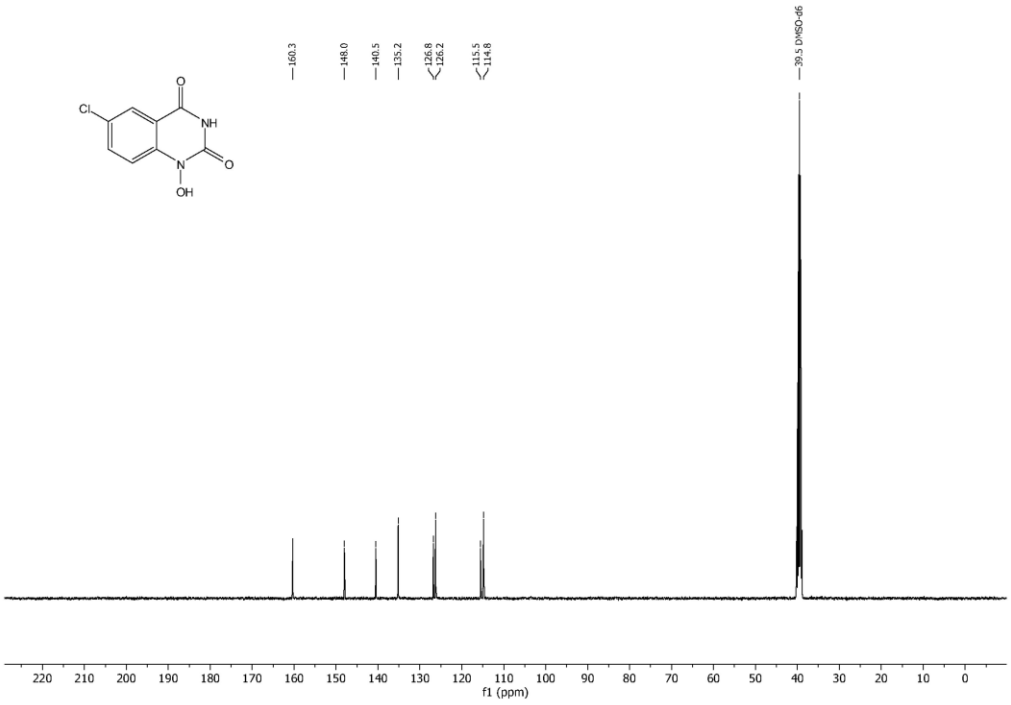
1*H*,3*H*-1-Hydroxy-8-methylquinazoline-2,4-dione (8c)





1*H*,3*H*-6-Chloro-1-hydroxyquinazoline-2,4-dione (8d)





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A-2.5 Supporting Information: Highly Selective Scalable Electrosynthesis of 4-Hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxides

Cell Reports Physical Science, Volume *5*

Supplemental information

Highly selective scalable electrosynthesis of 4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxides

Johannes Winter, Tobias Prenzel, Tom Wirtanen, María de Jesús Gálvez-Vázquez, Kamil Hofman, Dieter Schollmeyer, and Siegfried R. Waldvogel

1. Supplemental Experimental Procedures

General Information
If not stated otherwise, all reactions were performed under ambient conditions and chemicals in analytical grade were used as purchased without further purification. Cyclohexane and ethyl acetate were purchased in technical grade and purified by distillation under reduced pressure prior to use. Milli-Q® water was obtained using Simplicity® System (UV) (*Merck KGaA*, Darmstadt, Germany) for chromatography purposes. Anhydrous solvents were obtained from a solvent purification system SPS-5 (*M. Braun Incorporated*, Stratham, USA).

Chromatography
Thin layer chromatography was performed using DC silica gel 60 F254 on aluminum plates (*Merck KGaA,* Darmstadt, Germany). A UV lamp (λ = 254 nm, NU-4 KL, *Benda*, Wiesloch, Germany). Preparative flash column chromatography was performed on silica gel 60 M (0.040–0.063 mm, 12 g or 80 g, Macherey-Nagel GmbH & Co, Düren, Germany) using a Büchi Pure C-815 Flash (*Büchi-Labortechnik GmbH*, Essen, Germany). Reversed phase column chromatography of the different benzothiadiazine derivatives was performed on Puriflash® PF-30C18HP-F0080 (*Interchim SAS*, Montluçon Cedex, France) using a Sepacore® system with a Büchi Control Unit C-620, Büchi Pump Modules C-605, a UV detector Büchi UV photometer C-635, and Büchi Fraction Collector C-660 (*Büchi-Labortechnik GmbH*, Essen, Germany) using different mixtures of water (0.1% formic acid (*v/v*)) and acetonitrile as eluents.

High Resolution Mass Spectrometry
Mass spectra *via* electrospray-ionization (ESI+/ESI–) mass spectrometry were recorded using an Agilent 6545 QTOF-MS (*Agilent*, Santa Clara (CA), USA). Mass-charge ratios (*m/z*) were obtained for the characterized compounds.

X-ray Crystallography
The measurements of the crystal structures were carried out on a STOE IPDS-2T (*STOE & Cie GmbH*, Darmstadt, Germany) using a Mo source with graphite tube monochromator.

Gas Chromatography (GC-MS)
Gas chromatographic-mass spectra (GC-MS) measurements were carried out on a Shimadzu GC-2010 (*Shimadzu*, Kyoto, Japan) using a Hichrom HI-5 MS HI17-25-025-30 (*Avantor*™, Radnor, USA; length: 30 m, inner diameter: 0.25 mm, thickness of the stationary layer ((5%-phenyl)-polymethylsiloxane): 0.25 µm, pre-column: 5 m, carrier gas: helium) combined with a GCMS-QP2010 (*Shimadzu*, Kyoto, Japan) with 200 °C as ionization temperature. The used method "*medium*" starts at 50 °C with a heating rate of 15 °C min^{-1} up to 310 °C.

High Performance Liquid Chromatography (HPLC)
Analysis of crude reaction mixtures and purified products was performed using a modular system LC-20A *Prominence* (*Shimadzu Deutschland GmbH*, Duisburg, Germany), UV/VIS-detector SPD-20A/AV (*Shimadzu Deutschland GmbH*, Duisburg, Germany), and LCMS-2020 Single Quadrupole (*Shimadzu Deutschland GmbH*, Duisburg, Germany). Analytical separation was performed using an Eurospher II 100-5 C-18-Trennsäule (*Knauer Wissenschaftliche Geräte GmbH*, Berlin, Germany) column (length of 150 mm, diameter of 4 mm, pore size of 100 Å, particle size 5 µm). As eluents, acetonitrile, and water with 5% (*v/v*) acetonitrile and formic acid (0.1% (*v/v*)) were used. Given retention times were obtained at λ = 254 nm. Analytical HPLC measurements to analyze the enantiomeric excess of chiral compounds were performed on a 1260 Infinity II HPLC system (*Agilent*, Santa Clara (CA), USA) with a binary pump, a high-performance degasser, an automated injector, a multicolumn thermostat, and a diode array detector, using a CHIRALPAK™ AD-H column 250 mm x 4.6 mm with a particle size of 5 µm (*Daicel*, Illkirch Cedex, France). Ethanol (HPLC grade) and *n*-hexane (HPLC grade) were used as eluents. The measurements were performed at a column temperature of 40 °C and a flow rate of 1.0 mL min^{-1}. The data were analyzed with MestReNova (*Mestrelab Research*, Santiago de Compostela, Spain).

Microwave Synthesizer
Microwave reactions were performed using a Discover microwave reactor (*CEM Corporation*, Matthews (NC), USA) and 10 ml Pyrex Pressure Vessels (*CEM Corporation*, Matthews (NC), USA).

Optical Rotations:
Optical rotations were measured on a *Perkin-Elmer 241 polarimeter* (*Perkin-Elmer*, Rodgau, Germany) at λ = 589 nm (sodium D-line) using a 10 cm cell (1 mL). Specific rotations, $[\alpha]_D^{20}$, are reported in degree mL/(g·dm) at the specific temperature. Concentrations are given in grams per 100 mL of the specific solvent.

Nuclear Magnetic Resonance (NMR) Spectroscopy
Nuclear magnetic resonance experiments were performed using a nuclear magnetic resonance spectrometer Avance III HD300 (*Bruker*, Karlsruhe, Germany) ^{1}H NMR (300 MHz), ^{19}F NMR (282 MHz), Avance II 400 (*Bruker*, Karlsruhe, Germany) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz) and ^{31}P NMR (162 MHz) and Avance III 600 (*Bruker*, Karlsruhe, Germany) ^{1}H NMR (600 MHz), ^{13}C NMR (151 MHz). The spectra were recorded using deuterated solvents. To normalize the spectra obtained, reference was made to the existing solvent signal of non-deuterated fractions according to the data provided by Fulmer et al.:[1] $CDCl_3$ (^{1}H NMR: δ = 7.26 ppm, ^{13}C NMR: δ = 77.2 ppm), dichloromethane-d_2 (^{1}H NMR: δ = 5.32 ppm, ^{13}C NMR: δ =53.8 ppm), acetonitrile-d_3 (^{1}H NMR δ = 1.94 ppm, ^{13}C NMR: δ = 118.3 ppm), CD_3OD (^{1}H NMR δ = 3.31 ppm, ^{13}C NMR: δ =49.0 ppm), and DMSO-d_6 (^{1}H NMR δ = 2.50 ppm, ^{13}C NMR: δ =39.5 ppm). Besides ^{1}H, ^{13}C, ^{19}F NMR and ^{31}P NMR experiments, the 2D techniques ^{1}H,^{1}H COSY, ^{1}H,^{13}C HSQC, ^{1}H,^{13}C HMBC, and ^{1}H,^{1}H NOESY were used assisting to assign the signals. The following abbreviations were used to describe the signals: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), m (multiplet), q (quartet), sep (septet), ddd (doublet of doublets of doublets). The spectra obtained were evaluated with MestReNova 14.2.0-26256 (*Mestrelab Research S.L.*, Spain). ^{19}F NMR spectra were obtained with α-trifluorotoluene as external standard (δ = 63.9 ppm) and recorded without ^{1}H decoupling.

Cyclic Voltammetry (CV) Measurements
Cyclic voltammetry was performed using a PGSTAT204 potentiostat (*Metrohm AG*, Herisau, Switzerland) with a scan rate of 100 mV·s^{-1}. Working electrode: BDD electrode tip (2 mm diameter); counter electrode: glassy carbon rod; reference electrode: Ag/AgCl (*vs.* FcH/FcH^+ = ferrocene; saturated LiCl in ethanol, *Metrohm AG*, Herisau, Switzerland). 5 mM of the corresponding substrate dissolved in 0.5 M ammonium formate (97%, *Sigma Aldrich*, Darmstadt, Germany) was used. Trifluoroacetic acid (99.9%, *abcr GmbH*, Karlsruhe, Germany) was used in different concentrations from 1 M to 2.5 M or 0.5 M sulfuric acid (96%, *Fisher Scientific GmbH*, Schwerte, Germany). Prior to the CV measurements the electrolyte was purged with argon for 20–25 min. An argon atmosphere was kept flowing over the electrolyte during the measurements. The electrode potentials are reported with reference to the redox system ferrocene/ferrocenium (FcH/FcH^+).

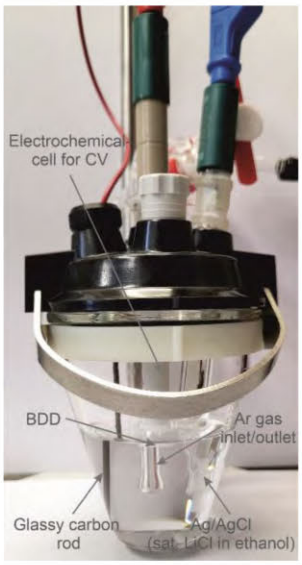


Figure S1: Electrochemical cell for cyclic voltammetry measurements.

Electrochemical Set-Up
Electrochemical reactions were carried out using a multichannel galvanostat HMP4040 (*Rohde & Schwarz*, München, Germany). The different cells used for screening or batch reactions are described below.

Electrode Materials
Electrode material, purity, and their supplier are listed in table S1. Boron-doped diamond (BDD) electrodes were treated prior to electrosynthesis in 20% aqueous sulfuric acid (10 $C \cdot cm^{-2}$) with current density of 10 $mA \cdot cm^{-2}$ by polarizing subsequently anodically and then cathodically. After the treatment, the cathode was rinsed with water, methanol, and dried.

Table S1: Electrode materials, purity, and their supplier.

Entry	Electrode Material	Purity	Supplier
1	Boron-doped diamond (DIACHEM™)	15 µm boron-doped diamond layer on silicon	*CONDIAS GmbH*, Itzehoe, Germany
2	Glassy carbon (Sigradur G)	-	*HTW*, Thierhaupten, Germany
3	Isostatic graphite (V2100)	-	*SGL Carbon*, Bonn, Germany

Screening Reactions
Teflon™ cells with a volume of 5 mL were used for the undivided set-up (figure S1, left). Divided Teflon™ screening cells with a volume of 7 mL were equipped with a glass frit or Nafion™ as separator material as shown (figure S1, right). Glass frits and Nafion™ used as separator materials were pre-treated in the corresponding electrolyte prior to use. Stirring bars were used during electrolysis in each cell. The described screening systems are commercially available as IKA Screening System Package (*IKA™ Werke GmbH & Co. KG*, Staufen, Germany).



Figure S2: Undivided screening set-up (left) and divided screening set-up (right).[2]

Scale-up Reactions
Scale-up experiments were performed in 10 mL, 80 mL, and 300 mL batch-type cells with a PTFE stopper and sleeve, electrodes, and electrode holders (figure S2). A TDK-Lambda Z+ series (*TDK-Lambda UK Limited*, Devon, United Kingdom) or a multichannel power supply HMP4040 (*Rohde & Schwarz*, München, Germany) were used as power sources. In the 10 mL electrolysis set-up glassy carbon and BDD electrodes with dimensions of 7 cm·1 cm were used. In the 80 mL electrolysis set-up glassy carbon and BDD electrodes with identical dimensions of 6 cm·2 cm were used. In the 300 mL electrolysis set-up glassy carbon and BDD electrodes with identical dimensions of 12 cm·4 cm were used.

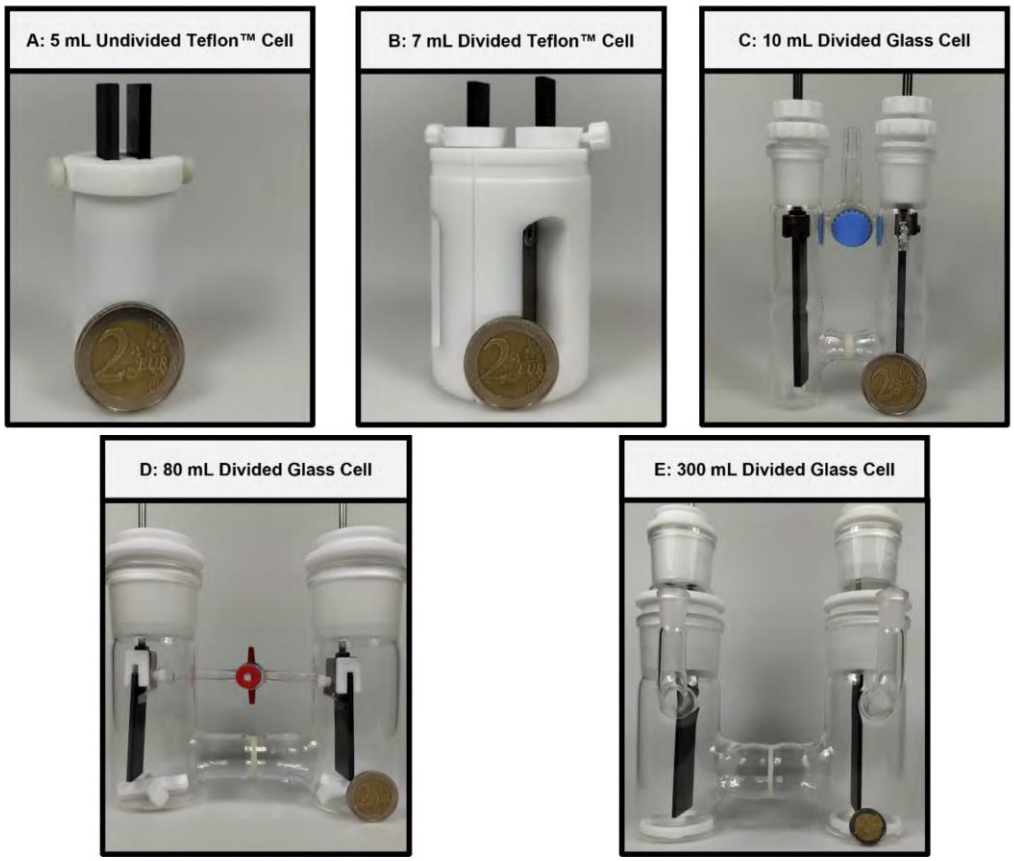
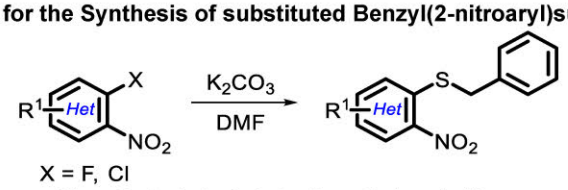


Figure S3: Different batch-type cells; size compared to a two euro coin (⌀ = 25.8 mm; 1.01 in): A - 5 mL undivided Teflon™ screening cell with glassy carbon and BDD electrodes; B - 7 mL divided Teflon™ screening cell with glassy carbon and BDD electrodes; C - 10 mL divided glass cell with glassy carbon and BDD electrodes; D - 80 mL divided glass cell with glassy carbon and BDD electrodes; E - 300 mL divided glass cell with glassy carbon and BDD electrodes.

2. General Protocols

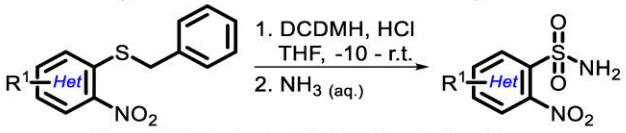
2.1. General Protocol for the Synthesis of substituted Benzyl(2-nitroaryl)sulfides (GPI)



Scheme S1: Synthesis of substituted benzyl(2-nitroaryl)sulfides.

Under argon atmosphere the corresponding 2-halo-1-nitroarene (1.0 eq.) and potassium carbonate (2.0 eq.) was stirred in DMF for 15 min. Benzyl mercaptan (1.0–1.3 eq.) was added at room temperature. After completion of the reaction the mixture was poured into water. The precipitates formed were collected and washed five times with 50 mL ethanol to obtain the purified product as solid.

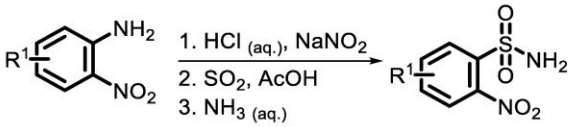
2.2. General Protocol for the Synthesis of substituted 2-Nitroarylsulfonamides (GPII)



Scheme S2: Synthesis of substituted 2-nitroarylsulfonamides.

The corresponding benzyl(2-nitroaryl)sulfide (1.0 eq.) was dissolved in THF and chilled below -5 °C. 5–15 mL concentrated hydrochloric acid (37% *w*:*v*) was added. 1,3-Dichloro-5,5-dimethylhydantoin (DCDMH, 2.1 eq.) was added as solid while the temperature was kept below -5 °C. After addition the mixture was stirred further below -5 °C for 2 h. The reaction mixture was neutralized with 150 mL aqueous 1 M sodium bicarbonate. The organic layer was separated and washed once with 50 mL brine. The solution was added dropwise to a concentrated ammonia solution (25% *w*:*v*) at 0 °C and stirred for additional 2 h. After completion of the reaction the solution was neutralized with concentrated hydrochloric acid (37% *w*:*v*) and extracted three times with 50 mL ethyl acetate. The combined organic fractions were washed once with 50 mL brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude products were crystallized from an appropriated solvent.

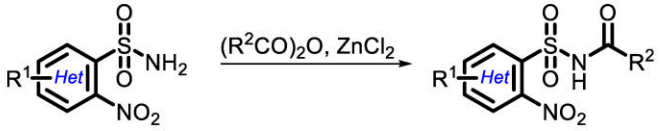
2.3. General Protocol for the Synthesis of substituted 2-Nitrobenzenesulfonamides (GPIII)



Scheme S3: Synthesis of substituted 2-nitrobenzenesulfonamides.

The corresponding aniline (1.0 eq.) was dissolved in the minimal amount of concentrated hydrochloric acid (37% *w*:*v*) and chilled below -5 °C. An aqueous 4 M sodium nitrite was added dropwise while the temperature was kept below -5 °C. After addition the reaction mixture was stirred for an additional 1 h. Copper(II) chloride (15 mol%) was added to an saturated solution of sulfur dioxide in glacial acetic acid. The freshly prepared diazonium salt solution was filtered, and the filtrate was added dropwise to the saturated solution of sulfur dioxide in glacial acetic acid while the temperature was kept below -5 °C. The precipitates were collected and added to a concentrated ammonia solution (25% *w*:*v*) at 0 °C and the reaction mixture was stirred for 2 h. After completion of the reaction the mixture was neutralized with hydrochloric acid (37% *w*:*v*) and extracted three times with 50 mL ethyl acetate. The combined organic fractions were washed once with 50 mL brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica).

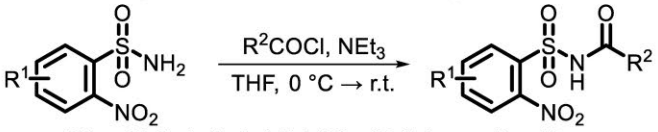
2.4. General Protocol for the Synthesis of substituted *N*-Acyl-2-nitroarylsulfonamides (GPIV)



Scheme S4: Synthesis of substituted *N*-acyl-2-nitrobenzensulfonamides.

Under argon atmosphere the corresponding 2-nitroarenelsulfonamide (1.0 eq.) was dissolved in acetic anhydride (5.0 eq) and zinc(II) chloride (10 mol%) was added. The reaction mixture was stirred at room temperature. After completion of the reaction the solution was added to 50 mL of water and stirred for 15 min. The aqueous solution was extracted three times with 50 mL ethyl acetate. The combined organic fractions were washed once with 50 mL brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was crystallized from an appropriated solvent or purified by column chromatography (silica).

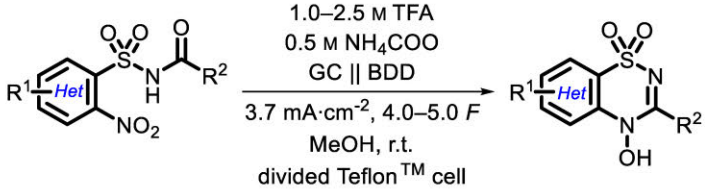
2.5. General Protocol for the Synthesis of substituted *N*-Acyl-2-nitrobenzensulfonamides (GPV)



Scheme S5: Synthesis of substituted *N*-acyl-2-nitrobenzensulfonamides.

Under argon atmosphere the corresponding 2-nitroarenesulfonamides (1.0 eq.) was dissolved in 70 mL anhydrous THF, triethylamine (2.0 eq.) was added, and the solution was cooled to 0 °C. The corresponding acid chloride (1.2 eq.) was diluted with 20 mL anhydrous THF and added dropwise to the cooled solution. After addition the reaction mixture was stirred starting at 0 °C slowly rising to room temperature for 24 h. After completion of the reaction the mixture was added to 50 mL of 1 M HCl. The aqueous layer was extracted three times with 50 mL ethyl acetate. The combined organic fractions were washed once with 50 mL brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was crystallized from an appropriated solvent or purified by column chromatography (silica).

2.6. General Protocol for the Electrochemical Synthesis of substituted 4-Hydroxybenzothiazine-1,1-dioxides using TFA as Additive (GPVI)



Scheme S6: Synthesis of substituted 4-hyroxybenzothiazine-1,1-dioxide.

7 mL divided Teflon™ screening cell: 0.15 mmol of the starting material was dissolved in 5 mL of 0.5 M ammonium formate in methanol in the cathodic compartment and 0.4–1.0 mL trifluoroacetic acid was added. The anodic compartment was equipped with 5.4–6.0 mL of 0.5 M ammonium formate solution in methanol. The anodic compartment was separated with a glass frit (Robu™ Por. 4, *ROBU Glasfilter-Geräte GmbH*, Hattert, Germany). The electrolysis was performed under constant current conditions (current density j = 3.7 mA·cm^{-2} for 65.1 C (4.5 F)). If the cyclo-condensation of the hydroxylamine intermediate was incomplete, the reaction mixture was further stirred at room temperature until completion (LC-MS). If necessary additional 7.2 C (0.5 F) were applied for full conversion of the starting material. If no cyclo-condensation was observed the solution of the cathodic compartment was treated in the microwave at 100 °C for 10 min (50 W) to complete the product formation. The reaction mixture was then diluted with methanol and the solvents were removed under reduced pressure. To remove residual trifluoroacetic acid the crude product was once co-evaporated with toluene. The crude product was purified with column chromatography (silica) or reverse phase column chromatography (C_{18}).

10 mL divided glass cell: Prior to use, both compartments of the cell were filled with 0.5 M ammonium formate in methanol to condition the glass frit. 0.30 mmol of the starting material was dissolved in 10 mL

of 0.5 M ammonium formate in methanol in the cathodic compartment and 0.8 mL trifluoroacetic acid was added. The anodic compartment was equipped with 10.8 mL of 0.5 M ammonium formate in methanol. The anodic compartment was separated with a glass frit (Robu™ Por. 4, *ROBU Glasfilter-Geräte GmbH*, Hattert, Germany). The electrolysis was performed under constant current conditions (current density j = 3.7 mA·cm^{-2} for 115.8 C (4.0 *F*)). If the cyclo-condensation of the hydroxylamine intermediate was incomplete, the reaction mixture was further stirred at room temperature until completion (LC-MS). If necessary additional 14.5 C (0.5 *F*) were applied for full conversion of the starting material. The reaction mixture was then diluted with methanol and the volatiles were removed under reduced pressure. To remove residual trifluoroacetic acid the crude product was once co-evaporated with toluene. The crude product was purified by reverse phase column chromatography (C_{18}).

80 mL divided glass cell: Prior to use both compartments of the cell were filled with 0.5 M ammonium formate solution in methanol to condition the glass frit. 2.4 mmol of the starting material was dissolved in 80 mL of 0.5 M ammonium formate in methanol in the cathodic compartment and 6 mL trifluoroacetic acid was added. The anodic compartment was equipped with 86 mL of 0.5 M ammonium formate solution in methanol. The anodic compartment was separated with a glass frit (Robu™ Por. 4, *ROBU Glasfilter-Geräte GmbH*, Hattert, Germany). The electrolysis was performed under constant current conditions (current density j = 3.7 mA·cm^{-2} for 926.3 C (4.0 *F*)). If the cyclo-condensation of the hydroxylamine intermediate was incomplete, the reaction mixture was further stirred at room temperature until completion (LC-MS). If necessary additional 115.8 C (0.5 *F*) were applied for full conversion of the starting material. The reaction mixture was then diluted with methanol and the volatiles were removed under reduced pressure. To remove residual trifluoroacetic acid the crude product was once co-evaporated with toluene. The residue was dissolved in 100 mL ethyl acetate and 100 mL water. The aqueous layer was extracted three times with 100 mL ethyl acetate. The combined organic fractions were washed once with 100 mL brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. The crude product was purified by reverse phase column chromatography (C_{18}).
300 mL divided glass cell: Prior to use both compartments of the cell were filled with 0.5 M ammonium formate in methanol to condition the glass frit. 9.0 mmol or 18.0 mmol of the starting material was dissolved in 300 mL of 0.5 M ammonium formate in methanol in the cathodic compartment and 23 mL trifluoroacetic acid was added. The anodic compartment was equipped with 323 mL of 0.5 M ammonium formate in methanol. The anodic compartment was separated with a glass frit (Robu™ Por. 4, *ROBU Glasfilter-Geräte GmbH*, Hattert, Germany). The electrolysis was performed under constant current conditions (current density j = 3.7 mA·cm^{-2} for 3473.5 C or 6949.9 C (4.0 *F*)). If the cyclo-condensation of the hydroxylamine intermediate was incomplete, the reaction mixture was further stirred at room temperature until completion (LC-MS). If necessary additional 434.2 or 868.4 C (0.5 *F*) were applied for full conversion of the starting material. The reaction mixture was then diluted with methanol and the volatiles were removed under reduced pressure. To remove residual trifluoroacetic acid the crude product was once co-evaporated with toluene. The residue was dissolved in 300 mL ethyl acetate and 300 mL water. The aqueous layer was extracted three times with 300 mL ethyl acetate. The combined organic fractions were washed once with 300 mL brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified by reverse phase column chromatography (C_{18}). The crude product was purified by filtration over silica and crystallization from ethanol.

For the scale-up experiment with portion wise addition of substrate, 9.0 mmol of the starting material was added to the electrolysis cell and 1736.7 C (2 *F*) were initially applied. Subsequently, 4.5 mmol of the substrate was added and further 1736.7 C (2 *F*) were applied. Finally, further 4.5 mmol of the substrate was added and 3820.6 C (4.2 *F*) were applied until full conversion of the starting material.

2.7. General Protocol for the Electrochemical Synthesis of substituted 4-Hydroxybenzothiazine 1,1-dioxides using Sulfuric Acid as Additive (GPVII)

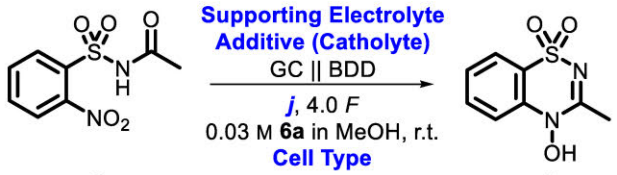


Scheme S7: Synthesis of substituted 4-hydroxy-benzothiazine-1,1-dioxide.

7 mL divided Teflon™ screening cell: 0.15 mmol of the starting material was dissolved in 5.0 mL of 0.5 M sulfuric acid in methanol in the cathodic compartment. The anodic compartment was equipped with 5.0 mL of 0.5 M sulfuric acid in methanol. The anodic compartment was separated with a glass frit (Robu®, Por. 4). The electrolysis was performed under constant current conditions (current density j = 3.7 mA·cm^{-2} for 65.1 C (4.5 F)). If the cyclo-condensation of the hydroxylamine intermediate was incomplete, the reaction mixture was further stirred at room temperature until completion (LC-MS). If necessary additional 7.2 C (0.5 F) were applied for full conversion of the starting material. The reaction mixture was then diluted with 10 mL of water. The aqueous layer was extracted twice with 20 mL of ethyl acetate. The combined organic fractions were washed once with 15 mL brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude product was purified with reverse phase column chromatography (C_{18}).

3. Optimization of the Electrolytic Conditions

Table S2: Optimization of the electrolytic reaction conditions for the synthesis of 4*H*-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7a).



6a **7a**

Entry	Supporting Electrolyte	Additive (Catholyte)	Cell Type	Current Density j [mA·cm^{-2}]	Yield[a] [%]
1	0.5 M H_2SO_4	-	undivided	8.2	36
2	0.5 M H_2SO_4	-	divided	2.0	71
3	0.5 M H_2SO_4	-	divided	3.7	52
4	0.5 M H_2SO_4	-	divided	5.2	76
5	0.5 M H_2SO_4	-	divided	10.4	78
6	0.5 M NH_4HCOO	1.0 M TFA	divided	5.2	85
7	0.5 M NH_4HCOO	1.0 M TFA	divided	3.7	97[b]
8	0.5 M NH_4HCOO	1.0 M TFA	divided	3.7	65[d]
9	0.5 M NH_4HCOO	-	divided	5.2	0
10	0.5 M HCOOH	0.5 M TFA[c]	divided	3.7	74
11	0.5 M HCOOH	1.0 M TFA[c]	divided	3.7	81
12	0.4 M NH_4HCOO	1.0 M TFA	divided	3.7	88
13	0.5 M NH_4HCOO	1.0 M MSA	divided	3.7	64
14	0.4 M NH_4HCOO	1.0 M MSA	divided	3.7	65
15	0.5 M HCOOH	1.0 M MSA	divided	3.7	61
16	0.5 M NH_4HCOO	1.0 M TFA	divided	8.2	79
17	0.5 M NH_4HCOO	1.0 M TFA	divided	10.0	67
18	0.5 M NH_4HCOO	1.0 M TFA	divided	20.0	53
19	0.5 M NH_4HCOO	1.0 M TFA	divided	30.0	39
20	0.5 M NH_4HCOO	1.0 M HCOOH	divided	3.7	0
21	0.5 M NH_4HCOO	1.0 M AcOH	divided	3.7	0

[a]Yield determined by ^{1}H NMR, internal standard: 1,3,5-Trimethoxybenzene; [b]Isolated yield; [c]Terminal voltage = 32 V; [d]Substrate concentration: 0.06 M.TFA = Trifluoroacetic acid; MSA = Methanesulfonic acid

Table S3: Comparison of different carbon-based cathode materials in the 0.15 mmol and 0.30 mmol scale for the synthesis of 4*H*-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7a).

Entry	Cathode	Yield[a] 0.15 mmol Scale	Yield[a] 0.30 mmol Scale
1	BDD	30.9 mg (0.146 mmol, 97%)	60.6 mg (0.286 mmol, 95%)
2	Glassy Carbon	28.6 mg (0.135 mmol, 90%)	59.3 mg (0.279 mmol, 93%)
3	Graphite	22.6 mg (0.106 mmol, 71%)	33.6 mg (0.158 mmol, 53%)

[a]Isolated yield.

4. Studies on the Conventional Oxidation of 4*H*-3-Methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide using Literature known Procedures

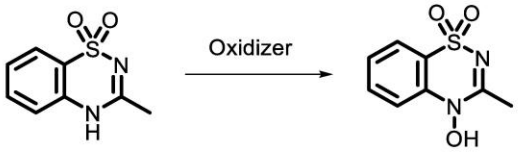
Oxidative Protocol with *m*CPBA[3]
4*H*-3-Methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (98.3 mg, 0.5 mmol, 1.0 eq.) was dissolved in 15 mL dichloromethane and cooled to 0 °C. *meta*-Chloroperbenzoic acid 75 weight% water (156.3 mg, 0.7 mmol, 1.4 eq.) was added at 0 °C. The reaction mixture was slowly brought to room temperature and stirred for 24 h. After 24 h nor conversion of the starting material neither product formation was detected by LC-MS analysis.

Oxidative Protocol with PODIC[4]
4*H*-3-Methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (98.1 mg, 0.5 mmol, 1.0 eq.) was dissolved in 10 mL methanol and 0.5 mL (5 vol%) acetonitrile was added. 10 mL (1.5 mmol, 3.0 eq.) freshly prepared 0.15 M PODIC (aqueous) was added and the reaction mixture was stirred at room temperature (set-up and procedure for the preparation of the PODIC solution reported in literature).[4] After 24 h nor conversion of the starting material neither product formation was detected by LC-MS analysis.

Oxidative Protocol with Peroxyacetic acid[5]
4*H*-3-Methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (98.1 mg, 0.5 mmol, 1.0 eq.) was dissolved in 10 mL glacial acetic acid and 2 mL peroxyacetic acid (30% *w*/*v*) was added. The resulting mixture was stirred at 70 °C. After 24 h nor conversion of the starting material neiher product formation was detected by LC-MS analysis.

Oxidative Protocol with Oxone™ [6]
4*H*-3-Methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (98.1 mg, 0.5 mmol, 1.0 eq.) was dissolved in 2 mL methanol and 8 mL of water. Concentrated sulfuric acid was added until pH ≈ 2 was reached. Oxone™ (201.5 mg, 0.7 mmol, 1.4 eq.) was added and the solution was stirred at 6 °C. After 24 h nor conversion of the starting material neither product formation was detected by LC-MS analysis.

Table S4: Oxidation of **8a** by conventional methods to synthesize 4*H*-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (**7a**).



8a **7a**

Entry	Oxidizer	Yield[a] [%]
1	*meta*-Chloroperoxybenzoic acid (*m*CPBA)[3]	0
2	Peroxodicarbonate (PODIC)[4]	0
3	Peroxyacetic acid[5]	0
4	Oxone™ [6]	0

[a]According to LC-MS analysis.

5. Scale-up of the Electrochemical Reductive Synthesis of 4*H*-4-Hydroxy-3-methylbenzo[e]-1,2,4-thiadiazine-1,1-dioxide

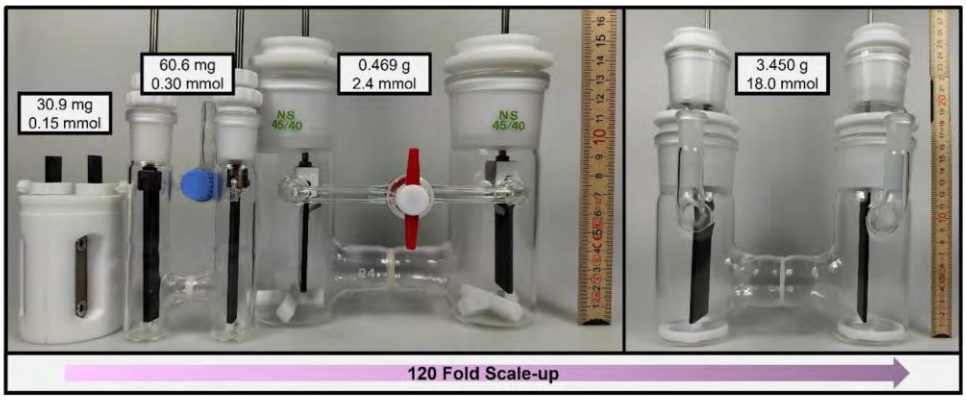


Figure S4: Different batch-type divided glass cells used for the scale-up of the reaction. The meter depicted on the right is in cm.

Table S5: Scale-up of the synthesis of 4*H*-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (**7a**) and 4*H*-7-chloro-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (**7af**, 4-Hydroxydiazoxide).



6a (R = H)
6af (R = Cl)

7a (R = H)
7af (R = Cl)

Cell Volume [mL]	Scale [mmol]	Purification Method	Scale-up of the electro-reduction of **6a** to **7a**		Scale-up of the electro-reduction of **6af** to **7af**	
			Applied Charge	Yield[a] [%] **7a**	Applied Charge	Yield[a] [%] **7af**
7	0.15	Reverse phase column	57.9 C (4.0 *F*)	30.9 mg (0.146 mmol, 97%)	65.1 C (4.5 *F*)	31.1 mg (0.126 mmol , 84%)
10	0.30	Reverse phase column	115.8 C (4.1 *F*)	60.6 mg (0.286 mmol, 95%)		-
80	2.4	Reverse phase column	1042 C (4.5 *F*)	469 mg (2.21 mmol, 92%)	1042 C (4.5 *F*)	493 mg (2.00 mmol, 83%)
300	9.0	Reverse phase column	3907 C (4.5 *F*)	1.720 g (8.15 mmol, 90%)		-
300[b]	9.0	Reverse phase column	3647 C (4.2 *F*)	1.830 g (8.62 mmol, 96%)	3647 C (4.2 *F*)	-
	9.0	Filtration over silica and crystallization	3647 C (4.2 *F*)	1.760 g (8.29 mmol, 92%)		2.008 g (8.14 mmol, 91%)
	18.0[c]	Filtration over silica and crystallization	7294 C (4.2 *F*)	3.420 g (16.12 mmol, 90%)		-
	18.0[d]	Filtration over silica and crystallization	7294 C (4.2 *F*)	3.450 g (16.30 mmol, 91%)		-

[a]Isolated yield; [b]Argon atmosphere; [c]Substrate concentration: 0.06 M; [d]Portion wise addition of substrate.

6. CV Studies

For mechanistic studies on the selectivity of the nitro reduction, cyclic voltammograms of the starting materials **6a** and **6af** were measured with and without TFA. The electrochemical stability of the products **7a** and **7af** were investigated by CV measurements with and without TFA. The influence of different additives (TFA or sulfuric acid) and the influence of different TFA concentrations were investigated using the starting material **6u**, which shows no cyclo-condensation at ambient conditions and only upon microwave-assisted treatment.

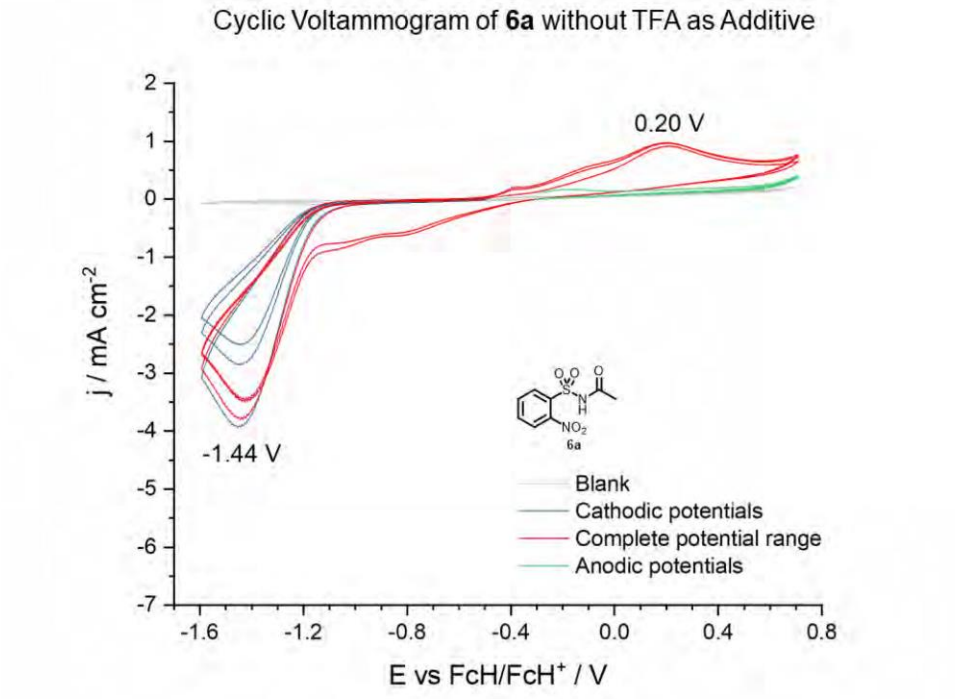


Figure S5: Cyclic voltammogram of **6a** without TFA as additive.

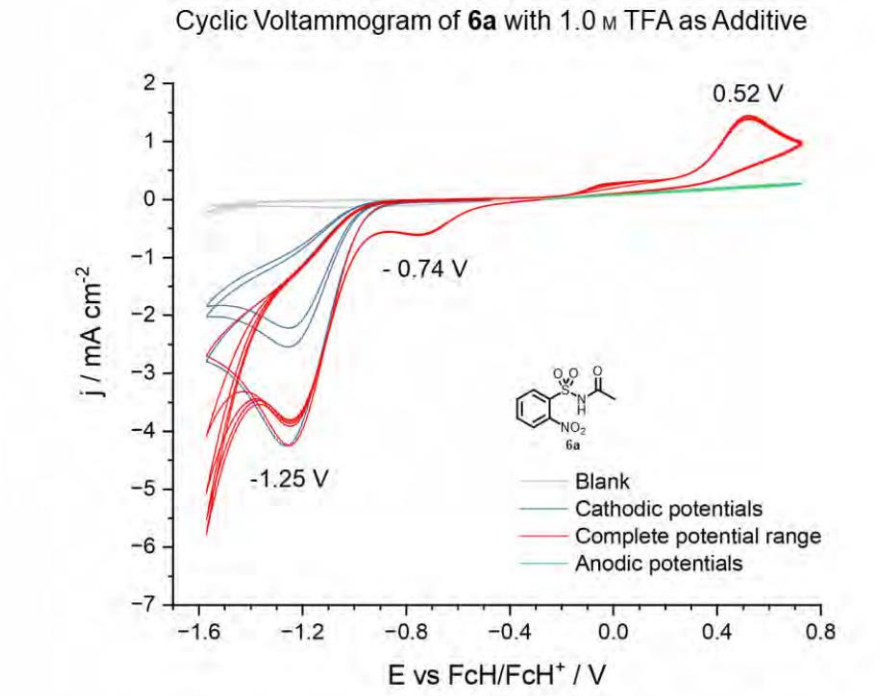


Figure S6: Cyclic voltammogram of **6a** with 1.0 M TFA as additive.

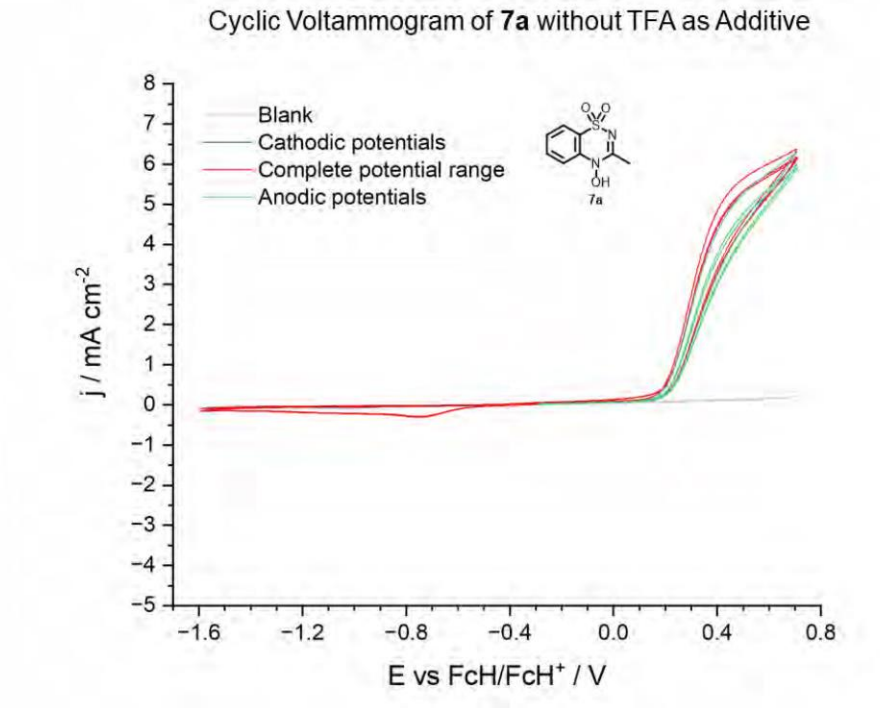


Figure S7: Cyclic voltammogram of **7a** without TFA as additive.

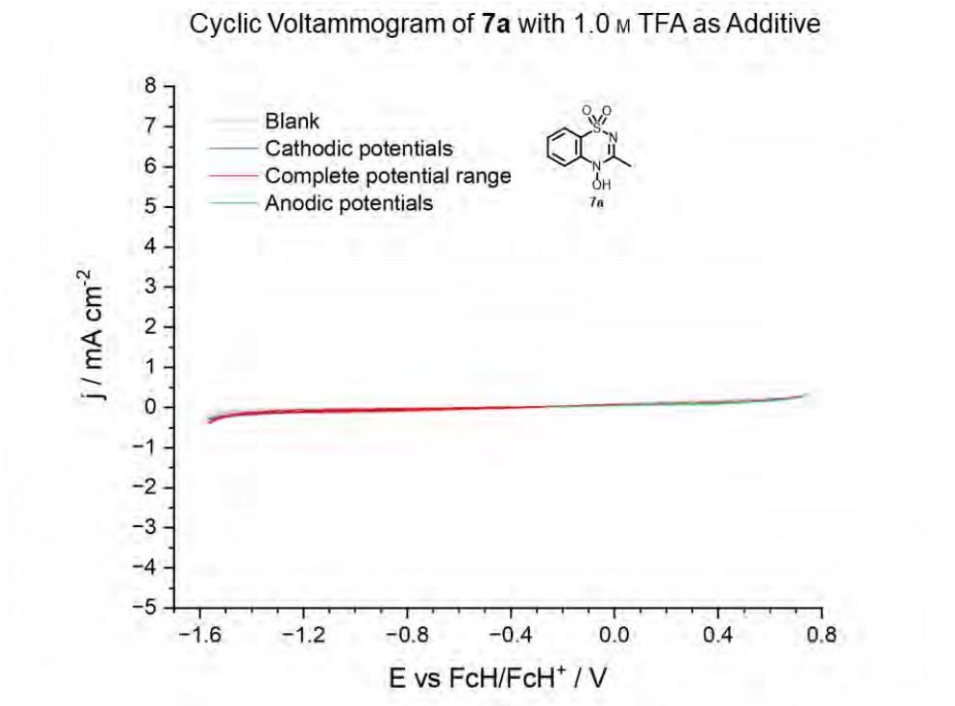


Figure S8: Cyclic voltammogram of **7a** with 1.0 M TFA as additive.

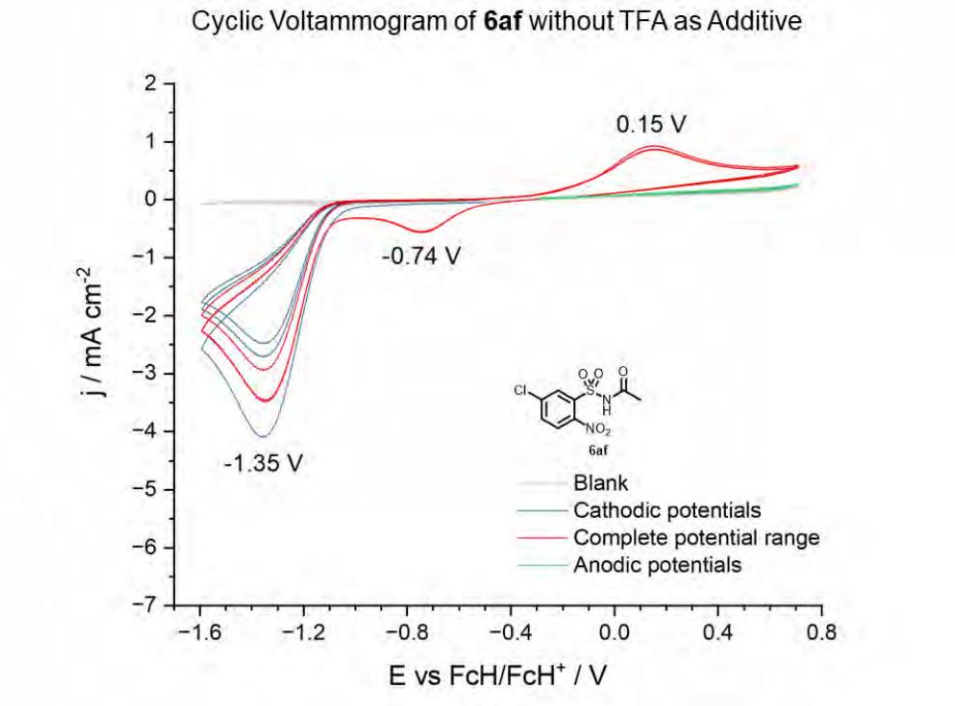


Figure S9: Cyclic voltammogram of **6au** without TFA as additive.

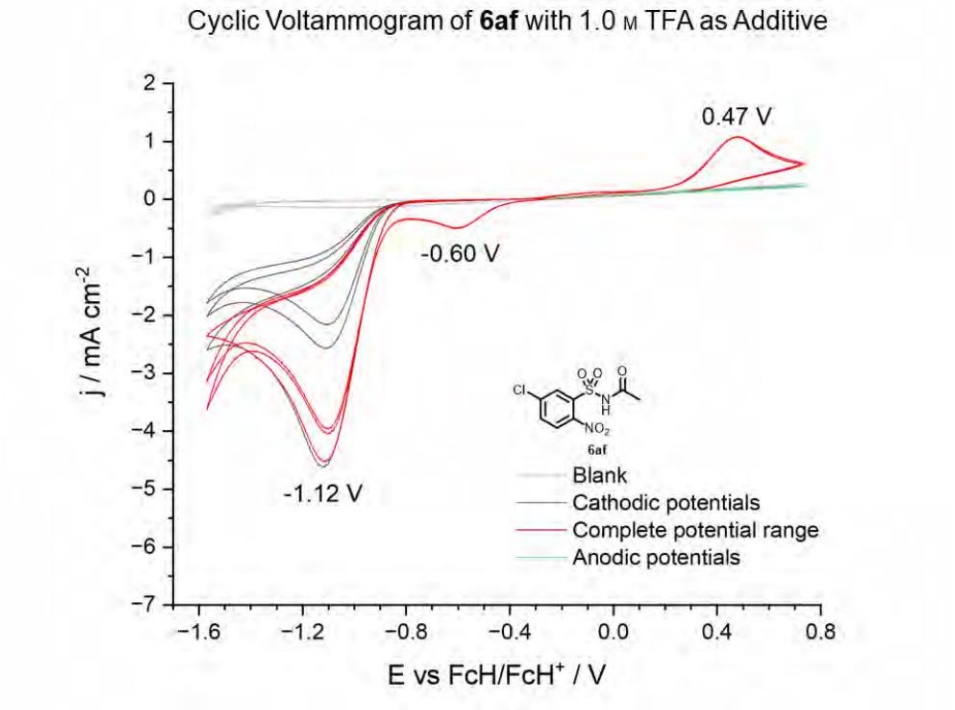


Figure S10: Cyclic voltammogram of **6au** with 1.0 M TFA as additive.

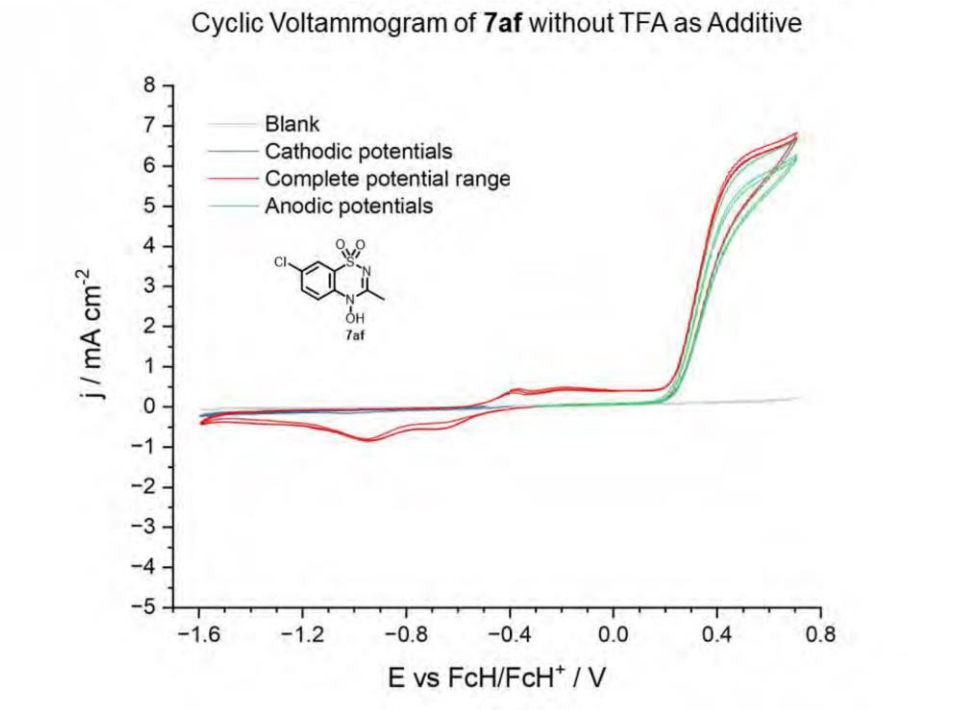


Figure S11: Cyclic voltammogram of **7au** without TFA as additive.

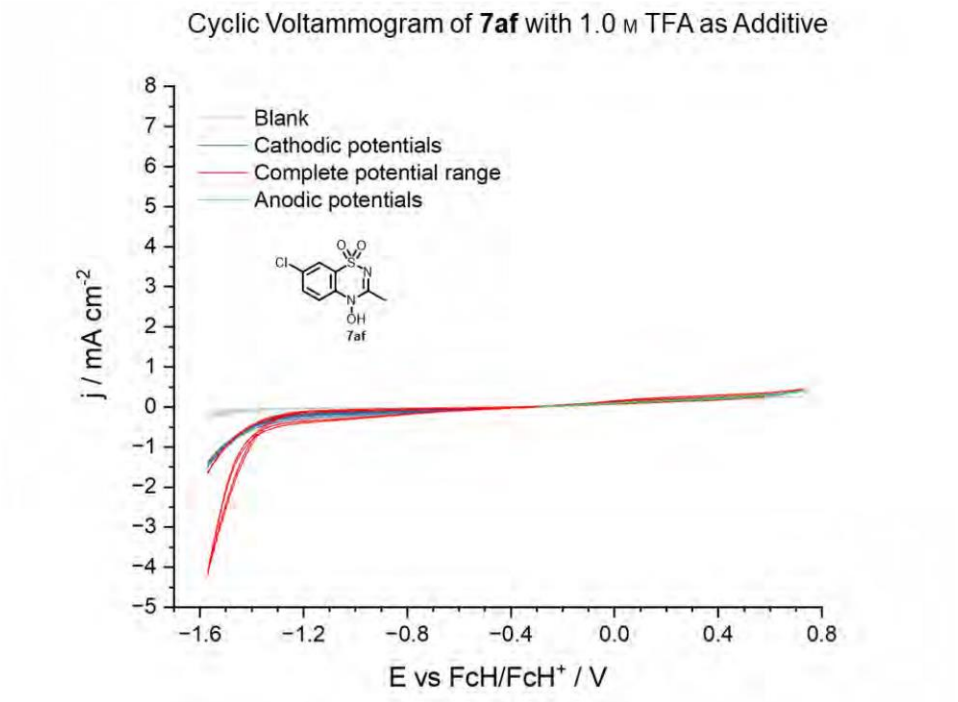


Figure S12: Cyclic voltammogram of **7au** with 1.0 M TFA as additive.

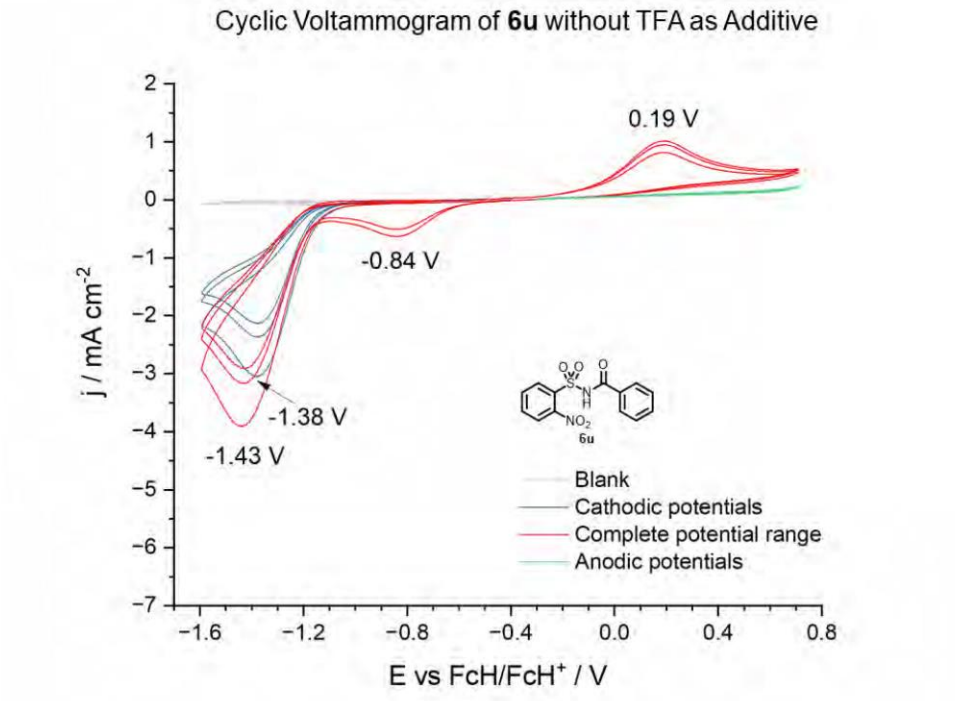


Figure S13: Cyclic voltammogram of **6u** without TFA as additive.

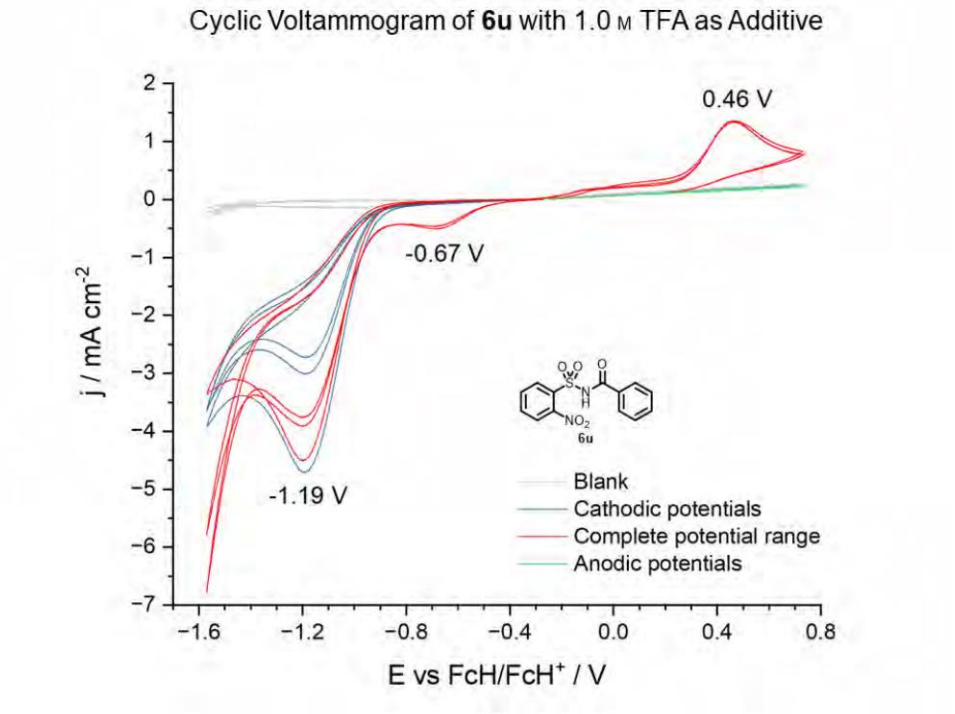


Figure S14: Cyclic voltammogram of **6u** with 1.0 M TFA as additive.

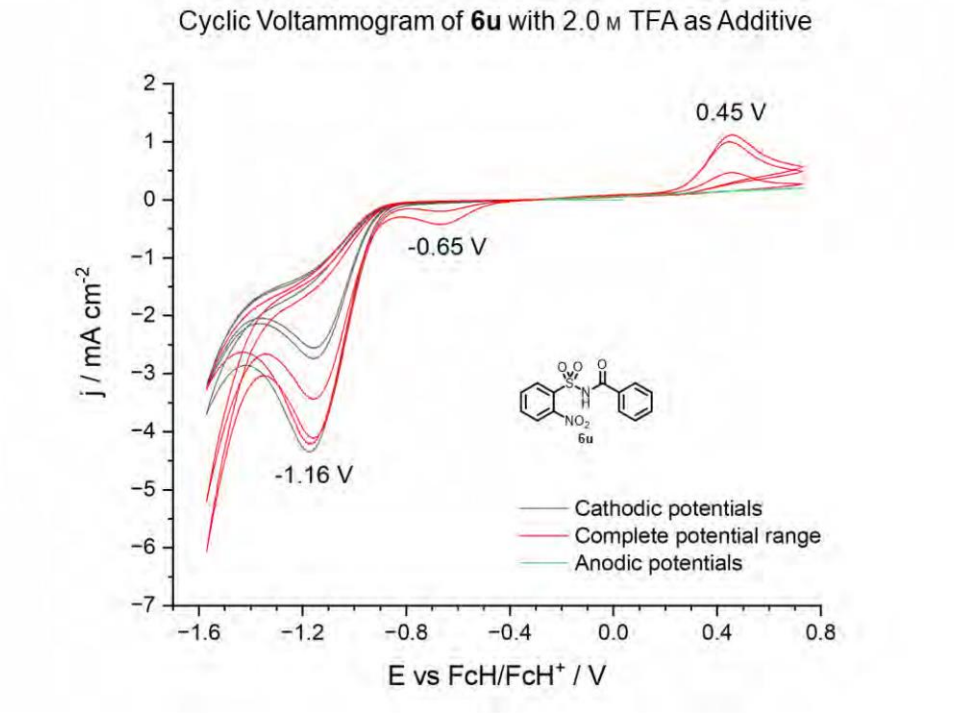


Figure S15: Cyclic voltammogram of **6u** with 2.0 M TFA as additive.

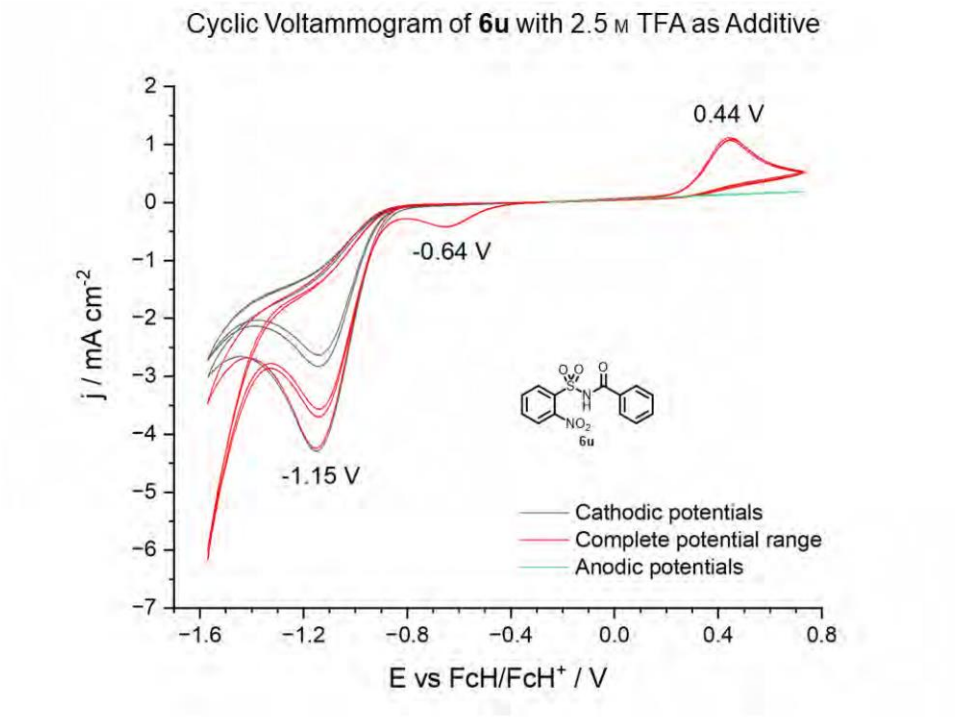


Figure S16: Cyclic voltammogram of **6u** with 2.5 M TFA as additive.

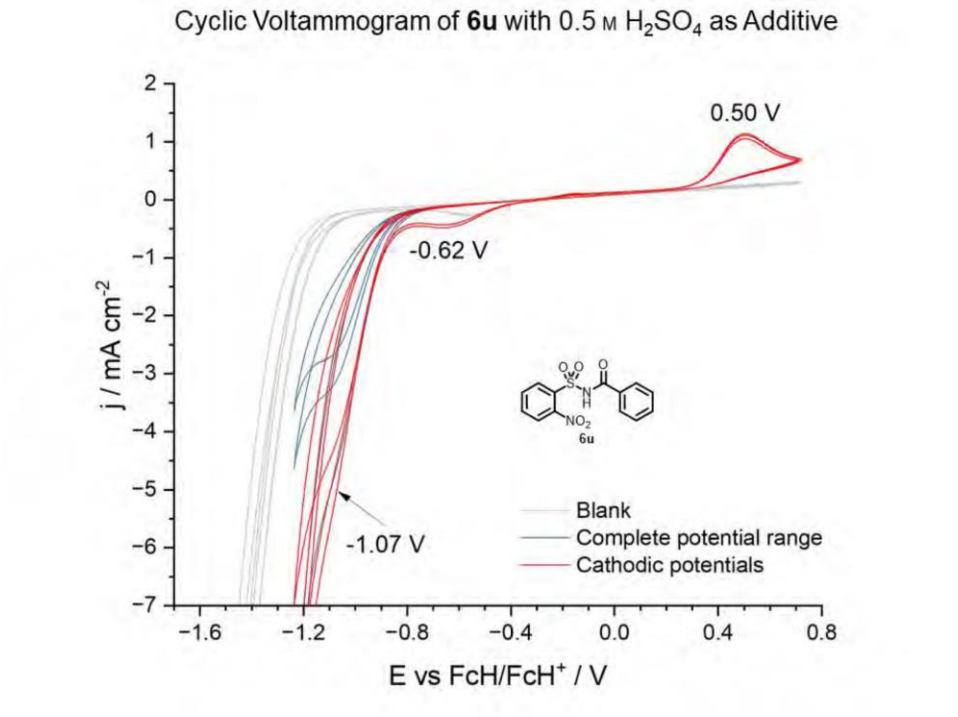
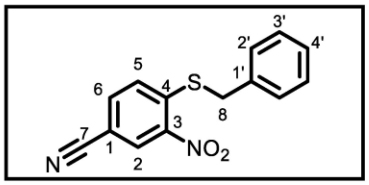


Figure S17: Cyclic voltammogram of **6u** with 0.5 M sulfuric acid as additive.

7. Preparation of Products and Analytical Data

7.1. Benzyl(2-nitroaryl)sulfides (11–22)

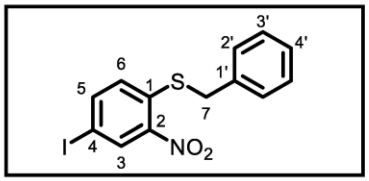
4-(Benzylsulfanyl)-3-nitrobenzonitrile (11)



According to general protocol **GPI**, 4-fluoro-3-nitrobenzonitrile (4.99 g, 30 mmol, 1.0 eq.) and benzyl mercaptan (5.59 g, 45 mmol, 1.5 eq.) were reacted. 7.438 g (27.52 mmol, 92%) of the product was obtained as a yellow solid after washing the solids with ethanol.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 8.70 (d, 1H, *J* = 1.8 Hz, *H*-2), 8.12 (dd, 1H, *J* = 8.5 Hz, 1.8 Hz, *H*-6), 7.90 (d, 1H, *J* = 8.5 Hz, *H*-5), 7.48 – 7.44 (m, 2H, *H*-2'), 7.40 – 7.27 (m, 3H, *H*-3', *H*-4'), 4.46 (s, 2H, *H*-8).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 145.2, 143.7, 136.7, 135.3, 130.5, 129.8, 129.2, 128.9, 128.2, 117.5, 108.0, 36.5.
HR-MS (ESI+): *m/z* for $C_{14}H_{10}N_2O_2S+Na^+$, $[M+Na]^+$ calculated: 293.0355; found: 293.0348.

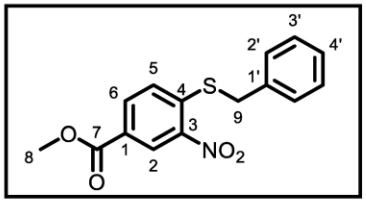
Benzyl(4-iodo-2-nitrophenyl)sulfide (12)



According to general protocol **GPI**, 1-fluoro-4-iodo-2-nitrobenzene (13.35 g, 50.0 mmol, 1.0 eq.) and benzyl mercaptan (7.1 mL, 60.0 mmol, 1.2 eq.) were reacted. 18.274 g (49.23 mmol, quant.) of the product was obtained as a yellow solid after washing the solids with ethanol.

^{1}H NMR (400 MHz, CD$_3$CN) δ [ppm]: 8.44 (d, 1H *J* = 2.0 Hz, *H*-3), 7.90 (dd, *J* = 8.6 Hz, 2.0 Hz, *H*-5), 7.45 – 7.40 (m, 2H, *H*-2'), 7.39 – 7.27 (m, 5H, *H*-6, *H*-3', *H*-4'), 4.26 (s, 2H, *H*-7).
^{13}C NMR (101 MHz, CD$_3$CN) δ [ppm]: 147.3, 143.2, 138.1, 136.4, 135.1, 130.2, 130.1, 129.8, 128.7, 88.0, 37.7.
HR-MS (ESI+): *m/z* for $C_{13}H_{10}INO_2S+Na^+$, $[M+Na]^+$ calculated: 393.9369; found: 393.9365.

Methyl 4-(benzylsulfanyl)-3-nitrobenzoate (13)

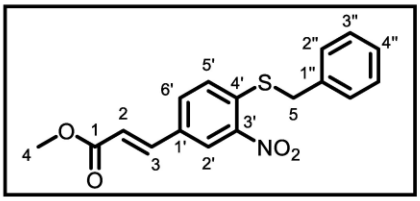


According to general protocol **GPI**, methyl 4-chloro-3-nitrobenzoate (16.20 g, 75.0 mmol, 1.0 eq.) and benzyl mercaptan (9.7 mL, 82.5 mmol, 1.1 eq.) were reacted. 17.686 g (58.31 mmol, 78%) of the product was obtained as a yellow solid after washing the solids with ethanol.

^{1}H NMR (400 MHz, CDCl$_3$) δ [ppm]: 8.86 – 8.81 (m, 1H, *H*-2), 8.12 (dd, 1H, *J* = 8.5 Hz, 1.9 Hz, *H*-6), 7.51 (d, 1H, *J* = 8.5 Hz, *H*-5), 7.45 – 7.40 (m, 2H, *H*-2'), 7.38 – 7.27 (m, 3H, *H*-3', *H*-4'), 4.24 (s, 2H, *H*-9), 3.94 (s, 3H, *H*-8).
^{13}C NMR (101 MHz, CDCl$_3$) δ [ppm]: 165.0, 145.1, 144.0, 134.3, 133.7, 129.2, 129.1, 128.1, 127.4, 126.8, 126.6, 52.7, 37.7.
HR-MS (ESI+): *m/z* for $C_{15}H_{13}NO_4S+Na^+$, $[M+Na]^+$ calculated: 326.0457; found: 326.0452.

The spectroscopic data are in accordance with those reported in the literature.[7]

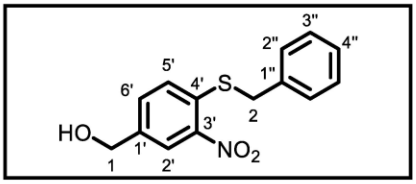
Methyl (*E*)-(4-(benzylsulfanyl)-3-nitrocinnamate (14)



According to general protocol **GPI**, methyl (*E*)-4-chloro-3-nitrocinnamate (4.83 g, 20.0 mmol, 1.0 eq.) and benzyl mercaptan (2.6 mL, 22.0 mmol, 1.1 eq.) were reacted. 5.390 g (16.36 mmol, 82%) of the product was obtained as a yellow solid after washing the solids with ethanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.34 (s, 1H, H-*2'*), 7.65 – 7.60 (m, 3H, *H*-2, *H*-6'), 7.46 (d, 1H, *J* = 8.5 Hz, *H*-5'), 7.43 – 7.40 (m, 2H, *H*-2''), 7.38 – 7.25 (m, 3H, *H*-3'', *H*-4''), 6.47 (d, 1H, *J* = 16.0 Hz, *H*-3), 4.22 (s, 2H, *H*-5), 3.81 (s, 3H, *H*-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 166.8, 145.7, 141.6, 140.3, 134.6, 132.2, 131.4, 129.1, 129.0, 128.0, 127.2, 125.4, 119.8, 52.1, 37.6.
HR-MS (ESI+): *m/z* for $C_{17}H_{15}NO_4S+Na^+$, $[M+Na]^+$ calculated: 352.0614; found: 352.0612.

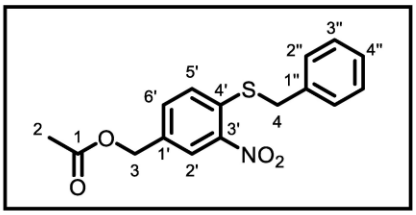
4-(Benzylsulfanyl)-3-nitrobenzyl alcohol (15)



According to general protocol **GPI**, 4-chloro-3-nitrobenzylalcohol (5.29 g, 28.0 mmol, 1.0 eq.) and benzyl mercaptan (3.85 g, 31.0 mmol, 1.1 eq.) were reacted. 5.911 g (21.47 mmol, 77%) of the product was obtained as yellow solid after washing the solids with ethanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.17 (d, 1H, *J* = 2.0 Hz, *H*-2'), 7.50 (dd, 1H, *J* = 8.3 Hz, 2.0 Hz, *H*-6'), 7.43 – 7.38 (m, 3H, *H*-5', *H*-2''), 7.37 – 7.27 (m, 3H, *H*-3'', *H*-4''), 4.71 (s, 2H, *H*-1), 4.19 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 145.8, 138.3, 136.8, 135.1, 132.0, 129.2, 128.9, 127.9, 127.2, 124.2, 63.6, 37.7.
HR-MS (ESI+): *m/z* for $C_{14}H_{13}NO_3S+Cl^-$, $[M+Cl]^-$ calculated: 310.0310; found: 310.0316.

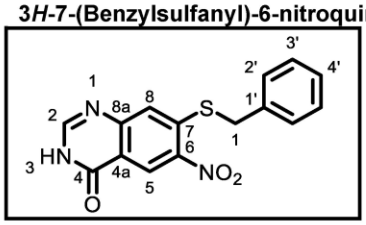
4-(Benzylsulfanyl)-3-nitrobenzyl acetate (16)



Under argon atmosphere **15** (4.13 g, 15.0 mmol, 1.0 eq.) was dissolved in 60 ml anhydrous THF and 10 mL triethylamine was added. The solution was cooled to 0 °C and acetic anhydride (4.3 mL, 45.0 mmol, 3.0 eq.) was added dropwise. The reaction mixture was stirred 0 °C rising the temperature slowly to room temperature for 24 h. The solution was added to 50 ml of water. The aqueous layer was extracted twice with 50 mL ethyl acetate. The combined organic fractions were washed once with 50 mL brine and dried over magnesium sulfate. 4.510 g (14.21 mmol, 95%) of the product was obtained after crystallization (50 mL Cy:EtOH 20:1 (*v:v*); crystalization at 6 °C) as yellow solid.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.18 – 8.13 (m, 1H, *H*-2'), 7.64 – 7.54 (m, 1H, *H*-6'), 7.46 – 7.41 (m, 3H, *H*-5', *H*-2''), 7.37 – 7.27 (m, 3H, *H*-3'', *H*-4''), 5.09 (s, 2H, *H*-3), 4.27 (s, 2H, *H*-4), 2.06 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 171.4, 146.7, 137.7, 136.7, 135.1, 134.2, 130.1, 129.7, 128.7, 128.6, 126.1, 65.1, 37.7, 21.0.
HR-MS (ESI+): *m/z* for $C_{16}H_{15}NO_4S+Na^+$, $[M+Na]^+$ calculated: 340.0614; found: 340.0609.
m.p. (Cy:EtOH): 102.0–103.9 °C.

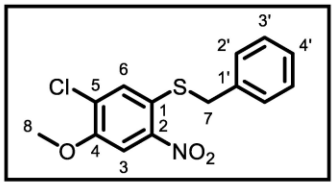
3*H*-7-(Benzylsulfanyl)-6-nitroquinazoline-4-one (17)



According to general protocol **GPI**, 3*H*-7-chloro-6-nitroquinazoline-4-one (4.78 g, 21.2 mmol, 1.0 eq.) and benzyl mercaptan (2.7 mL, 23.3 mmol, 1.1 eq.) were reacted. 5.250 g (16.76 mmol, 79%) of the product was obtained as beige solid after washing the solids with ethanol.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 12.60 (s, 1H, 3-N*H*), 8.75 (s, 1H, *H*-5), 8.25 (s, 1H, *H*-8), 7.74 (s, 1H, *H*-2), 7.51 – 7.47 (m, 2H, *H*-2'), 7.41 – 7.34 (m, 2H, *H*-3'), 7.33 – 7.27 (m, 1H, *H*-4'), 4.46 (s, 2H, *H*-1).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 159.8, 151.5, 149.6, 142.8, 142.6, 135.2, 129.3, 128.7, 127.7, 124.8, 124.7, 118.8, 36.3.
HR-MS (ESI-): *m/z* for $C_{15}H_{11}N_3O_3S$-H$^-$, [M-H]$^-$ calculated: 312.0448; found: 312.0451.

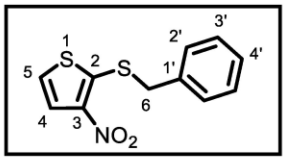
Benzyl(5-chloro-4-methoxy-2-nitrophenyl)sulfide (18)



According to general protocol **GPI**, 1-chloro-5-fluoro-2-methoxy-4-nitrobenzene (4.11 g, 20.0 mmol, 1.0 eq.) and benzyl mercaptan (2.6 mL, 22.0 mmol, 1.1 eq.) were reacted. 5.520 g (17.82 mmol, 89%) of the product was obtained as yellow solid after washing the solids with ethanol.

^{1}H NMR (400 MHz, CDCl$_3$) δ [ppm]: 7.76 (s, 1H, *H*-6), 7.45 (s, 1H, *H*-3), 7.41 – 7.29 (m, 5H, *H*-2', *H*-3', *H*-4'), 4.16 (s, 3H, *H*-7), 3.96 (s, 3H, *H*-8).
^{13}C NMR (101 MHz, CDCl$_3$) δ [ppm]: 152.5, 144.8, 134.9, 130.0, 129.8, 129.3, 129.0, 128.6, 128.0, 108.9, 56.9, 38.2.
HR-MS (ESI+): *m/z* for $C_{14}H_{12}{}^{35}ClNO_3S$+Na$^+$, [M+Na]$^+$ calculated: 332.0119; found: 332.0098.

2-(Benzylsulfanyl)-3-nitrothiophene (19)

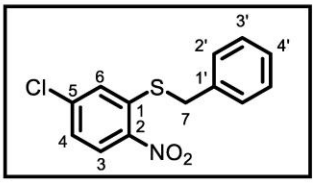


According to general protocol **GPI**, 2-chloro-3-nitrothiophene (4.00 g, 24.5 mmol, 1.0 eq.) and benzyl mercaptan (3.2 mL, 26.9 mmol, 1.1 eq.) were reacted. 5.310 g (21.13 mmol, 86%) of the product was obtained as yellow solid after washing the solids with ethanol.

^{1}H NMR (400 MHz, CDCl$_3$) δ [ppm]: 7.60 (d, 1H, *J* = 5.8 Hz, *H*-4), 7.46 – 7.41 (m, 2H, *H*-2'), 7.40 – 7.31 (m, 3H, *H*-3', *H*-4'), 7.07 (d, 1H, *J* = 5.8 Hz, *H*-5), 4.27 (s, 2H, *H*-6).
^{13}C NMR (101 MHz, CDCl$_3$) δ [ppm]: 148.2, 142.6, 134.4, 129.3, 129.0, 128.4, 124.5, 121.7, 40.0.
HR-MS (ESI+): *m/z* for $C_{11}H_9NO_2S_2$+H$^+$, [M+H]$^+$ calculated: 252.0147; found: 252.0143.

The spectroscopic data are in accordance with those reported in the literature.[8]

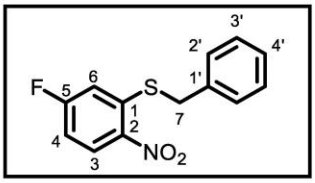
Benzyl(5-chloro-2-nitrophenyl)sulfide (20)



According to general protocol **GPI**, 4-chloro-2-fluoro-1-nitrobenzene (17.55 g, 100 mmol, 1.0 eq.) and benzyl mercaptan (11.7 mL, 12.4 g, 100 mmol, 1.0 eq.) were reacted. 27.20 g (97.2 mmol, 97%) of the product was obtained as yellow solid after washing the solids with ethanol.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.18 (d, 1H, *J* = 8.9 Hz, *H*-3), 7.44 – 7.41 (m, 3H, *H*-6, *H*-2'), 7.39 – 7.29 (m, 3H, *H*-3', *H*-4'), 7.21 (dd, 1H, *J* = 8.9 Hz, 2.1 Hz, *H*-4), 4.19 (s, 2H, *H*-7).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 143.9, 140.7, 140.5, 134.3, 129.3, 129.1, 128.2, 127.5, 126.4, 124.9, 37.9.
HR-MS (ESI+): *m/z* for $C_{13}H_{10}{}^{35}ClNO_2S+NH_4^+$, $[M+NH_4]^+$ calculated: 297.0459; found: 297.0458.

Benzyl(5-fluoro-2-nitrophenyl)sulfide (21)

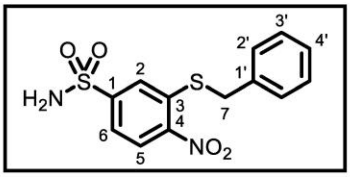


Under argon atmosphere 2,4-difluoro-1-nitrobenzene (15.90 g, 100 mmol, 1.0 eq.) and benzyl mercaptan (11.7 mL, 12.4 g, 100 mmol, 1.0 eq.) were dissolved in 150 mL toluene at 0 °C. Triethylamine (14.6 mL, 10.6 g, 105 mmol, 1.05 eq.) was added dropwise and the mixture was stirred for 16 h at room temperature. After completion of the reaction the solution was poured into 150 mL water. The organic layer was separated, washed once with 100 mL brine, dried over sodium sulfate, and the solvent was removed under reduced pressure. The crude product was washed five times with 50 mL ethanol to obtain 21.73 g (82.5 mmol, 83%) of the product as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.28 (dd, 1H, *J* = 9.2 Hz, 5.4 Hz, *H*-3), 7.46 – 7.40 (m, 2H, *H*-2'), 7.40 – 7.29 (m, 3H, *H*-3', *H*-4'), 7.14 (dd, 1H, *J* = 9.8 Hz, 2.6 Hz, *H*-6), 6.91 (ddd, 1H, *J* = 9.2 Hz, 7.0 Hz, 2.6 Hz, *H*-4), 4.16 (s, 2H, *H*-7).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 165.2 (d, *J* = 258.4 Hz), 142.2 (d, *J* = 9.7 Hz), 141.6, 134.2, 129.2, 129.1, 129.0 (d, *J* = 10.7 Hz), 128.0, 113.3 (d, *J* = 27.0 Hz), 112.0 (d, *J* = 23.7 Hz), 37.7.
^{19}F NMR (376 MHz, CD_3CN) δ [ppm]: -101.61 – -103.91 (m).
HR-MS (ESI+): *m/z* for $C_{13}H_{10}FNO_2S+Na^+$, $[M+Na]^+$ calculated: 286.0308; found: 286.0310.

The spectroscopic data are in accordance with those reported in the literature.[9]

4-Nitro-3-benzylsulfanyl-benzenesulfonamide (22)

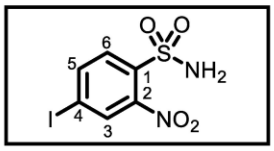


According to general protocol **GPI**, 3-fluoro-4-nitrobenzene-sulfonamide (10.12 g, 46 mmol, 1.0 eq.) and benzyl mercaptan (5.9 mL, 6.3 g, 51 mmol, 1.1 eq.) were reacted. 13.13 g (40.5 mmol, 88%) of the product was obtained after crystallization (200 mL EtOH; crystallization at 6 °C) as yellow crystals.

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 8.56 (d, 1H, *J* = 2.0 Hz, *H*-2), 8.04 (dd, 1H, *J* = 8.5 Hz, 2.0 Hz, *H*-6), 7.93 (d, 1H, *J* = 8.5 Hz, *H*-5), 7.50 – 7.45 (m, 2H, *H*-2'), 7.39 – 7.33 (m, 2H, *H*-3'), 7.32 – 7.26 (m, 1H, *H*-4'), 4.44 (s, 2H, *H*-7).
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 144.2, 141.5, 141.0, 135.1, 130.4, 129.3, 128.7, 128.3, 127.7, 123.1, 36.1.
HR-MS (ESI+): *m/z* for $C_{13}H_{12}N_2O_4S_2+Na^+$, $[M+Na]^+$ calculated: 347.0131; found: 347.0132.
m.p. (EtOH): decomposition at 230.4 °C.

7.2. 2-Nitroarenesulfonamides (23–41)

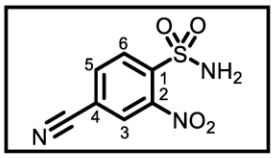
4-Iodo-2-nitrobenzenesulfonamide (23)



According to general protocol **GPII**, **12** (9.280 g, 25 mmol, 1.0 eq.), 1,3-dichloro-5,5-dimethylhydantoin (11.211 g, 57 mmol, 2.3 eq.), and concentrated hydrochloric acid (5 mL; 37% *w*:*v*) in 150 mL THF were reacted. 3.274 g (9.97 mmol, 40%) of the product was obtained after crystallization (70 mL EtOH; crystallization at 6 °C) as beige crystals.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 8.38 (d, 1H, *J* = 1.7 Hz, *H*-3), 8.26 (dd, 1H, *J* = 8.3 Hz, 1.7 Hz, *H*-5), 7.92 (s, 2H, -N*H*$_2$), 7.77 (d, 1H, *J* = 8.3 Hz, *H*-6).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 147.1, 141.3, 135.2, 132.1, 130.1, 99.9.
HR-MS (ESI-): *m/z* for $C_6H_5IN_2O_4S$-H$^-$, [M-H]$^-$ calculated: 326.8942; found: 326.8947.
m.p. (EtOH): 176.4–179.6 °C.

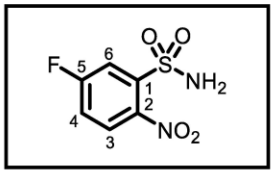
4-Cyano-2-nitrobenzenesulfonamide (24)



According to general protocol **GPII**, **11** (6.761 g, 25 mmol, 1.0 eq.), 1,3-dichloro-5,5-dimethylhydantoin (10.472 g, 53 mmol, 2.1 eq.), and concentrated hydrochloric acid (5 mL; 37% *w*:*v*) in 150 mL THF were reacted. 4.449 g (19.58 mmol, 78%) of the product was obtained after crystallization (65 mL EtOH; crystallization at 6 °C) as beige crystals.

^{1}H NMR (400 MHz, CD$_3$CN) δ [ppm]: 8.27 (d, 1H, *J* = 1.6 Hz, *H*-3), 8.23 (d, 1H, *J* = 8.2 Hz, *H*-6), 8.14 (dd, 1H, *J* = 8.2 Hz, 1.6 Hz, *H*-5), 6.24 (s, 2H, -N*H*$_2$).
^{13}C NMR (101 MHz, CD$_3$CN) δ [ppm]: 148.5, 140.1, 137.9, 131.66, 129.8, 118.1, 116.8.
HR-MS (ESI-): *m/z* for $C_7H_5N_3O_4S$-H$^-$, [M-H]$^-$ calculated: 225.9928; found: 225.9926.
m.p. (EtOH): 216.7–219.4 °C.

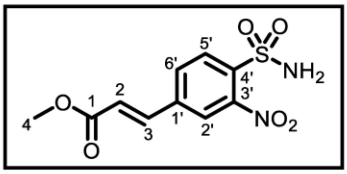
5-Fluoro-2-nitrobenzenesulfonamide (25)



According to general protocol **GPII**, **21** (6.577 g, 25 mmol, 1.0 eq.), 1,3-dichloro-5,5-dimethylhydantoin (10.531 g, 54 mmol, 2.2 eq.), and concentrated hydrochloric acid (5 mL; 37% *w*:*v*) in 150 mL THF were reacted. 3.694 g (16.78 mmol, 67%) of the product was obtained after crystallization (80 mL Cy:EtOH 9:1 (*v*:*v*); crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD$_3$CN) δ [ppm]: 8.00 (dd, 1H, *J* = 8.9 Hz, 4.6 Hz, *H*-3), 7.84 (dd, *J* = 8.0 Hz, 2.8 Hz, 1H), 7.52 (ddd, 1H, *J* = 8.9 Hz, 8.0 Hz, 2.8 Hz, *H*-4), 6.17 (s, 2H, -N*H*$_2$).
^{13}C NMR (101 MHz, CD$_3$CN) δ [ppm]: 164.6 (d, *J* = 257.0 Hz), 144.8, 139.5 (d, *J* = 7.5 Hz), 129.3 (d, *J* = 9.5 Hz), 121.4 (d, *J* = 23.5 Hz), 118.1.
^{19}F NMR (376 MHz, CD$_3$CN) δ [ppm]: -104.91 (td, *J* = 8.0 Hz, 4.6 Hz).
HR-MS (ESI-): *m/z* for $C_6H_5FN_2O_4S$-H$^-$, [M-H]$^-$ calculated: 218.9881; found: 218.9880.
m.p. (Cy:EtOH): 149.1–150.3 °C.

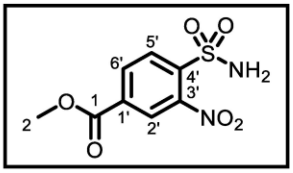
Methyl (*E*)-3-nitro-4-sulfamoylcinnamate (26)



According to general protocol **GPII**, **14** (5.387 g, 16 mmol, 1.0 eq.), 1,3-dichloro-5,5-dimethylhydantoin (6.813 g, 35 mmol, 2.2 eq.), and concentrated hydrochloric acid (5 mL; 37% *w*:*v*) in 150 mL THF were reacted. 2.734 g (9.55 mmol, 60%) of the product was obtained after crystallization (60 mL Cy:EtOH 9:1 (*v*:*v*); crystallization at 6 °C) as beige crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.09 (m, 2H, *H*-2', *H*-6'), 7.96 (dd, *J* = 8.3 Hz, 1.7 Hz, *H*-5'), 7.69 (d, 1H, *J* = 16.1 Hz, *H*-3), 6.70 (d, 1H, *J* = 16.1 Hz, *H*-2), 6.10 (s, 2H, -N*H*$_2$), 3.77 (s, 3H, *H*-4).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 167.1, 148.9, 141.1, 141.0, 136.8, 133.1, 131.2, 124.9, 124.3, 52.7.
HR-MS (ESI-): *m/z* for $C_{10}H_{10}N_2O_6S$-H$^-$, [M-H]$^-$ calculated: 285.0187; found: 285.0185.
m.p. (Cy:EtOH): 183.1–185.3 °C.

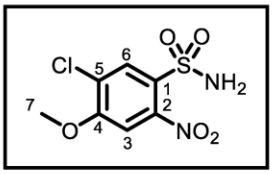
Methyl 3-nitro-4-sulfamoylbenzoate (27)



According to general protocol **GPII**, **13** (7.579 g, 25 mmol, 1.0 eq.), 1,3-dichloro-5,5-dimethylhydantoin (10.771 g, 55 mmol, 2.3 eq.), and concentrated hydrochloric acid (5 mL; 37% *w*:*v*) in 150 mL THF were reacted. 3.570 g (13.72 mmol, 55%) of the product was obtained after crystallization (85 mL Cy:EtOH 9:1 (*v*:*v*); crystallization at 6 °C) as beige crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.33 (d, 1H, *J* = 1.7 Hz, *H*-2'), 8.28 (dd, 1H, *J* = 8.2 Hz, 1.7 Hz, *H*-6'), 8.16 (d, 1H, *J* = 8.2 Hz, *H*-5'), 6.19 (s, 2H, -N$_2$), 3.92 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 164.8, 148.4, 139.7, 136.0, 134.4, 131.2, 126.5, 53.8.
HR-MS (ESI-): *m/z* for $C_8H_8N_2O_6S$-H$^-$, [M-H]$^-$ calculated: 259.0030; found: 259.0028.
m.p. (Cy:EtOH): 138.4–139.4 °C.

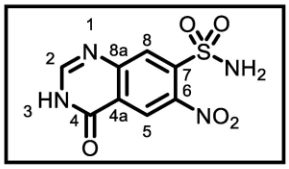
5-Chloro-4-methoxy-2-nitrobenzenesulfonamide (28)



According to general protocol **GPII**, **18** (5.311 g, 17 mmol, 1.0 eq.), 1,3-dichloro-5,5-dimethylhydantoin (7.392 g, 38 mmol, 2.2 eq.), and concentrated hydrochloric acid (5 mL; 37% *w*:*v*) in 150 mL THF were reacted. 3.269 g (12.30 mmol, 72%) of the product was obtained after crystallization (80 mL Cy:EtOH 9:1 (*v*:*v*); crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.04 (s, 1H, *H*-6), 7.53 (s, 1H, *H*-3), 6.07 (s, 2H, -N*H*$_2$), 4.00 (s, 3H, *H*-7).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 159.4, 148.0, 131.7, 128.9, 126.8, 110.1, 58.4.
HR-MS (ESI-): *m/z* for $C_7H_7{}^{35}ClN_2O_5S$-H$^-$, [M-H]$^-$ calculated: 264.9691; found: 264.9696.
m.p. (Cy:EtOH): 180.4–183.3 °C.

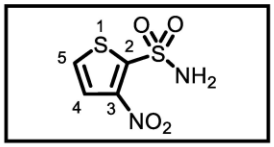
3,4-Dihydro-6-nitro-4-oxo-quinazoline-7-sulfonamide (29)



According to general protocol **GPII**, **17** (4.511 g, 14 mmol, 1.0 eq.), 1,3-dichloro-5,5-dimethylhydantoin (6.322 g, 32 mmol, 2.3 eq.), and concentrated hydrochloric acid (5 mL; 37% *w*:*v*) in 200 mL THF were reacted. 2.275 g 8.42 mmol, 56%) of the product was obtained after crystallization (120 mL EtOH; crystallization at 6 °C) as beige crystals.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 12.87 (s, 1H, 3-N*H*), 8.56 (s, 1H, *H*-5), 8.37 (s, 1H, *H*-8), 8.26 (s, 1H, *H*-2), 8.08 (s, 2H, -N*H*$_2$).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 159.3, 150.9, 149.7, 144.1, 141.1, 128.4, 125.0, 123.4.
HR-MS (APCI-): *m/z* for $C_8H_5N_4O_5S$-H$^-$, [M-H]$^-$ calculated: 268.9986; found: 268.9989.
m.p. (EtOH): decomposition at 250.1 °C.

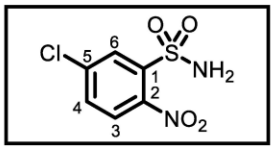
3-Nitrothiophene-2-sulfonamide (30)



According to general protocol **GPII**, **19** (2.513 g, 10 mmol, 1.0 eq.), 1,3-dichloro-5,5-dimethylhydantoin (4.153 g, 21 mmol, 2.1 eq.), and concentrated hydrochloric acid (5 mL; 37% *w*:*v*) in 150 mL THF were reacted. 1.297 g (6.23 mmol, 62%) of the product was obtained after crystallization (50 mL EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD$_3$CN) δ [ppm]: 7.69 (d, 1H, *J* = 5.6 Hz, *H*-4), 7.67 (d, 1H, *J* = 5.6 Hz, *H*-5), 6.32 (s, 2H, -N*H*$_2$).
^{13}C NMR (101 MHz, CD$_3$CN) δ [ppm]: 145.4, 145.2, 130.3, 126.6.
HR-MS (APCI-): *m/z* for $C_4H_4N_2O_4S_2$-H$^-$, [M-H]$^-$ calculated: 206.9540; found: 206.9541.
m.p. (EtOH): 163.9–166.9 °C.

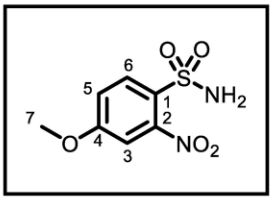
5-Chloro-2-nitrobenzenesulfonamide (31)



According to general protocol **GPII**, **20** (25.069 g, 90 mmol, 1.0 eq.), 1,3-dichloro-5,5-dimethylhydantoin (38.112 g, 188 mmol, 2.1 eq.), and concentrated hydrochloric acid (25 mL; 37% *w*:*v*) in 150 mL THF were reacted. 17.096 g (72.25 mmol, 81%) of the product was obtained after crystallization (170 mL EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD$_3$CN) δ [ppm]: 8.06 (d, 1H, *J* = 2.3 Hz, *H*-6), 7.88 (d, 1H, *J* = 8.6 Hz, *H*-3), 7.77 (dd, 1H, *J* = 8.6 Hz, 2.3 Hz, *H*-4), 6.16 (s, 2H, -N*H*$_2$).
^{13}C NMR (101 MHz, CD$_3$CN) δ [ppm]: 146.8, 139.6, 138.1, 134.6, 130.5, 127.8.
HR-MS (APCI-): *m/z* for $C_6H_5{}^{35}ClN_2O_4S$-H$^-$, [M-H]$^-$ calculated: 234.9586; found: 234.9591.
m.p. (EtOH): 160.2–162.4 °C.

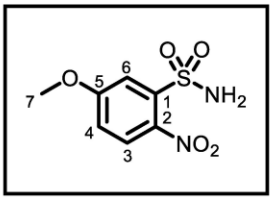
4-Methoxy-2-nitrobenzenesulfonamide (32)



According to general protocol **GPIII**, 4-methoxy-2-nitroaniline (8.410 g, 50 mmol, 1.0 eq.), sodium nitrite (5.170 g, 75 mmol, 1.5 eq.), concentrated hydrochloric acid (40mL; 37% *w*:*v*), copper(II) chloride (1.01 g, 7.5 mmol, 0.15 eq.), and 50 mL of a saturated solution of sulfur dioxide in glacial acetic acid were reacted. 7.640 g (31.54 mmol, 63%) of the product was obtained by column chromatography (80 g silica (irregular); cyclohexane:ethyl acetate 0 → 50% ethyl acetate) as off-white solid.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 7.95 (d, 1H, *J* = 8.9 Hz, *H*-6), 7.68 (s, 2H, -N*H*$_2$), 7.53 (d, 1H, *J* = 2.6 Hz, *H*-3), 7.38 (dd, 1H, *J* = 8.9 Hz, 2.6 Hz, *H*-5), 3.89 (s, 3H, *H*-7).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 162.1, 148.5, 130.7, 127.6, 117.5, 109.6, 56.6.
HR-MS (ESI-): *m/z* for $C_7H_8N_2O_5S$-H$^-$, [M-H]$^-$ calculated: 231.0081; found: 231.0071.

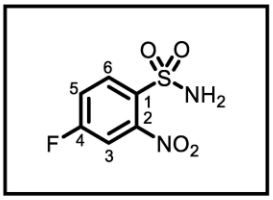
5-Methoxy-2-nitrobenzenesulfonamide (33)



According to general protocol **GPIII**, 5-methoxy-2-nitroaniline (8.411 g, 50 mmol, 1.0 eq.), sodium nitrite (5.171 g, 75 mmol, 1.5 eq), concentrated hydrochloric acid (40mL; 37% *w*:*v*), copper(II) chloride (1.01 g, 7.5 mmol, 0.15 eq.), and 50 mL of a saturated solution of sulfur dioxide in glacial acetic acid were reacted. 7.550 g (32.51 mmol, 65%) of the product was obtained by column chromatography (80 g silica (irregular); cyclohexane:ethyl acetate 0 → 50% ethyl acetate) as off-white solid.

^{1}H NMR (400 MHz, CD$_3$CN) δ [ppm]: 7.97 (d, 1H, *J* = 8.9 Hz, *H*-3), 7.57 (d, 1H, *J* = 2.8 Hz, *H*-6), 7.23 (dd, 1H, *J* = 8.9 Hz, 2.8 Hz, *H*-4), 6.10 (s, 2H, -N*H*$_2$), 3.93 (s, 3H, *H*-7).
^{13}C NMR (101 MHz, CD$_3$CN) δ [ppm]: 163.9, 141.2, 139.1, 129.2, 118.1, 116.5, 57.4.
HR-MS (ESI-): *m/z* for $C_7H_8N_2O_5S$-H$^-$, [M-H]$^-$ calculated: 231.0081; found: 231.0076.

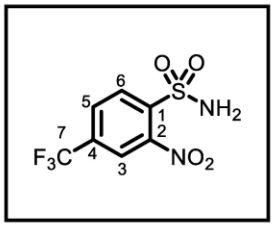
4-Fluoro-2-nitrobenzenesulfonamide (34)



According to general protocol **GPIII**, 4-fluoro-2-nitroaniline (7.811 g, 50 mmol, 1.0 eq.), sodium nitrite (5.170 g, 75 mmol, 1.5 eq), concentrated hydrochloric acid (40mL; 37% *w*:*v*), copper(II) chloride (1.01 g, 7.5 mmol, 0.15 eq.), and 50 mL of a saturated solution of sulfur dioxide in glacial acetic acid were reacted. 7.730 g (35.11 mmol, 70%) of the product was obtained by column chromatography (80 g silica (irregular); cyclohexane:ethyl acetate 0 → 50% ethyl acetate) as off-white solid.

^{1}H NMR (400 MHz, CD$_3$CN) δ [ppm]: 8.15 (dd, 1H, *J* = 8.9 Hz, 5.3 Hz, *H*-6), 7.70 (dd, 1H, *J* = 8.1 Hz, 2.6 Hz, *H*-3), 7.56 (ddd, 1H, *J* = 8.9 Hz, 7.8 Hz, 2.6 Hz, *H*-5), 6.08 (s, 2H, -N*H*$_2$).
^{13}C NMR (101 MHz, CD$_3$CN) δ [ppm]: 165.0 (d, *J* = 256.6 Hz), 149.7, 133.4 (d, *J* = 9.5 Hz), 133.0 (d, *J* = 4.0 Hz), 121.0 (d, *J* = 21.8 Hz), 114.2 (d, *J* = 28.2 Hz).
^{19}F NMR (376 MHz, CD$_3$CN) δ [ppm]: -105.32 (td, *J* = 8.1 Hz, 5.4 Hz).
HR-MS (ESI-): *m/z* for $C_6H_5FN_2O_4S$-H$^-$, [M-H]$^-$ calculated: 218.9881; found: 218.9873.

2-Nitro-4-(trifluoromethyl)benzenesulfonamide (35)

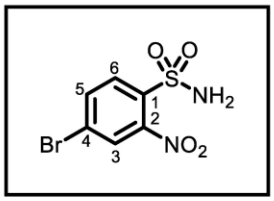


According to general protocol **GPIII**, 2-nitro-4-(trifluoromethyl)aniline (10.31 g, 50 mmol, 1.0 eq.), sodium nitrite (5.17 g, 75 mmol, 1.5 eq), concentrated hydrochloric acid (40mL; 37% *w*:*v*), copper(II) chloride (1.01 g, 7.5 mmol, 0.15 eq.), and 50 mL of a saturated solution of sulfur dioxide in glacial acetic acid were reacted. 9.722 g (35.98 mmol, 72%) of the product was obtained by column chromatography (80 g silica (irregular); cyclohexane:ethyl acetate 0 → 50% ethyl acetate) as off-white solid.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.28 (d, 1H, *J* = 9.2 Hz, *H*-6), 8.22 – 8.19 (m, 1H, *H*-3), 8.14 – 8.09 (m, 1H, *H*-5), 6.22 (s, 2H, -N*H*$_2$).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 148.7, 139.9, 135.5 (d, *J* = 34.5 Hz), 132.0, 131.1 (p, *J* = 3.7 Hz), 126.2 (q, *J* = 272.6 Hz), 123.5 (q, *J* = 4.0 Hz).
^{19}F NMR (376 MHz, CD_3CN) δ [ppm]: -65.02.
HR-MS: *m/z* for $C_7H_5F_3N_2O_4S$-H$^-$, [M-H]$^-$ calculated: 268.9849; found: 268.9848.

The spectroscopic data are in accordance with those reported in the literature.[10]

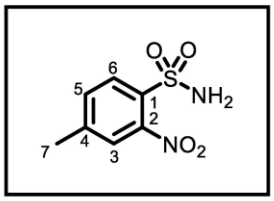
4-Bromo-2-nitrobenzenesulfonamide (36)



According to general protocol **GPIII**, 4-bromo-2-nitroaniline (10.85 g, 50 mmol, 1.0 eq.), sodium nitrite (5.17 g, 75 mmol, 1.5 eq), concentrated hydrochloric acid (40mL; 37% *w*:*v*), copper(II) chloride (1.01 g, 7.5 mmol, 0.15 eq.), and 50 mL of a saturated solution of sulfur dioxide in glacial acetic acid were reacted. 10.710 g (38.10 mmol, 76%) of the product was obtained by column chromatography (80 g silica (irregular); cyclohexane:ethyl acetate 0 → 50% ethyl acetate) as off-white solid.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.07 – 8.06 (m, 1H, *H*-3), 7.98 – 7.97 (m, 2H, *H*-5, *H*-6), 6.10 (s, 2H, -N*H*$_2$).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 148.8, 137.1, 135.7, 132.1, 128.9, 127.8.
HR-MS (ESI-): *m/z* for $C_6H_5{}^{79}BrN_2O_4S$-H$^-$, [M-H]$^-$ calculated: 278.9081; found: 278.9080.

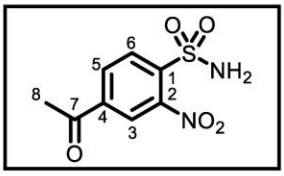
4-Methyl-2-nitrobenzenesulfonamide (37)



According to general protocol **GPIII**, 4-methyl-2-nitroaniline (7.610 g, 50 mmol, 1.0 eq.), sodium nitrite (5.17 g, 75 mmol, 1.5 eq), concentrated hydrochloric acid (40 mL; 37% *w*:*v*), copper(II) chloride (1.01 g, 7.5 mmol, 0.15 eq.), and 50 mL of a saturated solution of sulfur dioxide in glacial acetic acid were reacted. 7.41 g (34.27 mmol, 68%) of the product was obtained by column chromatography (80 g silica (irregular); cyclohexane:ethyl acetate 0 → 50% ethyl acetate) as off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.96 (d, 1H, *J* = 8.1 Hz, *H*-6), 7.70 (d, 1H, *J* = 0.9 Hz, *H*-3), 7.60 (dd, 1H, *J* = 8.1 Hz, 0.9 Hz, *H*-5), 6.03 (s, 2H, -N*H*$_2$), 2.46 (s, 3H, *H*-7).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 148.4, 146.7, 134.4, 133.7, 130.4, 126.3, 21.2.
HR-MS (ESI+): *m/z* for $C_7H_8N_2O_4S$+Na$^+$, [M+Na]$^+$ calculated: 239.0097; found: 239.0100.

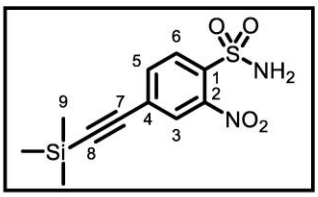
4-Acetyl-2-nitrobenzenesulfonamide (38)[11]



Under argon atmosphere thioacetic acid (3.3 mL, 3.5 g, 46 mmol, 1.6 eq.) and glycylglycine (5.28 g, 40 mmol, 1.33 eq.) was stirred in 110 mL DMF for 15 min. Cesium carbonate (29.30 g, 90 mmol, 3 eq.) was added at 0 °C followed by 4'-fluoro-3'-nitroacetophenon (5.49 g, 30 mmol, 1.0 eq.) in 55 mL DMF and stirred for 16 h. After completion of the reaction the mixture was diluted with 300 mL ethyl acetate, acidified with 300 mL 1 M hydrochloric acid, washed three times with 300 mL water and once with 300 mL brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was dissolved in 80 mL acetonitrile and 16 mL 2 M hydrochloric acid. *N*-Chlorosuccinimide (16.03 g, 120 mmol, 4 eq.) was added slowly at -5 °C and stirred for 2.5 h while the temperature was kept below 0 °C. After completion of the reaction the mixture was diluted with 200 mL ethyl acetate, neutralized with 100 mL 1 M sodium bicarbonate. The aqueous layer was extracted twice with 100 mL ethyl acetate. The combined organic fractions were washed twice with 200 mL water and once with 200 mL brine, dried over sodium sulfate, filtered, added at 0 °C to 100 mL concentrated ammonia solution (25% *w*:*v*) and stirred for 3 h. The reaction mixture was neutralized with concentrated hydrochloric acid (37% *w*:*v*). The aqueous layer was extracted twice 200 mL ethyl acetate, washed once with 300 mL water and once with 300 mL brine, dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. 1.49 g (6.10 mmol, 21%) of the product was obtained by column chromatography (80 g silica (irregular); cyclohexane:ethyl acetate 25 → 75% ethyl acetate) as a colorless solid.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.33 (d, 1H, *J* = 1.7 Hz, *H*-3), 8.29 (dd, 1H, *J* = 8.2 Hz, 1.7 Hz, *H*-5), 8.20 (d, 1H, *J* = 8.2 Hz, *H*-6), 6.17 (s, 2H, -N*H*$_2$), 2.64 (s, 3H, *H*-8).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 196.4, 148.8, 142.0, 139.4, 133.3, 131.3, 125.3, 27.4.
HR-MS (ESI-): *m/z* for $C_8H_8N_2O_5S$-H$^-$, [M-H]$^-$ calculated: 243.0081; found: 243.0079.

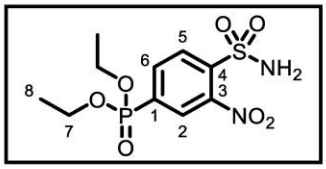
2-Nitro-4-((trimethylsilyl)ethynyl)benzenesulfonamide (39)



Under argon atmosphere **36** (1.687 g, 6.00 mmol, 1 eq.) in 45 mL triethylamine was treated with trimethylsilylacetylene (651 mg, 6.60 mmol, 1.1 eq.), copper(I) iodide (86 mg, 0.45 mmol; 7.5 mol%), and $PdCl_2(PPh_3)_2$ (0.30 mmol, 5 mol%) and the reaction mixture was stirred 22 h at room temperature. After completion of the reaction the solvent was removed under reduced pressure, the residue was dissolved in 50 mL ethyl acetate and filtered over celite™ 545. 0.905 g (3.03 mmol, 51%) of the product was obtained by column chromatography (80 g silica (irregular); cyclohexane:ethyl acetate 25 → 75% ethyl acetate) as a colorless solid.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.04 (d, 1H, *J* = 8.2 Hz, *H*-6), 7.89 (d, *J* = 1.6 Hz, *H*-3), 7.79 (dd, *J* = 8.2 Hz, 1.6 Hz, *H*-5), 6.10 (s, 2H, -N*H*$_2$), 0.26 (s, 9H, *H*-9).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 148.6, 136.6, 136.0, 131.0, 129.4, 128.6, 101.8, 101.7, -0.5.
HR-MS (ESI-): *m/z* for $C_{11}H_{14}N_2O_4SSi$-H$^-$, [M-H]$^-$ calculated: 297.0371; found: 297.0367.

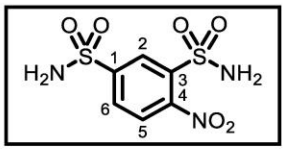
Diethyl (3-nitro-4-sulfamoylphenyl)phosphonate (40)



Under argon atmosphere **36** (2.90 g, 10.3 mmol, 1.0 eq.), diethyl phosphonate (1.81 g, 12.4 mmol, 1.2 eq.), and triethylamine (4.2 mL, 30.9 mmol, 3.0 eq.) were dissolved in 50 mL THF. The resulting solution was purged with argon for 15 min. Afterwards [1,1′-bis(diphenylphosphino)ferrocene-dichloropalladium(II)] (151 mg, 2.1 mmol, 2 mol%) was added and the mixture was stirred at 80 °C for 24 h. The reaction mixture was filtered over celite™ 545 and diluted with 50 mL of water. The aqueous layer was extracted three times with 50 mL ethyl acetate. The combined organic fractions were washed twice with 50 mL saturated sodium bicarbonate solution, once with 50 mL brine and dried over anhydrous magnesium sulfate. 1.809 g (5.35 mmol, 52%) of the product was obtained after crystallization (100 mL EtOH; crystallization at 6 °C) as a colorless crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.19 (dd, 1H, *J* = 8.0 Hz, 3.8 Hz, *H*-2), 8.19 – 8.06 (m, 2H, *H*-5, *H*-6), 6.25 (s, 2H, -N*H*$_2$), 4.21 – 4.03 (m, 4H, *H*-7), 1.29 (td, 6H, *J* = 7.0 Hz, 0.6 Hz, *H*-8).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 139.6, 137.6, 136.8 (d, *J* = 9.4 Hz), 135.7, 131.1 (d, *J* = 14.7 Hz), 128.6 (d, *J* = 11.9 Hz), 64.1 (d, *J* = 5.6 Hz), 16.6 (d, *J* = 6.3 Hz).
^{31}P NMR (162 MHz, CD_3CN) δ [ppm]: 12.08.
HR-MS (ESI+): *m/z* for $C_{10}H_{15}N_2O_7PS+H^+$, $[M+H]^+$ calculated: 339.0410; found: 339.0415.

4-Nitrobenzene-1,3-disulfonamide (41)

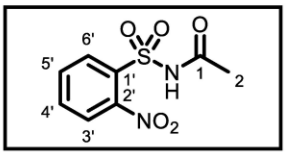


According to general protocol **GPII**, **22** (4.910 g, 15 mmol, 1.0 eq.), 1,3-dichloro-5,5-dimethylhydantoin (7.110 g, 36 mmol, 2.4 eq.), and concentrated hydrochloric acid (5 mL; 37% *w*:*v*) in 150 mL THF were reacted. 2.320 g (8.25 mmol, 55%) of the product was obtained after crystallization (90 mL EtOH; crystallization at 6 °C) as beige crystals.

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 8.33 (t, 1H, *J* = 1.1 Hz, *H*-2), 8.26 – 8.26 (m, 2H, *H*-5, *H*-6), 8.07 (s, 2H, 3-SO_2-N*H*$_2$), 7.82 (s, 2H, 1-SO_2-N*H*$_2$).
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 148.0, 147.0, 138.5, 130.5, 129.6, 121.8.
HR-MS (ESI+): *m/z* for $C_6H_7N_3O_6S_2+Na^+$, $[M+Na]^+$ calculated: 303.9668; found: 303.9667.
m.p. (EtOH): decomposition at 255.8 °C.

7.3. *N*-Acyl-2-nitrobenzenesulfonamides (6a-6ar)

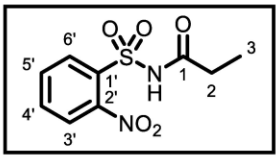
N-Acetyl-2-nitrobenzenesulfonamide (6a)



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (40.03 g, 198 mmol, 1.0 eq.), acetic anhydride (180 mL, 1.98 mol, 10 eq.), and zinc chloride (2.70 g, 19.8 mmol, 0.1 eq.) were reacted. 46.72 g (191 mmol, 97%) of the product was obtained after crystallization (350 mL EtOH; crystallization at 6 °C) as colorless crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.28 – 8.23 (m, 1H, *H*-3'), 7.90 – 7.79 (m, 3H, *H*-4', *H*-5', *H*-6'), 2.03 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.7, 149.0, 136.4, 133.8, 133.3, 132.0, 125.7, 23.8.
HR-MS (ESI-): *m/z* for $C_8H_8N_2O_5S\text{-}H^-$, $[M\text{-}H]^-$ calculated: 243.0081; found: 243.0076.
m.p. (EtOH): 189.3–190.0 °C.

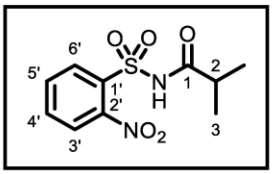
N-Propionyl-2-nitrobenzenesulfonamide (6b)



According to general protocol **GPV**, 2-nitrobenzensulfonamide (1.011 g, 5 mmol, 1.0 eq.), propionyl chloride (0.5 mL, 5 mmol, 1.0 eq.), and triethylamine (1.4 mL) were reacted in 50 mL anhydrous THF. 0.963 g (3.73 mmol, 75%) of the product was obtained as an off-white solid after evaporating the solvent and washing the product once with 10 mL toluene.

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.31 (dt, 1H, *J* = 7.3 Hz, 1.2 Hz, *H*-3'), 7.92 – 7.76 (m, 3H, *H*-4', *H*-5', *H*-6'), 2.33 (q, 2H, *J* = 7.5 Hz, *H*-2), 1.04 (t, 3H, *J* = 7.5 Hz, *H*-3).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 174.5, 149.7, 136.2, 134.4, 133.0, 132.9, 125.6, 30.1, 8.6.
HR-MS (ESI+): *m/z* for $C_9H_5N_2O_5S+Na^+$, $[M+Na]^+$ calculated: 281.0202; found: 281.0206.

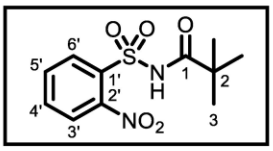
N-Isobutyryl-2-nitrobenzenesulfonamide (6c)



According to general protocol **GPV**, 2-nitrobenzensulfonamide (1.011 g, 5 mmol, 1.0 eq.), isobutyryl chloride (0.6 mL, 6 mmol, 1.2 eq.), and triethylamine (1.7 mL) were reacted in 50 mL anhydrous THF. 1.160 g (4.26 mmol, 85%) of the product was obtained as an off-white solid after evaporating the solvent and washing the product once with 10 mL cyclohexane:ethyl acetate (1:1; *v*:*v*).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.31 (dt, 1H, *J* = 7.4 Hz, 1.1 Hz, *H*-3'), 7.89 – 7.81 (m, 3H, *H*-4', *H*-5', *H*-6'), 2.54 (hept, 1H, *J* = 6.9 Hz, *H*-2), 1.08 (d, 6H, *J* = 6.9 Hz, *H*-3).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 177.7, 149.8, 136.2, 134.5, 133.0, 132.8, 125.6, 36.3, 18.9.
HR-MS (ESI+): *m/z* for $C_{10}H_{12}N_2O_5S+Na^+$, $[M+Na]^+$ calculated: 295.0359; found: 295.0358.

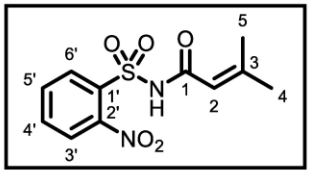
N-Pivaloyl-2-nitrobenzenesulfonamide (6d)



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.012 g, 5 mmol, 1.0 eq.), pivalic anhydride (12 mL, 6 mmol, 1.2 eq.), and zinc chloride (68 mg, 0.5 mmol, 0.1 eq.) were reacted. 0.733 g (2.55 mmol, 51%) of the product was obtained after crystallization (45 mL EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.46 (s, 1H, -N*H*), 8.44 – 8.39 (m, 1H, *H*-3'), 7.87 – 7.77 (m, 3H, *H*-4', *H*-5', *H*-6'), 1.21 (s, 9H, *H*-3).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 176.3, 148.3, 135.0, 134.2, 132.8, 131.7, 125.1, 40.4, 26.8.
HR-MS (ESI+): *m/z* for $C_{11}H_{14}N_2O_5S+H^+$, $[M+H]^+$ calculated: 287.0696; found: 287.0697.
m.p. (EtOH): 165.0–166.1 °C.

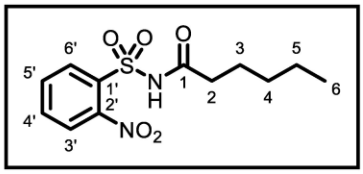
***N*-(3,3-Dimethylacryloyl)-2-nitrobenzenesulfonamide (6e)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.011 g, 5 mmol, 1.0 eq.), 3,3-dimethylacryloyl chloride (1.2 mL, 10 mmol, 2.0 eq.), and triethylamine (3.0 mL) were reacted in 50 mL anhydrous THF. 0.751 g (2.64 mmol, 53%) of the product was obtained as an off-white solid after evaporating the solvent and washing the product once with 10 mL methanol:water (1:3; *v*:*v*).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.37 – 8.30 (m, 1H, *H*-3'), 7.91 – 7.81 (m, 3H, *H*-4', *H*-5', *H*-6'), 5.76 (m, 1H, *H*-2), 2.09 (d, 3H, *J* = 1.3 Hz, *H*-5), 1.91 (d, 3H, *J* = 1.3 Hz, *H*-4).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 173.2, 169.0, 157.1, 144.8, 141.8, 140.5, 134.0, 125.0, 36.9, 29.6.
HR-MS (ESI+): *m/z* for $C_{11}H_{12}N_2O_5S+Na^+$, $[M+Na]^+$ calculated: 307.0359; found: 307.0371.

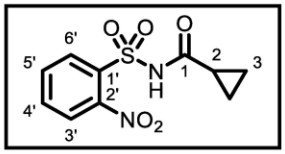
***N*-Capronyl-2-nitrobenzenesulfonamide (6f)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.011 g, 5 mmol, 1.0 eq.), hexanoic anhydride (12 mL, 6 mmol, 1.2 eq.), and zinc chloride (68 mg, 0.5 mmol, 0.1 eq.) were reacted. 1.053 g (3.51 mmol, 70%) of the product was obtained after crystallization (30 mL EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.47 (s, 1H, -N*H*), 8.39 – 8.33 (m, 1H, *H*-3'), 7.88 – 7.76 (m, 3H, *H*-4', *H*-5', *H*-6'), 2.33 (t, 2H, *J* = 7.5 Hz, *H*-2), 1.63 – 1.53 (m, 2H, *H*-3), 1.33 – 1.17 (m, 4H, *H*-4, *H*-5), 0.86 – 0.81 (m, 3H, *H*-6).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 171.3, 148.7, 135.7, 134.1, 133.1, 132.0, 125.5, 37.1, 31.5, 24.5, 22.8, 14.1.
HR-MS (ESI+): *m/z* for $C_{12}H_{16}N_2O_5S+H^+$, $[M+H]^+$ calculated: 301.0853; found: 301.0855.
m.p. (EtOH): 127.5–128.7 °C.

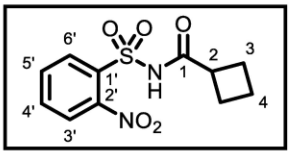
***N*-Cyclopropylcarbonyl-2-nitrobenzenesulfonamide (6g)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.609 g, 8 mmol, 1.0 eq.), cyclopropylcarboxylic chloride (1.5 mL, 17 mmol, 2.0 eq.), and triethylamine (3.3 mL) were reacted in 70 mL anhydrous THF. 0.811 g (3.00 mmol, 38%) of the product was obtained after crystallization (35 mL EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.26 – 8.22 (m, 1H, *H*-3'), 7.87 – 7.78 (m, 3H, *H*-4', *H*-5', *H*-6'), 1.75 – 1.66 (m, 1H, *H*-2), 0.94 – 0.82 (m, 6H, *H*-3).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 173.3, 149.1, 136.4, 133.9, 133.3, 132.0, 125.7, 14.9, 9.8.
HR-MS: *m/z* for $C_{10}H_{10}N_2O_5S+H^+$, $[M+H]^+$ calculated: 271.0383; found: 271.0380.
m.p. (EtOH): 163.1–164.9 °C.

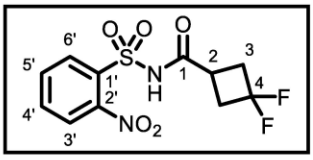
***N*-Cyclobutylcarbonyl-2-nitrobenzenesulfonamide (6h)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.015 g, 5 mmol, 1.0 eq.), cyclobutylcarboxyl chloride (0.8 mL, 7 mmol, 1.4 eq.), and triethylamine (2 mL) were reacted in 70 mL anhydrous THF. 1.331 g (4.68 mmol, 94%) of the product was obtained after crystallization (40 mL EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.47 – 8.42 (m, 1H, *H*-3'), 8.35 (s, 1H, -N*H*), 7.88 – 7.78 (m, 3H, *H*-4', *H*-5', *H*-6'), 3.16 (pd, 1H, *J* = 8.5 Hz, 1.1 Hz, *H*-2), 2.34 – 2.15 (m, 4H, *H*-3), 2.06 – 1.93 (m, 1H *H*-4), 1.92 – 1.81 (m, 1H, *H*-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 172.6, 148.3, 135.0, 134.0, 132.8, 131.9, 125.0, 39.8, 24.6, 18.0.
HR-MS: *m/z* for $C_{11}H_{12}N_2O_5S+H^+$, $[M+H]^+$ calculated: 285.0540; found: 285.0536.
m.p. (EtOH): 174.4–175.5 °C.

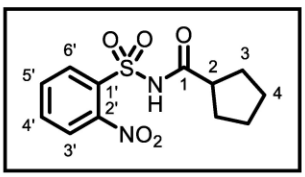
***N*-(3,3-Difluorocyclobutylcarbonyl)-2-nitrobenzenesulfonamide (6i)**



Under argon atmosphere 3,3-difluorocyclobutylcarboxylic acid (1.760 g, 13 mmol, 1.3 eq.), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (2.494 g, 13 mmol, 1.3 eq.), 1-hydroxybenzotriazol-hydrate (1.993 g, 13 mmol, 1.3 eq.), 2-nitrobenzenesulfonamide (2.022 g, 10 mmol, 1.0 eq.), and triethylamine (3 mL) were stirred in 70 mL anhydrous THF for 24 h. After completion of the reaction the mixture was poured into 50 mL of water. The THF was removed under reduced pressure. The aqueous layer was extracted three times with 50 mL of ethyl acetate. The combined organic fractions were washed three times with 1 M hydrochloric acid, once with 50 mL brine, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. 1.714 g (5.35 mmol, 54%) of the product was obtained after crystallization (50 mL Cy:EtOH 10:1 (*v*:*v*); crystallization at 6 °C) as a colorless crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.31 – 8.27 (m, 1H, *H*-3'), 7.92 – 7.82 (m, 3H, *H*-4', *H*-5', *H*-6'), 3.10 – 3.00 (m, 1H, *H*-2), 2.86 – 2.66 (m, 4H, *H*-3).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 172.0, 149.1, 136.6, 134.1, 133.4, 131.7, 125.8, 120.1 (dd, *J* = 281.2 Hz, 7.7 Hz), 38.4 (t, *J* = 24.6 Hz), 28.5 (dd, *J* = 13.4 Hz, 7.7 Hz).
^{19}F NMR (376 MHz, CD_3CN) δ [ppm]: -86.40 (m), -96.54 (m).
HR-MS (ESI-): *m/z* for $C_{11}H_{10}F_2N_2O_5S\text{-}H^-$, $[M-H]^-$ calculated: 319.0206; found: 319.0213.
m.p. (Cy:EtOH): 159.8–162.7 °C.

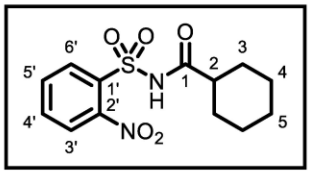
***N*-Cyclopentylcarbonyl-2-nitrobenzenesulfonamide (6j)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.510 g, 8 mmol, 1.0 eq.), cyclopentylcarboxyl chloride (1.1 mL, 9 mmol, 1.1 eq.), and triethylamine (2 mL) were reacted in 70 mL anhydrous THF. 1.307 g (4.38 mmol, 58%) of the product was obtained after crystallization (50 mL Cy:EtOH 12:1 (*v*:*v*); crystallization at 6 °C) as a colorless crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.26 (dt, 1H, *J* = 7.3 Hz, 1.3 Hz, *H*-3'), 7.91 – 7.76 (m, 3H, *H*-4', *H*-5', *H*-6'), 2.82 – 2.69 (m, 1H, *H*-2), 1.89 – 1.78 (m, 2H, *H*-3), 1.72 – 1.61 (m, 2H, *H*-3), 1.59 – 1.49 (m, 4H, *H*-4).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 175.5, 149.1, 136.4, 134.0, 133.2, 132.0, 125.7, 45.8, 30.1, 26.5
HR-MS (ESI-): *m/z* for $C_{12}H_{14}N_2O_5S\text{-}H^-$, $[M-H]^-$ calculated: 297.0551; found: 297.0554.
m.p. (Cy:EtOH): 138.5–140.8 °C.

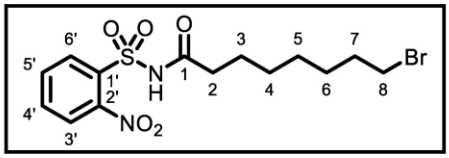
***N*-Cyclohexylcarbonyl-2-nitrobenzenesulfonamide (6k)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.011 g, 5.0 mmol, 1.0 eq.), cyclohexylcarboxyl chloride (0.8 mL, 6 mmol, 1.2 eq.), and triethylamine (1.7 mL) were reacted in 70 mL anhydrous THF. 0.800 g (2.56 mmol, 51%) of the product was obtained as an off-white solid after evaporating the solvent and washing the product once with 10 mL toluene.

^{1}H NMR (300 MHz, DMSO$_{d6}$) δ [ppm]: 12.47 (s, 1H, -N*H*), 8.17 (dd, 1H, *J* = 6.9 Hz, 2.4 Hz, *H*-3'), 8.05 – 7.86 (m, 3H, *H*-4', *H*-5', *H*-6'), 2.37 – 2.25 (m, 1H, *H*-2), 1.83 – 1.48 (m, 5H, *H*-3, *H*-5), 1.29 – 1.01 (m, 5H, *H*-4, *H*-5).
^{13}C NMR (75 MHz, DMSO$_{d6}$) δ [ppm]: 174.6, 147.6, 135.5, 132.5, 133.3, 130.8, 124.6, 43.6, 28.1, 25.1, 24.8.
HR-MS (ESI+): *m/z* for $C_{13}H_{15}N_2O_5S+H^+$, $[M+H]^+$ calculated: 313.0853; found: 313.0855.

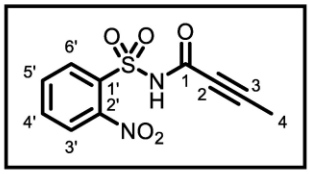
***N*-(8-Bromooctanoyl)-2-nitrobenzenesulfonamide 6l)**



8-Bromooctanoic acid (2.683 g, 12 mmol, 1.2 eq.) was dissolved in 30 mL of dichloromethane and three drops of DMF were added. Oxalyl chloride (2 mL, 20 mmol, 2.0 eq.) was added dropwise and the reaction mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure to obtain the crude acid chloride which was used directly without further purification. According to general protocol **GPIV**, 2-nitrobenzensulfonamide (2.022 g, 10.0 mmol, 1.0 eq.), the previously synthesized 8-bromooctanoyl chloride, and triethylamine (4 mL) were reacted in 100 mL anhydrous THF. 1.082 g (2.66 mmol, 27%) of the product was obtained by column chromatography (80 g silica (irregular); cyclohexane:ethyl acetate 17 → 33% ethyl acetate) as a colorless solid.

^{1}H NMR (400 MHz, CD$_3$CN) δ [ppm]: 9.66 (s, 1H, -N*H*), 8.26 (ddd, *J* = 7.4 Hz, 1.5 Hz, 0.8 Hz, *H*-3'), 7.90 – 7.79 (m, 3H, *H*-4', *H*-5', *H*-6'), 3.43 (t, 2H, *J* = 6.8 Hz, *H*-8), 2.30 (t, 2H, *J* = 7.4 Hz, *H*-2), 1.76 (dq, 2H, *J* = 8.4 Hz, 6.8 Hz, *H*-7), 1.52 (p, *J* = 7.4 Hz, *H*-3), 1.39 – 1.15 (m, 5H, *H*-4, *H*-5, *H*-6).
^{13}C NMR (101 MHz, CD$_3$CN) δ [ppm]: 172.6, 149.0, 136.4, 133.9, 133.3, 132.0, 125.6, 36.7, 35.3, 33.4, 29.9, 28.9, 28.5, 24.9.
HR-MS (ESI-): *m/z* for $C_{14}H_{19}{}^{79}BrN_2O_5$-$H^-$, $[M-H]^-$ calculated: 405.0125; found: 405.0126.

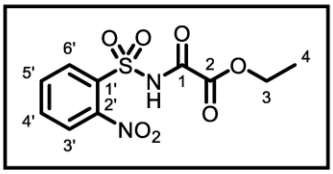
***N*-(2-Butynoyl)-2-nitrobenzenesulfonamide (6m)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.52 g, 7.5 mmol, 1.0 eq.), 2-butynoyl chloride (0.92 g, 9.0 mmol, 1.2 eq.), and triethylamine (2 mL) were reacted in 70 mL anhydrous THF. 0.613 g (2.29 mmol, 31%) of the product was obtained by column chromatography (80 g silica (irregular); cyclohexane:ethyl acetate 30 → 50% ethyl acetate) as a colorless solid.

^{1}H NMR (400 MHz, CD$_3$CN) δ [ppm]: 8.24 (dt, 1H, *J* = 7.7 Hz, 1.2 Hz, *H*-3'), 7.93 – 7.78 (m, 3H, *H*-4', *H*-5', *H*-6'), 2.01 (s, 3H, *H*-4).
^{13}C NMR (101 MHz, CD$_3$CN) δ [ppm]: 150.9, 149.0, 136.8, 133.9, 133.4, 131.6, 125.9, 91.5, 73.4, 3.9.
HR-MS (ESI+): *m/z* for $C_{10}H_8N_2O_5S+H^+$, $[M+H]^+$ calculated: 269.0227; found: 269.0219.

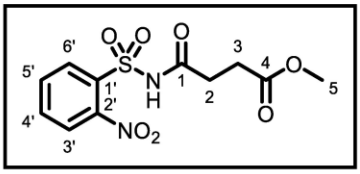
***N*-(*O*-Ethoxyoxalyl)-2-nitrobenzenesulfonamide (6n)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.01 g, 5.0 mmol, 1.0 eq.), ethyl 2-chloro-2-oxoacetate (2.0 mL, 15.0 mmol, 3.0 eq.), and triethylamine (3 mL) were reacted in 70 mL anhydrous THF. 1.285 g (4.25 mmol, 85%) of the product was obtained after crystallization (55 mL EtOH; crystallization at 6 °C) as a colorless crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 10.43 (s, 1H, -N*H*), 8.32 – 8.29 (m, 1H, *H*-3'), 7.94 – 7.85 (m, 3H, *H*-4', *H*-5', *H*-6'), 4.30 (q, 2H, *J* = 7.1 Hz, *H*-3), 1.30 (t, 3H, *J* = 7.1 Hz, *H*-4).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 158.5, 155.6, 149.1, 137.1, 133.9, 133.7, 131.1, 126.2, 64.9, 14.0.
HR-MS (ESI+): *m/z* for $C_{10}H_{10}N_2O_7S+Na^+$, $[M+Na]^+$ calculated: 325.0101; found: 325.0106.
m.p. (Cy:EtOH): 181.9–184.8 °C.

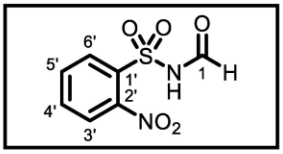
***N*-(4-Methoxy-4-oxobutyryl)-2-nitrobenzenesulfonamide (6o)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.01 g, 5.0 mmol, 1.0 eq.), methyl 4-chloro-4-oxobutanoate (1.3 mL, 10.0 mmol, 2.0 eq.), and triethylamine (2 mL) were reacted in 70 mL anhydrous THF. 0.903 g (2.86 mmol, 57%) of the product was obtained after crystallization (40 mL Cy:EtOH 9:1 (*v*:*v*); crystallization at 6 °C) as a colorless crystals.

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 8.38 – 8.31 (m, 1H, *H*-3'), 7.87 – 7.77 (m, 3H, *H*-4', *H*-5', *H*-6'), 3.65 (s, 3H, *H*-5), 2.69 – 2.58 (m, 4H, *H*-2, *H*-3).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 172.9, 169.6, 148.1, 135.1, 133.5, 132.5, 131.4, 124.9, 52.1, 31.4, 28.1.
HR-MS (ESI+): *m/z* for $C_{11}H_{12}N_2O_7+H^+$, $[M+H]^+$ calculated: 317.0438; found: 317.0440
m.p. (Cy:EtOH): 127.5–128.7 °C.

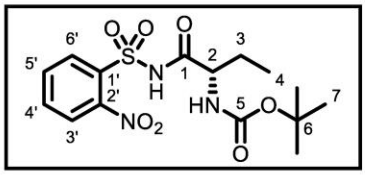
***N*-Formyl-2-nitrobenzenesulfonamide (6p)**



2-Nitrobenzenesulfonamide (5.05 g, 25 mmol, 1.0 eq.) in 50 mL 0.75 M methanolic sodium methoxide was stirred 1 h at 40 °C under argon atmosphere. Ethyl formate (9.3 g, 125 mmol, 5.0 eq.) was added dropwise and stirring was continued for 3 h. After completion of the reaction the reaction mixture was neutralized with 2 M hydrochloric acid, concentrated, and extracted three times with 100 mL ethyl acetate. The combined organic fractions were washed once with 150 mL water, once with 150 mL brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. 4.14 g (17.99 mmol, 72%) of the product was obtained after crystallization (100 mL *tert*-butyl methyl ether; crystallization at 6 °C) as colorless crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.54 (s, 1H, -N*H*), 8.17 (dd, 1H, *J* = 7.3 Hz, 2.0 Hz, *H*-3'), 8.09 (dd, 1H, *J* = 7.7, 1.5 Hz, *H*-6'), 8.02 – 7.92 (m, 2H, *H*-4', *H*-5').
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 162.4, 147.2, 135.8, 133.2, 131.4, 130.9, 125.1.
HR-MS (ESI-): *m/z* for $C_7H_6N_2O_5S-H^-$, $[M-H]^-$ calculated: 228.9925; found: 228.9926.
m.p. (*tert*-butyl methyl ether): 174.2–179.1 °C.

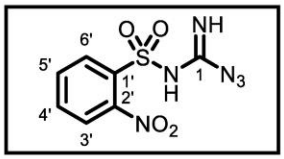
(*S*)-*N*-(2-((*tert*-Butoxycarbonyl)amino)butyryl)-2-nitrobenzenesulfonamide (6q)



Under argon atmosphere (*S*)-2-((*tert*-butoxycarbonyl)amino)-butanoic acid (1.33 g, 6.5 mmol, 1.3 eq.), 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimide hydrochloride (1.27 g, 6.6 mmol, 1.3 eq.), 1-hydroxybenzotriazol-hydrate (1.00 g, 6.5 mmol, 1.3 eq.), 2-nitrobenzenesulfonamide (1.01 g, 5.0 mmol, 1.0 eq.), and triethylamine (2 mL) were stirred in 70 mL anhydrous THF for 24 h. After completion of the reaction the mixture was poured into 50 mL of water. The THF was removed under reduced pressure. The aqueous layer was extracted three times with 50 mL of ethyl acetate. The combined organic fractions were washed three times with 1 M hydrochloric acid, once with 50 mL brine, dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. 1.006 g (2.60 mmol, 52%) of the product was obtained by reverse phase column chromatography (C_{18} silica gel, gradient: 35% → 60% acetonitrile) as a colorless solid.

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.35 – 8.24 (m, 1H, *H*-3'), 7.86 – 7.73 (m, 3H, *H*-4', *H*-5', *H*-6'), 3.97 (dd, 1H, *J* = 8.3 Hz, 5.1 Hz, *H*-2), 1.86 – 1.71 (m, 1H, *H*-3), 1.65 – 1.52 (m, 1H, *H*-3), 1.41 (s, 9H, *H*-7), 0.87 (t, 3H, *J* = 7.4 Hz, *H*-4).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 175.7, 157.8, 149.7, 135.3, 133.6, 132.8, 125.4, 80.5, 58.1, 28.7, 26.3, 10.3.
HR-MS (ESI+): *m/z* for $C_{15}H_{21}N_3O_7S+Na^+$, $[M+Na]^+$ calculated: 410.0992; found: 410.0994.
Optical Rotation: $[\alpha]_D^{20}$ = -22.2 (*c* = 1.00, MeOH).

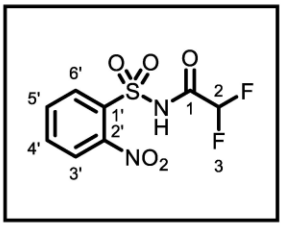
(2-Nitrophenyl)sulfonyl)carbamimidic azide (6r)



2-Nitrobenzenesulfonyl chloride (1.55 g, 6.1 mmol, 1.0 eq.) was dissolved in THF at 40 °C. 1*H*-5-Amino-tetrazole (1.23 g, 14.5 mmol, 2.4 eq.) in 10 mL THF was added dropwise at 40 °C. The reaction mixture was stirred at 40 °C for 24 h. After completion of the reaction the mixture was added to 50 mL of water and the THF was removed under reduced pressure. The aqueous layer was extracted three times with 50 mL of ethyl acetate. The combined organic fractions were washed once with 50 mL of brine, dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. 0.700 g (2.59 mmol, 42%) of the product was obtained after crystallization (50 mL Cy:EtOH 9:1 (*v:v*); crystallization at 6 °C) as a beige crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.18 – 8.13 (m, 1H, *H*-3'), 7.83 – 7.77 (m, 3H, *H*-4', *H*-5', *H*-6'), 7.32 (s, 1H, 1=N*H*), 7.01 (s, 1H, SO_2-N*H*).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 160.3, 148.6, 135.2, 135.0, 133.3, 130.4, 125.2.
HR-MS (ESI+): *m/z* for $C_7H_6N_6O_4S+H^+$, $[M+H]^+$ calculated: 271.0244; found: 271.0241.
m.p. (Cy:EtOH): 127.3–129.7 °C.

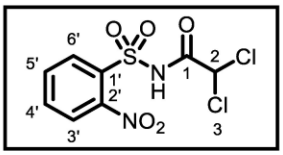
***N*-(2,2-Difluoroacetyl)-2-nitrobenzenesulfonamide (6s)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (2.02 g, 10.0 mmol, 1.0 eq.), 2,2-difluoroacetic anhydride (1.7 mL, 20.0 mmol, 2.0 eq.), and triethylamine (6 mL) were reacted in 70 mL anhydrous THF. 1.633 g (5.83 mmol, 58%) of the product was obtained by column chromatography (80 g silica (irregular); cyclohexane:ethyl acetate 30 → 60% ethyl acetate) as a colorless solid.
The product is moisture sensitive and is stored under argon at 6 °C in the fridge.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.16 – 8.10 (m, 1H, *H*-3'), 7.70 – 7.62 (m, 3H, *H*-4', *H*-5', *H*-6'), 5.73 (t, 1H, *J* = 55.3 Hz, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.0 (t, *J* = 24.8 Hz), 148.8, 136.4, 133.8, 132.6, 130.8, 124.6, 111.0 (t, *J* = 247.2 Hz).
^{19}F NMR (376 MHz, CD_3CN) δ [ppm]: -126.16 (dd, *J* = 55.3 Hz, 5.3 Hz).
HR-MS (ESI-): *m/z* for $C_8H_6F_2N_2O_5S$-H^-, $[M-H]^-$ calculated: 278.9893; found: 278.9892.

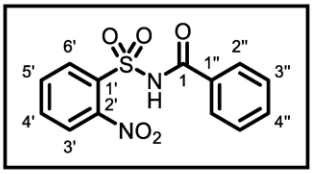
***N*-(2,2-Dichloroacetyl)-2-nitrobenzenesulfonamide (6t)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (2.02 g, 10.0 mmol, 1.0 eq.), dichloroacetyl chloride (1.2 mL, 12.0 mmol, 1.2 eq.), and triethylamine (3 mL) were reacted in 70 mL anhydrous THF. 2.256 g (7.21 mmol, 72%) of the product was obtained after crystallization (65 mL Cy:EtOH 7:3 (*v*:*v*); crystallization at 6 °C) as a colorless crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 10.44 (s, 1H, -N*H*), 8.33 – 8.31 (m, 1H, *H*-3'), 7.95 – 7.86 (m, 3H, *H*-4', *H*-5', *H*-6'), 6.19 (s, 1H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 162.7, 149.0, 137.2, 134.2, 133.7, 130.8, 126.1, 66.7.
HR-MS (ESI-): *m/z* for $C_8H_6{}^{35}Cl_2N_2O_5S$-H^-, $[M-H]^-$ calculated: 310.9302; found: 310.9304.
m.p. (Cy:EtOH): 144.1–146.4 °C.

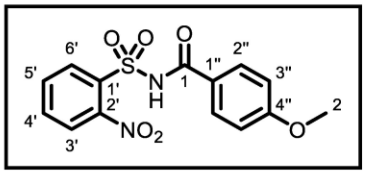
***N*-Benzoyl-2-nitrobenzenesulfonamide (6u)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.01 g, 5.0 mmol, 1.0 eq.), benzoyl chloride (0.8 mL, 5.5 mmol, 1.1 eq.), and triethylamine (1.7 mL) were reacted in 50 mL anhydrous THF. 1.002 g (3.27 mmol, 65%) of the product was obtained as a beige solid after evaporating the solvent and washing the product once with 10 mL methanol.

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.45 – 8.38 (m, 1H, *H*-3'), 7.93 – 7.83 (m, 5H, *H*-4', *H*-5', *H*-6', *H*-2''), 7.67 – 7.57 (m, 1H, *H*-4''), 7.55 – 7.44 (m, 2H, *H*-3'').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 167.8, 149.9, 136.3, 134.7, 134.5, 133.1, 133.0, 132.9, 129.8, 129.4, 125.7.
HR-MS (ESI-): *m/z* for $C_{13}H_{10}N_2O_5S$-H^-, $[M-H]^-$ calculated: 305.0237; found: 305.0229.

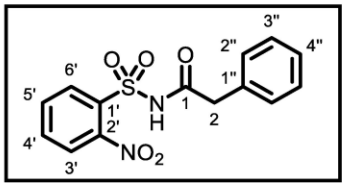
***N*-(4-Methoxybenzoyl)-2-nitrobenzenesulfonamide (6v)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.01 g, 5.0 mmol, 1.0 eq.), 4-methoxybenzoyl chloride (0.8 mL, 5.9 mmol, 1.2 eq.), and triethylamine (1.7 mL) were reacted in 50 mL anhydrous THF. 1.002 g (3.27 mmol, 65%) of the product was obtained as a beige solid after evaporating the solvent and washing the product once with 10 mL methanol.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 8.28 – 8.23 (m, 1H, *H*-3'), 8.05 – 7.98 (m, 1H, *H*-6'), 7.97 – 7.89 (m, 4H, *H*-4', *H*-5', *H*-2''), 7.09 – 7.01 (m, 2H, *H*-3''), 3.83 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 165.0, 163.4, 147.7, 135.3, 132.4, 132.3, 131.2, 130.8, 124.6, 123.2, 114.0, 55.6.
HR-MS (ESI-): *m/z* for $C_{14}H_{12}N_2O_6S$-H$^-$, [M-H]$^-$ calculated: 335.0343; found: 335.0339.

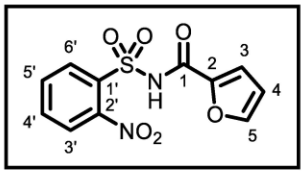
***N*-(2-Phenylacetyl)-2-nitrobenzenesulfonamide (6w)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.01 g, 5.0 mmol, 1.0 eq.), phenylacetyl chloride (0.8 mL, 6.0 mmol, 1.2 eq.), and triethylamine (1.7 mL) were reacted in 50 mL anhydrous THF. 0.890 g (2.78 mmol, 56%) of the product was obtained as a colorless solid after evaporating the solvent and washing the product once with 10 mL toluene.

^{1}H NMR (400 MHz, CD$_3$OD) δ [ppm]: 8.05 (d, 1H, *J* = 7.7 Hz, *H*-3'), 7.71 – 7.58 (m, 3H, *H*-4', *H*-5', *H*-6'), 7.28 – 7.14 (m, 5H, *H*-2'', *H*-3'', *H*-4''), 3.52 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, CD$_3$OD) δ [ppm]: 171.7, 149.7, 136.3, 134.6, 134.4, 133.0, 132.6, 130.4, 129.5, 128.2, 125.7, 43.4.
HR-MS (ESI+): *m/z* for $C_{14}H_{12}N_2O_5S$+H$^+$, [M+H]$^+$ calculated: 321.0540; found: 321.0537.

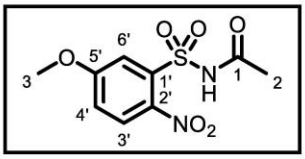
***N*-((2-Nitrophenyl)sulfonyl)furan-2-carboxamide (6x)**



According to general protocol **GPIV**, 2-nitrobenzensulfonamide (1.01 g, 5.0 mmol, 1.0 eq.), 2-furancarbonyl chloride (1.0 mL, 6.0 mmol, 1.2 eq.), and triethylamine (1.7 mL) were reacted in 50 mL anhydrous THF. 0.397 g (1.34 mmol, 27%) of the product was obtained after crystallization (45 mL; EtOH; crystallization at 6 °C) as a colorless crystals.

^{1}H NMR (400 MHz, CD$_3$CN) δ [ppm]: 8.37 – 8.31 (m, 1H, *H*-3'), 7.91 – 7.81 (m, 3H, *H*-4', *H*-5', *H*-6'), 7.73 (dd, 1H, *J* = 1.8 Hz, 0.8 Hz, *H*-3), 7.34 (dd, 1H, *J* = 3.7 Hz, 0.8 Hz, *H*-5), 6.63 (dd, *J* = 3.7 Hz, 1.8 Hz, *H*-4).
^{13}C NMR (101 MHz, CD$_3$CN) δ [ppm]: 155.9, 149.1, 148.6, 145.7, 136.6, 133.9, 133.4, 132.0, 125.8, 119.5, 113.8.
HR-MS: *m/z* for $C_{11}H_8N_2O_6S$+H$^+$, [M+H]$^+$ calculated: 287.0176; found: 287.0172.
m.p. (EtOH): 174.4–176.6 °C.

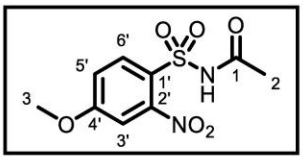
***N*-Acetyl-5-methoxy-2-nitrobenzenesulfonamide (6y)**



According to general protocol **GPIV**, **33** (4.64 g, 20 mmol, 1.0 eq.), acetic anhydride (9.4 mL, 10.2 g, 100 mmol, 5.0 eq.), and zinc chloride (0.273 g, 2 mmol, 0.1 eq.) were reacted. 5.12 g (18.67 mmol, 93%) of the product was obtained after crystallization (120 mL; EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 12.57 (s, 1H, -N*H*), 8.07 (d, 1H, *J* = 8.9 Hz, *H*-3'), 7.58 (d, *J* = 2.8 Hz, *H*-6'), 7.44 (dd, 1H, *J* = 8.9 Hz, 2.8 Hz, *H*-4'), 3.93 (s, 3H, *H*-3), 2.01 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 169.1, 161.3, 140.5, 133.4, 127.6, 118.5, 118.4, 56.7, 23.2.
HR-MS (ESI-): *m/z* for $C_9H_{10}N_2O_6S$-H$^-$, [M-H]$^-$ calculated: 273.0187; found: 273.0183.
m.p. (EtOH): 185.9–188.0 °C.

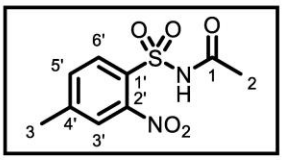
***N*-Acetyl-4-methoxy-2-nitrobenzenesulfonamide (6z)**



According to general protocol **GPIV**, **32** (4.64 g, 20 mmol, 1.0 eq.), acetic anhydride (9.4 mL, 10.2 g, 100 mmol, 5.0 eq.), and zinc chloride (0.273 g, 2 mmol, 0.1 eq.) were reacted. 5.20 g (18.96 mmol, 95%) of the product was obtained after crystallization (100 mL; EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 12.40 (s, 1H, -N*H*), 8.07 (d, 1H, *J* = 9.0 Hz, *H*-6'), 7.62 (d, 1H, *J* = 2.6 Hz, *H*-3'), 7.40 (dd, 1H, *J* = 9.0, 2.6 Hz, *H*-5'), 3.92 (s, 3H, *H*-3), 1.98 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 168.9, 163.7, 149.2, 134.4, 121.8, 116.8, 110.3, 56.8, 23.1.
HR-MS (ESI+): *m/z* for $C_9H_{10}N_2O_6S$+H$^+$, [M+H]$^+$ calculated: 275.0332; found: 275.0329.
m.p. (EtOH): 202.4–206.0 °C.

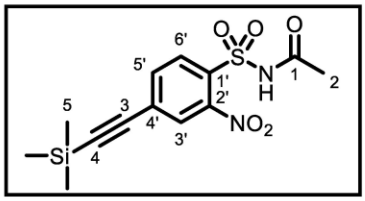
***N*-Acetyl-4-methyl-2-nitrobenzenesulfonamide (6aa)**



According to general protocol **GPIV**, **37** (4.32 g, 20 mmol, 1.0 eq.), acetic anhydride (9.4 mL, 10.2 g, 100 mmol, 5.0 eq.), and zinc chloride (0.273 g, 2 mmol, 0.1 eq.) were reacted. were reacted. 5.01 g (19.40 mmol, 97%) of the product was obtained after crystallization (110 mL, EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CDCl$_3$) δ [ppm]: 8.11 (d, 1H, *J* = 8.2 Hz, *H*-6'), 7.68 (d, 1H, *J* = 1.7 Hz, *H*-3'), 7.61 (dd, *J* = 8.2 Hz, 1.7 Hz, *H*-5'), 2.47 (s, 3H, *H*-3), 2.02 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CDCl$_3$) δ [ppm]: 169.6, 148.9, 148.6, 133.7, 133.6, 129.1, 126.0, 23.7, 21.40.
HR-MS (ESI+): *m/z* for $C_9H_{10}N_2O_5S$+H$^+$, [M+H]$^+$ calculated: 259.0383; found: 259.0378.
m.p. (EtOH): 159.3–162.6 °C.

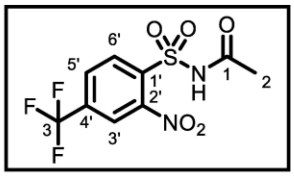
***N*-Acetyl-2-nitro-4-((trimethylsilyl)ethynyl)benzenesulfonamide (6ab)**



According to general protocol **GPIV**, **39** (850 mg, 2.8 mmol, 1.0 eq.), acetic anhydride (2.6 mL, 2.9 g, 28 mmol, 10 eq.), and zinc chloride (38 mg, 0.028 mmol, 0.1 eq.) were reacted. 868 mg (2.55 mmol, 91%) of the product was obtained by reversed phase column chromatography (C_{18} silica gel, gradient: 50% acetonitrile isocratic) as a colorless solid.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.18 (d, 1H, *J* = 8.2 Hz, *H*-6'), 7.86 (d, 1H, *J* = 1.6 Hz, *H*-3'), 7.78 (dd, 1H, *J* = 8.2 Hz, 1.6 Hz, *H*-5'), 2.03 (s, 3H, *H*-2), 0.26 (s, 9H, *H*-5).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.6, 149.1, 135.7, 134.2, 131.5, 130.8, 128.3, 102.9, 101.6, 23.8, -0.5.
HR-MS (ESI-): *m/z* for $C_{13}H_{16}N_2O_5SSi$-H$^-$, [M-H]$^-$ calculated: 339.0476; found: 339.0472.

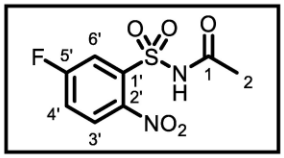
***N*-Acetyl-2-nitro-4-(trifluoromethyl)benzenesulfonamide (6ac)**



According to general protocol **GPIV**, **35** (5.40 g, 20 mmol, 1.0 eq.), acetic anhydride (9.4 mL, 10.2 g, 100 mmol, 5.0 eq.), and zinc chloride (0.273 g, 2 mmol, 0.1 eq.) were reacted. 6.07 g (19.44 mmol, 97%) of the product was obtained after crystallization (135 mL Cy:EtOH 10:1 (*v*:*v*); crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.43 (m, 1H, *H*-6'), 8.20 (m, 1H, *H*-3'), 8.12 (m, 1H, *H*-5'), 2.05 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.8, 149.2, 136.7 (q, *J* = 34.7 Hz), 135.5, 135.2, 130.2 (q, *J* = 3.7 Hz), 123.3 (q, *J* = 272.8 Hz), 123.2 (q, *J* = 3.9 Hz), 23.8.
^{19}F NMR (376 MHz, CD_3CN) δ [ppm]: -65.17.
HR-MS (ESI-): *m/z* for $C_9H_7F_3N_2O_5S$-H$^-$, [M-H]$^-$ calculated: 310.9955; found: 310.9962.
m.p. (Cy:EtOH**):** 147.9–150.2 °C.

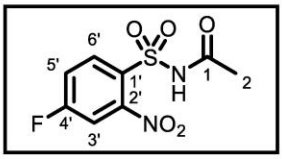
***N*-Acetyl-5-fluoro-2-nitrobenzenesulfonamide (6ad)**



According to general protocol **GPIV**, **21** (4.40 g, 20 mmol, 1.0 eq.), acetic anhydride (9.4 mL, 10.2 g, 100 mmol, 5.0 eq.), and zinc chloride (0.273 g, 2 mmol, 0.1 eq.) were reacted were reacted. 4.75 g (18.12 mmol, 91%) of the product was obtained after crystallization (100 mL EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 12.75 (s, 1H, -N*H*), 8.19 (dd, 1H, *J* = 8.9 Hz, 4.6 Hz, *H*-3'), 7.96 (dd, 1H, *J* = 8.2 Hz, 2.8 Hz, *H*-6'), 7.86 (ddd, 1H, *J* = 8.9 Hz, 7.7 Hz, 2.8 Hz, *H*-4'), 2.03 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 169.4, 162.0 (d, *J* = 255.4 Hz), 144.1 (d, *J* = 3.8 Hz), 133.6 (d, *J* = 7.8 Hz), 127.9 (d, *J* = 9.3 Hz), 122.3 (d, *J* = 23.2 Hz), 119.5 (d, *J* = 27.4 Hz), 23.2.
^{19}F NMR (376 MHz, $DMSO_{d6}$) δ [ppm]: -103.80 (td, *J* = 7.9 Hz, 4.6 Hz).
HR-MS (ESI-): *m/z* for $C_8H_7FN_2O_5S$-H$^-$, [M-H]$^-$ calculated: 260.9987; found: 260.9985.
m.p. (EtOH): 172.8–174.6 °C.

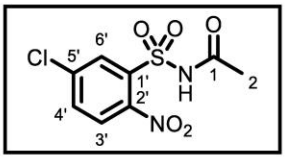
***N*-Acetyl-4-fluoro-2-nitrobenzenesulfonamide (6ae)**



According to general protocol **GPIV**, **34** (4.40 g, 20 mmol, 1.0 eq.), acetic anhydride (9.4 mL, 10.2 g, 100 mmol, 5.0 eq.), and zinc chloride (0.273 g, 2 mmol, 0.1 eq.) were reacted. 4.87 g (18.57 mmol, 93%) of the product was obtained after crystallization (95 mL, EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.30 (dd, 1H, *J* = 8.9 Hz, 5.3 Hz, *H*-6'), 7.68 (dd, *J* = 7.8 Hz, 2.6 Hz, *H*-3'), 7.56 (ddd, 1H, *J* = 8.9 Hz, 7.8 Hz, 2.6 Hz, *H*-5'), 2.03 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.7, 166.1 (d, *J* = 258.8 Hz), 150.3, 136.9 (d, *J* = 10.0 Hz), 128.4 (d, *J* = 4.0 Hz), 120.2 (d, *J* = 21.9 Hz), 114.0 (d, *J* = 28.3 Hz), 23.7.
^{19}F NMR (376 MHz, CD_3CN) δ [ppm]: -102.54 (td, *J* = 8.0 Hz, 5.4 Hz).
HR-MS (ESI-): *m/z* for $C_8H_7FN_2O_5S$-H$^-$, [M-H]$^-$ calculated: 260.9987; found: 260.9983.
m.p. (EtOH): 167.2–169.4 °C.

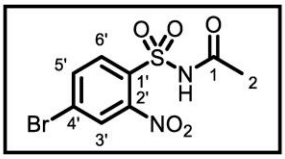
***N*-Acetyl-5-chloro-2-nitrobenzenesulfonamide (6af)**



According to general protocol **GPIV**, **31** (4.73 g, 20 mmol, 1.0 eq.), acetic anhydride (9.4 mL, 10.2 g, 100 mmol, 5.0 eq.), and zinc chloride (0.273 g, 2 mmol, 0.1 eq.) were reacted. 5.24 g (18.80 mmol, 94%) of the product was obtained after crystallization (100 mL EtOH; crystallization at 6 °C) as a colorless crystals.

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 12.77 (s, 1H, -N*H*), 8.14 – 8.05 (m, 3H, *H*-3', *H*-4', *H*-6'), 2.02 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 169.4, 146.1, 136.7, 135.3, 132.5, 131.6, 126.7, 23.2.
HR-MS (ESI-): *m/z* for $C_8H_7{}^{35}ClN_2O_5S$-H$^-$, [M-H]$^-$ calculated: 276.9691; found: 276.9693.
m.p. (EtOH): 222.2–227.4 °C.

