New Synthetic Strategies towards Indolizines and Pyrroles

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To my family

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

Ac	Acetyl
Bt	Benzotriazole
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl anion
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl acetylenedicarboxylate
DMA	*N*,*N*-Dimethylacetamide
DMF	*N*,*N*-Dimethylformamide
DNA	Deoxyribonucleic acid
EDG	Electron-donating group
ESI	Electrospray ionization
esp	Espionate; α,α,α′,α′-tetramethyl-1,3-benzenedipropionic acid
EWG	Electron-withdrawing group
FDA	Food and drug administration
GC	Gas chromatography
HMBC	Heteronuclear multiband coherence
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence
Hz	Hertz
IBCF	Isobutyl chloroformate
IR	Infrared
KHMDS	Potassium hexamethyldisilazane
LC	Liquid chromatography
LDA	Lithium diisopropylamide
LED	Light-emitting diode

LIST OF ABBREVIATIONS

MS	Mass spectrometry
NMM	*N*-Methylmorpholine
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
oct	Octanoate
PDE	Phosphodiesterase
ppm	Parts per million
REWG	Removable electron-withdrawing group
RNA	ribonucleic acid
rt	Room temperature
TBAB	Tetrabutylammonium bromide
TBAI	Tetrabutylammonium iodide
Tc	Thiophene-2-carboxylate
TEA	Triethylamine
Tf	Triflyl; trifluoromethanesulfonyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Trimethylsilyl
TOF	Time-of-flight
Ts	Tosyl

1 Introduction

1.1 Nitrogen Containing Heteroaromatic Compounds

Nitrogen heterocycles are the most common molecular scaffolds that can be found in nature. They can be considered as vital structures for the chemistry of living organisms.[1] For example, pyrimidine and purine which are the building blocks of DNA and RNA are two important mono- and bicyclic heteroaromatic compounds.[2] Besides, three of the twenty proteinogenic amino acids; namely histidine, tryptophan, and proline contain N-heterocyclic motifs (Figure 1). Imidazole and indole are two N-heteroaromatic structures that are found in the former two, respectively.[1]

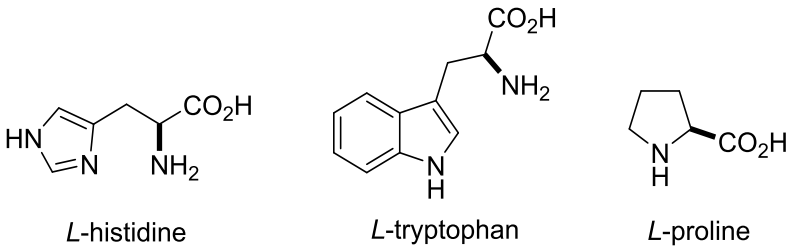


Figure 1. Amino acids with N-heterocycles

When considering the existence of N-heterocycles in nature, it is inevitable that medicinal chemists pay special attention to this class of compounds. A recently published report[3] analyzed that 59% of unique small-molecule drugs approved by the Food and Drug Agency (FDA) in the United States contains at least one nitrogen heterocycle. While the majority of N-heterocycles are five- and six-membered rings, around 40% of them are aromatic. Figure 2 shows the top five aromatic and non-aromatic N-heterocycles.

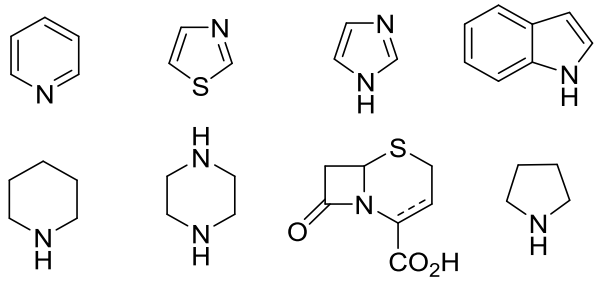


Figure 2. Common aromatic and non-aromatic N-heterocycles in small-molecule drugs

Pyridine and piperidine are the most common structures among aromatic and non-aromatic N-heterocyclic compounds, respectively. In addition to their pharmaceutical use, nitrogen

containing heteroaromatic compounds have many applications in materials science as well.[4-7]

1.2 Indolizines

Indolizine is a bicyclic heteroaromatic compound and analogue of indole. It can also be described as a fused heterocycle which is the combination of an electron-deficient pyridine and an electron-excessive pyrrole by overlapping of two C-N bonds from each ring (Figure 3).[8]

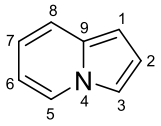


Figure 3. Structure of the indolizine

This fully conjugated 10π-system was first described by Angeli in 1890.[9] Twenty-two years later, the first synthesis of the unsubstituted indolizine was accomplished by Scholtz.[10] Since its discovery, indolizine had been called pyrrocoline, pyrrole[1,2-a]pyridine, pyrindole, and pyrrodine. The term indolizine was first suggested by Tschitschibabin and has been used by German and Japanese scientists.[11] Although the non-fused indolizines have not been found in nature,[12] some natural products contain the indolizine skeleton (Figure 4).

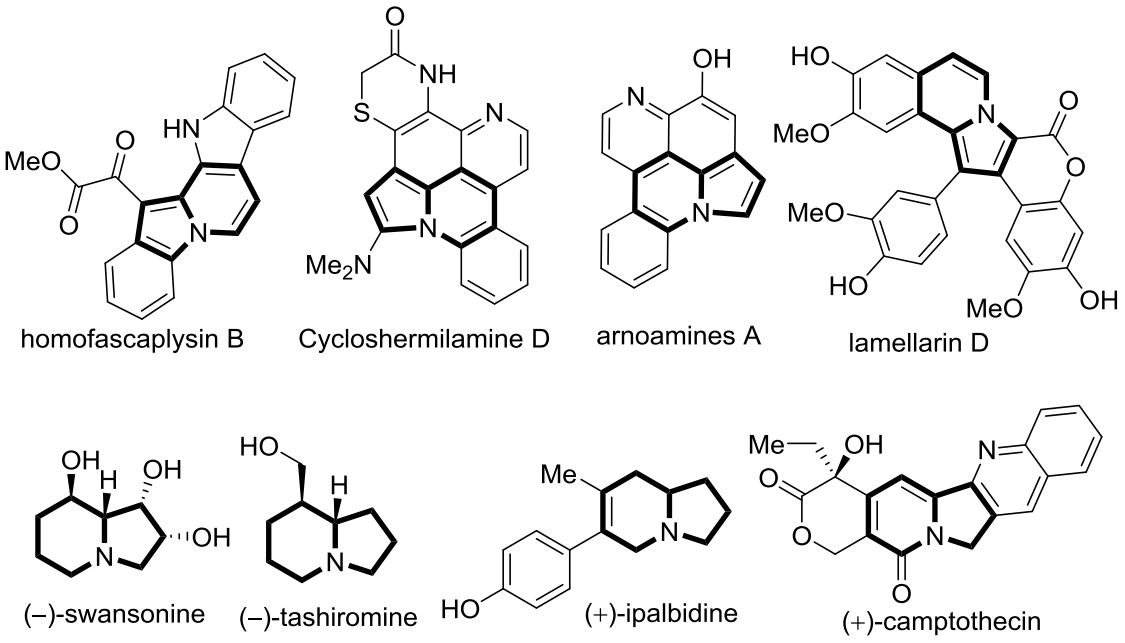


Figure 4. Indolizine framework found in natural products

On the other hand, partially reduced forms of indolizines are quite common in nature. For instance, camptothecin isolated from a stem of the Chinese tree *Camptotheca acuminate* [13] selectively inhibits DNA topoisomerase I.[14]

The most abundant form of indolizines are the fully saturated structures which are also known as indolizidine alkaloids. These alkaloids were isolated from a myriad of sources e.g. frogs, ants, plants, fungi, trees, etc.[15] They exist as simple alkaloids such as mono- and disubstituted indolizidines, phenanthroindolizidines, or polyhydroxylated indolizidines. Swainsonine is one of the most studied polyhydroxylated indolizidine alkaloids which inhibits glycosidase hydrolase.[16]

Indolizines, bioisosteric analogues of indoles, can be considered as privileged structures since they possess 30 different biological activities in the MDRR™ database including G-protein coupled receptors (GPCR) binding and modulation of DNA-protein interactions.[17] In addition to natural products, synthetic indolizines also possess many biological activities[12,18] such as anti-tubercular,[19-21] anti-cancer,[22] aromatase[23] and phosphodiesterase[24-26] inhibitors, herbicidal,[27] anti-histaminic,[28] and anti-inflammatory[29] (Figure 5). These properties makes indolizines much more attractive for both medicinal and synthetic chemists.

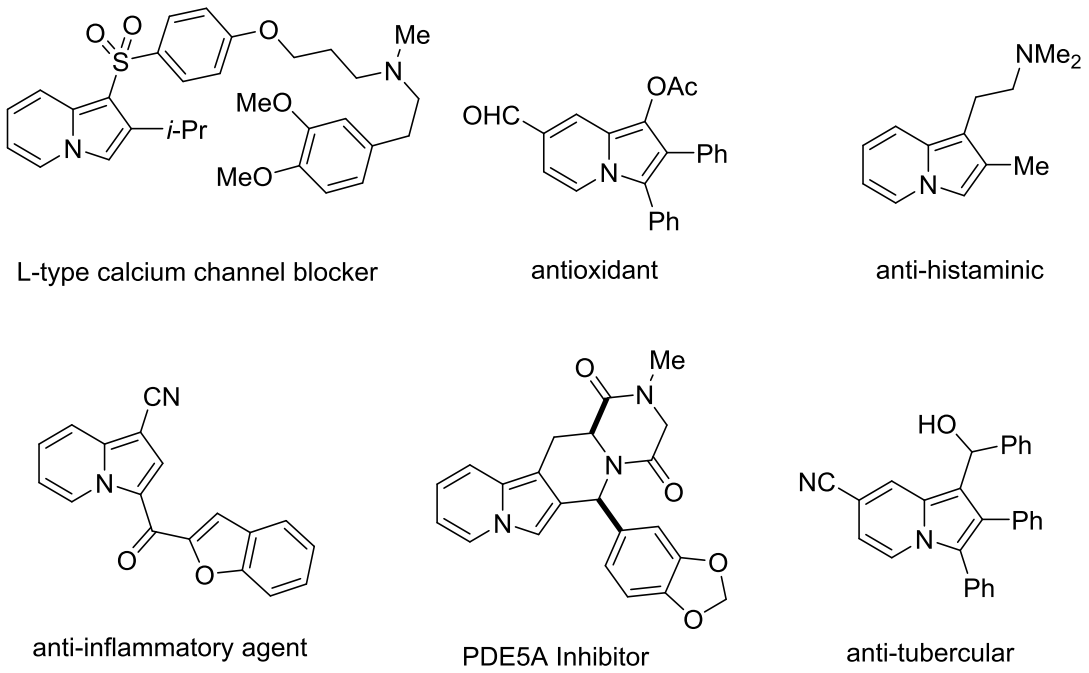


Figure 5. Some examples of bioactive indolizines

1.2.1 Synthesis of Indolizines

Many different approaches have been developed to access the indolizine skeleton.[30,31] They can be divided into two general groups based on the ring formation/annulation (Figure 6). The first group is the annulation of pyridines to indolizines via forming the pyrrole unit. Annulation of pyrroles to indolizines is the second group. While the former is the largest group, few examples exist for the latter comparing to the other.

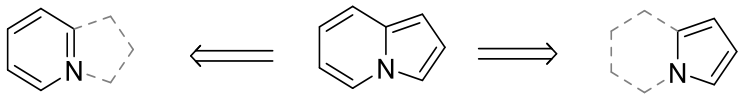
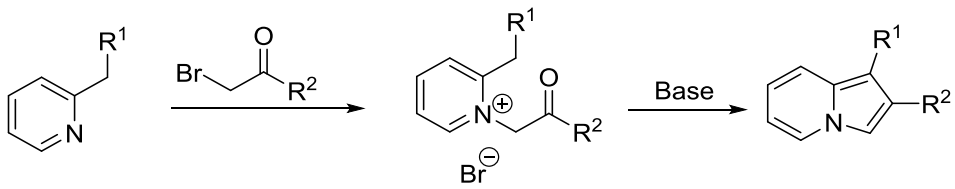


Figure 6. Two different approaches to indolizine framework

1.2.1.1 Annulation of Pyridines

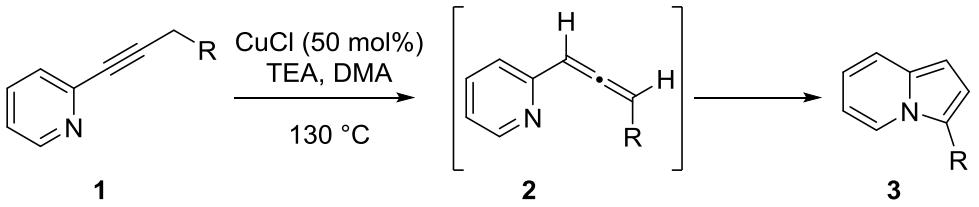
Among many approaches to indolizines, Tschitschibabin's route is still one of the simplest and most efficient way since the indolizines can be easily prepared by a quaternization of pyridines with α-halocarbonyl compounds and a subsequent intramolecular cyclization of pyridinium salts in presence of a base (Scheme 1).[32-34] Different bases are effective for this transformation including inorganic salts such as bicarbonates and carbonates in aqueous medium. The method allows to prepare 2-alkyl or aryl substituted indolizines in very high yields. However, introducing a bulky substituent at C-1 and C-3 of indolizines is not favorable or results in low yields.[32]



Scheme 1. Tschitschibabin indolizine synthesis

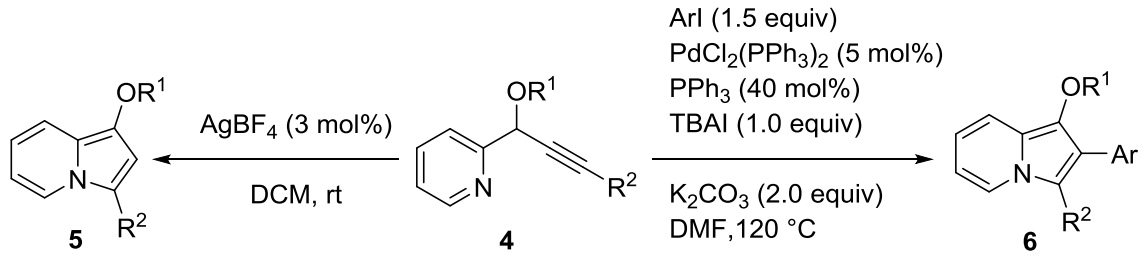
Another powerful way to indolizines is a cycloisomerization of functionalized pyridines. Gevorgyan and co-workers developed the copper-mediated cycloisomerization of 2-alkynylpyridines **1** into indolizines **3** (Scheme 2).[35] The method is not limited to alkynylpyridine but also works with alkynyl imines to access pyrroles. As an application of

this method to a natural product synthesis, (±)-monomorine was synthesized in three steps starting from 2-bromo-6-methylpyridine.



Scheme 2. Cycloisomerization of 2-alkynylpyridines **1**

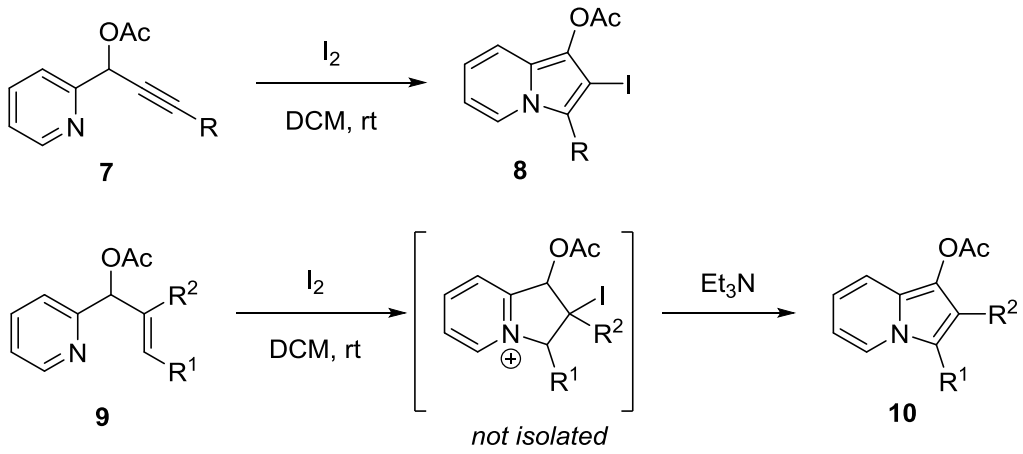
Alternatively, the same group reported the silver-catalyzed cycloisomerization of propargylic ethers or esters **4** to obtain 1,3-disubstituted indolizines **5** (Scheme 3).[36] The reaction proceed well without any ligand or base at room temperature. Later, this method was also extended to 1,2,3-trisubstituted indolizines **6** via a palladium-catalyzed arylation/cyclization sequence.[37] The reaction was proposed to proceed via a 5-endo-dig cyclization of the substrate activated by an ArPdI species. A deprotonation/reductive elimination sequence gives indolizines **6**. Other transition metals such as gold, palladium, platinum, and rhodium also works efficiently in transition metal-catalyzed cycloisomerization of functionalized pyridines.



Scheme 3. Cycloisomerization of propargylic ether or esters **4**

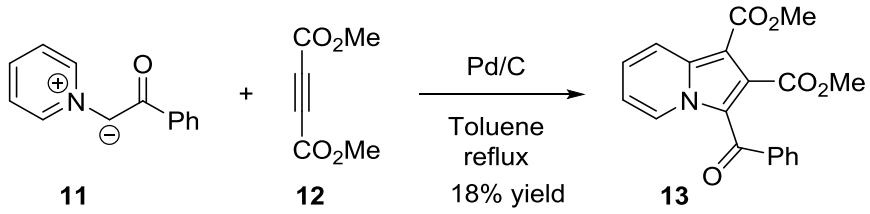
Kim et al. described a metal-free cycloisomerization of propargylic and allylic esters to access indolizines (Scheme 4). When propargylic esters **7** reacted with iodine in DCM at ambient temperature, 2-iodo indolizine **8** was obtained via 5-endo-dig iodocyclization.[38] However, the iodo group always remains at the C-2 position of the indolizine frame. As a complementary work, 1,2,3-trisubstituted indolizines **10** without iodo group were synthesized from allylic esters **9** via a 5-endo-trig iodocyclization/dehydroiodination

sequence.[39] Excess amount of iodine was used for the cyclization and same ratio of the base was added when the cyclization was completed.



Scheme 4. Iodocyclization of propargylic esters **7** and allylic esters **9**

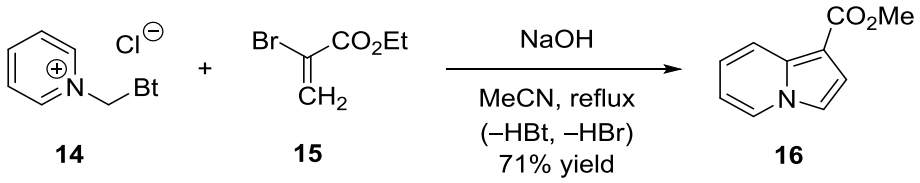
The most common method for the preparation of indolizines from pyridines is a 1,3-dipolar cycloaddition of pyridinium ylides to various dipolarophiles. In 1961, Boekelheide demonstrated a 1,3-dipolar cycloaddition reaction of pyridinium ylide **11** to the activated alkyne **12** in the presence of Pd/C (Scheme 5).[40]



Scheme 5. A 1,3-dipolar cycloaddition of pyridinium ylide **11**

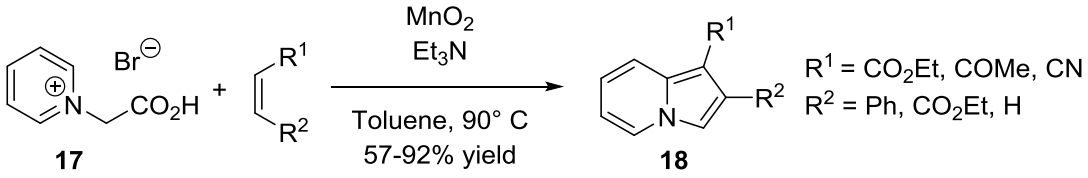
After the above example, many other dipolarophiles such as non-activated alkynes, alkenes, and allenes have been used for the annulation of pyridinium salts since 1961. A 1,3-dipolar cycloaddition of pyridinium ylides to alkenes forms tetrahydroindolizines which are instable and decompose to betaines.[41] Alkenes decorated with leaving groups such as nitro, fluoro, bromo, alkoxy, etc. have been selected in order to re-aromatize cycloadducts by an elimination reaction instead of a dehydrogenation. Katritzky and co-workers developed a 1,3-dipolar cycloaddition/double elimination sequence to prepare indolizines.[42] For

example, indolizine **16** was obtained in 71% yield from pyridinium salt **14** and bromoalkene **15** by base-assisted eliminations of benzotriazole (Bt) and bromo substituents from the corresponding cycloadduct (Scheme 6).



Scheme 6. Indolizine **16** from benzotriazole-stabilized pyridinium salt **14**

In the lack of such leaving groups in the cycloadduct, an oxidant is required in order to obtain stable indolizines. Zhang et al. reported the preparation of 1,2-disubstituted indolizines via a 1,3-dipolar cycloaddition/oxidation sequence.[43] Carboxylic acid substituted pyridinium salts **17** were reacted with activated alkenes in the presence of MnO_2 (Scheme 7). Decarboxylation of the carboxylic acid at C-3 position of the indolizine skeleton gave 1,2-disubstituted indolizines **18** in 57–92% yield. It is also stated that an oxidant is not required when alkynes are used as dipolarophiles.

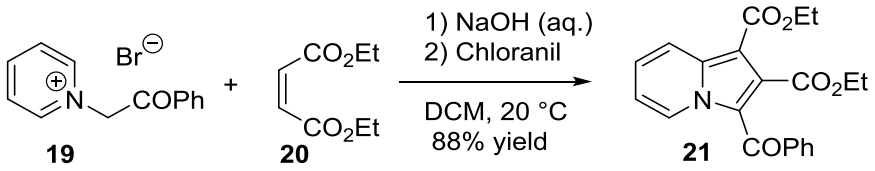


Scheme 7. MnO_2-mediated synthesis of indolizines **18**

Alternatively, tetrakis(pyridine)cobalt(II) dichromate (TPCD) can also be used as an oxidant.[44] Hu and co-workers showed that 1,2,3-trisubstituted indolizines could be synthesized from ester stabilized pyridinium ylides in DMF at 90 °C without decarboxylation.[45] Indolizines were obtained in low yields with TPCD (17–42%).

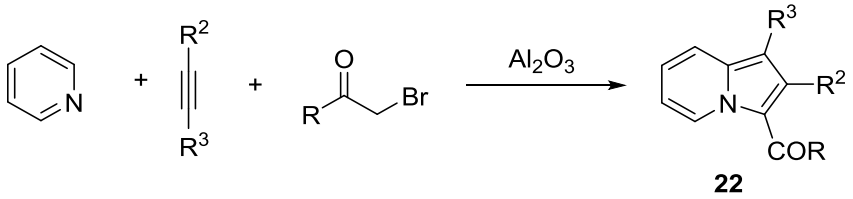
Recently, the chloranil-mediated indolizine synthesis from pyridinium ylides and electron-deficient alkenes were reported by Allgäuer and Mayr.[46] Cycloadduct formed from the 1,3-dipolar cycloaddition of pyridinium salt **19** and alkene **20** in a biphasic environment was oxidized in a one-pot fashion to give indolizine **21** in 88% yield (Scheme 8). When maleonitrile is used as a dipolarophile, the one-pot procedure under biphasic system fails. In

this case, a modified one-pot procedure was applied using Et_3N in DCM instead of an inorganic base in a biphasic medium.



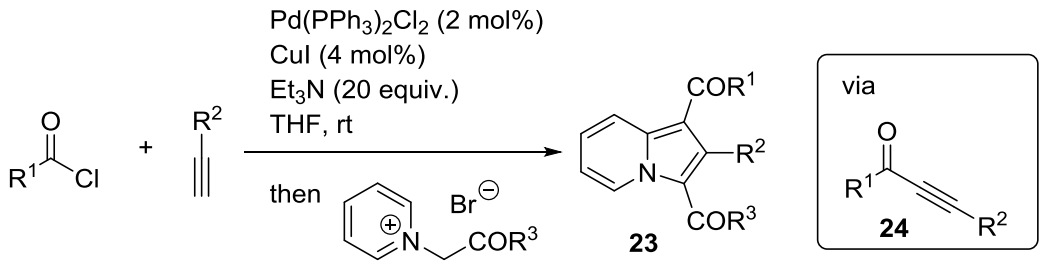
Scheme 8. Stepwise synthesis of indolizine **21** using chloranil

Multicomponent reactions are another way to prepare indolizines from pyridines. Boruah et al. developed an efficient microwave-assisted synthesis of indolizines via a three-component reaction using pyridines, α-haloketones, and alkynes (Scheme 9).[47] Interestingly, indolizines **22** were obtained in excellent yields (87–94%) when reactions were carried out at 250 °C without any solvent. Performing reactions in various solvents such as toluene, THF, and acetonitrile decreases the yield of indolizines **22** (35–45%).



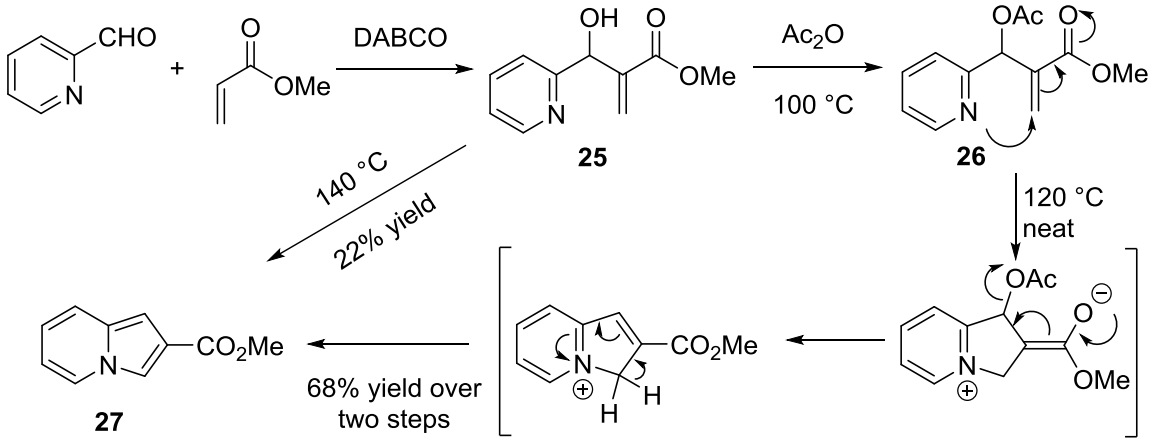
Scheme 9. Three-component approach to indolizines **22**

In 2005, Müller and co-workers demonstrated the three-component reaction of acyl chlorides, terminal alkynes, and pyridinium salts to access indolizines **23** through the formation of ynones **24** (Scheme 10).[48] The consecutive Sonogashira coupling/1,3-dipolar cycloaddition gave indolizines **23** in moderate yields (41–59%).



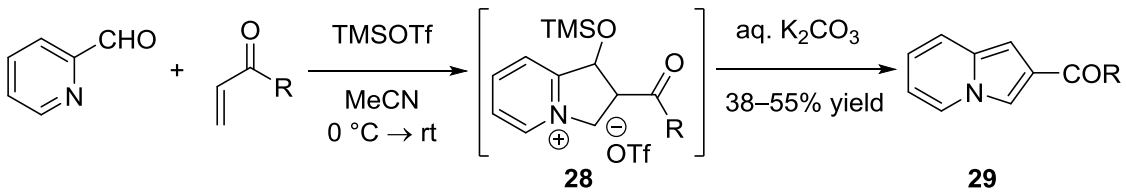
Scheme 10. One-pot synthesis of indolizines **23** via a Sonogashira coupling/cycloaddition

A thermal cyclization of the acetylated Baylis-Hillman adduct of picolinaldehyde and methyl acrylate to obtain indolizine **27** was reported by Bode and Kaye in 1990 (Scheme 11).[49] Direct thermal cyclization/dehydration of the free alcohol **25** gave indolizine only in 22% yield.



Scheme 11. Thermal cyclization of Baylis-Hillman adduct **25**

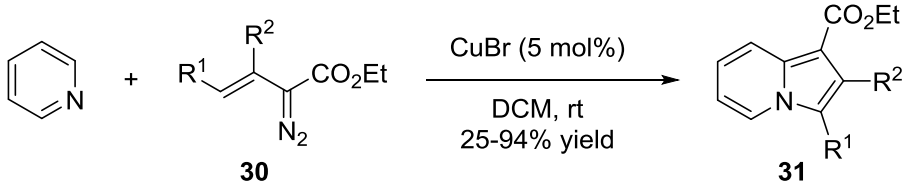
Later, Basavaiah et al. described the one-pot synthesis of 2-carboxyindolizines **29** from a picolinaldehyde and enones via an electrophile-induced Morita Baylis-Hillman reaction (Scheme 12).[50] Instead of indolizines, Baylis-Hillman alcohols were obtained when cyclic enones were used that requires an additional dehydration step through an acetylation/deacetylation sequence. Recently, the same group extended this methodology to (pyridin-2-yl) alkyl ketones which were reacted with enones to form 1,2-disubstituted indolizines in moderate yields (20–62%).[51]



Scheme 12. Electrophile induced Baylis-Hillman approach to indolizines **29**

In 2010, an interesting approach towards the synthesis of indolizines from unfunctionalized pyridines was developed by Barluenga and co-workers (Scheme 13).[52] The copper catalyzed annulation of pyridines with diazoesters **30** was achieved in DCM at ambient temperature to

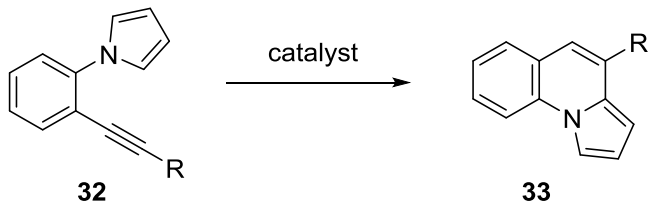
form 1,2,3-trisubstituted indolizines **31** in moderate to high yields (25–94%). It was stated that the method illustrates the first metal catalyzed annulation of π-deficient heterocycles with alkenyldiazo compounds.



Scheme 13. Copper catalyzed annulation of pyridines with diazoesters **30**

1.2.1.2 Annulation of Pyrroles

As previously stated, the synthesis of indolizines from pyrroles is not a very common route compared to pyridines. Benzo-fused indolizines such as pyrrolo[1,2-*a*]quinolines[53,54] and pyrrolo[2,1-*a*]isoquinolines are readily accessible starting from pyrroles. For example, Fürstner and co-workers developed the 6-endo-dig cycloisomerization of 1-arylpyrroles **32** to obtain pyrrolo[1,2-a]quinolines **33** (Scheme 14).[55]

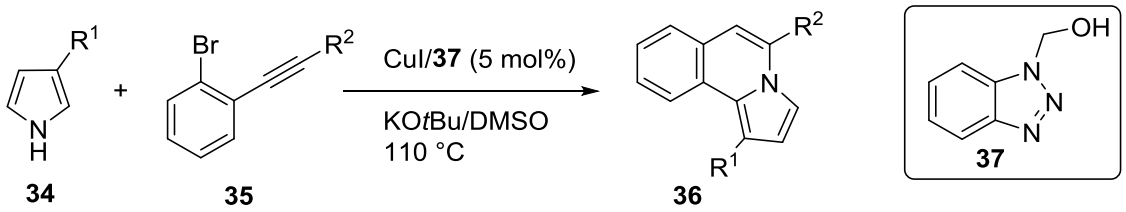


Scheme 14. Cycloisomerization of 1-arylpyrroles **32**

The reaction proceed with $InCl_3$ (5 mol%) or $GaCl_3$ (5 mol%) in toluene at 80 °C smoothly. Although $PtCl_2$ had been used as a catalyst, the yield decreased drastically.[56] The cycloisomerization of 1-arylpyrroles **32** was studied by other groups as well. While Alcarazo et al. developed gold complexes of cyclopropenylylidene-stabilized phosphenium cations for this cycloisomerization reaction,[57] Verma and co-workers demonstrated an access to 4-alkyl 5-iodopyrrolo[1,2-a]quinolines via a 6-endo-dig iodocyclization reaction of 1-arylpyrroles **32**.[58]

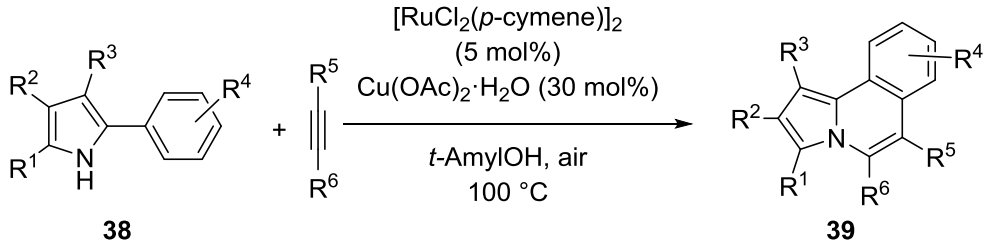
In 2009, Larock and co-workers developed the copper catalyzed tandem synthesis of indolo- and pyrrolo[2,1-*a*]isoquinolines from isoquinolines and pyrroles.[59] Hydroxymethyl benzotriazole (**37**) as a ligand source is required in order to perform the annulation of

pyrroles **34** to compounds **36**. The reaction proceeds through a formation of the *N*-alkenyl pyrroles which results from an addition reaction of pyrroles **34** to the alkynes **35**. Following intramolecular C-2 arylation of the alkenylpyrroles gives the annulated products **36**.



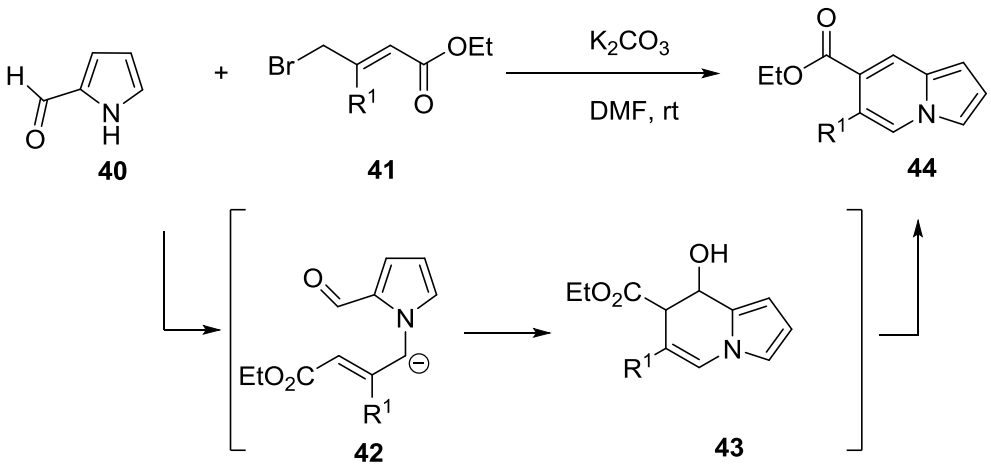
Scheme 15. Synthesis of pyrrole[2,1-*a*]isoquinolines **36**

An alternative route for the pyrrole annulation was reported by Ackermann et al.[60] Pyrrole[2,1-*a*]isoquinolines **39** were obtained via a rhodium catalyzed aerobic oxidative coupling of internal alkynes with 2-arylpyrroles **38** (Scheme 16). While symmetrical alkynes were employed, the method also works and gives mainly one regioisomer with unsymmetrical internal alkynes where one substituent is an alkyl group and the other one is an arene. Furthermore, this method tolerates many functional groups such as nitro, ester, and formyl.



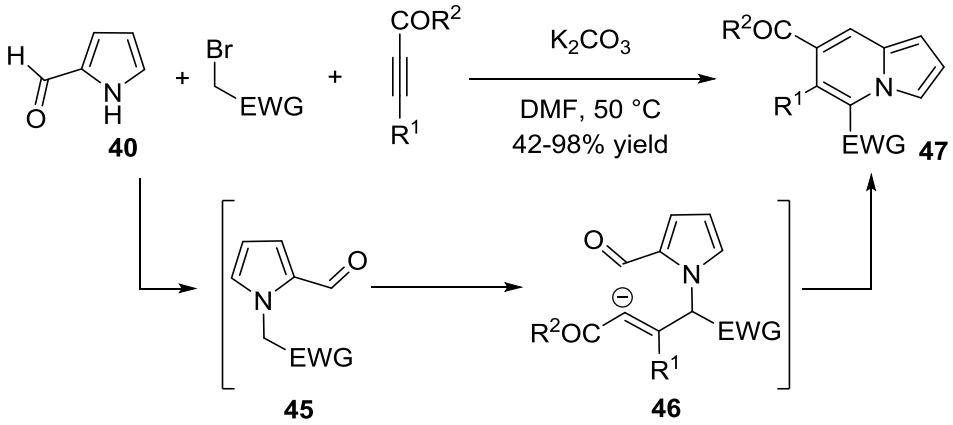
Scheme 16. Rh-catalyzed oxidative coupling of alkynes with pyrroles **38**

However, these strategies to access benzo-fused products has been never applied to obtain bicyclic indolizines. Wang and co-workers demonstrated the annulation of pyrrole-2-carbaldehyde (**40**) with γ-bromoacrylates **41** to obtain indolizines **44** via a tandem reaction in the presence of K_2CO_3.[61] Intramolecular cyclization of the deprotonated N-alkylated pyrroles **42** followed by dehydration gives indolizine-7-carboxylates **44** in high yield under mild conditions.



Scheme 17. Annulation of pyrrole **40**

Later, Zou and co-workers improved the above method and developed a very efficient one-pot multicomponent approach to indolizines from pyrroles (Scheme 18).[62] Pyrrole **40** was reacted with bromoalkanes, and activated alkynes to obtain 5,6,7-trisubstituted indolizines **47** in moderate to excellent yields (42–98%).

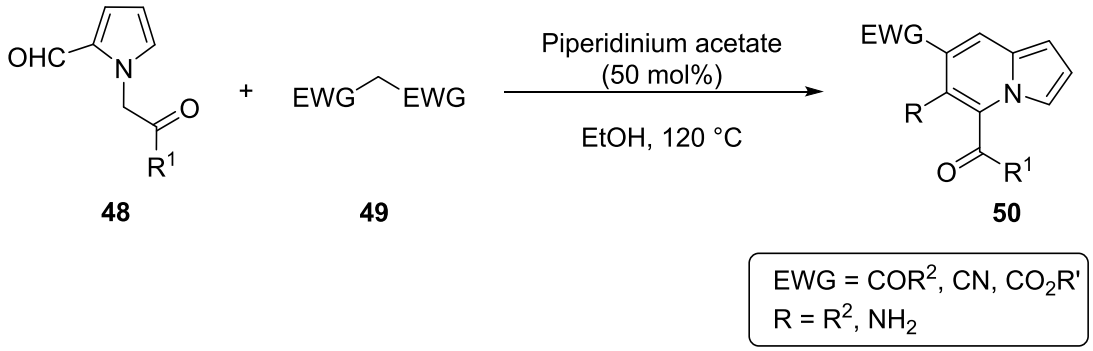


Scheme 18. Annulation of pyrroles via a multicomponent reaction

Similar to the previous example, N-alkylation of pyrrole **40** gives the intermediate **45** which can be deprotonated and attacks the triple bond to form the reactive intermediate **46**. Subsequent cyclization and dehydration of **46** furnishes indolizine **47**.

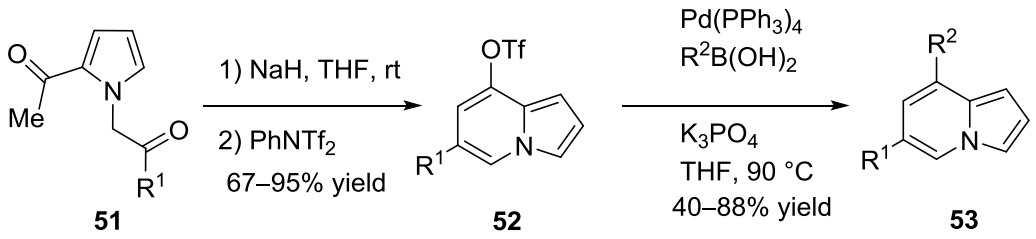
Moreover, Kim and co-workers reported an alternative method to access indolizines bearing the same substitution pattern.[63] In this case, N-alkylated product of pyrrole-2-carbaldehyde was isolated and various carboxylic acid derivatives or carbonyl compounds **49** having two acidic protons were used instead of alkynones as two-carbon units (Scheme 19). Pyrroles **48**

were annulated with 1,3-dicarbonyl compounds or malononitrile in the presence of piperidinium acetate in EtOH at 120 °C to furnish 5,6,7-trisubstituted indolizines **50** in high to excellent yields.



Scheme 19. Indolizines **50** via a Knoevenagel condensation/cyclization sequence

The same group also demonstrated the synthesis of 6,8-disubstituted indolizines via an intramolecular aldol condensation.[64] Pyrroles **51** was converted to 8-alkoxy indolizines which were trapped with *N*-phenyl-bis(trifluoromethanesulfonimide) ($PhNTf_2$) to furnish corresponding *O*-triflates **52** (Scheme 20).

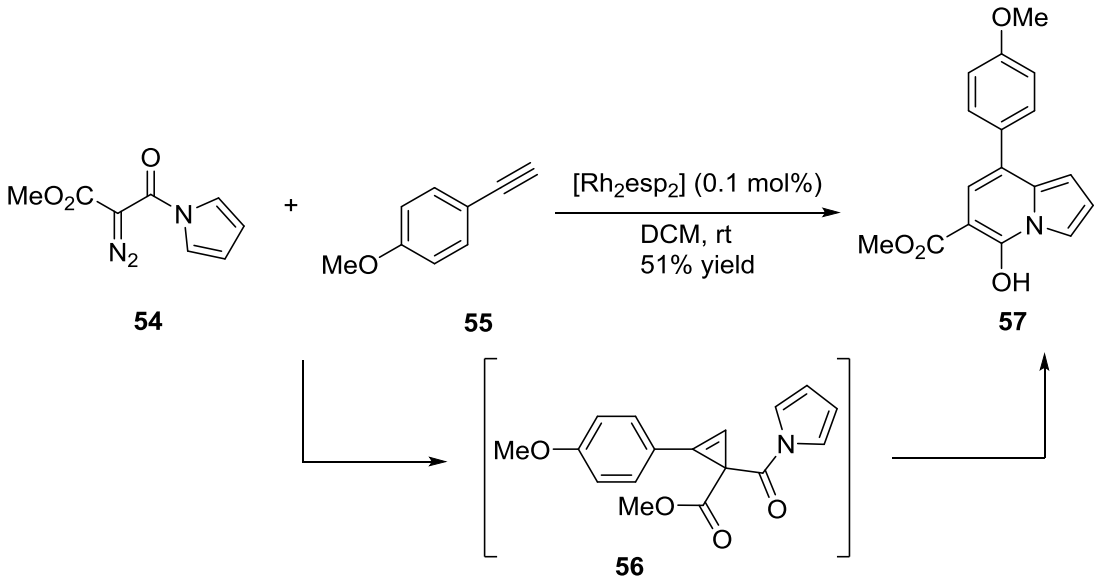


Scheme 20. Synthesis of 6,8-disubstituted indolizines **53**

Other electrophiles were also used to obtain *O*-acetates and *O*-tosylates. It was also illustrated that the triflate group could be replaced with an aryl unit (R^2) to obtain 6,8-disubstituted indolizines **53** by a palladium catalyzed Suzuki-Miyaura cross-coupling reaction with arylboronic acids. Besides, the intramolecular cyclization of other functionalized pyrrole-2-carbaldehydes were also reported in different studies.[65-68]

In 2012, France and co-workers reported an indium catalyzed cycloisomerization of cylopropene-3,3-dicarbonyl compounds which were prepared from α-diazo 1,3-dicarbonyls to benzo-annulated forms of various heteroaromatic compounds such as thiophenes, furans, pyrroles.[69] Interestingly, the rhodium catalyzed cyclopropenation of *N*-pyrrolyl α-diazo β-

amidoester **54** gave indolizine **57** in 51% yield (Scheme 21). Clearly, cyclopropene dicarbonyl **56** immediately isomerized to indolizine **57** without any requirement of indium (III) triflate.



Scheme 21. Rhodium catalyzed cycloisomerization of diazoester **54**

1.3 Pyrroles

Pyrrole is a five-membered aromatic heterocycle which was detected from a coal tar by Runge in 1834. In the original work of Runge, it was also called "Rothöl" which is a German word for red oil.[70] In 1857, it was isolated in pure form as a pyrolysis product of bone material by Anderson.[71] More than 150 years after its isolation, pyrroles have still been one of the most attractive heterocyclic motifs due to their abundance in a broad range of natural and unnatural compounds that are valuable in medicinal chemistry and materials science.[72] The pyrrole skeleton has been found in coenzymes, chlorins, corrins, porphyrins, and alkaloids. Some selected pyrrole containing natural products are shown in Figure 7.

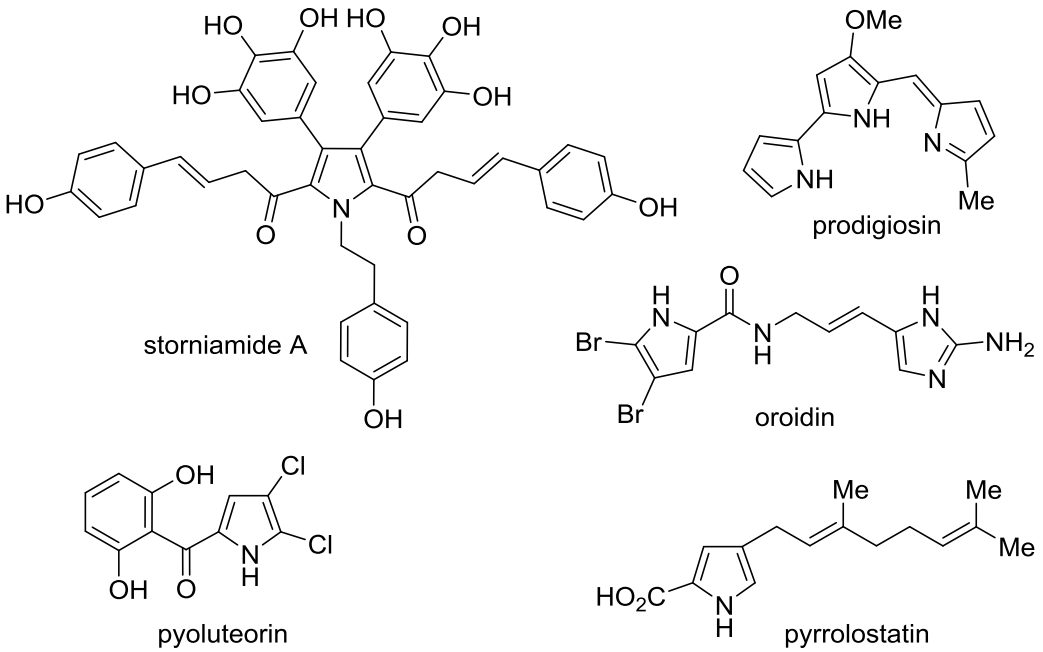
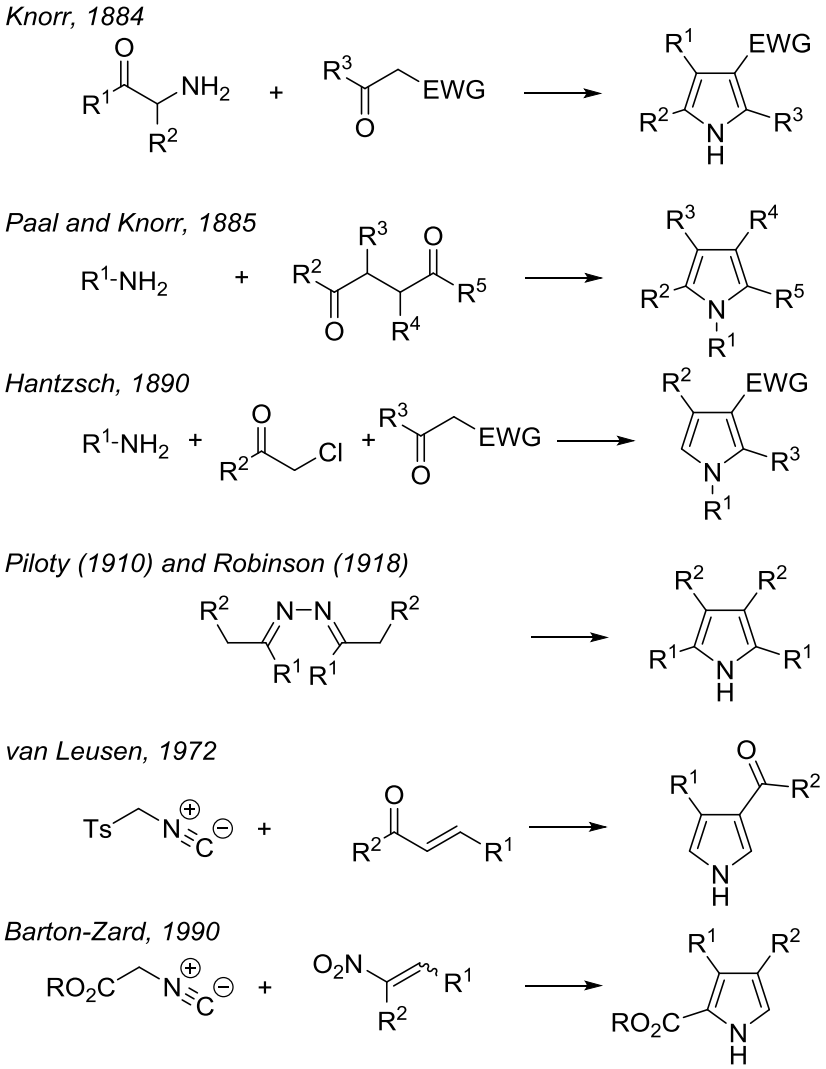


Figure 7. Some pyrrole containing natural compounds

For example, tripyrrolic prodigiosin is the red pigment that are biosynthesized by both Gram-positive and Gram-negative bacteria.[73] It also displays antibacterial, anticancer, and immunosuppressive activities.[74-76] Oroidin[77,78] was first isolated from the Sponge *Agelas oroides* in 1971 and represents the first example of about 100 pyrrole-imidazole alkaloids.[79,80] The role of oroidin is to defend the sponges chemically against predators such as reef fish.[81] In addition to pyrrole containing natural compounds, biological properties such as antifungal,[82,83] antibacterial,[83] anti-inflammatory[84] and antitumor[85] of synthetic pyrroles have been investigated. Atorvastatin (top-selling drug in the past), tolmetin, and sunitinib are some examples of the approved drugs that contain a pyrrole ring.[86,87]

1.3.1 Synthesis of Pyrroles

Many synthetic routes to pyrroles have been developed for more than a century. The synthesis of pyrroles have been reviewed deeply.[71,72,86,88-94] Knorr,[95] Paal-Knorr,[96,97] Hantzsch,[98] Piloty-Robinson,[99,100] van Leusen,[101] and Barton-Zard[102] reactions are some of the classical methods for the construction of the pyrrole ring from acyclic reactants (Scheme 22).



Scheme 22. Classical pyrrole syntheses

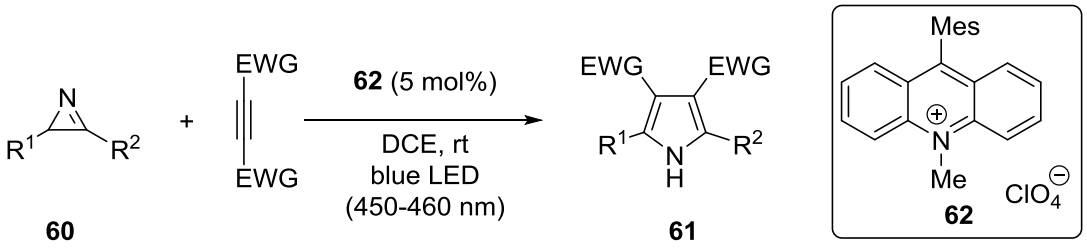
These classical methods have been extensively studied and modified in order to get a better efficiency, atom-economy, and functional group tolerance. Besides these routes, new pyrrole syntheses have also been reported including cycloisomerization reactions of complex substrates such as alkynyl imines, propargyl enamines, aziridines or homopropargylic azides,[88] multicomponent variants of the classical routes like Hantzsch[103] and Paal-Knorr[104] pyrrole syntheses, and [3+2]-cycloaddition reactions.[105,106]

Stuart and co-workers demonstrated the rhodium(III) catalyzed oxidative annulation of enamides **58** with internal alkynes to access N-acetylated pyrroles **59** (Scheme 23).[107] As an alternative condition, *t*-amyl alcohol was used instead of acetone at 60 °C. The method was applied to unsymmetrical alkynes, and tolerates many functional groups such as CO_2R, OTBS, and NHPhth. The function of copper/oxygen system is to re-oxidize the reduced rhodium species and complete the catalytic cycle.

Scheme 23. Oxidative annulation of enamides **58**

Later, the ruthenium-catalyzed oxidative annulation of the same substrates with alkynes to obtain identical products was reported by Wang and Ackermann.[108] Compared to the former method, a cheaper ruthenium catalyst was used and the reactions were performed under ambient atmosphere of air at 100 °C. Very recently, two further catalytic systems were applied for the same starting materials. While Guan et al.[109] reported the synthesis of pyrroles **59** using $Pd(OAc)_2$ and a stoichiometric amount of $Cu(OAc)_2$ as an oxidation system at 120 °C, Loh and co-workers[110] demonstrated that the palladium-catalyzed annulation of enamides **58** gave 2,3,5-trisubstituted 1*H*-pyrroles in the presence of KOAc (2 equiv) in DMSO at 80 °C.

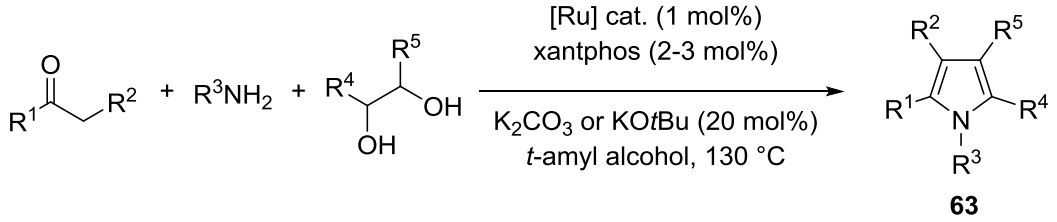
In 2014, Xiao et al. developed a metal-free photocatalytic formal [3+2]-cycloaddition of 2*H*-aziridines **60** with electron-deficient alkynes to obtain tetrasubstituted pyrroles **61** in good yields (Scheme 24).[111] The method tolerates (hetero)aryl and alkyl substituents on aziridines as well as terminal alkynes such as ethyl propiolate, but-3-yn-2-one, and propiolonitrile. As a disadvantage, the reaction requires an excess of an activated alkyne (5.0 equiv). Moreover, aziridines **60** were reacted with electron-rich ynamides in DCM to form tetrasubstituted pyrrole-2-amines in the presence of a gold (I) catalyst at ambient temperature.[112]



Scheme 24. Photocatalytic pyrrole synthesis

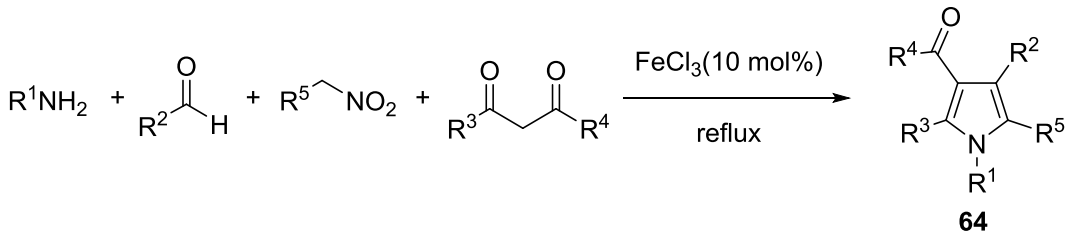
A general and regioselective synthesis of pyrroles from commercially available ketones, primary amines and diols was demonstrated by Beller and co-workers. The ruthenium-catalyzed three-component reaction was performed using either $[Ru_3(CO)_{12}]$[113] or $[RuCl_2(p$-

cymene)]$_2$ as ruthenium sources. This method tolerates many functional groups and applied to a broad range of substrates. The construction of the pyrrole unit is also atom-efficient since the only by-product is H_2O. The mechanism proposed by the authors starts with the condensation of ketones with primary amines to furnish corresponding enamines which then react with 1,2-diketones or 2-hydroxyketones formed via a dehydrogenation of diols. Further condensations and tautomerization result in polysubstituted pyrroles **63**.[113,114]



Scheme 25. The ruthenium-catalyzed three-component synthesis of pyrroles **63**

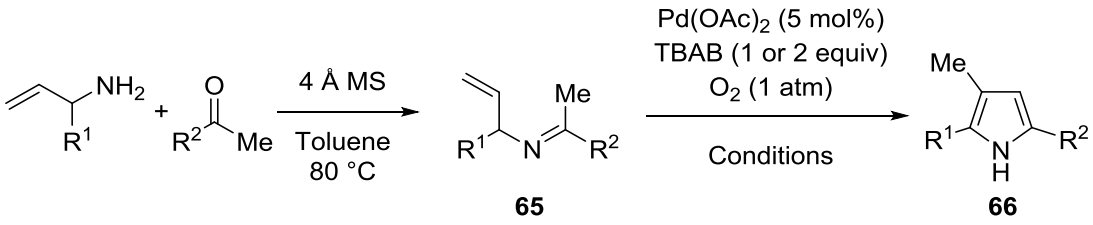
Pyrroles can also be prepared via a four-component reaction of ethyl glyoxylate, primary amines and two equivalents of α-bromoketones in the presence of pyridine by refluxing in MeCN.[115] This method allows to prepare 2-acylpyrroles in 28–70% yield but does not allow to use two different α-bromoketones resulting in regioselectivity problems. Another four-component synthesis of pyrrole-3-carboxylates **64** from nitroalkanes, aldehydes, 1,3-dicarbonyl compounds and primary amines was described by Jana and co-workers (Scheme 26).[116]



Scheme 26. Four-component synthesis of pyrroles **64**

The reaction proceeds through a nitro-aldol condensation reaction between nitroalkenes (from aldehydes and nitroalkanes) and β-enaminocarbonyl (from primary amines and 1,3-dicarbonyls) which are formed *in situ*. Later, other research groups demonstrated that the pyrroles **64** can be synthesized by replacing the iron catalyst with iodine,[117] $NiCl_2 \cdot 6H_2O$,[118] CuO nanoparticles,[119] solid supported tungstic acid,[120] or montmorillonite clay K10.[121]

Miscellaneous synthetic routes to access pyrroles **66** via an intramolecular dehydrogenative Heck reaction of *N*-allylimines **65** derived from methyl ketones and allyl amines was reported by Yoshikai,[122] Glorius,[123] and Lei,[124] simultaneously (Scheme 27).

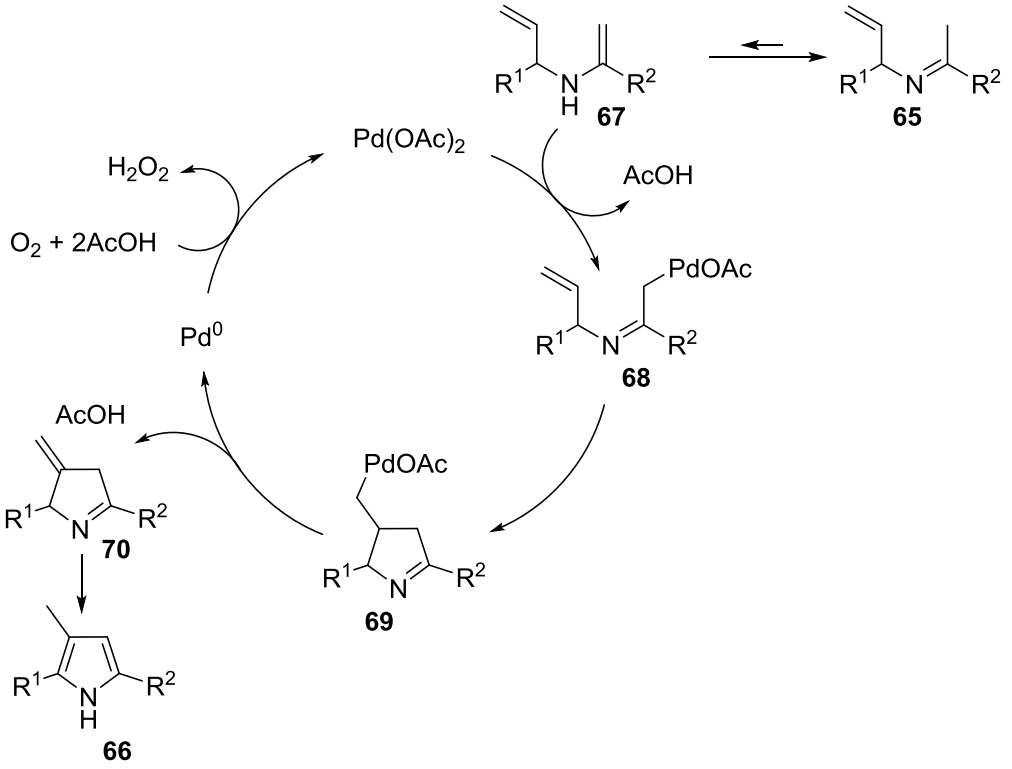


	conditions	yields	
Yoshikai	MS 3Å, DMSO, rt	40-76%	(21 examples)
Glorius	MS 4Å, DMSO, 30 °C	30-82%	(19 examples)
Lei	DMSO/toluene (1:10), 35 °C	46-78%	(12 examples)

Scheme 27. Aerobic synthesis of pyrroles

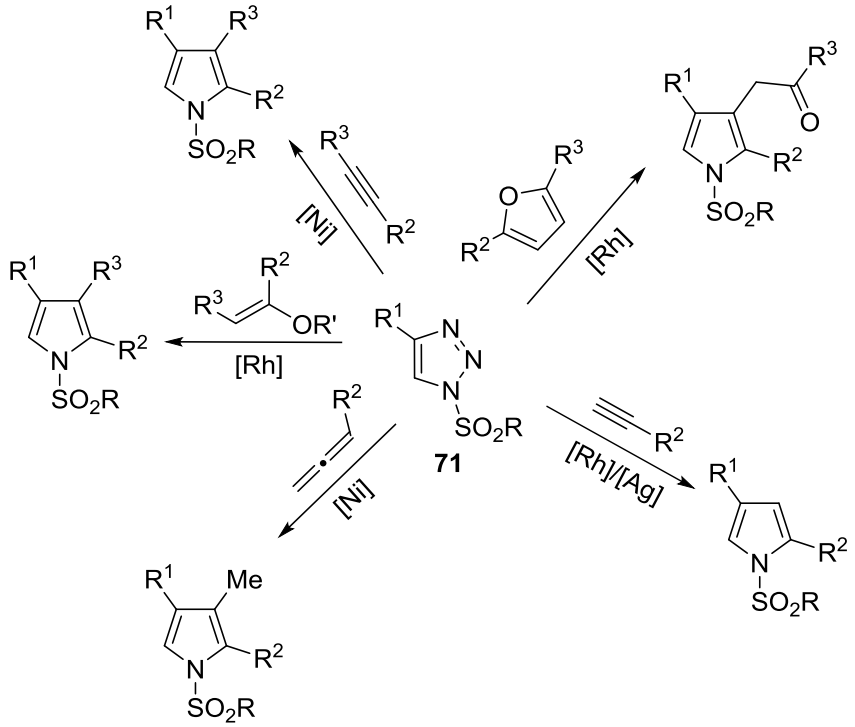
As a previous study, the identical conditions were applied in the synthesis of indoles[125] from *N*-arylimines one year prior to these reports. All reports used the same catalysts under very similar conditions. However, the method was restricted to methyl ketones and did not tolerate additional acidic protons. In other words, R^2 is limited to heteroaryl, aryl, or *t*-Bu groups. Despite these limitations, the method is very efficient for preparing 2-aryl-4-methyl-pyrroles **66** since the *N*-allylimines **65** could be easily prepared from a condensation reaction of various commercially available ketones with allylamine (where R^1 = H).

The proposed mechanism is outlined in Scheme 28.[122-125] The reaction starts with the imine–enamine tautomerization. Palladation of enamine **67** forms the palladated imine **68** which then transforms into intermediate **69** via a 5-exo-trig cyclization. Further β-hydride elimination/isomerization sequence gives the pyrrole **66**. Later, the formed Pd (0) is oxidized to $Pd(OAc)_2$ with molecular oxygen and two equivalents of AcOH to complete the catalytic cycle.



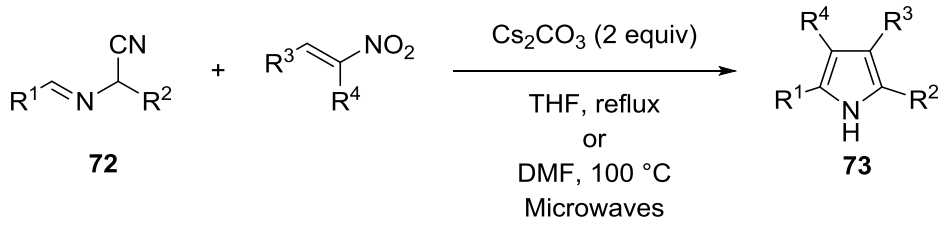
Scheme 28. Proposed catalytic cycle of dehydrogenative Heck reaction of imines **65**

A most recent method to access pyrroles is the transition metal-catalyzed transannulation of *N*-sulfonyl-1,2,3-triazoles **71** [126] with two-carbon units such as terminal/internal alkynes,[127-129] enol ethers,[130,131] furans,[132] or allenes (Scheme 29).[133,134] All reactions proceed through the formation of rhodium/nickel carbenoids which possess both electrophilic and nucleophilic moieties of the corresponding α-diazoimines. Since *N*-sulfonyl-1,2,3-triazoles **71** can be prepared from corresponding terminal alkynes via a copper-catalyzed "click chemistry" using tosyl azides in excellent yields, pyrroles were also prepared from terminal alkynes in a one-pot fashion.[127,131,133] Moreover, a rhodium-catalyzed intramolecular version of direct transannulation of the triazoles bearing an alkynyl group allows to prepare 3,4-fused pyrroles via an alkyne-carbene metathesis.[129] Alternatively, Sarpong and Schultz developed the one-pot azide-alkyne addition/intramolecular transannulation sequence to obtain fused pyrroles from allenyl alkynes using CuTc (Tc: thiophenes-2-carboxylate) and [$Rh_2(oct)_4$] (oct: octanoate).[134] Later, Davies and co-workers reported a synthesis of 2,3-fused pyrroles from conjugated enynes following the same pathway.[135]



Scheme 29. Transannulation of triazoles **71** to pyrroles

A highly modular synthesis of 2,3,4,5-tetrasubstituted pyrroles **73** from α-(alkylideneamino)nitriles **72** and nitroolefins was developed by the research group of Opatz (Scheme 30).[136] The starting materials which can be prepared from a nitroalkane, and three different aldehydes construct the pyrrole skeleton via a formal [3+2]-cycloaddition reaction. Unlike to similar reports previously described,[101,102,137] this method allows to prepare pyrroles without any electron-withdrawing group.



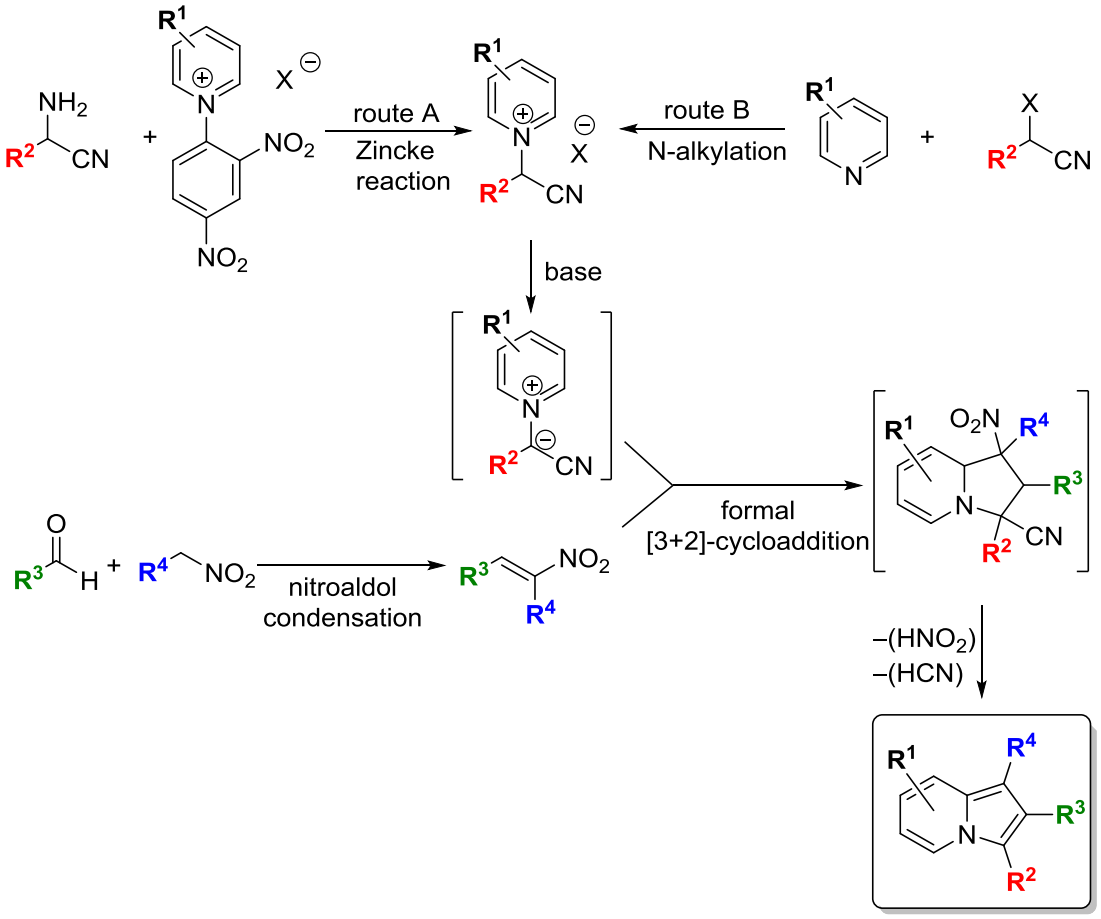
Scheme 30. Modular approach to pyrroles **73** from (alkylideneamino)nitriles **72**

Opatz also demonstrated that activated alkynes can also be used instead of nitroolefins as electrophiles.[138] Furthermore, an unsymmetrical alkyne was successfully applied on synthesis of the pyrrole frame of atorvastatin, the world's top-selling drug in the past. The same group represented a synthesis of 2,3,5-trisubstituted pyrroles from *a*-aminonitriles and enones.[139] The imine formed from the condensation of two components is deprotonated to

generate an azapentadienyl anion. Electrocyclization of the latter followed by re-protonation forms a cyanopyrroline which then furnishes a 2,3,5-trisubstituted pyrrole after the removal of the nitrile group.

2 Motivation

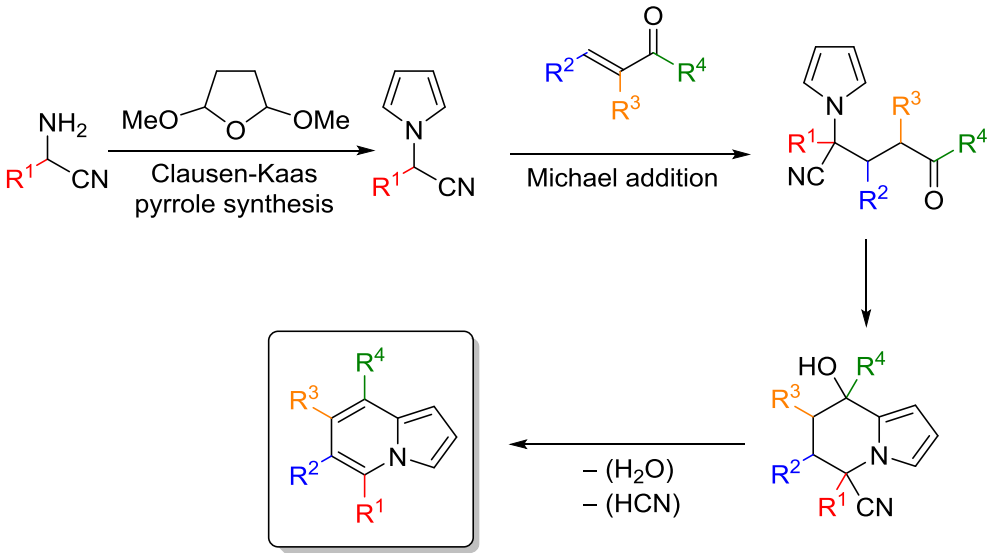
Developing new synthetic methodologies to prepare small, drug-like molecules is not only attractive from a synthetic point of view, but is also very crucial to discover new drug candidates. Inevitably, new strategies for the preparation of valuable heterocycles have been explored to find potential drugs. In the working group of Opatz, α-aminonitriles[140,141] have been used as a valuable precursor to synthesize N-heteroaromatic compounds such as pyrroles,[136,138,139] indoles,[142] β-carbolines,[143] imidazoles,[144,145] oxazoles,[144] and quinolones.[146] The aim of this study is to expand the application of α-aminonitriles by developing new synthetic methods for the preparation of indolizines and pyrroles. The first project is to access 1,2,3-trisubstituted indolizines without undesired functional groups via a formal [3+2]-cycloaddition of pyridinium ylides and nitroolefins (Scheme 31). The course of this reaction is similar to Opatz's pyrrole synthesis.



Scheme 31. Proposed synthesis of modular indolizine synthesis

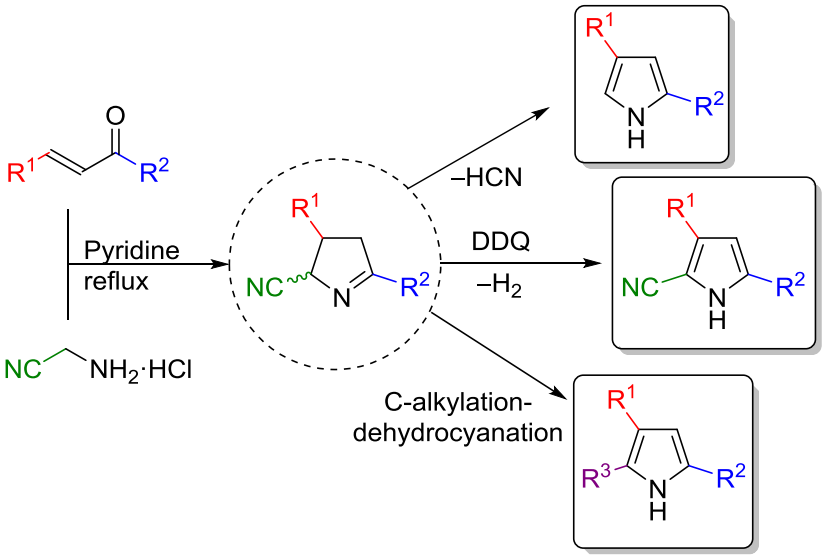
Pyridinium salts can be prepared either by the Zincke reaction[147] of α-aminonitriles (route A) or by N-alkylation of pyridine derivatives with nitriles bearing a leaving group such as an halide, triflate, tosylates, etc. on the neighboring carbon (route B).

As a second project, it was aimed to prepare indolizines with the substituents on the pyridine unit (Scheme 32). This can be achieved by annulation of pyrroles. Pyrrolonitriles which can be prepared by a Clausen-Kaas[148] pyrrole synthesis using α-aminonitriles and enones are appropriate starting points since they can attached easily with a Michael addition and can form the pyridine ring with the C-C bond formation between the carbonyl carbon and the C-2 of pyrrole via a Friedel-Crafts-type acylation. Dehydration and dehydrocyanation of tetrahydroindolizine will furnish 5,6,7,8-tetrasubstituted indolizines.



Scheme 32. Proposed synthesis of 5,6,7,8-tetrasubstituted indolizines

The final project was to obtain 2,4-di- and 2,3,5-trisubstituted pyrroles and 3,5-disubstituted pyrrole-2-carbonitriles from cyanopyrrolines (Scheme 33). Some of these reactions had already been applied in the research group of Opatz. The aim of this project is to increase the substrate scope of DDQ oxidation of cyanopyrrolines to pyrrole-2-carbonitriles[149] and to optimize the dehydrocyanation of cyanopyrroline to obtain 2,4-disubstituted pyrroles.



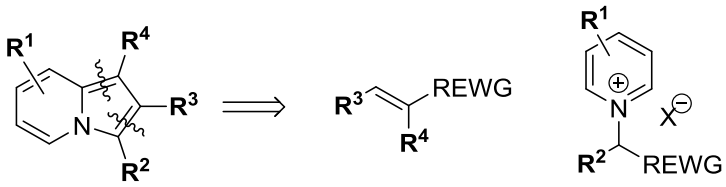
Scheme 33. Proposed synthesis of pyrroles with different substituent patterns

3 Results and Discussion

3.1 Indolizines

3.1.1 Decoration of the Pyrrole Unit

The synthesis of indolizines from pyridines via a formal [3+2]-cycloaddition reaction of a pyridinium ylide and a dipolarophile is one of the most common methods. In literature, many examples of this approach can be found.[12,150-153] However, in all cases at least one electron-withdrawing group (EWG) remains in the indolizines structure. In order to overcome this limitation, we have designed a synthetic route[136] that contains removable electron-withdrawing group (REWG), therefore, indolizines without any EWG can be synthesized via a formal [3+2]-cycloaddition reaction of pyridinium ylides and dipolarophiles (Scheme 34).

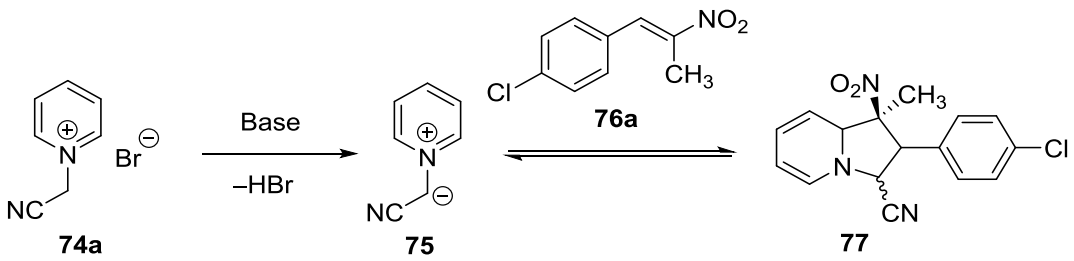


Scheme 34. Design of the synthesis of indolizines

Nitroalkenes as dipolarophiles were chosen due to the fact that the NO_2 group is a strong REWG and decreases the energy of the LUMO of the dipolarophile. For the pyridinium ylides, the cyano group was considered as a suitable candidate for being a REWG. Moreover, the preparation of nitroolefins is relatively easy and they can be constructed from aldehydes and nitroalkanes via a nitroaldol condensation.[154]

3.1.1.1 Initial Findings

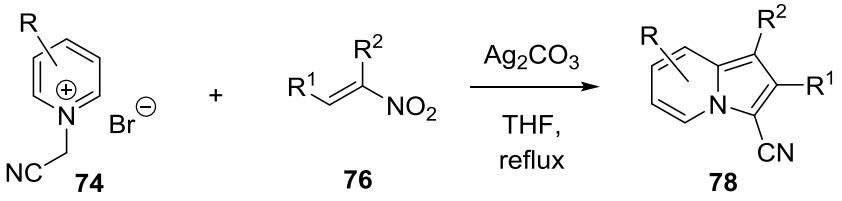
Following the literature,[41] 1-(cyanomethyl)pyridinium bromide (**74a**) was prepared from pyridine and bromoacetonitrile. The salt **74a** was then reacted with the nitroalkene **76a**[154] in the presence of different bases and solvents at various temperatures. From the initial investigation, it is found that the formal [3+2]-cycloaddition of pyridinium ylide **75** to nitroalkene **76a** works successfully. However, the cycloadduct **77** reverted to the starting nitroalkene **76a** and pyridinium ylide **75** (Scheme 35).[41]



Scheme 35. Reversible 1,3-dipolar cycloadditon

The cycloadduct **77** was proved by ^{1}H NMR spectrum of the crude product and all attempts to isolate it were unsuccessful. Luckily, it was found that cycloadduct **77** could be oxidized to indolizine **78a** using Pd/C (10 mol %) in low yield. This showed that the tetrahydroindolizines can be transformed into indolizines using a stoichiometric amount of an oxidant. Indeed, when an excess amount of Ag_2O (3.0 equiv.) used, the yield of indolizine increased to 82%. The direct synthesis of indolizines **78** can be achieved by using a reagent that acts both as a base and an oxidant. Silver (I) carbonate (2.0 equiv.) was found as an efficient reagent as Ag_2O for this purpose. Moreover, no additional step (formal [3+2]-cycloaddition) required when silver (I) carbonate used. Pyridinium salts **74** were reacted with different nitroalkenes **76** to obtain indolizine-3-carbonitriles **78** under the optimized conditions (Table 1).

Table 1. Indolizine-3-carbonitriles[a]



Entry	R	R^1	R^2	Product	Yield (%)
1	H	4-Cl-C_6H_4	Me	**78a**	81
2	H	2-Naph	Et	**78b**	82
3	H	4-NC-C_6H_4	Et	**78c**	70
4	H	4-F-C_6H_4	Me	**78d**	81
5	H	*i*Pr	Me	**78e**	53
6	4-Ph	*i*Pr	Me	**78f**	69
7	4-CN	*i*Pr	Me	**78g**	34

[a] Reaction conditions: Pyridinium salt **74** (1.00 equiv), nitroalkene **76** (1.00 equiv), Ag_2CO_3 (2.0 equiv), THF (0.05 M).

When the reaction was performed with two equivalents of silver (I) carbonate in THF under reflux, indolizine **78a** was obtained in 81% yield (Table 1, entry 1). When R^1 is an aromatic substituent, yields of the indolizine-3-carbonitriles **78a**–**d** are in the range of 70–82% (entries 1–4). However, an alkyl substituent at R^1 diminished the yield (entry 5). While a phenyl group at the para position of the parent pyridine ring increased the yield compared to the unsubstituted pyridinium salt (entry 6 compared to entry 5), a nitrile group at the same position lowered the efficiency (entry 7). The structures of indolizines **78d** and **78e** were also confirmed by X-ray crystallography (Figure 8).

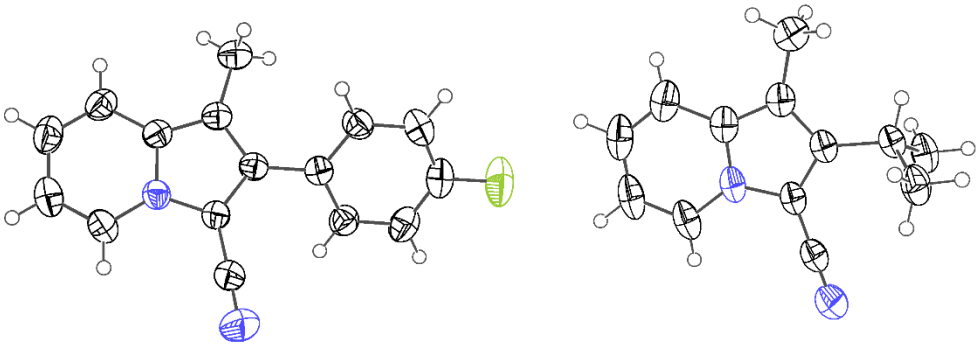
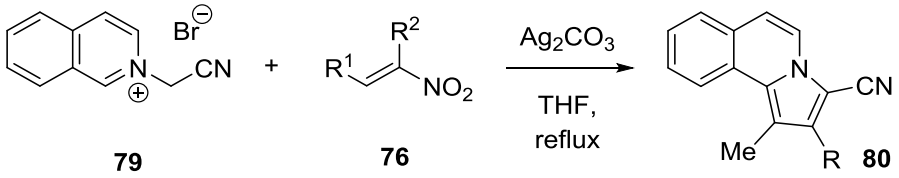


Figure 8. Ortep drawings of X-ray structures (left: **78d**, right: **78e**)

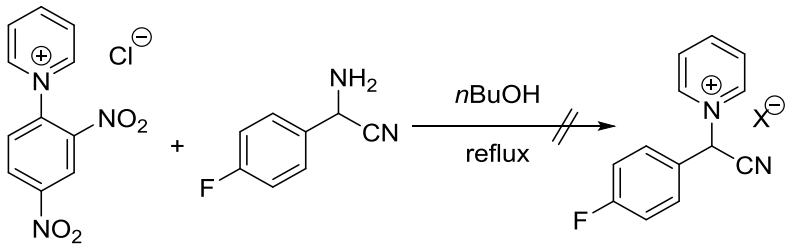
This reaction also worked on the isoquinoline system. Similar to pyridinium salts **74**, 2-(cyanomethyl)isoquinolin-2-ium bromide (**79**) was obtained from the reaction of isoquinoline and bromoacetonitrile, and reacted with two different nitroolefins under identical conditions (Scheme 36). Similar to indolizines **78**, the yield of annulated product **80a** is much higher when a β-arylnitroalkene **76a** was used.



80a: R^1= 4-Cl-C_6H_4 R^2= Me 80% yield
80b: R^1= *i*Pr R^2= Me 36% yield

Scheme 36. Annulation of isoquinolines

However, it is not possible to remove HCN from the cycloadduct to obtain 1,2-disubstituted indolizines when pyridinium salts **74** were used. This method is limited to indolizine-3-carbonitriles. Here, in this specific substituent pattern, cyano group only acts as an EWG and a base assisted elimination of the cyano group is not possible. The reason could be explained by bearing a highly acidic proton in the cycloadduct. To prove our hypothesis, pyridinium salts with an R substituent had to be prepared and tested in the cycloaddition to nitroolefins. An initial attempt to synthesize 1-(1-cyanoaryl)pyridinium salt **83** was failed when the aminonitrile **82**[139] was reacted with the Zincke salt **81** (Scheme 37).[147]

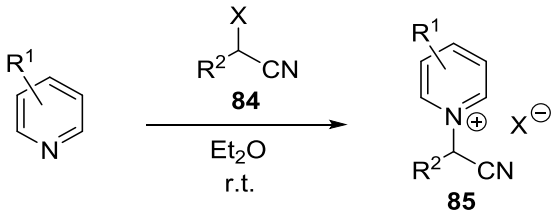


81 **82** **83**

Scheme 37. Attempts for the preparation of pyridinium salt **83**

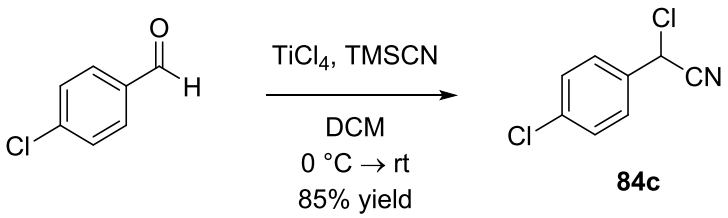
As an alternative route, pyridinium salts **85** were synthesized from pyridines and cyanohydrin triflates **84** that could be prepared by a Strecker reaction of aldehydes and a subsequent triflylation of the resulting cyanohydrins with triflic anhydride.[155,156] The results are summarized in Table 2.

Table 2. Preparation of pyridinium salts



Entry	R^1	R^2	Product	X	Yield (%)
1	H	Me	**85a**	OTf	95
2	H	^{i}Pr	**85b**	OTf	98
3	H	4-Cl-C_6H_4	**85c**	Cl	96
4	4-Ph	Me	**85d**	OTf	79
5	4-*t*Bu	Me	**85e**	OTf	64
6	2-Me	Me	**85f**	OTf	71
7	H	CH_2CH_2Ph	**85g**	OTf	74

Although the method is very efficient to prepare1-(1-cyanoalkyl)pyridinium salts, the triflylation of aryl substituted cyanohydrin failed. In order to increase the diversity of R^2, 4-chlorobenzaldehyde was converted to α-chloroarylacetonitrile **84c**[157] in a one-pot reaction using $TiCl_4$ and TMSCN in dry DCM which then used in N-alkylation of pyridine to obtain pyridinium salt **85c**.

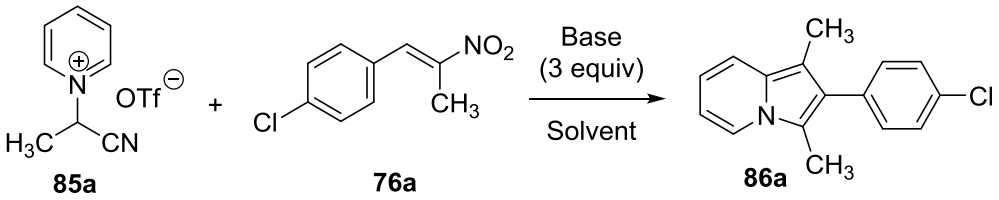


Scheme 38. Preparation of α-chloroarylacetonitrile **84c**

3.1.1.2 Reaction Optimization

Next, the transformation of the pyridinium salts **85** into indolizines **87** via the cycloaddition/double elimination sequence was examined. In order to optimize the reaction conditions pyridinium triflate **85a** and nitroalkene **76a** were chosen as substrates. Different solvents and bases were tested at various temperatures (Table 3).

Table 3. Optimization of the indolizine synthesis



Entry	Base	Solvent	Temp. (°C)	Yield (%)
1	K_2CO_3	MeOH	reflux	40
2	Al_2O_3[a]	none	250	n.d.
3	Et_3N	DMF	90	57
4	Cs_2CO_3[b]	DMF	90	59
5	Cs_2CO_3[c]	DMF	90	45
6	Cs_2CO_3	DMF	75	49
7	Cs_2CO_3	DMF	90	60
8	Cs_2CO_3	DMF	reflux	65
9	Li_2CO_3	THF	reflux	n.d.
10	Pyridine	pyridine	90	12
11	KO*t*Bu	THF	reflux	20
12	KO*t*Bu	THF	25	31
13	KO*t*Bu[d]	THF	0	72
14	**KO*t*Bu[d]**	**DMF**	**0**	**77**
15	KO*t*Bu	DMF/*t*BuOH	0	42
16	NaOMe[d]	DMF/MeOH	0→25	61
17	NaOMe[e]	MeOH	0→25	51

[a] Microwave heating. [b] Molecular sieves (3Å) were added. [c] Ag_2O (1.0 mmol) was added. [d] 4.0 equiv. of base were used. [e] 8.0 equiv. of base were used. [f] Not detected.

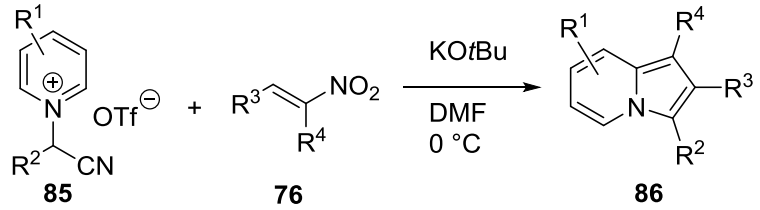
The reaction works with both organic and inorganic bases except lithium carbonate (entry 9). Under the same condition, indolizine **86a** was obtained in 65% yield when cesium carbonate was used as a base (entry 8). Small adjustments such as addition of molecular sieves (entry 4) and silver (I) oxide (entry 5) in the use of cesium carbonate did not improve the yield. While decreasing the reaction temperature from 90 °C to 75 °C lowered the yield (entry 6), refluxing in DMF gave indolizine **86a** in 65% yield (entry 8). It is found that the

highest yields could be obtained with 4.0 equiv. of KO*t*Bu in DMF or THF at 0 °C (entries 13 and 14).

3.1.1.3 Substrate Scope

The optimized conditions (4.0 equiv. KO*t*Bu, DMF, 0 °C) were then applied to the reaction of pyridinium salts **85** with other nitroalkenes (Table 4). The method is not only limited to aryl substituent at R^3; however, when R^3 is an alkyl, the yield of indolizine is lower comparing to aryl substituted (entry 7 compared to entry 12). The method tolerates various functional groups (such as fluoro, chloro, and cyano) on the phenyl ring attached to C-2 of the indolizine skeleton.

Table 4. Modular synthesis of indolizines[a]



Entry	R^1	R^2	R^3	R^4	Product	Yield (%)
1	H	Me	4-Cl-C_6H_4	Me	**86a**	77
2	H	Me	2-Naph	Et	**86b**	54
3	H	Me	4-NC-C_6H_4	Et	**86c**	62
4	H	Me	4-F-C_6H_4	Me	**86d**	65
5	H	Me	-$(CH_2)_4$-		**86e**	39
6	H	CH_2CH_2Ph	Ph	Me	**86f**	32
7	7-*t*Bu	Me	4-Cl-C_6H_4	Me	**86g**	71
8	7-Ph	Me	4-Cl-C_6H_4	Me	**86h**	72
9	H	*i*Pr	4-Cl-C_6H_4	Me	**86i**	55
10	H	4-Cl-C_6H_4	4-Cl-C_6H_4	Me	**86j**	39
11	5-Me	Me	4-Cl-C_6H_4	Me	**86k**	21
12	7-Ph	Me	*i*Pr	Me	**86l**	37

[a] Reaction conditions: Pyridinium salt **85** (1.00 equiv), nitroalkene **76** (1.00 equiv), KOtBu (4.00 equiv), DMF (0.20 M).

The *tert*-butyl and phenyl substituents on the para position of the pyridines did not have any significant influence on the efficiency. The 2-methyl substituent on the pyridine ring diminished the yield of indolizine **86k** (21%) due to a side reaction that will be discussed in detail in chapter 3.1.2.

The application of this method to other nitrogen containing heterocycles was also examined to increase the scope of the method. Similar to the pyridine case, different azinium salts were prepared by reacting corresponding nitrogen containing five or six membered heterocycles with cyanohydrin triflate in Et_2O at ambient temperature (Figure 9).

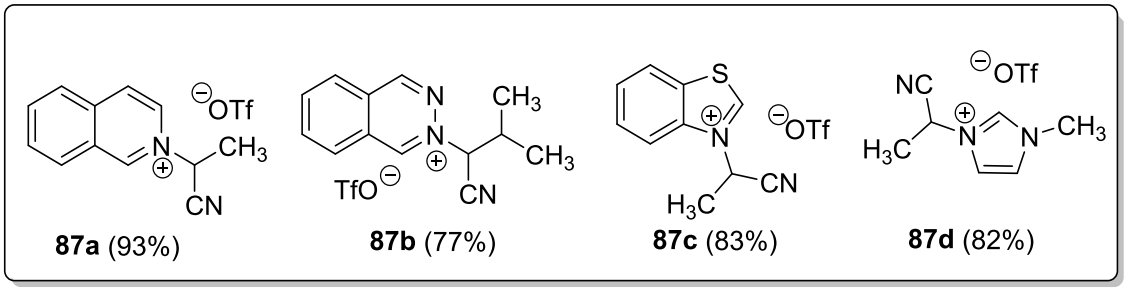
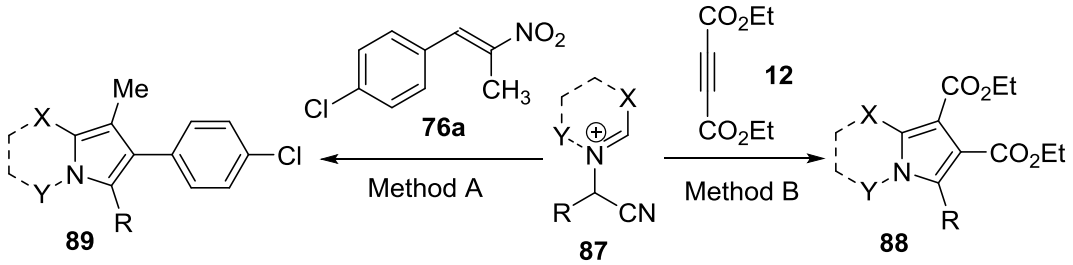
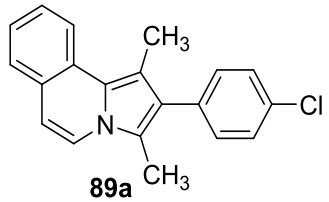
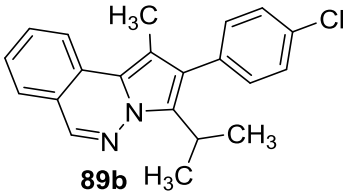
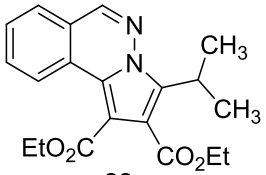
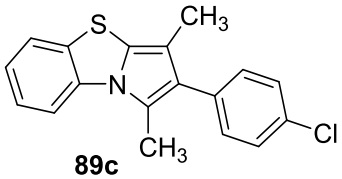
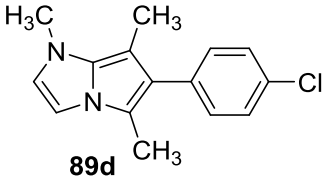
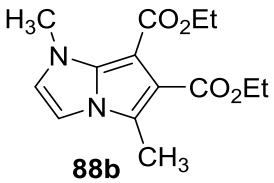
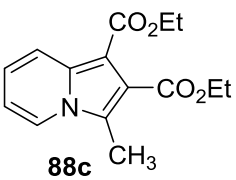


Figure 9. Azinium triflates **87**

The prepared azinium triflates were annulated with the nitroalkene **76a** in the presence of KO*t*Bu after a deprotonation/cyclization/double elimination sequence in the same manner (Table 5, method A). In order to show that the applicability of this annulation method is not strictly limited to nitroalkenes, an activated alkyne, diethyl acetylenedicarboxylate (DEAD, **12**), was also used in C_3-annulation of azinium salts (Table 5, method B). The C_3-annulation of isoquinoline, benzothiazole, and phthalazine was achieved by applying method A to obtain tricyclic products (entries 1, 2 and 4). Azinium triflates of phthalazine and pyridine were also reacted with DEAD in moderate to good yields (entries 3 and 7). However, while imidazolium triflate **87d** did not give annulated product with the nitroalkene **76a**, it was only reacted with DEAD to obtain pyrrolo[1,2-*a*]imidazole **88b** in 51% yield (entries 5 and 6). Moreover, azinium triflates of phenanthridine, 1-phenylpyrazole and pyridazine were subjected to the conditions in method A, only pyridazinium triflate gave product in low yield which could not be separated from by-products. Even though the method is not generally applicable, it can both work on five and six membered nitrogen containing heterocycles.

Table 5. C_3-Annulation of other azinium salts[a]

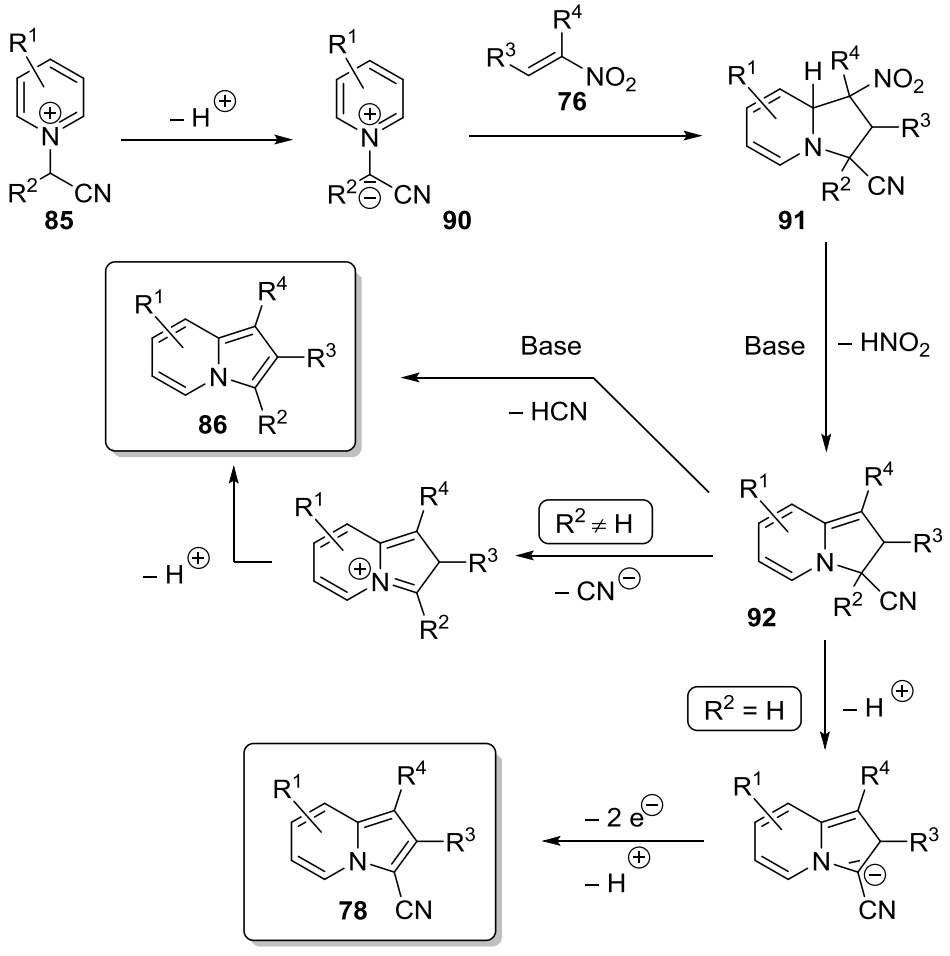


Entry	Azinium Salts	Method	Product	Yield (%)
1	**87a**	A	 **89a**	49
2	**87b**	A	 **89b**	34
3	**87b**	B	 **88a**	51
4	**87c**	A	 **89c**	26
5	**87d**	A	 **89d**	n.d.[b]
6	**87d**	B	 **88b**	58
7	**85a**	B	 **88c**	76

[a] Reaction conditions: Azinium salt **87** (1.00 equiv), electrophile (1.00 equiv), KOtBu (4.00 equiv.), DMF, 0 °C. [b] Not detected.

3.1.1.4 Mechanisms and Limitations

The proposed mechanism begins with the deprotonation of the pyridinium salt **85** to form the corresponding pyridinium ylides (Scheme 39). The ylide **90** then reacts with nitroalkene **76** to form tetrahydroindolizine **91** via a stepwise or concerted mechanism. Tetrahydroindolizine **91** transforms into dihydroindolizine **92** after a base-induced elimination of nitrite. At this point, two different pathways can be followed depending of the R^2 substituent. When $R^2 \neq H$, indolizine **86** is obtained from dihydroindolizine via a base-induced elimination of the cyanide. It should be noted when R^2 is a proton, pyridinium ylides reacts with activated alkenes to give stereospecific tetrahydroindolizines which strengthen the concerted mechanism path.[41]



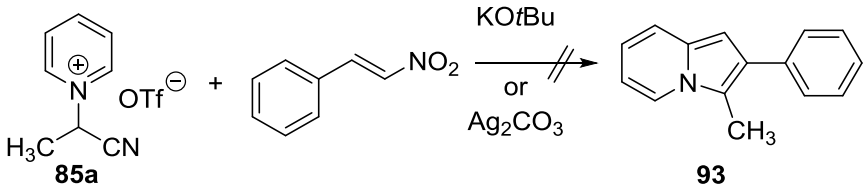
Scheme 39. Plausible mechanism for the indolizine formation

In case of R^2 = H, the elimination of the cyanide is not possible and the reaction cannot proceed unless there is an oxidant. Since silver(I) was used in our method as an oxidant, after

the reaction it was reduced to metallic silver. As an evidence, a silver mirror on the inner surface of the reaction flask is formed during the reaction (Figure 10).

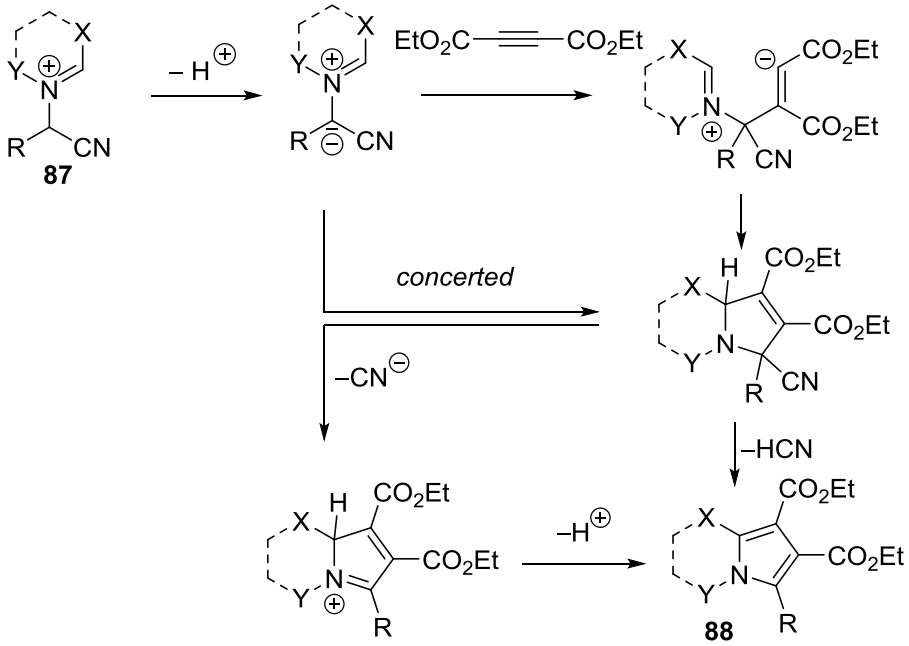
Figure 10. Silver mirror formed after the reaction for the synthesis of indolizine **78a**

One of the limitations of this method is the need to use trisubstituted nitroalkenes. When the disubstituted nitroalkene, β-nitrostyrene, was used, no indolizine **93** formation was detected even if there exists an oxidant (Scheme 40).



Scheme 40. Unsuccessful attempt to access 2,3-disubstituted indolizines

The mechanism for the reaction of azinium triflates **87** with the activated alkynes can probably be considered similar to the reaction with nitroalkenes (Scheme 41). Annulated products form either via a concerted or a stepwise mechanism. The base-induced elimination of the cyanide gives fully aromatic heterocycles **88**.

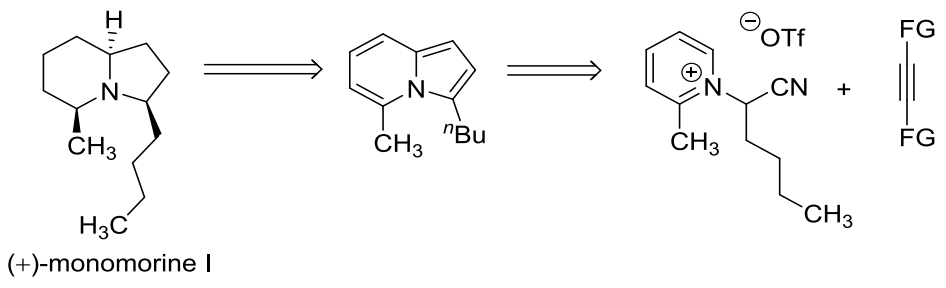


Scheme 41. Mechanism of an addition of azinium ylides to the activated alkyne

3.1.2 2-Aminoindolizines

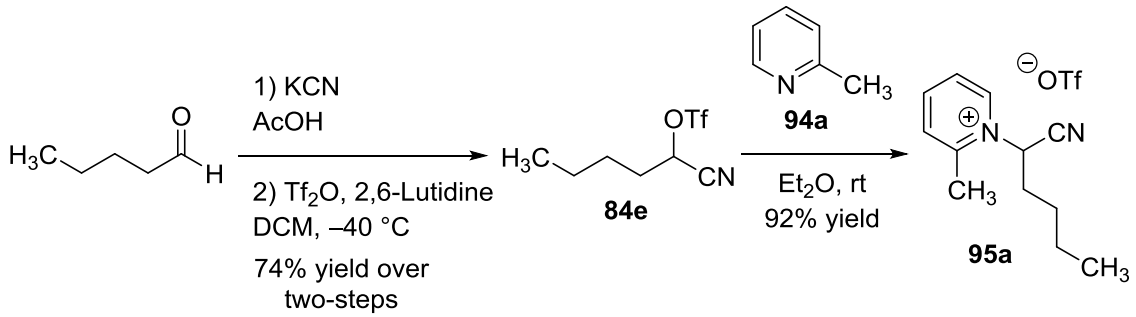
3.1.2.1 Initial Findings

As it is described in chapter 3.1.1, bearing an alkyl unit on the C-2 of the parent pyridinium ylides diminishes the yield of the indolizines. Later, the existence of an unexpected reaction which competes with the desired intermolecular formal [3+2]-cycloaddition/double elimination sequence was figured out. The unexpected reaction was first realized during attempts to find a short synthetic pathway to the indolizidine alkaloid called (+)-monomorine (Scheme 42).



