Iminium Induced Cascade Cyclizations: Access to Dihydroisoquinolinium (DHIQ) Salts, highly substituted Oxazoles, Furocoumarins and Pyridoxazoles

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This thesis entitled **"Iminium Induced Cascade Cyclizations: Access to Dihydroisoquinolinium (DHIQ) Salts, highly substituted Oxazoles, Furocoumarins and Pyridoxazoles"** by **Venkata Nagarjuna Babu** is approved for the degree of Doctor of Philosophy from IIT Hyderabad.

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My Beloved Family &

My Supervisor

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Venkata Nagarjuna Babu.

ABSTRACT

Introduction

The demand for sustainable and green chemistry has inspired chemists to hunt for efficient and economic ways to construct chemical bonds in organic synthesis. In particular, C-C, C-O and C-N bonds formation is a central aspect in synthetic chemistry. On the other hand, C-H bonds are ubiquitous in organic molecules. Therefore, the direct functionalization of C-H to C-C, C-O and C-N bonds becomes one of the most valuable and straightforward methods for the synthesis of complex structures.

Sustainability has become one of the important scientific challenges nowadays, due to environmental, health and societal concerns. Due to this, there is a need for developing facile, efficient, and non-polluting synthetic procedures to reduce the use of organic solvents and toxic reagents. One such approach, which involves green and sustainable chemistry, drives towards pollution prevention and environmental protection, and is now gaining importance. Which mainly involves designing chemical products and processes that reduce or eliminate the use of hazardous substances, volatile organic compounds, generation of waste materials, by-product formation and unnecessary derivatization (like blocking, protecting/deprotecting) *etc*.

One of the strategies widely implemented is the development of alternative sustainable routes involves catalyst-free and solvent-free reactions (CFR & SFR) which have gained importance recently. These approaches have several advantages over the conventional organic synthetic methods, like (a) reduced pollutant production, (b) reduced use or elimination of toxic and hazardous chemicals, (c) operational simplicity, (d) decreasing the reaction time (under SFR), (e) formation of pure products which avoids tedious purifications, (f) high yields, (g) reduced cost and many more.

Due to the various advantages of solvent-free and catalyst-free reactions, from the past decades tremendous efforts have been made by several groups for the synthesis of heterocyclic molecules.

Accordingly, we have developed the green protocols particularly solvent-free, catalyst-free techniques and designed acid catalyzed cyclizations for making Dihydroisoquinolinium (DHIQ) Salts, highly substituted Oxazoles, Furocoumarins and Pyridoxazoles.

PROPOSED CONTENTS OF THE THESIS:

Chapter I: Introduction

Chapter II: Metal-Free Cyclic Iminium Induced One-pot Double Annulation Cascade: Access to Dihydroisoquinolinium (DHIQ) Salts

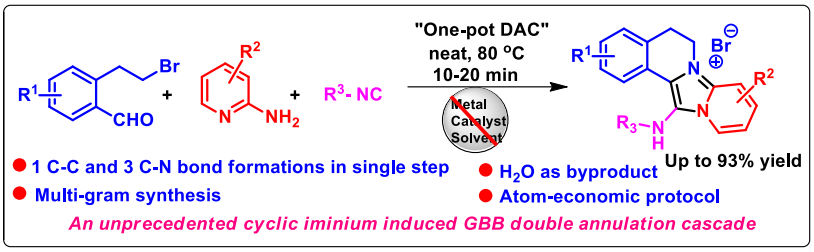
Chapter III: **An Exocyclic N-Acyliminium ion (NAI) Cyclization: Access to Fully Substituted Oxazoles and Furocoumarins**

Description of the research work

Chapter I: Introduction

In this chapter, we have described the introduction about reactivity of isocyanides, and their synthetic applications, importance of 2-(2-bromoethyl)benzaldehyde. Further we described about *N*-Acyliminium ions and its applications, Oxazoles and Furocoumarins importance and their applications.

Chapter II: Metal-Free Cyclic Iminium Induced One-pot Double Annulation Cascade: Access to Dihydroisoquinolinium (DHIQ) Salts



Scheme 1 Metal-Free Double Annulation Cascade: Access to Dihydroisoquinolinium (DHIQ) Salts

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The ubiquity of the isoquinoline (IQ) framework in biologically active natural products, besides its applications as pharmaceuticals, functional organic materials and ligands for asymmetric catalysis have turned the attention of synthetic organic chemists in recent years. Among IQ derivatives, fused IQ salts are naturally occurring alkaloids and promising lead structures in drug discovery. The iminium moiety in these derivatives was found to be essential for significant biological activities. Though several reports have been documented for the synthesis of these derivatives, most of the methods involve starting material with preformed IQ skeleton, expensive metal catalysts, multiple steps, lack of diversity, scalability, and tedious routes to access starting material. Beside isoquinoline motif dihydroisoquinolinium (DHIQ) ion and pyrido-imidazo[5,1-*a*]isoquinolinium ion also form an important core structure of natural products and pharmaceuticals (Figure 1).

Our interests in the development of metal-free protocols for the synthesis of heterocyclic scaffolds, persuaded us to design a strategy for the synthesis of azaheterocycles.

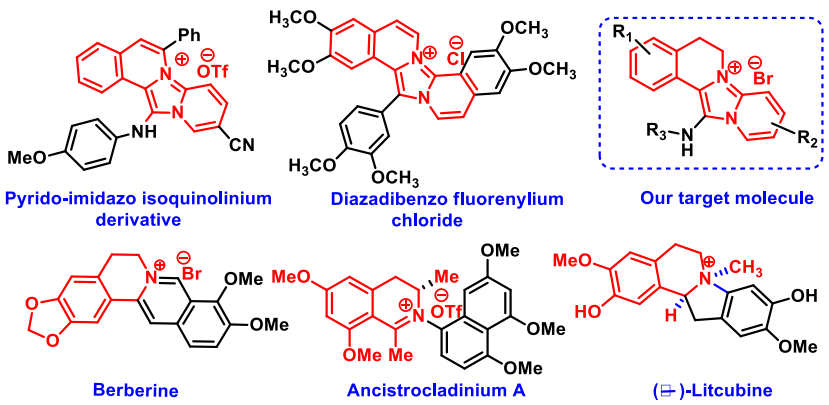


Figure 1 Representative examples of bioactive molecules and natural products

The versatility of 2-(2-bromoethyl)benzaldehyde (**1a**) as a promising bifunctional reactant in various organic transformations has been well documented, especially leading to tetrahydroisoquinoline (THIQ) motifs based natural products and their analogues (Figure 2).

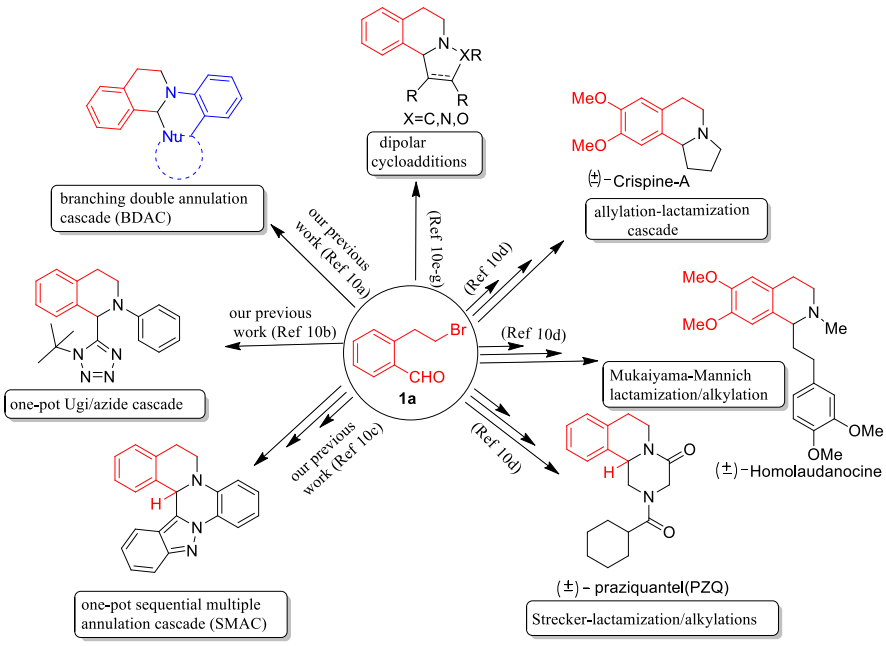
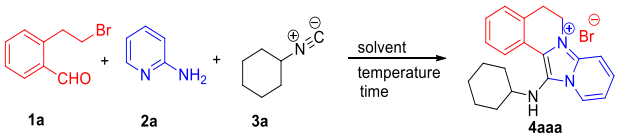


Figure 2

To test the above hypothesis, a preliminary reaction of equimolar mixture of 2-(2-bromoethyl)benzaldehyde **1a**, 2-aminopyridine **2a** and cyclohexylisocyanide **3a** was performed at ambient temperature (35 °C) in

methanol for 10h, which afforded the desired product 4aaa, albeit in low yield (Table 1, entry 1). Encouraged by this result, and to further explore, we increased the temperatures which resulted in improvement of yields up to 64%

Table 1 Double annulation cascade to pyridoimidazo-DHIQ salt **4aaa**[a,b]



entry	solvent	temp (°C)	time (h)	yield (%)
1	MeOH	35	10	10
2	MeOH	50	20	20
3	MeOH	70	22	54
4	MeOH	90	20	64
5	EtOH	100	20	67
6	H_2O	100	20	0
7	DCE	100	23	40
8	DCM	50	14	32
9	CH_3CN	90	21	43
10	THF	90	14	35
11	1,4 dioxane	110	10	55
12	No solvent	rt	10	Trace
13	No solvent	50	20	40
14	No solvent	60	2	66
15	**No solvent**	**80**	**10 min**	**91**
16	No	90	10 min	70

	solvent			
17	No solvent	100	10 min	66

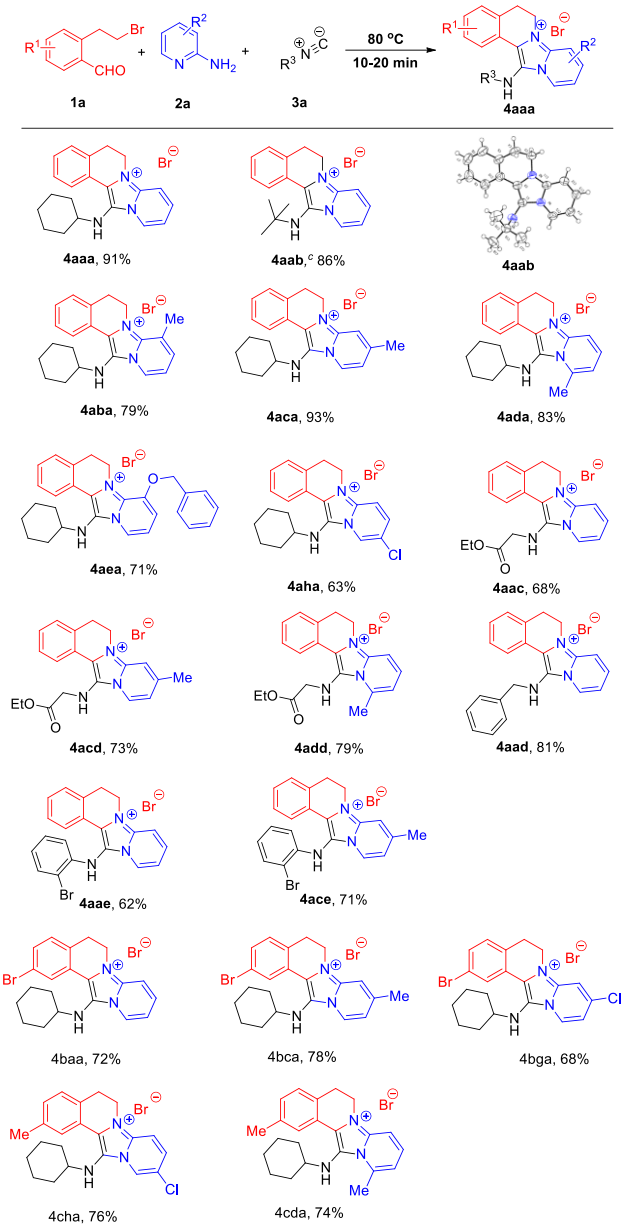
[a] Reaction conditions: **1a** (0.23 mmol), **2a** (0.23 mmol) and **3a** (0.23 mmol). [b] Yield of isolated product after column chromatography.

(Table 1, entries 2-4). Moreover, in protic and aprotic polar solvents, even after continuing the reaction for long hours the starting materials were not completely consumed (Table 1, entries 5-11).

When we perform the reaction under solvent-free conditions. Not surprisingly, higher temperatures resulted in improved yields of the products with drastic reduction in time (Table 1, entries 13-15). However, beyond 80 °C we have seen drop in the yields (Table 1, entries 16 and 17), which could be due to decomposition of reaction mixture.

With the reaction at 80 °C as optimized condition (Table 1, entry 15) for double annulation cascade (DAC) in hand we planned to evaluate the scope of our strategy. In this direction, we extended it to various aminoazines **2** and isocyanides **3**, keeping the aldehyde **1** component constant to obtain corresponding pyridoimidazoisoquinolinium derivatives (Table 2, **4aaa-4ace**) in good to excellent yields.

Table 2 Synthesis of pyridoimidazo-DHIQ scaffolds [a,b]

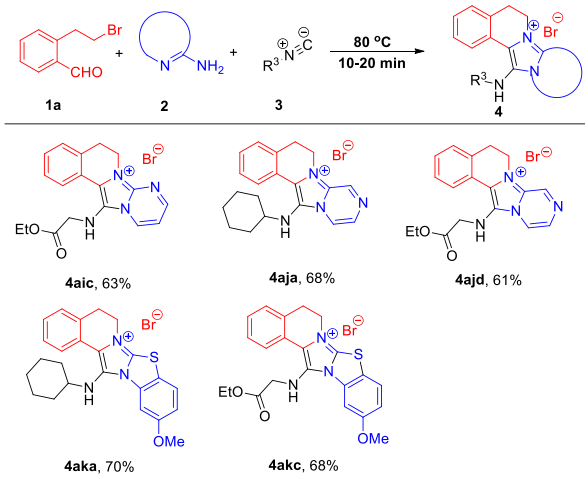


[a] Reactions were performed with **1** (0.23 mmol), **2** (0.23 mmol) and **3** (0.23 mmol) at 80 °C. [b] Yield of isolated product after column chromatography.

Our pursuit for diversity oriented synthesis (DOS) impelled us to examine diversity of our present strategy. Accordingly, we probed with structurally and skeletally different aminoazines, which to our delight provided interesting and diverse tetra- and pentacyclic IQ scaffolds (Table 3). When we have used

other heterocyclic aminoazines we have not observed any detrimental effect on reaction outcome.

Table 3 Synthesis of skeletally diverse DHIQ scaffolds [a,b]



[a] Reactions were performed with **1** (0.23 mmol), **2** (0.23 mmol) and **3** (0.23 mmol) at 80 °C. [b] Yield of isolated product after column chromatography.

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we have developed a mild, efficient and metal-free protocol for the synthesis of fused IQ derivatives under solvent-free conditions. We have demonstrated an unprecedented cyclic iminium induced GBB leading to construction of two privileged heterocyclic rings in one-pot. This double annulation cascade provided pyridoimidazo-DHIQs in excellent yields by easy isolation without tedious workup. In addition, readily accessible starting material, remarkably short reaction time, simplicity in operation, scope of skeletal diversity, H_2O as sole byproduct.

Chapter III: **An Exocyclic N-Acyliminium ion (NAI) Cyclization: Access to Fully Substituted Oxazoles and Furocoumarins**

N-acyliminium ions (NAIs) are well recognized as potent or highly reactive intermediates in C-C and C-heteroatom bond forming reactions, and extensively

explored for the synthesis of diverse natural-products and bioactive molecules due to their highly electrophilic nature. Chemists have developed N-acyl iminium ion based biomimetic approaches for the synthesis of various alkaloids inspired by nature's design principles. Owing to their significant importance, chemists have been paid substantial attention to the development of a variety of NAI precursors (Figure 3). Among them, pyrrolidine based NAI ion precursors have obtained a dominant position for enabling powerful access to the generation of cyclic NAIs particularly endo-cyclic by the treatment of Brønsted acid or Lewis acid, and which are mainly limited to intramolecular cyclization reactions. However, the development of a direct route to access NAI precursors and their further transformations toward diverse scaffolds in a single pot is a daunting challenge. The reason is the formation of NAI ion species prerequisite is a good leaving group at the α-position to the nitrogen atom. In order to bring leaving groups at the desired position in substrates involves multistep syntheses and which are highly difficult to operate in single pot. These challenges led us to examine a direct synthetic route to access NAI precursors and their further efficient transformations through a cascade process. The acid catalyzed reactions of NAI salts well explored in the literature, these transformations mainly involved the generation of cationic NAI ions in the presence of excess strong acid. As per the literature survey, these type of conditions lead to the formation of dicationic species are called super electrophiles, which can be explored in further transformations with suitable nucleophiles.

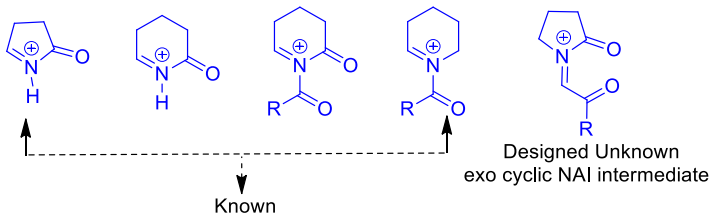
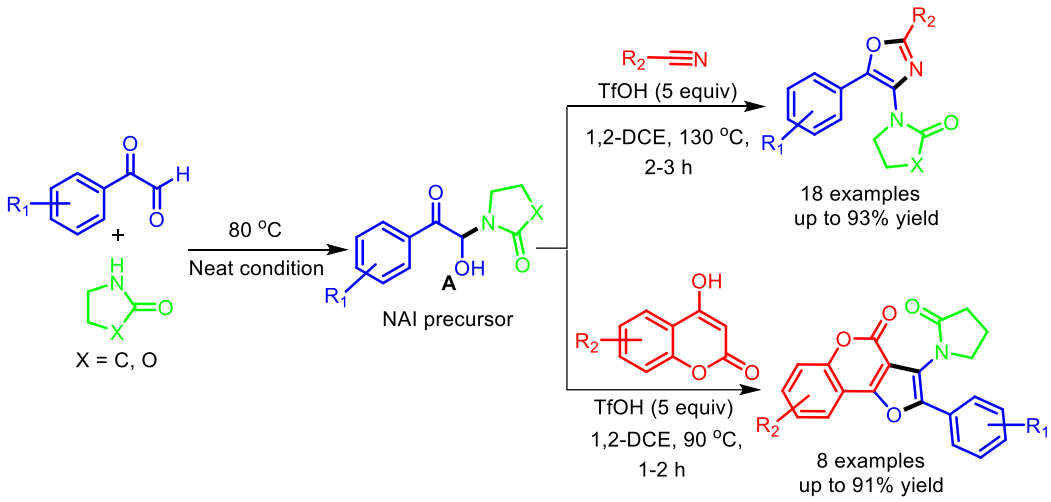


Figure 3. Literature known NAIs and our designed NAI

Recently, we have developed an iminium induced one-pot double annulation cascade strategy for the synthesis of dihydroisoquinolinium salts. Inspired by this work and our continuing interest in the development of metal-free and green

strategies for the synthesis of biologically important heterocyclic compounds, herein, we report a novel super-acid-promoted tandem cyclization strategy to synthesize diversified fully substituted Oxazoles and Furocoumarins from readily available starting materials *via* insituly generated exocyclic NAI precursor in one pot. The development of a straightforward method to access the above mentioned privileged scaffolds *via* insitu generation of NAI precursors would be of great importance.



Scheme 2 Synthesis of Fully Substituted Oxazoles and Furocoumarins

Having this catalyst and solvent-free conditions for NAI precursor **A** in hand, our attention was turned towards the utilization of it for the synthesis of Biologically active molecules.

firstly, we hypothesized to synthesize fully substituted Oxazole derivatives by using nitriles through 3+2 cycloaddition under Metal-free conditions.

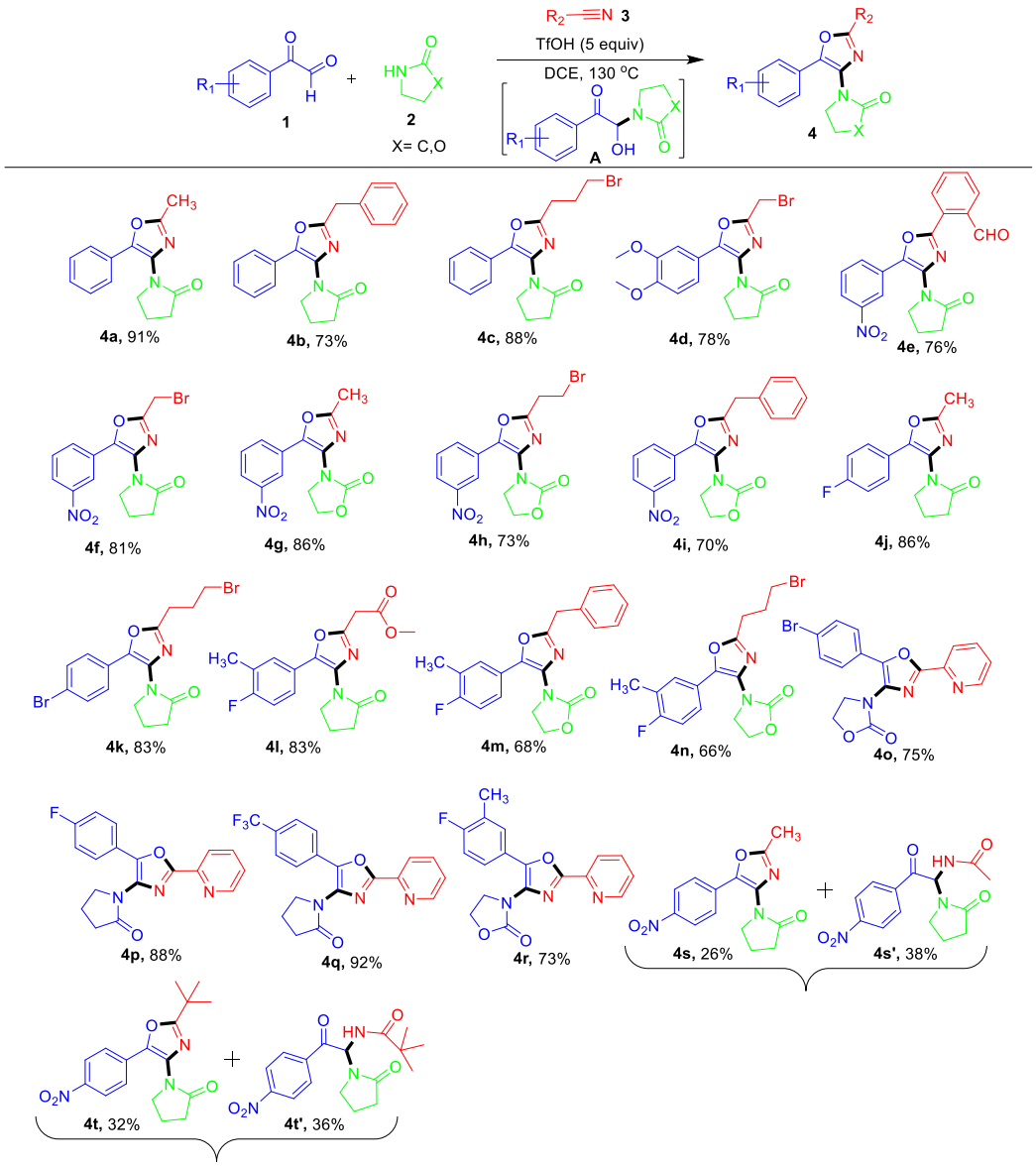
Due to Oxazole derivatives found in a wide range of pharmaceuticals, natural products and agrochemicals. Among these Oxazole derivatives serve as an important chiral sources or ligands in asymmetric transformations.

Accordingly, to test our hypothesis, first we generated the NAI precursor **A** by the reaction of phenylglyoxal **1a** with 2-pyrrolidinone **2a** under standard conditions, which could subsequently use as the model substrate without isolation.

Among the various Brønsted acids screened, only triflic acid effectively promoted the desired product. In order to evaluate the effects of acidity we screened with different equivalents of triflic acid under various temperatures, finally, 5.0 equiv of triflic acid was found to be effective at 130 °C to afford the desired product **4a** in excellent yield 91%.

After having the optimized conditions in hand, we have explored the substrate scope of the present protocol (Table 3). Arylglyoxals bearing electron-neutral (**4a, 4b** & **4c**), electron-rich (**4d**) and electron-deficient (**4e-4k**) substituents were smoothly converted to the corresponding oxazoles with moderate to very good yields. Interestingly, halo-substituted (**4j-4n**) arylglyoxals were also found to furnish the desired products with good yields (66-86%), which would provide possibilities for further functionalization. Pleasingly, 2-oxazolidinone in place of 2-pyrrolidinone were also found to furnish the desired products with very good yields (**4g**, **4h, 4m** & **4n**).

Table 4. Scope of the synthesis of various fully substituted oxazoles[a]



[a]Reaction conditions: 1st step: 1a (1.0 mmol), 2a (1.1 mmol), 80 °C, 10-20 min, 2nd step: DCE dry solvent (0.25 M), 3a (1.1 mmol), TfOH (5 mmol), 130 °C, for 2-3 h. [b] Isolated yields, after column chromatography.

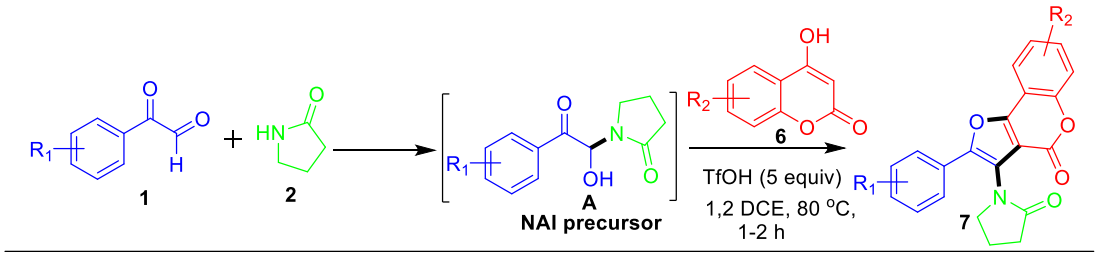
Next we checked the reactivity of strong electron withdrawing group (-NO_2) in the 4th position of arylglyoxal unit (Table 4, 4s & 4t), unfortunately in both the examples we got the both oxazole and bisamide products, after prolonged reaction hours also we didn't observe the complete conversion of bisamide to oxazole

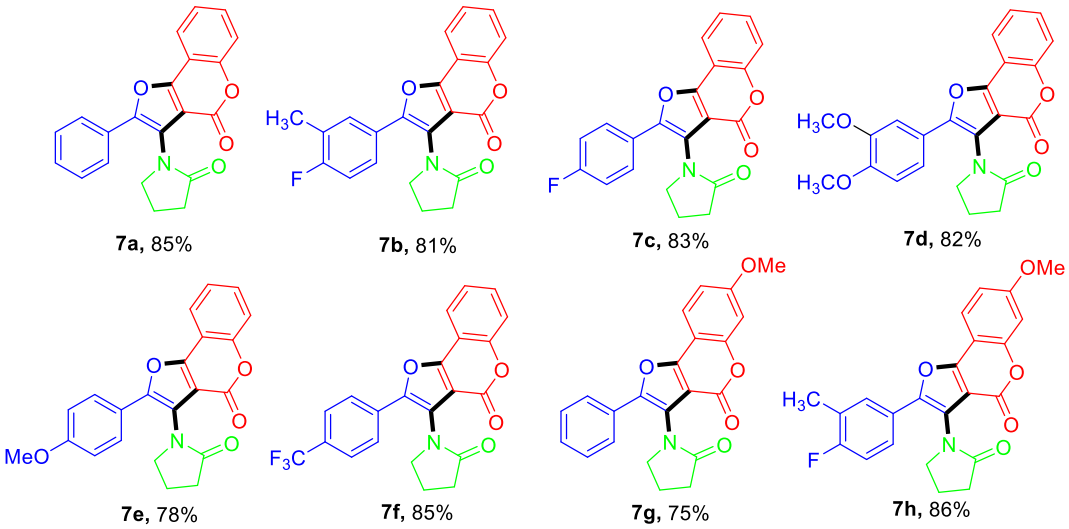
products. We achieved the less oxazole product yields in both 4s & 4t cases (26% & 32%).

In order to expand the molecular library of polyfunctional oxazole derivatives, we extended it to the heteroaryl nitriles, like 2-cyanopyridines, for the synthesis of valuable bis-hetero cycles those are pyrid-oxazoles skeletons as shown in table 3. In this transformations, 2-cyanopyridine is reacted smoothly with NAI intermediates generated from arylglyoxals and 2-oxazolidinone or 2-pyrrolidinone to afford the desired products from good to excellent yields (Table 4, **4o-4r**).

After successfully synthesis of fully substituted Oxazoles, further our attention was turned towards the synthesis of Furocoumarins, owing to the wide spectrum of biological activities, agrochemicals and synthetic applications, have triggered substantial interest for their synthesis. Accordingly, the new protocol was further demonstrated by using 4-hydroxy-2H-chromen-2-one as carbon-nucleophile (Table 5). Arylglyoxals with electron-neutral (**7a** & **7g**), electron rich (**7d** & **7e**) and electron-deficient (**7b, 7h, 7f** & **7c**) substituents were smoothly transformed into the corresponding privileged Furocoumarine under the optimized conditions with very good yields (Table 5).

Table 5. Scope of the Synthesis of Furocoumarins



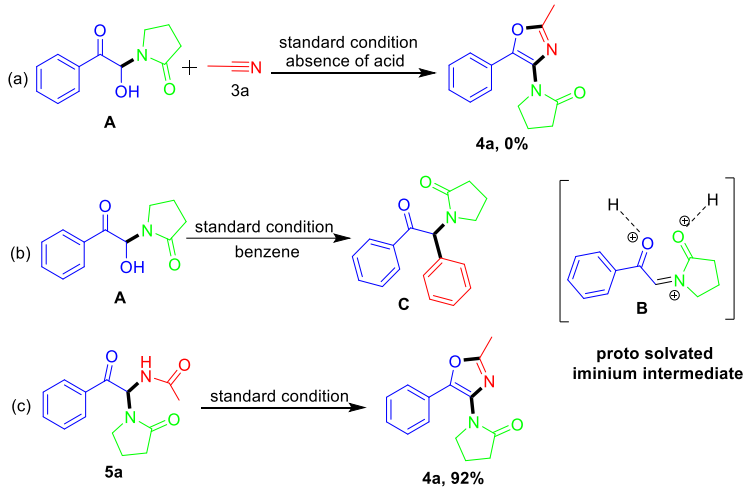


[a]Reaction conditions: 1st step: 1 (1.0 mmol), 2 (1.1 mmol), 80 °C, 10-20 min, 2nd step: DCE dry solvent (0.25 M), **6** (1.1 mmol), TfOH (5 mmol), 80 °C, 1-2 h. [b] Isolated yields, after column chromatography.

To gain insight into the reaction mechanism, preliminary control experiments were conducted. When the reaction was performed in the absence of acid, no desired product was formed, indicating that the presence of acid is crucial for this reaction (Scheme 3a). Since the present reaction requires excess acid to effect the transformations (standard conditions), we hypothesized that the reaction might be proceed through proto-solvation of N-acyliminium ion **B** (Scheme 3b). Accordingly, we have performed the reaction with weak nucleophile i.e. benzene instead of acetonitrile **3a**. To our delight, we could have isolated the benzene trapped product **C** with 80% yield.

This result suggested that a proto-solvated iminium intermediate **B** was most likely involved in this reaction. To know further possible intermediates as per our observations during optimization of reaction conditions, we assumed that either bisamide or nitrelium ion may be the reaction intermediates after attacking of nitrile **3a** to intermediate **B** to afford the oxazole **4a**. Accordingly, we have subjected the bisamide **5a** to standard conditions, which resulted in oxazole **4a** with excellent yield as we expected (Scheme 3c).

Scheme 3. Mechanistic Experiments.



Based on the above observed products and previous literature reports,[3a, 4] a plausible mechanism was proposed for the present reaction (Scheme 4**)**. Initially the NAI precursor **A** would form the iminium intermediate **B** under acidic conditions. Then cyclization was occur by two conceivable paths: In path **a**, acetonitrile would attack proto solvated iminium intermediate **B** to afford nitrilium ion **I**, which then would neutralized by the adjacent carbonyl oxygen to furnish the final product **4a**. In path **b**, the nitrilium ion **I** would be neutralized by the water molecule to form the bisamide **5a**, which would further undergo dehydration -cyclization to furnish the final product **4a.**

After having synthesized compounds in hand, we were keen to study the UV-visible and fluorescence characteristics of chosen Pyrid-oxazoles and Furocoumarins. The UV-visible spectra of compounds **4r**, **4p**, **4q** & **4o** in ethanol

(EtOH) exhibited maximum absorption wavelength (λ_{max}) at 320 nm. The fluorescence spectra of Pyrid-oxazole compounds showed emission wavelength (λ_{em}) at 414-464 nm.

Similarly, we have also recorded the UV-visible and fluorescence spectra of Furocoumarins (**7a-7h**) in EtOH. The UV-visible spectra of compounds **7a-7h** (Figure 3d) exhibited maximum absorption wavelengths at 205-210 nm. The fluorescence properties of the compounds **7a-7h** (Figure 3c) displayed emission wavelength (λ_{em}) at 396-449 nm.

In summary, we have described a concise, one-pot route to Oxazoles and Furocoumarins through N-acyliminium ion as a key intermediate. The key step in this transformation involves *insitu* generation of NAI precursor under catalyst and solvent free conditions, and their further transformations promoted by superacid in the same pot. The experimental evidence for the involvement of proto-solvated novel exocyclic N-acyliminium ion in superacid promoted reaction has been presented. We have also investigated the photophysical properties of Furocoumarins and Pyrid-oxazole derivatives, and these studies reveal that possible applications for the discovery of highly fluorescent probes.

LIST OF ABBREVIATIONS

Å	Angstrom
Ac	Acetyl
AcOH	Acetic acid
Ar	Aryl
BDAC cascade	Branching double annulation
br	Broad (spectral)
°C	Degree Celsius
CDC Coupling	Cross-Dehydrogenative
CO	Carbon monoxide
CPD	Carbon proton decoupling
Cy	Cyclohexyl
d	Doublet (spectral)
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU 7-ene	1,8-Diazabicyclo[5.4.0]undec-
DCE	1,2-Dichloroethene
DCM	Dichloromethane
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
dt	Doublet of triplet
DTBP	Di-*tert*-butyl peroxide
equiv.	Equivalent(s)

Et	Ethyl
EtOH	Ethanol
EWG	Electron withdrawing group
FTIR spectroscopy	Fourier transform infrared
GBB reaction	Groebke-Blackburn-Bienayme
GC-MS spectrometry	Gas chromatography–mass
h	Hour(s)
HR-MS Spectroscopy	High Resolution Mass
Hz	Hertz
IMCRs multicomponent reactions	Isocyanide based
i-Pr	Isopropyl
J Spectroscopy)	Coupling Constant (in NMR
K	Kelvin (Temperature)
m	Multiplet (spectral)
MCRs	Multicomponent reactions
Me	Methyl
MeCN	*Acetonitrile*
MeOH	Methanol
mg	Milligram
MHz	Mega Hertz
min	Minute(s)
MIR-ATR Reflectance	Mid infrared- Attenuated Total
mL	milliliter(s)

mmol	Millimole(s)
Mp	Melting point
MS	Molecular sieves
MW or µw	Microwave
NR	No reaction
n-Bu	*n*-Butyl
NMR	Nuclear Magnetic Resonance
Nu	Nucleophile
ORTEP	Oak ridge thermal ellipsoid plot
OTf	Triflate group
Ph	Phenyl
ppm	Parts per million
psi	Pounds per square inch
q	Quartet (spectral)
R	Alkyl
Rf	Retention factor
rt	Room temperature
s	Singlet (spectral)
SF	Solvent-free
SSMR	Solid-state melt reaction
t	Triplet (spectral)
^{t}Bu	*tert*-Butyl
Temp	Temperature
TEMPO oxyl	2,2,6,6-tetramethylpiperidine 1-
tert	tertiary
TFA	*Trifluoroacetic acid*

THF	Tetrahyrofuran
THIQ	Tetrahydroisoquinoline
TLC	Thin layer chromatography
TMS	Trimethylsilyl
XRD	X-ray *diffraction*
δ	Chemical shift in parts per million

CHAPTER 1

Introduction

1.1. Reactivity of isocyanides

Isocyanides are also called as isonitriles or carbylamines and they are the most valuable functional group in organic chemistry.[1] Isocyanide is a useful synthetic building block, owing to the unusual reactivity of terminal carbon center due to its ambiphilic nature which participates with various electrophiles and nucleophiles. In addition, isocyanides are isoelectronic with CO, due to its intrinsic property these compounds also show high affinity towards organometallic reagents and in recent years, radical reactions of isocyanides have found great use in various organic transformations.[2]

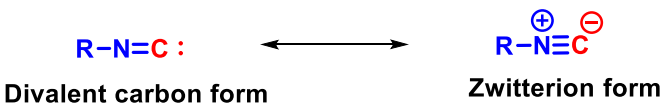
Isocyanides due to its peculiar intrinsic ambiphilic property and its affinity towards metal have been widely explored as C1 synthons for the synthesis of diverse nitrogen heterocycles of medicinal and biological relevance. Further, isocyanides have been successfully employed as C1 synthons in cycloaddition reactions.[3] On the other hand, the unique affinity of isocyanide towards metals has been explored with transition metals such as palladium, cobalt and nickel catalyzed insertions between various bisnucleophiles in recent times.[4]

1.2. Isomeric forms of isocyanide

Isocyanides exists in two isomeric structures viz.

(a) zwitterion form

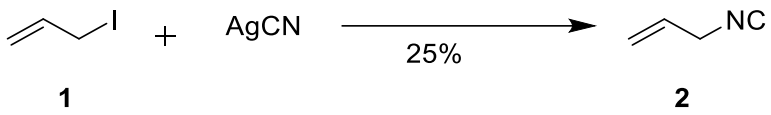
(**b)** exhibit like a carbene (Scheme 1)



Scheme 1. Resonance structures of isocyanides

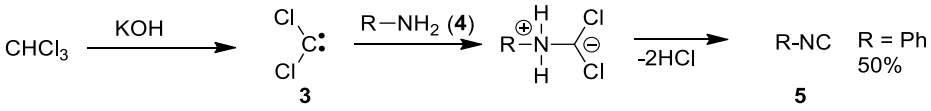
"Xanthocillicin" is the first reported natural product from marine sources in 1956 by Hagedorn and Toenjes.

Isocyanide was first discovered by Lieke[5] in 1859 by the treatment of silver cyanide with allyl iodides (Scheme 2).



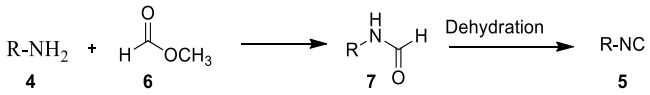
Scheme 2. Lieke's synthesis of isocyanide

In 1867, Hoffmnn[6] developed a new protocol for the synthesis of isocyanide by the condensation of a primary amine with dichlorocarbene, produced *insituly* by heating chloroform with potassium hydroxide. Nevertheless, this method has various drawbacks like reproducibility, low yield and difficulty of separation of isocyanides from amines (Scheme 3).



Scheme 3. Hoffmann's synthesis of isocyanide (Carbylamine method)

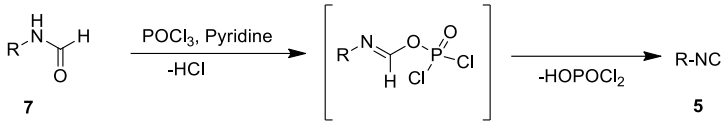
Later, Ivar Ugi after tremendous efforts discovered a convenient method for the formation of isocyanide *via* the dehydration of *N*-monosubstituted formamide which could be obtained from primary amines and methyl formate or formic acid (Scheme 4).[7]



Scheme 4. Ugi's synthesis of isocyanide

Commonly, isocyanides are synthesized by the dehydration of formamides. The formamide can be dehydrated with phosphorus oxychloride, toluene sulfonyl chloride, phosgene, diphosgene, or with the Burgess reagent in the presence of a base such as pyridine,

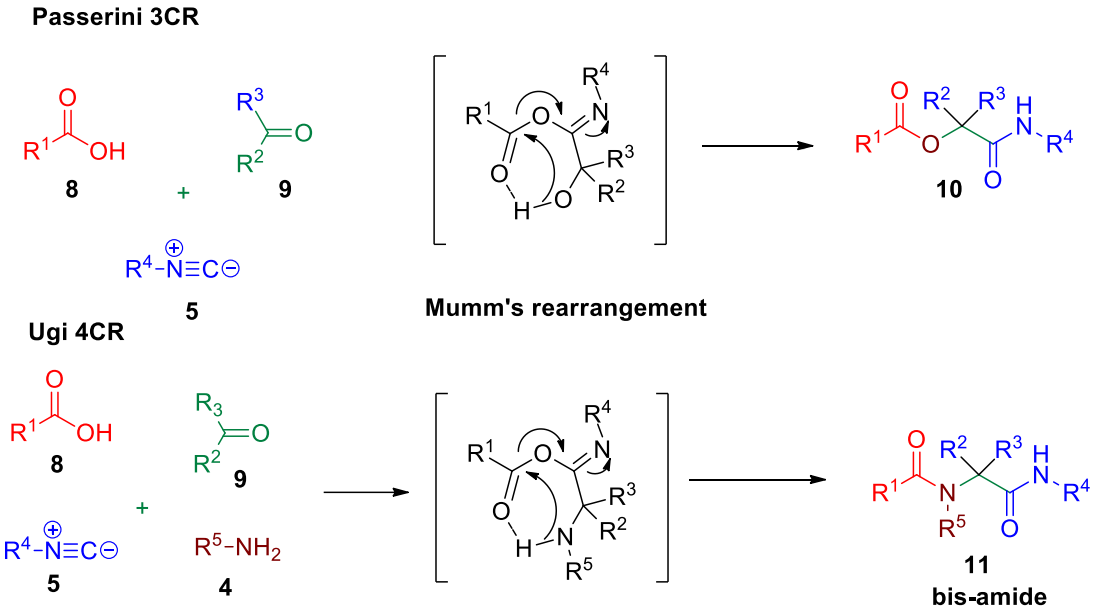
triethylamine and diisopropylethylamine (Scheme 5). Ugi made significant contributions by synthesizing more than 230 isocyanides.[8]



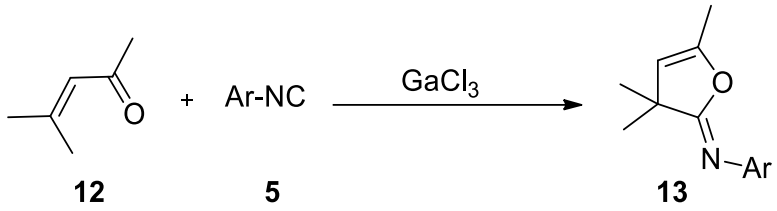
Scheme 5. Dehydration of formamide using $POCl_3$

1.3. Synthetic applications of Isocyanides

The unique reactivity nature of the isocyanides, diversity of bond forming processes, functional group tolerance, and the high levels of chemo-, regio-, and stereoselectivity have led to plethora of organic transformations like isocyanide based multicomponent reactions (IMCRs),[7-9] *e.g.* Ugi and Passerini reactions (Scheme 6), co-cyclizations utilizing isocyanides as one carbon donor,[10] (Scheme 7) transition-metal catalyzed insertions,[11] and oligo- and polymerizations.[12]



Scheme 6. The three-component Passerini and the four-component Ugi reaction



Scheme 7

Cycloadditions have emerged as the most efficient chemical processes, combining atom economy, stereoselectivity, stereospecificity, and the ability to generate molecular complexity in a single step. [4+1] cycloaddition is among most powerful reactions in the arsenal of the synthetic chemists for the synthesis of five-membered rings owing to the ubiquity of five-membered carbo- and heterocyclic substructures in natural products. The formal [4+1] annulation involves a reaction between four atom conjugated system and C1 source, providing an alternative and versatile approach to these compounds because of their distinct synthetic advantages and the immediate availability of the preliminary materials.

An example of a formal [4+1]-cycloaddition of *α, β*-unsaturated carbonyl compound with isocyanide (Figure 1).

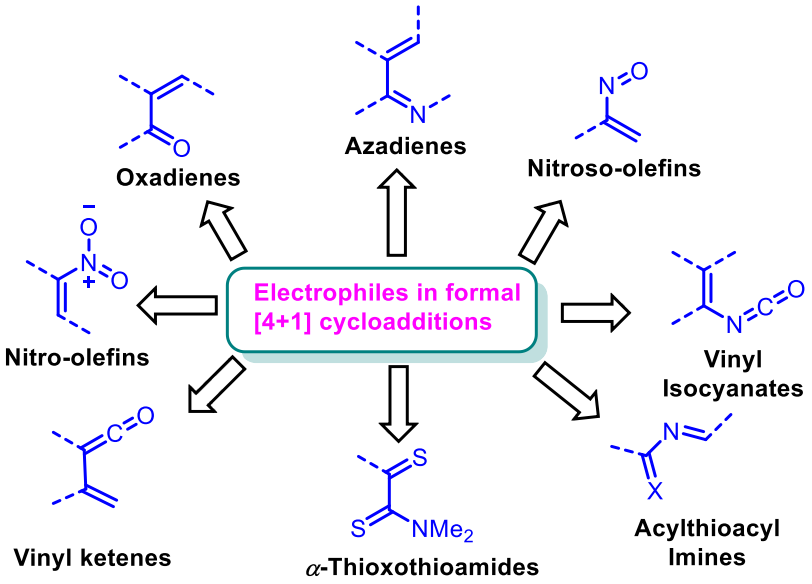


Figure 1. Diverse dienes in isocyanide based formal [4+1] cycloadditions

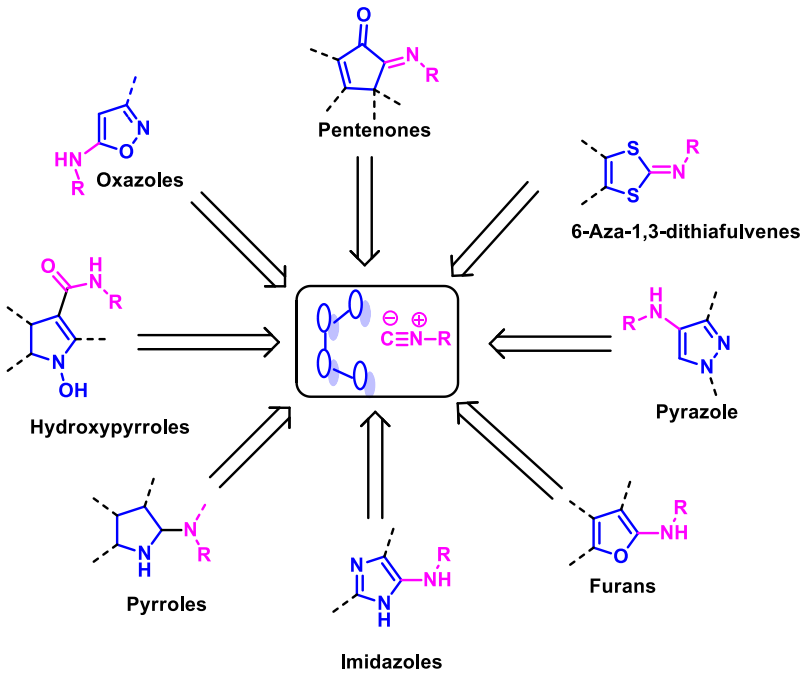


Figure 2. Synthesis of diverse heterocycles using isocyanides in formal [4+1] cycloadditions.

1.4. Synthetic applications of 2-(2-bromoethyl)benzaldehyde

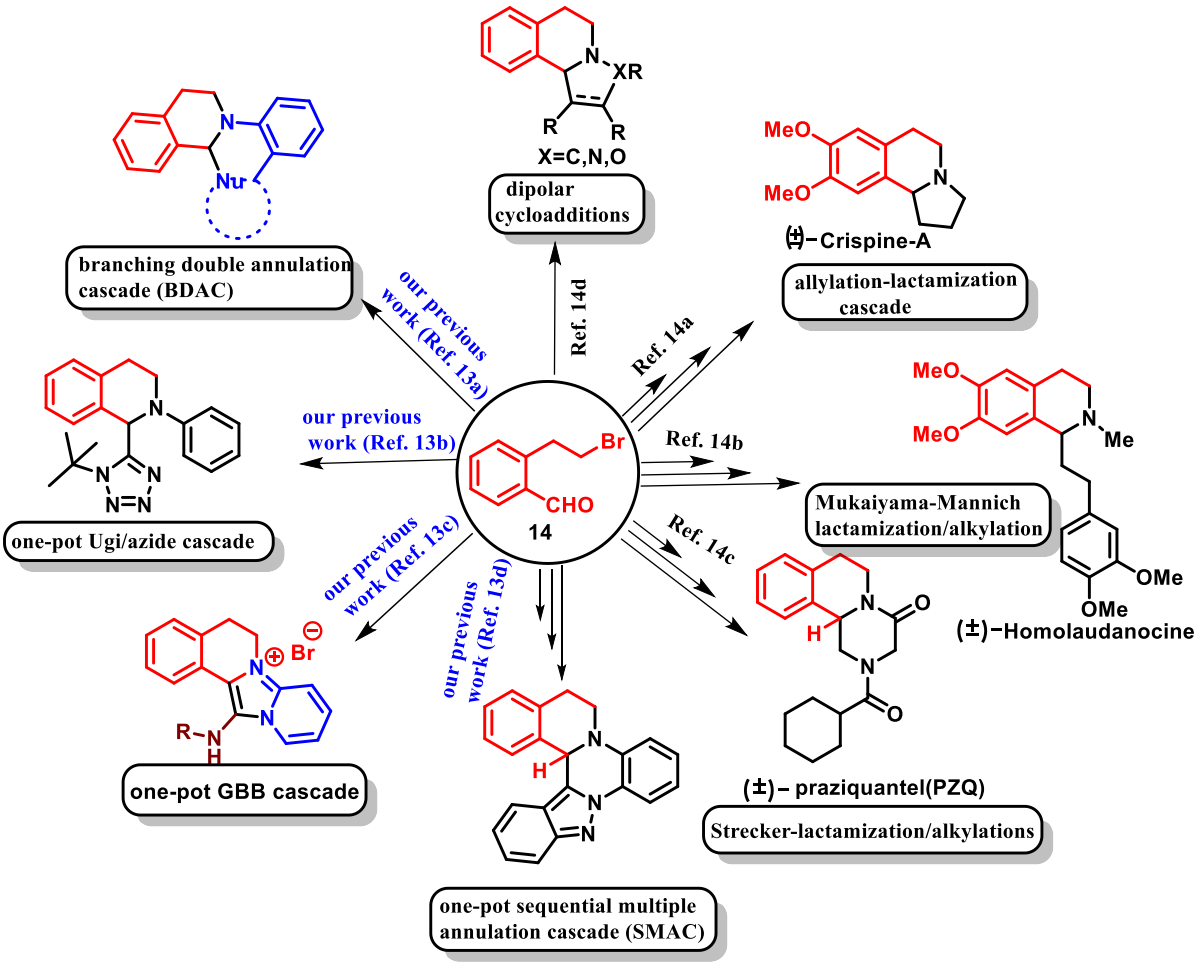


Figure 3. Various approaches to THIQ motifs starting from 2-(2 bromoethyl)benzaldehyde

The versatility of 2-(2-bromoethyl)benzaldehyde **14** as a promising bifunctional reactant in various organic transformations has been well documented by our group and others,[13,14] especially leading to tetrahydroisoquinoline (THIQ) motifs based natural products and their analogues (Figure 3). However, utilization of **14** in the synthesis of fused dihydroisoquinolinium salts is not explored to date. Very recently, in our lab, we have documented some interesting cascade strategies employing **14** for the synthesis of skeletally diverse THIQ skeletons (Scheme 2).[13]

1.5. *N*-Acyliminium ions and its applications

N-acyliminium ions (NAIs) are well recognized as potent or highly reactive intermediates in C-C and C-heteroatom bond forming reactions, and extensively explored for

the synthesis of diverse natural-products and bioactive molecules[15] (Figure 1) due to their highly electrophilic nature.

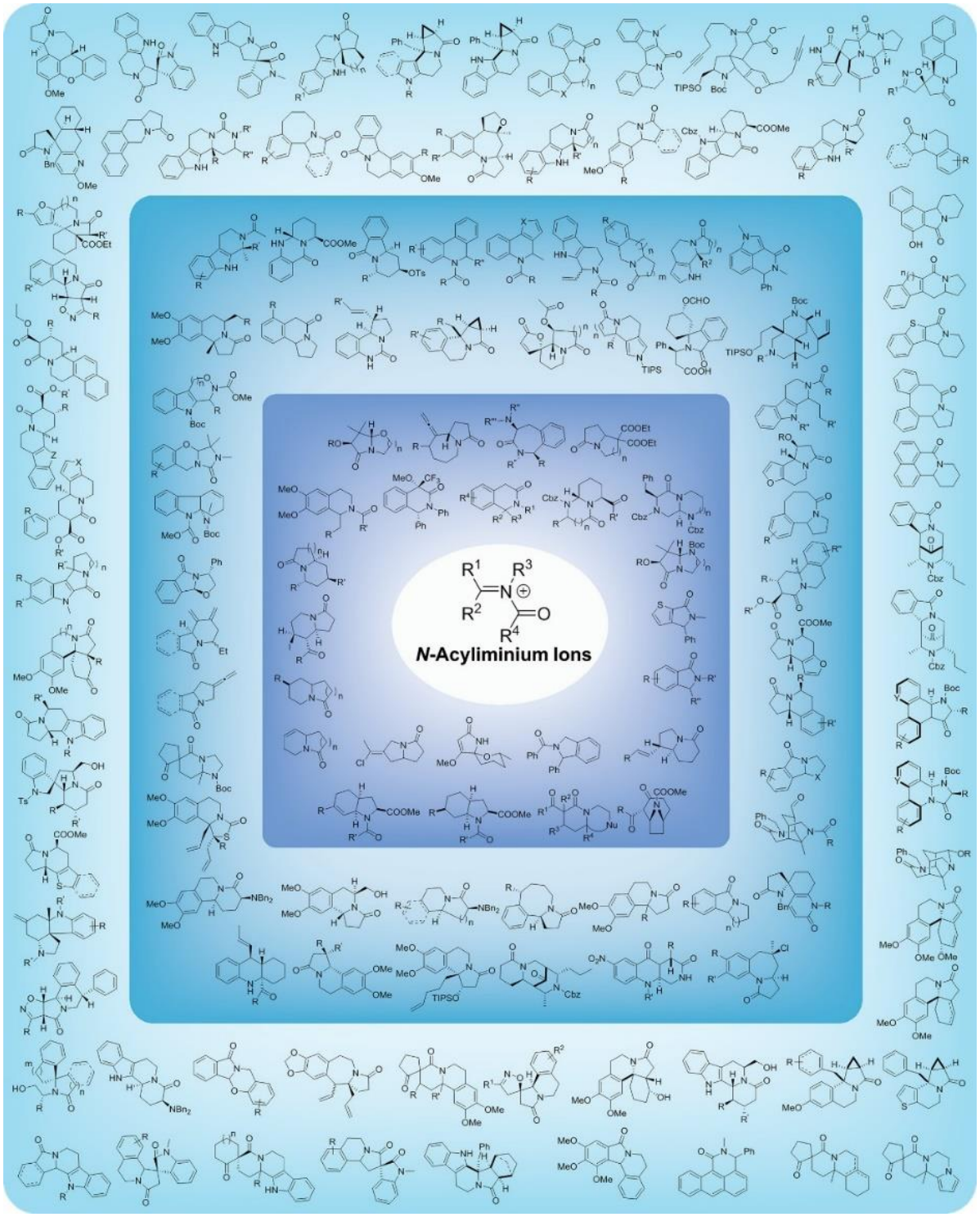


Figure 4: Plethora of structurally diverse compounds prepared through the cyclization of *N*-acyliminium ions (*Courtesy*: Chem rev.)[15a]

1.6. Oxazoles and Furocoumarins importance and their applications

Oxazoles are heterocyles containing nitrogen and oxygen atoms in the five-membered aromatic ring. They are known to bind to a variety of enzymes and receptors in the biological systems via various non-covalent bond interactions, and due to this it can able to display versatile biological activities.

The related oxazole-based scaffolds such as oxazoles, isoxazoles, benzoxazoles, oxazolines, oxazolidones, oxadiazoles, and so on (Figure 5), are well known medicinal drugs and has been an extremely attractive topic, and numerous excellent biological properties have been acquired.[16]

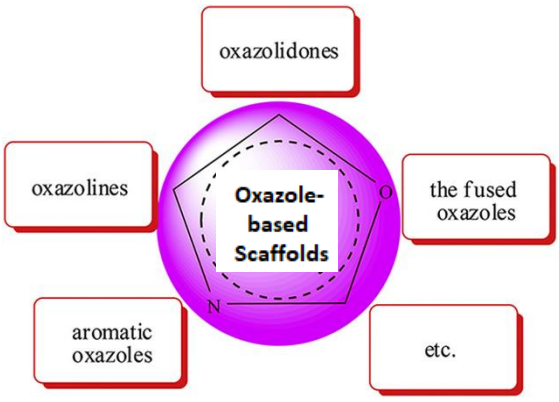


Figure 5: Oxazole-based scaffolds in medicinal chemistry

Noticeably, a high number of oxazole compounds as clinical drugs or candidates have been frequently used for the treatment of many types of diseases, which have shown their high development value and have broad potential as medicinal agents.[16]

Oxazole compounds are found to be useful as antifungal, antibacterial, antiviral, anticancer, anti-inflammatory, antitubercular, antiparasitic, analgesic, antidiabetic, anti-obesitic, anti-neuropathic, antioxidative as well as other biological activities,[16] and as

agrochemicals.[17] Among these oxazole derivatives serve as important chiral ligands or source in asymmetric transformations. Furthermore, dihydrooxazoles can be easily transformed into other useful functional groups, such as carboxylic acids and 'igure 6).[17]

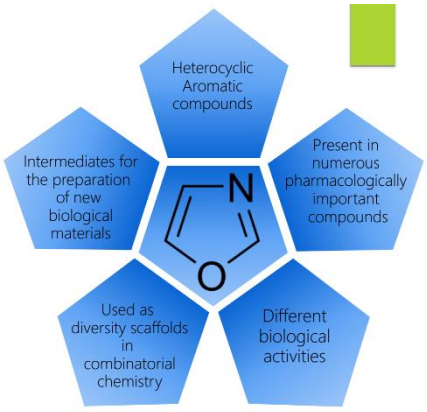


Figure 6: Importance of Oxazole derivatives

The coumarin ring is a key structural core unit for numerous natural products, synthetic pharmaceuticals, and a wide variety of biologically active compounds. Modified coumarin compounds are shown to exhibit a broad range of biological activities and also as potent anti-HIV agents and anticancer agents.[18]

Among them, furochromen-4-ones (furocoumarins), tricyclic systems in which a furan ring is fused to the chromen-2-one unit, are of particular interest since they exhibit potent biological and pharmacological activity.[19] (Figure 7)

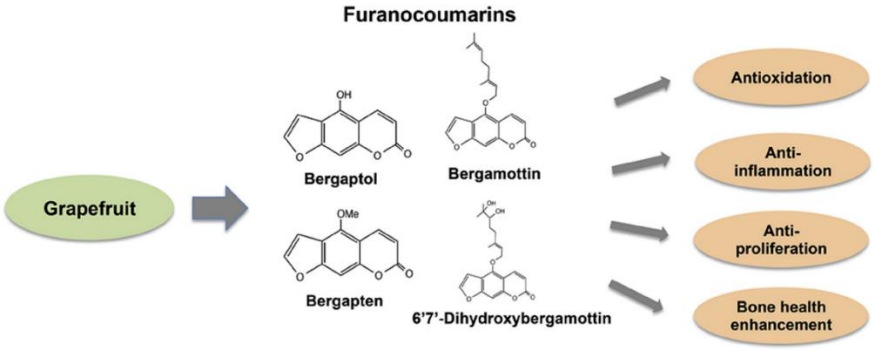


Figure 7: Importance of furocoumarins

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CHAPTER 2

Transition-Metal-Free Cyclic Iminium Induced One-pot Double Annulation Cascade: Direct Access to Dihydroisoquinolinium (DHIQ) based Privileged Scaffolds

2.1. Introduction

2.1.1 Importance of Isoquinolinium based Privileged Scaffolds

The ubiquity of the isoquinoline (IQ) framework[1] in biologically active natural products, besides its applications as pharmaceuticals, functional organic materials and ligands for asymmetric catalysis have turned the attention of synthetic organic chemists in recent years. Among IQ derivatives, fused IQ salts are naturally occurring alkaloids[2] and promising lead structures in drug discovery.[3]

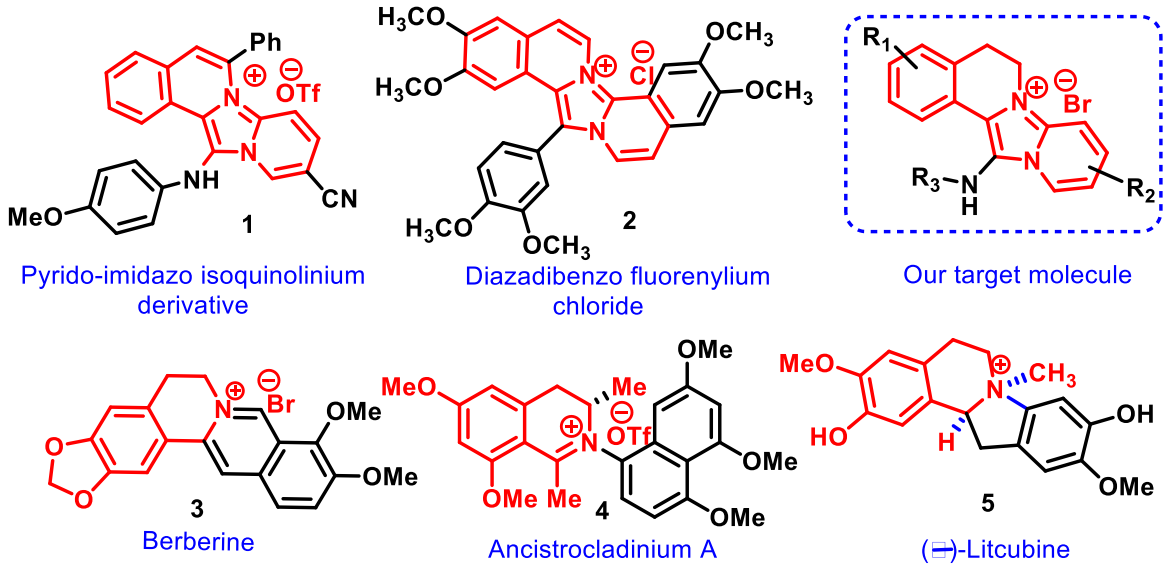


Figure 1 Representative examples of bioactive molecules and natural products.

The iminium moiety in these derivatives was found to be essential for significant biological activities.[4] Though several reports have been documented for the synthesis of these derivatives, most of the methods[5] involve starting material with preformed IQ skeleton, expensive metal catalysts, multiple steps, lack of diversity, scalability, and tedious routes to access starting material. Beside isoquinoline motif dihydroisoquinolinium (DHIQ) ion and pyrido-imidazo[5,1 *a*]isoquinolinium ion also form an important core structure[6] of natural products and pharmaceuticals (Figure 1), however, very few methods[7] have been reported for DHIQ derivatives.