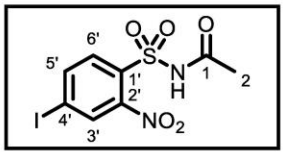
***N*-Acetyl-4-bromo-2-nitrobenzenesulfonamide (6ag)**



According to general protocol **GPIV**, **36** (5.62 g, 20 mmol, 1.0 eq.), acetic anhydride (9.4 mL, 10.2 g, 100 mmol, 5.0 eq.), and zinc chloride (0.273 g, 2 mmol, 0.1 eq.) were reacted. 6.13 g (18.97 mmol, 95%) of the product was obtained after crystallization (130 mL EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.12 (d, 1H, *J* = 8.5 Hz, *H*-5'), 8.05 (d, 1H, *J* = 1.9 Hz, *H*-3'), 7.97 (dd, 1H, *J* = 8.5 Hz, 1.9 Hz, *H*-6'), 2.03 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.7, 149.2, 136.3, 135.2, 131.1, 129.7, 128.6, 23.7.
HR-MS (ESI-): *m/z* for $C_8H_7{}^{79}BrN_2O_5S$-H$^-$, [M-H]$^-$ calculated: 320.9186; found: 320.9182.
m.p. (EtOH): 197.1–200.4 °C.

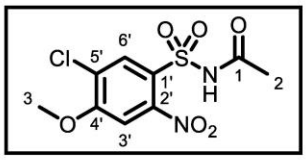
***N*-Acetyl-5-iodo-2-nitrobenzenesulfonamide (6ah)**



According to general protocol **GPIV**, **23** (1.640 g, 5.0 mmol, 1.0 eq.), acetic anhydride (4.7 mL, 5.1 g, 50 mmol, 10 eq.), and zinc chloride (79 mg, 0.5 mmol, 0.1 eq.) were reacted. 1.312 g (3.54 mmol, 71%) of the product was obtained after crystallization (20 mL Cy:EtOH 9:1 (*v*:*v*); crystallization at 6 °C) as beige crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.22 – 8.16 (m, 2H, *H*-3', *H*-5'), 7.92 (d, 1H, *J* = 8.3 Hz, *H*-6'), 2.02 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.7, 148.7, 142.4, 134.7, 134.1, 131.7, 101.8, 23.8.
HR-MS (ESI-): *m/z* for $C_8H_7IN_2O_5S$-H$^-$, [M-H]$^-$ calculated: 368.9048; found: 368.90484.
m.p. (Cy:EtOH): 164.0–169.9 °C.

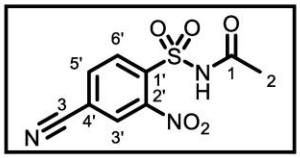
***N*-Acetyl-4-chloro-5-methoxy-2-nitrobenzenesulfonamide (6ai)**



According to general protocol **GPIV**, **28** (2.60 g, 9.75 mmol, 1.0 eq.), acetic anhydride (9.2 mL, 10.0 g, 97.5 mmol, 10 eq.), and zinc chloride (0.133 g, 0.975 mmol, 0.1 eq.) were reacted. 2.66 g (8.62 mmol, 88%) of the product was obtained after crystallization (70 mL EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.17 (s, 1H, *H*-3'), 7.51 (s, 1H, *H*-6'), 4.01 (s, 3H, *H*-3), 2.03 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.7, 160.7, 148.9, 134.7, 125.8, 123.9, 109.8, 58.6, 23.7.
HR-MS (ESI-): *m/z* for $C_9H_9{}^{35}ClN_2O_6S$-H$^-$, [M-H]$^-$ calculated: 306.9797; found: 306.9796.
m.p. (EtOH): 197.3–199.0 °C.

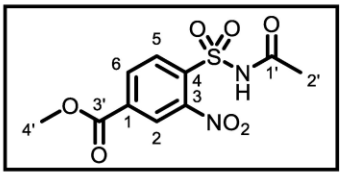
***N*-Acetyl-4-cyano-2-nitrobenzenesulfonamide (6aj)**



According to general protocol **GPIV**, **24** (1.14 g, 5.0 mmol, 1.0 eq.), acetic anhydride (4.7 mL, 5.1 g, 50 mmol, 10 eq.), and zinc chloride (57 mg, 0.5 mmol, 0.1 eq.) were reacted. 1.094 g (4.06 mmol, 81%) of the product was obtained after crystallization (20 mL Cy:^{i}PrOH 9:1 (*v*:*v*); crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.38 (d, 1H, *J* = 8.3 Hz, *H*-6'), 8.25 (d, 1H, *J* = 1.6 Hz, *H*-3'), 8.15 (dd, 1H, *J* = 8.3 Hz, 1.6 Hz, *H*-5'), 2.04 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.8, 148.9, 137.1, 135.7, 134.8, 129.5, 119.4, 116.6, 23.8.
HR-MS (ESI-): *m/z* for $C_9H_7N_3O_5S$-H$^-$, [M-H]$^-$ calculated: 268.0034; found: 268.0030.
m.p. (Cy:^{i}PrOH**):** 172.3–176.9 °C.

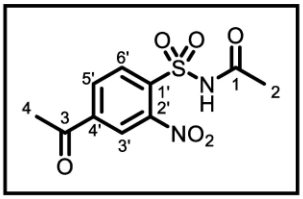
Methyl 4-(*N*-acetylsulfamoyl)-3-nitrobenzoate (6ak)



According to general protocol **GPIV**, **27** (1.31 g, 5.0 mmol, 1.0 eq.), acetic anhydride (4.7 mL, 5.1 g, 50 mmol, 10 eq.), and zinc chloride (71 mg, 0.5 mmol, 0.1 eq.) were reacted. 1.133 g (3.75 mmol, 75%) of the product was obtained after crystallization (55 mL Cy:EtOH 9:1 (*v*:*v*); crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.38 – 8.29 (m, 3H, *H*-2', *H*-5', *H*-2'), 3.93 (s, 3H, *H*-4), 2.04 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.8, 164.7, 149.1, 137.4, 135.4, 134.5, 133.5, 126.2, 53.9, 23.8.
HR-MS (ESI-): *m/z* for $C_{10}H_{10}N_2O_7S$-H$^-$, [M-H]$^-$ calculated: 301.0136; found: 301.0133.
m.p. (EtOH): 163.6–167.3 °C.

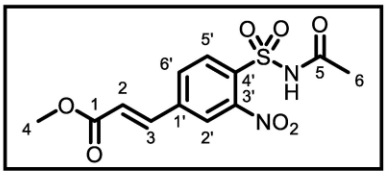
***N*-Acetyl-4-acetyl-2-nitrobenzenesulfonamide (6al)**



According to general protocol **GPIV**, **38** (1.20 g, 4.9 mmol, 1.0 eq.), acetic anhydride (4.6 mL, 5.0 g, 49 mmol, 10 eq.), and zinc chloride (67 mg, 0.49 mmol, 0.1 eq.) were reacted. 1.25 g (4.37 mmol, 89%) of the product was obtained after crystallization (40 mL EtOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.35 (m, 1H, *H*-6'), 8.32 – 8.28 (m, 2H, *H*-3', *H*-5'), 2.64 (s, 3H, *H*-4), 2.04 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 196.4, 169.7, 149.2, 143.1, 134.9, 134.5, 132.4, 124.9, 27.4, 23.8.
HR-MS (ESI-): *m/z* for $C_{10}H_{10}N_2O_6S$-H$^-$, [M-H]$^-$ calculated: 285.0187; found: 285.0182.
m.p. (EtOH**):** 168.9–172.8 °C.

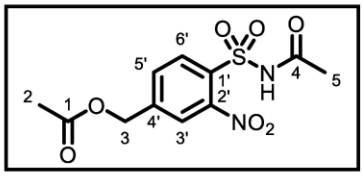
Methyl (*E*)-4-(*N*-acetylsulfamoyl)-3-nitrocinnamate (6am)



According to general protocol **GPIV**, **26** (1.42 g, 5.0 mmol, 1.0 eq.), acetic anhydride (9.4 mL, 20.2 g, 100 mmol, 20 eq.), and zinc chloride (61 mg, 0.5 mmol, 0.1 eq.) were reacted. 1.032 g (3.12 mmol, 62%) of the product was obtained after crystallization (75 mL EtOH; crystallization at 6 °C) as beige crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.24 (d, 1H, *J* = 8.2 Hz, *H*-5'), 8.08 (d, 1H, *J* = 1.8 Hz, *H*-2'), 7.98 (dd, 1H, *J* = 8.2 Hz, 1.8 Hz, *H*-6'), 7.70 (d, 1H, *J* = 16.1 Hz, *H*-3), 6.72 (d, 1H, *J* = 16.1 Hz, *H*-2), 3.78 (s, 3H, *H*-4), 2.03 (s, 3H, *H*-6).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.8, 167.0, 149.4, 148.9, 142.4, 141.0, 134.4, 132.2, 125.0, 124.5, 52.7, 23.8.
HR-MS (ESI-): *m/z* for $C_{12}H_{12}N_2O_7S$-H$^-$, [M-H]$^-$ calculated: 327.0292; found: 327.0286.
m.p. (EtOH): 220.8–229.8 °C.

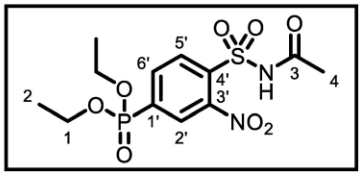
4-(*N*-Acetylsulfamoyl)-3-nitrobenzyl acetate (6an)



According to general protocol **GPII**, **16** (1.48 g, 4.6 mmol, 1.0 eq.), 3-dichloro-5,5-dimethylhydantoin (2.09 g, 10.6 mmol, 2.3 eq.), and concentrated hydrochloric acid (5 mL; 37% *w*:*v*) in 70 mL THF were reacted. The crude product was used without further purification.
According to general protocol **GPIV**, crude 3-nitro-4-sulfamoylbenzyl acetate, acetic anhydride (4.7 mL, 5.1 g, 50 mmol, 11 eq.), and zinc chloride (68 mg, 0.5 mmol, 0.1 eq.) were reacted. 0.983 g (2.98 mmol, 43%) of the product was obtained after crystallization (50 mL Cy; crystallization at 6 °C) as colorless crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.22 (d, 1H, *J* = 8.2 Hz, *H*-6'), 7.85 – 7.83 (m, 1H, *H*-3'), 7.80 – 7.75 (m, 1H, *H*-5'), 5.20 (s, 2H, *H*-3), 2.10 (s, 3H, *H*-2), 2.03 (s, 3H, *H*-5).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 171.4, 169.7, 149.1, 146.3, 134.1, 131.5, 131.1, 124.1, 64.6, 23.8, 20.9.
HR-MS (ESI-): *m/z* for $C_{11}H_{12}N_2O_7S$-H$^-$, [M-H]$^-$ calculated: 315.0292; found: 315.0292.
m.p. (Cy): 173.1–175.3 °C.

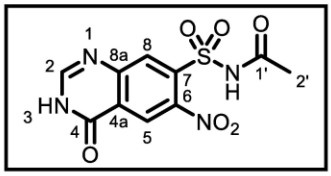
Diethyl (4-(*N*-acetylsulfamoyl)-3-nitrophenyl)phosphonate (6ao)



According to general protocol **GPIV**, **40** (0.68 g, 2.0 mmol, 1.0 eq.), acetic anhydride (4.7 mL, 5.1 g, 50 mmol, 25 eq.), and zinc chloride (28 mg, 0.2 mmol, 10 mol%.) were reacted. 0.588 g (1.38 mmol, 78%) of the product was obtained after crystallization (25 mL Cy:EtOH 9:1 (*v*:*v*); crystallization at 6 °C) as beige crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 10.19 (s, 1H, -N*H*), 8.35 (dd, 1H, *J* = 7.8 Hz, 3.6 Hz, *H*-2'), 8.18 – 8.11 (m, 2H, *H*-5', *H*-6'), 4.22 – 4.07 (m, 4H, *H*-1), 2.05 (s, 3H, *H*-4), 1.30 (td, 6H, *J* = 7.1 Hz, 0.6 Hz, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.8, 148.9 (d, *J* = 17.8 Hz), 138.9, 137.1, 135.9 (d, *J* = 9.4 Hz), 135.2 (d, *J* = 3.4 Hz), 134.2 (d, *J* = 14.7 Hz), 128.2 (d, *J* = 12.0 Hz), 64.3 (d, *J* = 5.7 Hz), 23.8, 16.6 (d, *J* = 6.2 Hz).
^{31}P NMR (162 MHz, CD_3CN) δ [ppm]: 11.69.
HR-MS (ESI+): *m/z* for $C_{12}H_{17}N_2O_8PS$+H$^+$, [M+H]$^+$ calculated: 381.0516; found: 381.0516.
m.p. (Cy:EtOH): 171.9–176.7 °C.

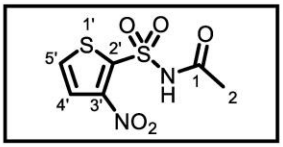
***N*-Acetyl-3,4-dihydro-6-nitro-4-oxo-quinazoline-7-sulfonamide (6ap)**



According to general protocol **GPIV**, **29** (1.72 g, 6.4 mmol, 1.0 eq.), acetic anhydride (9.4 mL, 10.2 g, 100 mmol, 16 eq.), and zinc chloride (0.091 g, 0.7 mmol, 0.1 eq.) were reacted. 0.931 g (2.98 mmol, 47%) of the product was obtained after crystallization (MeOH; crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 12.95 (s, 1H, 3-N*H*), 8.60 (s, 1H, *H*-5), 8.38 (s, 1H, *H*-8), 8.30 (s, 1H, *H*-2), 2.02 (s, 3H, *H*-2').
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 169.6, 159.2, 150.4, 149.9, 144.2, 136.0, 132.2, 126.3, 123.7, 23.4.
HR-MS (ESI-): *m/z* for $C_{10}H_8N_4O_6S$-H$^-$, [M-H]$^-$ calculated: 311.0092; found: 311.0095.
m.p. (MeOH**):** decomposition from 212.1 °C.

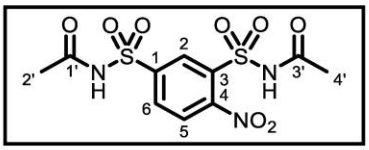
***N*-Acetyl-3-nitrothiophene-2-sulfonamide (6aq)**



According to general protocol **GPIV**, **30** (1.041 g, 5.0 mmol, 1.0 eq.), acetic anhydride (4.7 mL, 5.1 g, 50 mmol, 10 eq.), and zinc chloride (73 mg, 0.5 mmol, 0.1 eq.) were reacted. 1.131 g (4.52 mmol, 90%) of the product was obtained after crystallization (45 mL Cy:EtOH 9:1 (*v*:*v*); crystallization at 6 °C) as off-white crystals.

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 10.05 (s, 1H, -N*H*), 7.85 (d, 1H, *J* = 5.6 Hz, *H*-4'), 7.67 (d, 1H, *J* = 5.6 Hz, *H*-5'), 2.03 (s, 3H, *H*-2).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 169.6, 146.7, 139.9, 133.4, 126.7, 23.9.
HR-MS (ESI-): *m/z* for $C_6H_6N_2O_5S$-H^-, $[M-H]^-$ calculated: 248.9645; found: 248.9646.
m.p. (Cy:EtOH): 176.0–178.8 °C.

***N,N'*-Diacetyl-4-nitrobenzene-1,3-disulfonamide (6ar)**

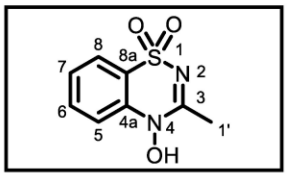


According to general protocol **GPIV**, **41** (0.665 g, 2.5 mmol, 1.0 eq.), acetic anhydride (5.0 mL, 5.4 g, 39 mmol, 15.6 eq.), and zinc chloride (53 mg, 0.4 mmol, 0.2 eq.) were reacted. 0.683 g (1.87 mmol, 75%) of the product was obtained after crystallization (25 mL MeOH; crystallization at 6 °C) as a colorless crystals.

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 8.50 (d, 1H, *J* = 1.7 Hz, *H*-2), 8.43 (d, 1H, *J* = 8.4 Hz, *H*-5), 8.39 (dd, 1H, *J* = 8.4 Hz, 1.7 Hz, *H*-6), 2.03 (s, 3H, *H*-4'), 1.99 (s, 3H, *H*-2').
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 169.6, 169.6, 147.4, 144.7, 134.9, 133.7, 131.3, 123.9, 23.4, 23.3.
HR-MS (ESI+): *m/z* for $C_{10}H_{11}N_3O_8S_2$+H^+, $[M+H]^+$ calculated: 366.0060; found: 366.0060.
m.p. (MeOH): 207.4–209.8 °C.

7.4. 4-Hydroxybenzo[*e*]-1,2,4-thiazine-1,1-dioxides (7a-7ar)

4*H*-4-Hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7a)

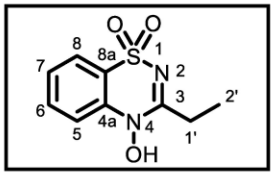


0.15 mmol, 0.30 mmol and 2.4 mmol Scale:
According to general protocol **GPVI**, **6a** (36.6 mg, 0.15 mmol) were reacted. Full conversion was achieved by applying 57.9 C (4.0 *F*). 30.9 mg (0.146 mmol, 97%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 10% → 90% acetonitrile). The yields of the scale-up experiments are listed in table S5.

9.0 mmol and 18.0 mmol Scale:
The crude product was purified after extraction by filtration over silica (200 g silica (irregular); ethyl acetate) and crystallization (80–160 mL EtOH; crystallization at -18 °C) as off-white crystals. The yields of the scale-up experiments are listed in table S5.

^{1}H NMR (300 MHz, CD_3OD) δ [ppm]: 7.86 (dd, 1H, *J* = 8.0 Hz, 1.4 Hz, *H*-8), 7.78 (ddd, *J* = 8.5 Hz, 7.1 Hz, 1.4 Hz, *H*-6), 7.71 (dd, 1H, *J* = 8.5 Hz, 1.4 Hz, *H*-5), 7.53 (ddd, 1H, *J* = 8.0 Hz, 7.1 Hz, 1.4 Hz, *H*-7), 2.49 (s, 3H, *H*-1').
^{13}C NMR (75 MHz, CD_3OD) δ [ppm]: 161.1, 138.5, 134.6, 127.7, 125.0, 123.7, 115.7, 21.6.
HR-MS (ESI+): *m/z* for $C_8H_8N_2O_3S+H^+$, $[M+H]^+$ calculated: 213.0329; found: 213.0330.
m.p. (EtOH): 212.4–218.7 °C.

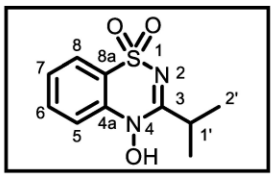
4*H*-4-Hydroxy-3-ethylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7b)



According to general protocol **GPVI**, **6b** (38.7 mg, 0.15 mmol) were reacted. Full conversion was achieved by applying 57.9 C (4.0 *F*) and 0.8 mL TFA as additive in the cathodic compartment. 19.1 mg (0.0840 mmol, 56%) of the product were obtained as an off-white solid by column chromatography (12 g silica (irregular); cyclohexane:ethyl acetate 50 → 66% ethyl acetate).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.85 (dd, 1H, *J* = 8.0 Hz, 1.4 Hz, *H*-8), 7.77 (ddd, 1H, *J* = 8.5 Hz, 7.2 Hz, 1.4 Hz, *H*-6), 7.71 (dd, 1H, *J* = 8.5 Hz, 1.3 Hz, *H*-5), 7.52 (ddd, 1H, *J* = 8.0 Hz, 7.2 Hz, 1.3 Hz, *H*-7), 2.87 (q, 2H, *J* = 7.4 Hz, *H*-1'), 1.28 (t, 3H, *J* = 7.4 Hz, *H*-2').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 164.4, 138.8, 134.6, 127.7, 125.0, 123.6, 115.7, 27.9, 9.9.
HR-MS (ESI+): *m/z* for $C_9H_{10}N_2O_3S+H^+$, $[M+H]^+$ calculated: 227.0485; found: 227.0484.

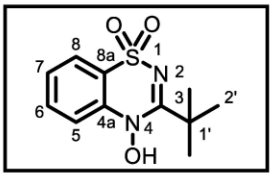
4*H*-4-Hydroxy-3-isopropylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7c)



According to general protocol **GPVI**, **6c** (41.0 mg, 0.15 mmol) were reacted. Full conversion was achieved by applying 57.9 C (4.0 *F*) and 0.8 mL TFA as additive in the cathodic compartment. 21.0 mg (0.0874 mmol, 58%) of the product were obtained as an off-white solid by column chromatography (12 g silica (irregular); cyclohexane:ethyl acetate 50 → 66% ethyl acetate).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.86 (dd, 1H, *J* = 8.0 Hz, 1.4 Hz, *H*-8), 7.81 – 7.69 (m, 2H, *H*-5, *H*-6), 7.53 (ddd, 1H, *J* = 8.0 Hz, 7.0 Hz, 1.5 Hz, *H*-7), 3.53 (hept, 1H, *J* = 6.8 Hz, *H*-1'), 1.29 (d, 1H, *J* = 6.8 Hz, *H*-2').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 167.5, 138.9, 134.6, 127.8, 125.0, 123.7, 115.9, 32.3, 19.8.
HR-MS (ESI+): *m/z* for $C_{10}H_{12}N_2O_3S+H^+$, $[M+H]^+$ calculated: 241.0642; found: 241.0638.

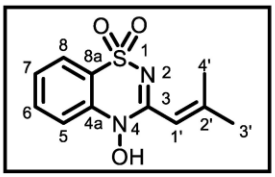
4*H*-4-Hydroxy-3-*tert*-butylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7d)



According to general protocol **GPVII**, **6d** (42.9 mg, 0.15 mmol) were reacted. 18.3 mg (0.0720 mmol, 48%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 30% → 60% acetonitrile).

^{1}H NMR (600 MHz, CD_3CN) δ [ppm]: 9.01 (s, 1H, -N-O*H*), 7.81 (dd, 1H, *J* = 8.0 Hz, 1.5 Hz, *H*-8), 7.73 (ddd, 1H, *J* = 8.7 Hz, 7.3 Hz, 1.5 Hz, *H*-6), 7.66 (dd, 1H, *J* = 8.7 Hz, 1.1 Hz, *H*-5), 7.49 (ddd, 1H, *J* = 8.0 Hz, 7.3 Hz, 1.1 Hz, *H*-7), 1.42 (s, 9H, *H*-2').
^{13}C NMR (151 MHz, CD_3CN) δ [ppm]: 166.8, 139.5, 134.2, 127.5, 124.5, 123.3, 115.8, 41.0, 28.1.
HR-MS (ESI-): *m/z* for $C_{11}H_{14}N_2O_3S$-H$^-$, [M-H]$^-$ calculated: 253.0652; found: 253.0652.

4*H*-4-Hydroxy-3-(2-methylprop-1-en-1-yl)benzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7e)

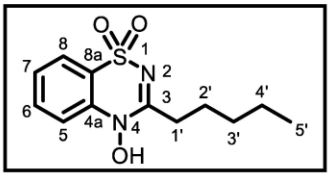


a) According to general protocol **GPVI**, **6e** (42.6 mg, 0.15 mmol) were reacted. Full conversion was achieved by applying 57.9 C (4.0 *F*) and 0.8 mL TFA as additive in the cathodic compartment. The reaction mixture was treated in the microwave after electrolysis. 12.0 mg (0.0476 mmol, 32%) of the product were obtained as beige solid by reversed phase column chromatography (12 g silica (irregular); cyclohexane:ethyl acetate 50% ethyl acetate).

b) According to general protocol **GPVII**, **6e** (42.6 mg, 0.15 mmol) were reacted. 27.1 mg (0.111 mmol, 74%) of the product were obtained as beige solid by reversed phase column chromatography (C_{18} silica gel, gradient: 30% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.88 – 7.81 (m, 1H, *H*-8), 7.79 – 7.73 (m, 2H, *H*-5, *H*-6), 7.53 (ddd, 1H, *J* = 8.2 Hz, 6.0 Hz, 2.3 Hz, *H*-7), 6.55 (p, 1H, *J* = 1.4 Hz, *H*-1'), 2.29 (d, 3H, *J* = 1.4 Hz, *H*-4'), 2.07 (d, 3H, *J* = 1.4 Hz, *H*-3').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 158.6, 157.1, 138.9, 134.5, 127.7, 124.7, 123.7, 116.0, 114.8, 28.4, 21.0.
HR-MS (ESI+): *m/z* for $C_{11}H_{12}N_2O_3S$+Na$^+$, [M+Na]$^+$ calculated: 275.0461; found: 275.0459.

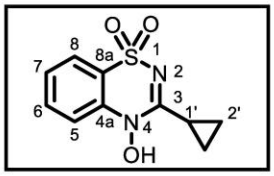
4*H*-4-Hydroxy-3-(1-pentyl)benzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7f)



According to general protocol **GPVI**, **6f** (45.3 mg, 0.15 mmol) were reacted. Full conversion was achieved by applying 57.9 C (4.0 *F*) and 0.8 mL TFA as additive in the cathodic compartment. 32.7 mg (0.122 mmol, 81%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 40% → 90% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.85 (dd, 1H, *J* = 8.1 Hz, 1.4 Hz, *H*-8), 7.77 (td, 1H, *J* = 7.1, 1.4 Hz, *H*-6), 7.71 (dd, 1H, *J* = 8.5 Hz, 1.3 Hz, *H*-5), 7.52 (td, 1H, *J* = 7.1 Hz, 1.3 Hz, *H*-7), 2.85 – 2.80 (m, 2H, *H*-1'), 1.84 – 1.73 (m, 2H, *H*-2'), 1.48 – 1.35 (m, 4H, *H*-3', *H*-4'), 0.98 – 0.92 (m, 3H, *H*-5').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 163.7, 138.7, 134.6, 127.8, 125.0, 123.7, 115.8, 34.3, 32.3, 26.3, 23.4, 14.3.
HR-MS (ESI-): *m/z* for $C_{12}H_{16}N_2O_3S$-H$^-$, [M-H]$^-$ calculated: 267.0809; found: 267.0806.

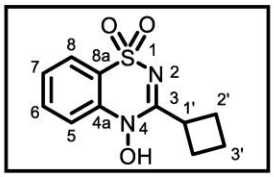
4*H*-3-Cyclopropyl-4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7g)



According to general protocol **GPVI**, **6g** (40.4 mg, 0.15 mmol) were reacted. 23.4 mg (0.0982 mmol, 65%) of the product were obtained as beige solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.83 (d, 1H, *J* = 7.3 Hz, *H*-8), 7.80 – 7.74 (m, 2H, *H*-5, *H*-6), 7.55 – 7.47 (m, 1H, *H*-7), 2.68 (hept, 1H, *J* = 4.7 Hz, *H*-1'), 1.27 – 1.15 (m, 4H, *H*-2').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 165.3, 138.9, 134.5, 127.7, 124.8, 124.1, 115.8, 12.2, 11.0.
HR-MS (ESI-): *m/z* for $C_{10}H_{10}N_2O_3S$-H$^-$, [M-H]$^-$ calculated: 237.0339; found: 237.0341.

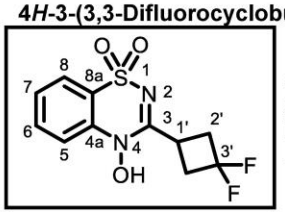
4*H*-3-Cyclobutyl-4-hydroxy-3-cyclobutylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7h)



According to general protocol **GPVI**, **6h** (42.7 mg, 0.15 mmol) were reacted. 28.6 mg (0.113 mmol, 75%) of the product were obtained as beige solid by reversed phase column chromatography (C_{18} silica gel, gradient: 30% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.85 (dd, 1H, *J* = 7.9 Hz, 1.4 Hz, *H*-8), 7.76 (ddd, 1H, *J* = 8.5, 7.3 Hz, 1.4 Hz, *H*-6), 7.67 (dd, 1H, *J* = 8.5 Hz, 1.2 Hz, *H*-5), 7.50 (ddd, 1H, *J* = 7.9 Hz, 7.3 Hz, 1.2 Hz, *H*-7), 3.95 (pd, 1H, *J* = 8.6 Hz, 1.1 Hz, *H*-1'), 2.52 – 2.39 (m, 2H, *H*-2'), 2.39 – 2.28 (m, 2H, *H*-2'), 2.16 – 2.02 (m, 1H, *H*-3'), 1.97 – 1.86 (m, 1H, *H*-3').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 164.8, 138.9, 134.6, 127.6, 125.0, 123.5, 115.6, 38.7, 26.7, 18.8.
HR-MS (ESI-): *m/z* for $C_{11}H_{12}N_2O_3S$-H$^-$, [M-H]$^-$ calculated: 251.0496; found: 251.0495.

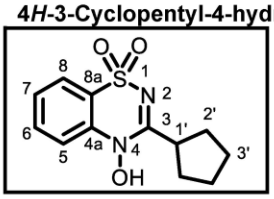
4*H*-3-(3,3-Difluorocyclobutyl)-4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7i)



According to general protocol **GPVI**, **6i** (48.1 mg, 0.15 mmol) were reacted. 28.7 mg (0.0996 mmol, 66%) of the product were obtained as beige solid by reversed phase column chromatography (C_{18} silica gel, gradient: 25% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.87 (dd, 1H, *J* = 7.9 Hz, 1.5 Hz, *H*-8), 7.78 (ddd, *J* = 8.5 Hz, 7.3 Hz, 1.5 Hz, *H*-6), 7.70 (dd, 1H, *J* = 8.5 Hz, 1.2 Hz, *H*-5), 7.53 (ddd, 1H, *J* = 7.9 Hz, 7.3 Hz, 1.2 Hz, *H*-7), 3.79 (pd, 1H, *J* = 8.7 Hz, 2.4 Hz, *H*-1'), 3.09 – 2.87 (m, 4H, *H*-2').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 162.4, 138.7, 134.7, 128.0, 125.1, 123.6, 115.7, 39.6 (t, *J* = 24.5 Hz), 27.2 (dd, *J* = 16.8 Hz, 5.5 Hz).
^{19}F NMR (376 MHz, CD_3OD) δ [ppm]: -85.37 (ttd, *J* = 11.7, 5.6, 2.5 Hz), -85.89 (ttd, *J* = 11.9, 5.6, 2.5 Hz), -100.09 (tt, *J* = 17.7, 13.8 Hz), -100.61 (tt, *J* = 17.3, 13.9 Hz).
HR-MS (ESI-): *m/z* for $C_{11}H_{10}F_2N_2O_3S$-H$^-$, [M-H]$^-$ calculated: 287.0307; found: 287.0309.

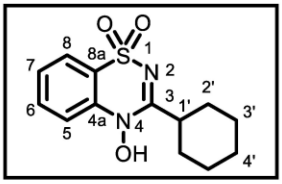
4*H*-3-Cyclopentyl-4-hydroxy-3-cyclopentylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7j)



According to general protocol **GPVI**, **6j** (44.7 mg, 0.15 mmol) were reacted. Full conversion was achieved by applying 65.1 C (4.5 *F*) and 0.8 mL TFA as additive in the cathodic compartment. 34.2 mg (0.128 mmol, 85%) of the product were obtained as beige solid by reversed phase column chromatography (C_{18} silica gel, gradient: 10% → 90% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.85 (dd, 1H, *J* = 7.9 Hz, 1.4 Hz, *H*-8), 7.80 – 7.71 (m, 2H, *H*-5, *H*-6), 7.52 (ddd, 1H, *J* = 7.9 Hz, 7.0 Hz, 1.5 Hz, *H*-7), 3.64 (p, 1H, *J* = 8.0 Hz, *H*-1‘),2.11 – 2.00 (m, 2H, *H*-2‘), 1.98 – 1.88 (m, 2H, *H*-2‘), 1.88 – 1.78 (m, 2H, *H*-3‘), 1.75 – 1.64 (m, 2H, *H*-3‘).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 166.8, 139.0, 134.5, 127.7, 125.0, 123.7, 115.9, 42.8, 31.60, 26.8.
HR-MS (ESI+): *m/z* for $C_{12}H_{14}N_2O_3S+H^+$, $[M+H]^+$ calculated: 267.0798; found: 267.0797.

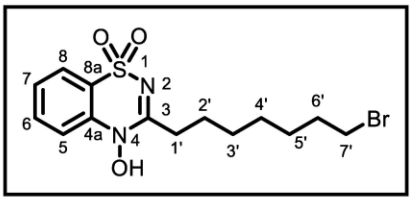
4*H*-3-Cyclohexyl-4-hydroxy-3-cyclohexylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7k)



According to general protocol **GPVI**, **6k** (47.1 mg, 0.15 mmol) were reacted. Full conversion was achieved by applying 57.9 C (4.0 *F*) and 1.0 mL TFA as additive in the cathodic compartment. 34.0 mg (0.121 mmol, 81%) of the product were obtained as beige solid by column chromatography (12 g silica (irregular); cyclohexane:ethyl acetate 50% ethyl acetate).

^{1}H NMR (300 MHz, CD_3OD) δ [ppm]: 7.83 (dd, 1H, *J* = 8.0 Hz, 1.4 Hz, *H*-8), 7.79 – 7.71 (m, 2H, *H*-5, *H*-6), 7.52 (ddd, 1H, *J* = 8.2 Hz, 6.7 Hz, 1.8 Hz, *H*-7), 3.28 – 3.18 (m, 1H, *H*-1‘), 2.03 – 1.72 (m, 4H, *H*-2‘), 1.65 – 1.26 (m, 6H, *H*-3‘,*H*-4‘).
^{13}C NMR (75 MHz, CD_3OD) δ [ppm]: 166.4, 138.9, 134.5, 127.8, 125.0, 123.6, 115.9, 41.8, 30.7, 26.8.
HR-MS (ESI+): *m/z* for $C_{13}H_{16}N_2O_3S+Na^+$, $[M+ Na]^+$ calculated: 303.0774; found: 303.0782.

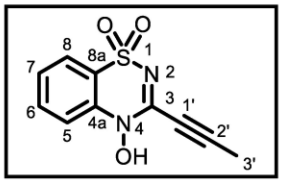
4*H*-3-(7-Bromoheptyl)-4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7l)



According to general protocol **GPVI**, **6l** (61.1 mg, 0.15 mmol) were reacted. Full conversion was achieved by applying 57.9 C (4.0 *F*) and 0.8 mL TFA as additive in the cathodic compartment. 40.9 mg (0.109 mmol, 73%) of the product were obtained as beige solid by reversed phase column chromatography (C_{18} silica gel, gradient: 50% → 100% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.85 (dd, 1H, *J* = 8.0 Hz, 1.4 Hz, *H*-8), 7.77 (ddd, 1H, *J* = 8.6 Hz, 7.2 Hz, 1.4 Hz, *H*-6), 7.72 (dd, 1H, *J* = 8.6 Hz, 1.3 Hz, *H*-5), 7.52 (ddd, 1H, *J* = 8.0 Hz, 7.2 Hz, 1.3 Hz, *H*-7), 3.44 (t, 2H, *J* = 6.8 Hz, *H*-7‘), 2.86 – 2.81 (m, 2H, *H*-1‘), 1.91 – 1.74 (m, 4H, *H*-2‘,*H*-6‘), 1.53 – 1.38 (m, 6H, *H*-3‘,*H*-4‘,*H*-5‘).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 163.6, 138.7, 134.6, 127.8, 125.0, 123.7, 115.8, 34.4, 34.3, 33.9, 29.8, 29.5, 29.0, 26.4.
HR-MS (ESI-): *m/z* for $C_{14}H_{19}{}^{79}BrN_2O_3S\text{-}H^-$, $[M-H]^-$ calculated: 373.0227; found: 373.0225.

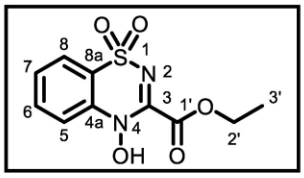
4*H*-4-Hydroxy-3-(prop-1-yn-1-yl)benzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7m)



According to general protocol **GPVI**, **6m** (40.2 mg, 0.15 mmol) were reacted. 14.2 mg (0.0601 mmol, 41%) of the product were obtained as beige solid by reversed phase column chromatography (C_{18} silica gel, gradient: 15% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 7.90 (dd, 1H, *J* = 7.9 Hz, 1.4 Hz, *H*-8), 7.79 (ddd, 1H, *J* = 8.7, 7.5 Hz, 1.4 Hz, *H*-6), 7.61 – 7.54 (m, 2H, *H*-5, *H*-7), 6.08 (s, 1H, N-O*H*), 2.47 (s, 3H, *H*-3‘).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 172.2, 157.1, 145.5, 134.2, 133.9, 128.4, 125.1, 113.8, 99.7, 13.1.
HR-MS (ESI+): *m/z* for $C_{10}H_8N_2O_3S+H^+$, $[M+H]^+$ calculated: 237.0328; found: 237.0329.

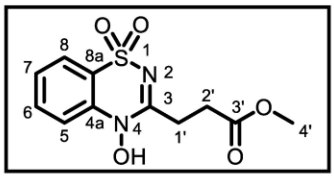
Ethyl 4*H*-4-hydroxybenzo[*e*]-1,2,4-thiadiazine-3-carboxylate-1,1-dioxide (7n)



According to general protocol **GPVI**, **6n** (45.2 mg, 0.15 mmol) were reacted. 30.2 mg (0.112 mmol, 75%) of the product were obtained as beige solid by reversed phase column chromatography (C_{18} silica gel, gradient: 30% → 90% acetonitrile).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 9.92 (s, 1H, 4-N-O*H*), 7.90 (dd, 1H, *J* = 8.0 Hz, 1.4 Hz, *H*-8), 7.81 (ddd, *J* = 8.5 Hz, 7.4 Hz, 1.4 Hz, *H*-6), 7.63 (dd, 1H, *J* = 8.5 Hz, 1.1 Hz, *H*-5), 7.58 (ddd, *J* = 8.0 Hz, 7.4 Hz, 1.1 Hz, *H*-7), 4.46 (q, 2H, *J* = 7.1 Hz, *H*-2‘), 1.38 (t, 3H, *J* = 7.1 Hz, *H*-3‘).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 159.2, 149.9, 137.0, 134.9, 128.9, 125.1, 123.6, 115.9, 64.9, 14.2.
HR-MS (ESI-): *m/z* for $C_{10}H_{10}N_2O_5S-H^-$, $[M-H]^-$ calculated: 269.0238; found: 269.0233.

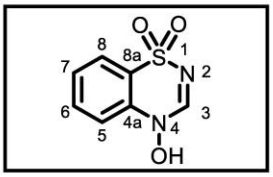
4*H*-4-Hydroxy-(3-methoxy-3-oxo-propyl)benzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7o)



According to general protocol **GPVI**, **6o** (47.6 mg, 0.15 mmol) were reacted. 31.3 mg (0.110 mmol, 73%) of the product were obtained as beige solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.84 (dd, 1H, *J* = 8.0 Hz, 1.6 Hz, *H*-8), 7.77 (ddd, 1H, *J* = 8.6 Hz 7.1 Hz, 1.6 Hz, *H*-6), 7.71 (dd, 1H, *J* = 8.6 Hz, 1.5 Hz, *H*-5), 7.56 – 7.47 (m, 1H, *H*-7), 3.70 (s, 3H, *H*-4‘), 3.22 – 3.14 (m, 2H, *H*-1‘), 2.81 – 2.77 (m, 2H, *H*-2‘).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 174.3, 161.9, 138.6, 134.6, 127.8, 125.0, 123.6, 115.7, 52.4, 29.6, 28.9.
HR-MS (ESI-): *m/z* for $C_{11}H_{12}N_2O_5S-H^-$, $[M-H]^-$ calculated: 283.0394; found: 283.0390.

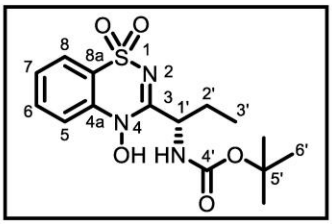
4*H*-4-Hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7p)



According to general protocol **GPVI**, **6p** (34.5 mg, 0.15 mmol) were reacted. The TFA was added after the electrolysis. 17.8 mg (0.0898 mmol, 60%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 10% → 90% acetonitrile).

^{1}H NMR (400 MHz, CD_3CN) δ [ppm]: 8.01 (s, 1H, *H*-3), 7.85 (dd, 1H, *J* = 8.0 Hz, 1.4 Hz, *H*-8), 7.75 (ddd, 1H, *J* = 8.7 Hz, 7.4 Hz, 1.4 Hz, *H*-6), 7.56 (dd, 1H, *J* = 8.7 Hz, 1.1 Hz, *H*-5), 7.52 (ddd, 1H, *J* = 8.0 Hz, 7.4 Hz, 1.1 Hz, *H*-7).
^{13}C NMR (101 MHz, CD_3CN) δ [ppm]: 149.7, 137.2, 134.4, 128.2, 125.0, 123.0, 115.3.
HR-MS (ESI-): *m/z* for $C_7H_6N_2O_3S$-H$^-$, [M-H]$^-$ calculated: 197.0026; found: 197.0030.

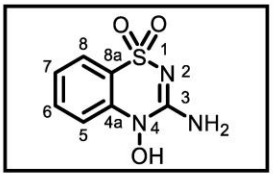
(S)-4*H*-3-((*tert*-Butoxycarbonyl)amino)propyl-4-hydroxy-benzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7q)



According to general protocol **GPVI**, **6q** (58.3 mg, 0.15 mmol) were reacted. 36.2 mg (0.102 mmol, 68%) of the product were obtained as colorless oil by reversed phase column chromatography (C_{18} silica gel, gradient: 40% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.85 (d, 1H, *J* = 7.9 Hz, *H*-8), 7.82 – 7.71 (m, 2H, *H*-5, *H*-6), 7.54 (t, 1H, *J* = 7.9 Hz, *H*-7), 5.02 – 4.97 (m, 1H, *H*-1'), 2.01 – 1.89 (m, 1H, *H*-2'), 1.79 – 1.65 (m, 1H, *H*-2'), 1.45 (s, 9H, *H*-6'), 1.06 (t, *J* = 7.4 Hz, 3H, *H*-3').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 163.4, 158.2, 138.7, 134.6, 128.1, 125.0, 123.9, 116.0, 80.9, 54.1, 28.7, 26.7, 10.8.
HR-MS (ESI-): *m/z* for $C_{15}H_{21}N_3O_5S$-H$^-$, [M-H]$^-$ calculated: 354.1129; found: 354.1137.
Optical Rotation: $[\alpha]_D^{20}$ = -52.3 (*c* = 1.00, MeOH).

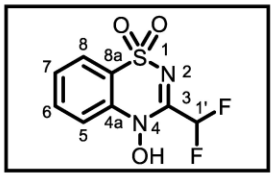
4*H*-3-Amino-4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7r)



According to general protocol **GPVI**, **6r** (40.8 mg, 0.15 mmol) were reacted. 21.2 mg (0.0994 mmol, 66%) of the product were obtained as beige solid by reversed phase column chromatography (C_{18} silica gel, gradient: 10% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.76 (dd, 1H, *J* = 7.8 Hz, 1.4 Hz, *H*-8), 7.68 (ddd, 1H, *J* = 8.4 Hz, 7.3 Hz, 1.4 Hz, *H*-6), 7.60 (dd, *J* = 8.4 Hz, 1.2 Hz, *H*-5), 7.39 – 7.34 (m, 1H, *H*-7).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 155.7, 139.4, 133.9, 125.4, 125.3, 124.1, 114.6.
HR-MS (ESI+): *m/z* for $C_7H_7N_3O_3S$+H$^+$, [M+H]$^+$ calculated: 214.0281; found: 214.0280.

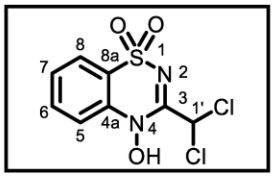
4*H*-3-(Difluoromethyl)-4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7s)



According to general protocol **GPVI**, **6s** (42.3 mg, 0.15 mmol) were reacted. 15.8 mg (0.0637 mmol, 43%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.92 (dd, 1H, *J* = 8.0 Hz, 1.4 Hz, *H*-8), 7.84 (ddd, 1H, *J* = 8.4 Hz, 7.4 Hz, 1.4 Hz, *H*-6), 7.75 (dd, 1H, *J* = 8.4 Hz, 1.2 Hz, *H*-5), 7.61 (ddd, 1H, *J* = 8.0 Hz, 7.4 Hz, 1.2 Hz, *H*-7), 6.94 (t, 1H, *J* = 52.9 Hz, *H*-1').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 151.2 (t, *J* = 26.2 Hz), 138.0, 135.0, 129.0, 125.3, 123.8, 115.9, 108.8 (t, *J* = 244.6 Hz).
^{19}F NMR (376 MHz, CD_3OD) δ [ppm]: -129.96 (d, *J* = 52.8 Hz).
HR-MS (ESI-): *m/z* for $C_8H_6F_2N_2O_3S$-H$^-$, [M-H]$^-$ calculated: 246.9994; found: 246.9988.

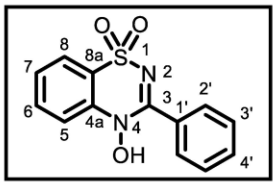
4*H*-3-(Dichloromethyl)-4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7t)



According to general protocol **GPVI**, **6t** (46.9 mg, 0.15 mmol) were reacted. 32.7 mg (0.119 mmol, 77%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.92 (dd, 1H, *J* = 7.9 Hz, 1.4 Hz, *H*-8), 7.84 (ddd, 1H, *J* = 8.5 Hz, 7.2 Hz, 1.4 Hz, *H*-6), 7.77 (dd, 1H, *J* = 8.5 Hz, 1.2 Hz, *H*-5), 7.61 (ddd, 1H, *J* = 7.9 Hz, 7.2 Hz, 1.2 Hz, *H*-7), 7.33 (s, 1H, *H*-1').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 155.5, 138.2, 135.0, 128.9, 125.3, 124.1, 116.3, 65.7.
HR-MS (ESI+): *m/z* for $C_8H_6{}^{35}ClN_2O_3S$-H$^-$, [M-H]$^-$ calculated: 280.9549; found: 280.9546.

4*H*-4-Hydroxy-3-phenylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7u)

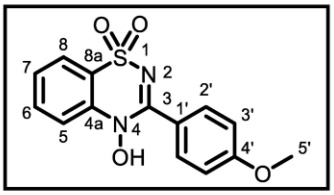


a) According to general protocol **GPVI**, **6u** (45.9 mg, 0.15 mmol) were reacted. Full conversion was achieved by applying 57.9 C (4.0 *F*) and 0.8 mL TFA as additive in the cathodic compartment. The reaction mixture was treated in the microwave after electrolysis. 14.0 mg (0.0510 mmol, 34%) of the product were obtained as beige solid by reversed phase column chromatography (12 g silica (irregular); cyclohexane:ethyl acetate 50% ethyl acetate).

b) According to general protocol **GPVII**, **6u** (45.9 mg, 0.15 mmol) were reacted. 32.2 mg (0.118 mmol, 79%) of the product were obtained as beige solid by reversed phase column chromatography (C_{18} silica gel, gradient: 30% → 70% acetonitrile).

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 12.13 (s, 1H, -N-O*H*), 7.92 (dd, 1H, *J* = 7.9 Hz, 1.4 Hz, *H*-8), 7.89 – 7.78 (m, 4H, *H*-5, *H*-6, *H*-2'), 7.64 – 7.53 (m, 4H, *H*-7, *H*-3',*H*-4').
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 156.6, 137.2, 133.7, 131.6, 131.5, 129.8, 128.1, 127.3, 123.7, 122.5, 115.6.
HR-MS (ESI+): *m/z* for $C_{13}H_{10}N_2O_3S$+Na$^+$, [M+Na]$^+$ calculated: 297.0298; found: 297.0304.

4*H*-4-Hydroxy-3-(4-methoxyphenyl)benzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7v)



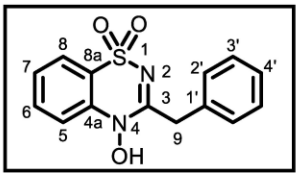
a) According to general protocol **GPVI**, **6v** (50.3 mg, 0.15 mmol) were reacted Full conversion was achieved by applying 57.9 C (4.0 *F*) and 0.8 mL TFA as additive in the cathodic compartment. The reaction mixture was treated in the microwave after electrolysis. 10.0 mg (0.0329 mmol, 22%) of the product were obtained as beige solid by reversed phase column chromatography (12 g silica (irregular); cyclohexane:ethyl acetate 50% ethyl acetate).

b) According to general protocol **GPVII**, **6v** (50.3 mg, 0.15 mmol) were reacted. 38.5 mg (0.127 mmol, 85%) of the product were obtained as beige solid by reversed phase column chromatography (C_{18} silica gel, gradient: 30% → 70% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 12.09 (s, 1H, -N-O*H*), 7.92 – 7.78 (m, 5H, *H*-5, *H*-6, *H*-8, *H*-2‘), 7.59 (ddd, 1H, *J* = 7.8 Hz, 7.0 Hz, 1.5 Hz, *H*-7), 7.12 – 7.07 (m, 2H, *H*-3‘), 3.86 (s, 3H, *H*-5‘).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 162.1, 156.2, 137.5, 133.5, 132.5, 127.1, 123.5, 123.2, 122.7, 115.7, 113.5, 55.5.
HR-MS (ESI+): *m/z* for $C_{14}H_{12}N_2O_4S+Na^+$, $[M+Na]^+$ calculated: 327.0410; found: 327.0405.

The spectroscopic data are in accordance with those reported in the literature.[12]

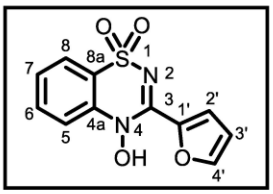
4*H*-3-Benzyl-4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7w)



According to general protocol **GPVI**, **6w** (48.1 mg, 0.15 mmol) were reacted. Full conversion was achieved by applying 57.9 C (4.0 *F*) and 0.8 mL TFA as additive in the cathodic compartment. 31.4 mg (0.109 mmol, 73%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 30% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD$_3$CN) δ [ppm]: 9.21 (s, 1H, -N-O*H*), 7.83 (dd, 1H, *J* = 7.9 Hz, 1.4 Hz, *H*-8), 7.72 (ddd, 1H, *J* = 8.7 Hz, 7.3 Hz, 1.4 Hz, *H*-6), 7.60 (dd, 1H, *J* = 8.7 Hz, 1.1 Hz, *H*-5), 7.48 (ddd, 1H, *J* = 7.9 Hz, 7.3 Hz, 1.1 Hz, *H*-7), 7.40 – 7.28 (m, 5H, *H*-2‘,*H*-3‘,*H*-4‘), 4.12 (s, 2H, *H*-9).
^{13}C NMR (101 MHz, CD$_3$CN) δ [ppm]: 161.3, 138.2, 135.4, 134.3, 130.5, 129.6, 128.2, 127.7, 124.7, 123.5, 115.6, 40.6.
HR-MS (ESI+): *m/z* for $C_{14}H_{12}N_2O_3S+Na^+$, $[M+Na]^+$ calculated: 311.0461; found: 311.0458.

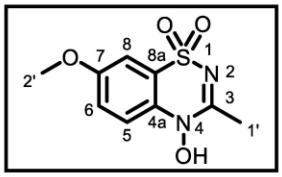
4*H*-3-(Furan-2-yl)-4-hydroxybenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7x)



According to general protocol **GPVII**, **6x** (44.4 mg, 0.15 mmol) were reacted. 24.3 mg (0.0920 mmol, 61%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 15% acetonitrile isocratic).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 12.48 (s, 1H, -N-O*H*), 8.15 (d, 1H, *J* = 1.0 Hz, *H*-4‘), 7.90 – 7.82 (m, 3H, *H*-6, *H*-8), 7.82 – 7.77 (m, 1H, *H*-5), 7.74 (dd, 1H, *J* = 3.7 Hz, 0.8 Hz, *H*-2‘), 7.58 (td, 1H, *J* = 7.5 Hz, 1.3 Hz, *H*-7), 6.84 (dd, 1H, *J* = 3.6 Hz, 1.7 Hz, *H*-3‘).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 148.4, 146.4, 142.4, 137.3, 133.6, 127.2, 123.5, 123.2, 122.5, 115.4, 113.3.
HR-MS (ESI+): *m/z* for $C_{11}H_9N_2O_4S+Na^+$, $[M+H]^+$ calculated: 265.0278; found: 265.0283.

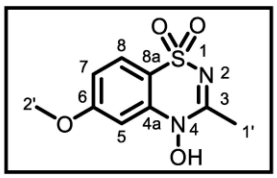
4*H*-4-Hydroxy-7-methoxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7y)



According to general protocol **GPVI**, **6y** (41.1 mg, 0.15 mmol) were reacted. 30.3 mg (0.125 mmol, 83%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 60% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.65 (d, *J* = 9.2 Hz, 1H), 7.33 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.29 (d, *J* = 2.8 Hz, 1H), 3.88 (s, 3H), 2.46 (s, 3H).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 159.9, 159.6, 132.2, 124.8, 122.3, 117.9, 107.0, 56.6, 21.3.
HR-MS (ESI+): *m/z* for $C_9H_{10}N_2O_4S+H^+$, $[M+H]^+$ calculated: 243.0434; found: 243.0433.

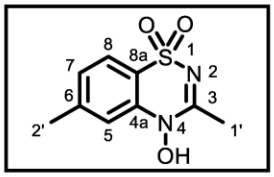
4*H*-4-Hydroxy-6-methoxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7z)



According to general protocol **GPVI**, **6z** (41.1 mg, 0.15 mmol) were reacted. 30.0 mg (0.124 mmol, 83%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 60% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.75 (d, 1H, *J* = 8.8 Hz, *H*-8), 7.13 (d, 1H, *J* = 2.4 Hz, *H*-5), 7.07 (dd, 1H, *J* = 8.8 Hz, 2.4 Hz, *H*-6), 3.91 (s, 3H, *H*-2'), 2.47 (s, 3H, *H*-1').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 165.0, 160.8, 140.3, 127.0, 116.2, 114.9, 99.6, 56.5, 21.7.
HR-MS (ESI-): *m/z* for $C_9H_{10}N_2O_4S-H^-$, $[M-H]^-$ calculated: 241.0289; found: 241.0284.

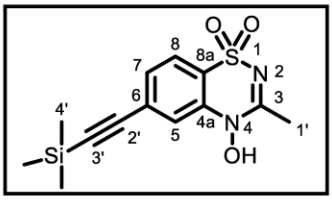
4*H*-4-Hydroxy-3,6-dimethylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7aa)



According to general protocol **GPVI**, **6aa** (38.7 mg, 0.15 mmol) were reacted. 26.1 mg (0.115 mmol, 77%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.72 (d, 1H, *J* = 8.1 Hz, *H*-8), 7.52 (s, 1H, *H*-5), 7.34 (ddd, 1H, *J* = 8.1 Hz, 1.6 Hz, 0.8 Hz, *H*-7), 2.49 (s, 3H, *H*-2'), 2.47 (s, 3H, *H*-1').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 160.8, 146.1, 138.5, 128.7, 125.0, 121.2, 115.6, 22.0, 21.6.
HR-MS (ESI+): *m/z* for $C_9H_{10}N_2O_3S+H^-$, $[M+H]^+$ calculated: 227.0485; found: 227.0483.

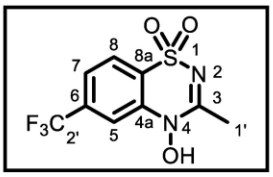
4*H*-4-Hydroxy-3-methyl-6-((trimethylsilyl)ethynyl)benzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7ab)



According to general protocol **GPVI**, **6ab** (51.1 mg, 0.15 mmol) were reacted. 38.7 mg (0.126 mmol, 84%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 35% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.81 (d, 1H, *J* = 8.2 Hz, *H*-8), 7.70 (d, 1H, *J* = 1.2 Hz, *H*-5), 7.53 (dd, 1H, *J* = 8.2, 1.2 Hz, *H*-7), 2.49 (s, 3H, *H*-1'), 0.27 (s, 9H, *H*-4').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 161.3, 138.7, 130.6, 129.6, 125.6, 123.4, 118.6, 103.8, 99.2, 21.7, -0.3.
HR-MS (ESI+): *m/z* for $C_{13}H_{16}N_2O_3SSi+H^+$, $[M+H]^+$ calculated: 309.0724; found: 309.0725.

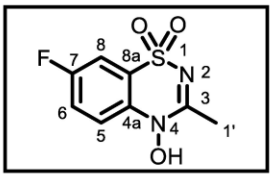
4*H*-4-Hydroxy-3-methyl-6-(trifluoromethyl)benzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7ac)



According to general protocol **GPVI**, **6ac** (46.8 mg, 0.15 mmol) were reacted. 38.2 mg (0.136 mmol, 91%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 30% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.06 (d, 1H, *J* = 8.2 Hz, *H*-8), 7.96 (dd, 1H, *J* = 1.1 Hz, 0.7 Hz, *H*-5), 7.81 (ddd, 1H, *J* = 8.2 Hz, 1.7 Hz, 0.7 Hz, *H*-7), 2.52 (s, 3H, *H*-1').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 161.8, 139.1, 135.9 (q, *J* = 33.3 Hz), 126.9, 126.6, 124.5 (q, *J* = 272.3 Hz), 124.1 (q, *J* = 3.6 Hz), 113.1 (q, *J* = 4.2 Hz), 21.7.
^{19}F NMR (376 MHz, CD_3OD) δ [ppm]: -65.91.
HR-MS (ESI-): *m/z* for $C_9H_7F_3N_2O_3S-H^-$, $[M-H]^-$ calculated: 279.0057; found: 279.0053.

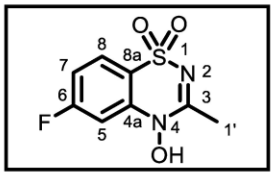
4*H*-7-Fluoro-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7ad)



According to general protocol **GPVI**, **6ad** (39.3 mg, 0.15 mmol) were reacted. 28.7 mg (0.125 mmol, 83%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 60% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.91 (dd, 1H, *J* = 8.8 Hz, 5.6 Hz, *H*-8), 7.44 (dd, 1H, *J* = 10.2 Hz, 2.4 Hz, *H*-5), 7.28 (td, 1H, *J* = 8.8 Hz, 2.5 Hz, *H*-6), 2.49 (s, 3H, *H*-1').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 166.6 (d, *J* = 252.0 Hz), 161.4, 140.7 (d, *J* = 11.8 Hz), 128.4 (d, *J* = 10.5 Hz), 120.2 (d, *J* = 3.1 Hz), 115.5 (d, *J* = 23.9 Hz), 103.0 (d, *J* = 29.1 Hz), 21.6.
^{19}F NMR (376 MHz, CD_3OD) δ [ppm]: -105.89 (td, *J* = 9.4 Hz, 5.5 Hz).
HR-MS (ESI-): *m/z* for $C_8H_7FN_2O_3S-H^-$, $[M-H]^-$ calculated: 229.0089; found: 229.0083.

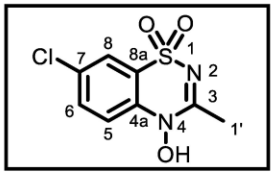
4*H*-6-Fluoro-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7ae)



According to general protocol **GPVI**, **6ae** (39.3 mg, 0.15 mmol) were reacted. 30.4 mg (0.132 mmol, 88%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 60% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.77 (dd, 1H, *J* = 9.2 Hz, 4.3 Hz, *H*-8), 7.61 – 7.52 (m, 2H, *H*-5, *H*-7), 2.48 (s, 3H, *H*-1').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 161.5 (d, *J* = 248.8 Hz), 160.9, 135.2, 125.0 (d, *J* = 7.2 Hz), 122.2 (d, *J* = 24.2 Hz), 118.8 (d, *J* = 7.9 Hz), 111.1 (d, *J* = 25.7 Hz), 21.5.
^{19}F NMR (376 MHz, CD_3OD) δ [ppm]: -116.17 (td, *J* = 7.7 Hz, 4.3 Hz).
HR-MS (ESI-): *m/z* for $C_8H_7FN_2O_3S$-H$^-$, [M-H]$^-$ calculated: 229.0089; found: 229.0092.

4*H*-7-Chloro-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7af)

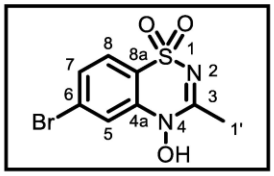


0.15 mmol and 2.4 mmol Scale:
According to general protocol **GPVI**, **6af** (41.8 mg, 0.15 mmol) were reacted. 31.1 mg (0.126 mmol, 84%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 70% acetonitrile). The yields of the scale-up experiments are listed in table S5.

9.0 mmol Scale:
The crude product was purified after extraction by filtration over silica (200 g silica (irregular); ethyl acetate) and crystallization (80 mL EtOH; crystallization at -18 °C) as off-white crystals. The yields of the scale-up experiments are listed in table S5.

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.82 – 7.79 (m, 1H, *H*-8), 7.77 – 7.67 (m, 2H), 2.48 (s, 1H).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 161.1, 137.3, 134.6, 132.8, 124.9, 124.5, 118.1, 21.6.
HR-MS (ESI-): *m/z* for $C_8H_7{}^{35}ClN_2O_3S$-H$^-$, [M-H]$^-$ calculated: 244.9793; found: 244.9787.
m.p. (EtOH): 225.1–226.8 °C.

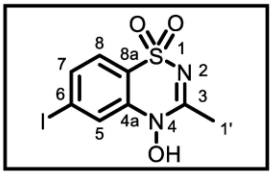
4*H*-6-Bromo-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7ag)



According to general protocol **GPVI**, **6ag** (48.5 mg, 0.15 mmol) were reacted. 37.1 mg (0.127 mmol, 85%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 30% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.87 (d, 1H, *J* = 1.8 Hz, *H*-5), 7.76 (d, 1H, *J* = 8.4 Hz, *H*-8), 7.67 (dd, 1H, *J* = 8.4 Hz, 1.8 Hz, *H*-7), 2.49 (s, 3H, *H*-1').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 161.3, 139.5, 130.9, 128.6, 127.0, 122.7, 118.6, 21.7.
HR-MS (ESI-): *m/z* for $C_8H_7{}^{79}BrN_2O_3S$-H$^-$, [M-H]$^-$ calculated: 288.9288; found: 288.9286.

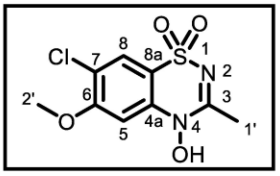
4*H*-4-Hydroxy-6-iodo-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7ah)



According to general protocol **GPVI**, **6ah** (55.2 mg, 0.15 mmol) were reacted. 42.7 mg (0.126 mmol, 84%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 30% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.06 (d, 1H, *J* = 1.6 Hz, *H*-5), 7.87 (dd, 1H, *J* = 8.3 Hz, 1.6 Hz, *H*-7), 7.57 (d, 1H, *J* = 8.3 Hz, *H*-8), 2.48 (s, 3H, *H*-1‘).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 161.2, 138.8, 136.8, 126.4, 124.6, 123.1, 100.5, 21.7.
HR-MS (ESI+): *m/z* for $C_8H_7IN_2O_3S+H^+$, $[M+H]^+$ calculated: 338.9295; found: 338.9287.

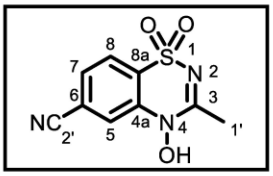
4*H*-7-Chloro-4-hydroxy-6-methoxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7ai)



According to general protocol **GPVI**, **6ai** (46.3 mg, 0.15 mmol) were reacted. 31.0 mg (0.112 mmol, 75%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 30% → 90% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.79 (s, 1H, *H*-8), 7.26 (s, 1H, *H*-5), 4.02 (s, 3H, *H*-2’), 2.48 (s, 3H, *H*-1’).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 160.9, 160.2, 139.1, 126.3, 122.1, 116.3, 99.0, 57.4, 21.7.
HR-MS (ESI+): *m/z* for $C_9H_9{}^{35}ClN_2O_4S+H^+$, $[M+H]^+$ calculated: 277.0044; found: 277.0045.

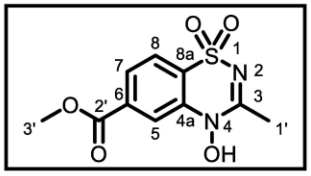
4*H*-6-Cyano-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7aj)



According to general protocol **GPVI**, **6aj** (40.5 mg, 0.15 mmol) were reacted. 29.6 mg (0.125 mmol, 83%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.08 (d, 1H, *J* = 1.5 Hz, *H*-5), 8.01 (d, 1H, *J* = 8.1 Hz, *H*-7), 7.83 (dd, 1H, *J* = 8.1 Hz, 1.5 Hz, *H*-8), 2.51 (s, 3H, *H*-1‘).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 162.0, 139.2, 130.5, 126.9, 126.7, 120.1, 118.1, 118.1, 21.7.
HR-MS (ESI-): *m/z* for $C_9H_7N_3O_3S-H^-$, $[M-H]^-$ calculated: 236.0135; found: 236.0131.

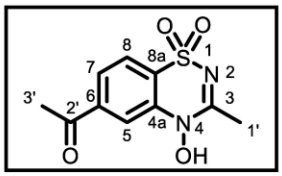
4*H*-4-Hydroxy-6-(methoxycarbonyl)-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7ak)



According to general protocol **GPVI**, **6ak** (45.2 mg, 0.15 mmol) were reacted. 36.1 mg (0.134 mmol, 89%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.25 (d, 1H, *J* = 1.5 Hz, *H*-5), 8.07 (dd, 1H, *J* = 8.2 Hz, 1.5 Hz, *H*-7), 7.94 (d, 1H*J* = 8.2 Hz, *H*-8), 3.97 (s, 3H, *H*-3‘), 2.51 (s, 3H, *H*-1‘).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 166.5, 161.5, 138.7, 135.8, 127.9, 126.9, 125.8, 116.9, 53.4, 21.7.
HR-MS (ESI-): *m/z* for $C_{10}H_{10}N_2O_5S$-H$^-$, [M-H]$^-$ calculated: 269.0238; found: 269.0235.

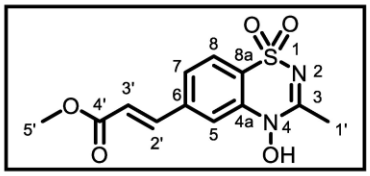
4*H*-6-Acetyl-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7al)



According to general protocol **GPVI**, **6al** (42.9 mg, 0.15 mmol) were reacted. 24.0 mg (0.0940 mmol, 63%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.17 (d, 1H, *J* = 1.5 Hz, *H*-5), 8.05 (dd, 1H, *J* = 8.2 Hz, 1.5 Hz, *H*-7), 7.93 (d, 1H, *J* = 8.2 Hz, *H*-8), 2.68 (s, 3H, *H*-3’), 2.51 (s, 3H, *H*-1’).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 198.2, 161.5, 142.0, 138.7, 127.1, 126.7, 125.9, 115.4, 27.0, 21.7.
HR-MS (ESI-): *m/z* for $C_{10}H_{10}N_2O_4S$-H$^-$, [M-H]$^-$ calculated: 253.0289; found: 253.0293.

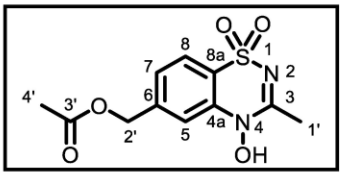
(*E*)-4*H*-4-Hydroxy-6-(1-methoxy-1-oxoprop-2-en-3-yl)-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7am)



According to general protocol **GPVI**, **6am** (49.2 mg, 0.15 mmol) were reacted. 31.3 mg (0.106 mmol, 71%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 30% → 90% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.89 – 7.85 (m, 2H, *H*-5, *H*-2’), 7.80 – 7.74 (m, 2H, *H*-7, *H*-8), 6.73 (d, 1H, *J* = 16.1 Hz, *H*-3‘), 3.82 (s, 3H, *H*-5‘), 2.50 (s, 3H, *H*-1‘).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 168.2, 161.2, 143.7, 140.9, 139.1, 126.4, 125.9, 124.4, 122.9, 115.6, 52.4, 21.7.
HR-MS (ESI-): *m/z* for $C_{12}H_{12}N_2O_5S$-H$^-$, [M-H]$^-$ calculated: 295.0394; found: 295.0391.

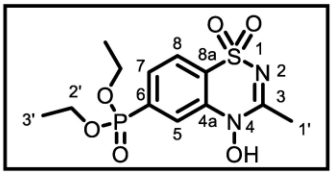
4*H*-6-(Acetoxymethyl)-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7an)



According to general protocol **GPVI**, **6an** (47.3 mg, 0.15 mmol) were reacted. 34.9 mg (0.123 mmol, 82%) of the product were obtained as a colorless oil by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 90% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.82 (d, 1H, *J* = 8.2 Hz, *H*-8), 7.68 (d, 1H, *J* = 1.3 Hz, *H*-5), 7.49 (dd, 1H, *J* = 8.2 Hz, 1.3 Hz, *H*-7), 5.23 (s, 2H, *H*-2‘), 2.48 (s, 3H, *H*-4‘), 2.12 (s, 3H, *H*-1‘).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 172.2, 161.1, 144.1, 138.7, 126.7, 125.4, 123.1, 114.5, 66.1, 21.7, 20.7.
HR-MS (ESI-): *m/z* for $C_{11}H_{12}N_2O_5S$-H$^-$, [M-H]$^-$ calculated: 283.0394; found: 283.0395.

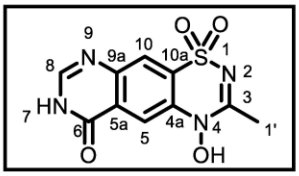
4*H*-4-Hydroxy-6-(diethylphosphonato)-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7ao)



According to general protocol **GPVI**, **6ao** (56.7 mg, 0.15 mmol) were reacted. 28.1 mg (0.0807 mmol, 54%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 10% → 70% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.08 (dd, 1H, *J* = 15.2 Hz, 1.3 Hz, *H*-5), 8.02 (dd, 1H, *J* = 8.0 Hz, 4.1 Hz, *H*-8), 7.86 (ddd, 1H, *J* = 12.4 Hz, 8.0 Hz, 1.3 Hz, *H*-7), 4.27 – 4.12 (m, 4H, *H*-2‘), 2.51 (s, 3H, *H*-1‘), 1.35 (t, 6H, *J* = 7.3 Hz, *H*-3‘).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 161.6, 138.6 (d, *J* = 19.1 Hz), 134.9 (d, *J* = 189.2 Hz), 129.8 (d, *J* = 9.5 Hz), 126.9, 126.0 (d, *J* = 15.7 Hz), 119.2 (d, *J* = 13.1 Hz), 64.6 (d, *J* = 5.9 Hz), 21.7, 16.6 (d, *J* = 6.2 Hz).
^{31}P NMR (162 MHz, CD_3OD) δ [ppm]: 15.42.
HR-MS (ESI+): *m/z* for $C_{12}H_{17}N_2O_6PS$+H$^+$, [M+H]$^+$ calculated: 349.0618; found: 349.0618.

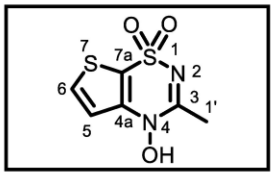
6*H*-4,7-Dihydro-4-hydroxy-3-methyl-1,2,4-thiadiazino[5,6-*g*]quinazoline-6-one-1,1-dioxide (7ap)



According to general protocol **GPVI**, **6ap** (46.8 mg, 0.15 mmol) were reacted. 24.3 mg (0.0867 mmol, 58%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 20% → 80% acetonitrile).

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 12.59 (s, 1H, 7-N*H*), 12.31 (s, 1H, 4-N-O*H*), 8.23 (s, 1H, *H*-10), 8.18 (s, 1H, *H*-5), 8.02 (s, 1H, *H*-8), 2.47 (s, 3H, *H*-1’).
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 160.3, 158.2, 146.6, 135.0, 131.9, 128.5, 126.6, 123.2, 112.5, 21.9.
HR-MS (ESI+): *m/z* for $C_{10}H_8N_4O_4S$+H$^+$, [M+H]$^+$ calculated: 281.0339; found: 281.0337.

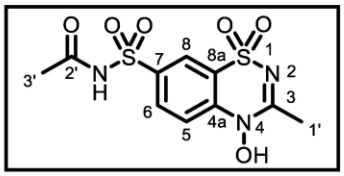
4*H*-4-Hydroxy-3-methylthieno[3,2-*e*]-1,2,4-thiadiazine-1,1-dioxide (7aq)



According to general protocol **GPVI**, **6aq** (37.4 mg, 0.15 mmol) were reacted. 9.3 mg (0.0426 mmol, 28%) of the product were obtained as an off-white solid by reversed phase column chromatography (C_{18} silica gel, gradient: 10% acetonitrile isocratic).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.91 (d, 1H, *J* = 5.4 Hz, *H*-5), 7.18 (d, 1H, *J* = 5.4 Hz, *H*-6), 2.44 (s, 3H, *H*-1').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 157.6, 143.1, 132.6, 117.8, 117.4, 20.0.
HR-MS (ESI-): *m/z* for $C_6H_6N_2O_3S$-H^-, $[M-H]^-$ calculated: 216.9747; found: 216.9747.

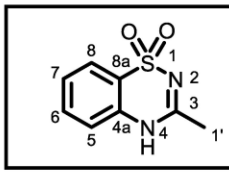
4*H*-7-(*N*-Acetylsulfamoyl)-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7ar)



According to general protocol **GPVI**, **6ar** (54.6 mg, 0.15 mmol) were reacted. 32.1 mg (0.0963 mmol, 64%) of the product were obtained as a colorless oil by reversed phase column chromatography (C_{18} silica gel, gradient: 15% → 50% acetonitrile).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 8.31 (s, 1H, *H*-8), 8.04 (s, 2H, *H*-5, *H*-6), 2.52 (s, 3H, *H*-1'), 1.99 (s, 3H, *H*-3').
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 171.0, 161.9, 145.5, 138.8, 127.2, 126.6, 126.2, 116.3, 23.4, 21.7.
HR-MS (ESI+): *m/z* for $C_{10}H_{11}N_3O_6S_2$+H^+, $[M+H]^+$ calculated: 334.0162; found: 334.0166.

4*H*-3-Methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (8a)



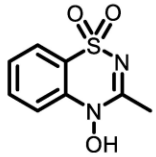
Under argon atmosphere 2-aminobenzesulfonamide (5.00 g, 29 mmol, 1.0 eq.) in 24 mL (21.30 g, 130 mmol, 4.5 eq.) triethyl orthoacetate was heated at 100 °C for 36 h. After completion of the reaction the solids were collected and washed three times with 20 mL diethylether. 3.791 g (19.3 mmol, 67%) of the product was obtained as a colorless crystals.

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 12.01 (s, 1H, 4-N*H*), 7.79 (dd, 1H, *J* = 8.0 Hz, 1.5 Hz, *H*-8), 7.64 (ddd, 1H, *J* = 8.5 Hz, 7.4 Hz, 1.5 Hz, *H*-6), 7.41 (ddd, 1H, *J* = 8.2 Hz, 7.4 Hz, 1.2 Hz, *H*-7), 7.29 (dd, 1H, *J* = 8.5 Hz, 1.2 Hz, *H*-5), 2.30 (s, 3H, *H*-1').
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 157.3, 135.2, 133.0, 126.2, 123.5, 121.0, 117.2, 22.6.
HR-MS (ESI+): *m/z* for $C_{10}H_{10}N_2O_6S$+H^+, $[M+H]^+$ calculated: 197.0379; found: 197.0375.
m.p. (EtOH): 267.9–270.2 °C.

The spectroscopic data are in accordance with those reported in the literature.[13]

8. Crystallographic Data

4*H*-4-Hydroxy-3-methylbenzo[e]-1,2,4-thiadiazine-1,1-dioxide (7a)



Crystallization was carried out by dissolving the compound in methanol. Slow evaporating resulted in crystal formation.

CCDC Number	2294500
Empirical formular	$C_8H_8N_2O_3S$
Moiety formular	$C_8H_8N_2O_3S$
Formular weight	212.22
Temperature	120(2) K
Wavelength, radiation type	0.71073 Å, MoKα
Diffractometer	STOE IPDS 2T
Crystal system	Monoclinic
Space group name, number	P 2_1/n, (14)
Unit cell dimensions	a = 7.5634(8) Å b = 7.5987(5) Å β = 93.130(8)° c = 15.0306(15) Å
Volume	862.55(14) Å^3
Number of reflections	12221
And range used for lattice parameters	2.70° <=Θ<= 28.26°
Z	4
Density (calculated)	1.634 Mg/m^3
Absorption coefficient	0.355 mm^{-1}
Absorption correction	None
F(000)	440
Crystal size, colour and form	0.150 · 0.270 · 0.370 mm^3, colorless block
Theta range for data collection	2.953–28.070°.
Index ranges	-10<=h<=9, -9<=k<=8, -19<=l<=16
Number of reflections:	
collected	4262
independent	2021 [R_{int} = 0.0139]
observed [I>2sigma(I)]	1808
Completeness to theta = 25.2°	98.8 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2021 / 0 / 157, Hydrogen localized and isotropic refined
Goodness-of-fit on F^2	1.104
Final R indices [I>2sigma(I)]	R1 = 0.0335, wR2 = 0.0806
R indices (all data)	R1 = 0.0403, wR2 = 0.0858
Largest diff. peak and hole	0.472 and -0.473 eÅ^{-3}

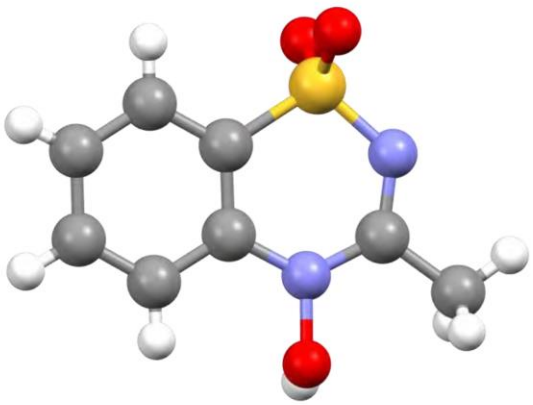


Figure S4: Molecular structure of **7a**.

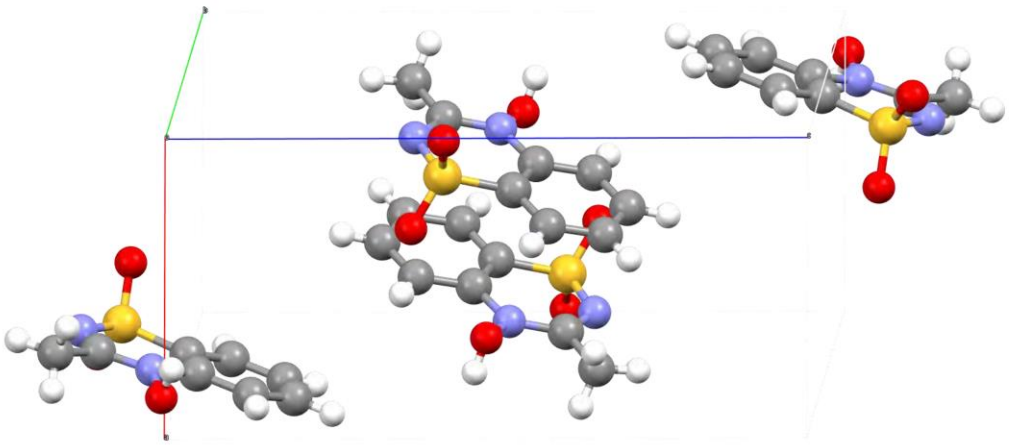
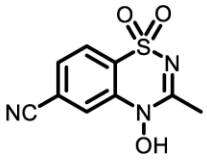


Figure S5: Packing of **7a.**

4*H*-6-Cyano-4-hydroxy-3-methylbenzo[*e*]-1,2,4-thiadiazine-1,1-dioxide (7aj)



Crystallization was carried out by dissolving the compound in methanol. Slow evaporating resulted in crystal formation.

CCDC Number	2294499
Empirical formular	$C_9H_9N_3O_4S$
Moiety formular	$C_9H_9N_3O_4S \cdot H_2O$
Formular weight	255.25
Temperature	120(2) K
Wavelength, radiation type	0.71073Å, MoKα
Diffractometer	STOE IPDS 2T
Crystal system	Monoclinic
Space group name, number	C 2/c, (15)
Unit cell dimensions	a = 9.4241(6) Å α = 90° b = 12.7019(6) Å β = 99.344(5)° c = 17.9663(11) Å γ = 90°
Volume	2122.1(2) $Å^3$
Number of reflections	9213
And range used for lattice parameters	2.71° <=Θ<= 28.31°
Z	8
Density (calculated)	1.598 Mg/m^3
Absorption coefficient	0.313 mm^{-1}
Absorption correction	Multiscans
F(000)	1056
Crystal size, colour and form	0.200 · 0.600 · 0.600 mm^3, colorless block
Theta range for data collection	2.715–27.861°.
Index ranges	-12<=h<=12, -15<=k<=16, -21<=l<=23
Number of reflections:	
collected	5049
independent	2533 [R_{int} = 0.0292]
observed [I>2sigma(I)]	2338
Completeness to theta = 25.2°	99.9 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2533 / 0 / 187
Goodness-of-fit on F^2	1.089
Final R indices [I>2sigma(I)]	R1 = 0.0472, wR2 = 0.1243
R indices (all data)	R1 = 0.0504, wR2 = 0.1285
Largest diff. peak and hole	0.744 and -0.631 $eÅ^{-3}$

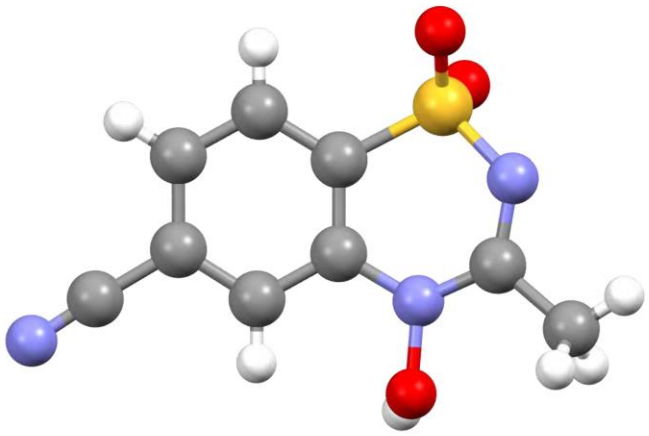


Figure S6: Molecular structure of **7aq**.

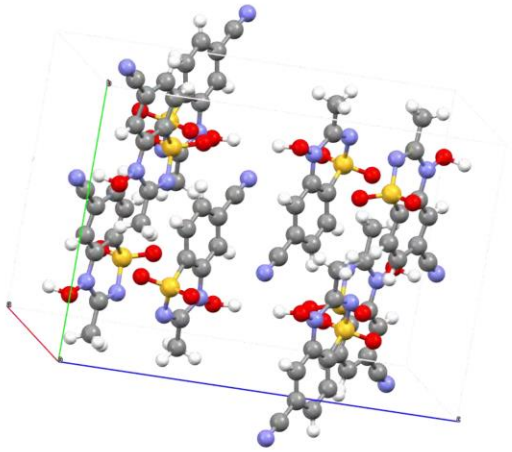
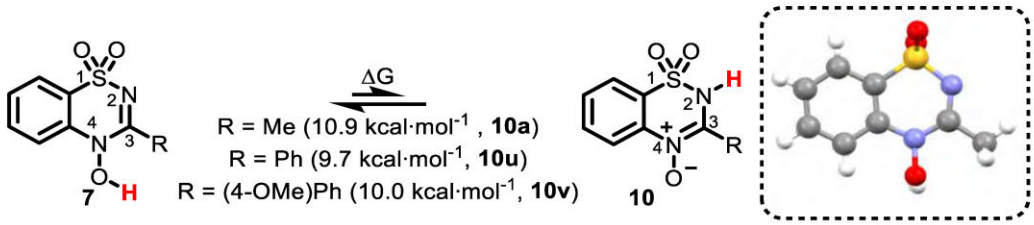


Figure S7: Packing of **7aq**.

9. Computational Methods and Analysis

All computations were performed with ORCA 5.0.3 program package.[14] Geometry optimizations were conducted with PBE0[15] hybrid functional with def2-TZVP basis sets[16, 17] augmented with atom-pairwise dispersion correction with the Becke-Johnson damping scheme.[18, 19] C-PCM solvation model with dielectric constant of methanol (32.63) was applied.[20] The Gibbs free energies were further refined by single-point calculations at PW6B95[21]-D3BJ[18, 19] / def2-TZVPD[22] / C-PCM(Methanol) level.
The described structural motif 4*H*-4-hydroxybenzo[e]-1,2,4-thiadiazine-1,1-dioxide (Scheme S8, **7**) and 2*H*-1,2,4-thiadiazine-1,1,4-trioxide (**10**) are tautomers. The molecular structure determined by single crystal X-ray diffraction (SC-XRD, Section 8) shows that **7a** (R = Me) is the preferred tautomer over **10a**. As Patel et al.[12] have reported several phenyl-substituted derivatives as 2*H*-3-arylbenzo[e]-1,2,4-thiadiazine-1,1,4-trioxide tautomers, we investigated the bond-lengths, dihedral angles, and Gibbs free energies of several tautomeric pairs with DFT-calculations.



7a	10a	7a-SC-XRD
N(2)-C(3): 1.297 Δ 0.014	N(2)-C(3): 1.371 Δ -0.06	N(2)-C(3): 1.311
C(3)-N(4): 1.351 Δ 0.00	C(3)-N(4): 1.312 Δ 0.039	C(3)-N(4): 1.351
N(4)-C(3)-N(2)-S(1): -4.8°	N(4)-C(3)-N(2)-S(1): -30.7°	N(4)-C(3)-N(2)-S(1): 0°

Scheme S8: Determined ΔG for differently substituted **7–10** tautomeric pairs (left) and molecular structure determined with SC-XRD (right). ΔG values are in kcal·mol^{-1} and bond lengths in Å.

The DFT-calculations show that **7** is energetically preferred tautomer in all of the examined substrates (R = Me, Ph, (4-OMe)Ph)) and the ΔG varies between 9.7 to 10.9 kcal·mol^{-1} (Scheme S8). Omitting the C-PCM solvation model from the calculations lowers the energy difference of **7a–10a** to 8.4 kcal·mol^{-1}, indicating that **7a** is also preferred tautomer in non-polar solvents. Furthermore, the DFT bond-lengths and dihedral angle of **7a** agree well with the values determined from the single crystal and disagree with **10a** (Scheme S8, Table S6).

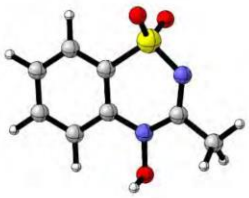
Table S6: Comparison of selected DFT bond-lengths and dihedral angels to the molecular structure determined with SC-XRD.

Compound	N(2)-C(3) length [Å]	N(4)-C(3) bond length [Å]	N(4)-C(3)-N(2)-S(1) dihedral angle
7a	1.297 (1.283)[a]	1.351 (1.364)[a]	-4.8 (-4.5)[a]
7u	1.302	1.356	13.6
7v	1.304	1.357	13.9
10a	1.371	1.312	-30.7
10u	1.377	1.321	33.7
10v	1.379	1.323	33.0
7a (SC-XRD)	1.311	1.351	0

[a]Bond-lengths and dihedrals in parenthesis were determined at vacuum.

10. XYZ-Coordinates and Energies

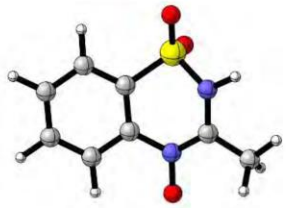
7a:



i-freq:
0
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol):
-1042,30299802
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol) // PW6B95/def2-TZVPD/C-PCM(Methanol):
-1044,26142195
CARTESIAN COORDINATES (Ångströms):

C	1.81060462401016	1.59909296839298	-1.05289081526289
C	3.10471266422063	1.13933460823734	-0.91495395345194
C	3.38657092211898	0.16471019937204	0.03825150724666
C	2.39291407102966	-0.35504510485609	0.84461709729046
C	1.08316058770874	0.10373344784369	0.70628803287161
C	0.80292811124746	1.08619817336734	-0.24336323520782
S	-0.81979043941761	1.70652832551149	-0.39665396553252
O	-1.27238088654220	1.52500340996572	-1.75197572349283
O	-0.85165522457177	3.05663702660713	0.10653856724140
N	-1.71431273008666	0.78849793905460	0.57191006756560
C	-1.24564166778206	-0.09191042336317	1.40026976612505
C	-2.18715861886389	-0.79960215019131	2.30671125835242
N	0.06141604849191	-0.42088992689556	1.49112997931105
O	0.42126221811555	-1.32566943058046	2.45058591109492
H	-3.19087713788054	-0.42643692612821	2.12313996518115
H	-1.90813231783733	-0.62617764769021	3.34760726997308
H	-2.15270508174228	-1.87688457448914	2.13195822492505
H	0.39145665695748	-2.20011510139488	2.03001306115358
H	2.62004864957983	-1.11208212743818	1.58133476710094
H	4.40027022695217	-0.20017514817255	0.15405408897936
H	3.89216683834060	1.53662953178813	-1.54305002836914
H	1.56690148595117	2.36007293105932	-1.78525184309519

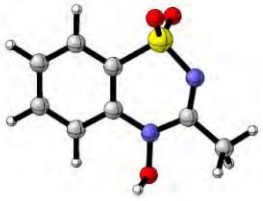
10a



i-freq:
0
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol):
-1042,28571377
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol) // PW6B95/def2-TZVPD/C-PCM(Methanol):
-1044,24407474
CARTESIAN COORDINATES (Ångströms):

C	1.79741577362943	1.44724834691664	-1.18866210889546
C	3.12156184996951	1.10748083104823	-0.98264291132751
C	3.47613112153093	0.35042820445606	0.12961990034460
C	2.52033418937061	-0.08920113787913	1.02721427873252
C	1.18485719321946	0.23046796936695	0.81926941386764
C	0.83953240547721	1.01601060739053	-0.28120355826069
S	-0.80007553457622	1.55894355737720	-0.43112876635886
O	-1.23705765650743	1.63124361593671	-1.79152930578011
O	-0.99022120096870	2.71131416224416	0.40068492041550
N	-1.51222524549138	0.23468858799452	0.24127620868054
C	-1.05768614420569	-0.33634091327463	1.40156928526710
C	-1.99125973838982	-1.04911979443710	2.29146563669938
N	0.21562267627199	-0.28992731704415	1.71556786637901
O	0.63757405136811	-0.80617544215939	2.82968607445216
H	-2.97745087866978	-1.12271762463818	1.83646770123017
H	-2.07011116029012	-0.51184673999421	3.24120909269406
H	-1.59932647290305	-2.04215132949714	2.51853349680902
H	-2.47167535868526	0.06063826327454	-0.03341430029108
H	2.77587705812040	-0.68849207991927	1.88920297608780
H	4.51512896218157	0.09162024052004	0.29532679237572
H	3.87791789061023	1.43778287784793	-1.68362032522272
H	1.49806721893799	2.04731411446967	-2.03951036789880

7a-vacuum



i-freq:
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Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol):
-1042,27371084
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol) // PW6B95/def2-TZVPD/C-PCM(Methanol):
-1044,23255945
CARTESIAN COORDINATES (Ångströms):

C	1.80229094120624	1.57426784760073	-1.06497575570737
C	3.09989396978433	1.12247540822858	-0.92555644686878
C	3.39129611190023	0.17240109410737	0.04594282174683
C	2.40058394277620	-0.33847054201836	0.86244832579424
C	1.08800963226235	0.10879863969275	0.71396826777296
C	0.79852717862490	1.07695576309640	-0.24582693694084
S	-0.82456941789213	1.72740626068984	-0.39702280518136
O	-1.26894679604114	1.52941094140825	-1.74168557755073
O	-0.81919497416300	3.05141858844032	0.14553183478647
N	-1.72253824344695	0.79503345203773	0.58308748099554
C	-1.25713528815399	-0.08104295286964	1.39595912725068
C	-2.19777678136764	-0.79976075912575	2.30331274122056
N	0.06136002432232	-0.41786525212829	1.49153313279100
O	0.41057201462659	-1.34764289396056	2.43878691171956
H	-3.19337629800185	-0.39888241662777	2.13560577284134
H	-1.90670782538814	-0.66218667709423	3.34565122002080
H	-2.19941556559697	-1.87330637066069	2.10246147284238
H	0.45298010043018	-2.19813326566684	1.97880910899527
H	2.63819961330070	-1.06419933158640	1.62698026101130
H	4.40868237830178	-0.17815768827613	0.17209576030790
H	3.88284895133013	1.51213214766706	-1.56363073641666
H	1.54617533118586	2.32079800704564	-1.80720598143110

10a-vacuum



i-freq:
0
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol):
-1042,2609716
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol) // PW6B95/def2-TZVPD/C-PCM(Methanol):
-1044,21914435
CARTESIAN COORDINATES (Ångströms):

C	1.79860435627826	1.45558088485925	-1.18464206831731
C	3.12092968188180	1.11047719740184	-0.97650677209837
C	3.47225820590758	0.34572367187752	0.13118149645212
C	2.51326480321529	-0.09843277075007	1.02188322232710
C	1.18151044468656	0.22613751816147	0.80635687748902
C	0.83632820253161	1.02196601305925	-0.28480238474620
S	-0.80699052913524	1.57452034960348	-0.43323514287166
O	-1.23958729220532	1.64890382121616	-1.79151446457673
O	-0.99726865984532	2.69411063952200	0.43137797857626
N	-1.50314081214157	0.21603358119190	0.21133524543510
C	-1.05964946296378	-0.34011761001820	1.39075432900811
C	-1.98515563831855	-1.03366824419808	2.30529377569523
N	0.21411897345610	-0.30590660518207	1.70594141506626
O	0.63235676080738	-0.81608719560785	2.80588507549822
H	-2.97934916499310	-1.12266781530882	1.86777809868235
H	-2.05191052083727	-0.48309694212712	3.24851881009714
H	-1.58331387734979	-2.01758633138390	2.55600715087343
H	-2.44574203659000	0.02222585721097	-0.08995258576562
H	2.74686124076736	-0.69817488900901	1.89089690113369
H	4.51085373545028	0.08658900745096	0.29822291985640
H	3.88014841820204	1.44397637960576	-1.67285809759759
H	1.49780417119571	2.05870248242454	-2.03253978021698

7u



i-freq:
0
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol):
-1233,83689483
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol) // PW6B95/def2-TZVPD/C-PCM(Methanol):
-1236,27756259
CARTESIAN COORDINATES (Ångströms):

C	2.08977627104564	1.93217986789577	-0.67018312862746
C	3.29634810677137	1.23858807911087	-0.72382814592162
C	3.45103152588332	0.05346993309919	-0.00637797620244
C	2.40050987170780	-0.43049486382740	0.75462752803390
C	1.18951423291074	0.25005633107508	0.78825318330815
C	1.03428978041576	1.43004245879585	0.07386764867568
C	4.40493629782817	1.84285865302929	-1.48858909745304
N	5.14615744360251	1.06264450499865	-2.31320305940110
C	6.39718016237709	1.42251594141807	-2.81458266311153
C	6.79799615641795	2.75811183355325	-2.76985186718964
S	5.60528679165017	3.93643192543576	-2.30766686438804
N	4.63332353888325	3.11297664017724	-1.31894780207459
C	8.07382049050254	3.13373988434839	-3.16922559242029
C	8.94439036883623	2.17698057591642	-3.65400933399523
C	8.53087842519319	0.85026328932605	-3.73782885321953
C	7.27180982098938	0.46292267223913	-3.31876230768742
O	4.78663466299467	-0.24641778409692	-2.47893139471606
O	4.85545223346903	4.31569235864975	-3.48088945041747
O	6.22605101283215	5.00043664707206	-1.56735142472609
H	0.36614025766192	-0.13948932918409	1.37573182847485
H	4.25165702270083	-0.27118195942337	-3.28756723304015
H	6.96549085464582	-0.57228310825217	-3.36255429233588
H	9.20815577830354	0.09818724334647	-4.12481753286014
H	9.93876307016622	2.46106234098065	-3.97496331045250
H	8.36339002930123	4.17579816018036	-3.10631907404229
H	4.39250505752757	-0.47908211134340	-0.03161495203096
H	2.52677555399241	-1.34518762839646	1.32182586192958
H	0.09169215141992	1.96391006497887	0.09992056968764
H	1.98566702996948	2.85897337889665	-1.22133026379630

10u



i-freq:
0
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol):
-1233,82132065
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol) // PW6B95/def2-TZVPD/C-PCM(Methanol):
-1236,26163717
CARTESIAN COORDINATES (Ångströms):

C	2.03119252587897	1.82177351667121	-1.05577323866662
C	3.23498144951669	1.11674926296222	-0.95274642713777
C	3.38138259390462	0.15538056774171	0.05308089143963
C	2.34288935329766	-0.08464026139154	0.93455024310801
C	1.14420680052838	0.60909886654288	0.81765181704629
C	0.99030180708812	1.56034669142969	-0.18101216667303
C	4.32103857769374	1.45660356958197	-1.86266247766450
N	5.21698378844594	0.58344882588301	-2.28807057259414
C	6.35711674987746	1.00018095683115	-3.03984869371505
C	6.41116572237873	2.21566833999965	-3.72237591990354
S	4.96429782345906	3.17156915382713	-3.77021033715943
N	4.41531487355803	2.76514624531650	-2.28227590839666
C	7.55489086702918	2.61580943731738	-4.39681076888882
C	8.65547853791004	1.77855678131800	-4.40955079139945
C	8.59931870681315	0.55217362200487	-3.75541128505328
C	7.46122899015780	0.15874639424560	-3.07437918043206
O	5.13915240848617	-0.67461578395861	-2.01775763971769
O	4.09595995882548	2.64253531389652	-4.77996988166149
O	5.23320363461897	4.57674462789068	-3.75606452528446
H	0.32987932898503	0.40599880766810	1.50365109753557
H	7.40653926736187	-0.78728281548220	-2.55518059590015
H	9.46037410814967	-0.10519156004608	-3.76882415663172
H	9.55424381186026	2.07849711914682	-4.93388066247800
H	7.56907805760165	3.57094798731617	-4.90757975915164
H	4.30768777392527	-0.39414390812468	0.13328267126523
H	2.46797677157143	-0.82324848496377	1.71775511950262
H	0.05629962705699	2.10018815472181	-0.28226488553503
H	1.90076590027020	2.56037420328272	-1.83783357867672
H	4.01841018374934	3.50141636837104	-1.71345638717609

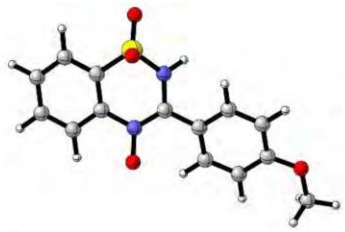
7v



i-freq:
0
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol):
-1348,26013147
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol) // PW6B95/def2-TZVPD/C-PCM(Methanol):
-1350,95805068
CARTESIAN COORDINATES (Ångströms):

N	2.08241446360259	1.92988167725857	-0.69106533848410
C	3.27980442930553	1.21813439029786	-0.76235670402041
C	3.42404018183282	0.02736822521256	-0.04952246933956
S	2.14967201418941	-0.41719160652770	1.04956166178336
N	0.85181584093853	0.29318507246865	0.42531516332573
C	0.91168177355168	1.41434785544299	-0.23799379344244
C	4.58074364036471	-0.73397289192629	-0.15993591627307
C	5.61357175336833	-0.29371595105266	-0.96425917483070
C	5.48180729008775	0.90758302876628	-1.65535493857197
C	4.32822762058642	1.66329587048238	-1.56543838239726
O	2.42980044118073	0.16144151588468	2.34193147650117
O	1.95132085982872	-1.84141466686880	1.01835898573903
C	-0.35238236403208	2.10970040992276	-0.50798263492698
O	2.07107503120130	3.14839615141248	-1.31212616054535
H	2.33483330374664	3.79038619310754	-0.63445992784424
H	4.22457487784974	2.58509972360686	-2.11943455931654
H	6.29010845070899	1.25815978391012	-2.28623000675776
H	6.52162973581130	-0.87742902644183	-1.04973304566145
H	4.66065403003466	-1.65933857429580	0.39788325044457
C	-0.66186695191815	2.67878656949987	-1.74113356387514
C	-1.90431497307983	3.24198090304348	-1.97148169071338
C	-2.85552654823980	3.26278325112689	-0.95103878179784
C	-2.55282421582737	2.69357665766905	0.28883807867507
C	-1.32335922529028	2.11204895219913	0.49820101028943
H	0.06189317939626	2.66556353944064	-2.54460272356644
H	-2.12309905684149	3.65871298160748	-2.94489263729549
O	-4.07859091643820	3.80146776073491	-1.07221025508655
H	-3.30048945539155	2.71446836746279	1.07268883540177
H	-1.09548145481004	1.65880837184492	1.45521168467207
C	-4.43822756155889	4.37366090684388	-2.31941808233977
H	-5.45568835015601	4.73873937863171	-2.19893535760769
H	-3.77736604790092	5.20636390405129	-2.57455747121897
H	-4.40875379610152	3.62544127518330	-3.11597953091906

10v

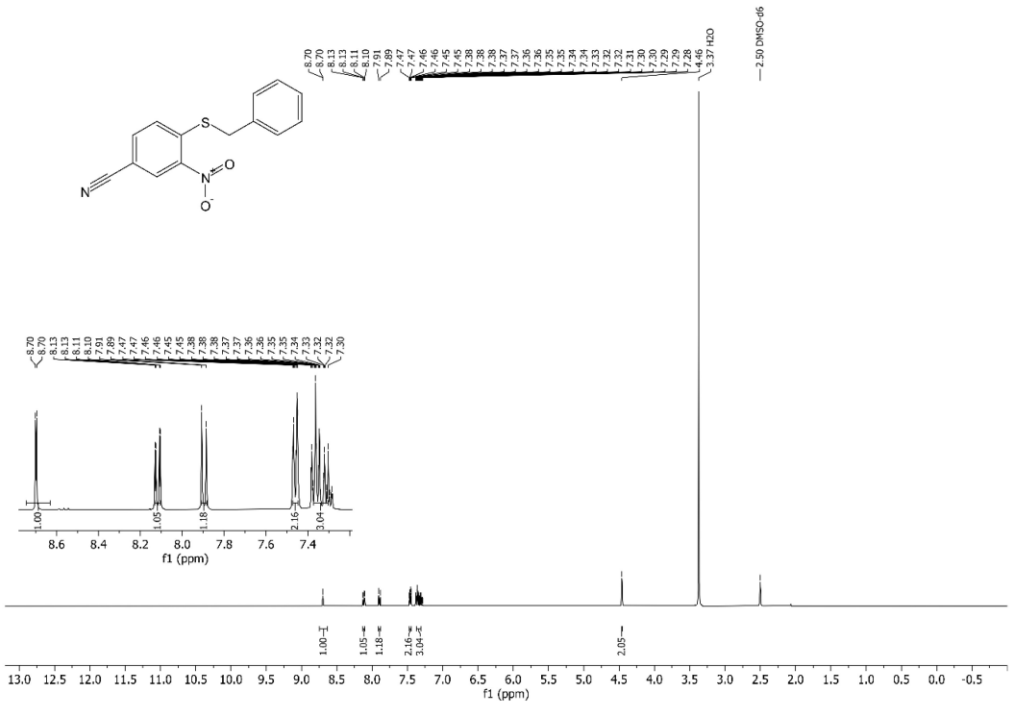


i-freq:
0
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol):
-1348,24496624
Gibbs free energy (PBE0/def2-TZVP/C-PCM(Methanol) // PW6B95/def2-TZVPD/C-PCM(Methanol):
-1350,94257007
CARTESIAN COORDINATES (Ångströms):

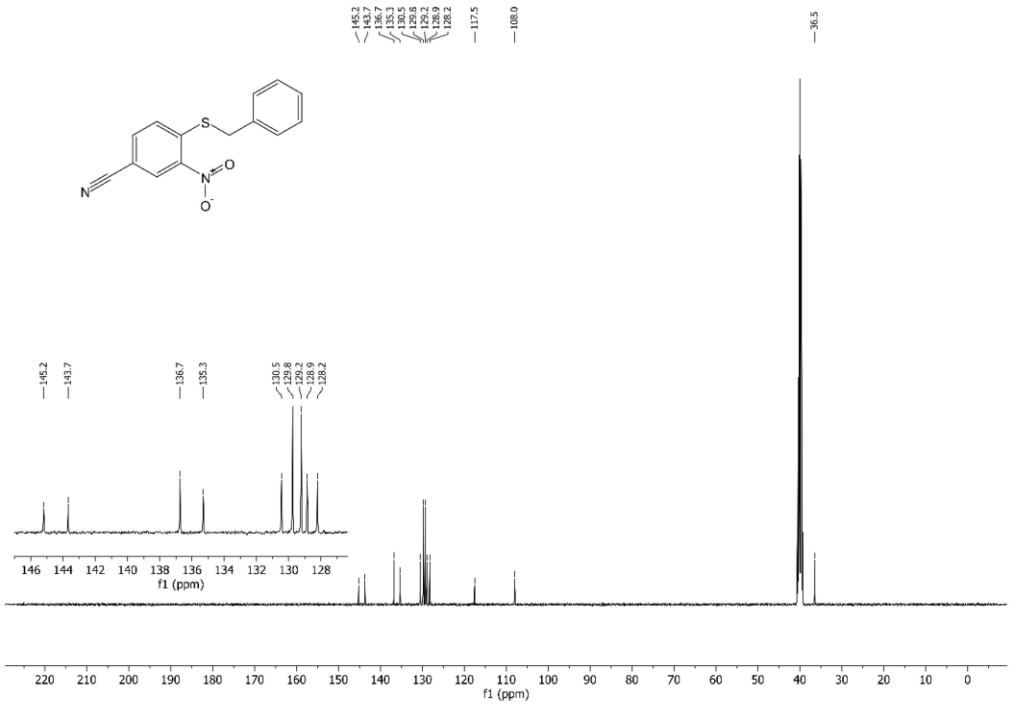
N	2.07299064501466	1.91863745638930	-0.88984615803988
C	3.27526939377778	1.15423474879246	-0.83705433793622
C	3.45689485459452	0.08240744284943	0.03812282448036
S	2.20330564980546	-0.22489744456107	1.19714681557829
N	0.94607127127285	0.24467353721446	0.26216231027913
C	0.93016249589260	1.44062315637193	-0.42455577803510
C	4.62051979745882	-0.67247797981318	0.02529228574090
C	5.62845308490329	-0.34111740230701	-0.86147783679471
C	5.46602289608842	0.74261727563662	-1.71853721881865
C	4.30243961358714	1.49029489230430	-1.70999581778160
O	2.36239142319011	0.67261881739548	2.30306435080583
O	2.03215122571863	-1.62062087287234	1.46343130944764
C	-0.35205255627053	2.08984536143031	-0.61294846790202
O	2.15453497592427	3.07532597755588	-1.46060929738254
H	4.15960038115323	2.33022650977596	-2.37425070533638
H	6.25634485210804	1.00498894959429	-2.41172709864523
H	6.54269374941172	-0.92111522709435	-0.88046325287038
H	4.72699536330789	-1.50415833350221	0.71119353655705
C	-0.64631707909225	2.86518412399453	-1.73883508946685
C	-1.90503642734383	3.40363472278483	-1.92484077334878
C	-2.90037762737069	3.19582707801054	-0.96866364725387
C	-2.61606649912216	2.43212660344380	0.16647065291048
C	-1.36658204405828	1.88230609214602	0.33476605684412
H	0.12312249402980	3.04182035853715	-2.47565101238648
H	-2.10207334639561	3.98809583720029	-2.81313999610714
O	-4.14364613501316	3.69024216330946	-1.05432212830511
H	-3.39187811814961	2.28466914781442	0.90821098851273
H	-1.16585940455676	1.29949742520457	1.22600521307649
C	-4.48371810091302	4.45926966765941	-2.19739019451864
H	-5.52370216941651	4.74862909576323	-2.06444163961631
H	-3.86005820937633	5.35422794428641	-2.26767267094962
H	-4.38120485270346	3.86814887227002	-3.11114328804017
H	0.13076840254298	-0.35376599758496	0.24661906530269

11. NMR Spectra

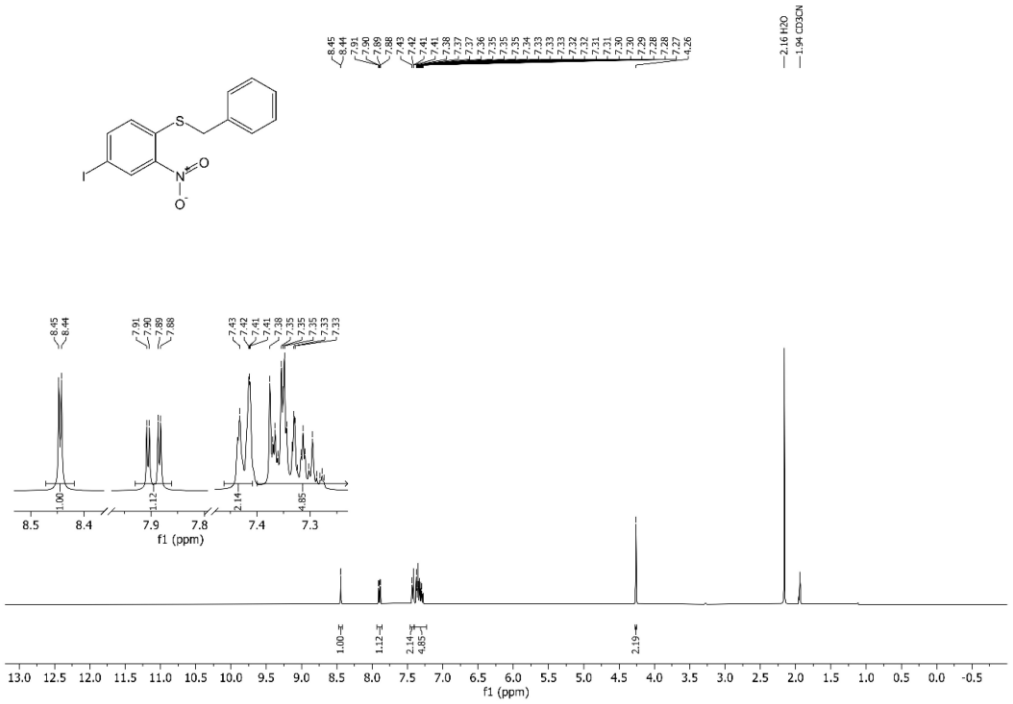
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **11**



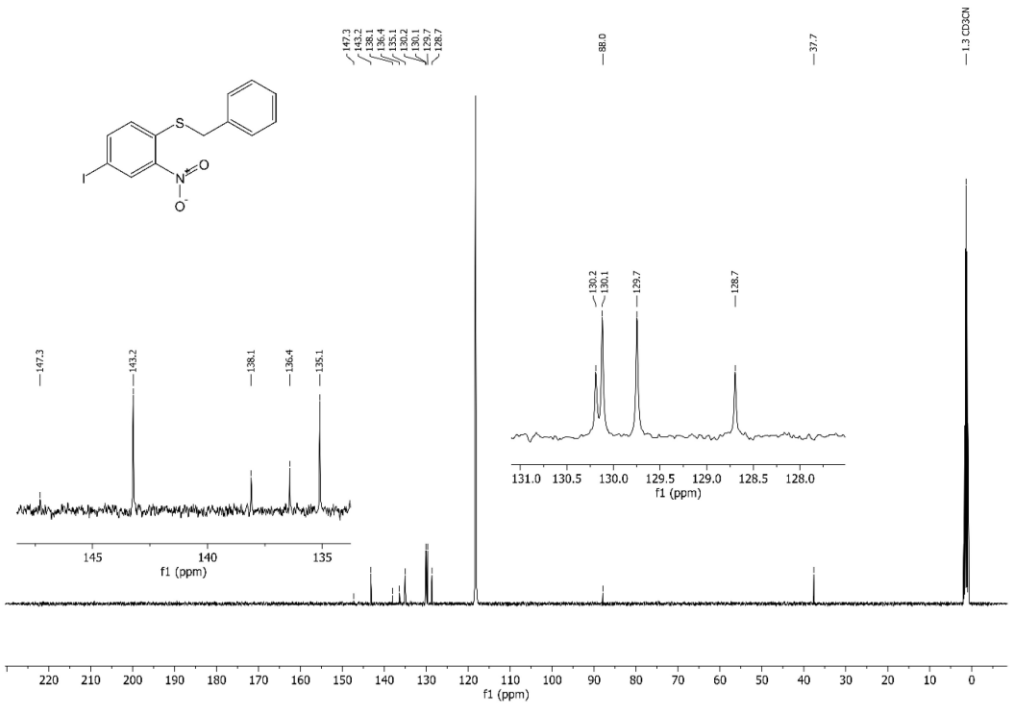
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **11**



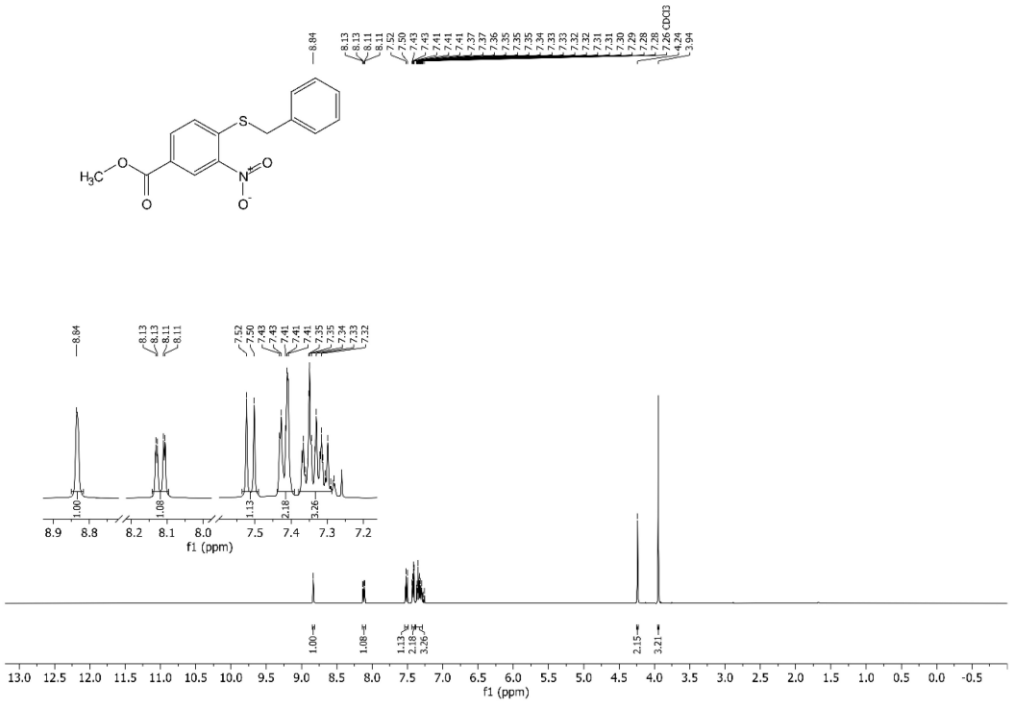
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **12**



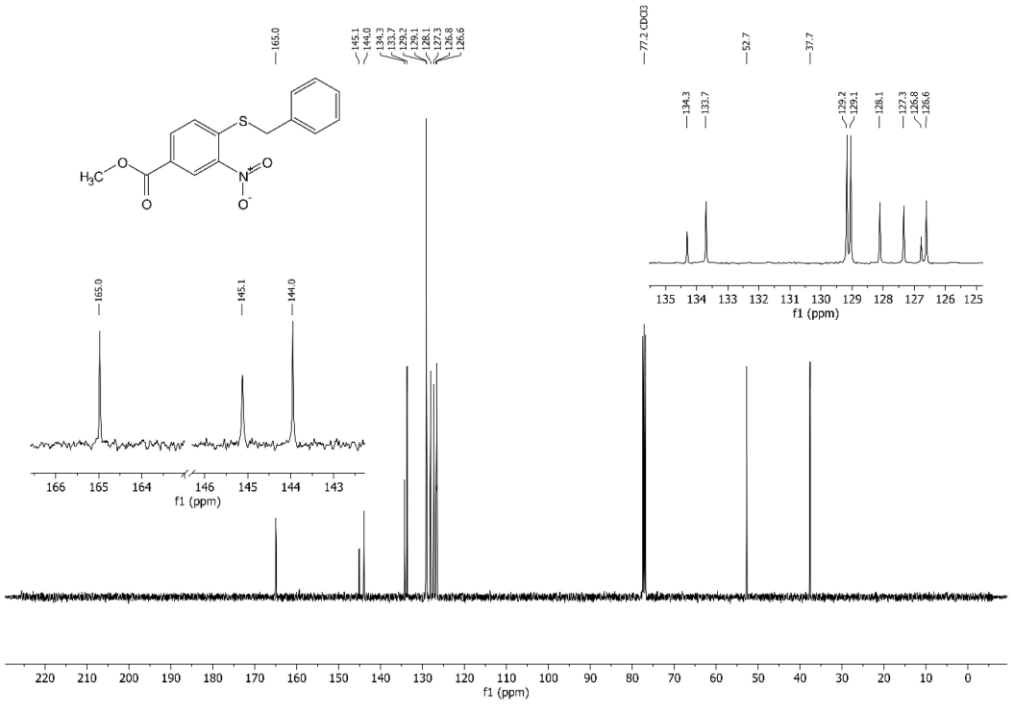
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **12**



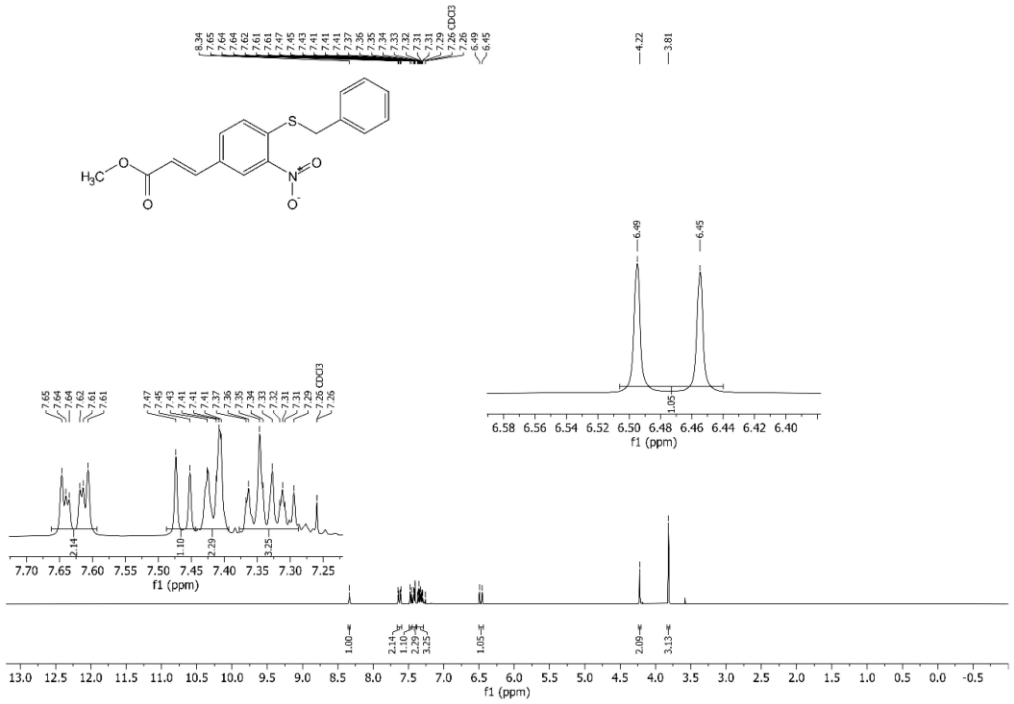
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **13**



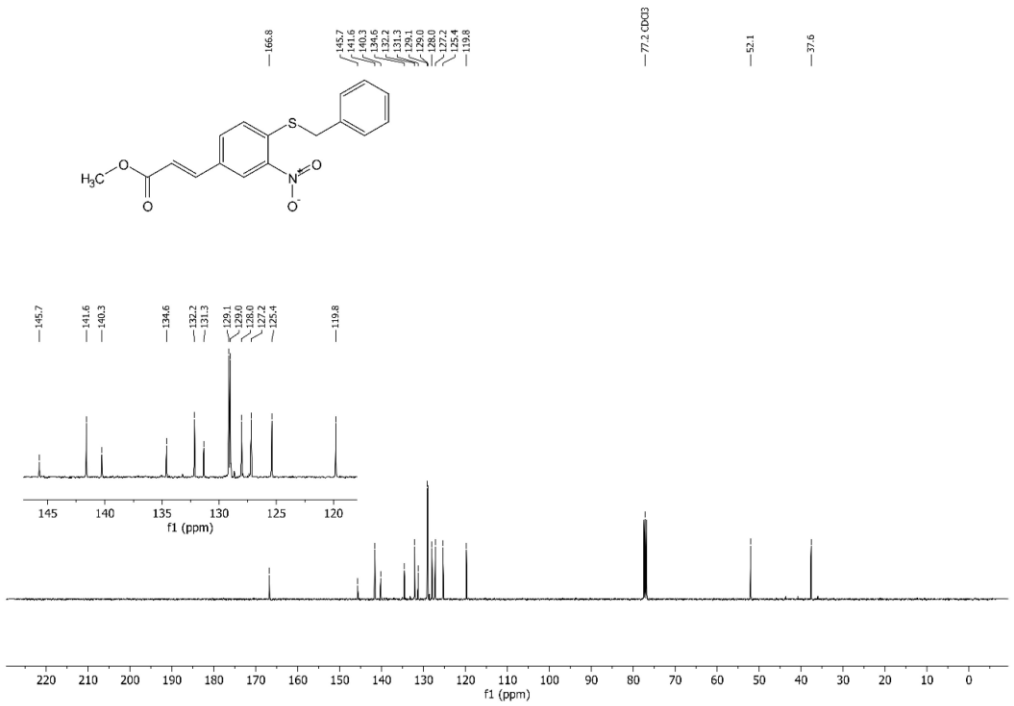
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **13**



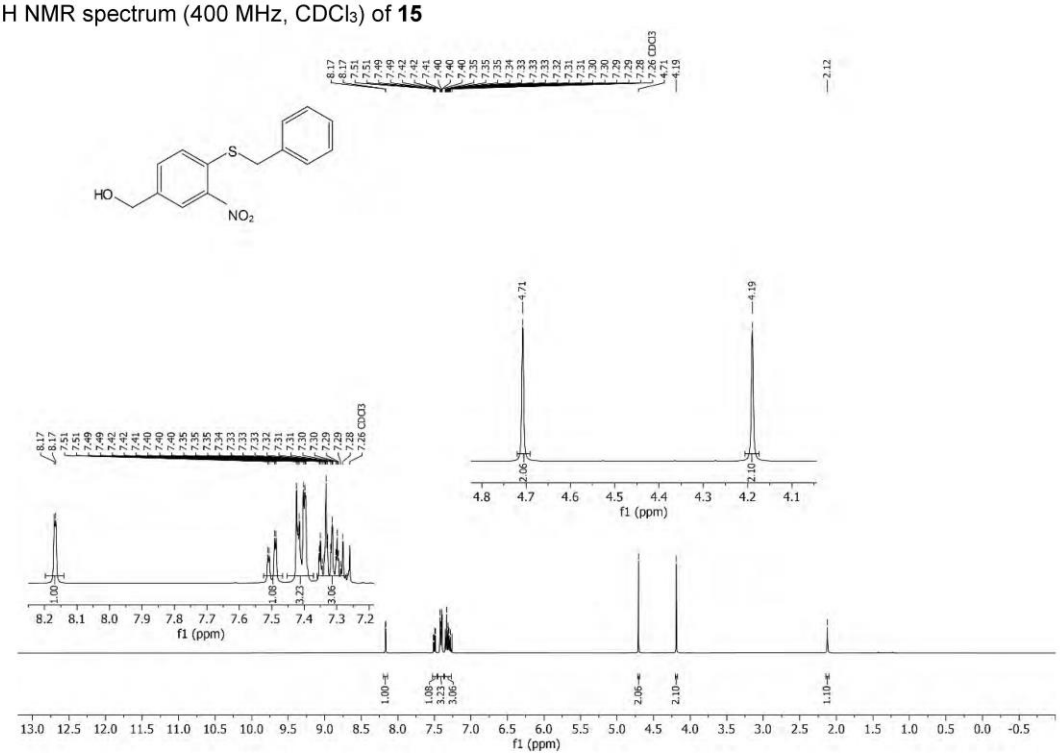
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **14**



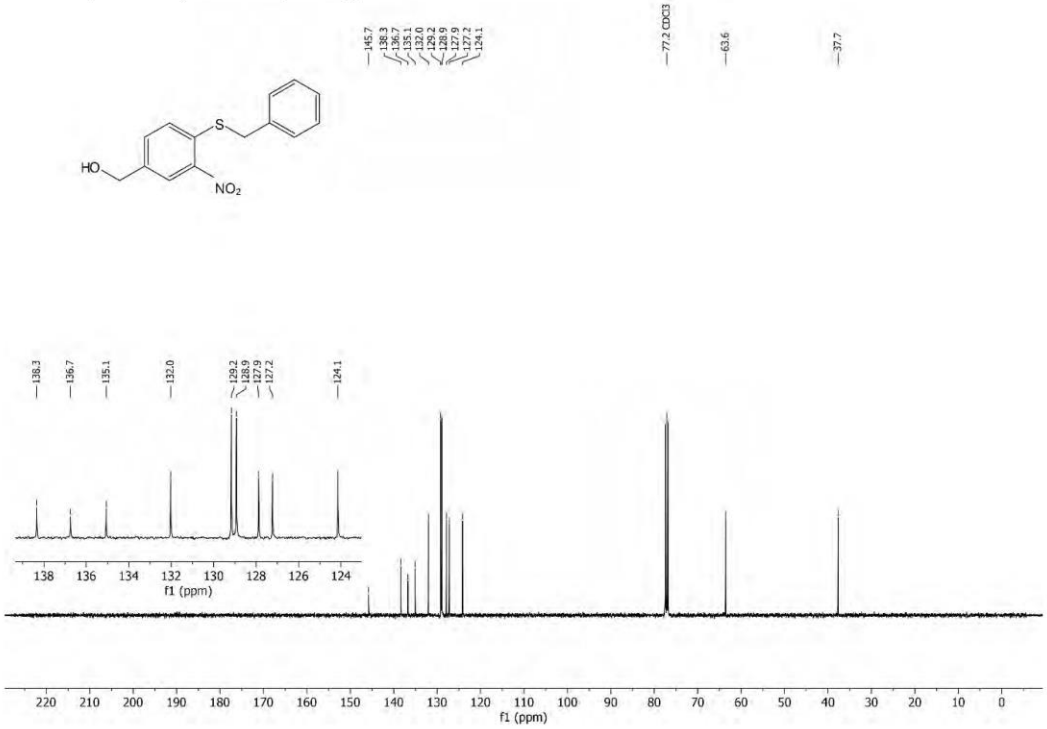
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **14**



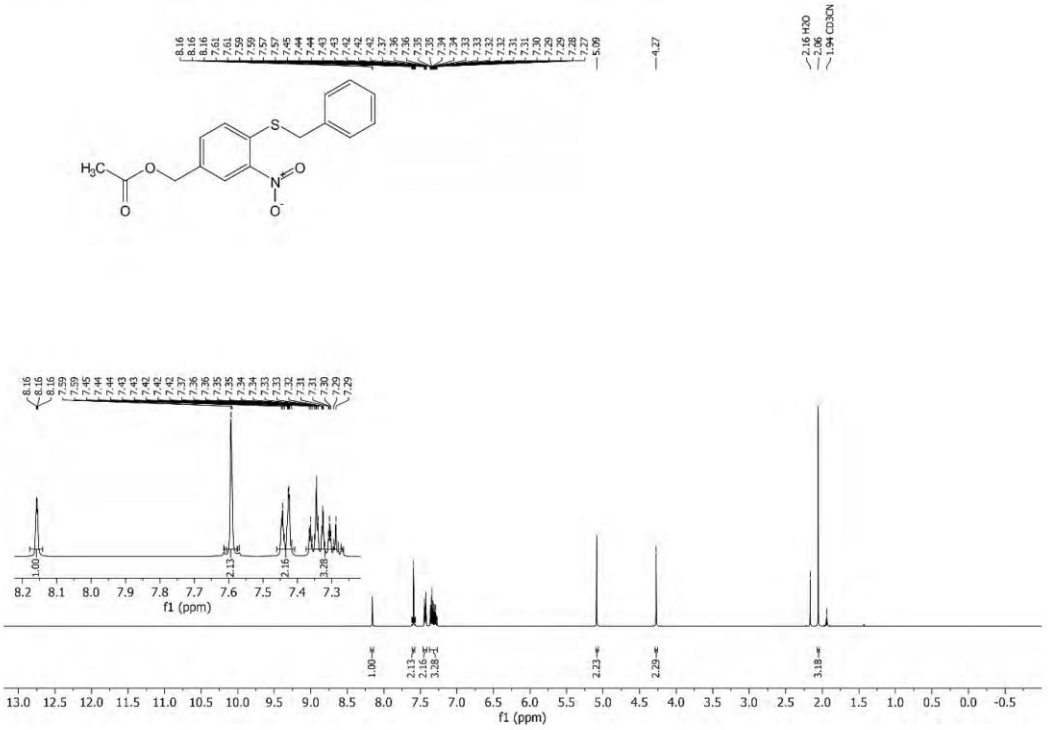
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **15**



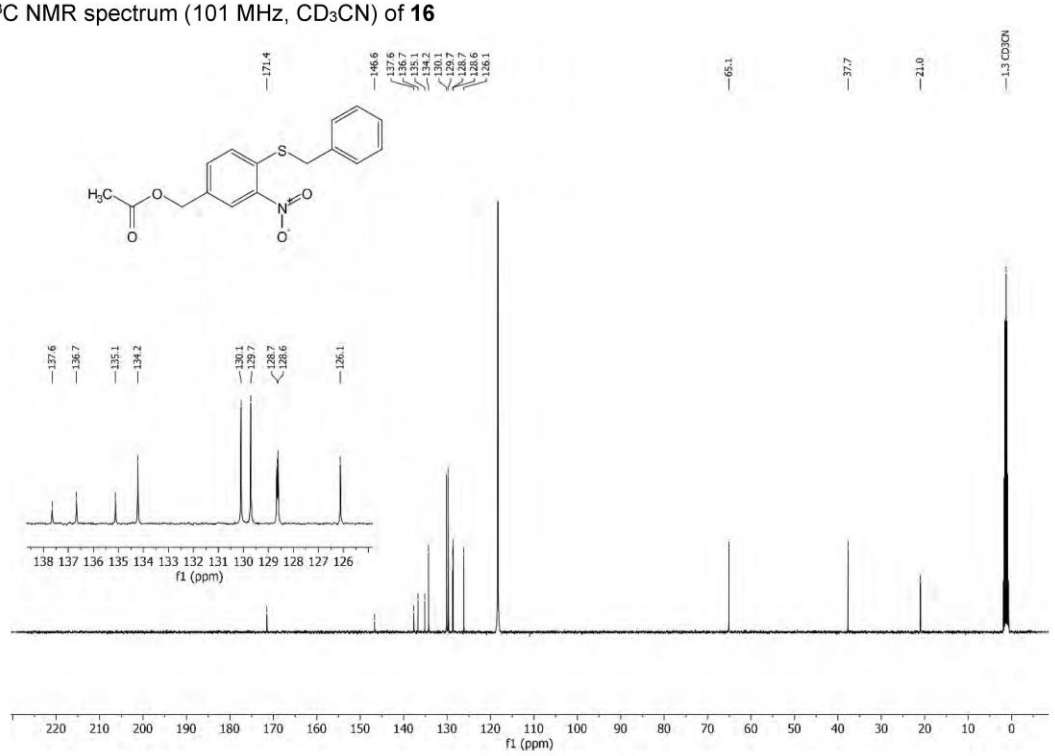
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **15**



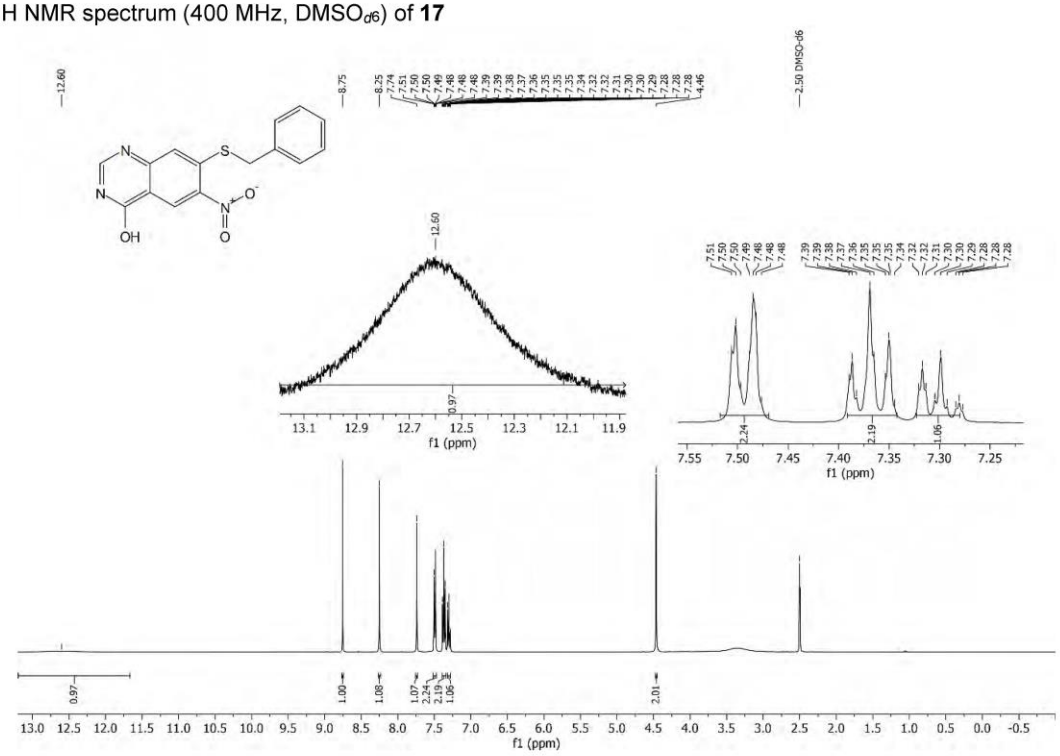
^{1}H NMR spectrum (400 MHz, CD_3CN) of **16**



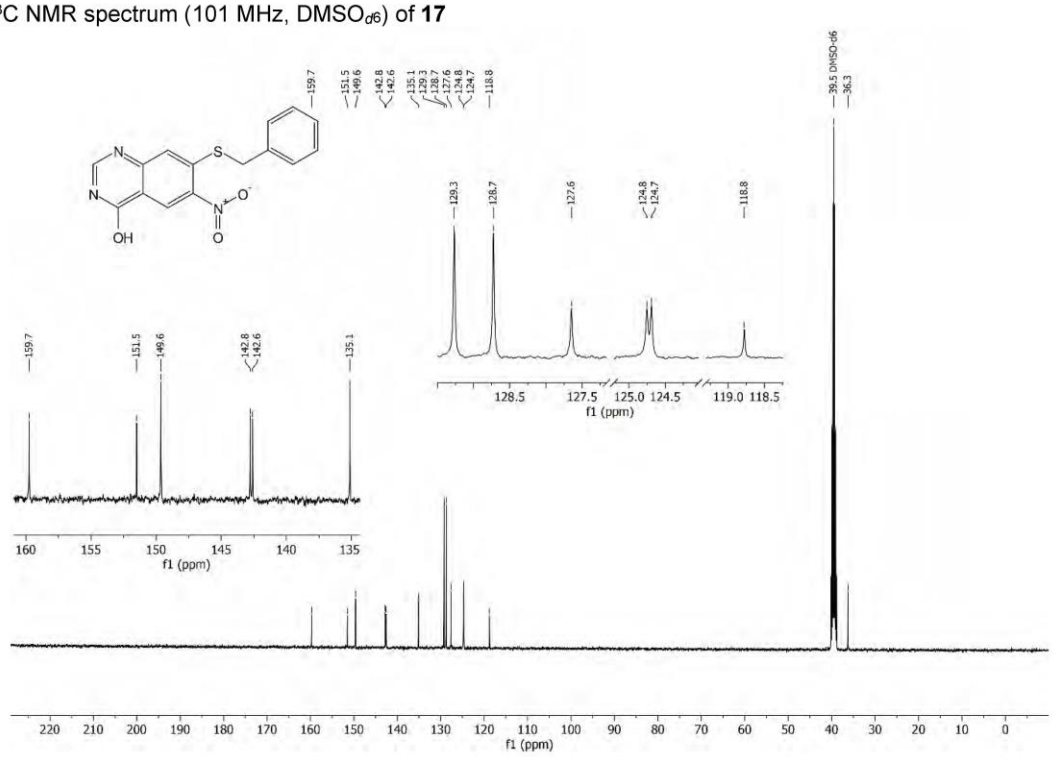
^{13}C NMR spectrum (101 MHz, CD_3CN) of **16**



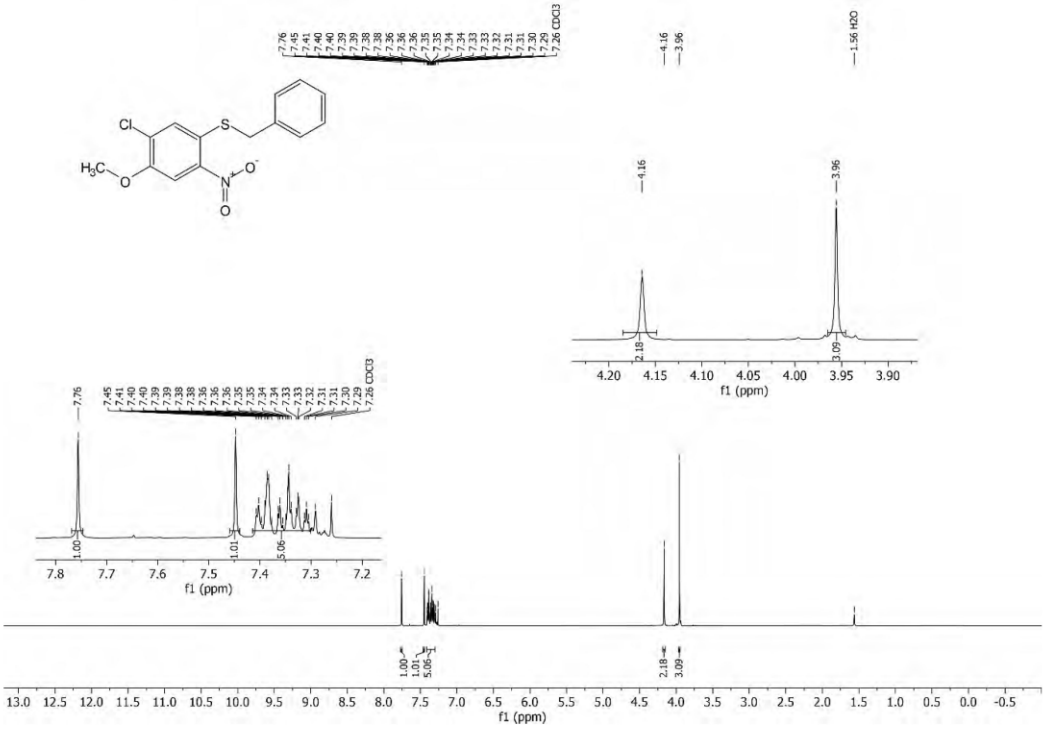
^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **17**



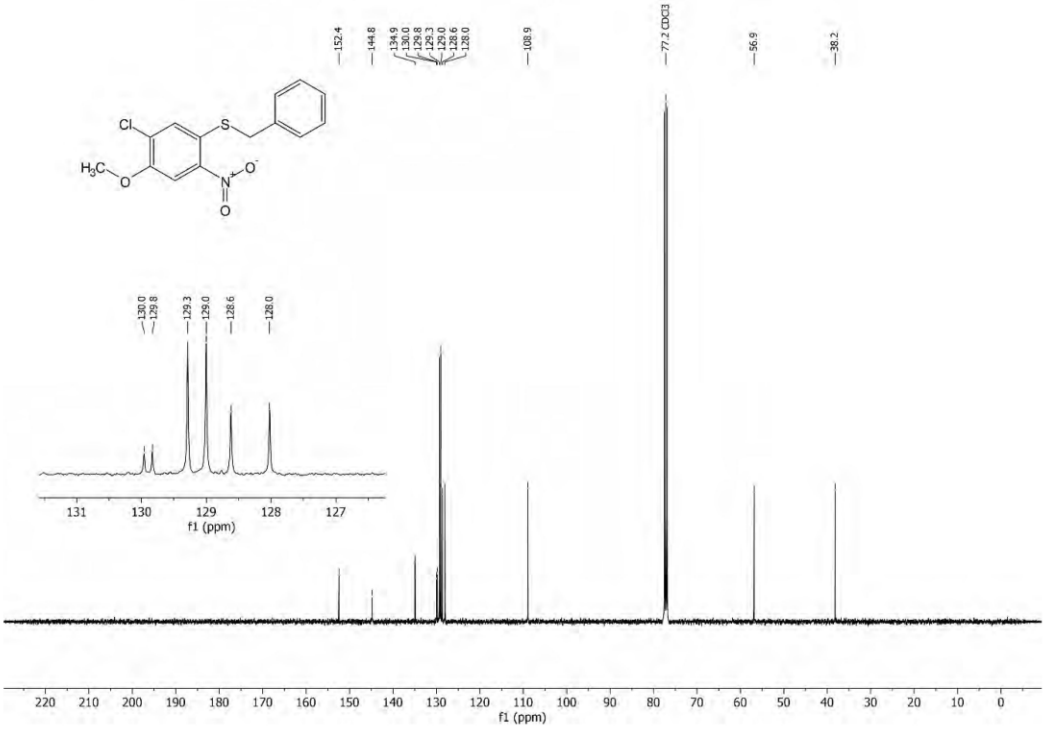
^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **17**



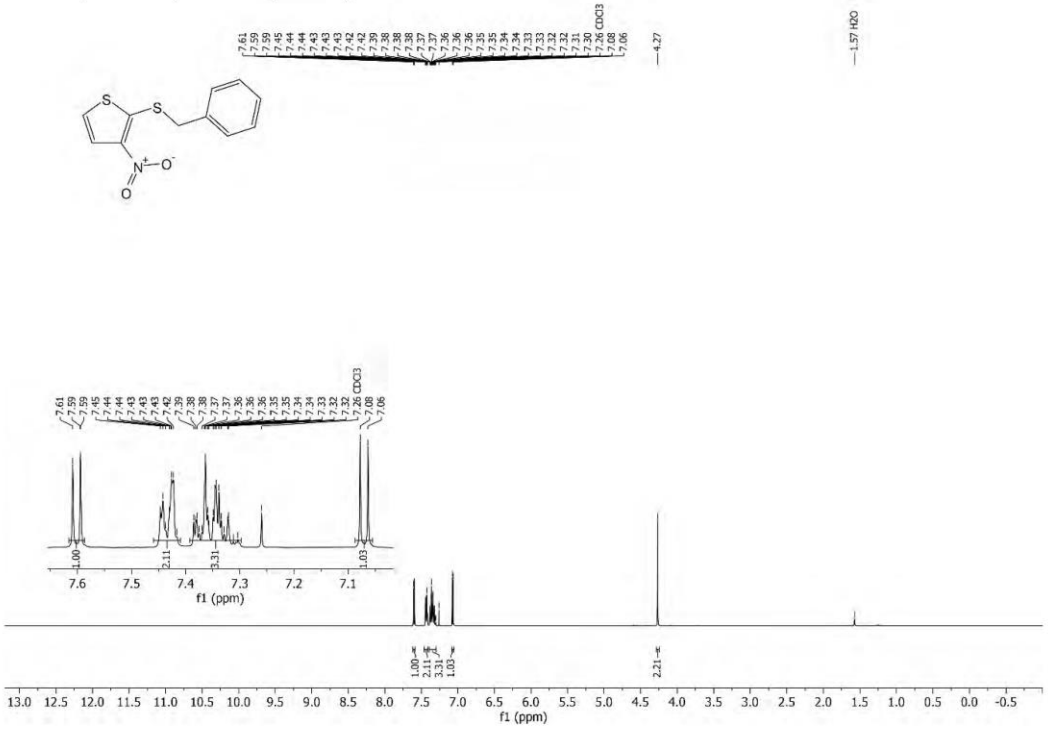
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **18**



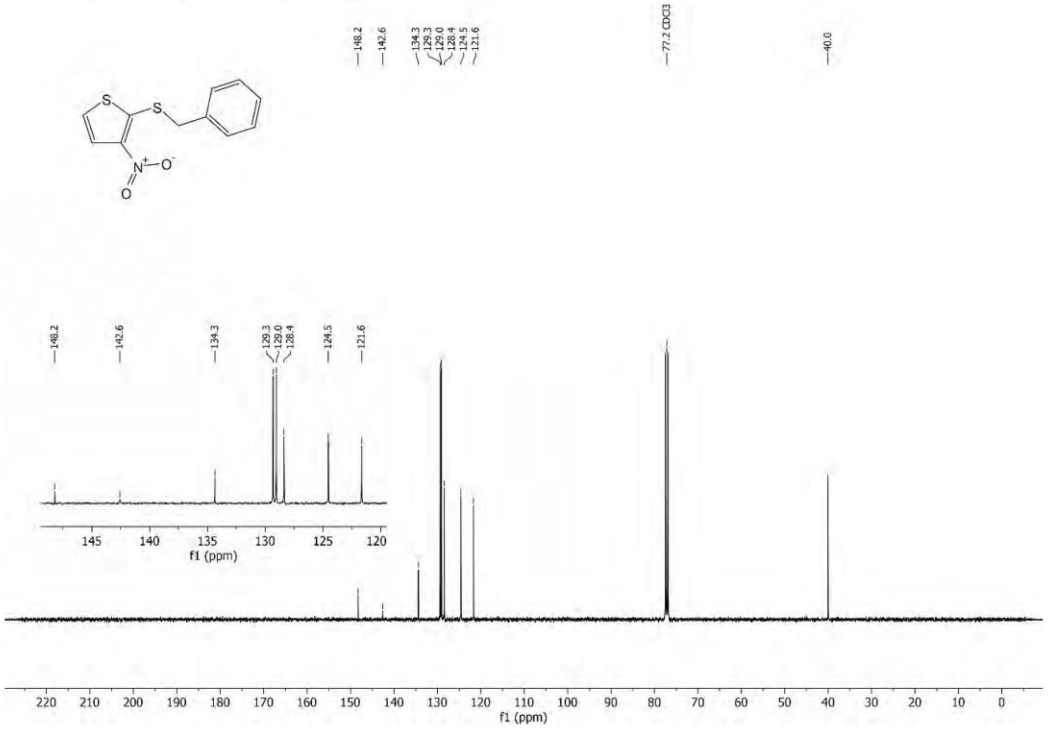
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **18**



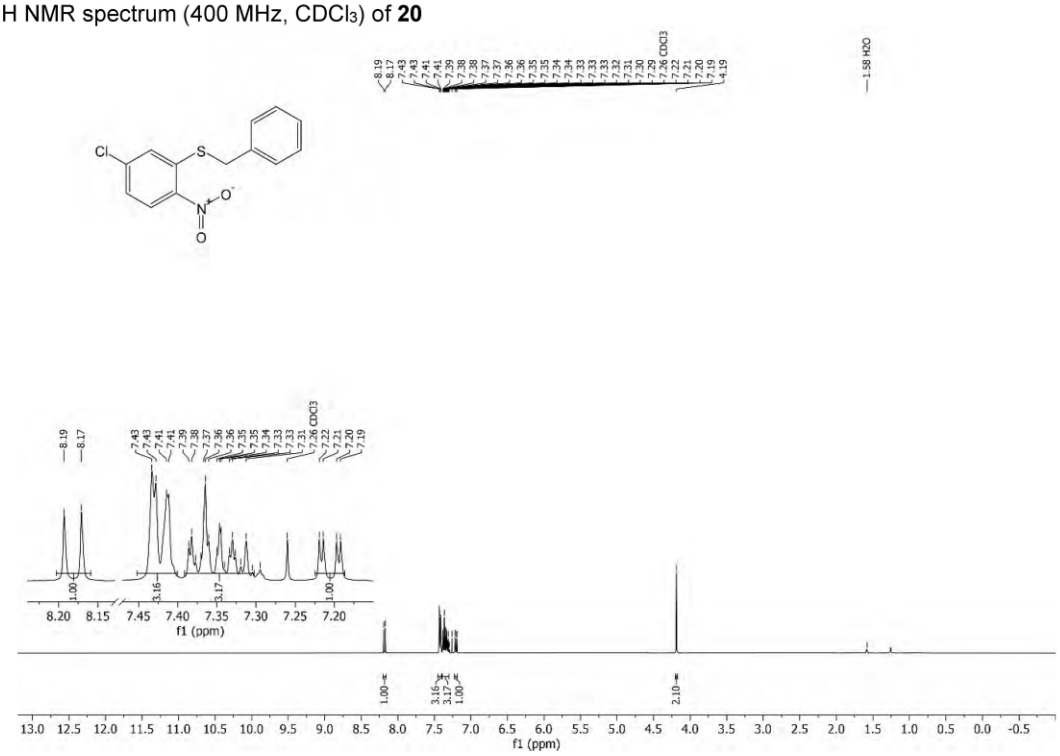
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **19**



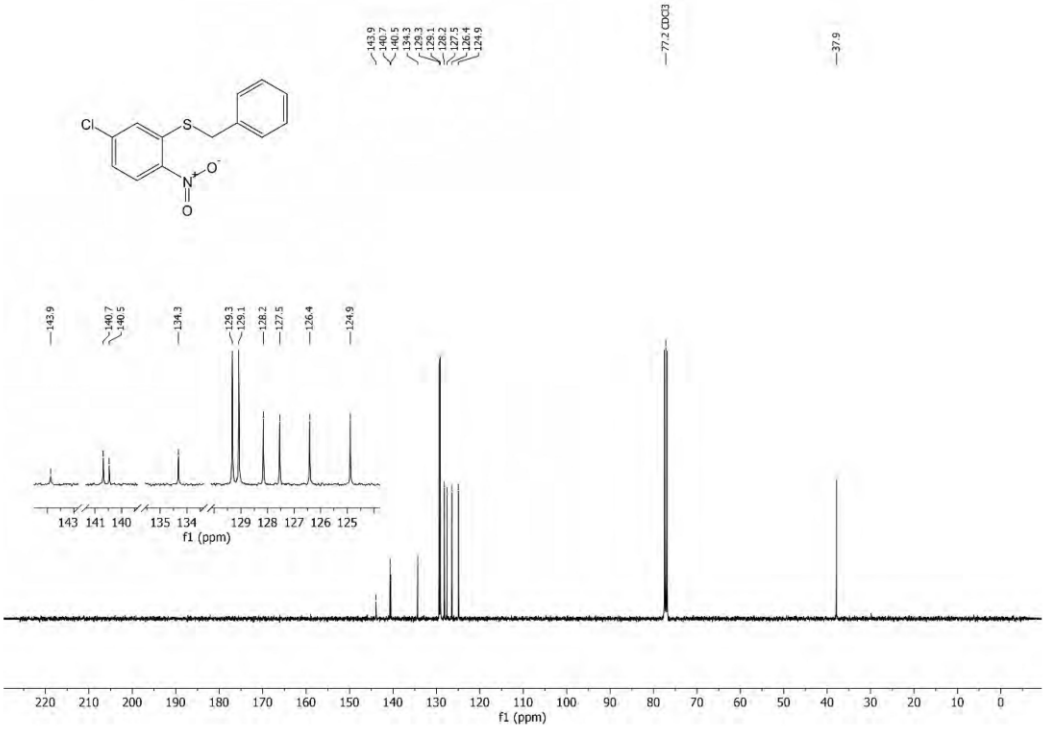
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **19**



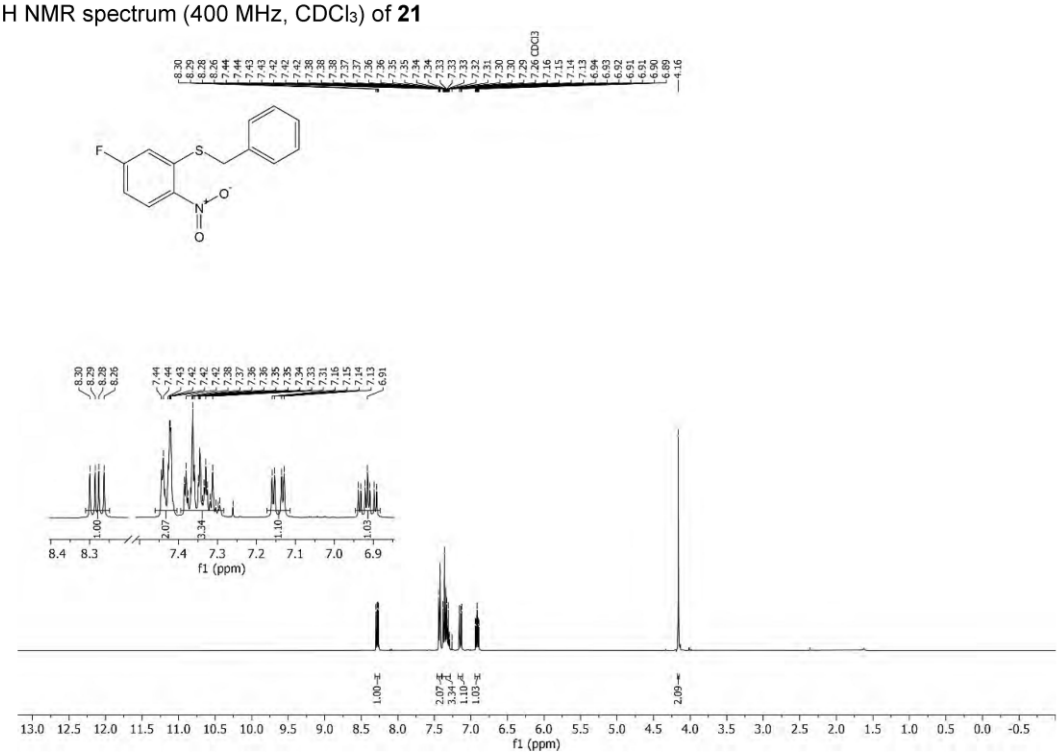
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **20**



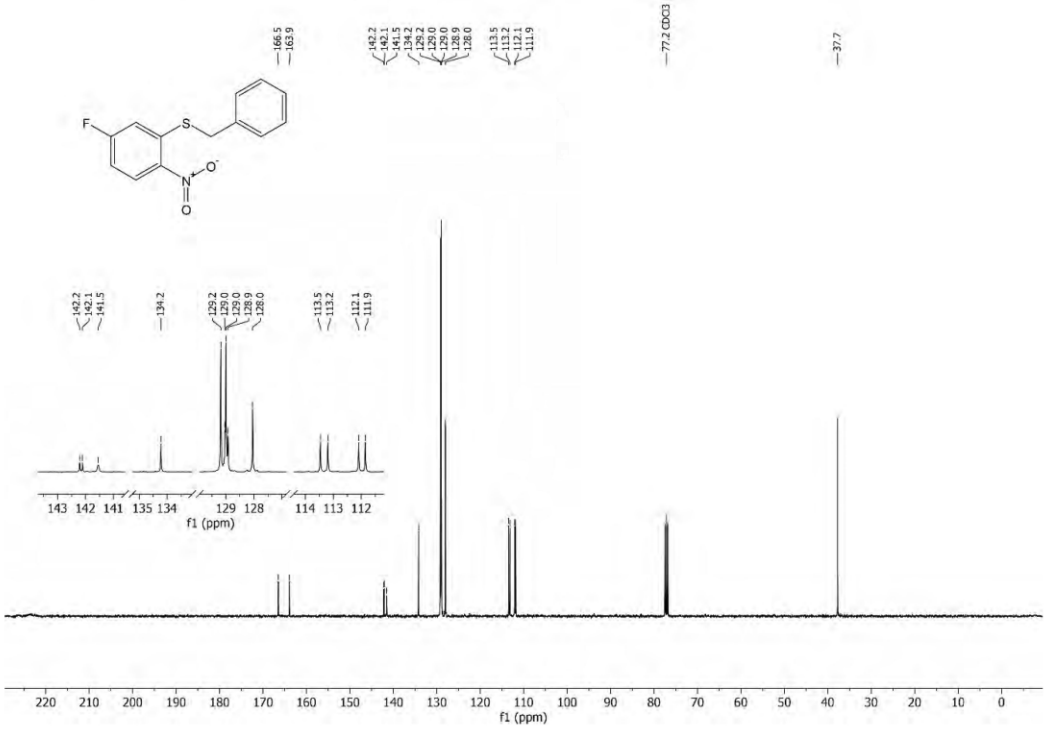
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **20**



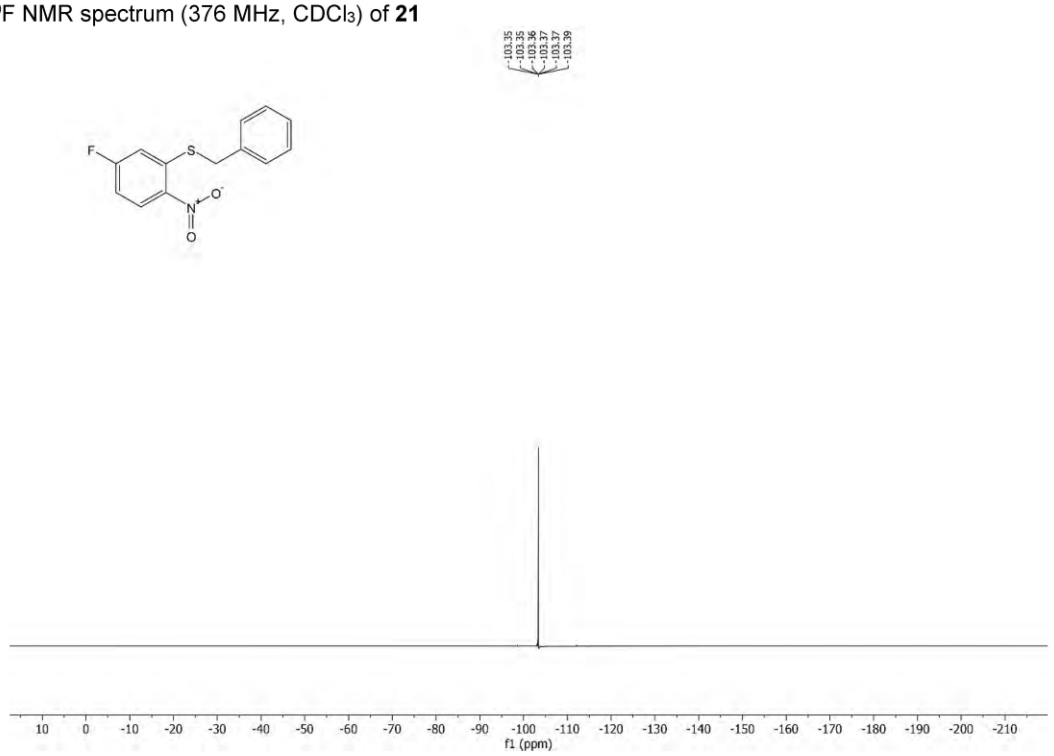
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **21**



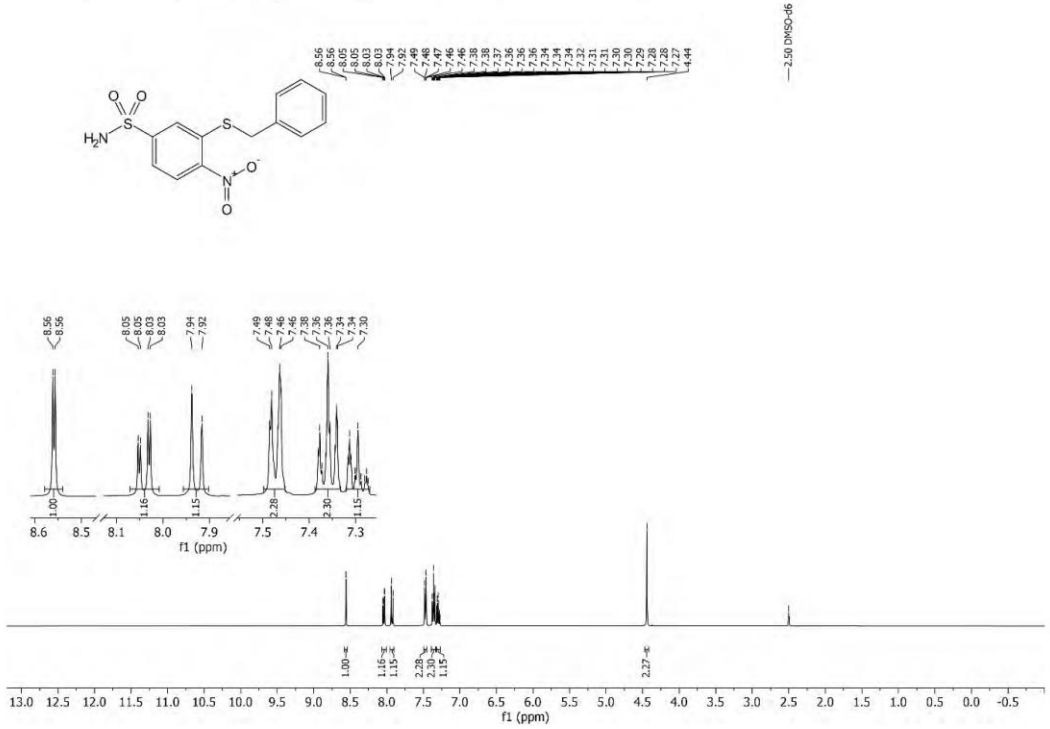
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **21**



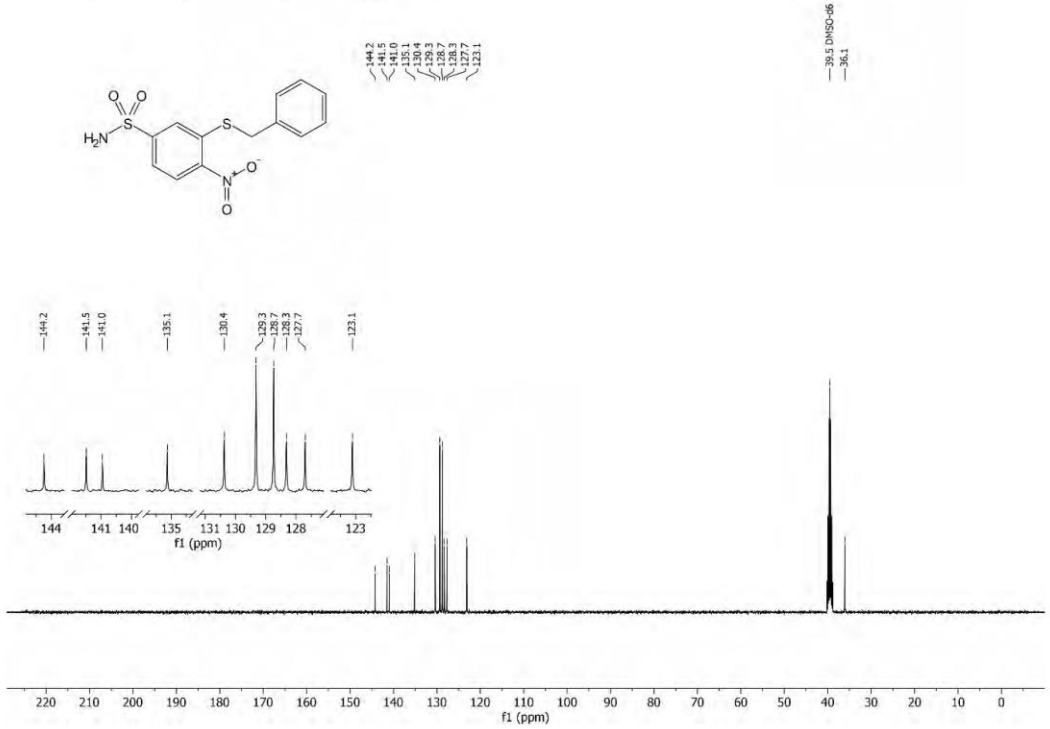
^{19}F NMR spectrum (376 MHz, $CDCl_3$) of **21**