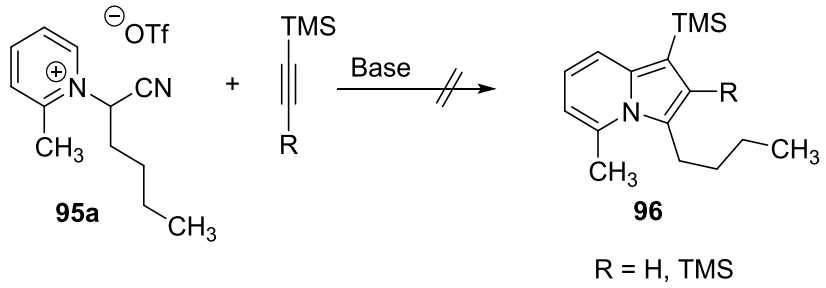
Scheme 42. The outlined synthesis of (+)-monomorine

The outlined synthesis starts with the readily available pyridinium salt **95a**. The annulation of the salt **95a** with an appropriate alkyne and the subsequent hydrogenation of indolizine would give racemic monomorine. Furthermore, the enantioselective synthesis of monomorine would be possible when an asymmetric hydrogenation is applied. In order to carry out the planned route, 1-cyanopentyl trifluoromethanesulfonate (**84e**) was prepared in two steps from pentanal (Scheme 43). Later, the prepared cyanohydrin triflate **84e** was reacted with 2-picoline (**94a**) to give pyridinium salt **95a** in 92% yield.



Scheme 43. Preparation of the pyridinium salt **95a**

In order to access to the monomorine, mono- or bis-TMS protected acetylenes were selected since the removal of silyl groups is straightforward after the cyclization. Several reaction conditions were tested and the reaction was monitored by HPLC-MS and TLC (Scheme 44).

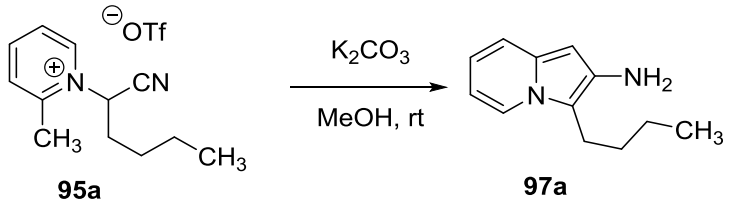


Scheme 44. Attempts for the synthesis of indolizine **96**

From HPLC-MS analysis, no cycloadduct was obtained. The m/z of the only observed peak was 189.1 which is the mass of the pyridinium cation. From the TLC experiments, only a highly polar compound was detected similar to the pyridinium salts. While all data indicated

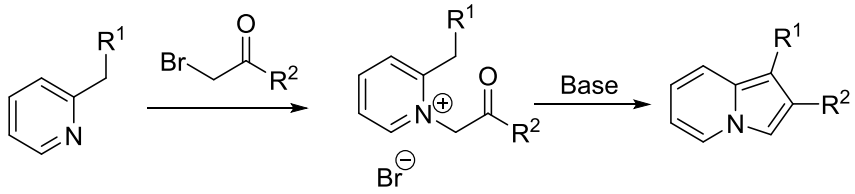
that there is no conversion, the sample solution taken from the reaction mixture and diluted with EtOAc was fluorescent at 360 nm unlike to the pyridinium salt.

The ^{1}H NMR of the crude product showed that the pyridinium salt was completely converted into another compound. The structure of the compound was elucidated by using 2D-NMR techniques. It is found that the alkyne did not participate in the reaction and the pyridinium salt **95a** was cycloisomerized to 2-aminoindolizine **97a** (Scheme 45).



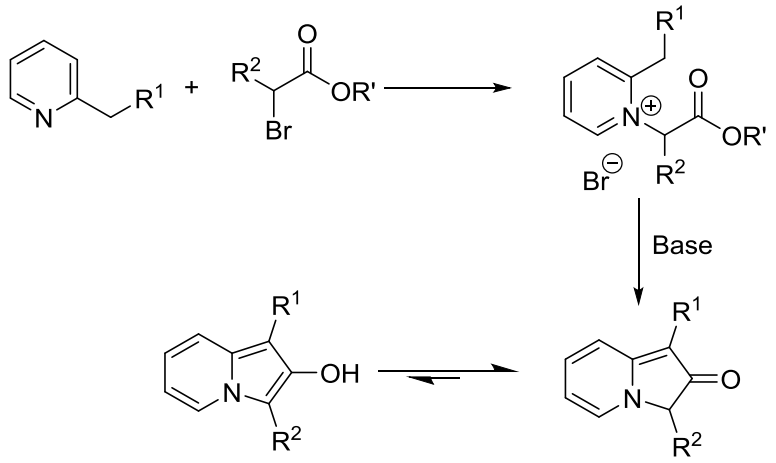
Scheme 45. Unexpected intramolecular cyclization of the pyridinium salt **95a**

Similar type of intramolecular cyclization of 2-alkyl-1-(2-oxoalkyl)pyridinium ylides is well known and it is one of the most common way of synthesizing 3-unsubstituted indolizines from pyridinium ylides that was discovered by Tschitschibabin (or Chichibabin) in 1927 (Scheme 46).[33]



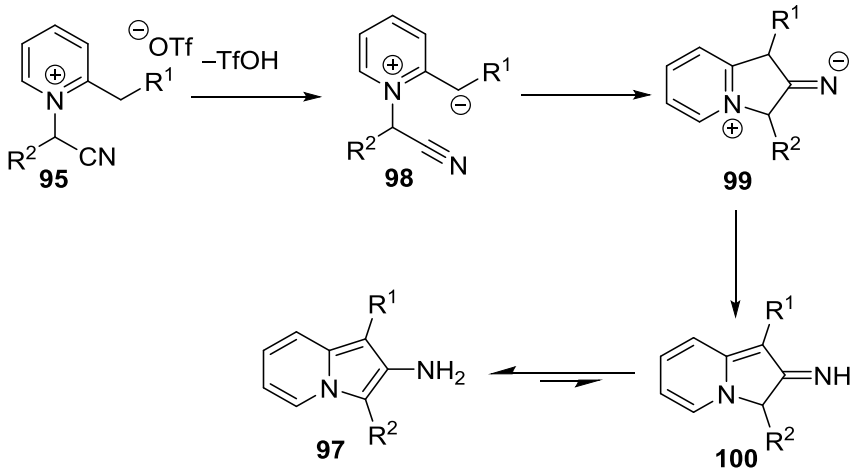
Scheme 46. Tschitschibabin indolizine synthesis

Later, an intramolecular cyclization of ester-stabilized 2-alkyl substituted pyridinium ylides was reported by Kakehi in 1980 (Scheme 47).[158] Similar to Tschitschibabin indolizine synthesis,[33] pyridinium salts prepared by using α-bromoesters were cyclized to the 2,3-dihydroindolizin-2-ones. The same author reported that the aromatic enol tautomers of these compounds are not favored.



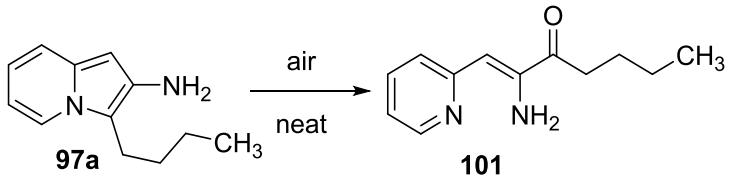
Scheme 47. The intramolecular cyclization of ester-stabilized pyridinium ylides

Therefore, the unexpected reaction can be called as a Tschitschibabin-type cyclization of nitrile-stabilized 2-alkylpyridinium ylides. Similar to previous variants of the reaction, the reaction starts with the removal of the benzylic proton. The resulting carbanion **98** attacks nitrile to form the cyclic betaine **99** via a 5-exo-dig cyclization. A proton transfer followed by an imine-enamine tautomerization gives 2-aminoindolizine **97** (Scheme 48). Unlike the dihydroindolizin-2-one,[158] aromatic enamine tautomer is the preferred form in this case.



Scheme 48. Proposed mechanism for the formation of 2-aminoindolizines **97**

However, 2-aminoindolizines are quite instable due to the electron-rich nature of the indolizines. All attempts to isolate them failed and resulted in low yields. It was found that indolizine **97a** degraded to the pyridine **101** when it was exposed to air during the storage (Scheme 49).



Scheme 49. Degradation of 2-Aminoindolizine **97a**

The structure of the pyridine **101** was proven by 2D-NMR spectroscopy. The ^{1}H, ^{1}H-NOESY correlations between the double bond proton and the alpha and beta protons of the carbonyl group show that the geometry of the double bond is *cis* (Figure 11).

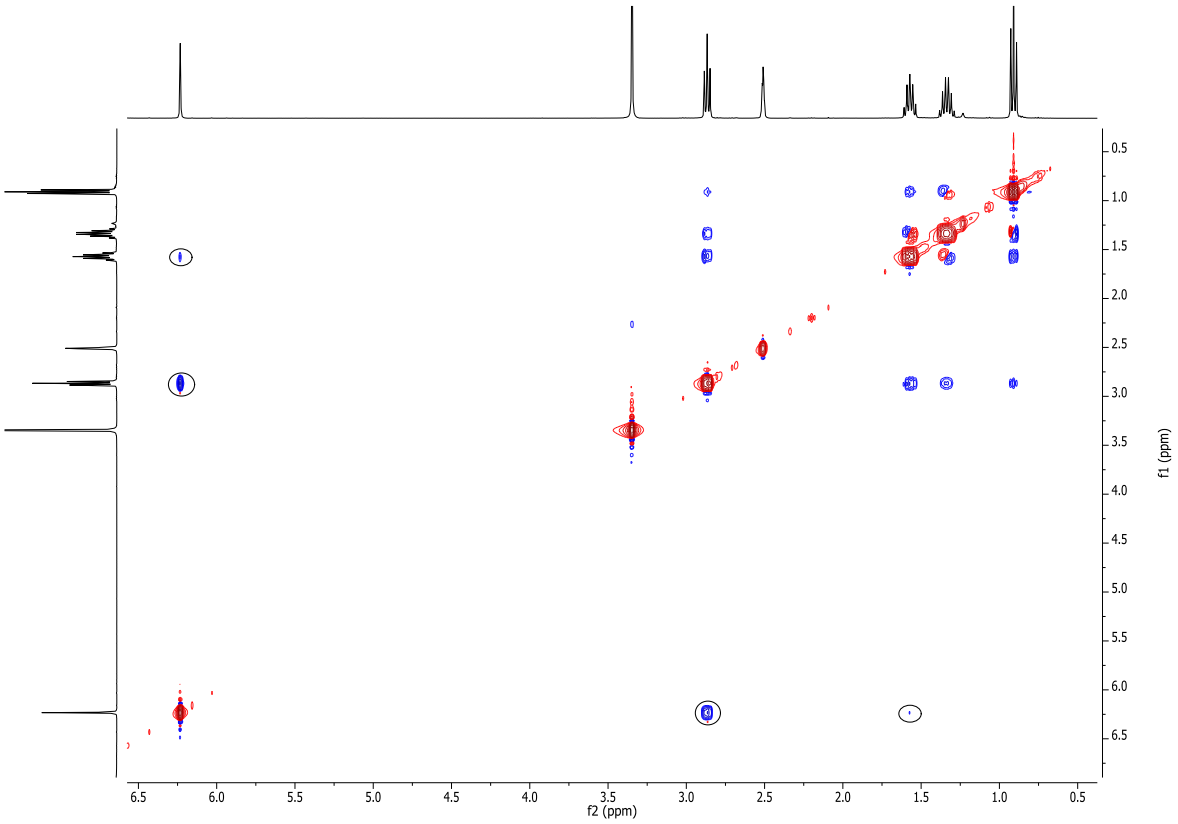
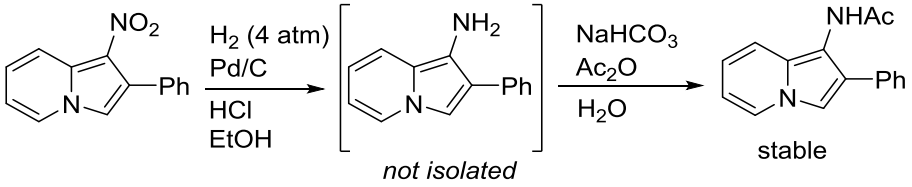


Figure 11. ^{1}H, ^{1}H-NOESY of the pyridine **101**

3.1.2.2 Reaction Optimization

Since 2-aminoindolizines **97** could not be isolated without decomposition, the reaction was optimized using ^{1}H NMR monitoring. Pyridinium salt **95a** was reacted with different bases to find the better condition that produces least by-products. Inorganic salts such as K_2CO_3, $NaHCO_3$, Na_2CO_3, and Cs_2CO_3 gave many by-products when the reactions were performed

in toluene, MeOH, *i*PrOH or THF at ambient or elevated temperatures. When H_2O was used as a solvent, no product was identified. The reaction also did not work when polymeric tertiary amine Amberlyst® A21 was used. However, TEA reacted slowly in DCM but the conversion was incomplete. Among all, KO*t*Bu was the only base which formed 2-aminoindolizine **97a** without any detected side reactions in THF at 0 °C. Although the ^1H NMR spectrum of the crude product indicated a very high conversion and yield, no suitable purification method was found. Hurst and co-workers prepared 1-aminoindolizines from the 1-nitroindolizine by reduction.[159] The instability of 1-aminoindolizines was reported and they were isolated as their corresponding amides by acetylation of the crude amine using acetic anhydride (Scheme 50).[159]

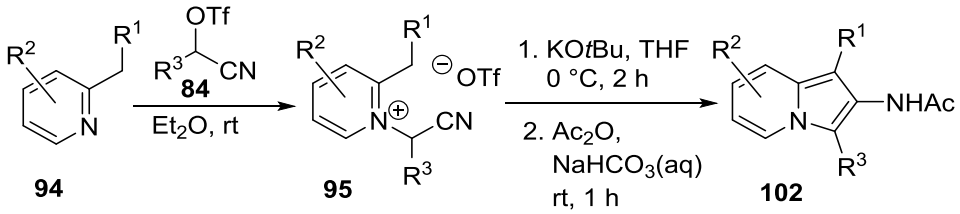


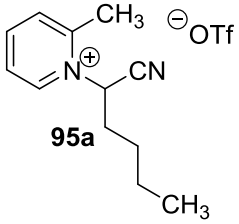
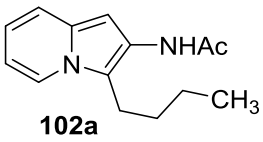
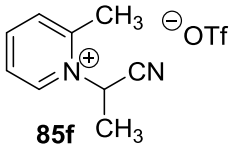
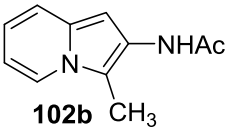
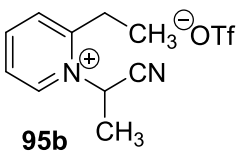
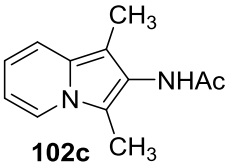
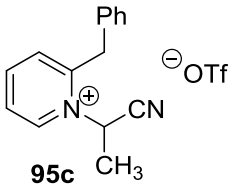
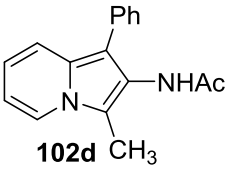
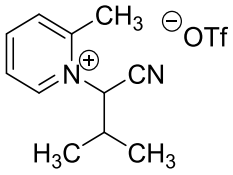
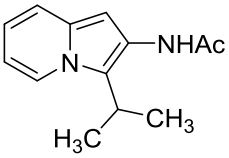
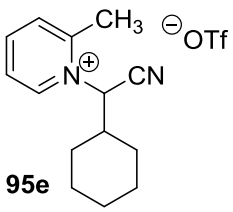
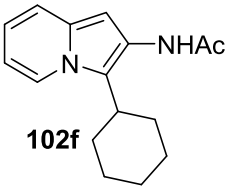
Scheme 50. Hurst's approach to 1-aminoindolizines

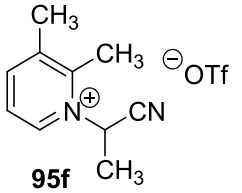
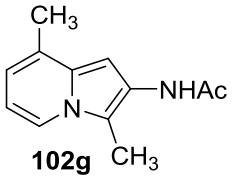
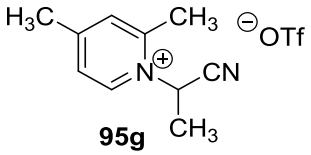
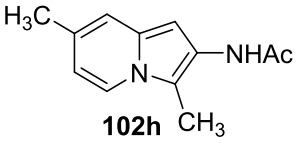
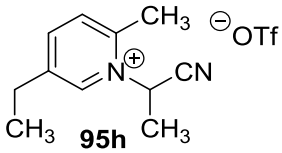
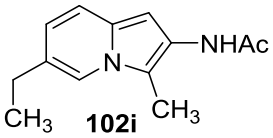
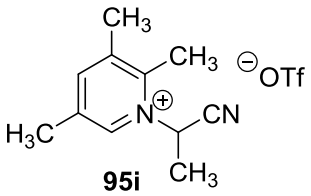
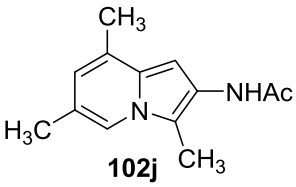
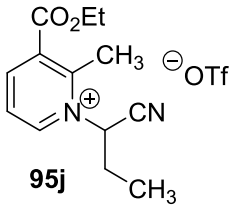
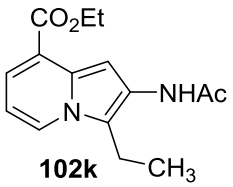
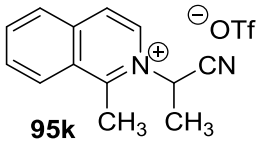
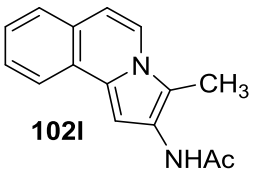
3.1.2.3 Substrate Scope Studies

Applying Hurst's approach to our case, the crude 2-aminoindolizine **97** was acetylated *in situ* and then isolated as amide **102a** in 95% yield (Table 6, entry 1). Since a convenient method for stabilization of the products was found, the substrate scope of the reaction was investigated. The pyridinium salts **95** were prepared as described before in multi-gram scale. The cyclization reactions of the salts were carried out in 0.30–1.00 mmol scale using 1.10 equiv. of KO*t*Bu in THF at 0 °C. Afterwards, the reaction mixture was quenched with aqueous $NaHCO_3$ and acetylated with an excess amount of Ac_2O at room temperature. The results are summarized in Table 6.

Table 6. Substrate scope studies of 2-aminoindolizines



Entry	Pyridinium Salt[a]	Yield[b]	Indolizine[c]	Yield[d]
1	 **95a**	92%	 **102a**	95%
2	 **85f**	71%	 **102b**	77%
3	 **95b**	90%	 **102c**	67%
4	 **95c**	91%	 **102d**	86%
5	 **95d**	71%	 **102e**	42%
6	 **95e**	77%	 **102f**	47%

Entry	Pyridinium Salt[a]	Yield[b]	Indolizine[c]	Yield[d]
7	 **95f**	90%	 **102g**	83%
8	 **95g**	85%	 **102h**	39%
9	 **95h**	75%	 **102i**	83%
10	 **95i**	91%	 **102j**	75%
11	 **95j**	75%	 **102k**	35%
12	 **95k**	98%	 **102l**	79%

[a] Reaction conditions: pyridine **94** (1.00 equiv), triflate **84** (1.00 equiv), Et_2O (1.0 M), rt,24–48 h. [b] Isolated yield of azinium salts **95**. [c] Reaction conditions: (1) pyridinium salt **95** (1.00 equiv), KO*t*Bu (1.10 equiv), THF (0.1 M), 0 °C, 2 h; (2) Ac_2O (2.0 mL), $NaHCO_3$(aq), rt, 1 h. [d] Isolated yield of indolizine **102**.

The *N*-Acetyl 2-aminoindolizines **102** were synthesized from 2-alkylpyridinium salts **95** in moderate to high yields. The effect of R^1 (H, Me, Ph) on the yield is relatively smaller (entries 1–4) compared to R^3. When R^3 was replaced with a bulkier substituent (*i*Pr and Cy), the yield of indolizine diminished significantly (entries 5 and 6). Furthermore, depending on the position of the R^2 on the pyridine ring, indolizines could be synthesized in high yields. For instance, alkyl substituents at C-3 and C-5 of the pyridine do not have a negative

influence since the products were obtained in high yields (entries 7, 9 and 10). In the case of an alkyl substituent at C-4, indolizine **102h** was obtained only in 39% yield (entry 8). The drastic effect of the position of R^2 can probably be related with bearing additional acidic protons when alkyl group attached to the para-position of the pyridine skeleton. Ethyl 2-methylnicotinate was converted to indolizine **102k** in 35% yield (entry 11). Even though, the yield is low, this method tolerates an ester functional group. The method is also not only limited to pyridines but also works with isoquinolines (entry 12). The structure of indolizine **102j** was confirmed by X-ray crystallography (Figure 12).

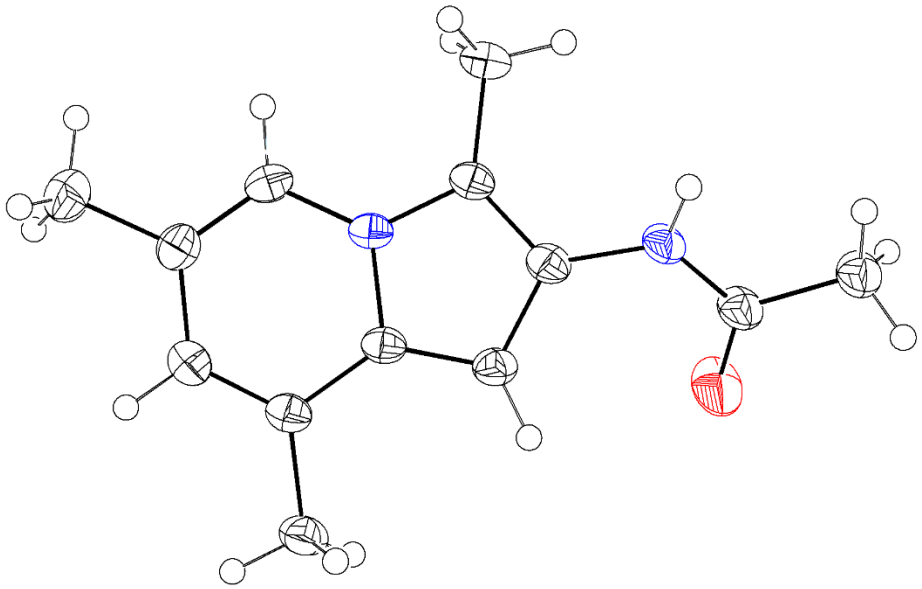
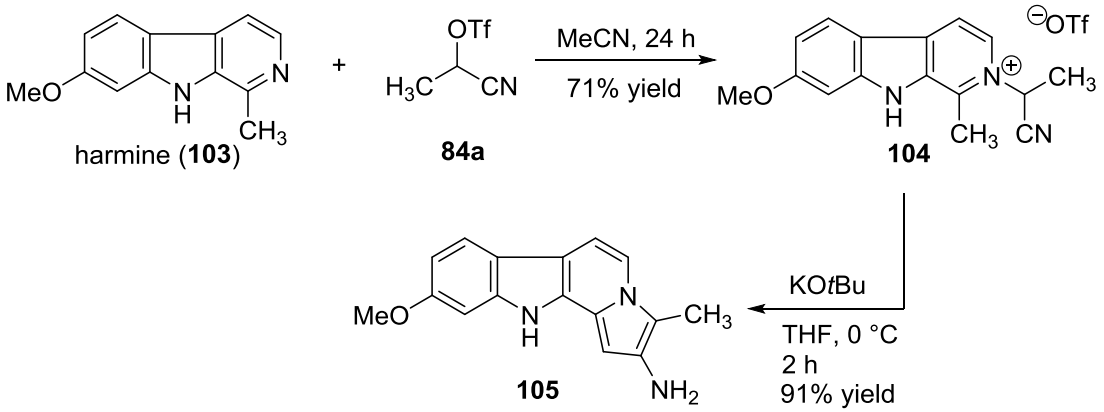


Figure 12. Ortep drawing of the X-ray structure of indolizine **102j**

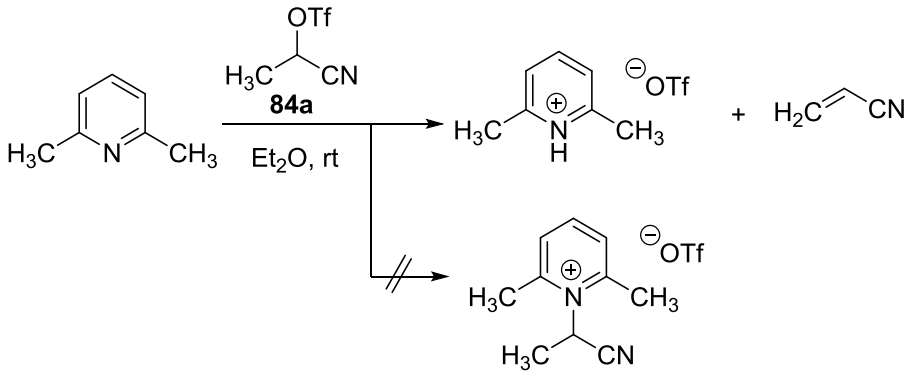
To increase the substrate scope of the reaction and to illustrate the validity of the method on natural products as well, harmine (**103**), a member of β-carboline alkaloids, was chosen as a substrate. First, the tricyclic carboline **103** was reacted with triflate **84a** to obtain the salt **104** which then converted to the tetracyclic compound **105** (Scheme 51). The tetracyclic indoloindolizine **105** was synthesized from the alkaloid **103** in two steps without the use of any chromatographic separation in 65% overall yield. In this case, amine **105** was bench stable, and further acetylation was not required.



Scheme 51. Synthesis of indoloindolizine **105**

3.1.2.4 Limitations

One of the drawbacks of the method is the unfeasibility of the salt formation from 2,6-disubstituted pyridines. It was found that the substrate acted as a base and was not alkylated due to a high steric hindrance when 2,6-lutidine was reacted with triflate **84a** (Scheme 52).



Scheme 52. Protonation of 2,6-lutidine

Another limitation of the method was observed in the case of other heterocycles. 2-Methylpyrimidine, 2-methylbenzothiazole and 3-methylisoquinoline were first alkylated with triflate **84a** (Figure 13). These prepared salts did not give the desired cyclization. It was observed that when pyrimidinium salt **106a** was dissolved in deuterated DMSO, the solution colorized and decomposed quickly. In the case of the salt **106b**, many by-products were formed. Unlike 1-methylisoquinolinium triflate **95k** which was successfully transformed into the product **102l** (Table 6, entry 12), the intramolecular cyclization of the salt **106c** derived from 3-methylisoquinoline failed.

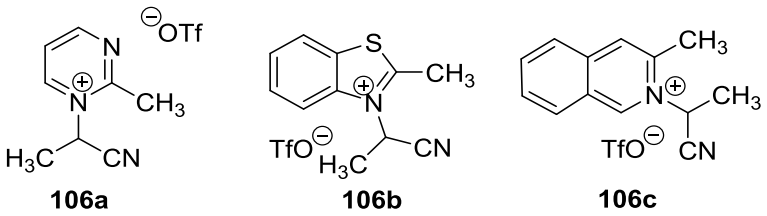
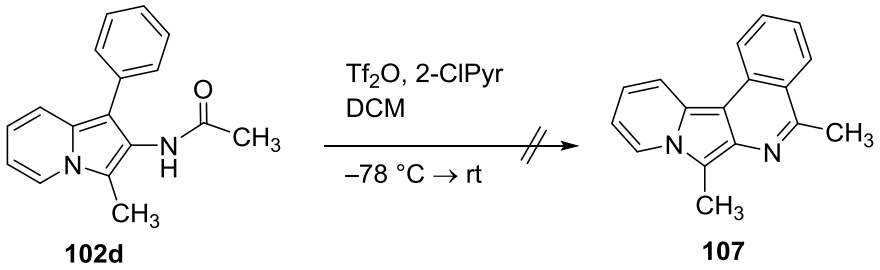


Figure 13. Unsuitable substrates for the intramolecular cyclization

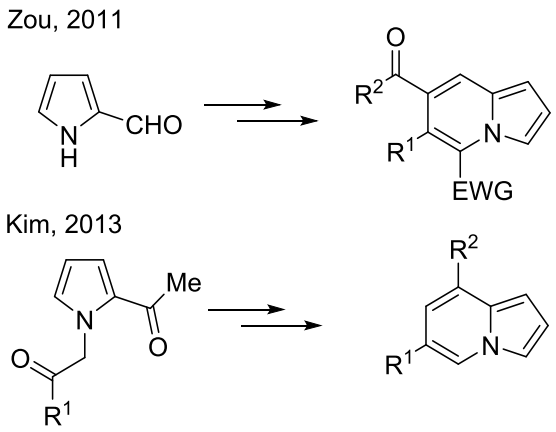
Besides the limitations, further transformation of the 2-aminoindolizines were tested. For example, indolizine **102d** is a suitable substrate for a Bischler-Napieralski reaction. Unfortunately, attempts to synthesize indolizino[2,1-*c*]isoquinoline **107** from indolizine **102d** in the presence of triflic anhydride and 2-chloropyridine failed.



Scheme 53. Failed Bischler-Napieralski cyclization[160]

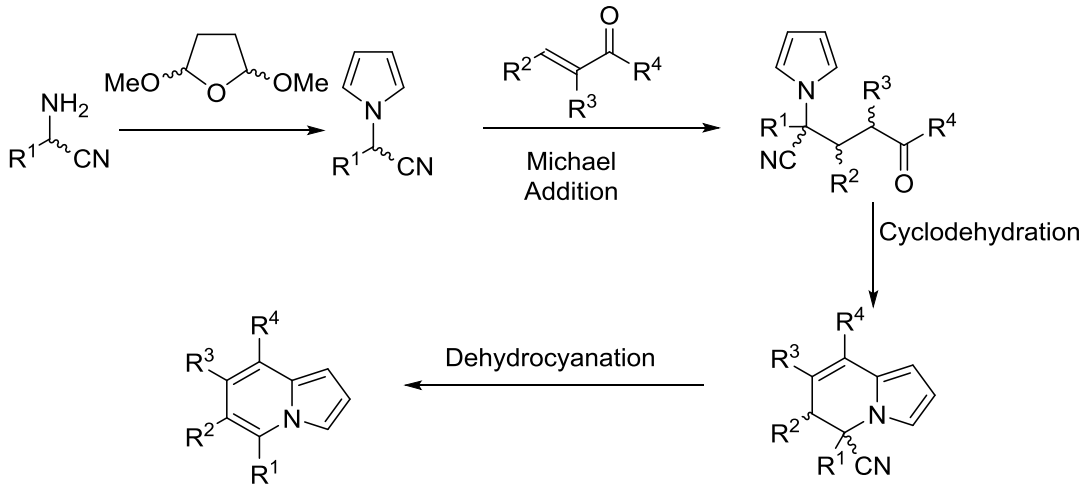
3.1.3 Decoration of the Pyridine Unit

As it was mentioned before, most of the indolizine syntheses start from pyridine derivatives. Although many routes are available to access indolizines with substituents on the pyrrole ring, few methods that indolizines could be obtained from pyrroles have been described in literature.[61,65-68,161-164] For example, Zou reported a synthesis of 5,6,7-trisubstituted indolizines starting from functionalized pyrrole-2-carbaldehydes (Scheme 54).[62] Another important method was described by Kim and Lee in 2013. Their cycloaromatization approach from 2-acetylpyrrole allows to obtain 6,8-disubstituted indolizines. Besides the resulting *O*-acetates and –tosylates, *O*-triflates were used in Suzuki-Miyaura cross-coupling reactions with arylboronic acids.[64]



Scheme 54. Some examples of the indolizines via a pyridine ring formation

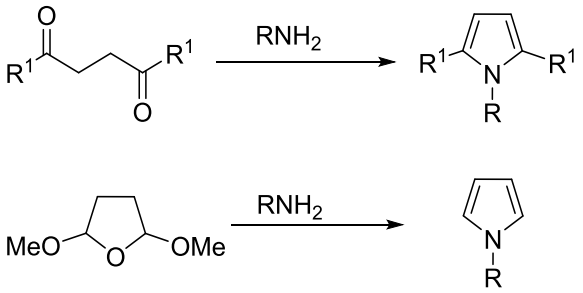
To the best of our knowledge, indolizines carrying four substituents in the pyridine unit of indolizines has not been described except the fused indolizines such as pyrrolo[1,2-*a*]quinolone[56-58,165,166] and pyrrolo[2,1-*a*]isoquinolines.[59,60,167,168] Therefore, we designed a possible synthetic route to obtain indolizines with a complete substitution on the pyridine unit starting from pyrrolonitriles (Scheme 55).



Scheme 55. Synthesis plan for the full-decoration of the pyridine unit.

The route starts with the conjugate addition of deprotonated pyrrolonitriles to enones. Dihydroindolizines which could be obtained from the 1,4-adduct via a cyclodehydration can be converted into indolizines by elimination of HCN.

N-Substituted pyrroles could be prepared by reacting 1,4-diketones with amines which is called Paal-Knorr pyrrole synthesis (Scheme 56). A modified version of the Paal-Knorr synthesis was discovered by Clausen-Kaas in 1948.[148] In his approach, 1,4-diketones were replaced with 2,5-dialkoxytetrahydrofuran.

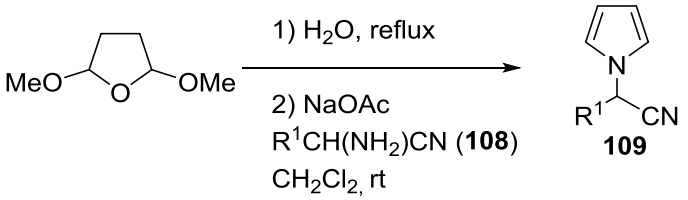


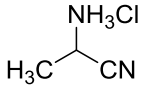
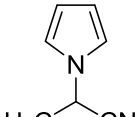
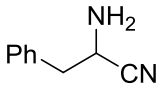
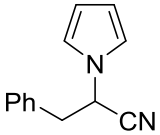
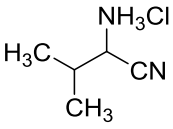
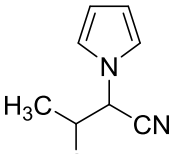
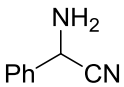
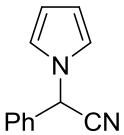
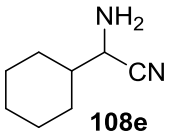
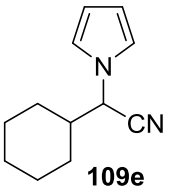
Scheme 56. Paal-Knorr (top) and Clausen-Kaas (below) pyrrole synthesis

In 2006, further improvement in Clausen-Kaas pyrrole synthesis was reported by Smith.[169] The two-phase synthesis and the introduction of amine components and acids, 1-substituted pyrroles were obtained in good yield without decomposition.

Following the Smith's approach, 2-(1*H*-pyrrol-1-yl)nitriles **109a**–**e** were readily prepared in the modified Clausen-Kaas procedure from 2,5-dimethoxytetrahydrofuran and aminonitriles. Aminonitriles **108** were prepared from corresponding aldehydes, ammonia and KCN according to the literature.[138,170,171] The results were summarized in Table 7. All reactions were performed under inert atmosphere and the yields were not optimized.

Table 7. Preparation of pyrrolonitriles

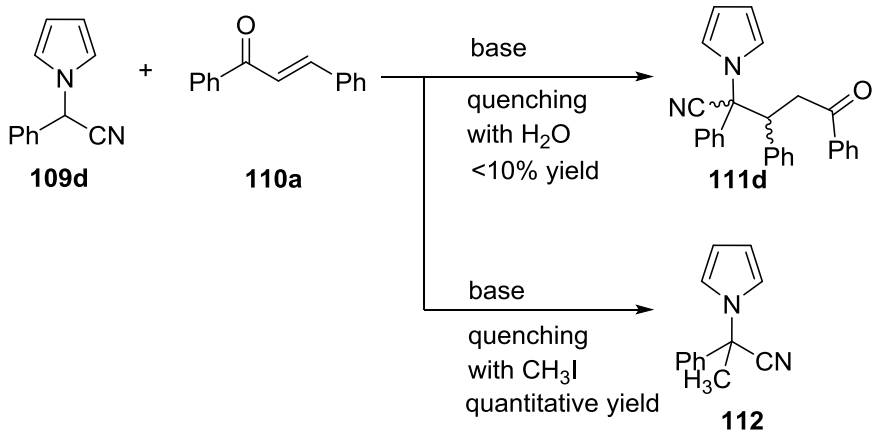


Entry	Aminonitrile	Product	Yield (%)
1	 **108a**	 **109a**	90
2	 **108b**	 **109b**	76
3	 **108c**	 **109c**	92
4	 **108d**	 **109d**	76
5	 **108e**	 **109e**	63

3.1.3.1 Initial Findings

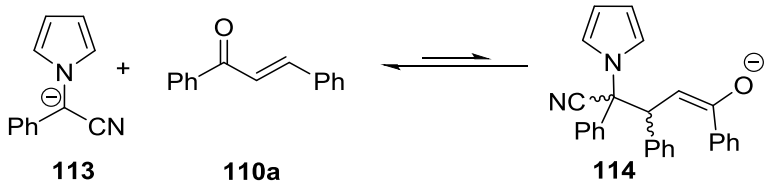
As it was outlined, the pyrrolonitrile **109d** and chalcone (**110a**) were chosen as model substrates. First, the Michael addition of deprotonated pyrrolonitrile **109d** to chalcone was investigated. Different bases such as KHMDS, LDA, NaH, and KO*t*Bu were used to deprotonate the alpha proton of the nitrile temperatures ranging from –78 °C to 25 °C in a polar aprotic solvent (*e.g.* THF, DMF). In all cases, the diastereomeric mixture of Michael adduct **111d** was obtained in less than 10% yield. To figure out the problem, some control experiments were performed. The reaction was performed in a similar way except at the end of the reaction it was quenched with an excess amount of iodomethane instead of H_2O. While

no product **111d** was detected, pyrrolonitrile **112** was obtained almost quantitatively (Scheme 57).



Scheme 57. Reactions of the deprotonated pyrrolonitrile **109d**

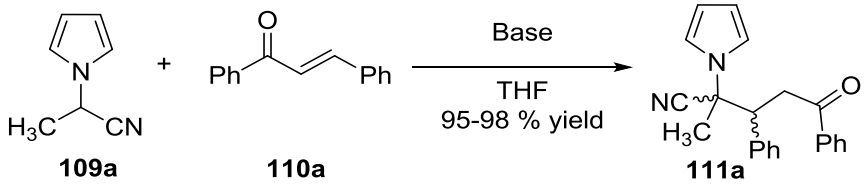
This finding proves that the pyrrolonitrile **109d** was deprotonated and was methylated. However, the formation of the Michael-adduct **111d** was reversible due to the formation of anion **113** which was more stabilized than enolate **114** (Scheme 58).



Scheme 58. Reversible Michael addition of the deprotonated pyrrolonitrile **113**

3.1.3.2 Reaction Optimization

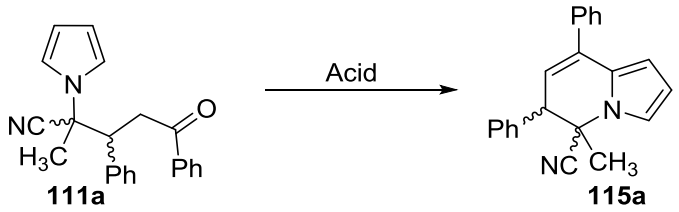
Based on this hypothesis, replacing the aryl substituent with an alkyl should overcome the problem. Indeed, when pyrrolonitrile **109a** was deprotonated with KHMDS at –78 °C or with KO*t*Bu at 0 °C or ambient temperature in dry THF, a diastereomeric mixture (1:1) of the Michael-adduct **111a** was isolated in excellent yields (Scheme 59). The highest yield (98%) was obtained in the case of KO*t*Bu in THF at 0 °C.



Scheme 59. Michael addition of pyrrolonitrile **109a**

After optimizing the conjugate addition of the deprotonated pyrrolonitrile **109a** to chalcone (**110a**), the cyclization step was investigated under various conditions. The results are summarized in Table 8. When $In(OTf)_3$ (10 mol%) was used, the cyclization and the spontaneous dehydration took place to obtain dihydroindolizine **115a** in 82% yield (entry 1). To check whether the indium has a function in the reaction or triflic acid which can be formed by the hydrolysis of the $In(OTf)_3$ plays a vital role in the cyclodehydration process, the control experiment was done by using triflic acid which is cheaper than $In(OTf)_3$. The use of triflic acid in THF resulted in the polymerization of the solvent. When THF was replaced with DMF, the target compound **115a** was obtained in 92% yield (entry 2). Cheaper acids such as AcOH or TFA either did not work or diminish the yield of the product (entries 3 and 4). The highest yield was obtained with the combination of BF_3 etherate and ethanolic AcOH (entry 6). Under these conditions, no appreciable polymerization of THF was observed.

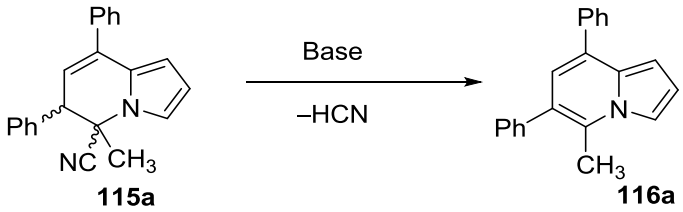
Table 8. Cyclodehydration of pyrrole **111a**



Entry	Acid	Temperature	Solvent	Yield
1	$In(OTf)_3$	25 °C	DCM	82%
2	TfOH	25 °C	DMF	92%
3	AcOH	25 °C	THF	no reaction
4	TFA	25 °C	THF	59%
5	$BF_3 \cdot OEt_2$	25 °C	THF	76%
6	**$BF_3 \cdot OEt_2$ + AcOH**	**25 °C**	**THF**	**95%**

As a last step, the dehydrocyanation reaction was investigated by reacting the dihydroindolizine **115a** with different bases (Table 9). Since the proton at *C*-6 is not strongly acidic, the use of weaker bases such as TEA and DIPEA did not produce indolizine **116a**. Inorganic salts were also ineffective except when KOH was used in ethanol–water mixture (entry 5). DBU gave 50% yield at room temperature and refluxing the reaction mixture increased the yield to 87% (entry 7).

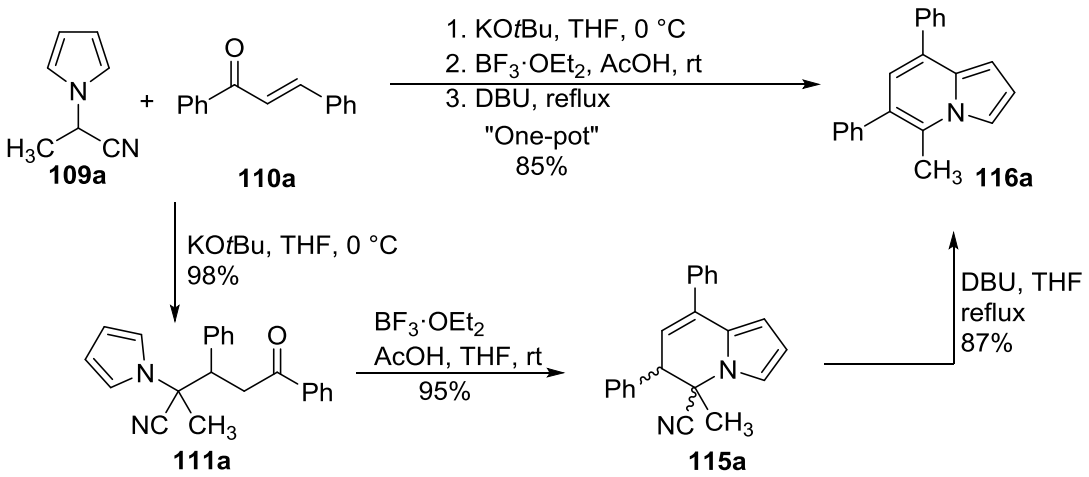
Table 9. Dehydrocyanation of dihydroindolizine **115a**



115a **116a**

Entry	Base	Temperature	Solvent	Yield
1	TEA	25 °C	THF	no reaction
2	DIPEA	25 °C	THF	no reaction
3	NaOH	25 °C	THF/H_2O	no reaction
4	KOH	25 °C	THF	no reaction
5	KOH	25 °C → reflux	EtOH/H_2O	65%
6	DBU	25 °C	THF	50%
7	**DBU**	**reflux**	**THF**	**87%**

Each of three steps were tried to optimize in THF since performing the three steps in a one-pot procedure could be easily accomplished. Applying the one-pot protocol should lower both cost and reaction time. Three reactions were then applied in a row by the consecutive addition of reagents. While the overall yield of stepwise synthesis of indolizine **116a** was 81%, the yield was slightly increased to 85% in one-pot procedure (Scheme 60).



Scheme 60. Comparison between one-pot and stepwise procedures

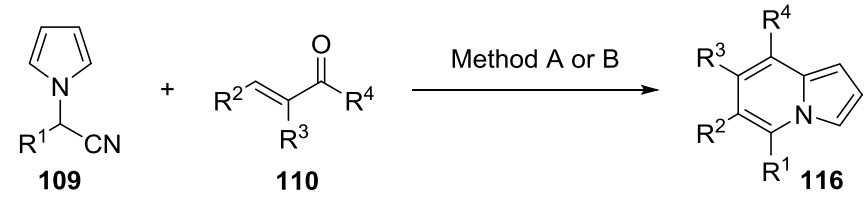
3.1.3.3 Substrate Scope Studies

Since the optimization of the one-pot procedure was successfully performed, we next examined the scope of both substrates (Table 10). All reactions were carried out on 0.50–1.00 mmol scale using 1.00 equiv. of α,β-unsaturated carbonyl compound **110**.

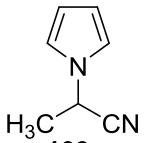
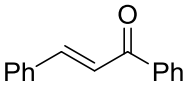
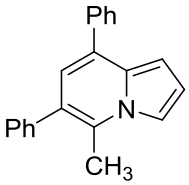
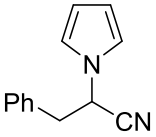
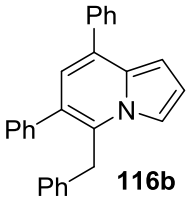
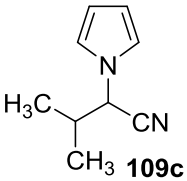
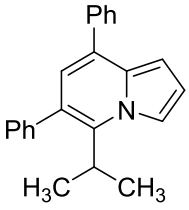
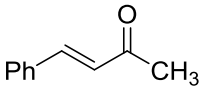
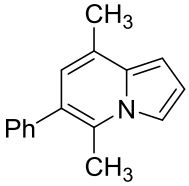
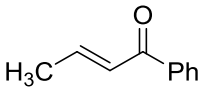
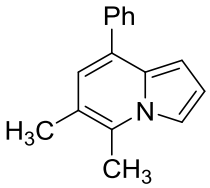
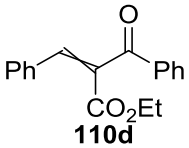
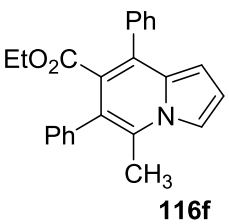
The optimized condition is named method A. An alternative method (B) was developed for harsher reaction conditions which were required in some cases. First, the substituent (R^1) on pyrroles was investigated by reacting with the enone **110a**. When the pyrroles **109c** gave indolizine **116c** in 41% yield, pyrrole **109a**–**b** and **109e** afforded indolizines in higher yields. As it was mentioned before, when R^1 is a phenyl group, the conjugate addition to the enone **110a** does not occur. However, the pyrrole **109d** was reacted with the enone **110d** containing an ester group which makes the resulting enolate more stable. Even though method A failed in the cyclodehydration step, the pyrrole **109d** was successfully annulated in one-pot to afford indolizine **116g** in 34% yield using the method B. Similarly, in order to synthesize 5,6,7,8-tetrasubstituted indolizine **116f**, it was found out that method B is much more effective than method A.

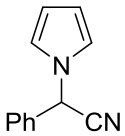
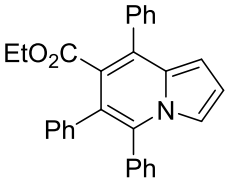
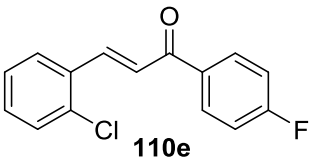
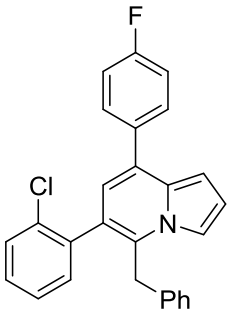
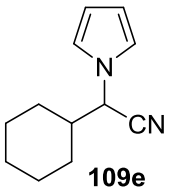
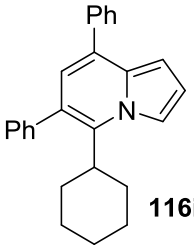
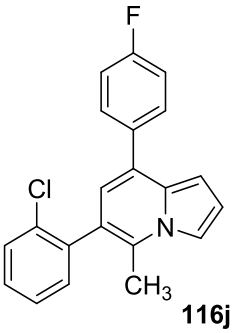
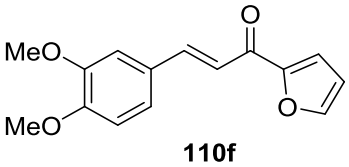
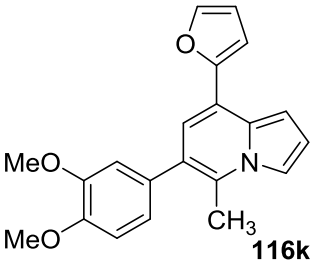
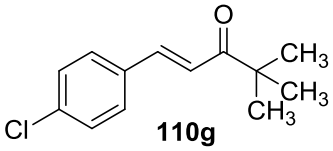
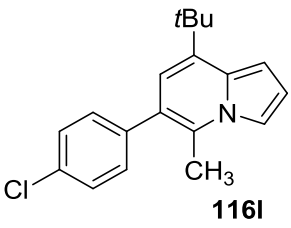
Moreover, different enones were tested by reacting them with pyrrole **109a**. It should be noted that an alkyl substituent on enones diminished the yield of indolizine **116d**–**e**. Still, a *tert*-butyl group on enone had no negative influence on the yield of indolizine **116l**.

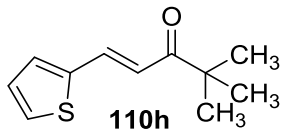
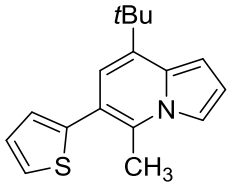
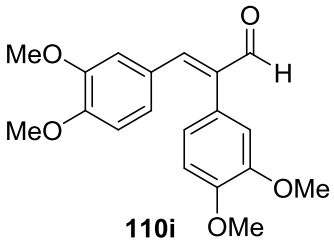
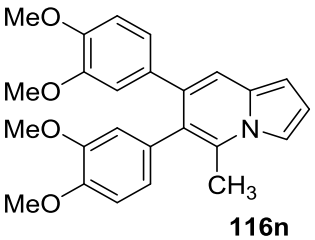
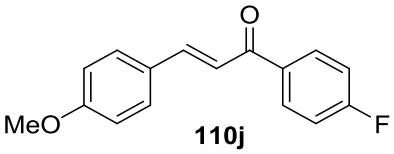
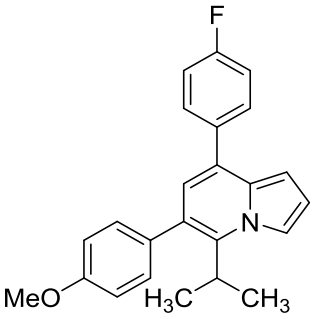
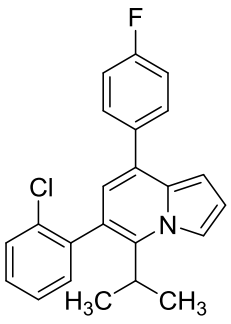
Table 10. One-pot synthesis of indolizines[a]



109 110 116

Pyrrole	Enone	Product	Method	Yield
 **109a**	 **110a**	 **116a**	A	85%
 **109b**	**110a**	 **116b**	A	54%
 **109c**	**110a**	 **116c**	A	41%
109a	 **110b**	 **116d**	A	31%
109a	 **110c**	 **116e**	A	10%
109a	 **110d**	 **116f**	B	31%

Pyrrole	Enone	Product	Method	Yield
 **109d**	**110d**	 **116g**	B	34%
109b	 **110e**	 **116h**	A	59%
 **109e**	**110a**	 **116i**	B	69%
109a	**110e**	 **116j**	A	67%
109a	 **110f**	 **116k**	A	71%
109a	 **110g**	 **116l**	A	80%

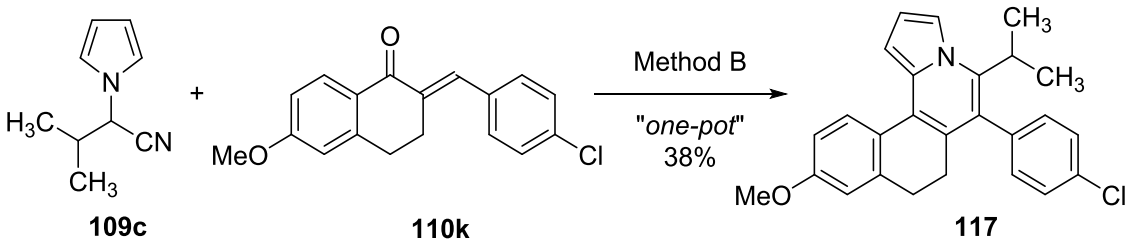
Pyrrole	Enone	Product	Method	Yield
109a	 **110h**	 **116m**	A	22%
109a	 **110i**	 **116n**	A	39% *b*
109c	 **110j**	 **116o**	A	36%
109c	**110e**	 **116p**	A	16%

[a] **Method A**: (i) KO*t*Bu, 0 °C, THF (ii) AcOH,EtOH, $BF_3 \cdot OEt_2$, rt (iii) DBU, reflux; **Method B**: (i) KOtBu, 0 °C, DMF (ii) TfOH, rt (iii) DBU, 90 °C. [b] The reaction was performed in two steps and KO*t*Bu was used for the dehydrocyanation instead of DBU at 25 °C.

In case of enone **110h**, low yield (22%) could be expected due to a highly electron-rich thiophene ring which is also susceptible to electrophilic substitution reactions. Surprisingly, indolizine **116k** was obtained in 71% yield despite bearing a furan ring on enone **110f**. Additional substituents on the aromatic ring of enones such as fluorine, chlorine, methoxy were also well tolerated. Both one-pot methods failed when acrylaldehyde **110i** was used instead of an enone. Even though the conjugate addition and cyclodehydration worked smoothly, elimination of HCN was not possible with DBU. Nevertheless, using KO*t*Bu on

the crude dihydroindolizine gave the desired 5,6,7-trisubstituted indolizine **116n** in 39% yield.

Finally, the one-pot procedure for the synthesis of indolizines was also applied to an exocyclic enone to increase the substrate scope. As an illustrative example, pyrrolonitrile **109c** was annulated with 2-(4-chlorobenzylidene)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**110k**) according to method B in one-pot fashion (Scheme 61). In other words, the nitrogen containing tetracyclic compound **117** was synthesized from pyrrole **109c** in one-pot by a conjugate addition/cyclodehydration/dehydrocyanation sequence.



Scheme 61. One-pot synthesis of tetracyclic compound **117**

One important feature of the method is easy tracking the final compounds since most of the indolizines are fluorescent. One can easily track final compounds during the whole purification steps using a portable UV-lamp (Figure 14). Although no quantitative analysis was done, it is a useful tool to monitor indolizines.

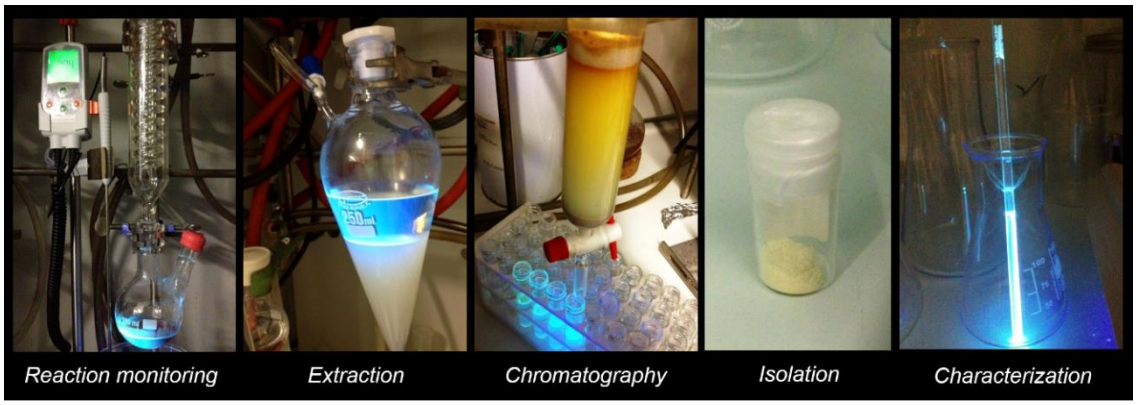
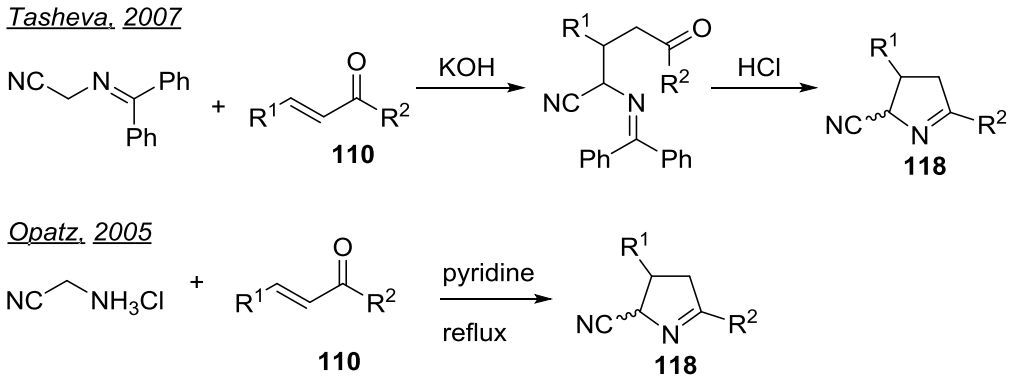


Figure 14. Tracking indolizines during the purification process

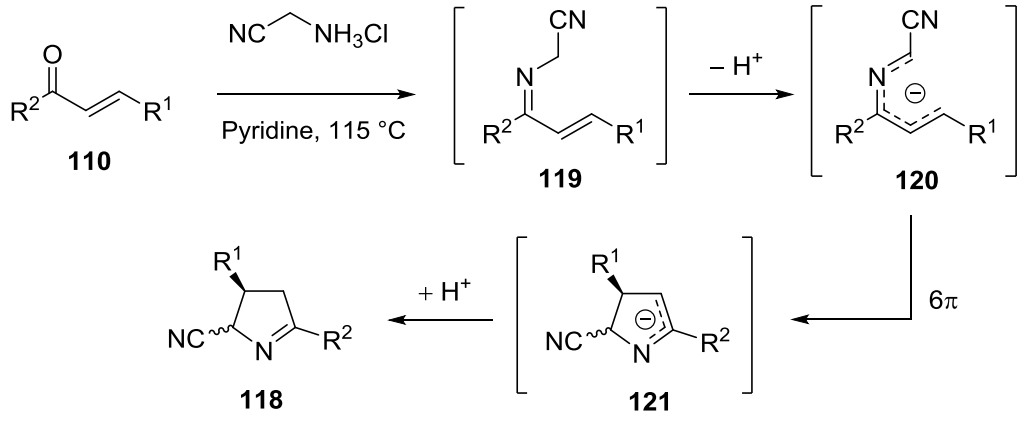
3.2 Pyrroles

3,5-Disubstituted 3,4-dihydro-2*H*-pyrrole-2-carbonitriles **118** can be considered as a common intermediate to access pyrroles with different substituent patterns. The first synthesis of cyanopyrrolines **118** has been accomplished in two steps starting from 2-(diphenylmethyleneamino) acetonitrile and enones by Tasheva in 2007 (Scheme 62).[172] Opatz and Meyer have been developed a new synthetic route to cyanopyrroline **118** by simply reacting aminonitriles with enones in the presence of pyridine.[139,173] The latter method is superior in terms of the atom-economy and efficiency to the former.



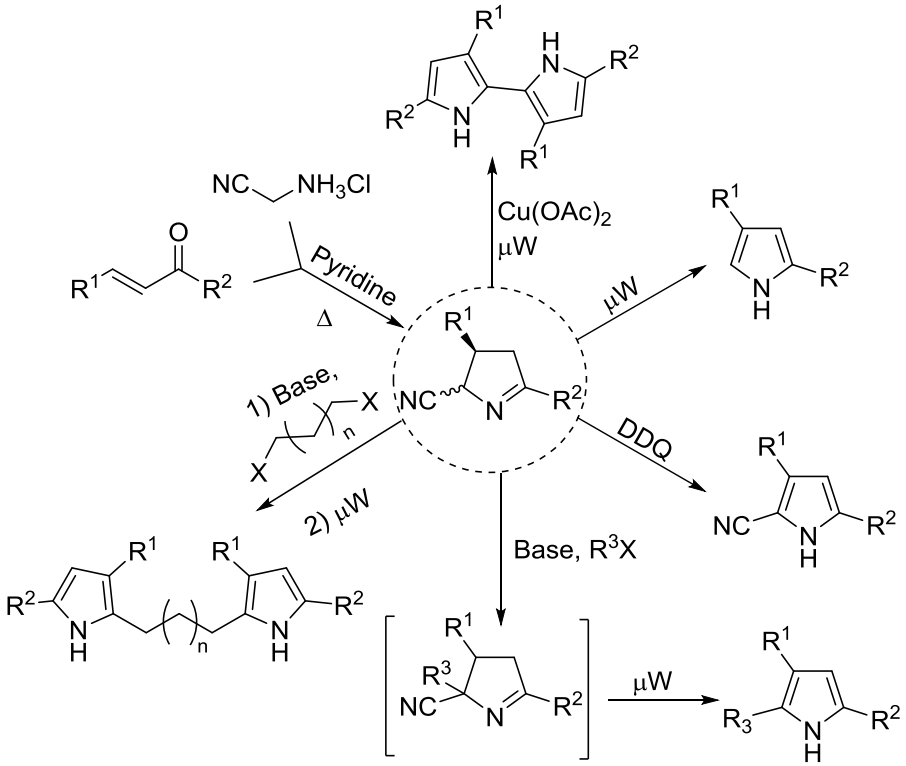
Scheme 62. Synthesis of cyanopyrrolines **118**

The proposed reaction mechanism[139,173] starts with the condensation of enone **110** with aminoacetonitrile hydrochloride. Deprotonation of α-(alkylideneamino)nitrile **119** gives 2-azapentadienyl anion **120** which transforms into 1-azaallyl anion **121** via an [6π]-electrocyclization. Diastereomeric mixture of cyanopyrroline **118** forms after a re-protonation of anion **121** (Scheme 63).



Scheme 63. Proposed reaction mechanism for the formation of cyanopyrroline **118**

Different methods were used to convert cyanopyrrolines **118** into pyrroles and bipyrroles with varied substitution patterns. These methods are depicted in Scheme 64 and further details will be discussed in the following sections.

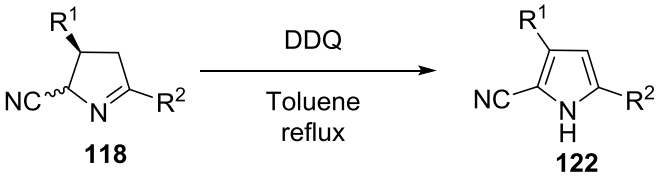


Scheme 64. Diversity-oriented pyrrole synthesis

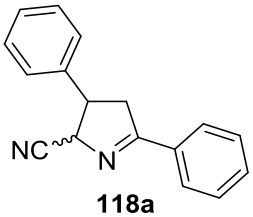
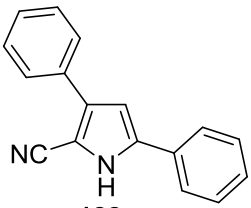
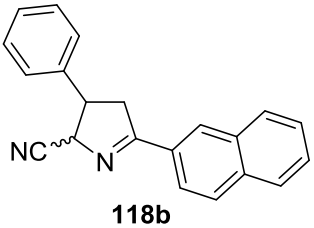
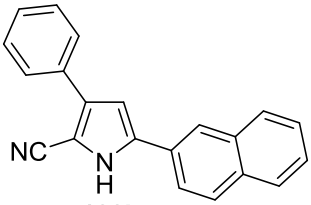
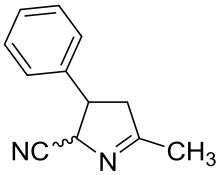
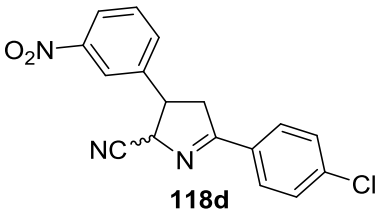
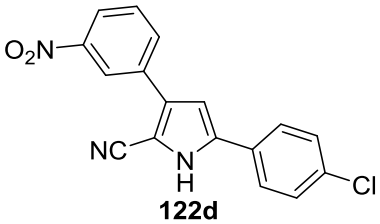
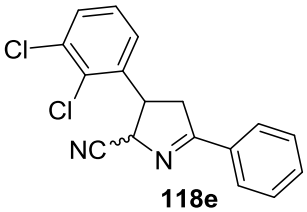
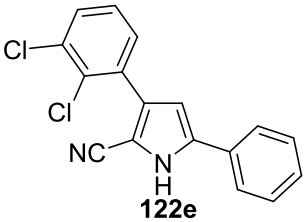
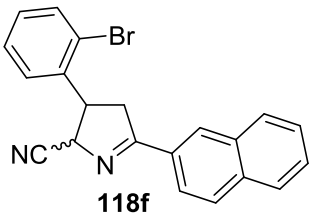
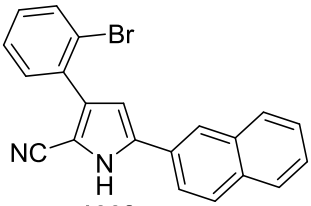
3.2.1 Pyrrole-2-carbonitriles

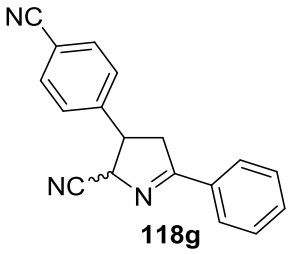
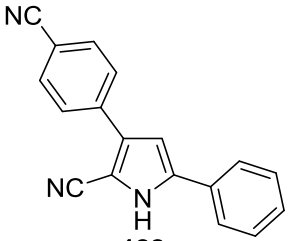
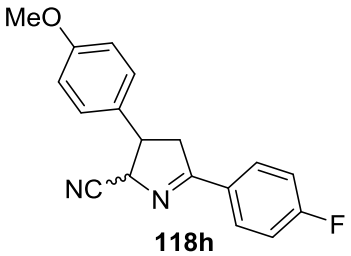
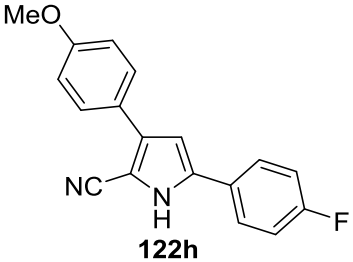
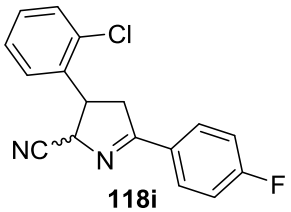
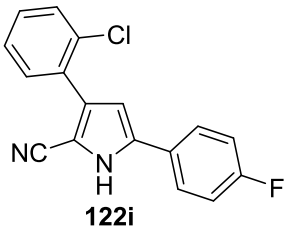
Pyrrole-2-carboxylates and 3-carboxylates could be obtained from the oxidation of pyrroline-3-carboxylates or pyrroline-2-carboxylates with chloranil[174-176] or DDQ.[177] Similar to their analogues, cyanopyrrolines **118** were also oxidized to pyrrole-2-carbonitriles **122**. The initial findings and the optimization of the reaction conditions were carried out by Marcel Heinz at the University of Hamburg.[149] The best result for the oxidation of cyanopyrrolines **118** to pyrrole-2-carbonitriles was obtained with DDQ in toluene under reflux. The optimized reaction conditions, which were developed by Heinz, were then applied to several enones to have a small library of pyrrole-2-carbonitriles **122**. The results are depicted in Table 11. The DDQ oxidation of cyanopyrrolines **118** yielded pyrrole-2-carbonitriles **122** in moderate to very high yield.

Table 11. Pyrrole-2-carbonitriles



118 122

Entry	Cyanopyrroline	Product	Yield
1	 118a	 122a	94%
2	 118b	 122b	59%
3	 118c	–	n.d.[b]
4	 118d	 122d	65%
5	 118e	 122e	71%
6	 118f	 122f	47%

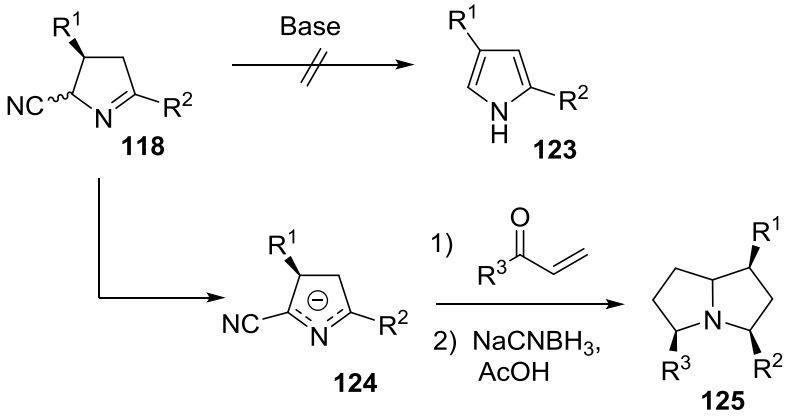
Entry	Cyanopyrroline	Product	Yield
7	 **118g**	 **122g**	70%
8	 **118h**	 **122h**	77%
9	 **118i**	 **122i**	71%

[a] Reaction conditions: Cyanopyrroline **118** (1.00 equiv), DDQ (1.15–1.20 equiv), toluene (0.05–0.07 M), 24 h. [b]Not detected.

The method tolerates both EWG and EDG functional groups such as nitro, cyano, fluoro, chloro, bromo, and methoxy on the aromatic substituents. However, cyanopyrroline **118c** which bears an alkyl substituent (entry 3) failed to give the desired pyrrole-2-carbonitrile. This can be explained by further oxidation of the product, 2-alkylpyrroles, since they can decompose via an autoxidation or oxidative dealkylation processes.[178,179]

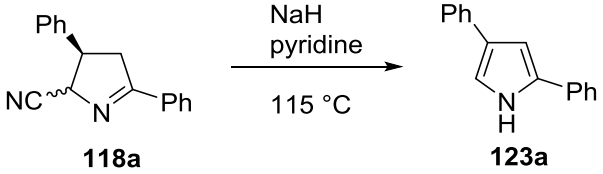
3.2.2 2,4-Disubstituted Pyrroles

In principle, cyanopyrrolines **118** can also be converted to 2,4-disubstituted pyrroles via a base induced HCN elimination. However, this path is strongly dependent on the substituent pattern of cyanopyrrolines. When the cyanopyrrolines **118** possess an acidic proton, H-2, base-induced dehydrocyanation fails since the α-elimination of the deprotonated cyanopyrroline **118** is difficult (Scheme 65). Moreover, the anion **124** could be converted to pyrrolizidine **125** via a conjugate addition/reductive cyclization sequence.[139]



Scheme 65. Deprotonated cyanopyrrolines **118**

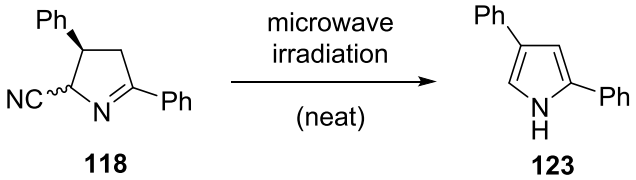
From the findings of the previous study, the dehydrocyanation of cyanopyrroline **118a** was achieved in 21% yield by using NaH in hot pyridine.[173] The use of stronger base did not improve the yield of pyrrole **123a**. Therefore, it is possible to conclude that the base may not play any important role for the dehydrocyanation reaction and the most important parameter for the reaction might be the temperature. In other words, the thermal elimination of HCN might be feasible at higher temperatures.

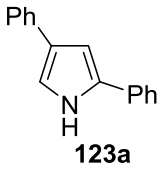
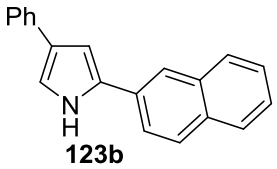
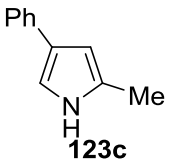
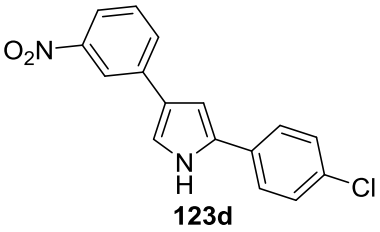
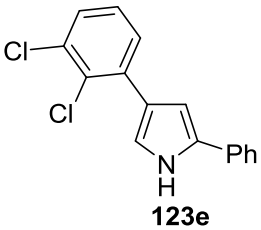
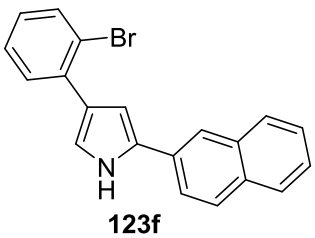


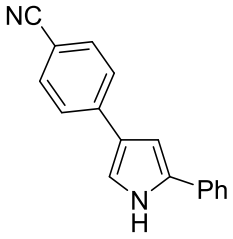
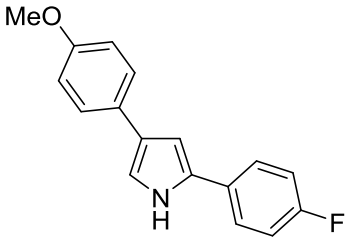
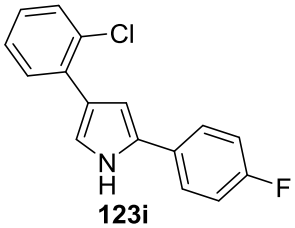
Scheme 66. Thermal dehydrocyanation of cyanopyrroline **123a**

Indeed, the product **123a** was obtained in 50% yield when the neat cyanopyrroline **118a** was heated with microwaves in the absence of a base at 150 °C. Since the reaction was performed without any solvent, it is important to set the temperature above the melting point of the cyanopyrrolines. When the reaction proceeds, the solid product forms and the rest of the starting material could be encapsulated inside the solid phase. This might explain the incomplete conversion. Therefore, the reaction temperatures were set by considering the melting point of the desired product so that full conversion can be obtained. A series of cyanopyrrolines **118** were then heated using microwave irradiation and the results are summarized in Table 12. The reactions were carried out in 0.50 mmol–1.00 mmol scale under argon atmosphere.

Table 12. 2,4-Disubstituted pyrroles



Entry	Cyano-pyrroline	Product	t(set)	t(max)	Yield
1	**118a**	 **123a**	250 °C	190 °C	81%
2	**118b**	 **123b**	250 °C	230 °C	83%
3	**118c**	 **123c**	250 °C	150 °C	43%
4	**118d**	 **123d**	250 °C	195 °C	n.d.[b]
5	**118e**	 **123e**	250 °C	220 °C	66%
6	**118f**	 **123f**	250 °C	200 °C	28%

Entry	Cyano-pyrroline	Product	t(set)	t(max)	Yield
7	**118g**	 **123g**	250 °C	230 °C	32%
8	**118h**	 **123h**	250 °C	180 °C	61%
9	**118i**	 **123i**	250 °C	160 °C	38%

[a] Microwave reaction parameters: 180 W, 30 min under air cooling. [b] Not detected.

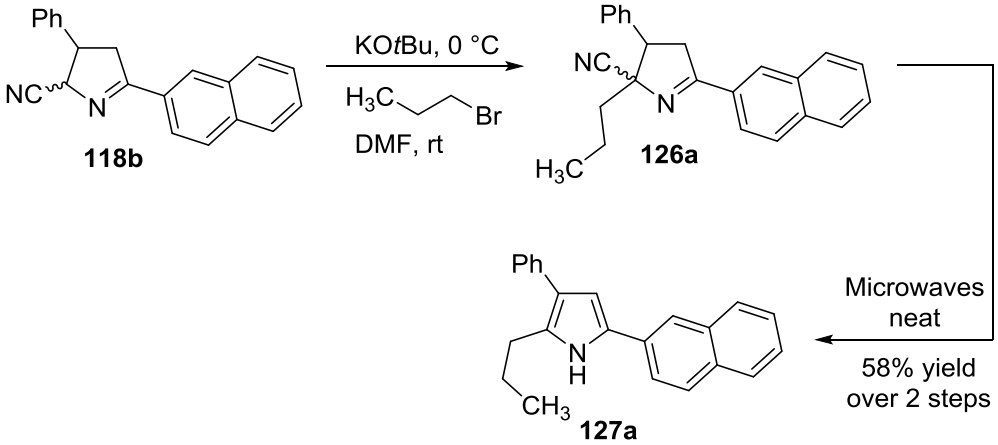
These 2,4-disubstituted pyrroles can be used as a precursor for the preparation of 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene[180,181] (known as BODIPY) dyes and their aza-analogues,[182] the 4,4-difluoro-4-bora-3a,4a,8-triaza-s-indacenes. Several multi-step synthetic procedures have been developed in the literature. For instance, 2,4-disubstituted pyrroles **123** can be obtained from conjugated unsaturated enones **110** in three steps. 1,4-Addition of nitromethane to enones followed by a partial reduction and the cyclization resulted in pyrroline which can be oxidized with selenium or sulphur at high temperature to obtain pyrrole **123** in moderate yields.[183,184] In addition, they can be synthesized in four steps (up to 50% overall yield) from enones through protected 1,4-dicarbonyl compounds obtained from the Nef reaction of nitromethane adducts.[185] The 2,4-disubsituted pyrroles **123** could be also prepared by the use of stoichiometric zirconocene dichloride, or the reaction of carbonyl compounds with vinyl azides.[186] Recently, a most practical route to these compound was reported by the use of carbohydrates as formaldehyde equivalents which are used for the microwave assisted Stetter reaction.[187] Nevertheless, our two-step synthesis of

pyrrole **123a** produces a higher overall yield starting from commercially available and inexpensive materials.

3.2.3 2,3,5-Trisubstituted Pyrroles

Further functionalization of 3,5-disubstituted 3,4-dihydro-2*H*-pyrrole-2-carbonitriles **118** is also possible by deprotonation of C-2 followed by an electrophilic addition. As mentioned before, Opatz and co-workers reported a conjugate addition of deprotonated cyanopyrrolines **118** to a Michael acceptor followed by a reductive amination/cyclization sequence to furnish pyrrolizidines **125** (Scheme 65).[139] Since the reaction works smoothly with DBU in THF at room temperature, the use of other electrophiles should also be possible to obtain more diverse pyrroles. However, Meyer reported that the reaction failed when benzyl chloride was used as an electrophile under identical condition due to a reaction between benzyl chloride and DBU.[173] Thus, DBU is not a suitable base for alkylation.

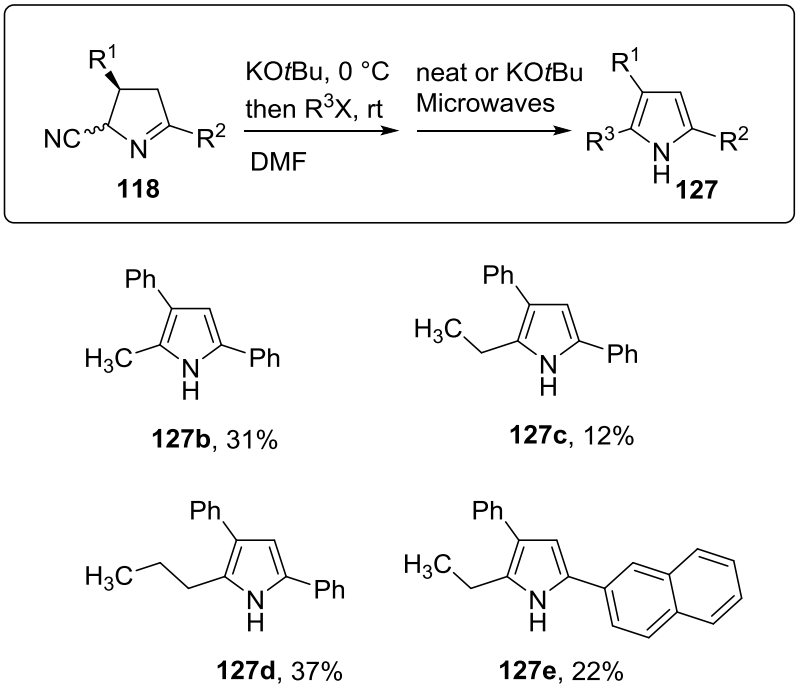
Based on this knowledge, a stronger base which can deprotonate cyanopyrrolines but not react with the alkylating agent has to be chosen. As a test reaction, cyanopyrroline **118b** was deprotonated with KO*t*Bu in DMF at 0 °C, followed by a C-2 alkylation with *n*-propyl bromide at room temperature. LC-MS and TLC analyses proved the complete conversion of the starting material **118b** into the alkylated dihydropyrrole **126a**. After an extractive work-up, the crude product was transferred into a microwave vessel for the dehydrocyanation process to obtain pyrrole **127a** in 58% yield based on the cyanopyrroline **118b**.



Scheme 67. Synthesis of pyrrole **127a**

Next, different alkyl halides were used to show the general applicability of the method. The results are summarized in Scheme 68. The reactions were carried out in 0.75–1.00 mmol

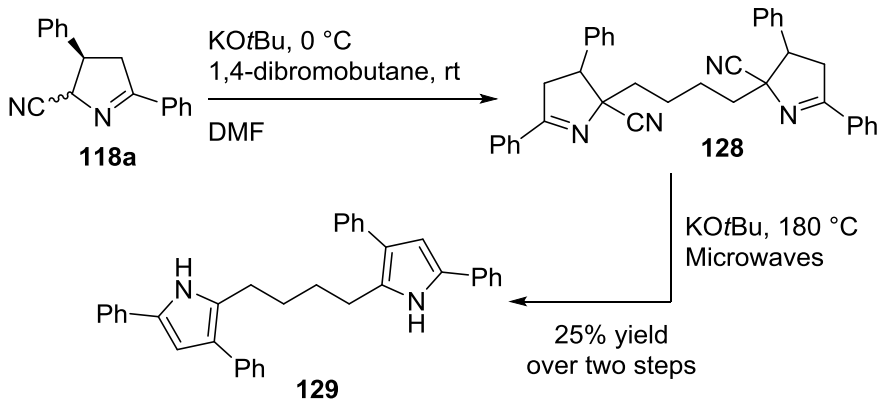
scale. In all cases, intermediates were not isolated and used immediately after an extractive work-up. For the dehydrocyanation step, an alternative method was used in some cases where KO*t*Bu was used in DMF.



Scheme 68. 2,3,5-Trisubstituted pyrroles **127**

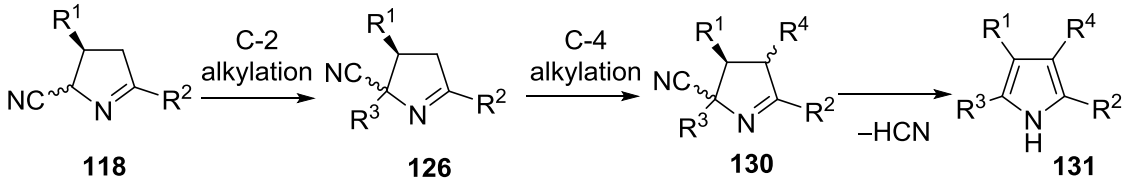
Although the alkylation proceeds smoothly, an efficient method for the elimination of HCN could not be found, yet. Both dehydrocyanation methods were resulted in the decomposition of the intermediate. Methylation was succeeded by the use of methyl iodide whereas corresponding alkyl bromides were used for ethylation and propylation. In none of the experiments, N-alkylated pyrroles were detected.

Furthermore, the method also allows to access dipyrroles that two pyrrole rings are connected with an alkyl chain. As an illustrative example, dipyrrole **129** was synthesized from cyanopyrroline **118a** (Scheme 69). When cyanopyrroline was deprotonated with KO*t*Bu and was reacted with half equivalent of 1,4-dibromobutane, dipyrrole **129** was obtained in 25% yield after a base assisted HCN elimination with microwave heating.



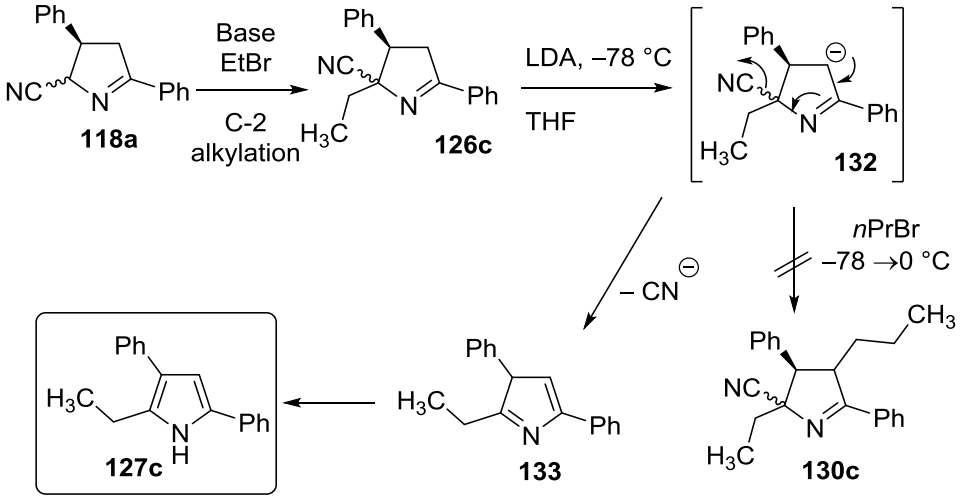
Scheme 69. Bis(pyrrol-2-yl)butane **129**

Later, application of the method was tried to expand for the synthesis of 2,3,4,5-tetrasubstituted pyrroles using a sequential alkylation. Since the C-2 alkylation of cyanopyrrolines **118** works well, it was planned to alkylate the fourth position of a dihydropyrrole by deprotonating C-4 using a strong base.



Scheme 70. Proposed double alkylation of cyanopyrrolines

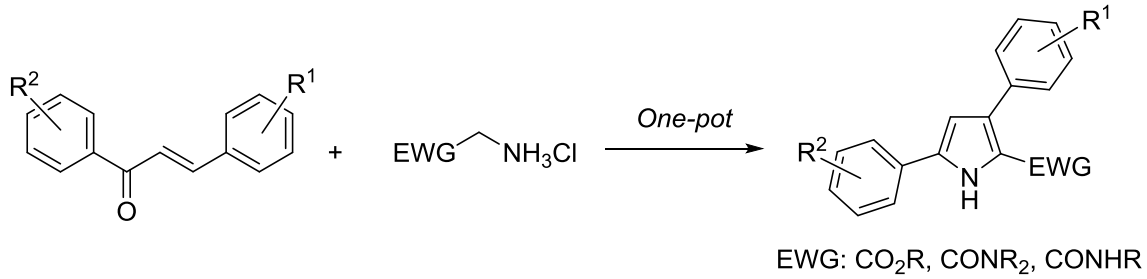
In order to apply the double alkylation method, several bases were used such as KO*t*Bu, KHMDS and LDA. Neither KHMDS was able to deprotonate C-4 of the C-2 alkylated intermediate nor KO*t*Bu. Since LDA is a stronger base than former bases, it deprotonated the C-4 however the C-alkylation did not proceed while a dehydrocyanation product was obtained in 62% yield (Scheme 71). It was not possible to trap the anion **132** using a primary halide even at low temperatures. Nevertheless, when LDA was used, the yield of pyrrole **127c** was higher than in the method shown in Scheme 68 (12% yield). LDA-assisted dehydrogenation of other C-2 alkylated cyanopyrrolines should also be investigated to increase the efficiency of 2,3,5-trisubstituted pyrroles.



Scheme 71. Failed double alkylation reaction

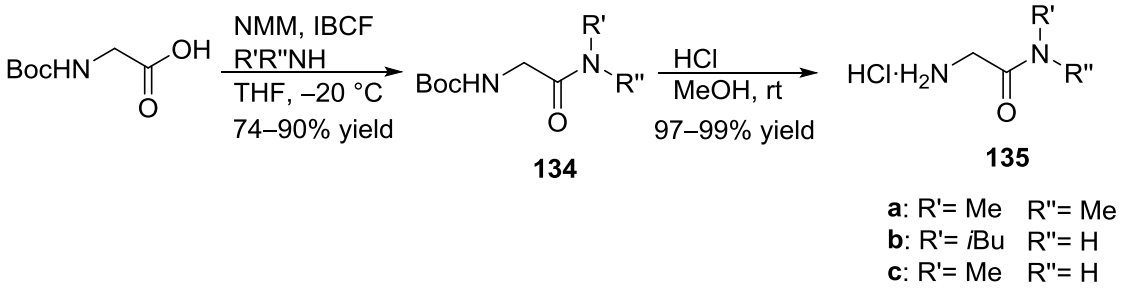
3.2.4 Pyrrole-2-carboxamides

Similar to the two-step synthesis of pyrrole-2-carbonitriles **122** (chapter 3.2.1), pyrrole-2-carboxylates and -carboxamides can also be prepared from enones using glycine ester or amides instead of aminoacetonitrile (Scheme 72). The method optimization and the synthesis of pyrrole-2-carboxylates were performed by Imbri and Netz.[188] Here, the preparation of glycine amides and pyrrole-2-carboxamides will be discussed in detail.



Scheme 72. One-pot access to pyrrole-2-carboxylates and –carboxamides

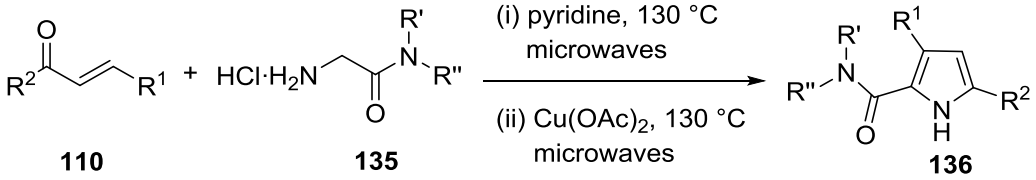
Although some of the glycine amides are commercially available, they were prepared on a gram-scale according to the literature with slight modifications. Haufe et al. reported an efficient racemization-free amidation of Boc protected amino acids via a mixed anhydride method using *N*-methyl morpholine (NMM) and isobutyl chloroformate (IBCF). The preparation of glycine amides **135** were achieved in two steps starting from Boc-Gly-OH via an amidation/deprotection sequence (Scheme 73).[189]



Scheme 73. Preparation of glycine amides **135**

After preparing glycine amides **135**, they were converted into pyrrole-2-carboxamides **136** by reacting with enones **110** in hot pyridine and oxidizing the corresponding dihydropyrroles with copper (II) acetate (1.2 or 2.0 equiv) in a one-pot fashion (Table 13).

Table 13. Pyrrole-2-carboxamides[a]



Entry	R^1	R^2	R’	R’’	Product	Yield
1	Ph	Ph	Me	Me	**136a**	46%[b]
2	Ph	Ph	Me	Me	**136a**	55%[c]
3	Ph	Ph	H	*i*Bu	**136b**	59%[b]
4	4-MeO-C_6H_4	4-F-C_6H_4	H	*i*Bu	**136c**	43%[c]
5	Ph	Ph	H	Me	–	n.r.
6	Ph	Ph	H	H	–	n.r.

[a] Reaction conditions: (i) enone **110** (1.00 mmol), glycine amide **135** (1.20 mmol), MS 3Å, pyridine (4 mL) at 130 °C, microwave irradiation (ii) $Cu(OAc)_2$ (1.20 or 2.00 mmol) at 130 °C, microwave irradiation. [b] Oxidation was performed with 1.20 equiv. $Cu(OAc)_2$.[c] Oxidation was performed with 2.00 equiv. $Cu(OAc)_2$.

Tertiary amide **135a** was reacted with chalcone (**110a**) smoothly and increasing the amount of the copper salt to 2.0 equiv improve the yield of pyrrole **136a** slightly (entry 2 compared to entry 1). The method can also tolerate secondary amines when R’’ is isobutyl (entries 3 and 4). Unfortunately, *N*-methyl glycine amide (**135c**) did not react with chalcone (entry 5). This activity difference can be explained by their solubilities in hot pyridine. It was observed that when a secondary amide has a small R-group (Me), it is either completely insoluble or

slightly soluble in this environment. A similar trend was observed with the primary amide (entry 6). The dimeric structure of pyrrole-2-carboxamide **136c** was also unambiguously proved by X-ray analysis (Figure 15).

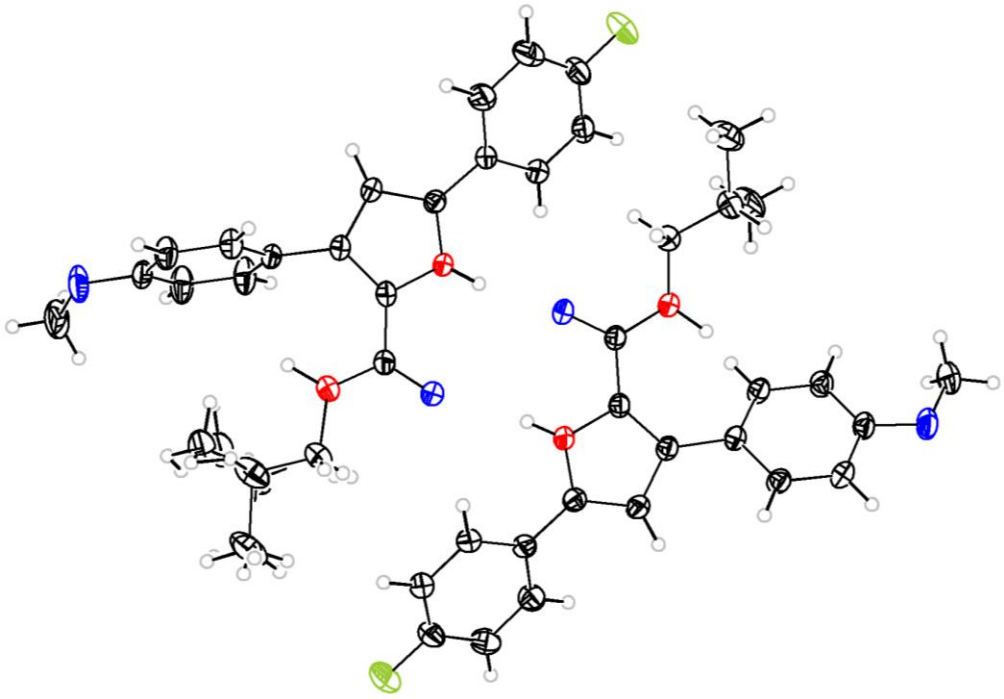
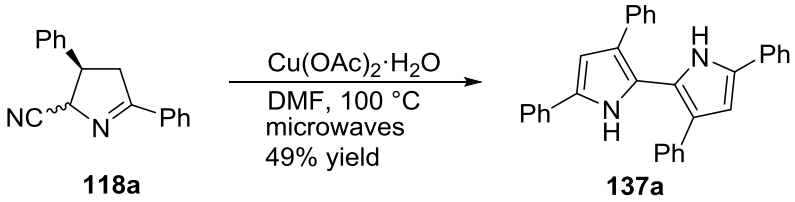


Figure 15. X-ray structure of pyrrole-2-carboxamide **136c**

3.2.5 2,2'-Bipyrroles

While the optimization of the dehydrocyanation reaction for the synthesis of 2,4-disubstituted pyrrole **123** was attempted, several transition metal salts were tested. Since the nitrile can coordinate to a metal cation from the nitrogen atom, adding metal salts might weaken the C–CN bond that ease the removal of the nitrile. During our investigation, it was observed that microwave heating of cyanopyrroline **118a** in the presence of copper (II) acetate monohydrate (3.0 equiv) resulted in a dimerized product **137a** (Scheme 74).



Scheme 74. Synthesis of 2,2'-bipyrrole **137a**

In order to optimize the reaction conditions, several conditions were applied. While the increase in temperature from 100 °C to 120 °C did not affect the yield, it was diminished when the reaction was performed at 150 °C. The reaction also worked with 1.00 equiv of $Cu(OAc)_2 \cdot H_2O$, it ceased completely with a catalytic amount (10 mol%) of the copper source. No product was obtained when iron (III) chloride was used instead of copper salt. Unfortunately, the yield of bipyrroles **137a** could not be improved.

From the reaction mixture, pyrrole-2-carbonitrile **122a** was obtained as a by-product. The structure of the by-product was also proved by X-ray analysis (Figure 16). The crystal structure of the compound **122a** is disordered and below only one structure is shown for clarity.

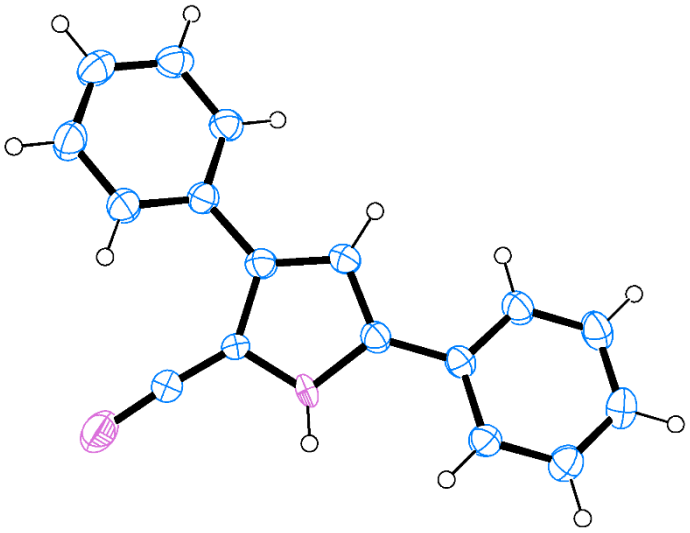
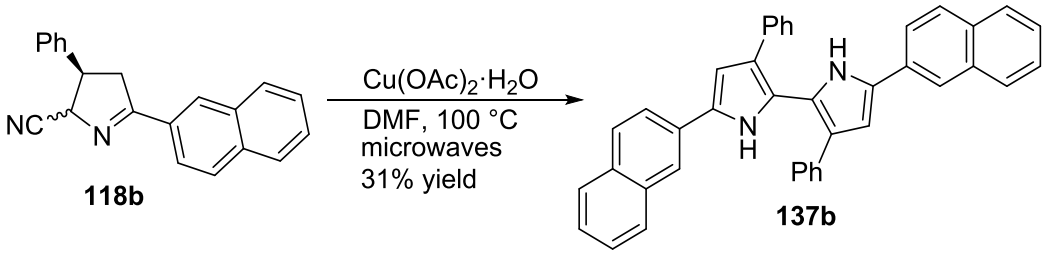


Figure 16. X-ray structure of pyrrole-2-carbonitrile **122a**

Moreover, bipyrrole **137b** was also obtained in 31% yield from the homo-coupling reaction of cyanopyrroline **118b** under identical conditions (Scheme 75).

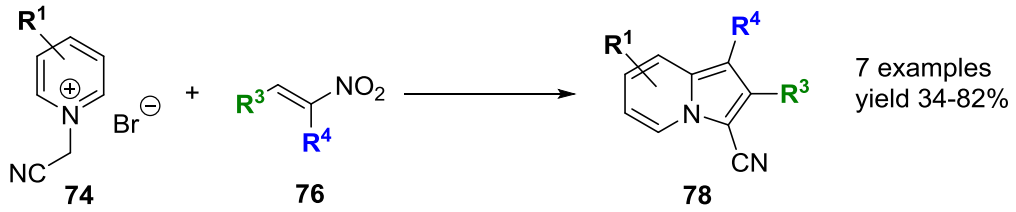


Scheme 75. Synthesis of 2,2'-bipyrrole **137b**

Formation of 2,2'-bipyrroles can be explained by a single electron transfer from copper (II) to the deprotonated cyanopyrrolines. Homo-coupling of the resulting aza-allyl radicals followed by the removal of two equivalents HCN gives bipyrroles. As an alternative route, firstly, dehydrocyanation of cyanopyrrolines to form 2,4-disubstituted pyrroles can takes place. Later, 2,2'-bipyrroles might form by dimerization. 2,4-Disubstituted pyrroles can be treated with $Cu(OAc)_2$ under identical condition and if 2,2'-bipyrroles do not form, the alternative route can be ruled out. In case of the formation of 2,2'-bipyrroles from directly 2,4-disubstituted pyrroles, further experiments should be performed to understand the reaction mechanism.

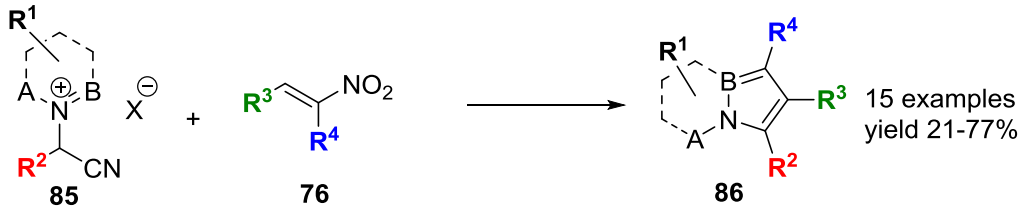
4 Conclusion and Outlook

Indolizine-3-carbonitriles **78** were prepared from pyridinium salts and nitroalkenes via a formal [3+2]-cycloaddition/oxidation sequence (Scheme 76). Silver (I) carbonate was chosen since it can be both used as an oxidant and a base. High yields were obtained from the reactions of β-arylnitroalkenes. However, yields decreased when R^3 is an alkyl substituent.



Scheme 76. Indolizine-3-carbonitriles

Furthermore, indolizines without any electron-deficient substituents were synthesized from pyridinium salts and nitroalkenes when R^2 is different than a proton (Scheme 77). Since all reported indolizine syntheses via a 1,3-dipolar cycloaddition are limited to at least one EWG in the structure, our method overcome this severe limitation using removable electron-withdrawing groups (REWG).

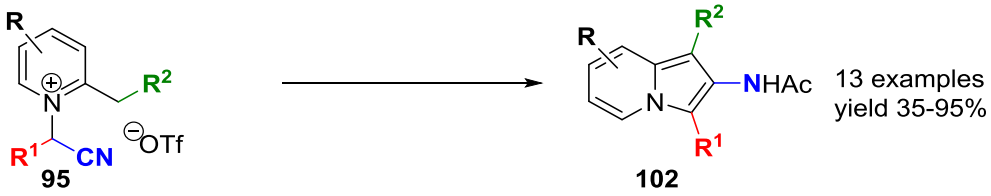


Scheme 77. Indolizines without EWGs

After the formal [3+2]-cycloaddition of pyridinium ylides **85** to nitroalkenes **76**, double elimination of HCN and HNO_2 yielded indolizines **86**. Unlike the synthesis of indolizine-3-carbonitriles **78**, the reaction requires an excess amount base and there is no need to use an oxidant. While pyridinium salts **85** were prepared from the corresponding pyridines and cyanohydrin triflates which were synthesized in two steps from aldehydes via a Strecker reaction followed by triflylation, nitroalkenes were obtained via a nitroaldol condensation of nitroalkanes with aldehydes. Overall, the indolizine core was constructed from two different aldehydes, a nitroalkane, and a pyridine. This method was then also applied to different

nitrogen-containing aromatic compounds such as isoquinolines, phthalazines, imidazoles, and benzothiazoles to access pyrroloisoquinolines, pyrrolophthalazines, pyrroloimidazoles and pyrrolobenzothiazoles, respectively.

While exploring the [3+2]-cycloaddition of pyridinium ylides to unactivated alkynes, the formation of an unexpected product was observed and it was identified as 2-aminoindolizine **97**. Mechanistically, the reaction is an analogue of Tschitschibabin's approach to indolizines which form via an intramolecular cyclization of carbonyl-stabilized 2-alkylpyridinium ylides. In the same manner, 2-aminoindolizines **97** were obtained via an intramolecular 5-exo-dig cyclization of nitrile-stabilized 2-alkylpyridinium ylides that were prepared by N-alkylation of 2-picolines **94** with cyanohydrin triflates **84**. It was found that the products **97** were unstable against light and moisture, the isolation of the free amines failed due to their high electron density. In a long term storage, the 2-aminoindolizine **97a** was decomposed to give α-amino-α,β-unsaturated ketone **101** (Scheme 49, p. 42). The isolation problem was overcome by storing 2-aminoindolizines as their acetylated forms (Scheme 78). The protection was performed *in situ* after cyclization. The structure was unambiguously proven by X-ray analysis (Figure 12, p. 46). The method also tolerates ester substituents and works with isoquinolinium salts. The substrate scope is limited to 6-unsubstituted 2-alkylpyridines.



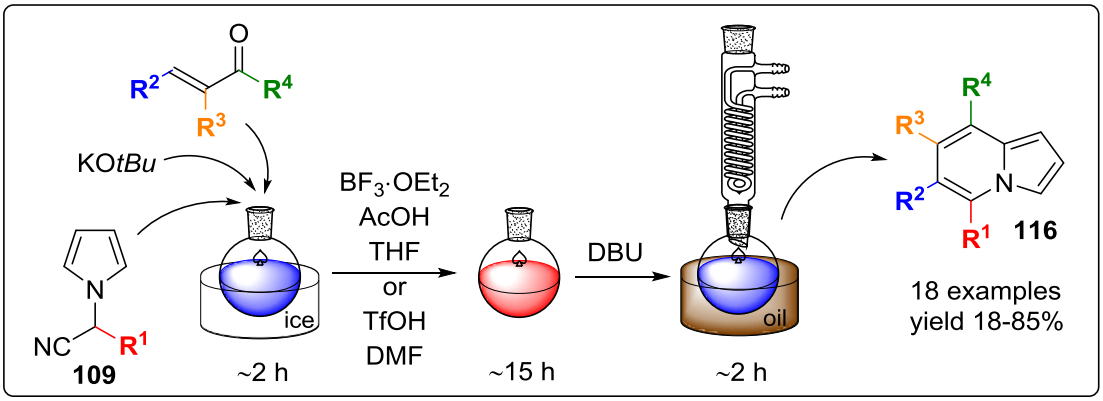
Scheme 78. Acetylated 2-aminoindolizines **102**

When 2,6-disubstituted pyridines were used, the N-alkylation failed and elimination of triflate was observed. Although other azinium salts from 2-methylpyrimidine, 2-methylbenzothiazole and 3-methylisoquinoline were prepared using triflate **84a**, the cyclization did not work in these cases (Figure 13, p. 48). Further transformation of *N*-acetyl-1-arylsubstituted 2-aminoindolizine **102d** to indolizino[2,1-*c*]isoquinoline **107** by a Bischler-Napieralski reaction also failed (Scheme 53, p.48).

The method was applied to harmine (**103**) and furnished the tetracyclic indoloindolizine **105** (Scheme 51, p. 47). In the reaction, the N–H proton of indole was also tolerated and the

annulation of harmine was achieved without prior N-protection. In this case, the free amine form was stable enough to isolate it without converting it into an amide.