2.2. Background

2.2.1. Selective Methods for Isoquinolinium and Imidazolium salts

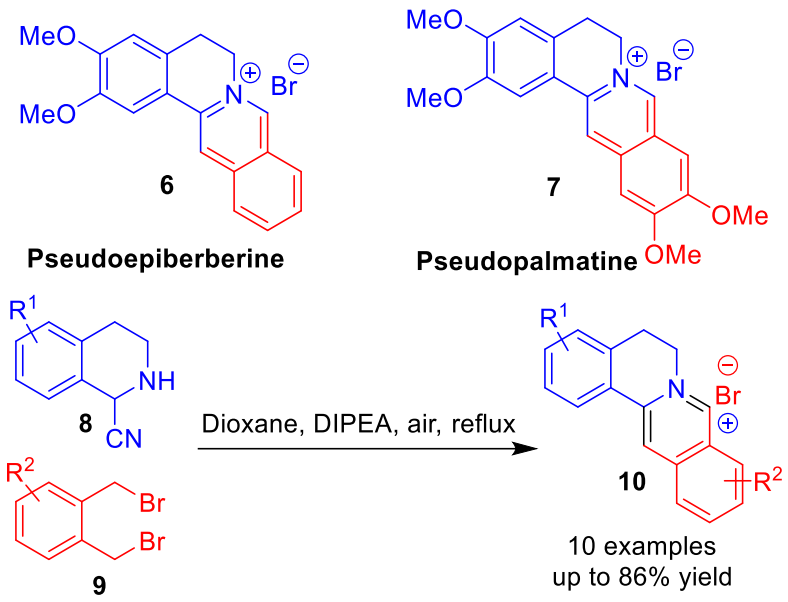
Isoquinolinium cation is an important structural motif found in many naturally occurring compounds, which exhibit numerous important biological activities.[8] They are also known as potential intermediates for the synthesis of many bioactive and heterocyclic compounds.[9] Owing to their broad application, several metal-mediated or catalyzed methods have been known for the synthesis of isoquinolinium salts.[10]

The protoberberines represent a large class of alkaloids characterized by the 5,6-dihydroisoquinolino[3,2-a]-isoquinolinium skeleton.[11] The quaternary protoberberines together with their partially reduced analogues, the dihydro and the tetrahydroprotoberberines, are widely distributed in plants and more than a hundred representatives are known to date.[12]

In particular, the permanently charged quaternary protoberberines possess pronounced biological activities, such as antimicrobial,[13] anti-in*fl*ammatory,[14] antimalarial,[15] and antitumor.[16] These activities have partly been attributed to their DNA intercalating capability[17] as well as to their general electrophilic reactivity.[18]

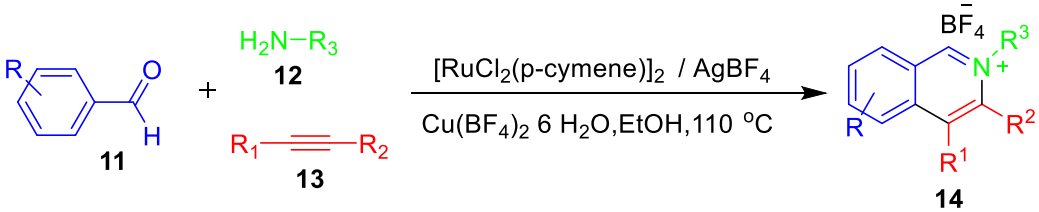
In 2015, Opatz et al. reported the synthesis of protoberberine alkaloids pseudoepiberberine and pseudopalmatine from readily available 1, 2, 3, 4-tetrahydroisoquinoline-1-carbonitriles and 1, 2-bis(bromomethyl)arenes is developed. Here

the important reaction step was Stevens rearrangement of nitrile-stabilized ammonium ylides (Scheme 1).[19]



Scheme 1

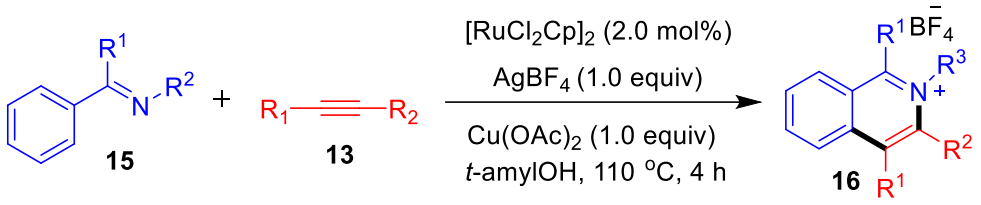
In 2015, Cheng et al.[20] reported a highly regioselective ruthenium-catalyzed synthesis of substituted isoquinolinium salts from the reaction of benzaldehydes, amines, and alkynes via C-H bond activation and annulation. The proposed mechanism is strongly supported by the isolation of a five-membered ruthenacycle and an intermediate organic compound (Scheme 2).



Scheme 2

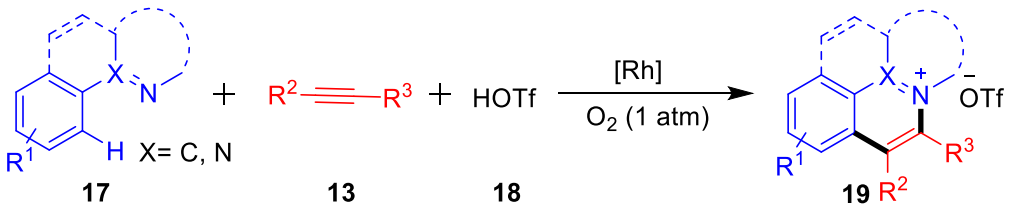
Recently, transition-metal-catalyzed C–H bond activation reactions have played an important role in the formation of carbon–carbon and carbon–heteroatom bonds. In particular, Rh(III)-complexes have revealed great potential in the synthesis of various

heterocyclic and carbocyclic compounds through the C–H bond activation reactions. In this context, in 2015, Chien-Hong Cheng et al.[21] reported the synthesis of various 1-substituted isoquinolinium salts from ketimines and alkynes via rhodium(III)-catalyzed C–H bond activation and annulation reaction.



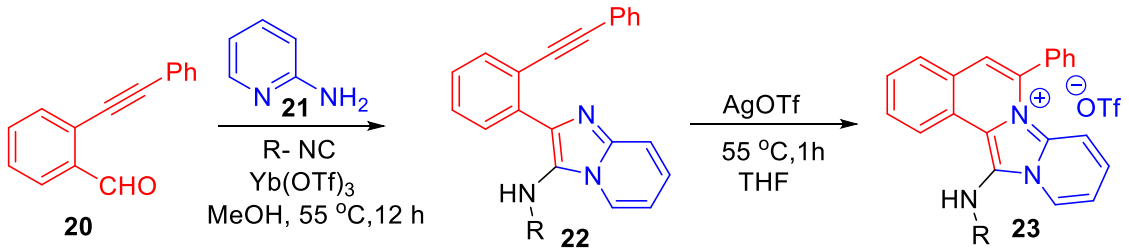
Scheme 3

In 2013, Huang et, al.[22] describes the synthesis of broad range of isoquinolinium salts. Here they disclosed a novel Rh/O_2 catalytic system that is efficient for the oxidative coupling of 2-arylpyridines and alkynes (Scheme 4).



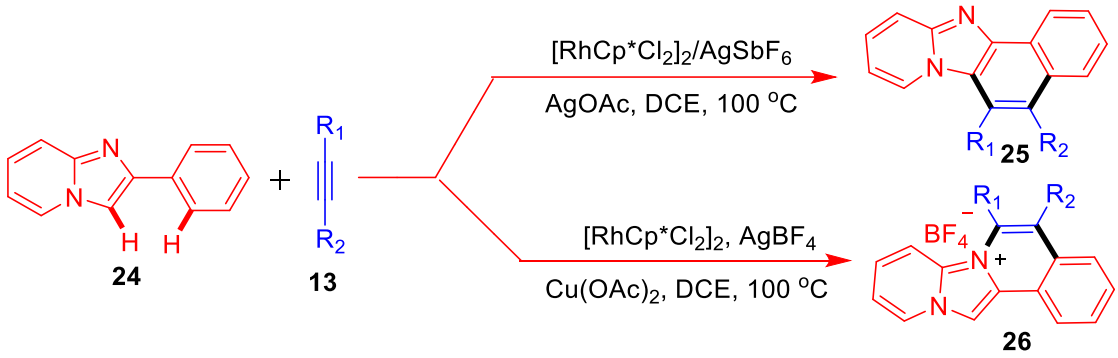
Scheme 4

In 2012, Shen *et al.* have developed an efficient approach to pyridoimidazoisoquinolinium compounds *via* Yb(OTf)$_3$ /AgOTf catalyzed one-pot synthesis (Scheme 5).[23] However, it involves use of expensive two metal catalysts, inaccessible starting material, lack of generality and lengthy synthetic steps.



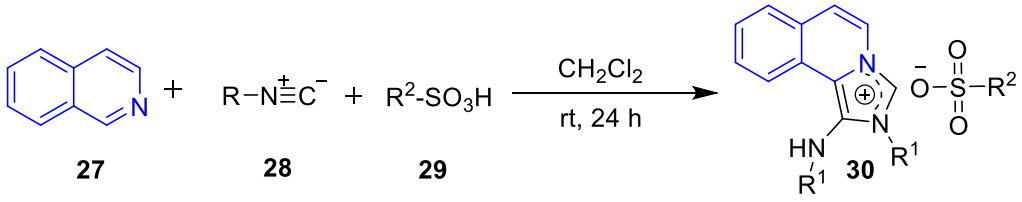
Scheme 5

In 2015, Li et al.[24] describes the synthesis of fused isoquinolinium tetrafluoroborates by Rhodium catalyzed oxidative annulation of 2-phenylimidazo[1,2-a]pyridines with alkynes. Here, when AgOAc was used as an oxidant, this coupling afforded 5,6-disubstituted naphtho-[1′,2′:4,5]imidazo[1,2-a]pyridines as a result of initial chelation assisted C-H activation at the benzene ring followed by rollover C-H activation at the heterocycle. In contrast, the reaction afforded a fused isoquinolinium as a result of C-C and C-N coupling while $AgBF_4$ was employed as a co-oxidant (Scheme 6).



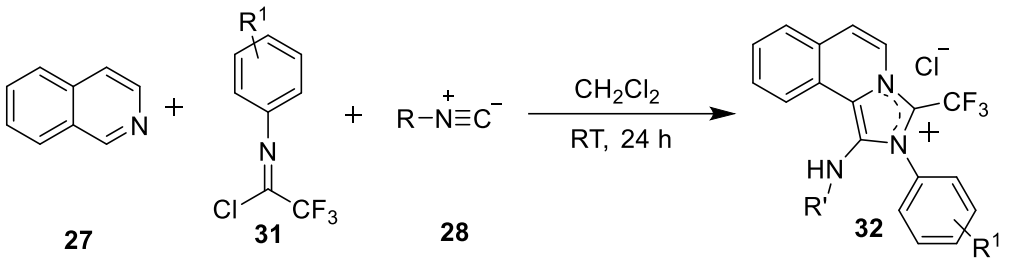
Scheme 6

Imidazo[5,1-a]isoquinolinium salts are used as orally effective blood sugar lowering agents in the treatment of diabetes. Several methods have been reported for the synthesis of 1-aminoimidazo [5, 1-a]isoquinoline. In 2008, Shaabani et, al.[25] reported the synthesis of 1-Aminoimidazo [5, 1-a]isoquinolinium Salts, from various isocyanides with isoquinoline in the presence of various sulfonic acids.



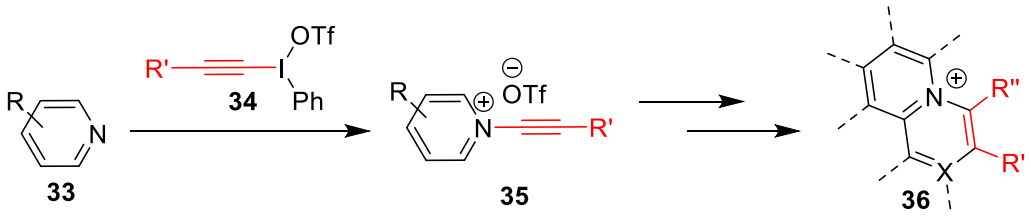
Scheme 7

Recently In 2018, Alireza *et al.*[26] have synthesized and characterized a new class of 3-(trifluoromethyl)-2H-imidazo[5,1-a]isoquinolinium chlorides under mild conditions, by the reaction of isoquinoline with trifluoroacetimidoyl chlorides and isocyanides in dry CH_2Cl_2 in excellent yields (Scheme 8).



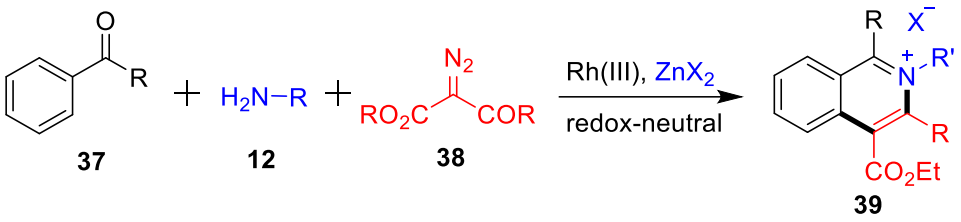
Scheme 8

Masanobu *et al.*[27] have reported the synthesis of N-alkynylpyridinium salts and revealed their highly electrophilic nature by means of spectroscopic and electrochemical measurements, and demonstrated their further facile conversion into various N-alkenylpyridiniums via Michael addition and 1,3-dipolar cycloaddition. Further, including quinolizinium and azaquinolizinium units were synthesized through intramolecular cyclization reactions, which showed a variety of optical and electrochemical properties (Scheme 9).



Scheme 9

Li *et al.*[28] recently developed the synthesis of Isoquinolinium Salts via C-H Activation of Imines. Rhodium(III)- catalyzed, redox-neutral coupling reaction between in situ generated imines with α diazo ketoesters provided a new method for isoquinolinium synthesis (Scheme 10).



Scheme 10

2.2.2. Multicomponent reactions (MCRs)

Multicomponent reactions (MCRs) provide diverse and highly functionalized molecules *via* the formation of multiple bonds[29] in a one-pot operation, without isolating the intermediates or changing the reaction conditions. It involves the use of three or more different starting materials to get a complex product which has incorporated in it most, if not all, of the starting materials. MCRs are very useful for diversity oriented synthesis of collection of compounds, and also allow a dramatic increase in structurally complexity by involving three or more diversity inputs with high degree of atom economy. Hence the very large chemical space which is amenable is a major characteristic of MCRs.[30] Additionally the scaffold diversity of MCR can be greatly enhanced by the introduction of orthogonal functional groups into the primary MCR product and further reacting them in subsequent transformations, *e.g.* ring forming reactions (Figure 2). These features have been routinely used in combinatorial and medicinal chemistry for drug discovery processes.

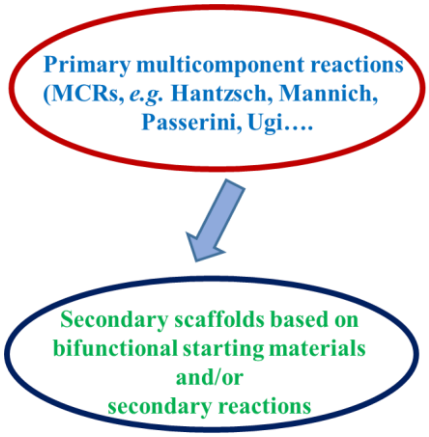


Figure 2. Scaffold diversity in MCRs.

Among MCRs, IMCRs[31] (*e.g.* Ugi and Passerini reactions) have occupied an outstanding position which could be traced to the wide applications in the production of diverse and complex small molecule libraries.

2.2.3. Isocyanides in [4+1] cycloadditon reactions

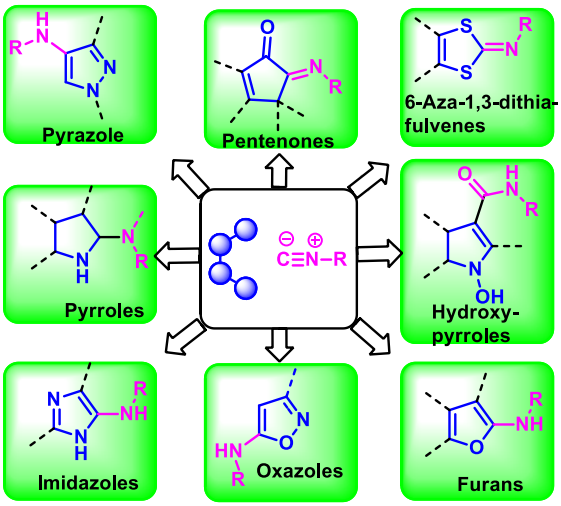


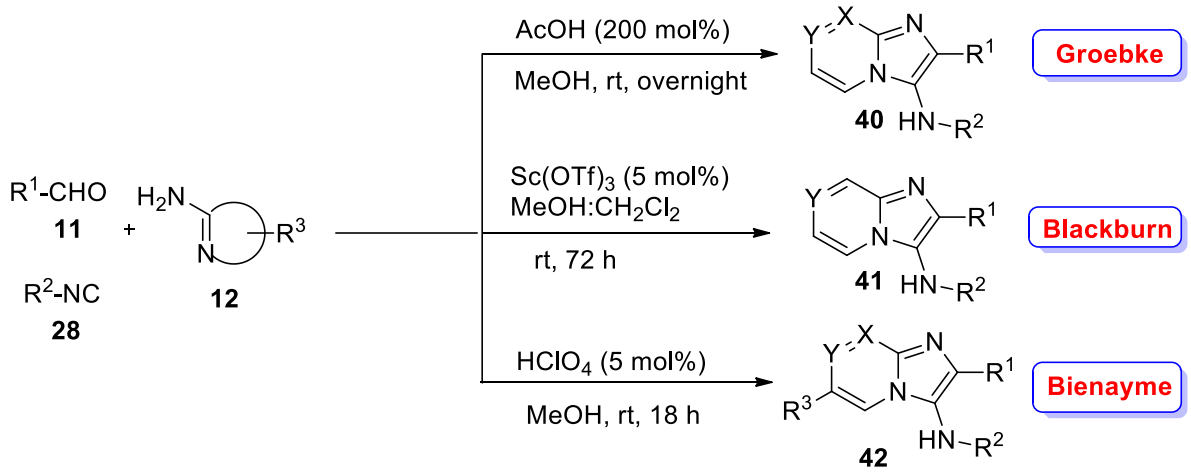
Figure 3. Synthesis of diverse heterocycles through isocyanide based formal [4+1] cycloadditions.

Owing to the importance of [4+1] cycloadditon and unique reactivity of isocyanides several formal [4+1] cycloaddition reactions employing isocyanides as C1 synthon have received extreme focus. The formal [4+1] cycloaddition of isocyanide with diverse dienes can offer concise construction of five-membered nitrogen heterocyclic compounds such as furans, oxazoles, pyrroles, imidazoles, pyrazoles *etc*., which are highly privileged in nature as depicted in Figure 3.

2.2.4 Groebke-Blackburn-Bienayme (GBB) Reaction

In recent decades, Groebke-Blackburn-Bienayme reaction (GBB)[32] a variant of Ugi reaction has emerged as an important tool for diversity oriented synthesis of fused imidazopyridine derivatives (Figure 4) for their applications in chemistry and biology.

GBB reaction involves formation of Schiff base by reaction of aminoazine with aldehyde. Next the Schiff's base which holds both the electrophile and nucleophile is involved in [4+1] cycloaddition with isocyanide to give bicyclic adduct followed by rearomatisation *via* 1,3-*H* shift leading to imidazopyridines Scheme 11.[32]



Scheme 11. Groebke's, Blackburn's and Bienaymè's reactions.

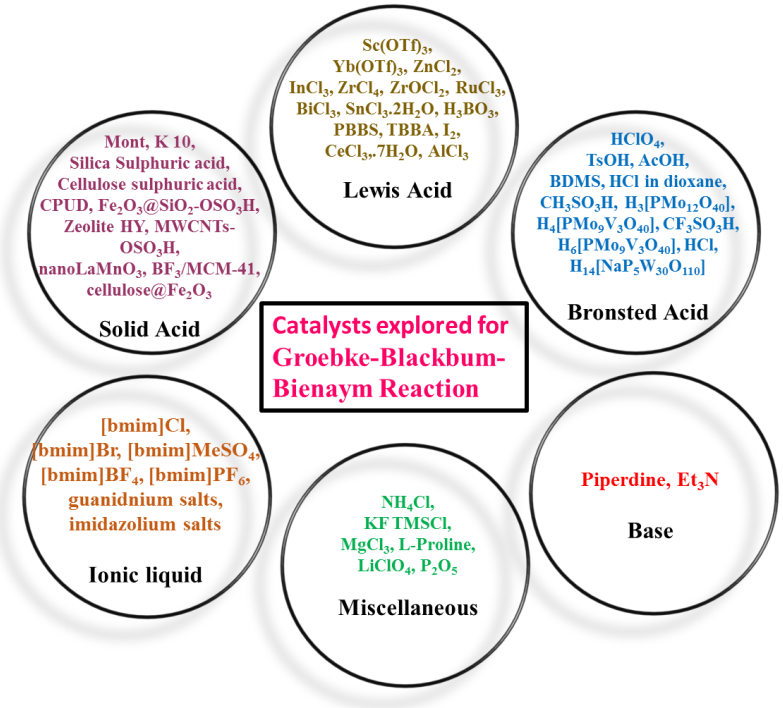


Figure 4. Different catalysts employed for Groebke–Blackburn–Bienayme reaction to generate fused imidazole derivatives.

2.2.5 Sustainable Methods: Solvent-Free and Catalyst-Free Reactions

Sustainability has become one of the important scientific challenges nowadays, due to environmental, health and societal concerns. Due to this, there is a need for developing facile, efficient, and non-polluting synthetic procedures to reduce the use of organic solvents and toxic reagents. One such approach, which involves green and sustainable chemistry,[37] drives towards pollution prevention and environmental protection, and is now gaining importance. Which mainly involves designing chemical products and processes that reduce or eliminate the use of hazardous substances, volatile organic compounds, generation of waste materials, by-product formation and unnecessary derivatization (like blocking, protecting/deprotecting) *etc*.

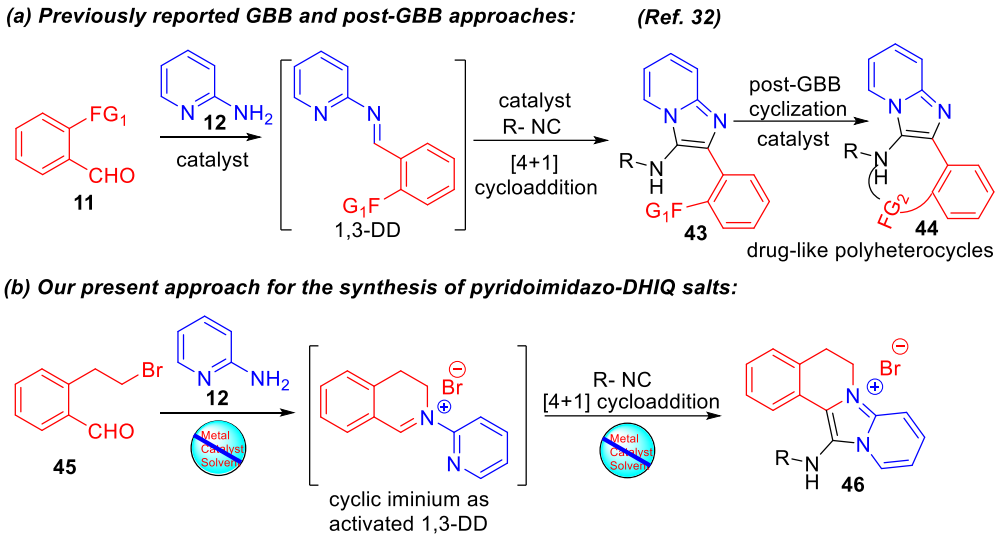
One of the strategies widely implemented is the development of alternative sustainable routes involves catalyst-free and solvent-free reactions (CFR & SFR)[38] which have gained importance recently. These approaches have several advantages over the conventional organic synthetic methods, like (a) reduced pollutant production, (b) reduced use or elimination of toxic and hazardous chemicals, (c) operational simplicity, (d) decreasing

the reaction time (under SFR), (e) formation of pure products which avoids tedious purifications, (f) high yields, (g) reduced cost and many more. Due to the various advantages of solvent-free and catalyst-free reactions, from the past decades several groups for the synthesis of heterocyclic molecules have made tremendous efforts.

2.3. Results and Discussion

Among IQ derivatives, fused IQ salts are naturally occurring alkaloids and promising lead structures in drug discovery. The iminium moiety in these derivatives was found to be essential for significant biological activities.[8] Though several reports have been documented for the synthesis of these derivatives, most of the methods involve starting material with preformed IQ skeleton, expensive metal catalysts, multiple steps, lack of diversity, scalability, and tedious routes to access starting material.

Recently, Shen *et al.* have developed an efficient approach to pyridimidazoisoquinolinium compounds *via* $Yb(OTf)_3$ /AgOTf catalyzed one-pot synthesis (Scheme 5).[23] However, it involves use of expensive two metal catalysts, inaccessible starting material, lack of generality and lengthy synthetic steps. Though there is a convenient approach reported for the synthesis of imidazoisoquinolinium salts, it involves preconstructed isoquinoline substrate rather than constructing the same.[25, 26]



Scheme 12. Various approaches to imidazopyridine based drug-like molecules *via* GBB reaction

The versatility of 2-(2-bromoethyl)benzaldehyde (**45**) as a promising bifunctional reactant in various organic transformations has been well documented, especially leading to tetrahydroisoquinoline (THIQ) motifs based natural products and their analogues.[33] However, utilization of **45** in the synthesis of fused dihydroisoquinolinium salts is not explored to date. Very recently, in our lab, we have documented some interesting cascade strategies employing **45** for the synthesis of skeletally diverse THIQ skeletons (Figure 5).[33a-c] Moreover, we have also reported step-economic and sustainable methods for the synthesis of imidazopyridines *via* GBB reaction.[34]

Groebke-Blackburn-Bienayme (GBB) reaction is an elegant example involving [4+1] cycloaddition as a key step between activated imine i.e. 1,3-diazadiene (1,3-DD) and isocyanide resulting in drug-like imidazopyridine heterocyclic entities which are further cyclized by post-GBB modifications (Scheme 12). However, most of the methods were realized by either use of stoichiometric or catalytic amount of Bronsted acids or bases, Lewis acids and metal catalysts for the generation of 1,3-DD and its activation.

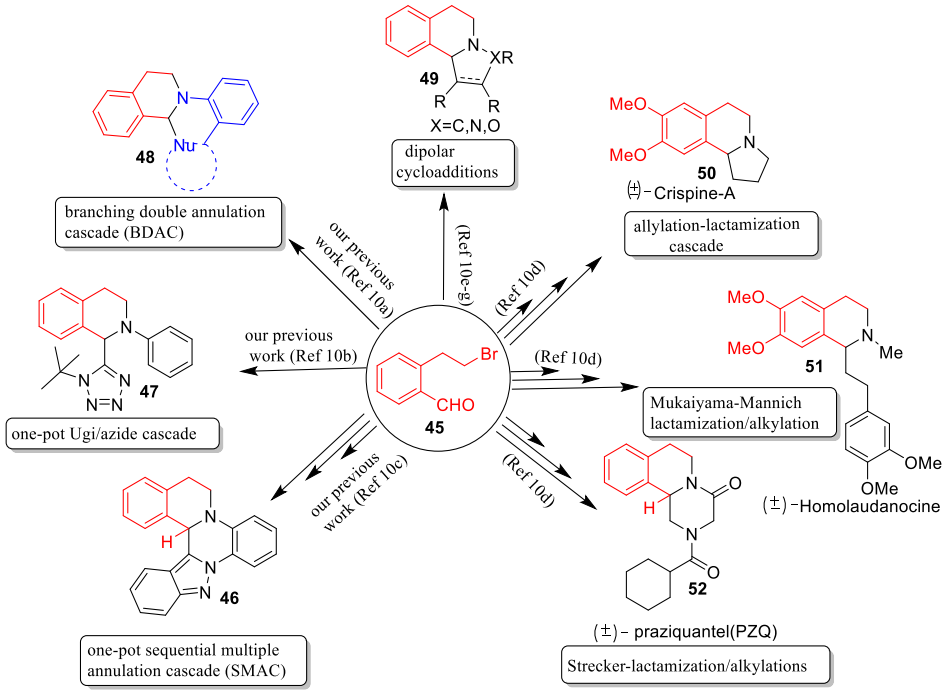
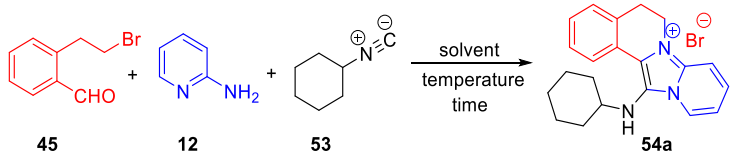


Figure 5. Various approaches to THIQ motifs starting from bromoethylbenzalaldehyde

Encouraged by our recent reports[33a-c] on employing **45** in various organic cascade transformations, we envisioned that the bifunctional reactivity of **45** could be tapped further (Scheme 12b). In this scenario, we conceptualized that **45** on reaction with 2-aminopyridine **12** would result in cyclic iminium *via* pre-GBB modification (imine formation and alkylation), which can be employed in GBB reaction as activated 1,3-DD under metal/catalyst-free conditions. Herein, we disclose the cyclic iminium induced GBB double annulation cascade reaction leading to pyridimidazo-DHIQ salts for the first time.

Table 1. Double annulation cascade to pyridoimidazo-DHIQ salt 4aaa[a,b]



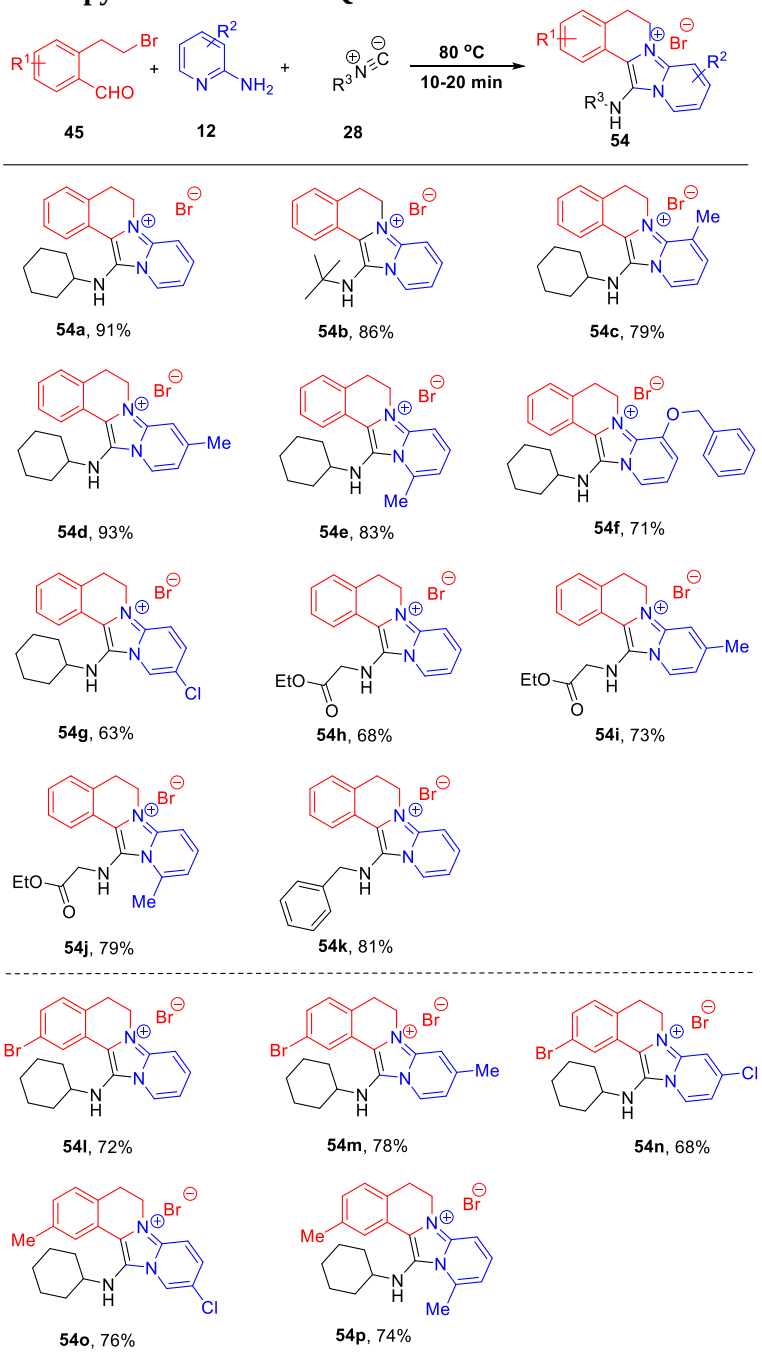
entry	Solvent	temp (°C)	time (h)	yield (%)
1	MeOH	rt	10	10
2	MeOH	50	20	20
3	MeOH	70	22	54

4	MeOH	90	20	64
5	EtOH	100	20	67
6	H_2O	100	20	0
7	DCE	100	23	40
8	DCM	50	14	32
9	CH_3CN	90	21	43
10	THF	90	14	35
11	1,4 dioxane	110	10	55
12	No solvent	rt	10	trace
13	No solvent	50	20	40
14	No solvent	60	2	66
15	**No solvent**	**80**	**10 min**	**91**
16	No solvent	90	10 min	70
17	No solvent	100	10 min	66

[a] Reaction conditions: **45** (0.23 mmol), **12** (0.23 mmol) and **53** (0.23 mmol). [b] Yield of isolated product after column chromatography.

To test the above hypothesis, a preliminary reaction of equimolar mixture of 2-(2-bromoethyl) benzaldehyde **45**, 2-aminopyridine 1**2** and cyclohexylisocyanide **53** was performed at ambient temperature (35 °C) in methanol for 10h, which afforded the desired product **54a**, albeit in low yield (Table 1, entry 1). Encouraged by this result, and to further explore, we increased the temperatures which resulted in improvement of yields up to 64% (Table 1, entries 2-4). Moreover, in protic and aprotic polar solvents, even after continuing the reaction for long hours the starting materials were not completely consumed (Table 1, entries 5-11). From the perspective of twelve principles of green chemistry, solvent-free reactions have seen tremendous growth both in academia and industry.[35] Our continued interests in development of sustainable methods for synthesis of diverse heterocyclic frameworks prompted us to perform the reaction under solvent-free conditions. Not surprisingly, higher temperatures resulted in improved yields of the products with drastic reduction in time (Table 1, entries 13-15). However, beyond 80 °C we have seen drop in the yields (Table 1, entries 16 and 17), which could be due to decomposition of reaction mixture.

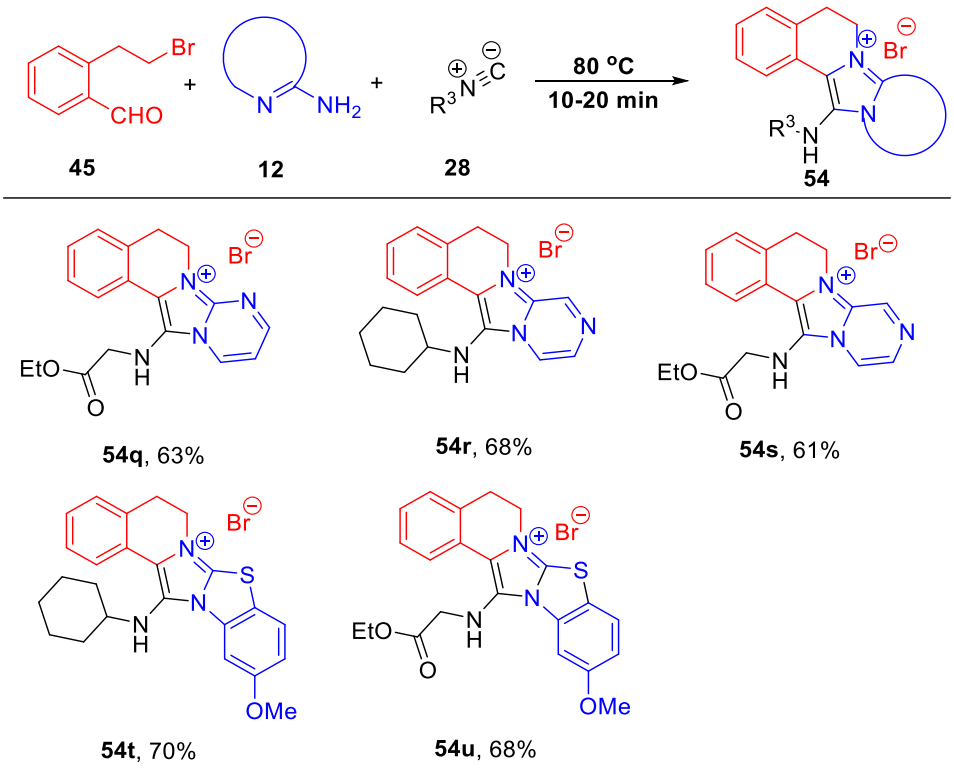
Scheme 13. Synthesis of pyridoimidazo-DHIQ scaffolds[a,b]



[a] Reactions were performed with **45** (0.23 mmol), 1**2** (0.23 mmol) and **28** (0.23 mmol) at 80 [o]C. [b] Yield of isolated product after column chromatography. [c]

With the reaction at 80 °C as optimized condition (Table 1, entry 15) for double annulation cascade (DAC) in hand we planned to evaluate the scope of our strategy. In this direction, we extended it to various aminoazines 1**2** and isocyanides **28**, keeping the aldehyde **45** component constant to obtain corresponding pyridoimidazoisoquinolinium derivatives (Scheme 13, **54a-54k**) in good to excellent yields. The structure of **54b** was further confirmed by single crystal X-ray crystallography. The aminoazine bearing electron withdrawing group (EWG), for example chloro substituent gave **54g** in moderate yield (64%) compared to other aminoazines. We next investigated employing a variety of 2-(2-bromoethyl)benzaldehydes **45** and aminoazines 1**2** with EWG and electron donating groups (EDG), which did not show any significant difference in the outcome of the reaction.

Scheme 14. Synthesis of skeletally diverse DHIQ scaffolds [a,b]

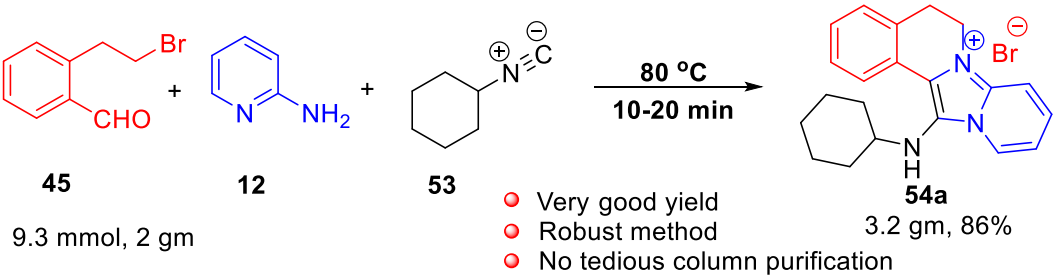


[a] Reactions were performed with **45** (0.23 mmol), 1**2** (0.23 mmol) and **28** (0.23 mmol) at 80 °C. [b] Yield of isolated product after column chromatography.

Gratifyingly, even when both aminoazines and aldehydes were employed with EWG, it resulted in good yield of the product (**54s**, Scheme 13). Our pursuit for diversity oriented synthesis (DOS) impelled us to examine diversity of our present strategy. Accordingly, we

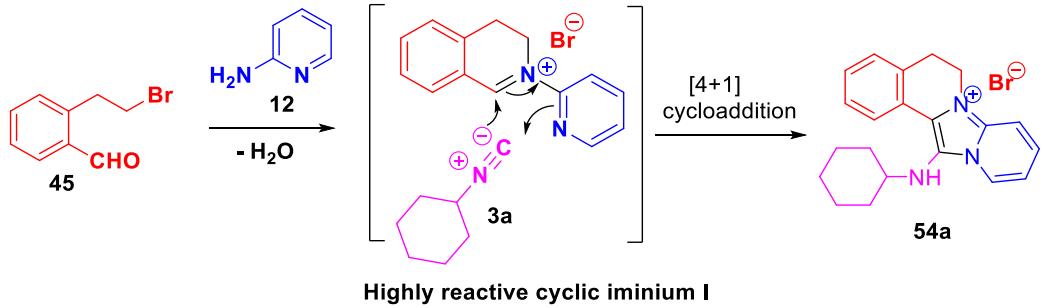
probed with structurally and skeletally different aminoazines, which to our delight provided interesting and diverse tetra- and pentacyclic IQ scaffolds (Scheme 14). When we have used other heterocyclic aminozines we have not observed any detrimental effect on reaction outcome.

After having successfully developed one-pot double annulation cascade (DAC) strategy for the synthesis of diverse pyridoimidazo-DHIQ scaffolds *via* GBB reaction, we envisaged to examine the scalability of the process. Consequently, we have performed the reaction on 2-gram scale and isolated the product **54a** as white solid in very good yield (86%) by direct filtration without the need for any tedious column purification (Scheme 15). As synthesized DHIQ compounds contain some privileged heterocyclic motifs present in drug molecules, the scalability of our method should prove industrially applicable.



Scheme 15. Scalability of present DAC protocol

Based on our reports[33a-c] and other literatures,[32] we have proposed a plausible mechanism for the formation of pyridoimidazo-DHIQ salt **54a** in Scheme 16. Initially, the reaction of 2-(2-bromoethyl)benzaldehyde **45** and 2-aminopyridine **12** will afford highly reactive cyclic iminium **I**, which on [4+1] cycloaddition with cyclohexylisocyanide **53** will lead to pyridoimidazo-DHIQ bromide **54a**.



Scheme 16. Plausible reaction mechanism for 54a

2.4 Conclusion

In summary, we have developed a mild, efficient and metal-free protocol for the synthesis of fused IQ derivatives under solvent-free conditions. We have demonstrated an unprecedented cyclic iminium induced GBB leading to construction of two privileged heterocyclic rings in one-pot. This double annulation cascade provided pyridoimidazo-DHIQs in excellent yields by easy isolation without tedious workup. In addition, readily accessible starting material, remarkably short reaction time, simplicity in operation, scope of skeletal diversity, H_2O as sole byproduct and scalability makes this approach greener, cost effective, and better alternative to existing ones. On the other hand, the scalability of the method should prove appealing for industrial applications. Further studies on biological activity of these scaffolds are currently under way in our laboratory.

2.5 Experimental section

General Information

IR spectra were recorded on the Bruker Tensor 37(FTIR) spectrophotometer. ^1H NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295K in $CDCl_3$; chemical shifts value (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either tetramethylsilane (TMS) (δH = 0.00 ppm) or $CHCl_3$ (δH = 7.26ppm). ^{13}C NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at rt in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [(δC = 77.00ppm) central line of triplet]. In the ^{13}C NMR, the nature of carbons (C, CH, CH_2, and CH_3) was determined by recording the DEPT- 135 spectra. In ^1H NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet and br s. = broad singlet. The assignment of the signals was confirmed by ^1H, ^{13}C and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using Agilent 6538 UHD Q-TOF using multimode source in +APCI method. Reactions were monitored by

TLC on silica gel (254 mesh) using a combination of petroleum ether and ethyl acetate as eluents.

General procedure 1: Preparation of isochromans

A mixture of the substituted phenylethyl alcohol (**i**) (4.97 mmol), chloromethylmethyl ether (7.046 mmol) and *N*, *N*-diisopropylethylamine (9.95 mmol) in dry dichloromethane (15 mL) was stirred under nitrogen atmosphere for 2.5 hours at rt. The reaction mixture was then washed with water, dried (Na_2SO_4) and the solvent was removed in vacuum. The crude MOM acetal (**ii**) was dissolved in dried acetonitrile and added to cooled (0 ^oC) solution of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (4.97 mmol). The reaction was carried out under nitrogen atmosphere for 3h. Then the mixture was quenched by the addition of l M $NaHCO_3$. The organic phase was washed with brine, dried with anhydrous sodium sulphate and evaporated under reduced pressure. Purification by column chromatography afforded corresponding substituted isochromans.

General procedure 2: Preparation of 2-(2-bromoethyl) benzaldehydes

To a solution of the substituted isochroman **iii** (7.46 mmol) derivatives in acetonitrile (15 mL), $CuBr_2$ (8.95 mmol) was added under nitrogen atmosphere. The solution was refluxed for about 2h and then cooled to room temperature. The reaction mixture was added water, extracted with ethyl acetate. The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4, filtered and concentrated and then purified by silica gel column chromatography to afford the products (**1a-1c)** in 68-74% yield.

General procedure 3: Synthesis of pyridoimidazo-DHIQ salts

2-(2-Bromoethyl) benzaldehyde (**1**, 0.23 mmol) and 2-aminoazine (**2,** 0.23 mmol) were taken in a 5 mL round bottom flask. Then isocyanide **3** (0.23 mmol) was added in succession to the reaction mixture and the reaction was stirred at 80 ^oC for 10-20 min. After completion of the reaction (monitored by TLC in 5% MeOH/DCM, 0.4 Rf), the crude reaction mixture was

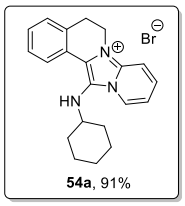
purified by filtration through a short pad of silica gel (100-200 mesh) column using DCM and MeOH as eluents to yield the desired products (**4aaa-4akc)** in 61-93% yields.

General procedure 4: Large scale synthesis of pyridoimidazodihydroisoquinolinium salt:

2-(2-Bromoethyl) benzaldehyde (**45,** 2 gm**,** 9.3 mmol) and 2-aminopyridine (**12**, 0.87 gm, 9.3 mmol) were taken in a 25 mL round bottom flask. Then cyclohexylisocyanide (**53**, 1.01 gm, 9.3 mmol) was added in succession to the reaction mixture and the reaction was stirred at 80 ºC for 15 min. After completion of the reaction (monitored by TLC in 5% MeOH/DCM, 0.4 Rf), the crude reaction mixture was washed with 5% ethylacetate in hexane to yield the desired product **4aaa** (3.2 gm, 86%).

Spectral Data of all Compounds

***13-(Cyclohexylamino)-5,6 dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54a)**



Physical state : White solid

Yield : 91%

Mp : 235-238 ˚C

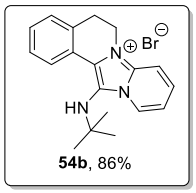
IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3411, 3174, 3017, 2927, 2853, 1646, 1615, 1527, 1450, 1417, 1266, 1224, 1156, 1082, 891, 728;

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 9.4 (d, J = 6.8 Hz, 1H), 8.35−8.28 (m, 2H), 7.79−7.75 (m, 1H), 7.37−7.25 (m, 4H), 5.84 (d, J = 6.8 Hz, 1H), 4.65 (t, J = 6.6 Hz, 2H), 3.28 (t, J = 6.6 Hz, 2H), 3.02−2.95 (m, 1H), 1.87 (d, J = 10.3 Hz, 2H), 1.71−1.52 (m, 5H), 1.19−1.10 (m, 3H);

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 134.9, 132.8, 132.4, 130.1, 128.7, 127.9, 127.2, 126.9, 125.8, 123.3, 122.5, 116.3, 111.0, 58.0, 42.2, 33.9, 28.0, 25.3, 25.1.

HR-MS (ESI+) *m/z* calculated for $[C_{21}H_{24}N_3]^+$ = 318.1965; found: 318.1968.

***13-(Tert-butylamino)-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-iumbromide* (54b):**



Physical state : Pale Yellow solid

Yield : 86%

Mp : 195-196 ˚C

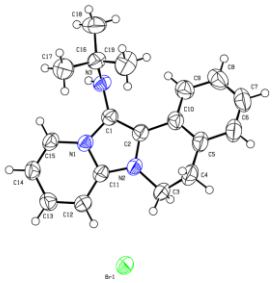
IR (MIR-ATR, 4000-600cm^{-1}): ν_{max} = 3192, 3040, 2967, 1647, 1528, 1472, 1365, 1265, 1202, 1157, 1029, 899, 729, 699, 618.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 9.4 (d, J = 6.8 Hz, 1H), 8.62–8.60 (m, 1H), 8.22 (d, J = 9.3 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.39–7.31 (m, 3H), 7.26–7.24 (m, 1H), 5.61 (s, 1H), 4.58 (br. s, 2H), 3.28 (t, J = 5.9 Hz, 2H), 1.25 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm = 135.4, 133.1, 132.7, 130.5, 128.5, 127.8, 127.7, 127.0, 125.5, 123.7, 116.1, 110.5, 57.9, 42.4, 30.5, 28.

HR-MS (ESI+) m/z calculated for $[C_{19}H_{22}N_3]^+$ = 292.1808; found: 292.1812.

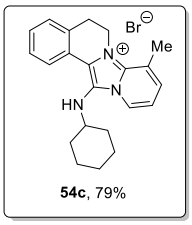
Single crystal X-ray structure data of compound 54b (CCDC 1478558): Thermal ellipsoids are drawn at 50% probability level.



Identification code	exp_4568
Empirical formula	$C_{9.5}H_{11}N_{1.5}Br_{0.5}$
Formula weight	372.31
Temperature/K	300
Crystal system	Triclinic
Space group	P-1
a/Å	9.8675(5)
b/Å	10.2949(5)
c/Å	11.0351(6)
α/°	117.594(5)

β/°	105.751(5)
γ/°	97.854(4)
Volume/Å^3	909.81(11)
Z	2
ρ_{calc}g/cm^3	1.3589
μ/mm^{-1}	3.087
F(000)	383.5
Crystal size/mm^3	0.6 × 0.4 × 0.2
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	9.74 to 141.4
Index ranges	-8 ≤ h ≤ 12, -12 ≤ k ≤ 12, -13 ≤ l ≤ 10
Reflections collected	7192
Independent reflections	3402 [R_{int} = 0.0439, R_{sigma} = 0.0396]
Data/restraints/parameters	3402/0/214
Goodness-of-fit on F^2	1.050
Final R indexes [I>=2σ (I)]	R_1 = 0.0354, wR_2 = 0.0904
Final R indexes [all data]	R_1 = 0.0396, wR_2 = 0.0939
Largest diff. peak/hole / e Å^{-3}	0.61/-0.65

***13-(Cyclohexylamino)-8-methyl-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54c):**



54c, 79%

Physical state : Brown semi solid

Yield : 79%

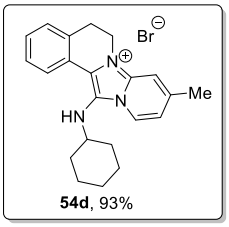
IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3744, 3669, 3395, 3182,3007, 2925, 2850, 2350, 2155, 1983, 1726, 1633, 1570, 1511, 1489, 1451, 1421, 1368, 1302, 1260, 1210, 1090, 1040, 949, 889, 802, 763, 731, 668, 605, 558.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 9.35 (d, J = 6.8 Hz, 1H), 8.40−8.38 (m, 1H), 7.5 (d, J = 6.8 Hz, 1H), 7.42−7.35 (m, 3H), 7.25−7.23 (m, 1H), 5.86 (br. s, 1H), 4.84 (t, J = 6.6 Hz, 2H), 3.33 (t, J = 6.6 Hz, 2H), 3.01 (t, J = 10.8 Hz, 1H), 2.92 (s, 3H), 1.87 (d, J = 10.3 Hz, 2H), 1.73−1.62 (m, 4H), 1.56 (dd, J_a = 15.2 and J_b = 11.2 Hz, 2H), 1.26−1.16 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm = 134.6, 134.5, 132.1, 129.9, 128.2, 127.9, 127.4, 126.0, 125.5, 123.6, 123.0, 121.7, 116.2, 57.6, 44.2, 33.8, 28.7, 25.3, 25.1, 20.1.

HR-MS (ESI$^+$): *m/z* calculated for $[C_{22}H_{26}N_3]^+$ = 332.2121; found: 332.2131.

***13-(Cyclohexylamino)-9-methyl-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54d):**



Physical state : White solid

Yield : 93%

Mp : 235-238 ˚C

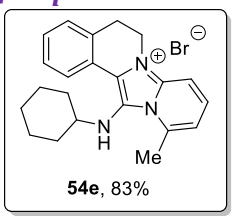
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3424, 3175, 3007, 2926, 2853, 2453, 1967, 1651, 1532, 1457, 1312, 1263, 1233, 1152, 1083, 889, 604, 540.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 9.22–9.18 (m, 1H), 8.27–8.25 (m, 1H), 8.06–8.03 (m, 1H), 7.31–7.30 (m, 3H), 7.06 (d, *J* = 6.8 Hz, 1H), 5.65–5.61 (m, 1H), 4.55 (t, *J* = 6.4 Hz, 2H), 3.26–3.23 (m, 2H), 2.97–2.94 (m, 1H), 2.5 (s, 3H), 2.11 (br. s, 1H), 1.84 (d, *J* = 7.8 Hz, 3H), 1.69 (br. s, 2H), 1.58–1.53 (m, 2H), 1.23–1.14 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm = 145.8, 135.3, 132.3, 129.9, 128.7, 127.9, 126.7, 126.1, 125.7, 123.5, 122.0, 118.8, 109.3, 57.9, 41.9, 33.9, 28.0, 25.3, 25.1,21.8.

HR-MS (ESI$^+$): *m/z* calculated for $[C_{22}H_{26}N_3]^+$ = 332.2121; found: 332.2127.

***13-(Cyclohexylamino)-11-methyl-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54e):**



Physical state : White solid

Yield : 83%

Mp : 295-297 ˚C

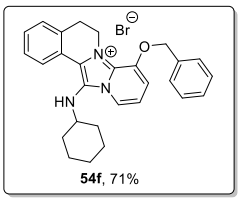
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3744, 3733, 3395, 3196, 3085, 3007, 2923, 2851, 2373, 2350, 2320, 2129, 1992, 1947, 1731, 1632, 1512, 1464, 1453, 1420, 1303, 1260, 1171, 1091, 1040, 889, 803, 763, 744, 668, 605, 576, 559.

^{1}H NMR (DMSO D_6, 400 MHz): δ ppm = 8.71 (d, *J* = 6.8 Hz, 1H), 8.34 (d, *J* = 6.8 Hz, 1H), 7.71 (d, *J* = 6.8 Hz, 1H), 7.45–7.41 (m, 4H), 5.56 (d, 1H), 4.87 (t, *J* = 6.4 Hz, 2H), 3.31–3.27 (m, 2H), 2.95 (s, 1H), 2.9 (s, 3H), 1.85 (d, *J* = 11.7 Hz, 2H), 1.7 (br. s, 2H), 1.56 (br. s, 1H), 1.37 (d, *J* = 10.3 Hz, 2H), 1.15 (br. s, 3H).

^{13}C NMR (100 MHz, DMSO D_6): δ ppm = 134.8, 134.0, 129.6, 128.2, 127.3, 125.9, 125.2, 123.3, 122.8, 122.5, 116.2,56.5, 33.3, 27.8, 25.0,24.5,19.0.

HR-MS (ESI^+): *m/z* calculated for $[C_{22}H_{26}N_3]^+$ = 332.2121; found: 332.2120.

***8-(Benzyloxy)-13-(cyclohexylamino)-5,6-dihydropyrido[2',1':2,3]imidazo[5,1a]isoquinolin-7-ium bromide* (54f):**



54f, 71%

Physical state : Brown solid

Yield : 71%

Mp : 157-158 ˚C

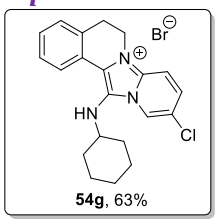
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3744, 3733, 3395, 3196, 3085, 3007, 2923, 2851, 2373, 2350, 2320, 2129, 1992, 1947, 1731, 1632, 1512, 1464, 1453, 1420, 1303, 1260, 1171, 1091, 1040, 889, 803, 763, 744, 668, 605, 576, 559.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 9.06 (d, *J* = 6.4 Hz, 1H), 8.4 (d, *J* = 6.8 Hz, 1H), 7.5-7.49 (m, 2H), 7.44-7.41 (m, 4H), 7.39-7.35 (m, 2H), 7.33-7.31 (m, 2H), 6.02 (d, *J* = 6.4 Hz, 1H), 5.4 (s, 2H), 4.75 (t, *J* = 6.4 Hz, 2H), 3.2 (t, *J* = 6.4 Hz, 2H), 3.01-2.98 (m, 1H), 1.87 (d, *J* = 12.2 Hz, 2H), 1.7-1.5 (m, 5H), 1.4-1.09 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm = 144.5, 134.2, 132.1, 129.9, 129.0, 128.2, 128.1, 128.0, 127.9, 126.1, 123.5, 123.0, 119.8, 116.6,112.4, 72.6, 57.7, 44.1, 33.8, 28.4, 25.3, 25.1.

HR-MS (ESI^+): *m/z* calculated for $[C_{28}H_{30}N_3O]^+$ = 424.2383; found: 424.2398.

***10-Chloro-13-(cyclohexylamino)-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54g):**



54g, 63%

Physical state : Pale yellow solid

Yield : 63%

Mp : 158-160 ˚C

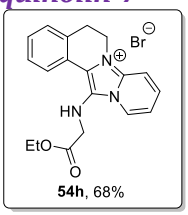
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3745, 3396, 3174, 2923, 2852, 1955, 1731, 1646, 1612, 1522, 1467, 1451, 1305, 1264, 1226, 1050, 888, 808, 767, 731.

^{1}H NMR (DMSO D_6, 400 MHz): δ ppm = 9.13 (s, 1H), 8.35–8.27 (m, 2H), 8.09 (dd, J_a = 9.3 and J_b = 1.5 Hz, 1H), 7.52–7.46 (m, 3H), 5.68 (d, J = 6.8 Hz, 1H), 4.6 (t, J = 6.6 Hz, 2H), 3.3 (t, J = 6.4 Hz, 2H), 2.98–2.95 (m, 1H), 1.87 (d, J = 11.7, 2H), 1.67 (br. s, 2 H), 1.53 (br. s, 1 H), 1.37 (d, J = 9.8 Hz, 2H), 1.23–1.13 (m, 3H).

^{13}C NMR (DMSO D_6, 100 MHz): δ ppm = 134.0, 133.4, 132.9, 129.9, 128.8, 127.5, 126.5, 125.2, 123.6, 123.2, 122.9, 112.2, 79.2, 56.8, 41.3, 33.1, 26.9, 25.1, 24.6.

HR-MS (ESI^+): *m/z* calculated for $[C_{21}H_{23}ClN_3]^+$ = 352.1575; found: 352.1590.

***13-((2-Ethoxy-2-oxoethyl)amino)-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54h):**



54h, 68%

Physical state : Brown semisolid

Yield : 68%

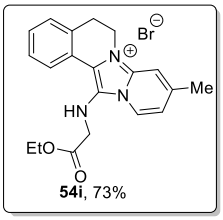
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3774, 3654, 3179, 3037, 2981, 2032, 1975, 1739, 1649, 1622, 1527, 1449, 1408, 1265, 1197, 1155, 1110, 1022, 862, 727, 697, 600.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 9.5 (d, 1H), 8.20–8.18 (m, 1H), 8.1 (d, J = 8.8 Hz, 1H), 7.28–7.74 (m, 1H), 7.41–7.38 (m, 2H), 7.37–7.33 (m, 1H), 7.26–7.24 (m, 1H), 6.84 (t, J = 6.24 Hz, 1H), 4.58 (t, J = 6.6 Hz, 2H), 4.02–3.96 (m, 4H), 3.28 (t, J = 6.4 Hz, 2H), 1.12 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm = 171.5, 134.8, 132.9, 132.3, 130.2, 128.8, 128.4, 127.7, 125.5, 123.0, 121.0, 115.8, 109.9, 61.1, 47.5, 42.1, 28.0, 14.0.

HR-MS (ESI$^+$): *m/z* calculated for $[C_{19}H_{20}N_3O_2]^+$ = 322.1550; found: 322.1554.

***13-((2-Ethoxy-2-oxoethyl)amino)-9-methyl-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54i):**



Physical state : Brown semisolid

Yield : 73%

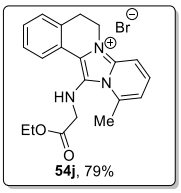
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3412, 3189, 2981, 2066, 2015, 1738, 1654, 1629, 1532, 1462, 1406, 1372, 1262, 1199, 1107, 1025, 859, 769, 729, 697, 608.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 9.4 (d, J = 6.8 Hz, 1H), 8.17-8.15 (m, 1H), 7.9 (s, 1H), 7.40-7.34 (m, 3H), 7.07 (dd, J = 7.3 Hz, 1H), 6.78 (t, J = 6.4 Hz, 1H), 4.52 (t, J = 6.6 Hz, 2H), 4.01-3.96 (m, 4H), 3.26 (t, J = 6.4 Hz, 2H), 2.53 (s, 3H), 1.13 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm = 171.6, 145.9, 135.1, 132.2, 129.9, 128.8, 128.4, 128.1, 128.3, 127.6, 127.2, 125.4, 123.2, 120.4, 118.2, 108.5, 61.1, 47.5, 41.9, 28.0, 21.9, 14.0.

HR-MS (ESI+): m/z calculated for $[C_{20}H_{22}N_3O_2]^+$ = 336.1707; found: 326.1712.

***13-((2-Ethoxy-2-oxoethyl)amino)-11-methyl-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54j):**



Physical state : Brown semisolid

Yield : 79%

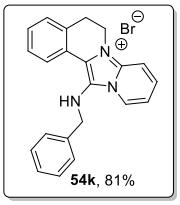
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3745, 3180, 3035, 2957, 2318, 1986, 1738, 1649, 1530, 1472, 1456, 1302, 1265, 1113, 1022, 948, 864, 768, 727, 697, 663, 602, 574.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 8.29 (dd, J = 5.1, 3.7 Hz, 1H), 8.02 (d, J = 9.3 Hz, 1H), 7.7 (dd, J_a = 9.3 and J_b = 7.3 Hz, 1H), 7.39-7.31 (m, 3H), 6.99 (d, J = 6.8 Hz, 1H), 6.29 (t, J = 4.4 Hz, 1H), 4.53 (t, J = 6.4 Hz, 2H), 4.03-3.96 (m, 4H), 3.38 (s, 3H), 3.27 (t, J = 6.6 Hz, 2H), 1.13 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm = 171.3, 142.4, 136.8, 133.3, 132.9, 130.4, 128.8, 128.6, 128.4, 126.3, 124.1, 122.7, 118.6, 108.2, 60.9, 47.9, 41.9, 28.1, 21.6, 14.0.

HR-MS (ESI+) *m/z* calculated for $[C_{20}H_{22}N_3O_2]^+$ = 336.1707; found: 336.1713.

***13-(Benzylamino)-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-iumbromide* (54k):**



Physical state : White solid

Yield : 81%

Mp : 232-235 ˚C

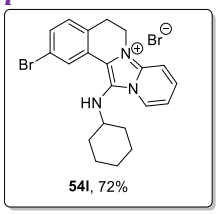
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3745, 3397, 3195, 2978, 2943, 2690, 1691, 1649, 1527, 1469, 1453, 1392, 1314, 1227, 1159, 1068, 1026, 755, 734, 702, 632.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.03 (d, J = 6.8 Hz, 1H), 8.25-8.24 (m, 1H), 8.17 (d, J = 9.3 Hz, 1H), 7.66 (ddd, J_a = 9, J_b = 7.1 and J_c = 1 Hz, 1H), 7.38-7.36 (m, 3H), 7.18 (dd, J_a = 6.6 and J_b = 2.7 Hz, 2H), 7.08-7.05 (m, 4H), 6.74 (t, J = 5.9 Hz, 1H), 4.58 (t, J = 6.6 Hz, 2H), 4.32 (d, J = 5.4 Hz, 2H), 3.21 (t, J = 6.4 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm = 138.6, 134.7, 132.7, 132.3, 130.2, 128.6, 128.4, 128.1, 127.6, 127.5, 126.6, 126.1, 123.0, 122.3, 116.0, 110.5, 51.0, 42.1, 28.1.

HR-MS (ESI+): *m/z* calculated for $[C_{22}H_{20}N_3]^+$= 326.1652; found: 326.1663.

***2-Bromo-13-(cyclohexylamino)-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54l):**



Physical state : Pale yellow solid

Yield : 72%

Mp : 275-278 ˚C

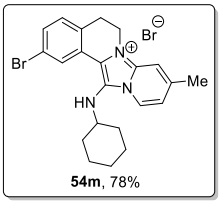
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3779, 3426, 3192, 3025, 2927, 2853, 1929, 1648, 1622, 1526, 1467, 1449, 1342, 1318, 1292, 1258, 1229, 1085, 874, 833, 759, 597.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 9.48-9.46 (m, 1H), 8.38-8.37 (m, 1H), 8.24-8.21 (m, 1H), 7.73-7.69 (m, 1H), 7.46-7.43 (m, 1H), 7.24-7.21 (m, 2H), 6.03 (d, *J* = 7.3 Hz, 1H), 4.64 (t, *J* = 6.6 Hz, 2H), 3.26 (t, *J* = 6.4 Hz, 2H), 2.96-2.93 (m, 1H), 1.87 (d, *J* = 12.2 Hz, 2H), 1.7-1.5 (m, 5H), 1.4-1.09 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.1, 133.2, 132.8, 131.1, 130.3, 128.3, 128.0, 127.2, 125.1, 121.6, 120.7, 116.5, 111.0, 58.5, 42.2, 34.1, 27.5, 25.24, 25.2.

HR-MS (ESI+): *m/z* calculated for $[C_{21}H_{23}BrN_3]^+$ = 396.1070; found: 396.1067.

***2-Bromo-13-(cyclohexylamino)-9-methyl-5,6-dihydropyrido[2',1':2,3]imidazo[5,1 a]isoquinolin-7-ium bromide* (54m):**



54m, 78%

Physical state : White solid

Yield : 78%

Mp : 180-183 ˚C

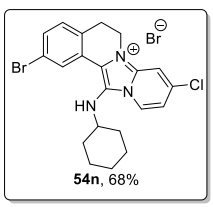
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3779, 3638, 3407, 3317, 3197, 3041, 2927, 2853, 1975, 1652, 1622, 1559, 1531, 1446, 1372, 1313, 1259, 1185, 1084, 1040, 890, 808, 730, 603, 563.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 9.3 (d, *J* = 7.3 Hz, 1H), 8.32 (d, *J* = 2 Hz, 1H), 8.05 (s, 1H), 7.36 (dd, *J* = 8.3 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 1H), 7.06 (d, *J* = 6.4 Hz, 1H), 5.94 (d, *J* = 6.8 Hz, 1H), 4.55 (t, *J* = 6.4 Hz, 2H), 3.2 (t, *J* = 6.4 Hz, 2H), 2.91-2.84 (m, 1H), 2.5 (s, 3H), 1.83-1.80 (m, 2H), 1.67 (d, *J* = 10.3 Hz, 2H), 1.60-1.49 (m, 3H), 1.14-1.11 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.2, 135.4, 132.4, 130.9, 130.3, 128.1, 127.6, 126.5, 125.2, 121.5, 120.0, 118.9, 109.5, 58.5, 41.8, 34.0, 27.5, 25.2, 25.1, 21.9.