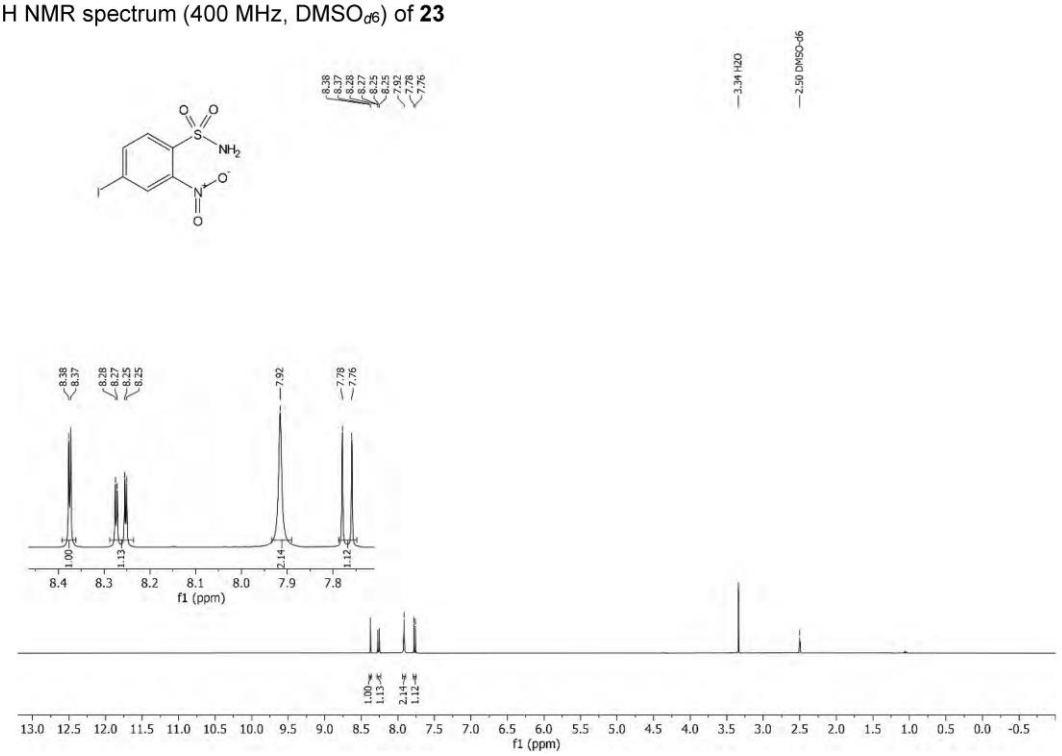
^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **22**



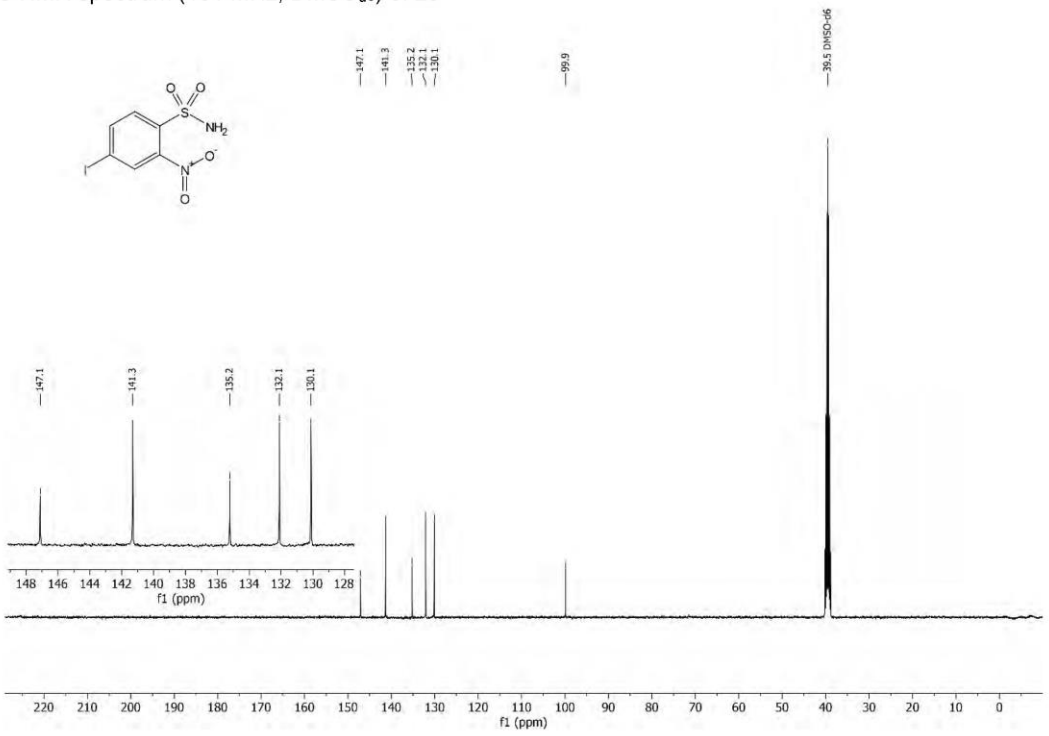
^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **22**



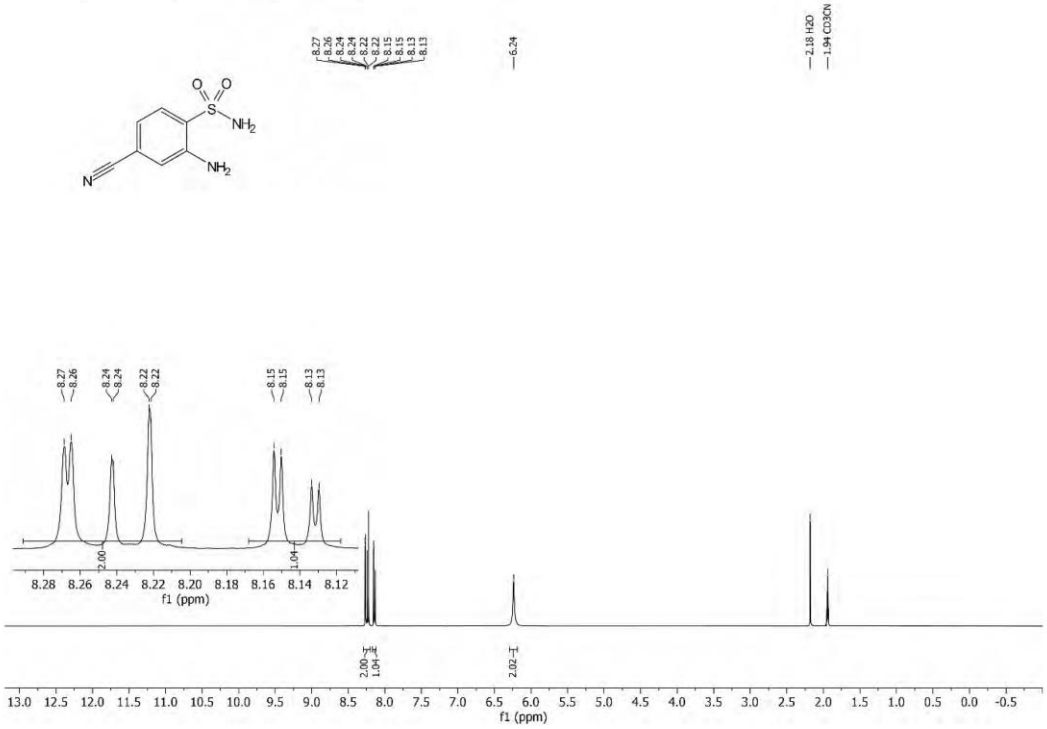
^{1}H NMR spectrum (400 MHz, DMSO$_{d6}$) of **23**



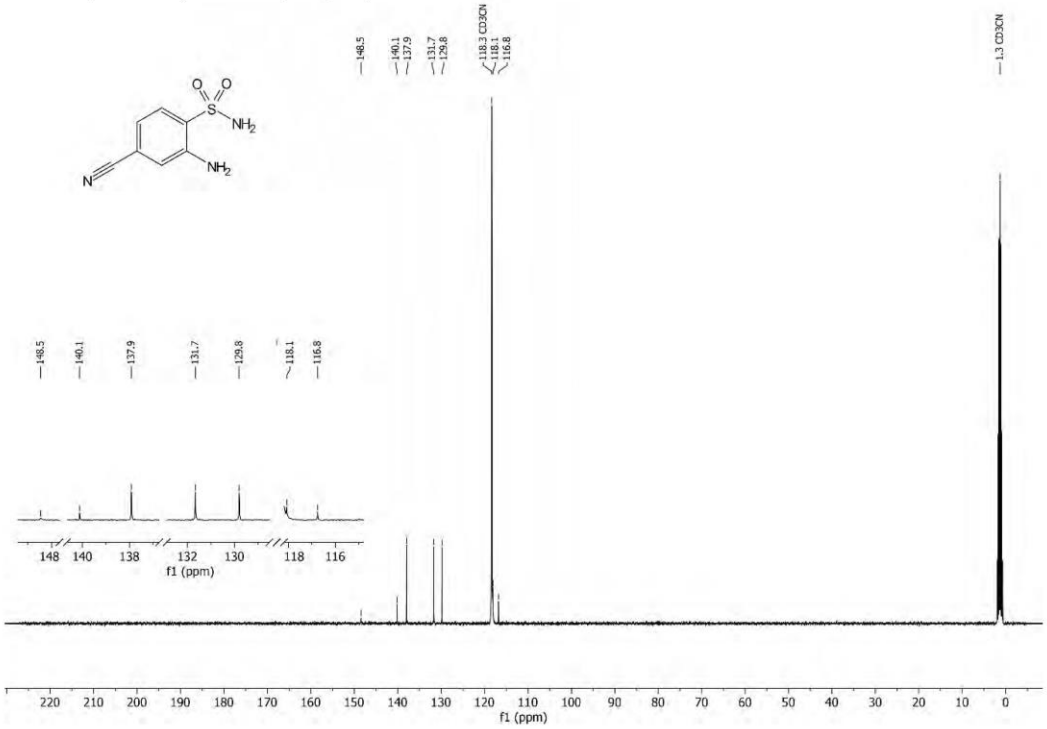
^{13}C NMR spectrum (101 MHz, DMSO$_{d6}$) of **23**



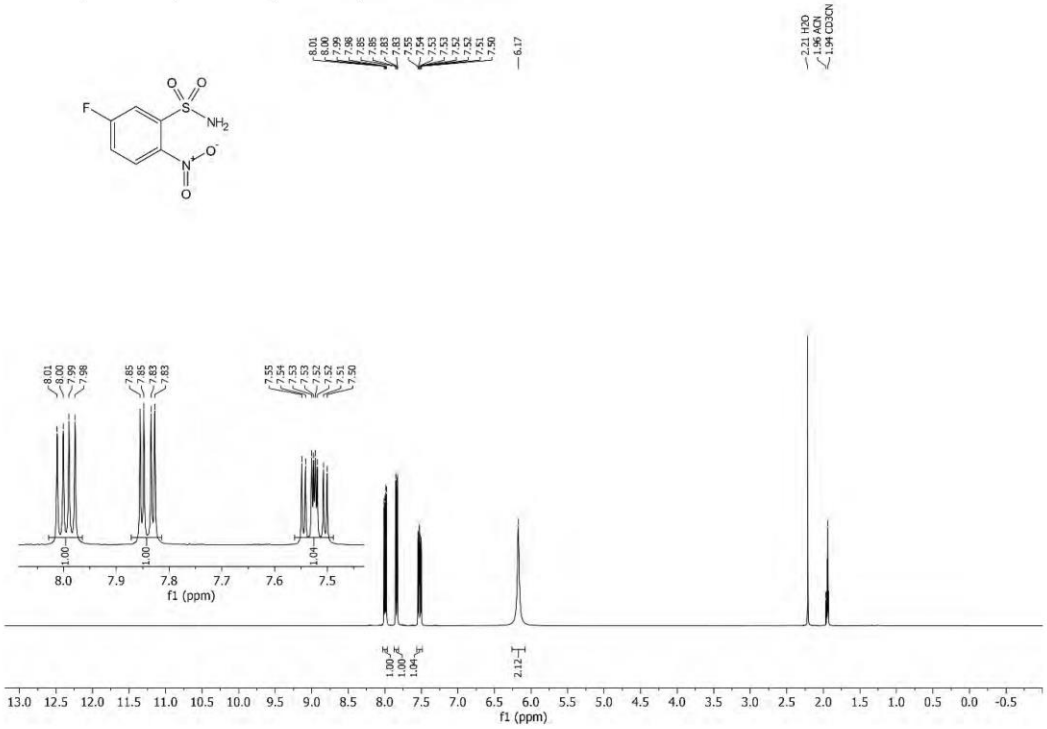
^{1}H NMR spectrum (400 MHz, CD_3CN) of **24**



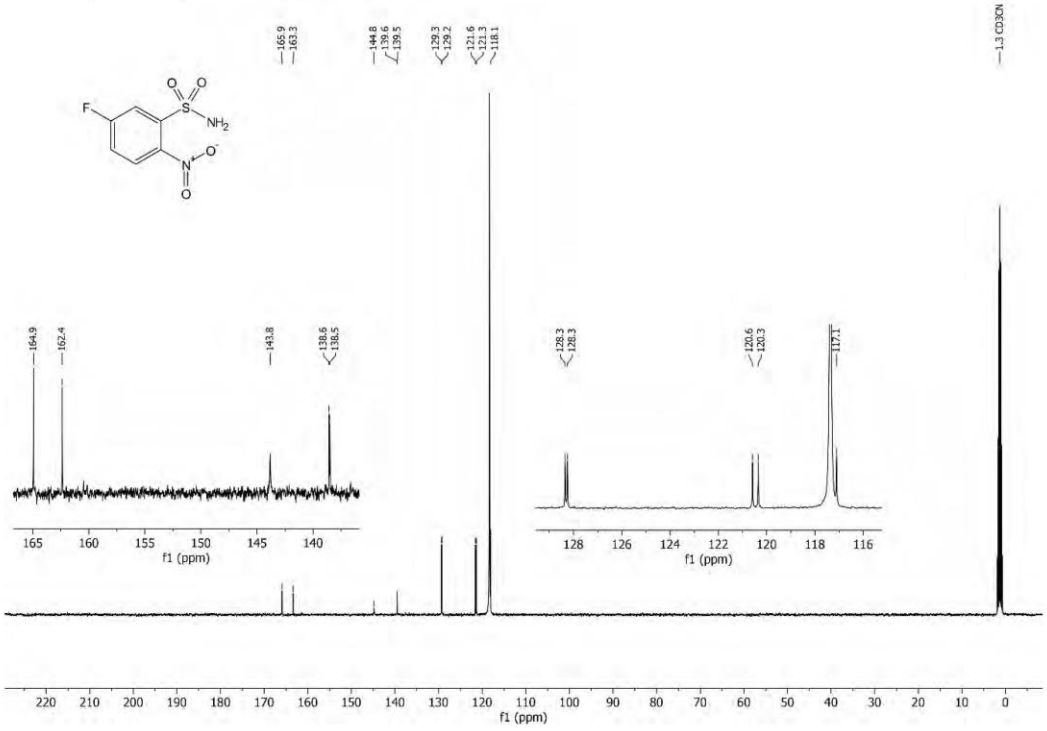
^{13}C NMR spectrum (101 MHz, CD_3CN) of **24**



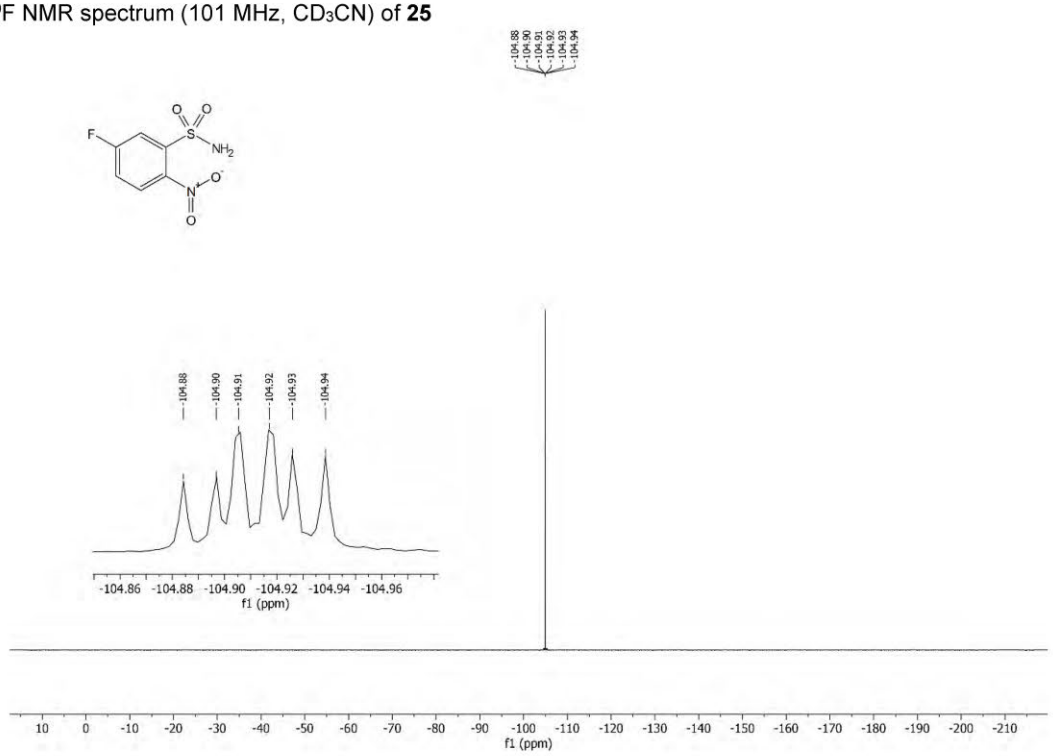
^{1}H NMR spectrum (400 MHz, CD_3CN) of **25**



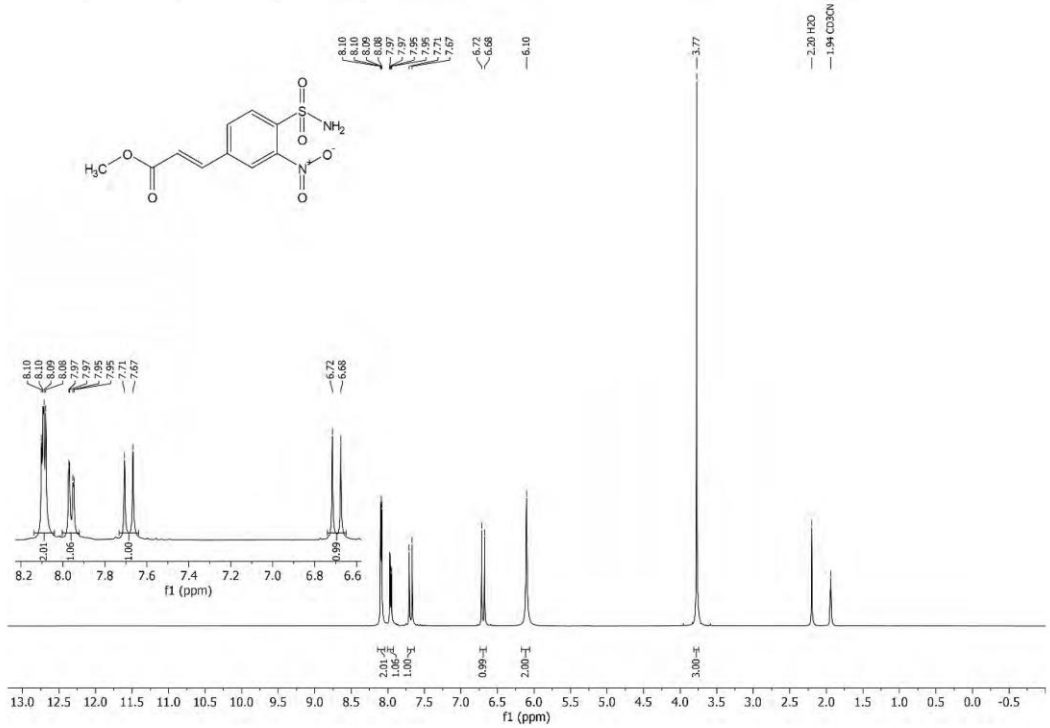
^{13}C NMR spectrum (101 MHz, CD_3CN) of **25**



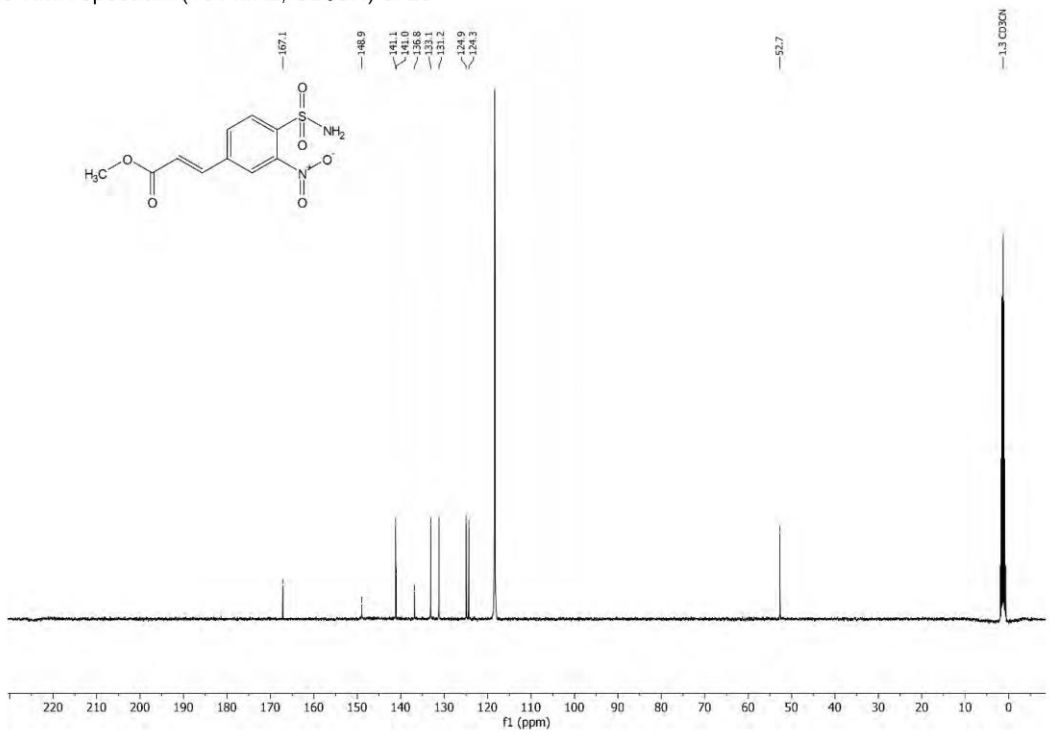
^{19}F NMR spectrum (101 MHz, CD_3CN) of **25**



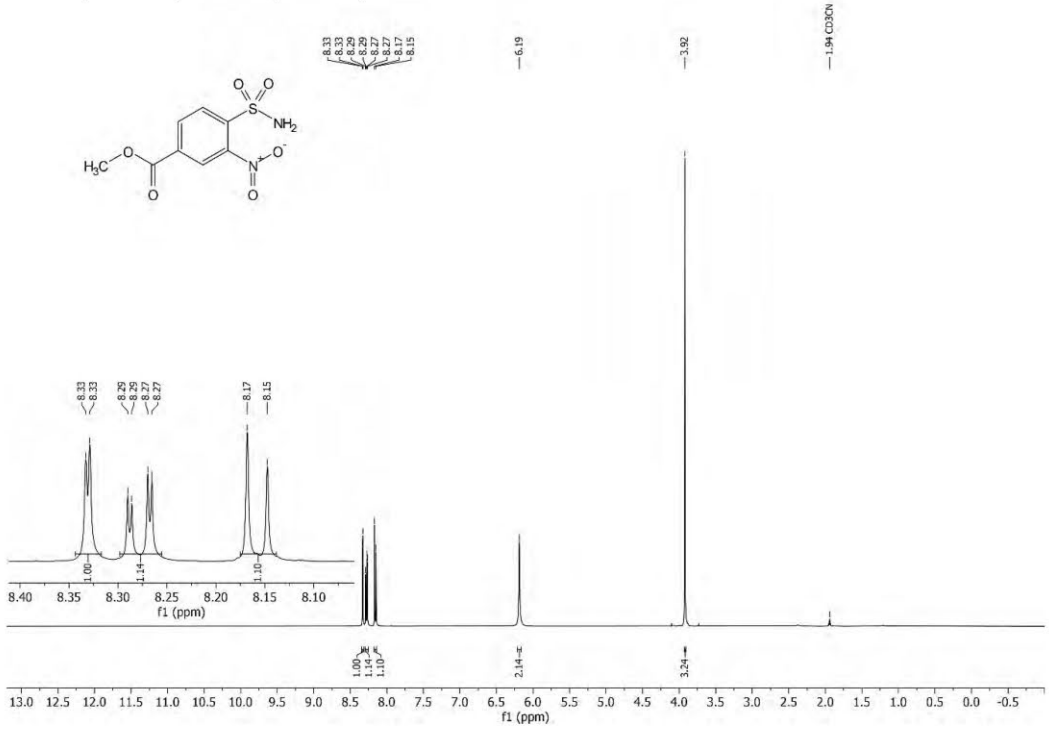
^{1}H NMR spectrum (400 MHz, CD_3CN) of **26**



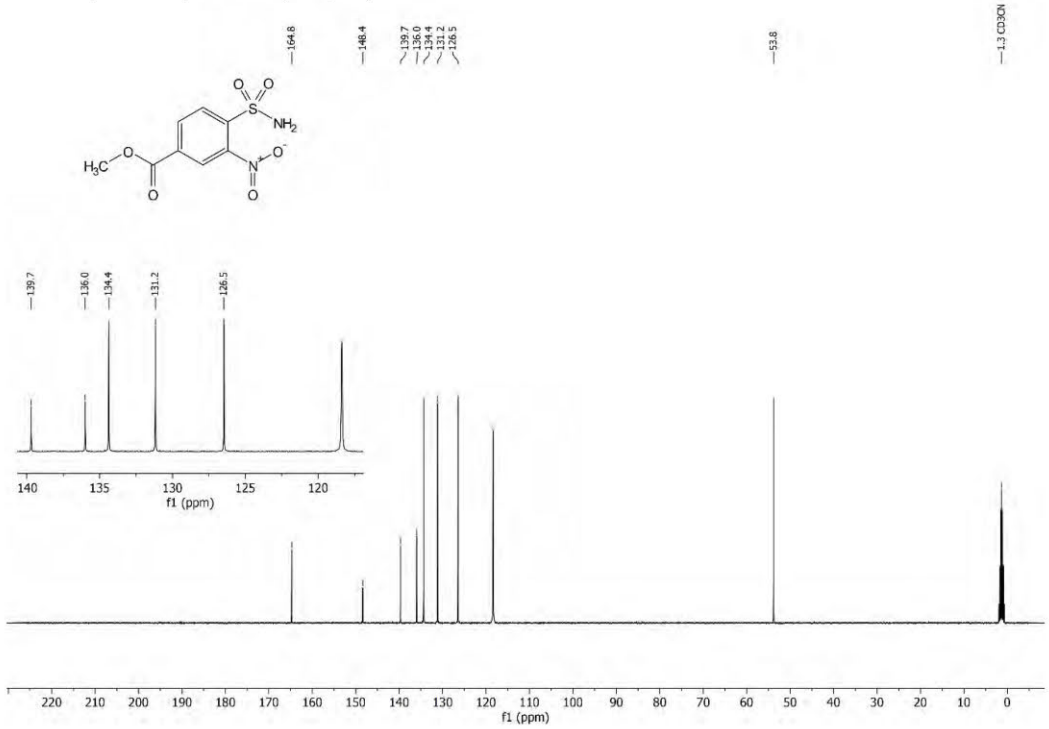
^{13}C NMR spectrum (101 MHz, CD_3CN) of **26**



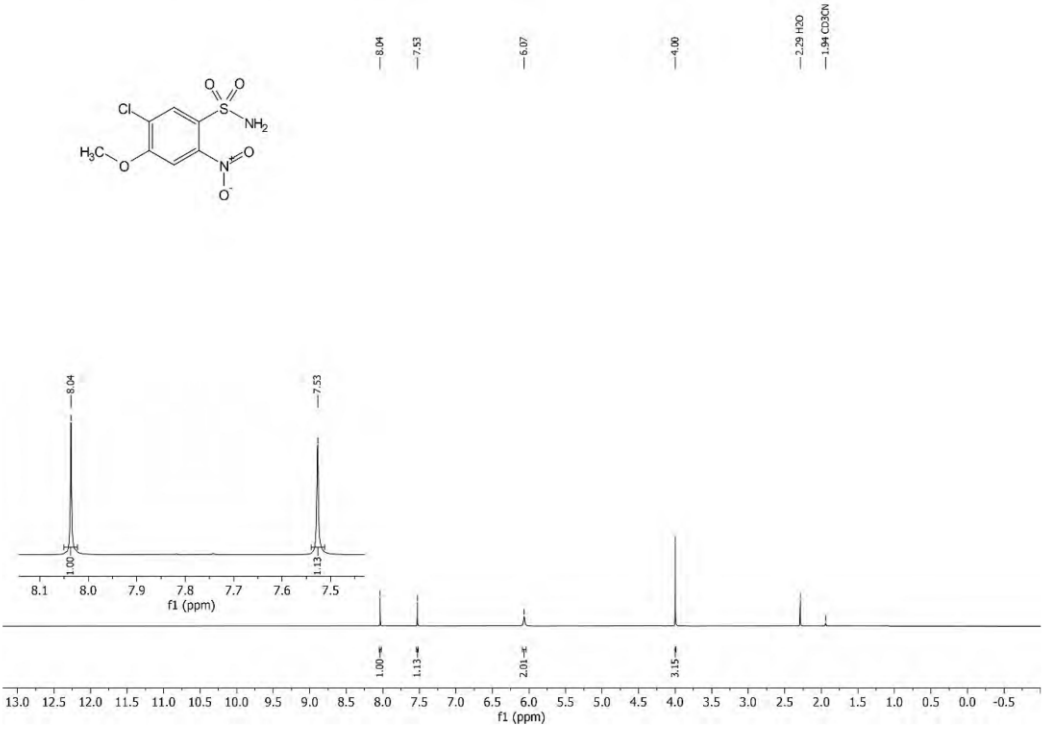
^{1}H NMR spectrum (400 MHz, CD_3CN) of **27**



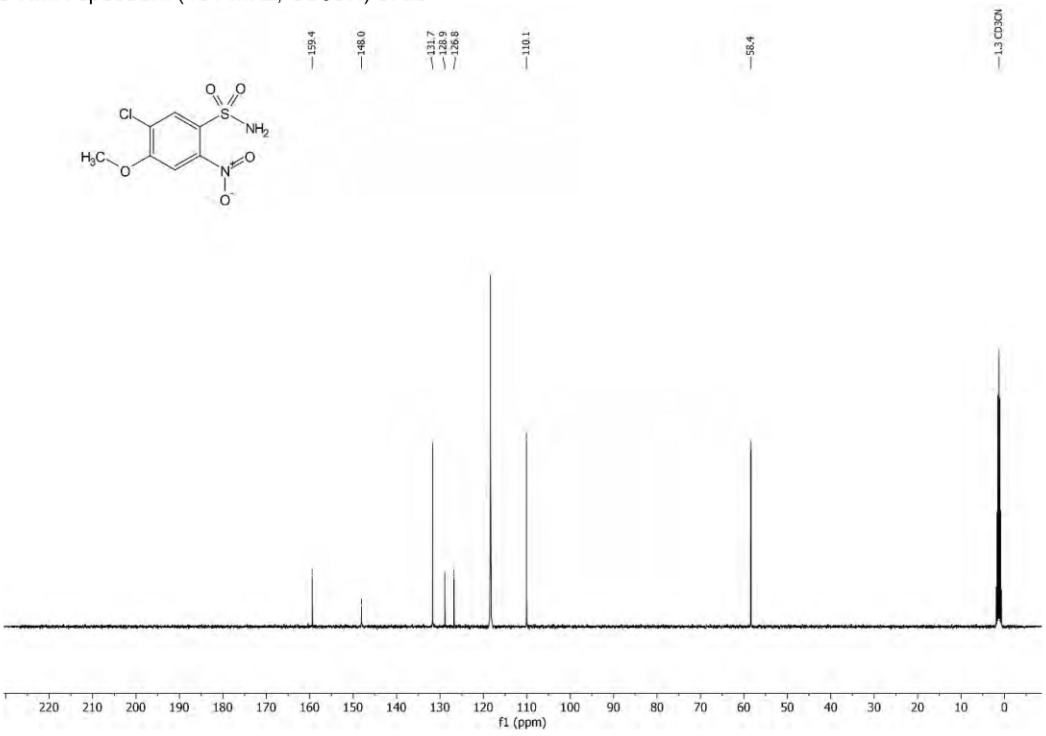
^{13}C NMR spectrum (101 MHz, CD_3CN) of **27**



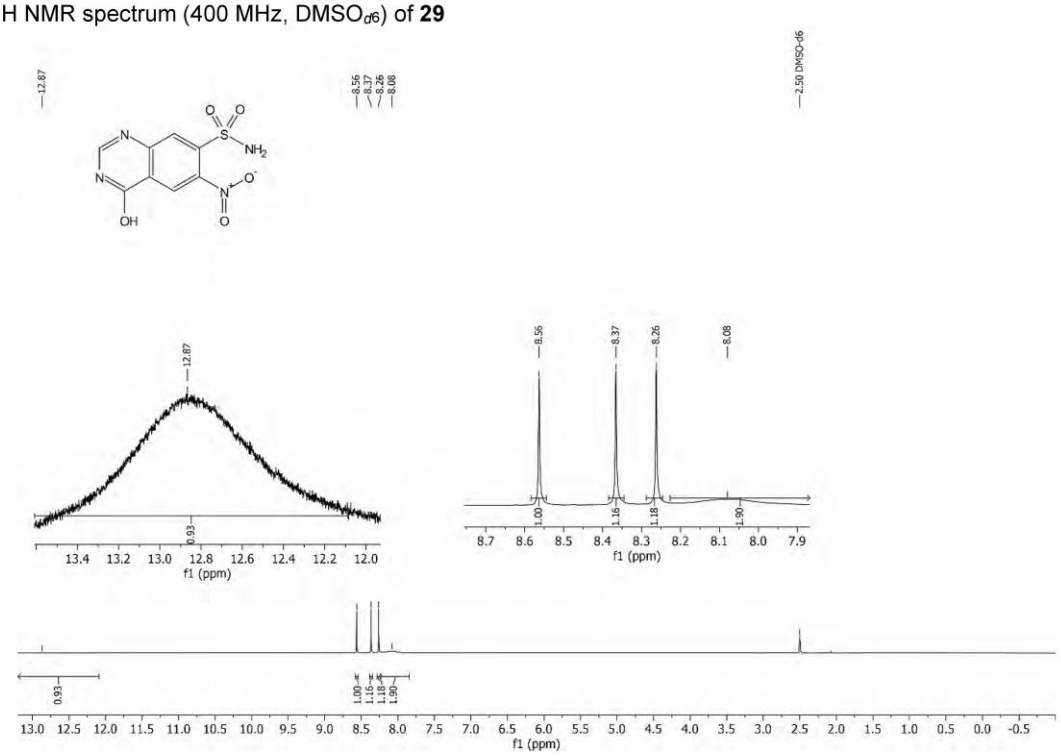
^{1}H NMR spectrum (400 MHz, CD_3CN) of **28**



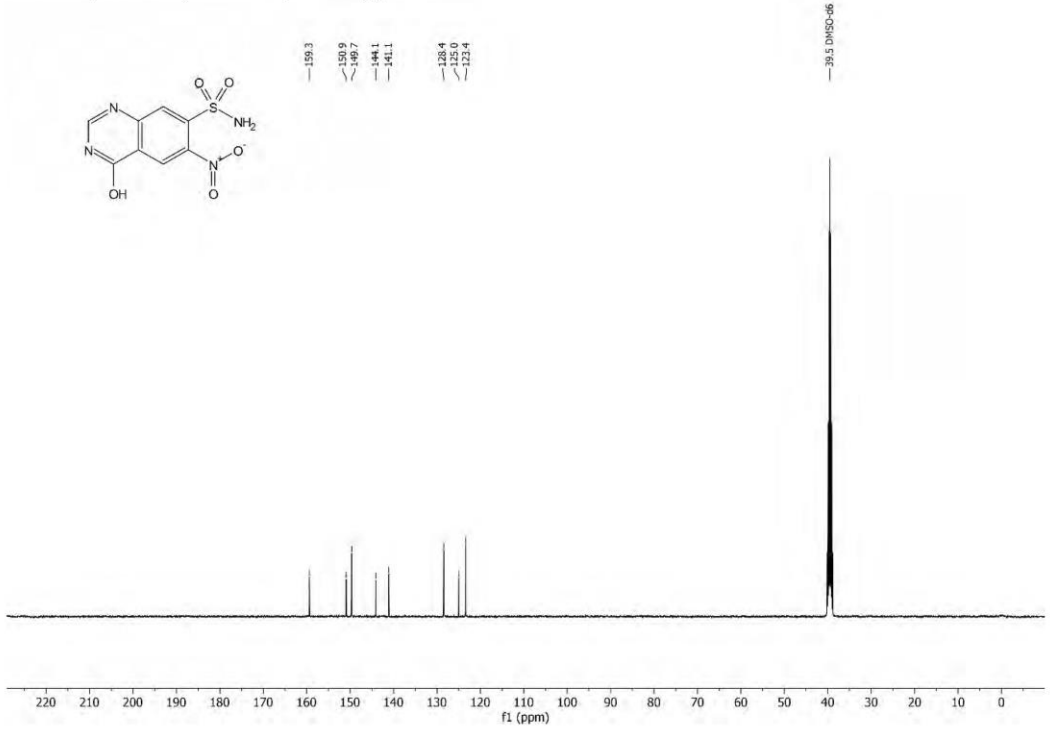
^{13}C NMR spectrum (101 MHz, CD_3CN) of **28**



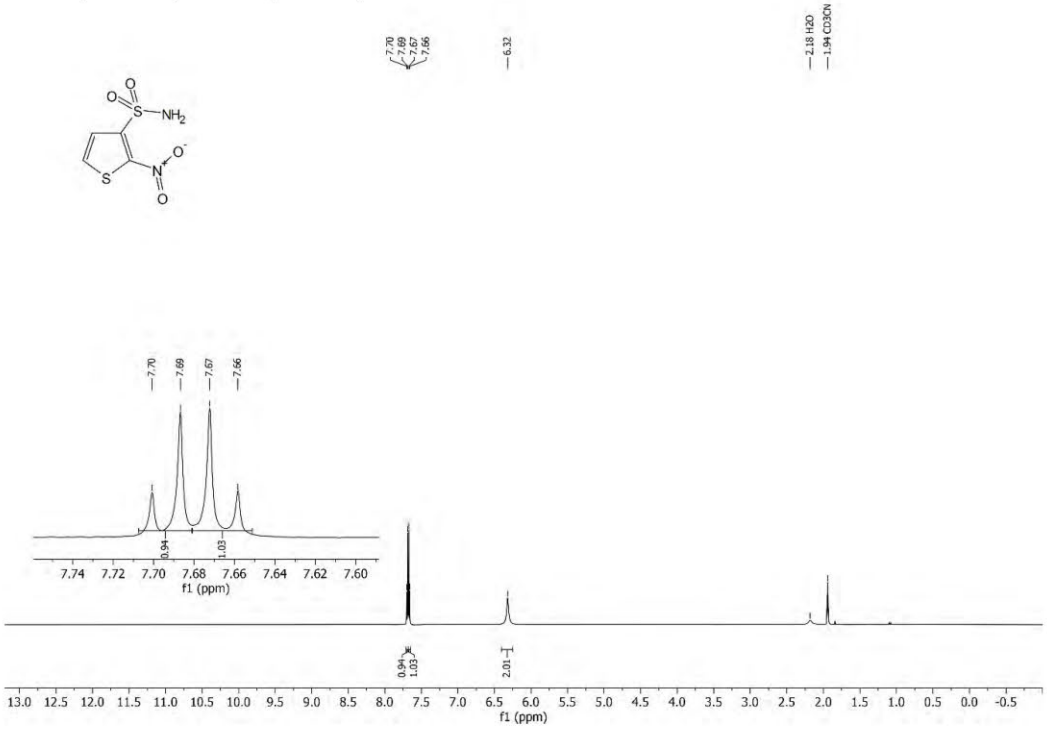
^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **29**



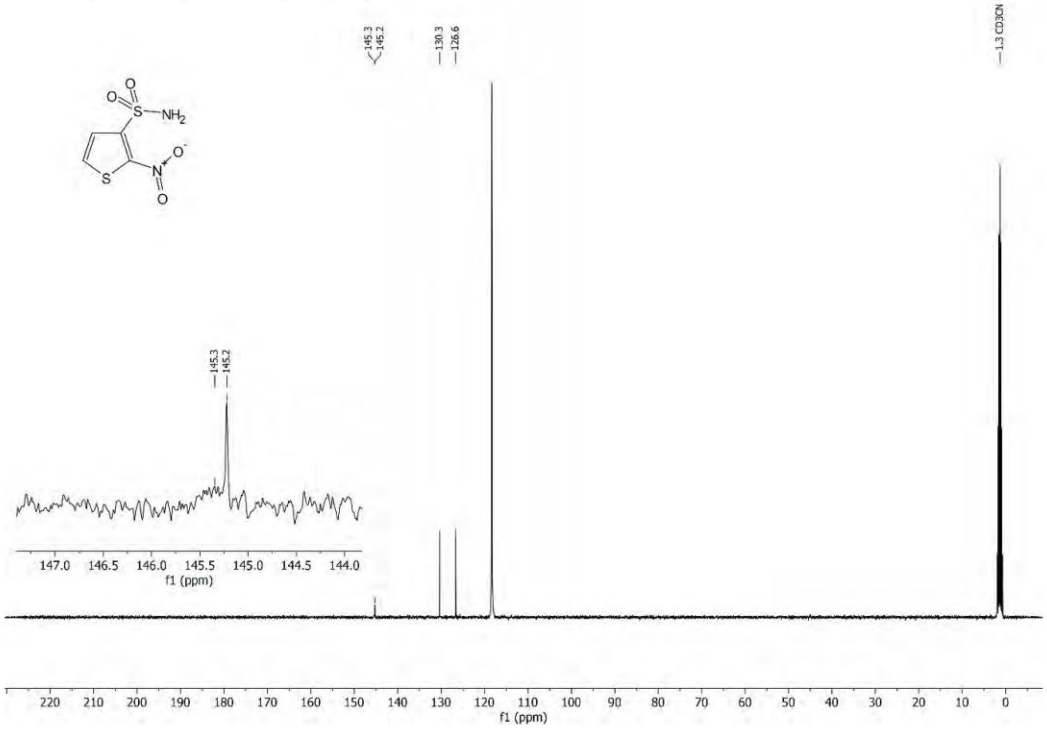
^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **29**



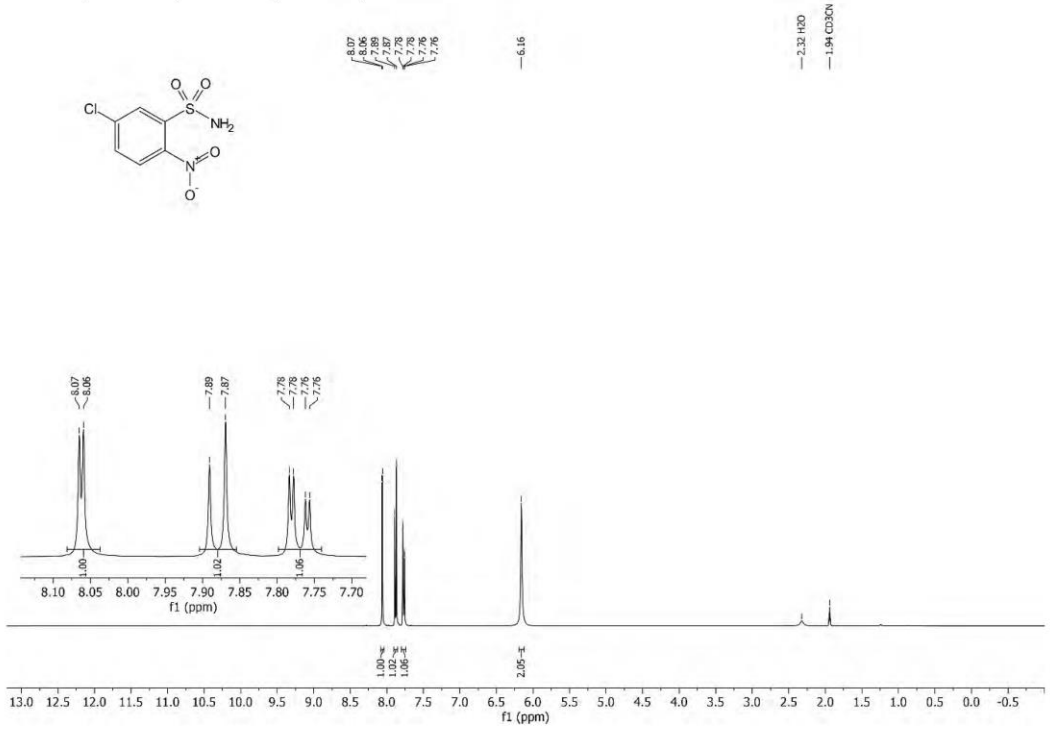
^{1}H NMR spectrum (400 MHz, CD_3CN) of **30**



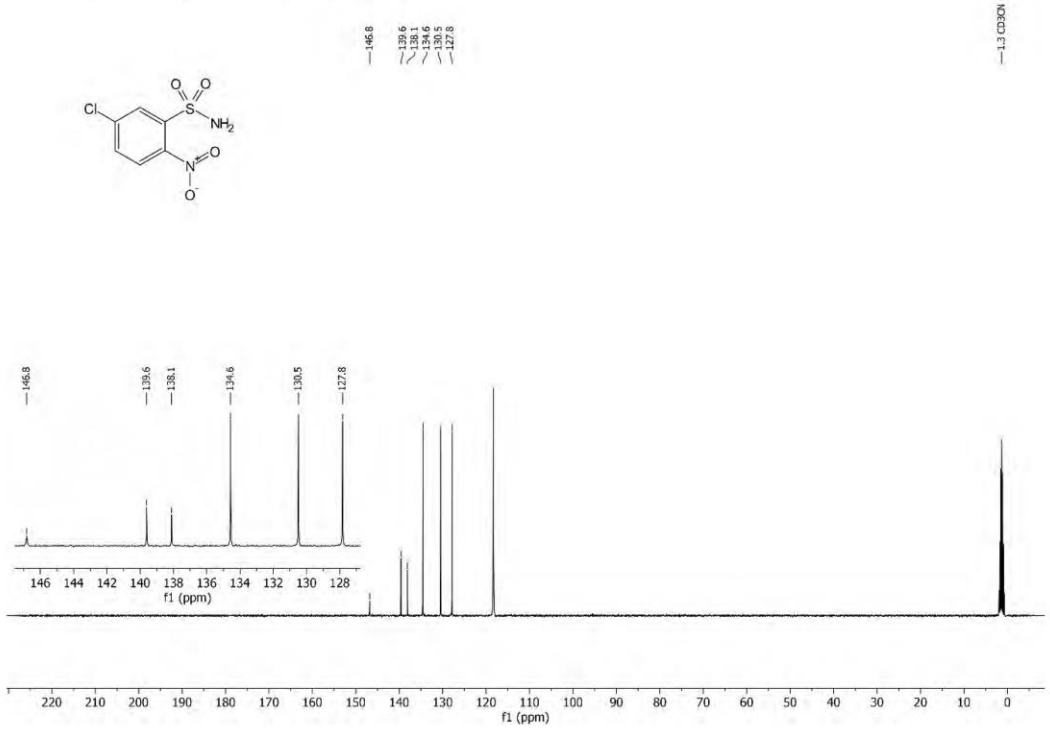
^{13}C NMR spectrum (101 MHz, CD_3CN) of **30**



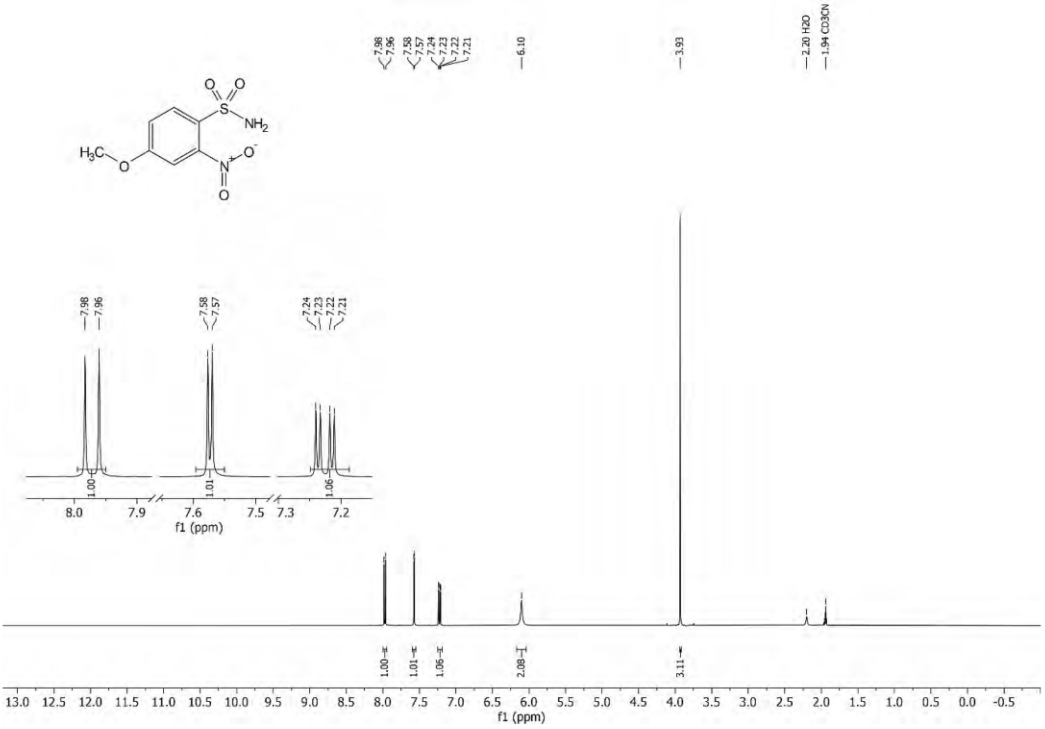
^{1}H NMR spectrum (400 MHz, CD_3CN) of **31**



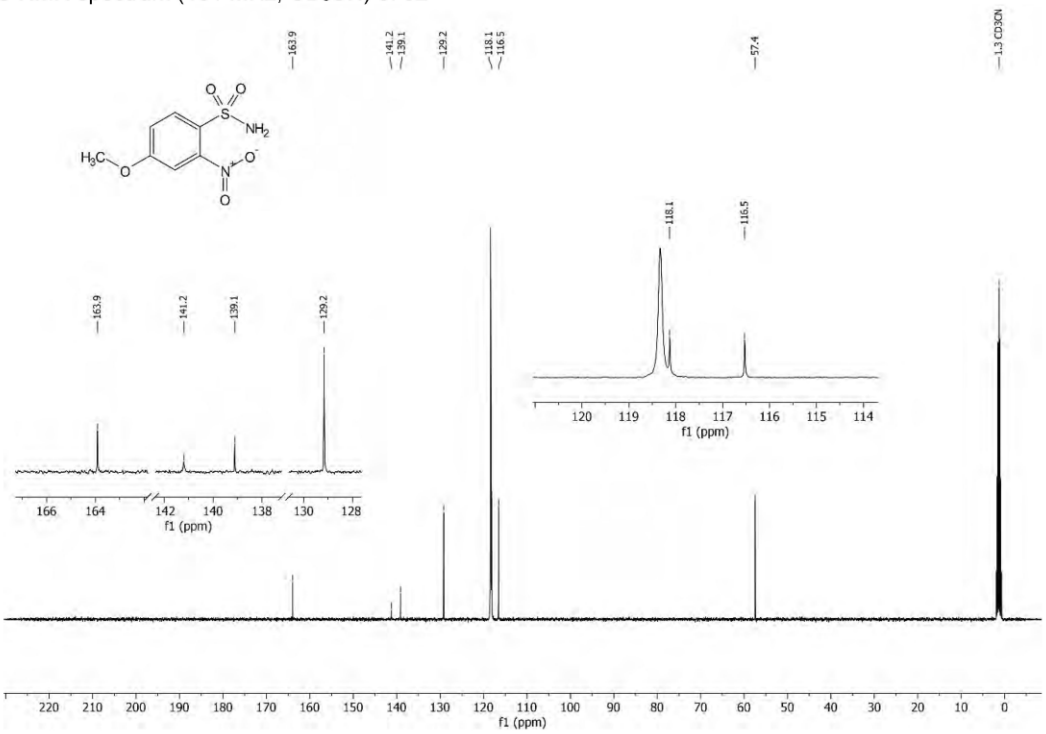
^{13}C NMR spectrum (101 MHz, CD_3CN) of **31**



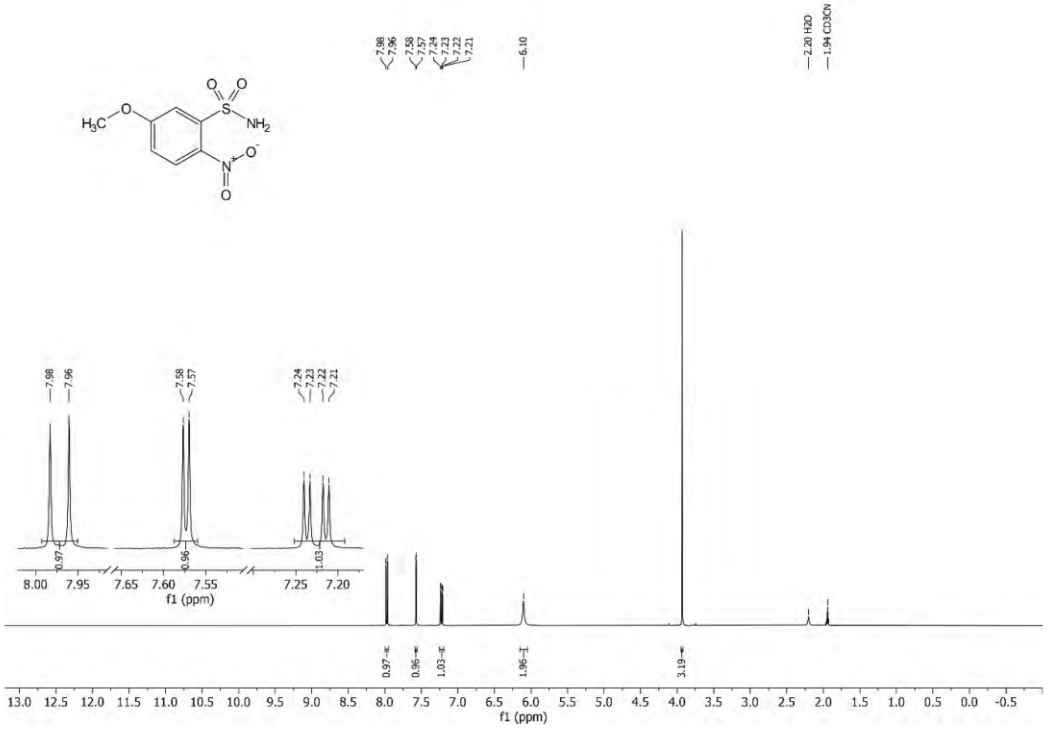
^{1}H NMR spectrum (400 MHz, CD_3CN) of **32**



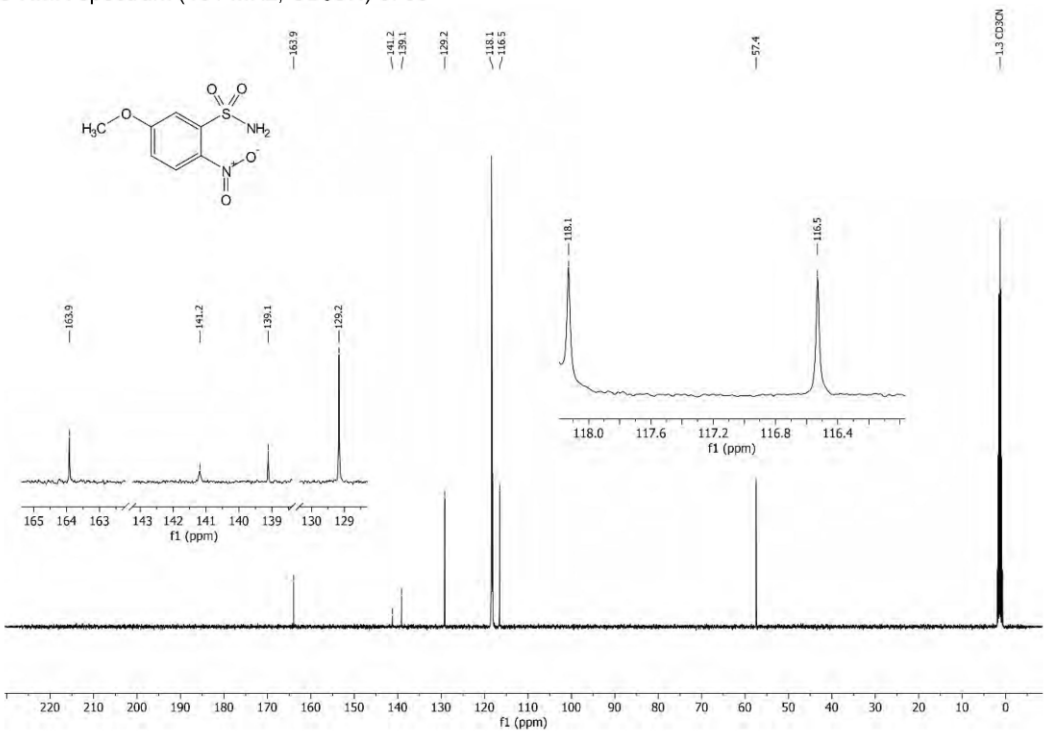
^{13}C NMR spectrum (101 MHz, CD_3CN) of **32**



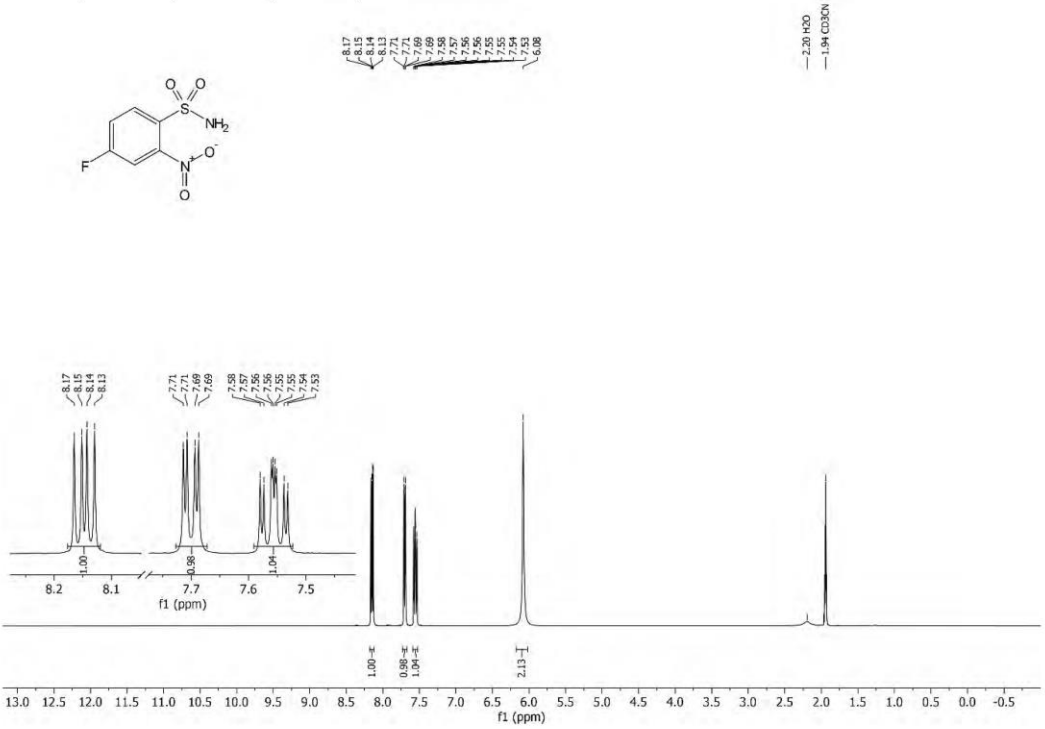
^{1}H NMR spectrum (400 MHz, CD_3CN) of **33**



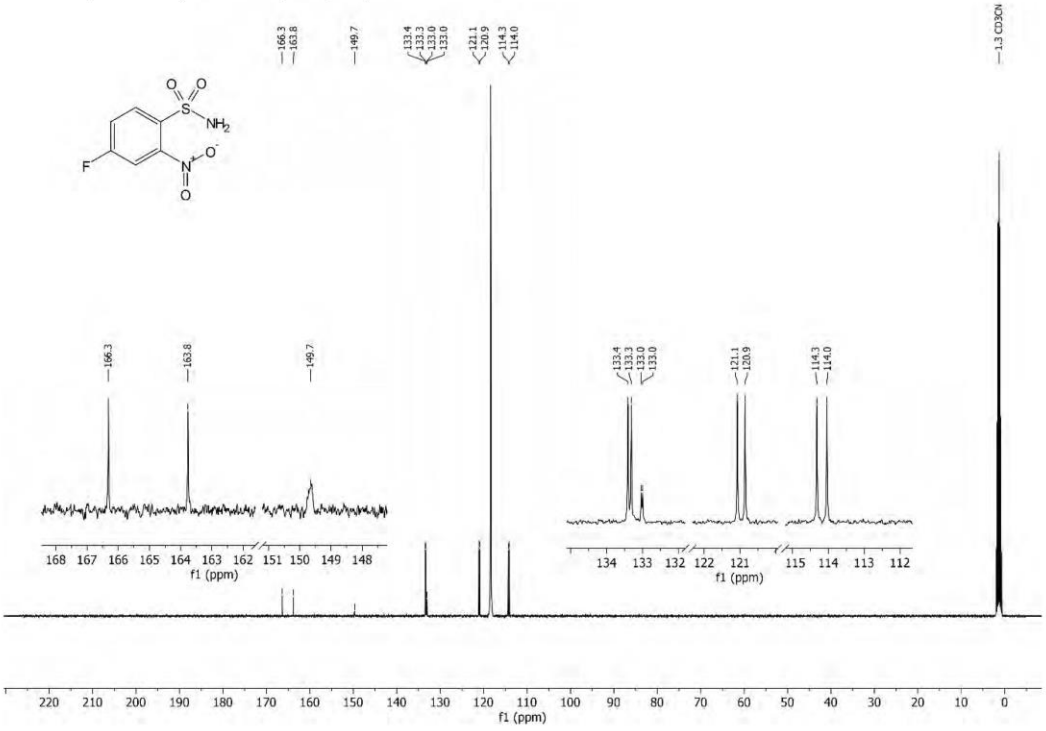
^{13}C NMR spectrum (101 MHz, CD_3CN) of **33**



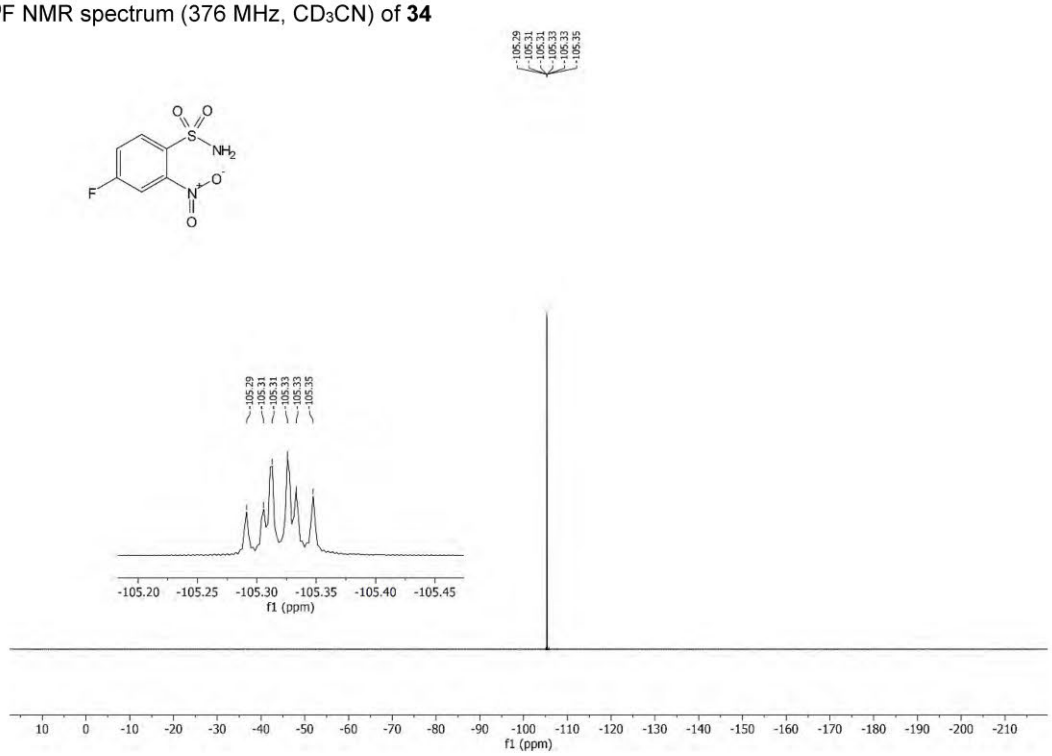
^{1}H NMR spectrum (400 MHz, CD_3CN) of **34**



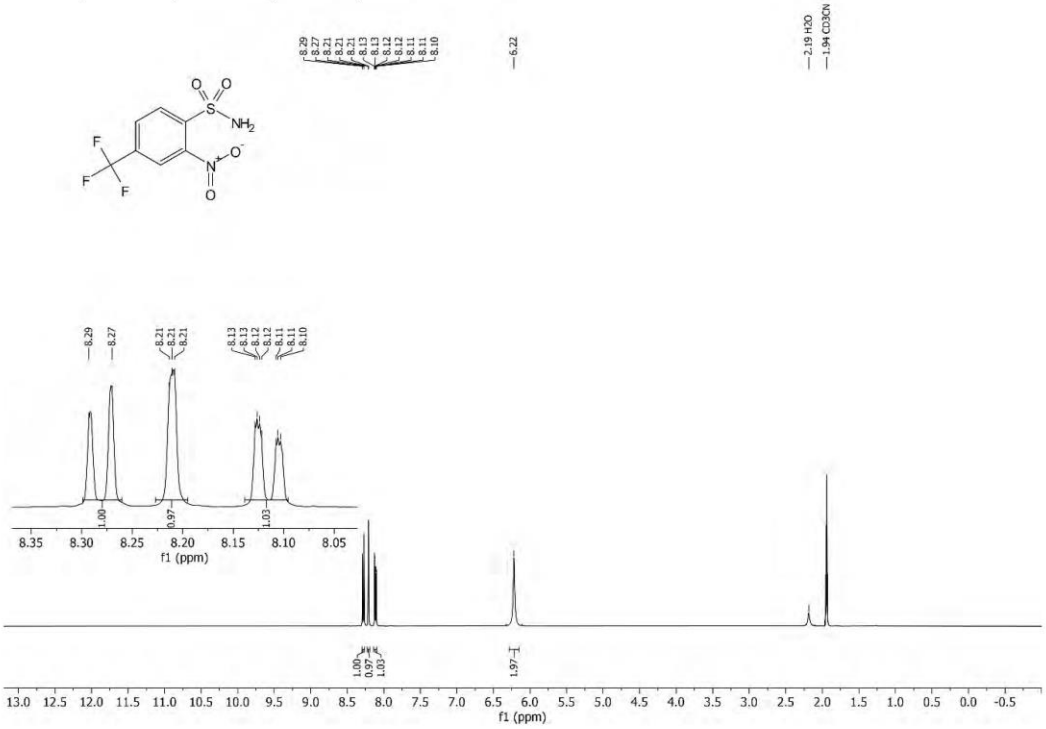
^{13}C NMR spectrum (101 MHz, CD_3CN) of **34**



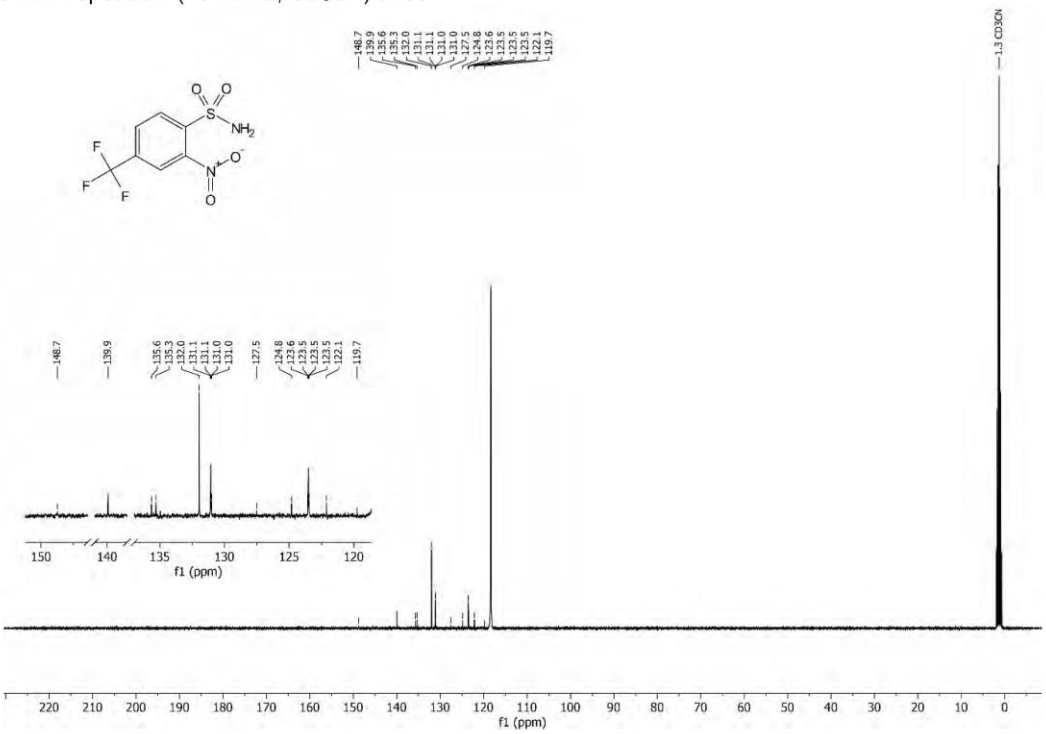
^{19}F NMR spectrum (376 MHz, CD_3CN) of **34**



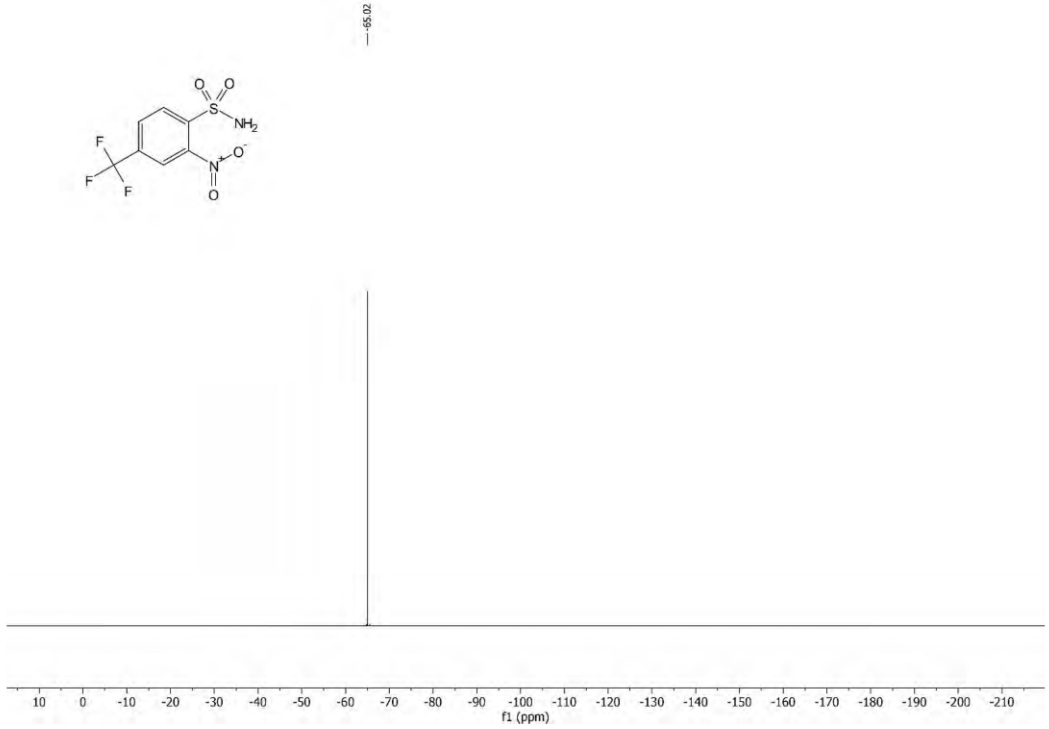
^{1}H NMR spectrum (400 MHz, CD_3CN) of **35**



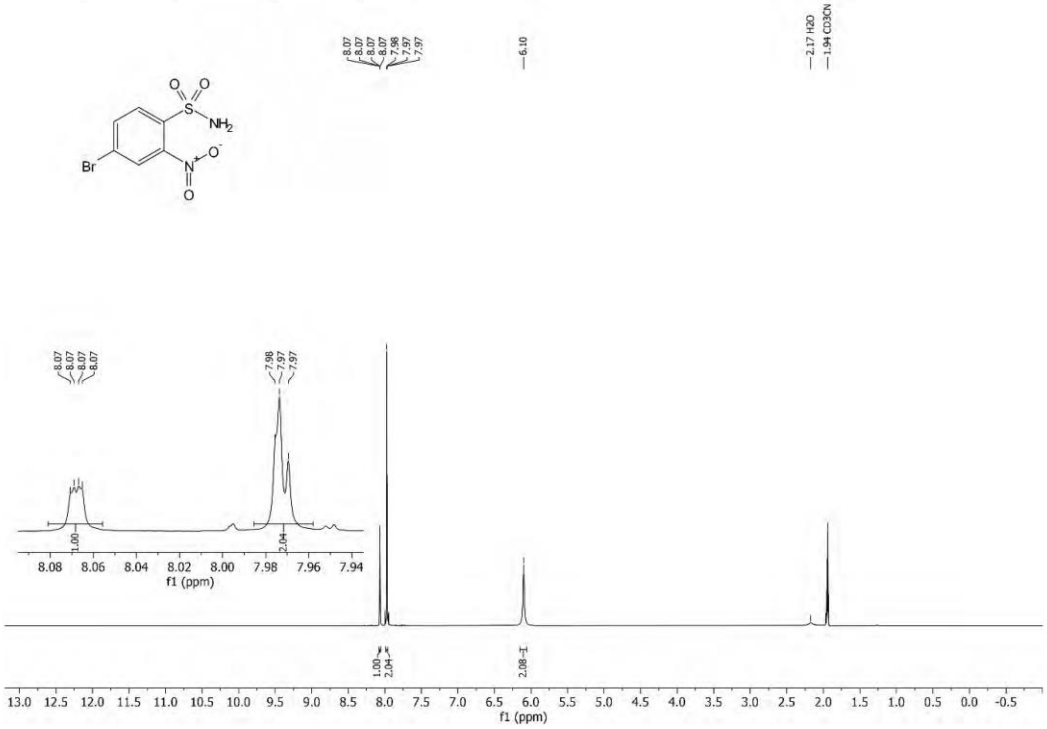
^{13}C NMR spectrum (101 MHz, CD_3CN) of **35**



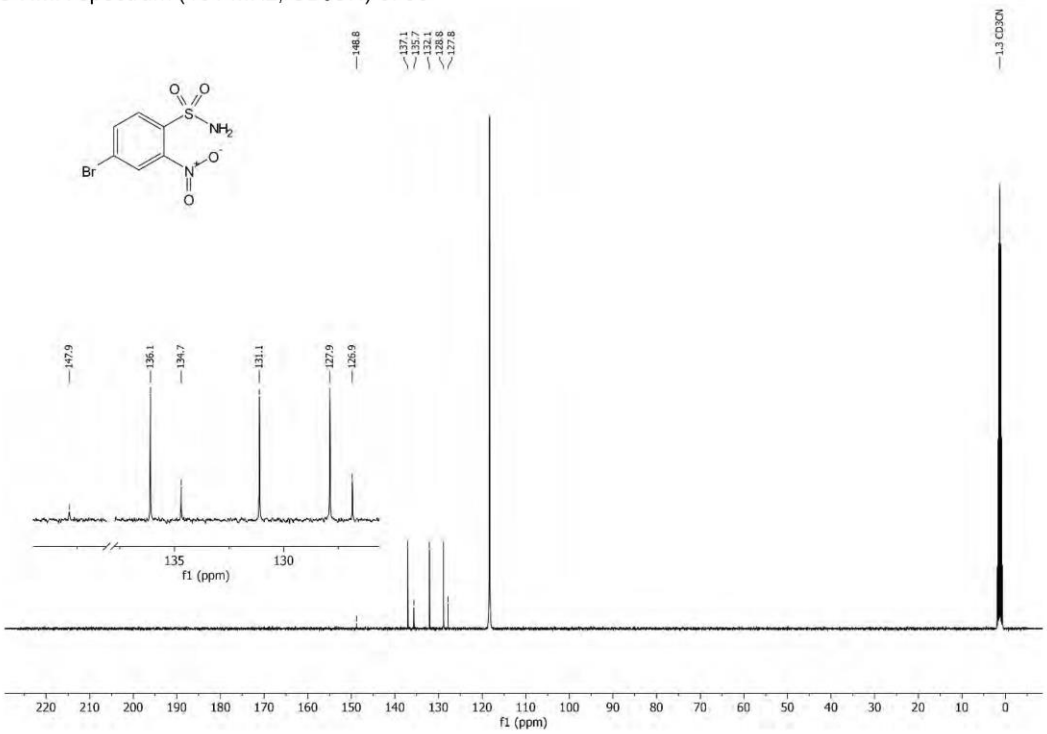
^{19}F NMR spectrum (376 MHz, CD_3CN) of **35**



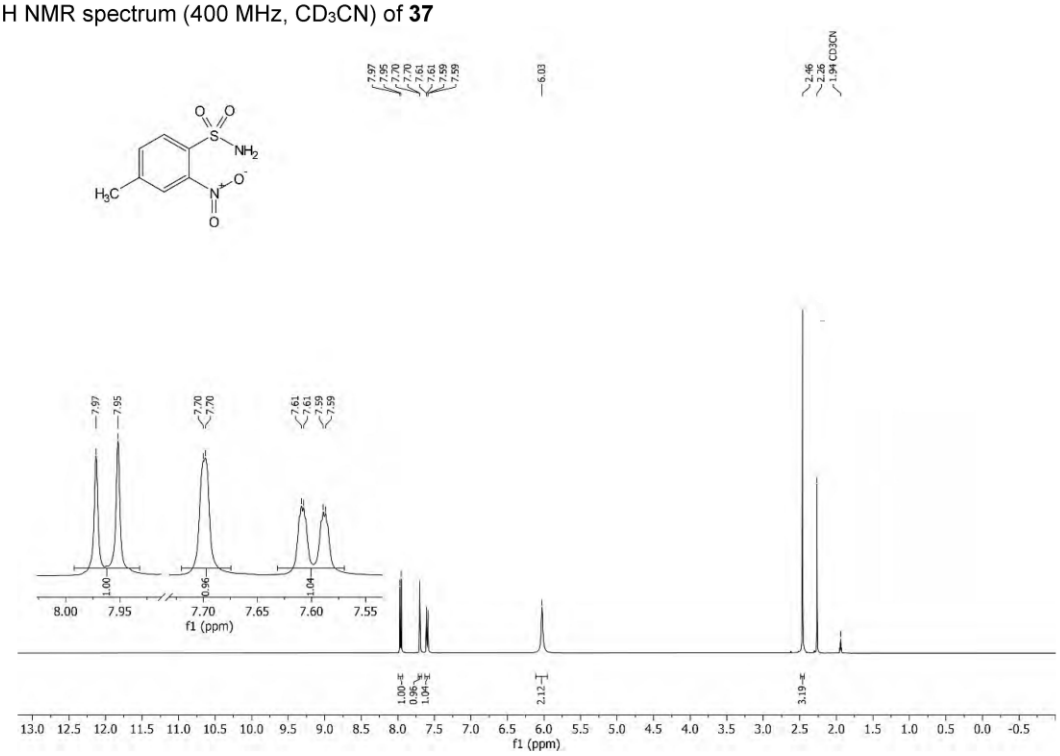
^{1}H NMR spectrum (400 MHz, CD_3CN) of **36**



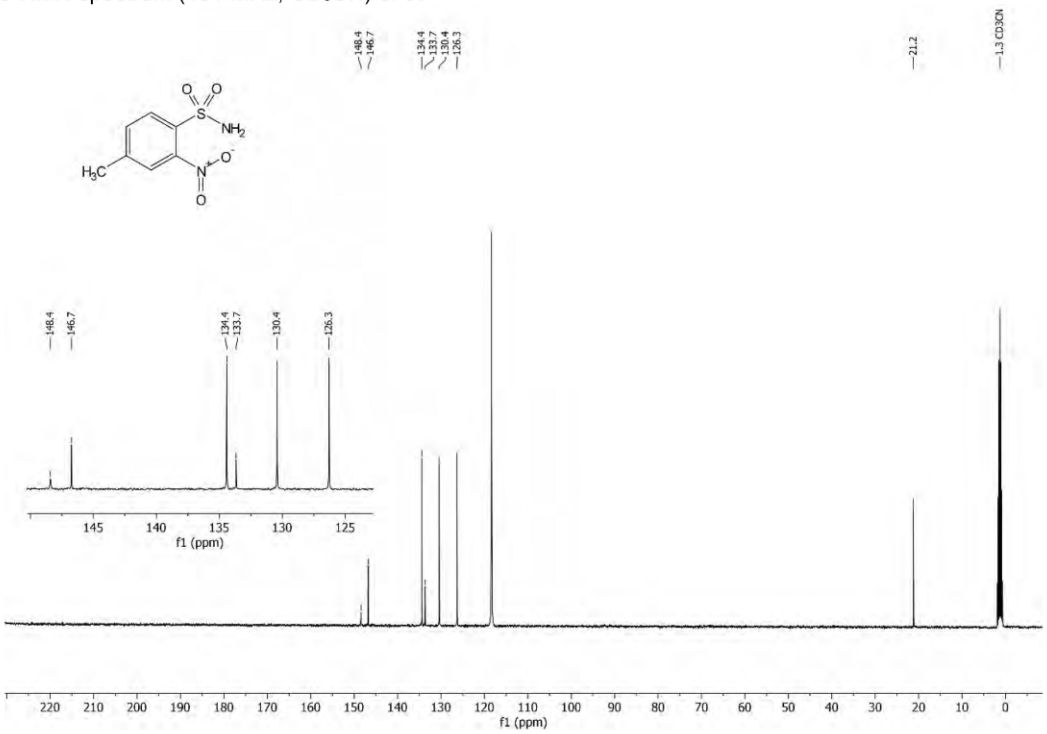
^{13}C NMR spectrum (101 MHz, CD_3CN) of **36**



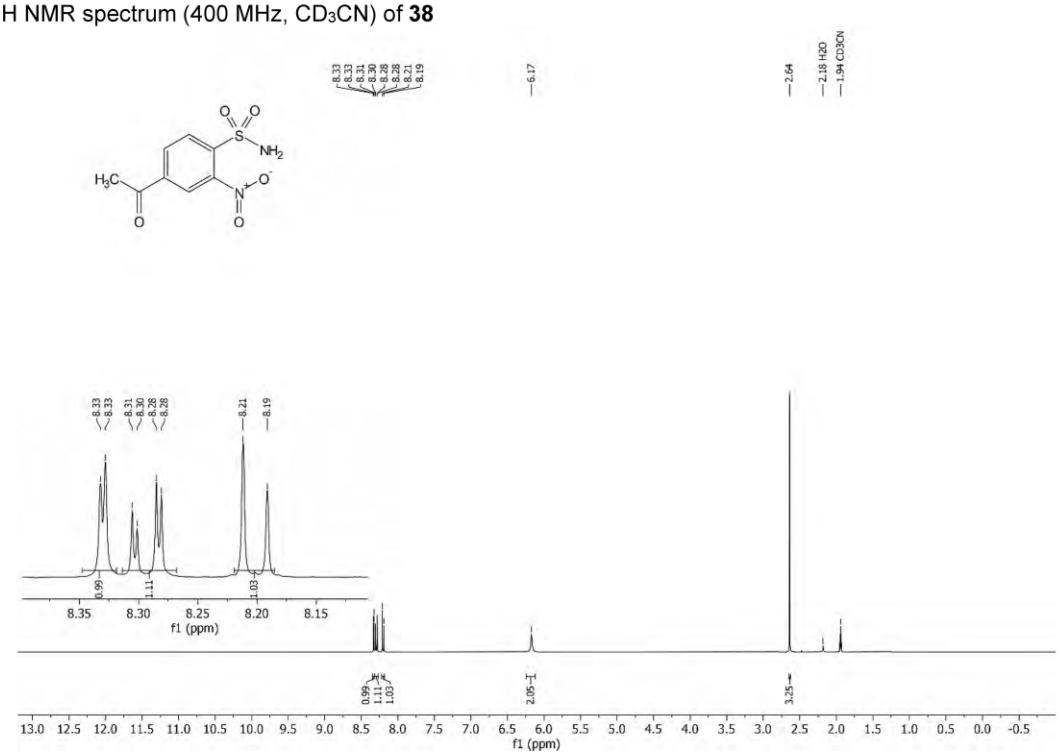
^{1}H NMR spectrum (400 MHz, CD_3CN) of **37**



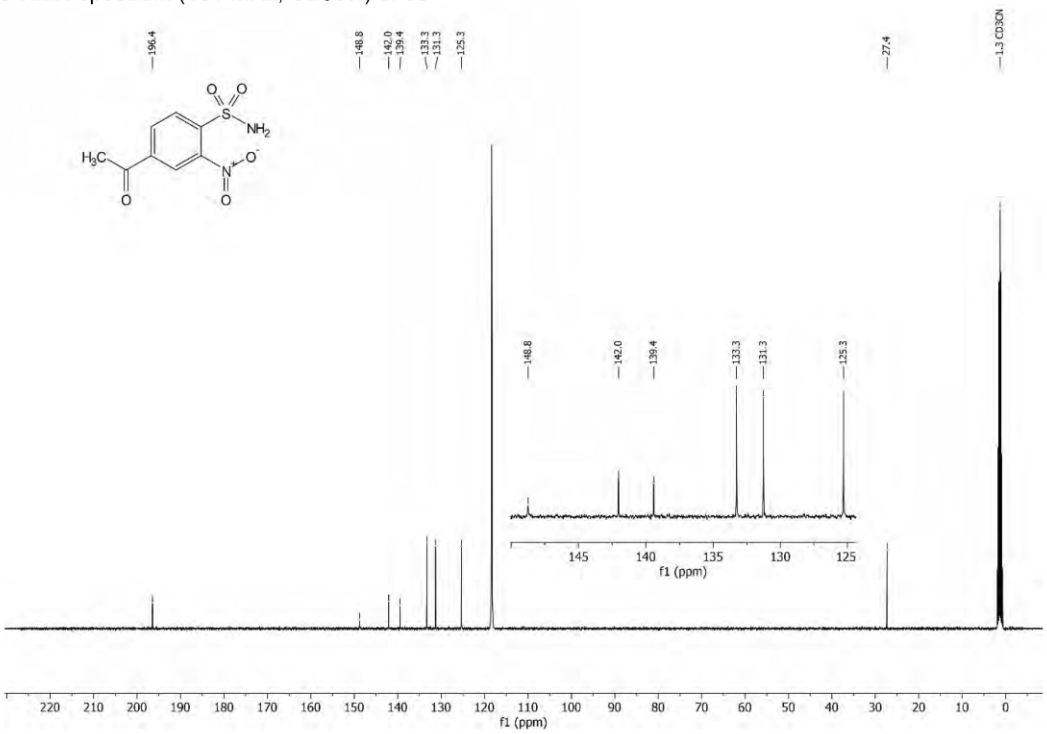
^{13}C NMR spectrum (101 MHz, CD_3CN) of **37**



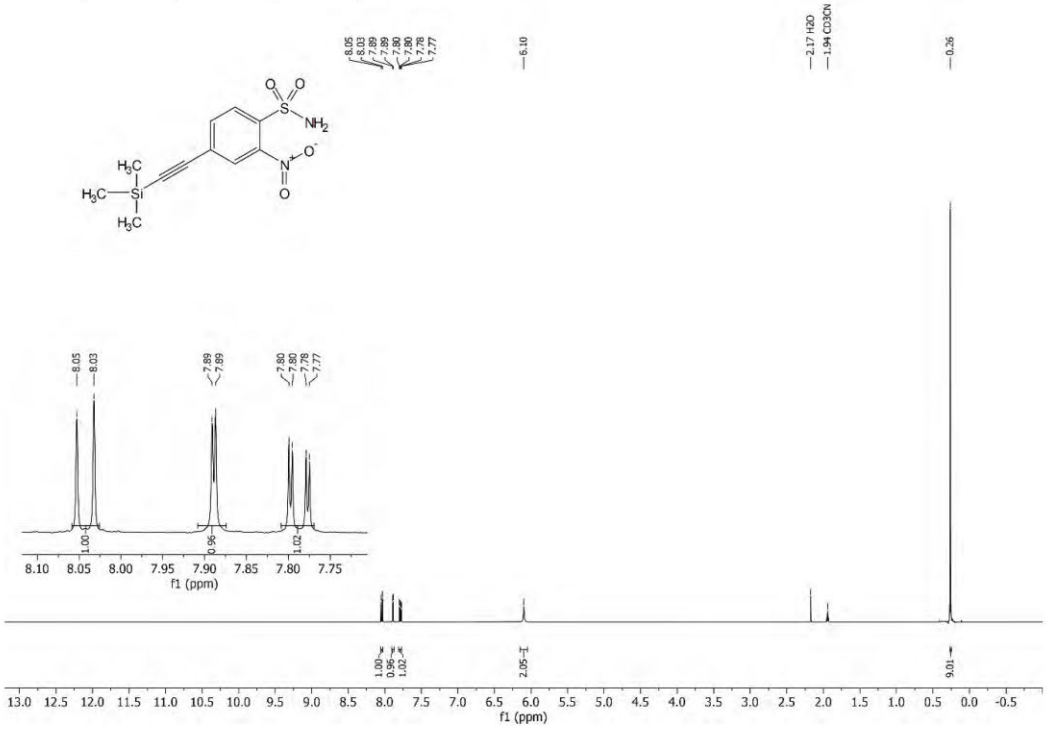
^{1}H NMR spectrum (400 MHz, CD_3CN) of **38**



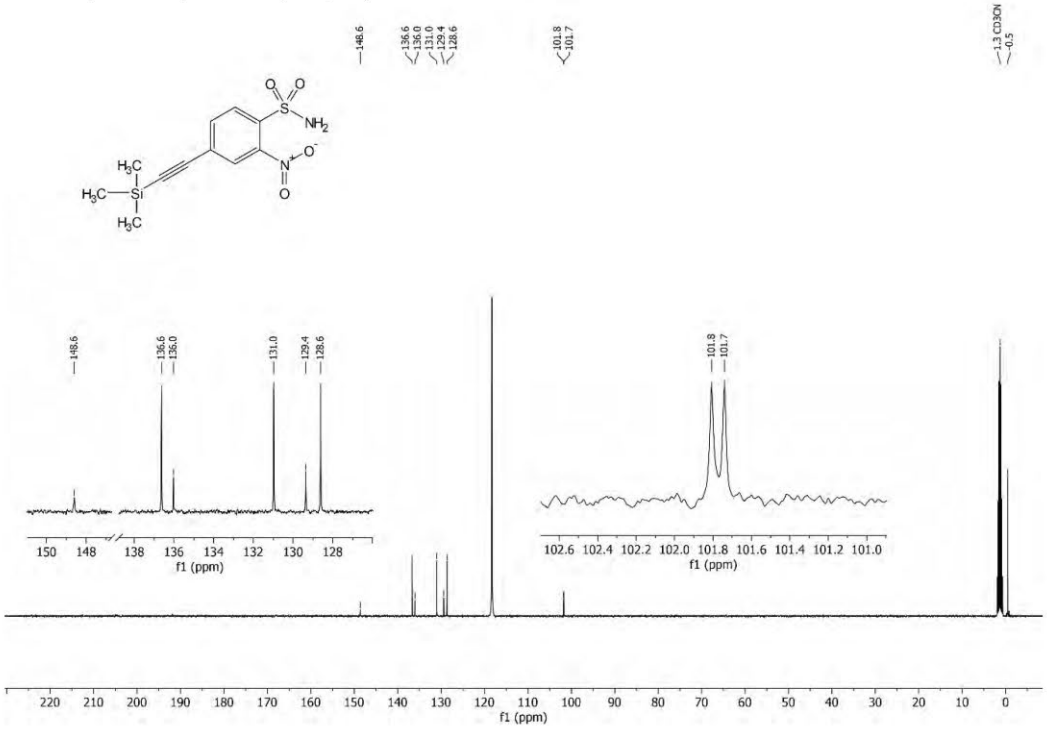
^{13}C NMR spectrum (101 MHz, CD_3CN) of **38**



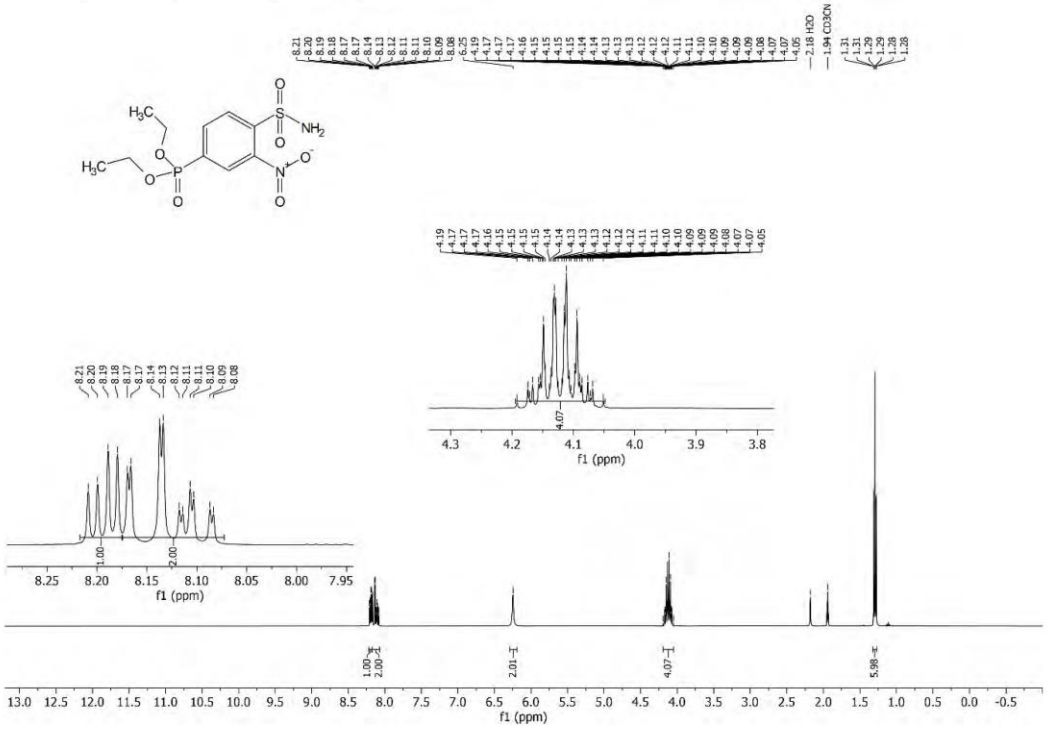
^{1}H NMR spectrum (400 MHz, CD_3CN) of **39**



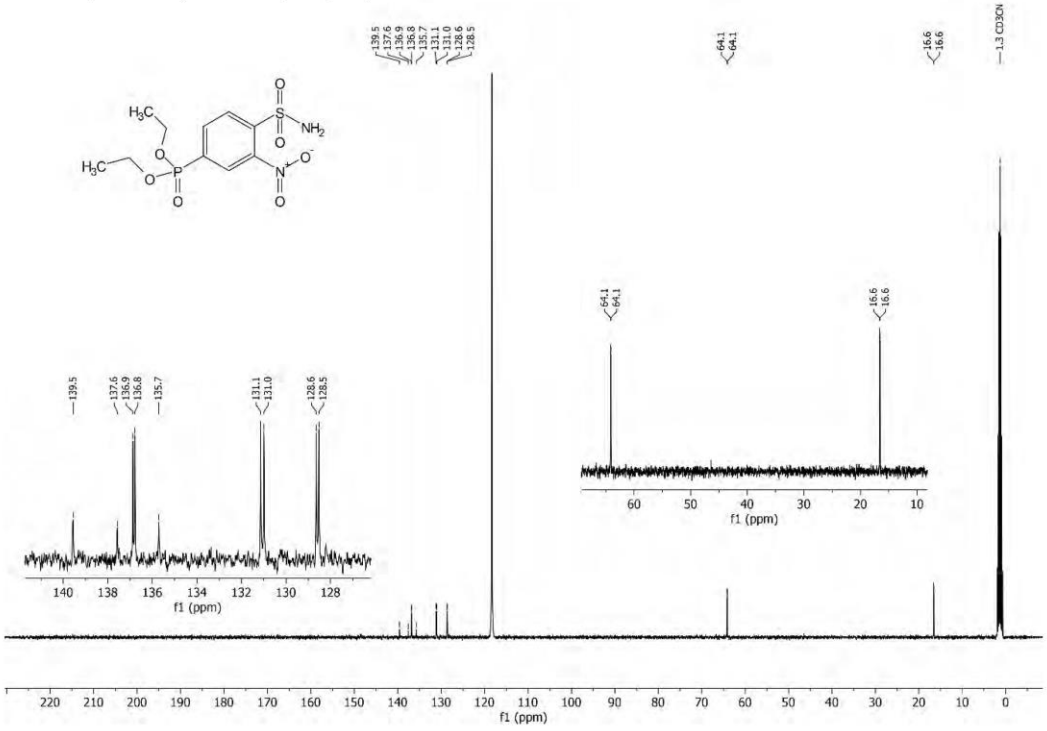
^{13}C NMR spectrum (101 MHz, CD_3CN) of **39**



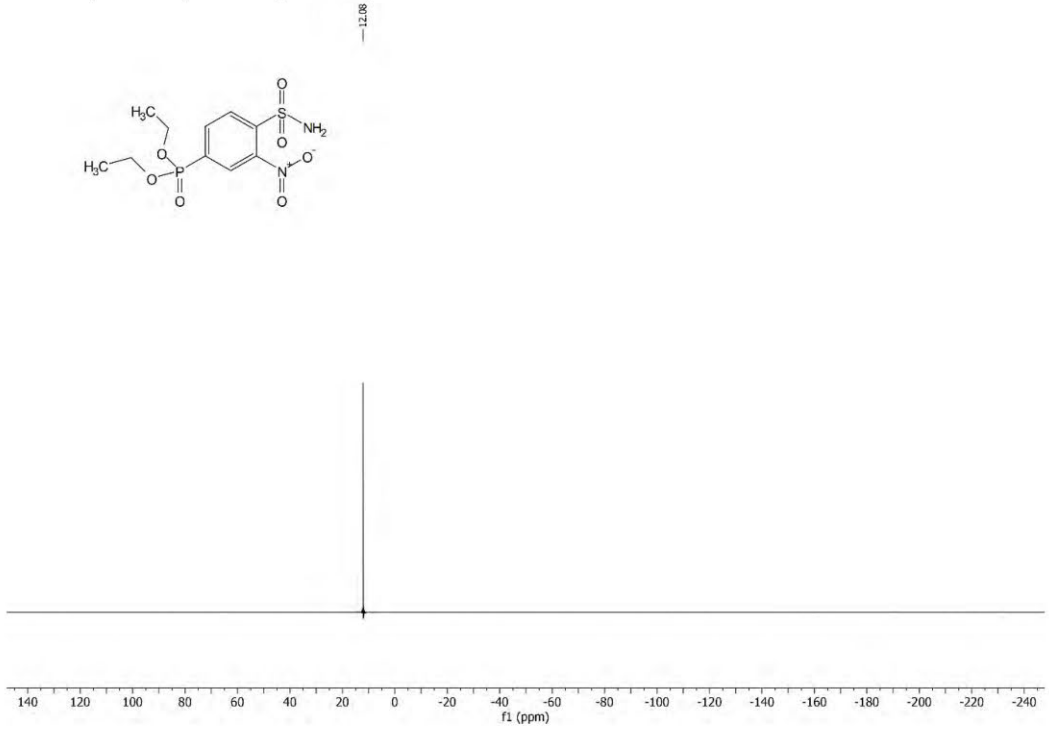
^{1}H NMR spectrum (400 MHz, CD_3CN) of **40**



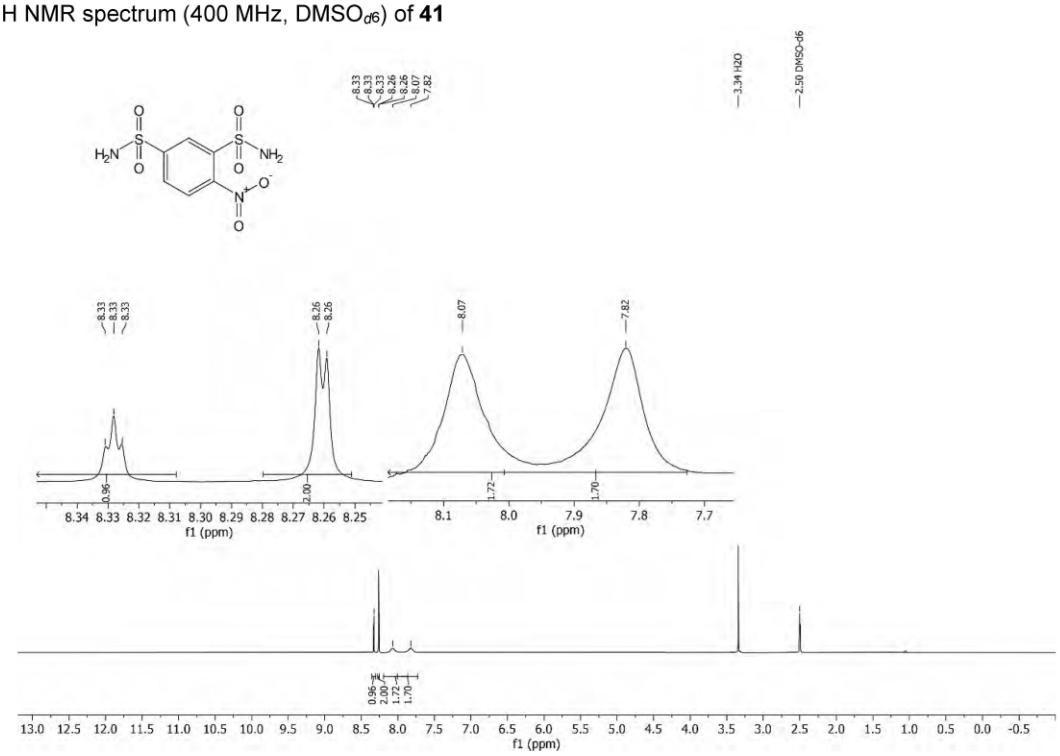
^{13}C NMR spectrum (101 MHz, CD_3CN) of **40**



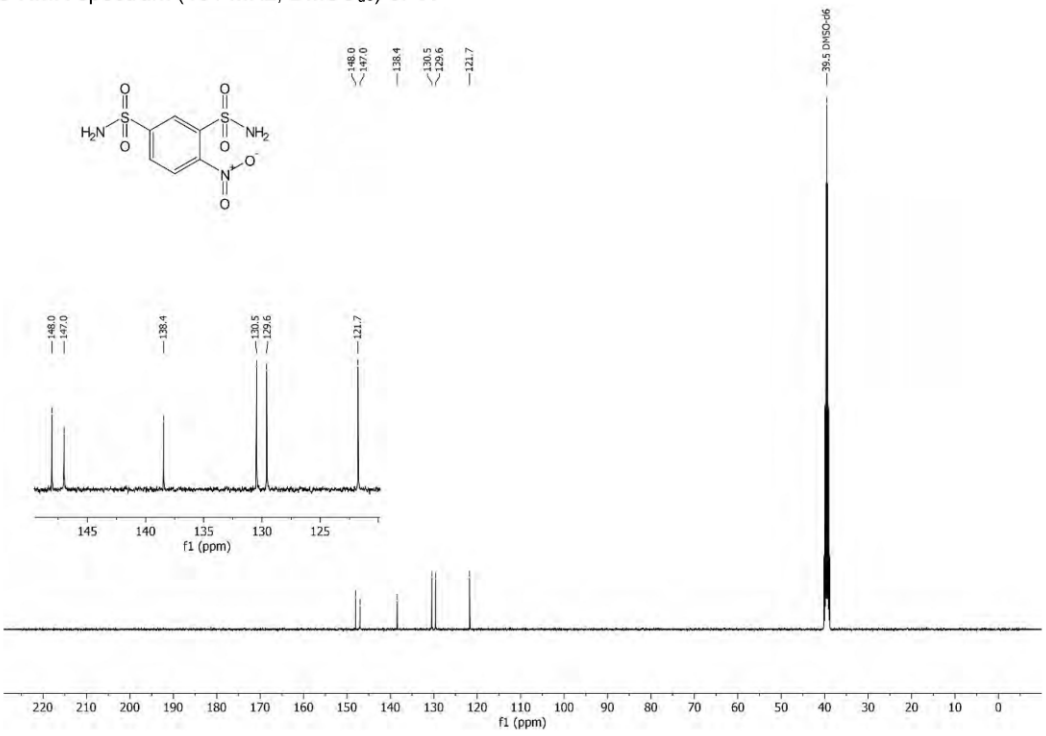
^{31}P NMR spectrum (162 MHz, CD_3CN) of **40**



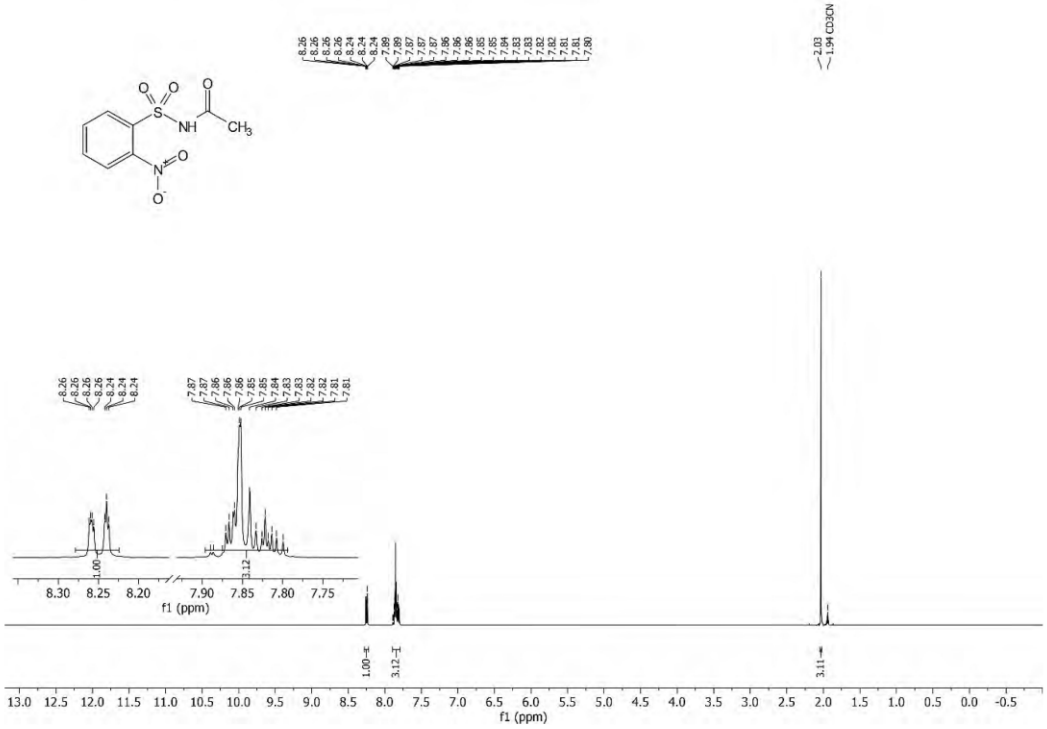
^{1}H NMR spectrum (400 MHz, DMSO$_{d6}$) of **41**



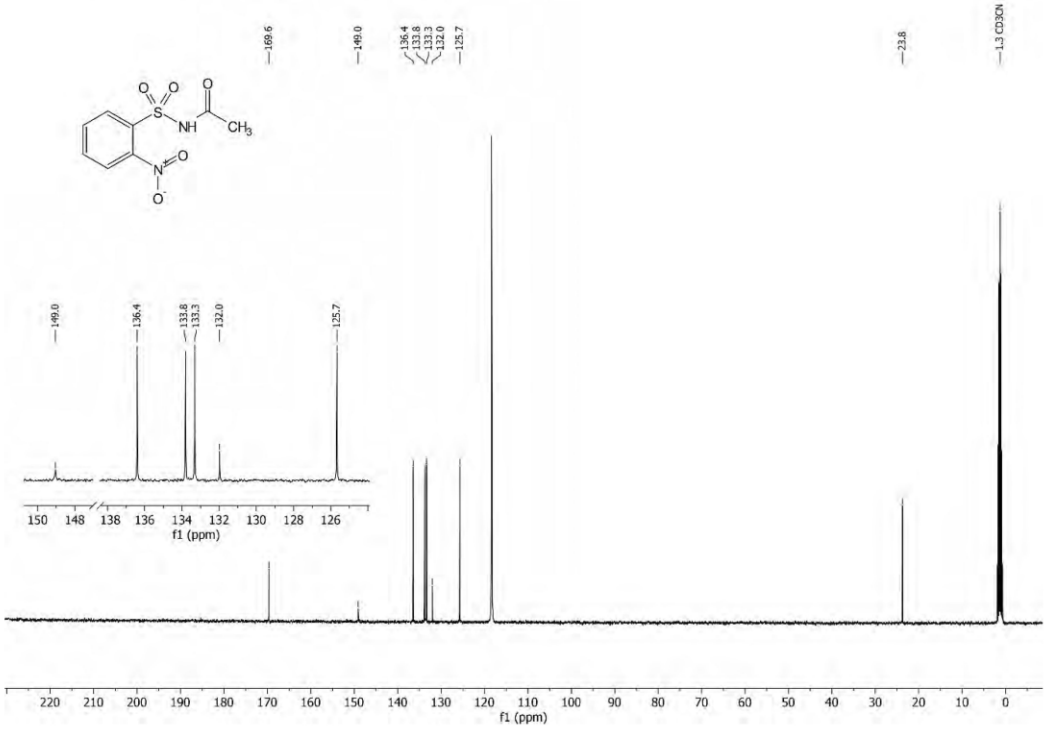
^{13}C NMR spectrum (101 MHz, DMSO$_{d6}$) of **41**



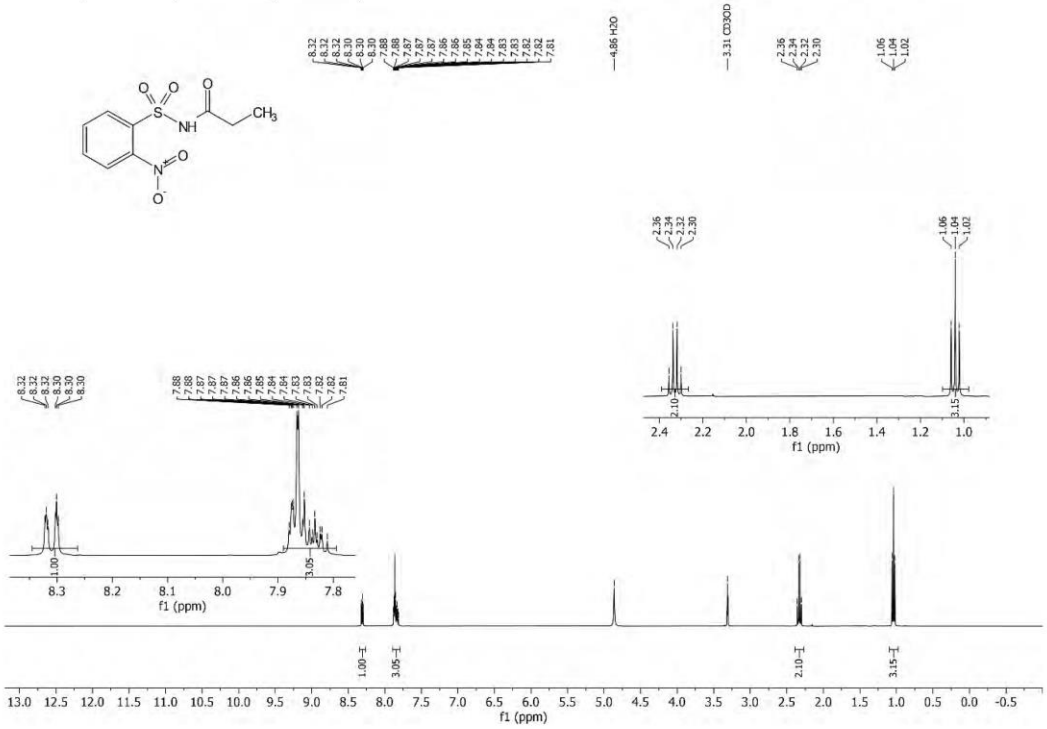
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6a**



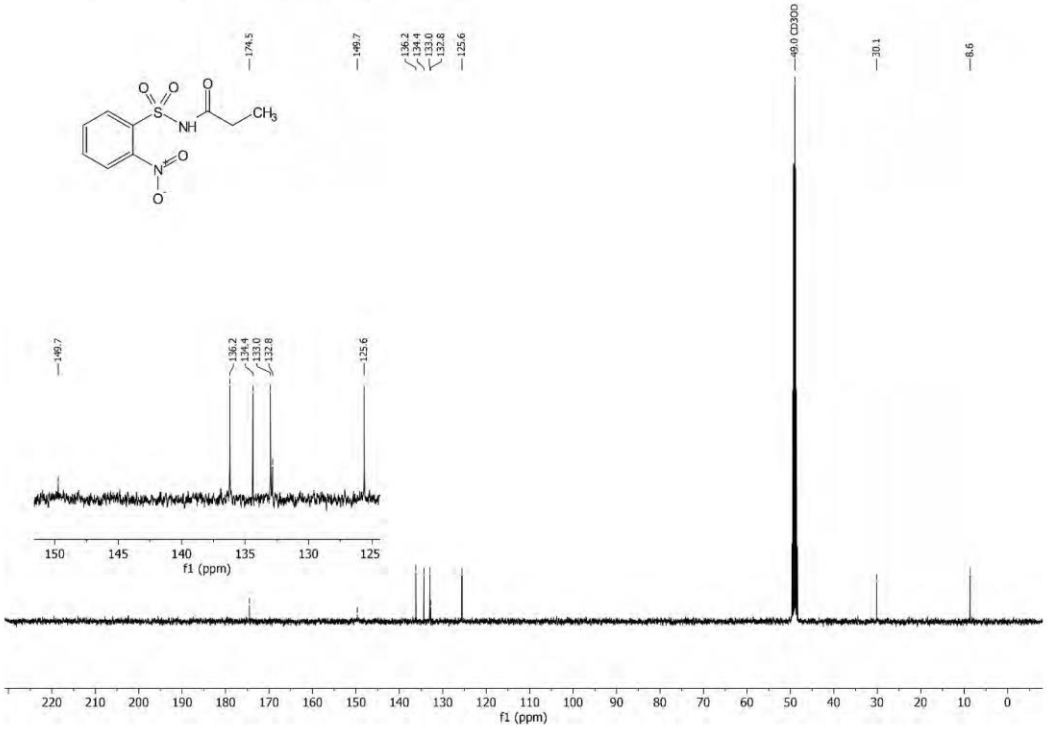
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6a**



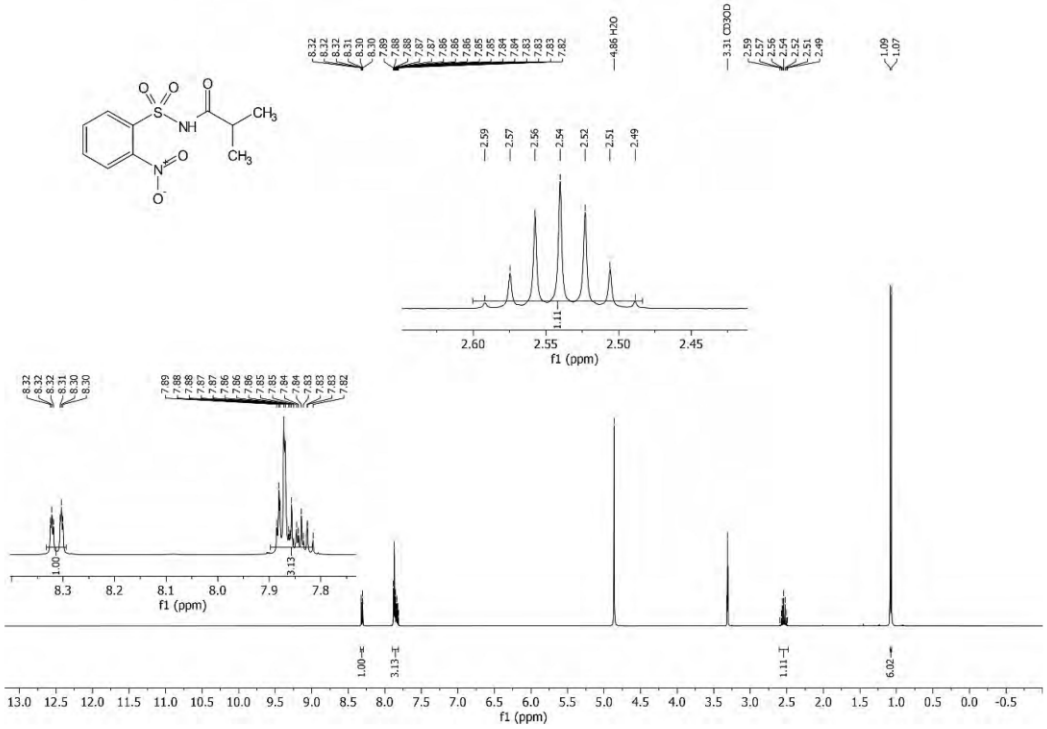
^{1}H NMR spectrum (400 MHz, CD_3OD) of **6b**



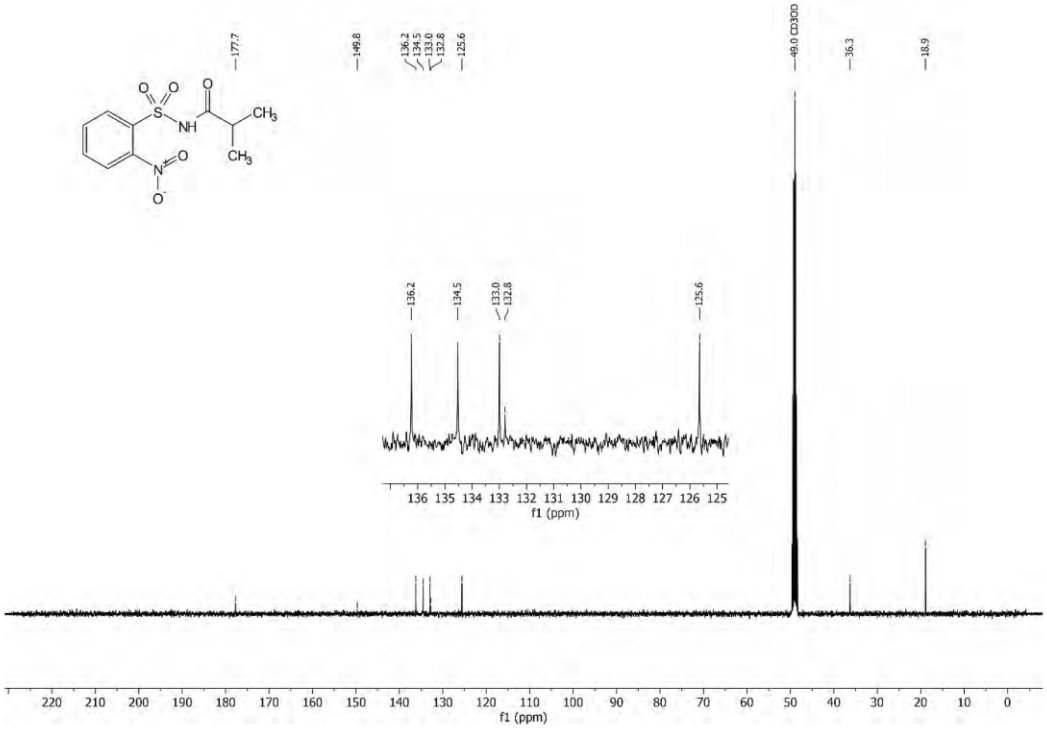
^{13}C NMR spectrum (101 MHz, CD_3OD) of **6b**



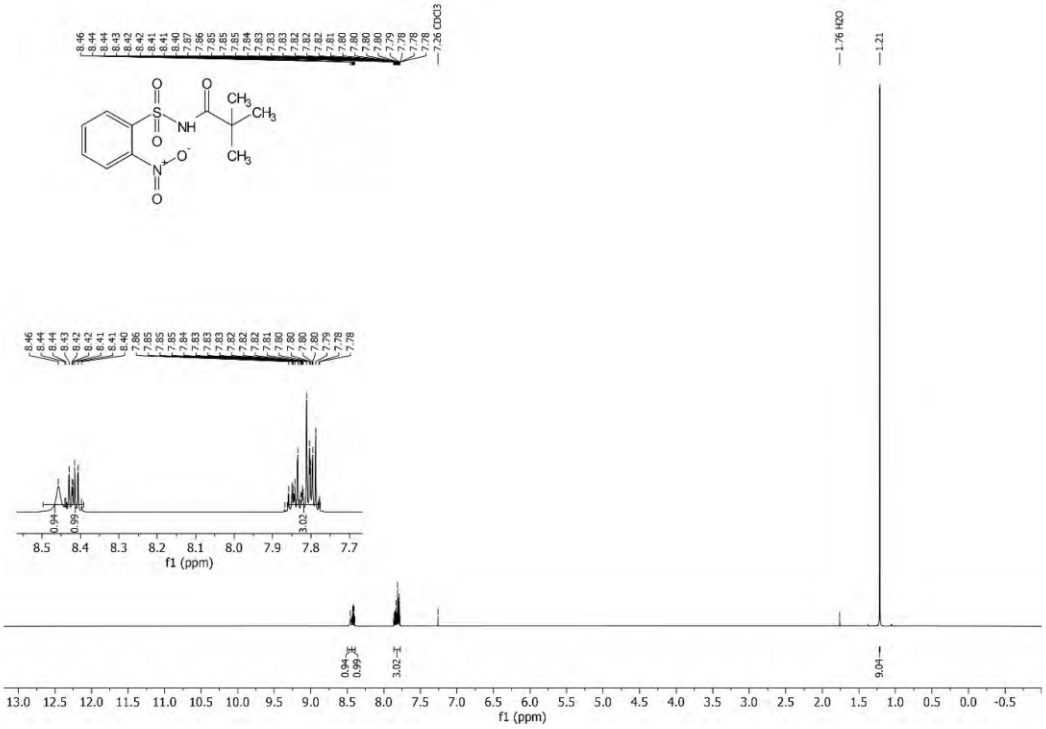
^{1}H NMR spectrum (400 MHz, CD_3OD) of **6c**



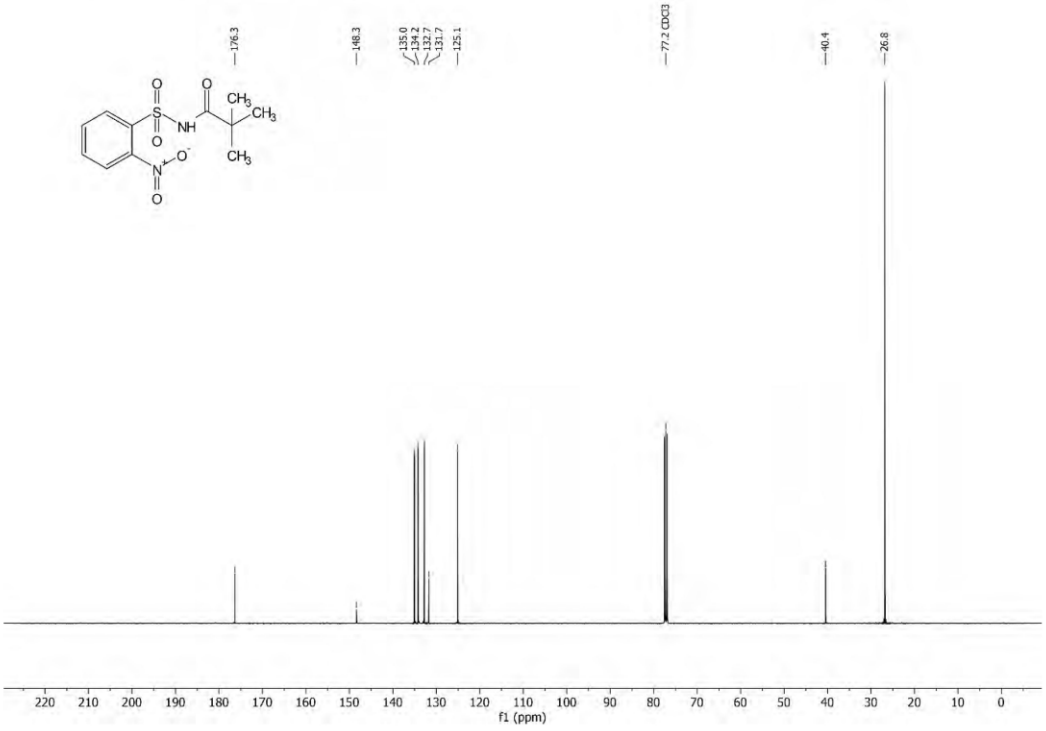
^{13}C NMR spectrum (101 MHz, CD_3OD) of **6c**



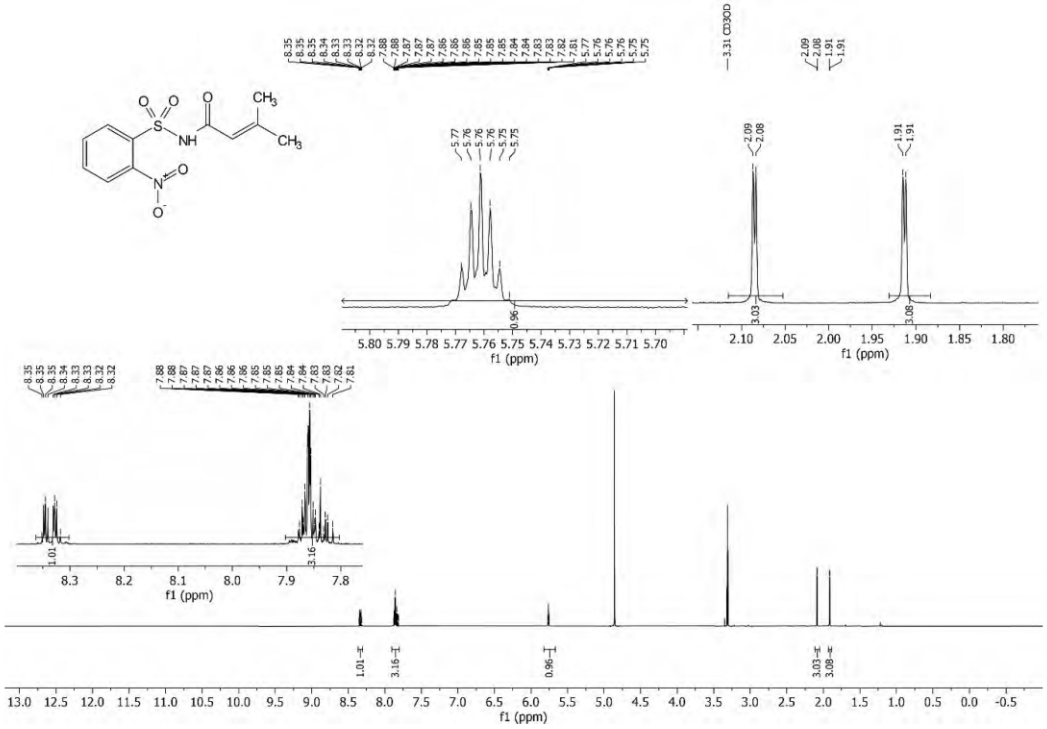
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6d**



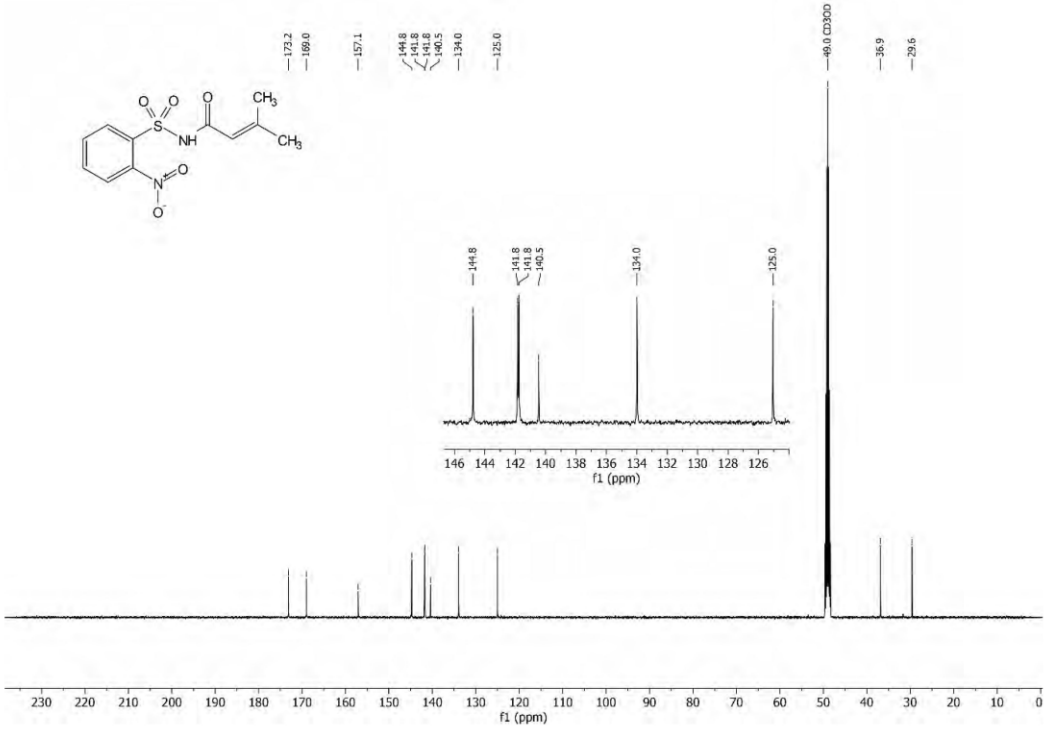
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6d**



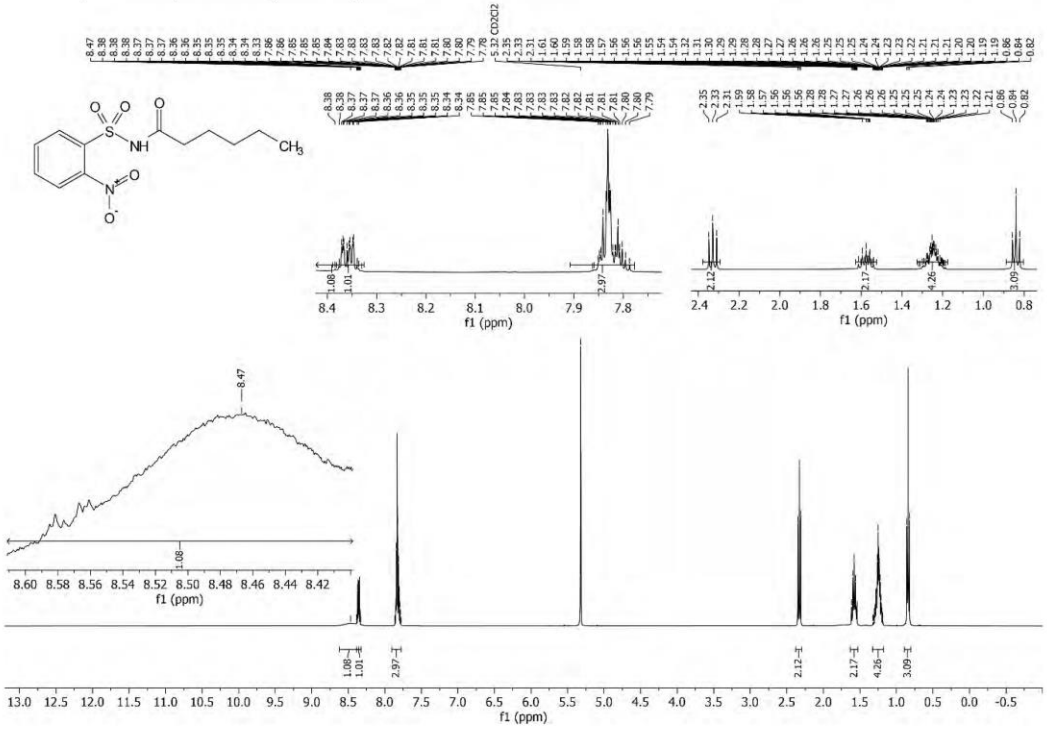
^{1}H NMR spectrum (400 MHz, CD_3OD) of **6e**



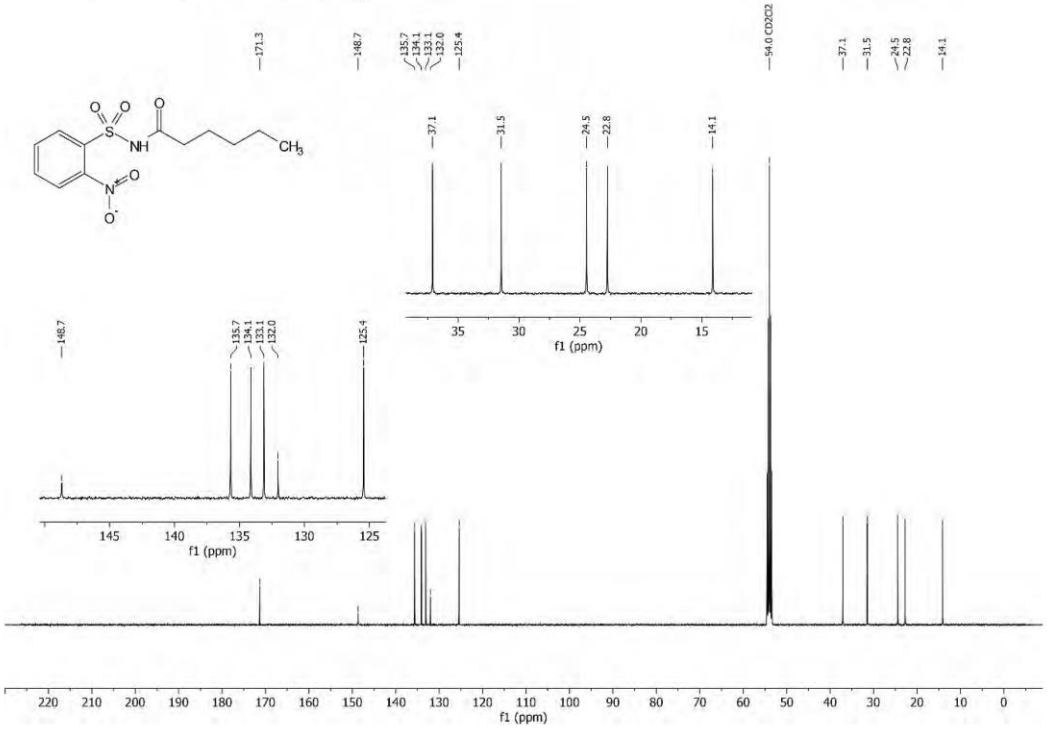
^{13}C NMR spectrum (101 MHz, CD_3OD) of **6e**



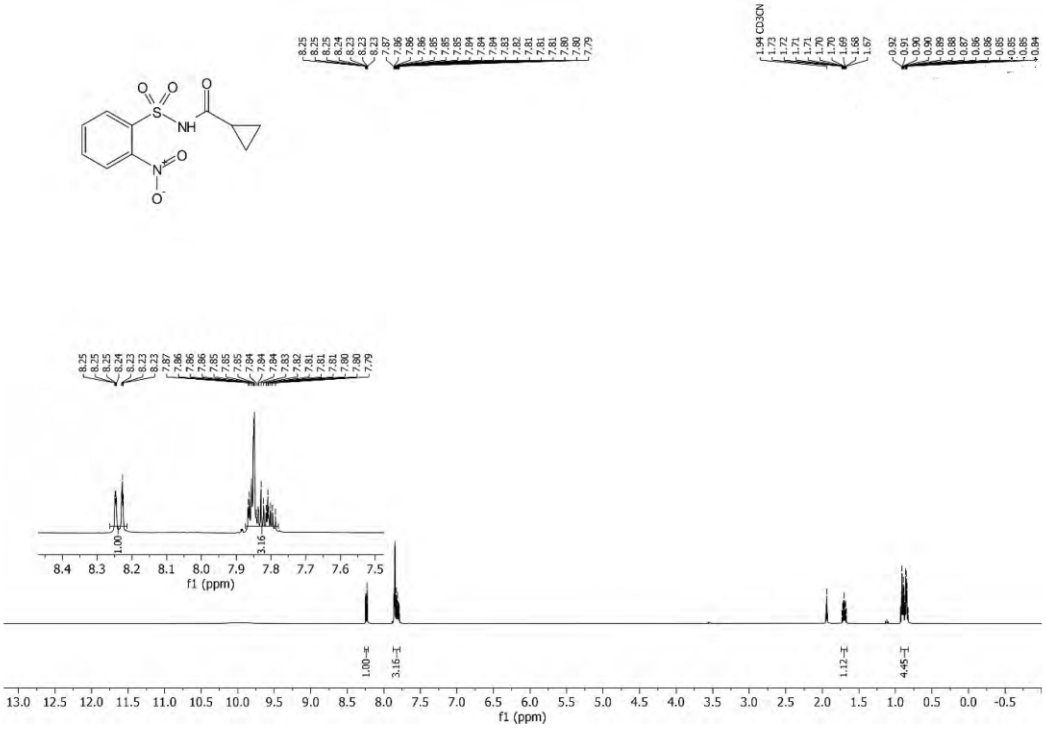
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6f**



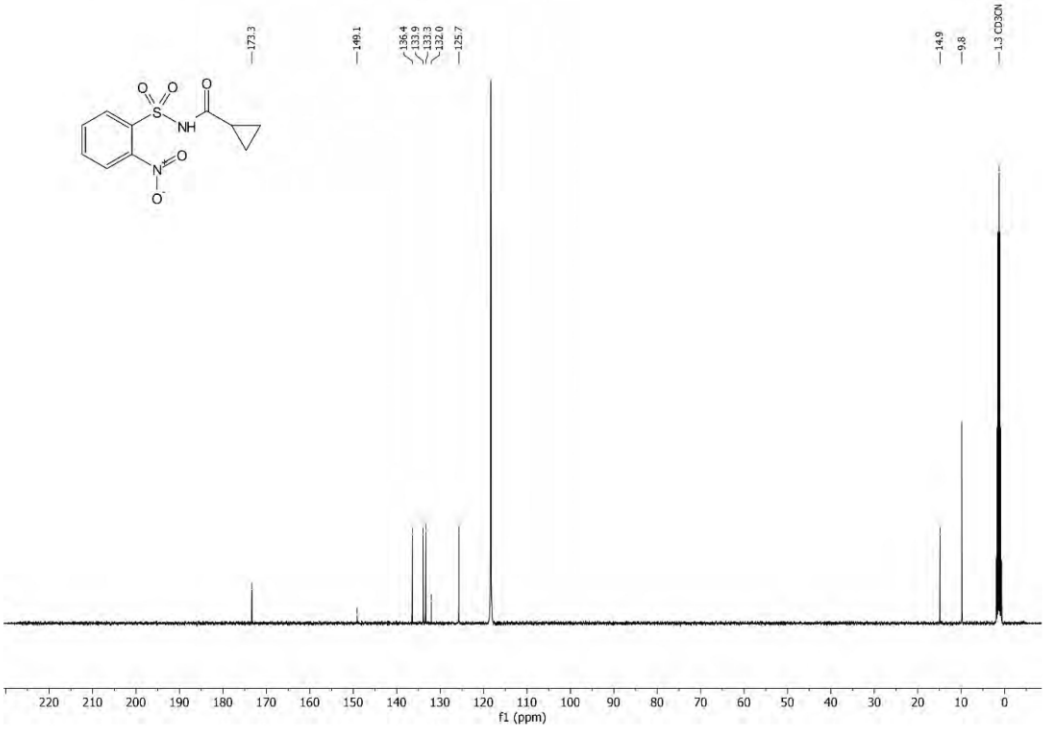
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6f**



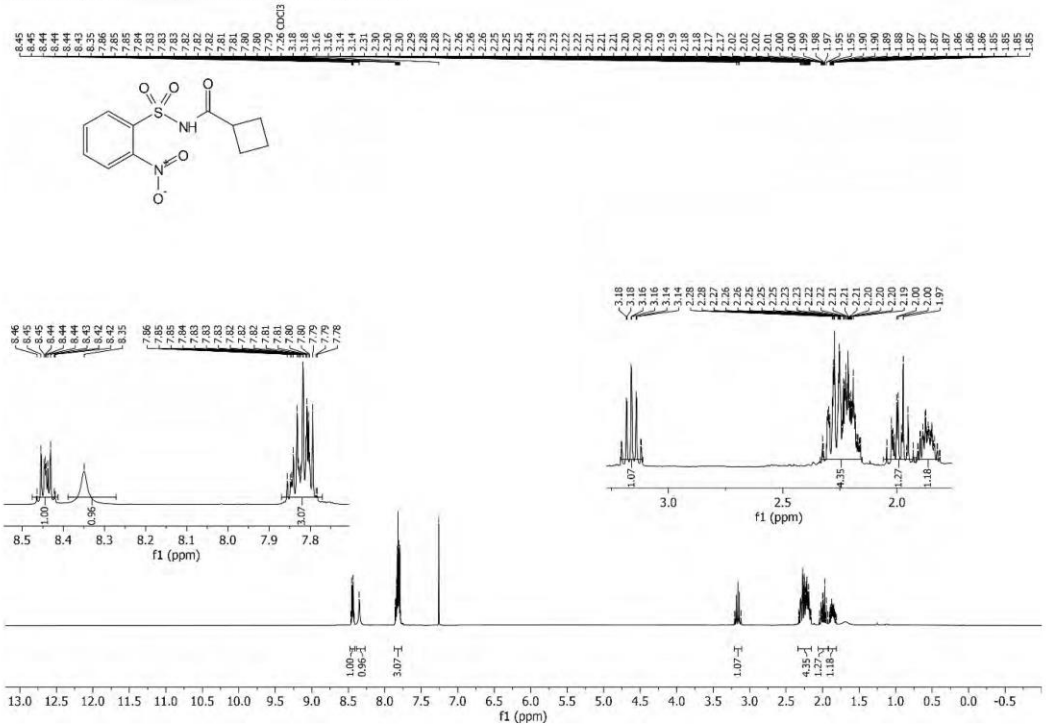
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6g**



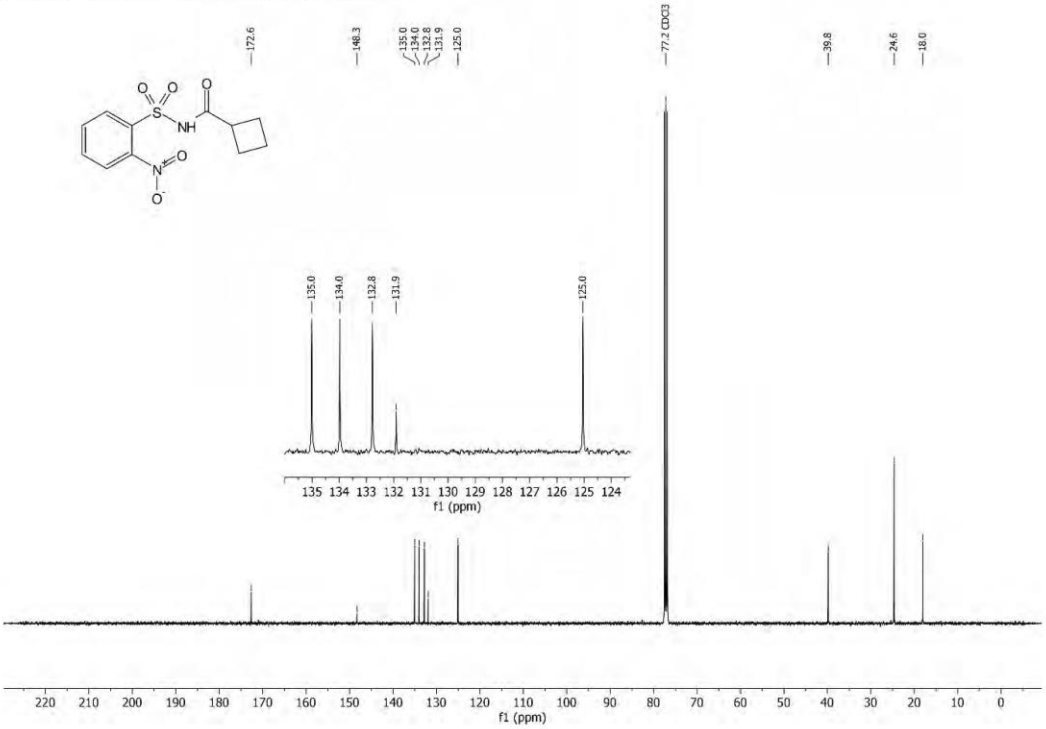
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6g**



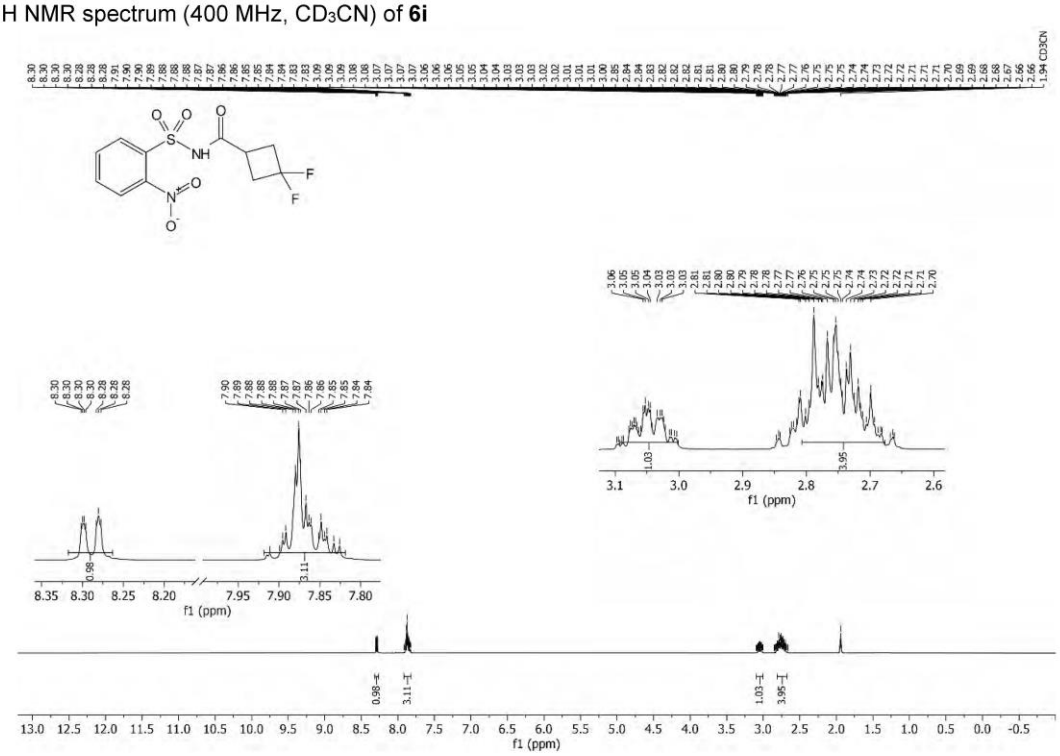
^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6h**



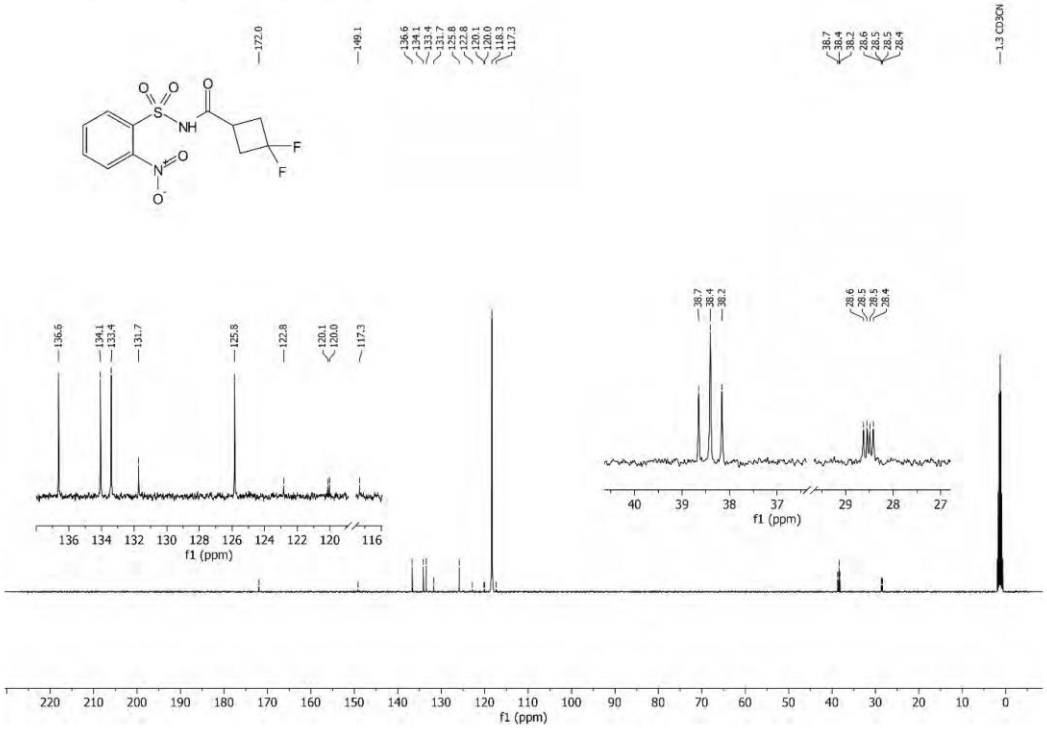
^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6h**



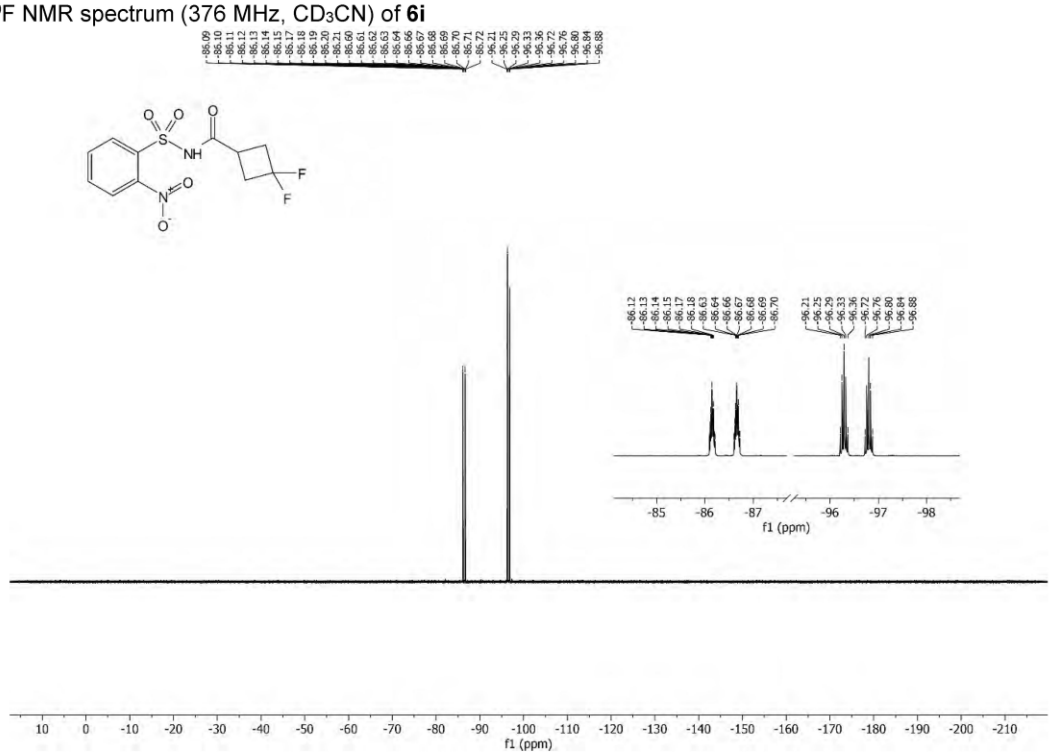
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6i**



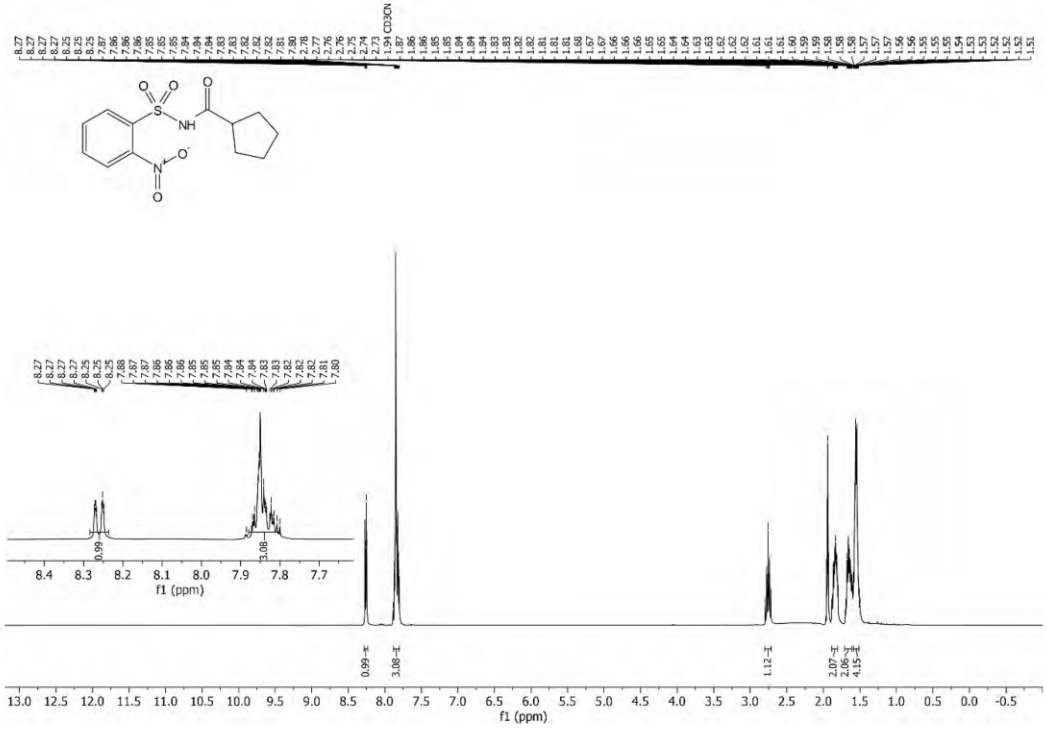
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6i**



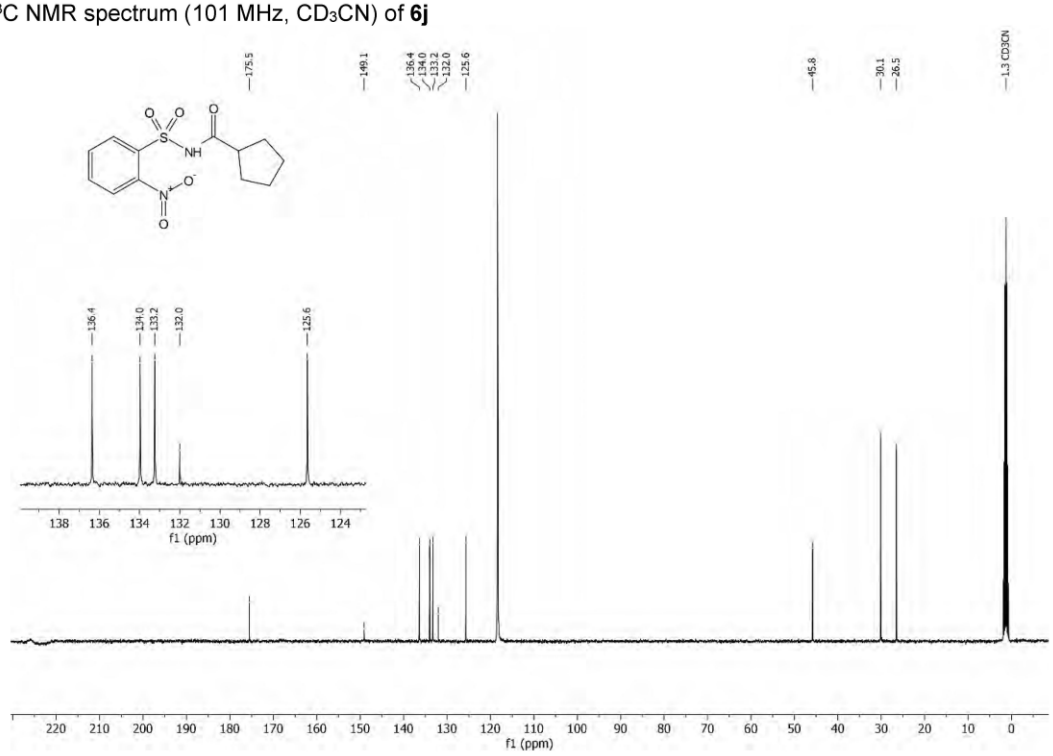
^{19}F NMR spectrum (376 MHz, CD_3CN) of **6i**



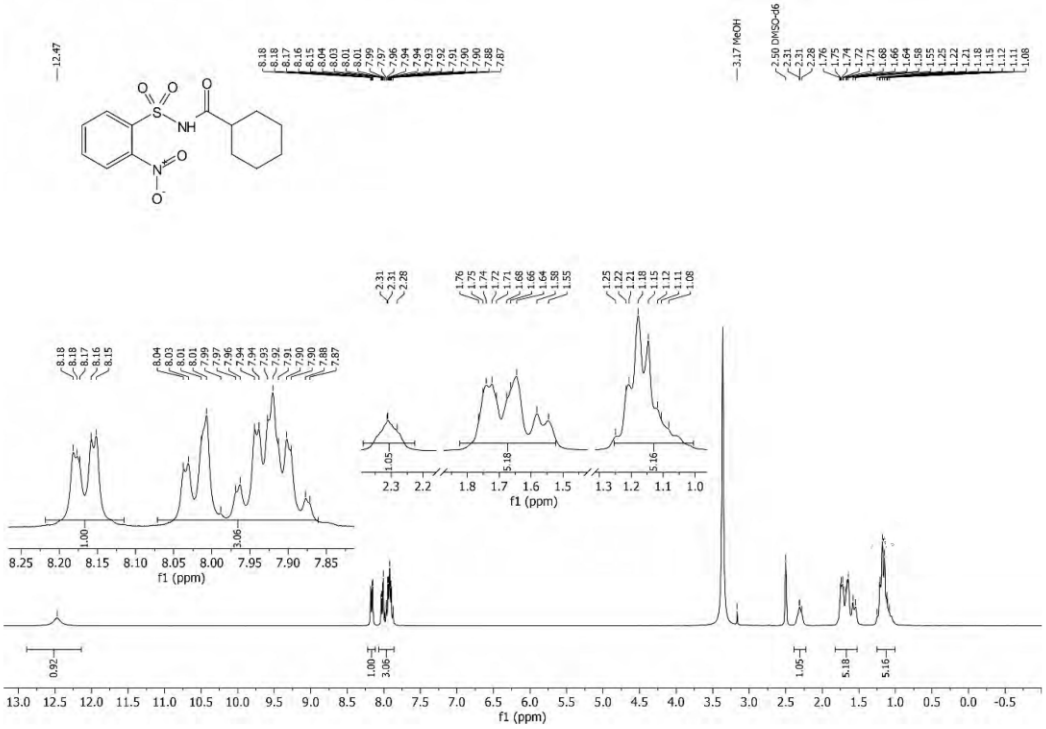
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6j**



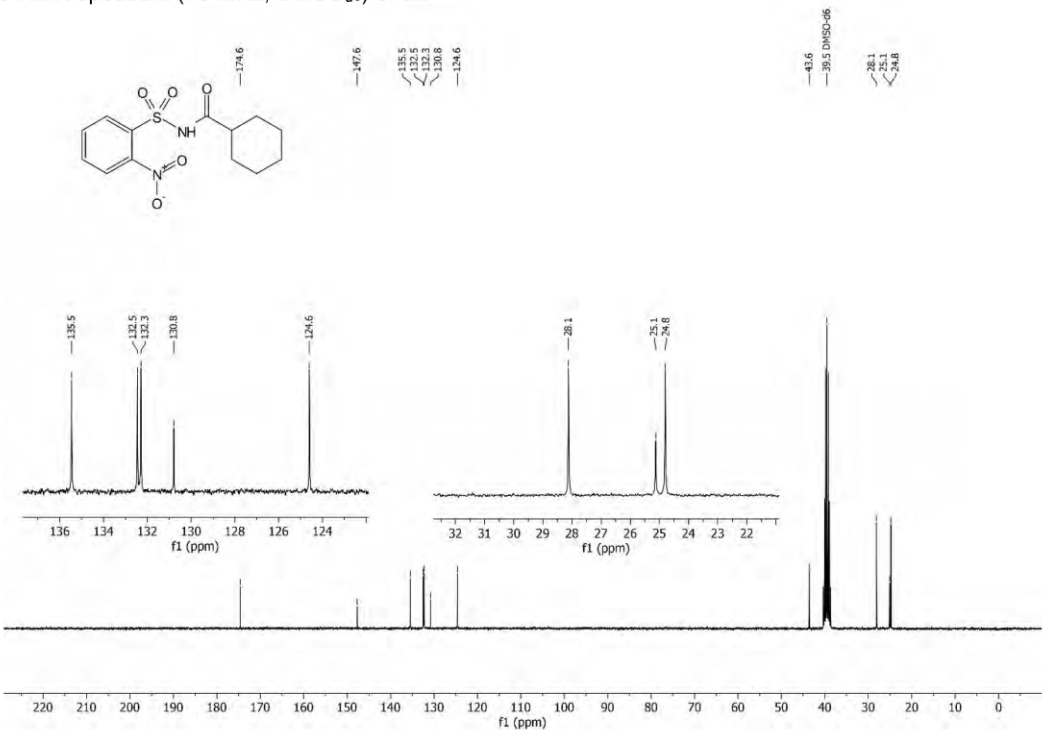
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6j**



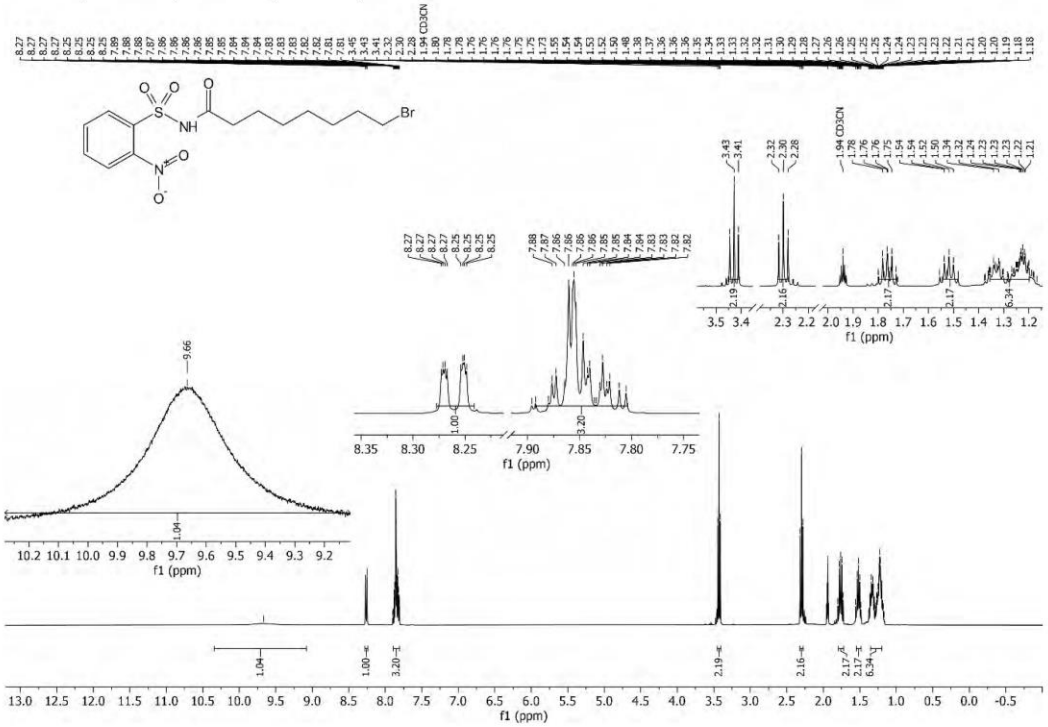
^{1}H NMR spectrum (300 MHz, DMSO$_{d6}$) of **6k**