In contrast to the synthesis of indolizines from pyridines, the annulation of pyrroles is rare. Few methods allow to prepare indolizines carrying various substituents in positions 5–8. In this context, a novel method was developed to synthesize 5,6,7,8-tetrasubstituted indolizines **116** from 1-(1-cyanoalkyl)pyrroles **109** in a one-pot strategy (Scheme 79). This method allows to prepare indolizines up to four substituents on the pyridine unit.

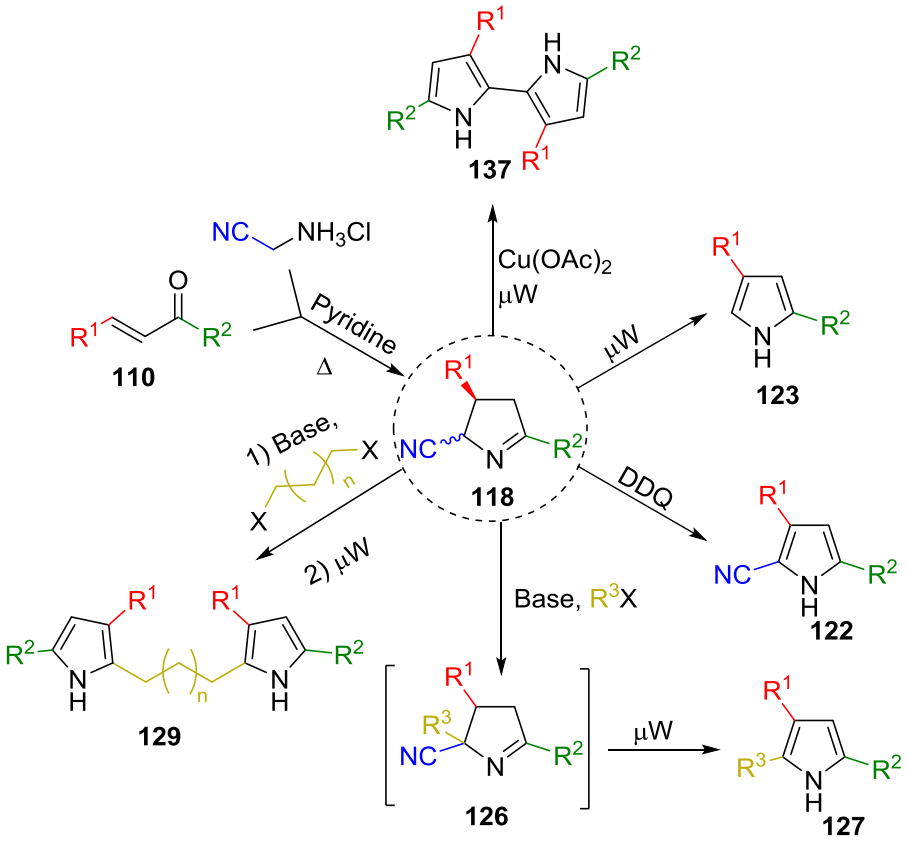


Scheme 79. Decoration of the pyridine ring of indolizines in a one-pot procedure

Pyrrolonitriles **109** were annulated with enones as three-carbon units via a conjugate addition/cyclodehydration/dehydrocyanation sequence. Each step was optimized separately and then the reaction was performed in a one-pot fashion. The Michael addition of the deprotonated aminonitriles to enones followed by acid-catalyzed cyclization and simultaneous dehydration produces 5,6-dihydroindolizines **115**. From these stable intermediates, the substituted indolizines **116** were obtained via base-induced dehydrocyanation in good yields. In other words, pyrrolonitriles **109** can be annulated by a consecutive addition of a base, acid, and base. Two different reagent systems were developed. The first method is the KO*t*Bu/BF_3·OEt_2+AcOH/DBU in THF. The second method which is KO*t*Bu/TfOH/DBU in DMF was used where the first one failed. DMF was preferred instead of THF since the latter polymerizes in the presence of TfOH. Exocyclic enones were also found to be suitable substrates for the annulation of pyrrolonitriles. As an illustrative example, pyrrolonitrile **109c** was annulated using exocyclic enone **110k** to furnish tetracyclic product **117** (Scheme 61, p. 59).

3,4-Dihydro-2*H*-pyrrole-2-carbonitriles **118** can be considered as a common precursor for the preparation of pyrroles bearing various substituents (Scheme 80). The optimization of

the DDQ oxidation of 3,4-dihydro-2*H*-pyrrole-2-carbonitriles which were prepared from enones and aminoacetonitrile hydrochloride in boiling pyridine[139,173] to obtain pyrrole-2-carbonitriles **122** was carried out by Heinz.[149] The optimized conditions were then applied to different cyanopyrrolines to get a small library of pyrrole-2-carbonitriles **122**. Moreover, the low yielding base-assisted dehydrocyanation of cyanopyrrolines **118** was improved and optimized by using microwave heating. The products, 2,4-disubstituted pyrroles **123** were obtained in moderate to high yields.

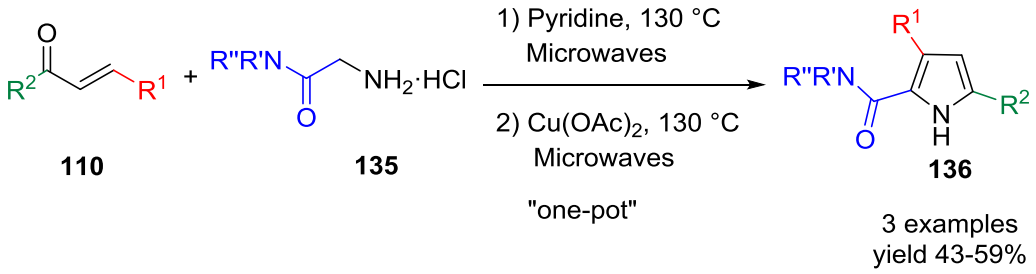


Scheme 80. Pyrroles with different substituent patterns

The diversity of products can be increased by further manipulations such as C-alkylation followed by dehydrocyanation. Cyanopyrrolines **118** were deprotonated with KO*t*Bu at 0 °C and were then alkylated using primary alkyl halides to obtain 2,3,5-trisubstituted cyanopyrrolines **126**. Subsequent elimination of HCN by microwave heating either neat or in the presence of KO*t*Bu gave 2,3,5-trisubstituted pyrroles **127**. The synthesis of similar products from the reaction of enones and α-aminonitriles which could be prepared from aldehydes via a Strecker reaction were previously reported by our group.[139] However, the alkylation/dehydrocyanation method allows to access different pyrroles in a modular fashion

in which the R^3 substituent on pyrrole ring can be inserted at a late stage. α,ω-Dihaloalkanes were also used in order to obtain dipyrroles **129** which are connected by alkyl linkers. Finally, 3,3',5,5'-tetrasubstituted 2,2'-bipyrroles **137** were synthesized from the same precursors **118** in the presence of superstoichiometric amounts of $Cu(OAc)_2$ under microwave heating. Two different mechanisms can be considered and further investigations should be done in order to rule out one of them. The reaction might proceed through the oxidative dimerization of 2,4-disubstituted pyrroles. The other possibility is the oxidative coupling of the deprotonated cyanopyrrolines followed by elimination of two equivalents HCN.

Similarly, the DDQ-oxidation of 3,4-dihydro-2*H*-pyrrole-2-carboxylates gave pyrrole-2carboxylates. The two steps can be performed in a one-pot procedure. This method was developed in the research group of Opatz by Imbri and Netz.[188] Later, it was observed that DDQ can also be replaced with Cu^{2+} and it is even possible to use catalytic amount of copper in some cases. As a part of this project, the substrate scope was increased by using glycine amides as well. Hydrochloride salts of glycine amides **135** were prepared from Boc-Gly-OH in two steps without using chromatographic separation. The one-pot synthesis of pyrrole-2-carboxamides **136** from glycine amides **135** were successfully achieved via an electrocyclization/oxidation sequence (Scheme 81).



Scheme 81. Pyrrole-2-carboxamides

5 Experimental Section

5.1 General Experimental Methods

Solvents and Chemicals

All reactions were carried out in dried glassware and in an inert atmosphere (argon) in anhydrous solvents using standard syringe and septa techniques. Anhydrous THF was distilled from potassium under argon. Diethyl ether and toluene were distilled from sodium and benzophenone under argon atmosphere. The solvents used for chromatography were distilled prior to use. All other solvents and reagents were purchased from commercial suppliers and were used without further purification. Anhydrous DMF and acetonitrile over molecular sieves were purchased from commercial suppliers. All the optically active compounds were prepared as a racemic mixture unless otherwise stated.

Chromatography

TLC experiments were carried out on aluminum sheets coated with silica gel 60 F_{254} (Merck) and spots were visualized with UV-light (254 nm or 360 nm) and developed with $KMnO_4$, Seebach's reagent, phosphomolybdic acid reagent or ninhydrin and heating if necessary. Column chromatography was carried out on silica gel purchased from Acros Organics (particle size: 32–63 μm, pore diameter: 60 Å) or Macherey-Nagel (particle size: 25–40 μm, pore diameter: 60 Å).

Melting Point Determination and Elemental Analysis

Melting point ranges were determined with a Krüss digital melting point apparatus or with a Dr. Tottoli apparatus from Büchi and are uncorrected. Elemental analysis of compounds was determined with a CHN-O-Rapid instrument (Heraeus).

NMR

NMR spectra were recorded with Bruker AC300, AV2-400, ARX400 and AV3-600 spectrometers. The spectra were measured in $CDCl_3$, DMSO-d_6, CD_3CN, or methanol-d_4 at ambient temperature and the chemical shifts were referenced to the residual solvent signal ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.16 ppm; DMSO-d_6: δ H = 2.50 ppm, δ C = 39.52 ppm, CD_3CN δ H = 1.94 ppm, δ C = 1.32 ppm).[190] ^{1}H NMR data are reported as follows: chemical

shift (parts per million, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sep = septet, dd = doublet of doublets, ddd = doublet of doublet of doublets dt = doublet of triplets, m = multiplet, br = broad, app = apparent), coupling constant (Hz), integration and assignment. The numbering is made according to the IUPAC name of the compounds.

Infrared Spectroscopy

IR spectra were recorded on routine FTIR spectrometer (Bruker Optics Tensor 27) using a diamond ATR unit.

Mass Spectroscopy

MS spectra were recorded on a linear ion trap LC/MSD detector (ESI-MS). ESI-HRMS spectra were recorded on Waters Q-TOF- Ultima III instrument with a dual source and a suitable external calibrant.

Microwave experiments

The Microwave experiments were carried out in a CEM Discover monomode apparatus at the indicated maximum temperature and power using air cooling.

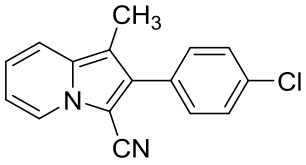
5.2 Annulation of pyridines

5.2.1 Synthesis of Indolizines from Pyridinium Ylides

General procedure-I for indolizine-3-carbonitriles 78

Pyridinium bromide **74** (1.00 equiv.) and the nitroolefin **76** (1.00 equiv.) were dissolved in freshly distilled THF (20 mL/mmol nitroolefin) at room temperature. Ag_2CO_3 (2.00 equiv.) was added in one portion and the reaction mixture was heated to reflux under argon atmosphere for 2 h. The solvent was removed in vacuo and the remaining solid was extracted with ethyl acetate. The solution was decanted and washed with water. The crude product was extracted with ethyl acetate and the combined organic layers were dried over $MgSO_4$ and the solvent was removed in vacuo.

2-(4-Chlorophenyl)-1-methylindolizine-3-carbonitrile (78a)



The title compound was prepared according to the general procedure-I from **74a** (1.00 mmol) and *(E)*-1-chloro-4-(2-nitroprop-1-enyl)benzene **(76a**, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 216 mg (0.81 mmol, 81%), colorless solid.

Mp: 156–159 °C.

R_f = 0.44 (ethyl acetate/cyclohexane 1:5).

IR (ATR) $\tilde{\nu}$ = 3094, 2922, 2195, 1382, 1096, 828, 740, 725 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 8.22 (dt, *J* = 6.8, 0.9 Hz, 1H, H-5), 7.50–7.44 (m, 5H, H-8, 4 H_{Ar}), 7.01 (ddd, *J* = 9.0, 6.8, 0.9 Hz, 1H, H-7), 6.80 (td, *J* = 6.8, 1.2 Hz, 1H, H-6), 2.33 (s, 3H, C*H*$_3$) ppm.

^{13}C NMR, HSQC, HMBC (75 MHz, $CDCl_3$) δ = 135.3 (C2), 135.2 (C9), 134.2 (C_q), 131.0 (C_q), 130.8 (2C, *C*H_{Ar}), 129.1 (2C, *C*H_{Ar}), 125.3 (C5), 121.6 (C7), 118.0 (C8), 114.7 (*C*N), 113.3 (C6), 108.4 (C1), 93.1 (C3), 9.3 (*C*H_3) ppm.

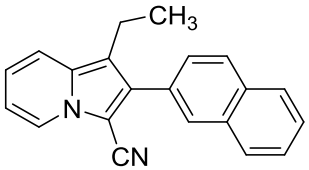
Elemental Analysis: Calcd: C: 72.05% H: 4.16% N: 10.50%

$C_{16}H_{11}ClN_2$ Found: C: 71.94% H: 4.26% N: 10.51%

MS (ESI): m/z = 288.9 (34) $[M + Na]^+$, 266.9 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{16}H_{11}NCl]^+$ 266.0611, found 266.0621.

1-Ethyl-2-(naphthalen-2-yl)indolizine-3-carbonitrile (78b)



The title compound was prepared according to the general procedure-I from **74a** (100 mg, 0.50 mmol) and *(E)*-2-(2-nitrobut-1-enyl)naphthalene (**76b**, 114 mg, 0.50 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 121 mg (0.41 mmol, 82%), yellow solid.

Mp: 113–116 °C.

R_f = 0.50 (ethyl acetate/cyclohexane 1:5).

IR (ATR) $\tilde{\nu}$ = 3054, 2964, 2928, 2194, 1427, 1216, 1130, 859, 814, 751, 728 cm^{-1}.

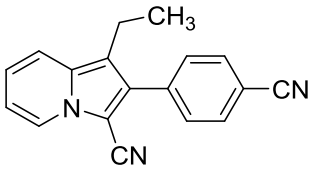
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.28 (dt, *J* = 6.9, 1.0 Hz, 1H, H-5), 8.00 (br s, 1H, H-1'), 7.99–7.88 (m, 3H, H_{Napht}), 7.66 (dt, *J* = 8.4, 1.7 Hz, 1H, H-8), 7.59–7.48 (m, 3H, H_{Napht}), 7.01 (ddd, *J* = 9.0, 6.7, 1.0 Hz, 1H, H-7), 6.81 (td, *J* = 6.9, 1.2 Hz, 1H, H-6), 2.88 (q, *J* = 7.5 Hz, 2H, CH_2), 1.21 (q, *J* = 7.5 Hz, 3H, CH_3) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.3 (C_q), 134.7 (C_q), 133.5 (C_q), 133.0 (C_q), 130.1 (C_q), 128.7 (CH_{Napht}), 128.5 (CH_{Napht}), 128.4 (CH_{Napht}), 127.9 (CH_{Napht}), 127.2 (CH_{Napht}), 126.5 (CH_{Napht}), 126.5 (CH_{Napht}), 125.4 (C5), 121.5 (C7), 118.0 (C8), 115.7 (C_q), 114.8 (C_q), 113.1 (C6), 93.7 (C3), 17.3 (CH_2), 15.9 (CH_3) ppm.

MS (ESI): m/z = 319.2 (21) $[M + Na]^+$, 297.2 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{21}H_{16}N_2 + Na]^+$ 319.1211, found 319.1211.

2-(4-Cyanophenyl)-1-ethylindolizine-3-carbonitrile (78c)



The title compound was prepared according to the general procedure-I from **74a** (100 mg, 0.50 mmol) and *(E)*-4-(2-nitrobut-1-enyl)benzonitrile (**76c**, 101 mg, 0.50 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 95 mg (0.35 mmol, 70%), colorless solid.

Mp: 147–149 °C.

R_f = 0.32 (ethyl acetate/cyclohexane 1:5).

IR (ATR) $\tilde{\nu}$ = 2965, 2926, 2227, 2196, 1534, 1453, 1356, 1224, 859, 754, 732 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.27 (dt, *J* = 6.9, 1.0 Hz, 1H, H-5), 7.82–7.76 (AA'-part of AA'BB' system, 2H, H-3',5'), 7.67–7.61 (BB'-part of AA'BB' system, 2H, H-2',6'), 7.54 (dt, *J* = 9.0, 1.1 Hz, 1H, H-8), 7.06 (ddd, *J* = 9.0, 6.7, 1.0 Hz, 1H, H-7), 6.87 (td, *J* = 6.8, 1.2 Hz, 1H, H-6), 2.80 (q, *J* = 7.6 Hz, 2H, C*H*$_2$), 1.18 (q, *J* = 7.6 Hz, 3H, C*H*$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.6 (C4'), 134.7 (C2), 134.0 (C9), 132.7 (2C, C2',6'), 130.1 (2C, C3',5'), 125.5 (C5), 122.0 (C7), 118.8 (C_q), 118.2 (C8), 115.7 (C_q), 114.2 (*C*N), 113.9 (C6), 111.9 (C1), 93.3 (C3), 17.2 (*C*H$_2$), 15.9 (*C*H$_3$) ppm.

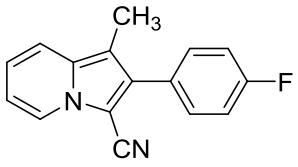
Elemental Analysis: Calcd: C: 79.68% H: 4.83% N: 15.49%

$C_{18}H_{13}N_3$ Found: C: 79.28% H: 4.77% N: 15.75%

MS (ESI): m/z = 294.0 (94) $[M + Na]^+$, 288.0 (37) $[M + O + H]^+$, 272.0 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{18}H_{13}N_3]^+$ 271.1109, found 271.1109.

2-(4-Fluorophenyl)-1-methylindolizine-3-carbonitrile (78d)



The title compound was prepared according to the general procedure-I from **74a** (100 mg, 0.50 mmol) and *(E)*-1-fluoro-4-(2-nitroprop-1-enyl)benzene (**76d**, 91 mg, 0.50 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 102 mg (0.41 mmol, 81%), colorless solid.

Mp: 162–164 °C.

R$_f$ = 0.44 (ethyl acetate/cyclohexane 1:5).

IR (ATR) $\tilde{\nu}$ = 3070, 2914, 2191, 1536, 1384, 1156, 859, 736, 726 cm^{-1}.

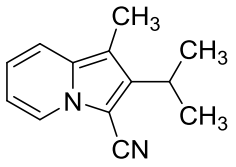
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.24 (dt, *J* = 6.8, 1.1 Hz, 1H, H-5), 7.55–7.49 (AA'-part of AA'BB' system, 2H, H-3',5'), 7.47 (dt, *J* = 9.0, 1.2 Hz, 1H, H-8), 7.24–7.14 (BB'-part of AA'BB' system, 2H, H2',6'), 7.01 (ddd, *J* = 9.0, 6.8, 1.1 Hz, 1H, H-7), 6.81 (td, *J* = 6.8, 1.2 Hz, 1H, H-6), 2.34 (s, 3H, C*H*$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.2 (d, $^1J_{C,F}$ = 247.8 Hz, C4'), 135.6 (C2), 135.1 (C9), 131.2 (d, $^3J_{C,F}$ = 8.1 Hz, 2C, C2',6'), 128.5 (d, $^4J_{C,F}$ = 3.6 Hz, C1'), 125.3 (C5), 121.5 (C7), 117.9 (C8), 116.0 (d, $^2J_{C,F}$ = 21.6 Hz, 2C, C3',5') ,114.8 (*C*N), 113.2 (C6), 108.3 (C1) , 93.2 (C3), 9.3 (*C*H_3) ppm.

MS (ESI): m/z = 273.1 (3) $[M + Na]^+$, 251.1 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{16}H_{11}N_2F + H]^+$ 251.0985, found 251.0993.

2-Isopropyl-1-methylindolizine-3-carbonitrile (78e)



The title compound was prepared according to the general procedure-I from **74a** (400 mg, 2.00 mmol) and (*E*)-4-methyl-2-nitropent-2-ene (**76e**, 298 mg, 2.00 mmol). The crude product was purified by column chromatography (ethyl acetate/hexanes 1:5).

Yield: 210 mg (1.06 mmol, 53%), colorless solid.

Mp: 68–69 °C.

R_f = 0.47 (ethyl acetate/hexanes 1:5).

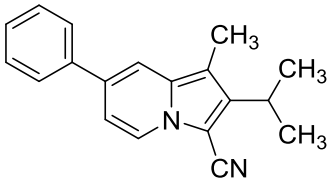
IR (ATR) $\tilde{\nu}$ = 2965, 2923, 2867, 2196, 1461, 1389, 1320, 1249, 741 cm^{-1}.

^{1}H NMR (300 MHz, CD_3OD) δ = 8.17 (dt, *J* = 6.8, 1.1 Hz, 1H, H-5) 7.46 (dt, *J* = 9.0, 1.2 Hz, 1H, H-8), 6.99 (ddd, *J* = 9.0, 6.8, 1.1 Hz, 1H, H-7), 6.78 (td, *J* = 6.8, 1.2 Hz, 1H, H-6), 3.23 (d, *J* = 7.0 Hz, 1H, C*H*$(CH_3)_2$), 2.25 (s, 3H, 1-C*H*$_3$), 1.40 (d, 6H, *J* = 7.0 Hz, CH(C*H*$_3$)$_2$) ppm.

^{13}C NMR (75 MHz, CD_3OD) δ = 144.2 (C2), 136.2 (C9), 126.0 (C8), 122.3 (C5), 118.2 (C7), 115.9 (CN), 113.6 (C6), 108.6 (C1), 92.5 (C3), 27.4 (*C*H$(CH_3)_2$), 23.0 (2C, (*C*H_3)$_2$CH), 8.4 (1-*C*H_3) ppm.

MS (ESI): m/z = 199.0 (100) $[M + H]^+$, 198.0 (8) $[M]^+$.

2-Isopropyl-1-methyl-7-phenylindolizine-3-carbonitrile (78f)



The title compound was prepared according to the general procedure-I from **74b** (550 mg, 2.00 mmol) and (*E*)-4-methyl-2-nitropent-2-ene (**76e**, 258 mg, 2.00 mmol, 1.00 equiv). The crude product was purified by column chromatography (ethyl acetate/hexanes 1:5).

Yield: 378 mg (1.38 mmol, 69%), yellow solid.

Mp: 97–100 °C.

R_f = 0.53 (ethyl acetate/hexanes 1:5).

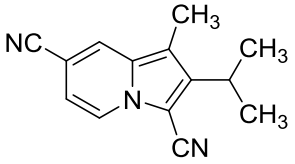
IR (ATR) $\tilde{\nu}$ = 2965, 2925, 2870, 2194, 1534, 1485, 1461, 1387, 1375, 1253, 868, 792, 756, 696 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 8.33 (dd, *J* = 7.2, 0.9 Hz, 1H, H-5), 7.93 (dd, *J* = 2.0, 0.9 Hz, 1H, H-8), 7.86–7.78 (m, 2H, H-2',6'), 7.52–7.47 (m, 2H, H-3',5'), 7.44–7.35 (m, 1H, H-4'), 7.24 (dd, *J* = 7.2, 2.0 Hz, 1H, H-6), 3.21 (sept, *J* = 7.0 Hz, 1H, C*H*$(CH_3)_2$), 2.31 (s, 3H, 1-C*H*$_3$), 1.36 (d, *J* = 7.0 Hz, 6H, (C*H*$_3$)$_2$CH) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 143.0 (C2), 137.7 (C1'), 134.5 (C9), 132.9 (C7), 129.0 (2C, C3',5'), 128.1 (C4'), 126.3 (2C, C2',6'), 125.4 (C5), 114.7 (CN), 113.9 (C8), 111.8 (C6), 108.3 (C1), 90.7 (C3), 25.6 (*C*H$(CH_3)_2$), 22.5 (2C, (*C*H$_3$)$_2$CH), 8.3 (1-*C*H$_3$) ppm.

HRMS (ESI-TOF): Calcd for $[C_{19}H_{18}N_2]^+$ 274.1470, found 274.1461.

2-Isopropyl-1-methylindolizine-3,7-dicarbonitrile (78g)



The title compound was prepared according to the general procedure-I from **74c** (448 mg, 2.00 mmol) and (*E*)-4-methyl-2-nitropent-2-ene (**76e**, 258 mg, 2.00 mmol). The crude product was purified by column chromatography (ethyl acetate/hexanes 1:5).

Yield: 149 mg (0.67 mmol, 34%), colorless solid.

Mp: 134–136 °C.

R_f = 0.36 (ethyl acetate/hexanes 1:5).

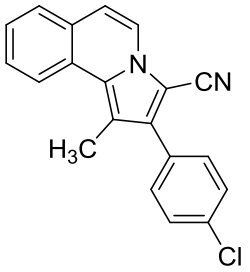
IR (ATR) $\tilde{\nu}$ = 3057, 2967, 2928, 2870, 2208, 1479, 1459, 1383, 1364, 1331, 1252, 1142, 871, 783 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.39–8.37 (m, 2H, H-5, H-8), 7.03 (dd, *J* = 6.9, 1.9 Hz, 1H, H-6), 3.21 (sept, *J* = 7.0 Hz, 1H, C*H*$(CH_3)_2$), 2.30 (s, 3H, 1-C*H*$_3$), 1.34 (d, *J* = 7.0 Hz, 6H, (C*H*$_3)_2$CH) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 143.4 (C2), 132.0 (C9), 126.0 (C8), 124.7 (C5), 118.2 (C7), 113.3 (CN), 112.4 (C1), 111.8 (C6), 102.7 (CN), 94.7 (C3), 25.5 (*C*H$(CH_3)_2$), 22.2 (2C, (*C*H$_3)_2$CH), 8.2 (1-*C*H$_3$) ppm.

HRMS (ESI-TOF): Calcd for $[C_{17}H_{13}N_3 + H]^+$ 224.1188, found 224.1177.

2-(4-Chlorophenyl)-1-methylpyrrolo[2,1-*a*]isoquinoline-3-carbonitrile (80a)



The title compound was prepared according to the general procedure-I from 2-(cyanomethyl)isoquinolinium bromide (**79**, 249 mg, 1.00 mmol) and *(E)*-1-chloro-4-(2-nitroprop-1-enyl)benzene (**76a**, 198 mg, 1.00 mmol). The crude product was purified by chromatography over silica (ethyl acetate/cyclohexane 1:10).

Yield: 150 mg (0.49 mmol, 49%), yellow solid.

Mp: 198–200 °C.

R_f = 0.48 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 3090, 2917, 2196, 1516, 1366, 1224, 1095, 820 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.39 (d, *J* = 8.1 Hz, 1H, H-10), 8.24 (d, *J* = 7.3 Hz, 1H, H-5), 7.89 (dd, *J* = 7.7, 0.9 Hz, 1H, H-7), 7.71–7.67 (m, 1H, H-9), 7.67–7.64 (AA' part of AA'-BB' system, 2H, H-3',5'), 7.64–7.59 (m, 1H, H-8), 7.59–7.53 (BB' part of AA'-BB' system, 2H, H-2',6'), 7.30 (d, *J* = 7.3 Hz, 1H, H-6), 2.58 (s, 3H, C*H*$_3$) ppm.

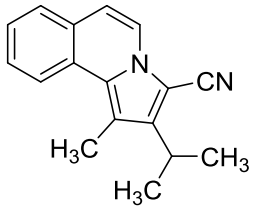
^{13}C NMR (101 MHz, DMSO-d_6) δ = 135.1 (C2), 133.2 (C1'), 131.5 (2C, C2',6'), 130.5 (C4'), 129.8 (C10b), 129.0 (2C, C3',5'), 128.5 (C9), 128.4 (C10a), 127.7 (C7), 127.6 (C8), 125.6 (C6a), 123.5 (C10), 123.1 (C5), 113.9 (C6), 113.6 (*C*N), 112.1 (C1), 94.7 (C3), 12.5 (*C*H_3) ppm.

Elemental Analysis: Calcd: C: 75.83% H: 4.14% N: 8.84%

$C_{20}H_{13}ClN_2$ Found: C: 75.46% H: 3.87% N: 8.74%

MS (ESI): m/z = 339.4 (100) $[M + Na]^+$, 317.5 (22) $[M + H]^+$.

2-Isopropyl-1-methylpyrrolo[2,1-a]isoquinoline-3-carbonitrile (80b)



The title compound was prepared according to the general procedure-I from 2-(cyanomethyl)isoquinolinium bromide (**79**, 498 mg, 2.00 mmol) and (*E*)-4-methyl-2-nitropent-2-ene (**76e**, 258 mg, 2.00 mmol). The crude product was purified by chromatography over silica (ethyl acetate/hexanes 1:5).

Yield: 179 mg (0.72 mmol, 36%), yellow solid.

Mp: 89–92 °C.

R_f = 0.49 (ethyl acetate/hexanes 1:5).

IR (ATR) $\tilde{\nu}$ = 3083, 3060, 2962, 2193, 1523, 1479, 1463, 1451, 1409, 1365, 1327, 1285, 1243, 1083, 782, 766, 740 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 8.34 (d, *J* = 8.2 Hz, 1H, H-10), 8.11 (d, *J* = 7.3 Hz, 1H, H-5), 7.83 (d, *J* = 7.9 Hz, 1H, H-7), 7.67–7.62 (m, 1H, H-9), 7.59–7.54 (m, 1H, H-8), 7.18 (d, *J* = 7.3 Hz, 1H, H-6), 3.35–3.26 (m, 1H, C*H*$(CH_3)_2$), 2.55 (s, 3H, C*H*$_3$), 1.38 (d, *J* = 7.0 Hz, 6H, (C*H*$_3)_2$CH) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 142.3 (C2), 129.2 (C10b), 128.4 (C6a), 128.2 (C9), 127.4 (C7), 127.2 (C8), 125.5 (C10a), 123.3 (C10), 122.8 (C5), 114.3 (CN), 112.8 (C6), 111.7 (C1), 93.1 (C3), 24.9 (*C*H$(CH_3)_2$), 22.7 (2C, (*C*$H_3)_2$CH), 11.6 (CH_3) ppm.

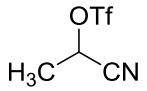
HRMS (ESI-TOF): Calcd for $[C_{17}H_{16}N_2 + H]^+$ 249.1392, found 249.1400.

General procedure-II for cyanohydrin triflates 84 [191]

General procedure-IIA: 1-Cyanoethyl trifluoromethanesulfonate (**84a**) and 1-cyano-2-methylpropyltrifluoromethane-sulfonate (**84b**) were prepared from corresponding cyanohydrin[192-195] and trifluoromethanesulfonic anhydride. To a solution of cyanohydrin (1.00 equiv.) and distilled pyridine (1.2 equiv.) in freshly distilled CH_2Cl_2 was slowly added trifluoromethanesulfonic anhydride (1.2 equiv.) at 0 °C. After stirring for 15 min., the solvent was evaporated in vacuo. The residue was dissolved in diethyl ether and was filtered to remove pyridinium triflate and the filtrate was evaporated to obtain the crude cyanohydrin triflate.

2-Chloro-2-(4-chlorophenyl)acetonitrile[157] (**84c**), 1-cyano-3-phenylpropyl trifluoromethanesulfonate[196] (**84d**) and cyano(cyclohexyl)methyl trifluoromethanesulfonate[196] (**84f**) was prepared according to the literature procedures.

1-Cyanoethyl trifluoromethanesulfonate (84a)



The title compound was synthesized according to the general procedure-IIA from acetaldehyde cyanohydrin (3.00 g, 42.2 mmol), Tf_2O (14.11 g, 50.0 mmol) and pyridine (3.95 g, 50.0 mmol) in CH_2Cl_2 (200 mL). The crude product was further purified by filtering through neutral Al_2O_3 to yield the triflate of acetaldehyde cyanohydrin.

Yield: 7.00 g (34.6 mmol, 82%), slightly pink oil.

IR (ATR): $\tilde{\nu}$ = 2981, 1423, 1213, 1141, 926 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.44 (q, *J* =6.9 Hz, 1H, C*H*), 1.83 (d, *J* = 6.9 Hz, 3H, CH_3) ppm.

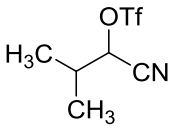
^{13}C NMR (101 MHz, $CDCl_3$) δ = 118.3 (q, $^1J_{C,F}$ = 320 Hz, *C*F_3), 114.6 (*C*N), 68.8 (*C*H), 20.1 (*C*H_3) ppm.

Elemental Analysis: Calcd.: C: 23.65% H: 1.98% N: 6.90%

$C_4H_4F_3NO_3S$ Found: C: 23.96% H: 1.94% N: 6.88%

MS (ESI): The compound was decomposed during the ESI-MS measurement.

1-Cyano-2-methylpropyl trifluoromethanesulfonate (84b)[191]



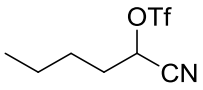
The title compound was synthesized according to the general procedure-IIA from 2-hydroxy-3-methylbutanenitrile (1.98 g, 20.0 mmol), Tf_2O (6.77 g, 24.0 mmol) and pyridine (1.90 g, 24.0 mmol) in CH_2Cl_2 (100 mL). The crude product was further purified by filtering through neutral Al_2O_3 to yield 1-cyano-2-methylpropyl trifluoromethanesulfonate.

Yield: 3.40 g (74%), colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.16 (d, *J* =5.6 Hz, 1H, C*H*-CN), 2.35 (m, 1H, C*H*), 1.19 (overlapping doublets, 6H, 2CH_3) ppm.

General procedure-IIB: To a solution of cyanohydrin (1.00 equiv) and 2,6-lutidine (1.20 equiv) in freshly distilled DCM (0.10 M) was slowly added trifluoromethanesulfonic anhydride (1.20 equiv) at 0 °C. After stirring 15 min., the solvent was evaporated in vacuo. The residue was dissolved in diethyl ether and was filtered to remove pyridinium triflate and the filtrate was evaporated in vacuo followed by a filtration through a pad of silica to obtain cyanohydrin triflates.

1-Cyanopentyl trifluoromethanesulfonate (84e)



The title compound was prepared according to the general procedure-IIB described above from 2-hydroxyhexanenitrile (4.30 g, 38.0 mmol).

Yield: 7.30 g (29.8 mmol, 78%), light yellow oil.

IR (ATR) $\tilde{\nu}$ = 2972, 2937, 2878, 1423, 1213, 1142, 1047, 917 cm^{-1}.

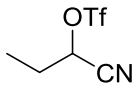
^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.33 (t, *J* = 6.6 Hz, 1H, H-1), 2.15–2.06 (m, 2H, H-2), 1.61–1.50 (m, 2H, H-3), 1.48–1.38 (m, 2H, H-4), 0.97 (t, *J* = 7.3 Hz, 3H, H-5) ppm.

^{13}C NMR, HSQC (101 MHz, $CDCl_3$) δ = 118.4 (q, $^1J_{C,F}$ = 319.8 Hz, *C*F_3), 114.0 (*C*N), 72.3 (C1), 33.6 (C2), 26.2 (C3), 21.8 (C4), 13.7 (C5) ppm.

Elemental Analysis: Calcd: C: 34.29% H: 4.11% N: 5.71% S: 13.08%

$C_7H_{10}F_3NO_3S$ Found: C: 34.75% H: 4.05% N: 5.90% S: 13.02%

1-Cyanopropyl trifluoromethanesulfonate (84g)



The title compound was prepared according to the general procedure-IIB described above from 2-hydroxybutanenitrile (5.03 g, 59.1 mmol).

Yield: 7.65 g (35.2 mmol, 59%), light orange oil.

IR (ATR) $\tilde{\nu}$ = 2988, 2951, 2892, 1421, 1245, 1207, 1138, 924 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.31 (t, *J* = 6.4 Hz, 1H, H-1), 2.22–2.10 (m, 2H, H-2), 1.22 (t, *J* = 7.4 Hz, 3H, H-3) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 118.4 (q, $^1J_{C,F}$ = 319.9 Hz, *C*F_3), 113.8 (*C*N), 73.2 (C1), 27.7 (C2), 8.7 (C3) ppm.

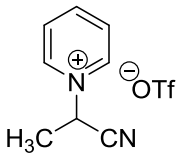
Elemental Analysis: Calcd: C: 27.65% N: 6.45%

$C_5H_6F_3NO_3S$ Found: C: 27.41% N: 6.52%

General procedure-III for pyridinium salts (85)

Cyanohydrin triflate or 2-chloro-2-(4-chlorophenyl) acetonitrile **84** (1.00 equiv.) and the corresponding heterocyclic compound (1.00 equiv.) were dissolved in anhydrous diethyl ether (1 mL/1 mmol) and the reaction mixture was stirred at room temperature for 2 h. The product was collected via filtration and the salt was washed with diethyl ether. In some cases where the removal of the excess N-heterocycle was not complicated, excess amount of the azine was used.

1-(1-Cyanoethyl)pyridinium triflate (85a)



The title compound was prepared according to the general procedure-III from pyridine (2.69 g, 34.0 mmol) and **84a** (6.90 g, 34.0 mmol). The crude product was further purified via recrystallization from EtOAc.

Yield: 9.11 g (32.0 mmol, 95%), colorless solid.

Mp: 65–67 °C.

IR (ATR): $\tilde{\nu}$ = 3136, 2970, 1255, 1149, 756 cm^{-1}.

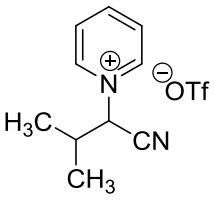
^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.30 (dd, J = 6.8, 1.3 Hz, 2H, H-2,6), 8.74 (tt, J = 7.8, 1.3 Hz, 1H, H-4), 8.28 (dd, J = 7.8, 6.8 Hz, 2H, H-3,5), 6.31 (q, J = 7.1 Hz, 1H, C*H*), 2.03 (d, J = 7.1 Hz, 3H, CH_3) ppm.

^{13}C NMR (75 MHz, DMSO-d_6) δ = 147.8 (C4), 144.1 (2C, C2,6), 128.8 (2C, C3,5), 120.7 (q, $^{1}J_{C,F}$ = 322 Hz, CF$_3$), 116.5 (C≡N), 56.3 (CH), 20.3 (CH$_3$) ppm.

Elemental Analysis:	Calcd.:	C: 38.30%	H: 3.21%	N: 9.93%	S: 11.36%
$C_9H_9F_3N_2O_3S$	Found:	C: 38.09%	H: 3.24%	N: 9.87%	S: 11.45%

MS (ESI): m/z = 133.1 (100) [M]$^{+}$.

1-(1-Cyano-2-methylpropyl)pyridinium triflate (85b)



The title compound was prepared according to the general procedure-III from excess pyridine (1.98 g, 25 mmol) and **84b** (1.20 g, 5.19 mmol). The crude product was recrystallized from EtOAc-ether mixture.

Yield: 1.54 g (5.07 mmol, 98%), colorless solid.

Mp: 99–102 °C.

IR (ATR): $\tilde{\nu}$ = 2968, 1259, 1028, 741 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.24 (d, *J* = 6.3 Hz, 2H, H-2,6), 8.79 (t, *J* = 7.4 Hz, 1H, H-4), 8.31 (t, *J* = 6.8 Hz, 2H, H-3,5), 6.19 (d, *J* = 8.0 Hz, 1H, H-1'), 2.65 (m, 1H, H-2'), 1.10 (d, *J* = 6.5 Hz, 3H, C*H*$_3$), 0.89 (d, *J* = 6.6 Hz, 3H, C*H*$_3$) ppm.

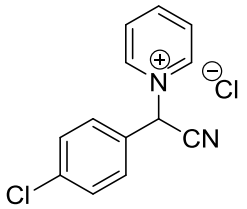
^{13}C NMR (75 MHz, DMSO-d_6) δ = 148.1 (C4), 144.2 (2C, C2,6), 129.0 (2C, C3,5), 120.7 (q, $^{1}J_{C,F}$ = 322 Hz, *C*F$_3$), 114.7 (*C*≡N), 65.8 (*C*HCN), 33.5 (*C*H(CH$_3$)$_2$), 17.7 (*C*H$_3$), 17.6 (*C*H$_3$) ppm.

Elemental Analysis: Calcd: C: 42.54% H: 4.22% N: 9.03% S: 10.33%

$C_{11}H_{13}F_3N_2O_3S$ Found: C: 42.39% H: 3.98% N: 9.07% S: 11.40%

MS (ESI) m/z = 161.1 (100) $[M]^+$.

1-((4-Chlorophenyl)(cyano)methyl)pyridinium chloride (85c)



2-Chloro-2-(4-chlorophenyl)acetonitrile **(84c**, 1.24 g, 6.67 mmol) was added to freshly distilled pyridine (4.91 g, 62.1 mmol) and the reaction mixture was stirred at room temperature for 2 days. Diethyl ether (20 mL) was added to the reaction vessel and crude product was collected via filtration after washing several times with diethyl ether, and then dried.

Yield: 1.70 g (6.41 mmol, 96%), yellow solid.

Mp: The melting point range could not be determined due to the high hygroscopicity of the material.

IR (ATR): $\tilde{\nu}$ = 2952, 1487, 1094, 799 cm^{-1}.

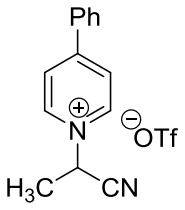
^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.61 (d, *J* = 5.7 Hz, 2H, H-2,6), 8.77 (t, *J* = 7.8 Hz, 1H, H-4), 8.59 (s, 1H, C*H*), 8.35–8.24 (m, 2H, H-3,5), 7.89 (AA'-part of AA'BB' system, 2H, H-3'',5''), 7.70–7.64 (BB'-part of AA'BB' system, 2H, H-2'',6'') ppm.

^{13}C NMR (75 MHz, DMSO-d_6) δ = 148.3 (C4), 144.2 (2C, C2,6), 136.3 (C4'), 130.4 (2C, *C*H$_{Ar}$), 129.9 (2C, *C*H$_{Ar}$), 129.3 (2C, *C*H$_{Ar}$), 126.8 (C$_q$), 114.6 (*C*≡N), 60.9 (*C*H) ppm.

MS (ESI) m/z = 229 (100) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{13}H_{10}ClN_2]^+$ 229.0533, found 229.0530.

1-(1-Cyanoethyl)-4-phenylpyridinium triflate (85d)



The title compound was prepared according to the general procedure-III from 4-phenylpyridine (1.15 g, 7.40 mmol) and **84a** (1.50 g, 7.40 mmol). The crude product was recrystallized from DCM.

Yield: 2.08 g (5.85 mmol, 79%), colorless solid.

Mp: 135–137 °C.

IR (ATR): ν = 3051, 1258, 1152, 994, 854 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.31 (d, J = 6.9 Hz, 2H, H-2,6), 8.64 (d, J = 6.8 Hz, 2H, H-3,5), 8.16–8.11 (m, 2H, H-Ph), 7.75–7.62 (m, 3H, H_{Ph}), 6.28 (q, J = 7.1 Hz, 1H, C*H*), 2.05 (d, J = 7.1 Hz, 3H, CH_3) ppm.

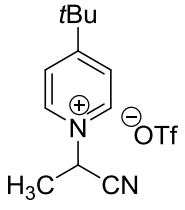
^{13}C NMR (75 MHz, DMSO-d_6) δ = 156.7(C4), 144.0 (2C, C2,6), 133.2 (C1'),132.7 (C4'), 129.8 (2C, *C*H_{Ar}), 125.0 (2C, *C*H_{Ar}), 120.7 (2C, *C*H_{Ar}), 116.6 (*C*≡N), 55.4 (*C*H), 20.0 (*C*H_3) ppm.

Elemental Analysis: Calcd: C: 50.28% H: 3.66% N: 7.82% S: 8.95%

$C_{15}H_{13}F_3N_2O_3S$ Found: C: 50.34% H: 3.73% N: 7.78% S: 8.95%

MS (ESI): m/z = 209.1 (100) $[M]^+$.

4-*tert*-Butyl-1-(1-cyanoethyl)pyridinium triflate (85e)



The title compound was prepared according to the general procedure-III from 4-*tert*-butylpyridine (676 mg, 5.0 mmol) and **84a** (1.02 g, 5.0 mmol). The crude product was recrystallized from EtOAc.

Yield: 1.08 g (3.2 mmol, 64%), colorless solid.

Mp: 137–140 °C.

IR (ATR): ν = 3081, 3056, 2968, 1463, 1253, 1029 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.19 (d, *J* = 7.0 Hz, 2H, H-2,6), 8.30 (d, *J* = 7.0 Hz, 2H, H-3,5), 6.26 (q, *J* = 7.1 Hz, 1H, C*H*), 2.01 (d, *J* = 7.1 Hz, 3H, CH_3), 1.38 (s, 9H, C(CH_3)$_3$) ppm.

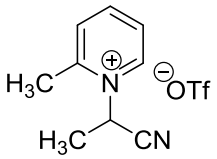
^{13}C NMR (101 MHz, DMSO-d_6) δ = 172.4 (C4), 143.4 (2C, C2,6), 125.8 (2C, C3,5), 120.7 (q, $^1J_{C,F}$ = 322 Hz, *C*F_3), 116.6 (*C*≡N), 55.4 (*C*H), 36.6 (*C*(CH$_3$)$_3$), 29.4 (3C, C(*C*H$_3$)$_3$), 20.1 (*C*H$_3$) ppm.

Elemental Analysis: Calcd: C: 46.15% H: 5.06% N: 8.28% S: 9.48%

$C_{13}H_{17}F_3N_2O_3S$ Found: C: 46.00% H: 4.97% N: 8.27% S: 9.46%

MS (ESI): m/z = 189.1 (100) $[M]^+$.

1-(1-Cyanoethyl)-2-methylpyridinium triflate (85f)



The title compound was prepared according to the general procedure-III from 2-picoline (466 mg, 5.0 mmol) and **84a** (1.02 g, 5.0 mmol). The solid was recrystallized from chloroform.

Yield: 1.05 g (3.55 mmol, 71%), colorless solid.

Mp: 150–151 °C.

IR (ATR): ν = 2957, 2925, 1261, 1150, 994 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.31 (dd, *J* = 6.4, 1.4 Hz, 1H, H-6), 8.59 (td, *J* = 7.9, 1.4 Hz, 1H, H-4), 8.16–8.07 (m, 2H, H-3, H-4), 6.37 (q, *J* = 7.0 Hz, 1H, C*H*), 2.90 (s, 3H, 2-CH_3), 1.97 (d, *J* = 7.0 Hz, 3H, CH_3) ppm.

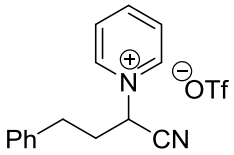
^{13}C NMR (75 MHz, DMSO-d_6) δ = 156.1 (C2), 147.0 (C4), 142.9 (C6), 130.6 (C3), 126.6 (C5), 120.7 (q, $^1J_{C,F}$ = 322 Hz, *C*F_3), 116.7 (*C*≡N), 52.2 (*C*H), 20.2 (*C*H$_3$), 19.7 (*C*H$_3$) ppm.

Elemental Analysis: Calcd: C: 40.54% H: 3.74% N: 9.46% S: 11.32%

$C_{10}H_{11}F_3N_2O_3S$ Found: C: 40.45% H: 3.40% N: 9.49% S: 10.64%

MS (ESI): m/z = 147.1 (100) $[M]^+$.

1-(1-Cyano-3-phenylpropyl)pyridinium triflate (85g)



The title compound was prepared according to the general procedure-III from pyridine (79 mg, 1.0 mmol) and triflate **84d** (293 mg, 1.0 mmol). The crude product was recrystallized from DCM/ether mixture.

Yield: 276 mg, (0.74 mmol, 74%), light yellow solid.

Mp: 82–84 °C.

IR (ATR): ν = 3062, 2950, 1255, 1157, 1029 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.30 (dd, J = 6.8, 1.2 Hz, 2H, H-2,6), 8.74 (tt, J = 7.8, 1.2 Hz, 1H, H-4), 8.28 (dd, J = 7.7, 6.8 Hz, 2H, H-3,5), 7.33–7.27 (m, 2H, H_{Ph}), 7.25–7.18 (m, 3H, H_{Ph}), 6.32 (t, J = 7.1 Hz, 1H, H-1'), 2.87–2.61 (m, 4H, H-2', H-3') ppm.

^{13}C NMR (75 MHz, DMSO-d_6) δ = 147.9, 144.3, 138.7, 128.9, 128.6, 128.3, 126.6, 115.5 (*C*N), 60.2 (*C*H), 34.9 (CH_2), 30.6 (CH_2) ppm.

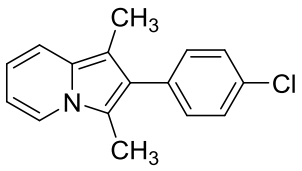
Elemental Analysis:	Calcd:	C: 51.61%	H: 4.06%	N: 7.52%	S: 8.61%
$C_{16}H_{15}F_3N_2O_3S$	Found:	C: 51.77%	H: 3.83%	N: 7.38%	S: 8.72%

MS (ESI): m/z = 223.1 (100) $[M]^+$.

General Procedure-IV for Indolizines 86

A solution of KO*t*Bu (4 mmol) in dry DMF (5.0 mL) was slowly added to a stirred solution of pyridinium salt **85** (1.00 mmol) and nitroolefin **76** (1.00 mmol) in dry DMF (10 mL) at 0 °C under argon. The mixture was stirred at 0 °C and the reaction was monitored by TLC. When the reaction was completed, the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate and washed with water. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed in vacuo.

2-(4-Chlorophenyl)-1,3-dimethylindolizine (86a)



The title compound was prepared according to the general procedure-IV from **85a** (282 mg, 1.0 mmol) and *(E)*-1-chloro-4-(2-nitroprop-1-enyl)benzene (**76a**, 198 mg, 1.0 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 196 mg (0.77 mmol, 77%), yellow solid.

Mp: 138–140 °C.

R_f = 0.74 (ethyl acetate/cyclohexane 1:10).

IR (ATR): ν = 3076, 3041, 2924, 2856, 1454, 1317, 842, 721 cm^{-1}.

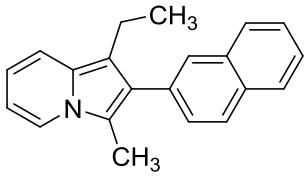
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.66 (dt, *J* = 7.1, 1.2 Hz, 1H, H-5), 7.45–7.41 (AA'-part of AA'BB' system, 2H, H-3',5'), 7.36 (dt, *J* = 9.0, 1.3 Hz, 1H, H-8), 7.32–7.27 (BB'-part of AA'BB' system, 2H, H-2',6'), 6.63 (ddd, *J* = 9.0, 6.4, 1.1 Hz, 1H, H-7), 6.53 (ddd, *J* = 7.1, 6.4, 1.3 Hz, 1H, H-6), 2.42 (s, 3H, 3-CH_3), 2.32 (s, 3H, 1-CH_3) ppm.

^{13}C NMR, HSQC, HMBC (75 MHz, $CDCl_3$) δ = 134.6 (C4'), 132.3 (C1'), 131.8 (2C, C2',6'), 129.3 (C9), 128.5 (2C, C3',5'), 126.3 (C2), 121.6 (C5), 117.5 (C8), 116.3 (C3), 114.6 (C7), 110.2(C6), 105.6 (C1), 10.2 (3-CH_3), 9.4 (1-CH_3) ppm.

MS (ESI): m/z = 288.0 (9) $[M + 2O + H]^+$, 271.9 (22) $[M + O + H]^+$, 256.0 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{16}H_{14}ClN]^+$ 255.0815, found 255.0819.

1-Ethyl-3-methyl-2-(naphthalene-2-yl)indolizine (86b)



The title compound was prepared according to the general procedure-IV from **85a** (282 mg, 1.0 mmol) and *(E)*-2-(2-nitrobut-1-enyl)naphthalene (**76b** , 227 mg, 1.0 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 154 mg (0.54 mmol, 54%), yellow oil.

R_f = 0.67 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 3053, 2965, 1460, 1016, 947, 860, 820, 736 cm^{-1}.

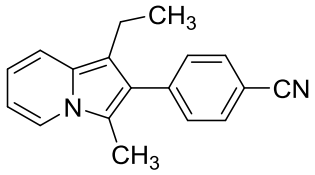
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.96–7.88 (m, 3H, $H_{Napht.}$), 7.83 (d, 1H, *J* = 1.6 Hz, $H_{Napht.}$), 7.70 (dt, *J* = 7.0, 1.0 Hz, 1H, H-5), 7.58–7.50 (m, 3H, $H_{Napht.}$), 7.45 (dt, *J* = 9.0, 1.2 Hz, 1H, H-8), 6.66 (ddd, *J* = 8.9, 6.4, 1.4 Hz, 1H, H-7), 6.56 (ddd, *J* = 6.9, 6.4, 1.4 Hz, 1H, H-6), 2.87 (q, *J* =7.5 Hz, 2H, CH_2), 2.45 (s, 3H, 3-CH_3), 1.16 (t, *J* = 7.5 Hz, 3H, CH_3) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 133.9 ($C_{q,Napht.}$), 133.6 ($C_{q,Napht.}$), 132.2 ($C_{q,Napht.}$), 129.1 ($CH_{Napht.}$), 129.0 ($CH_{Napht.}$), 128.7 (C9), 128.0 ($CH_{Napht.}$), 127.8 ($CH_{Napht.}$), 127.7 ($CH_{Napht.}$), 127.0 (C2), 126.1 ($CH_{Napht.}$), 125.7 ($CH_{Napht.}$), 121.7 (C5), 117.6 (C8), 116.6 (C3), 114.5 (C7), 113.4 (C1), 110.2 (C6), 17.6 (CH_2), 16.6 (CH_3), 10.2 (CH_3) ppm.

MS (ESI): m/z = 318.1 (30) $[M + 2O + H]^+$, 302.1 (47) $[M + O + H]^+$, 286.1 (100) $[M + H]^+$, 285.0 (33) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{21}H_{19}N]^+$ 285.1517, found 285.1515.

2-(4-Cyanophenyl)-1-ethyl-3-methylindolizine (86c)



The title compound was prepared according to the general procedure-IV from **85a** (282 mg, 1.0 mmol) and *(E)*-4-(2-nitrobut-1-enyl)benzonitrile (**76c**, 202 mg, 1.0 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 161 mg (0.62 mmol, 62%), yellow solid.

Mp: 98–100 °C.

R_f = 0.65 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 3067, 2970, 2931, 2227, 1360, 855, 795 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.76–7.70 (AA'-part of AA'BB' system, 2H, H-3',5'), 7.67 (dt, *J* = 7.0, 1.3 Hz, 1H, H-5), 7.49–7.43 (BB'-part of AA'BB' system, 2H, H-2',6'), 7.40

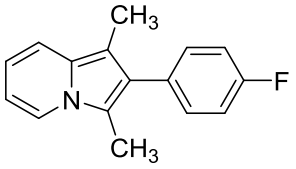
(dt, *J* = 9.0, 1.3 Hz, 1H, H-8), 6.65 (ddd, *J* = 9.0, 6.4, 1.2 Hz, 1H, H-7), 6.56 (td, *J* = 6.7, 1.3 Hz, 1H, H-6), 2.78 (q, *J* = 7.5 Hz, 3H, C*H*$_2$), 2.39 (s, 3H, 3-C*H*$_3$), 1.11 (t, *J* = 7.5 Hz, 3H, C*H*$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.7, 132.1, 131.0, 129.0, 125.3, 121.7, 119.4, 117.7, 116.4, 115.1, 112.9, 110.7, 110.0, 17.4, 16.5, 10.1 ppm.

MS (ESI): m/z = 293.1 (36) $[M + 2O + H]^+$, 277.0 (100) $[M + O + H]^+$, 261.0 (87) $[M + H]^+$, 260.1 (95) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{18}H_{16}N_2]^+$ 260.1313, found 260.1303.

2-(4-Fluorophenyl)-1,3-dimethylindolizine (86d)



The title compound was prepared according to the general procedure-IV from **85a** (282 mg, 1.0 mmol) and *(E)*-1-fluoro-4-(2-nitroprop-1-enyl)benzene (**76d**, 181 mg, 1.0 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 165 mg (0.65 mmol, 65%), yellow solid.

Mp: 118–119 °C.

R_f = 0.76 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 3067, 2992, 1505, 1470, 843, 784 cm^{-1}.

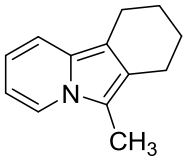
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65 (br d, *J* = 7.0 Hz, 1H, H-5), 7.36–7.27 (m, 3H, H-3',5', H-8), 7.18–7.07 (BB'-part of AA'BB' system, 2H, H-2',6'), 6.61 (br dd, *J* = 8.9, 6.4 Hz, 1H, H-7), 6.51 (ddd, *J* = 7.2, 6.4, 1.4 Hz, 1H, H-6), 2.39 (s, 3H, 3-C*H*$_3$), 2.29 (s, 3H, 1-C*H*$_3$) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 161.0 (d, $^1J_{C,F}$ = 243.1 Hz, C4'), 131.8 (d, $^3J_{C,F}$ = 8.0 Hz, 2C, C2',6'), 131.7 (d, $^4J_{C,F}$ = 3.1 Hz, C1'), 128.5 (C9), 125.5 (C2), 122.2 (C5), 117.1 (C8), 116.0 (C3), 115.2 (d, $^2J_{C,F}$ = 21.1 Hz, 2C, C3',5'), 114.5 (C7), 109.9 (C6), 104.6 (C1), 9.8 (3-*C*H$_3$), 9.2 (1-*C*H$_3$) ppm.

MS (ESI): m/z = 272.1 (52) $[M + 2O + H]^+$, 256.1 (63) $[M + O + H]^+$, 240.1 (100) $[M + H]^+$, 239.2 (73) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{16}H_{14}FN]^+$ 239.1110, found 239.1119.

6-Methyl-7,8,9,10-tetrahydropyrido[2,1-*a*]isoindole (86e)



The title compound was prepared according to the general procedure-IV from **85a** (282 mg, 1.0 mmol) and 1-nitrocyclohex-1-ene (**76f**, 127 mg, 113 µL, 1.0 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 72 mg (0.39 mmol, 39%), light yellow oil.

R_f = 0.72 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 2923, 1590, 1465 cm^{-1}.

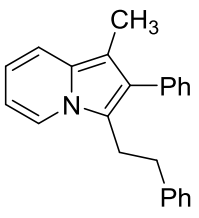
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.59 (d, *J* = 7.0 Hz, 1H, H-5), 7.24 (dd, *J* = 8.7, 1.2 Hz, 1H, H-1), 6.56-6.50 (m, 1H, H-2), 6.45 (td, *J* = 6.7, 1.2 Hz, 1H, H-3), 2.86–2.77 (m, 2H, CH_2), 2.77-2.68 (m, 2H, CH_2), 2.35 (s, 3H, CH_3), 1.90-1.84 (m, 4H, H-8, H-9) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 127.6 (C10b), 122.7 (C6a), 121.0 (C4), 116.6 (C1), 114.4 (C10a), 113.3 (C2), 109.5 (C3), 108.4 (C6), 24.2 (*C*H_2), 24.0 (*C*H_2), 22.1 (*C*H_2), 21.2 (*C*H_2), 9.2 (*C*H_3) ppm.

MS (ESI): m/z = 218.1 (14) $[M + 2O + H]^+$, 202.1 (100) $[M + O + H]^+$, 186.1 (2) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{13}H_{15}N]^+$ 185.1214, found 185.1204.

1-Methyl-2-phenyl-3-(2-phenylethyl)indolizine (86f)



The title compound was prepared according to the general procedure-IV from **85g** (186 mg, 0.50 mmol) and (*E*)-(2-nitroprop-1-enyl)benzene (**76g**, 82 mg, 0.50 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 50 mg (0.16 mmol, 32%), yellow oil.

R_f = 0.78 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 3063, 2923, 1453, 762, 731, 700 cm^{-1}.

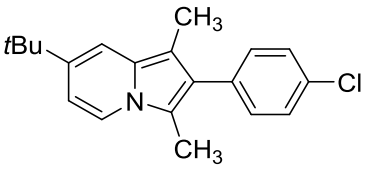
^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ = 8.04 (d, *J* = 7.0 Hz, 1H, H-5), 7.47–7.09 (m, 11H, H_{Ph}, H-8), 6.64 (ddd, *J* = 8.8, 6.3, 0.8 Hz, 1H, H-7), 6.57–6.51 (m, 1H, H-6), 3.20–3.12 (m, 2H CH_2), 2.94–2.87 (m, 2H, CH_2), 2.23 (s, 3H, CH_3) ppm.

^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ = 142.2, 137.6, 136.8, 130.9, 129.6, 129.1, 129.0, 128.8, 127.0, 126.7, 122.7, 120.6, 118.1, 115.2, 110.6, 106.2, 34.6, 27.2, 9.2 ppm.

MS (ESI): m/z = 384.2 (77) $[M + 2O + H]^+$, 328.3 (100) $[M + O + H]^+$, 312.2 (12) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{23}H_{21}N + H]^+$ 312.1752, found 312.1762.

7-*tert*-Butyl-2-(4-chlorophenyl)-1,3-dimethylindolizine (86g)



The title compound was prepared according to the general procedure-IV from **85e** (338 mg, 1.0 mmol) and *(E)*-1-chloro-4-(2-nitroprop-1-enyl)benzene (**76a**, 198 mg, 1.0 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 221 mg (0.71 mmol, 71%), yellow solid.

Mp: 136–138 °C.

R_f = 0.84 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 2964, 2869, 1592, 1488, 1090, 811, 740 cm^{-1}.

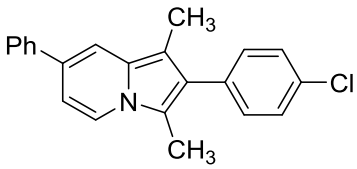
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.62 (br d, *J* = 7.4 Hz, 1H, H-5), 7.45–7.39 (AA'-part of AA'BB' system, 2H, H-3',5'), 7.32–7.26 (BB'-part of AA'BB' system, 2H, H-2',6'), 7.21 (d, *J* = 1.0 Hz, 1H, H-8), 6.61 (dd, *J* = 7.4, 2.0 Hz, 1H, H-6), 2.40 (s, 3H, 3-CH_3), 2.31 (s, 3H, 1-CH_3), 1.35 (s, 9H, C(CH_3)$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.0 (C7), 134.9 (C4'), 132.2 (C1'), 131.8 (2C, C2',6'), 130.6 (C9), 128.4 (2C, C3',5'), 126.3 (C2), 121.3 (C5), 115.3 (C3), 111.2 (C8), 109.7 (C6), 104.7 (C1), 34.4 ($C(CH_3)_3$), 30.7 (3C, $(CH_3)_3C$), 10.1 (3-CH_3), 9.4 (1-CH_3) ppm.

MS (ESI): m/z = 344.2 (28) $[M + 2O + H]^+$, 328.3 (100) $[M + O + H]^+$, 312.3 (28) $[M + H]^+$, 311.3 (32) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{20}H_{22}NCl]^+$ 311.1441, found 311.1452.

7-Phenyl-2-(4-chlorophenyl)-1,3-dimethylindolizine (86h)



The title compound was prepared according to the general procedure-IV from **85d** (358 mg, 1.0 mmol) and *(E)*-1-chloro-4-(2-nitroprop-1-enyl)benzene (**76a**, 198 mg, 1.0 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 240 mg (0.72 mmol, 72%), light green solid.

Mp: 194–195 °C.

R_f = 0.74 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 3025, 2924, 1489, 1091, 832, 796, 728 cm^{-1}.

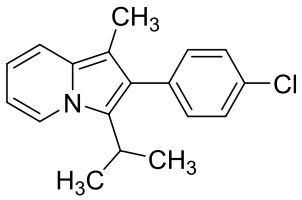
^{1}H NMR, COSY, (300 MHz, $CDCl_3$) δ = 7.72 (dd, *J* = 7.4, 1.0 Hz, 1H, H-5), 7.69–7.65 (m, 2H, H-2'',6''), 7.59 (dd, *J* = 1.9, 1.0 Hz, 1H, H-8), 7.48–7.41 (m, 4H, H-3'',5'', H-3',5'), 7.35–7.27 (m, 3H, H-2',6', H-4''), 6.86 (dd, *J* = 7.3, 1.9 Hz, 1H, H-6), 2.44 (s, 3H, 3-CH_3), 2.35 (s, 3H, 1-CH_3) ppm.

^{13}C NMR, HSQC, HMBC (75 MHz, DMSO-d_6) δ = 138.9 (C1''), 134.2 (C4'), 131.7 (2C, C2',6'), 131.2 (C1'), 128.9 (3C, C8a,3'',5''), 128.4 (2C, C3',5'), 126.8 (C4''), 126.1 (C2), 126.0 (C7), 125.6 (2C, C2'',6''), 122.6 (C5), 116.6 (C3), 113.7 (C8), 109.1 (C6), 106.3 (C1), 9.9 (3-CH_3), 9.3 (1-CH_3) ppm.

MS (ESI): m/z = 364.0 (33) $[M + 2O + H]^+$, 348.1 (100) $[M + O + H]^+$, 332.1 (17) $[M + H]^+$, 331.1 (31) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{22}H_{18}NCl]^+$ 331.1128, found 311.1118.

2-(4-Chlorophenyl)-1-isopropyl-3-methylindolizine (86i)



The title compound was prepared according to the general procedure-IV from **85b** (310 mg, 1.0 mmol) and *(E)*-1-chloro-4-(2-nitroprop-1-enyl)benzene (**76a**, 198 mg, 1.0 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 157 mg (0.55 mmol, 55%), yellow solid.

Mp: 140–142 °C.

R_f = 0.78 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 3073, 2965, 1480, 1092, 843, 731, 703 cm^{-1}.

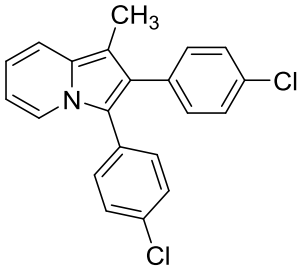
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.88 (dt, *J* = 7.2, 1.0 Hz, 1H, H-5), 7.42–7.36 (AA'-part of AA'BB' system, 2H, H-3',5'), 7.33 (dt, *J* = 9.0, 1.2 Hz, 1H, H-8), 7.26–7.20 (BB'-part of AA'BB' system, 2H, H-2',6'), 6.59 (ddd, *J* = 9.0, 6.4, 1.0 Hz, 1H, H-7), 6.46 (ddd, *J* = 7.2, 6.4, 1.2 Hz, 1H, H-6), 3.38 (sept, *J* = 7.2 Hz, 1H, 3-C*H*), 2.17 (s, 3H, 1-CH_3), 1.31 (d, *J* = 7.3 Hz, 6H, (CH_3)$_2$CH) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 135.5 (C4'), 132.6 (C1'), 132.1 (2C, C2',6'), 129.2 (C9), 128.2 (2C, C3',5'), 125.9 (C2), 125.6 (C3), 122.8 (C5), 117.9 (C8), 114.5 (C7), 109.9 (C6), 106.5 (C1), 25.8 (3-*C*H), 20.4 (2C, (*C*H$_3$)$_2$CH), 9.13 (1-*C*H$_3$) ppm.

MS (ESI): m/z = 316 (10) $[M+ 2O + H]^+$, 300.0 (6) $[M + O + H]^+$, 284.0 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{18}H_{18}NCl + H]^+$ 284.1206, found 284.1219.

2,3-Bis(4-chlorophenyl)-1-methylindolizine (86j)



The title compound was prepared according to the general procedure-IV from **85c** (265 mg, 1.0 mmol) and *(E)*-1-chloro-4-(2-nitroprop-1-enyl)benzene (**76a**, 198 mg, 1.0 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 110 mg (0.39 mmol, 39%), yellow solid.

Mp: 169–171 °C.

R_f = 0.68 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 3070, 3051, 2922, 1396, 1091, 833, 826, 737 cm^{-1}.

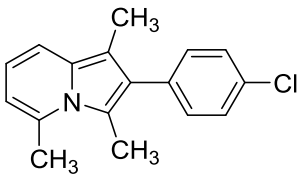
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.99 (bd, *J* = 7.1 Hz, 1H, H-5), 7.39 (dt, *J* = 9.0, 1.2 Hz, 1H, H-8), 7.36–7.30 (m, 2H, H_{Ar}), 7.29–7.17 (m, 2H, H_{Ar}), 7.14–7.08 (m, 2H, H_{Ar}), 6.74–6.64 (m, 1H, H-7), 6.45 (t, *J* = 7.0 Hz, 1H, H-6), 2.33 (s, 3H, C*H*$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 133.9 (C_q), 133.2 (C_q), 132.4 (C_q), 132.0 (*C*H_{Ar}), 131.7 (*C*H_{Ar}), 130.8 (C_q), 129.9 (C_q), 129.3 (*C*H_{Ar}), 128.5 (*C*H_{Ar}), 127.1 (C_q), 121.9 (C5), 120.3 (C3), 117.8 (C8), 116.6 (C7), 111.0 (C6), 107.3 (C1), 9.4 (*C*H_3) ppm.

MS (ESI): m/z = 384.1 (46) $[M + 2O + H]^+$, 368.2 (67) $[M + O + H]^+$, 352.2 (36) $[M + H]^+$, 351.2 (100) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{21}H_{15}NCl_2]^+$ 351.0582, found 351.0582.

2-(4-Chlorophenyl)-1,3,5-trimethylindolizine (86k)



The title compound was prepared according to the general procedure-IV from **85f** (296 mg, 1.0 mmol) and *(E)*-1-chloro-4-(2-nitroprop-1-enyl)benzene (**76a**, 198 mg, 1.0 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 56 mg (0.21 mmol, 21%), yellow solid.

Mp: 105–107 °C.

R_f = 0.75 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 2923, 1488, 1376, 1090, 830, 795, 725 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.42–7.37 (AA'-part of AA'BB' system, 2H, H-3',5'), 7.24–7.19 (BB'-part of AA'BB' system, 2H, H-2',6'), 7.15 (ddd, *J* = 9.0, 1.3, 0.6 Hz, 1H,

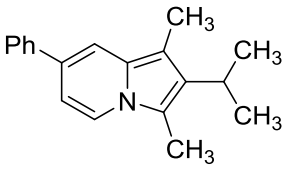
H-8), 6.44 (dd, *J* = 9.0, 6.4 Hz, 1H, H-7), 6.13-6.10 (m, 1H, H-6), 2.83 (s, 3H, 5-C*H*$_3$), 2.73 (s, 3H, 3-C*H*$_3$), 2.18 (s, 3H, 1-C*H*$_3$) ppm.

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ =134.7 (C4'), 134.4 (C5), 132.2 (2C, C2',6'), 131.2 (C1'), 130.6 (C9), 128.2 (2C, C3',5'), 127.2 (C2), 118.2 (C3), 115.6 (C8), 115.1 (C7), 111.4 (C6), 105.1 (C1), 21.3 (5-*C*H$_3$), 14.1 (3-*C*H$_3$), 9.2 (1-*C*H$_3$) ppm.

MS (ESI): m/z = 286.0 (60) $[M + O + H]^+$, 270.0 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{17}H_{16}NCl + H]^+$ 270.1050, found 270.1037.

2-Isopropyl-1,3-dimethyl-7-phenylindolizine (86l)



The title compound was prepared according to the general procedure-IV from **85d** (358 mg, 1.0 mmol) and (*E*)-4-methyl-2-nitropent-2-ene (**76e**, 129 mg, 1.0 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 97 mg (0.37 mmol, 37%), yellow solid.

Mp: 84–85 °C.

R_f = 0.75 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 2959, 2925, 1390, 1362, 1259, 750 cm^{-1}.

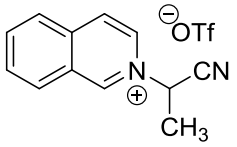
^{1}H NMR, COSY, (300 MHz, CD_3OD) δ = 7.75 (d, *J* = 7.3 Hz, 1H, H-5), 7.64 (d, *J* = 7.4 Hz, 2H, H-2',6'), 7.51 (br s, 1H, H-8), 7.42–7.37 (m, 2H, H-3',5'), 7.25 (t, *J* = 7.4 Hz, 1H, H-4'), 6.79 (dd, *J* = 7.3, 1.7 Hz, 1H, H-6), 3.18 (sept., *J* = 7.1 Hz, 1H, 2-C*H*), 2.42 (s, 3H, 3-C*H*$_3$), 2.37 (s, 3H, 1-C*H*$_3$), 1.36 (d, *J* = 7.1 Hz, 6H, (C*H*$_3$)$_2$CH) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, CD_3OD) δ = 141.6 (C1'), 132.5 (C2), 130.7 (C9), 129.8 (2C, C3',5'), 127.4 (C4'), 127.2 (C7), 126.8 (2C, C2',6'), 122.4 (C5), 116.1 (C3), 114.1 (C8), 109.5 (C6), 107.1 (C1), 27.3 (*C*H), 23.3(2C, (*C*H$_3$)$_2$CH), 10.0 (*C*H$_3$), 9.9 (*C*H$_3$) ppm.

MS (ESI): m/z = 296.1 (17) $[M + 2O + H]^+$, 280.1 (16) $[M + O + H]^+$, 264.1 (100) $[M + H]^+$, 263.1 (21) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{19}H_{21}N]^+$ 264.1752, found 264.1750.

2-(1-Cyanoethyl)isoquinolinium triflate (87a)



The title compound was prepared according to the general procedure-III from isoquinoline (646 mg, 5.0 mmol) and 1-cyanoethyl trifluoromethanesulfonate (**84a**, 1.22 g, 6.0 mmol). The colorless solid was filtered, washed with cold diethyl ether and recrystallized from diethyl ether.

Yield: 1.55 g (4.66 mmol, 93%), colorless solid.

Mp: 155–156 °C.

IR (ATR) $\tilde{\nu}$ = 3066, 1644, 1403, 1264, 1167 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 10.26 (s, 1H, H-1), 9.03 (d, *J* = 6.8 Hz, 1H, H-3), 8.72 (d, *J* = 6.8 Hz, 1H, H-4), 8.60 (d, *J* = 8.0 Hz, 1H, H-8), 8.38–8.32 (m, 2H, H-6, H-7), 8.15 (d, *J* = 8.0 Hz, 1H, H-5), 6.41 (q, *J* = 7.0 Hz, 1H, C*H*), 2.11 (d, *J* = 7.0 Hz, 3H, CH_3) ppm.

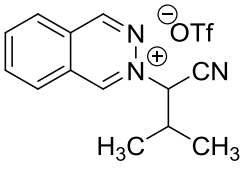
^{13}C NMR (75 MHz, DMSO-d_6) δ = 150.5 (C1), 138.1 (C6), 137.7 (C4a), 133.0 (C3), 131.7 (C7), 131.2 (C8), 127.4 (C5), 127.2 (C8a), 126.7 (C4), 120.7 (q, $^1J_{C,F}$ = 322 Hz, *C*F_3), 116.6 (*C*≡N), 56.1 (*C*H), 20.1 (*C*H_3) ppm.

Elemental Analysis: Calcd: C: 46.99% H: 3.34% N: 8.43% S: 9.65%

$C_{13}H_{11}F_3N_2O_3S$ Found: C: 46.84% H: 3.18% N: 8.10% S: 9.73%

MS (ESI): m/z = 183.1 (100) $[M]^+$, 158.1 (22).

2-(1-Cyano-2-methylpropyl)phthalazin-2-ium triflate (87b)



The title compound was prepared according to the general procedure-III from phthalazine (1.30 g, 10.0 mmol) and **84b** (2.31 g, 10.0 mmol). The solid was filtered, washed with diethyl ether and recrystallized from EtOAc.

Yield: 2.79 g (7.7 mmol, 77%), colorless solid.

Mp: 122–123 °C.

IR (ATR) $\tilde{\nu}$ = 3010, 2976, 1484, 1225, 1153, 1027 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 10.72 (s, 1H, H-1), 10.21 (s, 1H, H-4), 8.75 (d, *J* = 8.0 Hz, 1H, H-8), 8.68–8.59 (m, 2H, H5, H-7), 8.49 (ddd, *J* = 8.3, 6.4, 2.1 Hz, H-6), 6.41 (d, *J* = 7.1 Hz, 1H, H-1'), 2.83–2.65 (m, 1H, H-2'), 1.18 (d, *J* = 6.7 Hz, 3H, CH_3), 1.04 (d, *J* = 6.7 Hz, 3H, CH_3) ppm.

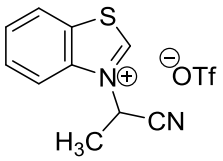
^{13}C NMR (75 MHz, DMSO-d_6) δ = 155.4 (*C*H), 153.3 (*C*H), 140.4 (*C*H), 136.7 (*C*H), 131.4 (*C*H), 128.7 (*C*H), 128.1 (C_q), 127.6 (C_q), 120.6 (q, $^1J_{C,F}$ = 322 Hz, *C*F_3), 114.4 (*C*N), 68.2 (C1'), 33.3 (C2'), 18.2 (*C*H_3), 17.7 (*C*H_3) ppm.

Elemental Analysis: Calcd: C: 46.54% H: 3.91% N: 11.63% S: 8.87%

$C_{14}H_{14}F_3N_3O_3S$ Found: C: 46.60% H: 3.90% N: 11.81% S: 8.92%

MS (ESI): m/z = 212.1 (100) $[M + H]^+$.

3-(1-Cyanoethyl)-1,3-benzothiazol-3-ium triflate (87c)



The title compound was prepared according to the general procedure-III from benzothiazole (541 mg, 4.00 mmol) and **84a** (1.22 g, 6.0 mmol). The solid was filtered, washed with diethyl ether and recrystallized from DCM.

Yield: 1.12 g (3.31 mmol, 83%).

Mp: 94–96 °C.

IR (ATR) $\tilde{\nu}$ = 3081, 1582, 1504, 1255, 1160, 1125 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 10.75 (s, 1H, H-2), 8.58 (d, *J* = 8.2 Hz, 1H, H-7), 8.48 (d, *J* = 8.4 Hz, 1H, H-4), 8.03 (pseudo t, *J* = 7.9 Hz, 1H, H-5), 7.92 (pseudo t, *J* = 7.7 Hz, 1H, H-6), 6.72 (q, *J* = 7.0 Hz, 1H, C*H*), 2.14 (d, *J* = 7.1 Hz, 3H, CH_3) ppm.

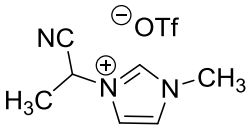
^{13}C NMR (75 MHz, DMSO-d_6) δ = 168.4 (C2), 164.4 (*C*H), 140.4 (C3a), 131.0 (C7a), 130.0 (*C*H), 128.8 (*C*H), 125.6 (*C*H), 120.7 (q, $^1J_{C,F}$ = 322 Hz, CF_3), 116.6 (*C*≡N), 60.7 (*C*H), 17.2 (*C*H_3) ppm.

Elemental Analysis: Calcd: C: 39.05% H: 2.68% N: 8.28% S: 18.96%

$C_{11}H_9F_3N_2O_3S_2$ Found: C: 39.17% H: 2.72% N: 8.27% S: 19.07%

MS (ESI): m/z = 207.0 (100) $[M + NH_4]^+$, 189.0 (64) $[M]^+$, 164.1 (39).

3-(1-Cyanoethyl)-1-methyl-1*H*-imidazol-3-ium triflate (87d)



The title compound was prepared according to the general procedure-III from 1-methyl-imidazole (328 mg, 4.0 mmol) and **84a** (813 mg, 4.0 mmol). The solid was filtered, washed with diethyl ether and recrystallized from DCM.

Yield: 938 mg (3.29 mmol, 82%), colorless solid.

Mp: 52–54 °C.

IR (ATR) $\tilde{\nu}$ = 3155, 3110, 2962, 1583, 1557, 1250, 1157, 1028, 733 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.35 (s, 1H, H-2), 8.07 (d, *J* = 1.4 Hz, 1H, H-4), 7.82 (d, *J* = 1.4 Hz, 1H, H-5), 5.98 (q, *J* = 7.1 Hz, 1H, H-1'), 3.88 (s, 3H, N-CH_3), 1.88 (d, *J* = 7.1 Hz, 3H, H-2') ppm.

^{13}C NMR (75 MHz, DMSO-d_6) δ = 137.0 (C2), 124.6 (C5), 120.9 (C4), 117.1 (*C*N), 45.3 (*C*H), 36.2 (N*C*H_3), 19.0 (*C*H_3) ppm.

Elemental Analysis: Calcd: C: 33.69% H: 3.53% N: 14.73% S: 11.24%

$C_8H_{10}F_3N_3O_3S$ Found: C: 33.50% H: 3.56% N: 14.85% S: 11.31%

MS (ESI): m/z = 136.2 (100) $[M + H]^+$.

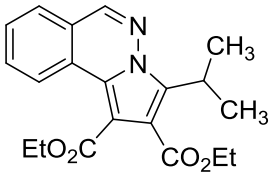
Synthesis of N-fused pyrrole containing heterocycles 88 and 89

Method A: To a solution of azinium salt **87** (1.00 equiv.) and nitroolefin **76** (1.00 equiv.) in dry DMF (10 mL/mmol azine) was slowly added the solution of KO*t*Bu (4 equiv.) in dry DMF (5.0 mL/mmol azine) at 0 °C. The mixture was stirred at this temperature and the reaction was monitored by TLC. When the reaction was completed, the solvent was

evaporated in vacuo. The residue was dissolved in ethyl acetate and washed with water. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed in vacuo. For Table 5, entry 5, Ag_2CO_3 (2 equiv.) was used instead of KO*t*Bu.

Method B: A solution of KO*t*Bu (4 equiv.) in dry DMF (5.0 mL/mmol azine) was slowly added to a stirred solution of azinium salt (1.00 equiv.) and DEAD (1.00 equiv.) in dry DMF (10 mL/mmol azine) at 0 °C. The mixture was stirred at 0 °C and the reaction was monitored by TLC. When the reaction was completed, the solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate and washed with water. The aqueous phase was extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent was removed in vacuo.

Diethyl 3-(propan-2-yl)pyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (88a)



The title compound was prepared according to method B from **87b** (361 mg, 1.00 mmol) and diethyl acetylenedicarboxylate (170 mg, 1.00 mmol). The crude product was purified by flash chromatography over silica (ethyl acetate/cyclohexane 1:5).

Yield: 180 mg (0.51 mmol, 51%), colorless solid.

Mp: 68–69 °C.

R_f = 0.31 (ethyl acetate/cyclohexane 1:5).

IR (ATR) $\tilde{\nu}$ = 2979, 2937, 1704, 1621, 1456, 1173, 757 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 8.88 (br d, *J* = 8.7 Hz, 1H, H-10), 8.44 (s, 1H, H-6), 7.75–7.68 (m, 2H, H-7, H-9), 7.54 (td, *J* = 7.5, 1.0 Hz, 1H, H-8), 4.42 (q, *J* = 7.2 Hz, 2H, H-2'), 4.37 (q, *J* = 7.2 Hz, 2H, H-2''), 4.01 (sept, *J* = 7.1 Hz, 1H, H-1'''), 1.46 (d, *J* = 7.1 Hz, 6H, ((C*H*$_3$)$_2$CH), 1.40 (t, *J* = 7.2 Hz, 3H, H-3'), 1.39 (t, *J* = 7.2 Hz, 3H, H-3'') ppm.

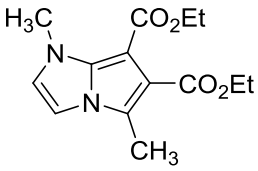
^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ = 166.3 (C1''), 166.1 (C1'), 145.1 (C6), 137.3 (C3), 132.7 (C7), 127.9 (C8), 127.8 (C9), 127.5 (C10a), 124.5 (C10), 122.9 (C10b),

120.8 (C6a), 114.9 (C2), 106.6 (C1), 61.2 (C2’), 61.1 (C2’’), 25.6 (C1’’’), 20.1 (2C, (CH$_3$)$_2$CH), 14.4 (C3’’), 14.3 (C3’) ppm.

MS (ESI): m/z = 377.2 (100) [M + Na]$^+$, 355.3 (30) [M + H]$^+$, 309.3 (71) [M-OC2H5]$^+$.

HRMS (ESI-TOF): Calcd for [$C_{20}H_{22}N_2O_4$ + Na]$^+$ 377.1477, found 377.1477.

Diethyl 1,5-dimethyl-1*H*-pyrrolo[1,2-*a*]imidazole-6,7-dicarboxylate (88b)



The title compound was prepared according to method B from **87d** (157 mg, 0.55 mmol) and DEAD (94 mg, 0.55 mmol). The crude product was purified by flash chromatography over silica (ethyl acetate/cyclohexane 1:3).

Yield: 89 mg, (0.32 mmol, 58%), yellow solid.

Mp: 118–120 °C.

R_f = 0.22 (ethyl acetate/cyclohexane 1:3).

IR (ATR) $\tilde{\nu}$ = 2980, 1670, 1589, 1454, 1189, 1083, 1048 cm^{-1}.

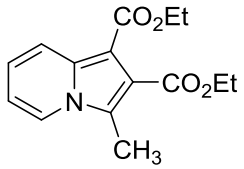
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 6.80 (d, *J* = 2.2 Hz, 1H, H-3), 6.67 (d, *J* = 2.2 Hz, 1H, H-2), 4.31 (q, *J* = 7.1 Hz, 2H, H-2’), 4.21 (q, *J* = 7.1 Hz, 2H, H-2’’), 3.96 (s, 3H, N-CH_3), 2.33 (s, 3H, 5-CH_3), 1.35 (t, *J* = 7.1 Hz, 3H, H-3’), 1.29 (t, *J* = 7.1 Hz, 3H, H-3’’) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ = 166.7 (C1’), 163.8 (C1’’), 139.0 (C7a), 123.8 (C2), 117.9 (C6), 115.5 (C5), 104.1 (C3), 85.1 (C7), 60.7 (C2’), 59.3 (C2’’), 35.8 (NCH$_3$), 14.6 (C3’’), 14.4 (C3’), 10.3 (5-CH$_3$) ppm.

MS (ESI): m/z = 301.3 (100) [M +Na]$^+$, 279.3 (51) [M + H]$^+$, 233.2 (49) [M-OC$_2$H$_5$]$^+$.

HRMS (ESI-TOF): Calcd for [$C_{14}H_{18}N_2O_4$ + H]$^+$ 279.1345, found 279.1346.

Diethyl 3-methylindolizine-1,2-dicarboxylate (88c)



The title compound was prepared according to method B from **85a** (282 mg, 1.00 mmol) and DEAD (170 mg, 1.00 mmol). The crude product was purified by flash chromatography over silica (ethyl acetate/cyclohexane 1:10).

Yield: 210 mg (0.76 mmol, 76%), yellow waxy oil.

R_f = 0.18 (ethyl acetate/cyclohexane 1:4).

IR (ATR) $\tilde{\nu}$ = 2982, 1734, 1689, 1527, 1236, 1200, 1088, 1041, 782, 739 cm^{-1}.

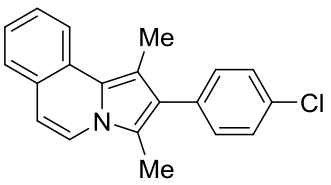
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.15 (dd, *J* = 9.0, 0.9 Hz, 1H, H-5), 7.78 (dd, *J* = 6.6, 0.9 Hz, 1H, H-8), 7.06 (ddd, *J* = 9.0, 6.6, 1.0 Hz, 1H, H-6), 6.79 (td, *J* = 6.6, 1.3 Hz, H-7), 4.40 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$), 4.34 (q, *J* = 7.2 Hz, 2H, OC*H*$_2$), 2.50 (s, 3H, 3-C*H*$_3$), 1.40 (t, *J* = 7.2 Hz, 3H, C*H*$_3$), 1.35 (t, *J* = 7.2 Hz, 3H, C*H*$_3$) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.7 (*C*O_2Et), 164.1 (*C*O_2Et), 135.1 (C_q), 122.8, 122.5, 122.1 (C_q), 120.6 (C_q), 120.4, 113.4 (*C*N), 101.7 (C_q), 61.3 (O*C*H_2), 59.9 (O*C*H_2), 14.6 (*C*H_3), 14.4 (*C*H_3), 10.1 (*C*H_3) ppm.

MS (ESI): m/z = 298.2 (100) $[M + Na]^+$, 276.2 (29) $[M + H]^+$, 230.1 (28) $[M\text{-}OC_2H_5]^+$.

HRMS (ESI-TOF): Calcd for $[C_{15}H_{17}NO_4 + Na]^+$ 298.1055, found 298.1056.

2-(4-Chlorophenyl)-1,3-dimethylpyrrolo[2,1-*a*]isoquinoline (89a)



The title compound was prepared according to method A from **87a** (332 mg, 1.0 mmol) and *(E)*-1-chloro-4-(2-nitroprop-1-enyl)benzene (**76a**, 198 mg, 1.0 mmol). The crude product was purified by column chromatography over silica (ethyl acetate/cyclohexane 1:10).

Yield: 150 mg (0.49 mmol, 49%), yellow solid.

Mp: 148–149 °C.

R_f = 0.54 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 2960, 2923, 1547, 1480, 1359, 1087, 848, 779, 757 cm^{-1}.

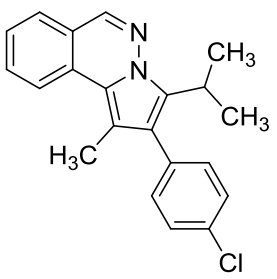
^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.23 (d, *J* = 8.1 Hz, 1H, H-5), 7.59 (pseudo-t, *J* = 8.1 Hz, 2H, H-9, H-10), 7.52–7.42 (m, 3H, H-8 or H-7, H-3',5'), 7.37–7.26 (m, 3H, H-7 or H-8, H-2',6'), 6.75 (d, *J* = 7.4 Hz, 1H, H-6), 2.57 (s, 3H, CH_3), 2.42 (s, 3H, CH_3) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ =134.3, 132.4, 132.3, 131.7, 128.5, 128.0, 127.24, 127.20, 126.9, 125.9, 124.5, 122.5, 121.5, 118.5, 110.7, 110.4, 13.1, 10.3 ppm.

MS (ESI): m/z = 338.2 (92) $[M + 2O + H]^+$, 322.2 (100) $[M + O + H]^+$, 306.2 (56) $[M + H]^+$, 305.2 (65) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{20}H_{16}NCl]^+$ 305.0971, found 305.0980.

2-(4-Chlorophenyl)-1-methyl-3-(propan-2-yl)pyrrolo[2,1-*a*]phthalazine (89b)



The title compound was prepared according to method B from **87b** (361 mg, 1.00 mmol) and nitroolefin **76a** (198 mg, 1.00 mmol). The crude product was purified by filtration over silica (ethyl acetate/cyclohexane 1:10).

Yield: 114 mg (0.34 mmol, 34%), yellow solid.

Mp: 136–138 °C.

R_f = 0.50 (ethyl acetate/cyclohexane 1:5).

IR (ATR) $\tilde{\nu}$ = 2962, 2932, 1357, 1202, 1016, 840, 752 cm^{-1}.

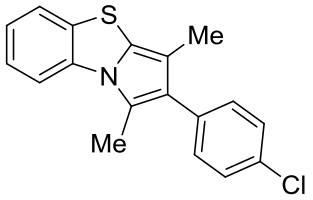
^{1}H NMR, COSY (600 MHz, $(CD_3)_2CO$) δ = 8.47 (s, 1H, H-6), 8.15 (dd, *J* = 8.2, 1.1 Hz, 1H, H-10), 7.87 (dd, *J* = 7.9, 1.4 Hz, 1H, H-7), 7.75 (ddd, *J* = 8.1, 7.3, 1.0 Hz, 1H, H-9), 7.52–7.50 (AA'-part of AA'BB' system, 2H, H-3',5'), 7.46 (ddd, *J* = 7.9, 7.5, 0.7 Hz, 1H, H-8), 7.37–7.34 (BB'-part of AA'BB' system, 2H, H-2',6'), 3.48 (sept, *J* = 7.2 Hz, 1H, 3-C*H*), 2.41 (s, 3H, 1-CH_3), 1.38 (d, *J* = 7.1 Hz, 6H, $(CH_3)_2$CH) ppm.

^{13}C NMR, HSQC, HMBC (151 MHz, $(CD_3)_2CO$) δ = 143.2 (C6), 135.6 (C4'), 133.5 (2C, C2',6'), 133.1 (C1'), 133.0 (C9), 131.8 (C3), 130.2 (C6a), 129.0 (2C, C3',5'), 128.8 (C7), 125.8 (C8), 123.7 (C2), 122.2 (C10), 120.5 (C10a), 118.5 (C10b), 109.9 (C1), 26.8 (3-*C*H), 20.9 (2C, $(CH_3)_2CH$), 12.3 (1-CH_3). ppm.

MS (ESI): m/z = 367.3 (39) $[M + 2O + H]^+$, 351.4 (100) $[M + O + H]^+$, 335.5 (34) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{21}H_{19}N_2Cl + H]^+$ 335.1315, found 335.1312.

2-(4-Chlorophenyl)-1,3-dimethylpyrrolo[2,1-*b*][1,3]benzothiazole (89c)



The title compound was prepared according to method A from **87c** (338 mg, 1.00 mmol) and nitroolefin **76a** (198 mg, 1.00 mmol). The crude product was purified by chromatography over silica (ethyl acetate/cyclohexane 1:10).

Yield: 80 mg (0.26 mmol, 26%), slightly brown solid.

Mp: 134–137 °C.

R_f = 0.60 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 3058, 3033, 2920, 1476, 1028, 763, 742 cm^{-1}.

^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.75 (dd, *J* = 8.2, 0.6 Hz, 1H, H-5), 7.61 (dd, *J* = 7.9, 1.0 Hz, 1H, H-8), 7.44–7.39 (AA'-part of AA'BB' system, 2H, H-3',5'), 7.31 (td, *J* = 7.9, 1.2 Hz, 1H, H-6), 7.28–7.24 (BB'-part of AA'BB' system, 2H, H-2',6'), 7.19 (ddd overlapped, *J* = 7.8, 7.6, 1.0 Hz, 1H, H-7), 2.67 (s, 3H, 1-CH_3), 2.12 (s, 3H, 3-CH_3) ppm.

^{13}C NMR, HSQC, HMBC (75 MHz, $CDCl_3$) δ = 136.4 (C8a), 134.2 (C4'), 132.2 (C1'), 131.7 (C4a), 131.6 (2C, C2',6'), 128.5 (2C, C3',5'), 127.2 (C2), 125.3 (C6), 124.0 (C8), 123.4 (C3a), 123.0 (C7), 120.1 (C1), 112.8 (C5), 106.3 (C3), 12.7 (1-CH_3), 10.8 (3-CH_3) ppm.

MS (ESI): m/z = 344.2 (23) $[M + 2O + H]^+$, 328.2 (100) $[M + O + H]^+$, 312.2 (28) $[M + H]^+$, 311.2 (46) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{18}H_{14}NClS]^+$ 311.0535, found 311.0545.

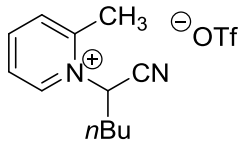
5.2.2 Synthesis of 2-Aminoindolizines

The preparation of cyanohydrin triflates **84** has been described in the chapter 5.2.1.

General procedure-V for Pyridinium Salts 95

To a solution of pyridines or other heterocycles in diethyl ether (1.0 M) was added cyanohydrin triflates (1.00 equiv) at ambient temperature and the reaction mixture was stirred overnight or for 48 h. The products were collected via filtration and were washed with appropriate solvents.

1-(1-Cyanopentyl)-2-methylpyridinium triflate (95a)



The title compound was prepared according to the general procedure-V described above from 2-methylpyridine (**94a**, 0.931 g, 10.0 mmol) and triflate **84e** (2.45 g, 10.0 mmol). After stirring overnight, the precipitate was collected and was washed with diethyl ether.

Yield: 3.11 g (9.2 mmol, 92%), colorless solid.

Mp: 76–77 °C.

IR (ATR) $\tilde{\nu}$ = 3105, 2938, 1637, 1507, 1261, 1145, 1029, 772 cm^{-1}.

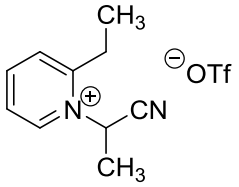
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 9.29 (dd, *J* = 6.5, 1.8 Hz, 1H, H-6), 8.60 (ddd, *J* = 9.3, 6.7, 1.8 Hz, 1H, H-4), 8.17–8.05 (m, 2H, H-3, H-5), 6.30 (dd, *J* = 9.0, 6.1 Hz, 1H, H-1'), 2.91 (s, 3H, 2-CH_3), 2.38–2.21 (m, 2H, H-2'), 1.53–1.40 (m, 2H, H-3'), 1.40–1.29 (m, 2H, H-4'), 0.90 (t, *J* = 7.2 Hz, 3H, H-5') ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 156.2 (C2), 147.0 (C4), 143.2 (C6), 130.8 (C3), 126.6 (C5), 120.7 (q, $^{1}J_{C,F}$ = 322.4 Hz, CF_3), 115.9 (*C*N), 56.3 (C1'), 33.0 (C2'), 26.7 (C3'), 21.4 (C4'), 20.4 (2-CH_3), 13.6 (C5') ppm.

Elemental Analysis: Calcd: C: 46.15% H: 5.06% N: 8.28% S: 9.48%

$C_{13}H_{17}F_3N_2O_3S$ Found: C: 46.20% H: 4.77% N: 8.36% S: 9.81%

1-(1-Cyanoethyl)-2-ethylpyridinium triflate (95b)



The title compound was prepared according to the general procedure-V described above from 2-ethylpyridine **(94b**, 121 mg, 1.13 mmol) and **84a** (229 mg, 1.13 mmol). After stirring overnight, the precipitate was collected and was washed with diethyl ether and chloroform.

Yield: 315 mg (0.90 mmol, 90%), colorless solid.

Mp: 146–148 °C.

IR (ATR) $\tilde{\nu}$ = 3113, 3012, 2997, 1634, 1504, 1262, 1154, 1033, 809, 777 cm^{-1}.

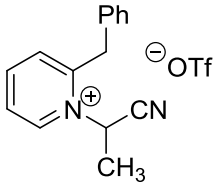
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 9.35 (dd, *J* = 6.9, 1.4 Hz, 1H, H-6), 8.64 (td, *J* = 7.8, 1.4 Hz, 1H, H-4), 8.17–8.10 (m, 2H, H-3, H-5), 6.47 (q, *J* = 6.8 Hz, 1H, H-1'), 3.30–3.11 (m, 2H, H-1''), 1.99 (d, *J* = 7.1 Hz, 3H, H-2'), 1.35 (t, *J* = 7.4 Hz, 3H, H-2'') ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 160.0 (C2), 147.3 (C4), 143.2 (C6), 128.5 (C3), 126.5 (C5), 120.7 (q, $^1J_{C,F}$ = 322.3 Hz, *C*F_3), 116.9 (*C*N), 51.4 (C1'), 25.7 (C1''), 20.1 (C2'), 11.9 (C2'') ppm.

Elemental Analysis: Calcd: C: 42.58% H: 4.22% N: 9.03% S: 10.33%

$C_{11}H_{13}F_3N_2O_3S$ Found: C: 42.52% H: 4.14% N: 9.07% S: 10.53%

2-Benzyl-1-(1-cyanoethyl)pyridinium triflate (95c)



The title compound was prepared according to the general procedure-V described above from 2-benzylpyridine **(94c**, 583 mg, 3.45 mmol) and **84a** (700 mg, 3.45 mmol). After stirring overnight, the precipitate was collected and was washed with DCM.

Yield: 1173 mg (3.15 mmol, 91%), colorless solid.

Mp: 120–121 °C.

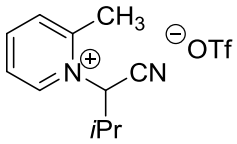
IR (ATR) $\tilde{\nu}$ = 3081, 3019, 2927, 1627, 1577, 1499, 1273, 1255, 1167, 1030, 741, 699 cm^{-1}.

^{1}H NMR, COSY (300 MHz, DMSO-d_6) δ = 9.46 (dd, *J* = 6.5, 1.6 Hz, 1H, H-6), 8.63 (td, *J* = 7.8, 1.6 Hz, 1H, H-4), 8.19 (ddd, *J* = 7.8, 6.5, 1.7 Hz, 1H, H-5), 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H, H-3), 7.50–7.28 (m, 5H, H_{Ph}), 6.51 (q, *J* = 6.9 Hz, 1H, H-1'), 4.73 (d, *J* = 17.0 Hz, 1H, C$H_{2\text{-a}}$), 4.60 (d, *J* = 17.0 Hz, 1H, C$H_{2\text{-b}}$), 1.87 (d, *J* = 6.9 Hz, 3H, H-2') ppm.

^{13}C NMR, HSQC, HMBC (75 MHz, DMSO-d_6) δ = 157.5 (C2), 147.6 (C4), 143.8 (C6), 134.1 (C1''), 129.8 (C3), 129.6 (2C, C2'',5''), 129.3 (2C, C3'',5''), 127.9 (C4''), 127.1 (C5), 120.7 (q, $^1J_{C,F}$ = 322.3 Hz, CF_3), 116.7 (*C*N), 51.8 (C1'), 37.8 (CH_2), 20.2 (C2') ppm.

Elemental Analysis:	Calcd:	C: 51.61%	H: 4.06%	N: 7.52%	S: 8.61%
$C_{16}H_{15}F_3N_2O_3S$	Found:	C: 51.66%	H: 3.72%	N: 7.57%	S: 8.70%

1-(1-Cyano-2-methylpropyl)-2-methylpyridinium triflate (95d)



The title compound was prepared according to the general procedure-V described above from **94a** (0.466 g, 5.00 mmol) and 1-cyano-2-methylpropyl trifluoromethanesulfonate (**84b**, 1.16 g, 5.00 mmol). After stirring overnight, the precipitate was collected and was washed with diethyl ether.

Yield: 1.25 g (3.85 mmol, 77%), colorless solid.

Mp: 89–90 °C.

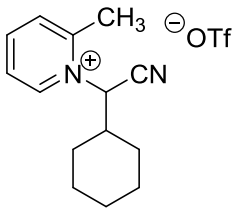
IR (ATR) $\tilde{\nu}$ = 3087, 3059, 2979, 1632, 1507, 1471, 1263, 1225, 1159, 1031, 778 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.26 (dd, *J* = 6.5, 1.3 Hz, 1H, H-6), 8.62 (td, *J* = 7.8, 1.3 Hz, 1H, H-4), 8.17 (dd, *J* = 7.8, 1.6 Hz, 1H, H-3), 8.11 (ddd, *J* = 7.8, 6.5, 1.6 Hz, 1H, H-5), 6.25 (d, *J* = 7.6 Hz, 1H, H-1'), 2.92 (s, 3H, 2-CH_3), 2.72–2.57 (m, 1H, H-2'), 1.14 (d, *J* = 6.6 Hz, 3H, H-3'), 0.96 (d, *J* = 6.7 Hz, 3H, 2'-CH_3) ppm.

^{13}C NMR, HSQC (101 MHz, DMSO-d_6) δ = 156.6 (C2), 147.2 (C4), 143.5 (C6), 131.0 (C3), 126.5 (C5), 120.7 (q, $^{1}J_{C,F}$ = 322.5 Hz, *C*F$_3$), 115.0 (*C*N), 61.6 (C1'), 32.7 (C2'), 20.6 (2-*C*H$_3$), 17.9 (C3'), 17.4 (2'-*C*H$_3$) ppm.

Elemental Analysis:	Calcd: C: 44.44%	H: 4.66%	N: 8.64%	S: 9.89%
$C_{12}H_{15}F_3N_2O_3S$	Found: C: 44.01%	H: 4.50%	N: 8.58%	S: 10.05%

1-(Cyano(cyclohexyl)methyl)-2-methylpyridinium triflate (95e)



The title compound was prepared according to the general procedure-V described above from **94a** (171 mg, 1.84 mmol) and cyano(cyclohexyl)methyl trifluoromethanesulfonate (**84f**, 500 mg, 1.84 mmol). After stirring overnight, the precipitate was collected and was washed with diethyl ether and THF.

Yield: 374 mg (1.03 mmol, 56%), colorless solid.

Mp: 125–126 °C.

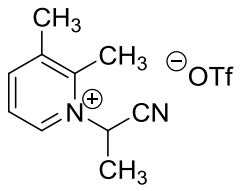
IR (ATR) $\tilde{\nu}$ = 3091, 2932, 2855, 1625, 1500, 1471, 1264, 1224, 1166, 1028 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6) δ = 9.23 (dd, *J* = 6.5, 1.6 Hz, 1H, H-6), 8.61 (td, *J* = 7.9, 1.3 Hz, 1H, H-4), 8.16 (dd, *J* = 7.9, 1.7 Hz, 1H, H-3), 8.11 (ddd, *J* = 7.9, 6.5, 1.7 Hz 1H, H-5), 6.24 (d, *J* = 7.9 Hz, 1H, H-1'), 2.91 (s, 3H, 2-C*H*$_3$), 2.42–2.31 (m, 1H, 1'-H$_{Cy}$), 1.84–1.73 (m, 2H, H$_{Cy}$), 1.73–1.58 (m, 2H, H$_{Cy}$), 1.46–1.29 (m, 2H, H$_{Cy}$), 1.27–1.06 (m, 4H, H$_{Cy}$) ppm.

^{13}C NMR, HMBC (75 MHz, DMSO-d_6) δ = 156.6 (C2), 147.1 (C4), 143.5 (C6), 131.0 (C3), 126.5 (C5), 120.7 (q, $^{1}J_{C,F}$ = 322.5 Hz, *C*F$_3$), 115.0 (*C*N), 60.9 (C1'), 40.9 (1'-*C*$_{Cy}$), 28.0 (C$_{Cy}$), 27.5 (C$_{Cy}$), 25.0 (C$_{Cy}$), 24.72 (C$_{Cy}$), 24.68 (C$_{Cy}$), 20.7 (2-*C*H$_3$) ppm.

HRMS (ESI-TOF): Calcd for $[C_{14}H_{19}N_2]^+$ 215.1548, found 215.1558.

1-(1-Cyanoethyl)-2,3-dimethylpyridinium triflate (95f)



The title compound was prepared according to the general procedure-V described above from 2,3-dimethylpyridine (**94d**, 246 mg, 2.30 mmol) and **84a** (467 mg, 2.30 mmol). After stirring for 48 h, the precipitate was collected and was washed with diethyl ether and DCM.

Yield: 639 mg (2.06 mmol, 90%), colorless solid.

Mp: 116–118 °C.

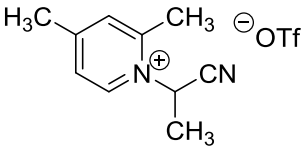
IR (ATR) $\tilde{\nu}$ = 3089, 3021, 1618, 1489, 1253, 1152, 1029 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.15 (dd, *J* = 6.4, 1.5 Hz, 1H, H-6), 8.48 (d, *J* = 7.8 Hz, 1H, H-4), 8.01 (dd, *J* = 7.8, 6.4 Hz, 1H, H-5), 6.48 (q, *J* = 7.0 Hz, 1H, H-1'), 2.79 (s, 3H, 2-CH_3), 2.51 (s, 3H, 3-CH_3), 1.96 (d, *J* = 7.0 Hz, 3H, H-2') ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 154.4 (C2), 146.9 (C4), 140.6 (C6), 139.2 (C3), 125.4 (C5), 120.7 (q, $^{1}J_{C,F}$ = 322.3 Hz, *C*F_3), 116.8 (*C*N), 52.7 (C1'), 19.8 (C2'), 19.6 (3-*C*H_3), 17.1 (2-*C*H_3) ppm.

Elemental Analysis:	Calcd:	C: 42.58%	H: 4.22%	N: 9.03%	S: 10.33%
$C_{11}H_{13}F_3N_2O_3S$	Found:	C: 42.61%	H: 4.05%	N: 9.04%	S: 10.46%

1-(1-Cyanoethyl)-2,4-dimethylpyridinium triflate (95g)



The title compound was prepared according to the general procedure-V described above from 2,4-dimethylpyridine (**94e**, 477 mg, 4.45 mmol) and **84a** (904 mg, 4.45 mmol). After stirring for 48 h, the precipitate was collected and was washed with diethyl ether.

Yield: 1.170 g (3.77 mmol, 85%), colorless solid.

Mp: 96–97 °C.

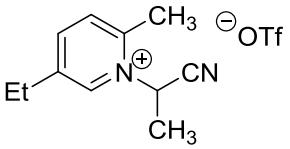
IR (ATR) $\tilde{\nu}$ = 3097, 3009, 2996, 1645, 1260, 1149, 1031 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.15 (d, *J* = 6.6 Hz, 1H, H-6), 7.98 (d, *J* = 2.4 Hz, 1H, H-3), 7.95 (dd, *J* = 6.6, 2.4 Hz, 1H, H-5), 6.30 (q, *J* = 6.7 Hz, 1H, H-1'), 2.84 (s, 3H, CH_3-2), 2.60 (s, 3H, CH_3-4), 1.95 (d, *J* = 6.7 Hz, 3H, H-2') ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 160.6 (C4), 154.6 (C2), 141.8 (C6), 130.5 (C3), 127.1 (C5), 116.8 (CN), 51.3 (C1'), 21.3 (*C*H_3-4), 19.9 (*C*H_3-2), 19.6 (C2') ppm.

