A FACILE ACCESS TO BIOLOGICALLY IMPORTANT SCAFFOLDS FROM BIFUNCTIONAL ALKYNENITRILES

Doctoral Thesis

by

“Chandresh Kumari”

(2017cyz0011)

DEPARTMENT OF CHEMISTRY

INDIAN INSTITUTE OF TECHNOLOGY ROPAR

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A Thesis Submitted
In Partial Fulfillment of the Requirements
for the Degree of

Doctor of Philosophy

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Dedicated

To

‘My Family’

DECLARATION

I declare that this work entitled "*A Facile Access to Biologically Important Scaffolds from Bifunctional Alkynenitriles*" has not previously been accepted in substance for any degree and is not being simultaneously submitted in candidature for any other degree. This thesis is being submitted in partial fulfillment of the requirements for the degree of PhD in Chemistry. This thesis is the result of my own independent investigation, except where otherwise stated. I have acknowledged all the other sources by stating the references explicitly. I declare that any idea/data/fact/source stated in my thesis has not been fabricated/falsified/misrepresented. All the principles of academic honesty and integrity have been followed. I understand that any violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed. I hereby give consent for my thesis, if accepted, to be available online in the Institute's Open Access repository and for inter-library loan, and for the title and abstract to be made available to outside organizations.

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CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "*A Facile Access to Biologically Important Scaffolds from Bifunctional Alkynenitriles*" was carried out by the candidate, Mrs. Chandresh Kumari (2017cyz0011) under my supervision in the Department of Chemistry, Indian Institute of Technology Ropar, Rupnagar, India. I am forwarding the above mentioned thesis of her being submitted for the degree of **Doctor of Philosophy** in **Chemistry** of this Institute. To the best of my knowledge, the present work or any part thereof has not been submitted elsewhere for a degree.

Ropar

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In addition, though I was unaware of it at the time, to those I may have wronged, I ask forgiveness.

ABSTRACT

The development of new and efficient strategies for constructing aliphatic/aromatic heterocyclic structural compounds specifically containing N, O and S heteroatoms has received tremendous attention owing to their ubiquitous presence in variety of natural products, agrochemicals, pharmaceuticals, dyes, cosmetics etc. Many are of fundamental importance to living systems and essential to life. Classical approaches to variously substituted heterocyclic and acyclic scaffolds mainly rely on the transition metal-catalyzed reactions. Reports on transition metal-catalyzed addition/cyclization reactions, coupling reactions, asymmetric synthesis, C-H bond activation/functionalization reactions, olefin metathesis reactions, etc. describes the dominance of transition metals in modern organic synthesis. However, the organic compounds which are synthesized using metal catalysts often suffer from severe contamination with residual metal impurities. In most of the cases, the expensive nature, tedious synthesis of the catalysts, cumbersome product isolation procedures, low sensitivity towards moisture and oxygen, toxicity, etc., limits the use of metal-catalyzed processes. The limitations of transition metal catalysis have encouraged chemists worldwide to bend towards metal-free chemistry. Therefore, our aim was to develop new methodologies for synthesizing diversely functionalized heterocyclic and acyclic scaffolds using transition metal-free appropriate milder reaction conditions.

After successful exploration of alkynenitriles and alkynethiocyanates (potent bifunctional compounds containing both an alkyne-π system and a nitrile group) to develop cycloaddition methodologies to synthesize fused cyanoarenes, 2-alkynyl pyridines, aryl thiocyanates, and propargylic cyclic imines under mild reaction conditions, we switched our interest to exploit these bifunctional alkynenitriles in our laboratory to carry out a diverse range of transition metal-free chemical transformations especially the transition metal-free intermolecular nucleophilic additions.

The thesis entitled "*A Facile Access to Biologically Important Scaffolds from Bifunctional Alkynenitriles*" has been described in the form of six chapters which cover discussions on four efficient transition metal-free approaches, developed by us, to access

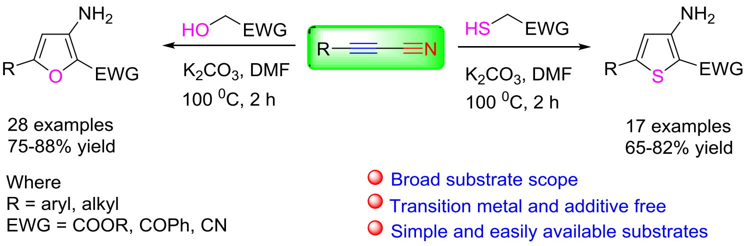
biologically important heterocyclic and acyclic scaffolds from bifunctional alkynenitriles and heteronucleophiles.

Chapter 1: Introduction

Heterocyclic compounds constitute nearly 50% of known organic compounds and nearly 90% of active pharmaceuticals. Cyclocondensation, multicomponent, cycloaddition, and ring expansion/contraction reactions are some of the efficient protocols to obtain a variety of heterocyclic adducts from various unsaturated substrates like alkynes, alkenes, etc. For the last couple of decades, bifunctional compounds like alkynenitriles possessing nitrile and acetylene functionalities have been exploited for the synthesis of various biologically and chemically important carbo- and heterocycles. In this chapter, heterocyclic compounds, their importance and general routes to synthesize has been concisely discussed. In addition, alkynenitriles and their use in nucleophilic conjugate addition reactions have been briefly documented.

Chapter 2: Access to 5-Substituted 3-Aminofuran/thiophene-2-carboxylates from Bifunctional Alkynenitriles

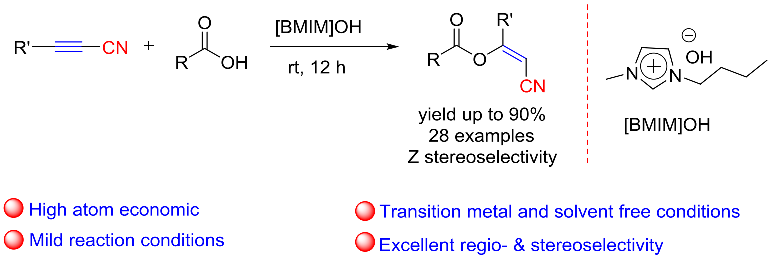
Five-membered heterocycles furans, thiophenes, and pyrroles and their derivatives are found as core structural motifs in various natural products, pharmaceuticals, and complex organic compounds. 3-amino substituted five-membered heterocycles are necessary scaffolds embedded in many molecules having potential biological activities. A majority of strategies include the reduction of 3-azido/3-nitro, rearrangements of furan-3-carboxylate derivatives, the cross-coupling of 3-halo/3-ylboronate derivatives with a nitrogen source, and so on. In addition, the strong base-assisted Thorpe-Ziegler cyclization of cyanovinyl ethers has become an efficient and atom-economical tool for synthesizing 3-amino furans. Thus, we can see that all these above mentioned protocols require pre-functionalized substrate that itself has to be prepared, often in multiple steps using undesirable reagents. In this chapter, we have described how alkynenitriles could act as suitable candidates to react with heteronucleophiles having EWG at α-position to construct 3-amino substituted five-membered heterocycles (Scheme 1). 3-aminofurans/thiophenes have been synthesized using K_2CO_3/DMF base solvent combination from cheap and readily available substrates in good to high yields.



Scheme 1 Synthesis of 5-substituted 3-aminofuran/thiophene-2-carboxylates from bifunctional alkynenitriles.

Chapter 3: A Facile Transition Metal-free Ionic Liquid [BMIM]OH Mediated Regio- and Stereoselective Hydrocarboxylation of Alkynenitriles

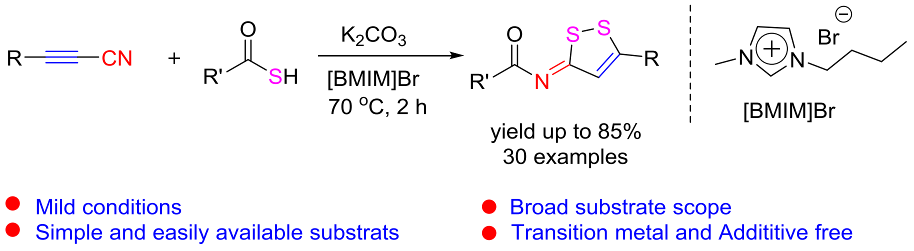
Enol esters are versatile synthons in various elegant synthetic transformations. They have been used in multicomponent reactions, hydroformylation, epoxidation, aldol reactions, cycloaddition reactions, α-functionalization reactions, Mannich type reactions and asymmetric hydrogenations reactions. Therefore, several methods have been developed to synthesize substituted enol esters. Among different approaches, the direct addition of carboxylic acids to alkynes is the most widely used atom-economical approach. However, it is very challenging to control the regio- and stereoselecivity during the addition process especially in the case of unsymmetrically substituted internal alkynes. Therefore, specific reagents and catalysts, transition metal complexes of ruthenium, palladium, rhodium, iridium, cobalt, rhenium, silver, iron, copper, gold and mercury are utilized for the hydrocarboxylation of the alkynes to synthesize substituted enol esters. In addition, a lot of efforts have been employed in literature to tailor the synthesis of metal complexes and ligands to achieve the required regio- and stereoselectivity. Thus, most of approaches are assisted by either toxic or expensive metal salts, drastic reaction conditions, poisonous reagents or costly ligands, while reports on metal-free hydrocarboxylation reactions are rather limited. In this chapter, we have presented highly efficient, transition metal-free, ionic liquid [BMIM]OH mediated synthesis of nitrile substituted enol esters in *Z*-stereoselection fashion with the reusability of the ionic liquid up to ten runs without loss of activity (Scheme 2).



Scheme 2 Ionic liquid [BMIM]OH-mediated regio- and stereoselective hydrocarboxylation of alkynenitriles.

Chapter 4: Ionic Liquid Mediated One-Pot 3-Acylimino-3*H*-1,2-dithioles Synthesis from Thiocarboxylic Acids and Alkynenitriles via *in situ* Generation of Disulfide Intermediates

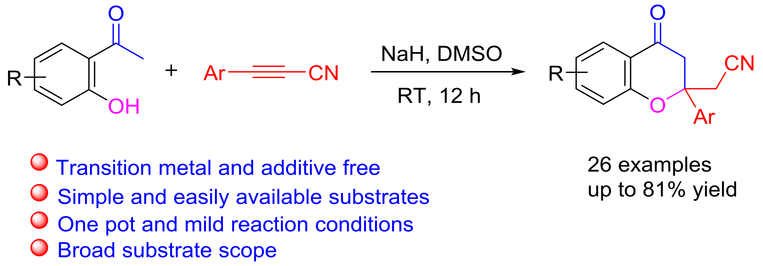
Functionalized 1,2-dithiol heterocyclic structural motifs are frequently found in various natural products and pharmaceuticals and show a broad spectrum of biological and pharmacological activity, like antioxidant, antibiotic, chemotherapeutic, antitumor and anti HIV etc. In addition, they are being used as building blocks for synthesizing novel sulfur or nitrogen atom(s) containing heterocycles. As a result, several synthetic methodologies are being developed for their preparation. However, 3-acylimino-1,2-dithiole derivatives another class of 1,2-dithiols remained underexplored and further development is much needed to widen the access to this class of compounds. So far, all the existing protocols rely on the already inbuilt 1,2-dithiole core containing substrates and are associated with the drawback of the limited availability and multistep synthesis of the pre-decorated precursors. In this context, we have developed the first quantitative one-pot ionic liquid [BMIM]Br-mediated synthesis of 3-acylimino-3*H*-1,2-dithiols from readily available thiocarboxylic acids and bifunctional alkynenitriles in the presence of K_2CO_3 as a base (Scheme 3).



Scheme 3 Ionic liquid mediated one-pot 3-acylimino-3*H*-1,2-dithioles synthesis from thiocarboxylic acids and alkynenitriles.

Chapter 5: Tetra Substituted Chromanone Synthesis via a Tandem Michael/oxa-Michael Addition between 2-Hydroxyacetophenones and Alkynenitriles

Polyfunctionalized Chroman-4-ones are widespread oxygen-based heterocycles with numerous applications in medicinal chemistry. They have been identified as an active core in many biologically active natural products and pharmaceuticals and are of great interest to organic chemists owing to their diverse biological activities. As a result, numerous elegant synthetic strategies have been developed to build up their fundamental cores. After successfully developing straightforward routes to five-membered N, O and S containing heterocycles utilizing bifunctional alkynenitriles, we paid our attention to further exploit these bifunctional substrates to develop a protocol to synthesize six membered oxygen-based heterocycles.

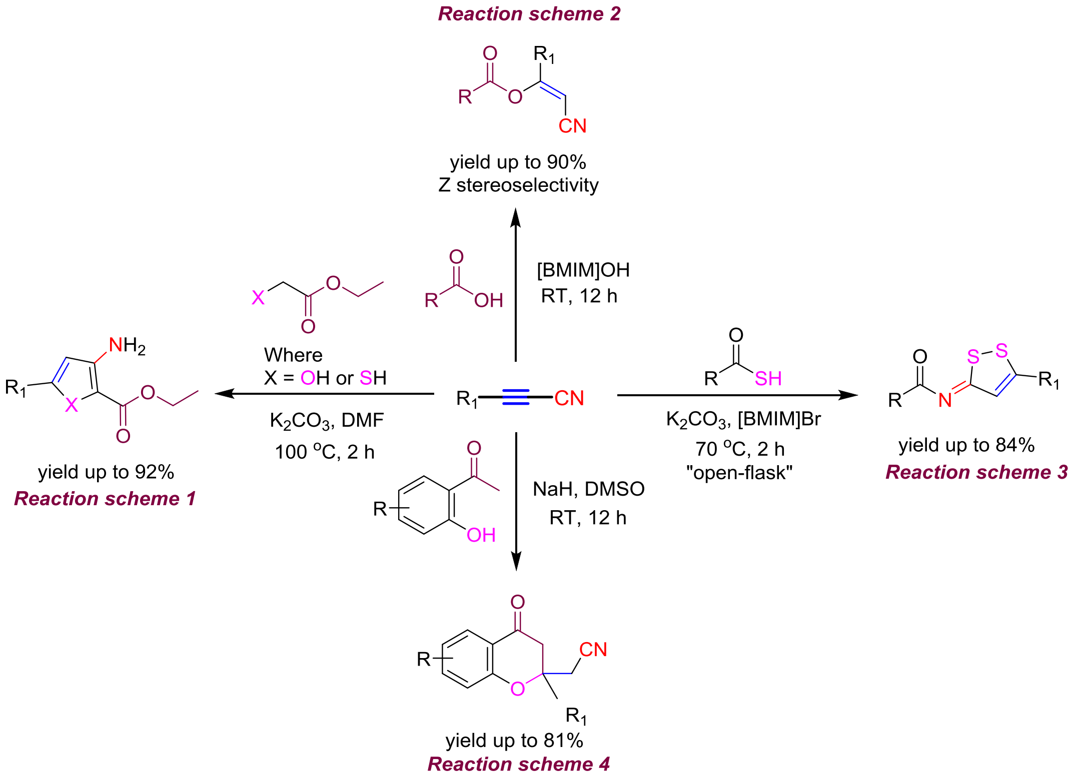


Scheme 4 Tetra substituted chromanone synthesis via Michael/oxa-Michael addition between 2-hydroxyacetophenones and alkynenitriles.

In this context, we have developed a transition metal-free, one-pot, NaH-mediated Michael/intramolecular oxo-Michael addition process to synthesize C2, tetrasubstituted chroman-4-ones from readily accessible starting materials 2-hydroxyacetophenones and alkynenitriles under mild reaction conditions (Scheme 4). The protocol proceeds via a sequence of 1,4-conjugate addition of enolate to alkynenitrile, followed by subsequent intramolecular oxa-Michael addition. This strategy provides a convenient method for accessing a broad range of tetrasubstituted chromanones in good to excellent yields with good functional-group tolerance.

Chapter 6: Conclusions

In this chapter, the summary of the whole work has been described (Scheme 5).



Scheme 5 Transition metal-free routes to synthetically important structural scaffolds, presented in the thesis.

Keywords: Heterocycles, thiophenes, furans, enolesters, ionic liquid, [BMIM]Br, [BMIM]OH, 1,2-dithiols, tetrasubstituted chromanones, 1,4-conjugate addition, intramolecular oxa-Michael addition, bifunctional alkynenitriles, 2-hydroxyacetophenones, Thorpe-Ziegler cyclization

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List of Abbreviations

Å	Angstrøm
Ac	Acetyl
AIBN	Azobisisobutyronitrile
ACN	Acetonitrile
Ar	Aryl
Benzyl	Benzyl
Bu	Butyl
n-BuLi	n-Butyllithium
[BMIM]NFT_2	1-butyl-2,3-dimethylimidazoliumbis(trifluoromethanesulfonyl)imide
[BMIM]BF_4	1-n-butyl-3-methylimidazolium tetrafluoroborate
[BMMIM]Br	1-butyl-2,3-dimethylimidazolium bromide
[BMIM]OH	1-n-butyl-3-methylimidazolium hydroxide
[BMIM]Br	1-n-butyl-3-methylimidazolium bromide
$BF_3 \cdot Et_2O$	Boron trifluoride diethyl etherate
Cp*Ru(COD)Cl	Chloro(pentamethylcyclopentadienyl)(cyclooctadiene)ruthenium(I)
CuCN	Copper cyanide
$Co(BF_4)_2$	Cobalt(II)tetrafluoroborate
MCPBA	3-Cholorobenzenecarboperoxoic acid
$Cu(NO_3)_2.3H_2O$	Copper(II)nitrate trihydrate
Cs_2CO_3	Cesium carbonate
$Cu(OTf)_2$	Copper(II)triflate
CuBr	Copper(I)bromide
CuI	Copper(I)iodide
$Ru_3(CO)_{12}$	Dodecacarbonyltriruthenium
DCE	1,2-Dichloroethane
DEAD	Diethyl azodicarboxylate

DME	Dimethoxyethane
DCM	Dichloromethane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dipimp	2-(2,6-diisopropylphenyl)-iminomethylpyridine
$[Rh(COD)Cl]_2$	Di-μ-chloro-bis[(cycloocta-1,5-diene)rhodium(I)]
DCC	N,N'-Dicyclohexylcarbodiimide
DMAP	4-Dimethylaminopyridine
DABCO	1,4-diazabicyclo[2.2.2]octane
$[Ru\text{-}(p\text{-}cymene)Cl_2(PPh_3)]$	Dichloro(η^6-p-cymene)(triphenylphosphine)ruthenium(II)
DMSO	Dimethyl sulphoxide
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
g	Gram
GC-MS	Gas Chromatography Mass Spectrometry
h	Hour
Hz	Hertz
Δ	Heat
HRMS	High Resolution Mass Spectrometry
[HMIM]Br	1-hexyl-3-methylimidazolium bromide
$FeCl_3$	Iron(III)chloride
J	Coupling constant
LiHMDS	Lithium hexamethyldisilazide
Ligand	Ligand
Me	Methyl
MeOH	Methanol
mg	Milligram
mL	Millilitre
mmol	Millimol
mp	Melting point

m/z	Mass over charge ratio
NOESY	Nuclear overhauser effect spectroscopy
NMR	Nuclear magnetic resonance spectroscopy
ppm	Parts per million
Ph	Phenyl
Pr	Propyl
P_2O_5	Phosphorous pentoxide
K_3PO_4	Potassium phosphate
KI	Potassium iodide
KO^tBu	Potassium tert-butoxide
KOH	Potassium hydroxide
$Cp^*RuCl(PPh_3)_2$	Pentamethylcyclopentadienylbis(triphenylphosphine)ruthenium(II)
1,10-phen	1,10-phenanthroline
RT	Room temperature
$RuCl_3.xH_2O$	Ruthenium(III)chloride hydrate
NaOAc	Sodium acetate
NaOEt/ C_2H_5ONa	Sodium ethoxide
$AgPF_6$	Silver hexafluorophosphate
AgOTf	Silver triflate
$AgSbF_6$	Silver hexafluoroantimonate(V)
Na_2SO_4	Sodium sulfate
NaH	Sodium hydride
^tBu	^{t}Butyl
PhMe	Toluene
THF	Tetrahydrofuran
Et_3N	Triethylamine
TBAF	Tetra-n-butylammonium fluoride
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
TMEDA	Tetramethylethylenediamine
PPh_3	Triphenyl phosphine
$P(OMe)_3$	Trimethoxy phosphine

TLC	Thin-layer chromatography
$TrBF_4$	Tritylium tetrafluoroborate
TMSCl	Trimethylsilyl chloride
$[Au(PPh_3)Cl]$	Triphenylphosphinegold(I)chloride
VAA	Vinyl acetate/acrylic

CHAPTER 1

Introduction

Chapter 1: Introduction

1.1 General introduction to heterocyclic compounds

Heterocyclic compounds, the largest section of organic chemistry, are cyclic organic compounds that contain at least one hetero atom, i.e. an atom other than carbon atom in the ring constituting the cyclic structure.[1] Based on the structural and electronic arrangement, these can be aliphatic and aromatic. The cyclic amines, cyclic amides, cyclic ethers, cyclic thioethers, etc., come in the aliphatic heterocyclic compounds. At the same time, the aromatic heterocyclic compounds follow Huckel’s rule. A heterocycle may comprise three or more than three atoms, can be saturated or unsaturated, may contain more than one heteroatom which may be either similar or different. In addition, these can be a fused or condensed form of two or more rings which may be partly carbocyclic and partly heterocyclic, typical examples of this category of heterocyclic compounds are indole, quinoline, isoquinoline, carbazole, etc. (Figure 1.1.1).

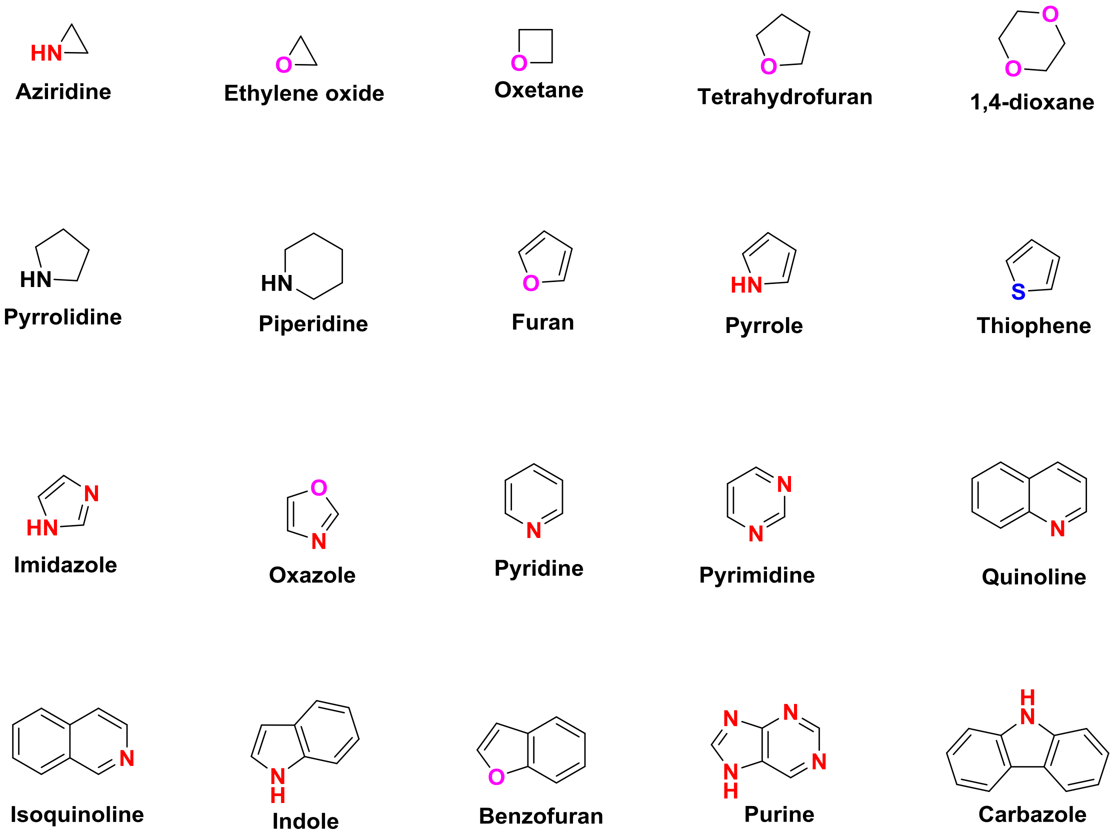


Figure 1.1.1 Examples of heterocyclic compounds.

More than half of the biologically active compounds produced by nature possess a heterocyclic moiety as a fundamental core in their structure. Alkaloids, proteins, natural dyes, drugs, enzymes, etc., constitute some important classes of natural heterocyclic compounds.[2] Most frequently, we can find nitrogen heterocycles or various positional combinations of nitrogen atoms, oxygen, and sulfur in five- or six-membered rings. Heterocyclic compounds containing nitrogen (N), oxygen (O), or sulfur (S) heteroatoms constitute about sixty-five percent of organic chemistry literature. The presence of heteroatoms (e.g., N, S, and O) in the cyclic molecular structures results in enhanced physicochemical properties that are often quite distinct from those of their all-carbon-ring analogs. Moreover, the presence of heterocycles could improve solubility, lipophilicity, polarity, and hydrogen bonding ability toward biologically active agents.

Heterocyclic compounds have been known since the 1800s, with the development of organic chemistry. Only noteworthy developments are shown in Figure 1.1.2,[3] for example, in 1818, Brugnatelli isolated alloxan (**2**) by oxidization of uric acid (**1**). Dobereiner, in 1832, synthesized a furan derivative, furfural (**3**), from starch by treating it with sulfuric acid. Runge obtained pyrrole ("fiery oil") during the dry distillation of bones in 1834 (**4**). In 1906, Friedlander synthesized the first thioindigo dye (**5**), further expanding synthetic chemistry. In 1936, Treibs isolated chlorophyll derivatives from crude oil, explaining the biological origin of petroleum. In 1951, Chargaff's rules described the role of heterocyclic compounds (purines and pyrimidines) in genetics.

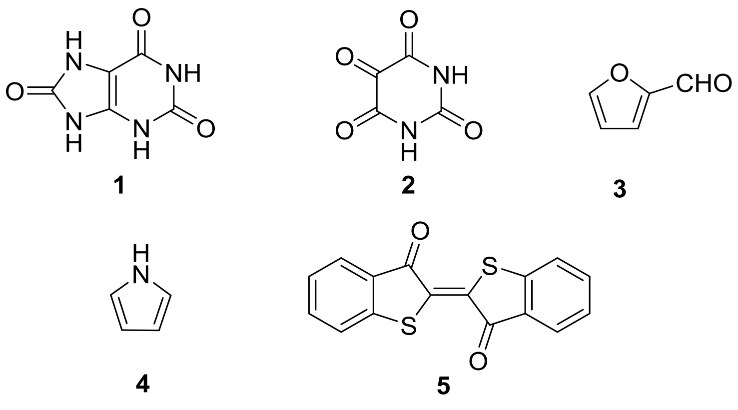
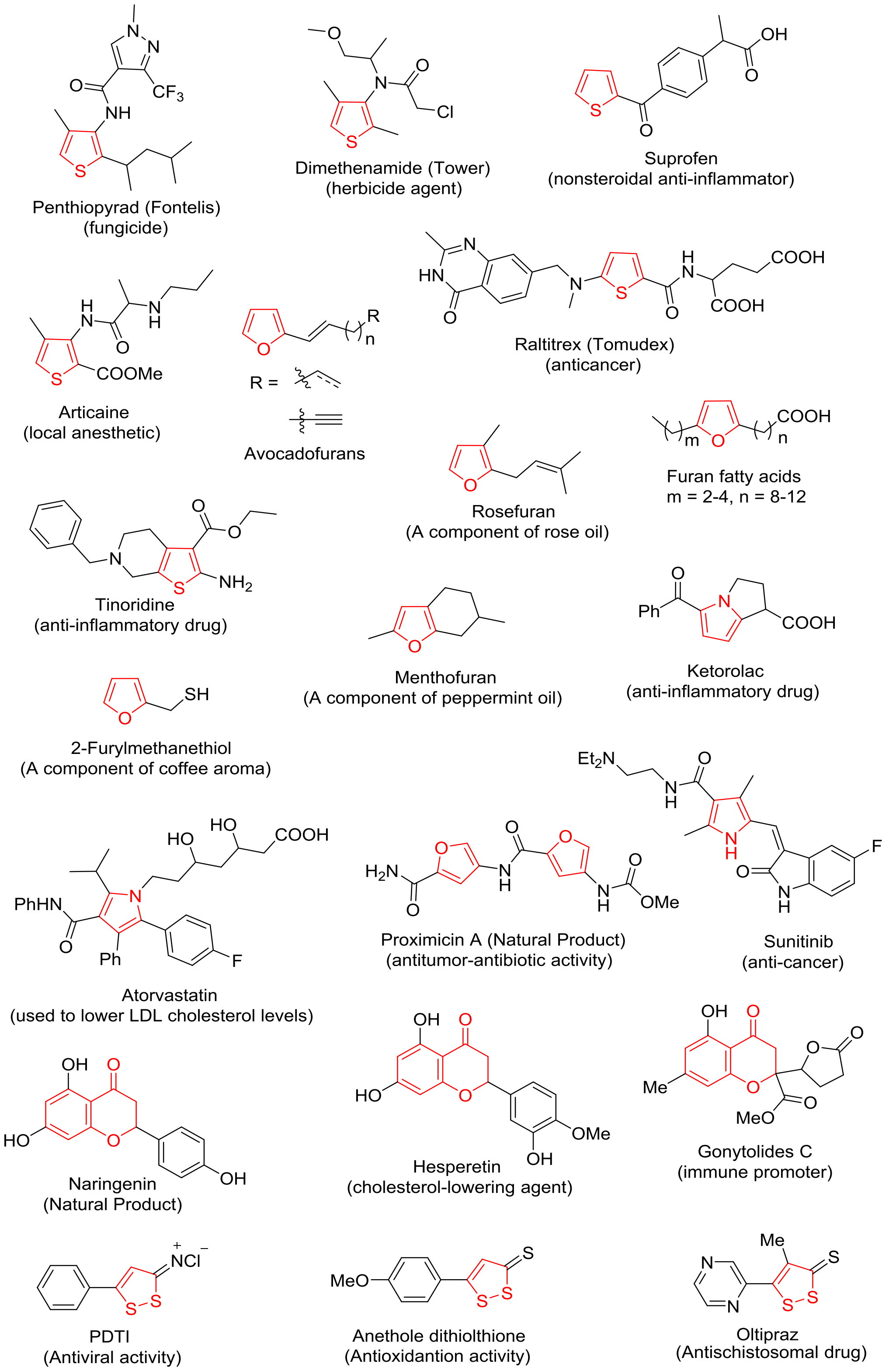


Figure 1.1.2 Some examples of noteworthy developments in the heterocyclic chemistry.

The polysubstituted five- and six-membered heterocyclic compounds furans, thiophenes, pyrroles, pyridines, coumarines, isocoumarines, chromones, and their derivatives are often found as core structural motifs in natural products, pharmaceuticals, and organic synthetic chemistry (Figure 1.1.3).[2] These compounds and their modified products have popularly been utilized as pharmacophores for preparing drugs. On the other hand, many heterocyclic lead compounds are being isolated from natural resources and subsequently simplified and modified by medicinal chemists.

Heteroatoms containing organic molecules have found widespread success and applications in pharmaceutical industries and synthetic chemistry in the form of catalysts, auxiliaries, additives, etc., to realize unprecedented chemical transformations.[4] Many pharmaceuticals and other heterocyclic compounds with practical applications are not extracted from natural sources but are synthesized. The increasing demand and growing need for more sustainable chemical processes have led the chemical community to develop more efficient and selective methods for designing these heterocyclic and acyclic molecules.



Penthiopyrad (Fontelis)
(fungicide)

Dimethenamide (Tower)
(herbicide agent)

Suprofen
(nonsteroidal anti-inflammator)

Articaine
(local anesthetic)

Avocadofurans

Raltitrex (Tomudex)
(anticancer)

Rosefuran
(A component of rose oil)

Furan fatty acids
m = 2-4, n = 8-12

Tinoridine
(anti-inflammatory drug)

Menthofuran
(A component of peppermint oil)

Ketorolac
(anti-inflammatory drug)

2-Furylmethanethiol
(A component of coffee aroma)

Atorvastatin
(used to lower LDL cholesterol levels)

Proximicin A (Natural Product)
(antitumor-antibiotic activity)

Sunitinib
(anti-cancer)

Naringenin
(Natural Product)

Hesperetin
(cholesterol-lowering agent)

Gonytolides C
(immune promoter)

PDTI
(Antiviral activity)

Anethole dithiolthione
(Antioxidantion activity)

Oltipraz
(Antischistosomal drug)

Figure 1.1.3 Representative examples of N, O or S heteroatoms containing natural products and drugs.

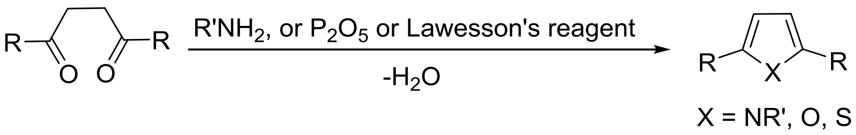
1.2 General routes to heterocycles synthesis

Among various synthetic protocols, the most frequently used routes include cyclocondensation,[5] multicomponent,[6] cycloaddition,[7] and ring expansion/contraction reactions.[8]

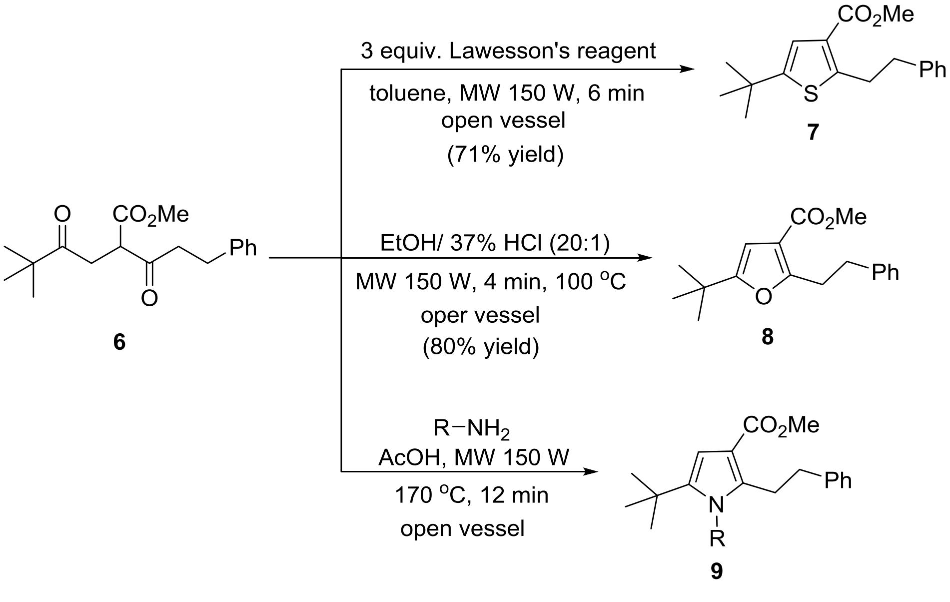
1.2.1 Cyclocondensation reactions

1.2.1.1 Paal-Knorr synthesis

The Paal-Knorr reaction is a well-known approach that produces either pyrroles, furans, or thiophenes from 1,4-diketones (Scheme 1.2.1.1.1). Its first report was documented for the preparation of furans in 1884 by German chemists Carl Paal and Ludwig Knorr and later adapted for synthesizing pyrroles as well as thiophenes.[5a-d] It is a synthetically beneficial strategy for accessing substituted five-membered aromatic heterocycles.

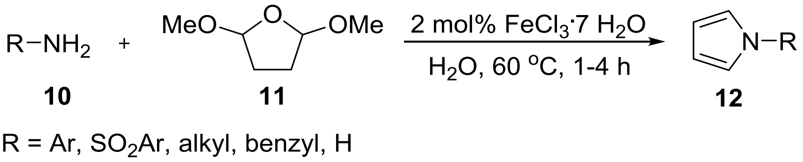


Scheme 1.2.1.1.1 Paal-Knorr synthesis to produce either pyrroles, furans, or thiophenes from 1,4-diketones.



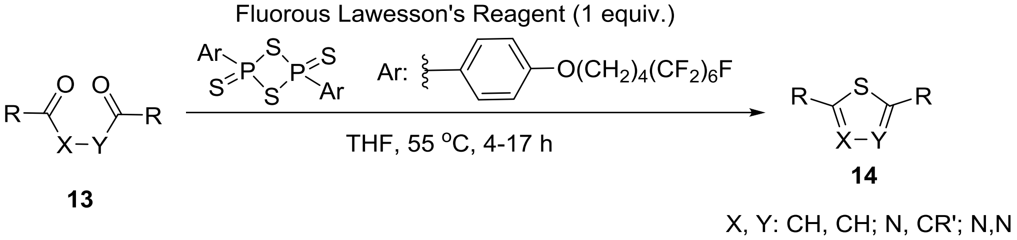
Scheme 1.2.1.1.2 Microwave-assisted Paal-Knorr synthesis of thiophenes, furans, and pyrroles.

Taddei *et al.,* in 2005, described an efficient and versatile microwave-assisted Paal-Knorr synthesis of 3-methoxycarbonylthiophenes/furans/pyrroles from easily available substituted 1,4-diketones (Scheme 1.2.1.1.2).[5e] The substituted 1,4-diketones (**6**), afforded the corresponding pyrroles (**9**) when reacted with different amines in AcOH in an open vessel at 120-150 °C for 2-10 min under microwave conditions. Whereas, heating in acid solution at 100 °C, under microwave irradiation, gave furans (**8**), and when reacted with Lawesson's reagent in toluene at 110 °C, thiophenes (**7**) were obtained along with 10-25% of furans as side products.



Scheme 1.2.1.1.3 Iron(III)chloride catalyzed Paal-Knorr pyrrole synthesis of substituted pyrroles from 2,5-dimethoxytetrahydrofuran and amines.

Aziz group in 2009 documented a one-step, environmentally friendly, and economical procedure for synthesizing *N*-aryl, sulfonyl, alkyl, and acyl pyrroles. The method involved a Paal-Knorr condensation reaction between 2,5-dimethoxytetrahydrofuran (**11**), various amines and sulfonamines (**10**) in water catalyzed by iron(III)chloride under very mild reaction conditions to afford *N*-substituted pyrroles (**12**) in good to excellent yields (Scheme 1.2.1.1.3).[5f]

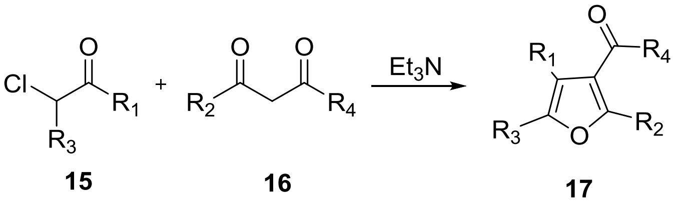


Scheme 1.2.1.1.4 A fluorous Lawesson's reagent used for Paal-Knorr synthesis of thiophenes, 1,3-thiazoles, and 1,3,4-thiadiazoles.

Dembinski research group, in 2006, reported the synthesizes of thiophenes, 1,3-thiazoles, and 1,3,4-thiadiazoles (**14**) by a fluorous Lawesson's reagent mediated thionation of 1,4-diketones, *N*-(2-oxoalkyl)amides, and *N,N'*-acylhydrazines (**13**) (Scheme 1.2.1.1.4).[5g] The fluorous approach is devoid of the separation problems encountered with Lawesson's reagent because of the simplification of the isolation protocol using a workup based upon solid-phase extraction without the need for fluorous solvents.

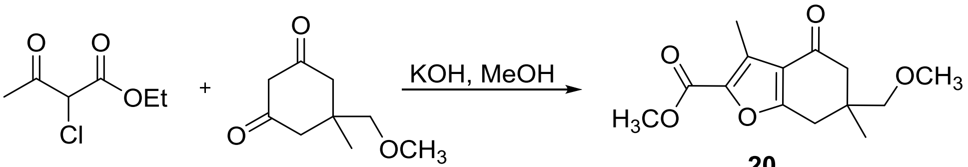
1.2.1.2 Feist-Bénary furan synthesis

The Feist-Bénary reaction, which is the base-catalyzed reaction of α-haloketones (**15**) with β-ketoesters (**16**), has been a practical approach for synthesizing various types of furans (**17**) having a carbonyl group at the C3 position (Scheme 1.2.1.2.1).[5h-i]



15 **16** **17**

Scheme 1.2.1.2.1 Feist-Bénary furan synthesis.

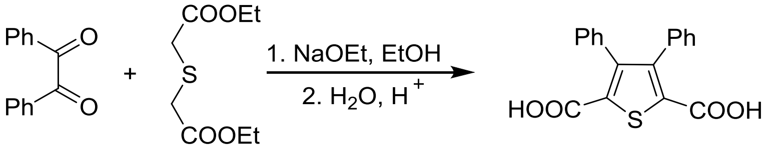


18 **19** **20**

Scheme 1.2.1.2.2 Feist-Bénary approach used to synthesize 3-methyltetrahydrobenzofuran.

Gopalan and Magnus in 1984 described the use of the Feist-Bénary approach in one of the steps used in synthesizing linderalactone, isolinderalactone, and neolinderalactone by condensing the symmetrical β-diketone (**19**) in aqueous methanolic potassium hydroxide with 2-chloroacetoacetate (**18**) to give the 3-methyltetrahydrobenzofuran (**20**) with 57% yield (Scheme 1.2.1.2.2).[5j]

1.2.1.3 Hinsberg synthesis

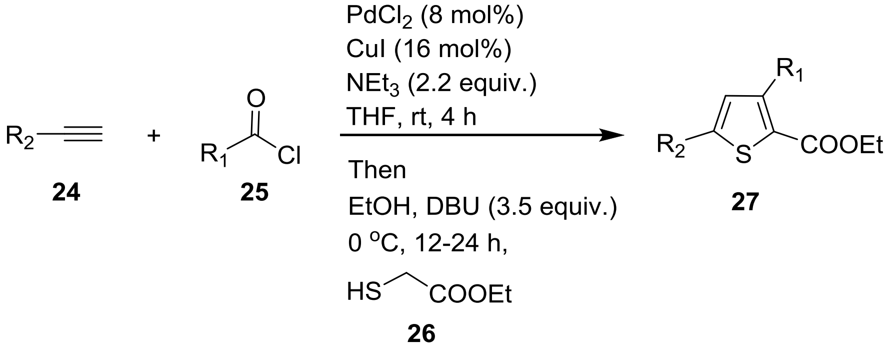


21 **22** **23**

Scheme 1.2.1.3.1 Hinsberg synthesis of thiophene-2,5-dicarboxylic acid derivatives from benzil and diethyl thiodiacetate.

In 1910, Hinsberg *et al.* first reported the synthesis of thiophene-2,5-dicarboxylic acid derivatives (**23**) through the condensation between 1,2-diketone (**21**) and diethyl thiodiacetate (**22**) in the presence of sodium ethoxide (Scheme 1.2.1.3.1).[5k-l] Later, it was found that both diester and half acid, half ester thiophene derivatives also form in this reaction. Kooreman, in 1965 proposed the mechanism involved in the reaction between diketones and thiodiacetates to generate thiophenes via a Stobbe-type condensation proceeding via a δ-lactone intermediate furnishing the half-acid, half-ester thiophene derivative in high yield.[5m] Moreover, reports on the synthesis of thiophenes, furans, selenophenes, and pyrroles from diketones, varying the ester component from the sulfur to the oxygen, selenium, and nitrogen analogs show the general applicability of this approach.[5q]

1.2.2 Multicomponent reactions

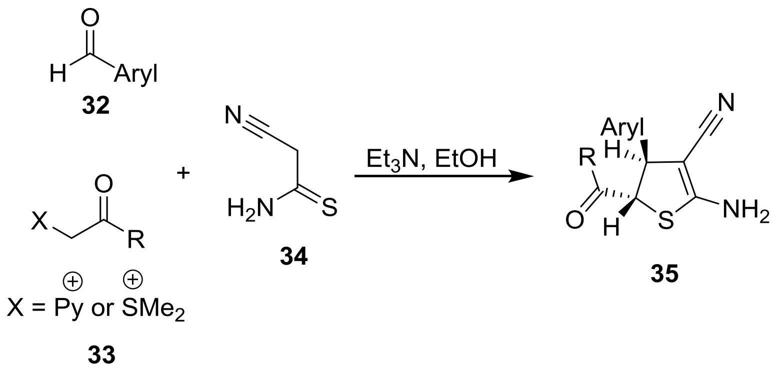


Scheme 1.2.2.1 3CR synthesis of thiophene reported by Muller group.

In 2012, Muller and Teiber delineated an efficient three-component route to 2,4-disubstituted thiophene 5-carboxylates (**27**) via a consecutive Sonogashira-Fiesselmann sequence using alkynes (**24**), aroyl chlorides (**25**), and ethyl 2-mercapto acetate (**26**) in good to excellent yields (Scheme 1.2.2.1).[6a] An alkynone generated by Sonogashira-coupling of the alkyne with the acid chloride is reacted with β-mercaptoester in the presence of the base DBU to afford the thiophene. This one-pot synthesis was further extended towards synthesizing symmetrical terthiophenes and quinquethiophene using difunctional acid chlorides or bisacetylenes.

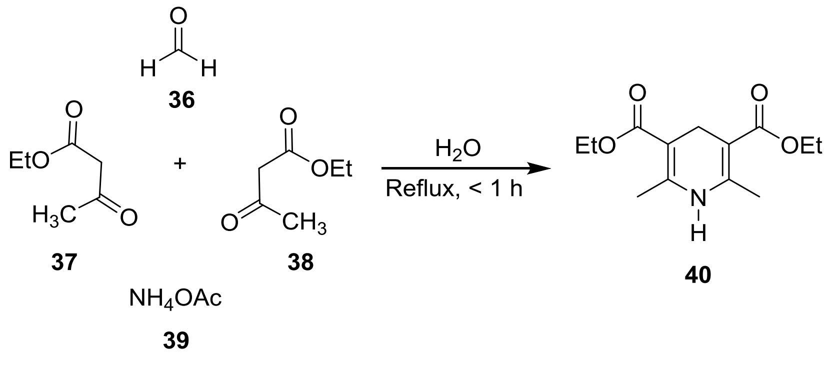
Scheme 1.2.2.2 Base-promoted Hantzsch pyrrole synthesis in water described by Meshram.

In 2012, Meshram and coworkers described a DABCO-catalyzed Hantzsch pyrrole (**31**) synthesis from phenacyl bromides (**30**), pentane-2,4-dione (**28**), and amine (**29**) using water as solvent.[6b] However, this approach showed less substrate scope as it was restricted to a single diketone substrate. In addition, variations in the primary amine and phenacyl bromide components, limited the substituents to 1st and 5th positions in final products (Scheme 1.2.2.2).



Scheme 1.2.2.3 3CR synthesis of 2-aminodihydrothiophene developed by Shestopalov *et al.*

Shestopalov *et al.* reported a diastereoselective three-component reaction of *β*-cyanothioamides (**34**), pyridinium or sulfonium salts (**33**), and aldehydes (**32**) to synthesize substituted trans-5-amino4-cyano-2,3-dihydrothiophene (**35**) in moderate to good yields (Scheme 1.2.2.3).[6c-e]

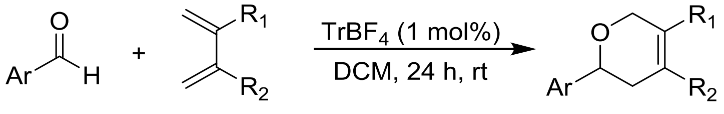


Scheme 1.2.2.4 Hantzsch synthesis of 1,4-dihydropyridines.

The Hantzch synthesis is one of the practical approaches for synthesizing heterocycles from readily available substrates under mild reaction conditions. In 1881, Arthur Rudolf Hantzsch, documented a one-pot multi-component approach generating dihydropyridines (**40**) via the reaction of aldehyde (**36**), two equivalents of a *β*-keto ester (**38**), and a source of nitrogen such as ammonium acetate or ammonia (**39**) (Scheme 1.2.2.4).[6d]

1.2.3 Cycloaddition reactions

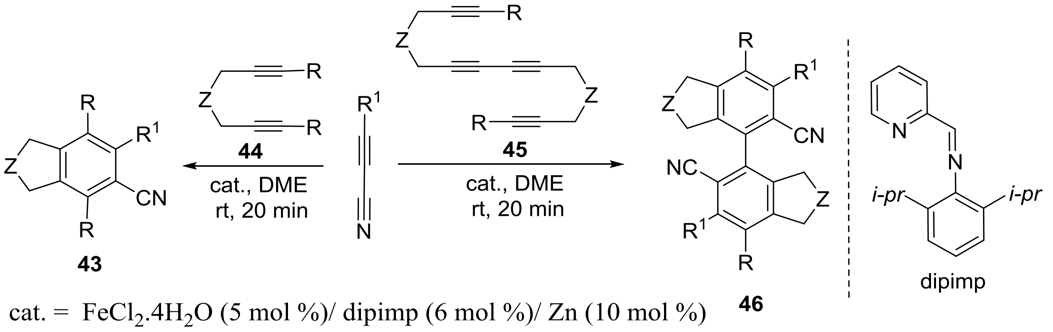
A cycloaddition reaction involves the reaction between two or more unsaturated molecules resulting in a cyclic adduct with a net reduction in bond multiplicity. Cycloaddition reactions provide an efficient, atom-economical route to synthesize various carbo and heterocyclic compounds. Cycloaddition reactions can be photochemical, catalyzed by transition metals or Lewis acids, or purely thermal. Some representative reports are discussed as follows.



32 **41** **42**

Scheme 1.2.3.1 The trityl cation ($TrBF_4$) catalyzed oxa-Diels-Alder reaction to give 3,6-dihydropyrane.

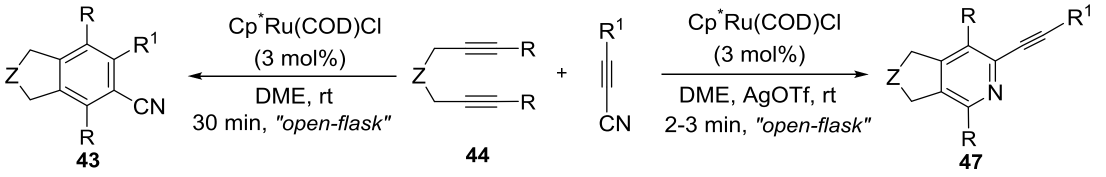
Franzén *et al.*, in 2015, reported the synthesis of different 3,6-dihydropyrane derivatives (**42**) from various unactivated dienes (**41**) and unactivated aliphatic and aromatic aldehydes (**32**) via a trityl cation ($TrBF_4$) catalyzed oxa-Diels-Alder reaction under mild reaction conditions giving moderate to excellent yields (Scheme 1.2.3.1).[7a] Along with remarkably low catalyst loadings, this strategy does not need substrate functional group activation.



cat. = $FeCl_2.4H_2O$ (5 mol %)/ dipimp (6 mol %)/ Zn (10 mol %)

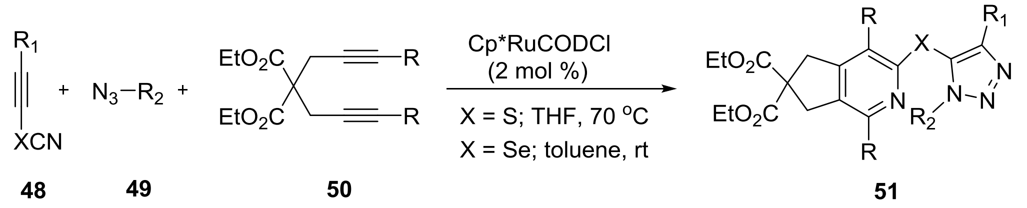
Scheme 1.2.3.2 Iron-catalyzed chemo- and regioselective cycloadditions between diynes/tetraynes and alkynenitriles.

In 2017, our group developed an efficient protocol for the synthesis of cyanoarenes (**43**) via an iron-catalyzed chemoselective [2+2+2] cycloaddition reaction of diynes (**44**) with alkynenitriles under mild reaction conditions with good to excellent yields. The reaction is catalyzed by the combination of $FeCl_2.4H_2O$ as a metal source, 2-(2,6-diisopropylphenyl)iminomethylpyridine (dipimp) as a ligand, and Zn as a reducing agent in DME. The protocol was further extended to the synthesis of 2,2'-dicyanobiarene (**46**) skeletons from the reaction of tetraynes (**45**) with alkynenitriles (Scheme 1.2.3.2).[7b]



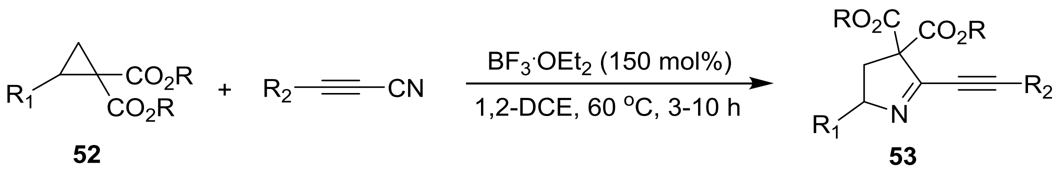
Scheme 1.2.3.3 Chemoselective ruthenium-catalyzed cycloadditions leading to cyanoarenes (**43**) and 2-alkynylpyridines (**47**).

The following year, we developed another protocol for the chemoselective synthesis of fused cyanoarenes (**43**) and 2-alkynylpyridines (**47**) by the reaction of 1,6-diynes (**44**) with alkynenitriles using chloro(pentamethylcyclopentadienyl)(cyclooctadiyne)ruthenium (II) as a catalyst in dimethoxyethane (DME). It was observed that the course of the reaction was drastically altered simply by adding catalytic amount of AgOTf as an additive resulting in a comprehensible shift in product formation from cyanoarenes to 2-alkynylpyridines (Scheme 1.2.3.3).[7c]



Scheme 1.2.3.4 Ruthenium-catalyzed synthesis of various 2-pyridyl thio-/selenotriazole derivatives via one-pot [3+2] and [2+2+2] cycloadditions.

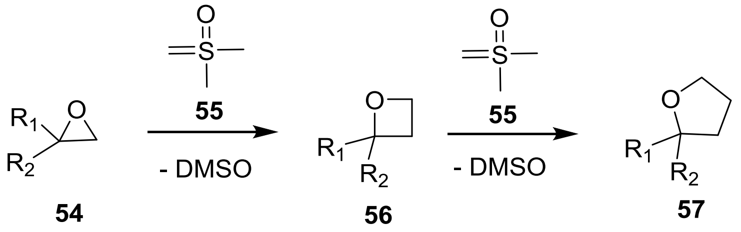
In 2020, we further extended the scope of this [2+2+2] cycloaddition approach to synthesize 2-triazolyl thio-/selenopyridines (**51**) using one-pot ruthenium-catalyzed [3+2]/[2+2+2] cycloaddition reaction of 1-alkynyl thio-/selenocyanates (**48**) with aryl/alkyl azides (**49**) and diynes (**50**) under mild reaction conditions (Scheme 1.2.3.4).[7d]



Scheme 1.2.3.5 $BF_3 \cdot OEt_2$ mediated [3+2] cycloaddition of donor-acceptor cyclopropanes and alkynenitriles for the synthesis of propargylic cyclic imines.

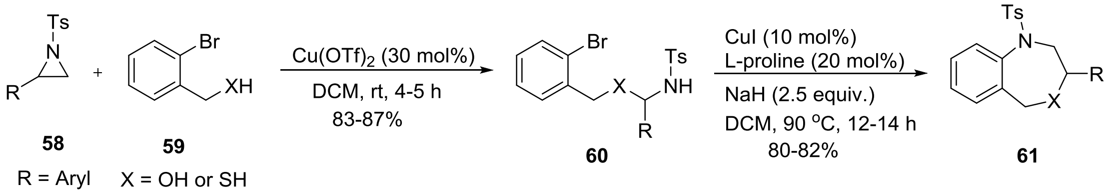
In 2022, we documented the synthesis of propargylic cyclic imines (**53**) from donor-acceptor cyclopropanes (**52**) and alkynenitriles via $BF_3 \cdot OEt_2$ mediated [3+2] cycloaddition under mild reaction conditions (Scheme 1.2.3.5).[7e] The developed protocol gives an easy access to a variety of propargylic cyclic imine derivatives in good to excellent yields.

1.2.4 Ring expansion/contraction reactions



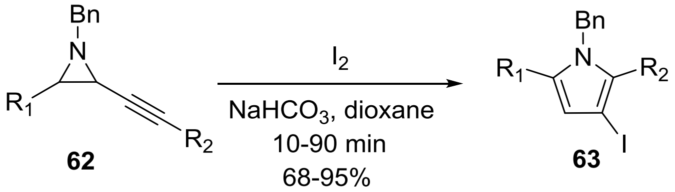
Scheme 1.2.4.1 Consecutive oxacycle ring expansion with dimethylsulfoxonium methylide.

Fokin *et al.,* in 2010, reported consecutive ring expansion reactions of oxiranes (**54**) with dimethylsulfxonium methylide (**55**) to oxetane ring (**56**) and further expansions to oxolanes (**57**) in high yields with the elimination of DMSO in each step (Scheme 1.2.4.1).[8a] This is a convenient general approach for the high-yielding preparation of optically active four and five-membered cyclic ethers from oxiranes.



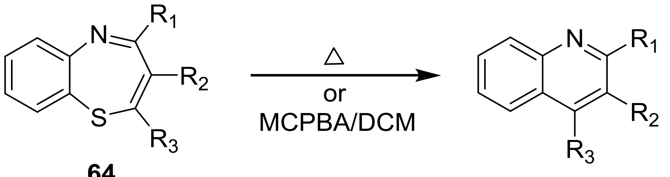
Scheme 1.2.4.2 Synthesis of tetrahydrobenzothiazepines.

Ghorai *et al*., in 2014 reported a ring expansion reaction of activated aziridines (**58**) with 2-bromobenzylthiol or 2- bromobenzylalcohol (**59**) generating seven-membered aza-heterocycles tetrahydrobenzothiazepines or tetrahydrobenzoxazepines (**61**) in good to excellent yields via S_N2-type ring-opening (**60**) of activated aziridines followed by copper-catalyzed cyclization reaction (Scheme 1.2.4.2).[8b]



Scheme 1.2.4.3 Synthesis of substituted 3-iodopyrroles by ring expansion of propargylic aziridines with iodine.

Yoshida and coworkers, in 2011, developed a strategy for synthesizing a library of substituted 3-iodopyrroles (**63**) by an electrophilic cyclization of benzyl-substituted propargylic aziridines (**62**) induced by iodine (Scheme 1.2.4.3).[8c] The reaction is proposed to involve a cyclic iodonium ion generated from the reaction of propargylic triple bond with iodine followed by the aziridine nitrogen attack furnishing 3-iodopyrroles after aromatization of the cyclized cationic intermediate formed.

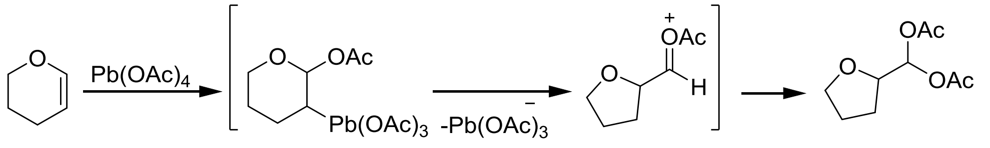


64 65

R_1 = H, OMe, SMe
R_2 = H, Ph
R_3 = H, Ph, CF_3

Scheme 1.2.4.4 Synthesis of quinolines by ring contraction the benzo[*b*]-1,4-thiazepines.

Selmi group, in 1991, reported the synthesis of quinolines (**65**) from the benzo[*b*]-1,4-thiazepines (**64**) by eliminating the sulfur atom on heating in inert solvents (Scheme 1.2.4.4).[8d] Earlier the same strategy was used in solvents like isopropanol/morpholine in the presence of m-chloroperbenzoic acid.



66 67 68

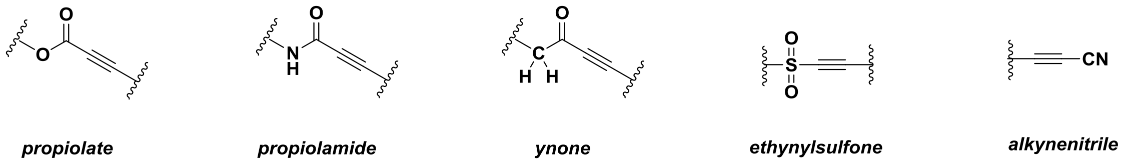
Scheme 1.2.4.5 Lead-promoted ring contraction of dihydropyran.

Thomas *et al*., in 1967 discussed the $Pb(OAc)_4$ promoted ring contractions of dihydropyran (**66**) to give (tetrahydrofuran-2-yl)methylene diacetate (**68**) (Scheme 1.2.4.5).[8e] This reaction is supposed to involve Pb-C bond formation followed by pinacol-type rearrangement with the intermediation of the cyclic acetoxonium ion (**67**).

1.3 Alkynenitriles

Among the various approaches used to synthesize heterocyclic scaffolds a popular route is the addition of an X-H bond (X = O, S, N, etc.) to unsaturated organic molecules such as an alkene or alkyne, generally named hydrofunctionalization (also known as heterofunctionalization).[9] These reactions are highly desirable as they have the potential to be 100% atom efficient and utilize easily accessible low-cost starting materials.

Activated alkynes are tremendously valuable synthetic intermediates. Even though, these can react via various pathways, they are most acclaimed for their reaction with nucleophiles/heteronucleophiles in conjugate addition reactions.[10] The heteronucleophilic 1,4-conjugate addition reactions have been extensively used for building various heterocycles.



propiolate *propiolamide* *ynone* *ethynylsulfone* *alkynenitrile*

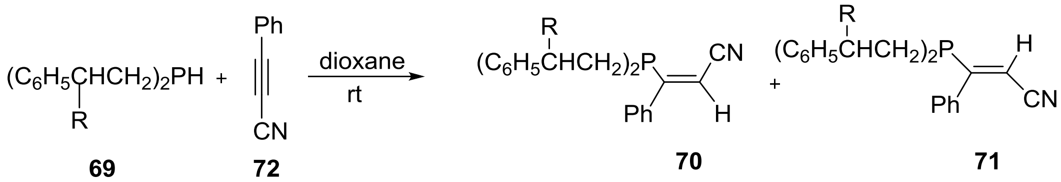
Figure 1.3.1 Activated alkynes.

In general, propiolates, ynones, and propiolamides are arguably the most commonly found substrates for conjugate addition transformations (Figure 1.3.1). Although, the use of ethynylsulfones, as a substrate in these transformations, is comparatively rare next to other activated alkynes; they are still very reactive in reported examples.

For the last few decades, bifunctional compounds like alkynenitriles[11] possessing nitrile and acetylene functionalities have been identified as versatile building blocks.[5] This synthon has been exploited for the synthesis of various carbo- and heterocycles which are biologically and chemically important. In addition, the nitrile and acetylene functional groups are also well known to undergo several vital transformations of synthetic utility individually.

1.3.1 Nucleophilic additions to alkynenitriles

Alkynenitriles are also susceptible to 1,4-conjugate additions from heteronucleophiles. However, if we see some synthesis of various carbo-/heterocycles via nucleophilic addition reactions employing alkynenitriles,[11] they are not as common in this context, providing ample opportunity for further work. In this context, Trofimov *et al.* in 1999, reported the synthesis of functionalized phosphines (**70-71**) by the reaction between secondary phosphines (**69**) and 3-phenyl-2-propynenitrile (**72**) (Scheme 1.3.1.1).[12]

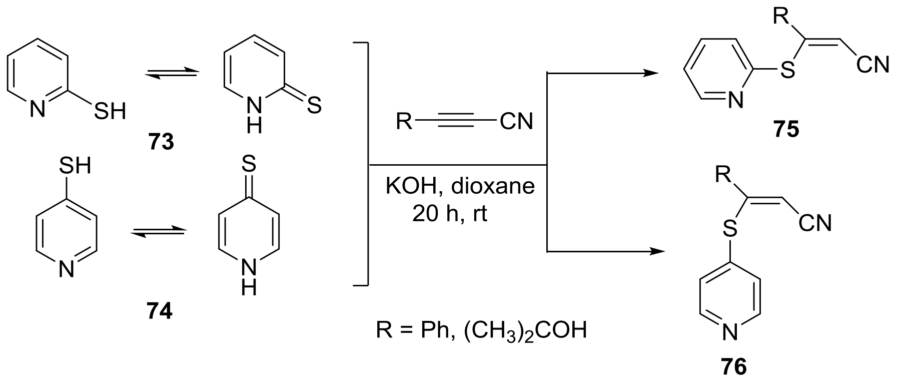


R = H; 1.5 h; **70** fomed majorly; 5% of **71** oberved
R = Me; 5 h; mixture of **70**:**71** in 3:2 ratio

Scheme 1.3.1.1 Addition of secondary phosphines to 3-phenyl-2-propynylnitrile (**72**).

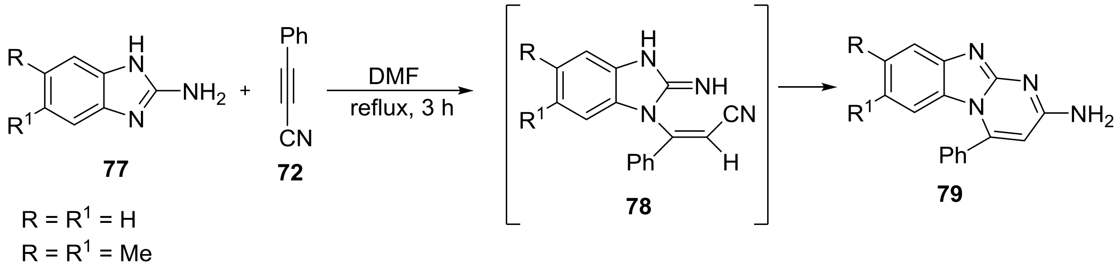
It was observed that the reaction of bis(2-phenylethyl)phosphine with 3-phenyl-2-propynylnitrile (**72**) proceeded stereoselectively to form the corresponding *Z*-isomer while the reaction with more branched bis(2-phenylpropyl)phosphine resulted in a mixture of *Z*- and *E*-isomers in 60:40 ratio.[71]

The same group in 2002, explored the nucleophilic additions of 2-mercaptopyridine (**73**) and 4-mercaptopyridine (**74**) with alkynenitriles (Scheme 1.3.1.2).[13]



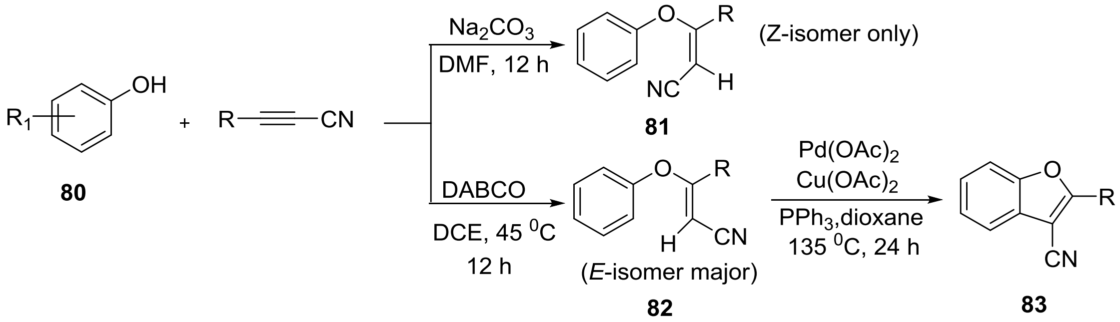
Scheme 1.3.1.2 Addition of mercaptopyridines to alkynenitriles.

It was observed that the reactions resulted in the formation of corresponding S-adducts (**75**, **76**) with *Z*-configuration.



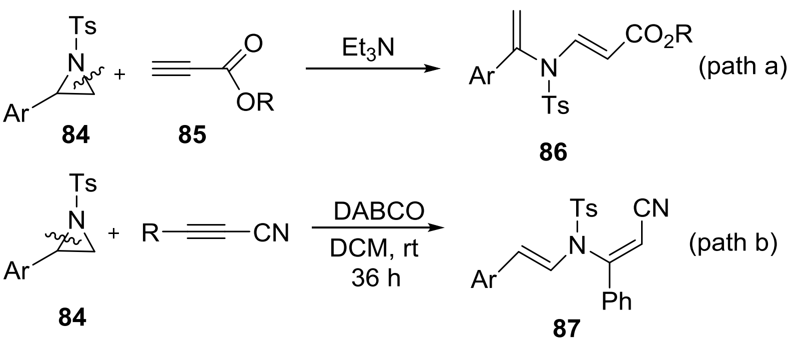
Scheme 1.3.1.3 Synthesis of pyrimidobenzimidazoles from 3-phenyl-2-propynylnitrile (**3**) and 2-aminobenzimidazoles.

In 2003, Doepp *et al*., showed that the reaction between 2-aminobenzimidazole (**77**) and 3-phenyl-2-propynylnitrile (**72**) could lead to biologically active pyrimidobenzimidazole (**79**) by the initial attack of the imino ring nitrogen of benzimidazole to the acetylenic *β*-carbon, followed by cyclization (Scheme 1.3.1.3).[14]



Scheme 1.3.1.4 Synthesis of (*Z*)/(*E*)-3-aryloxy-acrylonitriles and 3-cyanobenzofurans.

In 2012, Wang and co-workers reported a novel approach towards the synthesis of (*Z*)-3-aryloxy-acrylonitriles (**81**), (*E*)-3-aryloxy-acrylonitriles (**82**) and 3-cyanobenzofurans (**83**) by the corresponding reactions between phenols (**80**) and alkynenitriles (Scheme 1.3.1.4).[15] They observed that Na_2CO_3 and DABCO as a base afforded *Z*- and *E*-isomers, respectively. The palladium-catalyzed intramolecular cyclization of the *E*-isomers furnished 3-cyanobenzofurans in good yields through direct C-H bond functionalization. An intermolecular nucleophilic addition of phenol to alkynenitrile in the presence of DABCO generates 3-cyanobenzofurans.



84 85 86 84 87

Scheme 1.3.1.5 DABCO promoted ring opening of sulphonylaziridines with alkynenitriles.

In the same year, Meng *et al*. developed the highly regio- and stereoselective DABCO-promoted tandem ring opening of sulfonylaziridines (**84**) with alkynenitriles leading to a variety of (*Z*)-enenitriles (**87**) (path b). On the other hand, earlier the same group reported that the Et_3N promoted ring opening of sulfonylaziridines with terminal alkynoates (**85**) gave rise to functionalized enamines (**86**) involving a different C-N bond cleavage (path a) (Scheme 1.3.1.5).[16]

88 89

Scheme 1.3.1.6 Palladium-catalyzed tandem cyclization towards 2-cyanoindoles.

In 2016, Chen and co-workers developed an efficient Pd-catalyzed methodology towards the synthesis of 2-cyanoindoles (**89**) by treating unactivated anilines (**88**) and alkynenitriles using O_2 as an oxidant (Scheme 1.3.1.6).[17] The mechanism involves the nucleophilic addition of anilines to alkynenitriles to form aryl enamine intermediate **A** which is followed by Palladium-catalyzed double C-H activation.

Thus, alkynenitriles offer an alkyne-π system (acetylene) and a nitrile moiety in a single molecule, making their chemistry extremely important. The unique reactivity of alkynenitriles has encouraged organic chemists to develop new synthetic methods to prepare these compounds and study their applications.

1.4 Objective of the thesis

Nevertheless, the addition reaction to an alkene or alkyne is challenging due to the regio- and stereoselectivity issues during the addition process, especially in the case of unsymmetrically substituted internal alkenes or alkynes.[18] Therefore, many specific reagents and catalysts, transition metal complexes, are utilized for the hydrofunctionalization of these unsaturated scaffolds, leading to harsh reaction conditions and limited scope of the methodology.

The organic compounds which are synthesized using metal catalysts often suffer from severe contamination with residual metal impurities. In most of the cases, the expensive nature, tedious synthesis of the catalysts, cumbersome product isolation procedures, high sensitivity towards moisture and oxygen, toxicity, etc., limits the use of metal-catalyzed processes. The limitations of transition metal catalysis have encouraged chemists worldwide to bend towards metal-free chemistry. It is considered one of the burgeoning research areas in the past few decades, and among them, organocatalysis is the most prominent representative. Organocatalysis[19] uses small organic molecules to catalyze or mediate chemical reactions. The lack of sensitivity to moisture and oxygen, ready availability, low cost, and low toxicity confer a substantial direct benefit in synthetic chemistry compared with (transition) metal catalysts.

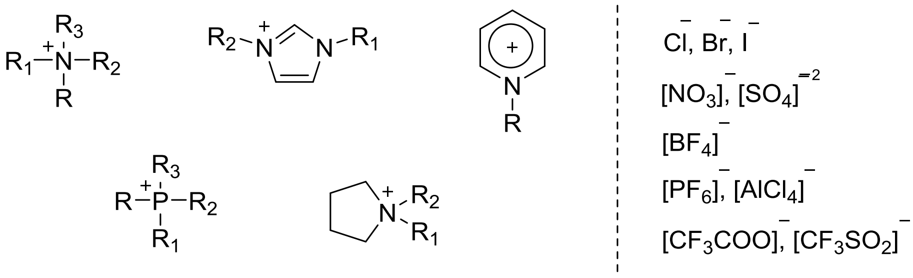


Figure 1.4.1 Ionic liquid cations and anions.

Besides widely used transition metal-free organocatalysts such as Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids, ionic liquids (ILs)[20] are highly instructive tools for enhancing the rates of chemical reactions. Besides their extremely useful properties as the solvent, the ionic nature of the IL anion and cation seems to be the origin of their fascinating function as organocatalyst/promoter through their strong Coulombic forces on other ionic species in the reaction and also through the formation of hydrogen bonds with various functional groups in substrates (Figure 1.4.1). ILs, thus tailored, can offer dual functionalities by acting simultaneously as a solvent for reactants and a catalyst for organic transformation reactions.

In the last few years, as discussed earlier, our group developed some efficient protocols for synthesizing a large variety of cyanoarenes and alkynylpyridines via transition metal-catalyzed chemoselective [2+2+2] cycloaddition reactions

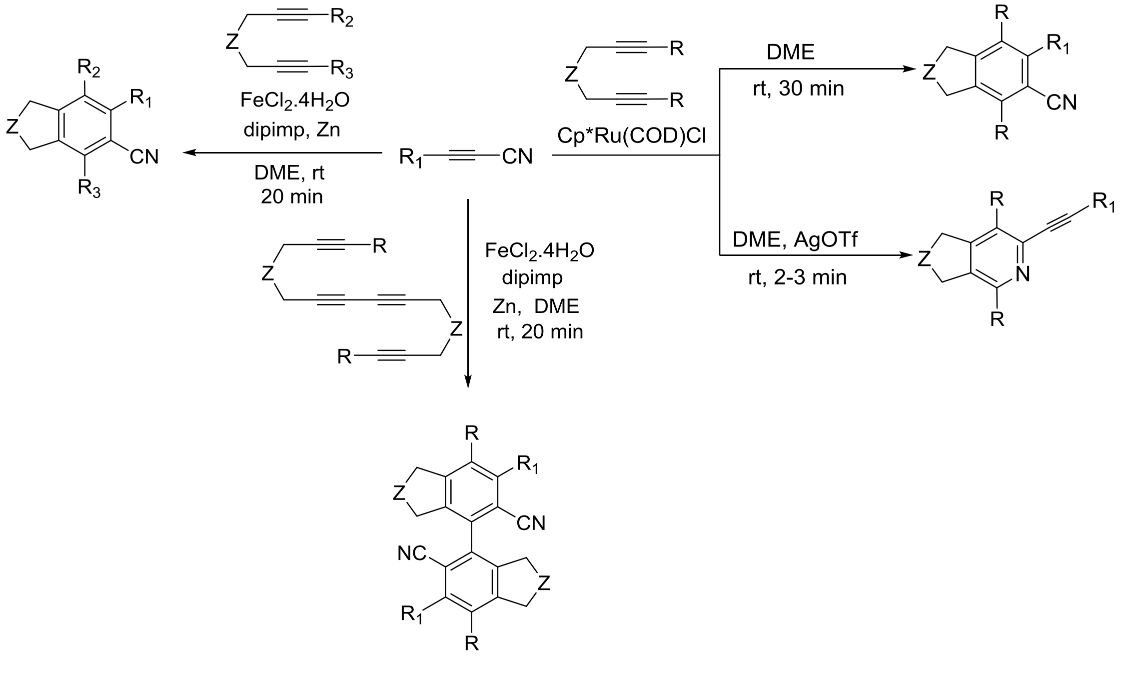


Figure 1.4.2 Some of the [2+2+2] cycloadditions with alkynenitriles reported by our lab.

of diynes with alkynenitriles under mild reaction conditions with good to excellent yields (Figure 1.4.2).[7b-e] Inspired by the unique property of the bifunctional alkynenitriles and their use as substrates in so many synthetic transformations especially transition metal-catalyzed [2+2+2] cycloadditions, we geared up our interest to exploit these bifunctional alkynenitriles in our laboratory to carry out a diverse range of transition metal-free chemical transformations especially the transition metal-free intermolecular nucleophilic additions. Therefore, this thesis entitled "A FACILE ACCESS TO BIOLOGICALLY IMPORTANT SCAFFOLDS FROM BIFUNCTIONAL ALKYNENITRILES" covers discussions on four efficient organocatalytic transition metal-free approaches,[18 and 21] developed by us, to access biologically important heterocyclic and acyclic scaffolds from bifunctional alkynenitriles and heteronucleophiles.

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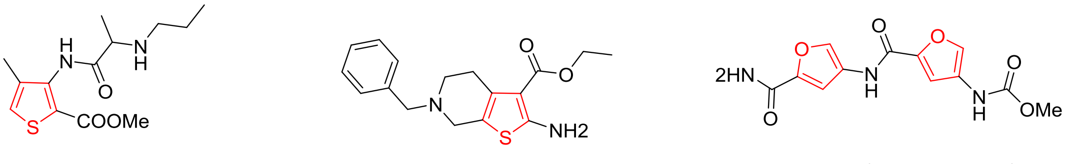
CHAPTER 2

Access to 5-Substituted 3-Aminofuran/thiophene-2-carboxylates from Bifunctional Alkynenitriles

Chapter 2: Access to 5-Substituted 3-Aminofuran/thiophene-2-carboxylates from Bifunctional Alkynenitriles

2.1 Introduction

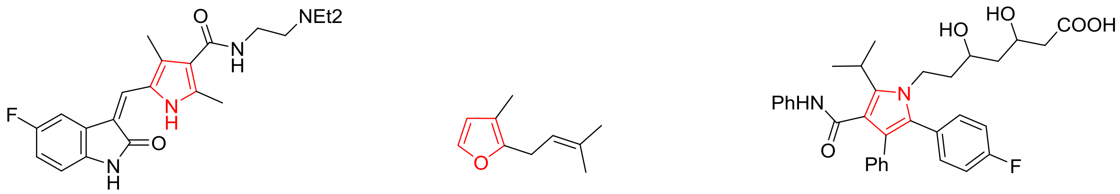
Polysubstituted five-membered heterocycles furans, thiophenes, and pyrroles and their derivatives are ubiquitous heterocycles. They are often found as core structural motifs in natural products, pharmaceuticals, and organic synthetic chemistry (Figure 2.1.1).[1] As a result, these are interesting targets for the researchers from synthetic and biological point of view. Five-membered heterocycles bearing amino functionality at the 3-position are necessary scaffolds embedded in many molecules which show potential biological activities. However, these are much less explored despite their remarkable biological profiles. The easy installment of an *N*-substituent on the five-membered heterocycles at the C3 position is not straightforward. A majority of strategies include the reduction of 3-azido/3-nitro derivatives (Scheme 2.1.1, eq. a),[2] rearrangements of furan-3-carboxylate derivatives (Scheme 2.1.1, eq. b),[3] the cross-coupling of 3-halo/3-ylboronate derivatives with a nitrogen source (Scheme 2.1.1, eq. c),[4] and so on, thus require pre-functionalized aromatic five-membered substrate that itself has to be prepared, often in multiple steps using undesirable reagents.



Articaine
(local anesthetic)

Tinoridine
(anti-inflammatory drug)

Proximicin A (Natural Product)
(antitumor-antibiotic activity)



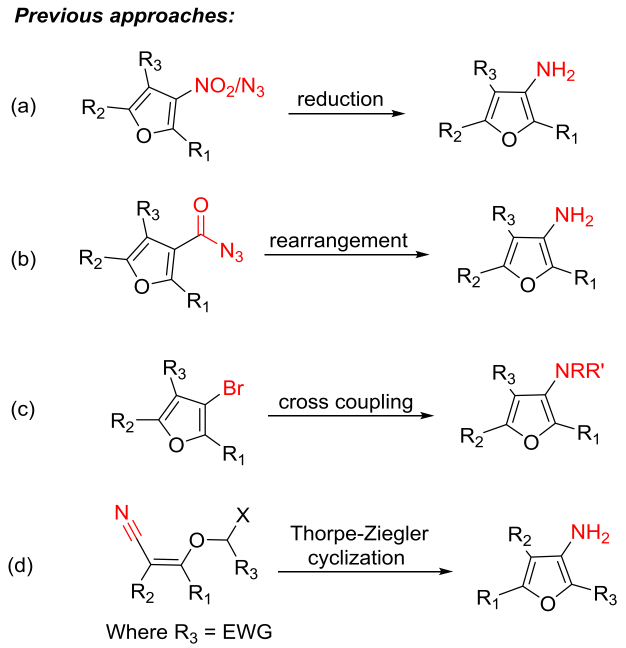
Sunitinib
(anti-cancer)

Rosefuran
(A component of rose oil)

Atorvastatin
(used to lower LDL cholesterol levels)

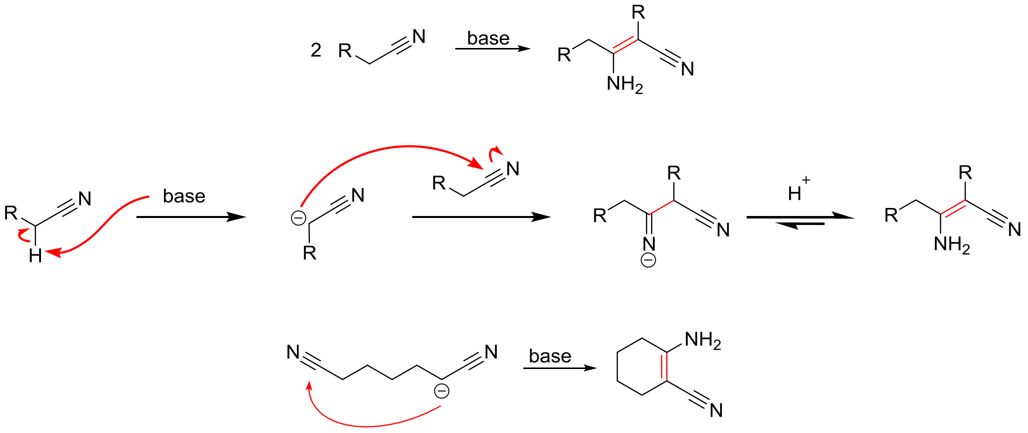
Figure 2.1.1 Some biologically important five-membered heterocycles.

In addition, some heterocyclisation[5] and multicomponent reactions[6] are presently being widely utilized for their synthesis.



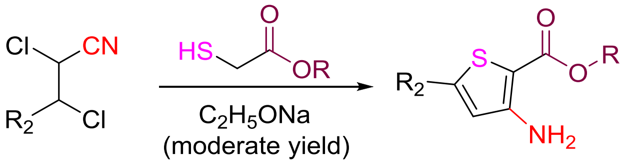
Scheme 2.1.1 Strategies used to synthesize 3-aminofurans.

The strong base-assisted Thorpe-Ziegler cyclization[7, 5a-d] of cyanovinyl ethers has become an efficient and atom-economical tool for synthesizing 3-amino furans (Scheme 2.1.1, eq. d).[5a-d] A self-condensation of aliphatic nitriles catalyzed by base to form enamines is the Thorpe reaction and its intramolecular version is called the Thorpe-Ziegler cyclization (Scheme 2.1.2).[7]



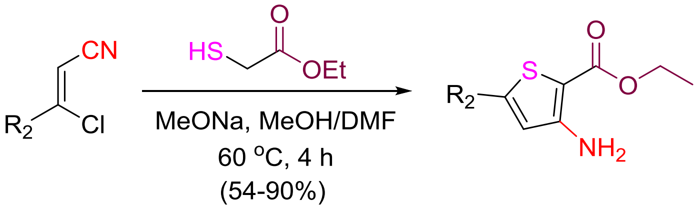
Scheme 2.1.2 Thorpe and Thorpe-Ziegler cyclization.

Cyanovinyl ethers can be prepared by treating the enolates with the appropriate halo derivatives,[5h-k] the reaction of the ketones with ethylglycolate under Mitsunobu conditions,[5a] the reaction of 2-halovinyl nitriles with alcohol derivatives,[1g, 5a and 5h] and from a 1-bromovinylnitrile.[8] For example, Fiesselmann, in 1959, reported the synthesis of 3-amino-thiophencarboxylate-2-esters by the reaction of 2,3-dihalogennitrile compounds with ethyl thioglycolate using sodium ethoxide base in moderate yields (Scheme 2.1.3).[9]



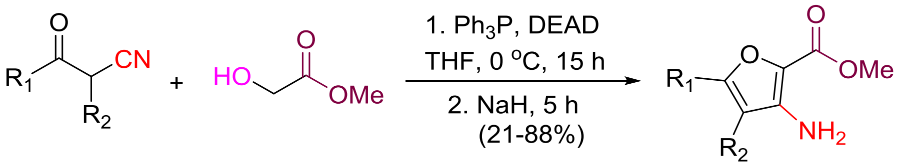
Scheme 2.1.3 Fiesselmann's synthesis of 3-amino-thiophencarboxylate-2-esters.

Recently in 2018, Romaganoli *et al*. reported the same kind of route to 3-amino-thiophencarboxylate-2-esters but with a little modification in the substrate molecules (Scheme 2.1.4). They condensed 3-chloroacrylonitriles with methyl or ethyl thioglycolate using sodium methoxide as base in the mixture of methanol/DMF solvent mixture at 60 ^oC to furnish 3-amino-thiophencarboxylate-2-ester derivatives in good yields.[10]



Scheme 2.1.4 Romaganoli's route to 3-amino-thiophencarboxylate-2-esters.

Analogous investigations were also conducted by Scott *et al.* to synthesize 3-aminofurancarboxylate-2-esters via a reaction of 3-chloroacrylonitriles with methyl glycolates as shown in Scheme 2.1.5. However, poor results were obtained. In 2000, they delineated a new protocol for generating vinyl ether from the reaction of α-cyanoketones with ethyl glycolate under Mitsunobu conditions in good yields, which on subsequent treatment with base afforded 3-aminofuran derivatives.[5a]

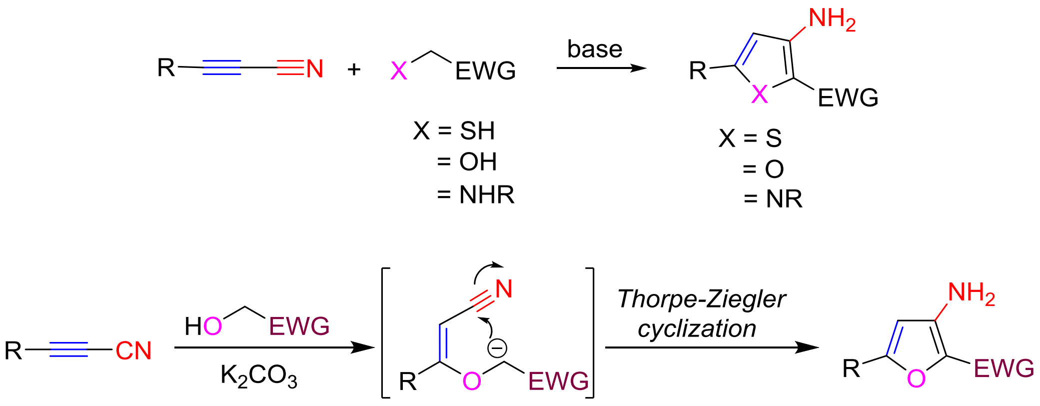


Scheme 2.1.5 Scott's protocol to synthesize 3-aminofurancarboxylate-2-esters using Mitsunobu conditions followed by base mediated cyclization.

Until our report, there was no protocol that could produce both heterocycles 3-amino furans and 3-amino thiophenes, keeping the substrate and reaction conditions unaltered and changing the nucleophile only. In addition, it has been found that the strategies successfully used in thiophene synthesis were unsuitable for furan synthesis and vice versa.[5a-5c] Being an important class of compounds, it is therefore highly desirable to develop them using common, general, atom-economical, cost and time-effective strategies from easily accessible starting materials.

Alkynenitriles[11] are bifunctional compounds with an alkyne-π system (acetylene) and a nitrile moiety in the same molecule. The electrophilic character of alkynenitriles offers opportunities for constructing various chemically and biologically important carbo- and heterocycles. The activated alkyne in alkynenitriles is susceptible to 1,4-conjugate additions from heteronucleophiles, whereas, the nitrile moiety can undergo Thorpe reaction if adequately placed in the molecule.

Thus, we envisioned that alkynenitriles could act as suitable candidates to react with heteronucleophiles having EWG at *α*-position under appropriate reaction conditions. The challenge was finding the suitable nucleophile and basic reaction conditions to construct 3-amino substituted five-membered heterocycles. The proposed scheme involves the *in situ* generation of cyanovinyl ether by the reaction of heteronucleophile having EWG at *α*-position with alkynenitrile, which subsequently could undergo modified intramolecular Thorpe-Ziegler cyclization leading to 3-amino substituted, five-membered heterocycle (Scheme 2.1.6). Thus, thiophenes, furans, or pyrroles can be constructed using this route.[5m]



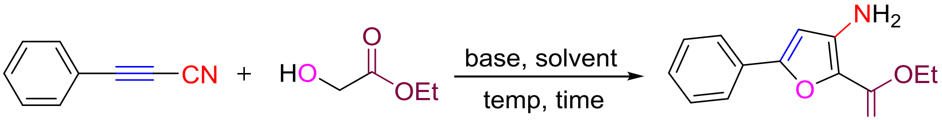
Scheme 2.1.6 Proposed scheme and plausible mechanism involved.

2.2 Results and Discussion

To investigate the optimized reaction conditions for preparing 3-aminofurans **3aa**, phenylacetylenenitrile **1a** and ethyl glycolate **2a** were chosen as model substrates for the said purpose. We started with reaction conditions described by Klein *et al.*[5c] for preparing 5-substituted 3-amino-2-cyanothiophenes from S-acetyl mercaptoacetonitrile and propionitrile in the presence of sodium ethoxide in ethanol (Table 2.2.1, entry 1). Unfortunately, these reaction conditions led to the formation of another compound, cyanovinyl ethyl ether (3-Ethoxy-3-phenyl-acrylonitrile), as the sole addition product instead of the desired outcome. Then, we investigated a list of bases in combination with various solvents (not shown in Table 2.2.1). However, K_2CO_3/DMF system was found to be the most suitable choice for the synthesis of desired cyclo product **3aa**. It was observed that the amount of base played an essential role in quantitative conversion in this transformation. The expected product **3aa** was obtained in 42% yield when 3 equiv. of K_2CO_3 base in DMF was treated with **1a** and **2a** at 50 ^{0}C for 2 h (Table 2.2.1, entry 2). An increase in reaction temperature to 100 ^{0}C enhanced the yield of the furan product to 78% within 2 h (Table 2.2.1, entry 3). However, a further increase in temperature to 120 ^{0}C decreased the yield to 56% with the formation of an unidentified mixture of products (Table 2.2.1, entry 4). In addition, the reaction was also conducted without using K_2CO_3 at 100 ^{0}C, but no product was observed (Table 2.2.1, entry 5). Next, a series of bases other than K_2CO_3, such as DBU, KO^{t}Bu, KOH, Cs_2CO_3, Et_3N, and NaOEt in DMF solvent at 100 ^{0}C were screened. However, none of them could provide better results (Table 2.2.1, entries 6-11). In addition, as shown in entries 12-17, solvents other than DMF were also verified for the reaction. Still, relatively lower yields revealed that DMF was the adequate choice of solvent for this transformation. At the same time, the reaction was also conducted using ionic liquids [BMIM]Br and [BMIM]OH as reaction medium at 100 ^{0}C. However, no noticeable increment in the yield of **3aa** was observed (Table 2.2.1, entries 18-19).

Having optimized the reaction conditions, we subsequently explored the substrate scope of this K_2CO_3-mediated synthesis of 3-aminofurans **3**. We observed that the reaction demonstrates a wide scope with respect to the alkynenitriles. Ethyl glycolate **2** was reacted with various alkynenitriles **1** under the optimized reaction conditions (Scheme 2.2.1).

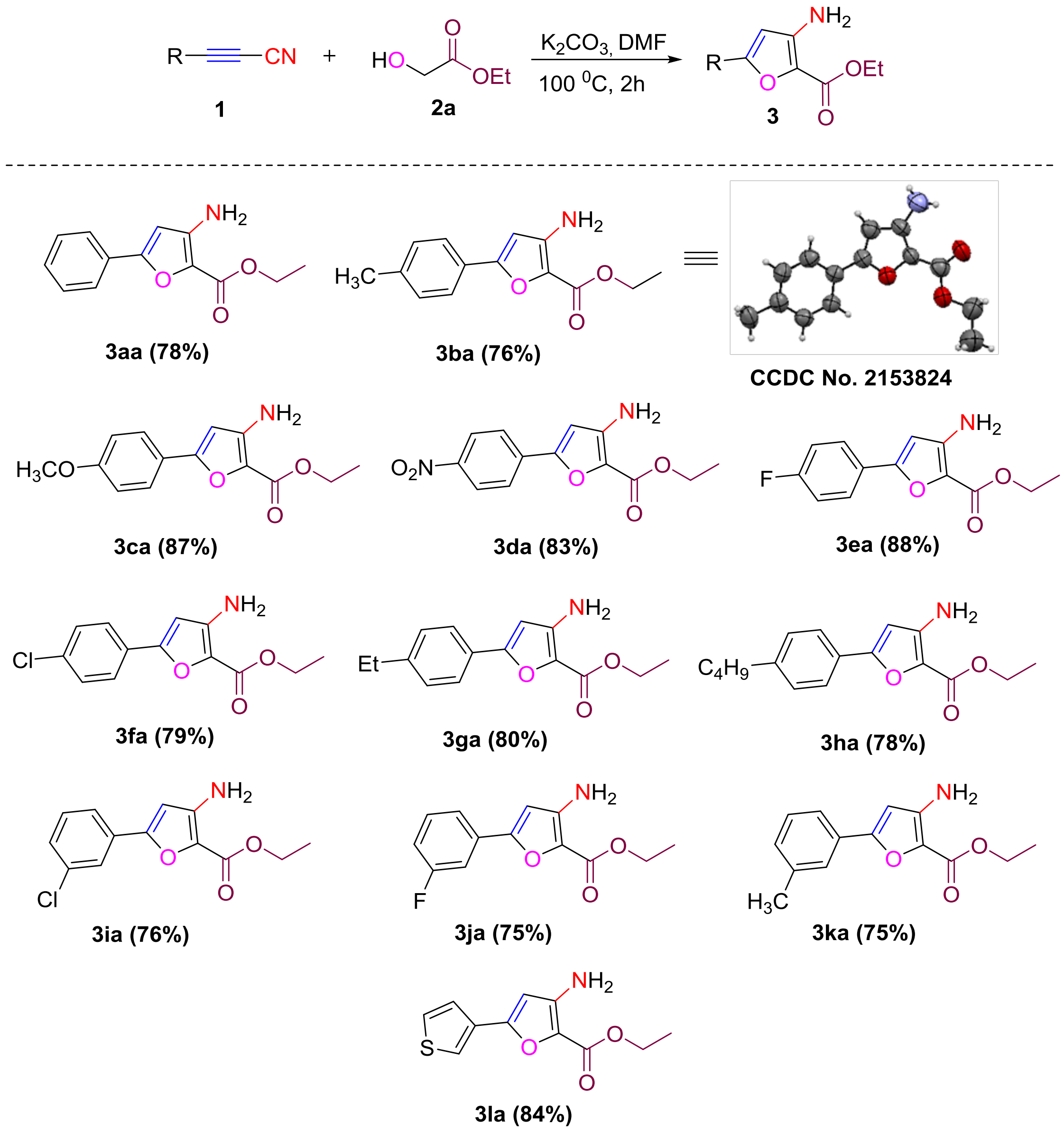
Table 2.2.1 Optimization studies.[a]



1a **2a** **3aa**

Entry	Base (equiv.)	Solvent (mL)	Temp (^{o}C)	Time (h)	Yield[b] (%) (3aa)[b]
1	NaOEt (3)	EtOH (1)	rt	12	0
2	K_2CO_3 (3)	DMF (1)	50	2	42
3	**K_2CO_3 (3)**	**DMF (1)**	**100**	**2**	**78**
4	K_2CO_3 (3)	DMF (1)	120	2	56
5	-	DMF (1)	100	12	0
6	DBU (3)	DMF (1)	100	2	12
7	KO^{t}Bu (3)	DMF (1)	100	2	35
8	KOH (3)	DMF (1)	100	2	62
9	Cs_2CO_3 (3)	DMF (1)	100	2	60
10	Et_3N (3)	DMF (1)	100	2	0
11	NaOEt (3)	DMF (1)	100	2	0
12	K_2CO_3 (3)	DME (1)	100	2	45
13	K_2CO_3 (3)	ACN (1)	100	2	0
14	K_2CO_3 (3)	THF (1)	100	2	38
15	K_2CO_3 (3)	PhMe (1)	100	2	25
16	K_2CO_3 (3)	dioxane (1)	100	2	15
17	K_2CO_3 (3)	DMSO (1)	100	2	65
18	K_2CO_3 (3)	[BMIM]Br (1)	100	2	58
19	-	[BMIM]OH (1)	100	2	40

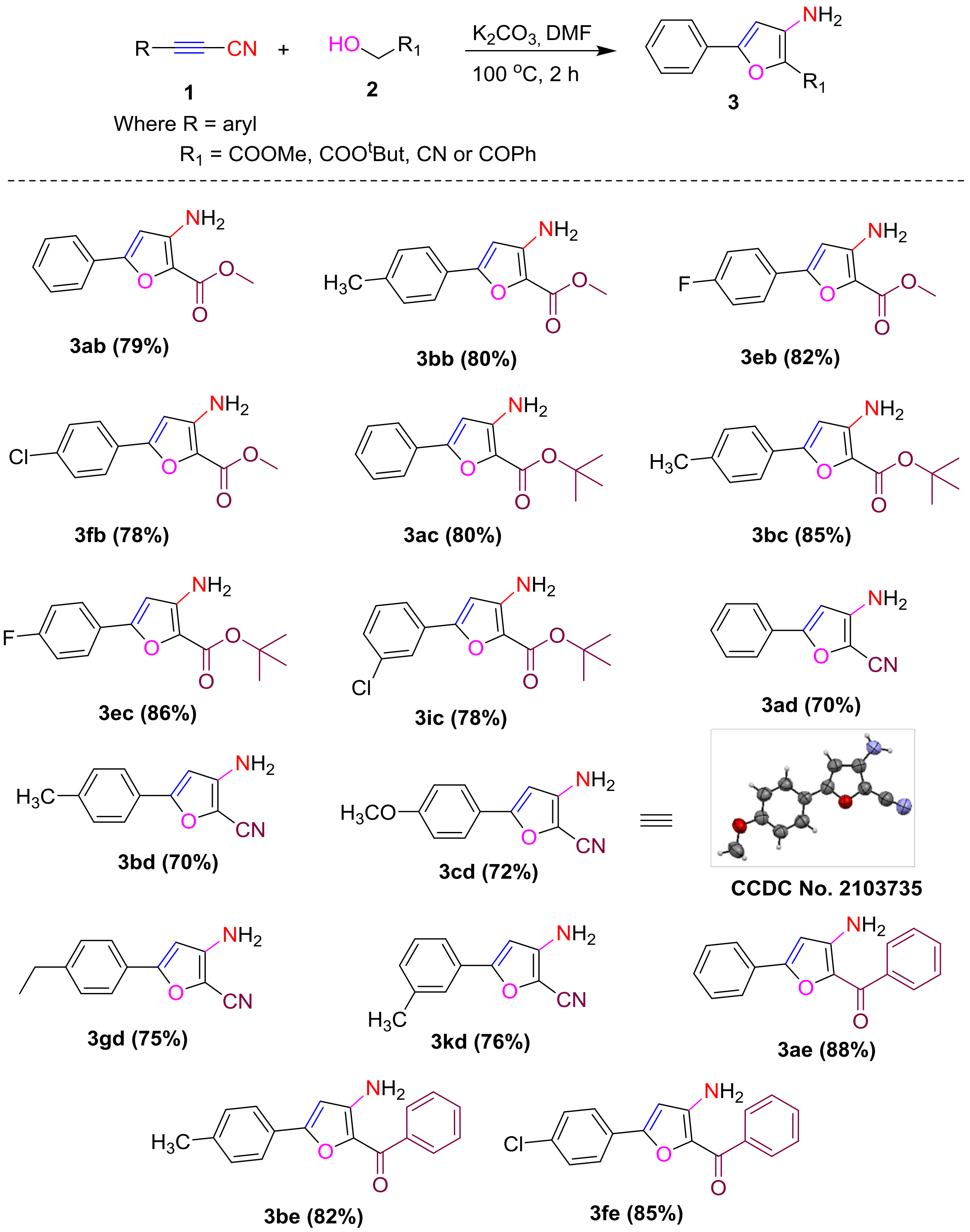
[a] Unless otherwise stated all the reactions were performed under inert conditions: **1a** (31.75 mg, 0.25 mmol), **2a** (0.047 mL, 0.5 mmol), K_2CO_3 (104 mg, 0.75 mmol), 100 ^{o}C, 2 h, [b] Isolated yield.



Reagents and conditions: **1** (0.25 mmol), **2a** (0.5 mmol), K_2CO_3 (0.75 mmol), 100 ^oC, 2 h.

Scheme 2.2.1 Synthesis of 3-amino-2-furan carboxylate esters **3** from alkynenitriles.

Gratifyingly, a library of variedly functionalized 5-substituted 3-amino furans **3** was synthesized in moderate to good yields within 2 h. It is noteworthy that the aryl propynylnitriles bearing electron-donating or electron-withdrawing groups (methyl, ethyl, butyl, methoxy, fluoro, chloro groups) at different positions of the aromatic ring performed well under the standard conditions affording 3-amino furans in moderate to



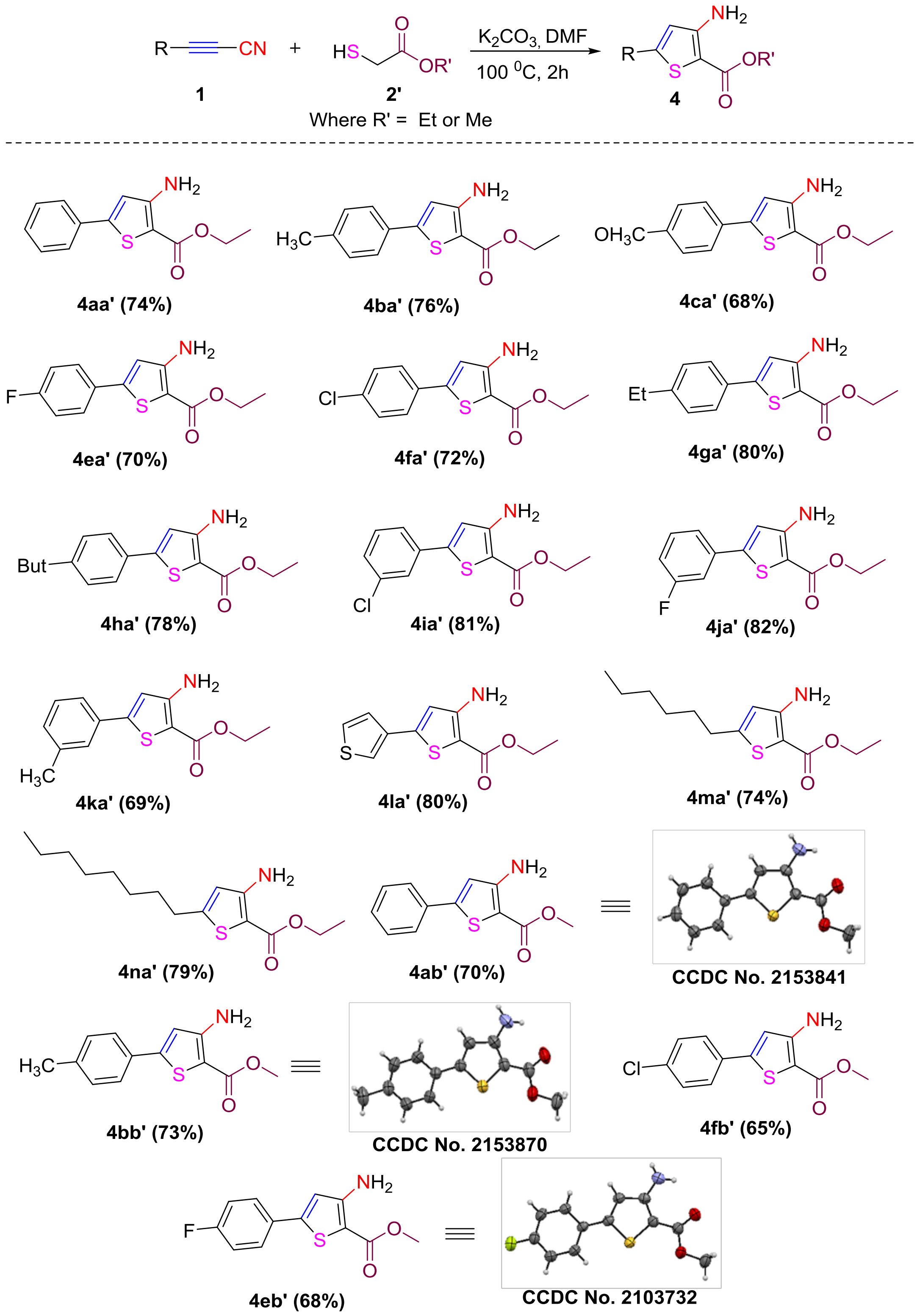
Reagents and conditions: **1** (0.25 mmol), **2** (0.5 mmol), K_2CO_3 (0.75 mmol), 100 °C, 2 h.

Scheme 2.2.2 Synthesis of 3-amino-2-furans **3** from alkynenitriles and substrate **2** with other EWGs.

good yields (**3ba**-**3ka**). In addition, alkynenitriles with a heteroaryl group (**3la**) also worked very well, with an 84% yield. Encouraged by the above results, we then analyzed more challenging substrates. We proceeded to extend the reaction scope to synthesize 3-aminofurans with other electron-withdrawing substituents as well. The results are summarized in Scheme 2.2.2. Various successful one-pot direct conversions to furans (**3ab-3ic)** were carried out using methylglycolate **2b** and *tert*. butylglycolate **2c** with alkynenitriles affording the target products in 78 to 86% yields, indicating the remarkable functional group compatibility of the protocol. In addition, electron-withdrawing groups other than carboxylic esters also proved compatible with this protocol furnishing the desired products in moderate to good yields, illustrating that the reaction was not limited only to carboxylic esters as electron-withdrawing groups. Moreover, 2-hydroxyacetonitrile **2d** was also suitable for this conversion, affording the desired cycloadducts (**3ad-3kd)** in 70 to 76% overall yield. 3-oxo-3-phenylpropanenitrile **2e** also showed excellent performance giving the desired furans (**3ae-3fe)** in 82 to 88% yield.

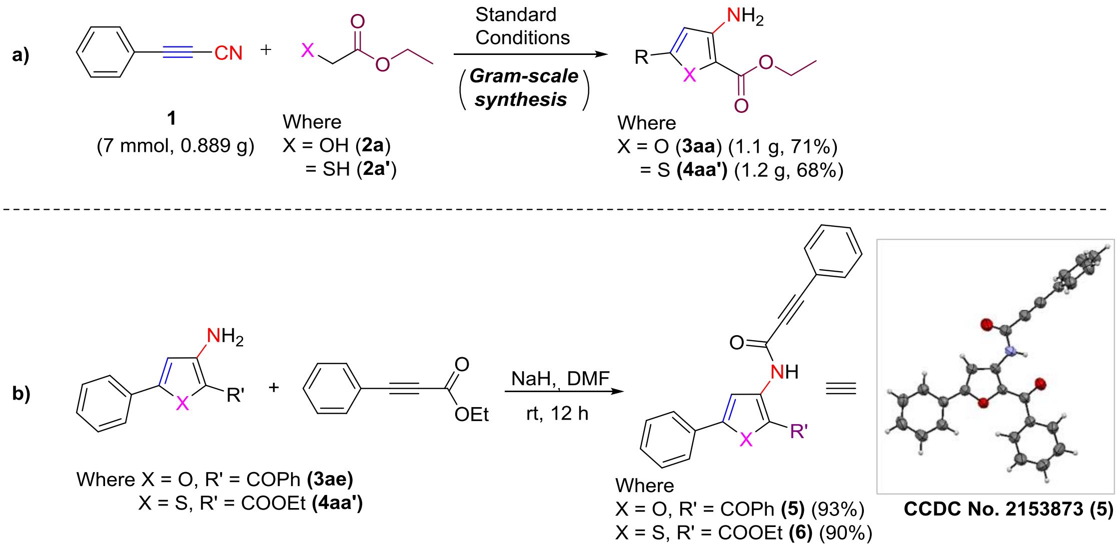
To further judge the applicability of the newly developed strategy, we conducted analogous investigations to synthesize 3-aminothiophene skeletons **4** *via* a reaction of various alkynenitriles **1** with thioglycolates **2a'** and **2b'** under optimized reaction conditions, and the results are summarized in Scheme 2.2.3. We were glad to obtain various thiophene derivatives in good to excellent yields by this convenient one-step conversion. It is noteworthy that alkynenitriles, whether aliphatic or aromatic, bearing electron-donating and electron-withdrawing groups on the phenyl ring were well-tolerated, affording desired thiophenes (**4ba'**-**4eb'**) in moderate to good yields showing the impressive functional group compatibility of this approach for thiophenes synthesis.

To our delight, the developed protocol could also be employed for a gram scale synthesis to check the practicality of this approach. To our satisfaction, 1.1 g of 3-aminofuran derivative **3aa** and 1.2 g of 3-aminothiophene derivative **4aa'** were obtained from their respective substrates with 71% and 68% yield, respectively, when synthesized at 7 mmol scale (Scheme 2.2.4a).



Reagents and conditions: **1** (0.25 mmol), **2** (0.5 mmol), K_2CO_3 (0.75 mmol), 100 °C, 2 h.

Scheme 2.2.3 Synthesis of 3-amino-2-thiophenecarboxylate esters **4** from alkynenitriles.



Scheme 2.2.4 Large-scale reaction and synthetic utilization.

Moreover, 3-aminofuran **3ae** and 3-aminothiophene **4aa'** were easily converted to synthetically important substituted propiolamides[12] *N*-(2-benzoyl-5-phenylfuran-3-yl)-3-phenylpropiolamide **5** and ethyl 5-phenyl-3-(3-phenylpropiolamido)thiophene-2-carboxylate **6** in 93% and 90%, respectively, when treated with ethyl 3-phenylpropiolate in the presence of NaH (2 equiv.) in DMF (Scheme 2.2.4b). It should be mentioned that the structure of products **3ba**, **3cd**, **4ab'**, **4bb'**, **4eb'** and **5** have also been confirmed by X-ray single-crystal analysis.[13]

2.3 Conclusions

In conclusion, we have developed and reported a convenient one-step, transition metal-free, one-pot synthetic method to synthesize a series of functionally rich 3-aminofurans/thiophenes from cheap and readily available substrates in good to high yields, using K_2CO_3/DMF base solvent combination. This one-pot synthetic strategy is applicable for aryl, heteroaryl, and alkynenitriles and produces 3-aminofurans/thiophenes at 100 ^{o}C within 2 h. In addition, protocol exhibit a wide range of functional group tolerance. Moreover, we found this route generally applicable to the synthesis of furans and thiophenes with a variety of EWGs at the C2 position, thus making them active scaffolds for further essential transformations. Future work based on the same approach to synthesize 3-amino-pyrroles is undergoing in our laboratory.

2.4 Experimental section

Reactions were performed in flame-dried glassware under a N_2 atmosphere unless otherwise stated. Solvents used were dried and purified by following standard procedures. Chemicals and reagents were purchased from commercial suppliers and used without further purification. Thin-layer chromatography was performed on Merck precoated silica gel 60 F254 aluminum sheets with detection under UV light at 254 nm. Column chromatography was performed using E. Merck silica gel 60 (100-200 mesh). NMR spectra were recorded in $CDCl_3$, at operating frequencies of 400 MHz (^1H) or 100 MHz (^{13}C) or 376 MHz (^{19}F), on JEOL JNM ECS-400 instrument as indicated in the individual spectrum. Chemical shifts (δ) are given in ppm relative to residual solvent (chloroform, δ= 7.26 for ^1H and 77.16 for proton decoupled ^{13}C NMR) and coupling constants (J) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, brs for broad singlet, t for triplet, q for quartet and m for multiplet. The HRMS data was recorded on XEVO G2-XS QTOF. Melting points were taken on Stuart digital melting point apparatus. All the X-ray data were recorded on Bruker D8 venture instrument. All the alkynenitriles (**1a**-**m**) except **1n** are known compounds and were synthesized according to the reported literature procedure without any modification.[14]

2.4.1 General procedure for the synthesis of 3-aminofurans/thiophenes (3 or 4)

In a dried Schlenk tube equipped with a stir bar, a mixture of alkynenitrile **1** (0.25 mmol), alcohols **2** or thiols **2’** with EWGs at α-positions (0.5 mmol), K_2CO_3 (0.75 mmol), and 1 mL of DMF was stirred for 2 h at 100 ^oC. After the reaction (monitored reaction by TLC) was completed, the reaction mixture was cooled to room temperature and the product was extracted with ethyl acetate three times and the combined organic layers were dried with anhydrous Na_2SO_4 and evaporated under vacuum. The crude was further purified through column chromatography over silica gel (100-200 mesh) with EtOAc/hexane (20-30%) to give the desired products **3 or 4**.

2.4.2 Procedure for gram scale synthesis of 3aa and 4aa'

In a dried Schlenk tube equipped with a stir bar, a mixture of phenylacetylenenitrile **1a** (0.889 g, 7.0 mmol, 1 equiv.), ethyl glycolate **2a** (1.32 mL, 14.0 mmol, 2 equiv.) or ethyl thioglycolate **2a'** (1.54 mL, 14.0 mmol, 2 equiv.), K_2CO_3 (2.90 g, 21.0 mmol, 3 equiv.), and 10 mL of DMF was stirred for 3 h at 100 ^oC. After the reaction (monitored reaction by TLC) was completed, the reaction mixture was cooled to room temperature and the product was extracted with ethyl acetate three times and the combined organic layers were dried with anhydrous Na_2SO_4 and evaporated under vacuum. The crude was further purified through column chromatography over silica gel (100-200 mesh) with EtOAc/hexane (20-30%) to give the desired products **3aa** (1.11 g, yield 71%) or **4aa'** (1.2 g, yield 68%) respectively.

2.4.3 Procedure for the synthesis of *N*-(2-benzoyl-5-phenylfuran-3-yl)-3-phenylpropiolamide (5)

In an oven-dried Schlenk round bottom flask equipped with a stir bar, a mixture of NaH (30 mg, 0.75 mmol), 3-aminofuran **3ae** (65.8 mg, 0.25 mmol) and ethyl 3-phenylpropiolate (0.04 mL, 0.25 mmol) in dry DMF (1 mL) under N_2 atmosphere was stirred for 12 h. After completion of the reaction detected by TLC, the reaction mixture was quenched with ice cold water and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography and the desired compound was eluted at 10-20% ethyl acetate in hexane to get *N*-(2-benzoyl-5-phenylfuran-3-yl)-3-phenylpropiolamide **5** (91 mg, 93% yield).

2.4.4 Procedure for the synthesis of ethyl 5-phenyl-3-(3-phenylpropiolamido)thiophene-2-carboxylate (6)

In an oven-dried Schlenk round bottom flask equipped with a stir bar, a mixture of NaH (30 mg, 0.75 mmol), 3-aminothiophene **4aa’** (61.8 mg, 0.25 mmol) and ethyl 3-phenylpropiolate (0.04 mL, 0.25 mmol) in dry DMF (1 mL) under N_2 atmosphere was stirred for 12 h. After completion of the reaction detected by TLC, the reaction mixture was quenched with ice cold water and the aqueous phase was extracted three times with ethyl acetate. The combined organic phases were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography and the desired compound was eluted at 10-20% ethyl acetate in hexane to get ethyl 5-phenyl-3-(3-phenylpropiolamido)thiophene-2-carboxylate **6** (85 mg, 90% yield).

2.4.5 Procedure for the synthesis of Undec-2-ynenitrile (1n) using literature procesure[14d]

To a stirred solution of 1-bromodec-1-yne (108 mg, 0.5 mmol) in DMSO (3 mL) was added CuCN (45 mg, 0.5 mmol) and KI (25 mg, 0.15 mmol), then the mixture was stirred for 12 h under 60 ^{o}C, until TLC analysis showed that the starting material was completely consumed. The reaction mixture was then cooled down to room temperature and extracted with EtOAc and saturated aqueous solution of ammonium chloride three times. The combined organic layers were dried over Na_2SO_4, then concentrated under vacuum. The residue was purified by column chromatography with PE/EtOAc (50:1) as eluent to provide the corresponding product **1n** (65 mg, 80% yield).