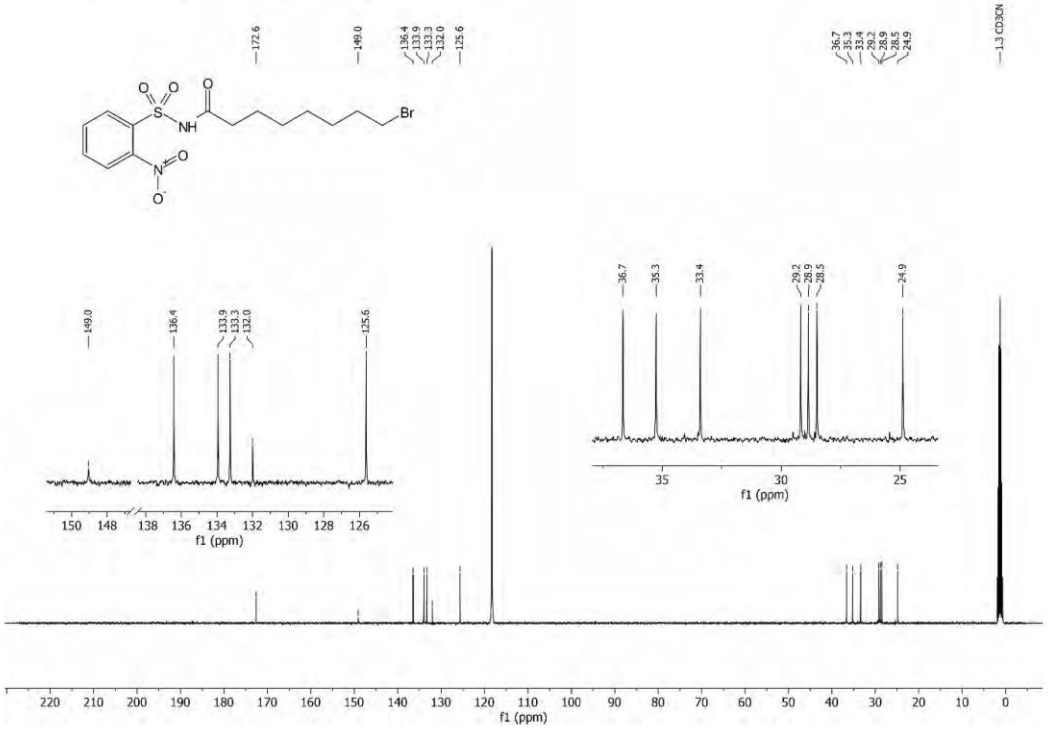
^{13}C NMR spectrum (75 MHz, DMSO$_{d6}$) of **6k**



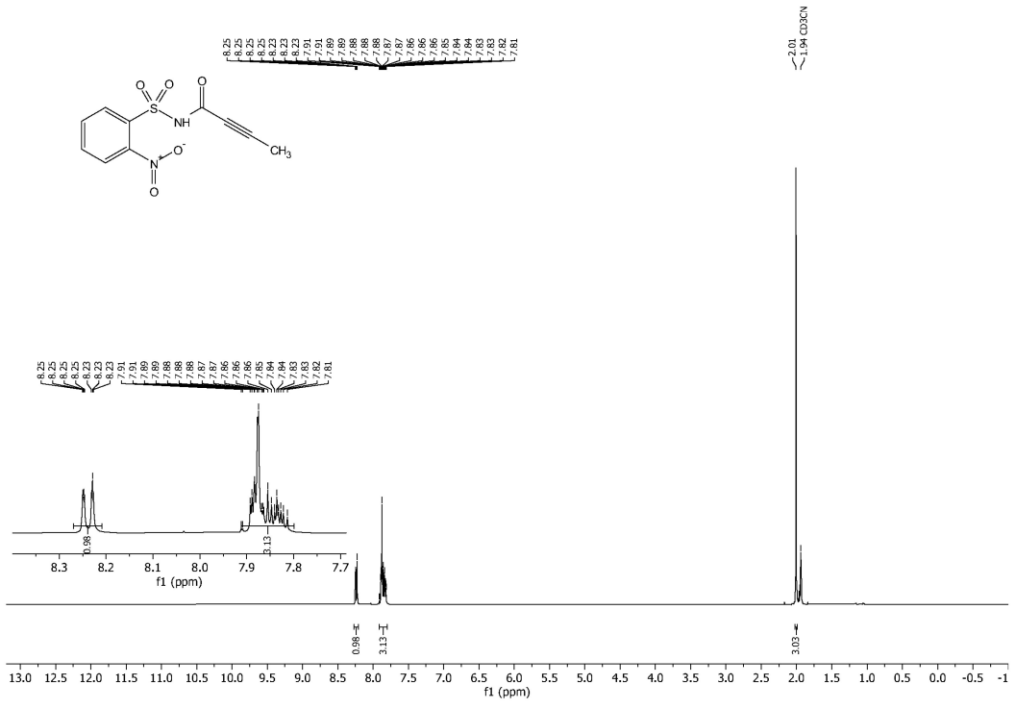
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6l**



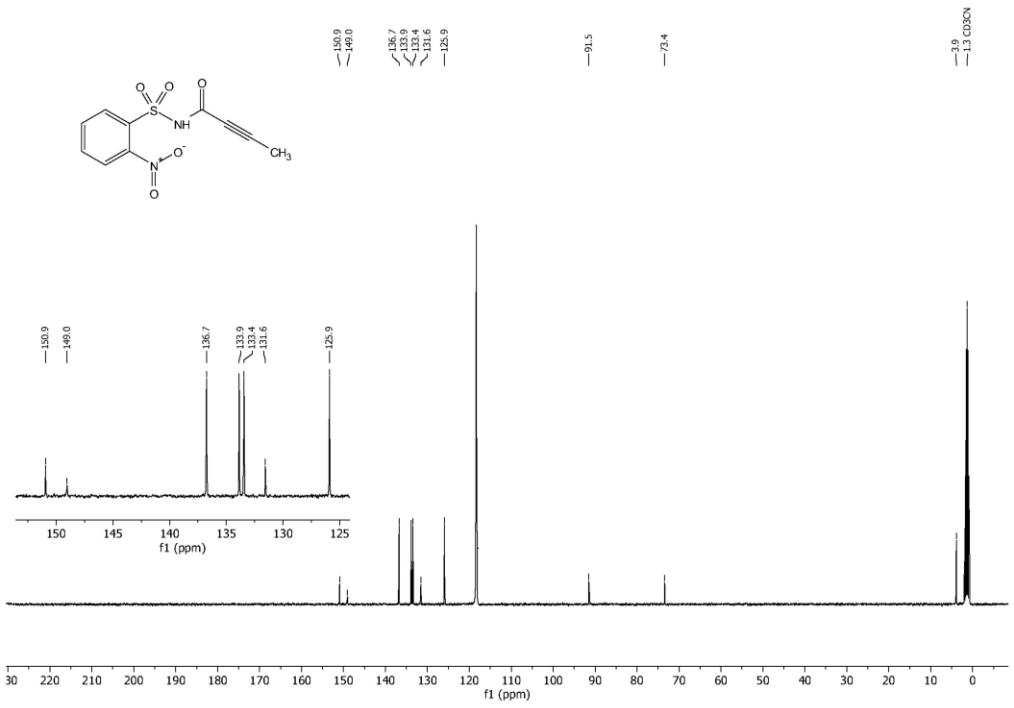
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6l**



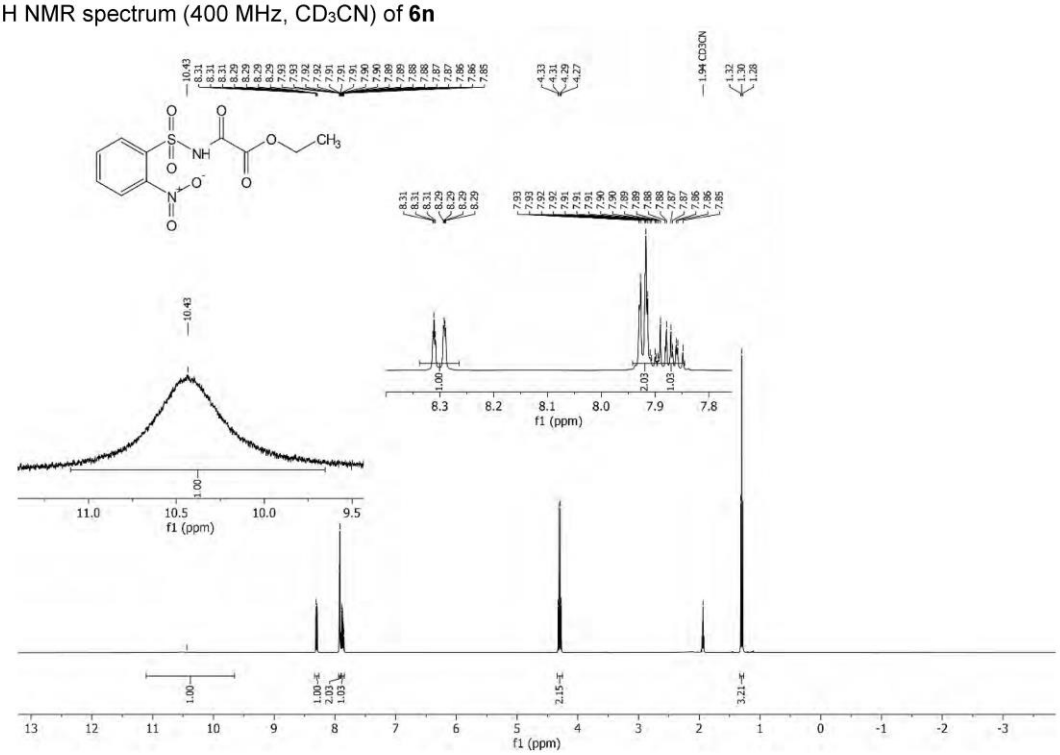
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6m**



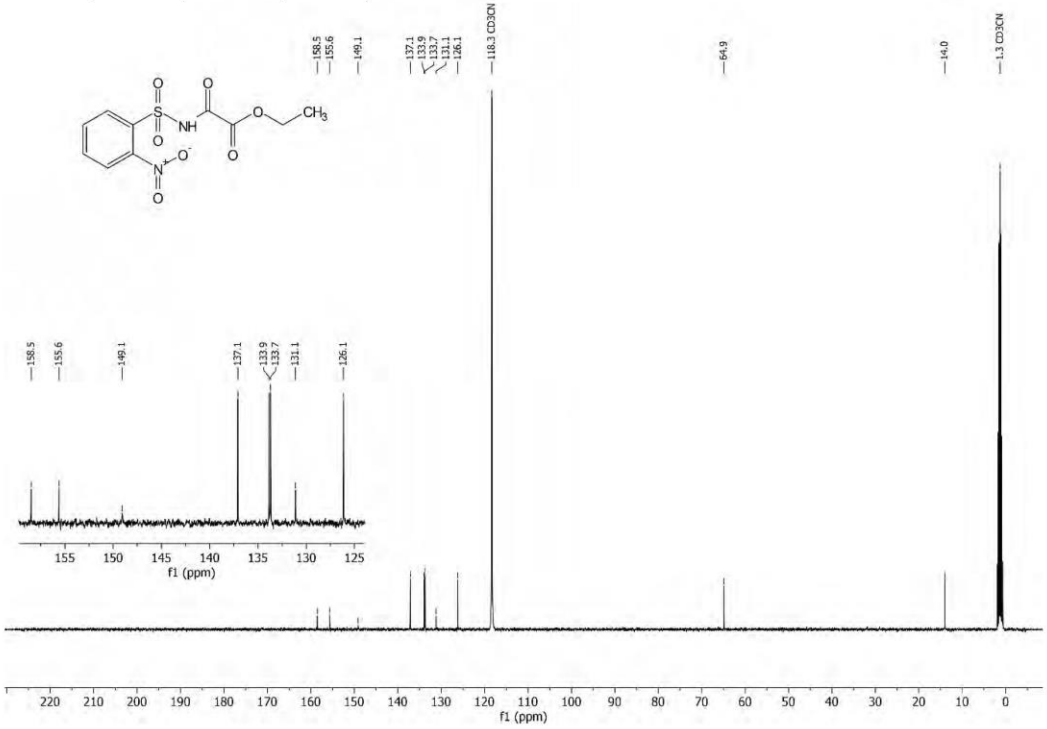
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6m**



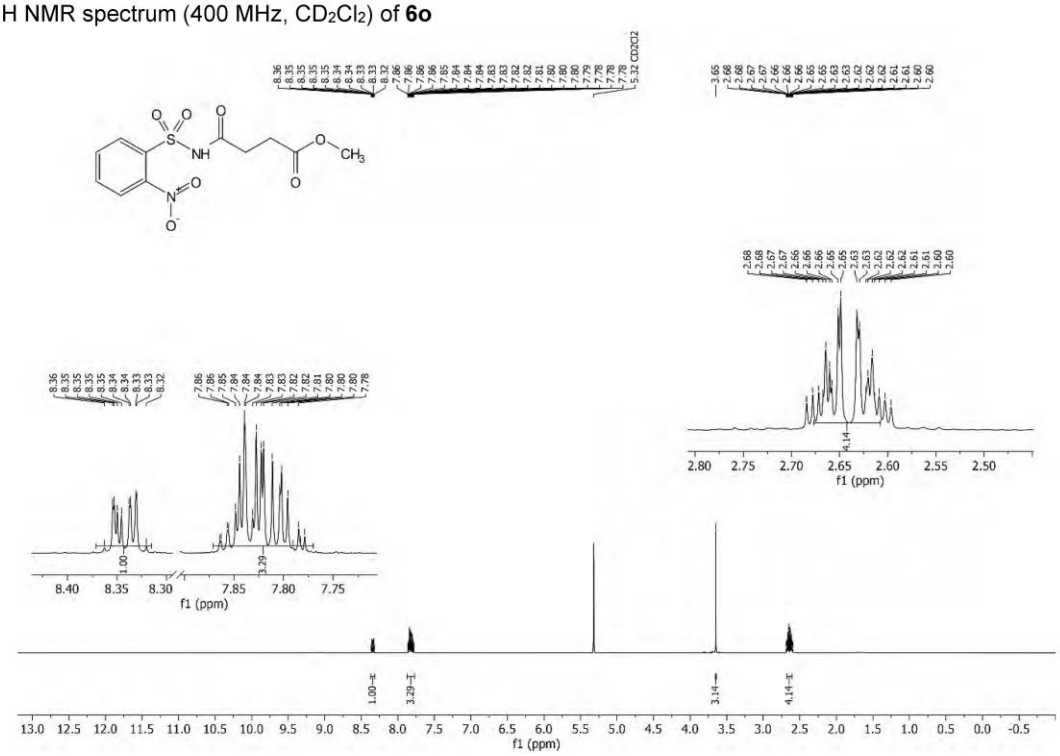
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6n**



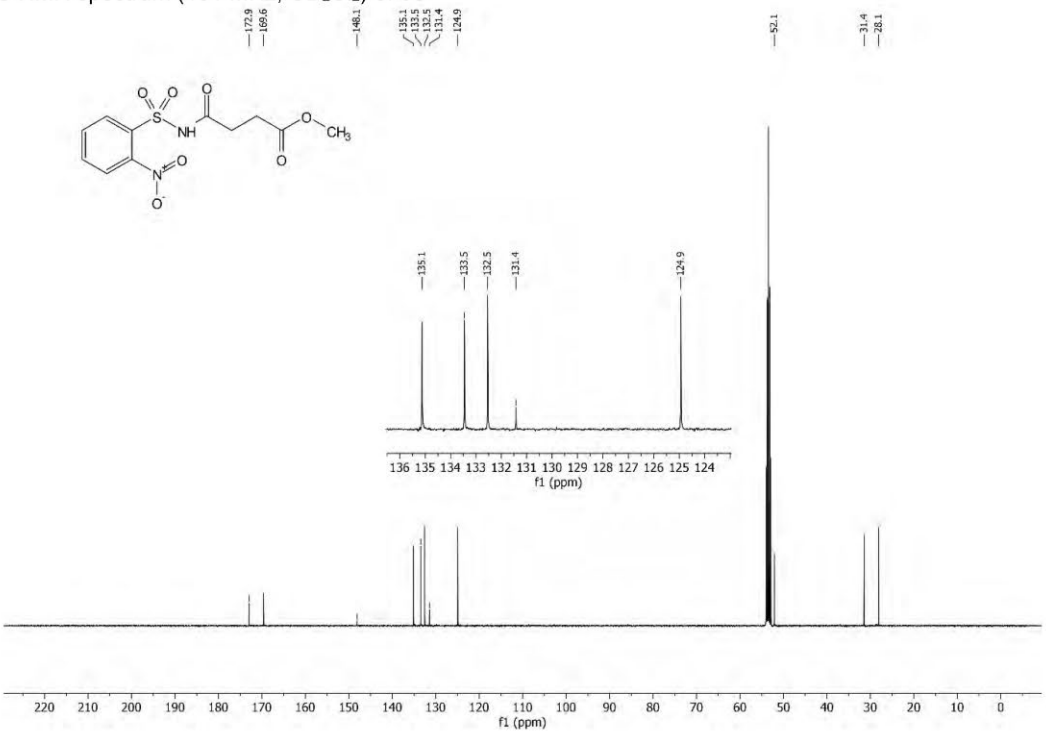
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6n**



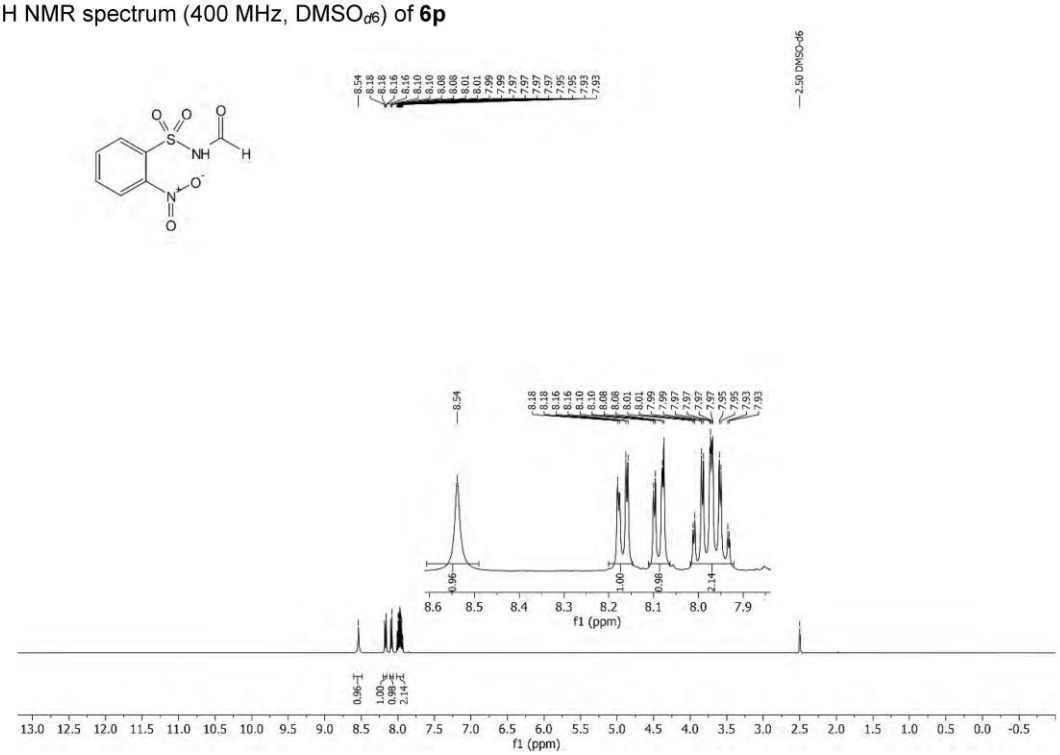
^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **6o**



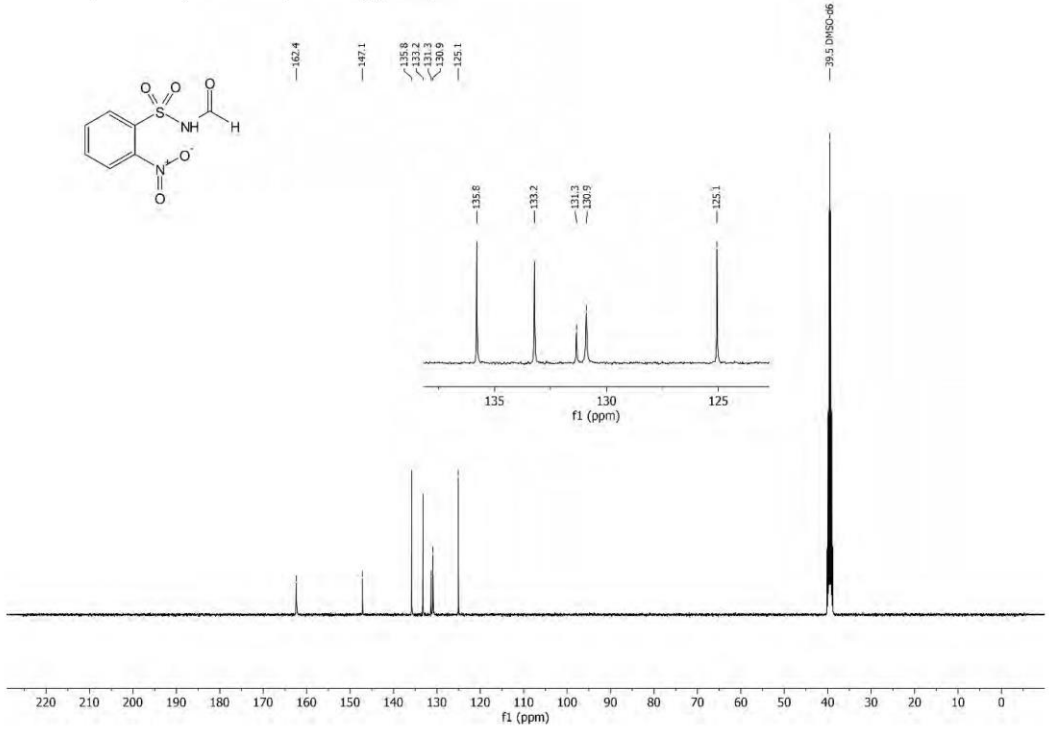
^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **6o**



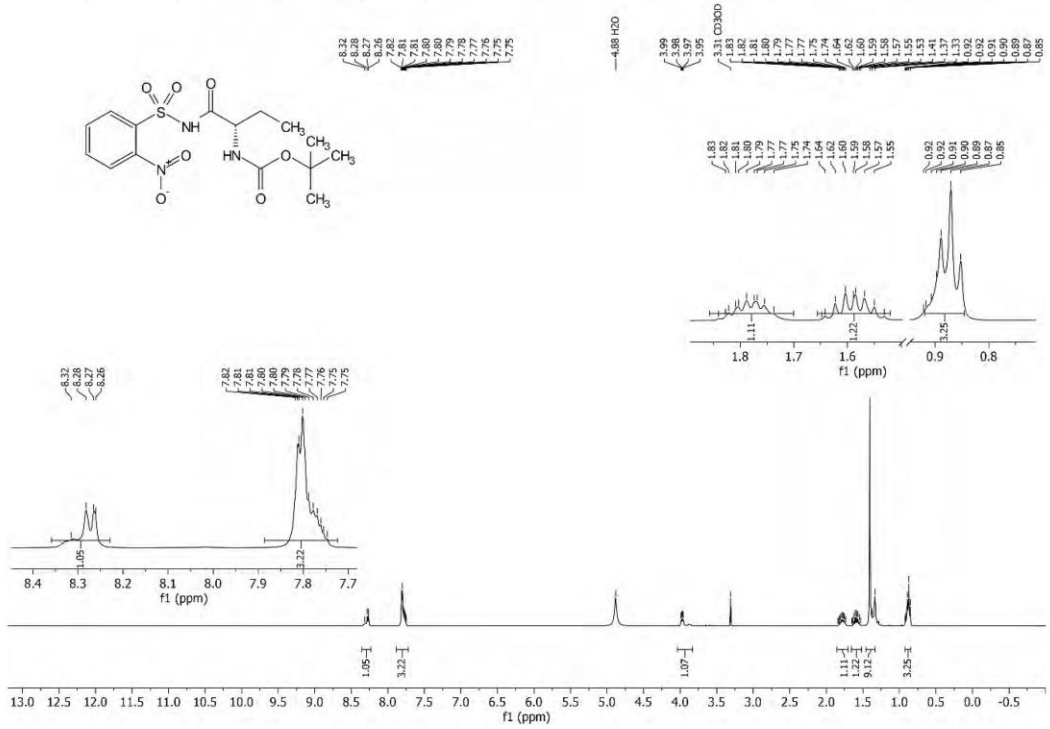
^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **6p**



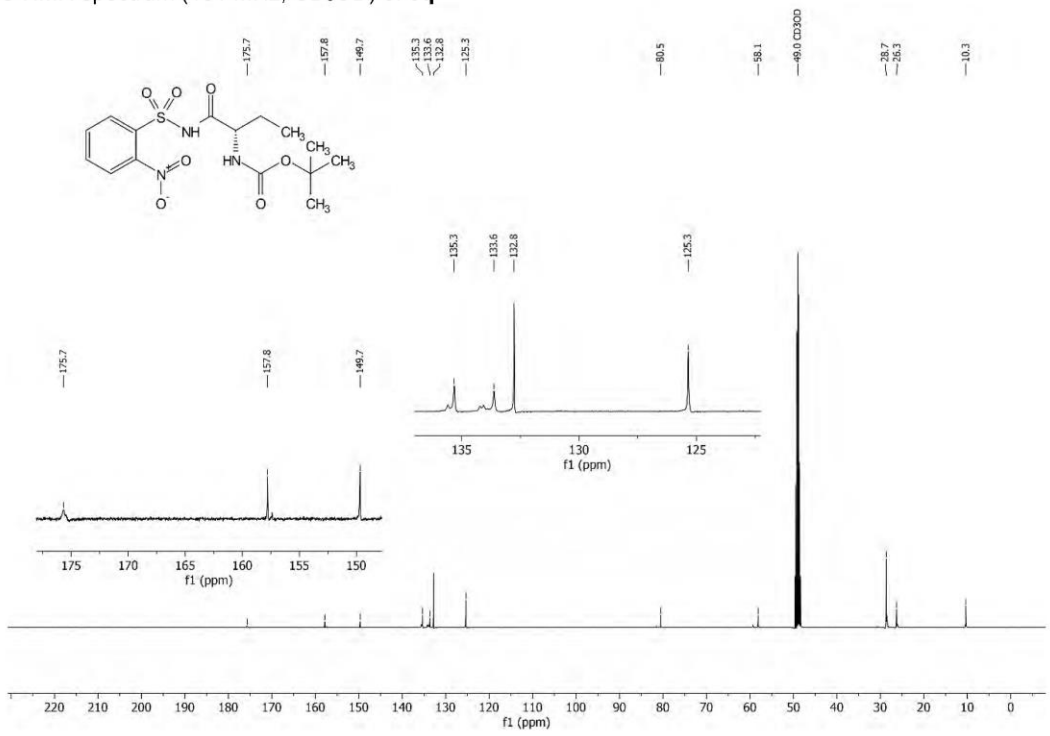
^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **6p**



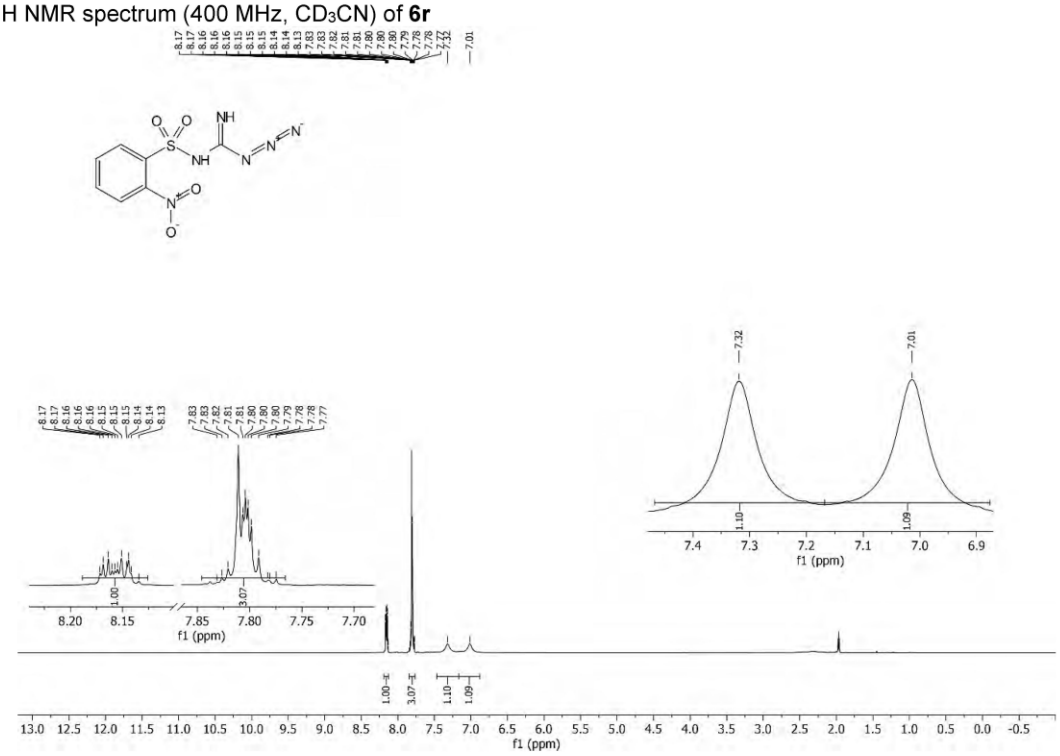
^{1}H NMR spectrum (400 MHz, CD_3OD) of **6q**



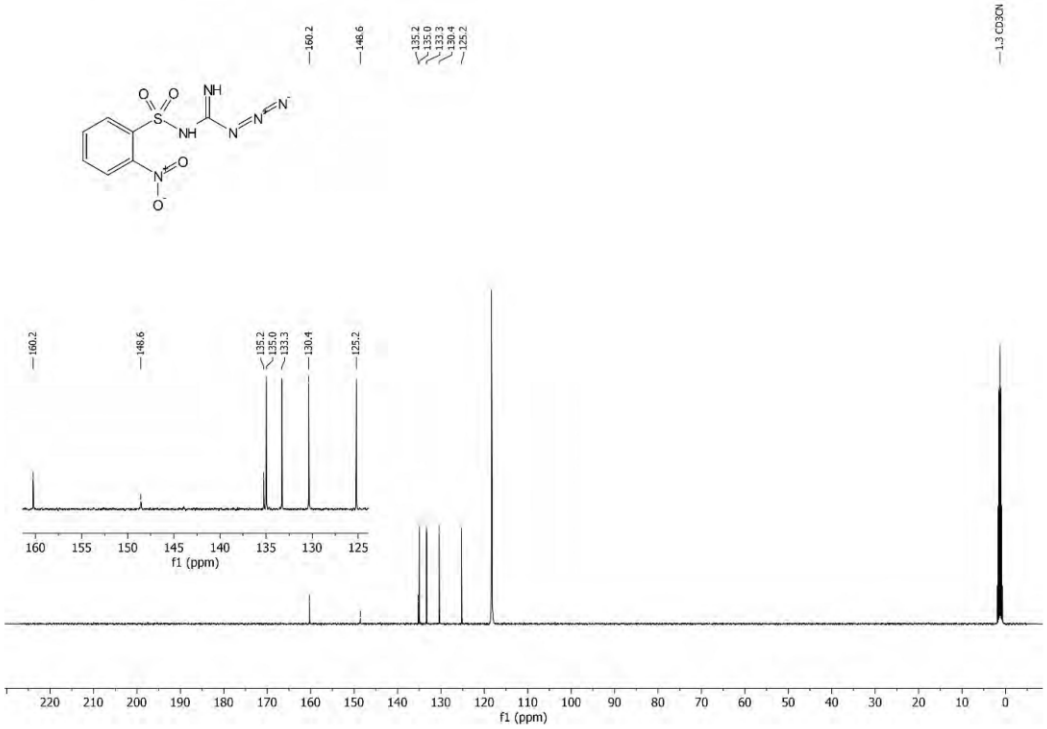
^{13}C NMR spectrum (101 MHz, CD_3OD) of **6q**



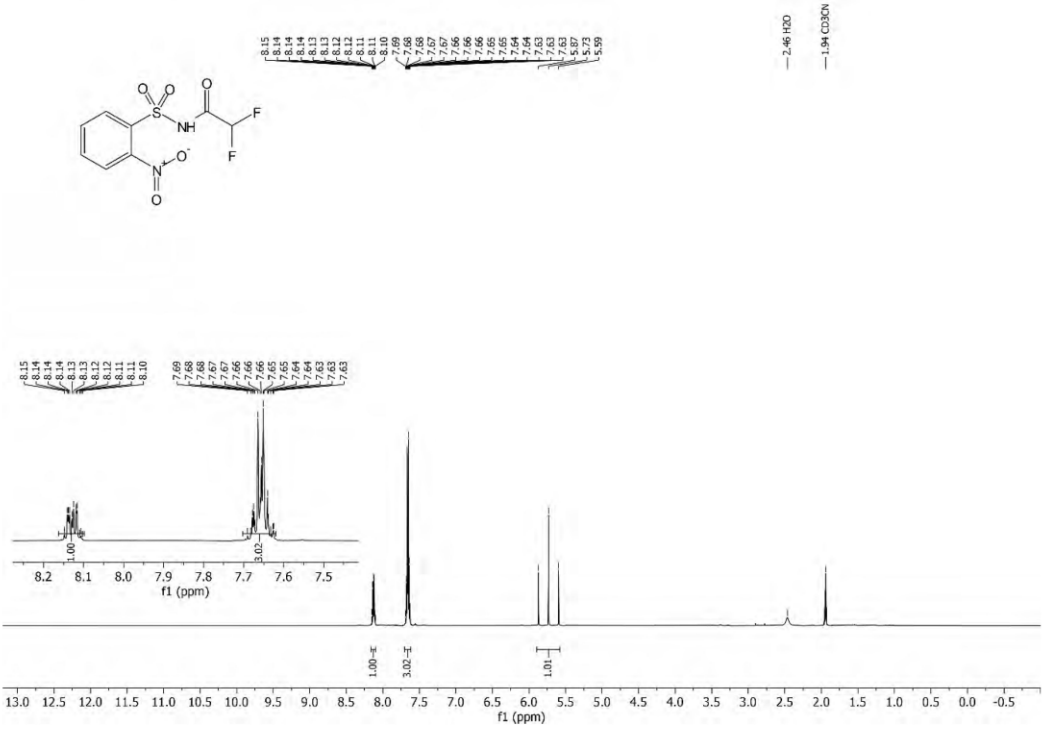
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6r**



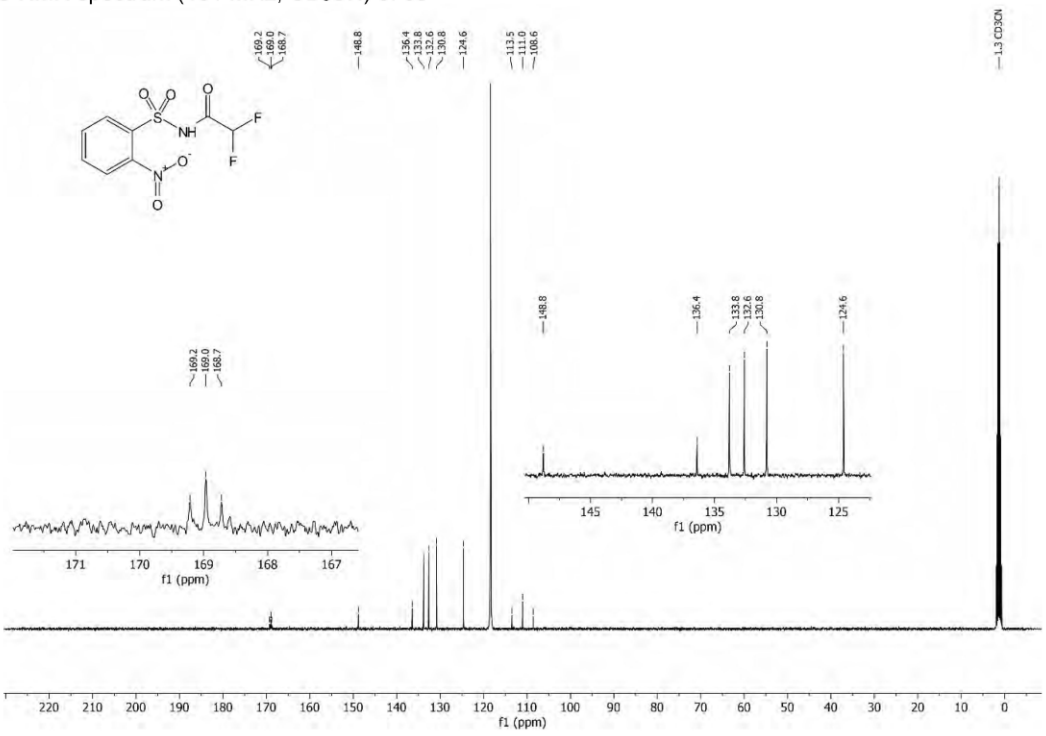
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6r**



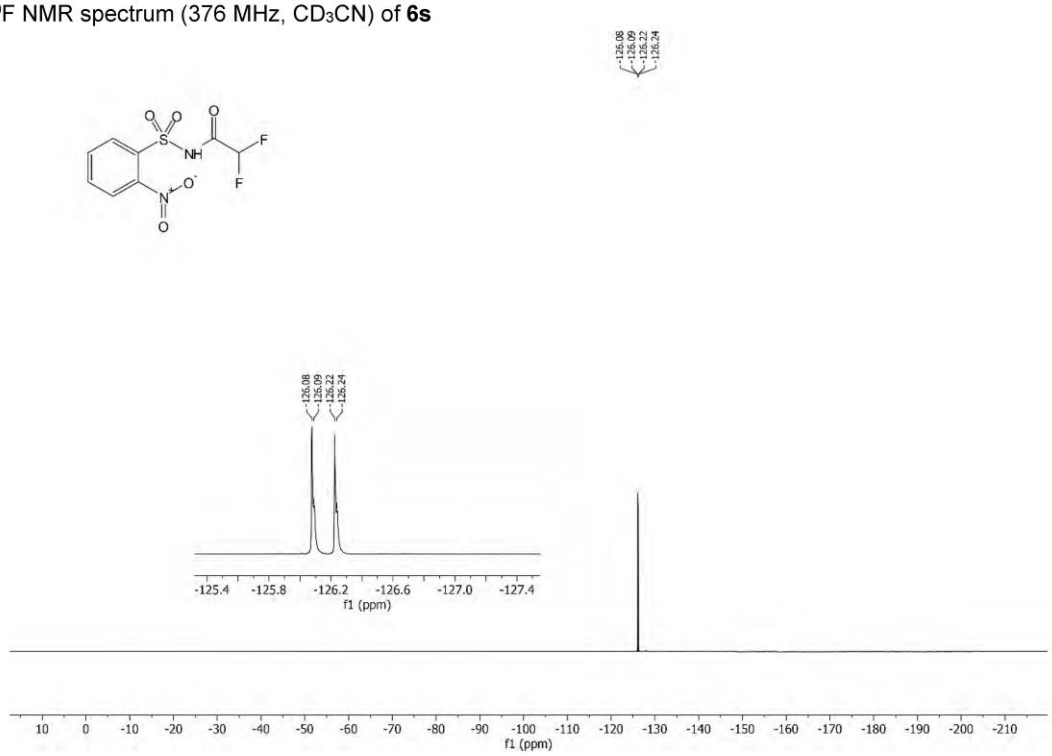
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6s**



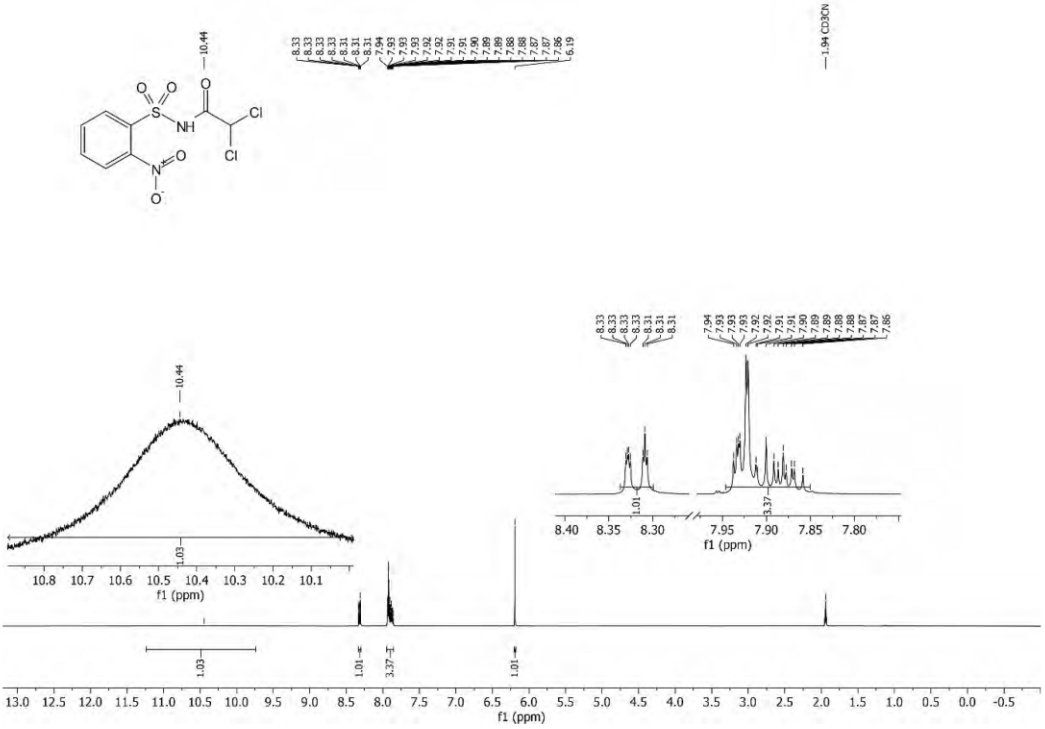
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6s**



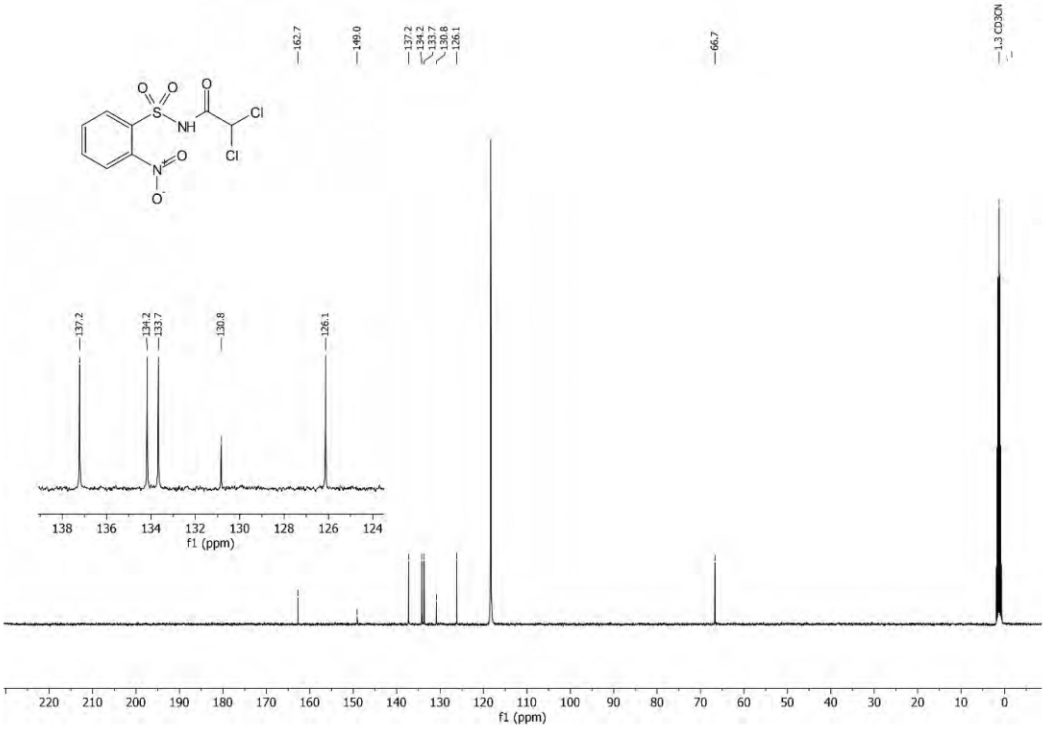
^{19}F NMR spectrum (376 MHz, CD_3CN) of **6s**



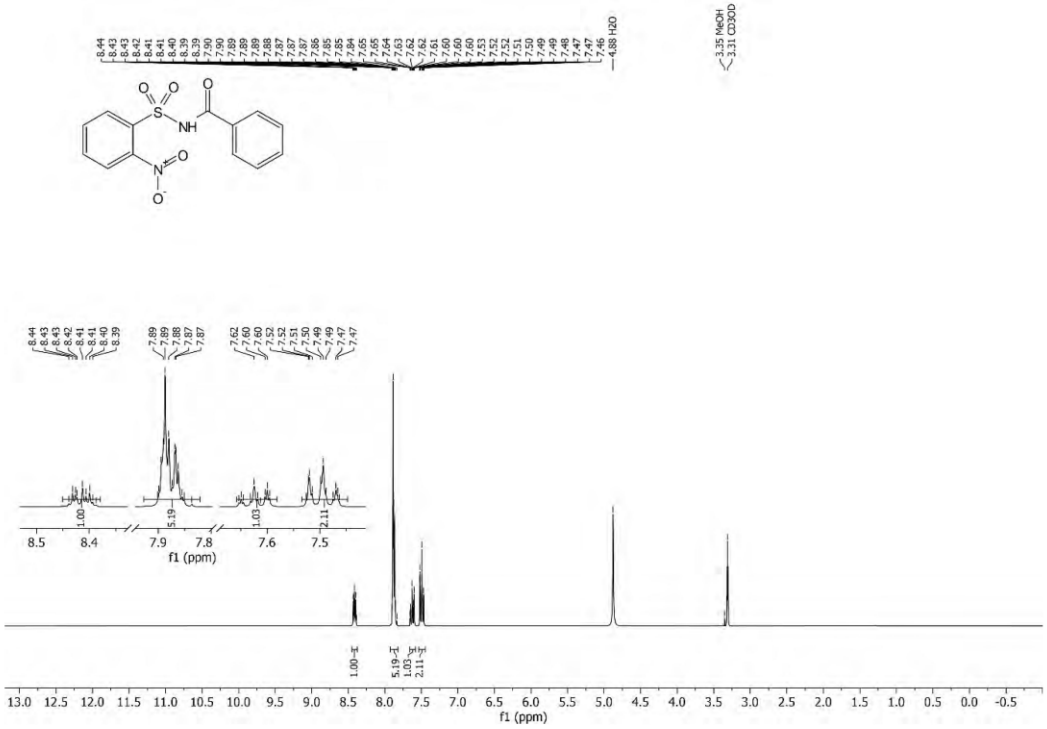
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6t**



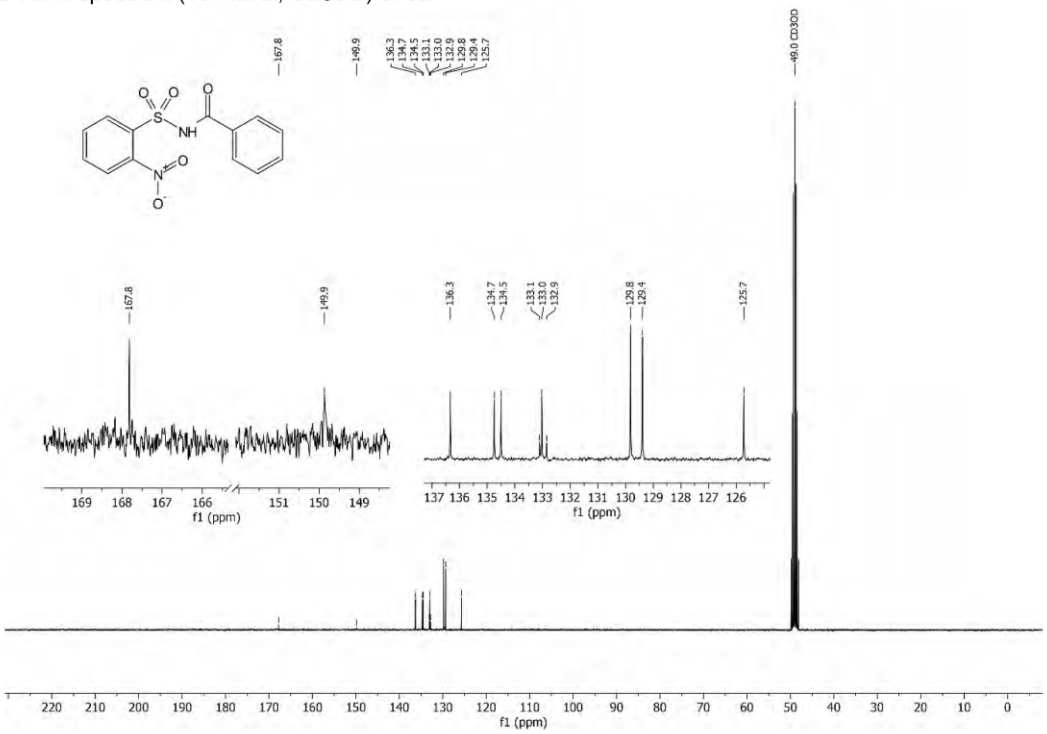
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6t**



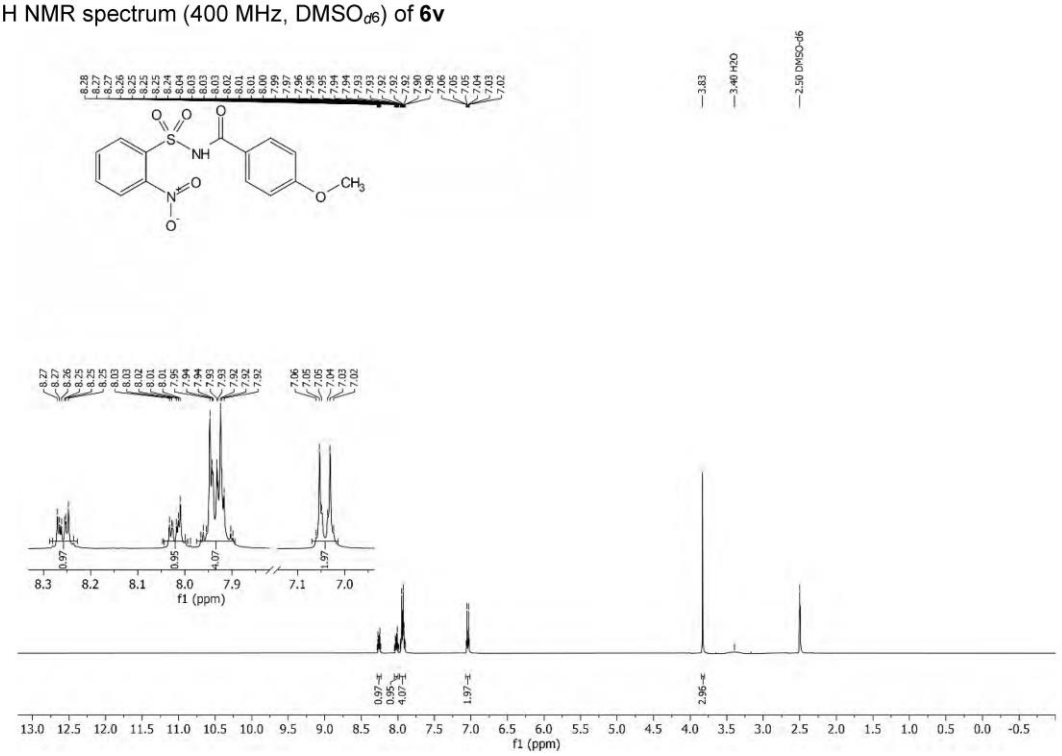
^{1}H NMR spectrum (400 MHz, CD_3OD) of **6u**



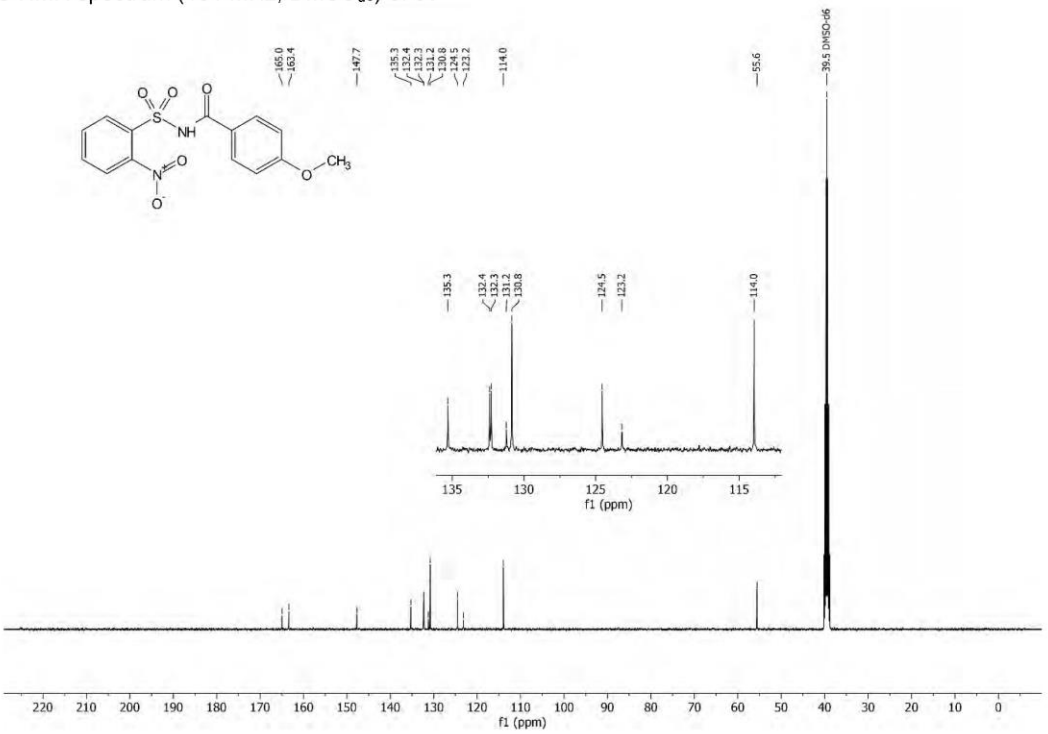
^{13}C NMR spectrum (101 MHz, CD_3OD) of **6u**



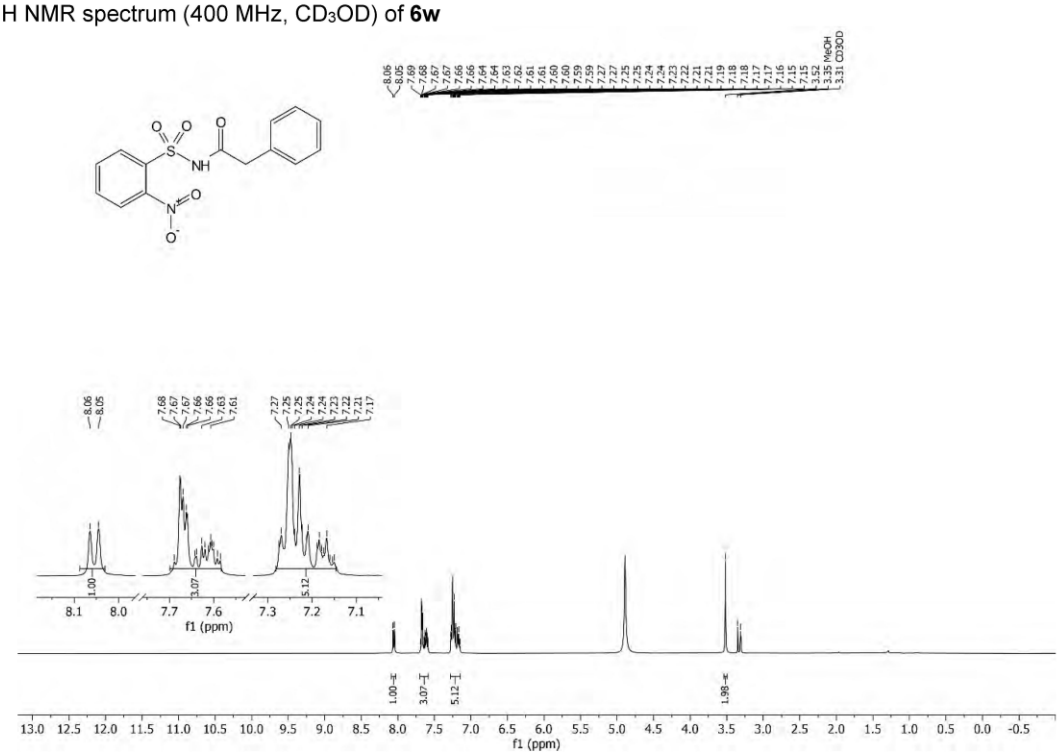
^{1}H NMR spectrum (400 MHz, DMSO$_{d6}$) of **6v**



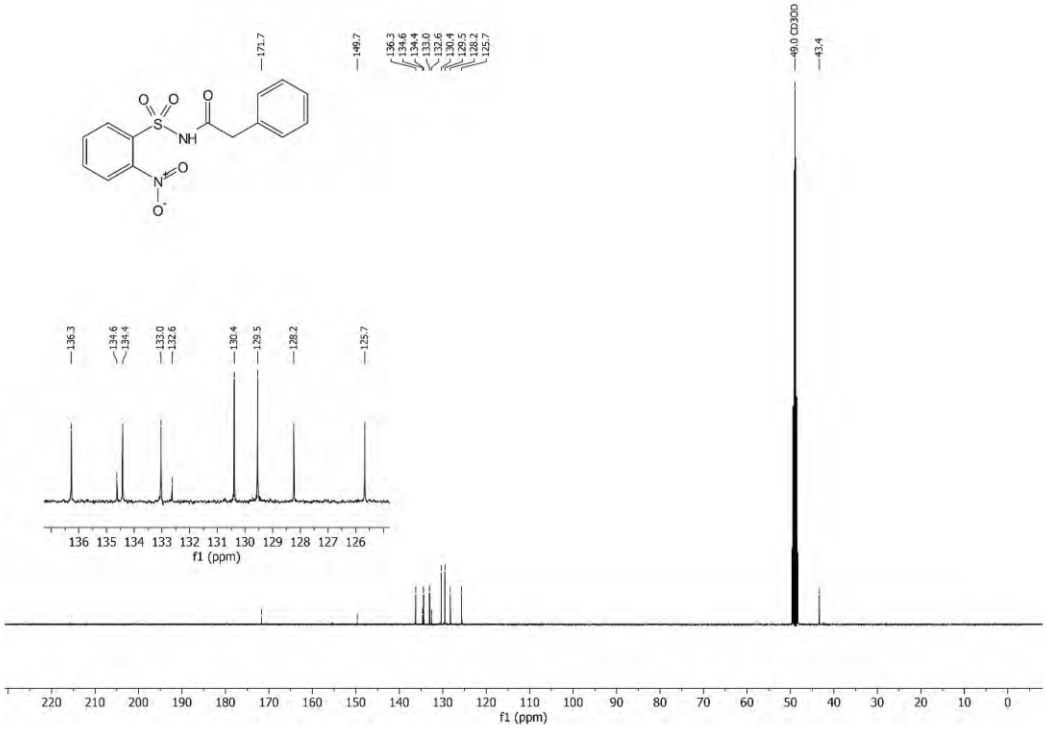
^{13}C NMR spectrum (101 MHz, DMSO$_{d6}$) of **6v**



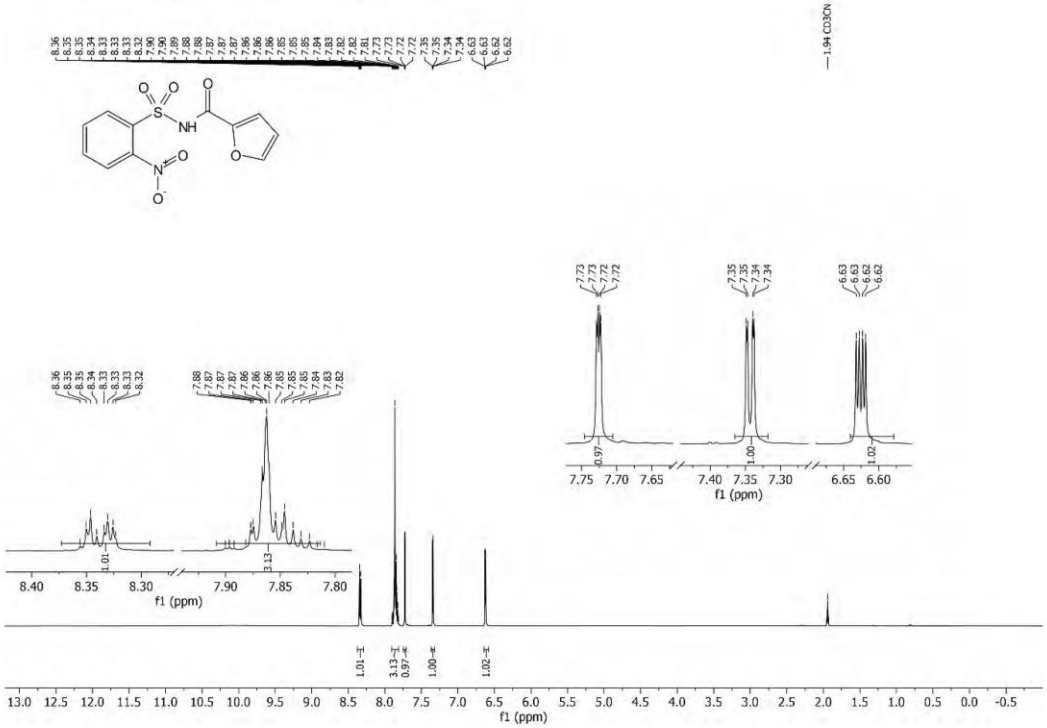
^{1}H NMR spectrum (400 MHz, CD_3OD) of **6w**



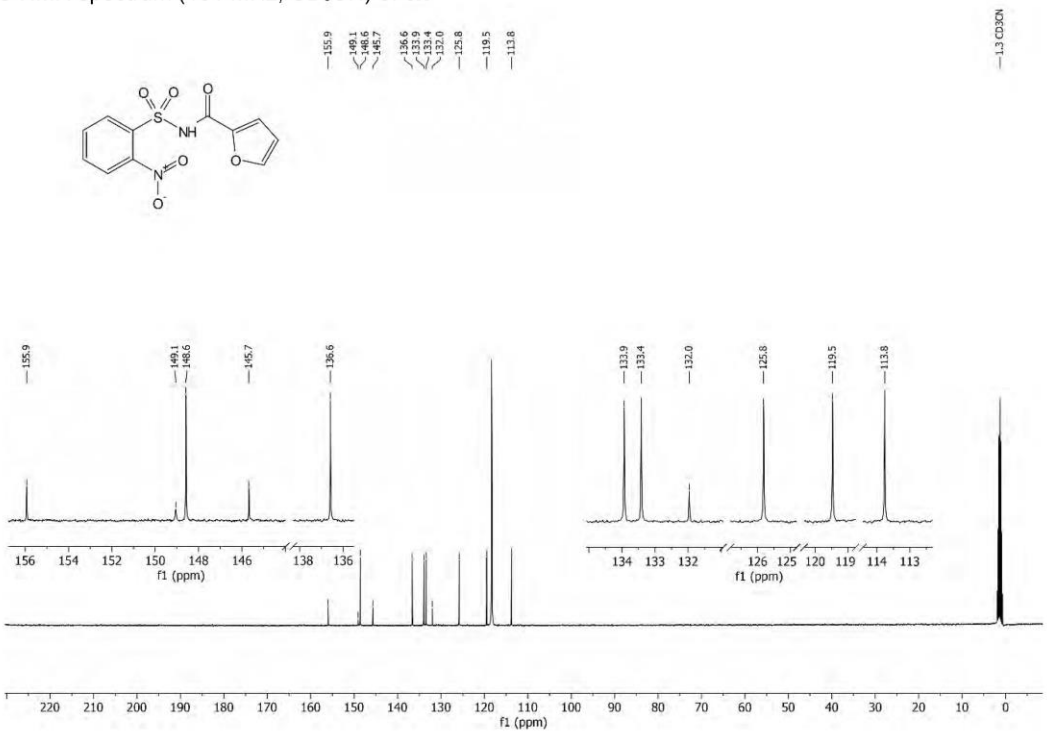
^{13}C NMR spectrum (101 MHz, CD_3OD) of **6w**



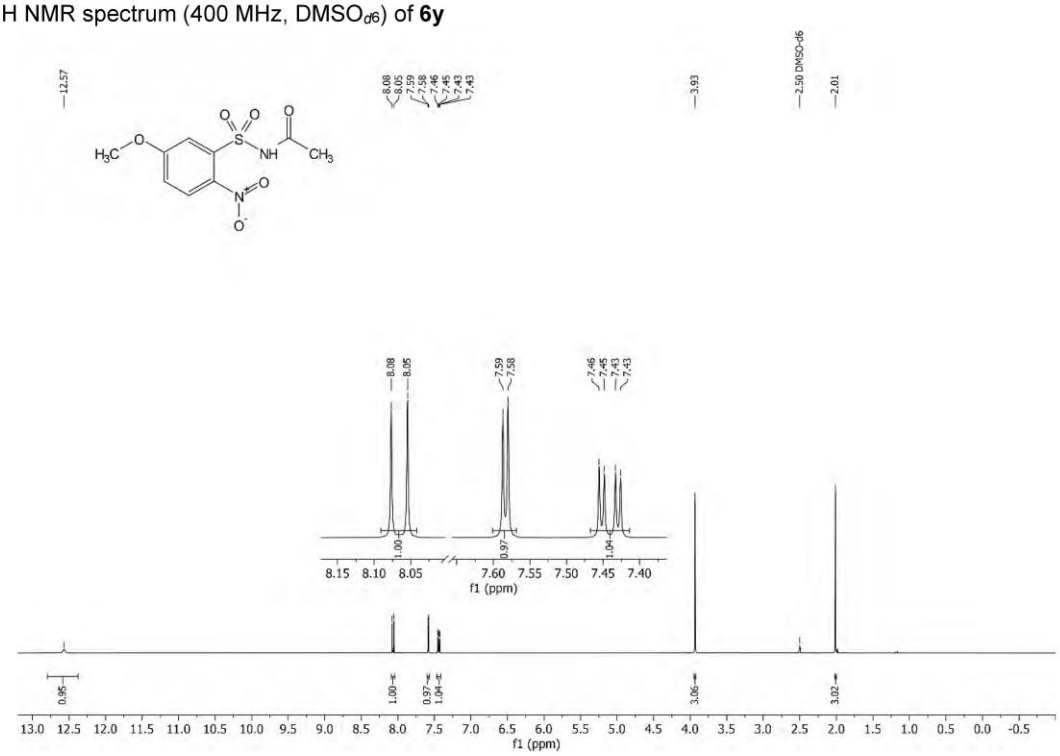
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6x**



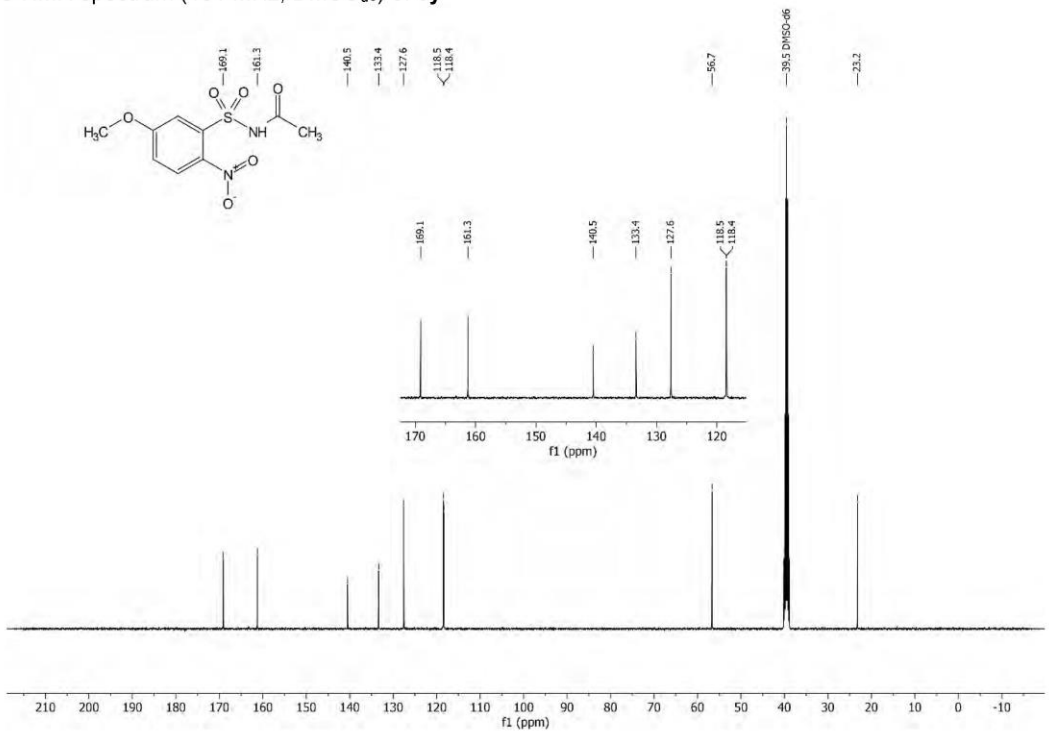
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6x**



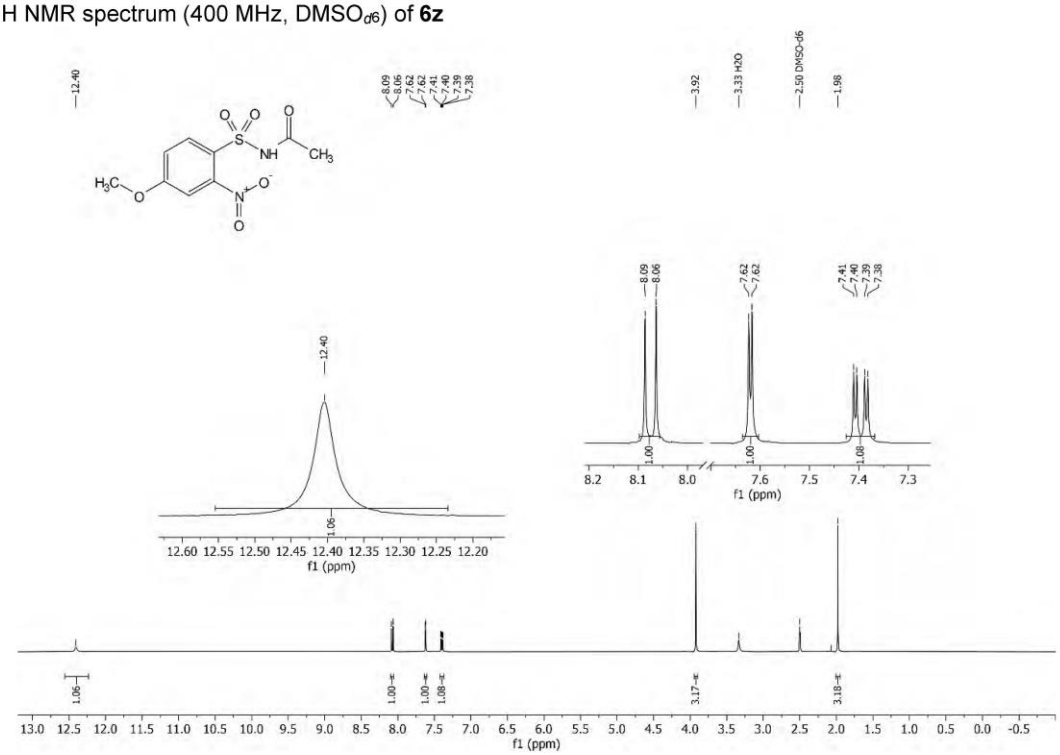
^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **6y**



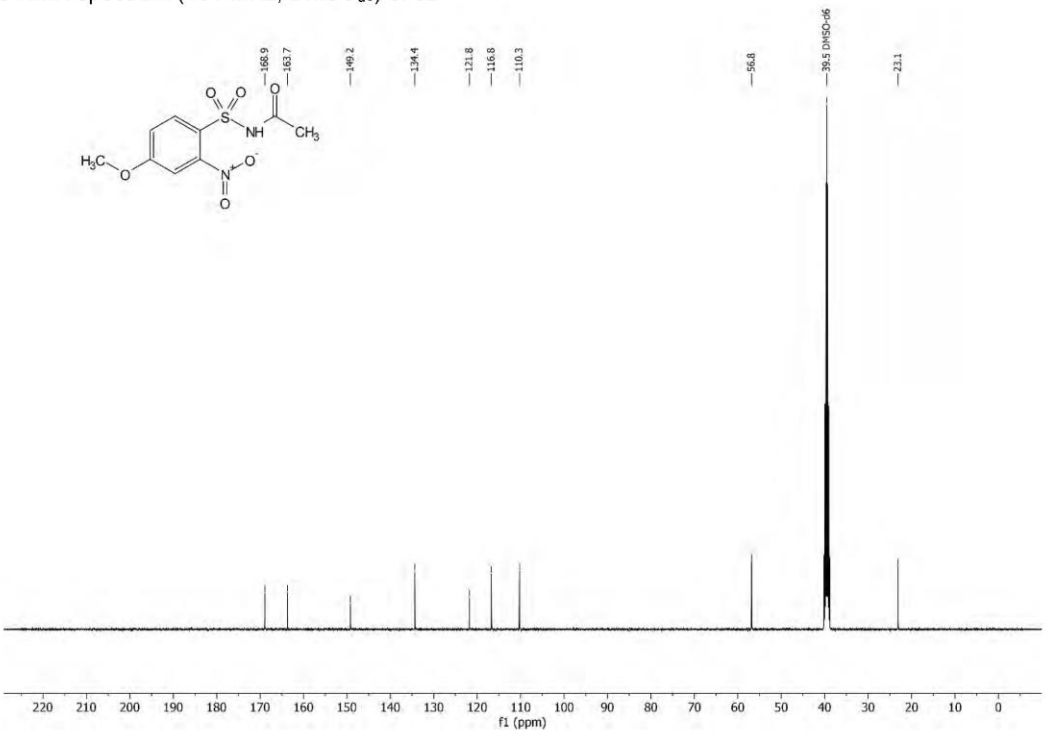
^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **6y**



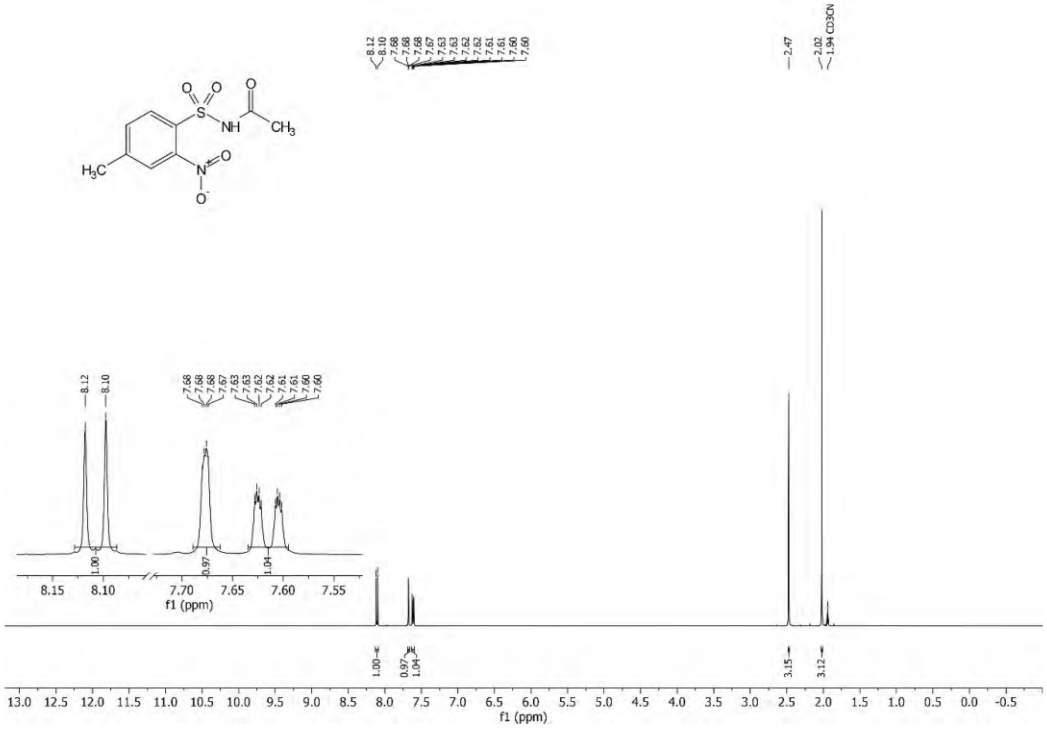
^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **6z**



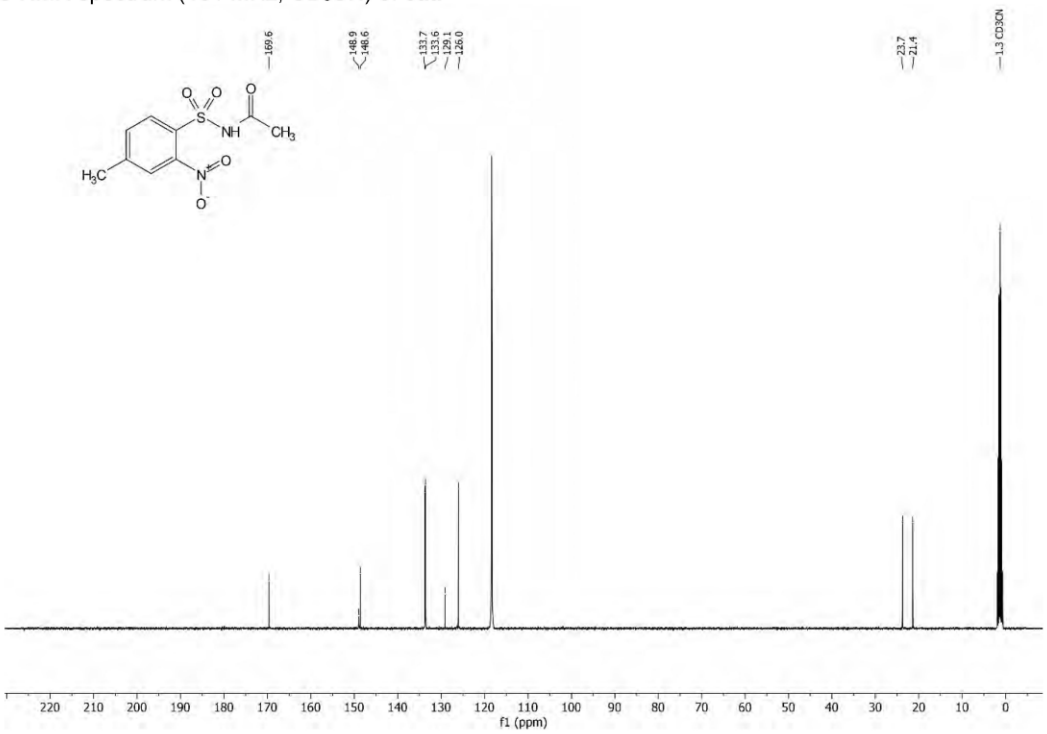
^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **6z**



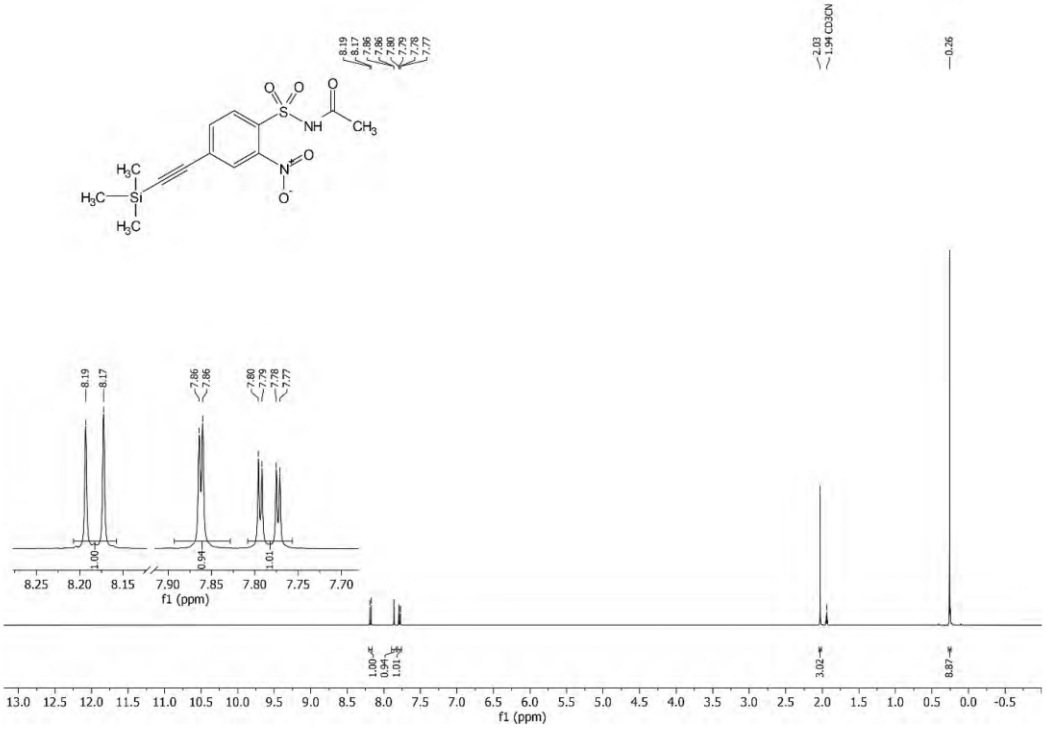
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6aa**



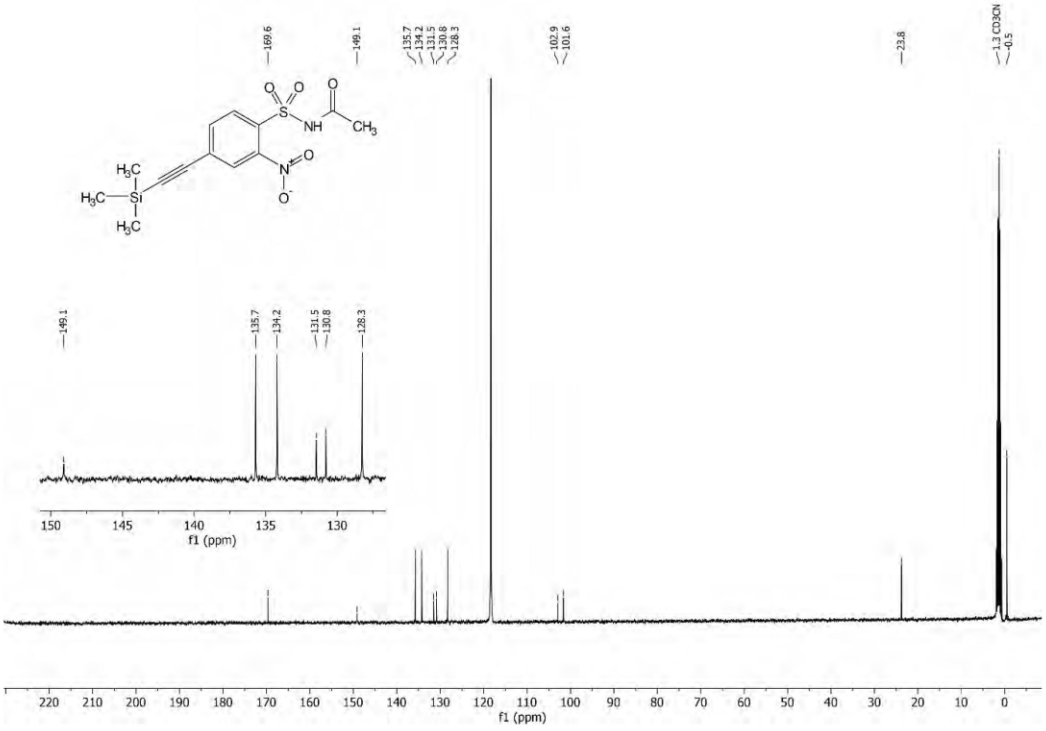
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6aa**



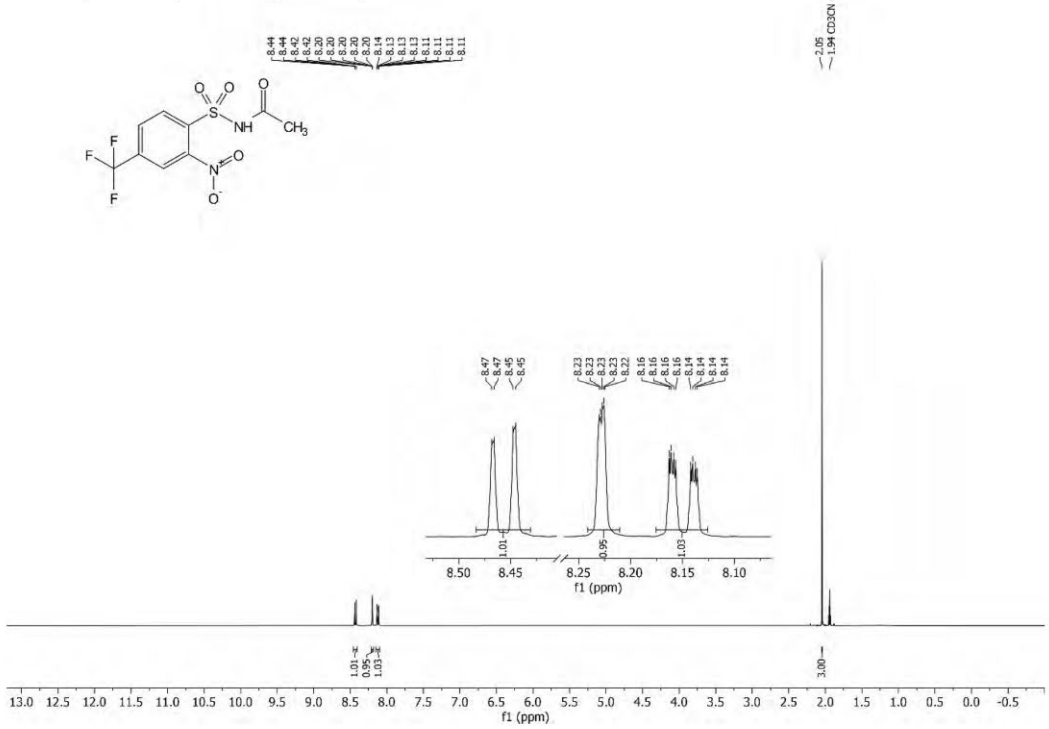
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6ab**



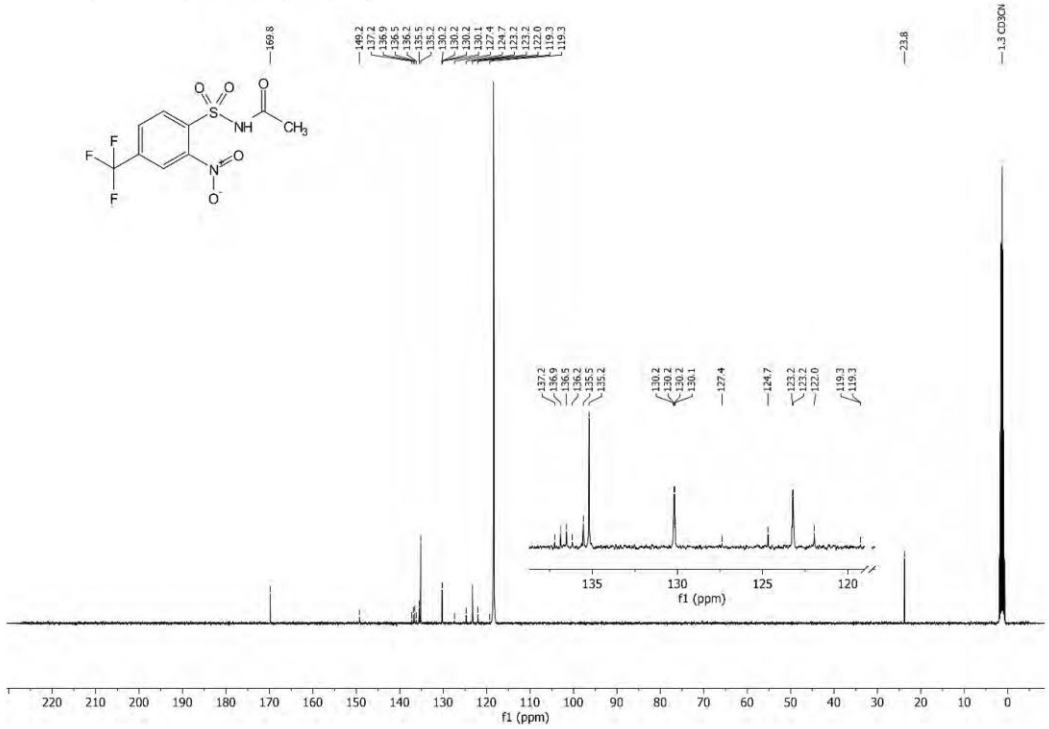
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6ab**



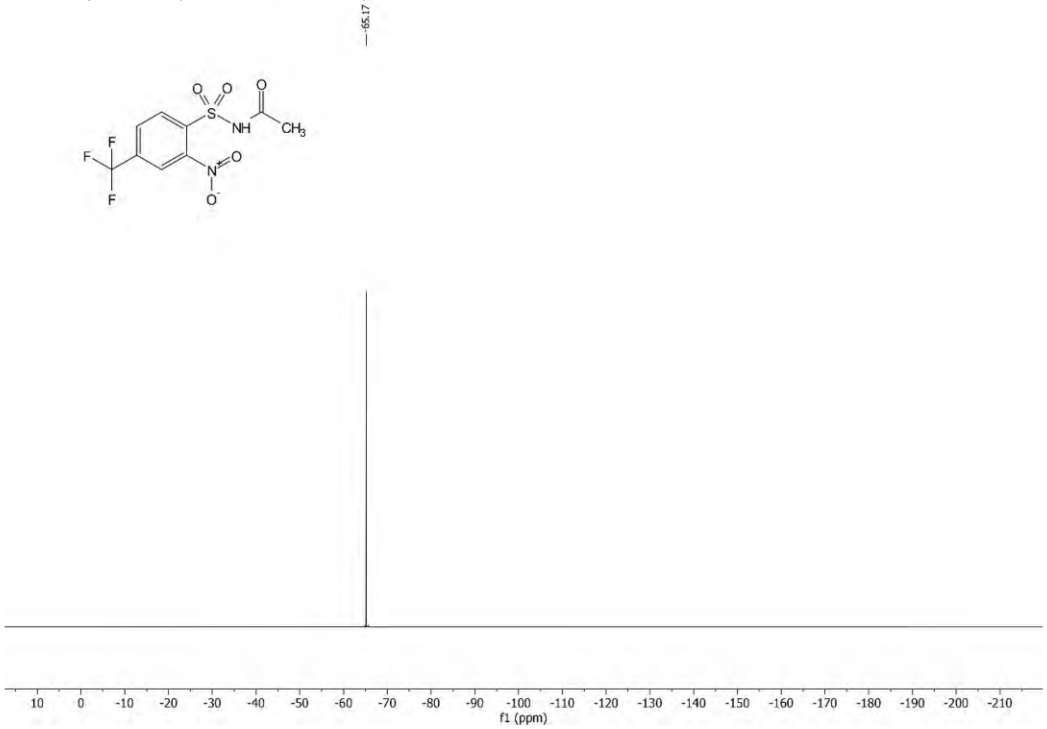
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6ac**



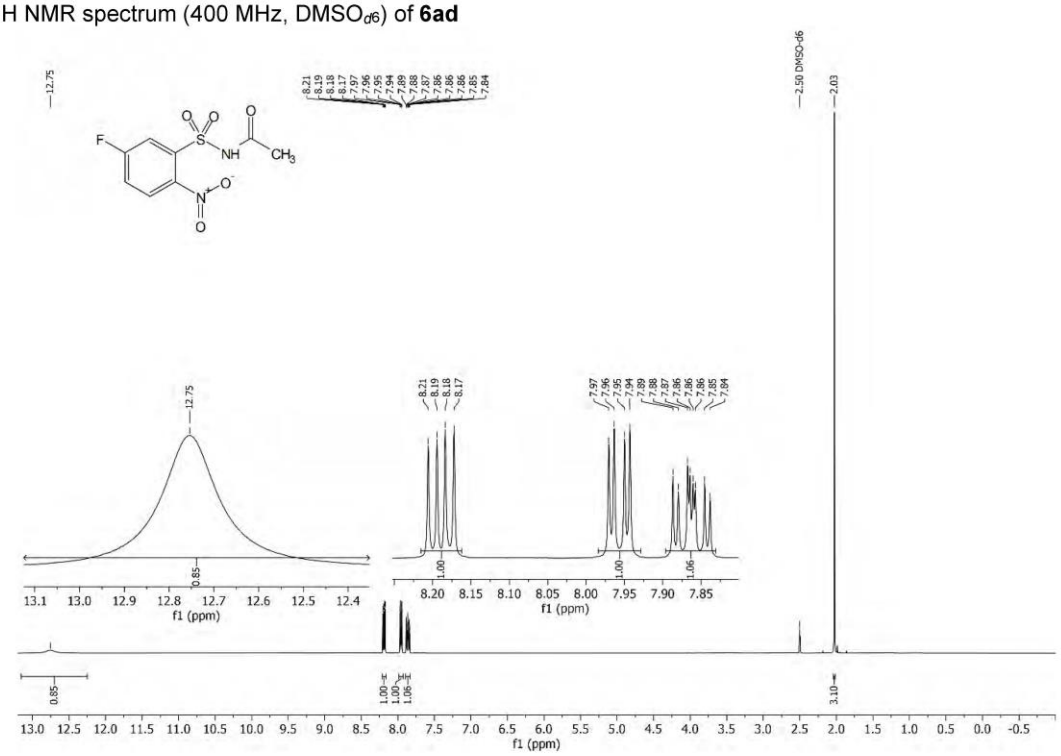
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6ac**



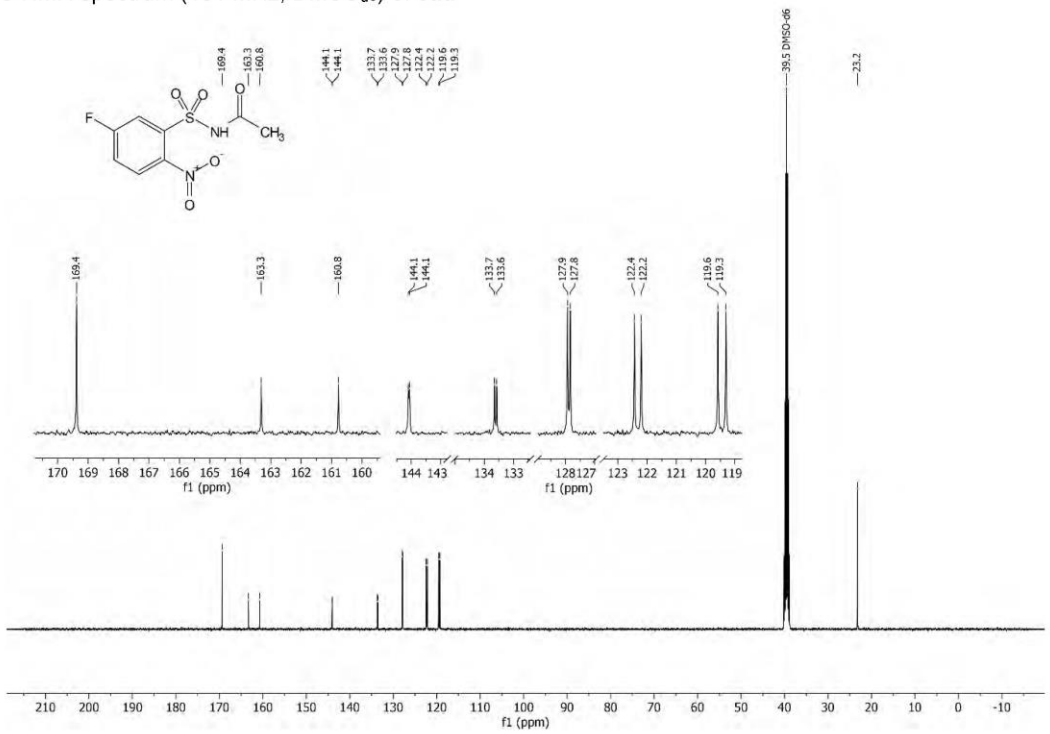
^{19}F NMR spectrum (376 MHz, CD_3CN) of **6ac**



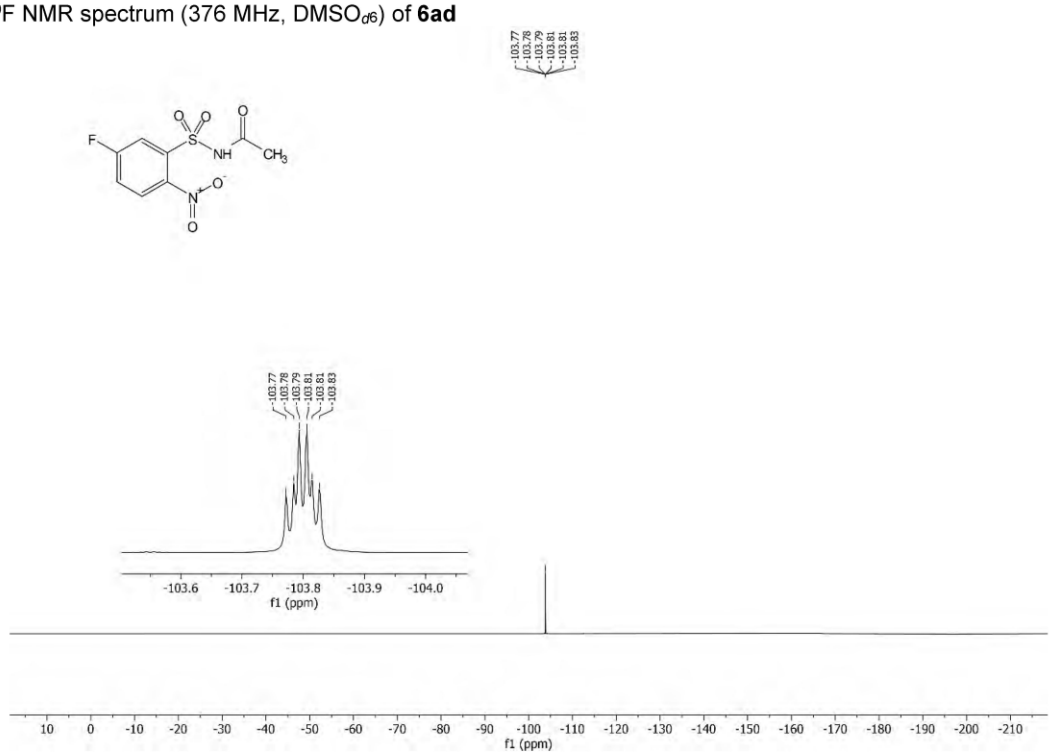
^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **6ad**



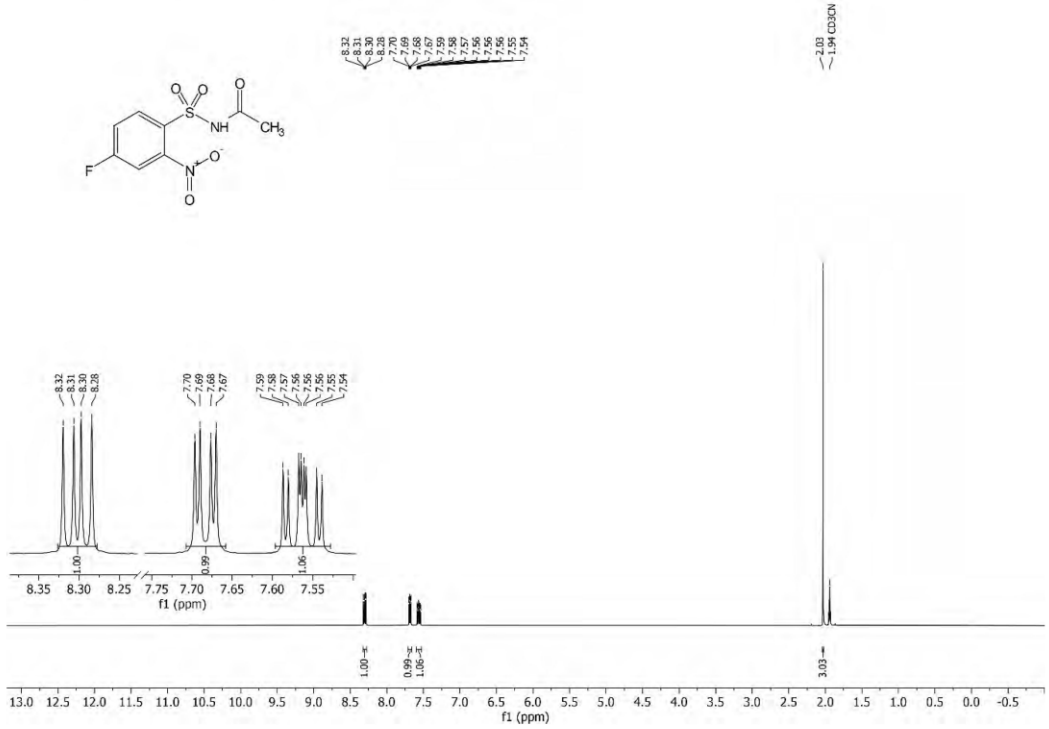
^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **6ad**



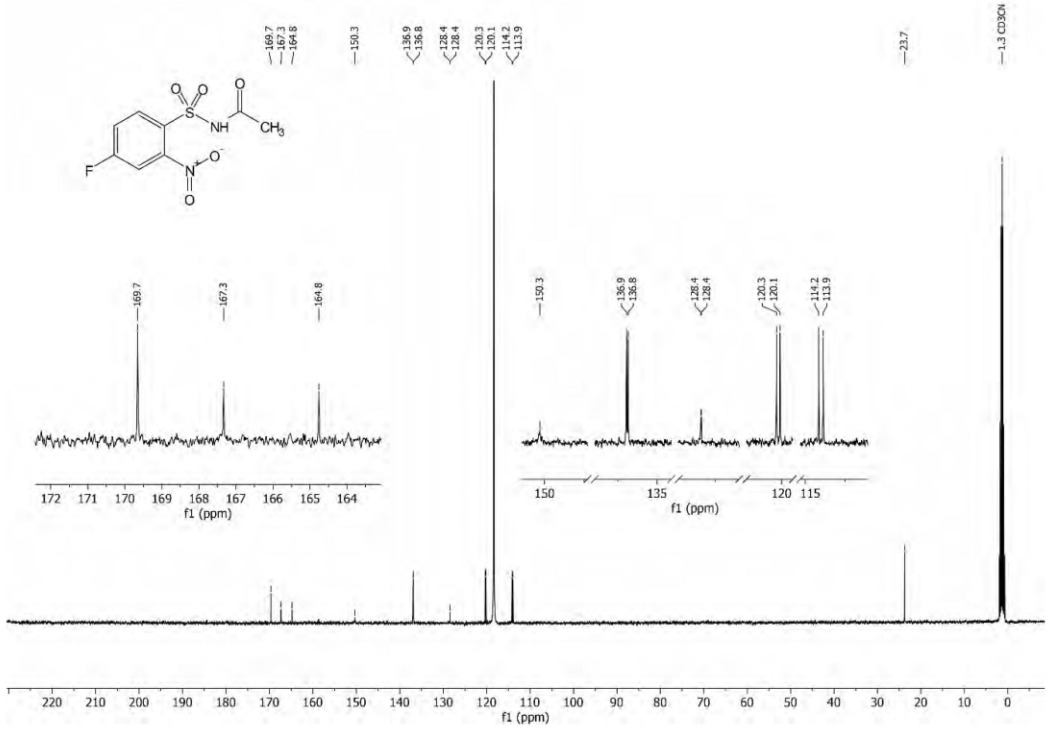
^{19}F NMR spectrum (376 MHz, $DMSO_{d6}$) of **6ad**



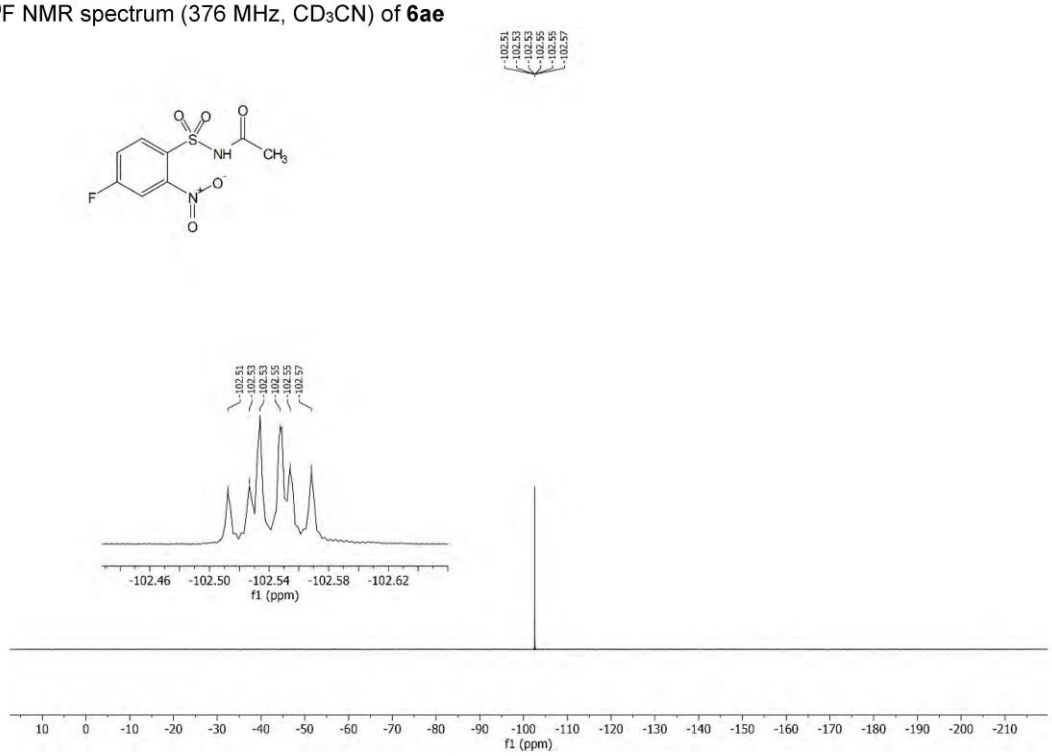
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6ae**



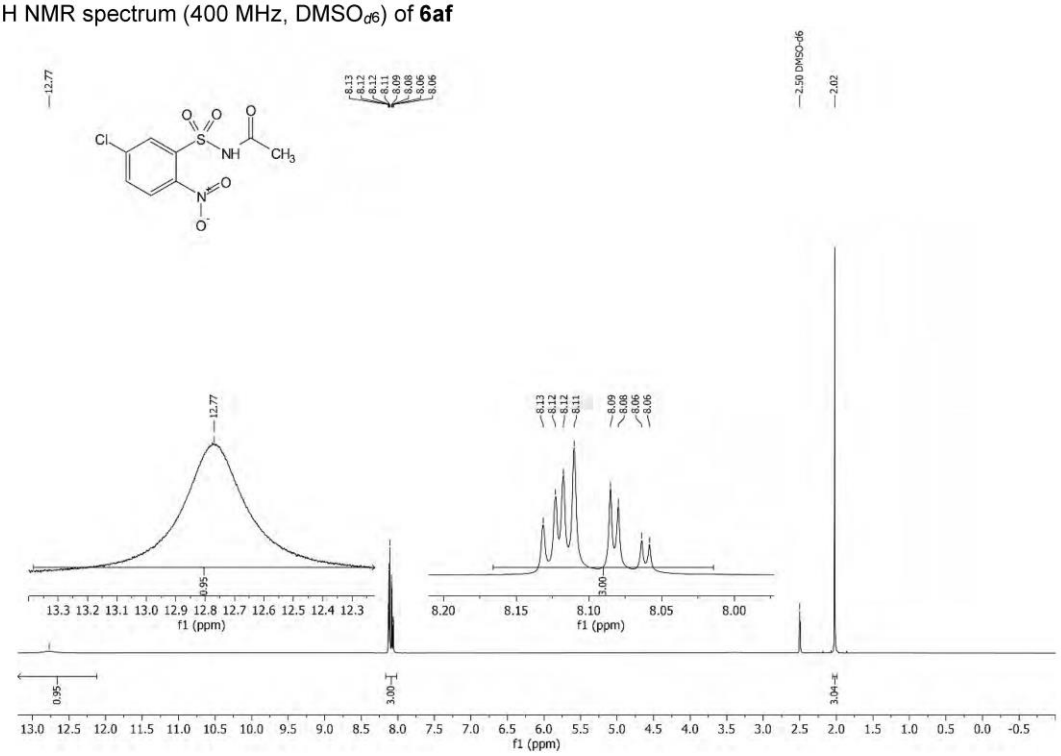
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6ae**



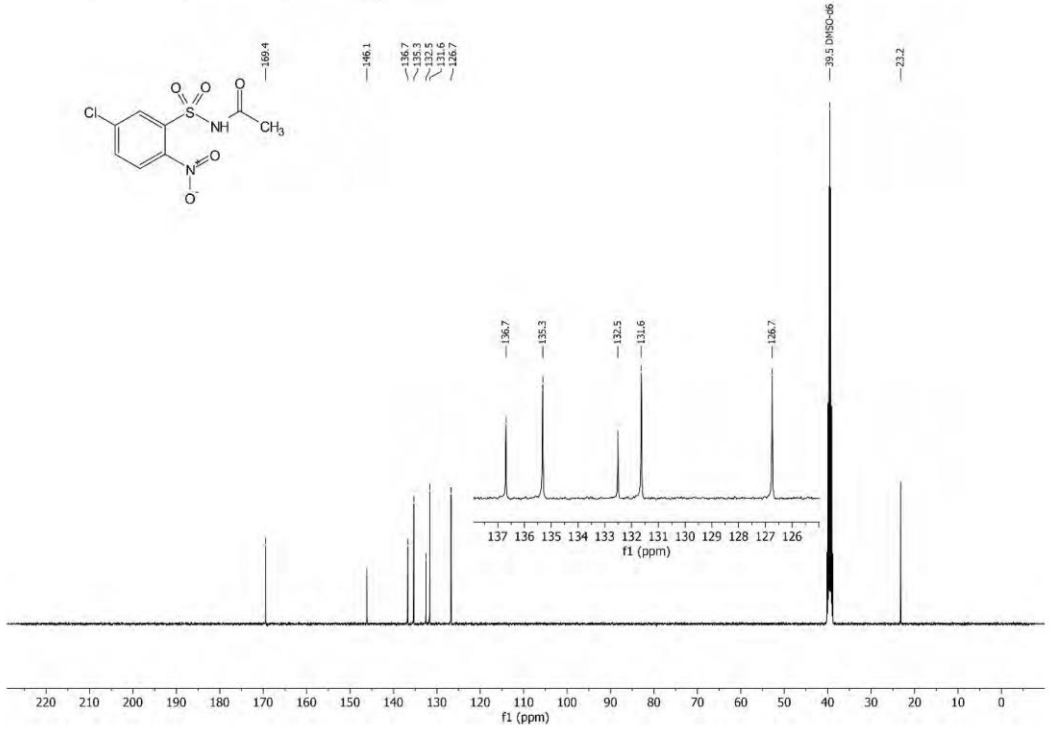
^{19}F NMR spectrum (376 MHz, CD_3CN) of **6ae**



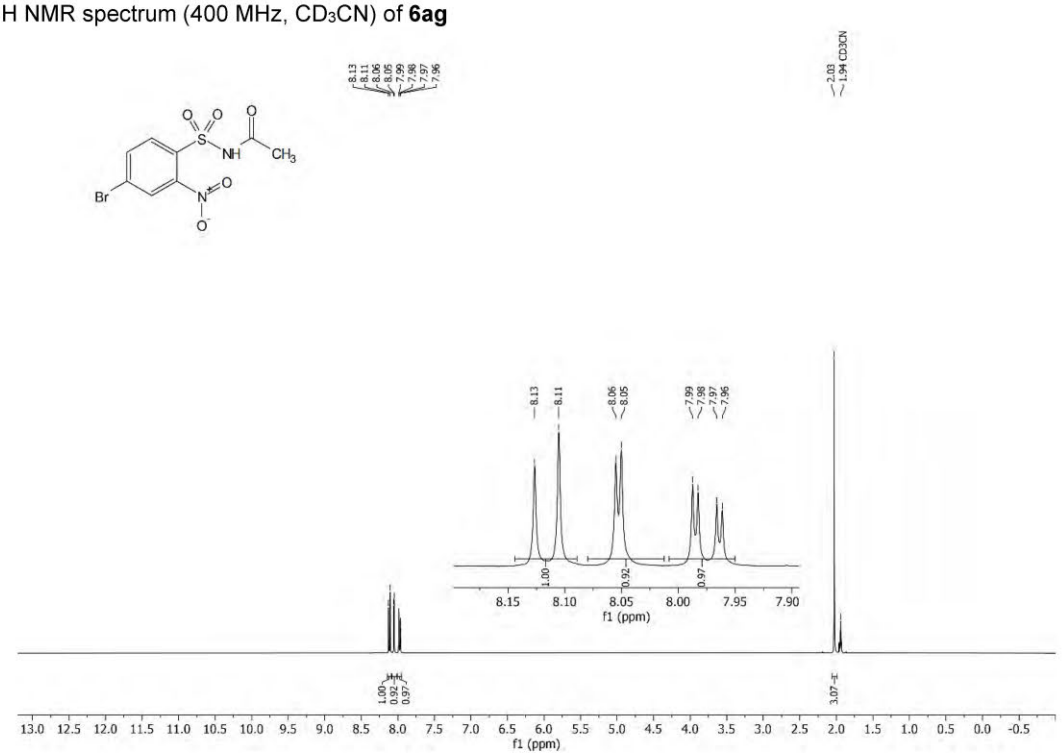
^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **6af**



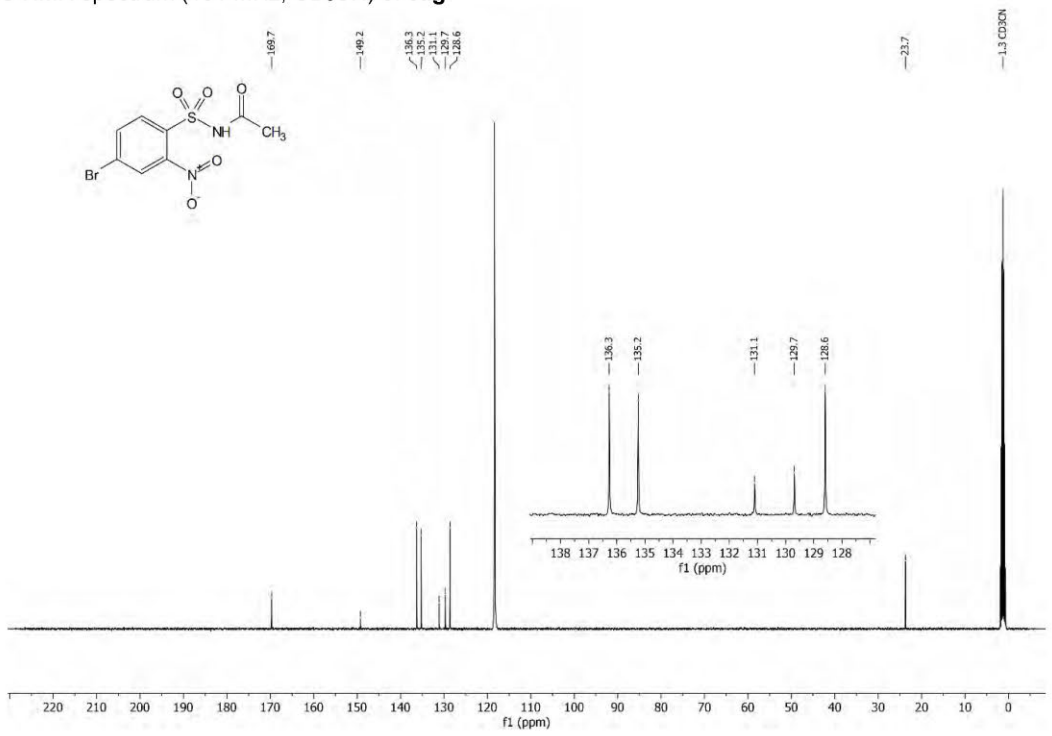
^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **6af**



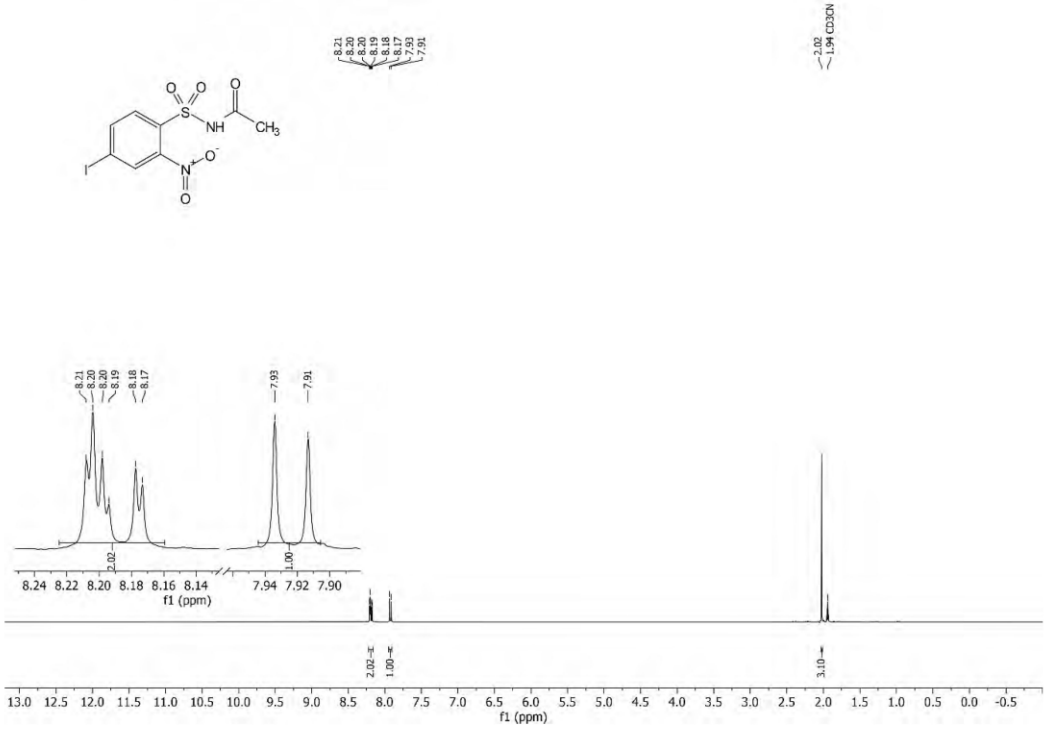
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6ag**



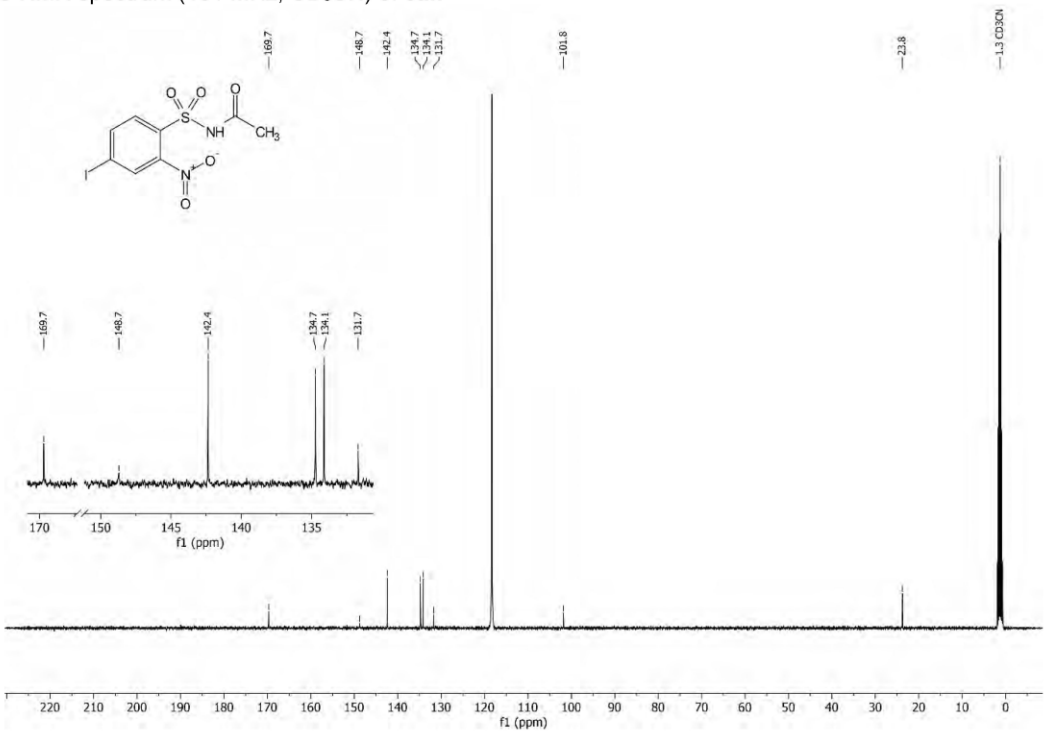
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6ag**



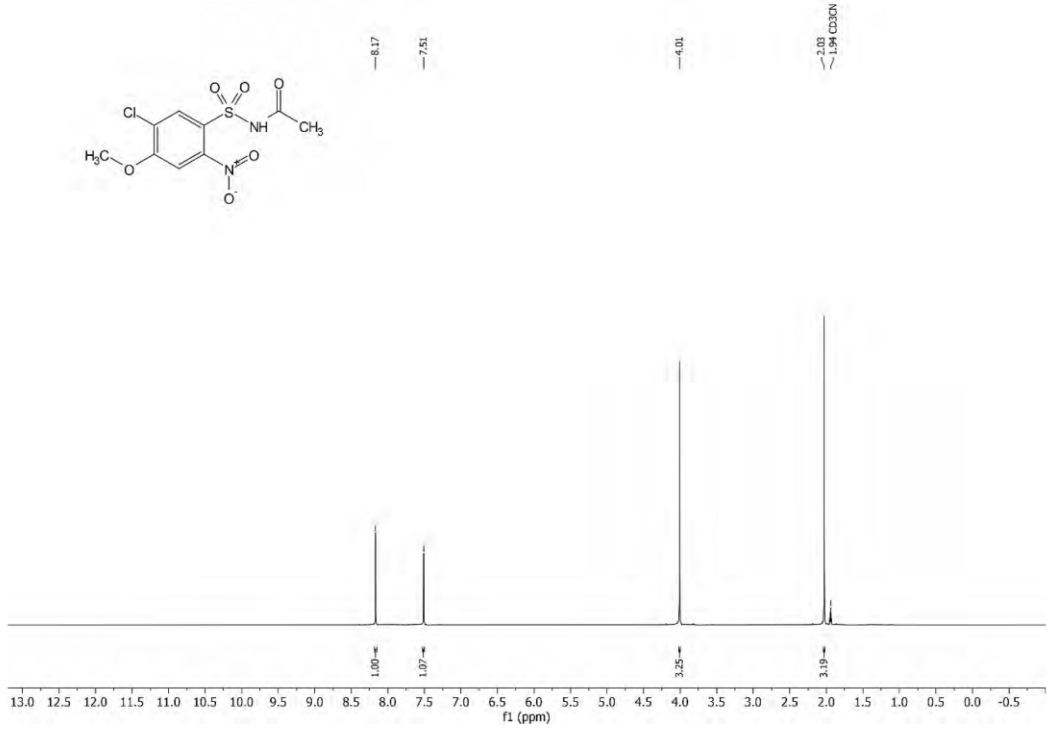
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6ah**



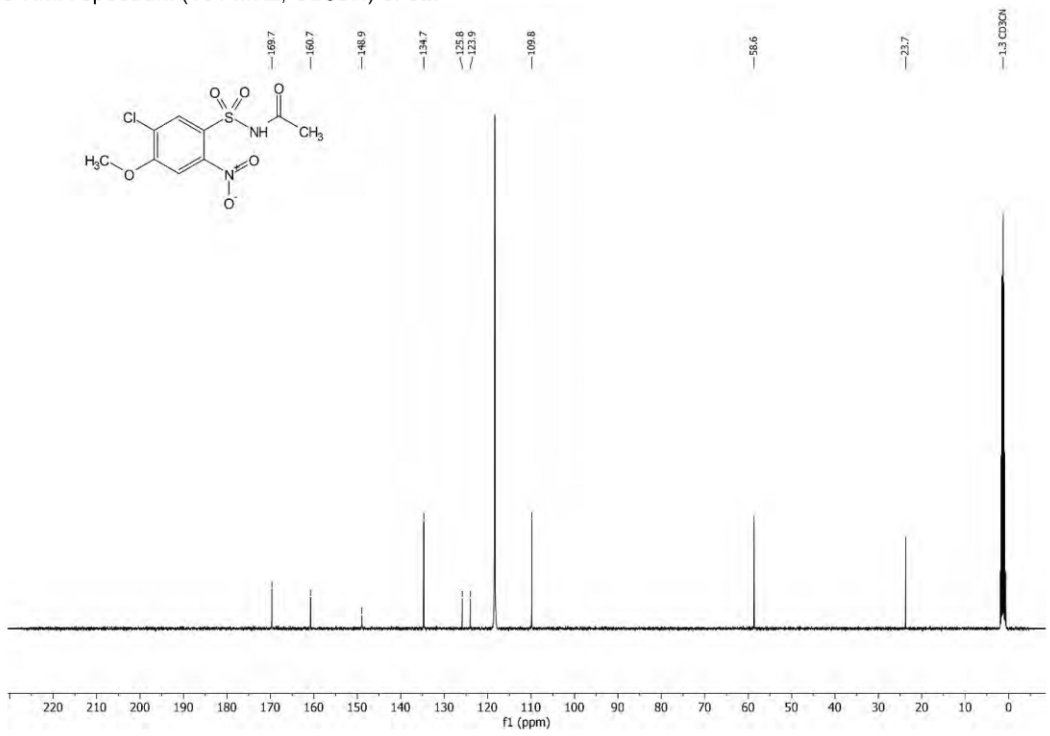
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6ah**



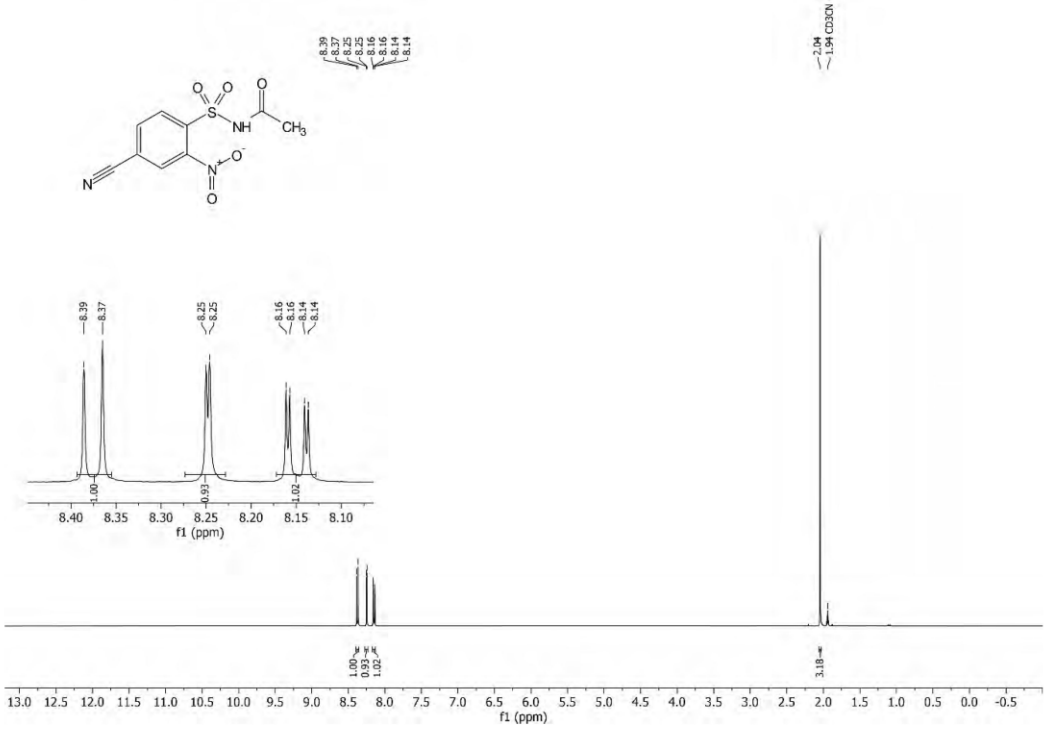
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6ai**



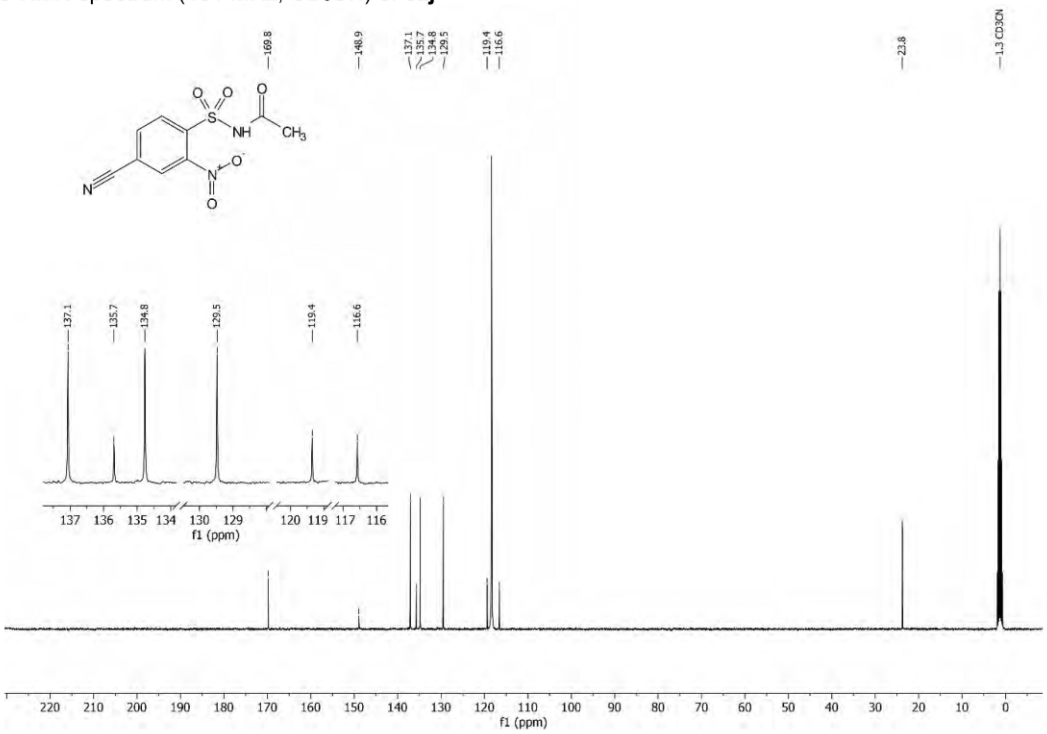
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6ai**



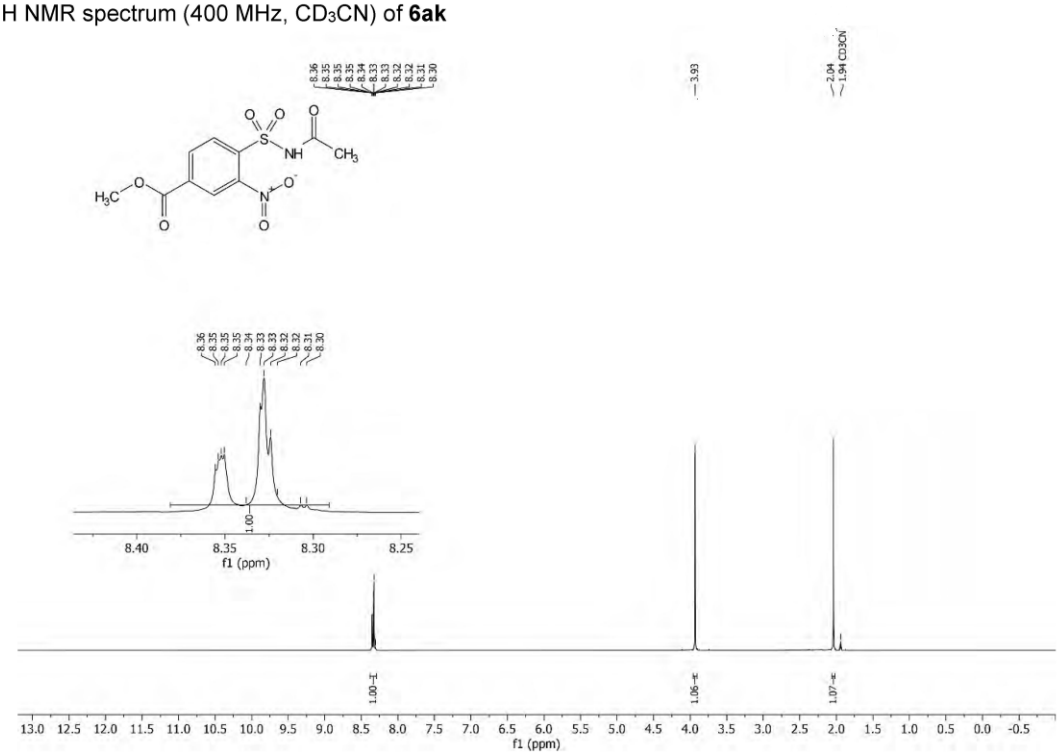
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6aj**



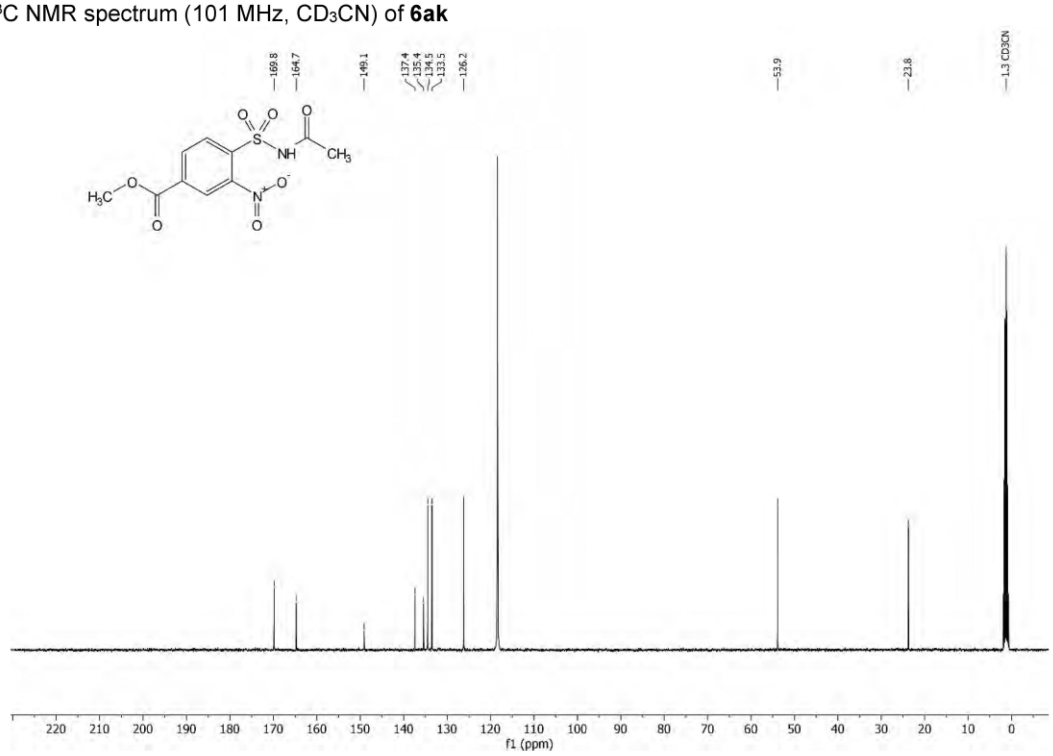
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6aj**



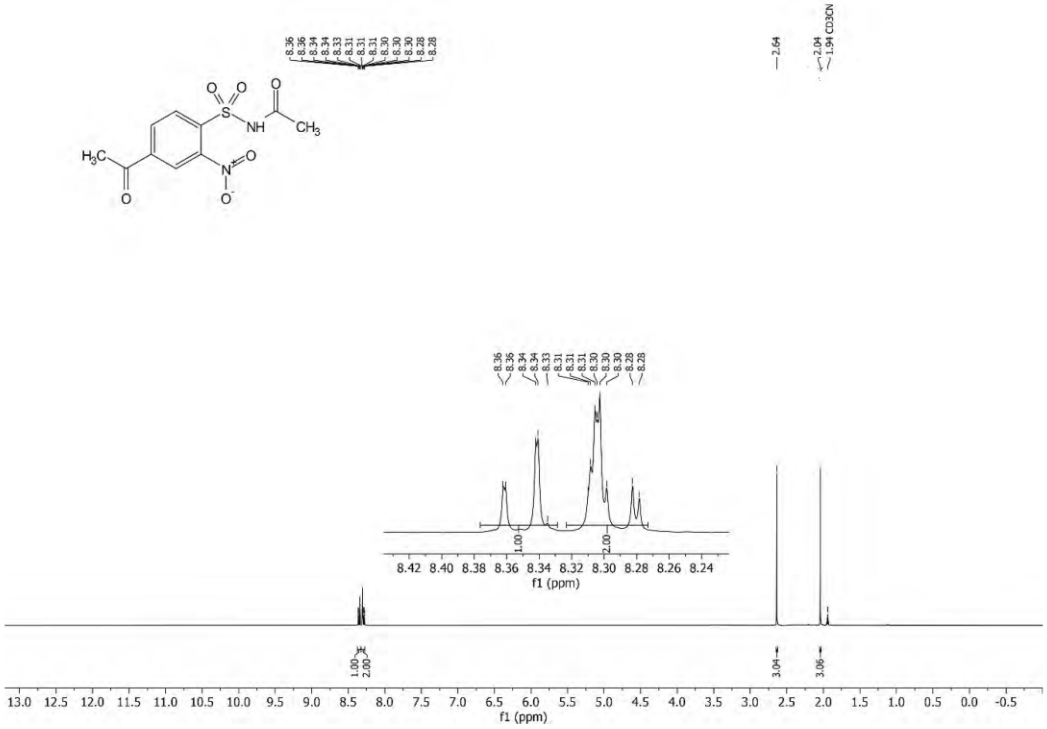
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6ak**



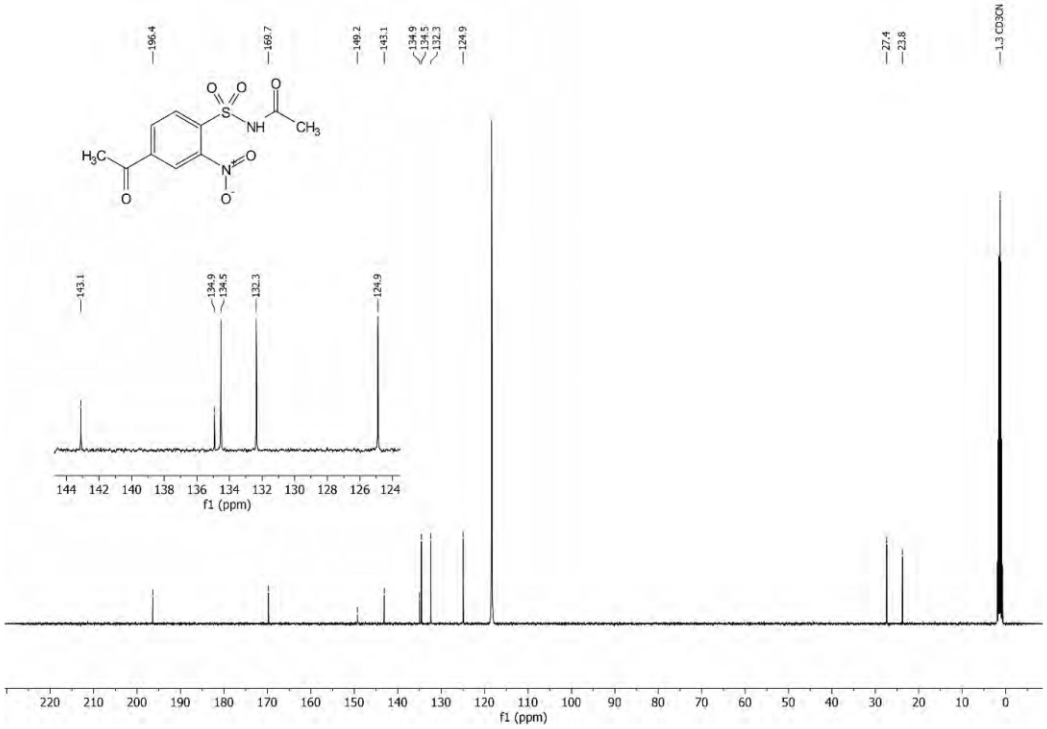
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6ak**



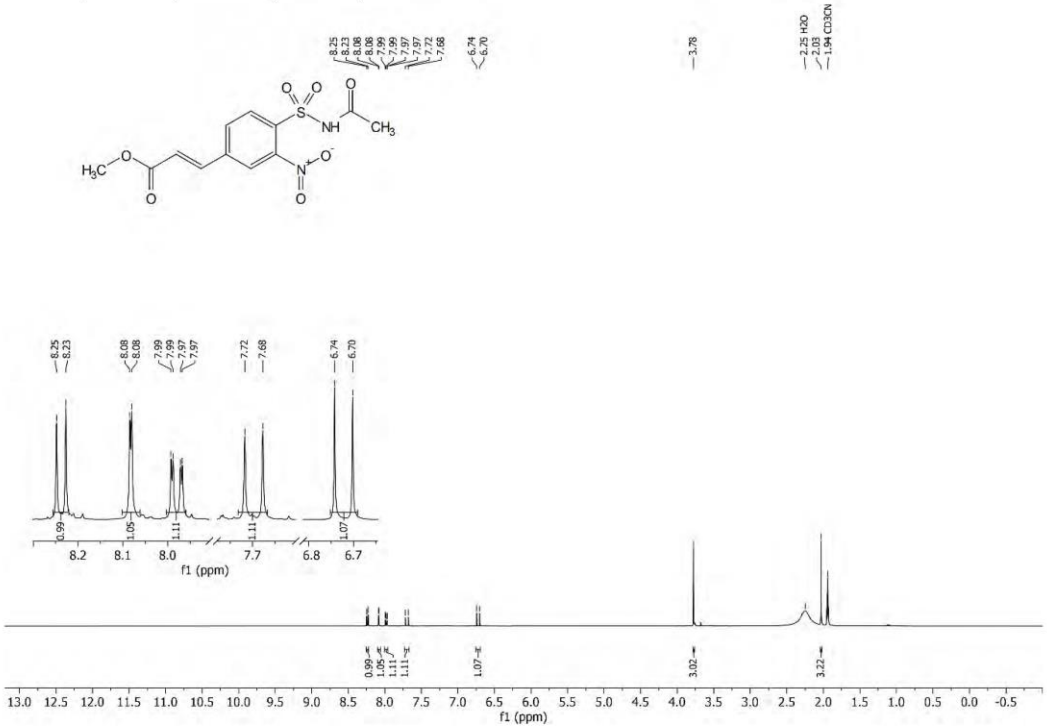
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6al**



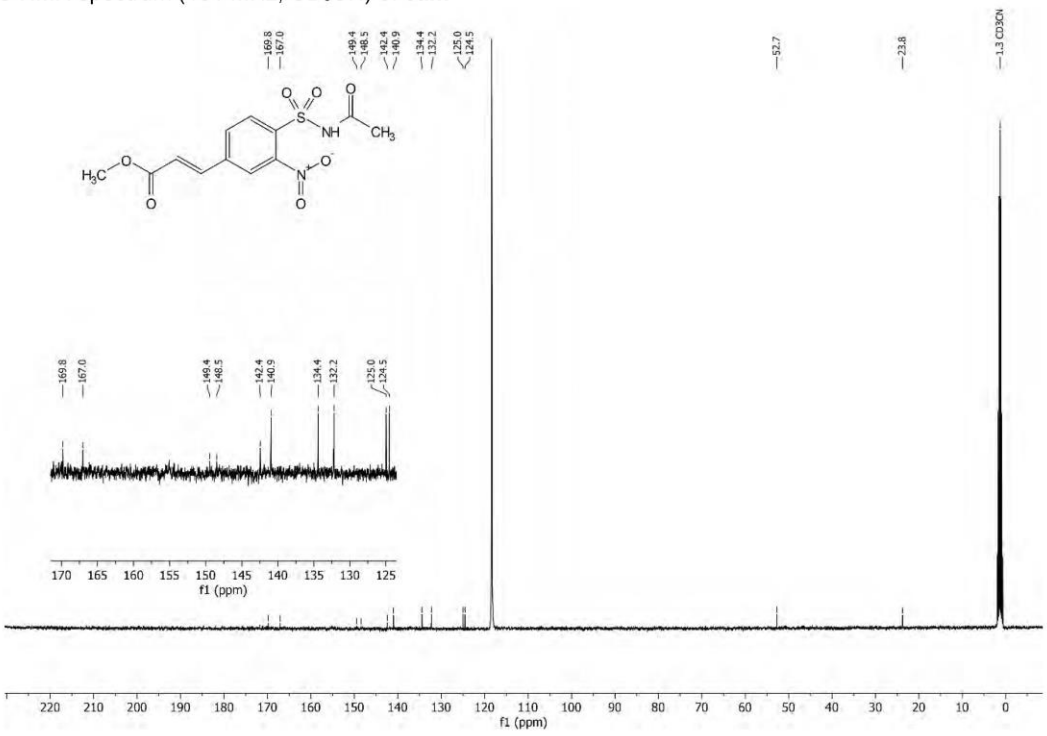
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6al**



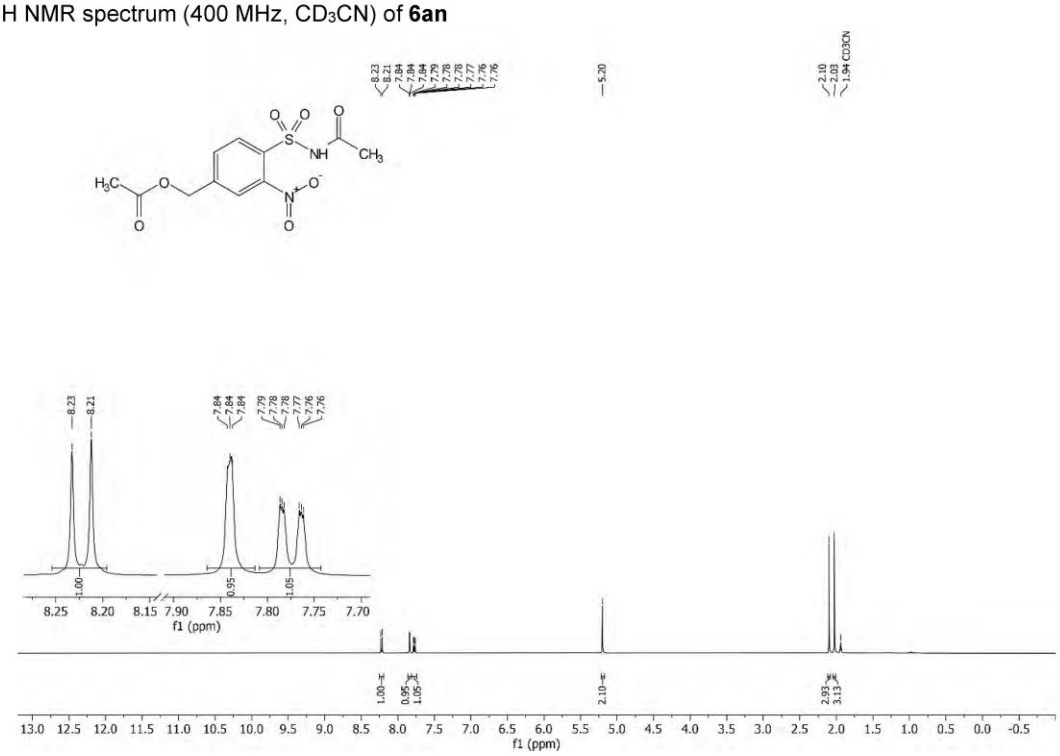
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6am**



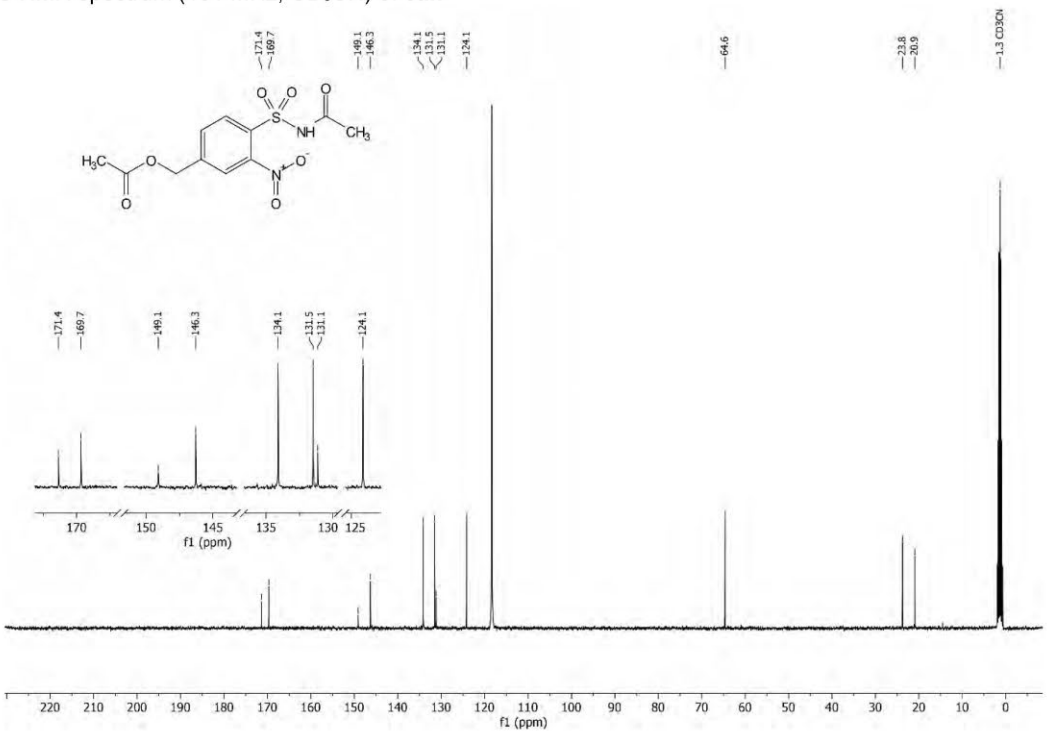
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6am**



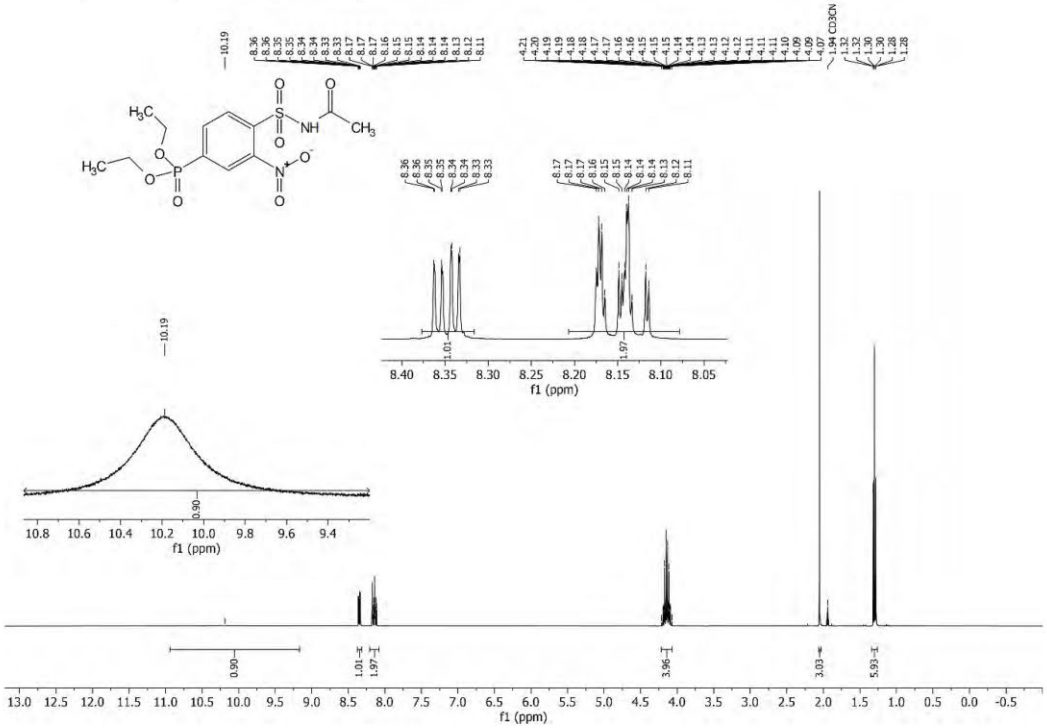
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6an**



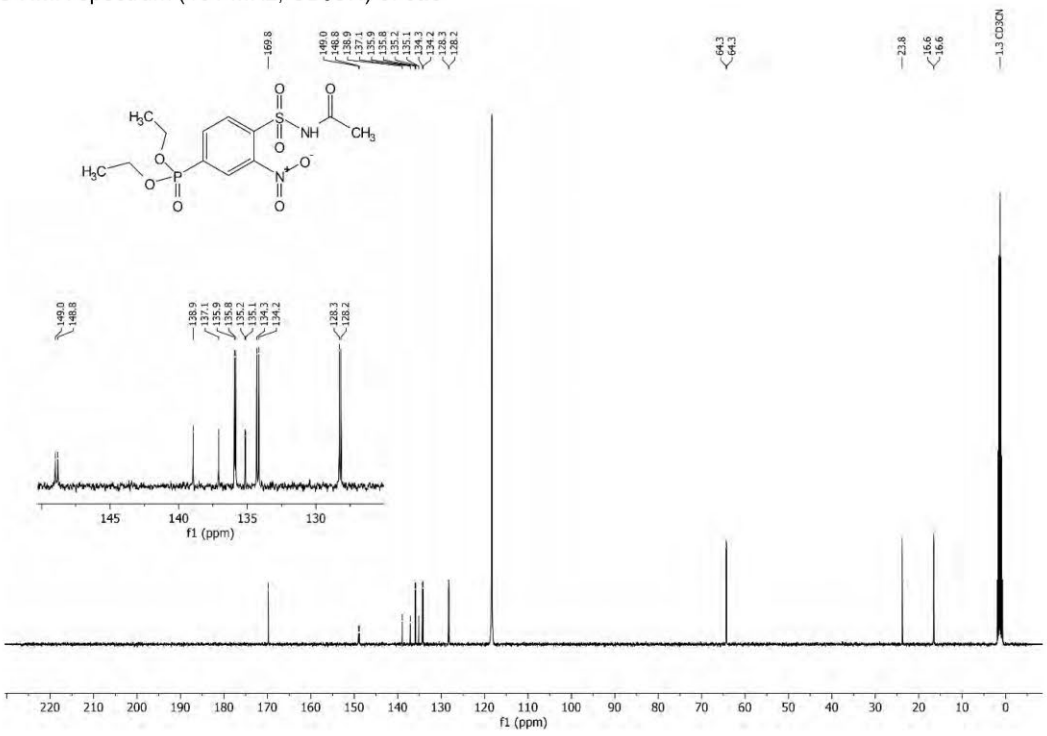
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6an**



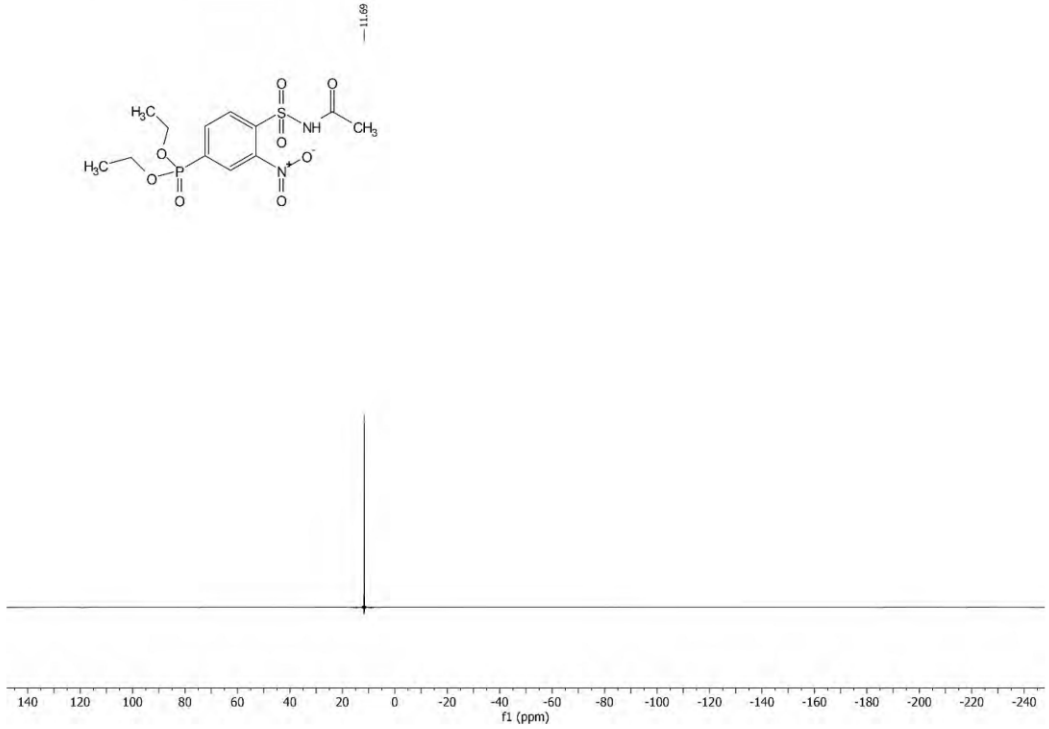
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6ao**



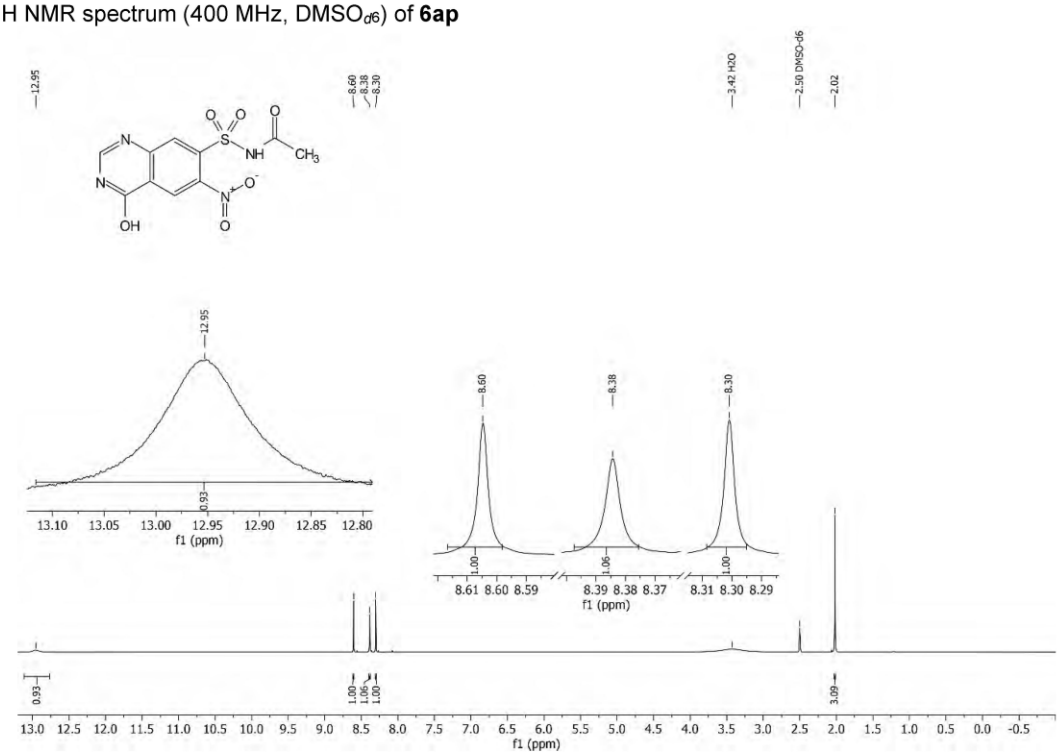
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6ao**



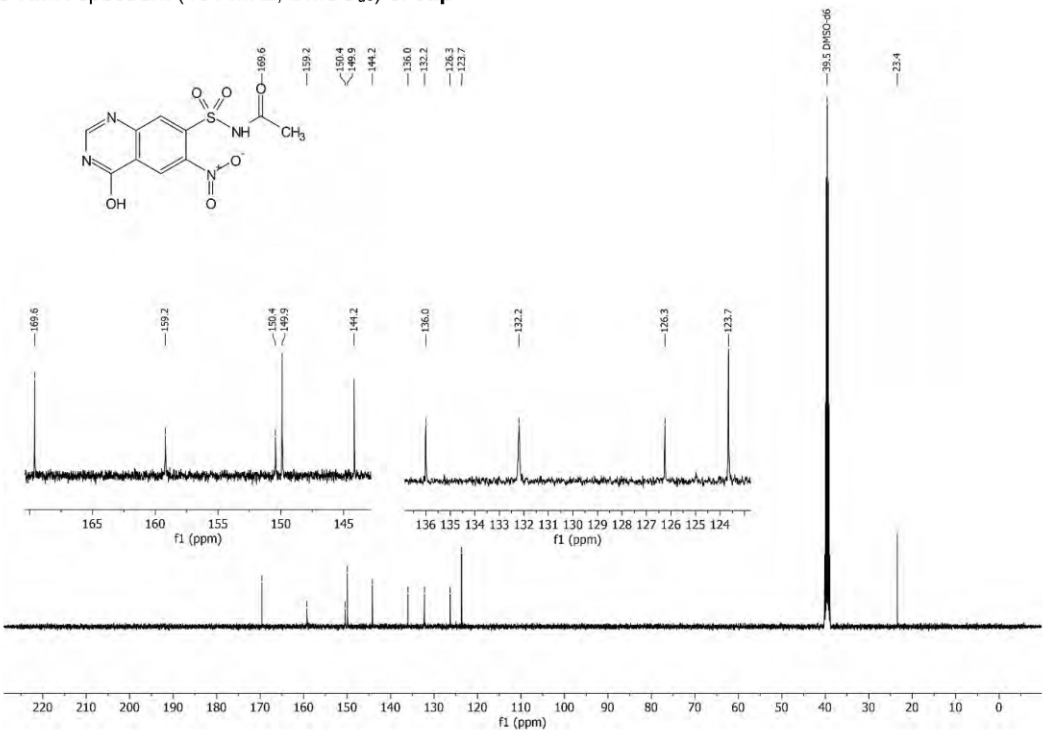
^{31}P NMR spectrum (162 MHz, CD_3CN) of **6ao**