Elemental Analysis:	Calcd: C: 42.58%	H: 4.22%	N: 9.03%	S: 10.33%
$C_{11}H_{13}F_3N_2O_3S$	Found: C: 42.39%	H: 3.69%	N: 9.16%	S: 10.72%

1-(1-Cyanoethyl)-5-ethyl-2-methylpyridinium triflate (95h)



The title compound was prepared according to the general procedure-V described above from 5-ethyl-2-methylpyridine (**94f**, 596 mg, 4.92 mmol) and **84a** (1.00 g, 4.92 mmol). After stirring for 24 h, the precipitate was collected and was washed with diethyl ether, DCM and acetonitrile.

Yield: 1.20 g (3.70 mmol, 75%), yellow solid.

Mp: 50–51 °C.

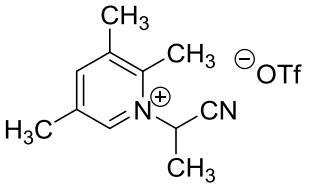
IR (ATR) $\tilde{\nu}$ = 3079, 2986, 1638, 1524, 1252, 1223, 1150, 1027, 852 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 9.17 (d, *J* = 1.6 Hz, 1H, H-6), 8.52 (dd, *J* = 8.2, 1.6 Hz, 1H, H-4), 8.06 (d, *J* = 8.2 Hz, 1H, H-3), 6.34 (q, *J* = 7.0 Hz, 1H, H-1'), 2.90–2.81 (m, 2H, H-1''), 2.86 (s, 3H, 2-CH_3), 1.99 (d, *J* = 7.0 Hz, 3H, H-2'), 1.26 (t, *J* = 7.6 Hz, 3H, H-2'') ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 153.5 (C2), 146.7 (C4), 142.9 (C5), 141.2 (C6), 130.1 (C3), 120.7 (q, $^1J_{C,F}$ = 322.4 Hz, *C*F_3), 116.7 (*C*N), 52.0 (C1'), 24.7 (C1''), 19.7 (2-*C*H_3), 19.6 (C2'), 14.6 (C2'') ppm.

HRMS (ESI-TOF): Calcd for $[C_{11}H_{15}N_2]^+$ 175.1235, found 175.1244.

1-(1-Cyanoethyl)-2,3,5-trimethylpyridinium triflate (95i)



The title compound was prepared according to the general procedure-V described above from 2,3,5-trimethylpyridine (**94g**, 484 mg, 4.00 mmol) and **84a** (812 mg, 4.00 mmol). After stirring for 48 h, the precipitate was collected and was washed with diethyl ether, and ethyl acetate.

Yield: 1.18 g (3.65 mmol, 91%), colorless solid.

Mp: 103–104 °C.

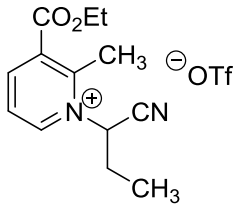
IR (ATR) $\tilde{\nu}$ = 3068, 3024, 2996, 1635, 1505, 1255, 1223, 1149, 1030 cm^{-1}.

^{1}H NMR, (400 MHz, DMSO-d_6) δ = 9.03 (s, 1H, H-6), 8.36 (s, 1H, H-4), 6.44 (q, *J* = 6.9 Hz, 1H, H-1'), 2.74 (s, 3H, 2-CH_3), 2.47 (br s, 6H, 3-CH_3, 5-CH_3), 1.96 (d, *J* = 6.9 Hz, 3H, H-2'') ppm.

^{13}C NMR, HMBC (101 MHz, DMSO-d_6) δ = 152.5 (C2), 147.9 (C4), 139.4 (C6), 138.3 (C3), 136.0 (C5), 120.7 (q, $^{1}J_{C,F}$ = 322.2 Hz, *C*F_3), 116.8 (*C*N), 52.4 (C1'), 19.8 (C2'), 19.5 (3-*C*H_3), 17.3 (5-*C*H_3), 16.6 (2-*C*H_3) ppm.

HRMS (ESI-TOF): Calcd for $[C_{11}H_{14}N_2 + H]^+$ 175.1235, found 175.1244.

1-(1-Cyanopropyl)-3-(ethoxycarbonyl)-2-methylpyridinium triflate (95j)



The title compound was prepared according to the general procedure-V described above from ethyl 2-methylnicotinate (**94h**, 496 mg, 3.00 mmol) and 1-cyanopropyl trifluoromethanesulfonate (**84g**, 652 mg, 3.00 mmol). After stirring for 48 h, the precipitate was collected and was washed with diethyl ether, and ethyl acetate.

Yield: 861 mg (2.25 mmol, 75%), colorless solid.

Mp: 140–141 °C.

IR (ATR) $\tilde{\nu}$ = 3126, 3097, 3041, 2999, 1734, 1627, 1269, 1249, 1158, 1028, 831 cm^{-1}.

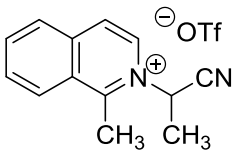
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 9.47 (dd, *J* = 6.5, 1.6 Hz, 1H, H-6), 8.93 (dd, *J* = 8.0, 1.6 Hz, 1H, H-4), 8.22 (dd, *J* = 8.0, 6.5 Hz, 1H, H-5), 6.46 (t, *J* = 7.5 Hz, 1H, H-1'), 4.43 (q, *J* = 7.1 Hz, 2H, OCH_2), 3.01 (s, 3H, 2-CH_3), 2.38–2.28 (m, 2H, H-2'), 1.36 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.11 (t, *J* = 7.4 Hz, 3H, H-3') ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 163.4 (CO_2Et), 156.8 (C2), 147.3 (C4), 145.9 (C6), 132.6 (C3), 126.2 (C5), 115.6 (*C*N), 63.0 (OCH_2), 58.0 (C1'), 27.0 (C2'), 18.1 (2-CH_3), 13.8 (OCH_2CH_3), 9.4 (C3') ppm.

Elemental Analysis: Calcd: C: 43.98% H: 4.48% N: 7.73% S: 8.39%

$C_{14}H_{17}F_3N_2O_5S$ Found: C: 43.91% H: 4.68% N: 7.31% S: 8.57%

2-(1-Cyanoethyl)-1-methylisoquinolinium triflate (95k)



The title compound was prepared according to the general procedure-V described above from 1-methylisoquinoline (716 mg, 5.00 mmol) and **84a** (1.016 g, 5.00 mmol). After stirring for 24 h, the precipitate was collected and was washed with diethyl ether.

Yield: 1.690 g (4.88 mmol, 98%), colorless solid.

Mp: 106–107 °C.

IR (ATR) $\tilde{\nu}$ = 3092, 3008, 2959, 1635, 1388, 1259, 1155, 1029 cm^{-1}.

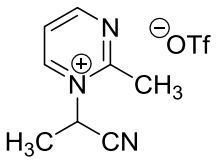
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 9.02 (d, *J* = 7.0 Hz, 1H, H-3), 8.84 (d, *J* = 8.7 Hz, 1H, H-8), 8.56 (d, *J* = 7.0 Hz, 1H, H-4), 8.36 (dd, *J* = 8.4, 1.7 Hz, H-5), 8.32–8.27 (m, 1H, H-6), 8.10 (ddd, *J* = 8.7, 7.1, 1.7 Hz, H-7), 6.70 (q, *J* = 6.9 Hz, 1H, H-1'), 3.34 (s, 3H, 1-CH_3), 2.03 (d, *J* = 6.9 Hz, 3H, H-2') ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 161.9 (C1), 132.1 (C3), 136.8 (C4a), 132.1 (C3), 131.5 (C7), 129.5 (C8), 128.1 (C5), 127.5 (C8a), 124.9 (C4), 120.7 (q, $^{1}J_{C,F}$ = 322.2 Hz, CF_3), 117.0 (*C*N), 52.5 (C1'), 19.8 (C2'), 17.3 (1-CH_3) ppm.

Elemental Analysis: Calcd: C: 48.55% H: 3.78% N: 8.09% S: 9.26%

$C_{14}H_{13}F_3N_2O_3S$ Found: C: 48.40% H: 3.66% N: 8.01% S: 9.38%

1-(1-Cyanoethyl)-2-methylpyrimidin-1-ium triflate (106a)



The title compound was prepared according to the general procedure-V described above from 2-methylpyrimidine (282 mg, 3.00 mmol) and **84a** (610 mg, 3.00 mmol). After stirring for 24 h, the precipitate was collected and was washed with diethyl ether. Since the compound was quickly decomposed in solution, NMR measurements were carried out immediately after preparing the NMR sample.

Yield: 695 mg (2.34 mmol, 78%), colorless solid.

Mp: 143–144 °C.

IR (ATR) $\tilde{\nu}$ = 2956, 2925, 2854, 1626, 1454, 1258, 1174, 1149, 1029 cm^{-1}.

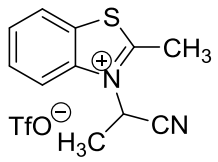
^{1}H NMR (600 MHz, DMSO-d_6) δ = 9.68 (dd, *J* = 6.2, 1.7 Hz, 1H, H-6), 9.45 (dd, *J* = 4.8, 1.7 Hz, 1H, H-4), 8.27 (dd, *J* = 6.2, 4.8 Hz, 1H, H-5), 6.42 (q, *J* = 7.0 Hz, 1H, H-1'), 3.05 (s, 3H, 2-CH_3), 1.98 (d, *J* = 7.0 Hz, 3H, H-2') ppm.

^{13}C NMR, HSQC (151 MHz, DMSO-d_6) δ = 165.9 (C4), 164.0 (C2), 151.0 (C6), 122.4 (C5), 120.7 (q, $^1J_{C,F}$ = 322.2 Hz, *C*F_3), 116.2 (*C*N), 52.6 (C1'), 23.3 (2-*C*H_3), 19.1 (C2') ppm.

Elemental Analysis: Calcd: C: 36.36% H: 3.39% N: 14.14% S: 10.79%

$C_9H_{10}F_3N_3O_3S$ Found: C: 36.30% H: 3.16% N: 14.26% S: 11.04%

3-(1-Cyanoethyl)-2-methylbenzo[*d*]thiazol-3-iumtriflate (106b)



The title compound was prepared according to the general procedure-V described above from 2-methylbenzo[*d*]thiazole (0.73 g, 4.92 mmol) and **84a** (1.00 g, 4.92 mmol). After stirring for 24 h, the precipitate was collected and was washed with diethyl ether and chloroform.

Yield: 1.06 g (3.00 mmol, 61%), yellow solid.

Mp: 124–126 °C.

IR (ATR) $\tilde{\nu}$ = 2985, 1372, 1261, 1147, 1030, 792 cm^{-1}.

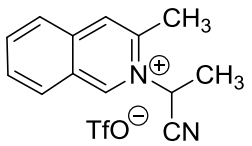
^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.52 (dd, *J* = 8.2, 1.0 Hz, 1H, H-4), 8.48 (dd, *J* = 8.6, 1.0 Hz, 1H, H-7), 7.96 (ddd, *J* = 8.6, 7.3, 1.0 Hz, 1H, H-6), 7.86 (ddd, *J* = 8.2, 7.3, 1.0 Hz, 1H, H-5), 6.68 (q, *J* = 7.2 Hz, 1H, H-1'), 3.28 (s, 3H, 2-CH_3), 2.04 (d, *J* = 7.2 Hz, 3H, H-2') ppm.

^{13}C NMR, HSQC (101 MHz, DMSO-d_6) δ = 180.8 (C2), 138.6 (C3a), 129.8 (C6), 129.2 (C7a), 128.3 (C5), 125.3 (C4), 120.7 (q, $^1J_{C,F}$ = 322.3 Hz, *C*F_3), 116.7 (C7), 115.6 (*C*N), 46.4 (C1'), 17.7 (2-*C*H_3), 17.6 (C2') ppm.

Elemental Analysis: Calcd: C: 40.90% H: 3.15% N: 7.95%

$C_{12}H_{11}F_3N_2O_3S_2$ Found: C: 40.86% H: 2.83% N: 7.85%

2-(1-Cyanoethyl)-3-methylisoquinolinium triflate (106c)



The title compound was prepared according to the general procedure-V described above from 3-methylisoquinoline (500 mg, 3.49 mmol) and **84a** (709 mg, 3.49 mmol). After stirring for 24 h, the precipitate was collected and was washed with diethyl ether.

Yield: 1.104 g (3.19 mmol, 91%), colorless solid.

Mp: 132–133 °C.

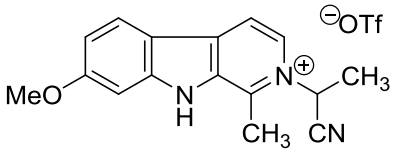
IR (ATR) $\tilde{\nu}$ = 3057, 2996, 1647, 1258, 1226, 1153, 1030, 766 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 10.38 (s, 1H, H-1), 8.60 (d, *J* = 8.2 Hz, 1H, H-8), 8.55 (s, 1H, H-4), 8.32–8.22 (m, 2H, H-5, H-6), 8.05 (ddd, *J* = 8.2, 6.4, 1.2 Hz, H-7), 6.51 (q, *J* = 6.9 Hz, 1H, H-1'), 2.95 (s, 3H, 3-CH_3), 2.10 (d, *J* = 6.9 Hz, 3H, H-2') ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 149.2 (C1), 144.0 (C3), 138.4 (C4a), 138.2 (C6), 130.8 (C7), 130.6 (C8), 126.7 (C4), 126.6 (C8a), 126.4 (C5), 120.7 (q, $^1J_{C,F}$ = 322.3 Hz, *C*F_3), 116.9 (*C*N), 52.1 (C1'), 20.0 (C2'), 19.3 (3-*C*H_3) ppm.

Elemental Analysis:	Calcd: C: 48.55%	H: 3.78%	N: 8.09%	S: 9.26%
$C_{14}H_{13}F_3N_2O_3S$	Found: C: 48.62%	H: 4.01%	N: 8.14%	S: 9.30%

2-(1-Cyanoethyl)-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indol-2-ium triflate (104)



The title compound was prepared according to the general procedure-V described above from harmine (1.00 g, 4.71 mmol) and **84a** (0.96 g, 4.71 mmol) in acetonitrile (5 mL). After stirring for 24 h, the precipitate was collected and was washed with acetonitrile.

Yield: 1.39 g (3.35 mmol, 71%), colorless solid.

Mp: 237–242 °C (dec.).

IR (ATR) $\tilde{\nu}$ = 3221, 3096, 3068, 2941, 1630, 1271, 1244, 1221, 1163, 1023, 802 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 12.87 (s, 1H, N*H*), 8.90 (d, *J* = 6.8 Hz, 1H, H-3), 8.63 (d, *J* = 6.8 Hz, 1H, H-4), 8.39 (d, *J* = 8.8 Hz, 1H, H-5), 7.12 (d, *J* = 2.0 Hz, 1H, H-8), 7.09 (dd, *J* = 8.8, 2.0 Hz, 1H, H-6), 6.47 (q, *J* = 6.9 Hz, 1H, H-1'), 3.97 (s, 3H, OC*H*$_3$), 3.13 (s, 3H, 1-C*H*$_3$), 2.02 (d, *J* = 6.9 Hz, 3H, H-2') ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 163.5 (C7), 146.5 (C8a), 139.5 (C1), 134.7 (C9a), 131.7 (C4a), 130.8 (C3), 125.1 (C5), 120.7 (q, $^1J_{C,F}$ = 322.3 Hz, *C*F$_3$) 117.5 (*C*N), 115.2 (C4), 113.6 (C4b), 113.5 (C6), 94.2 (C8), 55.9 (OC*H*$_3$), 50.6 (C1'), 20.3 (C2'), 15.5 (1-*C*H$_3$) ppm.

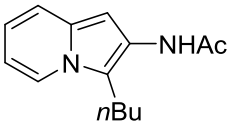
Elemental Analysis:	Calcd: C: 49.15%	H: 3.88%	N: 10.12%	S: 7.72%
$C_{17}H_{16}F_3N_3O_4S$	Found: C: 49.40%	H: 3.51%	N: 10.10%	S: 7.70%

General procedure-VI for *N*-Acetyl 2-Aminoindolizines 102

To a solution of pyridinium salt **3** in freshly distilled THF (0.1 M) was added a solution of KO*t*Bu (1.10 equiv) in THF (1.0 M) under argon at 0 °C. After 2h stirring at the same

temperature, the reaction mixture was quenched with water (1.0 mL) and all volatiles were removed in vacuo. The residue was re-dissolved in 2.5 (w/v)% aqueous solution of $NaHCO_3$ (10.0 mL/1.00 mmol **3**). Acetic anhydride (2.0 mL/1.00 mmol **3**) was added and the reaction mixture was stirred about 1 h at ambient temperature. The resulting solution was neutralized with Na_2CO_3. In case of precipitation, product was collected by filtration and the solid was washed with water and cold ethanol, and was recrystallized from ethanol. In the absence of precipitation, the product was extracted three times with ethyl acetate (20 mL/1.00 mmol **3**) after the neutralization. The product was purified by column chromatography.

***N*-(3-Butylindolizin-2-yl)acetamide (102a)**



The title compound was prepared according to the general procedure-VI described above from the salt **95a** (338 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane, 1:1).

Yield: 219 mg (0.95 mmol, 95%), yellow solid.

Mp: 130–131 °C.

R_f = 0.51 (ethyl acetate/cyclohexane, 1:1).

IR (ATR) $\tilde{\nu}$ = 3272, 3051, 2956, 2930, 2860, 1652, 1577, 1453, 1364, 1310, 1266, 731 cm^{-1}.

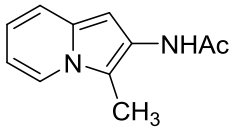
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 9.39 (s, 1H, N*H*), 7.94 (dd, *J* = 6.8, 0.9 Hz, 1H, H-5’), 7.31 (dt, *J* = 8.8, 1.2 Hz, 1H, H-8’), 6.70 (s, 1H, H-1’), 6.61 (ddd, *J* = 8.8, 6.8, 0.9 Hz, 1H, H-7’), 6.53 (td, *J* = 6.8, 1.2 Hz, 1H, H-6’), 2.91 (t, *J* = 7.4 Hz, 2H, H-1’’), 2.05 (s, 3H, H-2), 1.50–1.40 (m, 2H, H-2’’), 1.36–1.26 (m, 2H, H-3’’), 0.89 (t, *J* = 7.3 Hz, 3H, H-4’’) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 167.8 (C1), 129.3 (C8a’), 124.9 (C2’), 121.9 (C5’), 118.1 (C8’), 115.4 (C7’), 114.0 (C3’), 109.6 (C6’), 93.4 (C1’), 29.0 (C2’’), 23.3 (C2), 22.0 (C1’’), 21.9 (C3’’), 13.8 (C4’’) ppm.

MS (ESI): m/z = 253.1 (24) $[M + Na]^+$, 231.1 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{14}H_{18}N_2O + H]^+$ 231.1497, found 231.1493.

N-(3-Methylindolizin-2-yl)acetamide (102b)



The title compound was prepared according to the general procedure-VI described above from the salt **85f** (148 mg, 0.500 mmol). The product was collected by filtration and recrystallized from ethanol.

Yield: 72 mg (0.383 mmol, 77%), colorless solid.

Mp: 132–133 °C.

IR (ATR) $\tilde{\nu}$ = 3273, 3258, 3075, 3051, 2936, 1655, 1636, 1583, 1455, 1355, 1274, 763, 724 cm^{-1}.

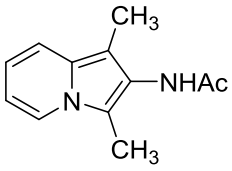
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 9.49 (s, 1H, N*H*), 7.87 (dd, *J* = 6.8, 1.1 Hz, 1H, H-5'), 7.32 (dd, *J* = 8.8, 1.3 Hz, 1H, H-8'), 6.70 (s, 1H, H-1'), 6.67–6.61 (m, 1H, H-7'), 6.56 (td, *J* = 6.8, 1.3 Hz, 1H, H-6'), 2.37 (s, 3H, 3'-C*H*$_3$), 2.05 (s, 3H, H-2) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 167.7 (C1), 129.3 (C8a'), 125.1 (C2'), 121.9 (C5'), 117.9 (C8'), 115.4 (C7'), 109.6 (C6'), 109.4 (C3'), 93.2 (C1'), 23.3 (C2), 8.7 (3'-*C*H$_3$) ppm.

MS (ESI): m/z = 211.0 (50) $[M + Na]^+$, 189.0 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{11}H_{12}N_2O + Na]^+$ 211.0847, found 211.0847.

N-(1,3-Dimethylindolizin-2-yl)acetamide (102c)



The title compound was prepared according to the general procedure-VI described above from the salt **95b** (270 mg, 0.87 mmol). The crude product was purified by column chromatography (ethyl acetate).

Yield: 118 mg (0.58 mmol, 67%), yellow solid.

Mp: 214–215 °C.

R_f = 0.45 (ethyl acetate).

IR (ATR) $\tilde{\nu}$ = 3222, 3055, 2923, 2853, 1646, 1571, 1318, 729, 713 cm^{-1}.

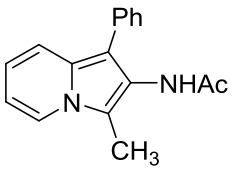
^{1}H NMR, COSY (300 MHz, DMSO-d_6) δ = 9.29 (s, 1H, N*H*), 7.82 (dt, *J* = 6.8, 1.3 Hz, 1H, H-5'), 7.32 (dt, *J* = 8.8, 1.3 Hz, 1H, H-8'), 6.61–6.64 (m, 1H, H-7'), 6.51 (td, *J* = 6.8, 1.3 Hz, 1H, H-6'), 2.23 (s, 3H, 3'-CH_3), 2.10 (s, 3H, 1'-CH_3), 2.04 (s, 3H, H-2) ppm.

^{13}C NMR, HSQC, HMBC (75 MHz, DMSO-d_6) δ = 168.4 (C1), 126.7 (C8a'), 123.4 (C2'), 121.9 (C5'), 116.7 (C8'), 113.9 (C7'), 113.5 (C3'), 109.4 (C6'), 102.9 (C1'), 22.8 (C2), 9.1 (3'-*C*H$_3$), 8.2 (1'-*C*H$_3$) ppm.

MS (ESI): m/z = 225.0 (38) $[M + Na]^+$, 203.0 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{12}H_{14}N_2O + Na]^+$ 225.1004, found 225.1010.

N-(3-Methyl-1-phenylindolizin-2-yl)acetamide (102d)



The title compound was prepared according to the general procedure-VI described above from the salt **95c** (372 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:1).

Yield: 226 mg (0.86 mmol, 86%), yellow solid.

Mp: 186–187 °C.

R_f = 0.12 (ethyl acetate/cyclohexane, 1:1).

IR (ATR) $\tilde{\nu}$ = 3243, 3028, 2903, 1650, 1510, 1435, 1354, 733, 700 cm^{-1}.

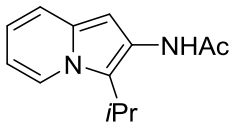
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 9.35 (s, 1H, N*H*), 8.00 (dt, *J* = 7.0, 1.2 Hz, 1H, H-5'), 7.51 (dt, *J* = 9.0, 1.2 Hz, 1H, H-8'), 7.44–7.40 (m, 4H, H-2'',6'', H-3'',5''), 7.26–7.21 (m, 1H, H-4''), 6.76 (ddd, *J* = 9.0, 7.0, 1.2 Hz, 1H, H-7'), 6.68 (td, *J* = 7.0, 1.2 Hz, 1H, H-6'), 2.27 (s, 3H, 3'-CH_3), 2.00 (s, 3H, H-2) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 169.4 (C1), 134.1 (C1''), 128.5 (2C, C_{Ph}), 128.3 (2C, C_{Ph}), 126.8 (C8a'), 125.4 (C4''), 122.7 (C5'), 121.6 (C2'), 117.1 (C7'), 116.9 (C8'), 116.7 (C3'), 110.7 (C6'), 109.4 (C1'), 22.7 (C2), 9.0 (3'-*C*H$_3$) ppm.

MS (ESI): m/z = 287.1 (41) $[M + Na]^+$, 265.1 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{17}H_{16}N_2O + H]^+$ 265.1341, found 265.1340.

N-(3-Isopropylindolizin-2-yl)acetamide (102e)



The title compound was prepared according to the general procedure-VI described above from the salt **95d** (300 mg, 0.93 mmol). The crude product was purified by column chromatography (ethyl acetate).

Yield: 84 mg (0.39 mmol, 42%), brown oil.

R_f = 0.50 (ethyl acetate).

IR (ATR) $\tilde{\nu}$ = 3269, 3056, 2917, 2850, 1628, 1535, 1375, 1243, 1162, 1031, 738 cm^{-1}.

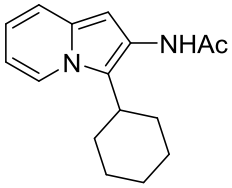
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 9.28 (s, 1H, N*H*), 8.07 (ddd, *J* = 6.8, 1.2, 1.1 Hz, 1H, H-5'), 7.32 (dt, *J* = 8.8, 1.1 Hz, 1H, H-8'), 6.61 (ddd, *J* = 8.8, 6.6, 1.2 Hz, 1H, H-7'), 6.54–6.49 (m, 1H, H-6'), 6.47 (s, 1H, H-1'), 3.51–3.42 (m, 1H, C*H*$(CH_3)_2$), 2.03 (s, 3H, H-2), 1.33 (d, *J* = 7.2 Hz, 6H, $(CH_3)_2$CH) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 168.4 (C1), 129.4 (C8a'), 123.3 (C2'), 123.0 (C5'), 120.2 (C3'), 118.5 (C8'), 115.3 (C7'), 109.6 (C6'), 95.6 (C1'), 23.9 ($CH(CH_3)_2$), 23.2 (C2), 19.0 (2C, $(CH_3)_2$CH) ppm.

MS (ESI): m/z = 239.1 (28) $[M + Na]^+$, 217.1 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{13}H_{16}N_2O + H]^+$ 217.1341, found 217.1341.

N-(3-Cyclohexylindolizin-2-yl)acetamide (102f)



The title compound was prepared according to the general procedure-VI described above from the salt **95e** (233 mg, 0.64 mmol). The product was collected by filtration and recrystallized from ethanol.

Yield: 77 mg (0.30 mmol, 47%), orange solid.

Mp: 141–142 °C.

R_f = 0.33 (ethyl acetate/cyclohexane, 2:1).

IR (ATR) $\tilde{\nu}$ = 3258, 3049, 2927, 2852, 1655, 1566, 1447, 1277, 722 cm^{-1}.

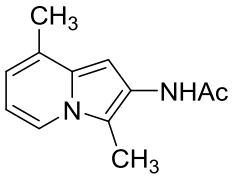
^{1}H NMR, COSY (300 MHz, DMSO-d_6) δ = 9.25 (s, 1H, N*H*), 8.12 (dt, *J* = 6.9, 1.2 Hz, 1H, H-5'), 7.30 (dt, *J* = 8.9, 1.2 Hz, 1H, H-8'), 6.60 (ddd, *J* = 8.9, 6.5, 1.0 Hz, 1H, H-7'), 6.50 (ddd, *J* = 6.9, 6.5, 1.2 Hz, 1H, H-6'), 6.46 (s, 1H, H-1'), 3.05 (tt, *J* = 12.3, 3.6 Hz, H-1''), 2.03 (s, 3H, H-2), 1.94–1.62 (m, 7H, H_{Cy}), 1.48–1.29 (m, 3H, H_{Cy}) ppm.

^{13}C NMR, HSQC, HMBC (75 MHz, DMSO-d_6) δ = 168.4 (C1), 129.4 (C8a'), 123.5 (C2'), 123.1 (C5'), 120.0 (C3'), 118.5 (C8'), 115.3 (C7'), 109.5 (C6'), 95.9 (C1'), 34.3 (C1''), 28.6 (2C, C_{Cy}), 26.5 (2C, C_{Cy}), 25.4 (C4''), 23.2 (C2) ppm.

MS (ESI): m/z = 279.1 (4) $[M + Na]^+$, 257.1 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{16}H_{20}N_2O + Na]^+$ 279.1473, found 279.1487.

N-(3,8-Dimethylindolizin-2-yl)acetamide (102g)



The title compound was prepared according to the general procedure-VI described above from the salt **95f** (155 mg, 0.500 mmol). The product was collected by filtration and recrystallized from ethanol.

Yield: 84 mg (0.415 mmol, 83%), colorless solid.

Mp: 183–184 °C.

R_f = 0.53 (ethyl acetate).

IR (ATR) $\tilde{\nu}$ = 3284, 2905, 1651, 1634, 1580, 1270, 747, 706 cm^{-1}.

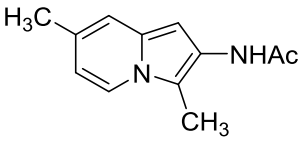
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 9.49 (s, 1H, N*H*), 7.76 (d, *J* = 6.6 Hz, 1H, H-5'), 6.67 (s, 1H, H-1'), 6.55–6.45 (m, 2H, H-6', H-7'), 2.36 (s, 3H, 3'-CH_3), 2.30 (s, 3H, 8'-CH_3), 2.06 (s, 3H, H-2) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 167.7 (C1), 129.9 (C8a'), 126.3 (C8'), 124.7 (C2'), 120.0 (C5'), 114.9 (C7'), 109.9 (C3'), 109.6 (C6'), 91.9 (C1'), 23.3 (C2), 17.6 (8'-*C*H_3), 8.9 (3'-*C*H_3) ppm.

MS (ESI): m/z = 225.0 (38) $[M + Na]^+$, 203.1 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{12}H_{14}N_2O + Na]^+$ 225.1004, found 225.1005.

N-(3,7-Dimethylindolizin-2-yl)acetamide (102h)



The title compound was prepared according to the general procedure-VI described above from the salt **95g** (310 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate).

Yield: 79 mg (0.39 mmol, 39%), orange solid.

Mp: 133–135 °C.

R_f = 0.48 (ethyl acetate).

IR (ATR) $\tilde{\nu}$ = 3273, 3168, 3048, 2912, 1647, 1589, 1457, 1357, 1276, 763, 734 cm^{-1}.

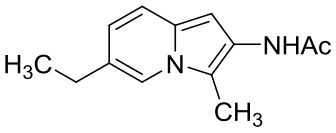
^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.43 (s, 1H, N*H*), 7.78 (d, *J* = 6.9 Hz, 1H, H-5'), 7.07 (dd, *J* = 2.2, 1.0 Hz, 1H, H-8'), 6.52 (s, 1H, H-1'), 6.40 (dd, *J* = 6.9, 2.2 Hz, 1H, H-6'), 2.33 (s, 3H, 3'-CH_3), 2.22 (s, 3H, 7'-CH_3), 2.05 (s, 3H, H-2) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 167.6 (C1), 129.5 (C8a'), 124.9 (2C, C2',C7'), 121.6 (C5'), 116.0 (C8'), 112.1 (C6'), 108.5 (C3'), 91.8 (C1'), 23.3 (C2), 20.5 (7'-*C*H_3), 8.7 (3'-*C*H_3) ppm.

MS (ESI): m/z = 225.0 (9) $[M + Na]^+$; 203.0 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{12}H_{14}N_2O + H]^+$ 203.1184, found 203.1186.

N-(6-Ethyl-3-methylindolizin-2-yl)acetamide (102i)



The title compound was prepared according to the general procedure-VI described above from the salt **95h** (259 mg, 0.80 mmol). The crude product was purified by column chromatography (ethyl acetate).

Yield: 143 mg (0.66 mmol, 83%), brown oil.

R_f = 0.34 (ethyl acetate).

IR (ATR) $\tilde{\nu}$ = 3275, 3045, 3051, 2976, 1661, 1634, 1548, 1506, 1261, 763 cm^{-1}.

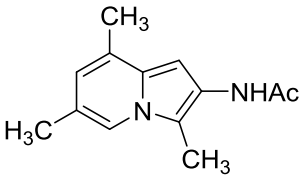
^{1}H NMR, COSY (300 MHz, DMSO-d_6) δ = 9.44 (s, 1H, N*H*), 7.66 (d, *J* = 1.1 Hz, 1H, H-5'), 7.27 (d, *J* = 9.0 Hz, 1H, H-8'), 6.62 (s, 1H, H-1'), 6.57 (dd, *J* = 9.0, 1.1 Hz, 1H, H-7'), 2.54 (q, *J* = 7.5 Hz, 2H, 6'-C*H*$_2$), 2.35 (s, 3H, 3'-C*H*$_3$), 2.04 (s, 3H, H-2), 1.19 (t, *J* = 7.5 Hz, 3H, C*H*$_3$CH$_2$) ppm.

^{13}C NMR, HSQC, HMBC (75 MHz, DMSO-d_6) δ = 167.6 (C1), 128.3 (C8a'), 124.9 (C6'), 124.8 (C2'), 118.6 (C5'), 117.7 (C8'), 117.4 (C7'), 109.4 (C3'), 92.9 (C1'), 25.5 (6'-*C*H$_2$), 23.3 (C2), 15.4 (*C*H$_3$CH$_2$), 8.8 (3'-*C*H$_3$) ppm.

MS (ESI): m/z = 239.1 (6) $[M + Na]^+$; 217.1 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{13}H_{16}N_2O + H]^+$ 217.1341, found 217.1343.

N-(3,6,8-Trimethylindolizin-2-yl)acetamide (102j)



The title compound was prepared according to the general procedure-VI described above from the salt **95i** (324 mg, 1.00 mmol). The product was collected by filtration and recrystallized from ethanol.

Yield: 163 mg (0.75 mmol, 75%), colorless solid.

Mp: 219–221 °C (dec.).

IR (ATR) $\tilde{\nu}$ = 3296, 2913, 1653, 1584, 1412, 1272, 814, 758 cm^{-1}.

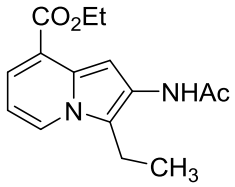
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 9.42 (s, 1H, N*H*), 7.57 (s, 1H, H-5'), 6.59 (s, 1H, H-1'), 6.36 (s, 1H, H-7'), 2.33 (s, 3H, 3'-C*H*$_3$), 2.27 (s, 3H, 8'-C*H*$_3$), 2.19 (s, 3H, 6'-C*H*$_3$), 2.04 (s, 3H, H-2) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 167.6 (C1), 128.8 (C8a'), 125.9 (C8'), 124.3 (C2'), 118.4 (C6'), 118.2 (C7'), 117.4 (C5'), 109.7 (C3'), 91.7 (C1'), 23.3 (C2), 18.1 (6'-*C*H$_3$), 17.5 (8'-*C*H$_3$), 8.9 (3'-*C*H$_3$) ppm.

MS (ESI): m/z = 239.1 (14) $[M + Na]^+$, 217.1 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{13}H_{16}N_2O + H]^+$ 217.1341, found 217.1335.

Ethyl 2-acetamido-3-ethylindolizine-8-carboxylate (102k)



The title compound was prepared according to the general procedure-VI described above from the salt **95j** (191 mg, 0.500 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:1).

Yield: 48 mg (0.175 mmol, 35%), orange solid.

Mp: 171–172 °C.

R_f = 0.20 (ethyl acetate/cyclohexane 1:1).

IR (ATR) $\tilde{\nu}$ = 3252, 2930, 1705, 1647, 1575, 1446, 1266, 749 cm^{-1}.

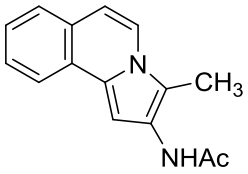
^{1}H NMR, COSY (400 MHz, CD_3CN) δ = 8.08 (dd, *J* = 7.0, 0.8 Hz, 1H, H-5), 8.05 (s, 1H, N*H*), 7.34 (s, 1H, H-1), 7.52 (dd, *J* = 7.0, 0.8 Hz, 1H, H-7), 6.63 (t, *J* = 7.0 Hz, 1H, H-6), 4.46 (q, *J* = 7.1 Hz, OCH_2), 2.93 (q, *J* = 7.5 Hz, CH_2-3), 2.10 (s, 3H, CH_3CO), 1.38 (t, *J* = 7.1 Hz, C$H_3$$CH_2$O), 1.16 (t, *J* = 7.5 Hz, 3-C$H_3$$CH_2$) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 169.3 (NH*C*O), 166.3 (*C*$O_2$$CH_2$), 128.1 (C9), 127.1 (C5), 126.6 (C2), 122.7 (C7), 120.7 (C8), 117.4 (C3), 109.2 (C6), 96.9 (C1), 61.9 (O*C*H_2), 23.7 (*C*H_3CO), 16.9 (*C*H_2-3), 14.6 (*C*$H_3$$CH_2$O), 11.9 (*C*$H_3$$CH_2$-3) ppm.

MS (ESI): m/z = 297.1 (100) $[M + Na]^+$, 275.1 (96) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{15}H_{18}N_2O_3 + H]^+$ 275.1396, found 275.1387.

***N*-(3-Methylpyrrolo[2,1-a]isoquinolin-2-yl)acetamide (102l)**



The title compound was prepared according to the general procedure-VI described above from the salt **95k** (346 mg, 1.00 mmol). The product was collected by filtration and recrystallized from ethanol.

Yield: 188 mg (0.79 mmol, 79%), colorless solid.

Mp: 238–239 °C.

R_f = 0.38 (ethyl acetate).

IR (ATR) $\tilde{\nu}$ = 3262, 3056, 2916, 1643, 1541, 1364, 1281, 794, 739 cm^{-1}.

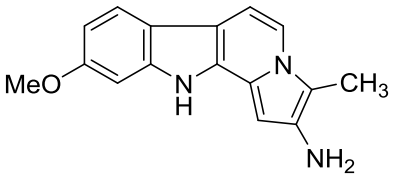
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 9.50 (s, 1H, N*H*), 8.00 (d, *J* = 8.0 Hz, 1H, H-10'), 7.87 (d, *J* = 7.4 Hz, 1H, H-5'), 7.63 (d, *J* = 8.1 Hz, 1H, H-7'), 7.44–7.40 (m, 1H, H-9'), 7.34–7.30 (m, 1H, H-8'), 7.24 (s, 1H, H-1'), 6.88 (d, *J* = 7.4 Hz, 1H, H-6'), 2.39 (s, 3H, C*H*$_3$-3'), 2.07 (s, 3H, H-2) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 167.8 (C1),127.2 (C9'), 126.8 (C7'), 125.73 (C6a'), 125.70 (C10b'), 125.2 (C10a'), 125.0 (C8'), 123.3 (C2'), 122.0 (C5'), 121.4 (C10'), 112.8 (C3'), 109.6 (C6'), 95.4 (C1'), 23.2 (C2), 8.8 (*C*H$_3$-3') ppm.

MS (ESI): m/z = 261.1 (54) $[M + Na]^+$, 239.1 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{15}H_{14}N_2O + H]^+$ 239.1184, found 239.1184.

9-Methoxy-3-methyl-11*H*-indolizino[8,7-*b*]indol-2-amine (105)



The title compound was prepared according to the general procedure-VI described above excluding the acetylation step from the salt **104** (415 mg, 1.00 mmol). H_2O (25 mL) was added to the reaction mixture. The product was collected by filtration and recrystallized from ethanol.

Yield: 242 mg (0.91 mmol, 91%), yellow solid.

Mp: 175–179 °C.

IR (ATR) $\tilde{\nu}$ = 3396, 3326, 3184, 3104, 1625, 1464, 1159, 1030, 819, 809, 767, 739 cm^{-1}.

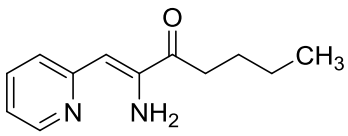
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.38 (s, 1H, H-11), 7.72 (d, *J* = 8.6 Hz, 1H, H-7), 7.49 (d, *J* = 6.9 Hz, 1H, H-5), 7.04 (d, *J* = 6.9 Hz, 1H, H-6), 6.94 (d, *J* = 2.4 Hz, 1H, H-10), 6.74 (dd, *J* = 8.6, 2.4 Hz, 1H, H-8), 6.15 (s, 1H, H-1), 4.27 (s, 2H, N*H*$_2$), 3.82 (s, 3H, OC*H*$_3$), 2.31 (s, 3H, C*H*$_3$-3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 156.5 (C9), 139.0 (C10a), 133.9 (C2), 128.4 (C11a), 120.4 (C11b), 119.1 (C7), 117.9 (C6b), 115.1 (C5), 108.01 (C6a), 107.99 (C8), 104.5 (C3), 101.7 (C6), 95.0 (C10), 86.5 (C1), 55.3 (O*C*H$_3$), 8.7 (*C*H$_3$-3) ppm.

MS (ESI): m/z = 298.2 (100) $[M + 2O + H]^+$, 282.2 (22) $[M + O + H]^+$, 266.1 (28) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{16}H_{15}N_3O + H]^+$ 266.1293, found 266.1302.

(*Z*)-2-Amino-1-(pyridin-2-yl)hept-1-en-3-one (101)



The title compound was obtained by storing 2-aminoindolizine **4a** at ambient temperature for about three weeks in an open flask. The product was purified by column chromatography (ethyl acetate/cyclohexane 1:1)

Yield: quantitative, yellow oil.

R_f = 0.45 (ethyl acetate/cyclohexane 1:1).

^{1}H NMR, COSY, NOESY (400 MHz, DMSO-d_6) δ = 8.53 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1H, H-6'), 7.71 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 1H, H-4'), 7.37 (dt, *J* = 8.0, 0.9 Hz, 1H, H-3'), 7.10 (ddd, *J* = 7.5, 4.9, 0.9 Hz, 1H, H-5'), 7.07 (br s, 2H, NH_2), 6.22 (s, 1H, H-1), 2.86 (t, *J* = 7.3 Hz, 2H, H-4), 1.61–1.51 (m, 2H, H-5), 1.38–1.27 (m, 2H, H-6), 0.90 (t, *J* = 7.3 Hz, 3H, H-7) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 198.5 (C3), 158.0 (C2'), 148.0 (C6'), 143.6 (C2), 136.2 (C4'), 124.1 (C3'), 119.6 (C5'), 100.7 (C1), 35.7 (C4), 26.6 (C5), 21.8 (C6), 13.9 (C7) ppm.

HRMS (ESI-TOF): Calcd for $[C_{12}H_{16}N_2O + H]^+$ 205.1341, found 205.1344.

5.3 Annulation of Pyrroles

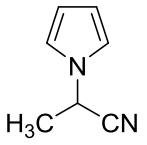
5.3.1 Synthesis of Indolizines from Pyrroles

General procedure-VII for pyrrolonitriles 109

Pyrrolonitriles were prepared according to the literature with slight modifications.[169] The solution of 2,5-dimethoxytetrahydrofuran (1.00 equiv) in deionized water was refluxed for 2 h. The mixture was allowed to cool down before adding CH_2Cl_2, the corresponding α-aminonitrile (1.00–1.20 equiv) and sodium acetate (2.4 equiv). The reaction mixture was

further stirred overnight at ambient temperature. It was made alkaline with 2 M Na_2CO_3 solution and the crude product was extracted three times with CH_2Cl_2. The combined extracts were dried over $MgSO_4$, filtered and then concentrated under reduced pressure. Further purification was either performed by filtration through a pad of silica or by vacuum distillation.

2-(1*H*-Pyrrol-1-yl)propanenitrile (**109a**)[197,198]



The title compound was prepared according to the general procedure-VII described above from 2-aminopropanenitrile hydrochloride[171] (5.33 g, 50.0 mmol) and 2,5-dimethoxytetrahydrofuran (5.49 g, 41.5 mmol). The product was purified by vacuum distillation.

Yield: 4.47 g (37.2 mmol, 90%), colorless oil.

Bp 68–70 °C, 1 mmHg (lit. bp 72–74 °C, 1.5 mmHg).[198]

R_f = 0.21 (ethyl acetate/petroleum ether 1:8).

IR (ATR) $\tilde{\nu}$ = 3104, 2993, 2946, 2248, 1488, 1277, 1100, 1053, 723, 698 cm^{-1}.

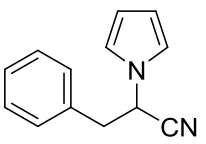
^{1}H NMR,[198] COSY (400 MHz, $CDCl_3$) δ = 6.79–6.78 (AA' part of AA'BB' system, 2H, H-2',5'), 6.26–6.22 (BB' part of AA'BB' system, 2H, H-3',4'), 5.03 (q, *J* = 7.2 Hz, 1H, H-2), 1.86 (d, *J* = 7.2 Hz, 3H, H-3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ = 119.2 (2C, C2',5'), 118.1 (*C*N), 110.3 (2C, C3',4'), 45.2 (C2), 21.4 (C3) ppm.

MS (ESI): m/z = 121.1 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_7H_8N_2 + H]^+$ 121.0766, found 121.0763.

3-Phenyl-2-(1*H*-pyrrol-1-yl)propanenitrile (**109b**)



The title compound was prepared according to the general procedure-VII described above from 2-amino-3-phenylpropanenitrile[170] (877 mg,

6.00 mmol) and 2,5-dimethoxytetrahydrofuran (661 mg, 5.00 mmol). The crude product was further purified by column chromatography (ethyl acetate/petroleum ether 1:5).

Yield: 744 mg (3.79 mmol, 76%), yellow solid.

Mp: 57–59 °C.

R_f = 0.24 (ethyl acetate/petroleum ether 1:5).

IR (ATR) $\tilde{\nu}$ = 3056, 3033, 2933, 2248, 1305, 1278, 1092, 727, 700 cm^{-1}.

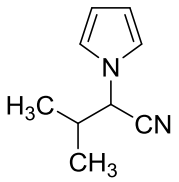
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.35–7.30 (m, 3H, H-3'',5'', H-4''), 7.11–7.07 (m, 2H, H-2'',6''), 6.70 (AA' part of AA'BB' system, 2H, H-2',5'), 6.23 (BB' part of AA'BB' system, 2H, H-3',4'), 5.03 (t, *J* = 7.3 Hz, 1H, H-2), 3.37 (dd, *J* = 13.8, 7.3 Hz, 1H, C$H_{2\text{-a}}$), 3.32 (dd, *J* = 13.8, 7.3 Hz, 1H, C$H_{2\text{-b}}$) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ = 133.9 (C1''), 129.3 (2C, C2'',6''), 128.9 (2C, C3'',6''), 128.0 (C5''), 119.7 (2C, C2',5'), 117.0 (*C*N), 110.1 (2C, C3',4'), 52.0 (C2), 42.1 (C3) ppm.

MS (ESI): m/z = 393.3 (100) $[2M + H]^+$, 235.1 (76) $[M + K]^+$, 197.1 (90) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{13}H_{12}N_2 + H]^+$ 197.1079, found 197.1071.

3-Methyl-2-(1*H*-pyrrol-1-yl)butanenitrile (**109c**)



The title compound was synthesized according to the general procedure-VII described above from 2-amino-3-methylbutanenitrile hydrochloride[171] (2.670 g, 19.8 mmol) and 2,5-dimethoxytetrahydrofuran (2.18 g, 16.5 mmol). The crude product was further purified by column chromatography (ethyl acetate/petroleum ether 1:5).

Yield: 2.259 g (15.2 mmol, 92%), light yellow oil.

R_f = 0.34 (ethyl acetate/petroleum ether 1:5).

IR (ATR) $\tilde{\nu}$ = 3107, 2969, 2248, 1487, 1278, 1089, 721 cm^{-1}.

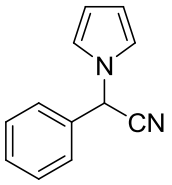
^{1}H NMR, COSY (300 MHz, $CDCl_3$) δ = 6.76 (AA' part of AA'BB' system, 2H, H-2',5'), 6.23 (BB' part of AA'BB' system, 2H, H-3',4'), 4.60 (d, *J* = 8.0 Hz, 1H, H-2), 2.40–2.23 (m, 1H, H-3), 1.13 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 0.95 (d, *J* = 6.8 Hz, 3H, C*H*$_3$) ppm.

^{13}C NMR, HSQC, HMBC (75 MHz, $CDCl_3$) δ = 120.0 (2C, C2',5'), 116.7 (*C*N), 109.8 (2C, C3',4'), 57.1 (C2), 34.6 (C3), 18.7 (*C*H_3), 18.6 (*C*H_3) ppm.

MS (ESI): m/z = 189.1 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_9H_{12}N_2 + H]^+$ 149.1079, found 149.1074.

2-Phenyl-2-(1*H*-pyrrol-1-yl)acetonitrile (109d)[199]



The title compound[199] was prepared according to the general procedure-VII described above from 2-amino-2-phenylacetonitrile[170] (1.15 g, 8.7 mmol) and 2,5-dimethoxytetrahydrofuran (1.15 g, 8.7 mmol). The crude product was further purified by column chromatography (ethyl acetate/petroleum ether 1:5).

Yield: 1.21 g (6.7 mmol, 76%), orange solid.

Mp:50–51 °C.

R_f = 0.29 (ethyl acetate/petroleum ether 1:5).

IR (ATR) $\tilde{\nu}$ = 3105, 2917, 2253, 1484, 1267, 1089, 772, 695 cm^{-1}.

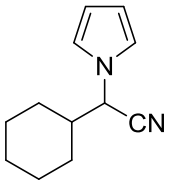
^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ = 7.48–7.42 (m, 3H, H-3'',5'', H-4''), 7.42–7.32 (m, 2H, H-2'',6''), 6.80 (AA' part of AA'BB' system, 2H, H-2',5'), 6.30 (BB' part of AA'BB' system, 2H, H-3',4'), 6.15 (s, 1H, H-2) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, $CDCl_3$) δ = 133.2 (C1''), 129.8 (C4''), 129.4 (2C, C3'',5''), 126.8 (2C, C2'',6''), 120.3 (2C, C2',5'), 116.5 (*C*N), 110.4 (2C, C3',4'), 53.5 (C2) ppm.

MS (ESI): m/z = 365.2 (100) $[2M + H]^+$, 183.1 (7) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{12}H_{10}N_2 + H]^+$ 183.0922, found 183.0917.

2-Cyclohexyl-2-(1*H*-pyrrol-1-yl)acetonitrile (**109e**)



The title compound was prepared according to the general procedure-VII described above from 2-amino-2-cyclohexylacetonitrile[170] (829 mg, 6.00 mmol) and 2,5-dimethoxytetrahydrofuran (661 mg, 5.00 mmol). The crude product was further purified by column chromatography (ethyl acetate/petroleum ether 1:10).

Yield: 591 mg (3.14 mmol, 63%), colorless solid.

Mp:39–40 °C.

R_f = 0.35 (ethyl acetate/petroleum ether 1:10).

IR (ATR) $\tilde{\nu}$ = 2930, 2855, 2246, 1487, 1277, 1093, 720 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.73 (AA' part of AA'BB' system, 2H, H-2',5'), 6.21 (BB' part of AA'BB' system, 2H, H-3',5'), 4.59 (d, *J* = 8.1 Hz, 1H, H-2), 2.01–1.90 (m, 2H), 1.86–1.66 (m, 3H), 1.50–1.44 (m, 1H), 1.31–1.10 (m, 4H), 1.05–0.93 (m, 1H) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 120.1 (2C, C2',5'), 116.8 (*C*N), 109.7 (2C, C3',4'), 56.4 (C2), 43.4, 29.4, 29.2, 25.8, 25.5 ppm.

MS (ESI): m/z = 399.2 (100) $[2M + Na]^+$, 377.2 (88) $[2M + H]^+$, 189.1 (28) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{12}H_{16}N_2 + H]^+$ 189.1392, found 189.1386.

General procedure-VIIIA for indolizines 116

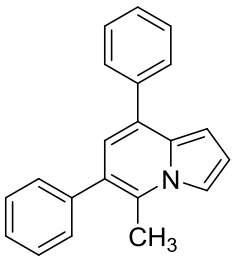
To a solution of corresponding 2-(1*H*-pyrrol-1-yl)nitrile **109** in freshly distilled THF (0.1 M) at 0 °C was added a solution of KO*t*Bu in THF (1.10 equiv, 1.0 M). The mixture was stirred for 5 min and a solution of corresponding α,β-unsaturated aldehyde/ketone (1.00 equiv) in freshly distilled THF (0.2 M) was added. The reaction was monitored by TLC. When the conversion of the pyrrolonitrile was complete (TLC monitoring, about 2 h), the reaction mixture was quenched with a solution of AcOH (7.00 equiv) in EtOH (1.4 M). The reaction mixture was stirred for 15–18 h at ambient temperature after $BF_3{\cdot}OEt_2$ (3.00 equiv) was added. DBU (20.00 equiv) was slowly added to an acidic solution (**caution, exothermic reaction**). After heating the mixture under reflux for about 2 h (TLC monitoring), it was

quenched with water (20 mL/mmol pyrrolonitrile). The product was extracted four times with EtOAc (30 mL/mmol pyrrolonitrile). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The resulting crude product was purified by column chromatography.

General procedure-VIIIB for indolizines 116

: To a solution of corresponding 2-(1*H*-pyrrol-1-yl)nitrile **109** in dry DMF (0.1 M) at 0 °C was added a solution of KO*t*Bu (1.10 equiv) in DMF (0.5 M). The mixture was stirred for 5 min and a solution of corresponding α,β-unsaturated aldehydes/ketone (1.00 equiv) in dry DMF (0.2 M) was added. When the conversion of pyrrolonitrile was complete (TLC monitoring, about 2 h), triflic acid (1.50 equiv) was added at 0 °C and the mixture was stirred for 15–18 h at ambient temperature. DBU (20.00 equiv) was slowly added to an acidic solution (**caution, exothermic reaction**). After heating the mixture to 90 °C for about 2 h (TLC monitoring), it was quenched with water (20 mL/mmol pyrrolonitrile). The product was extracted four times with EtOAc (30 mL/mmol pyrrolonitrile). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The resulting crude product was purified by column chromatography.

5-Methyl-6,8-diphenylindolizine (116a)



The title compound was prepared according to the general procedure-VIIIA from **109a** (120 mg, 1.00 mmol) and **110a** (208 mg, 1.00 mmol). The crude product was purified by column chromatography (petroleum ether).

Yield: 242 mg (0.85 mmol, 85%), yellow oil.

R_f = 0.14 (petroleum ether).

IR (ATR) $\tilde{\nu}$ = 2976, 2861, 1443, 1376, 1110, 773, 759, 724, 698 cm^{-1}.

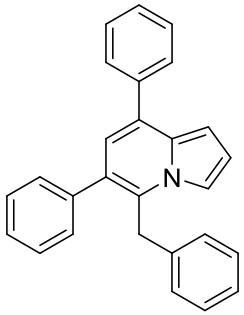
^{1}H NMR (300 MHz, CD_3OD) δ = 7.68–7.62 (m, 2H, H_{Ph}), 7.47–7.31 (m, 9H, H_{Ph}, H-3), 6.89 (dd, *J* = 4.0, 2.8 Hz, 1H, H-2), 6.68 (s, 1H, H-7), 6.60 (dd, *J* = 4.0, 1.4 Hz, 1H, H-1), 2.48 (s, 3H, C*H*$_3$) ppm.

^{13}C NMR (75 MHz, CD_3OD) δ = 141.5, 140.7, 133.1, 131.4, 131.0, 130.2, 129.6, 129.43, 129.37, 128.7, 128.1, 124.9, 120.8, 115.2, 112.3, 100.9, 16.4 (*C*H_3) ppm.

MS (ESI): m/z = 284.2 (100) $[M + H]^+$, 283.2 (18) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{21}H_{17}N + H]^+$ 284.1439, found 284.1430.

5-Benzyl-6,8-diphenylindolizine (116b)



The title compound was prepared according to the general procedure-VIIIA from **109b** (196 mg, 1.00 mmol) and **110a** (208 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 195 mg (0.54 mmol, 54%), yellow solid.

Mp: 180–181 °C (dec.).

R_f = 0.57 (ethyl acetate/cyclohexane 1:5).

IR (ATR) $\tilde{\nu}$ = 3141, 3058, 2930, 1493, 1265, 736, 699 cm^{-1}.

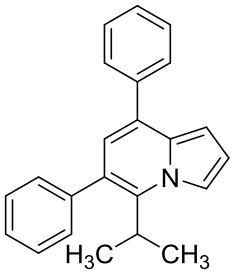
^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.78–7.74 (m, 2H), 7.53–7.49 (m, 4H), 7.48–7.43 (m, 3H), 7.43–7.36 (m, 1H), 7.30–7.25 (m, 3H), 7.22–7.15 (m, 1H), 6.82 (s, 1H, H-7), 6.78 (dd, *J* = 4.0, 2.8 Hz, 1H, H-2), 6.58 (dd, *J* = 4.0, 1.4 Hz, 1H, H-1), 4.36 (s, 2H, C*H*$_2$) ppm.

^{13}C NMR (75 MHz, DMSO-d_6) δ = 139.4, 138.3, 136.7, 130.9, 130.2, 130.1, 129.3, 128.8, 128.8, 128.6, 128.2, 128.1, 127.6, 127.4, 126.6, 124.8, 119.5, 114.4, 112.9, 99.8, 34.5 (*C*H_2) ppm.

MS (ESI): m/z = 360.2 (100) $[M + H]^+$, 359.2 (42) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{27}H_{21}N + H]^+$ 360.1752, found 360.1747.

5-Isopropyl-6,8-diphenylindolizine (116c)



The title compound was prepared according to the general procedure-VIIIA from **109c** (148 mg, 1.00 mmol) and **110a** (208 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 127 mg (0.41 mmol, 41%), colorless solid.

Mp: 115–117 °C.

R_f = 0.80 (ethyl acetate/cyclohexane 1:5).

IR (ATR) $\tilde{\nu}$ = 3056, 2967, 2876, 1576, 1264, 760, 734, 698 cm^{-1}.

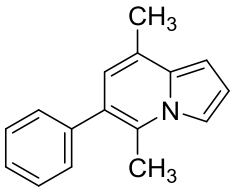
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 7.80 (dd, *J* = 2.8, 1.4 Hz, 1H, H-3), 7.67 (m, 2H, H_{Ph}), 7.51–7.36 (m, 8H, H_{Ph}), 6.89 (dd, *J* = 4.0, 2.8 Hz, 1H, H-2), 6.56 (m, 2H, H-1, H-7), 3.55 (sept, *J* = 7.0 Hz, 1H, C*H*$(CH_3)_2$), 1.39 (d, *J* = 7.0 Hz, 6H, (C*H*$_3)_2$CH) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ =140.5, 138.3, 137.0 (C5), 131.6 (C9), 129.4, 129.2 (C8), 128.7, 128.4, 128.1, 127.9, 127.2, 123.0 (C6), 120.3 (C7), 114.1 (C2), 113.8 (C3), 99.0 (C1), 29.2 (*C*H$(CH_3)_2$), 17.8 (2C, (*C*H$_3)_2$CH) ppm.

MS (ESI): m/z = 312.2 (100) $[M + H]^+$, 311.2 (13) $[M^+]$.

HRMS (ESI-TOF): Calcd for $[C_{23}H_{21}N + H]^+$ 312.1752, found 312.1746.

5,8-Dimethyl-6-phenylindolizine (116d)



The title compound was prepared according to the general procedure-VIIIA from **109a** (120 mg, 1.00 mmol) and 4-phenylbut-3-en-2-one[200] (**110b**, 146 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 69 mg (0.31 mmol, 31%), brown oil.

R_f = 0.75 (ethyl acetate/cyclohexane 1:5).

IR (ATR) $\tilde{\nu}$ = 2928, 2857, 1493, 1394, 1280, 1025, 769, 703, 680 cm^{-1}.

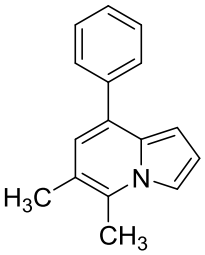
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 7.49–7.43 (m, 3H, H3, H-3',5'), 7.40–7.35 (m, 3H, H-2',6', H-4'), 6.85 (dd, *J* = 3.9, 2.7 Hz, 1H, H-2), 6.56 (s, 1H, H-7), 6.51 (dd, *J* = 3.9, 1.5 Hz, 1H, H-1), 2.43 (s, 3H, 5-CH_3), 2.40 (s, 3H, 8-CH_3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 139.7 (C1'), 132.8 (C9), 129.7 (2C, C2',6'), 128.3 (2C, C3',5'), 127.6 (C5), 126.9 (C4'), 124.6 (C8), 122.5 (C6), 119.3 (C7), 113.6 (C2), 111.5 (C3), 98.3 (C1), 17.5 (5-*C*H$_3$), 15.8 (8-*C*H$_3$) ppm.

MS (ESI): m/z = 222.1 (100) $[M + H]^+$, 221.1 (73) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{16}H_{15}N + H]^+$ 222.1283, found 222.1278.

5,6-Dimethyl-8-phenylindolizine (116e)



The title compound was prepared according to the general procedure-VIIIA from **109a** (120 mg, 1.00 mmol) and **110c** (146 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/petroleum ether 1:5).

Yield: 21 mg (0.10 mmol, 10%), red oil.

***R*$_f$** = 0.77 (ethyl acetate/petroleum ether 1:5).

IR (ATR) $\tilde{\nu}$ = 2924, 2853, 1444, 1377, 1279, 774, 722, 700 cm^{-1}.

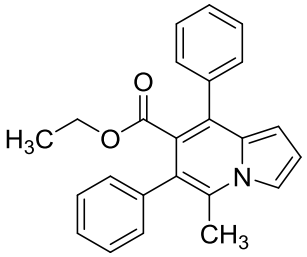
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 7.67–7.64 (m, 2H, H-2',6'), 7.51–7.46 (m, 2H, H-3',5'), 7.43 (dd, *J* = 2.7, 1.5 Hz, 1H, H-3), 7.42–7.38 (m, 1H, H-4'), 6.81 (dd, *J* = 4.0, 2.7 Hz, 1H, H-2), 6.69 (s, 1H, H-7), 6.49 (dd, *J* = 4.0, 1.5 Hz, 1H, H-1), 2.49 (s, 3H, 5-CH_3), 2.31 (s, 3H, 6-CH_3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 138.8 (C1'), 130.7 (C9), 128.8 (C5), 128.72 (C8), 128.70 (2C, C3',5'), 128.0 (2C, C2',6'), 127.6 (C4'), 120.8 (C7), 115.9 (C6), 113.6 (C2), 111.0 (C3), 99.0 (C1), 17.5 (6-*C*H$_3$), 14.6 (5-*C*H$_3$) ppm.

MS (ESI): m/z = 223.1 (72) $[M + H]^+$, 222.1 (100) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{16}H_{15}N + H]^+$ 222.1283, found 222.1277.

Ethyl 5-methyl-6,8-diphenylindolizine-7-carboxylate (116f)



The title compound was prepared according to the general procedure-VIIIB from **109a** (120 mg, 1.00 mmol) and ethyl 2-benzoyl-3-phenylacrylate[201] (**110d**, 280 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 109 mg (0.31 mmol, 31%), light yellow oil.

R_f = 0.62 (ethyl acetate/cyclohexane 1:5).

IR (ATR) $\tilde{\nu}$ = 2925, 1723, 1446, 1291, 1189, 1030, 726, 697 cm^{-1}.

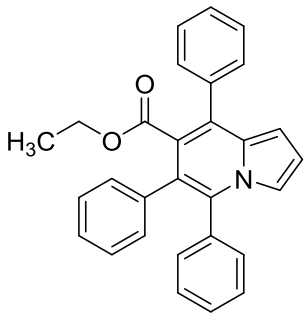
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 7.61 (dd, *J* = 2.7, 1.4 Hz, 1H, H-3), 7.50–7.35 (m, 8H, H_{Ph}), 7.33–7.27 (m, 2H, H_{Ph}), 6.94 (dd, *J* = 4.0, 2.7 Hz, 1H, H-2), 6.30 (dd, *J* = 4.0, 1.4 Hz, 1H, H-1), 3.58 (q, *J* = 7.1 Hz, 2H, OCH_2), 2.36 (s, 3H, 5-CH_3), 0.61 (t, *J* = 7.1 Hz, 3H, CH_3CH$_2$) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 167.4 (CO_2Et), 137.2, 136.5, 130.7 (C9), 130.2, 130.1 (C5), 128.8, 128.4, 128.1, 128.0, 127.5, 127.3, 123.6 (C7), 120.2 (C6), 115.2 (C2), 112.9 (C3), 102.4 (C1), 60.0 (OCH$_2$), 16.2 (5-CH$_3$), 13.2 (CH$_3$CH$_2$) ppm.

MS (ESI): m/z = 356.2 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{24}H_{21}NO_2 + H]^+$ 356.1651, found 356.1646.

Ethyl 5,6,8-triphenylindolizine-7-carboxylate (116g)



The title compound was prepared according to the general procedure-VIIIB from pyrrolonitrile **109d** (182 mg, 1.00 mmol) and enone **110d**[201] (280 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:10).

Yield: 142 mg (0.34 mmol, 34%), yellow solid.

Mp: 62–63 °C.

R_f = 0.36 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 3058, 2978, 1720, 1444, 1253, 1227, 1083, 1030, 721, 695 cm^{-1}.

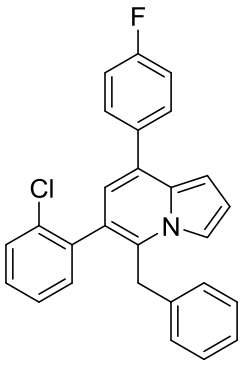
^{1}H NMR (400 MHz, DMSO-d_6) δ = 7.52–7.45 (m, 5H, H_{Ph}), 7.41–7.34 (m, 5H, H_{Ph}), 7.17–7.11 (m, 5H, H_{Ph}), 6.90 (dd, *J* = 2.8, 1.4 Hz, 1H, H-3), 6.80 (dd, *J* = 4.0, 2.8 Hz, 1H, H-2), 6.32 (dd, *J* = 4.0, 1.4 Hz, 1H, H-1), 3.59 (q, *J* = 7.1 Hz, 2H, CH_2), 0.61 (t, *J* = 7.1 Hz, 3H, CH_3) ppm.

^{13}C NMR (75 MHz, DMSO-d_6) δ = 167.2 (*C*O_2Et), 136.6, 136.2, 133.7, 133.1, 131.4, 130.5, 130.3, 129.0, 128.94, 128.93, 128.7, 128.5, 128.4, 127.4, 126.9, 124.2, 121.3, 115.1 (C2), 113.6 (C3), 102.4 (C1), 60.2 (*C*H_2), 13.2 (*C*H_3) ppm.

MS (ESI): m/z = 440.2 (7) $[M + Na]^+$, 418.2 (100) $[M + H]^+$, 417.2 (2) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{29}H_{23}NO_2 + H]^+$ 418.1807, found 418.1800.

5-Benzyl-6-(2-chlorophenyl)-8-(4-fluorophenyl)indolizine (116h)



The title compound was prepared according to the general procedure-VIIIA from **109b** (196 mg, 1.00 mmol) and **110e** (261 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:10).

Yield: 242 mg (0.59 mmol, 59%), yellow solid.

Mp: 71–72 °C.

R_f = 0.48 (ethyl acetate/cyclohexane 1:10).

IR (ATR) $\tilde{\nu}$ = 3058, 3032, 1506, 1265, 1223, 1158, 837, 736, 696 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 7.80–7.74 (m, 2H, H-2’’’,6’’’), 7.64–7.60 (m, 1H, H-3’’), 7.60–7.55 (m, 1H, H-6’’), 7.48–7.40 (m, 2H, H-4’’, H-5’’), 7.36–7.29 (m, 3H,

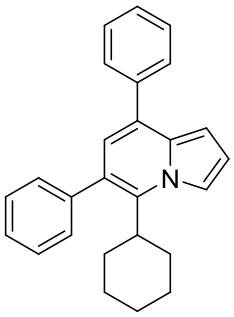
H-3, H-3’’’,5’’’), 7.27–7.14 (m, 5H, $H_{Ph'}$), 6.79 (dd, *J* = 4.0, 2.8 Hz, 1H, H-2), 6.70 (s, 1H, H-7), 6.57 (dd, *J* = 4.0, 1.2 Hz, 1H, H-1), 4.29 (d, *J* = 16.3 Hz, 1H, C$H_{2\text{-a}}$), 4.09 (d, *J* = 16.3 Hz, 1H, C$H_{2\text{-b}}$) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$) δ = 161.9 (d, $^1J_{CF}$ = 244.9 Hz, C4’’’), 137.5 (C1’), 136.1, 134.4 (d, $^4J_{CF}$ = 3.0 Hz, C1’’’), 133.2 (C2’), 132.3 (C6’), 131.3 (C5), 130.9 (C9), 130.1 (d, $^3J_{CF}$ = 8.1 Hz, 2C, C2’’’,6’’’), 129.8 (C4’), 129.7 (C3’), 128.73, 128.66, 127.7, 127.4 (C5’), 126.7, 122.0 (C6), 119.1 (C7), 115.6 (d, $^2J_{CF}$ = 21.4 Hz, 2C, C3’’’,5’’’), 114.4 (C2), 113.1 (C3), 99.9 (C1), 34.6 (*C*H$_2$) ppm.

MS (ESI): m/z = 412.2 (100) $[M + H]^+$, 411.2 (64) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{27}H_{19}ClFN + H]^+$ 412.1268, found 412.1265.

5-Cyclohexyl-6,8-diphenylindolizine (116i)



The title compound was prepared according to the general procedure-VIIIB from **109e** (188 mg, 1.00 mmol) and **110a** (208 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 244 mg (0.69 mmol, 69%), colorless solid.

Mp: 174–175 °C.

***R*$_f$** = 0.49 (ethyl acetate/cyclohexane 1:5).

IR (ATR) $\tilde{\nu}$ = 2928, 2853, 1445, 1261, 1028, 760, 699 cm^{-1}.

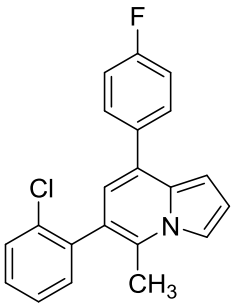
^{1}H NMR (600 MHz, DMSO-*d*$_6$, 70 °C) δ = 7.85 (s, 1H, H-3), 7.68–7.65 (m, 2H, H_{Ph}), 7.49–7.44 (m, 4H, H_{Ph}), 7.42–7.36 (m, 4H, H_{Ph}), 6.88 (dd, *J* = 3.7, 3.0 Hz, 1H, H-2), 6.55–6.53 (m, 2H, H-1, H-7), 3.20–3.14 (m, 1H, H-1’), 2.33–1.59 (m, 7H, H_{Cy}), 1.34–1.12 (m, 3H, H_{Cy}) ppm.

^{13}C NMR (151 MHz, DMSO-*d*$_6$, 70 °C) δ = 140.4, 138.1, 136.3, 131.7, 129.1, 128.9, 128.3, 127.9, 127.7, 127.5, 126.8, 123.2, 120.2 (C7), 113.5 (C2), 113.3 (br s, C3), 98.7 (C1), 40.6, 40.1, 26.0, 24.9 ppm.

MS (ESI): m/z = 352.3 (100) $[M + H]^+$, 351.3 (53) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{26}H_{25}N + H]^+$ 352.2065, found 352.2059.

6-(2-Chlorophenyl)-8-(4-fluorophenyl)-5-methylindolizine (116j)



The title compound was prepared according to the general procedure-VIIIA from **109a** (120 mg, 1.00 mmol) and **110e** (261 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/petroleum ether 1:10).

Yield: 225 mg (0.67 mmol, 67%), colorless solid.

Mp: 124–125 °C.

R_f = 0.56 (ethyl acetate/petroleum ether 1:10).

IR (ATR) $\tilde{\nu}$ = 3136, 3119, 3056, 2913, 1504, 1265, 1218, 1156, 837, 761, 736, 690 cm^{-1}.

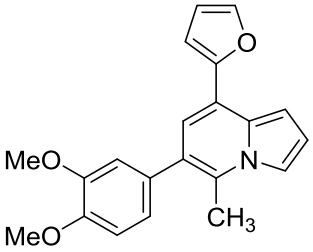
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 7.75–7.69 (m, 2H, H-2'',6''), 7.61–7.58 (m, 1H, H_{Ar}'), 7.57 (dd, *J* = 2.8, 1.4 Hz, 1H, H-3), 7.49–7.41 (m, 3H, H_{Ar}'), 7.33–7.26 (m, 2H, H-3'',5''), 6.94 (dd, *J* = 4.0, 2.8 Hz, 1H, H-2), 6.62 (s, 1H, H-7), 6.61 (d, *J* = 1.4 Hz, 1H, H-1), 2.33 (s, 3H, CH_3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ =161.8 (d, $^1J_{CF}$ = 244.8 Hz, C4''), 137.7 (C1'), 134.6 (d, $^4J_{CF}$ = 3.2 Hz, C1''), 133.2 (C2'), 132.4 (C6'), 130.8 (C9), 130.2 (C6), 130.0 (d, $^3J_{CF}$ = 8.2 Hz, 2C, C2'',6''), 129.5, 129.4, 127.8 (C8), 127.3, 120.2 (C5), 119.2 (C7), 115.6 (d, $^2J_{CF}$ = 21.4 Hz, 2C, C3'',5''), 114.6 (C2), 112.1 (C3), 99.9 (C1), 15.9 (CH$_3$) ppm.

MS (ESI): m/z = 336.1 (100) $[M + H]^+$, 335.1 (9) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{21}H_{15}ClFN + H]^+$ 336.0955, found 336.0949.

6-(3,4-Dimethoxyphenyl)-8-(furan-2-yl)-5-methylindolizine (116k)



The title compound was prepared according to the general procedure-VIIIA from **109a** (120 mg, 1.00 mmol) and 3-(3,4-dimethoxyphenyl)-1-(furan-2-yl)prop-2-en-1-one[202] (**110f**, 258 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/petroleum ether 1:5).

Yield: 237 mg (0.71 mmol, 71%), light yellow solid.

Mp: 140–142 °C (dec.).

R_f = 0.30 (ethyl acetate/petroleum ether 1:5).

IR (ATR) $\tilde{\nu}$ = 3055, 2934, 2834, 1505, 1257, 1240, 1025, 855, 810, 733 cm^{-1}.

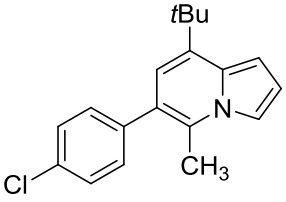
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 7.83 (d, *J* = 1.7 Hz, 1H, H-5''), 7.55 (dd, *J* = 2.8, 1.4 Hz, 1H, H-3), 7.18 (s, 1H, H-7), 7.11 (d, *J* = 3.4 Hz, 1H, H-3''), 7.05 (d, *J* = 8.3 Hz, 1H, H-5'), 7.02 (d, *J* = 2.0 Hz, 1H, H-2'), 6.99 (dd, *J* = 4.0, 1.4 Hz, 1H, H-1), 6.96–6.93 (m, 2H, H-2, H-6'), 6.67 (dd, *J* = 3.4, 1.7 Hz, 1H, H-4''), 3.81 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 2.52 (s, 3H, 5-CH_3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 150.8 (C2''), 148.5 (C3'), 148.0 (C4'), 142.8 (C5''), 131.8 (C1'), 129.7 (C5), 127.5 (C9), 122.4 (C6), 122.0 (C6'), 118.0 (C8), 116.7 (C7), 114.5 (C2), 113.6 (C2'), 112.0 (2C overlapped, C3, C4''), 111.7 (C5'), 108.1 (C3''), 100.3 (C1), 55.60 (O*C*H$_3$), 55.56 (O*C*H$_3$), 16.3 (5-*C*H$_3$) ppm.

MS (ESI): m/z = 334.2 (100) $[M + H]^+$, 333.2 (15) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{21}H_{19}NO_3 + H]^+$ 334.1443, found 334.1440.

8-*tert*-Butyl-6-(4-chlorophenyl)-5-methylindolizine (116l)



The title compound was prepared according to the general procedure-VIIIA from **109a** (120 mg, 1.00 mmol) and 1-(4-

chlorophenyl)-4,4-dimethylpent-1-en-3-one[138] (**110g**, 223 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:50).

Yield: 238 mg (0.80 mmol, 80%), colorless solid.

Mp: 84–85 °C.

R_f = 0.41 (ethyl acetate/cyclohexane 1:50).

IR (ATR) $\tilde{\nu}$ = 2968, 2871, 1491, 1265, 1090, 834, 732, 703 cm^{-1}.

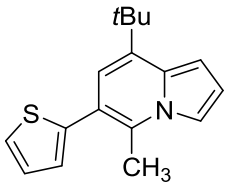
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 7.54–7.50 (AA' part of AA'BB' system, 2H, H-3',5'), 7.46–7.41 (m, 3H, H-3, H-2',6'), 6.87 (dd, *J* = 4.1, 2.8 Hz, 1H, H-2), 6.72 (dd, *J* = 4.1, 1.4 Hz, 1H, H-1), 6.52 (s, 1H, H-7), 2.42 (s, 3H, 5-CH_3), 1.45 (s, 9H, (CH_3)$_3$C) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 138.9 (C1'), 137.2 (C8), 131.7 (C4'), 131.6 (2C, C2',6'), 130.4 (C9), 128.33 (2C, C3',5'), 128.29 (C5), 120.9 (C6), 115.7 (C7), 113.4 (C2), 110.9 (C3), 101.8 (C1), 34.6 (*C*(CH$_3$)$_3$), 29.6 (3C, (*C*H$_3$)$_3$C), 16.0 (5-*C*H$_3$) ppm.

MS (ESI): m/z = 298.2 (60) $[M + H]^+$, 297.2 (100) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{19}H_{20}ClN + H]^+$ 298.1363, found 298.1359.

8-*tert*-Butyl-5-methyl-6-(thiophen-2-yl)indolizine (116m)



The title compound was prepared according to the general procedure-VIIIA from **109a** (120 mg, 1.00 mmol) and 4,4-dimethyl-1-(thiophen-2-yl)pent-1-en-3-one[203] (**110h**, 149 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/petroleum ether 1:5).

Yield: 58 mg (0.22 mmol, 22%), yellow oil.

R_f = 0.73 (ethyl acetate/petroleum ether 1:5).

IR (ATR) $\tilde{\nu}$ = 2956, 1436, 1268, 823, 760, 693 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 7.60 (dd, *J* = 5.0, 1.3 Hz, 1H, H-5'), 7.45 (dd, *J* = 2.8, 1.3 Hz, 1H, H-3), 7.16–7.12 (m, 2H, H-3', H-4'), 6.87 (dd, *J* = 4.0, 2.8 Hz, 1H, H-

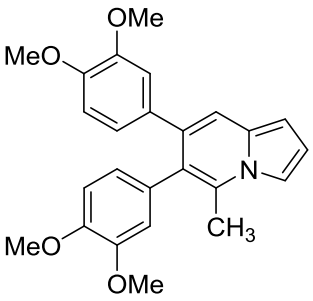
2), 6.72 (dd, *J* = 4.0, 1.3 Hz, 1H, H-1), 6.61 (s, 1H, H-7), 2.55 (s, 3H, 5-C*H*$_3$), 1.43 (s, 9H, (C*H*$_3$)$_3$C) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-*d*$_6$) δ = 141.3 (C2'), 137.1 (C8), 130.2 (C9), 129.2 (C5), 127.4, 127.3, 126.1 (C5'), 116.2 (C7), 114.9 (C6), 113.6 (C2), 111.3 (C3), 102.1 (C1), 34.6 (*C*(CH$_3$)$_3$), 29.5 (3C, (*C*H$_3$)$_3$C), 16.1 (5-*C*H$_3$) ppm.

MS (ESI): m/z = 270.1 (100) $[M + H]^+$, 269.1 (8) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{17}H_{19}NS + H]^+$ 270.1317, found 270.1313.

6,7-Bis(3,4-dimethoxyphenyl)-5-methylindolizine (116n)



The title compound was prepared according to the general procedure-VIIIA with a slight modification. To a solution of **109a** (60 mg, 0.50 mmol) in freshly distilled THF (5 mL) at 0 °C was added a solution of KO*t*Bu in THF (0.6 mL, 1.0 M). The mixture was stirred for 5 min and a solution of 2,3-bis(3,4-dimethoxyphenyl)acrylaldehyde[204] (**110i**, 104 mg, 0.50 mmol) in freshly distilled THF (2.5 mL) was added. When the conversion of the pyrrolonitrile was complete (TLC monitoring, about 2 h), the reaction mixture was quenched with a solution of AcOH (0.2 mL) in EtOH (2.5 mL). The reaction mixture was stirred for 15–18 h at ambient temperature after $BF_3 \cdot OEt_2$ (0.2 mL) was added. The reaction mixture was quenched with water (10 mL) and the dihydroindolizine was extracted three times with EtOAc (20 mL each). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. To a solution of the dihydroindolizine in THF (5 mL) was added a solution of KO*t*Bu in THF (1.0 mL, 1.0 M) and the reaction mixture was stirred for 2 h at ambient temperature (TLC monitoring). It was quenched with water (10 mL). The product was extracted four times with EtOAc (15 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The resulting crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:3).

Yield: 78 mg (0.19 mmol, 39%), colorless solid.

Mp: 179–180 °C.

R_f = 0.35 (ethyl acetate/cyclohexane 1:3).

IR (ATR) $\tilde{\nu}$ = 2998, 2933, 2834, 1509, 1248, 1135, 1024, 862, 765 cm^{-1}.

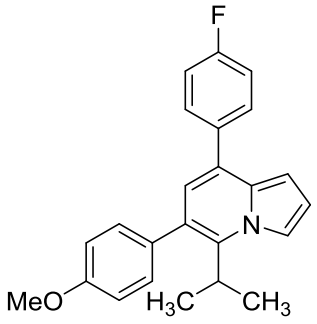
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 7.42 (br s, 1H, H-3), 7.40 (s, 1H, H-7), 6.90–6.86 (m, 2H, H-2, H-5'), 6.80 (d, *J* = 8.2 Hz, 1H, H-5''), 6.73 (dd, *J* = 8.2, 1.8 Hz, 1H, H-6''), 6.67–6.64 (m, 2H, H-2', H-6'), 6.53 (dd, *J* = 3.8, 1.1 Hz, 1H, H-1), 6.48 (d, *J* = 1.8 Hz, 1H, H-2''), 3.73 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.44 (s, 3H, OCH_3), 2.39 (s, 3H, CH_3-5) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 148.0 (C3'), 147.4 (2C overlapped, C4', C3''), 147.1 (C4''), 133.6 (C1''), 131.7 (C9), 131.6 (C1''), 130.8 (C1'), 130.6 (C5), 123.4, 122.3, 121.0 (C6''), 115.9 (C7), 115.3, 114.4 (C2), 113.3 (C2''), 111.14, 111.08, 110.5 (C3), 99.8 (C1), 55.4 (2 C overlapped, O*C*H_3), 55.3 (O*C*H_3), 55.0 (O*C*H_3), 16.7 (5-*C*H_3) ppm.

MS (ESI): m/z = 436.2 (12) $[M + Na]^+$, 404.2 (100) $[M + H]^+$, 403.2 (5) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{25}H_{25}NO_4 + H]^+$ 404.1862, found 404.1859.

8-(4-Fluorophenyl)-5-isopropyl-6-(4-methoxyphenyl)indolizine (116o)



The title compound was prepared according to the general procedure-VIIIA from **109c** (148 mg, 1.00 mmol) and **110j** (256 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/petroleum ether 1:20).

Yield: 130 mg (0.36 mmol, 36%), yellow solid.

Mp: 62–64 °C.

R_f = 0.12 (ethyl acetate/petroleum ether 1:20).

IR (ATR) $\tilde{\nu}$ = 2963, 2836, 1609, 1518, 1244, 1222, 1016, 832, 737, 701 cm^{-1}.

^{1}H NMR (400 MHz, CD_3CN) δ = 7.73–7.66 (m, 3H, H-3, H-2'',6''), 7.32–7.27 (AA' part of AA'BB' system, 2H, H-2',6'), 7.23–7.16 (m, 2H, H-3'',5''), 7.02–6.96 (BB' part of AA'BB' system, 2H, H-3',5'), 6.86 (dd, *J* = 4.0, 2.9 Hz, 1H, H-2), 6.58 (s, 1H, H-7), 6.54

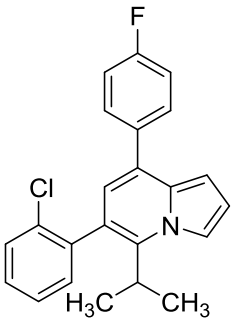
(dd, *J* = 4.0, 1.4 Hz, 1H, H-1), 3.83 (s, 3H, OC*H*$_3$), 3.60 (sept, *J* = 7.3 Hz, 1H, C*H*(CH$_3$)$_2$), 1.41 (d, *J* = 7.3 Hz, 6H, (C*H*$_3$)$_2$CH) ppm.

^{13}C NMR (75 MHz, CD$_3$CN) δ = 163.3 (d, $^1J_{CF}$ = 244.7 Hz), 159.9, 138.6, 136.2, 136.1, 134.0, 133.2, 131.7, 131.2 (d, $^3J_{CF}$ = 8.2 Hz), 129.4, 124.1, 122.0, 116.3 (d, $^2J_{CF}$ = 21.5 Hz), 114.7, 114.6, 99.9 (C1), 56.0 (O*C*H$_3$), 30.4 (*C*H(CH$_3$)$_2$), 18.2 (2C, (*C*H$_3$)$_2$CH) ppm.

MS (ESI): m/z = 360.2 (100) $[M + H]^+$, 359.2 (98) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{24}H_{22}FNO + H]^+$ 360.1764, found 360.1760.

6-(2-Chlorophenyl)-8-(4-fluorophenyl)-5-isopropylindolizine (116p)



The title compound was prepared according to the general procedure-VIIIA from **109c** (148 mg, 1.00 mmol) and **110e** (261 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/petroleum ether 1:5).

Yield: 58 mg (0.16 mmol, 16%), yellow oil.

R_f = 0.71 (ethyl acetate/petroleum ether 1:5).

IR (ATR) $\tilde{\nu}$ = 2963, 2878, 1608, 1504, 1244, 1175, 1032, 832, 736, 701 cm^{-1}.

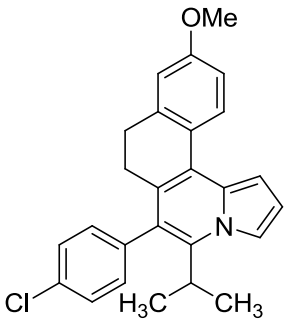
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 7.81 (dd, *J* = 2.8, 1.2 Hz, 1H, H-3), 7.72–7.66 (m, 2H, H-2'',6''), 7.62–7.58 (m, 1H, H$_{Ar'}$), 7.47–7.41 (m, 3H, H$_{Ar'}$), 7.33–7.26 (m, 2H, H-3'',5''), 6.91 (dd, *J* = 4.0, 2.8 Hz, 1H, H-2), 6.56 (dd, *J* = 4.0, 1.2 Hz, 1H, H-1), 6.43 (s, 1H, H-7), 3.23 (br s, 1H, C*H*(CH$_3$)$_2$), 1.39 (d, *J* = 7.1 Hz, 3H, C*H*$_{3\text{-a}}$), 1.30 (br s, 3H, C*H*$_{3\text{-b}}$) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 161.8 (d, $^1J_{CF}$ = 244.8 Hz, C4''), 138.6, 137.5, 134.5 (d, $^4J_{CF}$ = 3.1 Hz, C1''), 133.1, 131.9, 131.7, 130.1 (d, $^3J_{CF}$ = 8.2 Hz, 2C, C2'',6''), 129.6, 129.4, 128.2, 127.3, 120.1, 119.5 (C7), 115.6 (d, $^2J_{CF}$ = 21.4 Hz, 2C, C3'',5''), 114.2 (C2), 113.9 (C3), 99.3 (C1), 29.9 (*C*H(CH$_3$)$_2$), 17.4 (2C, CH(*C*H$_3$)$_2$) ppm.

MS (ESI): m/z = 364.2 (100) $[M + H]^+$, 363.2 (55) $[M]^+$.

HRMS (ESI-TOF): Calcd for $[C_{23}H_{19}ClFN + H]^+$ 364.1268, found 364.1263.

6-(4-Chlorophenyl)-5-isopropyl-10-methoxy-7,8-dihydrobenzo[h]pyrrolo[2,1-a]isoquinoline (**117**)



The title compound was prepared according to the general procedure-VIIIB from pyrrolonitrile **109c** (148 mg, 1.00 mmol) and enone **110k**[205] (299 mg, 1.00 mmol). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 151 mg (0.38 mmol, 38%), yellow solid.

Mp: 158–159 °C.

R_f = 0.52 (ethyl acetate/petroleum ether 1:5).

IR (ATR) $\tilde{\nu}$ = 3052, 2963, 2935, 2835, 1606, 1486, 1282, 1263, 1087, 840, 734, 699 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 8.04 (d, *J* = 8.6 Hz, 1H, H-12), 7.70 (dd, *J* = 2.7, 1.2 Hz, 1H, H-3), 7.54–7.48 (AA'-part of AA'BB' system, 2H, H-3',5'), 7.31–7.26 (BB'-part of AA'BB' system, 2H, H-2',6'), 6.92 (dd, *J* = 8.6, 2.7 Hz, 1H, H-11), 6.89–6.87 (m, 2H, H2, H-9), 6.85 (dd, *J* = 4.1, 1.2 Hz, 1H, H-1), 3.79 (s, 3H, OCH_3), 3.22 (br s, 1H, CH(CH_3)$_2$), 2.62–2.53 (m, 2H, H-8), 2.13–2.04 (m, 2H, H-7), 1.32 (br s, 6H, (CH_3)$_2$CH) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 158.2 (C10), 139.5 (C8*a*), 137.7 (C4'), 136.7 (C5), 132.2 (C1'), 131.7 (2C, C2',6'), 129.9 (C12c), 128.6 (2C, C3',5'), 126.5 (C12), 126.0 (C6a), 125.5 (C12a), 121.9 (C6), 121.8 (C12b), 113.9 (C2), 113.3 (C9), 112.9 (C3), 111.5 (C11), 98.4 (C1), 55.1 (CH$_3$O), 30.1 (CH(CH_3)$_2$), 28.4 (C8), 26.0 (C7), 17.4 (2C, (CH$_3$)$_2$CH) ppm.

MS (ESI): m/z = 404.1 (38), 403.1 (38), 402.2 (100) $[M + H]^+$.

HRMS (ESI-TOF): Calcd for $[C_{26}H_{24}ClNO + H]^+$ 402.1625, found 402.1621.

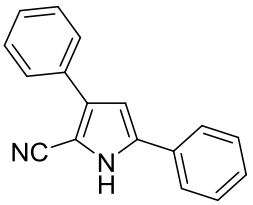
5.4 Synthesis of Pyrroles

5.4.1 Synthesis of Pyrrole-2-carbonitriles

General procedure-IX for pyrrole-2-carbonitriles 122

A round bottom flask equipped with a magnetic stir bar was charged with cyanopyrroline **118** and DDQ (1.15–1.20 equiv) in toluene (15–20 mL/mmol **6**). The reaction mixture was stirred under reflux until the starting material was consumed (TLC, 2–4 h). It was diluted with ethyl acetate and washed with 10% aqueous NaOH. The extracts were dried over $MgSO_4$ and concentrated in vacuo to obtain crude product which was purified by column chromatography.

3,5-Diphenyl-1*H*-pyrrole-2-carbonitrile (**122a**)



The title compound was prepared according to the general procedure-IX described above from **118a** (292 mg, 1.19 mmol) and DDQ (310 mg, 1.36 mmol) in 8 mL of toluene. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:10).

Yield: 273 mg (1.12 mmol, 94%), colorless solid.

Mp: 192–193 °C (lit. 194–195 °C).[206]

R_f = 0.23 (ethyl acetate/cyclohexane 1:10).

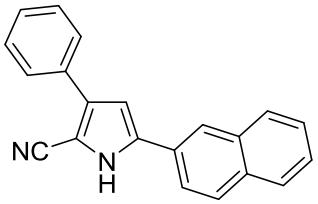
^{1}H NMR (400 MHz, DMSO-d_6) δ = 12.75 (br s, 1H, N*H*), 7.83–7.78 (m, 2H, H-2',6' or H-2'',6''), 7.76–7.72 (m, 2H, H-2',6'or H-2'',6''), 7.51–7.43 (m, 4H, H-3',5', H-3'',5''), 7.39–7.32 (m, 2H, H-4', H-4''), 7.13 (s, 1H, H-4) ppm.

^{13}C-NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 137.2 (C5), 134.8 (C3), 132.6, 130.4 (C1', C1''), 129.0, 128.9 (4C, C3',5', C3'',5''), 127.9, 127.6 (C4', C4''), 126.2, 124.8 (2C, C2',6', C2'',6''), 115.5 (*C*N), 106.1 (C4), 97.2 (C2) ppm.

Elemental Analysis: Calcd: C: 83.58% H: 4.95% N: 11.47%

$C_{17}H_{12}N_2$ Found: C: 83.47% H: 5.27% N: 11.14%

5-(Naphthalen-2-yl)-3-phenyl-1*H*-pyrrole-2-carbonitrile (**122b**)



The title compound was prepared according to the general procedure-IX described above from **118b** (207 mg, 0.70 mmol) and DDQ (191 mg, 0.84 mmol) in 14 mL of toluene. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:3).

Yield: 121 mg (0.41 mmol, 59%), colorless solid.

Mp: 227–229 °C.

R_f = 0.47 (ethyl acetate/cyclohexane 1:3).

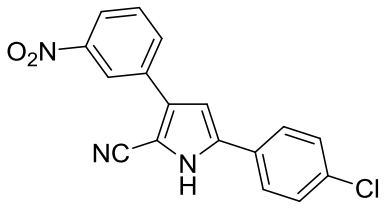
IR (ATR) $\tilde{\nu}$ = 3268, 3056, 2213, 1457, 1230, 863, 853, 808, 764 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 12.93 (br s, 1H, N*H*), 8.36 (d, *J* = 1.7 Hz, 1H, H-1''), 8.01 (d, *J* = 8.6 Hz, 1H, H-4''), 7.97 (dd, *J* = 8.6, 1.7 Hz, 1H, H-3''), 7.94–7.91 (m, 2H, H_{Naphth}), 7.80–7.76 (m, 2H, H-2',6'), 7.59–7.47 (m, 4H, H-3',5', $2H_{Naphth}$), 7.40–7.35 (m, 1H, H-4'), 7.29 (d, *J* = 2.7 Hz, 1H, H-4) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ =137.2, 134.9, 133.0, 132.6, 132.4, 129.0 (2C, C3',5'), 128.6 (C4''), 127.96, 127.92, 127.73, 127.72, 126.9, 126.4, 126.3 (2C, C2',6'), 123.23 (C1''), 123.20 (C3''), 115.6 (*C*N), 106.8 (C4), 97.5 (C2) ppm.

HRMS (ESI-TOF): Calcd for $[C_{21}H_{14}N_2 + H]^+$ 295.1235, found 295.1228.

5-(4-Chlorophenyl)-3-(3-nitrophenyl)-1*H*-pyrrole-2-carbonitrile (**122d**)



The title compound was prepared according to the general procedure-IX described above from **118d** (302 mg, 0.93 mmol) and DDQ (252 mg, 1.11 mmol) in 20 mL of toluene. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:6).

Yield: 195 mg (0.60 mmol, 65%), colorless foam.

R_f = 0.14 (ethyl acetate/cyclohexane 1:6).

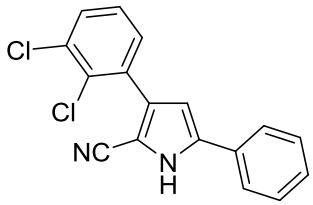
IR (ATR) $\tilde{\nu}$ = 3299, 2925, 2212, 1533, 1350, 1263, 1094, 799, 740 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.06 (br s, 1H, N*H*), 8.56 (t, *J* = 2.0 Hz, 1H, H-2'), 8.23–8.17 (m, 2H, H-4', H-6'), 7.88–7.83 (AA' part of AA'BB' system, 2H, H-2'',6''), 7.80 (t, *J* = 8.0 Hz, 1H, H-5'), 7.59–7.53 (BB' part of AA'BB' system, 2H, H-3'',5''), 7.41 (s, 1H, H-4) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 148.4 (C3'), 136.4 (C5), 134.1 (C1'), 132.7 (C4''), 132.4 (C6'), 132.2 (C3), 130.7 (C5'), 129.13 (C1''), 129.09 (2C, C3'',5''), 126.6 (2C, C2'',6''), 122.3 (C4'), 120.4 (C2'), 114.9 (*C*N), 107.2 (C4), 98.2 (C2) ppm.

HRMS (ESI-TOF): Calcd for $[C_{17}H_{10}N_3O_2Cl + H]^+$ 346.0359, found 346.0367.

3-(2,3-Dichlorophenyl)-5-phenyl-1*H*-pyrrole-2-carbonitrile (**122e**)



The title compound was prepared according to the general procedure-IX described above from **118e** (158 mg, 0.50 mmol) and DDQ (136 mg, 0.60 mmol) in toluene (10 mL). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 111 mg (0.35 mmol, 71%), yellow solid.

Mp: 204–205 °C.

R_f = 0.21 (ethyl acetate/cyclohexane 1:10).

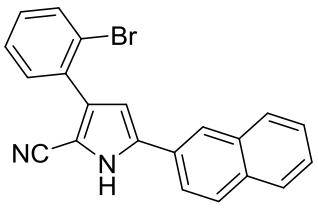
IR (ATR) $\tilde{\nu}$ = 3290, 2207, 1586, 1483, 1447, 1395, 1264, 1191, 1109, 1056, 1020, 820, 785, 774, 754, 684 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.26 (br s, 1H, N*H*), 7.56–7.52 (m, 2H, H-2'',6''), 7.49 (dd, *J* = 8.0, 1.6 Hz, 1H, H-4'), 7.47–7.41 (m, 2H. H-3'',5''), 7.40 (dd, *J* = 7.7, 1.6 Hz, 1H, H-2'), 7.38–7.33 (m, 1H, H-4''), 7.27 (dd, *J* = 8.0, 7.7 Hz, 1H, H-3'), 6.75 (d, *J* = 2.8 Hz, 1H, H-4) ppm.

^{13}C NMR (101 MHz, DMSO-d_6) δ = 136.5 (C5), 134.2 (C3), 132.5, 132.2, 130.3 (2 C_q), 130.18, 130.15, 129.0, 128.3, 128.0, 124.8, 114.1 (*C*N), 108.7 (C4), 100.1 (C2) ppm.

HRMS (ESI-TOF): Calcd for $[C_{17}H_{10}Cl_2N_2 + H]^+$ 313.0307, found: 313.0299.

3-(2-Bromophenyl)-5-(naphthalen-2-yl)-1*H*-pyrrole-2-carbonitrile (**122f**)



The title compound was prepared according to the general procedure-IX described above from **118f** (504 mg, 1.34 mmol) and DDQ (366 mg, 1.61 mmol) in toluene (25 mL). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 234 mg (0.63 mmol, 47%), colorless solid.

Mp: 180–181 °C.

R_f = 0.26 (ethyl acetate/cyclohexane 1:5).

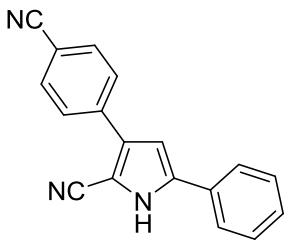
IR (ATR) $\tilde{\nu}$ = 3264, 3056, 2214, 1507, 1446, 1265, 812, 757, 725 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 13.05 (d, *J* = 2.6 Hz, 1H, N*H*), 8.35 (d, *J* = 1.1 Hz, 1H, H-1’’), 8.00 (d, *J* = 8.7 Hz, 1H, H-4’’), 7.96–7.90 (m, 3H, H-3’’, 2 H_{Naphth}), 7.79 (dd, *J* = 8.0, 0.8 Hz, 1H, H-3’), 7.59–7.47 (m, 4H, 2 H_{Naphth}, H-5’, H-6’), 7.36 (ddd, *J* = 8.0, 6.9, 2.3 Hz, 1H, H-4’), 7.05 (d, *J* = 2.6 Hz, 1H, H-4) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 136.2 (C5), 134.6 (C3), 133.9 (C1’), 133.2 (C3’), 133.1 (C8a’’), 132.4 (C4a’’), 131.7 (C6’), 130.0 (C4’), 128.7 (C4’’), 128.0 (*C*H), 127.96 (*C*H), 127.9 (C2’’), 127.7 (*C*H), 126.9, 126.4 (C6’’, C7’’), 123.24, 123.18 (C1’’, C3’’), 122.6 (C2’), 114.5 (*C*N), 109.3 (C4), 100.3 (C2) ppm.

HRMS (ESI-TOF): Calcd for $[C_{21}H_{13}N_2Br + Na]^+$ 395.0160, found 395.0154.

3-(4-Cyanophenyl)-5-phenyl-1*H*-pyrrole-2-carbonitrile (**122g**)



The title compound was prepared according to the general procedure-IX described above from **118g** (310 mg, 1.14 mmol) and DDQ (311 mg, 1.37 mmol) in toluene (20 mL). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:4).

Yield: 216 mg (0.80 mmol, 70%), yellow solid.

Mp: 228–229 °C.

R_f = 0.15 (ethyl acetate/cyclohexane 1:4).

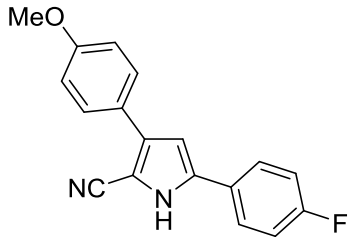
IR (ATR) $\tilde{\nu}$ = 3294, 3065, 2224, 2204, 1606, 1263, 840, 813, 758, 730, 689 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 13.01 (br s, 1H, NH), 7.98–7.95 (AA' part of AA'BB' system, 2H, H-3',5'), 7.94–7.91 (BB' part of AA'BB' system, 2H, H-2',6'), 7.83–7.79 (m, 2H, H-2'',6''), 7.50–7.45 (pseudo-t, J_{app} ≈ 7.7 Hz, 2H, H-3'',5''), 7.38–7.33 (pseudo-tt, J_{app} ≈ 7, 1 Hz, 1H, H-4''), 7.28 (d, J = 2.7 Hz, 1H, H-4) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 137.6 (C5), 137.2 (C1'), 133.0 (2C, C3',5'), 132.6 (C3), 130.2 (C1''), 129.1 (2C, C3'',5''), 128.2 (C4''), 126.8 (2C, C2',6'), 124.9 (2C, C2'',6''), 118.8 (4'-*C*N), 115.1 (2-*C*N), 109.9 (C4'), 106.7 (C4), 98.1(C2) ppm.

HRMS (ESI-TOF): Calcd for $[C_{18}H_{11}N_3 + Na]^+$ 292.0851, found 292.0861.

5-(4-Fluorophenyl)-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carbonitrile (**122h**)



The title compound was prepared according to the general procedure-IX described above from **118h** (293 mg, 1.00 mmol) and DDQ (271 mg, 1.20 mmol) in toluene (20 mL). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:4).

Yield: 225 mg (0.77 mmol, 77%), colorless solid.

Mp: 238–239 °C.

R_f = 0.26 (ethyl acetate/cyclohexane 1:4).

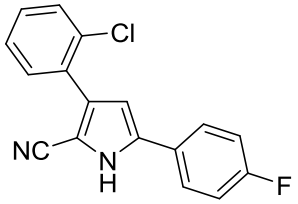
IR (ATR) $\tilde{\nu}$ = 3298, 2927, 2839, 2206, 1599, 1507, 1350, 1254, 1226, 1166, 840, 809 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 12.64 (br s, 1H, N*H*), 7.87–7.80 (m, 2H, H-2'',6''), 7.69–7.64 (AA' part of AA'BB' system, 2H, H-2',6'), 7.35–7.28 (m, 2H, H-3'',5''), 7.09–7.02 (m, 3H, H-4, H-3',5'), 3.80 (s, 3H, CH_3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 161.7 (d, $^{1}J_{CF}$ = 245.3 Hz, C4’’), 158.9 (C4’), 136.2 (C5), 134.8 (C3), 127.5 (2C, C2’,6’), 127.2 (d, $^{4}J_{CF}$ = 3.2 Hz, C1’’), 127.0 (d, $^{3}J_{CF}$= 8.3 Hz, 2C, C2’’,6’’), 125.0 (C1’’), 116.0 (d, $^{2}J_{CF}$ = 21.7 Hz, 2C, C3’’,5’’), 115.8 (*C*N), 114.4 (2C, C3’,5’), 105.8 (C4), 96.5 (C2), 55.2 (*C*H$_3$) ppm.

HRMS (ESI-TOF): Calcd for [$C_{18}H_{13}N_2OF$ + Na]$^+$ 315.0910, found 315.0912.

3-(2-Chlorophenyl)-5-(4-fluorophenyl)-1*H*-pyrrole-2-carbonitrile (**122i**)



The title compound was prepared according to the general procedure-IX described above from **118i** (149 mg, 0.50 mmol) and DDQ (136 mg, 0.60 mmol) in toluene (10 mL). The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:6).

Yield: 105 mg (0.354 mmol, 71%), colorless solid.

Mp: 214–216 °C.

***R*$_f$ =** 0.20 (ethyl acetate/cyclohexane 1:6).

IR (ATR) $\tilde{\nu}$ = 3290, 3068, 2926, 2214, 1600, 1508, 1235, 1158, 841, 805, 761, 749 cm^{-1}.

^{1}H NMR, COSY (300 MHz, DMSO-*d*$_6$) δ = 12.88 (br s, 1H, N*H*), 7.88–7.79 (m, 2H, H-2’’,6’’), 7.64–7.58 (m, 1H, H$_{Ar’}$), 7.54–7.49 (m, 1H, H$_{Ar’}$), 7.47–7.42 (m, 2H, H$_{Ar’}$), 7.36–7.26 (m, 2H, H-3’’,5’’), 6.91 (s, 1H, H-4) ppm.

^{13}C NMR, HSQC, HMBC (75 MHz, DMSO-d_6) δ = 161.8 (d, $^{1}J_{CF}$ = 245.7 Hz, C4’’), 135.5 (C5), 132.7 (C3), 131.7 (C$_q$), 131.6 (C$_q$), 130.0 (*C*H$_{Ar’}$), 129.8 (*C*H$_{Ar’}$), 127.5 (*C*H$_{Ar’}$), 127.15 (C1’’), 127.06 (d, $^{3}J_{CF}$ = 8.1 Hz, 2C, C2’’,6’’), 116.0 (d, $^{2}J_{CF}$ = 21.7 Hz, 2C, C3’’,5’’), 114.5 (*C*N), 108.8 (C4), 100.0 (C2) ppm.

HRMS (ESI-TOF): Calcd for [$C_{17}H_{10}N_2ClF$ + Na]$^+$ 319.0414, found 319.0408.

5.4.2 Synthesis of 2,4-Disubstituted Pyrroles

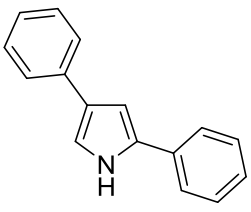
General procedure-X for 2,4-disubstituted pyrroles 123

A solution of cyanopyrroline **118**[139] in dichloromethane was transferred into a 10 mL microwave reaction vessel. After removing the solvent in vacuo, the vessel was flushed with argon and closed with a cap. It was irradiated for 30 min (P_{max}: 180 W) in a monomode microwave apparatus under air cooling. The temperatures reached (IR sensor) are listed in Table S1. The pressurized vessel was opened very carefully inside a well-ventilated hood (**caution, hydrogen cyanide!**) and the residue was purified by column chromatography.

Table S1. Temperature parameters of the microwave experiments

Entry	Product	t_{set} (°C)	t_{max}(°C)
1	**123a**	250	190
2	**123b**	250	230
3	**123c**	250	150
4	**123d**	250	195
5	**123e**	250	220
6	**123f**	250	200
7	**123g**	250	230
8	**123h**	250	180
9	**123i**	250	160

2,4-Diphenyl-1*H*-pyrrole (**123a**)



The title compound was prepared according to the general procedure-X described above from **118a** (123 mg, 0.50 mmol). The product was purified by column chromatography (ethyl acetate/cyclohexane 1:4).

Yield: 89 mg (0.41 mmol, 81%), colorless solid.

Mp: 178–179 °C (lit. 178–180 °C).[185]

R_f = 0.38 (ethyl acetate/cyclohexane 1:4).