2.4.6 Characterization data of products

undec-2-ynenitrile (1n): Colorless liquid (65 mg, 80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (t, *J* = 6.9 Hz, 2H), 1.62-1.54 (m, 2H), 1.41-1.34 (m, 2H), 1.31-1.23 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 105.3, 87.6, 55.2, 31.8, 29.1, 28.9, 28.8, 27.1, 22.7, 18.8, 14.1; HRMS: *m/z* calculated for $C_{11}H_{18}N$ $[M+H]^+$: 164.1439, found 164.1439

ethyl 3-amino-5-phenylfuran-2-carboxylate (3aa): Light brown solid (45 mg, 78%); mp 85-86 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.69 (m, 2H), 7.39-7.29 (m, 3H), 6.36

(s, 1H), 4.68 (brs, 2H), 4.37 (q, *J* = 7.3 Hz, 2H), 1.39 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 160.6, 156.2, 145.5, 129.5, 129.1, 128.8, 125.5, 125.0, 99.9, 59.9, 14.7; HRMS: *m/z* calculated for $C_{13}H_{14}NO_3$ [M+H]$^+$: 232.0974, found 232.0974

ethyl 3-amino-5-(*p*-tolyl)furan-2-carboxylate (3ba): Light brown solid (47 mg, 76%); mp 98-100 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.32 (s, 1H), 4.62 (brs, 2H), 4.37 (q, *J* = 7.4 Hz, 2H), 2.36 (s, 3H), 1.40 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 160.6, 156.6, 145.6, 139.4, 129.5, 126.9, 125.4, 125.1, 99.4, 60.0, 21.6, 14.8; HRMS**:** *m/z* calculated for $C_{14}H_{16}NO_3$ [M+H]$^+$: 246.1130, found 246.1134

ethyl 3-amino-5-(4-methoxyphenyl)furan-2-carboxylate (3ca): Light brown solid (57 mg, 87%); mp 92-93 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.66 (d, *J* = 9.2 Hz, 2H), 6.91 (d, *J* = 9.1 Hz, 2H), 6.24 (s, 1H), 4.63 (brs, 2H), 4.37 (q, *J* = 7.4 Hz, 2H), 3.83 (s, 3H), 1.40 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 160.7, 160.5, 156.5, 145.9, 126.7, 125.2, 122.5, 114.2, 98.6, 59.9, 55.5, 14.8; HRMS: *m/z* calculated for $C_{14}H_{16}NO_4$ [M+H]$^+$: 262.1079, found 262.1078

ethyl 3-amino-5-(4-nitrophenyl)furan-2-carboxylate (3da): Dark yellow solid (57 mg, 83%); mp 170-171 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.25 (d, *J* = 8.7 Hz, 2H), 7.86 (d, *J* = 8.8 Hz, 2H), 6.56 (s, 1H), 4.66 (brs, 2H), 4.40 (q, *J* = 7.4 Hz, 2H), 1.42 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 160.4, 153.2, 147.6, 144.8, 135.2, 127.1, 125.5, 124.3, 102.9, 60.4, 14.7; HRMS: *m/z* calculated for $C_{13}H_{13}N_2O_5$ [M+H]$^+$: 277.0824, found 277.0826

ethyl 3-amino-5-(4-fluorophenyl)furan-2-carboxylate (3ea): Light brown crystalline solid (55 mg, 88%); mp 106-107 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.72-7.67 (m, 2H), 7.11-7.05 (m, 2H), 6.31 (s, 1H), 4.64 (brs, 2H), 4.37 (q, *J* = 7.3 Hz, 2H), 1.39 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 163.3 (d, *J* = 252.4 Hz), 160.6, 155.3, 145.4, 127.0 (d, *J* = 6.9 Hz), 125.9, 125.7, 115.9 (d, *J* = 22.1 Hz), 99.8, 60.1, 14.8; ^{19}F NMR

(376 MHz, $CDCl_3$): δ -111.2 ppm; HRMS: *m/z* calculated for $C_{13}H_{13}FNO_3$ $[M+H]^+$: 250.0879, found 250.0880

ethyl 3-amino-5-(4-chlorophenyl)furan-2-carboxylate (3fa): Brown solid (52 mg, 79%); mp 102-103 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.35 (s, 1H), 4.63 (brs, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 155.0, 145.2, 135.1, 129.1, 128.1, 126.3, 125.9, 100.3, 60.1, 14.8; HRMS: *m/z* calculated for $C_{13}H_{13}ClNO_3$ $[M+H]^+$: 266.0584, found 266.0584

ethyl 3-amino-5-(4-ethylphenyl)furan-2-carboxylate (3ga): Brown solid (52 mg, 80%); mp 65-66 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.2 Hz, 2H), 6.32 (s, 1H), 4.65 (brs, 2H), 4.37 (q, *J* = 6.9 Hz, 2H), 2.65 (q, *J* = 7.4 Hz, 3H), 1.39 (t, *J* = 7.3 Hz, 3H), 1.23 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 150.6, 145.7, 128.3, 127.1, 125.4, 125.1, 99.4, 59.9, 28.8, 15.5, 14.8; HRMS: *m/z* calculated for $C_{15}H_{18}NO_3$ $[M+H]^+$: 260.1287, found 260.1286

ethyl 3-amino-5-(4-butylphenyl)furan-2-carboxylate (3ha): Dense brown liquid (56 mg, 78%); ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.20 (d, *J* = 8.3 Hz, 2H), 6.32 (s, 1H), 4.60 (brs, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.62 (t, *J* = 7.9 Hz, 2H), 1.64-1.56 (m, 2H), 1.42-1.32 (m, 5H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 156.7, 144.5, 128.9, 127.1, 125.1, 99.4, 60.0, 35.7, 33.6, 22.5, 14.9, 14.1; HRMS: *m/z* calculated for $C_{17}H_{22}NO_3$ $[M+H]^+$: 288.1600, found 288.1600

ethyl 3-amino-5-(3-chlorophenyl)furan-2-carboxylate (3ia): Brown solid (50 mg, 76%); mp 91-92 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.71-7.70 (m, 1H), 7.61-7.58 (m, 1H), 7.35-7.29 (m, 2H), 6.39 (s, 1H), 4.62 (brs, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 154.5, 145.1, 134.9, 131.2, 130.1, 129.1, 126.1, 125.1, 123.2, 100.9, 60.2, 14.8; HRMS: *m/z* calculated for $C_{13}H_{13}ClNO_3$ $[M+H]^+$: 266.0584, found 266.0584

ethyl 3-amino-5-(3-fluorophenyl)furan-2-carboxylate (3ja): Brown solid (47 mg, 75%); mp 107-108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51-7.48 (m, 1H), 7.44-7.40 (m, 1H), 7.38-7.33 (m, 1H), 7.06-7.00 (m, 1H), 6.38 (s, 1H), 4.63 (brs, 2H), 4.38 (q, J = 7.3 Hz, 2H), 1.40 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1 (d, J = 242.5 Hz), 160.6, 154.7, 145.1, 131.6 (d, J = 8.6 Hz), 130.5 (d, J = 8.2 Hz), 125.9, 120.8 (d, J = 3.1 Hz), 116.1 (d, J = 21.2 Hz), 111.9 (d, J = 23.6 Hz), 100.8, 60.2, 14.8; ^{19}F NMR (376 MHz, $CDCl_3$): δ -112.3 ppm; HRMS: m/z calculated for $C_{13}H_{13}FNO_3$ $[M+H]^+$: 250.0879, found 250.0879

ethyl 3-amino-5-(*m*-tolyl)furan-2-carboxylate (3ka): Light brown solid (46 mg, 75%); mp 65-66 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 6.35 (s, 1H), 4.67 (brs, 2H), 4.38 (q, J = 7.3 Hz, 2H), 2.36 (s, 3H), 1.39 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 156.4, 145.6, 138.5, 130.1, 129.4, 128.6, 125.6, 125.4, 122.3, 99.9, 60.0, 21.4, 14.8; HRMS: m/z calculated for $C_{14}H_{16}NO_3$ $[M+H]^+$: 246.1130, found 246.1131

ethyl 3-amino-5-(thiophen-3-yl)furan-2-carboxylate (3la): Brown solid (50 mg, 84%); mp 78-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.67 (t, J = 2.3 Hz, 2H), 7.32 (d, J = 2.3 Hz, 2H), 6.19 (s, 1H), 4.64 (brs, 2H), 4.36 (q, J = 7.3 Hz, 2H), 1.39 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 153.0, 145.4, 131.5, 126.6, 125.1, 124.9, 122.7, 99.9, 59.9, 14.8; HRMS: m/z calculated for $C_{11}H_{12}NO_3S$ $[M+H]^+$: 238.0538, found 238.0537

methyl 3-amino-5-phenylfuran-2-carboxylate (3ab): Light brown solid (43 mg, 79%); mp 81-83°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 7.4 Hz, 2H), 7.39-7.29 (m, 3H), 6.36 (s, 1H), 4.71 (brs, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 156.3, 145.8, 129.4, 129.2, 128.8, 125.3, 125.0, 99.9, 51.1; HRMS: m/z calculated for $C_{12}H_{12}NO_3$ $[M+H]^+$: 218.0817, found 218.0817

methyl 3-amino-5-(*p*-tolyl)furan-2-carboxylate (3bb): Off white solid (46 mg, 80%); mp 85-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 6.32 (s, 1H), 4.64 (brs, 2H), 3.90 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz,

$CDCl_3$): δ 160.9, 156.8, 145.9, 139.5, 129.5, 127.8, 126.8, 125.1, 99.3, 51.1, 21.5; HRMS: *m/z* calculated for $C_{13}H_{14}NO_3$ $[M+H]^+$: 232.0974, found 232.0974

methyl 3-amino-5-(4-fluorophenyl)furan-2-carboxylate (3eb): Light brown solid (48 mg, 82%); mp 76-77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.67 (m, 2H), 7.11-7.05 (m, 2H), 6.31 (s, 1H), 4.66 (brs, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3 (d, *J* = 250.1 Hz), 160.9, 155.5, 145.7, 127.1 (d, *J* = 3.0 Hz), 125.9 (d, *J* = 8.0 Hz), 125.5, 115.9 (d, *J* = 22.1 Hz), 99.7, 51.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ -111.0 ppm; HRMS: *m/z* calculated for $C_{12}H_{11}FNO_3$ $[M+H]^+$: 236.0723, found 236.0723

methyl 3-amino-5-(4-chlorophenyl)furan-2-carboxylate (3fb): Light brown solid (49 mg, 78%); mp 89-90 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.34 (s, 1H), 4.67 (brs, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 155.1, 145.5, 135.1, 129.1, 127.9, 126.3, 125.6, 100.3, 51.2; HRMS: *m/z* calculated for $C_{12}H_{11}ClNO_3$ $[M+H]^+$: 252.0427, found 252.0427

tert-butyl 3-amino-5-phenylfuran-2-carboxylate (3ac): Light brown crystalline solid (48 mg, 80%); mp 103-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 7.9 Hz, 2H), 7.40-7.30 (m, 3H), 6.36 (s, 1H), 4.51 (brs, 2H), 1.62 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 155.6, 144.4, 129.7, 129.0, 128.8, 126.7, 124.7, 100.1, 81.1, 28.8; HRMS: *m/z* calculated for $C_{15}H_{18}NO_3$ $[M+H]^+$: 260.1287, found 260.1288

tert-butyl 3-amino-5-(*p*-tolyl)furan-2-carboxylate (3bc): Off white solid (54 mg, 85%); mp 143-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.30 (s, 1H), 4.53 (brs, 2H), 2.35 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 155.9, 144.5, 139.1, 129.4, 126.9, 126.3, 124.9, 99.4, 80.9, 28.7, 21.5; HRMS: *m/z* calculated for $C_{16}H_{20}NO_3$ $[M+H]^+$: 274.1443, found 274.1445

tert-butyl 3-amino-5-(4-fluorophenyl)furan-2-carboxylate (3ec): Light brown solid (55 mg, 86%); mp 113-114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.65 (m, 2H), 7.08-7.04 (m, 2H), 6.29 (s, 1H), 4.53 (brs, 2H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

163.1 (d, *J* = 249.4 Hz), 160.2, 154.7, 144.3, 126.9 (d, *J* = 8.6 Hz), 126.7 (d, *J* = 8.0 Hz), 126.0 (d, *J* = 2.9 Hz), 115.9 (d, *J* = 22.1 Hz), 99.8, 81.2, 28.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ -111.5 ppm; HRMS: *m/z* calculated for $C_{15}H_{17}FNO_3$ $[M+H]^+$: 278.1192, found 278.1195

tert-butyl 3-amino-5-(3-chlorophenyl)furan-2-carboxylate (3ic): Yellowish liquid (53 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.33-7.27 (m, 2H), 6.37 (s, 1H), 4.52 (brs, 2H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 153.9, 143.9, 134.9, 131.4, 130.1, 128.9, 127.1, 124.9, 123.0, 100.9, 81.4, 28.7; HRMS: *m/z* calculated for $C_{15}H_{17}ClNO_3$ $[M+H]^+$: 294.0897, found 294.0900

3-amino-5-phenylfuran-2-carbonitrile (3ad): Dark brown solid (32 mg, 70%); mp 99-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.61 (m, 2H), 7.42-7.34 (m, 3H), 6.35 (s, 1H), 4.01 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 146.9, 129.6, 128.9, 124.9, 113.4, 109.4, 99.6; HRMS: *m/z* calculated for $C_{11}H_9N_2O$ $[M+H]^+$: 185.0715, found 185.0712

3-amino-5-(*p*-tolyl)furan-2-carbonitrile (3bd): Light brown solid (35 mg, 70%); mp 141.142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 6.29 (s, 1H), 3.96 (brs, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 146.9, 139.9, 129.7, 129.3, 124.9, 113.5, 109.1, 98.9, 21.6; HRMS: *m/z* calculated for $C_{12}H_{11}N_2O$ $[M+H]^+$: 199.0871, found 199.0867

3-amino-5-(4-methoxyphenyl)furan-2-carbonitrile (3cd): Dark brown solid (39 mg, 72%); mp 110-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.56 (m, 2H), 6.95-6.91 (m, 2H), 6.22 (s, 1H), 3.90 (brs, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 157.9, 146.9, 126.6, 121.9, 114.4, 113.5, 109.0, 98.1, 55.5; HRMS: *m/z* calculated for $C_{12}H_{11}N_2O_2$ $[M+H]^+$: 215.0821, found 215.0820

3-amino-5-(4-ethylphenyl)furan-2-carbonitrile (3gd): Dark brown solid (40 mg, 75%); mp 94-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.3

Hz, 2H), 6.30 (s, 1H), 3.92 (brs, 2H), 2.67 (q, J = 7.4 Hz, 2H), 1.24 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 146.9, 146.2, 128.5, 126.5, 125.0, 113.5, 109.2, 98.9, 28.9, 15.5; HRMS: *m/z* calculated for $C_{13}H_{13}N_2O$ $[M+H]^+$: 213.1028, found 213.1027

3-amino-5-(*m*-tolyl)furan-2-carbonitrile (3kd): Dark brown solid (38 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.29 (t, J = 7.7 Hz, 1H), 7.18 (d, J = 7.7 Hz, 1H), 6.33 (s, 1H), 3.98 (brs, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 146.9, 138.7, 130.4, 128.9, 125.5, 122.1, 113.4, 109.3, 99.5, 21.5; HRMS: *m/z* calculated for $C_{12}H_{11}N_2O$ $[M+H]^+$: 199.0871, found 199.0871

(3-amino-5-phenylfuran-2-yl)(phenyl)methanone (3ae): Dark yellow solid (58 mg, 88%); mp 114-115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21-8.17 (m, 2H), 7.73 (d, J = 7.5 Hz, 2H), 7.57-7.50 (m, 3H), 7.46-7.37 (m, 3H), 6.46 (s, 1H), 5.69 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.6, 157.2, 149.2, 138.0, 136.0, 131.6, 129.7, 129.4, 129.2, 129.0, 128.3, 125.4, 99.5; HRMS: *m/z* calculated for $C_{17}H_{14}NO_2$ $[M+H]^+$: 264.1025, found 264.1025

(3-amino-5-(*p*-tolyl)furan-2-yl)(phenyl)methanone (3be): Dark yellow solid (57 mg, 82%); mp 135-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19-8.17 (m, 2H), 7.63-7.60 (m, 2H), 7.55-7.49 (m, 3H), 7.23 (d, J = 7.8 Hz, 2H), 6.40 (s, 1H), 5.69 (brs, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3, 157.6, 149.4, 140.1, 138.1, 135.9, 131.5, 129.7, 129.2, 128.3, 126.7, 125.4, 98.9, 21.6; HRMS: *m/z* calculated for $C_{18}H_{16}NO_2$ $[M+H]^+$: 278.1181, found 278.1181

(3-amino-5-(4-chlorophenyl)furan-2 yl)(phenyl)methanone (3fe): Dark yellow solid (63 mg, 85%); mp 162-164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16-8.13 (m, 2H), 7.63 (d, J = 8.6 Hz, 2H), 7.57-7.50 (m, 3H), 7.39 (d, J = 8.6 Hz, 2H), 6.43 (s, 1H), 5.69 (brs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.7, 155.9, 148.9, 137.9, 136.1, 135.6, 131.7, 129.3, 129.1, 128.4, 127.9, 126.5, 99.8; HRMS: *m/z* calculated for $C_{17}H_{13}ClNO_2$ $[M+H]^+$: 298.0635, found 298.0638

ethyl 3-amino-5-phenylthiophene-2-carboxylate (4aa'): Off white solid (46 mg, 74%); mp 82-83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59-7.55 (m, 2H), 7.39-7.31 (m, 3H), 6.75 (s, 1H), 5.51 (brs, 2H), 4.32 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 154.3, 148.9, 133.4, 128.9, 125.9, 115.6, 100.8, 60.2, 14.6; HRMS: m/z calculated for $C_{13}H_{14}NO_2S$ $[M+H]^+$: 248.0745, found 248.0745

ethyl 3-amino-5-(*p*-tolyl)thiophene-2-carboxylate (4ba'): Off white solid (50 mg, 76%); mp 102-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.1 Hz, 2H), 7.19 (d, J = 7.8 Hz, 2H), 6.63 (s, 1H), 5.47 (brs, 2H), 4.31 (q, J = 7.4 Hz, 2H), 2.37 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 154.4, 149.3, 139.2 130.7, 129.7, 125.9, 115.1, 100.4, 60.2, 21.4, 14.7; HRMS: m/z calculated for $C_{14}H_{16}NO_2S$ $[M+H]^+$: 262.0902, found 262.0902

ethyl 3-amino-5-(4-methoxyphenyl)thiophene-2-carboxylate (4ca'): Light brown solid (47 mg, 68%); mp 100-111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 6.67 (s, 1H), 5.45 (brs, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 1.36 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.8, 160.4, 154.4, 149.2, 127.4, 126.3, 114.6, 114.4, 100.1, 60.2, 55.5, 14.7; HRMS: m/z calculated for $C_{14}H_{16}NO_2S$ $[M+H]^+$: 278.0851, found 278.0853

ethyl 3-amino-5-(4-fluorophenyl)thiophene-2-carboxylate (4ea'): Off white solid (46 mg, 70%); mp 91-92 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.51 (m, 2H), 7.08-7.04 (m, 2H), 6.68 (s, 1H), 5.49 (brs, 2H), 4.30 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 163.2 (d, J = 249.4 Hz), 154.3, 147.8, 129.8 (d, J = 3.8 Hz), 127.8 (d, J = 8.6 Hz), 116.1 (d, J = 22.1 Hz), 115.6, 100.8, 60.3, 14.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ -112.0 ppm; HRMS: m/z calculated for $C_{13}H_{13}FNO_2S$ $[M+H]^+$: 266.0651, found 266.0652

ethyl 3-amino-5-(4-chlorophenyl)thiophene-2carboxylate (4fa'): Light brown solid (51 mg, 72%); mp 78-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 6.74 (s, 1H), 5.46 (brs, 2H), 4.31 (q, J = 7.3 Hz, 2H), 1.37 (t, J =

6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.7, 154.2, 147.6, 134.9, 132.1, 129.3, 127.3, 115.9, 101.3, 60.3, 14.7; HRMS: *m/z* calculated for $C_{13}H_{13}ClNO_2S$ [M+H]$^+$: 282.0356, found 282.0359

ethyl 3-amino-5-(4-ethylphenyl)thiophene-2-carboxylate (4ga'): Light brown solid (55 mg, 80%); mp 84-85 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.51 (d, *J* = 8.2 Hz, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 6.73 (s, 1H), 5.46 (brs, 2H), 4.31 (q, *J* = 7.3 Hz, 2H), 2.66 (q, *J* = 7.8 Hz, 2H), 1.37 (t, *J* = 7.3 Hz, 3H), 1.25 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.8, 154.4, 149.3, 145.5, 130.9, 128.6, 126.0, 115.2, 100.5, 60.2, 28.8, 15.5, 14.7; HRMS: *m/z* calculated for $C_{15}H_{18}NO_2S$ [M+H]$^+$: 276.1058, found 276.1058

ethyl 3-amino-5-(4-ethylphenyl)thiophene-2-carboxylate (4ha'): Light brown solid (48 mg, 78%); mp 80-81 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.49 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.5 Hz, 2H), 6.73 (s, 1H), 5.46 (brs, 2H), 4.31 (q, *J* = 7.4 Hz, 2H), 2.62 (t, *J* = 7.8 Hz, 2H), 1.64-1.57 (m, 2H), 1.41-1.32 (m, 5H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.8, 154.4, 149.4, 144.3, 130.9, 129.1, 125.9, 115.1, 100.5, 60.2, 35.5, 33.6, 22.5, 14.7, 14.1; HRMS: *m/z* calculated for $C_{17}H_{22}NO_2S$ [M+H]$^+$: 304.1371, found 304.1371

ethyl 3-amino-5-(3-chlorophenyl)thiophene-2 carboxylate (4ia'): Off white solid (57 mg, 81%); mp 89-90 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.55-7.53 (m, 1H), 7.44-7.39 (m, 1H), δ 7.29-7.27 (m, 2H), 6.74 (s, 1H), 5.49 (brs, 2H), 4.31 (q, *J* = 7.3 Hz, 2H), 1.36 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.6, 154.1, 147.0, 135.2, 134.9, 130.3, 128.8, 125.9, 124.1, 116.3, 101.4, 60.3, 14.6; HRMS: *m/z* calculated for $C_{13}H_{13}NO_2SCl$ [M+H]$^+$: 282.0356, found 282.0356

ethyl 3-amino-5-(3-fluorophenyl)thiophene-2-carboxylate (4ja'): Pale yellow solid (54 mg, 82%); mp 85-86 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.37-7.31 (m, 2H), 7.29-7.25 (m, 1H), 7.07-7.01 (m, 1H), 6.76 (s, 1H), 5.48 (brs, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.7, 163.1 (d, *J* = 247.2 Hz), 154.1, 147.4 (d, *J* = 2.9 Hz), 135.6 (d, *J* = 8.1 Hz), 130.6 (d, *J* = 8.5 Hz), 121.8 (d, *J* = 2.9

Hz), 116.3, 115.8 (d, J = 22.9 Hz), 112.9, 101.4, 60.4, 14.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ -112.2 ppm; HRMS: m/z calculated for $C_{13}H_{13}NO_2SF$ [M+H]$^+$: 266.0651, found 266.0651

ethyl 3-amino-5-(*m*-tolyl)thiophene-2-carboxylate (4ka'): Brown solid (45 mg, 69%); mp 74-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.38 (m, 2H), 7.27 (t, J = 7.3 Hz, 1H), 7.16 (d, J = 7.7 Hz, 1H), 6.76 (s, 1H), 5.51 (brs, 2H), 4.33 (q, J = 7.4 Hz, 2H), 2.38 (s, 3H), 1.38 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 154.3, 149.2, 138.7, 133.3, 129.8, 128.9, 126.7, 123.1, 115.5, 100.6, 60.2, 21.4, 14.6; HRMS: m/z calculated for $C_{14}H_{16}NO_2S$ [M+H]$^+$: 262.0902, found 262.0902

ethyl 4-amino-[2,3'-bithiophene]-5-carboxylate (4la'): Off white solid (51 mg, 80%); mp 112-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.45 (m, 1H), 7.34-7.32 (m, 1H), 7.26-7.25 (m, 1H), 6.64 (s, 1H), 5.48 (brs, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 154.2, 143.7, 134.9, 126.8, 125.8, 121.8, 115.6, 99.8, 60.2, 14.7; HRMS: m/z calculated for $C_{11}H_{12}NO_2S_2$ [M+H]$^+$: 254.0309, found 254.0309

ethyl 3-amino-5-hexylthiophene-2-carboxylate (4ma'): Brown liquid (47 mg, 74%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.24 (s, 1H), 5.42 (brs, 2H), 4.25 (q, J = 7.1 Hz, 2H), 2.64 (t, J = 7.7 Hz, 2H), 1.64-1.57 (m, 2H), 1.38-1.24 (m, 9H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 154.0, 152.6, 117.5, 99.1, 59.9, 31.6, 30.9, 30.8, 28.8, 22.6, 14.6, 14.1; HRMS: m/z calculated for $C_{12}H_{20}NO_2S$ [M+H]$^+$: 242.1215, found 242.1213

ethyl 3-amino-5-octylthiophene-2-carboxylate (4na'): Brown liquid (56 mg, 79%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25 (s, 1H), 5.41 (brs, 2H), 4.25 (q, J = 7.2 Hz, 2H), 2.65 (t, J = 7.6 Hz, 2H), 1.65-1.57 (m, 2H), 1.33-1.22 (m, 13H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 154.0, 152.6, 117.5, 99.1, 59.9, 31.9, 30.9, 30.8, 29.4, 29.3, 29.1, 22.7, 14.7, 14.2; HRMS: m/z calculated for $C_{14}H_{24}NO_2S$ [M+H]$^+$: 270.1528, found 270.1527

methyl 3-amino-5-phenylthiophene-2-carboxylate (4ab'): Light brown crystalline solid (41 mg, 70%); mp 137-138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.56 (m, 2H), 7.41-7.32 (m, 3H), 6.77 (s, 1H), 5.48 (brs, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 154.4, 149.3, 133.5, 129.1, 126.1, 115.6, 100.6, 51.4; HRMS: *m/z* calculated for $C_{12}H_{12}NO_2S$ $[M+H]^+$: 234.0589, found 234.0591

methyl 3-amino-5-(*p*-tolyl)thiophene-2-carboxylate (4bb'): Light brown crystalline solid (45 mg, 73%); mp 96-97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, J = 8.2 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.73 (s, 1H), 5.47 (brs, 2H), 3.84 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 154.5, 149.5, 139.3, 130.7, 129.8, 125.9, 115.1, 100.1, 51.4, 21.4; HRMS: *m/z* calculated for $C_{13}H_{14}NO_2S$ $[M+H]^+$: 248.0745, found 248.0745

methyl 3-amino-5-(4-fluorophenyl)furan-2-carboxylate (4fb'): Light yellow solid (43 mg, 65%); mp 120-121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.49 (m, 2H), 7.38-7.34 (m, 2H), 6.74 (s, 1H), 5.48 (brs, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 154.4, 147.8, 135.0, 132.0, 129.3, 127.3, 115.9, 100.8, 51.5; HRMS: *m/z* calculated for $C_{12}H_{11}ClNO_2S$ $[M+H]^+$: 268.0199, found 268.0199

methyl 3-amino-5-(4-fluorophenyl)thiophene-2-carboxylate (4eb'): Light brown solid (42 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56-7.52 (m, 2H), 7.09-7.05 (m, 2H), 6.69 (s, 1H), 5.49 (brs, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 163.3 (d, J = 249.7 Hz), 154.4, 148.1, 129.8 (d, J = 2.9 Hz), 127.9 (d, J = 8.6 Hz), 116.1 (d, J = 22.1 Hz), 115.6, 100.4, 51.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ -111.9 ppm; HRMS: *m/z* calculated for $C_{12}H_{11}FNO_2S$ $[M+H]^+$: 252.0495, found 252.0493

***N*-(2-benzoyl-5-phenylfuran-3-yl)-3-phenylpropiolamide (5):** Yellow crystalline solid (91 mg, 93%); mp 182-183 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (s, 1H), 8.25-8.22 (m, 2H), 7.84 (s, 1H), 7.83-7.80 (m, 2H), 7.67-7.62 (m, 3H), 7.60-7.56 (m, 2H), 7.50-7.39 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.8, 157.4, 151.4, 138.7, 137.7, 136.9, 133.1, 132.9, 130.8, 130.1, 129.5, 129.2, 129.0, 128.8, 128.7, 125.5, 119.8, 102.7, 87.5, 83.3; HRMS: *m*/*z* calculated for $C_{26}H_{18}NO_3$ $[M+H]^+$: 392.1287, found 392.1288

ethyl 5-phenyl-3-(3-phenylpropiolamido)thiophene-2-carboxylate (6): White crystalline solid (85 mg, 90%); mp 143-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.55 (s, 1H), 8.36 (s, 1H), 7.70-7.68 (m, 2H), 7.64-7.62 (m, 2H), 7.48-7.36 (m, 6H), 4.39 (q, *J* = 7.4 Hz, 2H), 1.42 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 150.3, 149.9, 144.1, 133.1, 132.9, 130.6, 129.4, 129.2, 128.7, 126.3, 119.9, 118.5, 109.9, 86.8, 83.4, 61.4, 14.5; HRMS: *m*/*z* calculated for $C_{22}H_{18}NO_3S$ $[M+H]^+$: 376.1007, found 376.1015

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13. CCDC-2153824, 2103735, 2153841, 2153870, 2103732 and 2153873 contains the supplementary crystallographic data for **3ba**, **3cd**, **4ab'**, **4bb'**, **4eb'** and **5** respectively in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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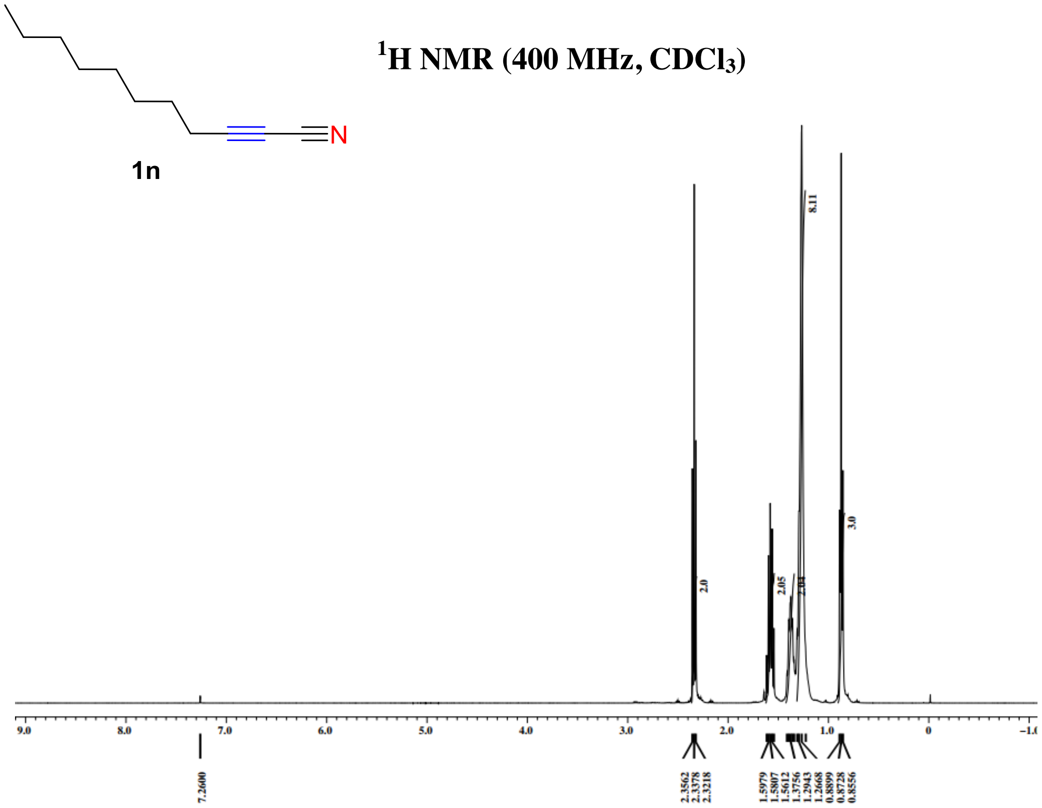
2.6 NMR spectra of compounds



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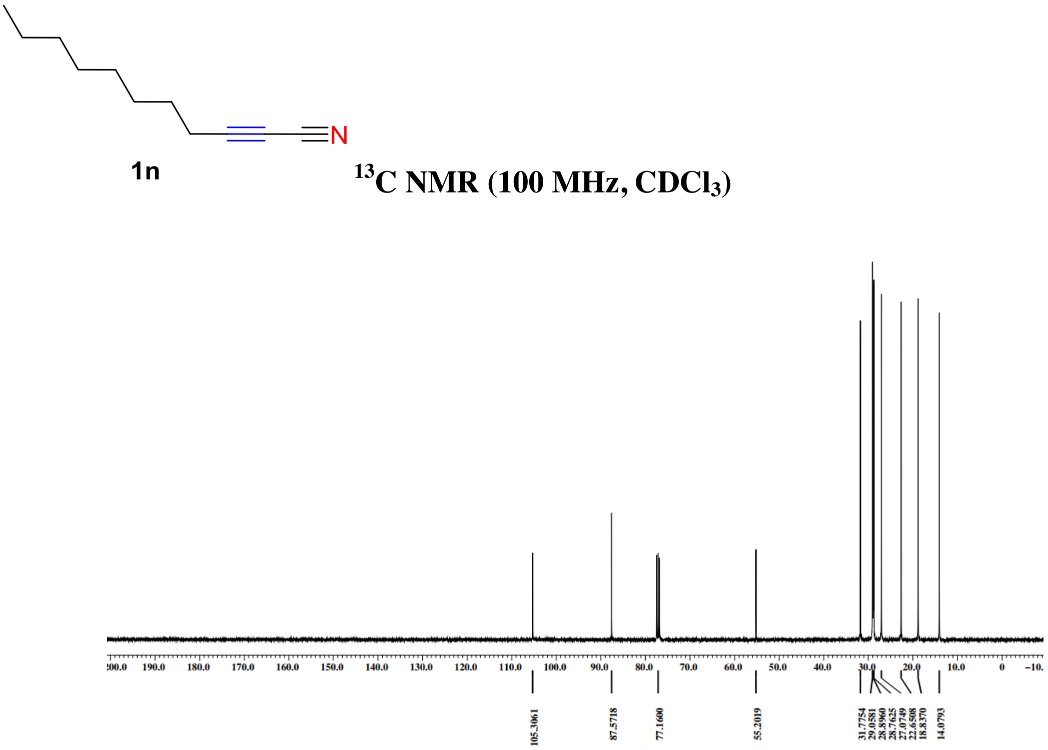

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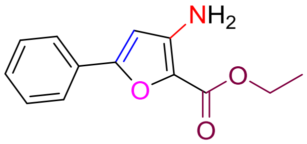

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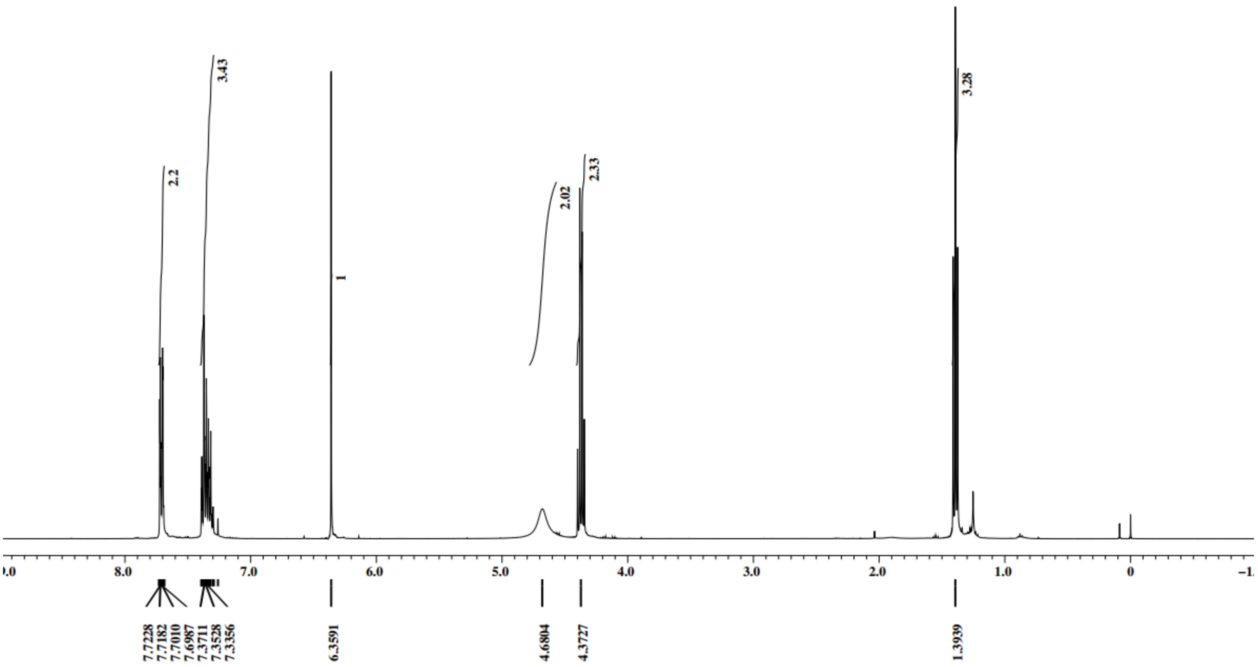

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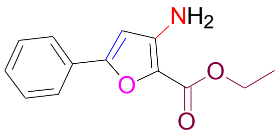

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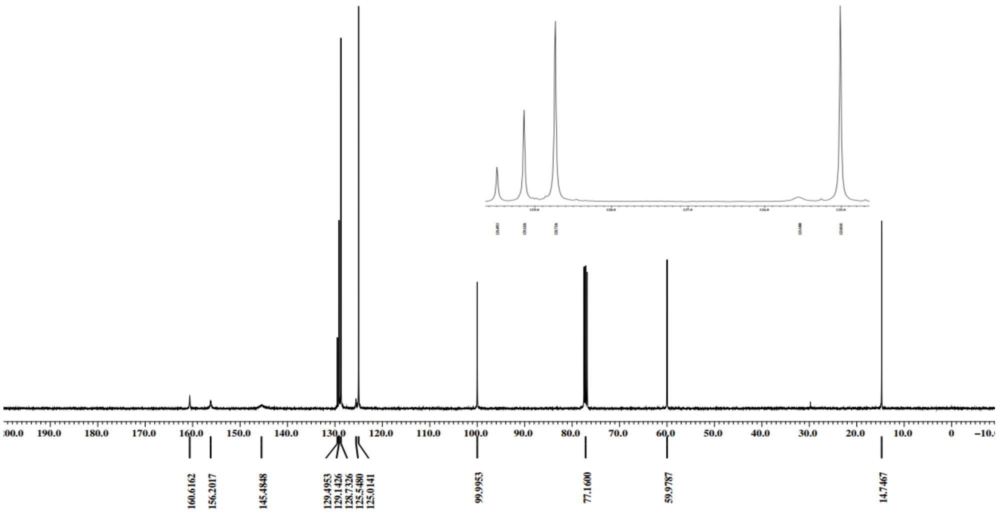

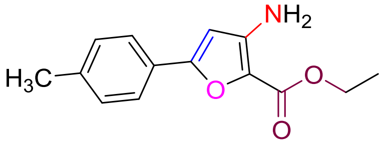

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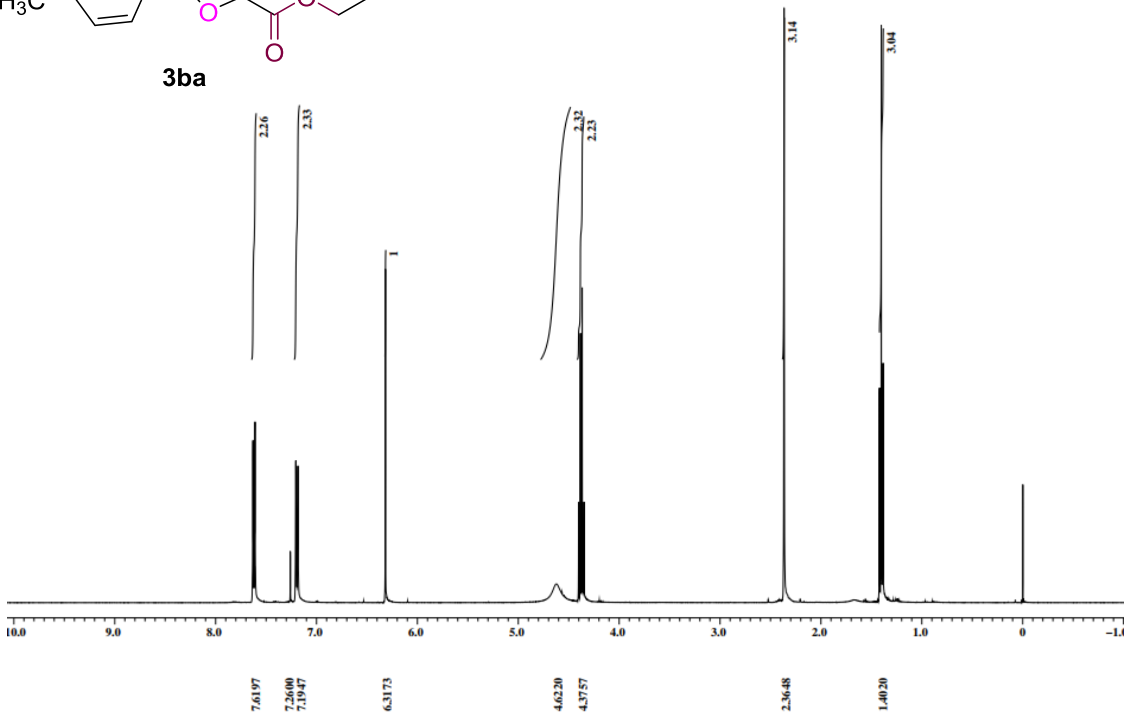

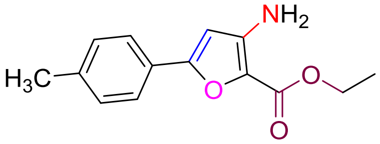

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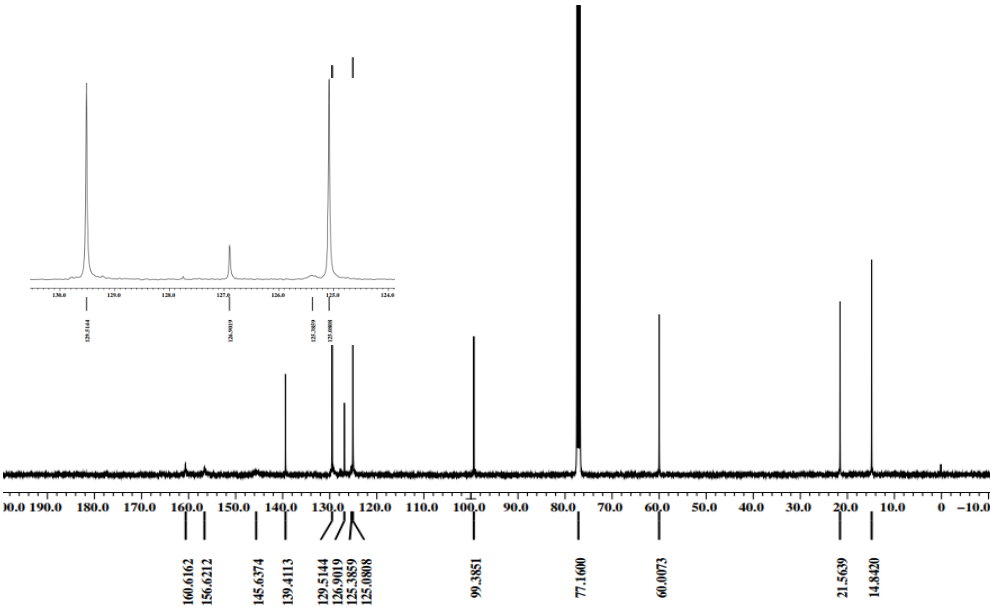

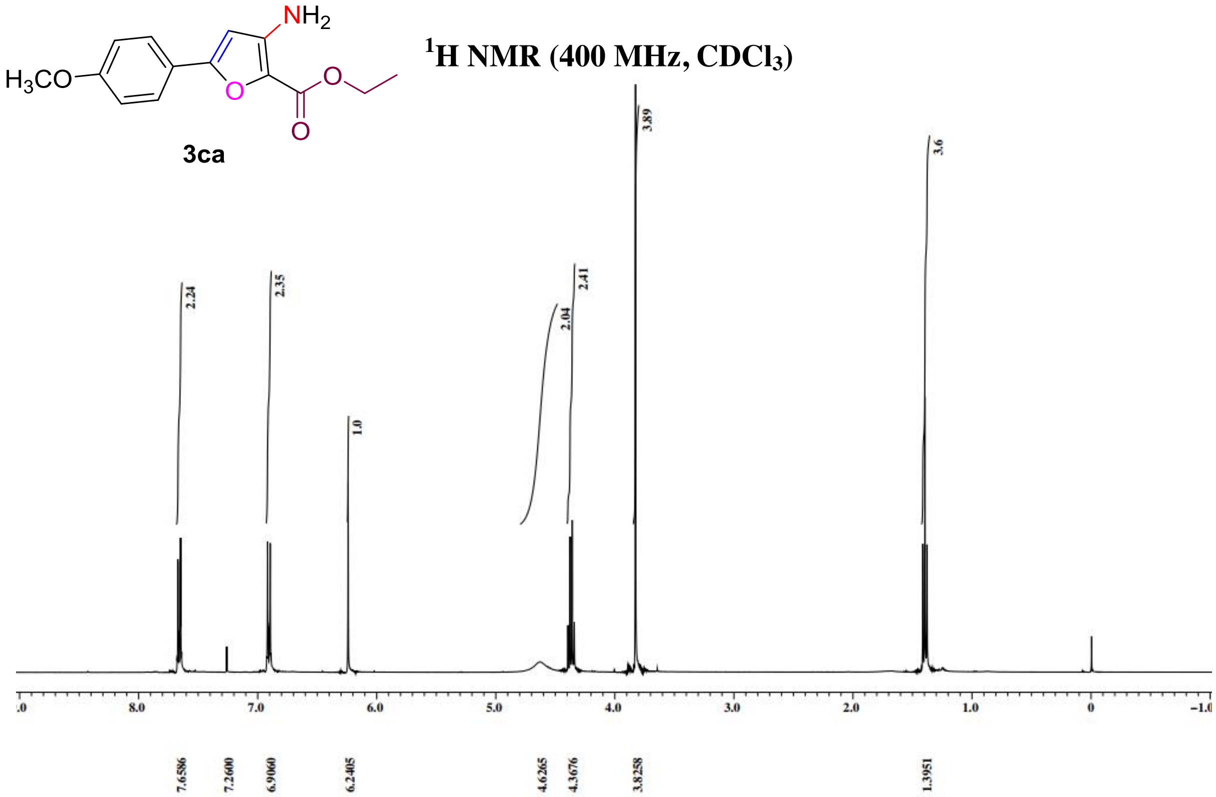

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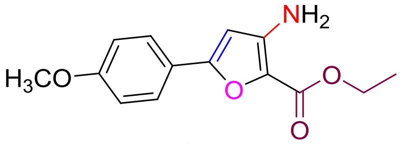

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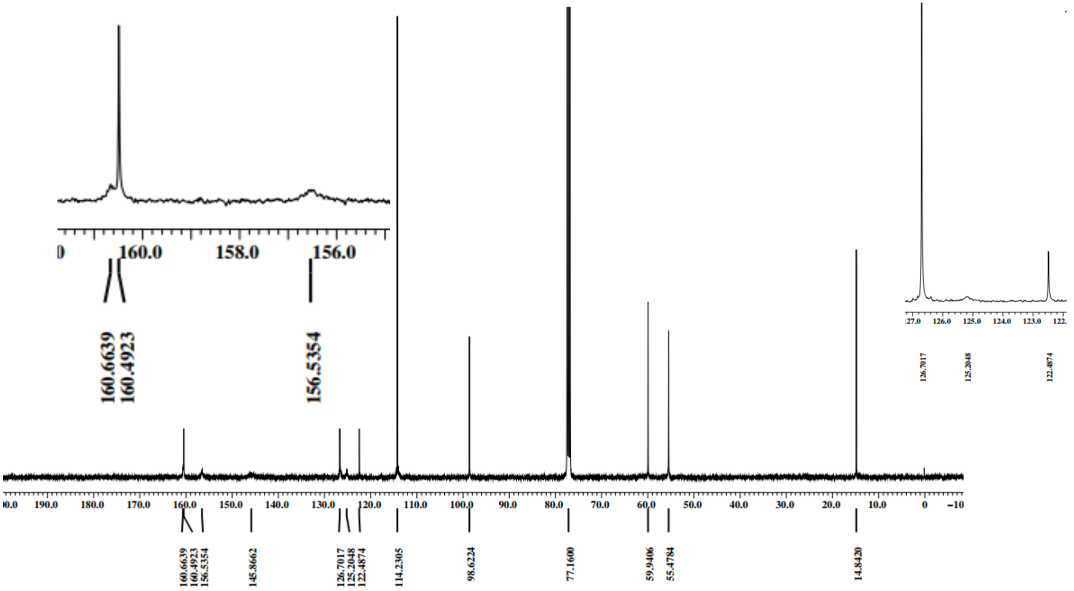

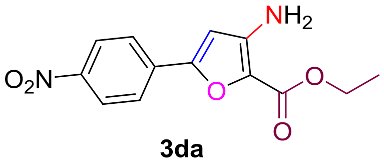

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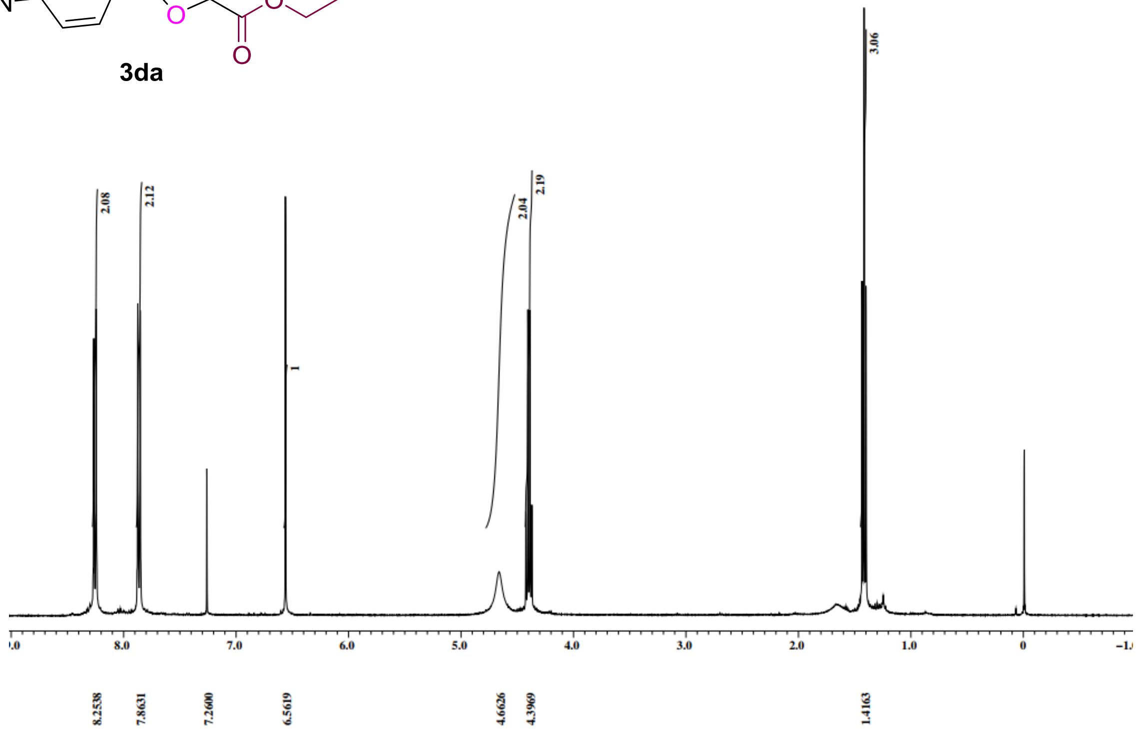

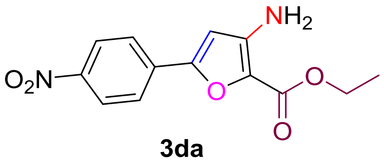

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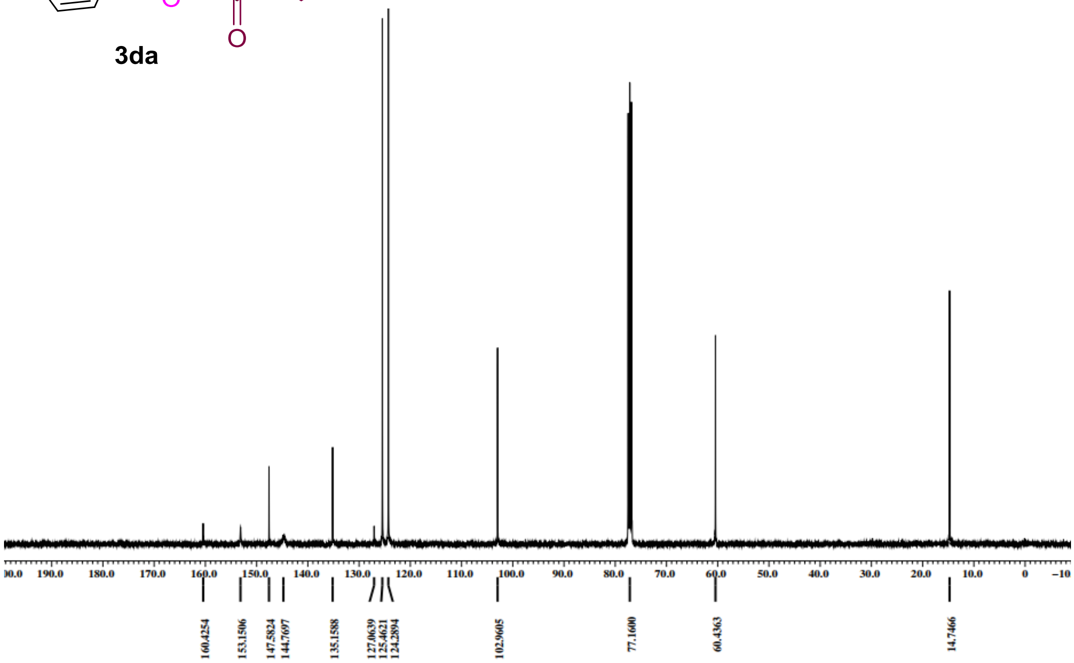

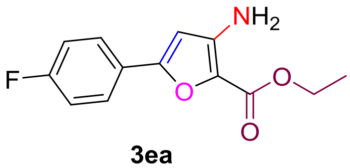

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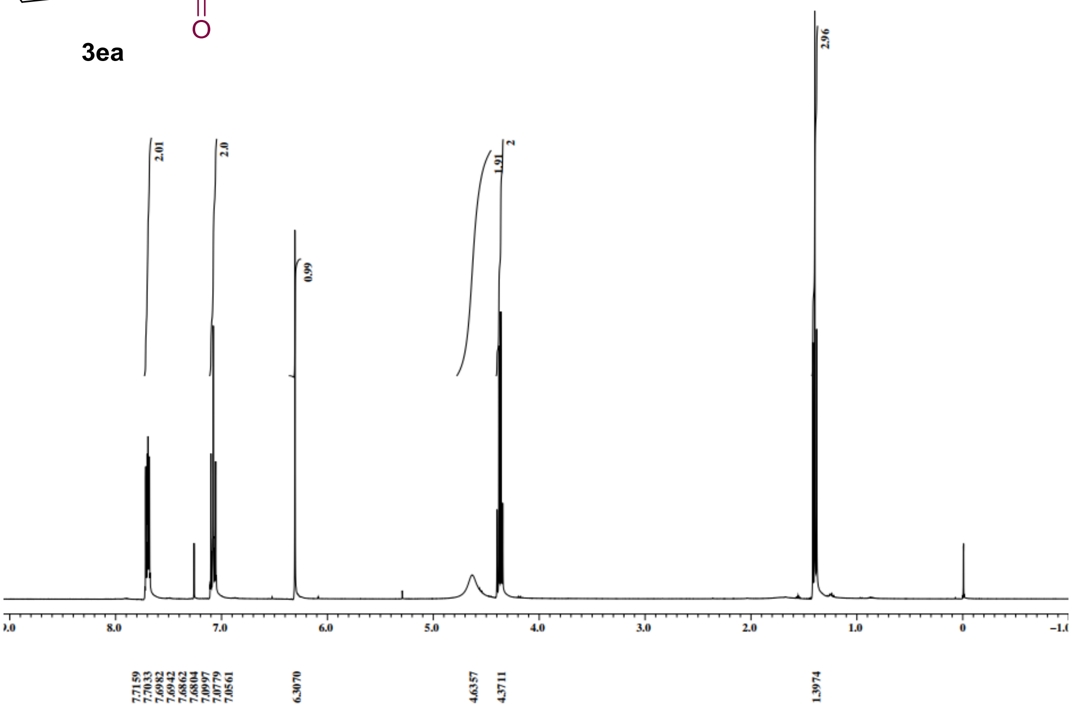

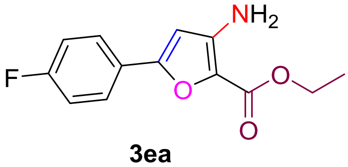

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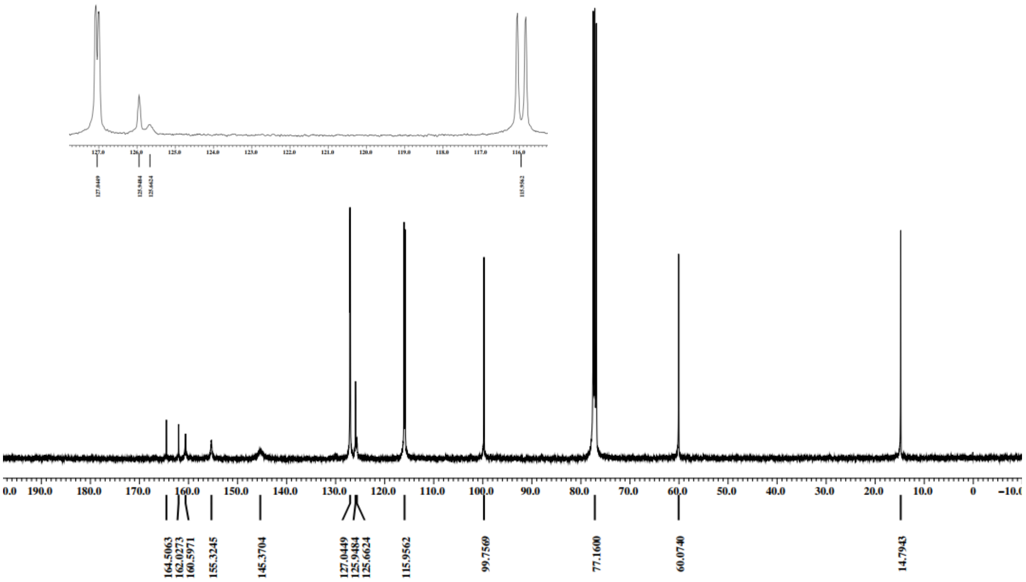

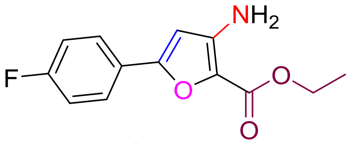

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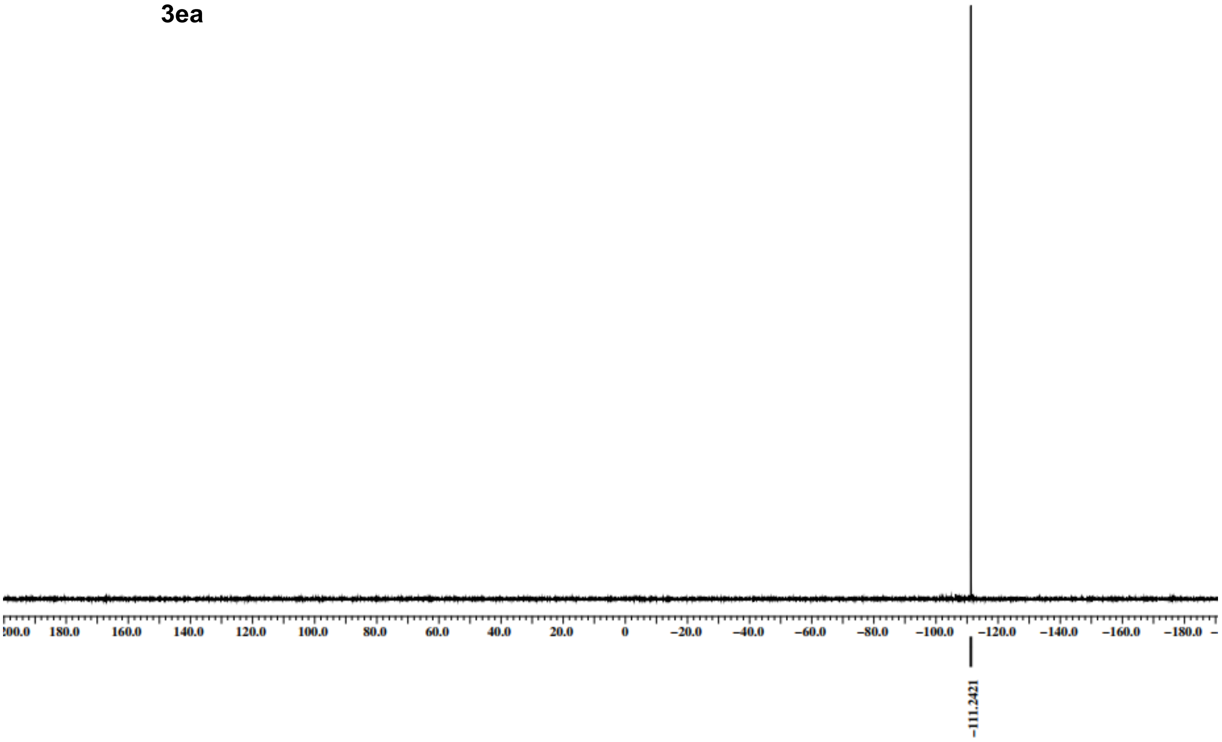

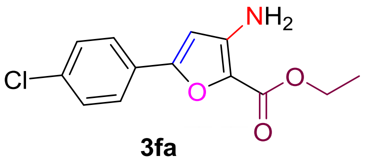

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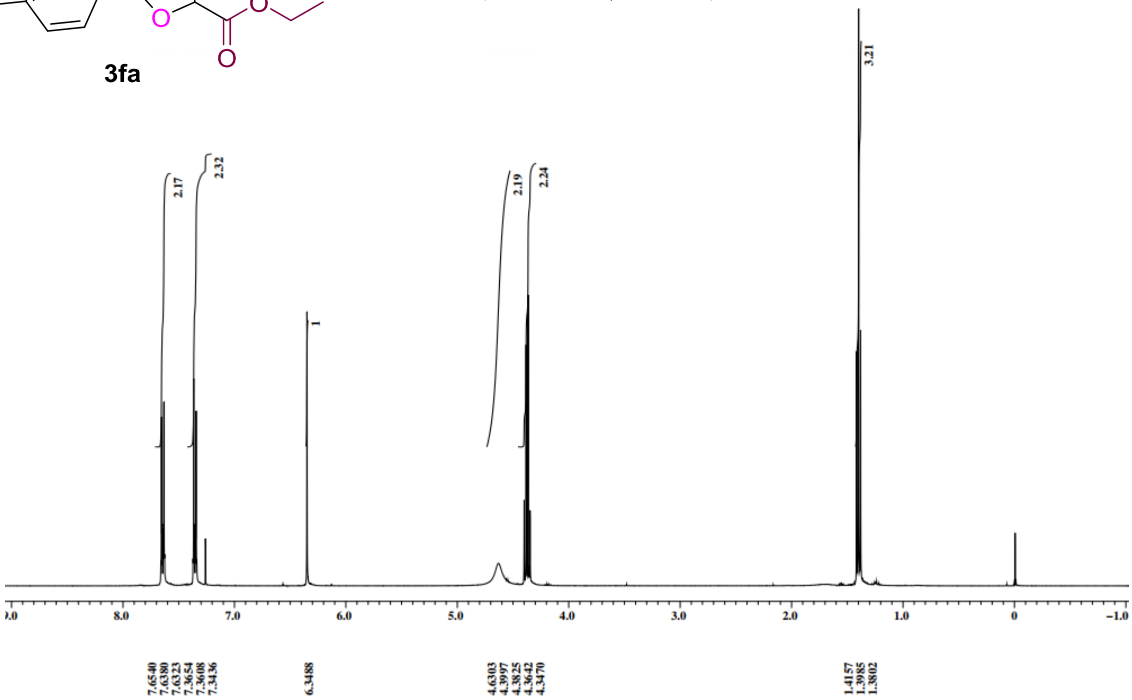

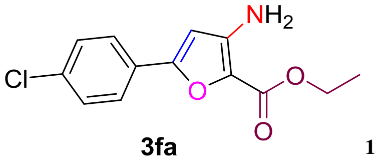

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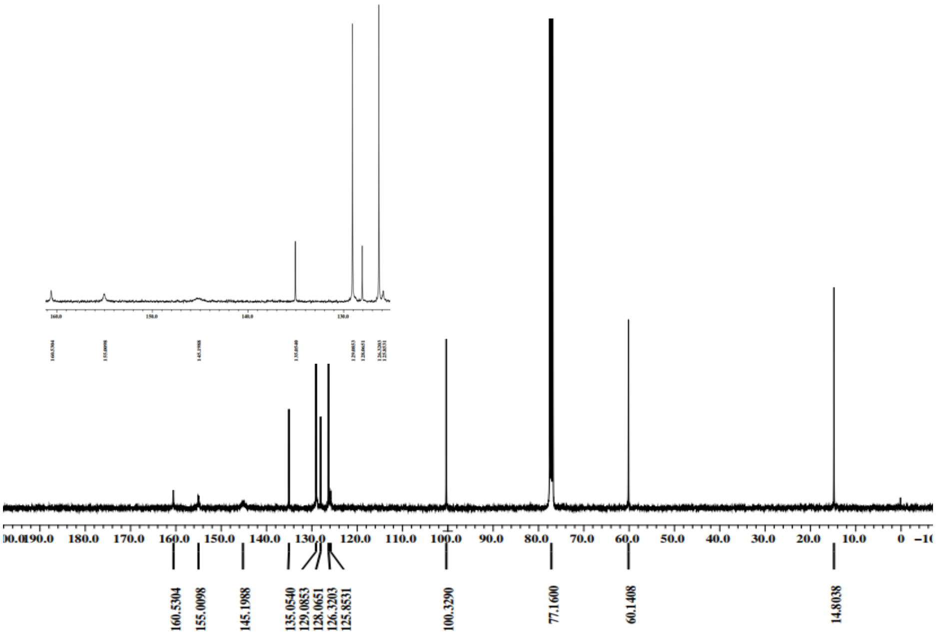

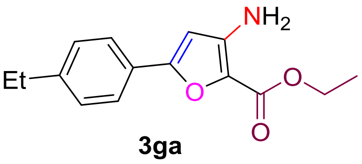

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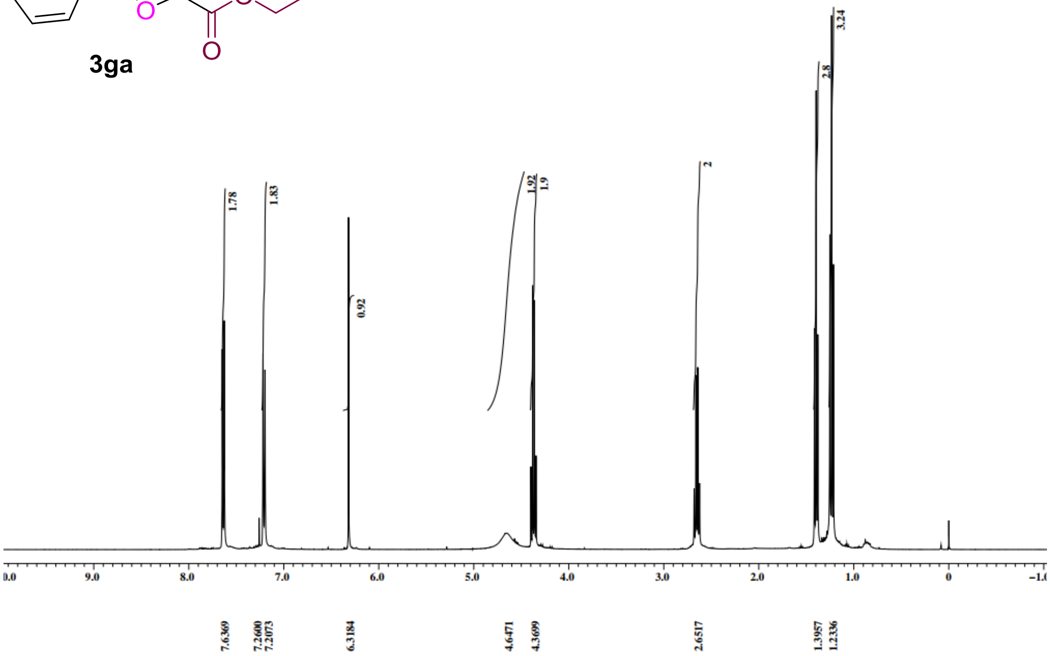

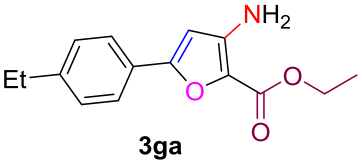

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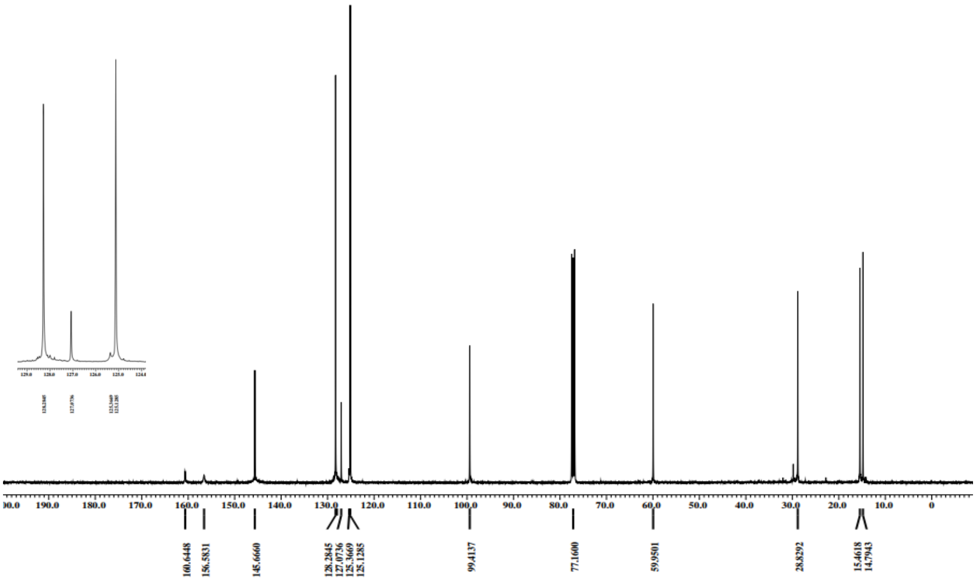

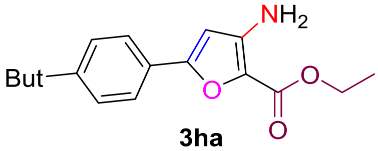

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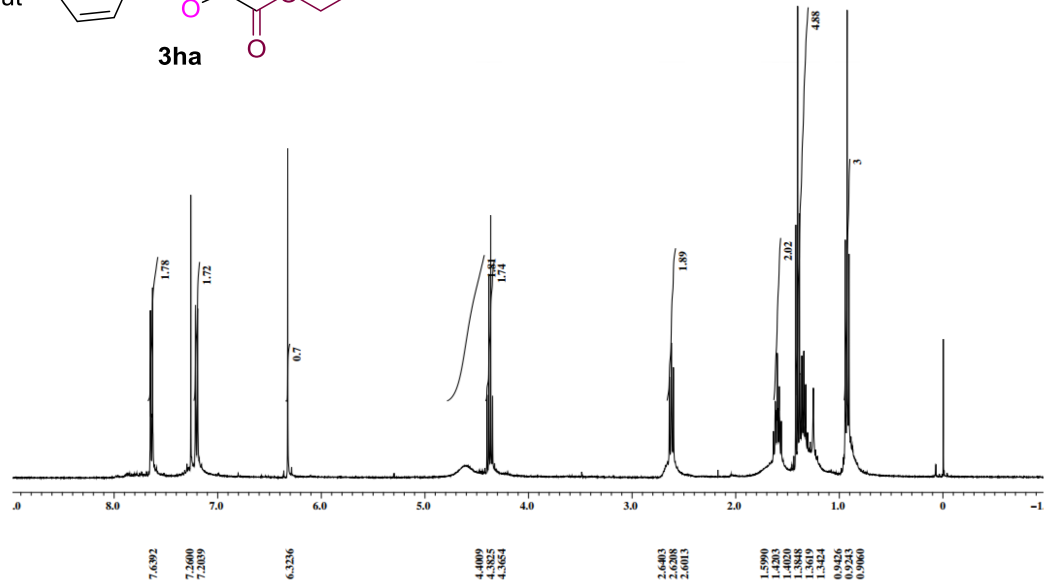

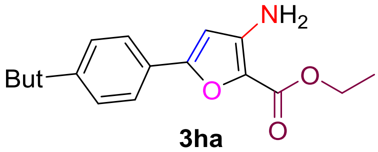

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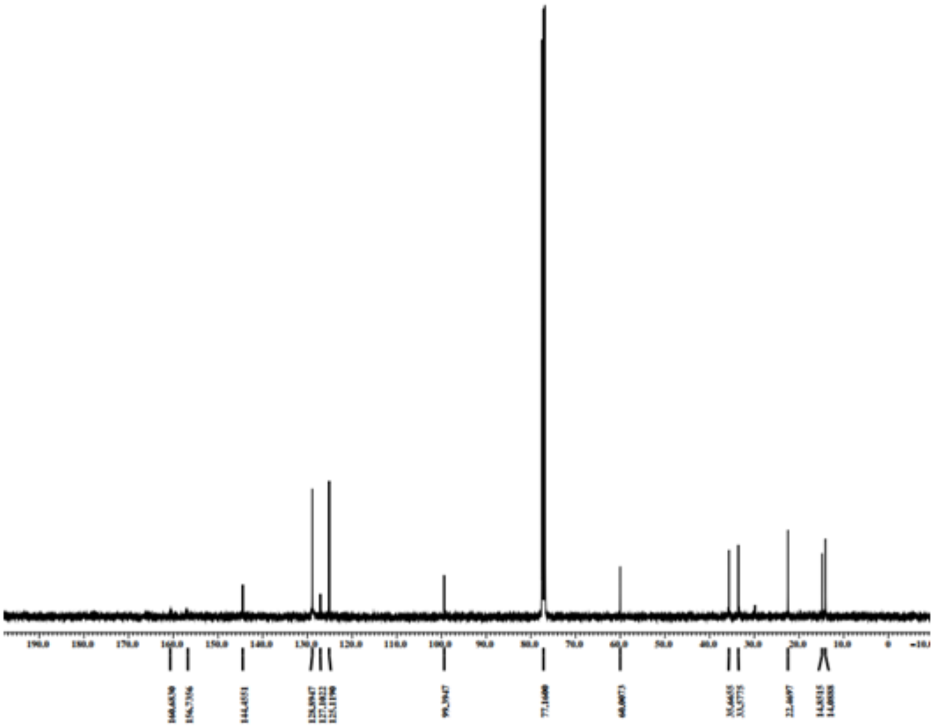

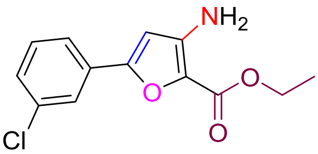

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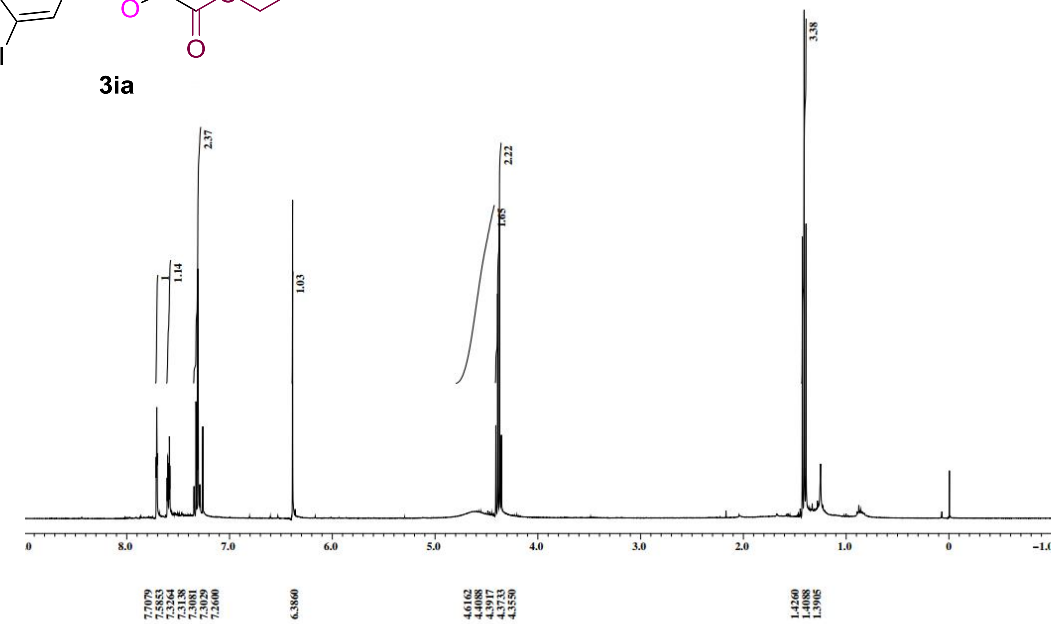

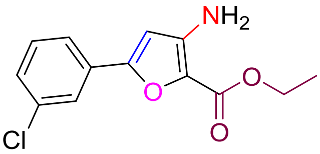

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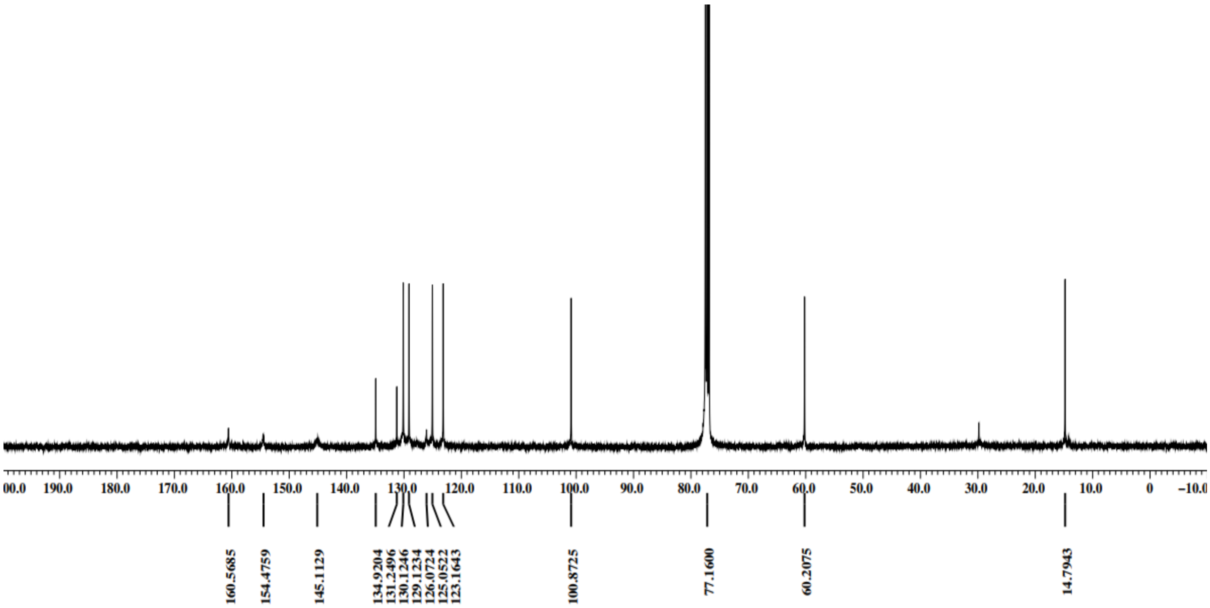

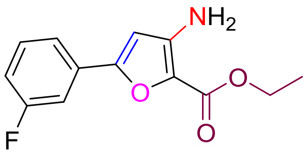

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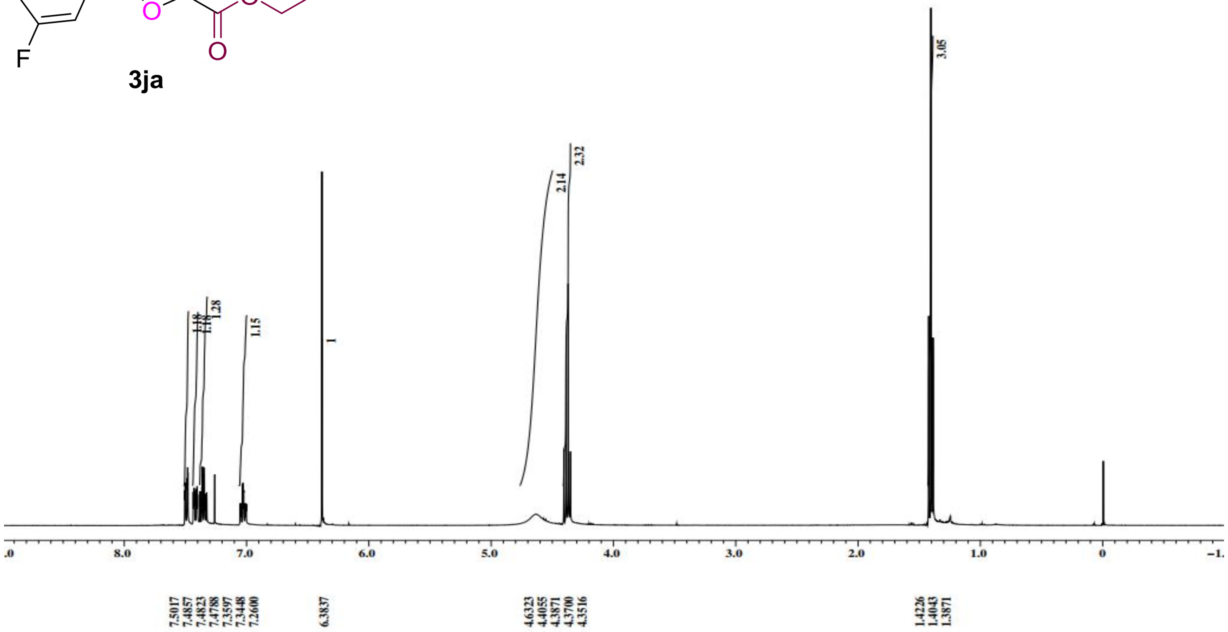

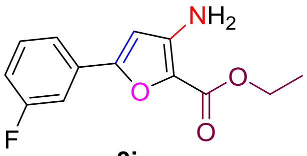

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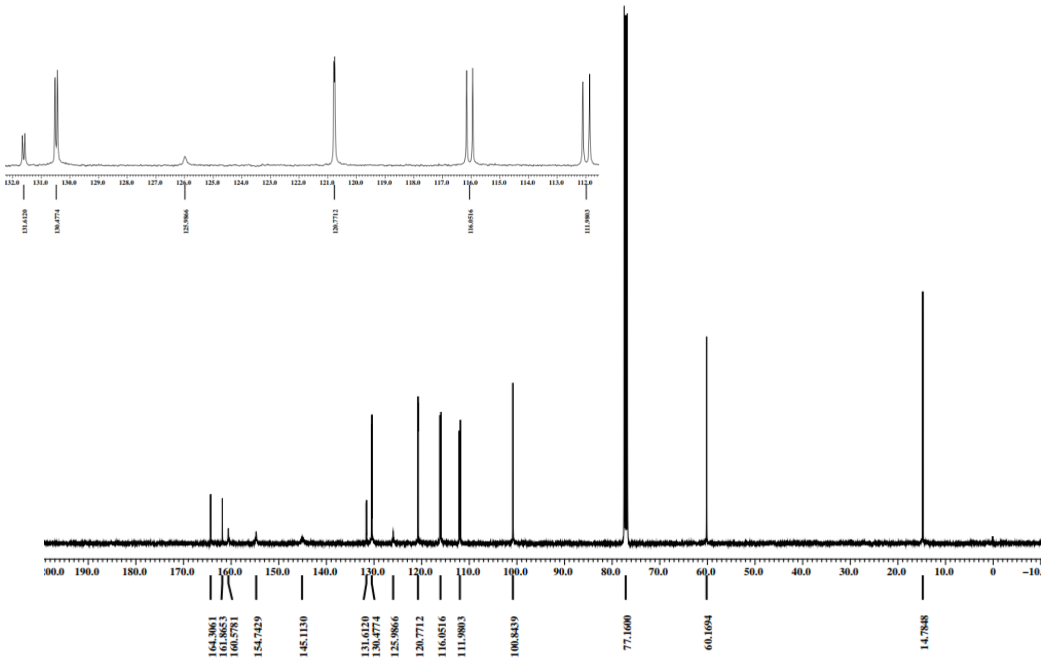

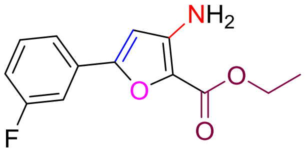

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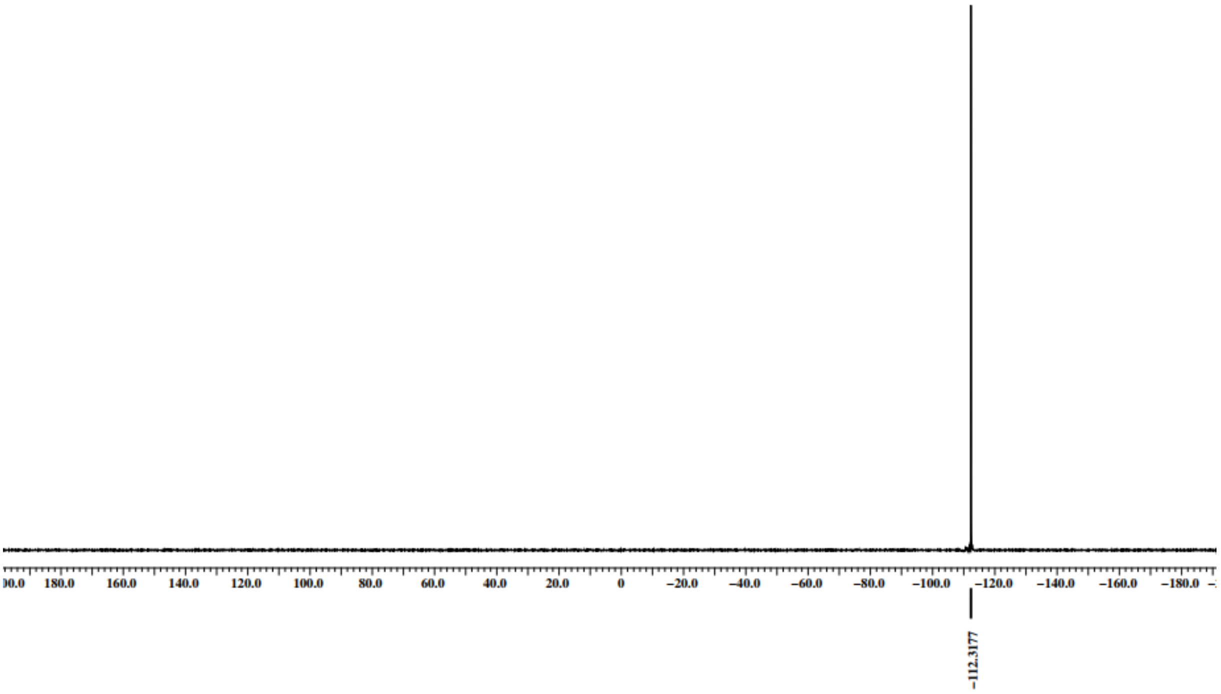

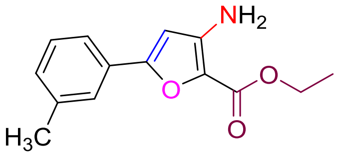

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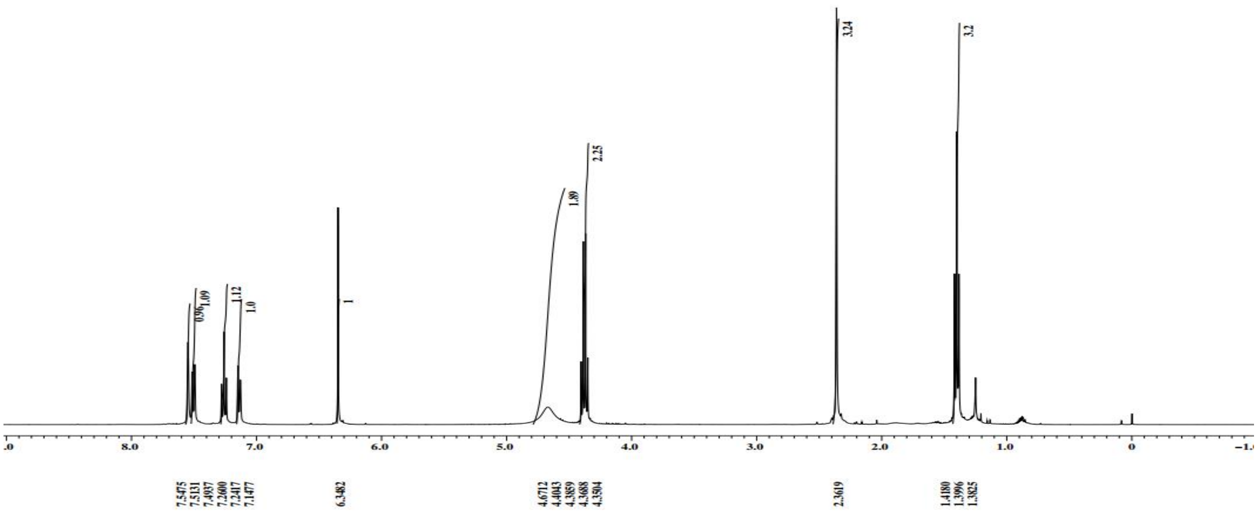

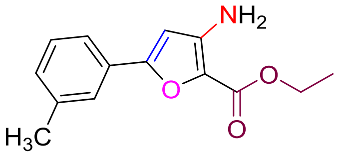

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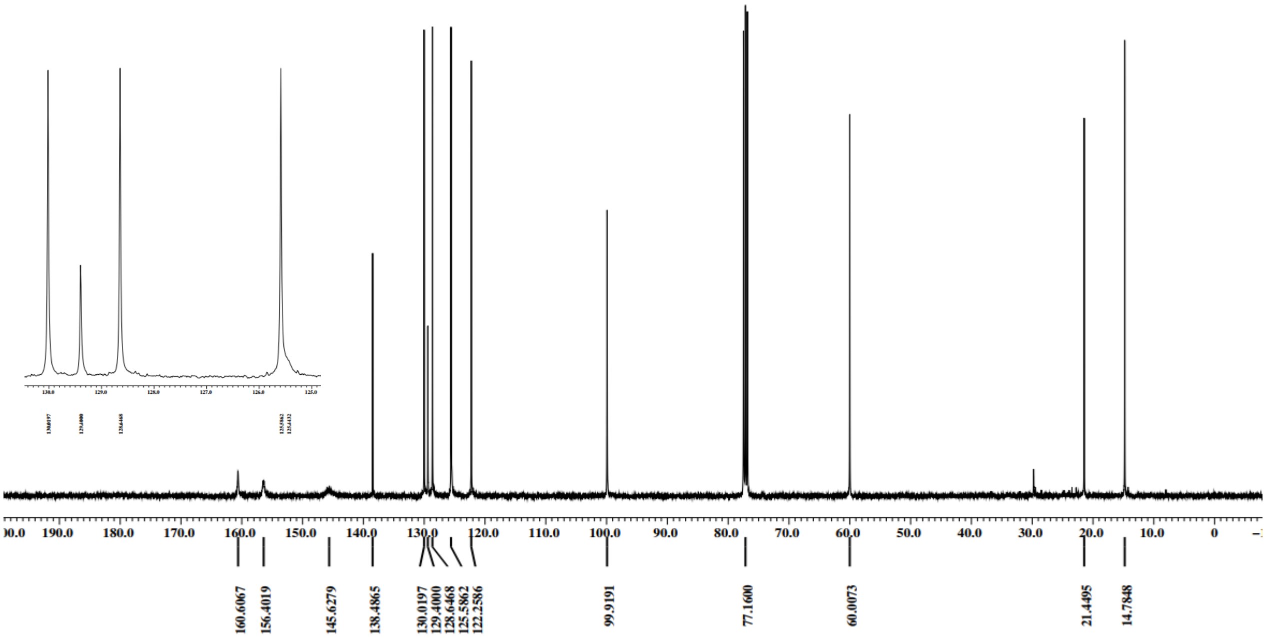

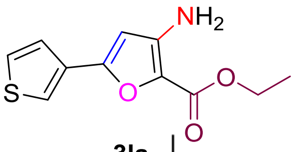

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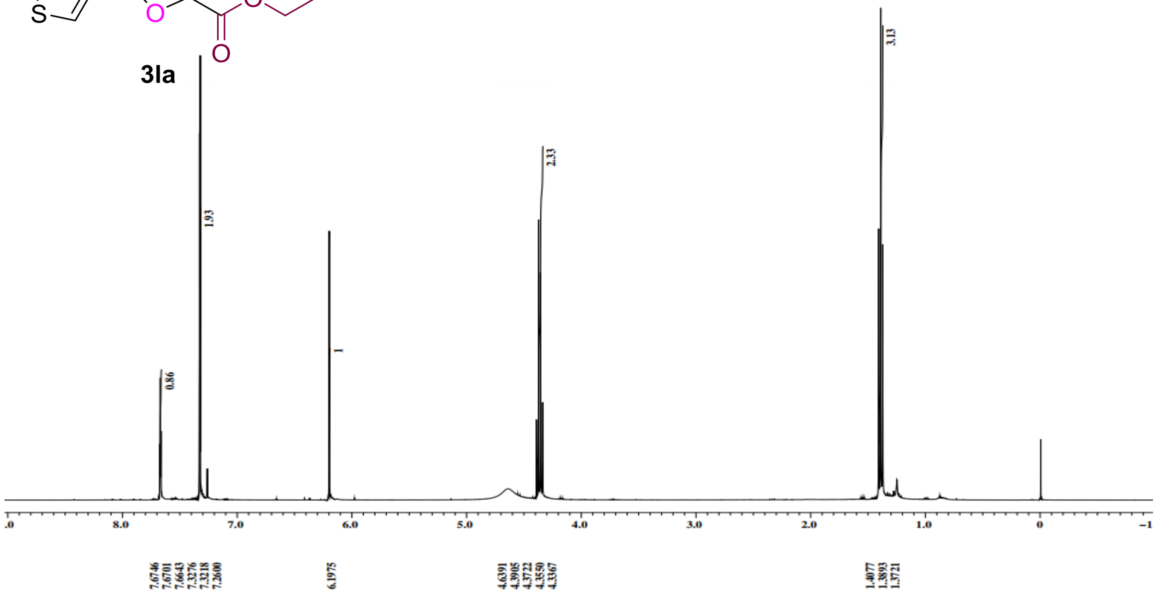

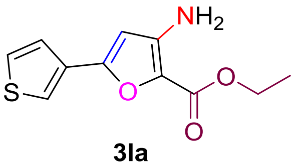

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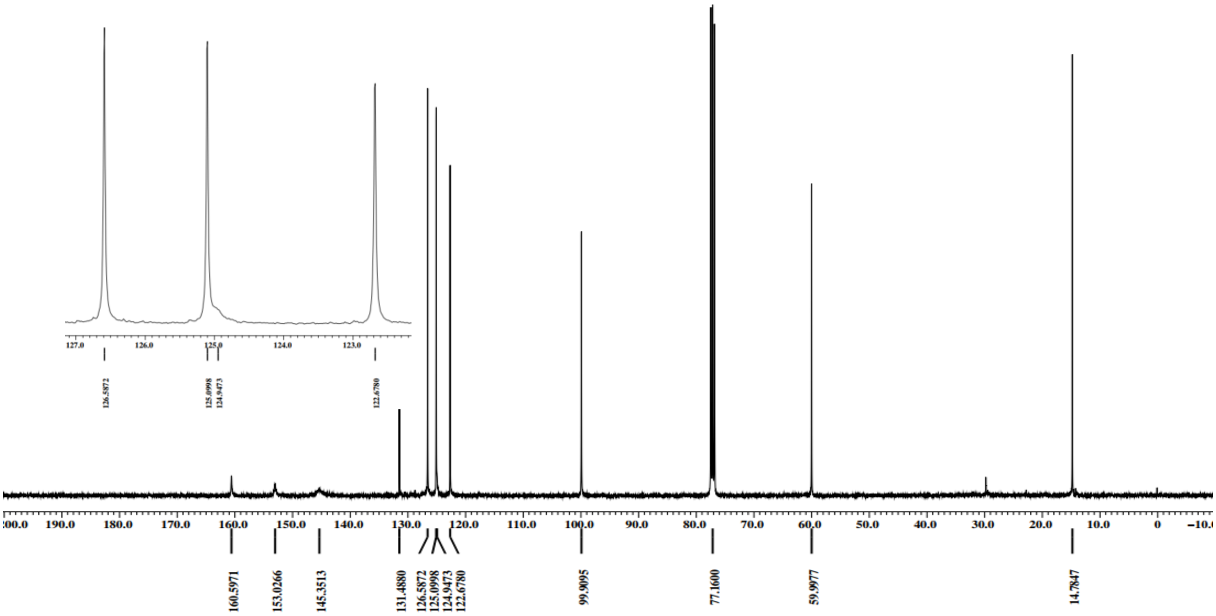
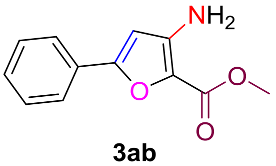
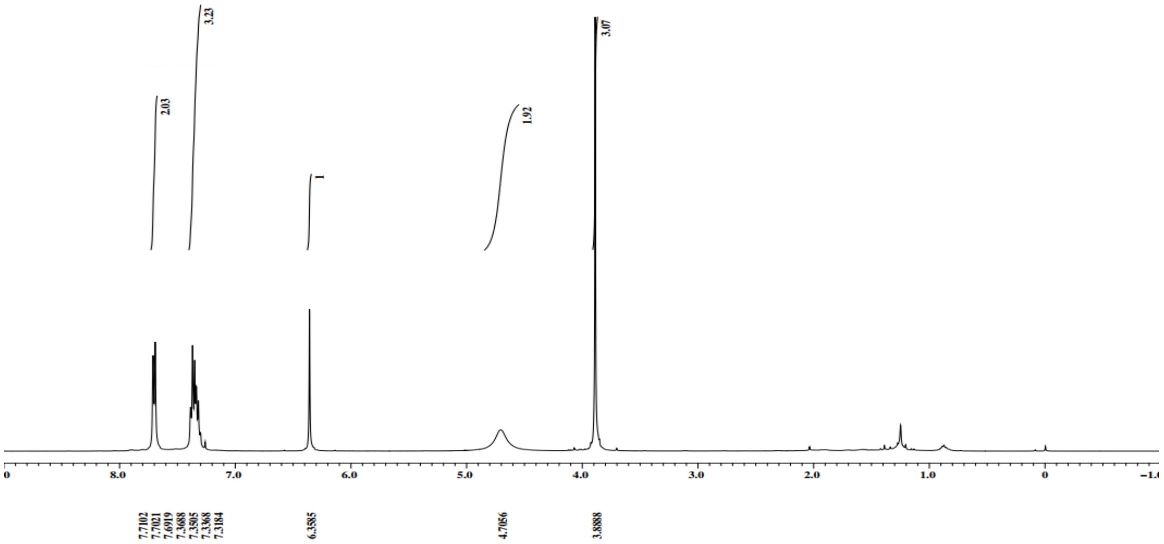
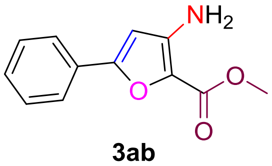




3ab

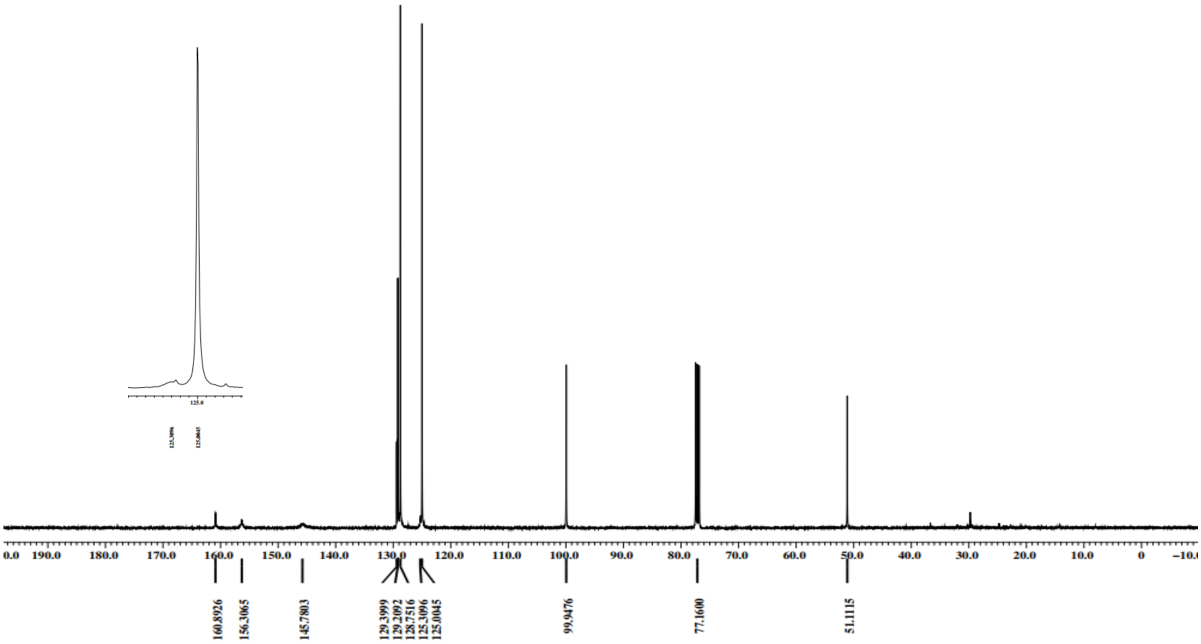
^{1}H NMR (400 MHz, CDCl$_3$)

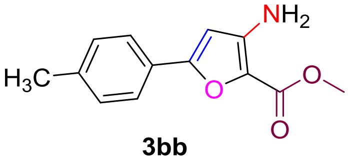




3ab

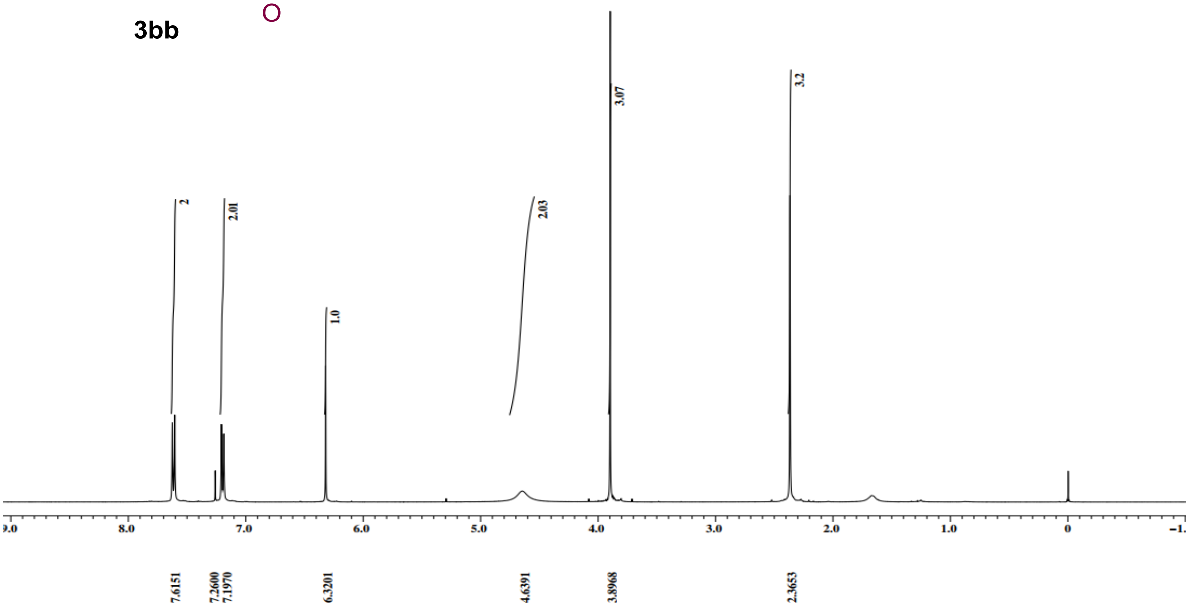
^{13}C NMR (100 MHz, CDCl$_3$)

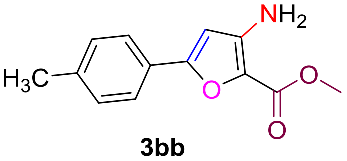




3bb

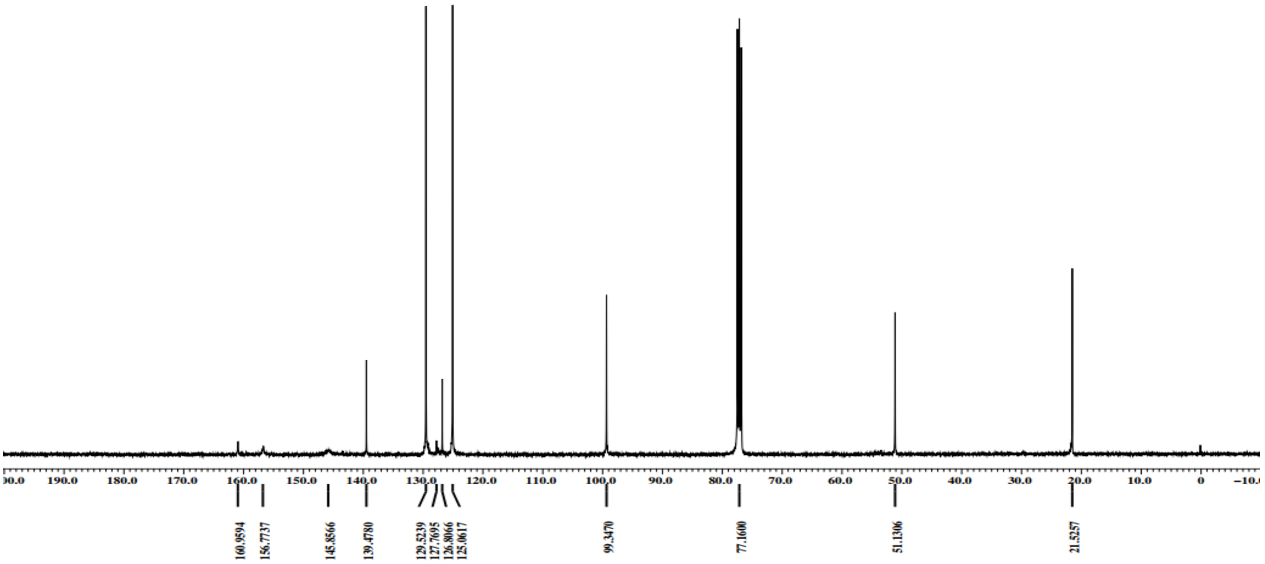
^{1}H NMR (400 MHz, CDCl$_3$)

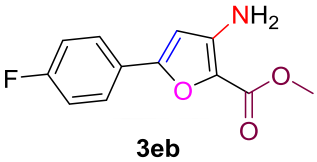




3bb

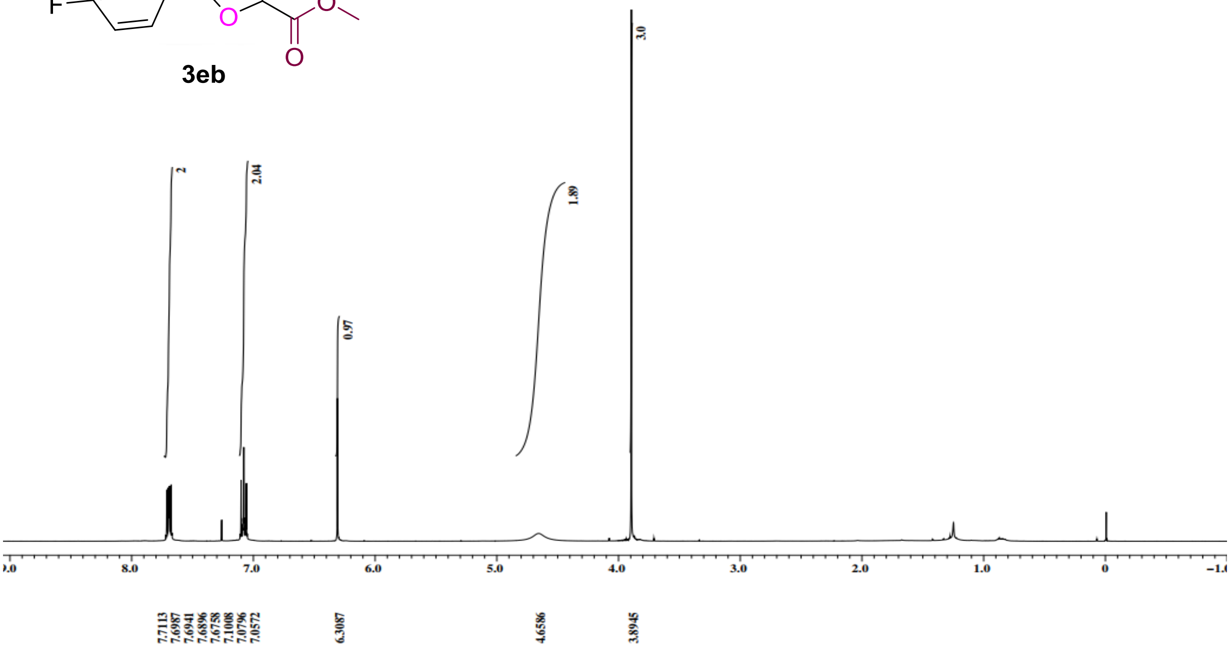
^{13}C NMR (100 MHz, CDCl$_3$)

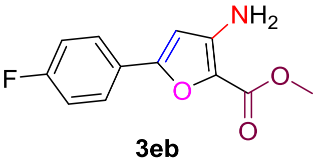




3eb

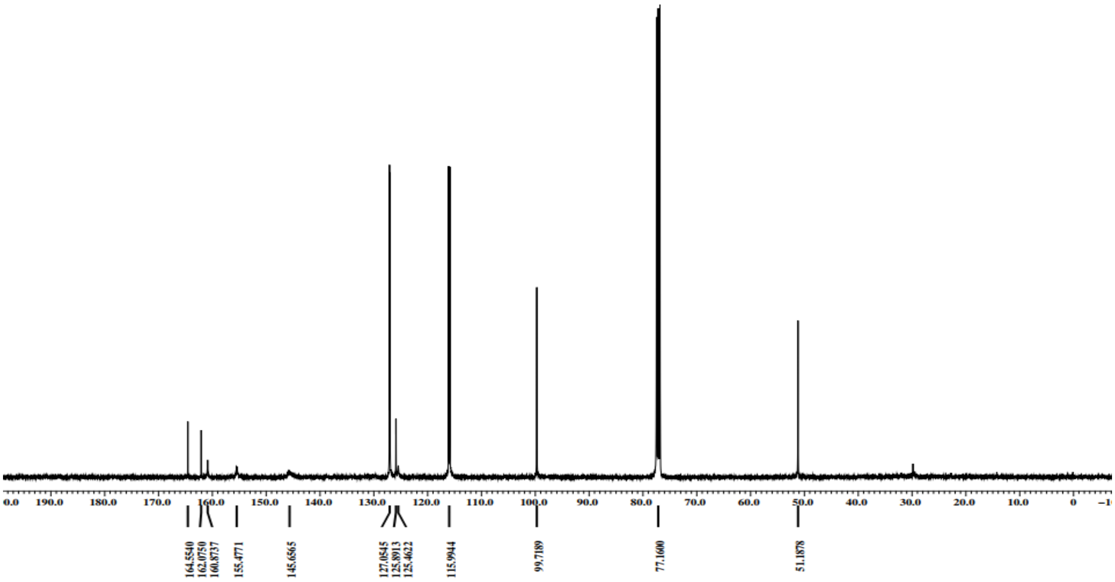
^{1}H NMR (400 MHz, CDCl$_3$)

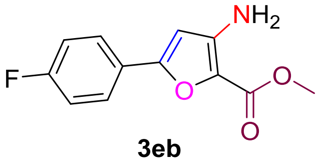




3eb

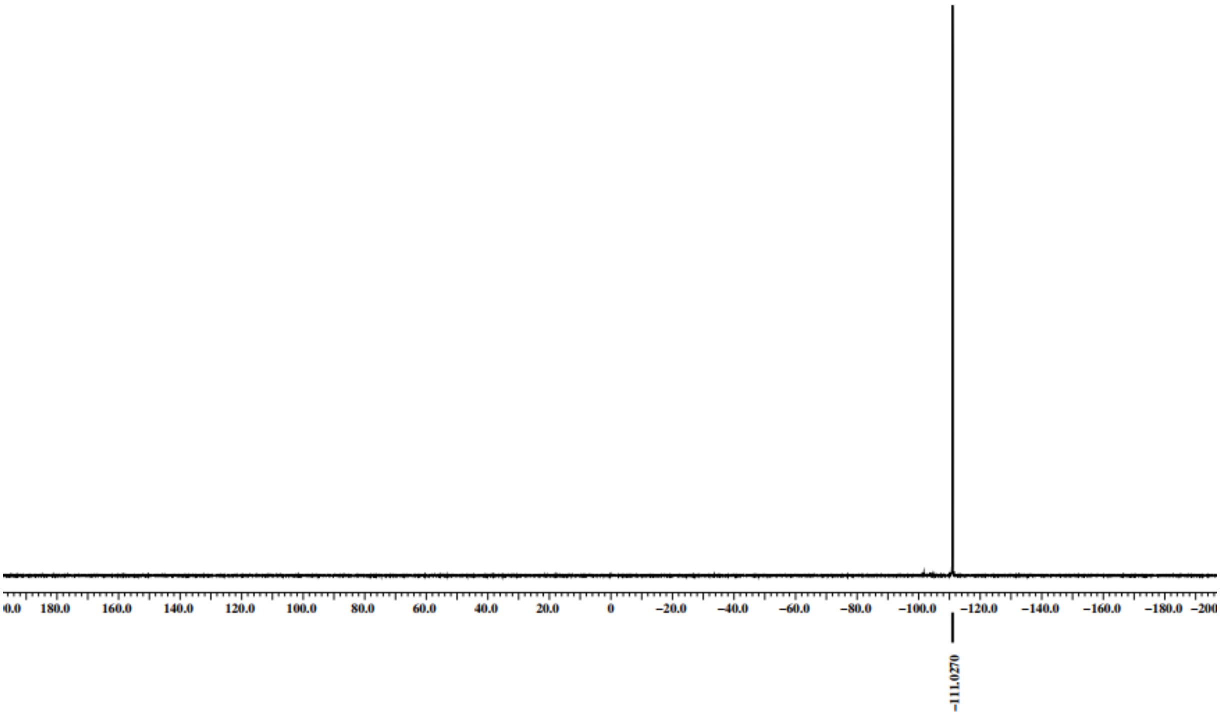
^{13}C NMR (100 MHz, CDCl$_3$)

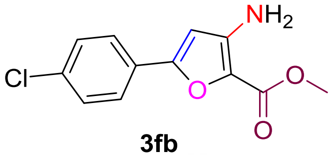




3eb

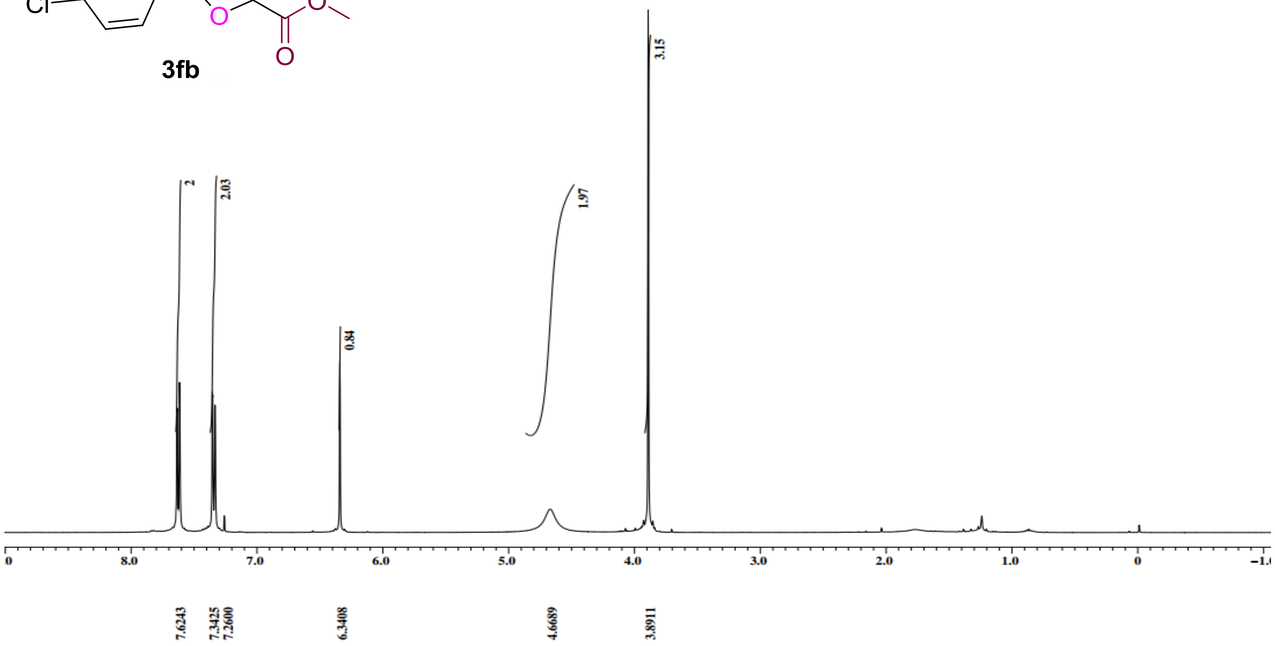
^{19}F NMR (376 MHz, CDCl$_3$)