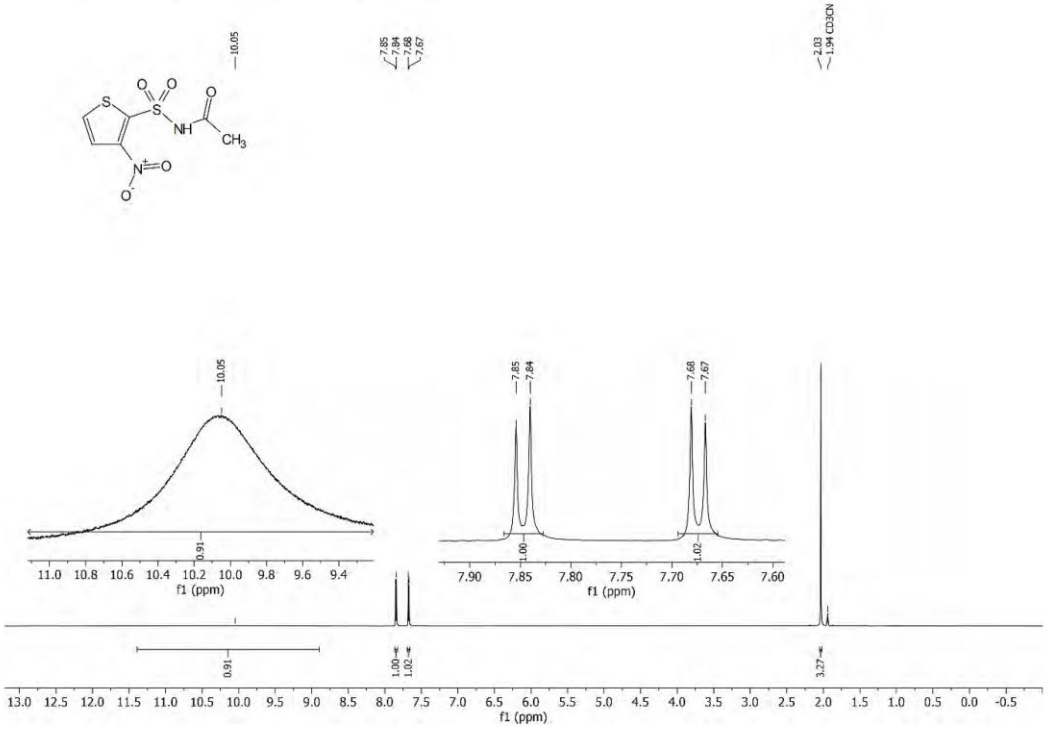
^{1}H NMR spectrum (400 MHz, DMSO$_{d6}$) of **6ap**



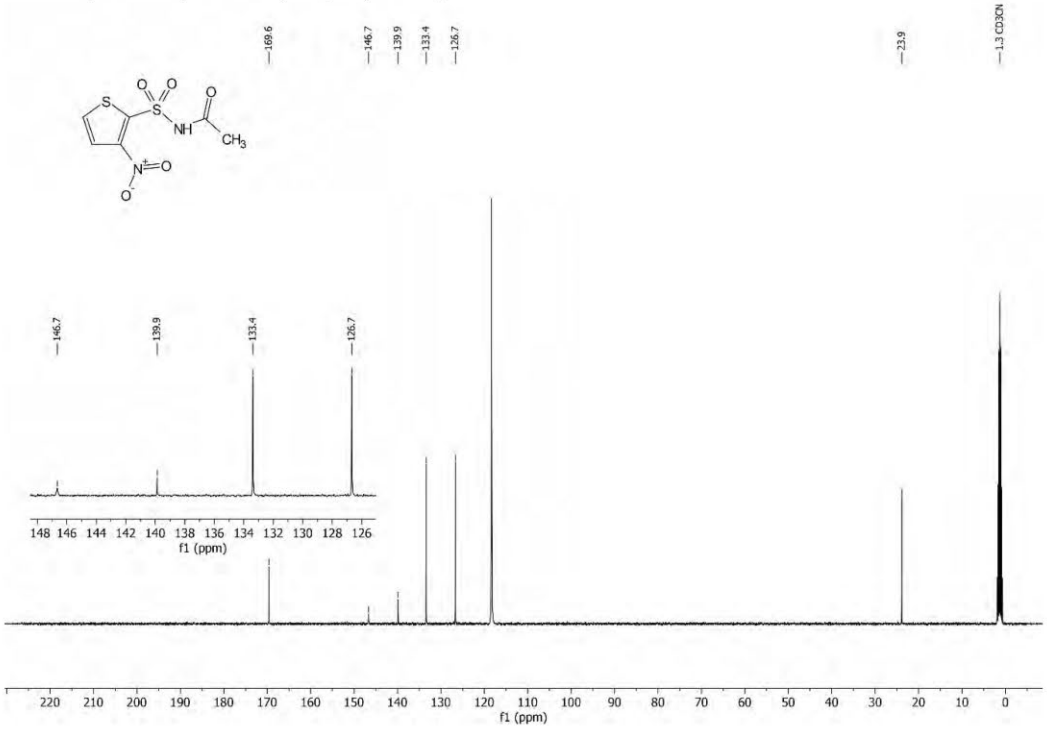
^{13}C NMR spectrum (101 MHz, DMSO$_{d6}$) of **6ap**



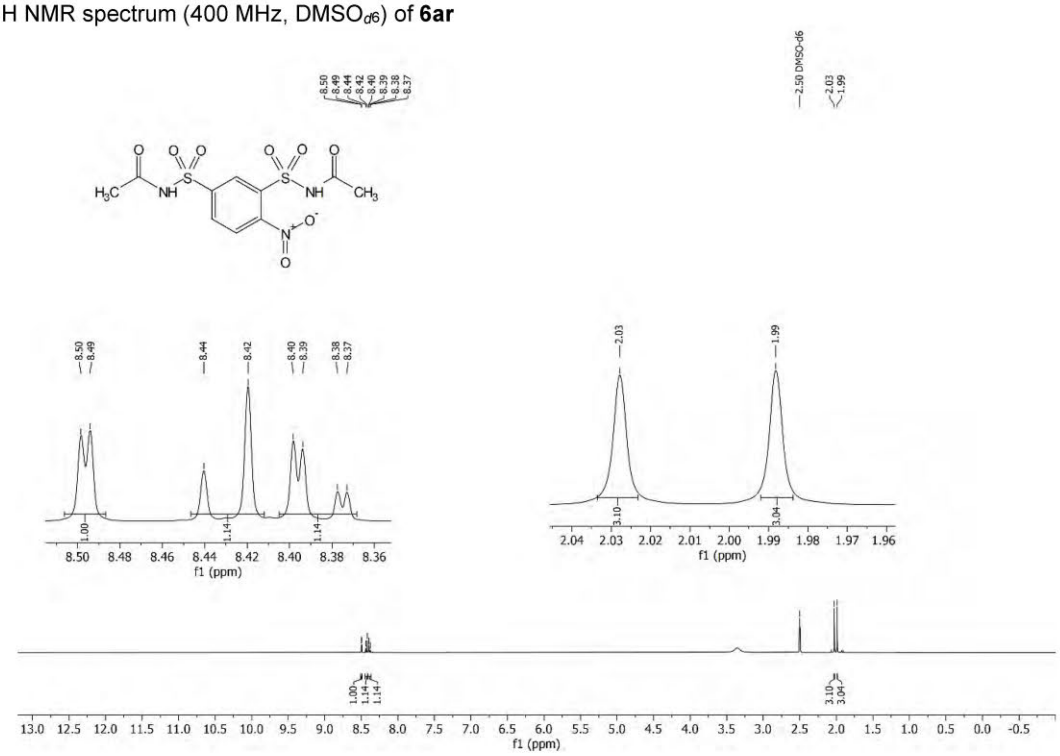
^{1}H NMR spectrum (400 MHz, CD_3CN) of **6aq**



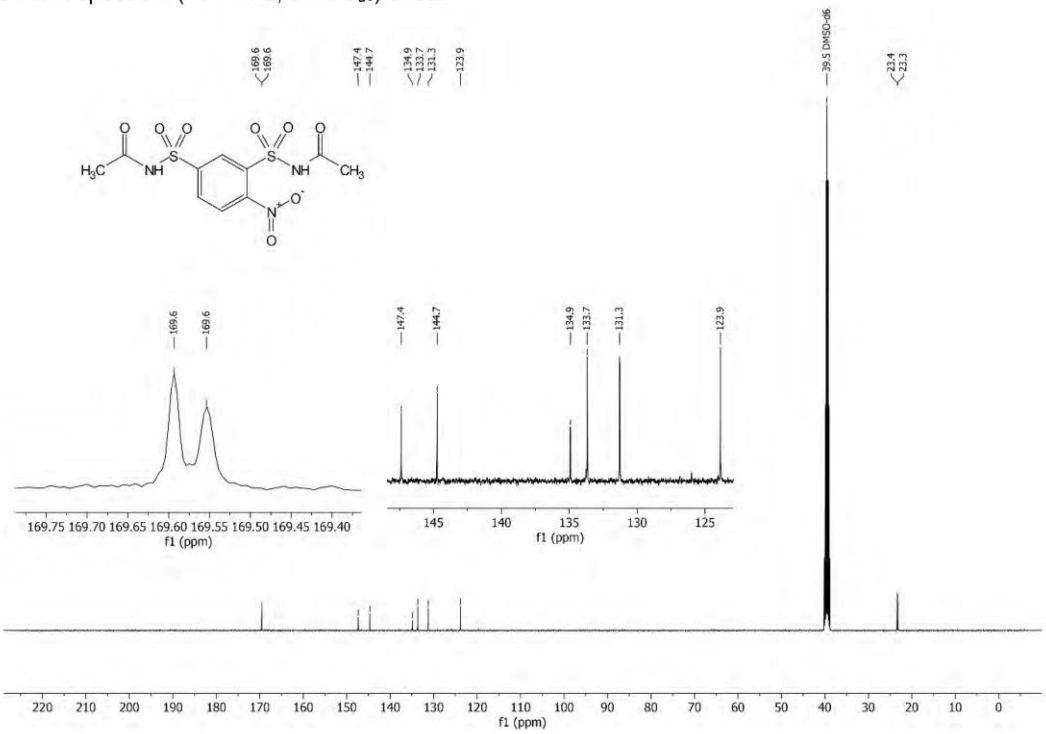
^{13}C NMR spectrum (101 MHz, CD_3CN) of **6aq**



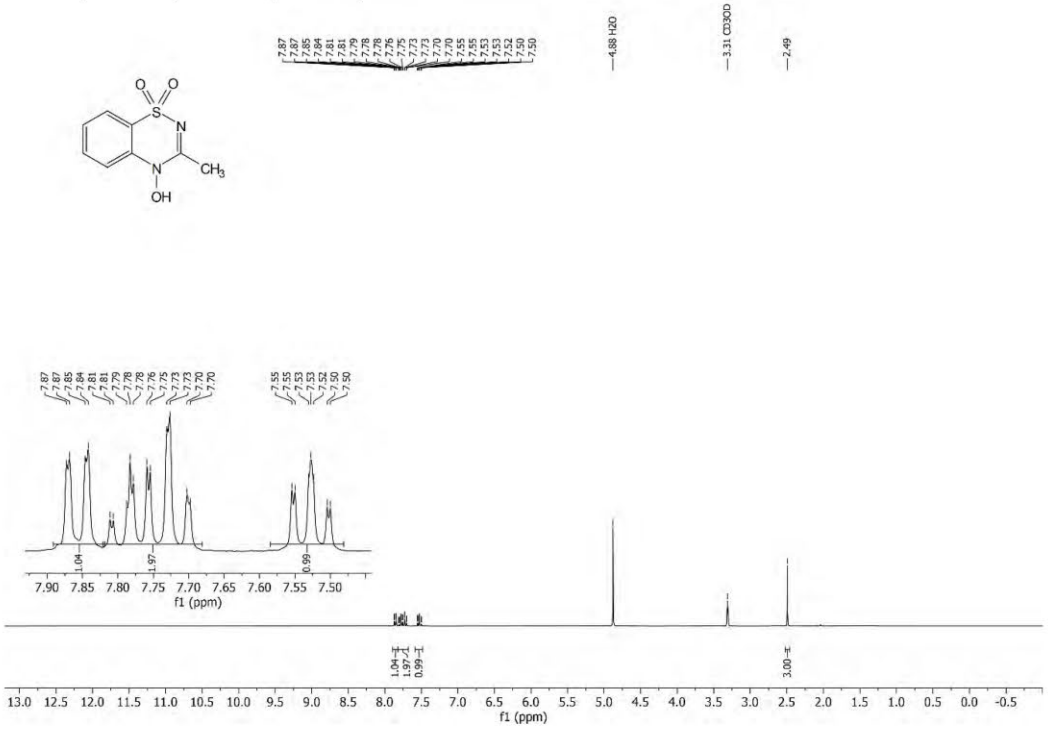
^{1}H NMR spectrum (400 MHz, DMSO$_{d6}$) of **6ar**



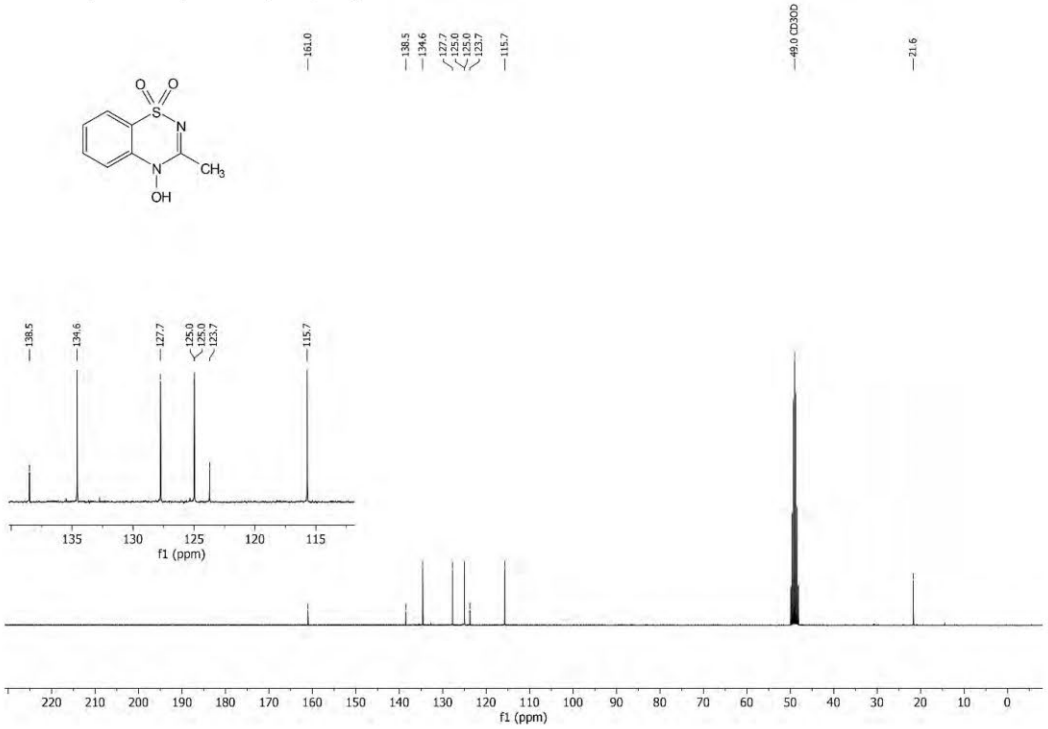
^{13}C NMR spectrum (101 MHz, DMSO$_{d6}$) of **6ar**



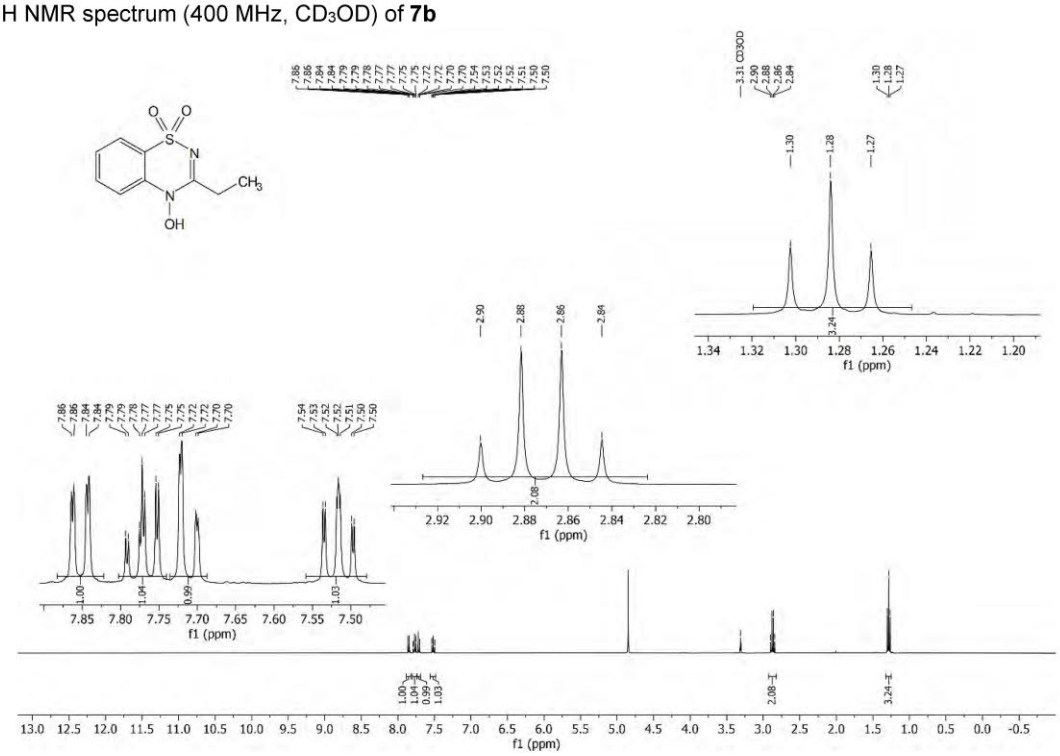
^{1}H NMR spectrum (300 MHz, CD_3OD) of **7a**



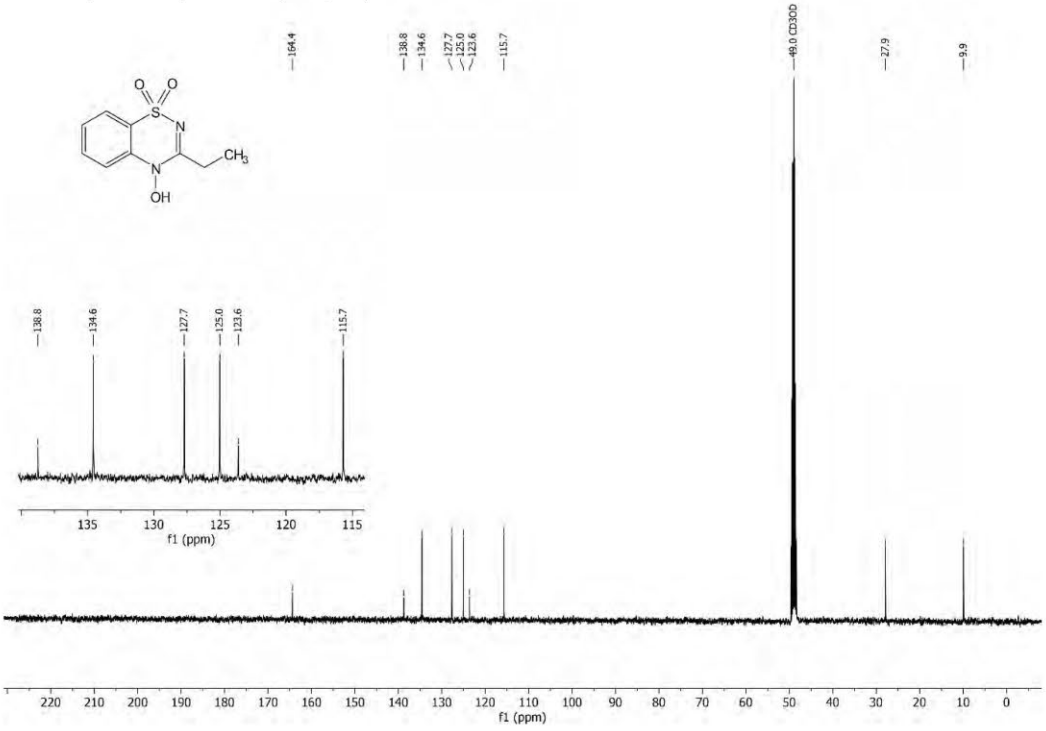
^{13}C NMR spectrum (75 MHz, CD_3OD) of **7a**



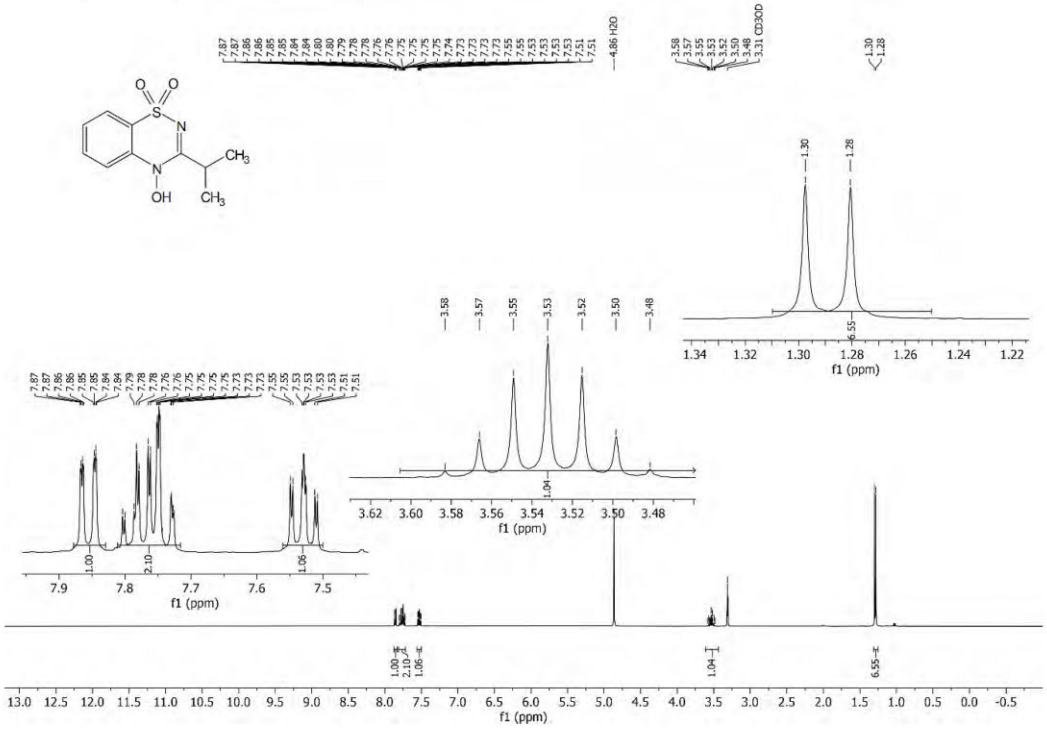
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7b**



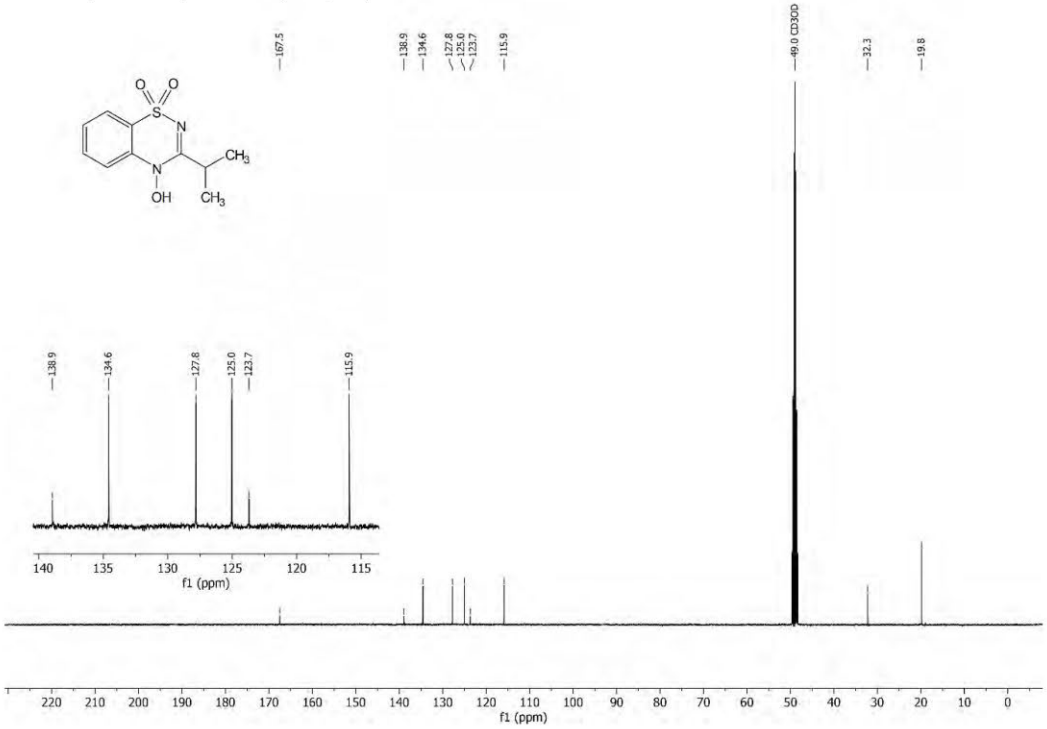
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7b**



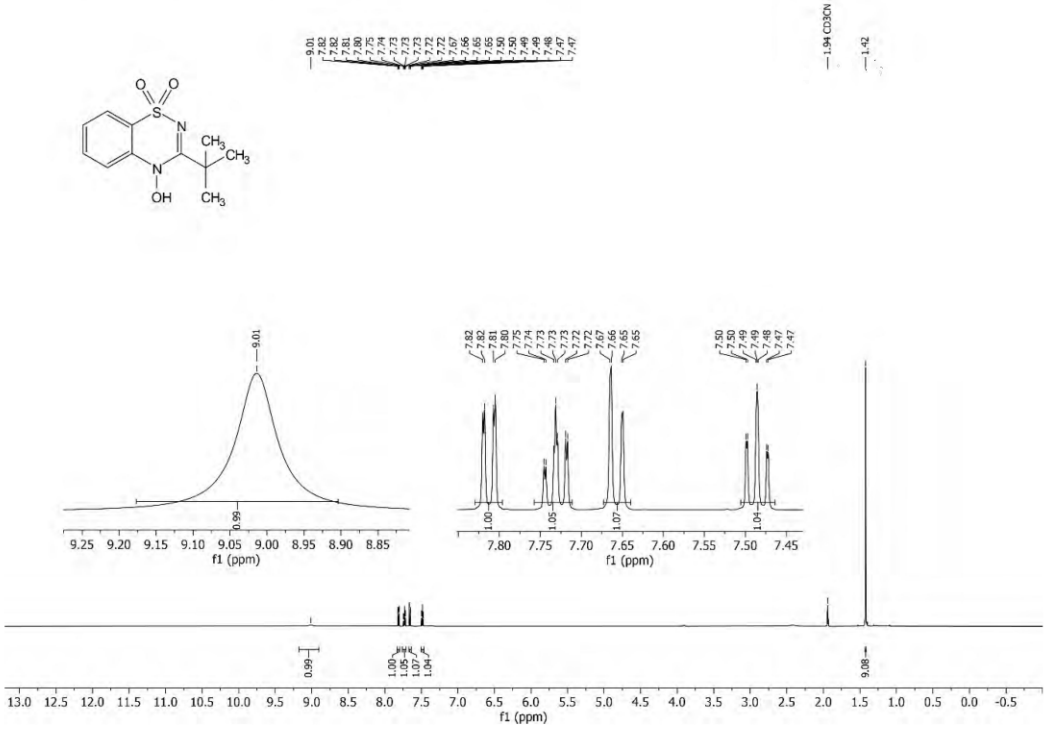
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7c**



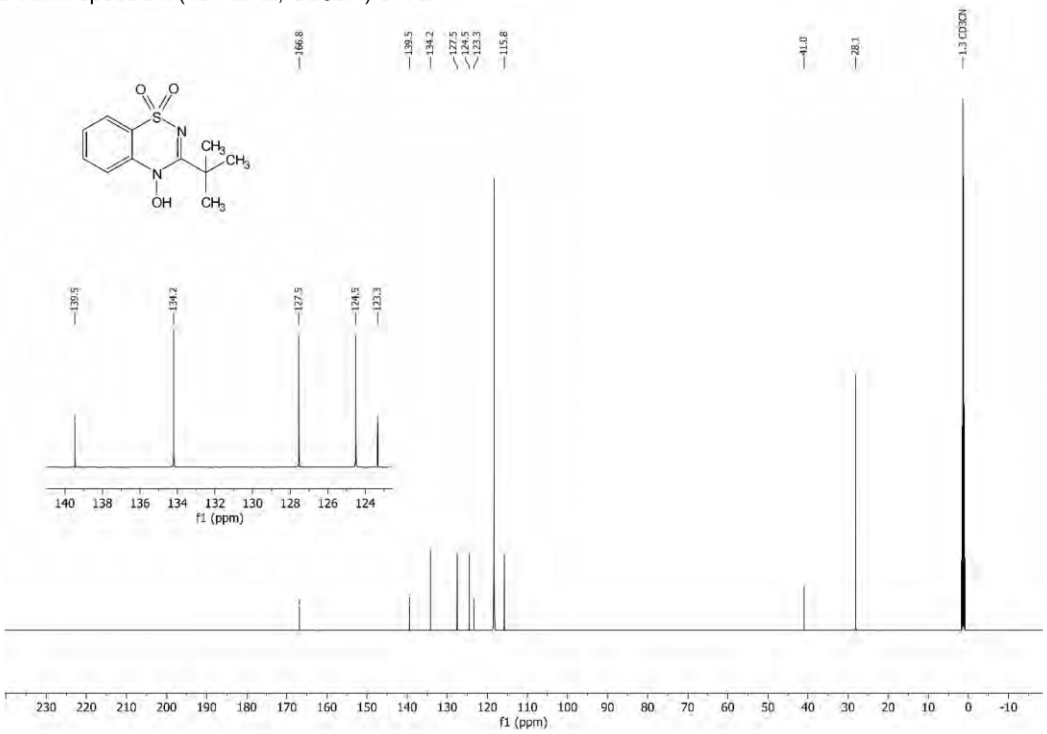
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7c**



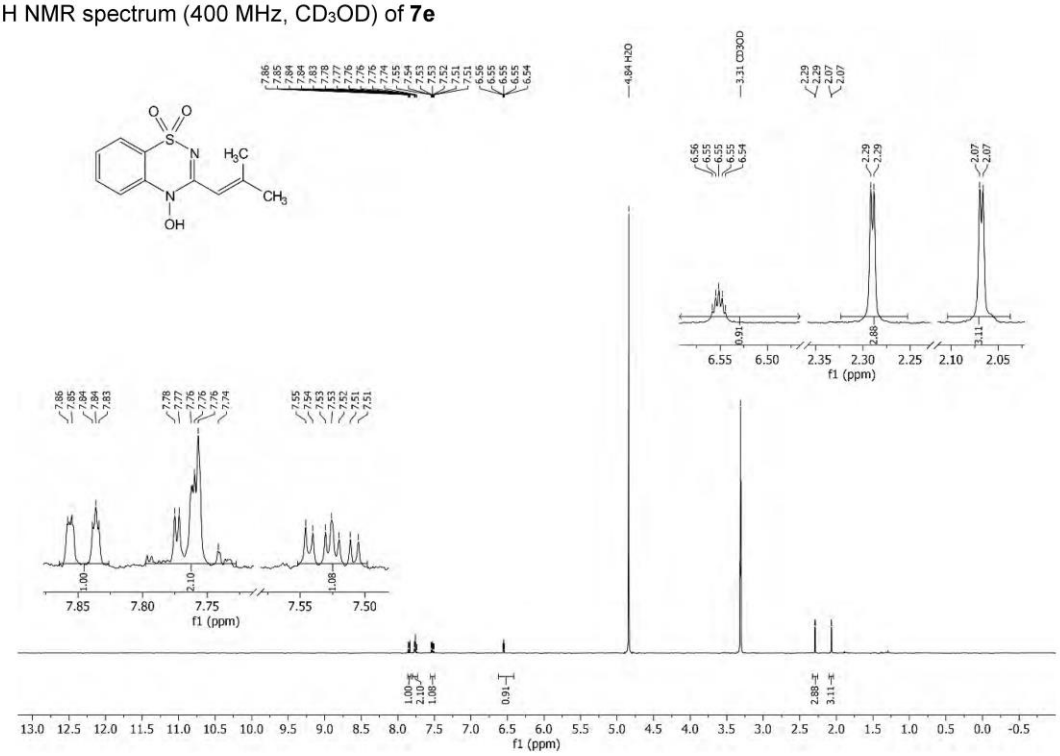
^{1}H NMR spectrum (400 MHz, CD_3CN) of **7d**



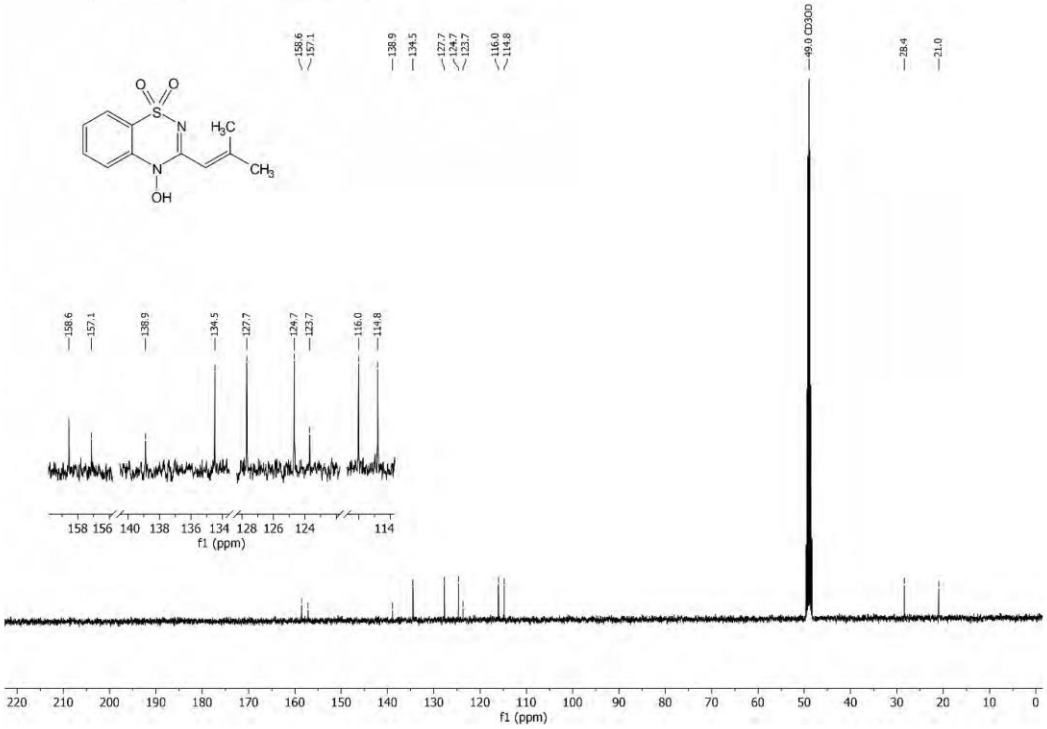
^{13}C NMR spectrum (101 MHz, CD_3CN) of **7d**



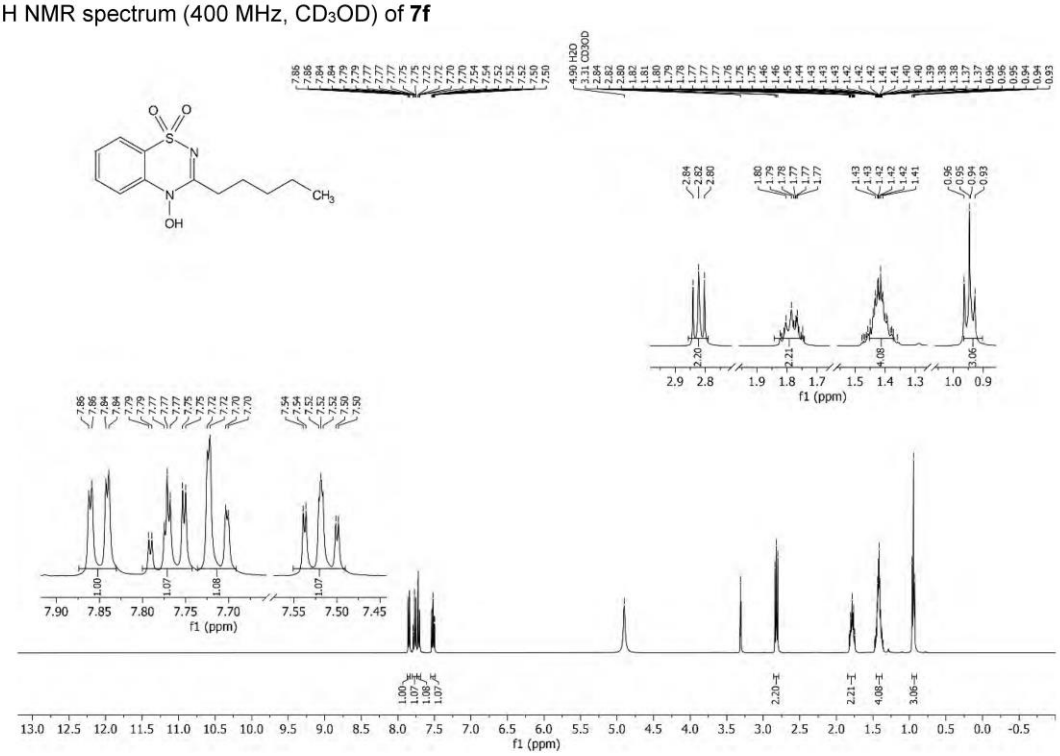
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7e**



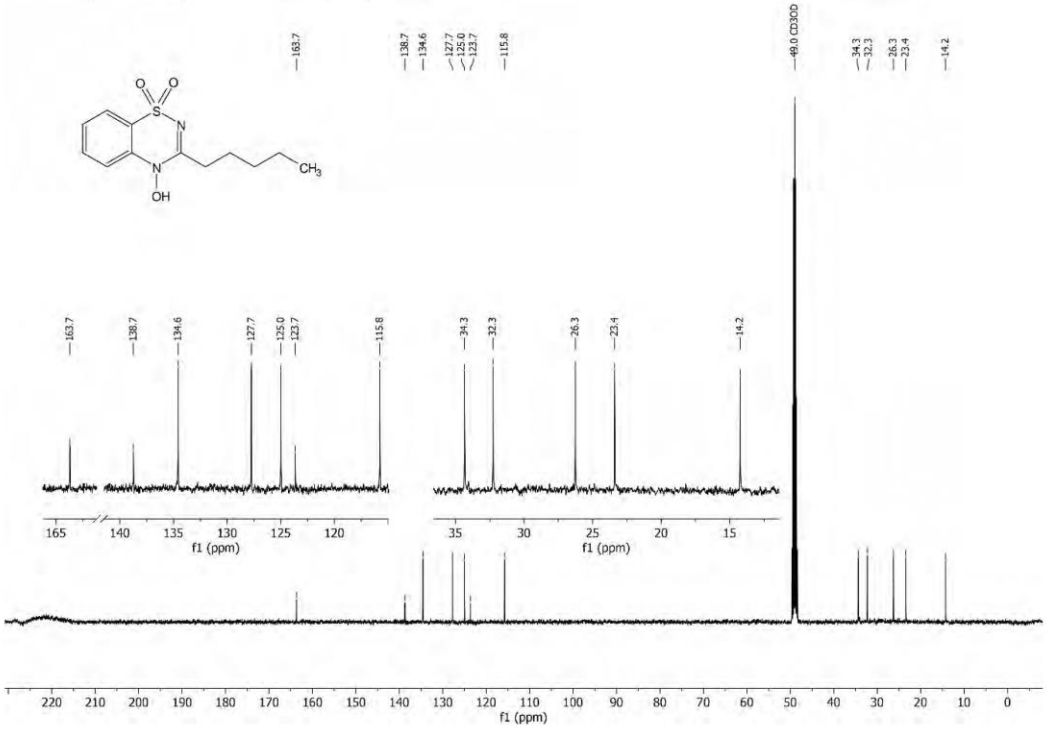
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7e**



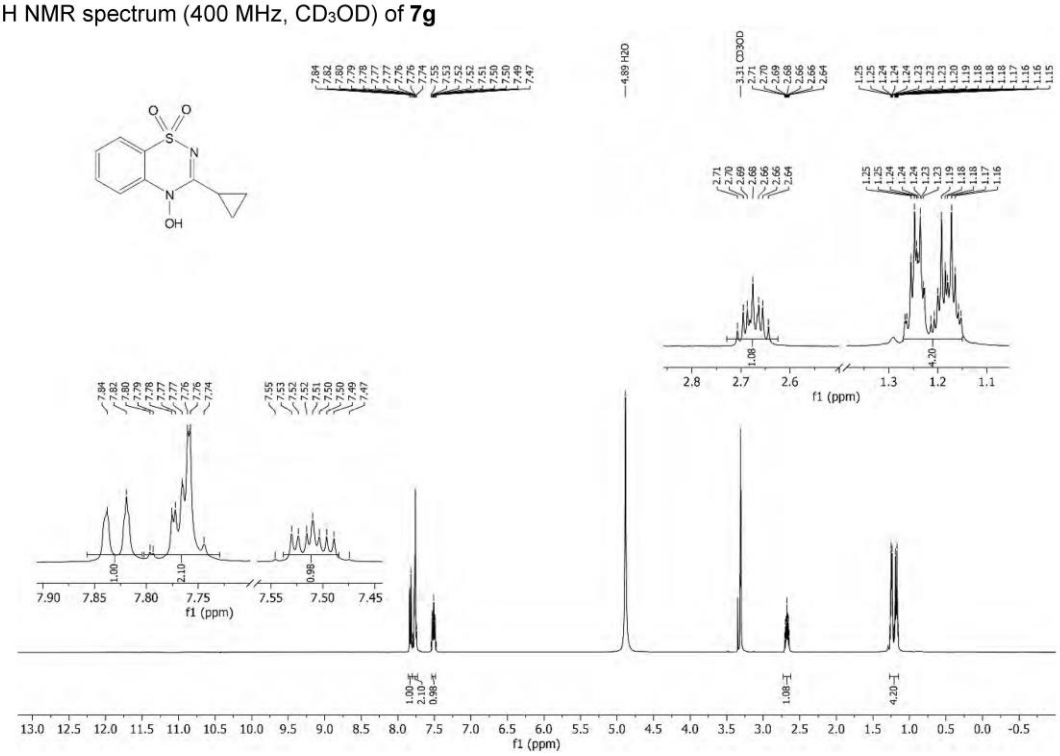
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7f**



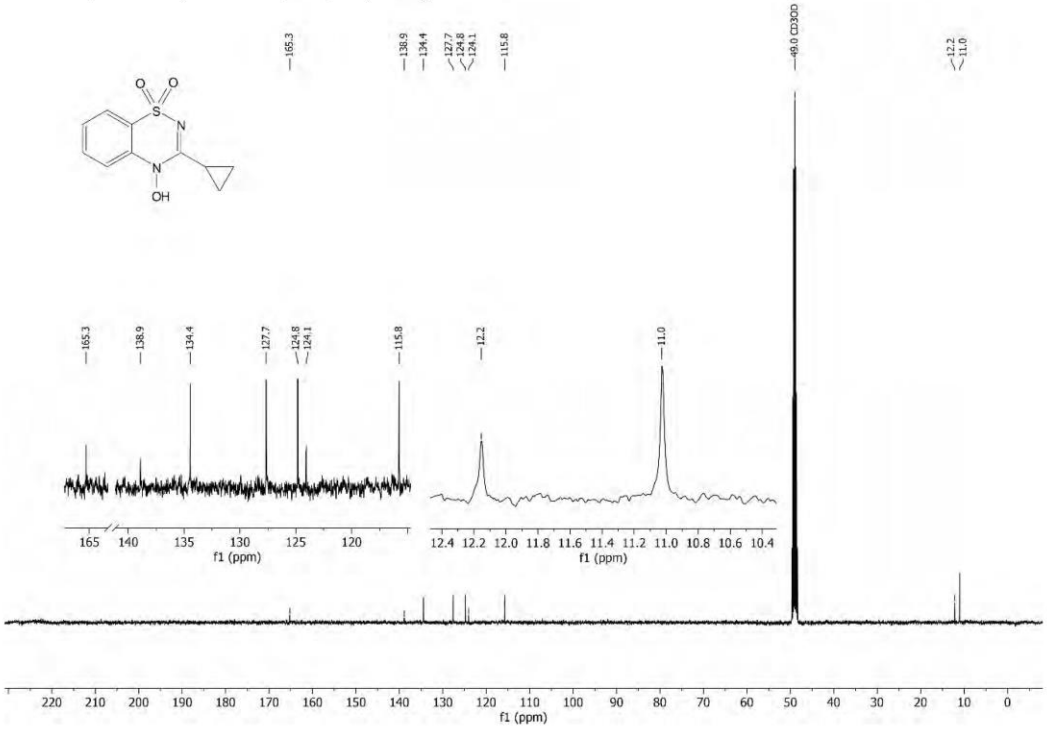
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7f**



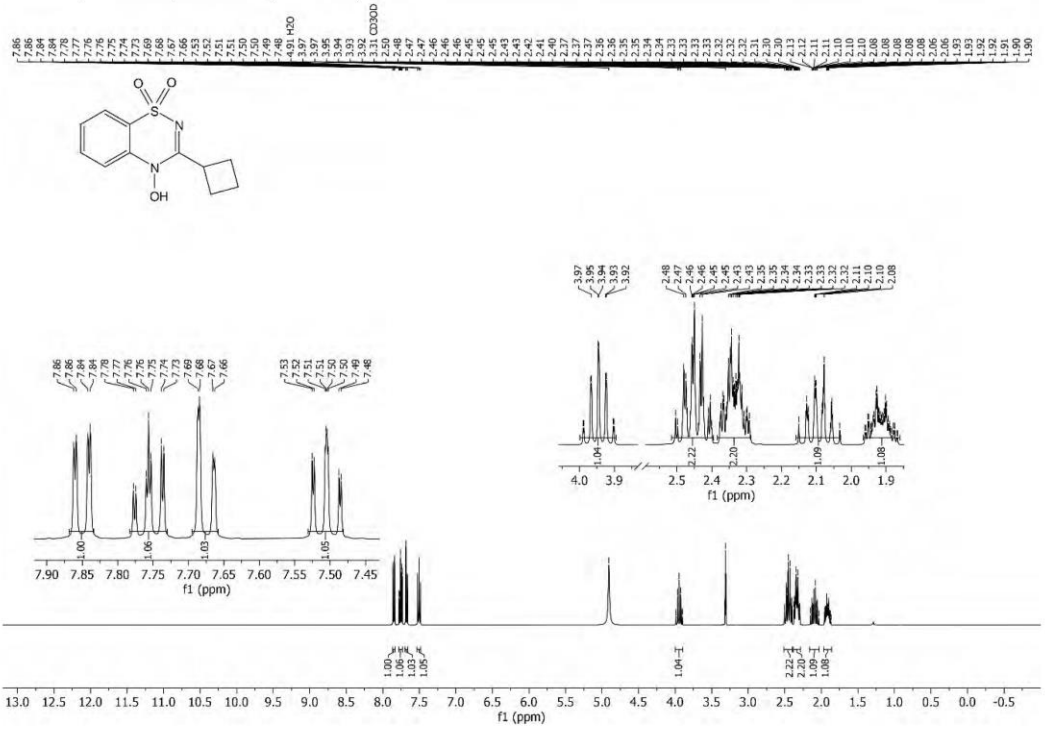
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7g**



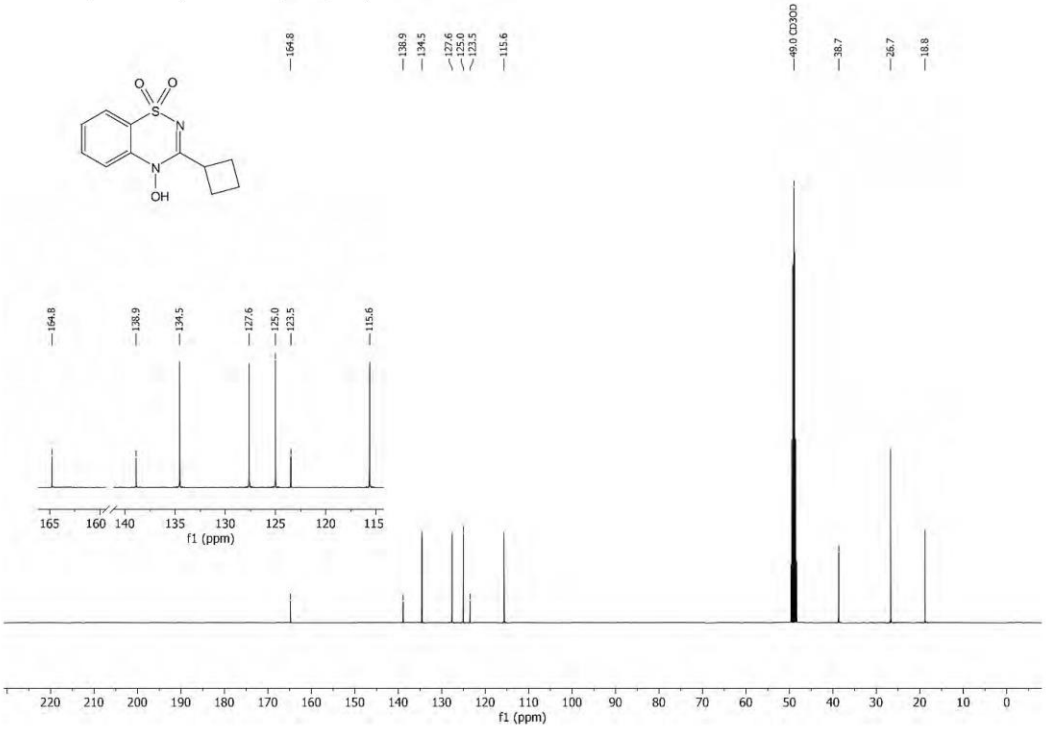
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7g**



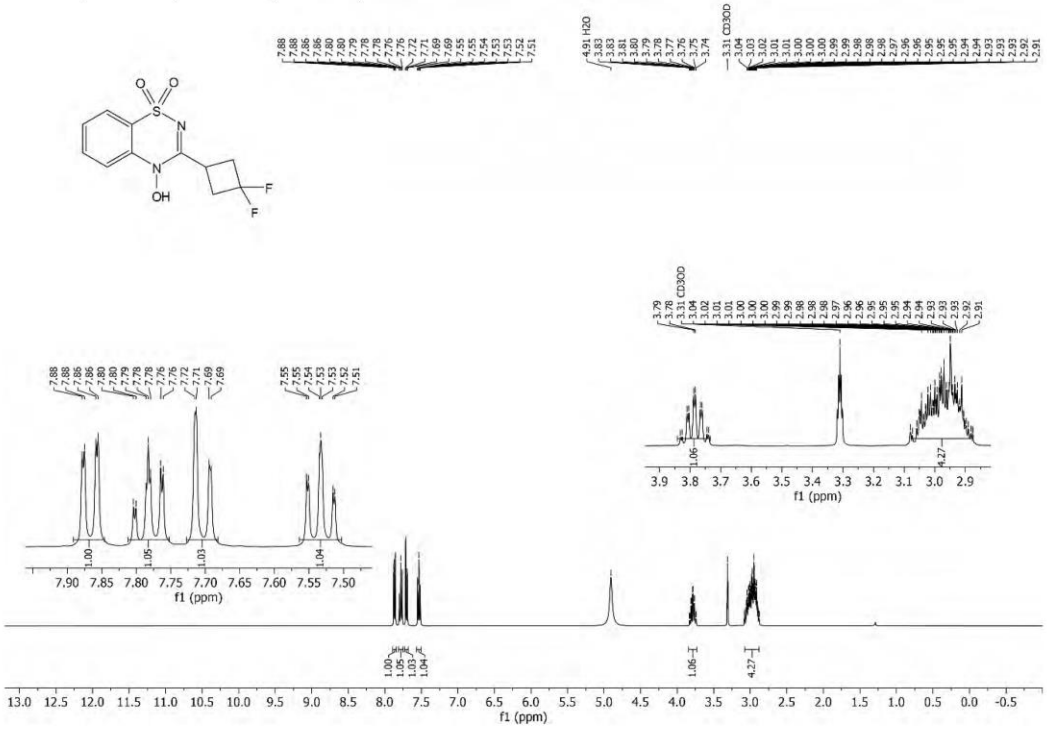
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7h**



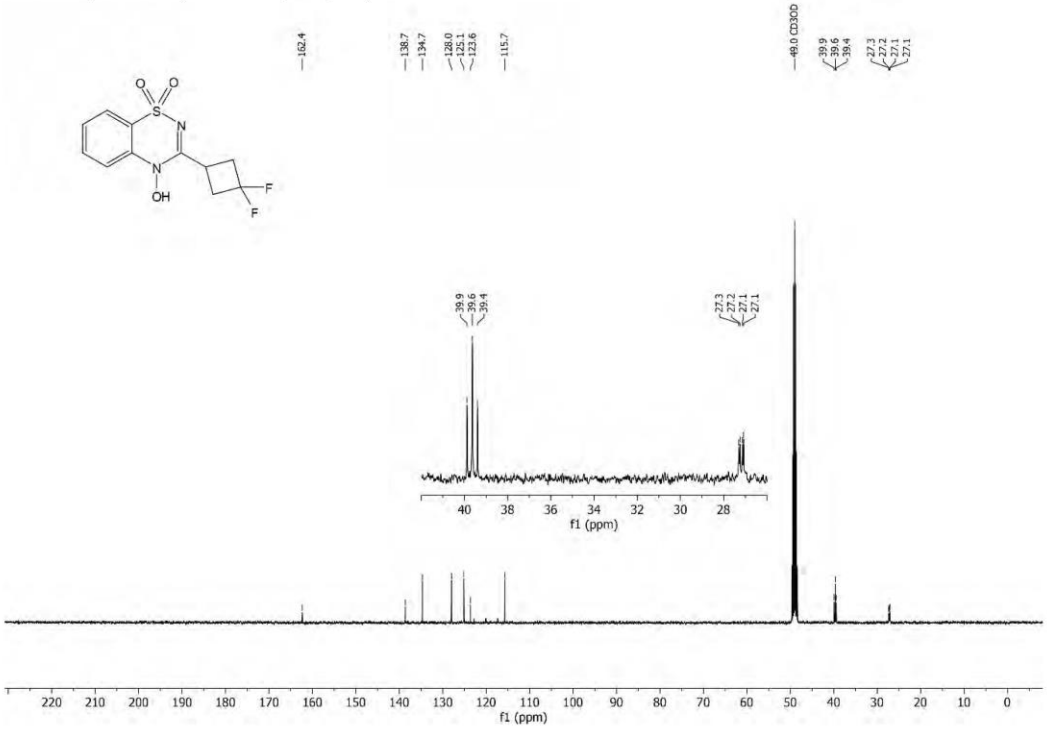
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7h**



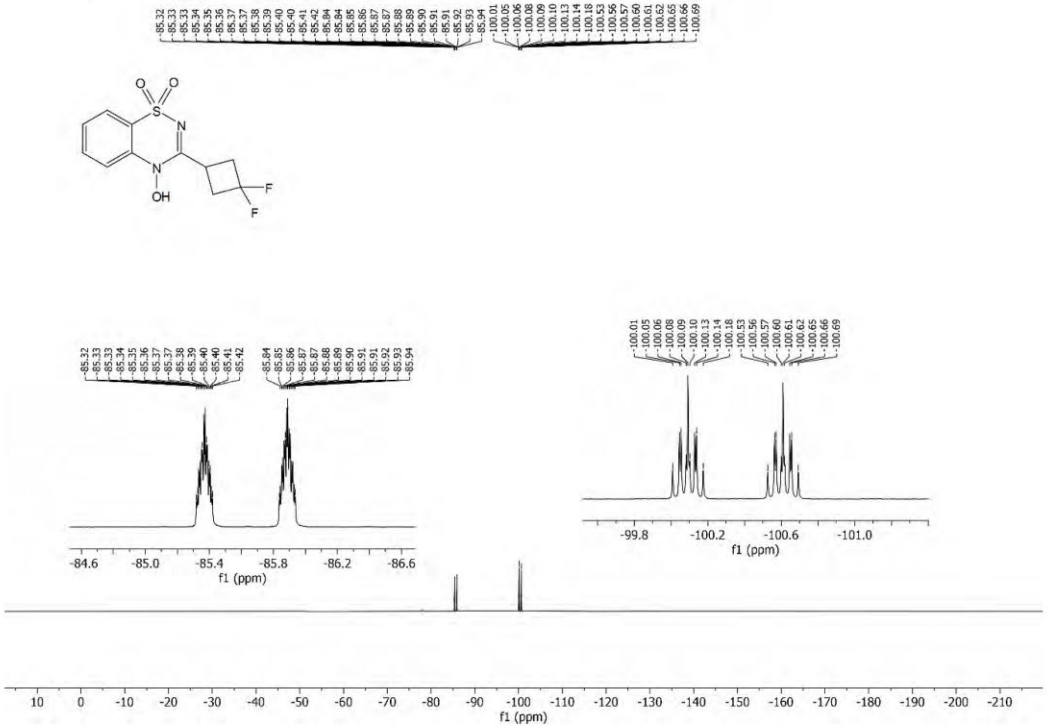
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7i**



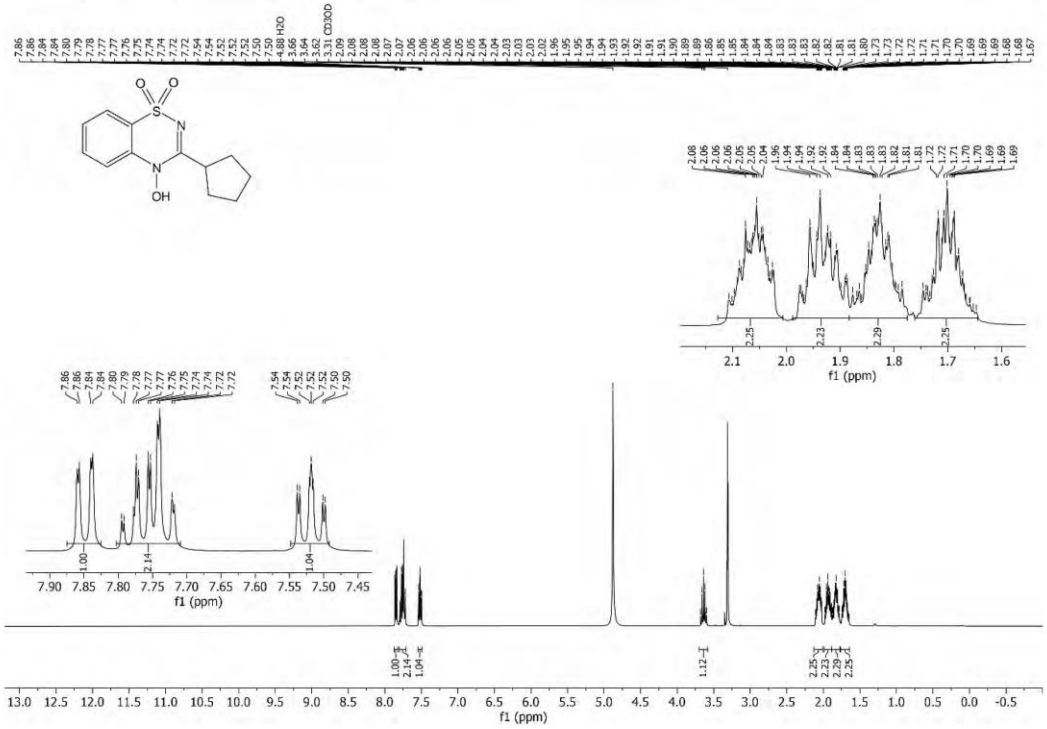
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7i**



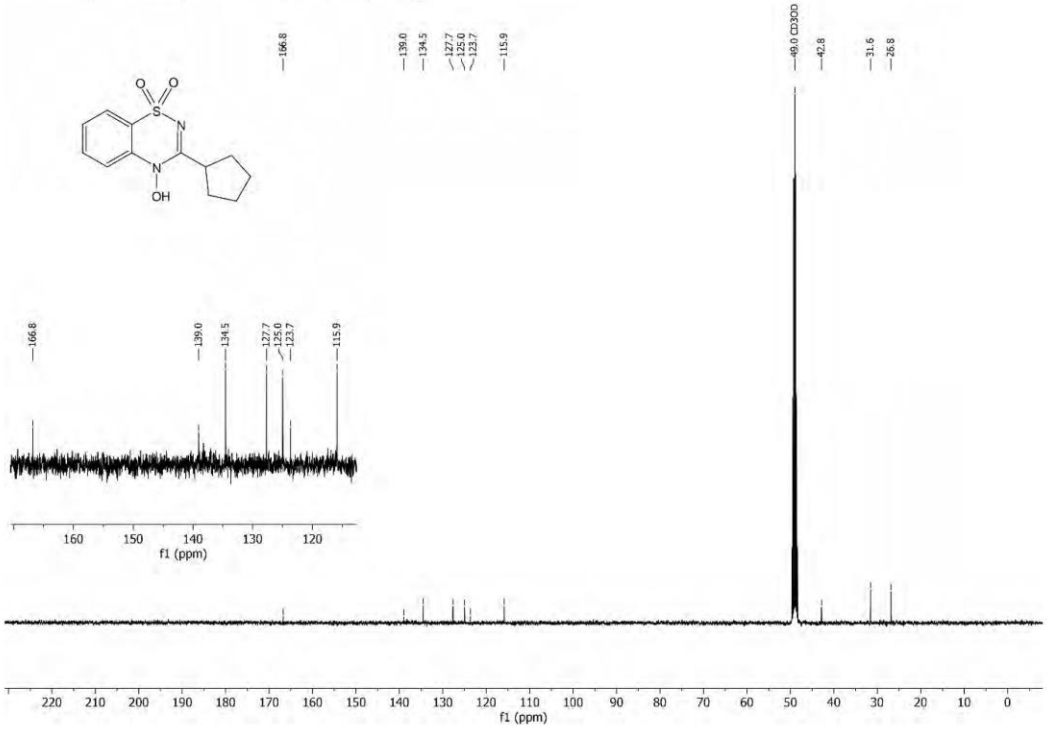
^{19}F NMR spectrum (376 MHz, CD_3OD) of **7i**



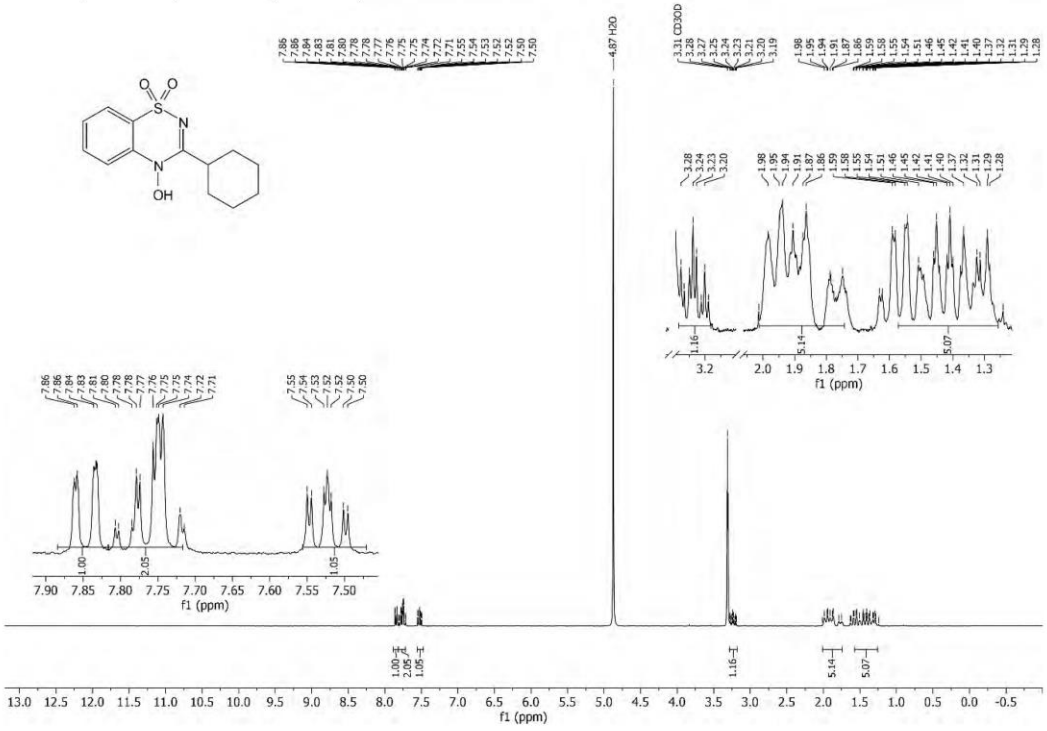
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7j**



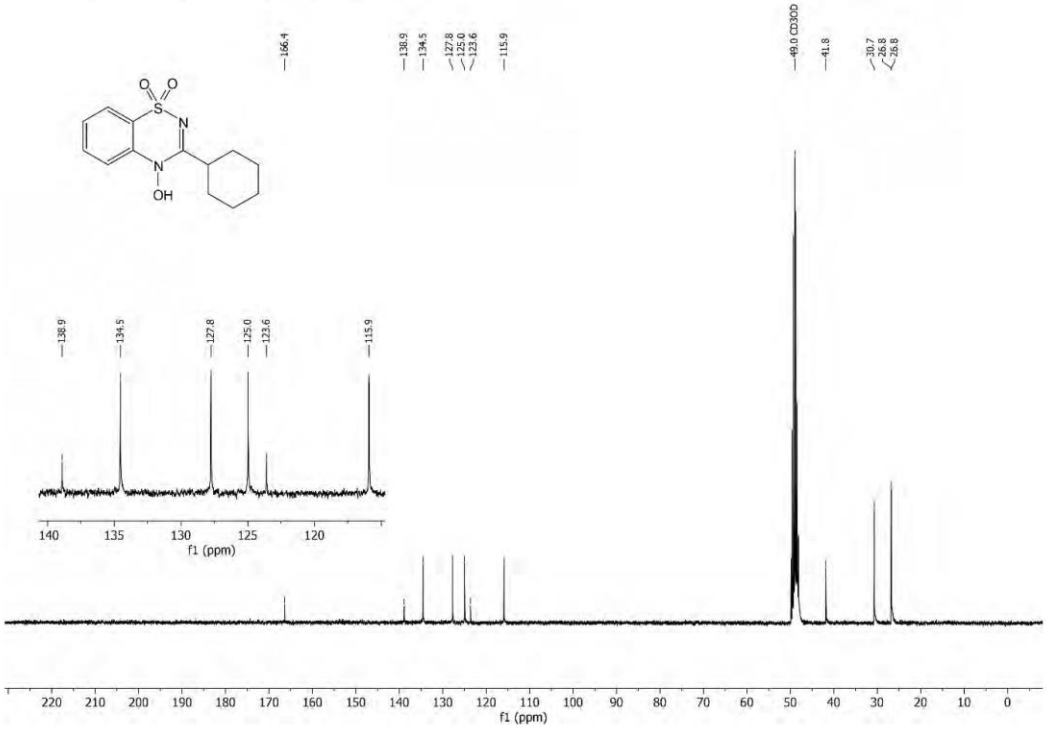
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7j**



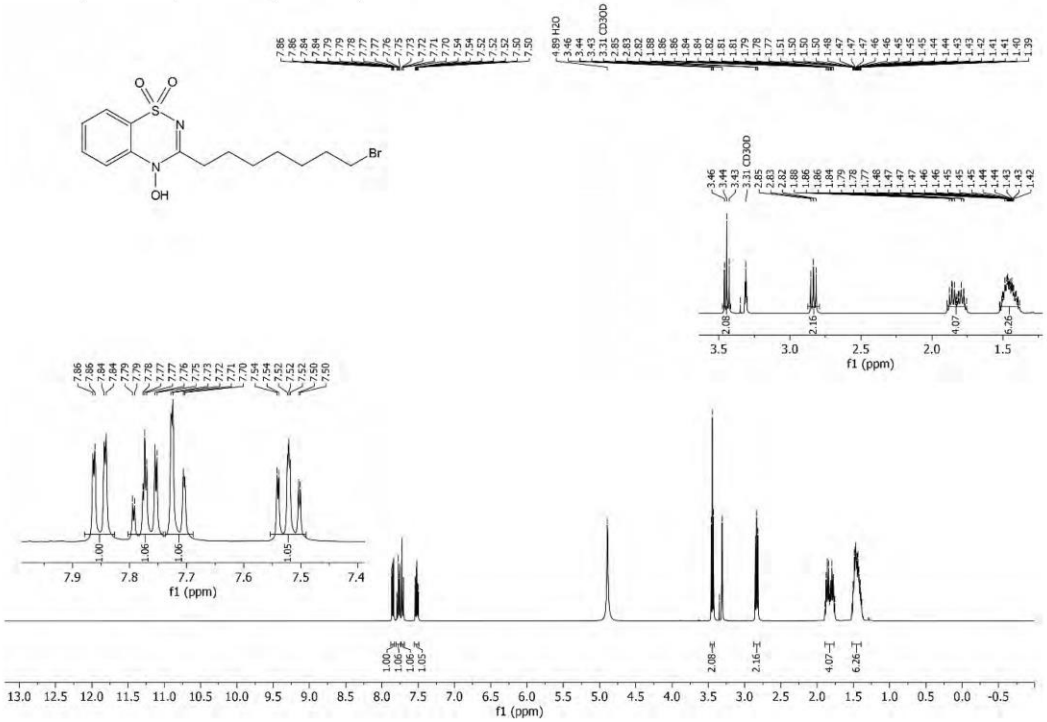
^{1}H NMR spectrum (300 MHz, CD_3OD) of **7k**



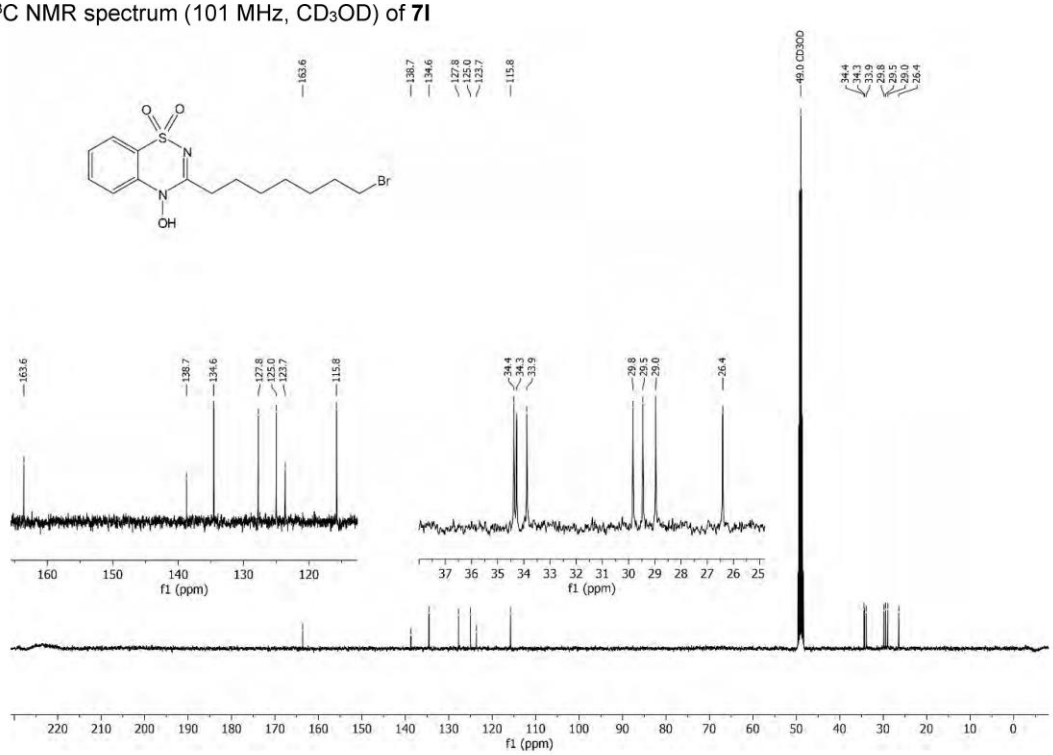
^{13}C NMR spectrum (75 MHz, CD_3OD) of **7k**



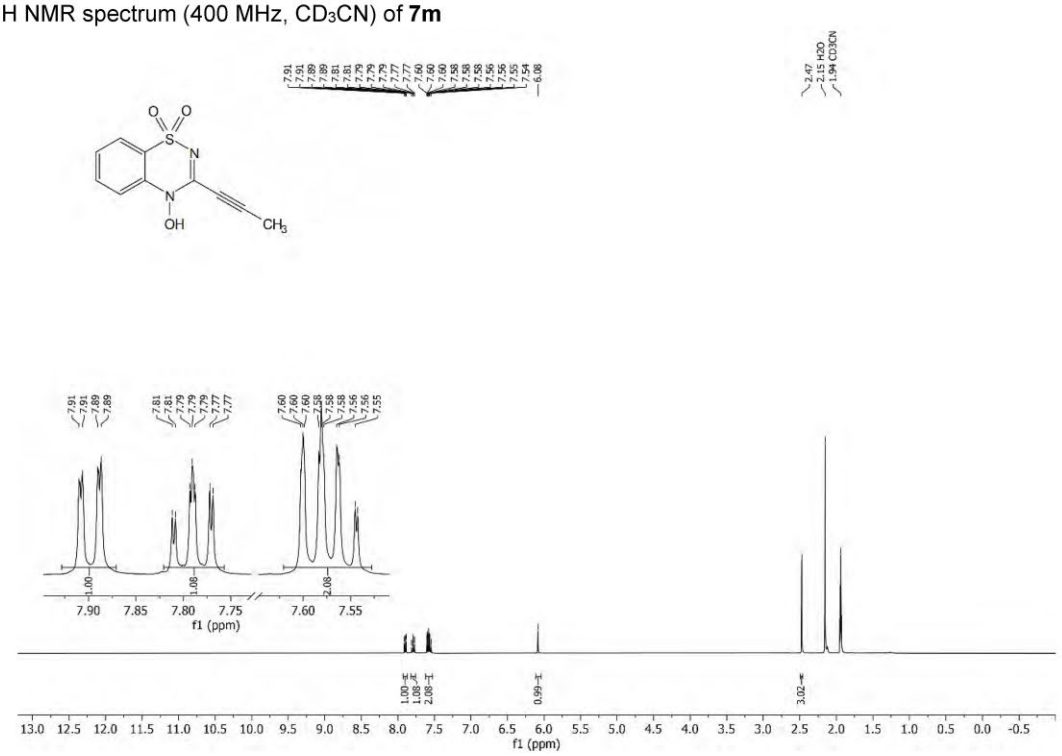
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7l**



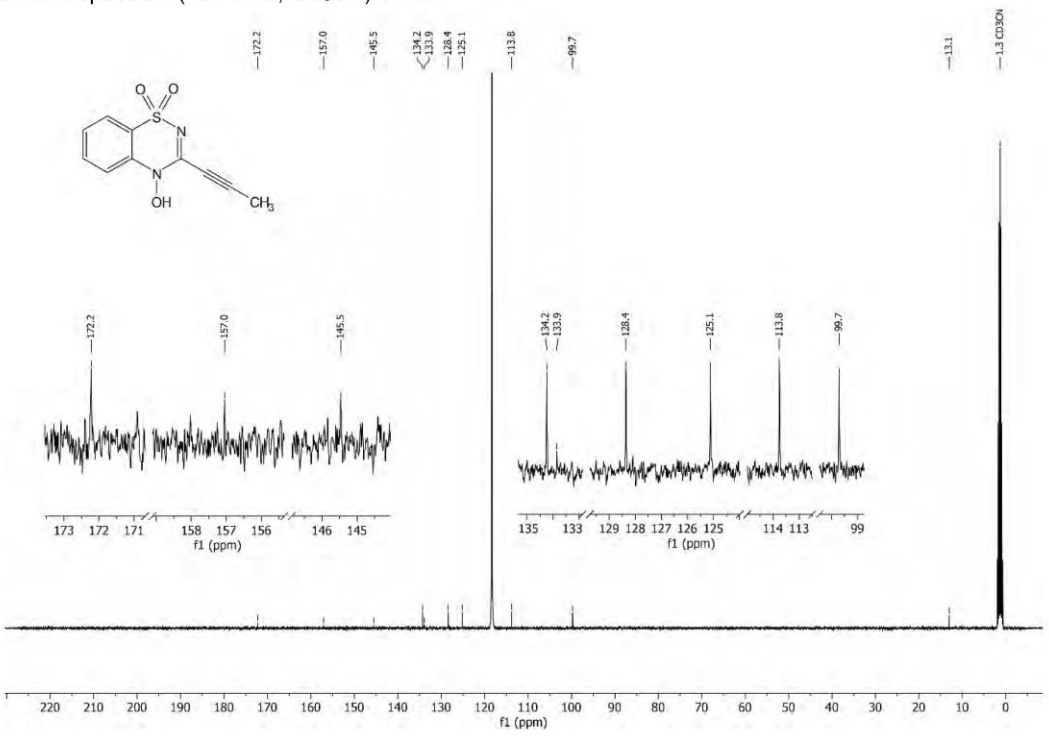
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7l**



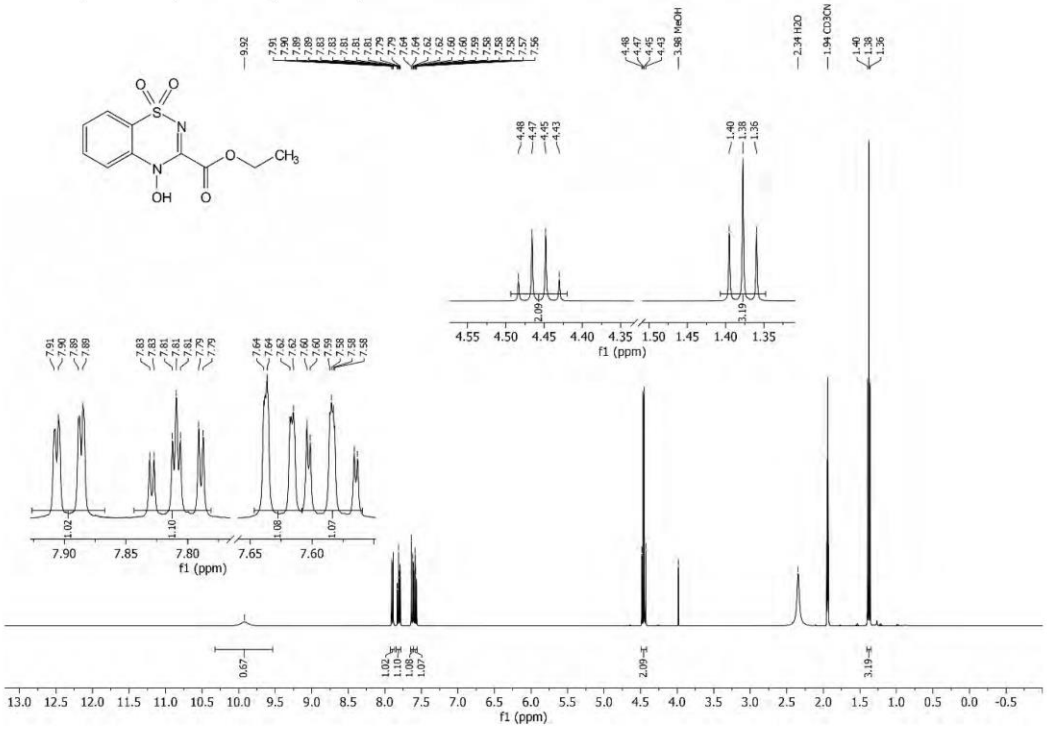
^{1}H NMR spectrum (400 MHz, CD_3CN) of **7m**



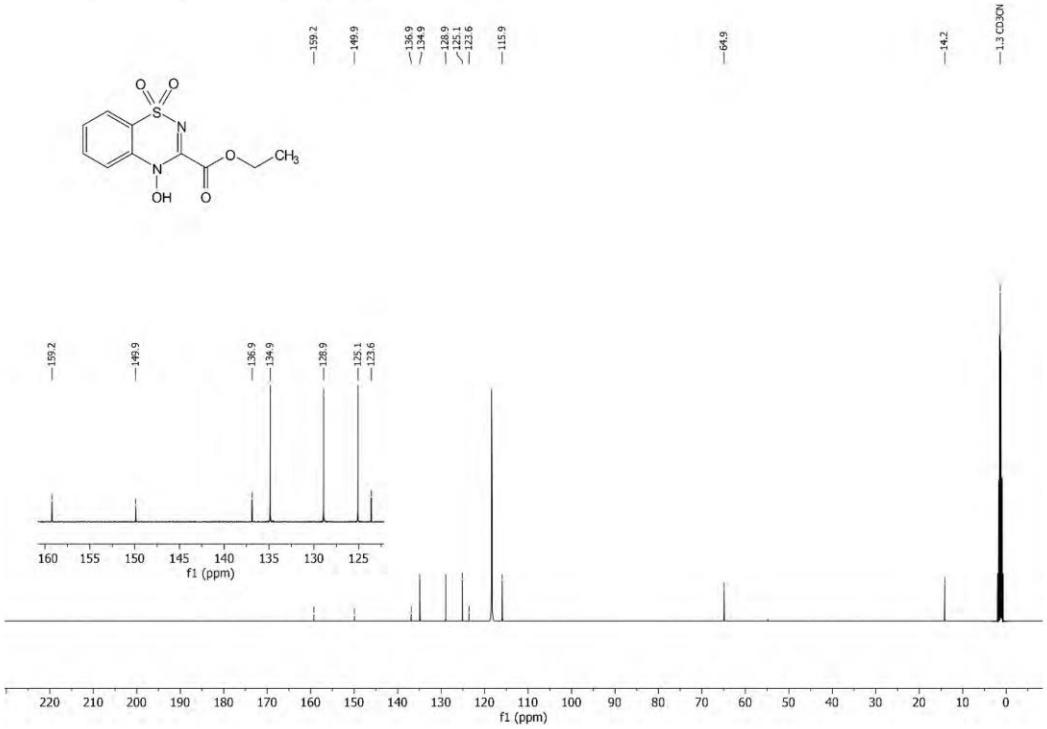
^{13}C NMR spectrum (101 MHz, CD_3CN) of **7m**



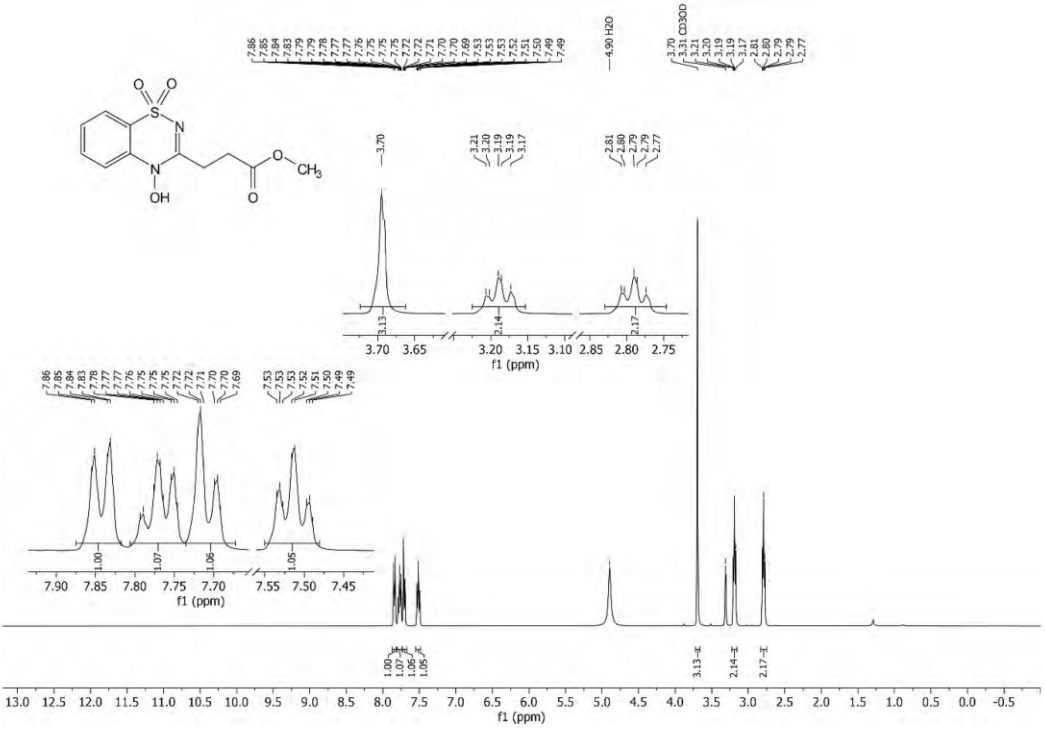
^{1}H NMR spectrum (400 MHz, CD_3CN) of **7n**



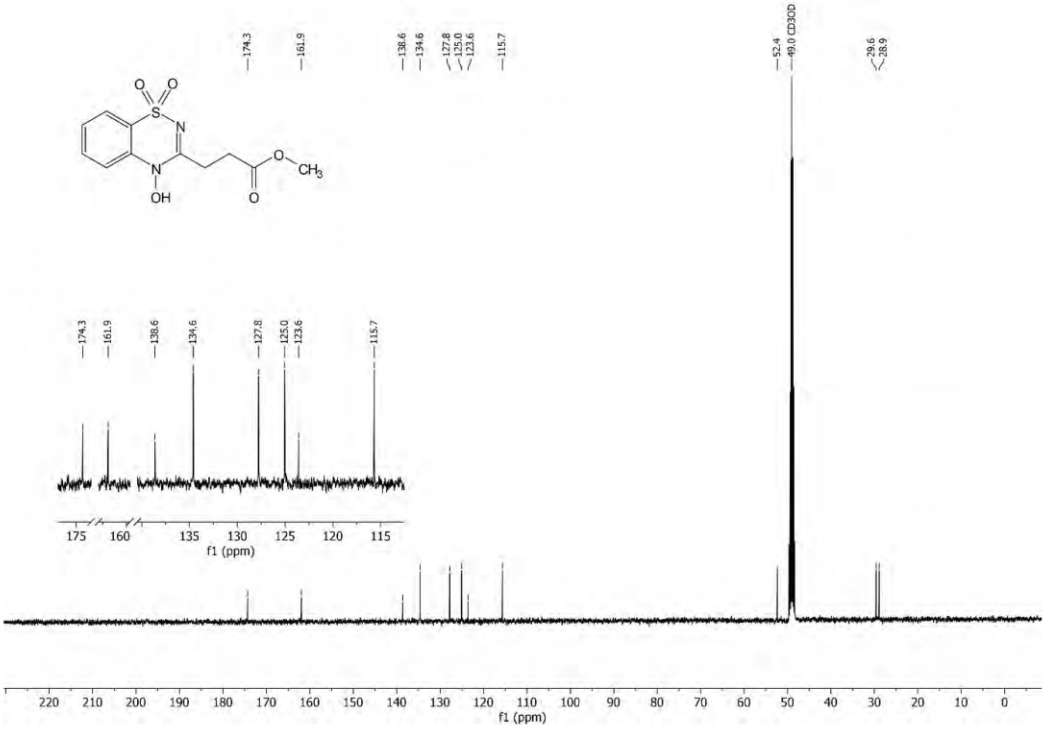
^{13}C NMR spectrum (101 MHz, CD_3CN) of **7n**



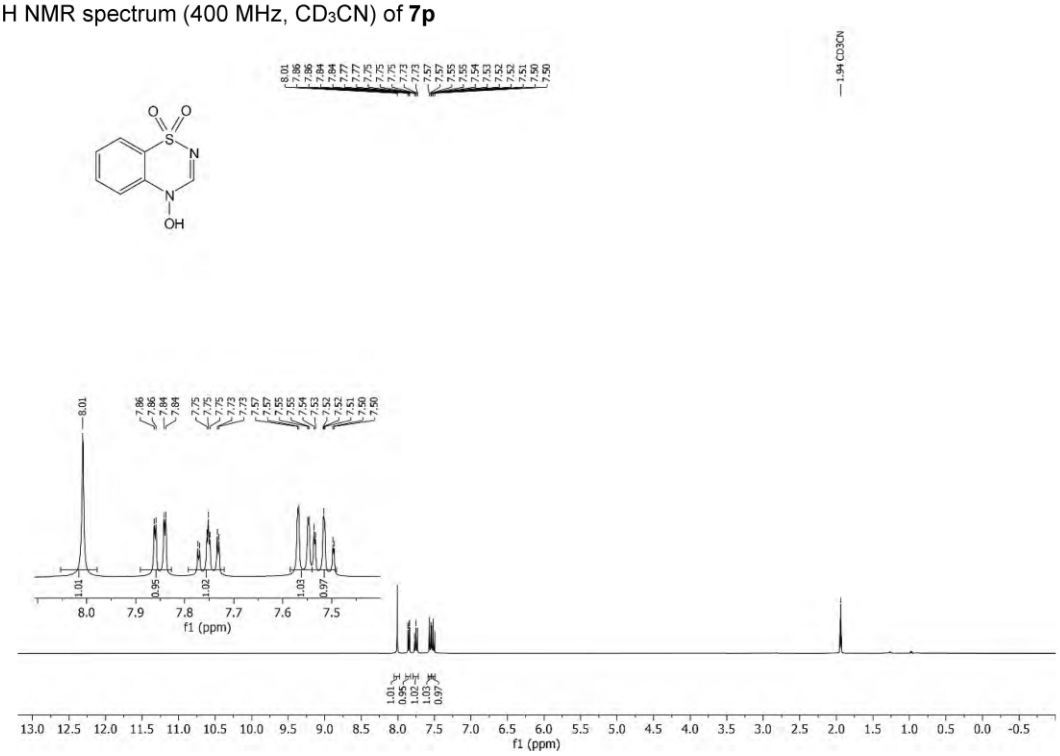
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7o**



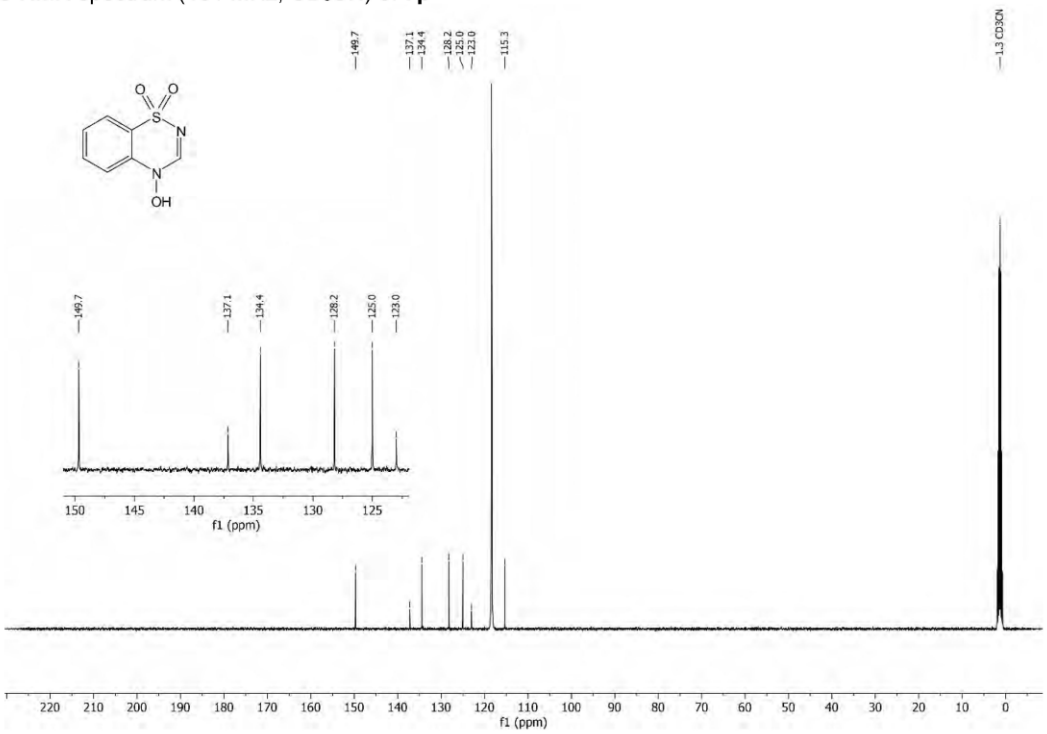
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7o**



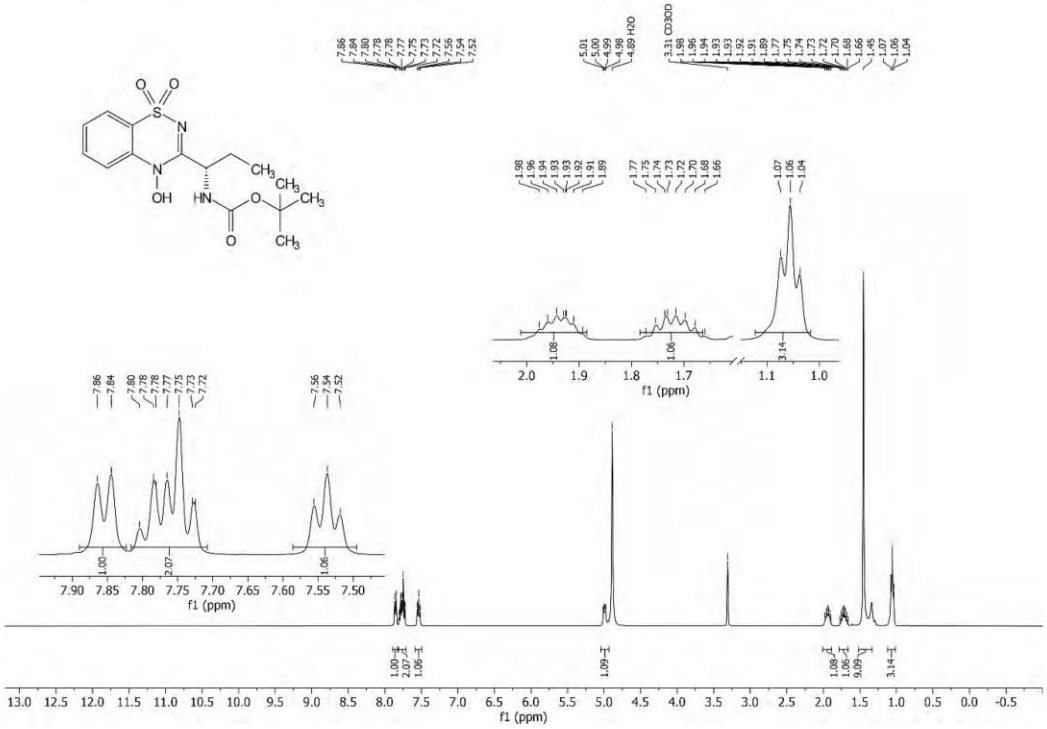
^{1}H NMR spectrum (400 MHz, CD_3CN) of **7p**



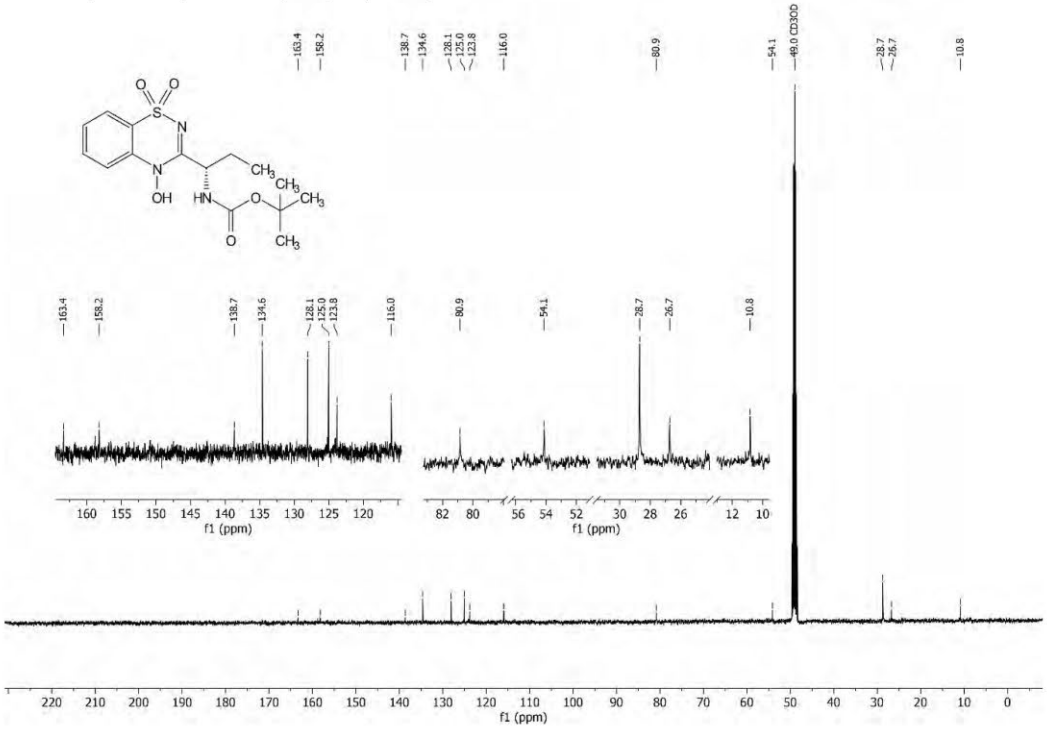
^{13}C NMR spectrum (101 MHz, CD_3CN) of **7p**



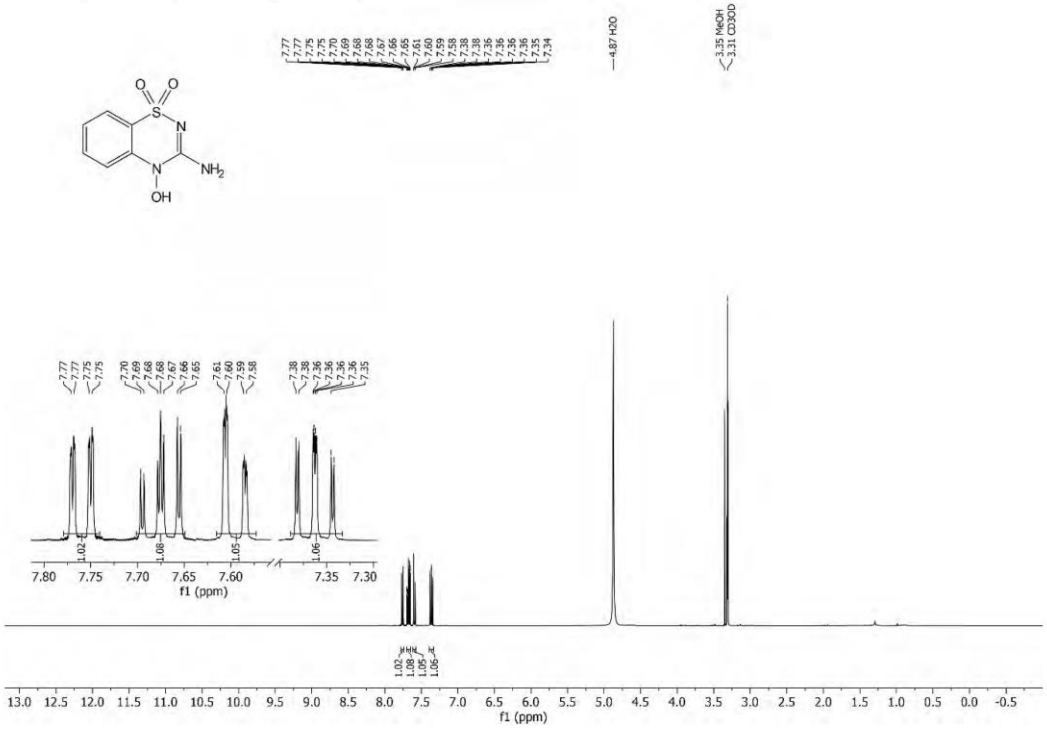
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7q**



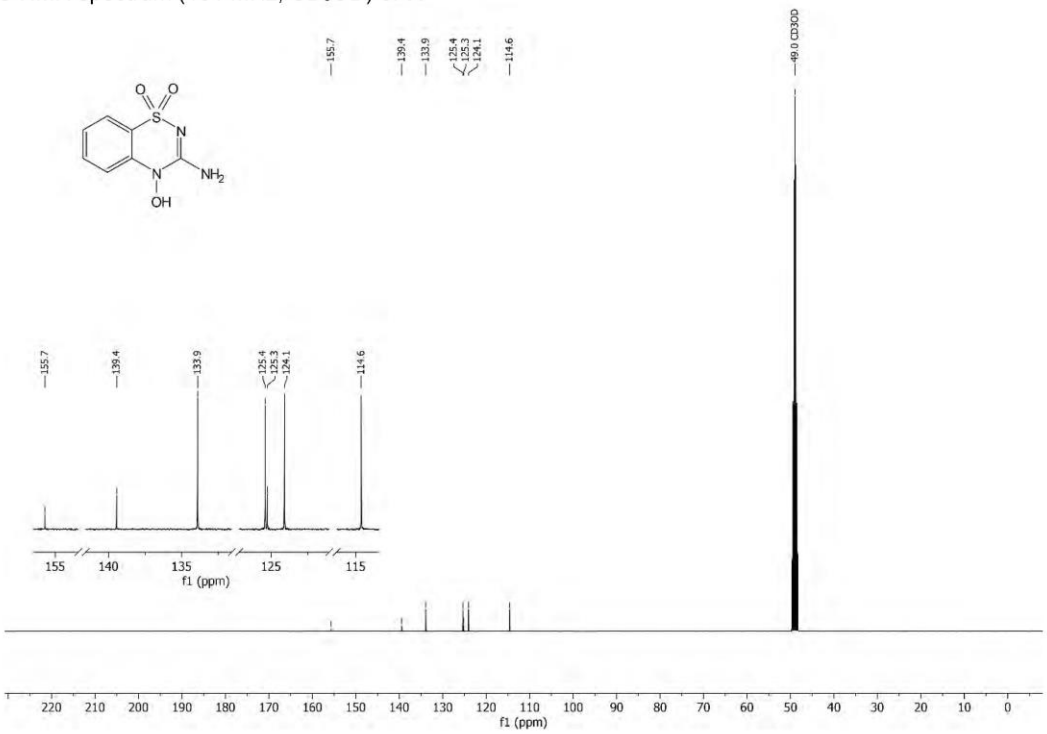
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7q**



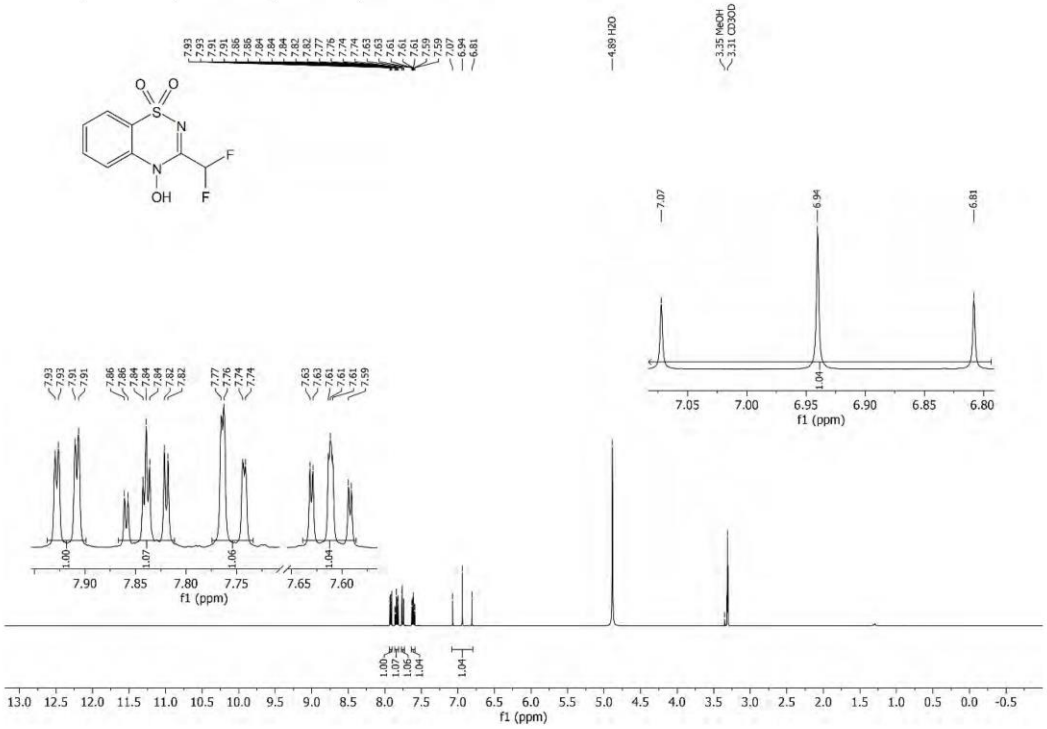
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7r**



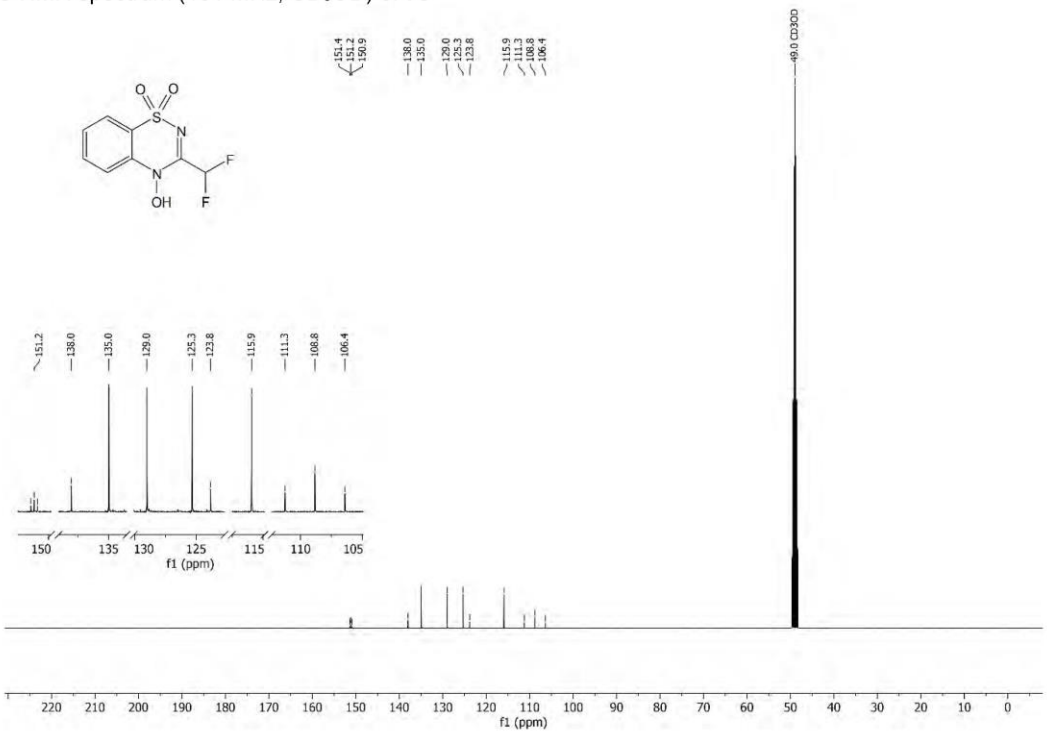
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7r**



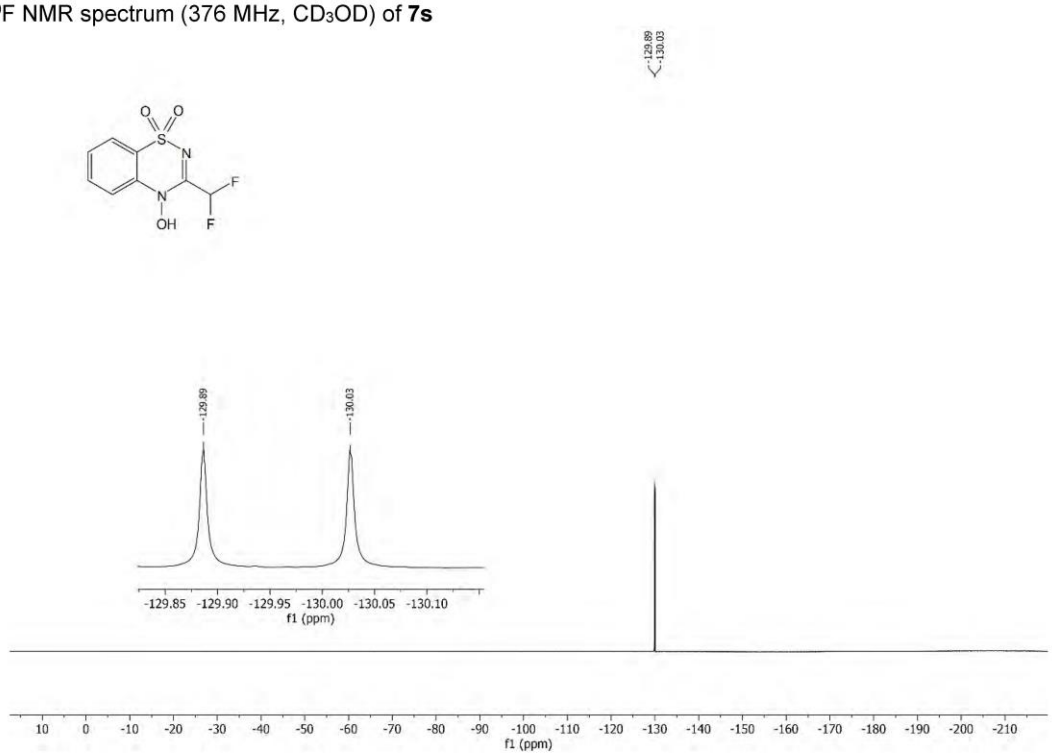
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7s**



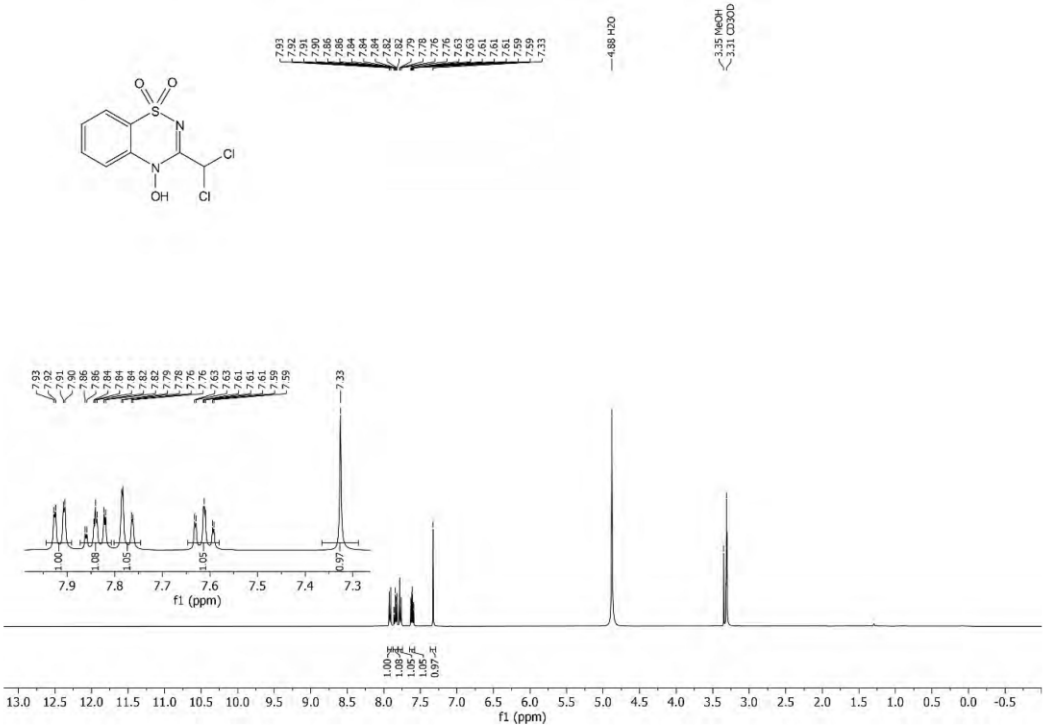
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7s**



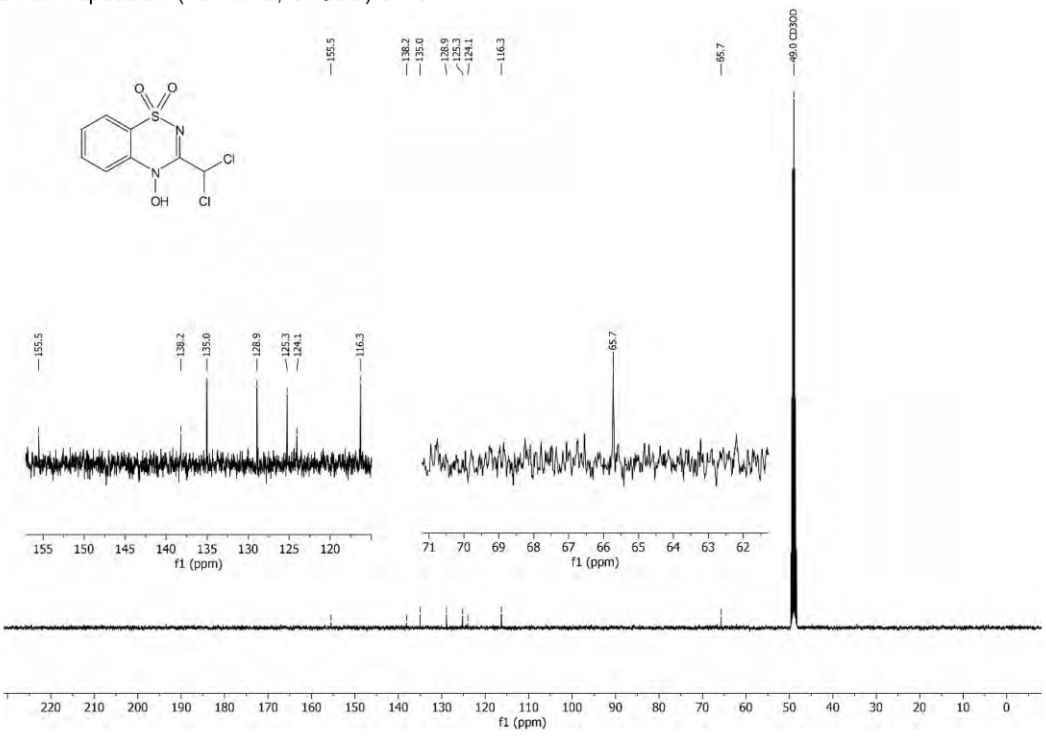
^{19}F NMR spectrum (376 MHz, CD_3OD) of **7s**



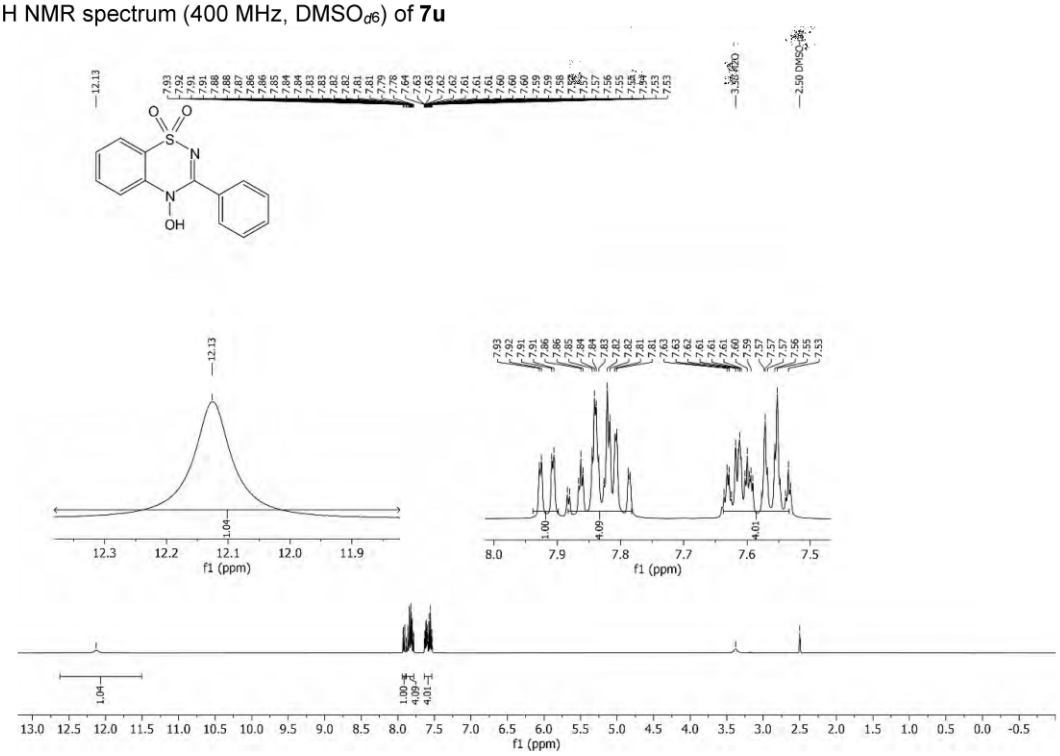
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7t**



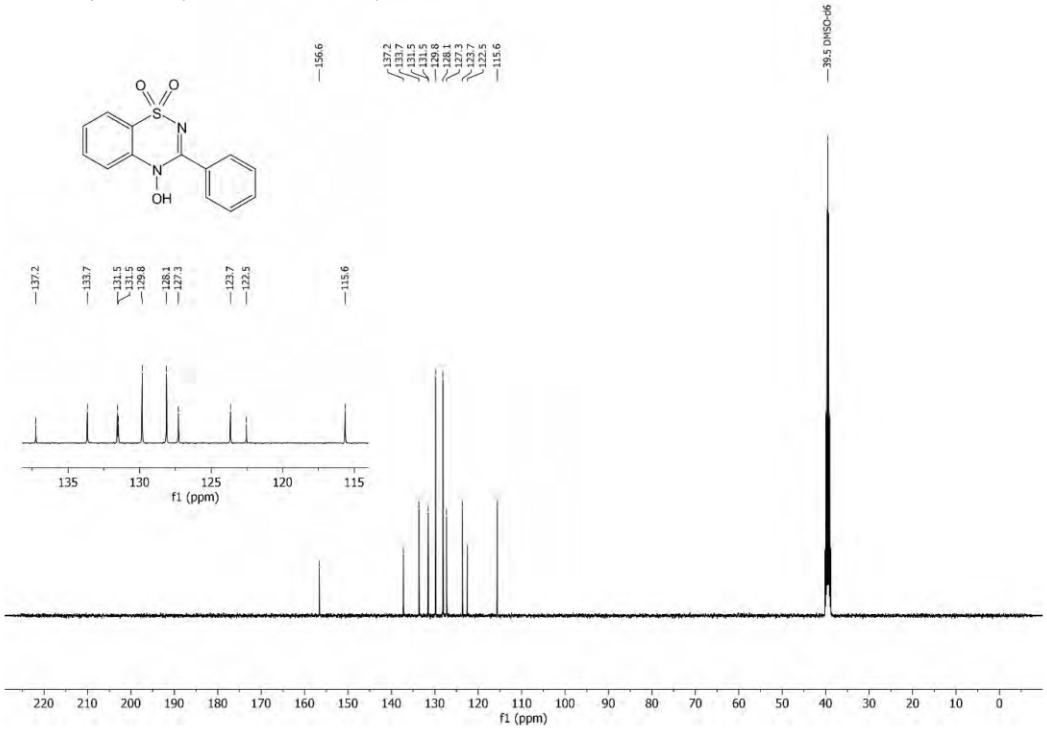
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7t**



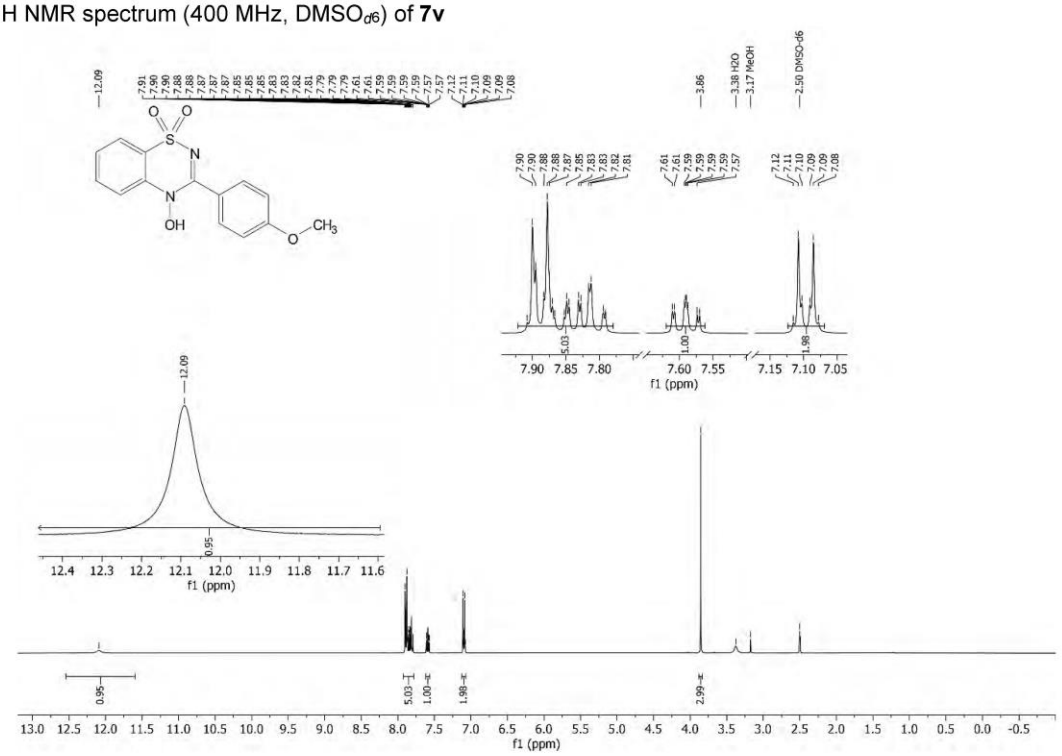
^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **7u**



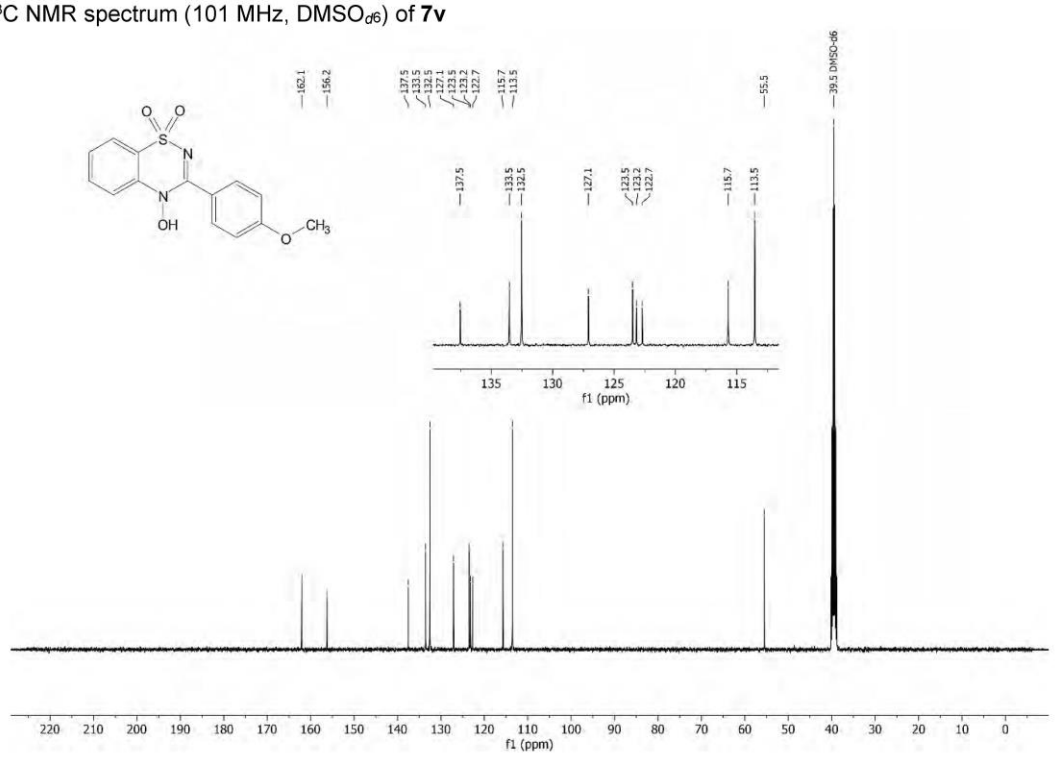
^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **7u**



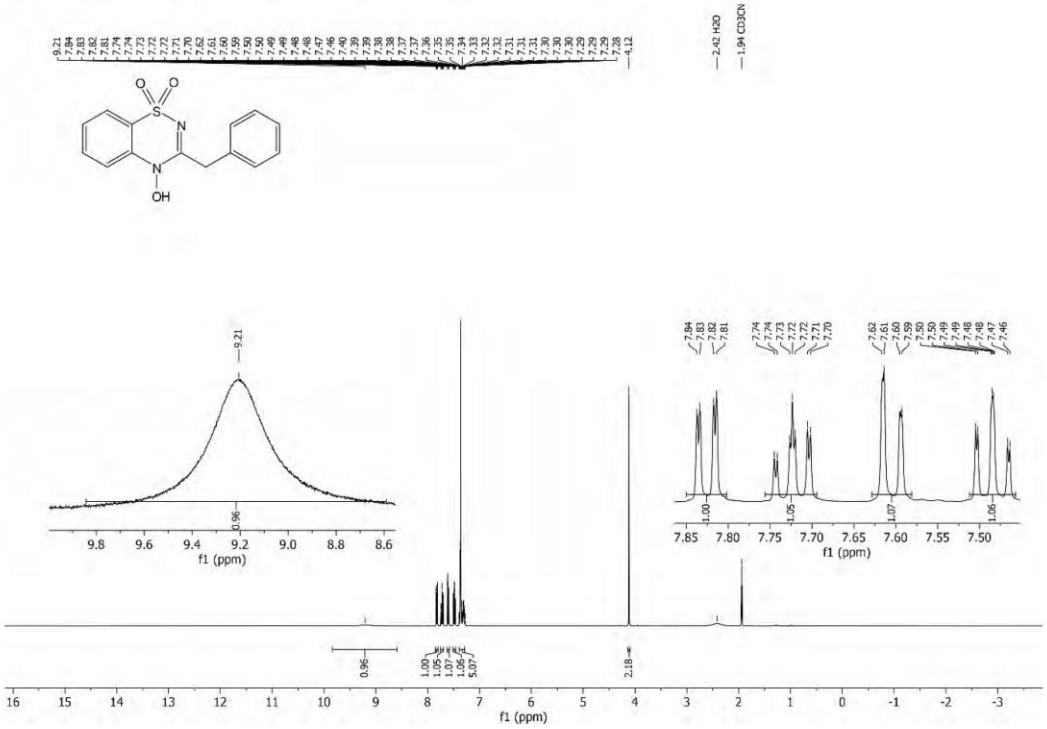
^{1}H NMR spectrum (400 MHz, DMSO$_{d6}$) of **7v**



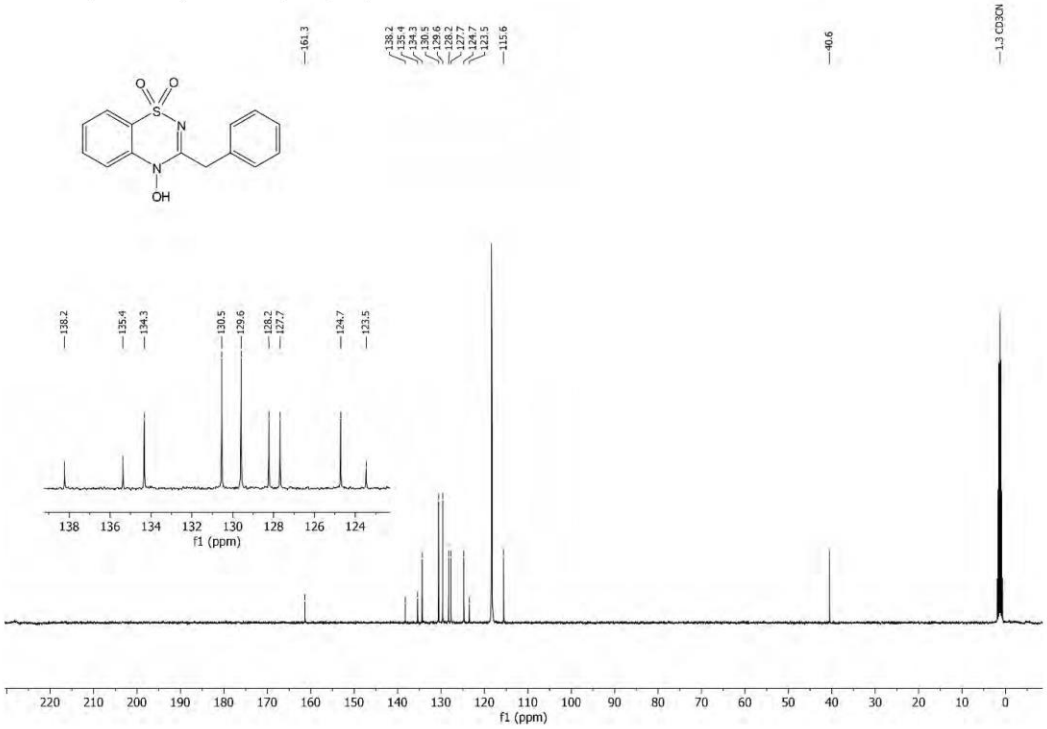
^{13}C NMR spectrum (101 MHz, DMSO$_{d6}$) of **7v**



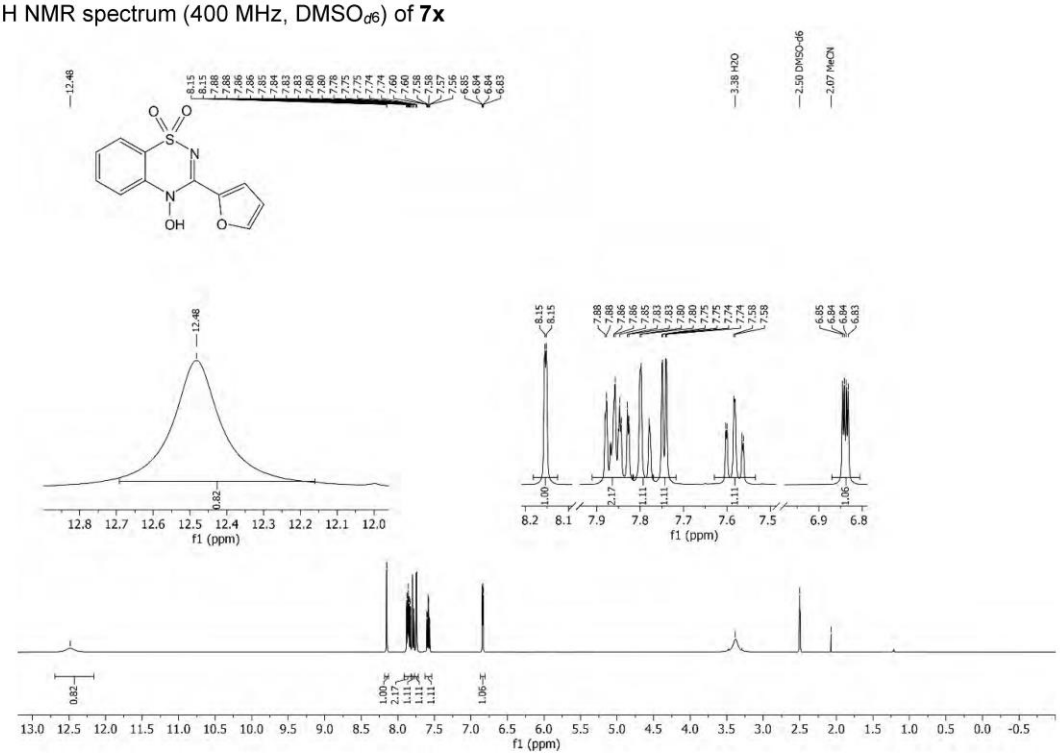
^{1}H NMR spectrum (400 MHz, CD_3CN) of **7w**



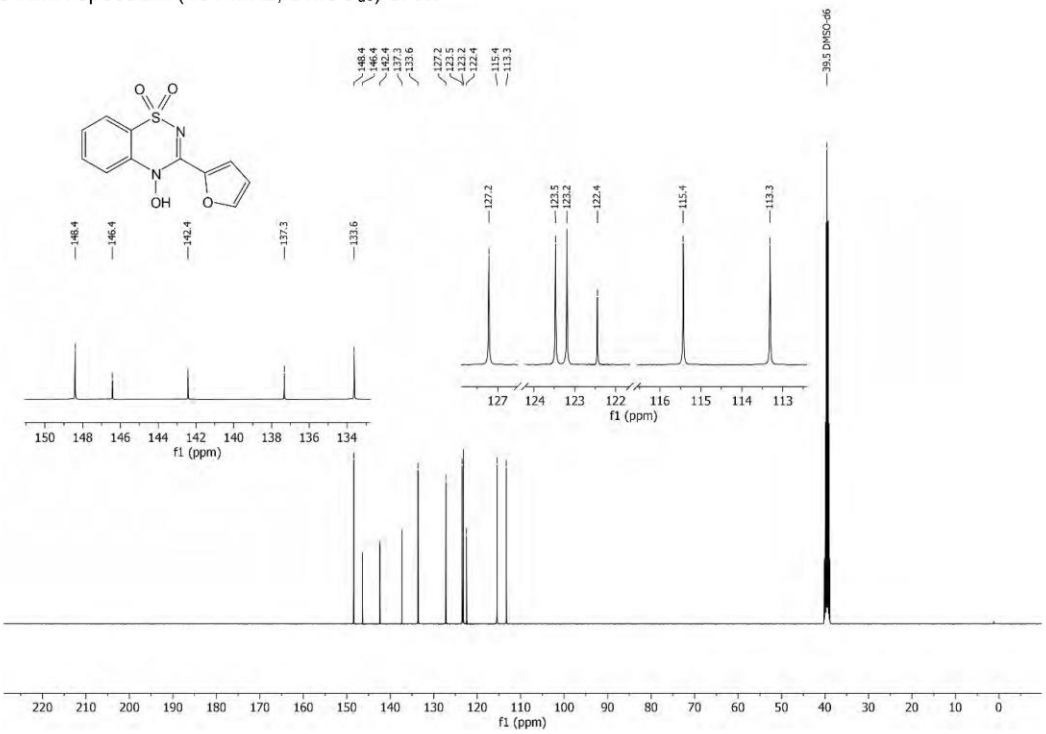
^{13}C NMR spectrum (101 MHz, CD_3CN) of **7w**



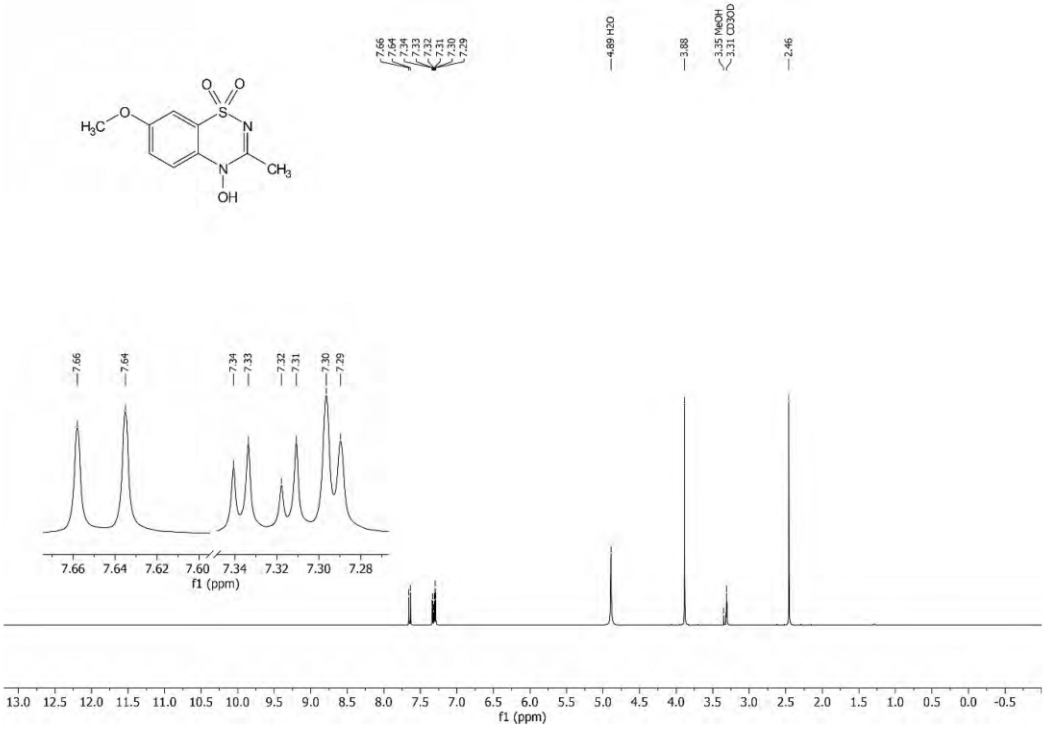
^{1}H NMR spectrum (400 MHz, DMSO$_{d6}$) of **7x**



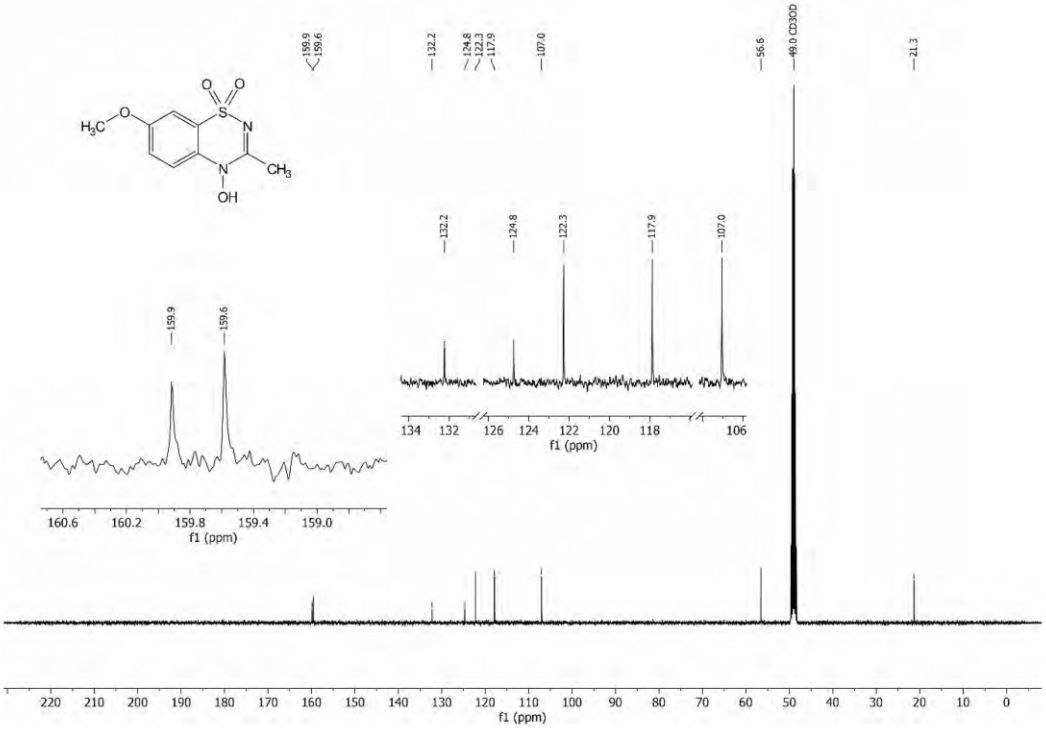
^{13}C NMR spectrum (101 MHz, DMSO$_{d6}$) of **7x**



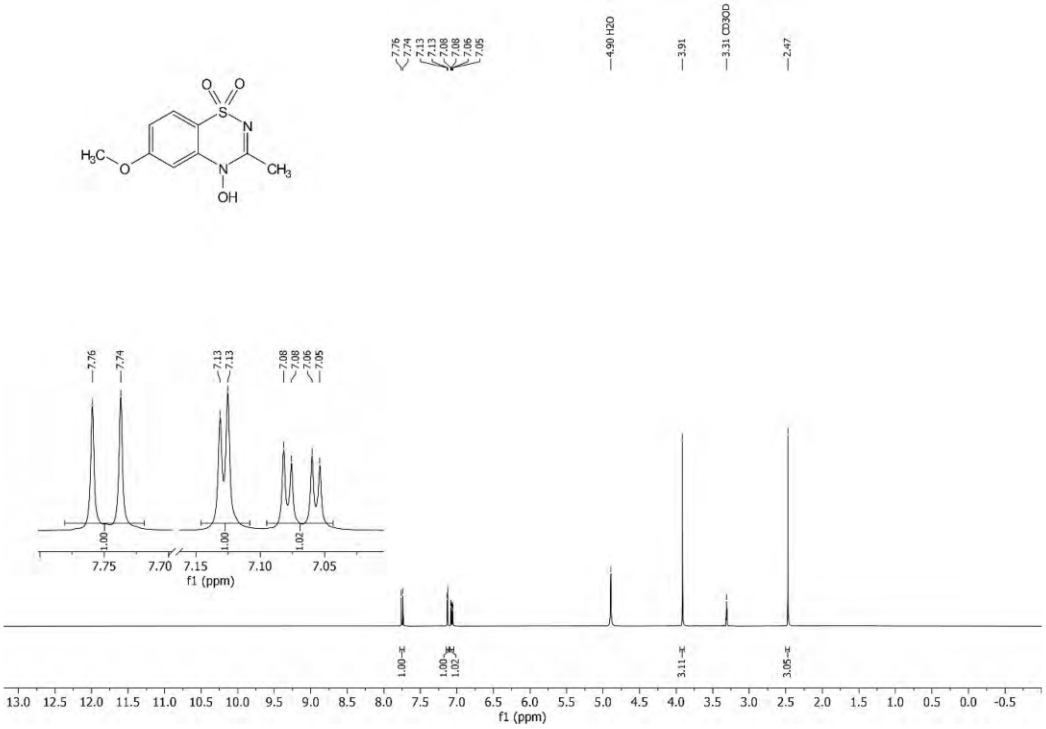
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7y**



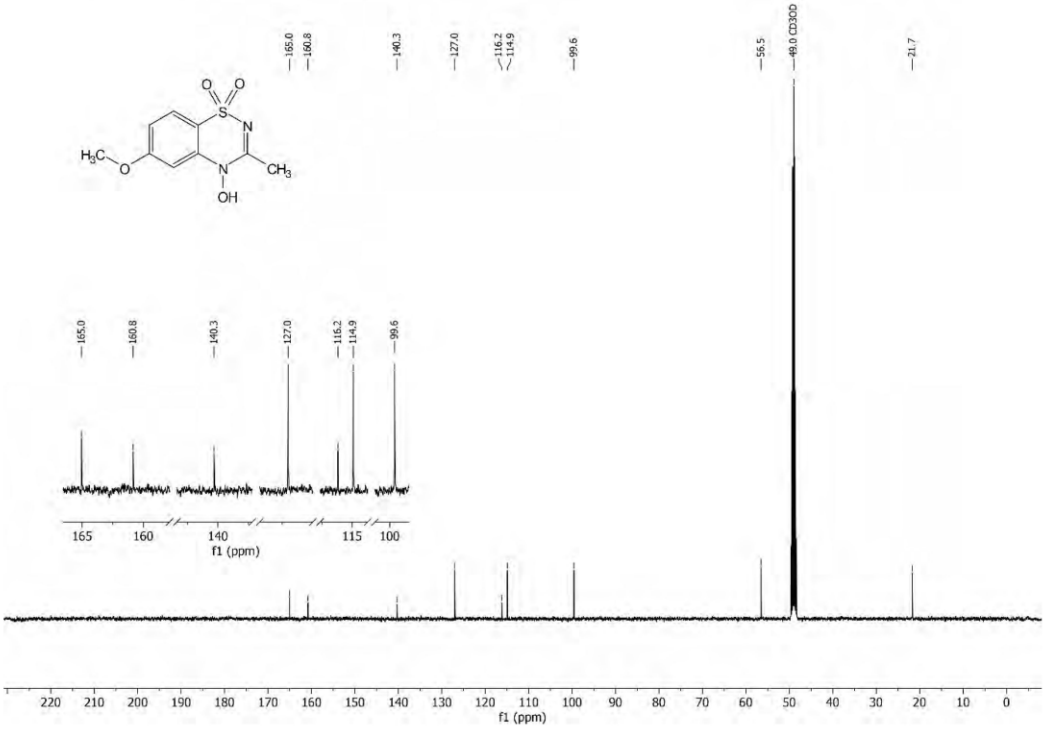
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7y**



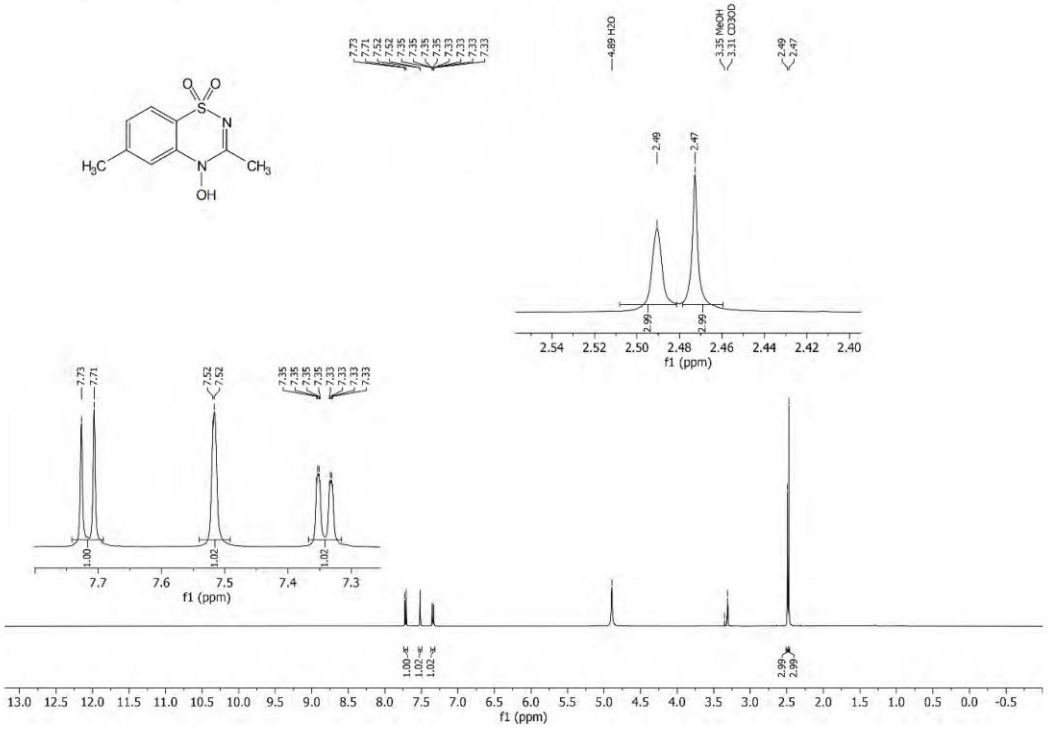
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7z**



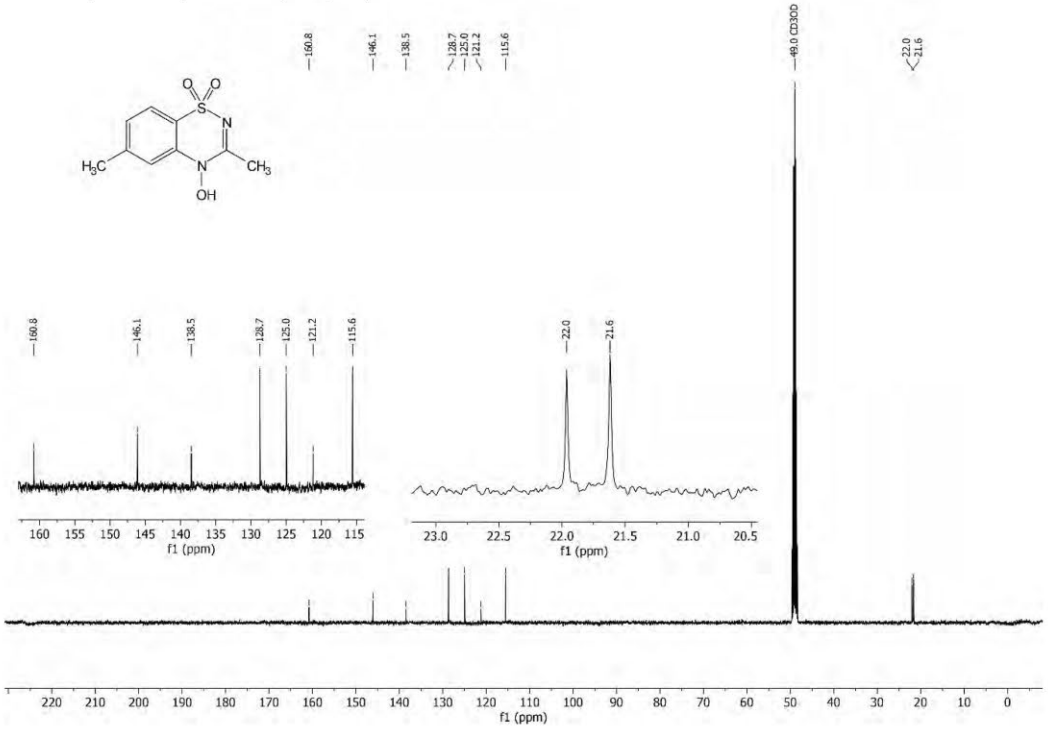
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7z**



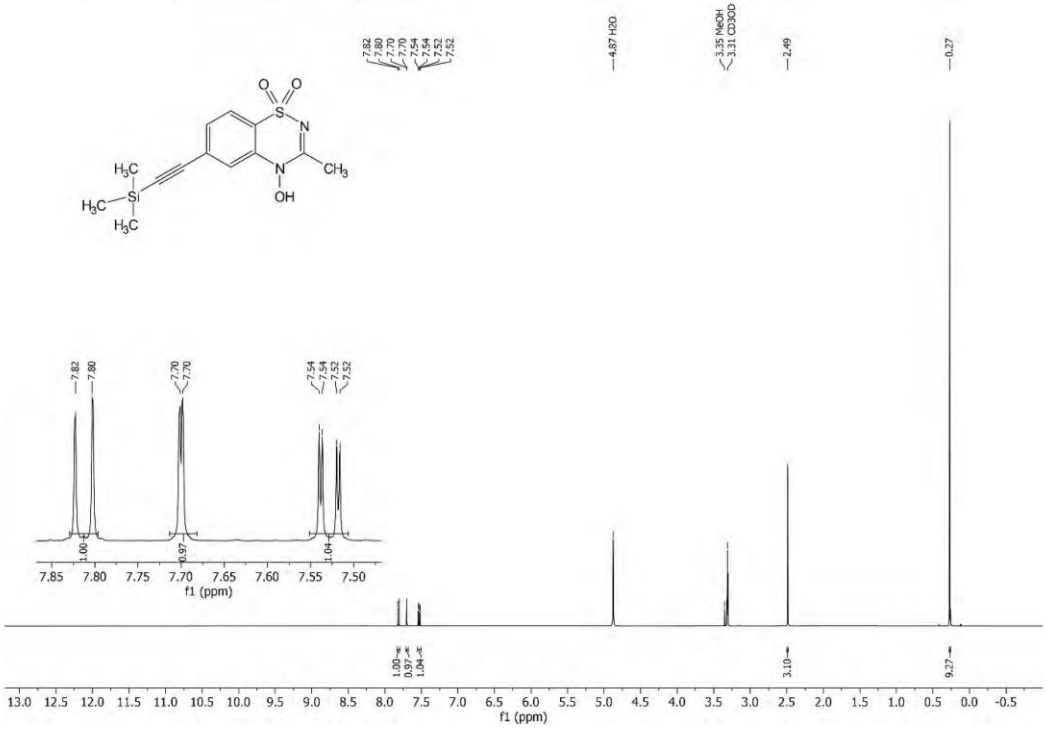
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7aa**



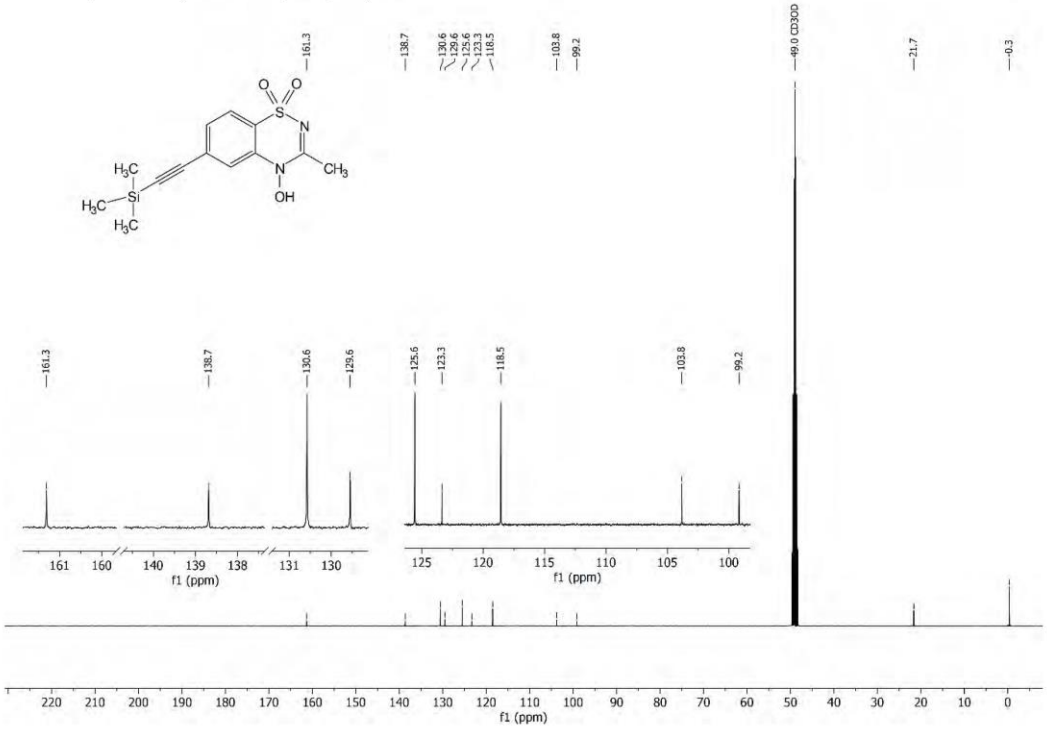
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7aa**



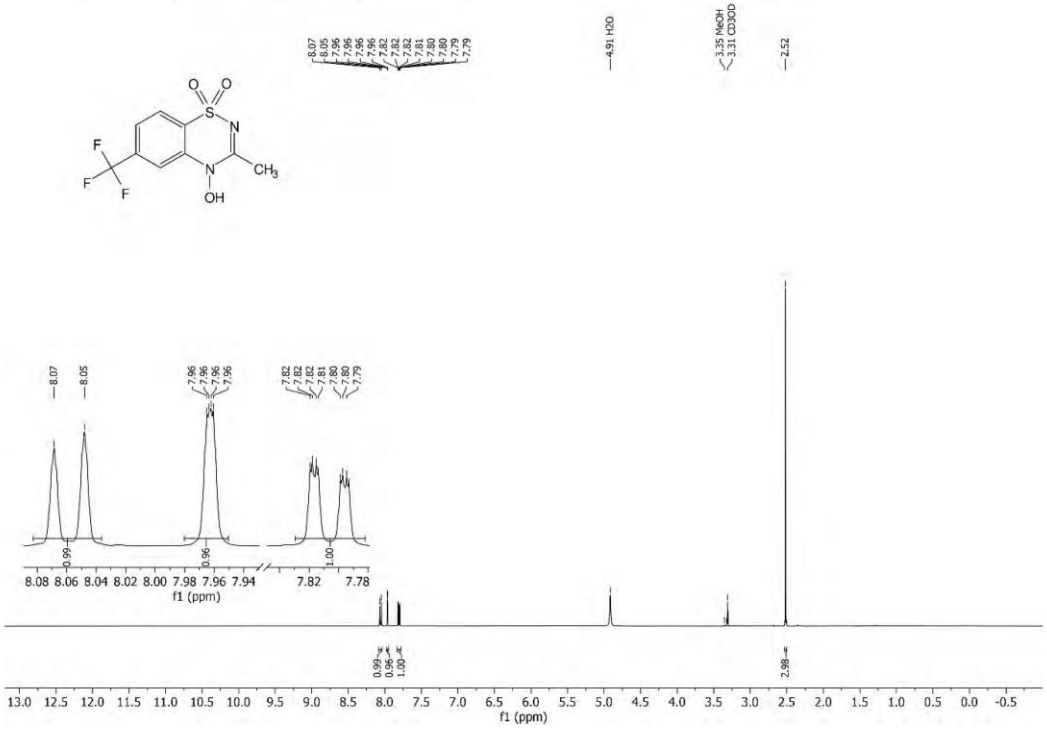
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7ab**



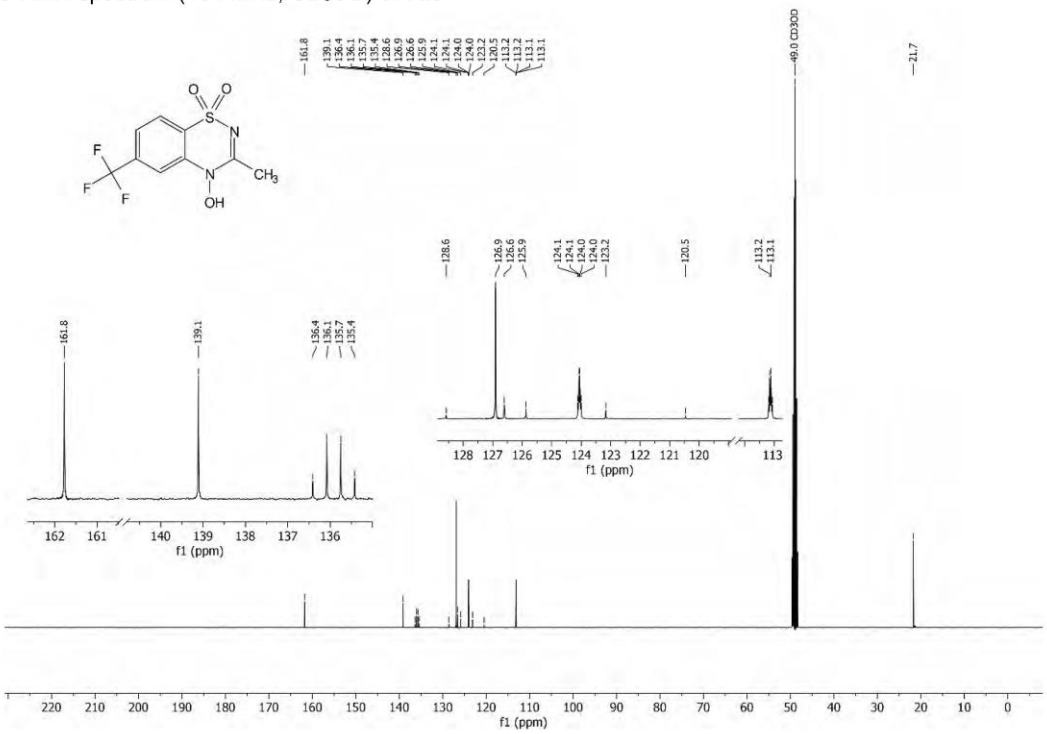
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7ab**



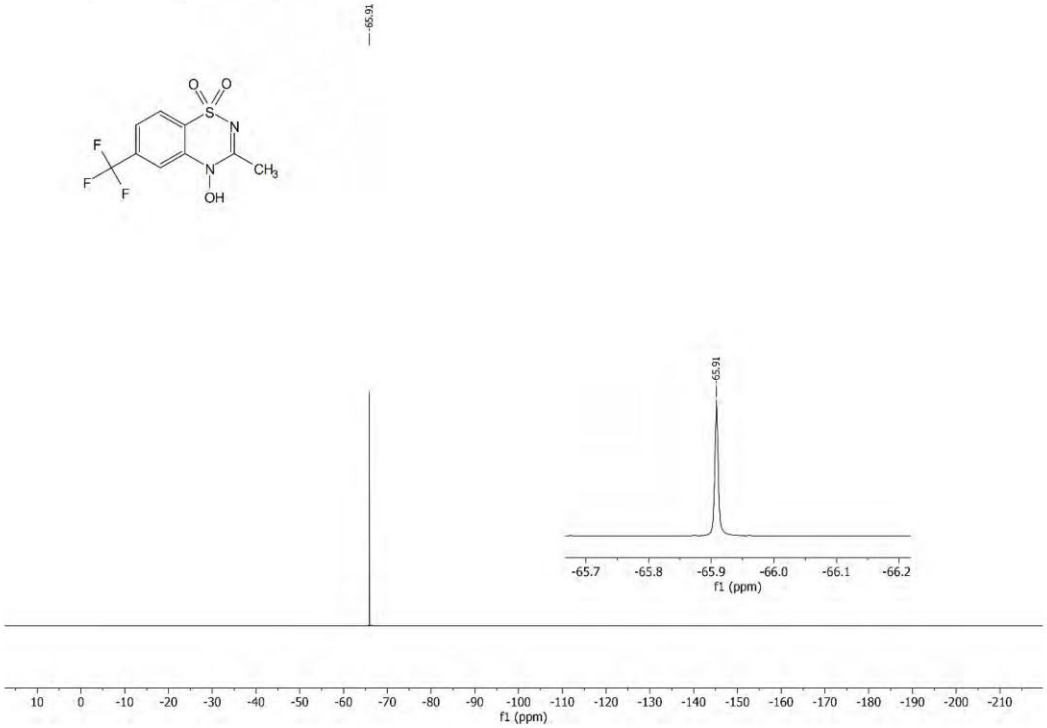
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7ac**



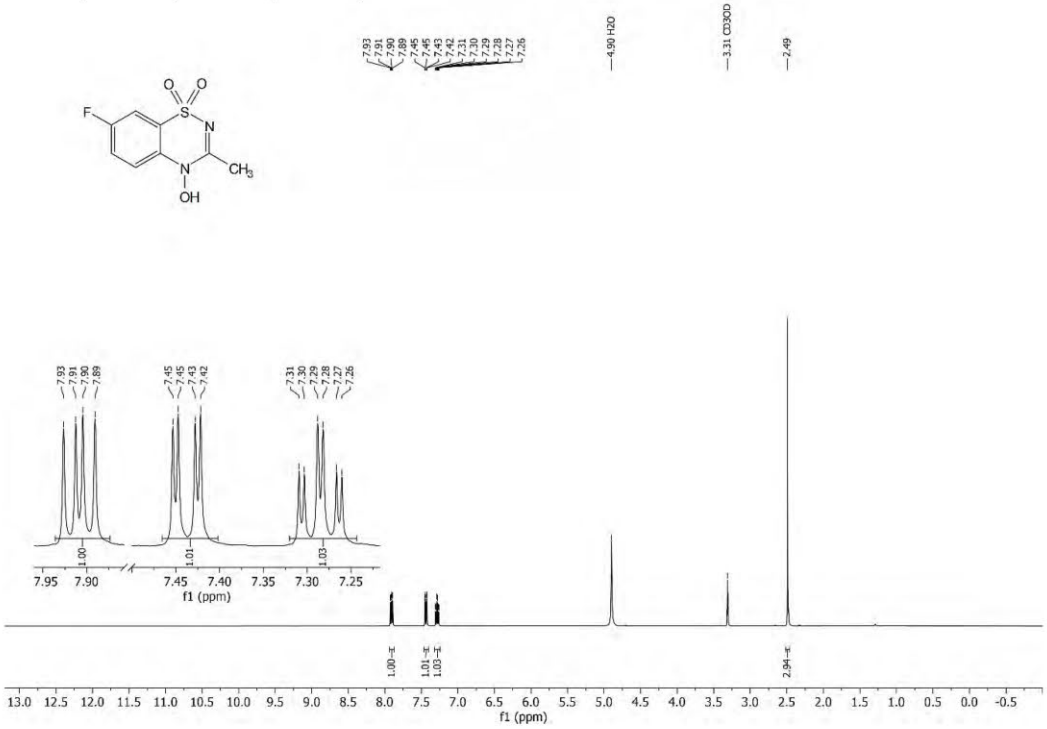
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7ac**