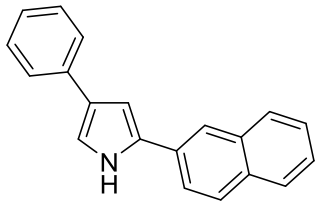
IR (ATR) $\tilde{\nu}$ = 3440, 3029, 1605, 1491, 1453, 1134, 808, 752, 691 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.44 (br s, 1H, N*H*), 7.70–7.66 (m, 2H, H-2',6'), 7.63–7.58 (m, 2H, H-2'',6''), 7.40–7.35 (m, 2H, H-3',5'), 7.35–7.30 (m, 3H, H-5, H-3'',5''), 7.20–7.15 (m, 1H, H-4'), 7.15–7.10 (m, 1H, H-4''), 6.96 (dd, *J* = 2.5, 1.9 Hz, 1H, H-3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 135.7 (C1''), 132.7 (C1'), 132.2 (C2), 128.7 (2C, C3'',5''), 128.5 (2C, C3',5'), 125.7 (C4'), 125.0 (C4''), 124.7 (C4), 124.4 (2C, C2'',6''), 123.4 (2C, C2',6'), 116.6 (C5), 103.2 (C3) ppm.

HRMS (ESI-TOF): Calcd for $[C_{16}H_{13}N + H]^+$ 220.1126, found 220.1126.

2-(Naphthalen-2-yl)-4-phenyl-1*H*-pyrrole (**123b**)



The title compound was prepared according to the general procedure-X described above from **118b** (207 mg, 0.70 mmol). The product was purified by column chromatography (ethyl acetate/cyclohexane 1:10).

Yield: 157 mg (0.58 mmol, 83%), pale yellow solid.

Mp: 219–220 °C (lit. 222–224 °C).[207]

R_f = 0.16 (ethyl acetate/cyclohexane 1:10).

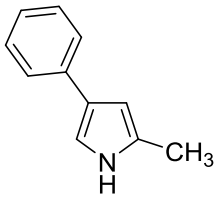
IR (ATR) $\tilde{\nu}$ = 3390, 3027, 1602, 1451, 1263, 1128, 856, 824, 802, 743, 690 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.64 (br s, 1H, N*H*), 8.17 (s, 1H, H-1'), 7.93–7.89 (m, 2H, H-3', H-4'), 7.89–7.83 (m, 2H, H-5', H-8'), 7.67–7.63 (m, 2H, H-2'',6''), 7.52–7.48 (m, 1H, H_{Naphth}), 7.46–7.41 (m, 2H, H_{Naphth}, H-5), 7.34 (pseudo-t, J_{app} ≈ 8 Hz, 2H, H-3'',5''), 7.17–7.10 (m, 2H, H-4'', H-3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 135.7 (C1''), 133.4 (C_{Naphth}), 132.2 (C2), 131.5 (C_{Naphth}), 130.2 (C2'), 128.6 (2C, C3'',5''), 128.2 (C4'), 127.6 (*C*H_{Naphth}), 127.5 (*C*H_{Naphth}), 126.5 (*C*H_{Naphth}), 125.2 (CH), 125.1 (*C*H), 124.9 (C4), 124.4 (2C, C2'',6''), 123.1 (C3'), 120.5 (C1'), 117.2 (C5), 104.1 (C3) ppm.

HRMS (ESI-TOF): Calcd for $[C_{20}H_{15}N + H]^+$ 270.1283, found 270.1273.

2-Methyl-4-phenyl-1*H*-pyrrole (**123c**)



The title compound was prepared according to the general procedure-X described above from **118c** (92 mg, 0.50 mmol). The product was purified by column chromatography (ethyl acetate/cyclohexane 1:4).

Yield: 34 mg (0.21 mmol, 43%), yellow oil.

R_f = 0.26 (ethyl acetate/cyclohexane 1:4).

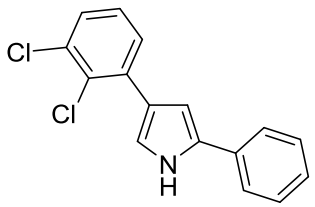
IR (ATR) $\tilde{\nu}$ = 3412, 3370, 3027, 2923, 1603, 1529, 1449, 1123, 795, 762, 697 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 10.64 (br s, 1H, N*H*), 7.49–7.44 (m, 2H, H-2',6'), 7.28–7.23 (m, 2H, H-3',5'), 7.08–7.03 (m, 1H, H-4'), 7.02 (dd, J = 2.8, 1.8 Hz, 1H, H-5), 6.12–6.10 (m, 1H, H-3), 2.19 (d, ^4J = 1.0 Hz, 3H, CH_3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 136.5 (C1'), 128.5 (2C, C3',5'), 128.1 (C2), 124.5 (C4'), 124.2 (2C, C2',6'), 123.2 (C4), 113.3 (C5), 103.3 (C3), 12.8 (*C*H_3) ppm.

HRMS (ESI-TOF): Calcd for $[C_{11}H_{12}N + H]^+$ 158.0970, found 158.0956.

4-(2,3-Dichlorophenyl)-2-phenyl-1*H*-pyrrole (**123e**)



The title compound was prepared according to the general procedure-X described above from **118e** (172 mg, 0.55 mmol). The product was purified by column chromatography (ethyl acetate/cyclohexane 1:4).

Yield: 104 mg (0.36 mmol, 66%), colorless solid.

Mp: 122–123 °C.

R_f = 0.40 (ethyl acetate/cyclohexane 1:4).

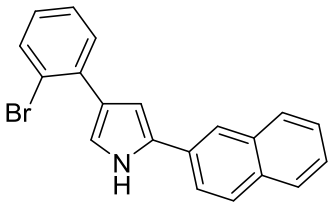
IR (ATR) $\tilde{\nu}$ = 3431, 3096, 3058, 1605, 1584, 1482, 1455, 1413, 1121, 1036, 814, 774, 756, 729, 692 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.65 (br s, 1H, N*H*), 7.71–7.66 (m, 2H, H-2',6'), 7.58 (dd, *J* = 7.8, 1.6 Hz, 1H, H-6''), 7.47 (dd, *J* = 8.0, 1.6 Hz, 1H, H-4''), 7.41–7.31 (m, 4H, H-3',5', H-5, H-5'), 7.20 (pseudo-tt, $J_{app} \approx 7$, 2 Hz, 1H, H-4'), 6.93 (dd, *J* = 2.6, 1.8 Hz, 1H, H-3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 136.9 (C1''), 132.6 (C3''), 132.3 (C1'), 131.5 (C2), 128.8 (2C, C3',5'), 128.7 (C6''), 128.4 (C2''), 128.0 (C5''), 127.4 (C4''), 126.0 (C4'), 123.6 (2C, C2',6'), 121.5 (C4), 120.0 (C5), 106.3 (C3) ppm.

HRMS (ESI-TOF): Calcd for $[C_{16}H_{11}NCl_2 + H]^+$ 288.0347, found 288.0354.

4-(2-Bromophenyl)-2-(naphthalen-2-yl)-1*H*-pyrrole (**123f**)



The title compound was prepared according to the general procedure-X described above from **118f** (329 mg, 0.88 mmol). The product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 87 mg (0.25 mmol, 28%), colorless solid.

Mp: 121–122 °C.

R_f = 0.33 (ethyl acetate/cyclohexane 1:5).

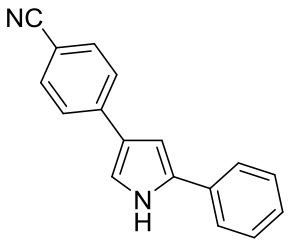
IR (ATR) $\tilde{\nu}$ = 3432, 3054, 1603, 1508, 1466, 1418, 1267, 1122, 855, 810, 749 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.75 (br s, 1H, N*H*), 8.17 (s, 1H, H-1'), 7.94–7.84 (m, 4H, 4 H_{Naphth}), 7.67 (dd, *J* = 8.0, 1.2 Hz, 1H, H-3''), 7.59 (dd, *J* = 7.8, 1.7 Hz, 1H, H-6''), 7.54–7.47 (m, 1H, H_{Naphth}), 7.47–7.36 (m, 2H, H_{Naphth}, H-5''), 7.34 (dd, *J* = 2.9, 1.7 Hz, 1H, H-5), 7.15 (ddd, *J* = 8.9, 8.0, 1.7 Hz, 1H, H-4''), 7.04 (dd, *J* = 2.8, 1.7 Hz, 1H, H-3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 136.4 (C1’’), 133.47 (C3’’), 133.45, 131.5, 131.2 (C2), 130.7 (C6’’), 130.0, 128.3, 127.8, 127.7, 127.5, 127.4, 126.5, 125.3, 123.5 (C4), 123.1, 121.1 (C2’’), 120.6 (C1’), 119.8 (C5), 107.2 (C3) ppm.

HRMS (ESI-TOF): Calcd for $[C_{20}H_{14}NBr + H]^+$ 348.0388, found 348.0398.

4-(5-Phenyl-1*H*-pyrrol-3-yl)benzonitrile (**123g**)



The title compound was prepared according to the general procedure-X described above from **118g** (282 mg, 1.04 mmol). The product was purified by column chromatography (ethyl acetate/cyclohexane 1:6).

Yield: 81 mg (0.33 mmol, 32%), pale yellow solid.

Mp: 205–207 °C.

R_f = 0.29 (ethyl acetate/cyclohexane 1:6).

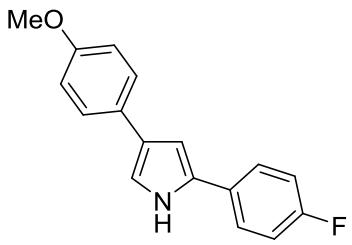
IR (ATR) $\tilde{\nu}$ = 3353, 3052, 2223, 1602, 1492, 1149, 926, 848, 809, 776, 753, 695 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.70 (br s, 1H, NH), 7.86–7.79 (AA’ part of AA’BB’ system, 2H, H-3,5), 7.77–7.73 (BB’ part of AA’BB’ system, 2H, H-2,6), 7.71–7.68 (m, 1H, H-2’’,6’’), 7.59 (dd, J = 2.8, 1.8 Hz, 1H, H-2’), 7.39 (pseudo-t, J_{app} ≈ 8 Hz, 2H, H-3’,5’), 7.23–7.18 (m, 1H, H-4’’), 7.09 (dd, J = 2.4, 1.8 Hz, 1H, H-4’) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 140.6 (C4), 133.0 (C5’), 132.6 (2C, C2,6), 132.3 (C1’’), 128.8 (2C, C3’’,5’’), 126.1 (C4’’), 124.8 (2C, C3,5), 123.6 (2C, C2’’,6’’), 123.1 (C3’), 119.5 (*C*N), 118.9 (C2’), 106.7 (C1), 103.5 (C4’) ppm.

HRMS (ESI-TOF): Calcd for $[C_{17}H_{12}N_2 + H]^+$ 245.1079, found 245.1078.

2-(4-Fluorophenyl)-4-(4-methoxyphenyl)-1*H*-pyrrole (**123h**)



The title compound was prepared according to the general procedure-X described above from **118h** (223 mg, 0.76 mmol). The product was purified by column chromatography (ethyl acetate/cyclohexane 1:8).

Yield: 123 mg (0.46 mmol, 61%), colorless solid.

Mp: 138–139 °C.

R_f = 0.11 (ethyl acetate/cyclohexane 1:8).

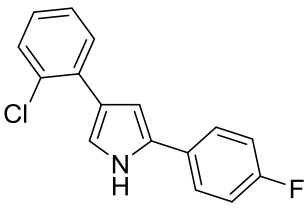
IR (ATR) $\tilde{\nu}$ = 3443, 3427, 3008, 2960, 2840, 1572, 1505, 1439, 1246, 1036, 835, 798 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.32 (br s, 1H, N*H*), 7.71–7.66 (m, 2H, H-2',6'), 7.53–7.49 (AA' part of AA'BB' system, 2H, H-2'',6''), 7.24–7.17 (m, 3H, H-3',5', H-5), 6.91–6.88 (BB' part of AA'BB' system, 2H, H-3'',5''), 6.84 (dd, *J* = 2.7, 1.7 Hz, 1H, H-3), 3.75 (s, 3H, CH_3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 160.4 (d, $^1J_{C,F}$ = 242.4 Hz, C4'), 157.1 (C4''), 131.1 (C2), 129.5 (d, $^4J_{C,F}$ = 2.9 Hz, C1'), 128.4 (C1''), 125.5 (2C, C2'',6''), 125.2 (d, $^3J_{C,F}$ = 7.8 Hz, 2C, C2',6'), 124.6 (C4), 115.6 (C5, overlapped with the doublet of C3',5'), 115.5 (d, $^2J_{C,F}$ = 21.8 Hz, 2C, C3',5'), 114.0 (2C, C3'',5''), 103.0 (C3), 55.0 (CH_3) ppm.

HRMS (ESI-TOF): Calcd for $[C_{17}H_{14}NOF + H]^+$ 268.1138, found 268.1129.

4-(2-Chlorophenyl)-2-(4-fluorophenyl)-1*H*-pyrrole (**123i**)



The title compound was prepared according to the general procedure-X described above from **118i** (224 mg, 0.75 mmol). The product was purified by column chromatography (ethyl acetate/cyclohexane 1:6).

Yield: 78 mg (0.29 mmol, 38%), colorless solid.

Mp: 124–126 °C.

R_f = 0.24 (ethyl acetate/cyclohexane 1:6).

IR (ATR) $\tilde{\nu}$ = 3434, 3267, 3065, 1661, 1492, 1230, 1097, 930, 835, 810, 753 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.58 (br s, 1H, N*H*), 7.74–7.68 (m, 2H, H-2',6'), 7.61 (dd, *J* = 7.8, 1.7 Hz, 1H, H-6''), 7.46 (dd, *J* = 8.0, 1.3 Hz, 1H, H-3''), 7.36–7.30 (m, 2H, H-5'', H-5), 7.26–7.17 (m, 3H, H-3',5', H-4''), 6.90 (dd, *J* = 2.6, 1.8 Hz, 1H, H-3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 160.6 (d, $^1J_{C,F}$ = 242.5 Hz, C4'), 134.2 (C1''), 130.5 (C2), 130.3 (C2''), 130.2 (C3''), 130.0 (C6''), 129.2 (d, $^4J_{C,F}$ = 3.1 Hz, C1'), 127.3 (C5''), 126.8 (C4''), 125.4 (d, $^3J_{C,F}$ = 7.9 Hz, 2C, C2',6'), 121.7 (C4), 119.5 (C5), 115.6 (d, $^2J_{C,F}$ = 21.5 Hz, 2C, C3',5'), 106.0 (C3) ppm.

HRMS (ESI-TOF): Calcd for $[C_{16}H_{11}NFCl + H]^+$ 272.0642, found 272.0634.

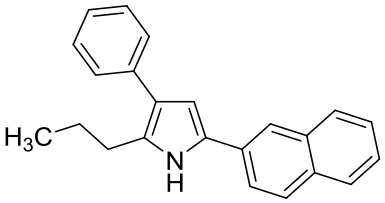
5.4.3 Synthesis of 2,3,5-Trisubstituted Pyrroles

General procedure-XI for 2,3,5-trisubstituted pyrroles 127

2,3,5-Trisubstituted pyrroles were prepared from cyanopyrrolines in two steps. **Alkylation**: To a solution of corresponding cyanopyrroline in DMF (0.25 M) was added KO*t*Bu (1.10–2.00 equiv) under argon atmosphere at 0 °C. After stirring 2 min, the alkyl halide (1.10–2.00 equiv) was added. The reaction mixture was stirred for 1h at 0 °C and then, the ice-bath was removed and it was stirred for another 1h. The mixture was quenched with H_2O, and the crude product was extracted with ethyl acetate (3×30 mL). The organic layers were combined and dried over $MgSO_4$. After the filtration, all volatiles were evaporated in vacuo to obtain 2-alkyl-3,5-diaryl-3,4-dihydro-2*H*-pyrrole-2-carbonitrile **126** which was used without further purification in the following step. **Dehydrocyanation**: The crude product was transferred into a 10 mL microwave vessel. After sealing it, the reaction mixture was heated to 140 °C at 150 W for 15 min. The crude product was then purified by a column chromatography (Method A). As an alternate method, the crude product was dissolved in DMF and transferred into a 10 mL microwave vessel. KO*t*Bu (1.10 equiv) was added to the vessel and the reaction mixture was heated to 100 °C at 150 W for 15 min. It was quenched with H_2O, and the crude product was extracted with ethyl acetate (3×10 mL). The organic

layers were combined and dried over $MgSO_4$. After the filtration, all volatiles were evaporated in vacuo. The product was isolated by a chromatographic separation (Method B).

5-(Naphthalen-2-yl)-3-phenyl-2-propyl-1*H*-pyrrole (127a)



The title compound was prepared according to the general procedure-XI described from cyanopyrroline **118b** (148 mg, 0.50 mmol), KO*t*Bu (62 mg, 0.55 mmol, 1.10 equiv), and propyl bromide (55 µL, 0.60 mmol, 1.20 equiv). Dehydrocyanation was performed as described in method A. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:10).

Yield: 90 mg (0.29 mmol, 58%), brown oil.

$\boldsymbol{R_f}$ = 0.57 (ethyl acetate/cyclohexane, 1:5).

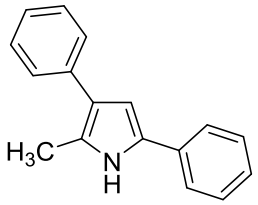
IR (ATR) $\tilde{\nu}$ = 3431, 3054, 3026, 2958, 2929, 2869, 1628, 1604, 1490, 1444, 1146, 805, 763, 699 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.23 (d, *J* = 2.8 Hz, 1H, N*H*), 8.13 (s, 1H, H-1’’), 7.91–7.78 (m, 4H,H_{Naphth}), 7.53–7.44 (m, 1H, H_{Naphth}), 7.47–7.41 (m, 3H, H_{Naphth}, H-2’,6’), 7.40–7.33 (m, 2H, H-3’,5’), 7.20 (m, 1H, H-4’), 6.81 (d, *J* = 2.8 Hz, 1H, H-4), 2.75 (t, *J* = 7.4 Hz, 2H, CH_2), 1.69 (sept, 2H, *J* = 7.4 Hz, C$H_2$$CH_3$), 0.94 (t, *J* = 7.4 Hz, 3H, CH_3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 137.0 (C1’), 133.5(C_{Naphth}), 131.3 (C2), 131.26 (C_{Naphth}) 130.2 (C_{Naphth}), 129.5 (C5), 128.5 (2C, C3’,5’), 128.1 (C_{Naphth}), 127.6 (C_{Naphth}), 127.3 (C_{Naphth}), 127.0 (2C, C2’,6’) 126.4 (C_{Naphth}), 125.0 (C4’), 124.9 (C_{Naphth}), 123.1 (C_{Naphth}), 121.6 (C3), 119.8 (C1’’), 106.6 (C4), 28.3 (*C*H_2), 23.3 (*C*$H_2$$CH_3$), 13.9 (*C*$H_3$) ppm.

HRMS (ESI-TOF): Calcd for $[C_{23}H_{22}N+H]^+$ 312.1752, found 312.1759.

2-Methyl-3,5-diphenyl-1*H*-pyrrole (127b)



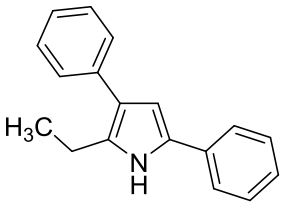
The title compound was prepared according to the general procedure-XI described from cyanopyrroline **118a** (241 mg, 0.98 mmol), KO*t*Bu (127 mg, 1.12 mmol, 1.12 equiv), and iodomethane (67 µL, 1.08 mmol, 1.10 equiv). Dehydrocyanation was performed using KO*t*Bu (130 mg, 1.16 mmol, 1.18 equiv) in DMF (2.0 mL) as described in method B. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5).

Yield: 69 mg (0.30 mmol, 31%), brown oil.

R_f = 0.46 (ethyl acetate/cyclohexane, 1:5).

^{1}H NMR (400 MHz, DMSO-d_6) δ = 11.04 (d, *J* = 2.8 Hz, 1H, N*H*), 7.67–7.64 (m, 2H, H-2'',6''), 7.42–7.39 (m, 2H, H-2',6'), 7.38–7.35 (m, 2H, H-3',5'), 7.35–7.32 (m, 2H, H-3'',5''), 7.20–7.15 (m, 1H, H-4'), 7.15–7.11 (m, 1H, H-4''), 6.64 (d, *J* = 2.8 Hz, 1H, H-4), 2.74–2.69 (m, 2H, CH_2), 1.65 (h, *J* = 7.3 Hz, 2H, CH_2CH$_3$), 0.92 (t, *J* = 7.3 Hz, 3H, CH_3) ppm. The data is in accordance with the literature.[138]

2-Ethyl-3,5-diphenyl-1*H*-pyrrole (127c)



The title compound was prepared according to the general procedure-XI described from cyanopyrroline **118a** (184 mg, 0.75 mmol), KO*t*Bu (168 mg, 1.50 mmol, 2.00 equiv), and ethyl bromide (0.11 mL, 1.50 mmol, 2.00 equiv). Dehydrocyanation was performed as described in method A. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:5)

Yield: 23 mg (0.09 mmol, 12%), brown oil.

R_f = 0.58 (ethyl acetate/cyclohexane, 1:5).

IR (ATR) $\tilde{\nu}$ = 3426, 3058, 3028, 2966, 2928, 2871, 2855, 1712, 1523, 1450, 756, 696 cm^{-1}.

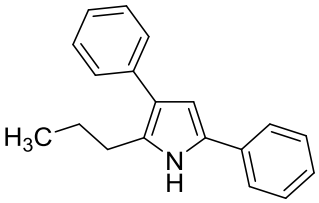
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.06 (br s, 1H, N*H*), 7.67–7.64 (m, 2H, H-2'',6''), 7.42–7.39 (m, 2H, H-2',6'), 7.38–7.36 (m, 2H, H-3',5'), 7.35–7.32 (m, 2H, H-

3’’,5’’), 7.20–7.16 (m, 1H, H-4’), 7.16–7.11 (m, 1H, H-4’’), 6.64 (d, *J* = 2.8 Hz, 1H, H-4), 2.76 (q, *J* = 7.5 Hz, 2H, C*H*$_2$), 1.25 (t, *J* = 7.5 Hz, 3H, C*H*$_3$) ppm.

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ = 136.9 (C1’), 132.8 (C1’’), 132.1 (C2), 129.5 (C5), 128.6 (2C, C3’’,5’’), 128.4 (2C, C3’,5’), 127.0 (2C, C2’,6’), 125.3 (C4’’), 124.9 (C4’), 123.2 (2C, C2’’,6’’), 120.9 (C3), 105.5 (C4), 19.4 (*C*H$_2$), 15.1 (*C*H$_3$) ppm.

HRMS (ESI-TOF): Calcd for [C$_{18}$H$_{17}$N+H]$^+$ 248.1439, found 248.1444.

3,5-Diphenyl-2-propyl-1*H*-pyrrole (127d)



The title compound was prepared according to the general procedure-XI described from cyanopyrroline **118a** (246 mg, 1.00 mmol), KO*t*Bu (133 mg, 1.20 mmol, 1.20 equiv), and propyl bromide (0.10 mL, 1.10 mmol, 1.10 equiv). Dehydrocyanation was performed using KO*t*Bu (123 mg, 1.10 mmol, 1.10 equiv) in DMF (2.0 mL) as described in method B. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:4)

Yield: 98 mg (0.37 mmol, 37%), brown oil.

***R*$_f$** = 0.61 (ethyl acetate/cyclohexane, 1:4).

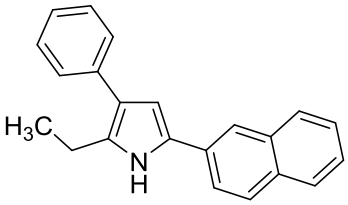
IR (ATR) $\tilde{\nu}$ = 3427, 3057, 3026, 2967, 2928, 2869, 1604, 1493, 1450, 753, 692 cm^{-1}

^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ = 11.04 (d, *J* = 2.8 Hz, 1H, N*H*), 7.67–7.64 (m, 2H, H-2’’,6’’), 7.42–7.39 (m, 2H, H-2’,6’), 7.38–7.35 (m, 2H, H-3’,5’), 7.35–7.32 (m, 2H, H-3’’,5’’), 7.20–7.15 (m, 1H, H-4’), 7.15–7.11 (m, 1H, H-4’’), 6.64 (d, *J* = 2.8 Hz, 1H, H-4), 2.74–2.69 (m, 2H, C*H*$_2$), 1.65 (h, *J* = 7.3 Hz, 2H, C*H*$_2$CH$_3$), 0.92 (t, *J* = 7.3 Hz, 3H, C*H*$_3$) ppm.

^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ = 137.0 (C1’), 132,8 (C1’’), 130.7 (C2), 129.5 (C5), 128.6 (2C, C3’’,5’’), 128.4 (2C, C3’,5’), 127.0 (2C, C2’,6’), 125.2 (C4’’), 124.9 (C4’), 123.2 (2C, C2’’,6’’), 121.3 (C3), 105.6 (C4), 28.2 (*C*H$_2$), 23.3 (*C*H$_2$CH$_3$), 13.9 (*C*H$_3$) ppm.

HRMS (ESI-TOF): Calcd for [C$_{19}$H$_{18}$N+H]$^+$ 262.1596, found 262.1585.

2-Ethyl-5-(naphthalen-2-yl)-3-phenyl-1*H*-pyrrole (127e)



The title compound was prepared according to the general procedure-XI described from cyanopyrroline **118b** (218 mg, 0.73 mmol), KO*t*Bu (100 mg, 0.89 mmol, 1.20 equiv), and ethyl bromide (58 µL, 0.80 mmol, 1.10 equiv). Dehydrocyanation was performed as described in method A. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:10).

Yield: 48 mg (0.16 mmol, 22%), yellow oil.

R_f = 0.57 (ethyl acetate/cyclohexane, 1:5).

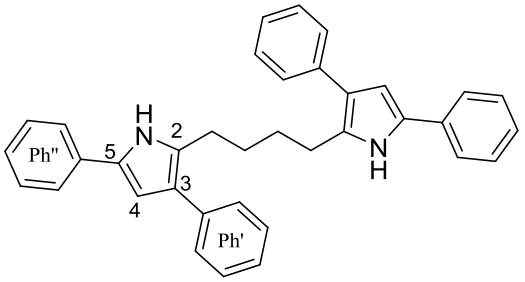
IR (ATR) $\tilde{\nu}$ = 3428, 3054, 3026, 2967, 2929, 2871, 1627, 1446, 805, 762, 699 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.26 (d, *J* = 2.8 Hz, 1H, N*H*)) 8.13 (s, 1H, H-1’’), 7.88–7.81 (m, 4H, H_{Naphth}), 7.51–7.46 (m, 1H, H_{Naphth}), 7.45–7.40 (m, 3H, H_{Naphth}, H-2’,6’), 7.40–7.36 (m, 2H, H-3’,5’), 7.20 (m, 1H, H-4’), 6.81 (d, *J* = 2.8 Hz, 1H, H-4), 2.79 (q, *J* = 7.4 Hz, 2H, CH_2), 1.28 (t, *J* = 7.4 Hz, 3H, CH_3)ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 136.9 (C1’), 133.5(C_{Naphth}), 132.7 (C2), 131.3 (C_{Naphth}), 130.2 (C_{Naphth}), 129.5 (C5),, 128.5 (2C, C3’,5’), 128.1 (C_{Naphth}), 127.6 (C_{Naphth}), 127.0 (2C, C2’,6’), 126.4 (C_{Naphth}), 125.0 (C4’, 124.9 (C_{Naphth}), 123.1 (C_{Naphth}), 121.2 (C3), 119.8 (C1’’), 106.5 (C4), 19.5 (*C*H_2) 15.0 (*C*H_3) ppm.

HRMS (ESI-TOF): Calcd for $[C_{22}H_{20}N+H]^+$ 298.1596, found 298.1593.

1,4-Bis(3,5-diphenyl-1*H*-pyrrol-2-yl)butane (129)



The title compound was prepared according to the general procedure-XI described from cyanopyrroline **118a** (248 mg, 1.01 mmol, 2.00 equiv), KO*t*Bu (136 mg, 1.21 mmol, 2.40 equiv), and 1,4-dibromobutane (118 mg, 0.55 mmol, 1.09 equiv). Dehydrocyanation was performed using KO*t*Bu (123 mg,

1.10 mmol, 2.18 equiv) in DMF (2.0 mL) as described in method B. The crude product was purified by column chromatography (ethyl acetate/cyclohexane 1:10)

Yield: 63 mg (0.13 mmol, 25%), light yellow solid.

Mp: 199–201 °C.

R_f = 0.46 (ethyl acetate/cyclohexane, 1:5).

IR (ATR) $\tilde{\nu}$ = 3410, 3057, 3026, 2929, 2854, 1604, 1494, 755, 694 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.05 (d, *J* = 2.8 Hz, 2H, N*H*), 7,66–7.62 (m, 4H, H-2'',6''), 7.40–7.31 (m, 12H, H-2',6', H-3',5', H-3'',5''), 7.19–7.09 (m, 4H, H-4', H-4''), 2.76 (t, *J* = 6.8 Hz, 4H, 2-CH_2) 1.74–1.68 (m, 4H, 2-CH_2CH_2) ppm.

^{13}C NMR, HSQC; HMBC (101 MHz, DMSO-d_6) δ = 137.0 (2C, C1'), 132.7 (2C, C1''), 130.7 (2C, C2) 129.5 (2C, C5), 128.6 (4C, C3'',5''), 128.4 (4C, C3',5'), 126.9 (4C, C2',6'), 125.2 (2C, C4''), 124.9 (2C, C4'), 123.2 (4C, C2'',6''), 121.2 (2C, C3), 105.7 (2C, C4), 30.1 (2C, 2-CH_2CH_2) 26.1 (2C, 2-CH_2) ppm.

HRMS (ESI-TOF): Calcd for $[C_{36}H_{33}N_2+H]^+$ 493.2644, found 493.2638.

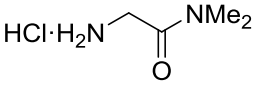
5.4.4 Synthesis of Pyrrole-2-carboxamides

General procedure-XII for glycine amides 135

Glycine amides were prepared in two steps according to the literature.[189] **Amidation**: To a solution of Boc-Gly-OH in THF (0.5 M) were added *N*-methyl morpholine (1.00 equiv) and isobutyl chloroformate (IBCF, 1.00 equiv) at –20 °C. The reaction was stirred for 5 min before adding the solution of amine (1.30– 5.00 equiv) in THF (5-10 mL). The reaction was stirred for 1h at the same temperature. It was then quenched with saturated $NaHCO_3$ solution for 30 min. The compound was extracted with dichloromethane (3×50 mL). The combined organic layer was then washed with saturated $NaHCO_3$ solution (2×20 mL) and dried over $MgSO_4$. After filtration and evaporation of all volatiles in vacuo gave *N*-alkyl Boc protected glycine amides (Boc-Gly-NR'R''). **Deprotection**: A portion of Boc-Gly-NR'R'' was added to a solution of HCl–MeOH which was also prepared by reacting acetyl chloride and MeOH. The reaction was stirred for 1 h at ambient temperature. All volatiles were then removed in

vacuo. The residue (oil or solid) was stirred in Et_2O for 1h. The pure product was obtained by filtration and washing with Et_2O.

2-Amino-*N*,*N*-dimethylacetamide (135a)



The title compound was prepared according to the general procedure-XII described above from Boc-Gly-OH (3.50 g, 20 mmol) and dimethylamine solution (14 mL, 5.6 M in EtOH). Boc-Gly-NMe_2 (**134a**, 3.58 g, 17.7 mmol) was isolated in 89% yield. From **134a**(3.03 g, 15.0 mmol), acetyl chloride (2.6 mL) and MeOH (40 mL), glycine amide **135a** (2.07 g, 14.9 mmol) was obtained in 99% yield.

Yield: 88% (over two steps), colorless solid.

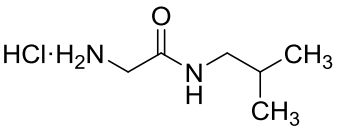
IR (ATR) $\tilde{\nu}$ = 3392, 2927, 2705, 1654, 1506, 1440, 1422, 1358, 1261, 1171, 1125, 914, 782, 730 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.23 (br s, 3H, NH_3Cl), 3.79 (q, J = 5.7 Hz, 2H, H-2), 2.93 (s, 3H, NCH_3), 2.87 (s, 3H, NCH_3) ppm.

^{13}C NMR, HSQC (101 MHz, DMSO-d_6): 165. 8 (C1), 39.3 (C2), 35.7 (NCH$_3$), 35.0 (NCH$_3$) ppm.

HRMS (ESI-TOF): Calcd for $[C_4H_{11}N_2O]^+$ 103.0871, found 103.0904.

2-Amino-*N*-isobutylacetamide (135b)



The title compound was prepared according to the general procedure-XII described above from Boc-Gly-OH (3.50 g, 20 mmol). Boc-Gly-NH*i*Bu (**134b**, 4.15 g, 18.0 mmol) was isolated in 90% yield. From **134b** (4.14 g, 18.0 mmol), acetyl chloride (2.6 mL) and MeOH (40 mL), glycine amide **135b** (2.97 g, 17.8 mmol) was obtained in 99% yield.

Yield: 89% (over two steps), colorless solid.

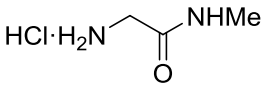
IR (ATR) $\tilde{\nu}$ = 34061, 3287, 3200, 3070, 2957, 2870, 1667, 1601, 1563, 1467, 1264, 1079, 904 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6) δ = 8.53 (t, J = 5.8 Hz, 1H, N*H*CO), 8.23 (br s, 3H, NH_3Cl), 3.53 (s, 2H, H-2), 2.94 (dd, J = 6.8, 5.8 Hz, 2H, H-1'), 1.69 (sept, J = 6.8 Hz, 1H, H-2'), 0.85 (d, J = 6.7 Hz, 6H, (CH_3)$_2$CH) ppm.

^{13}C NMR, HSQC (101 MHz, DMSO-d_6): 165. 7 (C1), 46.1 (C1'), 40.0 (C2), 28.0 (C2'), 20.1 (2C, *C*H$_3$)$_2$CH) ppm.

HRMS (ESI-TOF): Calcd for $[C_6H_{15}N_2O]^+$ 131.1184, found 131.1200.

2-Amino-*N*-methylacetamide (135c)



The title compound was prepared according to the general procedure-XII described above from Boc-Gly-OH (1.75 g, 10.0 mmol) and aqueous methylamine solution (1.7 mL, 40 wt%, 50.0 mmol). Boc-Gly-NHMe (**134c**, 1.39 g, 7.3 mmol) was isolated in 74% yield. From **134c** (1.38 g, 7.3 mmol) HCl–EtOH (20 mL, 1.25 M), glycine amide **135c** (890 mg, 7.1 mmol) was obtained in 97% yield.

Yield: 72% (over two steps), colorless solid.

Mp: 155–156 °C (lit. 154–156 °C).[208]

IR (ATR) $\tilde{\nu}$ = 3310, 3064, 2956, 2866, 1657, 1575, 1454, 1421, 1411, 1319, 1270, 1169, 1116, 1070, 885 cm^{-1}.

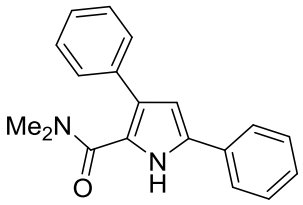
^{1}H NMR (300 MHz, DMSO-d_6) δ = 8.57 (br s, 1H, N*H*Me), 8.20 (br s, 3H, NH_3Cl), 3.49 (s, 2H, H-2), 2.64 (d, J = 4.6 Hz, 3H, CH_3) ppm.

General procedure-XIII for pyrroles-2-carboxamides 136

A 10 mL microwave vessel was charged with the corresponding enone (1.00 mmol, 1.00 equiv), amide (1.20 mmol, 1.20 equiv), and pyridine (4 mL). The vessel was sealed after adding molecular sieves 3 Å (100 mg) and a stir bar. Then, the reaction mixture was irradiated until temperature reaches to 130 °C for 60 min at 200 W in a microwave reactor. The reaction was heated until complete conversion of the enone was determined, as indicated

by TLC or HPLC-MS, 1–2 h). $Cu(OAc)_2$ (1.20 mmol, 218 mg, 1.20 equiv or 2.00 mmol, 363 mg, 2.00 equiv) was introduced in one portion and the mixture was heated using the same microwave settings until complete conversion of the dihydropyrrole was determined (1–2 h), as indicated by TLC or HPLC-MS. Upon completion, the solvent was removed by azeotropic distillation with toluene. The residue was dissolved in dichloromethane (60 mL) and subsequently washed with a 0.1M Na_2-EDTA solution (3 x 30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4 and filtered. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel.

***N*,*N*-Dimethyl-3,5-diphenyl-1*H*-pyrrole-2-carboxamide (136a)**



The general procedure-XIII was applied using enone **110a**, 2-amino-*N*,*N*-dimethylacetamide hydrochloride (**135a**) and $Cu(OAc)_2$ (1.20 mmol, 218 mg, 1.20 equiv). After cyclization (2 h) and oxidation (2 h), purification of crude reaction mixture by flash column chromatography (ethyl acetate/cyclohexane 1:3).

Yield: 133 mg (0.46 mmol, 46%), colorless solid.

Mp: 155–156 °C.

R_f = 0.16 (silica gel, ethyl acetate/cyclohexane 1:3).

IR (ATR) $\tilde{\nu}$ = 3145, 3062, 3025, 2929, 1650, 1595, 1491, 1274, 760, 696 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.78 (d, *J* = 2.8 Hz, 1H, N*H*), 7.80–7.73 (m, 2H, H-2’’,6’’), 7.43–7.32 (m, 6H, H-2’,6’, H-3’,5’, H-3’’,5’’), 7.27–7.17 (m, 2H, H-4’, H-4’’), 6.84 (d, *J* = 2.8 Hz, 1H, H-4), 2.95 (s, 3H, CH_3), 2.64 (s, 3H, CH_3) ppm.

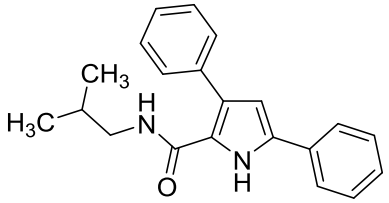
^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 164.4 (*C*=O), 135.4 (C1’), 132.3 (C5), 131.9 (C1’’), 128.7 (2C, C_{Ph}), 128.6 (2C, C_{Ph}), 126.43 (2C, C_{Ph}), 126.36 (C4’’), 126.0 (C4’), 124.2 (C3), 124.0 (2C, C2’’,6’’), 123.3 (C2), 105.3 (C4), 37.7 (*C*H_3), 34.4 (*C*H_3) ppm.

HRMS (ESI-TOF): Calcd for $[C_{19}H_{18}N_2O + H]^+$ 291.1497, found 291.1503.

The general procedure-XIII was applied using enone **110a**, **135a** and $Cu(OAc)_2$ (2.00 mmol, 363 mg, 2.00 equiv). After cyclization (2 h) and oxidation (2 h), purification of crude

reaction mixture by flash column chromatography (ethyl acetate/cyclohexane 1:3) yielded **136a** (160 mg, 55%) as a colorless solid.

N-Isobutyl-3,5-diphenyl-1*H*-pyrrole-2-carboxamide (136b)



The general procedure-XIII was applied using enone **110a**, 2-amino-*N*-isobutylacetamide hydrochloride (**135b**) and $Cu(OAc)_2$ (1.20 mmol, 218 mg, 1.20 equiv). After cyclization (1 h) and oxidation (2 h), purification of crude reaction mixture by flash column chromatography (ethyl acetate/cyclohexane 1:4).

Yield: 189 mg (0.59 mmol, 59%), colorless solid.

Mp: 143–144 °C.

$\boldsymbol{R_f}$ = 0.18 (silica gel, ethyl acetate/cyclohexane 1:4).

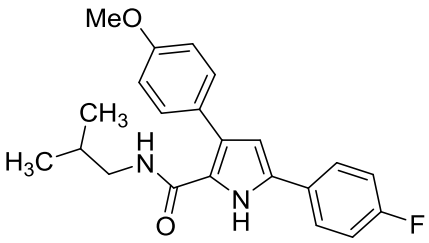
IR (ATR) $\tilde{\nu}$ = 3420, 3240, 3062, 2958, 1630, 1533, 1491, 1267, 817, 760, 701 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.60 (d, *J* = 2.8 Hz, 1H, N*H*), 7.84–7.77 (m, 2H, H-2’’,6’’), 7.54–7.47 (m, 2H, H-2’,6’), 7.45–7.32 (m, 4H, H-3’,5’, H-3’’,5’’), 7.35–7.20 (m, 3H, C(=O)N*H*, H-4’, H-4’’), 6.69 (d, *J* = 2.8 Hz, 1H, H-4), 3.02 (dd, *J* = 6.7, 5.8 Hz, 2H, CH_2), 1.69 (n, *J* = 6.7 Hz, 1H, C*H*), 0.82 (d, *J* = 6.7 Hz, 6H, CH_3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 161.1 (*C*=O), 135.7 (C1’), 132.7 (C5), 131.6 (C1’’), 128.8 (2C, C2’,6’), 128.7 (2C, C3’’,5’’), 128.1 (2C, C3’,5’), 127.3 (C3), 126.7 (C4’’), 126.4 (C4’), 124.6 (2C, C2’’,6’’), 123.6 (C2), 108.3 (C4), 46.3 (*C*H_2), 28.1 (*C*H), 20.2 (*C*H_3) ppm.

HRMS (ESI-TOF): Calcd for $[C_{21}H_{22}N_2O + H]^+$ 319.1810, found 319.1800.

5-(4-Fluorophenyl)-*N*-isobutyl-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxamide (136c)



The general procedure-XIII was applied using enone **110j**, **135b** and $Cu(OAc)_2$ (1.20 mmol, 218 mg, 1.20 equiv). After cyclization (2 h) and oxidation (1 h), purification of crude reaction mixture by flash column chromatography (ethyl acetate/cyclohexane 1:4).

Yield: 156 mg (0.43 mmol, 43%), colorless solid.

Mp: 175–176 °C (dec.).

R_f = 0.10 (silica gel, ethyl acetate/cyclohexane 1:5).

IR (ATR) $\tilde{\nu}$ = 3414, 3245, 2959, 2872, 1627, 1529, 1502, 1248, 837, 812 cm^{-1}.

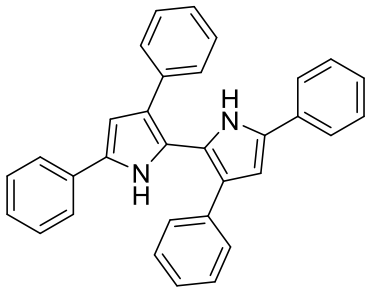
^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.53 (d, *J* = 2.8 Hz, 1H, N*H*), 7.88–7.79 (m, 2H, H-2’’,6’’), 7.47–7.38 (AA’-part of AA’BB’ system, 2H, H-2’,6’), 7.28–7.18 (m, 2H, H-3’’,5’’), 7.11 (t, *J* = 5.8 Hz, C(=O)N*H*), 6.98–6.21 (BB’-part of AA’BB’ system, 2H, H-3’,5’), 6.61 (d, *J* = 2.8 Hz, 1H, H-4), 3.77 (s, 3H, OCH_3), 3.01 (dd, *J* = 6.7, 5.8 Hz, 2H, CH_2), 1.68 (n, *J* = 6.7 Hz, 1H, C*H*), 0.81 (d, *J* = 6.7 Hz, 6H, CH_3) ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 161.13 (d, $^1J_{C,F}$ = 243.6 Hz, C4’’), 161.08 (*C*=O), 158.1 (C4’), 131.8 (C5), 130.0 (2C, C2’,6’), 128.4 (d, $^4J_{C,F}$ = 3.4 Hz, C1’’), 127.9 (C1’), 127.2 (C3), 126.6 (d, $^3J_{C,F}$ = 8.0 Hz, 2C, C2’’,6’’), 123.2 (C2), 115.5 (d, $^2J_{C,F}$ = 21.7 Hz, 2C, C3’’,5’’), 113.6 (2C, *C*3’,5’), 108.4 (C4), 55.1 (O*C*H_3), 46.2 (*C*H_2), 28.1 (*C*H), 20.2 (*C*H_3) ppm.

HRMS (ESI-TOF): Calcd for $[C_{22}H_{23}N_2O_2F + H]^+$ 367.1822, found 367.1830.

5.4.5 Synthesis of 2,2'-Bipyrroles

3,3',5,5'-Tetraphenyl-1*H*,1'*H*-2,2'-bipyrrole (137a)



A 10 mL microwave vessel was charged with cyanopyrroline **118a** (246 mg, 1.00 mmol, 2.00 equiv) and a stir bar. The solid was dissolved in DMF (4.00 mL) and $Cu(OAc)_2 \cdot H_2O$ (599 mg, 3.00 mmol, 6.00 equiv) was added to the resulting solution. The mixture was irradiated to 100 °C at 150 W for 15 min in the microwave apparatus. The solution was diluted with ethyl acetate and filtered through a pad of celite. The crude product was purified by a column chromatography (ethyl acetate/cyclohexane 1:10).

Yield: 107 mg (0.245 mmol, 49%), colorless foam.

R_f = 0.73 (silica gel, ethyl acetate/cyclohexane 1:5).

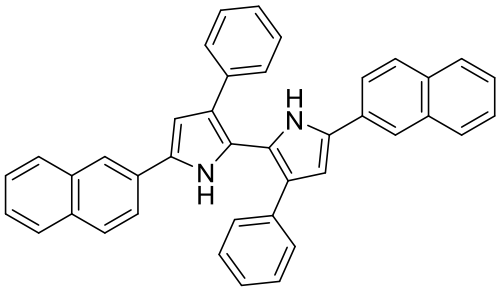
IR (ATR) $\tilde{\nu}$ = 3412, 3060, 3025, 2957, 2924, 2855, 1723, 1602, 1490, 1462, 1278, 1025, 758, 694 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.71 (d, *J* = 2.6 Hz, 2H, H-1), 7.81–7.79 (m, 4H, H-2'',6''), 7.38–7.31 (m, 8H, H-3'',5'', H-2',6'), 7.20–7.12 (m, 6H, H-4'', H-3',5'), 7.07 (d, *J* = 2.6 Hz, 2H, H-4), 7.02–6.98 (m, 2H, H-4') ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 136.1 (2C, C1'), 132.6 (2C, C1''), 131.9 (2C, C5), 128.9 (4C, C3'',5''), 128.4 (4C, C3',5'), 126.0 (2C, C4''), 125.8 (4C, C2',6'), 125.2 (2C, C4'), 124.7 (2C, C3), 123.8 (4C, C2'',6''), 121.7 (2C, C2), 105.5 (2C, C4) ppm.

HRMS (ESI-TOF): Calcd for $[C_{32}H_{24}N_2]^+$ 436.1939, found 436.1932.

5,5'-Di(naphthalen-2-yl)-3,3'-diphenyl-1*H*,1'*H*-2,2'-bipyrrole (137b)



A 10 mL microwave vessel was charged with cyanopyrroline **118b** (148 mg, 0.50 mmol, 2.00 equiv) and a stir bar. The solid was dissolved in DMF (2.00 mL) and anhydrous $Cu(OAc)_2$ (272 mg, 1.50 mmol, 6.00 equiv) was added to the resulting solution. The mixture was irradiated to 100 °C at 150 W for 15 min in the microwave apparatus. The solution was diluted with ethyl acetate and filtered through a pad of celite. The crude product was purified by a column chromatography (ethyl acetate/cyclohexane 1:6).

Yield: 42 mg (0.079 mmol, 31%), yellow foam.

R_f = 0.39 (silica gel, ethyl acetate/cyclohexane 1:6).

IR (ATR) $\tilde{\nu}$ = 3393, 3055, 2954, 2922, 1628, 1598, 1502, 1160, 799, 765 cm^{-1}.

^{1}H NMR, COSY (400 MHz, DMSO-d_6) δ = 11.91 (d, *J* = 2.5 Hz, 2H, N*H*), 8.33 (br s, 2H, H-1''), 8.02 (dd, *J* = 8.7, 1.7 Hz, 2H, H-3''), 7.92 (d, *J* = 8.7 Hz, 2H, H-4''), 7.87 (dd, *J* = 8.0, 1.3 Hz, 2H, H-5''), 7.82 (dd, *J* = 8.3, 1.2 Hz, 2H, H-8''), 7.49 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 2H, H-7''), 7.44 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 2H, H-6''), 7.40–7.37 (m, 4H, H-2',6'), 7.26 (d, *J* = 2.5 Hz, 2H, H-4), 7.18–7.14 (m, 4H, H-3',5'), 7.04–6.99 (m, 2H, H-4') ppm.

^{13}C NMR, HSQC, HMBC (101 MHz, DMSO-d_6) δ = 135.8 (2C, C1'), 133.5 (2C, C8a''), 131.8 (2C, C5), 131.5 (2C, C4a''), 129.8 (2C, C2''), 128.21 (4C, C3',5'), 128.15 (2C, C4''), 127.6 (2C, C5''), 127.5 (2C, C8''), 126.5 (2C, C7''), 125.6 (4C, C2',6'), 125.2 (2C, C6''), 125.1 (2C, C4'), 124.7 (2C, C3), 123.1 (2C, C3''), 122.0 (2C, C2), 120.8 (2C, C1''), 106.1 (2C, C4) ppm.

HRMS (ESI-TOF): Calcd for $[C_{40}H_{28}N_2 + H]^+$ 537.2331, found 537.2323.

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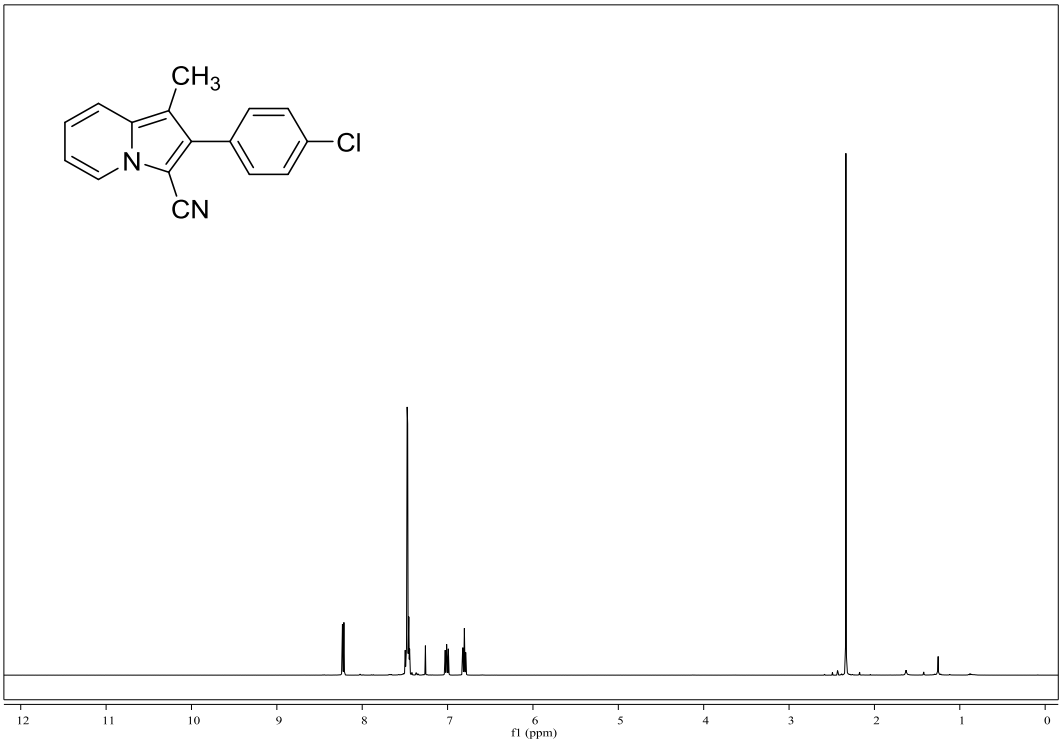
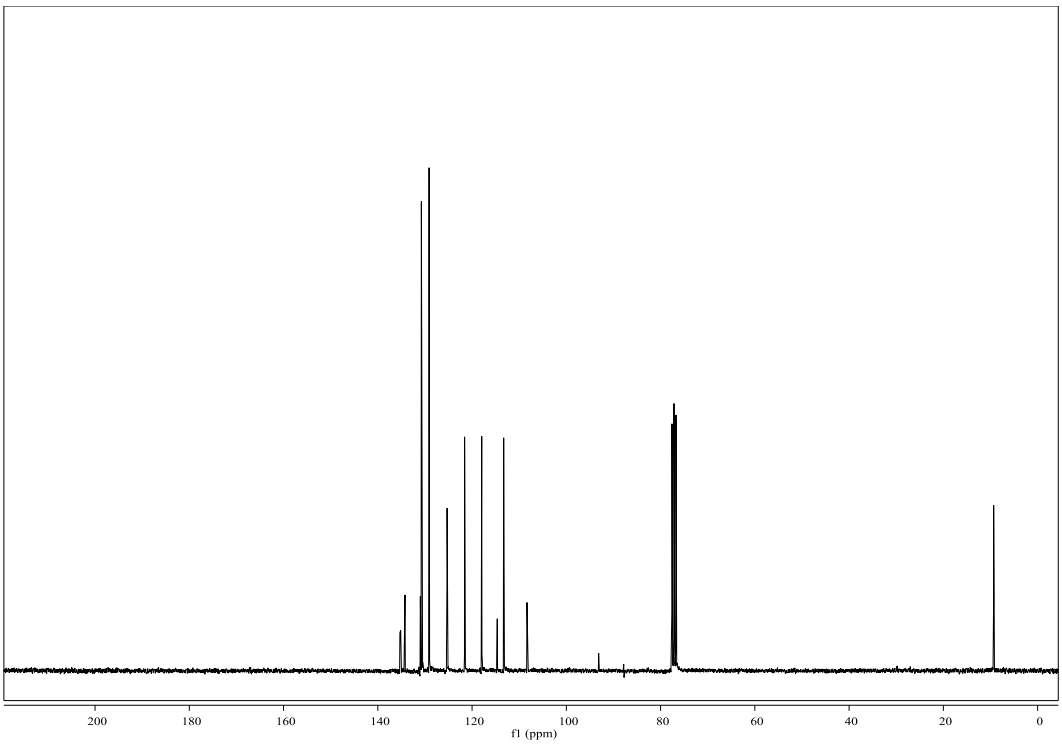
Appendix A: NMR Spectra

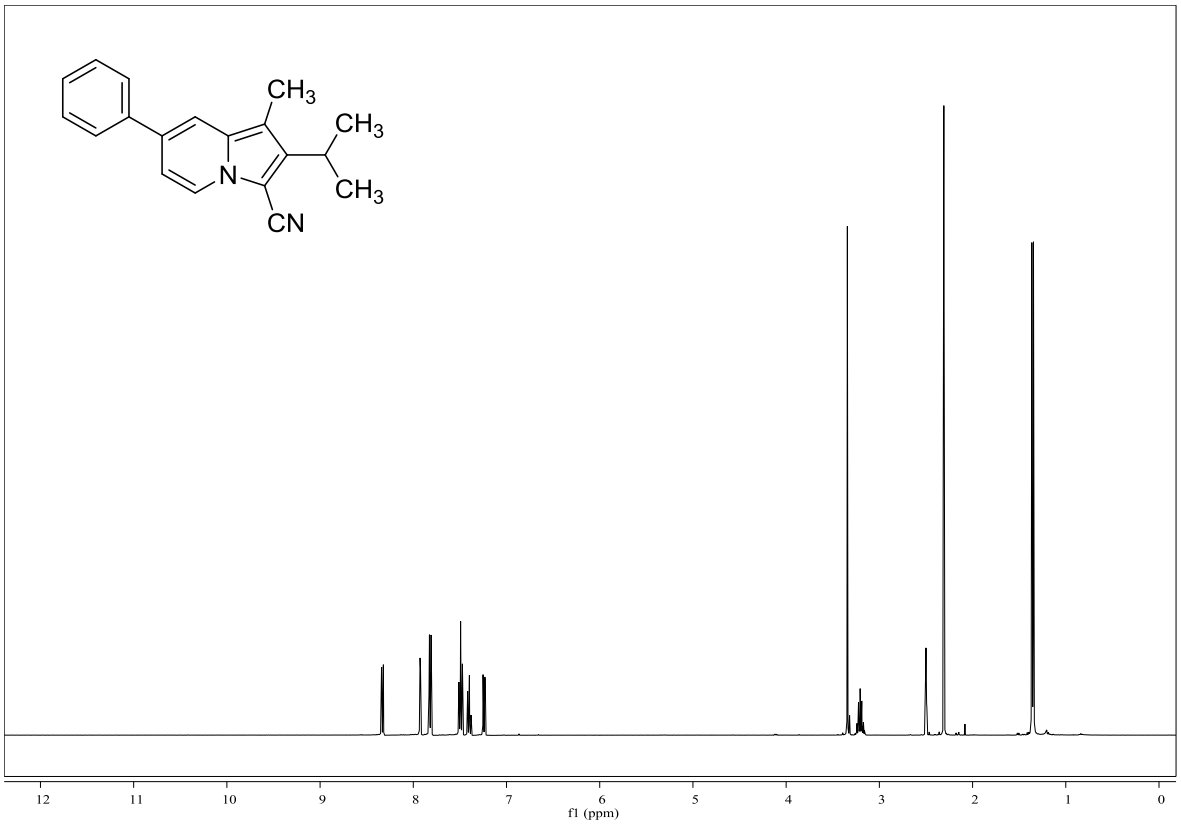
^{1}H and ^{13}C NMR spectra of arbitrarily selected compounds



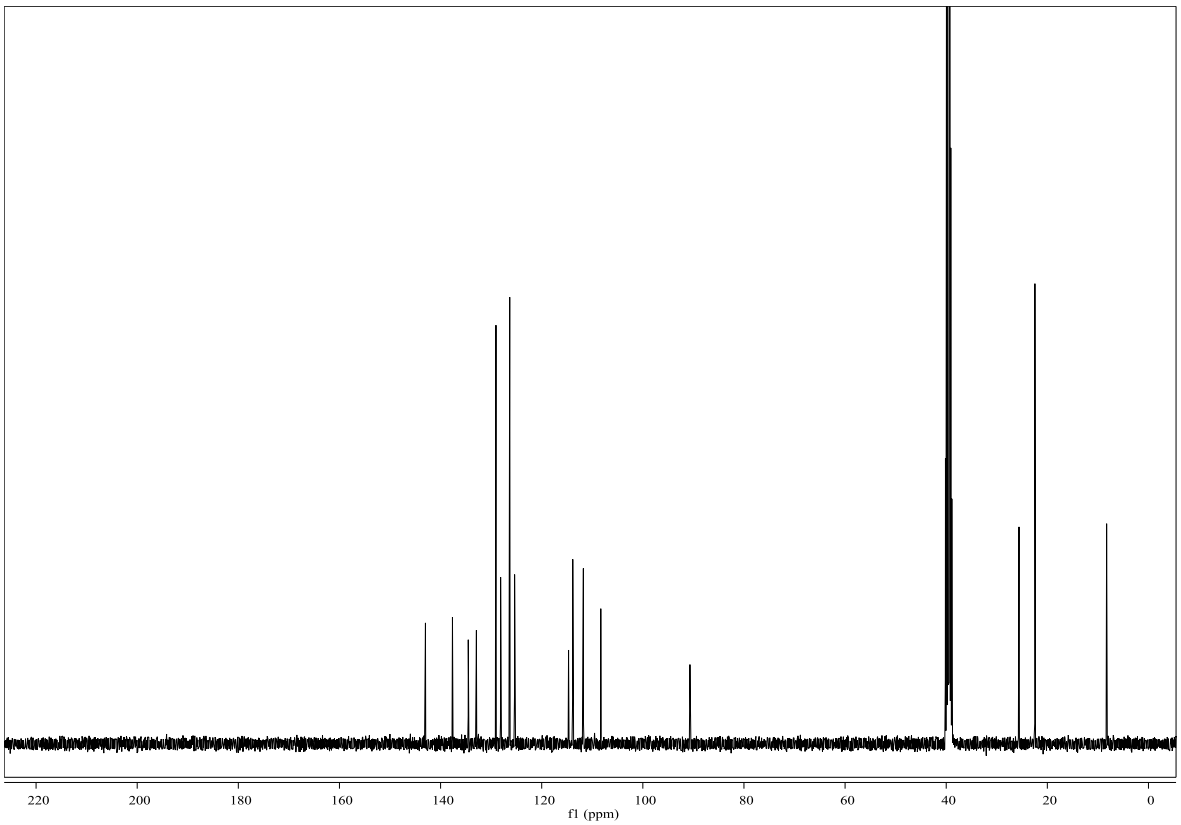
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **78a**



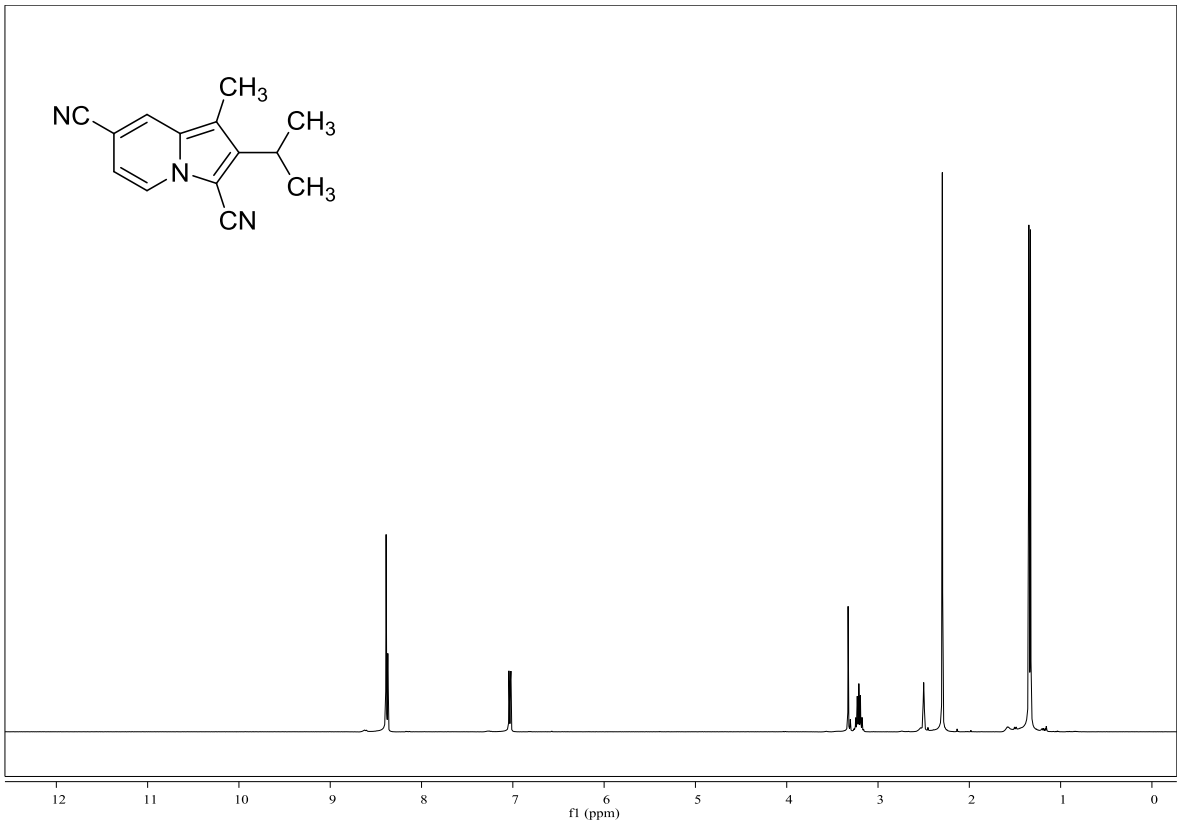
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **78a**



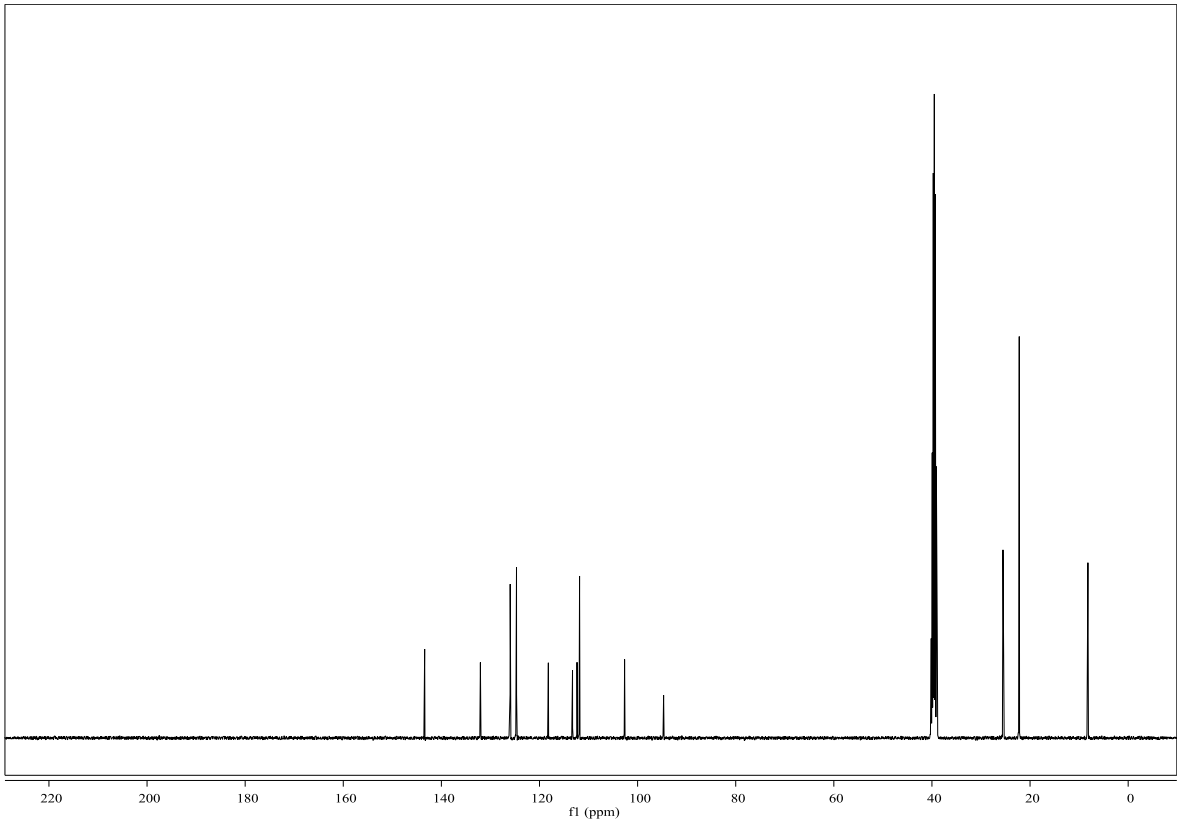
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **78f**



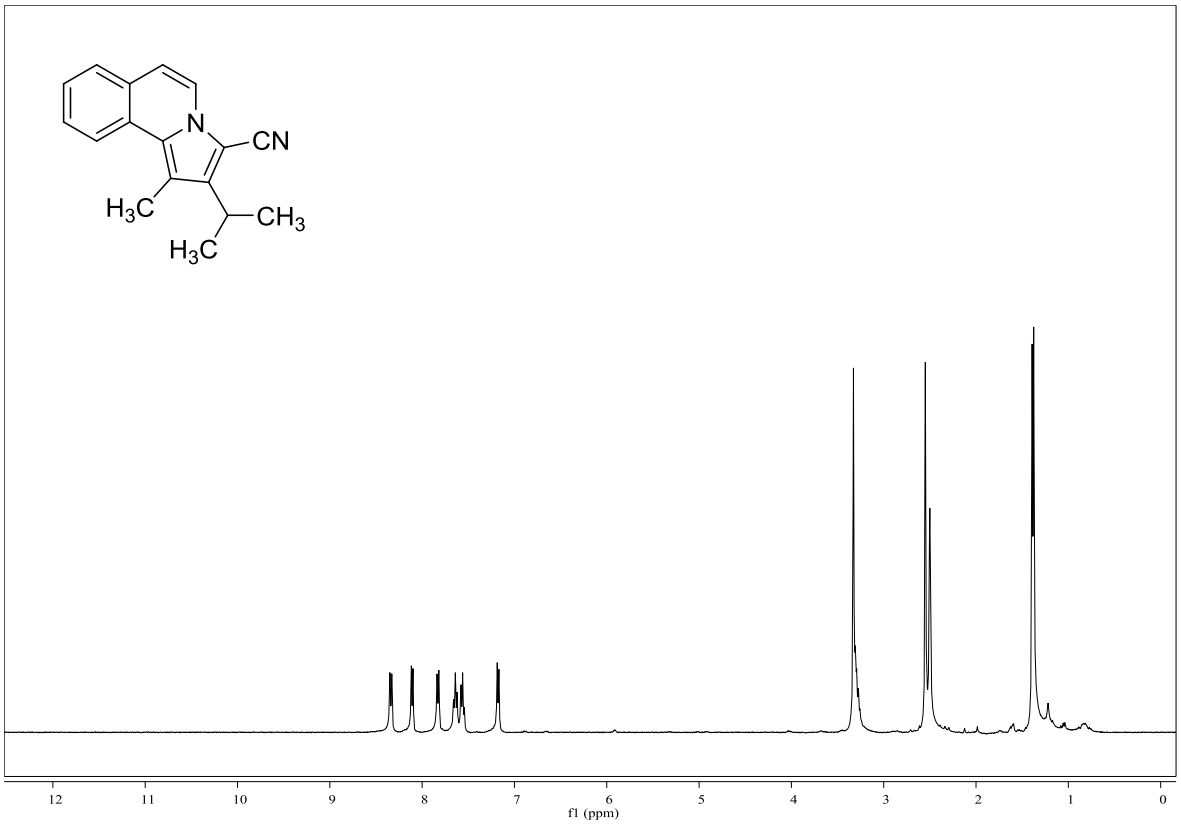
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **78f**



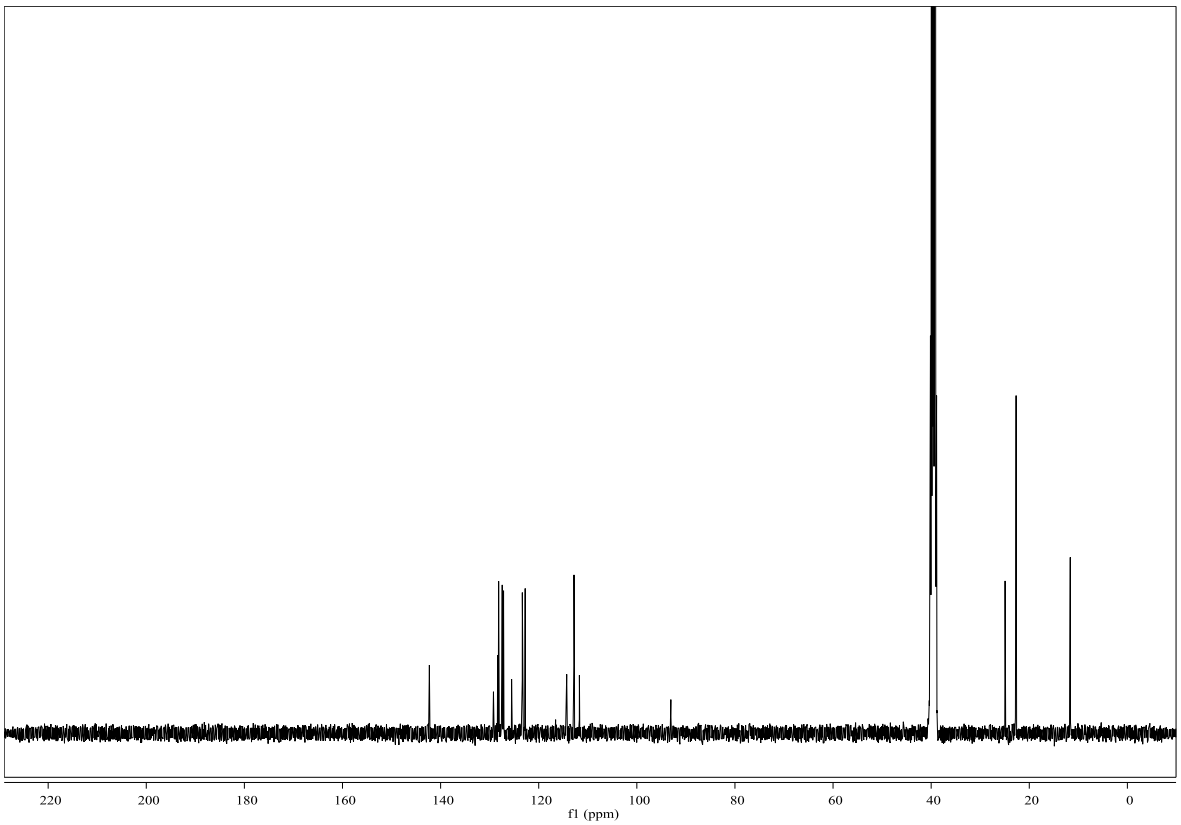
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **78g**



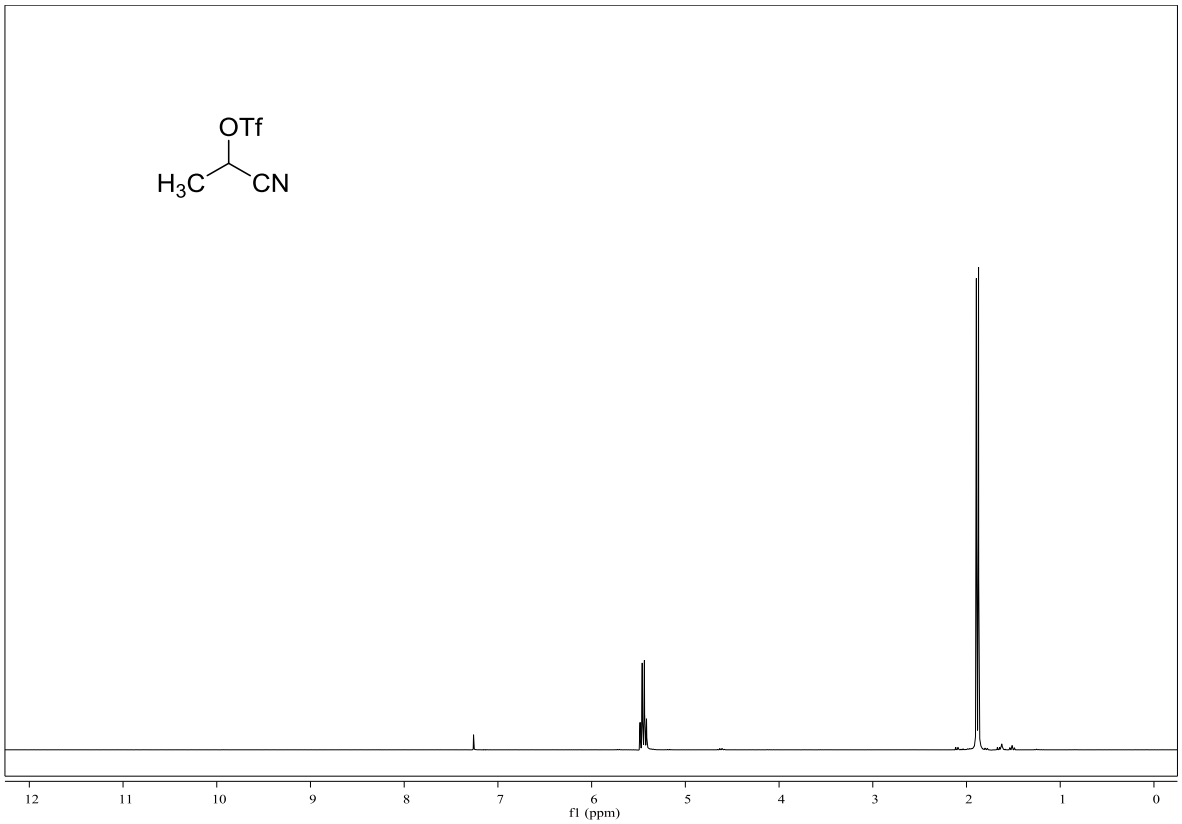
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **78g**



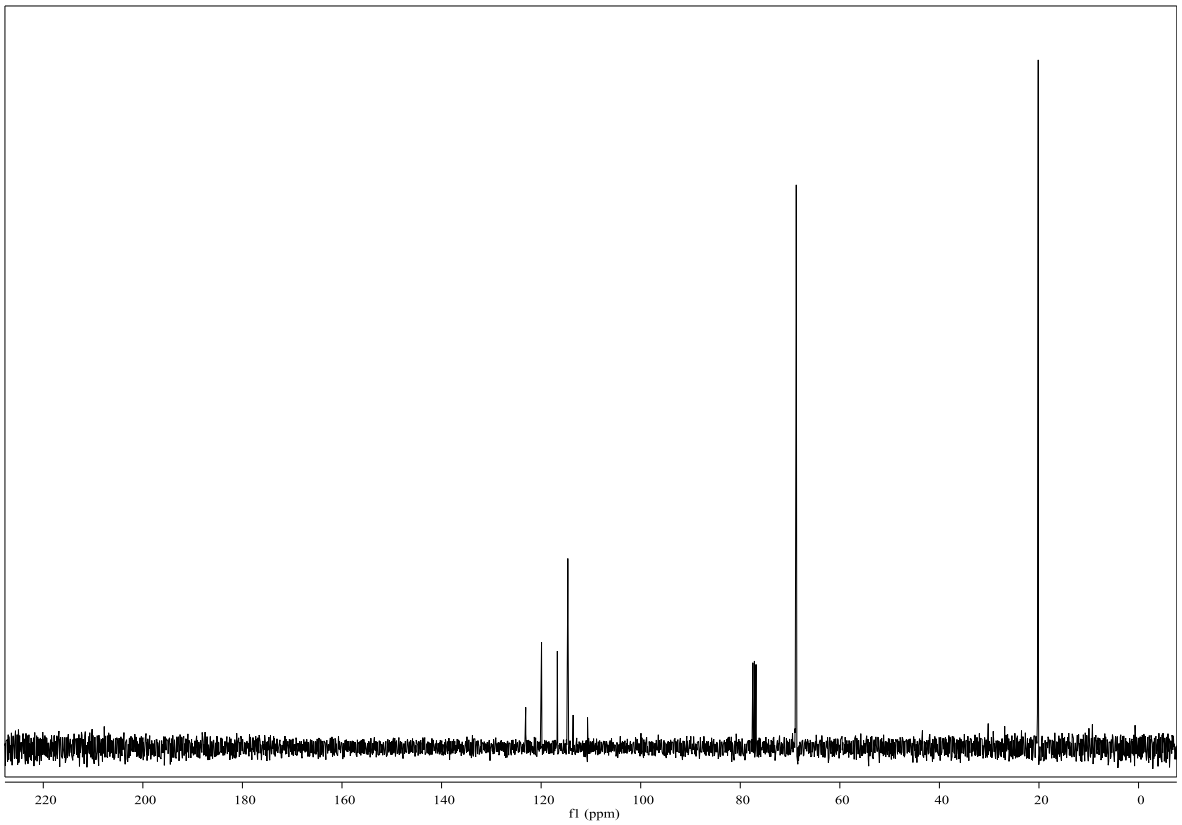
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **80b**



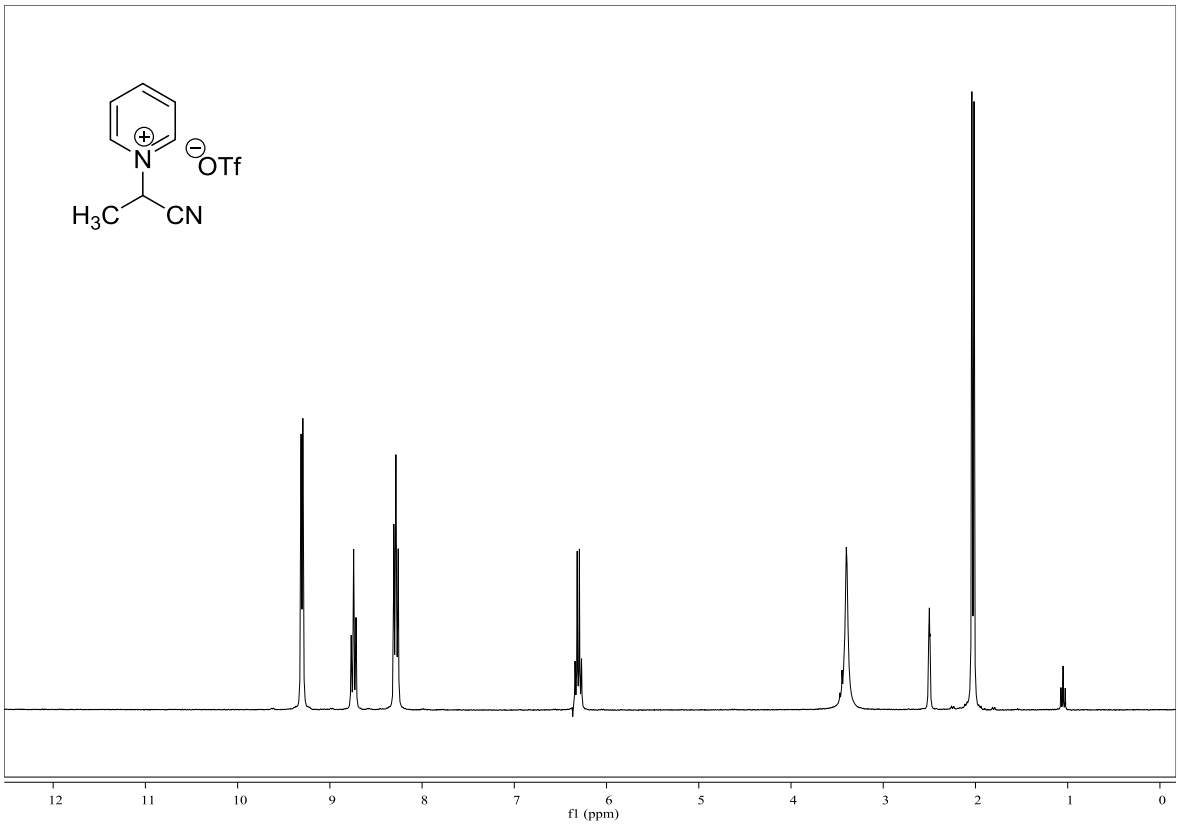
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **80b**



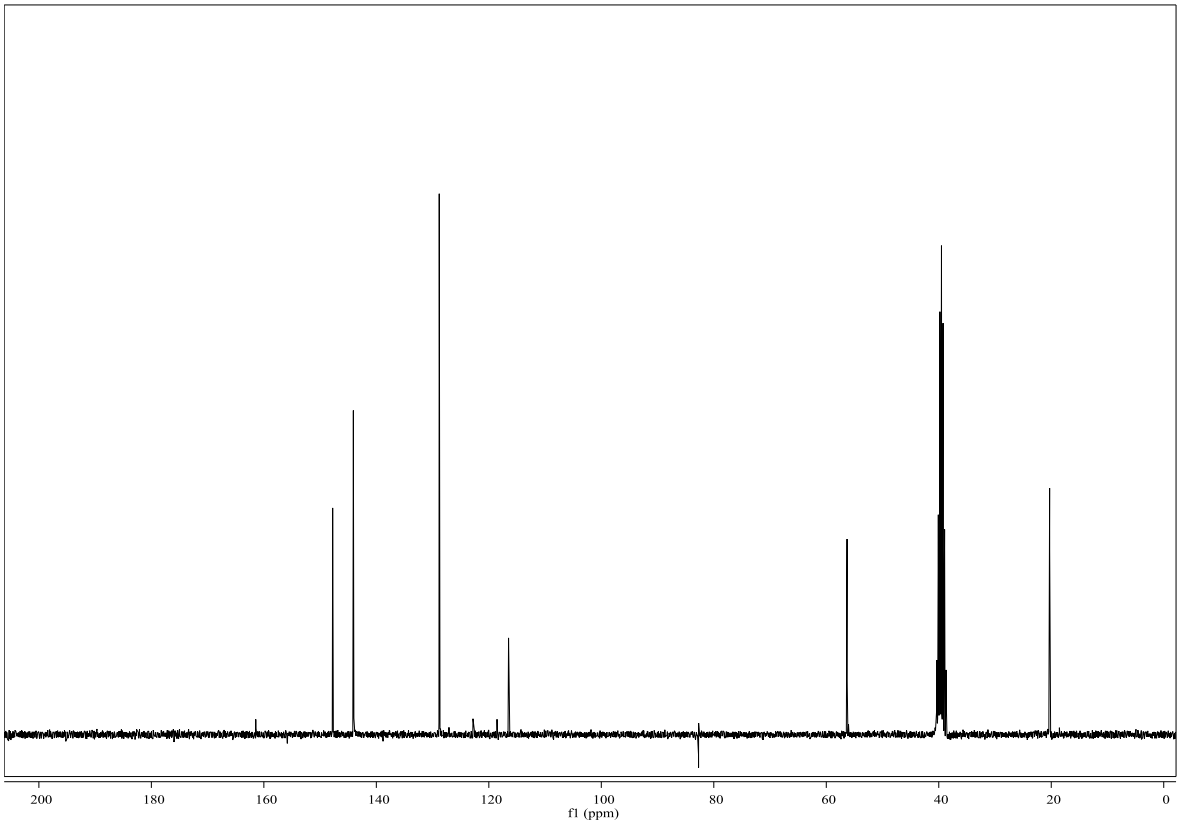
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **84a**



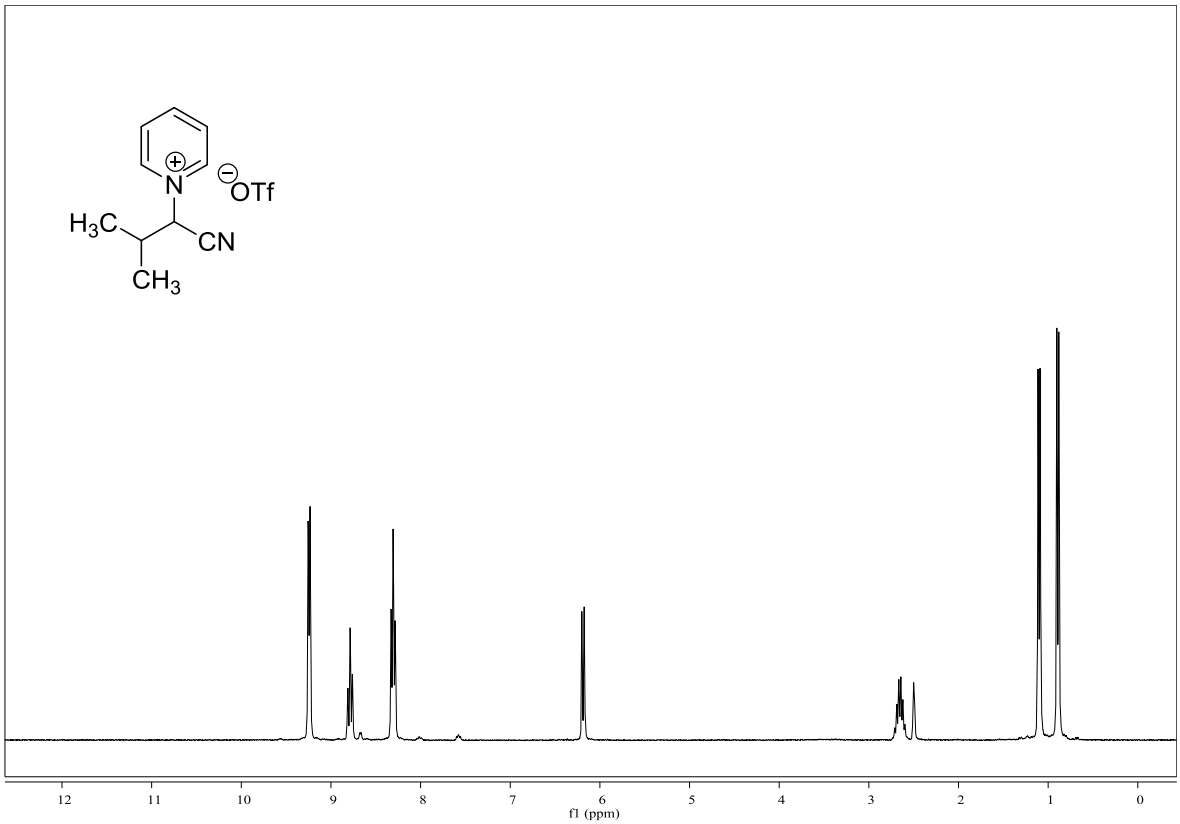
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **84a**



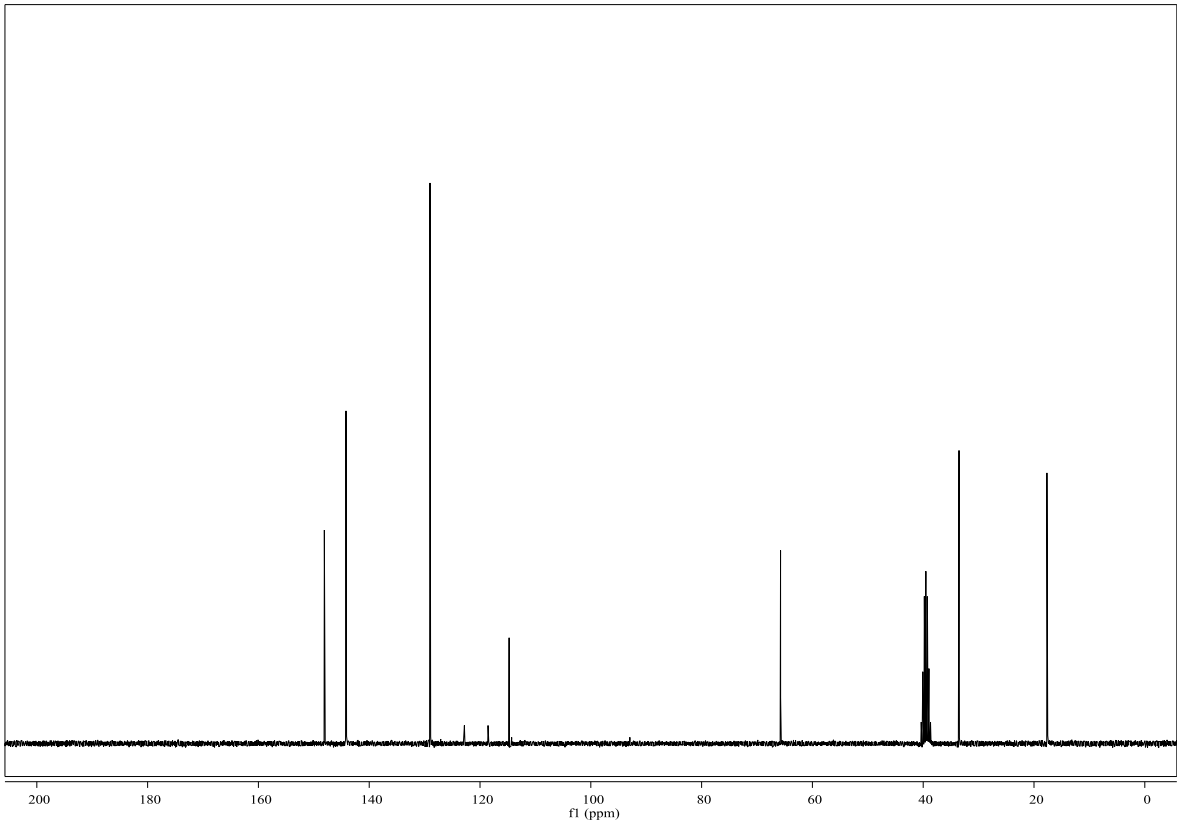
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **85a**



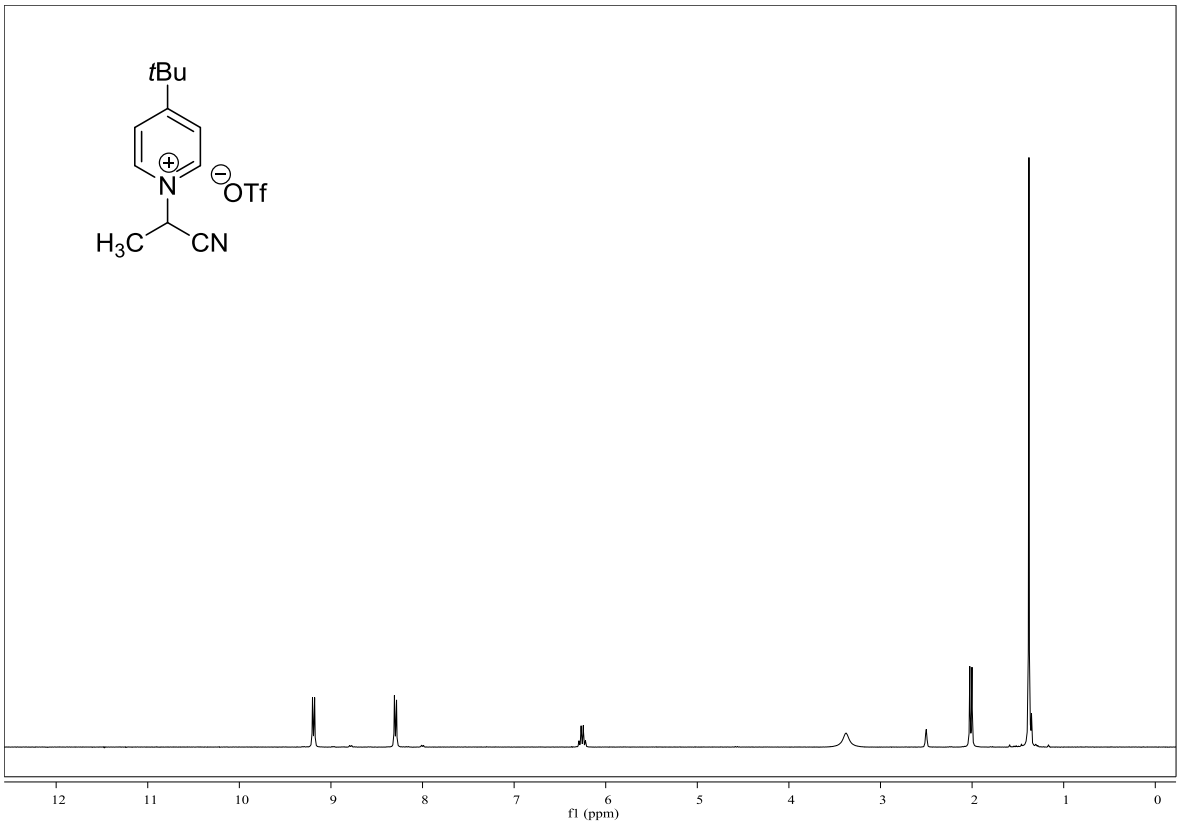
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **85a**



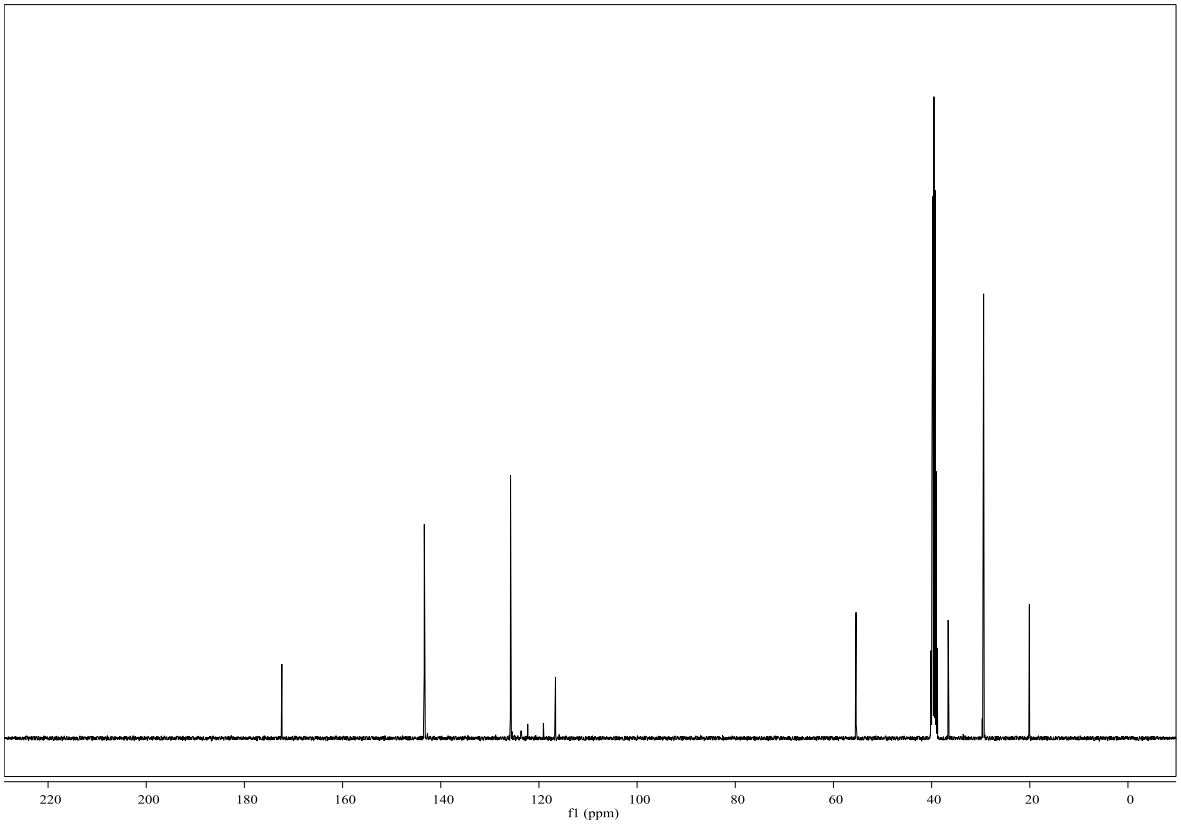
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **85b**



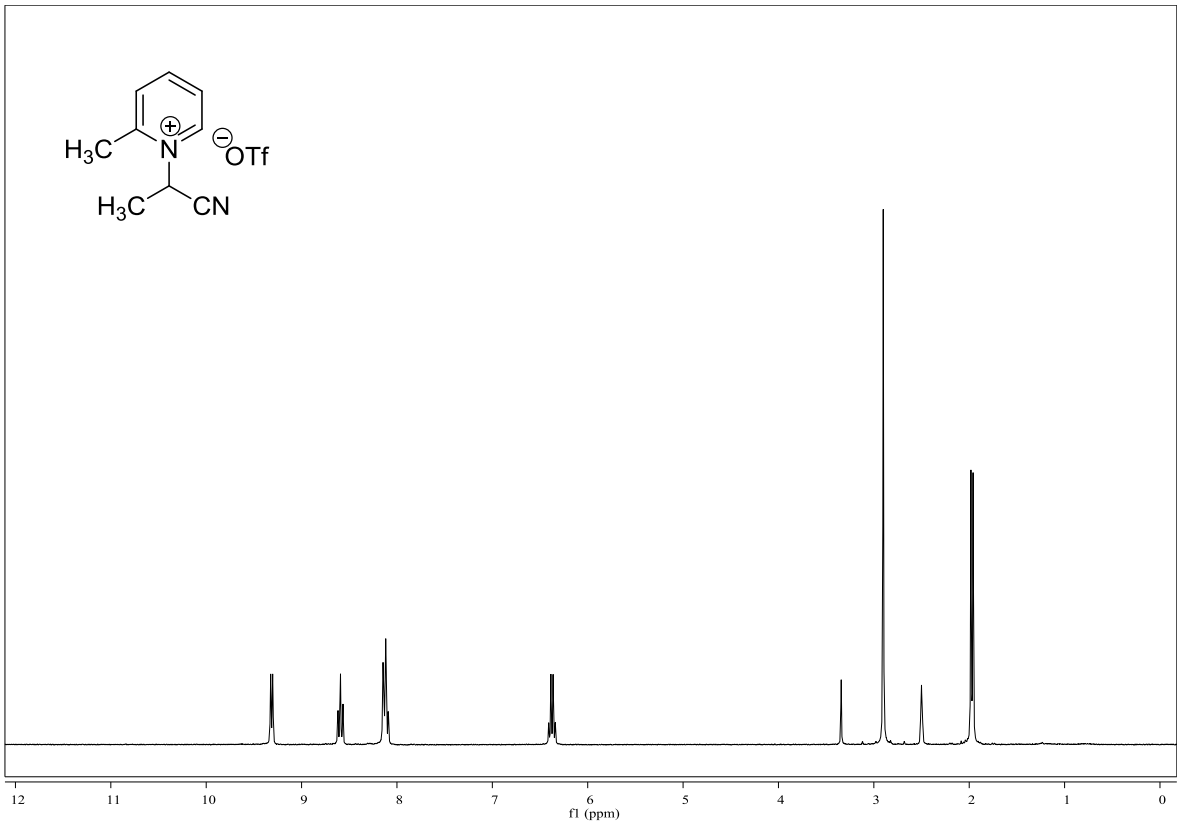
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **85b**



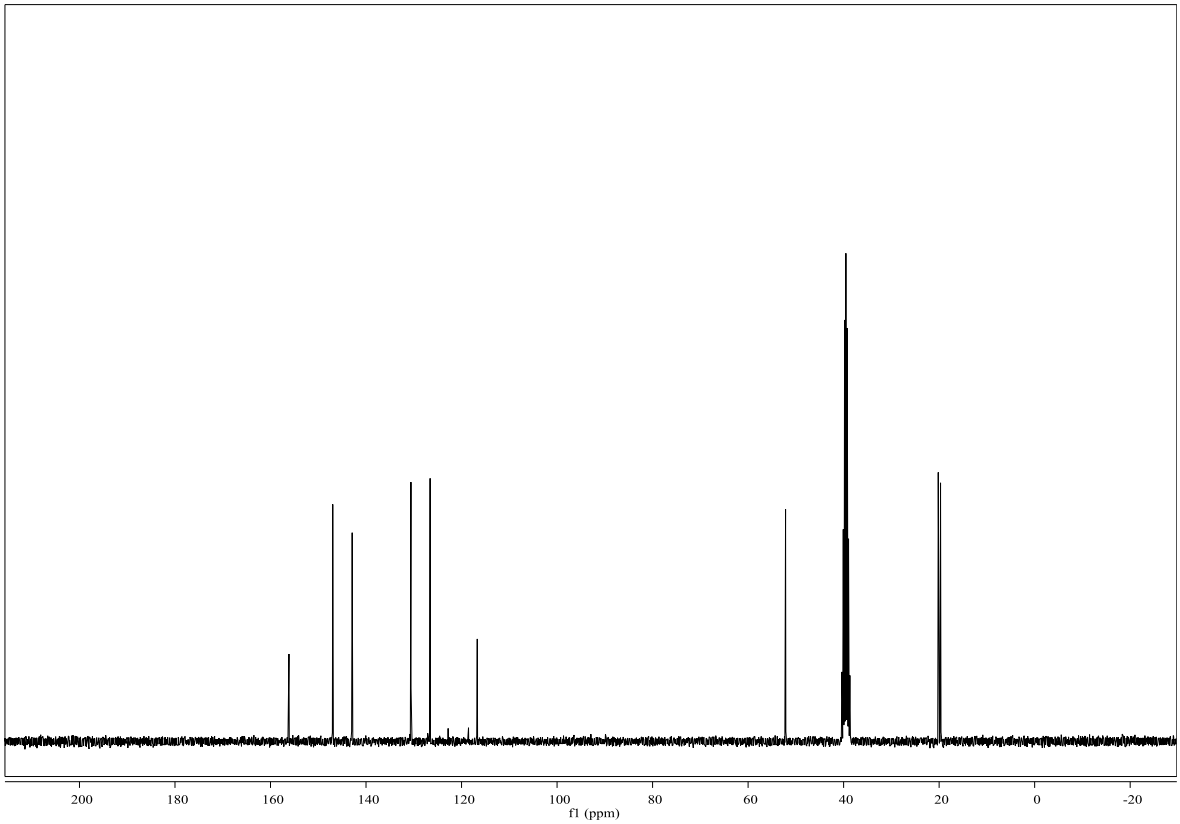
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **85e**



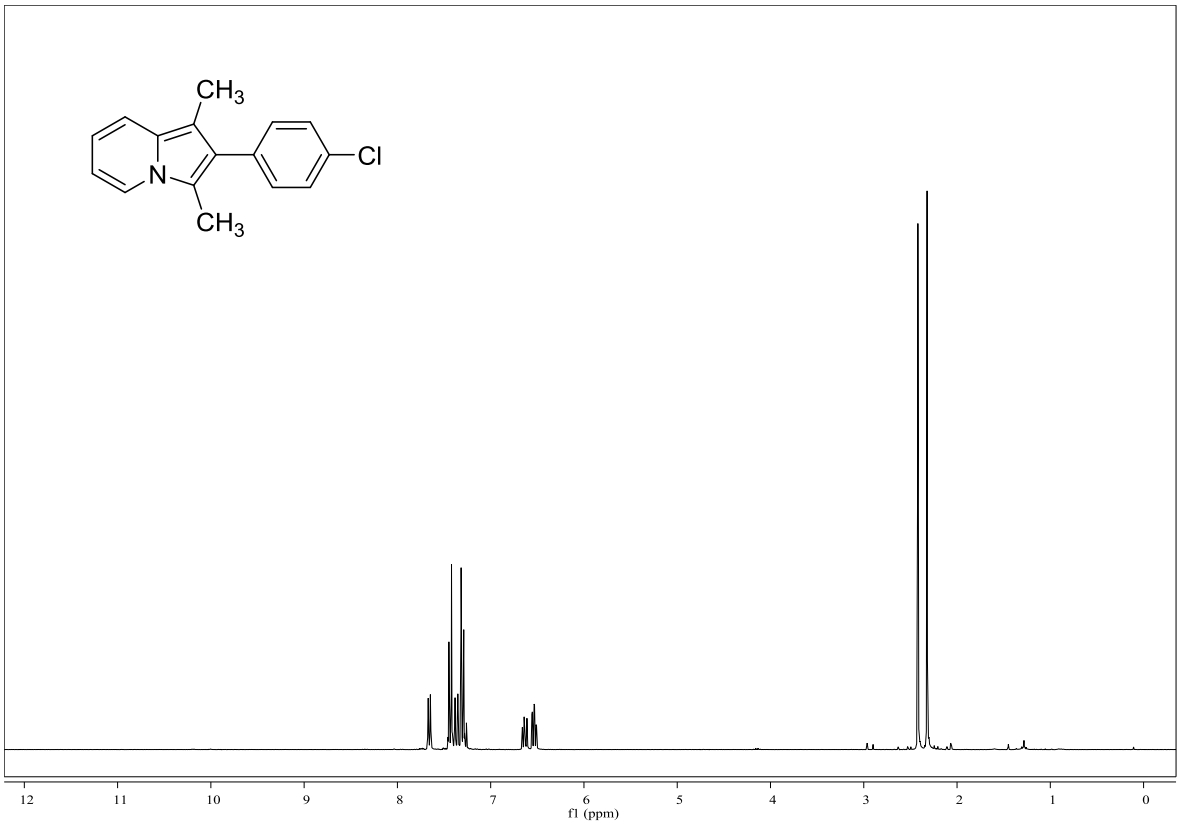
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **85e**



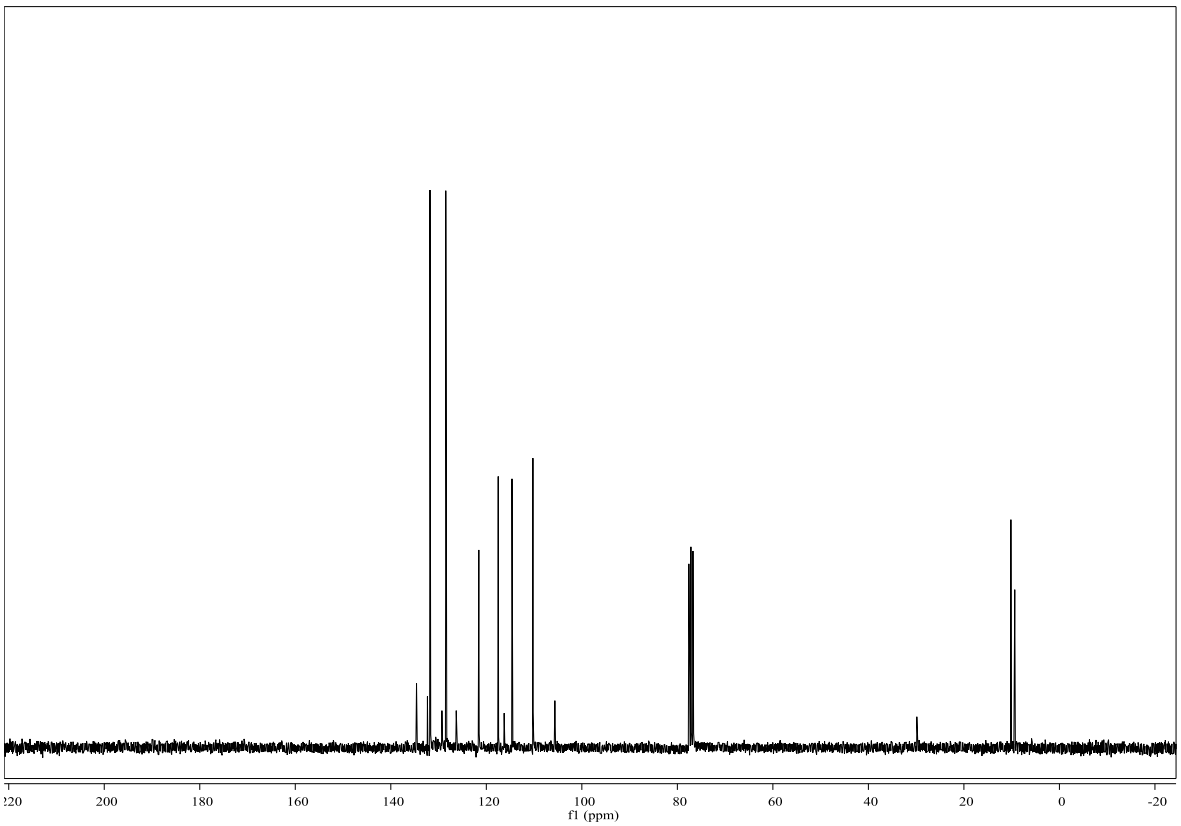
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **85f**