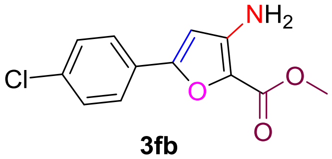




3fb

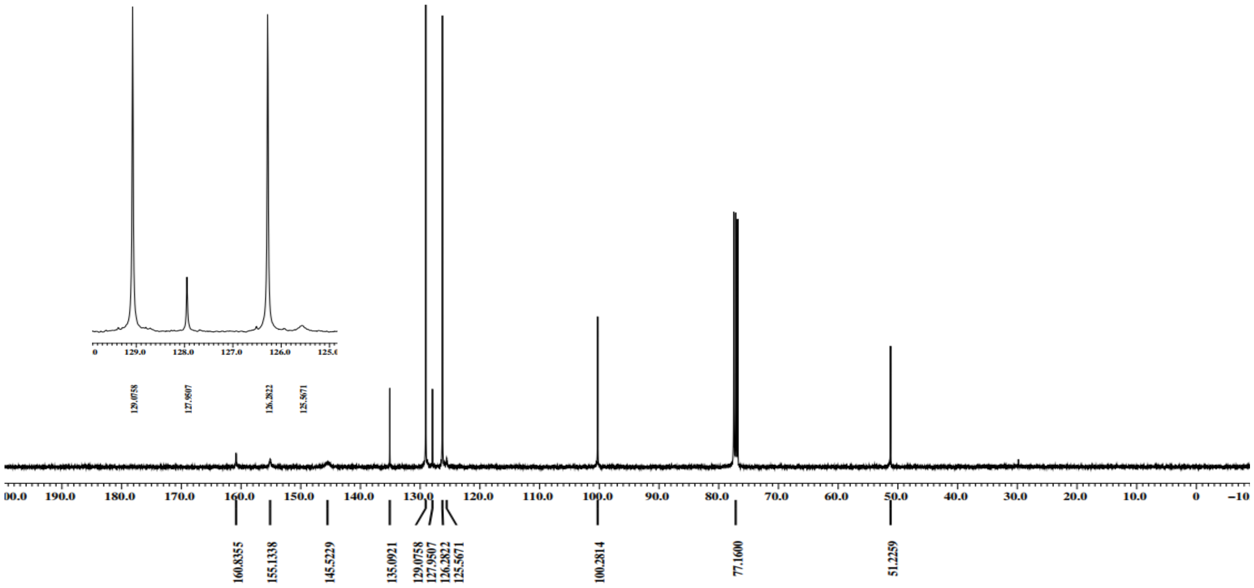
^{1}H NMR (400 MHz, $CDCl_3$)

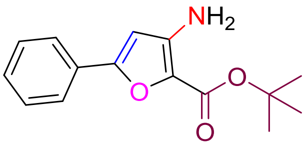




3fb

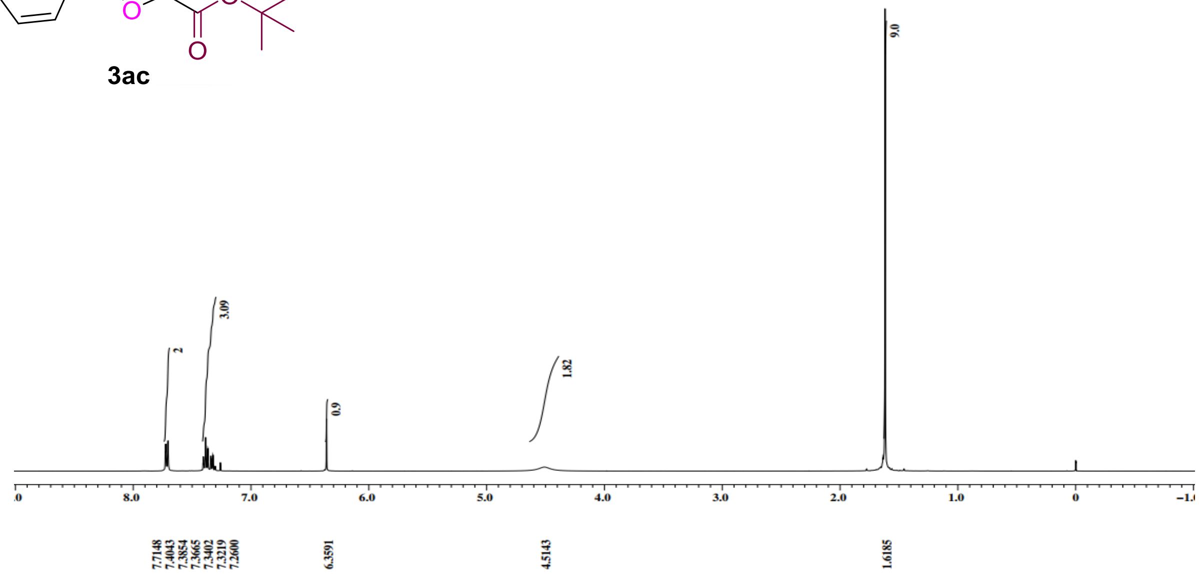
^{13}C NMR (100 MHz, $CDCl_3$)

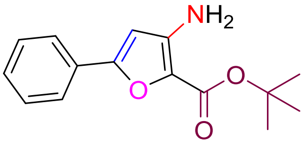




3ac

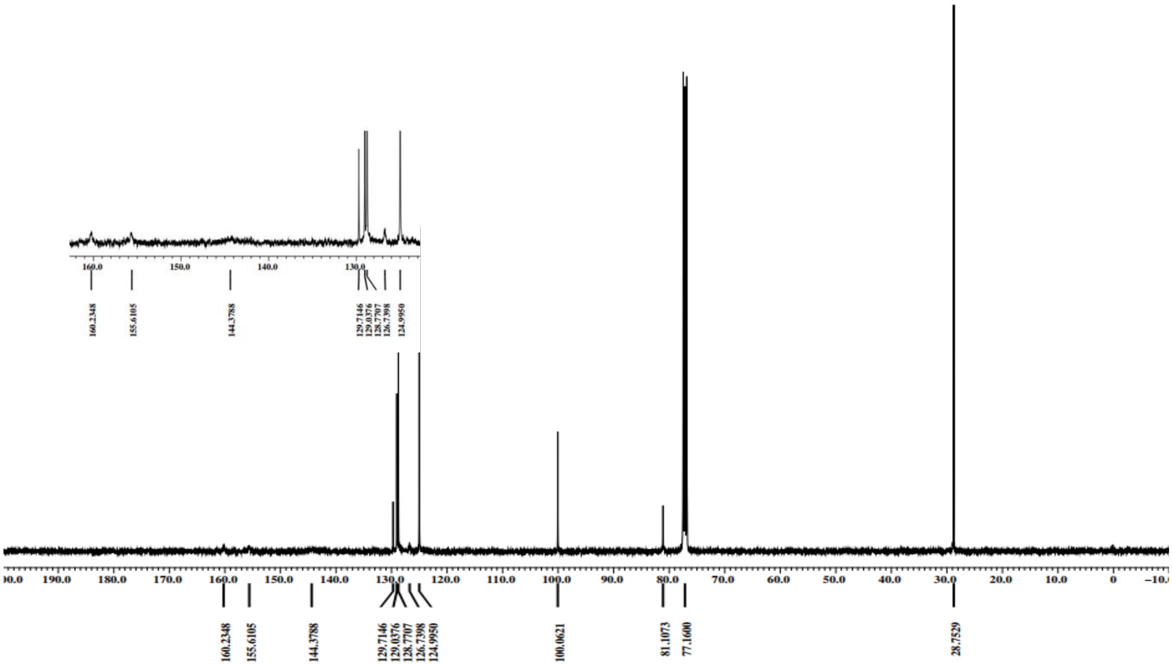
^{1}H NMR (400 MHz, CDCl$_3$)

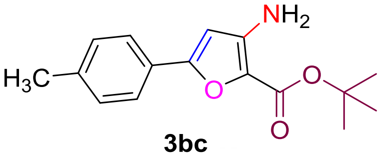




3ac

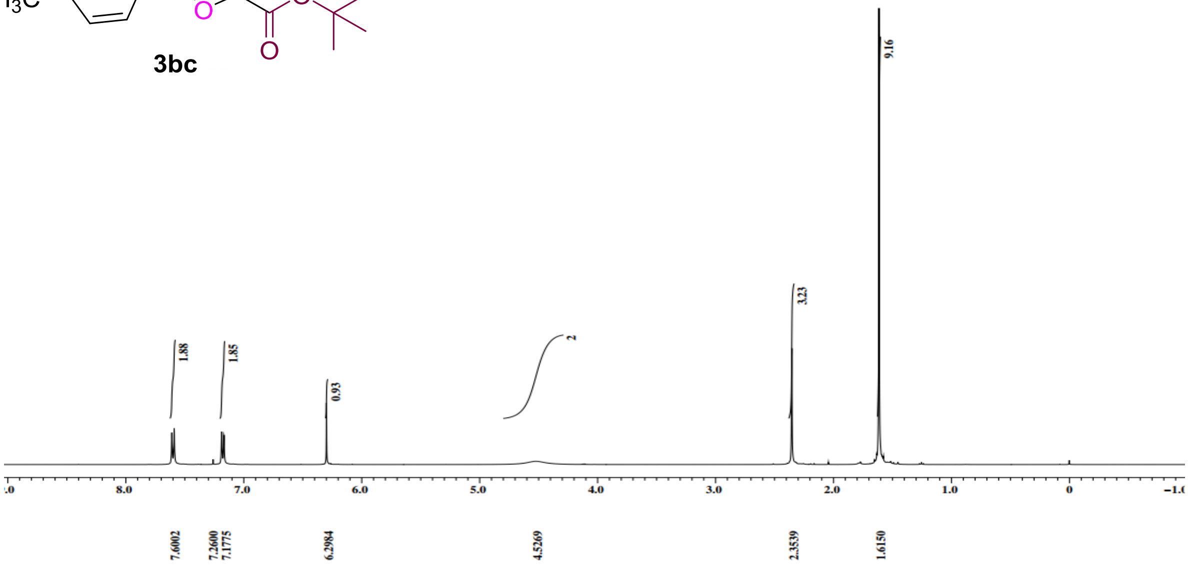
^{13}C NMR (100 MHz, CDCl$_3$)

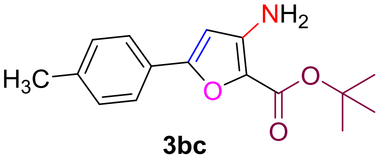




3bc

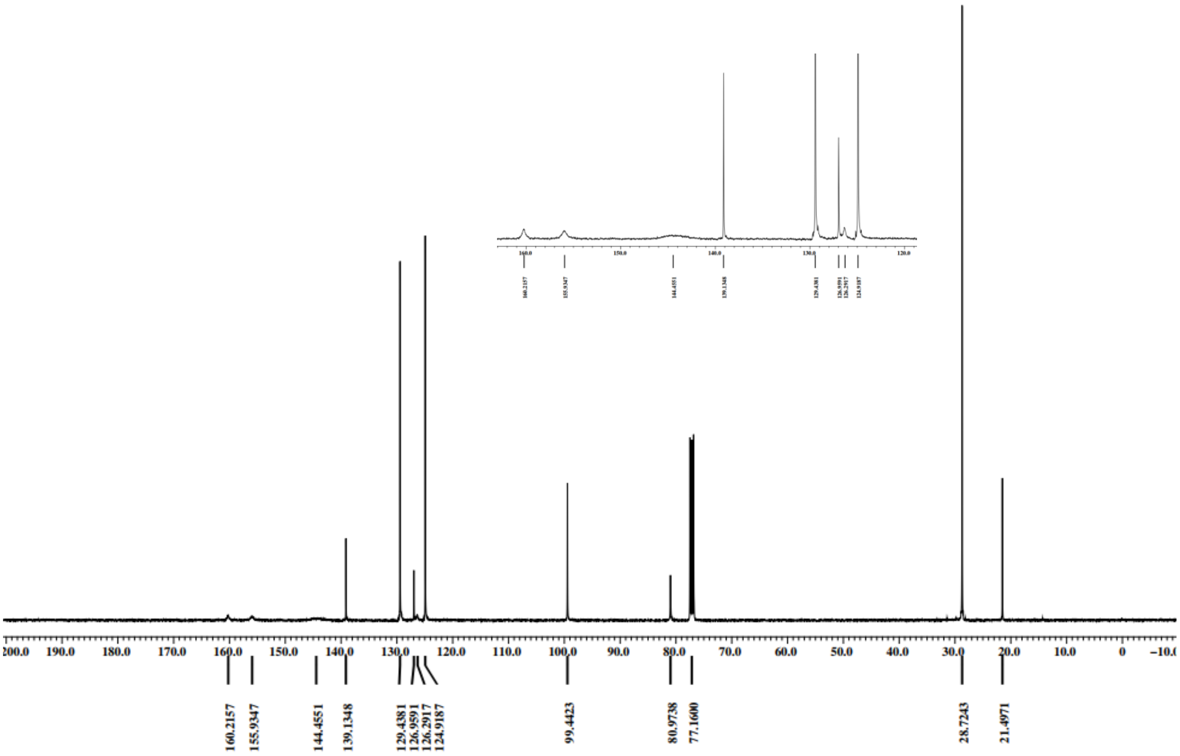
^{1}H NMR (400 MHz, CDCl$_3$)

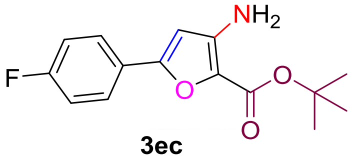




3bc

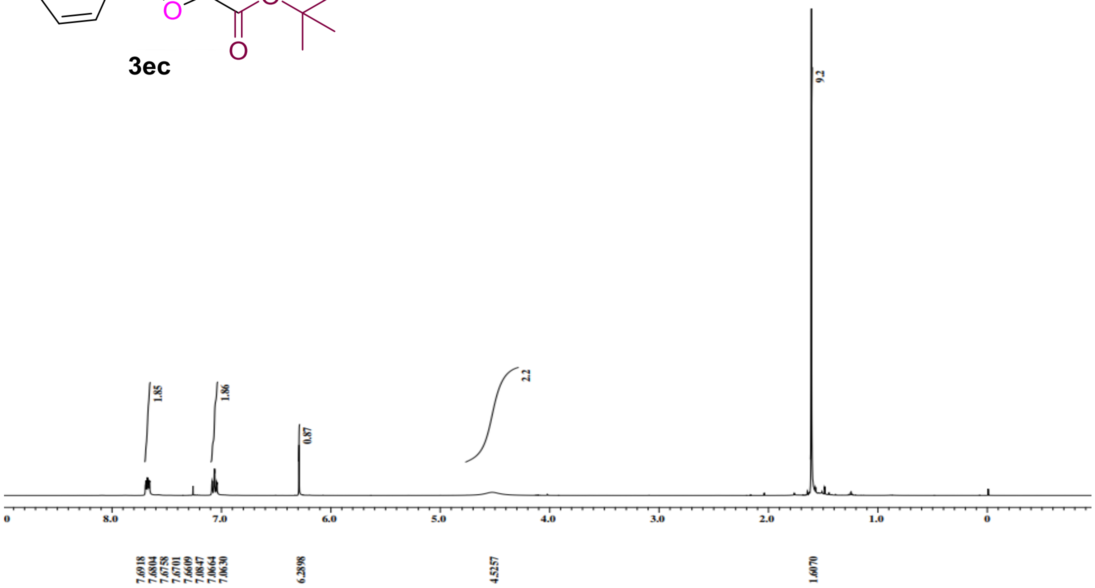
^{13}C NMR (100 MHz, CDCl$_3$)

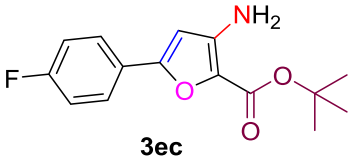




3ec

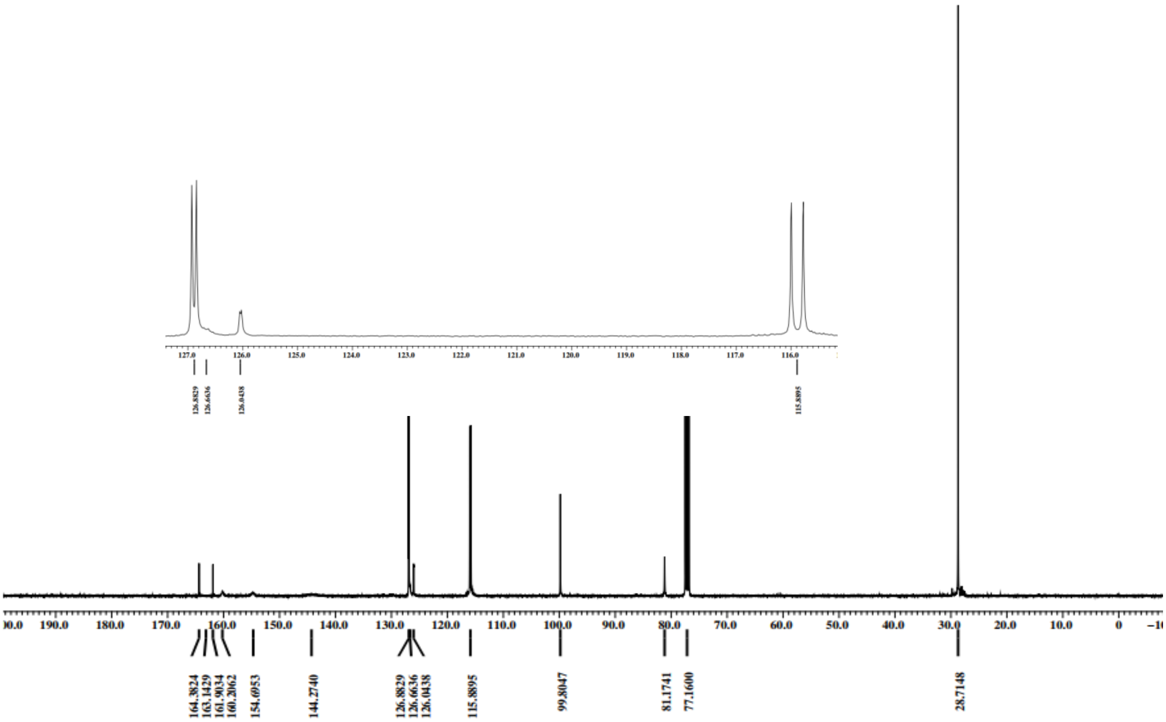
^{1}H NMR (400 MHz, CDCl$_3$)

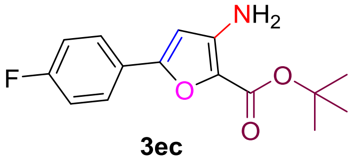




3ec

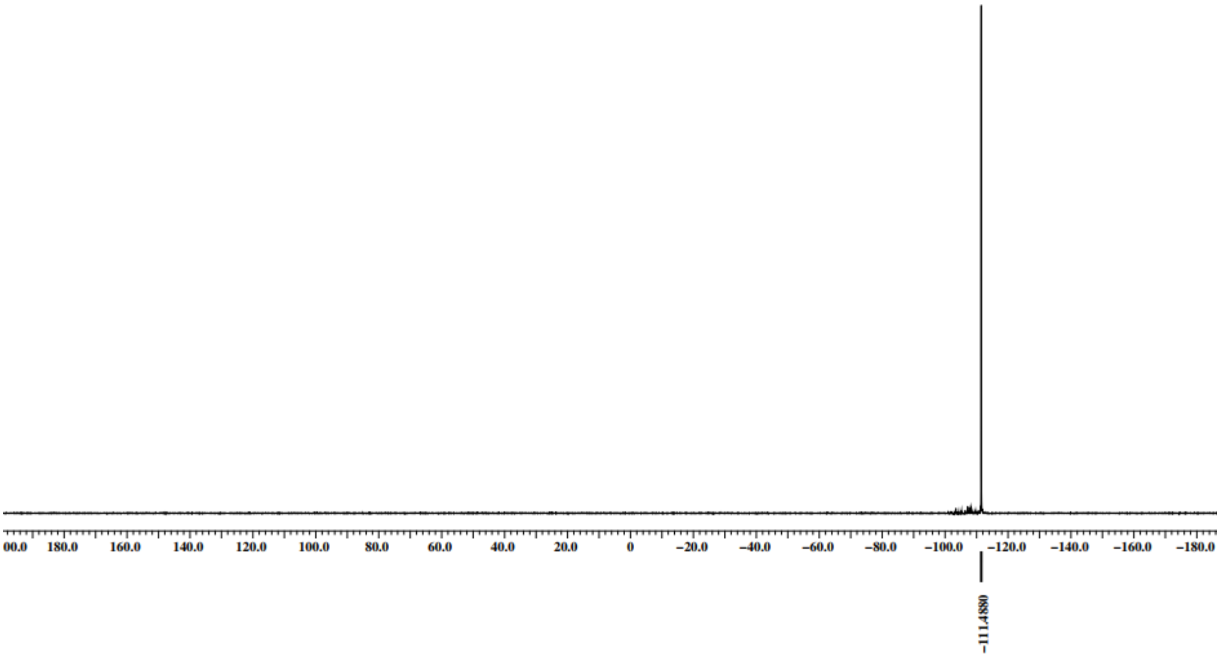
^{13}C NMR (100 MHz, CDCl$_3$)

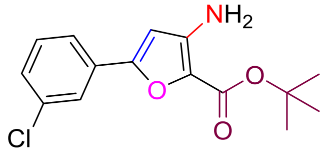




3ec

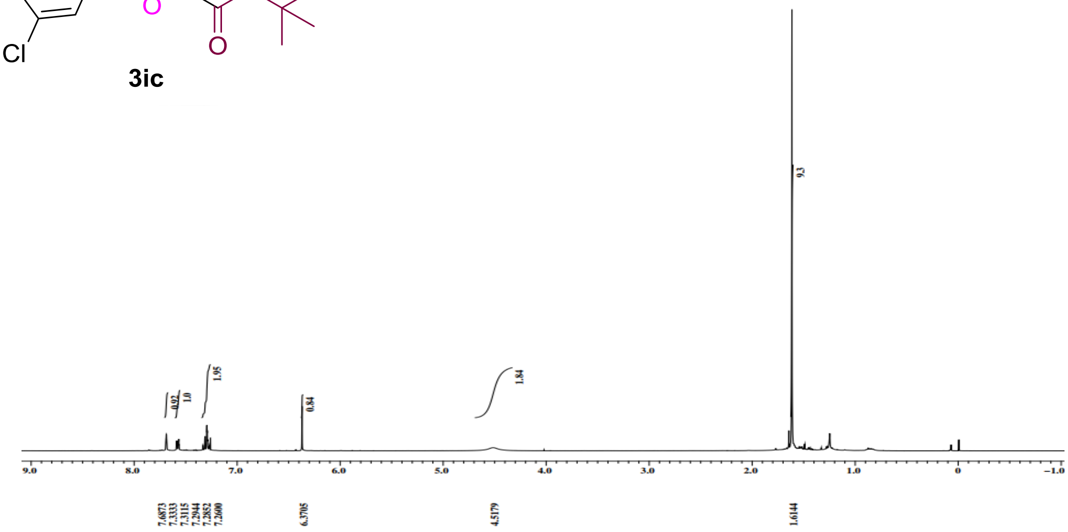
^{19}F NMR (376 MHz, CDCl$_3$)

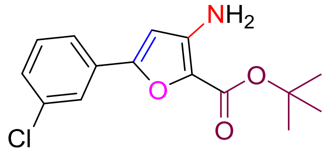




3ic

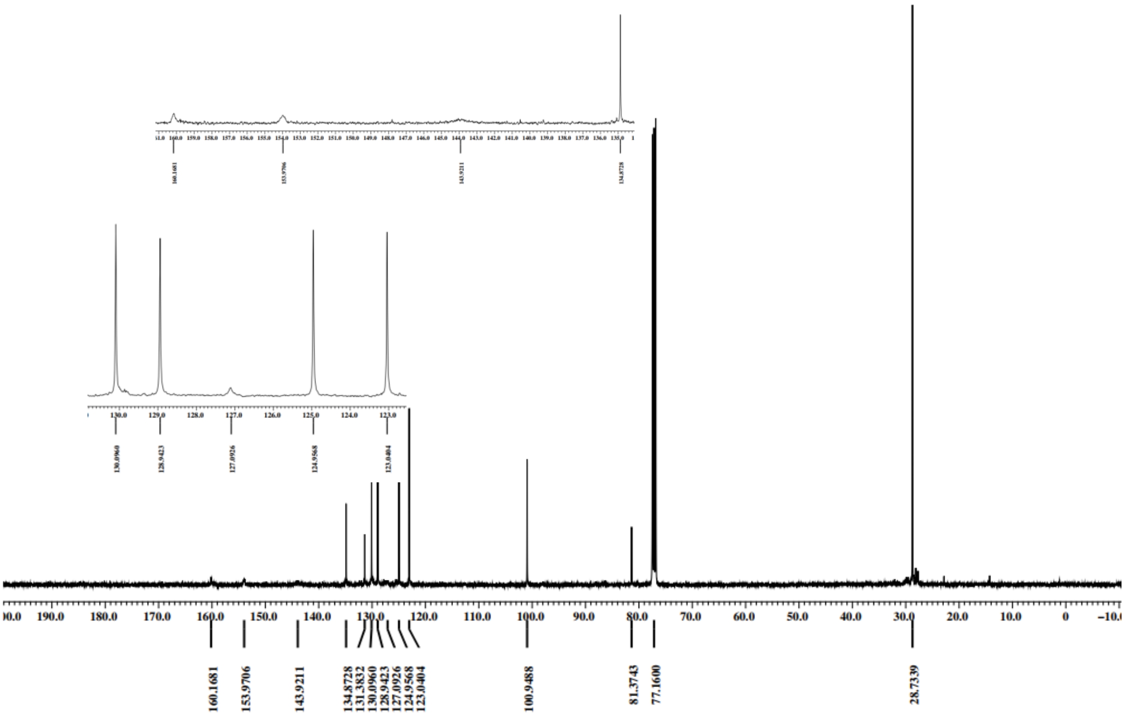
^{1}H NMR (400 MHz, CDCl$_3$)

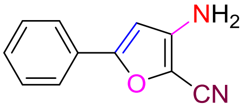




3ic

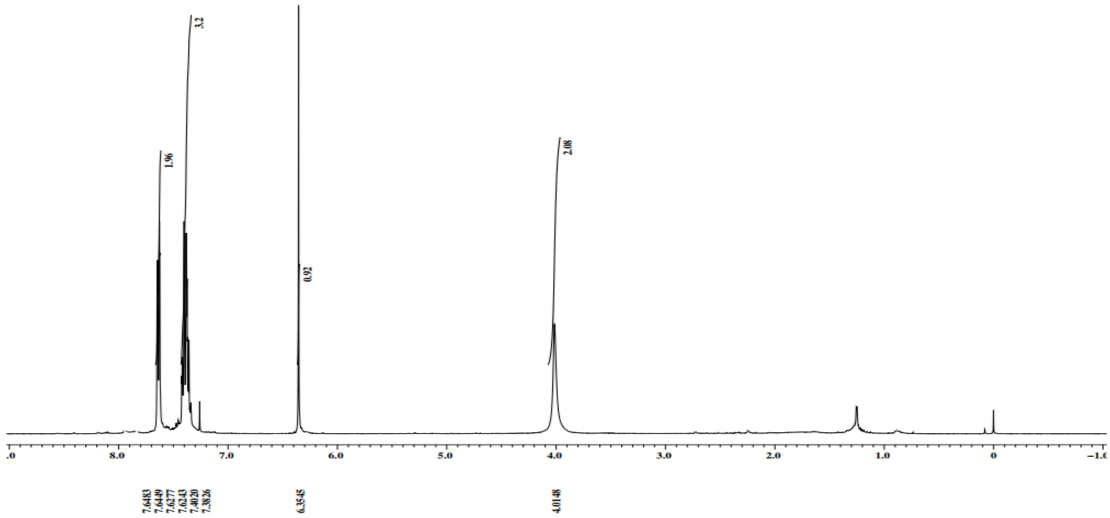
^{13}C NMR (100 MHz, CDCl$_3$)

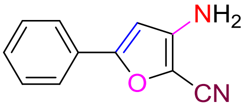




3ad

^{1}H NMR (400 MHz, CDCl$_3$)





3ad

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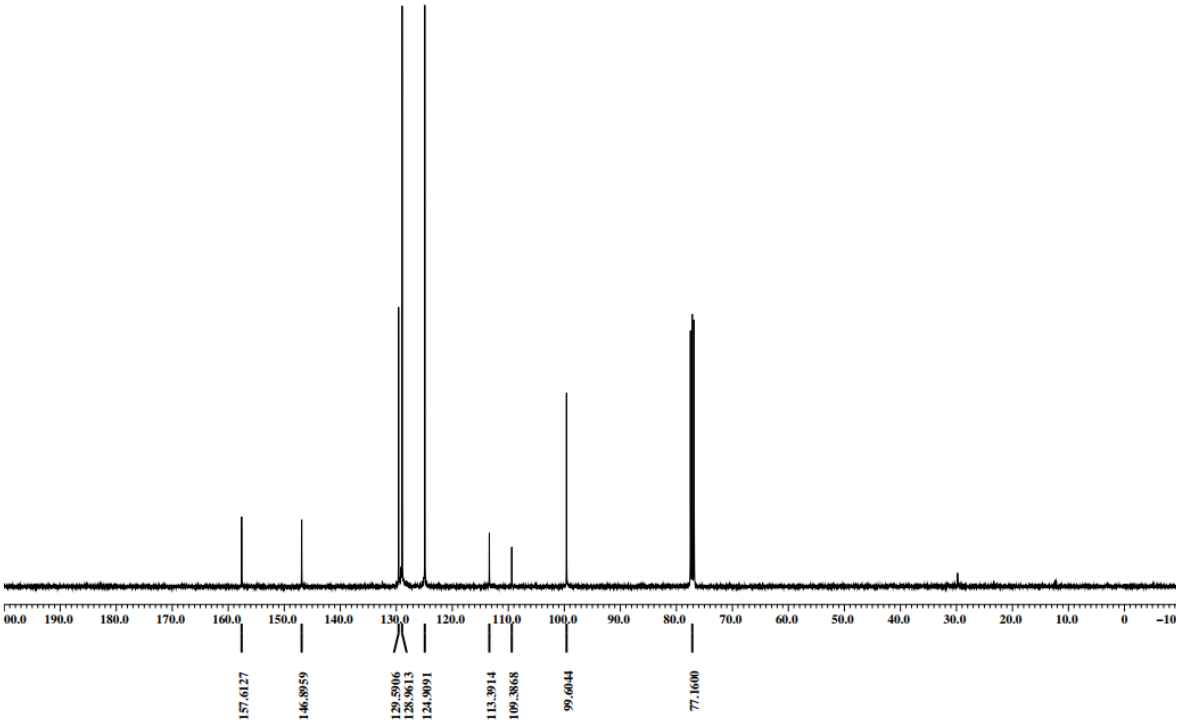
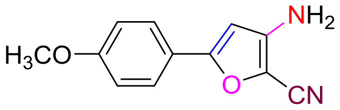
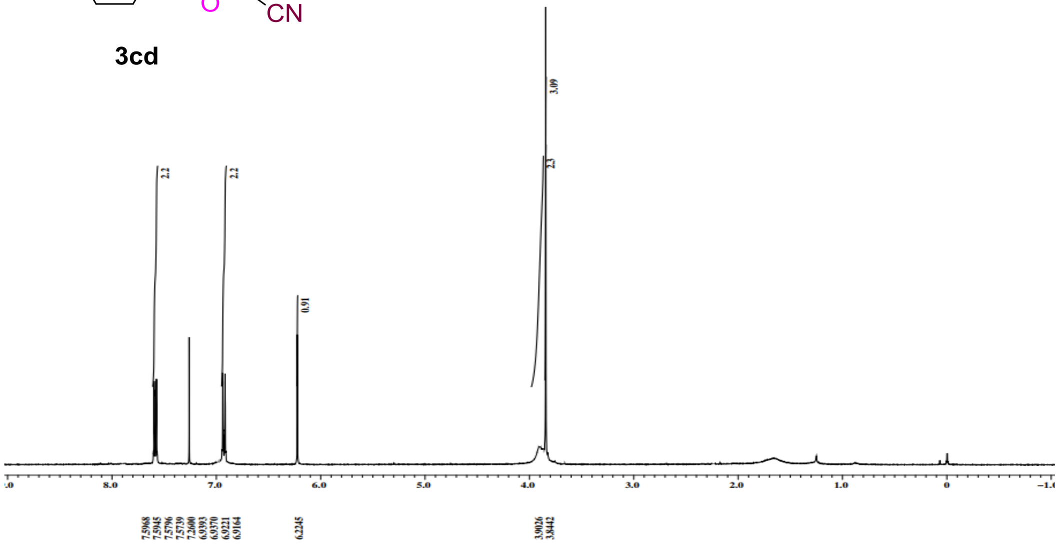
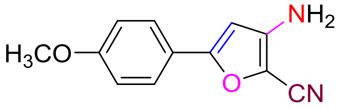




3cd

^{1}H NMR (400 MHz, CDCl$_3$)





3cd

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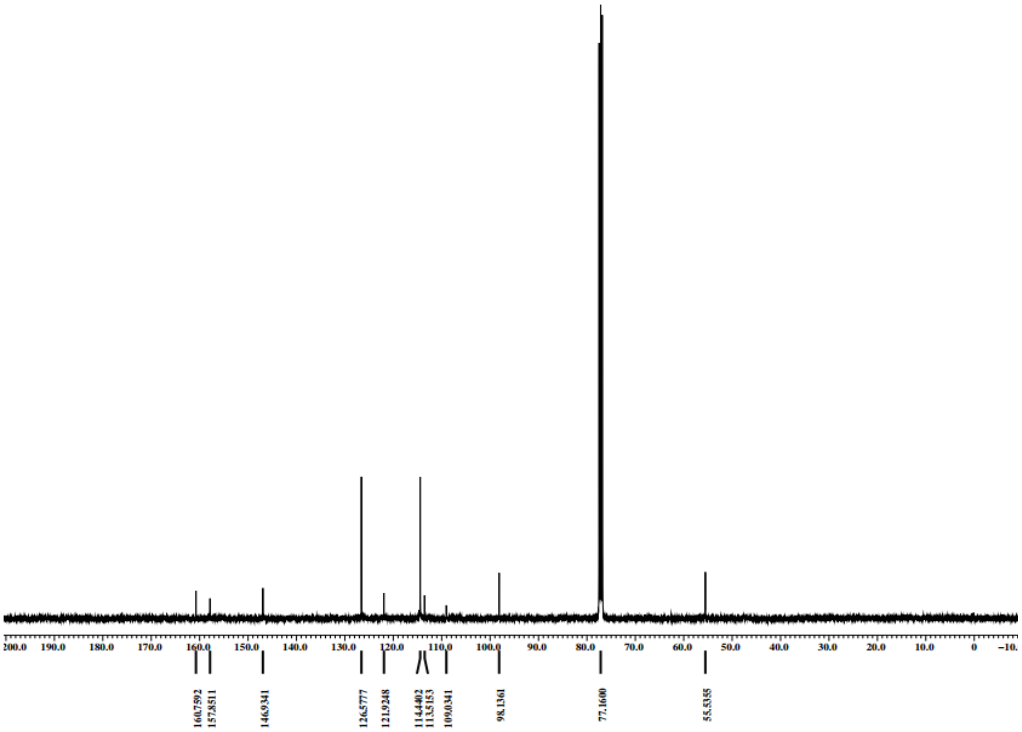

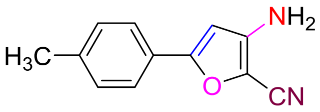

3bd

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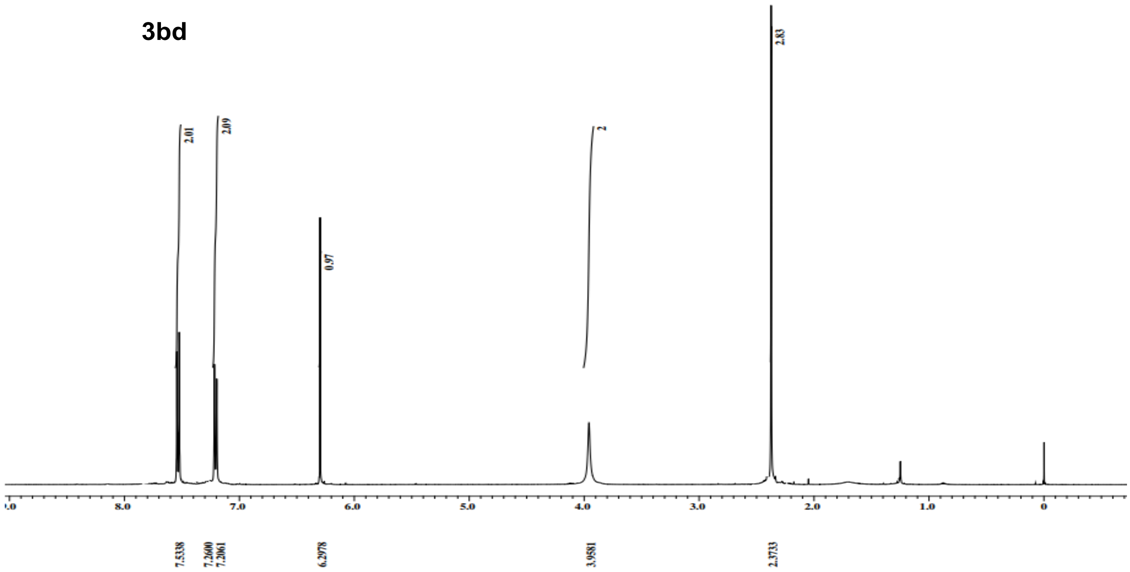
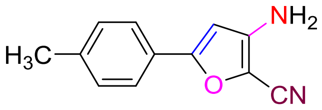
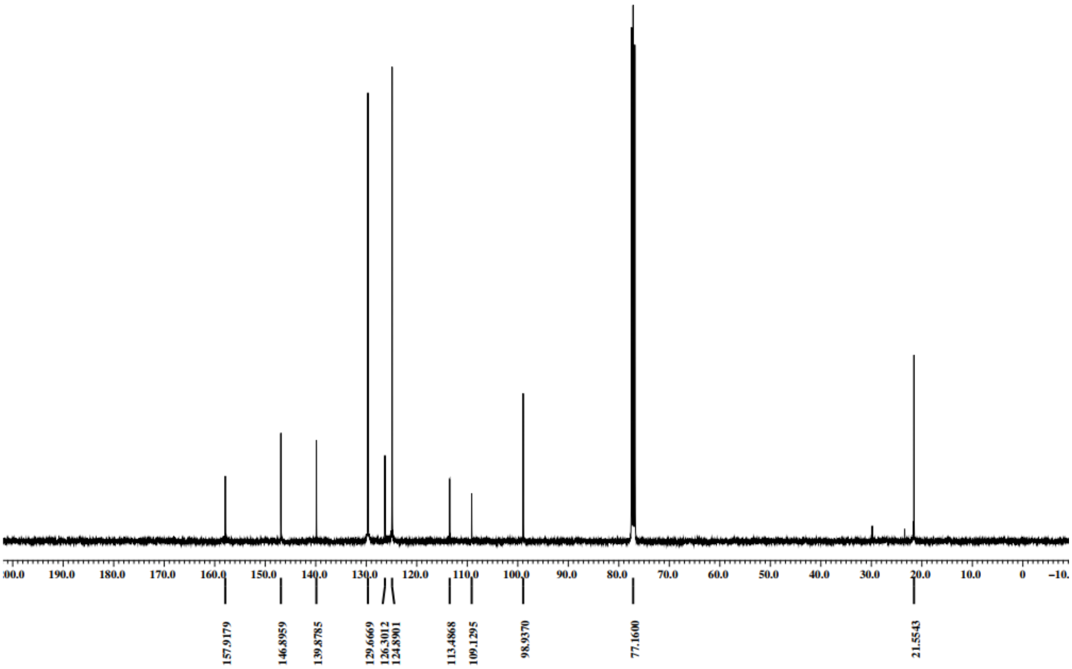
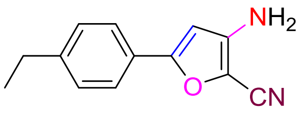




3bd

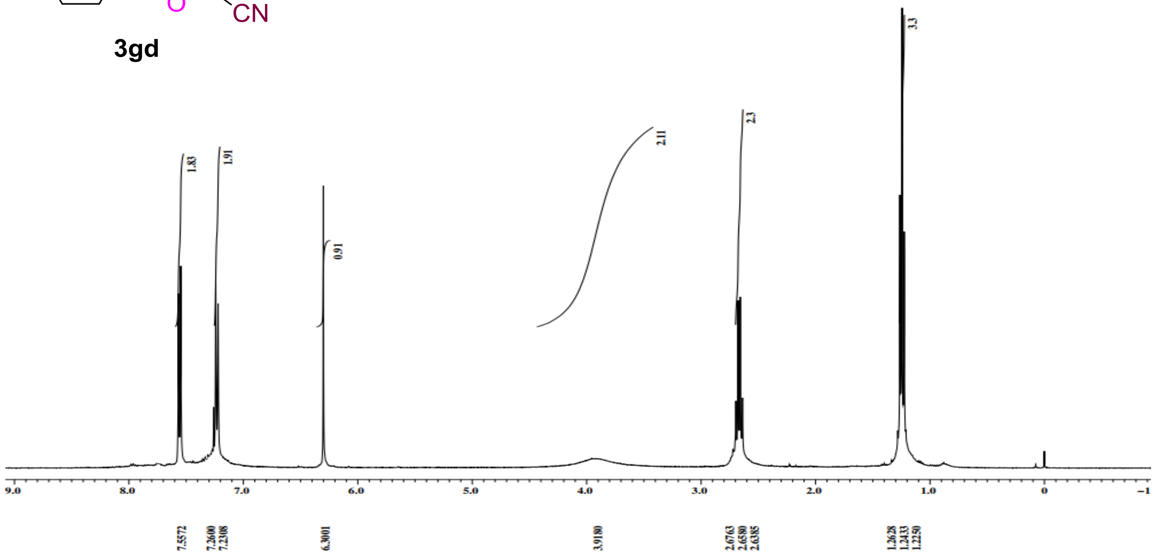
^{13}C NMR (100 MHz, CDCl$_3$)

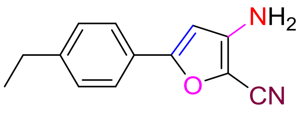




3gd

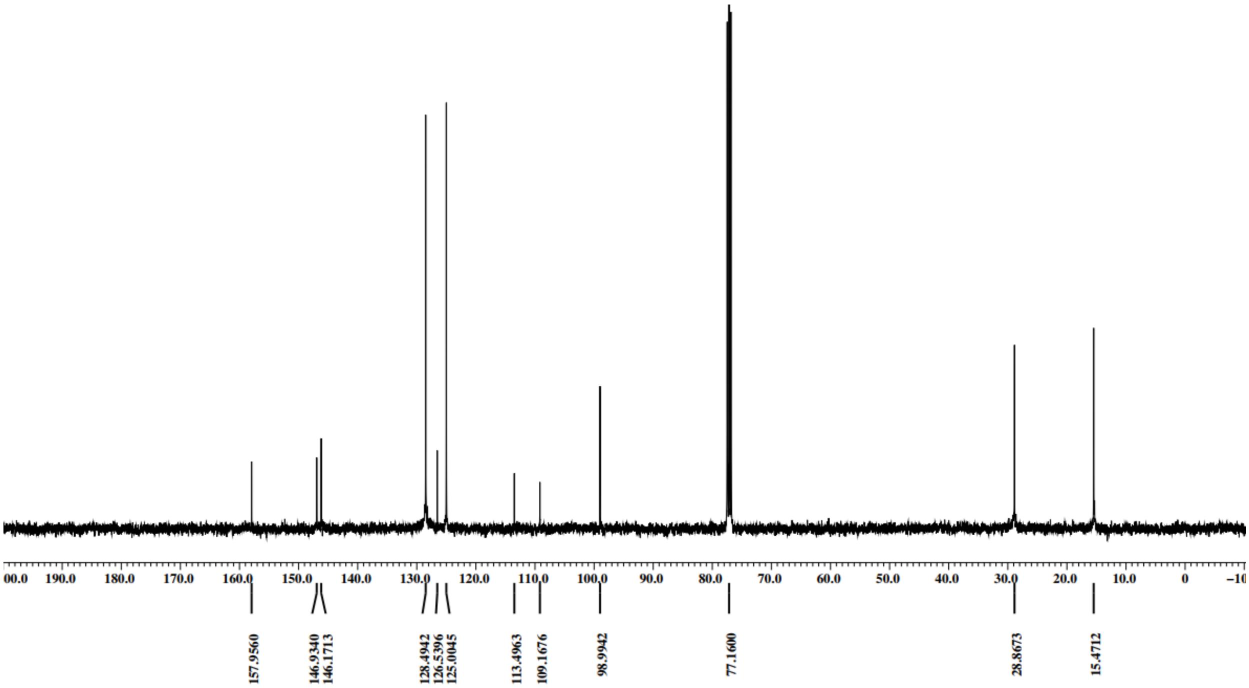
^{1}H NMR (400 MHz, CDCl$_3$)

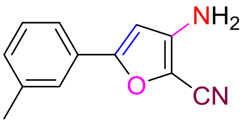




3gd

^{13}C NMR (100 MHz, CDCl$_3$)





3kd

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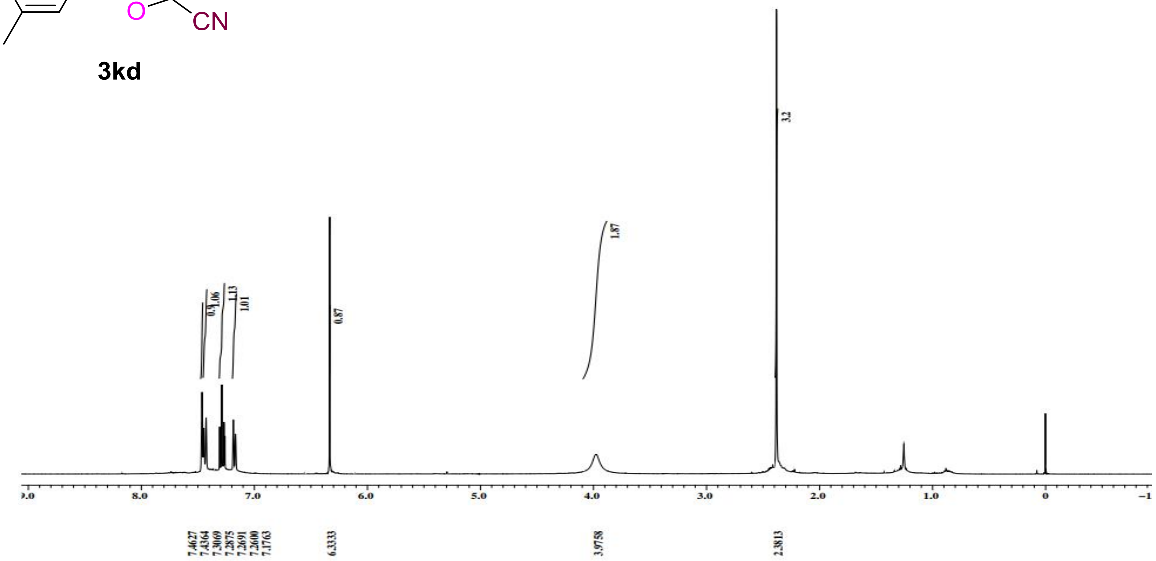

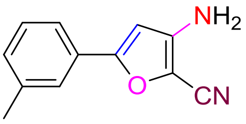

3kd

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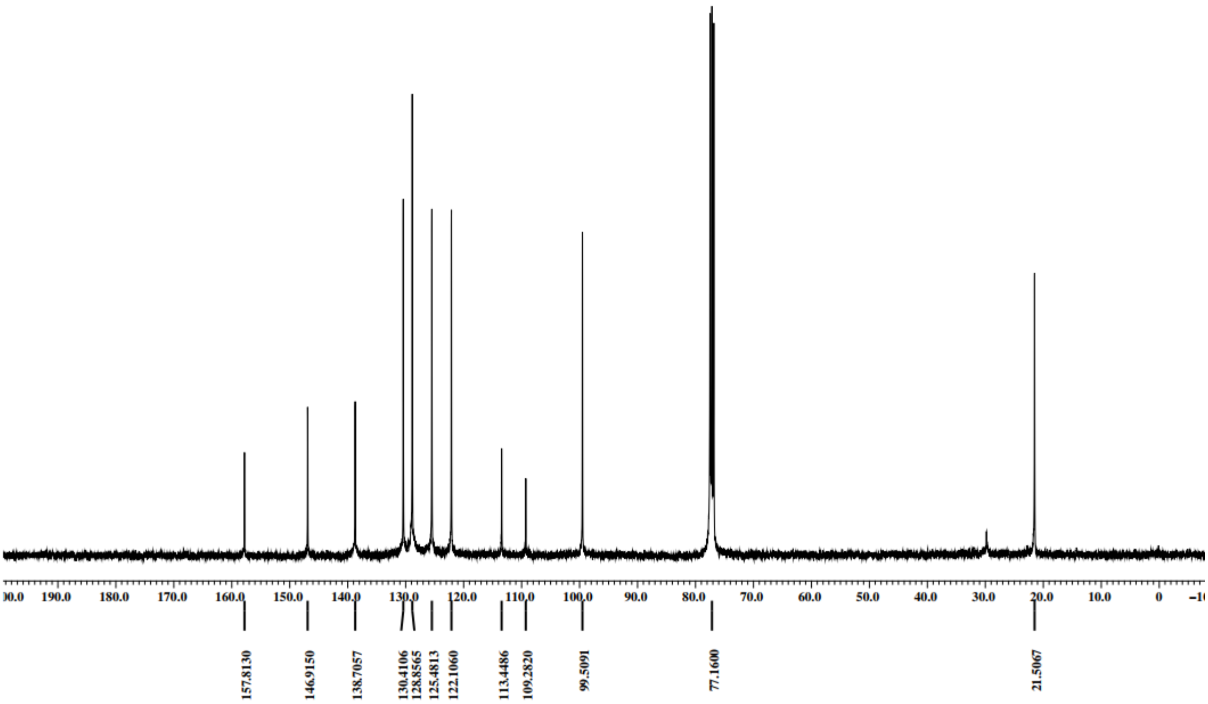
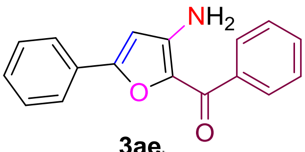
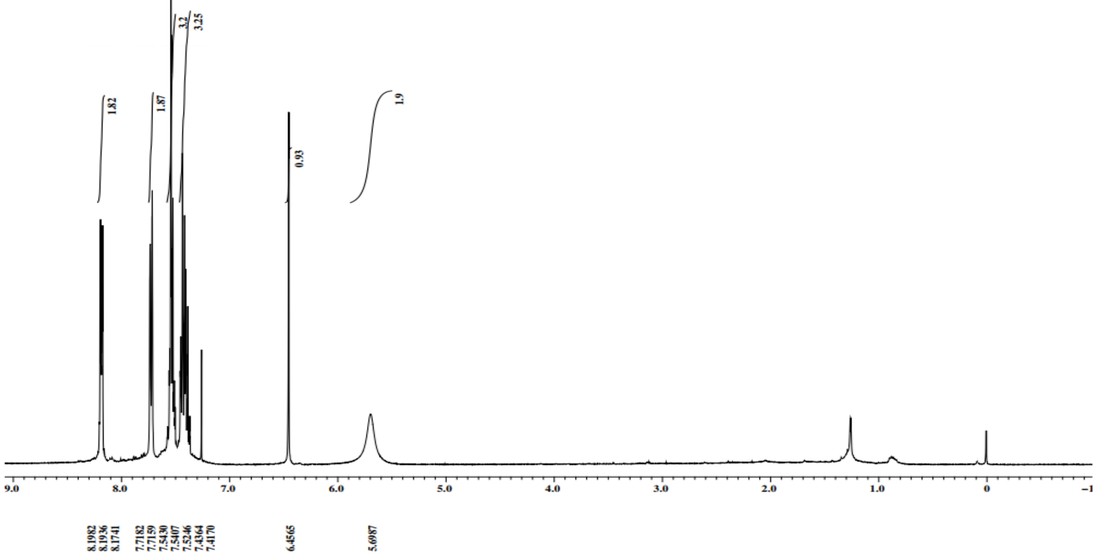
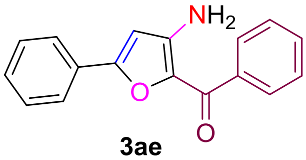




3ae

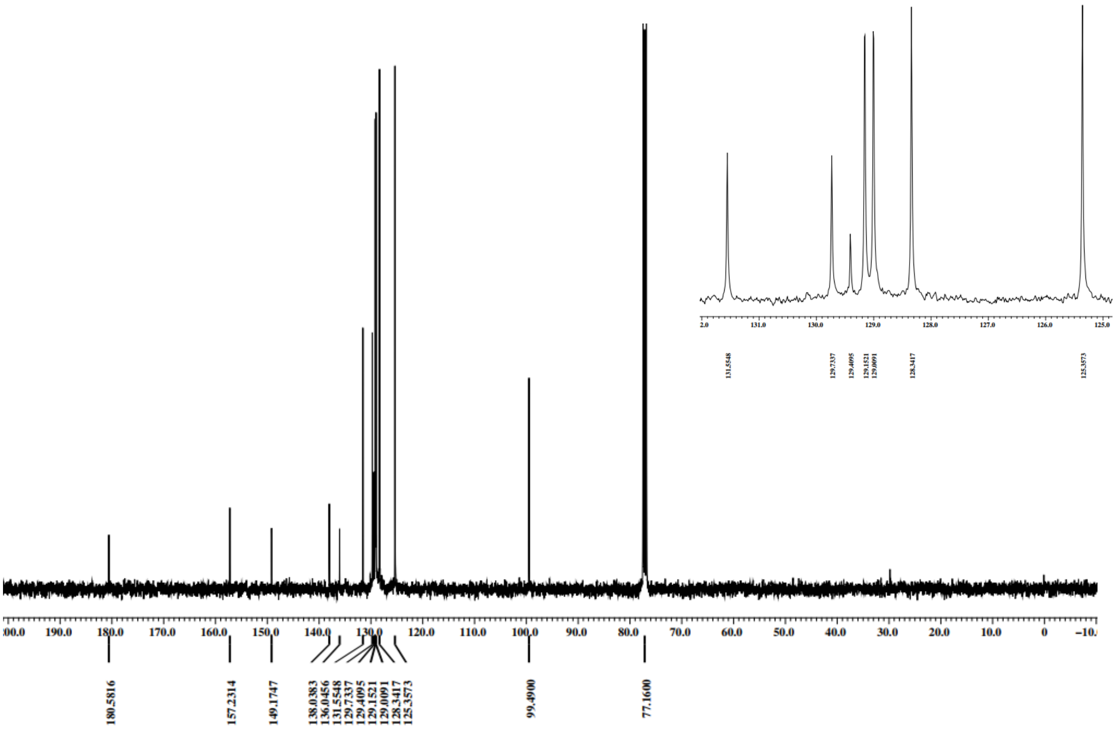
^{1}H NMR (400 MHz, CDCl$_3$)

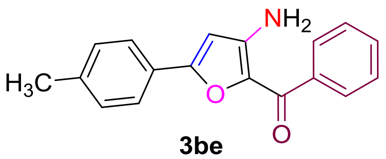




3ae

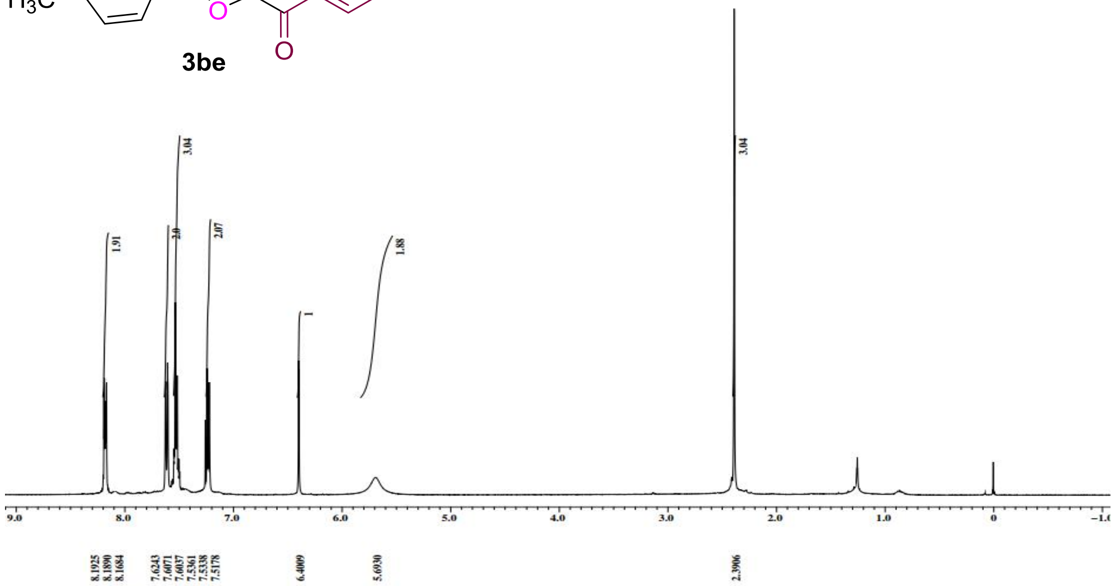
^{13}C NMR (100 MHz, CDCl$_3$)

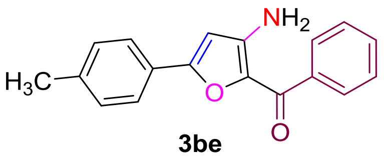




3be

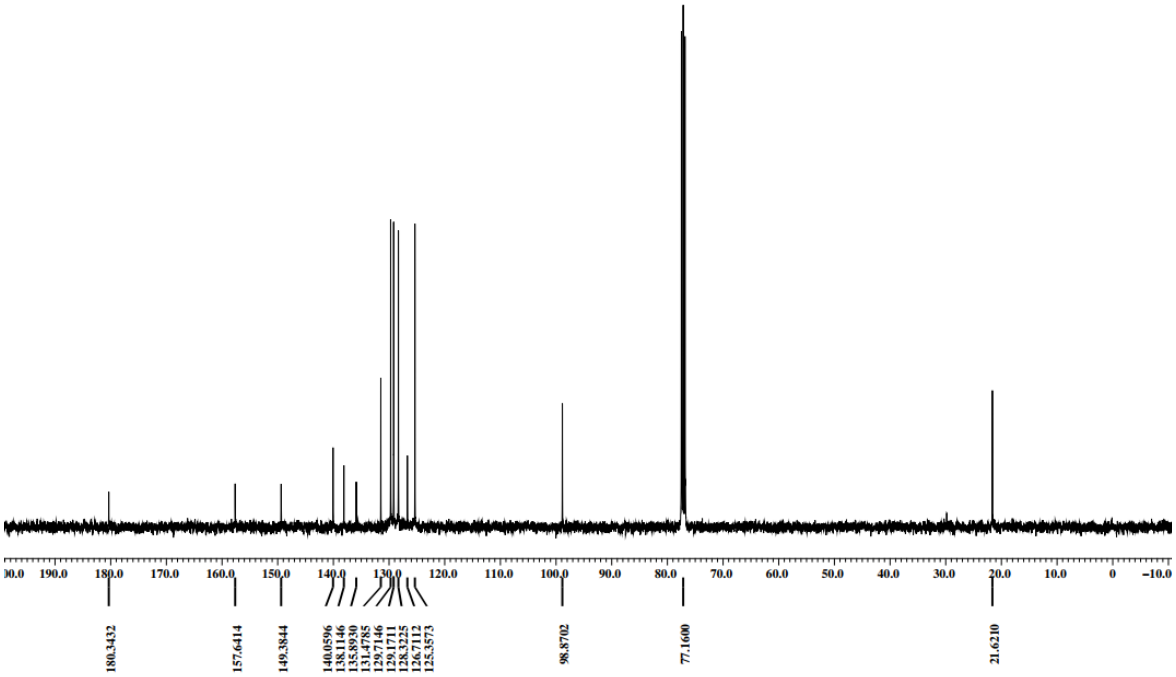
^{1}H NMR (400 MHz, CDCl$_3$)

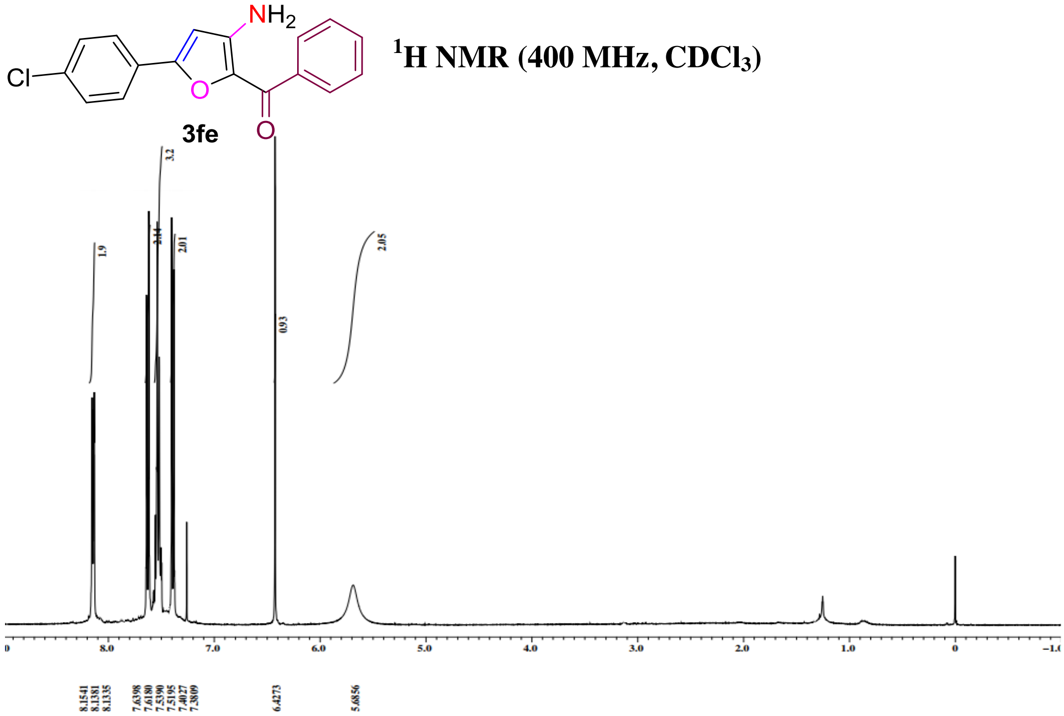




3be

^{13}C NMR (100 MHz, CDCl$_3$)





3fe

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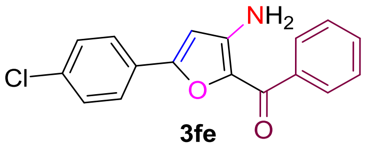

3fe

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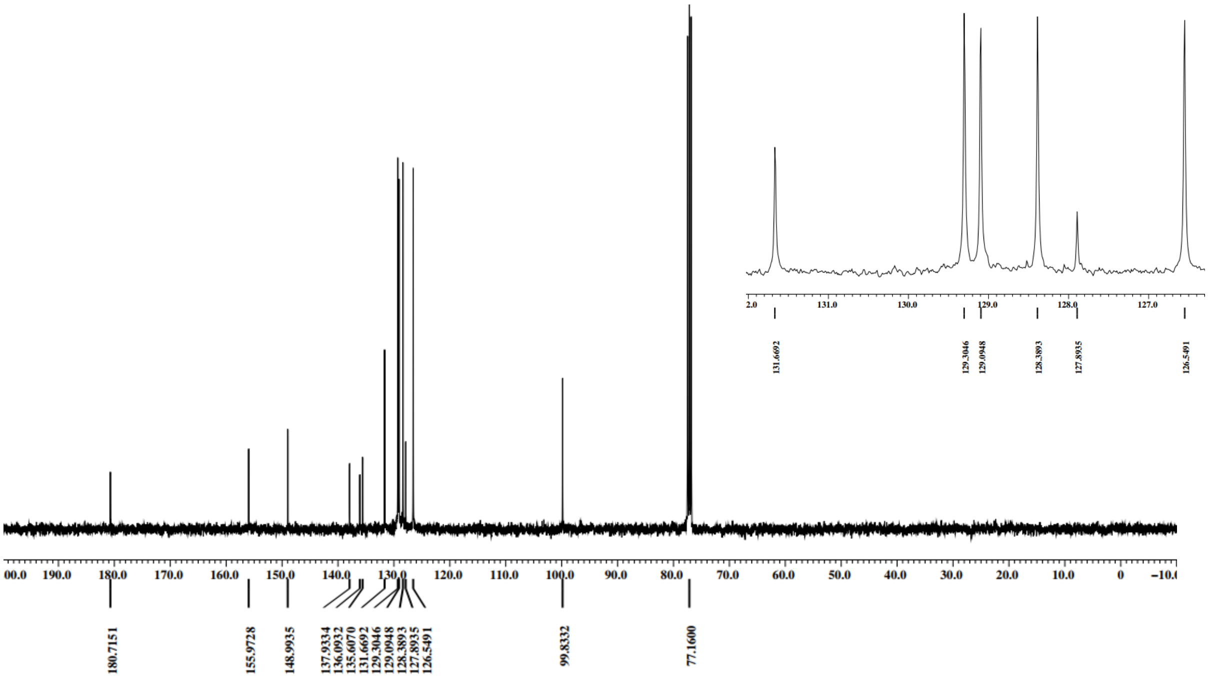
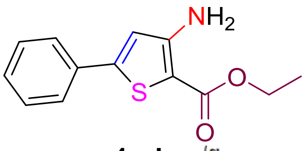
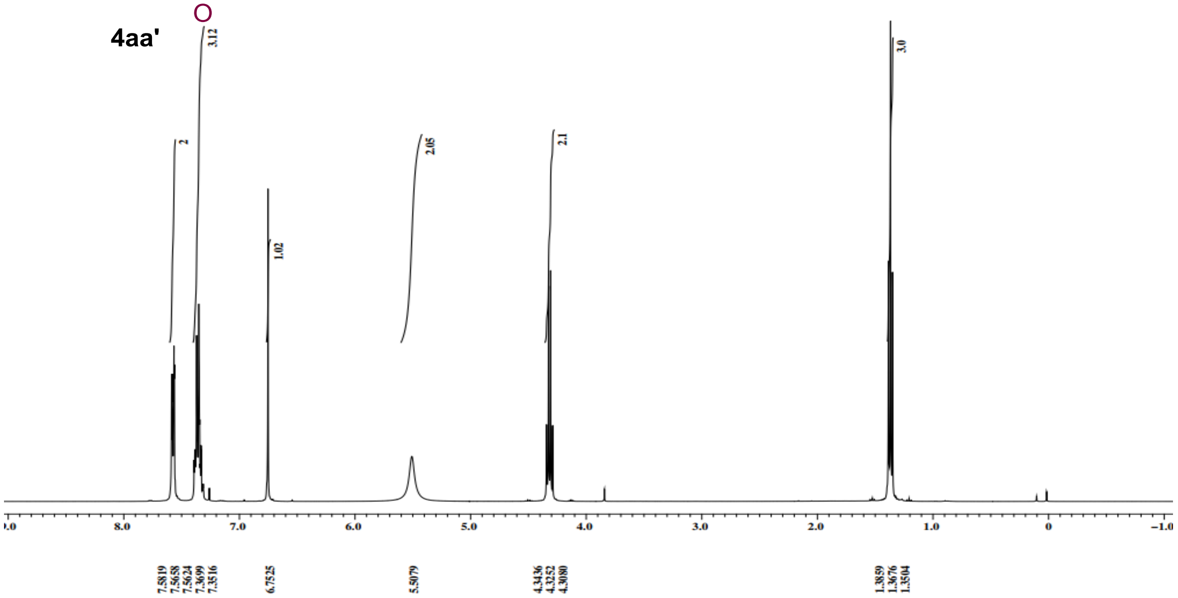
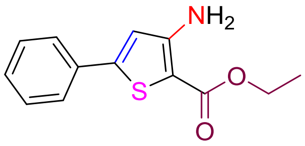




4aa'

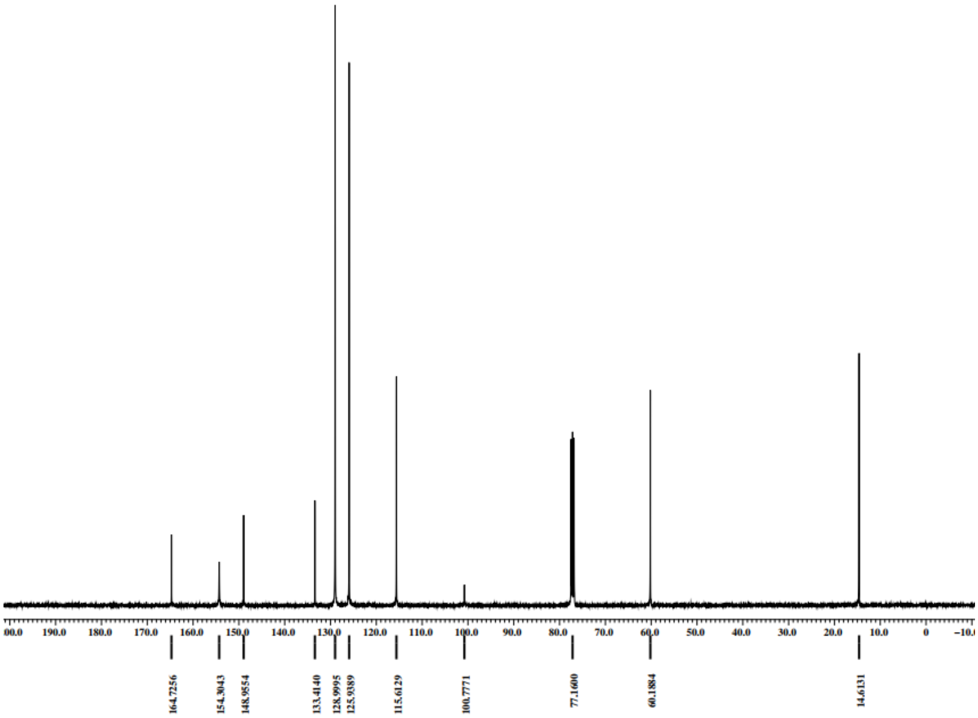
^{1}H NMR (400 MHz, CDCl$_3$)

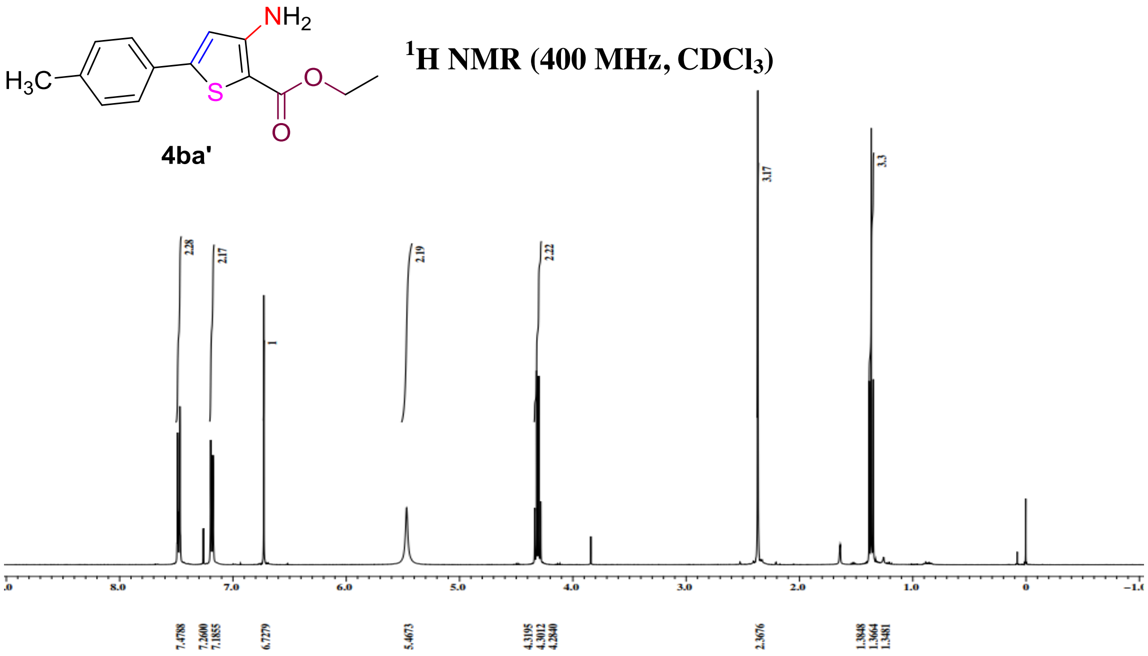




4aa'

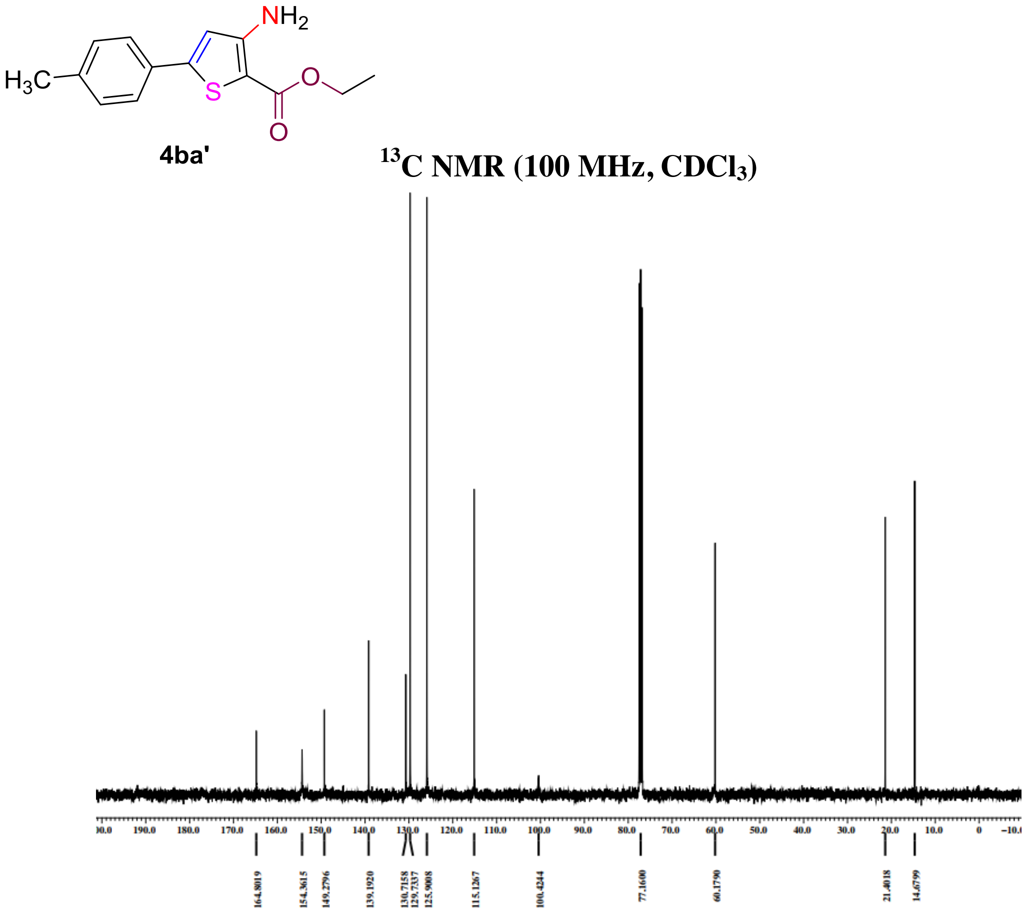
^{13}C NMR (100 MHz, CDCl$_3$)





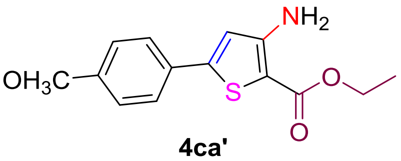
4ba'

^{1}H NMR (400 MHz, CDCl$_3$)



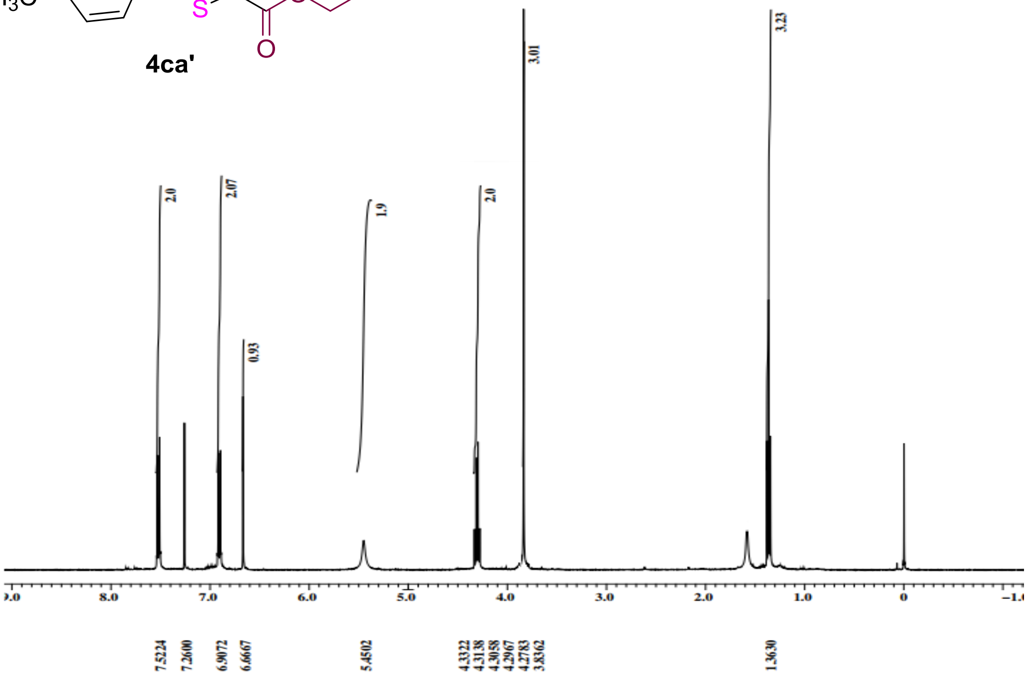
4ba'

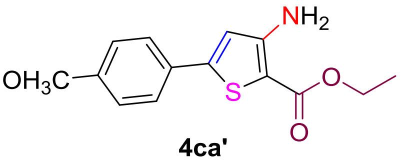
^{13}C NMR (100 MHz, CDCl$_3$)



4ca'

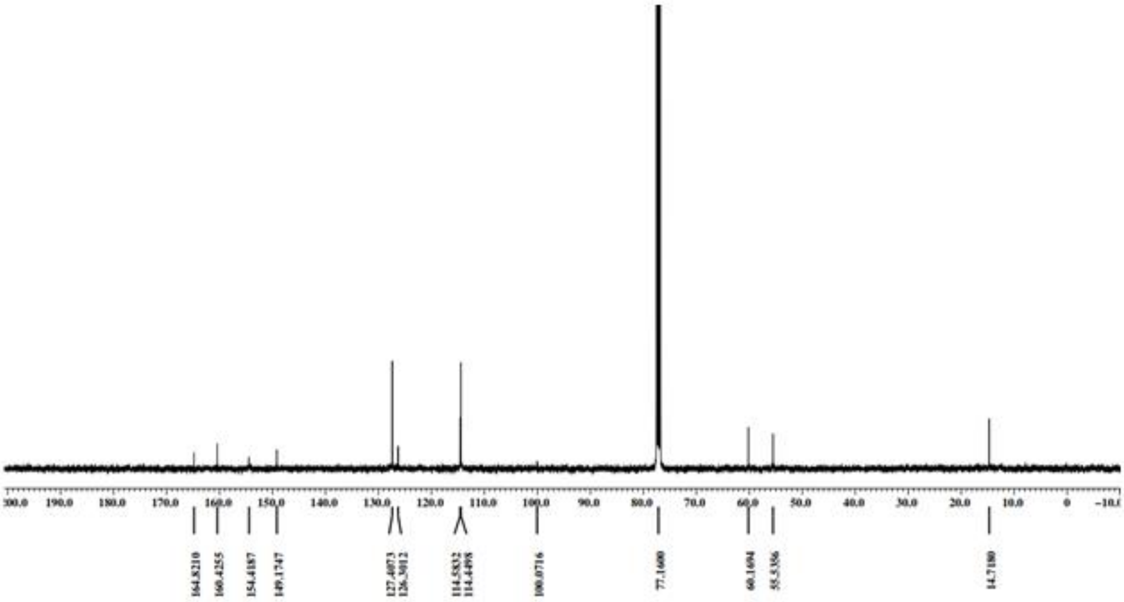
^{1}H NMR (400 MHz, $CDCl_3$)

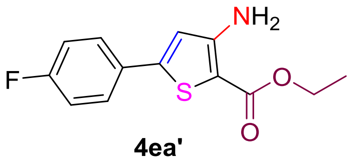




4ca'

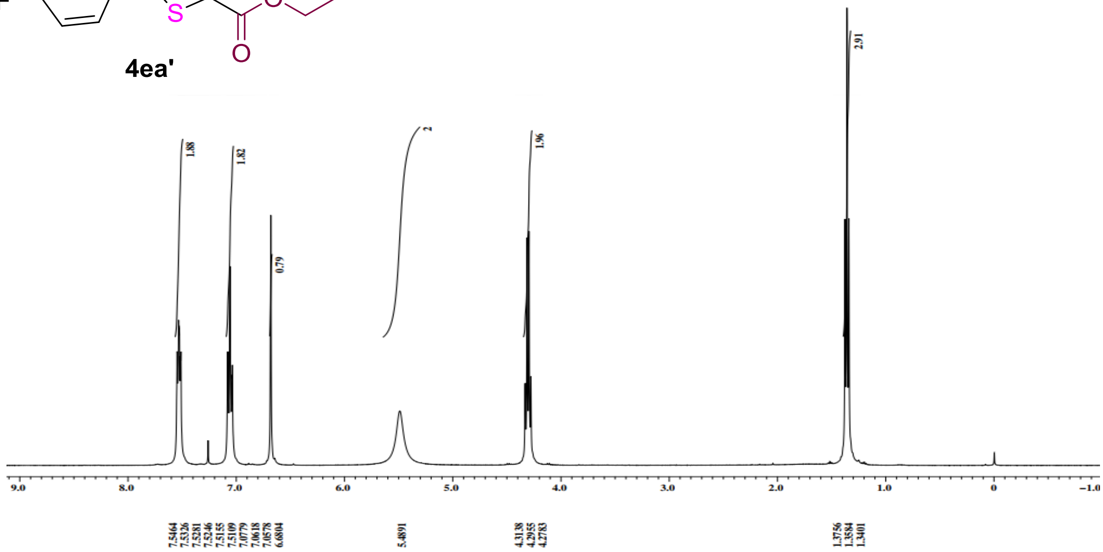
^{13}C NMR (100 MHz, $CDCl_3$)

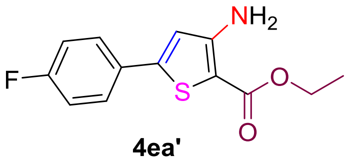




4ea'

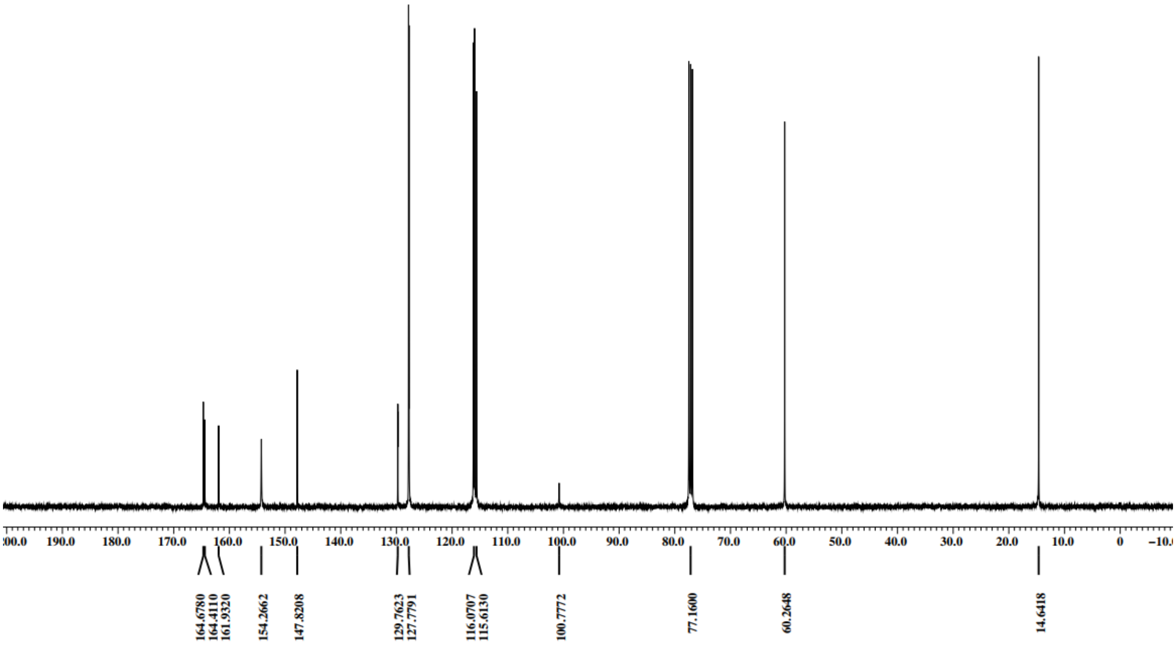
^{1}H NMR (400 MHz, CDCl$_3$)

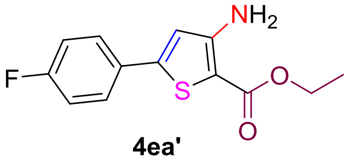




4ea'

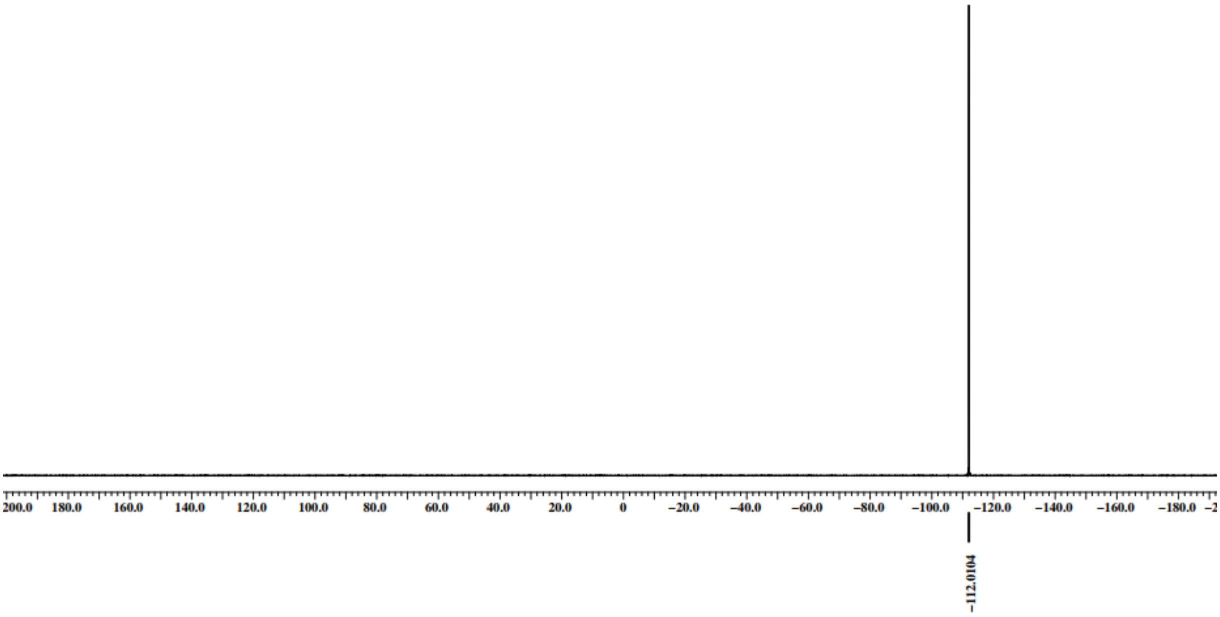
^{13}C NMR (100 MHz, CDCl$_3$)

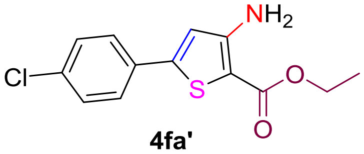




4ea'

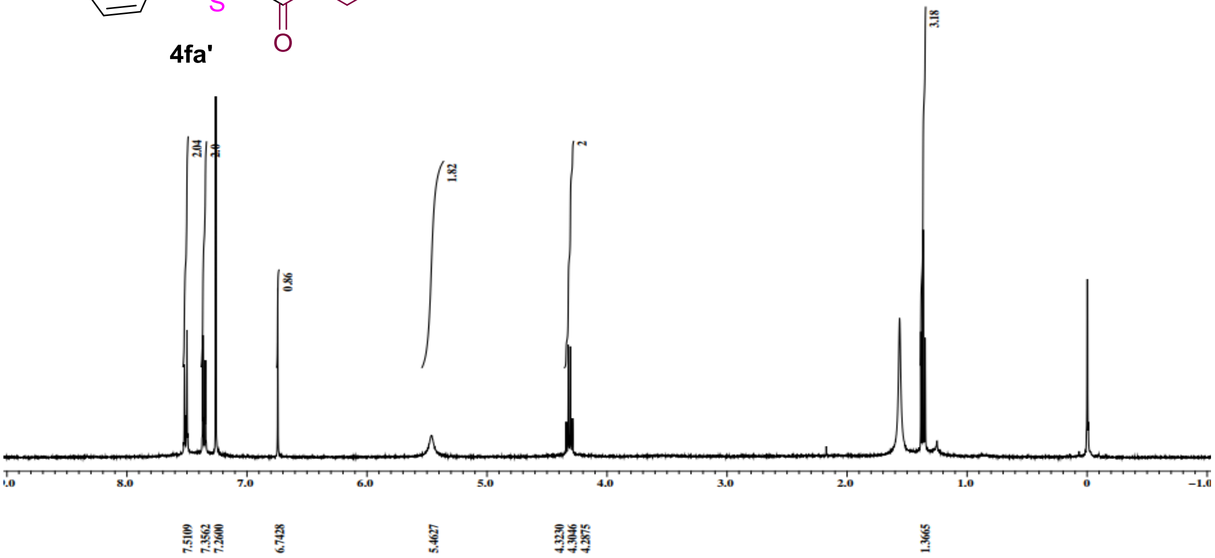
^{19}F NMR (376 MHz, CDCl$_3$)

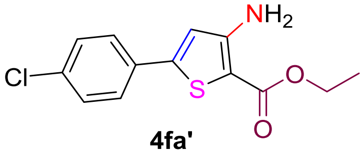




4fa'

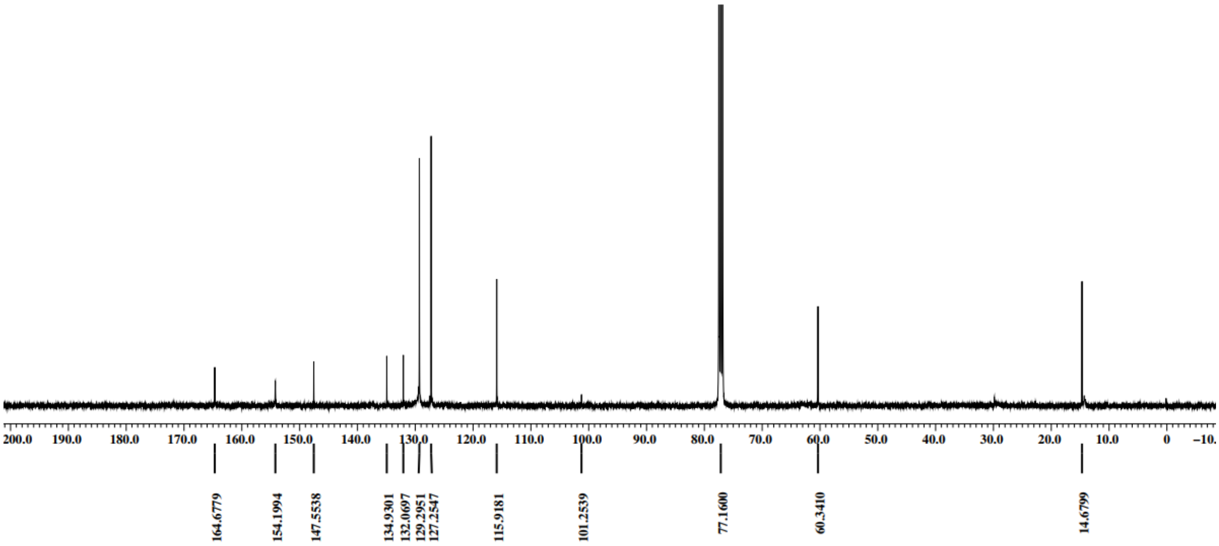
^{1}H NMR (400 MHz, CDCl$_3$)

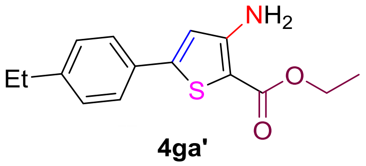




4fa'

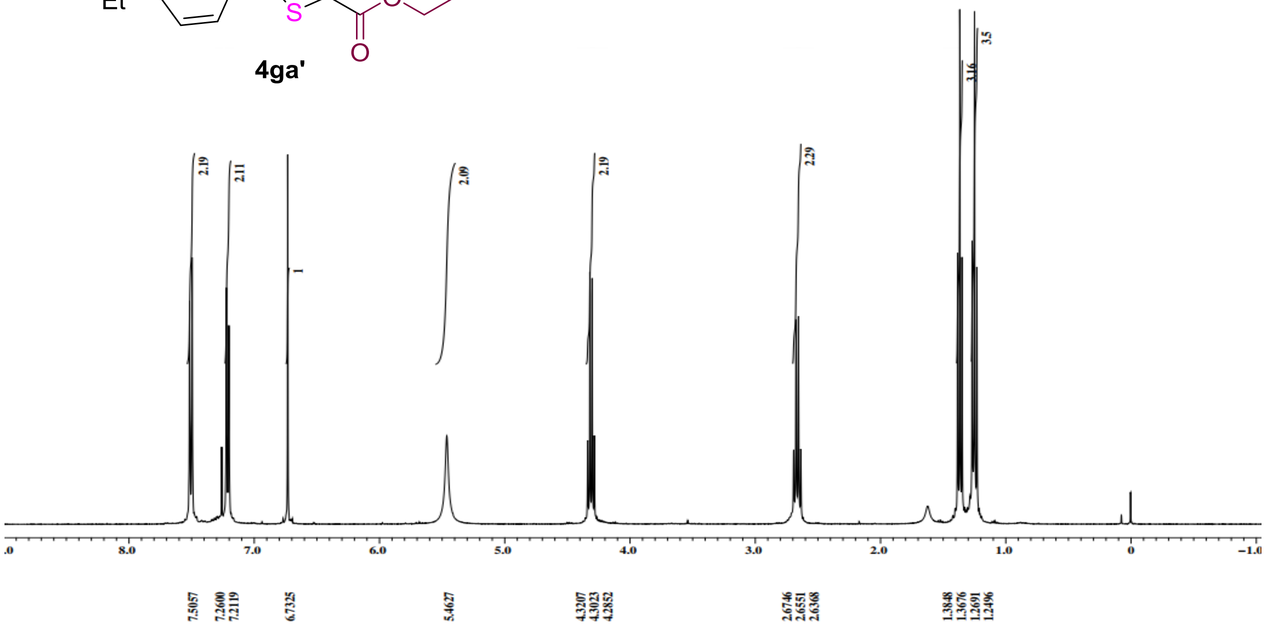
^{13}C NMR (100 MHz, CDCl$_3$)

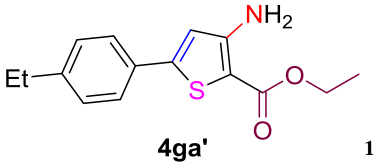




4ga'

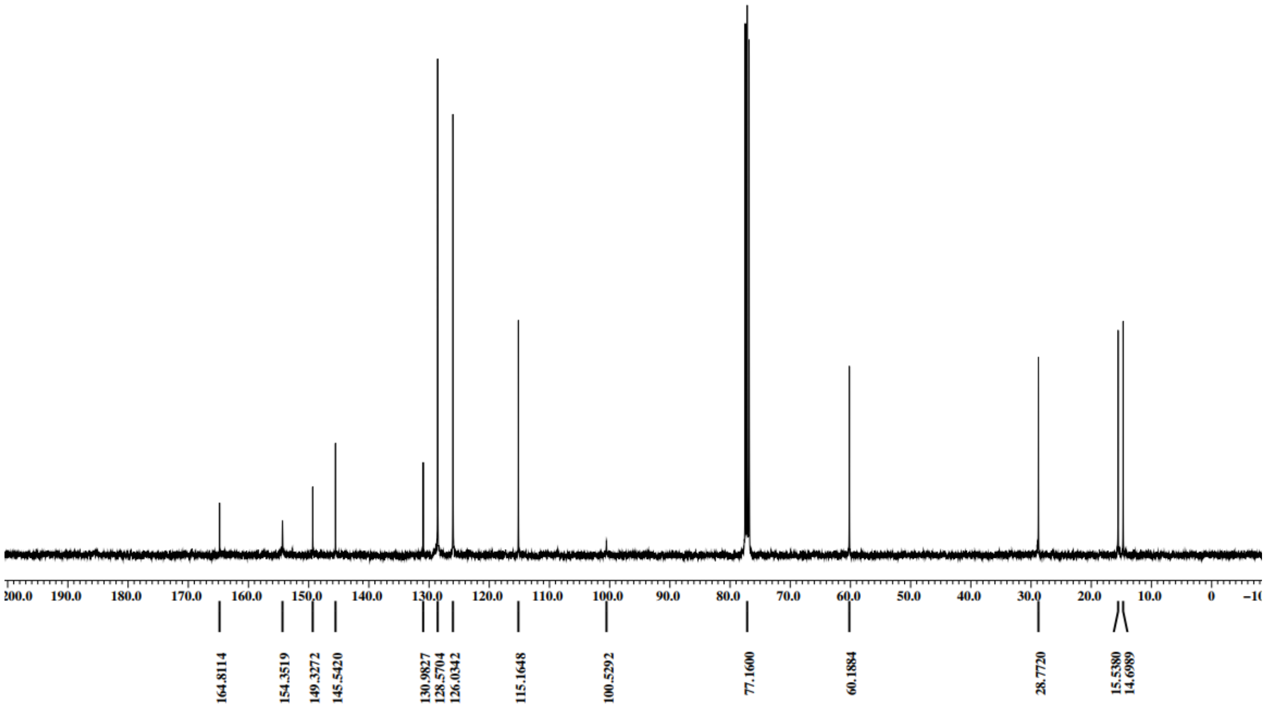
^{1}H NMR (400 MHz, $CDCl_3$)

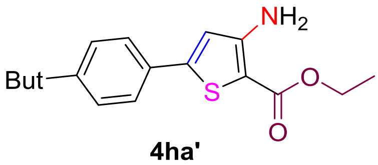




4ga'

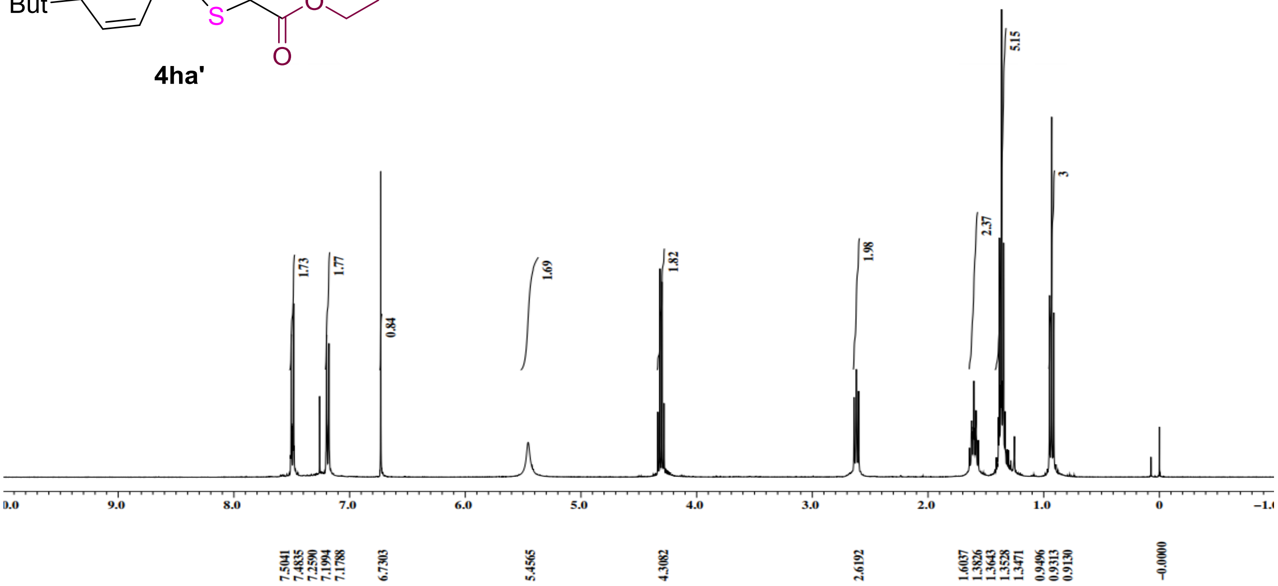
^{13}C NMR (100 MHz, $CDCl_3$)

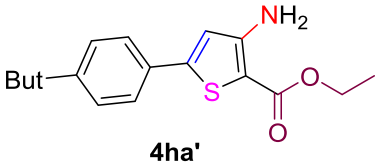




4ha'

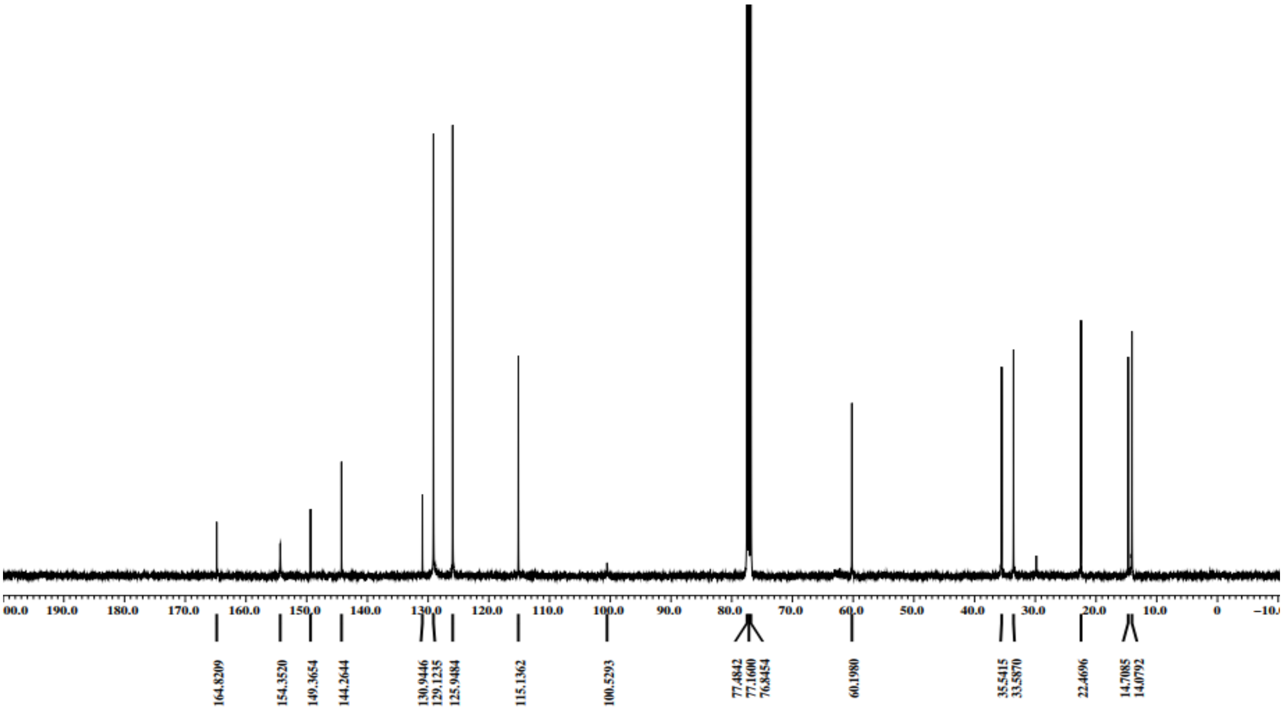
^{1}H NMR (400 MHz, CDCl$_3$)

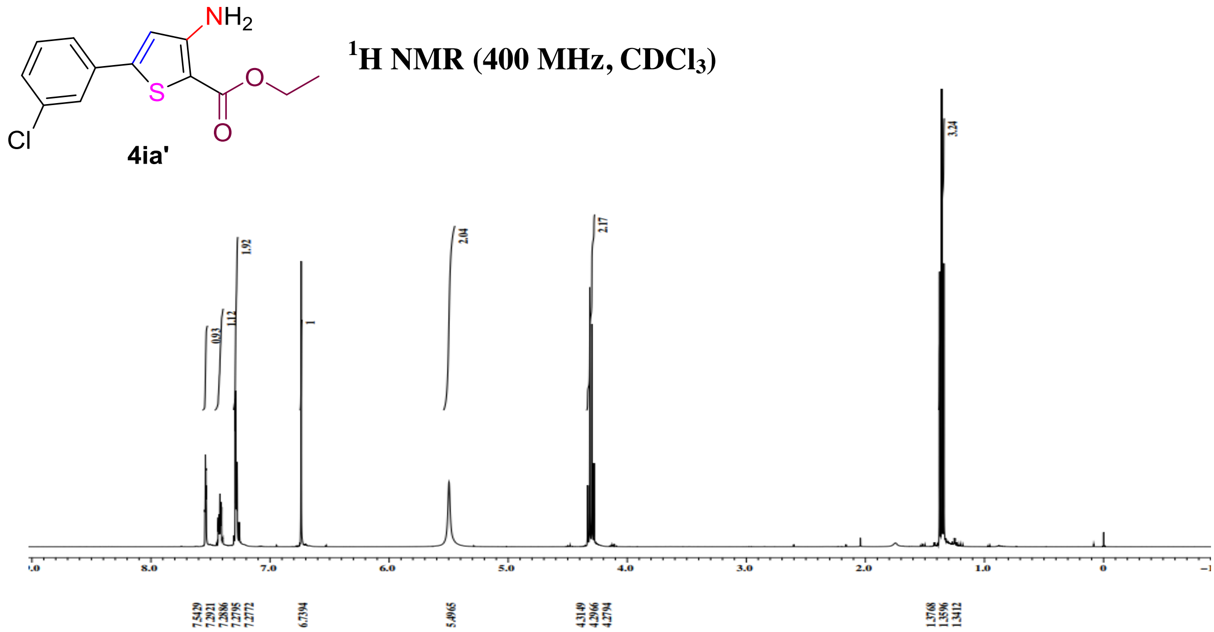




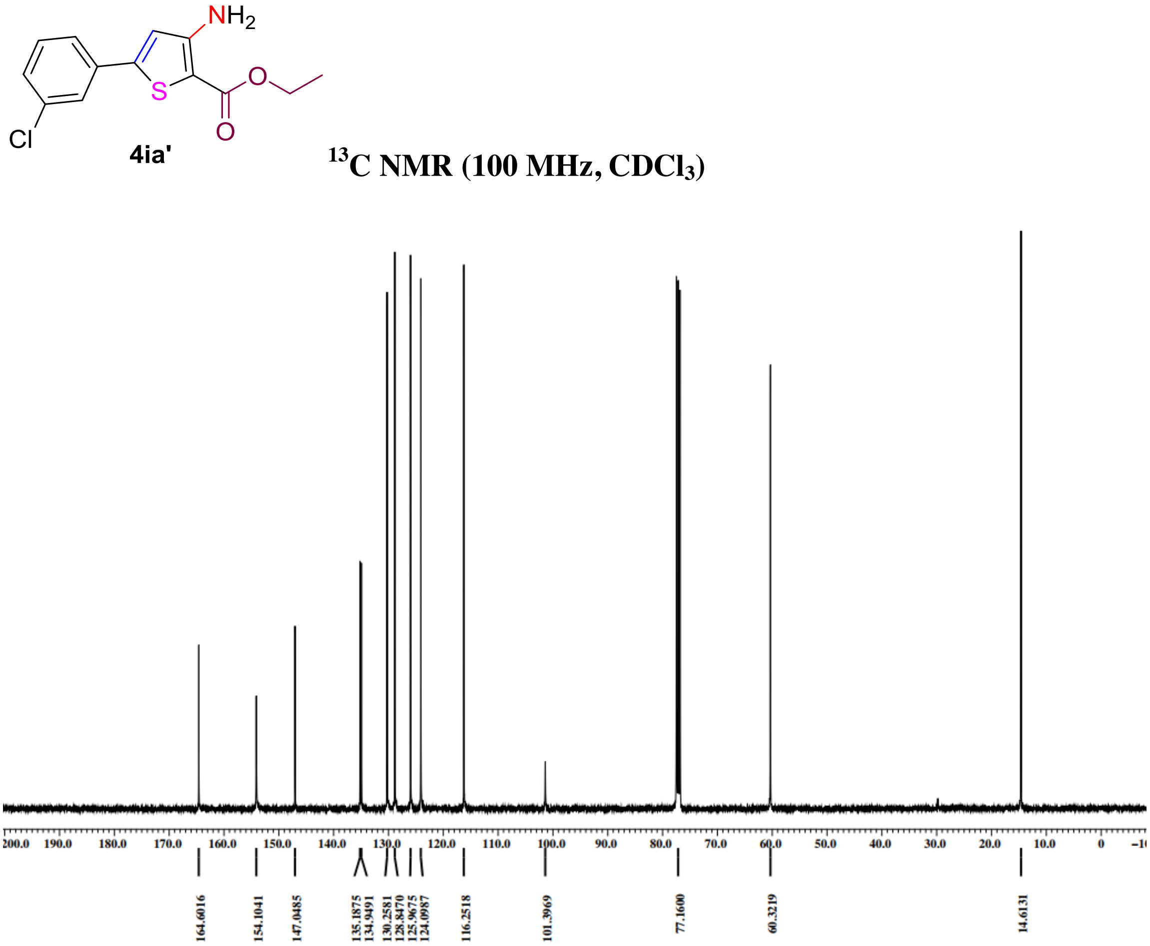
4ha'

^{13}C NMR (100 MHz, CDCl$_3$)

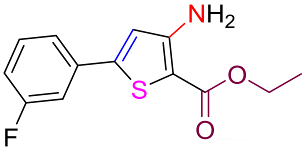




^{1}H NMR (400 MHz, CDCl$_3$)

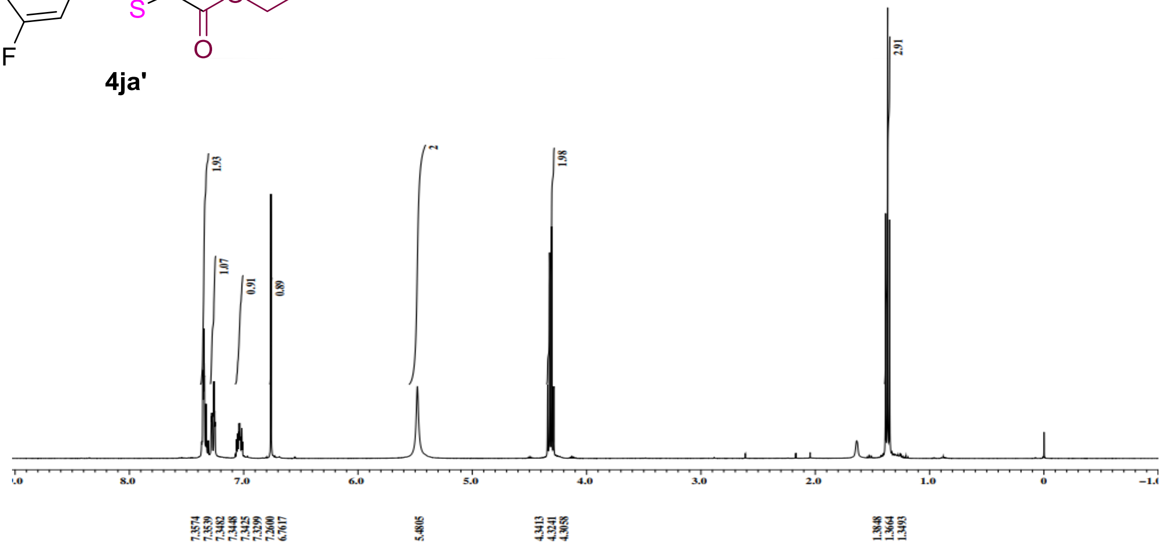


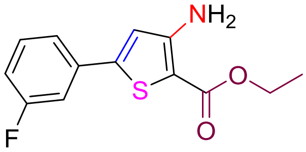
^{13}C NMR (100 MHz, CDCl$_3$)



4ja'

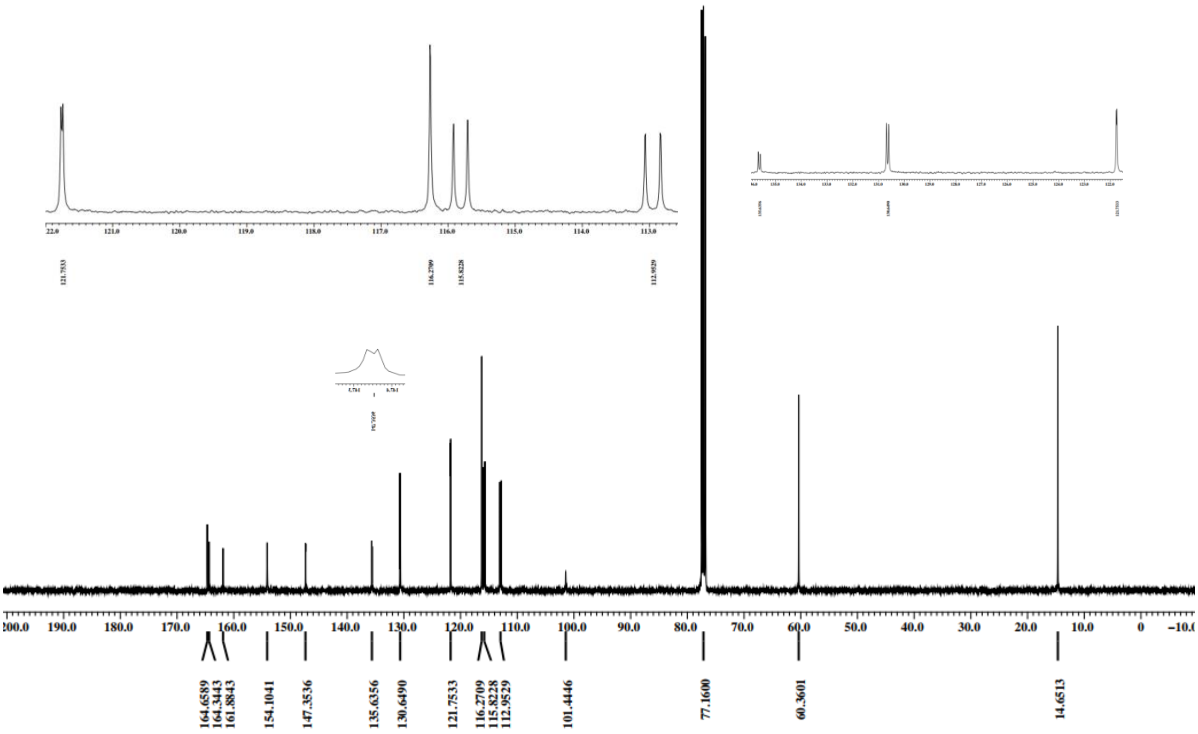
^{1}H NMR (400 MHz, CDCl$_3$)

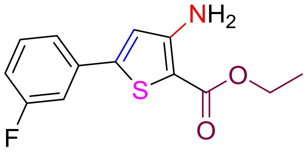




4ja'

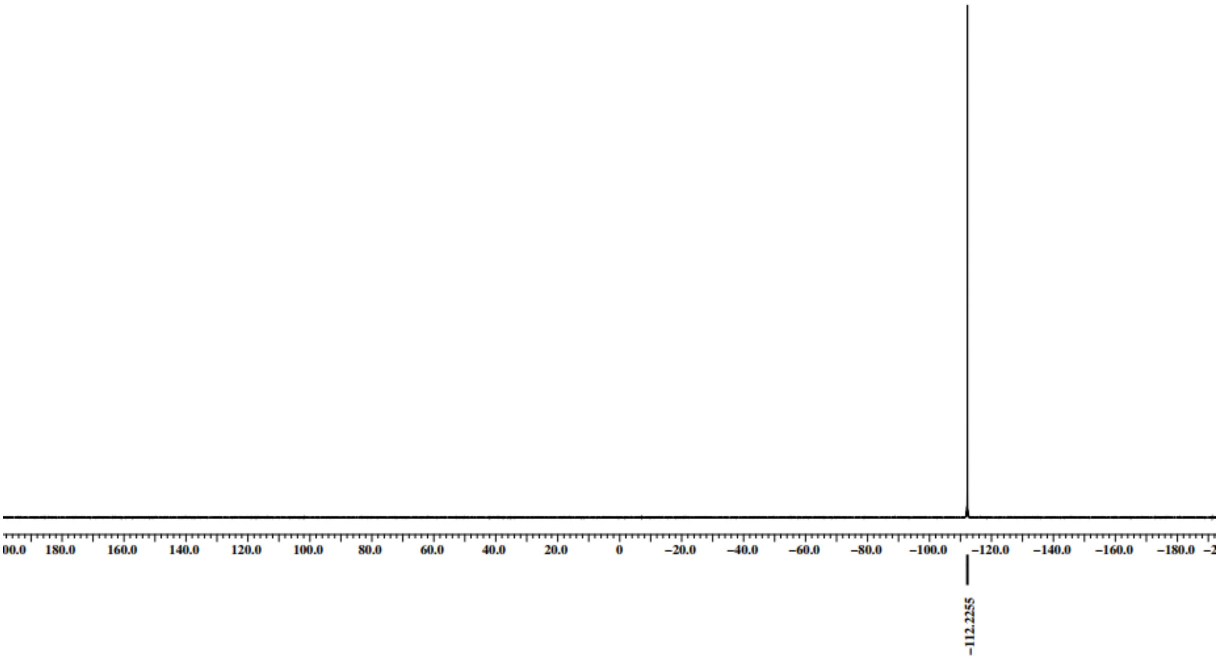
^{13}C NMR (100 MHz, CDCl$_3$)