HR-MS (ESI+): *m/z* calculated for $[C_{22}H_{25}BrN_3]^+$ = 410.1226; found: 410.1228.

***2-Bromo-9-chloro-13-(cyclohexylamino)-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54n):**



54n, 68%

Physical state : Pale yellow

Yield : 68%

Mp : 155-157 ˚C

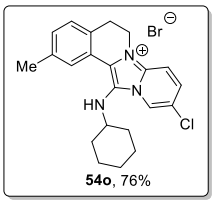
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3691, 3570, 3406, 3181, 3006, 2927, 2853, 1977, 1707, 1647, 1616, 1597, 1560, 1522, 1464, 1424, 1369, 1343, 1308, 1257, 1097, 1078, 945, 890, 840, 816, 731, 665.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.47 (d, J = 7.3 Hz, 1H), 8.53 (d, J = 9.3 Hz, 1H), 8.32 (d, J = 2Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.48 (dd, J = 7.8 Hz, 1H), 7.24 (d, J = 8.3 Hz, 1H), 5.96 (d, J = 7.3 Hz, 1H), 4.76 (t, J = 6.4 Hz, 2H), 3.27 (t, J = 6.1 Hz, 2H), 2.96-2.94 (m, 1H), 1.86 (m, J = 9.3 Hz, 2H), 1.76 (d, J = 12.7 Hz, 2H), 1.60-1.64 (m, 4H), 1.22-1.18 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.9, 133.5, 132.4, 133.2, 131.2, 130.3, 128.4, 127.9, 125.2, 124.7, 124.4, 121.7, 112.4, 58.4, 42.8, 34.1, 27.4, 25.2, 25.1.

HR-MS (ESI+): *m/z* calculated for $[C_{21}H_{22}BrClN_3]^+$ = 430.0680; found: 430.0689.

***10-Chloro-13-(cyclohexylamino)-2-methyl-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54o):**



54o, 76%

Physical state : White solid

Yield : 76%

Mp : 228-230 ˚C

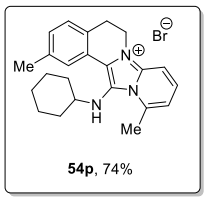
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3413, 3180, 2926, 2853, 2028, 1647, 1613, 1524, 1490, 1450, 1344, 1307, 1266, 1228, 1148, 1093, 1049, 947, 890, 817, 730, 699, 602, 558.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.41 (d, J = 1 Hz, 1H), 8.54 (d, J = 9.8 Hz, 1H), 8.1 (s, 1H), 7.61 (dd, J_a = 9.5 and J_b = 1.7 Hz, 1H), 7.22-7.18 (m, 2H), 5.9 (d, J = 6.8 Hz, 1H), 4.69 (t, J = 6.6 Hz, 2H), 3.23 (t, J = 6.6 Hz, 2H), 3.0-2.97 (m, 1H), 2.4 (s, 3H), 1.88-1.80 (m, 3H), 1.72-1.58 (m, 4H), 1.28-1.18 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 133.3, 133.1, 131.3, 129.4, 128.5, 127.2, 126.3, 124.9, 124.2, 123.6, 122.7, 112.2, 57.9, 43.1, 34.1, 27.4, 25.2, 25.1, 21.2.

HR-MS (ESI+): *m/z* calculated for $[C_{22}H_{25}ClN_3]^+$ = 366.1732; found: 366.1738.

***13-(Cyclohexylamino)-2,11-dimethyl-5,6-dihydropyrido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54p):**



54p, 74%

Physical state : Pale yellow solid

Yield : 74%

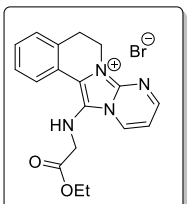
Mp : 217-219 ˚C

IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3395, 3195, 3027, 2925, 2852, 1729, 1646, 1532, 1491, 1449, 1420, 1386, 1264, 1210, 1140, 1110, 868, 820, 781, 727, 696, 592.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.25 (s, 1H), 8.11(d, *J* = 8.8 Hz, 1H), 7.63 (dd, *J* = 8.8 Hz, 1H), 7.18-7.13 (m, 2H), 6.93 (d, *J* = 7.3 Hz, 1H), 5.12 (d, *J* = 2.4 Hz, 1H), 4.51 (t, *J* = 6.4 Hz, 2H), 3.26 (s, 3H), 3.18 (t, *J* = 6.4 Hz, 2H), 2.97-2.91 (m, 1H), 2.02 (br. s, 1H), 1.8 (d, *J* = 12.2 Hz, 2H), 1.64-1.52 (m, 3H), 1.3-1.18 (m, 4H), 1.09-1.05 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm = 141.0, 137.7, 136.9, 133.1, 131.2, 130.0, 128.2, 127.5, 127.2, 126.2, 123.1, 118.8, 108.9, 58.1, 42.2, 33.3, 29.6, 27.8, 25.6, 24.8, 21.2, 21.2; HR-MS (ESI+) *m/z* calculated for $[C_{23}H_{28}N_3]^+$ = 346.2278; found: 346.2277.

***13-((2-Ethoxy-2-oxoethyl)amino)-5,6-dihydropyrimido[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54q):**



54q, 63%

Physical state : White solid

Yield : 63%

Mp : 186-188 ˚C

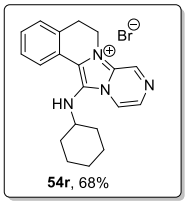
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3185, 3102, 2181, 2123, 1969, 1738, 1641, 1609, 1536, 1471, 1436, 1376, 1333, 1274, 1207, 1154, 1111, 1030, 760, 736, 637, 568.

^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm = 10.22 (dd, J_a = 7.1 and J_b = 1.7 Hz, 1H), 8.81 (s, 1H), 8.21-8.19 (m, 1H), 7.51 (dd, J_a = 6.8 and J_b = 4.4 Hz, 1H), 7.46-7.38 (m, 3H), 7.19 (t, *J* = 6.6 Hz, 1H), 4.60-4.57 (m, 2H), 4.0-3.96 (m, 4H), 3.28 (t, *J* = 6.6 Hz, 2H), 1.12 (t, *J* = 7.1 Hz,

3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 155.7, 138.0, 137.9, 132.6, 130.7, 128.9, 128.6, 126.5, 125.9, 122.8, 121.3, 122.8, 61.2, 47.3, 40.6, 27.8, 14.0.

HR-MS (ESI+): *m/z* calculated for $[C_{18}H_{19}N_4O_2]^+$ = 323.1503; found: 323.1509.

***13-(Cyclohexylamino)-5,6-dihydropyrazino[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54r):**



54r, 68%

Physical state : Green solid

Yield : 68%

Mp : 197-199 ˚C

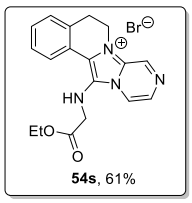
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3422, 3182, 3040, 2930, 2855, 1584, 1529, 1294, 1264, 1083, 1027, 892, 768, 728, 698, 593, 570.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.97 (s, 1H), 9.43 (d, *J* = 3.9 Hz, 1H), 8.31-8.28 (m, 2H), 7.42-7.35 (m, 3H), 6.11 (d, *J* = 7.8 Hz, 1H), 4.93 (t, *J* = 6.4 Hz, 2H), 3.36 (t, *J* = 6.4 Hz, 2H), 3.02-2.98 (m, 1H), 1.85 (d, *J* = 10.8 Hz, 2H), 1.71-1.51 (m, 5H), 1.19-1.09 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm = 137.0, 133.9, 133.0, 131.1, 128.9, 128.5, 128.1, 126.3, 124.2, 122.7, 118.5, 58.1, 43.3, 34.0, 27.7, 25.1; 27.4, 25.2, 25.1, 21.2.

HR-MS (ESI+): *m/z* calculated for $[C_{20}H_{23}N_4]^+$ = 319.1917; found: 319.1933.

***13-((2-Ethoxy-2-oxoethyl) amino)-5,6-dihydropyrazino[2',1':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54s):**



54s, 61%

Physical state : White solid

Yield : 61%

Mp : 212-214 ˚C

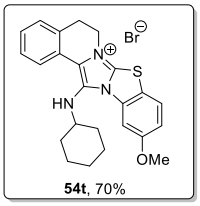
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3744, 3733, 3611, 3395, 3162, 2977, 2378, 2322, 2211, 2154, 2130, 1992, 1735, 1679, 1640, 1587, 1530, 1471, 1394, 1298, 1201, 1114, 1025, 931, 856, 770, 652, 605, 575.

^{1}H NMR (400 MHz, $CDCl_3$): δ ppm = 9.7 (d, J = 1.5 Hz, 1H), 8.97 (dd, J = 4.6 Hz, 1H), 8.56 (d, J = 4.4 Hz, 1H), 8.24-8.22 (m, 1H), 7.56-7.53 (m, 3H), 6.51-6.47 (m, 1H), 4.74 (t, J = 6.6 Hz, 2H), 4.05-3.98 (m, 4H), 3.31 (t, J = 6.8 Hz, 2H), 1.1 (t, J = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ ppm = 171.1, 137.5, 133.9, 133, 130.6, 128.9, 127.9, 127.5, 122.8, 122.6, 118.0, 60.7, 47.6, 41.7, 26.7, 13.8.

HR-MS (ESI+):*m/z* calculated for $[C_{18}H_{19}N_4O_2]^+$ = 323.1503; found: 323.1512.

***14-(Cyclohexylamino)-11-methoxy-5,6-dihydrobenzo[4',5']thiazolo[2',3':2,3]imidazo[5,1-a]isoquinolin-7-ium bromide* (54t):**



54t, 70%

Physical state : White solid

Yield : 70%

Mp : 292-293 ˚C

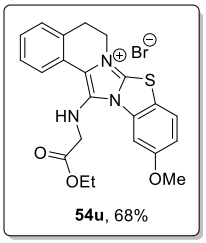
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3745, 3730, 3670, 3611, 3395, 3181, 2926, 2852, 2370, 2322, 2168, 2128, 1992, 1840, 1786, 1678, 1641, 1535, 1484, 1451, 1301, 1246, 1164, 1028, 870, 818, 706, 667, 590, 574.

^{1}H NMR (DMSO D_6, 400 MHz): δ ppm = 8.28-8.22 (m, 2H), 8.01 (d, J = 2.4, 1H), 7.48-7.37 (m, 4H), 5.67 (d, J = 5.9 Hz, 1H), 4.45 (t, J = 6.4 Hz, 2H), 3.89 (s, 3H), 3.25 (t, J = 6.6 Hz, 2H), 2.97-2.94 (m, 1H), 1.94 (d, J = 11.7 Hz, 2H), 1.66 (br. s, 2H), 1.53 (m, 1H), 1.33-1.28 (m, 2H), 1.11 (br. s, 3H).

^{13}C NMR (100 MHz, DMSO D_6): δ ppm = 157.9, 141.6, 132.1, 130.4, 129.0, 128.8, 127.4, 125.7, 125.1, 124.3, 124.0, 116.5, 115.4, 109.6, 57.2, 56.0, 43.6, 32.8, 27.2, 25.2, 24.5.

HR-MS (ESI+): *m/z* calculated for $[C_{24}H_{26}BrN_3OS]^+$ = 404.1791; found: 404.1787.

***14((2Ethoxy2oxoethyl)amino)11 methoxy5,6 dihydrobenzo[4',5']thiazolo[2',3':2,3]imidazo [5,1-a]isoquinolin-7-ium bromide* (54u):**



54u, 68%

Physical state : White solid

Yield : 68%

Mp : 242-244 ˚C

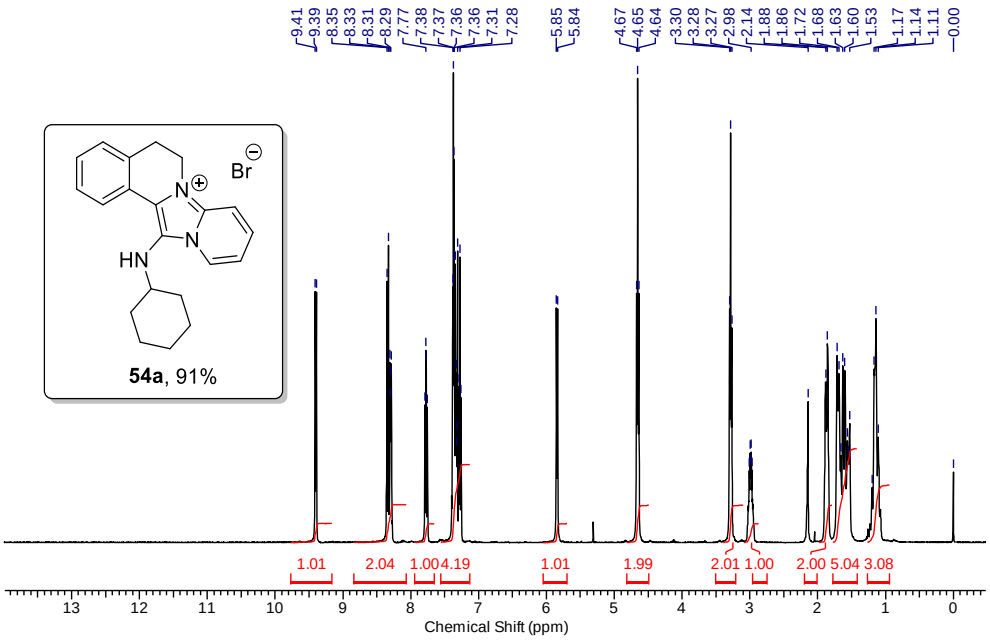
IR (MIR-ATR, 4000–600 cm^{-1}): υ_{max} = 3190, 2976, 2935, 1740, 1604, 1539, 1479, 1464, 1377, 1300, 1273, 1236, 1200, 1111, 1092, 1045, 1019, 813, 769, 726, 691, 596.

^{1}H NMR (DMSO D_6, 400 MHz): δ ppm = 8.47 (d, J = 8.8 Hz, 1H), 8.11 (d, J = 7.3 Hz, 1H), 7.98 (d, J = 2 Hz, 1H), 7.49-7.40 (m, 3H), 7.33 (dd, J = 9, 2.2 Hz, 1H), 6.16 (s, 1H), 4.45 (t, J = 6.4 Hz, 2H), 4.04-3.97 (m, 4H), 3.89 (s, 3H), 3.23 (t, J = 6.1 Hz, 2H), 1.06 (t, J = 7.1 Hz, 3H).

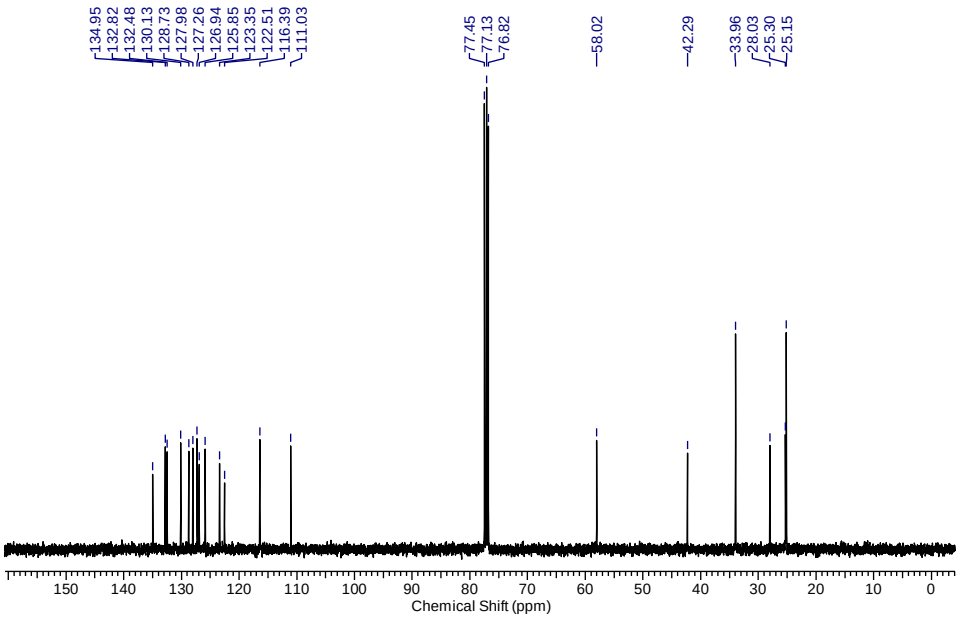
^{13}C NMR (100 MHz, DMSO D_6): δ ppm = 171.1, 130.7, 130.0, 129.6, 128.7, 125.1, 115.6, 61.0, 56.0, 14.0.

HR-MS (ESI+): *m/z* calculated for $[C_{22}H_{22}BrN_3O_3S]^+$ = 408.1376; found: 408.1381.

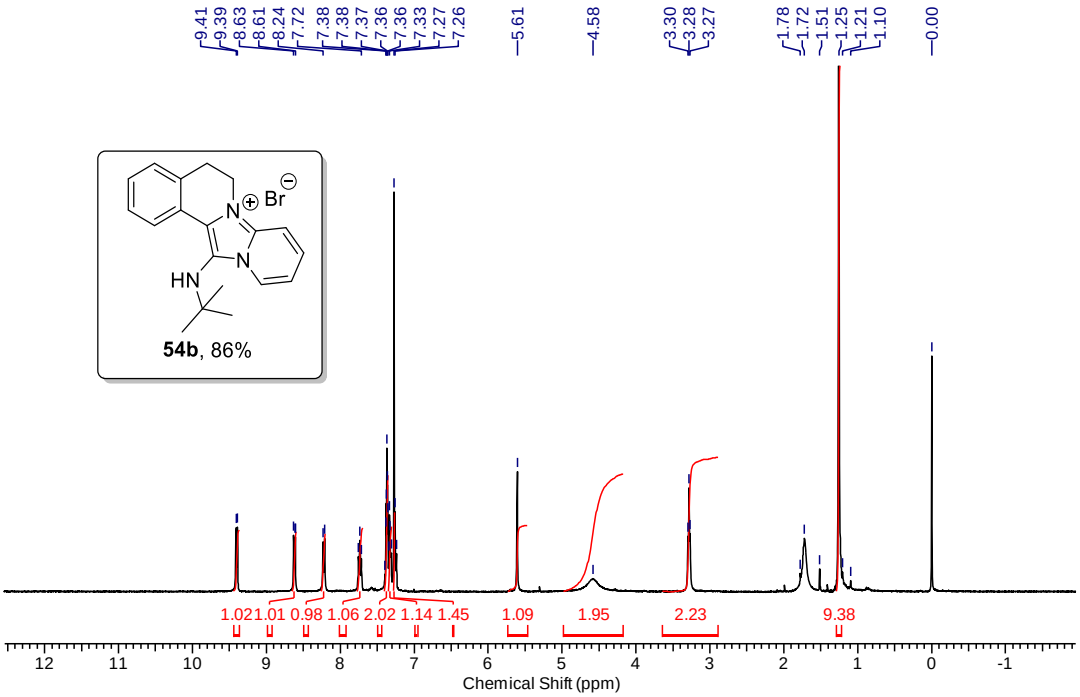
Representative ^{1}H, ^{13}C NMR spectral Copies



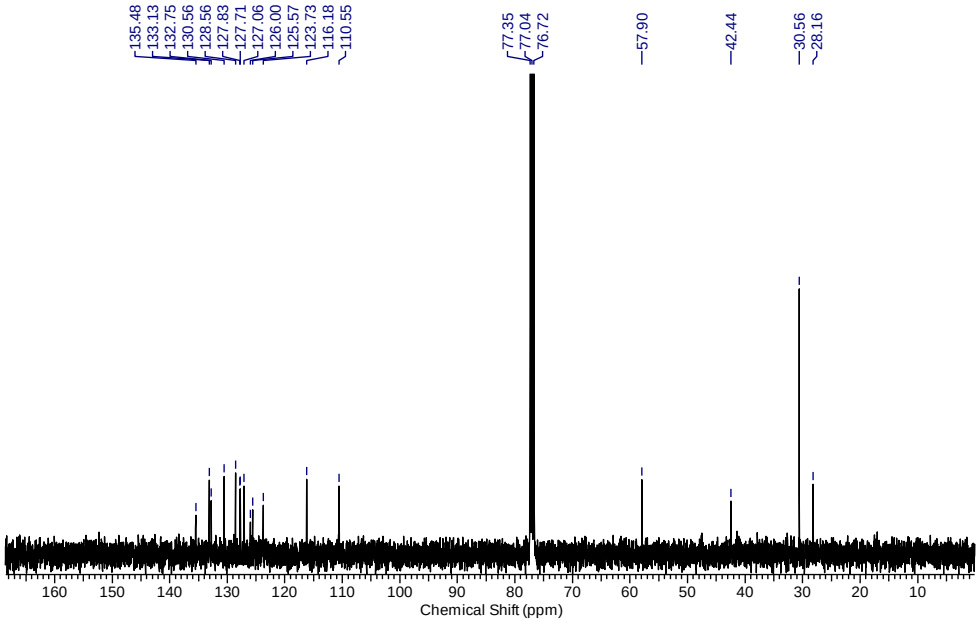
^{1}H NMR (400 MHz) spectrum of compound **54a** in $CDCl_3$



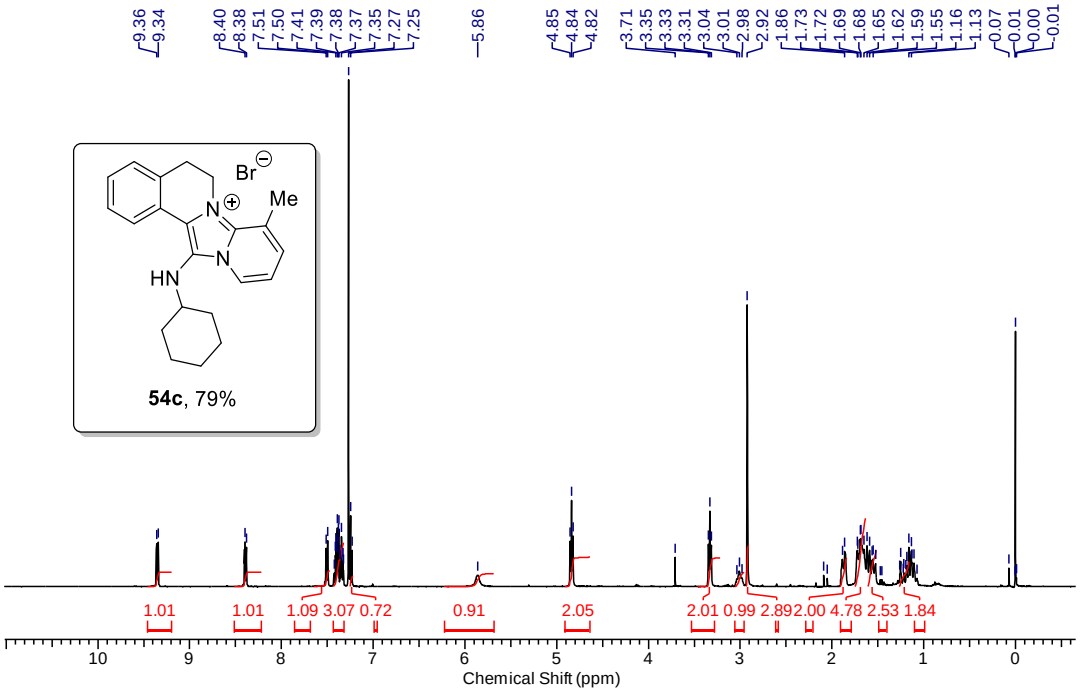
^{13}C NMR (100 MHz) spectrum of compound **54a** in $CDCl_3$



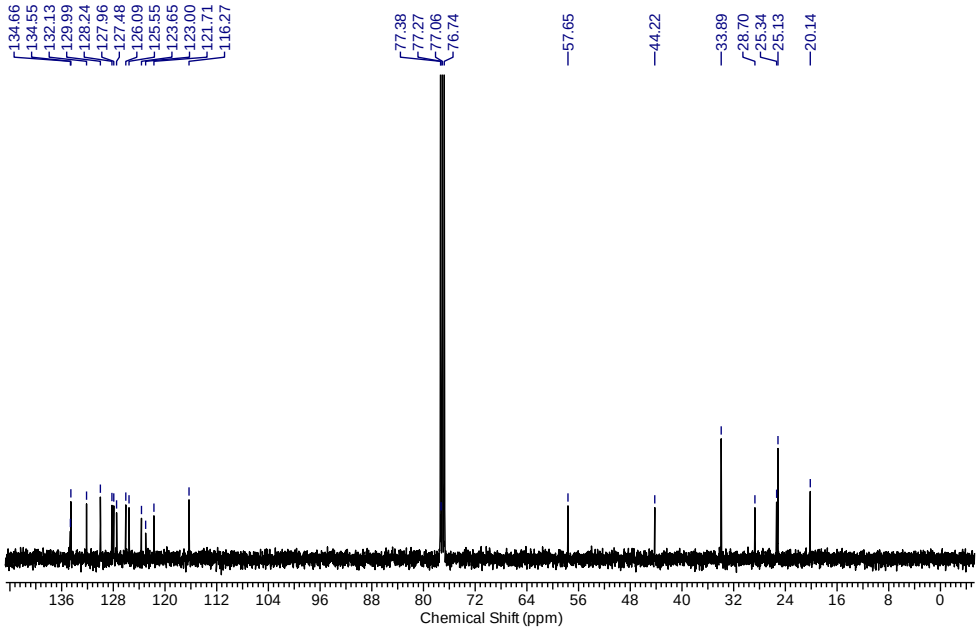
^{1}H NMR (400 MHz) spectrum of compound **54b** in $CDCl_3$



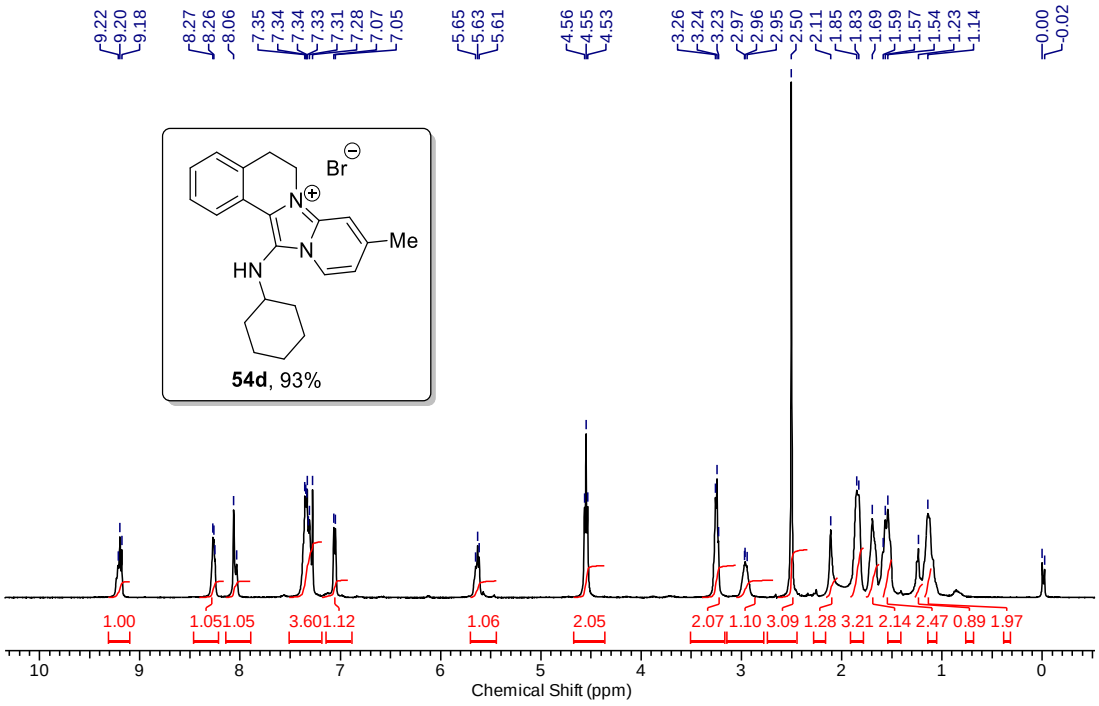
^{13}C NMR (100 MHz) spectrum of compound **54b** in $CDCl_3$



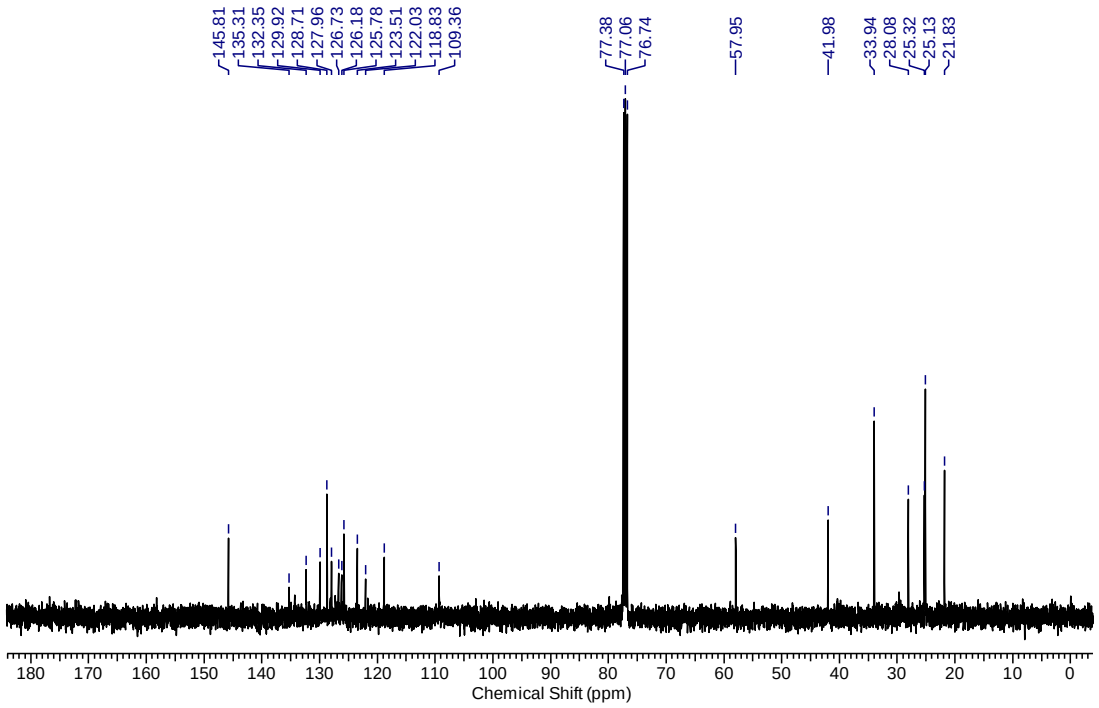
^{1}H NMR (400 MHz) spectrum of compound **54c** in $CDCl_3$



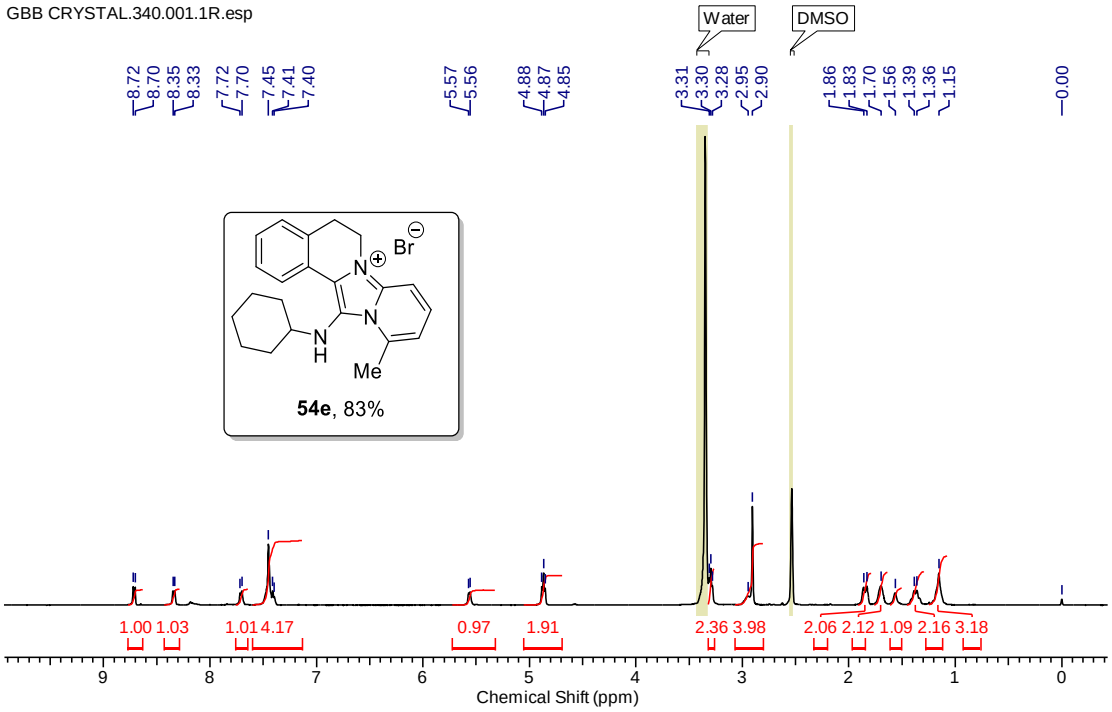
^{13}C NMR (100 MHz) spectrum of compound **54c** in $CDCl_3$



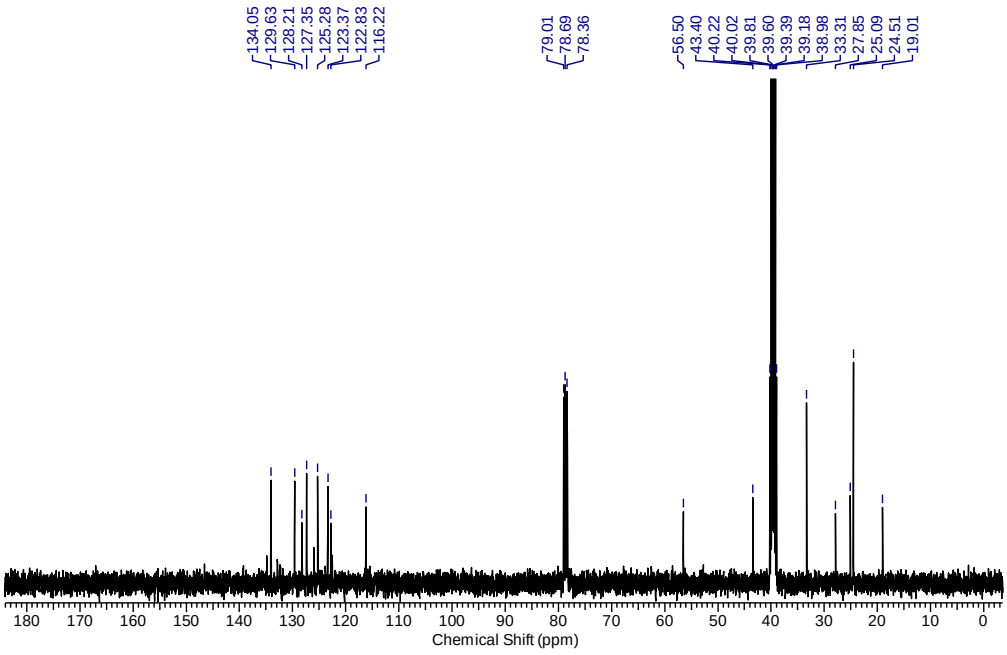
^{1}H NMR (400 MHz) spectrum of compound **54d** in $CDCl_3$



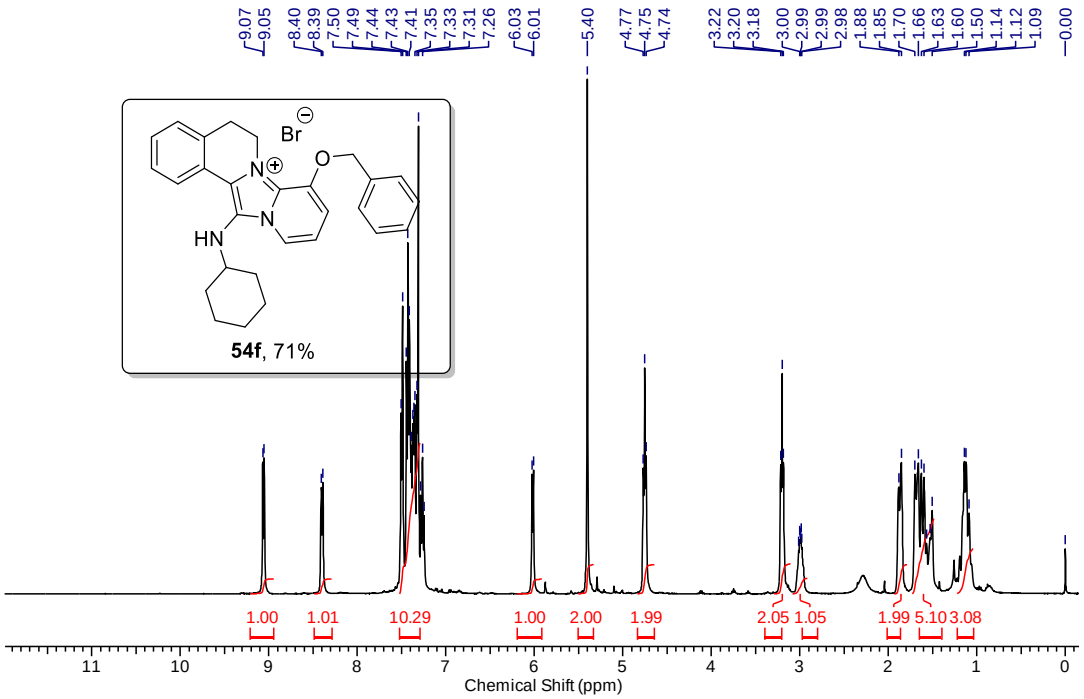
^{13}C NMR (100 MHz) spectrum of compound **54d** in $CDCl_3$



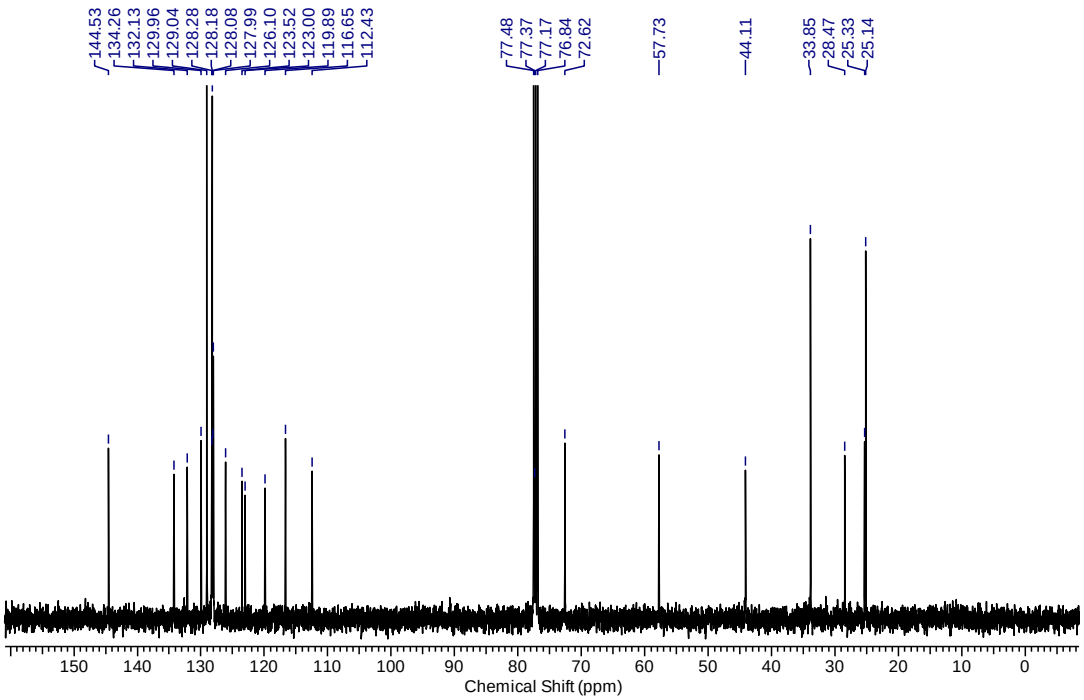
^{1}H NMR (400 MHz) spectrum of compound **54e** in $CDCl_3$



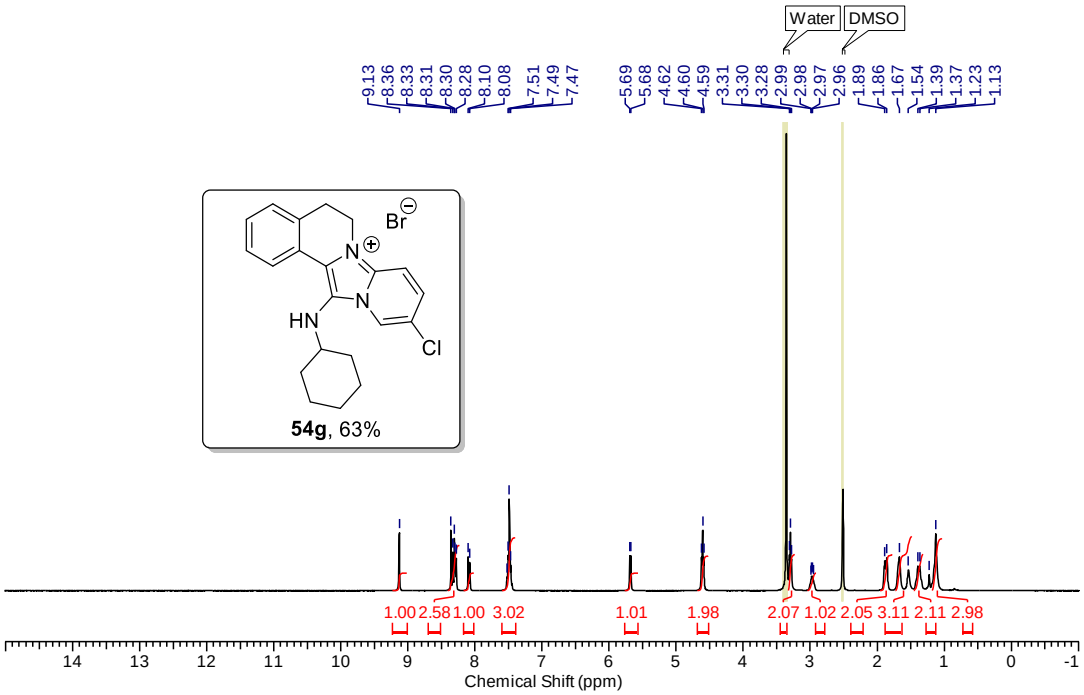
^{13}C NMR (100 MHz) spectrum of compound **54e** in $CDCl_3$



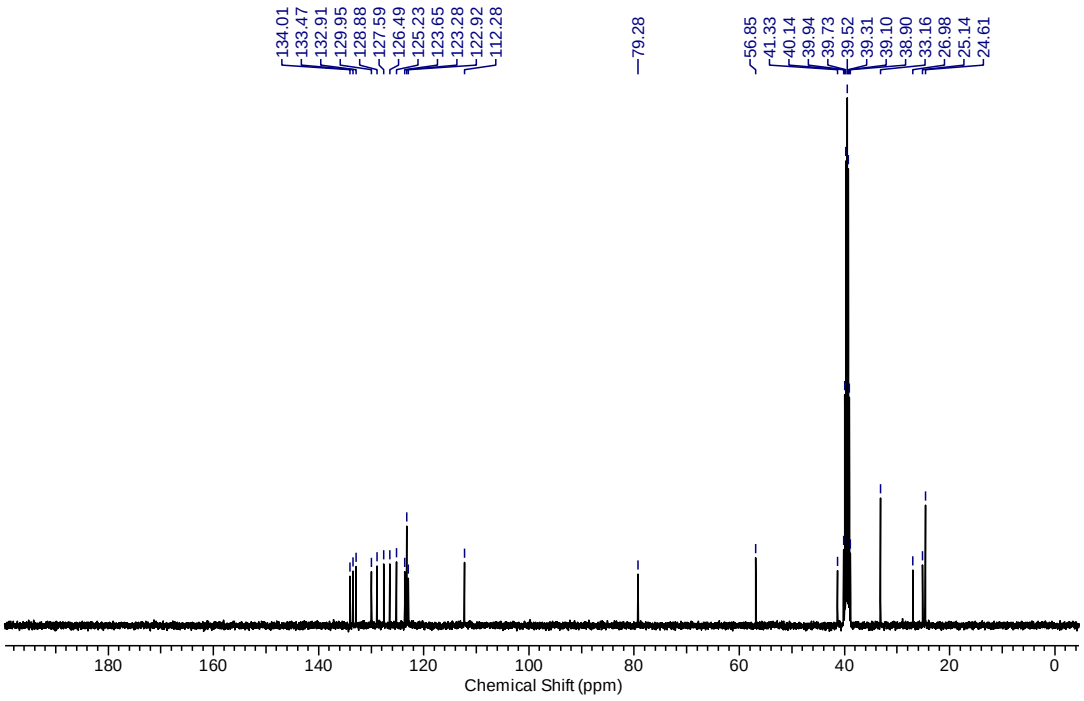
^{1}H NMR (400 MHz) spectrum of compound **54f** in $CDCl_3$



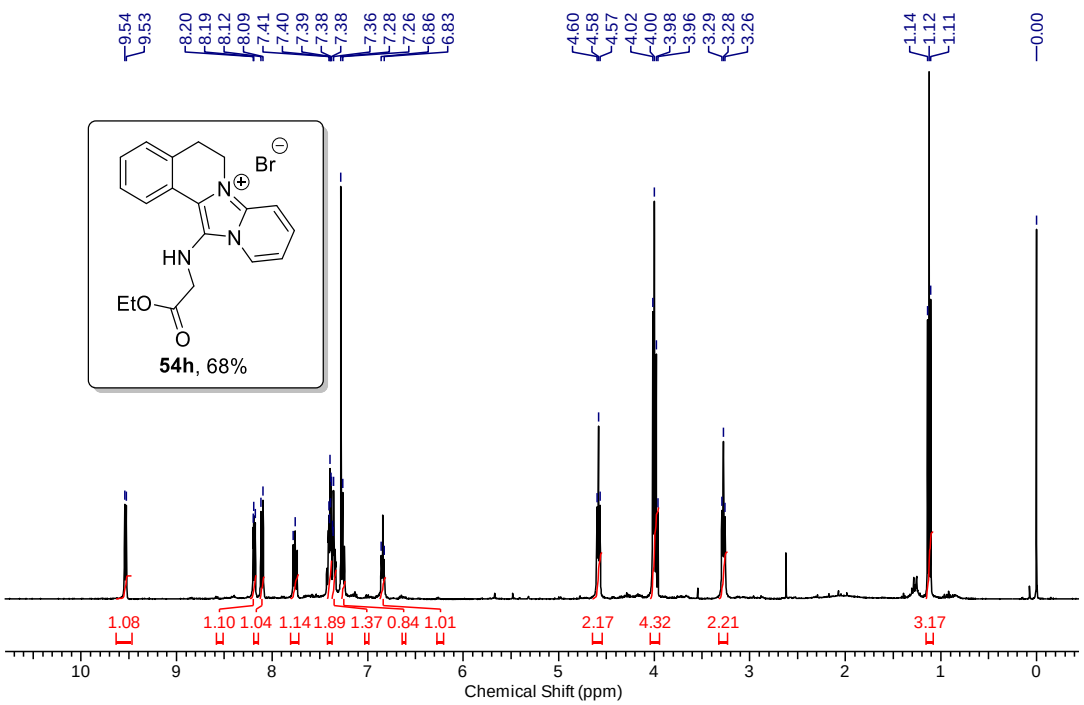
^{13}C NMR (100 MHz) spectrum of compound **54f** in $CDCl_3$



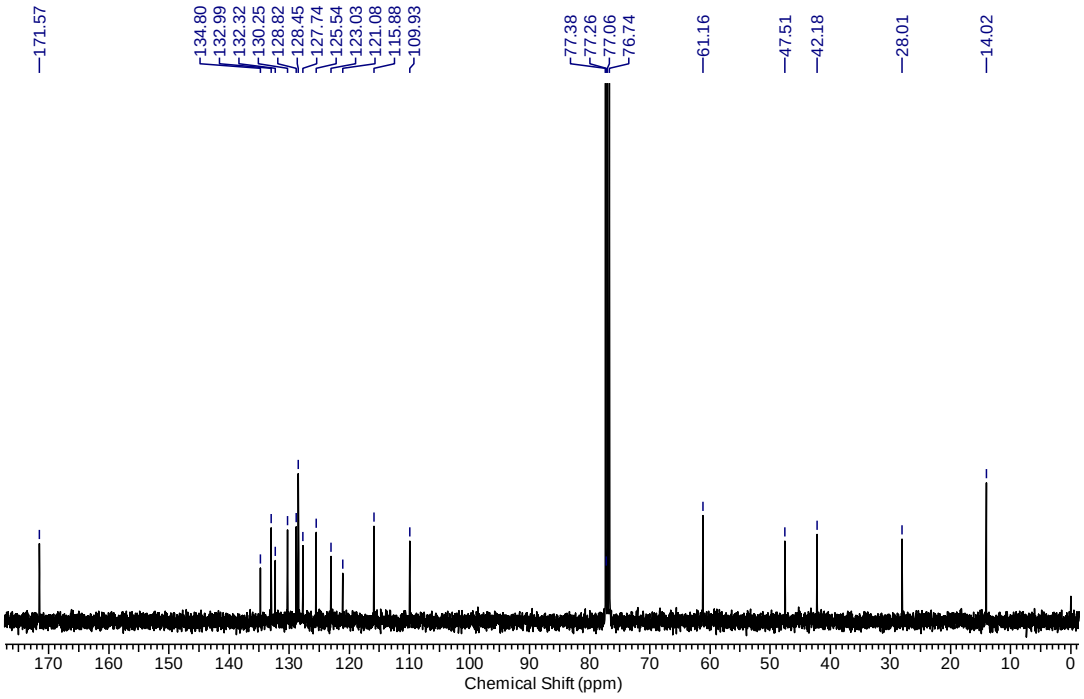
^{1}H NMR (400 MHz) spectrum of compound **54g** in DMSO-d_6



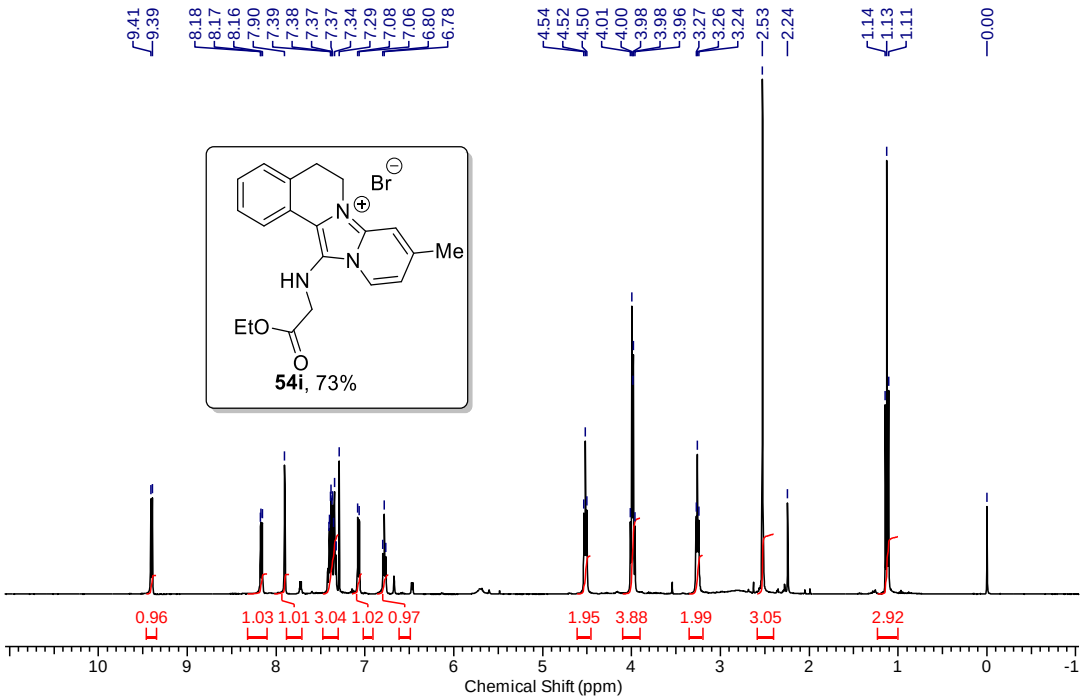
^{13}C NMR (100 MHz) spectrum of compound **54g** in DMSO-d_6



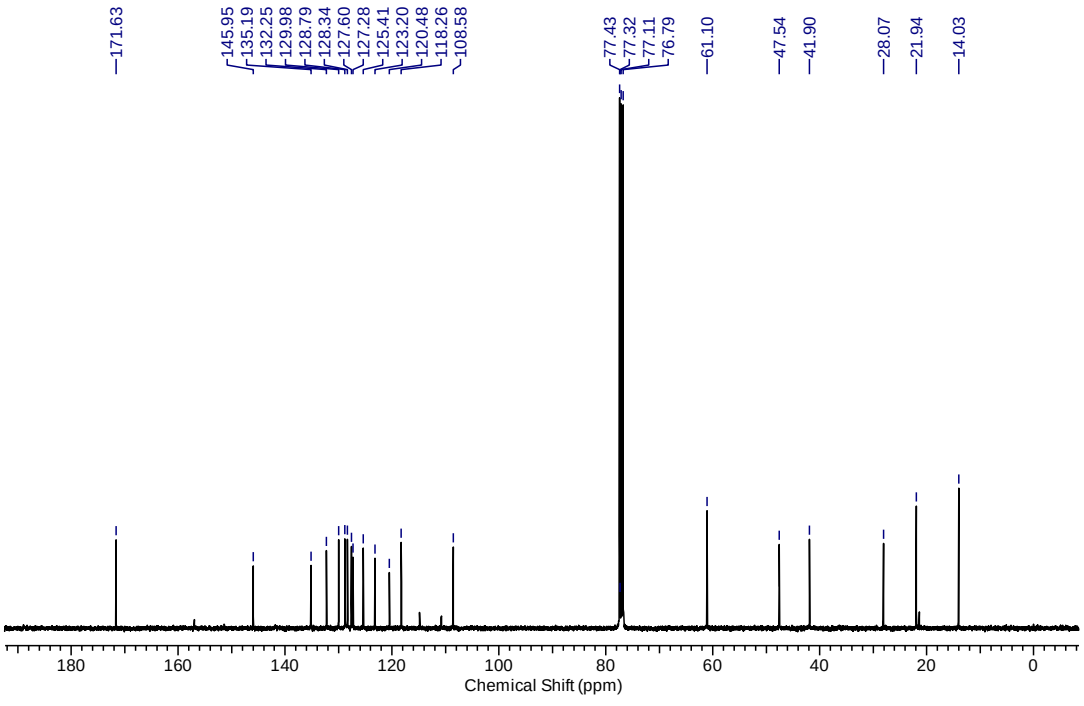
^{1}H NMR (400 MHz) spectrum of compound **54h** in $CDCl_3$



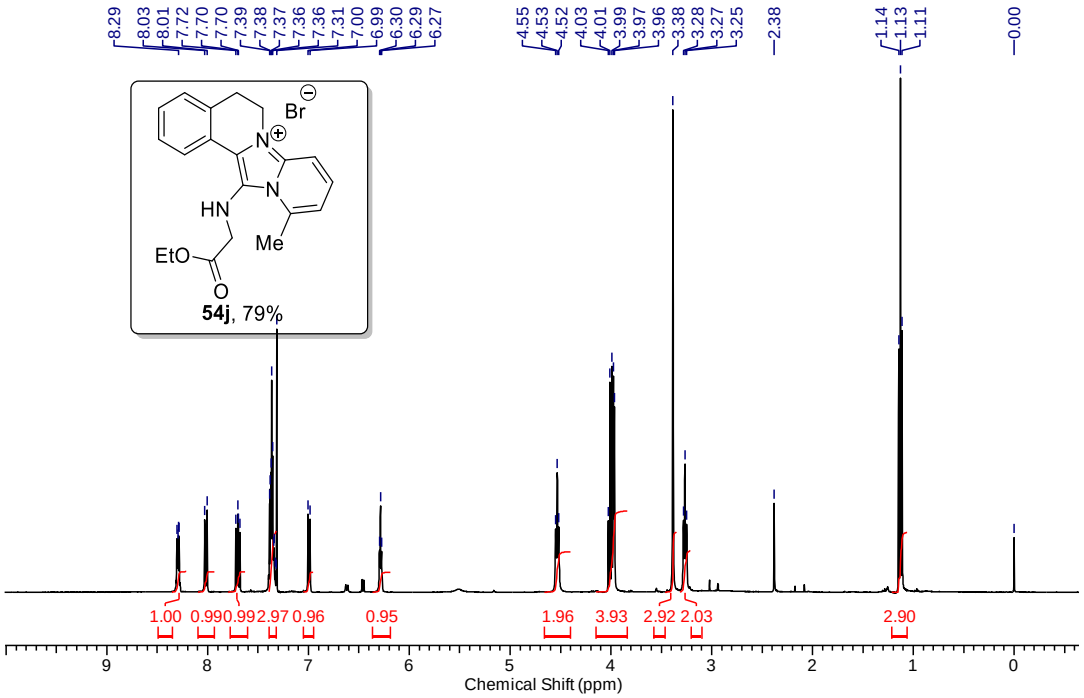
^{13}C NMR (100 MHz) spectrum of compound **54h** in $CDCl_3$



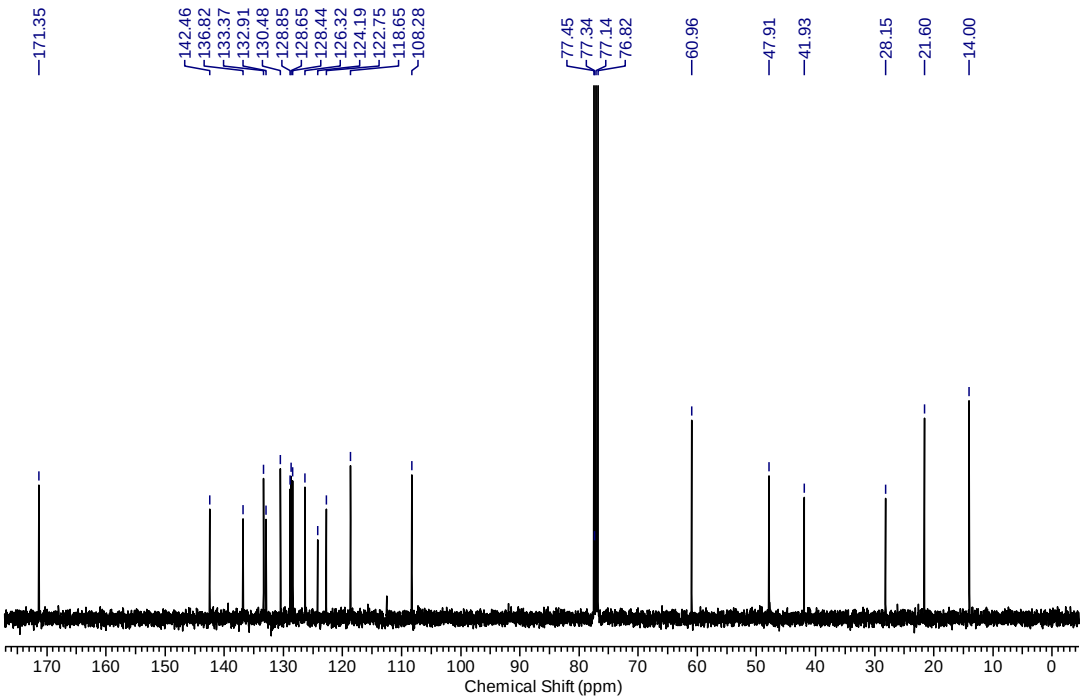
^{1}H NMR (400 MHz) spectrum of compound **54i** in $CDCl_3$



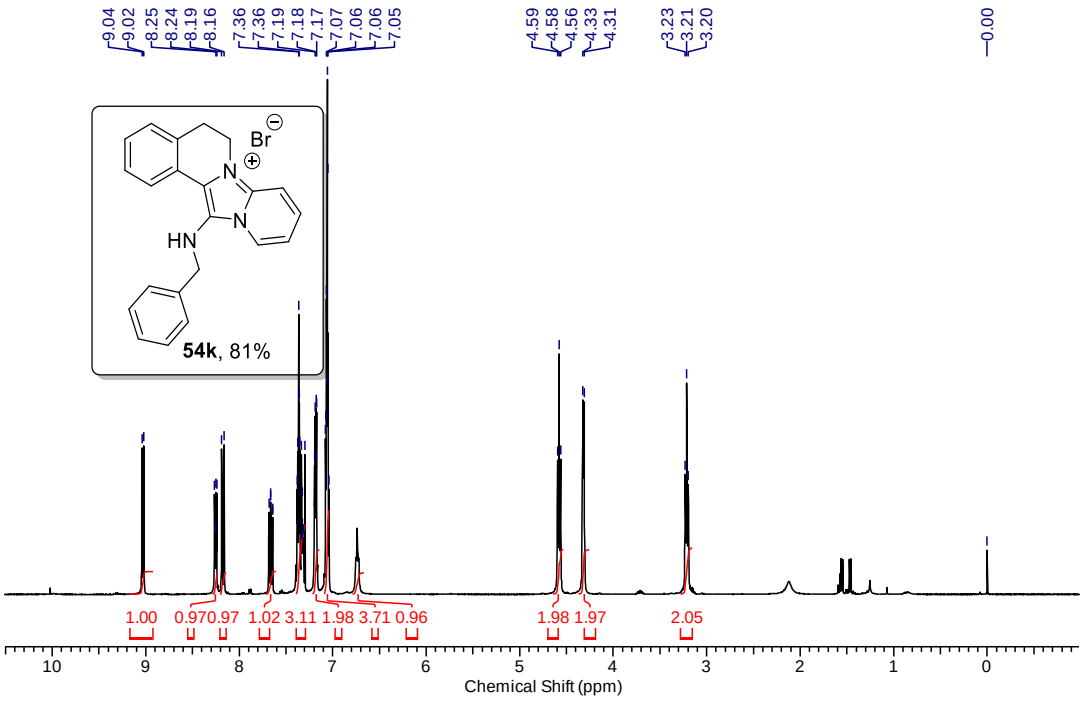
^{13}C NMR (100 MHz) spectrum of compound **54i** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of compound **54j** in $CDCl_3$



^{13}C NMR (100 MHz) spectrum of compound **54j** in $CDCl_3$



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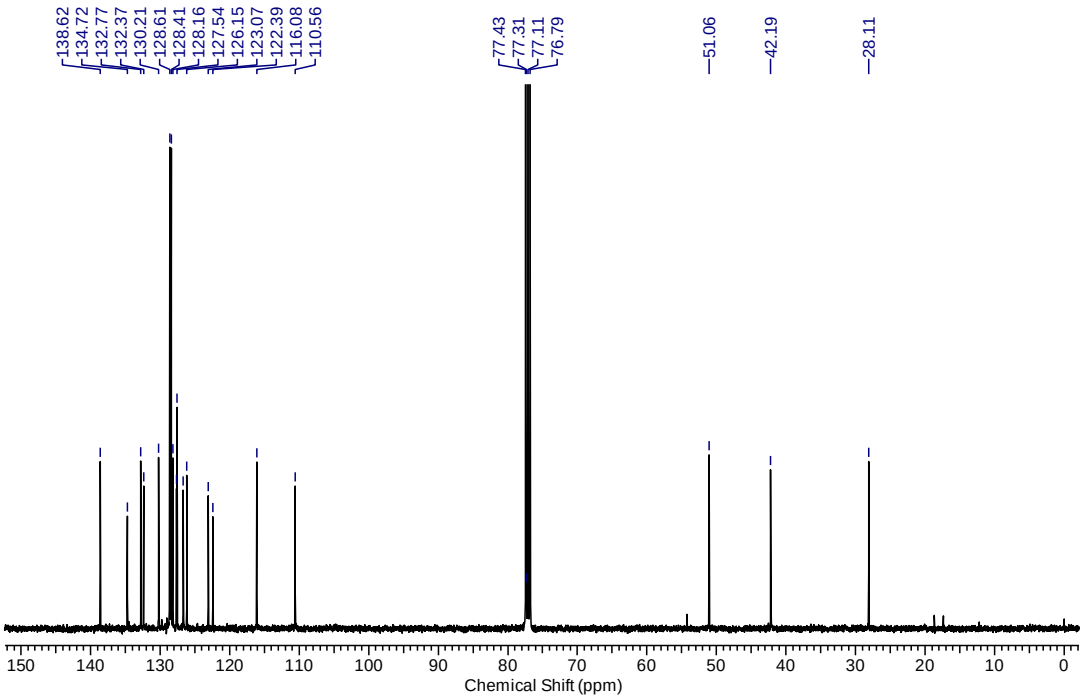