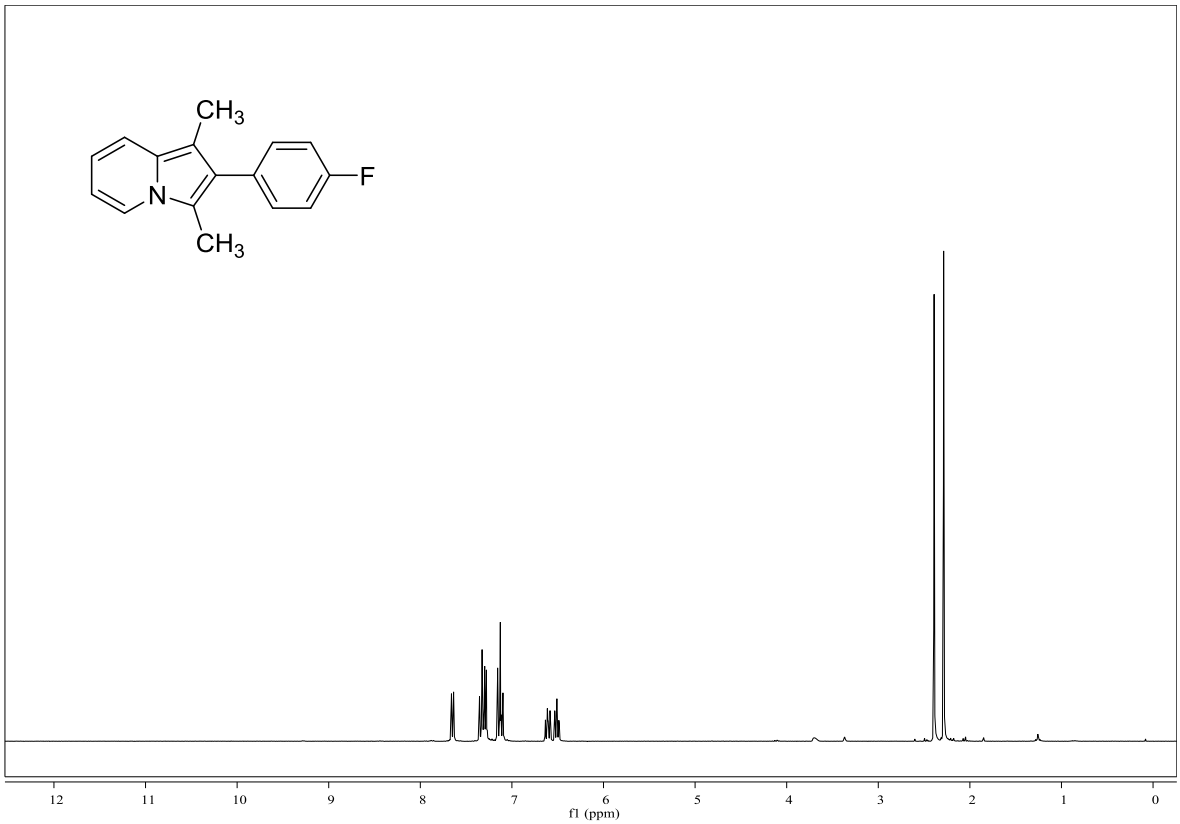
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **85f**



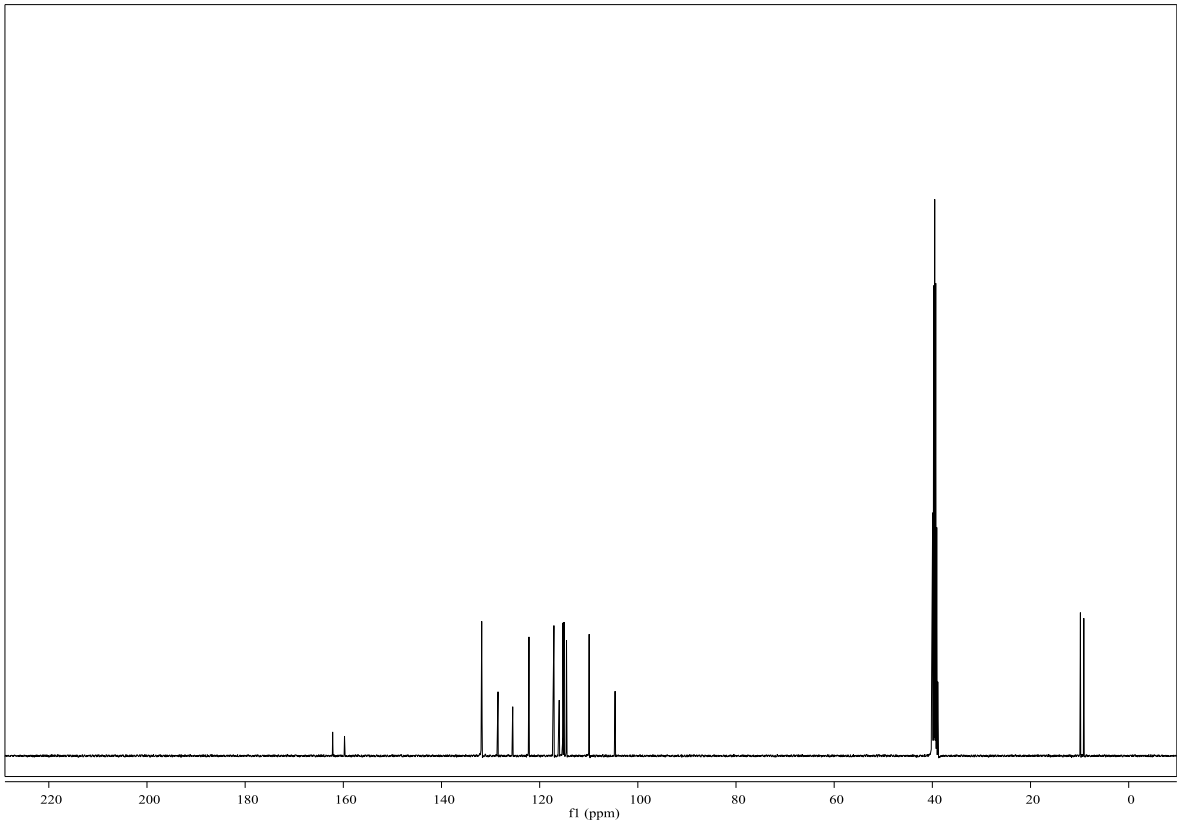
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **86a**



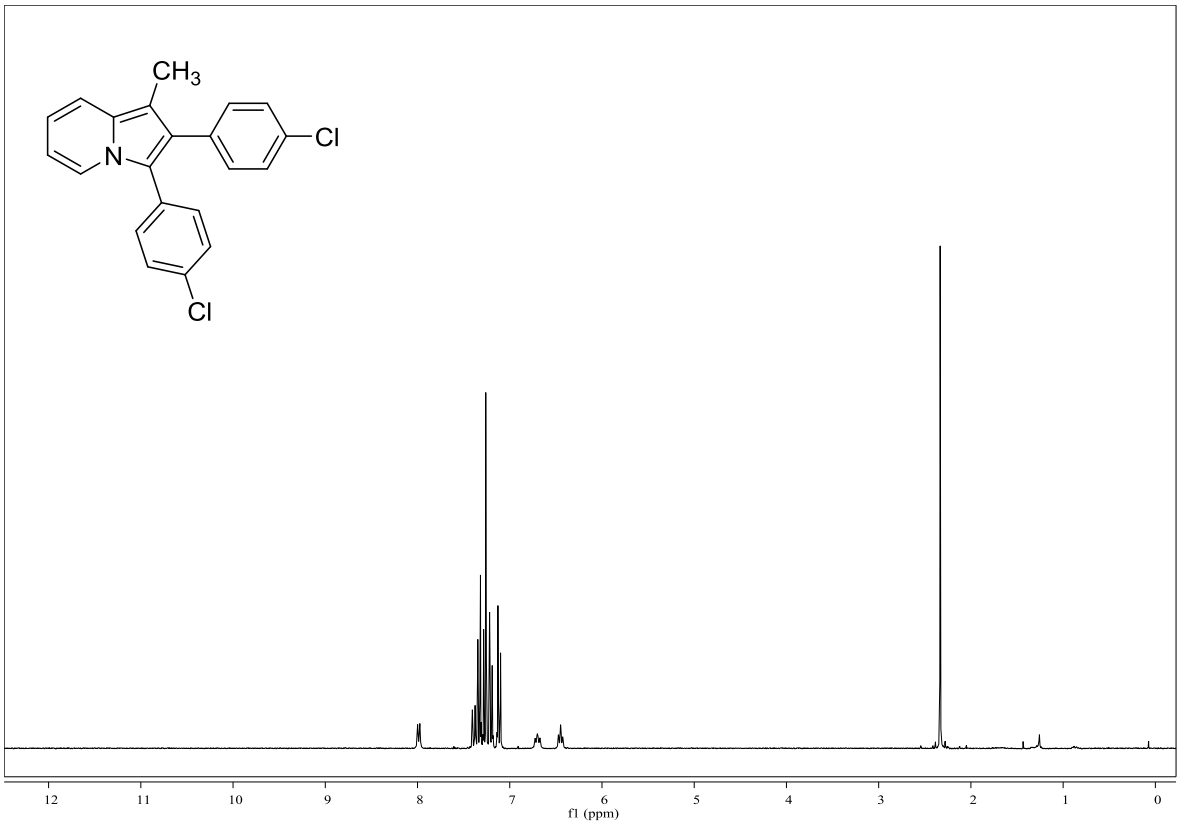
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **86a**



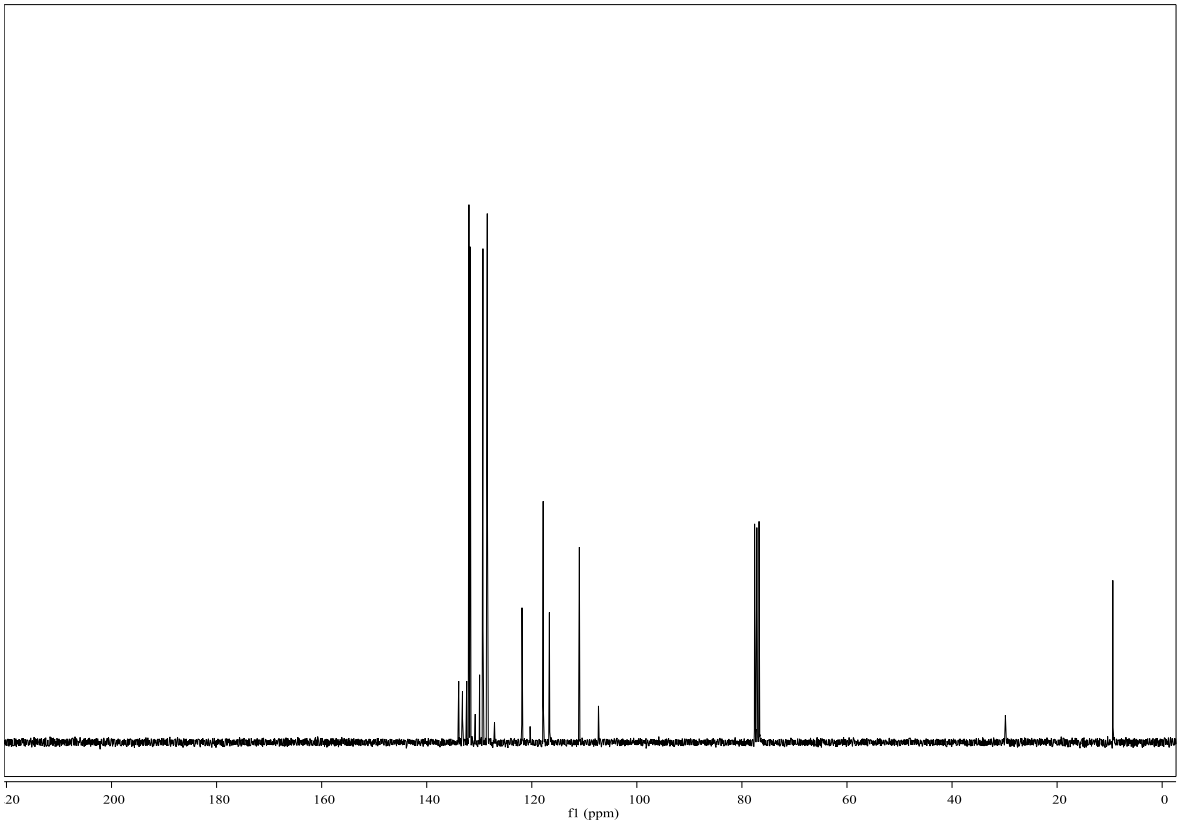
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **86d**



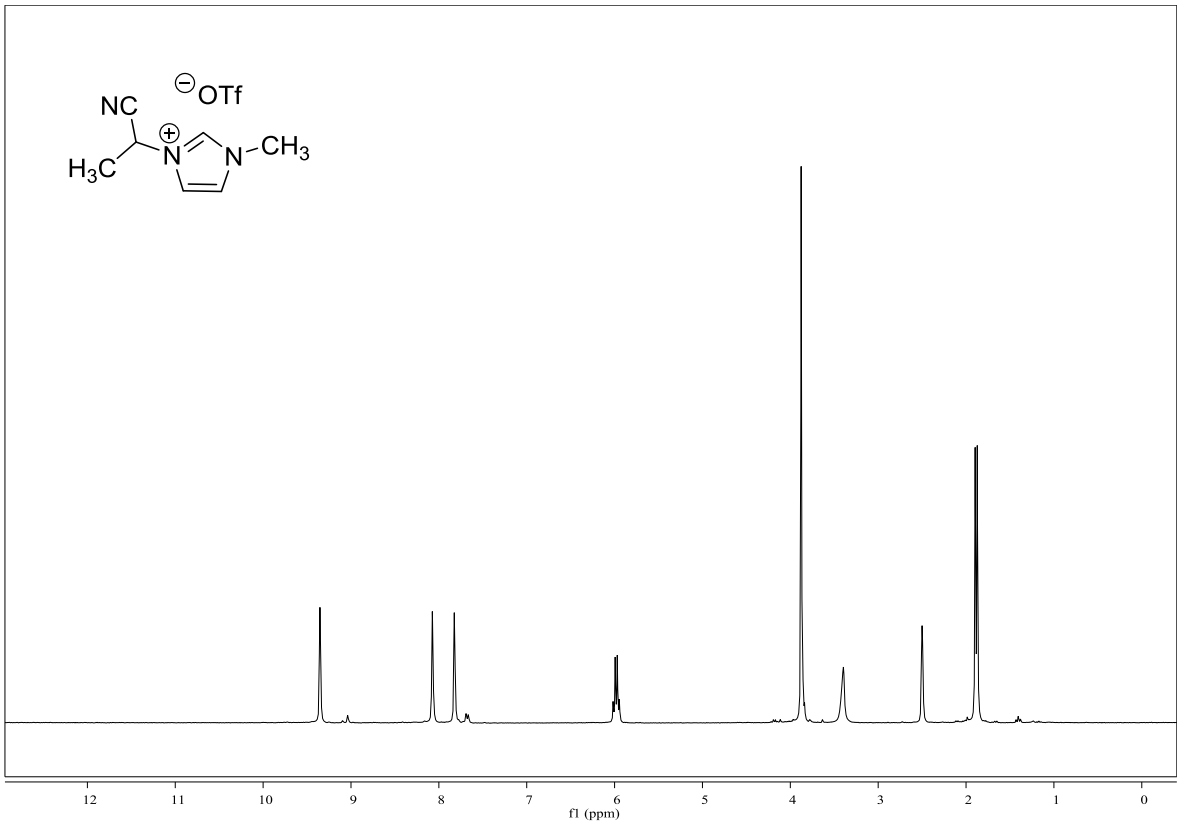
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **86d**



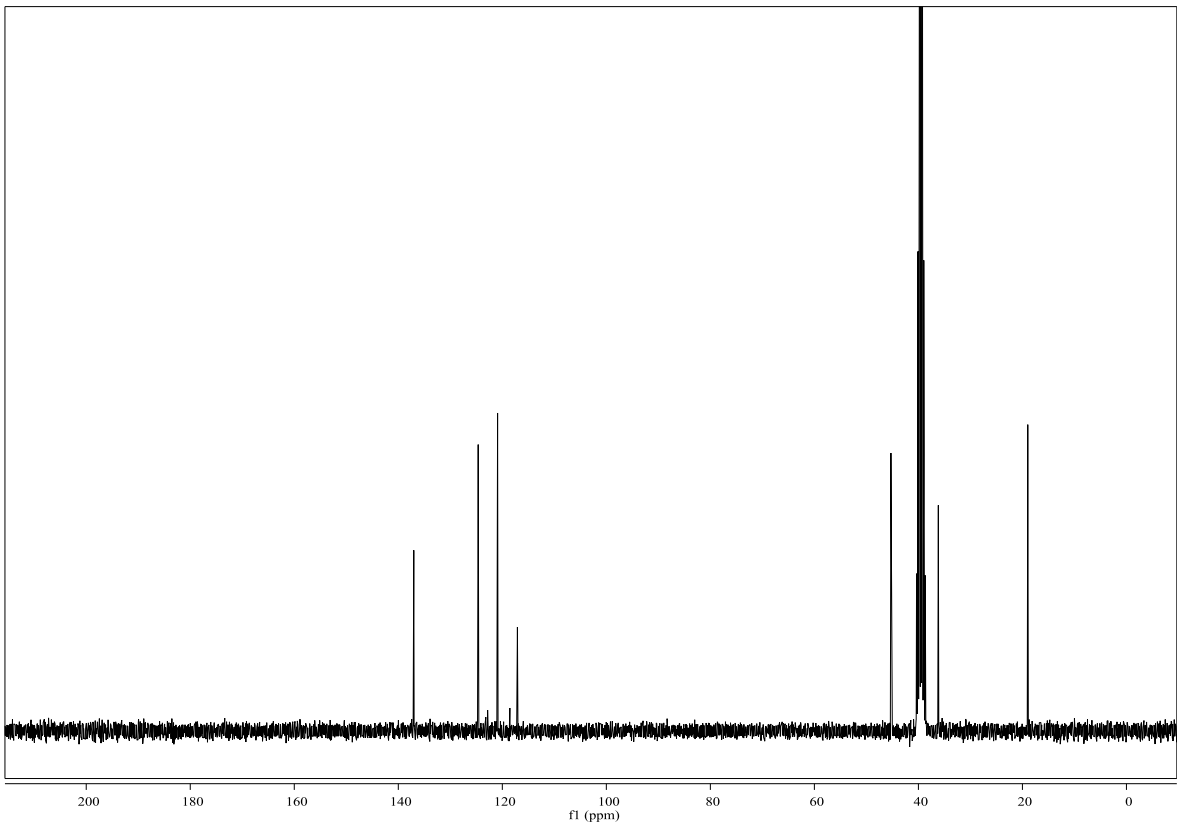
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **86j**



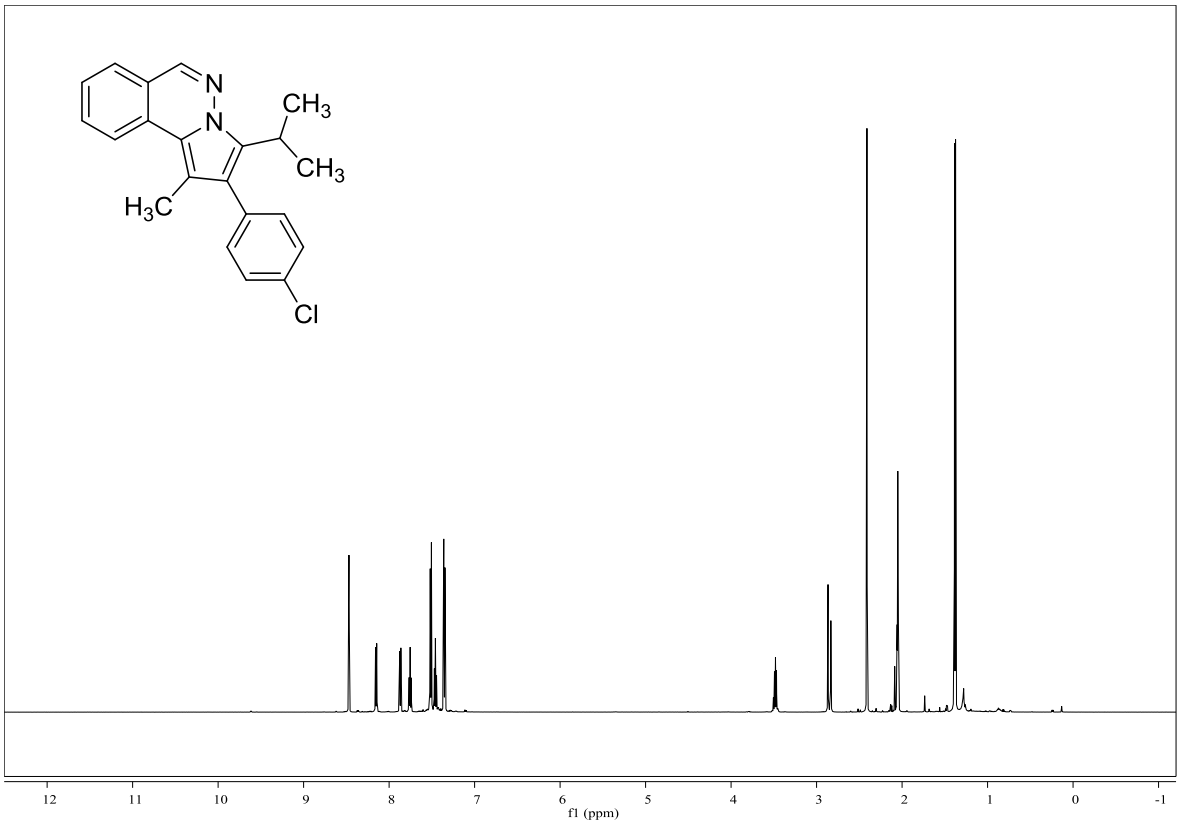
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **86j**



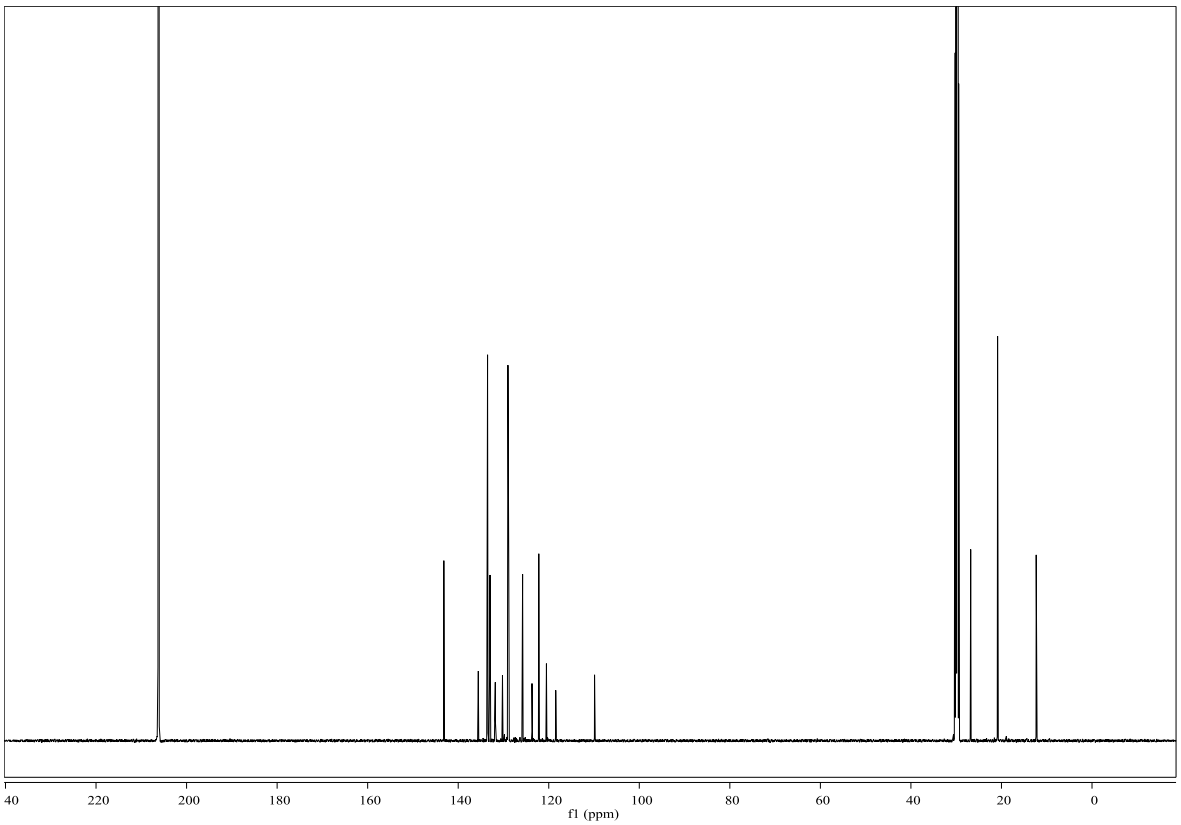
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **87d**



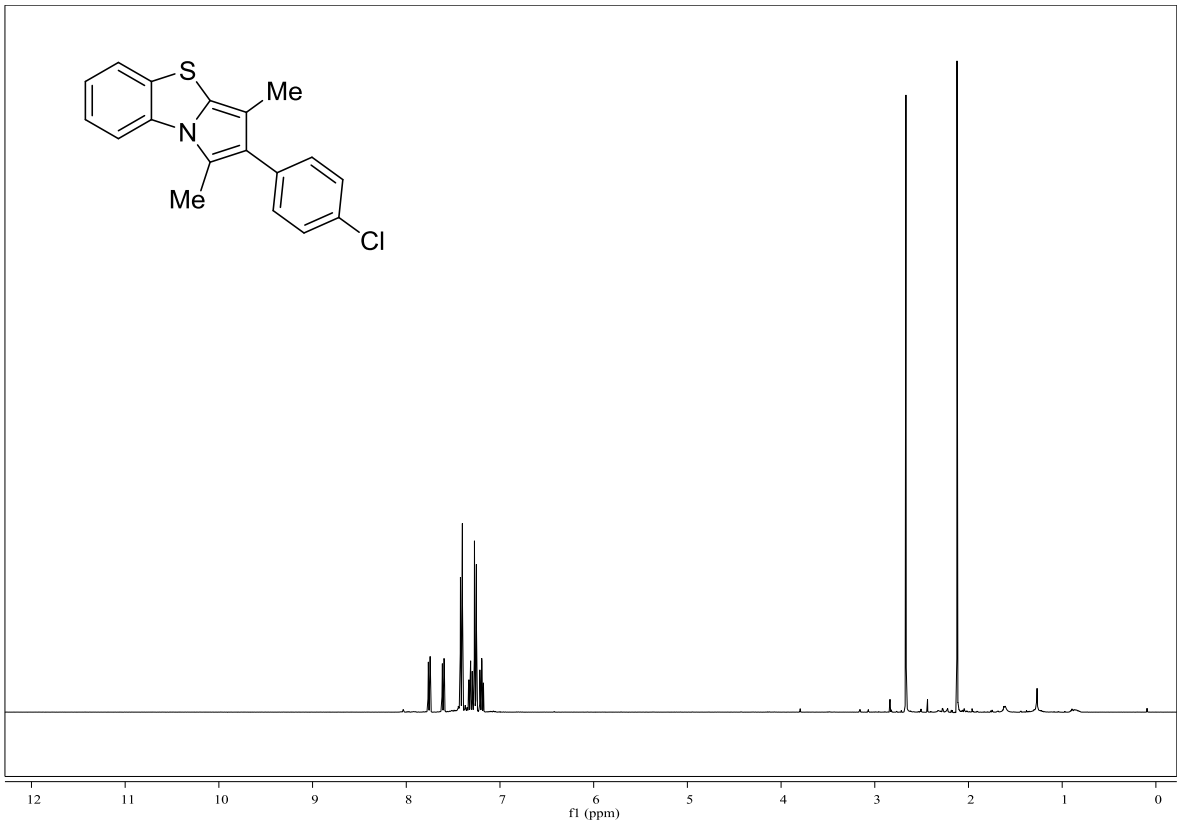
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **87d**



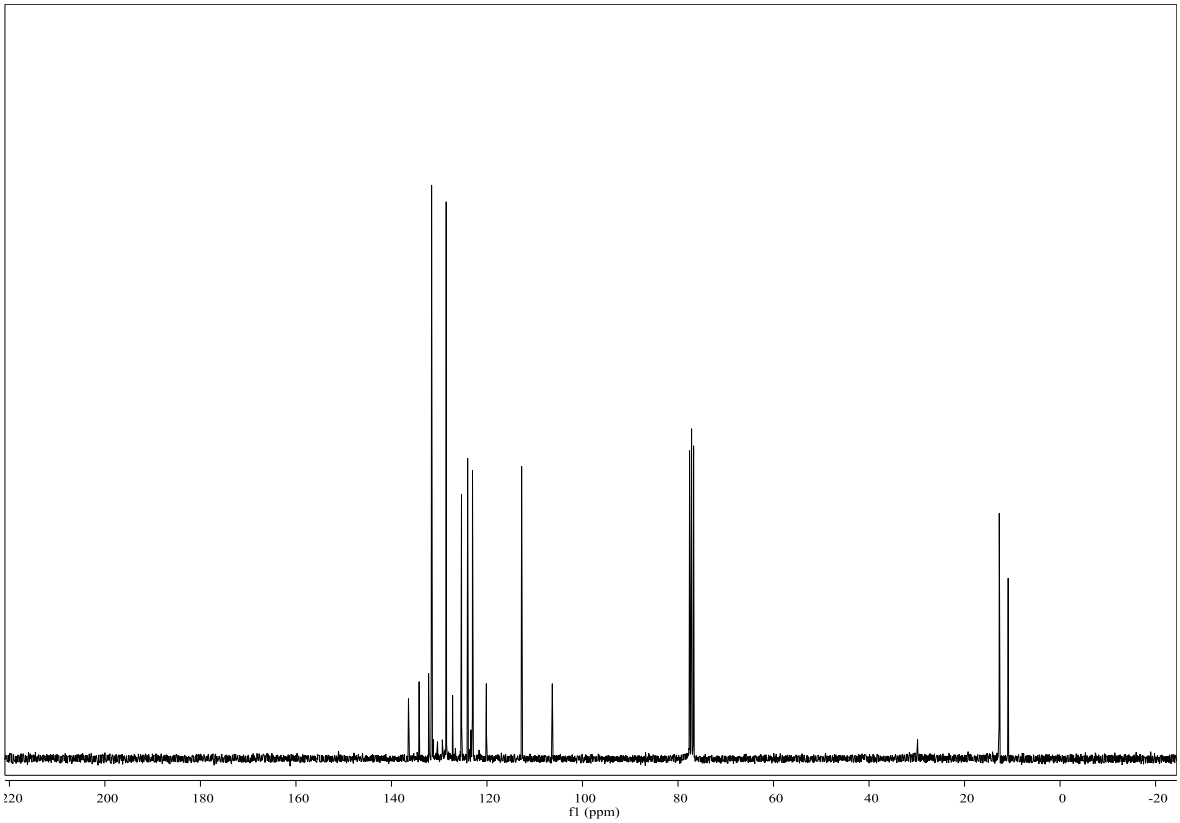
^{1}H NMR (600 MHz, $(CD_3)_2CO$) spectrum of **89b**



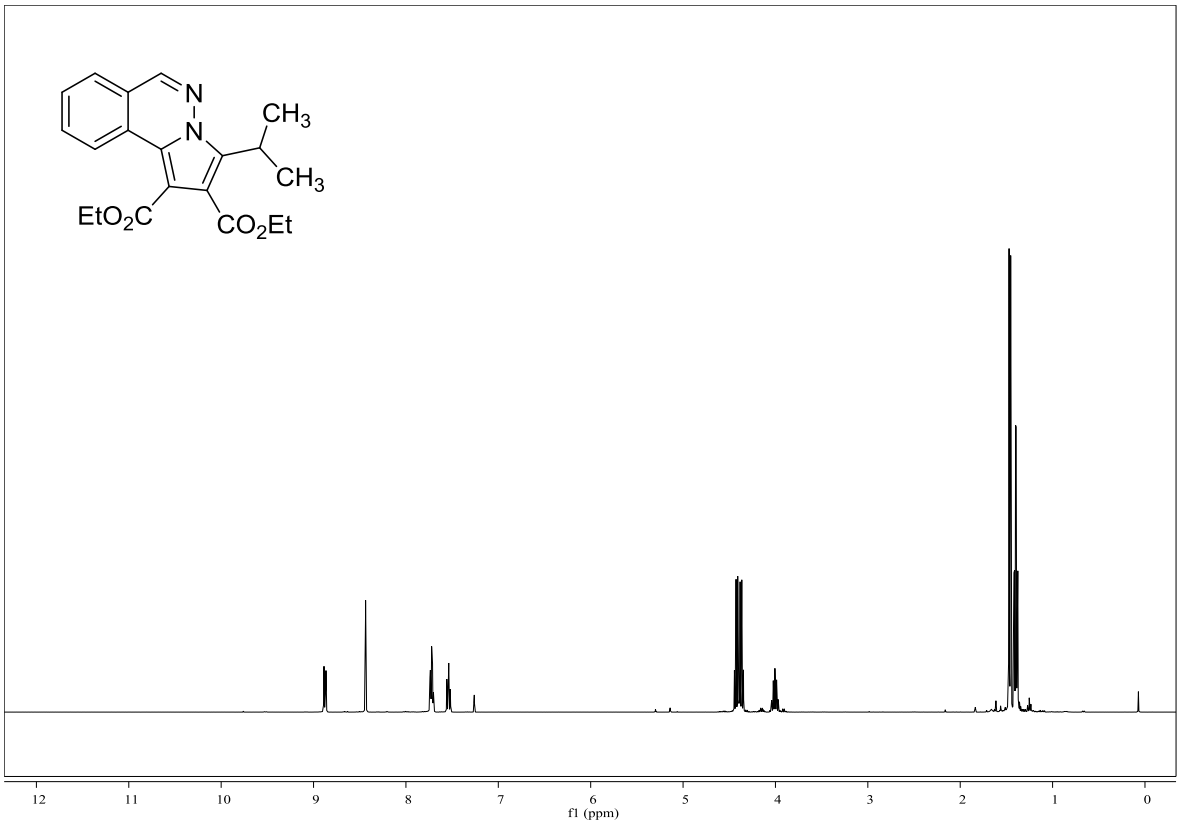
^{13}C NMR (151 MHz, $(CD_3)_2CO$) spectrum of **89b**



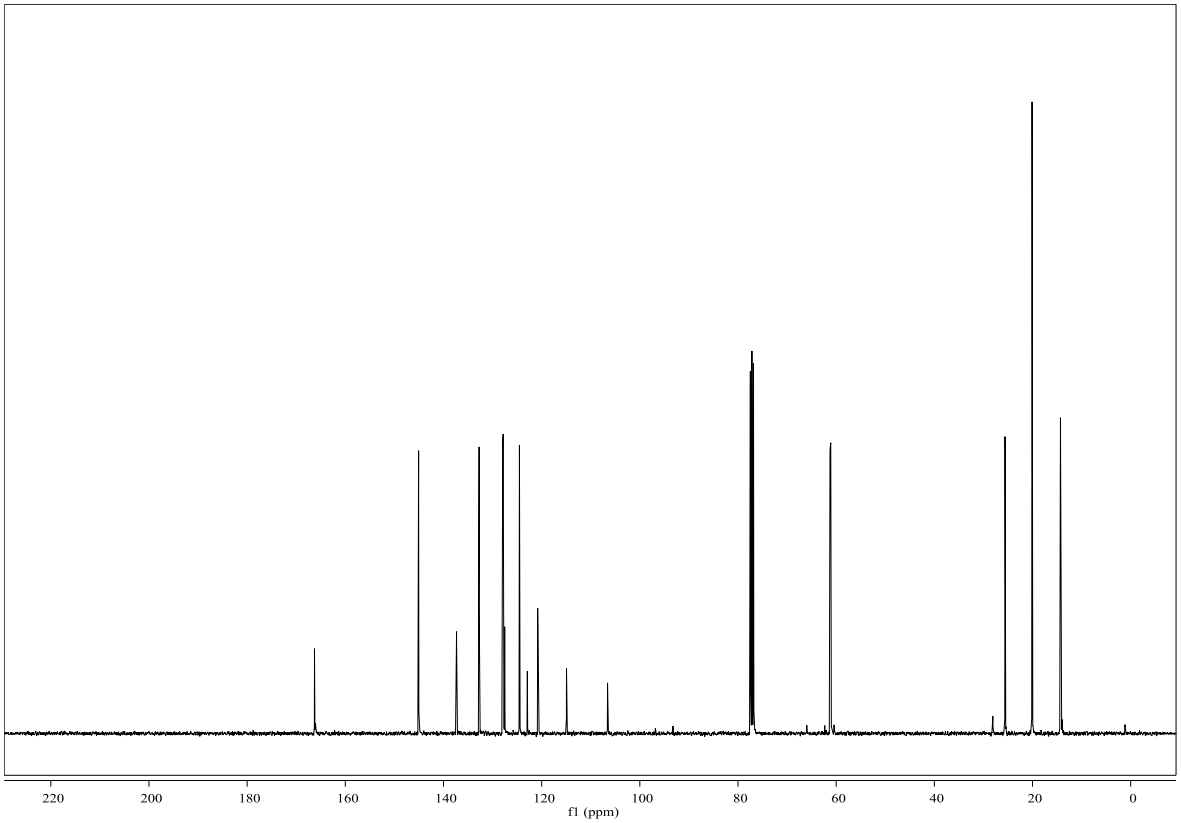
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **89c**



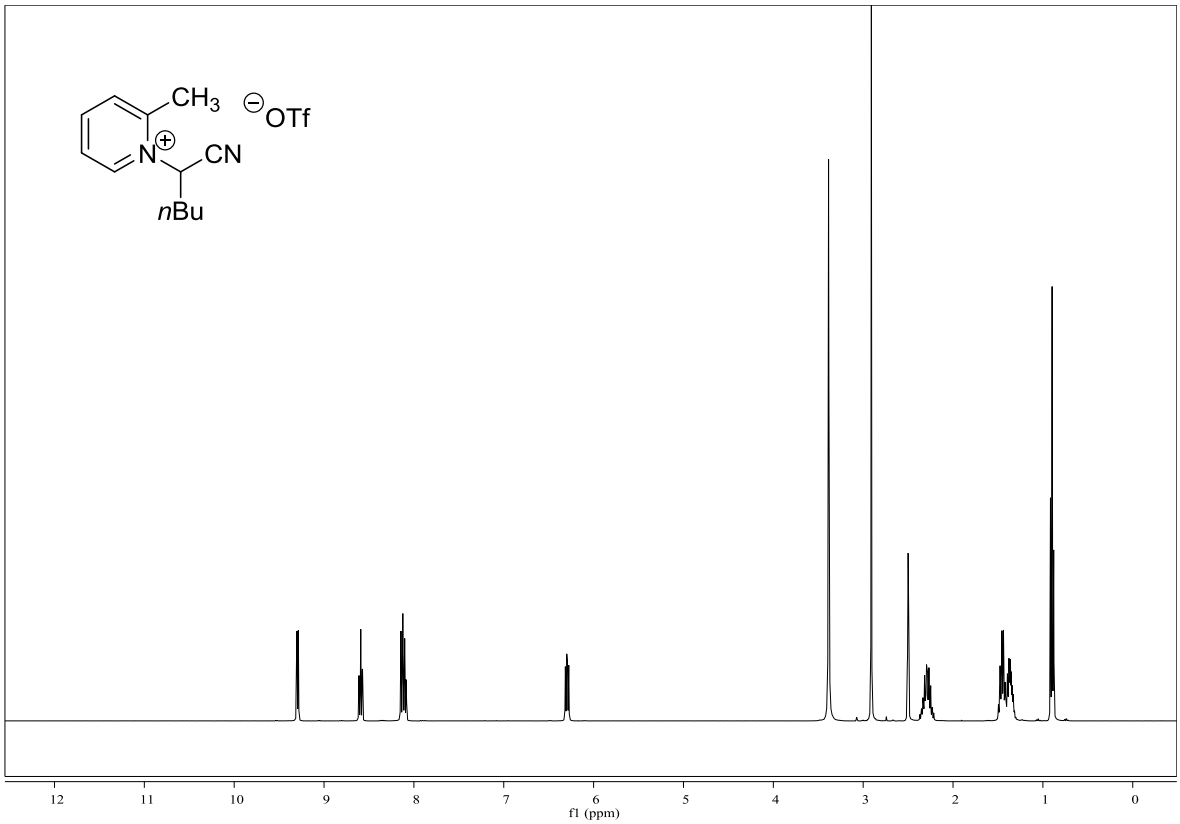
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **89c**



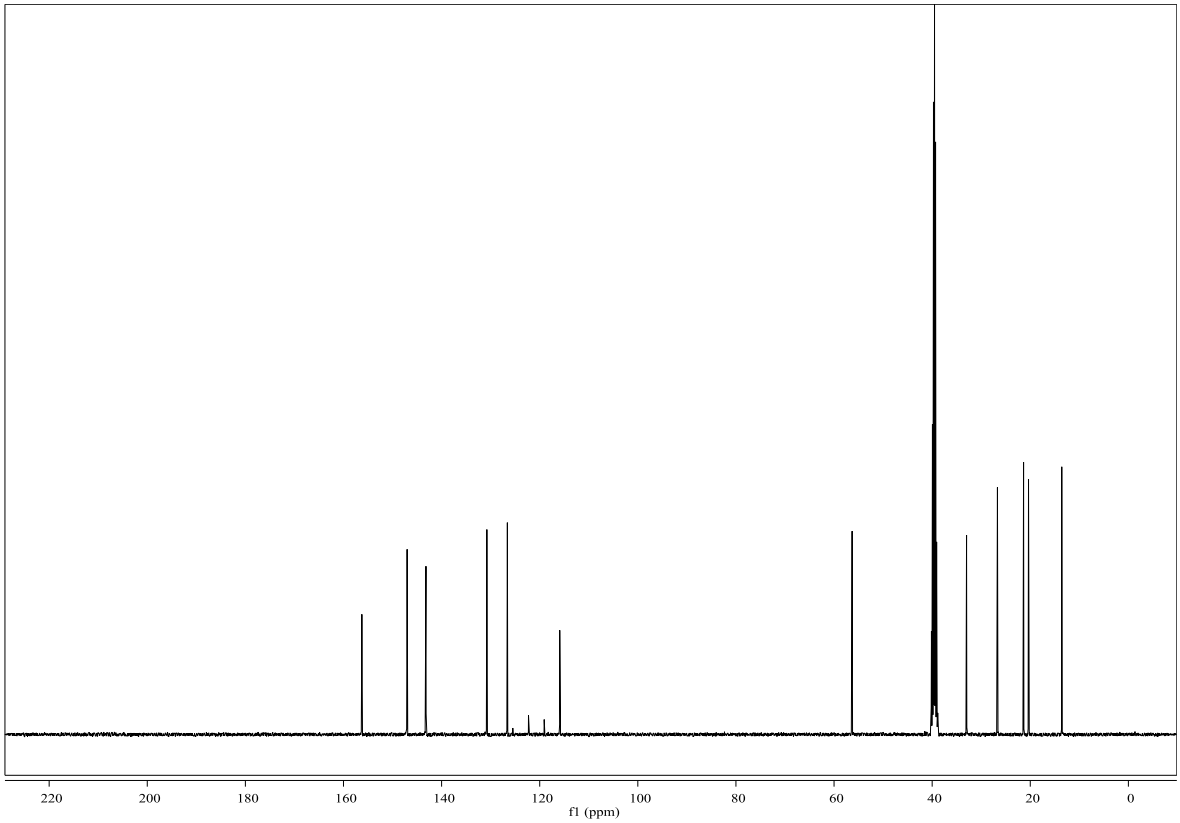
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **88a**



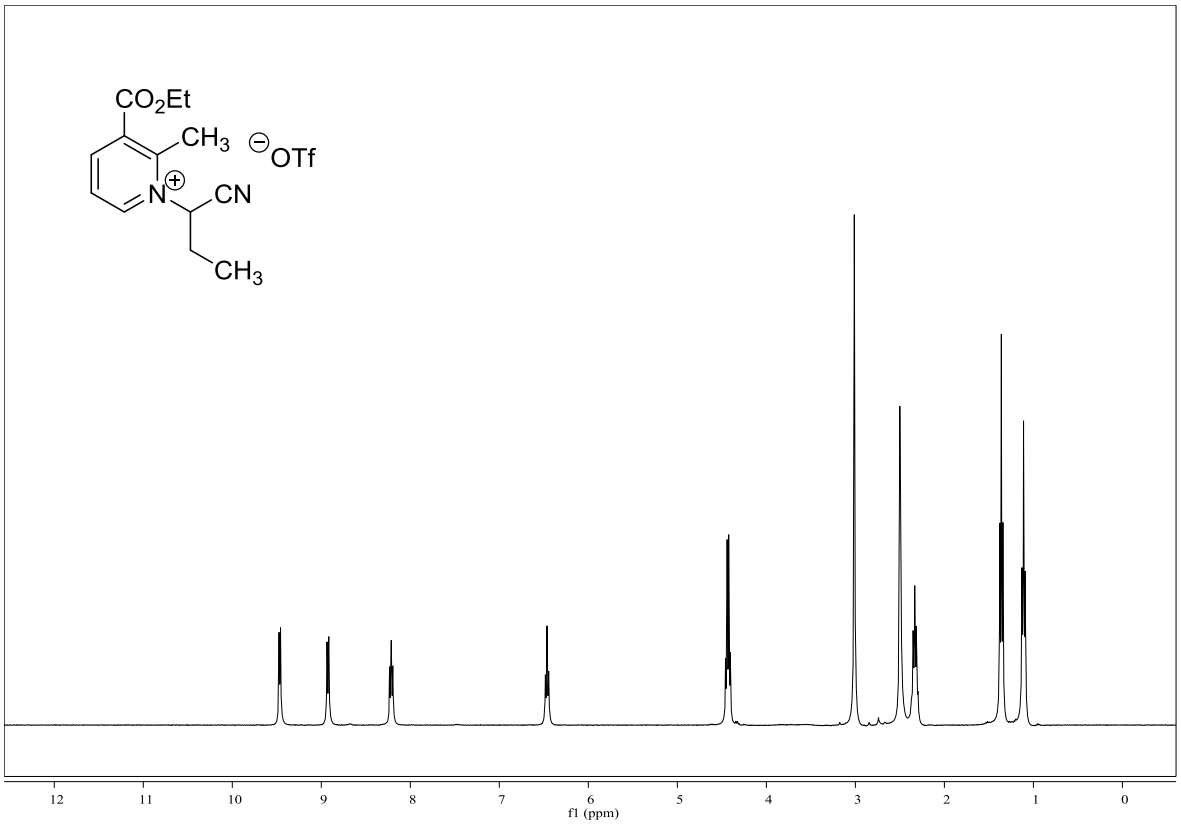
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **88a**



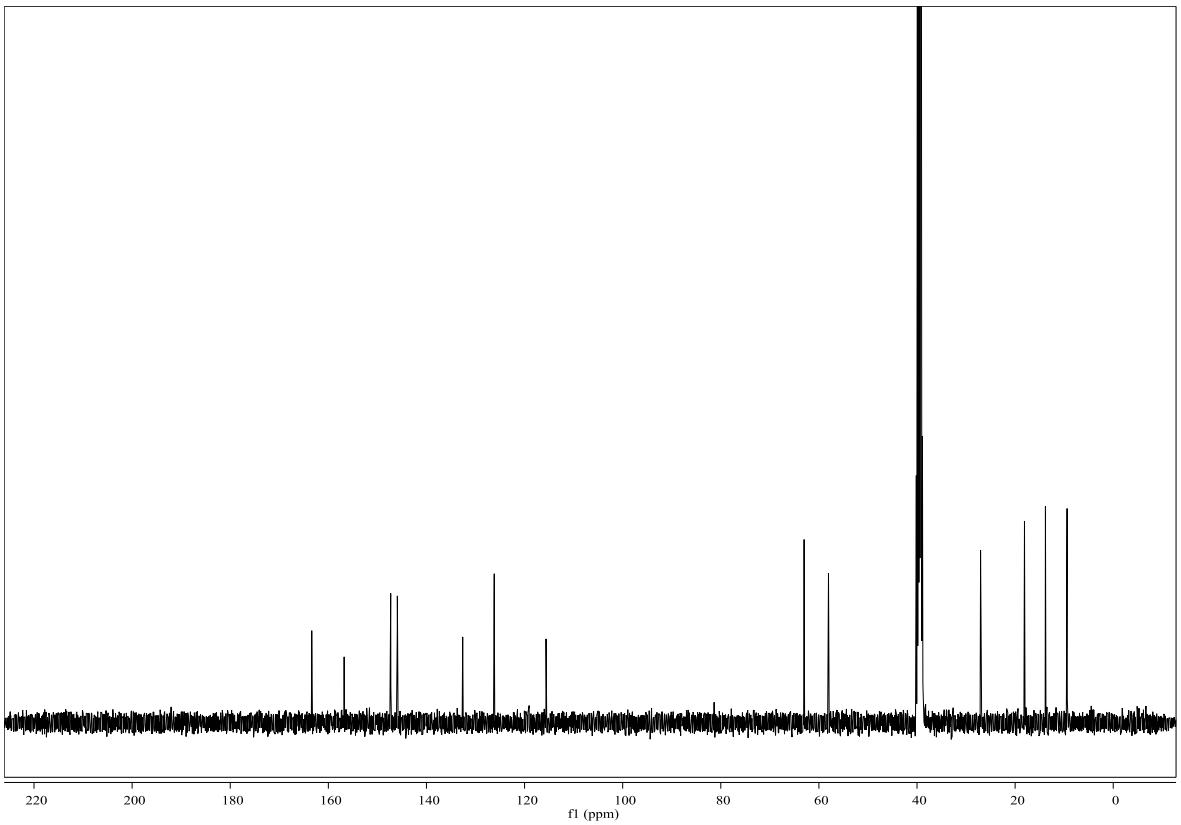
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **95a**



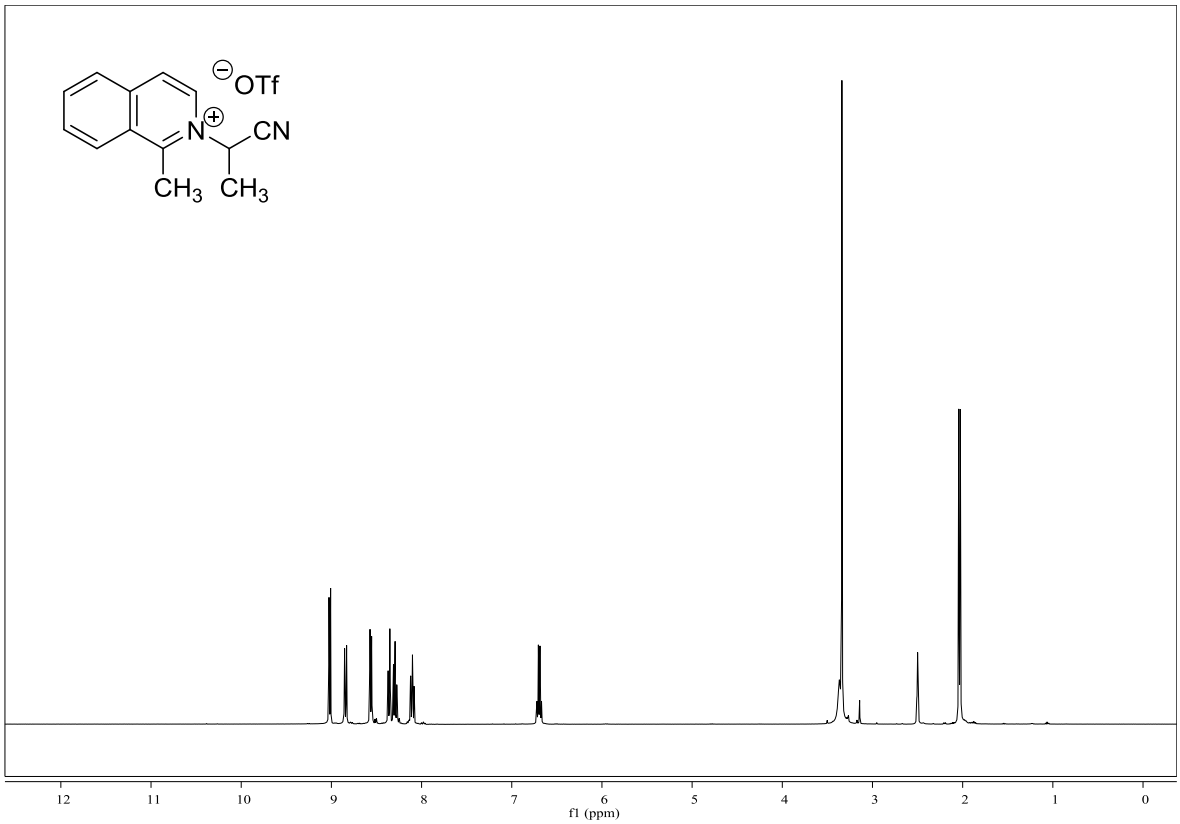
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **95a**



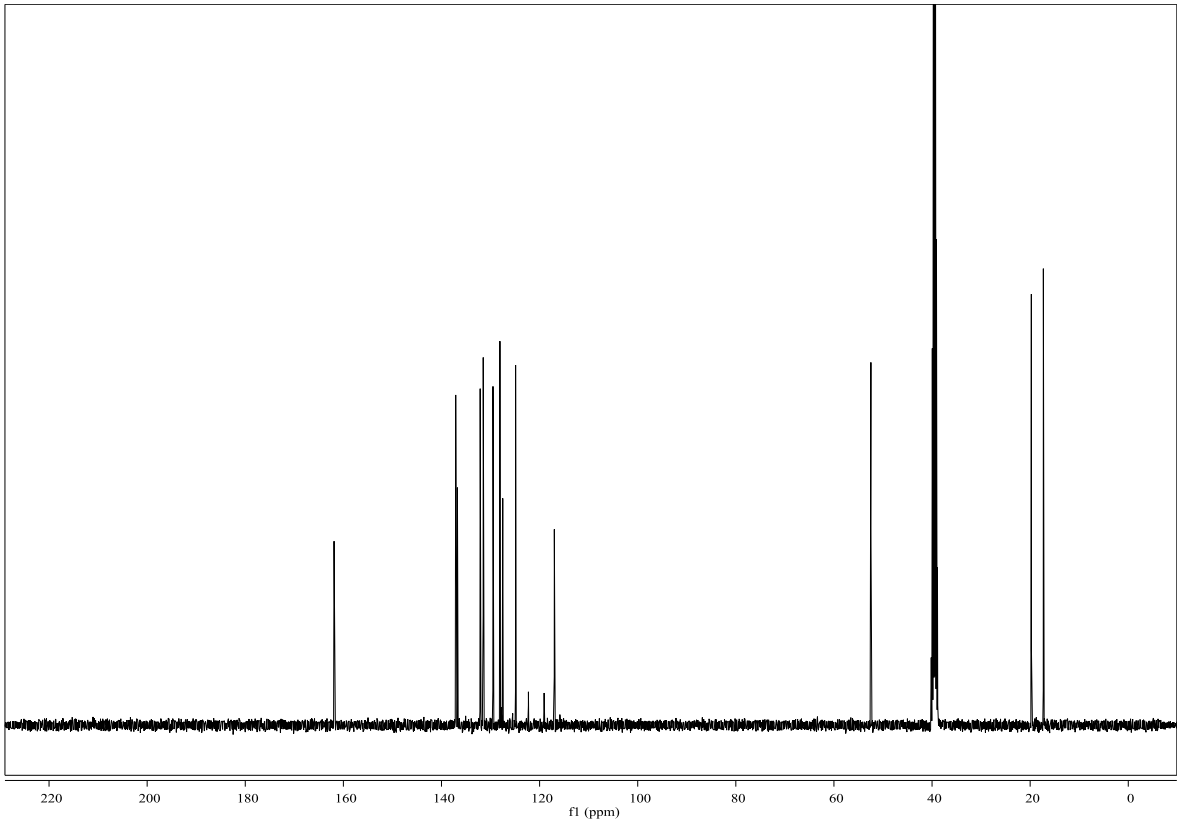
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **95j**



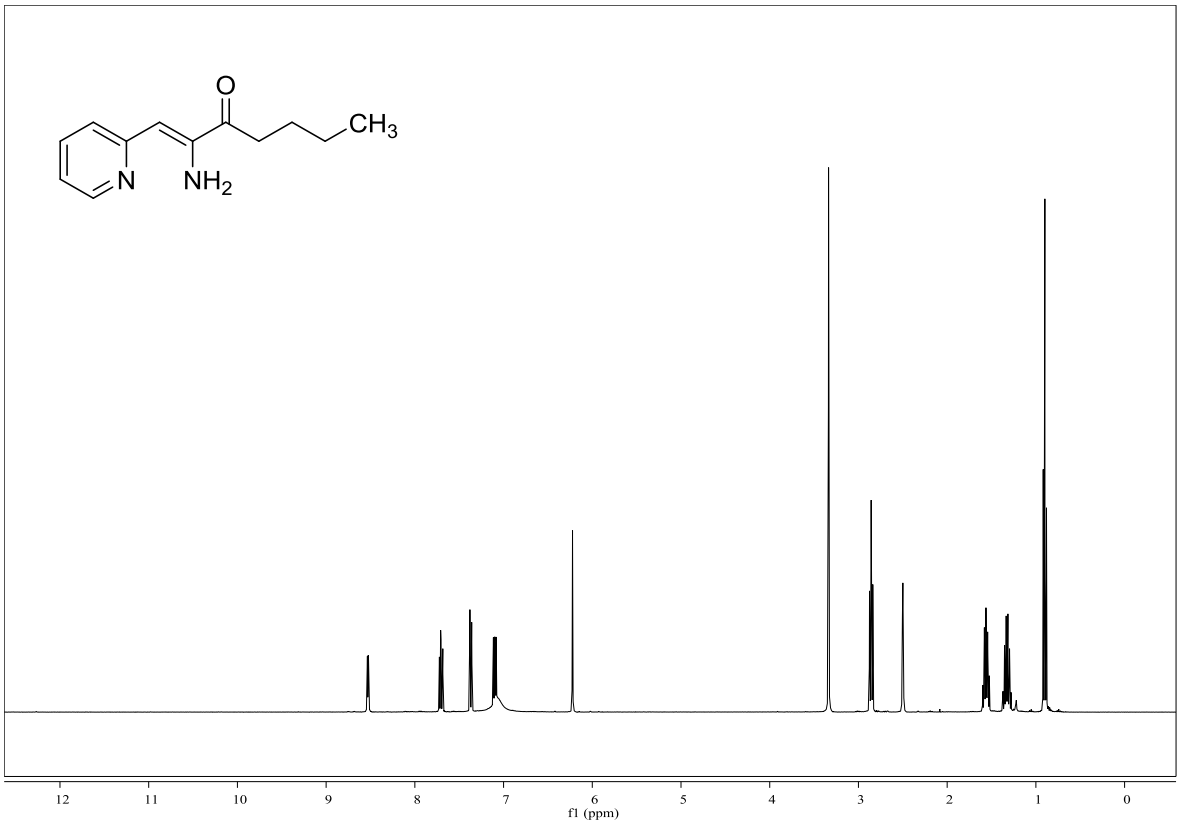
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **95j**



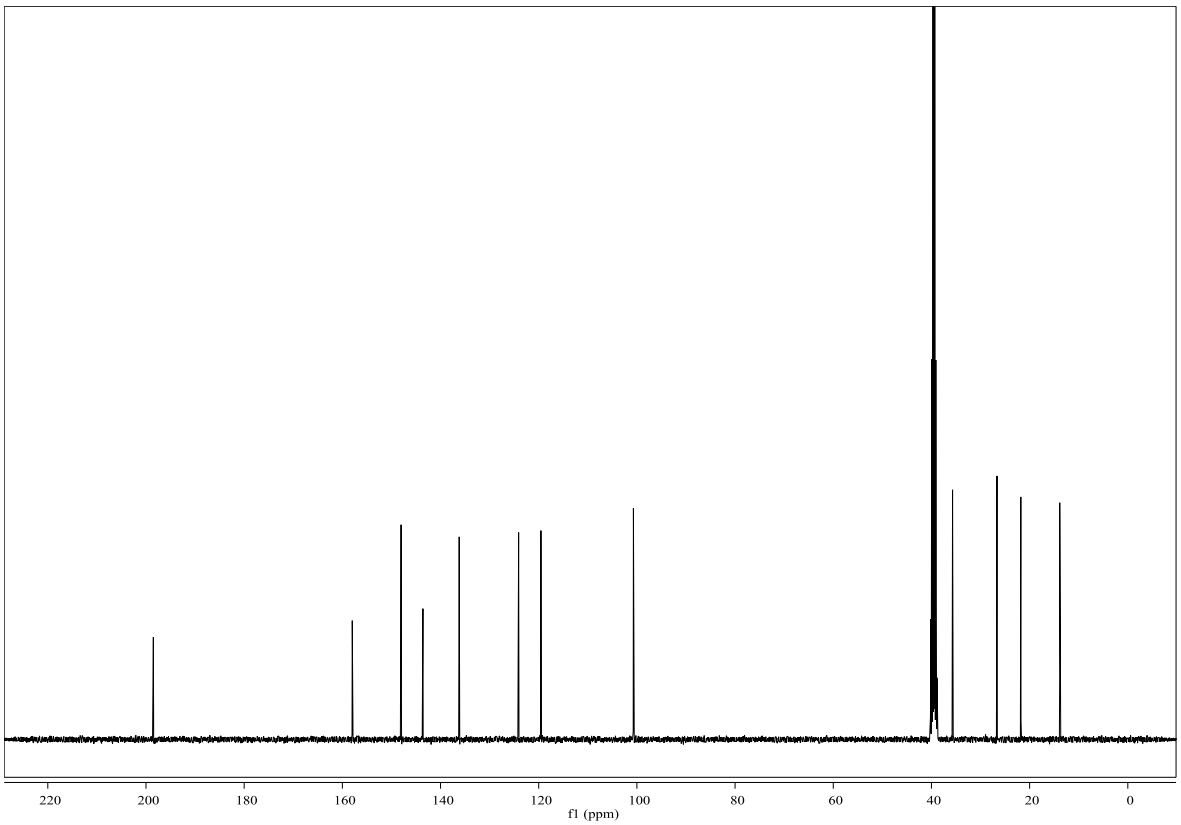
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **95k**



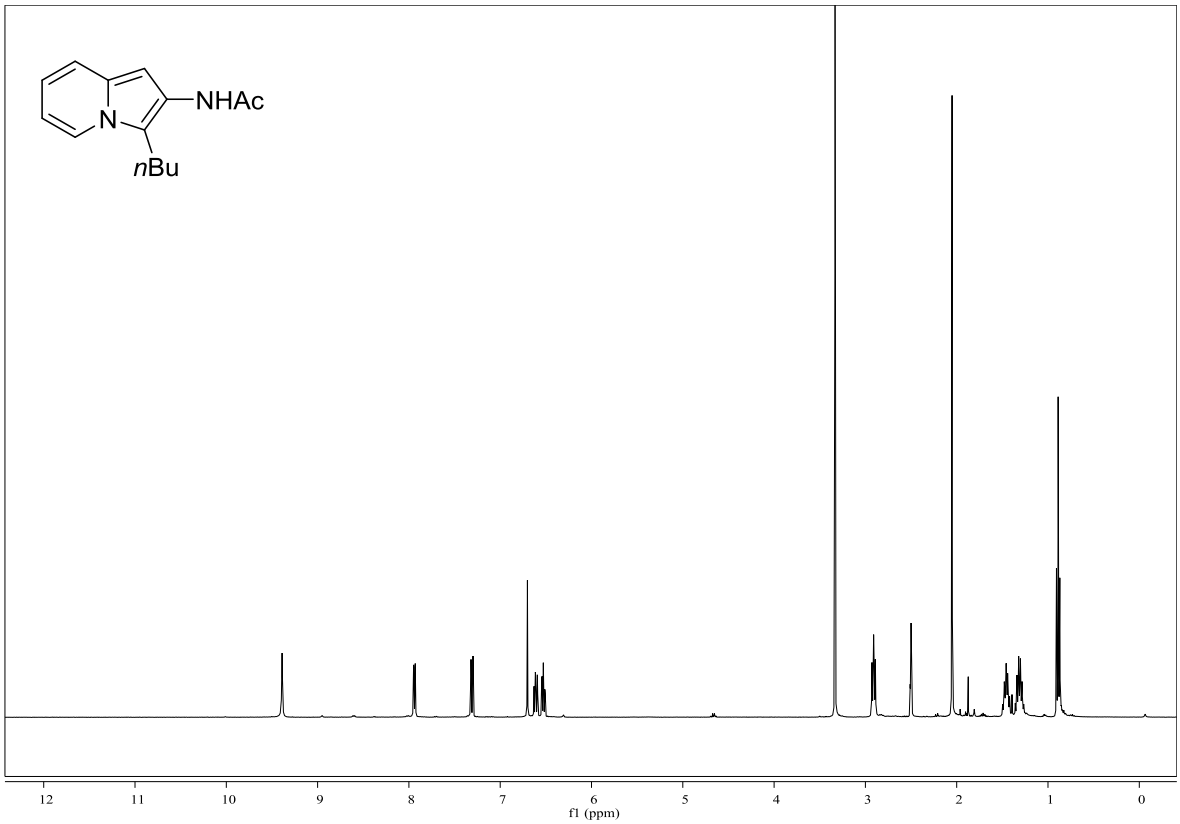
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **95k**



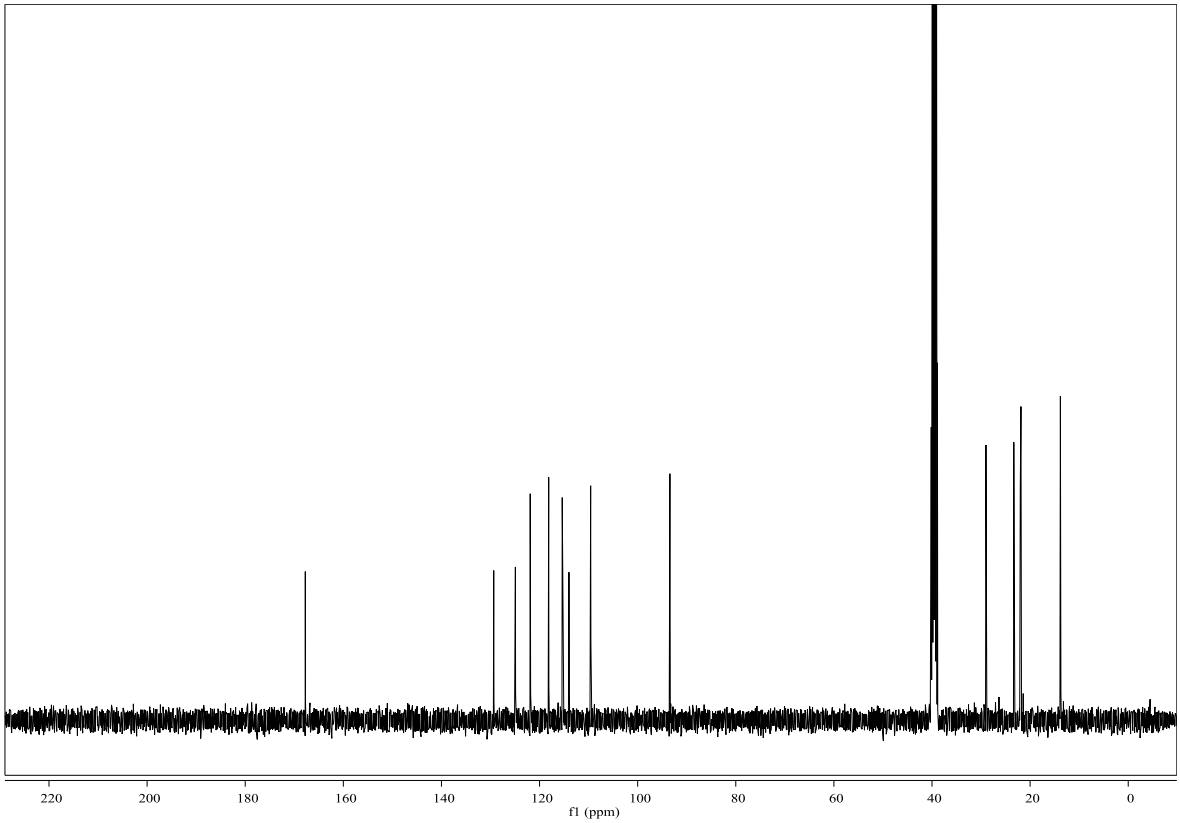
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **101**



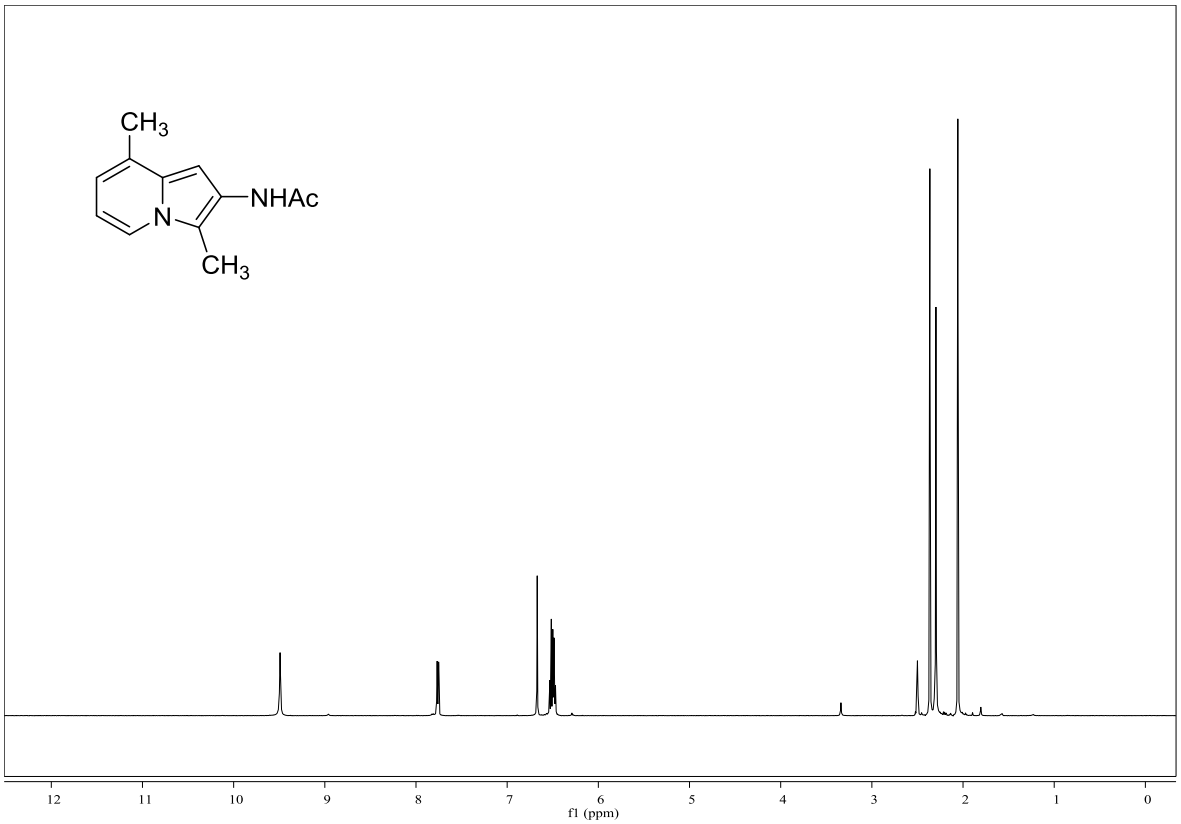
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **101**



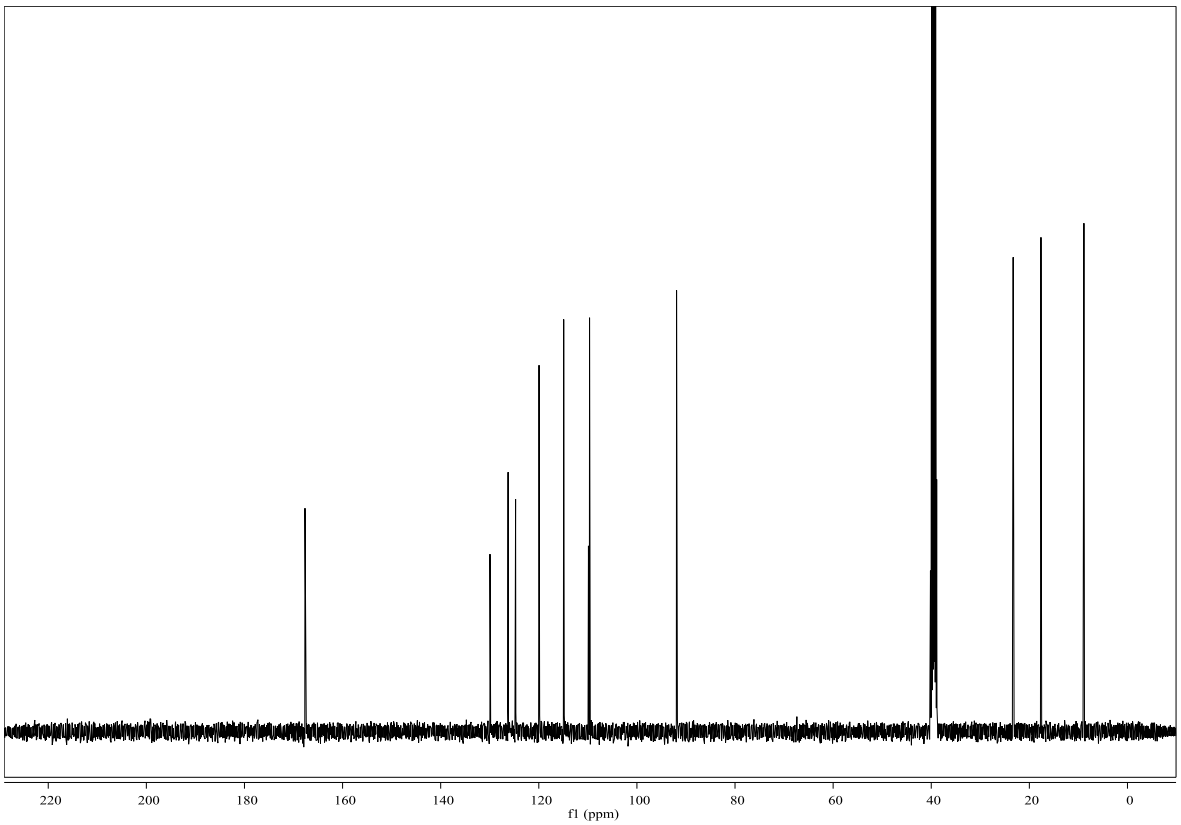
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **102a**



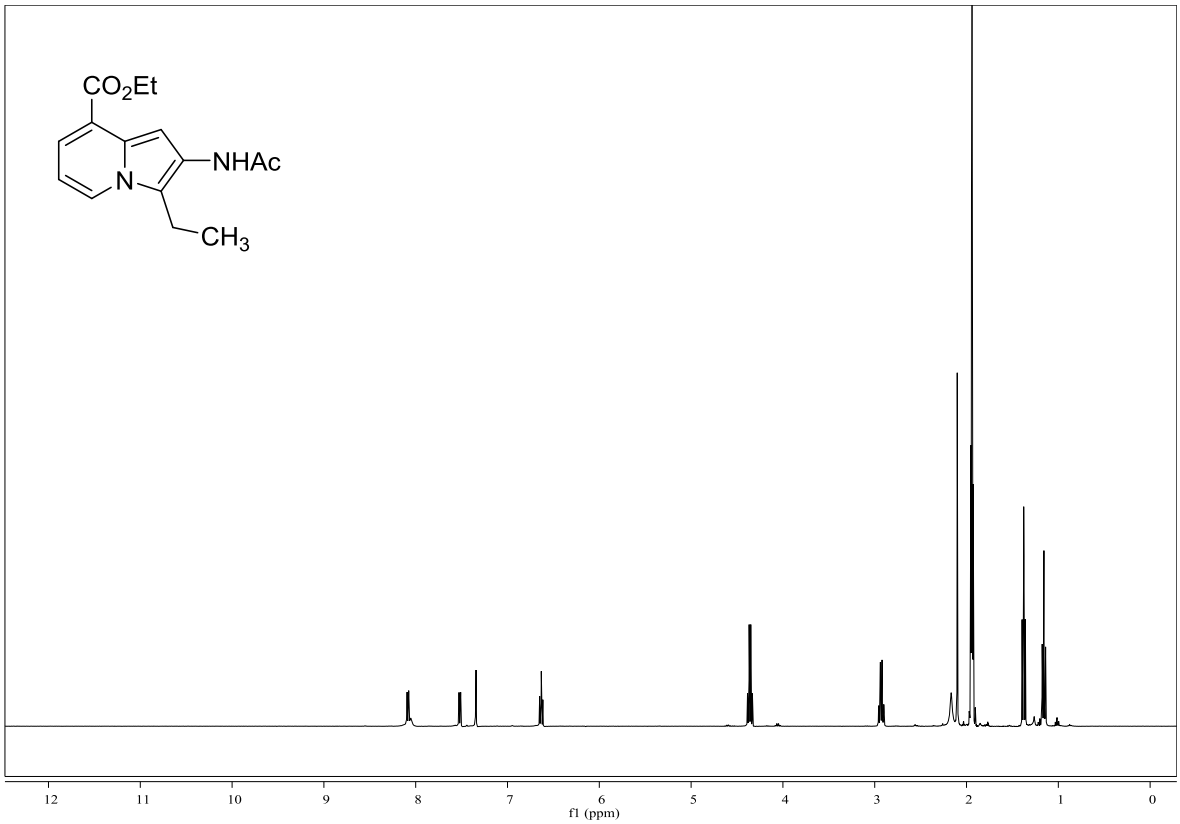
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **102a**



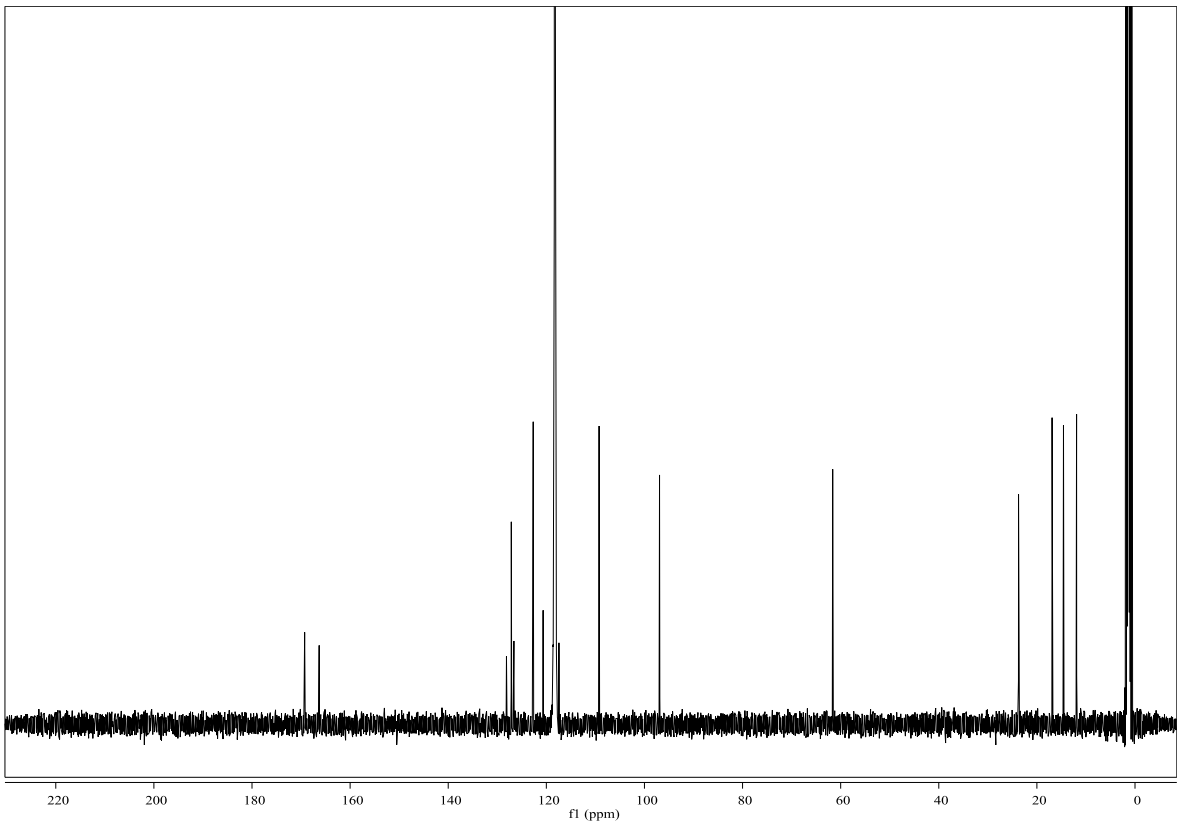
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **102g**



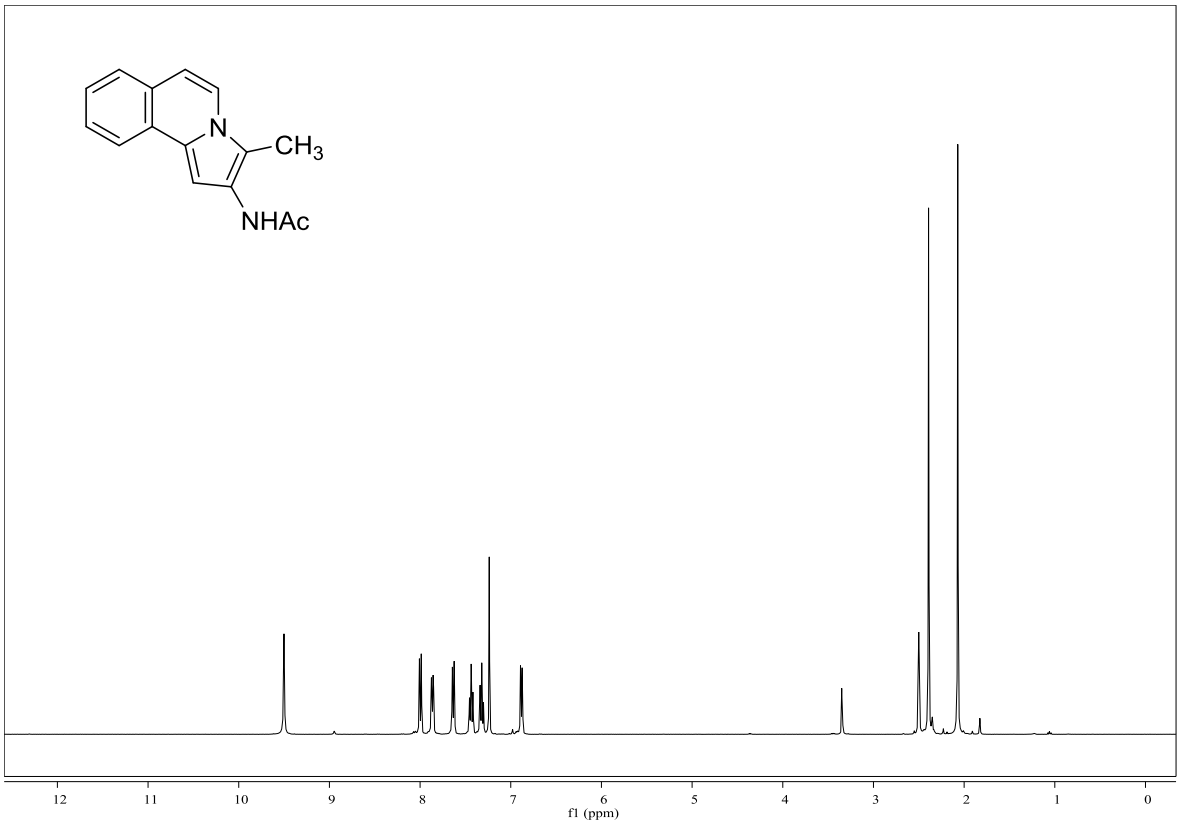
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **102g**



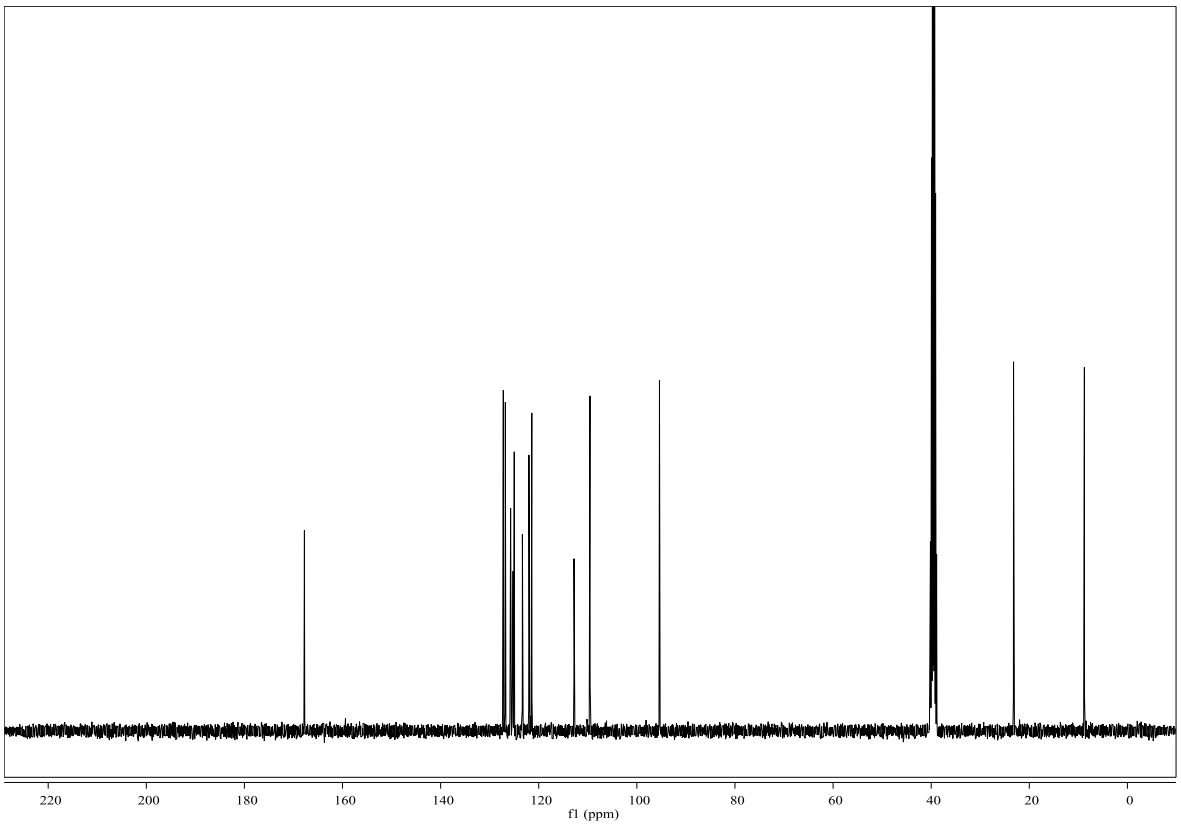
^{1}H NMR (400 MHz, CD_3CN) spectrum of **102k**



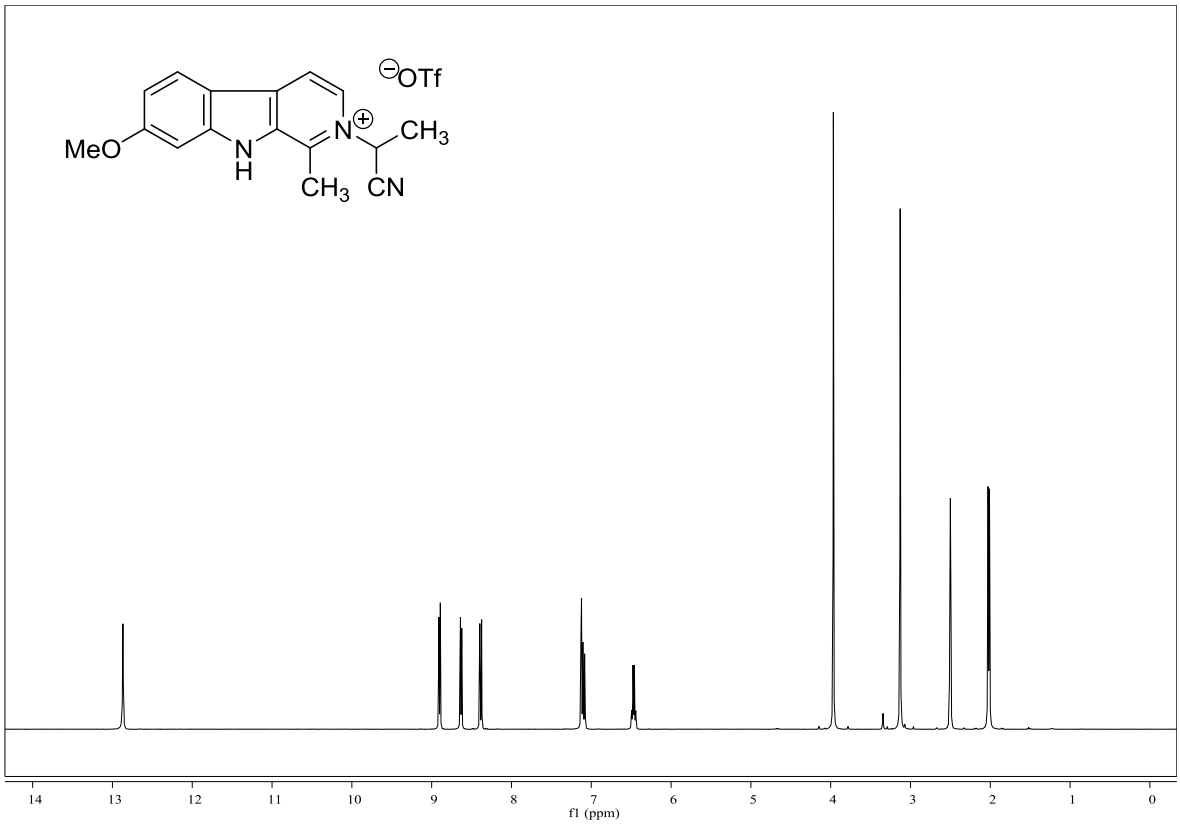
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **102k**



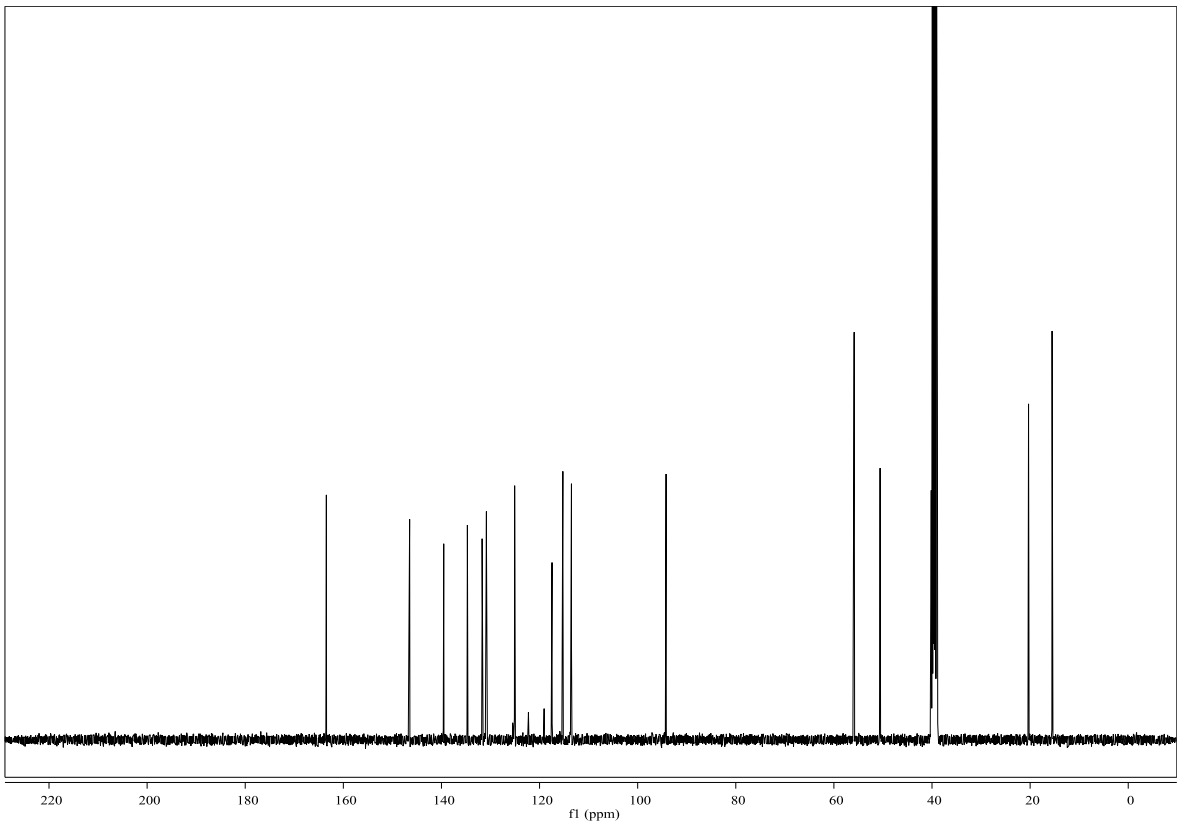
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **102l**



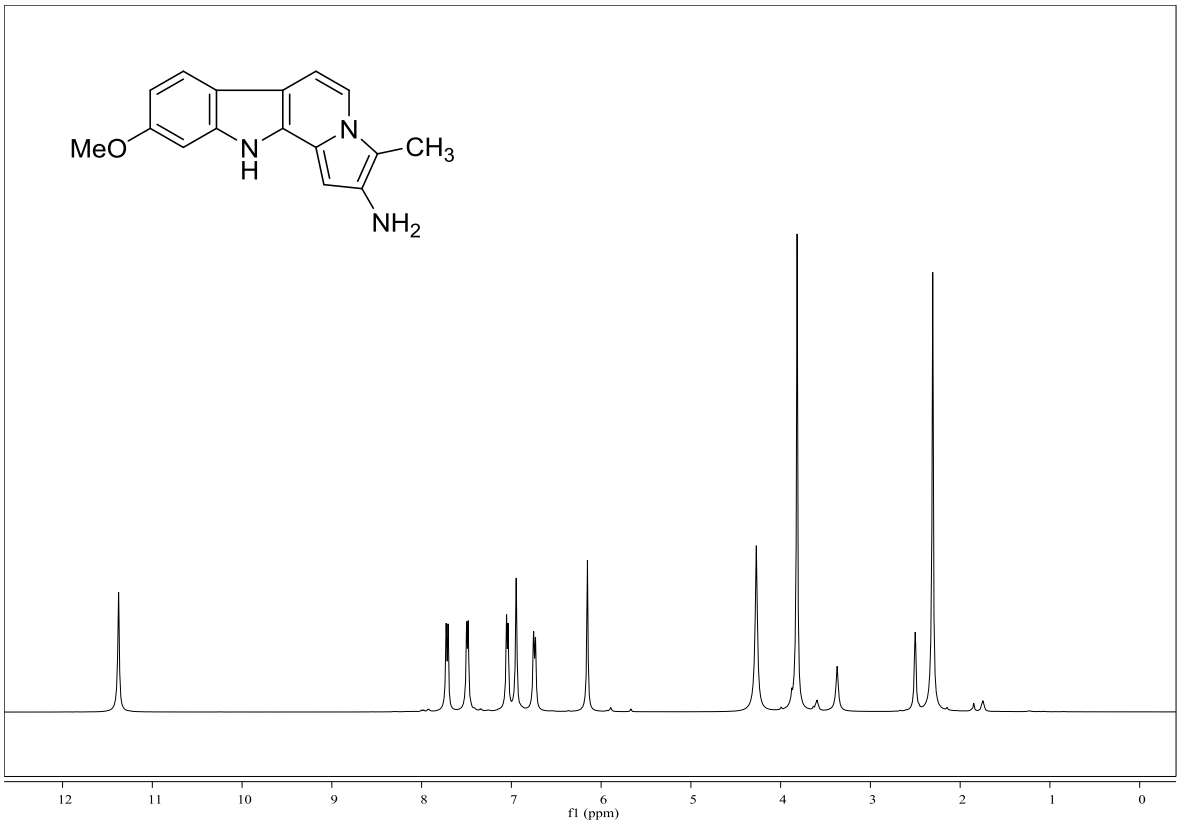
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **102l**



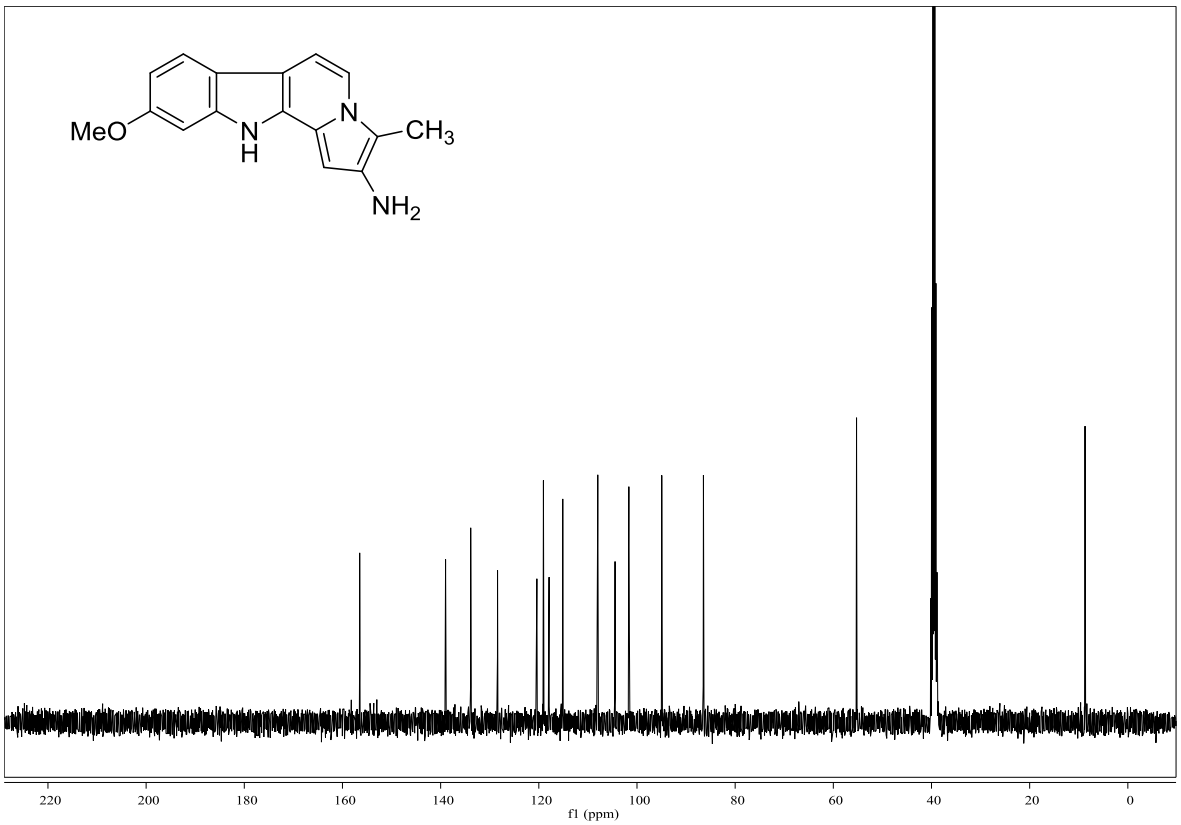
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **104**



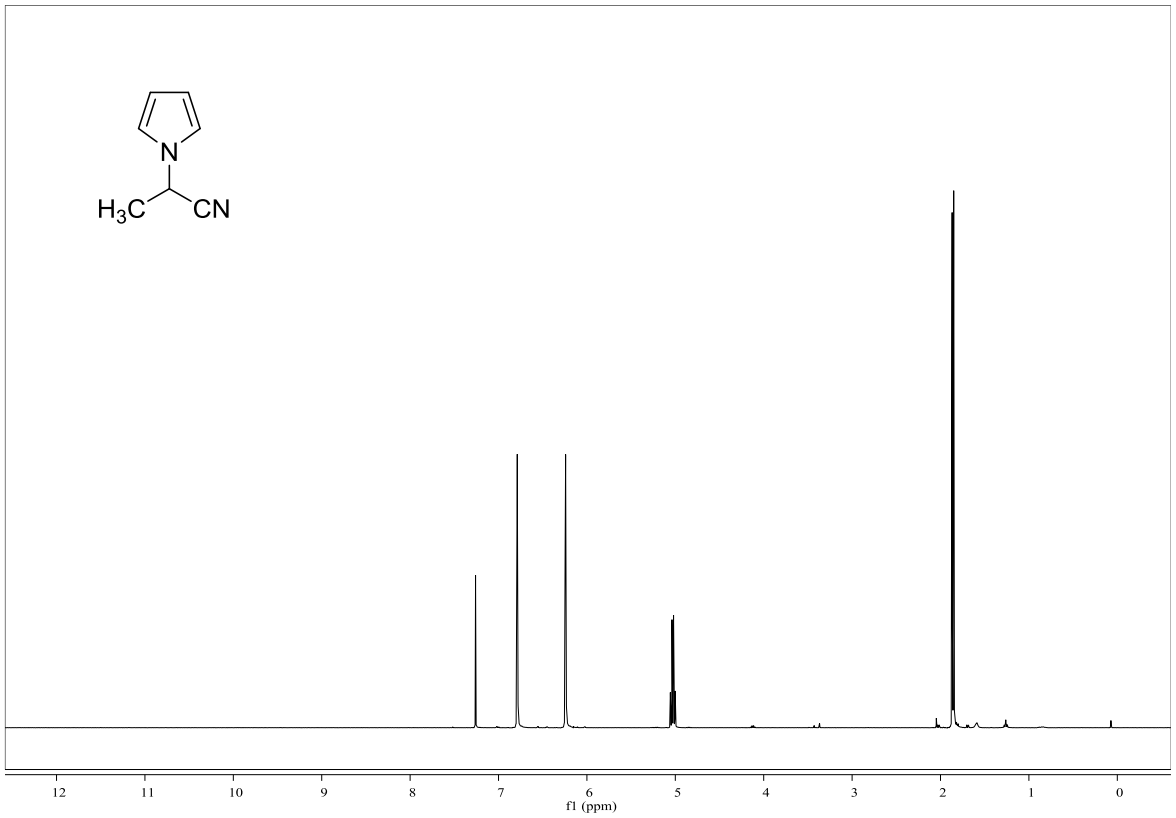
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **104**



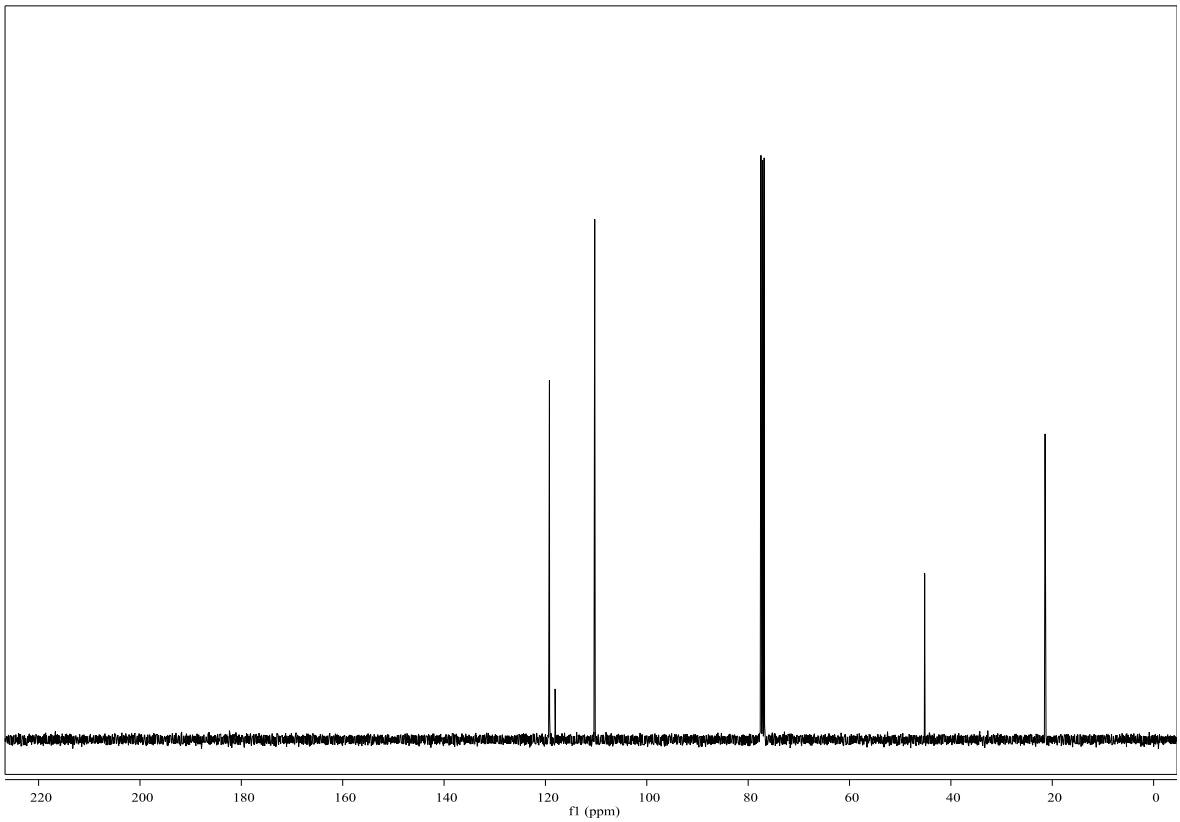
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **105**