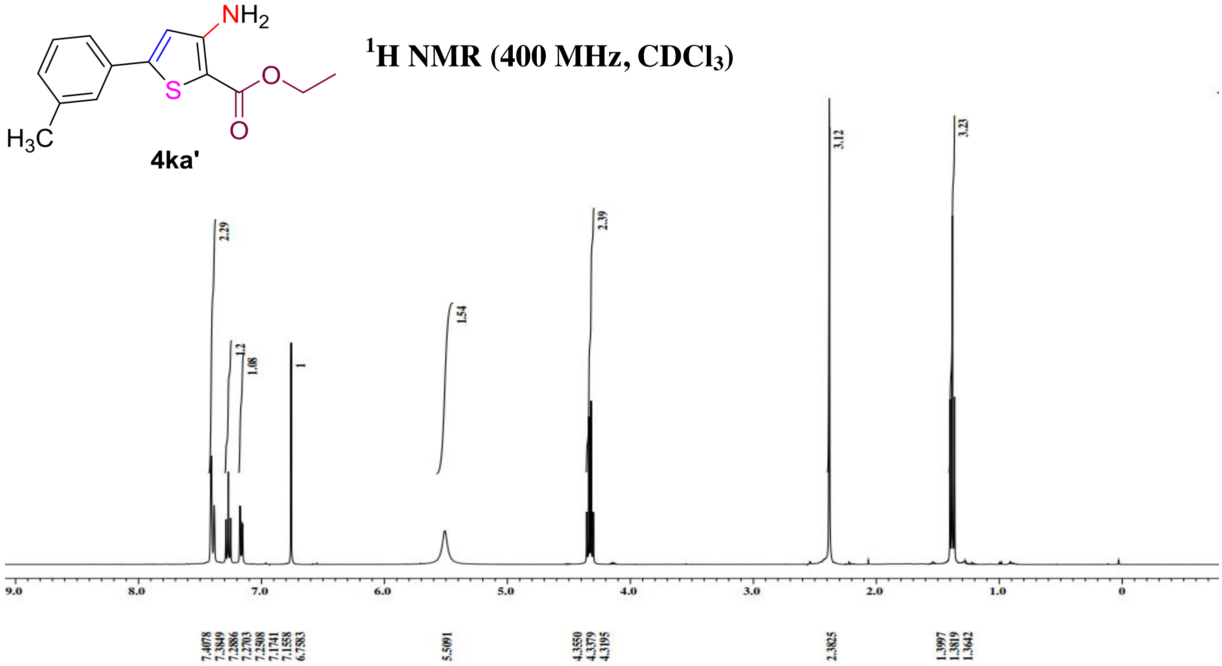




4ja'

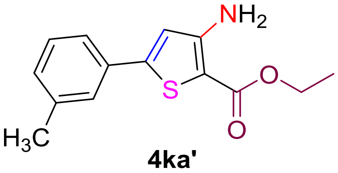
^{19}F NMR (376 MHz, $CDCl_3$)





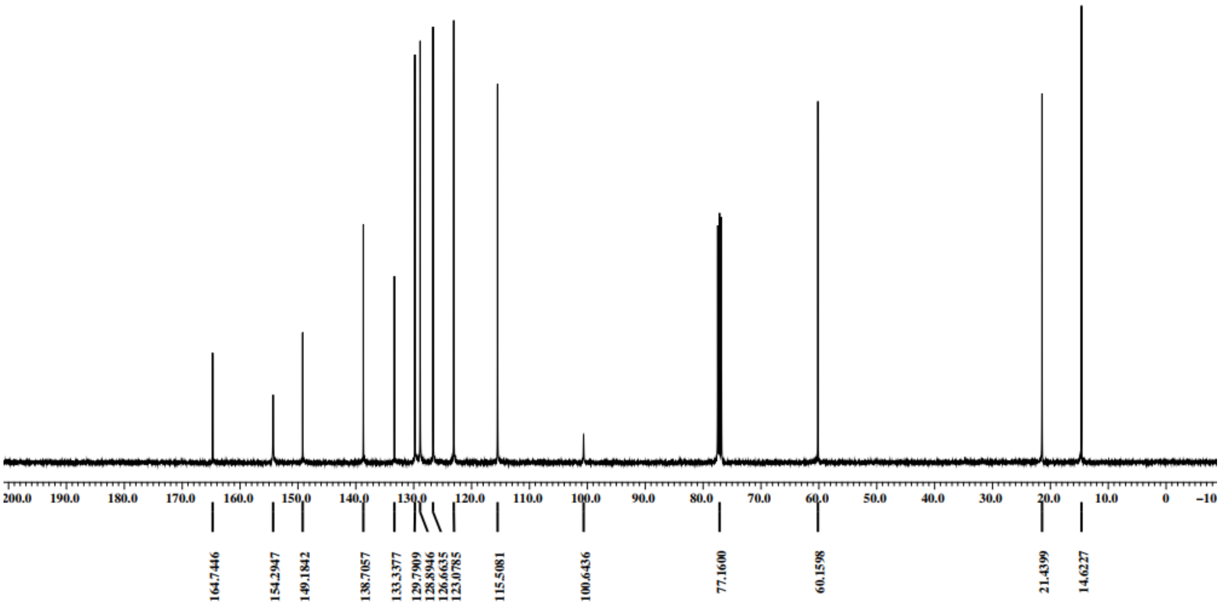
4ka'

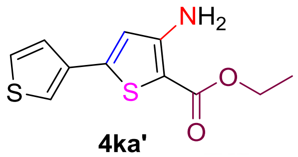
^{1}H NMR (400 MHz, CDCl$_3$)



4ka'

^{13}C NMR (100 MHz, CDCl$_3$)





4ka'

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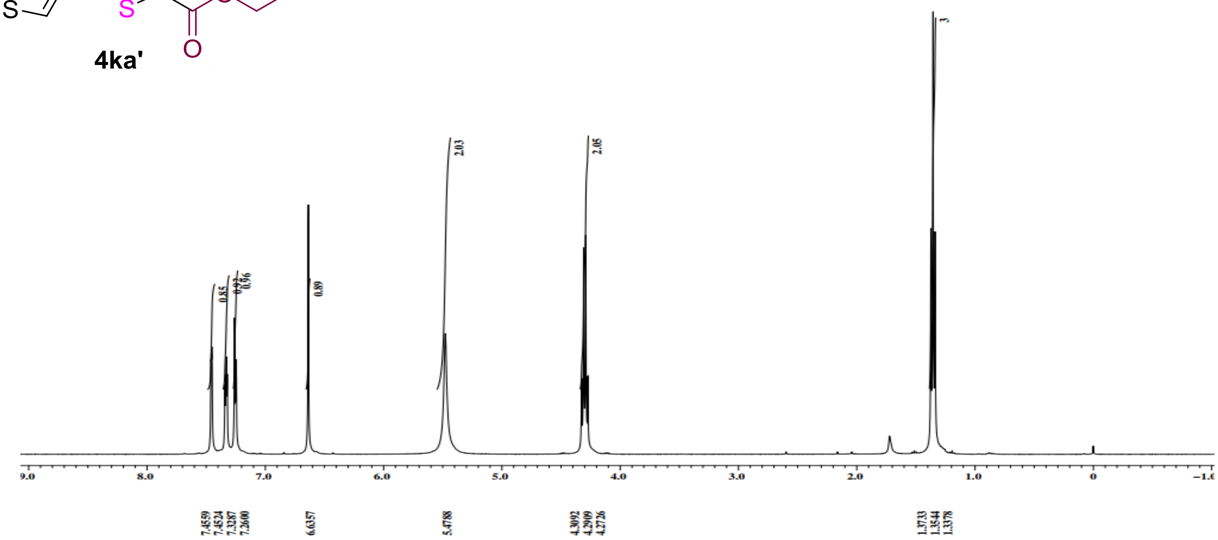
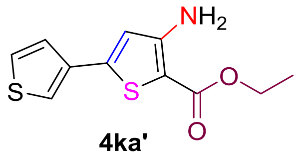
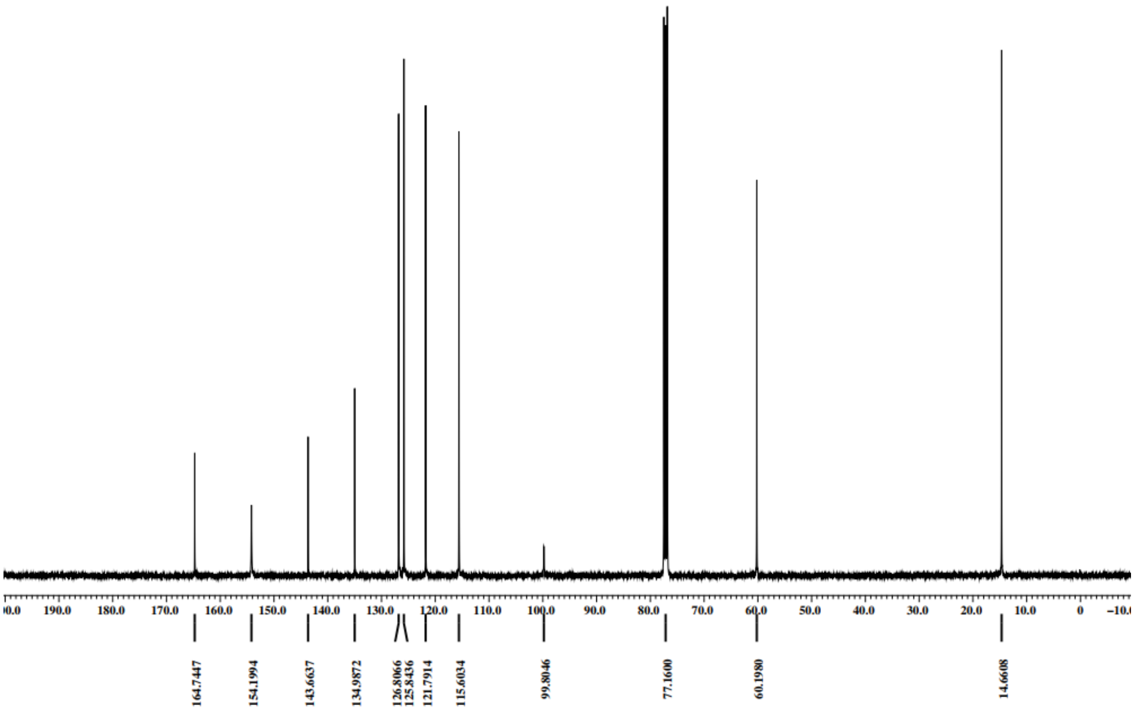
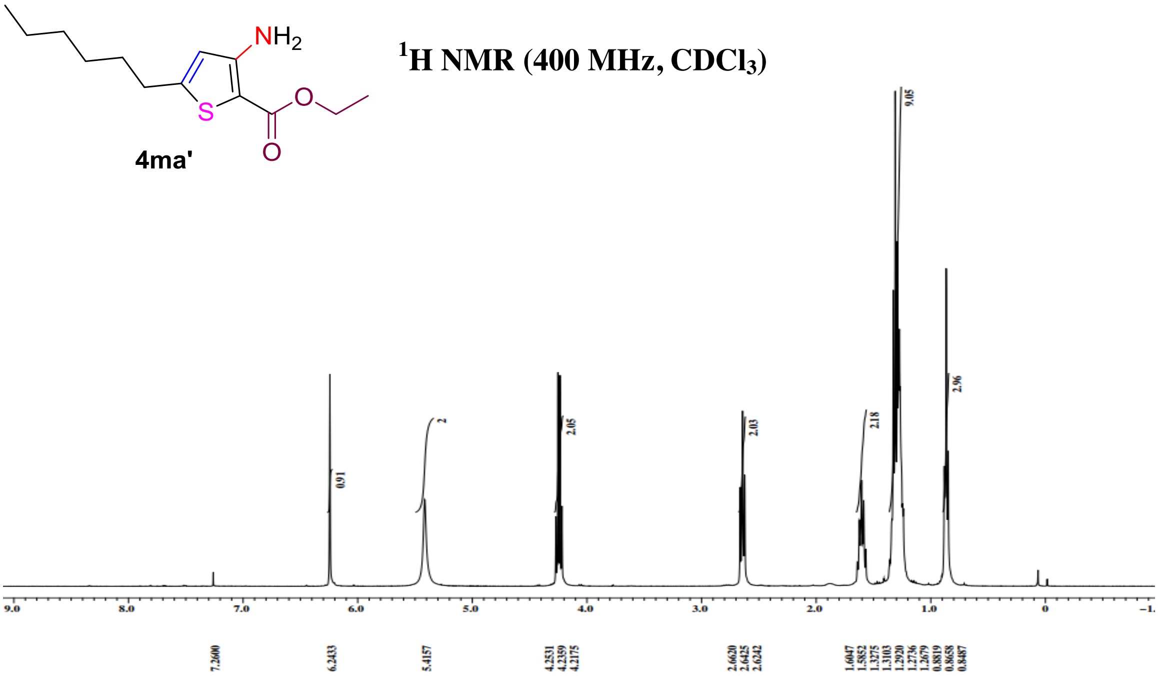




4ka'

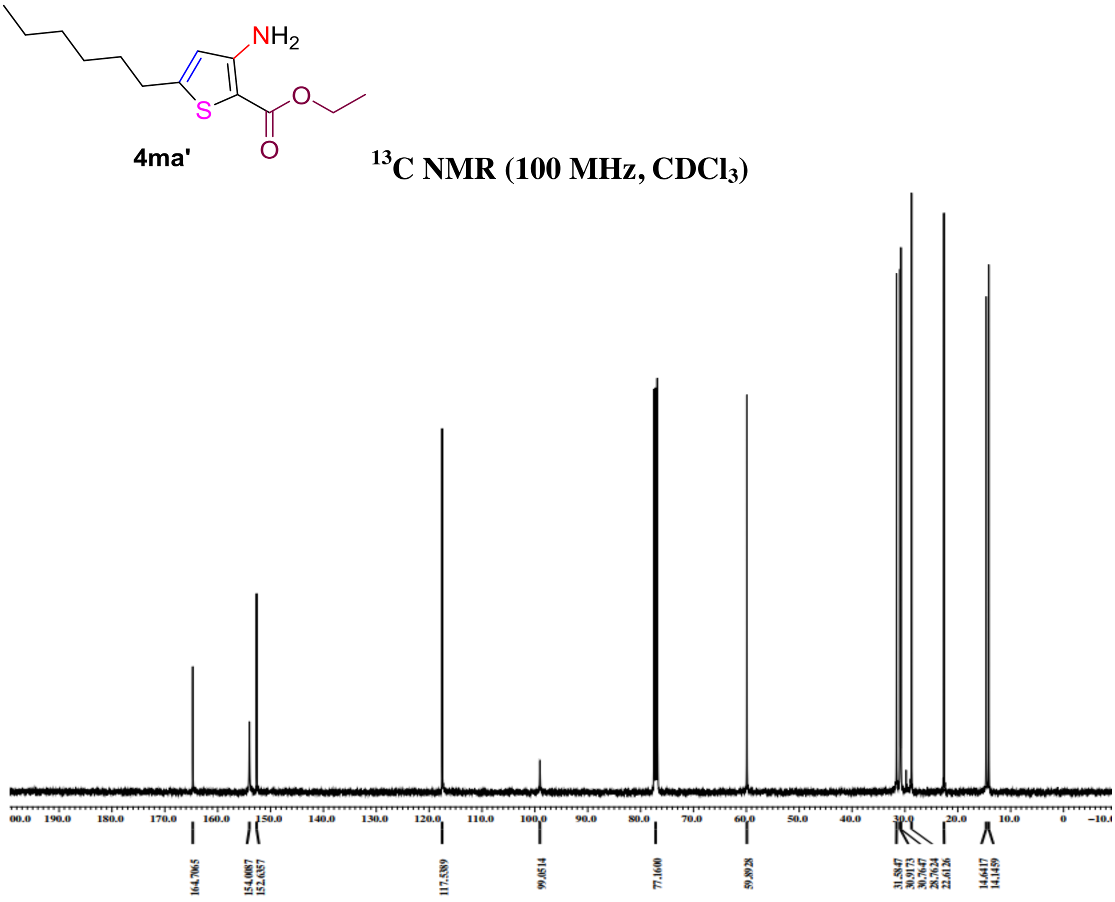
^{13}C NMR (100 MHz, CDCl$_3$)





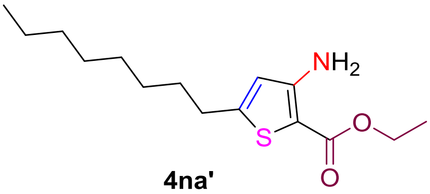
4ma'

^{1}H NMR (400 MHz, CDCl$_3$)



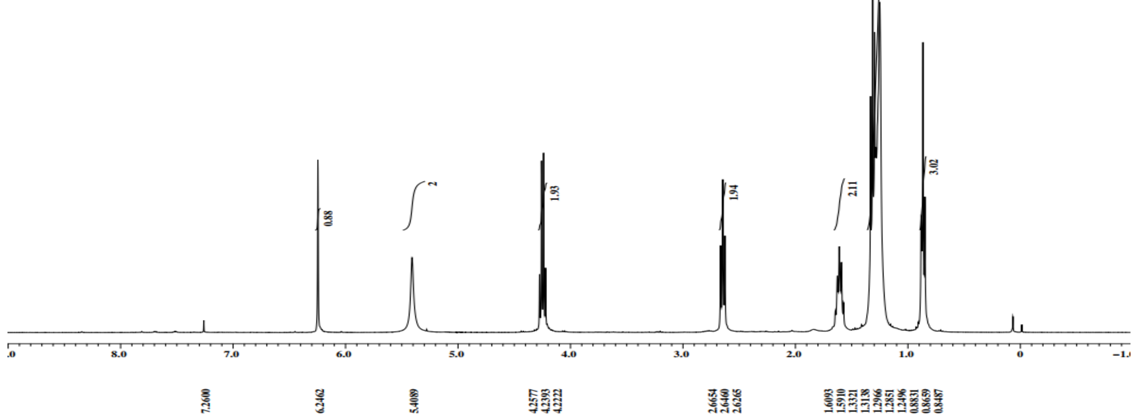
4ma'

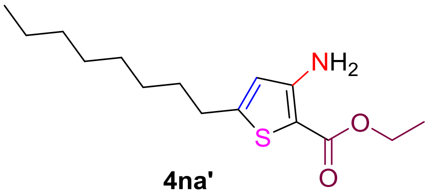
^{13}C NMR (100 MHz, CDCl$_3$)



4na'

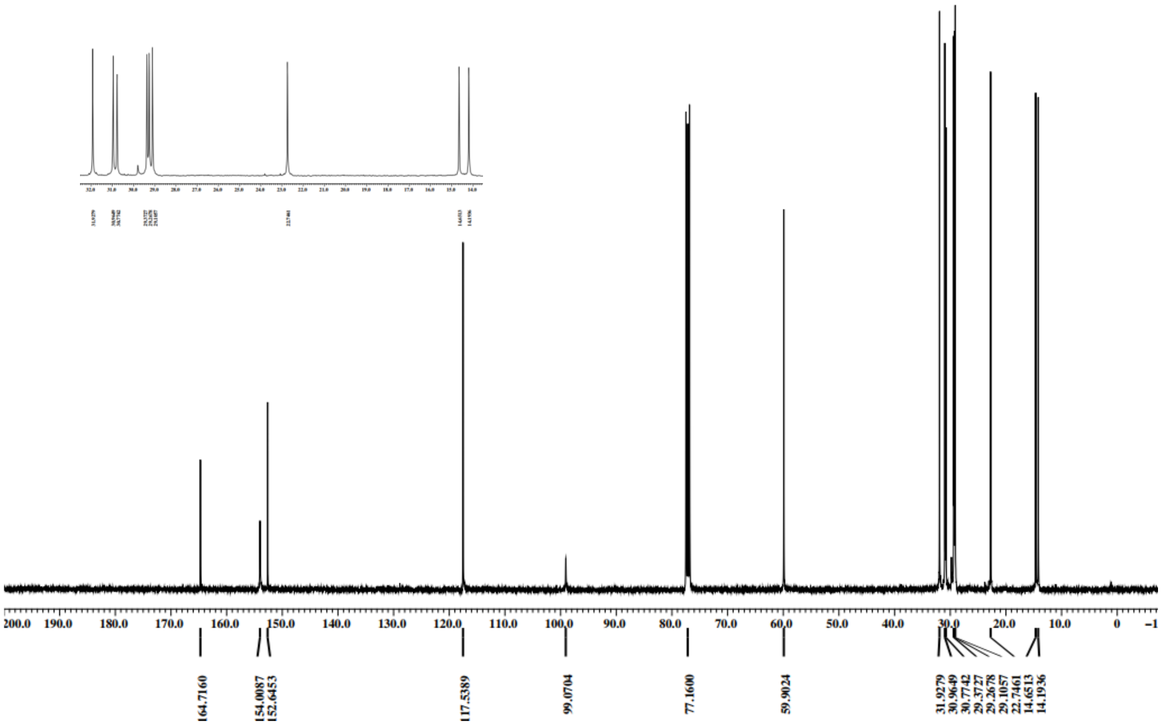
^{1}H NMR (400 MHz, CDCl$_3$)

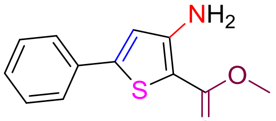




4na'

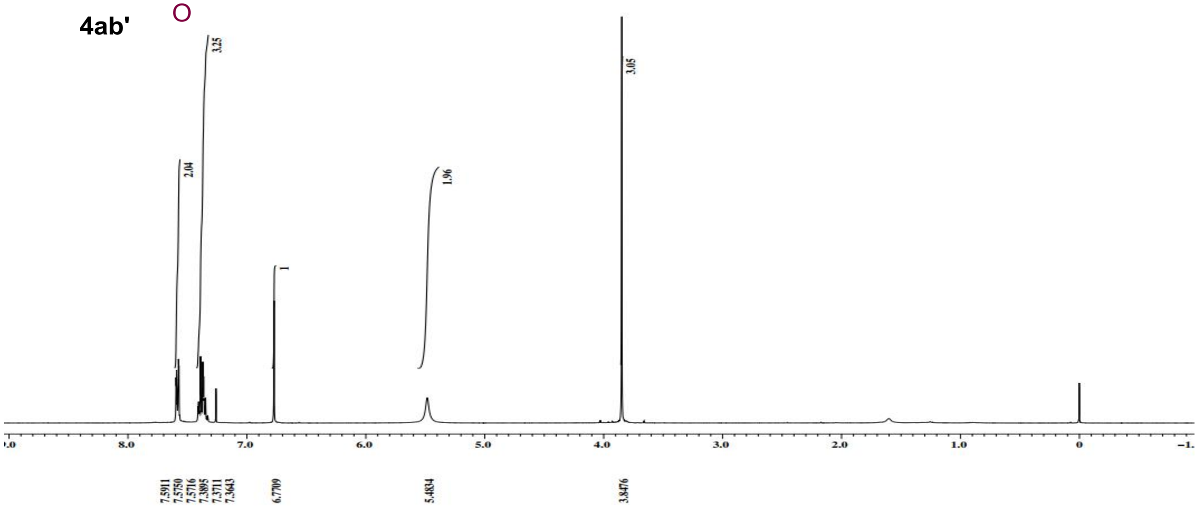
^{13}C NMR (100 MHz, CDCl$_3$)

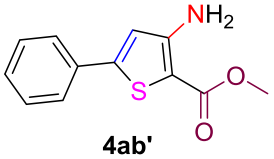




4ab'

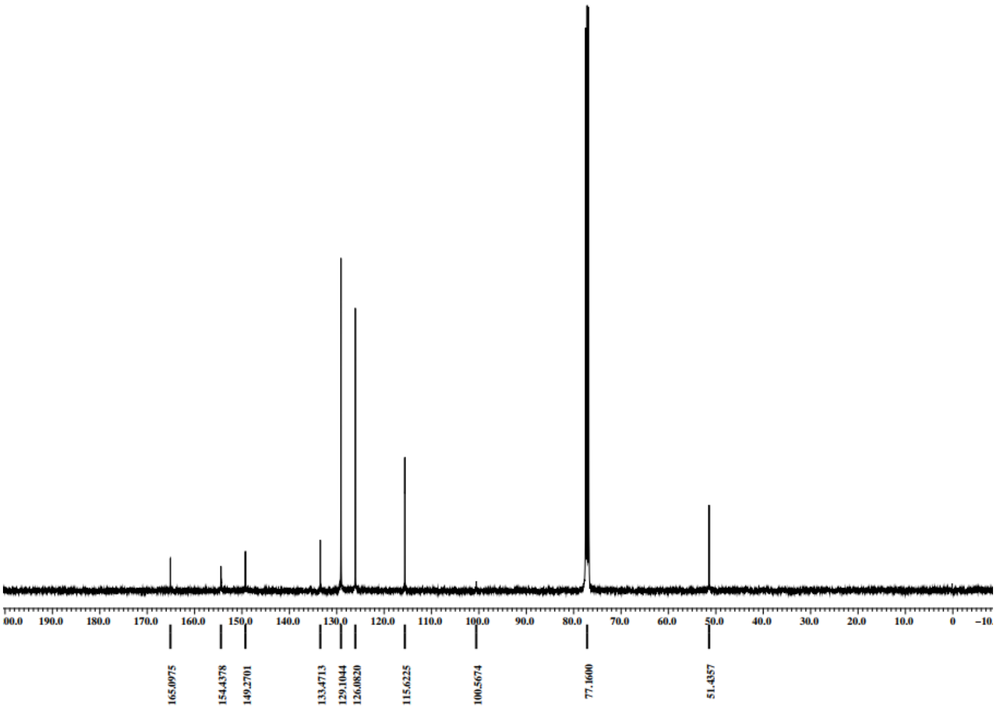
^{1}H NMR (400 MHz, CDCl$_3$)

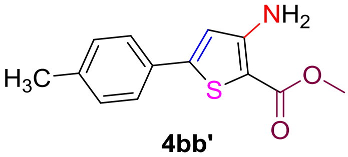




4ab'

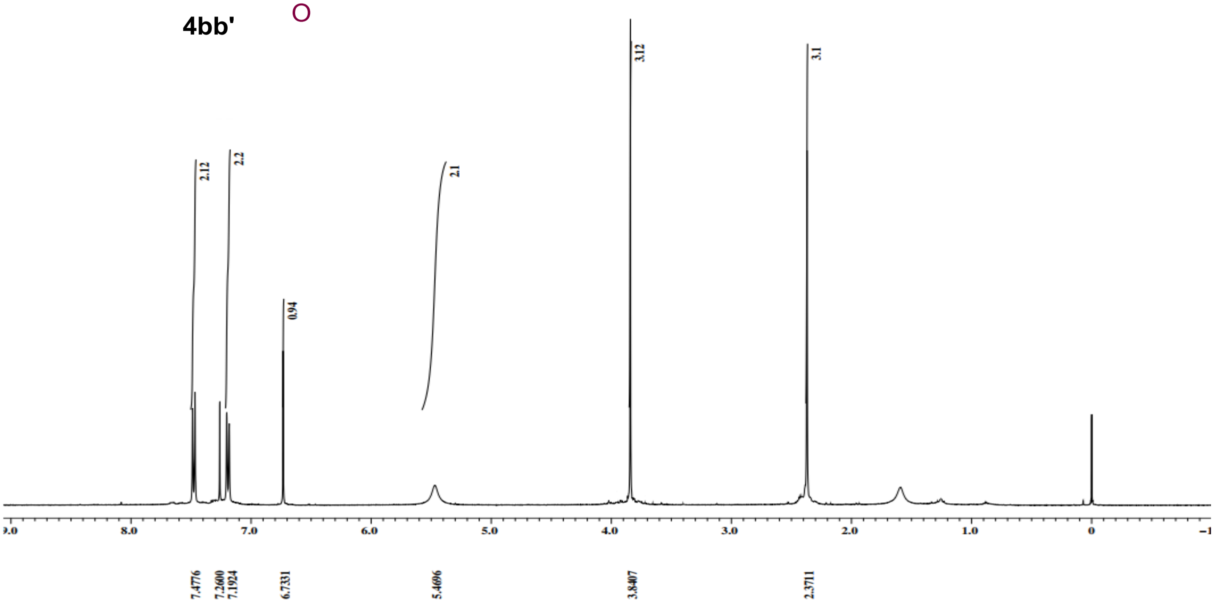
^{13}C NMR (100 MHz, CDCl$_3$)

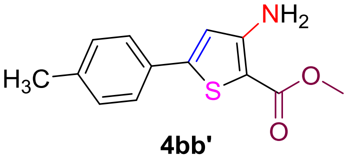




4bb'

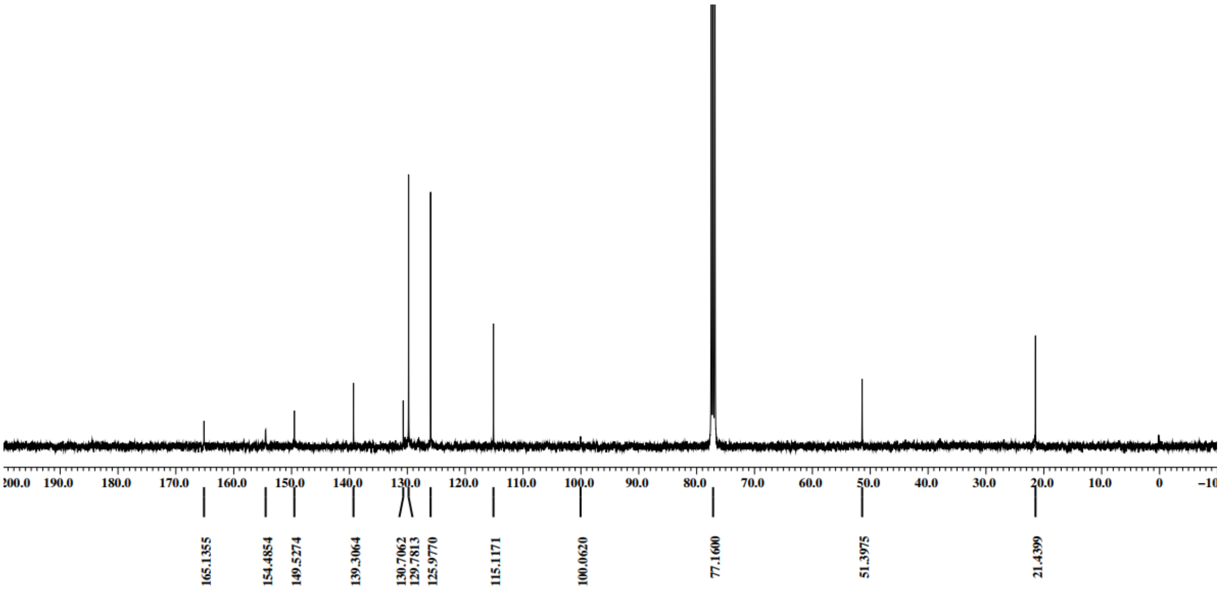
^{1}H NMR (400 MHz, $CDCl_3$)

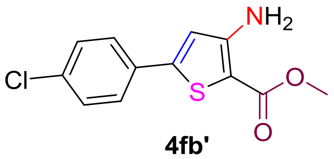




4bb'

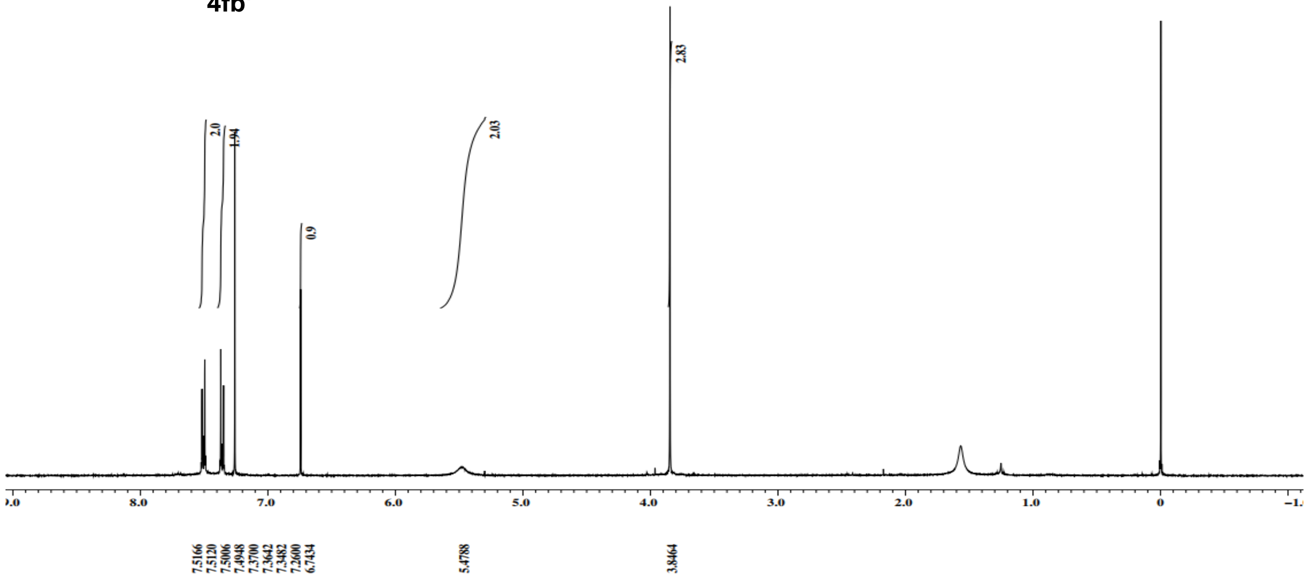
^{13}C NMR (100 MHz, $CDCl_3$)

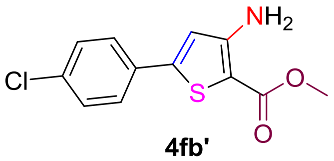




4fb'

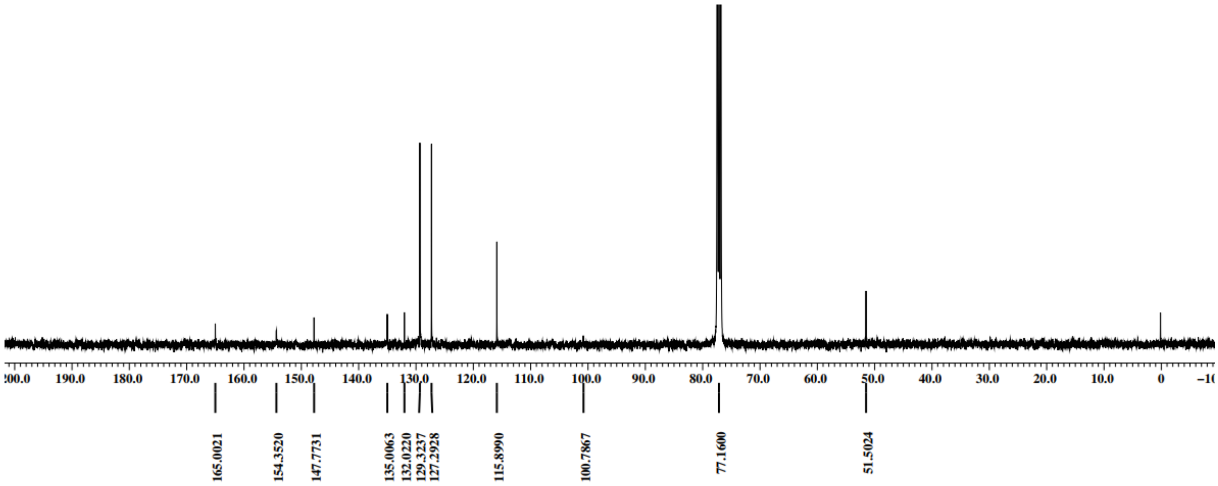
^1H NMR (400 MHz, $CDCl_3$)

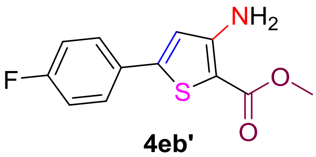




4fb'

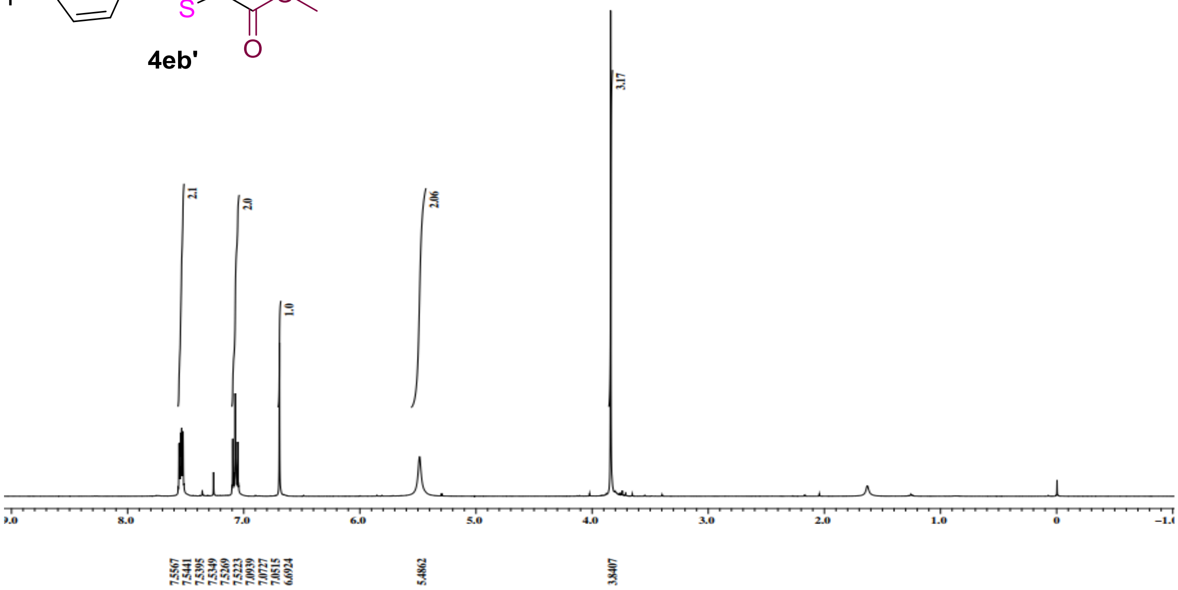
^{13}C NMR (100 MHz, $CDCl_3$)

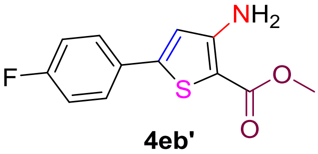




4eb'

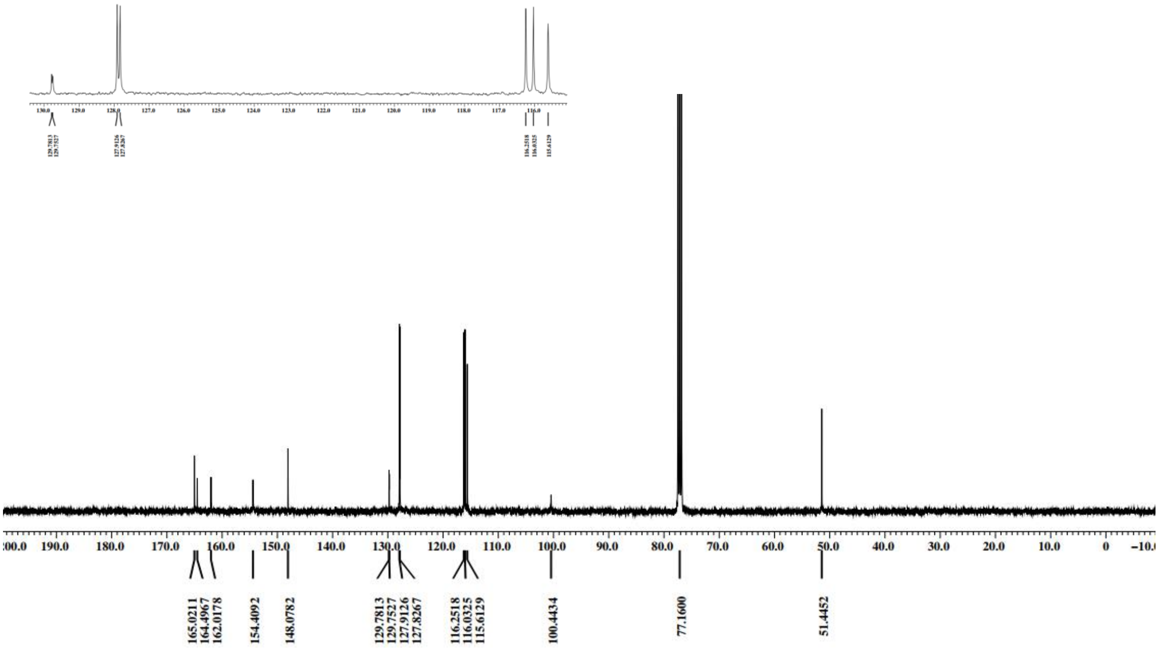
^{1}H NMR (400 MHz, CDCl$_3$)

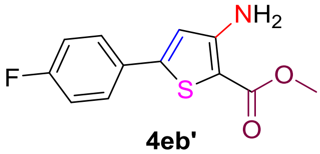




4eb'

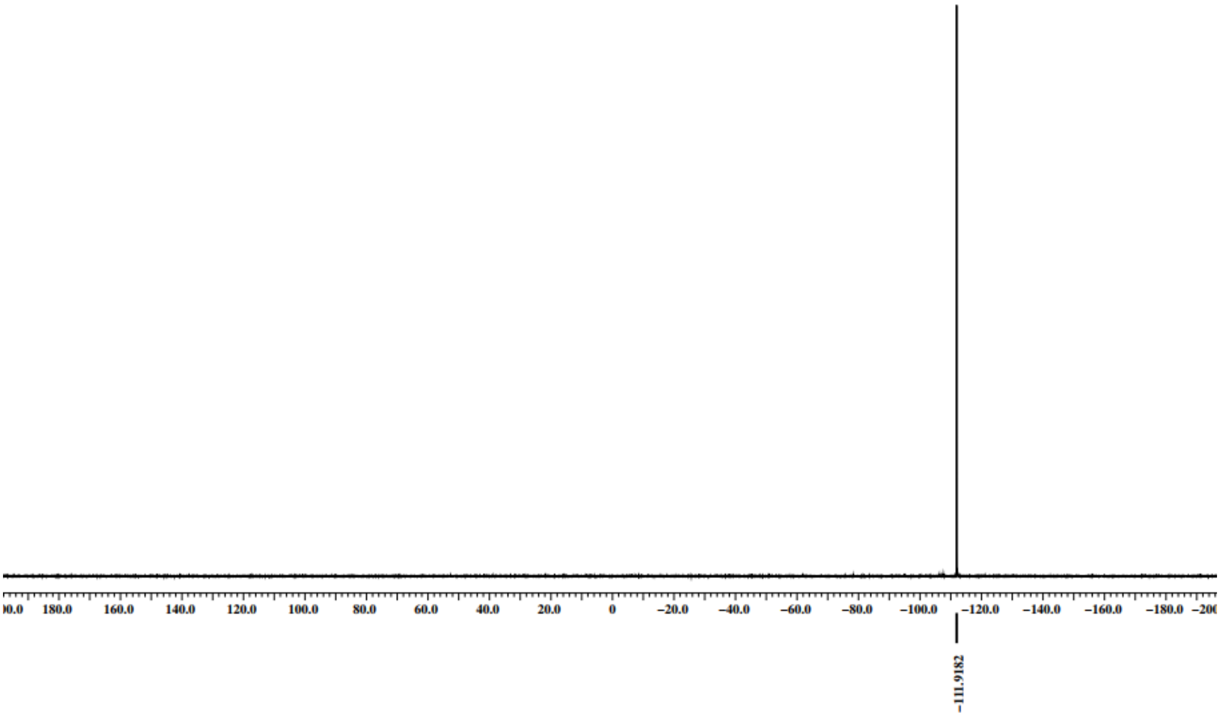
^{13}C NMR (100 MHz, CDCl$_3$)

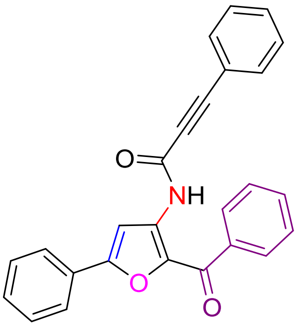




4eb'

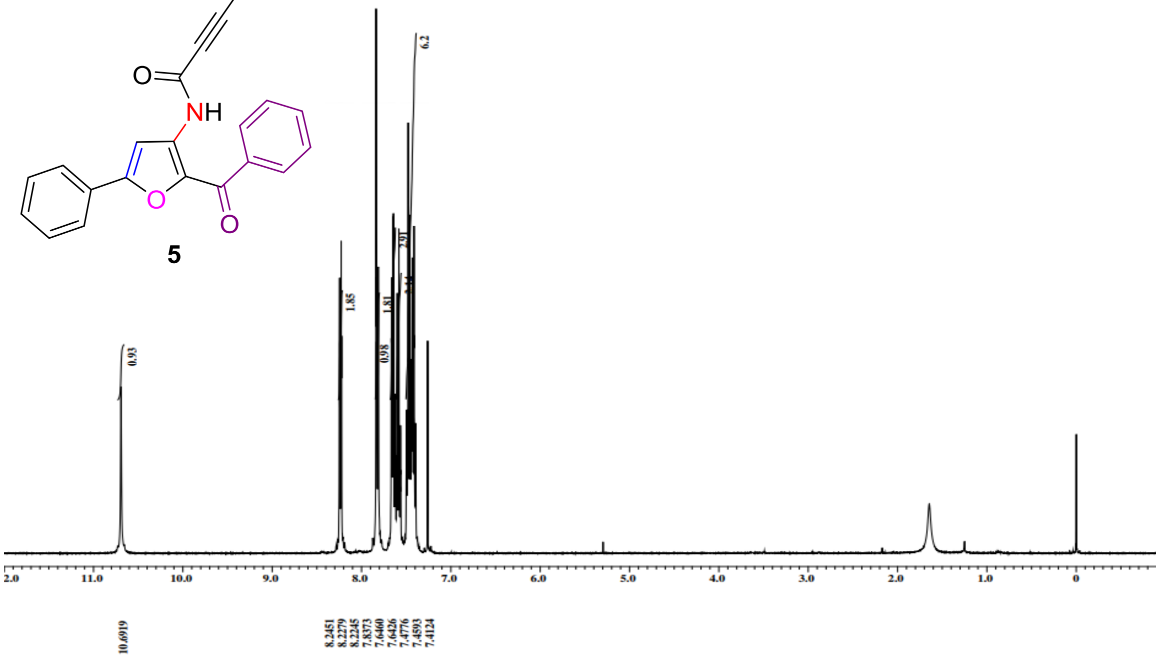
^{19}F NMR (376 MHz, CDCl$_3$)

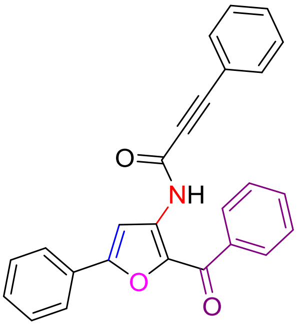




5

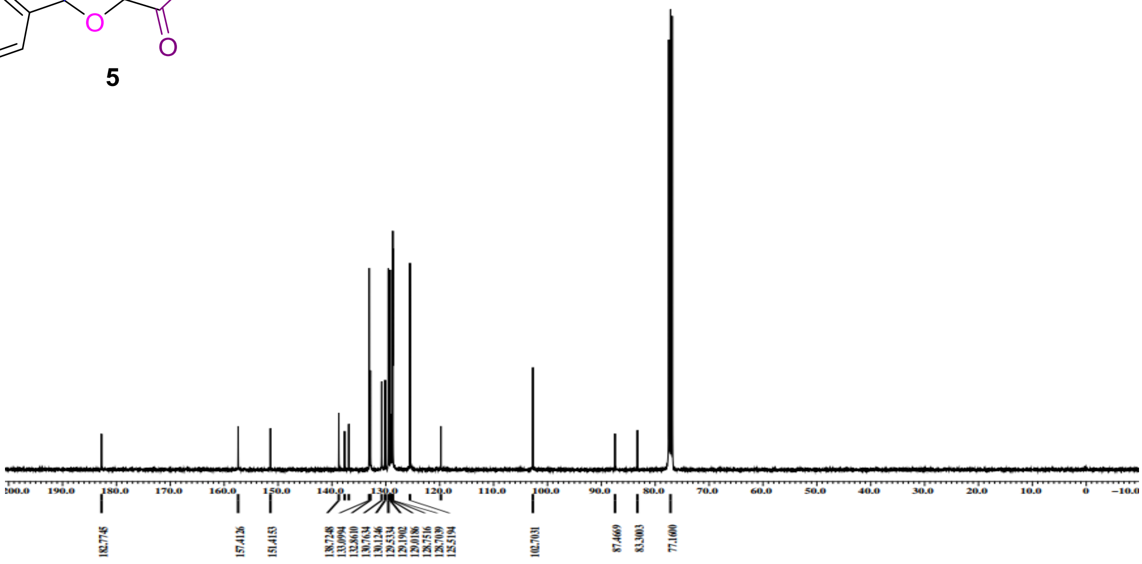
^{1}H NMR (400 MHz, CDCl$_3$)

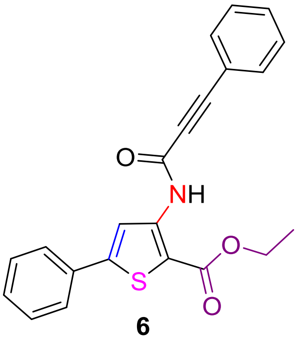




5

^{13}C NMR (100 MHz, CDCl$_3$)





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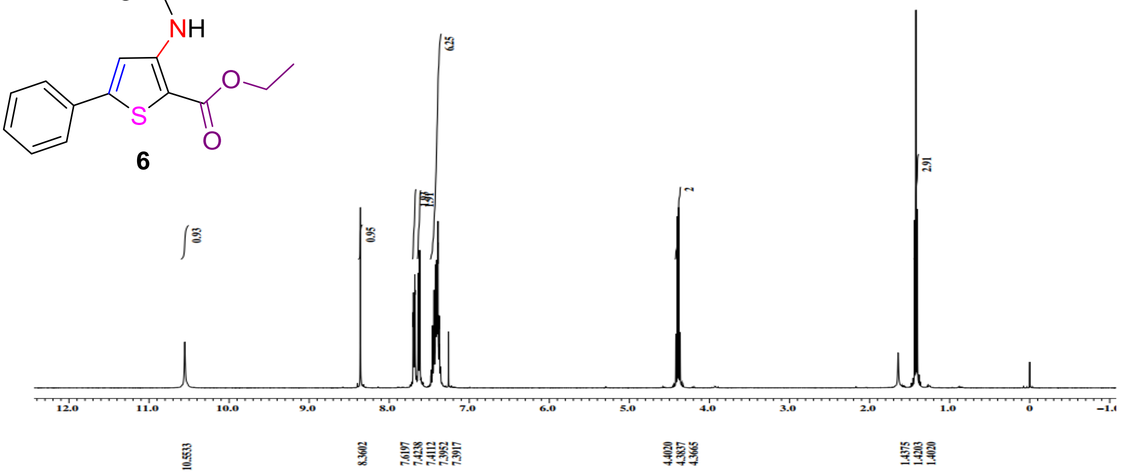
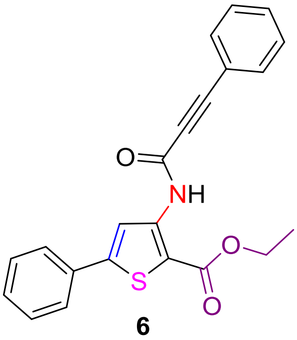
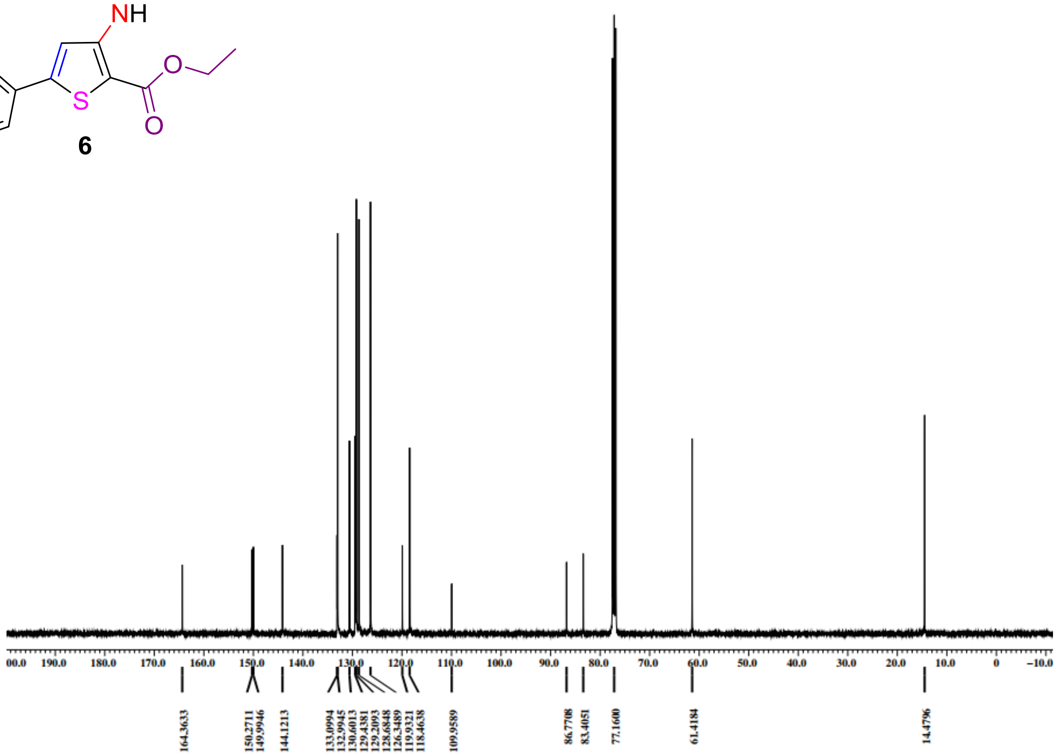
^{1}H NMR (400 MHz, CDCl$_3$)





6

^{13}C NMR (100 MHz, CDCl$_3$)



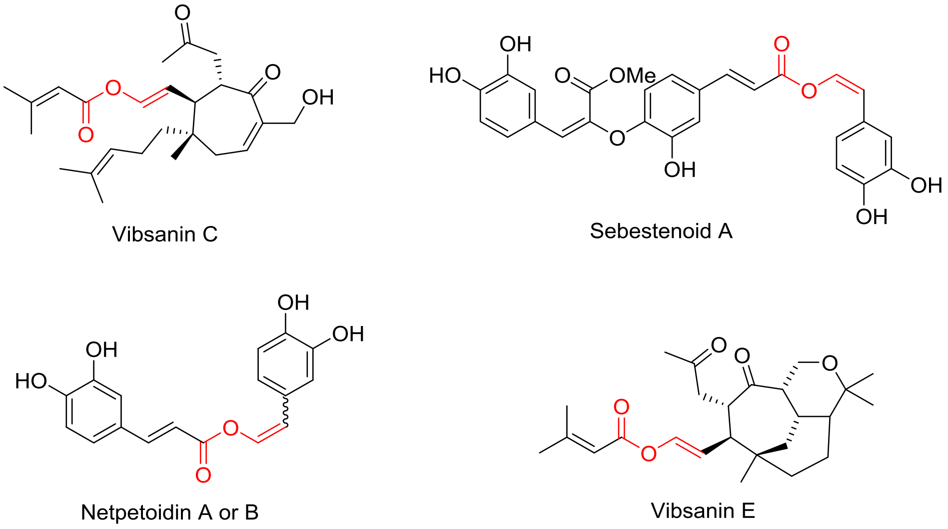
CHAPTER 3

A Facile Transition Metal-free Ionic Liquid [BMIM]OH Mediated Regio- and Stereoselective Hydrocarboxylation of Alkynenitriles

Chapter 3: A Facile Transition Metal-free Ionic Liquid [BMIM]OH Mediated Regio- and Stereoselective Hydrocarboxylation of Alkynenitriles

3.1 Introduction

Enol esters are frequently found as structural units in natural products and the most versatile synthons in various elegant synthetic transformations (Figure 3.1.1).[1] For instance, enol esters have been used in multicomponent reactions,[1a] hydroformylation,[1b] epoxidation,[1c] Aldol reactions,[1p] cycloaddition reactions,[1q] α-functionalization reactions,[1f-g] Mannich type reactions[1a] and asymmetric hydrogenations reactions.[1r] In addition, enol esters have proven versatile acylating agents.[1s] These can readily acylate alcohols, amides, or imides. Enol esters are also used extensively for synthesizing various heterocyclic compounds such as oxetanes,[1h] *N*-aryl lactams and isocoumarins.[1i] Moreover, these have been applied for the synthesis of vinyl acetate/acrylic (VAA) copolymers and ethylene-vinyl acetates (EVA) copolymers.[1t-u] Considering their great importance as substrates and intermediates in organic synthesis, polymer and pharmaceutical chemistry, several methods have been developed to synthesize substituted enol esters.[2]



Vibsanin C

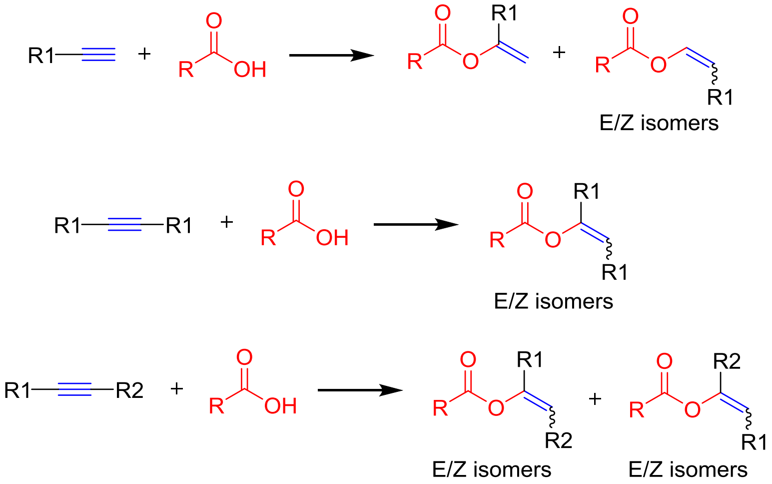
Sebestenoid A

Netpetoidin A or B

Vibsanin E

Figure 3.1.1 Representative biologically potent enol esters.

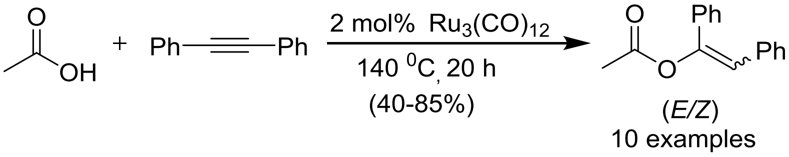
Classical methods to synthesize enol esters involve the acylation of enols/enolates. However, such reactions are associated with C-acylation as a competitive reaction to the O-acylation process. The most widely used atom-economical approach to synthesize enol esters is the direct addition of carboxylic acids to alkynes. However, it is very challenging to control the regio- and stereoselecivity during the addition process, especially in the case of unsymmetrically substituted internal alkynes.[3] The addition reaction often affords an inseparable mixture of regio- and stereoisomers (Scheme 3.1.1).



Scheme 3.1.1 Regio- and stereoselective issue during addition of carboxylic acids to alkynes.

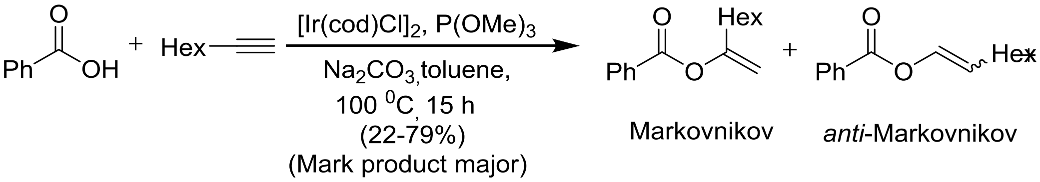
As a result, the primary ongoing research has shifted towards synthesizing widely substituted stereo-defined enol esters using specific reagents and catalysts. The transition metal-catalyzed addition of carboxylic acids to alkynes has proved as an attractive method to access the stereo-defined enol esters. Mercury salts were the first to be used as catalysts in this transformation.[13] However, their high toxicity limits their use. Many transition metal complexes of ruthenium,[3b-d, 4] palladium,[5] rhodium,[6] iridium,[7] cobalt,[8] rhenium,[9] silver,[10] iron,[11] copper,[12] and gold[14a, 14e and 15] have proved capable of hydrocarboxylation of alkynes involving different mechanisms and resulting in diverse selectivities in the products. For representative examples, in 1983, Rotem and Shvo were the first to report that ruthenium complexes $Ru_3(CO)_{12}$ as well as $[Ru(CO)_2(O_2CCH_3)]_n$ facilitates the addition of aliphatic and aromatic carboxylic acids to di- and monosubstituted alkynes yielding vinyl esters along with a rearranged side product

(Scheme 3.1.2).[3d] After this finding, several reports based on Ru-catalyzed hydrocarboxylation of the alkynes were documented with high selectivity.



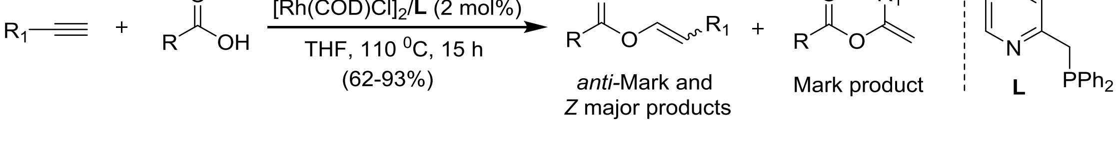
Scheme 3.1.2 Ruthenium-catalyzed hydrocarboxylation of alkynes for the synthesis of enol esters.

Ishii *et al*., in 2002 reported the addition of carboxylic acids to alkynes in the presence of $[Ir(cod)Cl]_2$, small amounts of $P(OMe)_3$ and Na_2CO_3 giving Markovnikov addition product as major product, however, suffered from slightly low yields and poor selectivity (Scheme 3.1.3).[7a]



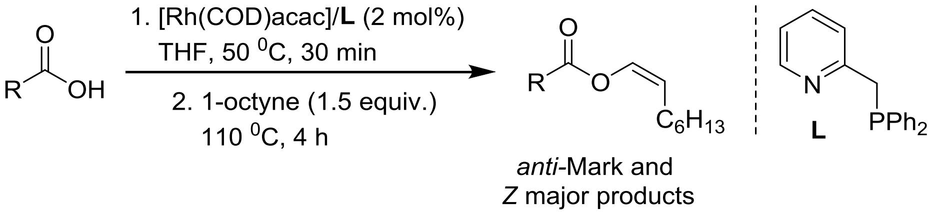
Scheme 3.1.3 Iridium-catalyzed hydrocarboxylation of alkynes for the synthesis of enol esters.

Breit group, in 2010, delineated a first rhodium-catalyzed hydro-oxycarbonylation protocol involving $[Rh(COD)Cl]_2$/DPPMP catalyst system, which furnished the desired *Z*-enol esters by intermolecular anti-Markovnikov addition of carboxylic acids to terminal alkynes in good to high yields with excellent stereoselectivities in 16-24 h (Scheme 3.1.4).[6b]



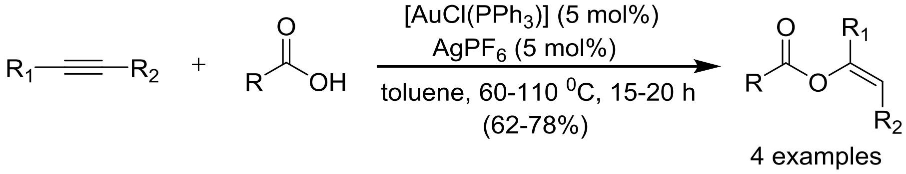
Scheme 3.1.4 Rhodium-catalyzed hydrocarboxylation of alkynes using DPPMP as a phosphine ligand for the synthesis of enol esters.

The same group, in 2016, reported a more active Rh(COD)acac/DPPMP catalyst system producing *Z*-enol esters in equally high yields and selectivities within 4 h with a broad substrate scope (Scheme 3.1.5).[6d]



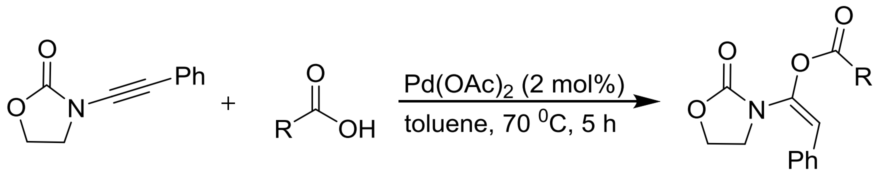
Scheme 3.1.5 Rhodium-catalyzed hydrocarboxylation of alkynes using a more active Rh(COD)acac/DPPMP catalyst system.

In addition, gold catalysts have also been extensively used for the intermolecular addition of carboxylic acids to alkynes.[15] Kim *et al*., in 2010, described the Au(I)-catalyzed hydrocarboxylation of alkynes using 5 mol% of [Au(PPh$_3$)Cl]/AgPF$_6$ (Scheme 3.1.6).[15d] It was found that PPh$_3$AuCl/AgPF$_6$ catalyst affords the Markonikov addition products, whereas, PPh$_3$AuCl/AgOTf catalyst gives more stable thermodynamic products via the isomerization of kinetic Markonikov products in toluene solvent. It showed good scope with terminal alkynes but was only demonstrated with four internal alkynes with poor results using diaryl-substituted alkynes.



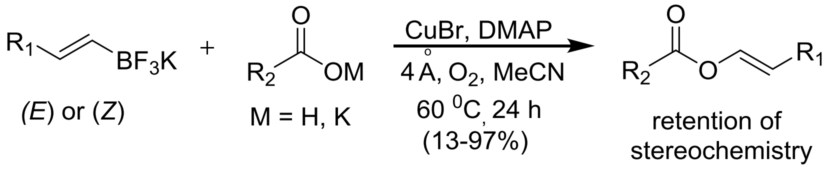
Scheme 3.1.6 Gold-catalyzed hydrocarboxylation of alkynes using 5 mol% of [Au(PPh$_3$)Cl]/AgPF$_6$ catalyst affording the Markonikov addition products.

In 2012, the Lam group developed the first Palladium-catalyzed regio- and stereoselective additions of carboxylic acids to ynamides using the substoichiometric amount of Pd(OAc)$_2$, carboxylic acids to give acyloxyenamides in good yields (Scheme 3.1.7).[5a]



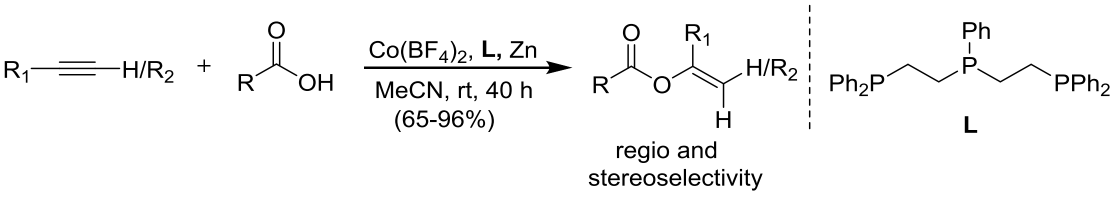
Scheme 3.1.7 Palladium-catalyzed regio- and stereoselective hydroacyloxylation of ynamides.

Batey *et al*., in 2013, reported the cross-coupling reaction of the carboxylate salts or carboxylic acids with potassium alkenyltrifluoroborate salts to produce regio- and stereoselective enol esters in the presence of CuBr/DMAP as a catalyst with 4 Å molecular sieves under O_2 at 60 °C (Scheme 3.1.8).[12a] This stereospecific copper-catalyzed cross-coupling method provides a solution for regiochemistry and *E*/*Z* diastereoselectivity issues during the metal-catalyzed additions of carboxylic acids to alkynes, using stereo-defined alkenyltriflouroborate salts.



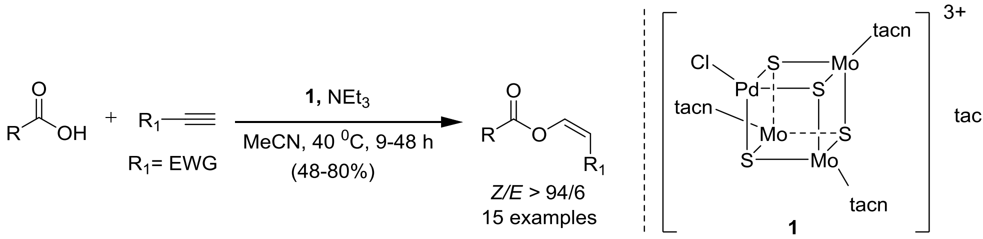
Scheme 3.1.8 Copper-catalyzed cross-coupling method to produce regio- and stereoselective enol esters using potassium alkenyltrifluoroborate salts.

Recently, in 2018, Li *et al*. reported a cobalt/triphosphine ligand complex-catalyzed syn addition of carboxylic acids to both terminal and internal alkynes with high regio- and stereoselectivity to give enol esters in high yields (Scheme 3.1.9).[8]



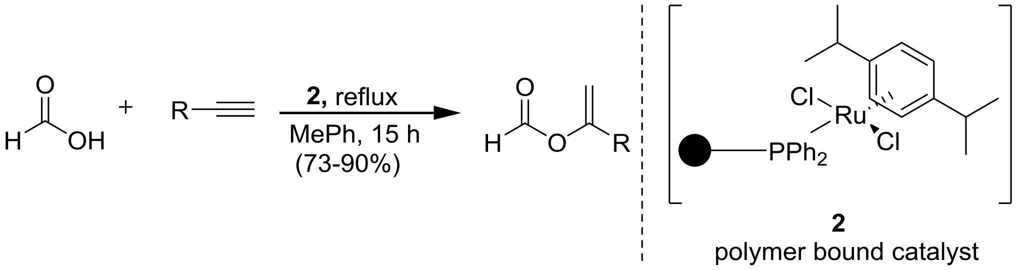
Scheme 3.1.9 Cobalt/triphosphine ligand complex-catalyzed syn addition of carboxylic acids to alkynes.

Moreover, some research groups have worked explicitly designing the ligands and tailoring the metal complexes to achieve the stereoselective addition of carboxylic acids to alkynes.[3e, 5d and 14] For instance, Hidai *et al*., in 1995, synthesized a highly efficient and selective cuboidal mixed-metal sulfide cubane-type cluster complex $[PdMo_3S_4(tacn)_3Cl]PF_6]_3$ (1; tacn = 1,4,7-triazacyclononane), to catalyze the stereoselective addition of carboxylic acids to both terminal and internal acetylenes with electron-withdrawing groups to exclusively get trans addition products in good yields under mild reaction conditions in the presence of base triethylamine (Scheme 3.1.10).[5d]



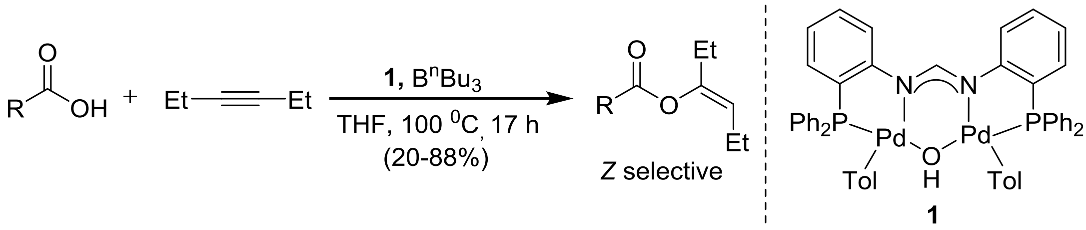
Scheme 3.1.10 Use of mixed-metal sulfide cubane-type cluster complex for the stereoselective addition of carboxylic acids to electron deficient acetylenes.

Scott *et al*., in 2000, reported the synthesis of a resin-bound arene-ruthenium complex in which $[Ru\text{-}(p\text{-}cymene)Cl_2(PPh_3)]$ is attached to polymer-supported triphenylphosphine for the enol formate synthesis (Scheme 3.1.11).[14f] This air-stable, immobilized catalyst was reused several times, and no leaching from the polymer support was observed.



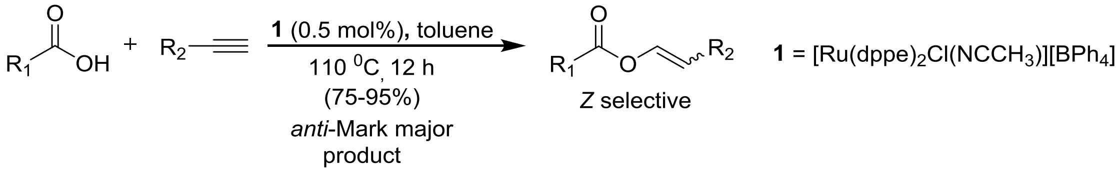
Scheme 3.1.11 Use of a resin-bound arene-ruthenium complex for the enol formate synthesis.

Tsukada *et al*., in 2010, showed that dinuclear palladium complex **1** affords trans-adducts selectively upon catalysis of the addition reactions of carboxylic acid to unactivated internal alkynes in moderate yields (Scheme 3.1.12).[5e]



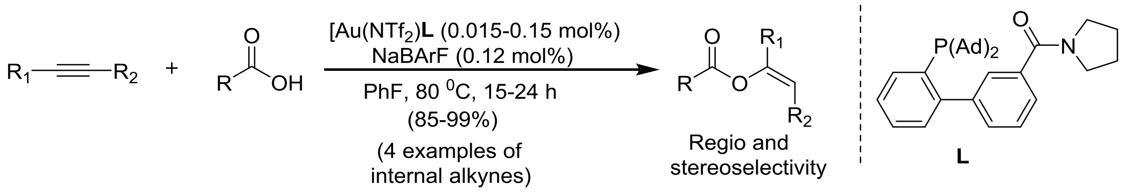
Scheme 3.1.12 Dinuclear palladium complex-catalyzed addition reactions of carboxylic acid to unactivated internal alkynes.

Later in 2012, Bhattacharjee *et al*. documented the synthesis of Ru catalyst [Ru(dppe)$_2$(CH$_3$CN)Cl][BPh$_4$] from the precursor [(PPh$_3$)$_2$Ru(CH$_3$CN)$_3$Cl][BPh$_4$] for anti-Markovnikov addition of carboxylic acids to terminal alkynes to result in *Z*-vinyl esters (Scheme 3.1.13).[14b]



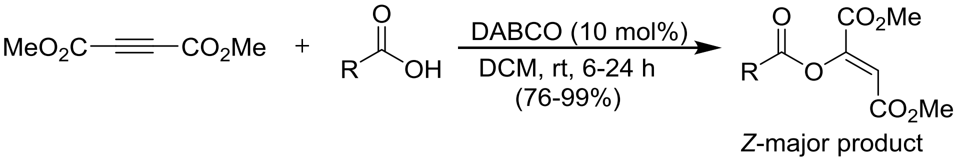
Scheme 3.1.13 Use of Ruthenium complex synthesized for anti-Markovnikov addition of carboxylic acids to terminal alkynes.

In 2014, Zhang *et al*. reported a novel ligand design based on the (1,10-biphenyl)-2-ylphosphine framework that made a significant improvement to the gold-catalyzed hydrocarboxylation (Scheme 3.1.14).[14a] The gold(I) complex derived from the biarylphosphine ligand, having a basic, H-bond accepting (pyrrolidin-1-yl)carbonyl group at the 3'-position, direct and promote an intramolecular nucleophilic anti-attack of the acid on the gold-activated alkynes giving regio- and stereo-selective enol esters in excellent yield. However, this methodology was demonstrated with four internal alkynes using low loadings of [Au] with prolonged reaction times (15-24 h).



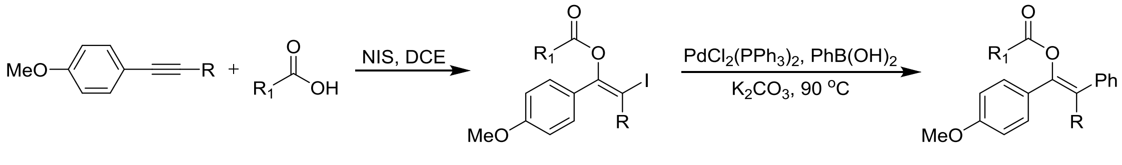
Scheme 3.1.14 Gold-catalyzed hydrocarboxylation of internal alkynes using ligand design based on the (1,10-biphenyl)-2-ylphosphine framework.

Other than the transition metal-catalyzed acid addition to alkynes, a few efforts have been made on the metal-free addition of carboxylic acid to alkynes.[16] In 2006, Liang *et al*. described 1,4-diazabicyclo[2.2.2]octane (DABCO)-catalyzed stereoselective addition of carboxylic acids to activated alkyne dimethyl acetylenedicarboxylate (DMAD) under mild reaction conditions affording enol esters in good yield (Scheme 3.1.15).[16f]



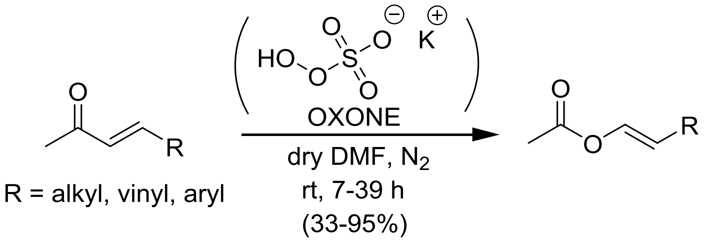
Scheme 3.1.15 DABCO-catalyzed addition of carboxylic acids to DMAD.

In 2011, Yanada *et al*. developed a one-pot protocol for the regio- and stereoselective synthesis of multisubstituted enol esters via successive cohalogenation and cross-coupling reactions from alkynylbenezenes (Scheme 3.1.16).[16g] The stereoselectivity of the reaction was observed to be dependent upon the substituent on the acetylene terminus. Alkyl-substituted alkynylbenzene yielded *E*-iodoalkene via anti-addition, while aryl-substituted alkynylbenzene afforded syn addition products.



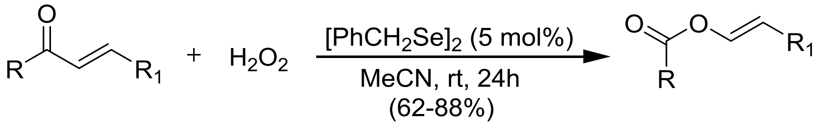
Scheme 3.1.16 The regio- and stereoselective synthesis of multisubstituted enol esters via successive cohalogenation and cross-coupling reactions from alkynylbenzenes.

Amo *et al*., in 2013, developed a completely different route to stereo-defined enol esters from *α,β*-unsaturated methyl ketones through a Baeyer-Villiger reaction employing oxone as an oxidant (Scheme 3.1.17).[16b] The enol ester products retain the stereochemistry of the *α,β*-unsaturated methyl ketones used as substrates. However, this method has limited substrate scope, and excess potassium monopersulfate triple salt results in large amounts of solid waste.



Scheme 3.1.17 The Baeyer-Villiger oxidation of *α,β*-unsaturated ketones using oxone oxidant to access stereo-defined enol esters.

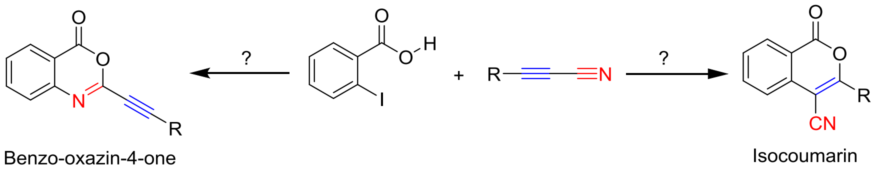
Based on the same concept, Zang *et al*., in 2015, developed organoselenium-catalyzed chemoselective Baeyer-Villiger oxidation of *α,β*-unsaturated ketones by using H_2O_2 as a greener oxidant to access enol esters. The strategy showed good substrate scope with water as a green side product (Scheme 3.1.18).[16h]



Scheme 3.1.18 The organoselenium-catalyzed Baeyer-Villiger oxidation of *α,β*-unsaturated ketones using H_2O_2 oxidant to access stereo-defined enol esters.

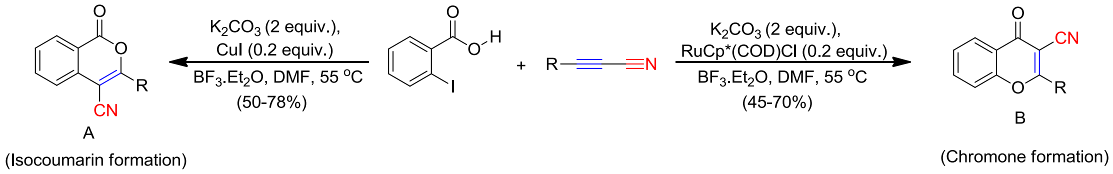
All the methods discussed till now for the synthesis of enol esters are assisted by either toxic or expensive metal salts, harsh reaction conditions, lengthy troublesome procedures, toxic reagents, and costly ligands. Moreover, reports on metal-free hydrocarboxylation reactions are rather limited. Thus, it is highly desirable to develop transition metal-free general and practical methods to synthesize regio- and stereo-defined enol esters under mild reaction conditions.

Parallelly, we were working on another research project which involved the chemoselective synthesis of isocoumarins and benzo-oxazin-4-one derivatives from 2-iodobenzoic acid and bifunctional alkynenitriles (Scheme 3.1.19).



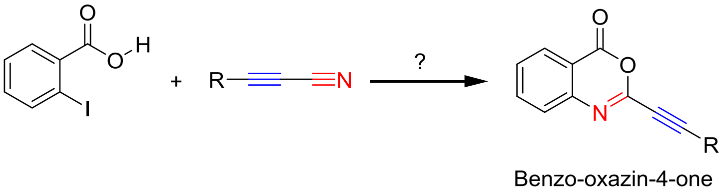
Scheme 3.1.19 Project based on chemoselective synthesis of isocoumarins and benzo-oxazin-4-one derivatives from 2-iodobenzoic acid and bifunctional alkynenitriles.

To our delight, we were able to find suitable conditions not only for isocoumarins synthesis but also for chromones from the same substrate molecules just by changing the metal catalyst used, as shown in Scheme 3.1.20.



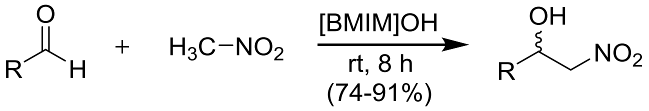
Scheme 3.1.20 Ruthenium-catalyzed chromone and copper-catalyzed isocoumarin synthesis from alkynenitriles.

However, we could not meet the challenge of finding suitable conditions to make the CN group react chemoselectively in the presence of acetylene moiety to afford benzo-oxazin-4-one derivatives (Scheme 3.1.21).



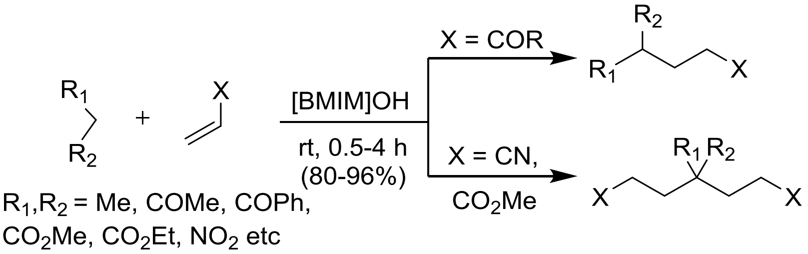
Scheme 3.1.21 Unsuccessful synthesis of benzo-oxazin-4-one derivative from alkynenitrile.

It has been found that besides widely used transition metal-free organocatalysts such as Lewis bases, Lewis acids, Brønsted bases, and Brønsted acids, ionic liquids (ILs) have proven highly instructive tools for enhancing the rates of chemical reactions.[17] Besides their extremely useful properties as the solvent, the ionic nature of the IL anion and cation can offer dual functionalities by acting simultaneously as a solvent for reactants and a catalyst for organic transformation reactions. For instance, Wu *et al*., in 2008, reported an efficient protocol for the Henry reaction using basic ionic liquid [BMIM]OH as catalyst and reaction medium, giving desired product in good to excellent yields (Scheme 3.1.22).[17e]



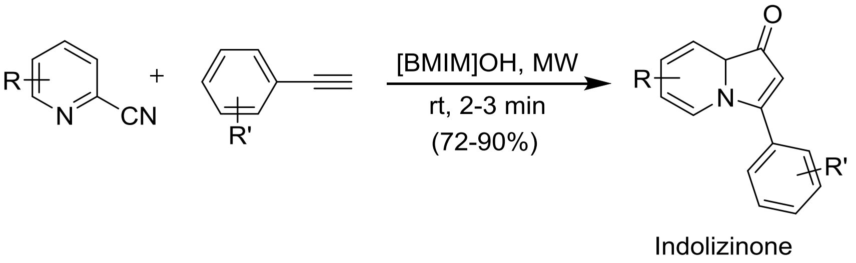
Scheme 3.1.22 Henry reaction using basic ionic liquid [BMIM]OH as catalyst and reaction medium.

Ranu group has also reported the dramatic influence of a task-specific ionic liquid, [BMIM]OH, in Michael addition of active methylene compounds to conjugated ketones, carboxylic esters, and nitriles when used as a reaction medium (Scheme 3.1.23).[17b]



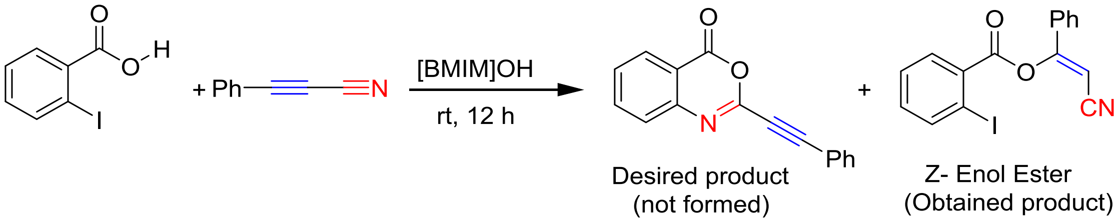
Scheme 3.1.23 Ionic liquid, [BMIM]OH mediated Michael addition of active methylene compounds to conjugated ketones, carboxylic esters, and nitriles.

Siddiqui *et al*., in 2013, reported an efficient and eco-compatible strategy for synthesizing indolizinones by hydroalkynylation of nitrile and intramolecular hydroamination of the carbon-carbon multiple bond using [BMIM]OH as catalyst and reaction medium (Scheme 3.1.24).[17f]



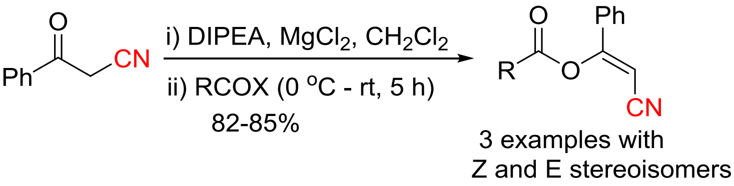
Scheme 3.1.24 [BMIM]OH promoted hydroalkynylation of nitrile and intramolecular hydroamination of the carbon-carbon multiple bond affording indolizinones.

Based on a literature survey on such ionic liquid-mediated transformations and taking a hint from work done by Siddiqui and co-workers in 2013, we reacted 2-iodobenzoic acid with phenylacetylenenitrile using [BMIM]OH as a reaction medium. Instead of getting the desired product, we obtained nitrile substituted enol ester as the sole isolated product in good yield. ^{1}H-NMR and 2D NOE analysis showed the formation of *Z*-enol ester with complete regioselectivity. We repeated the reaction many times and obtained the same result every time (Scheme 3.1.25).[17g]



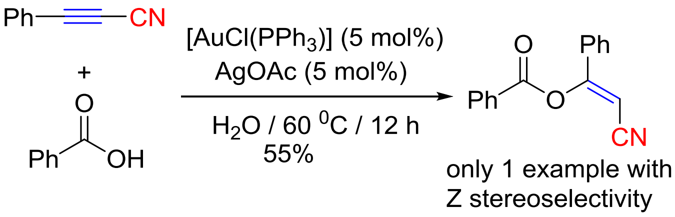
Scheme 3.1.25 Use of Siddiqui's reaction conditions i.e. ionic liquid [BMIM]OH as reaction medium for reaction of 2-iodobenzoic acid with phenylacetylenenitrile.

We found only two reports in the literature on nitrile-substituted enol ester synthesis (Scheme 3.1.26). Mansour, in 1988, reported only three examples of nitrile-substituted enol esters as mixtures of *Z*- and *E*-isomers prepared by reacting benzoylacetonitriles and benzoyl bromide in the presence of diisopropylethylamine (DIPEA), $MgCl_2$ in DCM solvent (Scheme 3.1.26).[18]



Scheme 3.1.26 Mansour’s report on nitrile-substituted enol ester synthesis via reacting benzoylacetonitriles and benzoyl bromide.

In 2017, the Cadierno group reported the [AuCl(PPh_3)]/AgOAc (5 mol%)-catalyzed addition of carboxylic acids to internal alkynes, in which only one example of nitrile-substituted enol ester with *Z* stereoselectivity was demonstrated albeit, in low yield (Scheme 3.1.27).[14e]



Scheme 3.1.27 [AuCl(PPh_3)]/AgOAc-catalyzed addition of carboxylic acids to internal alkynes.

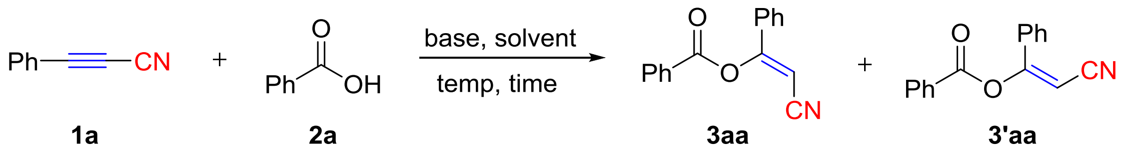
The nitrile group is a highly privileged functionality widely found in various natural products and biologically active molecules. Moreover, these are versatile precursors to building other helpful functional groups. Owing to their synthetic versatility, synthesizing stereo-defined nitrile-substituted enol esters in a green, atom-economical, straightforward way is appealing. Again, no example of exclusive regio- and stereoselective nitrile substituted enol ester synthesis has been reported via a transition metal-free, ionic liquid [BMIM]OH mediated hydrocarboxylation of alkynenitriles. We herein report the synthesis of nitrile-substituted enol esters in a *Z*-stereoselective fashion with the reusability of the ionic liquid for up to ten runs without loss of activity.

3.2 Results and Discussion

To accomplish the initial investigation of the transition metal-free, ionic liquid [BMIM]OH mediated stereoselective hydrocarboxylation of alkynenitriles presented herein, phenylacetytelenentrile **1a** and benzoic acid **2a** were selected as model substrates for the synthesis of enol ester **3aa** and the results are summarized in Table 3.2.1.

Initially, [BMIM]OH was tested in a stochiometric amount in water at room and elevated temperatures. However, only traces of desired product were observed (Table 3.2.1, entries 1-2). The use of polar solvent ACN in place of water afforded an inseparable isomeric mixture (Table 3.2.1, entries 3-4). When we used [BMIM]OH as a reaction medium, we obtained the expected product in 70% yield in 12 h (Table 3.2.1, entry 5). While accomplishing the optimized reaction conditions, we surveyed a set of bases and found K_2CO_3, Cs_2CO_3, and NEt_3 afforded the desired product in acetonitrile but as an inseparable isomeric mixture (Table 3.2.1, entries 7-9). The reaction using only a phase transfer reagent in place of ionic liquid [BMIM]OH in water as well as in ACN solvent resulted an isomeric enol ester mixture in low yield taking 36 h (Table 3.2.1, entries 10-11). At the same time, the reaction with K_2CO_3 as a base and TBAF as a phase transfer reagent in water increased the yield of the isomeric enol ester mixture to 70% (Table 3.2.1, entry 12). Ionic liquid [BMIM]Br, was also assessed for this transformation. However, it couldn’t give the expected product without base (Table 3.2.1, entry 13). In contrast, when K_2CO_3 was used as a base, *Z*-enol ester was obtained as the sole isolated product in 60% yield (Table 3.2.1, entry 14). Moreover, increased temperature resulted in decreased output and the formation of undesired side products (Table 3.2.1, entry 15).

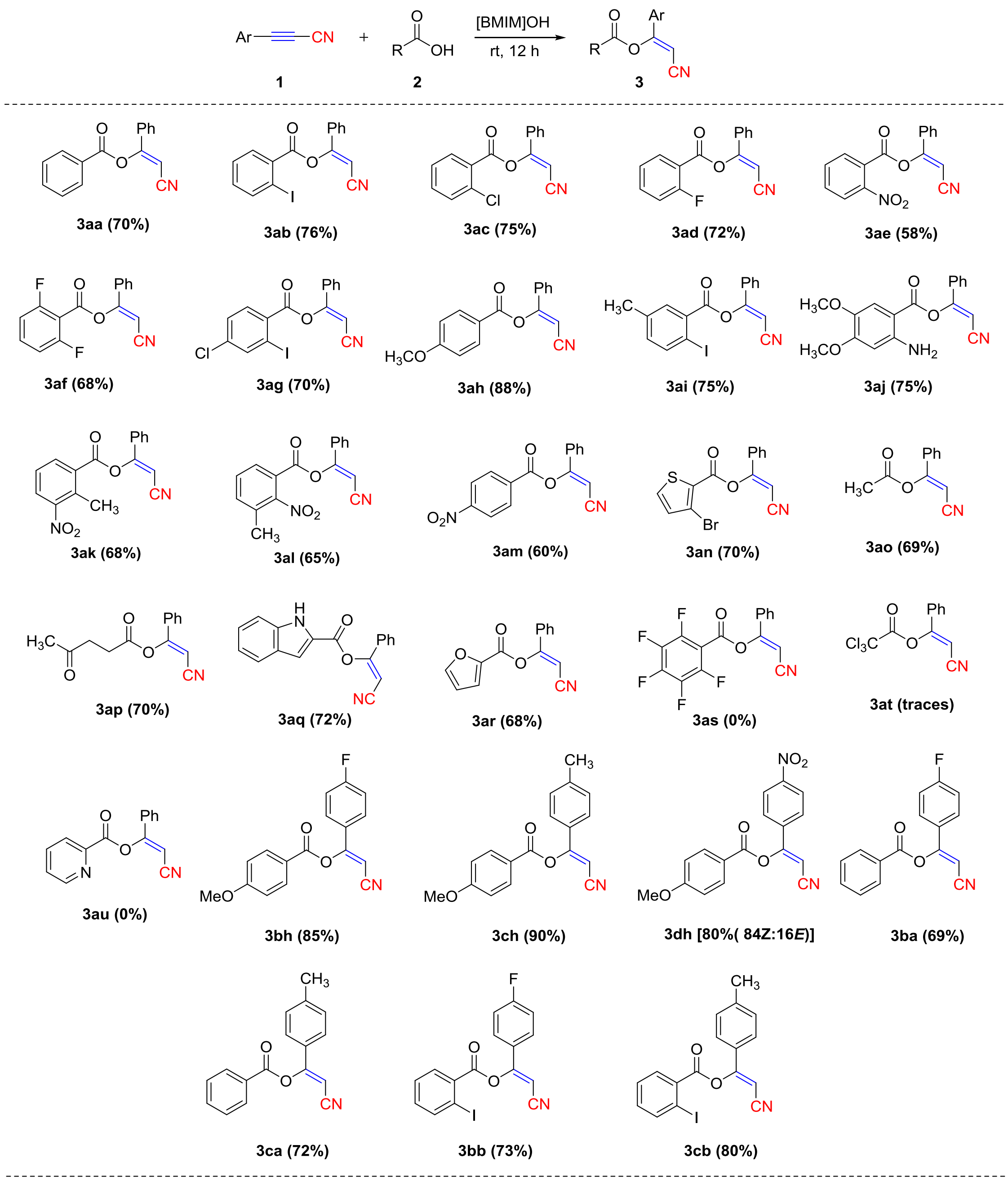
Table 3.2.1 Optimization of reaction conditions.[a]



Entry	Base (equiv.)	Solvent (mL)	Temp (°C)	Time (h)	Yield[b] (%) (3aa:3'aa)
1	[BMIM]OH (1)	H_2O (1)	rt	12	traces
2	[BMIM]OH (1)	H_2O (1)	55	12	traces
3	[BMIM]OH (1)	MeCN (1)	rt	12	50 (1.2:1)[c]
4	[BMIM]OH (1)	MeCN (1)	55	12	37 (1.2:1)[c]
5	**-**	**[BMIM]OH (2)**	**rt**	**12**	**70 (1:0)**
6	K_2CO_3 (0.5)	DMF (1)	rt	12	traces
7	K_2CO_3 (0.5)	MeCN (1)	rt	12	39 (1.2:1)[c]
8	NEt_3 (1)	MeCN (1)	rt	12	46 (1.2:1)[c]
9	Cs_2CO_3 (0.5)	MeCN (1)	rt	12	50 (1.7:1)[c]
10	TBAF (1)	H_2O (1)	rt	36	30 (1.1:1)[c]
11	TBAF (1)	MeCN (1)	rt	36	39 (1.1:1)[c]
12	K_2CO_3/TBAF (0.5/1)	H_2O (1)	rt	36	70 (1.2:1)[c]
13	-	[BMIM]Br (2)	rt	12	-
14	K_2CO_3 (0.5)	[BMIM]Br (2)	rt	12	60 (1:0)
15	K_2CO_3 (0.5)	[BMIM]Br (2)	75	12	30 (1:0)

[a] Optimized reaction conditions: **1a** (63.5 mg, 0.5 mmol) and **2a** (61 mg, 0.5 mmol), [BMIM]OH (1 mL), rt, 12 h, [b] isolated yield, [c] ratio determined by ^{1}H-NMR.

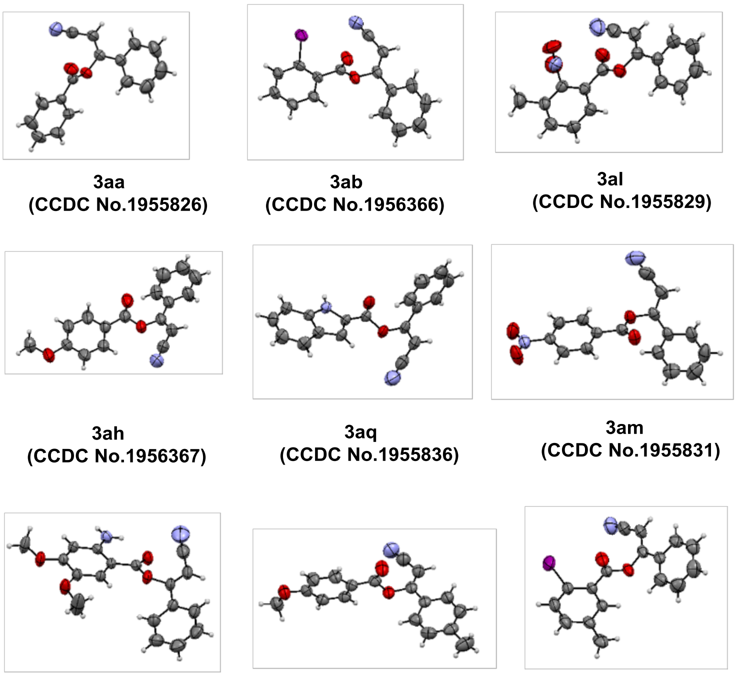
With the optimized reaction conditions in hand, the investigation was extended to different widely substituted aliphatic and aromatic carboxylic acids **2** and various alkynenitriles **1** to determine the substrate scope for the ionic liquid [BMIM]OH mediated hydrocarboxylation reaction leading to **3** (Scheme 3.2.1).



Reagents and conditions: **1** (0.5 mmol) and **2** (0.5 mmol), [BMIM]OH (1 mL), rt, 12 h

Scheme 3.2.1 Ionic liquid [BMIM]OH mediated addition of carboxylic acids to alkynenitriles.

As shown in Scheme 3.2.1, a library of regio- and *Z* stereoselective enol esters **3** were synthesized in good to excellent yields, which exhibited the general applicability of the protocol. It was noticed that different benzoic acids with various functional groups attached at different positions of the aryl ring, including electron-rich and electron-poor groups (methyl, methoxy, amine, iodo, chloro, fluoro and nitro groups), were conveniently transformed to respective functionalized enol ester derivatives indicating the remarkable functional group compatibility of this protocol. Observation showed that the isolated yields of the products obtained using benzoic acids with electron-donating groups were relatively higher than electron-donating groups substituting benzoic acids, most likely due to their enhanced nucleophilicity. As expected, the considerably more acidic hexaflourobenzoic acid (**3as**) and trichloroacetic acid (**3at**) are too weak nucleophiles and afforded no products. In addition, aliphatic carboxylic acids (**3ao** and **3ap**) could participate equally well in the reaction. It is noteworthy that heteroaryl carboxylic acids could also give good yields for the desired esters. Although pyridine-2-carboxylic acid (**3au**) could not provide the desired product, 2-furoicacid (**3ar**), indole 2-carboxylic acid (**3aq**), and 3-bromo-2-thiophenecarboxylic acid (**3an**) gave the corresponding enol esters in good yields. Compounds **3aa, 3ab, 3ah, 3al, 3ch, 3am, 3aq, 3ai,** and **3aj** were isolated as pure single crystals, and the structures were confirmed by single-crystal X-ray analysis and are shown in Figure 3.2.1.[19]



3aa
(CCDC No.1955826)

3ab
(CCDC No.1956366)

3al
(CCDC No.1955829)

3ah
(CCDC No.1956367)

3aq
(CCDC No.1955836)

3am
(CCDC No.1955831)

3aj
(CCDC No.1955847)

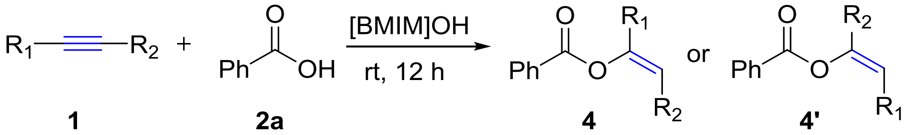
3ch
(CCDC No.1955825)

3ai
(CCDC No.1955838)

Figure 3.2.1 X-ray crystal structures of enol esters.

We also tried the addition reactions of benzoic acid with the non-nitrile substituted terminal, symmetrical and unsymmetrical internal alkynes as shown in Table 3.2.2. However, the expected products were not observed in these cases. Only highly activated internal alkyne with diester groups could afford 50% yield with *Z* stereoselectivity (Table 3.2.2, entry 4). Whereas, internal alkyne with a nitrile group gave the corresponding enol ester in good yield with excellent stereoselectivity, as shown earlier. This indicates that the nitrile group of bifunctional alkynylnitrile in the presence of [BMIM]OH plays a significant role in directing the reactants to result in a complete regio- and *Z* stereoselective enol esters (Table 3.2.2, entries 1, 2, 5 and 6).

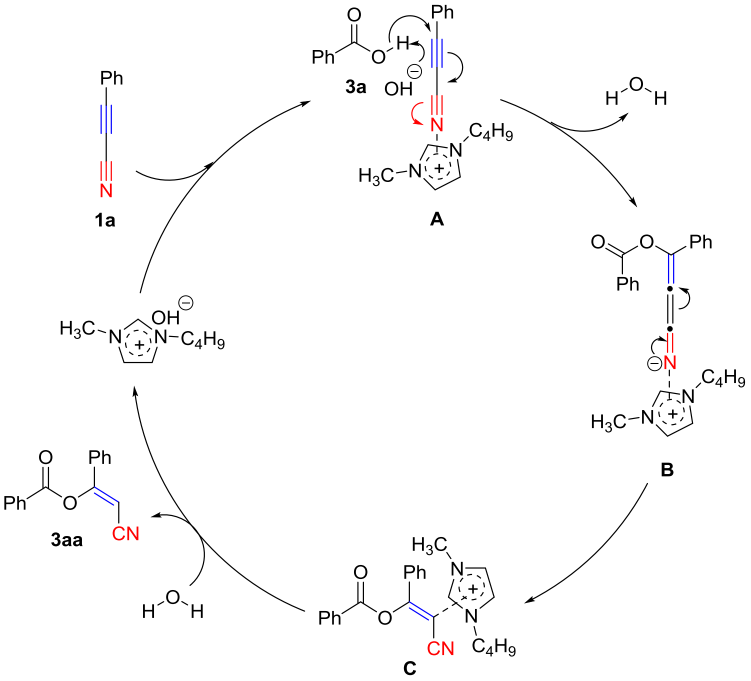
Table 3.2.2 [BMIM]OH mediated addition of benzoic acid to various alkynes.[a]



Entry	R_1	R_2	Yield[b] %	4:4'
1	Ph	H	traces	-
2	Ph	Ph	traces	-
3	Ph	COOEt	traces	-
4	COOEt	COOEt	50	1:0
5	Ph	SeCN	no reaction	-
6	Ph	SCN	no reaction	-

[a] Optimized reaction conditions: **1a** (0.5 mmol) and **2a** (0.5 mmol), [BMIM]OH (1 mL), rt, 12 h, [b] isolated yield.

Based on experimental results and the literature survey,[20] the plausible mechanism for the [BMIM]OH-mediated hydrocarboxylation of alkynenitriles is proposed in Scheme 3.2.2. Initially, the cationic imidazolium ring activates the bifunctional alkynenitrile by coordinating to the nitrile group to form complex **A**, while the hydroxide ion generates carboxylate ion by deprotonating the carboxylic acid. Subsequent nucleophilic attack of carboxylate ion on the more electrophilic carbon of the activated alkyne in complex **A** leads to complex **B**, followed by complex **C**, in which the cationic imidazolium ring stabilizes the negative charge. Subsequently, it is replaced by the proton of the eliminated water. Then, as a result, desired product is formed with the regeneration of the [BMIM]OH, and the catalytic cycle continues. In this context, it is essential to mention that complex **C**'s stereochemistry helps us access the *Z*-enol ester product exclusively.



Scheme 3.2.2 Plausible mechanism.

To judge the reusability of the ionic liquid [BMIM]OH used in the newly developed strategy, the synthesis of **3aa** and **3ah** from the reaction of corresponding alkynenitriles **1** and aromatic carboxylic acids **2** was checked. After each run, the reaction mixture was extracted with ether. The ionic liquid left was reused for the next run after drying under a vacuum. The ionic liquid [BMIM]OH could be effectively used for 10 cycles without noticeable loss in the quantity of the ionic liquid and the isolated yields of **3aa** and **3ah** (Figure 3.2.2).

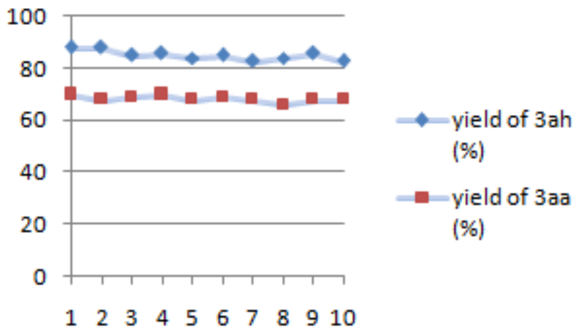
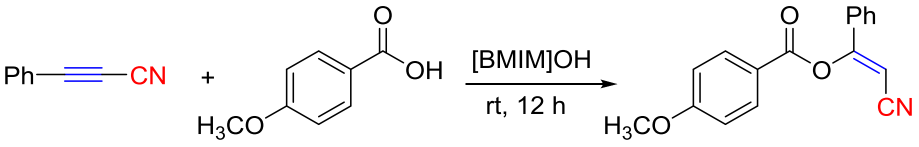


Figure 3.2.2 Reusability studies of ionic liquid [BMIM]OH for the synthesis of **3aa** and **3ah.**

A 5 mmol scale reaction was conducted under optimized reaction conditions to synthesize **3ah** from **1a** and **2h**. To our delight, 1.2 g of **3ah** with 82% yield was obtained (Scheme 3.2.3), which shows this protocol's general applicability and large-scale productivity.

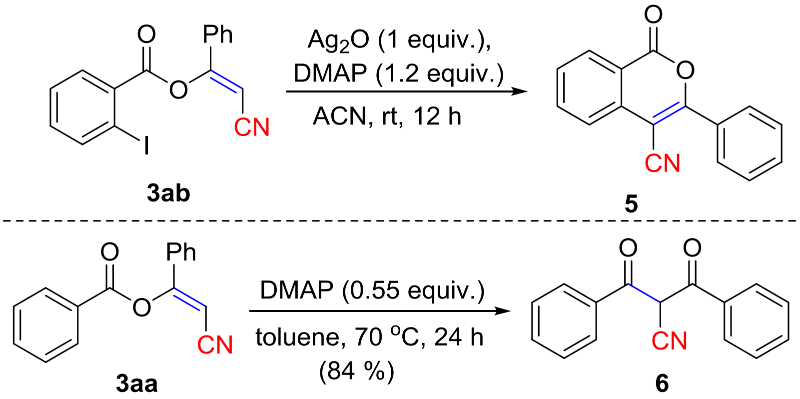


1a **2h** **3ah** (82%)[b]

Reagents and conditions: **1a** (0.635 g, 5 mmol), **2h** (0.76 g, 5 mmol), [BMIM]OH (3 mL), rt, 12 h, [b] isolated yield.

Scheme 3.2.3 [BMIM]OH mediated hydrocarboxylation reaction for the gram scale synthesis of **3ah**.

Motivated by these excellent results of this protocol, we initiated the studies for some significant transformations of enol esters (Scheme 3.2.4). To our delight, treating **3ab** with a stochiometric amount of Ag_2O and DMAP in ACN led to biologically important, nitrile substituted isocoumarin[21] **5** in 77% yield. In addition, heating **3aa** with DMAP gave 2-cyano-1,3-diphenyl-1,3-propanedione[22] **6** in 84% yield.



Scheme 3.2.4 Synthetic applications of enol esters.

3.3 Conclusions

In conclusion, we have demonstrated the first example of transition metal-free ionic liquid [BMIM]OH mediated regio- and stereoselective hydrocarboxylation of alkynenitriles, leading to a library of nitrile substituted enol esters in good to excellent yields in the absence of any additive or solvent. The operational simplicity, high efficiency, use of readily available inexpensive reagents, mild reaction conditions, high atom economical, general applicability, recyclability of the ionic liquid, and complete regio- and stereoselectivity are the salient features of this approach.

3.4 Experimental Section

Chemicals and reagents were purchased from commercial suppliers and used without further purification. Thin layer chromatography (TLC) was performed using pre-coated plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm). Column chromatography was performed using E. Merck silica gel 60 (100-200 mesh. NMR spectra were recorded in $CDCl_3$, on JEOL JNM-ECS spectrometer at operating frequencies of 400 MHz (^{1}H) or 100 MHz (^{13}C) as indicated in the individual spectrum. Chemical shifts (δ) are given in ppm relative to residual solvent (chloroform, δ = 7.26 for ^{1}H and 77.16 for proton decoupled ^{13}C NMR) and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, q for quartet and m for multiplet. High-resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) methods on waters mass spectrometer. Melting points were determined using BIBBY-SMP30 melting point meter. Single crystal X-ray structural data was collected on a CMOS based Bruker D8 Venture PHOTON 100 diffractometer equipped with a INCOATEC micro-focus source with graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) operating at 50 kV and 30 mA. The alkynenitriles (**1a-d**),[23] were prepared according to the reported literature procedure.

3.4.1 General procedure for the synthesis of compound 3

In a round bottom flask, a mixture of alkynenitrile **1** (0.5 mmol), carboxylic acid **2** (0.5 mmol) and [BMIM]OH (1 mL) was stirred for 12 h at room temperature. After completion of reaction checked by TLC, the product was extracted with ether (3x20 mL and evaporated under reduced pressure. The crude was further purified through column chromatography over silica gel (100-200 mesh) with EtOAc/hexane as elute. After isolation of the product, the remaining ionic liquid was washed with ether (3x10 mL) to remove organic impurity and evaporated under reduced pressure to afford [BMIM]OH, which was reused in subsequent runs without further purification.

3.4.2 General procedure for the synthesis of compound 5 from 3ab

To a solution of enol ester **3ab** (80 mg) in CH_3CN (3 mL) at room temperature were added silver oxide (1 equiv.) and DMAP (1.2 equiv.). The mixture was stirred for 12 h and then it was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

3.4.3 General procedure for the synthesis of compound 6 from 3aa

To a solution of (*Z*)-2-cyano-1-phenylvinylbenzoate **3aa** (63 mg) in toluene (2 mL) was added DMAP (0.55 equiv.). The mixture was heated at 70 °C for 16 h. Afterward, the solvent was removed under reduced pressure and reaction crude was purified by column chromatography to afford 2-benzoyl-3-oxo-3-phenylpropanenitrile **6**.