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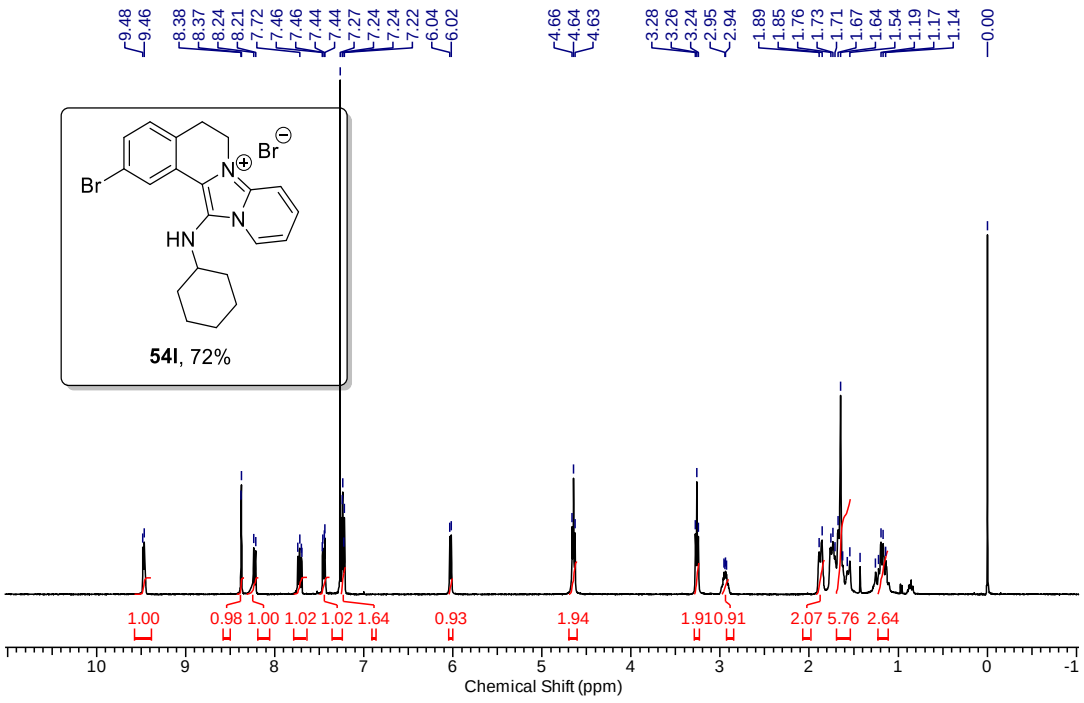

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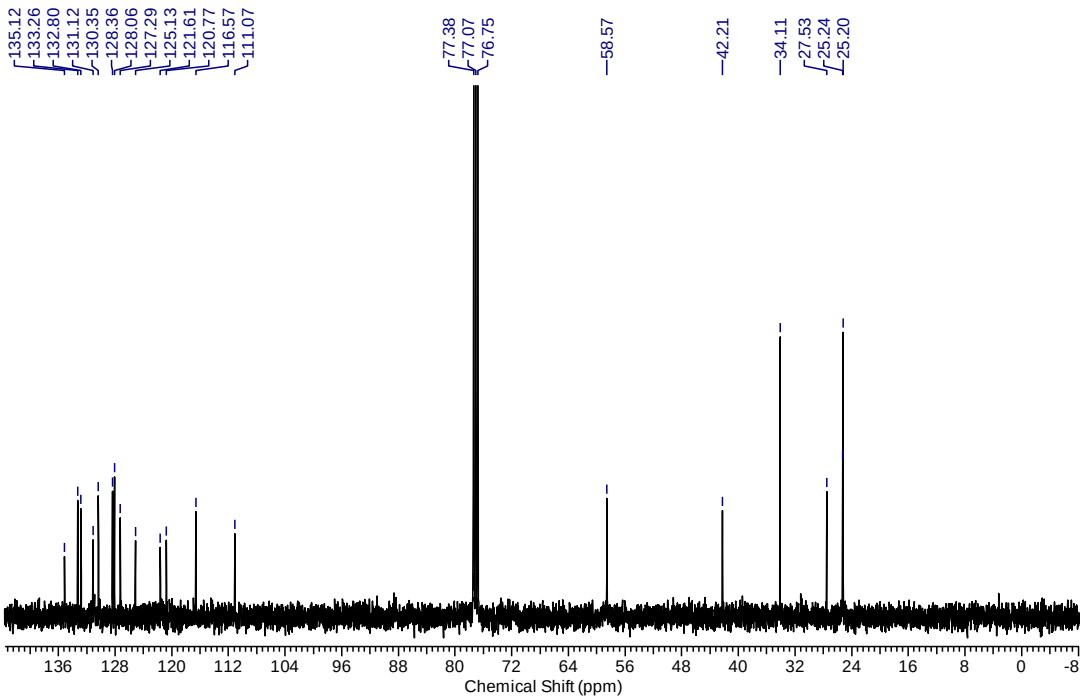

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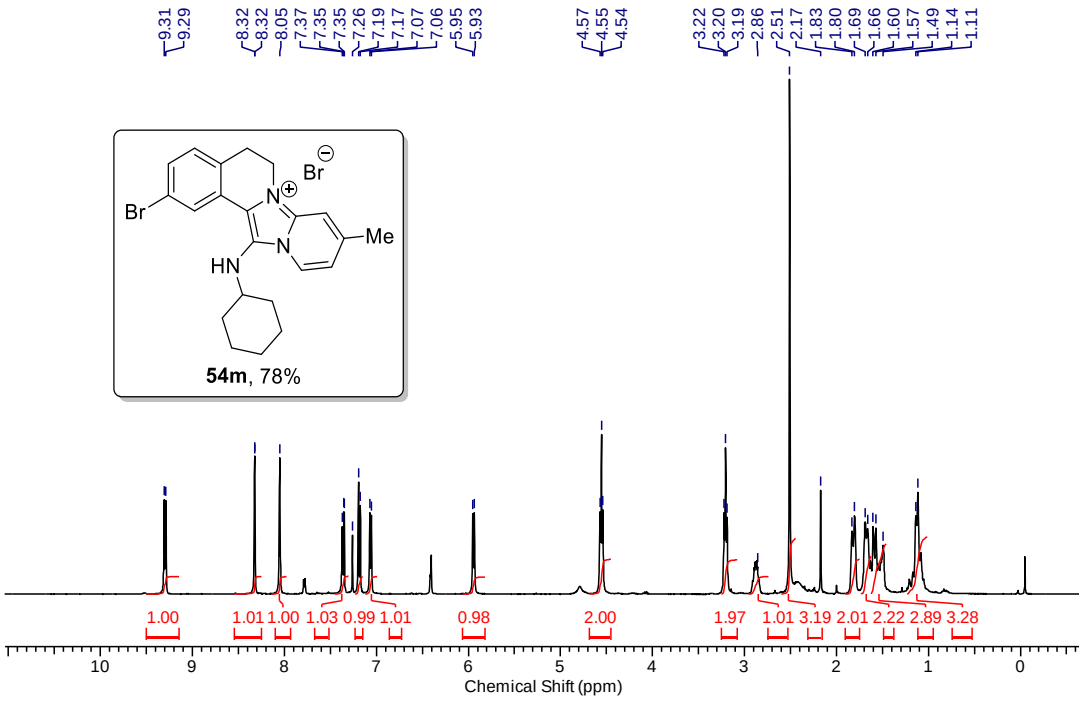

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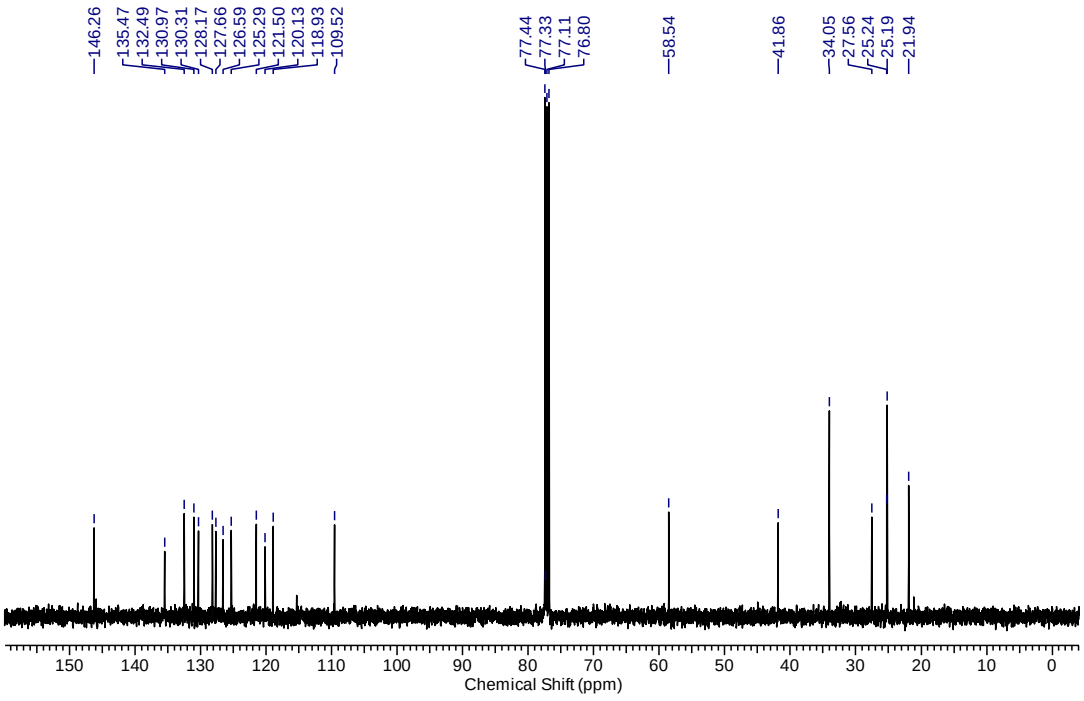

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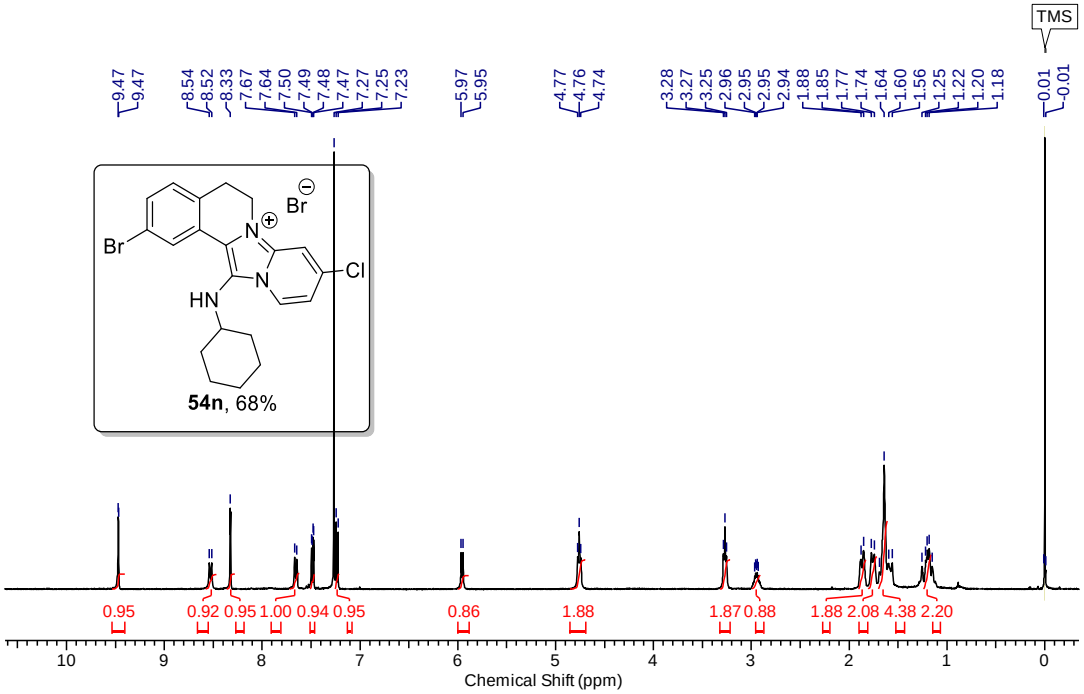

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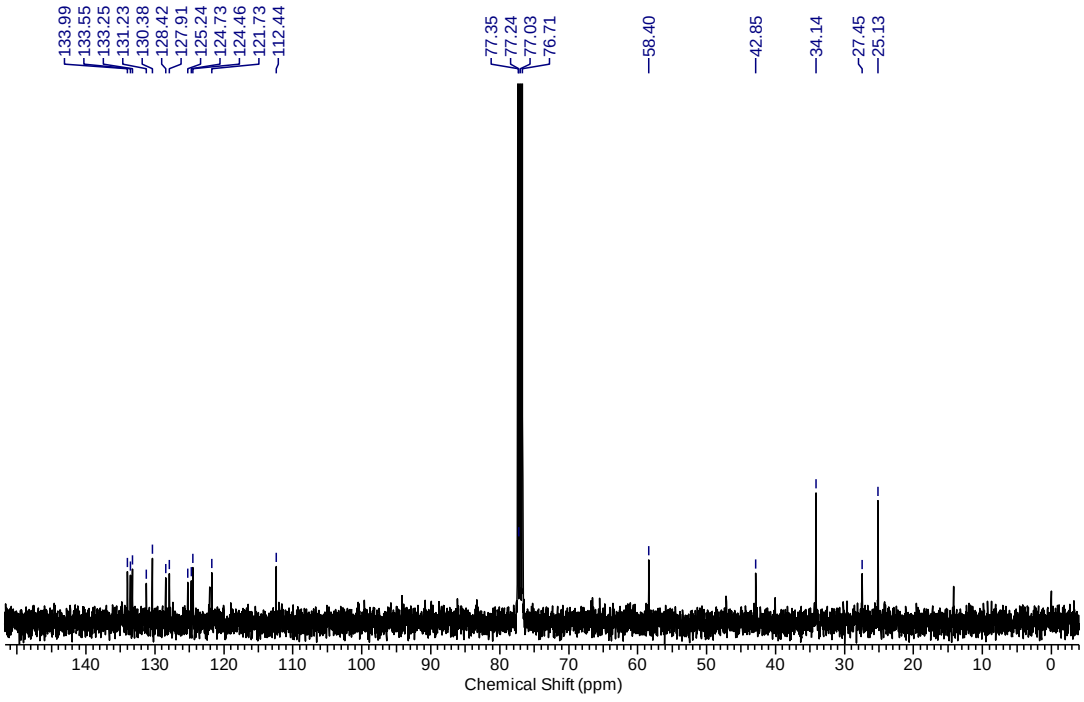

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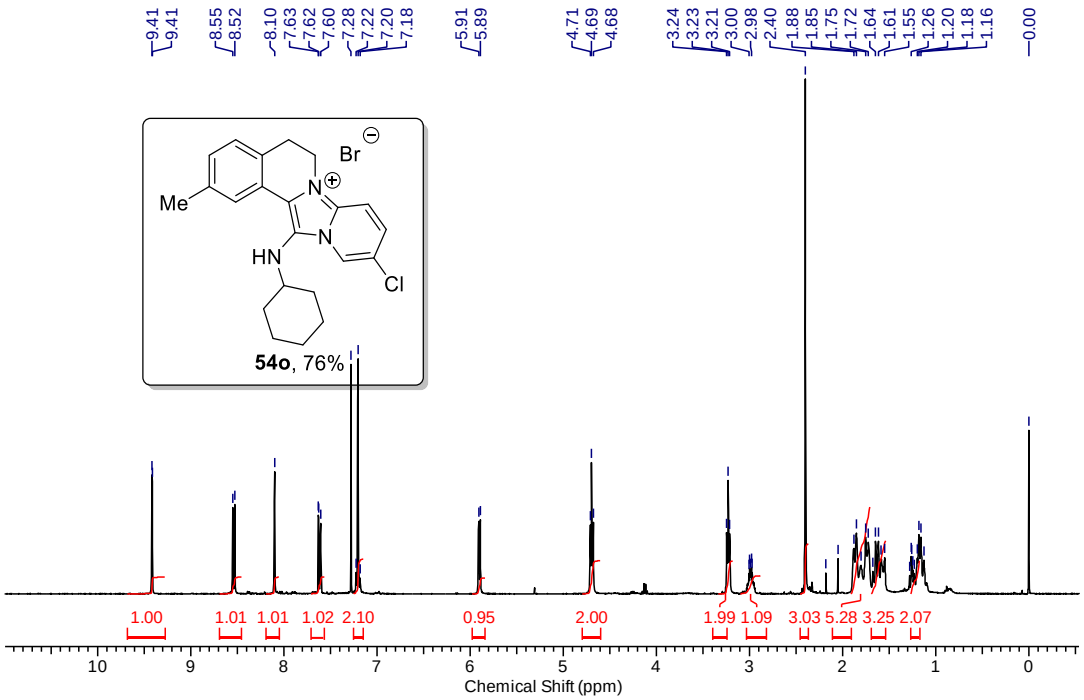

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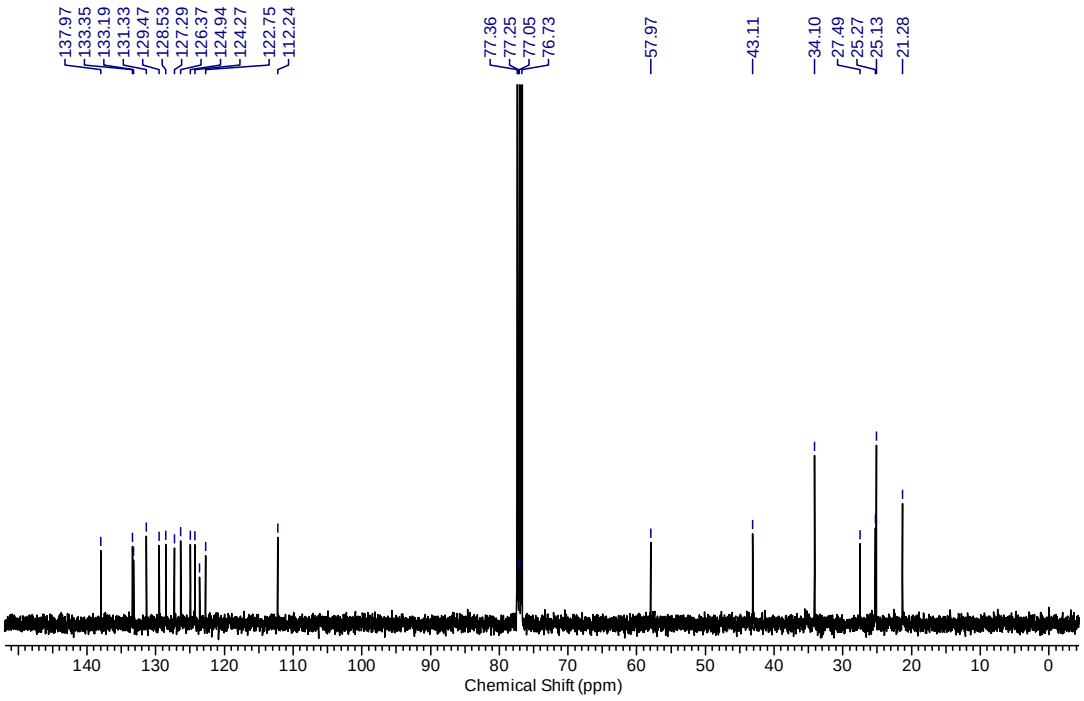

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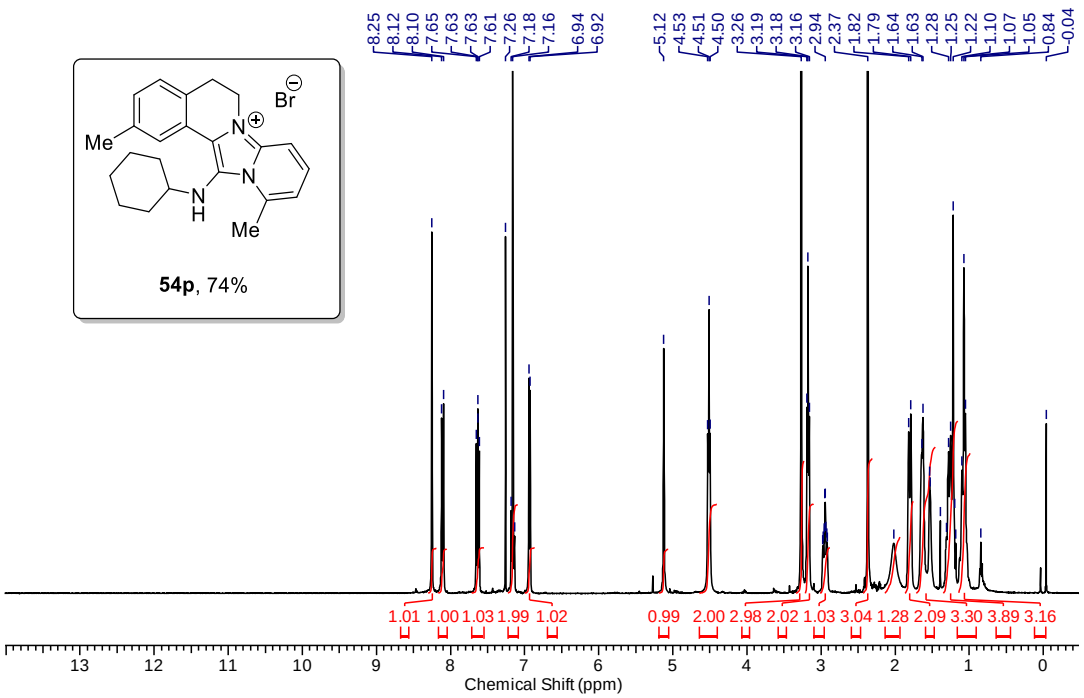

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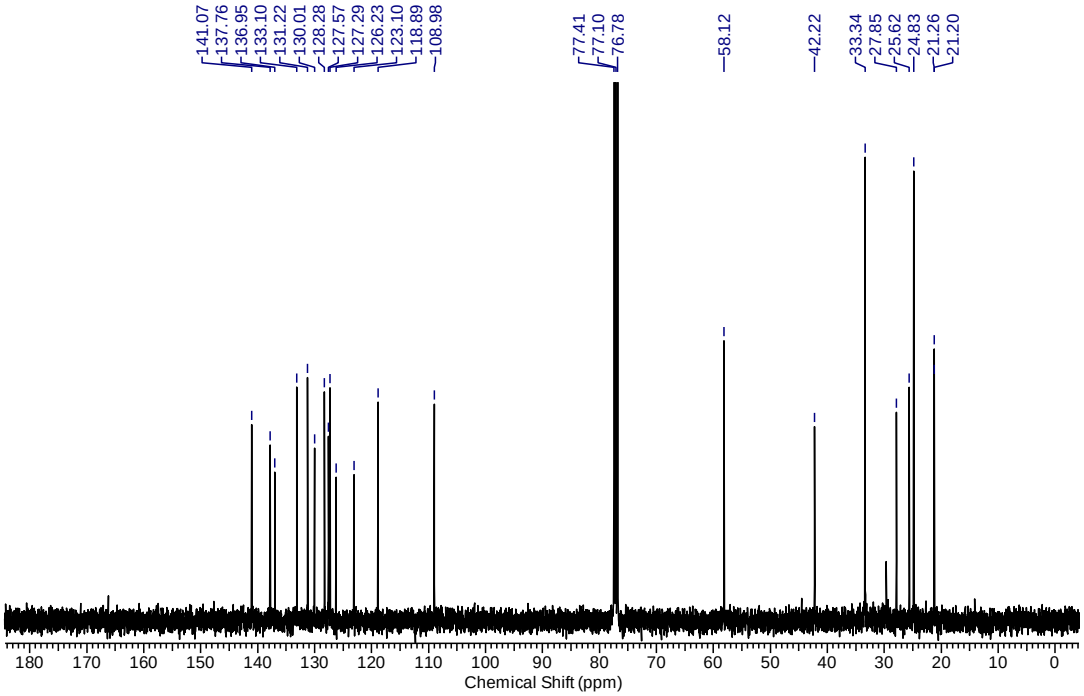

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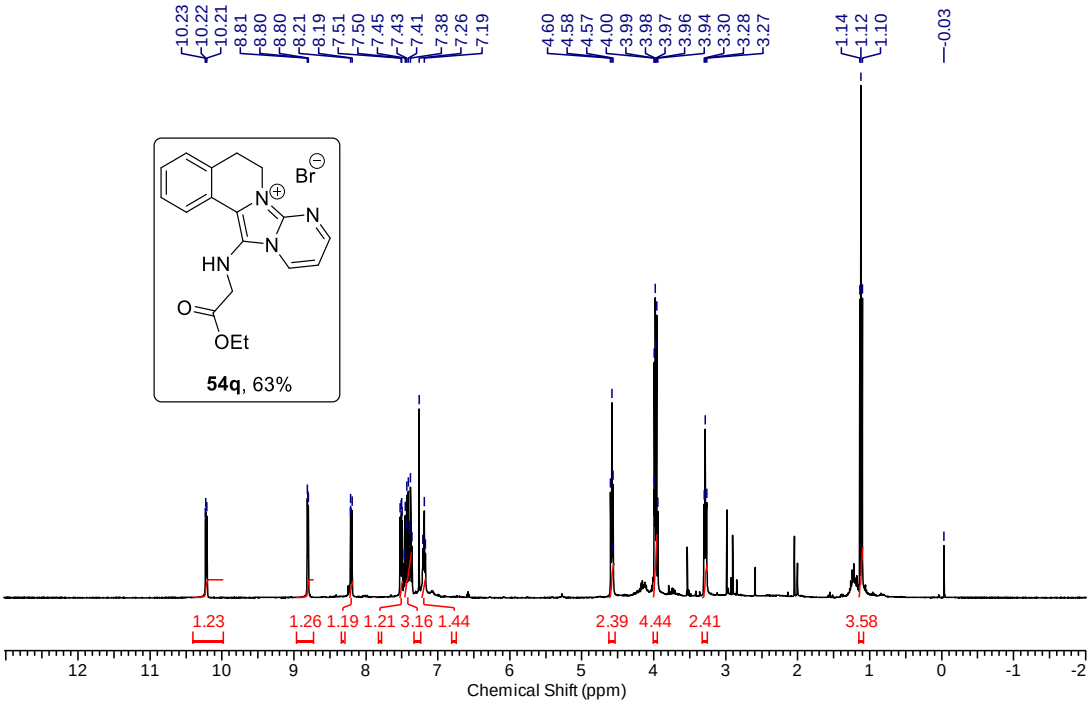

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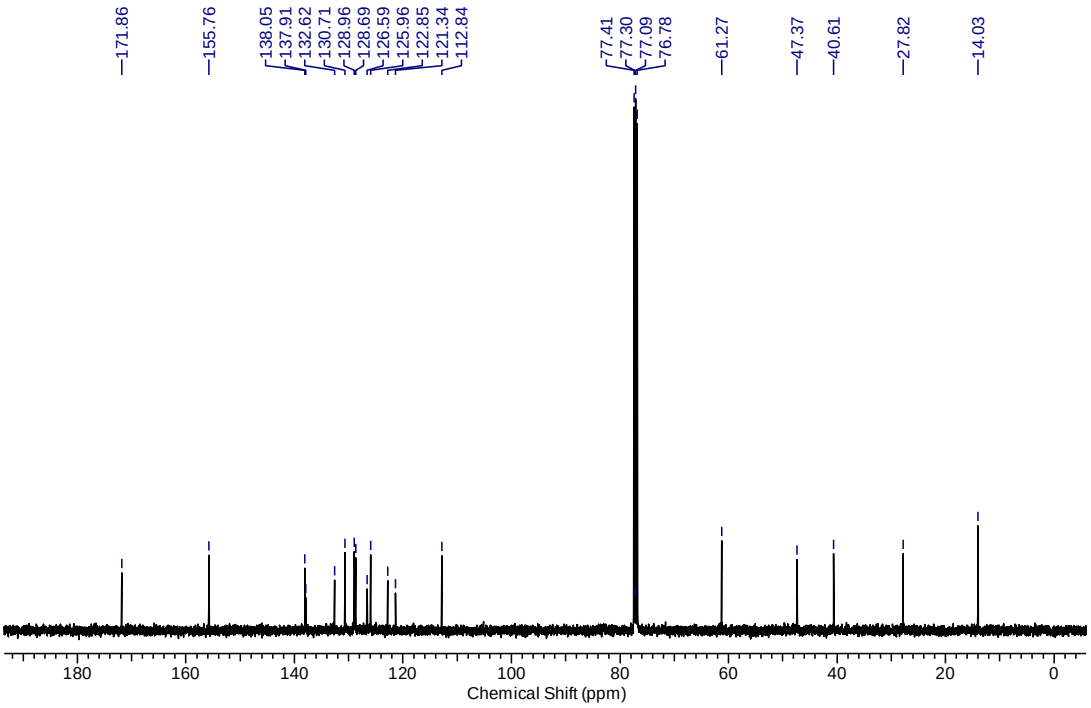

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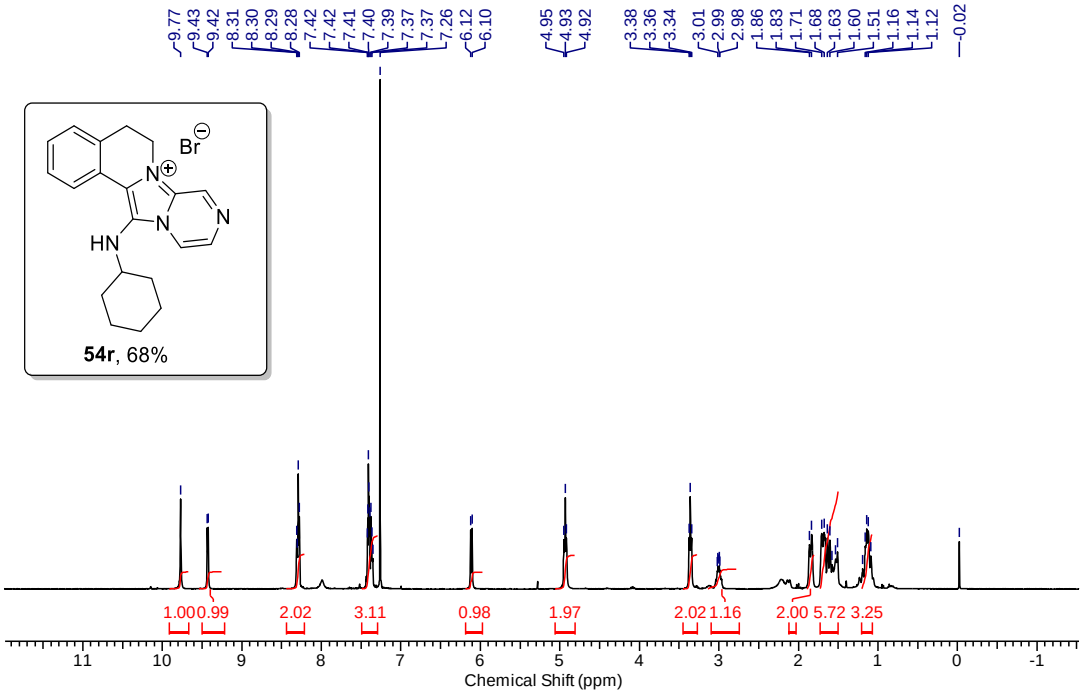
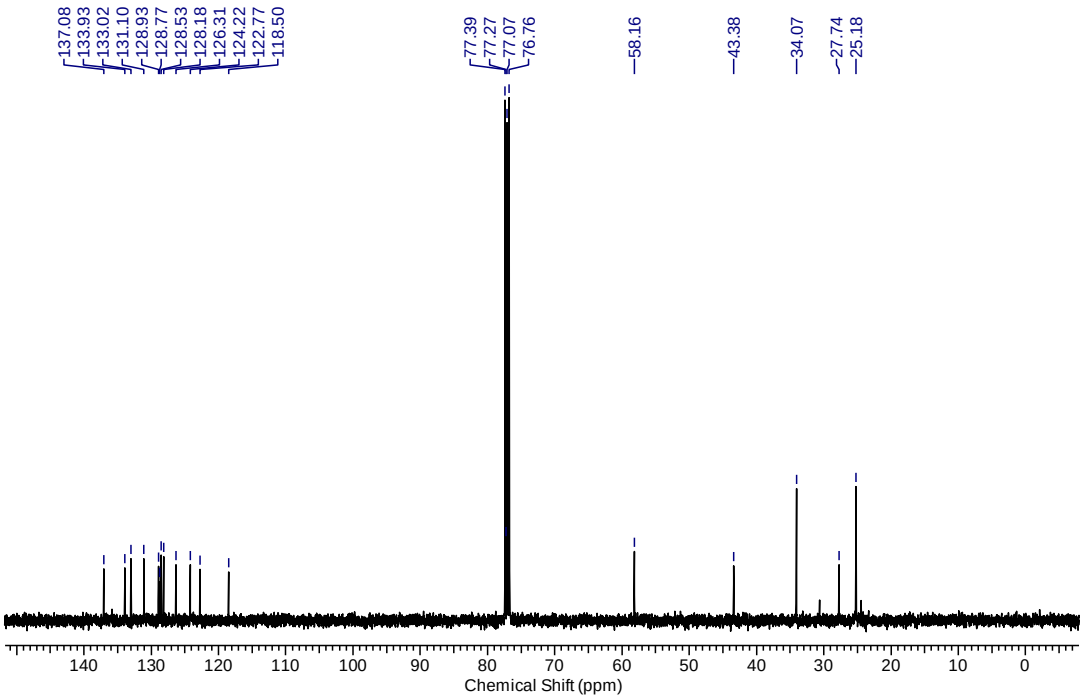


^{1}H NMR (400 MHz) spectrum of compound **54r** in $CDCl_3$



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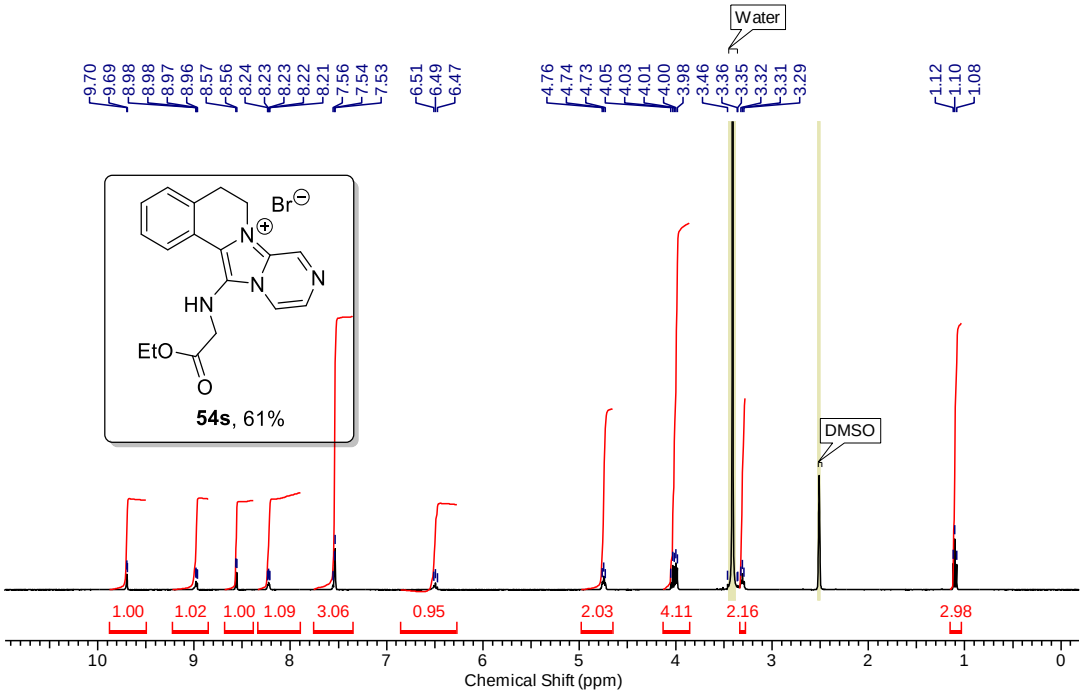
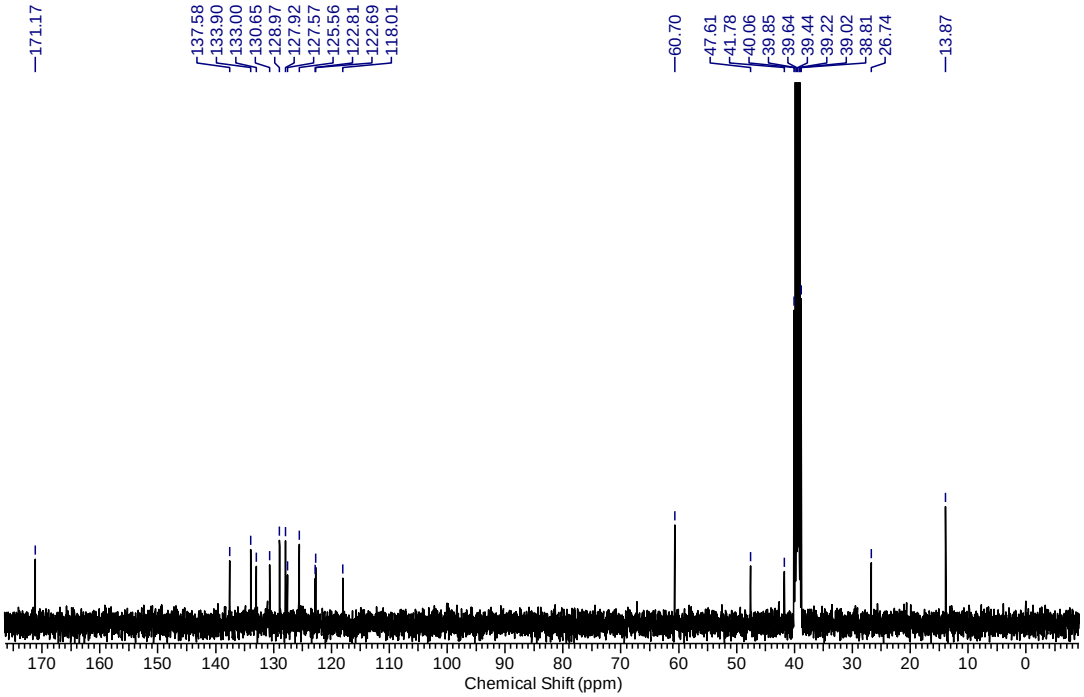


^{1}H NMR (400 MHz) spectrum of compound **54s** in DMSO-d_6



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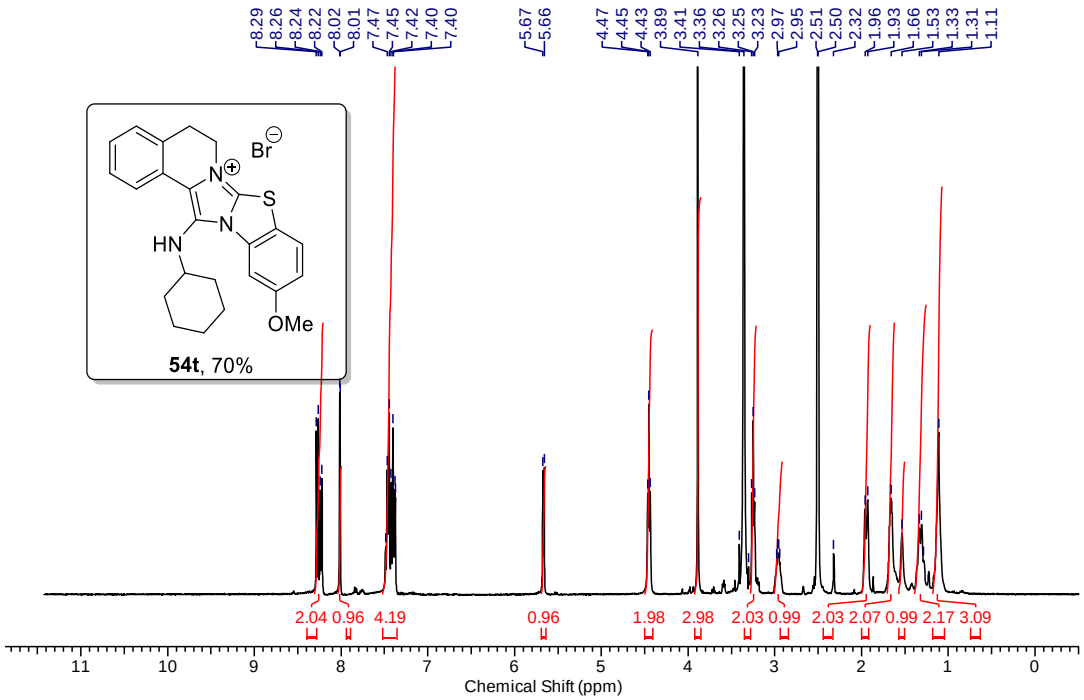
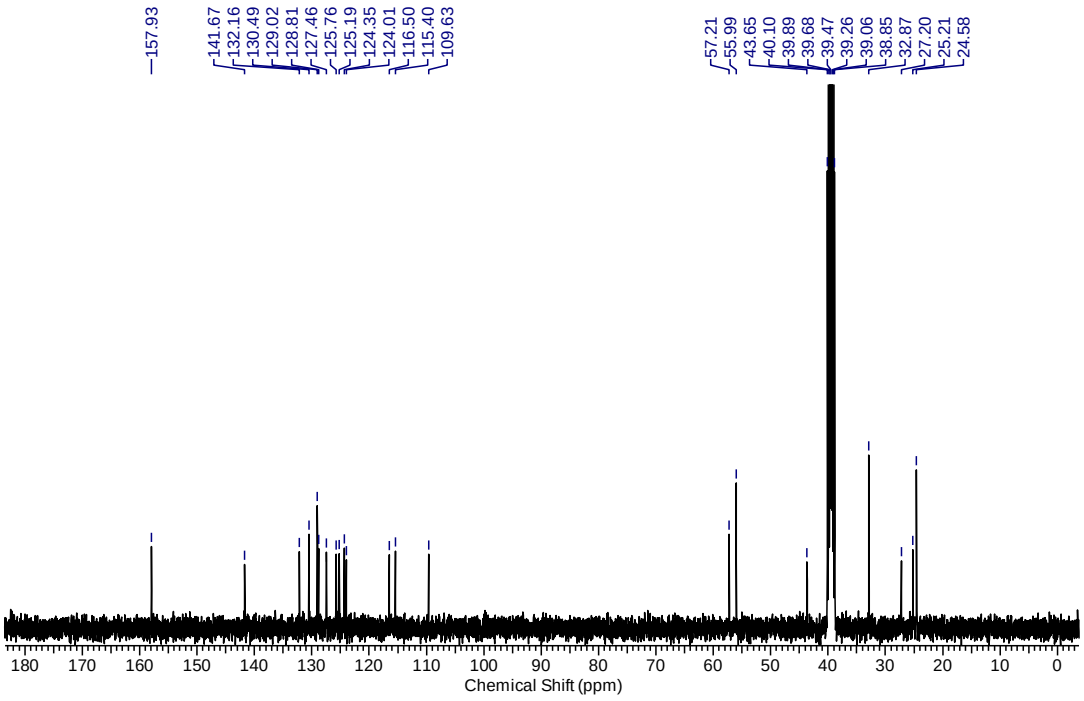


^{1}H NMR (400 MHz) spectrum of compound **54t** in $CDCl_3$



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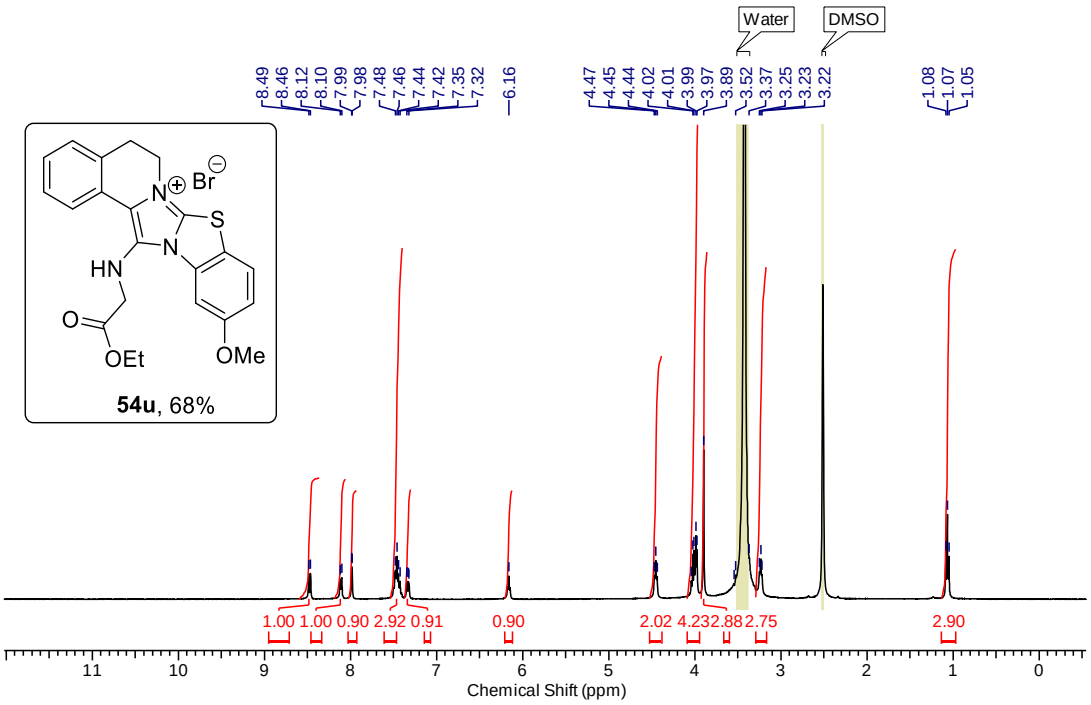
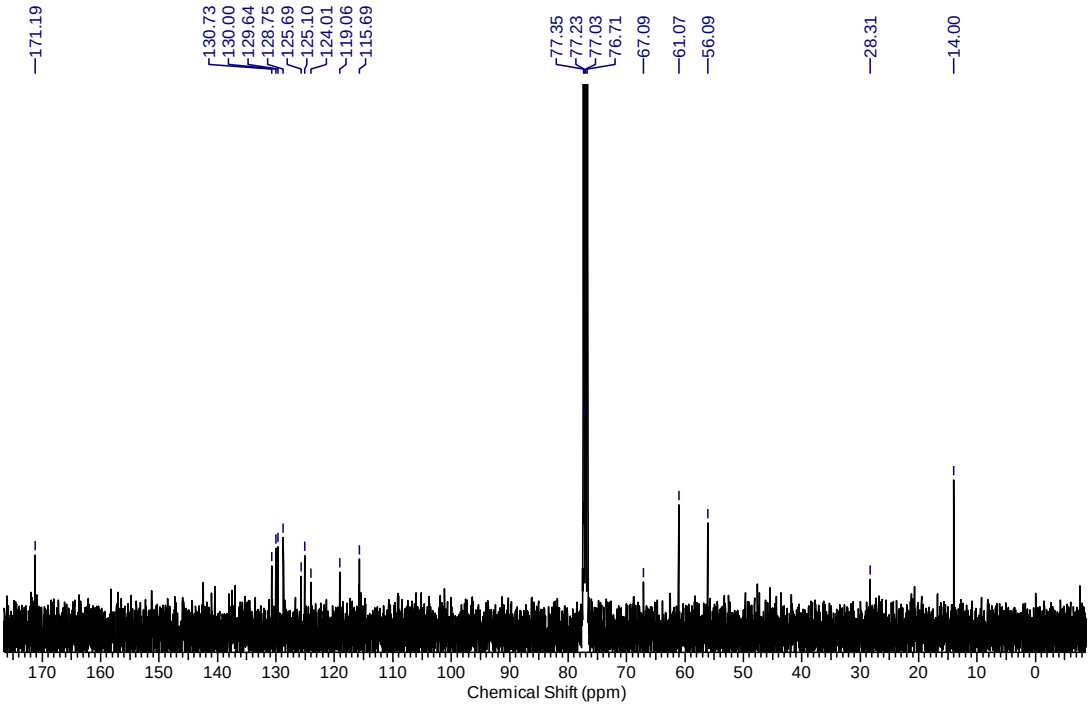


^{1}H NMR (400 MHz) spectrum of compound **54u** in DMSO-d_6



^{13}C NMR (100 MHz) spectrum of compound **54u** in DMSO-d_6

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CHAPTER 3

An Exocyclic N-Acyliminium ion (NAI) Cyclization: Access to Fully Substituted Oxazoles and Furocoumarins

3.1 Introduction

3.1.1. Reactivity of N-Acyliminium ions (NAI's)

As an important subfamily of the iminium ion classes, NAIs are more reactive than other types of iminium ions because of the electron-withdrawing nature of the carbonyl group (Figure 1).

Among all the cyclization methods in organic synthetic chemistry, NAI based cyclization methods have emerged as a powerful versatile approach[1] for accessing structurally diverse scaffolds of broad biological interest.

Here the beauty of NAI was, it can able to trap with various nucleophiles such as very strong to very weak. Most methods involve trapping the intermediate NAI with heteroatom nucleophiles or π-type carbon nucleophiles, including aromatic and heteroaromatic rings, as well as double and triple bonds. The viability of the intramolecular cyclization depends on both strength and ability to form the NAI and the reactivity of the nucleophiles.

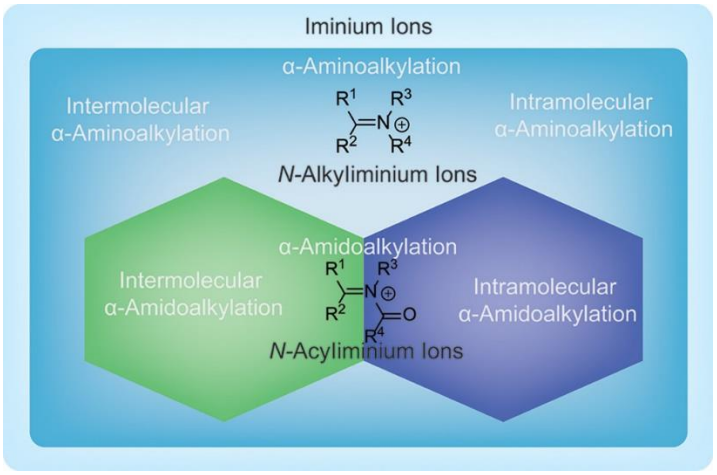


Figure 1: Classification of iminium ion chemistry

3.1.2. Types of N-Acyliminium ions

Chemists have developed N-acyl iminium ion based biomimetic approaches for the synthesis of various alkaloids inspired by nature's design principles.[2] Owing to their significant importance, chemists have been paid substantial attention to the development of a variety of NAI precursors and structurally related chemo types (Figure 2).

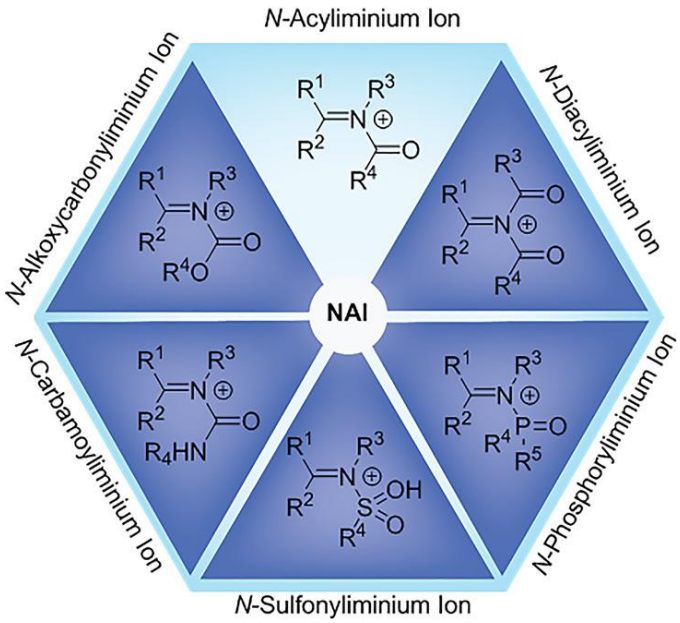


Figure 2. Structures of *N*-acyliminium ion (NAI) and structurally related chemotypes

Among them, pyrrolidine based NAI ion precursors[3] have obtained a dominant position for enabling powerful access to the generation of cyclic NAIs particularly endo-cyclic (Figure 3) by the treatment of Brønsted acid or Lewis acid, and which are mainly limited to intramolecular cyclization reactions.[4] However, the synthesis of these NAI precursors often required multistep syntheses.[3]

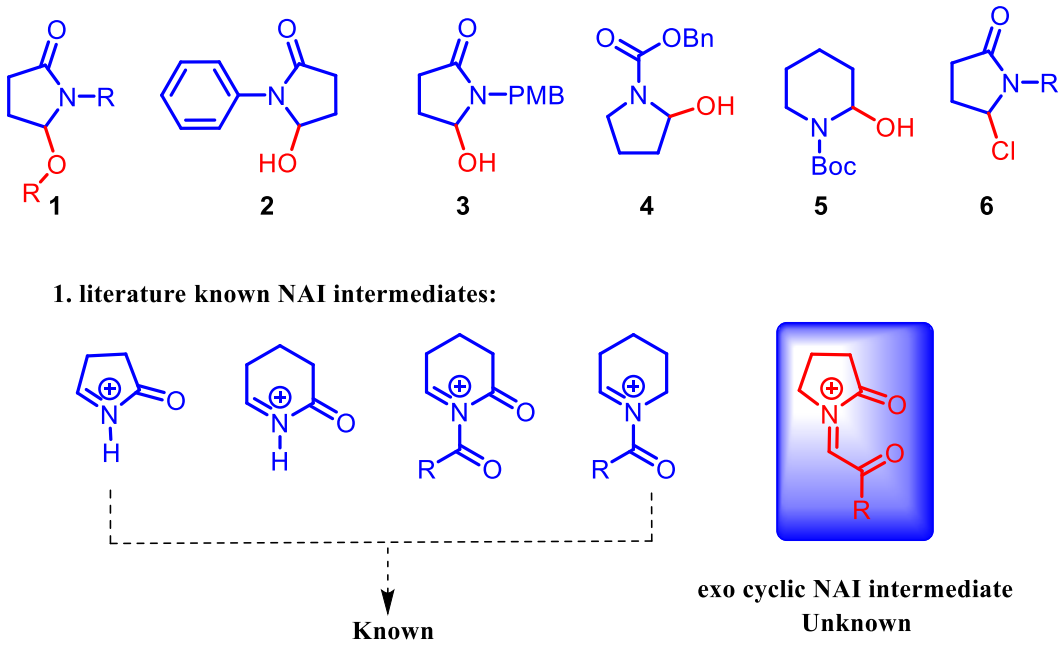


Figure 3. Literature known NAIs and our designed NAI

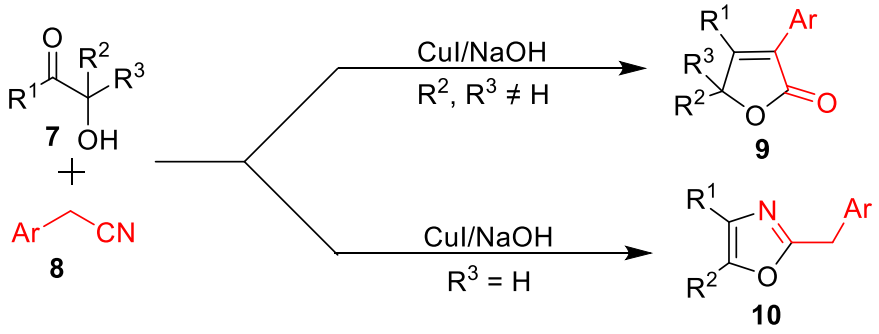
The development of a direct route to access NAI precursors and their further transformations toward diverse scaffolds in a single pot is a daunting challenge. The reason is the formation of NAI ion species prerequisite is a good leaving group at the α-position to the nitrogen atom. In order to bring leaving groups at the desired position in substrates involves multistep syntheses and which are highly difficult to operate in single pot.

3.2. Background

3.2.1. Selective Methods for Oxazoles synthesis

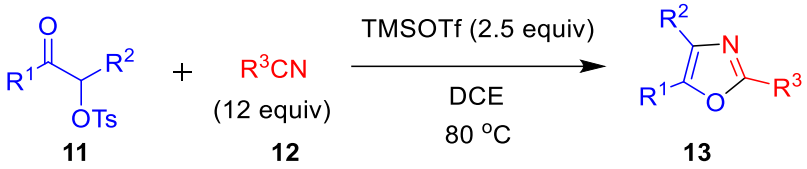
Recently, Jiang *et al.*[5] have developed an efficient approach to butenolides and oxazoles *via* metal-catalyzed [2 + 3] cyclization. In this work a copper-catalyzed [2 + 3]

formal cyclization reaction between α-hydroxyl ketones and aryl-acetonitriles has been developed. Tertiary α-hydroxy ketones gave 3,4,5,5-tetrasubstituted butenolides as the sole products, while secondary α-hydroxy ketones furnished 2,4,5 trisubstituted oxazoles selectively (Scheme 1).



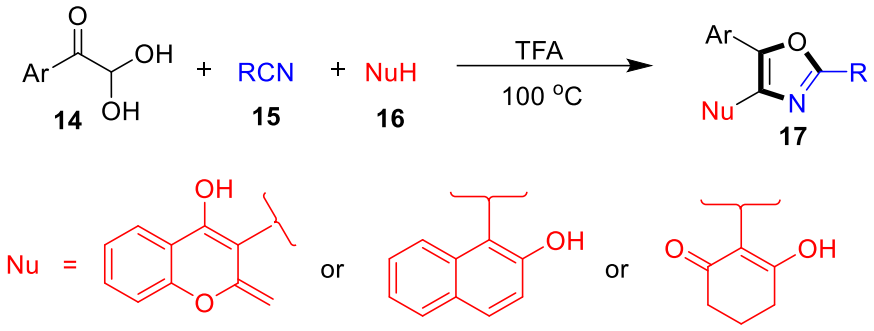
Scheme 1

Taylor *et al.*[6] prepared substituted oxazoles by Ritter reaction. The Lewis acid catalyzed Ritter reaction of a-oxo tosylates with nitriles forms the basis of an efficient synthesis of oxazoles. The Ritter reaction of a-carbonyl carbocations represents a useful strategy for the preparation of trisubstituted oxazoles.



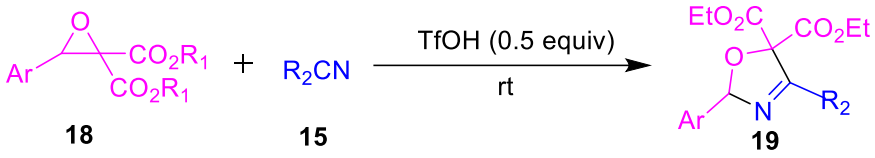
Scheme 2

Recently, Wu *et al.*[7] have reported an acid-promoted multi component reaction for the synthesis of diverse fully substituted oxazole derivatives from simple and readily available arylglyoxal monohydrates, nitriles, and various C-nucleophiles has been developed. This work demonstrates that a traditional Robinson−Gabriel reaction served as the key advance for this transformation.



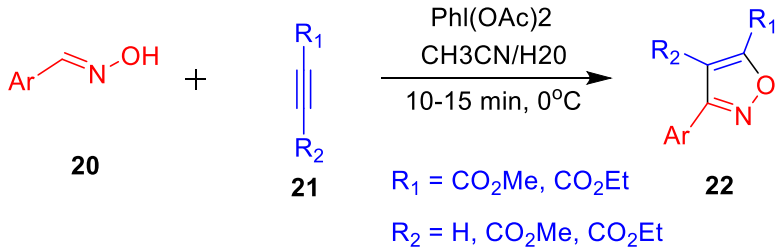
Scheme 3

In 2015, Zhong *et al.*[8] a Triflic acid-catalyzed chemo selective [3 + 2] cycloaddition of donor and acceptor oxiranes and nitriles is described. The reactions involve in situ generation of 1,3-dipoles through Lewis acid promoted C−C bond or C−O bond cleavage of oxiranes, which are then trapped by dipolarophiles bearing C−X (X = O, C) multiple bonds.



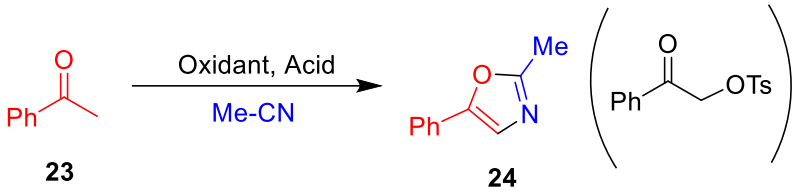
Scheme 4

In 2015 Peddinti et al.[9] have developed a hypervalent iodine mediated synthesis of di- and tri-substituted isoxazoles via [3+2] cycloaddition of nitrile oxides.



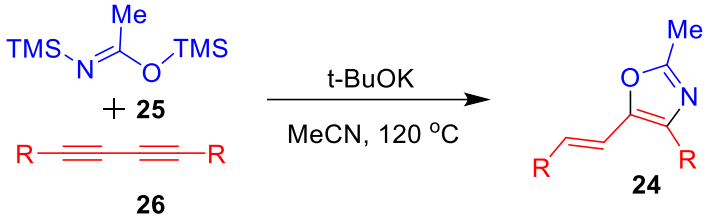
Scheme 5

In 2012, Hanzawa *et al.*[10] highly substituted oxazoles from ketones and nitriles by the use of iodosobenzene with trifluoromethanesulfonic acid or bis(trifluoromethanesulfonyl)imide.



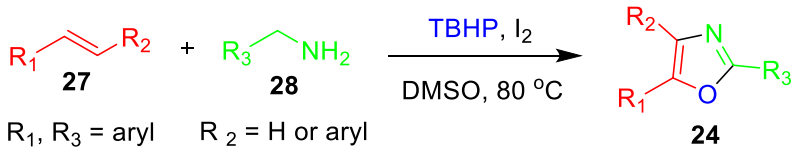
Scheme 6

In 2015, Zhao *et al.*[11] developed transition-metal free heterocyclization reaction between 1,3-diynes with N,O-bis(trimethylsiyl)acetamide was accomplished in the presence of *t*BuOK and acetonitrile at 120 °C. This method regioselectively gave 2,4,5-trisubstituted oxazoles.



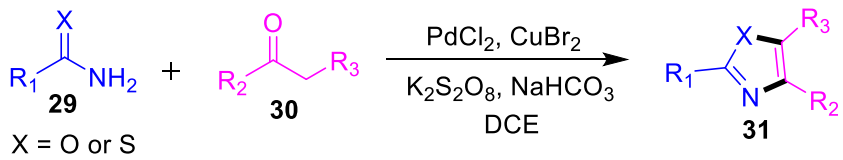
Scheme 7

In 2010, Qi *et al.* [12] developed a new type of one-pot, transition-metal free protocol through a TBHP/I_2-mediated oxidative cyclization from easily available aryl alkenes and benzylic amines for the synthesis of polysubstituted oxazoles.



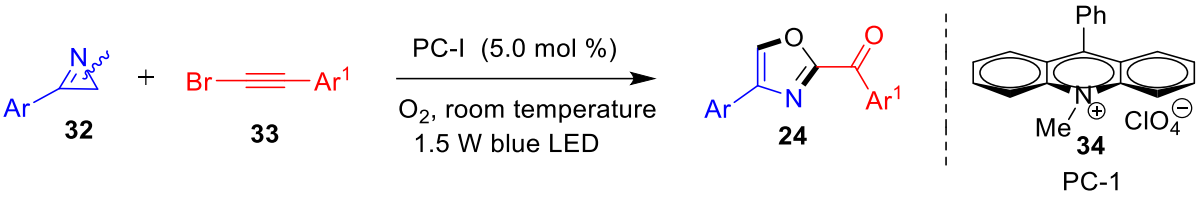
Scheme 8

In 2014, Jiang et al.[13] developed a novel and effective method has been developed to construct highly substituted oxazoles via a palladium-catalyzed dehydration/C-H functionalization/C-O bond-forming reaction between amides and ketones.



Scheme 9

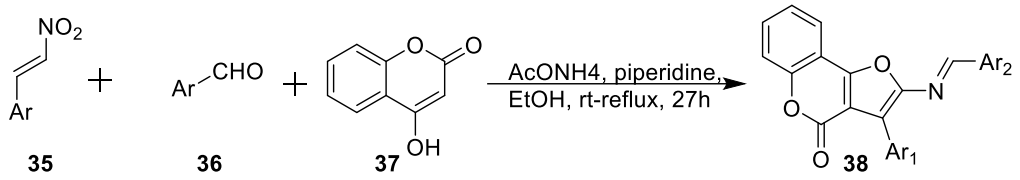
In 2016, Wang et al.[14] developed a novel three-component cyclization reaction of 2H-azirines, alkynyl bromides, and molecular oxygen under visible light photoredox catalysis at room temperature has been developed, which provides a direct approach to a wide range of substituted oxazoles in this method they used acridinium salt (PC-I, 5.0 mol %) as an organic photocatalyst at room temperature under visible light irradiation. The radical cycloaddition proceeded smoothly to generate oxazoles in moderate to good yields under mild reaction conditions.