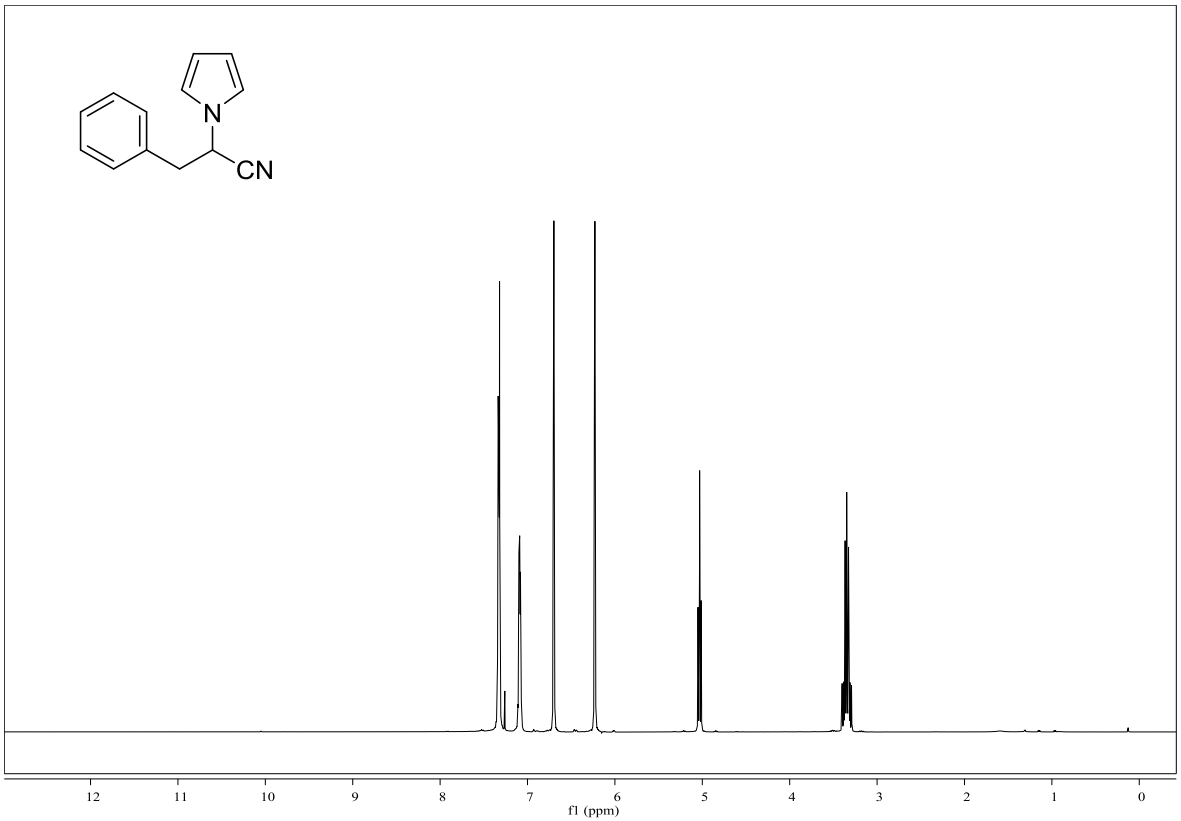
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **105**



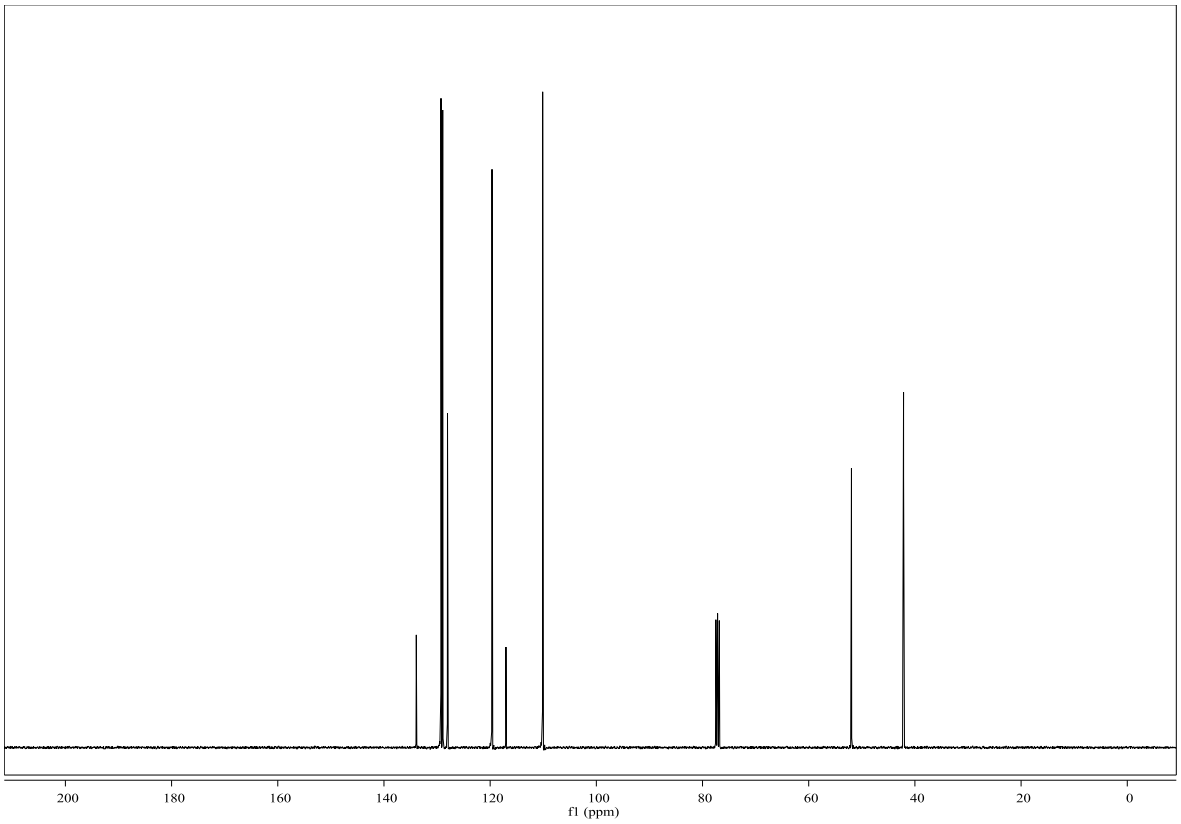
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **109a**



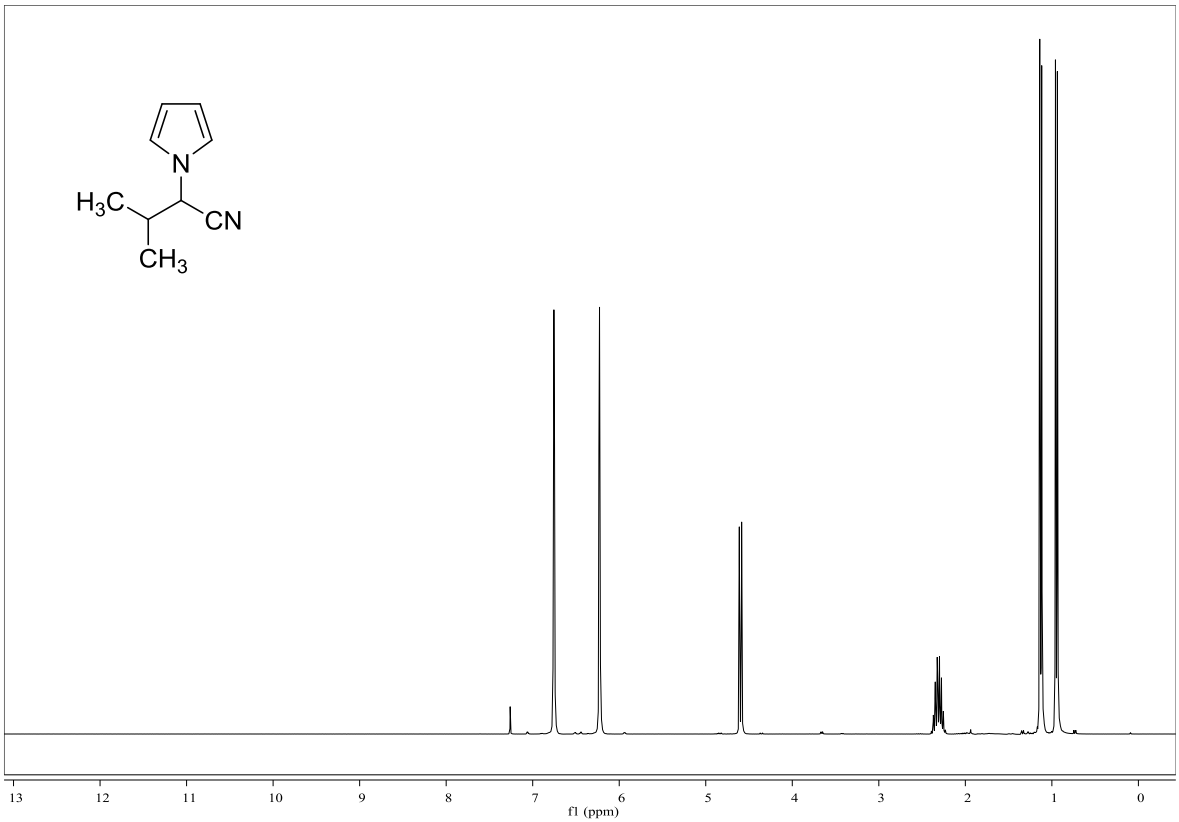
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **109a**



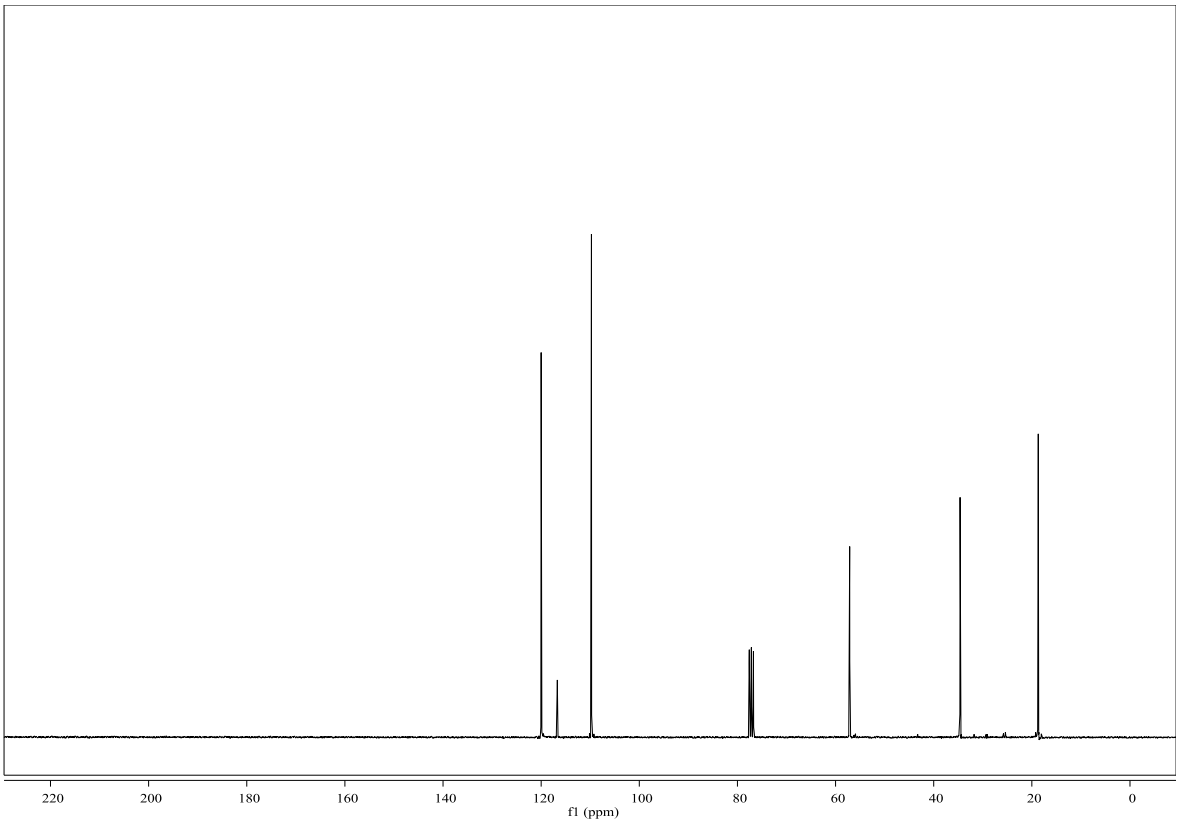
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **109b**



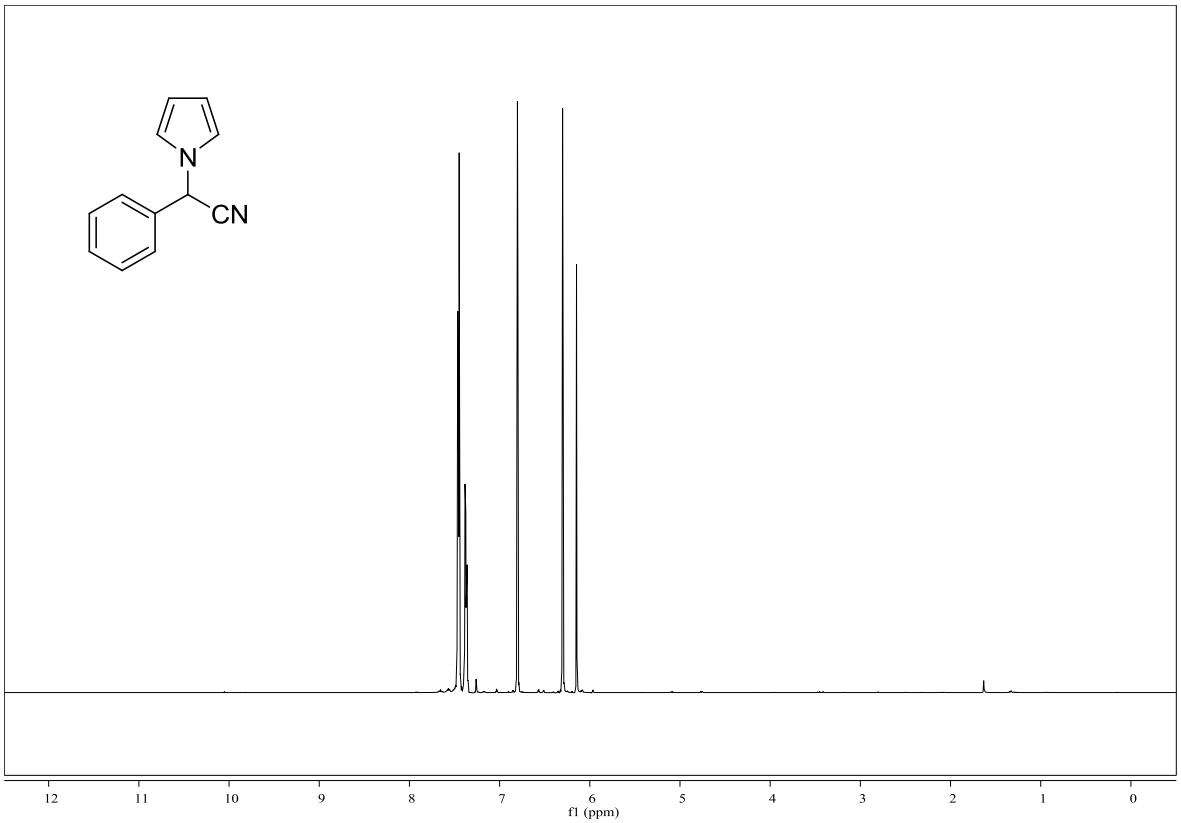
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **109b**



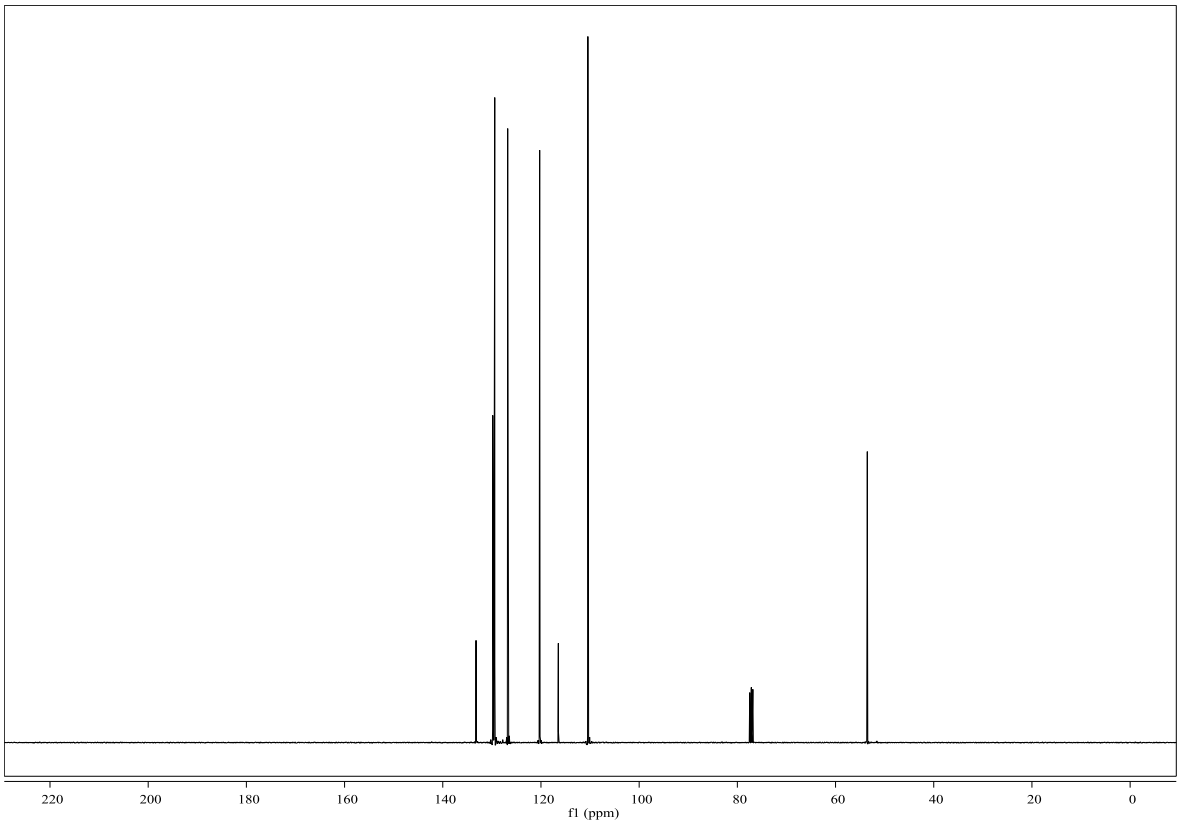
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **109c**



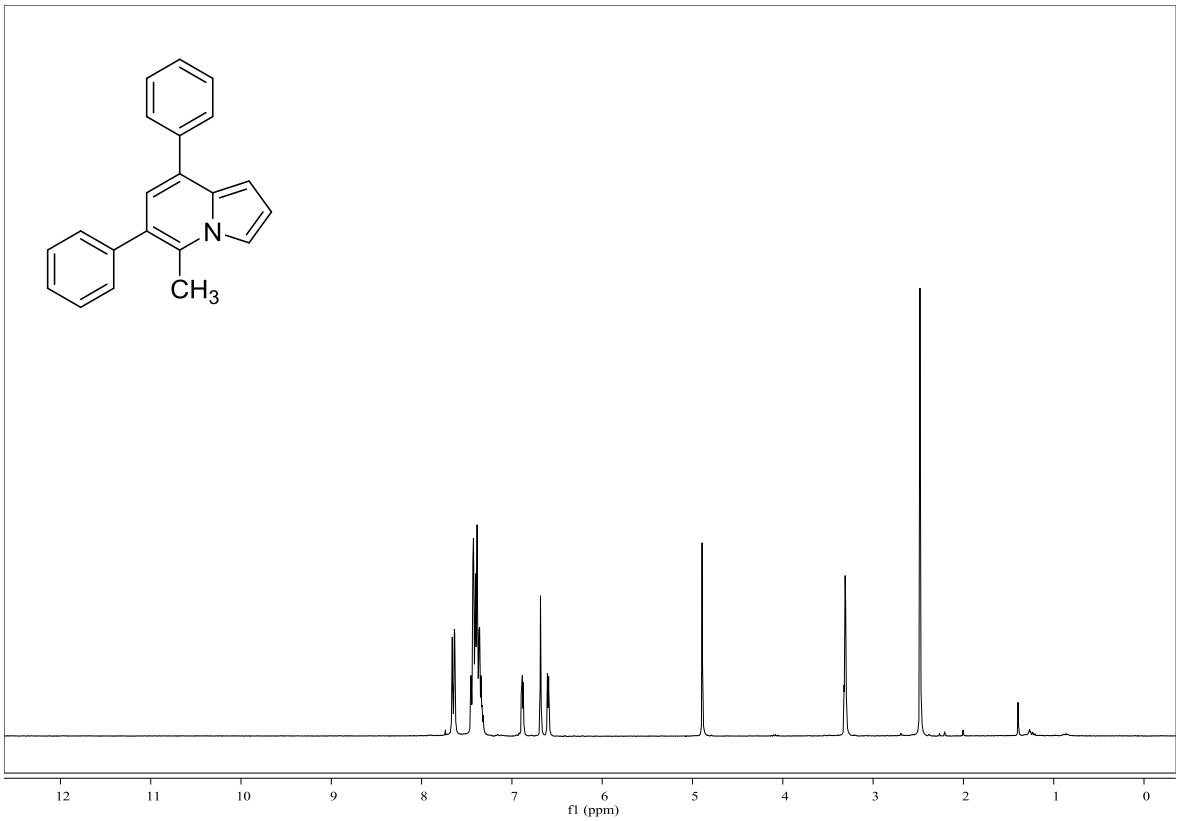
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **109c**



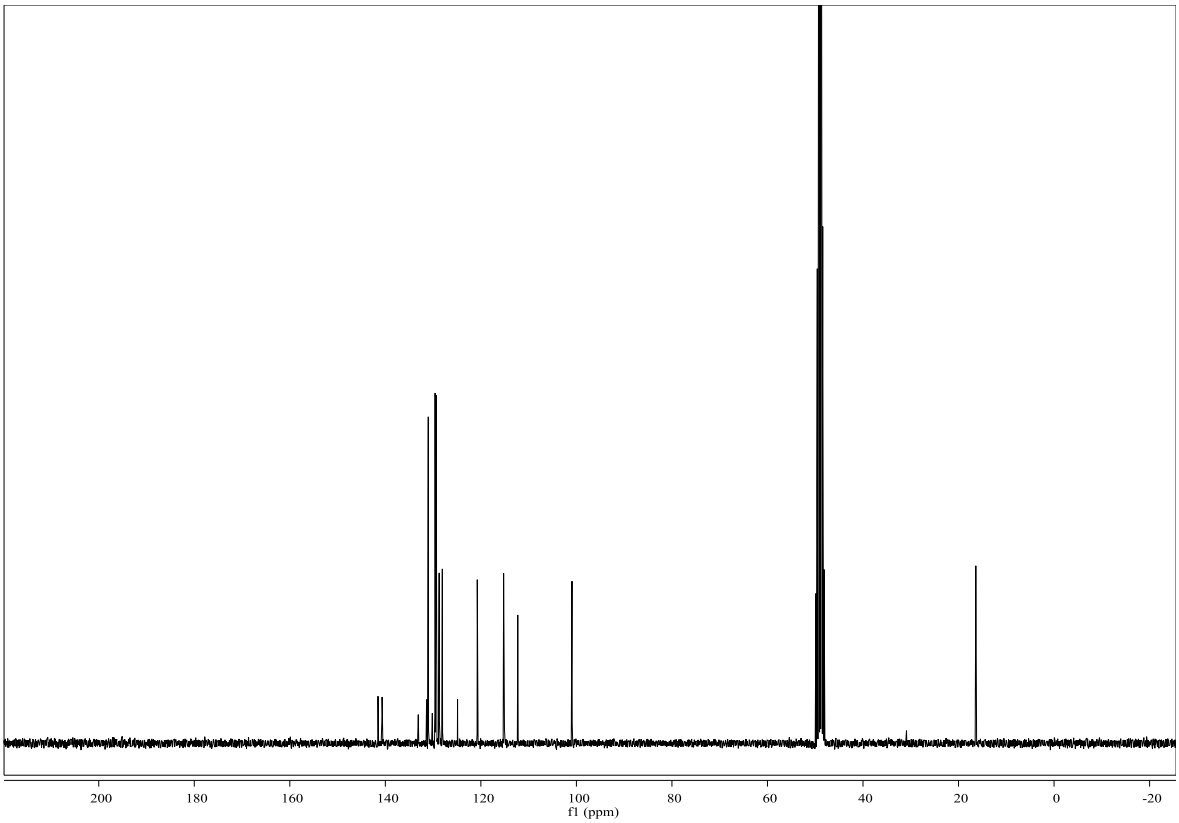
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **109d**



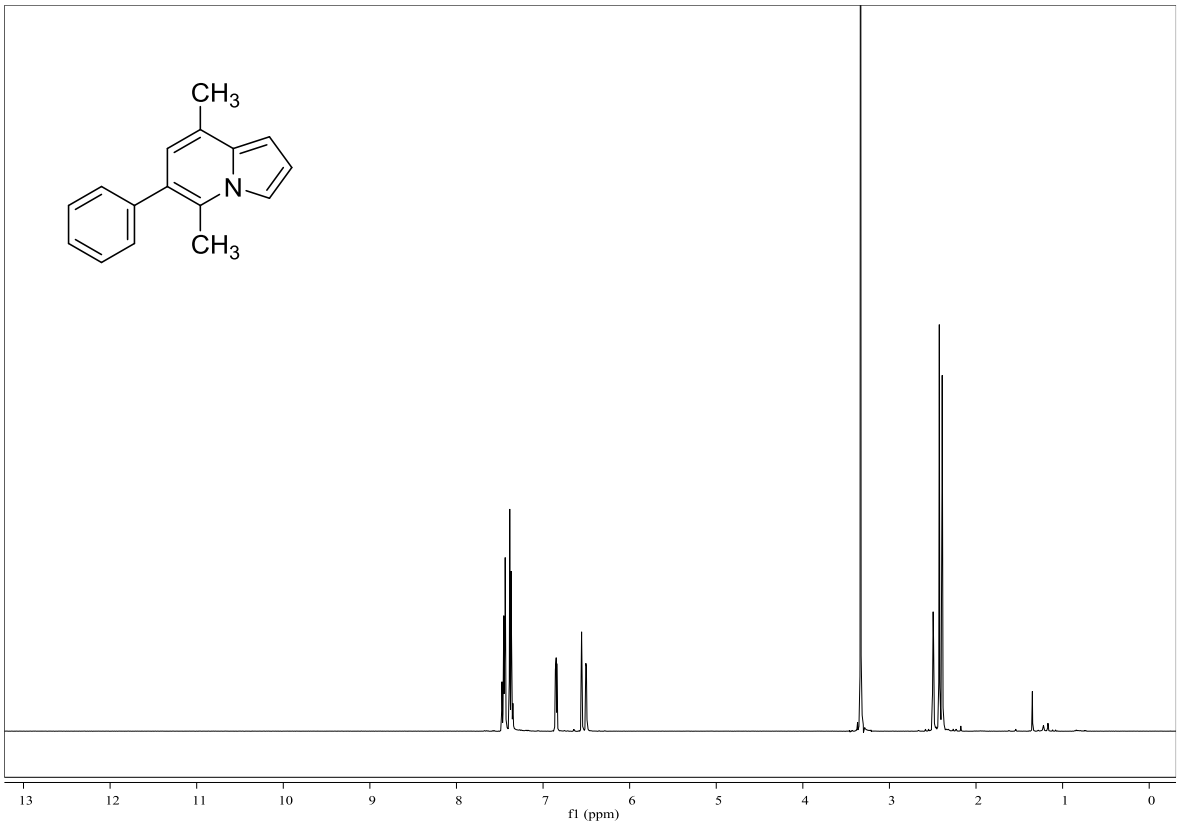
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **109d**



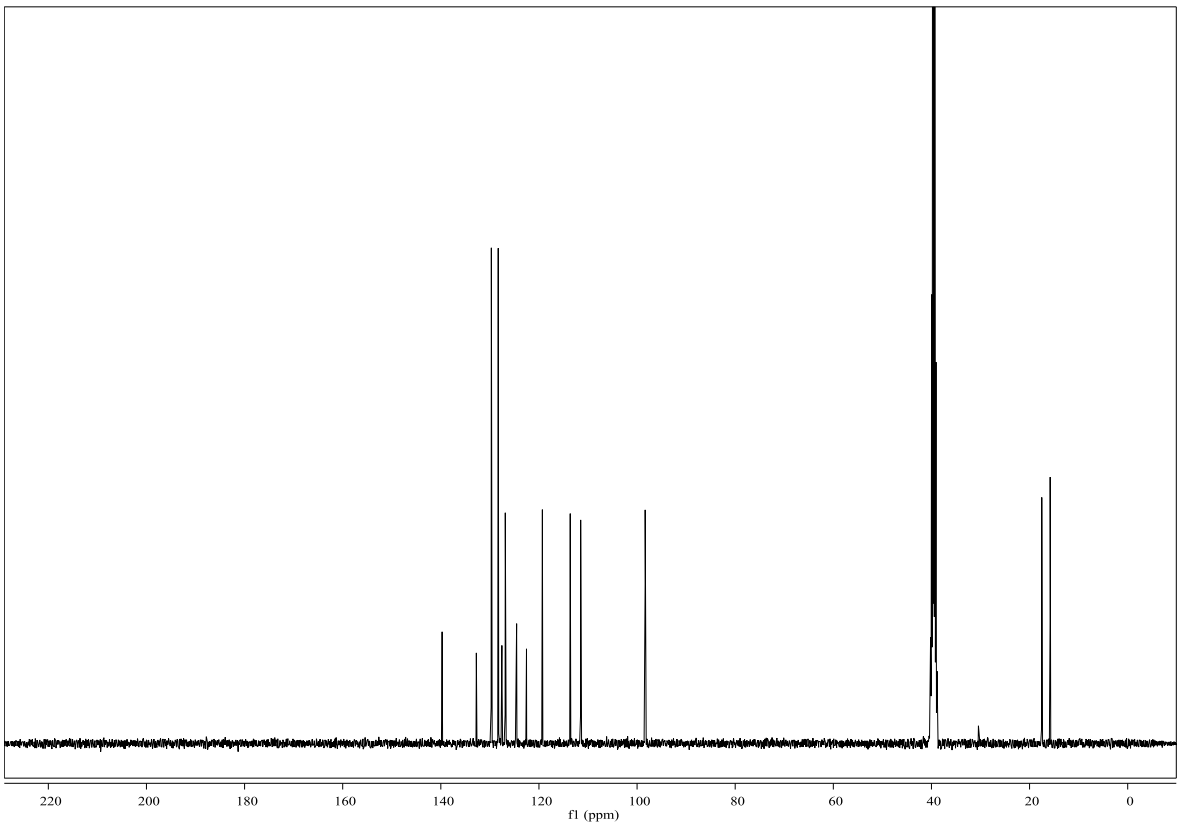
^{1}H NMR (300 MHz, CD_3OD) spectrum of **116a**



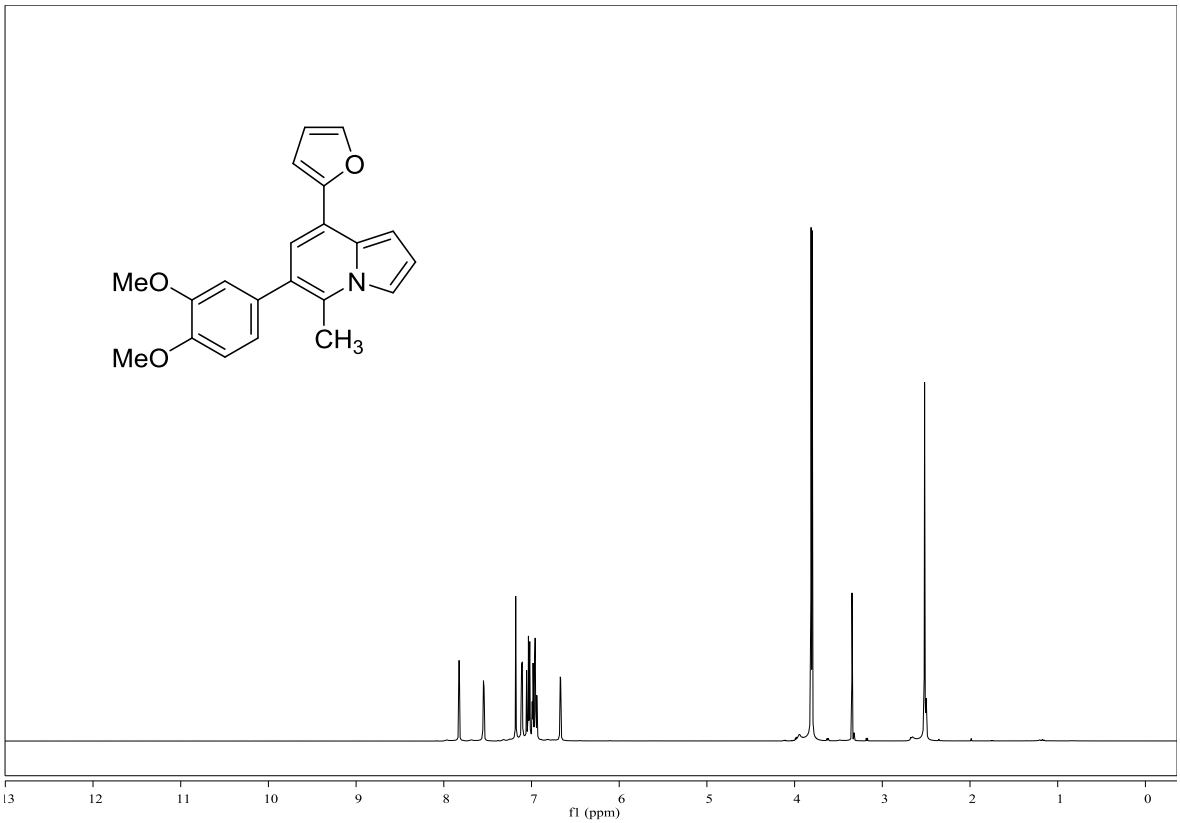
^{13}C NMR (75 MHz, CD_3OD) spectrum of **116a**



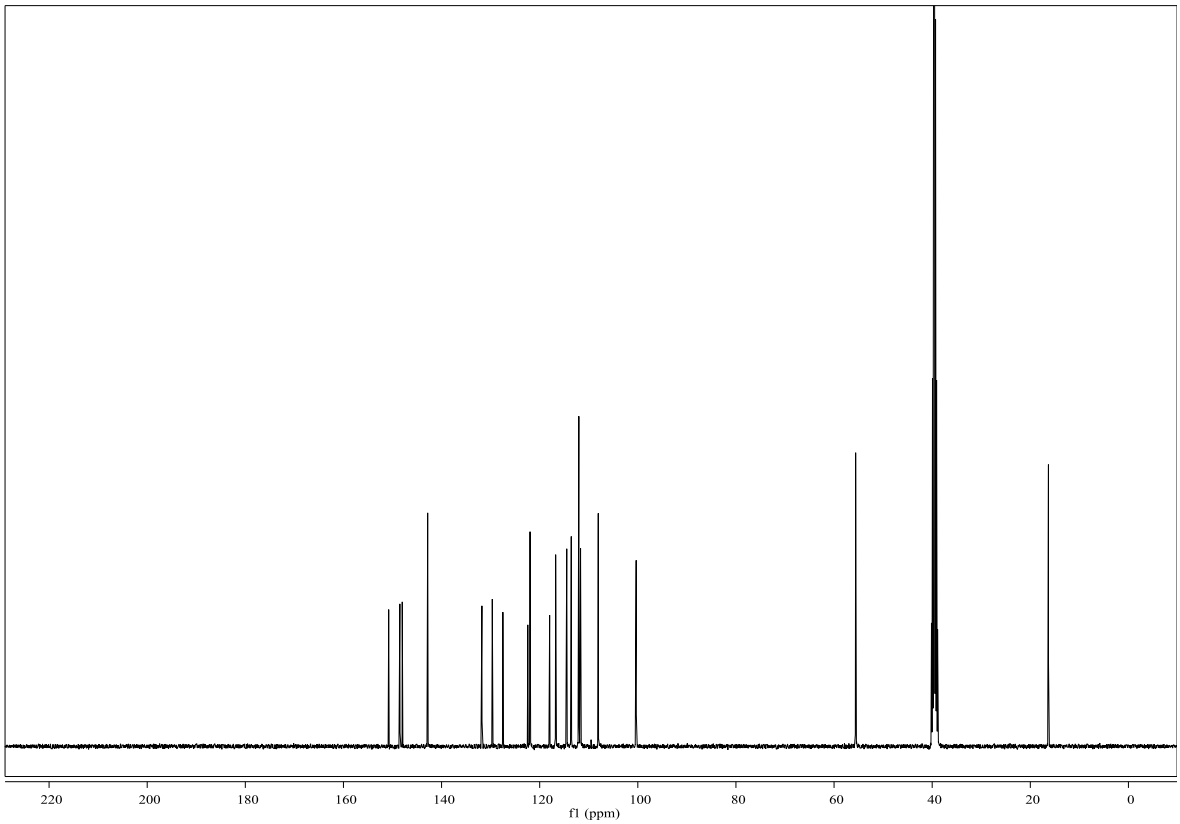
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **116d**



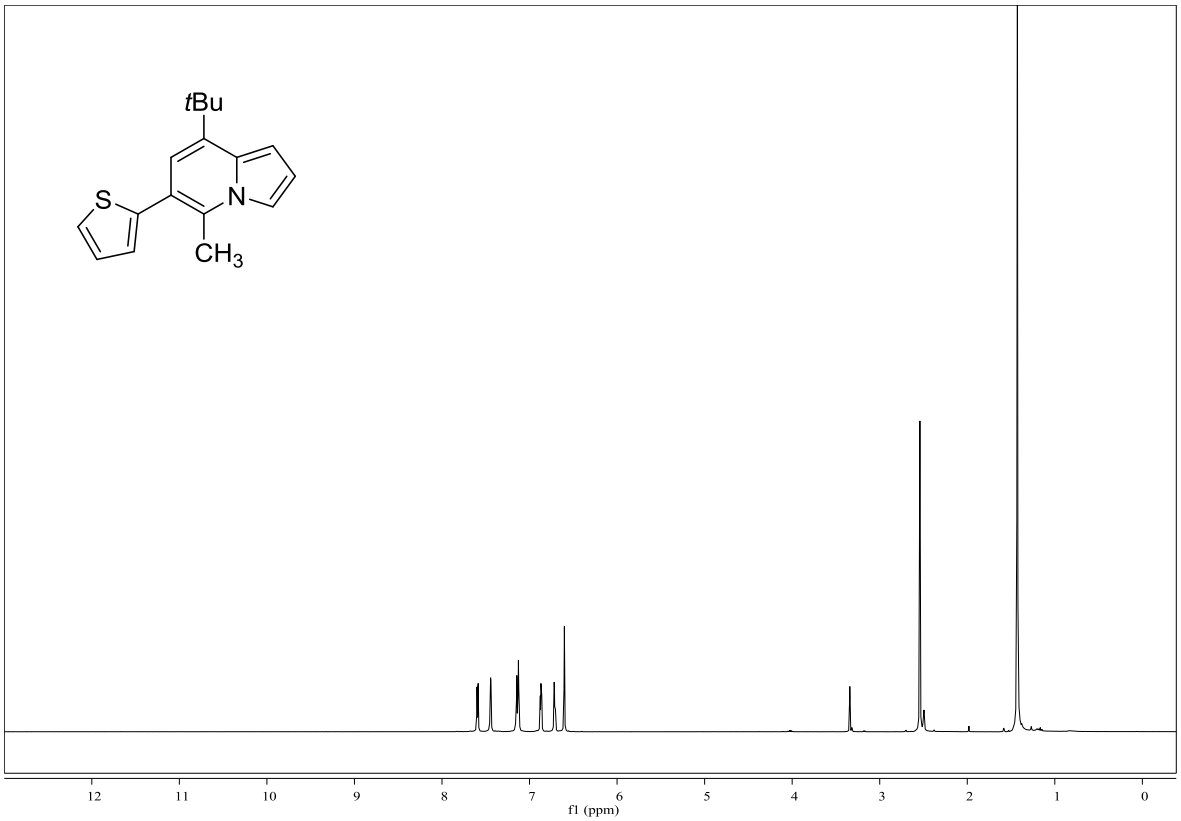
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **116d**



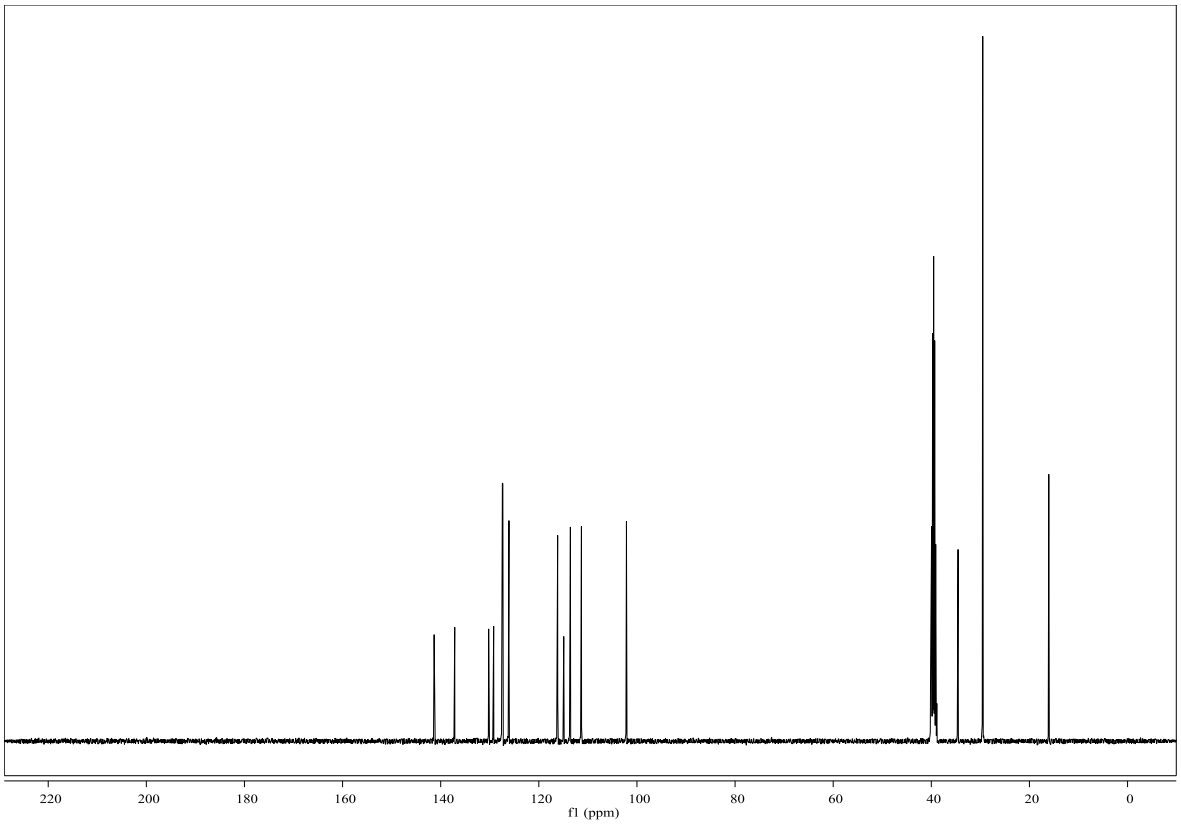
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **116k**



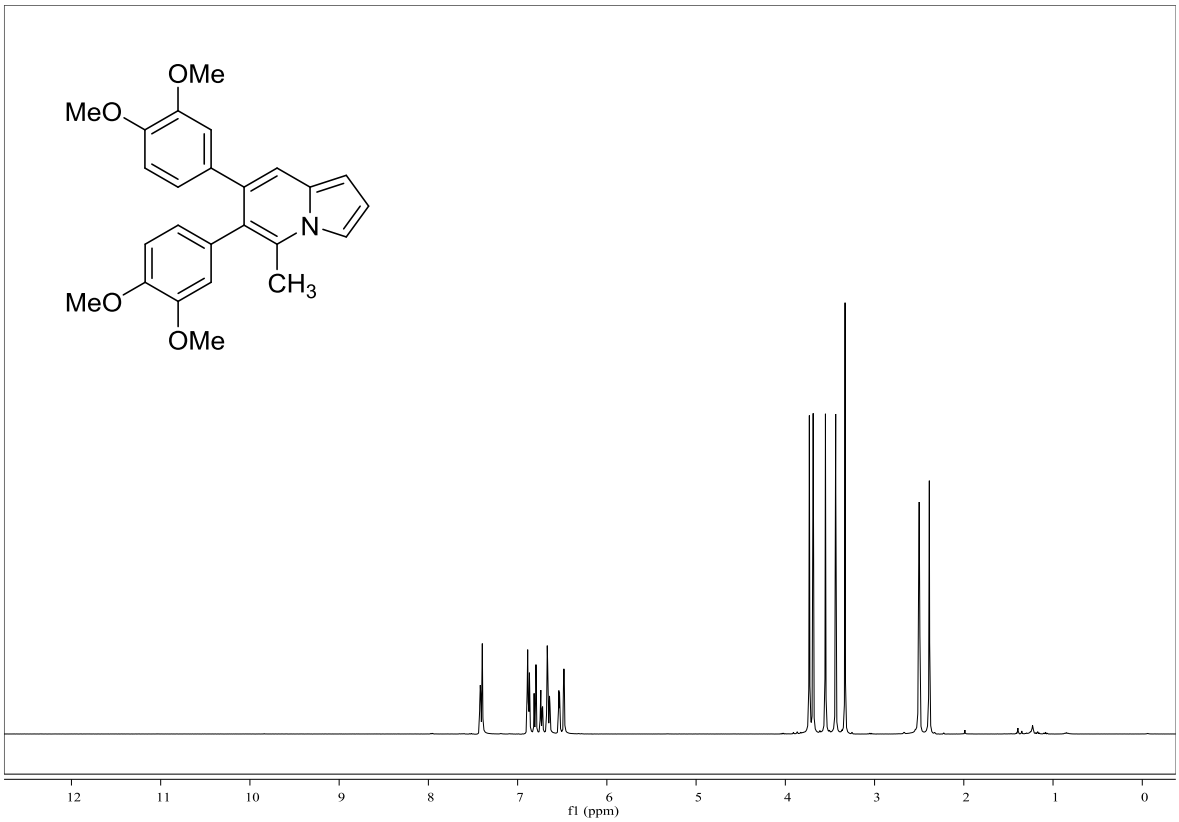
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **116k**



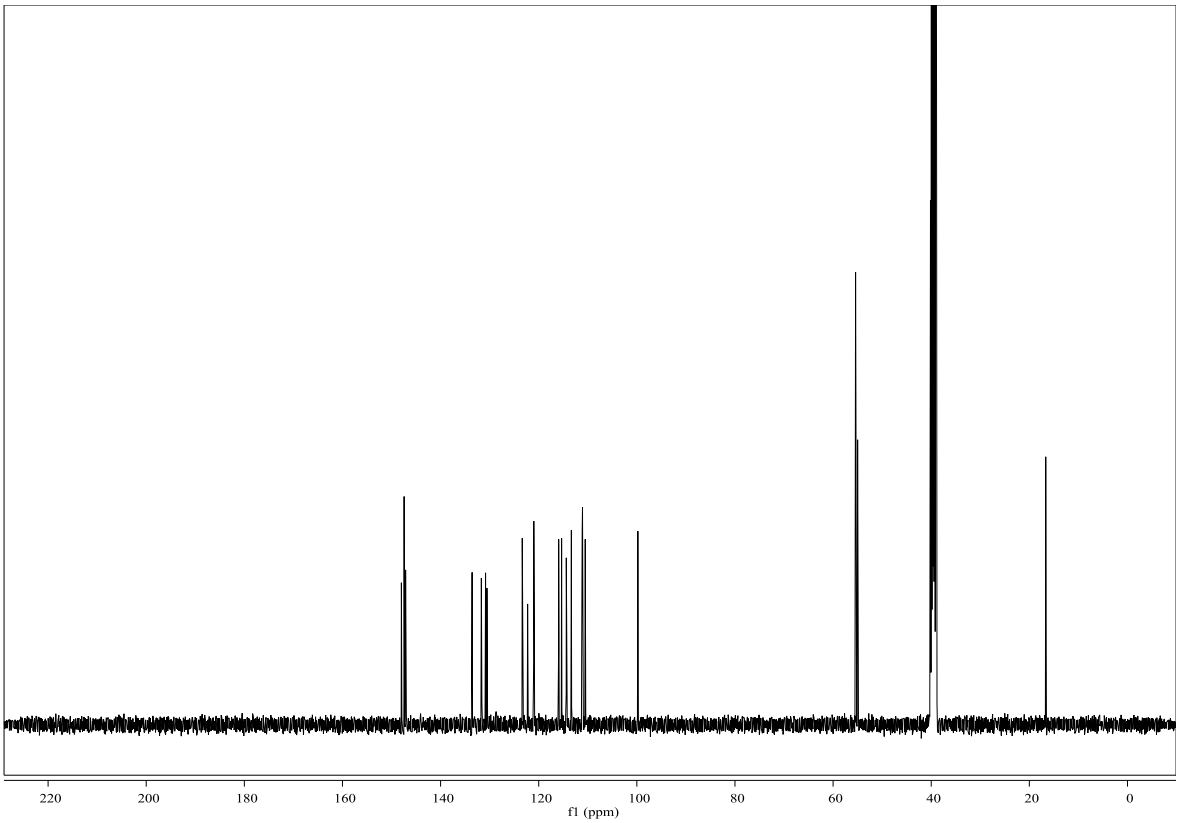
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **116m**



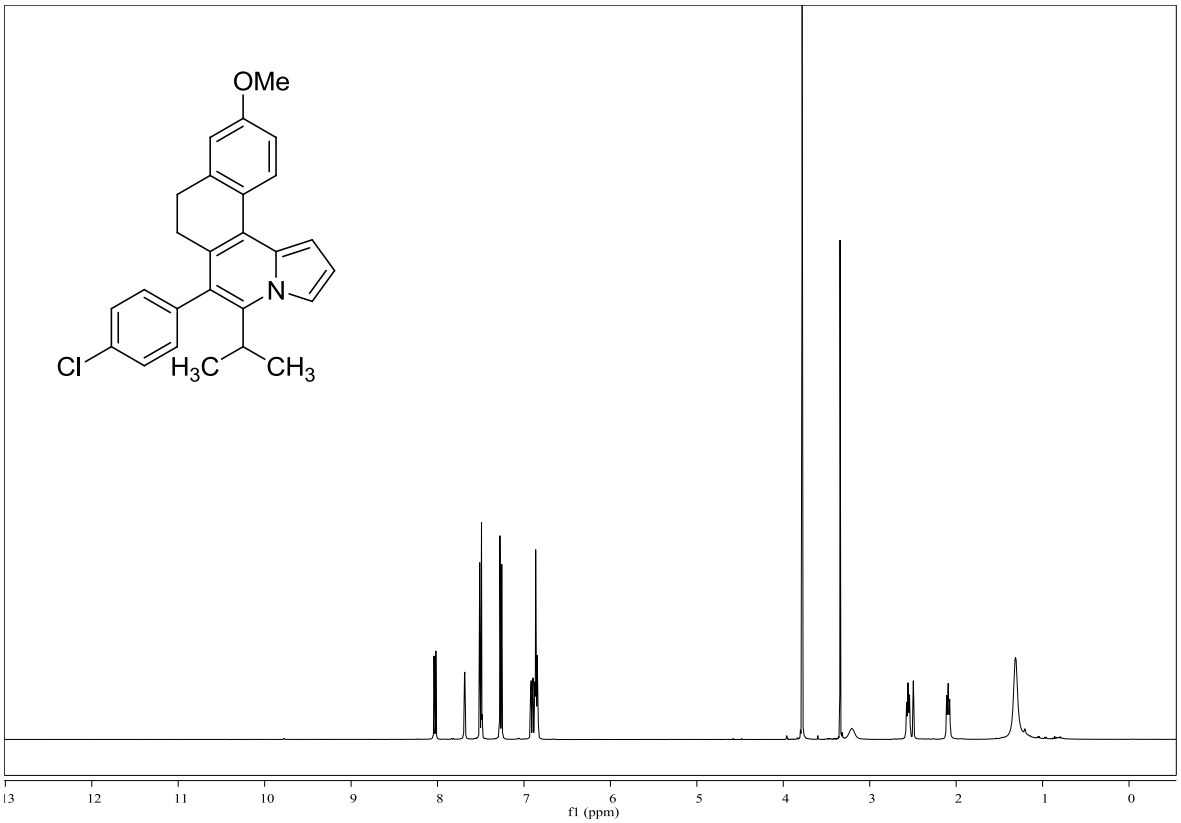
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **116m**



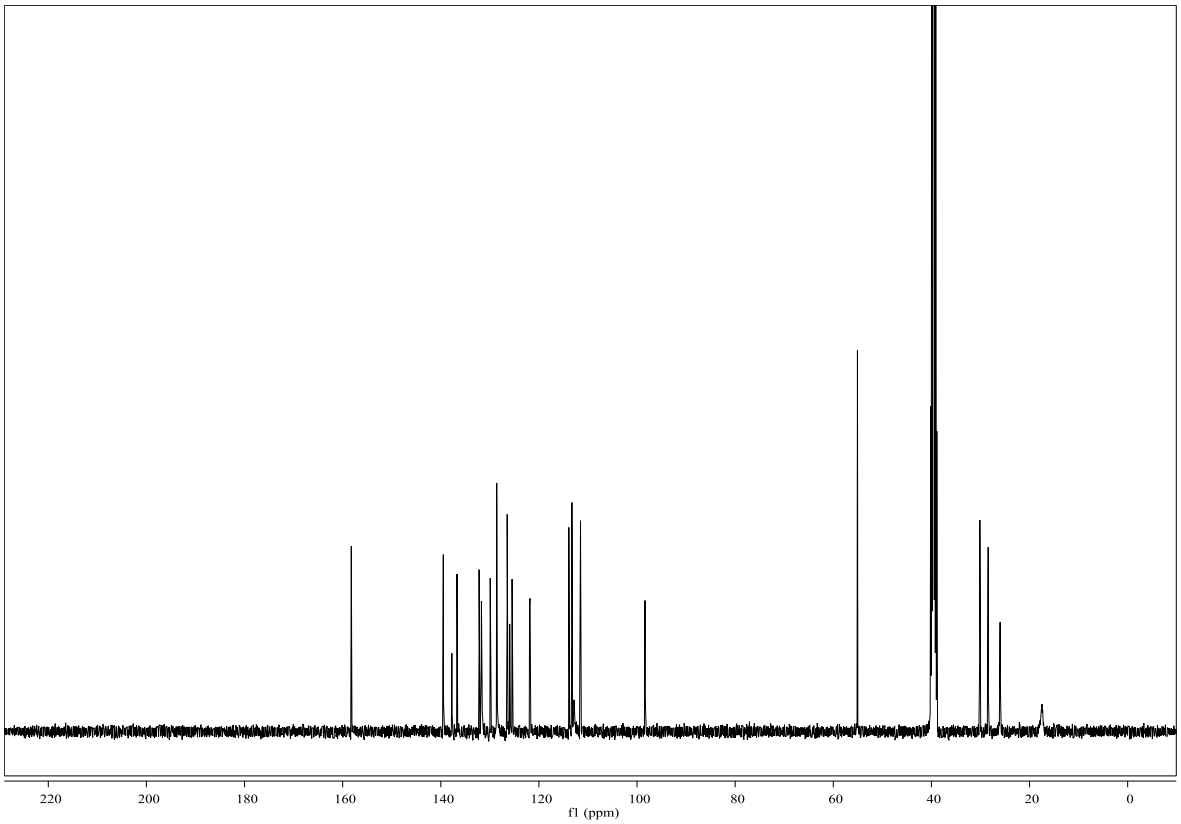
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **116n**



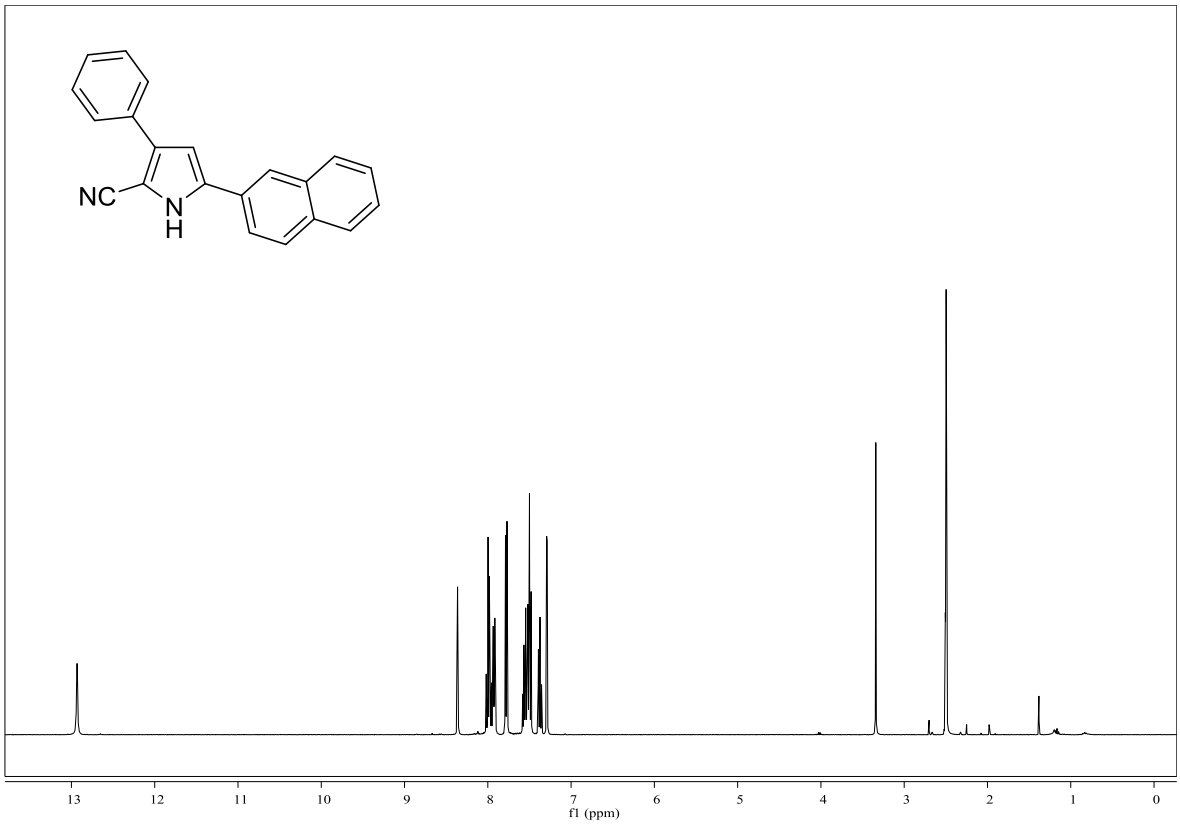
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **116n**



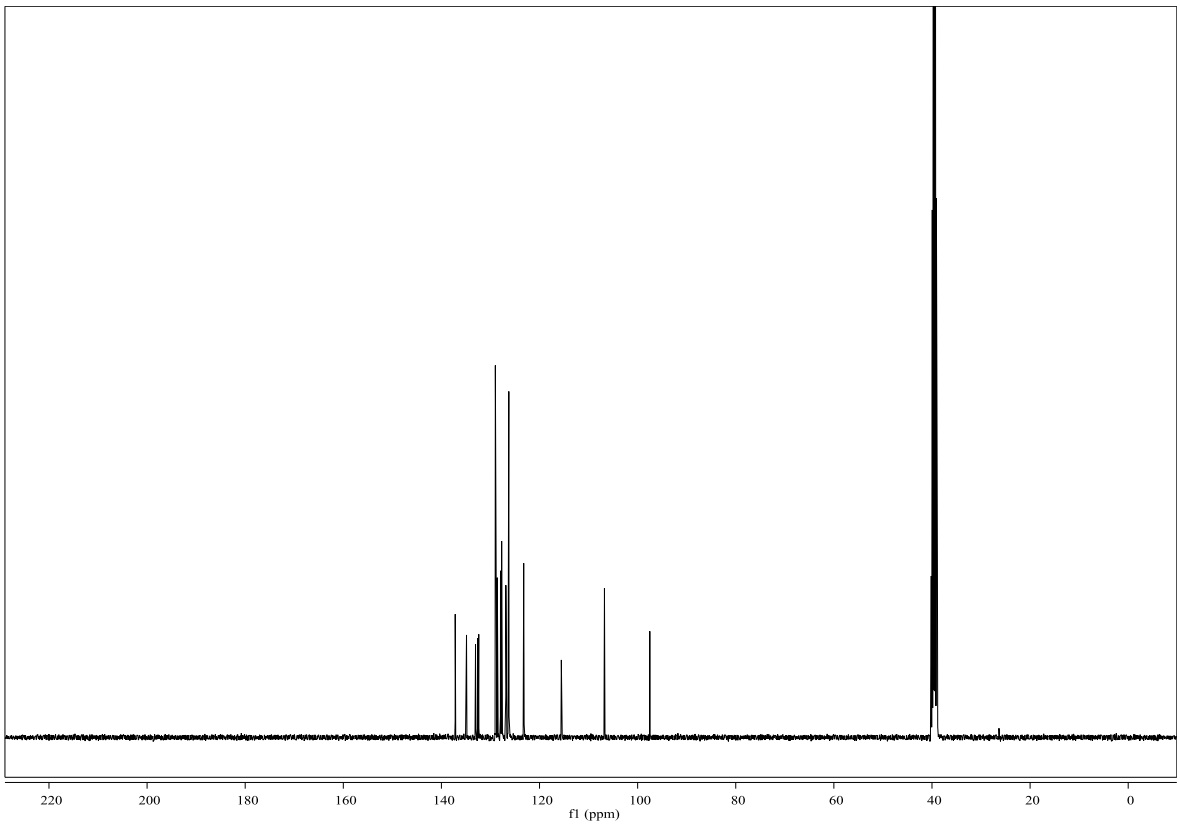
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **117**



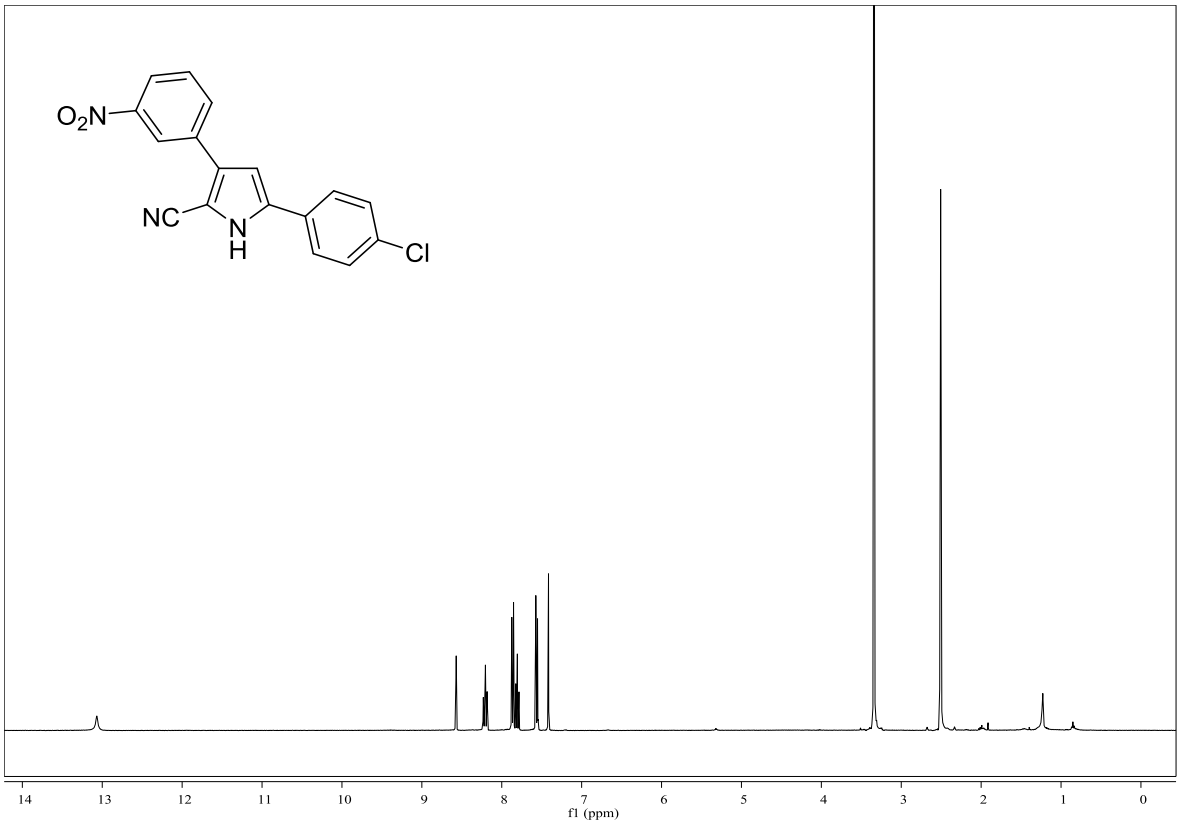
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **117**



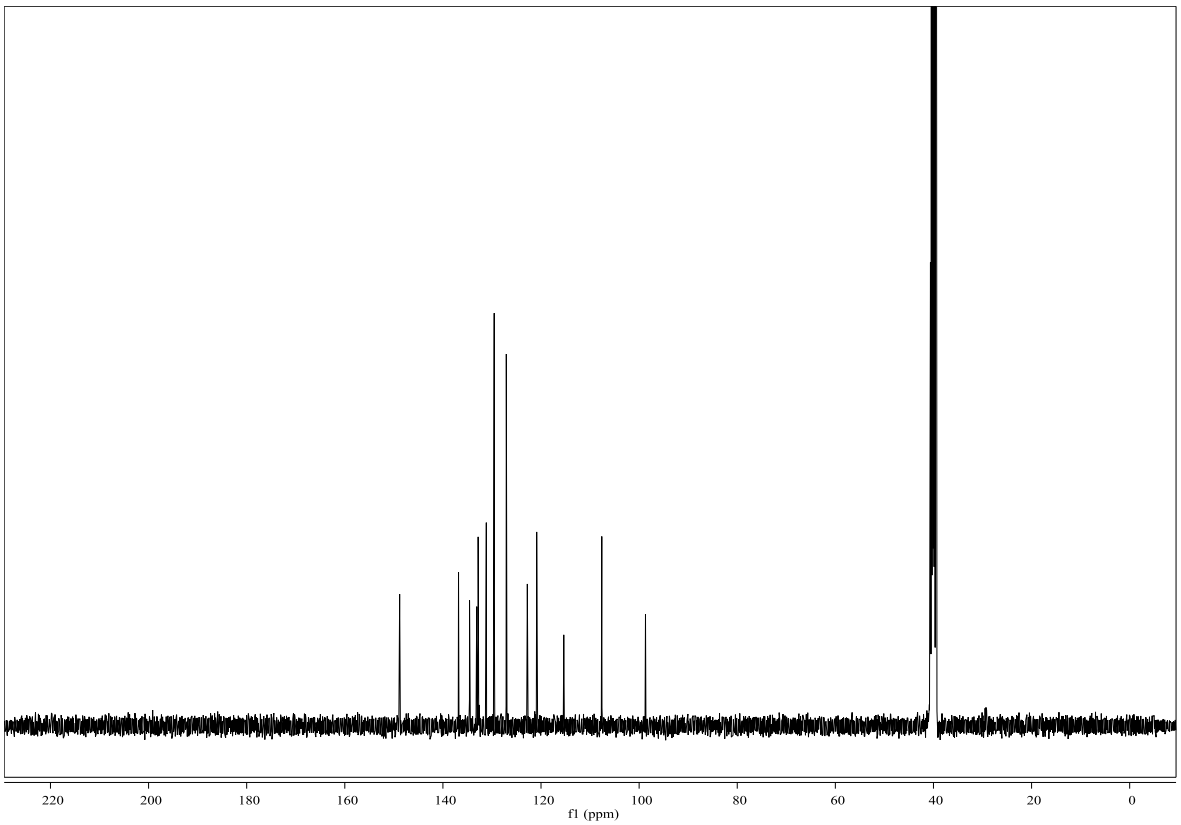
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **122b**



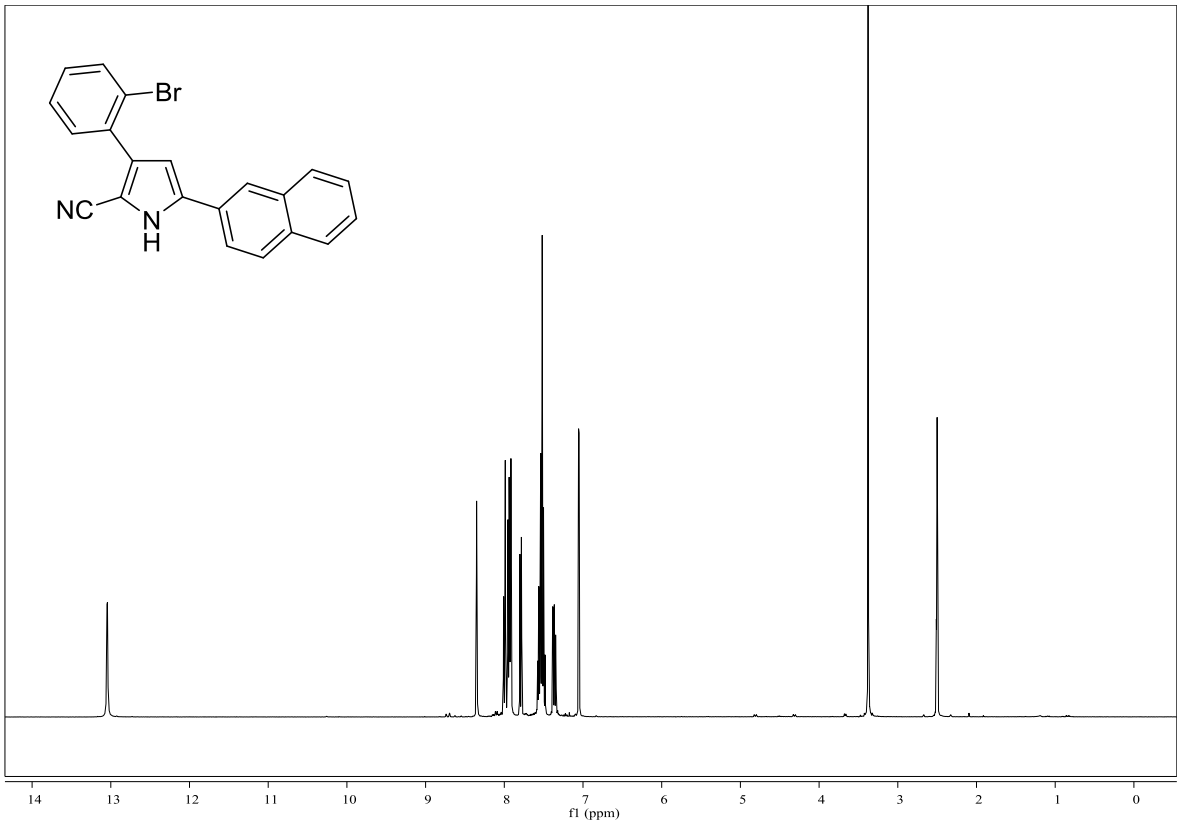
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **122b**



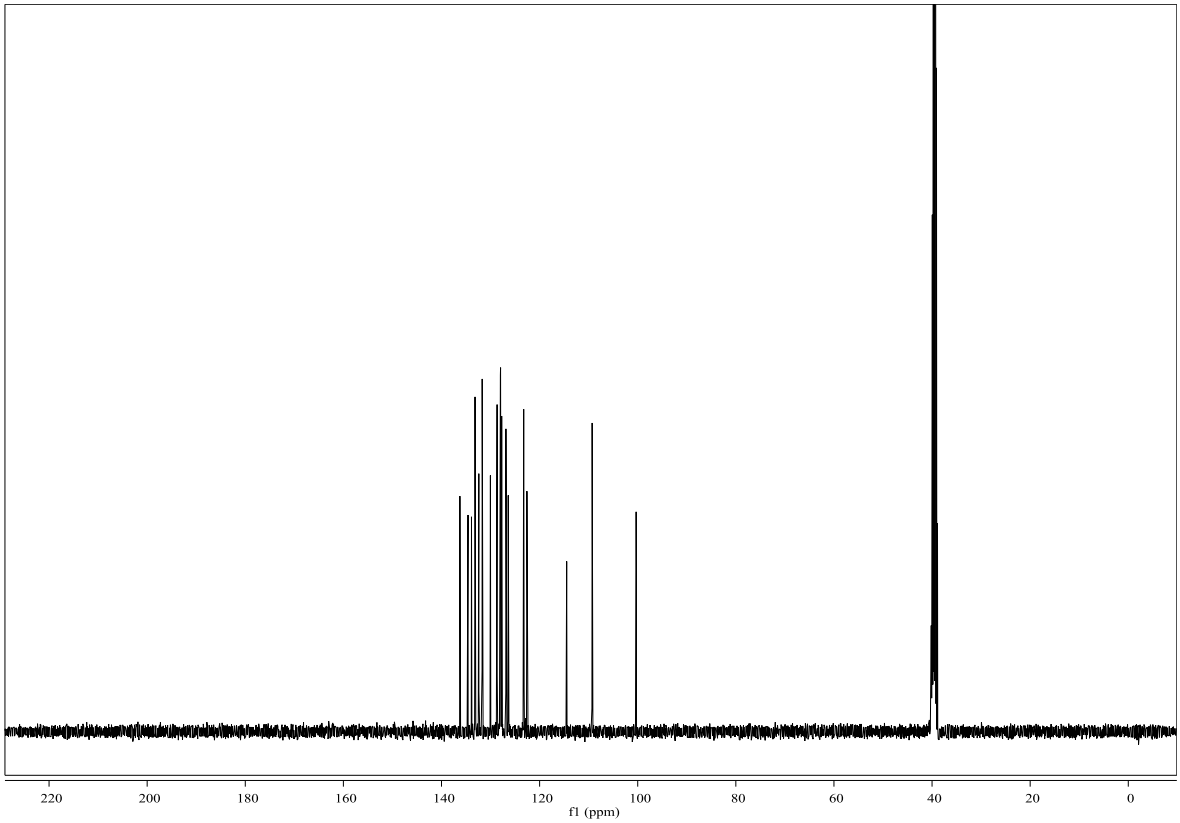
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **122d**



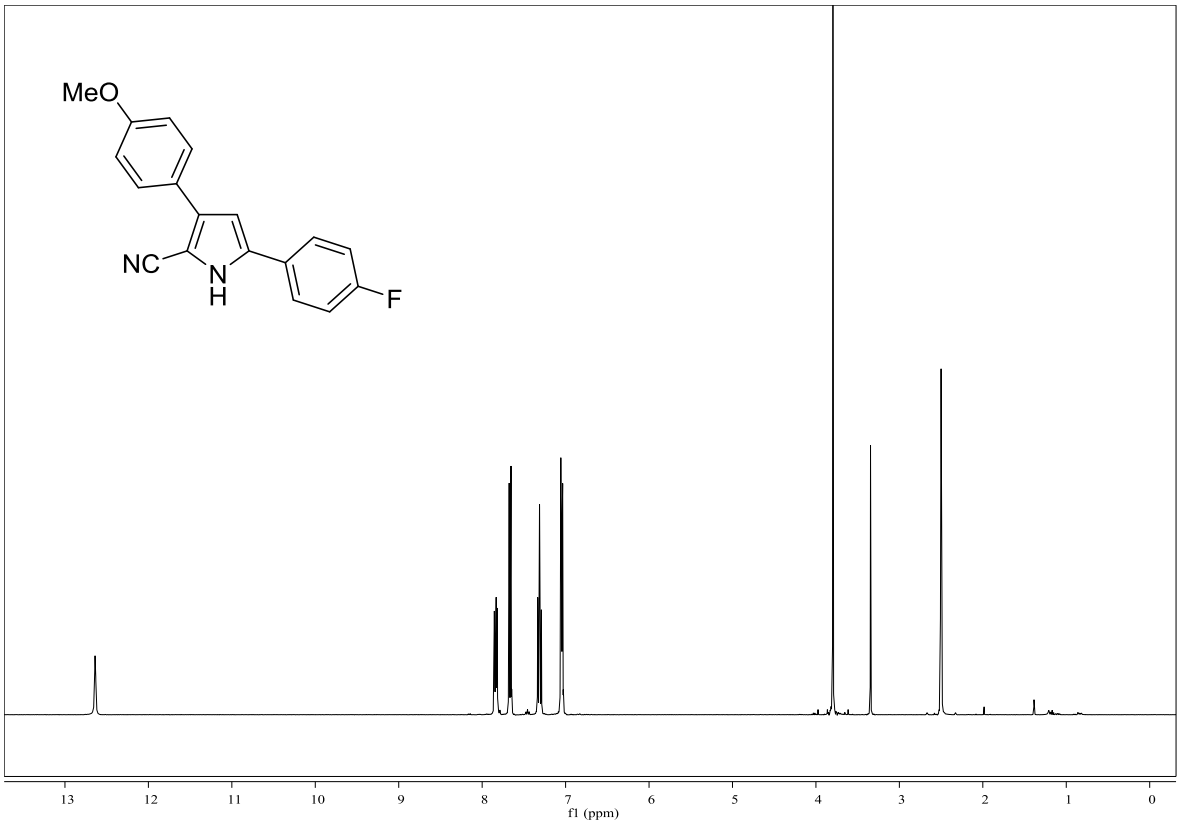
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **122d**



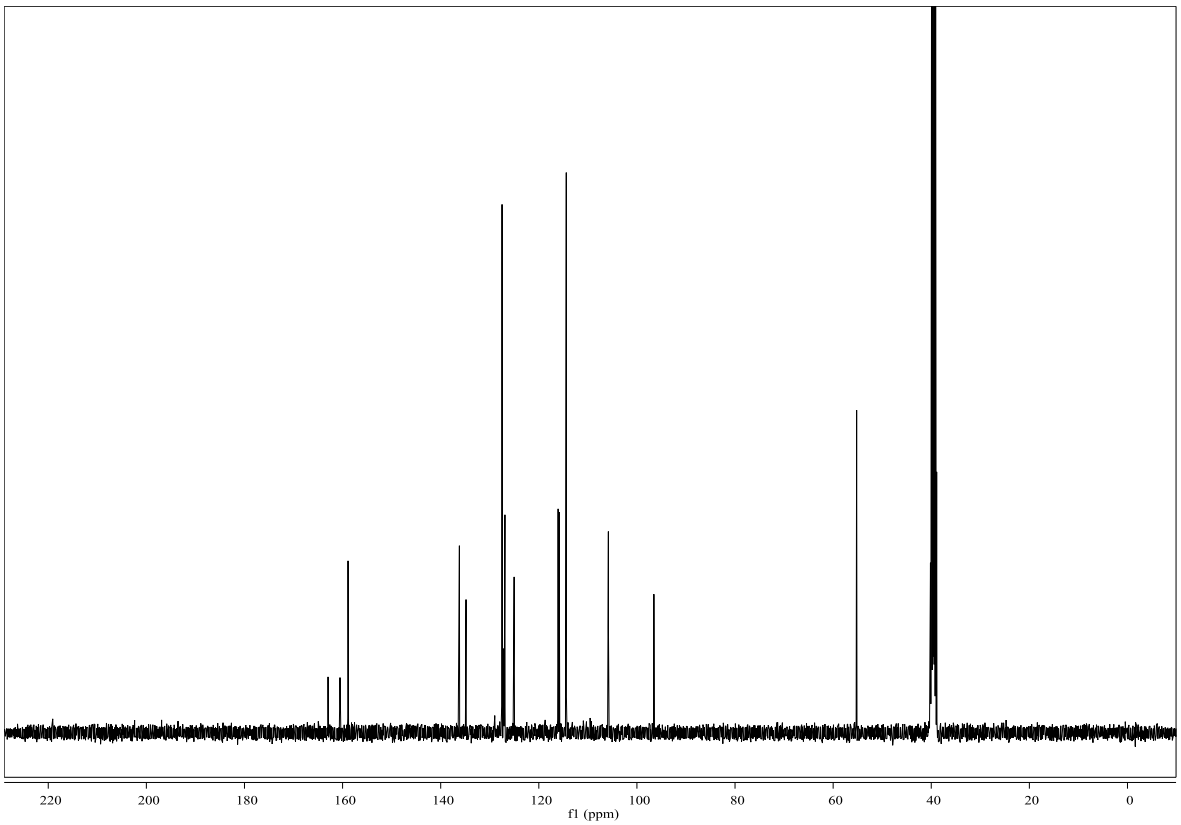
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **122f**



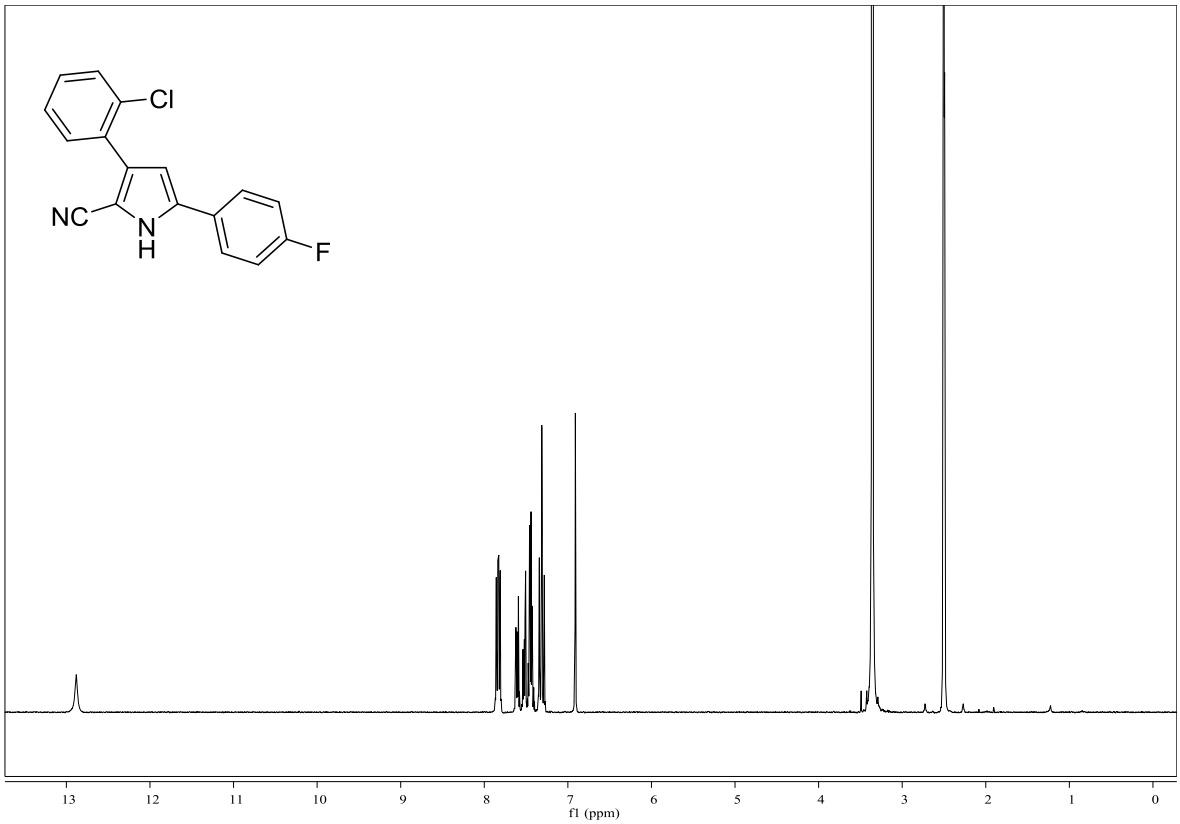
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **122f**



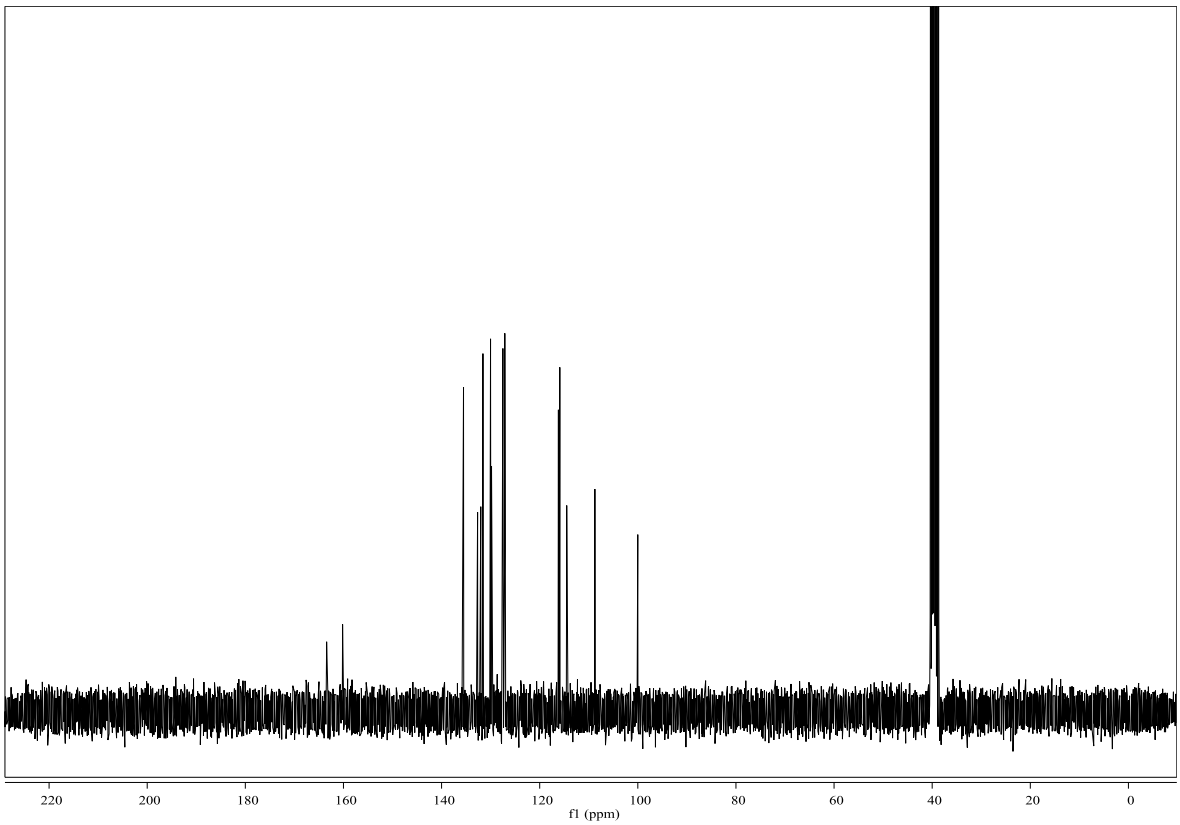
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **122h**



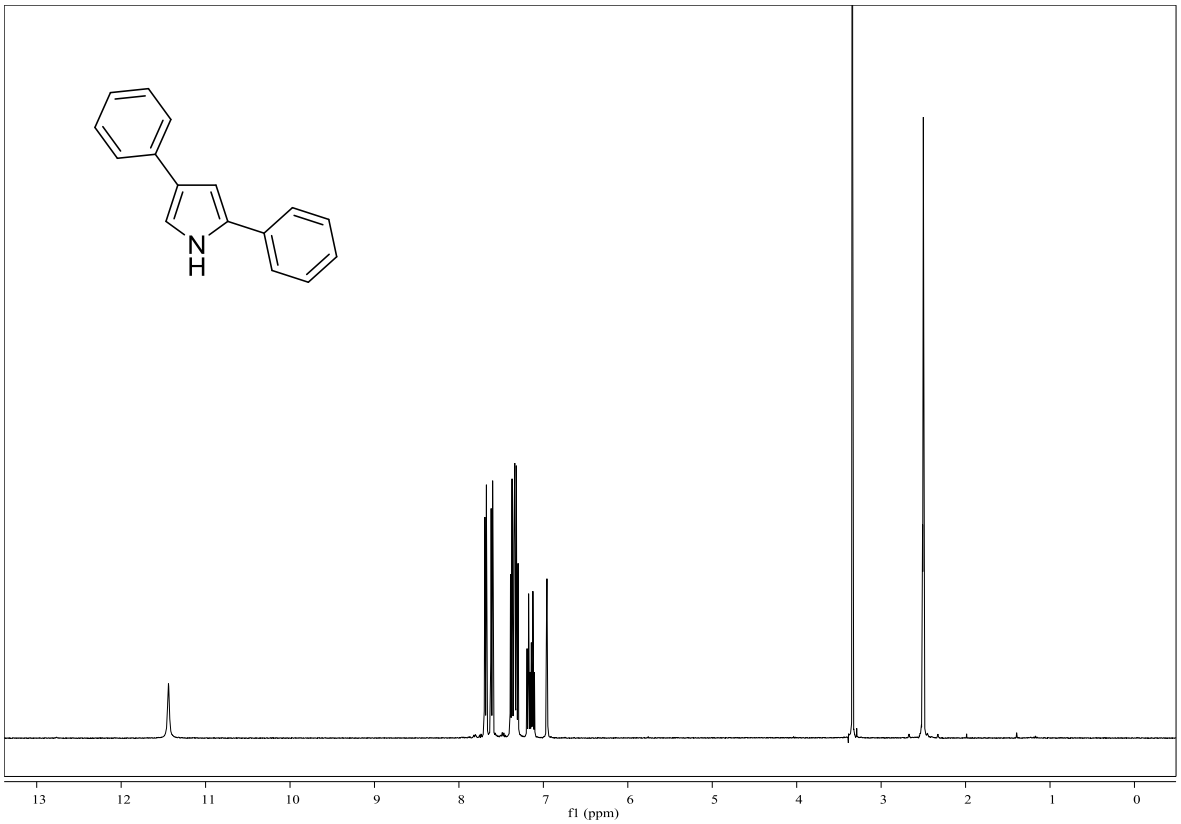
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **122h**



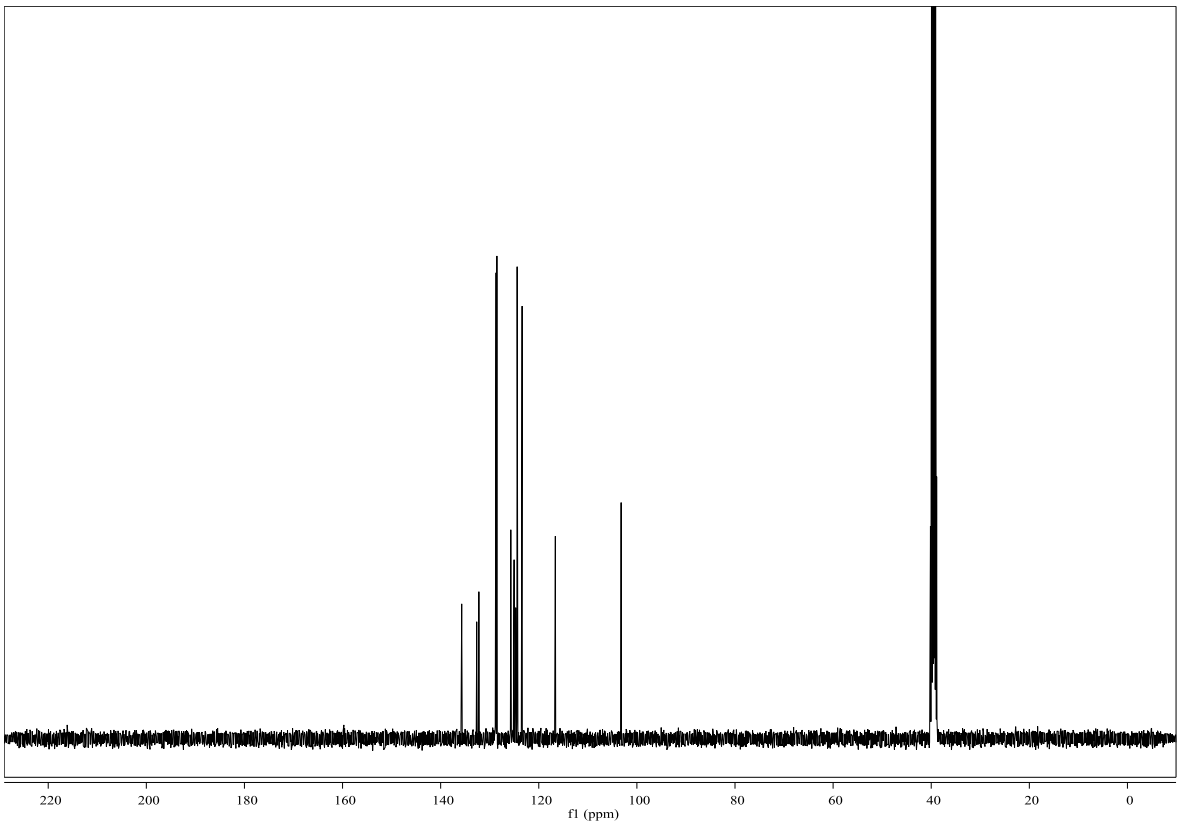
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **122i**



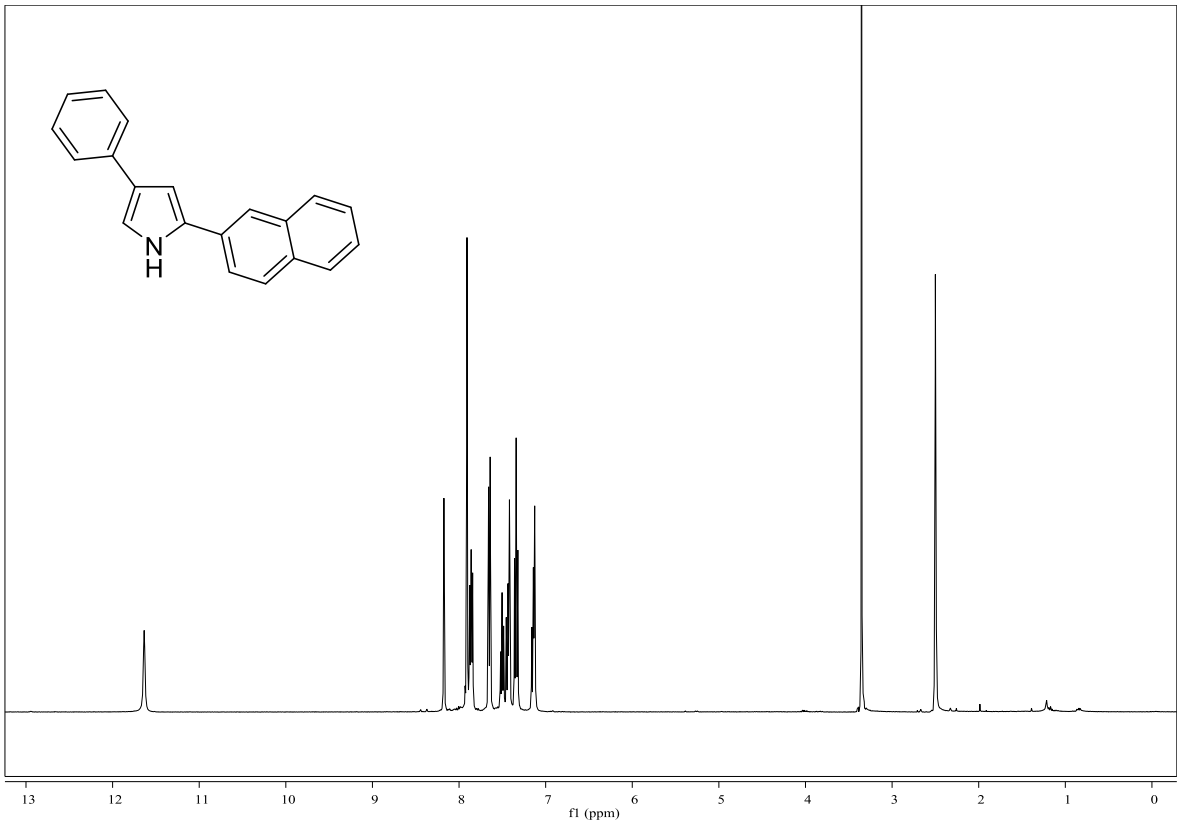
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **122i**



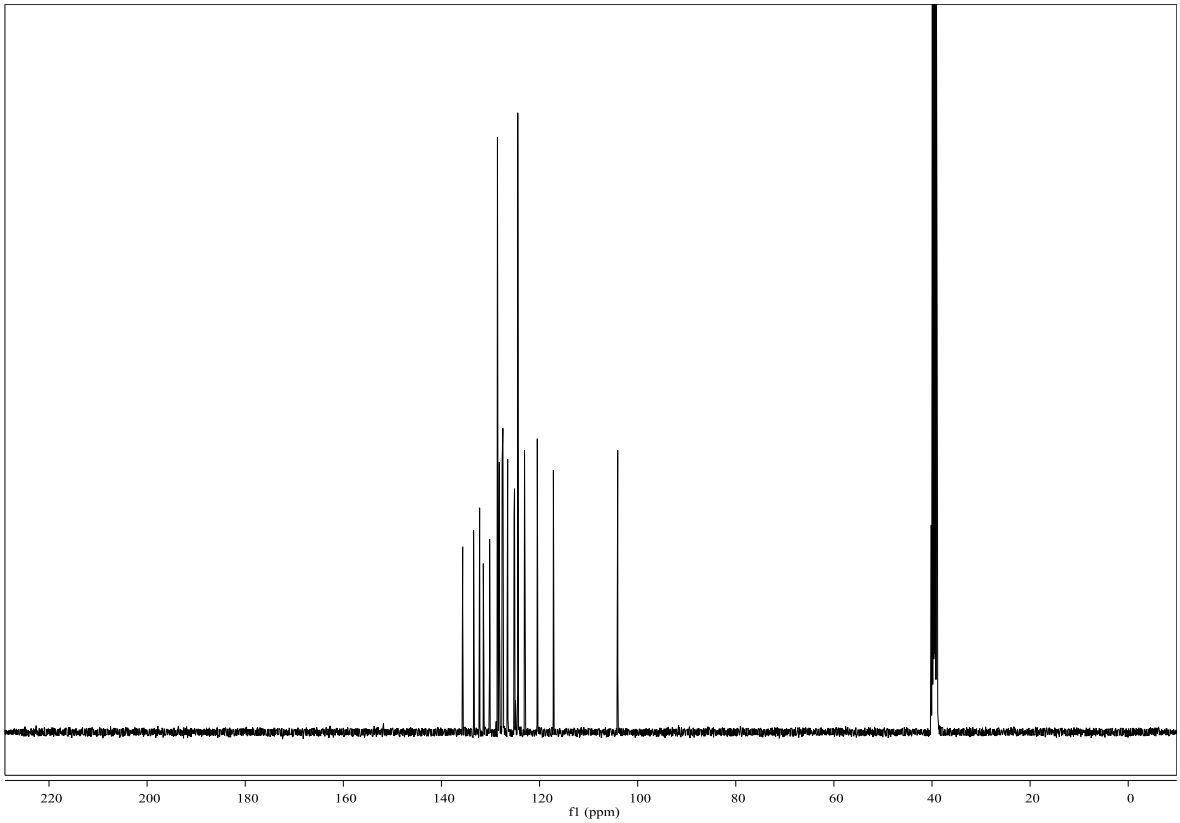
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **123a**



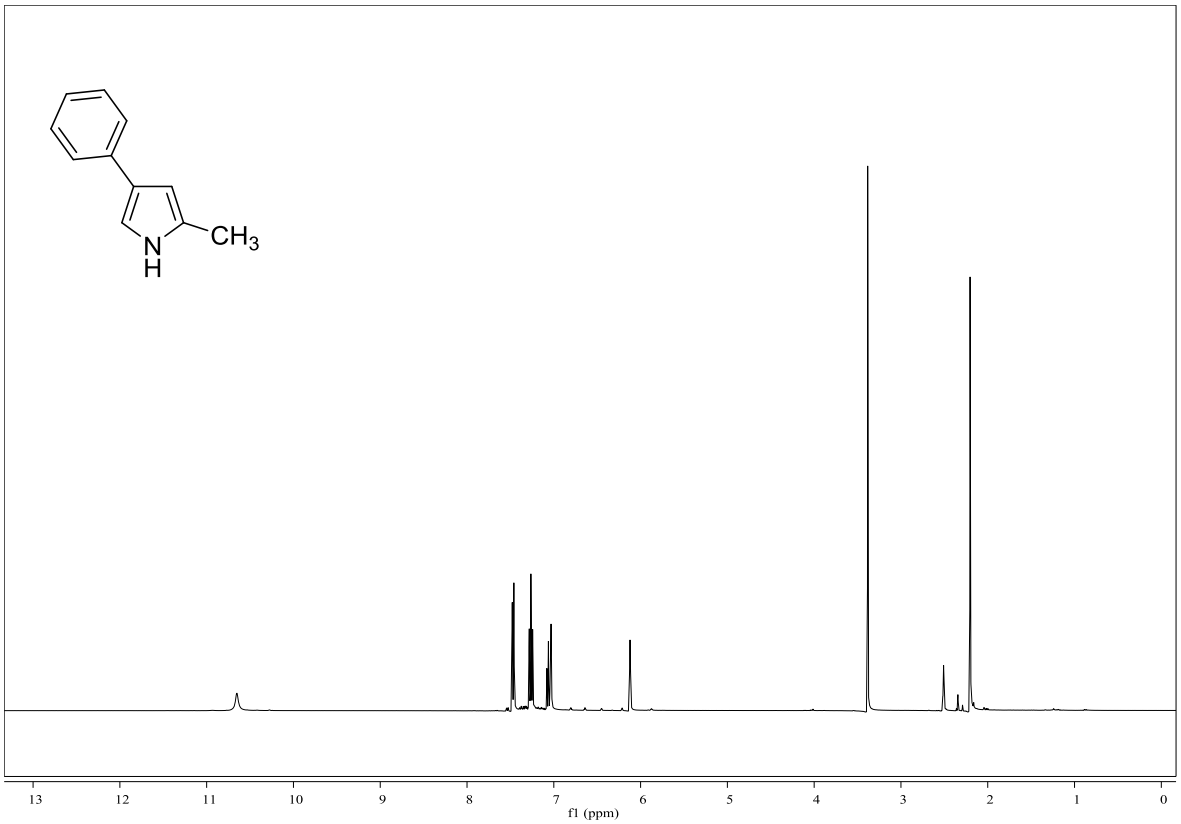
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **123a**



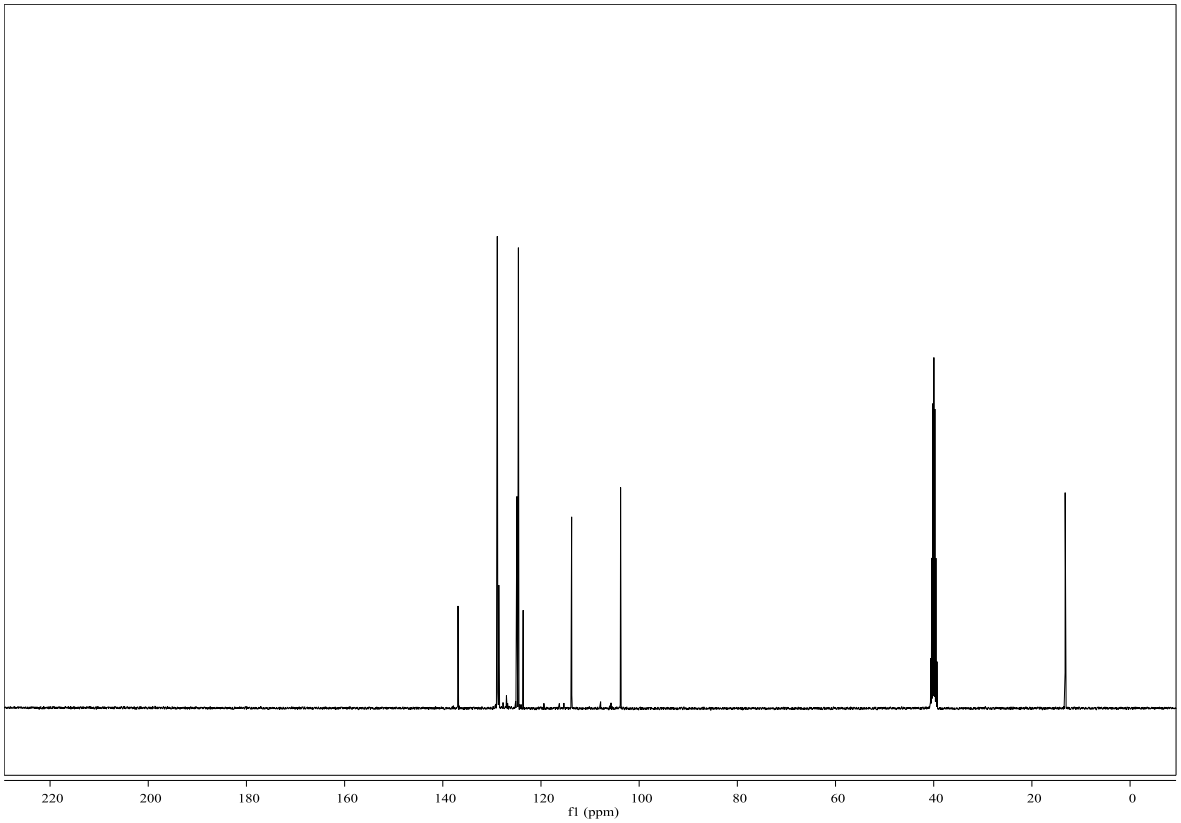
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **123b**



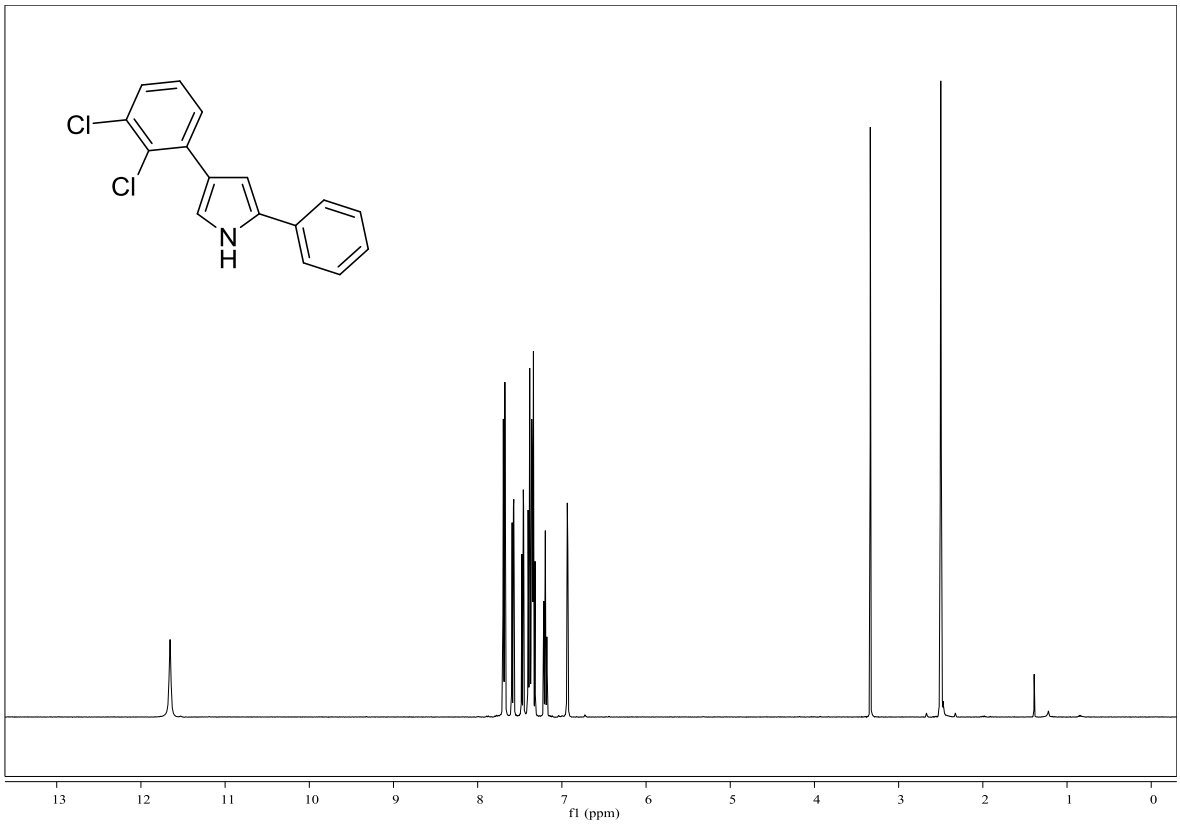
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **123b**