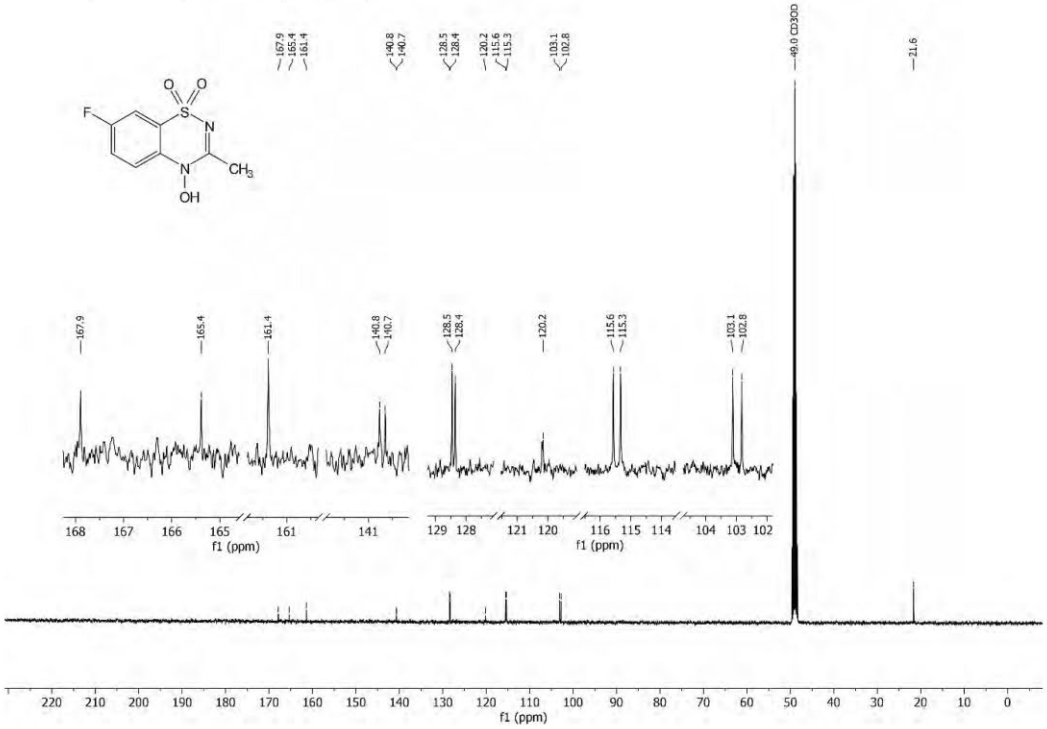
^{19}F NMR spectrum (376 MHz, CD_3OD) of **7ac**



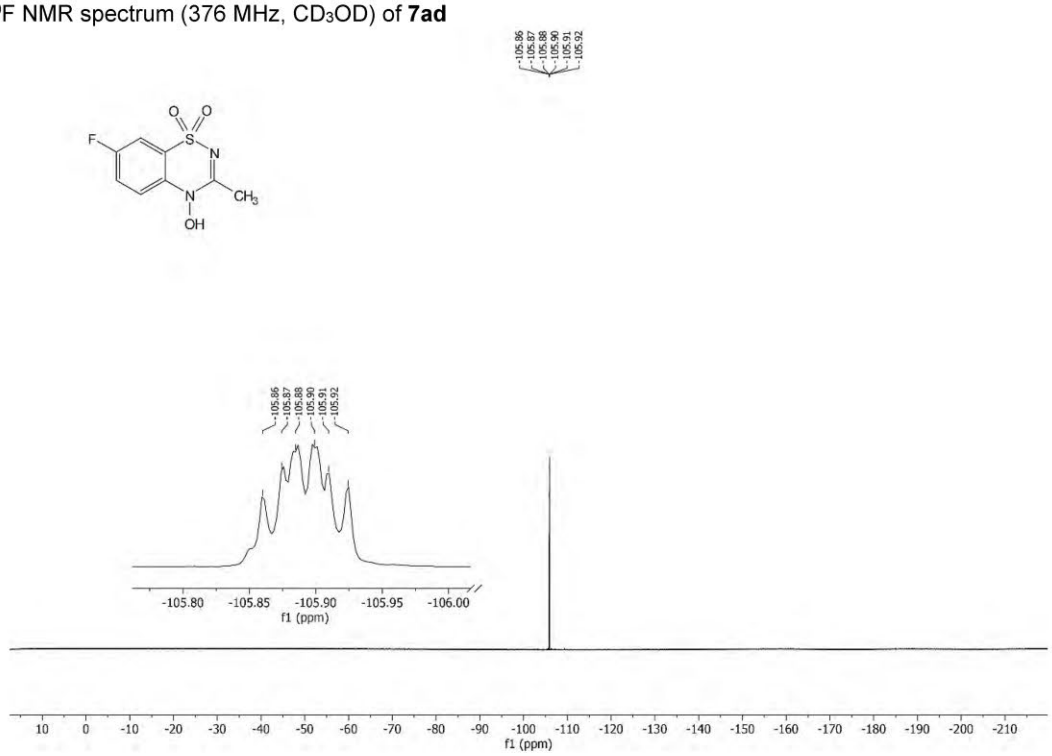
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7ad**



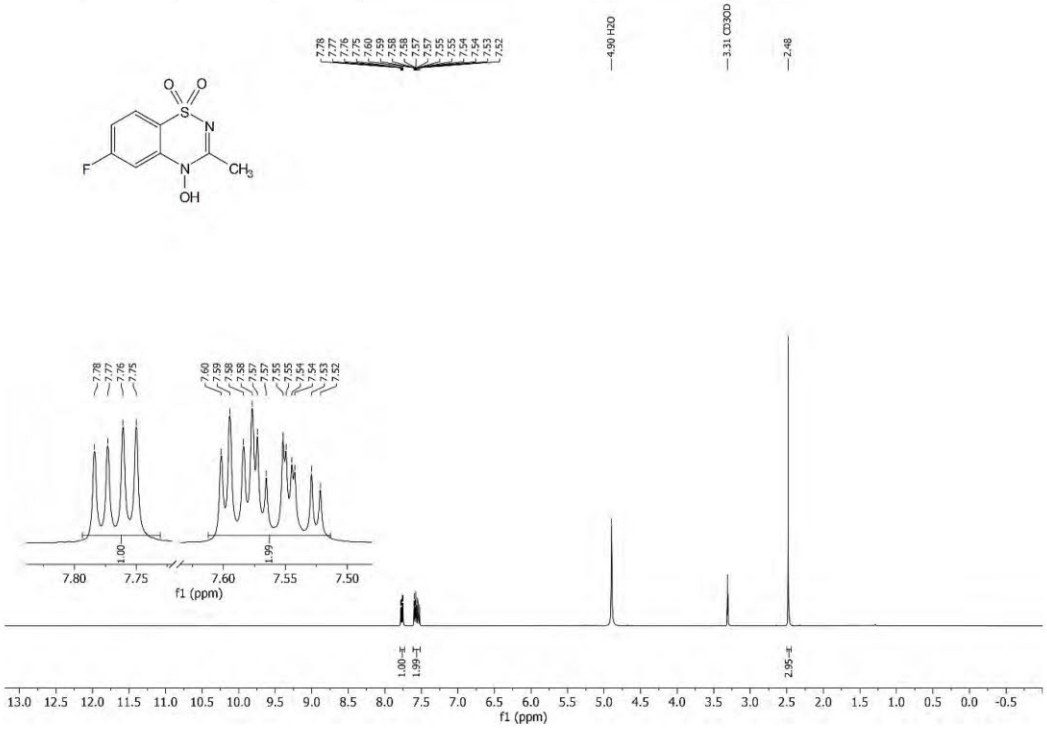
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7ad**



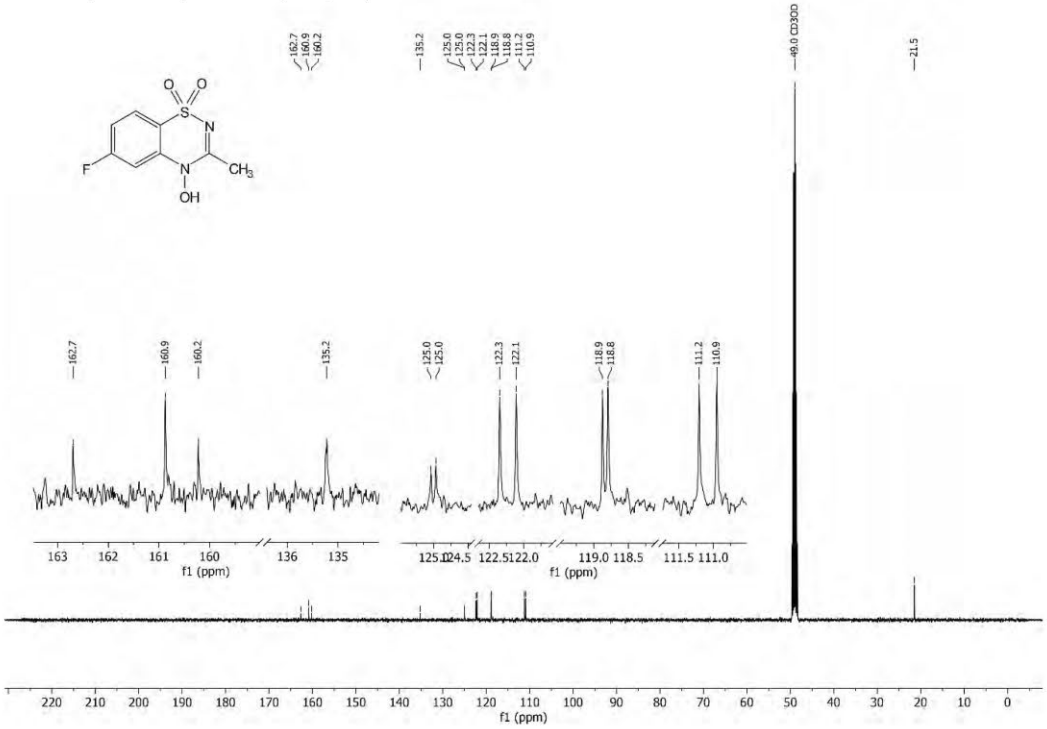
^{19}F NMR spectrum (376 MHz, CD_3OD) of **7ad**



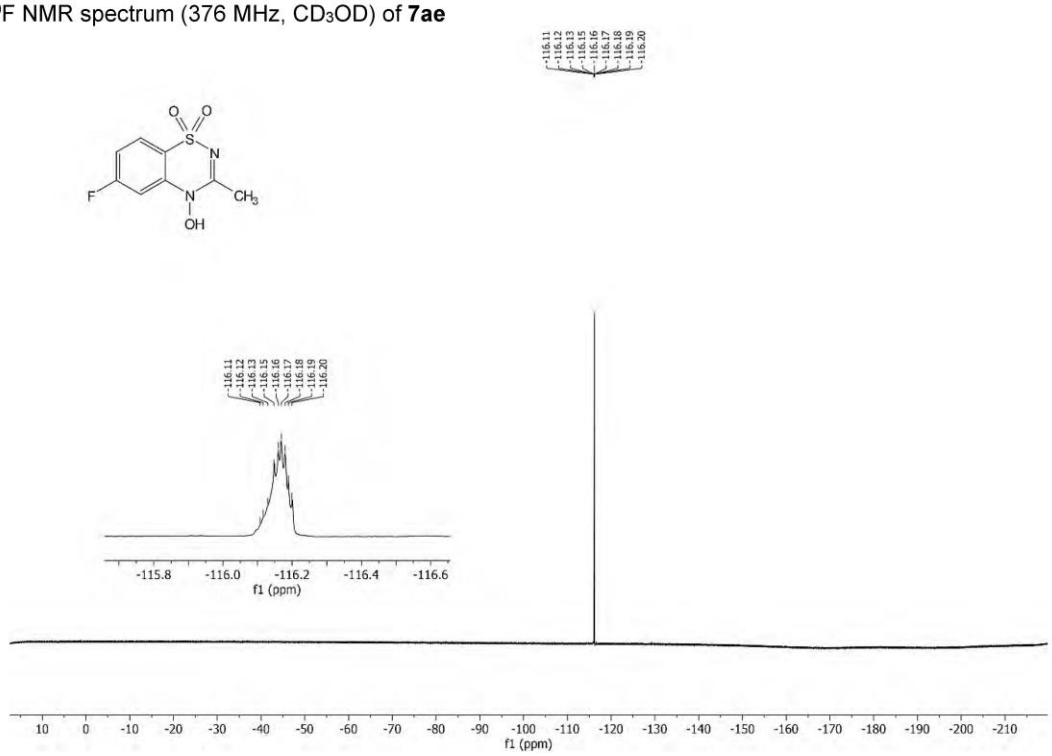
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7ae**



^{13}C NMR spectrum (101 MHz, CD_3OD) of **7ae**



^{19}F NMR spectrum (376 MHz, CD_3OD) of **7ae**



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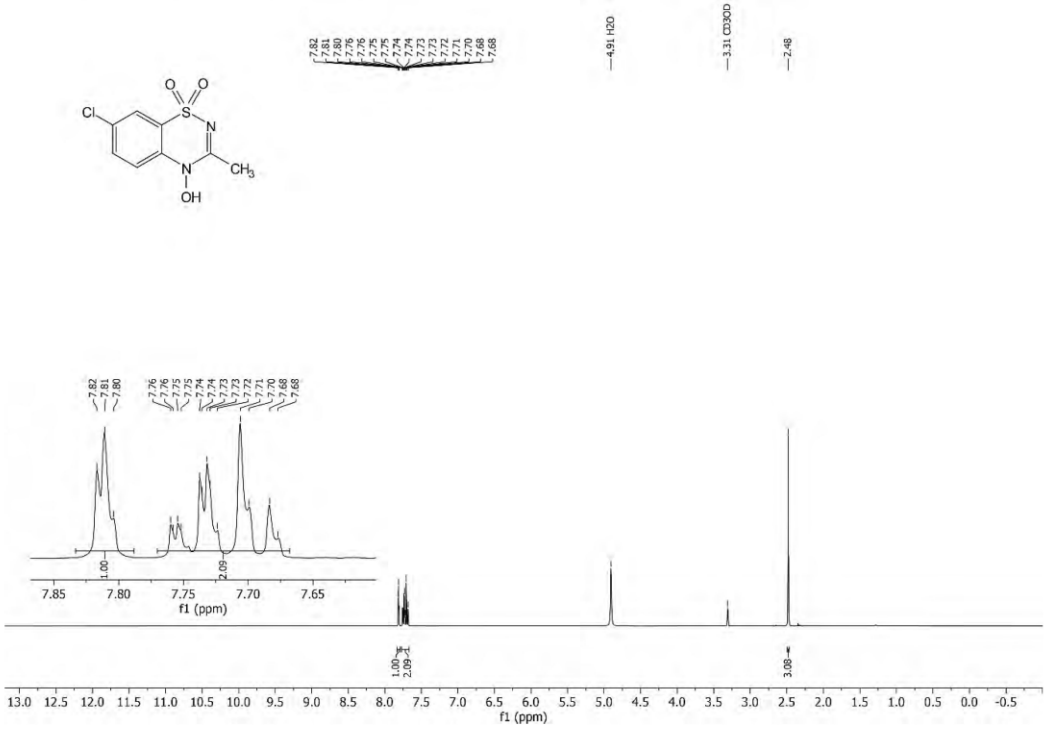
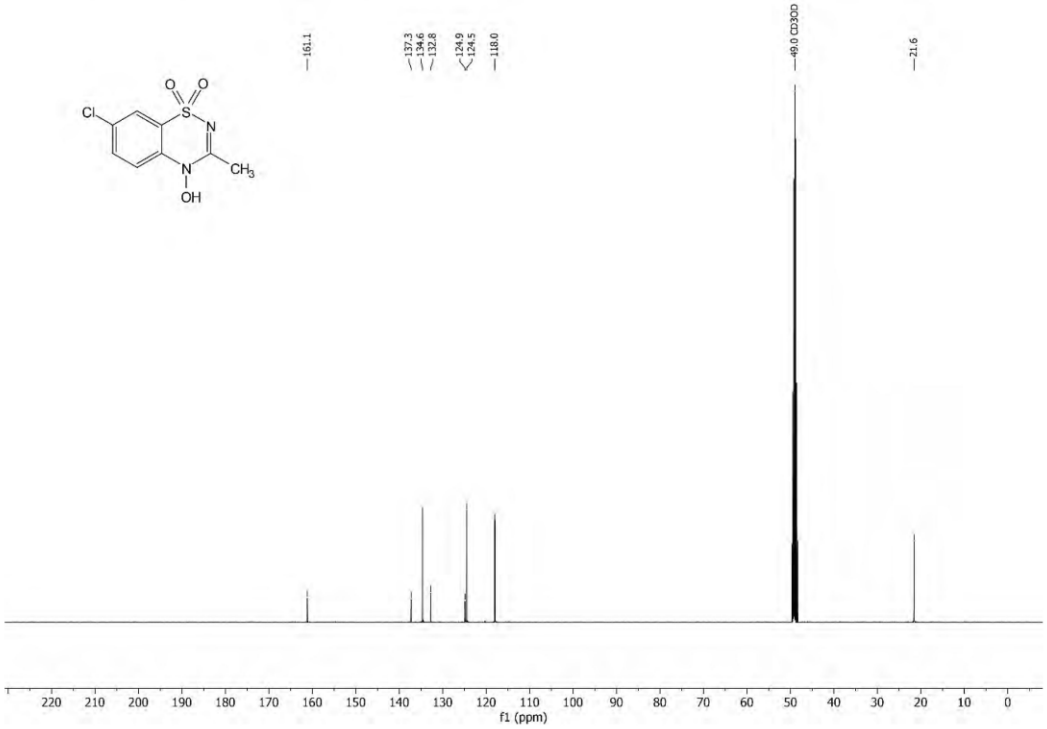


^{13}C NMR spectrum (101 MHz, CD_3OD) of **7af**



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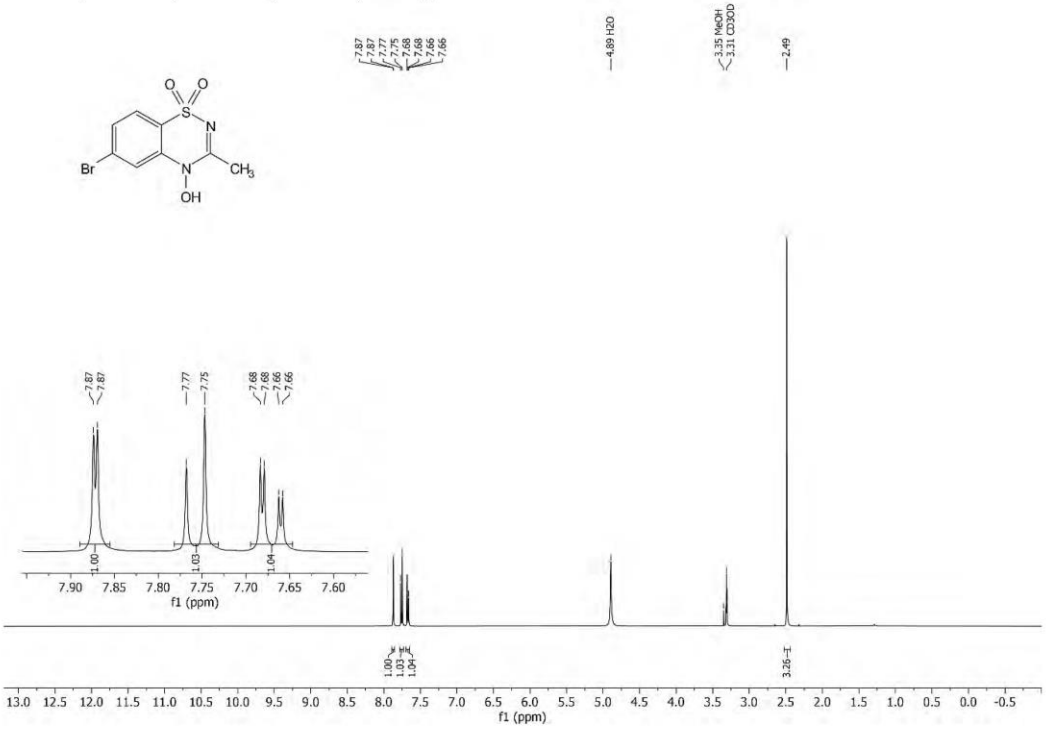
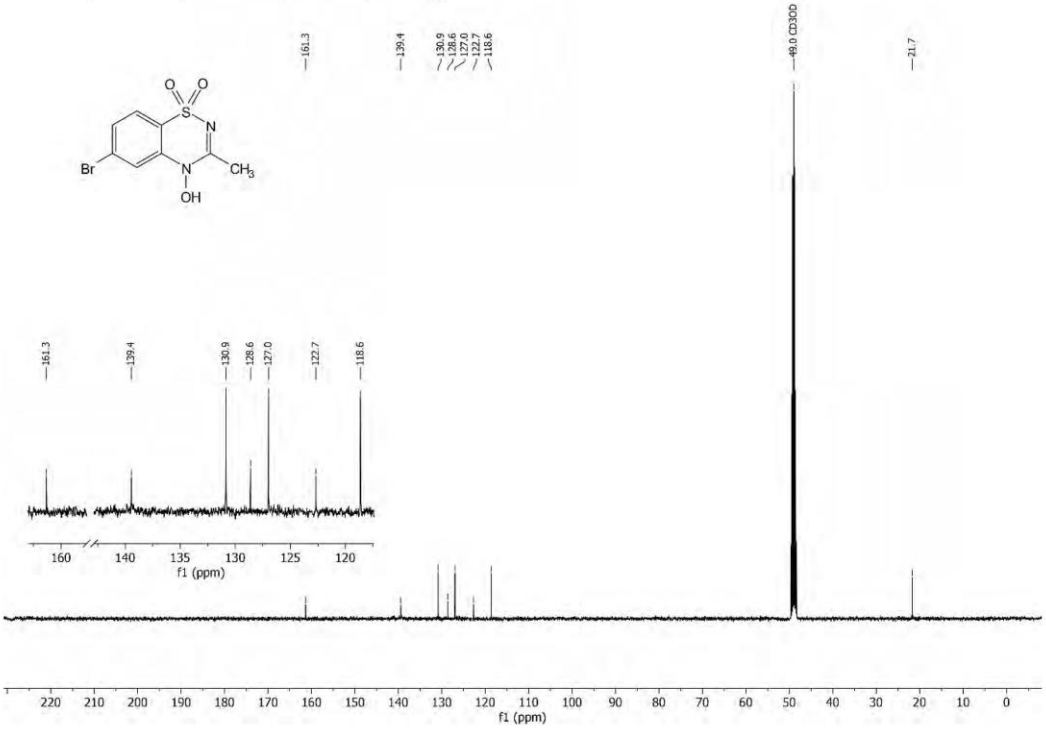


^{13}C NMR spectrum (101 MHz, CD_3OD) of **7ag**



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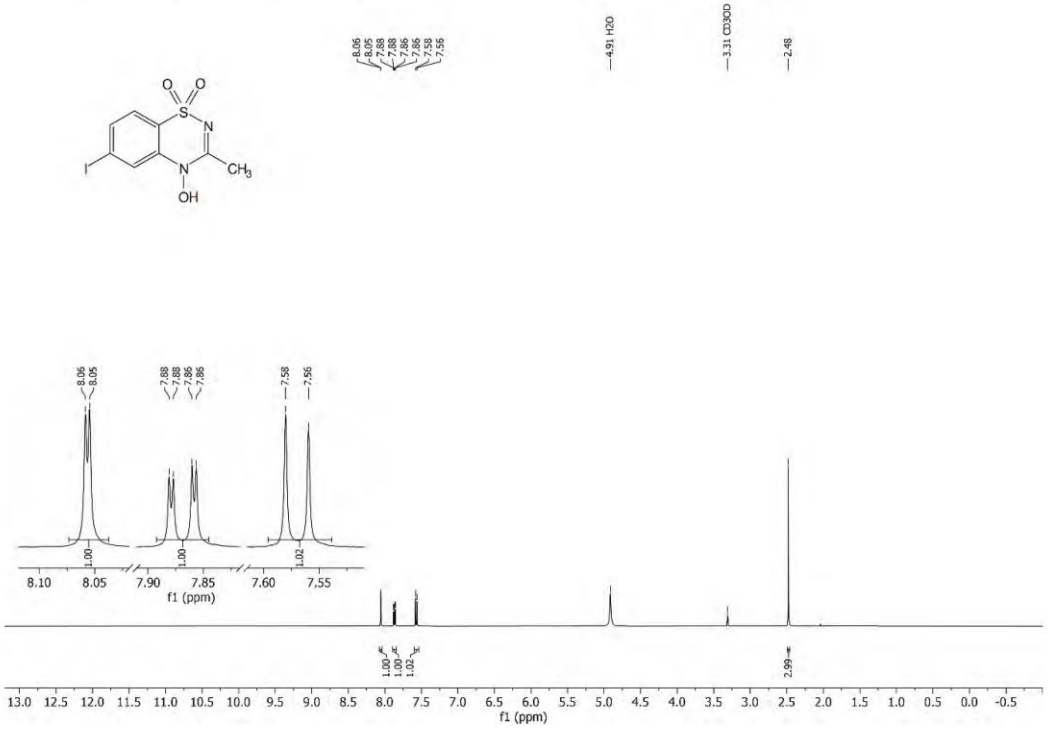
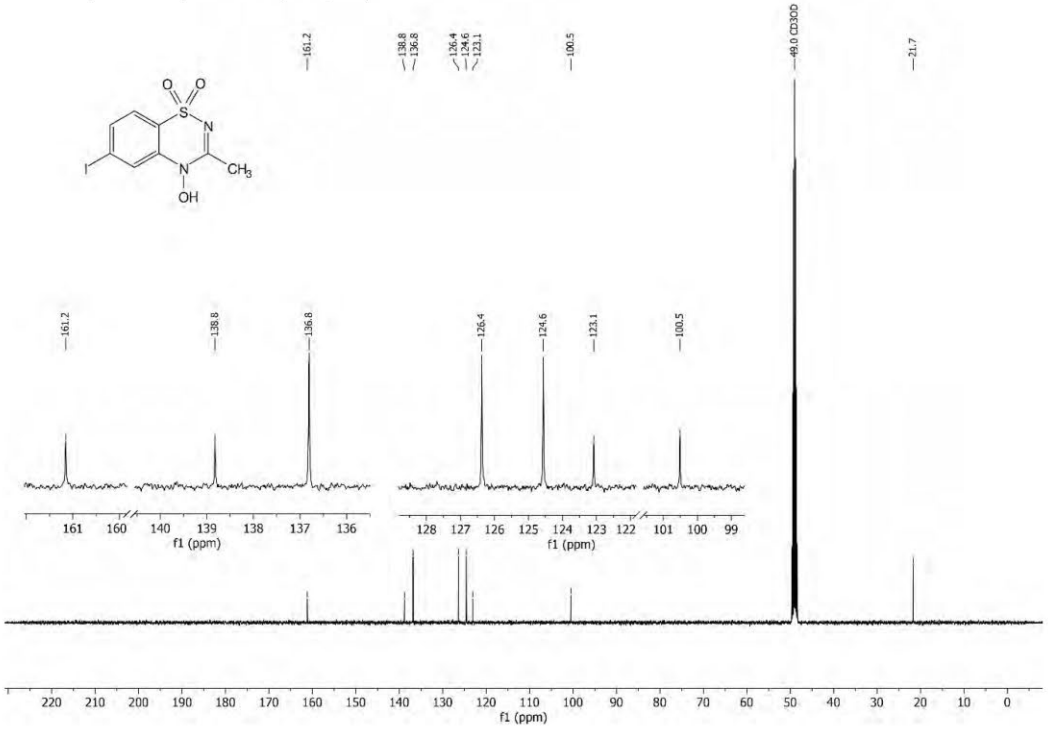


^{13}C NMR spectrum (101 MHz, CD_3OD) of **7ah**



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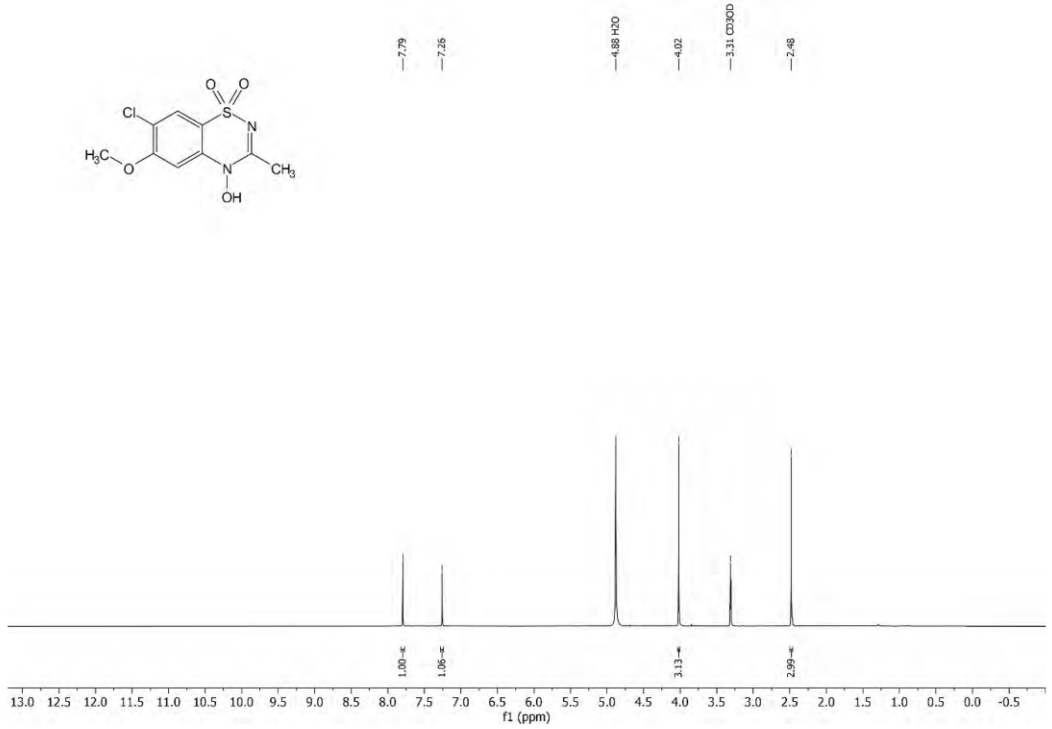
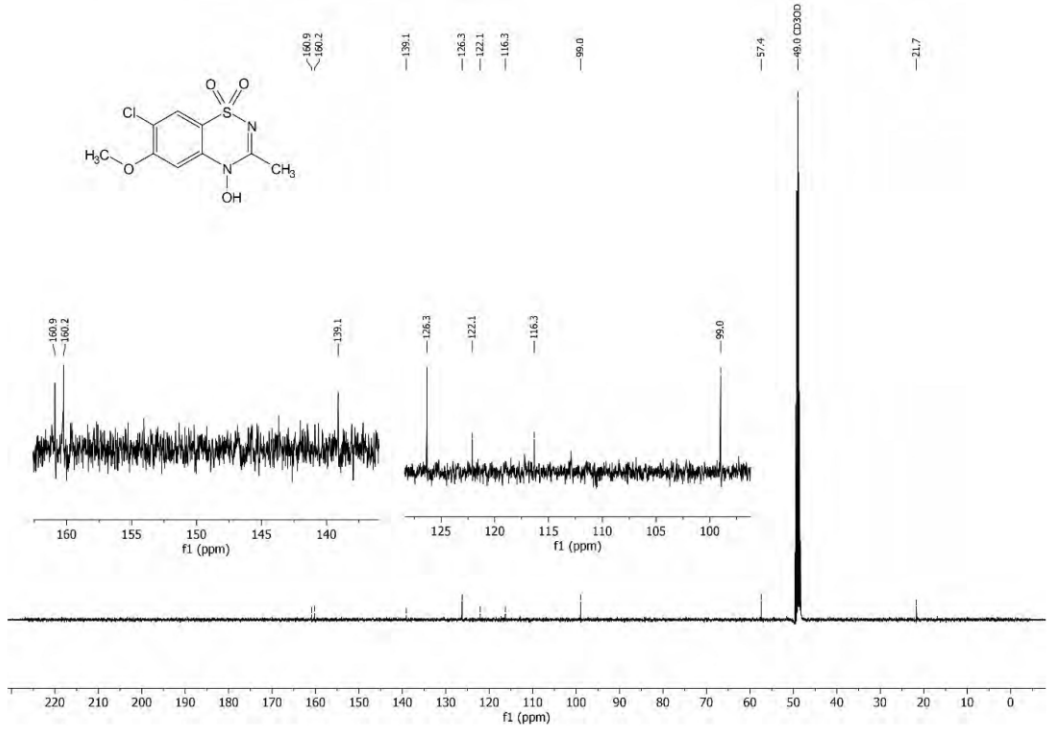


^{13}C NMR spectrum (101 MHz, CD_3OD) of **7ai**



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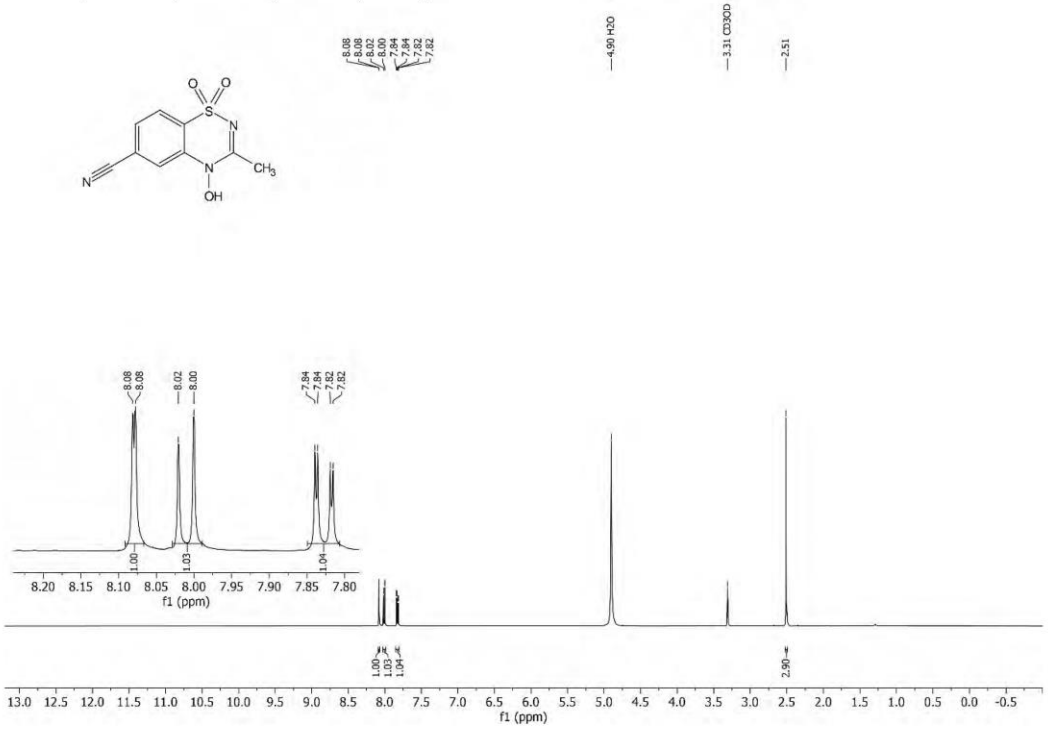
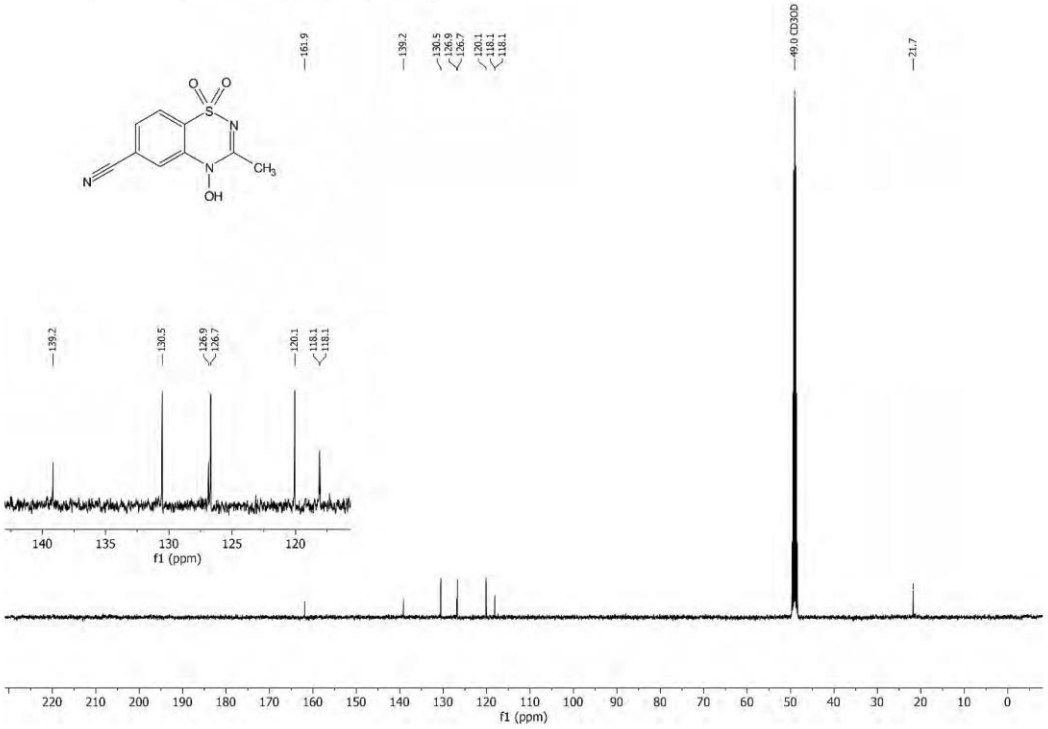


^{13}C NMR spectrum (101 MHz, CD_3OD) of **7aj**



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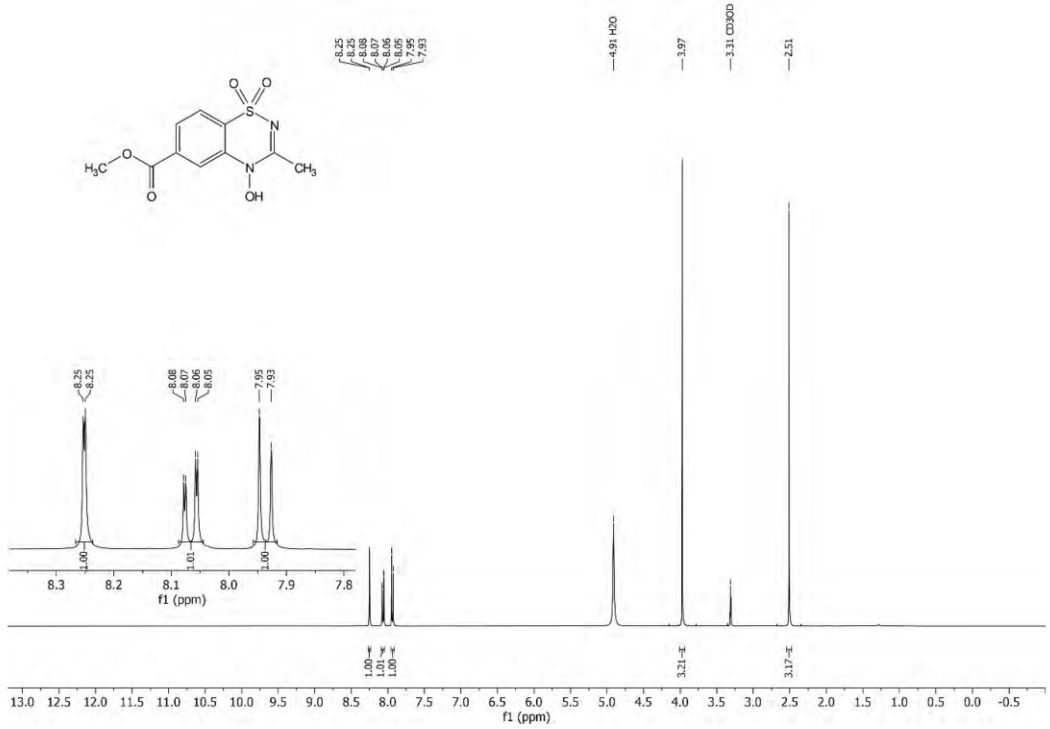
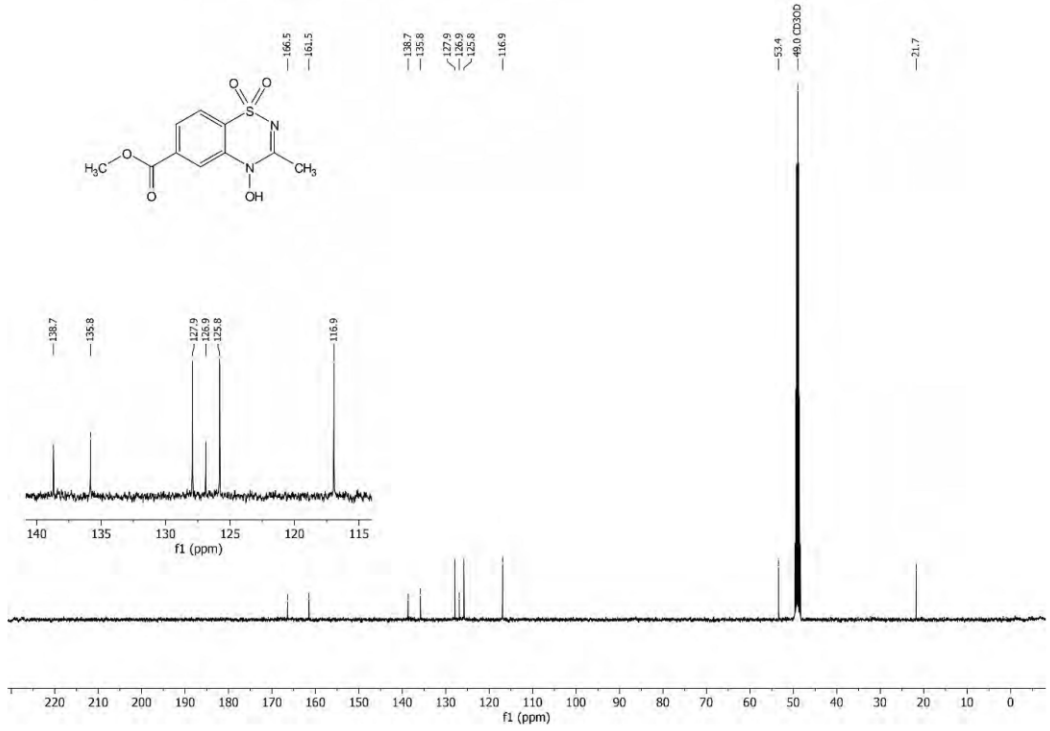


^{13}C NMR spectrum (101 MHz, CD_3OD) of **7ak**



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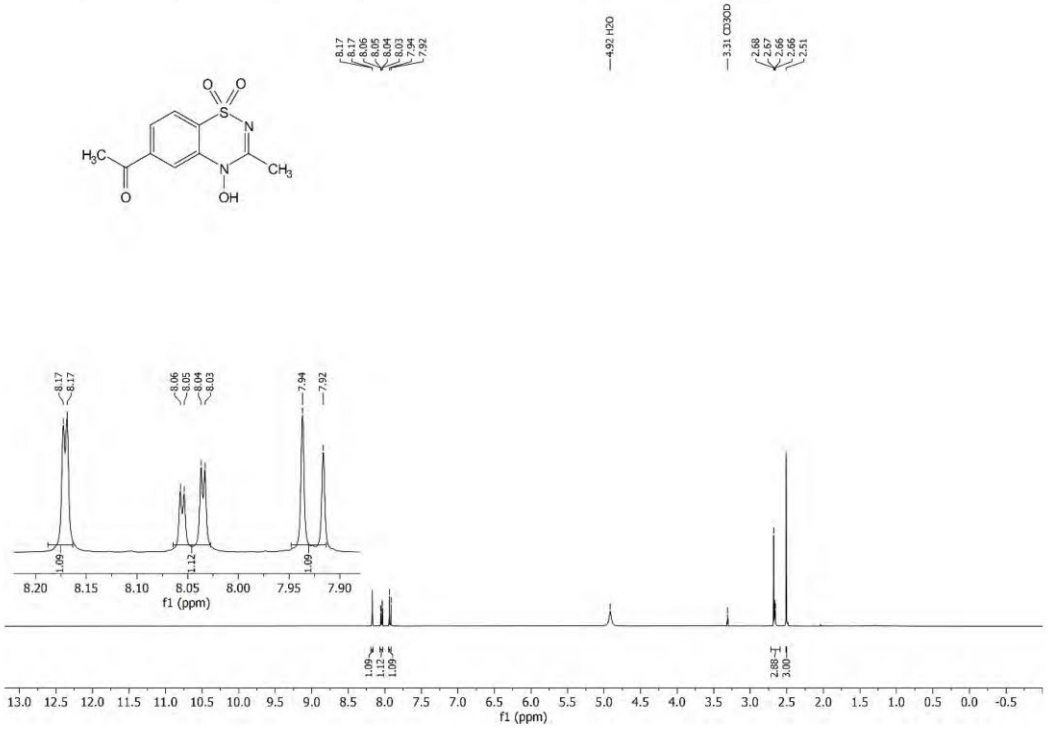

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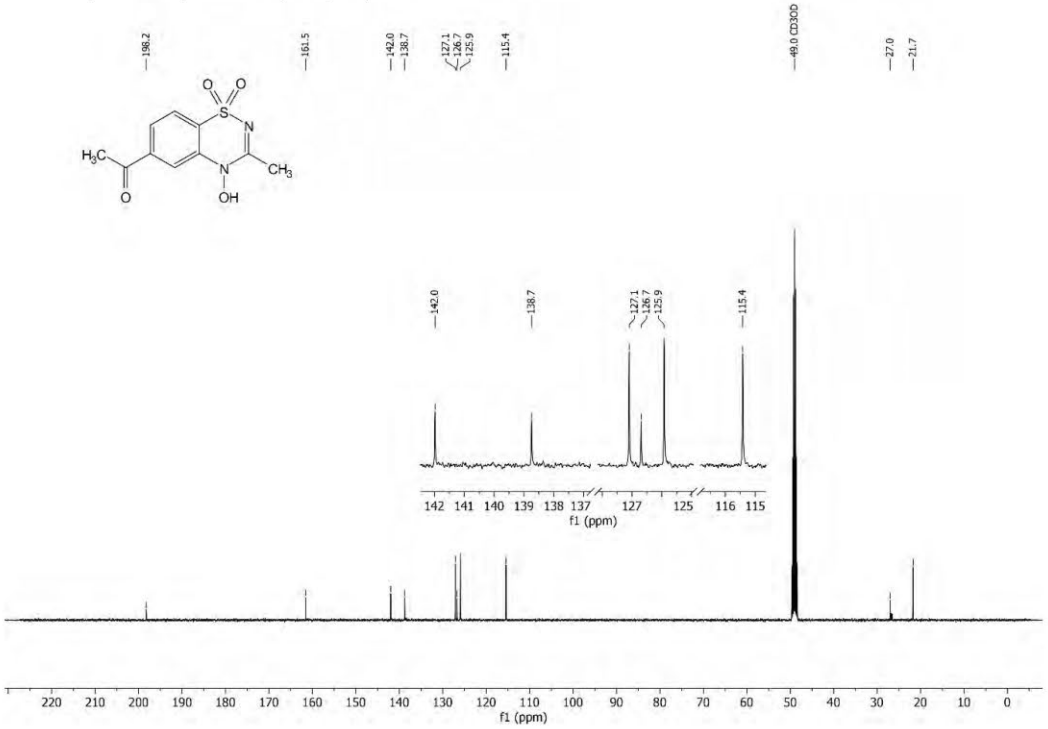

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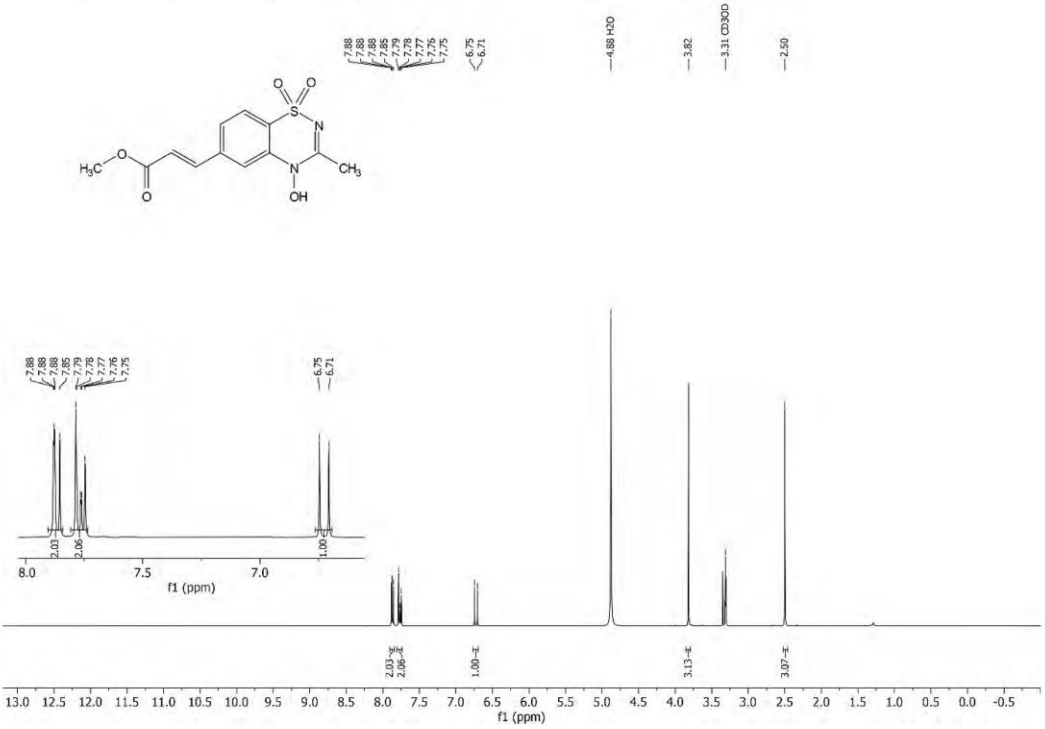

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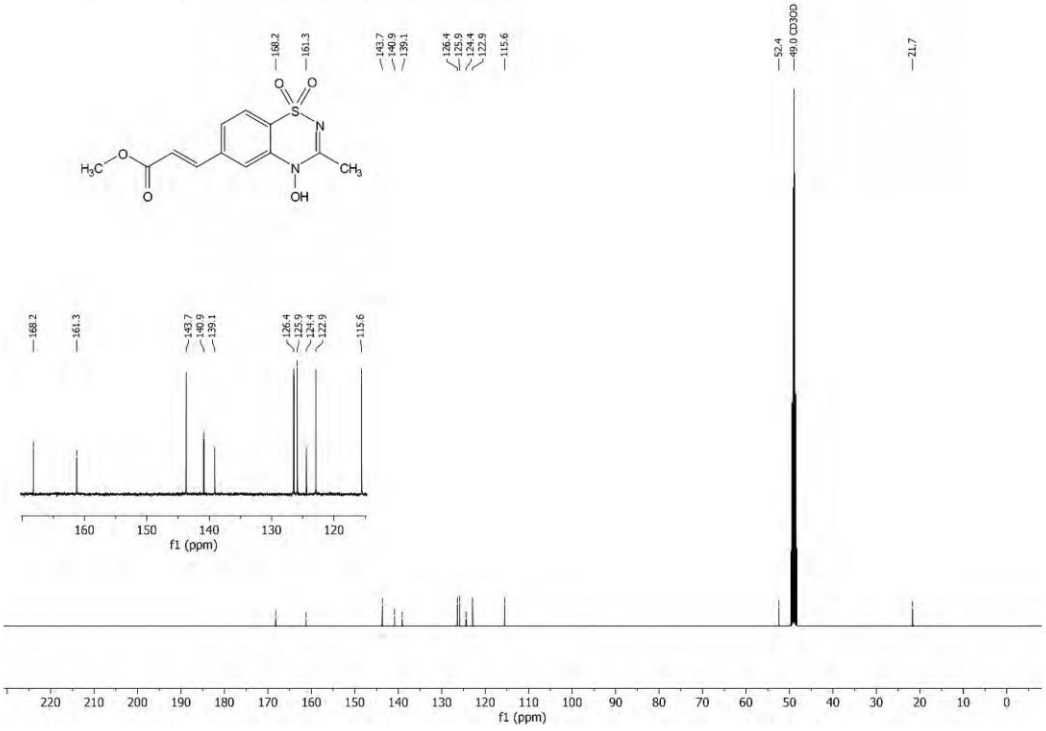
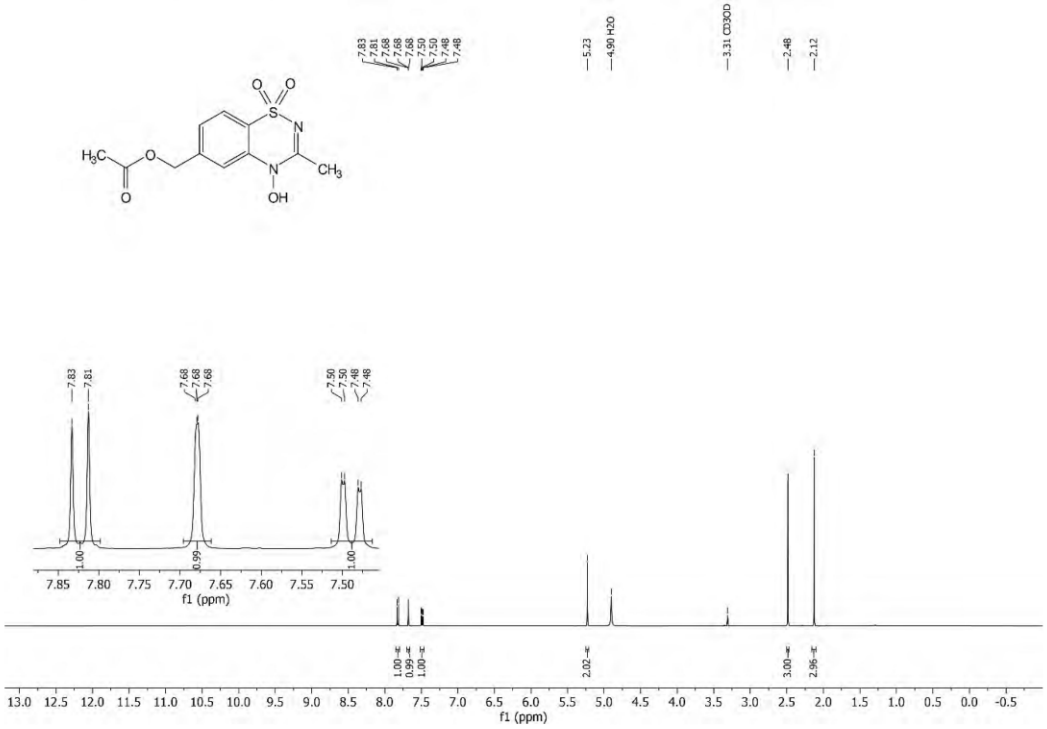
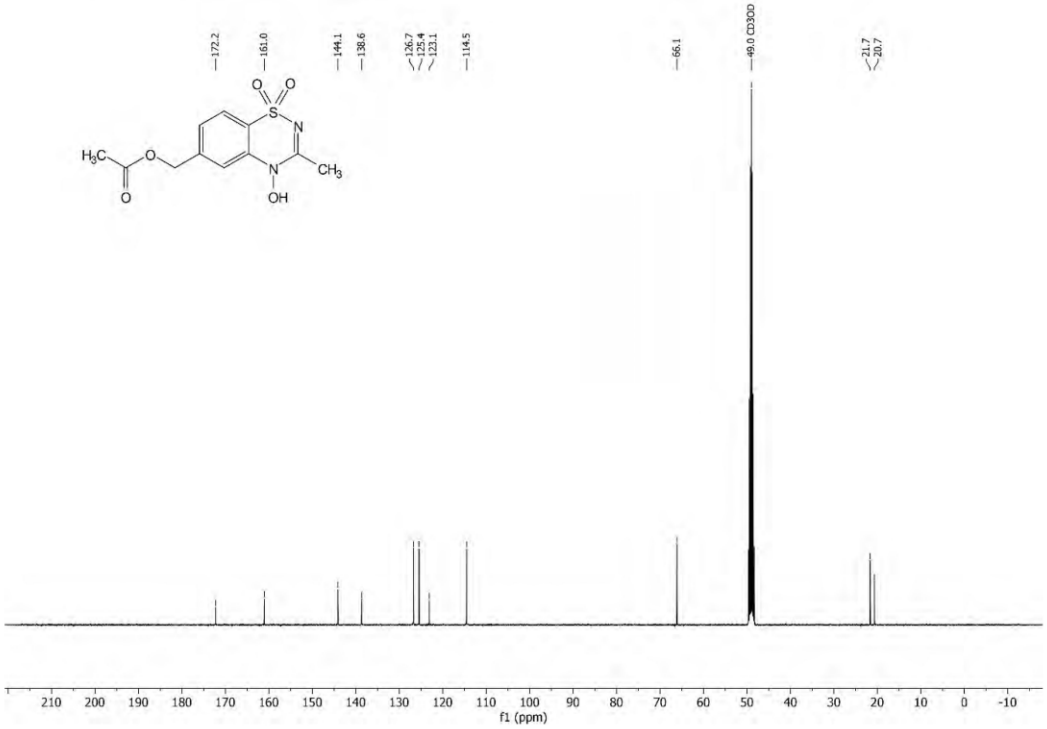


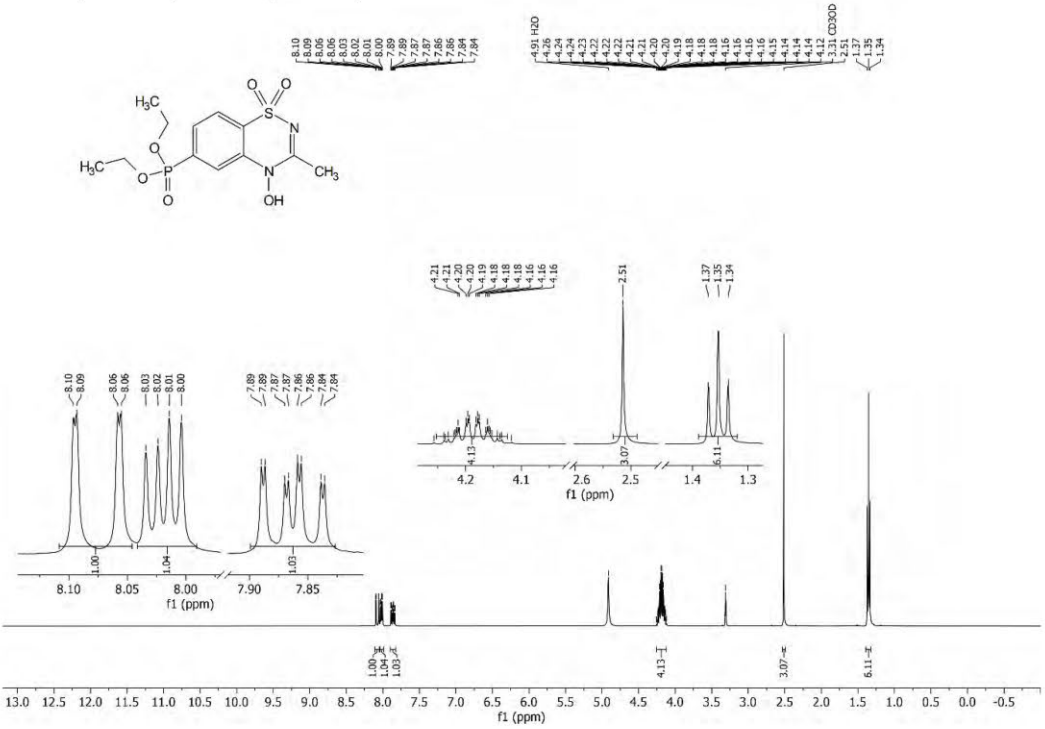
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7an**



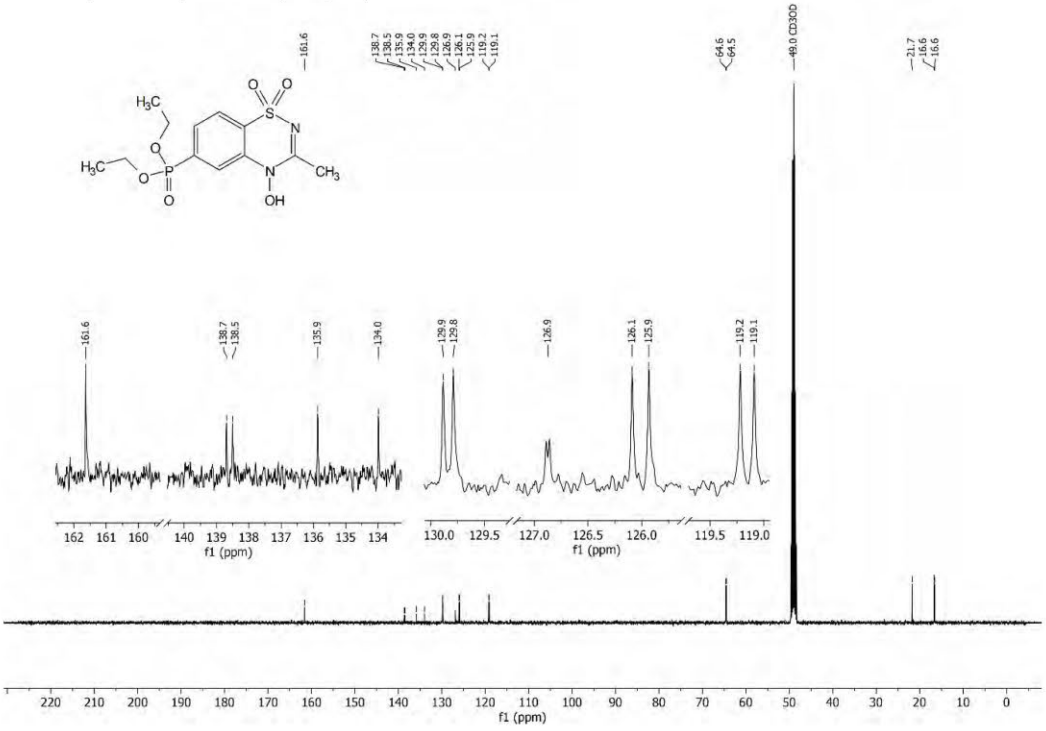
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7an**



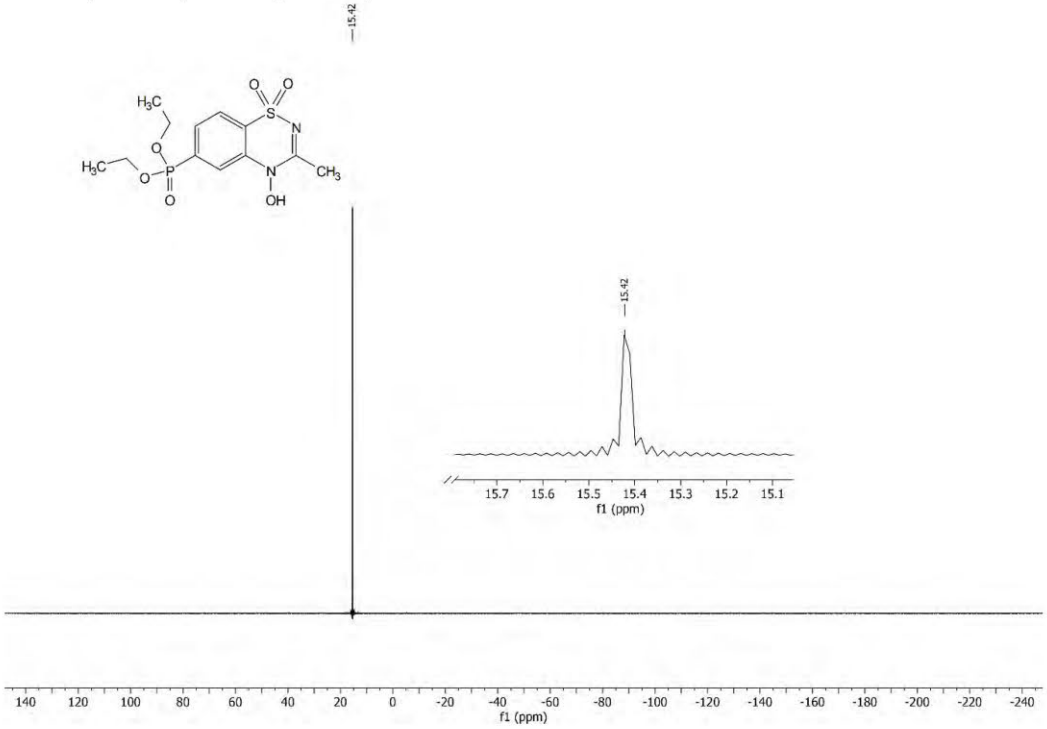
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7ao**



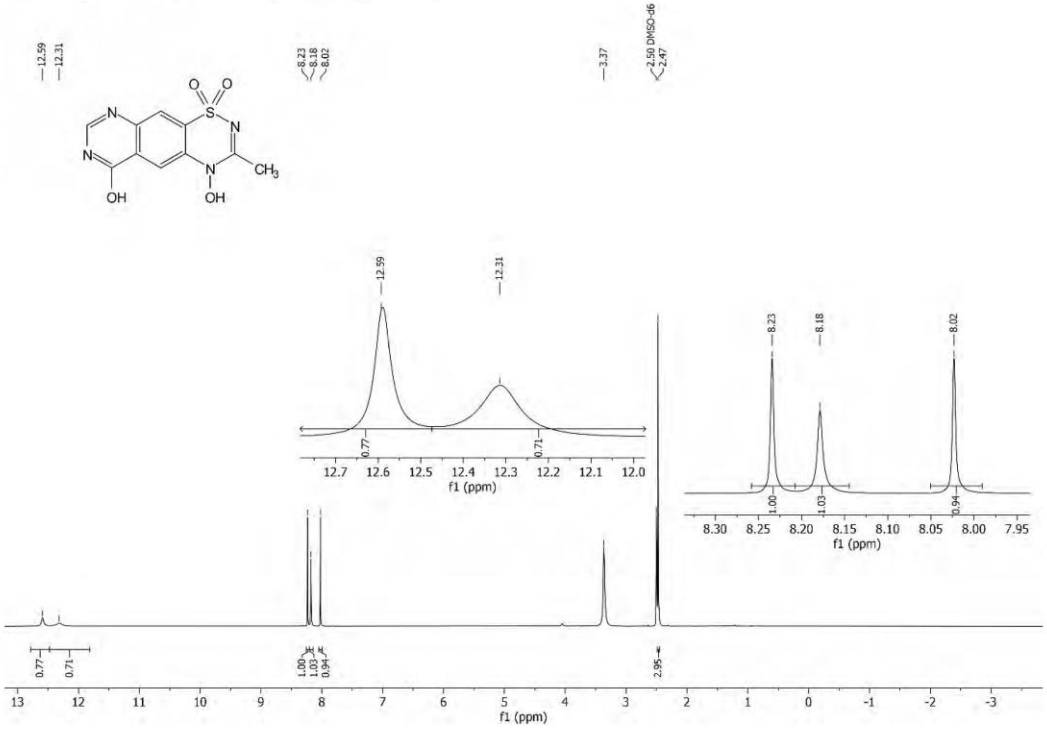
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7ao**



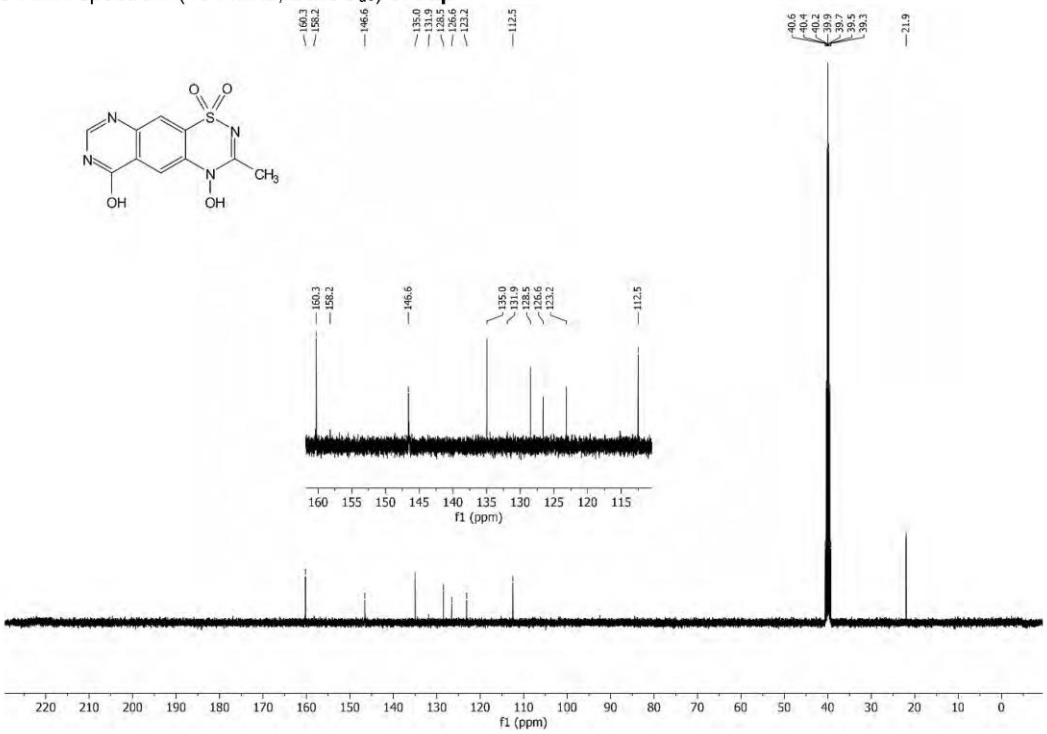
^{31}P NMR spectrum (162 MHz, CD_3OD) of **7ao**



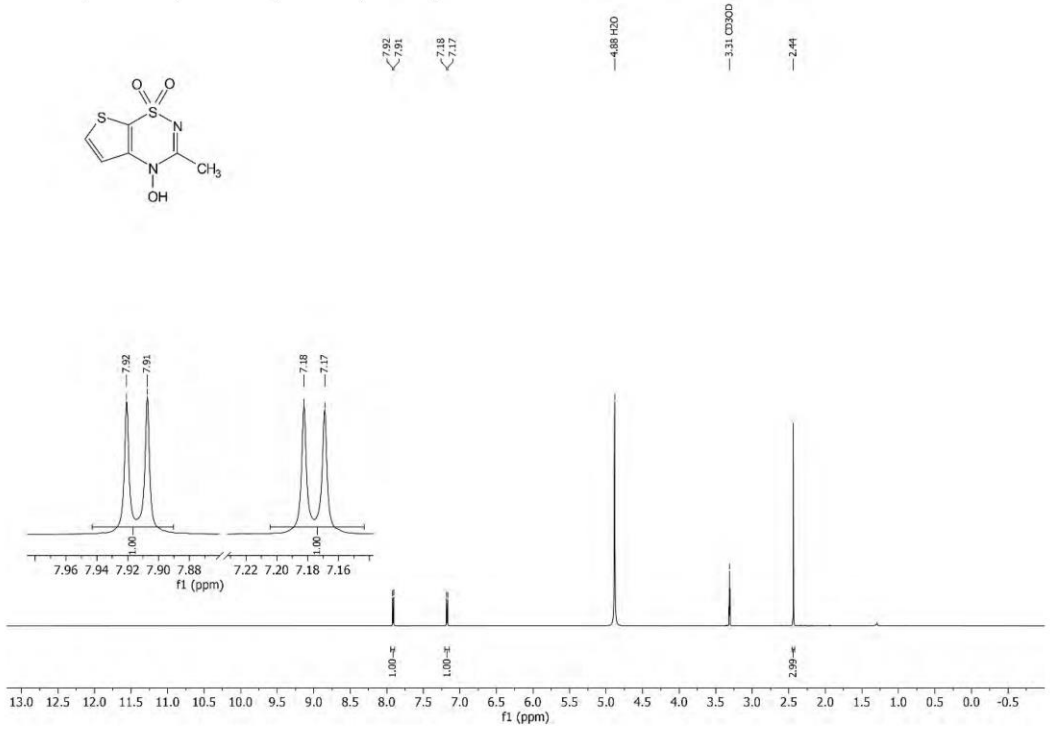
^{1}H NMR spectrum (400 MHz, DMSO$_{d6}$) of **7ap**



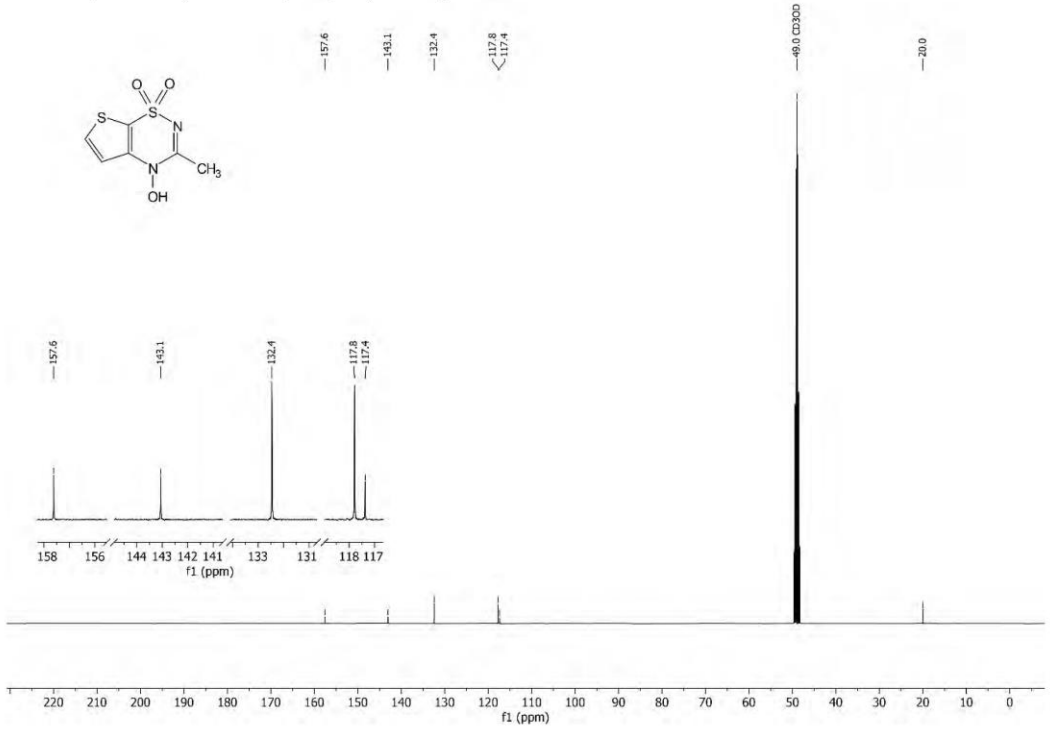
^{13}C NMR spectrum (101 MHz, DMSO$_{d6}$) of **7ap**



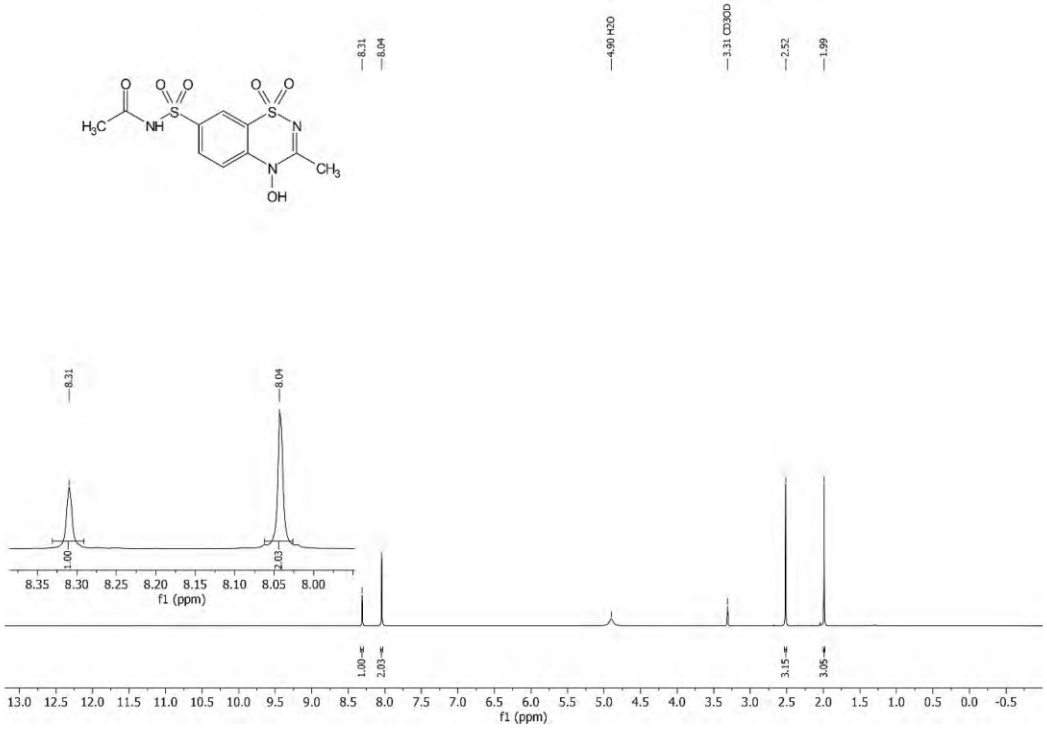
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7aq**



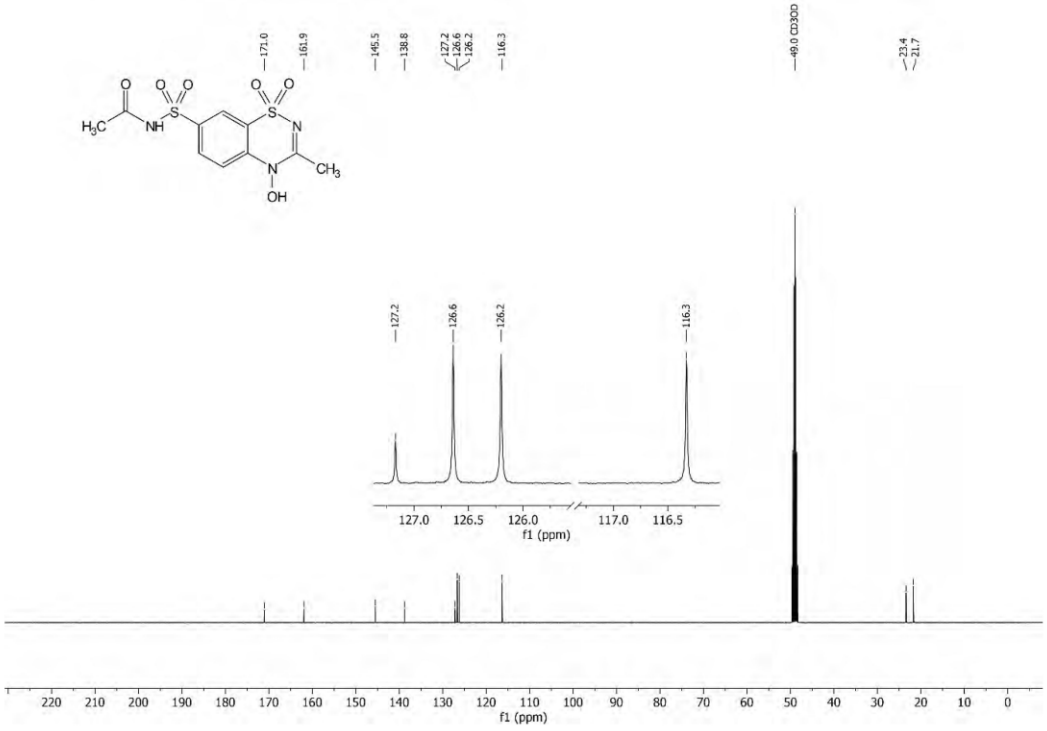
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7aq**



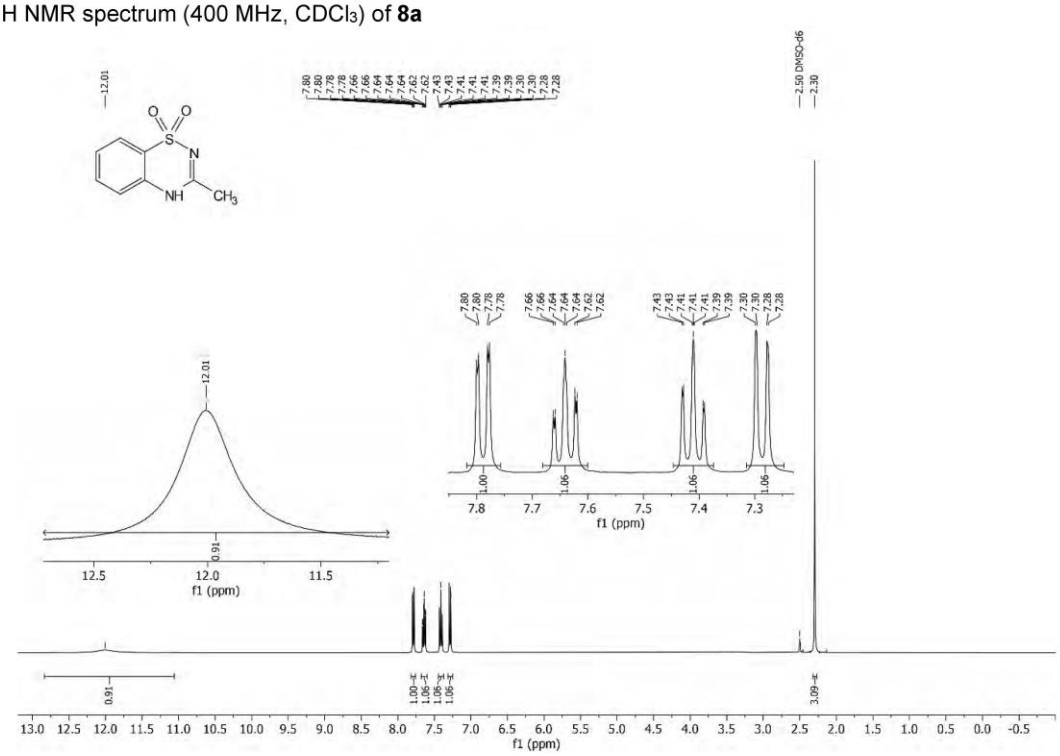
^{1}H NMR spectrum (400 MHz, CD_3OD) of **7ar**



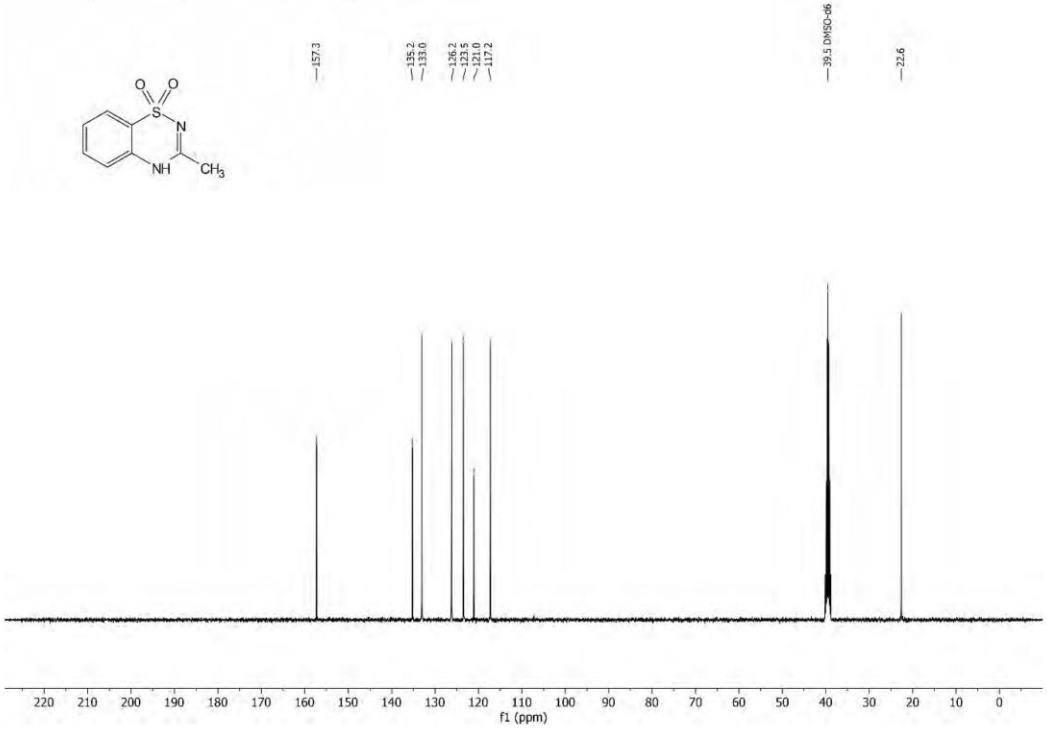
^{13}C NMR spectrum (101 MHz, CD_3OD) of **7ar**



^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **8a**



^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **8a**



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A-2.6 Supporting Information: Simple Electrochemical Synthesis of Cyclic Hydroxamic Acids by Reduction of Nitro Arenes

Electronic Supplementary Material (ESI) for ChemComm.
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Electronic Supporting Information (ESI)

Simple Electrochemical Synthesis of Cyclic Hydroxamic Acids by Reduction of Nitro Arenes

Johannes Winter, Susan Lühr, Kyra Hochadel, María de Jesús Gálvez-Vázquez, Tobias Prenzel, Dieter Schollmeyer and Siegfried R. Waldvogel

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1. General Information

If not stated otherwise, all reactions were performed under ambient conditions and chemicals in analytical grade were used as purchased without further purification. Cyclohexane and ethyl acetate were purchased in technical grade and purified by distillation under reduced pressure prior to use. Milli-Q® water was obtained using Simplicity® System (UV) (*Merck KGaA*, Darmstadt, Germany) for chromatography purposes. Anhydrous solvents were prepared by a solvent purification system SPS-5 (*M. Braun Incorporated*, Stratham, USA).

Chromatography
Thin layer chromatography was performed using DC silica gel 60 F254 on aluminum plates (*Merck KGaA,* Darmstadt, Germany). A UV lamp (λ = 254 nm, NU-4 KL, *Benda*, Wiesloch, Germany) was used for detection. Preparative flash column chromatography was performed on silica gel 60 M (0.040–0.063 mm, 12 g or 80 g, Macherey-Nagel GmbH & Co, Düren, Germany) using a Büchi Pure C-815 Flash (*Büchi-Labortechnik GmbH*, Essen, Germany). Reversed phase column chromatography of the different products was performed on a Puriflash® PF-30C18HP-F0080 (*Interchim SAS*, Montluçon Cedex, France) column using a Sepacore® system with a Büchi Control Unit C-620, Büchi Pump Modules C-605, a UV detector Büchi UV photometer C-635, and Büchi Fraction Collector C-660 (*Büchi-Labortechnik GmbH*, Essen, Germany) using different mixtures of water (0.1% formic acid (*v/v*)) and acetonitrile as eluents.

High Resolution Mass Spectrometry
Mass spectra *via* electrospray-ionization (ESI+/ESI–) mass spectrometry were recorded using an Agilent 6545 QTOF-MS (*Agilent*, Santa Clara (CA), USA). Mass-charge ratios (*m/z*) were obtained for the characterized compounds.

X-ray Crystallography
The measurements of the crystal structures were carried out on a STOE IPDS-2T (*STOE & Cie GmbH*, Darmstadt, Germany) using a Mo source with graphite tube monochromator.

High Performance Liquid Chromatography (HPLC)
Analysis of crude reaction mixtures, purified products and method development was performed using a modular system LC-20A *Prominence* (*Shimadzu Deutschland GmbH*, Duisburg, Germany), UV/VIS-detector SPD-20A/AV (*Shimadzu Deutschland GmbH*, Duisburg, Germany), and LCMS-2020 Single Quadrupole (*Shimadzu Deutschland GmbH*, Duisburg, Germany). Analytical separation was performed using an Eurospher II 100-5 C-18-Trennsäule (*Knauer Wissenschaftliche Geräte GmbH*, Berlin, Germany) column (length of 150 mm, diameter of 4 mm, pore size of 100 Å, particle size 5 µm). As eluents, acetonitrile, and water with 5% (*v/v*) acetonitrile and formic acid (0.1% (*v/v*)) were used. Given retention times were obtained at λ = 254 nm.

Nuclear Magnetic Resonance (NMR) Spectroscopy
Nuclear magnetic resonance experiments were performed using a nuclear magnetic resonance spectrometer Avance III HD300 (*Bruker*, Karlsruhe, Germany) ^{1}H NMR (300 MHz), ^{19}F NMR (282 MHz), Avance II 400 (*Bruker*, Karlsruhe, Germany) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz) and Avance III 600 (*Bruker*, Karlsruhe, Germany) ^{1}H NMR (600 MHz), ^{13}C NMR (151 MHz). The spectra were recorded using deuterated solvents. To normalize the spectra obtained, reference was made to the existing solvent signal of non-deuterated fractions according to the data provided by *Fulmer et al.*:[1] $CDCl_3$ (^{1}H NMR: δ = 7.26 ppm, ^{13}C NMR: δ = 77.2 ppm), dichloromethane-d_2 (^{1}H NMR: δ = 5.32 ppm, ^{13}C NMR: δ =53.8 ppm), acetonitrile-d_3 (^{1}H NMR δ = 1.94 ppm, ^{13}C NMR: δ = 118.3 ppm), CD_3OD (^{1}H NMR δ = 3.31 ppm, ^{13}C NMR: δ =49.0 ppm) and $DMSO_{d6}$ (^{1}H NMR δ = 2.50 ppm, ^{13}C NMR: δ =39.5 ppm). Besides ^{1}H, ^{13}C and ^{19}F NMR experiments, the 2D techniques ^{1}H,^{1}H COSY, ^{1}H,^{13}C HSQC and ^{1}H,^{13}C HMBC were used assisting to assign the signals. The following abbreviations were used to describe the signals: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), m (multiplet), q (quartet), sep (septet), ddd (doublet of doublets of doublets). The spectra obtained were evaluated with MestReNova 14.2.0-26256 (*Mestrelab Research S.L.*, Spain).

Melting Points
Melting points of crystallised products were determined using a M-565 (*Büchi Labortechnik*, Essen, Germany) with a heating rate of 1 °C/min. The melting points are reported uncorrected.

Cyclic Voltammetry (CV) Measurements

The mechanism of the reaction was studied by cyclic voltammetry using an electrochemical glass cell (figure S1) equipped with a BDD tip electrode (with a diameter of 4 mm), a boron-doped diamond disc (diameter: 2 mm), glassy carbon rod and a Ag/AgCl (saturated LiCl in ethanol, *Metrohm AG*, Herisau, Switzerland) as working, counter and reference electrode, respectively. The electrode potentials are reported with reference to the redox system ferrocene/ferrocenium (FcH/FcH^+).
Cyclic voltammograms were measured using a potentiostat/galvanostat PGSTAT302N (*Metrohm AG*, Herisau, Switzerland) with a scan rate of 50 mV s^{-1} in a methanol (HPLC LC-MS grade, *VWR International GmbH*, Darmstadt, Germany) and water solution (1:1 v/v) containing 0.5 M of H_2SO_4 (analytical reagent grade, *Fisher Scientific GmbH*, Schwerte, Germany) and 5 mM of the corresponding molecule. Prior to the CV measurements, the electrolyte was degassed with an argon flow for 25 min. An argon flow was kept flowing over the electrolyte during the measurements.

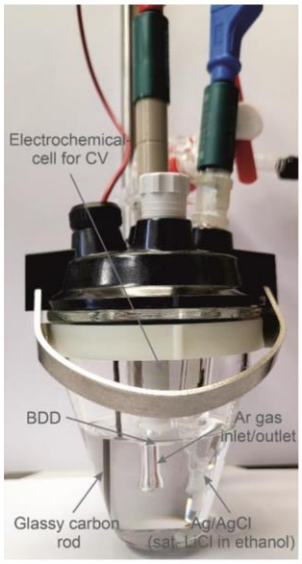


Figure S1: Electrochemical cell for cyclic voltammetry measurements.

Electrode Materials
Electrode material, purity, and their supplier are listed in table S1. Boron-doped diamond (BDD) electrodes were treated prior to electrosynthesis in 20% aqueous sulfuric acid (10 $C \cdot cm^{-2}$) with current density of 10 $mA \cdot cm^{-2}$ by polarizing subsequently anodically and then cathodically. After the treatment, the cathode was rinsed with water, methanol, and dried. Lead and leaded bronze CuSn7Pb15 were polished with sandpaper (600 grit and 1000 grit), rinsed with water and methanol and dried. Isostatic graphite was polished with sandpaper (1000 grit), rinsed with methanol and dried.

Table S1: Electrode materials, purity, and their supplier.

Entry	Electrode Material	Purity	Supplier
1	Boron-doped diamond (DIACHEM™)	15 µm boron-doped diamond layer on silicon	*CONDIAS GmbH*, Itzehoe, Germany
2	Glassy carbon (Sigradur G)	-	*HTW*, Thierhaupten, Germany
3	Isostatic graphite (V2100)	-	*SGL Carbon*, Bonn, Germany
4	Lead	-	*Globus Fachmärkte GmbH & Co. KG,* Völklingen, Germany
5	Leaded bronze (CuSn7Pb15 and CuSn7ZnPb7)	-	*Metallwerk Langenau GMBH,* Langenau, Germany
6	Dimensionally Stable Anodes (DSA) (Ru/Ir)O2 on Ta	-	*DeNora,* Mailand, Italy
7	Stainless Steel (1.4571)	-	*Montanstahl GmbH,* Oelde, Deutschland
8	Zinc	-	*Grillo-Werke AG,* Duisburg, Germany
9	Reticulated Vitreous Carbon (RVC)	-	*ERG Aerospace Corporation*, USA

Electrochemical Set-Up

Electrochemical reactions were carried out using a multichannel galvanostat HMP4040 (*Rohde & Schwarz*, München, Germany). The different cells used for screening or batch reactions are described below.

Screening Reactions

Teflon™ cells with a volume of 5 mL were used for the undivided set-up (figure S2, left). Divided Teflon™ screening cells with a volume of 7 mL were equipped with a glass frit as separator material as shown (figure S2, right). Glass frits used as separator materials were pre-treated in the corresponding electrolyte prior to use. Stirring bars were used during electrolysis in each cell. The described screening systems are commercially available as IKA Screening System Package (*IKA™ Werke GmbH & Co. KG*, Staufen, Germany).



Figure S2: Undivided screening set-up (left) and divided screening set-up (right).[2]

Scale-up Reactions

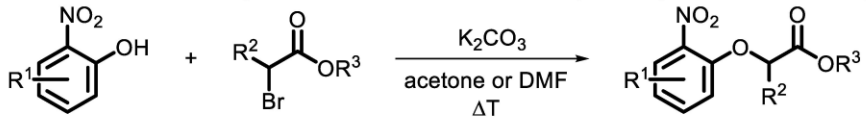
Scale-up experiments were performed in undivided 25 mL, 100 mL and 250 mL batch-type cells with a PTFE stopper and sleeve, electrodes, and electrode holders (figure S2). A TDK-Lambda Z+ series (*TDK-Lambda UK Limited*, Devon, United Kingdom) or a multichannel power supply HMP4040 (*Rohde & Schwarz*, München, Germany) were used as power sources. In the undivided 5 mL electrolysis set-up glassy carbon and BDD electrodes with dimensions of 7 cm·1 cm were used. In the undivided 25 mL and 100 mL electrolysis set-up glassy carbon and BDD electrodes with identical dimensions of 6 cm·2 cm were used. In the undivided 250 mL electrolysis set-up glassy carbon and BDD electrodes with identical dimensions of 12 cm·4 cm were used.



Figure S3: Different batch-type cells; size compared to a ruler: top: 5 mL undivided Teflon™ screening cells with glassy carbon and BDD electrodes and screening cell holder with integrated radiator loop; bottom left: 25 mL undivided glass cell with glassy carbon and BDD electrodes; bottom centre: 100 mL undivided glass cell with glassy carbon and BDD electrodes; bottom right: 300 mL divided glass cell with glassy carbon and BDD electrodes.

2. General Protocols

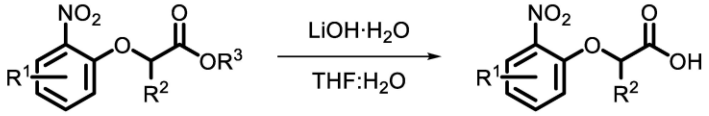
2.1. General Protocol for the Synthesis of Substituted 2-Nitrophenoxyaceticacid esters (GPI)



Scheme S1: Synthesis of substituted 2-nitrophenoxyaceticacid esters.

Under argon atmosphere potassium carbonate (2.0-3.0 eq.) was suspended in anhydrous acetone and degassed for 15 min. The corresponding 2-nitrophenol (1.0 eq.) was added and the reaction mixture was stirred for 10 min at room temperature. Afterwards the corresponding 2-bromoacetate (1.0–2.0 eq.) was added and the reaction mixture was stirred under reflux until completion of the reaction (TLC). The crude mixture was filtered, and the acetone was removed under reduced pressure. 50 mL of water and 50 mL of ethyl acetate were added, and the fractions were separated. The aqueous fraction was extracted three times with 50 mL of ethyl acetate. The combined organic fractions were washed twice with saturated sodium carbonate solution to remove residual phenol. Afterwards the organic fractions were washed once with 50 mL of brine, dried over sodium sulphate and the solvent was removed under reduced pressure. The crude product was purified by crystallisation or flash column chromatography.

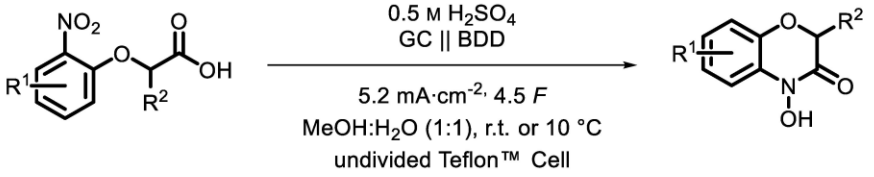
2.2. General Protocol for the Synthesis of Substituted 2-Nitrophenoxyacetic acids (GPII)



Scheme S2: Synthesis of substituted 2-nitrophenoxyacetic acids.

The corresponding 2-nitrophenoxyaceticacid ester (1.0 eq.) was dissolved in THF at room temperature. Lithium hydroxide monohydrate (1.5 eq.) was dissolved in water and added in one portion to the reaction mixture. The solution was stirred at room temperature until completion of the reaction (TLC). Afterwards the solution was neutralized with 1 M hydrochloric acid. The THF was removed under reduced pressure and the aqueous fraction was extracted three times with 50 mL dichloromethane. The combined organic fractions were washed once with 50 mL of brine, dried over sodium sulphate and the solvent was removed under reduced pressure. If necessary, the crude product was further purified by crystallisation or flash column chromatography.

2.3. General Protocol for the Electrochemical Synthesis of substituted 2*H*,4*H*-4-Hydroxy-benzo[*b*]-1,4-oxazin-3-one (GPIII)



Scheme S3: Synthesis of substituted 2-nitrobenzenesulfonamides.

5 mL Undivided Teflon™ Screening Cell: 0.15 mmol of the starting material was dissolved in 2.5 mL of methanol in the undivided cell and 2.5 mL of 1.0 M sulphuric acid was added. The electrodes (1 cm·7 cm) immersed 1.5 cm into the solution resulting in an area of 1.5 cm^{-2}. Prior to the electrolysis the solution was cooled to 10 °C, if necessary. The electrolysis was performed under constant current conditions (current density j = 5.2 $mA \cdot cm^{-2}$ for 65.1 C (4.5 F)). After the electrolysis the reaction mixture was diluted with 5 mL of water and 5 mL of brine and extracted three times with 10 mL of ethyl acetate. The aqueous fraction was analysed via LC-MS to ensure the complete extraction of the product. If necessary, the aqueous fraction was extracted additionally twice with 10 mL of ethyl acetate. The combined organic fractions were washed once with 5 mL of brine, dried over sodium sulphate and the solvent was removed under reduced pressure. The crude product was purified with reverse phase column chromatography (C_{18}).

25 mL Undivided Glass Cell: 0.75 mmol of the starting material was dissolved in 12.5 mL of methanol in the undivided cell and 12.5 mL of 1.0 M sulphuric acid was added. The electrodes (2 cm·6 cm) immersed 3.0 cm into the solution resulting in an area of 6.0 cm^{-2}. The electrolysis was performed under constant current conditions (current density j = 5.2 $mA \cdot cm^{-2}$ for 325.6 C (4.5 F)). After the electrolysis the reaction mixture was diluted with 15 mL of water and 15 mL of brine and extracted three times with 30 mL of ethyl acetate. The aqueous fraction was analysed via LC-MS to ensure the complete extraction of the product. If necessary, the aqueous fraction was extracted additionally twice with 30 mL of ethyl acetate. The combined organic fractions were washed once with 15 mL of brine, dried over sodium sulphate and the solvent was removed under reduced pressure. The crude product was purified with reverse phase column chromatography (C_{18}).

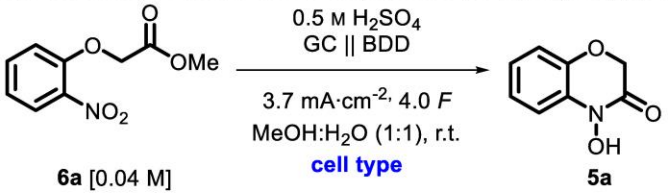
100 mL Undivided Glass Cell: 3.0 mmol of the starting material was dissolved in 50 mL of methanol in the undivided cell and 50 mL of 1.0 M sulphuric acid was added. The electrodes (2 cm·6 cm) immersed 3.0 cm into the solution resulting in an area of 6.0 cm^{-2}. The electrolysis was performed under constant current conditions (current density j = 5.2 $mA \cdot cm^{-2}$ for 1302.6 C (4.5 F)). After the electrolysis the reaction mixture was diluted with 25 mL of water and 25 mL of brine and extracted three times with 30 mL of ethyl acetate. The aqueous fraction was analysed via LC-MS to ensure the complete extraction of the product. If necessary, the aqueous fraction was extracted additionally twice with 30 mL of ethyl acetate. The combined organic fractions were washed once with 25 mL of brine, dried over sodium sulphate and the solvent was removed under reduced pressure. The crude product was purified with reverse phase column chromatography (C_{18}).

250 mL Undivided Glass Cell: 7.5 mmol of the starting material was dissolved in 125 mL of methanol in the undivided cell and 125 mL of 1.0 M sulphuric acid was added. The electrodes (4 cm·13 cm) immersed 8.0 cm into the solution resulting in an area of 32.0 cm^{-2}. The electrolysis was performed under constant current conditions (current density j = 5.2 $mA \cdot cm^{-2}$ for 3256.4 C (4.5 F)). After the electrolysis the reaction mixture was diluted with 50 mL of water and 50 mL of brine and extracted three times with 50 mL of ethyl acetate. The aqueous fraction was analysed via LC-MS to ensure the complete extraction of the product. If necessary, the aqueous fraction was extracted additionally twice with 50 mL of ethyl acetate. The combined organic fractions were washed once with 50 mL of brine, dried over sodium sulphate and the solvent was removed under reduced pressure. The crude product was purified by crystallisation.

Note: *It is advisable to use sodium sulphate as a drying agent as we observed more consistent yields compared to magnesium sulphate. We suspect a complexation of* Mg^{2+} *by the 2H,4H-4-Hydroxybenzo[b]-1,4-oxazin-3-ones. Furthermore, by using glassware it is possible to form metal complexes which can be observed by a strong colouration of the product. To avoid this problem, it is necessary to use formic acid as an additive during column chromatography.*

3. Optimization of the Electrolytic Conditions

Table S2: Optimisation of the electrolytic reaction conditions for the synthesis of 2*H*,4*H*-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5a).



6a [0.04 M] **5a**

Entry	Cell Type	Yield[a] [%]
1	undivided	31
2	divided	20

[a]Yield determined by ^{1}H NMR, internal standard: 1,3,5-Trimethoxybenzene.

Table S3: Optimisation of the electrolytic reaction conditions for the synthesis of 2*H*,4*H*-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5a).

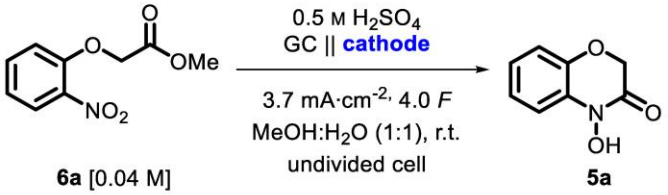


6a [0.04 M] **5a**

Entry	Anode Material	Yield[a] [%]
1	graphite	12
2	glassy carbon	31
3	BDD	10
4	RVC	2
5	stainless steel (1.4571)	5
6	DSA (Ru/Ir)O_2 on Ta	28

[a]Yield determined by ^{1}H NMR, internal standard: 1,3,5-Trimethoxybenzene.

Table S4: Optimisation of the electrolytic reaction conditions for the synthesis of 2*H*,4*H*-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5a).

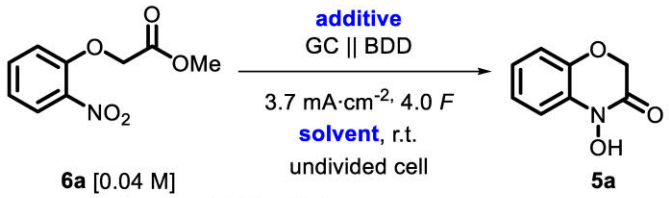


6a [0.04 M] **5a**

Entry	Cathode Material	Yield[a] [%]
1	graphite	24
2	glassy carbon	23
3	BDD	31
4	RVC	24
5	Zn	0[b]
6	Pb	3
7	CuSn7Pb15	13
8	CuSn7Zn4Pb7	10

[a]Yield determined by ^{1}H NMR, internal standard: 1,3,5-Trimethoxybenzene; [b]repeated twice, full reduction without electricity observed.

Table S5: Optimisation of the electrolytic reaction conditions for the synthesis of 2*H*,4*H*-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5a).

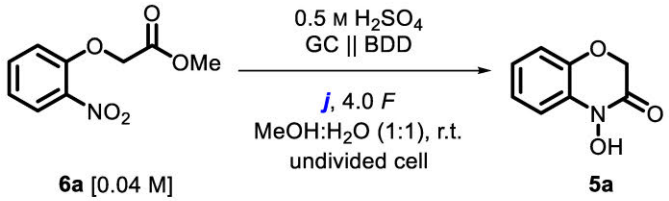


6a [0.04 M] **5a**

Entry	Additive/Solvent	Yield[a] [%]
1	0.5 M H_2SO_4 in methanol:water (1:1)	31
2	0.5 M H_2SO_4 in methanol	4
3	0.05 M H_2SO_4 in methanol	0
4	0.5 M $MeSO_3H$ in methanol	0
5	0.05 M $MeSO_3H$ in methanol	0
6	0.01 M Bu_4NBF_4 in methanol	0
7	0.025 M H_2SO_4+0.25 M NH_4COO in methanol	0
8	0.5 M AcOH+0.05 M NaOAc in methanol	3
9	0.5 M H_2SO_4 in methanol+5 vol% water	5
10	0.5 M H_2SO_4 in methanol+10 vol% water	9
11	0.5 M H_2SO_4 in methanol+20 vol% water	27
12	0.5 M H_2SO_4 in methanol+30 vol% water	19
13	0.5 M H_2SO_4 in methanol+40 vol% water	23

[a]Yield determined by ^{1}H NMR, internal standard: 1,3,5-Trimethoxybenzene.

Table S6: Optimisation of the electrolytic reaction conditions for the synthesis of 2*H*,4*H*-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5a).

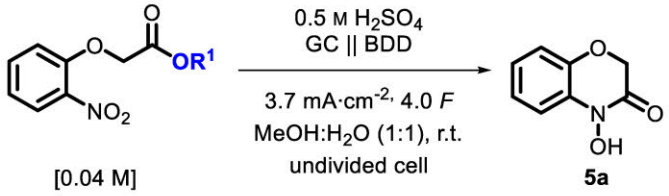


6a [0.04 M] **5a**

Entry	*j* = Current Density / mA·cm^{-2}	Yield[a] [%]
3	3.7	31
4	4.2	29
5	4.7	29
6	5.2	30
7	5.7	35

[a]Yield determined by ^{1}H NMR, internal standard: 1,3,5-Trimethoxybenzene.

Table S7: Optimisation of the electrolytic reaction conditions for the synthesis of 2*H*,4*H*-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5a).

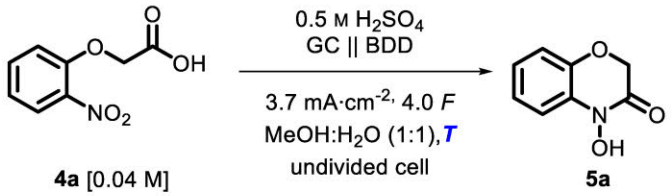


[0.04 M] **5a**

Entry	Carbonyl Motif	Yield[a] [%]
1	**6a** R^1 = Me	31
2	**4a** R^1 = H	47
3	**6s** R^1 = Et	6
4	**6t** R^1 = *t*-Bu	0[b]

[a]Yield determined by ^{1}H NMR, internal standard: 1,3,5-Trimethoxybenzene; [b]Low solubility of the substrate, 0.03 M of the substrate was used.

Table S8: Optimisation of the electrolytic reaction conditions for the synthesis of 2*H*,4*H*-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5a).

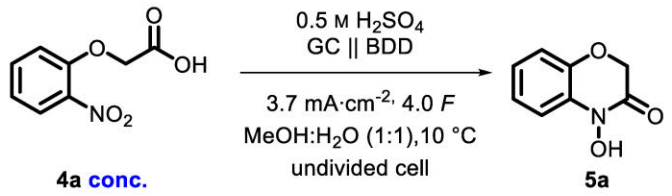


4a [0.04 M] **5a**

Entry	Temperature / °C	Yield[a] [%]
1	10	70 [b] (60)[c]
2	r.t.	47
3	30	42
4	40	39
5	50	22

[a]Yield determined by ^{1}H NMR, internal standard: 1,3,5-Trimethoxybenzene; [b]Low solubility of the substrate, 0.03 M of the substrate was used; [c]isolated yield.

Table S9: Optimisation of the electrolytic reaction conditions for the synthesis of 2*H*,4*H*-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5a).



4a conc. **5a**

Entry	Substrate Concentration	Yield[a] [%]
1	0.03 M	70 [b] (60)[c]
2	0.05 M	42
3	0.06 M	36
4	0.08 M	26

[a]Yield determined by ^{1}H NMR, internal standard: 1,3,5-Trimethoxybenzene; [b]Low solubility of the substrate, 0.03 M of the substrate was used; [c]isolated yield.

NMR Quantification

After work-up of the crude reaction mixture according to general protocol III (**GPIII**) 0.1 mmol (16.8 mg) of 1,3,5-trimethoxybenzene was added. The mixture was completely dissolved in 1 mL of $DMSO_{d6}$ and analysed by NMR. The signals were assigned according to figure S4.

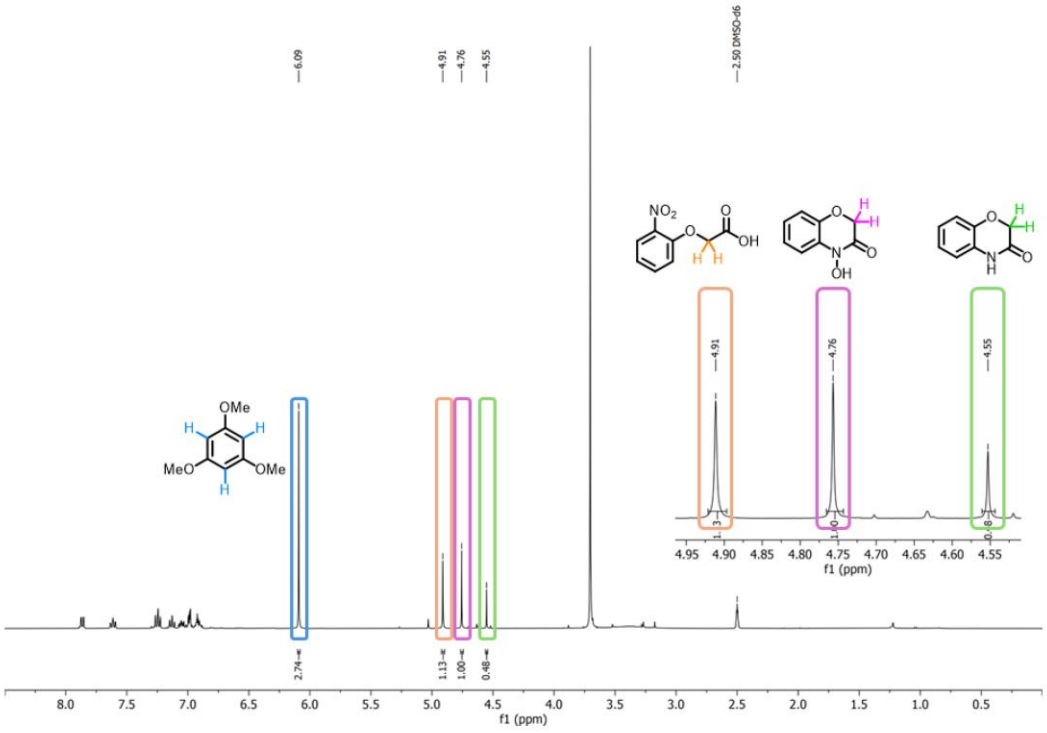


Figure S4: Assignment of the ^{1}H NMR signals for NMR quantification of the optimisation of the electrolytic conditions.

4. Scale-up of the Electrochemical Reductive Synthesis of 2*H*,4*H*-2,2-Dimethyl-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5c)

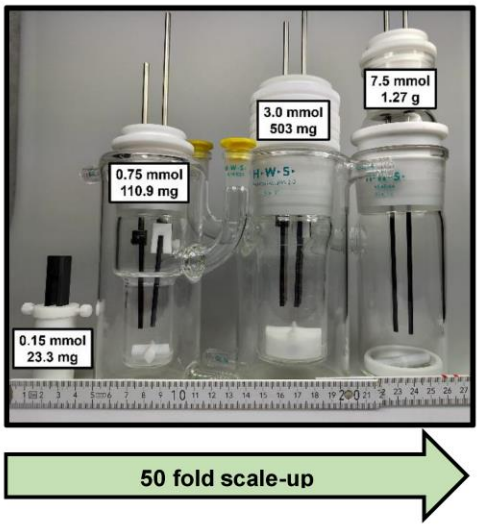
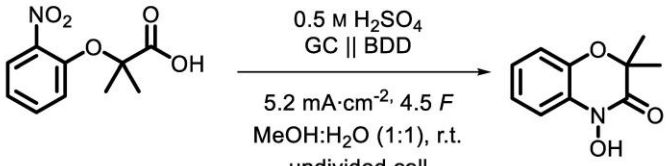


Figure S5: Different batch-type undivided cells used for the scale-up of the reaction. The ruler depicted on the bottom is in cm.

Table S10: Scale-up of the synthesis of **5c**.



4c [0.04 M] **5c**

Cell Volume [mL]	Scale [mmol]	Purification Method	Applied Charge	Yield[a] [%] of **5c**
5	0.15	Reverse phase column	57.9 C (4.0 *F*)	23.3 mg (0.121 mmol, 81%)
25	0.75	Reverse phase column	325.6 C (4.5 *F*)	110.9 mg (0.574 mmol, 77%)
100	3.0	Reverse phase column	1302.6 C (4.5 *F*)	503 mg (2.6 mmol, 87%)
250	7.5	crystallisation	3256.4 C (4.5 *F*)	1.27 g (7.5 mmol, 88%)

5. CV Studies

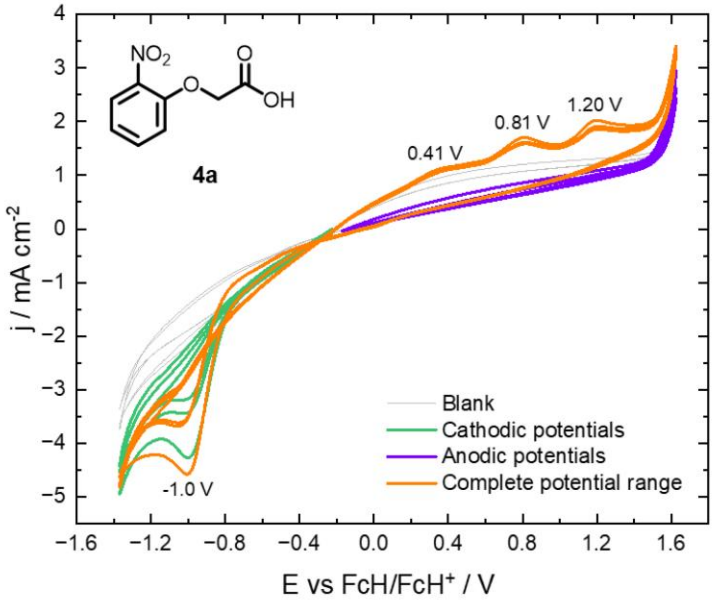


Figure S6: Cyclic voltammogram of **4a** with 0.5 M H_2SO_4 as additive.

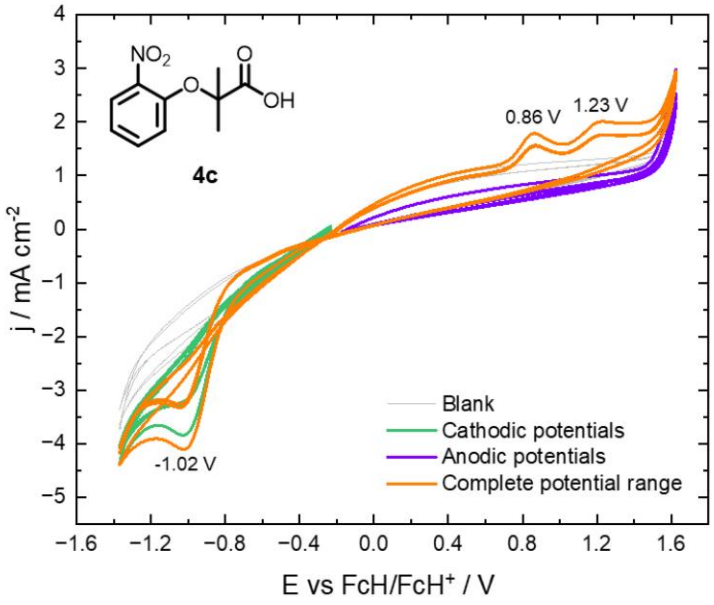


Figure S7: Cyclic voltammogram of **4c** with 0.5 M H_2SO_4 as additive.

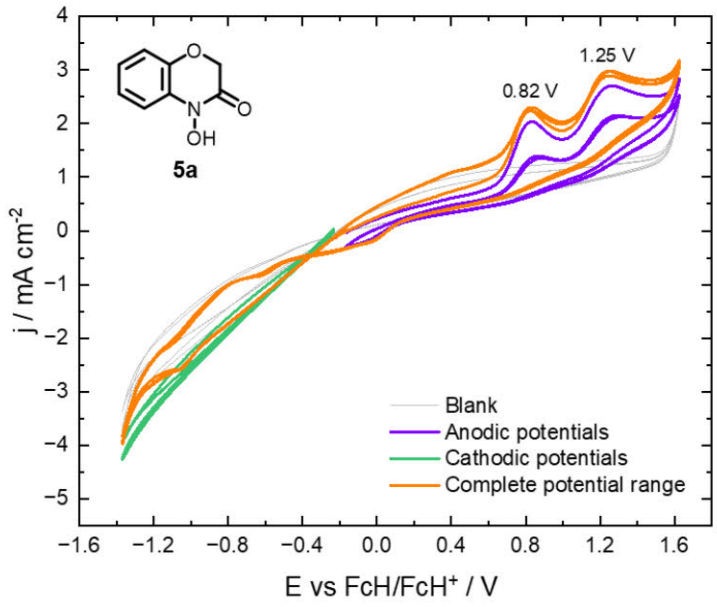


Figure S8: Cyclic voltammogram of **5a** with 0.5 M H_2SO_4 as additive.

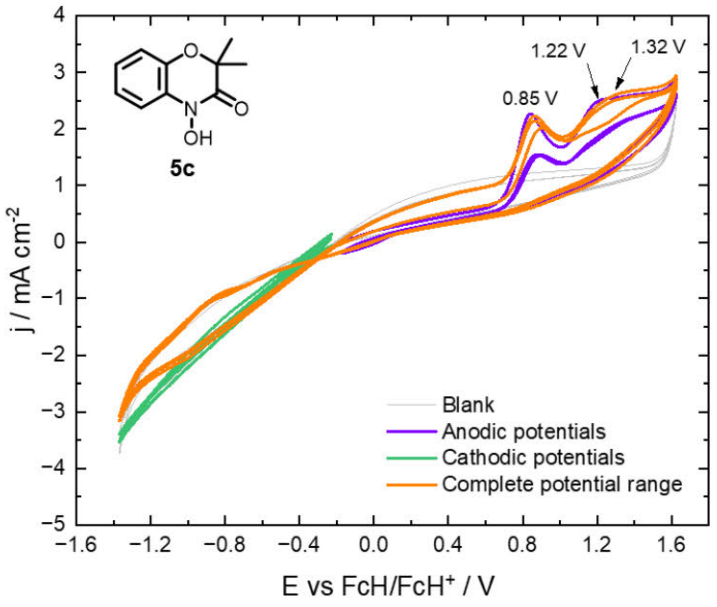
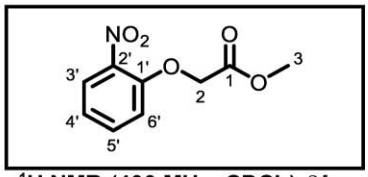


Figure S9: Cyclic voltammogram of **5c** with 0.5 M H_2SO_4 as additive.

6. Preparation of Products and Analytical Data

6.1. 2-Nitrophenoxyaceticacid esters (6a–6t)

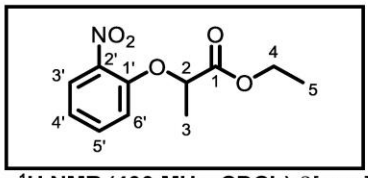
Methyl 2-(2-nitrophenoxy)acetate (6a)



According to general protocol **GPI**, 2-nitrophenol (7.24 g, 52 mmol, 1.0 eq.), potassium carbonate (20.83 g, 151 mmol, 2.9 eq.) and methyl bromoacetate (11.93 g, 78 mmol, 1.5 eq.) were reacted in 150 mL of anhydrous acetone. 9.31 g (44.1 mmol, 85%) of the product was obtained as a colourless solid after crystallisation (80 mL ^{i}PrOH; crystallisation at 6 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.84 (dd, 1H, *J* = 8.2 Hz, 1.7 Hz, *H*-3'), 7.51 (ddd, *J* = 8.4 Hz, 7.5 Hz, 1.7 Hz, *H*-5'), 7.08 (ddd, 1H, *J* = 8.2 Hz, 7.5 Hz, 1.1 Hz, *H*-4'), 6.98 (dd, 1H, *J* = 8.4 Hz, 1.1 Hz, *H*-6'), 4.77 (s, 2H, *H*-2), 3.78 (s, 3H, *H*-3).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 168.3, 151.2, 140.4, 134.2, 125.9, 121.9, 115.2, 66.5, 52.6.
LC-MS: t_R = 11.027 min (method: 10 → 90% acetonitrile in 10 min, 5 min at 100% acetonitrile), m/z for $C_9H_9NO_5^+$ [M+H]+ = 212.
m.p. (^{i}PrOH): 54.1–54.6 °C.
Known compound, spectroscopic data match to literature.[1]

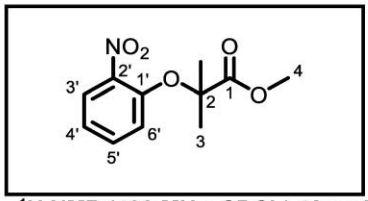
Ethyl 2-(2-nitrophenoxy)propanoate (6b)



According to general protocol **GPI**, 2-nitrophenol (1.40 g, 10 mmol, 1.0 eq.), potassium carbonate (4.16 g, 30 mmol, 3.0 eq.) and ethyl 2-bromopropanoate (2.76 g, 15 mmol, 1.5 eq.) were reacted in 30 mL of anhydrous acetone. 1.59 g (6.6 mmol, 66%) of the product was obtained as a slightly yellow solid after crystallisation (30 mL cyclohexane; crystallisation at 6 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.82 (dd, 1H, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.47 (ddd, 1H, *J* = 8.4 Hz, 7.4 Hz, 1.7 Hz, *H*-5'), 7.11 – 7.02 (m, 1H, *H*-4'), 6.95 (dd, 1H, *J* = 8.4 Hz, 1.1 Hz, *H*-6'), 4.83 (q, 1H, *J* = 6.8 Hz, *H*-2), 4.21 (qd, 2H, *J* = 7.1 Hz, 2.9 Hz, *H*-4), 1.68 (d, 3H, *J* = 6.8 Hz, *H*-3), 1.23 (t, 3H, *J* = 7.1 Hz, *H*-5).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 171.0, 151.1, 140.9, 133.9, 125.8, 121.6, 115.9, 74.7, 61.8, 18.5, 14.2.
LC-MS: t_R = 6.464 min (method: 50 → 100% acetonitrile in 10 min, 5 min at 100% acetonitrile), m/z for $C_9H_9NO_5^+$ [M+H]+ = 240.
m.p. (Cy): 43.8–47.2 °C.
Known compound, spectroscopic data match to literature.[1]

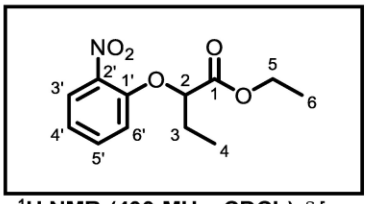
Methyl 2-methyl-2-(2-nitrophenoxy)propanoate (6c)



According to general protocol **GPI**, 2-nitrophenol (16.02 g, 115 mmol, 1.0 eq.), potassium carbonate (47.91 g, 347 mmol, 3.0 eq.) and methyl 2-bromo-2-methylpropanoate (31.31 g, 173 mmol, 1.5 eq.) were reacted in 150 mL of anhydrous acetone. 17.50 g (78 mmol, 68%) of the product was obtained and used without further purification as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.74 (dd, 1H, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.42 (ddd, 1H, *J* = 8.4 Hz, 7.4 Hz, 1.7 Hz, *H*-5'), 7.07 (ddd, 1H, *J* = 8.1 Hz, 7.4 Hz, 1.2 Hz, *H*-4'), 6.93 (dd, 1H, *J* = 8.4 Hz, 1.2 Hz, *H*-6'), 3.78 (s, 3H, *H*-4), 1.64 (s, 6H, *H*-3).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 174.2, 148.8, 143.2, 133.1, 125.3, 122.2, 120.1, 81.6, 52.9, 25.2.
LC-MS: t_R = 3.876 min (method: 60 → 100% acetonitrile in 10 min, 5 min at 100% acetonitrile), m/z for $C_9H_9NO_5^+$ [M+H]+ = 240.

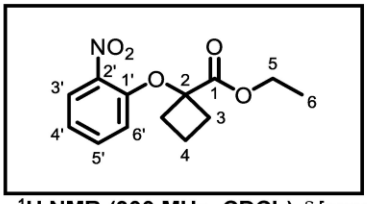
Ethyl 2-(2-nitrophenoxy)butanoate (6d)



According to general protocol **GPI**, 2-nitrophenol (1.40 g, 10 mmol, 1.0 eq.), potassium carbonate (4.20 g, 30 mmol, 3.0 eq.) and ethyl 2-bromobutyrate (2.95 g, 15 mmol, 1.5 eq.) were reacted in 30 mL of anhydrous acetone. 1.82 g (7.2 mmol, 72%) of the product was obtained as a slightly yellow solid after column chromatography (SiO_2; cyclohexane:ethyl acetate, gradient: 0 → 10% ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.82 (dd, 1H, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.46 (ddd, 1H, *J* = 8.4, 7.4 Hz, 1.7 Hz, *H*-5'), 7.04 (ddd, 1H, *J* = 8.1 Hz, 7.4 Hz, 1.1 Hz, *H*-4'), 6.90 (dd, 1H, *J* = 8.4 Hz, 1.1 Hz, *H*-6'), 4.67 (t, 1H, *J* = 6.0 Hz, *H*-2), 4.20 (qd, 2H, *J* = 7.1 Hz, 2.8 Hz, *H*-5), 2.05 (qd, 2H, *J* = 7.4 Hz, 6.0 Hz, *H*-3), 1.22 (t, 3H, *J* = 7.1 Hz, *H*-6), 1.10 (t, 3H, *J* = 7.4 Hz, *H*-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 170.5, 151.4, 140.5, 133.9, 125.8, 121.3, 115.2, 79.1, 61.6, 26.1, 14.2, 9.5.
HR-MS (ESI+): *m/z* for $C_{12}H_{15}NO_5$+H^+, $[M+H]^+$ calculated: 254.1023; found: 254.1012.

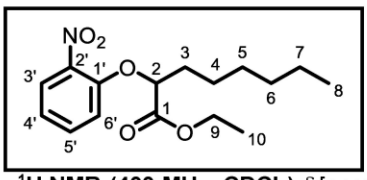
Ethyl 1-(2-nitrophenoxy)cyclobutane-1-carboxylate (6e)



According to general protocol **GPI**, 2-nitrophenol (2.08 g, 15 mmol, 1.0 eq.), potassium carbonate (4.22 g, 31 mmol, 2.0 eq.) and ethyl 1-bromocyclobutane-1-carboxylate (4.76 g, 23 mmol, 1.5 eq.) were reacted in 70 mL of anhydrous DMF. 0.74 g (2.8 mmol, 19%) of the product was obtained as a slightly yellow oil after column chromatography (SiO_2; cyclohexane:ethyl acetate, gradient: 0 → 5% ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 7.80 (dd, 1H, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.38 (ddd, *J* = 8.5, 7.4, 1.7 Hz, 1H), 7.00 (ddd, *J* = 8.4, 7.4, 1.1 Hz, 1H), 6.55 (dd, *J* = 8.5, 1.1 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.74 (dddd, *J* = 11.3, 5.6, 4.3, 2.4 Hz, 2H), 2.58 – 2.44 (m, 2H), 2.08 – 1.95 (m, 2H), 1.14 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 172.0, 149.3, 140.5, 133.5, 125.9, 120.8, 115.9, 81.0, 61.8, 32.4, 13.8.
HR-MS (ESI+): *m/z* for $C_{13}H_{15}NO_5$+H^+, $[M+H]^+$ calculated: 266.1023; found: 266.1028.

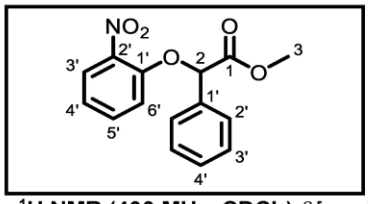
Ethyl 2-(2-nitrophenoxy)octanoate (6f)



According to general protocol **GPI**, 2-nitrophenol (1.40 g, 10 mmol, 1.0 eq.), potassium carbonate (4.18 g, 30 mmol, 3.0 eq.) and ethyl 2-bromooctanoate (3.80 g, 15 mmol, 1.5 eq.) were reacted in 30 mL of anhydrous acetone. 2.36 g (7.6 mmol, 76%) of the product was obtained as a slightly yellow solid after crystallisation (35 mL cyclohexane; crystallisation at 6 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.83 (dd, 1H, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.46 (ddd, 1H, *J* = 8.4, 7.5 Hz, 1.7 Hz, *H*-5'), 7.07 – 7.02 (m, 1H, *H*-4'), 6.90 (dd, 1H, *J* = 8.4 Hz, 1.1 Hz, *H*-6'), 4.71 (dd, 1H, *J* = 7.4 Hz, 4.9 Hz, *H*-2), 4.20 (qd, 2H, *J* = 7.1 Hz, 2.3 Hz, *H*-9), 2.09 – 1.92 (m, 2H, *H*-3), 1.63 – 1.46 (m, 2H, *H*-4), 1.40 – 1.27 (m, 6H, *H*-5, *H*-6, *H*-7), 1.22 (t, 3H, *J* = 7.1 Hz, *H*-10), 0.92 – 0.85 (m, 3H, *H*-8).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 170.7, 151.4, 140.6, 133.9, 125.9, 121.3, 115.2, 78.2, 61.7, 32.7, 31.7, 28.9, 25.0, 22.7, 14.2, 14.2.
HR-MS (ESI+): *m/z* for $C_{16}H_{23}NO_5$+H^+, $[M+H]^+$ calculated: 310.1649; found: 310.1641.
m.p. (Cy): 48.0–49.8 °C.

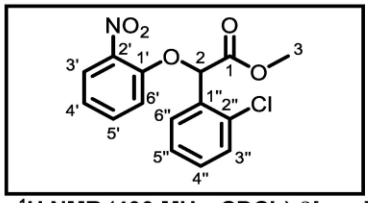
Methyl 2-(2-nitrophenoxy)-2-phenylacetate (6h)



According to general protocol **GPI**, 2-nitrophenol (1.40 g, 10 mmol, 1.0 eq.), potassium carbonate (4.19 g, 30 mmol, 3.0 eq.) and methyl 2-bromo-2-phenylacetate (3.61 g, 16 mmol, 1.6 eq.) were reacted in 30 mL of anhydrous acetone. 1.01 g (3.5 mmol, 35%) of the product was obtained as a slightly yellow solid after column chromatography (SiO_2; cyclohexane:ethyl acetate, gradient: 3 → 15% ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.90 (dd, 1H, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.62 (dd, 2H, *J* = 7.7 Hz, 1.8 Hz, *H*-2''), 7.49 (ddd, 1H, *J* = 8.4 Hz, 7.5 Hz, 1.7 Hz, *H*-5'), 7.47 – 7.34 (m, 3H, *H*-3'', *H*-4''), 7.10 (ddd, 1H, *J* = 8.4 Hz, 7.5 Hz, 1.1 Hz, *H*-4'), 6.99 (dd, 1H, *J* = 8.4 Hz, 1.2 Hz, *H*-6'), 5.76 (s, 1H, *H*-2), 3.73 (s, 3H, *H*-3).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 169.4, 150.7, 140.8, 134.2, 129.5, 129.1, 128.2, 127.1, 126.2, 121.9, 115.9, 79.9, 53.1.
HR-MS (ESI+): *m/z* for $C_{15}H_{13}NO_5$+NH_4^+, $[M+ NH_4]^+$ calculated: 305.1132; found: 305.1133.
Known compound, spectroscopic data match to literature.[2]

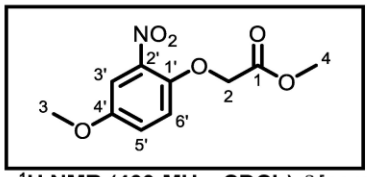
Methyl 2-(2-chlorophenyl)-2-(2-nitrophenoxy)acetate (6i)



According to general protocol **GPI**, 2-nitrophenol (0.87 g, 6 mmol, 1.0 eq.), potassium carbonate (2.55 g, 18 mmol, 3.0 eq.) and 2-bromo-2-(2-chlorophenyl)acetate (2.42 g, 9 mmol, 1.5 eq.) were reacted in 30 mL of anhydrous acetone. 1.52 g (4.7 mmol, 77%) of the product was obtained as a beige solid after column chromatography (SiO_2; cyclohexane:ethyl acetate, gradient: 3 → 15% ethyl acetate)

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.87 (dd, 1H, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.78 – 7.73 (m, 1H, *H*-3''), 7.49 (ddd, 1H, *J* = 8.4 Hz, 7.4, 1.7 Hz, *H*-5'), 7.44 – 7.40 (m, 1H, *H*-5''), 7.37 – 7.29 (m, 2H, *H*-4'', *H*-6''), 7.09 (ddd, 1H, *J* = 8.1 Hz, 7.4 Hz, 1.1 Hz, *H*-4'), 7.05 (dd, 1H, *J* = 8.4 Hz, 1.1 Hz, *H*-6'), 6.28 (s, 1H, *H*-2), 3.76 (s, 3H, *H*-3).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 168.5, 150.4, 140.8, 134.2, 133.3, 132.5, 130.7, 129.8, 129.2, 127.9, 126.1, 122.1, 116.0, 76.1, 53.1.
HR-MS (ESI+): *m/z* for $C_{15}H_{12}{}^{35}ClNO_5$+$Na^+$, $[M+Na]^+$ calculated: 322.0477; found: 322.0466.

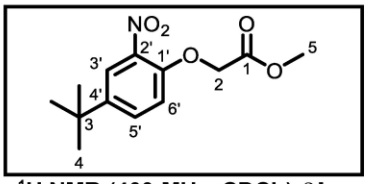
Methyl 2-(4-methoxy-2-nitrophenoxy)acetate (6j)



According to general protocol **GPI**, 4-methoxy-2-nitrophenol (1.73 g, 10 mmol, 1.0 eq.), potassium carbonate (4.29 g, 31 mmol, 3.1 eq.) and methyl 2-bromoacetate (2.32 g, 15 mmol, 1.5 eq.) were reacted in 30 mL of anhydrous acetone. 2.17 g (9.0 mmol, 90%) of the product was obtained as a colourless solid and was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.38 (d, 1H, *J* = 3.0 Hz, *H*-3'), 7.07 (dd, 1H, *J* = 9.1 Hz, 3.0 Hz, *H*-5'), 7.01 (d, 1H, *J* = 9.1 Hz, *H*-6'), 4.71 (s, 2H, *H*-2), 3.81 (s, 3H, *H*-3), 3.78 (s, 3H, *H*-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 168.8, 154.4, 145.6, 141.1, 120.8, 118.4, 110.1, 68.1, 56.2, 52.5.
HR-MS (ESI-): *m/z* for $C_9H_9NO_6$-H^-, $[M-H]^-$ calculated: 226.0357; found: 226.0361.

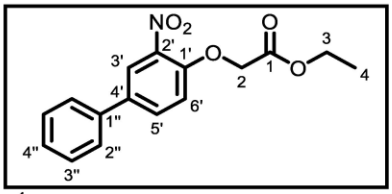
Methyl 2-(4-*tert*-butyl-2-nitrophenoxy)acetate (6k)



According to general protocol **GPI**, 4-*tert*-butyl-2-nitrophenol (1.97 g, 10 mmol, 1.0 eq.), potassium carbonate (4.22 g, 31 mmol, 3.1 eq.) and methyl 2-bromoacetate (2.35 g, 15 mmol, 1.5 eq.) were reacted in 30 mL of anhydrous acetone. 2.61 g (9.8 mmol, 98%) of the product was obtained as a beige solid and was used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.86 (d, 1H, *J* = 2.5 Hz, *H*-3'), 7.52 (dd, 1H, *J* = 8.8 Hz, 2.5 Hz, *H*-5'), 6.92 (d, 1H, *J* = 8.8 Hz, *H*-6'), 4.76 (s, 2H, *H*-2), 3.80 (s, 3H, *H*-5), 1.31 (s, 9H, *H*-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 1 168.6, 149.1, 145.6, 140.1, 131.3, 122.9, 115.2, 66.8, 52.6, 34.6, 31.2.
HR-MS (ESI+): *m/z* for $C_{13}H_{17}NO_5$+Na^+, $[M+Na]^+$ calculated: 290.0999; found: 290.0988.

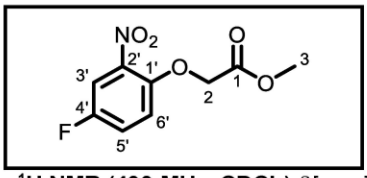
Ethyl 2-((3-nitro-biphenyl-4-yl)oxy)acetate (6l)



According to general protocol **GPI**, 3-nitro-biphenyl-4-ol (4.30 g, 20 mmol, 1.0 eq.), potassium carbonate (5.57 g, 40 mmol, 3.0 eq.) and ethyl 2-bromoacetate (5.01 g, 30 mmol, 1.5 eq.) were reacted in 150 mL of anhydrous acetone. 5.18 g (17.2 mmol, 86%) of the product was obtained as a slightly yellow solid after washing the solids with methanol.

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm]: 8.08 (d, 1H, *J* = 2.4 Hz, *H*-3'), 7.72 (dd, 1H, *J* = 8.7 Hz, 2.4 Hz, *H*-5'), 7.55 – 7.51 (m, 2H, *H*-2''), 7.48 – 7.33 (m, 3H, *H*-3'', *H*-4''), 7.06 (d, 1H, *J* = 8.7 Hz, *H*-6'), 4.81 (s, 2H, *H*-2), 4.28 (q, 1H, *J* = 7.1 Hz, *H*-3), 1.30 (t, *J* = 7.1 Hz, 3H, *H*-4).
^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm]: 167.8, 150.6, 140.6, 138.2, 135.3, 132.4, 129.2, 128.1, 126.8, 124.2, 115.7, 66.7, 61.9, 14.2.
HR-MS (ESI+): *m/z* for $C_{16}H_{15}NO_5$+Na^+, $[M+Na]^+$ calculated: 324.0842; found: 324.0835.

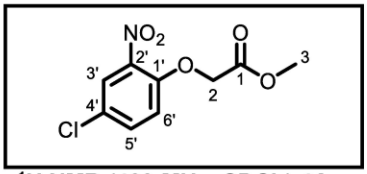
Methyl 2-(4-fluoro-2-nitrophenoxy)acetate (6m)



According to general protocol **GPI**, 4-fluoro-2-nitrophenol (1.58 g, 10 mmol, 1.0 eq.), potassium carbonate (4.17 g, 30 mmol, 3.0 eq.) and methyl 2-bromoacetate (2.34 g, 15 mmol, 1.5 eq.) were reacted in 30 mL of anhydrous acetone. 2.06 g (9.0 mmol, 90%) of the product was obtained as a slightly yellow solid after washing the solids with cyclohexane:ethanol (1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.63 (dd, 1H, *J* = 7.7 Hz, 3.1 Hz, *H*-3'), 7.31 – 7.22 (m, 1H, *H*-5'), 7.03 (dd, 1H, *J* = 9.2 Hz, 4.3 Hz, *H*-6'), 4.76 (s, 2H, *H*-2), 3.80 (s, 3H, *H*-3).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 168.3, 156.4 (d, *J* = 246.1 Hz), 148.0 (d, *J* = 3.1 Hz), 140.7, 121.2 (d, *J* = 23.0 Hz), 117.7 (d, *J* = 8.0 Hz), 113.3 (d, *J* = 27.4 Hz), 67.5, 52.7.
^{19}F NMR (376 MHz, $CDCl_3$) δ [ppm]: -119.36 – -119.42 (m).
HR-MS (ESI+): *m/z* for $C_9H_8FNO_5$+Na^+, $[M+Na]^+$ calculated: 252.0279; found: 252.0269.

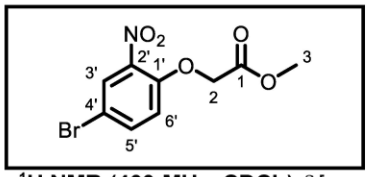
Methyl 2-(4-chloro-2-nitrophenoxy)acetate (6n)



According to general protocol **GPI**, 4-chloro-2-nitrophenol (4.37 g, 25 mmol, 1.0 eq.), potassium carbonate (10.38 g, 30 mmol, 3.0 eq.) and methyl 2-bromoacetate (5.75 g, 15 mmol, 1.5 eq.) were reacted in 30 mL of anhydrous acetone. 4.14 g (16.8 mmol, 67%) of the product was obtained as a slightly yellow solid after crystallisation (42 mL cyclohexane; crystallisation at 6 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.86 (d, 1H, *J* = 2.6 Hz, *H*-3'), 7.48 (dd, 1H, *J* = 8.9 Hz, 2.6 Hz, *H*-5'), 6.95 (d, 1H, *J* = 8.9 Hz, *H*-6'), 4.77 (s, 2H, *H*-2), 3.80 (s, 3H, *H*-3).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 168.0, 150.1, 140.7, 134.0, 127.1, 125.9, 116.8, 66.8, 52.7.
HR-MS (ESI+): *m/z* for $C_9H_8{}^{35}ClNO_5$+Na^+, $[M+Na]^+$ calculated: 267.9983; found: 267.9977.

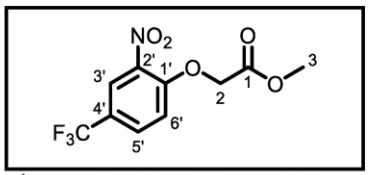
Methyl 2-(4-bromo-2-nitrophenoxy)acetate (6o)



According to general protocol **GPI**, 4-bromo-2-nitrophenol (2.18 g, 10 mmol, 1.0 eq.), potassium carbonate (4.21 g, 30 mmol, 3.0 eq.) and methyl 2-bromoacetate (2.33 g, 15 mmol, 1.5 eq.) were reacted in 30 mL of anhydrous acetone. 2.65 g (9.1 mmol, 91%) of the product was obtained as a yellow solid after washing the solids with cyclohexane:ethanol (1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.98 (d, 1H, *J* = 2.5 Hz, *H*-3'), 7.60 (dd, 1H, *J* = 8.9 Hz, 2.5 Hz, *H*-5'), 6.89 (d, 1H, *J* = 8.9 Hz, *H*-6'), 4.77 (s, 2H, *H*-2), 3.79 (s, 3H, *H*-3).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 168.0, 150.5, 140.8, 136.9, 128.6, 117.0, 113.6, 66.6, 52.7.
HR-MS (ESI+): *m/z* for $C_9H_8{}^{79}BrNO_5$+Na^+, $[M+Na]^+$ calculated: 311.9478; found: 311.9475.
Known compound, spectroscopic data match to literature.[3]

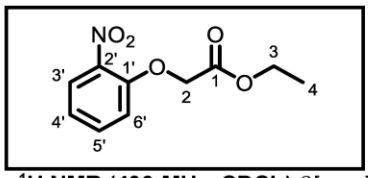
Methyl 2-(2-nitro-4-trifluoromethylphenoxy)acetate (6p)



According to general protocol **GPI**, 2-nitro-4-trifluoromethylphenol (2.09 g, 10 mmol, 1.0 eq.), potassium carbonate (4.16 g, 30 mmol, 3.0 eq.) and methyl 2-bromoacetate (2.31 g, 15 mmol, 1.5 eq.) were reacted in 30 mL of anhydrous acetone. 1.67 g (6.0 mmol, 60%) of the product was obtained as a beige solid after washing the solids with cyclohexane:ethanol (1:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 8.16 (d, *J* = 2.3 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 4.86 (s, 2H), 3.82 (s, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 167.6, 153.6, 140.0, 130.9 (d, *J* = 3.7 Hz), 127.8 – 124.0 (m), 123.8 (q, *J* = 3.5 Hz), 115.2, 66.3, 52.9.
^{19}F NMR (376 MHz, $CDCl_3$) δ [ppm]: -63.34.
HR-MS (ESI+): *m/z* for $C_{10}H_8F_3NO_5$+Na^+, $[M+Na]^+$ calculated: 302.0247; found: 302.0237.

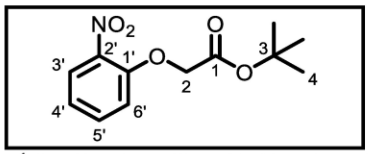
Ethyl 2-(2-nitrophenoxy)acetate (6s)



According to general protocol **GPI**, 2-nitrophenol (13.91 g, 100 mmol, 1.0 eq.), potassium carbonate (42.23 g, 300 mmol, 3.0 eq.) and ethyl 2-bromoacetate (23.1 mL, 20 mmol, 2.0 eq.) were reacted in 300 mL of anhydrous acetone. 15.90 g (70.6 mmol, 71%) of the product was obtained as a colourless solid after crystallisation (100 mL ethanol; crystallisation at 6 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.81 (dd, 1H, *J* = 8.1 Hz, 1.6 Hz, *H*-3'), 7.52 – 7.45 (m, 1H, *H*-5'), 7.06 (ddd, 1H, *J* = 8.3 Hz, 7.4 Hz, 1.1 Hz, *H*-4'), 6.97 (dd, 1H, *J* = 8.3 Hz, 1.1 Hz, *H*-6'), 4.74 (s, 2H, *H*-2), 4.22 (q, 2H, *J* = 7.1 Hz, *H*-3), 1.24 (t, 3H, *J* = 7. Hz, *H*-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 167.7, 151.2, 140.3, 134.1, 125.8, 121.7, 115.2, 66.5, 61.7, 14.1.
HR-MS (ESI+): *m/z* for $C_{10}H_{11}NO_5$+Na^+, $[M+Na]^+$ calculated: 248.0529; found: 248.0522.
m.p. (EtOH): 44.0–45.1 °C.
Known compound, spectroscopic data match to literature.[4]

***tert*-Butyl 2-(2-nitrophenoxy)acetate (6t)**

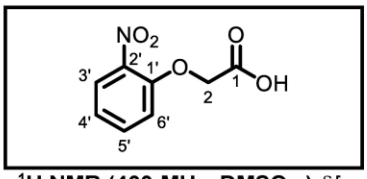


According to general protocol **GPI**, 2-nitrophenol (1.39 g, 10 mmol, 1.0 eq.), potassium carbonate (2.81 g, 20 mmol, 2.0 eq.) and *tert*-butyl 2-bromoacetate (2.98 g, 15 mmol, 1.5 eq.) were reacted in 30 mL of anhydrous acetone. 1.59 g (6.6 mmol, 66%) of the product was obtained as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.87 – 7.81 (m, 1H, *H*-3'), 7.54 – 7.46 (m, 1H, *H*-5'), 7.10 – 7.04 (m, 1H, *H*-4'), 6.98 – 6.93 (m, 1H, *H*-6'), 4.66 (s, 2H, *H*-2), 1.45 (s, 9H, *H*-4).
^{13}C NMR (101 MHz, $CDCl_3$) δ [ppm]: 166.8, 151.5, 140.3, 134.0, 125.9, 121.5, 114.9, 83.1, 66.8, 28.1.
HR-MS (ESI+): *m/z* for $C_{12}H_{15}NO_5$+Na^+, $[M+Na]^+$ calculated: 276.0842; found: 276.0829.
Known compound, spectroscopic data match to literature.[1]

6.2. 2-Nitrophenoxyacetic acid (4a-4r)

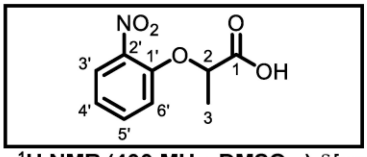
2-(2-Nitrophenoxy)acetic acid (4a)



According to general protocol **GPII**, methyl 2-(2-nitrophenoxy)acetate (**6a**, 2.12 g, 10 mmol, 1.0 eq.) and lithium hydroxide monohydrate (1.01 g, 20 mmol, 2.0 eq.) were reacted in 40 mL THF and 20 mL of water. 1.90 g (9.7 mmol, 97%) of the product was obtained as a colourless solid without further purification.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 13.25 (s, 1H, 1-COO*H*), 7.86 (dd,1H, *J* = 8.0 Hz, 1.7 Hz, *H*-3'), 7.61 (ddd, 1H, *J* = 8.6 Hz, 7.4 Hz, 1.7 Hz, *H*-5'), 7.25 (dd, 1H, *J* = 8.6 Hz, 1.1 Hz, , *H*-6'), 7.13 (ddd, 1H, *J* = 8.0 Hz, 7.4 Hz, 1.1 Hz, *H*-4'), 4.91 (s, 2H, , *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 169.8, 150.9, 140.1, 134.5, 125.4, 121.5, 115.5, 65.7.
HR-MS (ESI-): *m/z* for $C_8H_7NO_5$-H$^-$, [M-H]$^-$ calculated: 196.0251; found: 196.0254.
Known compound, spectroscopic data match to literature.[1]

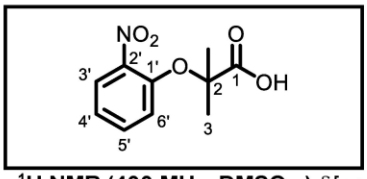
2-(2-Nitrophenoxy)propanoic acid (4b)



According to general protocol **GPII**, ethyl 2-(2-nitrophenoxy)propionate (**6b**, 1.00 g, 4 mmol, 1.0 eq.) and lithium .hydroxide monohydrate (0.37 g, 9 mmol, 2.3 eq.) were reacted in 40 mL THF and 20 mL of water. 0.41 g (1.9 mmol, 45%) of the product was obtained as a beige solid without further purification.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 13.25 (s, 1H, 1-COO*H*), 7.85 (dd, 1H, *J* = 8.0 Hz, 1.7 Hz, *H*-3'), 7.61 (ddd, 1H, *J* = 8.5 Hz, 7.4 Hz, 1.7 Hz, *H*-5'), 7.19 (dd, 1H, *J* = 8.5 Hz, 1.1 Hz, *H*-6'), 7.12 (ddd, 1H, *J*= 8.0 Hz, 7.4 Hz, 1.1 Hz, *H*-6'), 5.11 (q, 1H, *J* = 6.8 Hz, *H*-2), 1.52 (d, 3H, *J* = 6.8 Hz, *H*-3).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 172.1, 150.1, 140.0, 134.1, 125.0, 121.1, 115.5, 72.9, 18.0.
HR-MS (ESI-): *m/z* for $C_9H_9NO_5$-H$^-$, [M-H]$^-$ calculated: 210.0408; found: 210.0412.

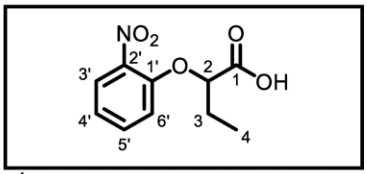
2-Methyl-2-(2-nitrophenoxy)propanoic acid (4c)



According to general protocol **GPII**, methyl 2-methyl-2-(2-nitrophenoxy)propanoate (**6c**, 20.34 g, 85 mmol, 1.0 eq.) and lithium hydroxide monohydrate (5.38 g, 128 mmol, 1.5 eq.) were reacted in 100 mL THF and 60 mL of water. 17.41 g (77.3 mmol, 91%) of the product was obtained as a colourless solid without further purification.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 13.37 (s, 1H, 1-COO*H*), 7.83 (dd, 1H, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.58 (ddd, 1H, *J* = 8.5 Hz, 7.4 Hz, 1.7 Hz, *H*-5'), 7.16 (ddd, 1H, *J* = 8.3 Hz, 7.5 Hz, 1.1 Hz, *H*-4'), 7.05 (dd, 1H, *J* = 8.5 Hz, 1.1 Hz, *H*-6'), 1.55 (s, 6H, *H*-3).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 174.1, 147.8, 142.2, 133.3, 124.8, 121.8, 119.0, 80.6, 24.9.
HR-MS (ESI-): *m/z* for $C_{10}H_{11}NO_5$-H$^-$, [M-H]$^-$ calculated: 224.0564; found: 224.0570.

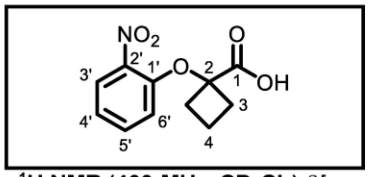
2-(2-Nitrophenoxy)butyric acid (4d)



According to general protocol **GPII**, ethyl 2-(2-nitrophenoxy)butanoate (**6d**, 0.92 g, 4 mmol, 1.0 eq.) and lithium hydroxide monohydrate (0.32 g, 8 mmol, 2.0 eq.) were reacted in 40 mL THF and 20 mL of water. 0.63 g (2.8 mmol, 70%) of the product was obtained as a colourless solid without further purification.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 13.24 (s, 1H, 1-COO*H*), 7.86 (dd, 1H, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.60 (ddd, 1H, *J* = 8.6 Hz, 7.4 Hz, 1.7 Hz, *H*-5'), 7.16 (dd, 1H, *J* = 8.6 Hz, 1.1 Hz, *H*-6'), 7.11 (ddd, 1H, *J* = 8.1 Hz, 7.4 Hz, 1.1 Hz, *H*-4'), 4.97 (dd, 1H, *J* = 6.9 Hz, 4.6 Hz, *H*-2), 2.03 – 1.83 (m, 2H, *H*-3), 1.00 (t, 3H, *J* = 7.4 Hz, *H*-4).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 171.4, 150.5, 139.9, 134.2, 125.1, 121.0, 115.3, 77.3, 25.3, 9.2.
HR-MS (ESI-): *m/z* for $C_{10}H_{11}NO_5$-H$^-$, [M-H]$^-$ calculated: 224.0564; found: 224.0569.

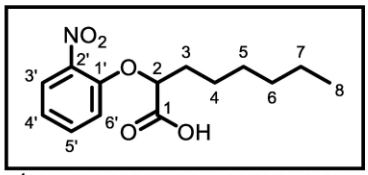
1-(2-Nitrophenoxy)cyclobutane-1-carboxylic acid (4e)



According to general protocol **GPII**, ethyl 1-(2-nitrophenoxy)cyclobutane-1-carboxylate (**6e**, 0.74 g, 3 mmol, 1.0 eq.) and lithium hydroxide monohydrate (0.18 g, 4 mmol, 1.3 eq.) were reacted in 40 mL THF and 20 mL of water. 0.442 g (1.9 mmol, 63%) of the product was obtained as a colourless solid without further purification.

^{1}H NMR (400 MHz, CD_2Cl_2) δ [ppm]: 7.82 (dd, 1H, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.46 (ddd, 1H, *J* = 8.4 Hz, 7.5 Hz, 1.7 Hz, *H*-5'), 7.07 (ddd, 1H, *J* = 8.1 Hz, 7.4 Hz, 1.1 Hz, *H*-4'), 6.65 (dd, 1H, *J* = 8.4 Hz, 1.1 Hz, *H*-6'), 2.87 – 2.74 (m, 2H, *H*-3), 2.63 – 2.41 (m, 2H, *H*-3), 2.18 – 1.97 (m, 2H, *H*-4).
^{13}C NMR (101 MHz, CD_2Cl_2) δ [ppm]: 176.9, 148.9, 140.9, 134.0, 126.2, 121.6, 116.4, 80.8, 32.7, 14.0.
HR-MS (ESI-): *m/z* for $C_{11}H_{11}NO_5$-H$^-$, [M-H]$^-$ calculated: 236.0564; found: 236.0569.

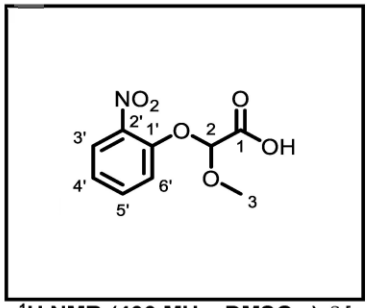
2-(2-Nitrophenoxy)caprylic acid (4f)



According to general protocol **GPII**, ethyl 2-(2-nitrophenoxy)octanoate (**6f**, 1.51 g, 5 mmol, 1.0 eq.) and lithium hydroxide monohydrate (0.45 g, 11 mmol, 2.2 eq.) were reacted in 40 mL THF and 20 mL of water. 1.350 g (4.8 mmol, 96%) of the product was obtained as a colourless solid without further purification.

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 13.25 (s, 1H, 1-COO*H*), 7.86 (dd, 1H, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.60 (ddd, 1H, *J* = 8.5 Hz, 7.5 Hz, 1.7 Hz, *H*-3'), 7.19 – 7.07 (m, 2H), 4.99 (dd, *J* = 7.1, 4.7 Hz, 1H), 1.95 – 1.80 (m, 2H), 1.53 – 1.36 (m, 1H), 1.36 – 1.21 (m, 7H), 0.88 – 0.83 (m, 3H).
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 167.8, 150.6, 140.6, 138.2, 135.3, 132.4, 129.2, 128.1, 126.8, 124.2, 115.7, 66.7, 61.9, 14.2.
HR-MS (ESI-): *m/z* for $C_{14}H_{19}NO_5$-H$^-$, [M-H]$^-$ calculated: 280.1190; found: 280.1197.

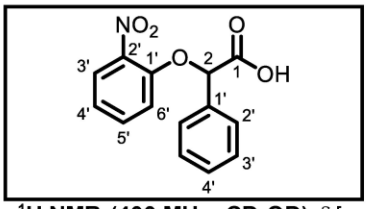
1-(2-Nitrophenoxy)cyclobutane-1-carboxylic acid (4g)



According to general protocol **GPI**, 2-nitrophenol (0.70 g, 5 mmol, 1.0 eq.), potassium carbonate (2.11 g, 15 mmol, 3.0 eq.) and methyl 2-chloro-2-methoxyacetate (technical grade 90%, 0.91 g, 6 mmol, 1.2 eq.) were reacted in 50 mL of DMF. The crude product was directly saponificated after work-up.
According to general protocol **GPII**, the crude ester and lithium hydroxide monohydrate (0.32 g, 8 mmol, 1.6 eq.) were reacted in 40 mL THF and 20mL of water. 0.271 g (1.2 mmol, 24%) of the product was obtained as a colourless solid after column chromatography (SiO_2; cyclohexane:ethyl acetate, gradient: 0 → 33% ethyl acetate +0.5 vol% AcOH).

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 13.68 (s, 1H, 1-COO*H*), 7.89 (dd, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.64 (ddd, 1H, *J* = 8.5 Hz, 7.4 Hz, 1.7 Hz, *H*-5'), 7.37 (dd, 1H, *J* = 8.5 Hz, 1.1 Hz, *H*-6'), 7.22 (ddd, 1H, *J* = 8.1 Hz, 7.5 Hz, 1.1 Hz, *H*-4'), 5.84 (s, 1H, *H*-2), 3.44 (s, 3H, *H*-3).
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 166.8, 148.2, 140.7, 134.1, 124.9, 122.5, 117.7, 97.9, 54.7.
HR-MS (ESI-): *m/z* for $C_9H_9NO_6$-H$^-$, [M-H]$^-$ calculated: 226.0357; found: 226.0360.

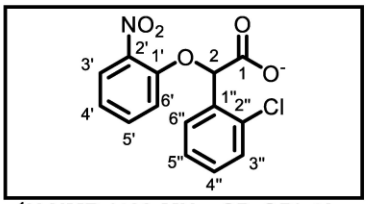
2-(2-Nitrophenoxy)-2-phenylacetic acid (4h)



According to general protocol **GPII**, methyl 2-(2-nitrophenoxy)-2-phenylacetate (**6h**, 0.58 g, 2 mmol, 1.0 eq.) and lithium hydroxide monohydrate (0.17 g, 4 mmol, 2.0 eq.) were reacted in 40 mL THF and 20 mL of water. 0.357 g (1.3 mmol, 65%) of the product was obtained as a yellow solid after column chromatography (SiO_2; cyclohexane:ethyl acetate, gradient: 40 → 67% ethyl acetate +0.5 vol% AcOH).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.83 (dd, 1H, *J* = 8.3 Hz, 1.7 Hz, *H*-3'), 7.65 – 7.61 (m, 2H, *H*-2''), 7.52 (ddd, 1H, *J* = 8.6 Hz, 7.4 Hz, 1.7 Hz, *H*-5'), 7.42 – 7.33 (m, 3H, *H*-3'', *H*-4''), 7.19 (dd, 1H, *J* = 8.6 Hz, 1.1 Hz, *H*-6'), 7.08 h, (ddd, 1H, *J* = 8.3 Hz, 7.4 Hz, 1.1 Hz, *H*-4'), 5.94 (s, 1H, *H*-2).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 172.1, 151.6, 142.0, 136.5, 135.0, 130.0, 129.7, 128.3, 126.5, 122.5, 116.8, 80.2.
HR-MS (ESI-): *m/z* for $C_{14}H_{11}NO_5$-H$^-$, [M-H]$^-$ calculated: 272.0564; found: 272.0569.

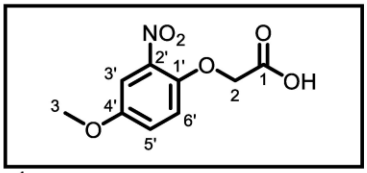
2-(2-Chlorophenyl)-2-(2-nitrophenoxy)acetic acid (4i)



According to general protocol **GPII**, methyl 2-(2-chlorophenyl)-2-(2-nitrophenoxy)acetate (**6i**, 0.82 g, 3 mmol, 1.0 eq.) and lithium hydroxide monohydrate (0.22 g, 5 mmol, 1.7 eq.) were reacted in 40 mL THF and 20 mL of water. 0.430 g (1.4 mmol, 56%) of the product was obtained as a yellow solid after column chromatography (SiO_2; cyclohexane:ethyl acetate, gradient: 40 → 67% ethyl acetate +0.5 vol% AcOH).