Scheme 10

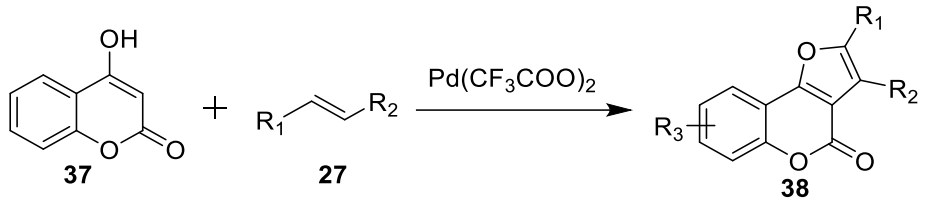
3.2.2. Selective Methods for furocoumarins synthesis

In 2013, Wang et al.[15] have developed 2-alkylamino-3-aryl-4H-furo[3,2-c]chromen-4 ones via a one-pot, multicomponent reaction from substituted nitrostyrenes, aromatic aldehydes, 4-hydroxycoumarin, and ammonium acetate which involves sequential Michael addition, aza-nucleophilic addition of imine to the double bond, intermolecular nucleophilic addition, and dehydration reactions.



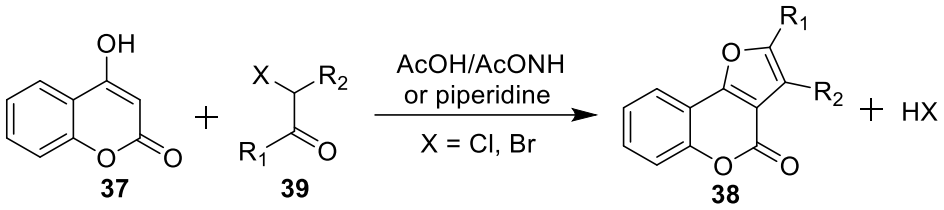
Scheme 11

In 2015, Feng *et al.*[16] have developed an efficient synthetic method for the synthesis of furo[3,2-c]coumarins from readily available 4-oxohydrocoumarins and alkenes. This operationally simple method gives a rapid access to the furo[3,2-c]coumarins.



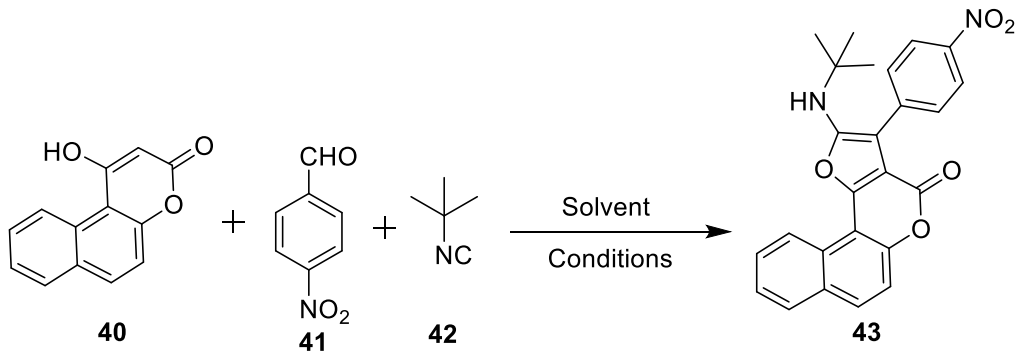
Scheme 12

In 2012 Sameh *et al.*[17] have developed a new method for the synthesis of angular furocoumarins were carried out through Williamson reaction of 4-hydroxycoumarin with *α*-haloketones followed by cyclization. Photooxygenation of the synthesized furocoumarin derivatives was performed and the photoproducts were isolated and characterized.



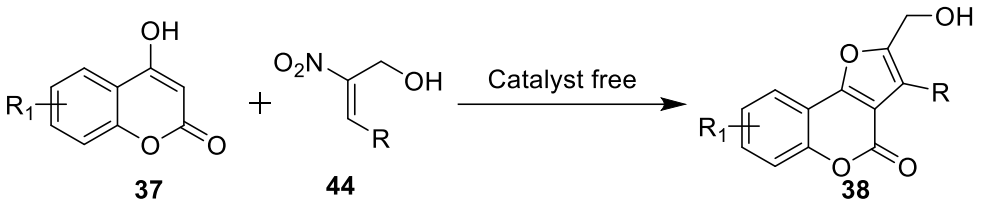
Scheme 13

Sharma *et al.*[18] developed a green, three-component reaction with 1-hydroxy-3H-benzo[*f*]chromen-3-ones and 4-hydroxyquinolin-2(1H)-ones, an aromatic aldehyde and isonitrile, was developed for the first time, which resulted in a variety of substituted functionalized benzo[f]furo[3,2-c]chromen-4-(5H)-ones and furo[3,2-c]quinolin-4-(5H)-ones.



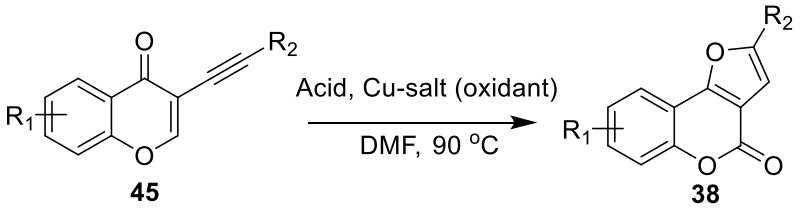
Scheme 14

Samanta *et.al* [19] have developed observed a remarkable solvent effect on one-pot reaction of 4-hydroxycoumarin derivatives with (E)-3-aryl-substituted-2-nitroprop-2-enols and it was used for expeditious synthesis of highly substituted furo/pyrano[3,2-30 c]chromenes, by choosing water or DMSO as a solvent.



Scheme 15

In 2007, Hu *et al.*[20] have developed a new one-pot cascade reaction for regioselective synthesis of furo[3,2-*c*]coumarins. Herein, authors reported a highly efficient, acid-promoted and regioselective one-pot reaction to construct furo[3,2-*c*]coumarins by addition–cyclization–oxidation.



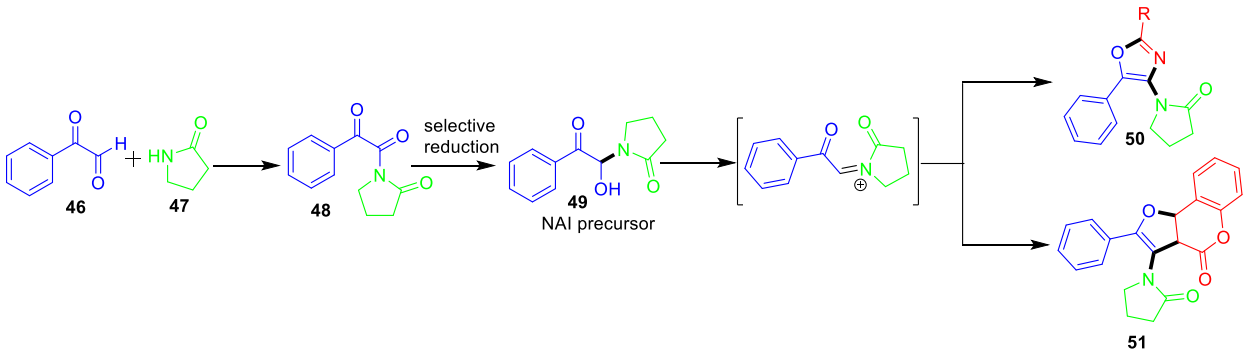
Scheme 16

3.3 Results and Discussion

The challenges led us to examine a direct synthetic route to access NAI precursors and their further efficient transformations through a cascade process. The acid catalyzed reactions of NAI salts well explored in the literature, these transformations mainly involved the generation of cationic NAI ions in the presence of excess strong acid. As per the literature survey, these type of conditions lead to the formation of dicationic species are called super electrophiles, which can be explored in further transformations with suitable nucleophiles.[1]

Recently, we have developed an iminium induced one-pot double annulation cascade strategy for the synthesis of dihydroisoquinolinium salts.[21] Inspired by this work and our continuing interest in the development of metal-free and green strategies for the synthesis of biologically important heterocyclic compounds,[22] herein, we report a novel super-acid-promoted tandem cyclization strategy to synthesize diversified fully substituted Oxazoles and Furocoumarins from readily available starting materials *via* insituly generated exocyclic NAI precursor in one pot. The development of a straightforward method to access the above mentioned privileged scaffolds *via* insitu generation of NAI precursors would be of great importance.

At first, we envisaged to design NAI precursor by cross dehydrogenative coupling (CDC) of amines and phenylglyoxals, followed by selective reduction (Scheme 17).

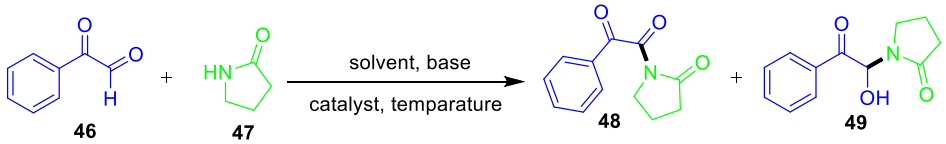


Scheme 17. Designed Strategy for the Synthesis of NAI, Oxazoles and Furocoumarins

Accordingly, we carried out the reaction with phenylglyoxal **46** and 2-pyrrolidinone **47** for the synthesis of α-ketoamide **48** under conditions developed in our previous CDC strategy.[23] Surprisingly, we isolated our desired α-hydroxyl β-keto amide **49** (NAI precursor)

instead of α-ketoamide **48** after prolonged reaction time, albeit in very poor yield 15% (Table 1, entry 1). This interesting result motivated us to improve the yield of the desired product. Then we carried out the reactions at various temperatures, which resulted no much improvements in the yield of product **49**. We have also screened other metal catalysts instead of Iodine. Unfortunately, all these reactions led to the formation of mixture of products **48** & **49** (Table 1, entries 5-12). Without losing hope, we have checked the reaction under catalyst free conditions, surprisingly it furnished the desired compound **49** in 40% yield (Table 1, entry 13). When we performed the reaction in the absence of catalyst, base and solvent, to our delight, the desired product obtained with excellent yield i.e. 98% within minutes (Table 1, entry 14).

Table 1. Optimization of the reaction conditions for NAI precursor **49**[a]



entry	catalyst (equiv.)	base (equiv.)	solvent	Temp (°C)	Time (h)	yield (%)[b] 3aa	yield (%)[b] **A**
1	Iodine (1.5)	K_2CO_3 (2.0)	Toluene	rt	24	0	15
2	Iodine (1.5)	K_2CO_3 (2.0)	Toluene	60	24	0	22
3	Iodine (1.5)	K_2CO_3 (2.0)	Toluene	80	24	-	-
4	Iodine (1.5)	K_2CO_3 (2.0)	DMF	80	24	-	-
5	$CuBr_2$ (0.2)	K_2CO_3 (2.0)	Toluene	rt	24	30	10
6	$FeBr_2$ (0.2)	K_2CO_3 (2.0)	DCE	rt	24	20	20
7	CuI (0.2)	K_2CO_3 (2.0)	Toluene	rt	24	10	22

8	$Cu(OAc)_2$ (0.2)	K_2CO_3 (2.0)	Toluene	50	24	20	30
9	$Cu(OAc)_2$ (0.2)	K_2CO_3 (2.0)	Toluene	60	24	32	36
10	$Cu(OAc)_2$ (0.2)	K_2CO_3 (2.0)	Toluene	70	24	40	42
11	$Cu(OAc)_2$ (0.2)	K_2CO_3 (2.0)	Toluene	70	24	50	32
12	$Cu(OAc)_2$ (0.2)	K_2CO_3 (2.0)	Toluene	80	24	60	20
13	-	K_2CO_3 (2.0)	Toluene	80	24	-	40
14	-	-	**-**	**80**	**10 min**	**0**	**98**

[a]Reaction conditions: **46** (1.0 equiv), **47** (1.1 equiv). [b]Isolated yields after column chromatography.

Having this catalyst and solvent-free conditions for NAI precursor **49** in hand, our attention was turned towards the utilization of it for the synthesis of biologically active molecules.

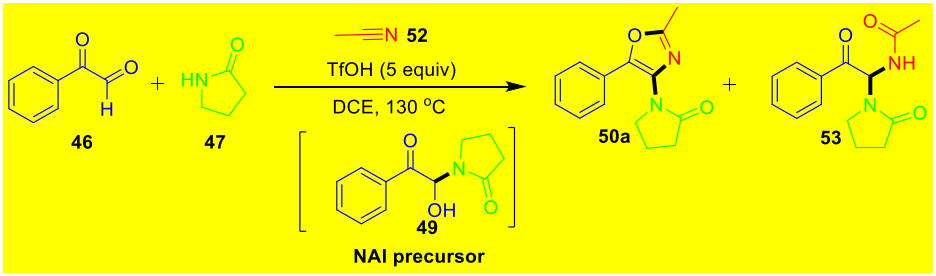
Keeping this in mind firstly we hypothesized to synthesize fully substituted Oxazole derivatives by using nitriles through 3+2 cycloaddition under Metal-free conditions.

Accordingly, to test our hypothesis, first we generated the NAI precursor **49** by the reaction of phenylglyoxal **46** with 2-pyrrolidinone **47** under standard conditions, which could subsequently use as the model substrate without isolation.

Then the model reaction was performed by the addition of CH_3CN **52** in the presence of Brønsted acid (methyl sulfonic acid MsOH), afforded the expected product **50a** albeit in 40% yield along with by-product bisamide **53** in 20% yield (Table 2, entry 1). The formation of by-product might be due to the release of H_2O in the reaction. Encouraged by this preliminary result, we further screened with various Brønsted and Lewis acids at different temperatures in DCE as a solvent and the results were summarized in Table 2. From the results we understand that the nature of acid and temperature had a significant effect on the outcome of the reaction. Among the various Brønsted acids screened, only triflic acid effectively promoted the desired product (Table 2, entries 1-11). In order to evaluate the effects of acidity we screened with different equivalents of triflic acid under various

temperatures, finally, 5.0 equiv of triflic acid was found to be effective at 130 °C to afford the desired product **50a** in excellent yield 91%. (Table 2, entry 11). The results revealed that the employment of Lewis acids was not useful (Table 2, entries 16 to 20).

Table 2. Optimization studies for the synthesis of Oxazole **50a**[a]



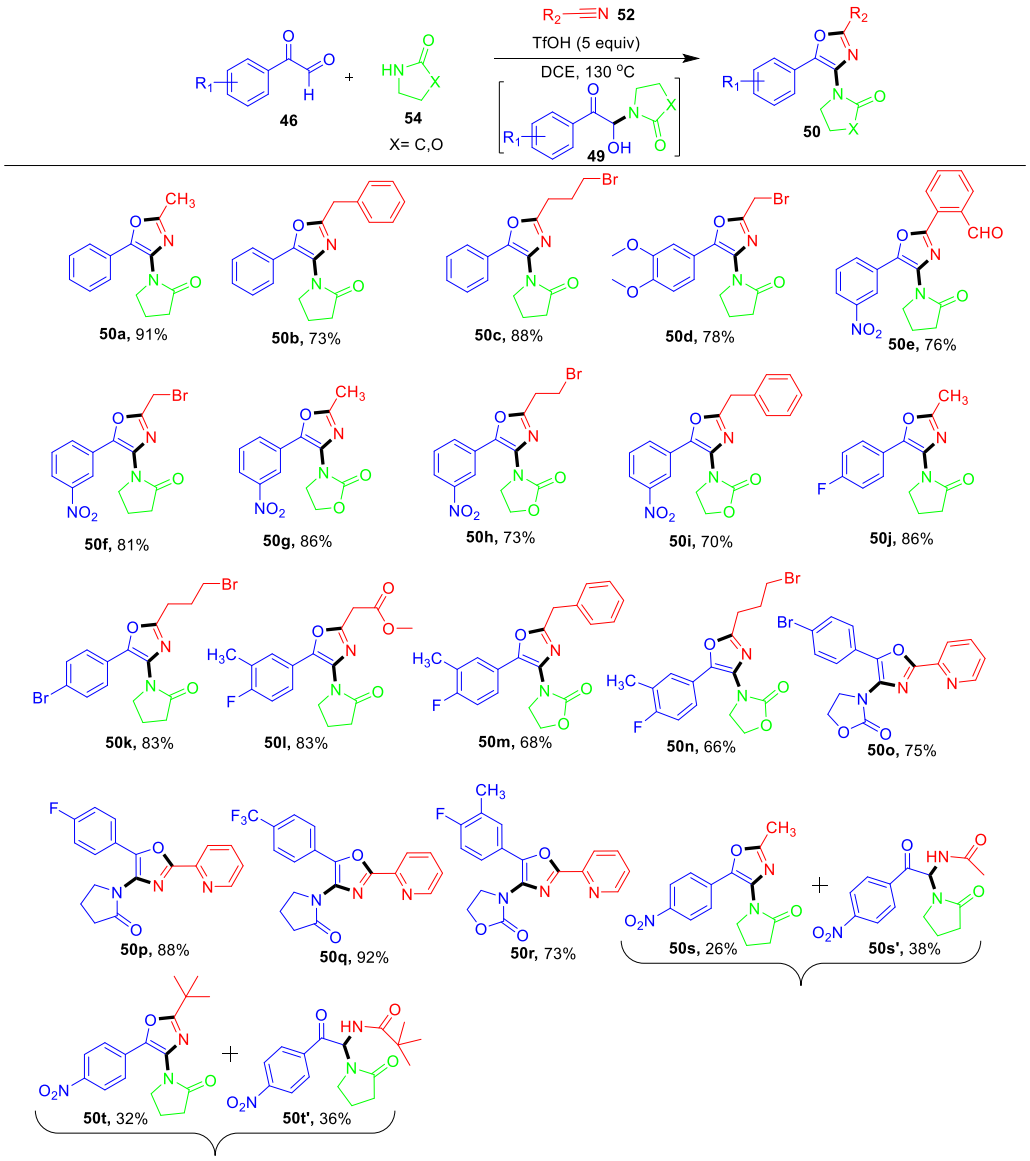
entry	acid (equiv)	solvent	temp	Isolated yield (%)	
				50a	**53**
1	MsOH (5.0)	DCE	rt	40	20
2	MsOH (5.0)	DCE	rt	30	47
3	MsOH (5.0)	DCE	80 °C	48	9
4	MsOH (5.0)	DCE	100 °C	55	4
5	MsOH (5.0)	DCE	120 °C	71	Nd
6	MsOH (5.0)	DCE	120 °C	61	Nd
7	MsOH (5.0)	DCE	130 °C	75	Nd
8	TfOH (5.0)	DCE	120 °C	81	Nd
10	TfOH (4.0)	DCE	130 °C	75	Nd
11	**TfOH (5.0)**	**DCE**	**130 °C**	**91**	**Nd**
12	TfOH (6.0)	DCE	130 °C	85	Nd
13	HCl (5.0)	DCE	130 °C	Nd	Nd
14	H_2SO_4 (5.0)	DCE	130 °C	Nd	Nd
15	CH_3COOH (5.0)	DCE	130 °C	Nd	Nd
16	$FeCl_3$ (0.2)	DCE	130 °C	Nd	Nd
17	$AlCl_3$ (0.2)	DCE	130 °C	Nd	Nd
18	$InCl_3$ (0.2)	DCE	130 °C	Nd	Nd
19	$Sc(Otf)_3$ (0.2)	DCE	130 °C	Nd	Nd
20	Bf_3OEt_2 (0.2)	DCE	130 °C	Nd	Nd

[a]Reaction conditions: 1st step: **46** (1.0 mmol), **47** (1.1 mmol), 80 °C, 10 min, 2nd step: DCE dry solvent (0.25 M), **52** (1.1 mmol), TfOH (5 mmol), 130 °C, 2 h. [b]Isolated yields after column chromatography, Nd = not detected.

After having the optimized conditions in hand, we have explored the substrate scope of the present protocol (Table 3). Arylglyoxals bearing electron-neutral (**50a, 50b** & **50c**), electron-rich (**50d**) and electron-deficient (**50e-50k**) substituents were smoothly converted to the corresponding oxazoles with moderate to very good yields. Interestingly, halo-substituted (**50j-50n**) arylglyoxals were also found to furnish the desired products with good yields (66-86%), which would provide possibilities for further functionalization. Pleasingly, 2-oxazolidinone in place of 2-pyrrolidinone were also found to furnish the desired products with very good yields (**50g**, **50h, 50m** & **50n**).

Next we checked the reactivity of strong electron withdrawing group ($-NO_2$) in the 4^{th} position of arylglyoxal unit (Table 3, **50s** & **50t**), unfortunately in both the examples we got the both oxazole and bisamide products, after prolonged reaction hours also we didn't observe the complete conversion of bisamide to oxazole products. We achieved the less oxazole product yields in both **50s** & **50t** cases (26% & 32%).

Table 3. Scope of the synthesis of various fully substituted oxazoles[a]



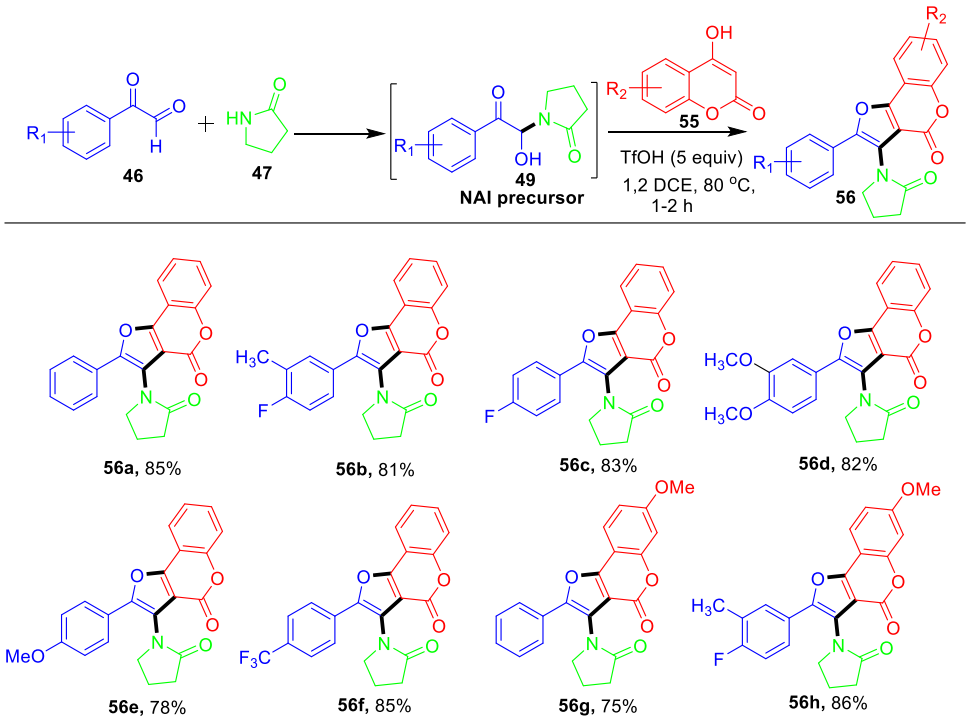
[a]Reaction conditions: 1st step: **46** (1.0 mmol), **54** (1.1 mmol), 80 °C, 10-20 min, 2nd step: DCE dry solvent (0.25 M), **52** (1.1 mmol), TfOH (5 mmol), 130 °C, for 2-3 h. [b] Isolated yields, after column chromatography.

In order to expand the molecular library of polyfunctional oxazole derivatives, we extended it to the heteroaryl nitriles, like 2-cyanopyridines, for the synthesis of valuable bis-hetero cycles those are pyrid-oxazoles skeletons as shown in table 3. In this transformations, 2-cyanopyridine is reacted smoothly with NAI intermediates generated from arylglyoxals and 2-oxazolidinone or 2-pyrrolidinone to afford the desired products from good to excellent yields (Table 3, **50o-50r**).

After successfully synthesis of fully substituted Oxazoles, further our attention was turned towards the synthesis of Furocoumarins. Accordingly, the new protocol was further

demonstrated by using 4-hydroxy-2H-chromen-2-one as carbon-nucleophile (Table 4). Arylglyoxals with electron-ne utral (**56a** & **56g**), electron rich (**56d** & **56e**) and electron-deficient (**56b, 56h, 56f** & **56c**) substituents were smoothly transformed into the corresponding privileged Furocoumarine under the optimized conditions with very good yields (Table 4).

Table 4. Scope of the Synthesis of Furocoumarins



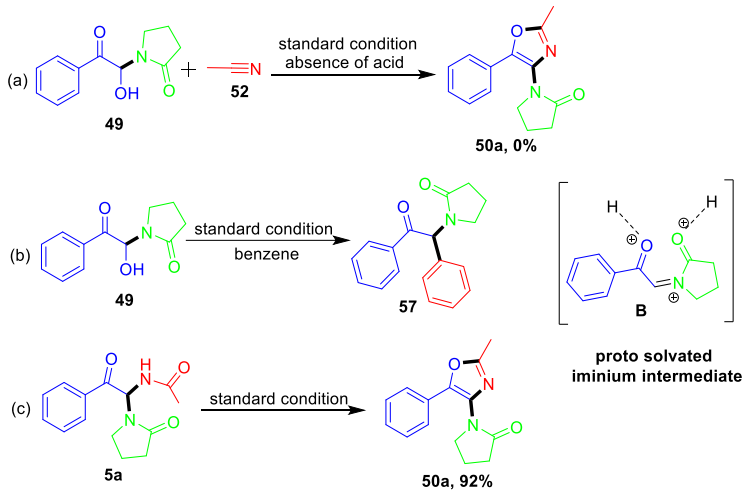
[a]Reaction conditions: 1st step: **46** (1.0 mmol), **47** (1.1 mmol), 80 °C, 10-20 min, 2nd step: DCE dry solvent (0.25 M), **55** (1.1 mmol), TfOH (5 mmol), 80 °C, 1-2 h. [b]Isolated yields, after column chromatography.

To gain insight into the reaction mechanism, preliminary control experiments were conducted. When the reaction was performed in the absence of acid, no desired product was formed, indicating that the presence of acid is crucial for this reaction (Scheme 18a). Since the present reaction requires excess acid to effect the transformations (standard conditions), we hypothesized that the reaction might be proceed through proto-solvation of N-acyliminium ion **B** (Scheme 18b). Accordingly, we have performed the reaction with weak

nucleophile i.e. benzene instead of acetonitrile **52**. To our delight, we could have isolated the benzene trapped product **C** with 80% yield.

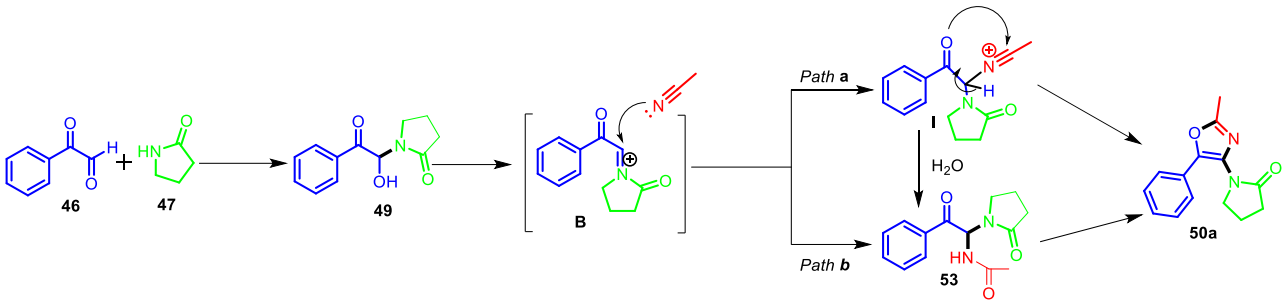
This result suggested that a proto-solvated iminium intermediate **B** was most likely involved in this reaction. To know further possible intermediates as per our observations during optimization of reaction conditions (Table 2, entry1 and 3), we assumed that either bisamide or nitrelium ion may be the reaction intermediates after attacking of nitrile **52** to intermediate **B** to afford the oxazole **50a**. Accordingly, we have subjected the bisamide **53** to standard conditions, which resulted in oxazole **4a** with excellent yield as we expected (Scheme 18c).

Scheme 18. Mechanistic Experiments

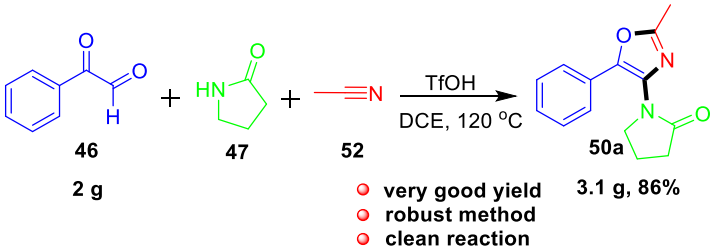


Based on the above observed products and previous literature reports,[3] a plausible mechanism was proposed for the present reaction (Scheme 19**)**. Initially the NAI precursor **49** would form the iminium intermediate **B** under acidic conditions. Then cyclization was occur by two conceivable paths: In path **a**, acetonitrile would attack proto solvated iminium intermediate **B** to afford nitriliumion **I**, which then would neutralized by the adjacent carbonyl oxygen to furnish the final product **50a**. In path **b**, the nitriliumion **I** would be

neutralized by the water molecule to form the bisamide **53**, which would further undergo dehydration -cyclization to furnish the final product **50a.**



Scheme 19. Plausible reaction mechanism for **50a**



Scheme 20. Gram Scale Synthesis

After having successfully developed super acid promoted a one-pot strategy for the synthesis of fully substituted oxazoles and furocoumarin scaffolds. We envisaged to examine the scalability of the process. Consequently, we have performed the reaction on the 2g scale and isolated the product **50a** as a white solid with very good yield (86%) after column purification (Scheme 20). The scalability of our protocol should prove industrially applicable.

Photophysical Properties of Pyrid-oxazoles and Furocoumarins

After having synthesized compounds in hand, we were keen to study the UV-visible and fluorescence characteristics of chosen Pyrid-oxazoles and Furocoumarins. The UV-visible spectra of compounds **50r**, **50p**, **50q** & **50o** in ethanol (EtOH) exhibited maximum absorption wavelength (λ_{max}) at 320 nm and the data are summarized in Table 5 and Figure 4.

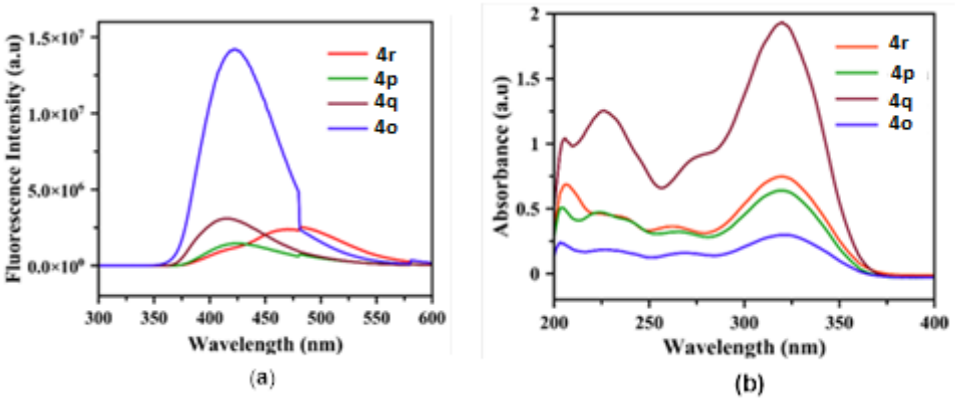


Figure 4. Fluorescence (**a**) and Absorption (**b**) spectra of Pyrid-oxazoles **50o-50r** in ethanol at room temperature.

Table 5. UV-Vis Absorption and Fluorescence Emission Properties of Compounds **4o-4r**[a,b]

entry	compound	A λ_{max} (abs) in nm[a]	B λ_{max} (abs) in nm[a]	C λ_{max} (abs) in nm[a]	λ_{em} in nm[b]
1	**50r**	206	262	320	464
2	**50p**	205	225	320	420
3	**50q**	206	226	320	414
4	**50o**	205	227	320	422

[a]UV-visible absorption wavelengths, [b]Emission wavelengths at room temperature at concentration of $1x10^{-3}$ M in EtOH.

The fluorescence spectra of pyrid-oxazole compounds showed emission wavelength (λ_{em}) at 414-464 nm (Table 5). The presence of more electronegative atom (Fluorine) and strong electron withdrawing group (trifluoromethyl group) in the *para* position of the aromatic ring in compounds **50r**, **50p** & **50q** showed the less fluorescence intensity (Figure 4).

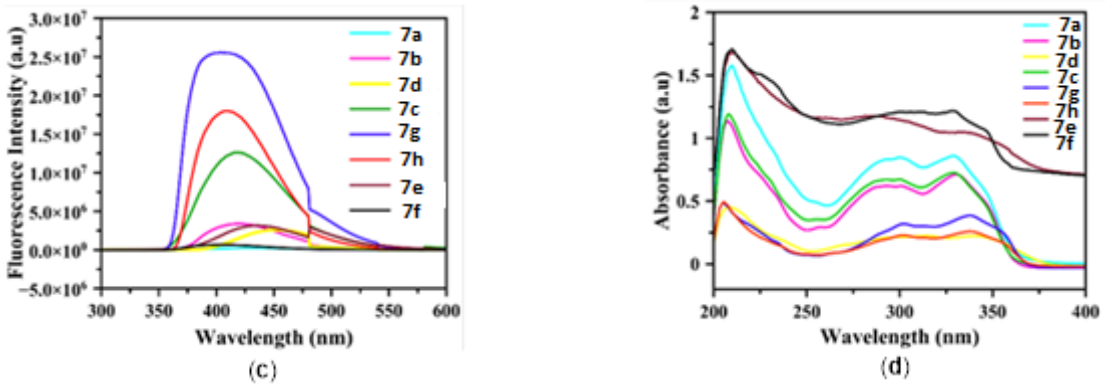


Figure 5. Fluorescence (**c**) and Absorption (**d**) spectra of Furocoumarins **56a-56h** in ethanol at room temperature.

Similarly, we have also recorded the UV-visible and fluorescence spectra of Furocoumarins (**56a-56h**) in EtOH. The UV-visible spectra of compounds **56a-56h** (Figure 5d) exhibited maximum absorption wavelengths at 205-210 nm (Table 6). The absorption bands shift values indicated that there was no significance difference with regardless of substituents presence in the aromatic rings, and an increase in absorption intensity in the compounds **56f**, **56e** and **56a** was observed. The fluorescence properties of the compounds **56a-56h** (Figure 5c) displayed emission wavelength (λ_{em}) at 396-449 nm (Table 6). Among all the compounds, **56g**, **56h** and **56f** showed an increase in fluorescence intensity along with an increase of the electron with drawing properties of the substituent in aromatic ring were also observed.

Table 6. UV-Vis Absorption and Fluorescence Emission Properties of Compounds **7a-7h**[a,b]

entry	compound	A λ_{max} (abs) in nm[a]	B λ_{max} (abs) in nm[a]	C λ_{max} (abs) in nm[a]	λ_{em} (nm)[b]
1	**56a**	210	300	328	412
2	**56b**	207	294	330	415
3	**56d**	208	314	340	449
4	**56c**	208	300	329	417
5	**56g**	205	302	338	404
6	**56h**	205	301	337	408
7	**56e**	211	286	345	436
8	**56f**	210	301	328	396

[a]UV-visible absorption wavelengths, [b]Emission wavelengths at room temperature at concentration of $1x10^{-3}$ M in EtOH.

3. 4. Conclusion

In conclusion, we have described a concise, one-pot route to Oxazoles and Furocoumarins through N-acyliminium ion as a key intermediate. The key step in this transformation involves *insitu* generation of NAI precursor under catalyst and solvent free conditions, and their further transformations promoted by superacid in the same pot. The experimental evidence for the involvement of proto-solvated novel exocyclic N-acyliminium ion in superacid promoted reaction has been presented. We have also investigated the photophysical properties of Furocoumarins and Pyrid-oxazole derivatives, and these studies reveal that possible applications for the discovery of highly fluorescent probes.

3.5 Experimental section

General Information

IR spectra were recorded on a FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 400 MHz spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on 100 MHz spectrometer at 25 °C in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the ^{1}HNMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, dd = doublet of doublets, m = multiplet and br s. = broad singlet. The assignment of signals was confirmed by ^{1}H, ^{13}C CPD, and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using Q-TOF multimode source. Melting points were determined on an electro thermal melting point apparatus and are uncorrected. Other reagents were purchased as reagent grade and used without further purification. All dry solvents were used. DCE and DCM was dried over CaH_2.

Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. All reactions were performed under air atmosphere in standard glassware, heated at 80 °C for 3 h before use. Solvents were distilled prior to use; petroleum ether with a boiling range of 40 to 60 ˚C was used. Organic solutions were concentrated by rotary evaporation under vacuum. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

General procedure (GP-I) for the synthesis of Phenylglyoxals (46a to 46h)

All the phenylglyoxals were synthesized according to the literature procedures,[12] to a 50 mL two-neck round bottom flask SeO_2 (4.99 g, 45.0 mmol), H_2O (0.76g, 42.5 mmol) and 1,4-dioxane (25.0 ml) were added and fixed a condenser. Then the mixture was heated to reflux with stirring until the solid was dissolved. Then, substituted aryl ketones (25.0 mmol) was added to the solution. The reaction mixture was allowed to reflux for 2 to 6 h. After the reaction was completed (monitoring by TLC), the reaction mixture was cooled to room temperature and filtered through a Celite pad. The Celite pad was washed several times with diethyl ether. The combined filtrate was evaporated on a rotary evaporator to afford the crude

product. The crude residue was purified through a silica gel column using petroleum ether/ethyl acetate (8:2) as eluent.

General procedure 2: for the synthesis of Oxazoles (50a to 50r)

Phenylglyoxal **46a** (1 mmol) was taken in a dried 10 mL round bottom flask, and 2-pyrrolidinone **47** (1.1 mmol) was added and the reaction mixture was stirred under neat conditions at 80^{o}C temperature for 10 min to 20 min. After the formation of intermediate **49** (confirmed by TLC), then added DCE (2 mL) and nitrile partner **52** (1.1 mmol), followed by addition of Triflic acid (5 mmol) then the reaction flask was connected to a condenser circulating with cold water and kept at 130 ^{o}C in oil bath. The progress of the reaction was monitored by TLC till the reaction is completed (2-3 h). The reaction mixture was quenched by addition of saturated solution of $NaHCO_3$ and extracted with ethyl acetate, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified through a silica gel column using petroleum ether/ethyl acetate (8:2) as eluent. All the compounds **(50a to 50r)** were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and HR-MS spectral analyses.

Large Scale procedure for the synthesis of Oxazole (50a)

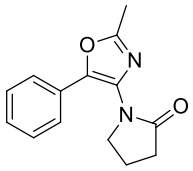
Phenylglyoxal **46** (14.91 mmol, 2g) was taken in a dried 100 mL round bottom flask, and 2-pyrrolidinone **47** (16.40 mmol, 1.395g) was added and the reaction mixture was stirred under neat conditions at 80 ^{o}C temperature for 10 min to 20 min, after the formation of intermediate **49** (confirmed by TLC), then added DCE 40mL and triflicacid (74.55 mmol, 11.18g) was added and RB connected to the condenser circulating with cold water then the reaction setup was shifted to 130 ^{o}C, oil bath after 2h, after completion of the reaction confirmed by TLC then the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with ethyl acetate, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified through a silica gel column using petroleum ether/ethyl acetate (8:2) as eluent. Final compound was isolated with 86% yield, 3.1g,

General procedure 3: for the synthesis of Furocoumarins (56a to 56h)

Phenyl glyoxal **46** (1 mmol) was taken in a dried 10 mL round bottom flask, and 2-pyrrolidinone **47** (1.1 mmol) was added and the reaction mixture was stirred under neat conditions at 80 ^{o}C temperature for 10 min to 20 min. After the formation of intermediate **49** (confirmed by TLC), then added DCE (2 mL) and 4-Hydroxycoumarin partner **6**, followed by

addition of Triflic acid (5 mmol) then the reaction was kept at 80 ºC. The progress of the reaction was monitored by TLC till the reaction is completed (1-2 h). The reaction mixture was quenched by addition of saturated solution of $NaHCO_3$ and extracted with ethyl acetate, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified through a silica gel column using petroleum ether/ethyl acetate (8:2) as eluent. All the compounds **56a to 56h** were confirmed by FTIR, ^{1}H NMR, ^{13}C NMR and HR-MS spectral analysis.

1-(2-methyl-5-phenyloxazol-4-yl) pyrrolidin-2-one (50a)



Physical state : white solid

Yield : 91%

Mp : 85-87 ˚C

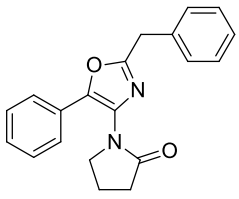
IR (MIR-ATR, 4000–600 cm^{-1}) ν_{max} = 3054, 2926, 1706, 1628, 1585, 1494, 1412, 1262, 1225, 1018, 913, 835, 729, 692, 591, 546.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 - 7.51 (m, 2H), 7.43 - 7.37 (m, 2H), 7.34 - 7.28 (m, 1H), 3.80 (t, J = 7.1 Hz, 2H), 2.59 (t, J = 8.1 Hz, 2H), 2.50 (s, 3 H), 2.24 (quin, J = 7.6 Hz, 2H).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 175.2, 159.2, 143.0, 130.5, 128.7, 128.3, 127.5, 124.9, 48.8, 31.1, 19.0, 14.3.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{14}H_{15}N_2O_2]^+$ 243.1128; Found 243.1129.

1-(2-benzyl-5-phenyloxazol-4-yl)pyrrolidin-2-one (50b)



Physical state : Light yellow solid

Yield :73%

Mp : 87-89 ˚C

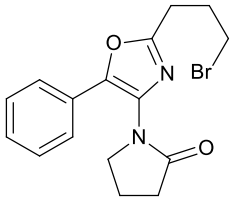
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3465, 3060, 3030, 2923, 1706, 1625, 1572, 1493, 1451, 1409, 1256, 1222, 1170, 1070, 1020, 912, 835, 766, 729, 692, 549.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 - 7.48 (m, 2 H), 7.40 - 7.32 (m, 6 H), 7.32 - 7.23 (m, 2 H), 4.12 (s, 2 H), 3.83 - 3.77 (m, 2 H), 2.56 (t, J = 8.1 Hz, 2 H), 2.21 (quin, J = 7.6 Hz, 2 H).

^{13}C{^{1}H}NMR(100 MHz, $CDCl_3$): δ 175.0, 160.5, 143.3, 135.0, 130.7, 128.9, 128.8, 128.7, 128.4, 127.5, 127.2, 125.0, 77.5, 77.4, 77.2, 76.8, 48.8, 35.0, 31.2, 19.0.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{20}H_{19}N_2O_2]^+$ 319.1441; Found 319.1442.

1-(2-(3-bromopropyl)-5-phenyloxazol-4-yl) pyrrolidin-2-one (50c):



Physical state : White solid

Yield :88%

Mp : 138-140 ˚C

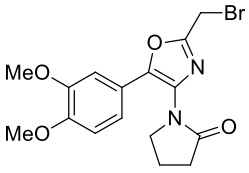
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3059, 2961, 1709, 1628, 1600, 1578, 1445, 1261, 1227, 1178, 1021, 915, 836, 767, 692.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 7.3 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.35 - 7.29 (m, 1H), 3.81 (t, J = 7.1 Hz, 2H), 3.55 (t, J = 6.4 Hz, 2H), 2.99 (t, J = 7.3 Hz, 2H), 2.59 (t, J = 8.1 Hz, 2H), 2.37 (quin, J = 6.8 Hz, 2H), 2.25 (quin, J = 7.6 Hz, 2H).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 175.2, 160.9, 143.1, 130.5, 128.7, 128.5, 128.4, 127.4, 125.0, 48.8, 32.4, 31.1, 29.5, 26.9, 18.9.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{16}H_{18}BrN_2O_2]^+$ 349.0546; Found 349.0547.

Methyl 2-(5-(4-fluoro-3-methylphenyl)-4-(2-oxopyrrolidin-1-yl)oxazol-2-yl)acetate (50d):



Physical state : Pale Yellow solid

Yield :78%

Mp : 150-151 ˚C

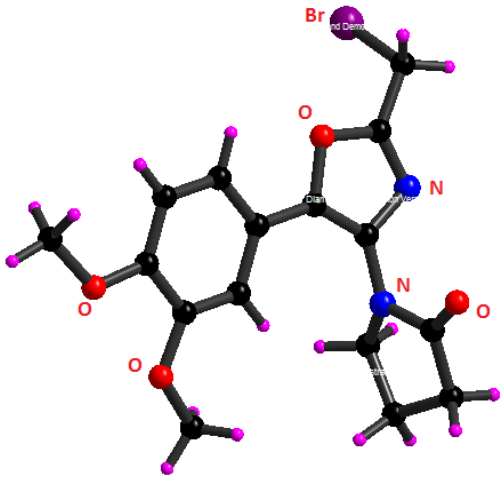
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3046, 2936, 2836, 1703, 1601, 1513, 1460, 1416, 1262, 1235, 1212, 1171, 1140, 1020, 924, 860, 810, 765,731,698,623,582.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 1H), 7.1 (d, *J* = 2 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 4.4 (s, 2H), 3.88 (s, 6H), 3.8 (t, *J* = 7.1, 2H), 2.5 (t, *J* = 8.3 Hz, 2H), 2.2 (q, *J* = 7.6, 2H).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 175.0, 155.7, 149.7, 149.0, 144.7, 130.1, 119.7, 118.7, 111.3, 108.7, 55.9, 48.8, 31.1, 20.5, 19.0.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{16}H_{18}BrN_2O_4]^+$ 381.0444; Found 381.0447.

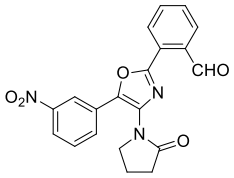
Single crystal X-ray structure data of compound 50d (CCDC 1835405): Thermal ellipsoids are drawn at 50% probability level.



Identification code	exp_5510
Empirical formula	$C_{16}H_{17}BrN_2O_4$
Formula weight	381.23
Temperature/K	293
Crystal system	Triclinic
Space group	P-1
a/Å	9.1144(10)
b/Å	9.4623(10)
c/Å	10.9816(12)
α/°	79.346(9)
β/°	72.139(10)
γ/°	65.185(11)
Volume/$Å^3$	816.48(17)

Z	2
ρ_{calc}g/cm^3	1.5505
μ/mm^{-1}	3.628
F(000)	387.7
Crystal size/mm^3	0.08 × 0.06 × 0.05
Radiation	Cu Kα (λ = 1.54184)
2Θ range for data collection/°	8.48 to 142.3
Index ranges	-11 ≤ h ≤ 10, -11 ≤ k ≤ 8, -13 ≤ l ≤ 12
Reflections collected	5203
Independent reflections	3025 [R_{int} = 0.0303, R_{sigma} = 0.0465]
Data/restraints/parameters	3025/0/207
Goodness-of-fit on F^2	1.105
Final R indexes [I>=2σ (I)]	R_1 = 0.0452, wR_2 = 0.1345
Final R indexes [all data]	R_1 = 0.0625, wR_2 = 0.1441
Largest diff. peak/hole / e Å^{-3}	0.49/-0.73

2-(5-(3-nitrophenyl)-4-(2-oxopyrrolidin-1-yl)oxazol-2-yl)benzaldehyde (50e):



Physical state : White solid

Yield :76%

Mp : 234-237 ˚C

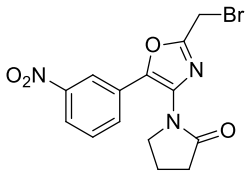
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3078, 2922, 2852, 1701, 1605, 1526, 1410, 1348, 1259, 1204, 1166, 1097, 1015, 835, 804, 739,721, 693.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1 H), 8.37 (t, *J* = 2.0 Hz, 1 H), 8.22 - 8.16 (m, *J* = 8.3 Hz, 2 H), 8.11 (ddd, *J* = 1.0, 2.0, 8.3 Hz, 1 H), 7.98 - 7.90 (m, 2 H), 7.85 (td, *J* = 1.3, 8.1 Hz, 1 H), 7.55 (t, *J* = 8.1 Hz, 1 H), 3.98 (t, *J* = 7.1 Hz, 2 H), 2.66 - 2.55 (m, 2 H), 2.30 (quin, *J* = 7.6 Hz, 2 H)

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) : δ 191.4, 174.5, 158.2, 148.4, 140.8, 137.7, 134.5, 131.4, 130.9, 130.2, 129.7, 129.1, 127.0, 122.9, 120.3, 77.4, 77.0, 76.7, 48.6, 31.2, 19.0.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{20}H_{16}N_3O_5]^+$378.1084; Found: 378.1093.

1-(2-(bromomethyl)-5-(3-nitrophenyl) oxazol-4-yl)pyrrolidin-2-one (50f):



Physical state : Light Yellow solid

Yield :81%

Mp : 128-130 ˚C

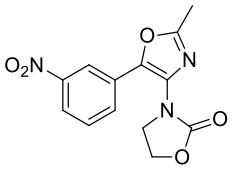
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3041, 2984, 2888, 1709, 1611, 1524, 1405, 1348, 1324, 1255, 1207, 1109, 920, 816, 766, 739, 720, 674, 588.

^{1}H NMR (400 MHz, $CDCl_3$) : δ 8.36 (s, 1H), 8.18 (dd, J = 1.2, 8.1 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.60 (t, J = 8.1 Hz, 1H), 4.48 (s, 2H), 3.97 (t, J = 7.1 Hz, 2H), 2.63 (t, J = 8.1 Hz, 2H), 2.32 (quin, J = 7.5 Hz, 2H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 174.3, 157.4, 148.3, 141.1, 133.1, 130.9, 129.6, 128.9, 123.0, 120.4, 48.5, 31.1, 19.9, 19.0.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{14}H_{13}BrN_3O_4]^+$366.0084; Found 366.0090.

3-(2-methyl-5-(3-nitrophenyl) oxazol-4-yl)oxazolidin-2-one (50g):



Physical state : Yellow solid

Yield :86%

Mp : 126-127 ˚C

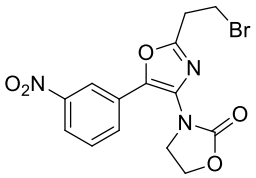
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3648, 3087, 2923, 2854, 1754, 1632, 1582, 1526, 1481, 1415, 1385, 1347, 1311, 1253, 1211, 1183, 1117, 1054, 1034, 983, 945, 898, 869, 807, 761, 731, 678, 597.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (t, J = 1.7 Hz, 1H), 8.22 - 8.10 (m, 1H), 7.89 (d, J = 7.8 Hz, 1H), 7.60 (t, J = 8.1 Hz, 1H), 4.62 (t, J = 8.1 Hz, 2H), 4.13 (t, J = 7.8 Hz, 2H), 2.55 (s, 3H).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 160.2, 155.8, 148.4, 140.2, 131.9, 130.7, 129.8, 129.0, 122.7, 119.9, 63.1, 45.8, 14.3.

HR-MS (ESI-TOF) m/z: [M+ Na]$^+$ calcd for [$C_{13}H_{11}N_3NaO_5$]$^+$ 312.0591; Found 312.0593.

3-(2-(2-bromoethyl)-5-(3-nitrophenyl) oxazol-4-yl)oxazolidin-2-one (50h):



Physical state : Light Yellow solid

Yield :73%

Mp : 132-134 ˚C

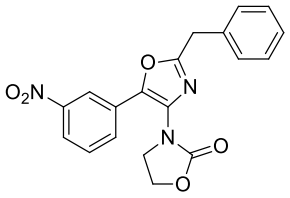
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3086, 2980, 2920, 1757, 1631, 1577, 1529, 1482, 1416, 1348, 1252, 1213, 1114, 1032, 983, 945, 808, 732, 678, 560.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (s, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 4.63 (t, J = 7.8 Hz, 2H), 4.16 (t, J = 7.8 Hz, 2H), 3.76 (t, J = 6.8 Hz, 2H), 3.43 (t, J = 6.8 Hz, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.1, 155.6, 148.4, 140.4, 132.1, 130.9, 129.8, 128.8, 122.9, 120.1, 63.2, 45.7, 32.0, 26.6.

HR-MS (ESI-TOF) m/z: [M+ H]$^+$ calcd for [$C_{14}H_{13}BrN_3O_5$]$^+$ 382.0033; Found: 382.0040.

3-(2-benzyl-5-(3-nitrophenyl) oxazol-4-yl)oxazolidin-2-one (50i):



Physical state : Light brown solid

Yield :70%

Mp : 148-151 ˚C

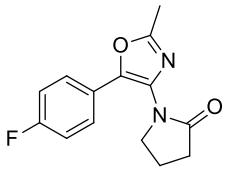
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3062, 2986, 2918, 1756, 1630, 1573, 1527, 1481, 1413, 1347, 1252, 1211, 1183, 1116, 1052, 1032, 982, 945, 898, 869, 806, 728, 696, 566.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (t, J = 1.7 Hz, 1H), 8.14 (dd, J = 1.0, 8.3 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 8.1 Hz, 1H), 7.40 - 7.34 (m, 4 H), 7.33 - 7.28 (m, 1H), 4.60 (t, J = 8.1 Hz, 2H), 4.16 (s, 2H), 4.15 - 4.10 (m, 2H).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 161.6, 155.6, 148.4, 140.3, 134.4, 132.1, 130.8, 129.7, 128.9, 128.9, 127.5, 122.8, 120.0, 63.1, 45.7, 34.9.

HR-MS (ESI-TOF) m/z: [M+ H]$^+$ calcd for [$C_{19}H_{16}N_3O_5$]$^+$ 366.1084; Found 366.1087.

1-(5-(4-fluorophenyl)-2-methyloxazol-4-yl)pyrrolidin-2-one (50j)



Physical state : White solid

Yield :86%

Mp : 78-80 ˚C

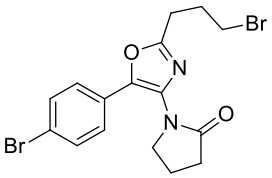
IR (MIR-ATR, 4000–600 cm^{-1})*:* ν_{max} = 3747, 3066, 2926, 2891, 1703, 1631, 1589, 1509, 1411, 1299, 1260, 1225, 1158, 1092, 1036, 1010, 957, 915, 836, 728, 606, 579.

^{1}H NMR (400 MHz, $CDCl_3$) δ : 7.54 - 7.47 (m, 2H), 7.12 - 7.05 (m, 2H), 3.80 (t, *J* = 7.1 Hz, 2H), 2.58 (t, *J* = 8.3 Hz, 2H), 2.48 (s, 3H), 2.28 - 2.18 (m, 2H).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 175.1, 163.7, 161.2, 159.1, 142.1, 130.2, 127.0, 126.9 (d, *J* = 8), 123.9 (d, *J* = 4), 115.9 (d, *J* = 22), 48.8, 31.1, 19.0, 14.2.

HR-MS (ESI-TOF) m/z: [M+ H]$^+$ calcd for [$C_{14}H_{14}FN_2O_2$]$^+$ 261.1034; Found: 261.1035.

3-(5-(4-bromophenyl)-2-(3-bromopropyl)oxazol-4-yl)oxazolidin-2-one (50k):



Physical state : Light Yellow solid

Yield :83%

Mp : 128-131 ˚C

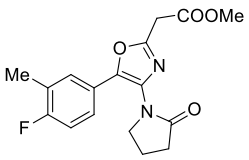
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3059, 2921, 2851, 1710, 1628, 1580, 1490, 1414, 1260, 1072, 1007, 913, 827, 728.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 2H), 3.83 (t, *J* = 6.8 Hz, 2H), 3.54 (t, *J* = 6.4 Hz, 2H), 2.98 (t, *J* = 7.3 Hz, 2H), 2.59 (t, *J* = 8.1 Hz, 2H), 2.37 (quin, *J* = 6.8 Hz, 2H), 2.25 (quin, *J* = 7.6 Hz, 2H).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 174.9, 161.2, 141.9, 131.9, 131.0, 126.5, 126.4, 122.4, 48.7, 32.3, 31.2, 29.4, 26.8, 18.9.

HR-MS (ESI-TOF) m/z: [M+ Na]$^+$ calcd for [$C_{16}H_{16}Br_2N_2NaO_2$]$^+$ 448.9471; Found 448.9464.

methyl 2-(5-(4-fluoro-3-methylphenyl)-4-(2-oxopyrrolidin-1-yl)oxazol-2-yl)acetate (50l):



Physical state : Yellow solid

Yield : 83%

Mp : 126-128 ˚C

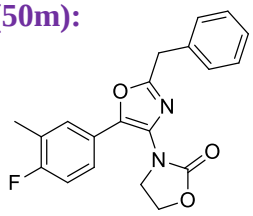
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 2956, 2893, 1744, 1706, 1630, 1586, 1501, 1413, 1350, 1254, 1119, 1010, 887, 824, 731, 702, 635, 549.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4 (dd, J = 7.1, 1.7 Hz, 1H), 7.32 (ddd, J = 7.9, 5, 2.2 Hz, 1H), 7.03 (t, J = 8.8 Hz, 1H), 3.87 (s, 2H), 3.83 (t, J = 7.3 Hz, 2H), 3.77 (s, 3H), 2.57 (t, J = 8.1 Hz, 2H), 2.29 (s, 3H), 2.28-2.20 (m, 2H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 174.9, 167.5, 162.5, 160.0, 154.5, 143.3, 130.3, 128.6, 128.5, 125.3 (d, J = 18), 124.7, (d, J = 9), 123.28 (d, J = 4), 115.55 (d, J = 24), 52.7, 48.7, 34.6, 31.1, 18.9, 14.67, 14.64.

HR-MS (ESI-TOF) m/z: $[M+ Na]^+$ calcd for $[C_{17}H_{17}FN_2O_4]^+$ 355.1065; Found 355.1066.

3-(2-benzyl-5-(4-fluoro-3-methylphenyl)oxazol-4-yl)oxazolidin-2-one (50m):



Physical state : White solid

Yield :68%

Mp : 96-98 ˚C

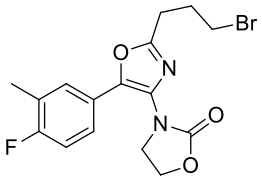
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3060, 2985, 2922, 1757, 1682, 1574, 1501, 1423, 1258, 1228, 1171, 1120, 1054, 1033, 982, 948, 795, 757, 716, 640.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (dd, J = 1.7, 7.6 Hz, 1H), 7.40 - 7.37 (m, 1H), 7.37 - 7.33 (m, 4H), 7.32 - 7.25 (m, 1H), 7.03 (t, J = 9.0 Hz, 1H), 4.53 (t, J = 7.8 Hz, 2H), 4.12 (s, 2H), 4.02 (dd, J = 7.3, 8.8 Hz, 2H), 2.29 (d, J = 1.5 Hz, 3H).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 162.6, 160.4, 160.1, 156.3, 143.2, 134.8, 129.4, 128.9, 128.8, 128.6, 128.5, 127.3, 125.6 (d, *J* = 17), 124.7 (d, *J* = 9), 123.0 (d, *J* = 4), 115.5 (d, *J* = 24), 62.9, 46.0, 34.9, 14.7.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{20}H_{18}FN_2O_3]^+$ 353.1296; Found 353.1303.

3-(2-(3-bromopropyl)-5-(4-fluoro-3-methylphenyl)oxazol-4-yl)oxazolidin-2-one (50n):



Physical state : White solid

Yield :66%

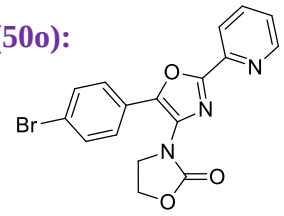
Mp : 118-121 ˚C

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 2967, 2921, 1755, 1639, 1580, 1502, 1423, 1256, 1229, 1170, 1119, 1034, 980, 946, 877, 821, 733, 630, 559.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (dd, *J* = 1.5, 7.3 Hz, 1H), 7.43 - 7.34 (m, 1H), 7.05 (t, *J* = 8.8 Hz, 1H), 4.56 (dd, *J* = 7.3, 8.8 Hz, 2H), 4.02 (dd, *J* = 7.3, 8.8 Hz, 2H), 3.55 (t, *J* = 6.4 Hz, 2H), 2.98 (t, *J* = 7.3 Hz, 2H), 2.41 - 2.32 (m, 2H), 2.31 (d, *J* = 1.5 Hz, 3H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 162.6, 160.7, 160.1, 156.4, 143.0, 129.3, 128.5 (d, *J* = 5), 125.7, 125.5, 124.7 (d, *J* = 8), 123.0 (d, *J* = 4), 115.7, 115.5, 62.9, 46.0, 32.3, 29.4, 26.8, 14.7. HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{16}H_{17}BrFN_2O_3]^+$383.0401; Found 383.0396.

3-(5-(4-bromophenyl)-2-(pyridin-2-yl)oxazol-4-yl)oxazolidin-2-one (50o):



Physical state : Light green solid

Yield :75%

Mp : 212-214 ˚C

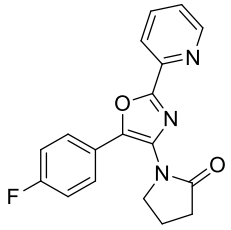
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3564, 3364, 2259, 2131, 1746, 1734, 1698, 1649, 1557, 1540, 1521, 1256, 1045, 1023, 989, 826, 763, 666, 632, 574, 548.

^{1}H NMR (400 MHz, DMSO-D_6): δ 8.77 (d, J = 4.4 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.03 (dt, J = 1.5, 7.8 Hz, 1H), 7.71 (q, J = 8.8 Hz, 4H), 7.59 (dd, J = 4.9, 6.8 Hz, 1H), 4.63 (t, J = 7.8 Hz, 2H), 4.13 (t, J = 8.1 Hz, 2H).

^{13}C{^{1}H}NMR (100 MHz, DMSO-D_6): δ 157.1, 155.4, 150.1, 144.5, 142.0, 137.7, 132.4, 131.9, 127.1, 125.8, 125.7, 122.3, 122.2, 63.3, 45.6.

HR-MS (ESI-TOF) m/z: [M+ Na]$^{+}$ calcd for [$C_{17}H_{12}BrN_3NaO_3$]$^{+}$ 407.9954; Found 407.9974.

1-(5-(4-fluorophenyl)-2-(pyridin-2-yl)oxazol-4-yl)pyrrolidin-2-one (50p):



Physical state : White solid

Yield :88%

Mp : 188-191 ˚C

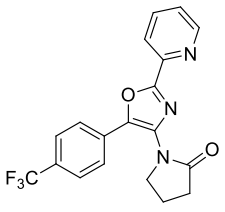
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3054, 2983, 2891, 1702, 1617, 1587, 1508, 1459, 1411, 1332, 1258, 1222, 1157, 1111, 1045, 1012, 838, 793, 738, 623, 601.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 - 8.74 (m, 1H), 8.16 - 8.09 (m, 1H), 7.84 (dt, J = 2.0, 7.8 Hz, 1H), 7.73 - 7.66 (m, 2H), 7.39 (ddd, J = 1.0, 4.8, 7.5 Hz, 1H), 7.17 - 7.11 (m, 2H), 3.97 (t, J = 7.1 Hz, 2H), 2.62 (t, J = 7.1 Hz, 2H), 2.29 (quin, J = 7.5 Hz, 2H).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 175.0, 161.6, 150.3, 145.5, 143.5, 137.0, 127.7 (d, J = 8), 123.6 (d, J = 4), 122.1, 116.0 (d, J = 22), 48.9, 31.2, 19.0.

HR-MS (ESI-TOF) m/z: [M+ H]$^{+}$ calcd for [$C_{18}H_{15}FN_3O_2$]$^{+}$ 324.1143; Found 324.1144.

1-(2-(pyridin-2-yl)-5-(4-(trifluoromethyl)phenyl)oxazol-4-yl)pyrrolidin-2-one (50q):



Physical state : white solid

Yield :92%

Mp : 202-205 ˚C

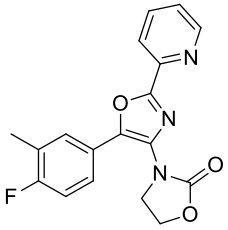
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3055, 2986, 2895, 1710, 1616, 1460, 1411, 1323, 1259, 1165, 1117, 1067, 1013, 843, 795, 740, 707, 619.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 - 8.72 (m, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.86 (dt, J = 1.5, 7.8 Hz, 1H), 7.83 - 7.77 (m, 2H), 7.73 - 7.65 (m, 2H), 7.42 (ddd, J = 1.0, 4.9, 7.8 Hz, 1H), 4.03 (t, J = 7.1 Hz, 2H), 2.64 (t, J = 8.1 Hz, 2H), 2.32 (quin, J = 7.5 Hz, 2H).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 174.7, 158.0, 150.4, 145.3, 142.3, 137.1, 133.9, 130.7, 130.3, 130.0, 125.7, 125.6 (d, J = 11), 125.3, 125.2, 122.3, 48.8, 31.3, 19.0.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{19}H_{15}F_3N_3O_2]^+$ 374.1111; Found 374.1118.