3.4.4 Characterization data of products

(Z)-2-Cyano-1-phenylvinylbenzoate (3aa): White crystalline solid (87 mg, 70%); mp 95-97°C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.24 (d *J* = 7.9 Hz, 2H), 7.71-7.67 (m, 1H), 7.58-7.53 (m, 4H), 7.50-7.46 (m, 1H), 7.43-7.39 (m, 2H), 5.83 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.3, 163.1, 134.5, 131.9, 131.5, 130.5, 129.1, 128.9, 127.7, 125.6, 114.6, 87.4; HRMS: *m/z* calculated for $C_{16}H_{12}NO_2$ $[M+H]^+$: 250.0868, found 250.0874

(Z)-2-Cyano-1-phenylvinyl 2-iodobenzoate (3ab): Pale yellow crystalline solid (142.5 mg, 76%); mp 98-101 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.21 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.58-7.56 (m, 2H), 7.52-7.46 (m, 2H), 7.43-7.39 (m, 2H), 7.27-7.23 (m, 1H), 5.81 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.2, 162.4, 142.07, 134.1, 132.1, 132.0, 131.9, 131.2, 129.2, 128.4, 125.7, 114.6, 95.2, 87.5; HRMS: *m/z* calculated for $C_{16}H_{11}INO_2$ $[M+H]^+$: 375.9834, found 375.9827

(Z)-2-Cyano-1-phenylvinyl 2-chlorobenzoate (3ac): Pale yellow solid (106 mg, 75%); mp 84-87 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.19 (d, *J* = 7.7 Hz, 1H), 7.61-7.58 (m, 2H), 7.56-7.54 (m, 2H), 7.51-7.48 (m, 1H), 7.46-7.41 (m, 3H), 5.81 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.3, 161.6, 135.0, 134.2, 132.5, 132.1, 131.6, 131.4, 129.2, 127.4, 127.1, 125.8, 114.6, 87.6; HRMS: *m/z* calculated for $C_{16}H_{11}$ $ClNO_2$ $[M+H]^+$: 284.0478, found 284.0451

(Z)-2-Cyano-1-phenylvinyl 2-fluorobenzoate (3ad): Pale yellow solid (96 mg, 72%); mp 99-104 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.14 (td, *J* = 7.3, 1.8 Hz, 1H), 7.69-7.63 (m, 1H), 7.60-7.58 (m, 2H), 7.52-7.47 (m, 1H), 7.45-7.41 (m, 2H), 7.31 (td, *J* = 7.5, 1.2 Hz, 1H), 7.27-7.22 (m, 1H), 5.81 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.2, 163 (d, *J* = 262 Hz), 160.6 (d, *J* = 4 Hz), 136.3(d, *J* =9Hz), 132.9, 132.0, 131.5, 129.3, 125.8, 124.6 (d, *J* = 3.7 Hz), 117.5 (d, *J* = 21.3 Hz), 116.5(d, *J* = 9.4 Hz),114.6, 87.6; HRMS: *m/z* calculated for $C_{16}H_{11}FNO_2$ $[M+H]^+$: 268.0774, found 268.0745

(Z)-2-Cyano-1-phenylvinyl 2-nitrobenzoate (3ae): Yellowish white solid (85.26 mg, 58%); mp 107-111 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.13-8.07 (m, 2H), 7.82 (td, *J* = 7.6, 1.3 Hz, 1H), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H), 7.71-7.67 (m, 2H), 7.56-7.46 (m, 3H), 5.84 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.3, 162.1, 147.6, 134.0, 132.8, 132.5, 130.9, 130.6, 129.4, 126.4, 126.3, 124.5, 114.7, 87.8; HRMS: *m/z* calculated for $C_{16}H_{11}N_2O_4$ [M+H]$^+$: 295.0719, found 295.0710

(*Z*)-2-Cyano-1-phenylvinyl 2,6-difluorobenzoate (3af): Pale yellow viscous liquid (97 mg, 68%); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.64-7.60 (m, 2H), 7.58-7.54 (m, 1H), 7.53-7.48 (m, 1H), 7.47-7.43 (m, 2H), 7.06 (t, *J* = 8.6 Hz, 2H), 5.81 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 163.7, 161.5 (dd, *J* = 260, 5.1 Hz), 157.7, 134.8 (t, *J* = 10.8 Hz), 132.1, 131.1, 129.3, 125.9, 114.3, 112.6 (dd, *J* = 21.8, 3.7 Hz), 108.6 (t, *J* = 16.2 Hz), 87.9; HRMS: *m/z* calculated for $C_{16}H_{10}F_2NO_2$ [M+H]$^+$: 286.0680, found 286.0663

(*Z*)-2-Cyano-1-phenylvinyl 4-chloro-2-iodobenzoate (3ag): Pale yellow solid (143 mg, 70%); mp 115-118 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.17 (d, *J* = 8.2 Hz, 1H), 8.12 (d, *J* = 2.2 Hz, 1H), 7.58-7.55 (m, 2H), 7.53-7.49 (m, 2H), 7.46-7.42 (m, 2H), 5.81 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.2, 161.7, 141.8, 140.0, 132.9, 132.2, 131.2, 130.2, 129.3, 128.8, 125.8, 114.6, 95.9, 87.7; HRMS: *m/z* calculated for $C_{16}H_{10}ClINO_2$ [M+H]$^+$: 409.9445, found 409.9454

(*Z*)-2-Cyano-1-phenylvinyl 4-methoxybenzoate (3ah): White crystalline solid (122.8 mg, 88%); mp 95-100 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.17 (d, *J* = 9.1 Hz, 2H), 7.56-7.54 (m, 2H), 7.49-7.45 (m, 1H), 7.43-7.38 (m, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 5.79 (s, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.7, 164.6, 162.9, 132.9, 131.9, 129.2, 125.7, 120.0, 114.8, 114.3, 87.3, 55.7; HRMS: *m/z* calculated for $C_{17}H_{14}NO_3$ [M+H]$^+$: 280.0974, found 280.0946

(*Z*)-2-Cyano-1-phenylvinyl 2-iodo-5-methylbenzoate (3ai): White crystalline solid (145.9 mg, 75%); mp 102-104 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.03 (d, *J* = 1.95 Hz, 1H), 7.95(d, *J* = 8.1 Hz, 1H), 7.60-7.57 (m, 2H), 7.52-7.48 (m, 1H), 7.46-7.42 (m, 2H), 7.10(dd, *J* = 8.1, 1.9 Hz, 1H), 5.81 (s, 1H), 2.41(s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.4, 162.5, 142.0, 138.8, 135.3, 133.0, 132.1, 131.7, 131.4, 129.3, 125.9, 114.7, 91.4, 87.6, 21.0; HRMS: *m/z* calculated for $C_{17}H_{13}INO_2$ [M+H]$^+$: 389.9991, found 389.9971

(*Z*)-2-Cyano-1-phenylvinyl 2-amino-4,5-dimethoxybenzoate (3aj): Pale yellow crystalline solid (121.5 mg, 75%); mp 170-175 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.57-

7.54 (m, 2H), 7.49-7.46 (m, 2H), 7.43-7.39 (m, 2H), 6.16 (s, 1H), 5.78 (s, 1H), 5.63 (s, broad, 2H), 3.89 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 164.1, 156.6, 149.3, 141.1, 132.2, 131.8, 129.2, 125.7, 115.0, 112.1, 99.1, 98.9, 87.2, 56.6, 56.0; HRMS: *m/z* calculated for $C_{18}H_{17}N_2O_4$ $[M+H]^+$: 325.1188, found 325.1162

(*Z*)-2-Cyano-1-phenylvinyl 2-methyl-3-nitrobenzoate (3ak): Yellow solid (104.72 mg, 68%); mp 100-104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, *J* = 7.8 Hz, 1H), 7.97(d, *J* = 8.3 Hz, 1H), 7.56-7.50 (m, 4H), 7.49-7.44 (m, 2H), 5.84 (s, 1H), 2.68(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 162.3, 152.4, 134.9, 134.5, 132.3, 131.3, 130.4, 129.4, 128.2, 127.1, 125.7, 114.7, 87.9, 16.3; HRMS: *m/z* calculated for $C_{17}H_{13}$ N_2O_4 $[M-H]^+$: 307.0719, found 307.0700

(*Z*)-2-Cyano-1-phenylvinyl 3-methyl-2-nitrobenzoate (3al): Pale Yellow crystalline solid (100 mg, 65%); mp 128-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 7.6 Hz, 1H), 7.64-7.58 (m, 2H), 7.56-7.48 (m, 3H), 7.46-7.42 (m, 2H), 5.79 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 160.2, 150.8, 137.1, 132.3, 131.4, 130.9, 130.5, 129.5, 129.4, 125.8, 121.3, 114.3, 87.9, 17.4; HRMS: *m/z* calculated for $C_{17}H_{13}$ N_2O_4 $[M+H]^+$: 309.0875, found 309.0853

(*Z*)-2-Cyano-1-phenylvinyl 4-nitrobenzoate (3am): Pale Yellow crystalline solid (88.2 mg, 60%); mp 180-185 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 4H), 7.56-7.50 (m, 3H), 7.47-7.42 (m, 2H), 5.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 161.5, 151.5, 133.2, 132.4, 131.8, 131.0, 129.4, 125.7, 124.2, 114.4, 88.0; HRMS: *m/z* calculated for $C_{16}H_{11}N_2O_4$ $[M+H]^+$: 295.0719, found 295.0691

(*Z*)-2-Cyano-1-phenylvinyl 3-bromothiophene-2-carboxylate (3an): Pale Yellow viscous liquid (116.6 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 5.2 Hz, 1H), 7.58-7.55 (m, 2H), 7.52-7.47 (m, 1H), 7.45-7.41 (m, 2H), 7.21 (d, *J* = 5.4 Hz, 1H), 5.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 156.9, 133.8, 132.1, 131.5, 129.3, 125.8, 124.8, 124.1, 120.6, 114.5, 88.0; HRMS: *m/z* calculated for $C_{14}H_9BrNO_2S$ $[M+H]^+$: 333.9537, found 333.9516

(*Z*)-2-Cyano-1-phenylvinyl acetate (3ao): Yellowish brown viscous liquid (64.5 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.46 (m, 3H), 7.45-7.39 (m, 2H), 5.71 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 167.2, 164.2, 132.0, 131.5, 129.2, 125.6, 114.7, 87.3, 20.7; HRMS: *m/z* calculated for $C_{16}H_{10}F_2NO_2$ [M-H]$^+$: 186.0555, found 186.0537

(*Z*)-2-Cyano-1-phenylvinyl 4-oxopentanoate (3ap): Yellow viscous liquid (85 mg, 70%); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.57-7.53 (m, 2H), 7.46-7.39 (m, 3H), 5.70 (s, 1H), 2.93-2.85 (m, 4H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 206.2, 169.5, 164.2, 132.0, 131.2, 129.1, 125.8, 114.7, 86.9, 37.7, 29.7, 27.9; HRMS: *m/z* calculated for $C_{14}H_{10}NO_3$ [M+H]$^+$: 244.0974, found 244.0963

(*Z*)-2-Cyano-1-phenylvinyl 1*H*-indole-2-carboxylate (3aq): Pale yellow crystalline solid (103.7 mg, 72%); mp 190-195 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.14 (broad, s, 1H), 7.75 (d, *J* = 8.2 Hz, 1H), 7.60 - 7.57 (m, 3H), 7.51 – 7.46 (m, 1H), 7.44-7.36 (m, 4H), 7.20 (td, *J* = 7.5, 1.3 Hz, 1H), 5.83 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 163.7, 158.2, 137.9, 132.1, 131.5, 129.2, 127.4, 126.8, 125.7, 124.6, 123.1, 121.5, 114.6, 112.2, 112.1, 87.7; HRMS: *m/z* calculated for $C_{18}H_{13}N_2O_2$ [M+H]$^+$: 289.0977, found 289.0976

(*Z*)-2-Cyano-1-phenylvinyl furan-2-carboxylate (3ar): Yellow viscous liquid (81.26 mg, 68%); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.72-7.71 (m, 1H), 7.57-7.52 (m, 2H), 7.50-7.46 (m, 2H), 7.43-7.37 (m, 2H), 6.64-6.62 (m, 1H), 5.81 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 163.4, 154.5, 148.4, 142.4, 132.1, 131.3, 129.2, 125.7, 121.4, 114.5, 112.7, 87.8; HRMS: *m/z* calculated for $C_{14}H_{10}NO_3$ [M+H]$^+$: 240.0661, found 240.0668

(*Z*)-2-Cyano-1-(p-tolyl)vinyl benzoate (3ca): Pale yellow solid (94.7 mg, 72%); mp 97-99 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.22 (d, *J* = 8.2 Hz, 2H), 7.69 (t, *J* = 7.4 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 5.76 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.3; HRMS: *m/z* calculated for $C_{17}H_{14}NO_2$ [M+H]$^+$: 264.1025, found 264.1027

(*Z*)-2-Cyano-1-(4-fluorophenyl)vinyl benzoate (3ba): Pale yellow solid (92 mg, 69%); mp 100-103°C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.21 (dd, *J* = 8.2, 1.5 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.58-7.53 (m, 4H), 7.11 (t, *J* = 8.6 Hz, 2H), 5.75 (s, 1H); ^{13}C NMR(100 MHz, CDCl$_3$): δ 164.93 (d, *J* = 254 Hz), 163.5, 163.2, 134.7, 130.7, 129.0, 128.1, 128.0, 127.7, 116.63 (d, *J* = 22 Hz), 116.3, 114.6, 114.5, 87.4

(Z)-2-Cyano-1-(p-tolyl)vinyl 2-iodobenzoate (3cb): Pale yellow solid (155.6 mg, 80%); mp 99-105 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.22 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.54-7.50 (m, 1H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.28 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 2H), 5.76 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.4, 162.6, 142.9, 142.2, 134.1, 132.2, 130.0, 128.6, 128.5, 125.9, 114.9, 95.3, 86.5, 21.7; HRMS: *m/z* calculated for $C_{17}H_{13}INO_2$ [M+H]$^+$: 389.9991, found 389.9975

(Z)-2-Cyano-1-(4-fluorophenyl)vinyl 2-iodobenzoate (3bb): Pale yellow dense viscous liquid (143 mg, 73%); ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.19 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.08 (dd, *J* = 8.2, 1.0 Hz, 1H), 7.60-7.56 (m, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 8.6 Hz, 2H), 5.76 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.8 (d, *J* = 254.8 Hz), 163.2, 162.4, 142.1, 134.3, 132.2, 131.8, 128.5, 128.2 (d, *J* = 9 Hz), 127.6 (d, *J* = 2.9 Hz),, 116.5 (d, *J* = 21.6 Hz), 114.4, 95.3, 87.5; HRMS: *m/z* calculated for $C_{16}H_{10}FINO_2$ [M+H]$^+$: 393.9740, found 393.9729

(Z)-2-Cyano-1-(p-tolyl)vinyl 4-methoxybenzoate (3ch): White crystalline solid (132.3 mg, 90%); mp 145-155 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.17 (d, *J* = 9.1 Hz, 2H), 7.43(d, *J* = 8.4 Hz, 2H), 7.20(d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 9.1Hz, 2H), 5.73 (s, 1H), 3.90 (s, 3H), 2.37(s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.8, 164.7, 162.9, 142.7, 132.9, 129.9, 129.2, 125.7, 120.2, 115.1, 114.3, 86.3, 55.7, 21.6; HRMS: *m/z* calculated for $C_{18}H_{16}NO_3$ [M+H]$^+$: 294.1130, found 294.1104

(Z)-2-Cyano-1-(4-fluorophenyl)vinyl 4-methoxybenzoate (3bh): Yellow solid (126.2 mg, 85%); mp 90-95 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.16 (d, *J* = 8.6 Hz, 2H), 7.57-7.53 (m, 2H), 7.09 (t, *J* = 8.6 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 5.74 (s, 1H), 3.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 164.83(d, *J* = 254 Hz), 164.81, 163.6, 162.8, 132.9, 128.2 (d, *J* = 3.4 Hz), 128.0 (d, *J* = 9.2 Hz), 119.8, 116.5 (d, *J* = 22 Hz), 114.7, 114.3, 87.2, 55.7; HRMS: *m/z* calculated for $C_{17}H_{13}FNO_3$ [M+H]$^+$: 298.0879, found 298.0881

(Z)-2-Cyano-1-(4-nitrophenyl)vinyl 4-methoxybenzoate (3dh): Pale yellow solid (130 mg, 80%); mp 109-114 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.27 (d, *J* = 8.6 Hz, 2H), 8.16 (d, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 9.1 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 5.91 (s, 1H), 3.92

(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 162.7, 162.4, 149.5, 137.9, 133.0, 128.7, 126.8, 124.5, 119.3, 114.5, 91.0, 55.8

1-Oxo-3-phenyl-1H-isochromene-4-carbonitrile (5): Yellowish dense viscous liquid (53 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, *J* = 7.9 Hz, 1H), 8.06-8.10 (m, 2H), 7.91 (m, 2H), 7.64-7.68 (m, 1H), 7.60-7.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 159.5, 136.2, 134.1, 132.4, 130.2, 130.1, 130.0, 129.1, 128.5, 124.6, 119.0, 115.2, 90.8; HRMS: *m/z* calculated for $C_{16}H_{10}NO_2$ $[M+H]^+$: 248.0712, found 248.0697

2-Benzoyl-3-oxo-3-phenylpropanenitrile (6): Pale yellowish viscous liquid (53 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): 18.31 (bs, 1H), 8.06 (d, *J* = 7.7 Hz, 4H), 7.64 (t, *J* = 7.7 Hz, 2H), δ 7.54 (t, *J* = 7.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 134.0, 133.8, 129.0, 128.7, 118.7, 86.3; HRMS: *m/z* calculated for $C_{16}H_{12}NO_2$ $[M+H]^+$: 250.0868, found 250.0861

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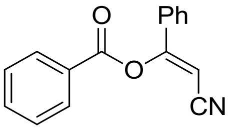
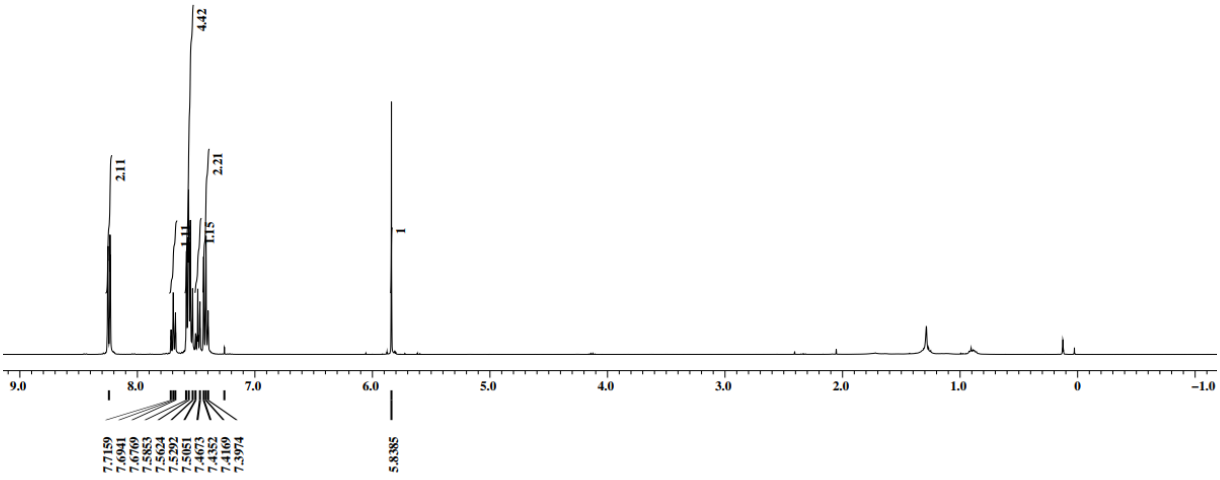
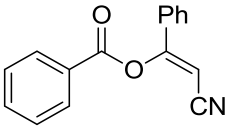
3.6 NMR spectra of compounds



3aa

^{1}H NMR (400 MHz, CDCl3)





3aa

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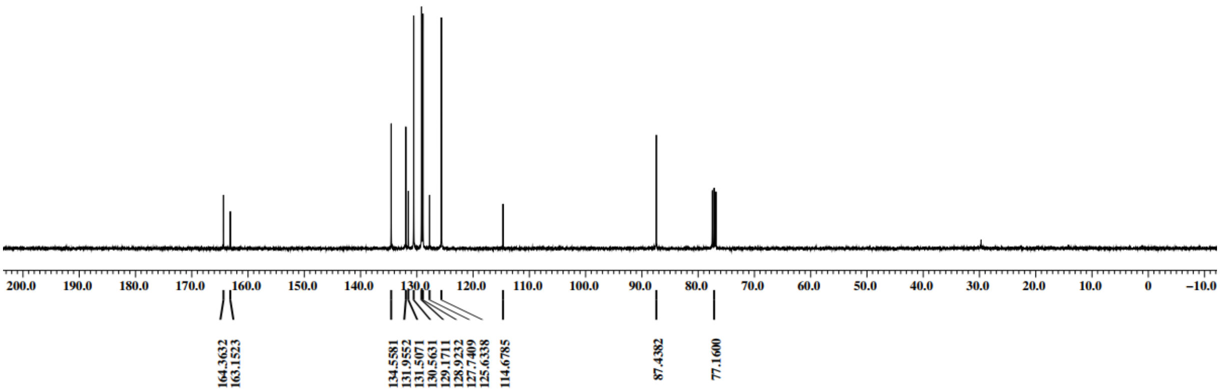

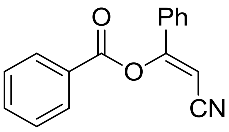

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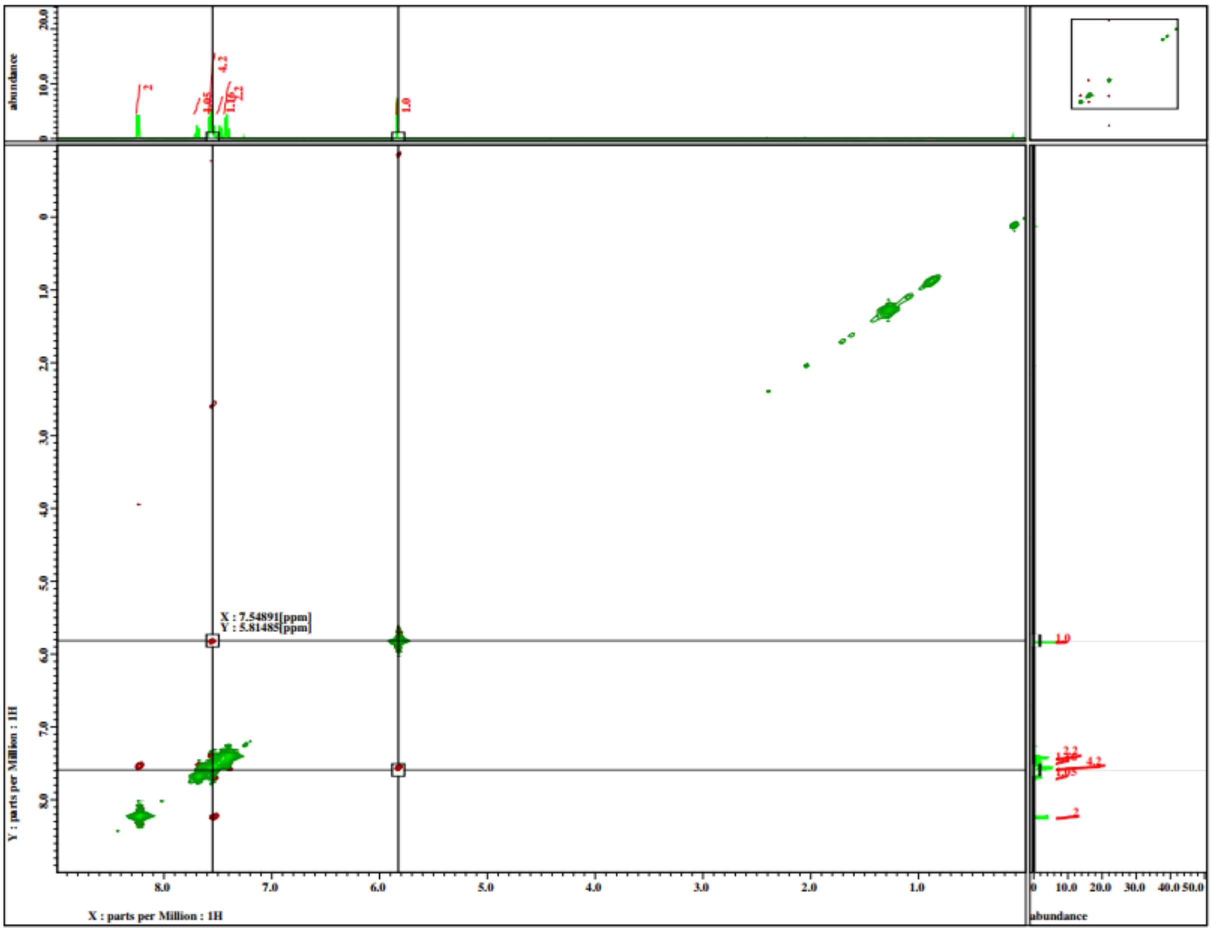

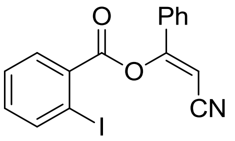

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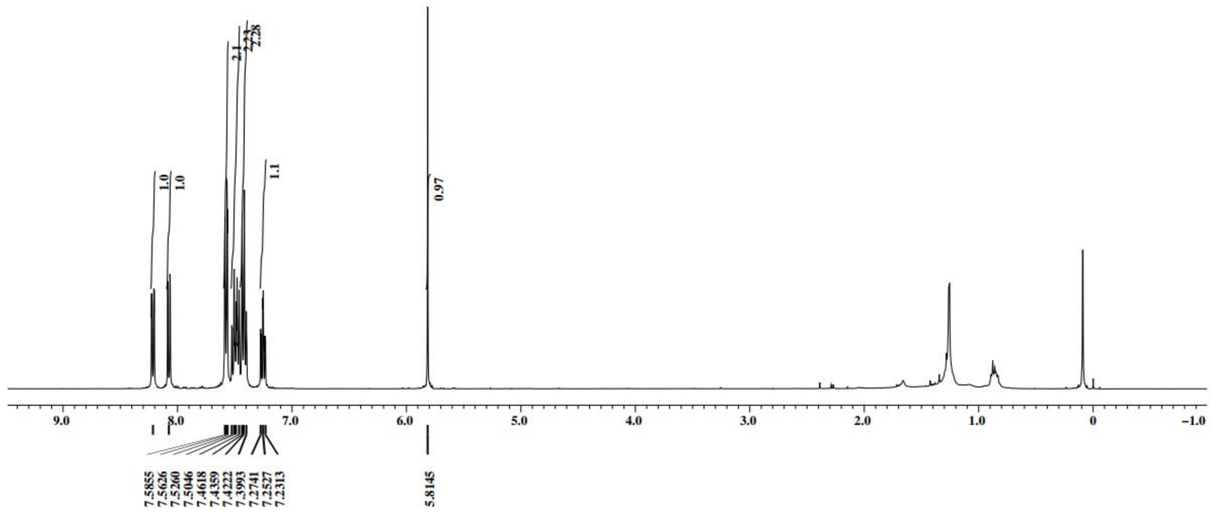

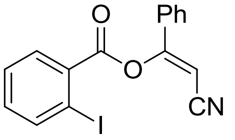

3ab

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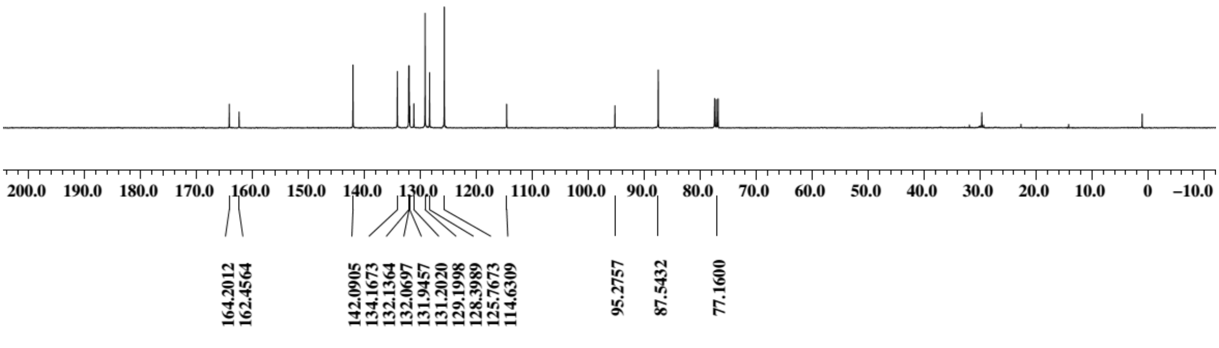

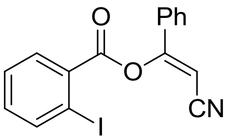

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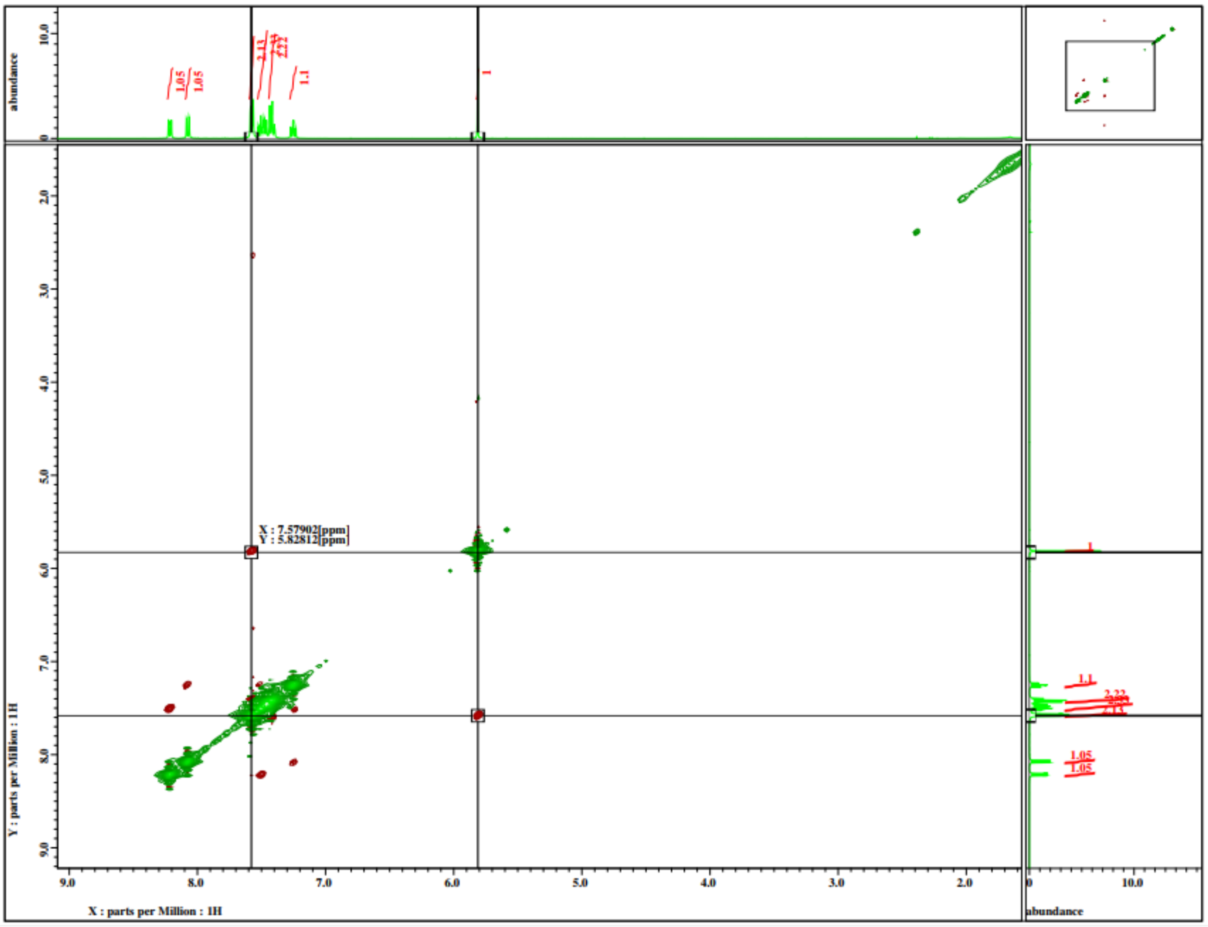

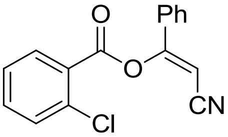

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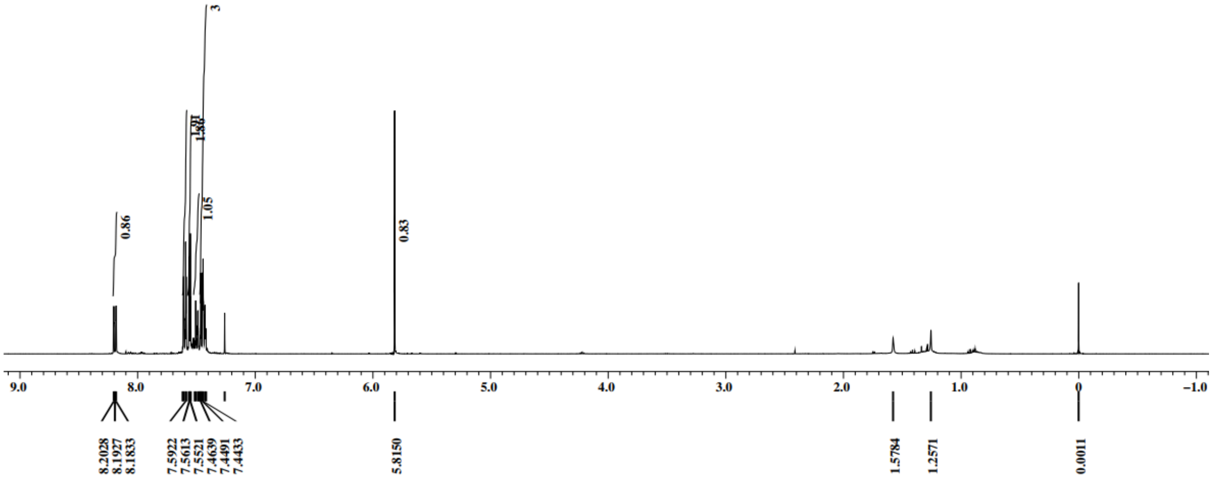

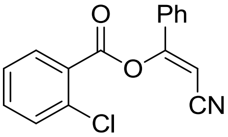

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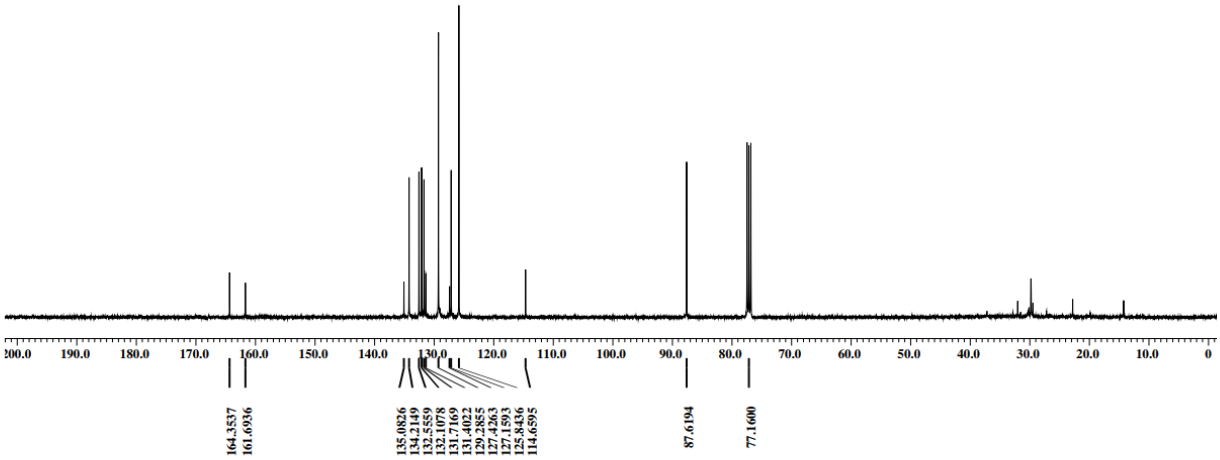

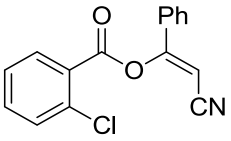

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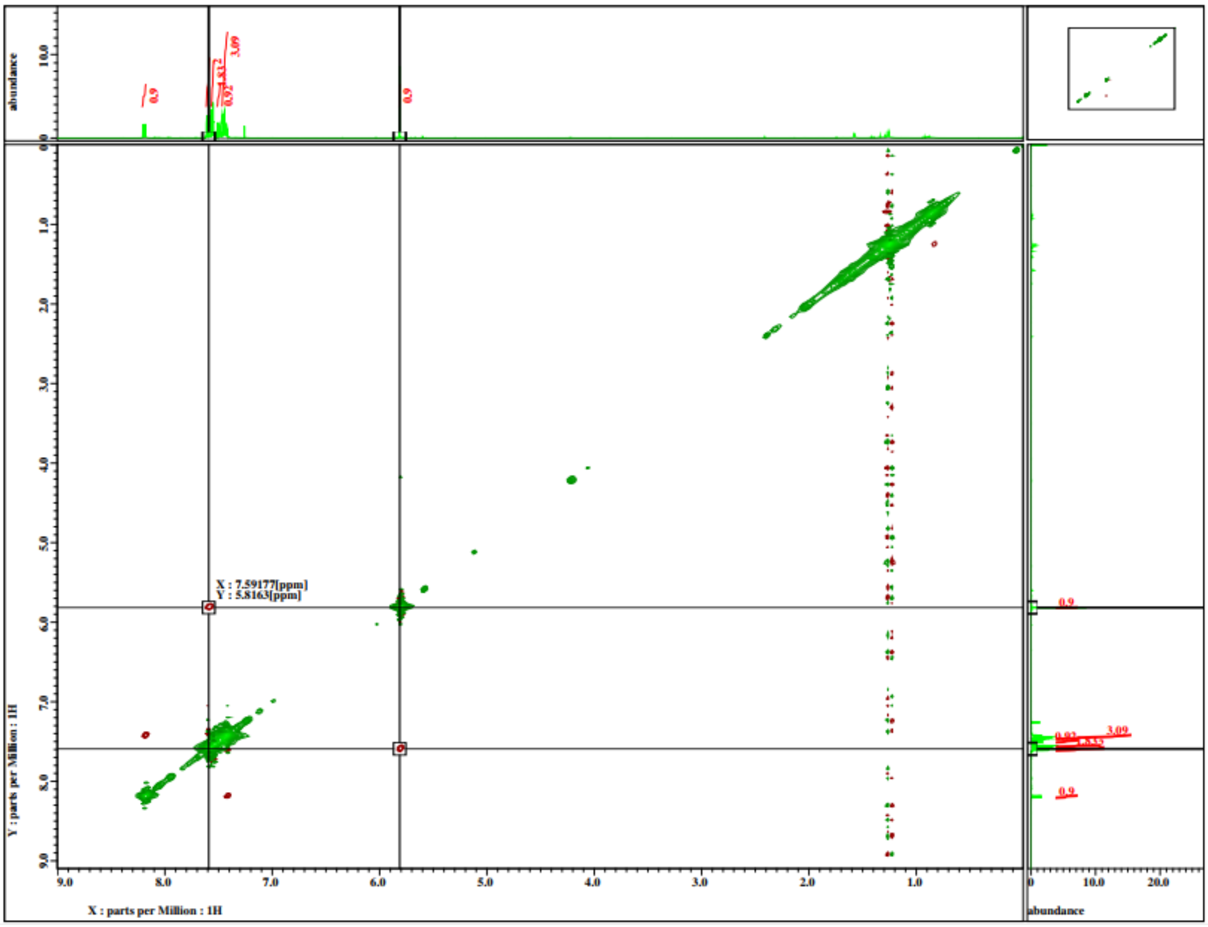

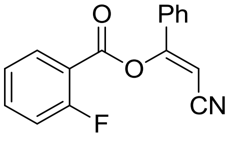

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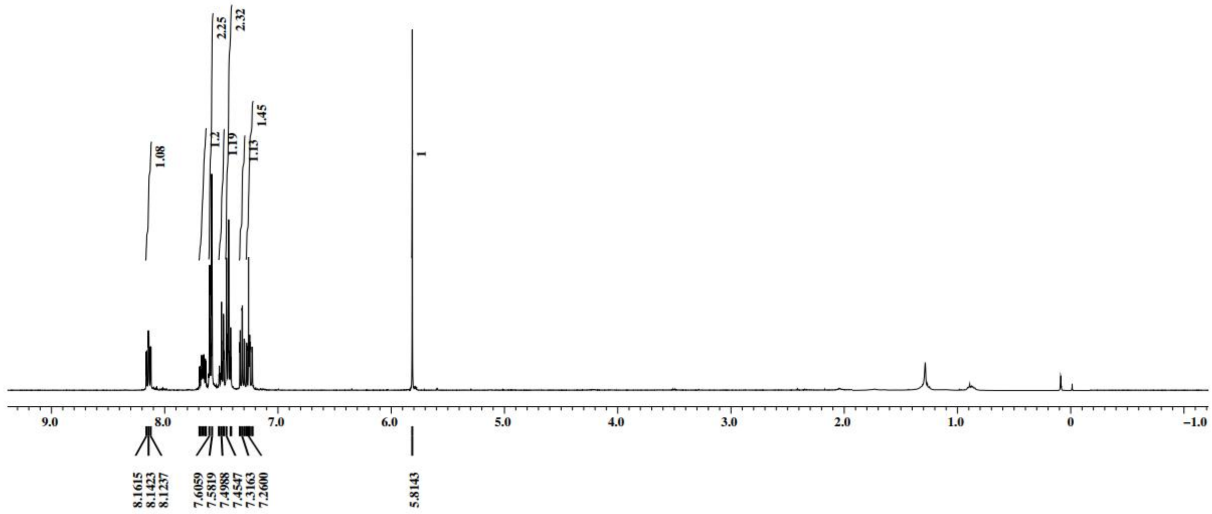

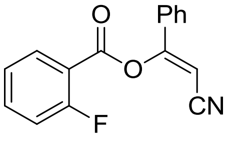

3ad

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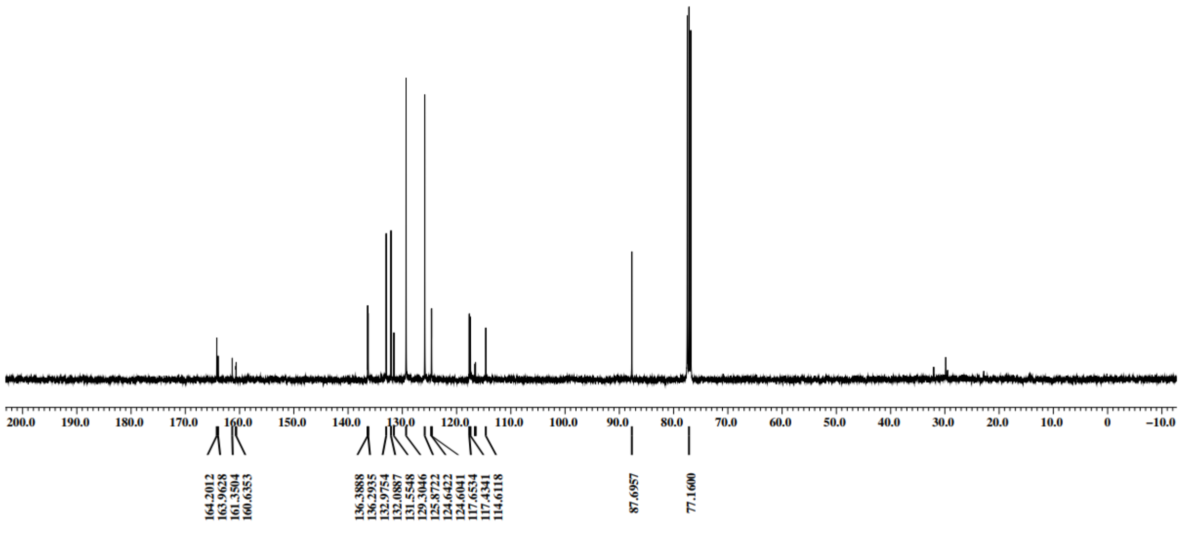

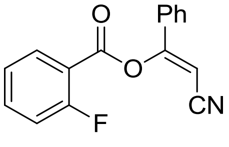

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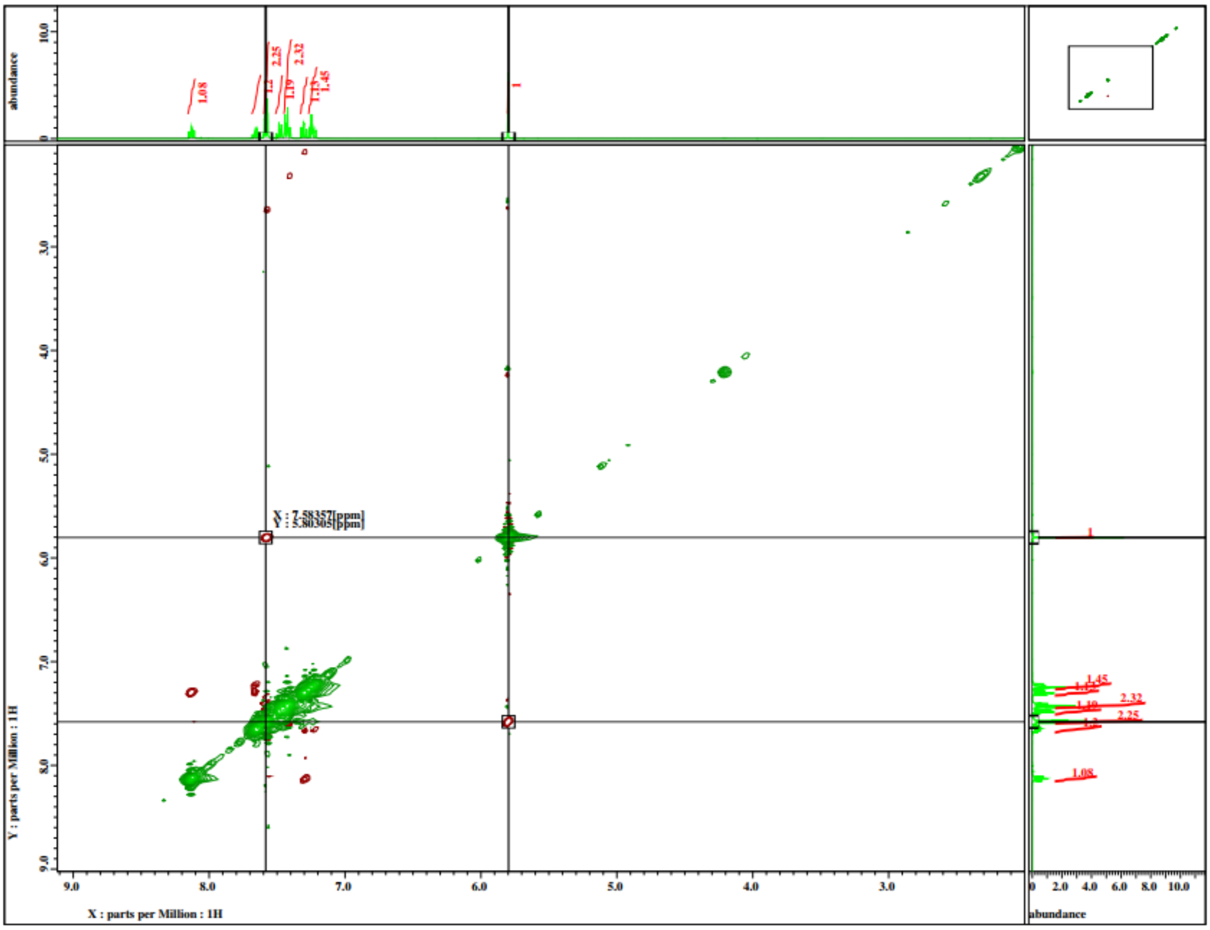

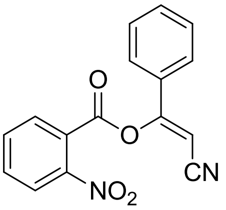

3ae

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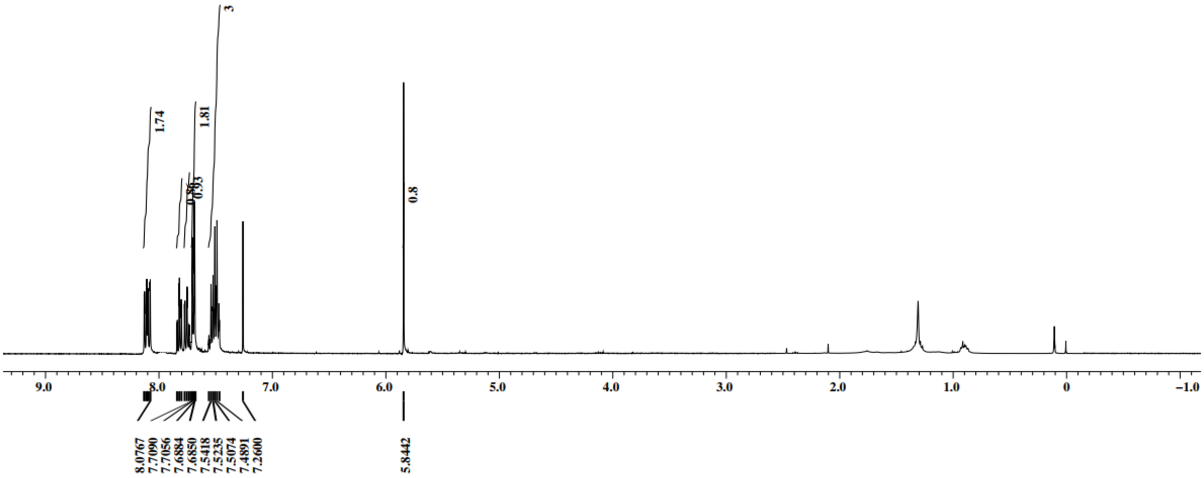

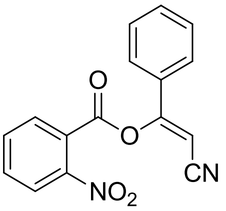

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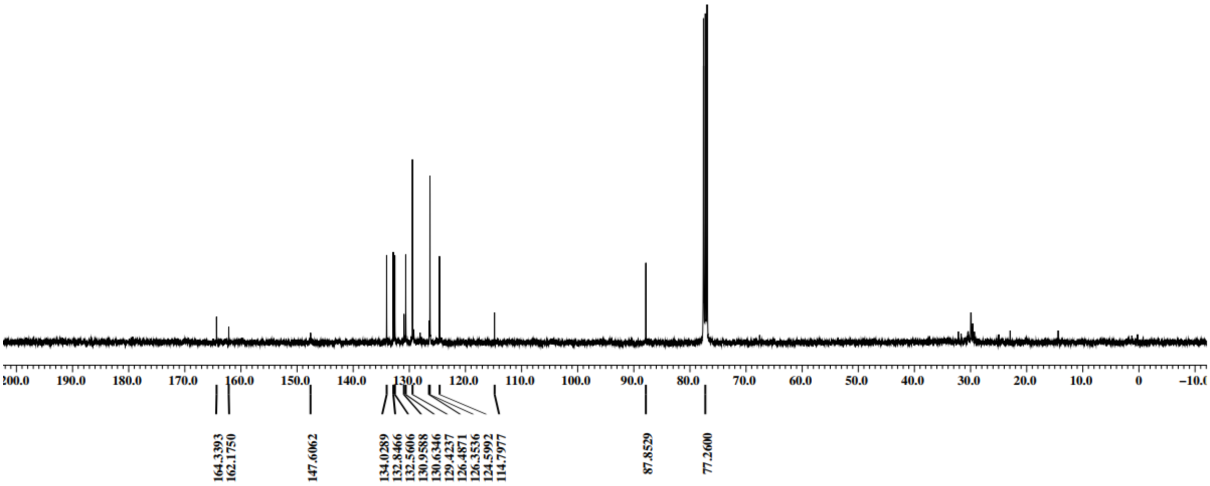

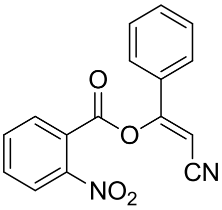

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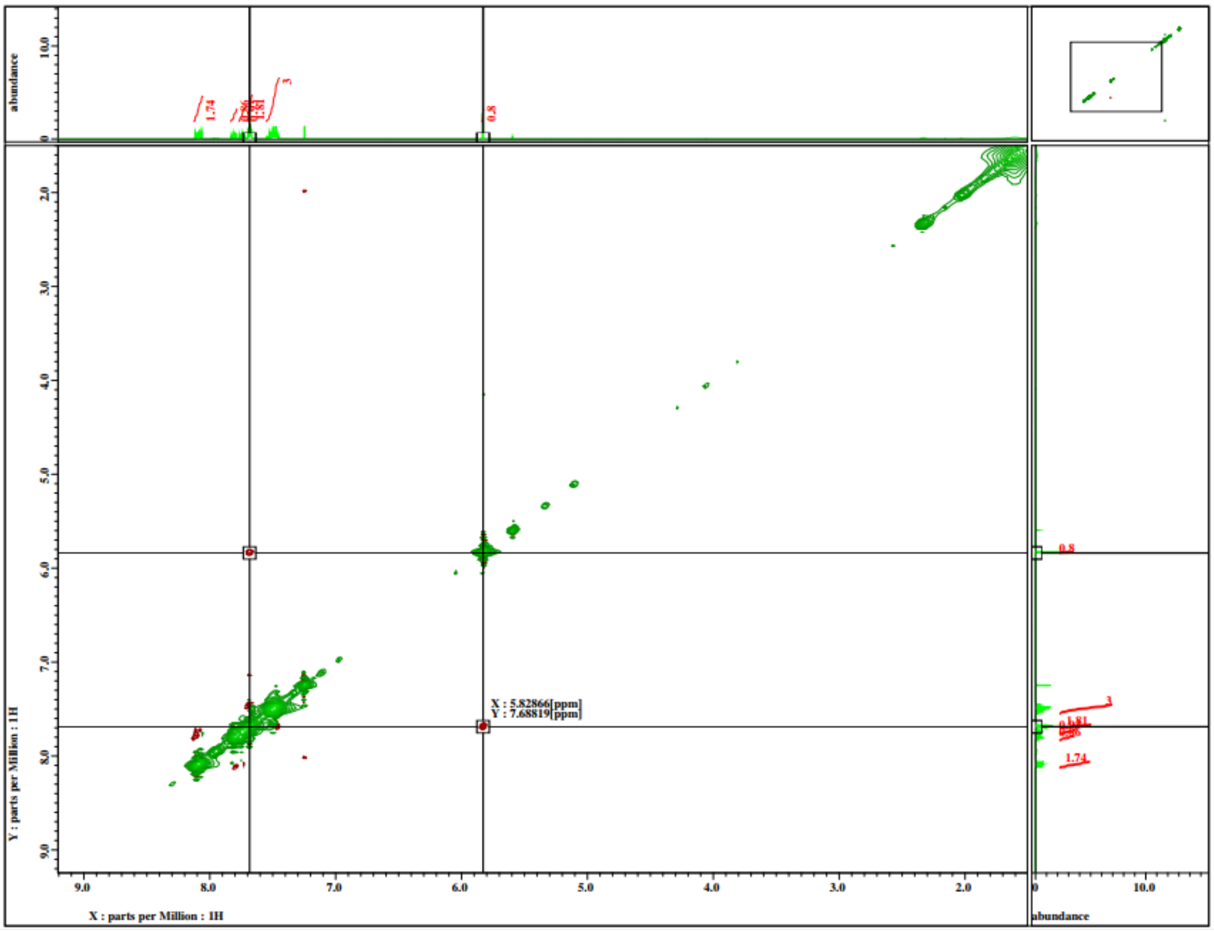

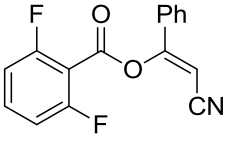

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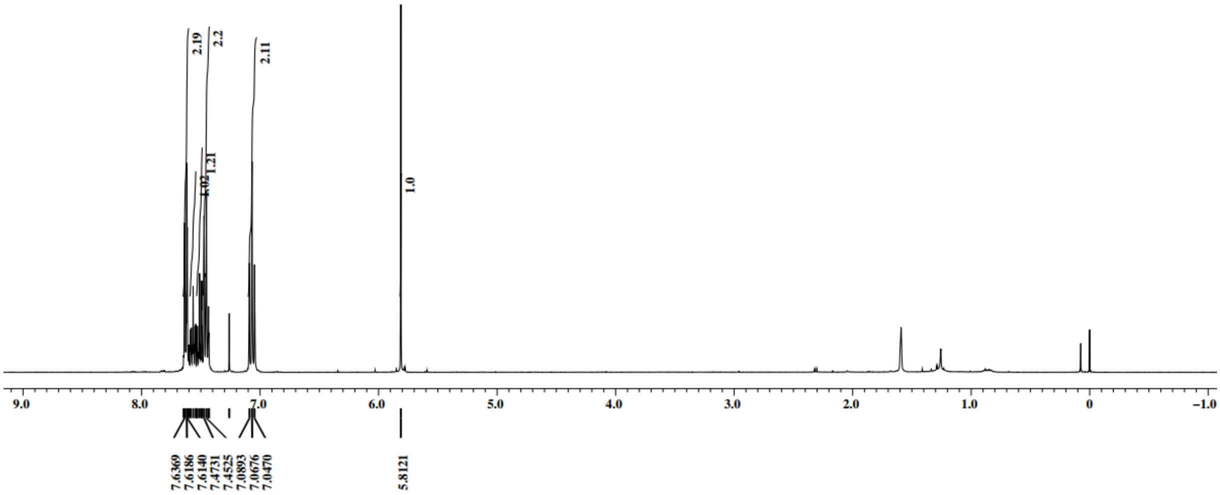

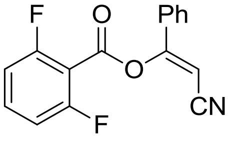

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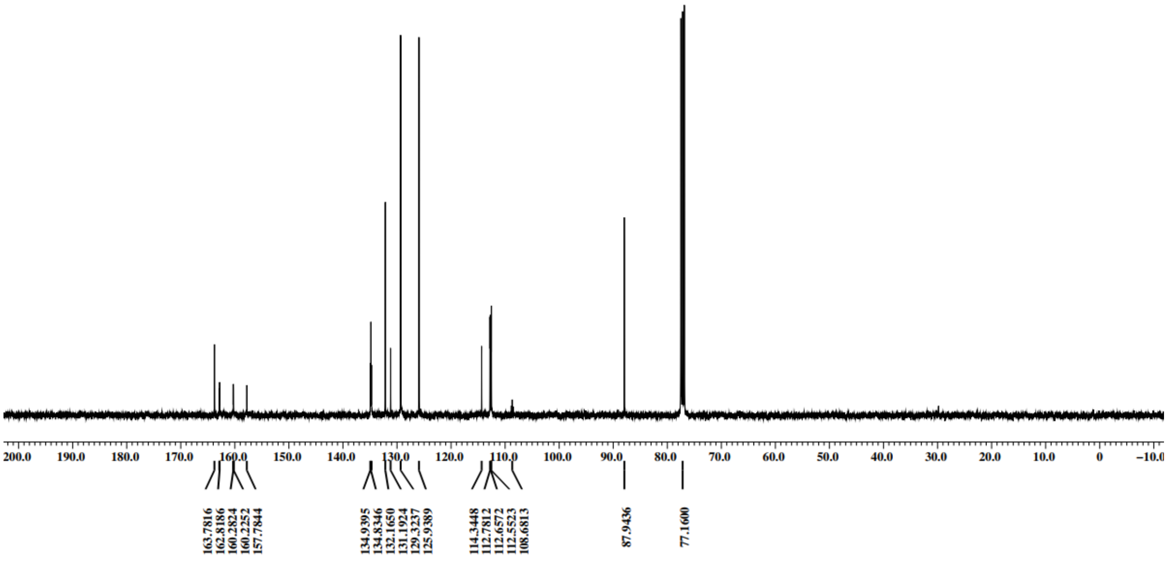

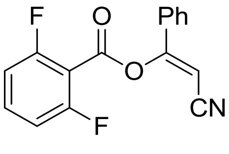

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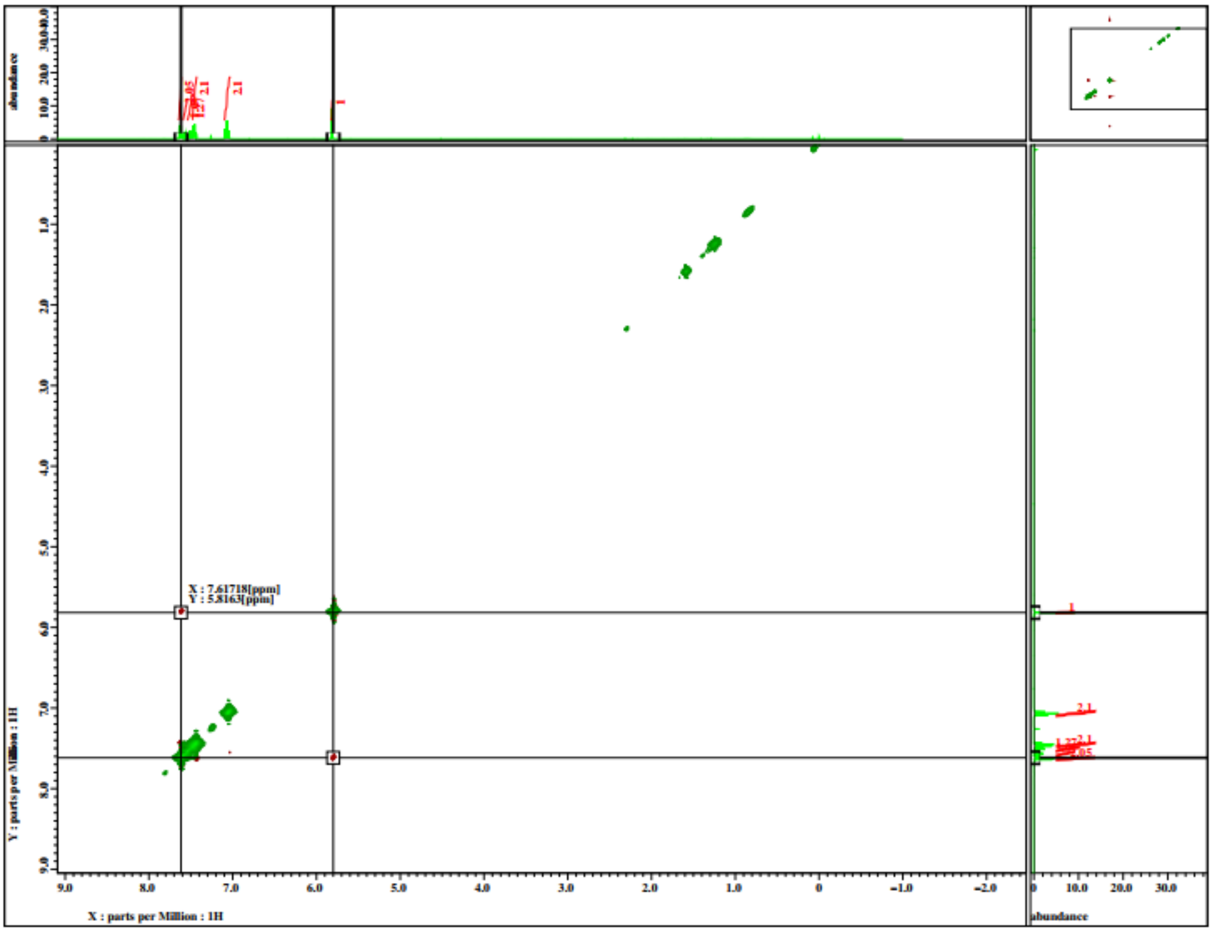

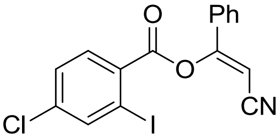

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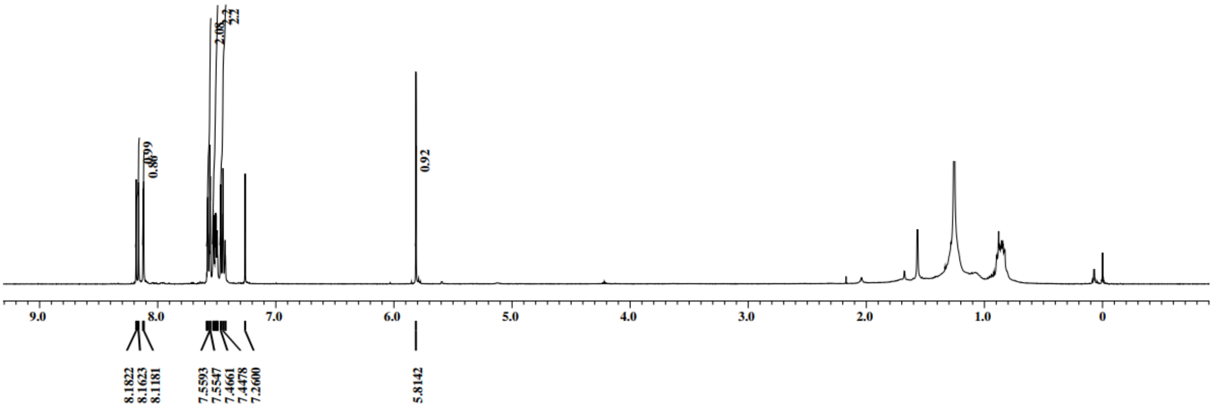

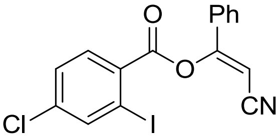

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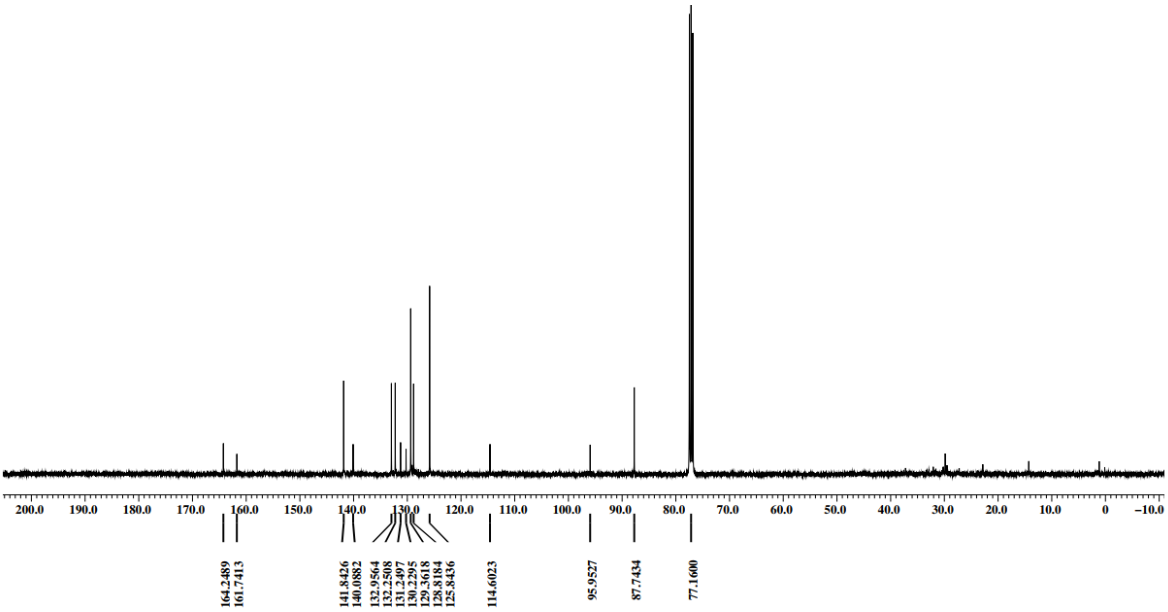

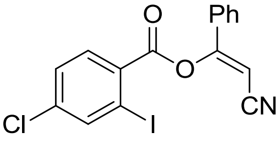

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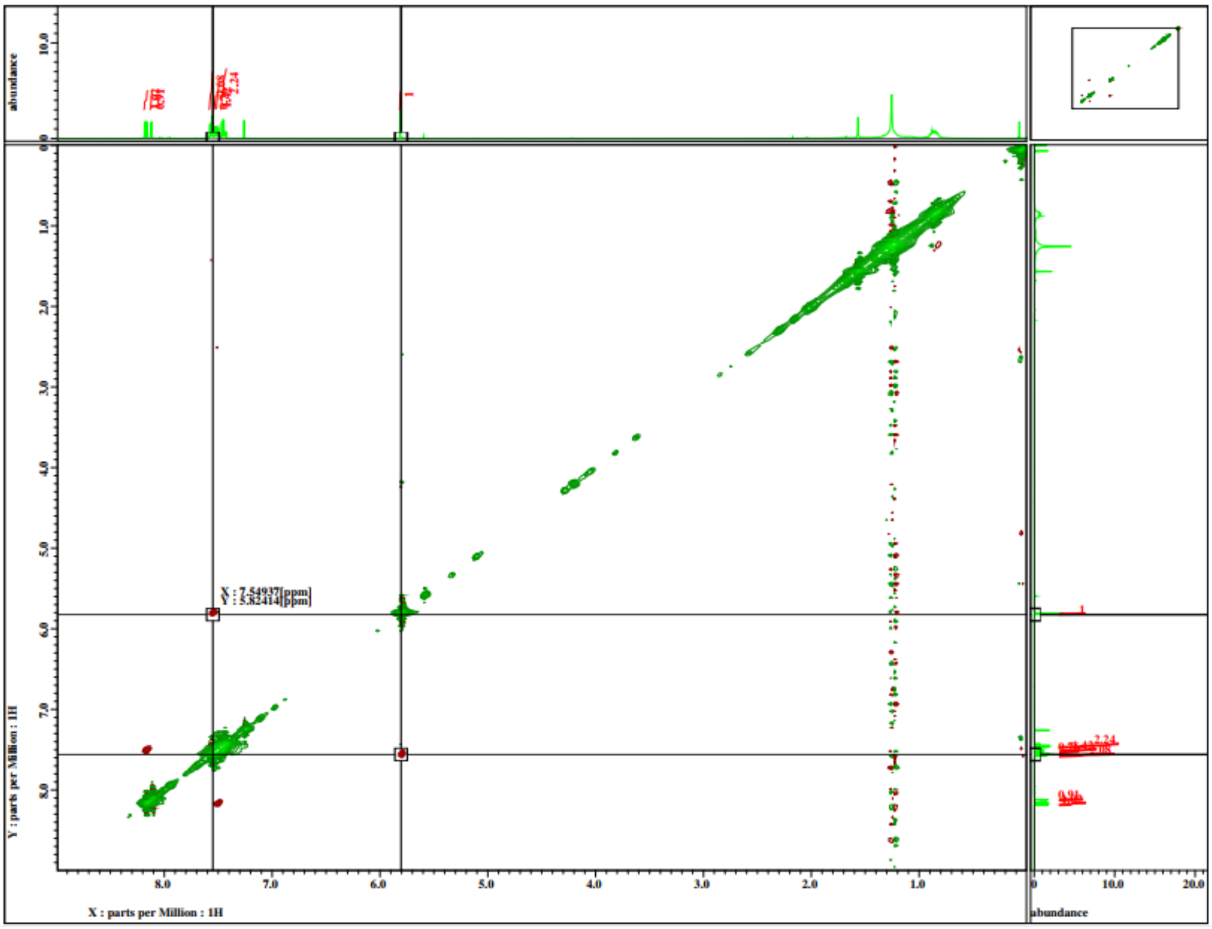

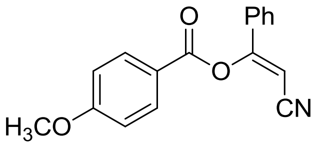

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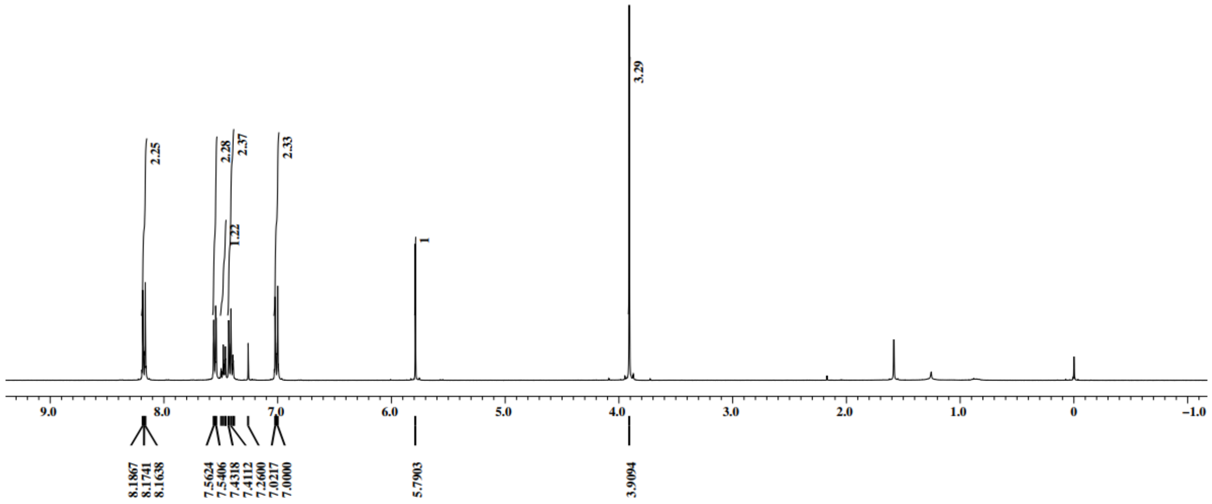

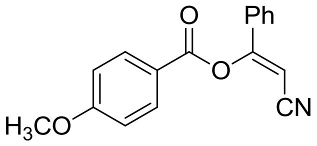

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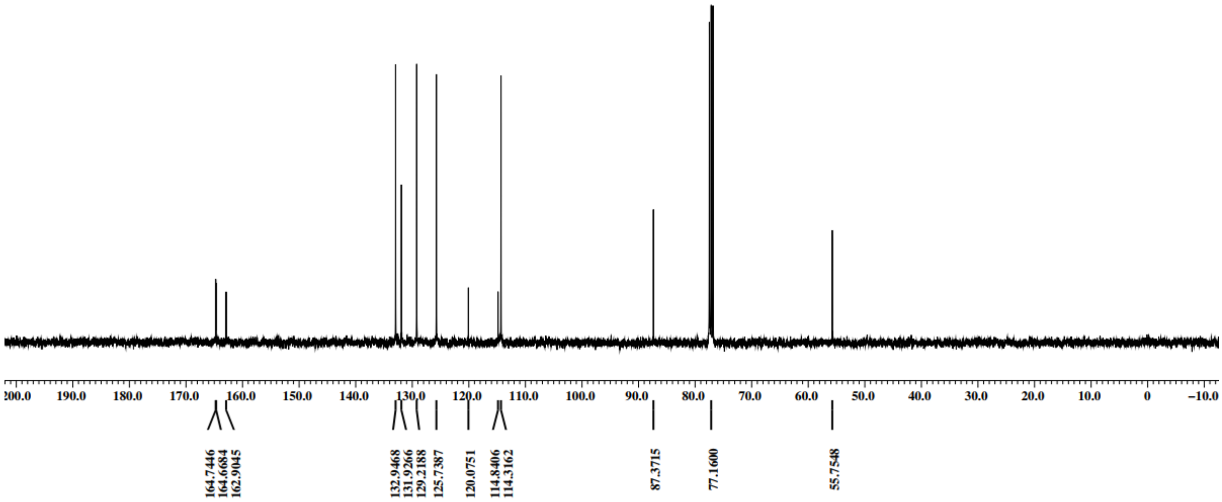

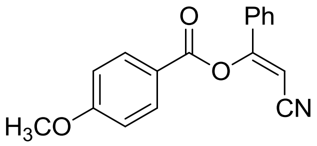

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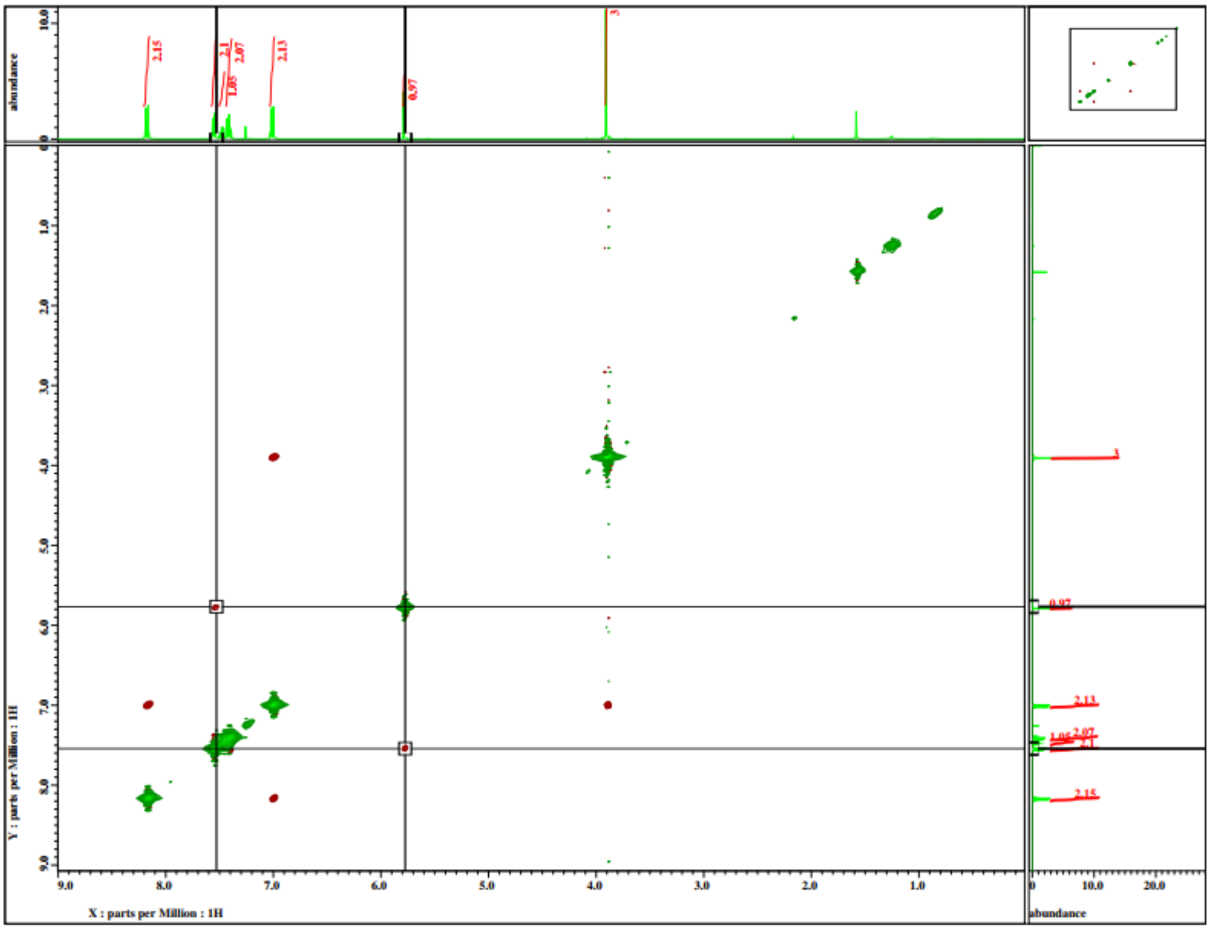

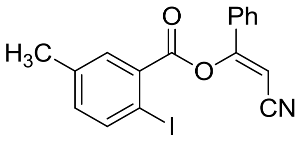

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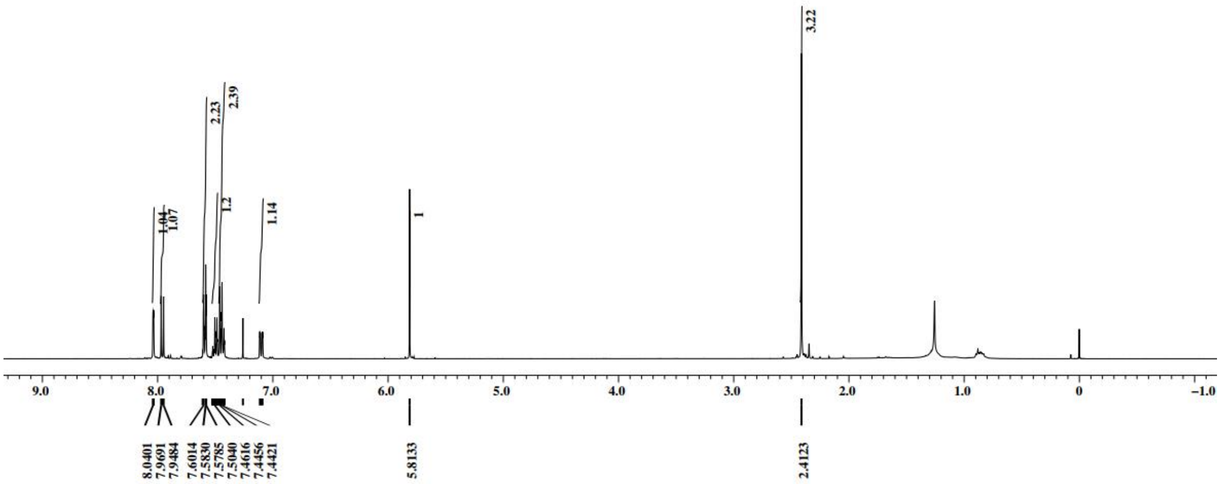

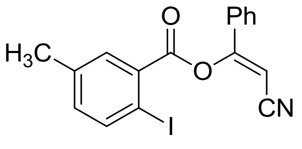

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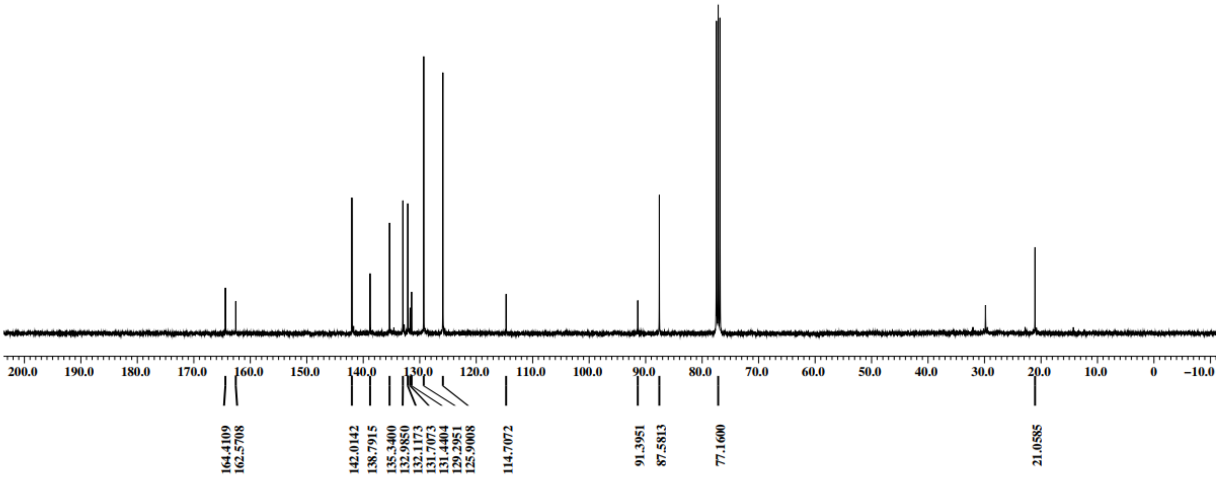

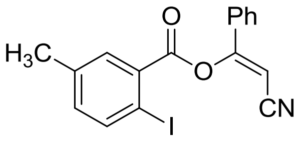

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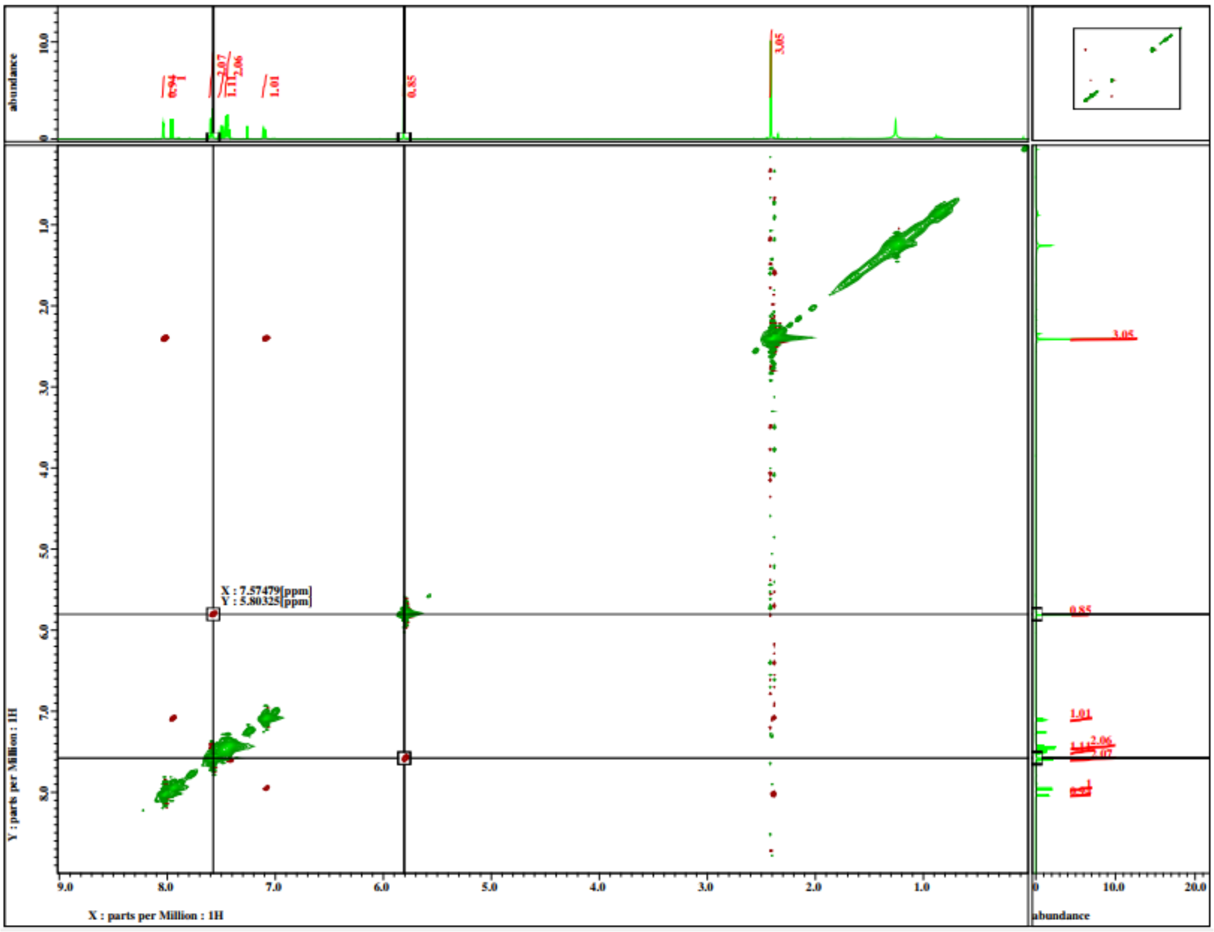
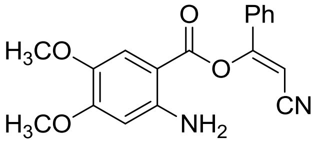
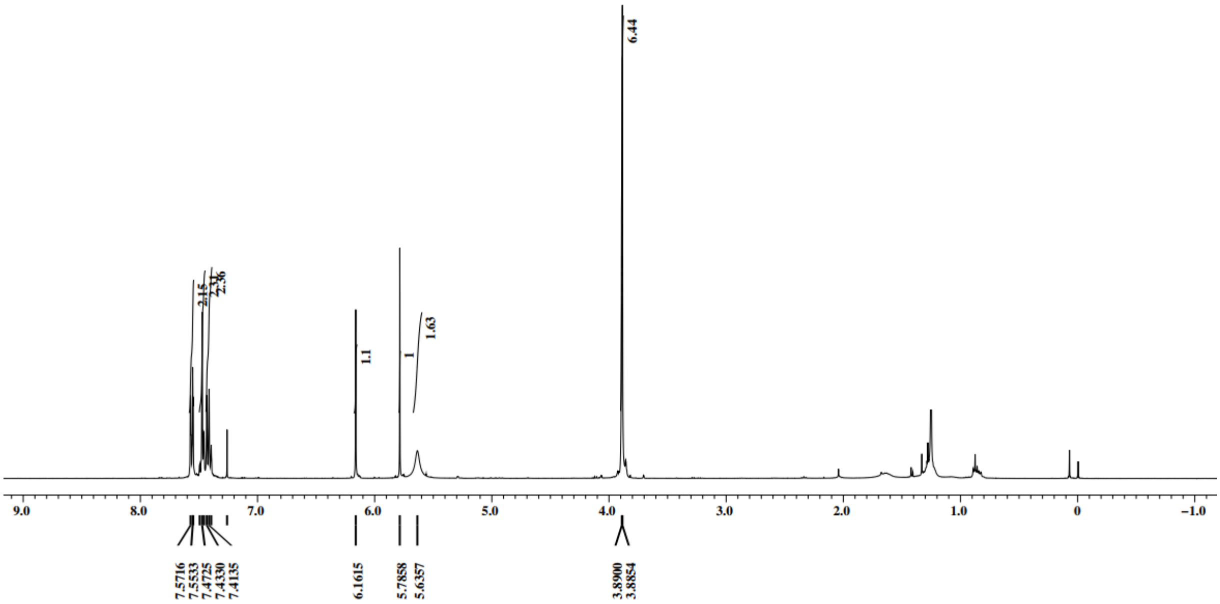
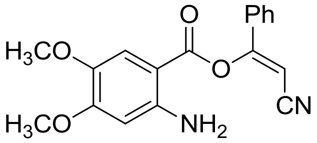




3aj

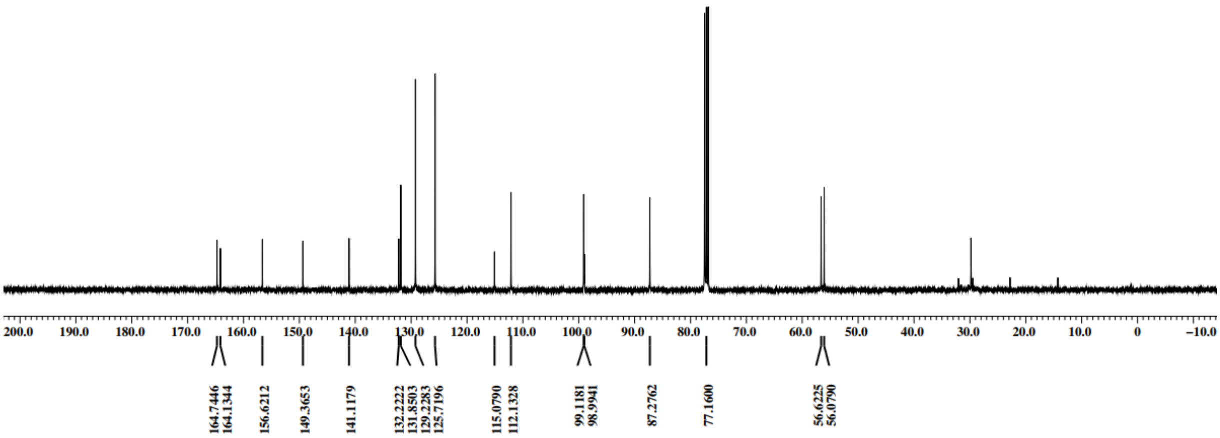
^{1}H NMR (400 MHz, $CDCl_3$)

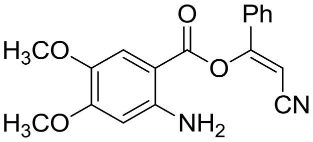




3aj

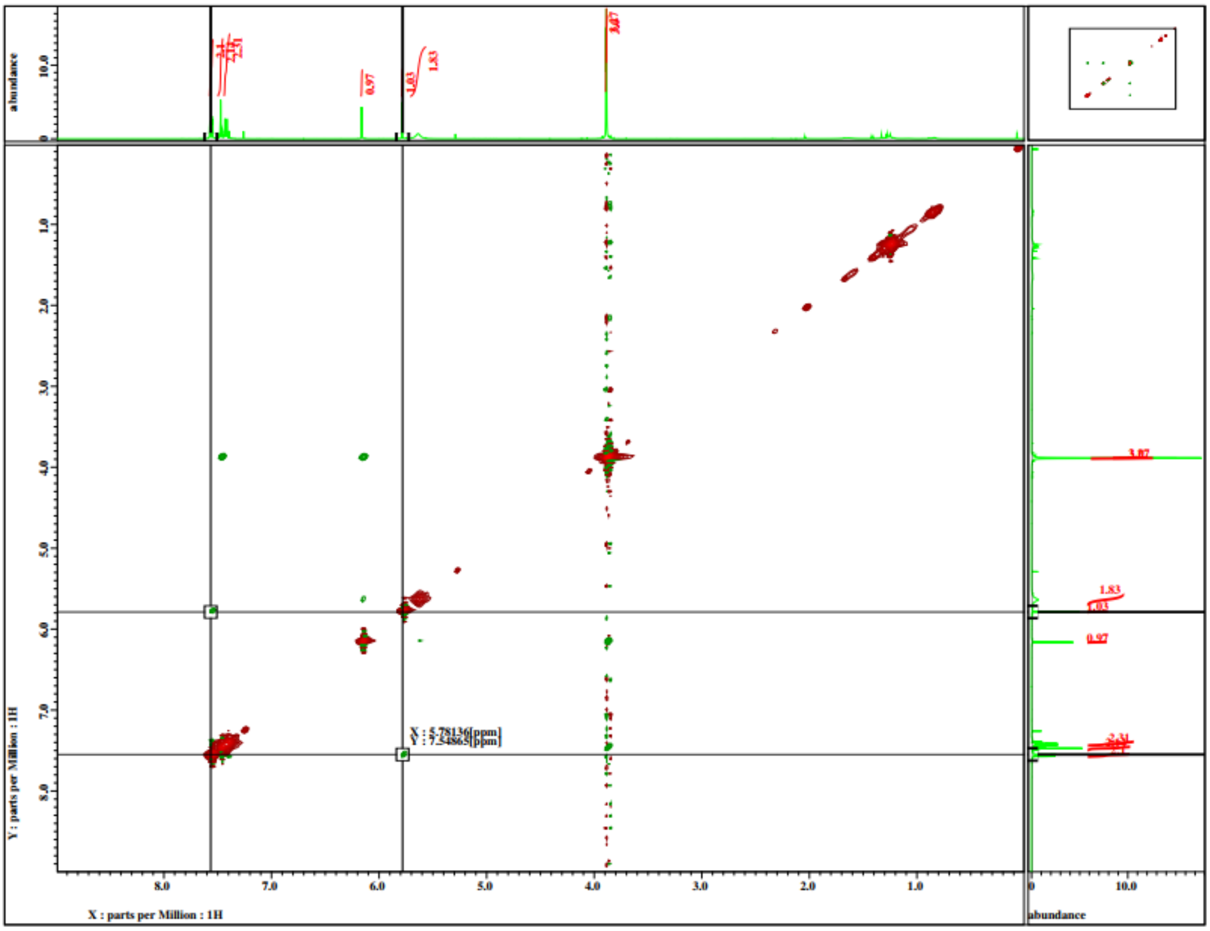
^{13}C NMR (100 MHz, $CDCl_3$)

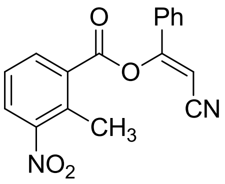




3aj

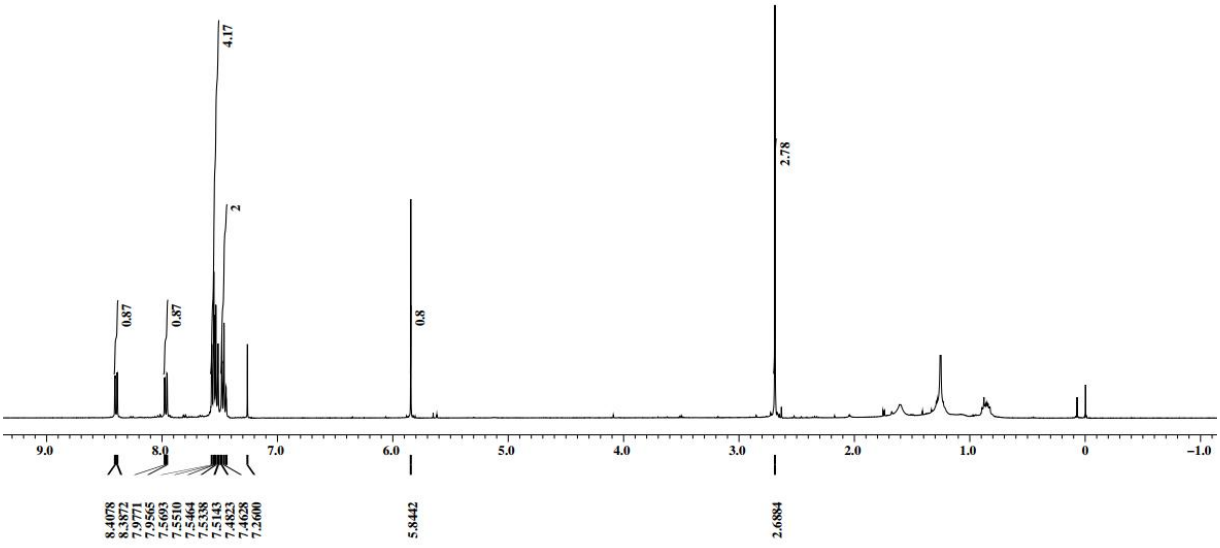
NOESY NMR (400 MHz, CDCl$_3$)

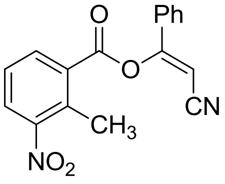




3ak

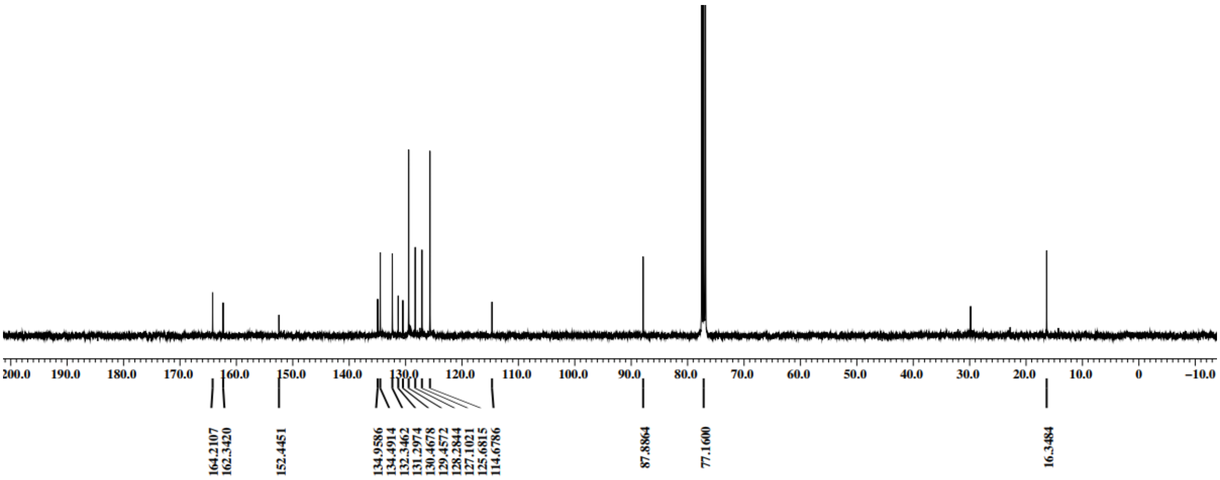
^{1}H NMR (400 MHz, CDCl$_3$)

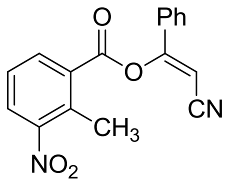




3ak

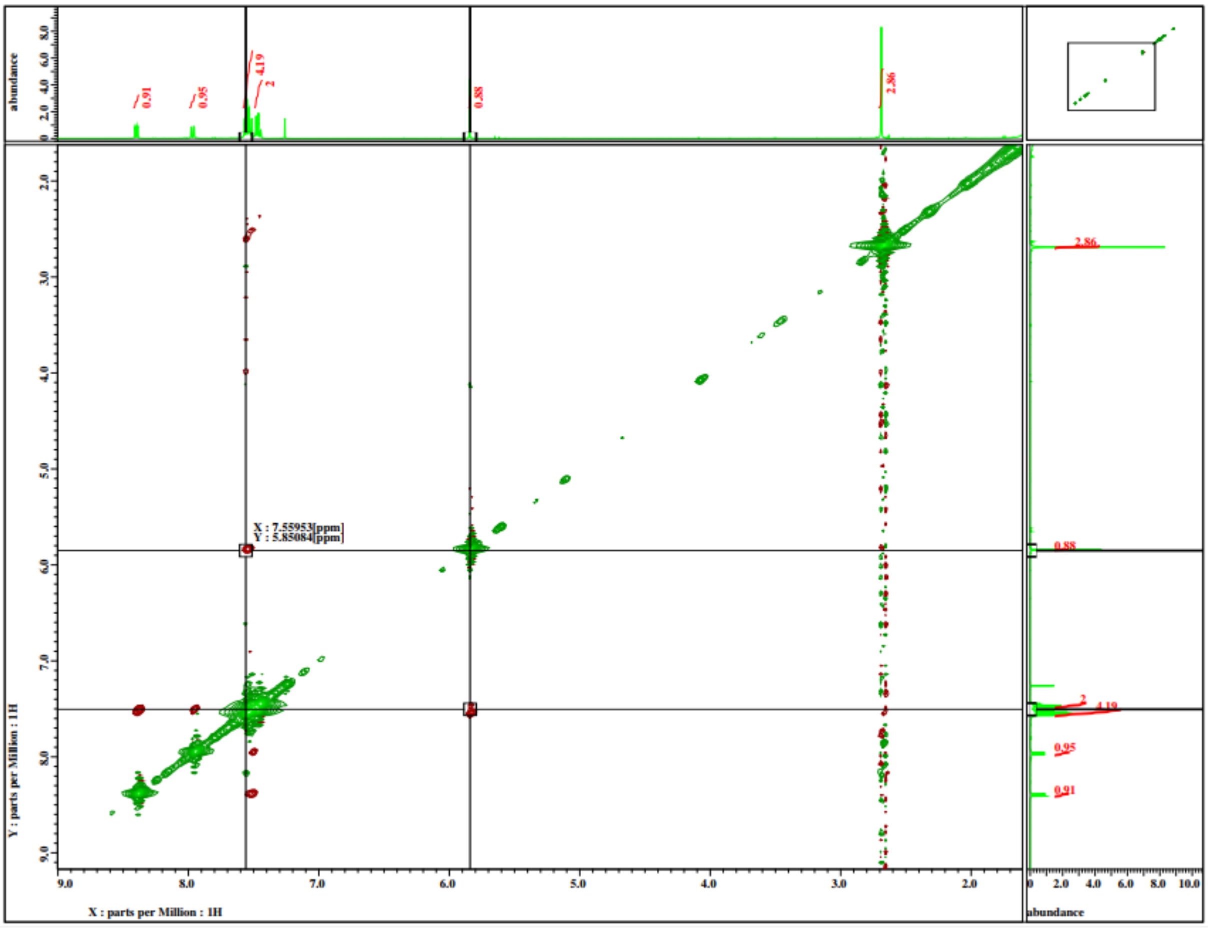
^{13}C NMR (100 MHz, CDCl$_3$)

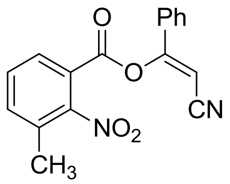




3ak

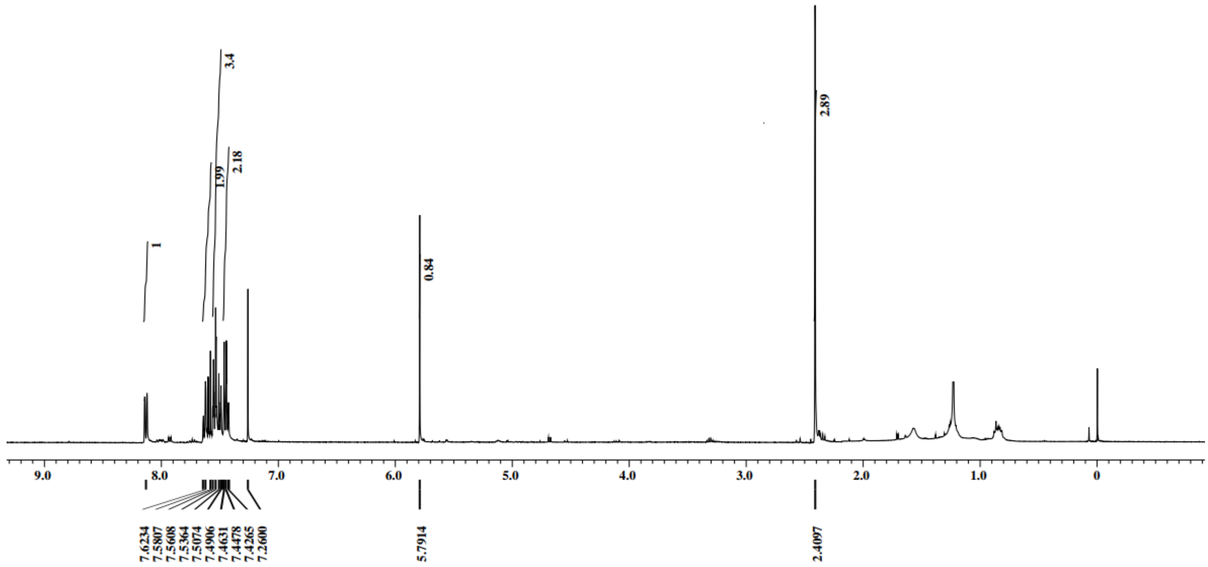
NOESY NMR (400 MHz, $CDCl_3$)

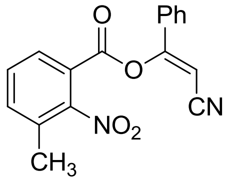




3al

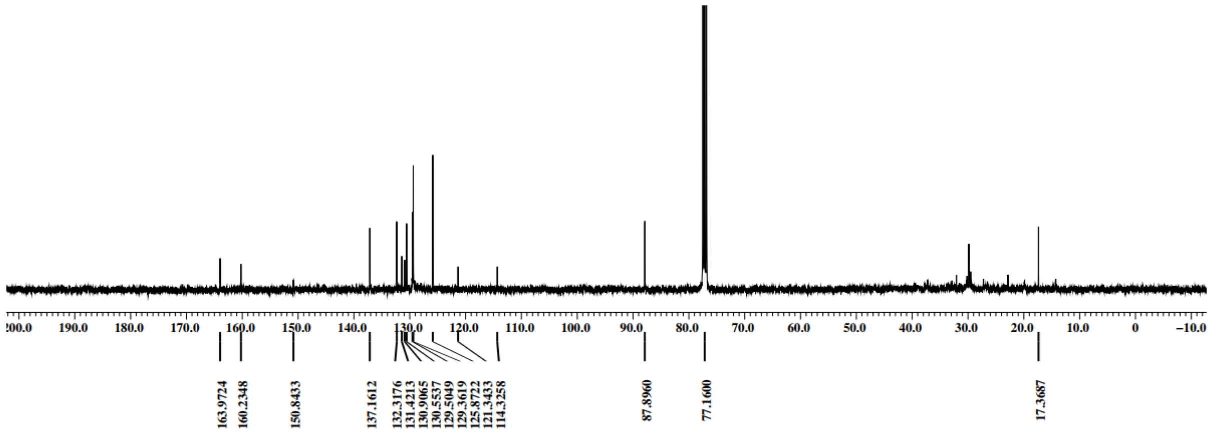
^{1}H NMR (400 MHz, CDCl$_3$)

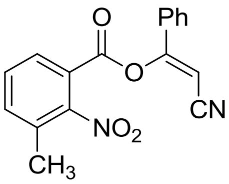




3al

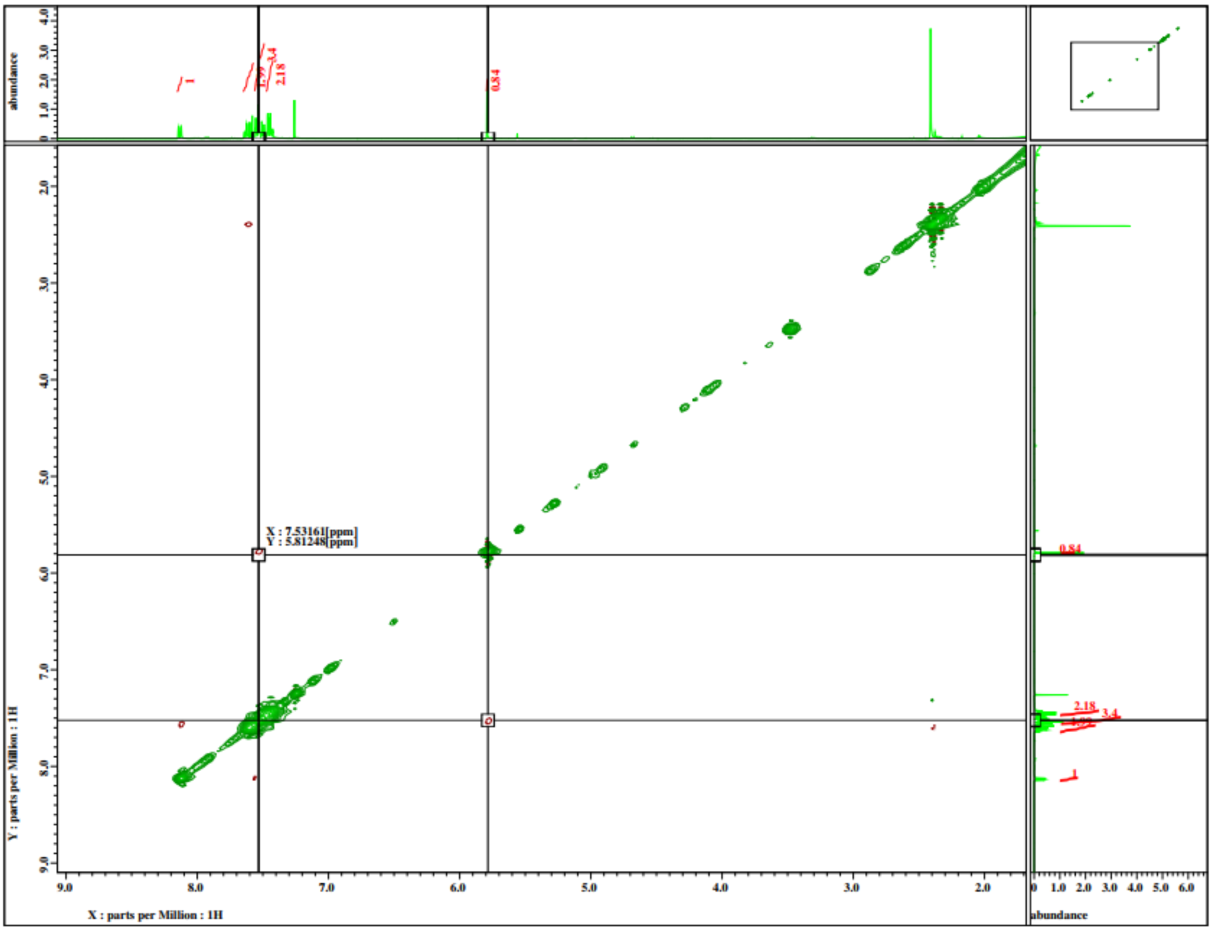
^{13}C NMR (100 MHz, CDCl$_3$)

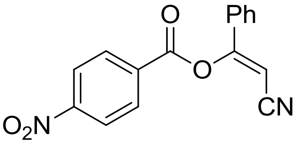




3al

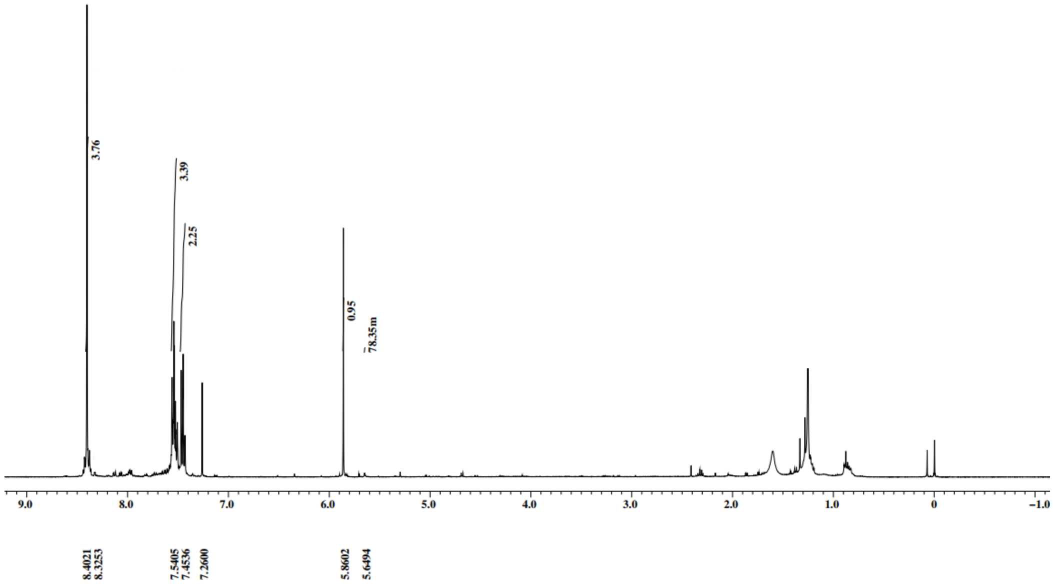
NOESY NMR (400 MHz, $CDCl_3$)

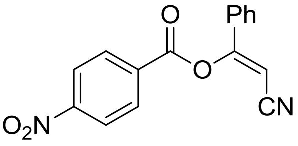




3am

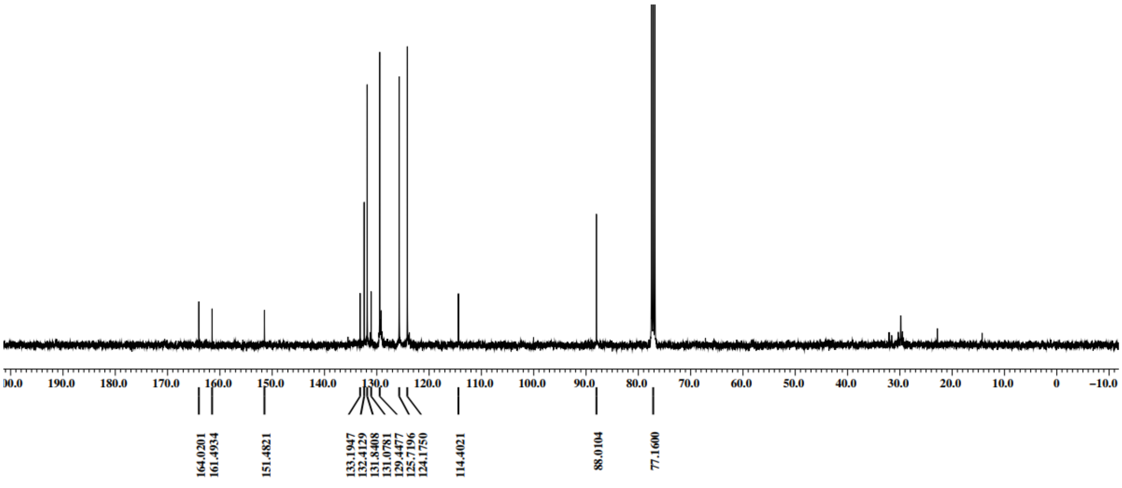
^{1}H NMR (400 MHz, $CDCl_3$)

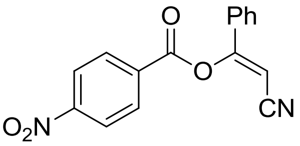




3am

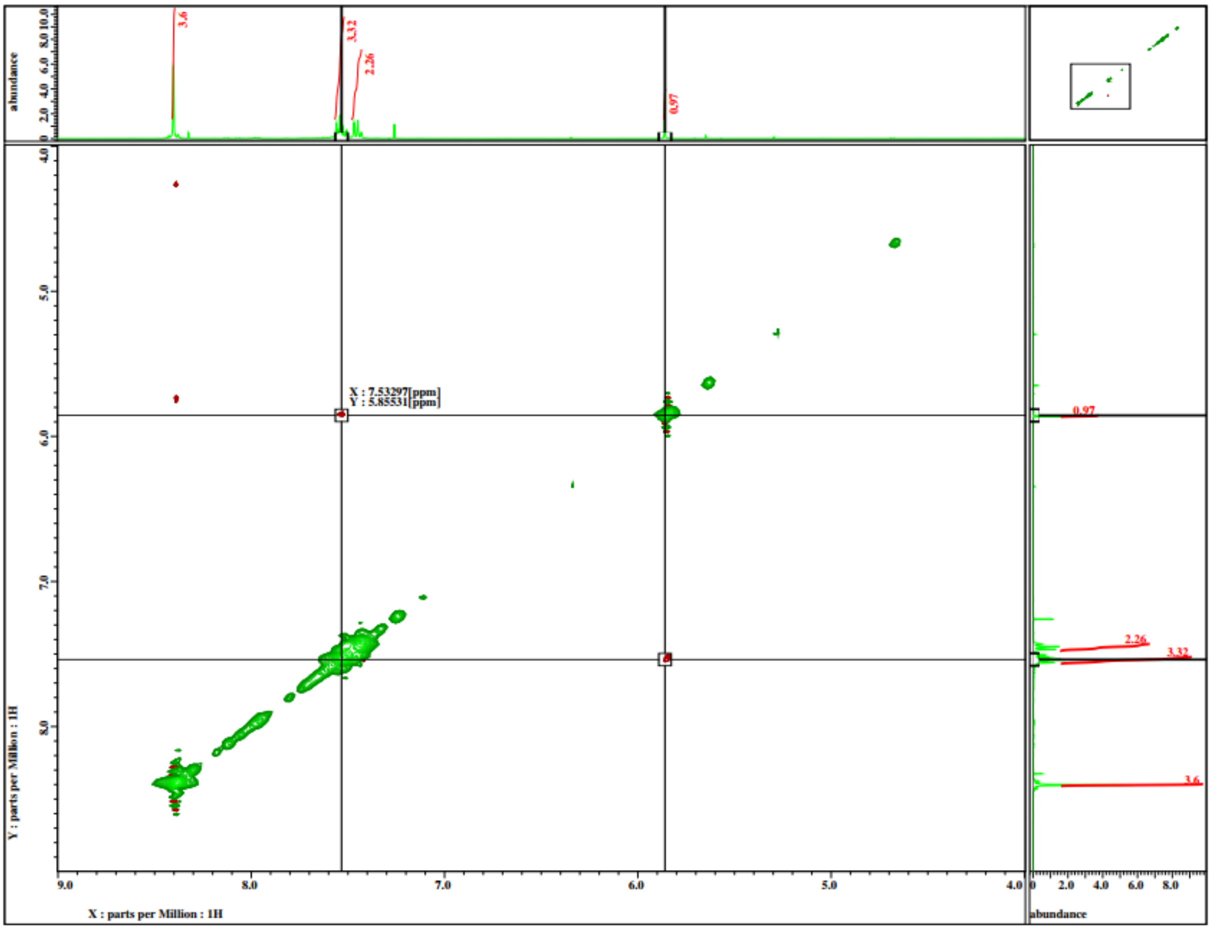
^{13}C NMR (100 MHz, $CDCl_3$)

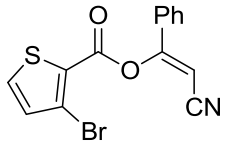




3am

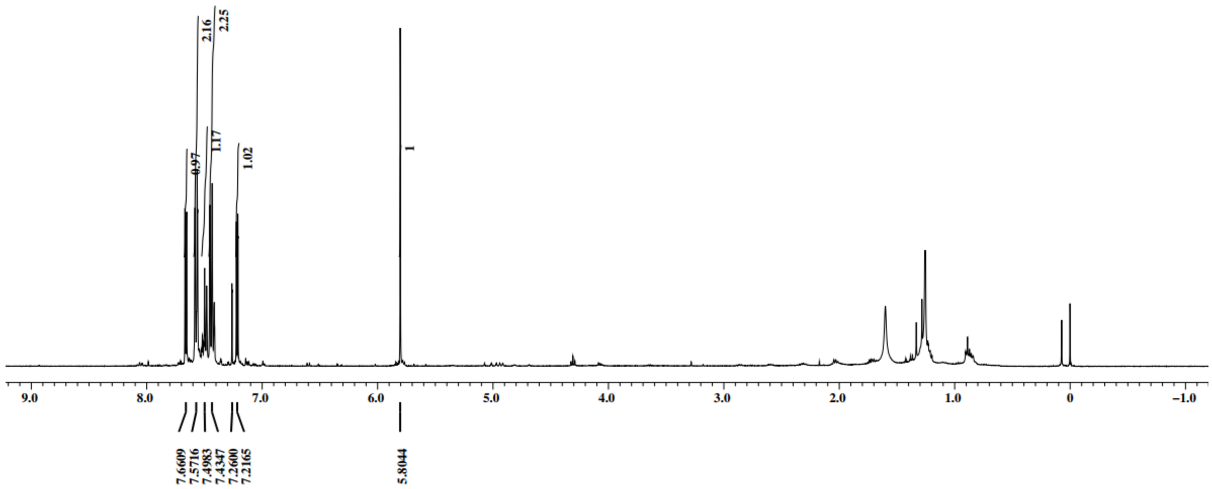
NOESY NMR (400 MHz, $CDCl_3$)

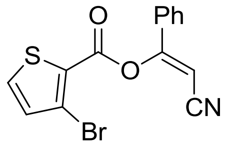




3an

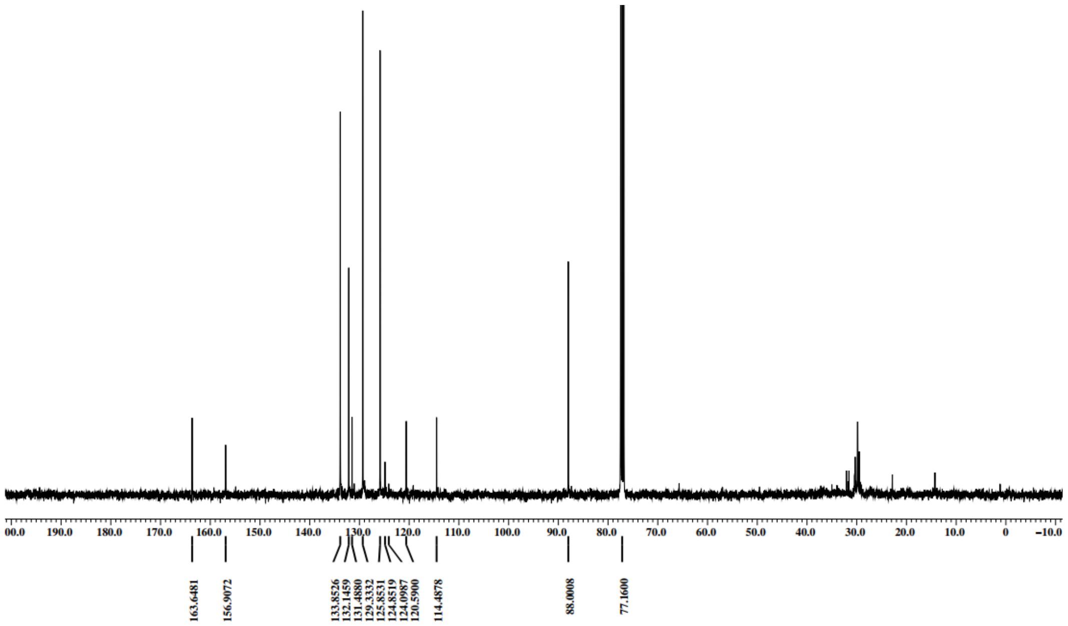
^{1}H NMR (400 MHz, CDCl$_3$)