^{1}H NMR (400 MHz, CD_3OD) δ [ppm]: 7.83 (dd, 1H, *J* = 8.1 Hz, 1.7 Hz, *H*-3'), 7.68 (dt, 1H, *J* = 6.9 Hz, 2.3 Hz, *H*-3''), 7.55 (ddd, 1H, *J* = 8.8 Hz, 7.5 Hz, 1.7 Hz, *H*-5'), 7.47 (dt, 1H, *J* = 6.8 Hz, 2.3 Hz, *H*-5''), 7.39 – 7.34 (m, 2H, *H*-4''. *H*-6''), 7.21 – 7.17 (m, 1H, *H*-6'), 7.15 – 7.09 (m, 1H, *H*-4'), 6.32 (s, 1H, *H*-2).
^{13}C NMR (101 MHz, CD_3OD) δ [ppm]: 171.2, 151.4, 142.2, 135.0, 134.8, 134.5, 131.7, 130.8, 130.3, 128.6, 126.5, 122.9, 117.1, 77.1.
HR-MS (ESI-): *m/z* for $C_8H_6{}^{35}ClNO_5$-H$^-$, [M-H]$^-$ calculated: 306.0175; found: 306.0169.

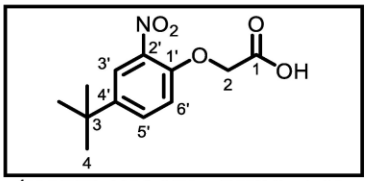
2-(4-Methoxy-2-nitrophenoxy)acetic acid (4j)



According to general protocol **GPII**, methyl 2-(4-methoxy-2-nitrophenoxy)acetate (**6j**, 1.08 g, 5 mmol, 1.0 eq.) and lithium hydroxide monohydrate (0.40 g, 10 mmol, 2.0 eq.) were reacted in 40 mL THF and 20 mL of water. 0.949 g (4.2 mmol, 93%) of the product was obtained as a colourless solid without further purification.

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 13.14 (s, 1H, 1-COO*H*), 7.45 – 7.43 (m, 1H, *H*-3'), 7.23 – 7.20 (m, 2H, *H*-5', *H*-6'), 4.83 (s, 2H, *H*-2), 3.77 (s, 3H, *H*-3).
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 169.6, 152.9, 144.5, 140.0, 120.1, 116.7, 109.4, 65.9, 56.1.
HR-MS (ESI-): *m/z* for $C_9H_9NO_6$-H$^-$, [M-H]$^-$ calculated: 226.0357; found: 226.0361.

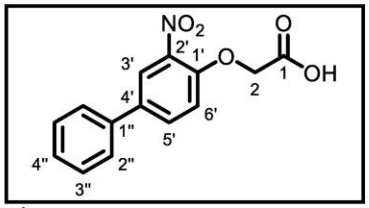
2-(4-*tert*-Butyl-2-nitrophenoxy)acetic acid (4k)



According to general protocol **GPII**, methyl 2-(4-*tert*-butyl-2-nitrophenoxy)acetate (**6k**, 1.34 g, 5 mmol, 1.0 eq.) and lithium hydroxide monohydrate (0.43 g, 10 mmol, 2.0 eq.) were reacted in 40 mL THF and 20 mL of water. 1.189 g (4.7 mmol, 94%) of the product was obtained as a colourless solid without further purification.

^{1}H NMR (400 MHz, $DMSO_{d6}$) δ [ppm]: 7.80 (d, 1H, *J* = 2.5 Hz, *H*-3'), 7.64 (dd, 1H, *J* = 8.9 Hz, 2.5 Hz, *H*-5'), 7.16 (d, 1H, *J* = 8.9 Hz, *H*-6'), 4.87 (s, 2H, *H*-2), 1.27 (s, 9H, *H*-4).
^{13}C NMR (101 MHz, $DMSO_{d6}$) δ [ppm]: 169.5, 148.2, 143.9, 139.3, 131.0, 121.4, 114.7, 65.3, 34.2, 30.9.
HR-MS (ESI-): *m/z* for $C_{12}H_{15}NO_5$-H$^-$, [M-H]$^-$ calculated: 252.0877; found: 252.0881.

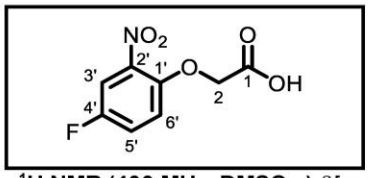
2-((3-Nitro-biphenyl-4-yl)oxy)acetic acid (4l)



According to general protocol **GPII**, ethyl 2-((3-nitro-biphenyl-4-yl)oxy)acetate (**6l**, 3.01 g, 10 mmol, 1.0 eq.) and lithium hydroxide monohydrate (0.70 g, 17 mmol, 1.7 eq.) were reacted in 70 mL THF and 30 mL of water. 2.490 g (9.1 mmol, 91%) of the product was obtained as a colourless solid without further purification.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 13.28 (s, 1H, 1-COO*H*), 8.15 (d, 1H, *J* = 2.4 Hz, *H*-3'), 7.93 (dd, 1H, *J* = 8.8 Hz, 2.4 Hz, *H*-5'), 7.73 – 7.67 (m, 2H, *H*-2''), 7.50 – 7.43 (m, 2H, *H*-3''), 7.41 – 7.33 (m, 1H, *H*-4''), 4.97 (s, 2H, *H*-2'').
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 169.4, 149.7, 140.2, 137.5, 133.1, 131.8, 129.1, 127.9, 126.5, 122.6, 115.6, 65.4.
HR-MS (ESI-): *m/z* for $C_{14}H_{11}NO_5$-H$^-$, [M-H]$^-$ calculated: 272.0564; found: 272.0568.

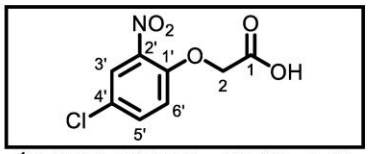
2-(4-Fluoro-2-nitrophenoxy)acetic acid (4m)



According to general protocol **GPII**, methyl 2-(4-fluoro-2-nitrophenoxy)acetate (**6m**, 1.03 g, 5 mmol, 1.0 eq.) and lithium hydroxide monohydrate (0.39 g, 9 mmol, 1.8 eq.) were reacted in 40 mL THF and 20 mL of water. 0.904 g (4.2 mmol, 93%) of the product was obtained as a colourless solid without further purification.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 13.22 (s, 1H, 1-COO*H*), 7.88 (dd, 1H, *J* = 8.1 Hz, 3.2 Hz, *H*-3'), 7.54 (ddd, 1H, *J* = 9.3 Hz, 7.9 Hz, 3.2 Hz, *H*-4'), 7.33 (dd, 1H, *J* = 9.3 Hz, 4.4 Hz, *H*-5'), 4.90 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 169.3, 154.9 (d, *J* = 241.0 Hz), 147.1 (d, *J* = 2.6 Hz), 139.5 (d, *J* = 9.1 Hz), 120.8 (d, *J* = 23.1 Hz), 116.9 (d, *J* = 8.3 Hz), 112.1 (d, *J* = 28.2 Hz), 65.8.
^{19}F NMR (376 MHz, DMSO$_{d6}$) δ [ppm]: -122.06 (td, *J* = 7.9 Hz, 4.4 Hz).
HR-MS (ESI-): *m/z* for $C_8H_6FNO_5$-H$^-$, [M-H]$^-$ calculated: 214.0157; found: 214.0158.

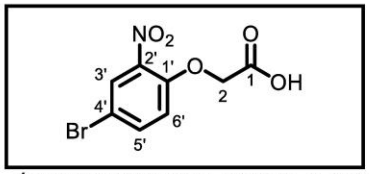
2-(4-Chloro-2-nitrophenoxy)acetic acid (4n)



According to general protocol **GPII**, methyl 2-(4-chloro-2-nitrophenoxy)acetate (**6n**, 2.46 g, 10 mmol, 1.0 eq.) and lithium hydroxide monohydrate (1.01 g, 20 mmol, 2.0 eq.) were reacted in 40 mL THF and 20mL of water. 2.15 g (9.3 mmol, 93%) of the product was obtained as a beige solid without further purification.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 13.28 (s, 1H, 1-COO*H*), 8.03 (d, 1H, *J* = 2.7 Hz, *H*-3'), 7.69 (dd, 1H, *J* = 9.1 Hz, 2.7 Hz, *H*-5'), 7.32 (d, 1H, *J* = 9.1 Hz, *H*-6'), 4.93 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 169.2, 149.3, 140.0, 133.6, 124.5, 117.0, 65.6.
HR-MS (ESI-): *m/z* for $C_8H_6{}^{35}ClNO_5$-H$^-$, [M-H]$^-$ calculated: 229.9862; found: 229.9868.

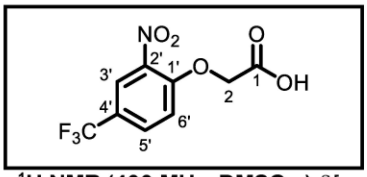
2-(4-Bromo-2-nitrophenoxy)acetic acid (4o)



According to general protocol **GPII**, methyl 2-(4-bromo-2-nitrophenoxy)acetate (**6o**, 1.30 g, 5 mmol, 1.0 eq.) and lithium hydroxide monohydrate (0.39 g, 9 mmol, 1.8 eq.) were reacted in 40 mL THF and 20 mL of water. 1.187 g (4.3 mmol, 96%) of the product was obtained as a colourless solid without further purification.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 13.27 (s, 1H, 1-COO*H*), 8.12 (d, 1H, *J* = 2.5 Hz, *H*-3'), 7.80 (dd, 1H, *J* = 9.0 Hz, 2.5 Hz, *H*-5'), 7.26 (d, 1H, *J* = 9.0 Hz, *H*-6'), 4.93 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 169.1, 149.7, 140.4, 136.4, 127.1, 117.3, 111.6, 65.5.
HR-MS (ESI-): *m/z* for $C_8H_6{}^{79}BrNO_5$-H$^-$, [M-H]$^-$ calculated: 273.9357; found: 273.9357.

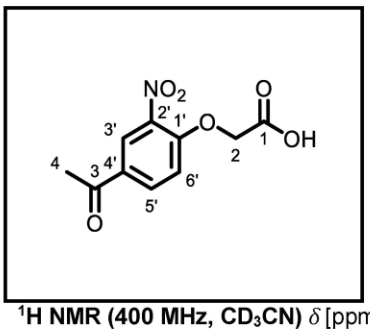
2-(2-Nitro-4-trifluoromethylphenoxy)acetic acid (4p)



According to general protocol **GPII**, methyl 2-(2-nitro-4-trifluoromethylphenoxy)acetate (**6p**, 0.84 g, 3 mmol, 1.0 eq.) and lithium hydroxide monohydrate (0.26 g, 6 mmol, 2.0 eq.) were reacted in 40 mL THF and 20 mL of water. 0.689 g (2.6 mmol, 87%) of the product was obtained as a beige solid without further purification.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 13.38 (s, 1H, 1-COO*H*), 8.31 (dd, 1H, *J* = 2.4 Hz, 0.8 Hz, *H*-3'), 7.99 (ddd, 1H, *J* = 8.9 Hz, 2.4 Hz, 0.8 Hz, *H*-5'), 7.49 (dd, 1H, *J* = 8.9, 0.9 Hz, *H*-6'), 5.05 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 168.9, 153.1, 139.5, 130.8 (d, *J* = 3.6 Hz), 123.3 (q, *J* = 271.8 Hz), 122.5 (q, *J* = 3.8 Hz), 121.7, 121.3, 65.7.
^{19}F NMR (376 MHz, DMSO$_{d6}$) δ [ppm]: -61.52.
HR-MS (ESI-): *m/z* for $C_9H_6F_3NO_5$-H$^-$, [M-H]$^-$ calculated: 264.0125; found: 264.0130.

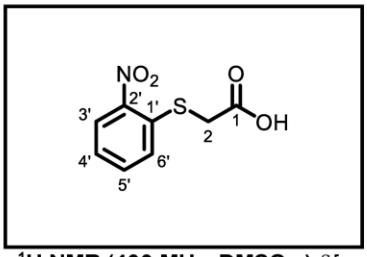
2-(4-Acetyl-2-nitrophenoxy)acetic acid (4q)



According to general protocol **GPI**, 4-acetyl-2-nitrophenol (1.84 g, 10 mmol, 1.0 eq.), potassium carbonate (4.15 g, 30 mmol, 3.0 eq.) and methyl 2-bromoacetate (2.29 g, 15 mmol, 1.5 eq.) were reacted in 30 mL of anhydrous acetone. The crude product was directly saponificated after work-up.
According to general protocol **GPII**, the crude ester and lithium hydroxide monohydrate (1.01 g, 20 mmol, 2.0 eq.) were reacted in 40 mL THF and 20mL of water. 0.831 g (3.5 mmol, 35%) of the product was obtained as a yellow solid after column chromatography (SiO_2; Cy:EA, gradient: 25 → 50% EA+0.5 vol% AcOH).

^{1}H NMR (400 MHz, CD$_3$CN) δ [ppm]: 8.33 (d, 1H, *J* = 2.2 Hz, *H*-3'), 8.12 (dd, 1H, *J* = 8.9 Hz, 2.2 Hz, *H*-5'), 7.20 (d, 1H, *J* = 8.9 Hz, *H*-6'), 4.90 (s, 2H, *H*-2), 2.54 (s, 3H, *H*-4).
^{13}C NMR (101 MHz, CD$_3$CN) δ [ppm]: 196.4, 169.1, 154.8, 140.9, 134.7, 131.6, 126.3, 115.8, 66.6, 26.8.
HR-MS (ESI-): *m/z* for $C_{10}H_9NO_6$-H$^-$, [M-H]$^-$ calculated: 238.0357; found: 238.0362.

2-((2-Nitrophenyl)thio)acetic acid (4r)

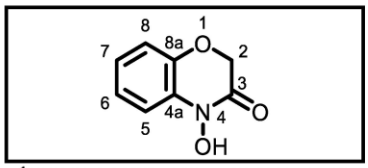


Sodium hydroxide (1.83 g, 46 mmol, 2.1 eq.) was dissolved in 15 mL of water and thioglycolic acid (1.8 mL, 25 mmol, 1.1 eq.) was added at 10 °C. 2-fluoronitrobenzene (3.11 g, 22 mmol, 1.0 eq.) dissolved in 100 mL of ethanol was added dropwise. The mixture was refluxed for 1 h. After completion of the reaction the mixture was added to 50 mL of water and acidified using 1 M hydrochloric acid. The solids were filtered and dried under reduced pressure. 3.433 g (16.1 mmol, 73%) of the product was obtained as a yellow solid.

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 13.01 (s, 1H, 1-COO*H*), 8.21 (dd, 1H, *J* = 8.3 Hz, 1.5 Hz, *H*-3'), 7.73 (ddd, 1H, *J* = 8.6 Hz, 7.2 Hz, 1.5 Hz, *H*-5'), 7.58 (dd, 1H, *J* = 8.4 Hz, 1.3 Hz, *H*-4'), 7.41 (ddd, *J* = 8.4 Hz, 7.2 Hz, 1.3 Hz, 1H), 4.01 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 170.0, 145.5, 135.9, 134.3, 127.3, 125.9, 125.6, 34.4.
HR-MS (ESI-): *m/z* for $C_8H_7NO_4S$-H$^-$, [M-H]$^-$ calculated: 212.0023; found: 212.0027.
Known compound and literature, spectroscopic data match to literature.[5]

6.3. 4-Hydroxybenzo[*b*]-1,4-oxazin-3-ones (5a-5r)

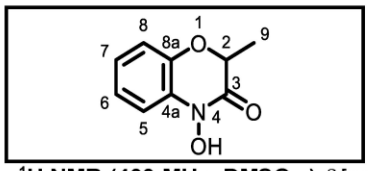
2*H*,4*H*-4-Hydroxybenzo[*b*]-1,4-oxazin-3-one (5a, D-DIBOA)



According to general protocol **GPIII**, 2-(2-nitrophenoxy)acetic acid (**4a**, 29.6 mg, 0.15 mmol), were reacted. 14.9 mg (0.090 mmol, 60%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 0 → 15% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 10.74 (s, 1H, 4-N-O*H*), 7.25 – 7.21 (m, 1H, *H*-5), 7.08 – 6.96 (m, 3H, *H*-6, *H*-7, *H*-8), 4.76 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 160.2, 143.6, 129.6, 123.7, 122.5, 115.9, 113.0, 67.8.
HR-MS (ESI+): *m/z* for $C_8H_7NO_3$+H^+, $[M+H]^+$ calculated: 166.0499; found: 166.0500.
Known compound and literature, spectroscopic data match to literature.[6]

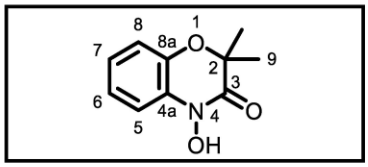
2*H*,4*H*-4-Hydroxy-2-methylbenzo[*b*]-1,4-oxazin-3-one (5b)



According to general protocol **GPIII**, 2-(2-nitrophenoxy)propionic acid (**4b**, 31.7 mg, 0.15 mmol), were reacted. 21.7 mg (0.121 mmol, 81%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 20 → 70% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 10.80 (s, 1H, 4-N-O*H*), 7.25 – 7.19 (m, 1H, *H*-5), 7.10 – 6.96 (m, 3H, *H*-6, *H*-7, *H*-8), 4.87 (q, 1H, *J* = 6.7 Hz, *H*-2), 1.46 (d, 3H, *J* = 6.7 Hz, *H*-9).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 162.3, 142.7, 129.8, 123.8, 122.7, 116.2, 113.1, 74.0, 16.4.
HR-MS (ESI+): *m/z* for $C_9H_9NO_3$+Na^+, $[M+Na]^+$ calculated: 202.0475; found: 202.0446.

2*H*,4*H*-2,2-Dimethyl-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5c)

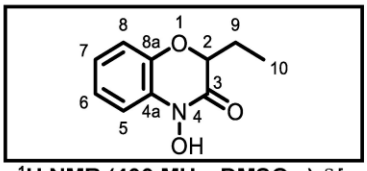


0.15 mmol scale: According to general protocol **GPIII**, 2-methyl-2-(2-nitrophenoxy)propanoic acid (**4a**, 34.4 mg, 0.15 mmol), were reacted. 23.3 mg (0.121 mmol, 81%) of the product was obtained as an off-white solid.
0.75 mmol scale: According to **GPIII**, (**4a**, 168.8 mg, 0.75 mmol), were reacted. 110.9 mg (0.574 mmol, 77%).
3.0 mmol scale: According to **GPIII**, (**4a**, 676 mg, 3.0 mmol), were reacted. 503 mg (2.6 mmol, 87%).
Purification 0.15–3.0 mmol scale: reversed phase column chromatography (C_{18} silica, gradient: 20 → 70% acetonitrile).

7.5 mmol scale: According to **GPIII**, (**4a**, 1.69 g, 7.5 mmol), were reacted. 1.27 g (6.6 mmol, 88%) of the product was obtained as a beige solid after crystallisation (30 mL MeCN; crystallisation at 6 °C).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 10.76 (s, 1H, 4-N-O*H*), 7.20 (dd, 1H, *J* = 7.8 Hz, 1.7 Hz, *H*-5), 7.05 (td, 1H, *J* = 7.8 Hz, 1.8 Hz, *H*-6), 7.00 (td, 1H, *J* = 7.5, 1.7 Hz, *H*-7), 6.96 (dd, 1H, *J* = 7.5, 1.8 Hz, *H*-8), 1.43 (s, 6H, *H*-9).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 164.0, 141.2, 129.6, 123.9, 122.5, 116.7, 112.7, 79.1, 23.6.
HR-MS (ESI+): *m/z* for $C_{10}H_{11}NO_3$+H^+, $[M+H]^+$ calculated: 194.0812; found: 194.0804.
m.p. (MeCN): 132.3–134.1 °C.

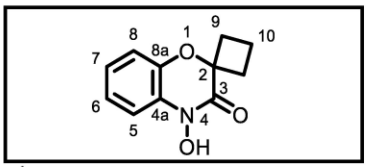
2*H*,4*H*-2-Ethyl-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5d)



According to general protocol **GPIII**, 2-(2-nitrophenoxy)butyric acid (**4d**, 33.7 mg, 0.15 mmol), were reacted. 21.1 mg (0.109 mmol, 73%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 20 → 60% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 10.77 (s, 1H, 4-N-O*H*), 7.21 (dd, 1H, *J* = 7.4 Hz, 1.1 Hz, *H*-5), 7.07 – 6.98 (m, 3H, *H*-6, *H*-7, *H*-8), 4.73 – 4.69 (m, 1H, *H*-2), 1.92 – 1.73 (m, 2H, *H*-9), 0.99 (t, 3H, *J* = 7.4 Hz, *H*-10).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 161.8, 142.5, 129.6, 123.8, 122.5, 116.3, 112.9, 78.4, 23.6, 9.1.
HR-MS (ESI-): *m/z* for $C_{10}H_{11}NO_3$-H$^-$, [M-H]$^-$ calculated: 192.0666; found: 192.0672.
Known compound and literature, spectroscopic data match to literature.[7]

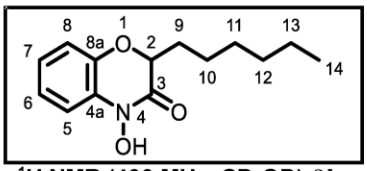
4*H*-4-Hydroxyspiro[benzo[*b*]-1,4-oxazine-2,1'-cyclobutan]-3-one (5e)



According to general protocol **GPIII**, 1-(2-nitrophenoxy)-cyclobutane-1-carboxylic acid (**4e**, 35.7 mg, 0.15 mmol), were reacted. 21.1 mg (0.103 mmol, 69%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 35 → 50% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 10.79 (s, 1H, 4-N-O*H*), 7.20 (dd, 1H, *J* = 7.8 Hz, 1.5 Hz, *H*-5), 7.10 – 6.97 (m, 3H, *H*-6, *H*-7, *H*-8), 2.55 – 2.45 (m, 2H, *H*-9), 2.31 – 2.21 (m, 1H, *H*-9), 2.00 – 1.89 (m, 1H, *H*-9), 1.87 – 1.74 (m, 2H, *H*-10).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 162.9, 141.2, 129.7, 123.8, 122.9, 116.8, 112.9, 80.3, 31.0, 12.8.
HR-MS (ESI-): *m/z* for $C_{11}H_{11}NO_3$-H$^-$, [M-H]$^-$ calculated: 204.0666; found: 204.0661.

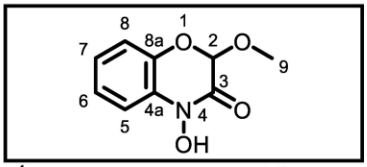
2*H*,4*H*-2-(*n*-Hexyl)-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5f)



According to general protocol **GPIII**, 2-(2-nitrophenoxy)caprylic acid (**4f**, 42.0 mg, 0.15 mmol), were reacted. 22.6 mg (0.0907 mmol, 61%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 50 → 60% acetonitrile).

^{1}H NMR (400 MHz, CD$_3$OD) δ [ppm]: 7.31 – 7.27 (m, 1H, *H*-5), 7.08 – 7.00 (m, 2H, *H*-6, *H*-7), 6.98 – 6.93 (m, 1H, *H*-8), 4.68 (dd, 1H, *J* = 8.0 Hz, 4.7 Hz, *H*-2), 1.93 – 1.77 (m, 2H, *H*-9), 1.62 – 1.43 (m, 2H, *H*-10), 1.41 – 1.24 (m, 6H, *H*-11, *H*-12, *H*-13), 0.93 – 0.87 (m, 3H, *H*-14).
^{13}C NMR (101 MHz, CD$_3$OD) δ [ppm]: 164.5, 144.3, 130.5, 125.6, 123.6, 117.6, 114.3, 79.3, 32.8, 31.6, 29.9, 25.8, 23.6, 14.4.
HR-MS (ESI+): *m/z* for $C_{14}H_{19}NO_3$+H$^+$, [M+H]$^+$ calculated: 250.1438; found: 250.1435.

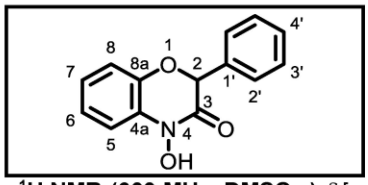
2*H*,4*H*-4-Hydroxy-2-methylbenzo[*b*]-1,4-oxazin-3-one (5g)



According to general protocol **GPIII**, 2-methoxy-2-(2-nitrophenoxy)acetic acid (**4g**, 34.2 mg, 0.15 mmol), were reacted. 20.5 mg (0.105 mmol, 70%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 20 → 30% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 11.08 (s, 1H, 4-N-O*H*), 7.31 – 7.26 (m, 1H, *H*-5), 7.17 – 7.04 (m, 3H, *H*-6, *H*-7, *H*-8), 5.55 (s, 1H, *H*-2), 3.44 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 155.9, 140.0, 128.8, 124.2, 123.2, 117.2, 113.2, 97.8, 55.9.
HR-MS (ESI-): *m/z* for $C_9H_9NO_4$-H$^-$, [M-H]$^-$ calculated: 194.0459; found: 194.0465.
Known compound and literature, spectroscopic data match to literature.[6]

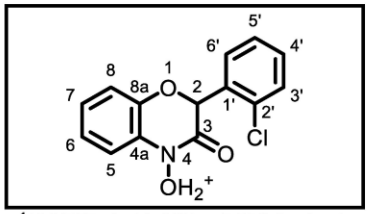
2*H*,4*H*-4-Hydroxy-2-phenylbenzo[*b*]-1,4-oxazin-3-one (5h)



According to general protocol **GPIII**, 2-(2-nitrophenoxy)-2-phenylacetic acid (**4g**, 41.4 mg, 0.15 mmol), were reacted. 21.4 mg (0.0887 mmol, 59%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 35 → 50% acetonitrile).

^{1}H NMR (600 MHz, DMSO$_{d6}$) δ [ppm]: 11.14 (s, 1H, 4-N-O*H*), 7.40 – 7.34 (m, 5H, *H*-2', *H*-3', *H*-4'), 7.25 (dd, 1H, *J* = 7.9 Hz, 1.5 Hz, *H*-5), 7.07 – 6.98 (m, 3H, *H*-6, *H*-7, *H*-8), 5.99 (s, 1H, *H*-7).
^{13}C NMR (151 MHz, DMSO$_{d6}$) δ [ppm]: 160.2, 142.4, 135.6, 129.3, 129.0, 128.7, 127.2, 124.1, 122.8, 116.6, 113.2, 78.9.
HR-MS (ESI-): *m/z* for $C_{14}H_{11}NO_3$-H$^-$, [M-H]$^-$ calculated: 240.0666; found: 240.0675.

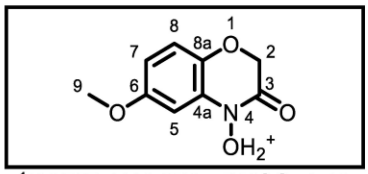
2*H*,4*H*-4-Hydroxy-2-phenylbenzo[*b*]-1,4-oxazin-3-one (5i)



According to general protocol **GPIII**, 2-(2-chlorophenyl)-(2-nitrophenoxy)acetic acid (**4h**, 48.2 mg, 0.15 mmol), were reacted. 24.3 mg (0.0883 mmol, 59%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 35 → 60% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 11.02 (s, 1H, 4-N-O*H*), 7.56 (dd, 1H, *J* = 8.0 Hz, 1.3 Hz, *H*-3'), 7.48 – 7.42 (m, 2H, *H*-5', *H*-6'), 7.38 (ddd, 1H, *J* = 8.3 Hz, 6.8 Hz, 1.3 Hz, *H*-4'), 7.30 (dd, 1H, *J* = 7.9 Hz, 1.5 Hz, *H*-5), 7.09 (td, 1H, *J* = 7.6 Hz, 1.7 Hz, *H*-6), 7.03 – 6.95 (m, 2H, *H*-7, *H*-8), 6.16 (s, 1H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 159.9, 142.4, 133.6, 133.2, 131.1, 130.5, 130.1, 129.4, 127.4, 124.0, 122.8, 116.2, 113.1, 77.4.
HR-MS (ESI+): *m/z* for $C_{14}H_{10}{}^{35}ClNO_3$+H$^+$, [M+H]$^+$ calculated: 276.0422; found: 276.0418.

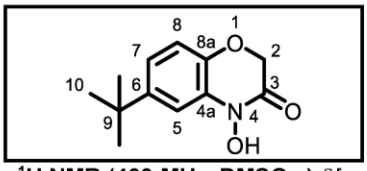
2*H*,4*H*-4-Hydroxy-6-methoxybenzo[*b*]-1,4-oxazin-3-one (5j)



According to general protocol **GPIII**, 2-(4-methoxy-2-nitrophenoxy)acetic acid (**4i**, 33.6 mg, 0.15 mmol), were reacted. 12.4 mg (0.0635 mmol, 42%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 10 → 90% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 10.80 (s, 1H, 4-N-O*H*), 6.91 (d, 1H, *J* = 8.7 Hz, *H*-8), 6.77 (d, 1H, *J* = 2.9 Hz, *H*-5), 6.55 (dd, 1H, *J* = 8.7 Hz, 2.9 Hz, *H*-7), 4.68 (s, 2H, *H*-2), 3.72 (s, 3H, *H*-9).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 160.8, 154.9, 137.4, 130.5, 116.5, 107.9, 99.3, 67.9, 55.6.
HR-MS (ESI+): *m/z* for $C_9H_9NO_4$+H$^+$, [M+H]$^+$ calculated: 196.0604; found: 196.0609.
Known compound and literature, spectroscopic data match to literature.[8]

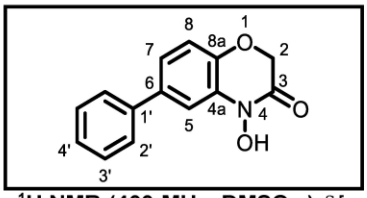
2*H*,4*H*-6-*tert*-Butyl-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5k)



According to general protocol **GPIII**, 2-(4-*tert*-butyl-2-nitrophenoxy)acetic acid (**4j**, 37.9 mg, 0.15 mmol), were reacted. 12.1 mg (0.0547 mmol, 36%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 35 → 45% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 10.75 (s, 1H, 4-N-O*H*), 7.23 (d, *J* = 2.3 Hz, 1H, *H*-5), 7.01 (dd, *J* = 8.4 Hz, 2.3 Hz, 1H, *H*-7), 6.90 (d, *J* = 8.4 Hz, 1H, *H*-8), 4.71 (s, 2H, *H*-2), 1.26 (s, 9H, *H*-10).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 160.3, 145.2, 141.5, 129.0, 120.3, 115.4, 109.9, 67.9, 34.2, 31.2.
HR-MS (ESI-): *m/z* for $C_{12}H_{15}NO_3$-H$^-$, [M-H]$^-$ calculated: 220.0979; found: 220.0972.

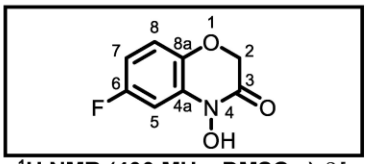
2*H*,4*H*-4-Hydroxy-6-phenylbenzo[*b*]-1,4-oxazin-3-one (5l)



According to general protocol **GPIII**, 2-(2-nitro-4-phenyl-phenoxy)acetic acid (**4k**, 40.9 mg, 0.15 mmol), were reacted. 18.8 mg (0.0781 mmol, 52%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 40 → 50% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 10.96 (s, 1H, 4-N-O*H*), 7.64 – 7.57 (m, 2H, *H*-2‘), 7.48 – 7.42 (m, 3H, *H*-5, *H*-3‘), 7.39 – 7.32 (m, 1H, *H*-4), 7.29 (dd, 1H, *J* = 8.3 Hz, 2.1 Hz, *H*-7), 7.07 (d, 1H, *J* = 8.3 Hz, *H*-8), 4.81 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 160.2, 143.2, 139.5, 134.8, 130.0, 129.0, 127.3, 126.4, 121.9, 116.5, 111.0, 67.9.
HR-MS (ESI-): *m/z* for $C_{14}H_{11}NO_3$-H$^-$, [M-H]$^-$ calculated: 240.0666; found: 240.0665.

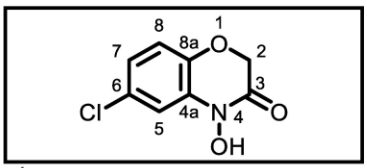
2*H*,4*H*-6-Fluoro-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5m)



According to general protocol **GPIII**, 2-(4-fluoro-2-nitro-phenoxy)acetic acid (**4j**, 32.4 mg, 0.15 mmol), were reacted. 21.9 mg (0.120 mmol, 80%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 20 → 40% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 10.97 (s, 1H, 4-N-O*H*), 7.04 – 6.95 (m, 2H, *H*-5, *H*-7), 6.88 – 6.72 (m, 1H, *H*-8), 4.75 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 160.6, 158.8, 156.4, 139.8 (d, *J* = 2.2 Hz), 130.9 (d, *J* = 11.0 Hz), 117.0 (d, *J* = 9.2 Hz), 109.3 (d, *J* = 23.3 Hz), 100.5 (d, *J* = 29.7 Hz), 67.8.
^{19}F NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: -120.79 (d, *J* = 5.2 Hz).
HR-MS (ESI-): *m/z* for $C_8H_6FNO_3$-H$^-$, [M-H]$^-$ calculated: 182.0259; found: 182.0264.
Known compound and literature, spectroscopic data match to literature.[9]

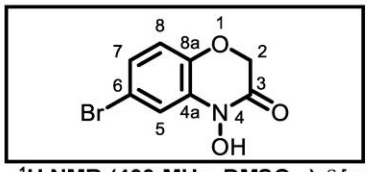
2*H*,4*H*-6-Chloro-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5n)



According to general protocol **GPIII**, 2-(4-chloro-2-nitro-phenoxy)acetic acid (**4m**, 33.8 mg, 0.15 mmol), were reacted. 18.5 mg (0.101 mmol, 67%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 20 → 40% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 10.93 (s, 1H, 4-N-O*H*), 7.18 (d, 1H, *J* = 2.2 Hz, *H*-5), 7.06 – 6.99 (m, 2H, *H*-7, *H*-8), 4.80 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 160.3, 142.4, 130.9, 126.3, 123.1, 117.5, 112.5, 67.8.
HR-MS (ESI-): *m/z* for $C_8H_6{}^{35}ClNO_3$-H$^-$, [M-H]$^-$ calculated: 197.9963; found: 197.9969.
Known compound and literature, spectroscopic data match to literature.[9]

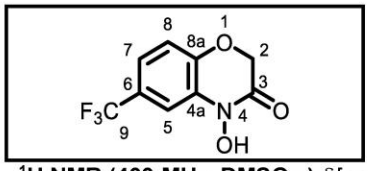
2*H*,4*H*-6-Bromo-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5o)



According to general protocol **GPIII**, 2-(4-bromo-2-nitro-phenoxy)acetic acid (**4n**, 41.4 mg, 0.15 mmol), were reacted. 26.5 mg (0.109 mmol, 73%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 30 → 40% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 11.04 (s, 1H, 4-N-O*H*), 7.35 – 7.26 (m, 1H, *H*-5), 7.22 – 7.08 (m, 1H, *H*-7), 7.06 – 6.85 (m, 1H, *H*-8), 4.79 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 160.2, 142.9, 131.1, 126.0, 117.9, 115.3, 113.7, 67.8.
HR-MS (ESI-): *m/z* for $C_8H_6{}^{79}BrNO_3$-H$^-$, [M-H]$^-$ calculated: 241.9458; found: 241.9466.

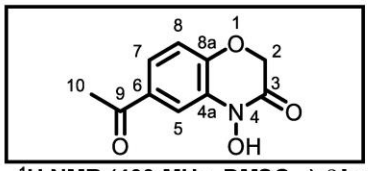
2*H*,4*H*-4-Hydroxy-trifluoromethylbenzo[*b*]-1,4-oxazin-3-one (5p)



According to general protocol **GPIII**, 2-(4-trifluoromethyl-2-nitro-phenoxy)acetic acid (**4p**, 39.9 mg, 0.15 mmol), were reacted. 20.9 mg (0.0896 mmol, 60%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 35 → 45% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 11.13 (s, 1H, 4-N-O*H*), 7.43 (d, 1H, *J* = 2.2 Hz, *H*-5), 7.36 (dd, 1H, *J* = 8.5 Hz, 2.2 Hz, *H*-7), 7.17 (d, 1H, *J* = 8.5 Hz, *H*-8), 4.89 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 159.9, 146.5, 130.2, 124.1 (q, *J* = 271.4 Hz), 123.0 (q, *J* = 32.4 Hz), 120.9 (q, *J* = 3.9 Hz), 116.7, 109.5 (q, *J* = 4.0 Hz), 67.9.
^{19}F NMR (376 MHz, DMSO$_{d6}$) δ [ppm]: -60.41.
HR-MS (ESI-): *m/z* for $C_9H_6F_3NO_3$-H$^-$, [M-H]$^-$ calculated: 232.0227; found: 232.0228.
Known compound and literature, spectroscopic data match to literature.[9]

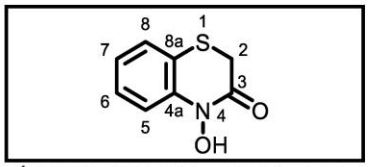
2*H*,4*H*-6-Acetyl-4-hydroxybenzo[*b*]-1,4-oxazin-3-one (5q)



According to general protocol **GPIII**, 2-(4-acetyl-2-nitro-phenoxy)acetic acid (**4q**, 35.9 mg, 0.15 mmol), were reacted. 21.3 mg (0.0896 mmol, 60%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 15 → 30% acetonitrile).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 11.07 (s, 1H, 4-N-O*H*), 7.75 – 7.71 (m, 1H, *H*-5), 7.69 – 7.65 (m, 1H, *H*-7), 7.12 – 6.95 (m, 1H, *H*-8), 4.89 (s, 2H, *H*-2), 2.54 (s, 3H, *H*-10).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 196.2, 159.6, 147.5, 131.4, 129.5, 125.2, 115.9, 112.3, 67.9, 26.5.
HR-MS (ESI-): *m/z* for $C_{10}H_9NO_4$-H$^-$, [M-H]$^-$ calculated: 206.0459; found: 206.0463.

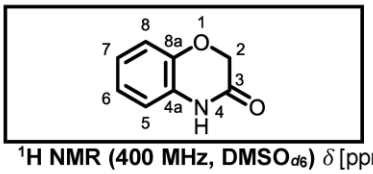
2*H*,4*H*-4-Hydroxybenzo[*b*]-1,4-thiazin-3-one (5r)



According to general protocol **GPIII**, 2-((2-nitrophenyl)thio)acetic acid (**4q**, 31.7 mg, 0.15 mmol), were reacted. 11.5 mg (0.0635 mmol, 42%) of the product was obtained as an off-white solid by reversed phase column chromatography (C_{18} silica, gradient: 20% acetonitrile isocratic).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 10.76 (s, 1H, 4-N-O*H*), 7.38 – 7.33 (m, 2H, *H*-5, *H*-8), 7.28 (td, 1H, *J* = 7.3 Hz, 1.4 Hz, *H*-6), 7.03 (td, 1H, *J* = 7.5 Hz, 1.3 Hz, *H*-7), 3.66 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 161.0, 139.5, 127.3, 127.1, 123.4, 120.0, 115.4, 29.9.
HR-MS (ESI-): *m/z* for $C_8H_7NO_2S$-H$^-$, [M-H]$^-$ calculated: 180.0125; found: 180.0126.
Known compound and literature, spectroscopic data match to literature.[10]

2*H*,4*H*-Benzo[*b*]-1,4-oxazin-3-one (5s)

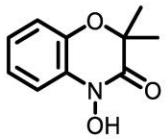


According to general protocol **GPIII**, using a zinc electrode, methyl 2-(2-nitrophenoxy)acetate (**4a**, 42.2 mg, 0.20 mmol), were reacted. **No electricity was applied.** 26.4 mg (0.177 mmol, 89%) of the product was obtained as an off-white solid by flash column chromatography (SiO_2, gradient: 5 → 47% ethyl acetate).

^{1}H NMR (400 MHz, DMSO$_{d6}$) δ [ppm]: 10.69 (s, 1H, 4-N*H*), 6.98 – 6.86 (m, 4H, *H*-5, *H*-6, *H*-7, *H*-8), 4.55 (s, 2H, *H*-2).
^{13}C NMR (101 MHz, DMSO$_{d6}$) δ [ppm]: 165.0, 143.3, 127.3, 123.1, 122.5, 116.2, 115.9, 66.8.
HR-MS (ESI+): *m/z* for $C_8H_7NO_2+H^+$, $[M+H]^+$ calculated: 150.0550; found: 150.0553.
Known compound and literature, spectroscopic data match to literature.[11]

7. Crystallographic Data

2*H*,4*H*- 2,2-Dimethyl-4-hydroxy-benzo[*b*]-1,4-oxazin-3-one (5c)



Crystallization was carried out by dissolving the compound in acetonitrile. Slow evaporating resulted in crystal formation.

CCDC Number	2349053
Empirical formular	$C_{10}H_{11}NO_3$
Moiety formular	$C_{10}H_{11}NO_3$
Formular weight	193.20 $g \cdot mol^{-1}$
Temperature	120(2) K
Wavelength, radiation type	0.71073 Å, MoKα
Diffractometer	STOE IPDS 2T
Crystal system	monoclinic
Space group name, number	P 2_1/c, (14)
Unit cell dimensions	a = 9.9227(7) Å, α = 90° b = 5.6720(5) Å, β = 99.498(6)° c = 16.1656(12) Å, γ = 90°
Volume	897.35(12) $Å^3$
Number of reflections	10411
And range used for lattice parameters	3.02° ≤ Θ ≤ 28.29°
Z	4
Density (calculated)	1.430 Mg/m^3
Absorption coefficient	0.107 mm^{-1}
Absorption correction	none
F(000)	408
Crystal size, colour and form	0.200 · 0.230 · 0.590 mm^3, colorless block
Theta range for data collection	3.018 to 28.045°.
Index ranges	-13 ≤ h ≤ 12, -7 ≤ k ≤ 7, -21 ≤ l ≤ 21
Number of reflections:	
collected	4613
independent	2133 [R_{int} = 0.0186]
observed [I>2sigma(I)]	1864
Completeness to theta = 25.2°	99.5%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2133 / 0 / 167
Goodness-of-fit on F^2	1.074
Final R indices [I>2sigma(I)]	R1 = 0.0374, wR2 = 0.0921
R indices (all data)	R1 = 0.0455, wR2 = 0.0991
Largest diff. peak and hole	0.277 und -0.163 $eÅ^{-3}$

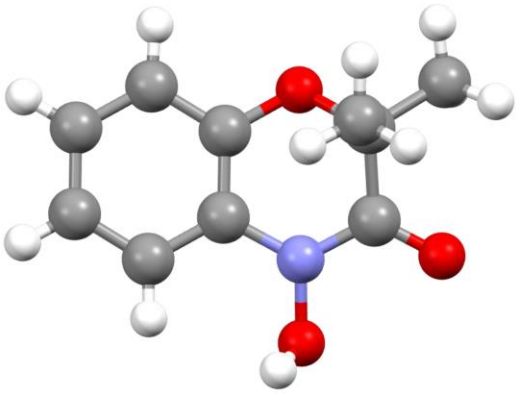


Figure S10: Molecular structure of **5c.**

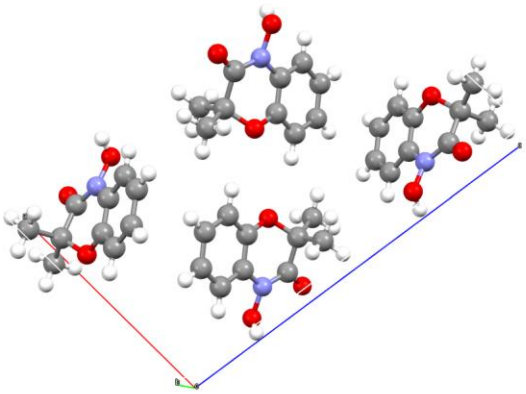


Figure S11: Packing of **5c**.

8. NMR Spectra

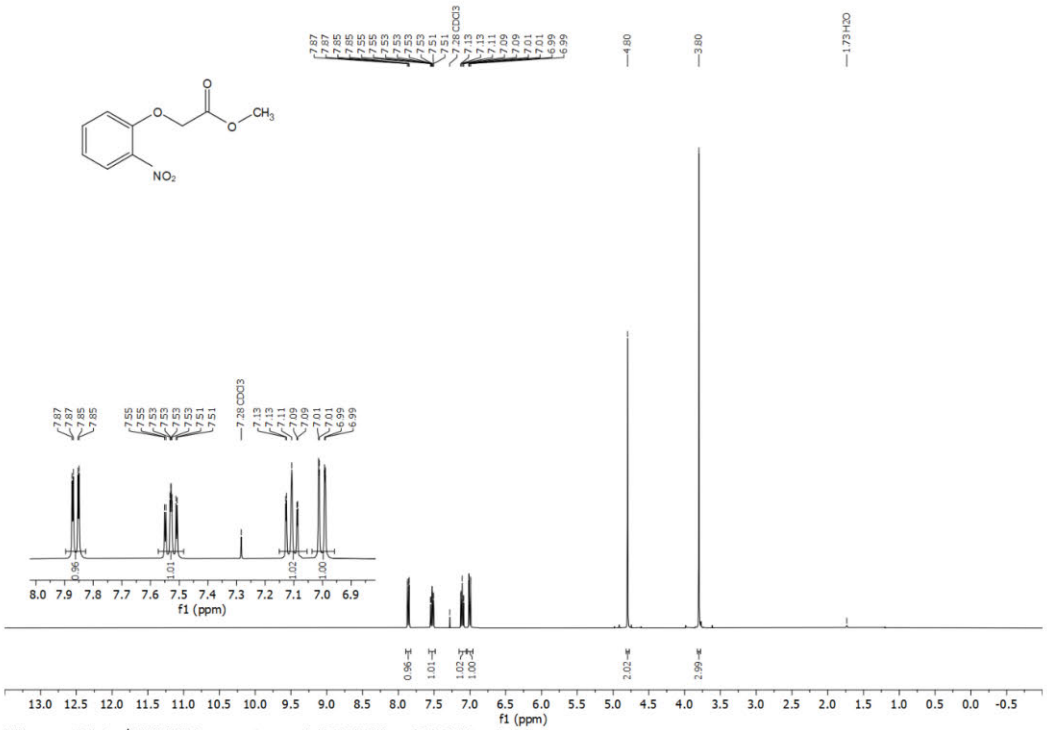


Figure S12: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6a**.

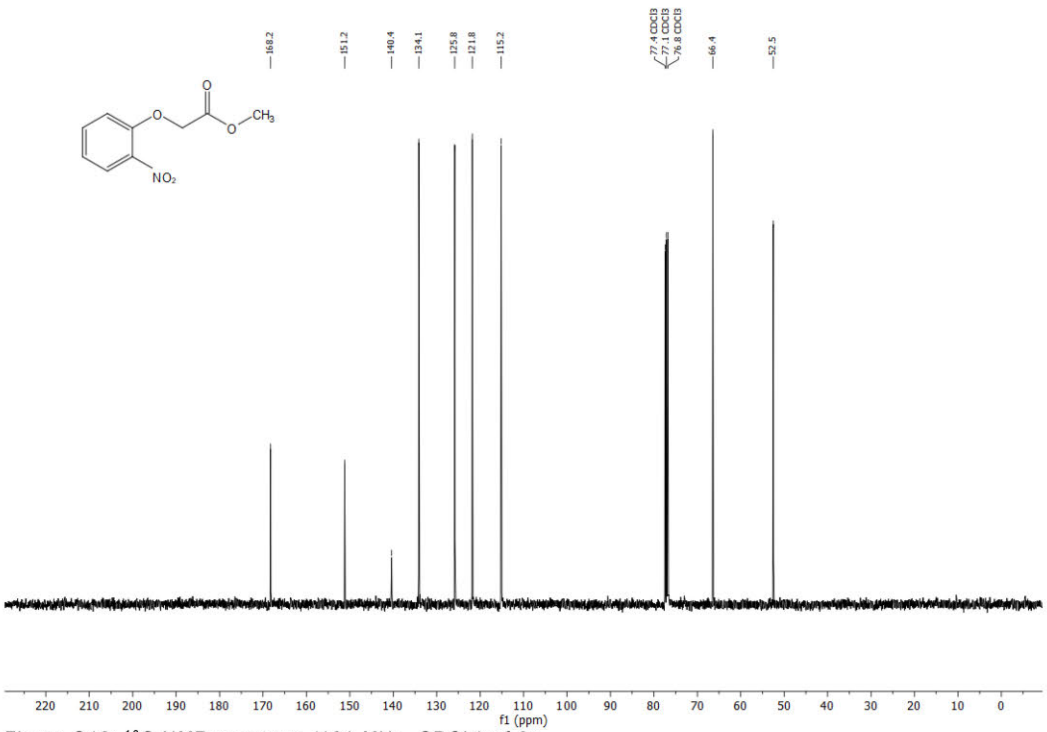


Figure S13: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6a**.

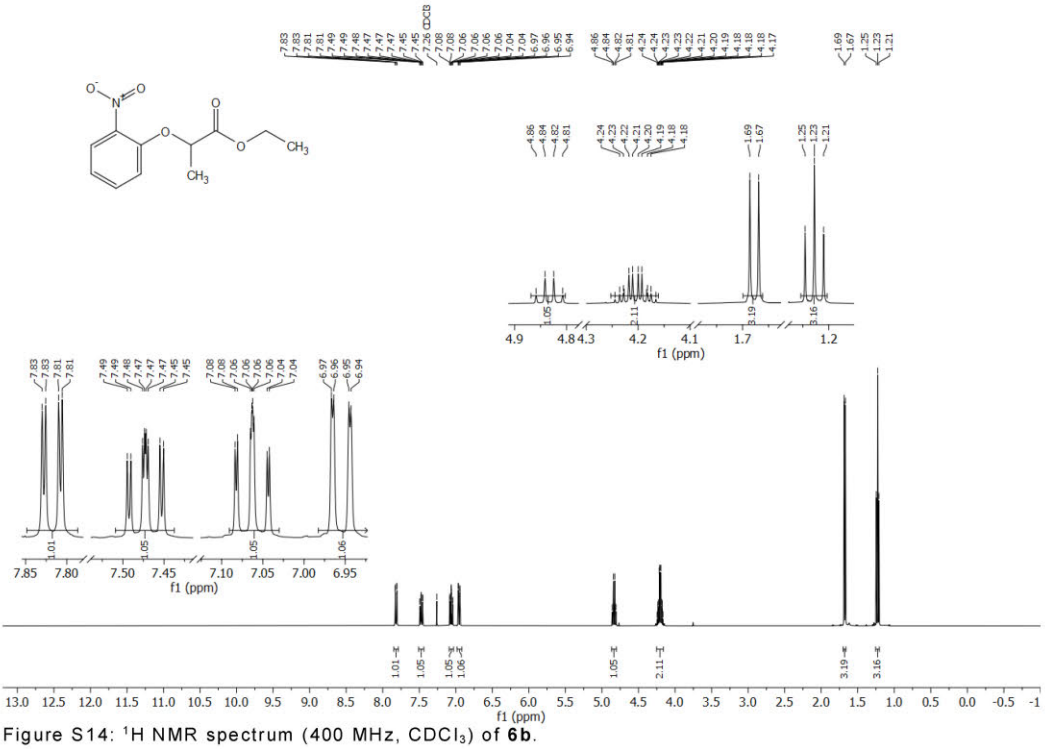


Figure S14: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6b**.

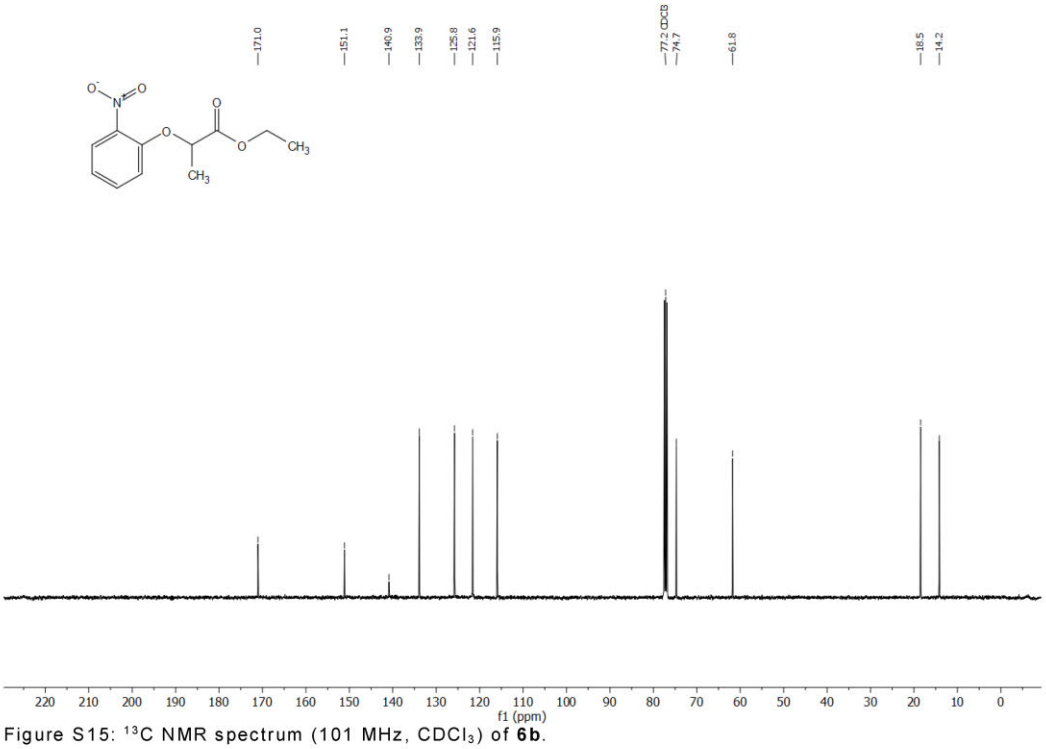


Figure S15: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6b**.

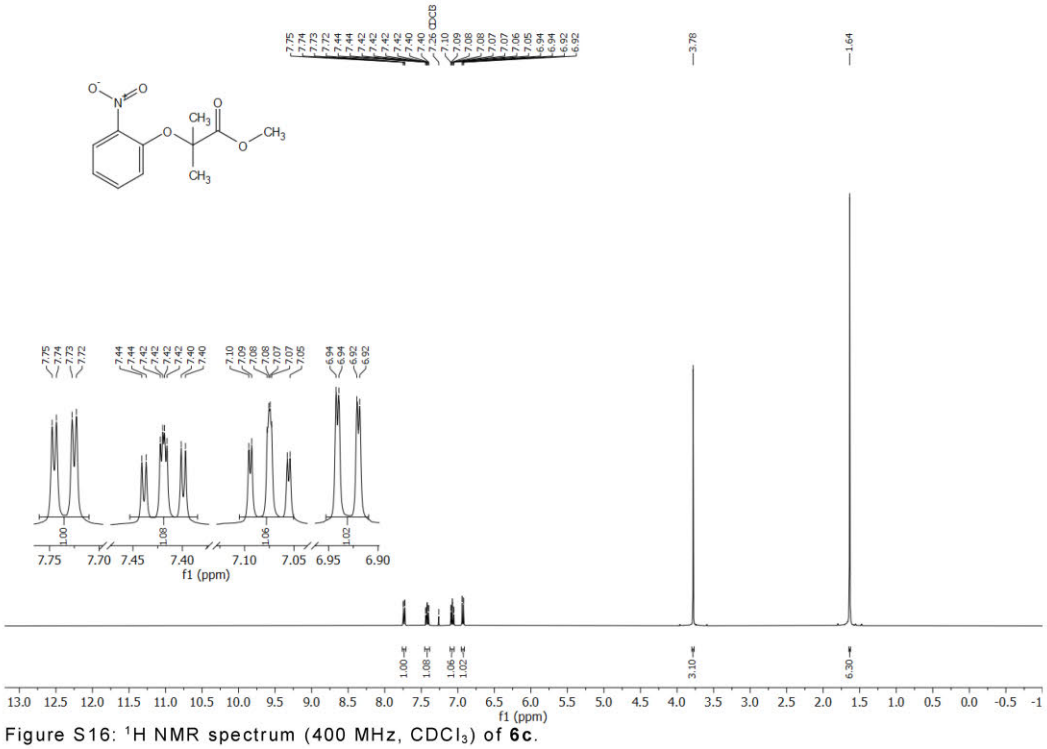


Figure S16: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6c**.

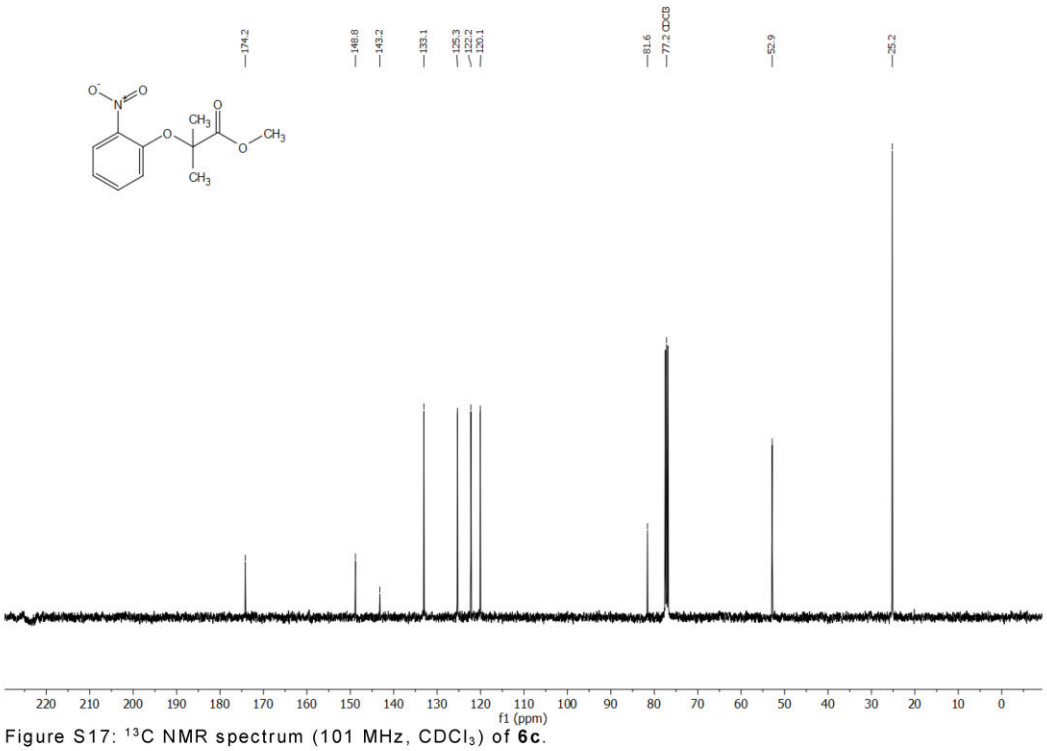


Figure S17: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6c**.

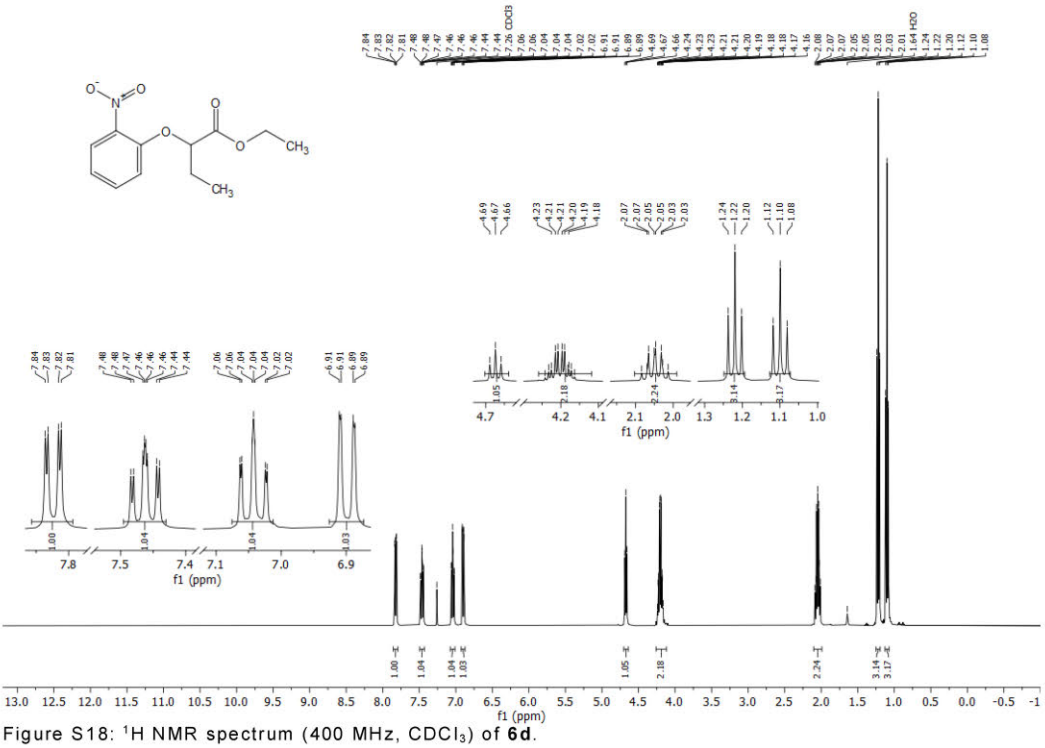


Figure S18: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6d**.

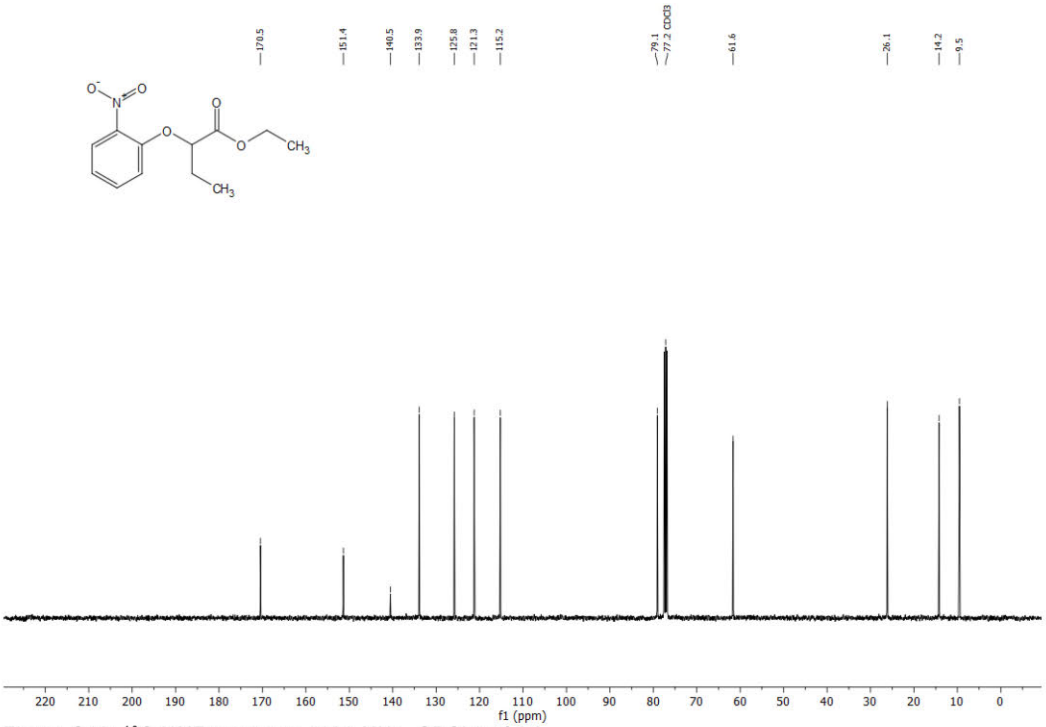


Figure S19: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6d**.

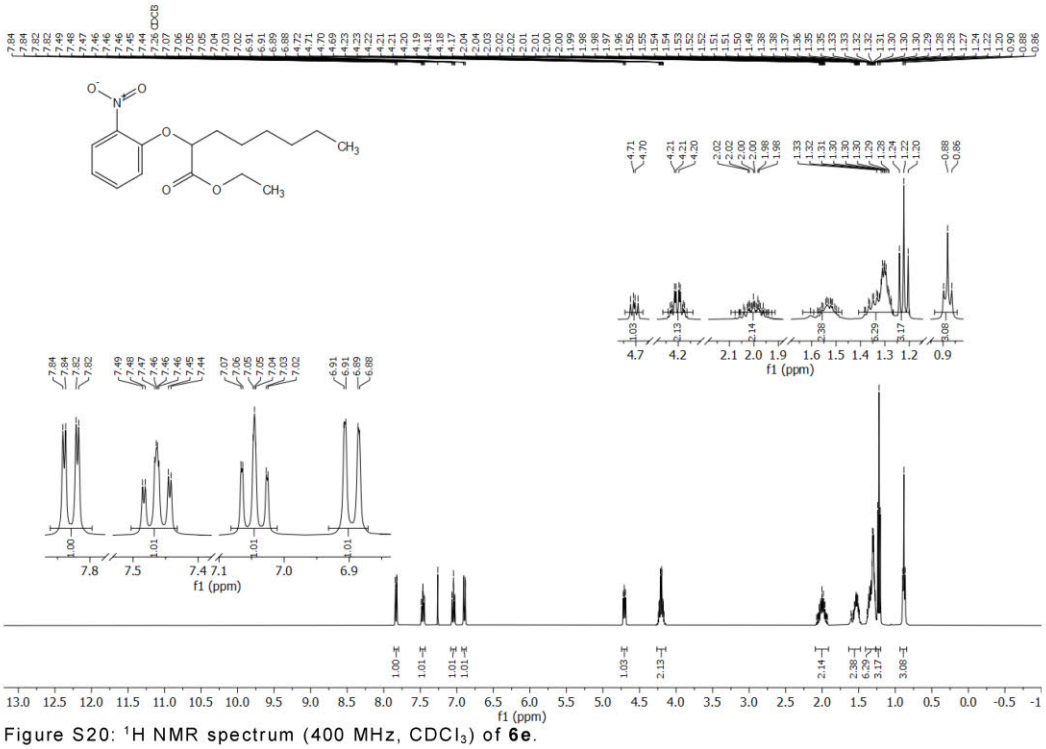


Figure S20: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6e**.

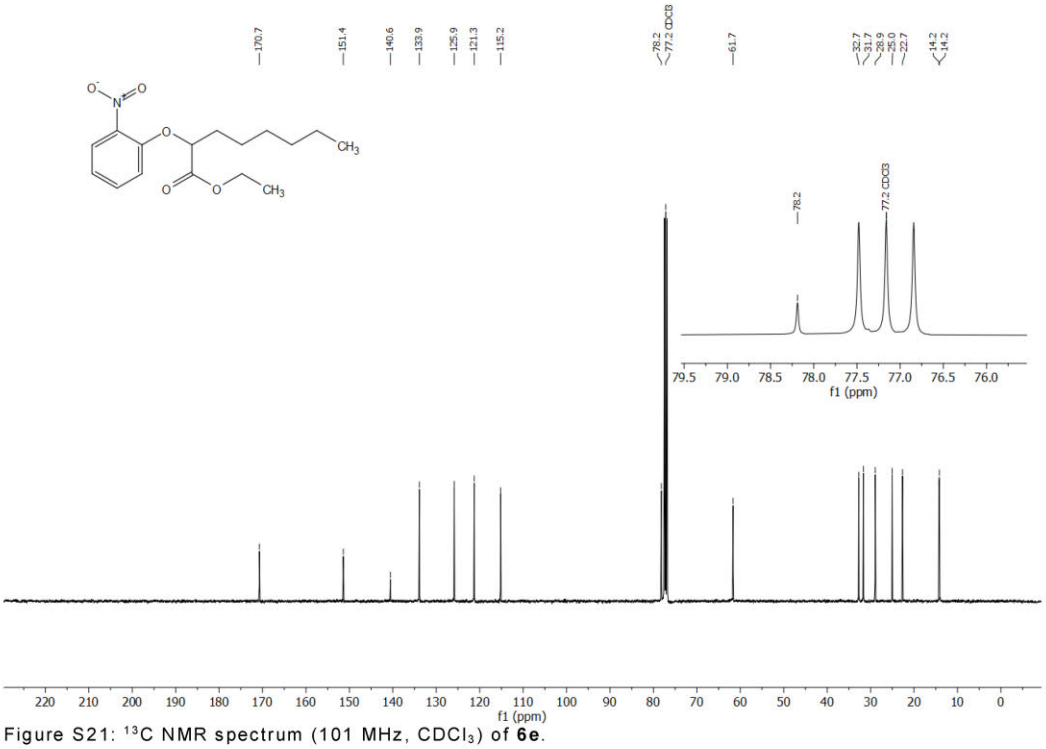


Figure S21: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6e**.

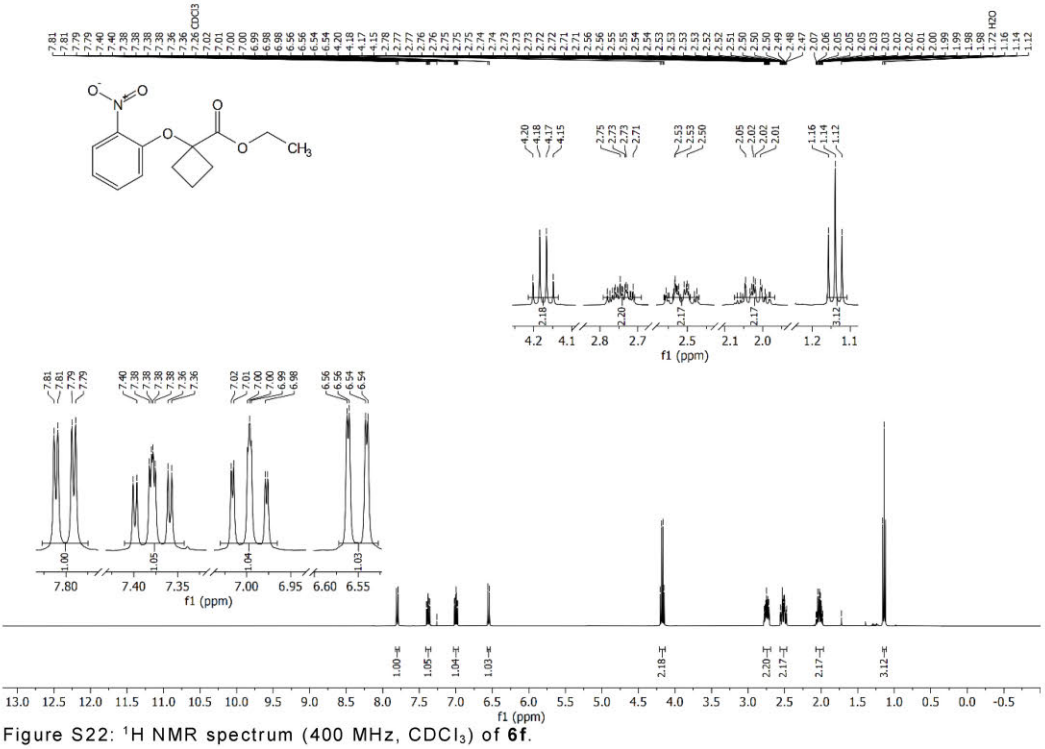


Figure S22: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6f**.

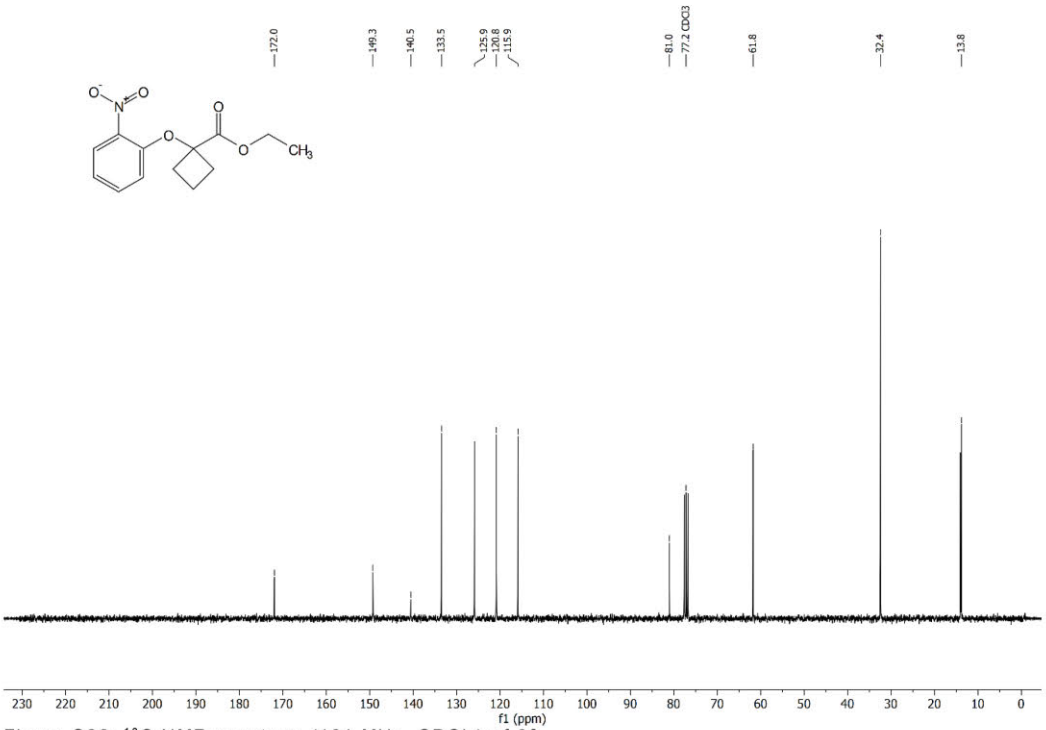


Figure S23: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6f**.

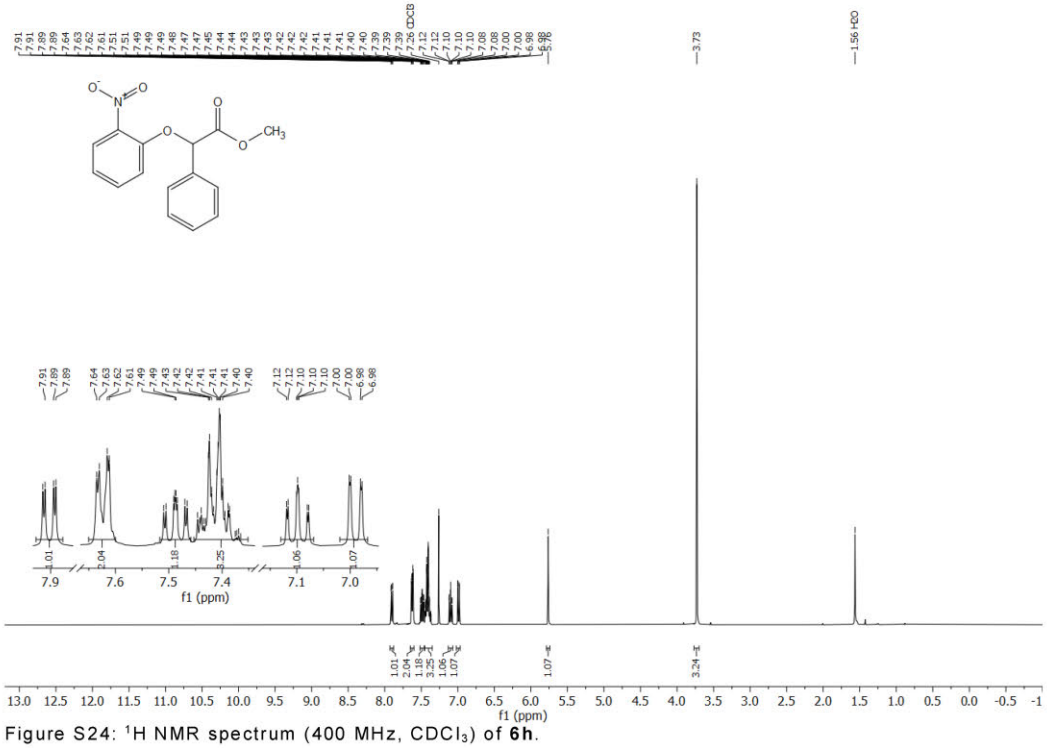


Figure S24: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6h**.

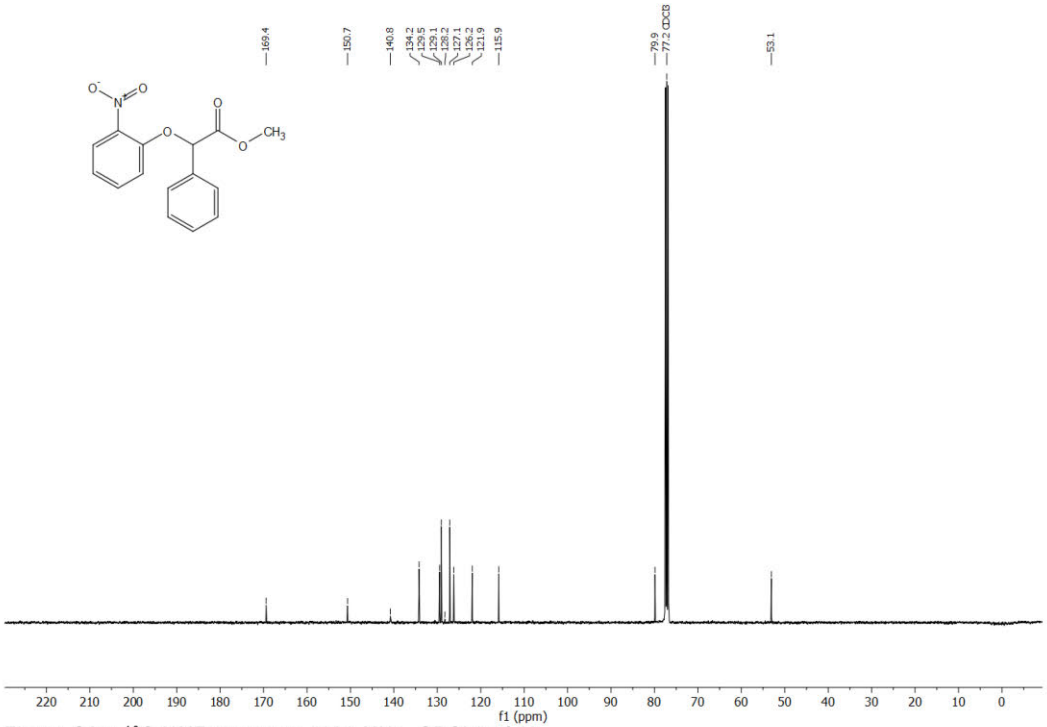


Figure S25: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6h**.

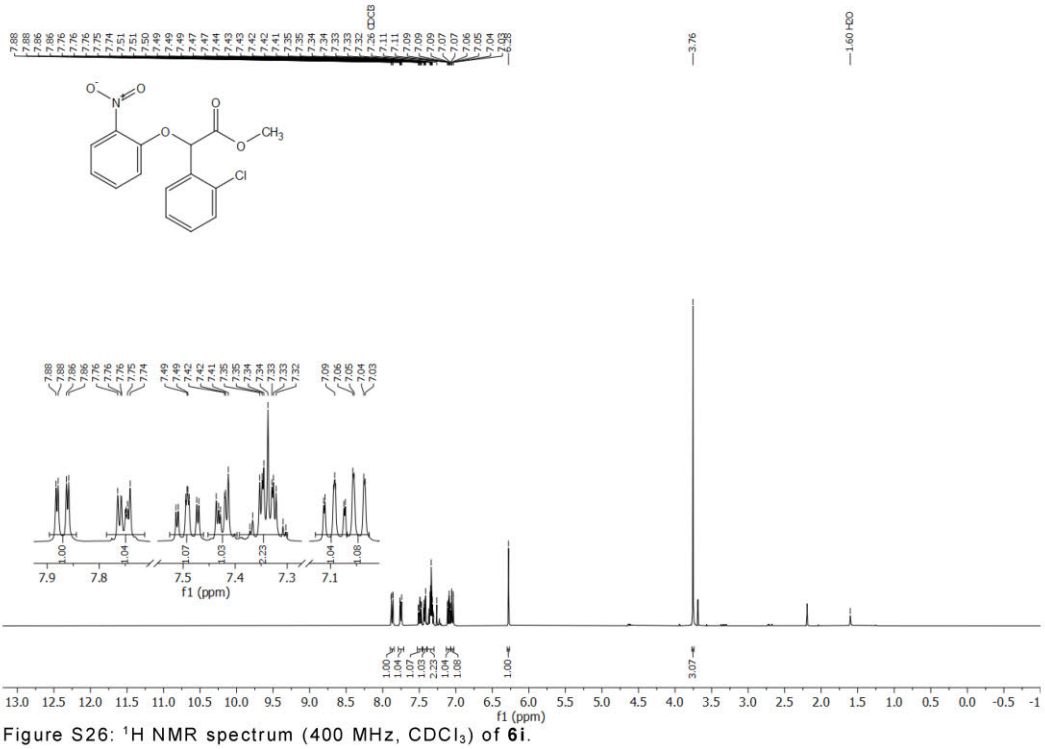


Figure S26: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6i**.

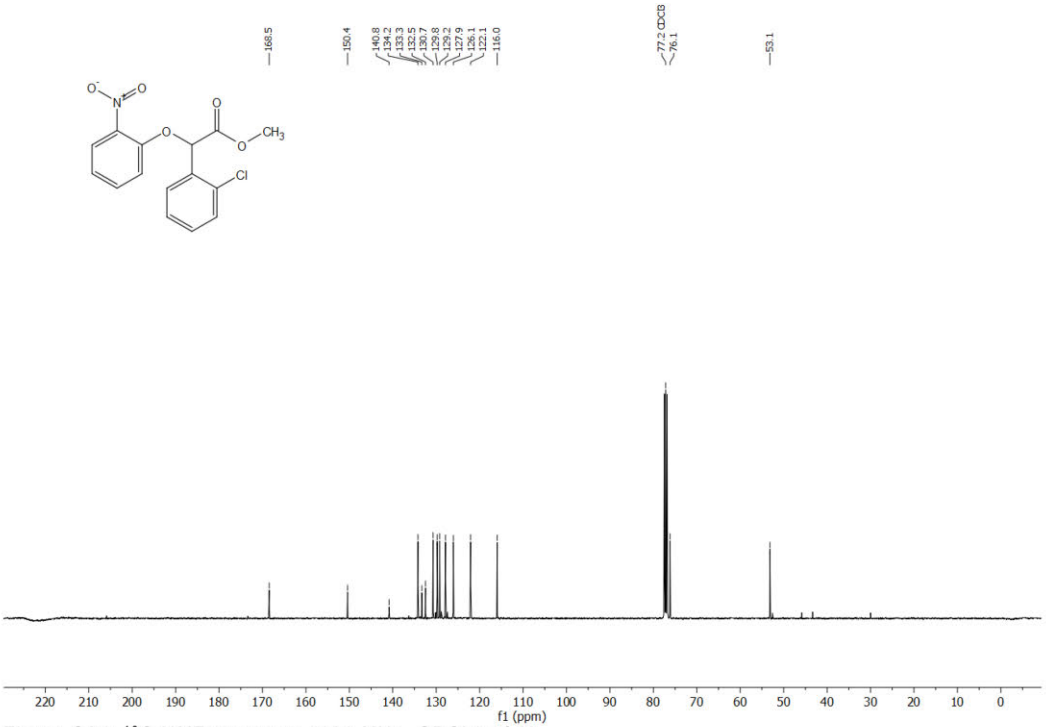


Figure S27: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6i**.

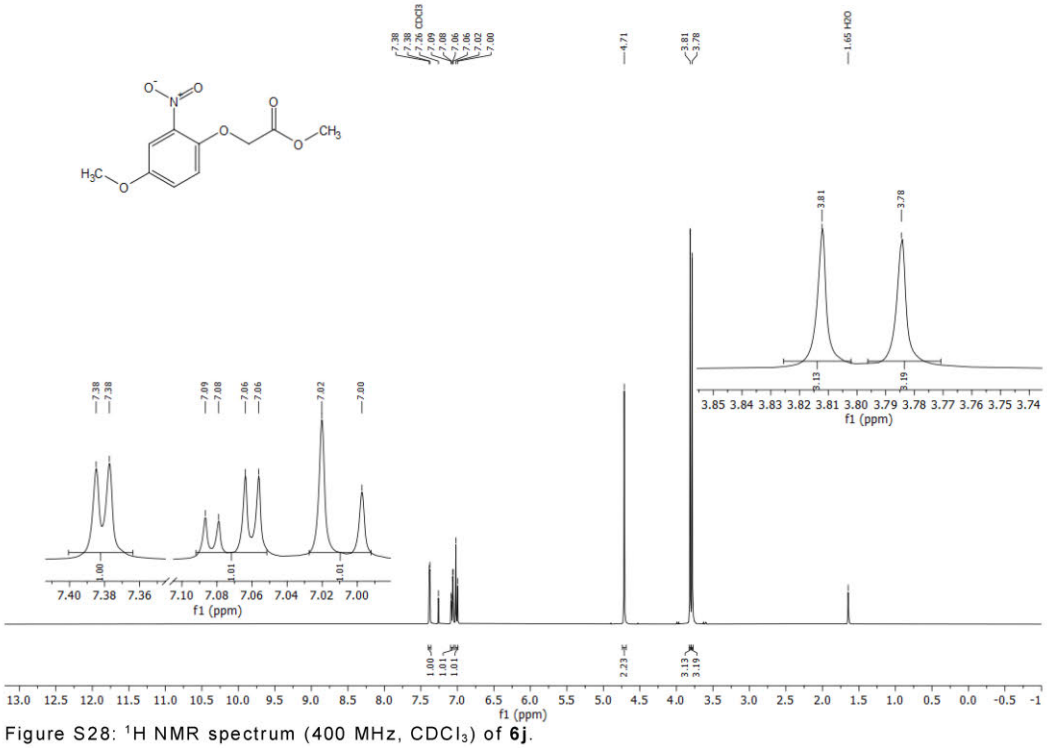


Figure S28: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6j**.

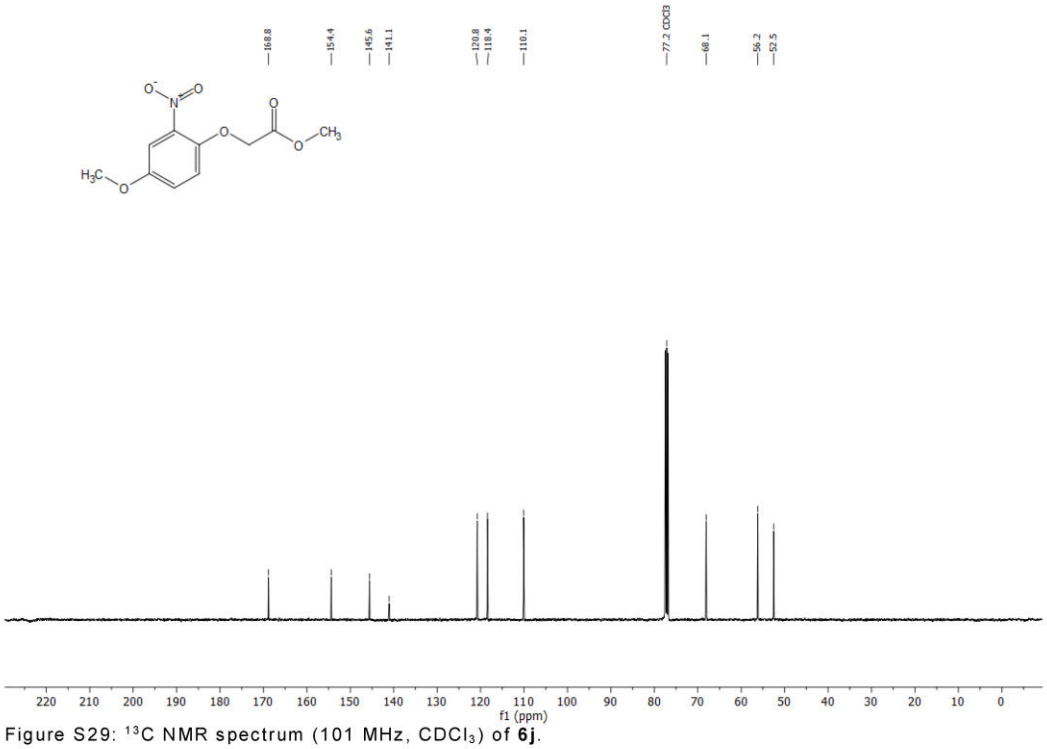


Figure S29: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6j**.

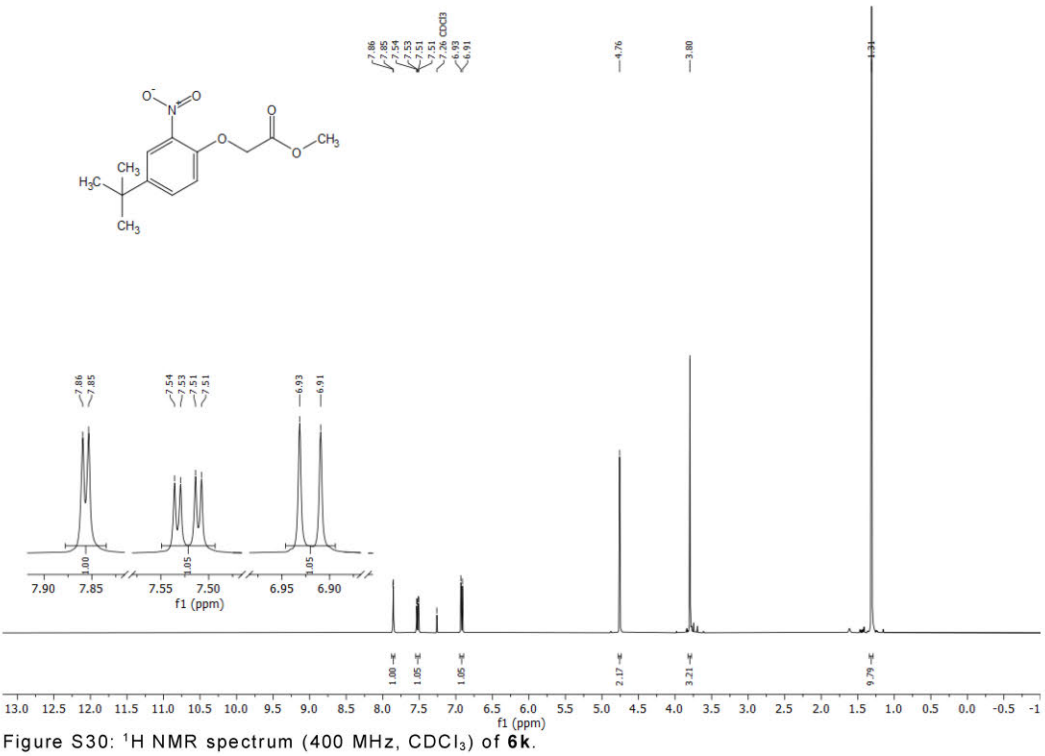


Figure S30: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6k**.

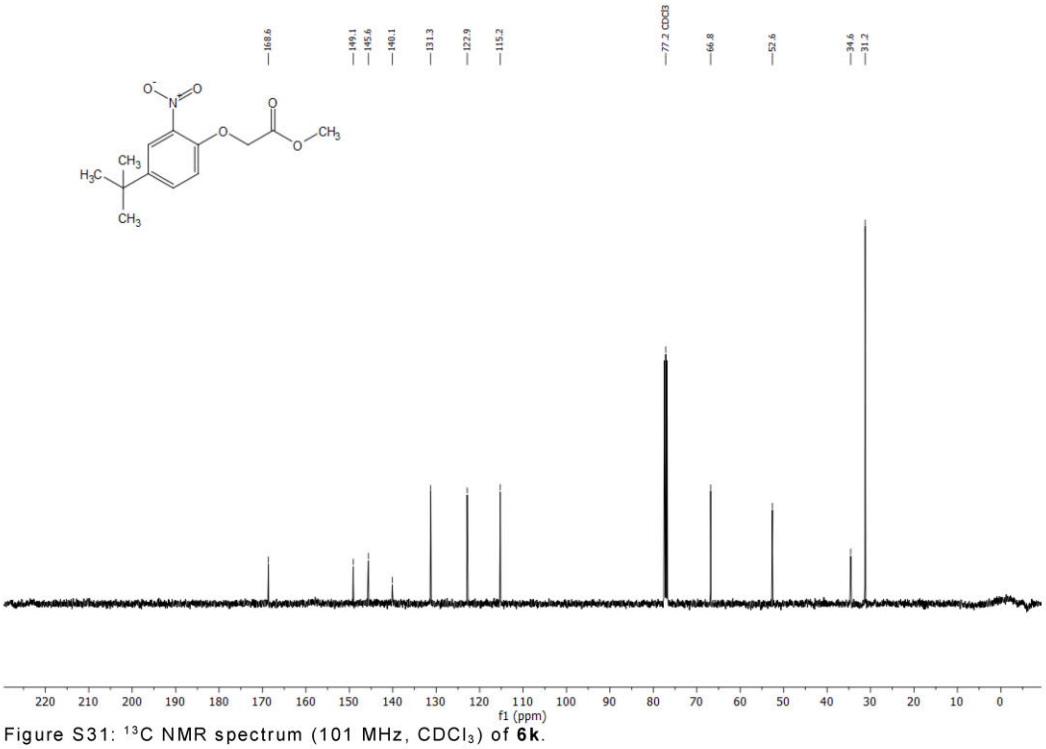


Figure S31: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6k**.

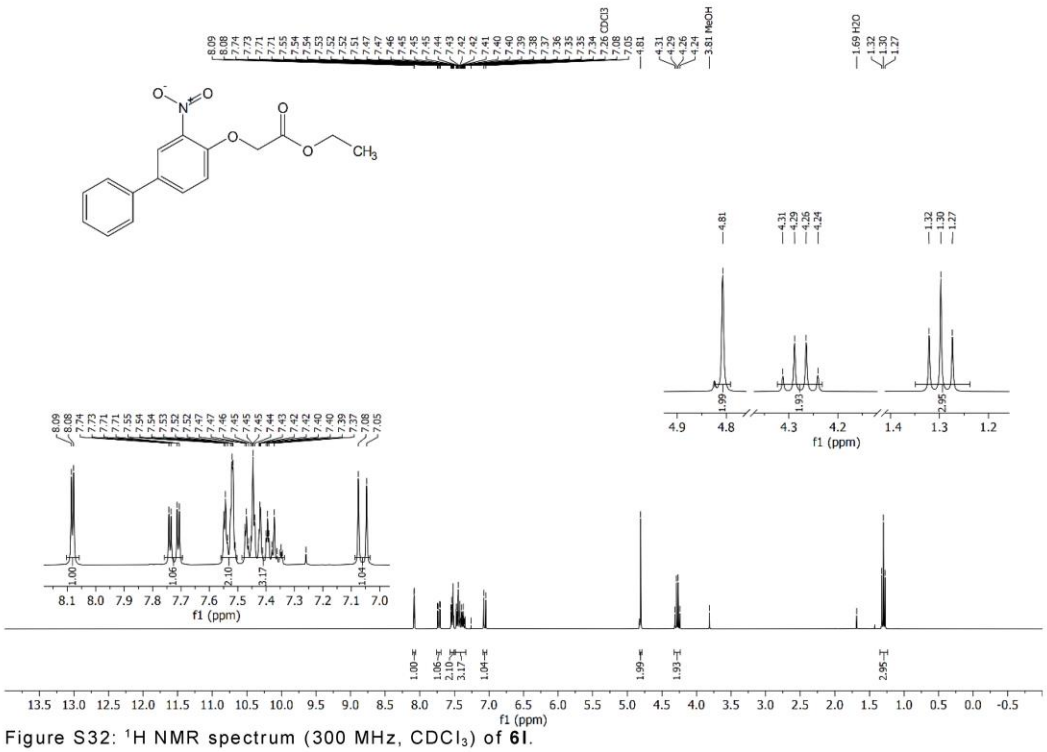


Figure S32: ^{1}H NMR spectrum (300 MHz, $CDCl_3$) of **6l**.

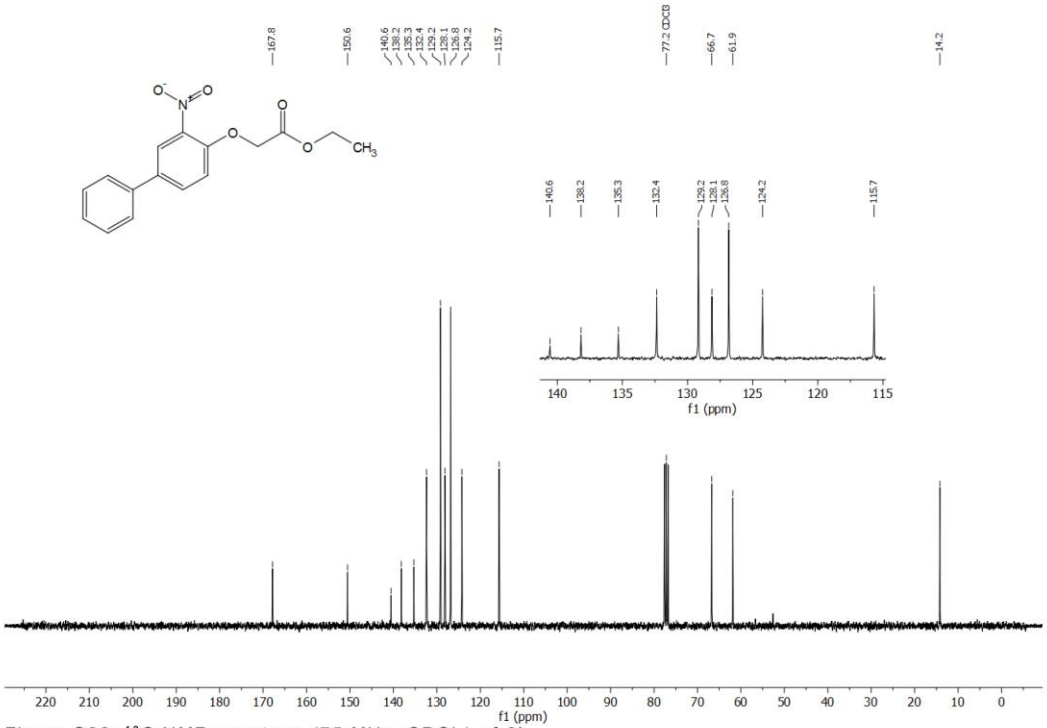


Figure S33: ^{13}C NMR spectrum (75 MHz, $CDCl_3$) of **6l**.

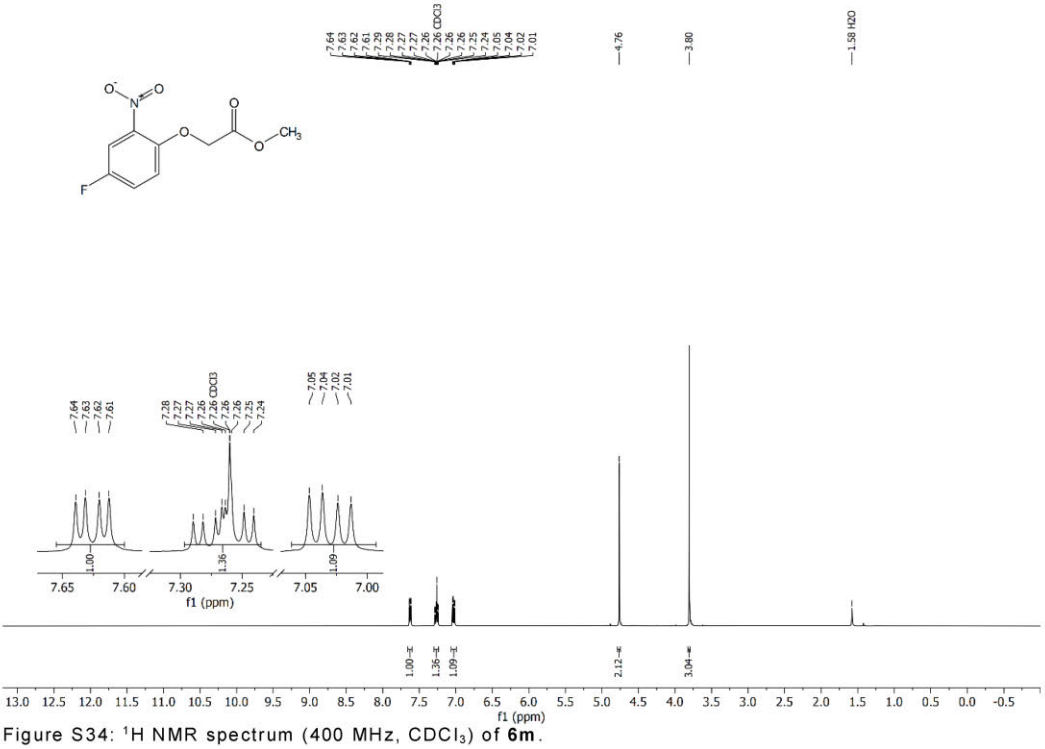


Figure S34: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6m**.

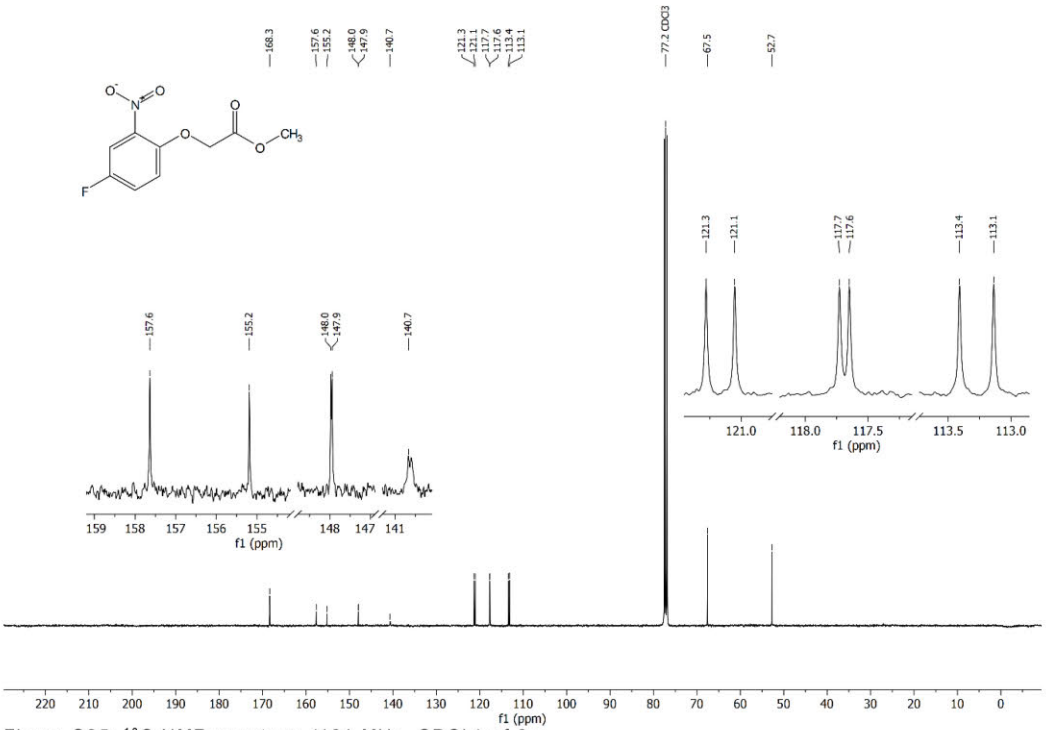


Figure S35: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6m**.

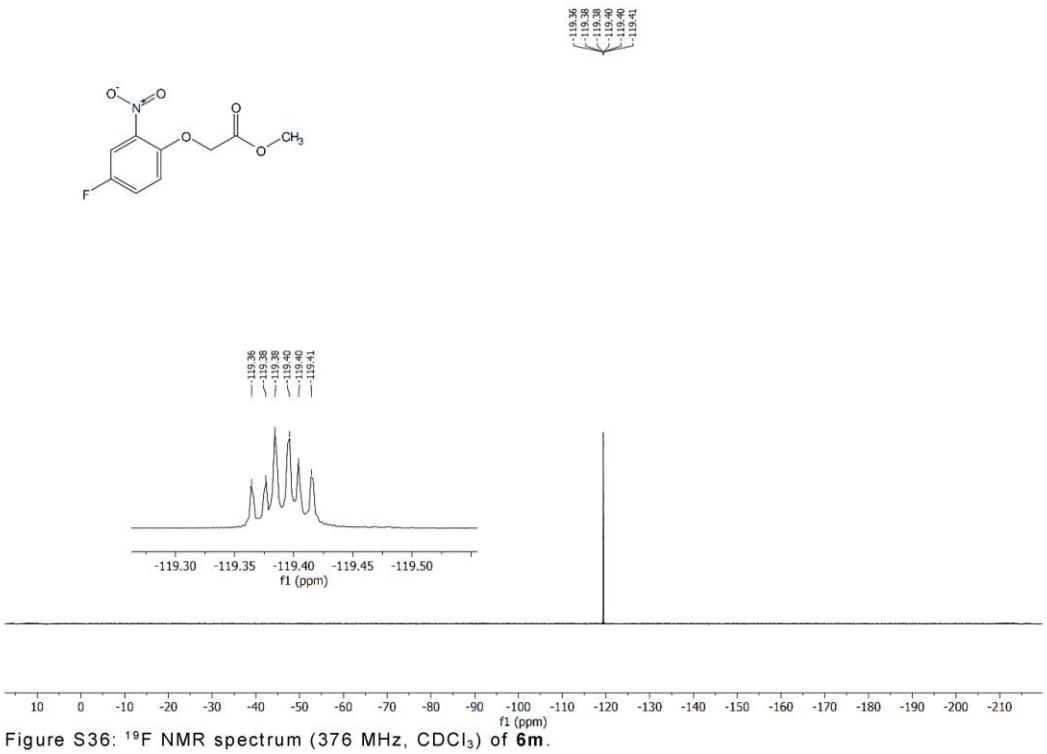


Figure S36: ^{19}F NMR spectrum (376 MHz, $CDCl_3$) of **6m**.

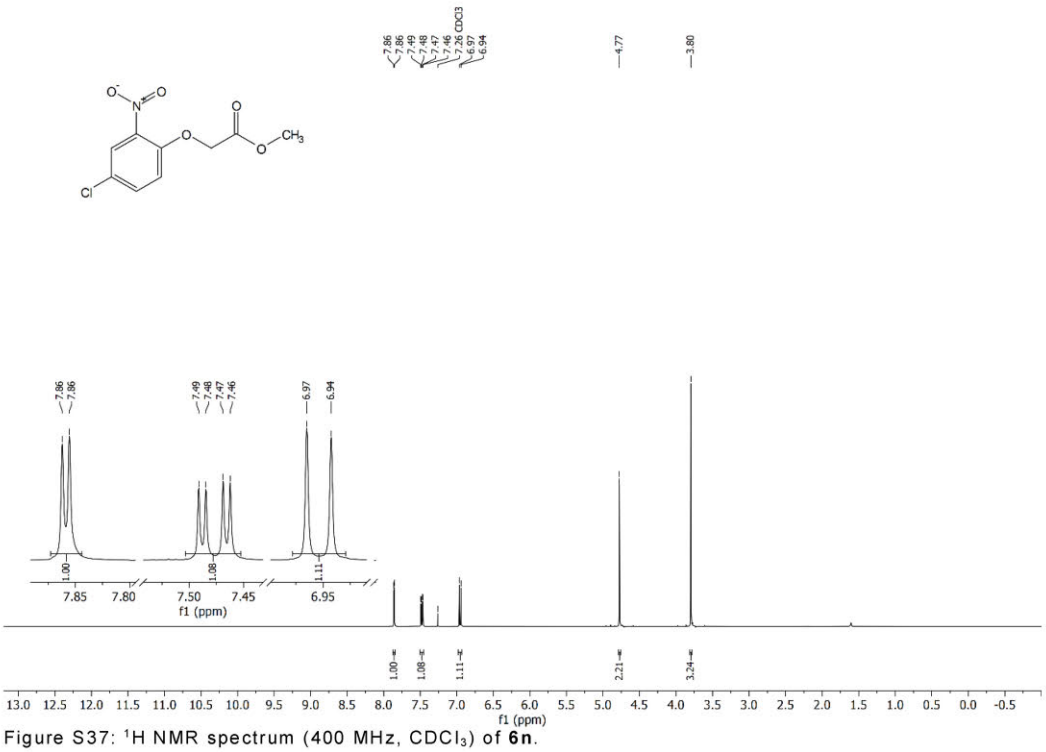


Figure S37: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6n**.

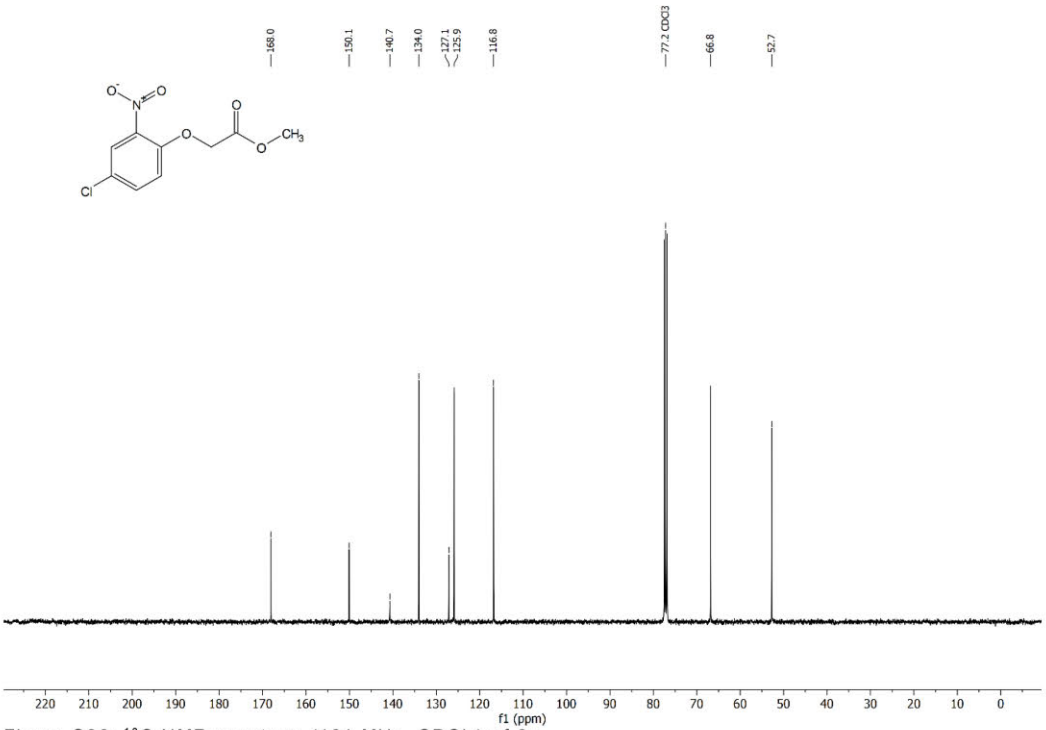


Figure S38: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6n**.

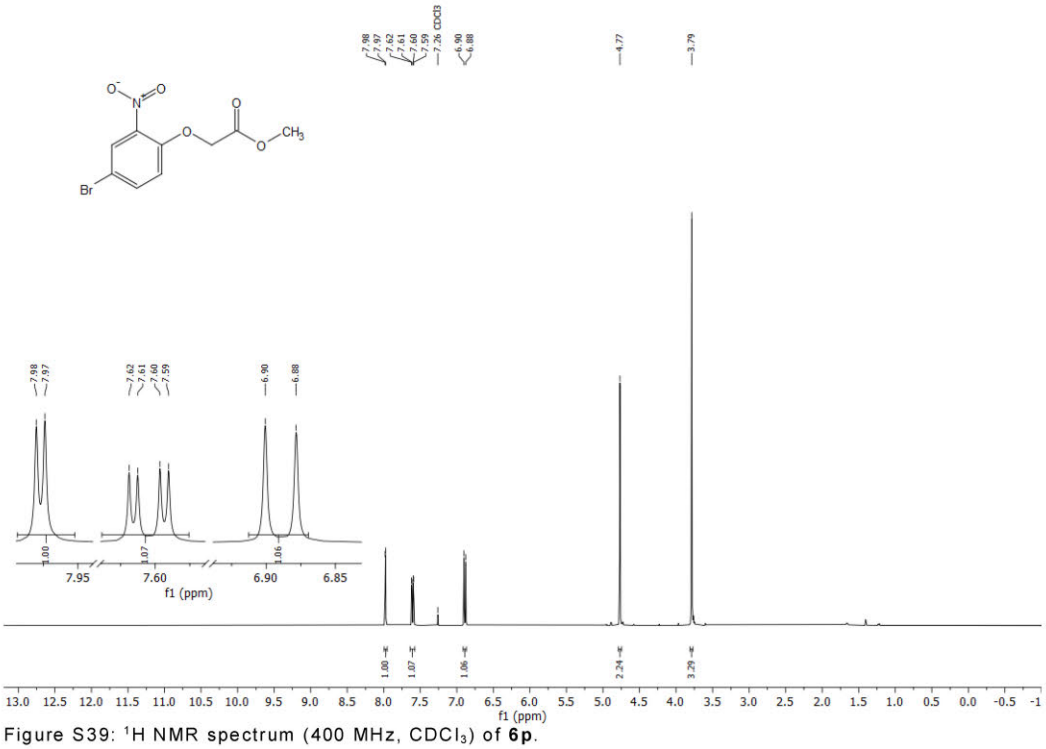


Figure S39: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6p**.

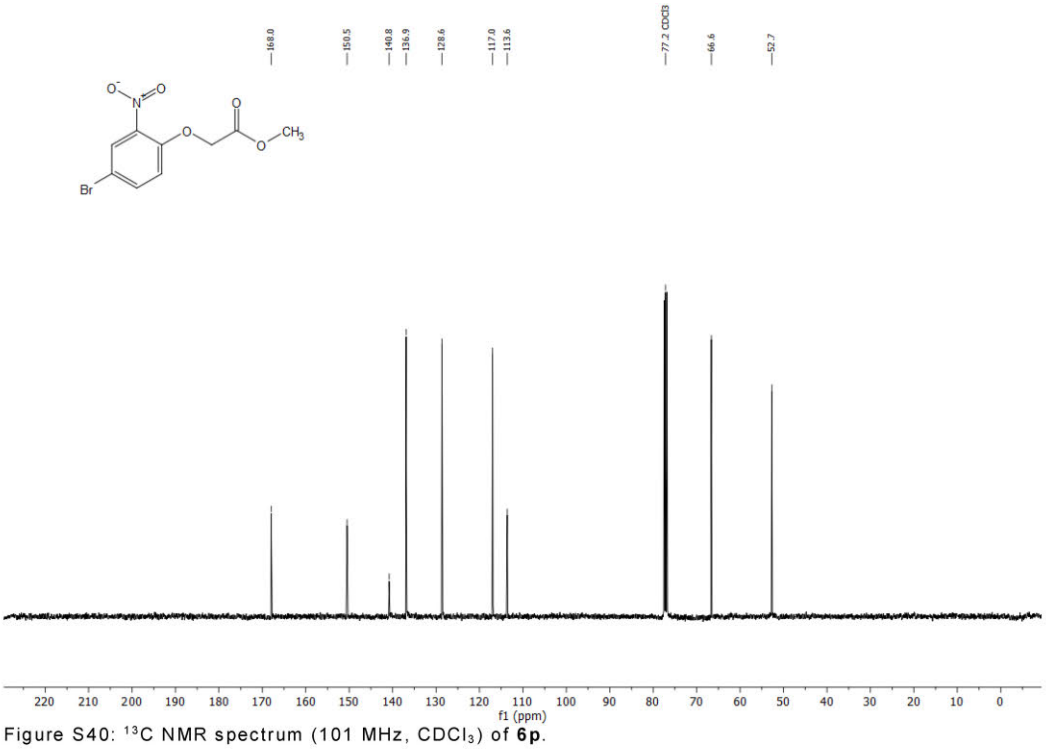


Figure S40: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6p**.

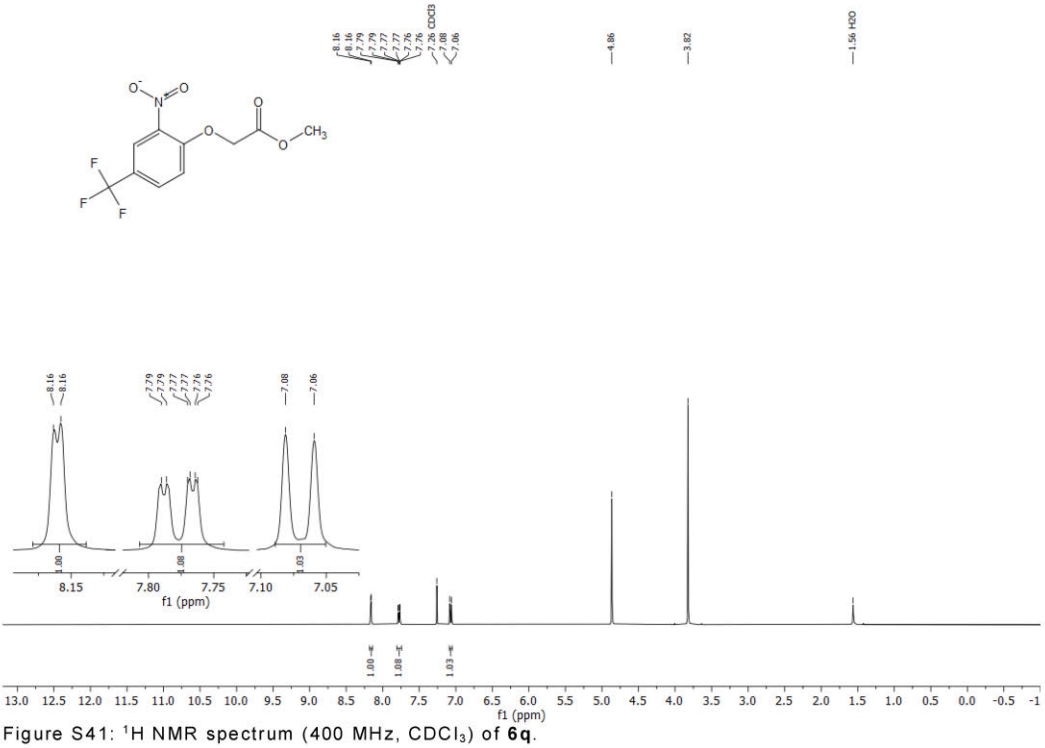


Figure S41: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6q**.

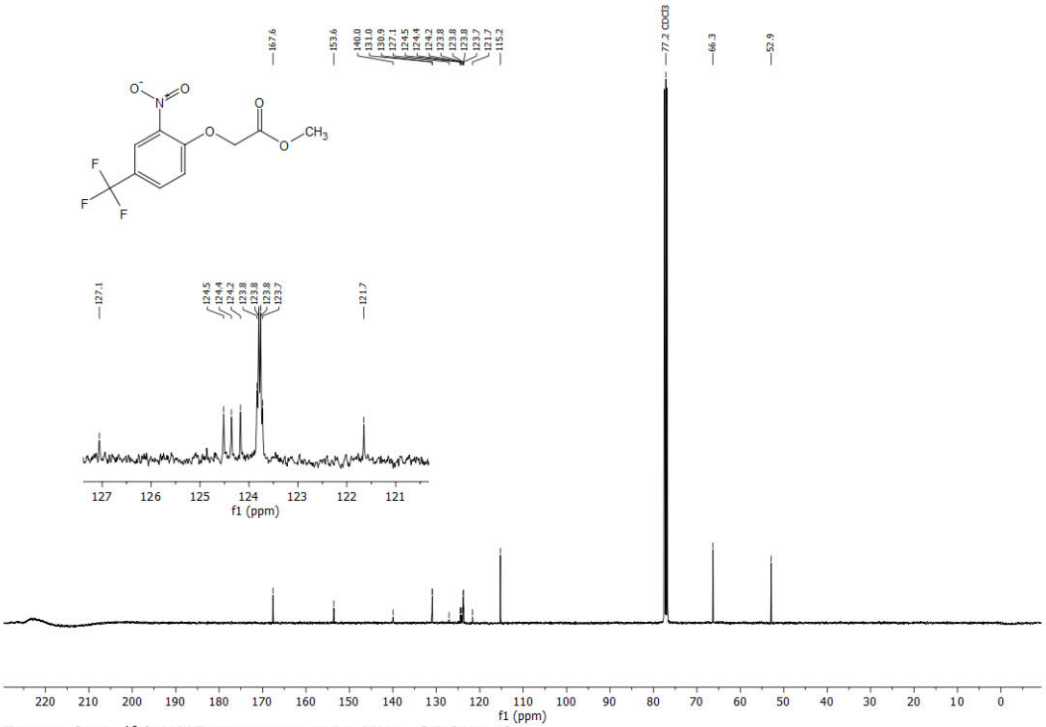


Figure S42: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6q**.

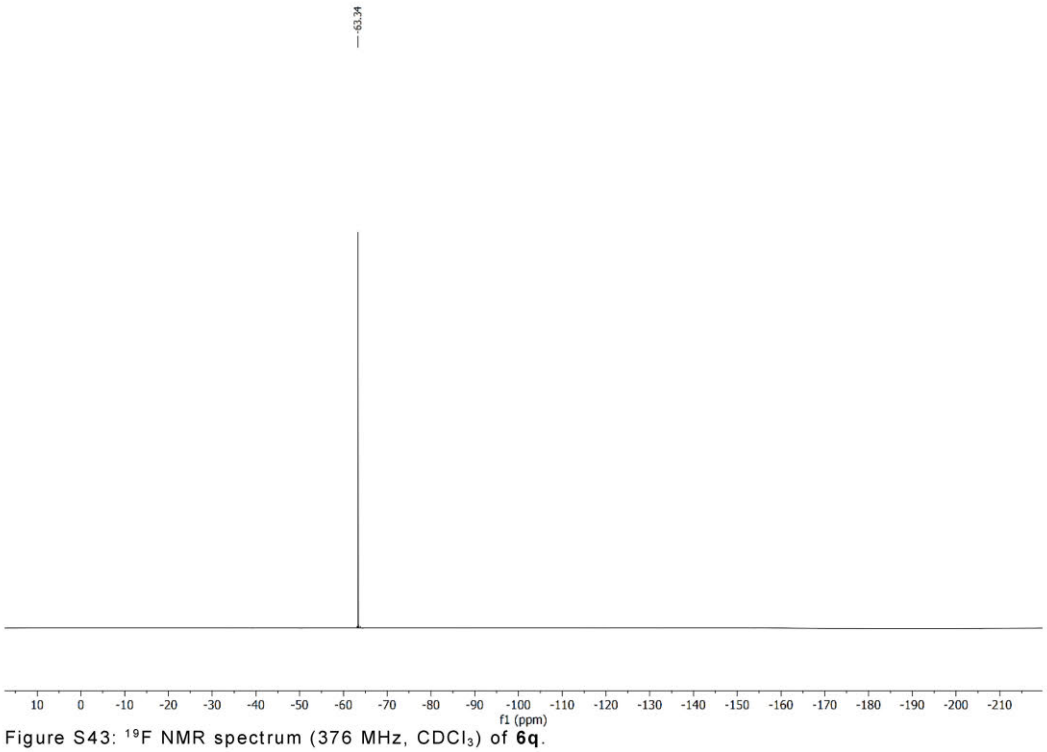


Figure S43: ^{19}F NMR spectrum (376 MHz, $CDCl_3$) of **6q**.

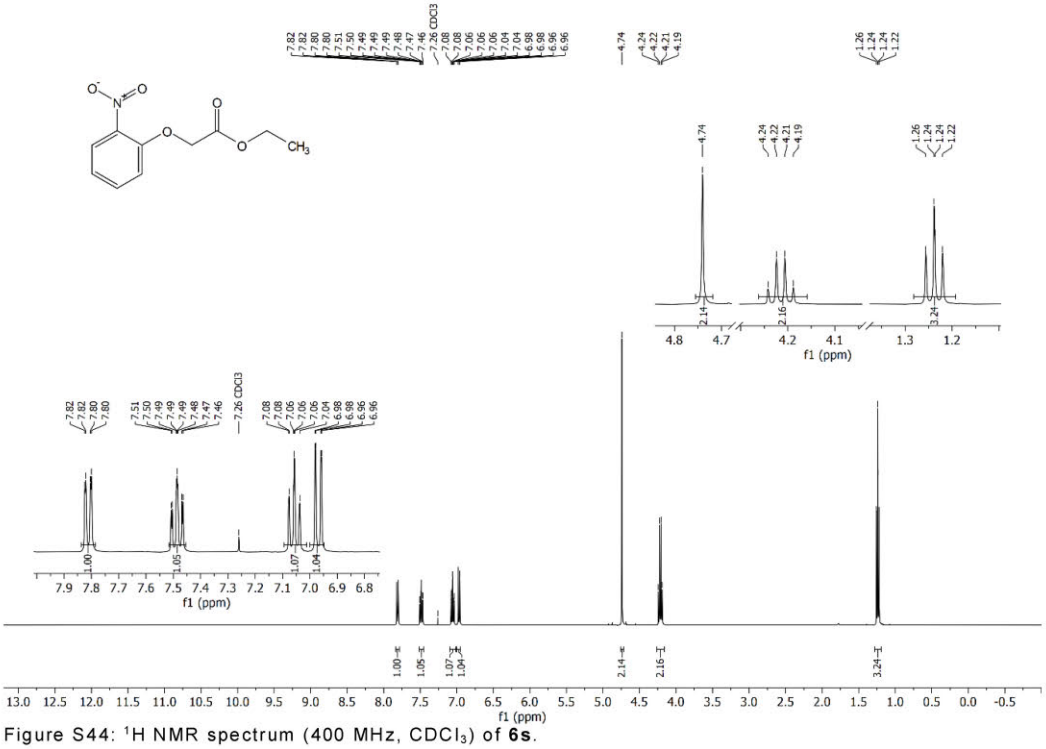


Figure S44: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6s**.

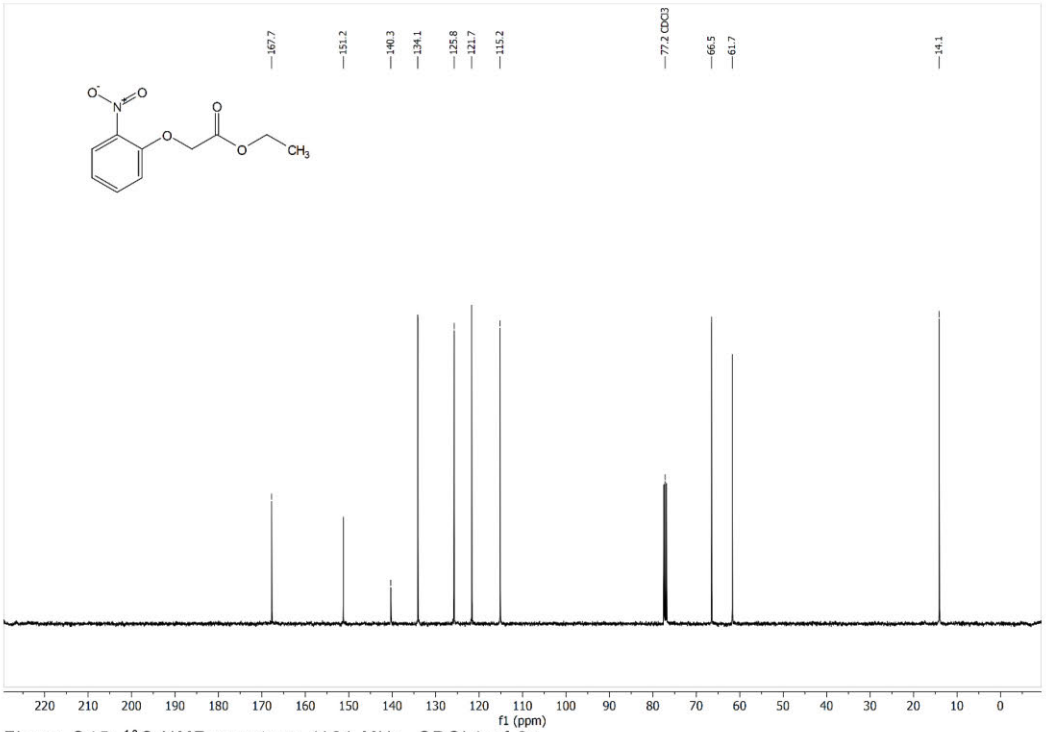


Figure S45: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6s**.

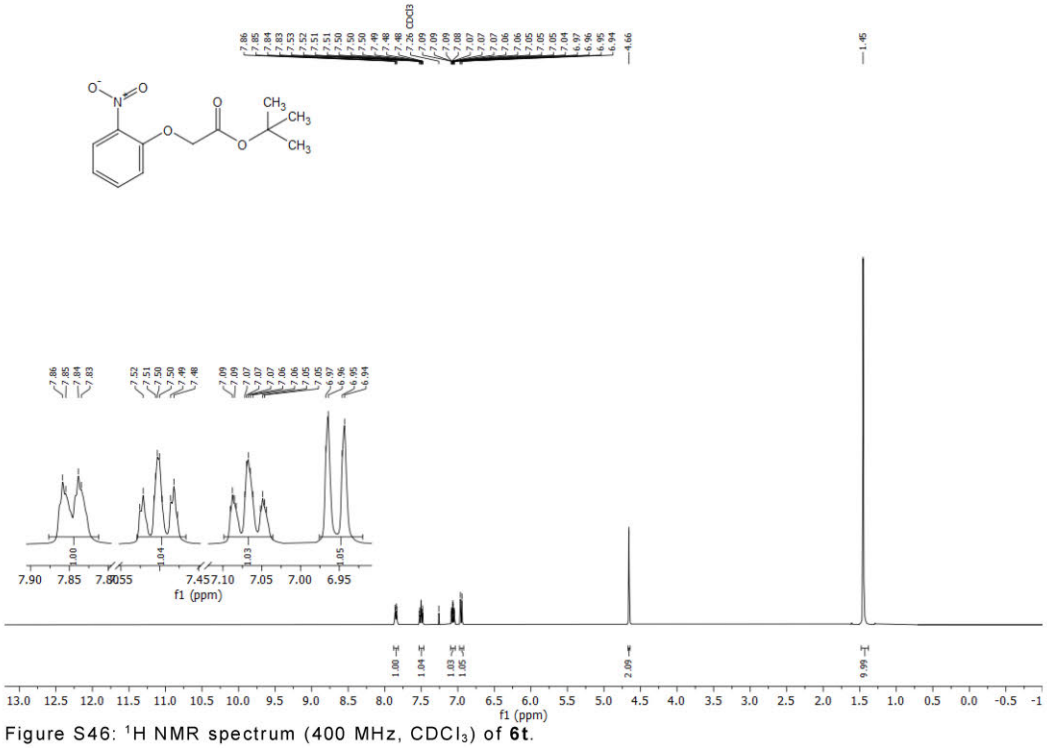


Figure S46: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6t**.

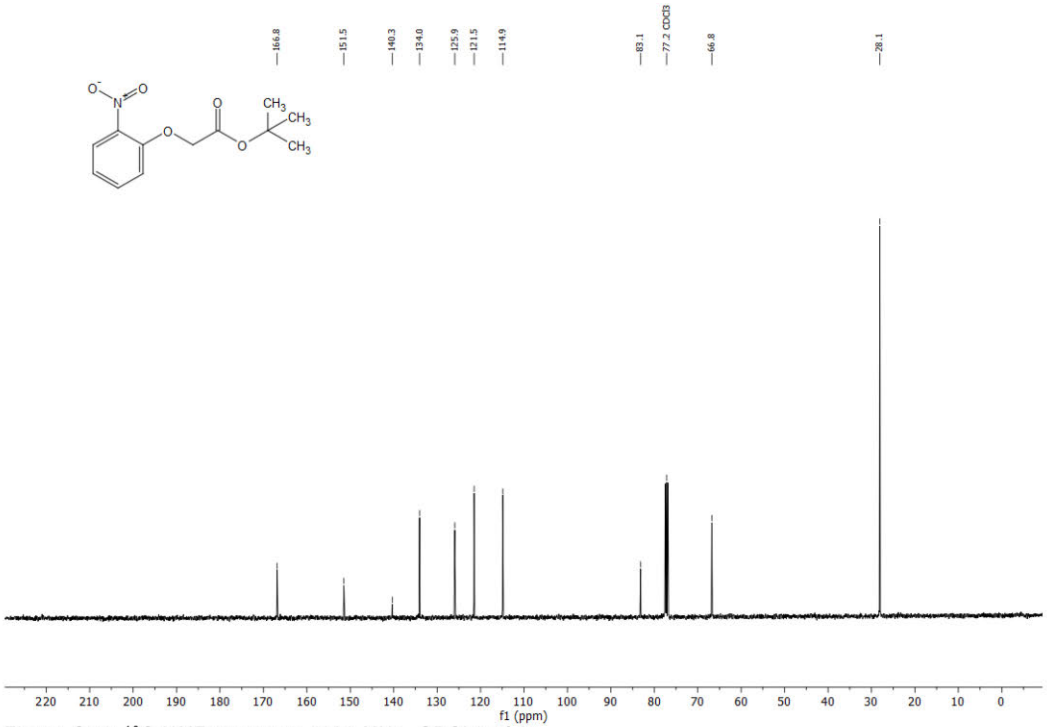


Figure S47: ^{13}C NMR spectrum (101 MHz, $CDCl_3$) of **6t**.

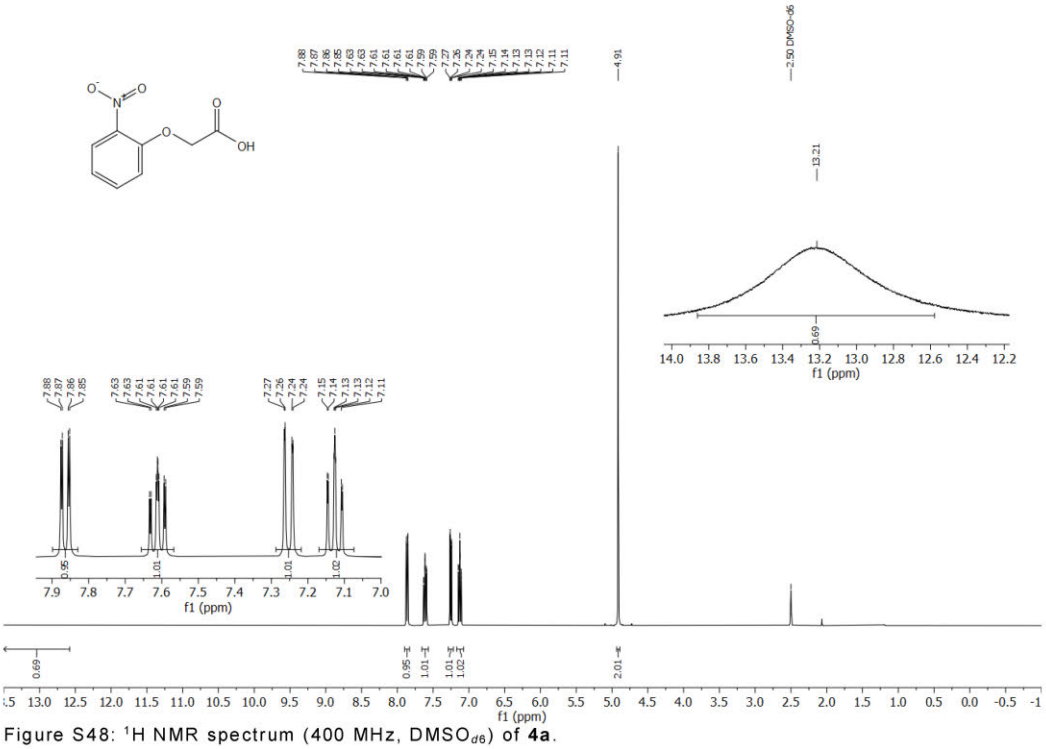


Figure S48: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **4a**.

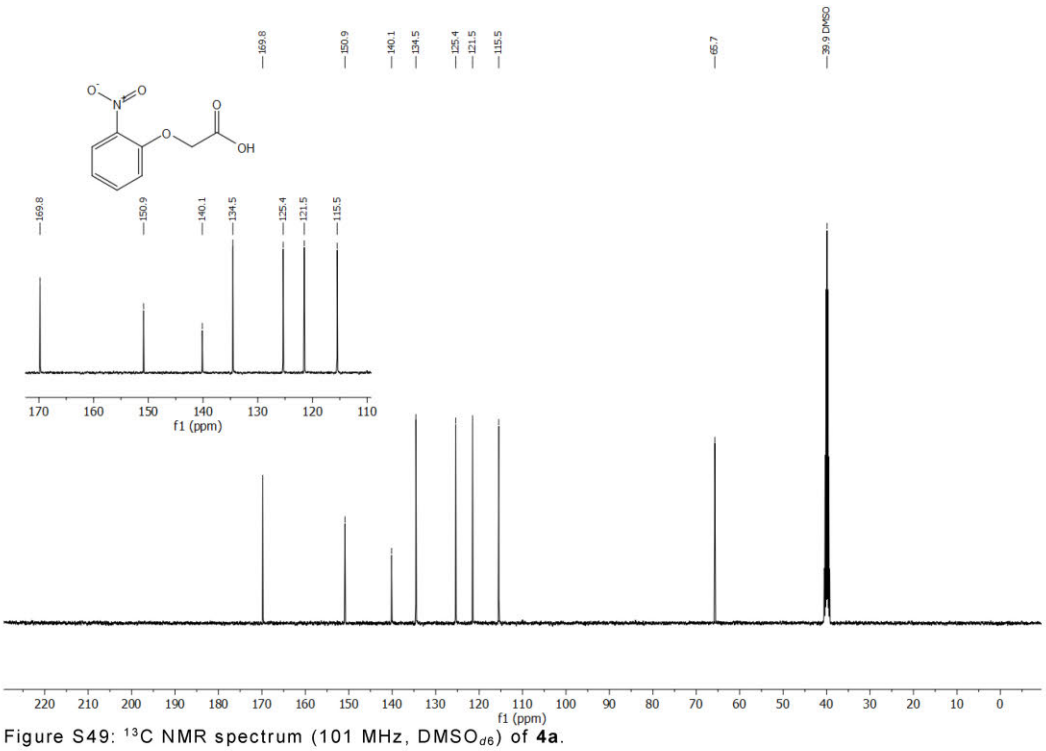


Figure S49: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **4a**.

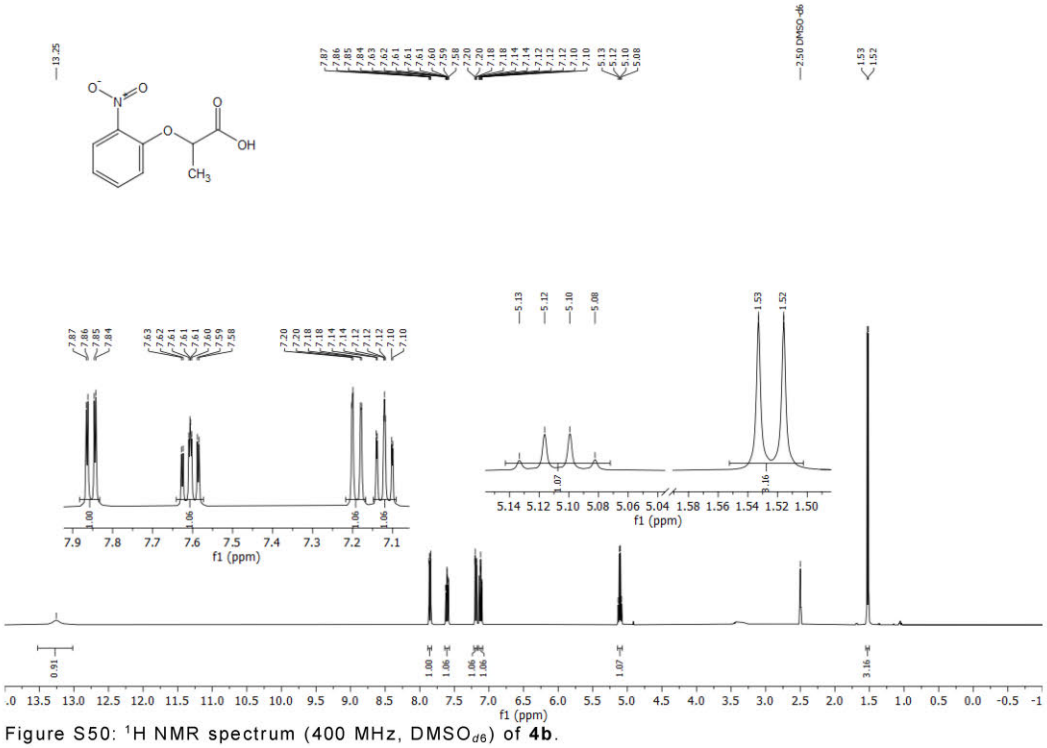


Figure S50: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **4b**.

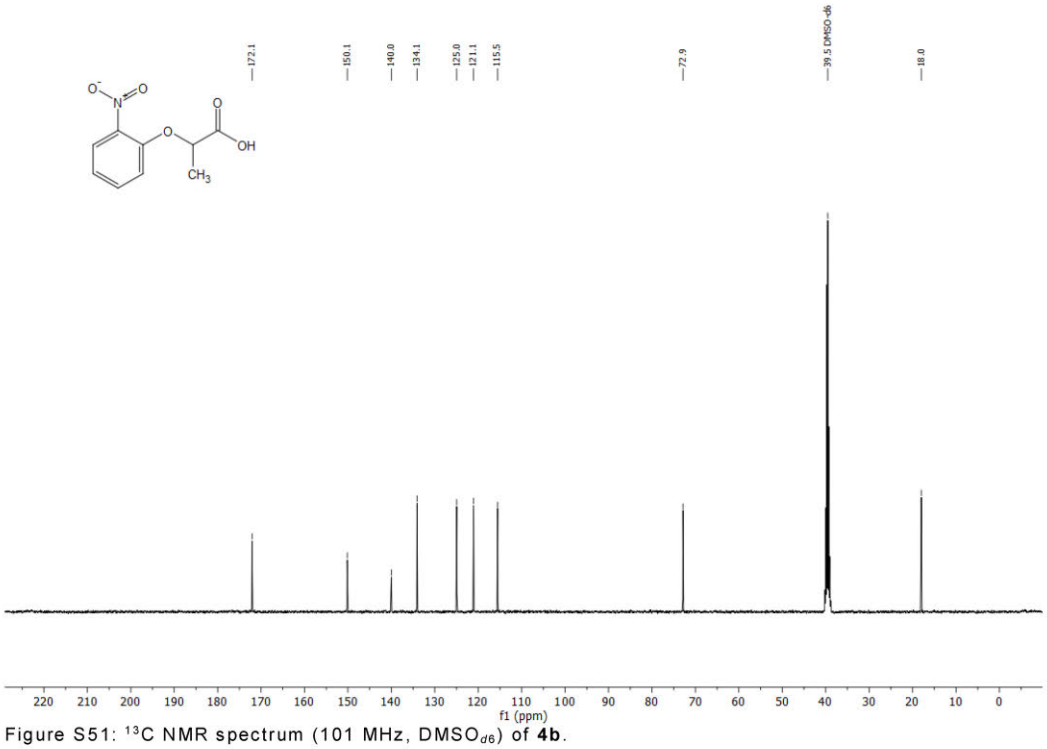


Figure S51: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **4b**.

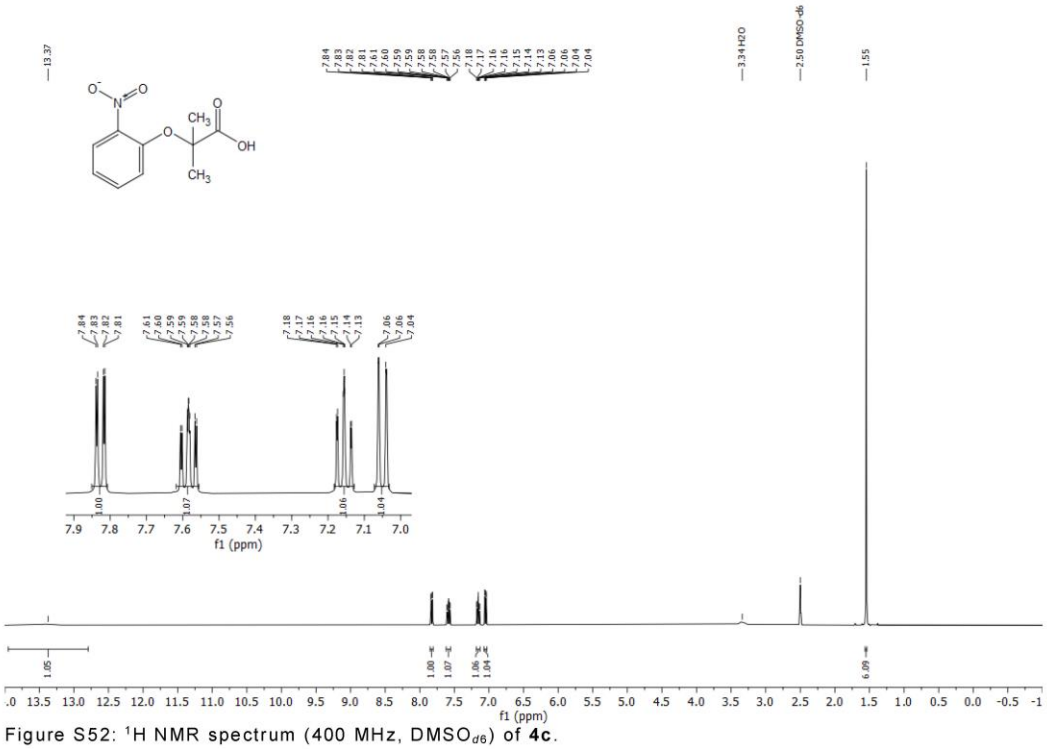


Figure S52: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **4c**.

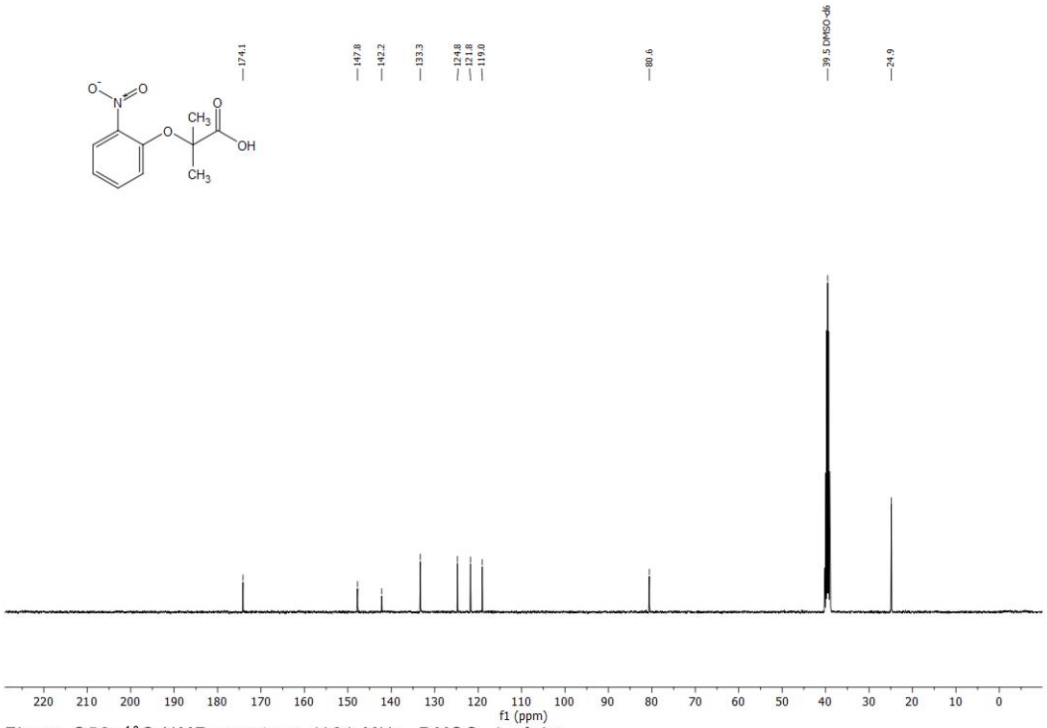


Figure S53: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **4c**.

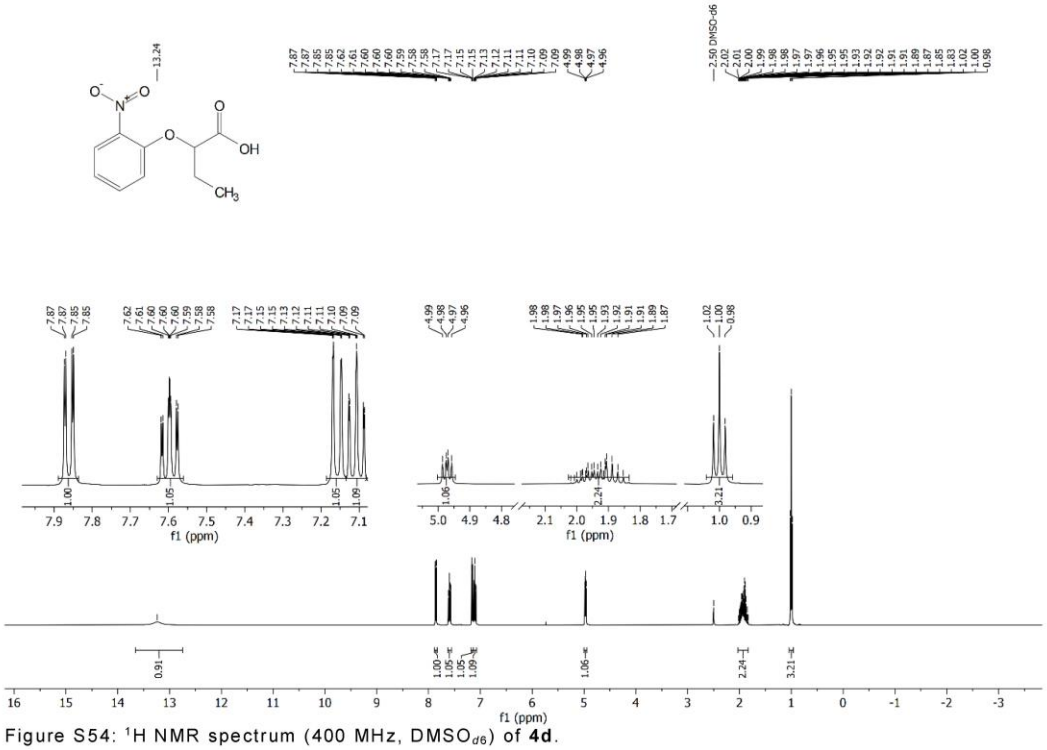


Figure S54: ^{1}H NMR spectrum (400 MHz, DMSO$_{d6}$) of **4d**.

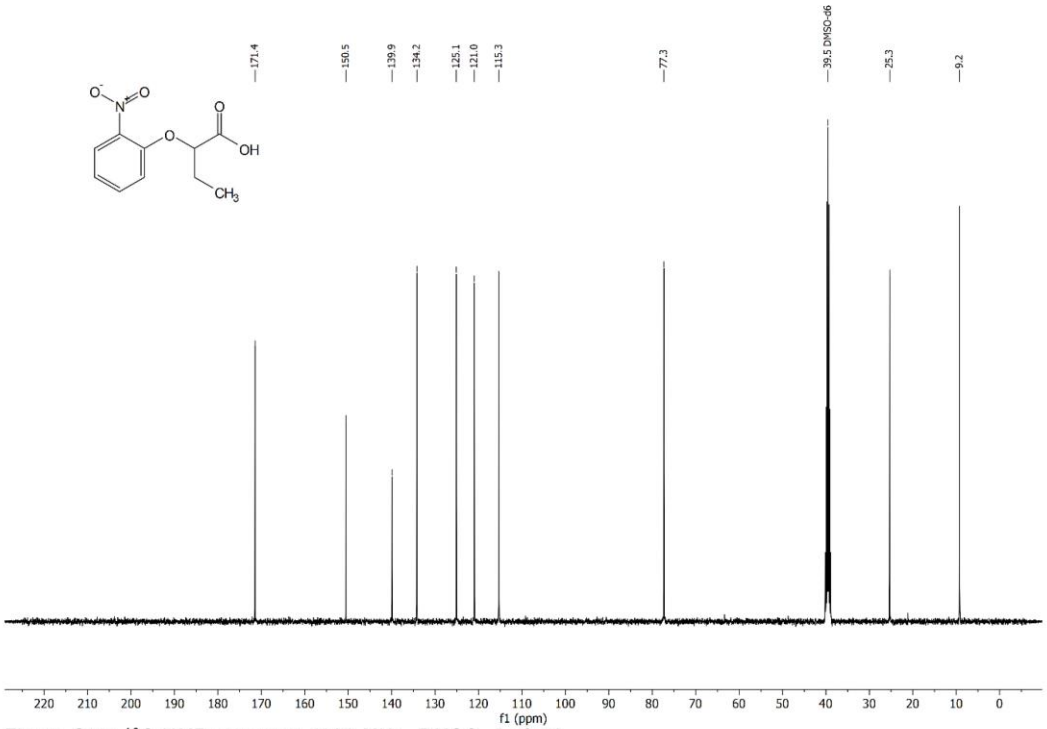


Figure S55: ^{13}C NMR spectrum (101 MHz, DMSO$_{d6}$) of **4d**.

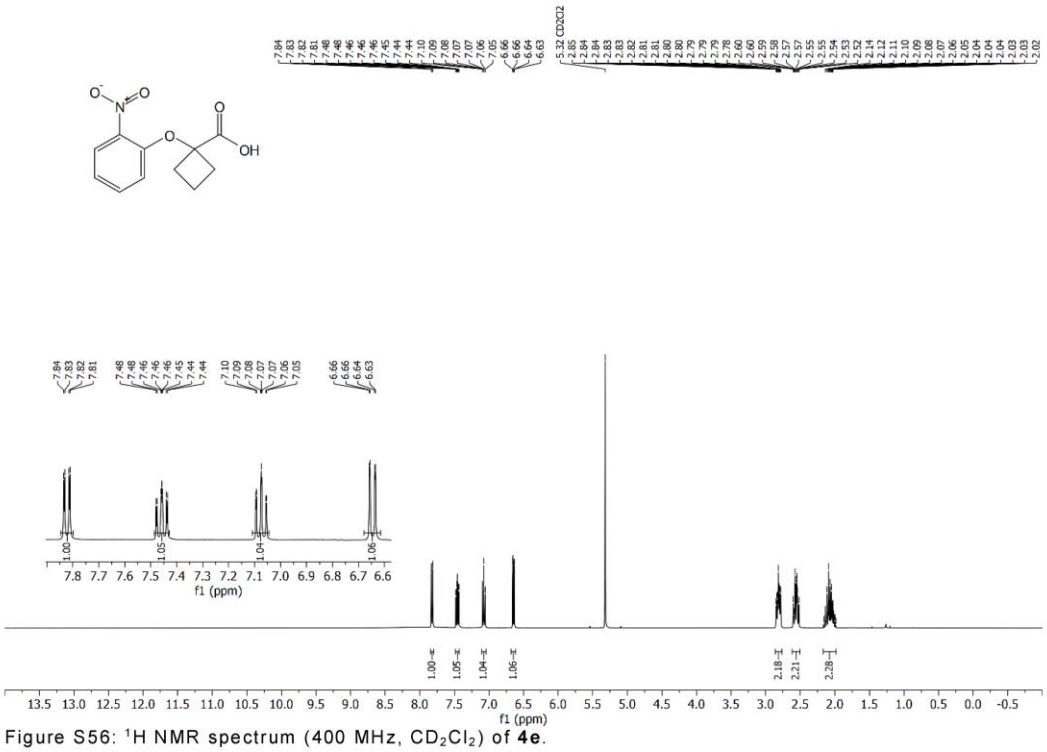


Figure S56: ^{1}H NMR spectrum (400 MHz, CD_2Cl_2) of **4e**.

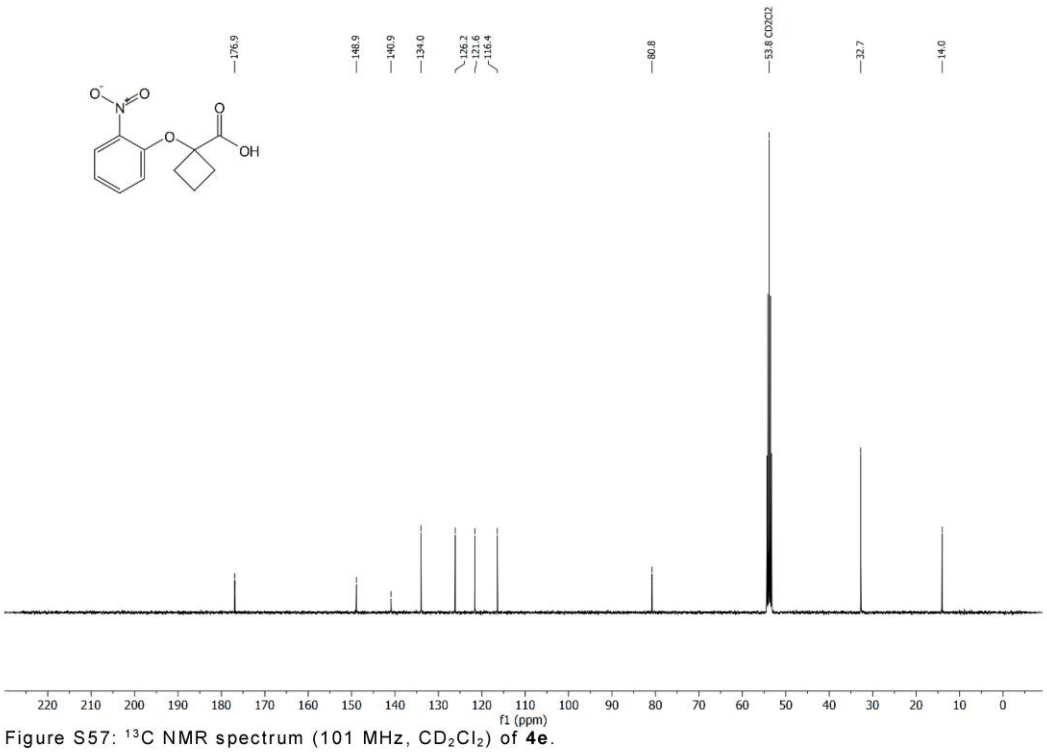


Figure S57: ^{13}C NMR spectrum (101 MHz, CD_2Cl_2) of **4e**.

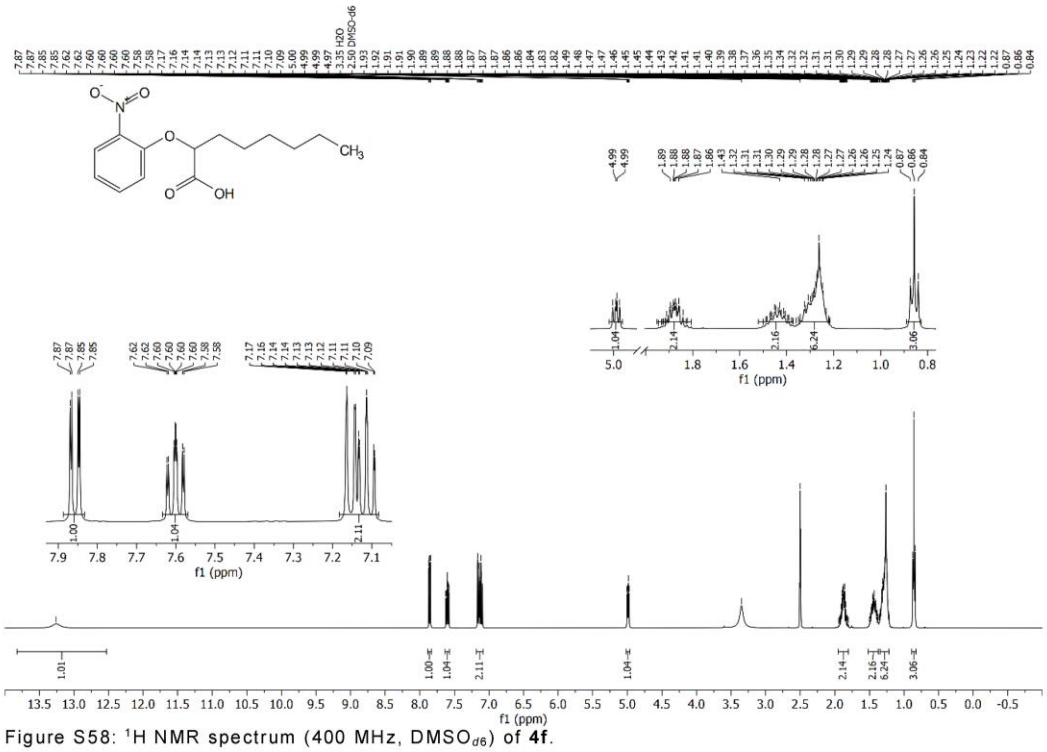


Figure S58: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **4f**.

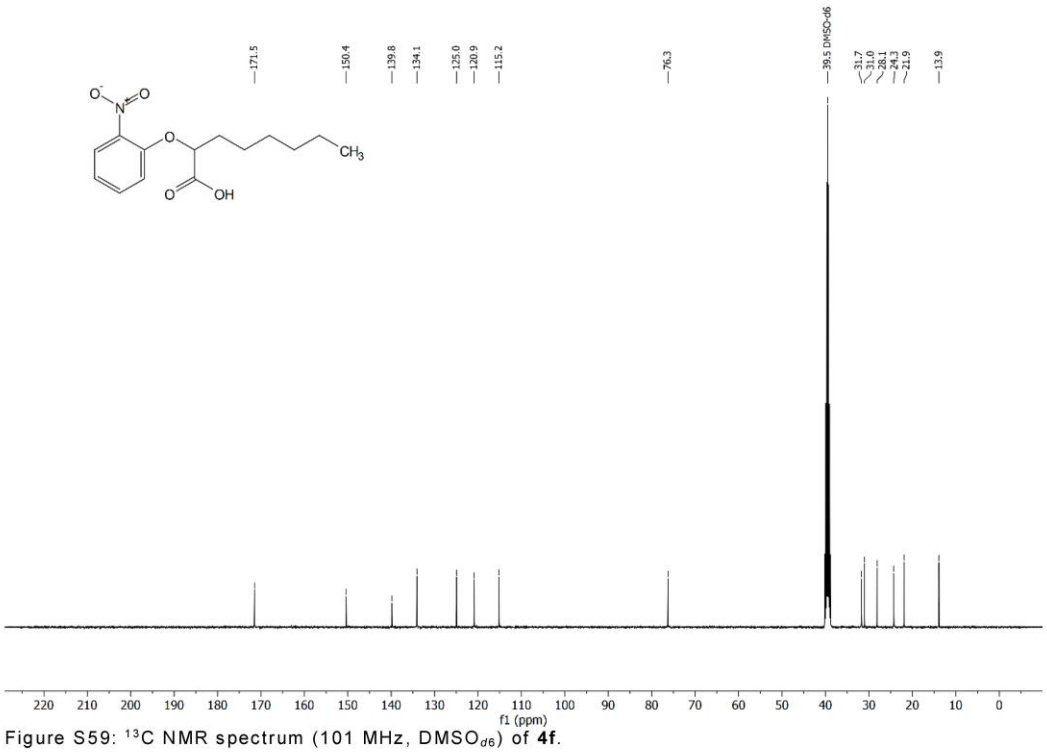


Figure S59: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **4f**.