1-(5-(4-fluoro-3-methylphenyl)-2-(pyridin-2-yl)oxazol-4-yl)pyrrolidin-2-one (50r):



Physical state : White solid

Yield :73%

Mp : 162-164 ˚C

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3055, 2991, 2920, 1756, 1627, 1589, 1502, 1423, 1331, 1227, 1120, 1032, 949, 795, 757, 716, 640.

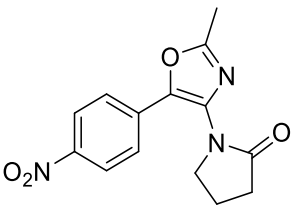
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, J = 4.9 Hz, 1H), 8.17 (d, J = 7.8 Hz, 1H), 8.02 (t, J = 7.8 Hz, 1H), 7.68 (d, J = 7.3 Hz, 1H), 7.64 - 7.51 (m, 2H), 7.30 (t, J = 9.0 Hz, 1H), 4.62 (t, J = 7.8 Hz, 2H), 4.10 (t, J = 7.8 Hz, 2H), 2.33 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$ & DMSO-D_6): δ 162.0, 159.6, 156.7, 155.7, 150.0, 144.5, 142.8, 137.7, 131.4, 128.5 (d, J = 4), 125.6, 125.3, 125.1 (d, J = 5), 125.0, 122.8 (d, J = 6), 122.2, 122.1, 118.9, 115.8 (d, J = 25), 63.2, 45.7, 14.1.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{18}H_{15}FN_3O_3]^+$ 340.1092; Found: 340.1093.

1-(2-methyl-5-(4-nitrophenyl)oxazol-4-yl)pyrrolidin-2-one (50s):

Physical state : Light yellow solid



Yield :78%

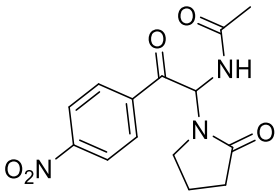
Mp : 166-168 ˚C

IR (MIR-ATR, 4000–600 cm^{-1}) ν_{max} = 3258, 3049, 2923, 2883, 2513, 1670, 1526, 1407, 1347, 1322, 1265, 1220, 1185, 1133, 877, 821, 790, 679, 611.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 - 8.27 (m, 2H), 8.26 - 8.11 (m, 2H), 7.33 (1H, d, J = 6.8 Hz), 6.80 (1H, d, J = 6.8 Hz), 3.50 (1H, dt, J_a = 6.4 and J_b = 8.6 Hz), 3.39 (1H, dt, J_a = 5.9 and J_b = 8.8 Hz), 2.36 - 2.26 (m, 2H), 2.12 (s, 3H), 2.09 - 1.91 (m, 3H).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 191.6, 175.5, 170.2, 150.7, 138.6, 129.7, 123.9, 60.6, 44.6, 30.3, 23.0, 18.3.

(2-(4-nitrophenyl)-2-oxo-1-(2-oxopyrrolidin-1-yl)ethyl)acetamide (50s'):



Physical state : White solid

Yield :38%

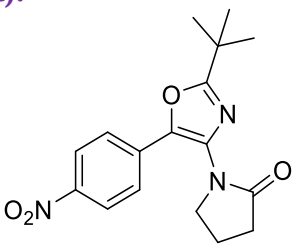
Mp : 184-186 ˚C

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3111, 2924, 2898, 1696, 1598, 1577, 1512, 1416, 1326, 1267, 1222, 1175, 1036, 852, 689, 644.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 - 8.34 (m, 2H) 7.56 - 7.71 (m, 2H) 3.82 - 4.00 (m, 2H) 2.56 - 2.72 (m, 2H) 2.54 (s, 3H) 2.19 - 2.37 (m, 2H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 174.4, 160.7, 146.6, 140.0, 133.7, 125.4, 123.9, 48.6, 31.2, 19.0, 14.3.

1-(2-(tert-butyl)-5-(4-nitrophenyl)oxazol-4-yl)pyrrolidin-2-one (50t):



Physical state : Yellow solid

Yield :32%

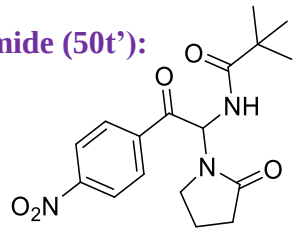
Mp : 168-170 ˚C

IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3215, 2975, 2940, 1520, 1661, 1523, 1345, 1284, 1198, 810, 780, 729, 690.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 - 8.38 (m, 2H) 8.19 - 8.27 (m, 2H) 7.39 (1H, d, J_a = 6.36 Hz) 6.78 (1H, d, J_a = 6.36 Hz) 3.24 - 3.45 (m, 2H) 2.23 - 2.44 (m, 2H) 1.91 - 2.09 (m, 2H) 1.23 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 191.8, 178.5, 175.6, 150.8, 138.5, 129.8, 123.9, 60.7, 44.3, 39.0, 30.4, 27.6, 27.4, 18.3.

N-(2-(4-nitrophenyl)-2-oxo-1-(2-oxopyrrolidin-1-yl)ethyl)pivalamide (50t'):



Physical state : Viscous liquid

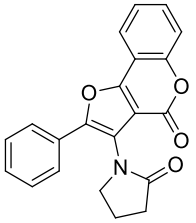
Yield :78%

IR (MIR-ATR, 4000–600 cm^{-1}) ν_{max} = 3111, 2974, 2932, 1709, 1599, 1514, 1413, 1337, 1265, 1194, 1110, 1021, 853, 756, 634.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 - 8.21 (m, 2H), 7.68 - 7.58 (m, 2H), 3.96 (2H, t, J = 7.1 Hz), 2.67 - 2.57 (m, 2H), 2.29 (2H, quin, J = 7.6 Hz), 1.44 (s, 9H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 174.2, 170.3, 146.5, 139.4, 134.0, 133.5, 125.4, 123.9, 48.6, 34.1, 31.3, 28.5, 18.8.

1-(4-oxo-2-phenyl-4H-furo[3,2-c]chromen-3-yl)pyrrolidin-2-one (56a):



Physical state : White solid

Yield :85%

Mp : 222-225 ˚C

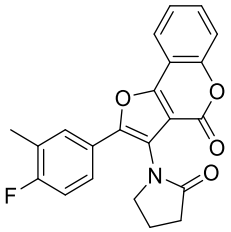
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3057, 2957, 1737, 1702, 1633, 1495, 1401, 1255, 1161, 1116, 1095, 958, 834, 756, 731, 690.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, J = 1.0, 7.8 Hz, 1H), 7.82 - 7.76 (m, 2H), 7.56 - 7.33 (m, 6H), 3.86 (br. s., 2H), 2.66 (t, J = 8.1 Hz, 2H), 2.32 (quin, J = 7.5 Hz, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 176.5, 156.8, 156.0, 152.8, 150.9, 131.1, 129.5, 129.0, 128.2, 125.4, 124.7, 120.7, 118.2, 117.4, 112.5, 109.3, 49.8, 30.9, 19.4.

HR-MS (ESI-TOF) m/z: [M+ H]$^{+}$ calcd for $[C_{21}H_{16}NO_4]^{+}$ 346.1074; Found 346.1065.

1-(2-(4-fluoro-3-methylphenyl)-4-oxo-4H-furo[3,2-c]chromen-3-yl)pyrrolidin-2-one (56b):



Physical state : White solid

Yield :81%

Mp : 270-273 ˚C

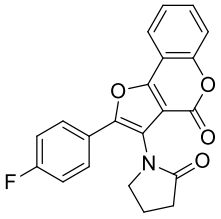
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3055, 2923, 2889, 1739, 1698, 1635, 1506, 1438, 1413, 1262, 1238, 1119, 1042, 963, 897, 816, 760, 721, 635.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (dd, J = 1.0, 7.8 Hz, 1H), 7.67 - 7.60 (m, 1H), 7.59 - 7.51 (m, 2H), 7.47 - 7.42 (m, 1H), 7.41 - 7.34 (m, 1H), 3.86 (br. s., 2H), 2.77 - 2.51 (m, 2H), 2.40 - 2.34 (m, 3H), 2.34 - 2.21 (m, 2H).

^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 176.5, 163.1, 160.6, 156.8, 155.9, 152.7, 150.4, 131.1, 128.9 (d, J = 6), 125.9 (d, J = 18), 125.0, 124.9, 124.7, 124.2 (d, J = 3), 120.6, 117.6, 117.4, 116.0, 115.7 (d, J = 23), 112.5, 109.3, 49.8, 30.9, 19.4, 14.8, 14.8.

HR-MS (ESI-TOF) m/z: [M+ H]$^{+}$ calcd for $[C_{22}H_{17}FNO_4]^{+}$ = 378.1136; Found 378.1128.

1-(2-(4-fluorophenyl)-4-oxo-4H-furo[3,2-c]chromen-3-yl)pyrrolidin-2-one (56c):



Physical state : Light Yellow solid

Yield :83%

Mp : 268-271 ˚C

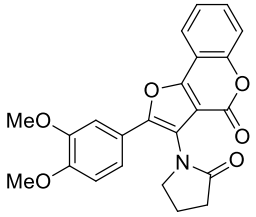
IR (MIR-ATR, 4000–600 cm^{-1}) ν_{max} = 3067, 2889, 1730, 1629, 1604, 1503, 1440, 1406, 1322, 1257, 1225, 1159, 1115, 1029, 959, 894, 833, 756, 724, 682, 622, 565, 516.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, J = 1.5, 7.8 Hz, 1H), 7.81 - 7.73 (m, 2H), 7.54 (ddd, J = 1.5, 7.2, 8.4 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.41 - 7.33 (m, 1H), 7.21 - 7.11 (m, 2H), 3.86 (br. s., 2H), 2.75 - 2.56 (m, 2H), 2.32 (quin, J = 7.5 Hz, 2H).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 176.6, 164.4, 161.9, 156.8, 156.0, 152.8, 150.1, 131.2, 127.6 (d, J = 9), 124.8, 124.5 (d, J = 4), 120.6, 117.9, 117.4, 116.4 (d, J = 22), 112.4, 109.2, 49.9, 30.8, 19.4.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{21}H_{15}FNO_4]^+$ 364.0980; Found 364.0976.

1-(2-(3,4-dimethoxyphenyl)-4-oxo-4H-furo[3,2-c]chromen-3-yl)pyrrolidin-2-one (56d):



Physical state : Light brown solid

Yield : 82%

Mp : 253-255 ˚C

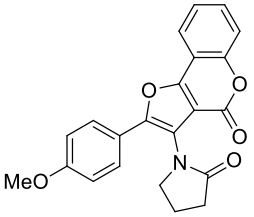
IR (MIR-ATR, 4000–600 cm^{-1}) ν_{max} = 3747, 3673, 3614, 3055, 2308, 2134, 1741, 1701, 1649, 1540, 1515, 1458, 1419, 1263, 1144, 1026, 965, 896, 730, 702, 559.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dd, J = 1.5, 7.8 Hz, 1 H), 7.54 (dt, J = 1.5, 7.8 Hz, 1 H), 7.45 (d, J = 7.8 Hz, 1 H), 7.41 - 7.35 (m, 2 H), 7.34 (d, J = 2.0 Hz, 1 H), 6.97 (d, J = 8.8 Hz, 1 H), 3.95 (d, J = 3.9 Hz, 7 H), 2.66 (br. s., 2 H), 2.31 (br. s., 2 H), 1.66 (br. s., 2 H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 176.5, 156.9, 155.6, 152.7, 151.2, 150.2, 149.2, 130.9, 124.7, 120.9, 120.6, 119.0, 117.4, 116.8, 112.6, 111.5, 109.4, 108.7, 56.0, 56.0, 49.9, 30.9, 19.5.

HR-MS (ESI-TOF) m/z: $[M+H]^+$ calcd for $[C_{23}H_{20}NO_6]^+$ 406.1285; Found 406.1286.

1-(2-(4-methoxyphenyl)-4-oxo-4H-furo[3,2-c]chromen-3-yl)pyrrolidin-2-one (56e):



Physical state : Pale Yellow solid

Yield :78%

Mp : 253-255 ˚C

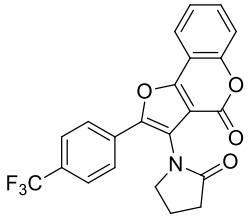
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 2961, 2840, 1738, 1706, 1609, 1570, 1511, 1440, 1401, 1305, 1255, 1176, 1117, 1034, 959, 835, 757, 687.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (dd, J = 1.5, 7.8 Hz, 1H), 7.76 - 7.70 (m, 2H), 7.53 (ddd, J = 2.0, 7.1, 8.6 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.40 - 7.33 (m, 1H), 7.03 - 6.94 (m, 2H), 4.00 - 3.70 (m, 5H), 2.65 (t, J = 7.8 Hz, 2H), 2.31 (t, J = 7.3 Hz, 2H).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 160.5, 155.5, 152.7, 151.2, 130.8, 127.1, 124.7, 120.9, 120.5, 117.4, 116.6, 114.5, 112.7, 109.4, 55.4, 49.9, 30.9, 19.4.

HR-MS (ESI-TOF) m/z: [M+Na]+ calcd for $[C_{22}H_{17}NO_5]^+$ 398.0999; Found: 398.1002.

1-(4-oxo-2-(4-(trifluoromethyl)phenyl)-4H-furo[3,2-c]chromen-3-yl)pyrrolidin-2-one (56f):



Physical state : White solid

Yield :85%

Mp : 238-241 ˚C

IR (MIR-ATR, 4000–600 cm^{-1}) : ν_{max} = 2889, 1976, 1740, 1703, 1625, 1506, 1442, 1409, 1319, 1253, 1164, 1115, 1066, 1022, 956, 893, 843, 756, 690, 596.

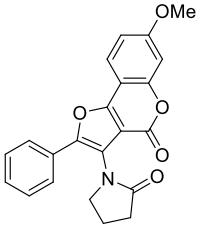
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (dd, J = 1.0, 7.8 Hz, 1H), 7.93 - 7.87 (m, J = 8.3 Hz, 2H), 7.78 - 7.69 (m, J = 8.3 Hz, 2H), 7.63 - 7.52 (m, 1H), 7.49 - 7.33 (m, 2H), 3.90 (br. s., 2H), 2.67 (t, J = 7.8 Hz, 2H), 2.35 (quin, J = 7.5 Hz, 2H).

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$): δ 176.4, 156.7, 156.6, 152.9, 149.2, 131.6, 131.4, 131.1, 130.7, 126.0 (d, J = 11), 125.1, 124.9, 122.4, 120.8, 120.1, 117.5, 112.3, 109.3, 49.8, 30.8, 19.5.

HR-MS (ESI-TOF) m/z: [M+ Na]+ calcd for $[C_{22}H_{14}F_3NNaO_4]^+$ 436.0767; Found 436.0765.

1-(7-methoxy-4-oxo-2-phenyl-4H-furo[3,2-c]chromen-3-yl)pyrrolidin-2-one (56g):

Physical state : White solid



Yield :75%

Mp : 190-193 ˚C

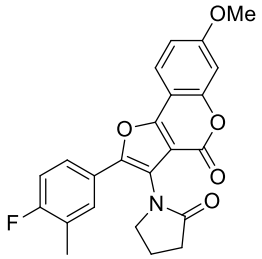
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3061, 2934, 2846, 1735, 1633, 1603, 1495, 1460, 1408, 1372, 1330, 1256, 1198, 1160, 1121, 1027, 969, 946, 838, 766, 693, 634, 570.

^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 8.3 Hz, 1H), 7.79 - 7.74 (m, 2H), 7.50 - 7.44 (m, 2 H), 7.42 - 7.36 (m, 1H), 6.99 - 6.92 (m, 2H), 3.89 (s, 3H), 3.89 - 3.70 (m, 2H), 2.71 - 2.61 (m, 2 H), 2.32 (t, J = 7.6 Hz, 2H).

$^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 176.5, 162.3, 157.1, 156.8, 154.6, 149.9, 129.2, 129.0, 128.3, 125.3, 121.7, 118.0, 113.1, 106.8, 106.0, 101.4, 55.8, 49.8, 30.9, 19.4.

HR-MS (ESI-TOF) m/z: [M+ H]+ calcd for $[C_{22}H_{17}FNO_5]^+$ 376.1179; Found 376.1178.

1-(2-(4-fluoro-3-methylphenyl)-7-methoxy-4-oxo-4H-furo[3,2-c]chromen-3-yl)pyrrolidin-2 one (56h):



Physical state : White solid

Yield :86%

Mp : 204-207 ˚C

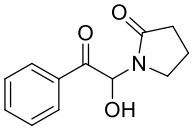
IR (MIR-ATR, 4000–600 cm^{-1}: ν_{max} = 3633, 2933, 2886, 1734, 1699, 1635, 1608, 1503, 1460, 1420, 1337, 1249, 1161, 1114, 1026, 973, 945, 835, 766, 720, 696, 623, 552.

^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.8 Hz, 1H), 7.59 (dd, J = 1.5, 7.3 Hz, 1H), 7.57 - 7.50 (m, 1H), 7.08 (t, J = 8.8 Hz, 1H), 6.98 - 6.91 (m, 2H), 3.89 (s, 3H), 3.88 - 3.79 (m, 2H), 2.74 - 2.49 (m, 2H), 2.34 (d, J = 1.5 Hz, 3H), 2.33 - 2.26 (m, 2H).

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 176.4, 162.9, 162.3, 160.4, 157.1, 156.6, 154.6, 149.4, 128.7 (d, J = 6), 125.8, 125.7, 124.8 (d, J = 8), 124.3 (d, J = 3), 121.2, 117.5, 115.9 (d, J = 23), 113.1, 106.8, 105.9, 101.4, 55.8, 49.8, 30.9, 19.4, 14.8, 14.7.

HR-MS (ESI-TOF) m/z: [M+ H] + calcd for $[C_{23}H_{19}FNO_5]^+$ 408.1242; Found 408.1247.

1-(1-hydroxy-2-oxo-2-phenylethyl)pyrrolidin-2-one (49):



Physical state : White solid

Yield :96%

Mp : 98-101 ˚C

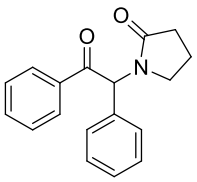
IR (MIR-ATR, 4000–600 cm^{-1}) : ν_{max} = 3225, 3074, 2959, 2883, 1692, 1668, 1594, 1491, 1417, 1352, 1265, 1233, 1177, 1116, 1024, 1000, 963, 850, 798, 756, 683, 616, 567, 535.

^1H NMR (400 MHz, $CDCl_3$): δ 8.13 - 8.05 (m, 2H), 7.69 - 7.62 (m, 1H), 7.55 - 7.47 (m, 2H), 6.69 (d, *J* = 6.8 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 1H), 3.48 (dt, *J* = 6.1, 8.9 Hz, 1H), 2.86 (dt, *J* = 5.1, 8.9 Hz, 1H), 2.45 (ddd, *J* = 7.1, 9.7, 17.0 Hz, 1H), 2.39 - 2.26 (m, 1H), 2.08 - 1.95 (m, 1H), 1.92 - 1.78 (m, 1H).

$^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 195.9, 175.4, 135.0, 131.9, 129.1, 129.0, 77.4, 77.1, 76.7, 73.3, 41.3, 30.9, 17.8.

HR-MS (ESI-TOF) m/z: [M+ H]+ calcd for $[C_{12}H_{14}NO_3]^+$ 220.0968; Found 220.0969.

1-(2-oxo-1,2-diphenylethyl)pyrrolidin-2-one (57):



Physical state : Pale Yellow solid

Yield :78%

Mp : 104-106 ˚C

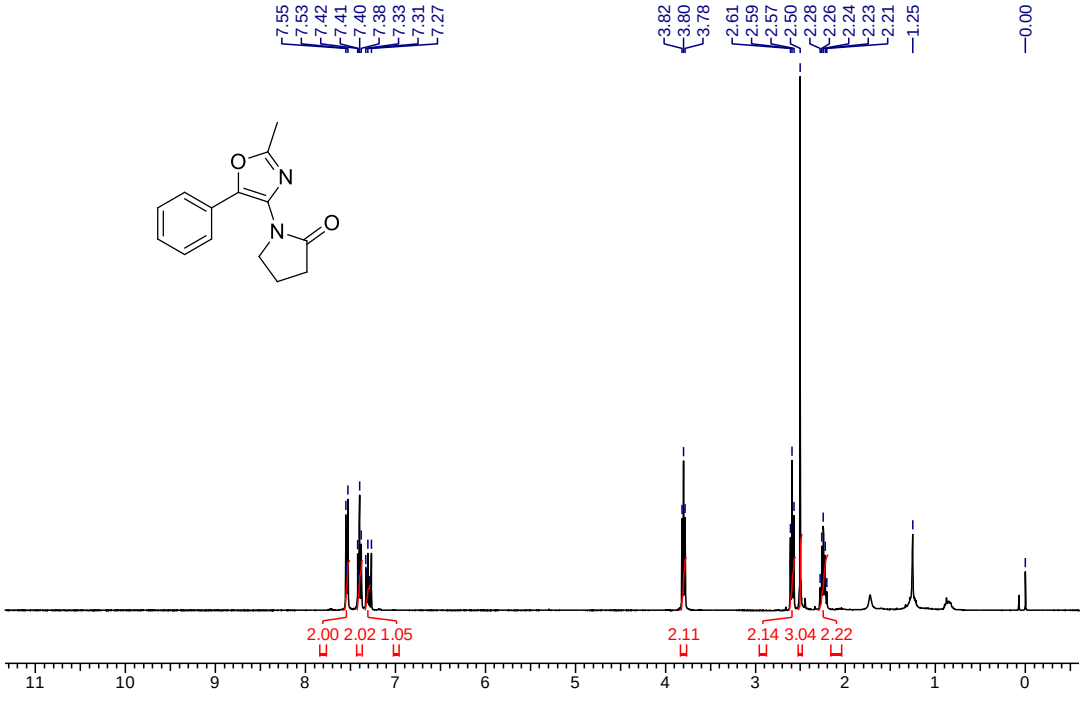
IR (MIR-ATR, 4000–600 cm^{-1}): ν_{max} = 3747, 3689, 3673, 3649, 3614, 3565, 3061, 2978, 2891, 1676, 1596, 1579, 1520, 1450, 1416, 1362, 1268, 1206, 1100, 1076, 1030, 934, 854, 794, 762, 743, 697, 635, 590, 555.

^1H NMR (400 MHz, $CDCl_3$): δ 7.96 - 7.87 (m, 2 H), 7.52 - 7.45 (m, 1 H), 7.41 - 7.31 (m, 5 H), 7.30 - 7.24 (m, 2 H), 6.84 (s, 1 H), 3.81 (dt, *J* = 5.9, 8.8 Hz, 1 H), 2.92 (dt, *J* = 5.4, 9.0 Hz, 1 H), 2.57 - 2.36 (m, 2 H), 2.16 - 2.03 (m, 1 H), 1.97 - 1.83 (m, 1 H).

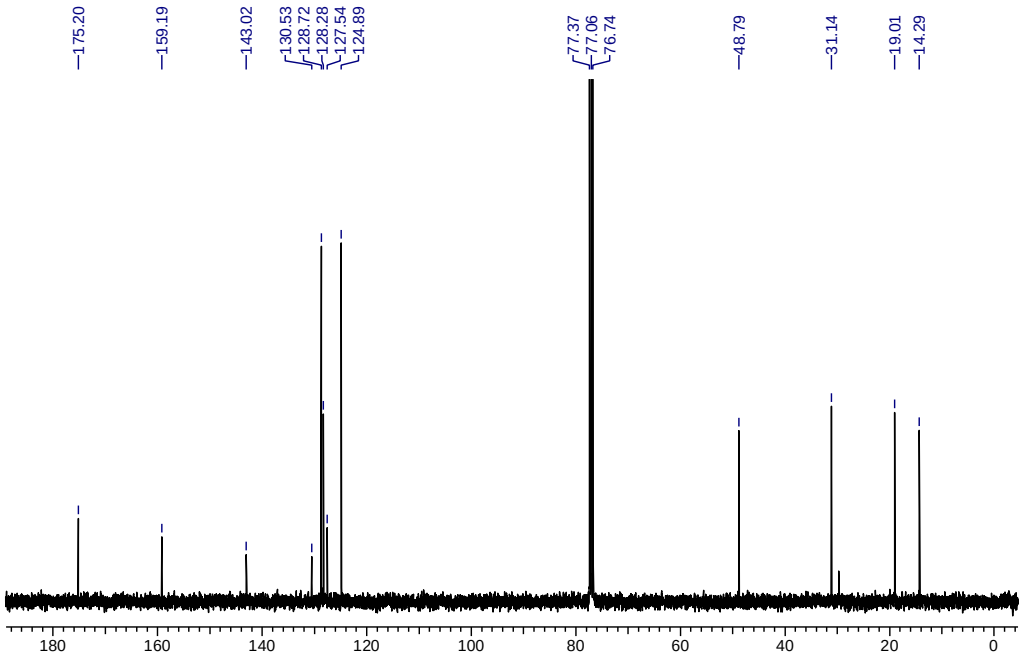
$^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): δ 196.5, 175.2, 135.0, 134.5, 133.4, 129.4, 129.2, 129.0, 128.6, 77.4, 77.1, 76.7, 60.7, 45.2, 31.1, 18.3.

HR-MS (ESI-TOF) m/z: [M+ H]+ calcd for $[C_{18}H_{18}NO_2]^+$ 280.1332; Found: 280.1326.

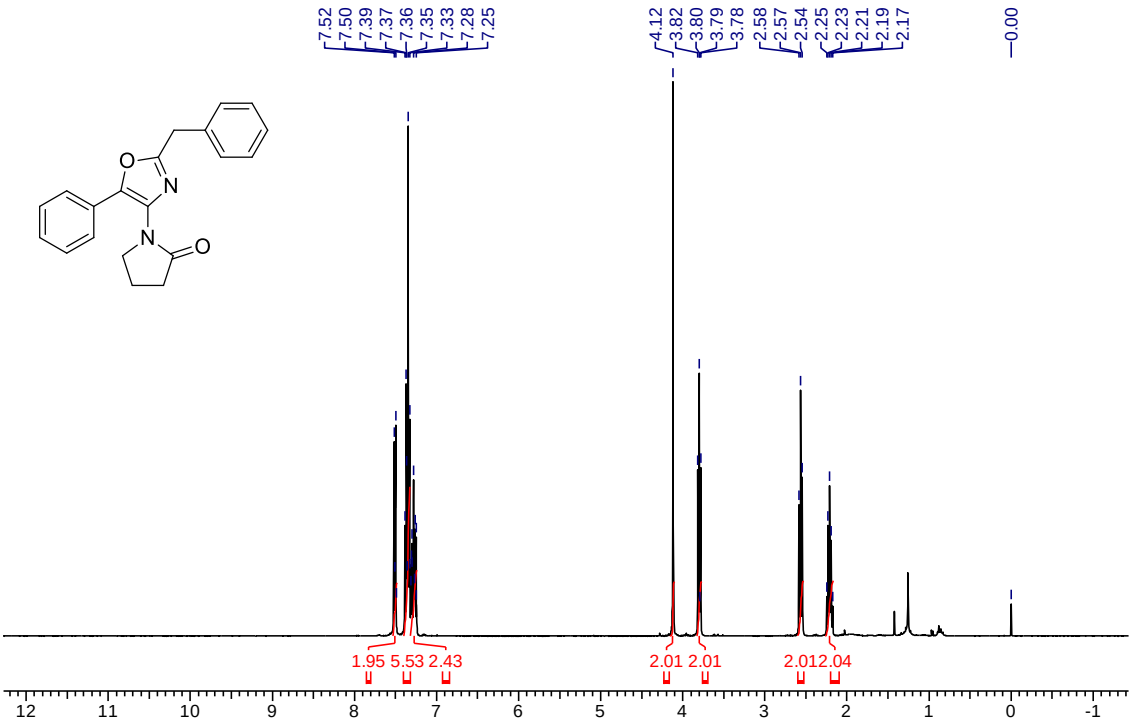
Representative ^{1}H, ^{13}C NMR spectral Copies



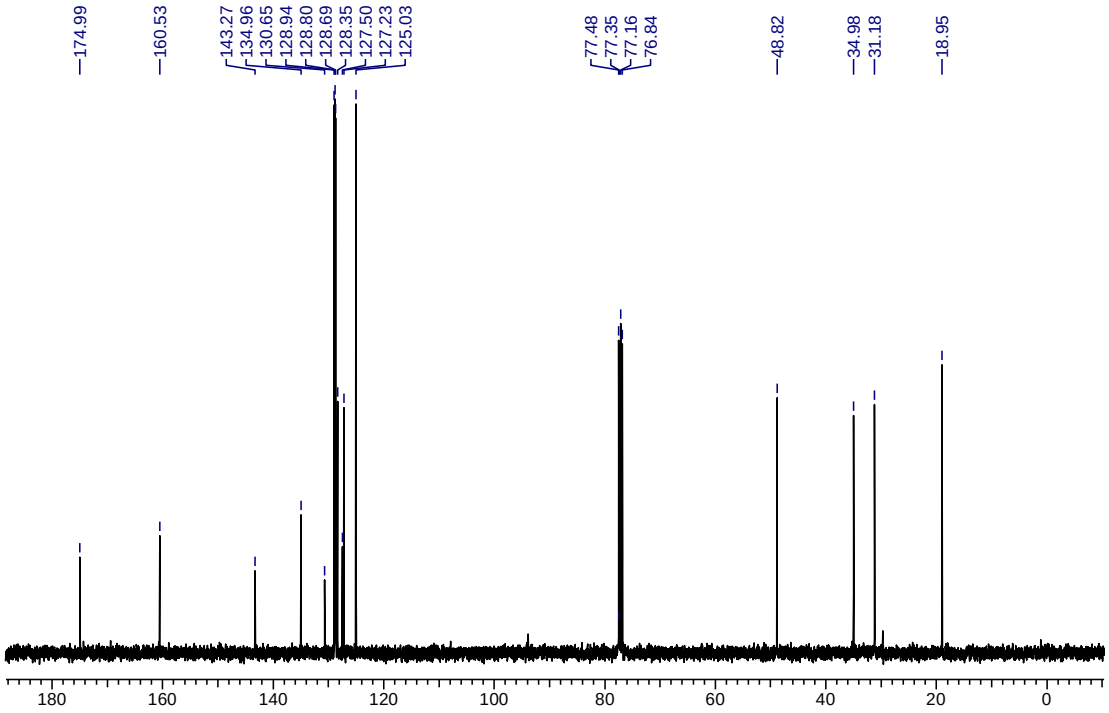
^{1}H NMR (400 MHz) spectrum of compound **50a** in $CDCl_3$



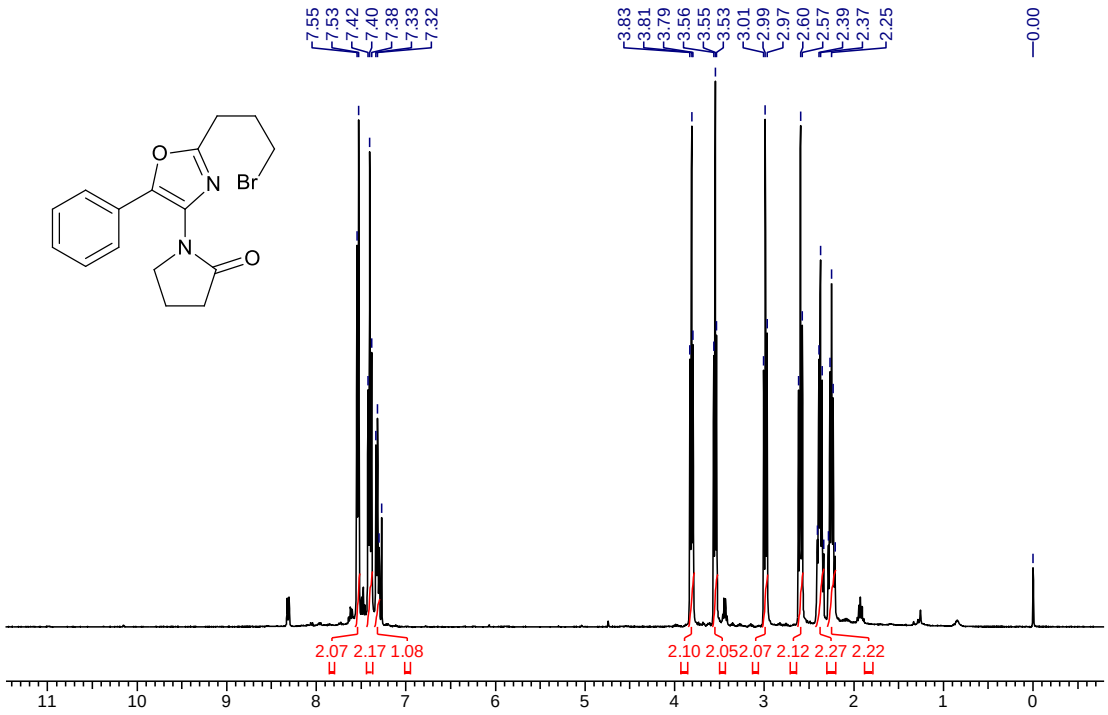
^{13}C NMR (100 MHz) spectrum of compound **50a** in $CDCl_3$



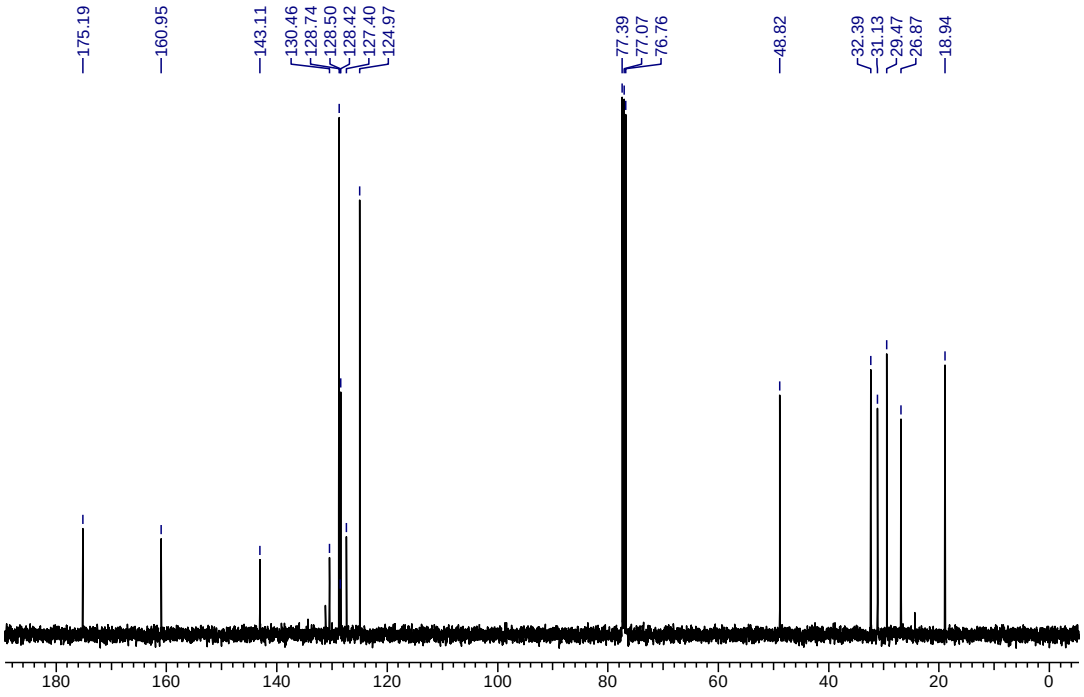
^{1}H NMR (400 MHz) spectrum of compound **50b** in $CDCl_3$



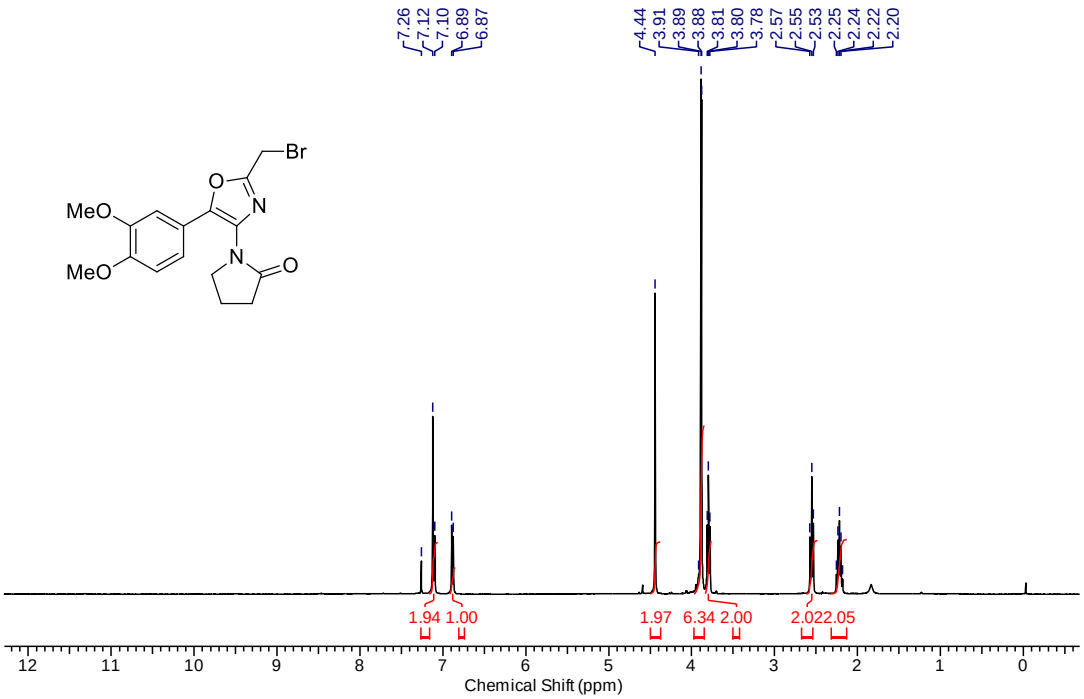
^{13}C NMR (100 MHz) spectrum of compound **50b** in $CDCl_3$



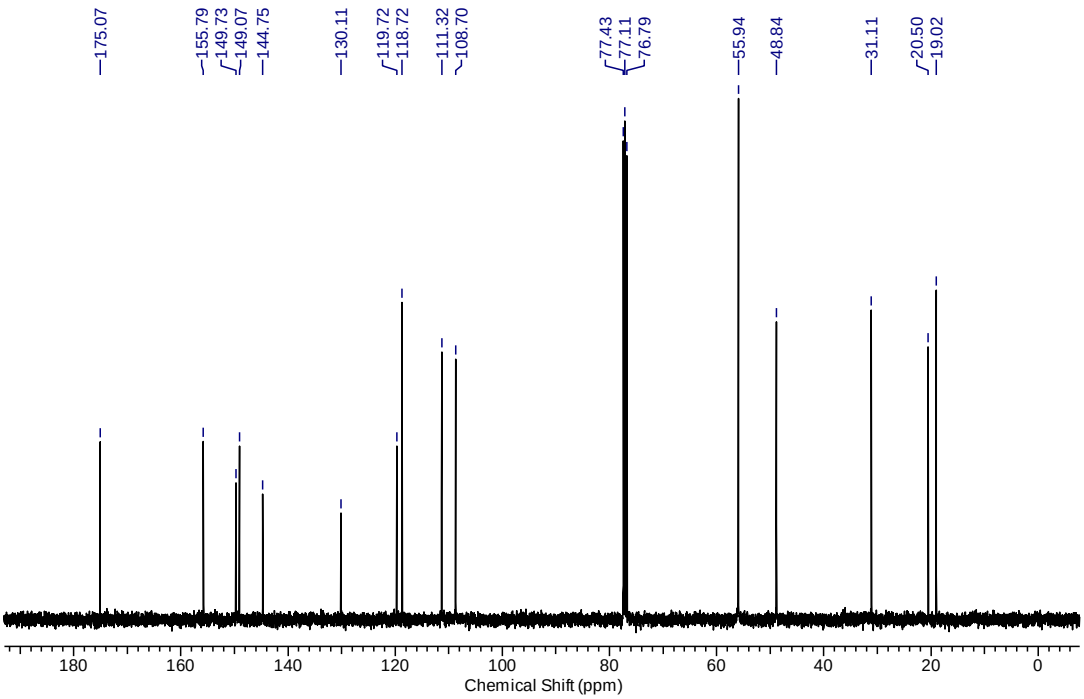
^{1}H NMR (400 MHz) spectrum of compound **50c** in $CDCl_3$



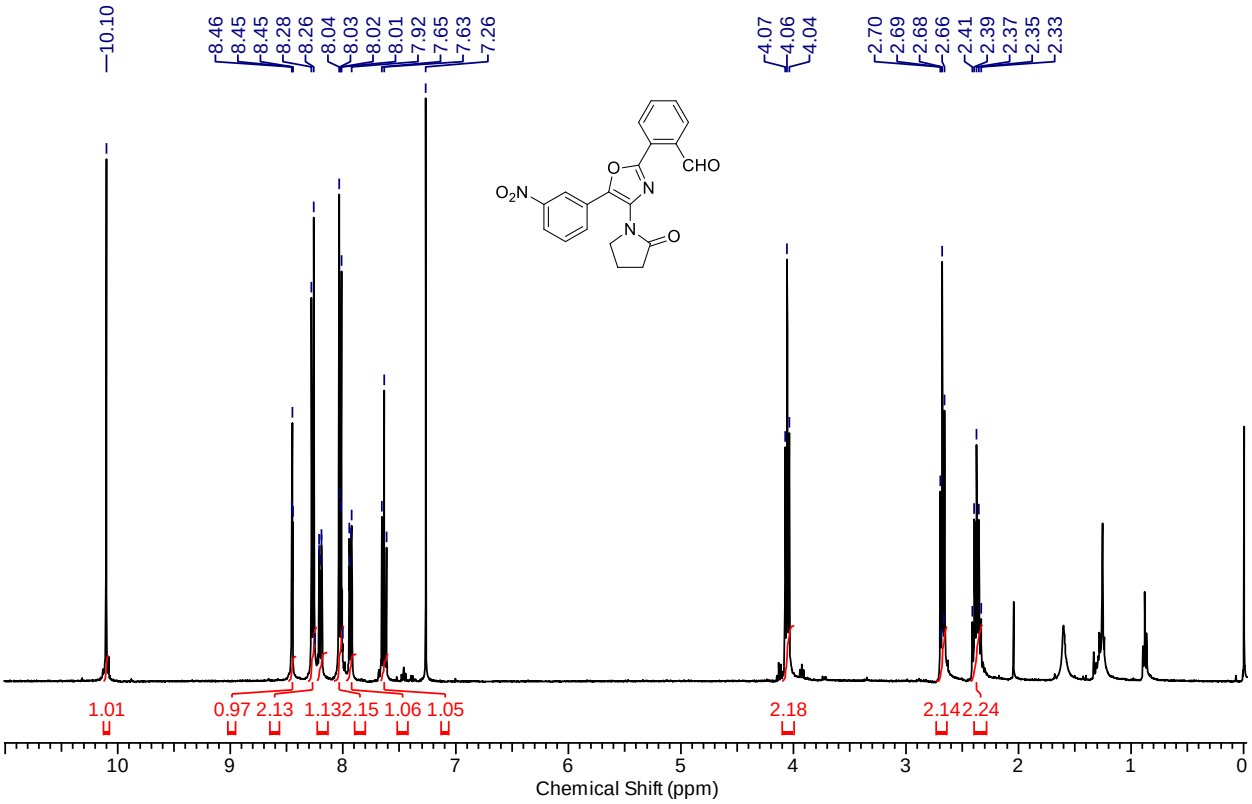
^{13}C NMR (100 MHz) spectrum of compound **50c** in $CDCl_3$



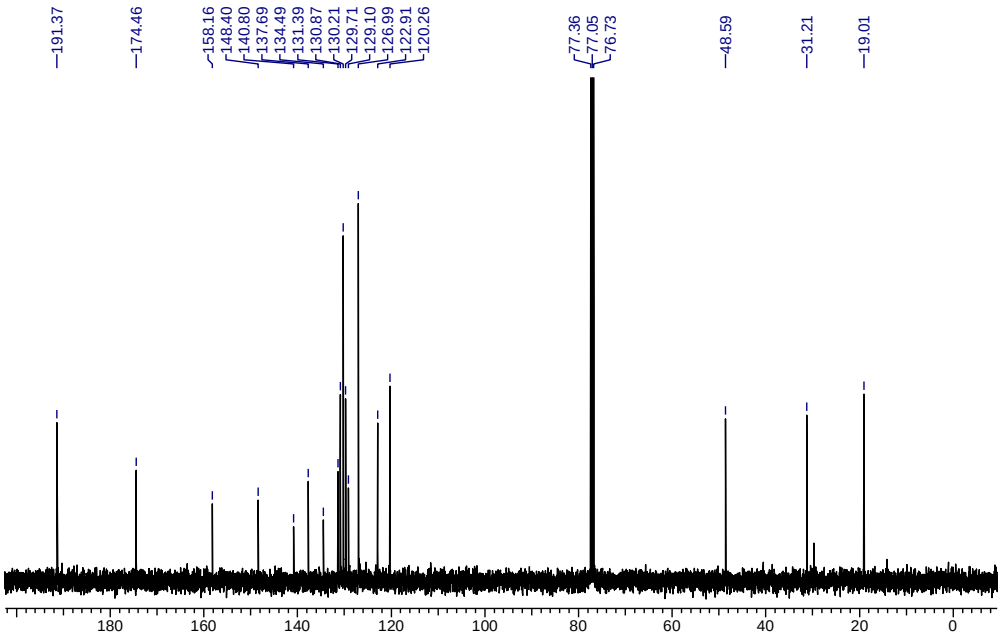
^{1}H NMR (400 MHz) spectrum of compound **50d** in $CDCl_3$



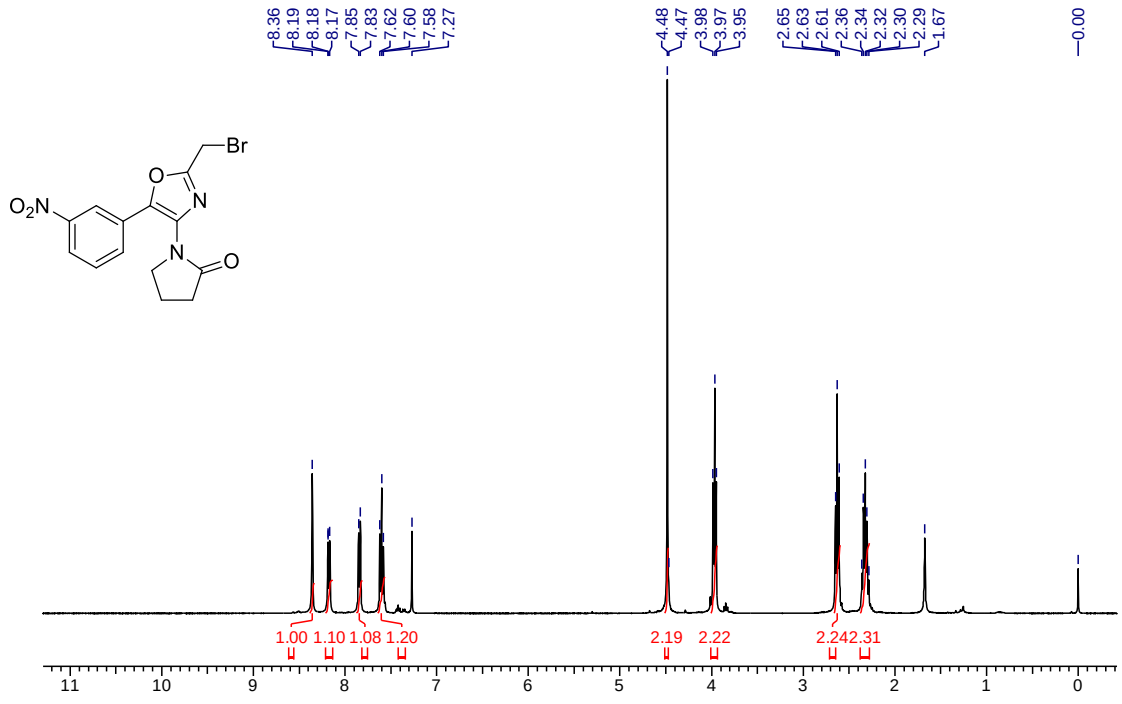
^{13}C NMR (100 MHz) spectrum of compound **50d** in $CDCl_3$



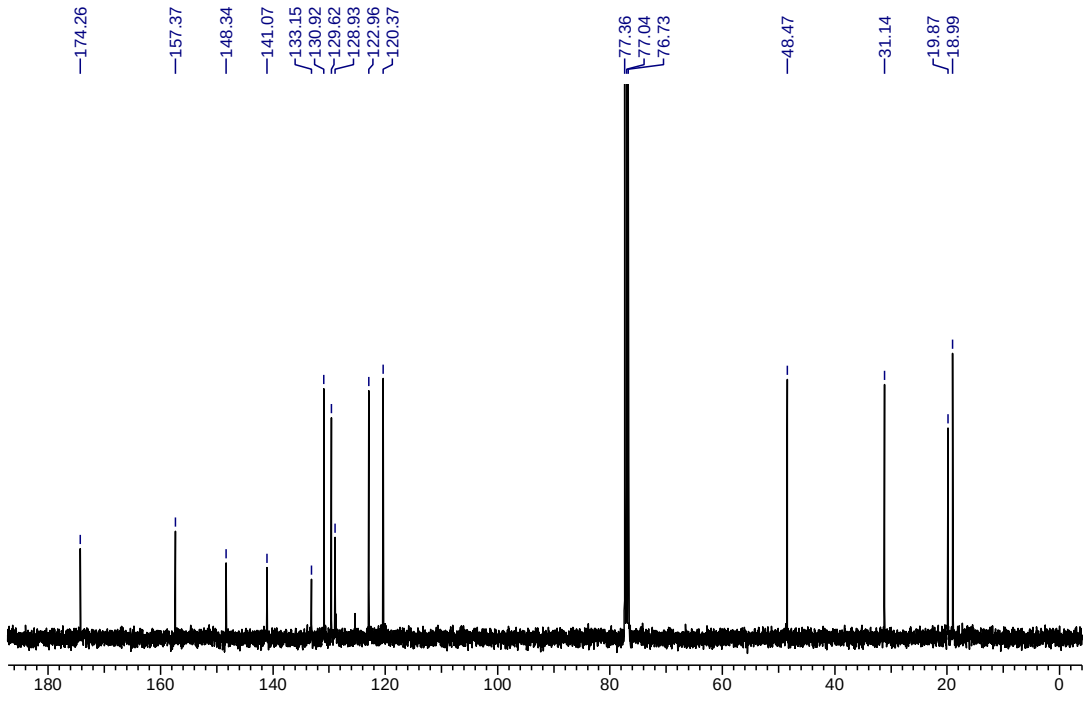
^{1}H NMR (400 MHz) spectrum of compound **50e** in $CDCl_3$



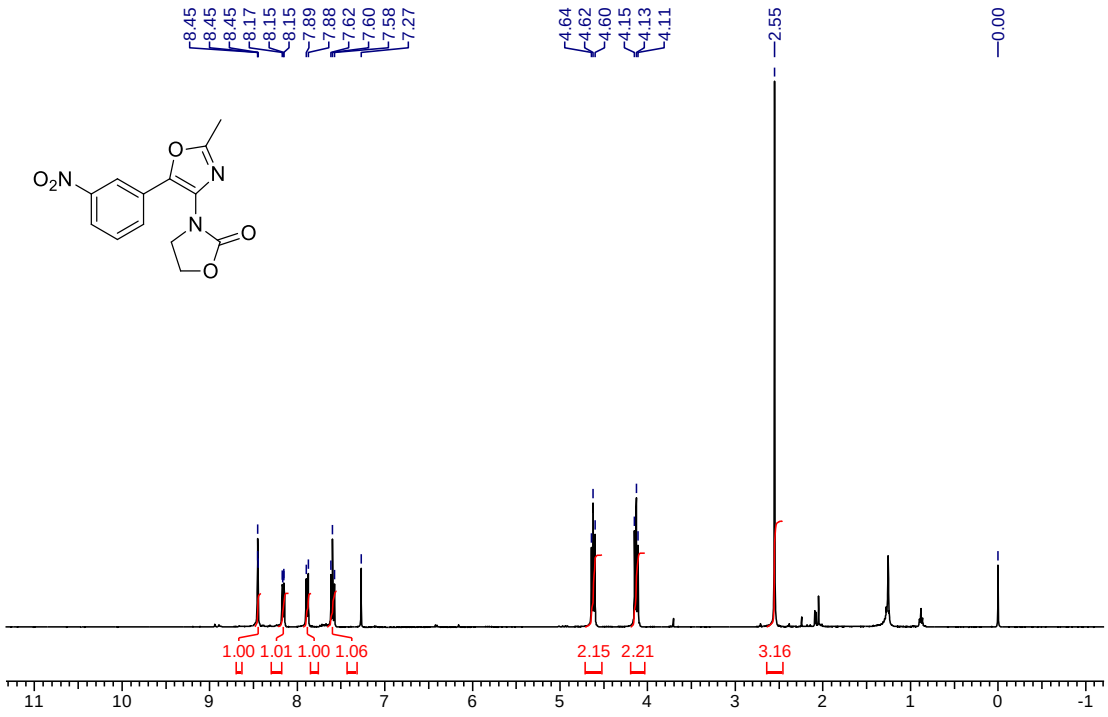
^{13}C NMR (100 MHz) spectrum of compound **50e** in $CDCl_3$



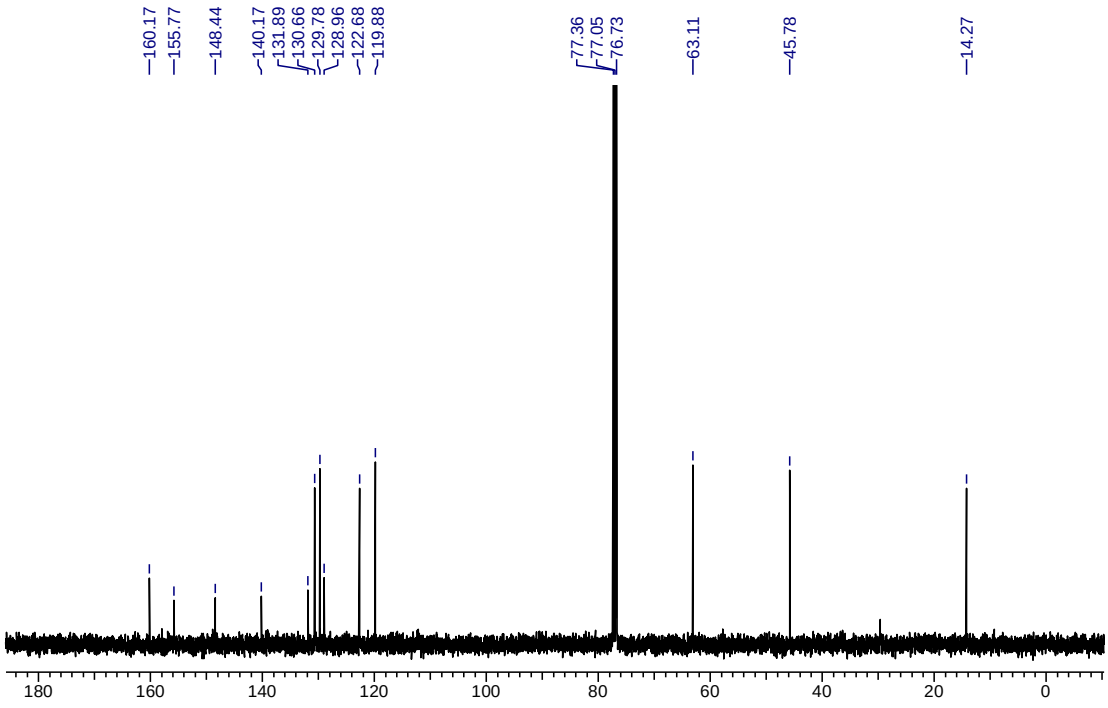
^{1}H NMR (400 MHz) spectrum of compound **50f** in $CDCl_3$



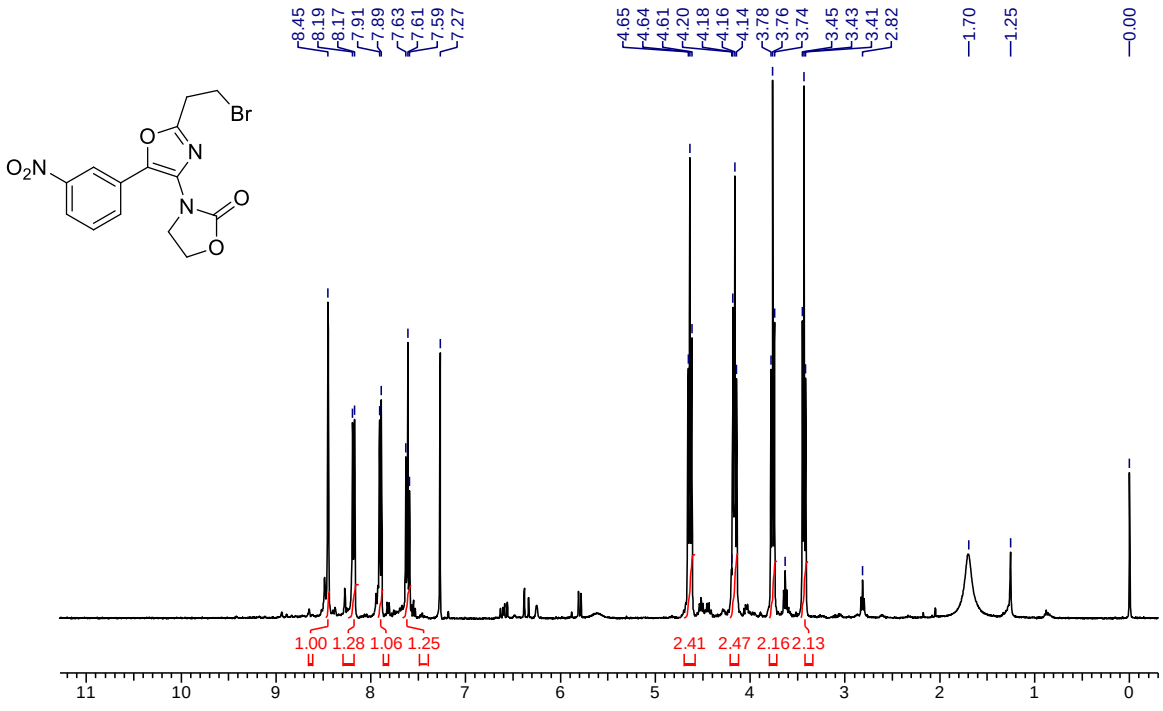
^{13}C NMR (100 MHz) spectrum of compound **50f** in $CDCl_3$



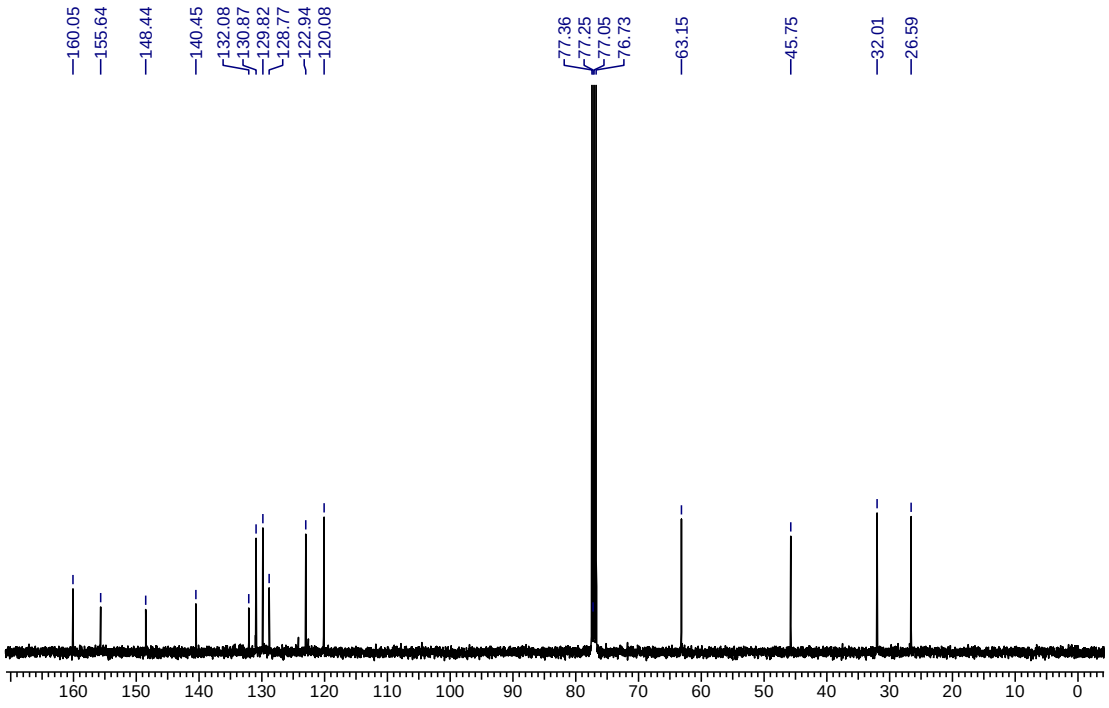
^{1}H NMR (400 MHz) spectrum of compound **50g** in $CDCl_3$



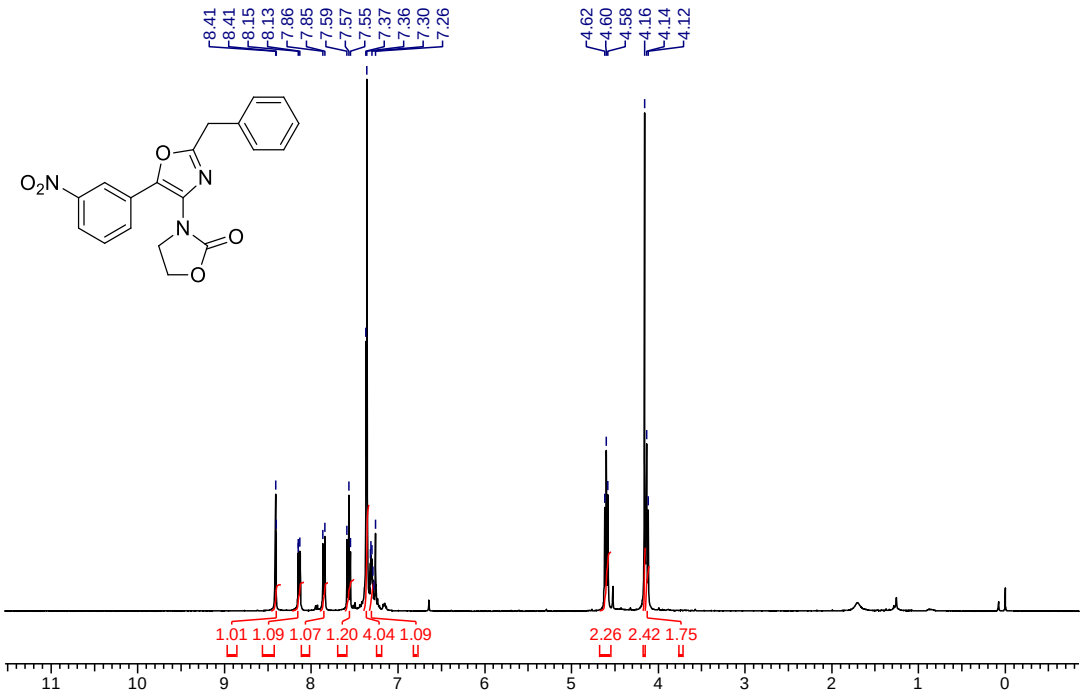
^{13}C NMR (100 MHz) spectrum of compound **50g** in $CDCl_3$



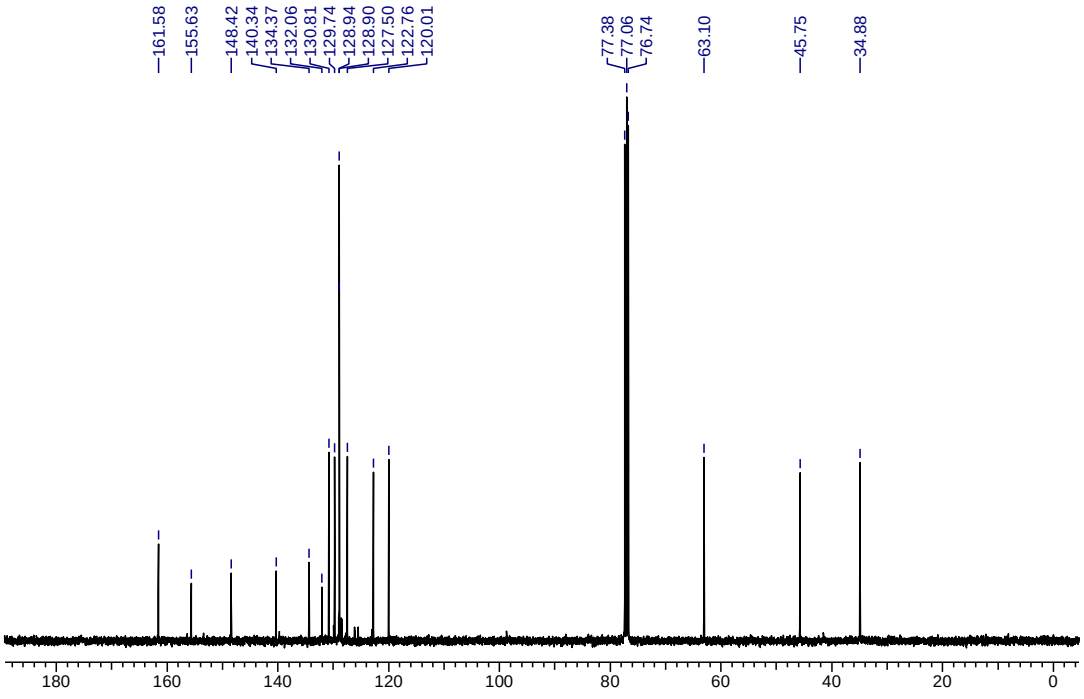
^{1}H NMR (400 MHz) spectrum of compound **50h** in $CDCl_3$