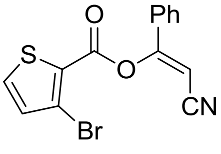




3an

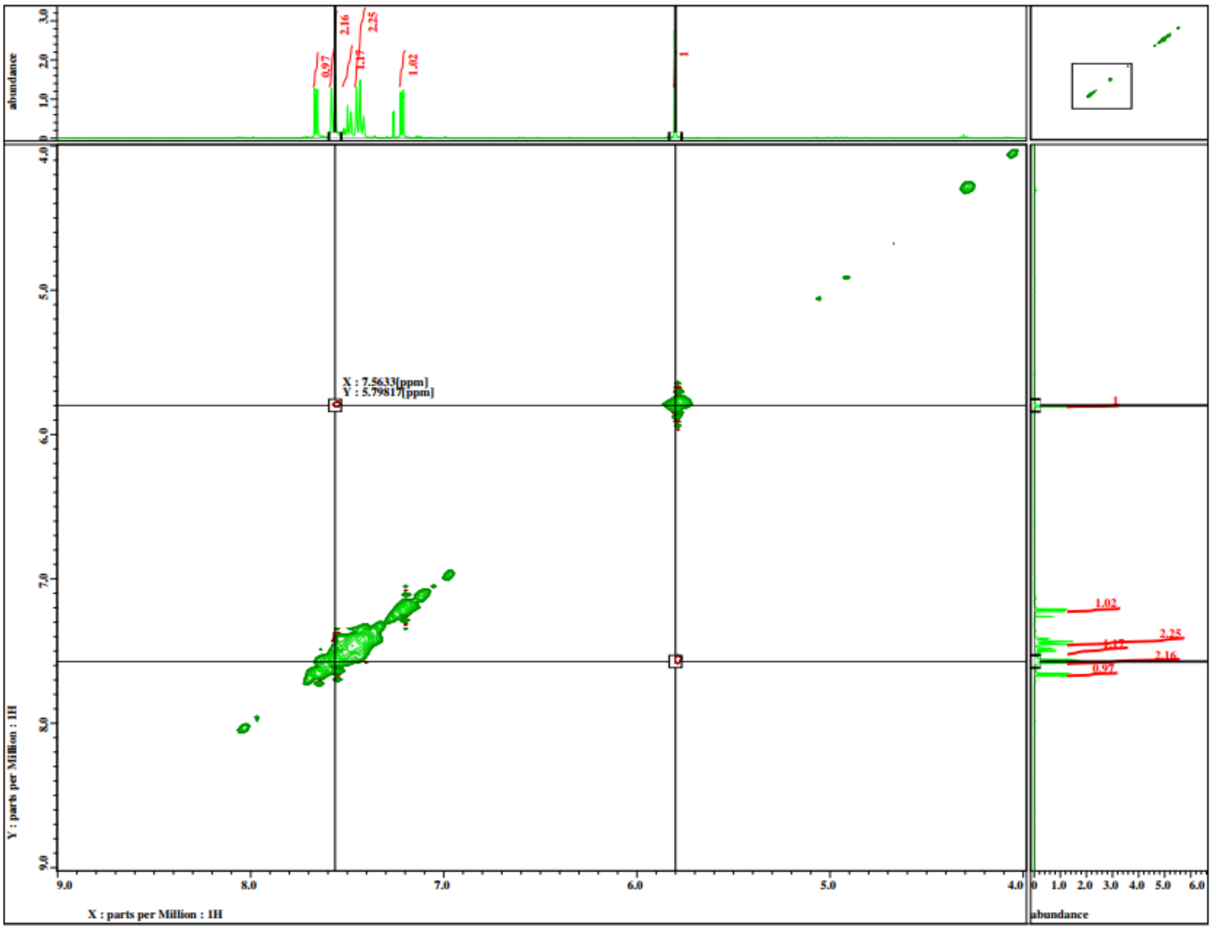
^{13}C NMR (100 MHz, CDCl$_3$)

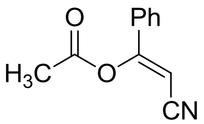




3an

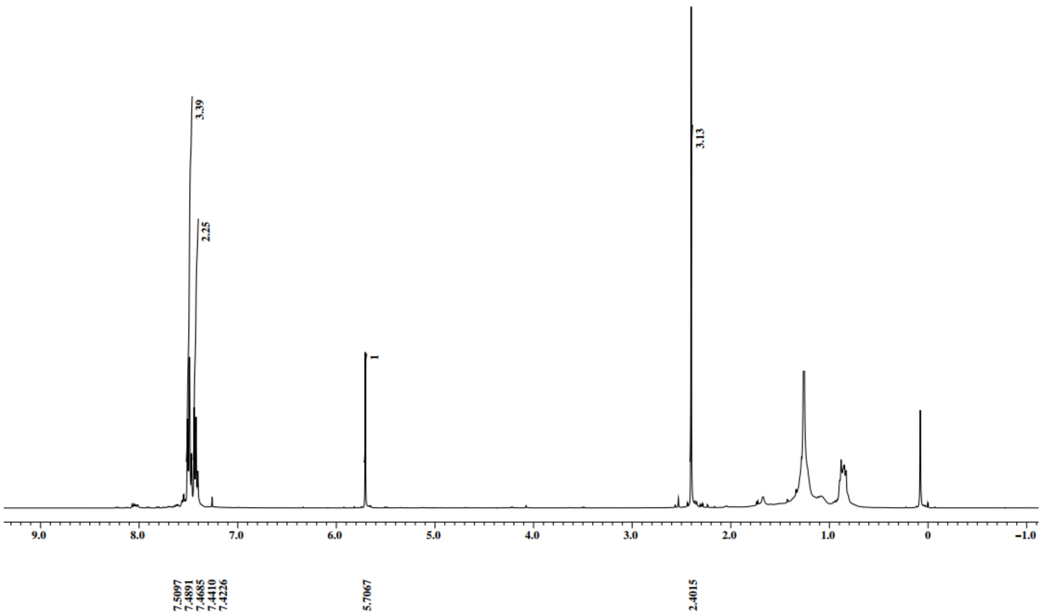
NOESY NMR (400 MHz, $CDCl_3$)

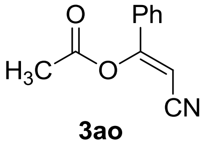




3ao

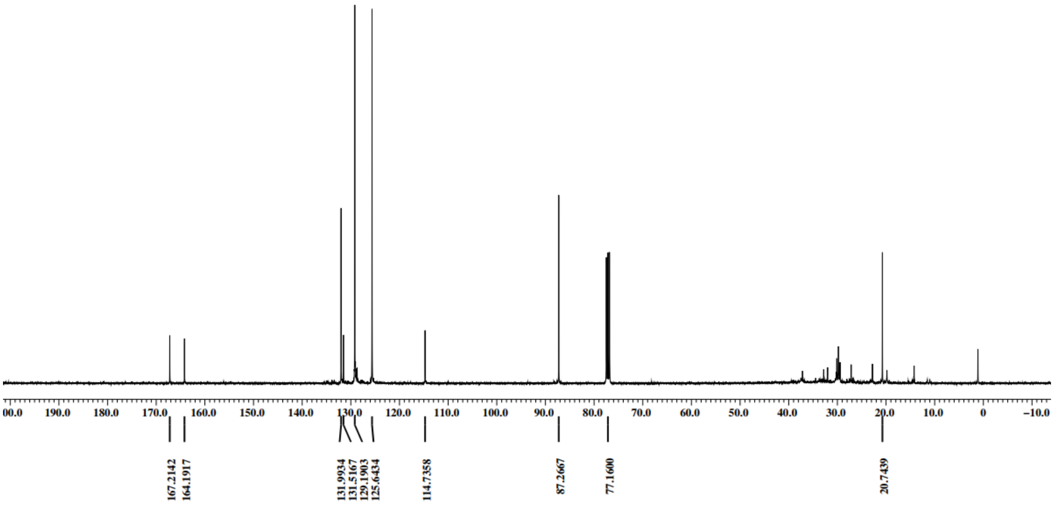
^{1}H NMR (400 MHz, $CDCl_3$)

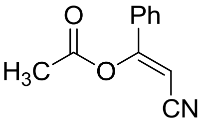




3ao

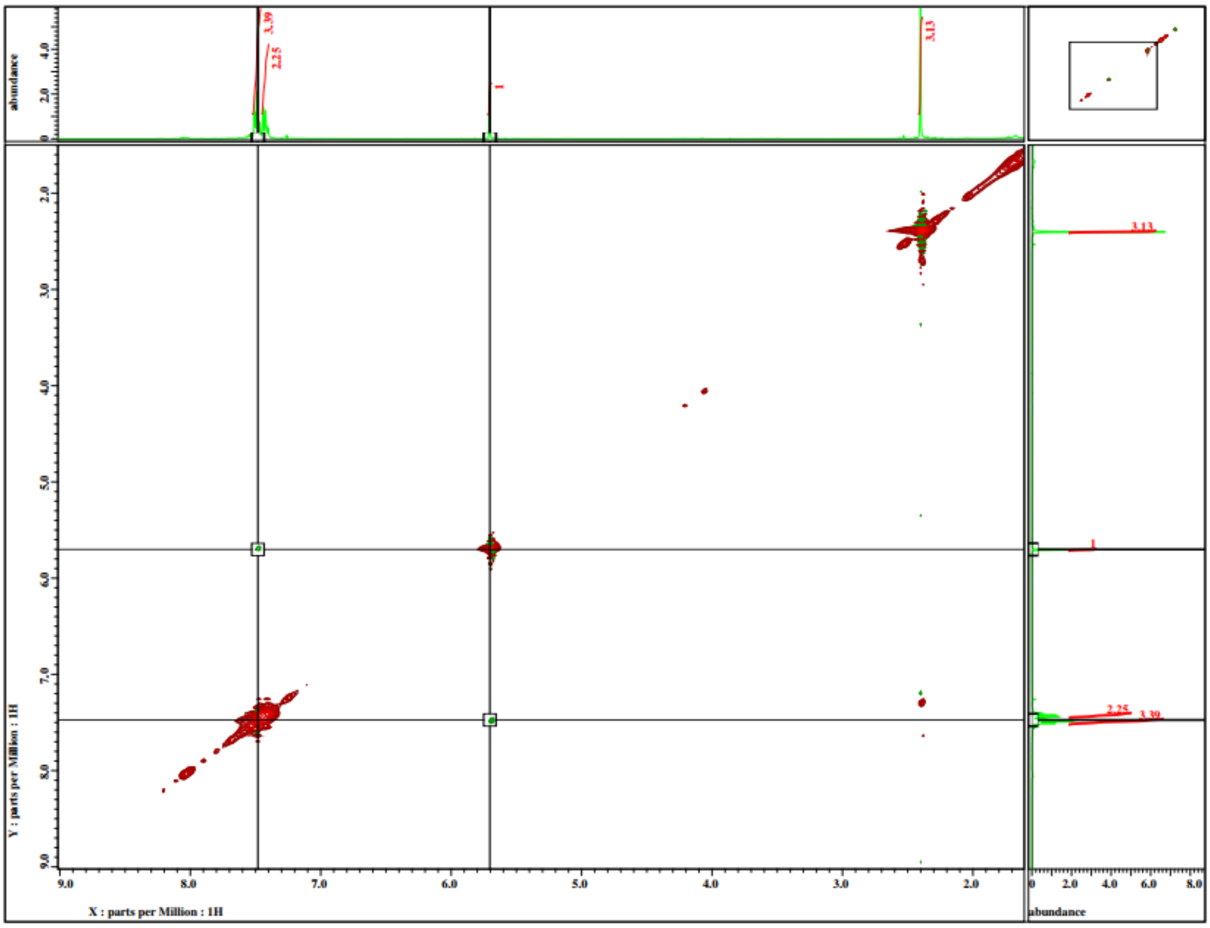
^{13}C NMR (100 MHz, $CDCl_3$)

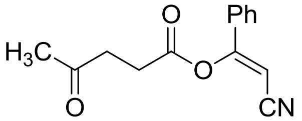




3ao

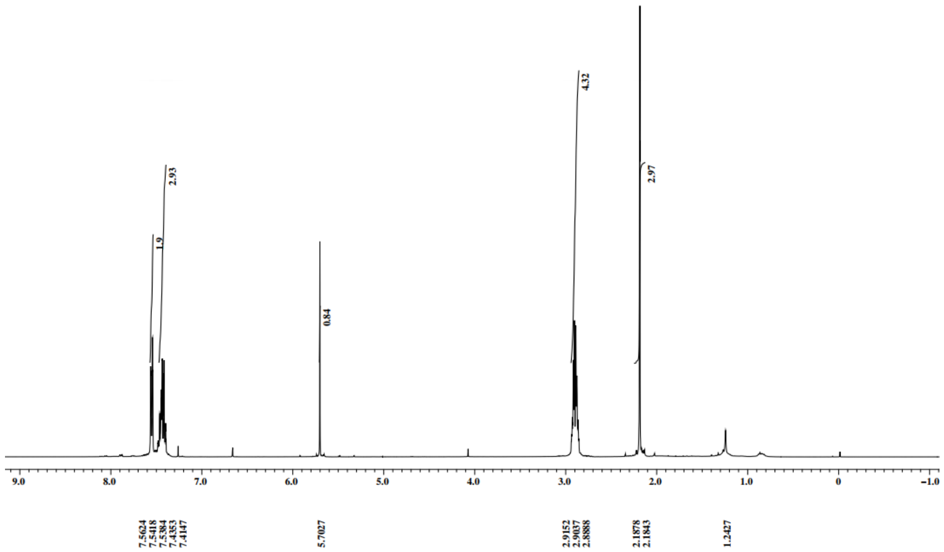
NOESY NMR (400 MHz, $CDCl_3$)

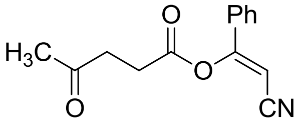




3ap

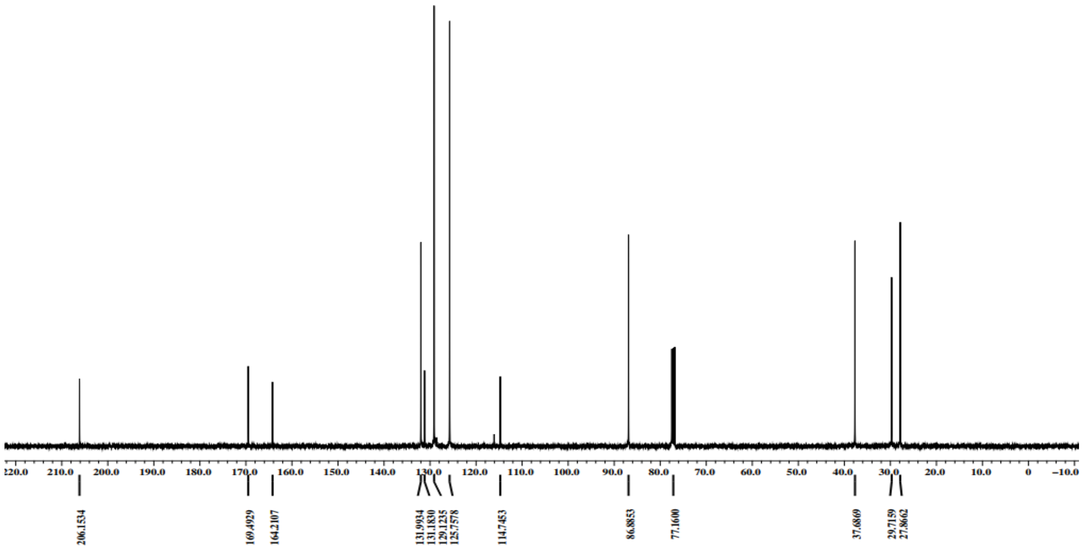
^{1}H NMR (400 MHz, CDCl$_3$)

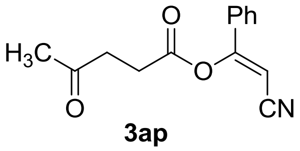




3ap

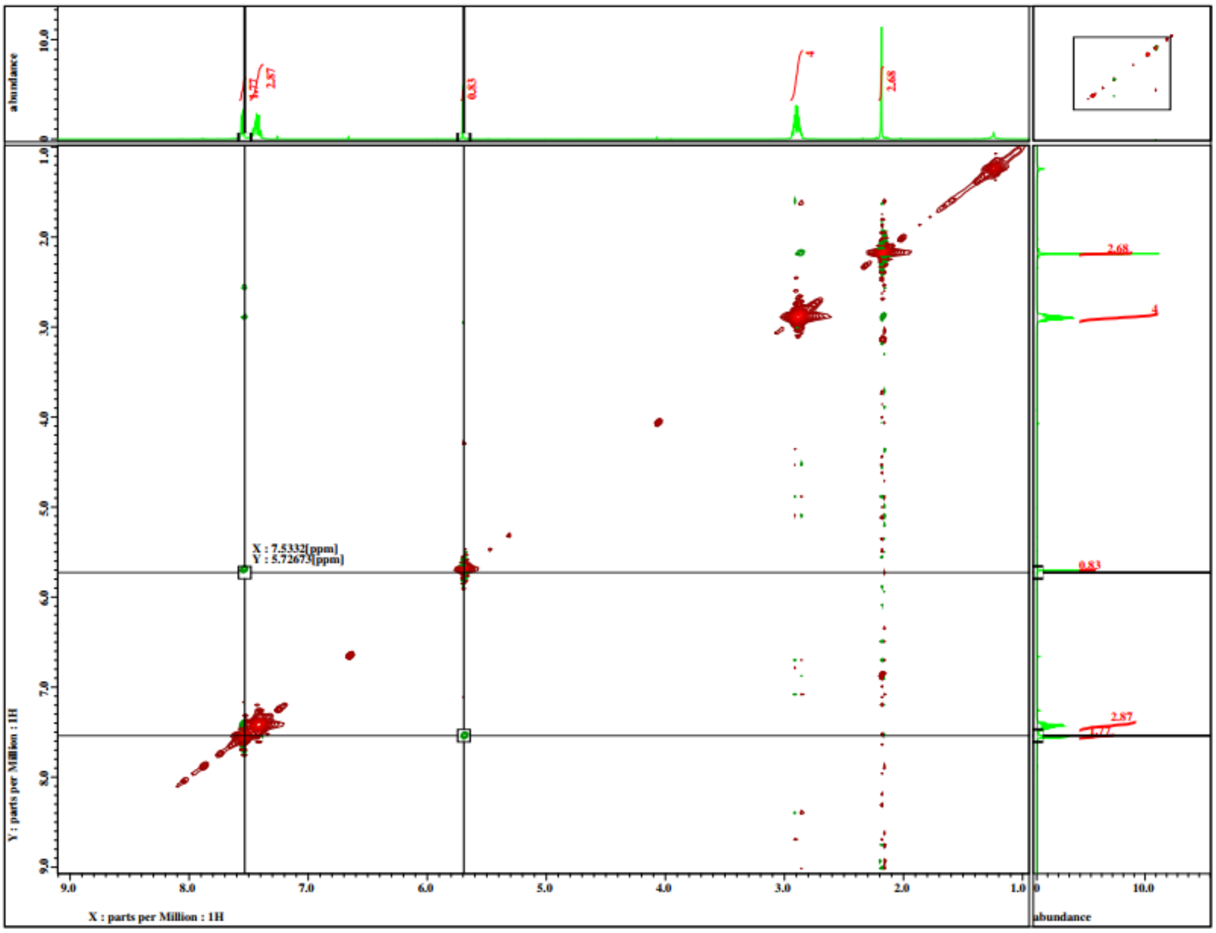
^{13}C NMR (100 MHz, CDCl$_3$)

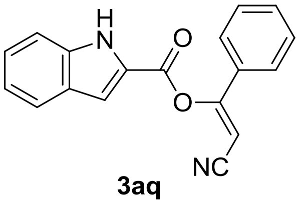




3ap

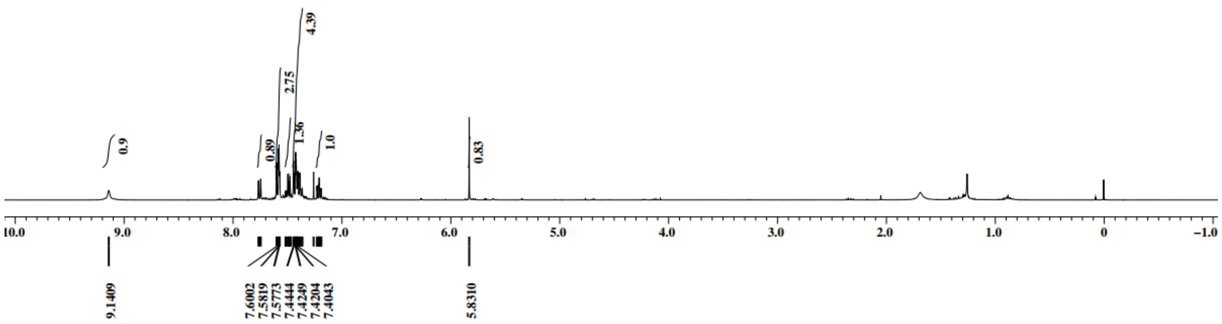
NOESY NMR (400 MHz, $CDCl_3$)

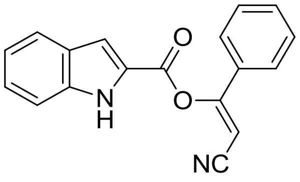




3aq

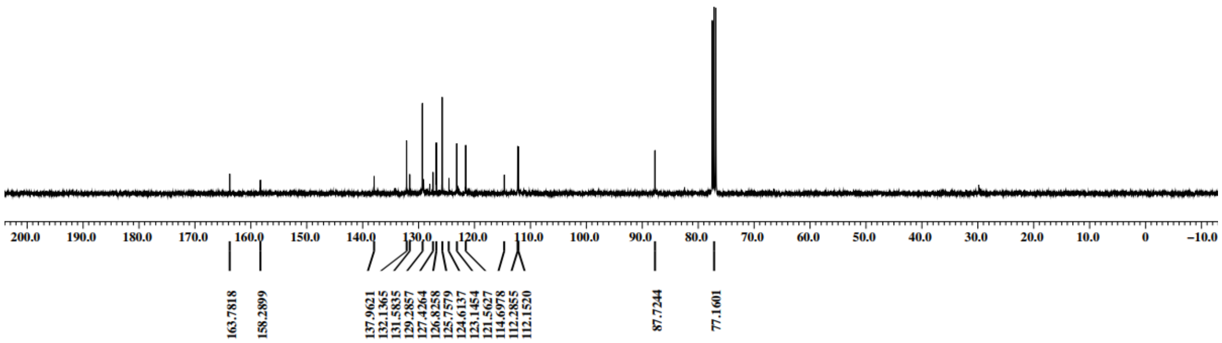
^{1}H NMR (400 MHz, CDCl$_3$)

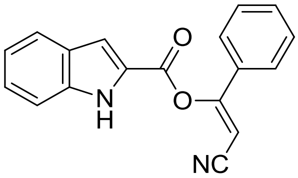




3aq

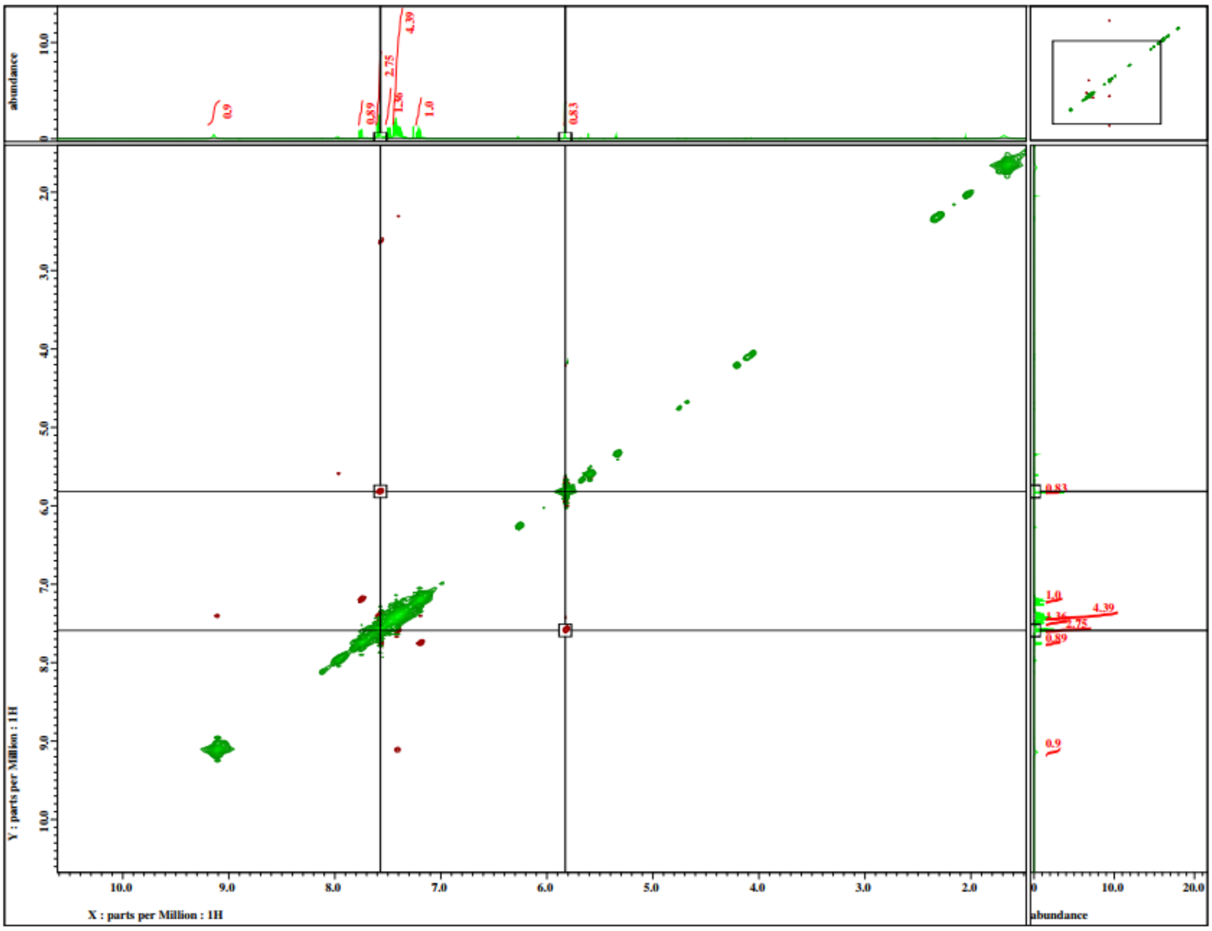
^{13}C NMR (100 MHz, CDCl$_3$)

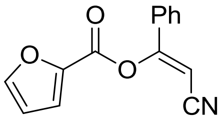




3aq

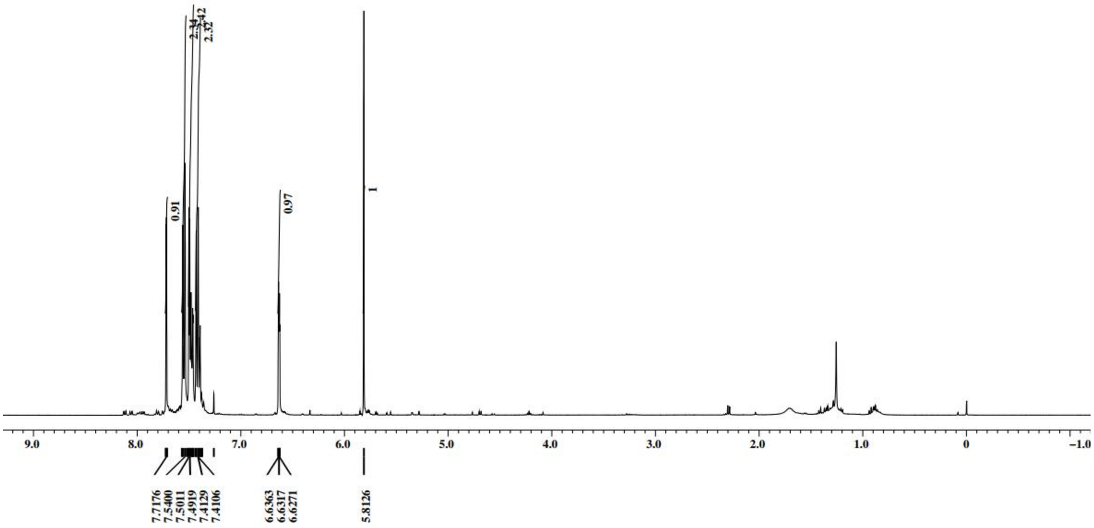
NOESY NMR (400 MHz, $CDCl_3$)

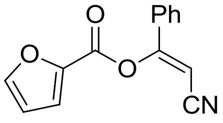




3ar

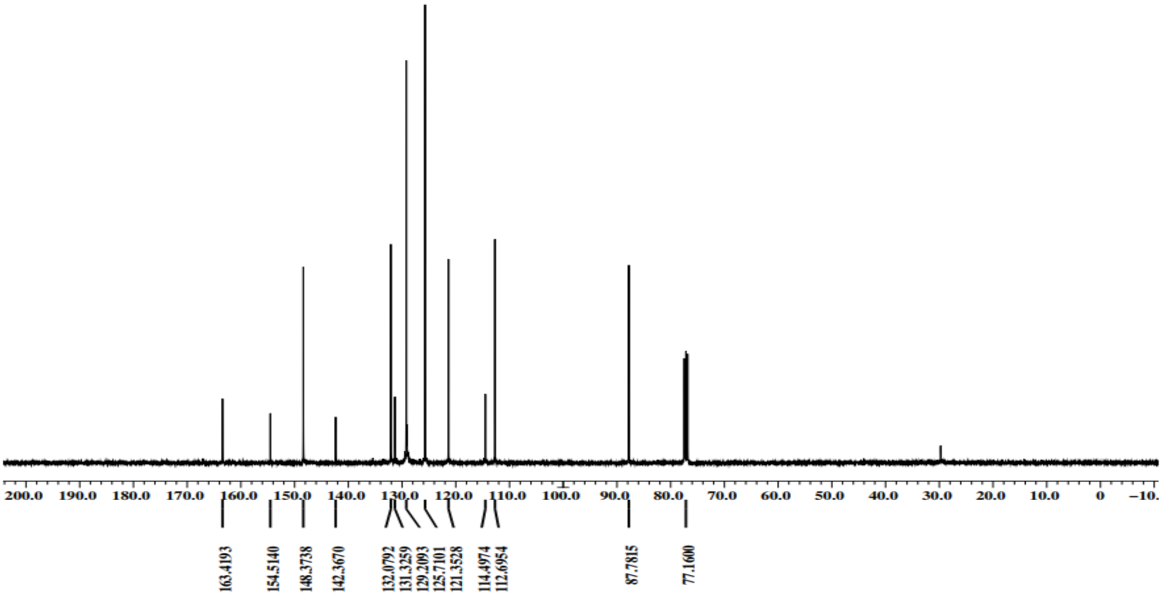
^{1}H NMR (400 MHz, $CDCl_3$)

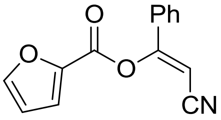




3ar

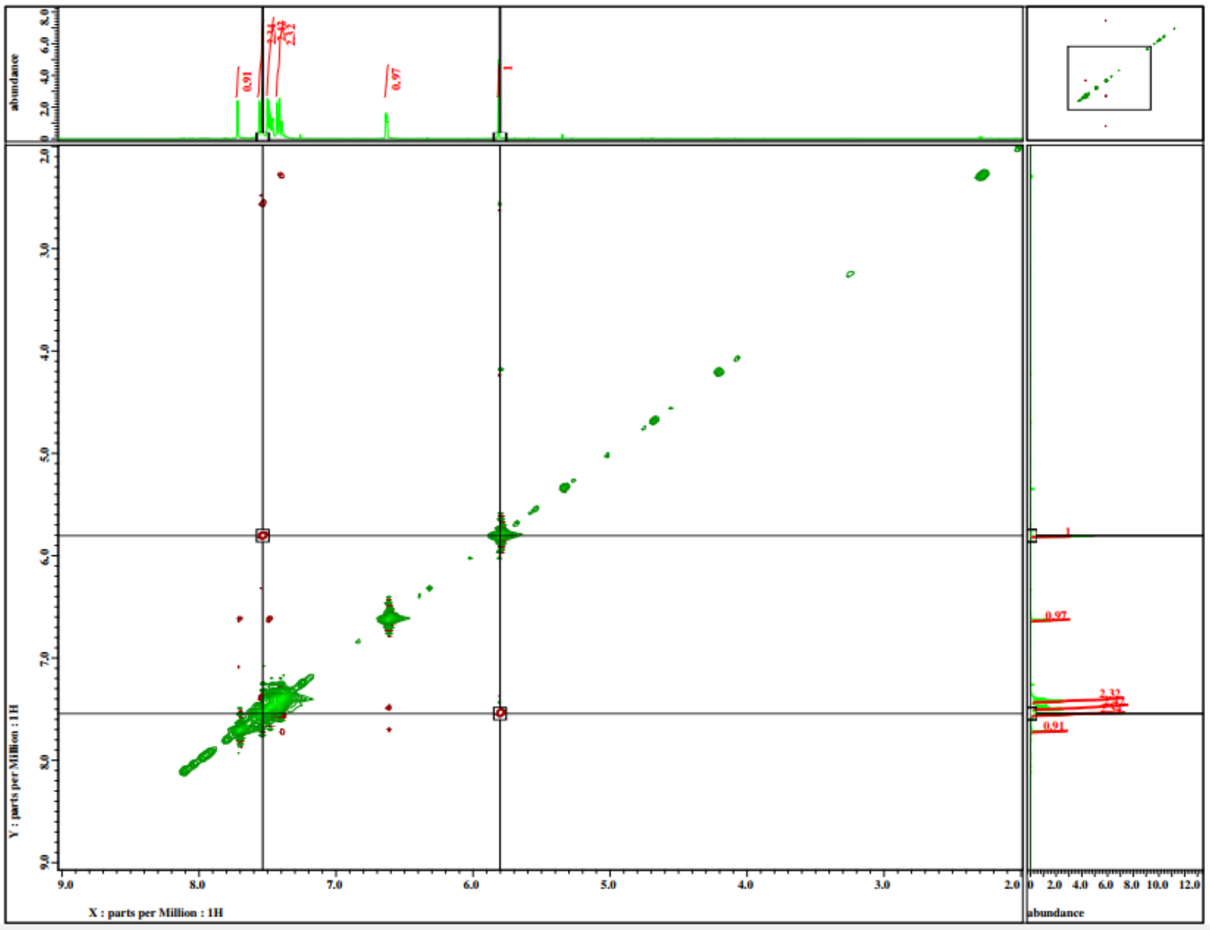
^{13}C NMR (100 MHz, $CDCl_3$)

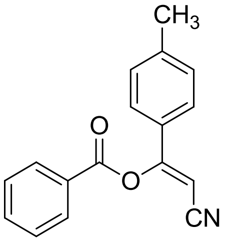




3ar

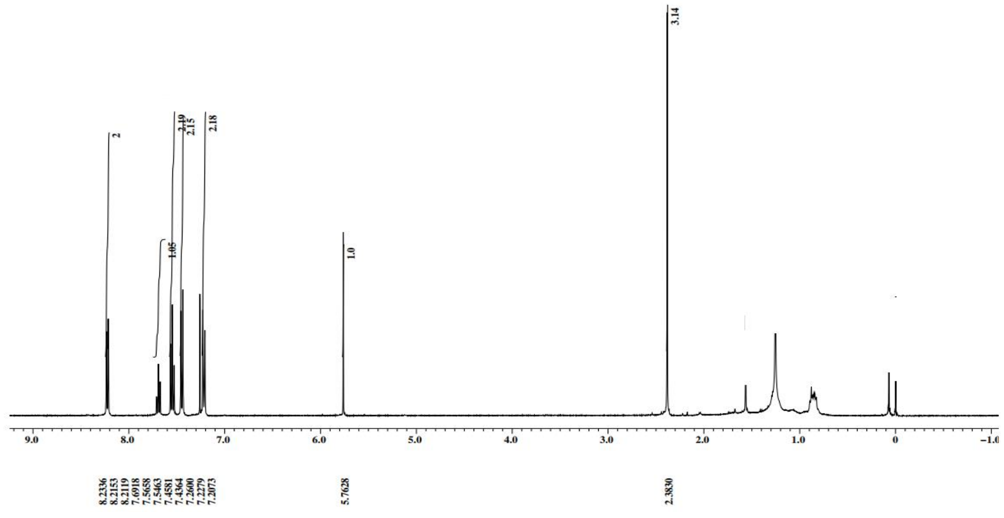
NOESY NMR (400 MHz, $CDCl_3$)

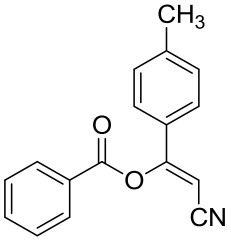




3ca

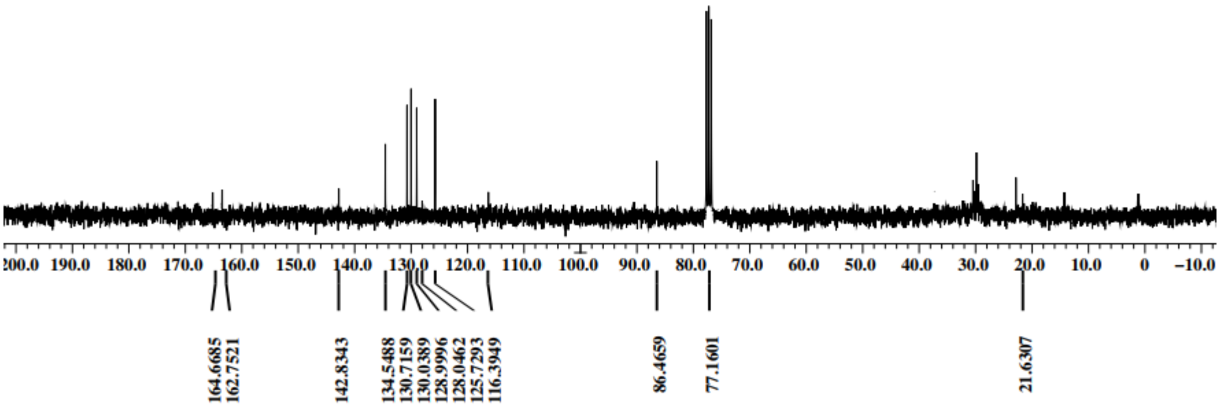
^{1}H NMR (400 MHz, CDCl$_3$)

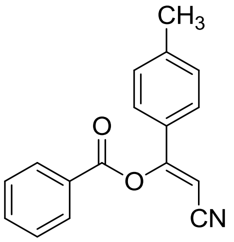




3ca

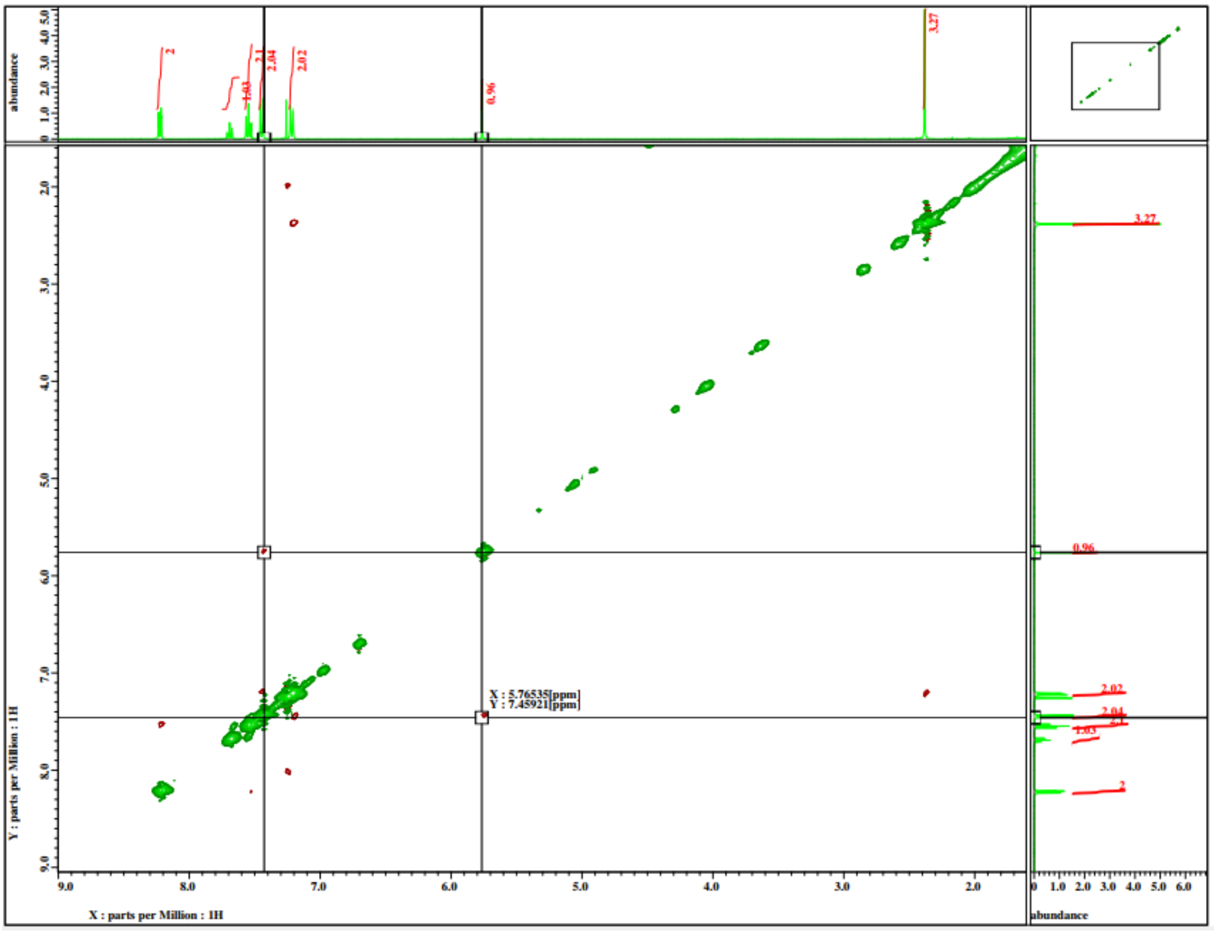
^{13}C NMR (100 MHz, CDCl$_3$)

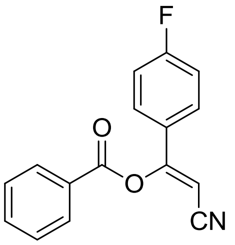




3ca

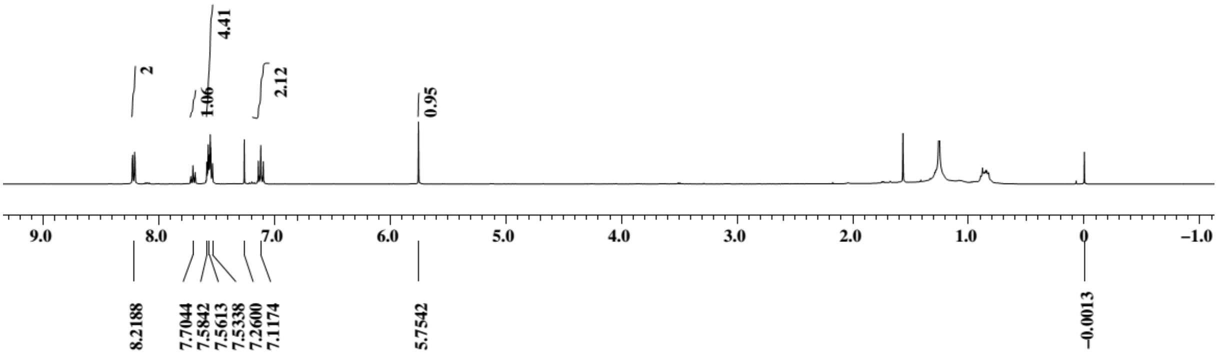
NOESY NMR (400 MHz, $CDCl_3$)

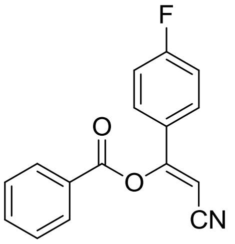




3ba

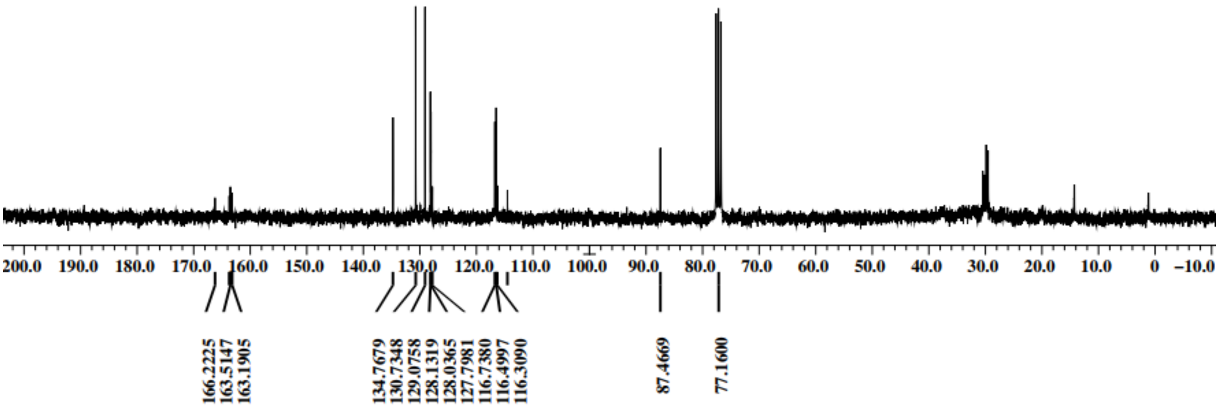
^{1}H NMR (400 MHz, CDCl$_3$)

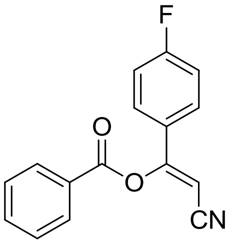




3ba

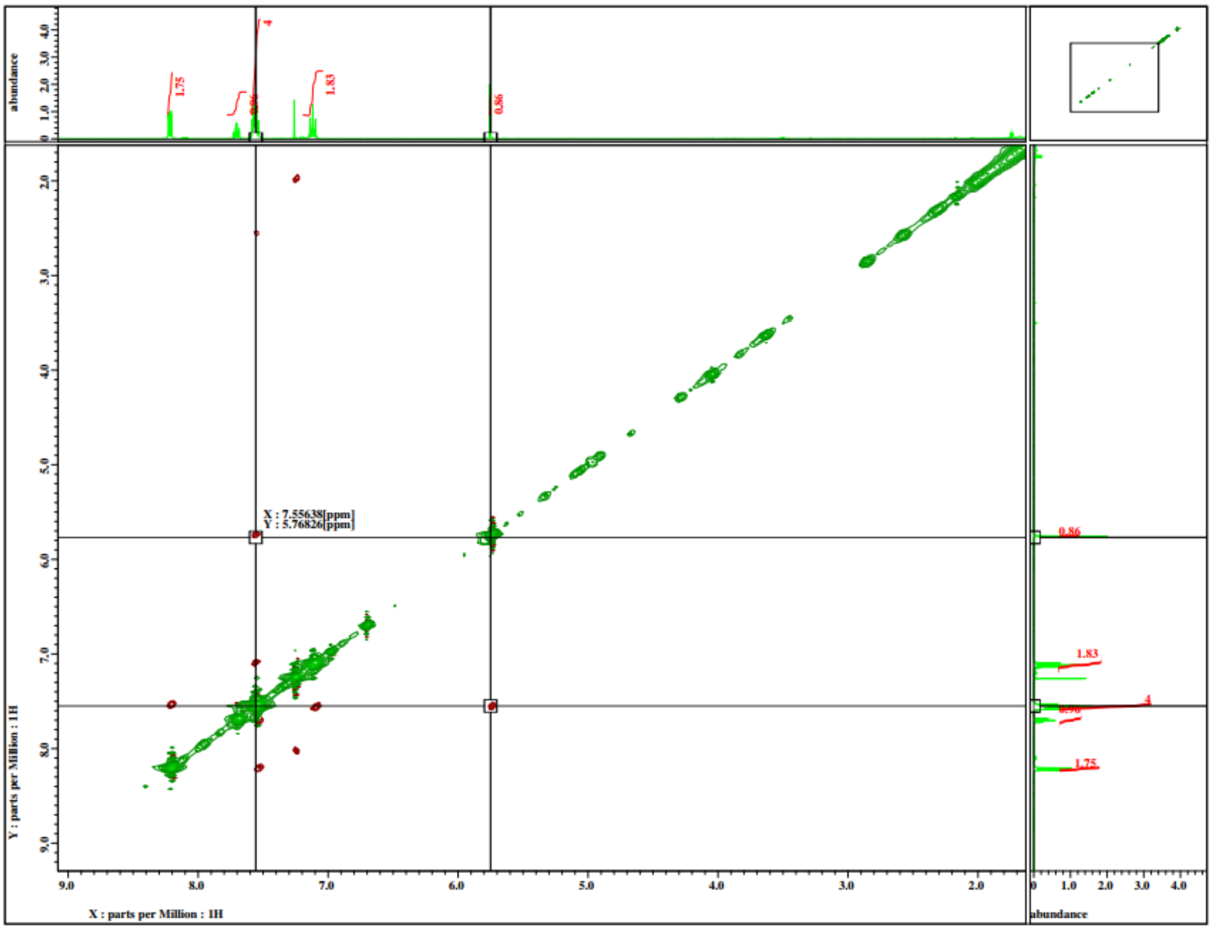
^{13}C NMR (100 MHz, CDCl$_3$)

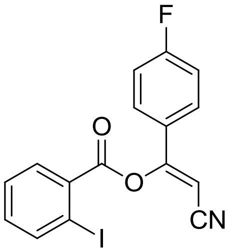




3ba

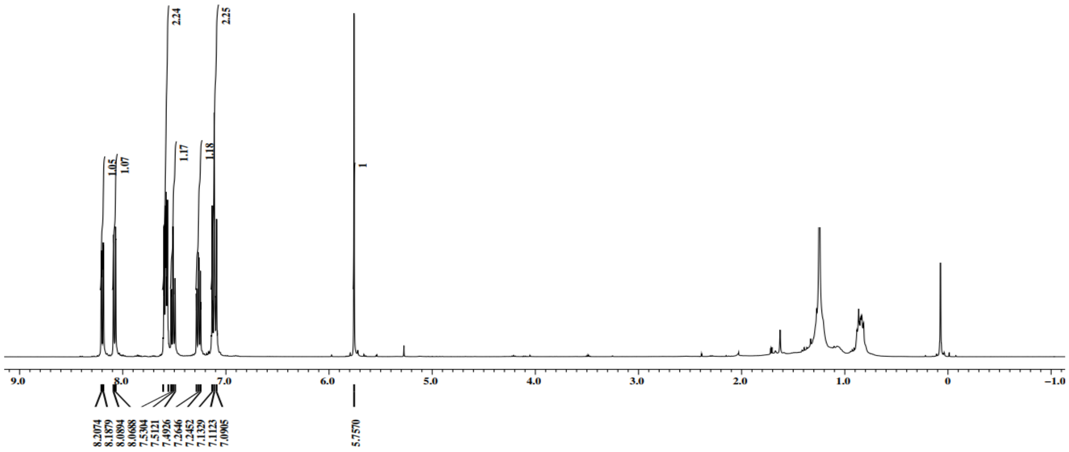
NOESY NMR (400 MHz, $CDCl_3$)

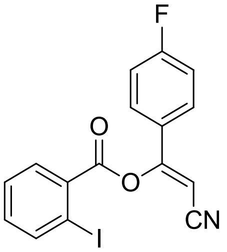




3bb

^{1}H NMR (400 MHz, CDCl$_3$)





3bb

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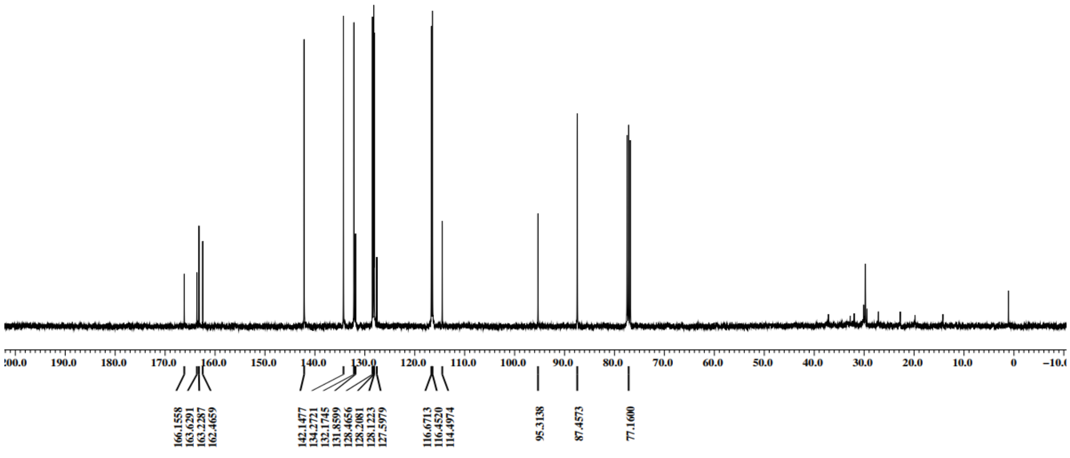

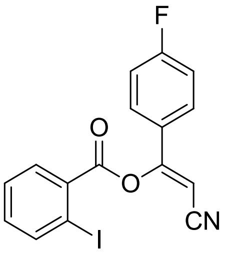

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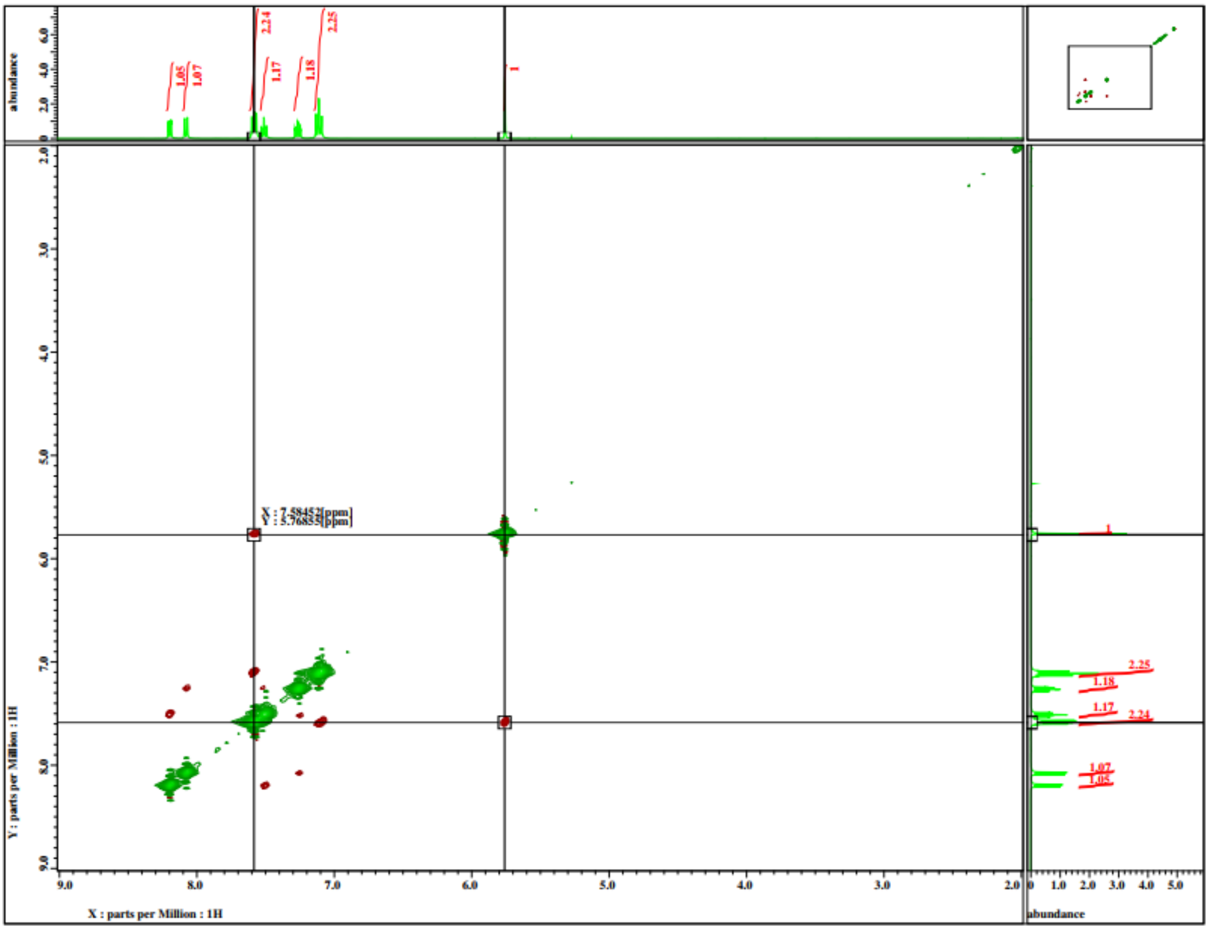

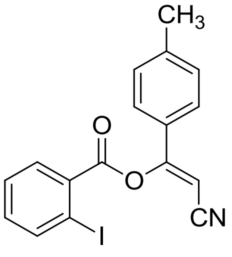

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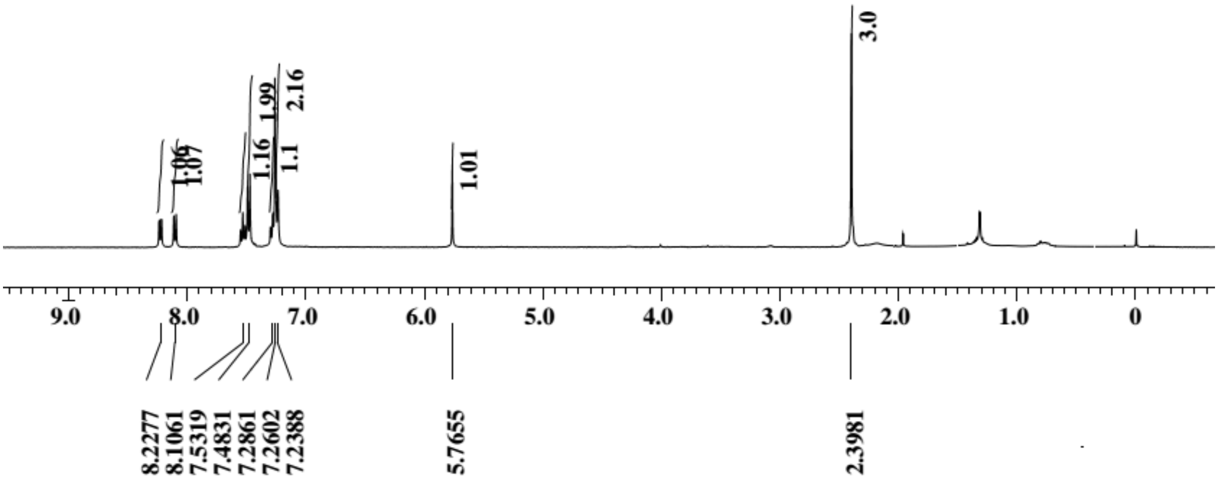

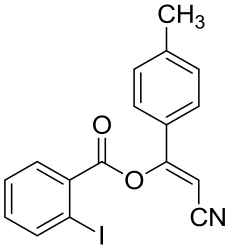

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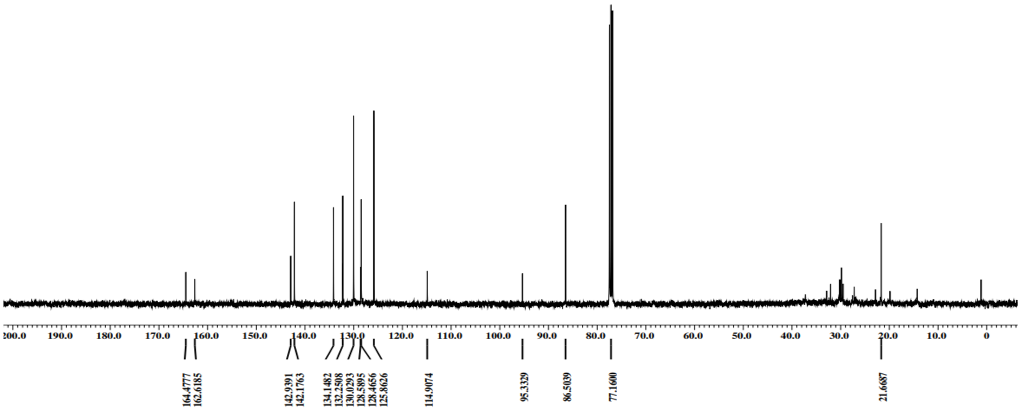

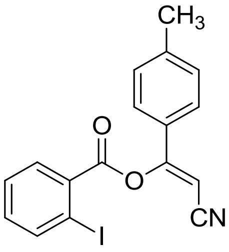

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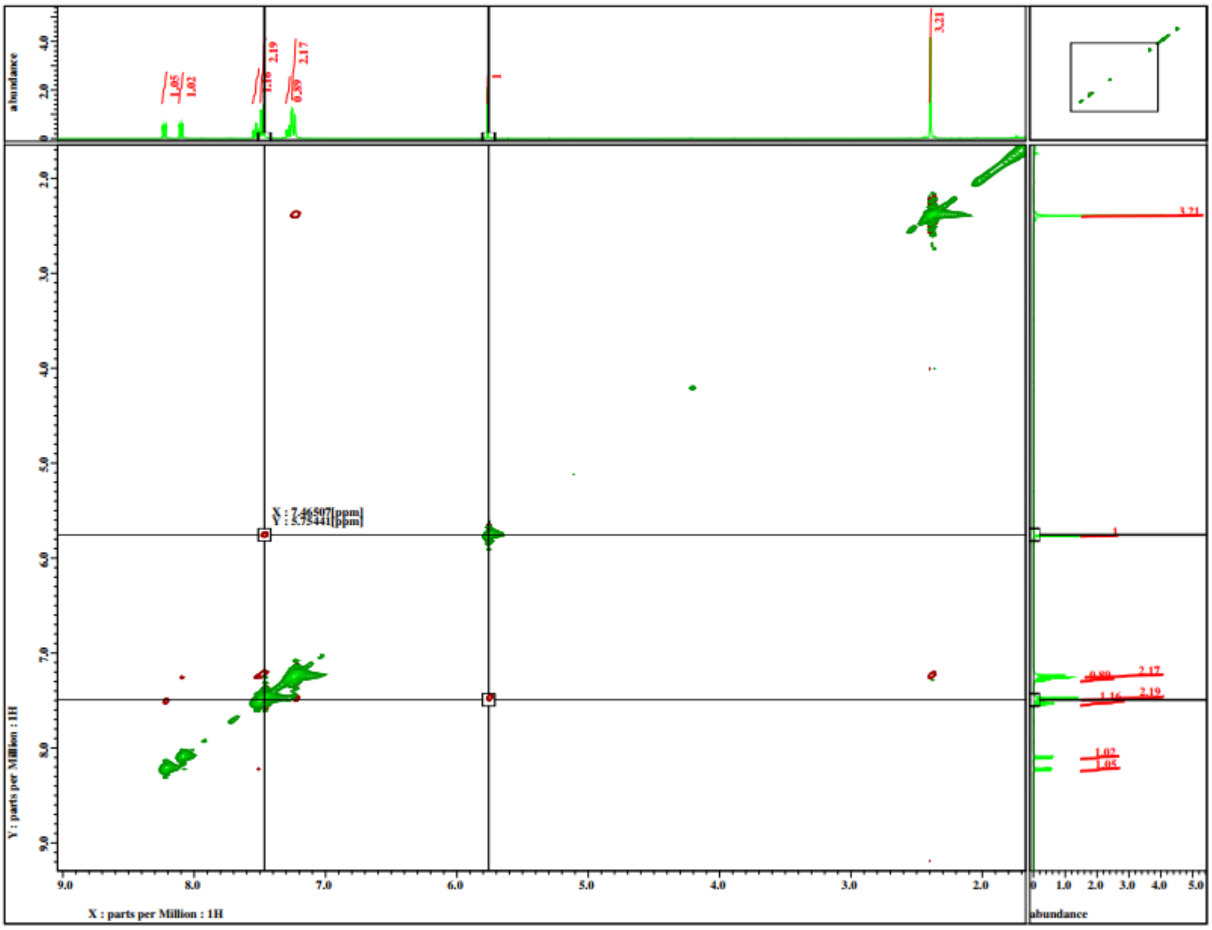

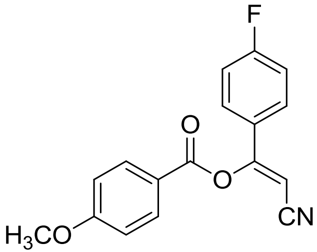

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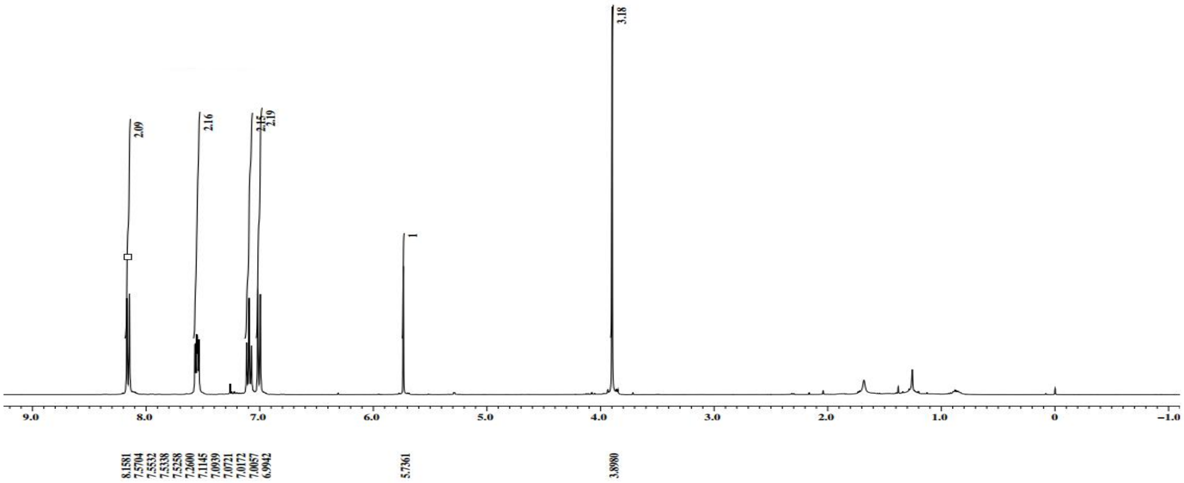

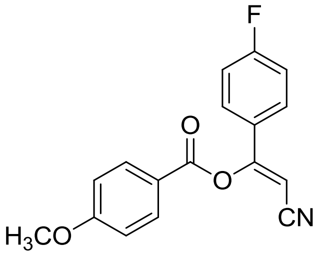

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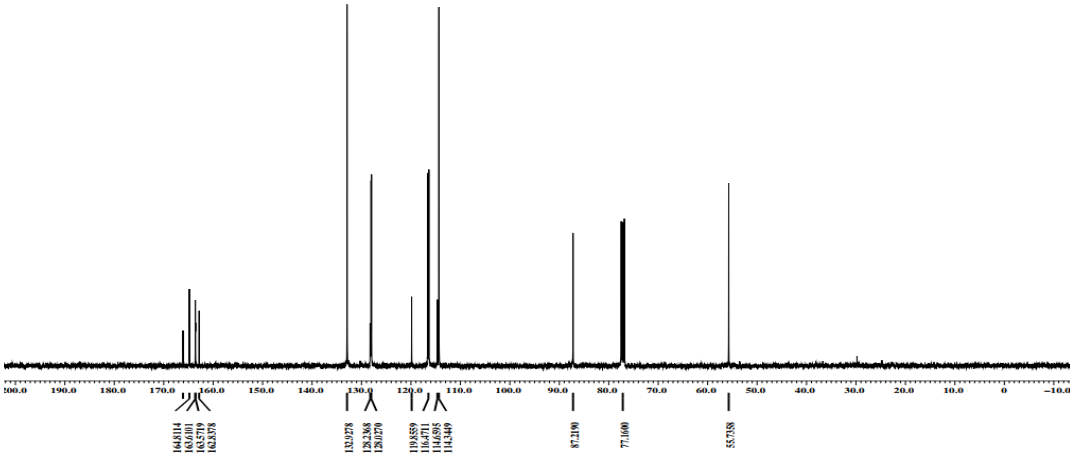

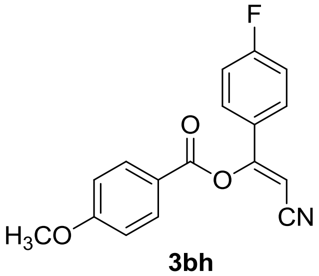

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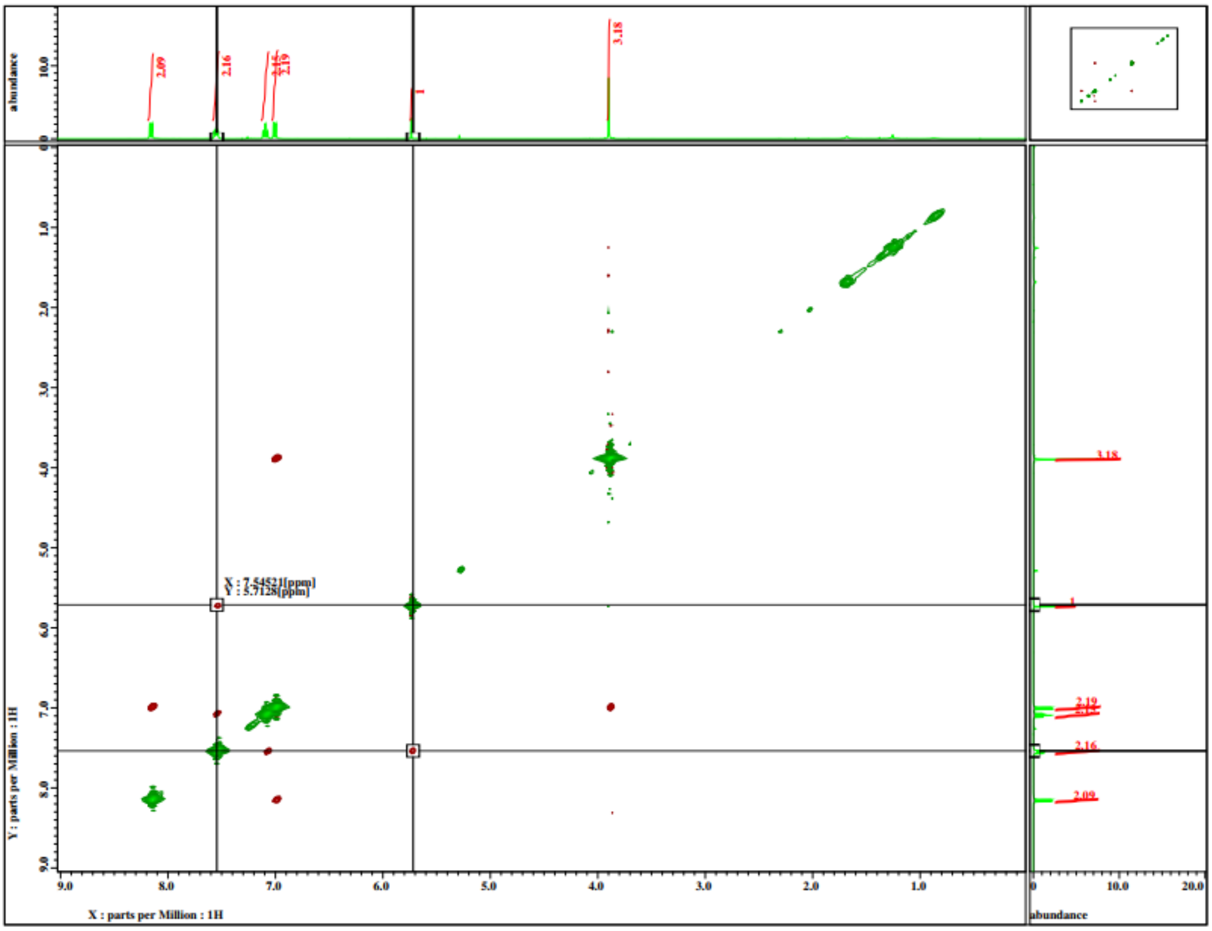

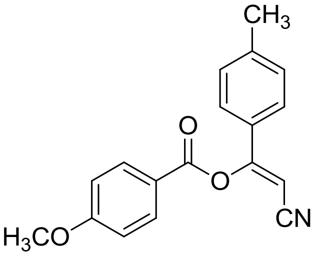

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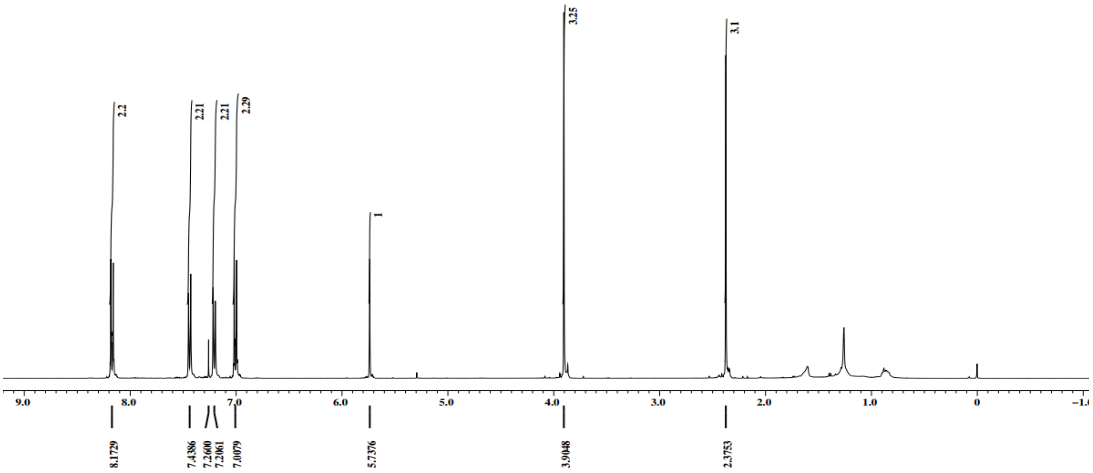

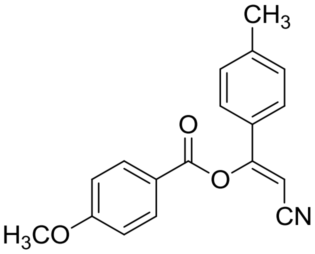

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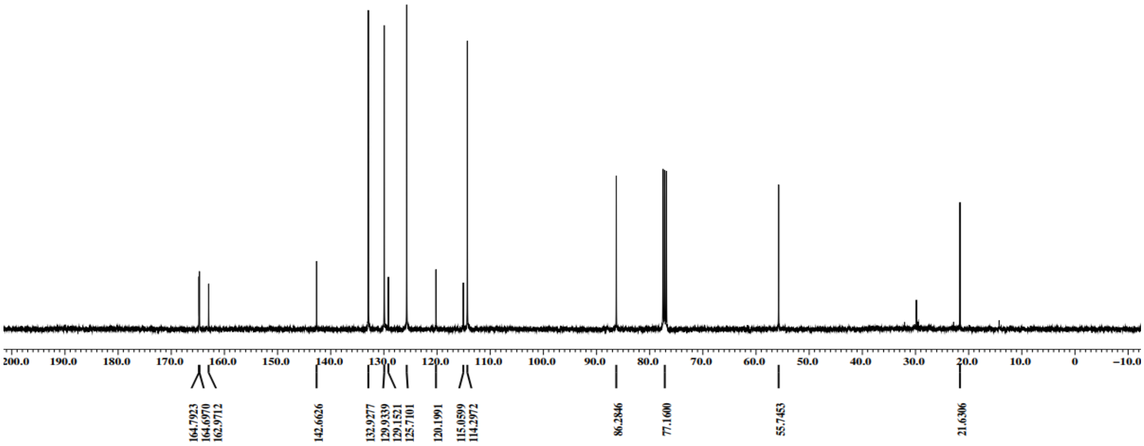

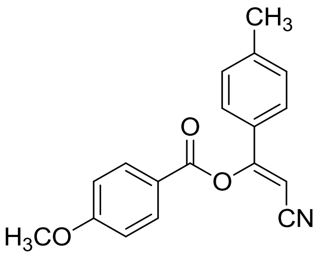

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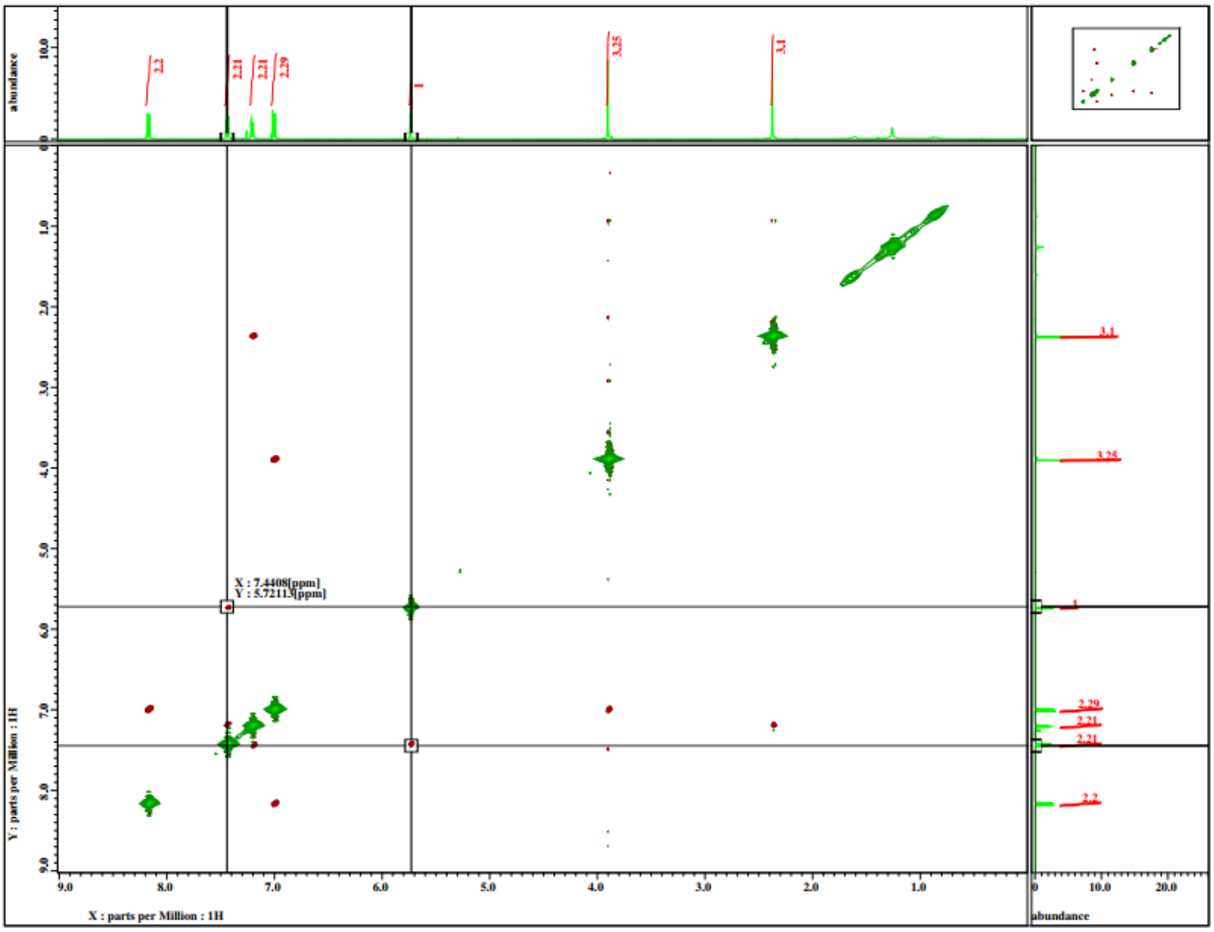

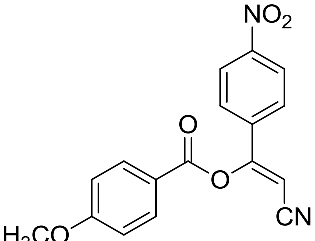

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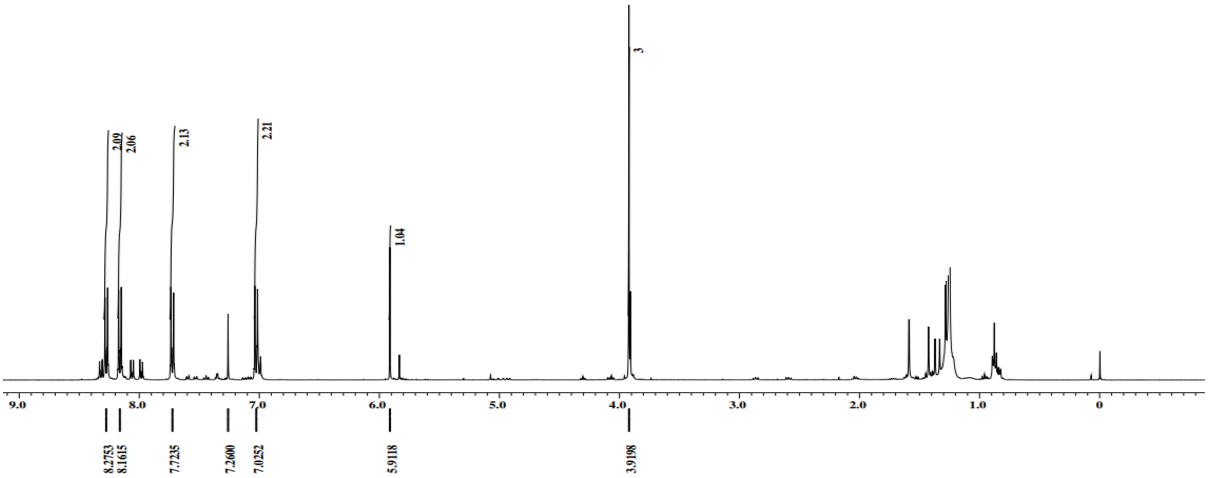

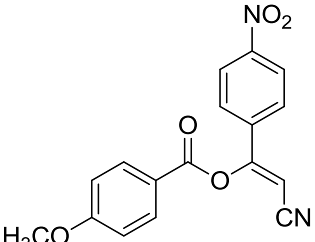

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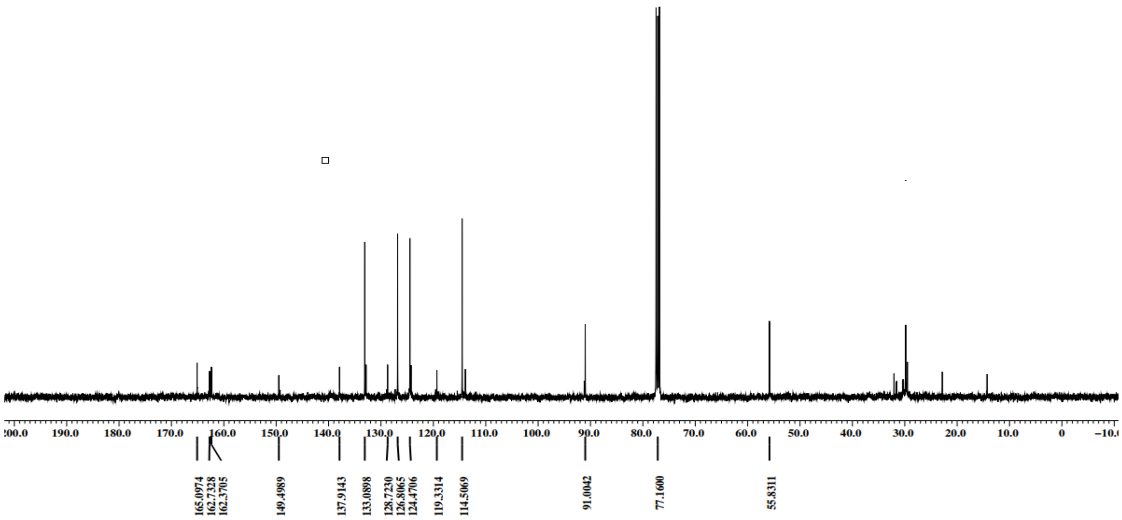

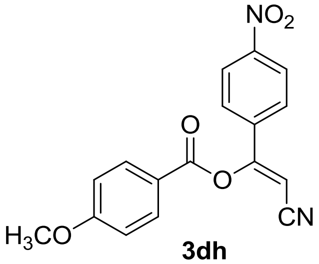

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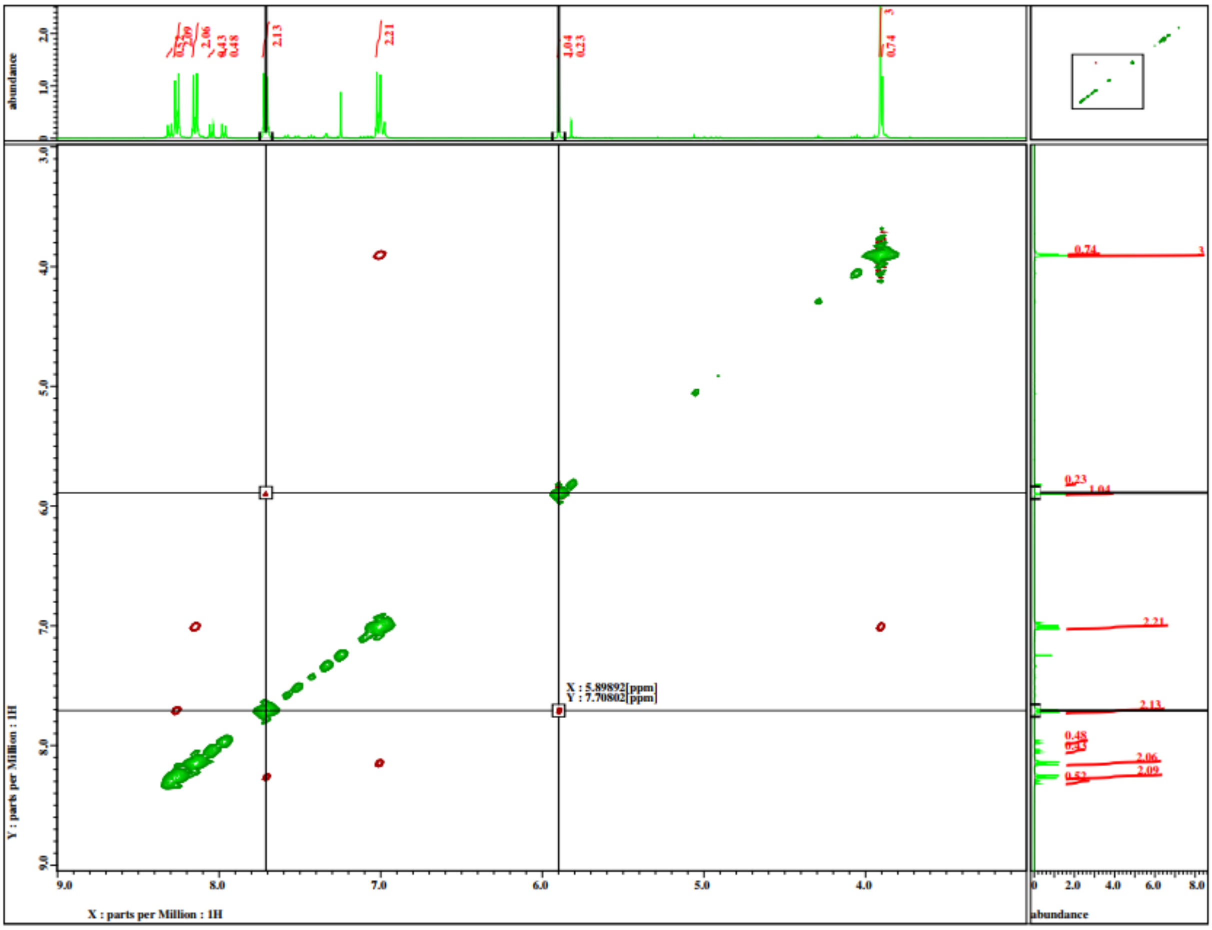

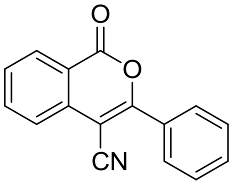

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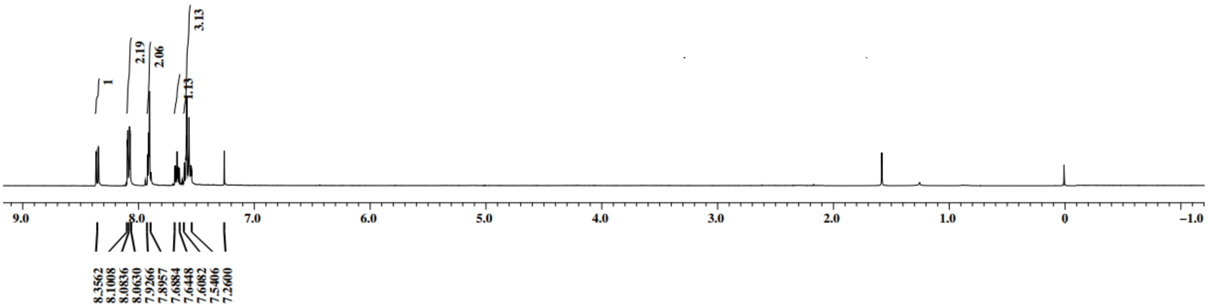

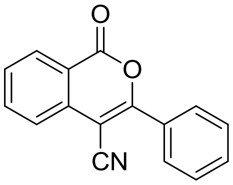

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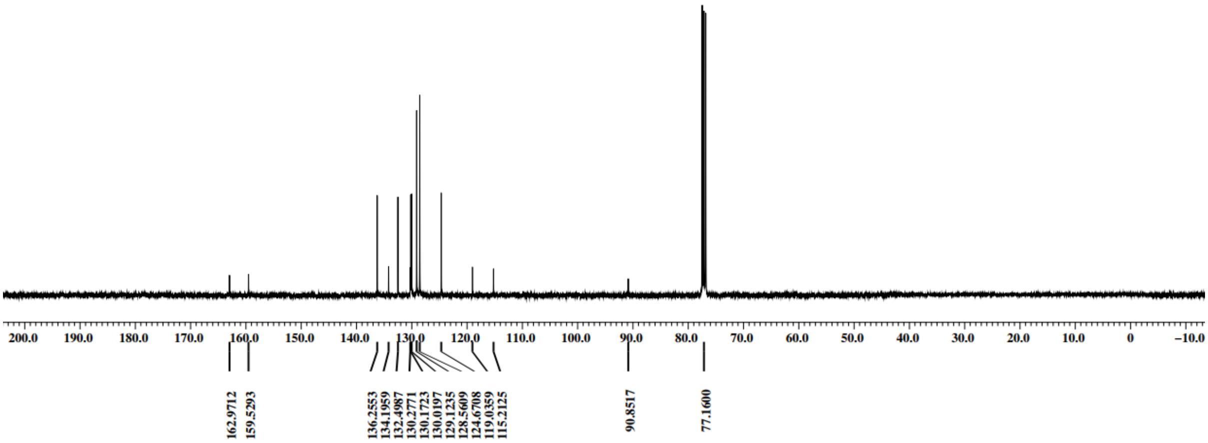

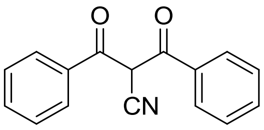

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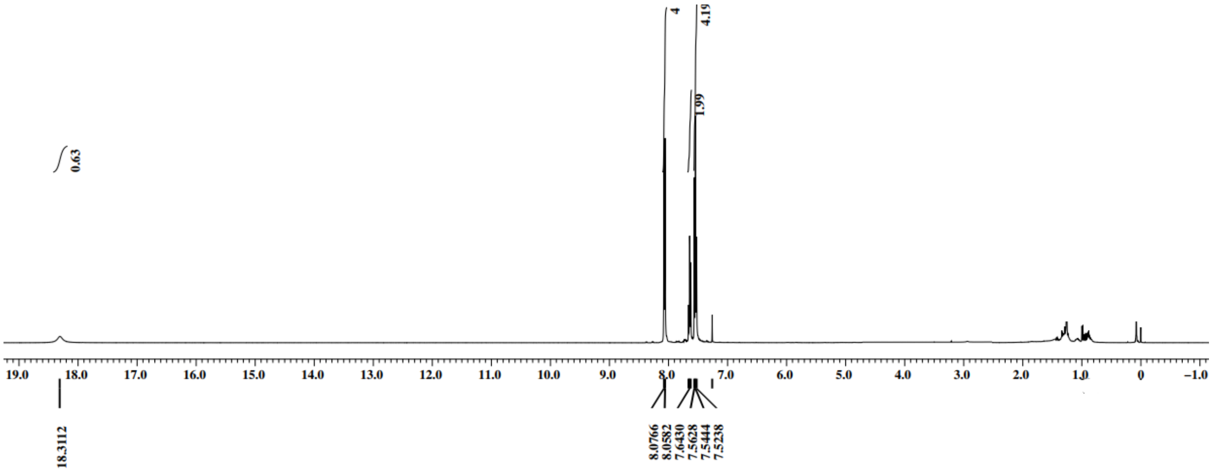

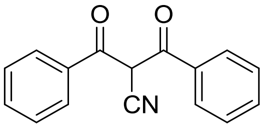

6

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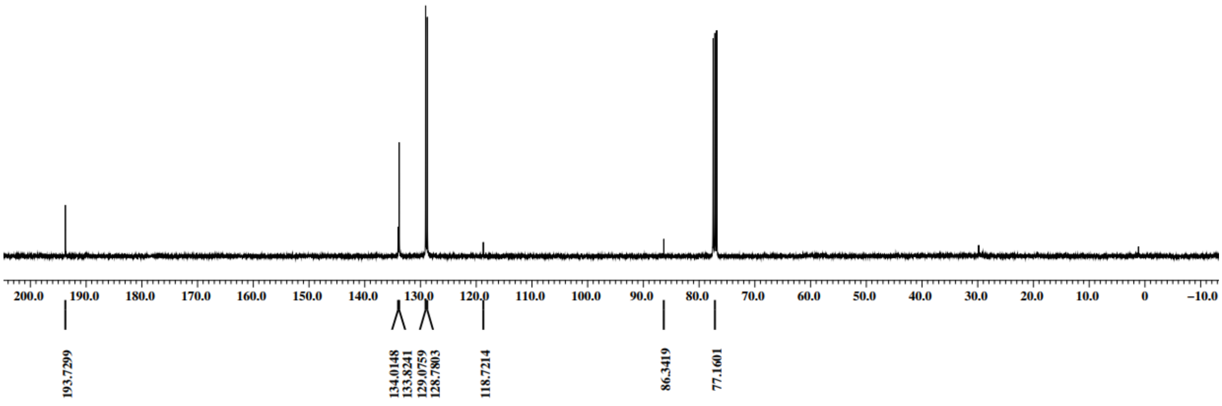


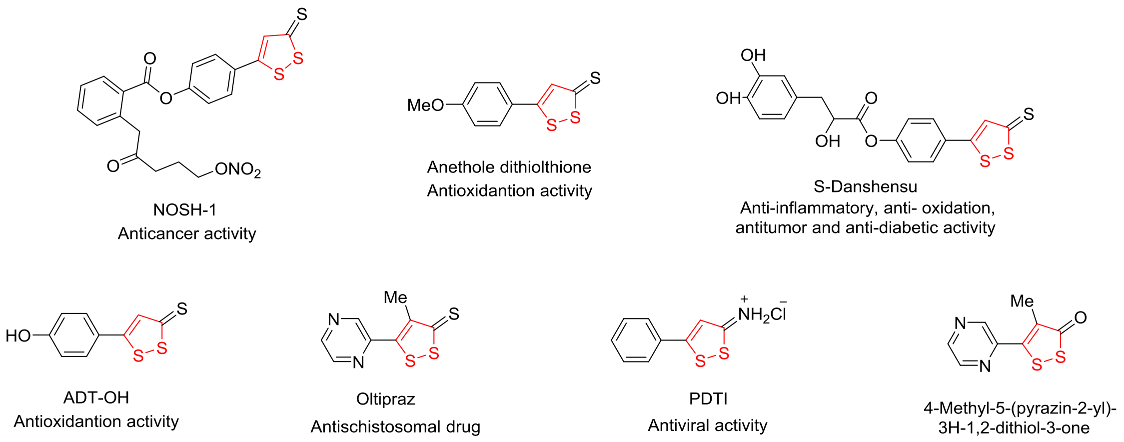
CHAPTER 4

Ionic Liquid Mediated One-Pot 3-Acylimino-3*H*-1,2-dithioles Synthesis from Thiocarboxylic Acids and Alkynenitriles via *in situ* Generation of Disulfide Intermediates

Chapter 4: Ionic Liquid Mediated One-Pot 3-Acylimino-3*H*-1,2-dithioles Synthesis from Thiocarboxylic Acids and Alkynenitriles via *in situ* Generation of Disulfide Intermediates

4.1 Introduction

Functionalized 1,2-dithiols have been an important class of sulfur-containing heterocycles. These heterocyclic structural motifs are frequently found in various natural products and pharmaceuticals and show a broad spectrum of biological and pharmacological activity, like antioxidant, antibiotic, chemotherapeutic, antitumor and anti-HIV etc. (Figure 4.1.1).[1] In addition, they are being used as building blocks for synthesizing novel sulfur or nitrogen atom(s) containing heterocycles.[2] As a result, these are interesting targets for the synthetic organic community and remains a subject of active research.



NOSH-1
Anticancer activity

Anethole dithiolthione
Antioxidantion activity

S-Danshensu
Anti-inflammatory, anti- oxidation, antitumor and anti-diabetic activity

ADT-OH
Antioxidantion activity

Oltipraz
Antischistosomal drug

PDTI
Antiviral activity

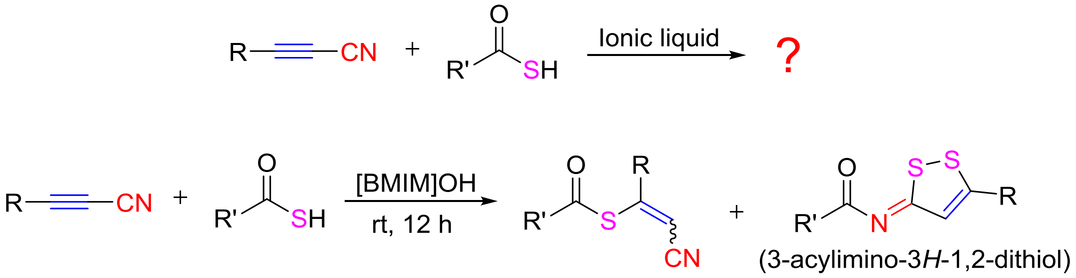
4-Methyl-5-(pyrazin-2-yl)-3H-1,2-dithiol-3-one

Figure 4.1.1 Some biologically important 1,2-dithiol containing heterocycles.

Until recently, 1,2-dithiole-3-thione organosulfur heterocycles have been intensively studied and used as scaffolds and precursors in various synthetic transformations.[3] Contrarily, 3-acylimino-1,2-dithiole derivatives have remained underexplored. These have been mainly exploited for synthesizing biologically important isothiozole products, which are essential S and N containing heterocyclic scaffolds, owing to their great importance in synthetic and biological chemistry.[2a-c, g] These compounds could be potential precursors in heterocyclic and pharmaceutical chemistry.

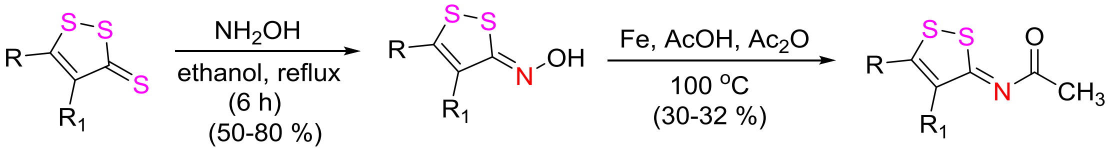
If these are appropriately worked upon, they can lead to exciting results. We have explored one aspect of these compounds to form interestingly substituted thiophenes that can be difficult to synthesize from already reported approaches. Since there are no suitable and convenient synthetic methods to access 3-acylimino-3*H*-1,2-dithioles, there are a few reports on the synthesis and the related biological and pharmacological importance of these compounds. Thus, further development is needed to widen access to this class of compounds.

After in-depth studies on the ionic liquid-mediated synthesis of *Z*-enol esters from the reaction of bifunctional alkynenitriles with carboxylic acids, we thought of synthesising thioisocoumarins through the formation of thioenolesters by reacting alkynenitriles with thiocarboxylic acids under same reaction conditions. However, we noticed a spontaneous formation of 3-acylimino-3*H*-1,2-dithiole along with thioenol ester (Scheme 4.1.1). Being a class of most intensively studied biologically important 1,2-dithioles, this preliminary experimental result strongly motivated us to investigate this ionic liquid-mediated addition of thiocarboxylic acids to alkynenitriles to produce 3-acylimino-3*H*-1,2-dithiole derivatives in detail.



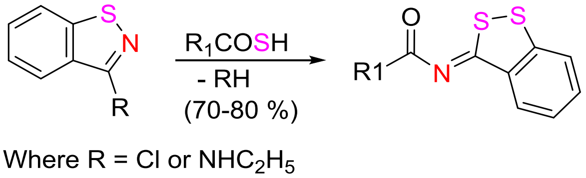
Scheme 4.1.1 Ionic liquid [BMIM]OH mediated reaction of thiocarboxylic acid with alkynenitrile.

These compounds were previously reported in the early 1960s from 3*H*-1,2-dithiol-3-thiones.[3] However, these multiple step protocols involving relatively lengthy procedures suffer from harsh reaction conditions and low yields. For example, 3-acylimino-3*H*-1,2-dithioles were produced by acetylating reduction of the corresponding oximes, which were obtained from the 3*H*-1,2-dithiol-3-thiones by refluxing with hydroxylamine in ethanol solvent for 6 h (Scheme 4.1.2).[4]



Scheme 4.1.2 3-acylimino-3*H*-1,2-dithioles synthesis from *3H*-1,2-dithiol-3-thiones by acetylating reduction of the corresponding oximes.

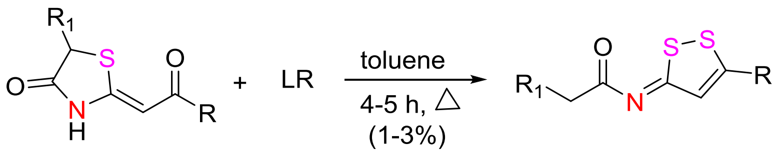
Since then, a few reports dealing with the synthesis of 3-acylimino-3*H*-1,2-dithioles have been documented. In 1968, Boshagen and Geiger uncovered the synthesis of 3-acylimino-3*H*-1,2-benzodithiole derivatives by reacting thiocarboxylic acids with 3-chloro-1,2-benzisothiazoles or 3-ethylamino-1,2-benzisothiazols in pyridine solvent at 50 °C (Scheme 4.1.3).[2c]



Scheme 4.1.3 Boshagen and Geiger's synthesis of 3-acylimino-3*H*-1,2-benzodithiole derivatives from 3-chloro or 3-ethylamino-1,2-benzisothiazoles.

Ammick *et al*. in 1971 also obtained 3-acylimino-1,2-dithioles in moderate yields from 1,2-dithiole-3-ylidene thiones by oxidation with $Hg(OAc)_2$ in acetic acid under reflux conditions.[5] After three decades, in 2003, Pazdera and co-workers synthesized 3-acylimino-1,2-dithiole derivatives from 5-amino-3-thioxo-3*H*-1,2-dithioles by converting them to their corresponding 1,2-dithiol-1-ium iodides or amides or salts of these amides.[6] Later in 2006, the same group synthesized 3-acylimino-1,2-dithiole from the 5-acetamido-3-thioxo-*3H*-1,2-dithioles by reaction with bromoethanones and one equivalent of triethylamine in acetone.[7]

The following year, in 2007, Markovic *et al*. reported the formation of 3-acylimino-l,2-dithioles as a side product with 1-3% yield during the synthesis of 1,2-dithiole-3-ylidene thiones from 2-alkylidene-4-oxothiazolidines through a ring-opening-closing process sequence in the presence of Lawesson's reagent (Scheme 4.1.4).[8]



Where LR = Lawesson's reagent

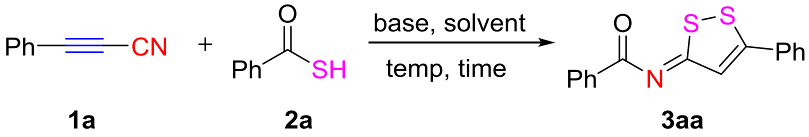
Scheme 4.1.4 Synthesis of 1,2-dithiole-3-ylidene thiones from 2-alkylidene-4-oxothiazolidines.

So far, as demonstrated, all these mentioned protocols rely on the already inbuilt 1,2-dithiole core containing substrates and are associated with the drawback of the limited availability and multistep synthesis of the pre-decorated precursors. Even though 3-acylimino-1,2-dithioles have been discovered much earlier but have gained much less considerable attention in advancing further development. Therefore, developing an efficient, more general approach that enables direct access to 3-acylimino-1,2-dithiole derivatives from simple precursors is much awaited. In this context, we have revealed the first quantitative one-pot ionic liquid [BMIM]Br-mediated synthesis of 3-acylimino-3*H*-1,2-dithioles from readily available thiocarboxylic acids and bifunctional alkynenitriles[9a-b] in the presence of K_2CO_3 as a base.[9c]

4.2 Results and Discussion

We initiated our investigation with the thought process of the involvement of the disulfide intermediate in forming the 1,2-dithiole core moiety. It is to be noted that several research groups have reported the auto aerial oxidation of the thioacids and thiols to disulfides in the reaction mechanism.[10] Sinha *et al*., in 2008, successfully demonstrated the aerobic oxidation of thiols into disulfides in neat [HMIM]Br without using any base or metal.[10d] Chen *et al*., in 2016, uncovered a visible-light-promoted photoredox catalytic route to synthesize amides from amines and potassium thioacids through a diacyl disulfide intermediate.[10a]

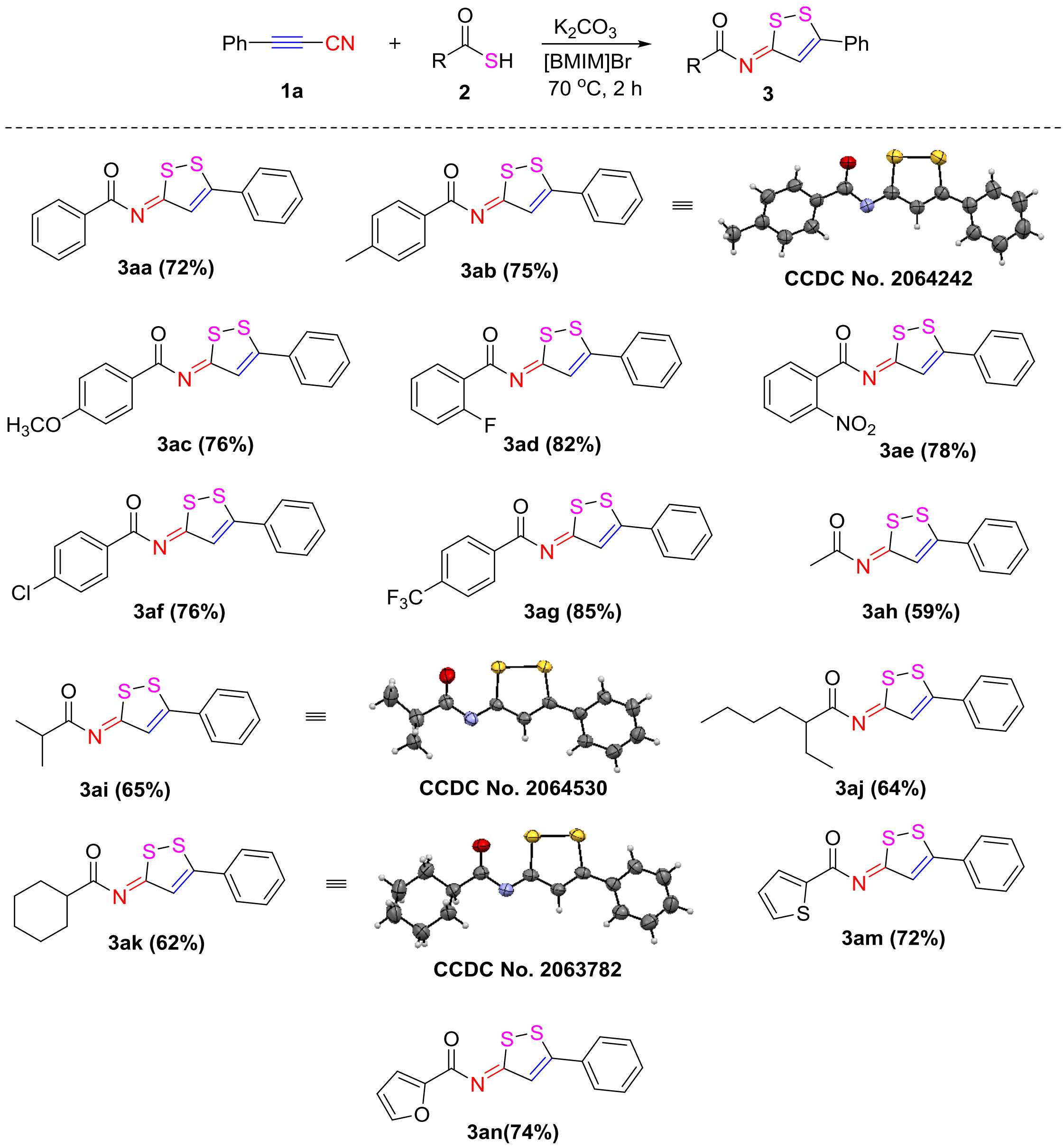
Table 4.2.1 Optimization studies.[a]



Entry	Base (equiv.)	Solvent (mL)	Temp (°C)	Time (h)	Yield[b] (%) (3aa)
1	K_2CO_3 (1)	[BMIM]Br (1)	rt	12	20[c]
2	K_2CO_3 (1)	[BMIM]Br (1)	40	12	54
3	**K_2CO_3 (1)**	**[BMIM]Br (1)**	**70**	**2**	**72**
4	K_2CO_3 (1)	[BMIM]Br (1)	100	2	63
5	Cs_2CO_3 (1)	[BMIM]Br (1)	70	2	52
6	Et_3N (2)	[BMIM]Br (1)	70	2	27
7	KO^tBu (2)	[BMIM]Br (1)	70	2	21
8	KOH (2)	[[BMIM]Br (1)	70	2	36
9	-	[BMIM]Br (1)	70	2	40
10	K_2CO_3 (1)	[HMIM]Br (1)	70	2	42
11	K_2CO_3 (1)	$[BMIM]BF_4$ (1)	70	2	30
12	K_2CO_3 (1)	$[BMIM]NFT_2$ (1)	70	2	trace
13	K_2CO_3 (1)	[BMMIM]Br (1)	70	2	38
14	-	[BMIM]OH (1)	70	2	40
15	K_2CO_3 (1)	DMSO (1)	70	2	5[d]
16	K_2CO_3 (1)	DMF (1)	70	2	10[d]
17	K_2CO_3 (1)	ACN (1)	70	2	5[d]
18	K_2CO_3 (1)	THF (1)	70	2	22
19	K_2CO_3 (1)	HFIP (1)	70	2	3[d]
20	K_2CO_3 (1)	DMF (1)	110	2	10[d]
21	K_2CO_3 (1) + BF_3Et_2O (0.2)	DMF (1)	70	2	5[d]

[a] Unless otherwise stated all the reactions were performed under open air conditions: **1a** (31.75 mg, 0.25 mmol), **2a** (69 mg, 0.5 mmol), K_2CO_3 (69 mg, 0.5 mmol) and [BMIM]Br (1 mL), 70 ^oC, 2 h, [b] Isolated yield, [c] Reaction under inert conditions, [d] Yield from crude NMR.

We began our study by reacting phenylacetylene nitrile **1a** and thiobenzoic acid **2a** as the model substrates for the optimization of the reaction conditions in [BMIM]Br mediated synthesis of 3-acylimino-3*H*-1,2-dithioles using K_2CO_3 as a base. Table 4.2.1 summarizes the optimization results. The initial optimization revealed that in inert conditions very low yield for the expected 3-acylimino-3*H*-1,2-dithiole **3aa** was obtained. However, it improved to 54% by just changing the reaction set up to open air conditions and increasing the temperature from rt to 40 ^oC (Table 4.2.1, entries 1-2). This significant increase in the yield points towards the involvement of the disulfide intermediate, which turned out to be a crucial and essential step for the formation of 1,2-dithiole moiety. To our delight, further increasing temperature to 70 ^oC, desired product **3aa** was obtained in excellent yield within 2 h (Table 4.2.1, entry 3). Again, performing the reaction at 100 ^oC decreased the product yield (Table 4.2.1, entry 4). Next, a series of bases other than K_2CO_3, like Cs_2CO_3, Et_3N, KO^tBu, KOH were screened, however, none of them could provide satisfactory results (Table 4.2.1, entries 5-8). At the same time, several ionic liquids [HMIM]Br, [BMIM]BF_4, [BMIM]NFT_2, [BMMIM]Br and [BMIM]OH were assessed in a combination of K_2CO_3 at 70 ^oC, however, no noticeable increment in the yield of **3aa** was observed (Table 4.2.1, entries 9-14). To our surprise, the said reaction did not give any significant result when performed in common organic solvents like DMSO, DMF, ACN, THF and HFIP in the absence of ionic liquid (Table 4.2.1, entries 15-19) indicating the crucial role of the ionic liquid in activation of the reactants. Finally, the presence of Lewis acids $BF_3{\cdot}Et_2O$, AgOTf and $SnCl_4$ (not shown in Table 4.2.1) and refluxing temperature conditions were further screened hoping to enhance the productivity of ionic liquid-free reactions. Unfortunately, neither Lewis acids nor refluxing temperature could promote the transformation (Table 4.2.1, entries 20-21).



Reagents and conditions: **1a** (0.25 mmol), **2** (0.5 mmol), K_2CO_3 (0.5 mmol) and [BMIM]Br (1 mL), 70 °C, 2 h.

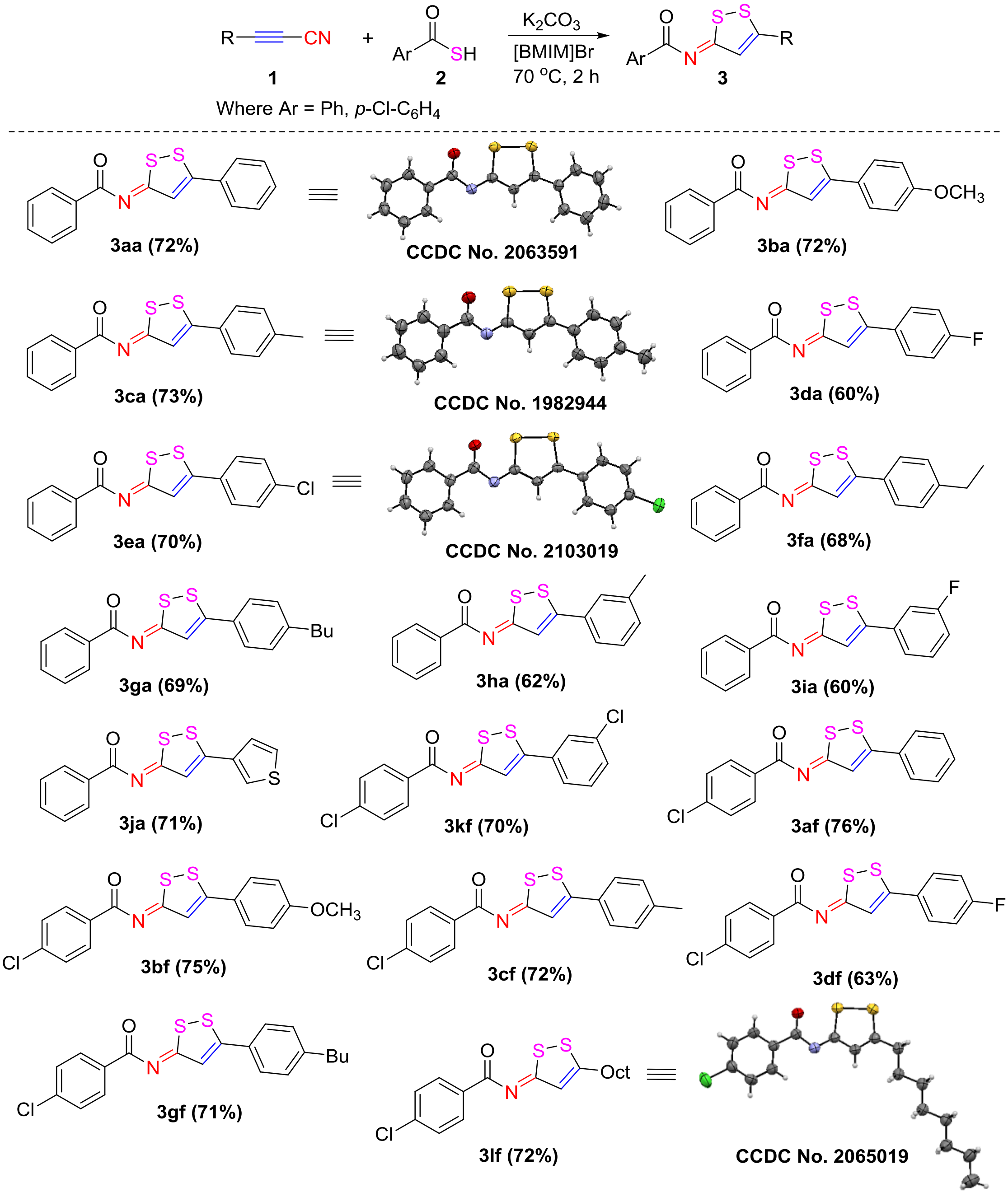
Scheme 4.2.1 Substrate scope of thiocarboxylic acids.