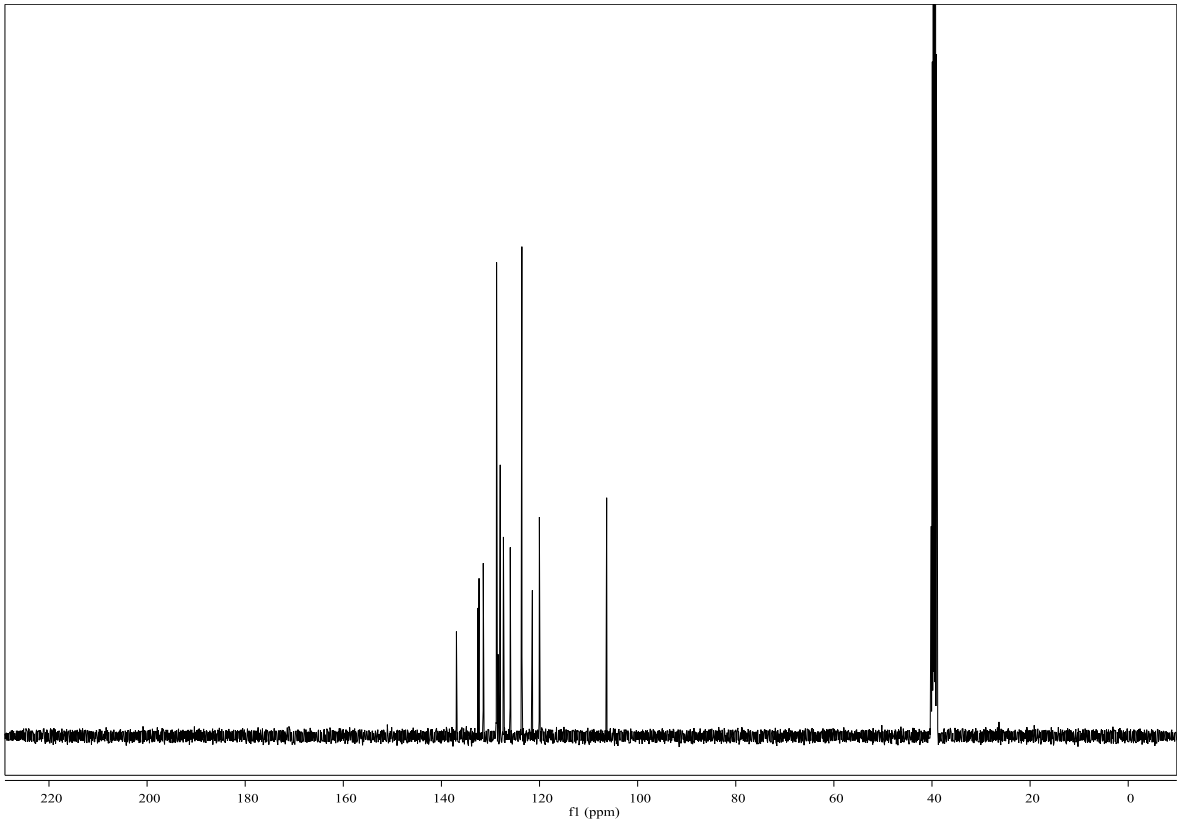
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **123c**



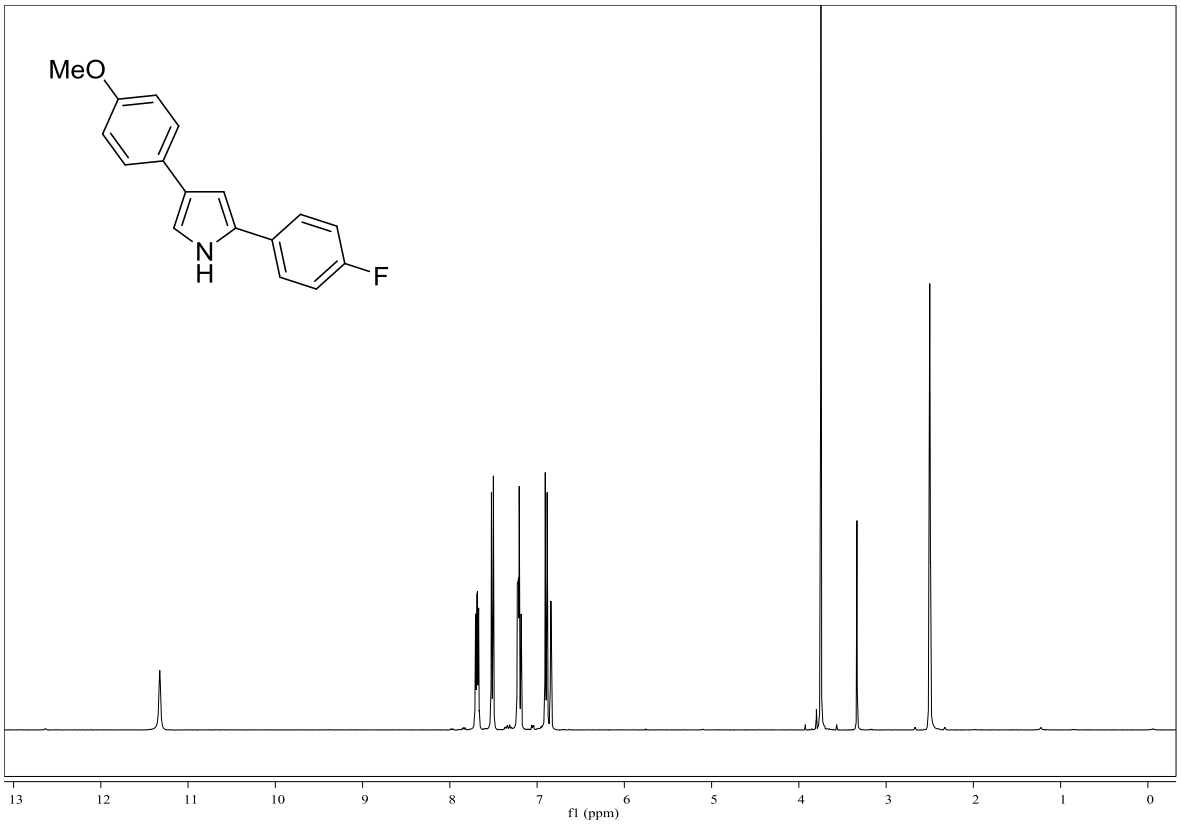
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **123c**



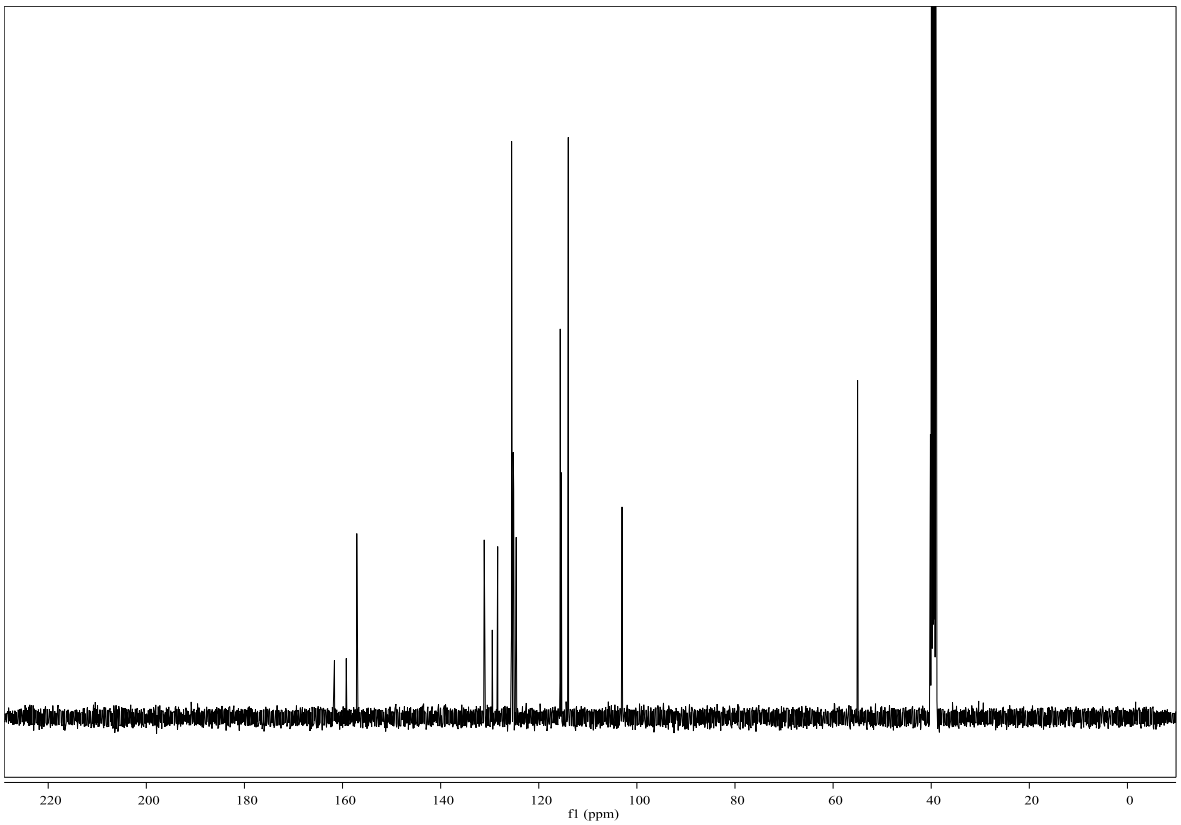
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **123e**



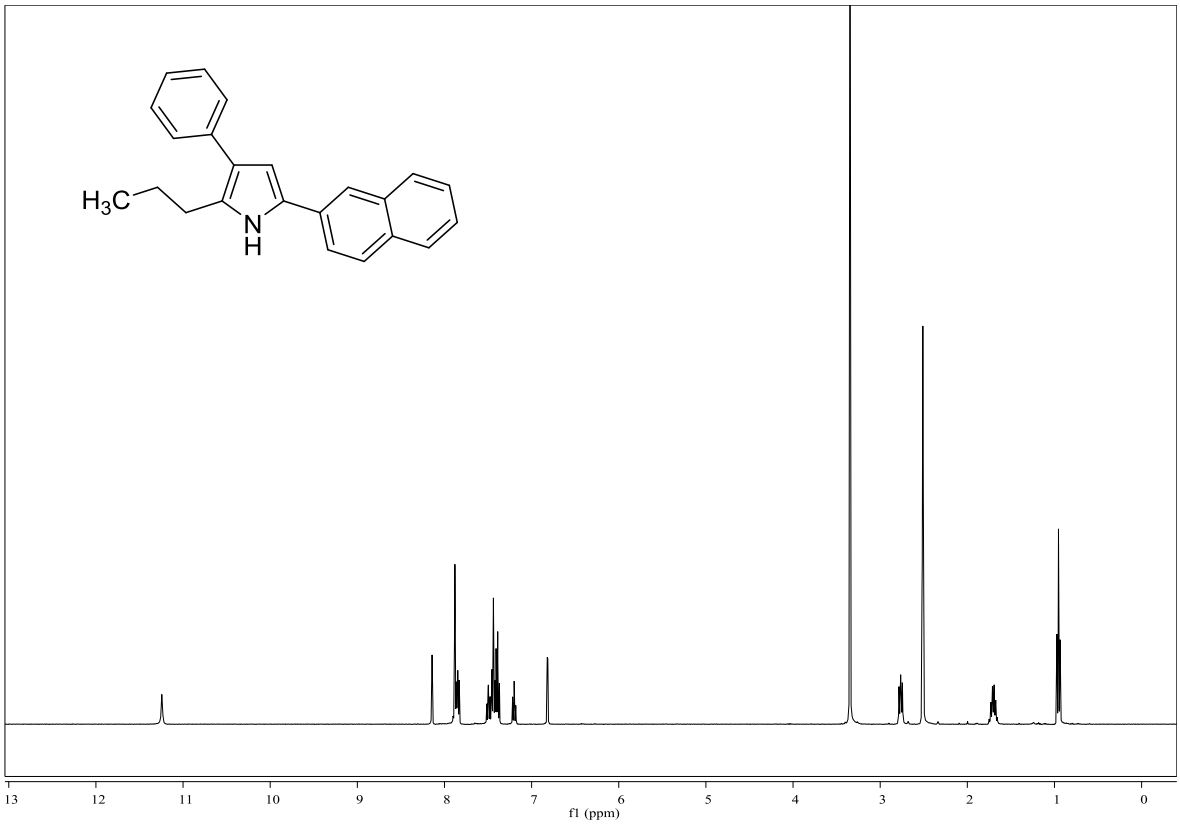
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **123e**



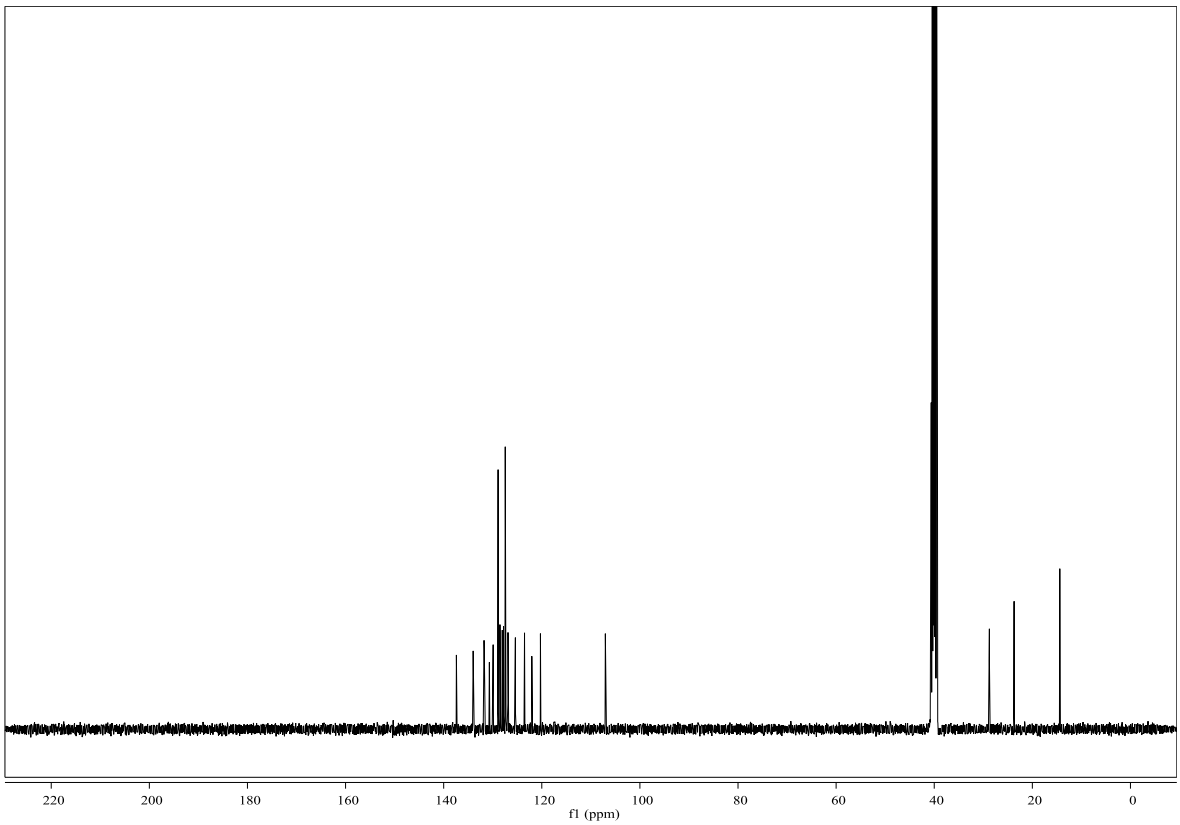
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **123h**



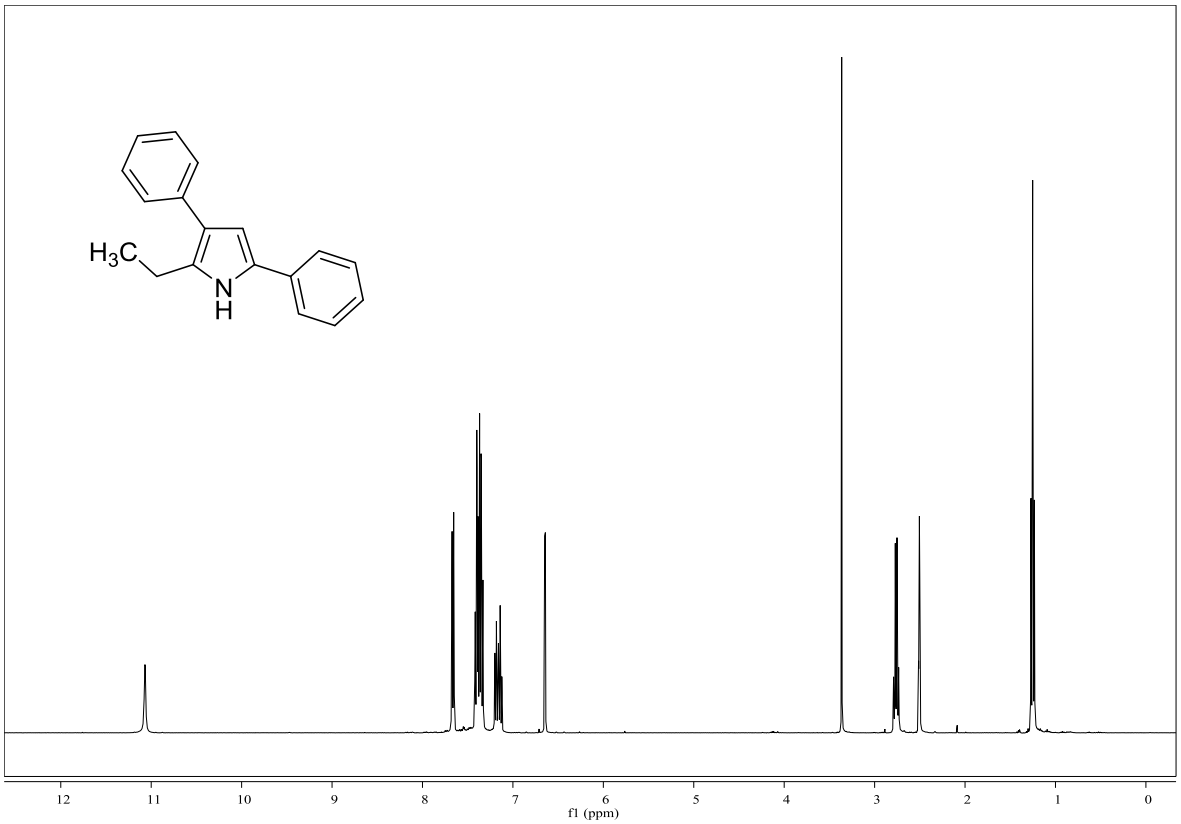
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **123h**



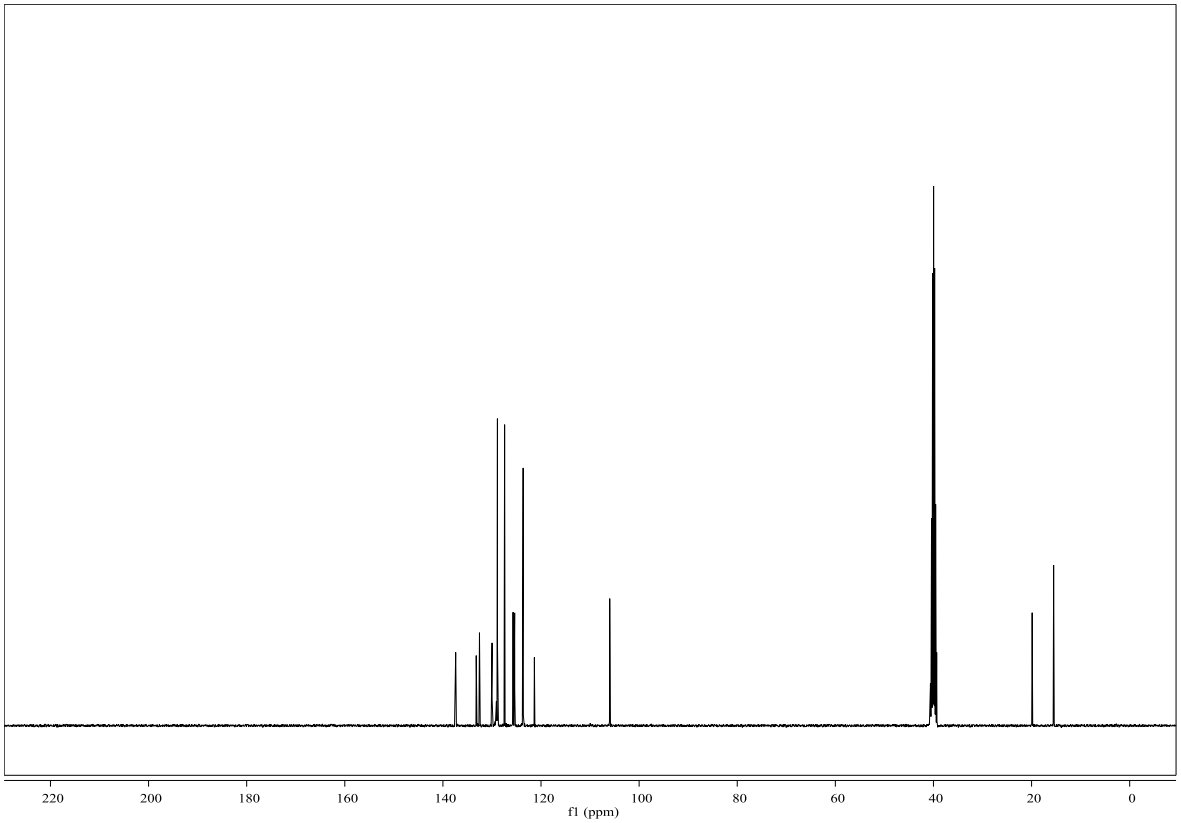
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **127a**



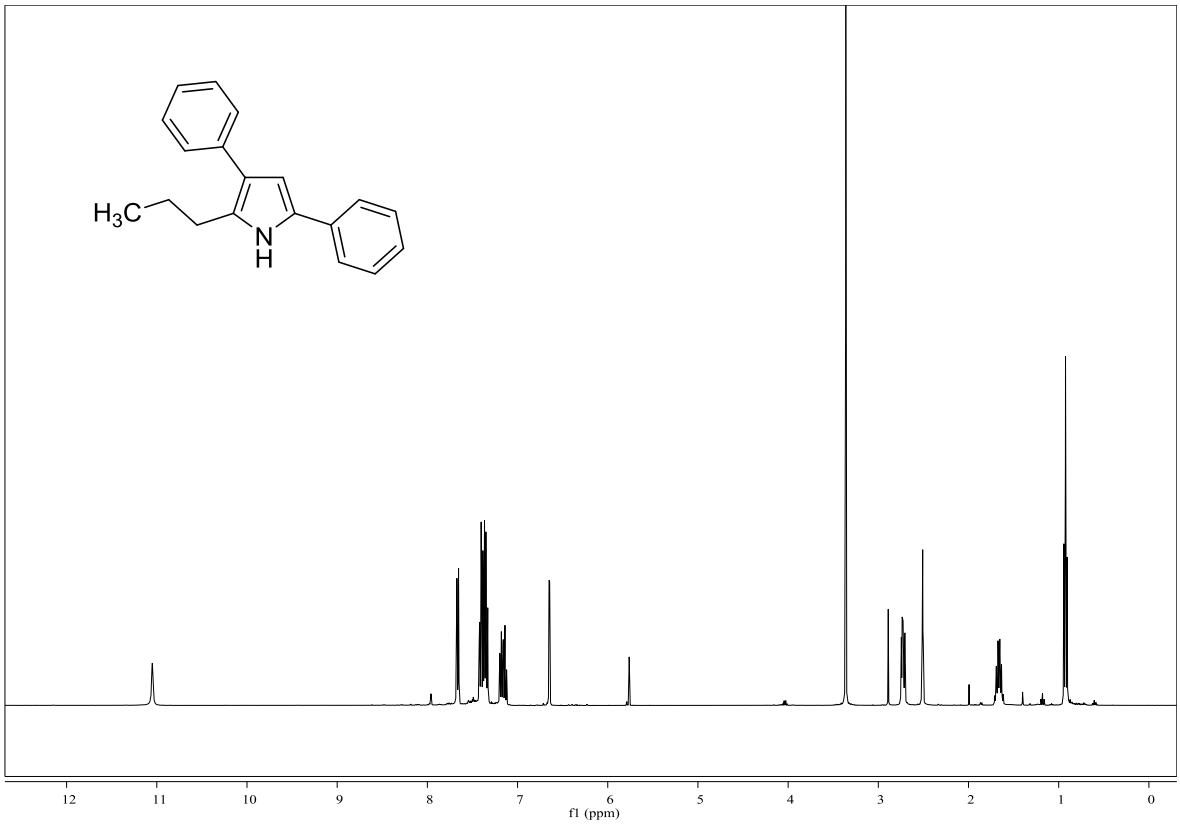
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **127a**



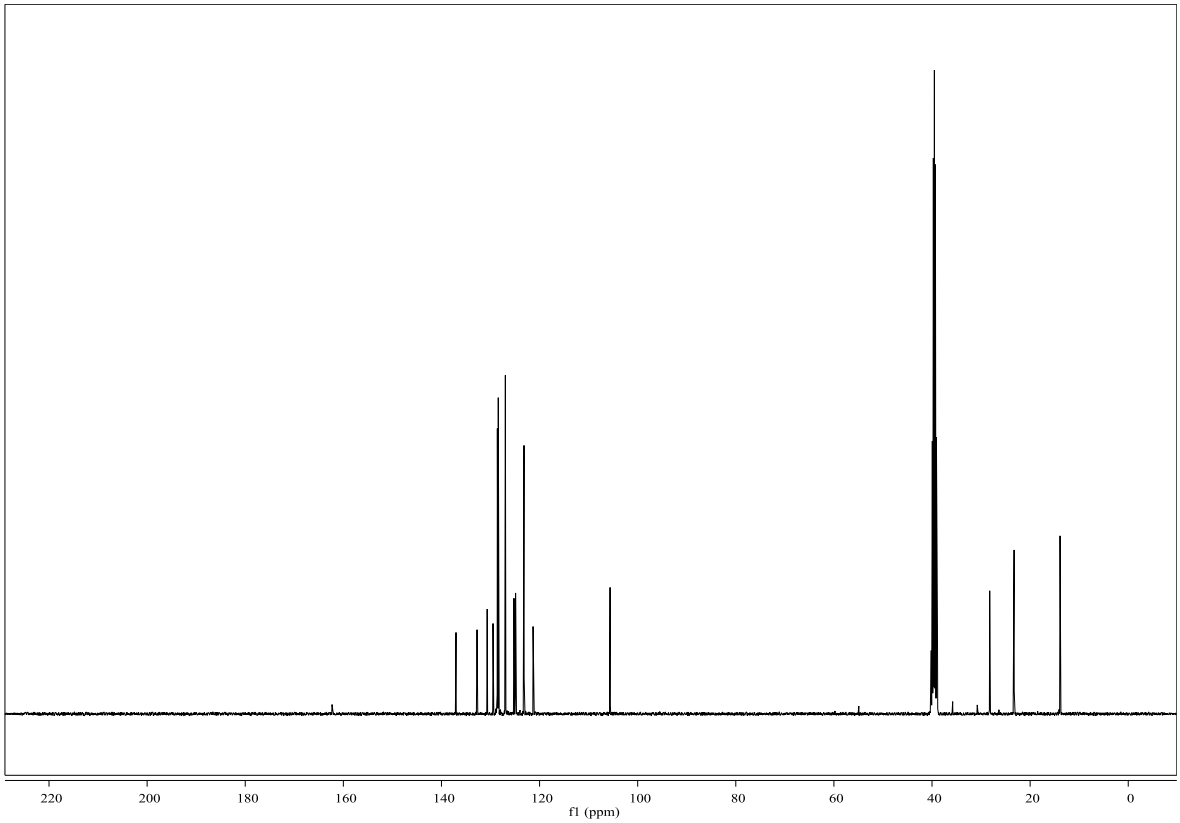
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **127c**



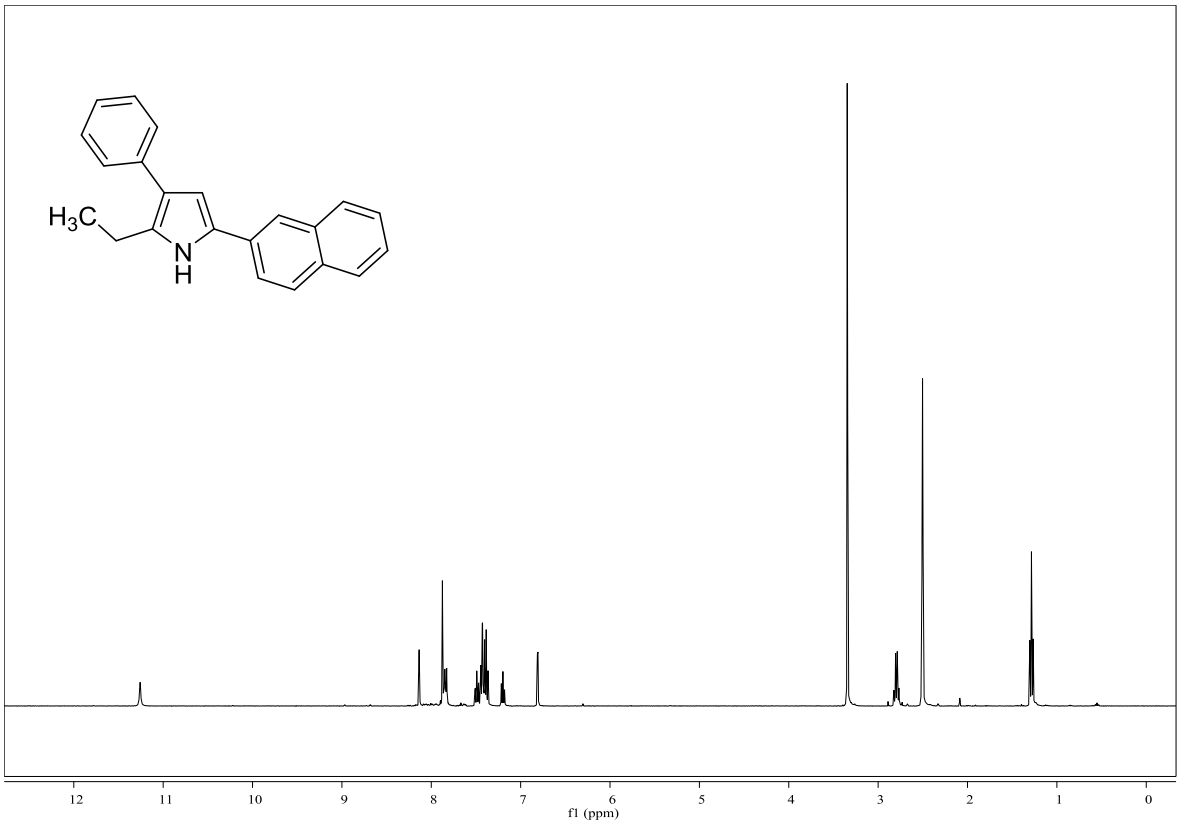
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **127c**



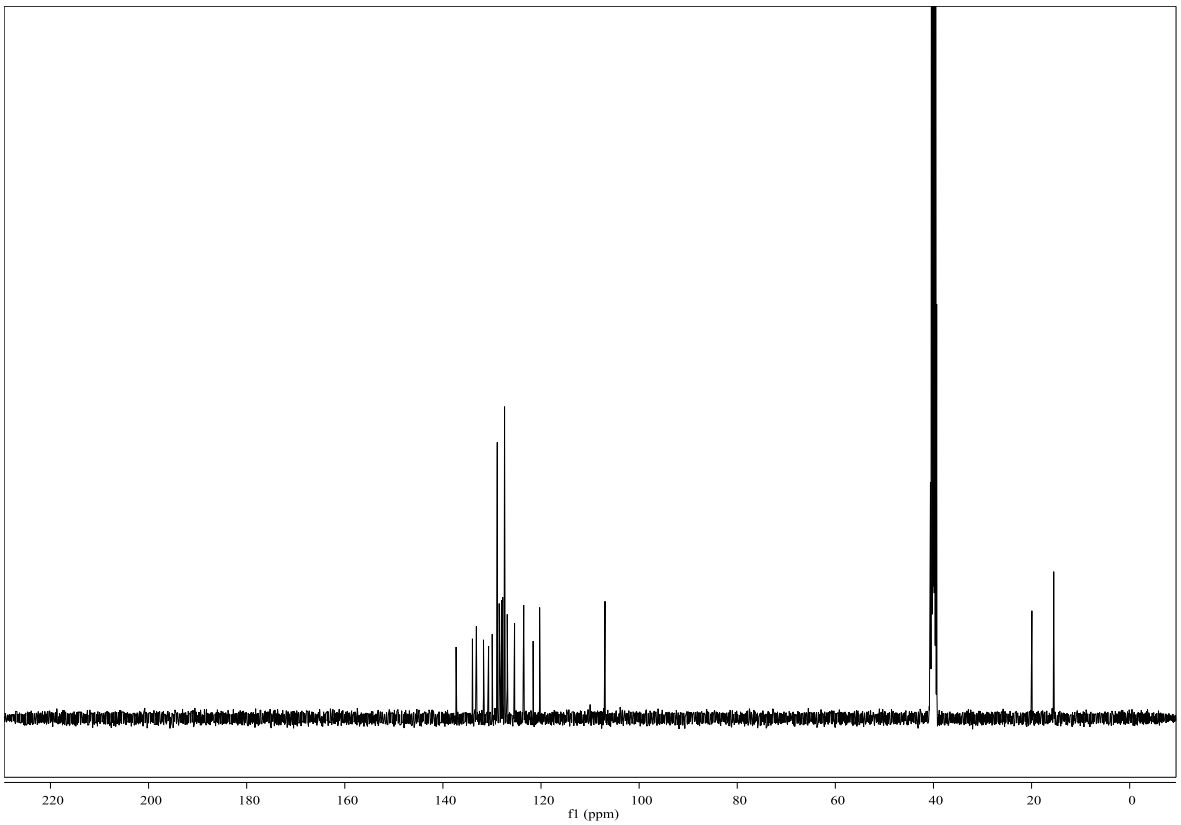
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **127d**



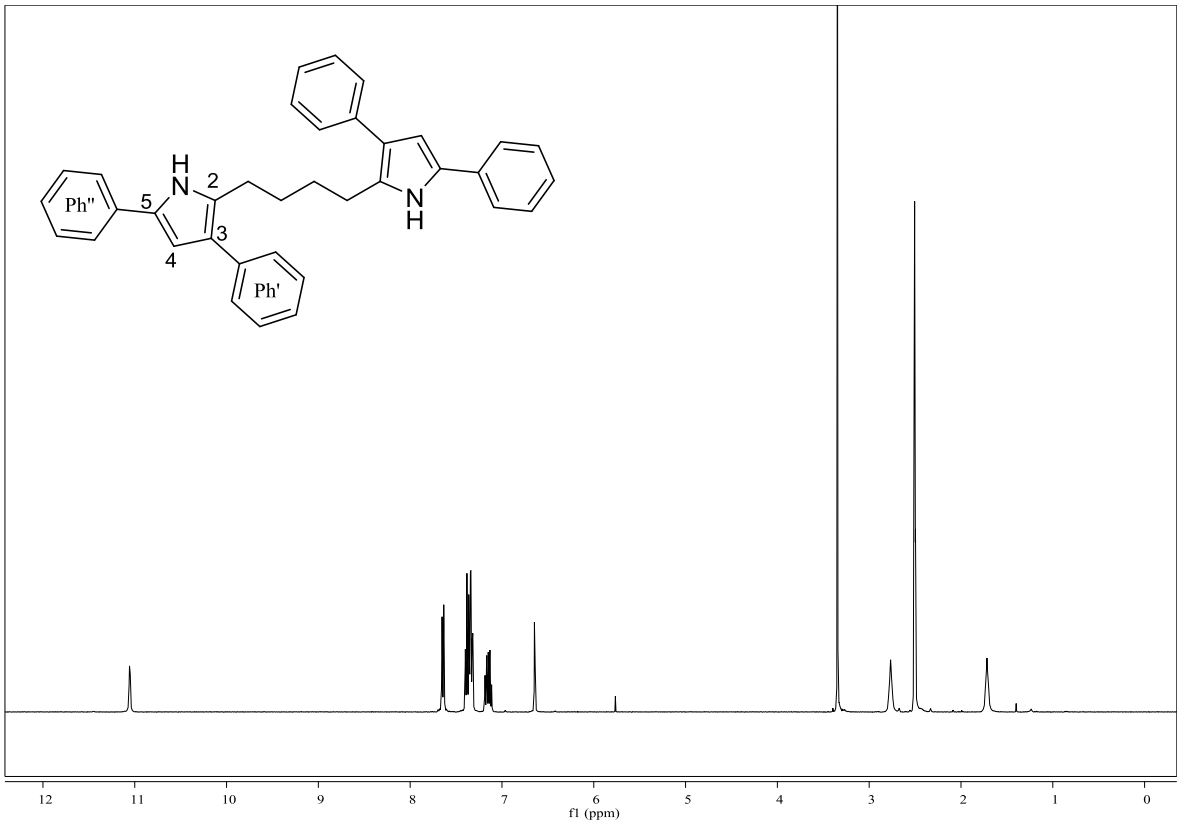
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **127d**



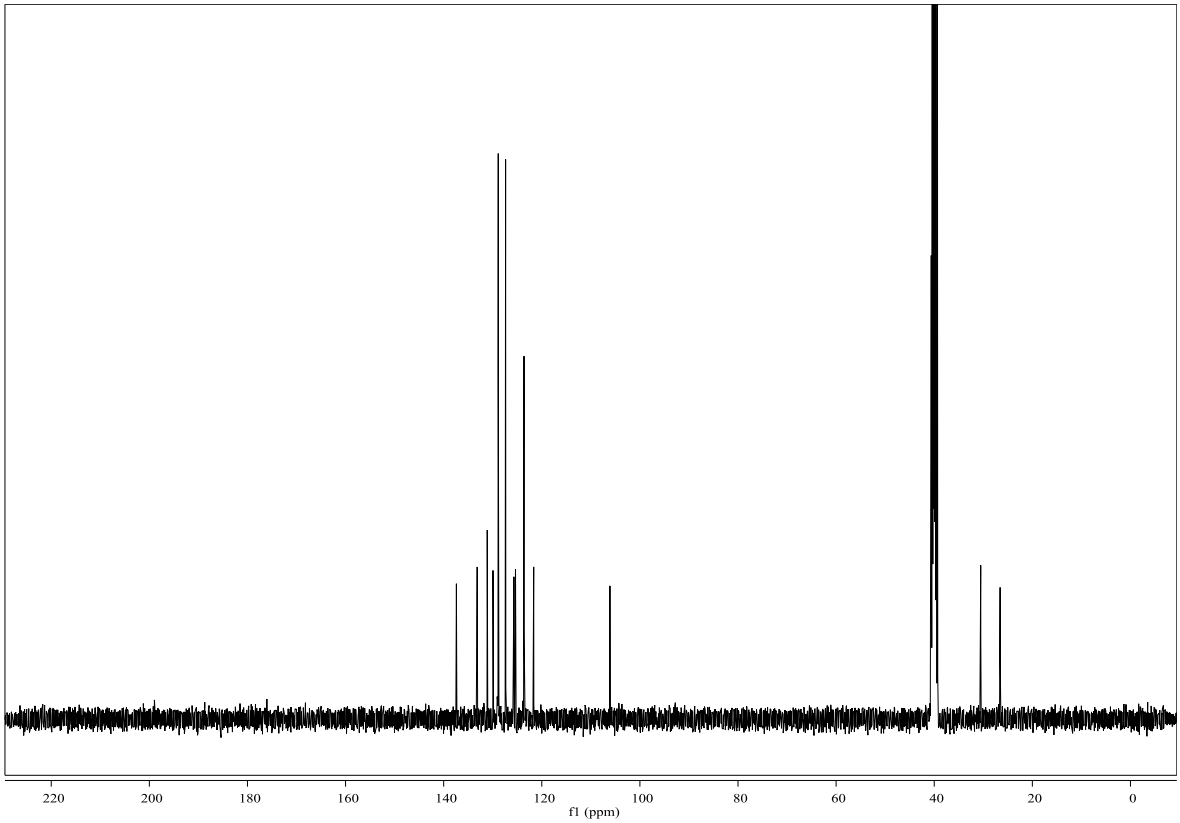
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **127e**



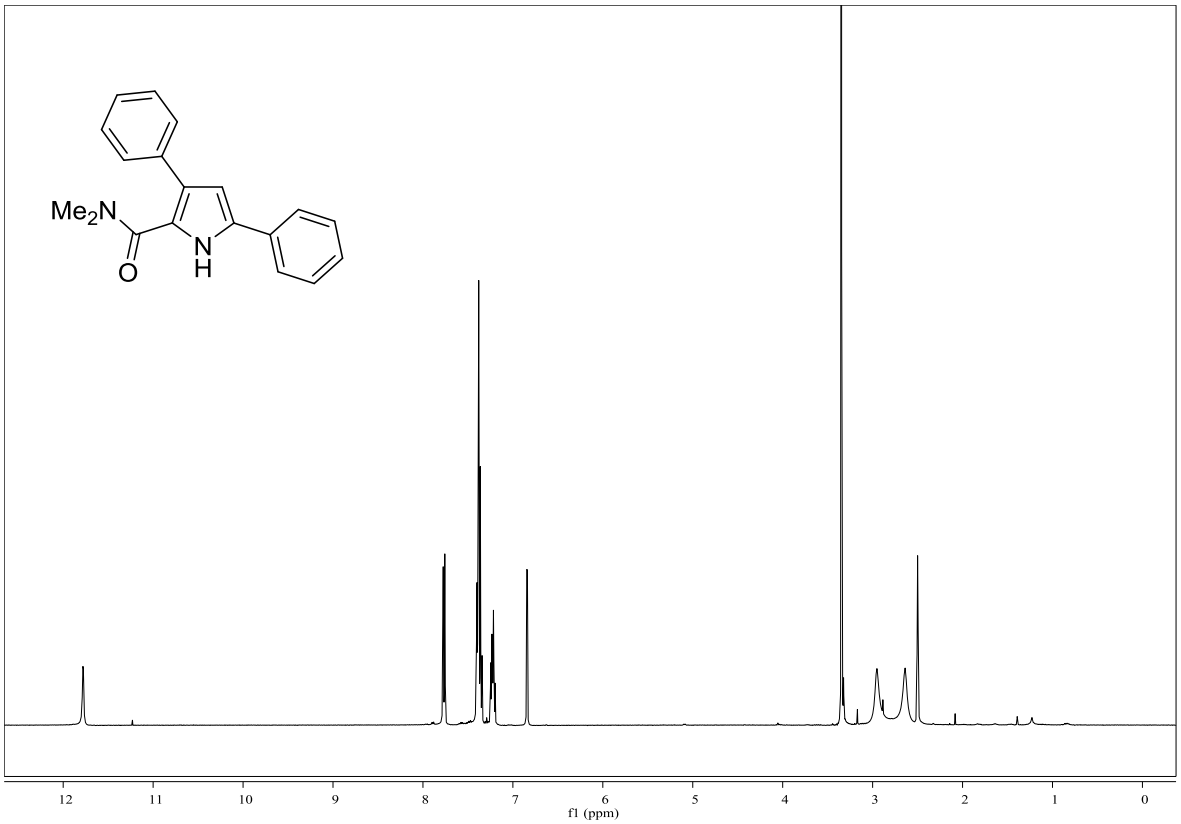
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **127e**



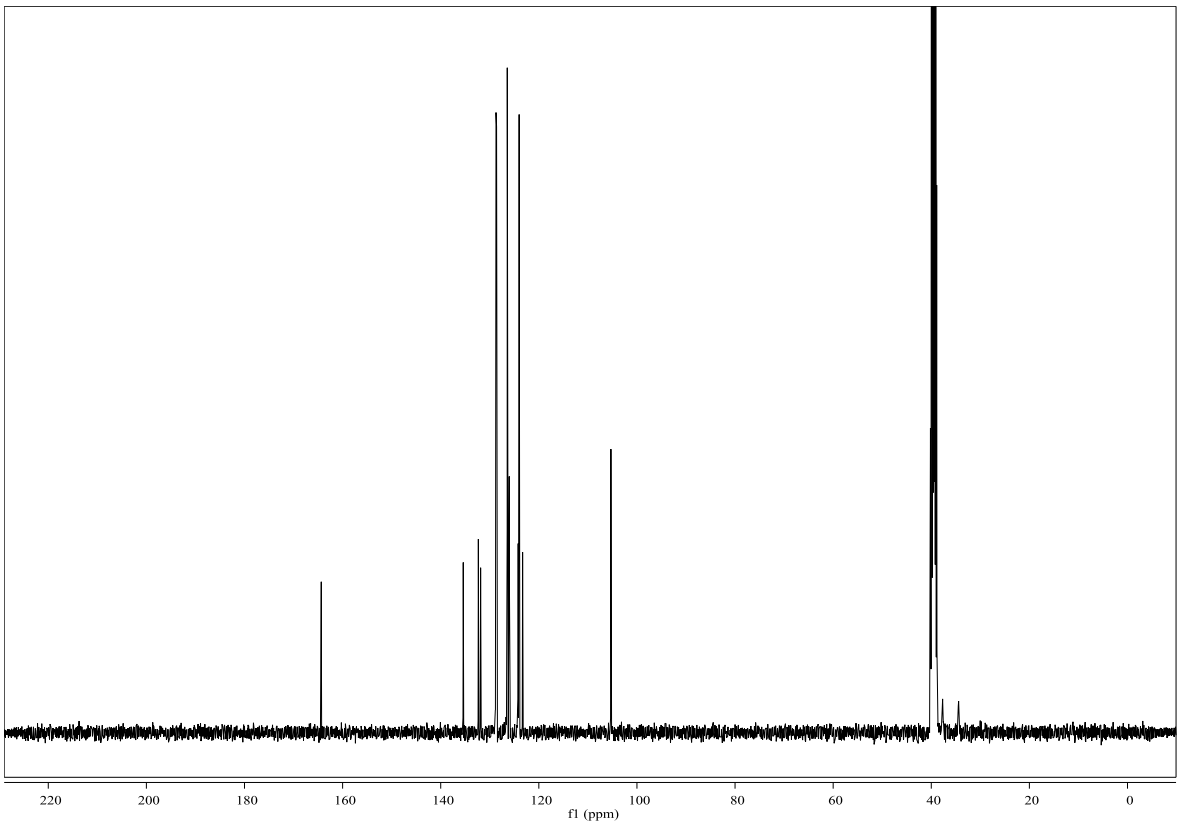
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **129**



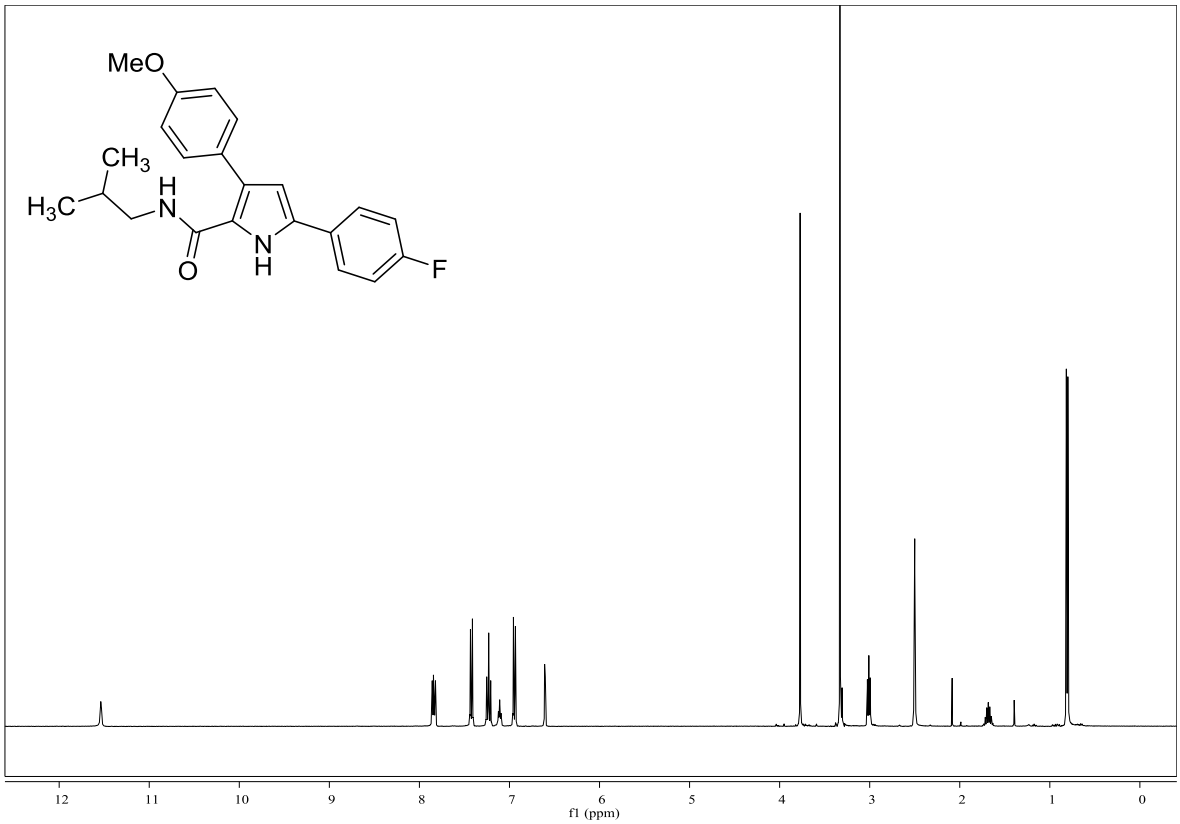
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **129**



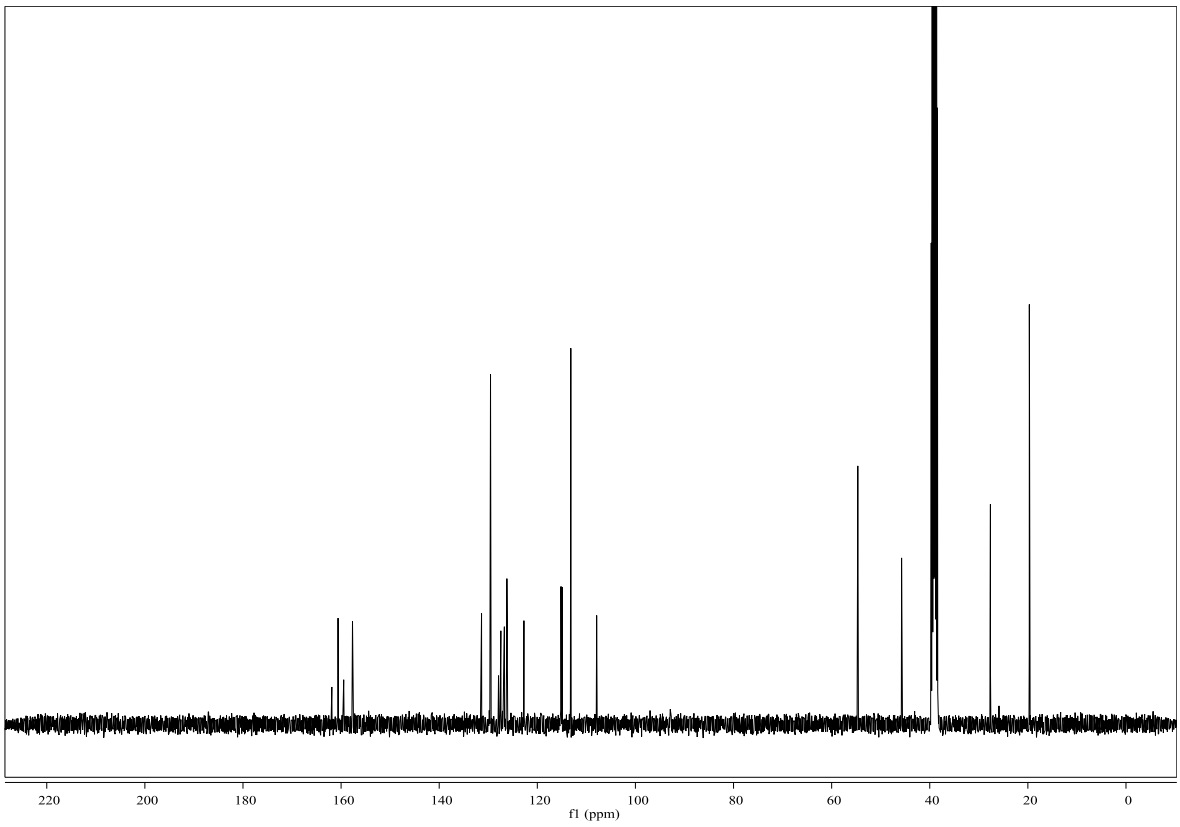
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **136a**



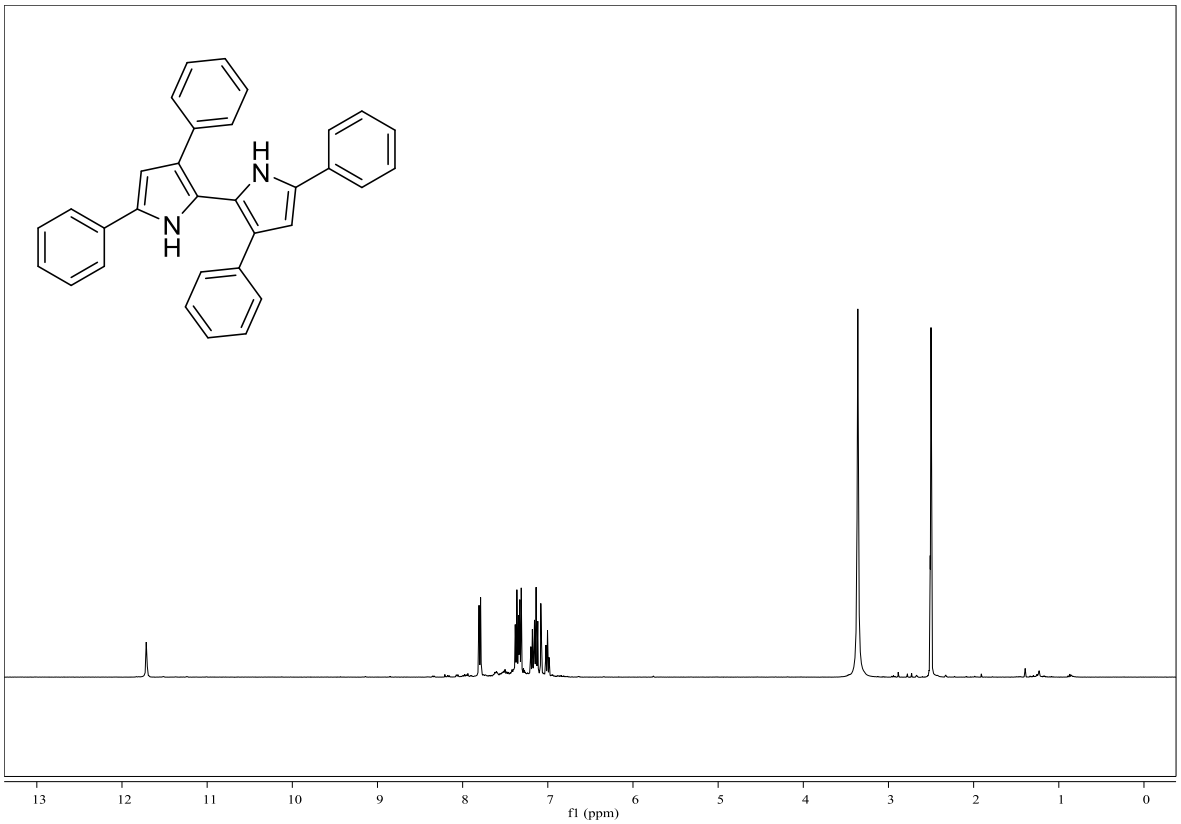
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **136a**



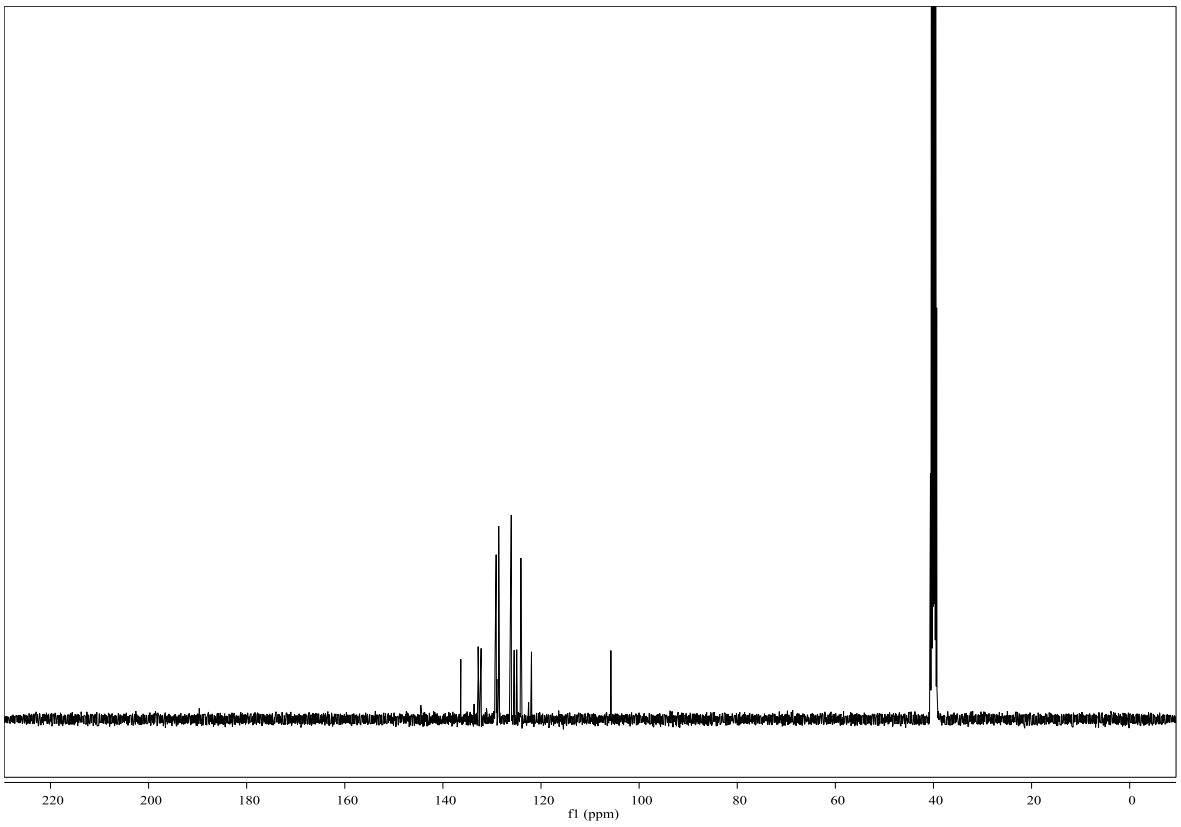
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **136c**



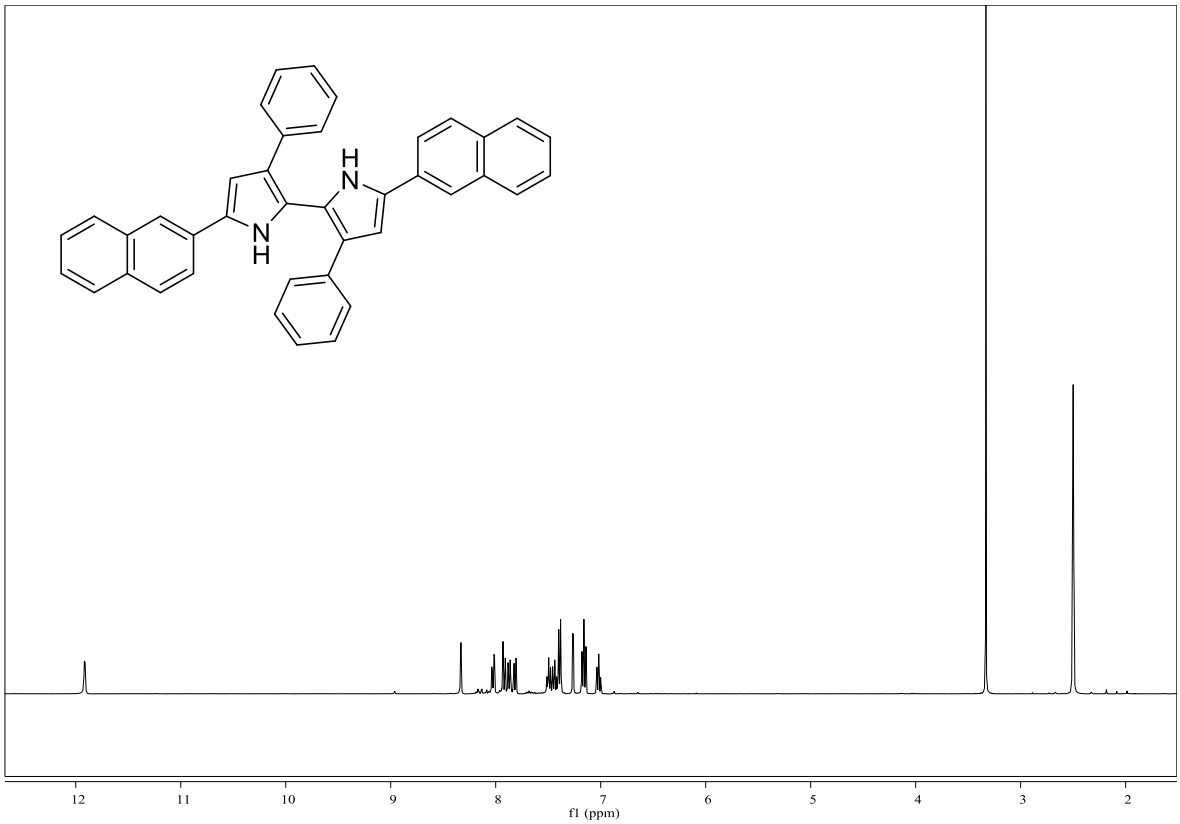
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **136c**



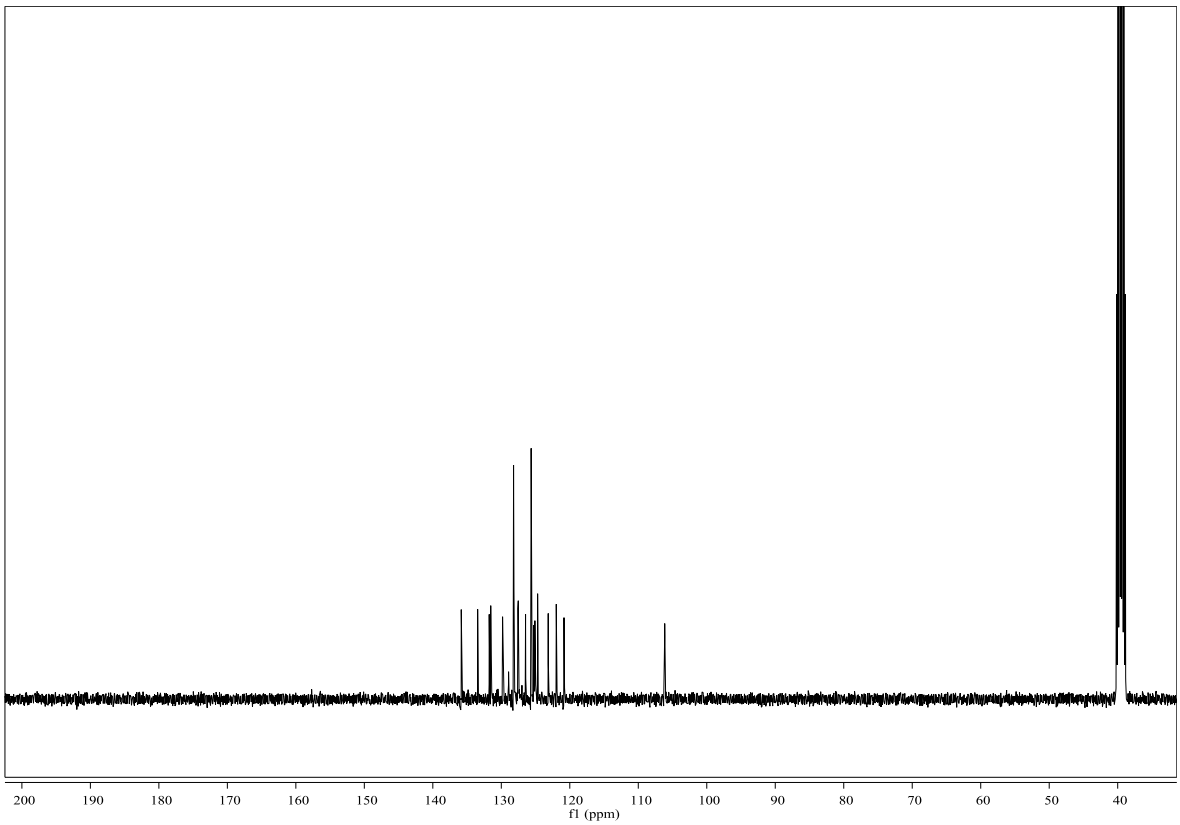
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **137a**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **137a**



^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **137b**



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **137b**

Appendix B: X-Ray Data

Crystal data for 78d

formula	$C_{16}H_{11}N_2F$
molecular weight	250.25 $gmol^{-1}$
absorption	μ = 0.09 mm^{-1} corrected wit SADABS
transmission	T_{min} = 0.607, T_{max} = 0.746
crystal size	0.4 x 0.4 x 0.8 mm^3 colourless Block
space group	P 2_1/c (monoclinic)
lattice parameters	a =18.3071(9)Å
(calculate from 2729	b =9.2344(5)Å ß = 99.164(2)°
reflections with	c =7.6538(4)Å
2.3° < θ < 27.3°)	V = 1277.4(2)$Å^3$ z = 4 F(000) = 520
temperature	25°C
density	d_{xray} = 1.301 gcm^{-3}

data collection

diffractometer	Smart CCD
radiation	Mo-K_α graphit monochromator
scan type	φ,ω-scans
scan – width	0.5°
scan range	2° ≤ θ < 28°
	-23 ≤ h ≤ 23 -12 ≤ k ≤ 12 -9 ≤ l ≤ 9
number of reflections:	
measured	13321
unique	2960 (R_{int} = 0.0380)
observed	2163 (|F|/σ(F) > 4.0)

data correction, structure solution and refinement

corrections	Lorentz and polarisation correction.
Structure solution	Program: SIR-97 (Direct methods)
refinement	Program: SHELXL-97 (full matrix). 173 refined parameters, weighting scheme: $w=1/[\sigma^2(F_o^2) + (0.0626*P)^2+0.19*P]$ with $(Max(F_o^2,0)+2*F_o^2)/3$. H-atoms at calculated positions and refined with isotropic displacement parameters, non H- atoms refined anisotropically.
R-values	wR2 = 0.1286 (R1=0.0431 for observed reflections, 0.0618 for all reflections)
goodness of fit	S = 1.029
maximum deviation of parameters	0.001 * e.s.d
maximum peak height in diff. Fourier synthesis	0.19, -0.20 $eÅ^{-3}$

final coordinates and equivalent displacement parameters (Å^2)

$U_{äq}= (1/3)*\sum\sum_{ij}a_i^* a_j^* \mathbf{a}_i\mathbf{a}_j$

Atom	X	Y	Z	U_{eq}
F1	0.48656(6)	0.7612(1)	0.9473(2)	0.0914(5)
N1	0.14384(6)	0.3212(1)	0.4975(1)	0.0423(4)
C2	0.18698(7)	0.4415(1)	0.5514(2)	0.0425(4)
C3	0.25624(7)	0.3941(1)	0.6416(2)	0.0400(4)
C4	0.25543(7)	0.2414(1)	0.6403(2)	0.0412(4)
C5	0.18548(7)	0.1979(1)	0.5524(2)	0.0409(4)
C6	0.15118(8)	0.0621(2)	0.5120(2)	0.0514(5)
C7	0.08049(9)	0.0550(2)	0.4208(2)	0.0611(6)
C8	0.04052(9)	0.1828(2)	0.3668(2)	0.0615(6)
C9	0.07229(8)	0.3136(2)	0.4058(2)	0.0522(5)
C10	0.16009(8)	0.5819(2)	0.5050(2)	0.0544(5)
N11	0.1373(1)	0.6937(2)	0.4637(3)	0.0877(7)
C12	0.31602(9)	0.1385(2)	0.7174(2)	0.0542(5)
C13	0.31681(7)	0.4908(1)	0.7220(2)	0.0412(4)
C14	0.30197(8)	0.6177(2)	0.8103(2)	0.0487(5)
C15	0.35854(9)	0.7093(2)	0.8859(2)	0.0572(5)
C16	0.43022(9)	0.6721(2)	0.8729(2)	0.0591(5)
C17	0.44785(8)	0.5492(2)	0.7872(2)	0.0583(5)
C18	0.39097(7)	0.4590(2)	0.7122(2)	0.0494(4)

anisotropic displacement parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
F1	0.0758(7)	0.1010(9)	0.0958(8)	-0.0440(6)	0.0086(6)	-0.0256(7)
N1	0.0388(6)	0.0435(6)	0.0452(6)	-0.0020(5)	0.0085(5)	0.0011(5)
C2	0.0396(7)	0.0400(7)	0.0476(7)	-0.0006(5)	0.0066(5)	0.0015(5)
C3	0.0400(7)	0.0420(7)	0.0392(6)	0.0016(5)	0.0095(5)	0.0004(5)
C4	0.0437(7)	0.0421(7)	0.0390(6)	0.0029(5)	0.0103(5)	0.0011(5)
C5	0.0428(7)	0.0407(7)	0.0415(7)	0.0000(5)	0.0136(5)	0.0006(5)
C6	0.0569(9)	0.0426(7)	0.0584(8)	-0.0043(6)	0.0201(7)	-0.0032(6)
C7	0.0587(9)	0.0576(9)	0.0694(10)	-0.0193(8)	0.0171(8)	-0.0111(8)
C8	0.0460(8)	0.075(1)	0.0624(10)	-0.0149(8)	0.0051(7)	-0.0042(8)
C9	0.0393(7)	0.0617(9)	0.0541(8)	-0.0017(6)	0.0025(6)	0.0046(7)
C10	0.0464(8)	0.0464(8)	0.0674(9)	0.0012(6)	-0.0005(7)	0.0048(7)
N11	0.085(1)	0.0514(9)	0.118(1)	0.0091(8)	-0.0103(10)	0.0109(8)
C12	0.0578(9)	0.0484(8)	0.0564(9)	0.0087(7)	0.0094(7)	0.0047(6)
C13	0.0419(7)	0.0436(7)	0.0379(6)	-0.0008(5)	0.0057(5)	0.0015(5)
C14	0.0497(8)	0.0466(8)	0.0513(8)	-0.0025(6)	0.0128(6)	-0.0024(6)
C15	0.069(1)	0.0498(8)	0.0543(9)	-0.0113(7)	0.0144(7)	-0.0091(7)
C16	0.0576(9)	0.0652(10)	0.0530(9)	-0.0221(7)	0.0041(7)	-0.0040(7)
C17	0.0409(7)	0.075(1)	0.0572(9)	-0.0052(7)	0.0036(6)	-0.0008(8)
C18	0.0434(7)	0.0549(8)	0.0486(7)	0.0031(6)	0.0036(6)	-0.0035(6)

final coordinates and isotropic displacement parameters (Å^2) for H- atoms

Atom	X	Y	Z	U_{iso}
H6	0.17668	-0.02270	0.54752	0.0617
H7	0.05854	-0.03479	0.39412	0.0734
H8	-0.00738	0.17695	0.30470	0.0737
H9	0.04623	0.39800	0.37131	0.0627
H12A	0.29449	0.04996	0.75080	0.0812
H12C	0.34495	0.18175	0.81974	0.0812
H12B	0.34721	0.11832	0.63069	0.0812
H14	0.25323	0.64117	0.81853	0.0584
H15	0.34818	0.79353	0.94383	0.0686
H17	0.49683	0.52721	0.77976	0.0699
H18	0.40219	0.37550	0.65394	0.0593

Crystal data for 78e

formula	$C_{13}H_{14}N_2$
molecular weight	198,3 $gmol^{-1}$
space group	P nma (orthorhombic)
absorption	$\mu = 0.07\ mm^{-1}$
crystal size	0.3 x 0.45 x 0.5 mm^3 colourless Block
lattice parameters	a =11.9649(7)Å
(calculate from	b =6.8449(4)Å
12099 reflections with	c =13.5151(9)Å
2.3°< θ < 29.8°)	V =1106.9(1)$Å^3$ z = 4 F(000) = 424
temperature	-80°C
density	$d_{xray} = 1.19\ gcm^{-3}$

data collection

diffractometer	STOE IPDS 2T
radiation	Mo-K_α graphit monochromator
scan type	ω scans
scan – width	1°
scan range	$2° \leq \theta \leq 28°$
	$-15 \leq h \leq 15$ $-9 \leq k \leq 9$ $-17 \leq l \leq 17$
number of reflections:	
measured	13811
unique	1436 (R_{int} = 0.0468)
observed	1208 ($\|F\|/\sigma(F) > 4.0$)

data correction, structure solution and refinement

corrections	Lorentz and polarisation correction.
Structure solution	Program: SIR-97 (Direct methods)
refinement	Program: SHELXL-97 (full matrix). 90 refined parameters, weighting scheme: $w=1/[\sigma^2(F_o^2) + (0.0553*P)^2+0.16*P]$ with $P=(Max(F_o^2,0)+2*F_c^2)/3$. H-atoms at calculated positions and refined with isotropic displacement parameters, non H- atoms refined anisotropically..
R-values	wR2 = 0.1153 (R1 = 0.0400 for observed reflections, 0.0472 for all reflections)
goodness of fit	S = 1.064
maximum deviation of parameters	0.001 * e.s.d
maximum peak height in diff. Fourier synthesis	0.20, -0.17 $eÅ^{-3}$
Note	Structure is mirror symmetric.

final coordinates and equivalent displacement parameters (Å^2)

$U_{äq}= (1/3)*\sum\sum_{ij}a_i^* a_j^* \mathbf{a}_i\mathbf{a}_j$

Atom	X	Y	Z	U_{eq}
C1	0.6610(1)	0.25000	0.4030(1)	0.0419(4)
N2	0.56033(9)	0.25000	0.4536(1)	0.0444(4)
C3	0.4529(1)	0.25000	0.4171(2)	0.0538(5)
C4	0.3657(1)	0.25000	0.4811(2)	0.0619(7)
C5	0.3850(2)	0.25000	0.5835(2)	0.0639(7)
C6	0.4909(2)	0.25000	0.6198(2)	0.0576(6)
C7	0.5833(1)	0.25000	0.5543(1)	0.0464(5)
C8	0.6991(1)	0.25000	0.5665(1)	0.0438(4)
C9	0.7474(1)	0.25000	0.4726(1)	0.0403(4)
C10	0.6635(1)	0.25000	0.2995(1)	0.0473(5)
N11	0.6653(1)	0.25000	0.2143(1)	0.0631(5)
C12	0.7575(2)	0.25000	0.6640(1)	0.0581(6)
C13	0.8706(1)	0.25000	0.4488(1)	0.0432(4)
C14	0.90474(9)	0.0658(2)	0.3929(1)	0.0567(4)

anisotropic displacement parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C1	0.0319(6)	0.0361(7)	0.0576(9)	0.00000	0.0006(6)	0.00000
N2	0.0322(6)	0.0300(6)	0.0709(9)	0.00000	0.0037(5)	0.00000
C3	0.0337(7)	0.0367(7)	0.091(1)	0.00000	-0.0022(7)	0.00000
C4	0.0341(7)	0.0359(8)	0.116(2)	0.00000	0.0100(8)	0.00000
C5	0.0456(9)	0.0414(8)	0.105(2)	0.00000	0.0268(9)	0.00000
C6	0.0547(9)	0.0377(8)	0.080(1)	0.00000	0.0215(8)	0.00000
C7	0.0434(8)	0.0286(6)	0.0671(10)	0.00000	0.0090(7)	0.00000
C8	0.0430(7)	0.0306(6)	0.0579(9)	0.00000	0.0036(6)	0.00000
C9	0.0352(6)	0.0298(6)	0.0561(8)	0.00000	-0.0003(6)	0.00000
C10	0.0344(7)	0.0454(8)	0.062(1)	0.00000	-0.0051(6)	0.00000
N11	0.0505(8)	0.072(1)	0.0669(10)	0.00000	-0.0075(7)	0.00000
C12	0.064(1)	0.0557(10)	0.0550(10)	0.00000	0.0020(8)	0.00000
C13	0.0317(6)	0.0416(7)	0.0565(9)	0.00000	-0.0028(6)	0.00000
C14	0.0381(5)	0.0466(6)	0.0853(9)	0.0058(5)	0.0028(5)	-0.0061(6)

final coordinates and isotropic displacement parameters (Å^2) for H- atoms

Atom	X	Y	Z	U_{iso}
H3	0.43998	0.25000	0.34775	0.0646
H4	0.29134	0.25000	0.45650	0.0743
H5	0.32338	0.25000	0.62788	0.0767
H6	0.50296	0.25000	0.68930	0.0691
H12A	0.70718	0.19885	0.71499	0.0872
H12B	0.77949	0.38376	0.68104	0.0872
H12C	0.82426	0.16740	0.66001	0.0872

H13	0.91196	0.25000	0.51308	0.0519
H14A	0.88607	-0.04952	0.43256	0.0850
H14B	0.98541	0.06840	0.38041	0.0850
H14C	0.86464	0.06007	0.32969	0.0850

Crystal data for 102j

formula	$C_{13}H_{16}N_2O$
molecular weight	216.28 $gmol^{-1}$
absorption	$\mu = 0.08\ mm^{-1}$
crystal size	0.05 x 0.11 x 1.0 mm^3 colourless needle
space group	P -1 (triclinic)
lattice parameters	a =4.8572(6)Å α = 75.456(11)°
(calculate from	b =7.9878(11)Å ß = 81.806(11)°
4450 reflections with	c =15.509(2)Å γ = 81.763(10)°
3.2° < θ < 28.7°)	V = 572.8(1)$Å^3$ z = 2 F(000) = 232
temperature	-100°C
density	$d_{xray} = 1.254\ gcm^{-3}$

data collection

diffractometer	STOE IPDS 2T
radiation	Mo-K_α Graphitmonochromator
Scan – type	ω scans
Scan – width	1°
scan range	$3° \leq \theta < 28°$ $-6 \leq h \leq 6$ $-10 \leq k \leq 10$ $-20 \leq l \leq 20$
number of reflections:	
measured	5925
unique	2767 ($R_{int} = 0.401$)
observed	1748 ($\|F\|/\sigma(F) > 4.0$)

data correction, structure solution and refinement

corrections	Lorentz and polarisation correction.
Structure solution	Program: SIR-97 (Direct methods)
refinement	Program: SHELXL-97 (full matrix). 152 refined parameters, weighting scheme: $w=1/[\sigma^2(F_o^2) + (0.0568*P)^2]$ with $(Max(F_o^2,0)+2*F_c^2)/3$. H-atoms at calculated positions (NH localized) and refined with isotropic displacement parameters, non H- atoms refined anisotropically.
R-values	wR2 = 0.1117 (R1=0.0432 for observed reflections, 0.0808 for all reflections)
goodness of fit	S = 0.979
maximum deviation of parameters	0.001 * e.s.d
maximum peak height in diff. Fourier synthesis	0.24, -0.16 $eÅ^{-3}$

final coordinates and equivalent displacement parameters (Å^2)

$U_{äq}= (1/3)*\sum\sum_{ij}a_i^* a_j^* \mathbf{a}_i\mathbf{a}_j$

Atom	X	Y	Z	U_{eq}
C1	0.5493(3)	0.3202(2)	0.1997(1)	0.0247(5)
C2	0.4975(3)	0.4646(2)	0.2358(1)	0.0269(5)
C3	0.6721(3)	0.4336(2)	0.3048(1)	0.0267(5)
C4	0.8264(3)	0.2728(2)	0.3118(1)	0.0261(5)
N5	0.7522(2)	0.2030(2)	0.24667(8)	0.0251(4)
C6	0.8578(3)	0.0480(2)	0.2236(1)	0.0287(5)
C7	0.7634(3)	0.0052(2)	0.1548(1)	0.0306(5)
C8	0.5519(3)	0.1200(2)	0.1080(1)	0.0311(5)
C9	0.4443(3)	0.2738(2)	0.1288(1)	0.0271(5)
N10	0.7021(3)	0.5502(2)	0.35746(9)	0.0282(5)
C11	0.4898(3)	0.6544(2)	0.3890(1)	0.0317(6)
O12	0.2447(2)	0.6546(2)	0.3778(1)	0.0570(6)
C13	0.5718(3)	0.7727(2)	0.4404(1)	0.0346(6)
C14	1.0358(3)	0.1792(2)	0.3734(1)	0.0319(5)
C15	0.8845(4)	-0.1603(3)	0.1272(1)	0.0432(7)
C16	0.2224(3)	0.3974(2)	0.0809(1)	0.0333(6)

anisotropic displacement parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C1	0.0187(6)	0.0290(8)	0.0246(7)	-0.0029(6)	-0.0027(6)	-0.0028(6)
C2	0.0209(7)	0.0283(8)	0.0313(8)	-0.0017(6)	-0.0058(6)	-0.0055(7)
C3	0.0196(6)	0.0323(9)	0.0292(8)	-0.0056(6)	-0.0035(6)	-0.0069(7)
C4	0.0206(7)	0.0309(8)	0.0267(8)	-0.0049(6)	-0.0046(6)	-0.0045(6)
N5	0.0194(6)	0.0284(7)	0.0262(7)	-0.0018(5)	-0.0047(5)	-0.0033(5)
C6	0.0261(7)	0.0245(8)	0.0311(8)	0.0005(6)	-0.0039(6)	0.0000(6)
C7	0.0321(8)	0.0264(8)	0.0323(8)	-0.0042(7)	-0.0003(7)	-0.0061(7)
C8	0.0315(8)	0.0346(9)	0.0288(8)	-0.0058(7)	-0.0050(6)	-0.0087(7)
C9	0.0230(7)	0.0318(9)	0.0252(8)	-0.0042(6)	-0.0040(6)	-0.0031(6)
N10	0.0189(6)	0.0355(8)	0.0339(7)	-0.0043(5)	-0.0066(5)	-0.0125(6)
C11	0.0215(7)	0.0410(10)	0.0358(9)	-0.0044(7)	-0.0045(6)	-0.0136(8)
O12	0.0193(6)	0.083(1)	0.086(1)	-0.0017(6)	-0.0093(6)	-0.0526(10)
C13	0.0263(7)	0.0410(10)	0.0406(10)	-0.0029(7)	-0.0045(7)	-0.0173(8)
C14	0.0271(8)	0.0359(9)	0.0308(8)	-0.0024(7)	-0.0101(6)	-0.0014(7)
C15	0.051(1)	0.0326(10)	0.047(1)	0.0018(8)	-0.0074(9)	-0.0137(8)
C16	0.0284(8)	0.0400(10)	0.0321(9)	-0.0002(7)	-0.0104(7)	-0.0075(7)

final coordinates and isotropic displacement parameters (Å^2) for H- atoms

Atom	X	Y	Z	U_{iso}
H2	0.36941	0.56498	0.21774	0.0323
H6	0.99643	-0.02832	0.25598	0.0344
H8	0.48350	0.08807	0.06065	0.0373
H10	0.868(4)	0.561(2)	0.368(1)	0.0338
H13A	0.50043	0.89326	0.41433	0.0519
H13B	0.77625	0.76248	0.43728	0.0519
H13C	0.49204	0.73929	0.50320	0.0519
H14A	1.21864	0.16294	0.33873	0.0478
H14B	0.97740	0.06542	0.40542	0.0478
H14C	1.04964	0.24751	0.41670	0.0478
H15A	0.73271	-0.22799	0.12591	0.065
H15B	1.01106	-0.22873	0.17024	0.065
H15C	0.98857	-0.13176	0.06739	0.065
H16A	0.29673	0.50791	0.05151	0.0500
H16B	0.06079	0.41781	0.12413	0.0500
H16C	0.16433	0.34717	0.03574	0.0500

Crystal data for 122a

formula	$C_{17}H_{12}N_2$
molecular weight	244.3 $gmol^{-1}$
absorption	$\mu = 0.08\ mm^{-1}$
crystal size	0.08 x 0.1 x 0.36 mm^3 colourless needle
space group	C 2/c (monoclinic)
lattice parameters	a =25.188(2)Å
(calculate from	b =5.7807(3)Å ß = 118.440(5)°
10445 reflections with	c =19.7935(13)Å
$2.3° < \theta < 28.5°$)	$V = 2534.2(3)Å^3$ z = 8 F(000) = 1024
temperature	-80°C
density	$d_{xray} = 1.281\ gcm^{-3}$

data collection

diffractometer	STOE IPDS 2T
radiation	Mo-K_α Graphitmonochromator
Scan – type	ω scans
Scan – width	1°
scan range	$2° \leq \theta < 28°$
	$-27 \leq h \leq 32$ $-7 \leq k \leq 7$ $-26 \leq l \leq 26$
number of reflections:	
measured	11351
unique	3059 ($R_{int} = 0.0561$)
observed	2078 ($\|F\|/\sigma(F) > 4.0$)

data correction, structure solution and refinement

corrections	Lorentz and polarisation correction.
Structure solution	Program: SIR-97 (Direct methods)
refinement	Program: SHELXL-97 (full matrix). 188 refined parameters, weighting scheme: $w=1/[\sigma^2(F_o^2) + (0.0636*P)^2+0.34*P]$ with $(Max(F_o^2,0)+2*F_c^2)/3$. H-atoms at calculated positions and refined with isotropic displacement parameters, non H- atoms refined anisotropically.
R-values	wR2 = 0.1277 (R1 = 0.0447 for observed reflections, 0.0733 for all reflections)
goodness of fit	S = 1.020
maximum deviation of parameters	0.001 * e.s.d
maximum peak height in diff. Fourier synthesis	0.14, .0.20 $eÅ^{-3}$
remark	structure is disordered

final coordinates and equivalent displacement parameters (Å^2)

$U_{äq}= (1/3)*\sum\sum_{ij}a_i^* a_j^* \mathbf{a}_i\mathbf{a}_j$

Atom	X	Y	Z	U_{eq}
N1	0.5587(6)	0.228(3)	0.6201(8)	0.037(2)
C2	0.5020(6)	0.333(2)	0.5813(10)	0.033(2)
C1	0.5632(6)	0.234(2)	0.6299(8)	0.033(2)
N2	0.5084(4)	0.348(2)	0.5905(6)	0.037(2)
C3	0.50291(7)	0.5122(3)	0.63296(8)	0.0369(6)
C4	0.55787(7)	0.5095(3)	0.70097(8)	0.0379(6)
C5	0.59398(7)	0.3321(3)	0.69598(8)	0.0362(6)
C6	0.65480(7)	0.2627(3)	0.75366(8)	0.0356(6)
C7	0.69020(7)	0.4133(3)	0.81326(8)	0.0421(6)
C8	0.74870(8)	0.3548(3)	0.86660(9)	0.0485(7)
C9	0.77300(8)	0.1448(3)	0.86168(9)	0.0473(7)
C10	0.73789(7)	-0.0085(3)	0.8041(1)	0.0451(7)
C11	0.67935(7)	0.0483(3)	0.75077(9)	0.0397(6)
C12	0.45039(7)	0.6616(3)	0.61290(8)	0.0370(6)
C13	0.45787(8)	0.8761(3)	0.64869(9)	0.0414(6)
C14	0.40853(8)	1.0135(3)	0.6339(1)	0.0467(7)
C15	0.35102(8)	0.9418(3)	0.5821(1)	0.0506(8)
C16	0.34296(8)	0.7322(3)	0.5451(1)	0.0512(7)
C17	0.39218(8)	0.5923(3)	0.56065(9)	0.0456(7)
C18	0.4629(2)	0.2486(7)	0.5138(2)	0.042(1)
N19	0.42359(8)	0.1339(4)	0.45012(9)	0.0735(8)
C20	0.5725(1)	0.0470(5)	0.5848(2)	0.040(1)

anisotropic displacement parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N1	0.030(2)	0.044(3)	0.022(2)	-0.003(1)	0.001(1)	-0.008(1)
C2	0.030(2)	0.031(2)	0.034(4)	0.005(2)	0.011(3)	-0.006(2)
C1	0.030(2)	0.031(2)	0.034(4)	0.005(2)	0.011(3)	-0.006(2)
N2	0.030(2)	0.044(3)	0.022(2)	-0.003(1)	0.001(1)	-0.008(1)
C3	0.0403(8)	0.0334(7)	0.0359(7)	0.0025(6)	0.0171(6)	-0.0009(6)
C4	0.0409(8)	0.0345(7)	0.0353(7)	0.0000(6)	0.0157(6)	-0.0056(6)
C5	0.0361(8)	0.0347(7)	0.0341(7)	-0.0027(6)	0.0136(6)	-0.0028(6)
C6	0.0367(8)	0.0347(8)	0.0332(7)	-0.0039(6)	0.0150(6)	-0.0015(6)
C7	0.0431(9)	0.0377(8)	0.0382(7)	-0.0037(7)	0.0135(7)	-0.0047(6)
C8	0.0452(9)	0.0489(10)	0.0388(8)	-0.0092(8)	0.0098(7)	-0.0049(7)
C9	0.0365(8)	0.052(1)	0.0431(8)	-0.0015(8)	0.0105(7)	0.0068(7)
C10	0.0390(9)	0.0432(9)	0.0510(9)	0.0013(7)	0.0198(7)	0.0025(7)
C11	0.0373(8)	0.0367(8)	0.0426(8)	-0.0016(6)	0.0170(7)	-0.0044(6)
C12	0.0400(8)	0.0347(8)	0.0345(7)	0.0046(6)	0.0162(6)	0.0029(6)
C13	0.0460(9)	0.0376(8)	0.0400(7)	0.0030(7)	0.0199(7)	0.0002(6)
C14	0.057(1)	0.0377(8)	0.0481(9)	0.0093(8)	0.0276(8)	0.0027(7)
C15	0.050(1)	0.0491(10)	0.0549(9)	0.0150(8)	0.0262(8)	0.0095(8)

C16	0.0406(9)	0.050(1)	0.0521(9)	0.0073(8)	0.0131(7)	0.0054(8)
C17	0.0453(9)	0.0381(8)	0.0435(8)	0.0059(7)	0.0132(7)	-0.0002(7)
C18	0.037(2)	0.044(2)	0.040(2)	0.005(2)	0.014(2)	-0.004(2)
N19	0.057(1)	0.107(2)	0.0480(9)	0.036(1)	0.0181(8)	0.0034(9)
C20	0.034(1)	0.042(2)	0.035(1)	0.003(1)	0.010(1)	-0.006(1)

final coordinates and isotropic displacement parameters ($Å^2$) for H- atoms

Atom	X	Y	Z	U_{iso}
H1	0.57138	0.11540	0.60145	0.044
H2	0.48082	0.31446	0.54329	0.044
H4	0.56895	0.61064	0.74343	0.0455
H7	0.67400	0.55785	0.81736	0.0505
H8	0.77229	0.45955	0.90680	0.0582
H9	0.81345	0.10651	0.89759	0.0568
H10	0.75409	-0.15416	0.80101	0.0541
H11	0.65556	-0.05957	0.71179	0.0476
H13	0.49731	0.92835	0.68365	0.0497
H14	0.41426	1.15783	0.65942	0.0560
H15	0.31717	1.03626	0.57206	0.0607
H16	0.30351	0.68353	0.50888	0.0615
H17	0.38608	0.44745	0.53531	0.0547

Crystal data for 136c

formula	$C_{22}H_{23}FN_2O_2$
molecular weight	366.4 $gmol^{-1}$
absorption	μ = 0.09 mm^{-1}
crystal size	0.4 x 0.6 x 0.6 mm^3 colourless block
space group	P -1 (triclinic)
lattice parameters	a =11.7244(9)Å α = 80.454(7)°
(calculate from	b =13.1147(10)Å ß = 84.455(6)°
15648 reflections with	c =13.1273(11)Å γ = 76.543(6)°
2.5° < θ < 28.7°)	V = 1932.3(3)$Å^3$ z = 4 F(000) = 776
temperature	-60°C
density	d_{xray} = 1.26 gcm^{-3}

data collection

diffractometer	STOE IPDS 2T
radiation	Mo-K_α Graphitmonochromator
Scan – type	ω scans
Scan – width	1°
scan range	2° ≤ θ < 28°
	-15 ≤ h ≤ 15 -17 ≤ k ≤ 14 -17 ≤ l ≤ 17
number of reflections:	
measured	20237
unique	9316 (R_{int} = 0.0402)
observed	5916 (|F|/σ(F) > 4.0)

data correction, structure solution and refinement

corrections	Lorentz and polarisation correction.
Structure solution	Program: SIR-2004 (Direct methods)
refinement	Program: SHELXL-2014 (full matrix). 507 refined parameters, weighting scheme: $w=1/[\sigma^2(F_o^2) + (0.0676*P)^2+0.20*P]$ with $(Max(F_o^2,0)+2*F_c^2)/3$. H-atoms at calculated positions and refined with isotropic displacement parameters, non H- atoms refined anisotropically.
R-values	wR2 = 0.1394 (R1 = 0.0492 for observed reflections, 0.0840 for all reflections)
goodness of fit	S = 1.027
maximum deviation of parameters	0.001 * e.s.d
maximum peak height in diff. Fourier synthesis	0.41, -0.31 $eÅ^{-3}$
remark	structure contains two slightly different molecules, one i-propylic group is disorderd

final coordinates and equivalent displacement parameters (Å^2)
$U_{äq}= (1/3)*\sum\sum_{ij}a_i^* a_j^* \mathbf{a}_i\mathbf{a}_j$

Atom	X	Y	Z	U_{eq}
C1A	0.5489(1)	0.6141(1)	0.5588(1)	0.0313(5)
C2A	0.4902(1)	0.5835(1)	0.6540(1)	0.0344(5)
C3A	0.5423(1)	0.4803(1)	0.6912(1)	0.0327(5)
N4A	0.6310(1)	0.4468(1)	0.6215(1)	0.0310(4)
C5A	0.6374(1)	0.5261(1)	0.5400(1)	0.0302(5)
C6A	0.5130(1)	0.4116(1)	0.7855(1)	0.0340(5)
C7A	0.5335(2)	0.3019(1)	0.7899(1)	0.0411(6)
C8A	0.5045(2)	0.2384(2)	0.8795(2)	0.0477(7)
C9A	0.4566(2)	0.2856(2)	0.9642(1)	0.0473(7)
C10A	0.4326(2)	0.3931(2)	0.9626(1)	0.0480(7)
C11A	0.4608(2)	0.4561(2)	0.8728(1)	0.0419(6)
C12A	0.5173(1)	0.7208(1)	0.4970(1)	0.0314(5)
C13A	0.3986(1)	0.7691(1)	0.4828(1)	0.0348(5)
C14A	0.3664(2)	0.8707(1)	0.4306(1)	0.0374(5)
C15A	0.4511(2)	0.9278(1)	0.3905(1)	0.0359(5)
C16A	0.5688(2)	0.8816(1)	0.4038(1)	0.0382(6)
C17A	0.6002(2)	0.7797(1)	0.4574(1)	0.0348(5)
C18A	0.7268(1)	0.4996(1)	0.4562(1)	0.0299(5)
N19A	0.7251(1)	0.5675(1)	0.3677(1)	0.0340(4)
C20A	0.8024(2)	0.5394(1)	0.2773(1)	0.0389(6)
C21A	0.8119(2)	0.6339(2)	0.1965(1)	0.0442(6)
C22A	0.8617(3)	0.7149(2)	0.2369(2)	0.0657(9)
C23A	0.8859(2)	0.5952(2)	0.1023(2)	0.0660(9)
F24A	0.4310(1)	0.2230(1)	1.0534(1)	0.0712(5)
O25A	0.4097(1)	1.0278(1)	0.3401(1)	0.0488(5)
C26A	0.4934(2)	1.0907(2)	0.3036(2)	0.0575(8)
O27A	0.8013(1)	0.41525(9)	0.46821(9)	0.0403(4)
C1B	1.0837(1)	0.0817(1)	0.5998(1)	0.0303(5)
C2B	1.1469(1)	0.1221(1)	0.5115(1)	0.0324(5)
C3B	1.0873(1)	0.2241(1)	0.4771(1)	0.0296(5)
N4B	0.9893(1)	0.2468(1)	0.5417(1)	0.0288(4)
C5B	0.9849(1)	0.1611(1)	0.6163(1)	0.0305(5)
C6B	1.1209(1)	0.3007(1)	0.3917(1)	0.0318(5)
C7B	1.1818(2)	0.2656(2)	0.3039(2)	0.0563(8)
C8B	1.2196(3)	0.3356(2)	0.2243(2)	0.0697(10)
C9B	1.1967(2)	0.4408(2)	0.2348(2)	0.0505(7)
C10B	1.1371(2)	0.4793(1)	0.3196(2)	0.0409(6)
C11B	1.0995(2)	0.4082(1)	0.3984(1)	0.0353(5)
C12B	1.1213(1)	-0.0229(1)	0.6644(1)	0.0312(5)
C13B	1.1674(2)	-0.0305(1)	0.7593(2)	0.0509(7)
C14B	1.2015(2)	-0.1277(2)	0.8213(2)	0.0538(8)
C15B	1.1902(2)	-0.2189(1)	0.7888(1)	0.0393(6)
C16B	1.1473(2)	-0.2136(1)	0.6932(2)	0.0446(6)
C17B	1.1139(2)	-0.1164(1)	0.6319(1)	0.0387(6)
C18B	0.8835(2)	0.1675(1)	0.6920(1)	0.0351(5)
N19B	0.8760(2)	0.0775(1)	0.7555(1)	0.0556(6)

C20B	0.7781(2)	0.0691(2)	0.8314(2)	0.0665(9)
C21B	0.8052(4)	-0.0112(5)	0.9230(4)	0.056(2)

Atom	X	Y	Z	U_{eq}
C21C	0.7916(10)	-0.0371(8)	0.8903(7)	0.056(3)
C22B	0.6954(3)	-0.0232(3)	0.9905(2)	0.096(1)
C23B	0.8675(5)	-0.1159(4)	0.9050(4)	0.098(2)
C23C	0.9120(9)	-0.0518(6)	0.9592(7)	0.098(2)
F24B	1.2351(1)	0.5095(1)	0.1569(1)	0.0758(6)
O25B	1.2189(2)	-0.3176(1)	0.8461(1)	0.0583(6)
C26B	1.2338(3)	-0.3228(2)	0.9527(2)	0.076(1)
O27B	0.8092(1)	0.2506(1)	0.6952(1)	0.0440(4)

anisotropic displacement parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C1A	0.0295(8)	0.0260(8)	0.0375(8)	-0.0044(6)	-0.0034(6)	-0.0038(6)
C2A	0.0326(8)	0.0301(8)	0.0386(9)	-0.0035(7)	0.0010(7)	-0.0062(7)
C3A	0.0302(8)	0.0314(8)	0.0358(8)	-0.0061(7)	-0.0011(6)	-0.0045(7)
N4A	0.0308(7)	0.0248(6)	0.0346(7)	-0.0041(5)	-0.0004(5)	-0.0002(5)
C5A	0.0299(8)	0.0254(7)	0.0338(8)	-0.0054(6)	-0.0039(6)	-0.0006(6)
C6A	0.0292(8)	0.0370(9)	0.0336(8)	-0.0058(7)	-0.0011(6)	-0.0020(7)
C7A	0.0402(9)	0.0364(9)	0.0412(9)	-0.0034(7)	0.0074(8)	-0.0024(7)
C8A	0.045(1)	0.0378(10)	0.051(1)	-0.0020(8)	0.0091(8)	0.0030(8)
C9A	0.046(1)	0.053(1)	0.0371(9)	-0.0110(9)	0.0036(8)	0.0071(8)
C10A	0.053(1)	0.057(1)	0.0343(9)	-0.0127(9)	0.0045(8)	-0.0102(8)
C11A	0.047(1)	0.0398(10)	0.0394(9)	-0.0104(8)	0.0006(8)	-0.0089(8)
C12A	0.0324(8)	0.0252(7)	0.0349(8)	-0.0028(6)	-0.0026(6)	-0.0048(6)
C13A	0.0324(8)	0.0293(8)	0.0415(9)	-0.0037(7)	-0.0008(7)	-0.0069(7)
C14A	0.0318(8)	0.0316(8)	0.0458(9)	0.0018(7)	-0.0059(7)	-0.0074(7)
C15A	0.0426(9)	0.0253(8)	0.0370(9)	-0.0016(7)	-0.0055(7)	-0.0033(7)
C16A	0.0382(9)	0.0304(8)	0.0454(10)	-0.0080(7)	-0.0028(7)	-0.0030(7)
C17A	0.0304(8)	0.0279(8)	0.0447(9)	-0.0030(6)	-0.0047(7)	-0.0045(7)
C18A	0.0285(8)	0.0255(7)	0.0346(8)	-0.0050(6)	-0.0039(6)	-0.0014(6)
N19A	0.0322(7)	0.0278(7)	0.0370(7)	-0.0007(6)	0.0003(6)	0.0000(6)
C20A	0.0418(9)	0.0353(9)	0.0373(9)	-0.0075(7)	0.0025(7)	-0.0027(7)
C21A	0.047(1)	0.042(1)	0.0403(10)	-0.0101(8)	-0.0021(8)	0.0029(8)
C22A	0.091(2)	0.052(1)	0.061(1)	-0.036(1)	0.006(1)	-0.006(1)
C23A	0.081(2)	0.068(2)	0.047(1)	-0.024(1)	0.015(1)	-0.003(1)
F24A	0.0862(10)	0.0690(9)	0.0454(7)	-0.0137(7)	0.0165(6)	0.0119(6)
O25A	0.0506(8)	0.0301(6)	0.0578(8)	-0.0005(6)	-0.0086(6)	0.0069(6)
C26A	0.067(1)	0.035(1)	0.063(1)	-0.0079(10)	-0.003(1)	0.0121(9)
O27A	0.0396(7)	0.0310(6)	0.0405(7)	0.0048(5)	0.0016(5)	0.0022(5)
C1B	0.0319(8)	0.0238(7)	0.0342(8)	-0.0041(6)	-0.0054(6)	-0.0022(6)
C2B	0.0322(8)	0.0258(8)	0.0363(8)	-0.0013(6)	-0.0016(6)	-0.0040(6)
C3B	0.0298(8)	0.0274(8)	0.0311(8)	-0.0043(6)	-0.0015(6)	-0.0054(6)
N4B	0.0286(6)	0.0239(6)	0.0313(7)	-0.0025(5)	-0.0019(5)	-0.0016(5)

C5B	0.0332(8)	0.0243(7)	0.0332(8)	-0.0060(6)	-0.0058(6)	-0.0001(6)
C6B	0.0318(8)	0.0290(8)	0.0312(8)	-0.0033(6)	-0.0015(6)	-0.0001(6)
C7B	0.077(1)	0.039(1)	0.045(1)	-0.006(1)	0.018(1)	-0.0077(9)
C8B	0.093(2)	0.058(1)	0.045(1)	-0.008(1)	0.028(1)	-0.003(1)
C9B	0.051(1)	0.050(1)	0.043(1)	-0.0130(9)	0.0034(9)	0.0127(9)
C10B	0.0385(9)	0.0334(9)	0.048(1)	-0.0080(7)	-0.0061(8)	0.0045(7)
C11B	0.0346(8)	0.0321(8)	0.0370(9)	-0.0054(7)	0.0002(7)	-0.0031(7)
C12B	0.0311(8)	0.0251(7)	0.0344(8)	-0.0016(6)	-0.0041(6)	-0.0008(6)
C13B	0.078(1)	0.0275(9)	0.050(1)	-0.0071(9)	-0.027(1)	-0.0037(8)
C14B	0.080(1)	0.0360(10)	0.044(1)	-0.0032(10)	-0.030(1)	-0.0009(8)
C15B	0.0470(10)	0.0258(8)	0.0384(9)	0.0020(7)	-0.0053(7)	0.0016(7)
C16B	0.062(1)	0.0253(8)	0.047(1)	-0.0074(8)	-0.0109(9)	-0.0054(7)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C17B	0.050(1)	0.0297(8)	0.0366(9)	-0.0066(7)	-0.0109(8)	-0.0031(7)
C18B	0.0328(8)	0.0312(8)	0.0370(9)	-0.0034(7)	-0.0029(7)	0.0029(7)
N19B	0.0470(9)	0.0408(9)	0.062(1)	0.0005(7)	0.0146(8)	0.0168(8)
C20B	0.060(1)	0.056(1)	0.066(1)	-0.006(1)	0.019(1)	0.020(1)
C21B	0.051(2)	0.063(3)	0.048(3)	-0.015(2)	-0.008(2)	0.015(2)
C21C	0.076(5)	0.066(5)	0.036(4)	-0.039(4)	0.002(4)	-0.006(3)
C22B	0.070(2)	0.123(3)	0.075(2)	-0.030(2)	0.003(1)	0.051(2)
C23B	0.124(4)	0.051(2)	0.088(3)	0.005(2)	0.034(3)	0.015(2)
C23C	0.124(4)	0.051(2)	0.088(3)	0.005(2)	0.034(3)	0.015(2)
F24B	0.090(1)	0.0703(9)	0.0559(8)	-0.0246(8)	0.0154(7)	0.0212(7)
O25B	0.091(1)	0.0285(7)	0.0470(8)	-0.0002(7)	-0.0156(7)	0.0078(6)
C26B	0.115(2)	0.051(1)	0.044(1)	0.007(1)	-0.013(1)	0.0137(10)
O27B	0.0407(7)	0.0354(7)	0.0458(7)	0.0015(5)	0.0069(6)	0.0036(5)

final coordinates and isotropic displacement parameters ($Å^2$) for H- atoms

Atom	X	Y	Z	U_{iso}
H2A	0.42618	0.62642	0.68661	0.0413
H4A	0.67718	0.38398	0.62759	0.0372
H7A	0.56742	0.27064	0.73151	0.0494
H8A	0.51737	0.16458	0.88215	0.0573
H10A	0.39767	0.42337	1.02130	0.0576
H11A	0.44454	0.53007	0.87041	0.0502
H13A	0.34023	0.73168	0.50935	0.0418
H14A	0.28653	0.90173	0.42206	0.0449
H16A	0.62689	0.91910	0.37675	0.0459
H17A	0.68010	0.74962	0.46718	0.0418
H19A	0.65489	0.62318	0.36176	0.0408
H20A	0.77259	0.48870	0.24589	0.0467
H20B	0.88099	0.50427	0.30008	0.0467
H21A	0.73187	0.66869	0.17458	0.0530
H22A	0.81240	0.73933	0.29557	0.0985

H22B	0.86424	0.77449	0.18265	0.0985
H22C	0.94060	0.68273	0.25826	0.0985
H23A	0.96600	0.56455	0.12099	0.0990
H23B	0.88512	0.65450	0.04711	0.0990
H23C	0.85337	0.54206	0.07907	0.0990
H26A	0.53619	1.09708	0.36103	0.0862
H26B	0.45300	1.16065	0.27275	0.0862
H26C	0.54790	1.05732	0.25216	0.0862
H2B	1.21750	0.08591	0.48134	0.0389
H4B	0.93754	0.30662	0.53624	0.0346
H7B	1.19775	0.19303	0.29824	0.0676
H8B	1.26012	0.31155	0.16435	0.0836
H10B	1.12200	0.55193	0.32450	0.0491
H11B	1.05854	0.43328	0.45765	0.0423
H13B	1.17570	0.03140	0.78231	0.0611
H14B	1.23228	-0.13102	0.88559	0.0646
H16B	1.14092	-0.27589	0.66981	0.0536
H17B	1.08542	-0.11371	0.56671	0.0464
H19B	0.92424	0.00272	0.74572	0.0667

Atom	X	Y	Z	U_{iso}
H20C	0.71505	0.05315	0.79711	0.0798
H20D	0.74801	0.13824	0.85444	0.0798
H20E	0.70481	0.08696	0.79574	0.0798
H20F	0.77264	0.12032	0.87914	0.0798
H21B	0.85539	0.01507	0.96450	0.067
H21C	0.79062	-0.09509	0.85092	0.067
H22D	0.66155	0.04228	1.01794	0.145
H22E	0.71550	-0.08052	1.04724	0.145
H22F	0.63889	-0.03907	0.94960	0.145
H22G	0.73160	-0.06249	1.05286	0.145
H22H	0.62789	-0.05021	0.97974	0.145
H22I	0.67030	0.05126	0.99774	0.145
H23D	0.81293	-0.15364	0.88547	0.146
H23E	0.90365	-0.15435	0.96765	0.146
H23F	0.92791	-0.11019	0.84967	0.146
H23G	0.98266	-0.06914	0.91485	0.146
H23H	0.91183	-0.10834	1.01707	0.146
H23I	0.90985	0.01391	0.98492	0.146
H26D	1.30225	-0.29587	0.96075	0.114
H26E	1.24471	-0.39587	0.98607	0.114
H26F	1.16469	-0.28027	0.98420	0.114

Erklärung

Mainz, den 02.03.2015

Hiermit erkläre ich, dass ich die vorliegende Arbeit selbständig angefertigt habe. Es wurden nur die in der Arbeit ausdrücklich benannten Quellen und Hilfsmittel benutzt. Wörtlich oder sinngemäß übernommenes Gedankengut habe ich als solches kenntlich gemacht.

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(Murat Kücükdisli)