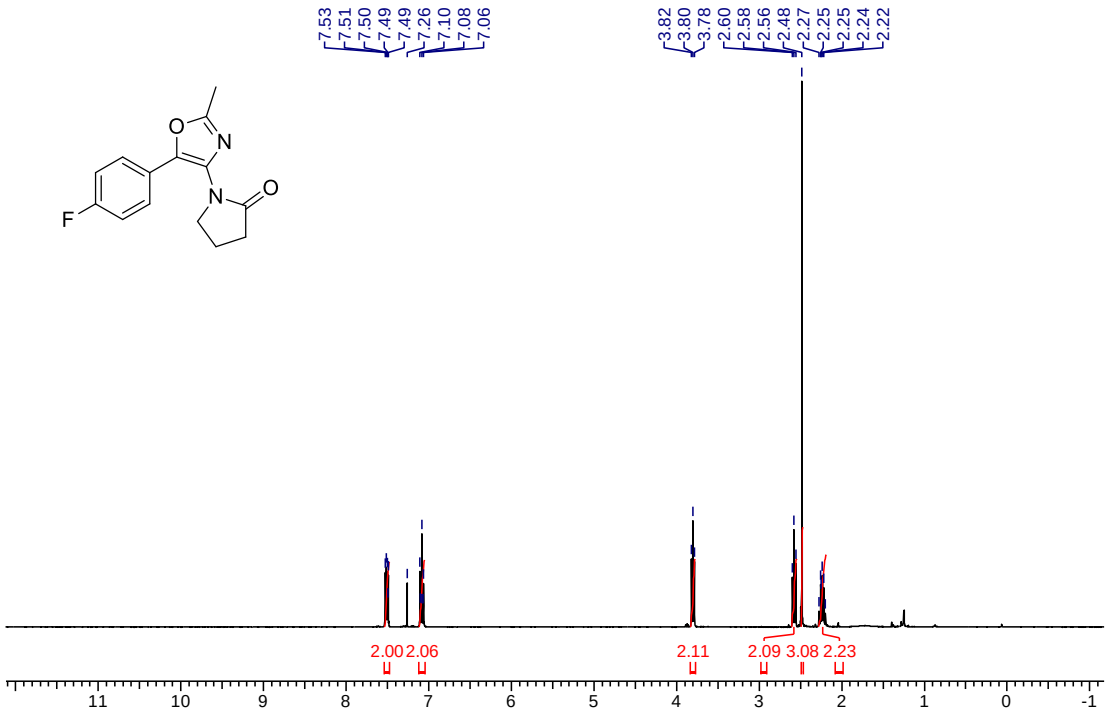
^{13}C NMR (100 MHz) spectrum of compound **50h** in $CDCl_3$



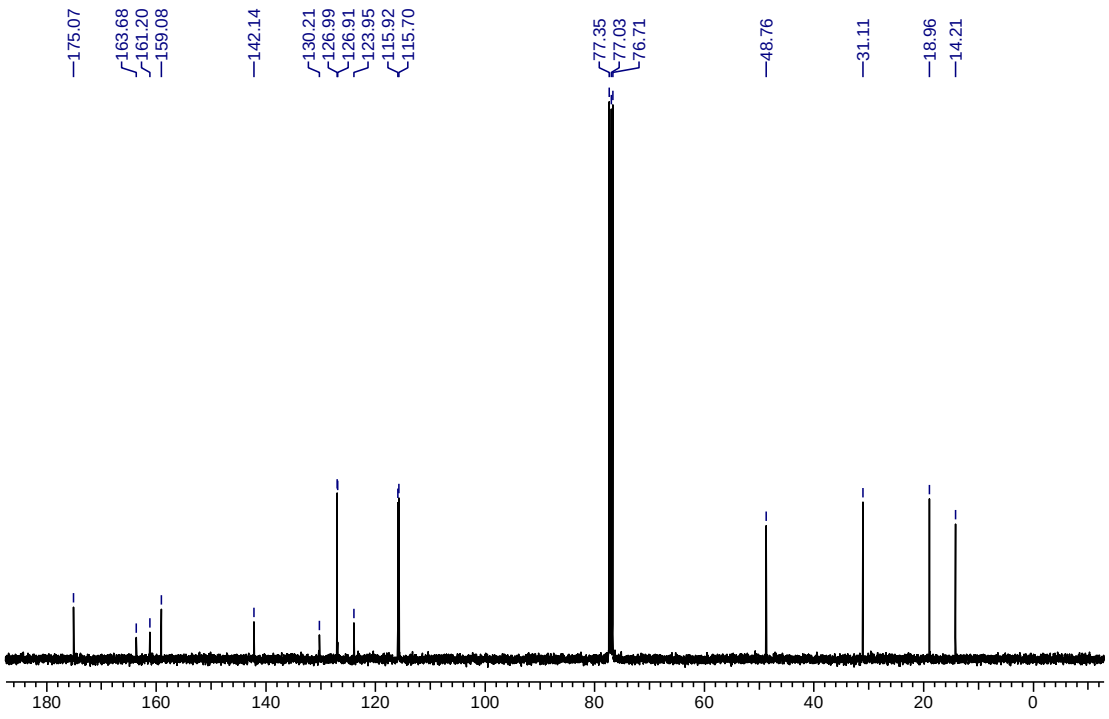
^{1}H NMR (400 MHz) spectrum of compound **50i** in $CDCl_3$



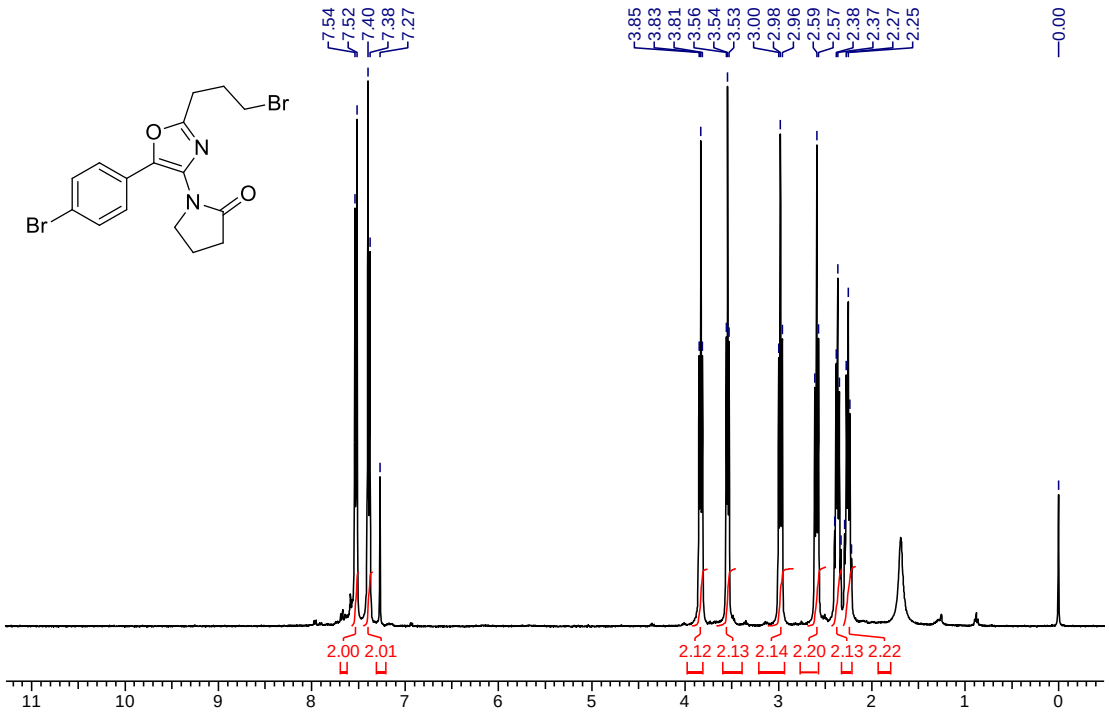
^{13}C NMR (100 MHz) spectrum of compound **50i** in $CDCl_3$



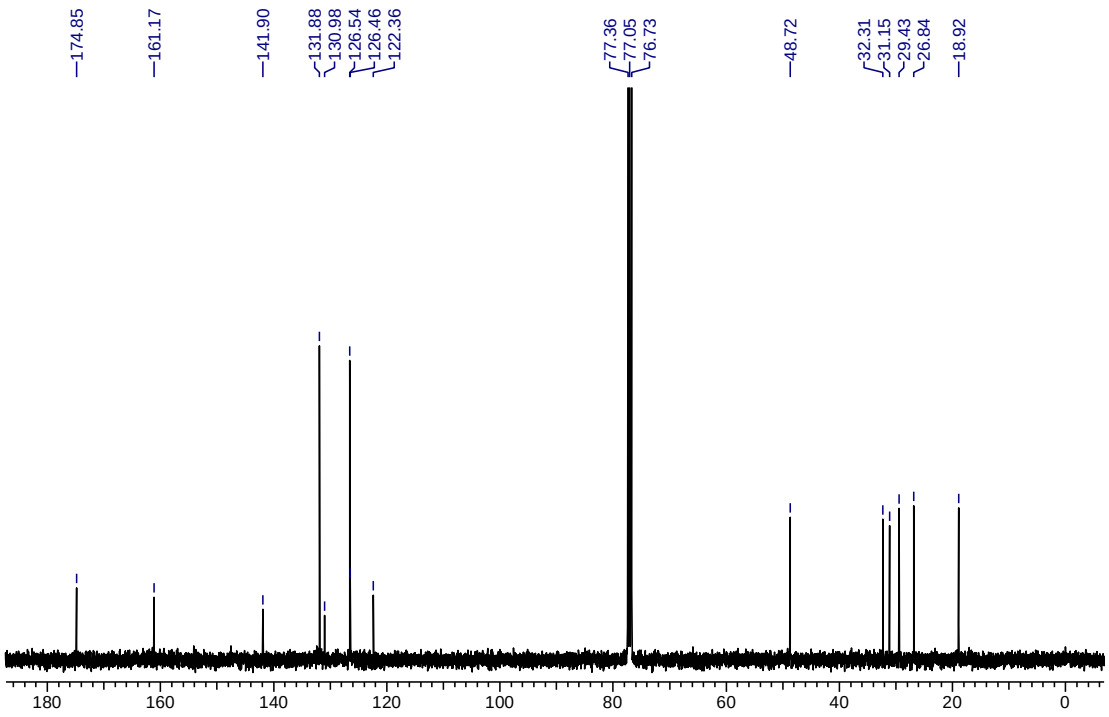
^{1}H NMR (400 MHz) spectrum of compound **50j** in $CDCl_3$



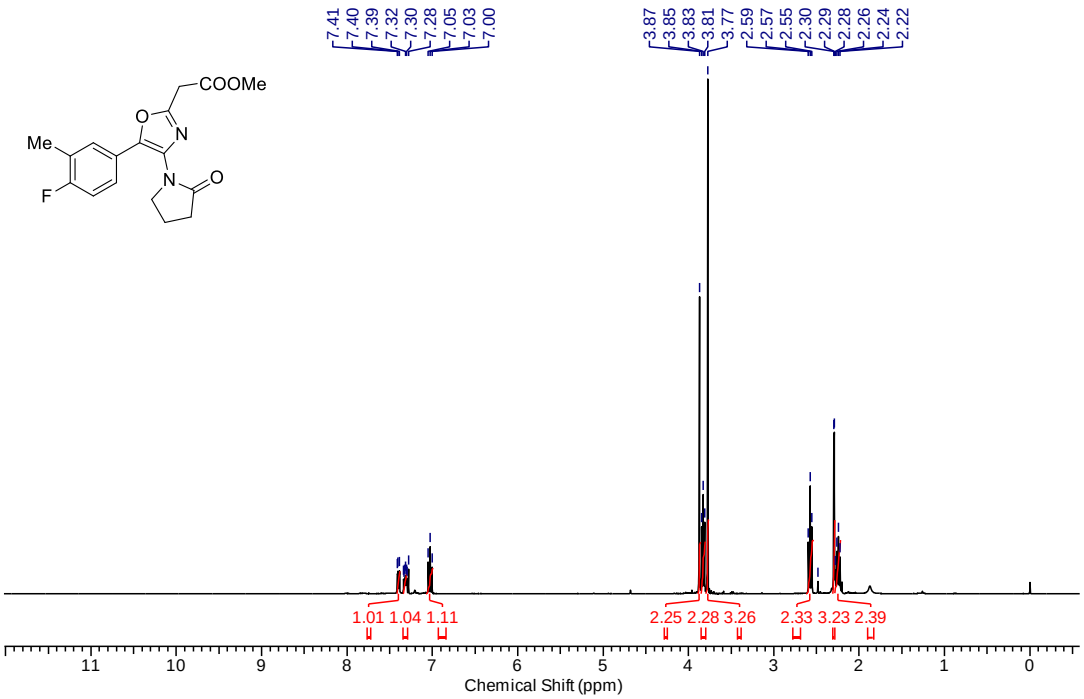
^{13}C NMR (100 MHz) spectrum of compound **50j** in $CDCl_3$



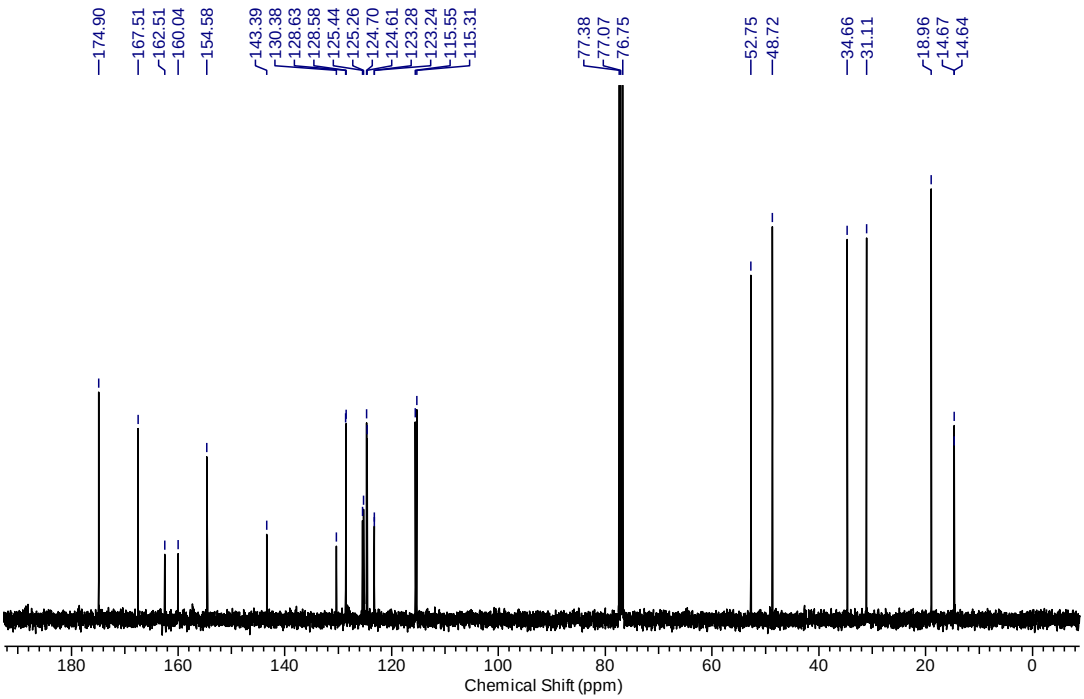
^{1}H NMR (400 MHz) spectrum of compound **50k** in $CDCl_3$



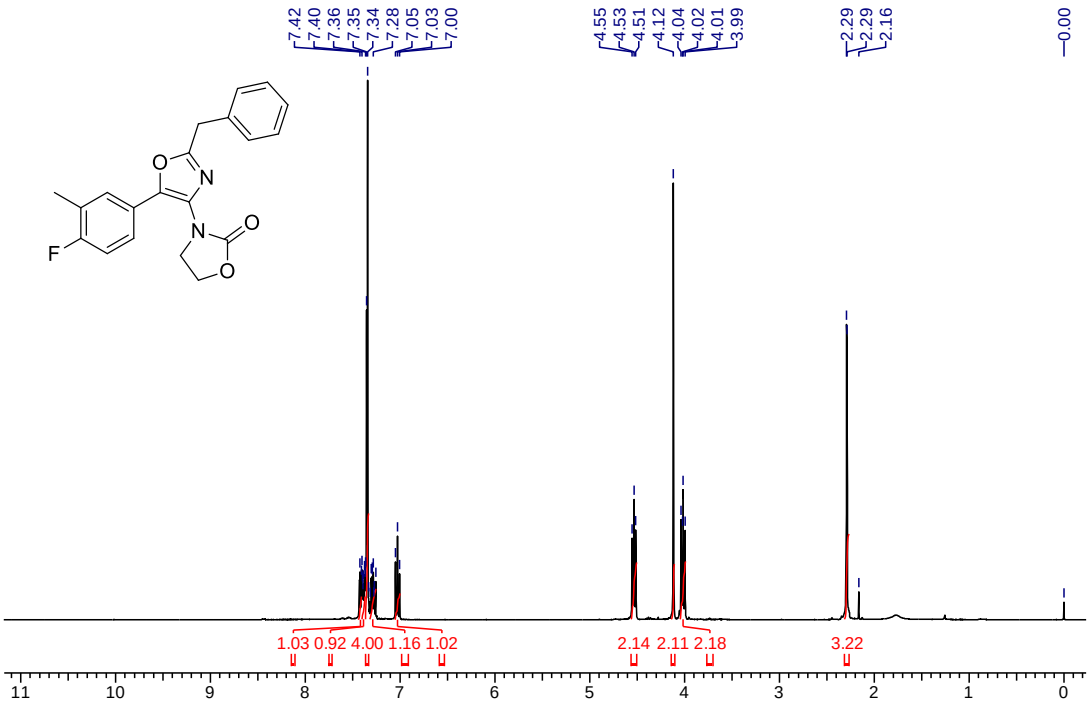
^{13}C NMR (100 MHz) spectrum of compound **50k** in $CDCl_3$



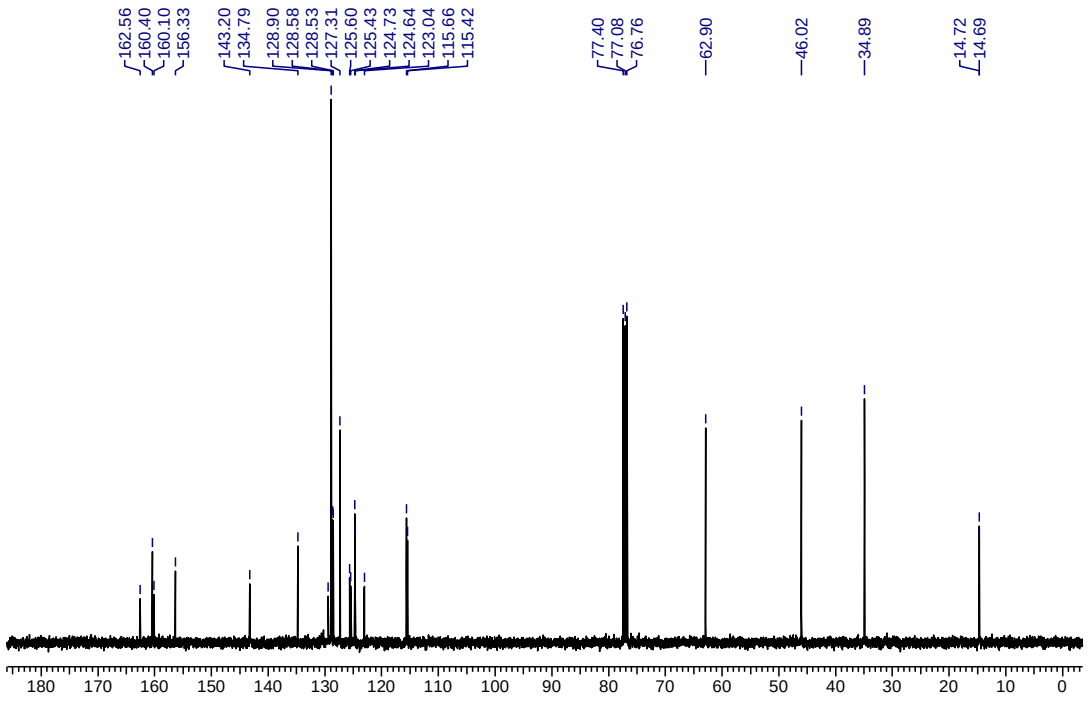
^{1}H NMR (400 MHz) spectrum of compound **50l** in $CDCl_3$



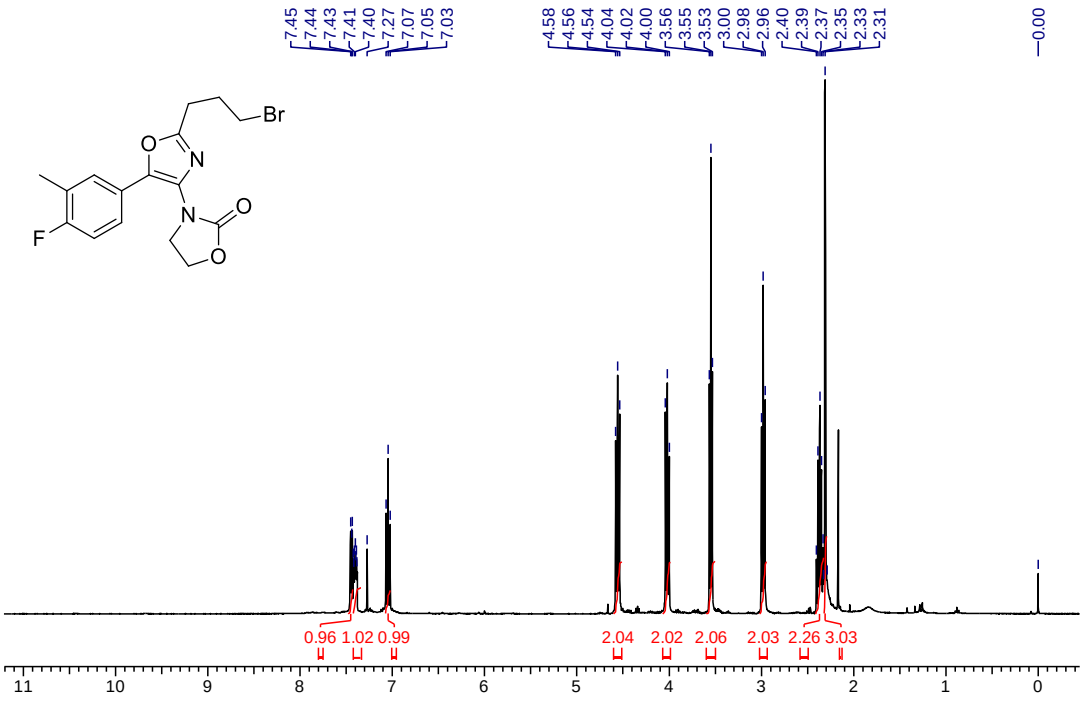
^{13}C NMR (100 MHz) spectrum of compound **50l** in $CDCl_3$



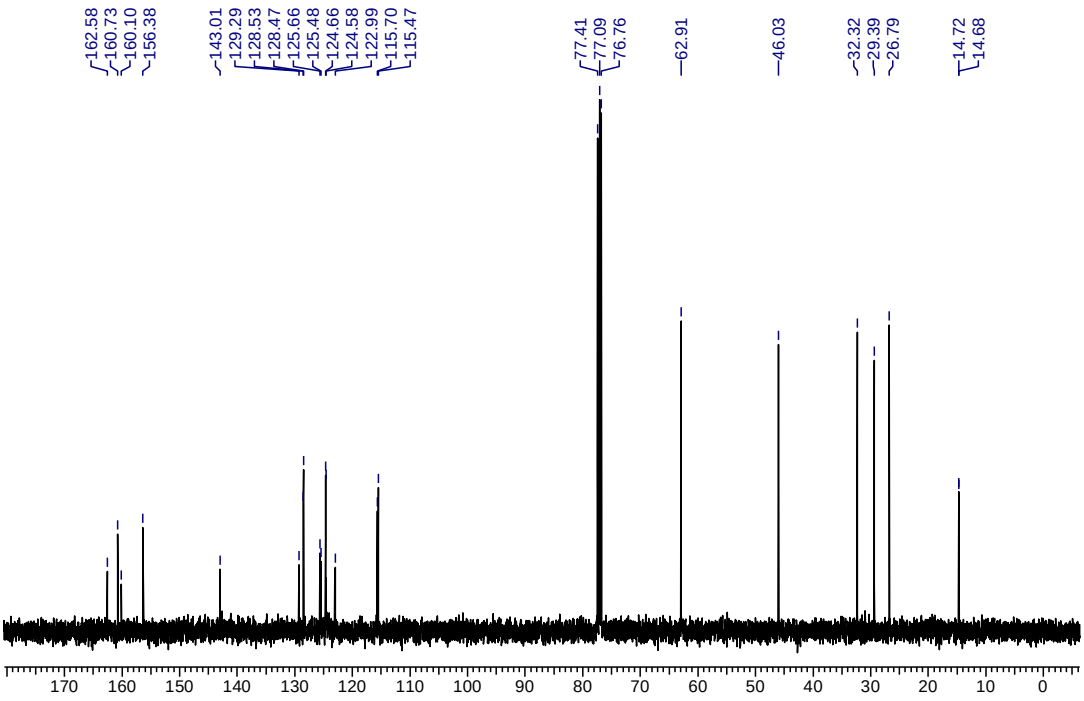
^{1}H NMR (400 MHz) spectrum of compound **50m** in $CDCl_3$



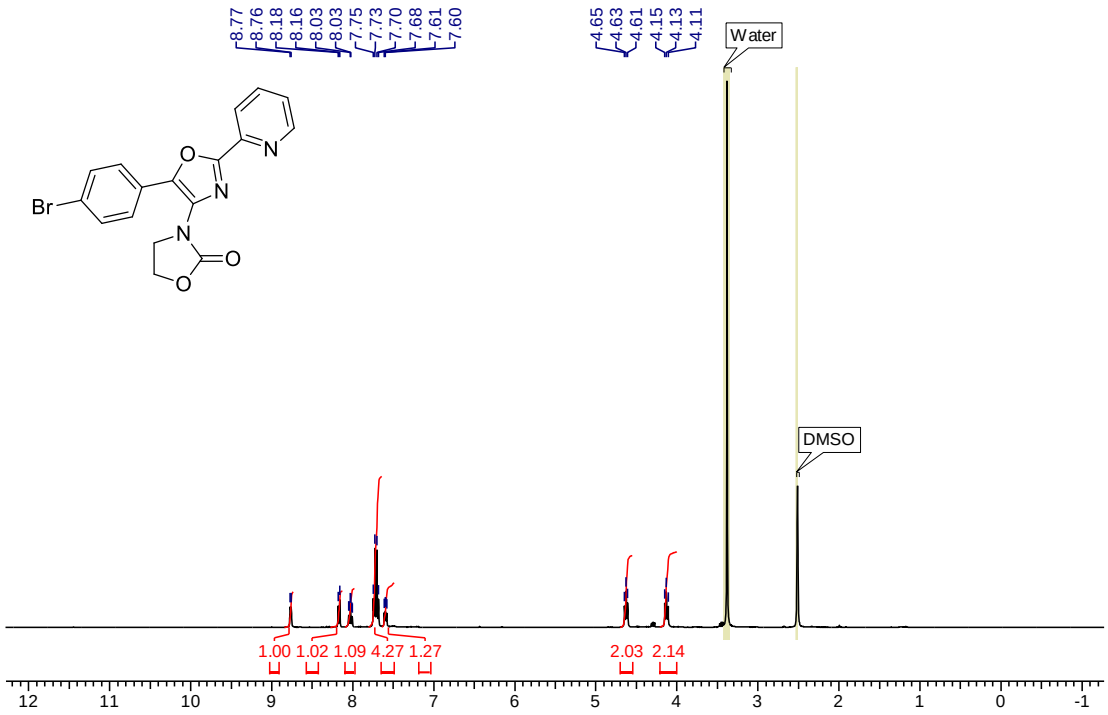
^{13}C NMR (100 MHz) spectrum of compound **50m** in $CDCl_3$



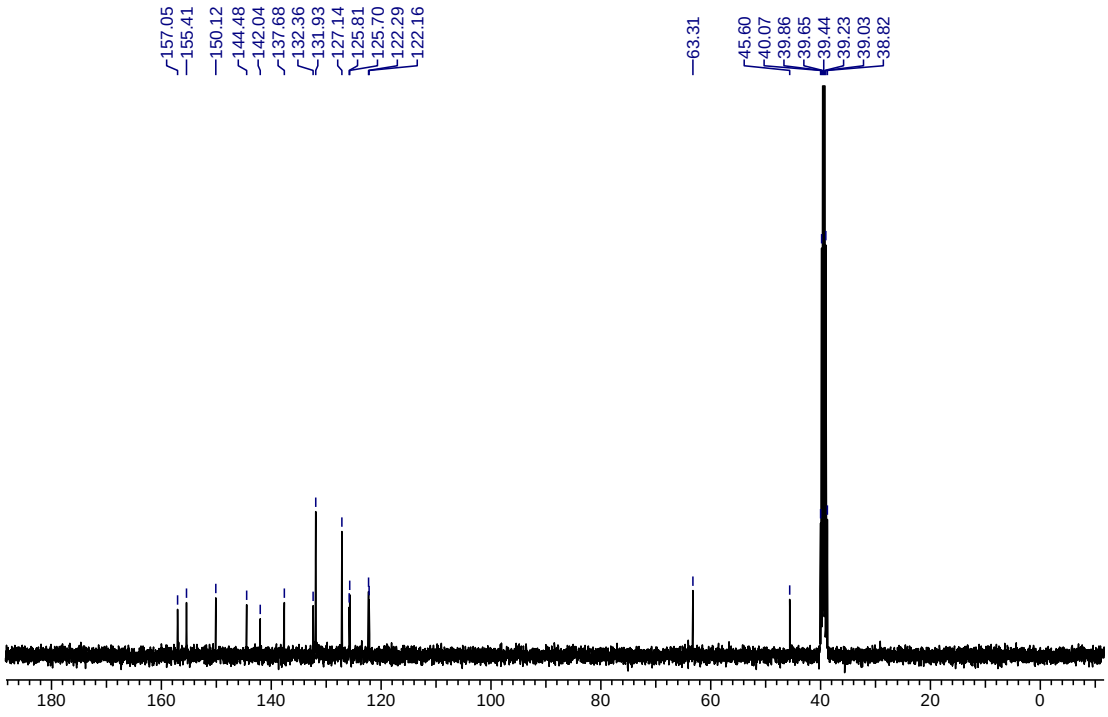
^{1}H NMR (400 MHz) spectrum of compound **50n** in $CDCl_3$



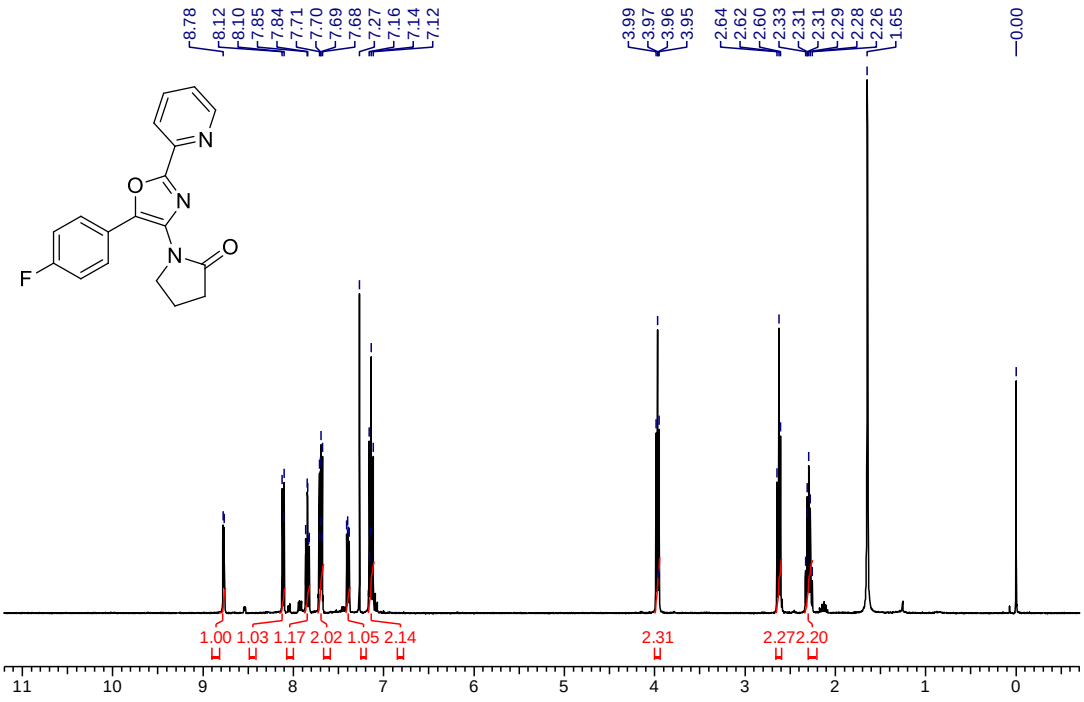
^{13}C NMR (100 MHz) spectrum of compound **50n** in $CDCl_3$



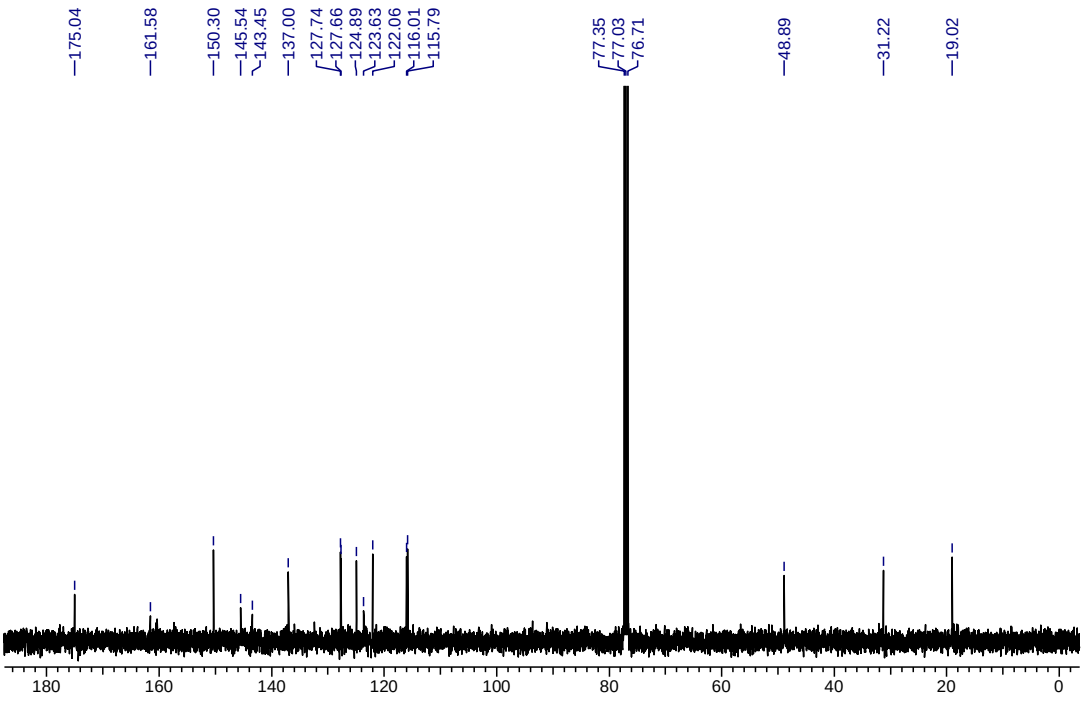
^{1}H NMR (400 MHz) spectrum of compound **50o** in DMSO-D_6



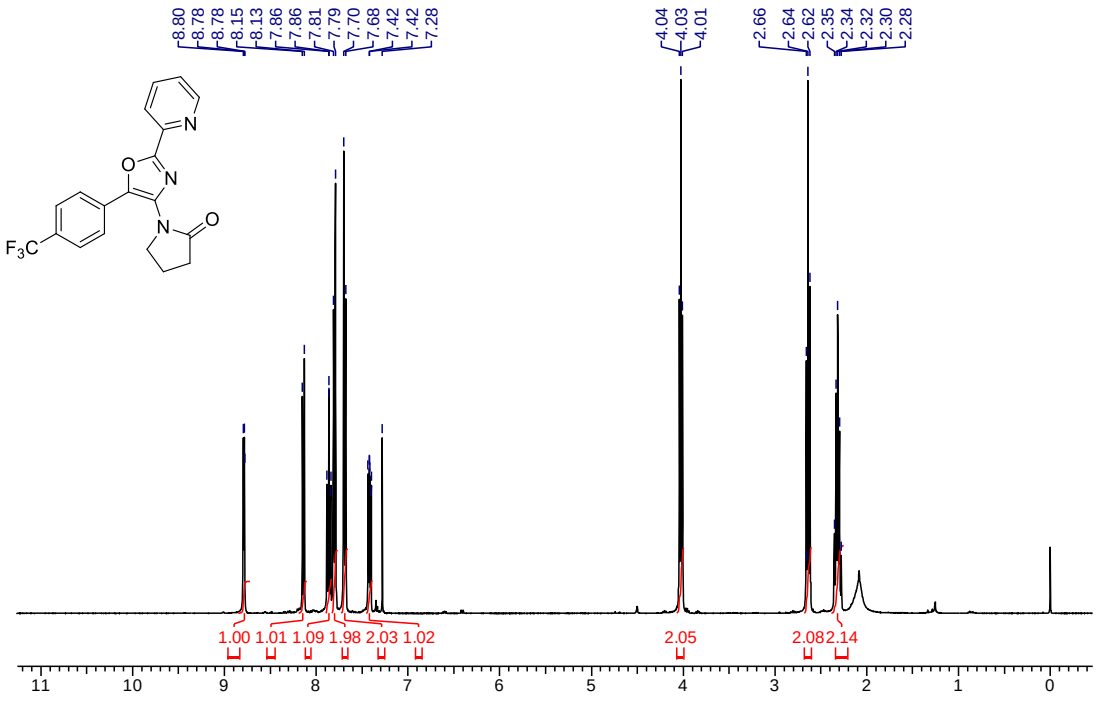
^{13}C NMR (100 MHz) spectrum of compound **50o** in DMSO-D_6



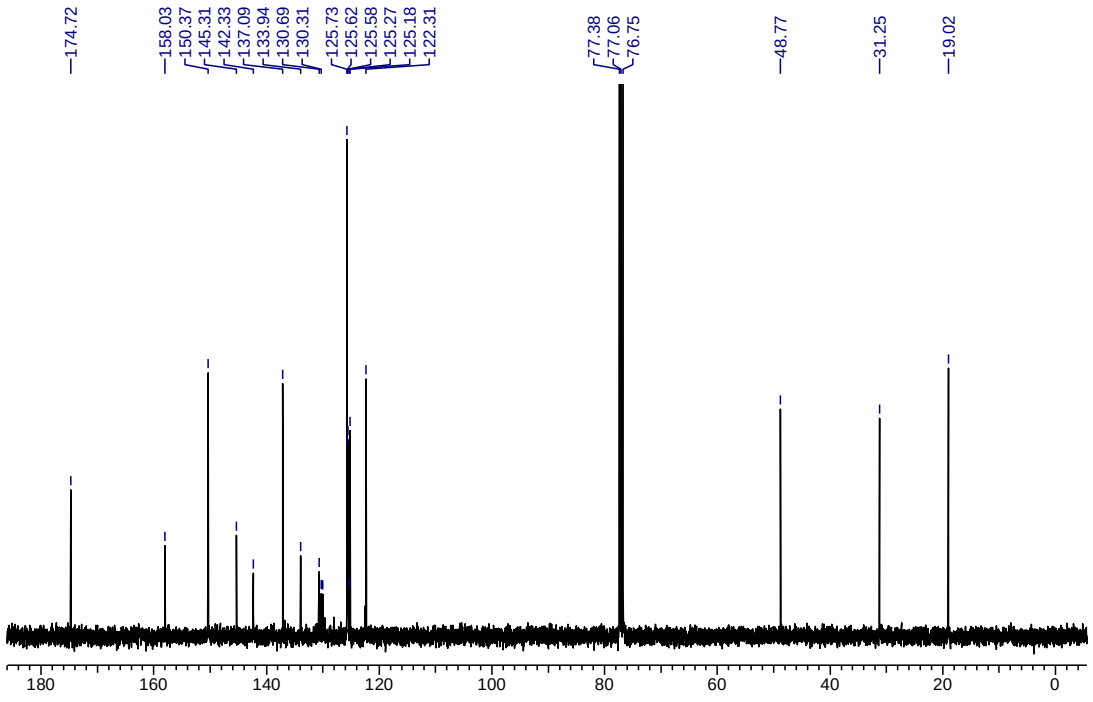
^{1}H NMR (400 MHz) spectrum of compound **50p** in $CDCl_3$



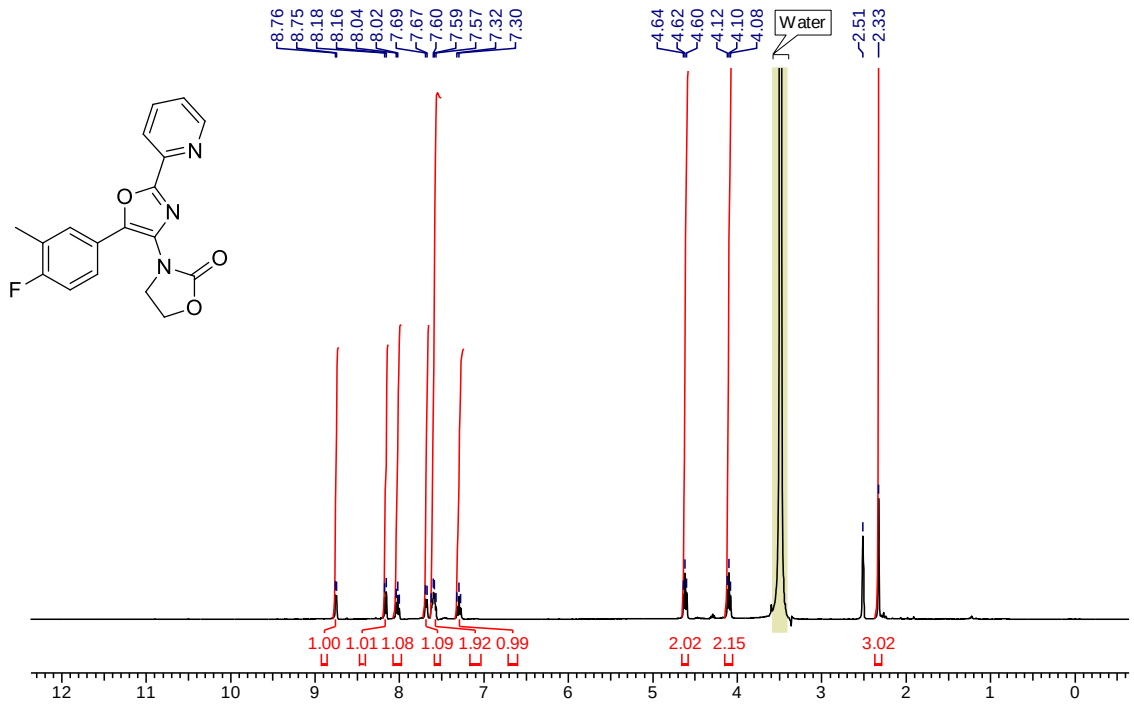
^{13}C NMR (100 MHz) spectrum of compound **50p** in $CDCl_3$



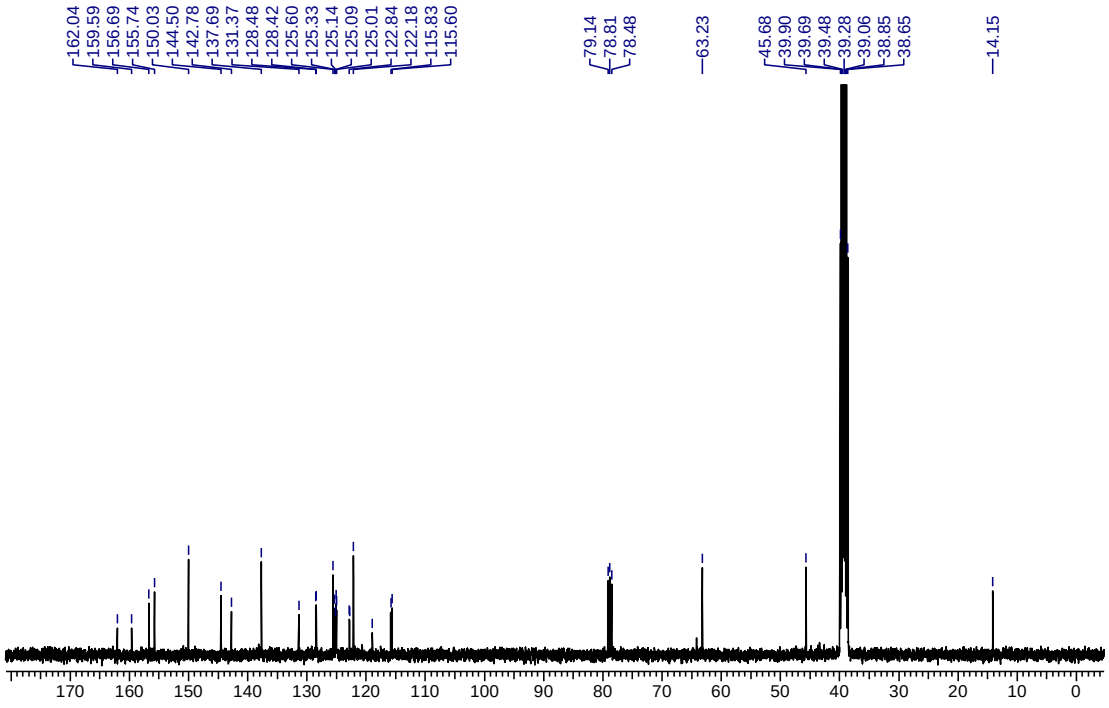
^{1}H NMR (400 MHz) spectrum of compound **50q** in $CDCl_3$



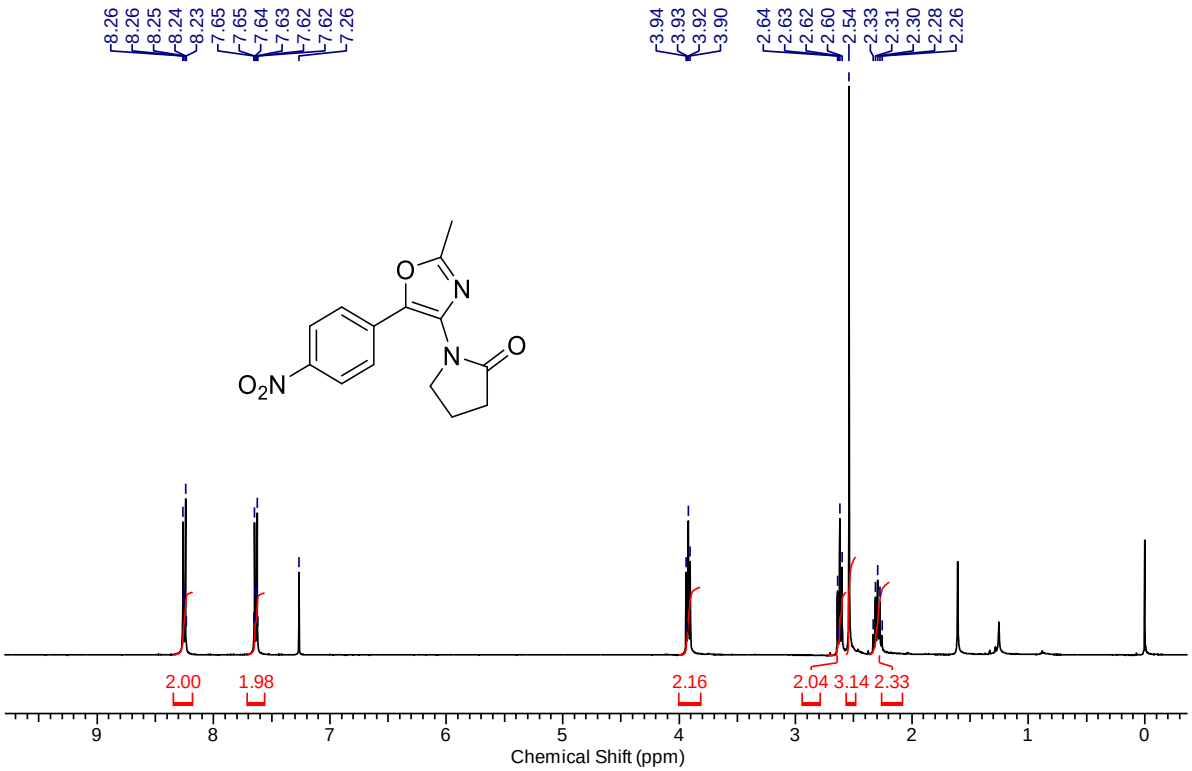
^{13}C NMR (100 MHz) spectrum of compound **50q** in $CDCl_3$



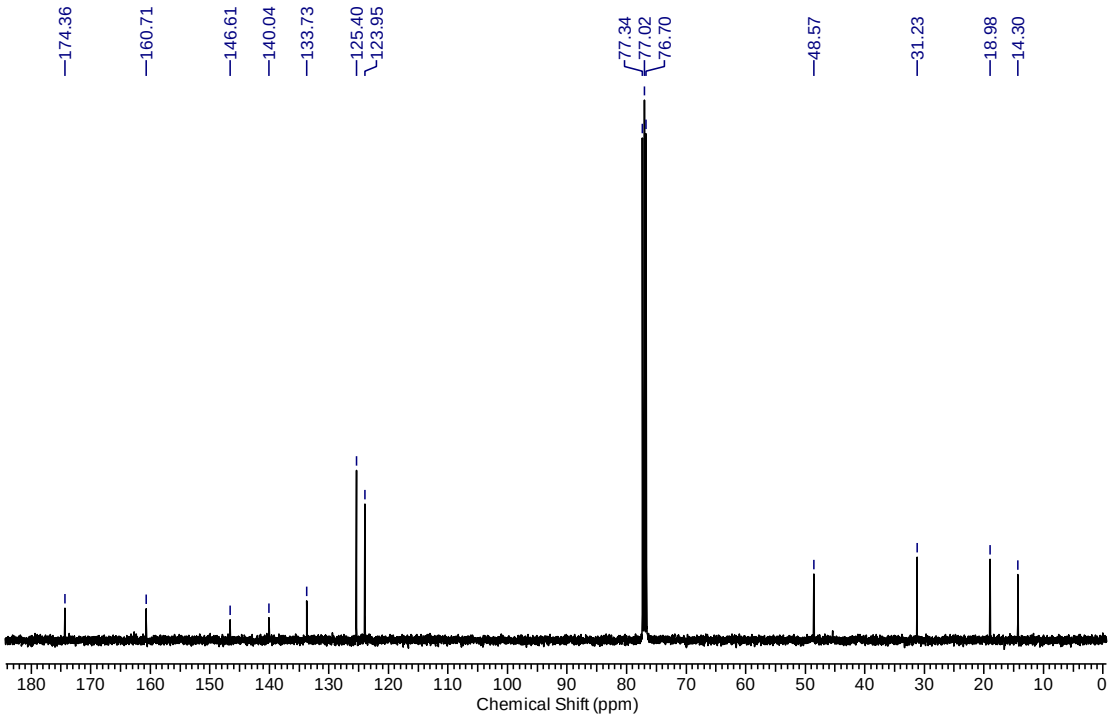
^{1}H NMR (400 MHz) spectrum of compound **50r** in DMSO-D_6



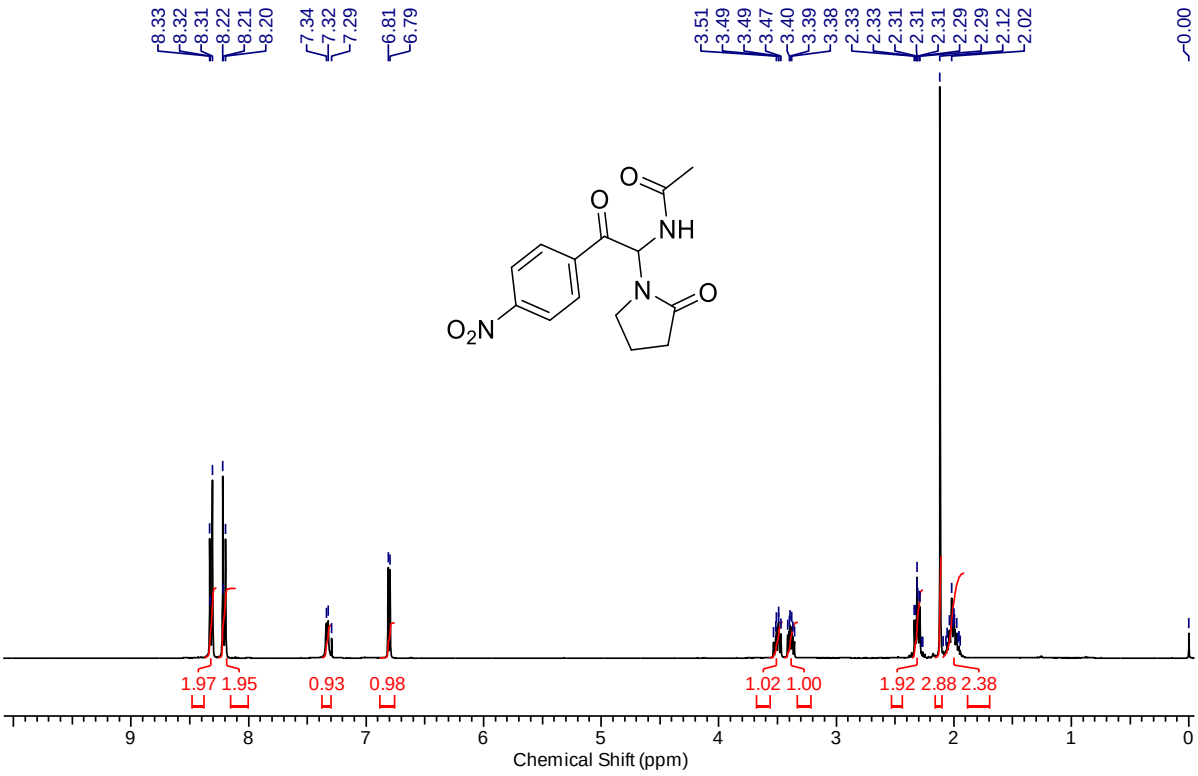
^{13}C NMR (100 MHz) spectrum of compound **50r** in mixture of $CDCl_3$ & DMSO-D_6



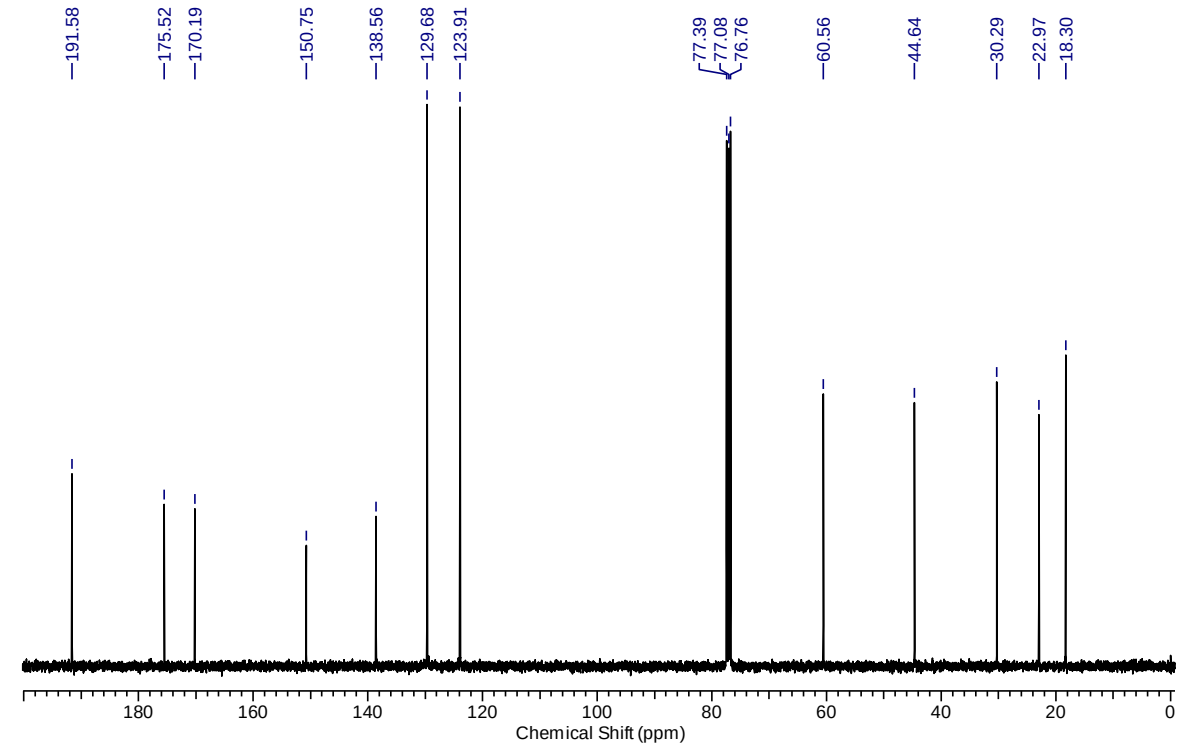
^{1}H NMR (400 MHz) spectrum of compound **50s** in $CDCl_3$



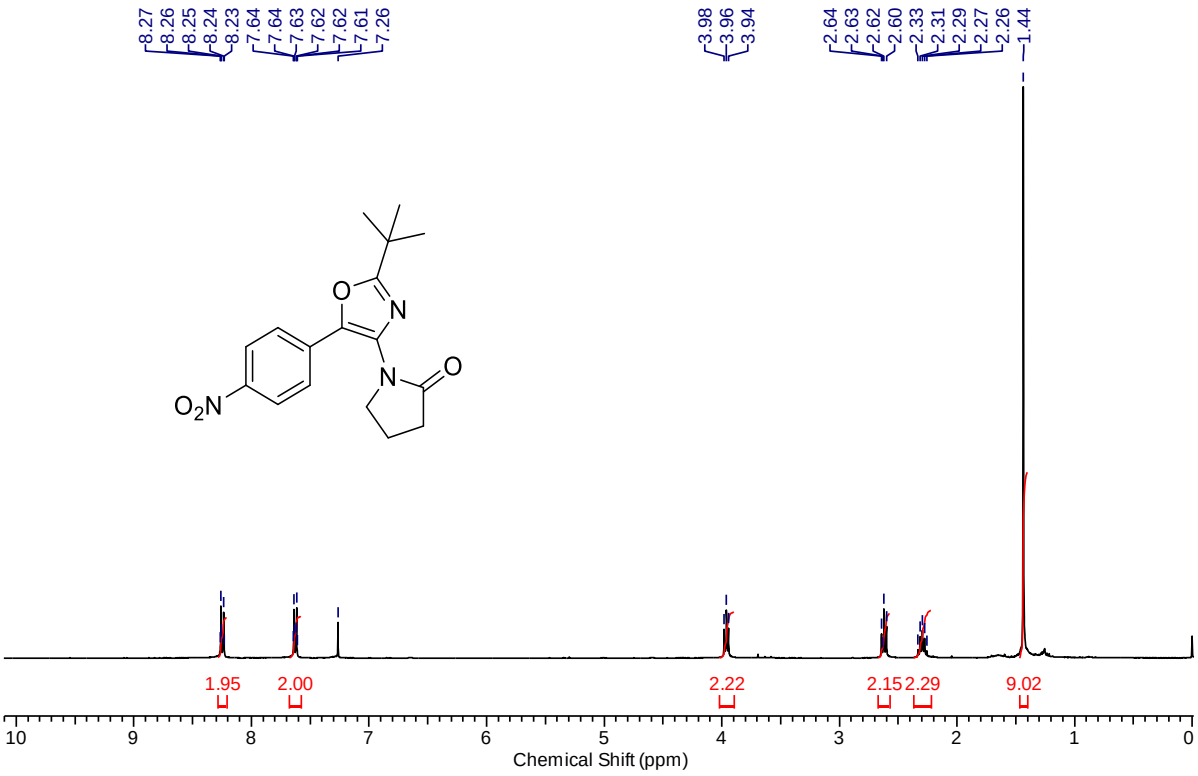
^{13}C NMR (100 MHz) spectrum of compound **50s** in $CDCl_3$



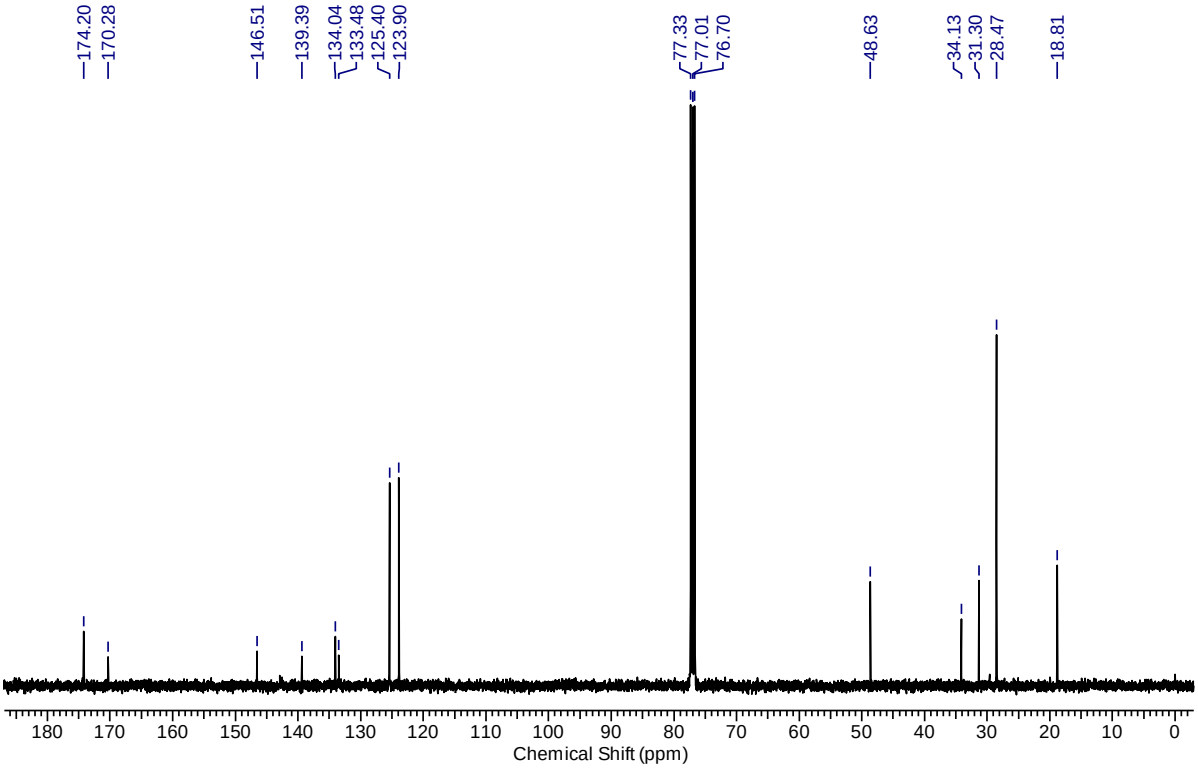
^{1}H NMR (400 MHz) spectrum of compound **50s'** in $CDCl_3$