Next, with the optimization conditions in hand, we explored the substrate scope of this [BMIM]Br mediated protocol in synthesizing a library of 3-acylimino-3*H*-1,2-dithioles. At first, the scope of thiocarboxylic acids was explored by reacting a wide range of thiocarboxylic acids **2** with phenylacetylenenitrile **1a**, as summarized in Scheme 4.2.1. It can be noticed that all kinds of thiocarboxylic acids, whether aromatic, aliphatic, alicyclic, or heterocyclic, exhibit excellent compatibility with this approach. Aromatic thiocarboxylic acids containing electron-donating and electron-withdrawing substituents worked well to afford desired products (**3ab**-**3ag**) in good to high yields showing impressive functional group compatibility. Similarly, aliphatic thiocarboxylic acids provided the expected outcomes in moderate to good yield (**3ah**-**3ak**). In addition, heteroaryl thiocarboxylic acids such as thiophene-2-thiocarboxylic acid and furoic-2-thiocarboxylic acid exhibited good reactivity leading to the desired cycloadducts (**3am** and **3an**) in good yields.

After investigating the scope of thiocarboxylic acids, we proceeded to study the scope of various alkynenitriles **1** using thiobenzoic acid **2a** and 4-chloro-thiobenzoic acid **2f** as the thioacids as shown in Scheme 4.2.2. It was delighting to find that both alkyl and aryl propynylnitriles with various functional groups (methyl, ethyl, butyl, methoxy, fluoro, and chloro groups) at different positions of the aromatic ring, reacted well under the standard conditions affording moderate to good yields. Alkynenitriles having a heteroaryl group (**3ja**) also worked well with 71% yield. In addition, undec-2-ynenitrile (**3lf**) was found to be equally reactive.

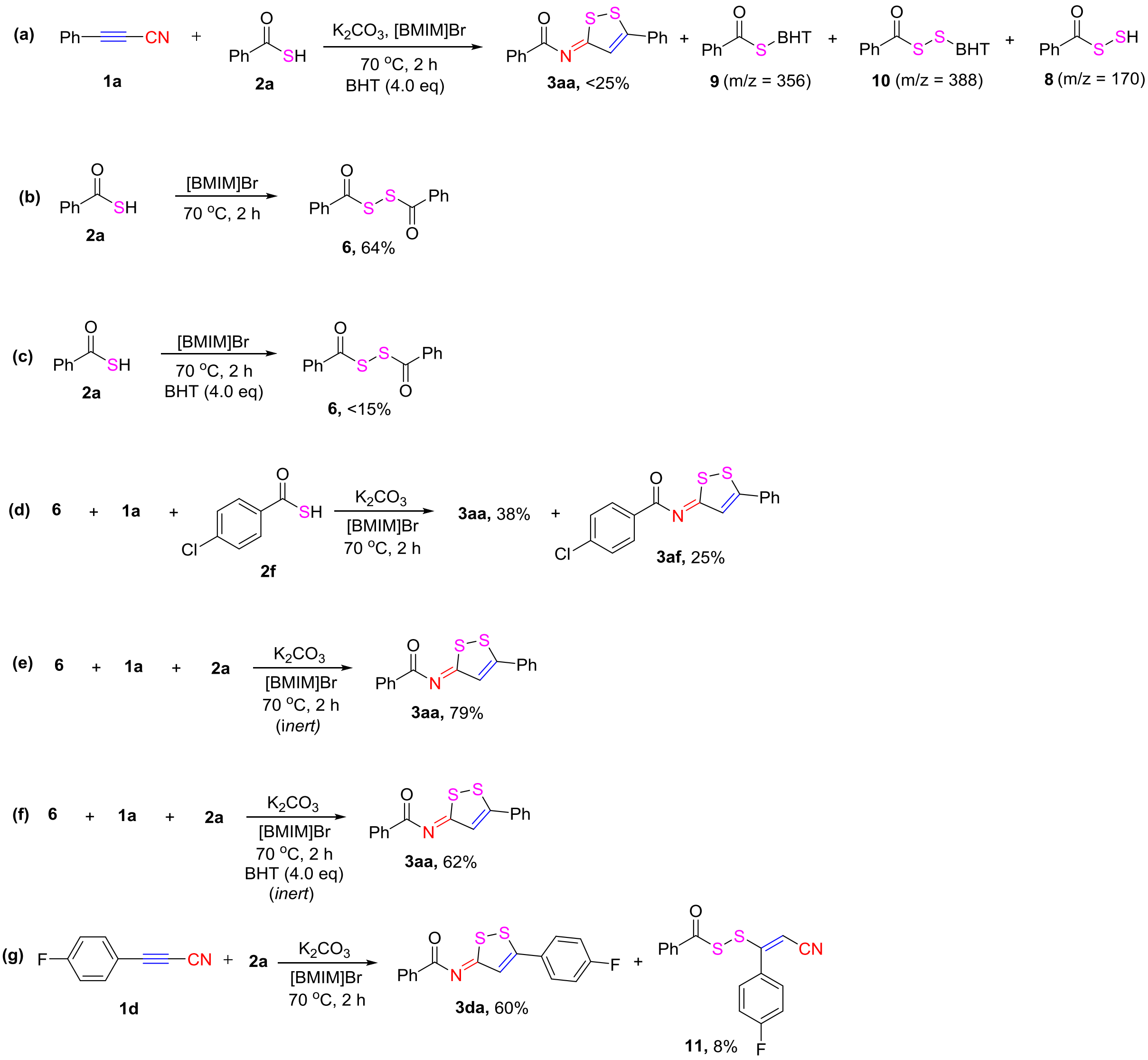
As stated earlier, we thought of the involvement of the disulfide intermediate in forming the 1,2-dithiole core moiety, and the formation of disulfide linkage points towards the involvement of a radical pathway. To further understand the mechanism's details, the control experiments of phenylacetylenenitrile **1a** and thiobenzoic acid **2a** with the radical scavenger BHT (4 equiv.) were examined under the optimized reaction conditions (Scheme 4.2.3). A significant decrease in the yield of the desired product **3aa**, along with the detection of the adducts **9** and **10** in the mass spectroscopy, was observed. This observation clearly indicates the involvement of the radical pathway (Scheme 4.2.3a). On the other hand, to better understand the reaction mode of thioacids in ionic liquid, only **2a** was stirred in the ionic liquid under standard conditions. Gratifyingly, disulfide intermediate **6** was obtained with 64% isolated yield within 2 h (Scheme

4.2.3b). When the same reaction was performed with the addition of BHT (4 equiv.), a significant decrease in the yield of disulfide formation to less than 15% was observed



Reagents and conditions: **1a** (0.25 mmol), **2** (0.5 mmol), K_2CO_3 (0.25 mmol) and [BMIM]Br (1 mL), 70 °C, 2 h.

Scheme 4.2.2 Substrate scope of alkynenitriles.

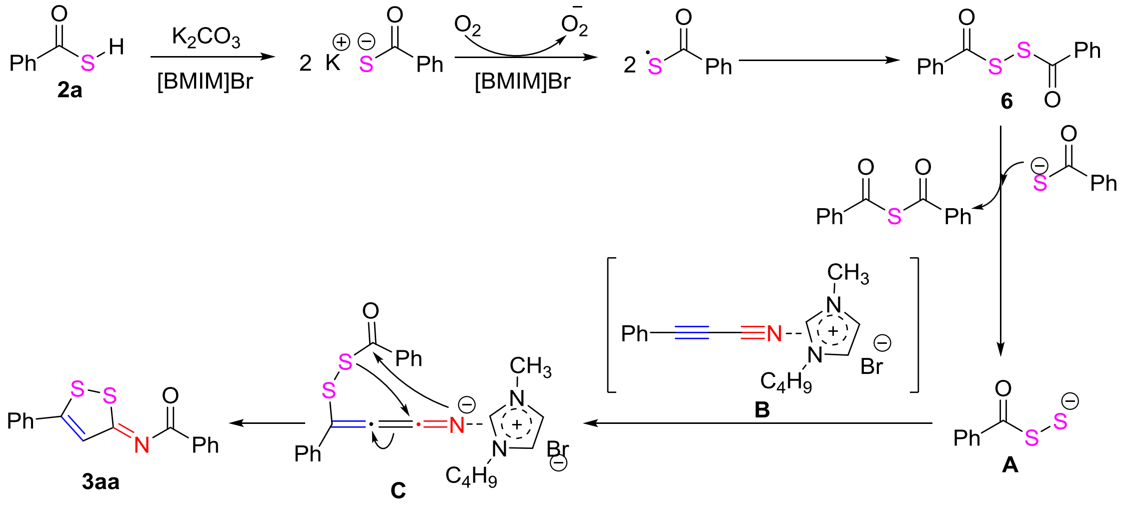


Scheme 4.2.3 Control experiments.

was observed (Scheme 4.2.3c). Meanwhile, an orthogonal experiment involving thioacid **2f** and the intermediate **6** with different acyl moieties under standard conditions was set up. The formation of **3aa** along with **3af** clearly indicates the involvement of disulfide intermediate **6** in the reaction mechanism (Scheme 4.2.3d). After that, the intermediate **6**, **1a**, and **2a** were reacted under inert conditions, **3aa** was obtained with 79% yield (Scheme 4.2.3e), and the addition of BHT did not lead to any significant decrease in yield, which shows the radical pathway is involved till disulfide formation

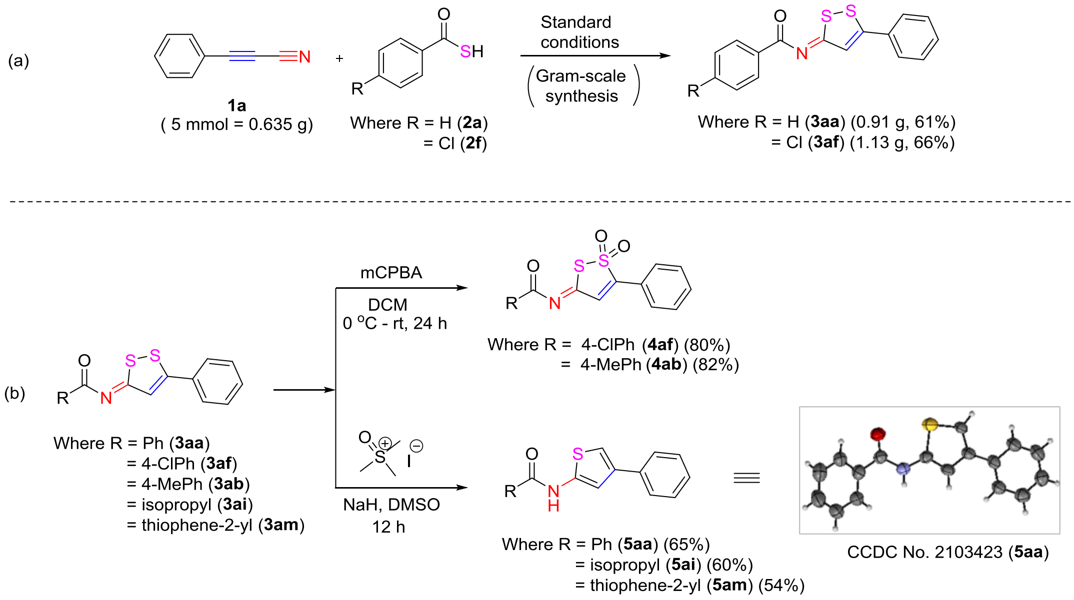
(Scheme 4.2.3f). Moreover, during the synthesis of **3da,** compound **11** was also isolated from the reaction of **1d** and **2a**, which further clarifies the attack of disulfide nucleophile to the alkynenitriles **1d** (Scheme 4.2.3g).

On the basis of the above experimental observations and the literature reports,[10] a plausible pathway is portrayed in Scheme 4.2.4. Initially, the benzoylthio radicals are produced by the aerial oxidation of the **2a**, which undergoes radical dimerization to form disulfide intermediate **6**. Nucleophilic addition/elimination of the thiobenzoate ion with **6** results in the formation of the nucleophile **A**. Subsequent Michael addition of **A** on the [BMIM]Br activated alkynenitrile (complex **B**) generates the intermediate **C**. Finally, sequential annulation, elimination, and annulation followed by protonation of the intermediate **C** produces the final product **3aa**. It is important to mention that ionic liquid [BMIM]Br plays the key role in promoting the reaction by coordinating to nitrile group of the alkynenitriles as shown in Scheme 4.2.4.



Scheme 4.2.4 Proposed mechanism.

After, the successful synthesis of 3-acylimino-3*H*-1,2-dithiole derivatives, we devoted our attention to explore their synthetic potential. To check the practical utility of this approach as a synthetic tool, a gram scale experiment was carried out. Gratifyingly, 0.91 g of **3aa** and 1.13 g of **3af** were obtained with 61% and 66% yield, respectively, when synthesized at 5 mmol scale under optimized reaction conditions (Scheme 4.2.5a). Furthermore, **3ab** and **3af** afforded (*Z*)-*N*-(1,1-dioxido-5-phenyl-3*H*-1,2-dithiol-3-ylidene)-4-methylbenzamide **4ab** and (*Z*)-4-chloro-*N*-(1,1-dioxido-5-phenyl-3*H*-1,2-dithiol-3-ylidene)benzamide **4af,** when treated with mCPBA in 82% and 80% isolated yield, respectively. Moreover, **3aa, 3ai** and **3am** on reaction with trimethylsulfoxonium ylide in DMSO led to *N*-(4-phenylthiophen-2-yl)benzamide **5aa,** *N*-(4-phenylthiophen-2-yl)isobutyramide **5ai** and *N*-(4-phenylthiophen-2-yl)thiophene-2-carboxamide **5am** in 65%, 60% and 54% yields, respectively (Scheme 4.2.5b).



Scheme 4.2.5 Synthetic application of 3-acylimino-1,2-dithioles.

Next, the most important aspect of the ionic liquid i.e. reusability was checked for the synthesis of **3aa** from the reactants **1a** and **2a** using this synthetic protocol. Gratifyingly, the ionic liquid [BMIM]Br could be effectively used for 5 cycles without significant loss in the isolated yields of **3aa** (Figure 4.2.1).

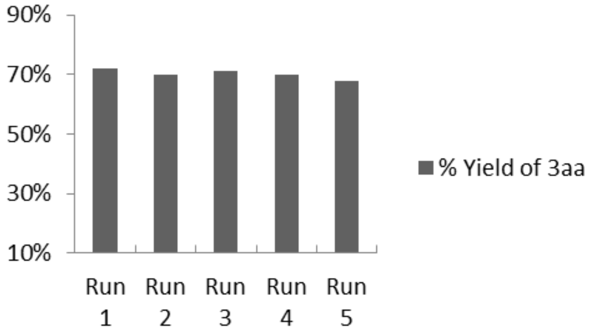


Figure 4.2.1 Reusability studies of the IL [BMIM]Br for the synthesis of 1,2-dithiole **3aa**.

4.3 Conclusions

In conclusion, we have documented an ionic liquid [BMIM]Br mediated direct construction of 3-acylimino1,2-dithioles cycloadducts from the radical conjugate addition of thiocarboxylic acids to the bifunctional alkynenitriles using K_2CO_3 as a base in moderate to good yields. A library of valuable 1,2-dithioles can be constructed using this eco-friendly and operationally simple protocol without involving pre-decorated substrates or multiple synthetic steps.

4.4 Experimental section

Reactions were performed in flame-dried glassware under open air atmosphere unless otherwise stated. Solvents used were dried and purified by following standard procedures. Chemicals and reagents were purchased from commercial suppliers and used without further purification. Thin-layer chromatography was performed on Merck precoated silica gel 60 F254 aluminum sheets with detection under UV light at 254 nm. Column chromatography was performed using E. Merck silica gel 60 (100-200 mesh). NMR spectra were recorded in $CDCl_3$, at operating frequencies of 400 MHz (^1H) or 100 MHz (^{13}C) on JEOL JNM ECS-400 instrument as indicated in the individual spectrum. Chemical shifts (δ) are given in ppm relative to residual solvent (chloroform, $\delta = 7.26$ for ^1H NMR and 77.16 for proton decoupled ^{13}C NMR) and coupling constants (J) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, dd for doublet of doublet, t for triplet, q for quartet and m for multiplet. The HRMS data was recorded on XEVO G2-XS QTOF. Melting points were taken on Stuart digital melting point apparatus. All the X-ray data were recorded on Bruker D8 venture instrument. The alkynenitriles (**1a-l**),[11] and thiocarboxylic acids (except **2a** and **2h**)[12] were prepared according to the reported literature procedure.

4.4.1 Mechanistic experiments for the dithiole formation

4.4.1.1 Control experiment with BHT

In an open oven-dried round bottom flask equipped with a stir bar, a mixture of alkynenitrile **1a** (31.75 mg, 0.25 mmol), thiocarboxylic acid **2a** (69 mg, 0.5 mmol), K_2CO_3 (69 mg, 0.5 mmol), BHT (220 mg, 1 mmol, 4 equiv.) and 1 mL of [BMIM]Br was stirred in an oil bath at 70 °C for 2 h. Reaction was monitored by TLC. The yield decreased to less than 35% and BHT adducts **9** and **10** along with **8** were also detected in mass spectra (**Figure 4.4.1.1**) indicating radical pathway and the involvement of disulfide intermediate.

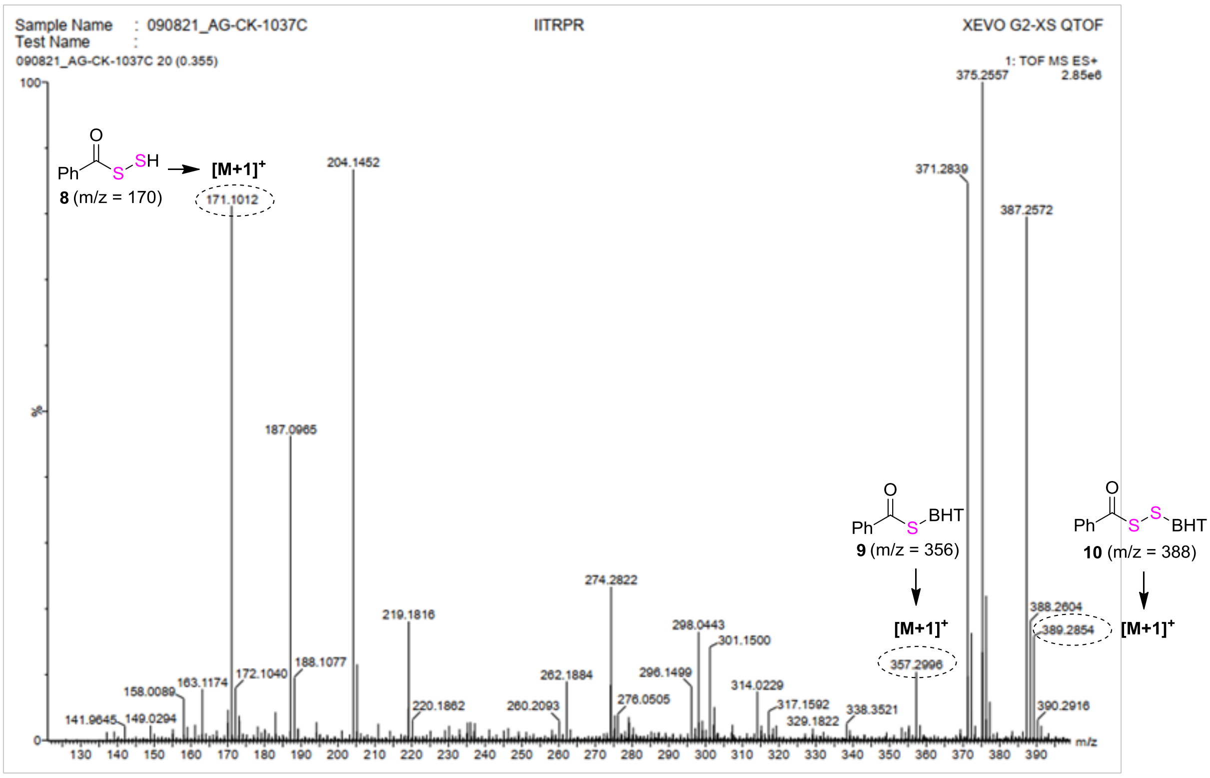


Figure 4.4.1.1 D-Mass data of **8**, **9** and **10**.

4.4.1.2 Synthesis of disulfide intermediate 6

In an open oven-dried round bottom flask equipped with a stir bar, thiocarboxylic acid **2a** (138 mg, 1 mmol) and 1 mL of [BMIM]Br were stirred in an oil bath at 70 °C for 2 h. After completion of the reaction as monitored by TLC, the product was extracted with ethyl acetate (3x20 mL) and the combined organic layers were dried with anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. The crude was further purified through column chromatography over silica gel (100-200 mesh) with PE/EA = 20/1 as an eluent to give the intermediate 6.

4.4.1.3 Control experiment with BHT

In an open oven-dried round bottom flask equipped with a stir bar, thiocarboxylic acid **2a** (69 mg, 0.5 mmol), BHT (220 mg, 1 mmol, 4 equiv.) and 1 mL of [BMIM]Br were stirred in an oil bath at 70 ^{o}C for 2 h. After completion of the reaction as monitored by TLC, less than 10% of desired product was observed with BHT.

4.4.1.4 An orthogonal experiment

In an open oven-dried round bottom flask equipped with a stir bar having 1 mL of [BMIM]Br, alkynenitrile **1a** (31.75 mg, 0.25 mmol), 4-chlorobenzothioic *S*-acid **2f** (43 mg, 0.25 mmol), K_2CO_3 (34.5 mg, 0.25 mmol), benzoic dithioperoxyanhydride **6** (68.5 mg, 0.25 mmol) were added and stirred in an oil bath at 70 ^{o}C for 2 h. Both products **3aa** and **3af** were detected by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3x20 mL) and the combined organic layers were dried with anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. The crude was purified through column chromatography (PE/EA = 20/1) to give the pure product **3aa** (38%) and **3af** (25%).

4.4.1.5 Control experiment under inert conditions

In an oven-dried round bottom Schlenk flask equipped with a stir bar, a mixture of alkynenitrile **1a** (31.75 mg, 0.25 mmol), thiocarboxylic acid **2a** (69 mg, 0.5 mmol), disulfide intermediate **6** (137 mg, 0.5 mmol), K_2CO_3 (69 mg, 0.5 mmol) and 1 mL of [BMIM]Br was stirred in an oil bath at 70 ^{o}C for 2 h. Reaction was monitored by TLC. **3aa** was obtained with 79% isolated yield indicating radical pathway is involved till disulfide intermediate formation.

4.4.1.6 Control experiment with BHT under inert conditions

In an oven-dried round bottom Schlenk flask equipped with a stir bar, a mixture of alkynenitrile **1a** (31.75 mg, 0.25 mmol), thiocarboxylic acid **2a** (69 mg, 0.5 mmol), disulfide intermediate **6** (137 mg, 0.5 mmol), K_2CO_3 (69 mg, 0.5 mmol), BHT (220 mg, 1 mmol, 4 equiv.) and 1 mL of [BMIM]Br was stirred in an oil bath at 70 ^{o}C for 2 h.

Reaction was monitored by TLC. No significant decrease in the **3aa** yield was observed indicating ionic pathway is followed after disulfide intermediate formation.

4.4.2 General procedure for the synthesis of 3-acylimino-3*H*-1,2-dithioles (3)

In an open oven-dried round bottom flask equipped with a stir bar, a mixture of 1-alkynenitrile **1** (0.25 mmol), thiocarboxylic acid **2** (0.5 mmol), K_2CO_3 (0.5 mmol), and 1 mL of [BMIM]Br was stirred in an oil bath at 70 ^{o}C for 2 h. After the reaction (monitored reaction by TLC) was completed, the product was extracted with ethyl acetate (3x20 mL), and the combined organic layers were dried with anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. The crude was further purified through column chromatography over silica gel (100-200 mesh) with EA/PE (5-10%) as an eluent to give the desired products **3**. After complete extraction of the product, the remaining ionic liquid was washed with ethyl acetate (3x10 mL) to remove organic impurity and rota evaporated under reduced pressure to afford [BMIM]Br, which after 3-4 h high vacuum was reused in subsequent runs without further purification.

4.4.3 Procedure for the gram scale synthesis of 3aa and 3af

In an open oven-dried round bottom flask equipped with a stir bar, a mixture of 1-alkynenitrile **1a** (0.64 g, 5 mmol), thiocarboxylic acid **2a** (1.4 g, 10 mmol) or **2f** (1.7 g, 10 mmol) , K_2CO_3 (1.4 g, 10 mmol), and 10 mL of [BMIM]Br was stirred in an oil bath at 70 ^{o}C for 2 h. After the reaction (monitored reaction by TLC) was completed, the product was extracted with ethyl acetate (3x50 mL), and the combined organic layers were dried with anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. The crude was further purified through column chromatography over silica gel (100-200 mesh) with PE/EA (20/1) as an eluent to get the desired products **3aa** (0.91 g, 61%) or **3af** (1.13 g, 66%) .

4.4.4 Synthesis of compound 4af and 4ab

In an oven-dried Schlenk round bottom flask equipped with a stir bar, to a mixture of (*Z*)-4-chloro-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)benzamide **3af** (83 mg, 0.25 mmol) or (*Z*)-4-methyl-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)benzamide **3ab** (78 mg, 0.25 mmol) in 20 mL of dry DCM under N_2 atmosphere, at 0 ^{o}C, mCPBA (86.5 mg, 0.5 mmol) was added. After 1 h the reaction mixture was allowed to stir at room temperature for 24 h. After completion of the reaction detected by TLC, solvent was evaporated in vacuo. The crude was purified through column chromatography (PE/EA = 4/1) to give the pure product **4af** (80%) or **4ab** (82%).

4.4.5 Synthesis of compound 5aa, 5ai and 5am

In an oven-dried Schlenk round bottom flask equipped with a stir bar, to a mixture of NaH (33 mg, 0.75 mmol) in dry DMSO (5 mL) under N_2 atmosphere, trimethylsufoxonium iodide (165 mg, 0.75 mmol) was added and stirred for 1 h. Then, at 0 ^{o}C (icebath), (*Z*)-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)benzamide **3aa** (88.5 mg, 0.3 mmol) or **3ai** (78.9 mg, 0.3 mmol) or **3am** (90.9 mg, 0.3 mmol) was added in a portionwise manner and the resulting reaction mixture was allowed to stir at room temperature for 12 h. After completion of the reaction detected by TLC, the reaction mixture was quenched with ice cold water (30 mL) and the aqueous phase was extracted with ethylacetate (3x15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography and the desired compound was eluted at 10 to 20% EA/PE to get **5aa** (65%) or **5ai** (60%) or **5am** (54%).

4.4.6. Synthesis of disulfide intermediate (6)

In an open oven-dried round bottom flask equipped with a stir bar, thiocarboxylic acid **2a** (138 mg, 1 mmol) and 1 mL of [BMIM]Br were stirred in an oil bath at 70 ^{o}C for 2 h. After completion of the reaction as monitored by TLC, the product was extracted with ethylacetate (3x20 mL) and the combined organic layers were dried with anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. The crude was further purified through column chromatography over silica gel (100-200 mesh) with EA/PE (5%) as an eluent to give the intermediate **6**.

4.4.7 Characterization data of products

(*Z*)-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)benzamide (3aa): Yellow crystalline solid (53 mg, 72%); mp 150-151 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.38-8.35 (m, 2H), 7.89 (s, 1H), 7.79-7.75 (m, 2H), 7.59-7.53 (m, 1H), 7.52-7.48 (m, 5H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 186.4, 177.3, 170.9, 134.5, 133.1, 132.7, 131.7, 129.8, 129.6, 128.6, 127.4, 123.7; HRMS: *m*/*z* calculated for $C_{16}H_{12}NOS_2$ [M+H]$^+$: 298.0351, found 298.0360; IR (neat): 3049, 2947, 2920, 1588, 1551, 1447, 1425, 1320, 1293, 882, 760, 723, 686, 651 cm^{-1}

(*Z*)-4-methyl-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)benzamide (3ab): Yellow solid (58 mg, 75%); mp 91-92 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.26 (d, *J* = 8.2 Hz, 2H), 7.86 (s, 1H), 7.77-7.73 (m, 2H), 7.53-7.48 (m, 3H), 7.29 (d, *J* = 8.2 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 186.1, 177.2, 170.6, 143.4, 133.1, 131.8, 131.6, 129.9, 129.5, 129.4, 127.3, 123.6, 21.9; HRMS: *m*/*z* calculated for $C_{17}H_{14}NOS_2$ [M+H]$^+$: 312.0517, found 312.0509; IR (neat): 3057, 2922, 2850, 1583, 1543, 1503, 1425, 1313, 1097, 885, 838, 752, 680, 653 cm^{-1}

(*Z*)-4-methoxy-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)benzamide (3ac): Yellow solid (62 mg, 76%); mp 143-144 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.35-8.31 (m, 2H), 7.84 (s, 1H), 7.78-7.75 (m, 2H), 7.54-7.50 (m, 3H), 7.01-6.97 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 185.8, 176.7, 170.5, 163.4, 133.2, 131.9, 131.6, 129.5, 127.4, 127.1, 123.5, 113.9, 55.6; HRMS: *m*/*z* calculated for $C_{17}H_{14}NO_2S_2$ [M+H]$^+$: 328.0466, found 328.0467; IR (neat): 3051, 2950, 2923, 1586, 1504, 1431, 1306, 1247, 1161, 1020, 759, 686, 644 cm^{-1}

(*Z*)-2-fluoro-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)benzamide (3ad): Reddish yellow solid (4 mg, 82%); mp 123-124 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.27 (td, *J* = 7.8 Hz, 1.8 Hz 1H), 7.90 (s, 1H), 7.77-7.74 (m, 2H), 7.56-7.48 (m, 4H), 7.28-7.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.3, 175.1 (d, *J* = 2.9 Hz), 171.4, 163.4 (d, *J* = 258.9 Hz), 134.0 (d, *J* = 9.6 Hz), 132.9, 132.4, 131.8, 129.6, 127.4, 124.1 (d, *J* = 3.8 Hz), 123.9, 123.0 (d, *J* = 8.9 Hz), 117.1 (d, *J* = 22.6 Hz); HRMS: *m/z* calculated for $C_{16}H_{11}NOS_2F$ $[M+H]^+$: 316.0266, found 316.0258; IR (neat): 3059, 2921, 2850, 1592, 1555, 1452, 1422, 1319, 1263, 891, 732 cm^{-1}

(*Z*)-2-nitro-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)benzamide (3ae): Orange solid (67 mg, 78%); mp 181-182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.85-7.83 (m, 1H), 7.82 (s, 1H), 7.76-7.73 (m, 2H), 7.70-7.66 (m, 1H), 7.63-7.59 (m, 1H), 7.56-7.49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.7, 175.5, 172.2, 149.3, 132.7, 132.5, 132.1, 131.4, 131.1, 130.6, 129.7, 127.5, 124.3, 123.9; HRMS: *m/z* calculated for $C_{16}H_{11}N_2O_3S_2$ $[M+H]^+$: 342.0211, found 342.0207; IR (neat): 3051, 2922, 2852, 1555, 1453, 1423, 1377, 1319, 1221, 1079, 891, 759, 688 cm^{-1}

(*Z*)-4-chloro-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)benzamide (3af): Yellow solid (3 mg, 76%); mp 172-173 °C; ^{1}H NMR (400 MHz, $CDCl_3$):δ 8.31-8.28 (m, 2H), 7.87 (s, 1H), 7.77-7.75 (m, 2H), 7.55-7.49 (m, 3H), 7.48-7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.5, 176.2, 171.3, 138.9, 133.1, 132.9, 131.8, 131.2, 129.6, 128.9, 127.4, 123.8; HRMS: *m/z* calculated for $C_{16}H_{11}NOS_2Cl$ $[M+H]^+$: 331.9971, found 331.9977; IR (neat): 3052, 2950, 2921,1591, 1553, 1488, 1429, 1320, 1263, 1013, 735 cm^{-1}

(*Z*)-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)-4-(trifluoromethyl)benzamide (3ag): Yellowish green solid (77 mg, 85%); mp 189-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, *J* = 8.1 Hz, 2H), 7.91 (s, 1H), 7.79-7.73 (m, 4H), 7.58-7.50 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.9, 175.9, 171.7, 137.8, 133.8 (q, *J* = 32.9 Hz), 132.9, 131.9, 130.1, 129.7, 127.4, 127.5, 125.5 (q, *J* = 3.9 Hz), 124.0 (q, *J* = 272.8 Hz); HRMS: *m/z* calculated for $C_{17}H_{11}NOS_2F_3$ $[M+H]^+$: 366.0234, found 366.0229; IR (neat): 3030, 2960, 2855, 1591, 1547, 1430, 1409, 1314, 1111, 1096, 1061, 862, 759, 679 cm^{-1}

(*Z*)-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)acetamide (3ah): Brown solid (35 mg, 59%); mp 116-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.73-7.70 (m, 2H), 7.55-7.47 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.7, 182.9, 171.5, 132.9, 131.8, 129.6, 127.4, 122.9, 25.0; HRMS: *m/z* calculated for $C_{11}H_{10}NOS_2$ $[M+H]^+$: 236.0204, found 236.0210; IR (neat): 3060, 2922, 2851, 1563, 1419, 1362, 1285, 1225, 1001, 828, 764, 730, 692, 653 cm^{-1}

(*Z*)-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)isobutyramide (3ai): Yellow solid (3 mg, 65%); mp 88-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.72-7.69 (m, 2H), 7.52-7.45 (m, 3H), 2.9 (m, 1H), 1.31 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 185.9, 170.9, 133.1,131.6, 129.5, 127.3, 123.1, 37.1, 19.8; HRMS: *m/z* calculated for $C_{13}H_{14}NOS_2$ $[M+H]^+$ 264.0512, found 264.0514; IR (neat): 3052, 2953, 2919, 1571, 1408, 1339, 1212, 1150, 1103, 1072, 937, 756, 676, 655 cm^{-1}

(*Z*)-2-ethyl-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)hexanamide (3aj): Yellowish liquid (51 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.72-7.70 (m, 2H), 7.52-7.45 (m, 3H), 2.69-2.62 (m, 1H), 1.83-1.71 (m, 2H), 1.67-1.55 (m, 2H), 1.33-1.20 (m, 4H), 0.91-0.83 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 185.6, 170.9, 133.1, 131.6, 129.5, 127.3, 123.2, 50.3, 32.6, 29.9, 26.3, 22.9, 14.1, 12.2; HRMS: *m/z* calculated for $C_{17}H_{22}NOS_2$ $[M+H]^+$: 320.1143, found 320.1152; IR (neat): 3053, 2957, 2928, 1570, 1421, 1377, 1220, 1140, 759, 735, 686 cm^{-1}

(*Z*)-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)cyclohexanecarboxamide (3ak): Light brownish solid (47 mg, 62%); mp 195-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.73-7.71 (m, 2H), 7.54-7.47 (m, 3H), 2.67 (tt, *J* = 11.6, 3.6 Hz, 1H), 2.07-2.01 (m, 2H), 1.86-1.79 (m, 2H), 1.73-1.68 (m, 1H), 1.61-1.51 (m, 2H), 1.42-1.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.6, 185.8, 170.9, 133.1, 131.6, 129.6, 127.3, 123.1, 46.7, 29.9, 26.1, 25.9; HRMS: *m/z* calculated for $C_{16}H_{18}NOS_2$ $[M+H]^+$: 304.0830, found 304.0828; IR (neat): 3051, 2960, 2925, 1576, 1427, 1370, 1308, 1258, 1201, 1159, 1128, 944, 736, 687, 644 cm^{-1}

(*Z*)-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)thiophene-2-carboxamide (3am): Yellowish brown solid (55 mg, 72%); mp 140-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (dd, *J* = 3.84, 1.40 Hz, 1H), 7.82 (s, 1H), 7.76-7.73 (m, 2H), 7.61 (dd, *J* = 5.07, 1.16 Hz, 1H), 7.55-7.47 (m, 3H), 7.17-7.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.6, 172.2, 170.8, 139.9, 132.8, 132.7, 131.7, 129.6, 128.5, 127.3, 123.5; HRMS: *m/z* calculated for $C_{14}H_{10}NOS_3$ $[M+H]^+$: 303.9925, found 303.9926; IR (neat): 3047, 2949, 2850, 1557, 1438, 1402, 1357, 1292, 1220, 1191, 1094, 1028, 842, 755, 714, 650 cm^{-1}

(*Z*)-*N*-(5-phenyl-3*H*-1,2-dithiol-3-ylidene)furan-2-carboxamide (3an): Yellowish brown solid (51 mg, 74%); mp 129-130 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.73-7.71 (m, 2H), 7.66-7.64 (m, 1H), 7.55-7.47 (m, 3H), 7.39 (d, *J* = 3.50 Hz, 1H), 6.58-6.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.0, 171.0, 168.3, 149.6, 146.5, 132.8, 131.8, 129.6, 127.3, 123.8, 117.9, 112.5; HRMS: *m/z* calculated for $C_{14}H_{10}NO_2S_2$ $[M+H]^+$: 288.0153, found 288.0158; IR (neat): 3045, 2921, 2852, 1596, 1552, 1431, 1389, 1323, 1238, 1102, 1007, 937, 836, 751, 679, 647, 603 cm^{-1}

(*Z*)-*N*-(5-(4-methoxyphenyl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3ba)[4b]: Yellow solid (59 mg, 72%); mp 139-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37-8.34 (m, 2H), 7.81 (s, 1H), 7.75-7.71 (m, 2H), 7.58-7.54 (m, 1H), 7.52-7.48 (m, 2H), 7.03-6.99 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.3, 177.2, 170.9, 162.5, 134.7, 132.6, 129.7, 128.9, 128.6, 125.8, 122.3, 114.9, 55.7; HRMS: *m/z* calculated for $C_{17}H_{14}NO_2S_2$ $[M+H]^+$: 328.0466, found 328.0455; IR (neat): 3050, 2921, 2851, 1600, 1549, 1433, 1327, 1258, 1180, 1026, 818, 708, 687 cm^{-1}

(*Z*)-*N*-(5-(p-tolyl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3ca)[4b]: Yellowish solid (57 mg, 73%); mp 121-122 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37-8.35 (m, 2H), 7.87 (s, 1H), 7.69-7.66 (m, 2H), 7.59-7.54 (m, 1H), 7.53-7.48 (m, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.4, 177.2, 171.2, 142.5, 134.6, 132.7, 130.4, 130.3, 129.8, 128.6, 127.3, 123.1, 21.7; HRMS: *m/z* calculated for $C_{17}H_{14}NOS_2$ $[M+H]^+$: 312.0517, found 312.0519; IR (neat): 2957, 2922, 2852, 1552, 1430, 1320, 1291, 883, 810, 717, 689 cm^{-1}

(*Z*)-*N*-(5-(4-fluorophenyl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3da): Yellow solid (47 mg, 60%); mp 163-164 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.37-8.34 (m, 2H), 7.82 (s, 1H), 7.79-7.74 (m, 2H), 7.59-7.55 (m, 1H), 7.52-7.48 (m, 2H), 7.23-7.18 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 186.4, 177.3, 169.6, 164.7 (d, *J* = 254.4 Hz), 134.4, 132.8, 129.8, 129.5 (d, *J* = 8.6 Hz), 128.6, 123.7, 116.8 (d, *J* = 22.0 Hz); HRMS: *m/z* calculated for $C_{16}H_{11}NOFS_2$ $[M+H]^+$: 316.0266, found 316.0269; IR (neat): 3033, 2923, 2850, 1599, 1549, 1494, 1449, 1334, 1235, 827, 712, 690 cm^{-1}

(*Z*)-*N*-(5-(4-chlorophenyl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3ea): Yellow solid (58 mg, 70%); mp 200-201 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.37-8.34 (m, 2H), 7.86 (s, 1H), 7.72-7.68 (m, 2H), 7.59-7.55 (m, 1H), 7.53-7.47 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 186.3, 177.3, 169.4, 137.9, 134.3, 132.8, 131.6, 129.87, 129.84, 128.7, 128.6, 123.9; HRMS: *m/z* calculated for $C_{16}H_{11}NOClS_2$ $[M+H]^+$: 331.9971, found 331.9976; IR (neat): 3029, 2922, 2852, 1592, 1550, 1451, 1335, 1259, 1091, 1023, 799, 709 cm^{-1}

(*Z*)-*N*-(5-(4-ethylphenyl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3fa): Yellow solid (55 mg, 68%); mp 94-95 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.37-8.35 (m, 2H), 7.88 (s, 1H), 7.71-7.68 (m, 2H), 7.59-7.54 (m, 1H), 7.52-7.48 (m, 2H), 7.34(d, *J* = 8.3 Hz, 2H), 2.73 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 186.4, 177.2, 171.3, 148.7, 134.6, 132.7, 130.6, 129.8, 129.1, 128.6, 127.4, 123.2, 28.9, 15.4; HRMS: *m/z* calculated for $C_{18}H_{16}NOS_2$ $[M+H]^+$: 326.0673, found 326.0668; IR (neat): 3049, 2962, 2924, 1589, 1546, 1427, 1320, 1292, 882, 819, 713, 686, 653 cm^{-1}

(*Z*)-*N*-(5-(4-butylphenyl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3ga): Yellow solid (61 mg, 69%); mp 60-61 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.38-8.35 (m, 2H), 7.87 (s, 1H), 7.70-7.67 (m, 2H), 7.59-7.54 (m, 1H), 7.52-7.48 (m, 2H), 7.32(d, *J* = 8.3 Hz, 2H), 2.69 (t, *J* = 7.8 Hz, 2H), 1.68-1.60 (m, 2H), 1.43-1.34 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 186.4, 177.2, 171.3, 147.4, 134.6, 132.7, 130.6, 129.8, 129.7, 128.6, 127.3, 123.1, 35.7, 33.4, 22.5, 14.1; HRMS: *m/z* calculated for $C_{20}H_{20}NOS_2$ $[M+H]^+$: 354.0986, found 354.0981; IR (neat): 3051,2922, 2854, 1591, 1549, 1448, 1430, 1321, 1292, 884, 818, 714, 688, 652 cm^{-1}

(*Z*)-*N*-(5-(m-tolyl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3ha): Orange solid (48 mg, 62%); mp 102-103 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38-8.35 (m, 2H), 7.88 (s, 1H), 7.59-7.54 (m, 3H), 7.52-7.48 (m, 2H), 7.41-7.33 (m, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.4, 177.2, 171.3, 139.5, 134.5, 133.0, 132.7, 132.5, 129.8, 129.4, 128.6, 128.0, 124.5, 123.6, 21.6; HRMS: *m/z* calculated for $C_{17}H_{14}NOS_2$ $[M+H]^+$: 312.0517, found 312.0511; IR (neat): 3050, 2921, 2854, 1672, 1589, 1553, 1445, 1320, 1292, 885, 712, 684, 646 cm^{-1}

(*Z*)-*N*-(5-(3-fluorophenyl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3ia): Yellowish brown solid (47 mg, 60%); mp 109-110 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38-8.35 (m, 2H), 7.87 (s, 1H), 7.59-7.44 (m, 6H), 7.25-7.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.3, 177.4, 169.0, 163.1 (d, *J* = 248.3 Hz), 135.0 (d, *J* = 7.9 Hz), 134.3, 132.9, 131.3 (d, *J* = 8.7 Hz), 129.9, 128.7, 124.4, 123.2 (d, *J* = 3.4 Hz), 118.4 (d, *J* = 21.2 Hz), 114.4 (d, *J* = 23.0 Hz); HRMS: *m/z* calculated for $C_{16}H_{11}FNOS_2$ $[M+H]^+$: 316.0266, found 316.0261; IR (neat): 3049, 2920, 2850, 1586, 1550, 1453, 1419, 1337, 834, 783, 713, 652 cm^{-1}

(*Z*)-*N*-(5-(thiophen-3-yl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3ja): Orange solid (54 mg, 71%); mp 135-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37-8.34 (m, 2H), 7.84-7.83(m, 1H), 7.81 (s, 1H), 7.59-7.54 (m, 1H), 7.52-7.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.2, 177.1, 164.7, 134.7, 134.4, 132.7, 129.8, 128.6, 128.1, 126.6, 126.0, 123.2; HRMS: *m/z* calculated for $C_{14}H_{10}NOS_3$ $[M+H]^+$: 303.9925, found 303.9919; IR (neat): 3048, 2920, 2850, 1590, 1546, 1449, 1330, 1296, 885, 830, 785, 708, 684, 635 cm^{-1}

(*Z*)-4-chloro-*N*-(5-(3-chlorophenyl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3kf): Yellow solid (64 mg, 71%); mp 211-212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.3 Hz, 2H), 7.86 (s, 1H), 7.56-7.75 (m, 1H), 7.66-7.64 (m, 1H), 7.54-7.51 (m, 1H), 7.48-7.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.4, 176.4, 169.3, 139.2, 135.7, 134.7, 132.9, 131.6, 131.3, 130.9, 128.9, 127.4, 125.5, 124.5; HRMS: *m/z* calculated for

$C_{16}H_{10}Cl_2NOS_2$ $[M+H]^+$: 365.9581, found 365.9575; IR (neat): 3051, 2921, 2852, 1591, 1552, 1437, 1409, 1321, 1165, 1083, 887, 847, 757, 658 cm^{-1}

(Z)-4-chloro-*N*-(5-(4-methoxyphenyl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3bf): Yellow solid (68 mg, 75%); mp 200-201 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.7 Hz, 2H), 7.80 (s, 1H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.46 (d, *J* = 8.7 Hz, 2H), 7.01(d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.4, 176.1, 171.3, 162.6, 138.9, 133.2, 131.1, 129.0, 128.9, 125.6, 122.3, 114.9, 55.7; HRMS: *m/z* calculated for $C_{17}H_{13}ClNO_2S_2$ $[M+H]^+$: 362.0076, found 362.0070; IR (neat): 3051, 2923, 2851, 1603, 1587, 1549, 1497, 1437, 1328, 1265, 1181, 1090, 1033, 886, 821, 762 cm^{-1}

(Z)-4-chloro-*N*-(5-(p-tolyl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3cf): Yellow solid (62 mg, 72%); mp 195-196 °C; ^1H NMR (400 MHz, $CDCl_3$):δ 8.29 (d, *J* = 8.7 Hz, 2H), 7.84 (s, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.5, 176.1, 171.6, 142.6, 138.9, 133.2, 131.2, 130.3, 128.9, 127.3, 123.2, 21.7; HRMS: *m/z* calculated for $C_{17}H_{13}ClNOS_2$ $[M+H]^+$: 346.0127, found 346.0133; IR (neat): 3051, 2921, 2853, 1588, 1550, 1440, 1330, 1088, 1013, 885, 810, 762 cm^{-1}

(Z)-4-chloro-*N*-(5-(4-fluorophenyl)-3*H*-1,2-dithiol-3-ylidene)benzamide (3df): Yellow solid (55 mg, 63%); mp 199-200 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.31-8.28 (m, 2H), 7.81 (s, 1H), 7.79-7.74 (m, 2H), 7.49-7.45 (m, 2H), 7.24-7.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.5, 176.3, 169.9, 164.8 (d, *J* = 253.7 Hz), 139.1, 132.9, 131.2, 129.5 (d, *J* = 8.6 Hz), 129.4 (d, *J* = 2.9 Hz), 128.9, 123.8, 116.8 (d, *J* = 22.0 Hz); HRMS: *m/z* calculated for $C_{16}H_{10}ClFNOS_2$ $[M+H]^+$: 349.9876, found 349.9879; IR (neat): 3053, 2923, 2852, 1588, 1554, 1500, 1440, 1321, 1241, 1157, 1086, 884, 826, 759, 612 cm^{-1}

(Z)-*N*-(5-(4-butylphenyl)-3*H*-1,2-dithiol-3-ylidene)-4-chlorobenzamide (3gf): Yellow solid (69 mg, 71%); mp 136-137 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.9 Hz, 2H), 7.85 (s, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 2.69 (t, *J* = 7.7 Hz, 2H), 1.68-1.60 (m, 2H), 1.43-1.34 (m, 2H), 0.95 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.5, 176.2, 171.6, 147.6, 138.9, 133.2, 131.2, 130.4, 129.7, 128.9, 127.3, 123.2, 35.7, 33.4, 22.5, 14.1; HRMS: *m/z* calculated for $C_{20}H_{19}ClNOS_2$ $[M+H]^+$: 388.0597, found 388.0591; IR (neat): 3051, 2961, 2829, 1587, 1549, 1442, 1326, 1088, 1013, 885, 820, 763, 653 cm^{-1}

(*Z*)-4-chloro-*N*-(5-octyl-3*H*-1,2-dithiol-3-ylidene)benzamide (3lf): Light orange solid (66 mg, 72%); mp 87-88 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 8.5 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 2H), 7.41 (s, 1H), 2.96 (t, *J* = 7.7 Hz, 2H), 1.83-1.75 (m, 2H), 1.44-1.36 (m, 2H), 1.32-1.26 (m, 8H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.8, 176.3, 176.1, 138.8, 133.2, 131.2, 128.9, 125.9, 33.9, 31.9, 30.6, 29.3, 29.2, 29.1, 22.8, 14.2; HRMS: *m/z* calculated for $C_{18}H_{23}NOS_2Cl$ $[M+H]^+$: 368.0910, found 368.0905; IR (neat): 3050, 2955, 2923, 2853, 1587, 1555, 1435, 1317, 1263, 1088, 1010, 886, 765, 736, 647 cm^{-1}

(*Z*)-*N*-(1,1-dioxido-5-phenyl-3*H*-1,2-dithiol-3-ylidene)-4-methylbenzamide (4ab): Yellow solid (71 mg, 82%); mp 140-141 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.21 (m, 2H), 7.85-7.81 (m, 2H), 7.58-7.54 (m, 3H), 7.47 (s, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.9, 176.1, 167.6, 145.7, 132.2, 131.2, 131.0, 129.9, 129.8, 129.7, 128.6, 22.1; HRMS: *m/z* calculated for $C_{17}H_{14}NO_3S_2$ $[M+H]^+$: 344.0415, found 344.0420; IR (neat): 3030, 2916, 2858, 1625, 1603, 1518, 1499, 1286, 1169, 1052, 754, 685 cm^{-1}

(*Z*)-4-chloro-*N*-(1,1-dioxido-5-phenyl-3*H*-1,2-dithiol-3-ylidene)benzamide (4af): Yellow solid (73 mg, 80%); mp 196-197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29-8.26 (m, 2H), 7.85-7.82 (m, 2H), 7.60-7.54 (m, 3H), 7.52-7.49 (m, 2H), 7.47 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 177.2, 168.3, 141.1, 132.4, 132.3, 132.2, 129.90, 129.88, 129.6, 129.3, 128.7; HRMS: *m/z* calculated for $C_{16}H_{11}ClNO_3S_2$ $[M+H]^+$: 363.9869, found 363.9861; IR (neat): 3033, 2924, 2850, 1631, 1585, 1512, 1442, 1268, 1056, 851, 757, 681 cm^{-1}

***N*-(4-phenylthiophen-2-yl)benzamide (5aa):** Off white solid (54 mg, 65%); mp 197-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (bs, 1H), 7.93-7.91 (m, 2H), 7.59-7.56 (m, 3H), 7.53-7.49 (m, 2H), 7.41-7.38 (m, 2H), 7.31-7.27 (m, 1H), 7.11 (d, *J* = 1.59 Hz, 1H), 7.08 (d, *J* = 1.58 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 139.8, 138.9, 135.9, 133.1, 132.5, 129.1, 128.9, 127.3, 127.3, 126.3, 113.5, 111.4; HRMS: *m/z* calculated for $C_{17}H_{14}NOS$ $[M+H]^+$: 280.0796, found 280.0786; IR (neat): 3186, 3085, 3036, 1633, 1560, 1526, 1367, 1311, 900, 823, 728, 688, 524 cm^{-1}

***N*-(4-phenylthiophen-2-yl)isobutyramide (5ai):** Off white solid (44 mg, 60%); mp 116-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (bs, 1H), 7.58-7.55 (m, 2H), 7.50 (d, *J* = 1.25 Hz, 1H), 7.37 (t, *J* = 7.84 Hz, 2H), 7.30-7.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.8, 143.1, 136.2, 134.1, 129.0, 127.9, 125.7, 117.1, 109.5, 36.3, 19.8; HRMS: *m/z* calculated for $C_{14}H_{16}NOS$ $[M+H]^+$: 246.0953, found 280.0953; IR (neat): 3265, 3058, 2968, 2930, 1652, 1538, 1497, 1220, 1098, 946, 829, 758, 688 cm^{-1}

***N*-(4-phenylthiophen-2-yl)thiophene-2-carboxamide (5am):** White solid (46 mg, 54%); mp 276-277 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (bs, 1H), 7.64-7.55 (m, 5H), 7.41-7.36 (m, 3H), 7.33-7.29 (m, 1H), 7.15-7.13 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 143.4, 138.7, 135.7, 134.0, 130.95, 129.1, 128.6, 128.0, 125.8, 117.2, 110.3; HRMS: *m/z* calculated for $C_{17}H_{14}NOS$ $[M+H]^+$: 286.0360, found 286.0359; IR (neat): 3238, 3081, 1630, 1568, 1542, 1289, 1073, 830, 756, 715, 683 cm^{-1}

Benzoicdithioperoxyanhydride (6): White crystalline solid (88 mg, 64%); mp 111-112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10-8.09 (m, 4H), 7.67-7.63 (m, 2H), 7.55-7.50 (m,4); ^{13}C NMR (100 MHz, $CDCl_3$): δ 186.3, 135.4, 134.6, 129.1, 128.3. Compound **6** is known compound and the proton spectrum is fully consistent with literature reported.[12]

(*Z*)-*SS*-(2-cyano-1-(4-fluorophenyl)vinyl)-benzo(dithioperoxoate) (11): Yellowish solid (7 mg, 8%); mp 136-137 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99-7.96 (m, 2H), 7.68-7.63 (m, 3H), 7.53-7.49 (m, 2H), 7.13-7.08 (m, 2H), 6.21 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.9, 164.5 (d, *J* = 253.3 Hz), 151.4, 135.9, 134.8, 133.3 (d, *J* = 3.8

Hz), 129.5 (d, *J* = 9.2 Hz), 129.1, 128.1, 116.3 (d, *J* = 22.8 Hz), 115.9, 106.5; HRMS: *m/z* calculated for $C_{16}H_{11}FNOS_2$ $[M+H]^+$: 316.0266, found 316.0269; IR (neat): 3054, 2959, 2919, 2214, 1687, 1597, 1502, 1237, 1204, 1160, 889, 835, 735, 682 cm^{-1}

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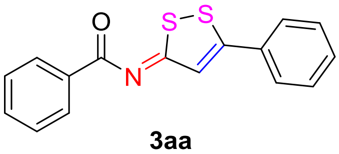
4.6 NMR spectra of compounds



3aa

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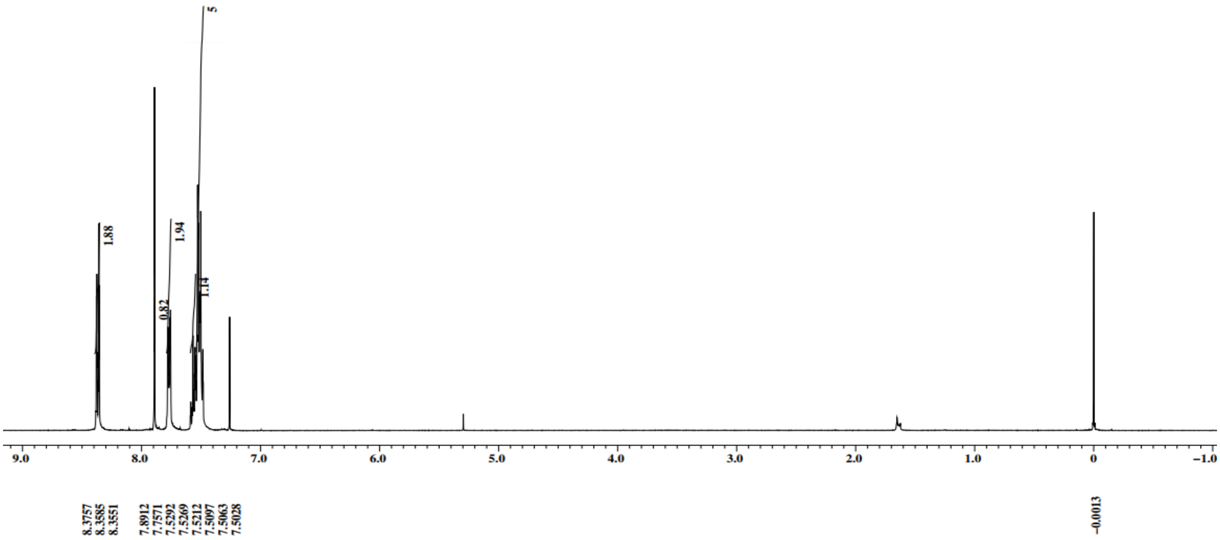

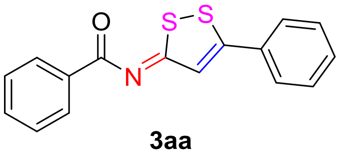

3aa

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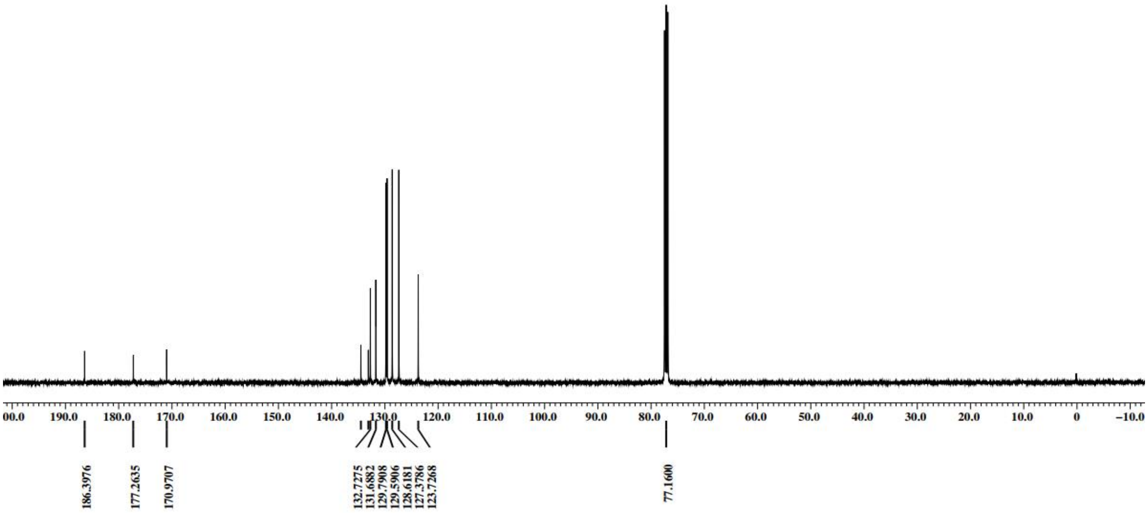
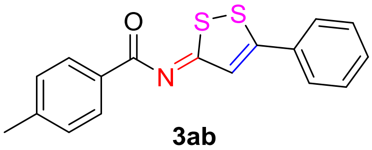
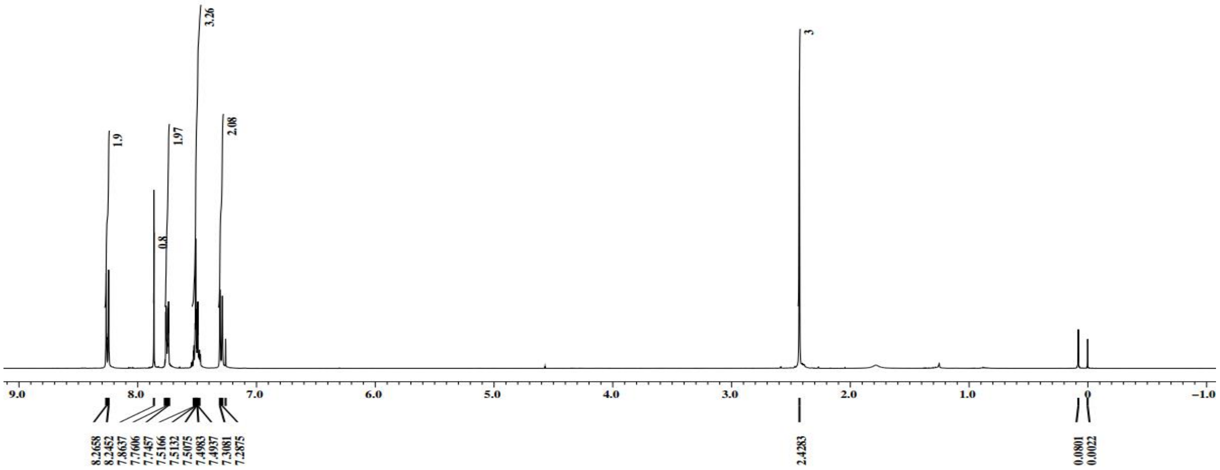



O
S
S
N

3ab


¹H NMR (400 MHz, CDCl₃)
1.9
0.8
1.97
3.26
2.08
3
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0
−1.0
8.2658
8.2452
7.8637
7.7606
7.7457
7.5166
7.5132
7.5075
7.4983
7.4937
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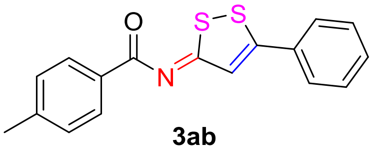
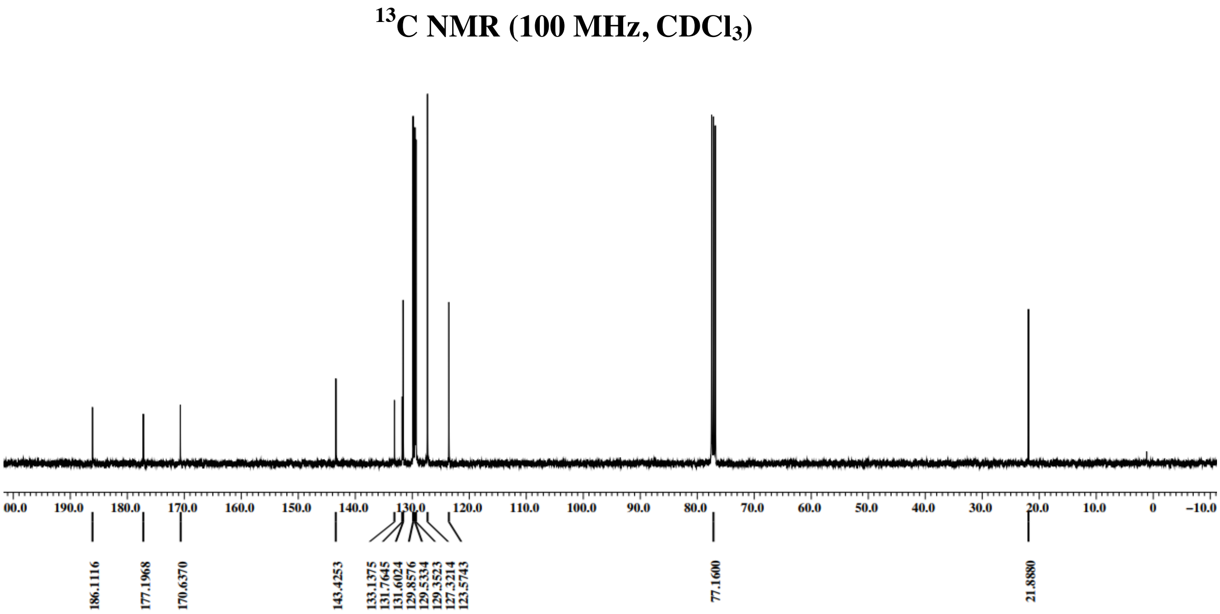
2.4283
0.0801
0.0022


O
S
S
N

3ab


¹³C NMR (100 MHz, CDCl₃)
00.0
190.0
180.0
170.0
160.0
150.0
140.0
130.0
120.0
110.0
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0
−10.0
186.1116
177.1968
170.6370
143.4253
133.1375
131.7645
131.6024
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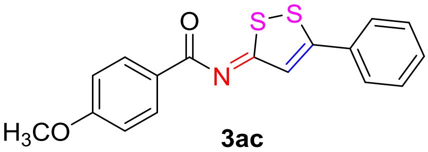
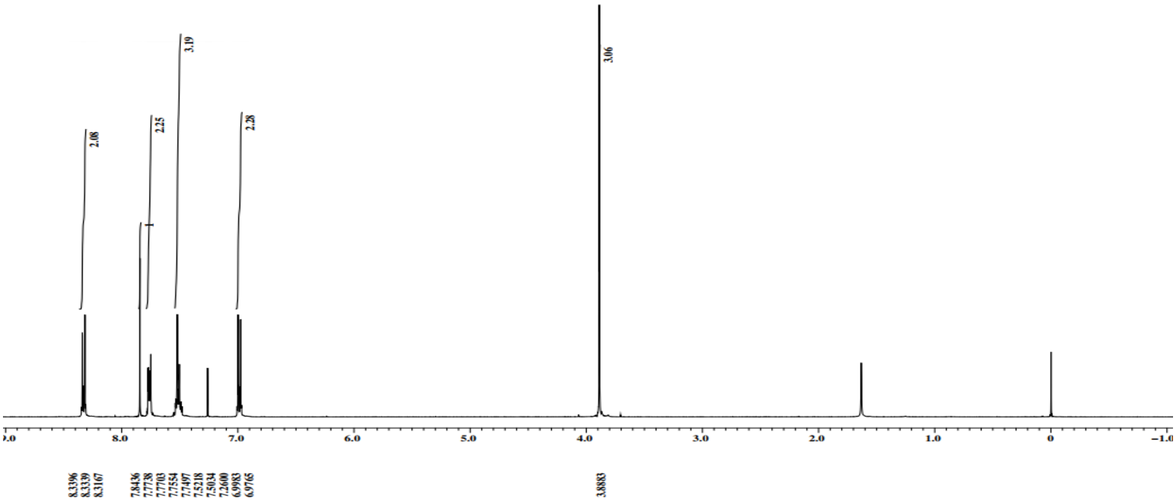
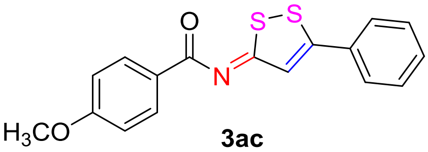
129.5334
129.3523
127.3214
123.5743
77.1600
21.8880



3ac

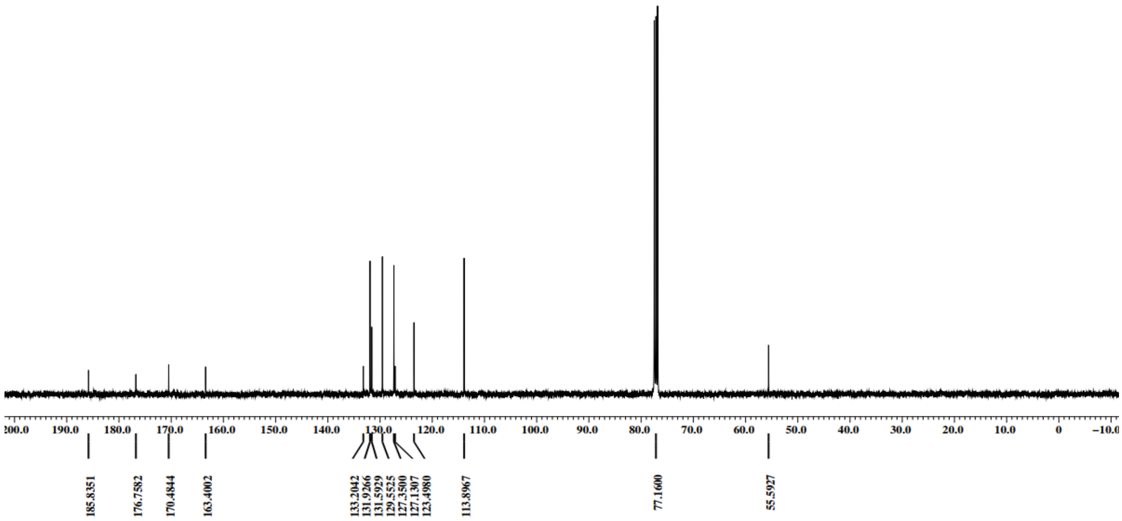
^{1}H NMR (100 MHz, CDCl$_3$)

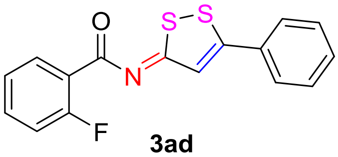




3ac

^{13}C NMR (100 MHz, CDCl$_3$)





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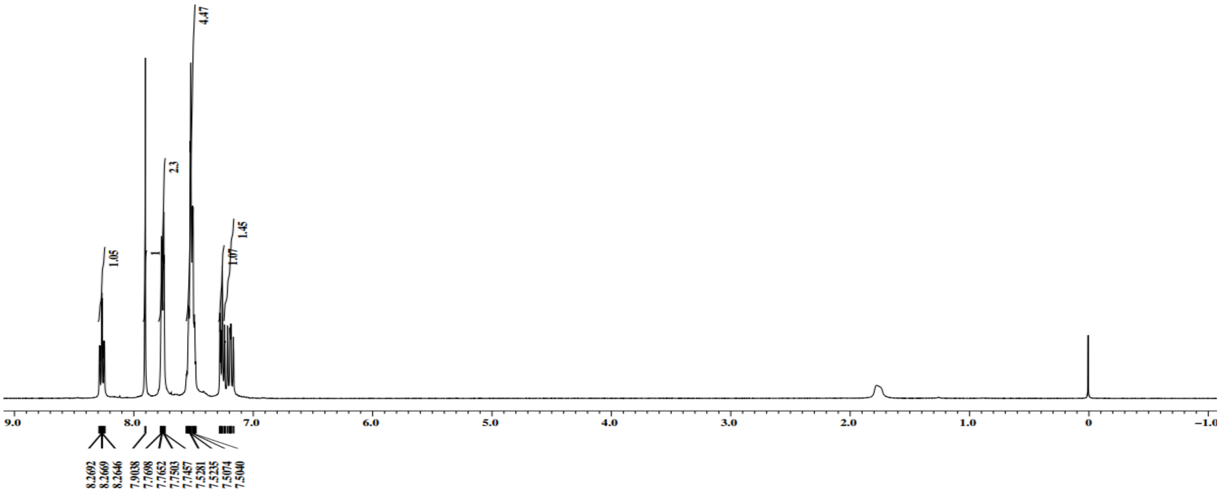

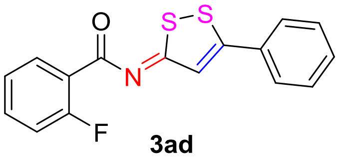

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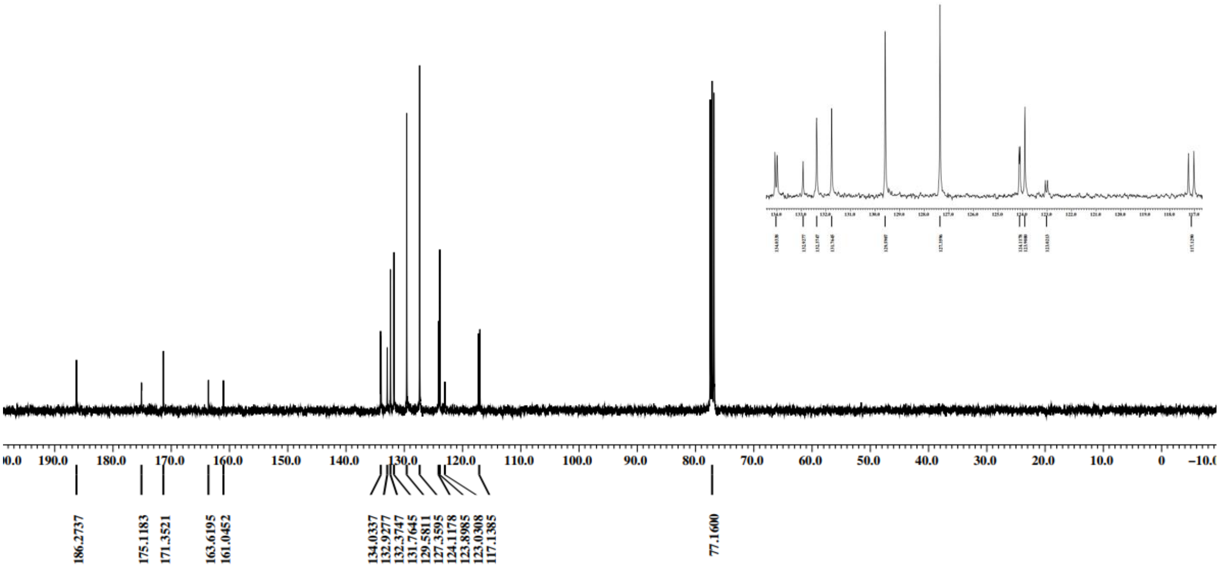

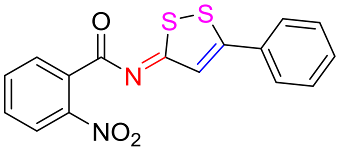

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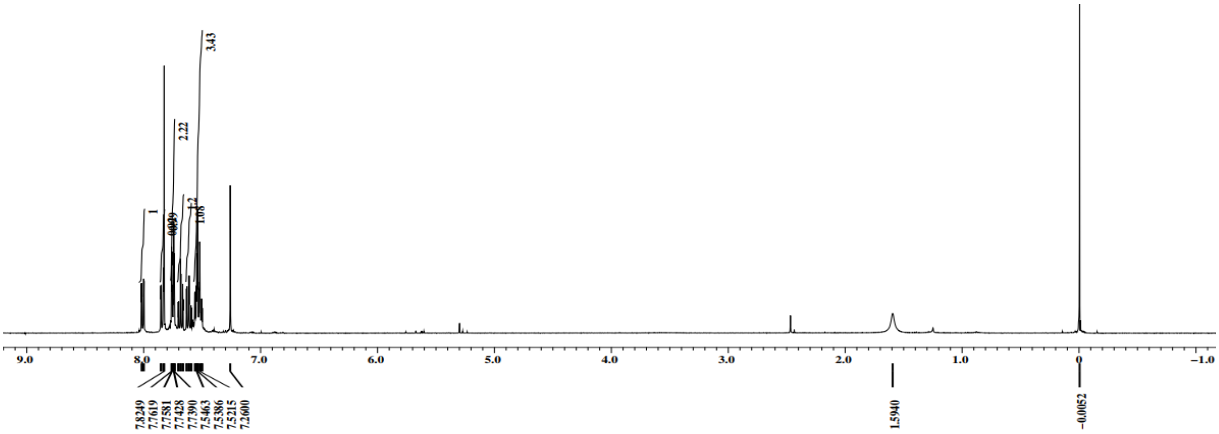

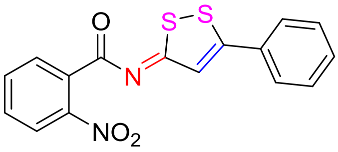

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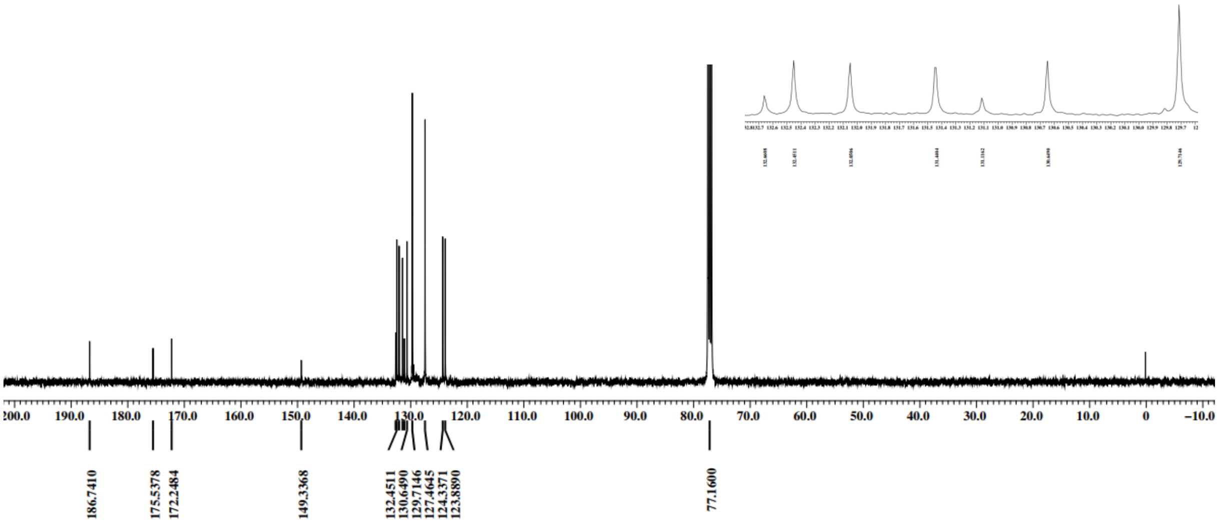

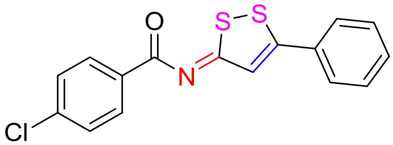

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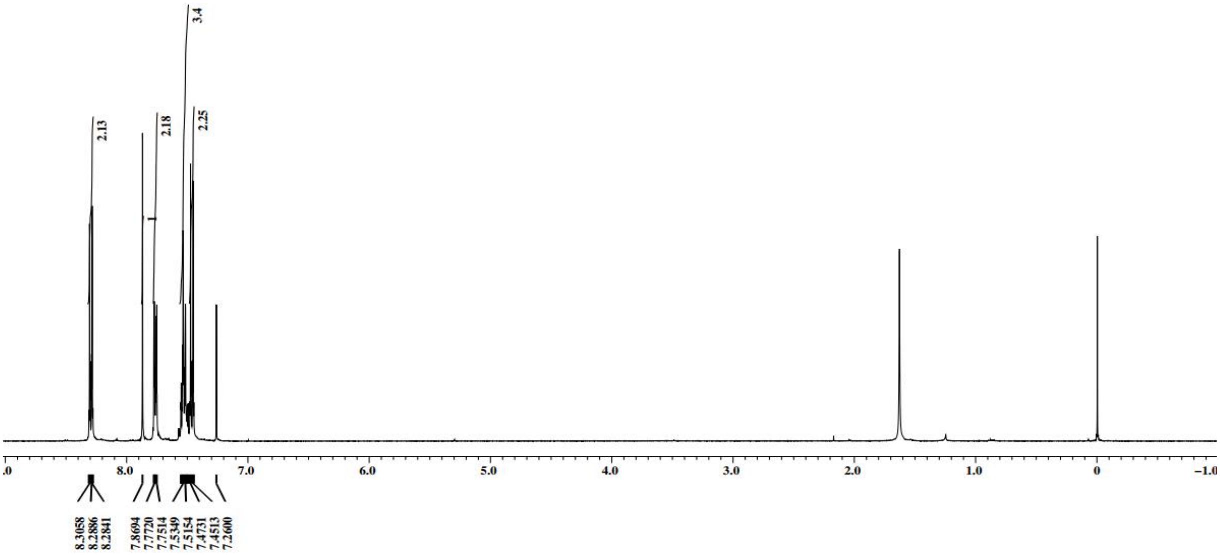

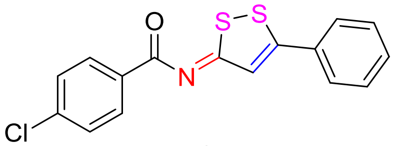

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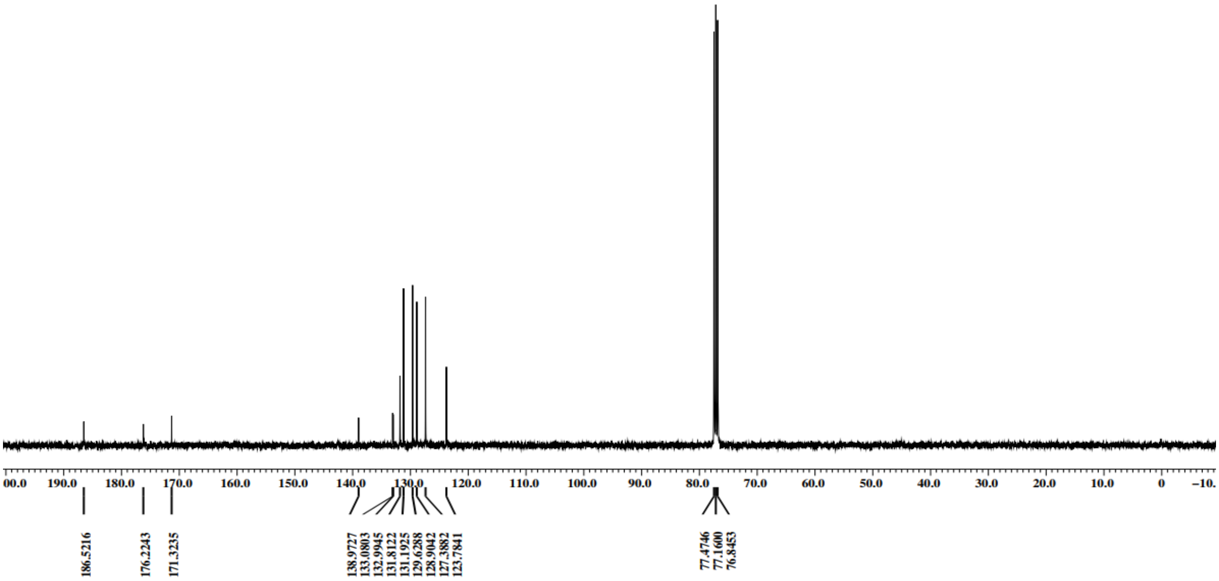

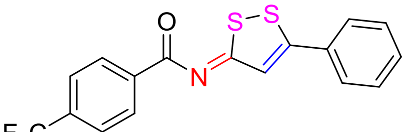

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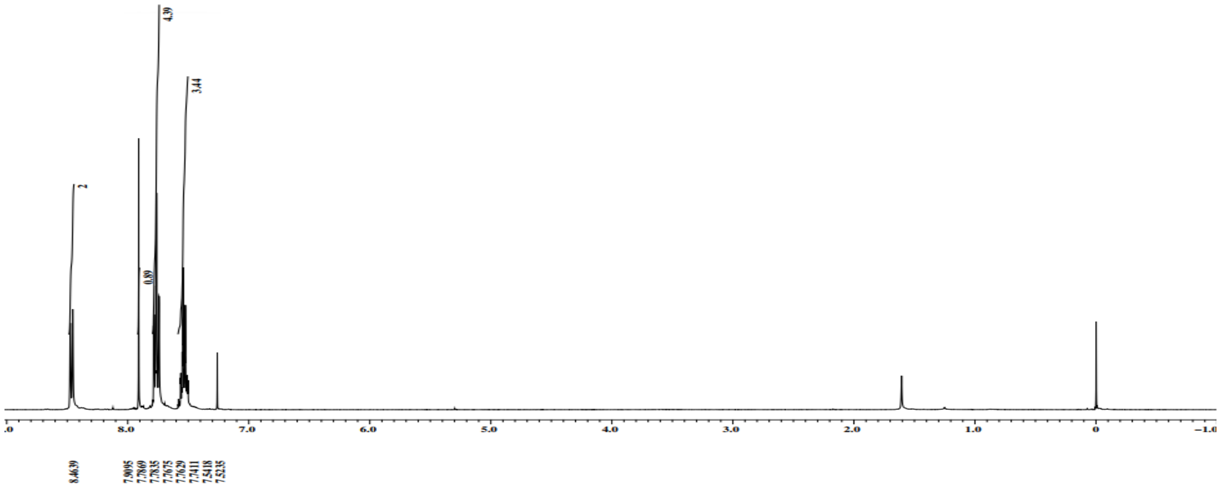

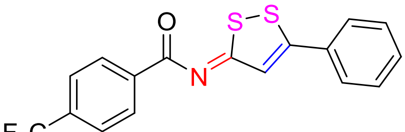

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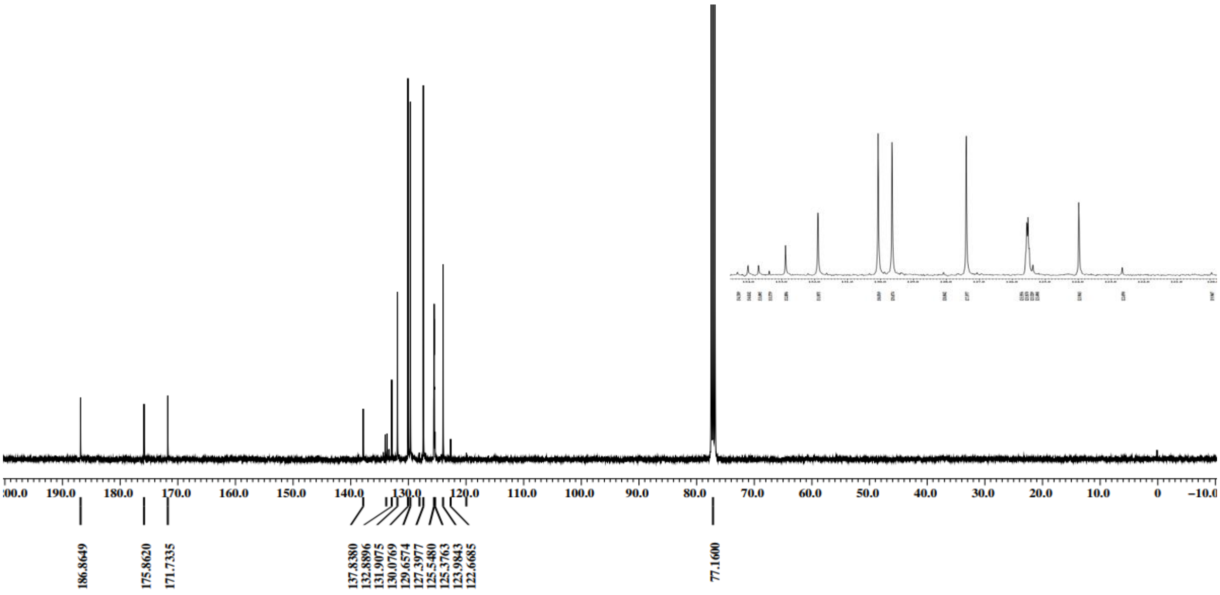

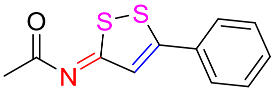

3ah

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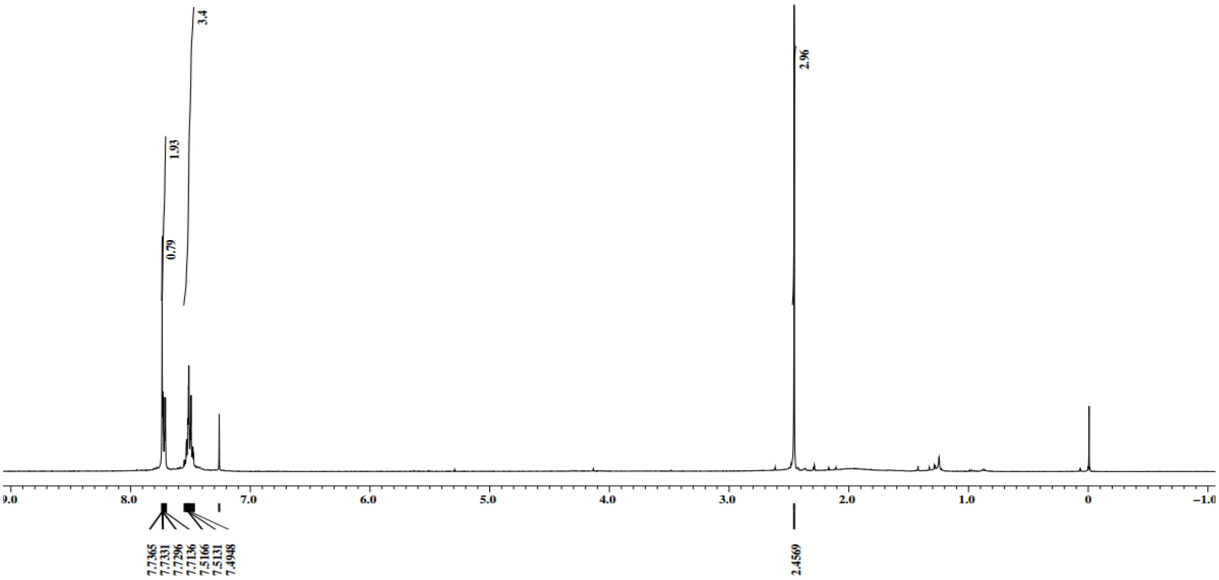

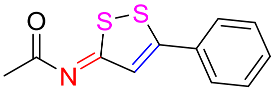

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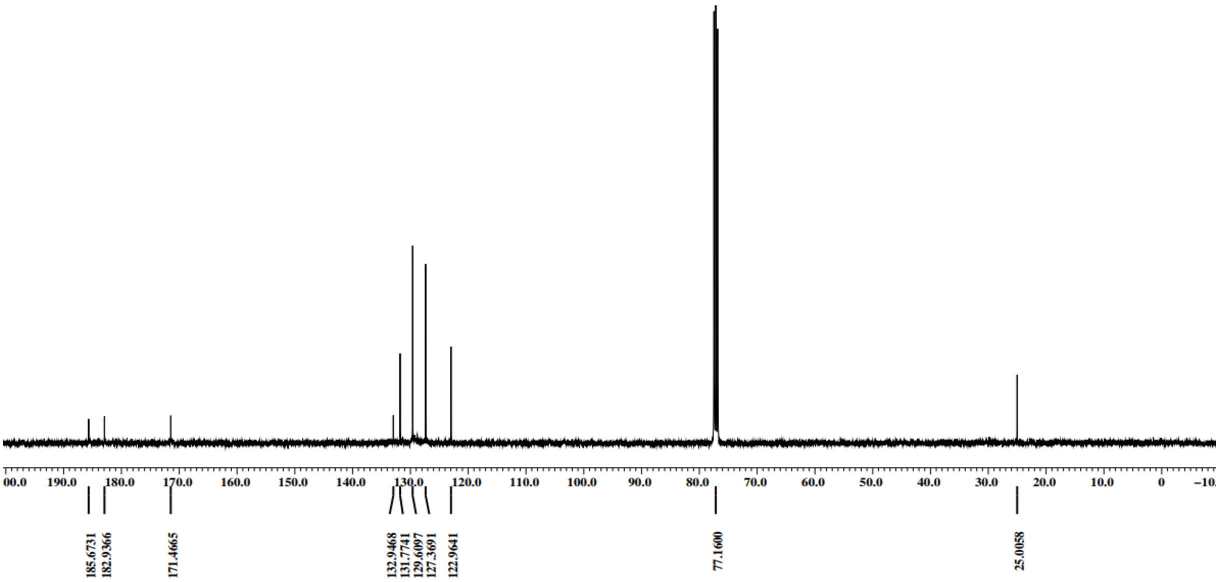

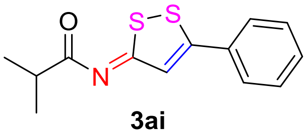

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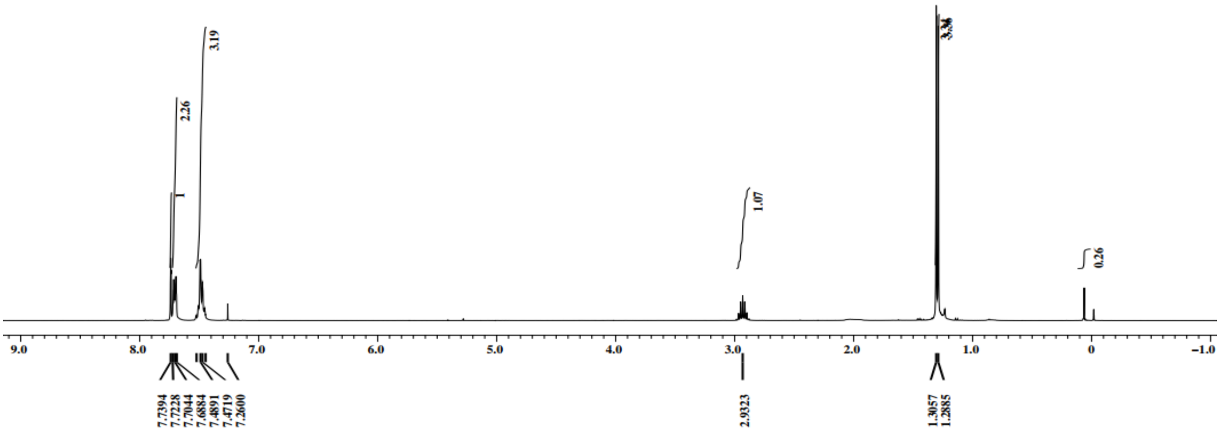

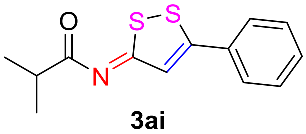

3ai

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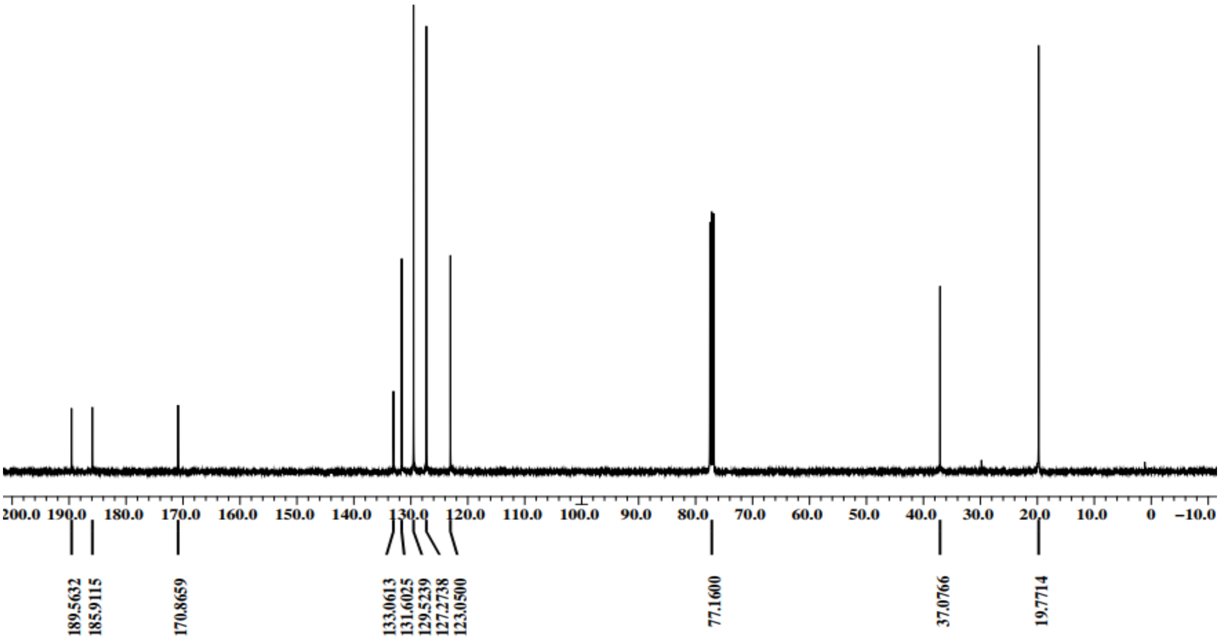

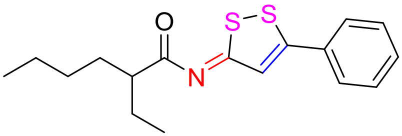

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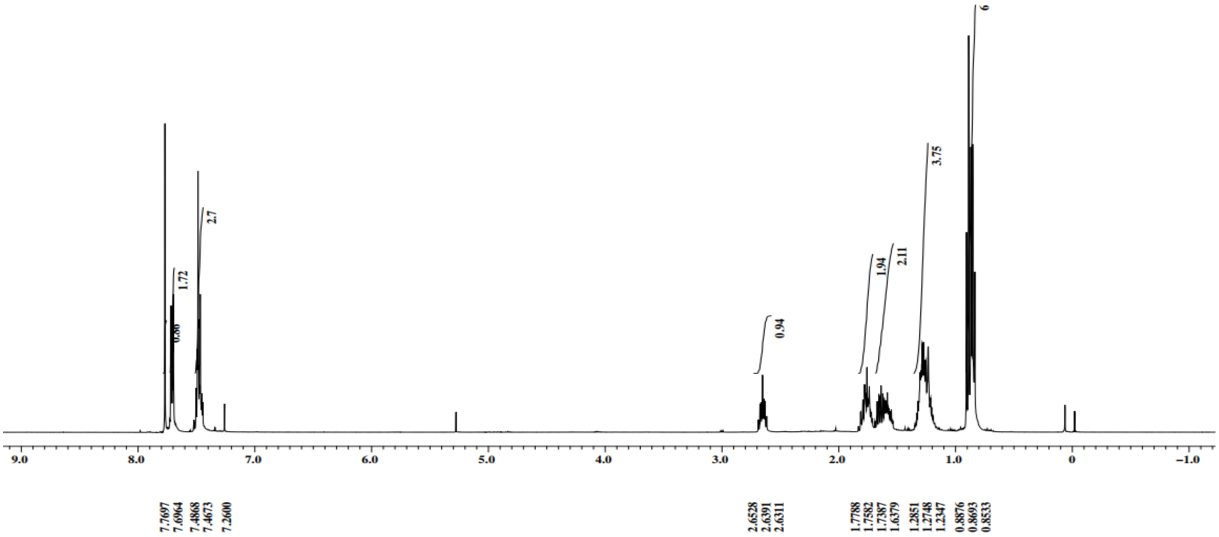

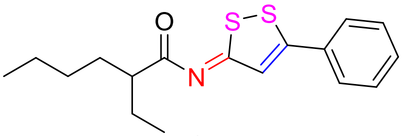

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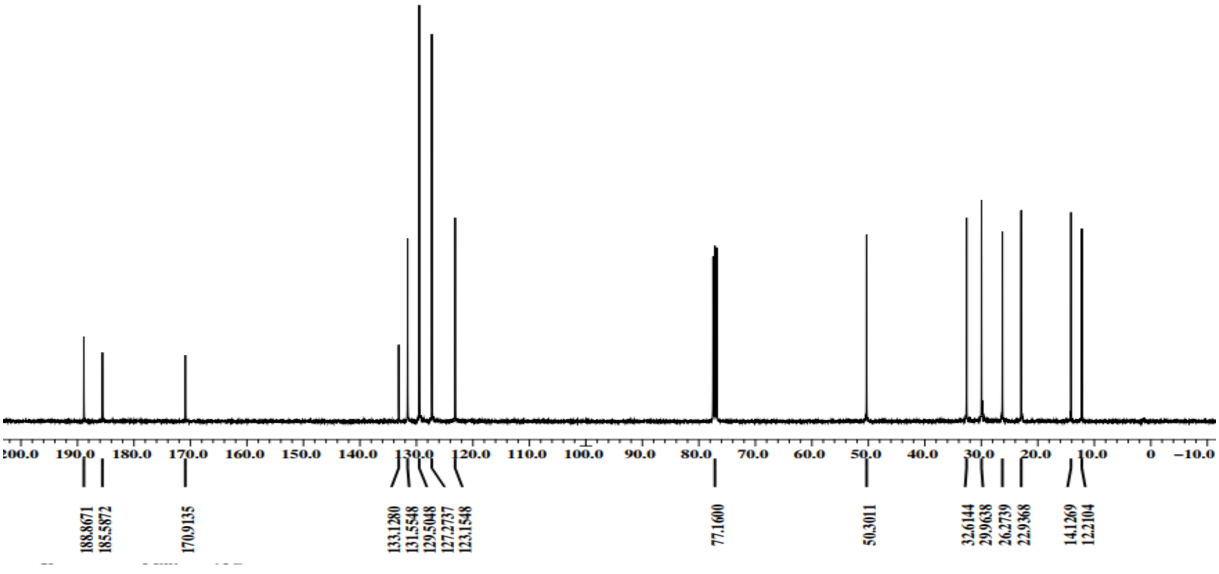
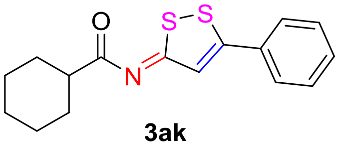
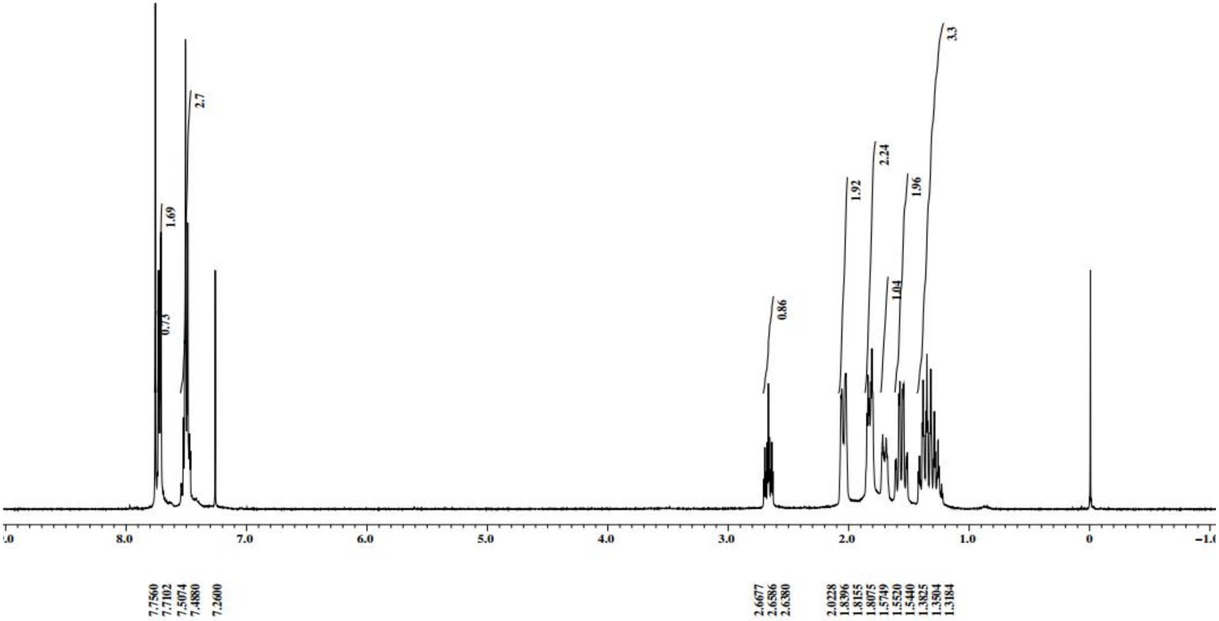
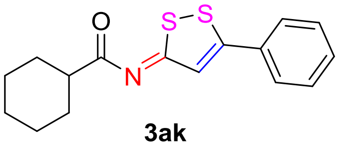




3ak

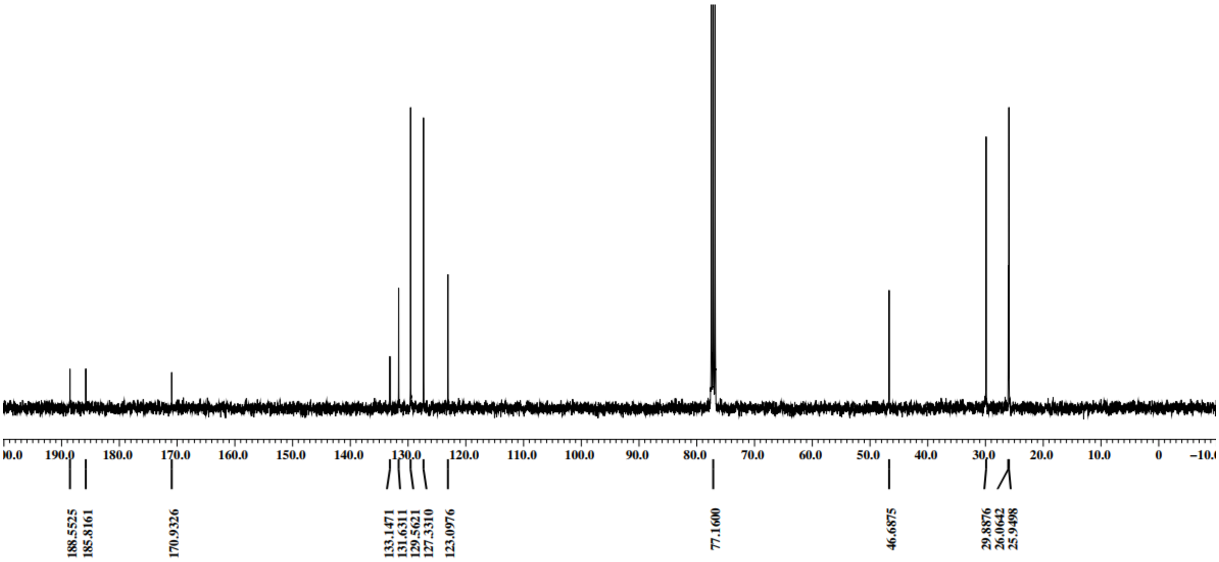
^{1}H NMR (100 MHz, CDCl$_3$)

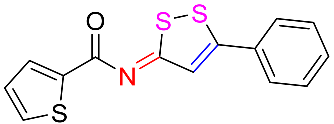




3ak

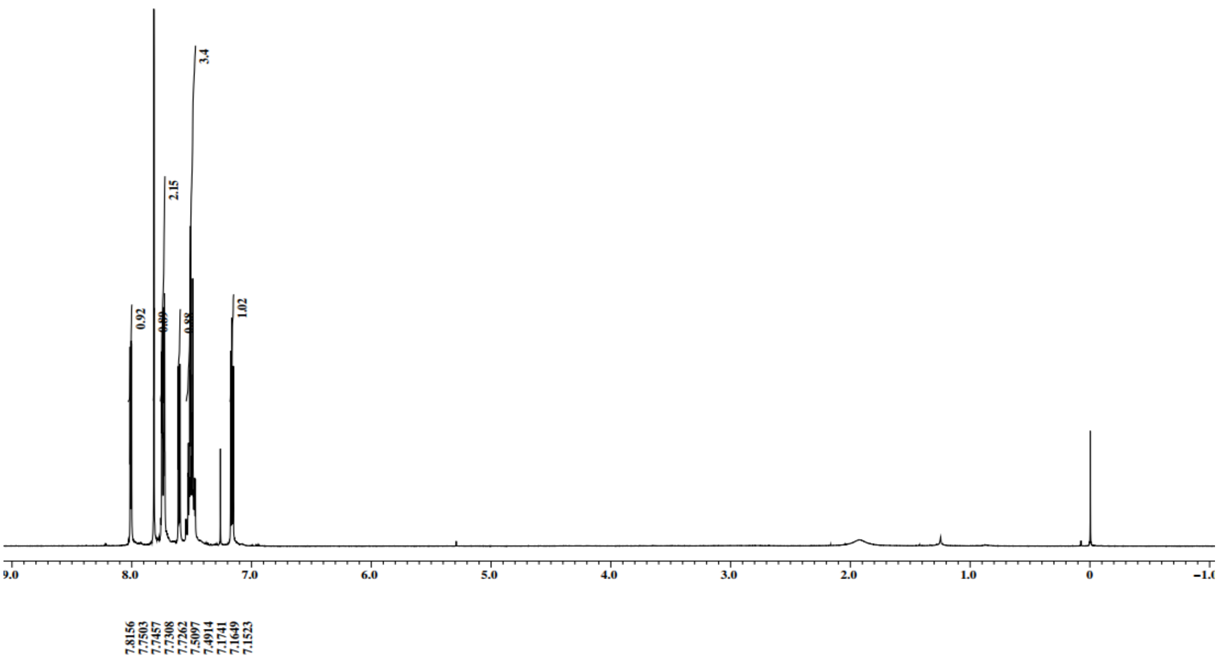
^{13}C NMR (100 MHz, CDCl$_3$)

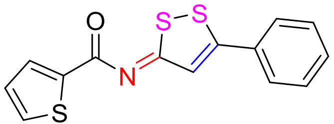




3am

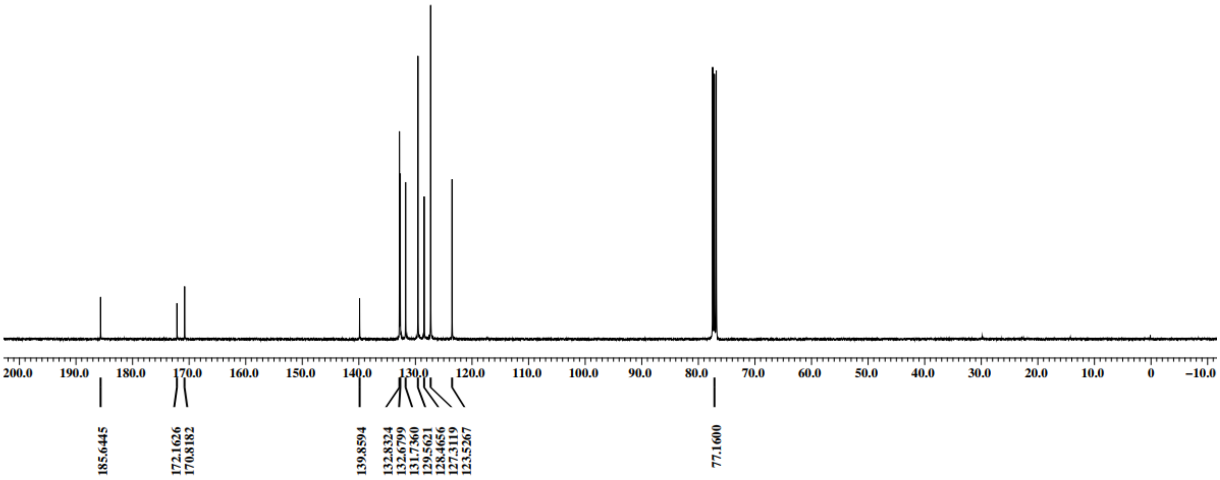
^{1}H NMR (100 MHz, CDCl$_3$)

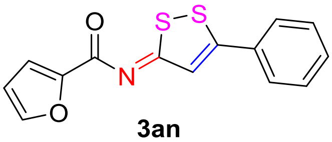




3am

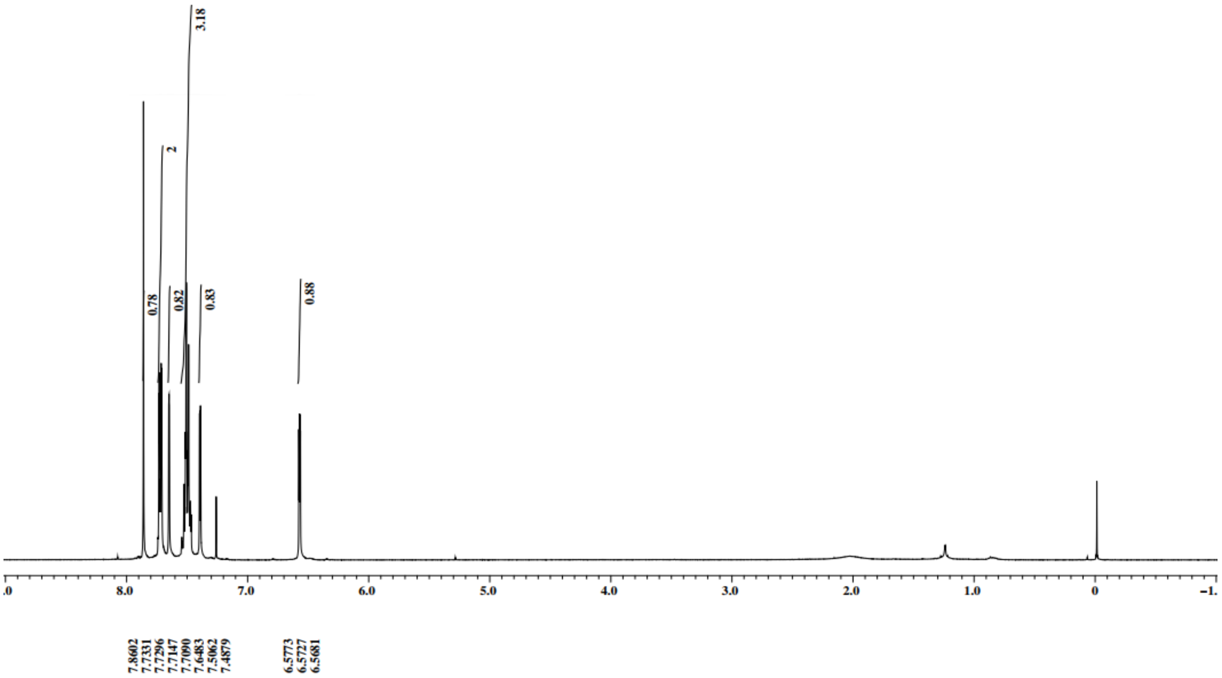
^{13}C NMR (100 MHz, CDCl$_3$)

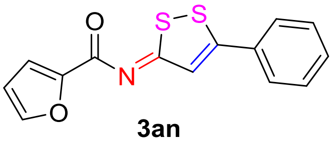




3an

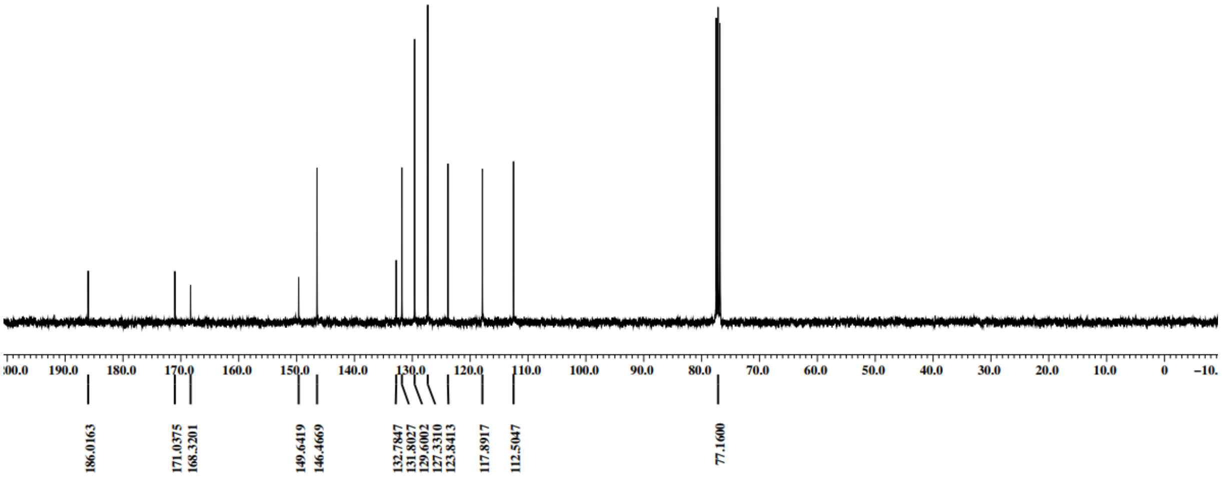
^{1}H NMR (100 MHz, CDCl$_3$)

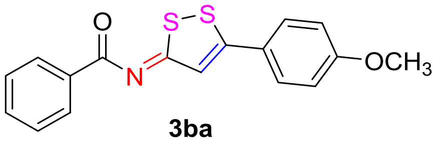




3an

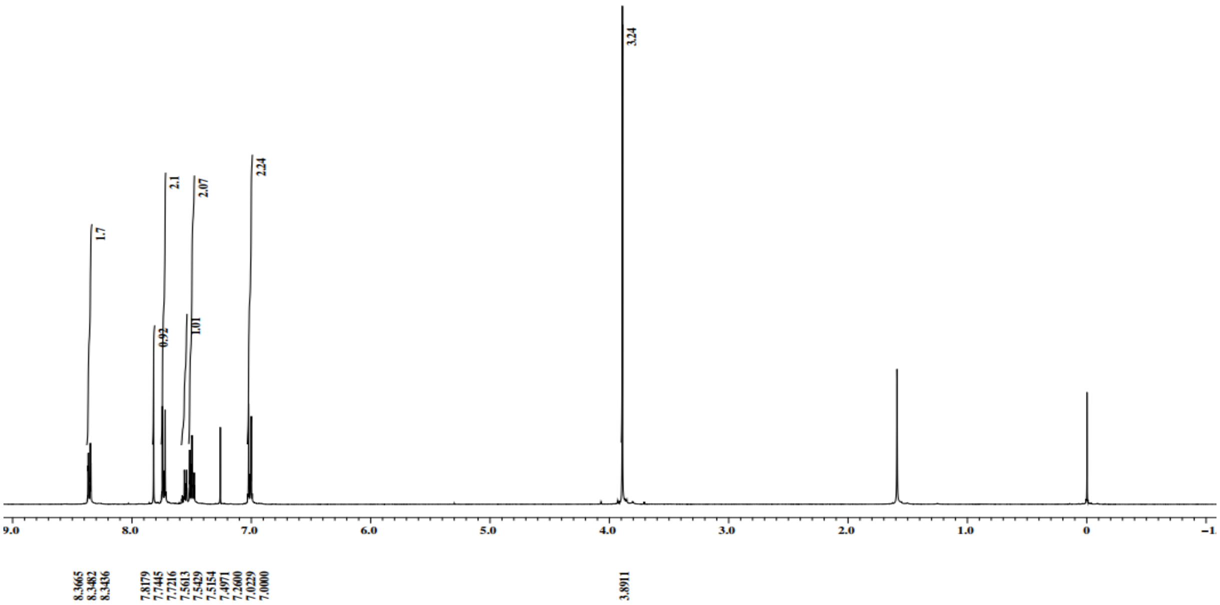
^{13}C NMR (100 MHz, CDCl$_3$)

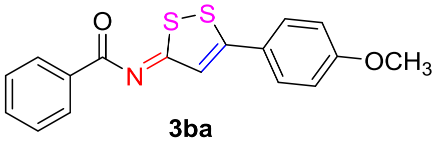




3ba

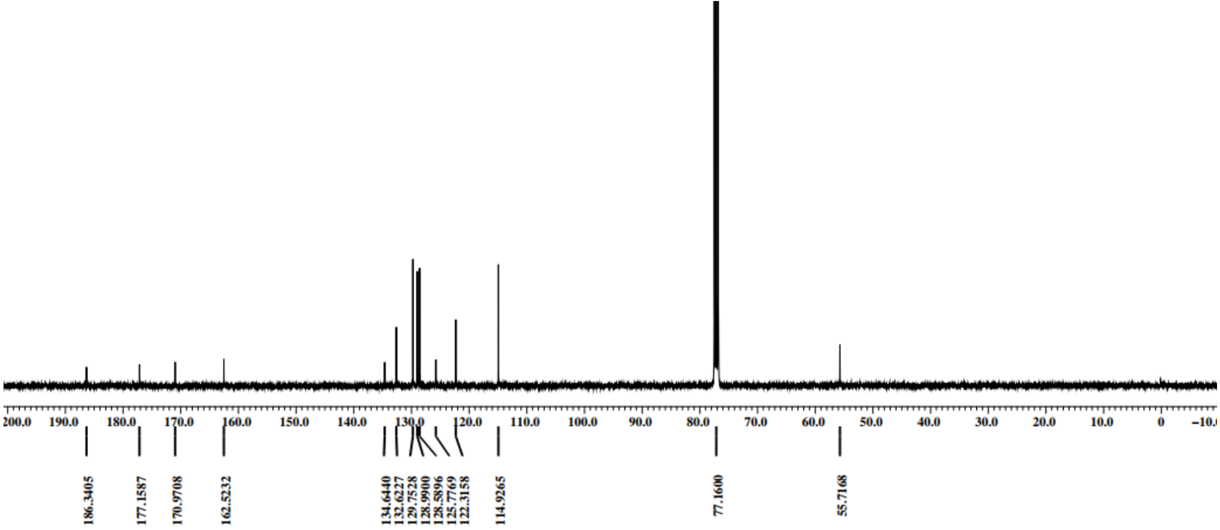
^{1}H NMR (100 MHz, CDCl$_3$)