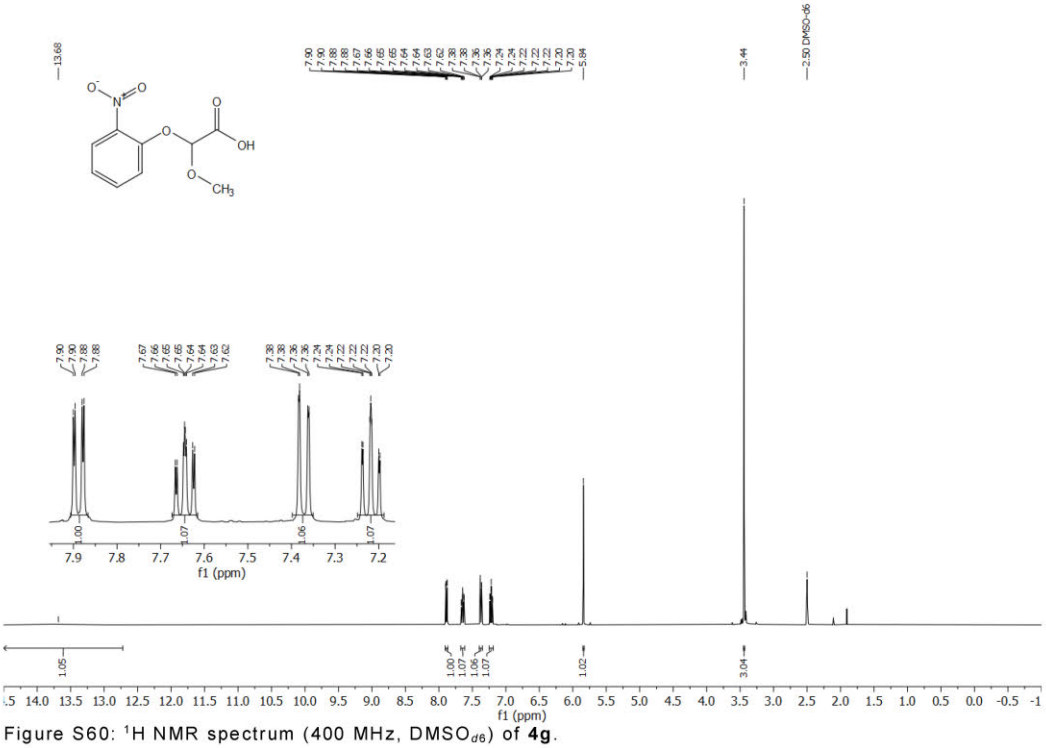


Figure S60: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **4g**.

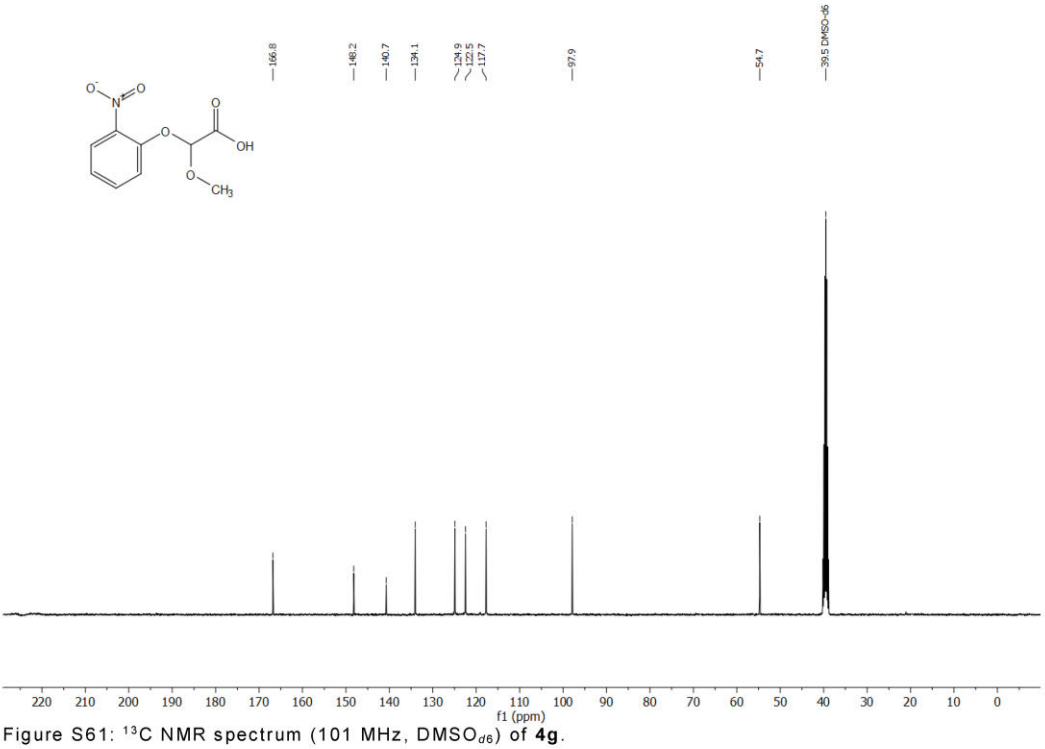


Figure S61: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **4g**.

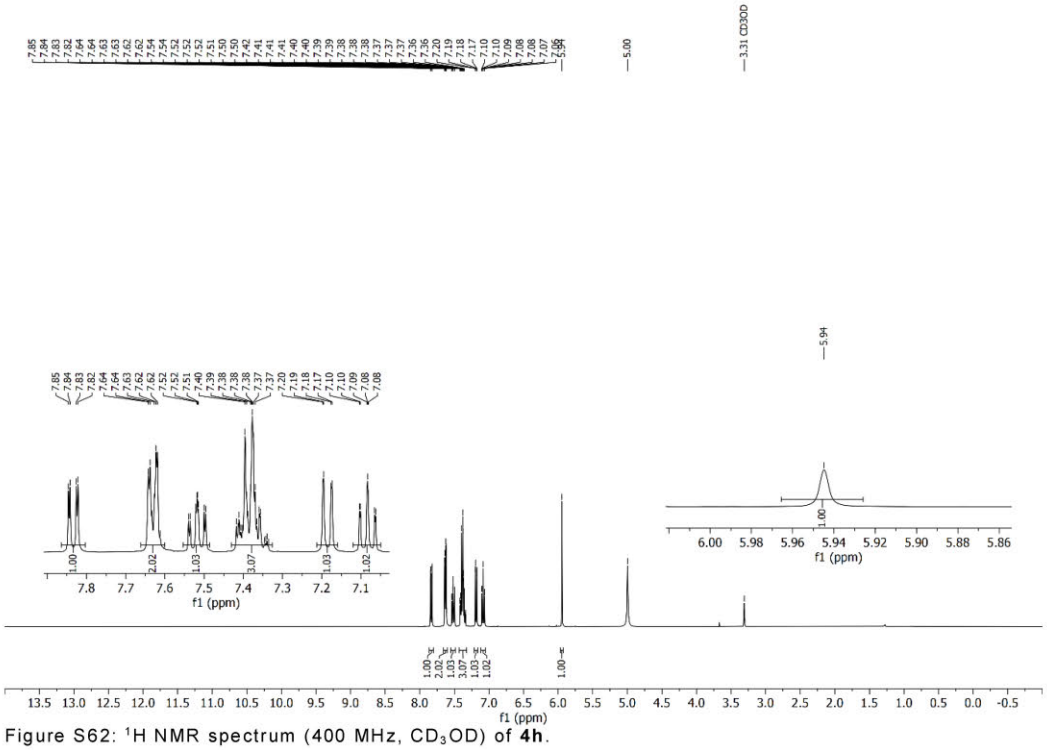


Figure S62: ^{1}H NMR spectrum (400 MHz, CD_3OD) of **4h**.

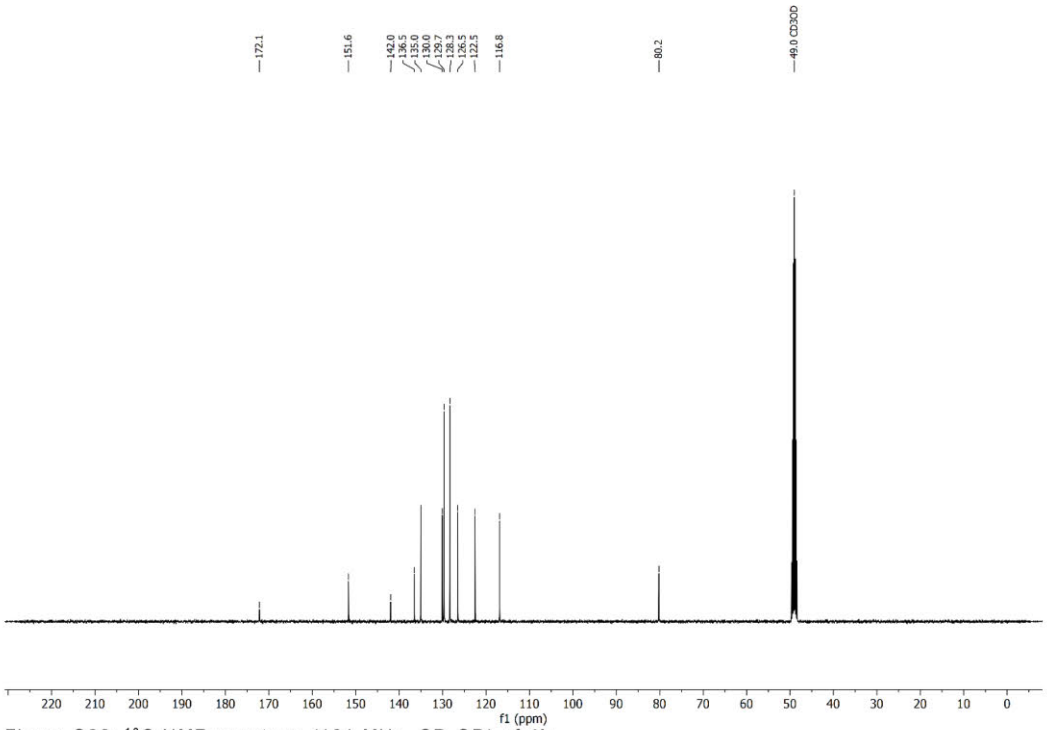


Figure S63: ^{13}C NMR spectrum (101 MHz, CD_3OD) of **4h**.

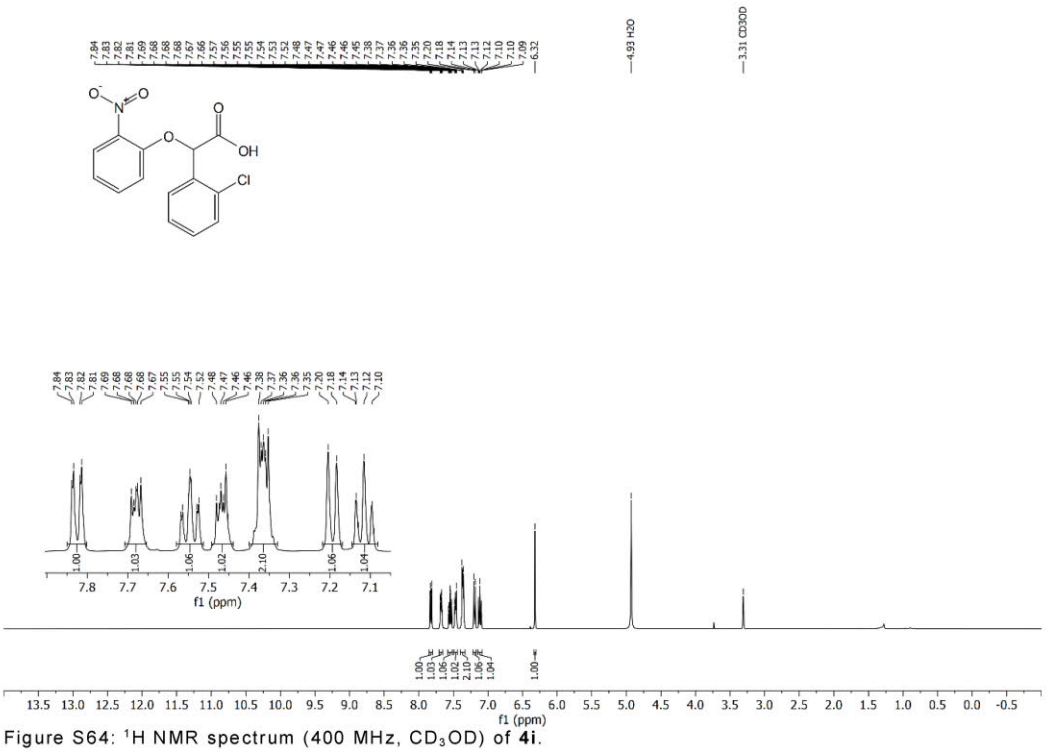


Figure S64: ^{1}H NMR spectrum (400 MHz, CD_3OD) of **4i**.

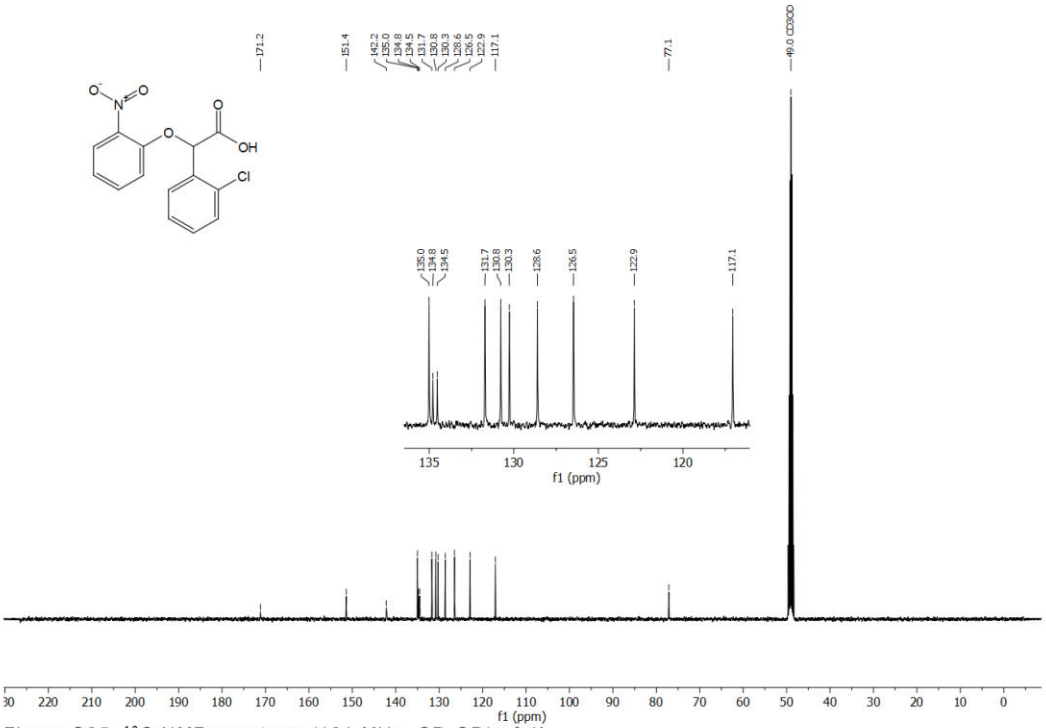


Figure S65: ^{13}C NMR spectrum (101 MHz, CD_3OD) of **4i**.

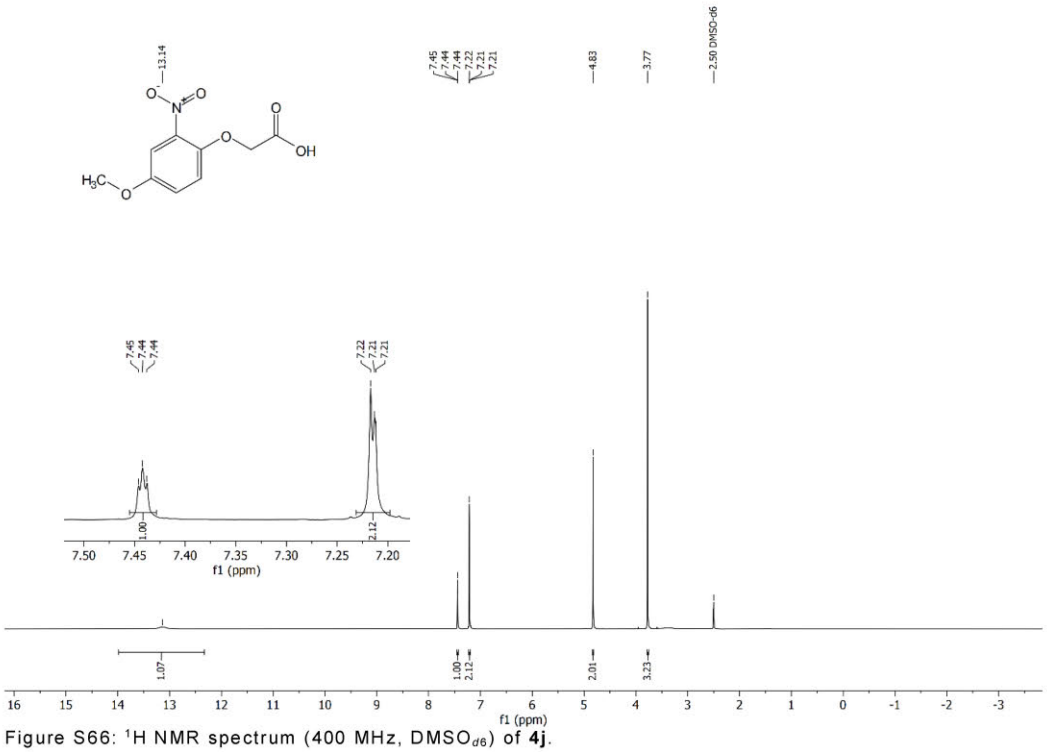


Figure S66: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **4j**.

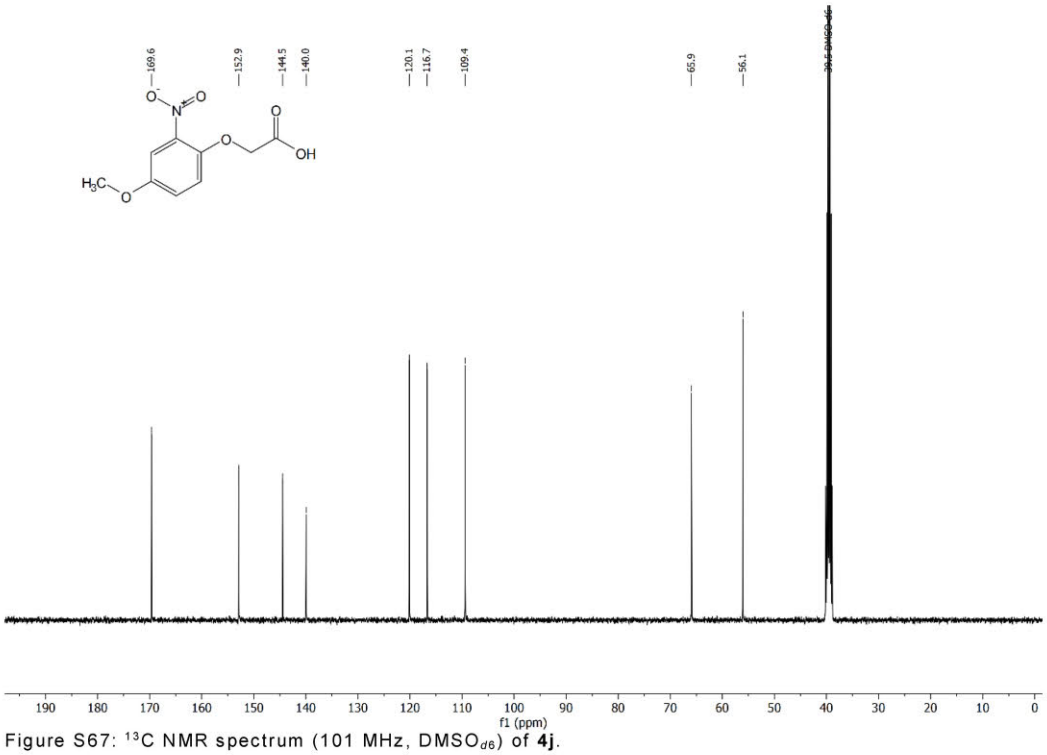


Figure S67: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **4j**.

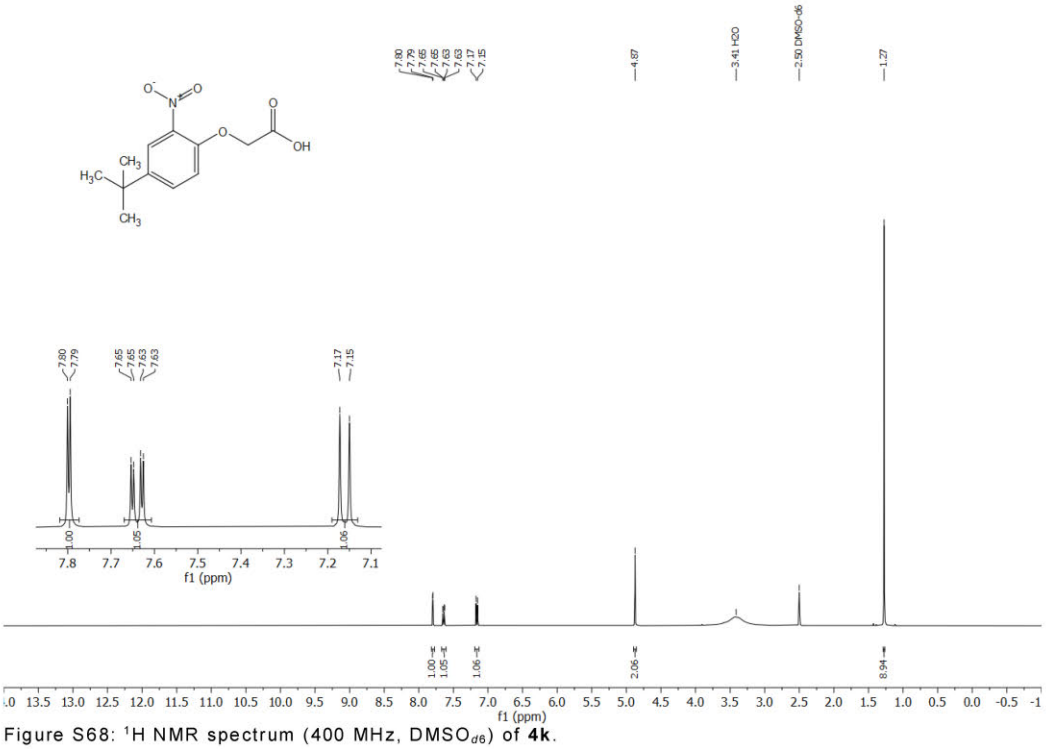


Figure S68: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **4k**.

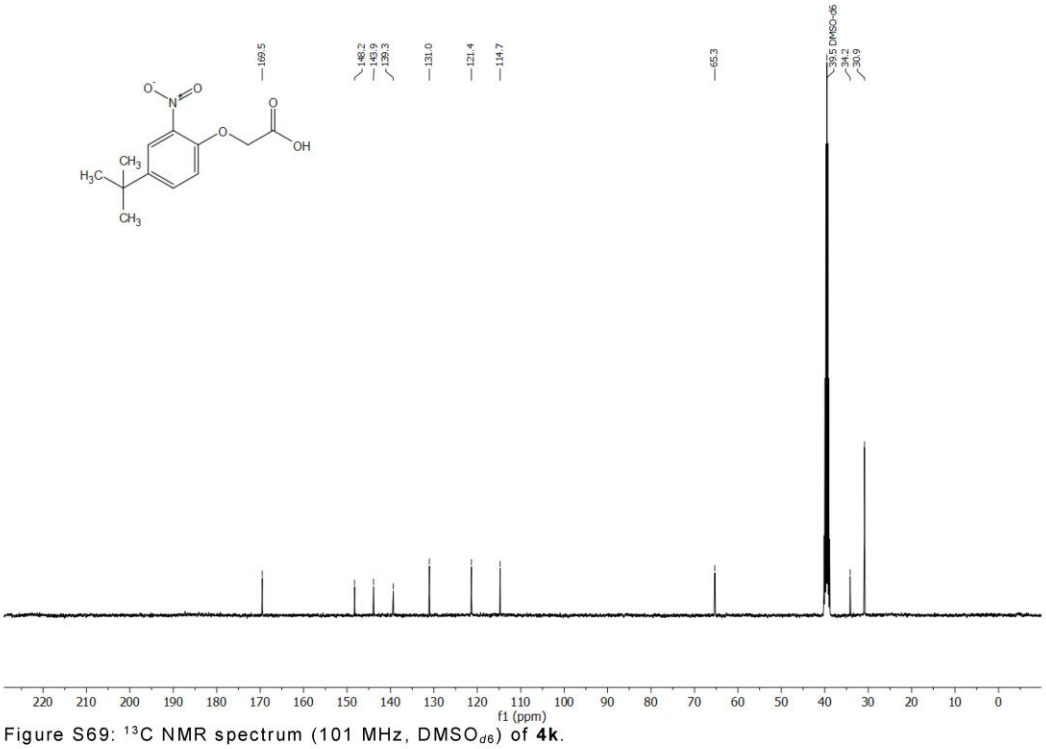


Figure S69: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **4k**.

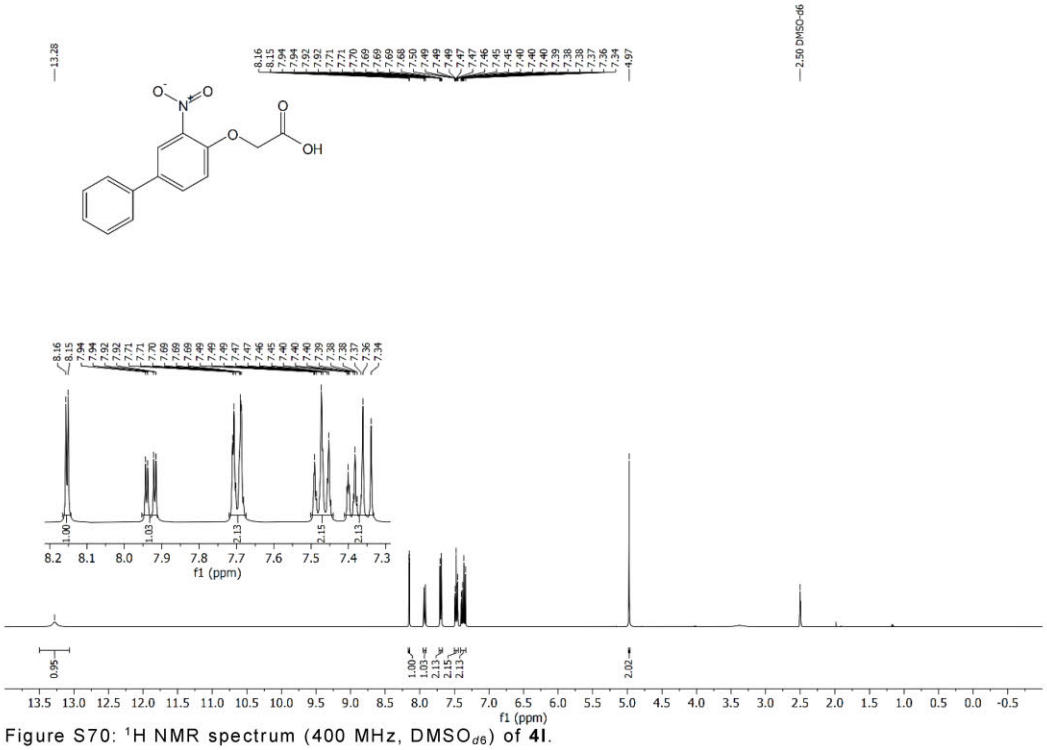


Figure S70: ^{1}H NMR spectrum (400 MHz, DMSO$_{d6}$) of **4l**.

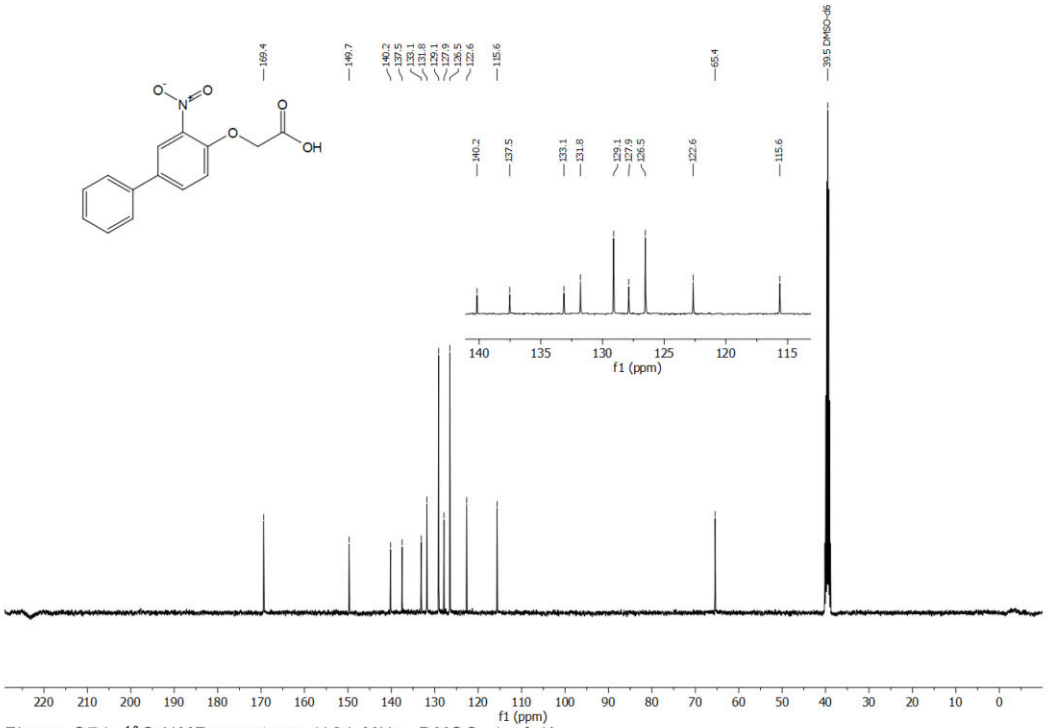


Figure S71: ^{13}C NMR spectrum (101 MHz, DMSO$_{d6}$) of **4l**.

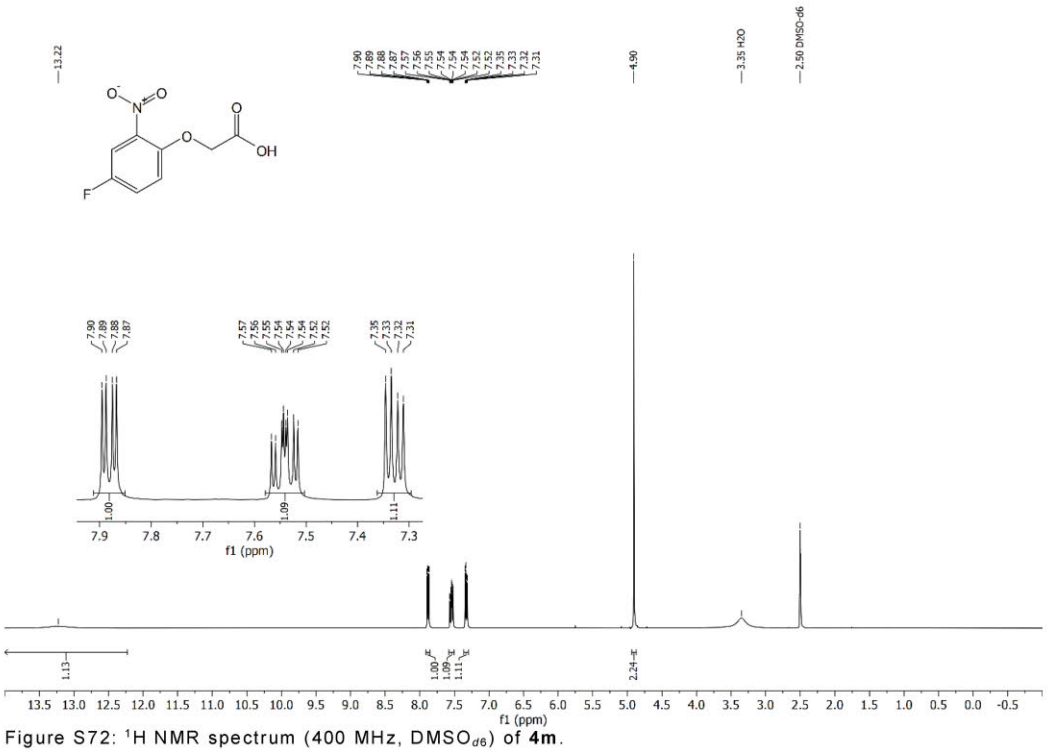


Figure S72: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **4m**.

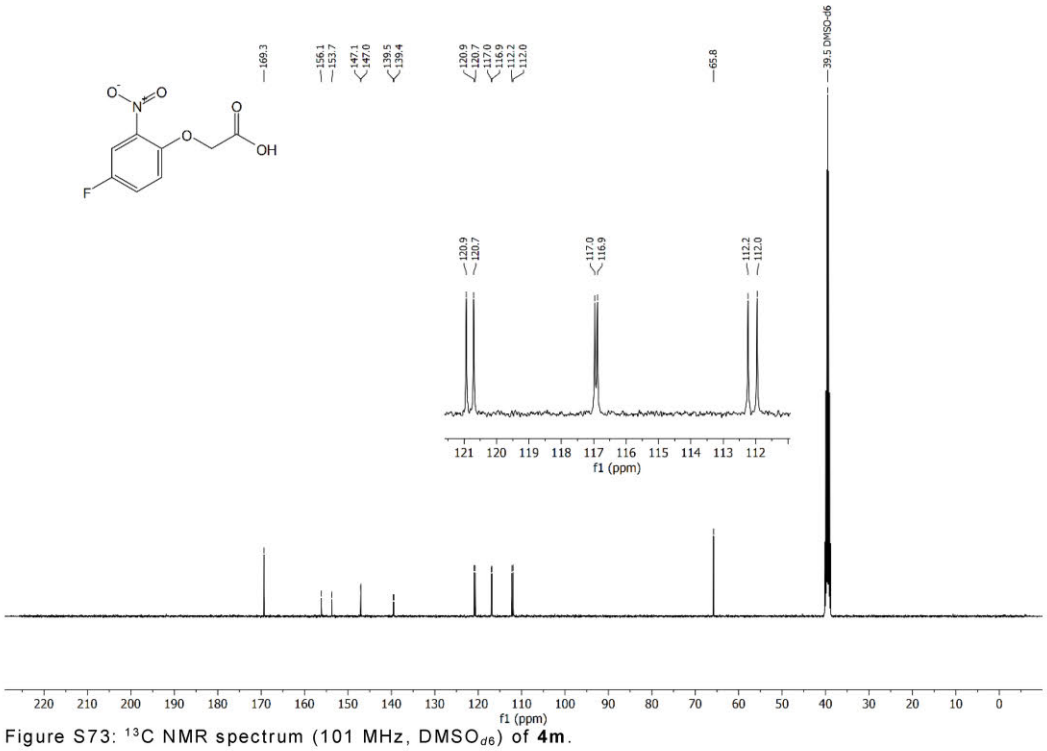


Figure S73: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **4m**.

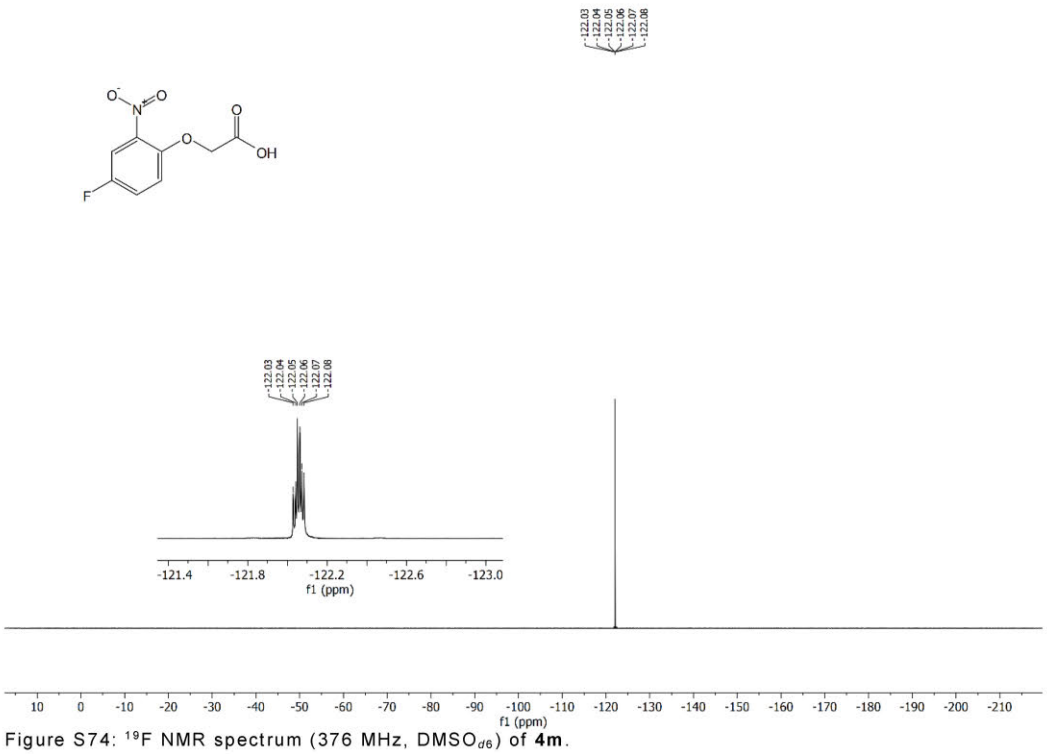


Figure S74: ^{19}F NMR spectrum (376 MHz, $DMSO_{d6}$) of **4m**.

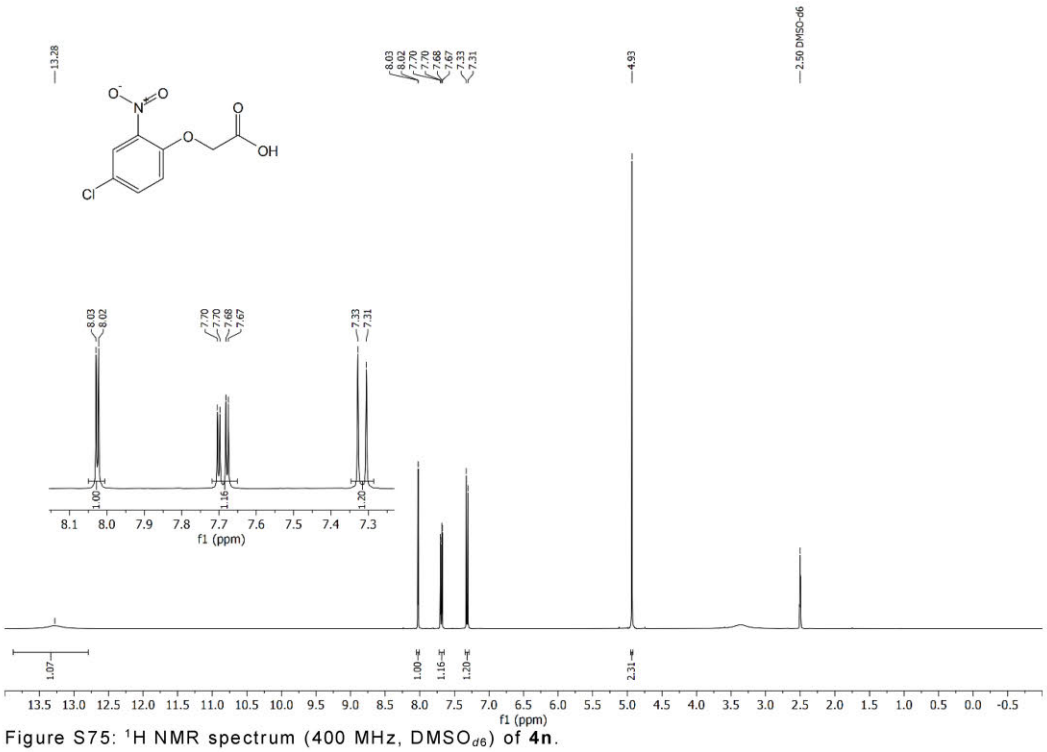


Figure S75: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **4n**.

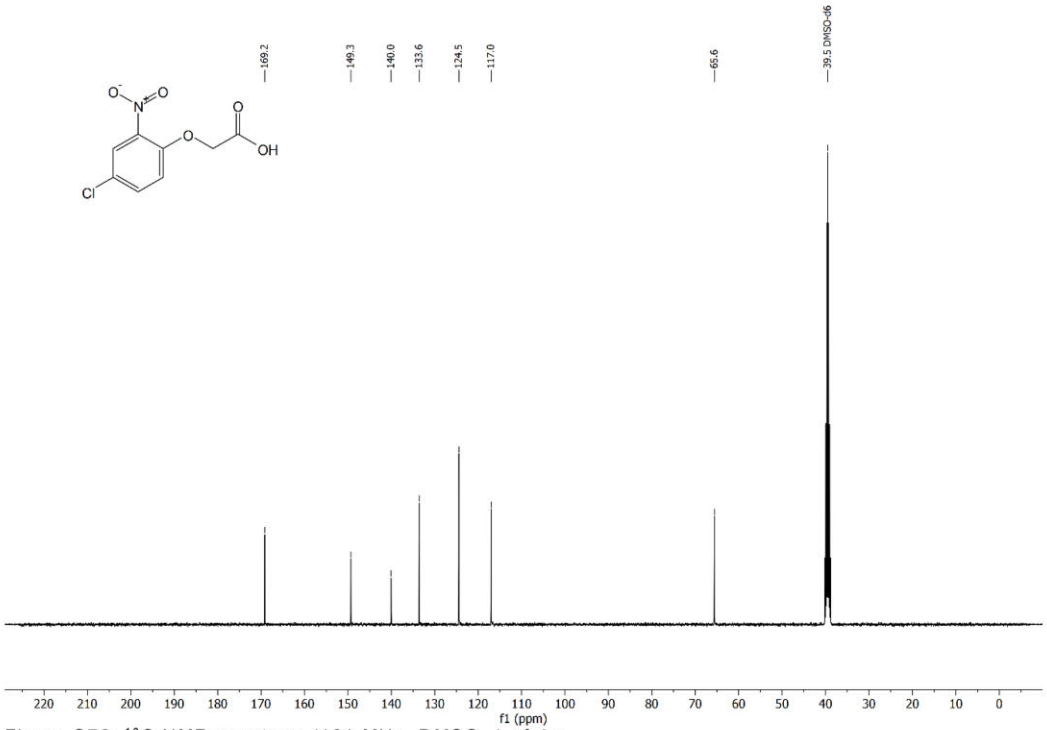


Figure S76: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **4n**.

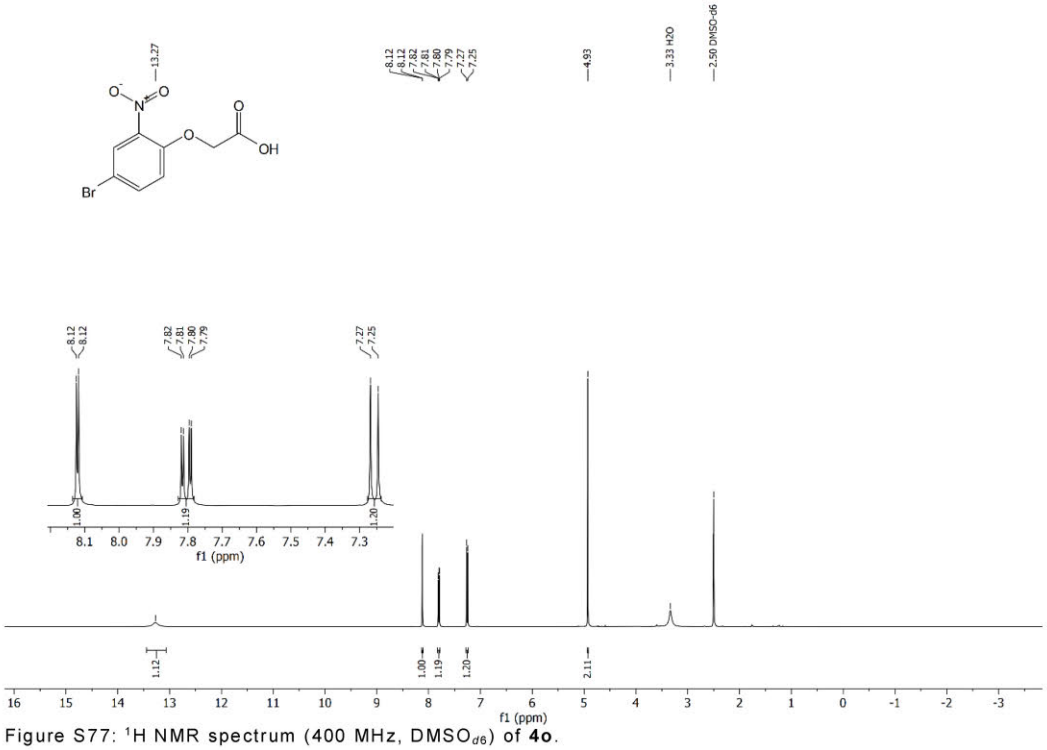


Figure S77: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **4o**.

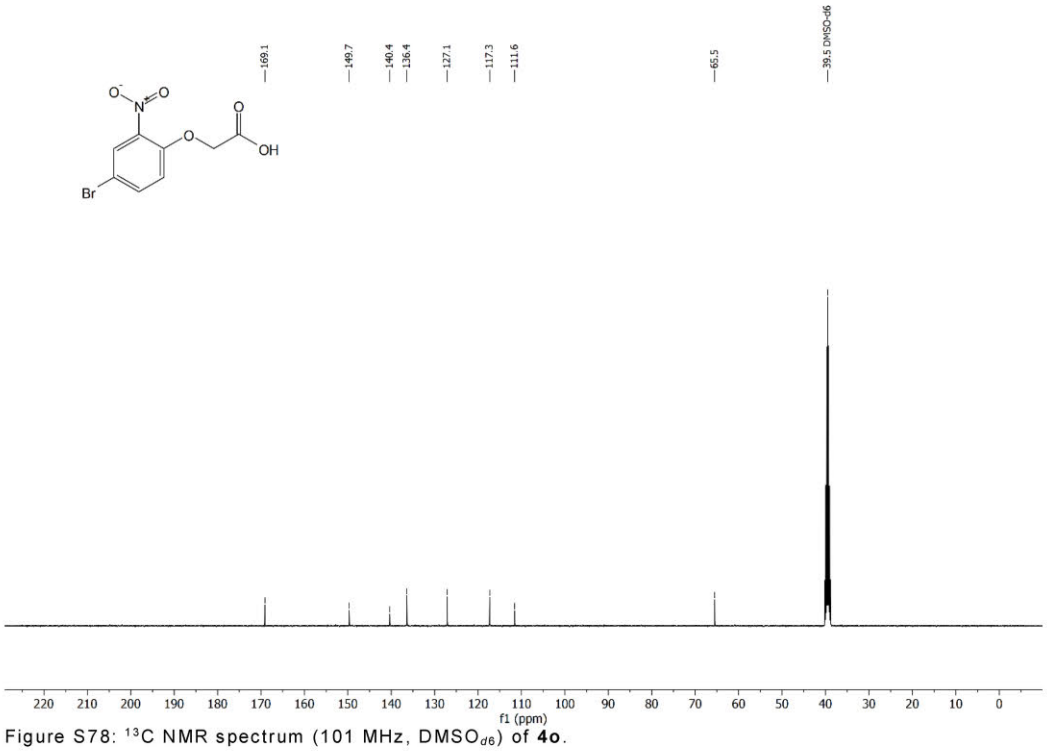


Figure S78: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **4o**.

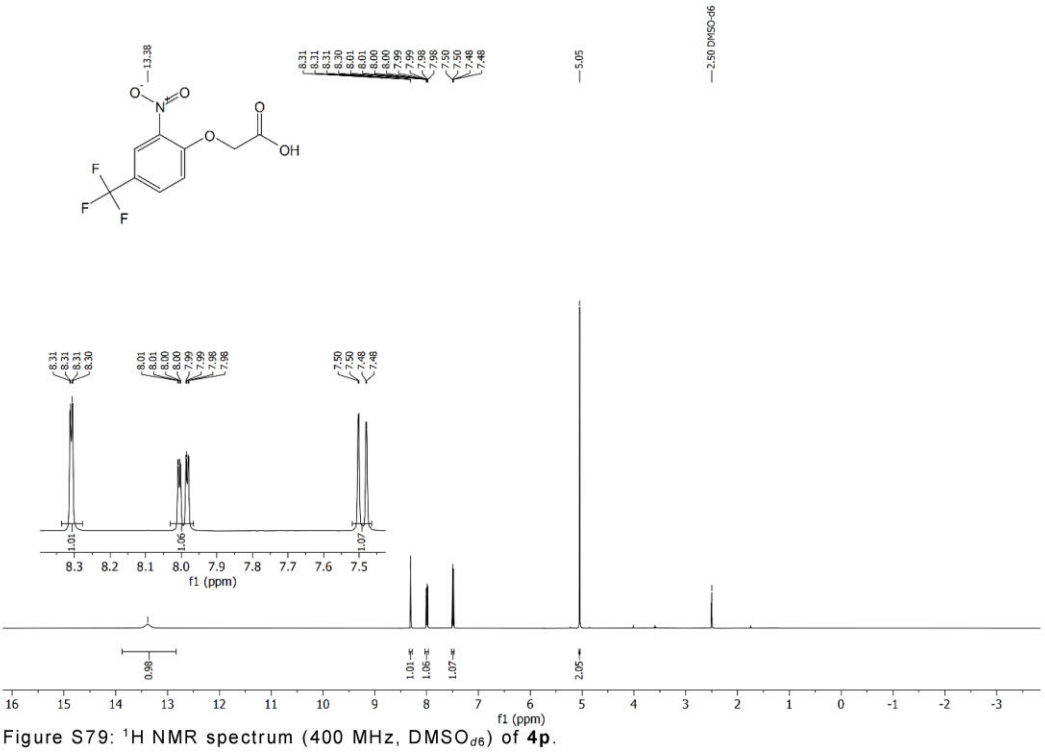


Figure S79: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **4p**.

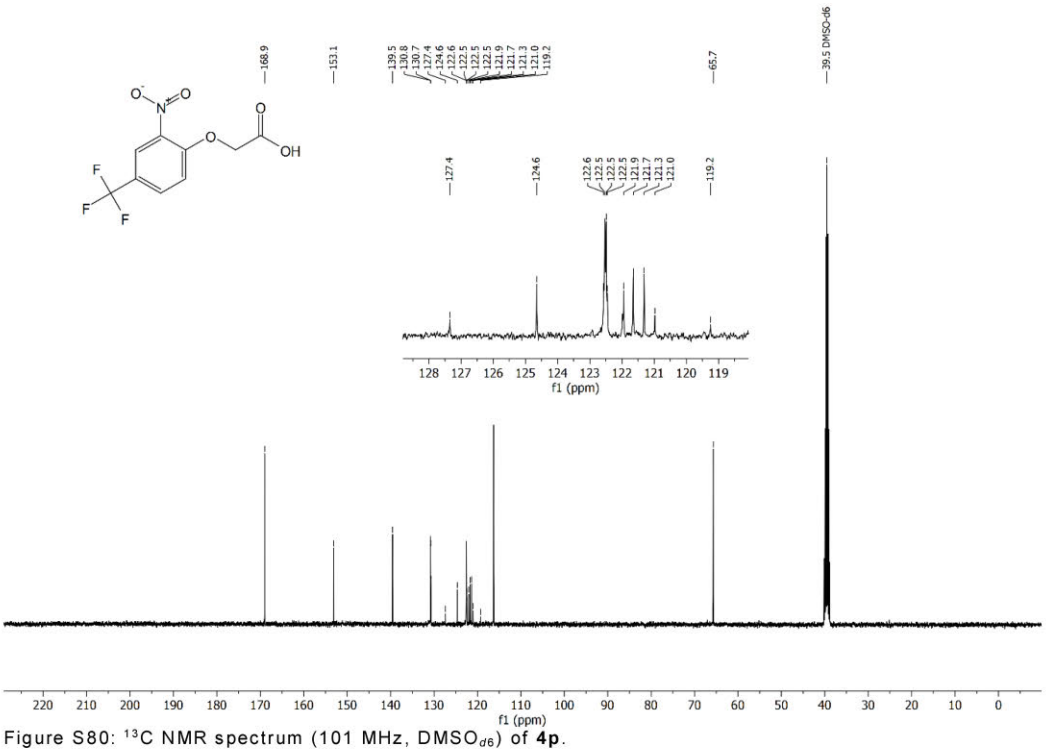


Figure S80: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **4p**.

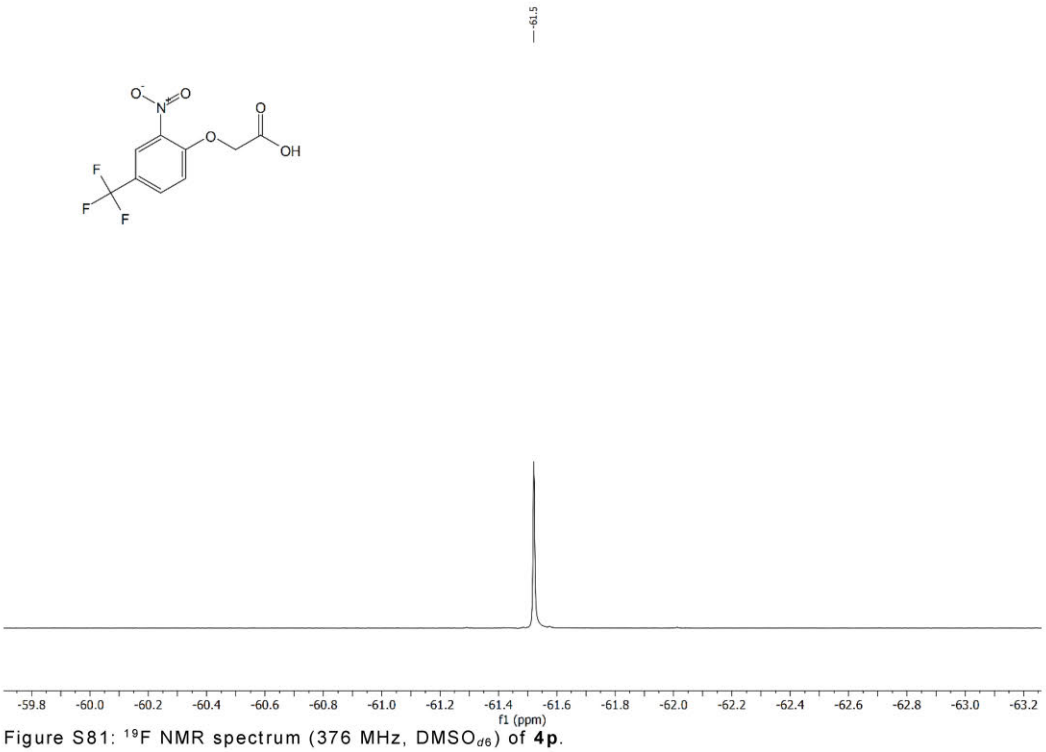


Figure S81: ^{19}F NMR spectrum (376 MHz, $DMSO_{d6}$) of **4p**.

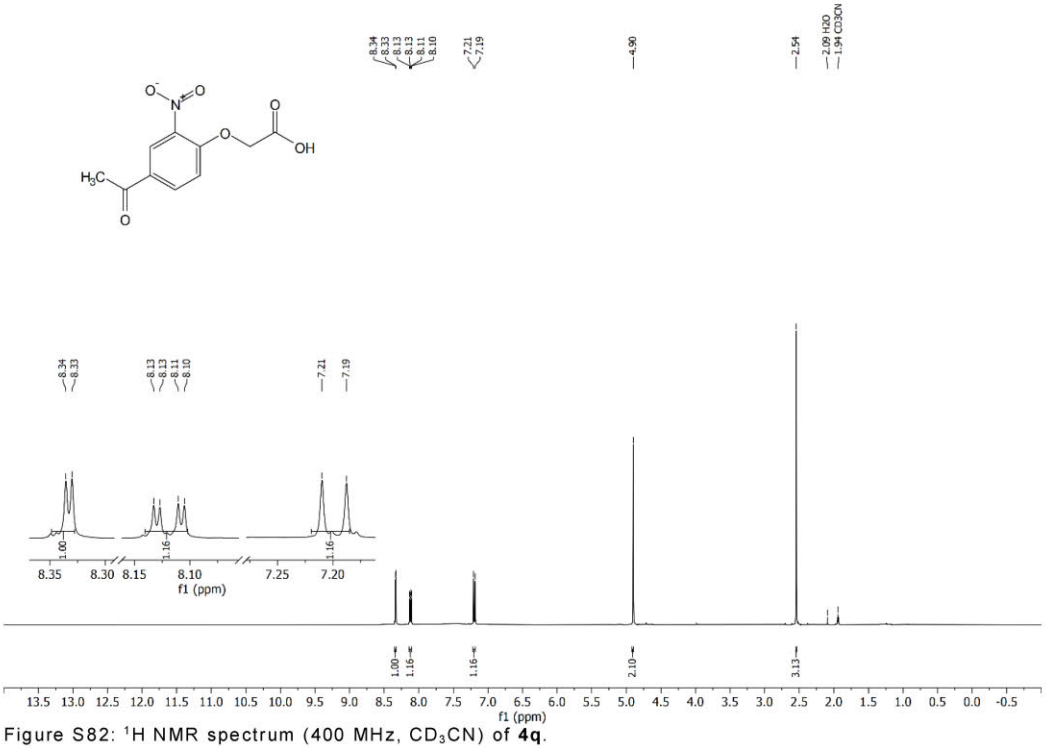


Figure S82: ^{1}H NMR spectrum (400 MHz, CD_3CN) of **4q**.

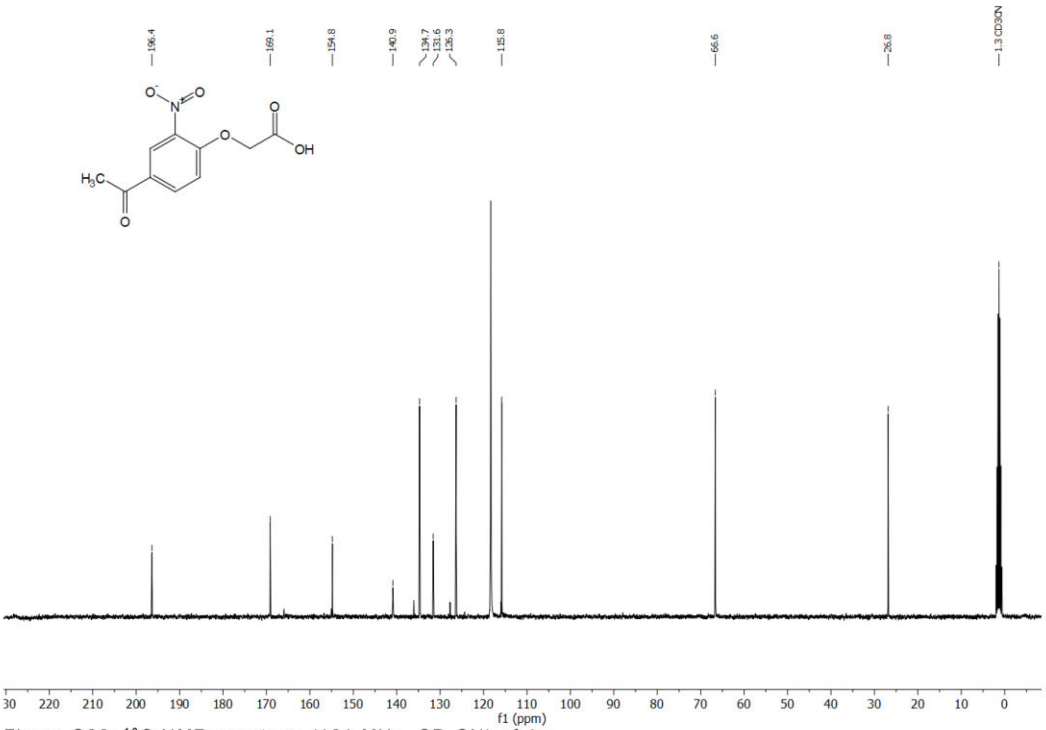


Figure S83: ^{13}C NMR spectrum (101 MHz, CD_3CN) of **4q**.

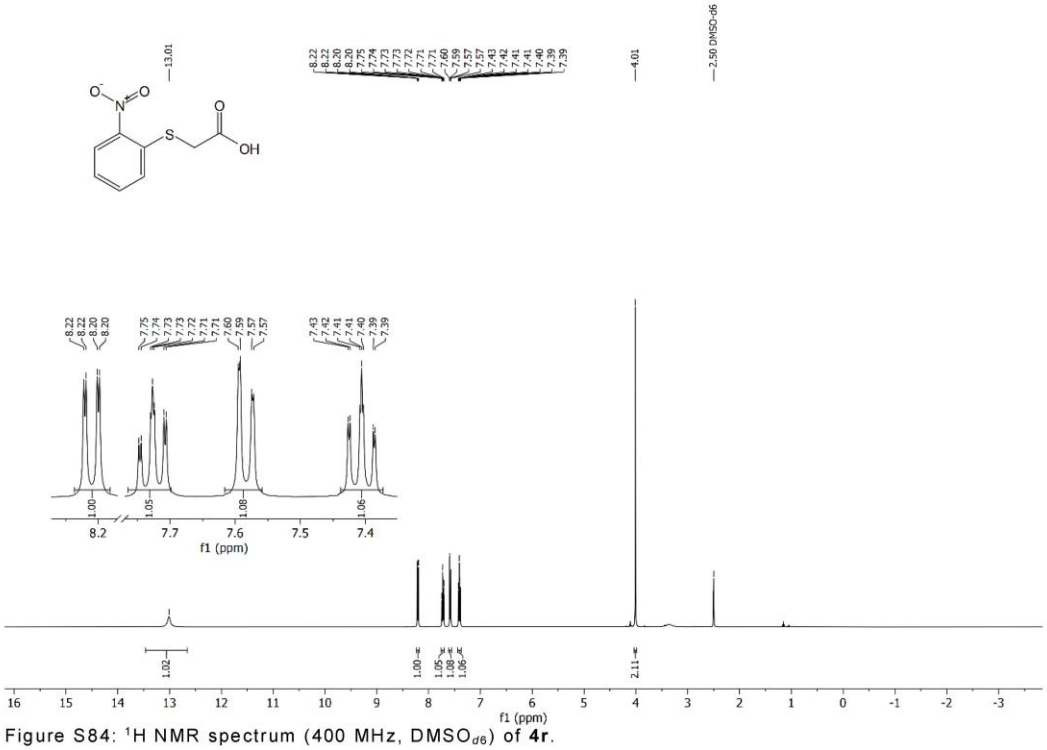


Figure S84: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **4r**.

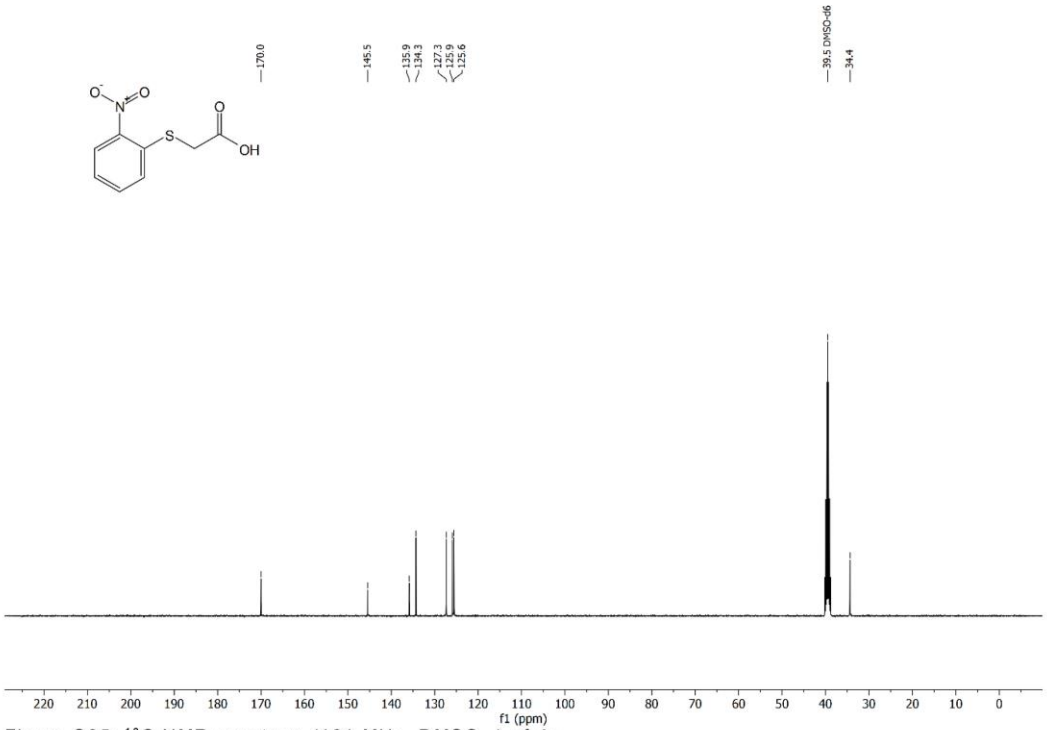


Figure S85: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **4r**.

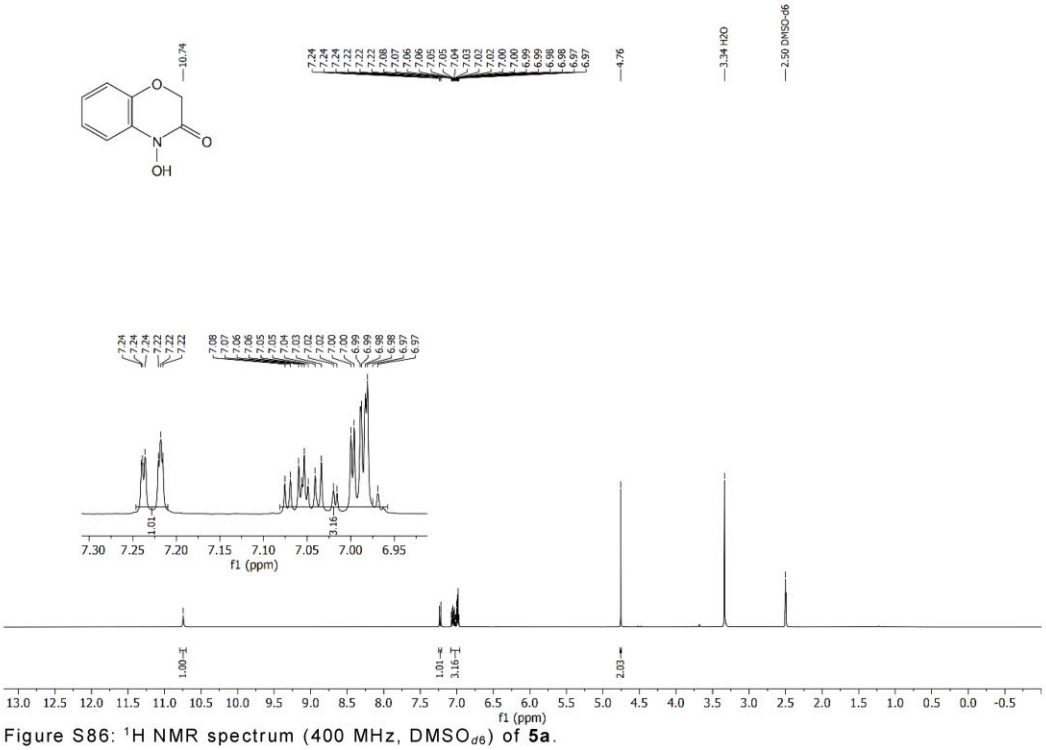


Figure S86: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5a**.

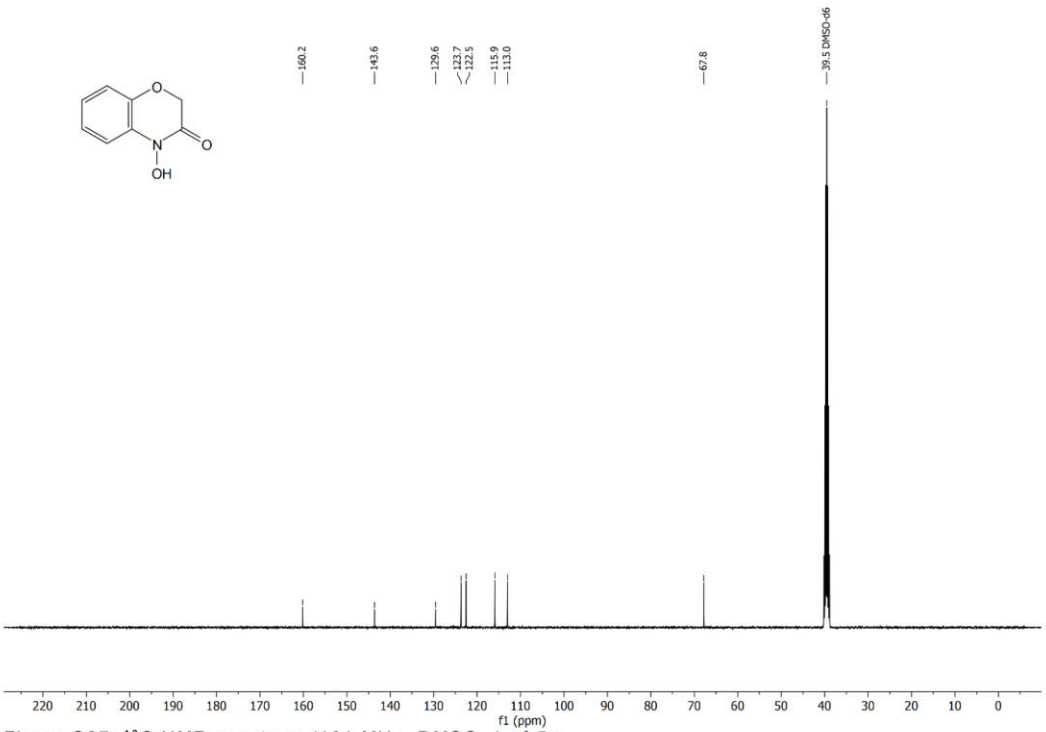


Figure S87: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5a**.

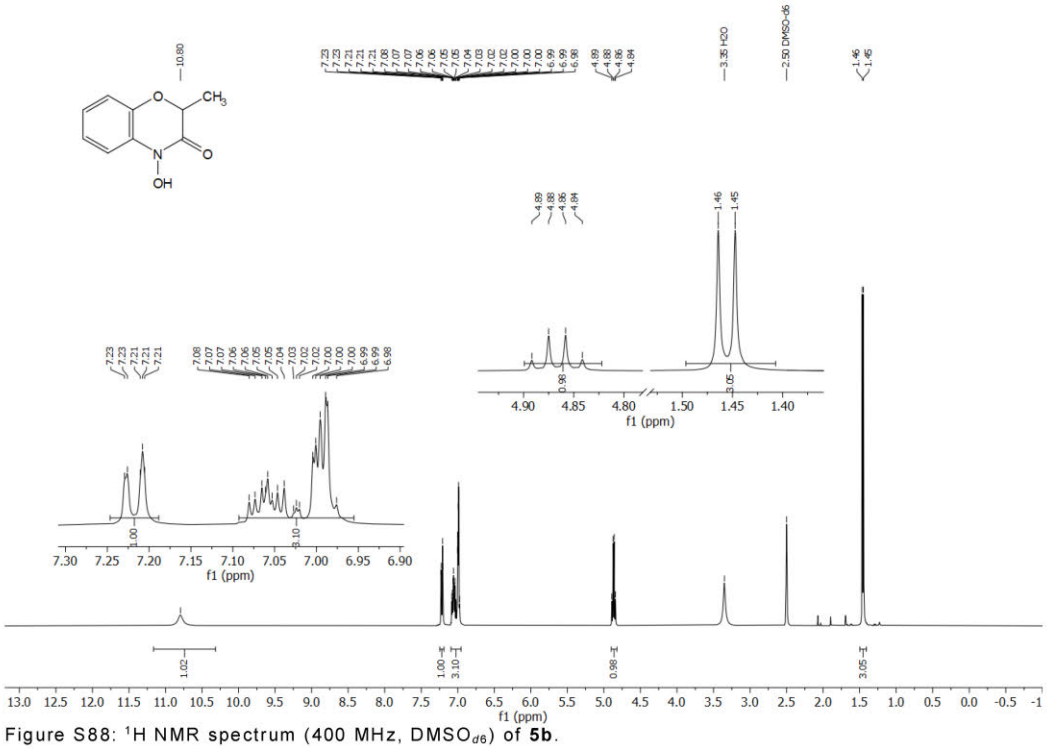


Figure S88: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5b**.

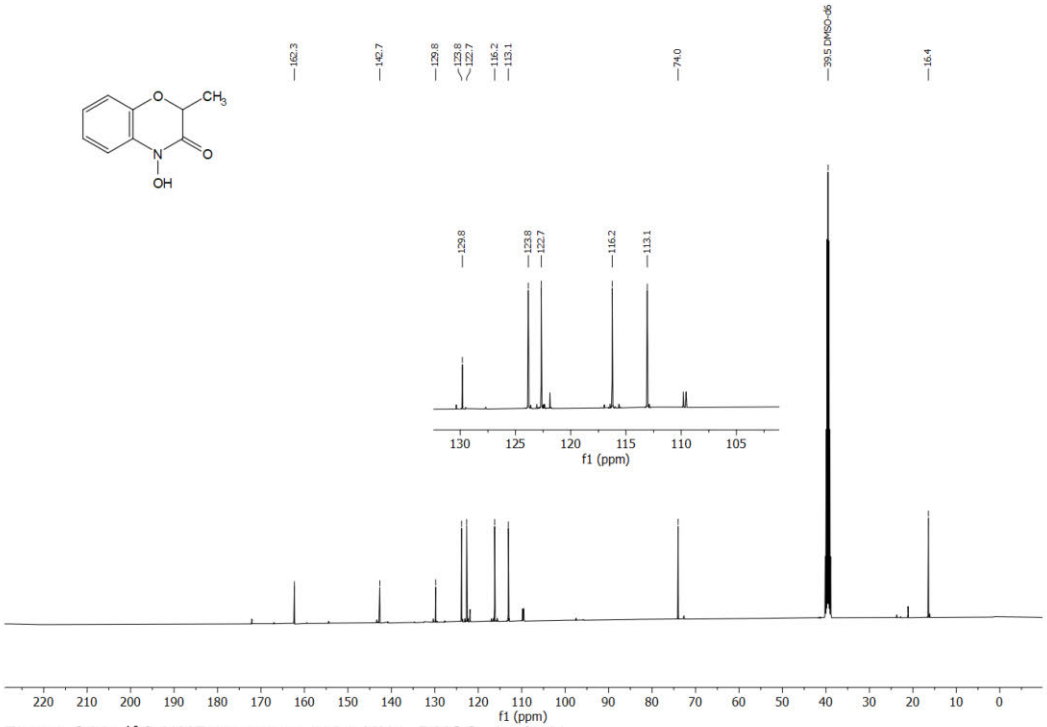


Figure S89: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5b**.

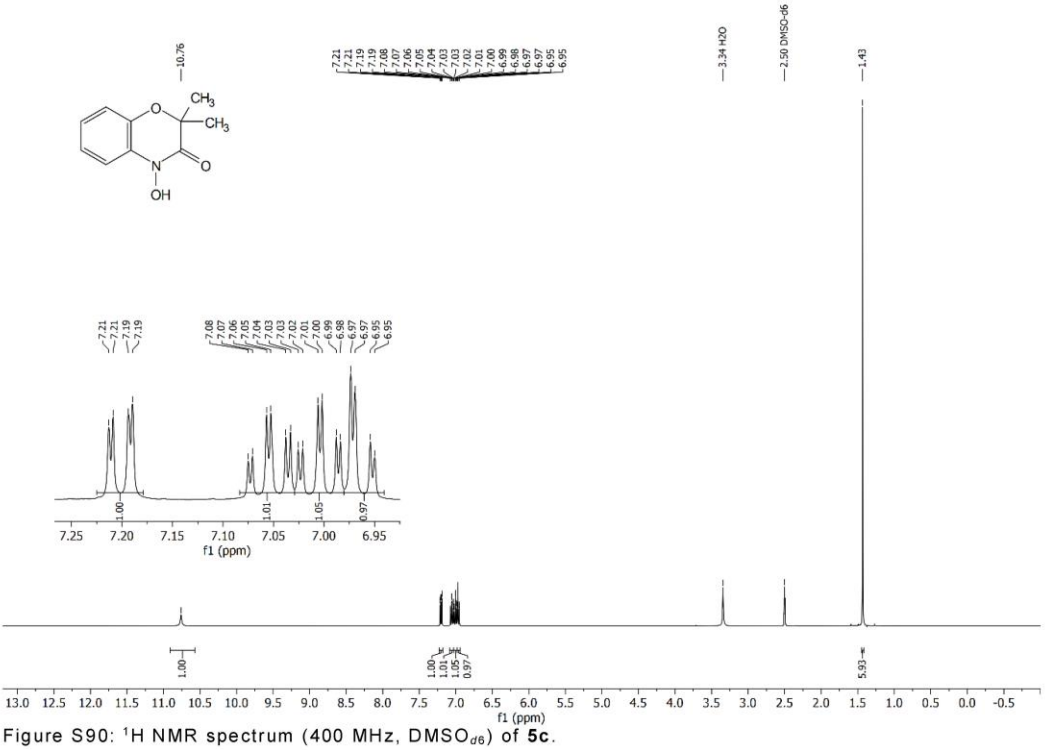


Figure S90: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5c**.

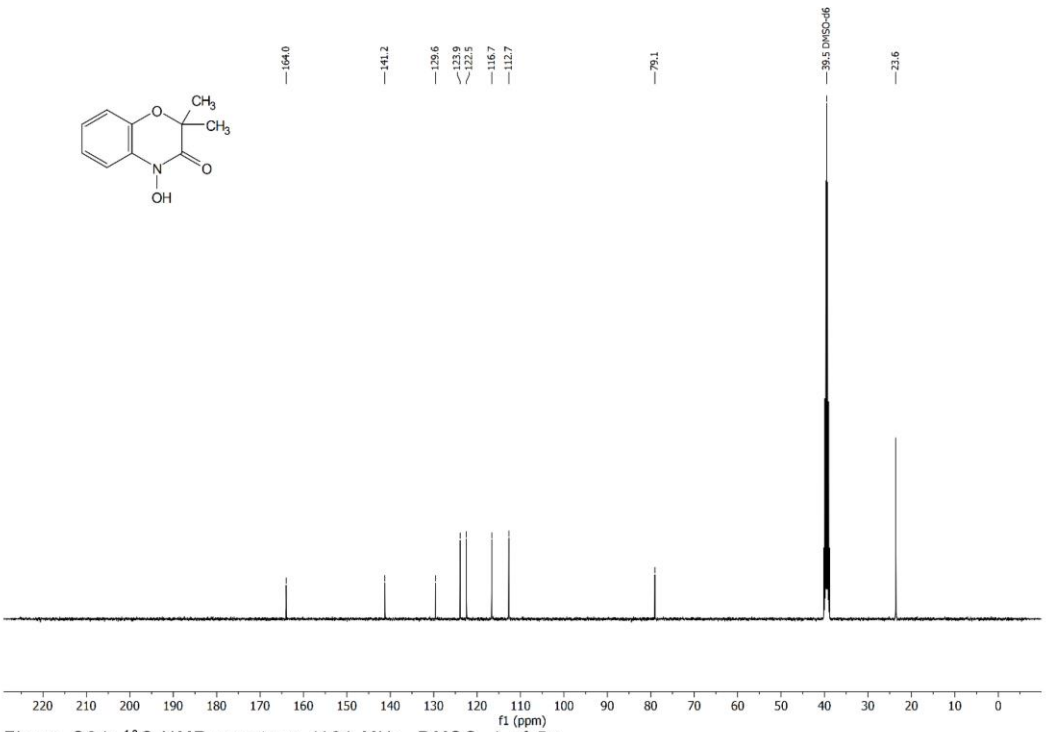


Figure S91: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5c**.

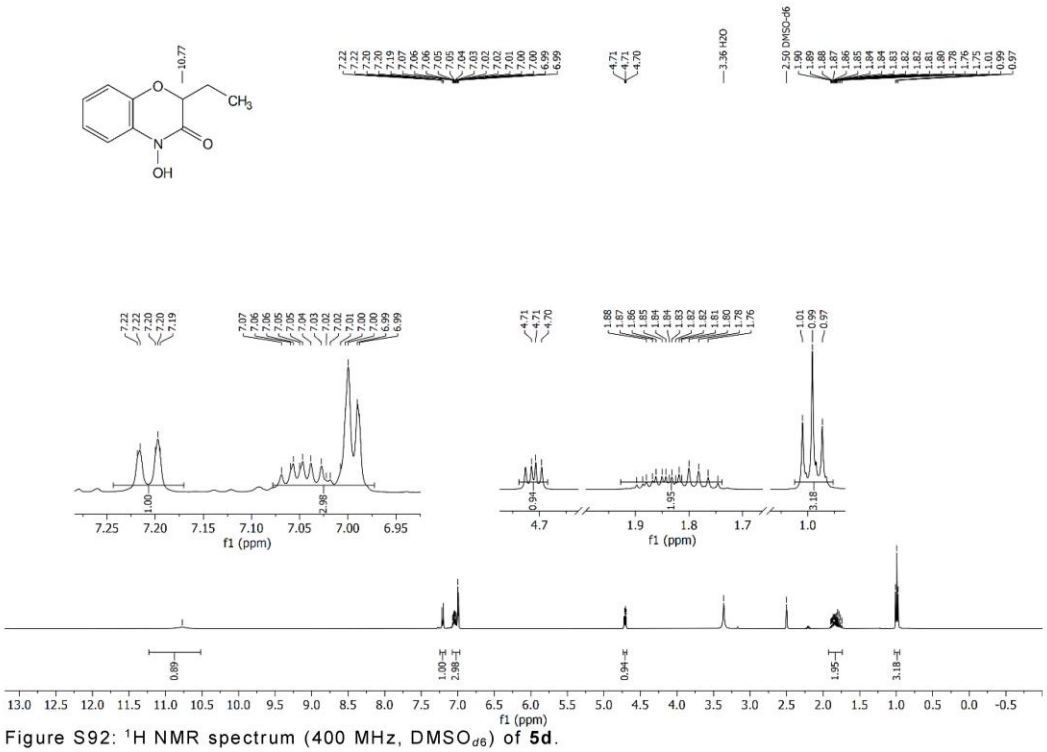


Figure S92: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5d**.

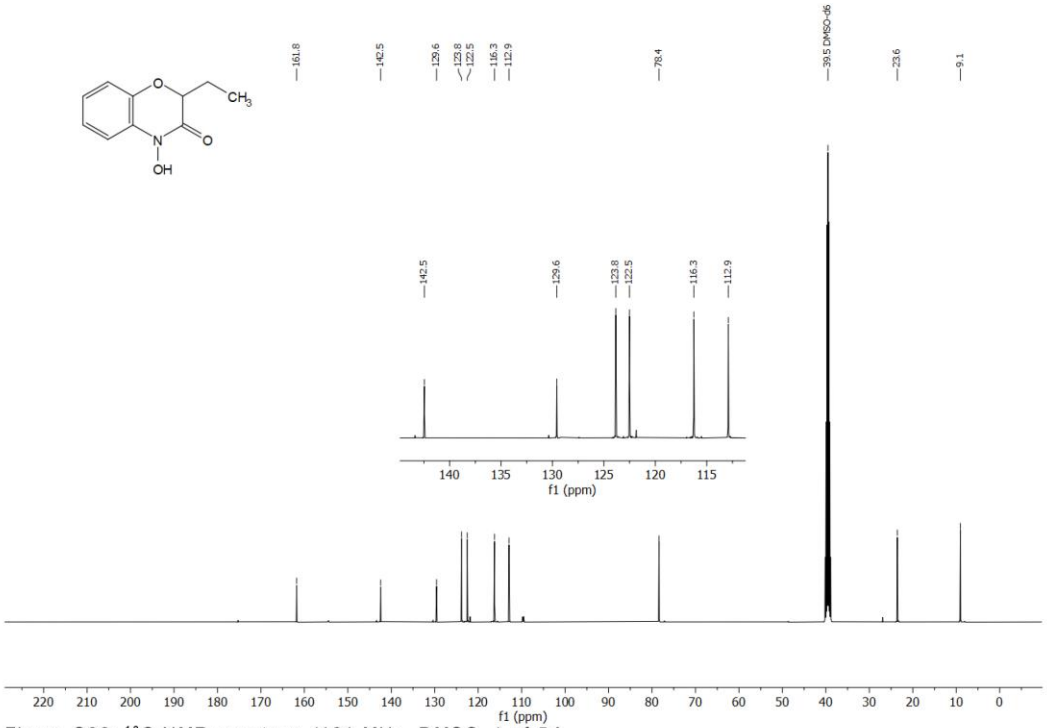


Figure S93: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5d**.

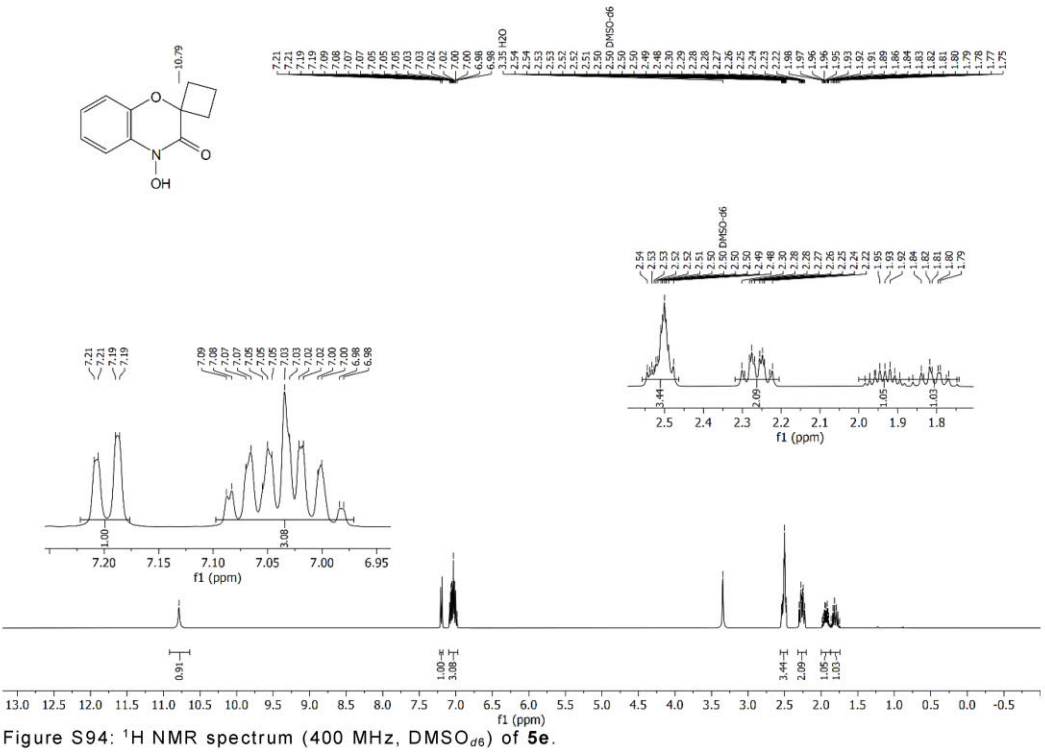


Figure S94: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5e**.

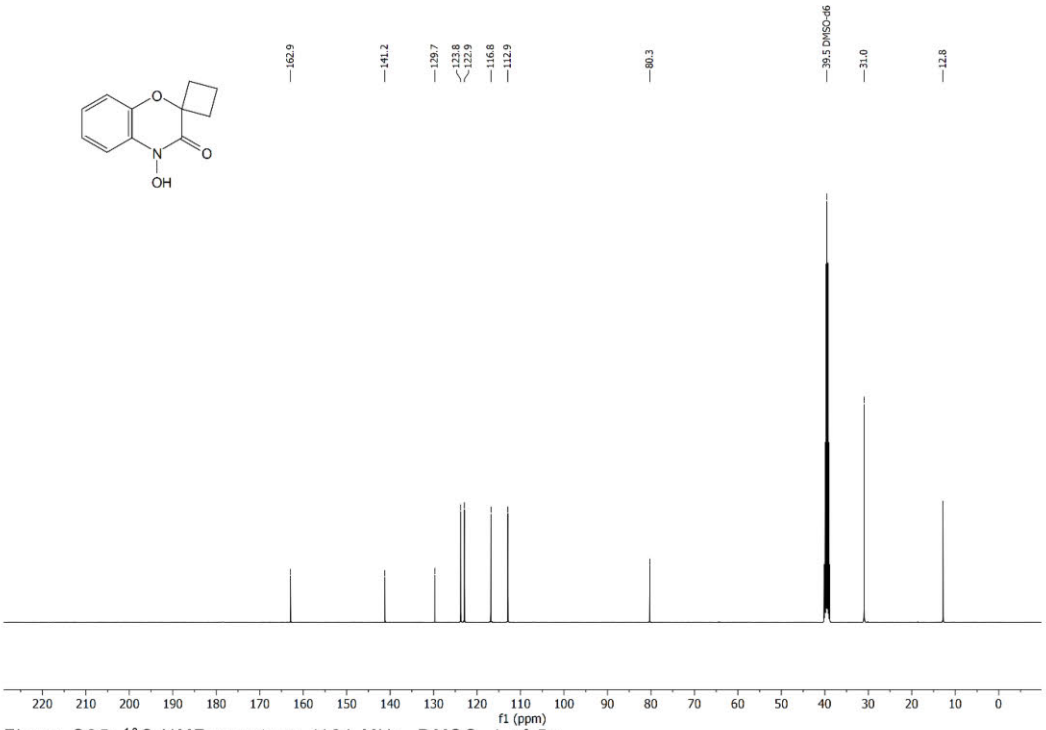


Figure S95: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5e**.

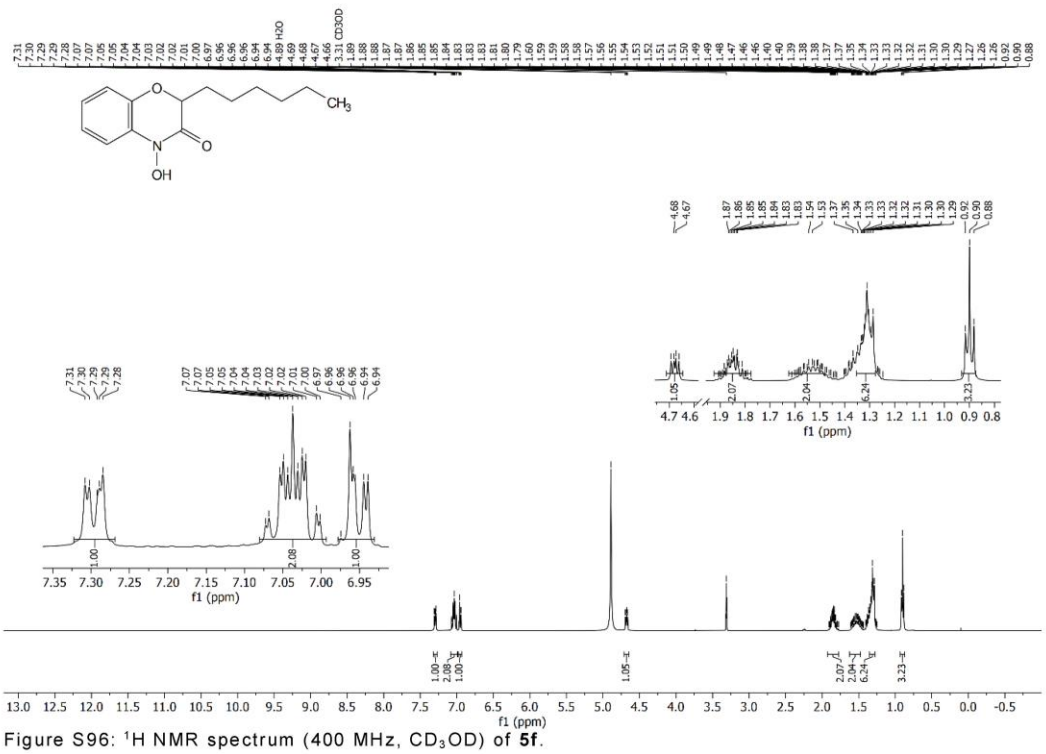


Figure S96: ^{1}H NMR spectrum (400 MHz, CD_3OD) of **5f**.

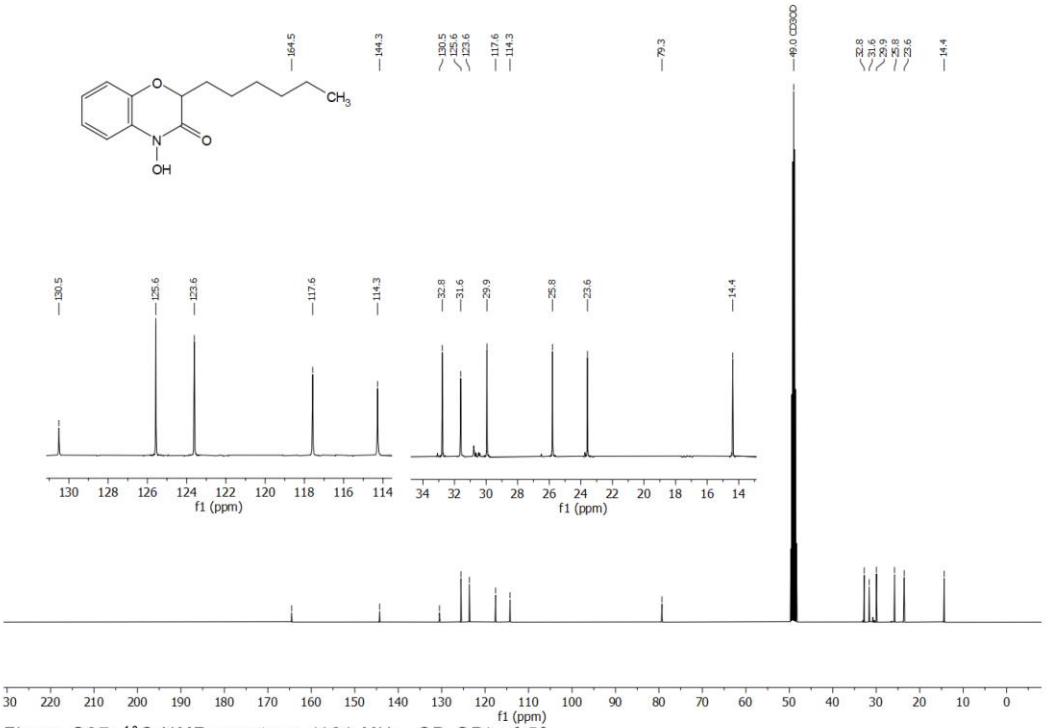


Figure S97: ^{13}C NMR spectrum (101 MHz, CD_3OD) of **5f**.

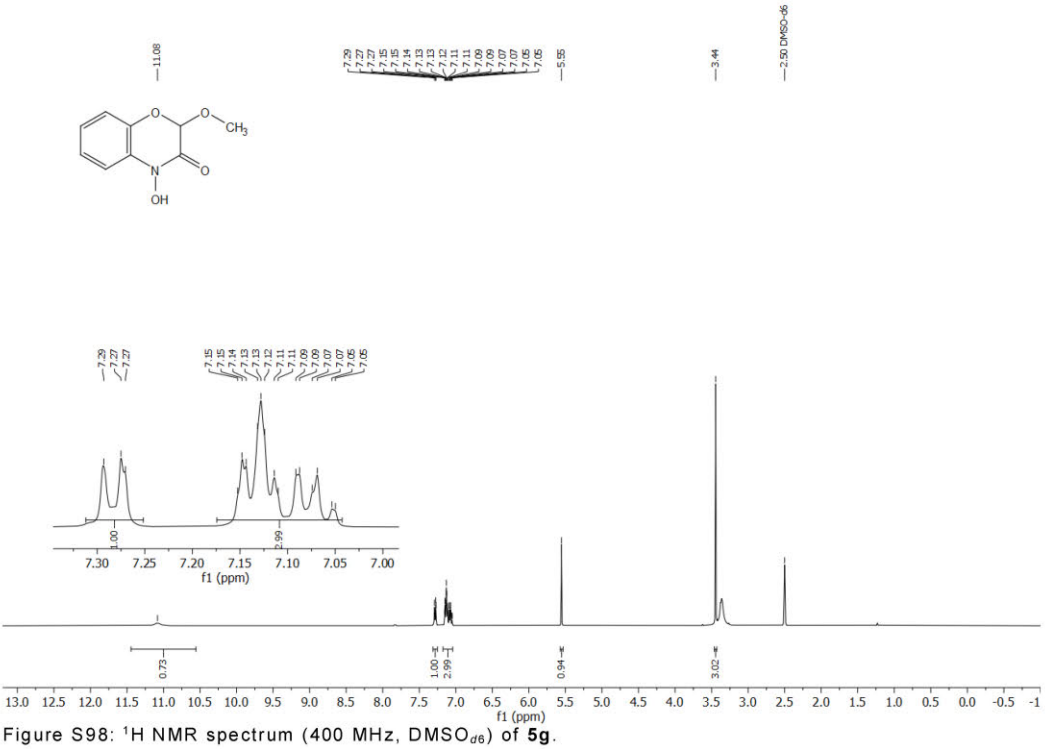


Figure S98: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5g**.

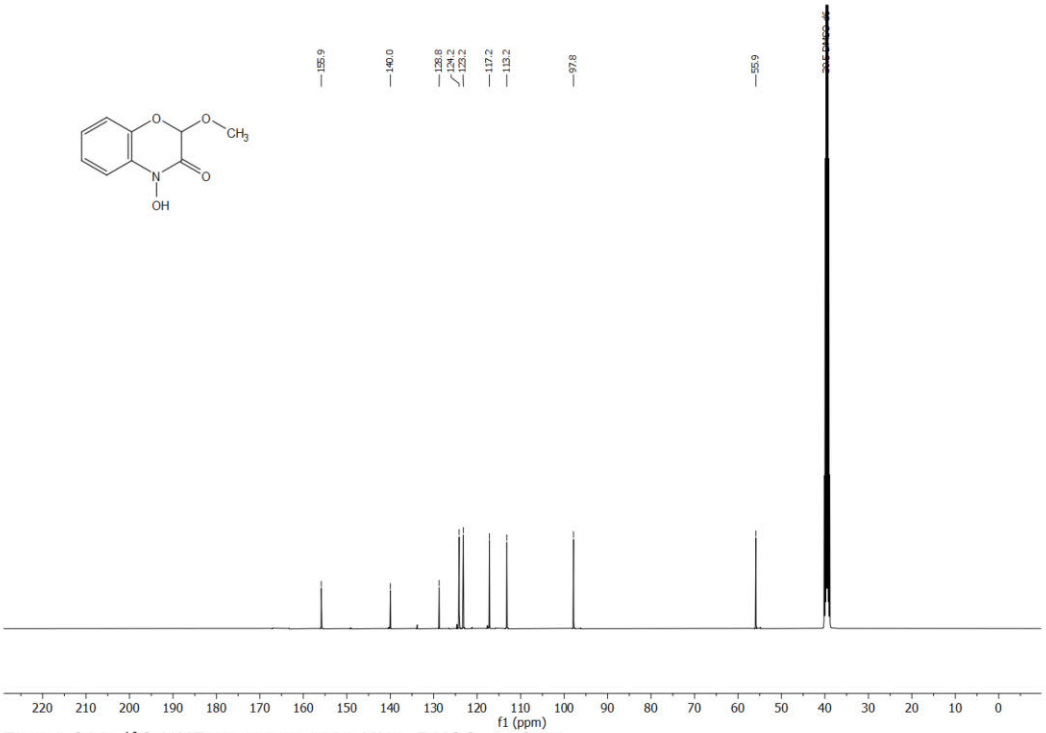


Figure S99: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5g**.

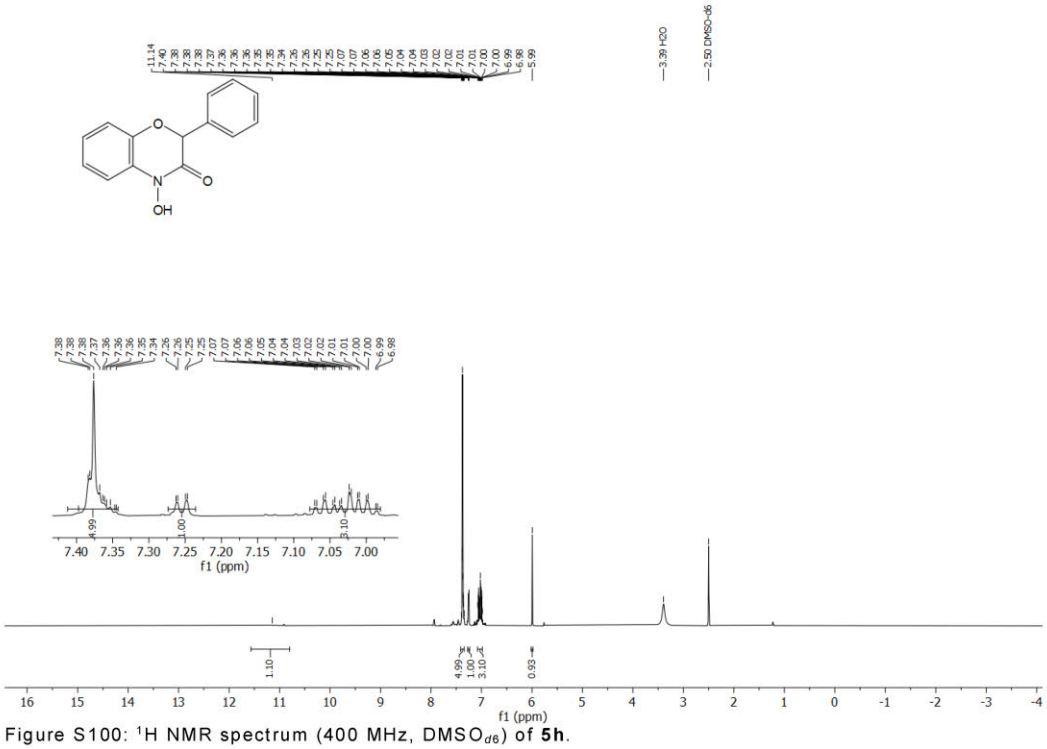


Figure S100: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5h**.

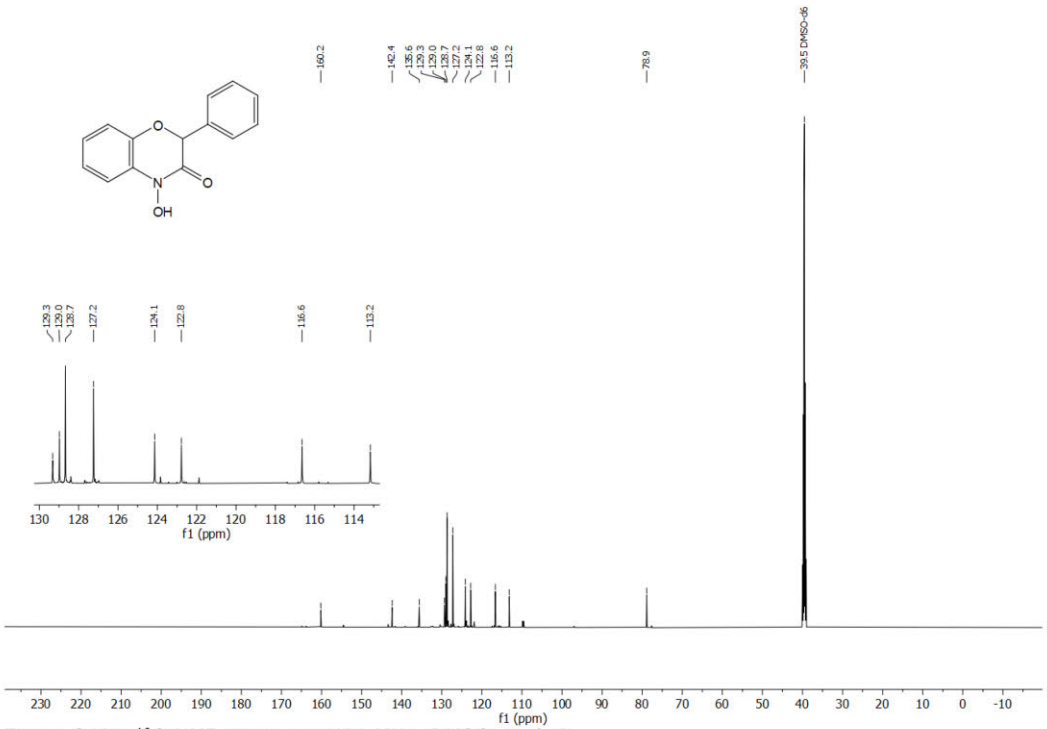


Figure S101: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5h**.

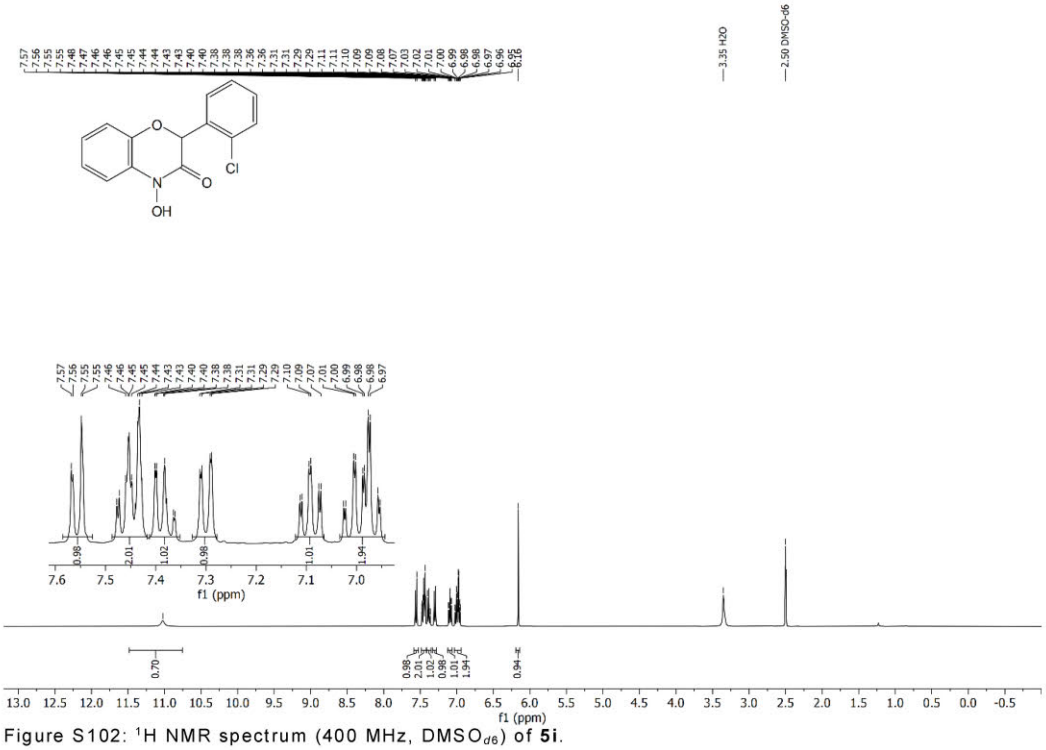


Figure S102: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5i**.

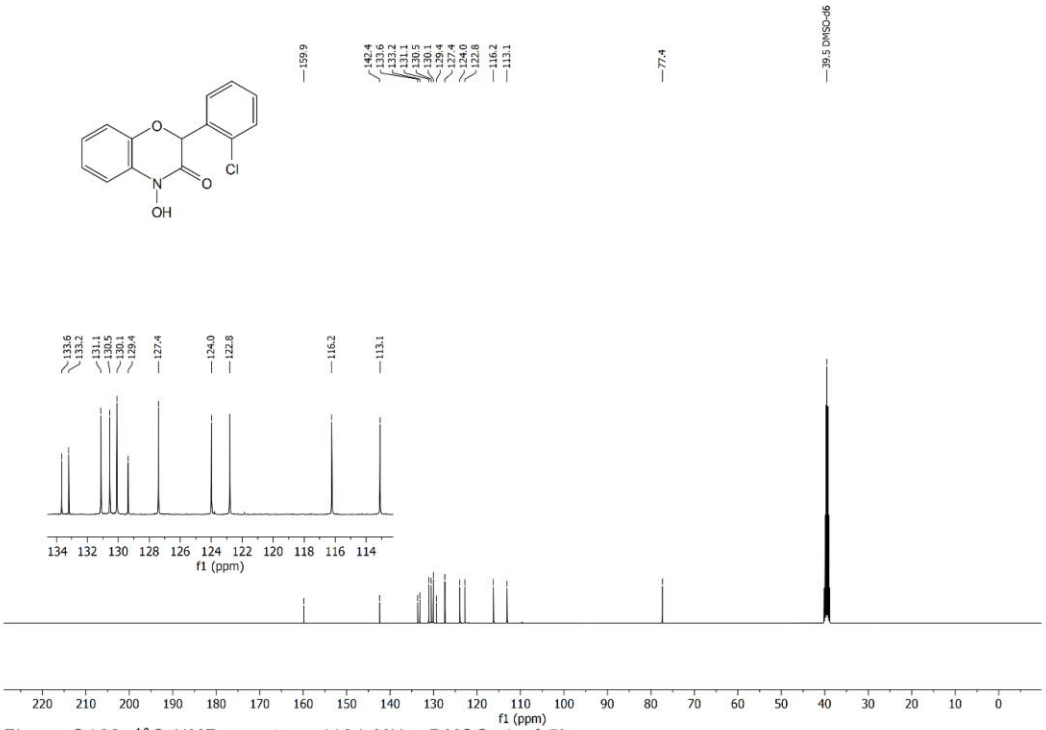


Figure S103: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5i**.

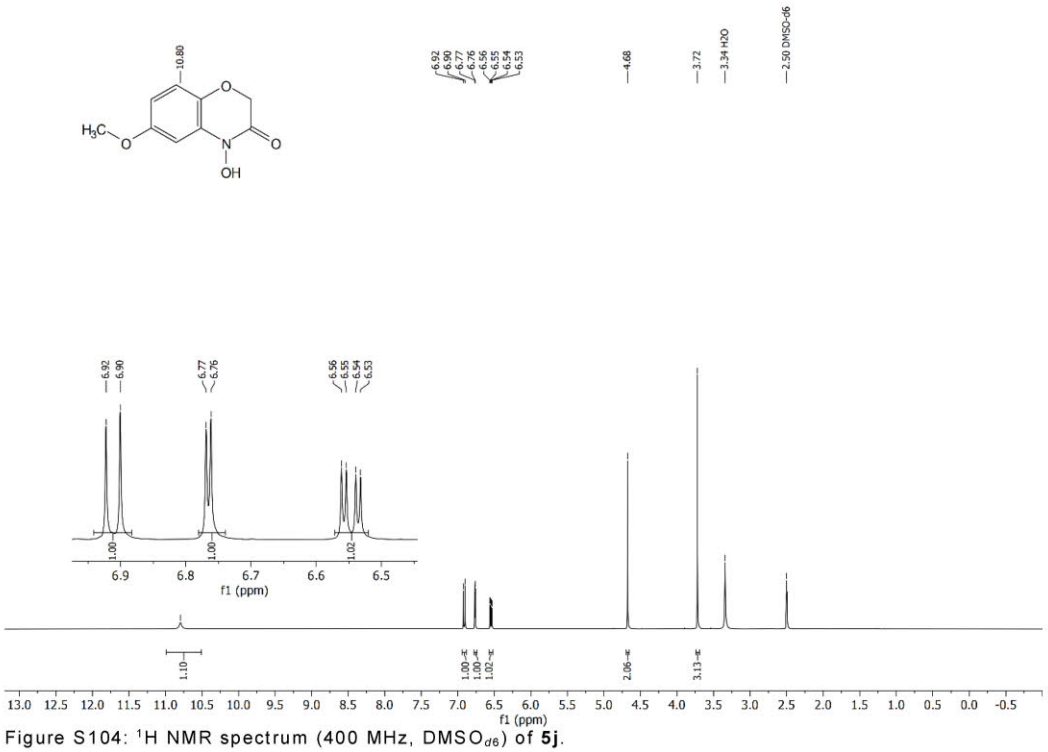


Figure S104: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5j**.

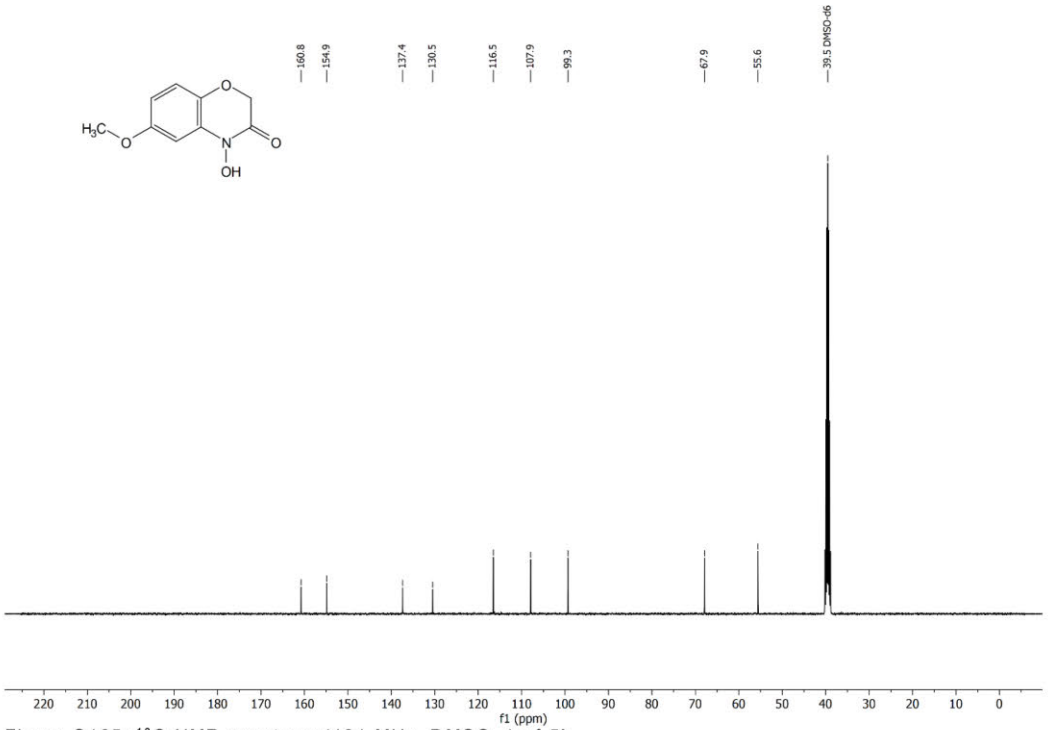


Figure S105: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5j**.

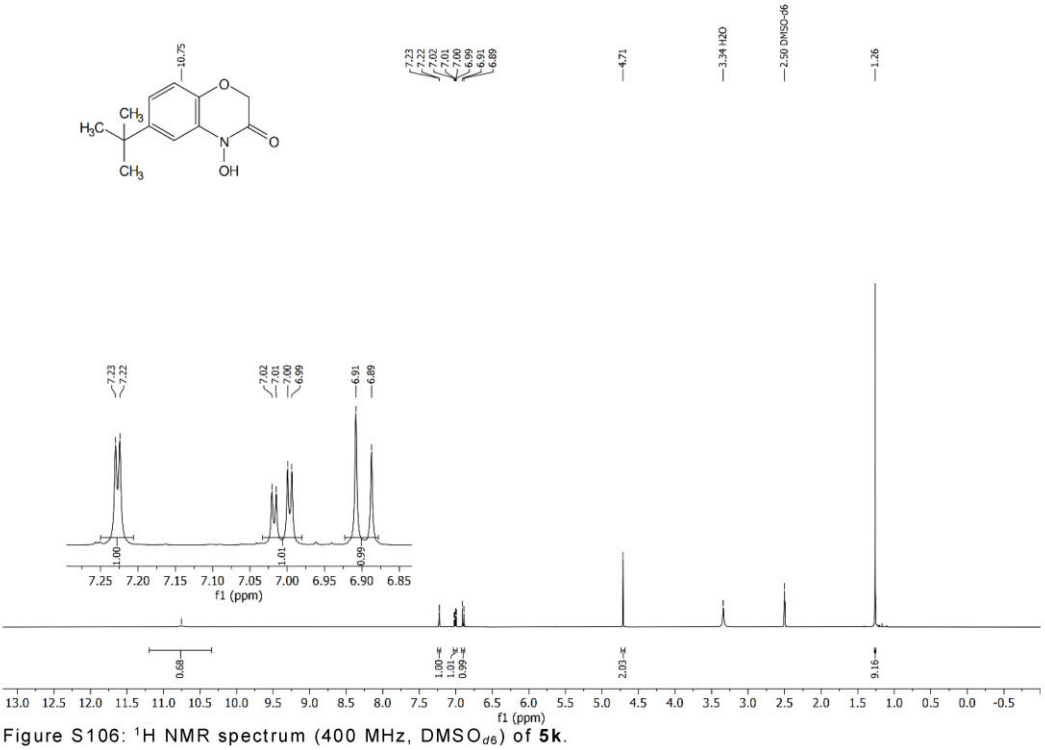


Figure S106: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5k**.

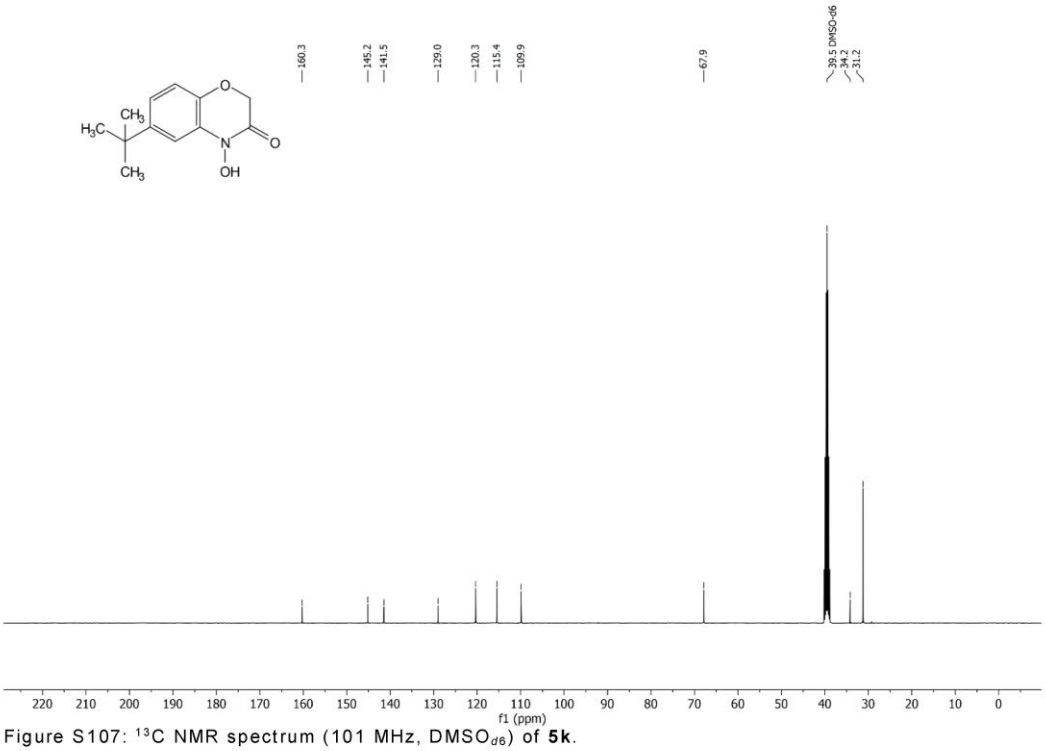


Figure S107: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5k**.

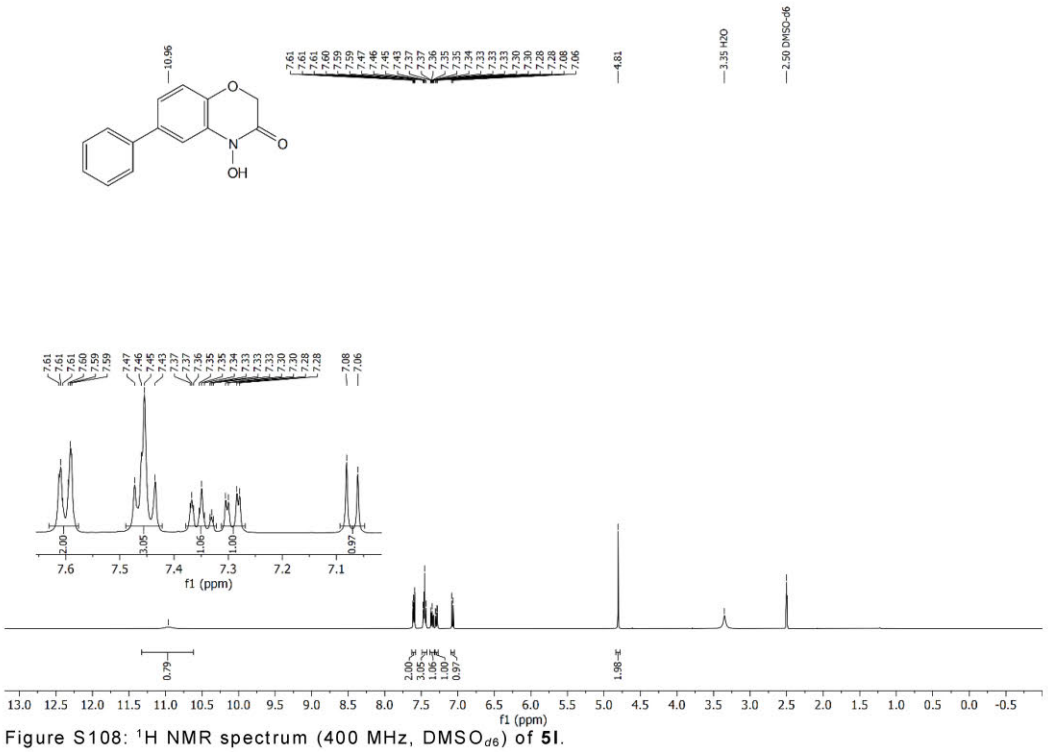


Figure S108: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5l**.

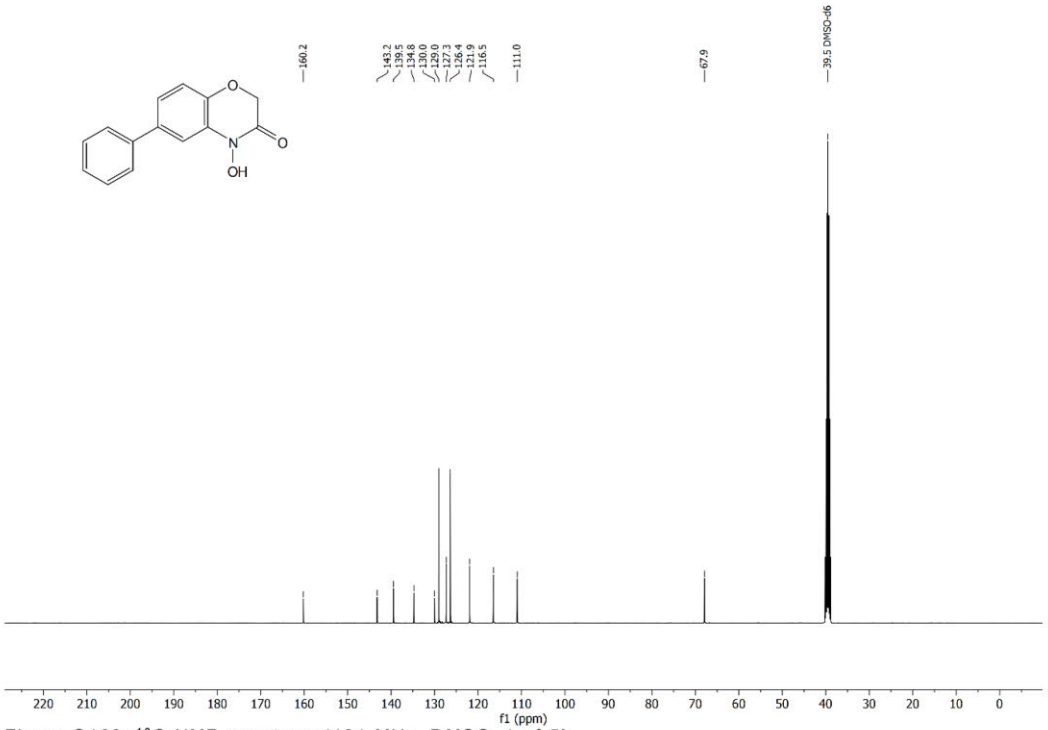


Figure S109: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5l**.

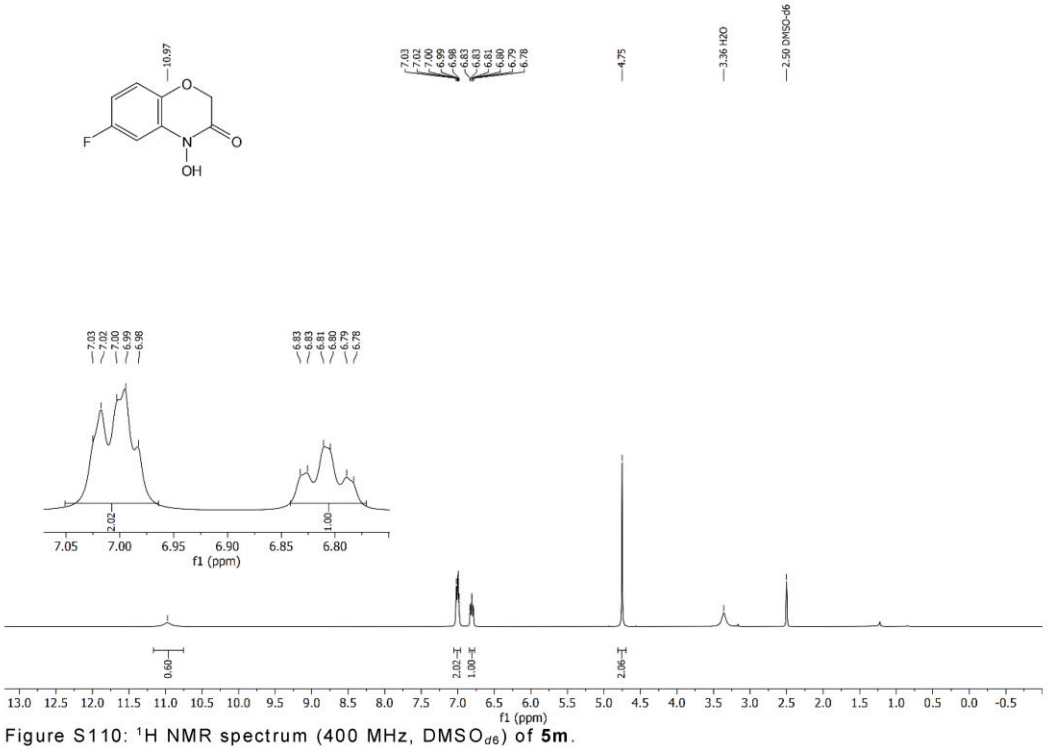


Figure S110: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5m**.

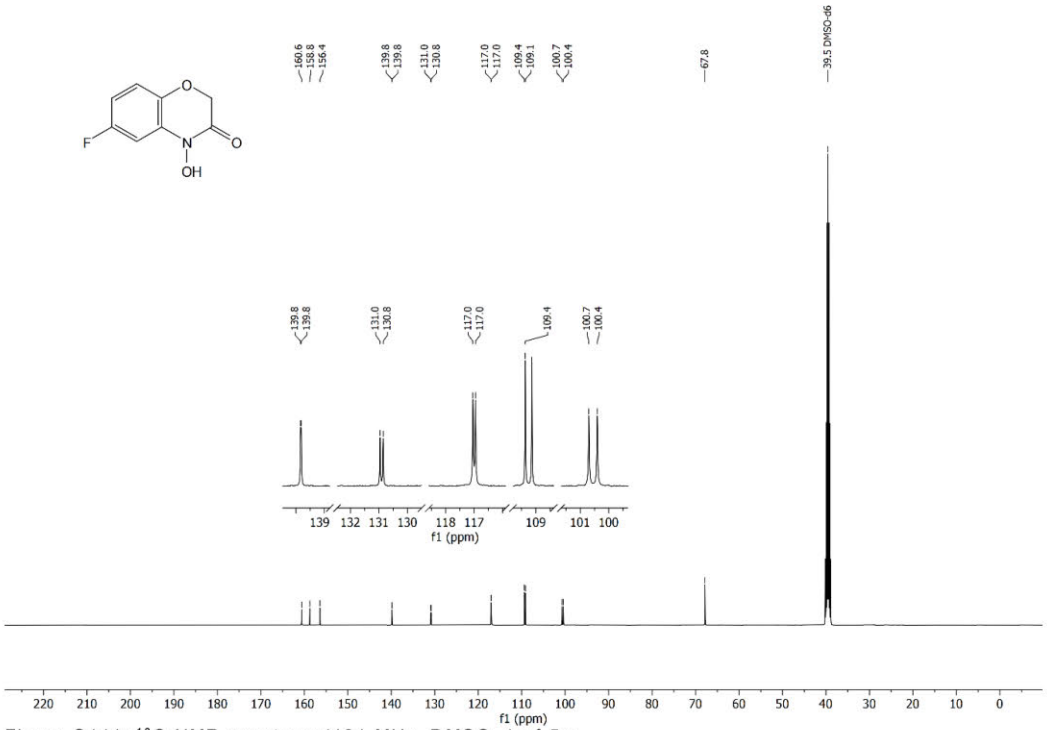


Figure S111: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5m**.

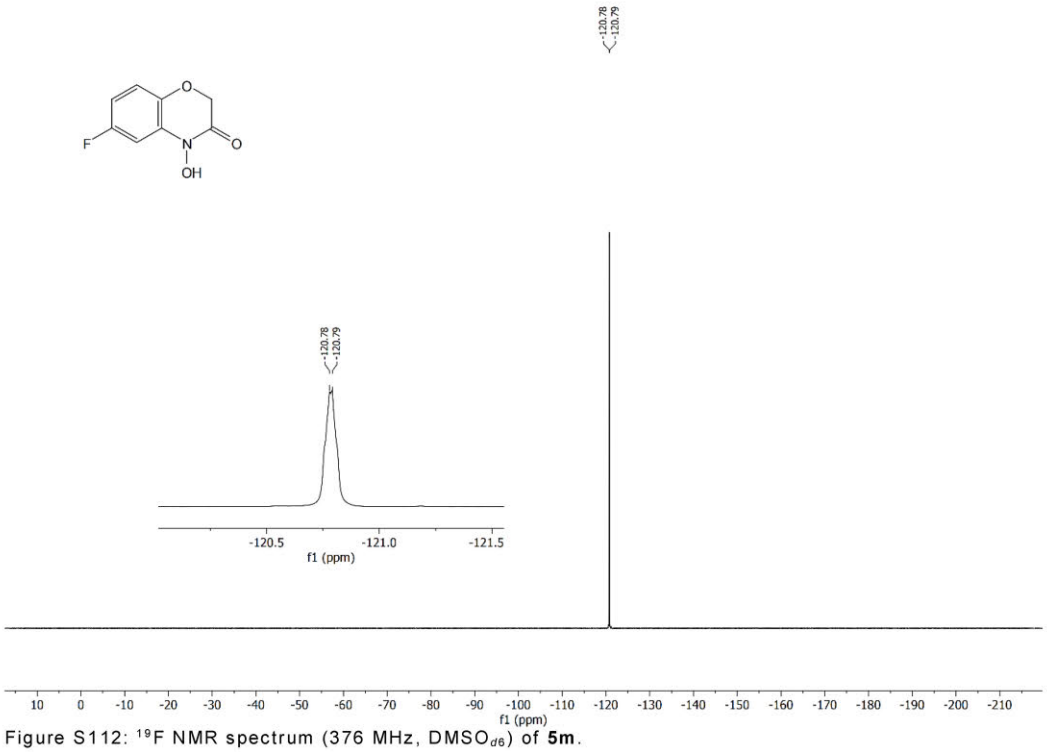


Figure S112: ^{19}F NMR spectrum (376 MHz, $DMSO_{d6}$) of **5m**.

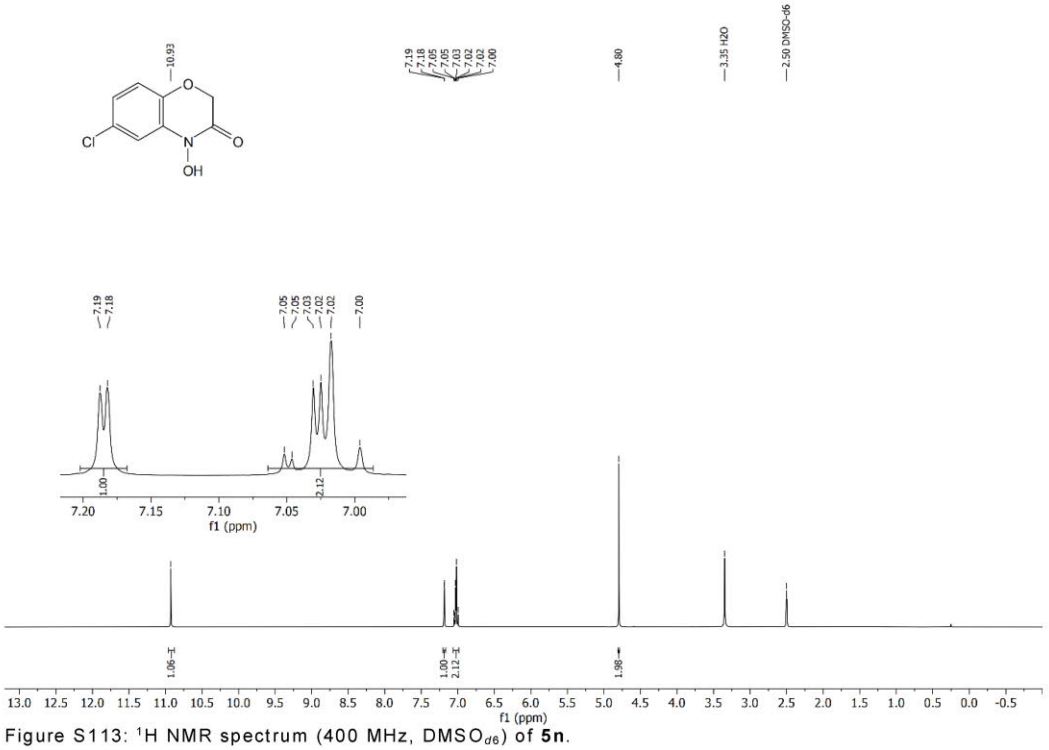


Figure S113: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5n**.

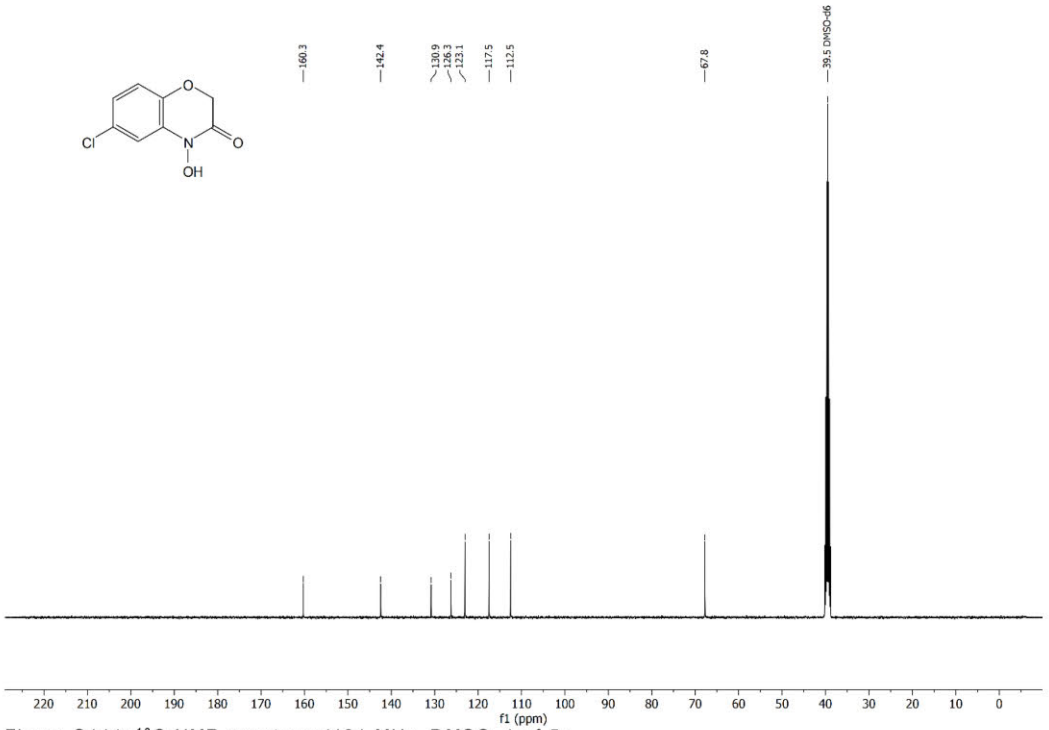


Figure S114: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5n**.

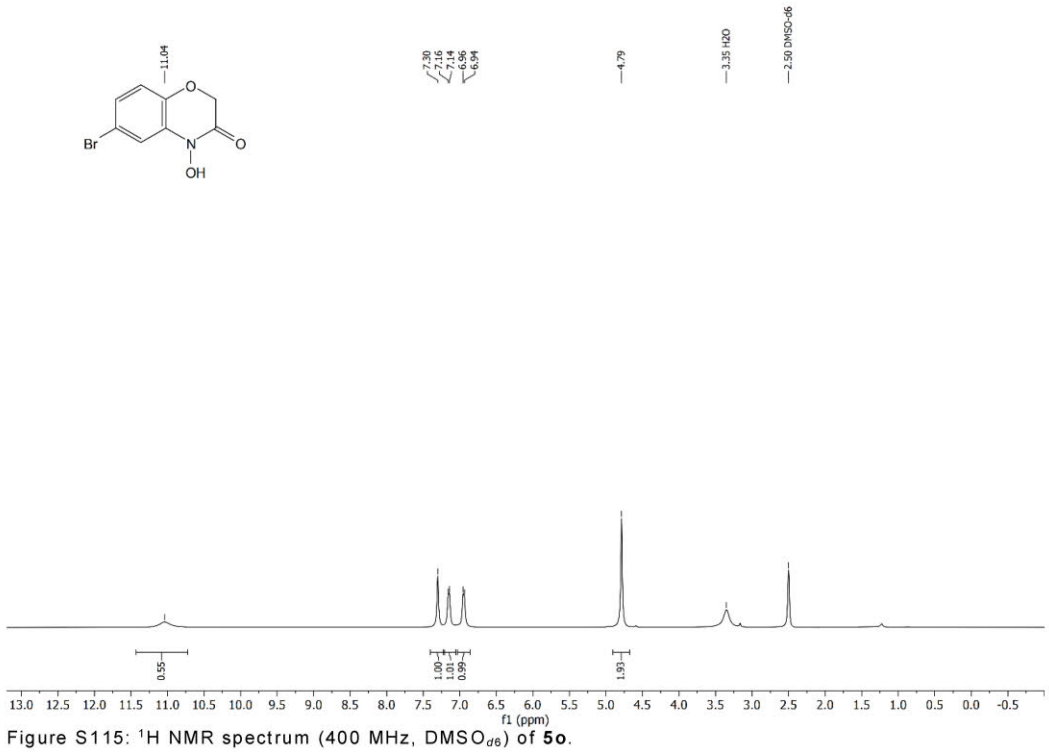


Figure S115: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5o**.

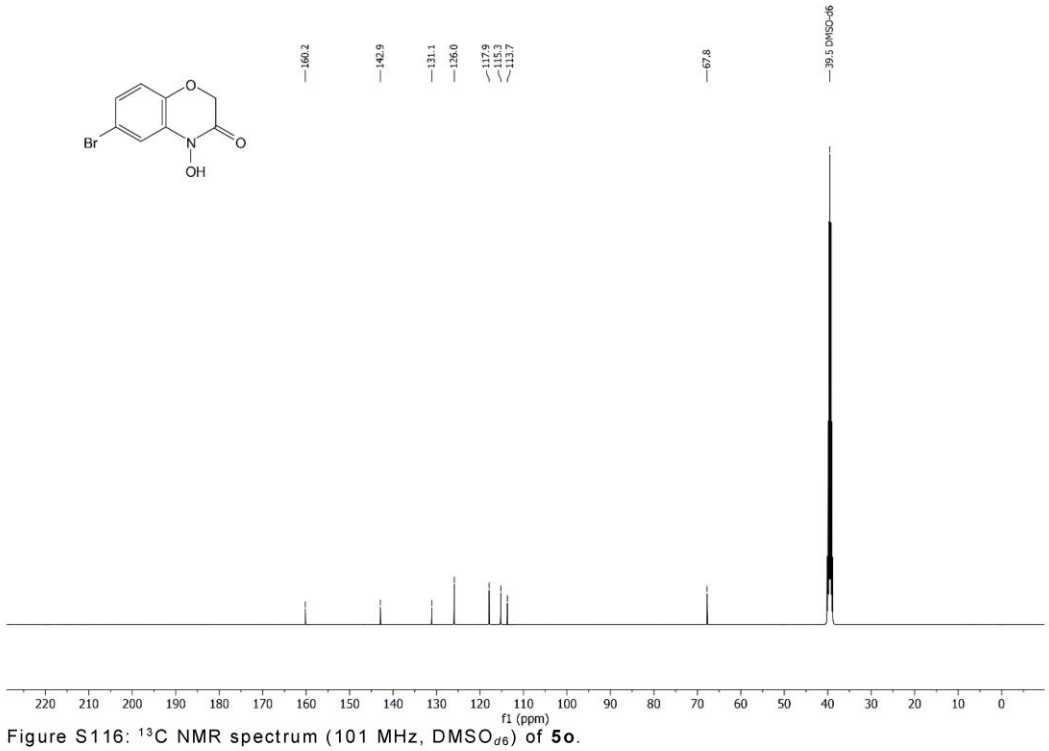


Figure S116: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5o**.

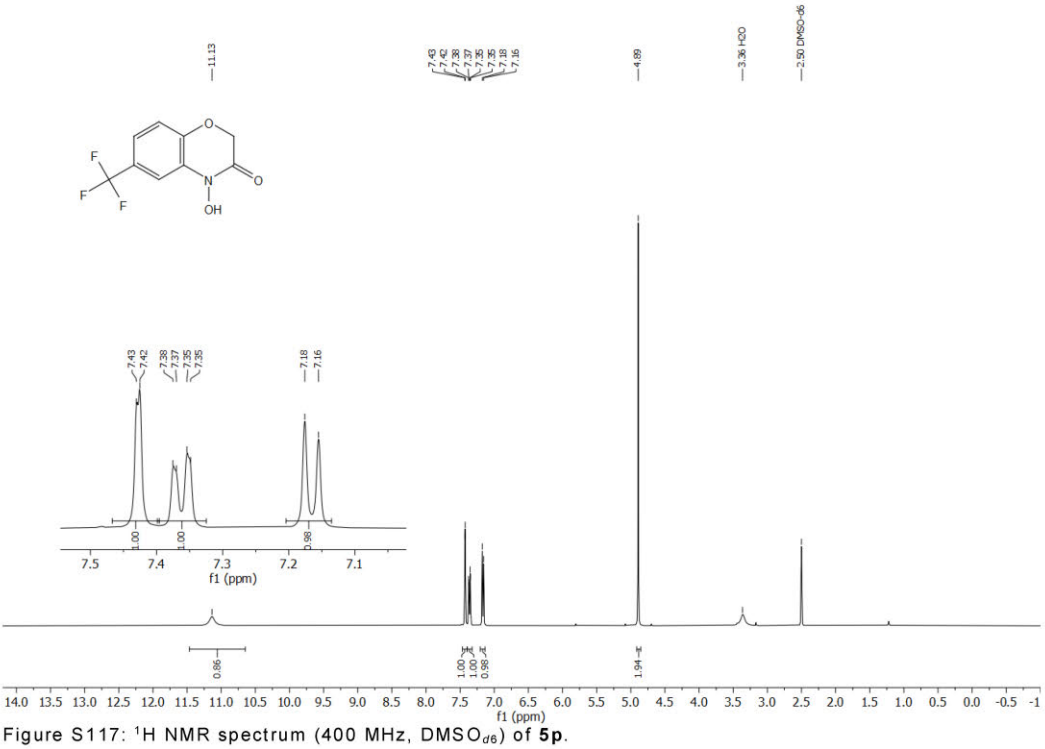


Figure S117: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5p**.

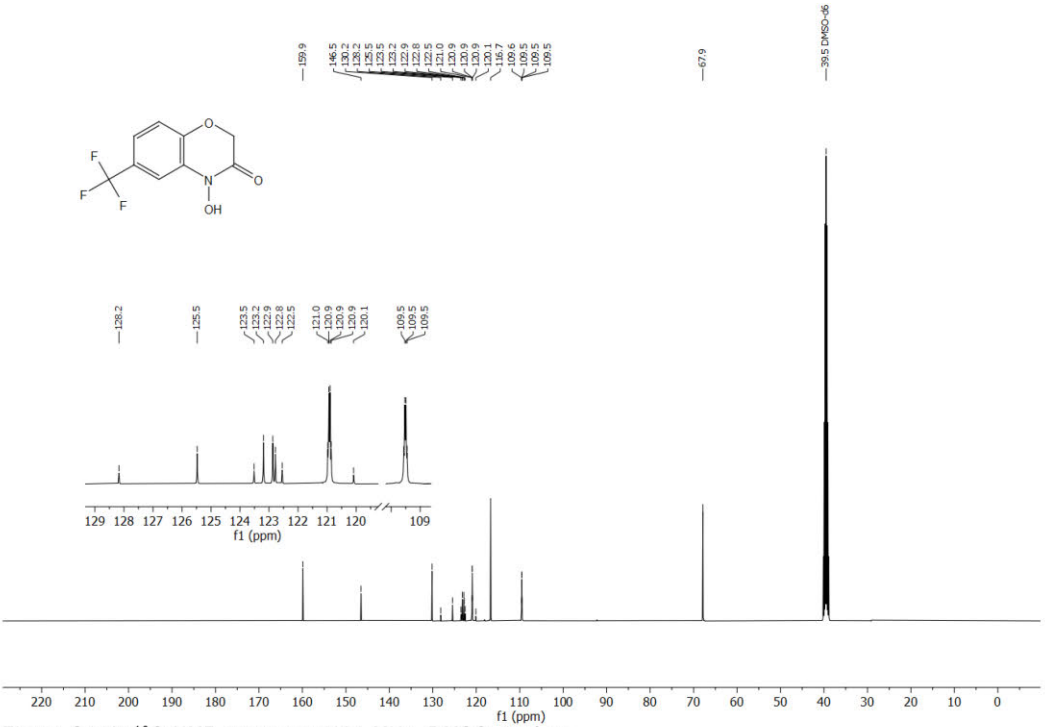


Figure S118: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5p**.

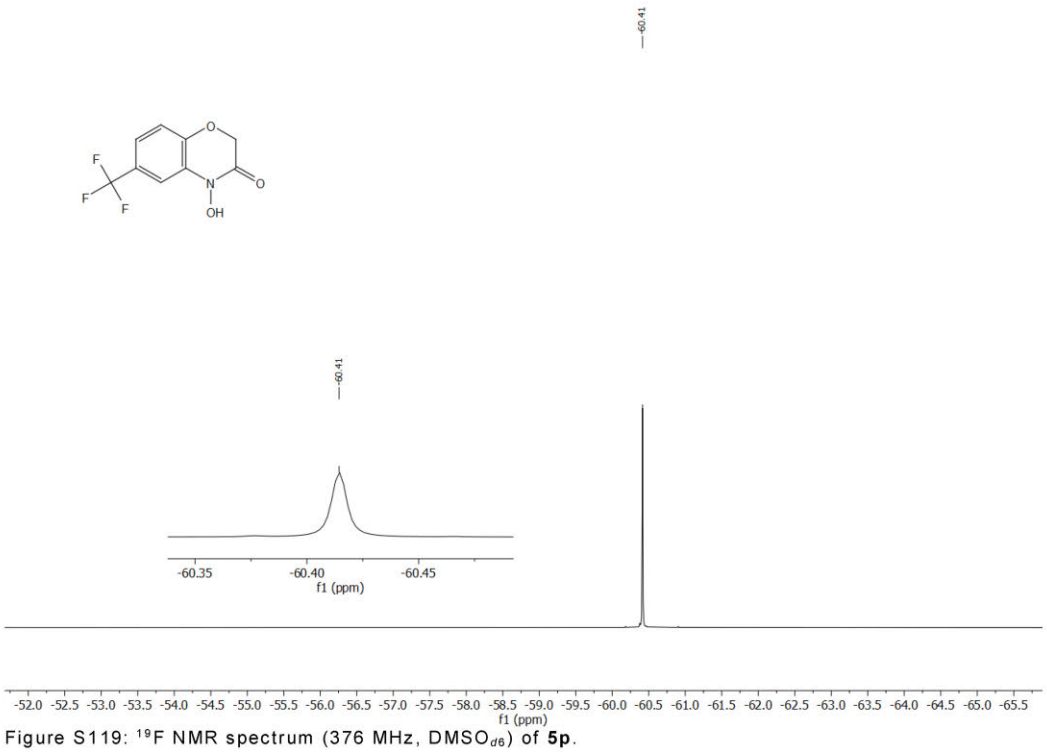


Figure S119: ^{19}F NMR spectrum (376 MHz, $DMSO_{d6}$) of **5p**.

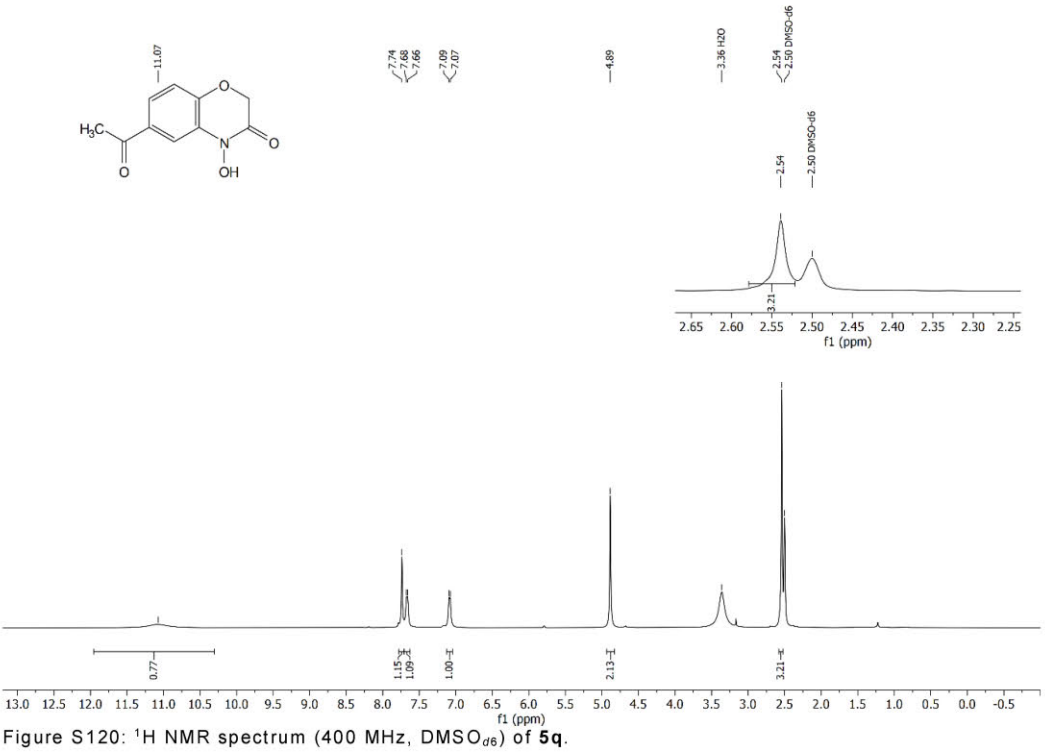


Figure S120: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5q**.

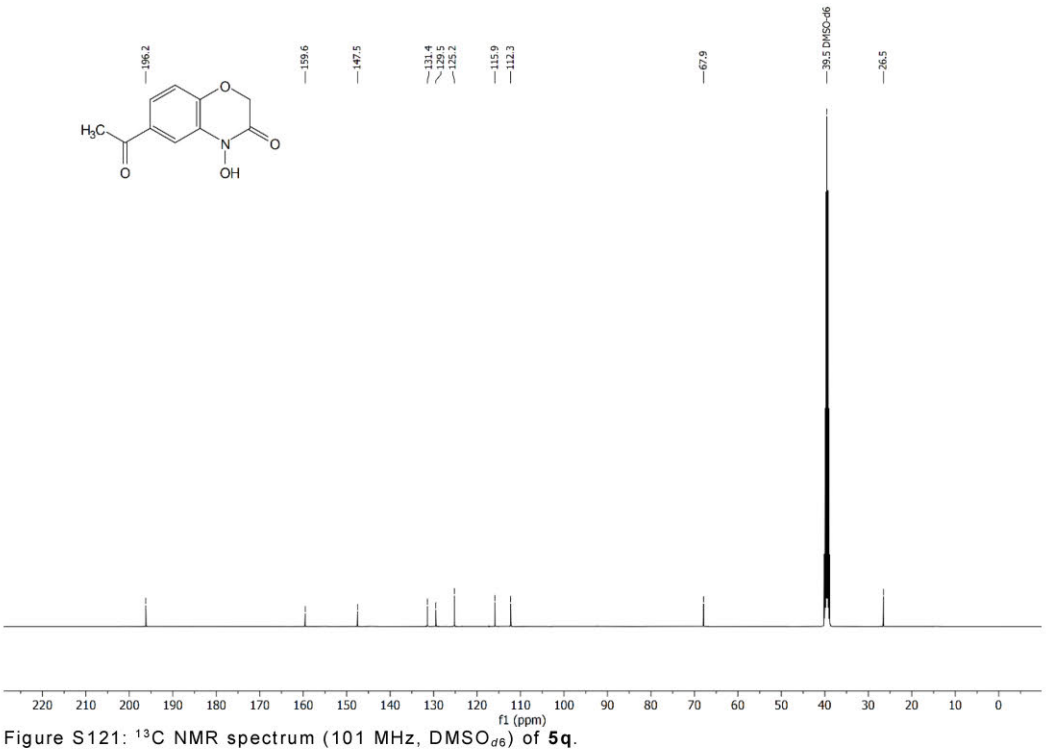


Figure S121: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5q**.

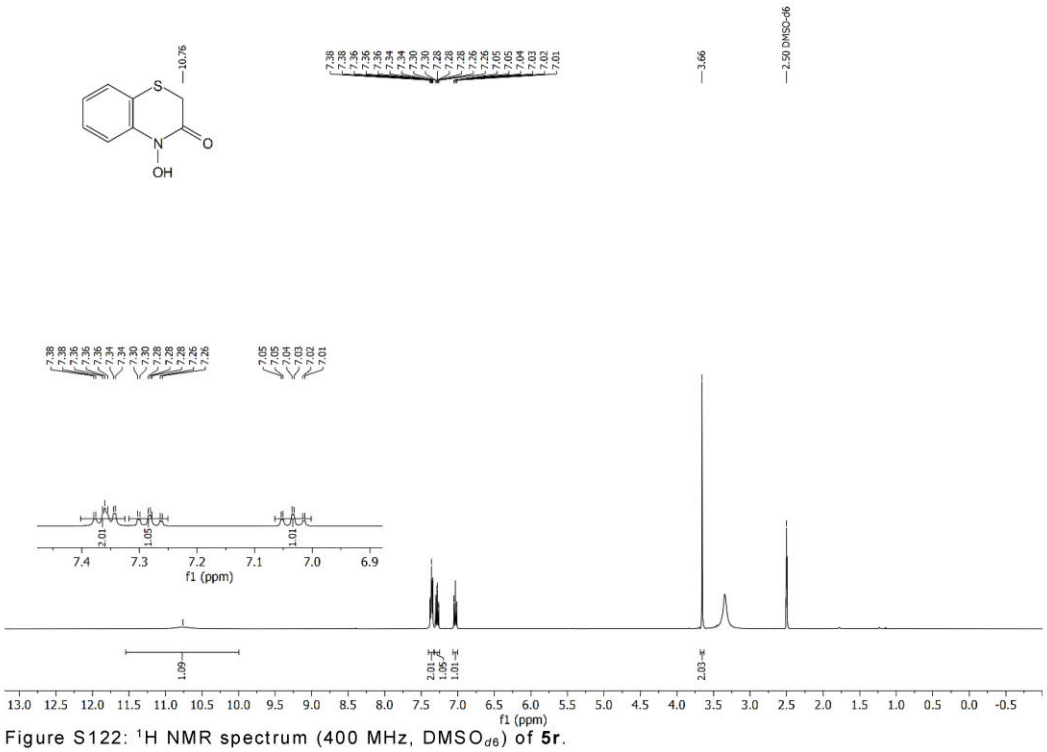


Figure S122: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5r**.

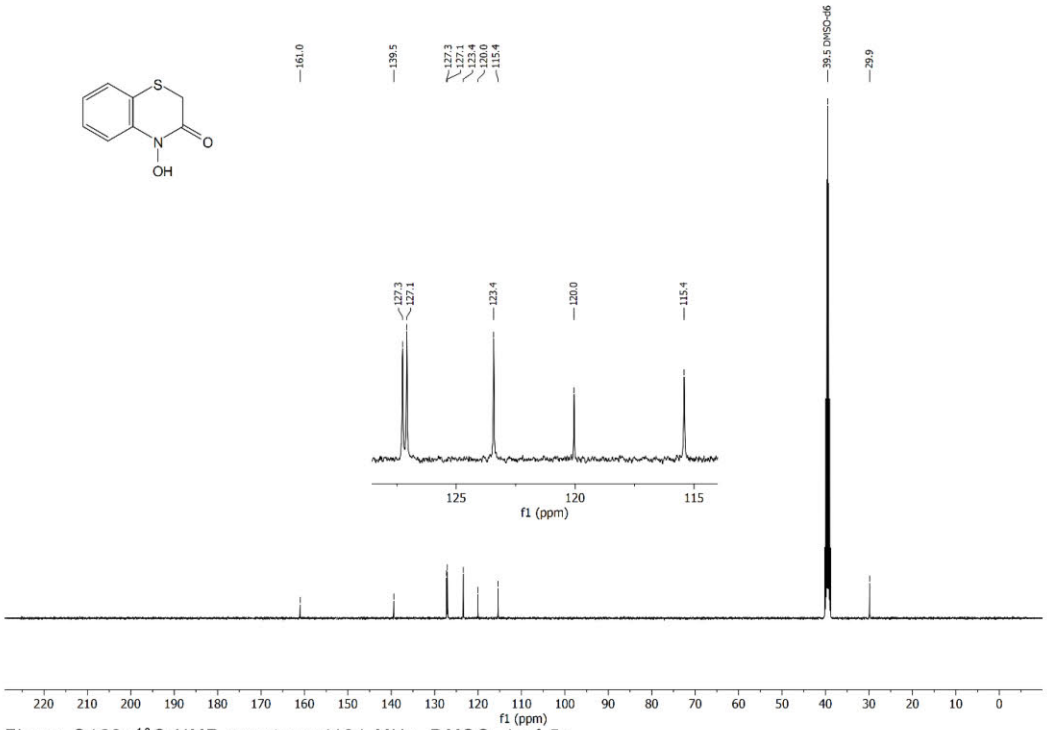


Figure S123: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5r**.

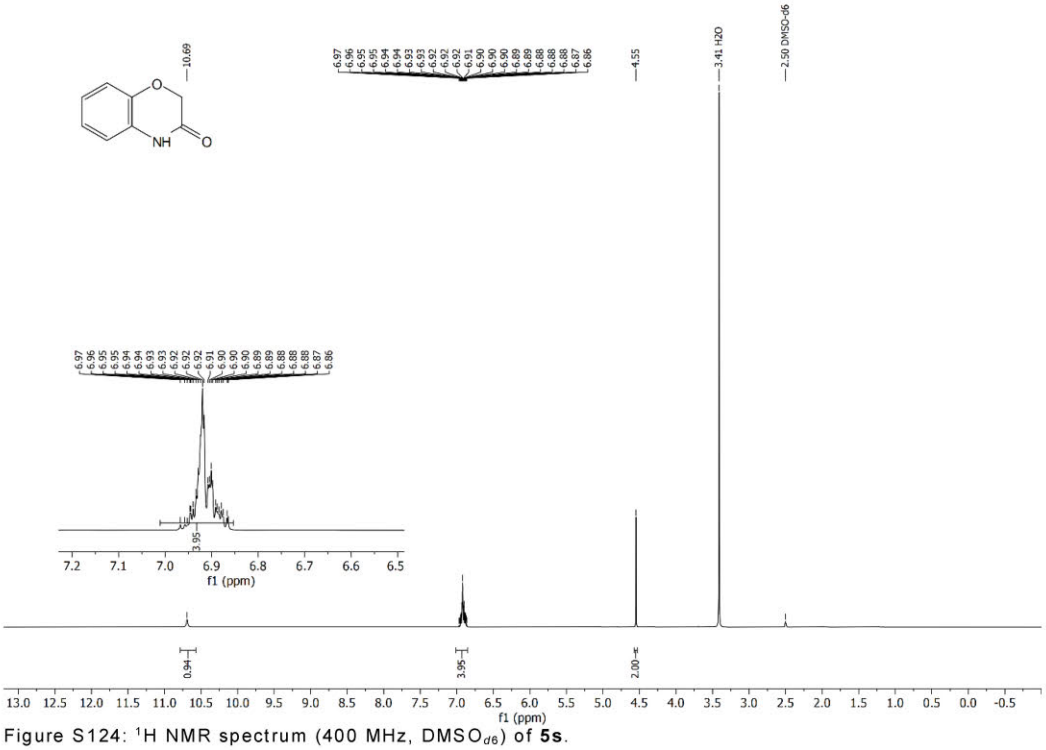


Figure S124: ^{1}H NMR spectrum (400 MHz, $DMSO_{d6}$) of **5s**.

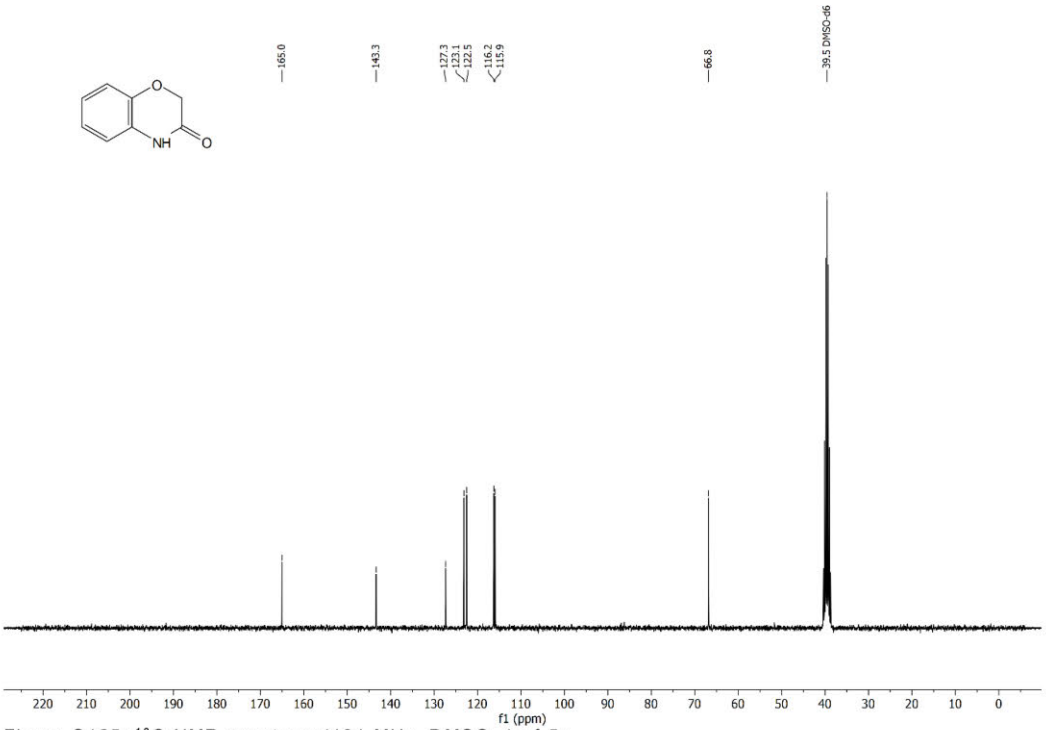


Figure S125: ^{13}C NMR spectrum (101 MHz, $DMSO_{d6}$) of **5s**.

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A-2.7 Book Chapter: Electrochemical Heterocyclic Ring Formation Reactions by Making C-N and N-N Bonds

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