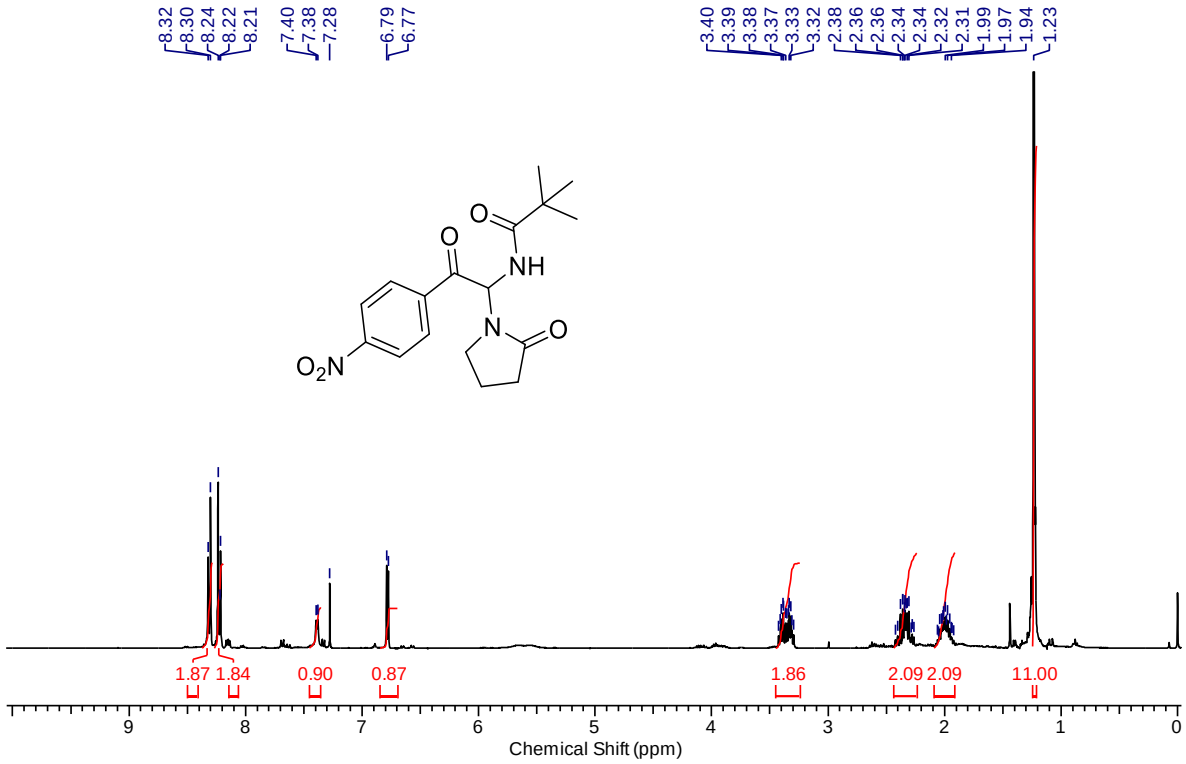
^{13}C NMR (100 MHz) spectrum of compound **50s'** in $CDCl_3$



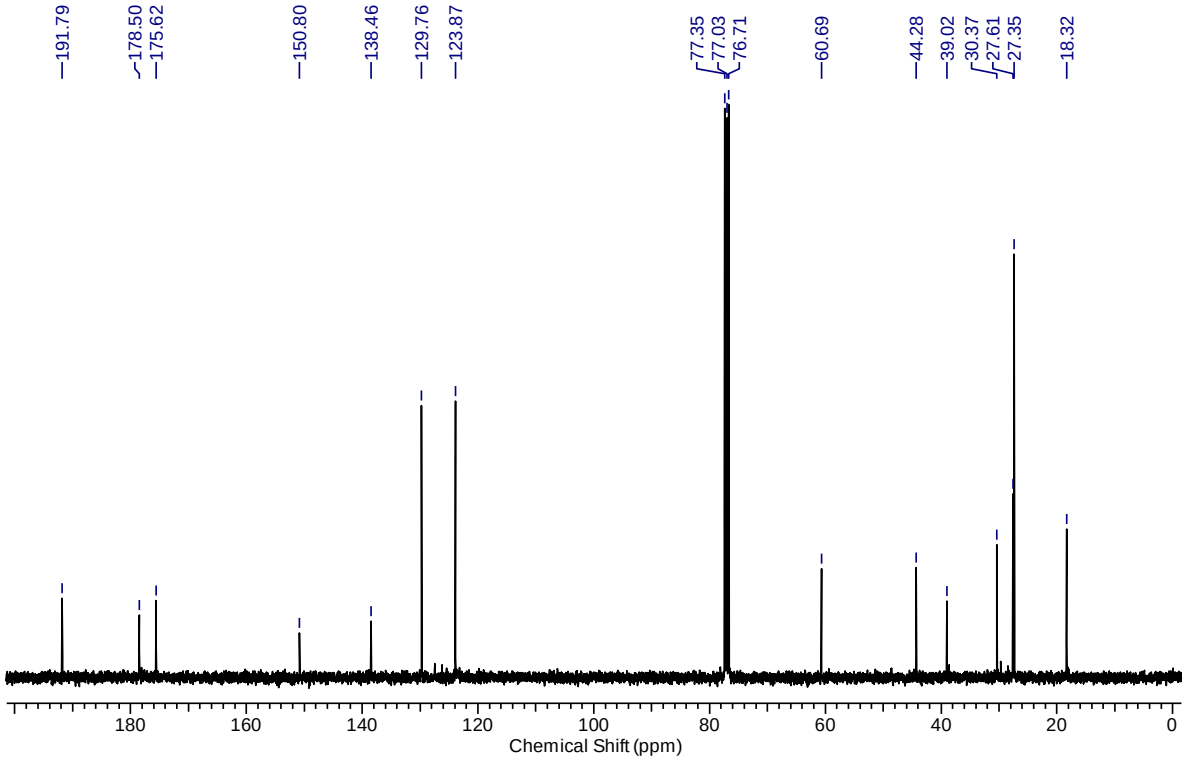
^{1}H NMR (400 MHz) spectrum of compound **50t** in $CDCl_3$



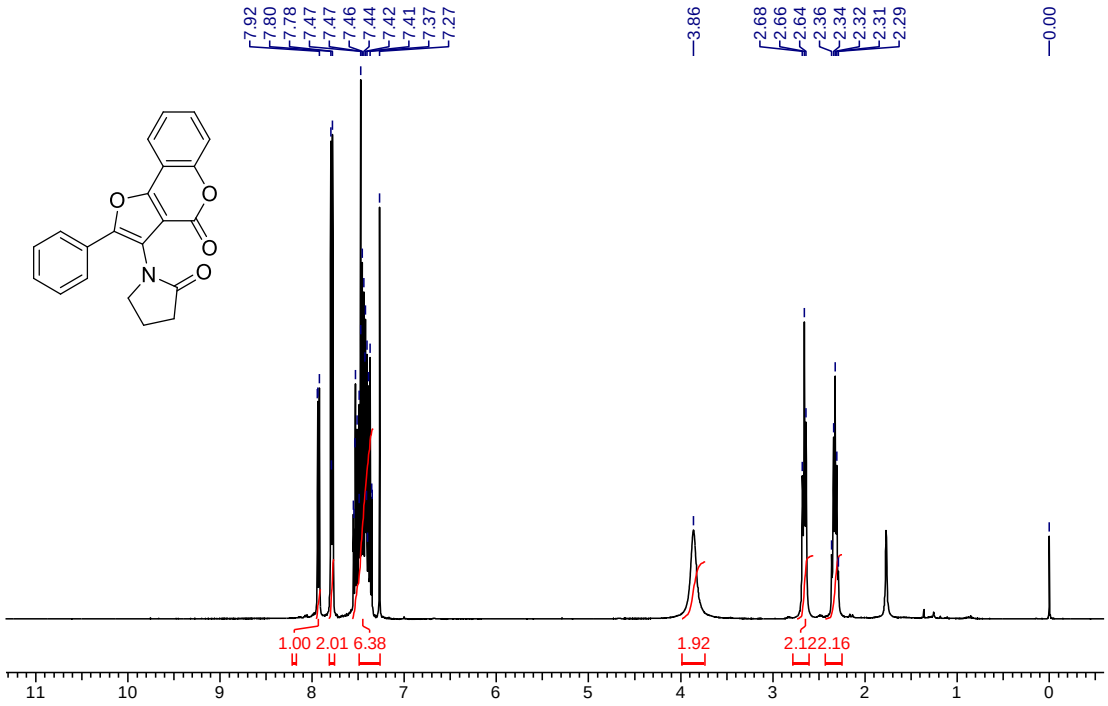
^{13}C NMR (100 MHz) spectrum of compound **50t** in $CDCl_3$



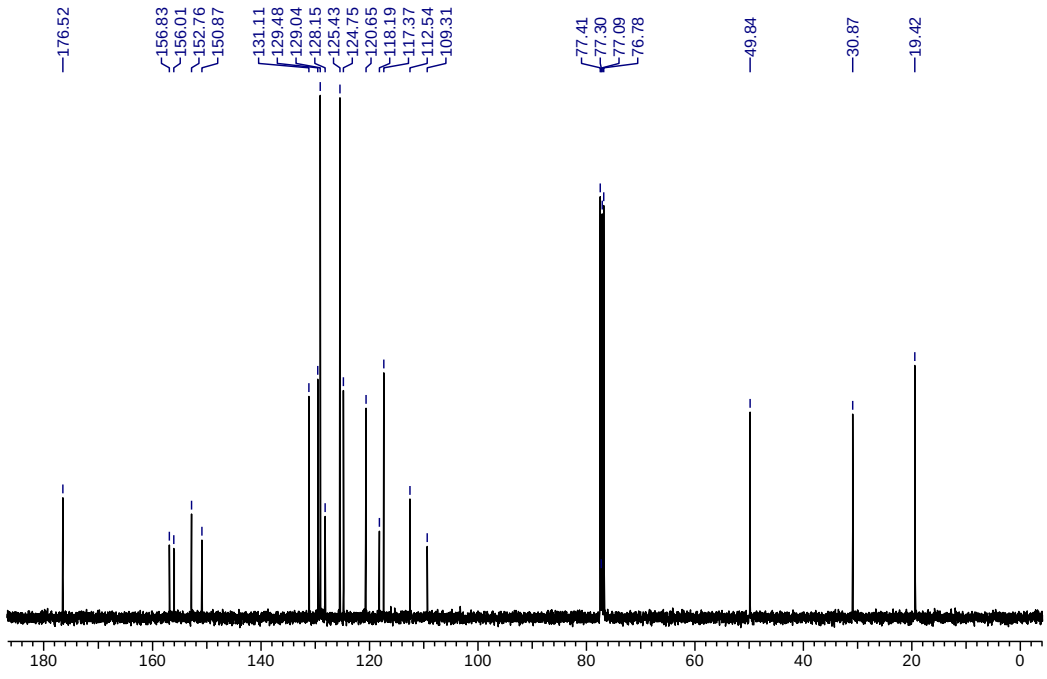
^{1}H NMR (400 MHz) spectrum of compound **50t'** in $CDCl_3$



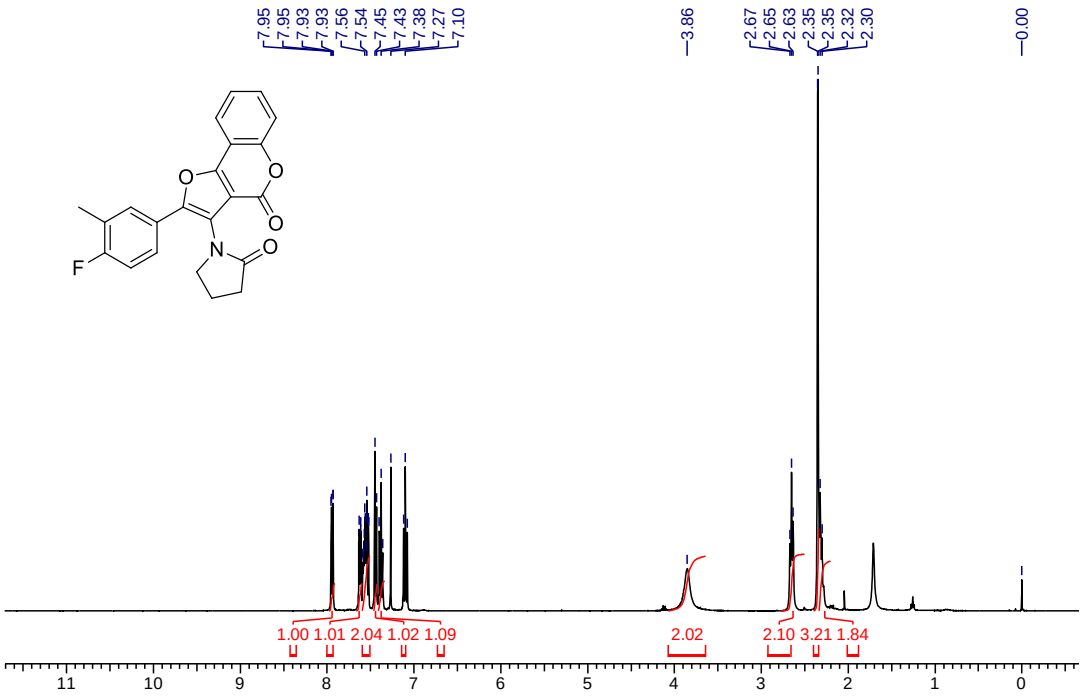
^{13}C NMR (100 MHz) spectrum of compound **50t'** in $CDCl_3$



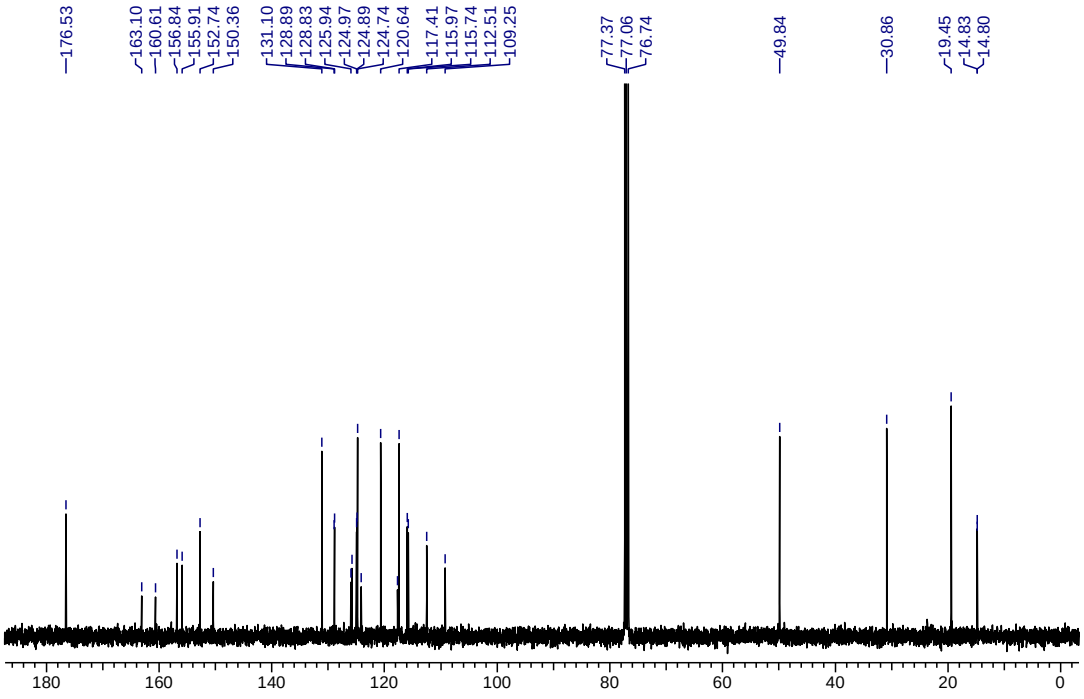
^{1}H NMR (400 MHz) spectrum of compound **56a** in $CDCl_3$



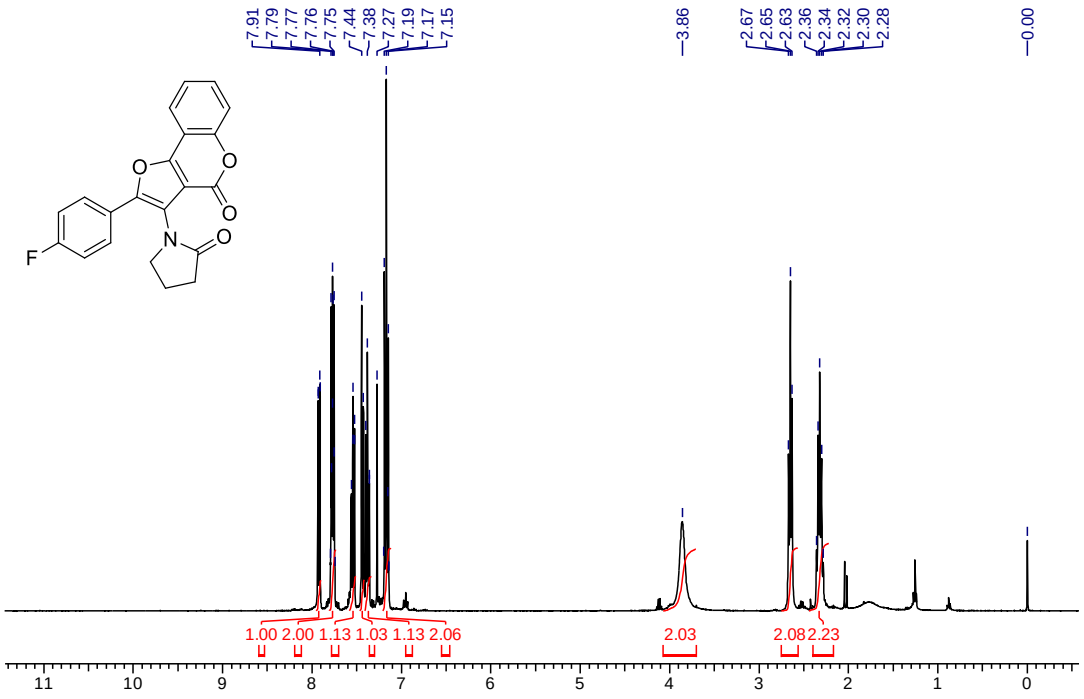
^{13}C NMR (100 MHz) spectrum of compound **56a** in $CDCl_3$



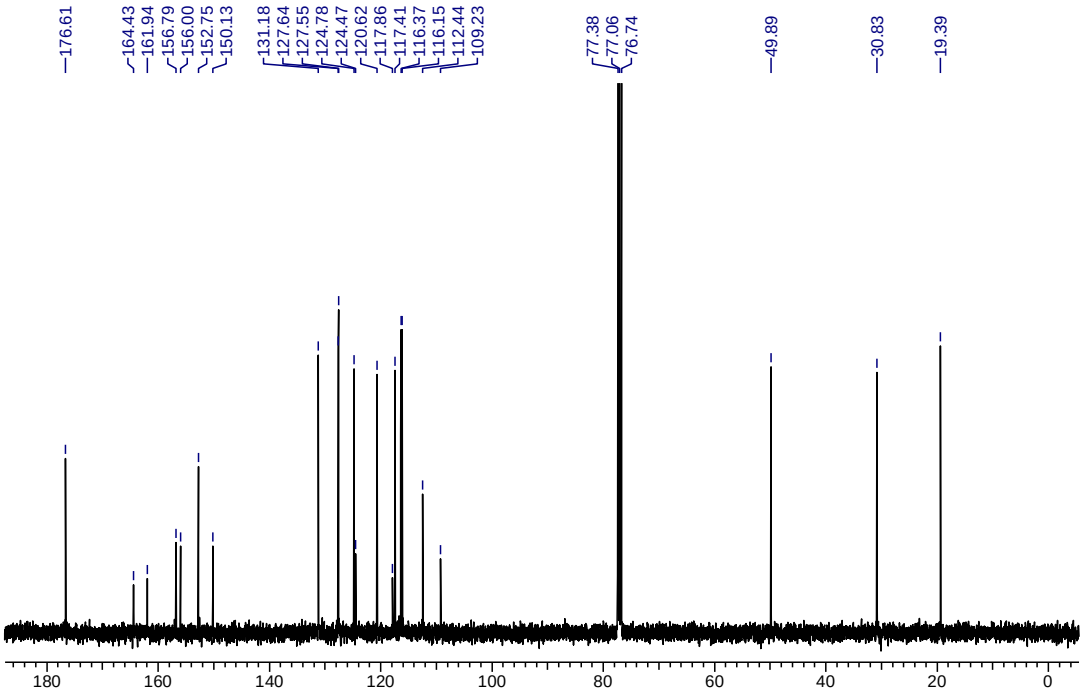
^{1}H NMR (400 MHz) spectrum of compound **56b** in $CDCl_3$



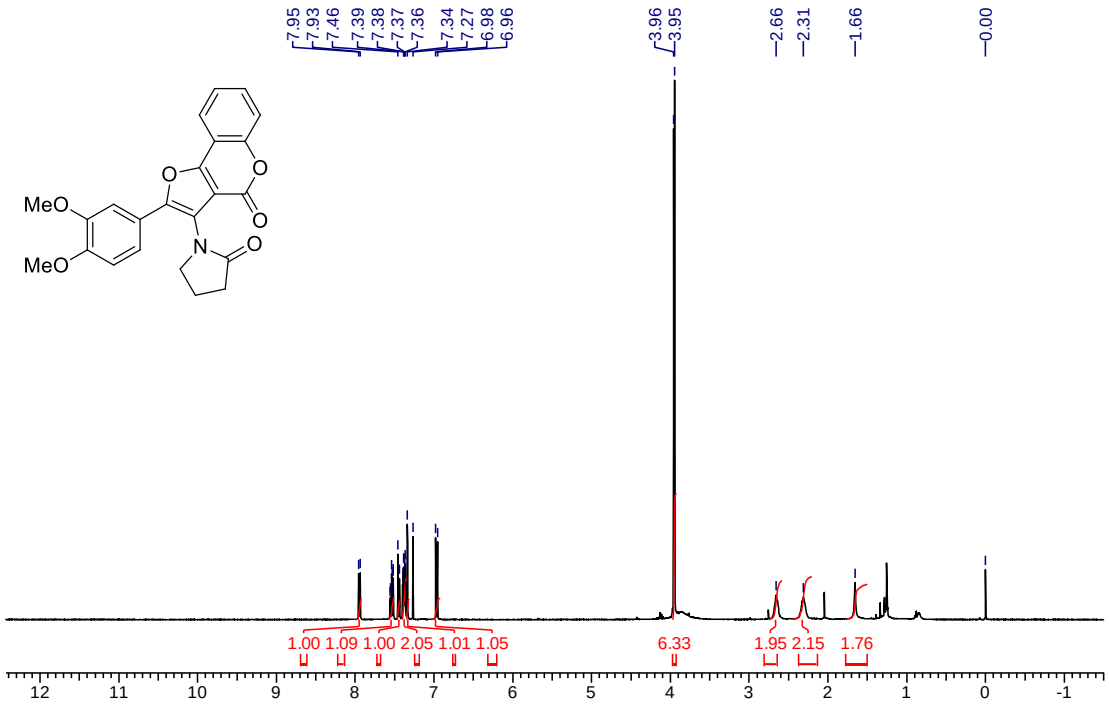
^{13}C NMR (100 MHz) spectrum of compound **56b** in $CDCl_3$



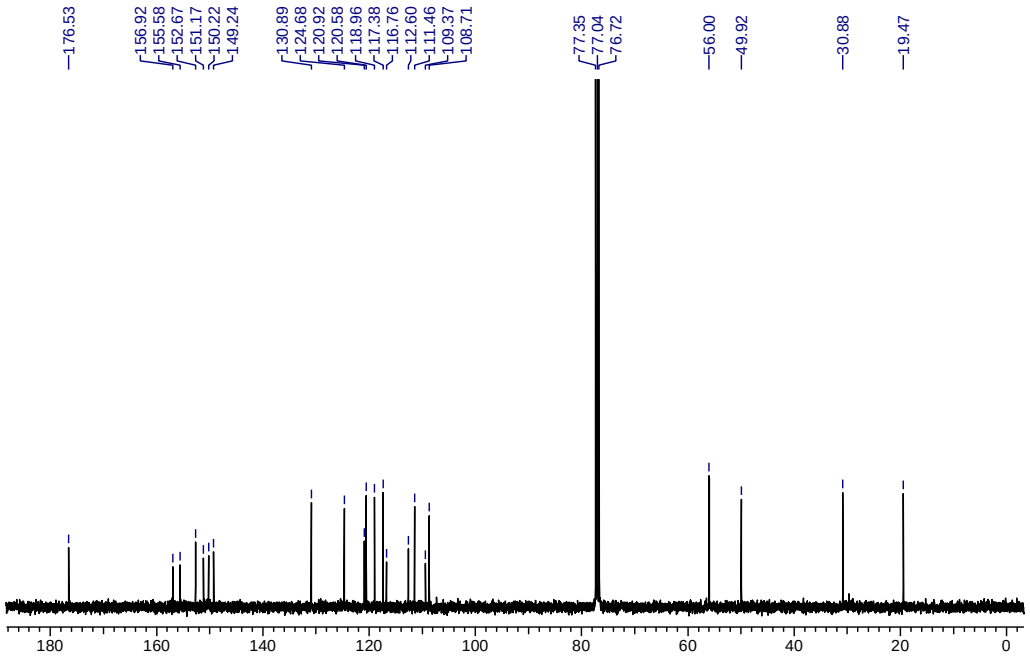
^{1}H NMR (400 MHz) spectrum of compound **56c** in $CDCl_3$



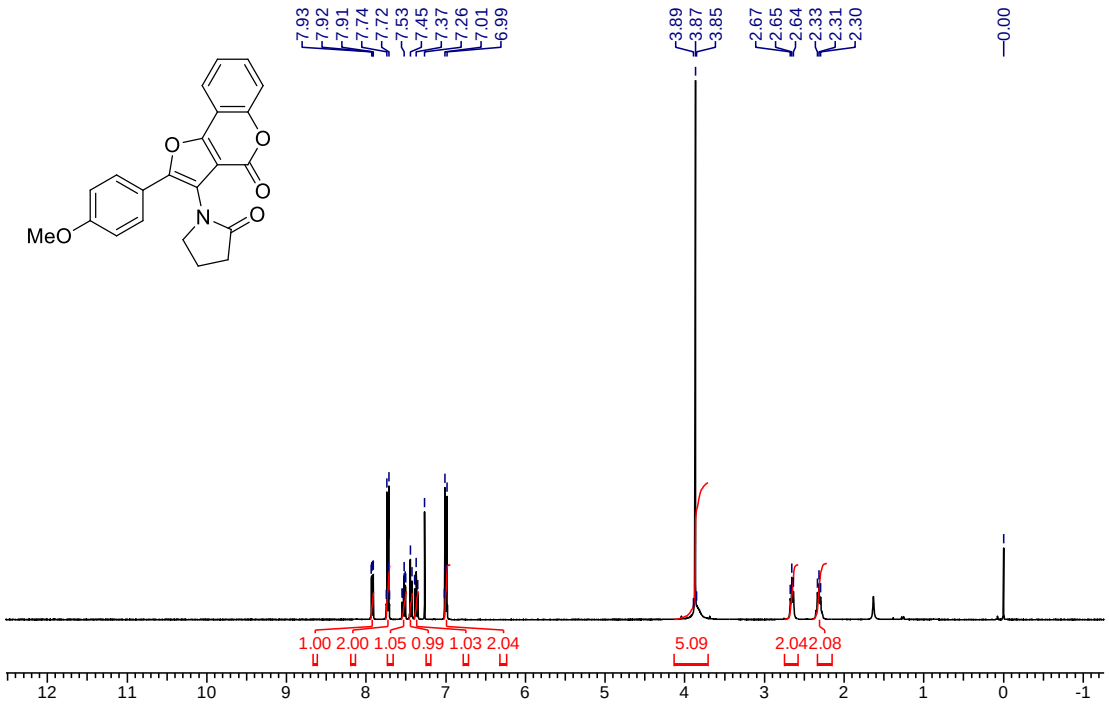
^{13}C NMR (100 MHz) spectrum of compound **56c** in $CDCl_3$



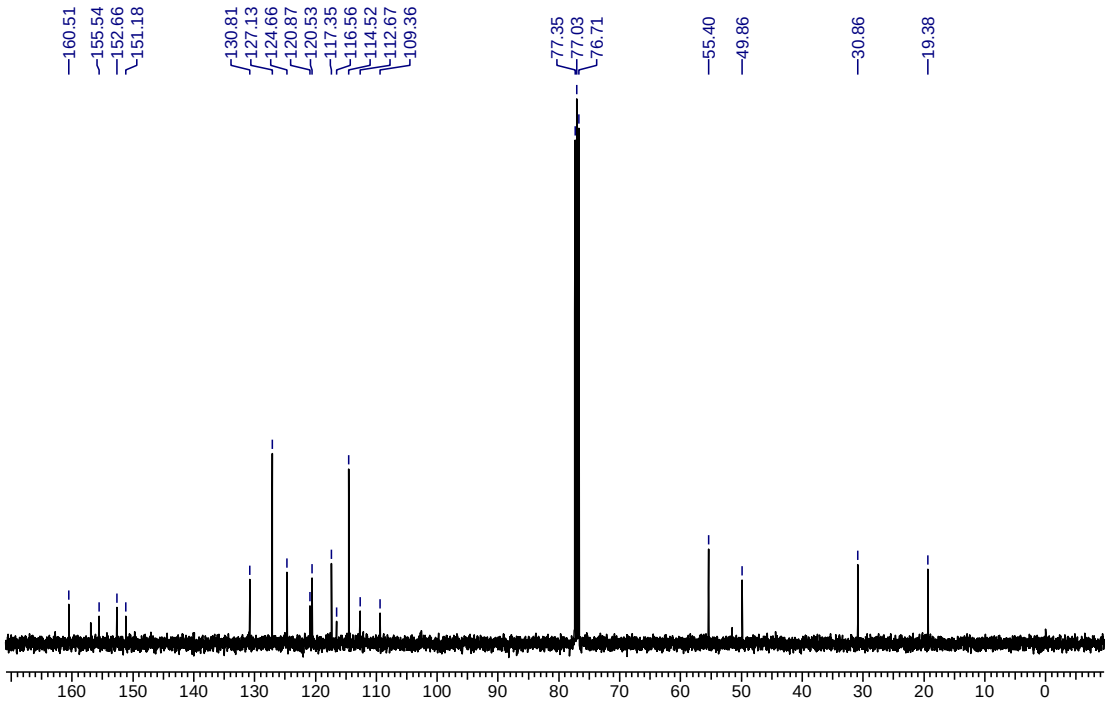
^{1}H NMR (400 MHz) spectrum of compound **56d** in $CDCl_3$



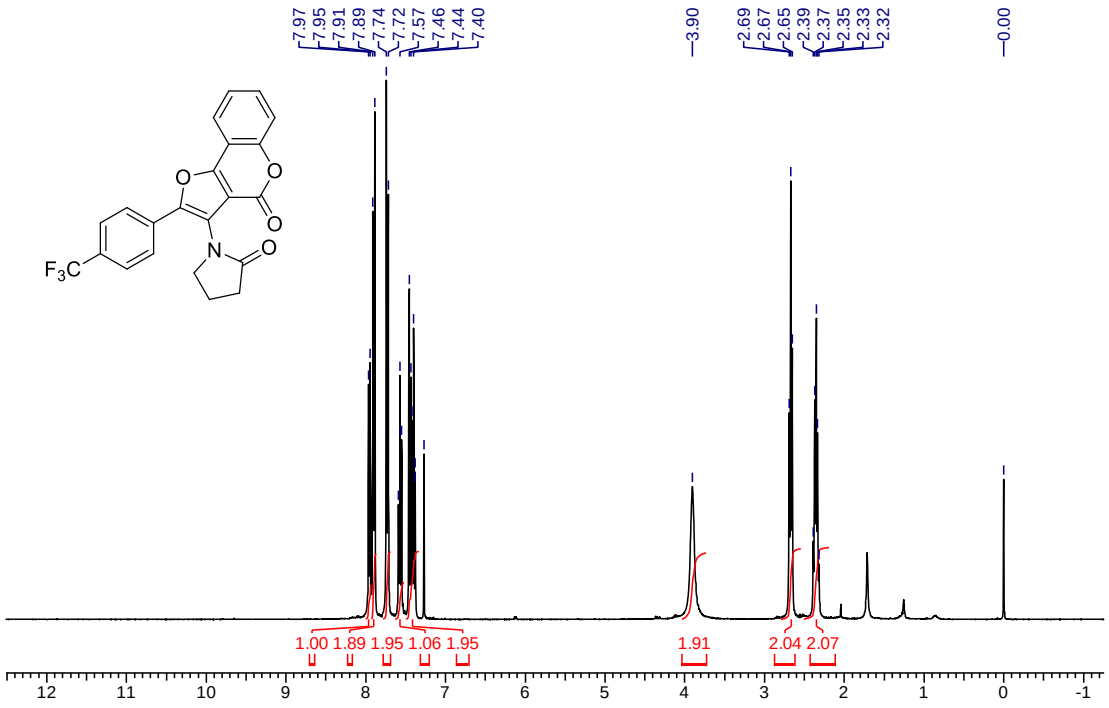
^{13}C NMR (100 MHz) spectrum of compound **56d** in $CDCl_3$



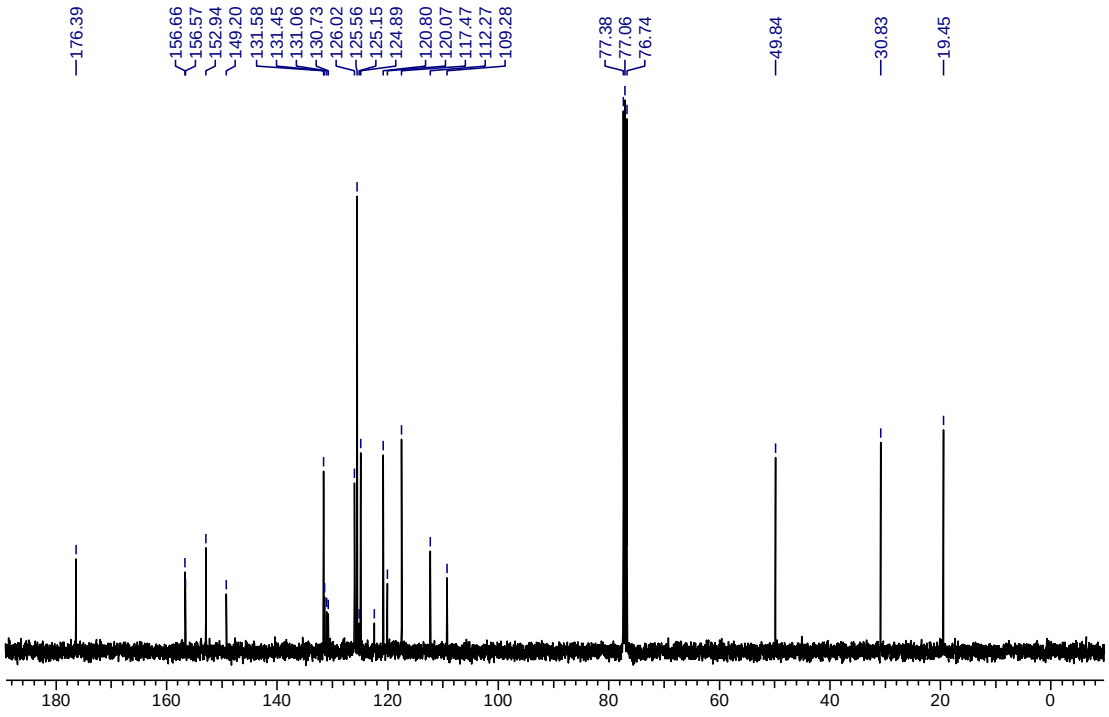
^{1}H NMR (400 MHz) spectrum of compound **56e** in $CDCl_3$



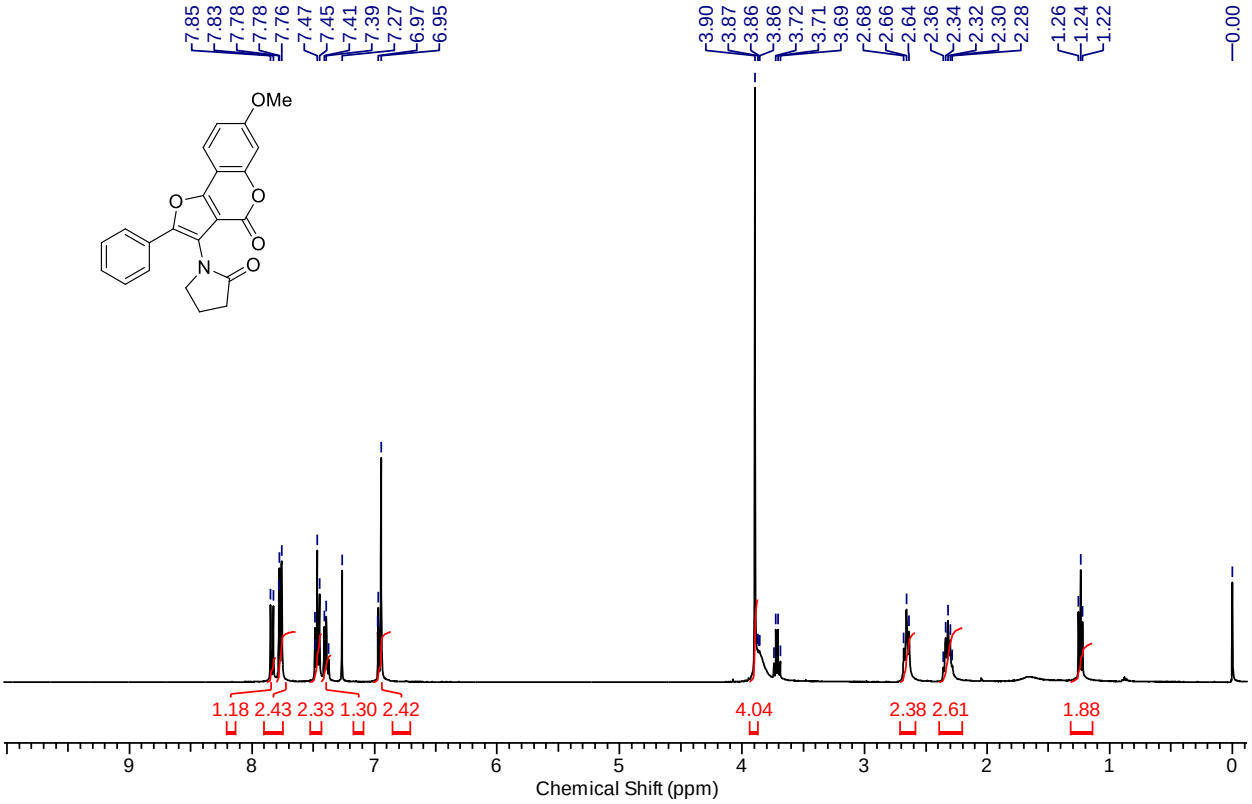
^{13}C NMR (100 MHz) spectrum of compound **56e** in $CDCl_3$



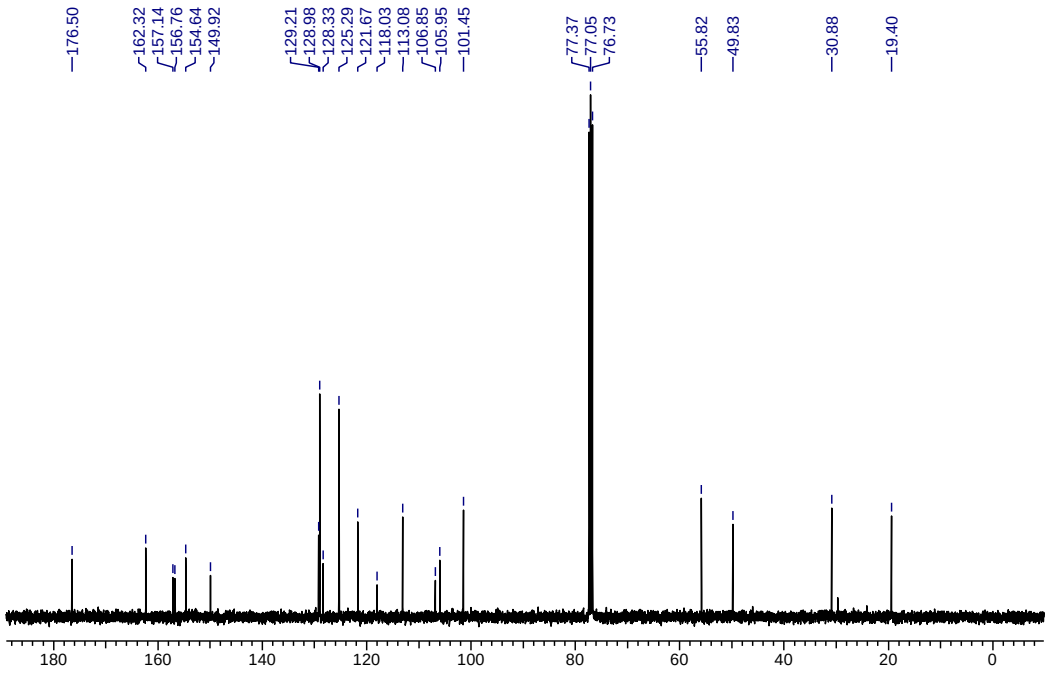
^{1}H NMR (400 MHz) spectrum of compound **56f** in $CDCl_3$



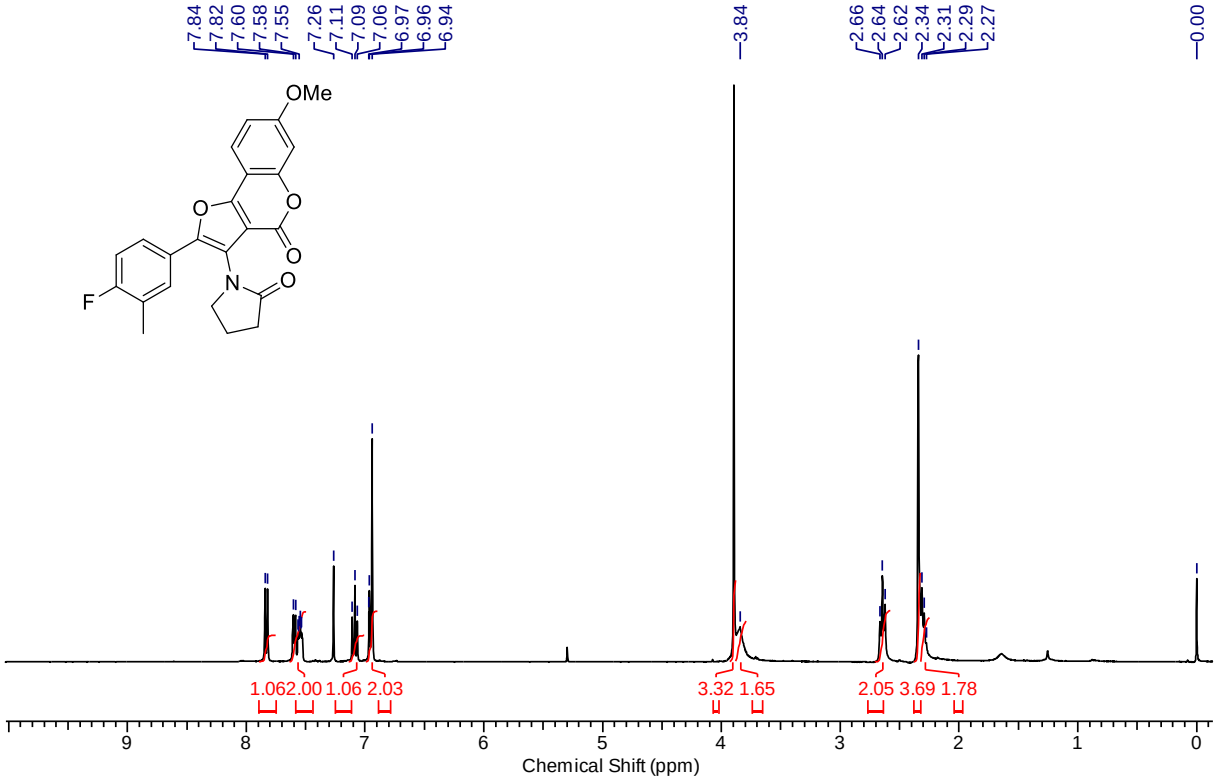
^{13}C NMR (100 MHz) spectrum of compound **56f** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of compound **56g** in $CDCl_3$

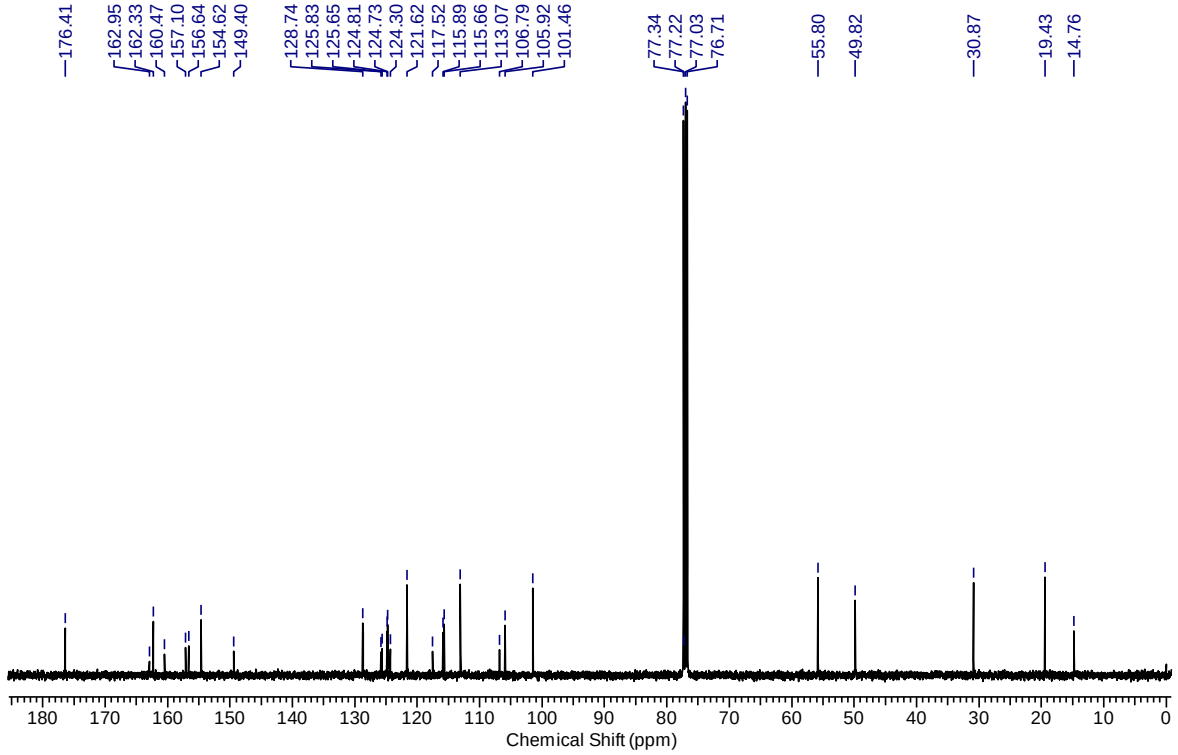


^{13}C NMR (100 MHz) spectrum of compound **56g** in $CDCl_3$

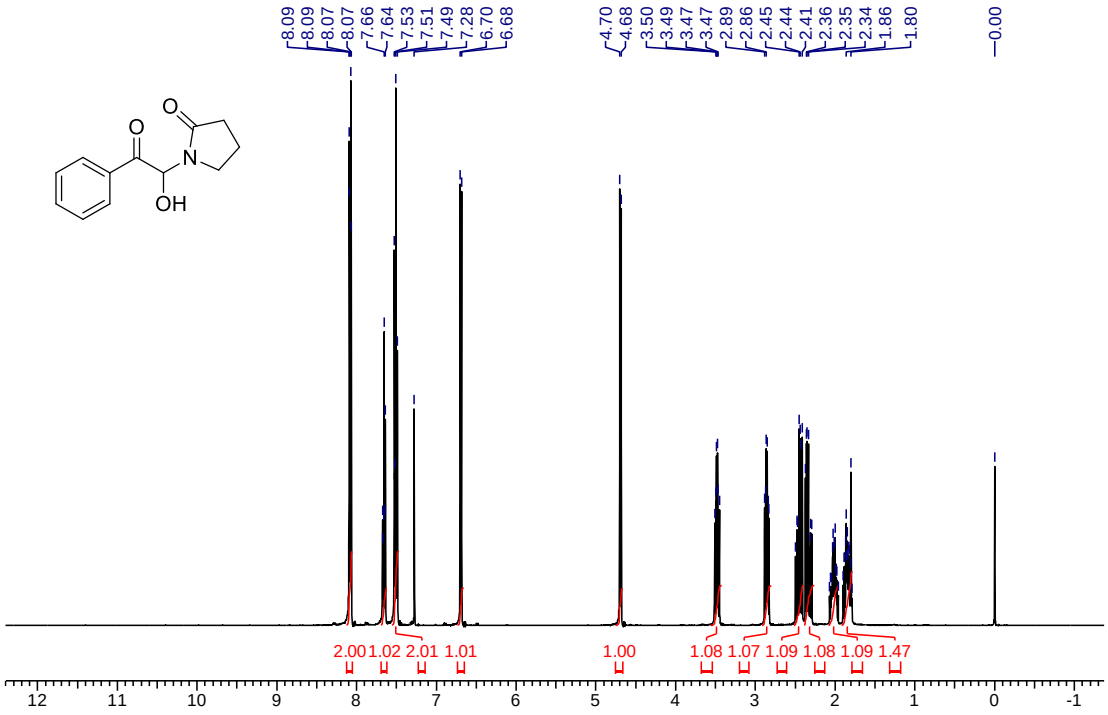


^{1}H NMR (400 MHz) spectrum of compound **56h** in

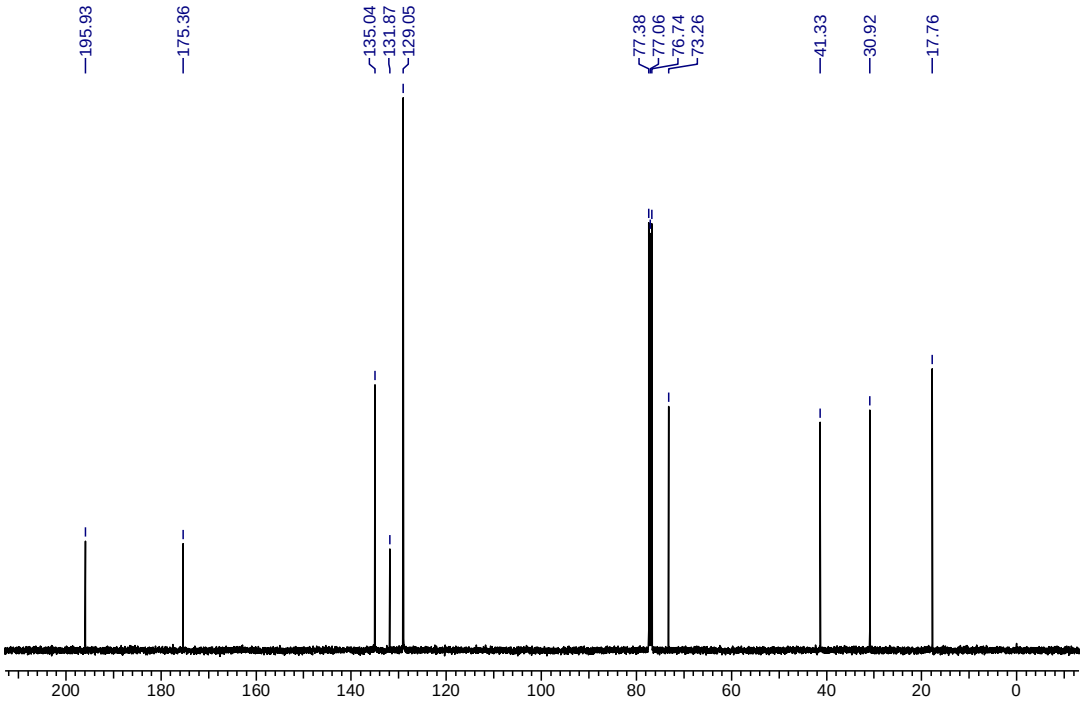
$CDCl_3$



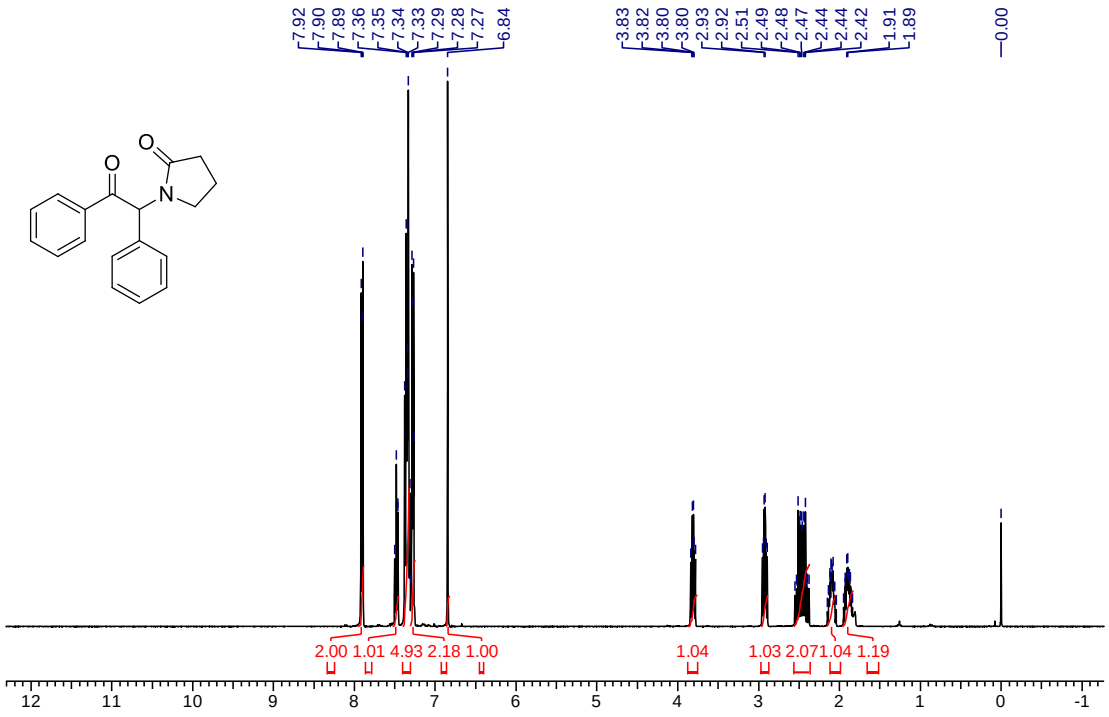
^{13}C NMR (100 MHz) spectrum of compound **56h** in $CDCl_3$



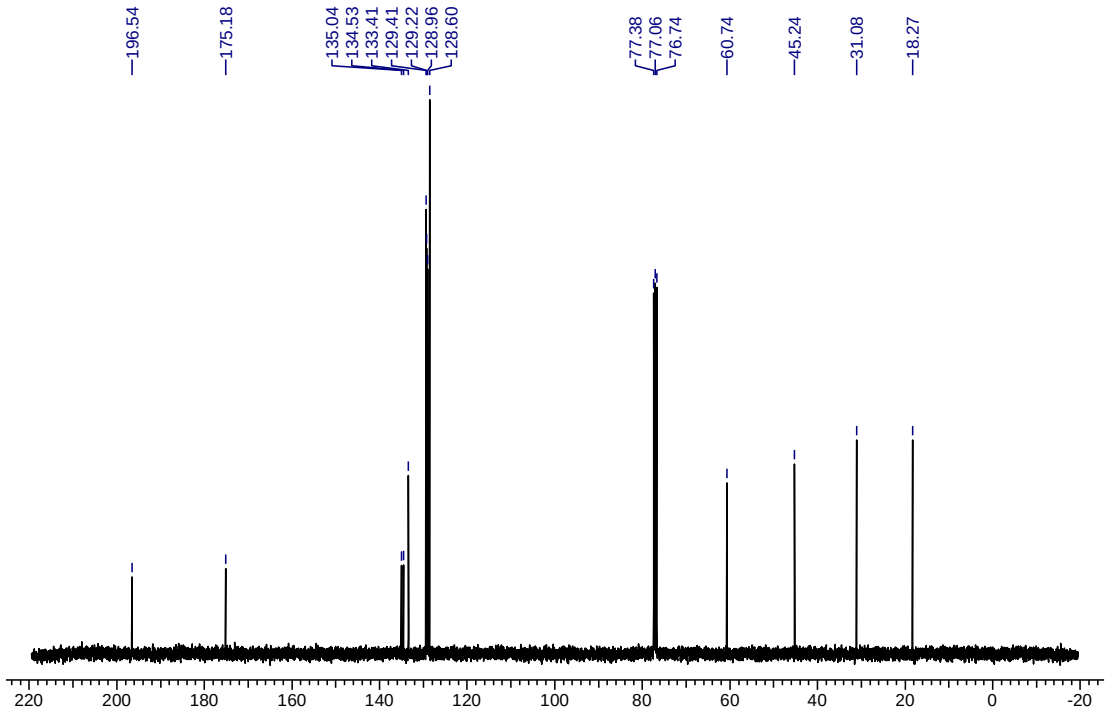
^{1}H NMR (400 MHz) spectrum of compound **49** in $CDCl_3$



^{13}C NMR (100 MHz) spectrum of compound **49** in $CDCl_3$



^{1}H NMR (400 MHz) spectrum of compound **57** in $CDCl_3$



^{13}C NMR (100 MHz) spectrum of compound **57** in $CDCl_3$

3.6. References

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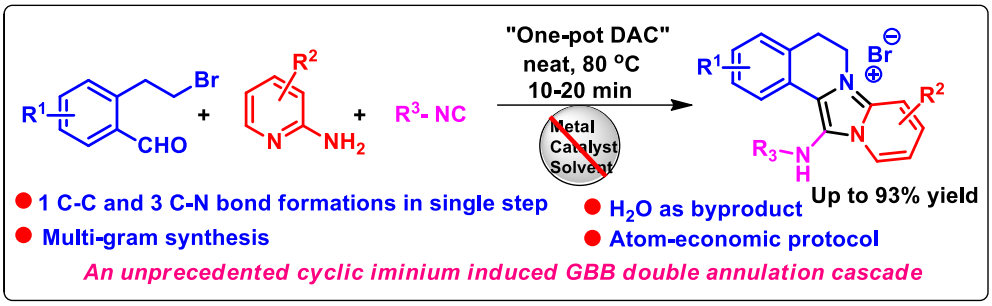
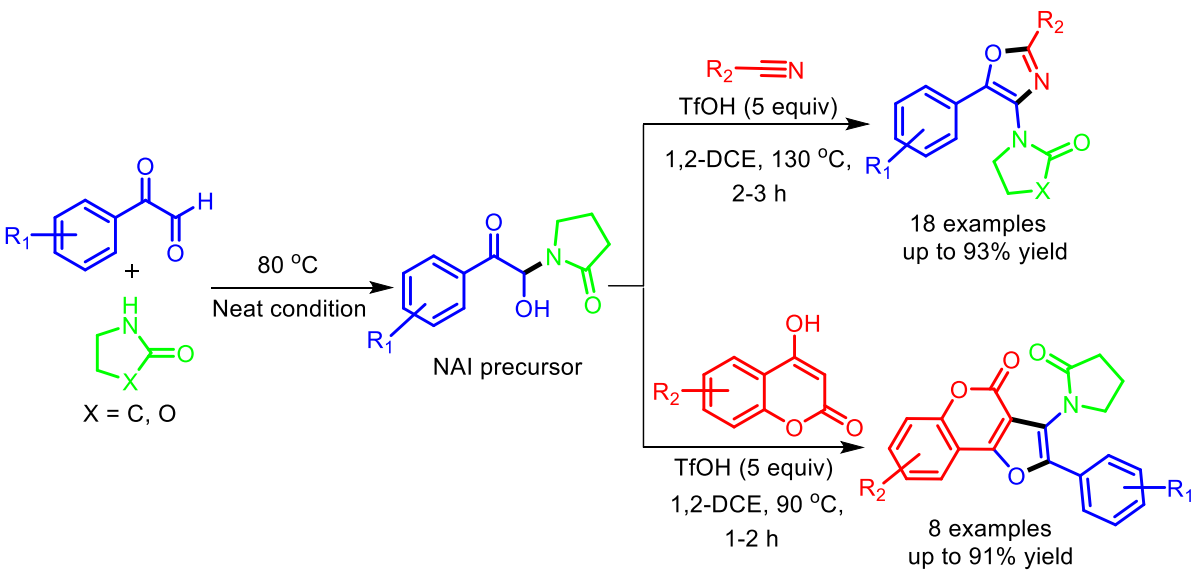
1. Metal-Free Cyclic Iminium Induced One-pot Double Annulation Cascade: Access to Dihydroisoquinolinium (DHIQ) Salts



2. An Exocyclic N-Acyliminium ion (NAI) Cyclization: Access to Fully Substituted Oxazoles and Furocoumarins



CURRICULUM VITAE

Venkata Nagarjuna Babu

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Career objective:

Seeking a challenging environment that encourages continuous learning and creativity. To implement my thoughts and ideas in developing new technology in the rising scenario of chemistry.

Educational qualifications:

Course	Board/ University	Year of Completion	Percentage Secured
Ph.D (Synthetic Methodology)	Indian Institute of Technology Hyderabad	2014-2019	Thesis under preparation

M.Sc (Organic Chemistry)	Osmania University, Hyderabad	2009-2011	68.00%
B.Sc (botany, Physics, Chemistry)	Dr. B. R. Ambedkar Open University, Giriraj Government College, Nizamabad.	2006-2009	70.00%

Technical skills:

- Extensive experience in macro and micro scale synthesis from 10 mg to 200 g. Capable of handling moisture & Light sensitive reactions.
- Comfortable with analysis of NMR, MASS CHNS, Polari meter & IR spectral data of organic molecules.
- Working knowledge of Chem Draw Pro-12, SciFinder and Reaxys Literature search, ACD NMR calculator, NMR processer, familiar with Single crystal XRD software's such as Olex2-1.1.

Strengths:

- Good interpersonal and communication skills writing in international journals
- Ability to work independently and efficiently
- Dedication and Determination to achieve goals
- Good at coordinating and a very good team player

Achievements:

- Qualified **CSIR-JRF** and Secured 82 Rank **(National Eligibility Test) June-2013**
- Awarded Junior Research Fellowship (***JRF***) by the CSIR-India **Jan-2014**
- Awarded Senior Research Fellowship (***SRF***) by the CSIR-India **Jan- 2016**

- Research Excellence Award for the year **2015**, **2016** & **2017** given by IIT Hyderabad

List of publications:

1. Exocyclic N-Acyliminium ion (NAI) Cyclization: Access to Fully Substituted Oxazoles and Furocoumarins. **Venkata Nagarjuna Babu,** Arumugavel Murugan, Narenderreddy Katta, Suman Devatha and Duddu S. Sharada. J. Org. Chem. ***2019,*** DOI: 10.1021/acs.joc.9b00096.
2. A Direct Cycloaminative Approach to Imidazole Derivatives via Dual C-H Functionalization. Sagar Arepally,[#] **Venkata Nagarjuna Babu**,[#] Manickam Bakthadoss and Duddu S. Sharada. Org Lett. 2017, 19, 5014–5017. (equally contributed)[#].
3. Transition-Metal-Free Cyclic Iminium Induced One-pot Double Annulation Cascade: Direct Access to Dihydroisoquinolinium (DHIQ) based Privileged Scaffolds. A. Sagar, [#] **Venkata Nagarjuna Babu,**[#] Anand H. Shinde[#] and Duddu S. Sharada. Org. Biomol. Chem., 2016, 14, 10366. (equally contributed)
4. Regioselective C3-H trifluoromethylation of 2H-indazole under transition-metal-free photoredox catalysis Arumugavel Murugan, **Venkata Nagarjuna Babu**, Ashok Polu, Sabarinathan Nagaraj and Duddu, S. Sharada. *J. Org. Chem.* ***2019,*** DOI:10.1021/acs.joc.9b00676.
5. PIDA/TBAB-Promoted Oxidative Geminal Dibromofunctionalization of Alkynes: Direct Synthesis of Geminal Diazides. Sagar Arepally, **Venkata Nagarjuna Babu**, Ashok Polu and Duddu S. Sharada. Eur. J. Org. Chem. 2018, 5700-5705.
6. I2-Promoted Denitration Strategy: One-pot Three Component Synthesis of Pyrrole-Fused Benzoxazines. A. Sagar, **Venkata Nagarjuna Babu**, Arnab Dey, Duddu S. Sharada. Tetrahedron Lett. 2015, 56, 2710-2713.
7. Silica gel promoted environment-friendly synthesis of α-amino amidines and regioselective transformation of α-amino amidines into amidino substituted indazoles. A. Sagar, **Venkata Nagarjuna Babu**, Arnab Dey, Duddu S. Sharada. *RSC Adv*. **2015**, 5, 29066-29071.

CONFERENCES:

Poster Presentations:

- A poster presentation entitled as **"Transition-Metal-Free Cyclic Iminium Induced One-pot Double Annulation Cascade: Direct Access to Dihydroisoquinolinium (DHIQ) based Privileged Scaffolds" Venkata Nagarjuna Babu** presented in **21st International Conference on Organic Synthesis (ICOS 21)**, **Dec 11-16**, **2016** at Indian Institute of Technology Bombay.

Oral Presentations:

- An oral presentation entitled "**Catalyst - Solvent Free "Synthesis of *N*-acyliminium ion (NAI) precursors; Tandem Cyclization to Fully Substituted Oxazoles, Furocoumarins and Benzils"** presented in **Chemistry In House Symposium-2018**, **March 10, 2018** atIndian Institute of Technology Hyderabad.

- Invited talk entitled as "**PIDA/TBAB-Promoted Oxidative Geminal Dibromofunctionalization of Alkynes: Direct Synthesis of Geminal Diazides**" presented in **"14th J-NOST conference", 28 Nov -1 Dec 2018**, at Indian Institute of chemical technology.