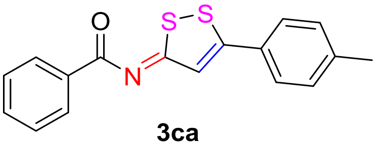




3ba

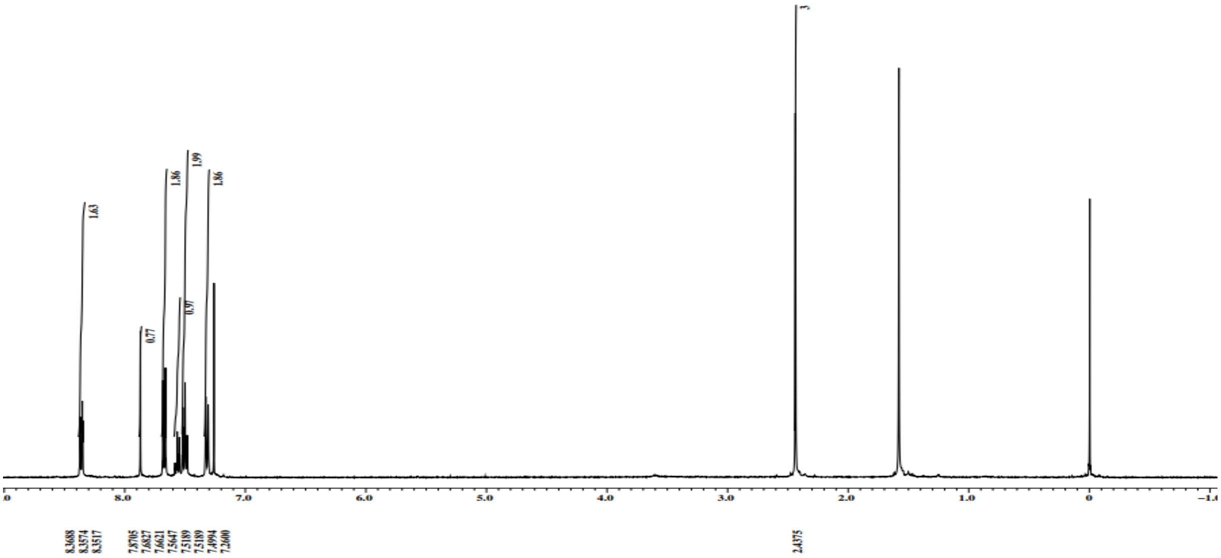
^{13}C NMR (100 MHz, CDCl$_3$)

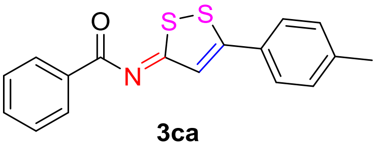




3ca

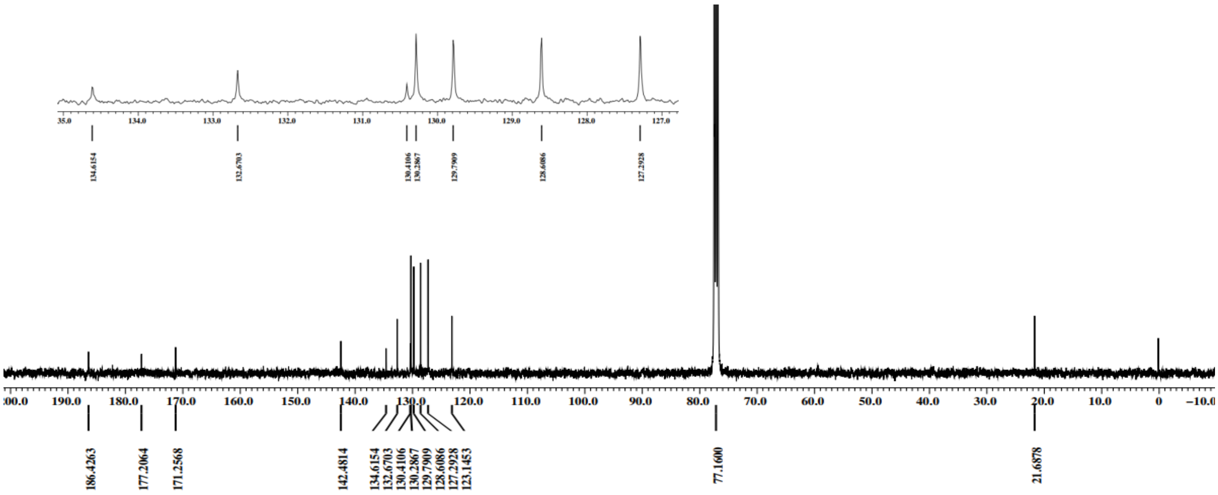
^{1}H NMR (100 MHz, CDCl$_3$)

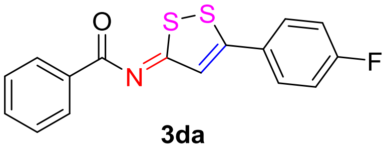




3ca

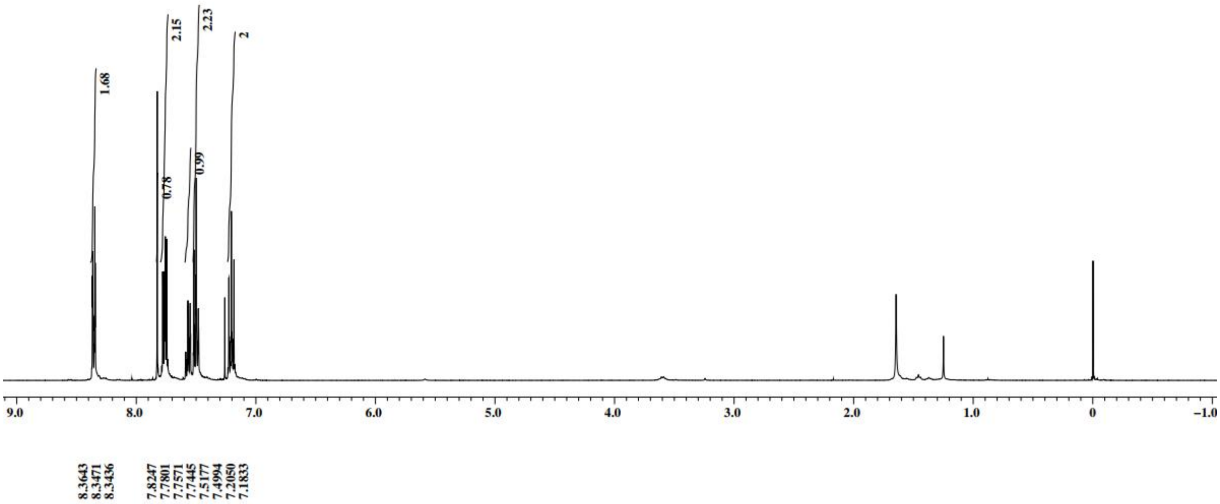
^{13}C NMR (100 MHz, CDCl$_3$)

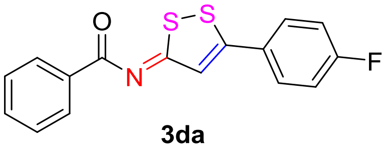




3da

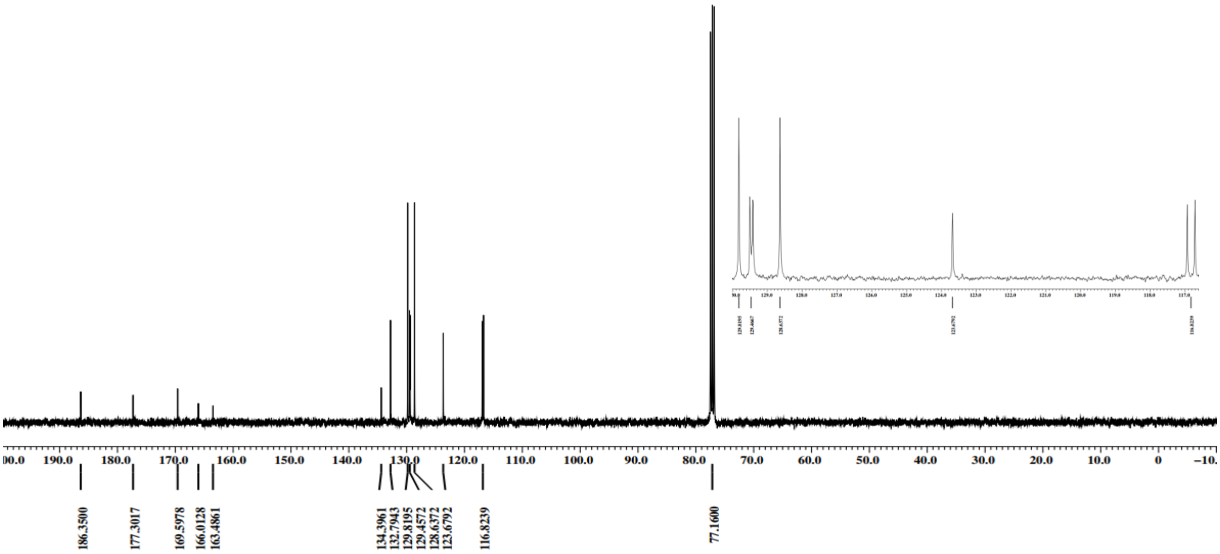
^{1}H NMR (100 MHz, CDCl$_3$)

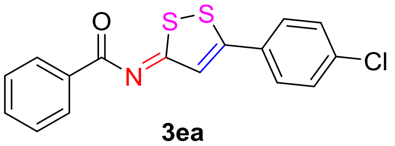




3da

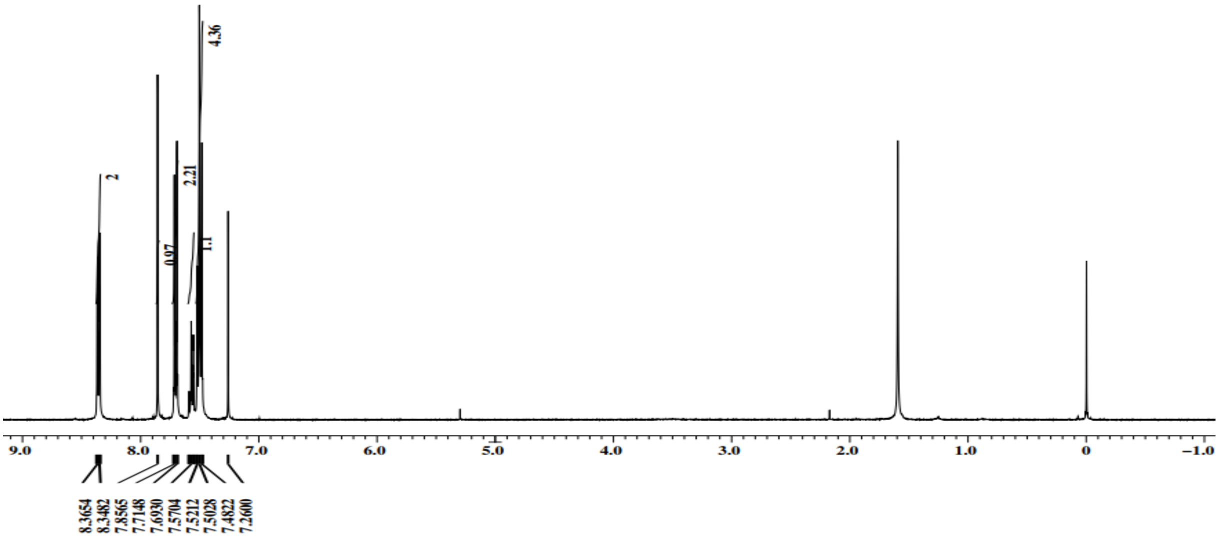
^{13}C NMR (100 MHz, CDCl$_3$)

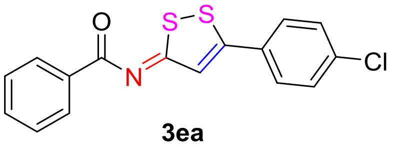




3ea

^{1}H NMR (100 MHz, CDCl$_3$)





3ea

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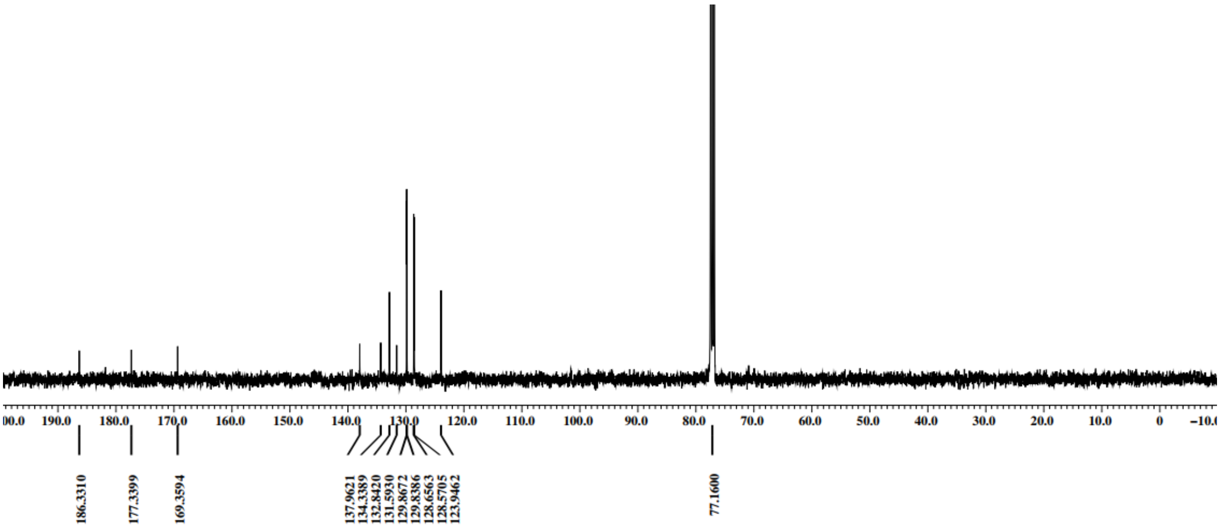
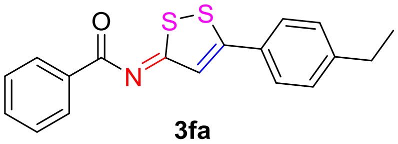
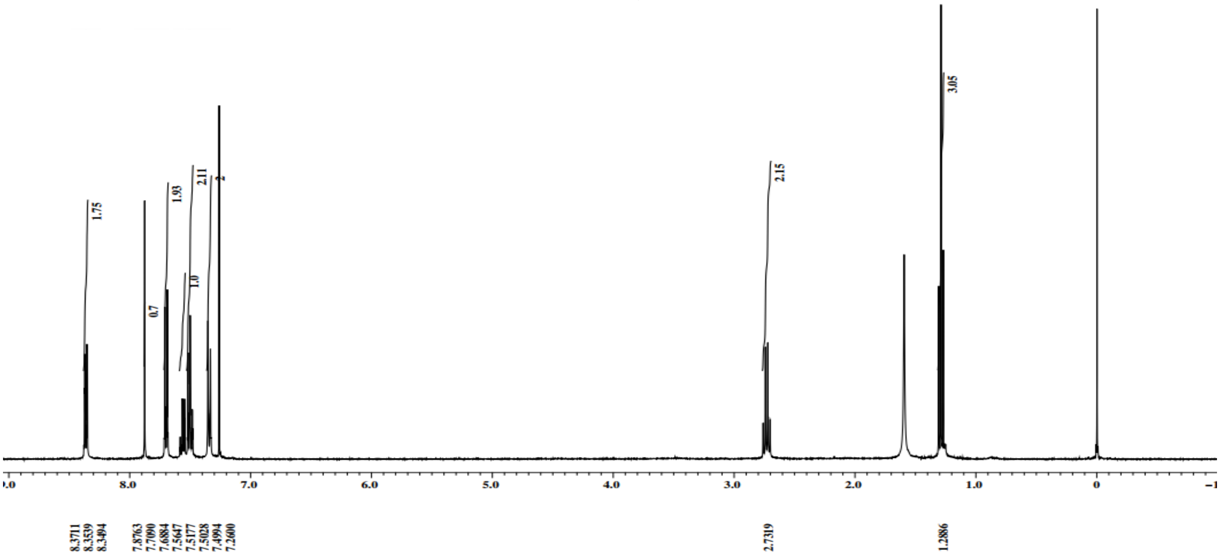
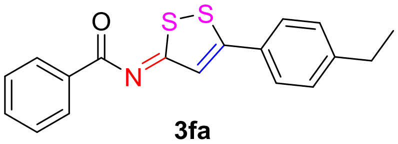




3fa

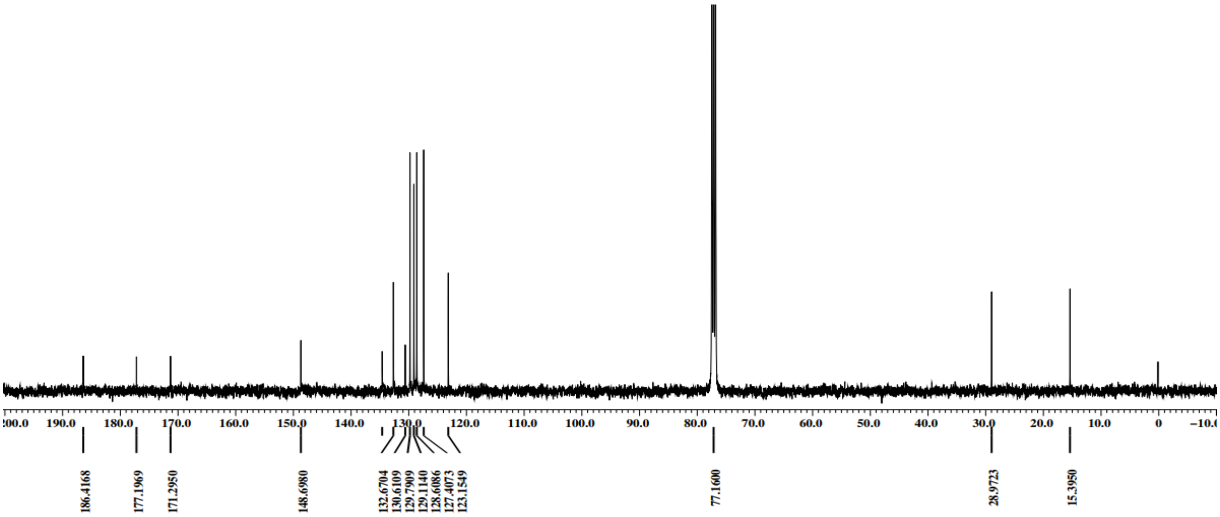
^{1}H NMR (100 MHz, CDCl$_3$)

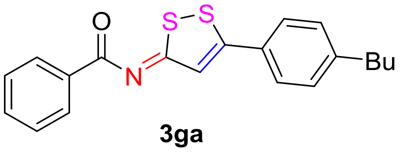




3fa

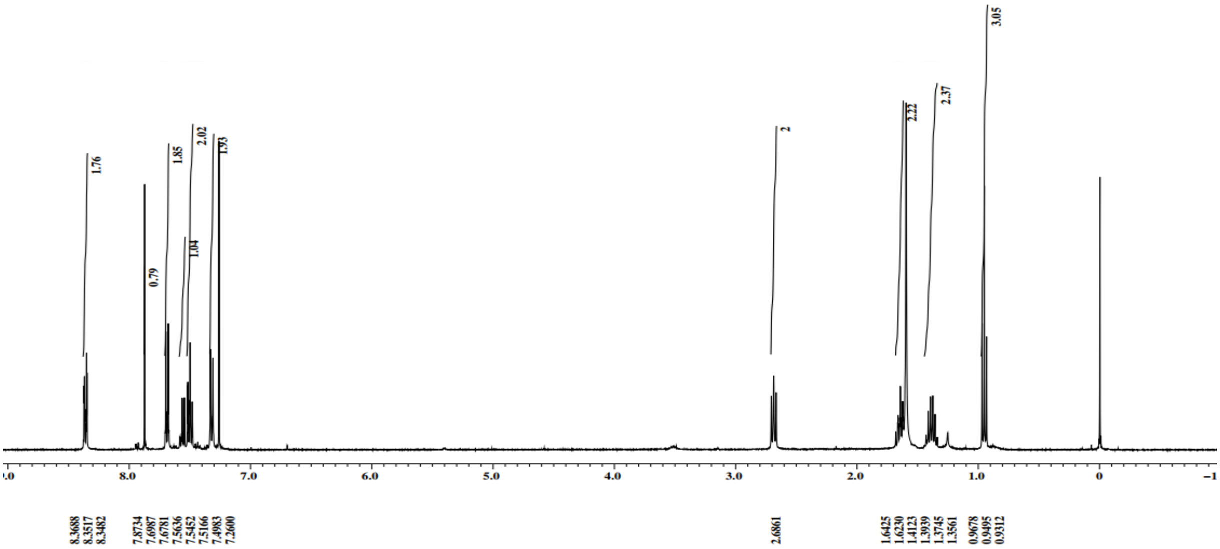
^{13}C NMR (100 MHz, CDCl$_3$)

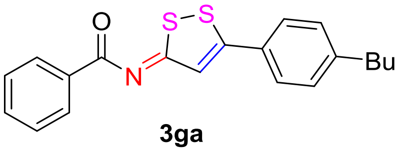




3ga

^{1}H NMR (100 MHz, CDCl$_3$)





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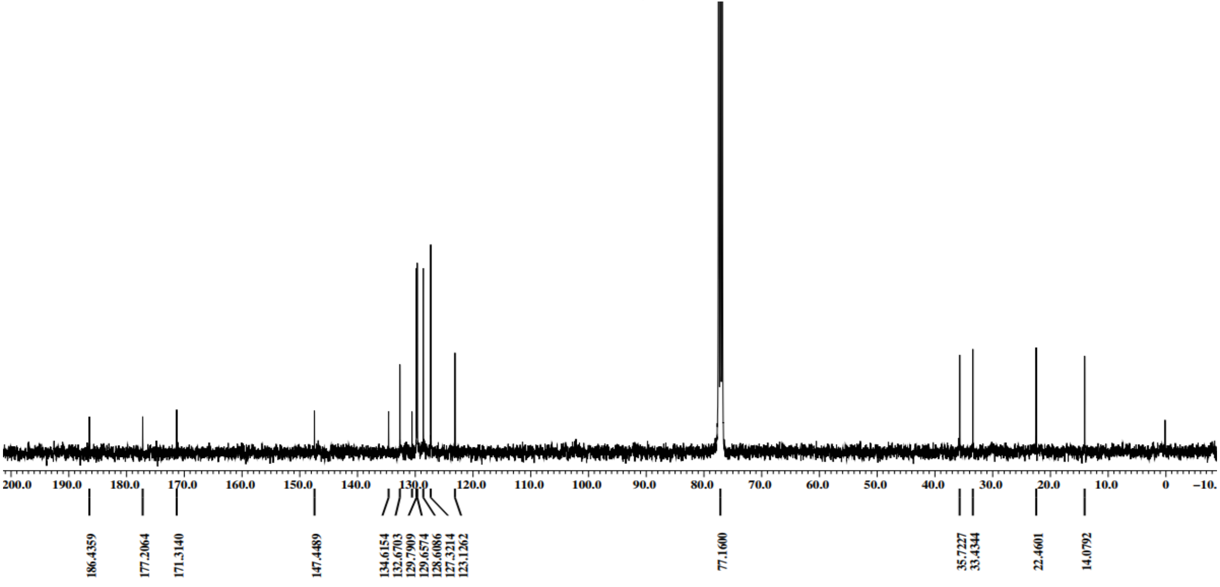
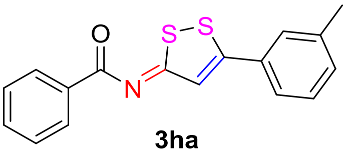
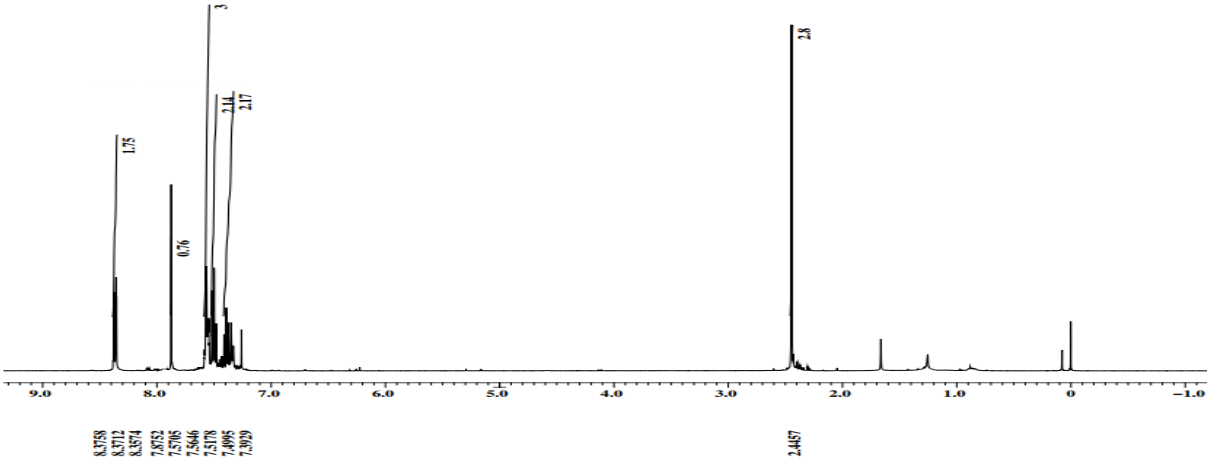
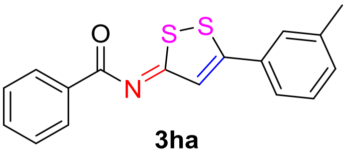




3ha

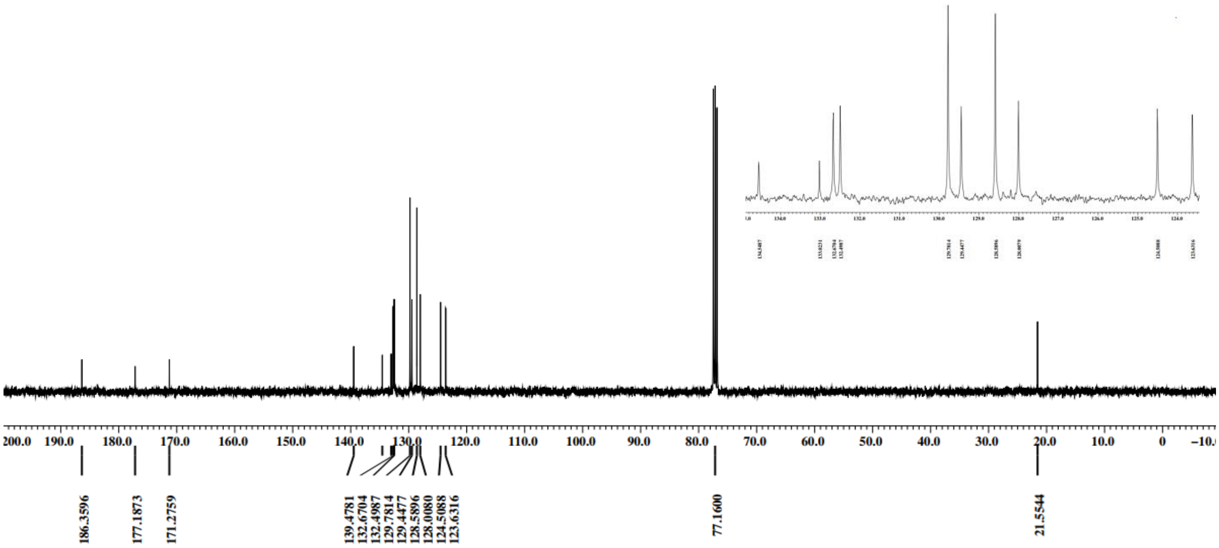
^{1}H NMR (100 MHz, CDCl$_3$)

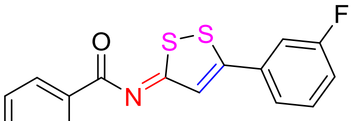




3ha

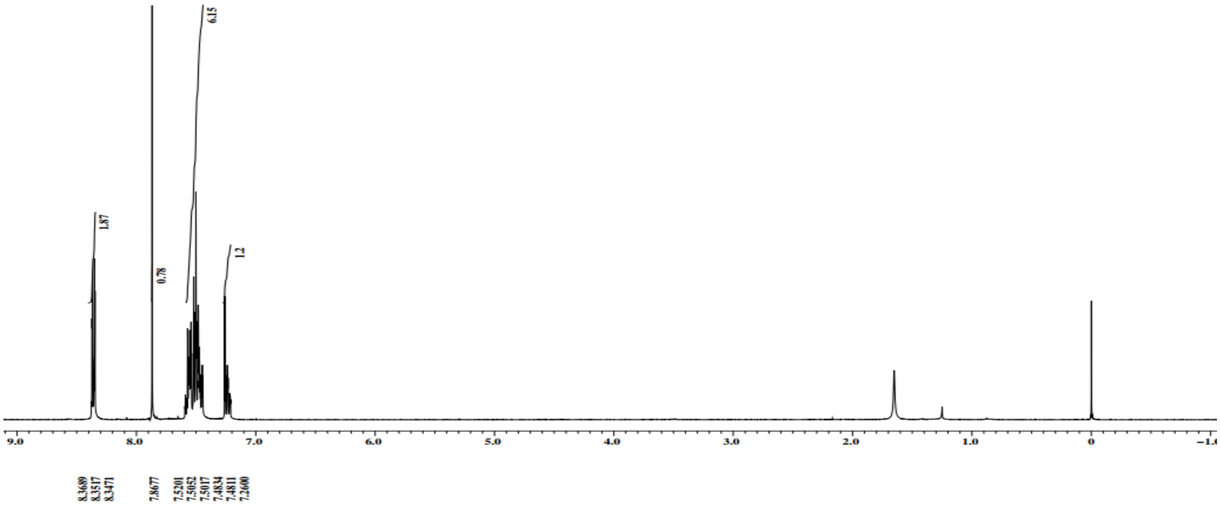
^{13}C NMR (100 MHz, CDCl$_3$)

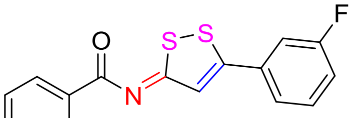




3ia

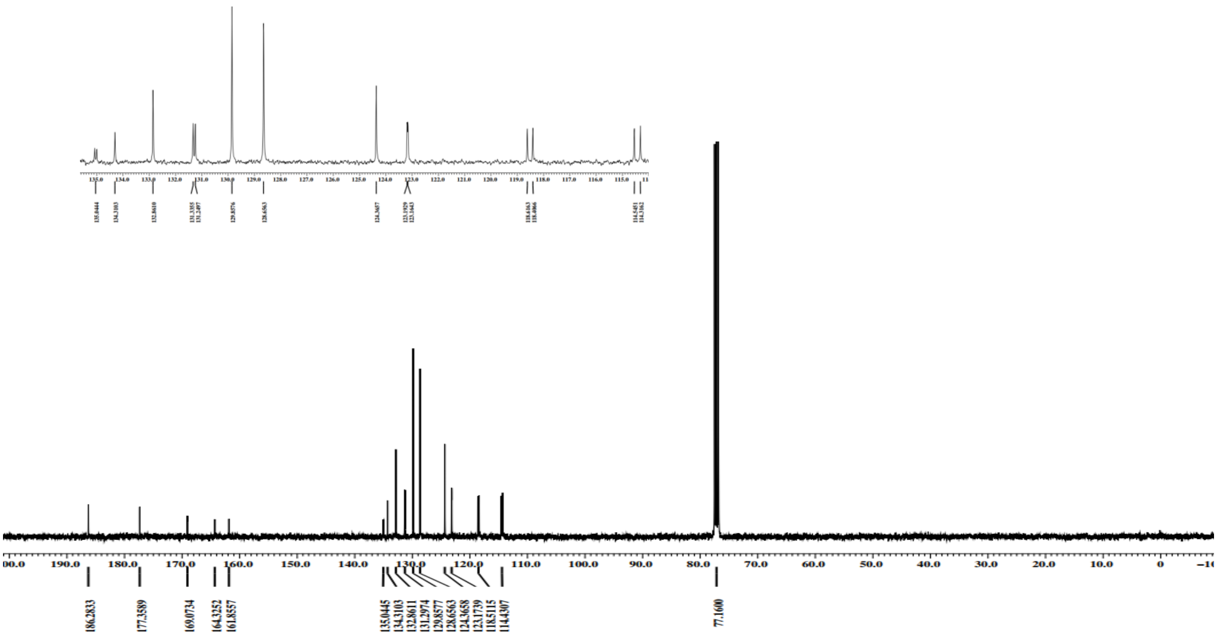
^{1}H NMR (100 MHz, CDCl$_3$)

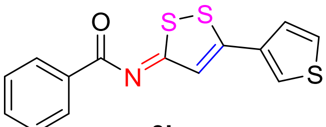




3ia

^{13}C NMR (100 MHz, CDCl$_3$)





3ja

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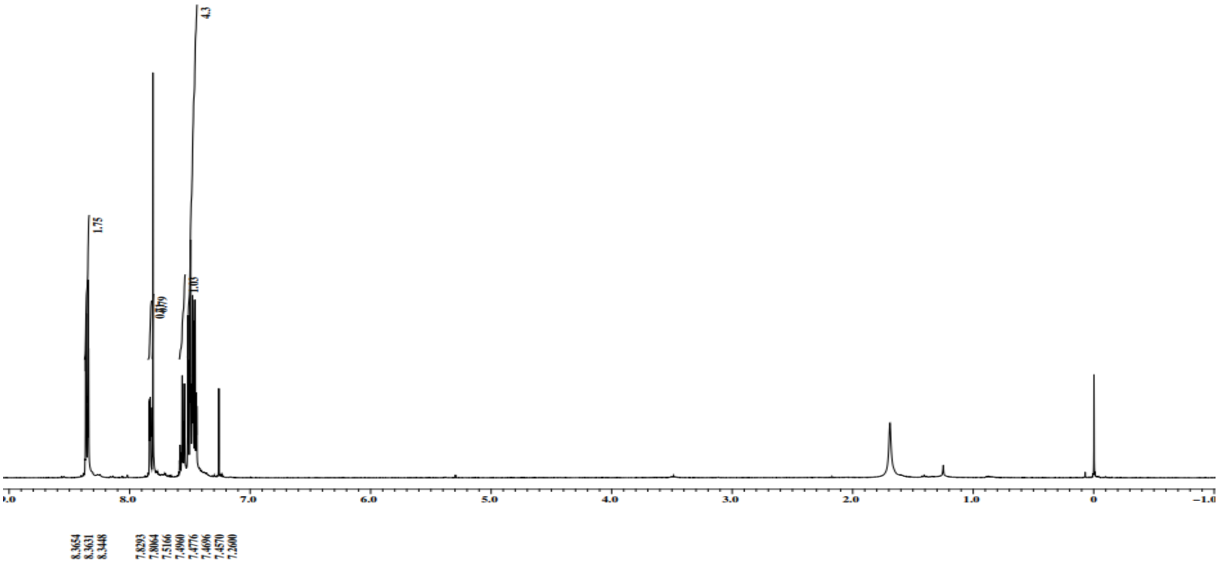

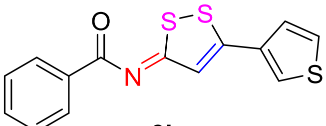

3ja

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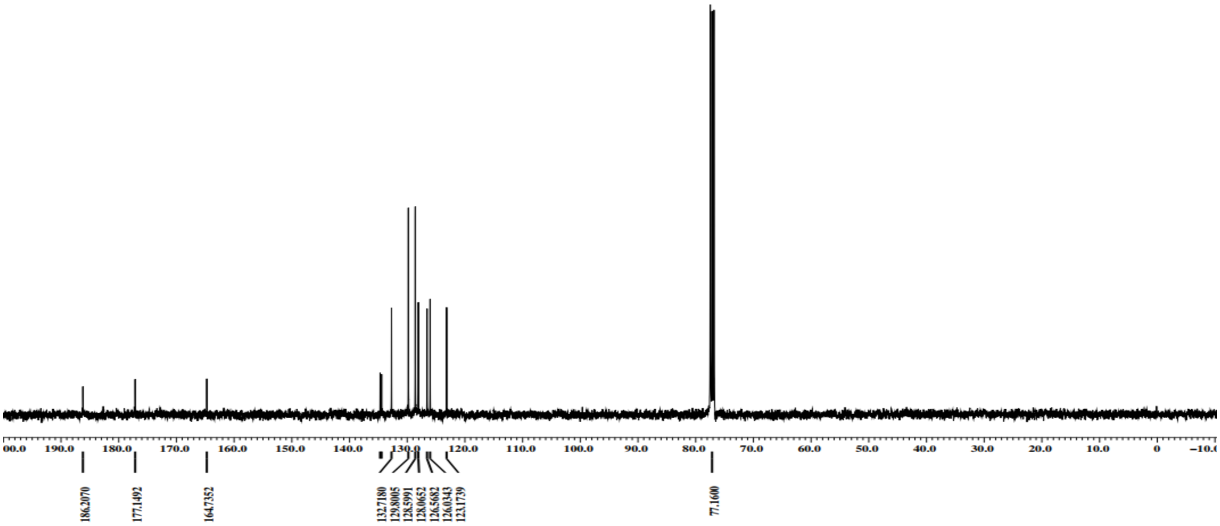
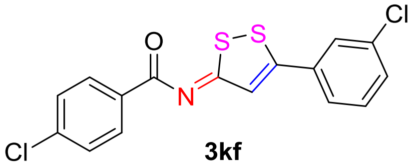
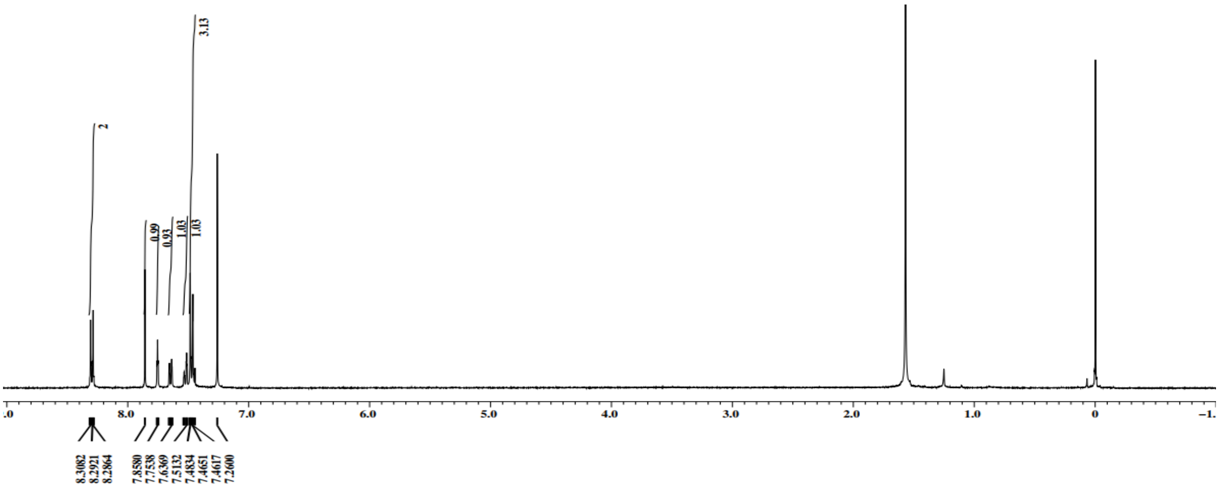
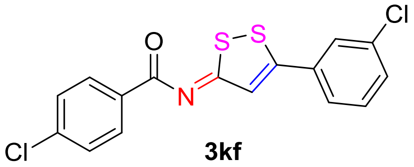




3kf

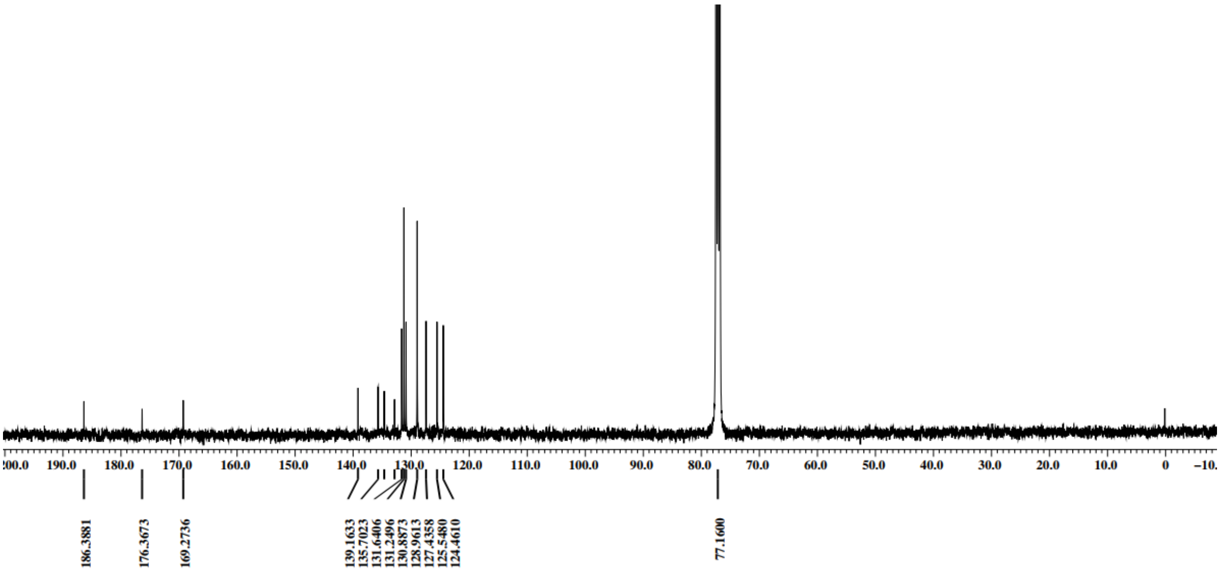
^1H NMR (100 MHz, CDCl$_3$)

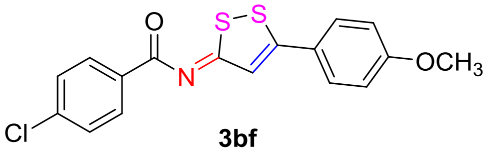




3kf

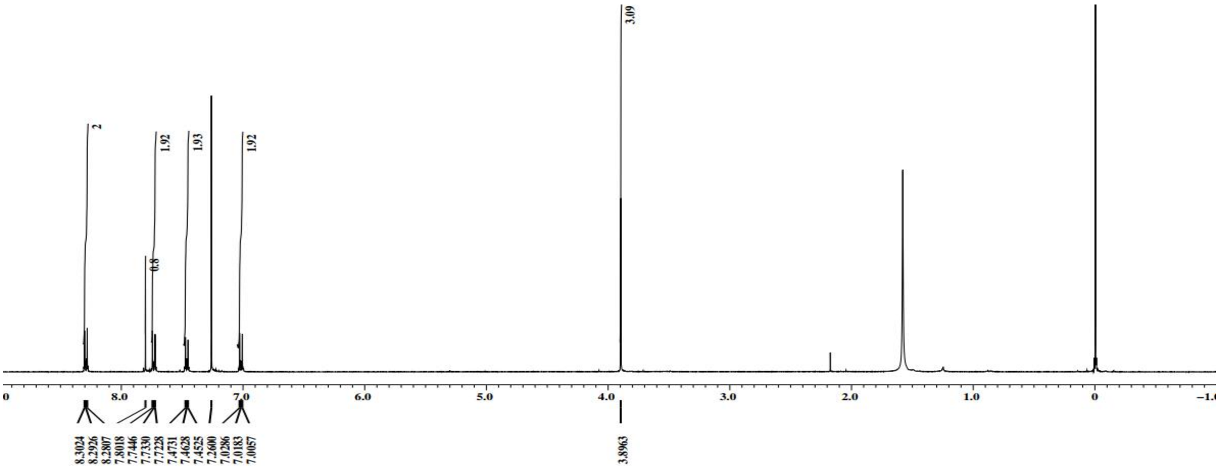
^{13}C NMR (100 MHz, CDCl$_3$)

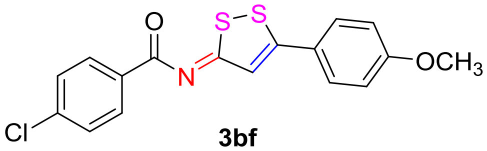




3bf

^{1}H NMR (100 MHz, CDCl$_3$)





3bf

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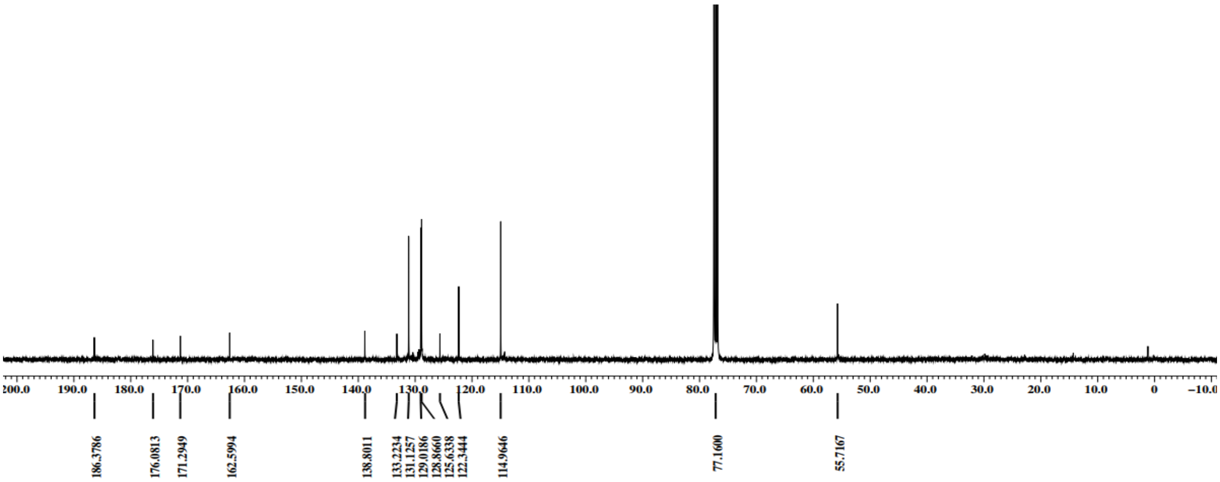

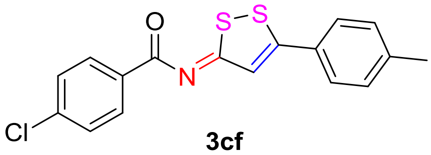

3cf

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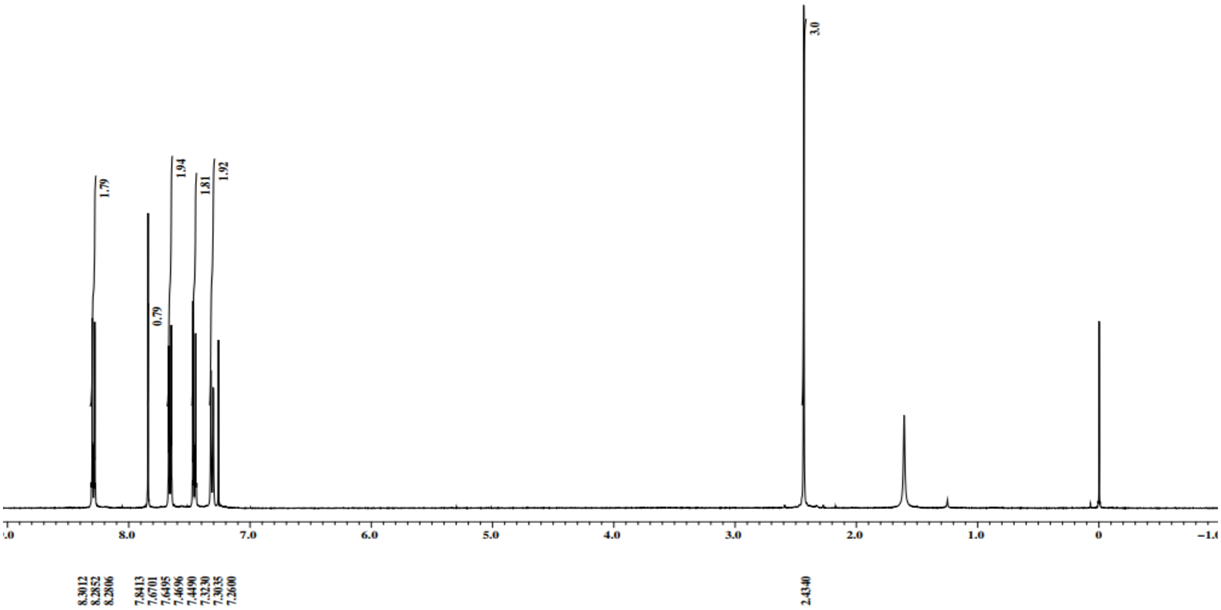

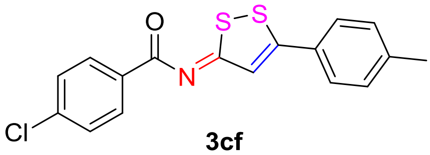

3cf

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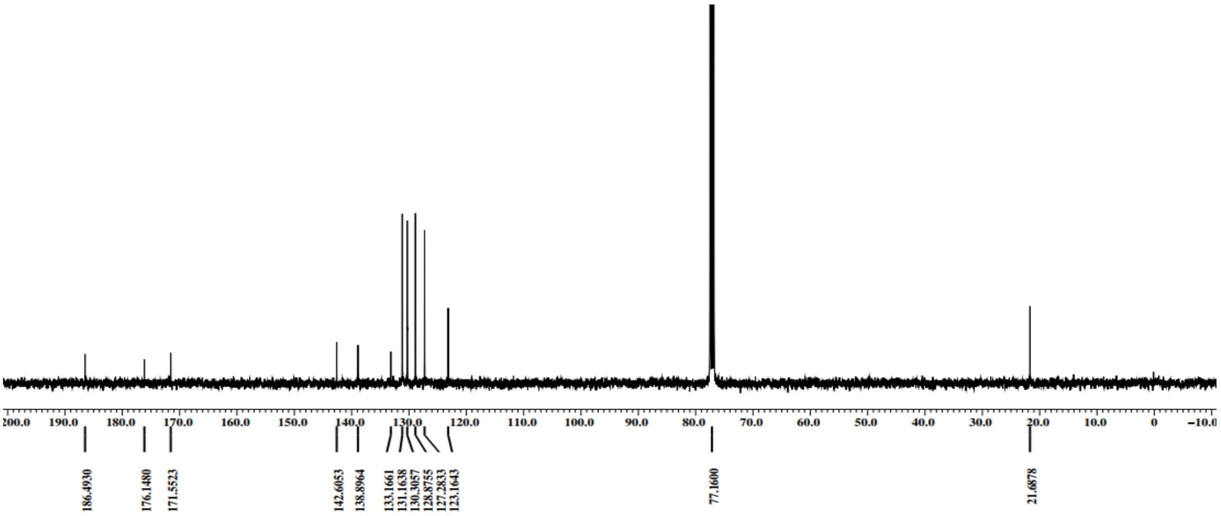

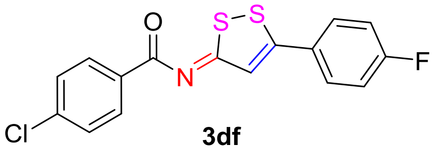

3df

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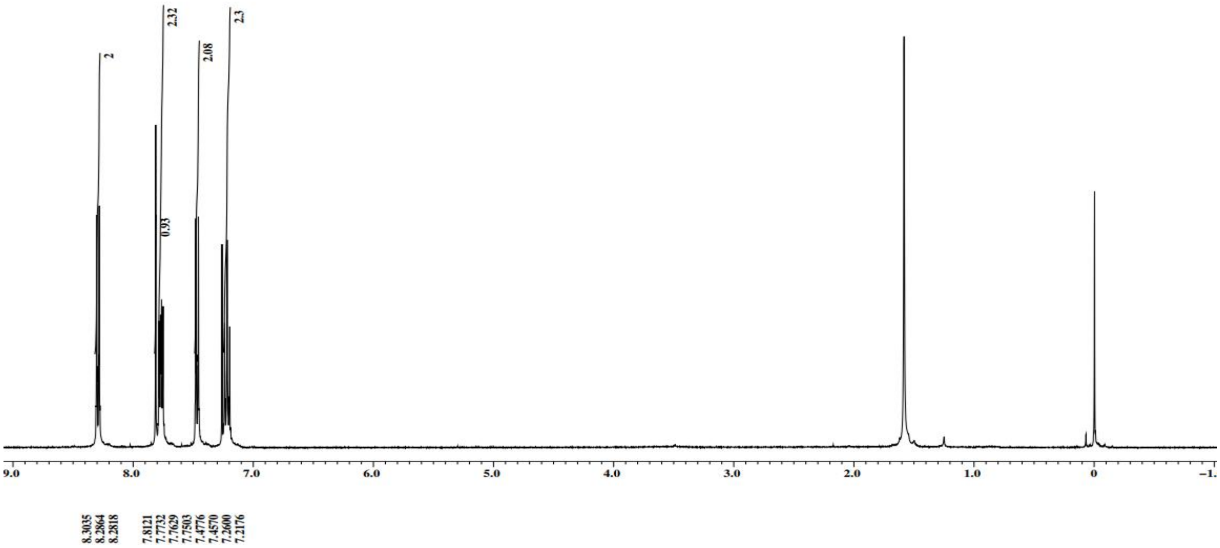

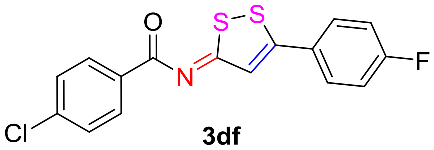

3df

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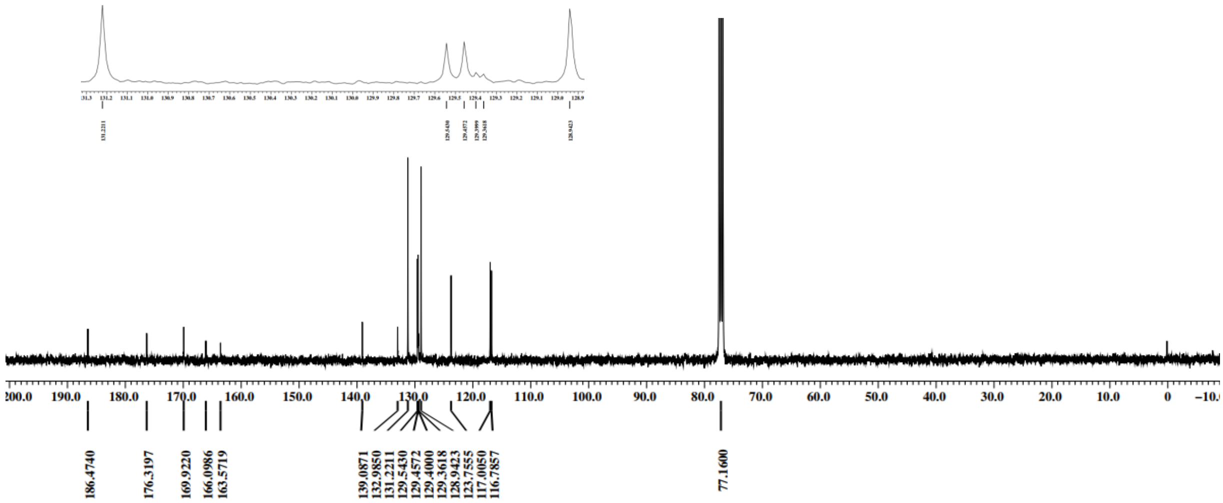

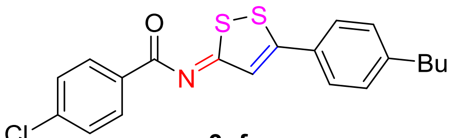

3gf

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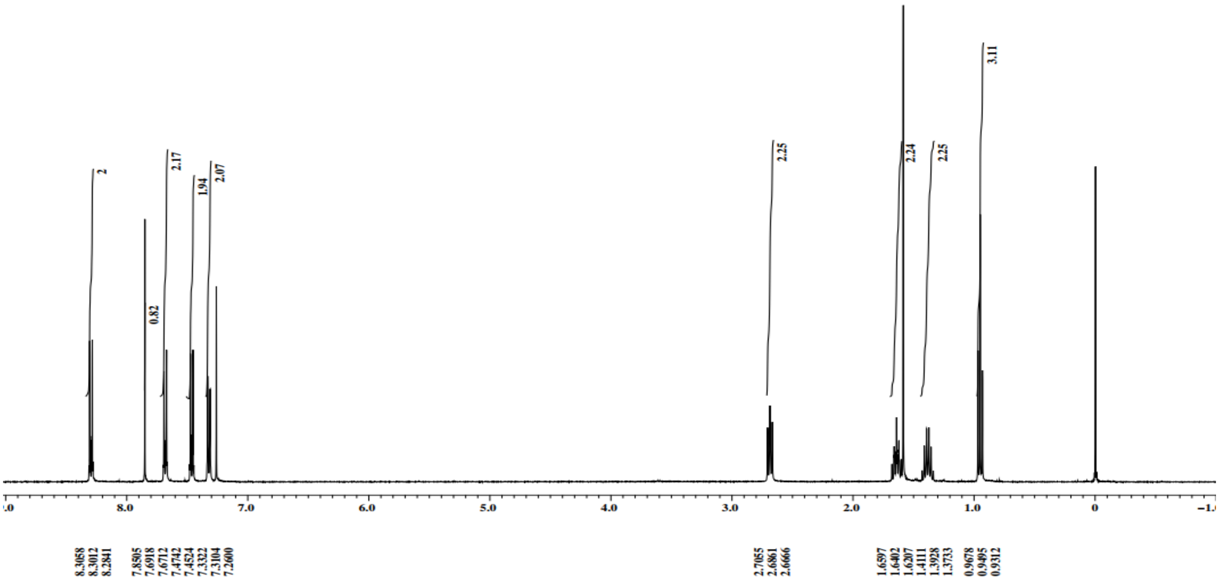

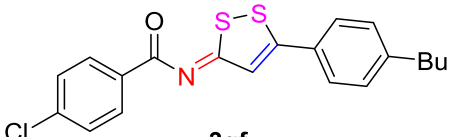

3gf

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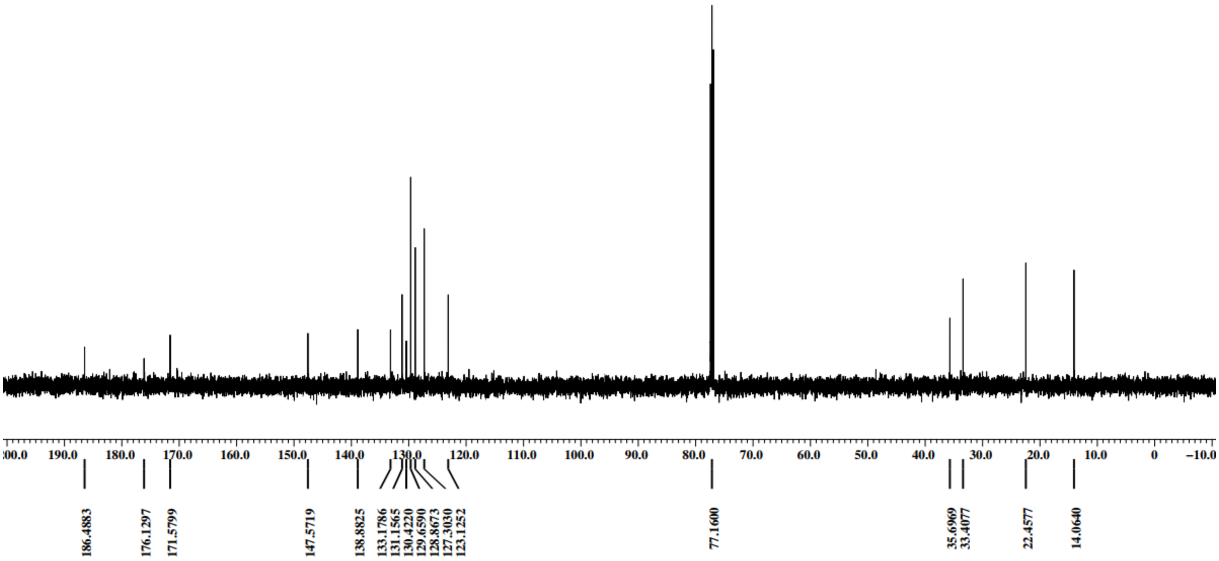

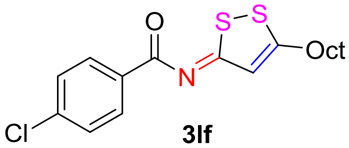

3lf

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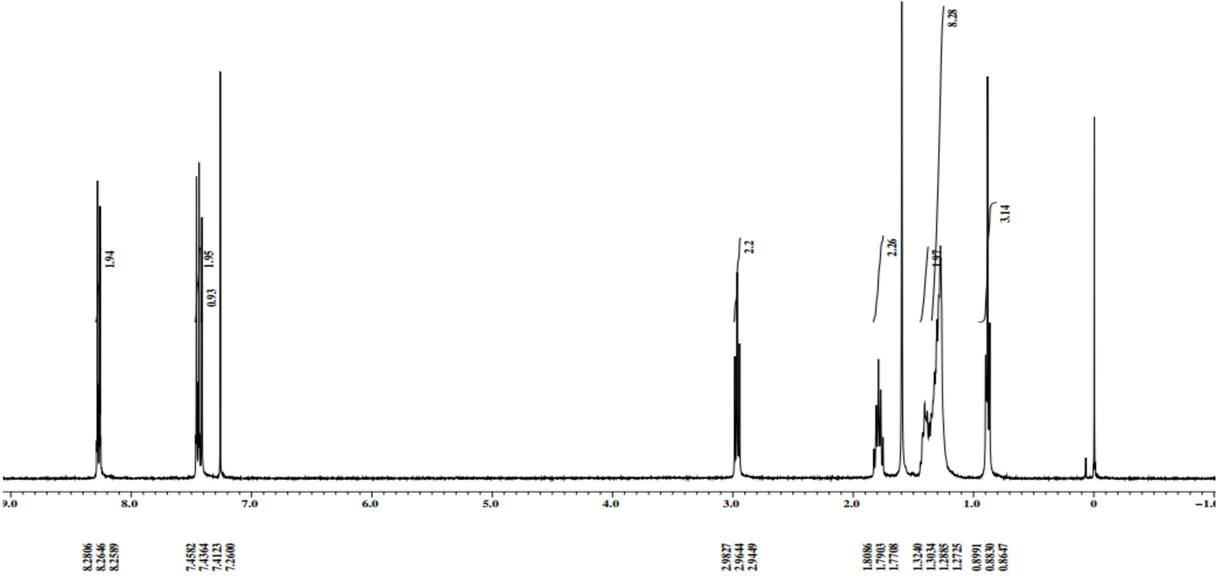
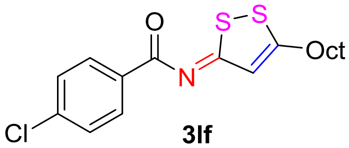
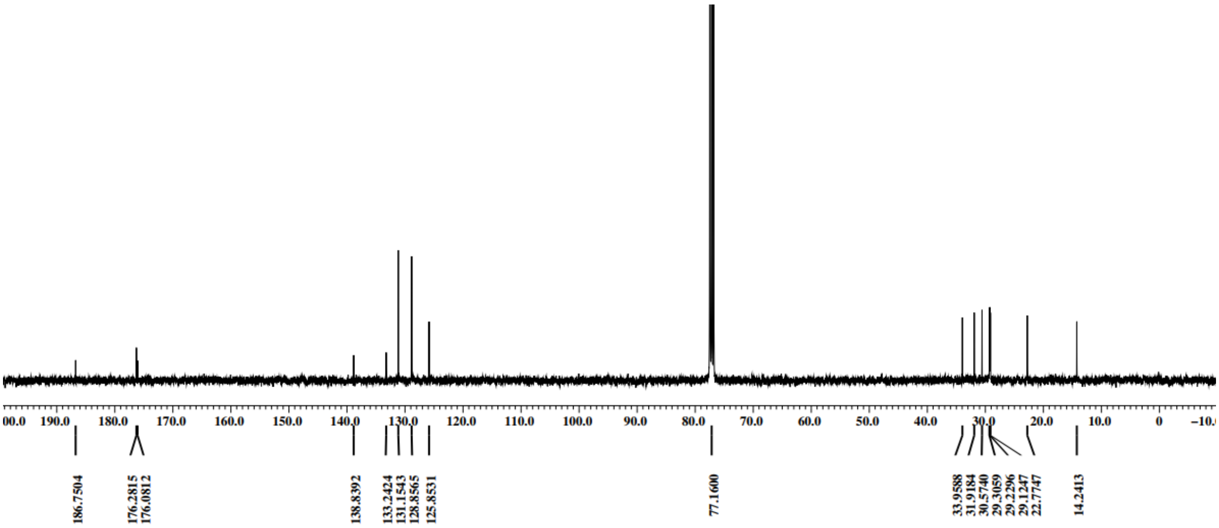
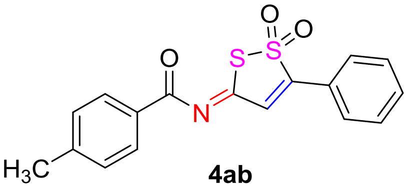




3lf

^{13}C NMR (100 MHz, CDCl$_3$)





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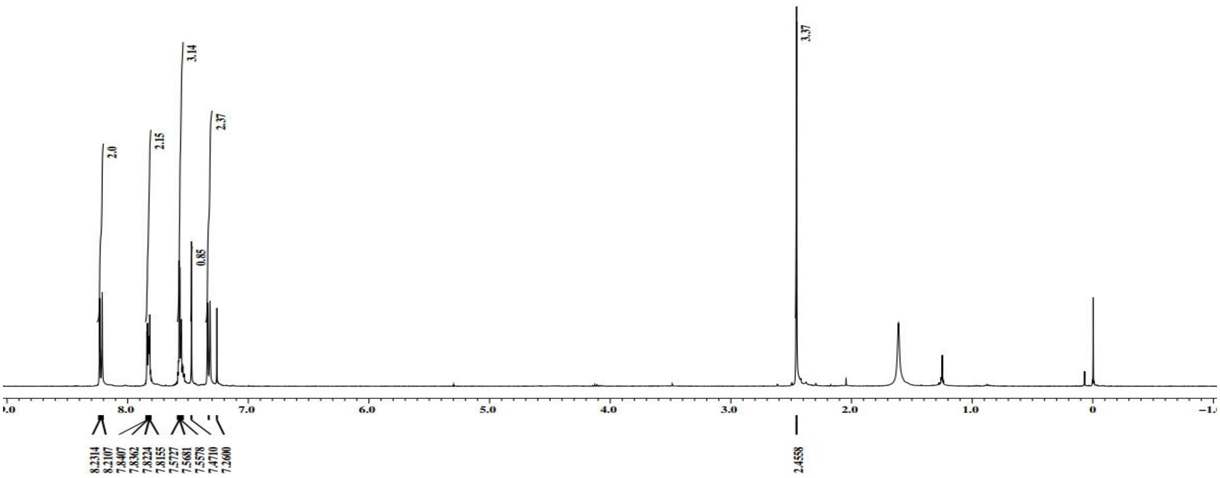

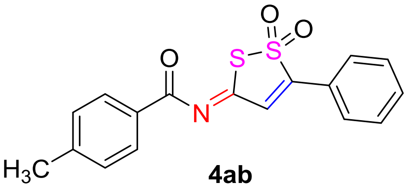

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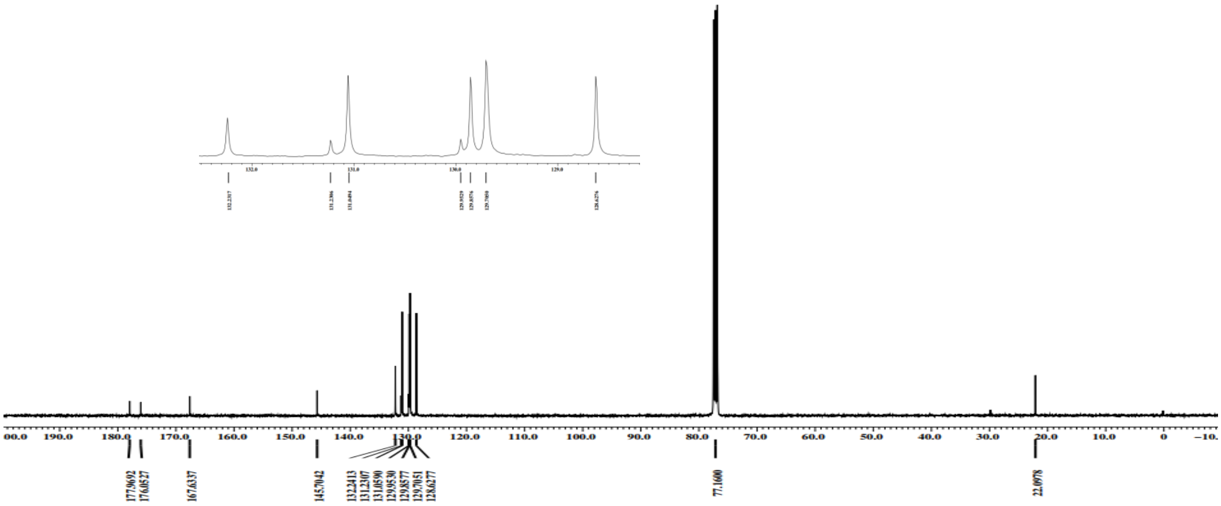

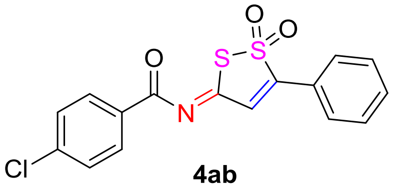

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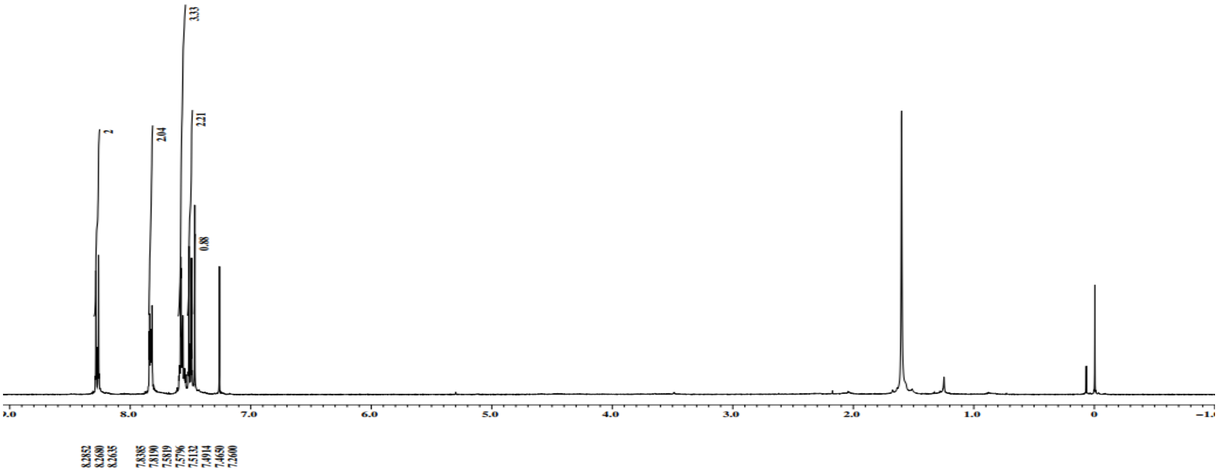

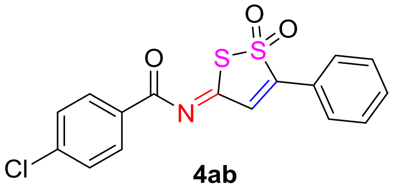

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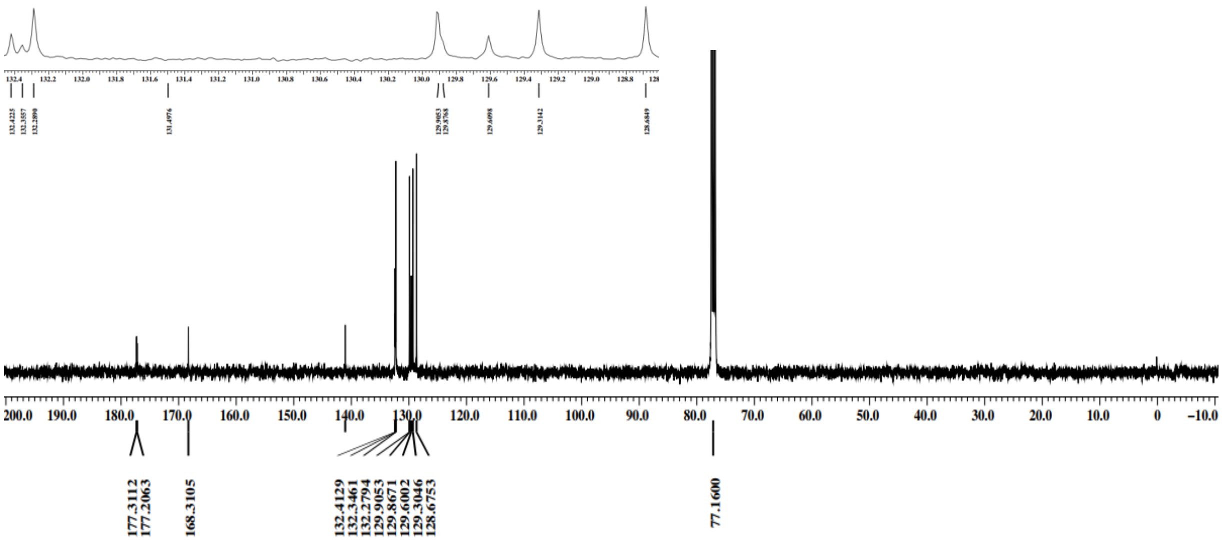

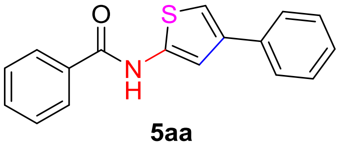

5aa

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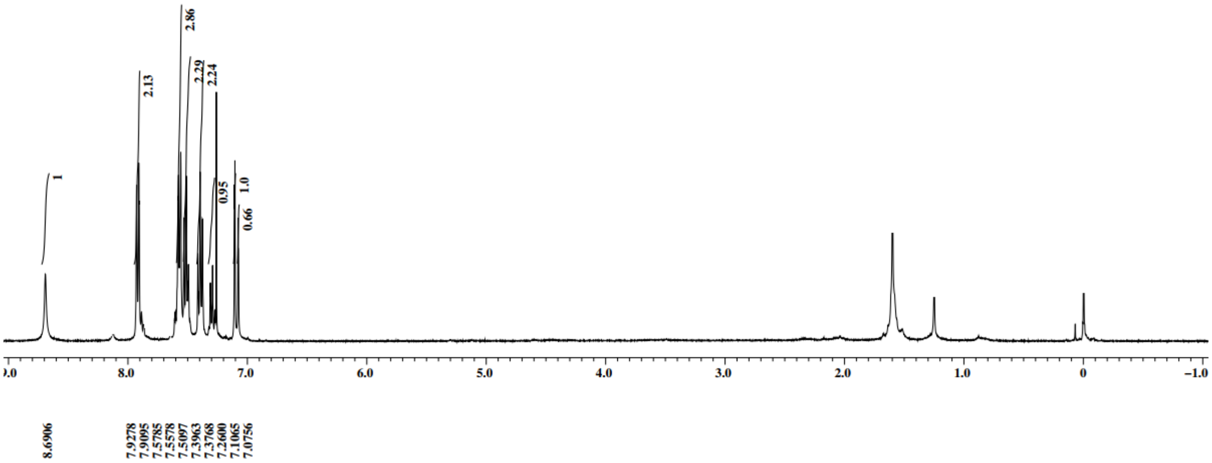

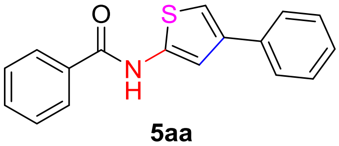

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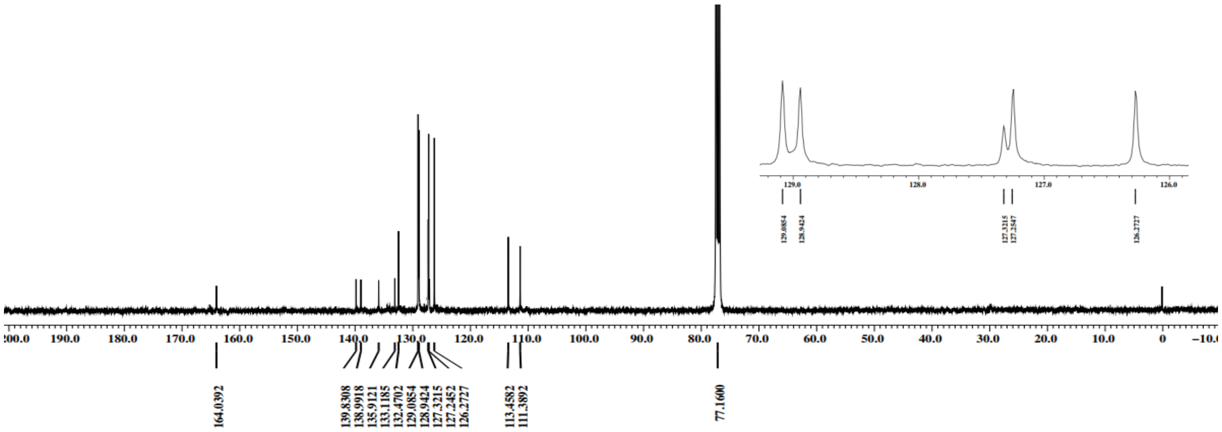

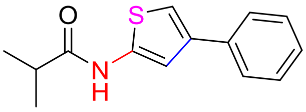

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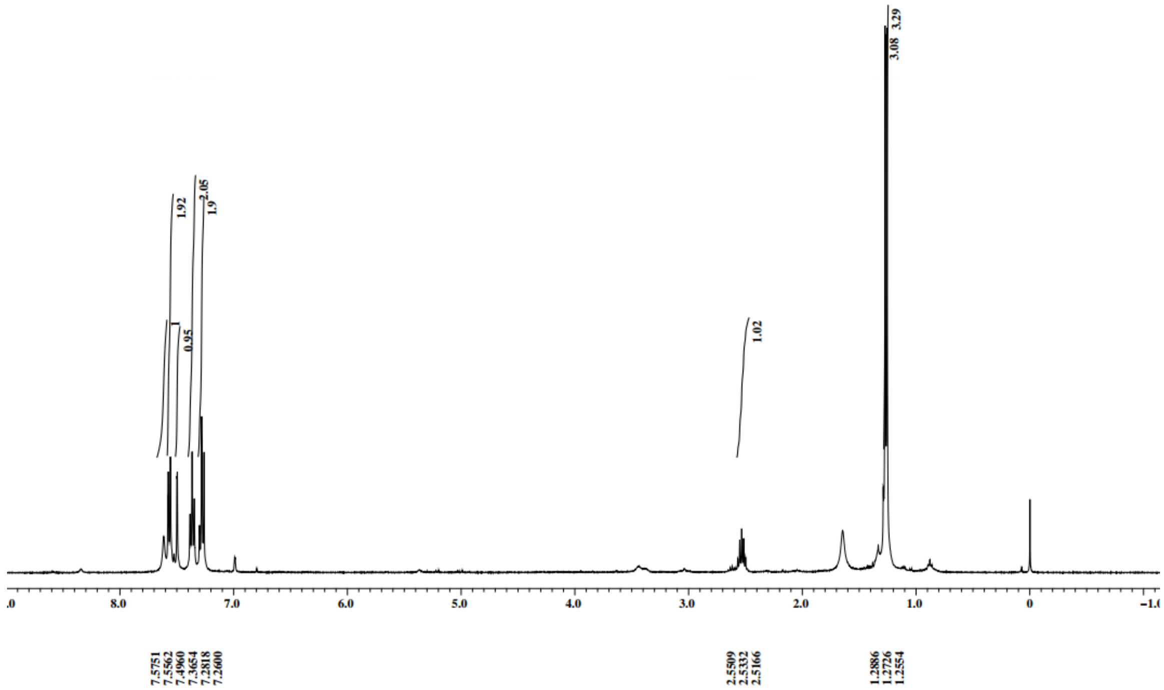

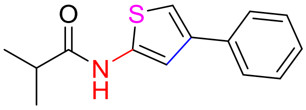

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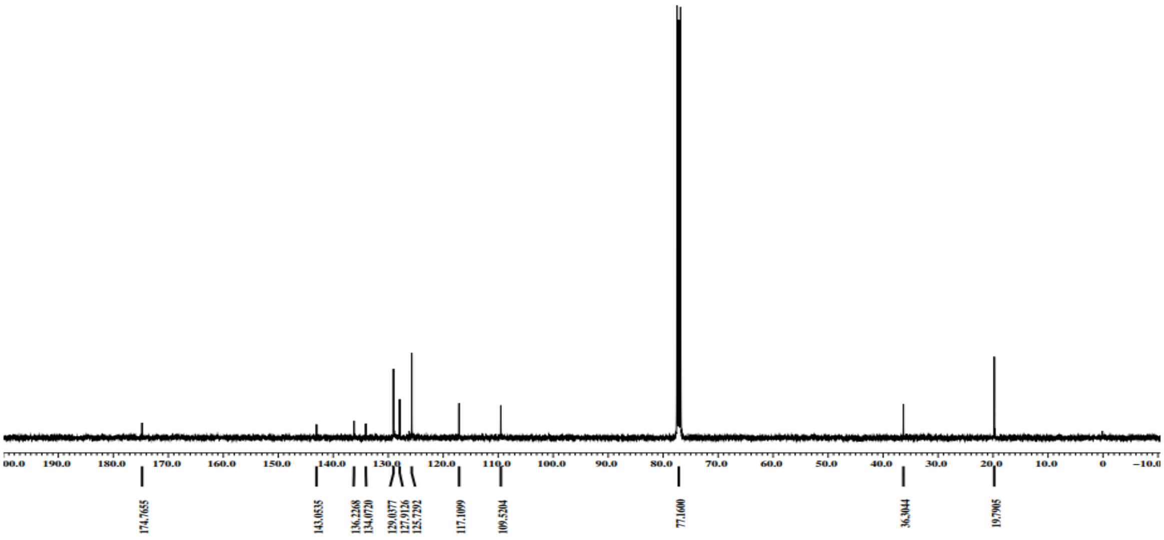

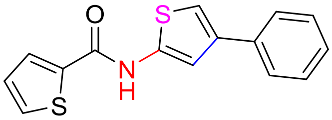

5am

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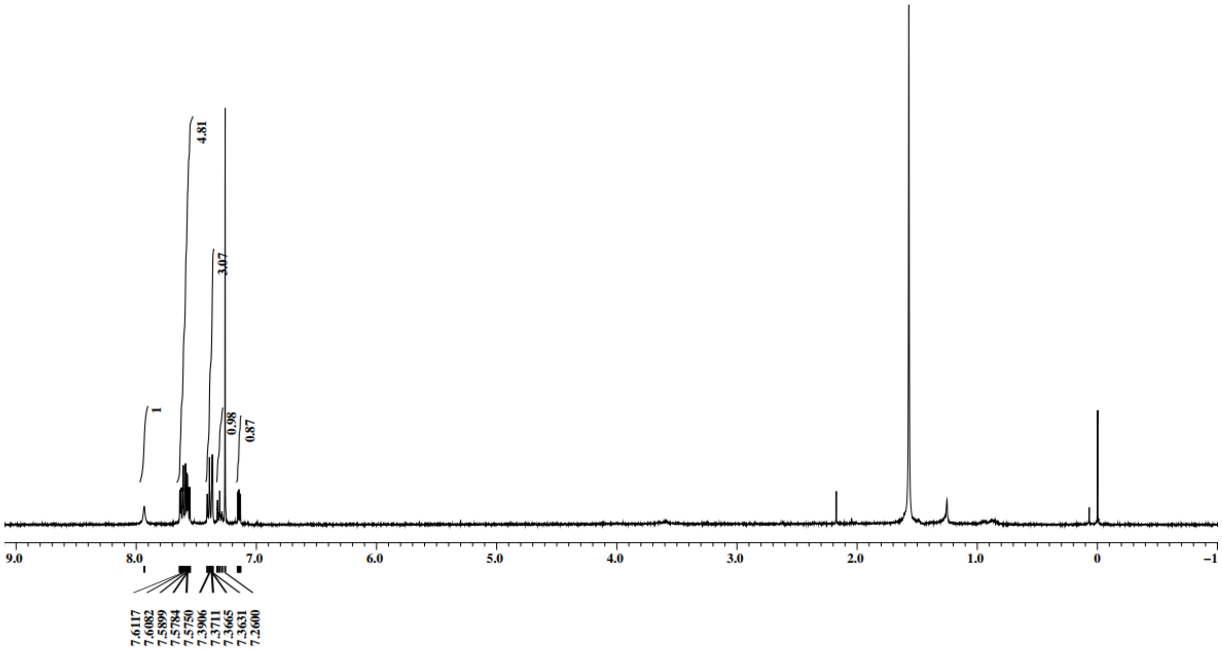

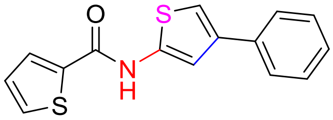

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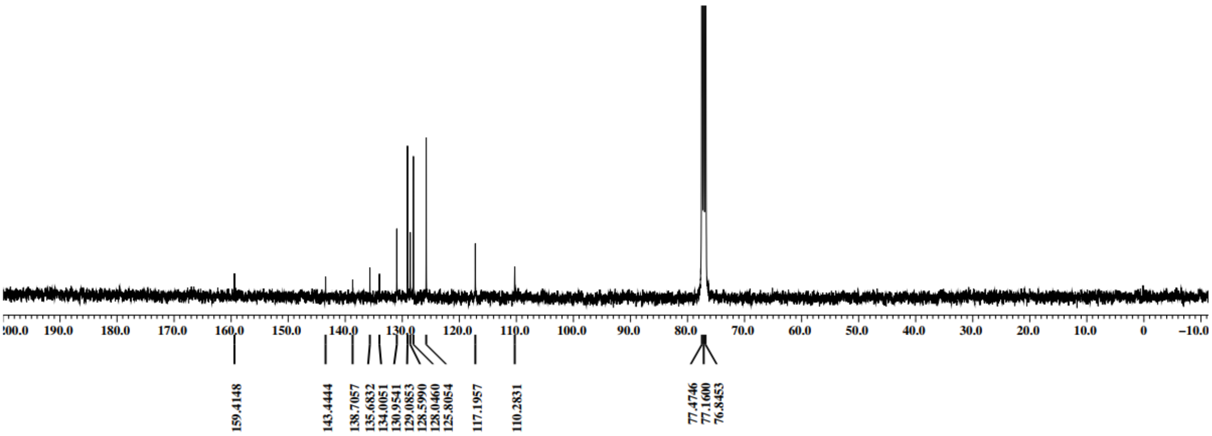

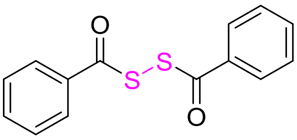

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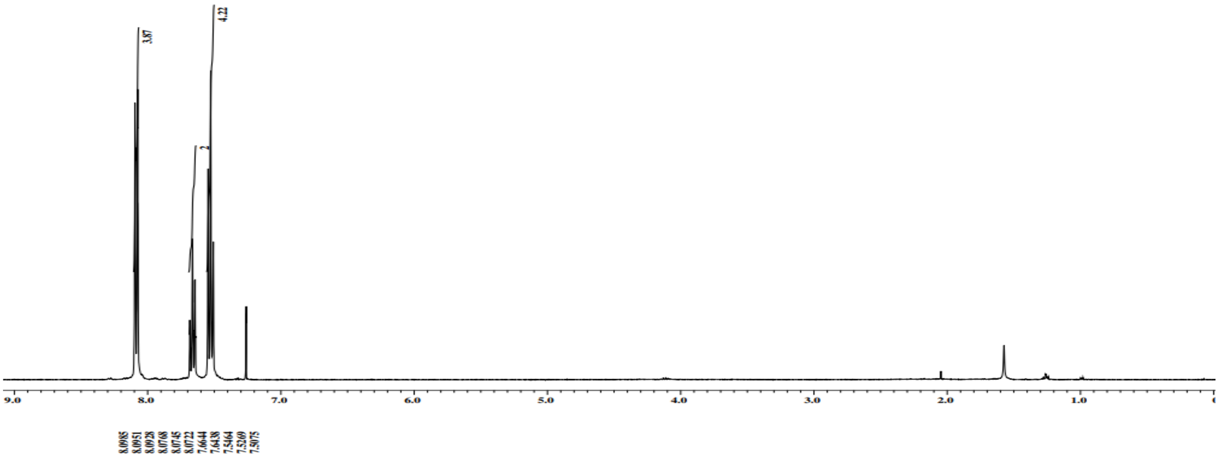

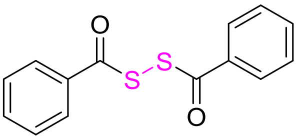

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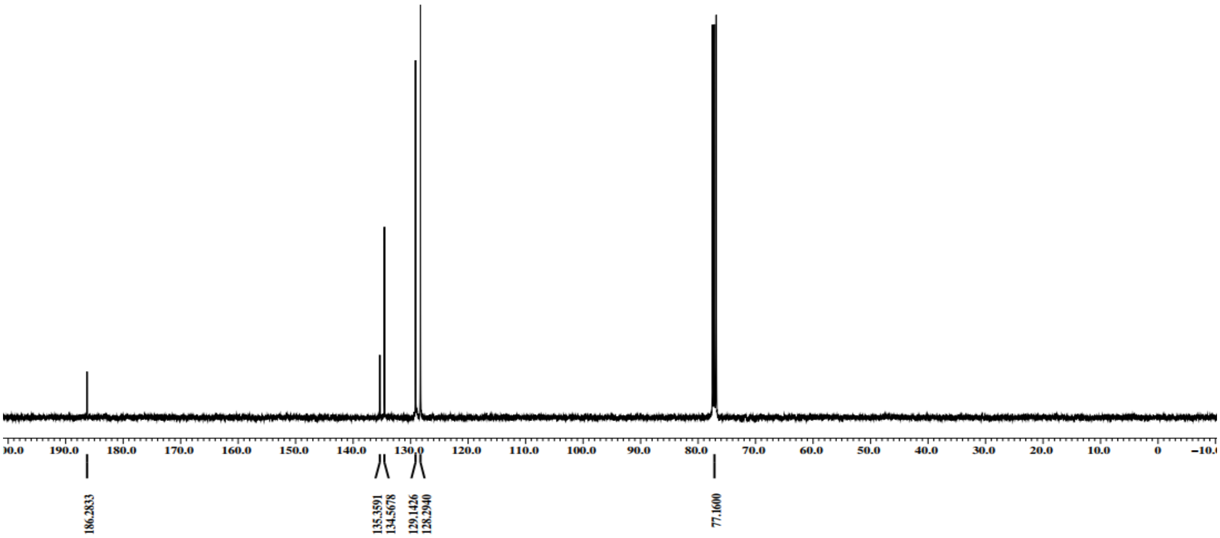

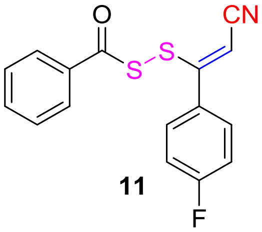

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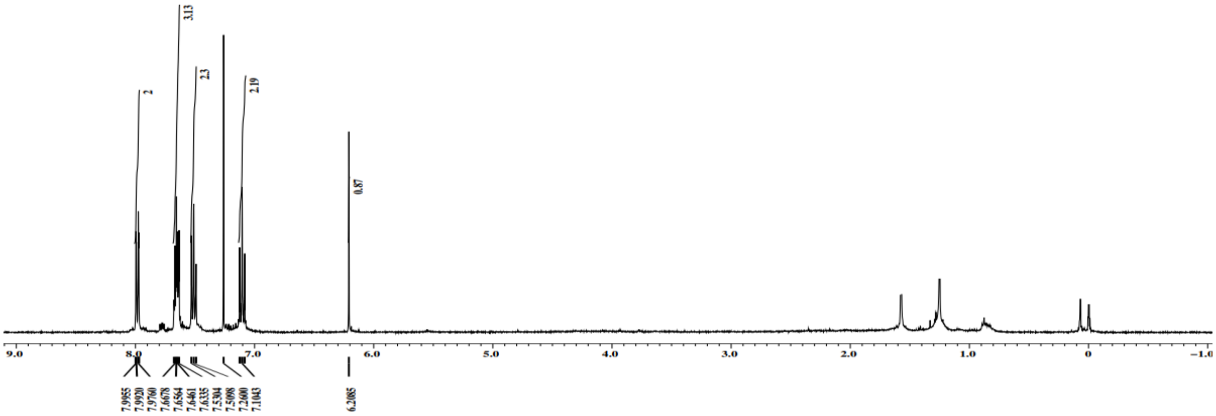

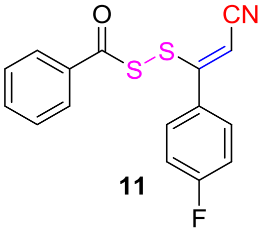

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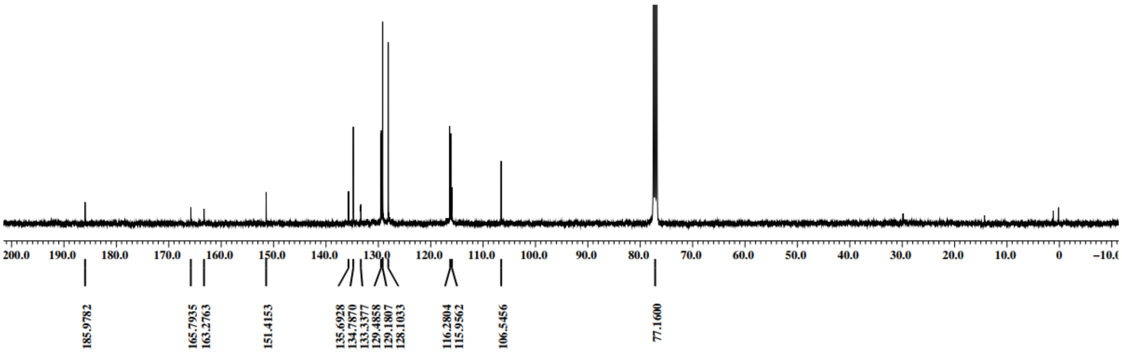


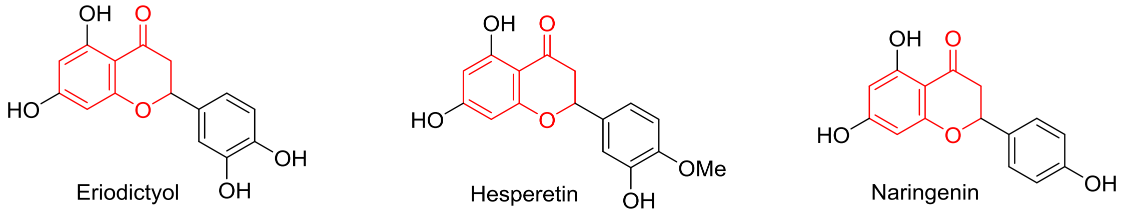
CHAPTER 5

Tetra Substituted Chromanone Synthesis via a Tandem Michael/oxa-Michael Addition Between 2-Hydroxyacetophenones and Alkynenitriles

Chapter 5: Tetra Substituted Chromanone Synthesis via a Tandem Michael/oxa-Michael Addition Between 2-Hydroxyacetophenones and Alkynenitriles

5.1 Introduction

After successfully developing straightforward routes to five membered N, O and S containing heterocycles utilizing bifunctional alkynenitriles, we paid our attention to further exploit these bifunctional substrates to develop a protocol to synthesize six membered heterocycles. Polyfunctionalized Chroman-4-ones are widespread oxygen-based heterocycles with numerous applications in the medicinal chemistry. They have been identified as an active core in many biologically active natural products and pharmaceuticals and are of great interest to organic chemists owing to their diverse biological activities (Figure 5.1.1).[1] As a consequence, numerous elegant synthetic strategies have been developed to build up their fundamental cores.


Eriodictyol Hesperetin Naringenin

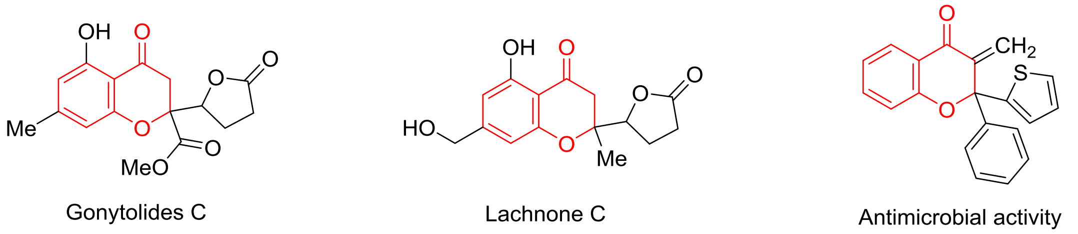
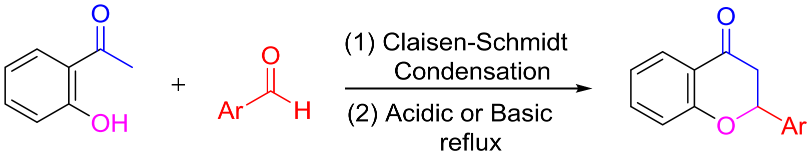

Gonytolides C Lachnone C Antimicrobial activity

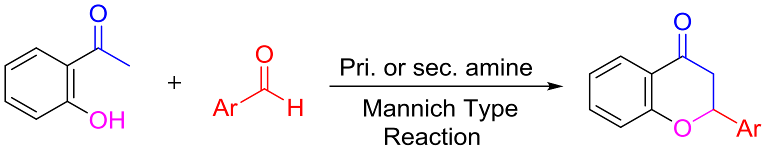
Figure 5.1.1 Representative natural products and biologically active chromanones.

Traditionally, this family of compounds is accessed employing either the Claisen-Schmidt condensation[2] or Mannich reaction[3] of 2-hydroxyacetophenones and benzaldehydes, intramolecular oxa-Michael reaction of alkylidene *β*-ketoesters or 2-

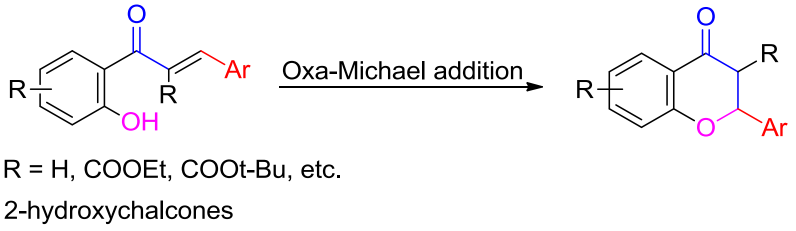
hydroxychalcones,[4] or 1,4-conjugate addition to the electrophilic *β*-sites of chromones[5] (Schemes 5.1.1-5.1.4).



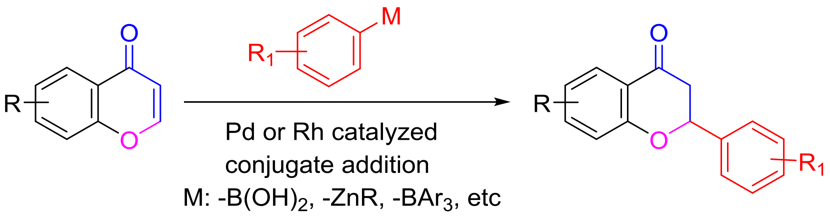
Scheme 5.1.1 The Claisen-Schmidt condensation of 2-hydroxyacetophenones and benzaldehydes.



Scheme 5.1.2 Mannich type reaction of 2-hydroxyacetophenones and benzaldehydes.

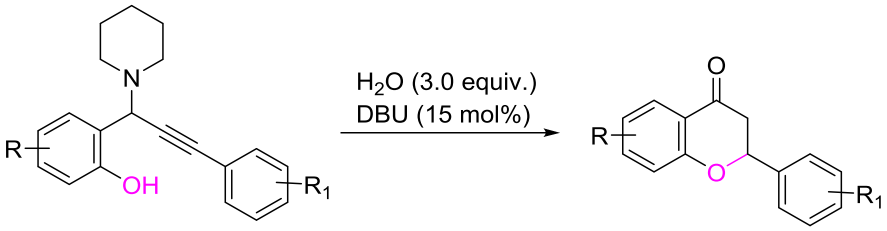


Scheme 5.1.3 Intramolecular oxa-Michael reaction of alkylidene *β*-ketoesters or 2-hydroxychalcones.



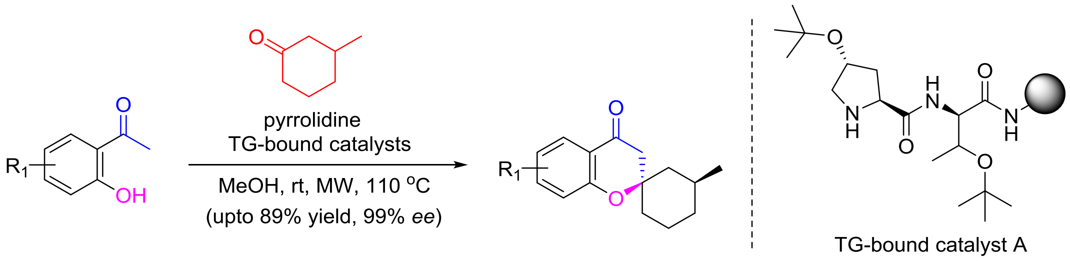
Scheme 5.1.4 1,4-conjugate addition to the electrophilic *β*-sites of chromones.

Recently, Kwong *et al.* in 2020, described the synthesis of chroman-4-one derivatives via one-pot cascade reaction of water with propargylamines catalyzed by organic base DBU.[6] This protocol gives access to a wide range of chroman-4-ones in good to excellent yields showing good functional group compatibility (Scheme 5.1.5).



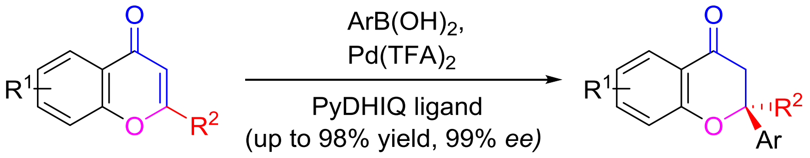
Scheme 5.1.5 DBU-catalyzed cascade reaction of propargylamines with water.

While most reports described ways to synthesize C2 trisubstituted 4-chromanone cores, examples of the tetrasubstituted 4-chromanones remain few. Kurth *et al*., in 2008, reported the synthesis of resin-bound asymmetric pyrrolidine catalysts toward the synthesis of chiral tetrasubstituted spirocyclic chromanones via aldol/oxa-Michael tandem reactions (Scheme 5.1.6).[7]



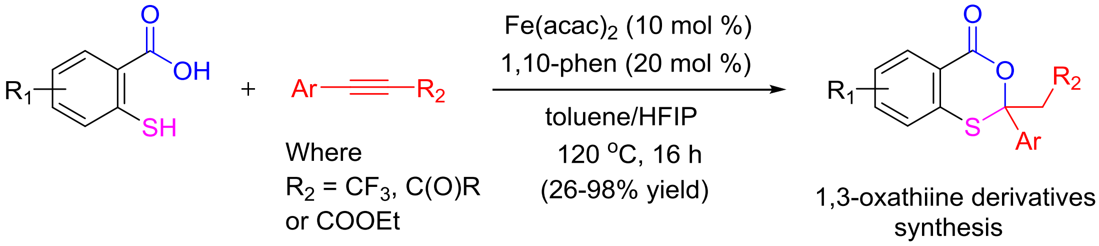
Scheme 5.1.6 Resin-bound asymmetric pyrrolidine catalyzed synthesis of chiral tetrasubstituted spirocyclic chromanones.

Thereafter, the Stoltz group,[8] the Stanley group,[9] and then recently the Stoltz and Hong group[5a] synthesized the chiral C2-tetrasubstituted chromanones from 2-substituted chromones via Pd-catalyzed asymmetric conjugate addition reactions (Scheme 5.1.7). Apparently, the most of strategies rely on already predecorated or inbuilt chroman-core-containing substrates.



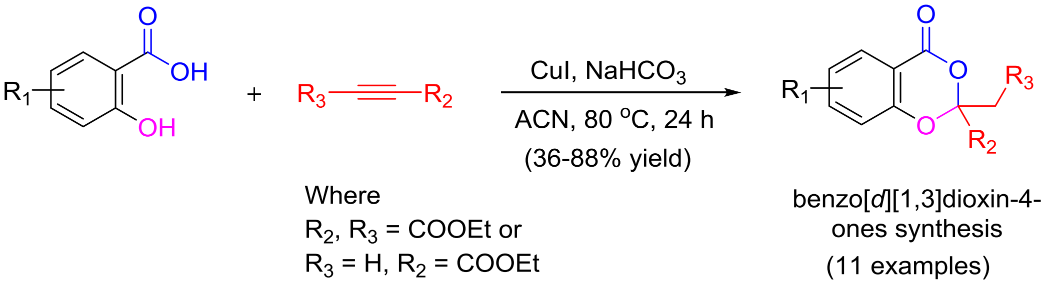
Scheme 5.1.7 Pd-catalyzed synthesis of chiral C2-tetrasubstituted chromanones from 2-substituted chromones.

Recently, the Kawatsura group demonstrated the Fe-catalyzed synthesis of 1,3-oxathiine derivatives from internal alkynes and thiosalicylic acid derivatives by intermolecular hydrothiolation and sequential intramolecular cyclization (Scheme 5.1.8).[10]



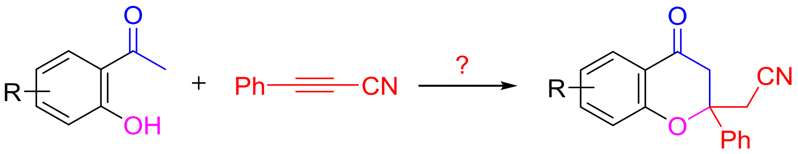
Scheme 5.1.8 Fe-catalyzed synthesis of 1,3-oxathiine derivatives from internal alkynes and thiosalicylic acids.

Furthermore, the Babu group documented CuI and $NaHCO_3$-mediated synthesis of benzo[*d*][1,3]dioxin-4-ones from salicylic acid and acetylenic esters in acetonitrile (Scheme 5.1.9).[11]



Scheme 5.1.9 CuI and $NaHCO_3$-mediated synthesis of benzo[*d*][1,3]dioxin-4-ones from salicylic acid and acetylenic esters.

Literature studies show that the potential of the same approach to deliver 4-chromanones bearing tetrasubstituted stereocenters at the C2 position has not yet been realized. These reports envisioned that 2-hydroxyacetophenones could be potential candidates to react with alkynenitriles to build a 4-chromanone core (Scheme 5.1.10).



Scheme 5.1.10 Proposed reaction 2-hydroxyacetophenones reaction with alkynenitriles to generate a 4-chromanone core.

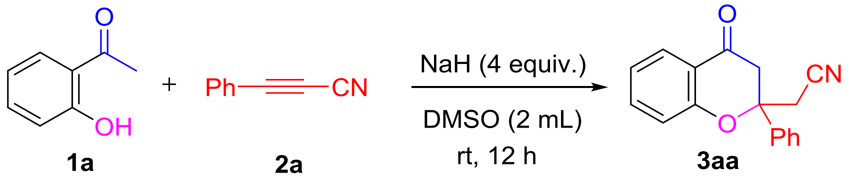
Remarkably, to the best of our knowledge, 4-chromanone synthesis via double Michael additions on alkynenitriles has not been reported.

5.2 Results and Discussion

Thus, we thought of synthesizing tetrasubstituted 4-chromanones derivatives by one-pot double hydrofunctionalization of alkynenitriles with 2-hydroxyaceophenones through the intermolecular Michael addition and sequential intramolecular cyclization via oxa-Michael addition reaction.

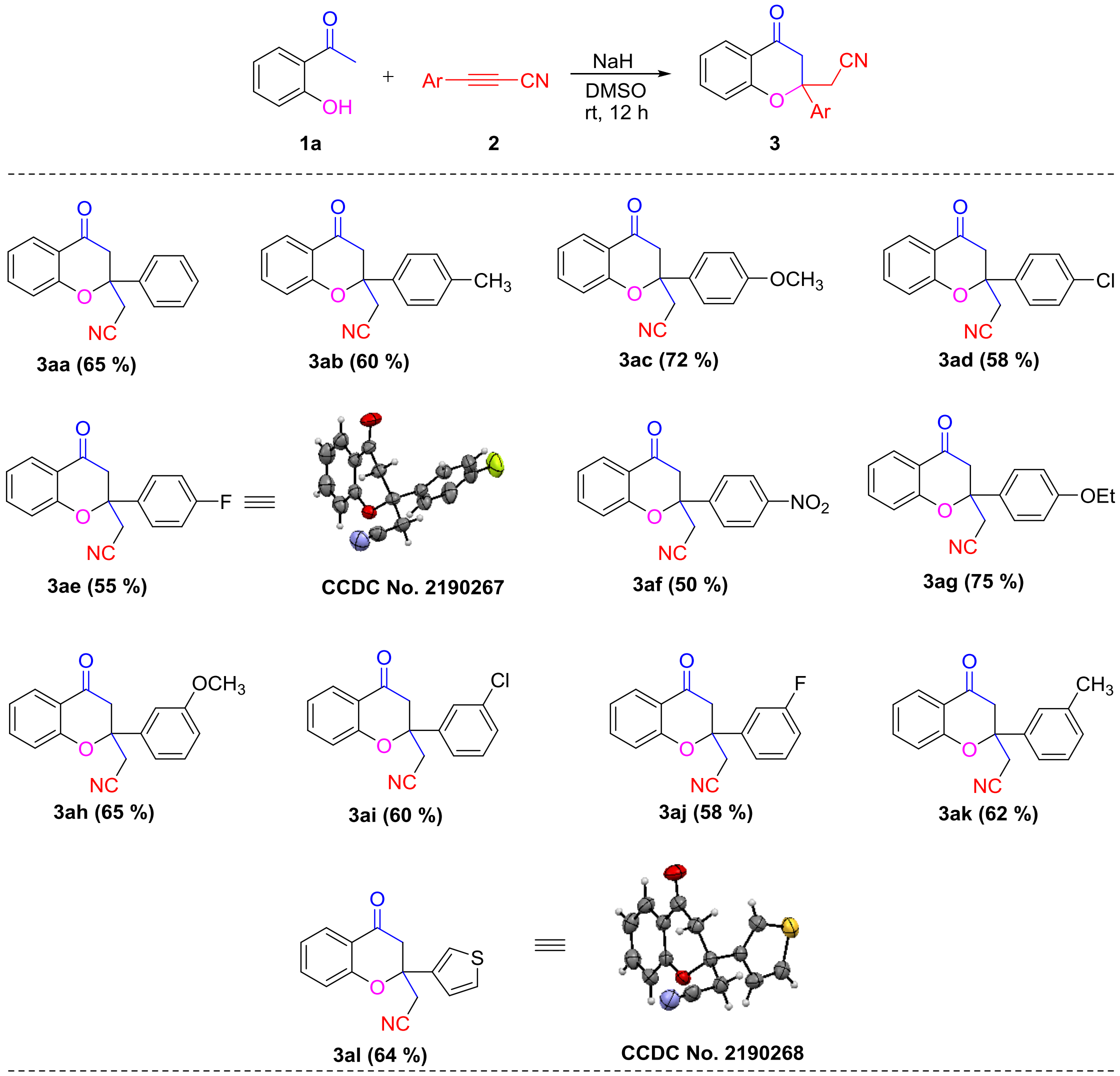
Taking a lead from Babu's work, we began our studies by exploring the reaction of phenylacetylenenitrile **1a** with 2-hydroxyacetophenone **2a** using CuI/$NaHCO_3$ in ACN solvent at 80 °C. Performing the reaction under the Babu group's reaction conditions was found to be ineffective; however, using DMSO in place of ACN provided inferior result (Table 5.2.1, entries 2-3). Then, various base-solvent combinations were tried. Among the wide range of bases, NaH in DMSO solvent showed the best reactivity, providing the desired chroman-4-one **3aa** in 40% yield in 2 h (Table 5.2.1, entry 4). The excess NaH and longer reaction time improved the isolated yield to 65% (Table 5.2.1, entries 1 and 5). Performing the reaction at a high temperature decreased the yield (Table 5.2.1, entry 6). Other solvents reduced the product yield dramatically (Table 5.2.1, entries 7-8). Organic bases such as pyridine, Et_3N, DBU, DBN, and DABCO didn't afford the desired product (Table 5.2.1, entry 9). Instead, they produced either a major byproduct 5-(2-hydroxyphenyl)-5-oxo-3-phenylpent-2-enenitrile or 3-(2-acetylphenoxy)-3-phenylacrylonitrile or a mixture of both. Out of inorganic bases, K_2CO_3, $NaHCO_3$, NaHMDS, NaOEt and LDA also showed the same results (Table 5.2.1, entry 10), whereas, bases t-BuOK and Cs_2CO_3 yielded the expected product **3aa**, albeit in low conversion (Table 5.2.1, entry 11). The use of Lewis acids and additives like $BF_3.Et_2O$, $FeCl_3$, AgOTf, CuI, and CuBr did not improve the outcome (Table 5.2.1, entries 12-13).

Table 5.2.1 Optimization of reaction conditions.[a]



Entry	Variation of the standard conditions	Yield[b](%) (3aa)
1	**none**	**65**
2	$NaHCO_3$ (2 equiv.) + CuI (1 equiv.) in ACN solvent	traces
3	$NaHCO_3$ + CuI (1 equiv.) instead of NaH	<10
4	Reaction time 2 h instead of 12 h	40
5	NaH (2 equiv.)	54
6	at 70 or 100 °C	<20
7	DMF instead of DMSO	48
8	THF, ACN, DME, DCE or PhMe	<25
9	Pyr, Et_3N, DBU, DBN, DMAP or DABCO	0
10	K_2CO_3, $NaHCO_3$, NaOEt, NaHMDS, or LDA instead of NaH	0
11	t-BuOK or Cs_2CO_3 instead of NaH	<20
12	+ CuI or CuBr (1 equiv.)	nc
13	+ $BF_3{\cdot}Et_2O$, $FeCl_3$ or AgOTf (0.2 euiv)	nc

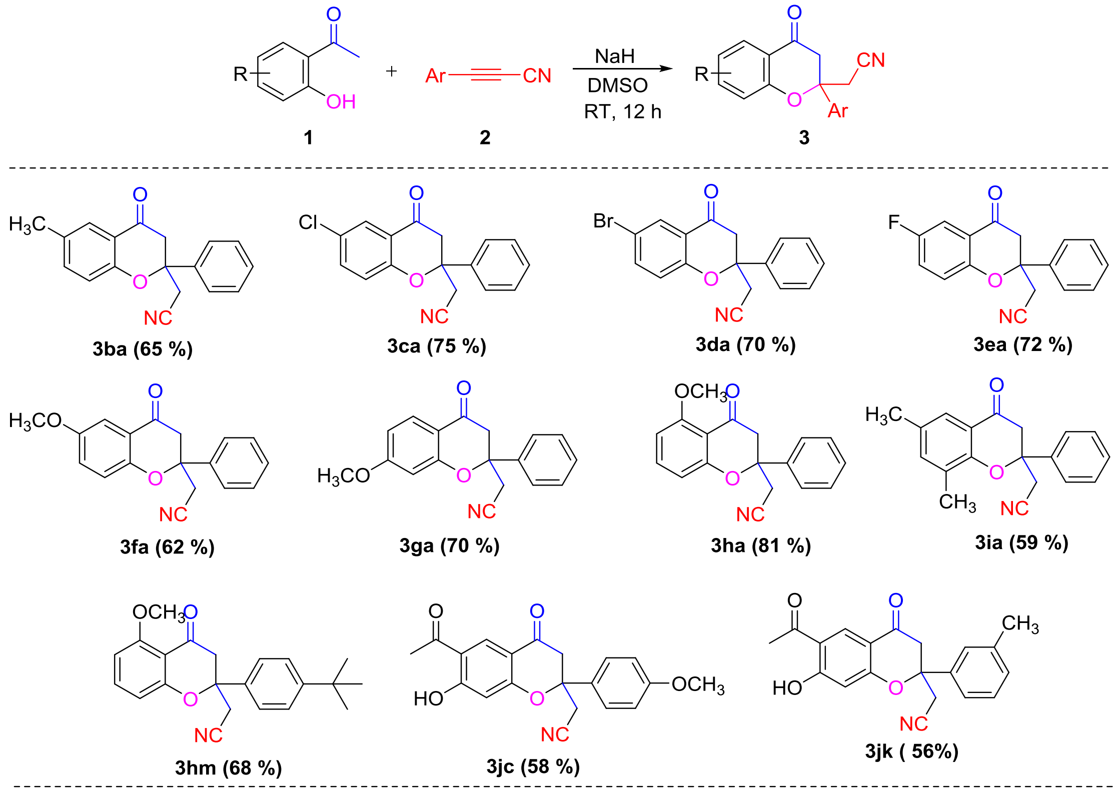
[a] Unless otherwise stated all the reactions were performed under inert conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), NaH (2.0 mmol), rt, 12 h, [b] Isolated yield, nc (no change in the yield of **3aa**).



Reagents and conditions: **1a** (0.5 mmol), **2** (0.6 mmol), NaH (2.0 mmol), rt, 12 h.

Scheme 5.2.1 Synthesis of compounds **3** using various alkynenitriles.

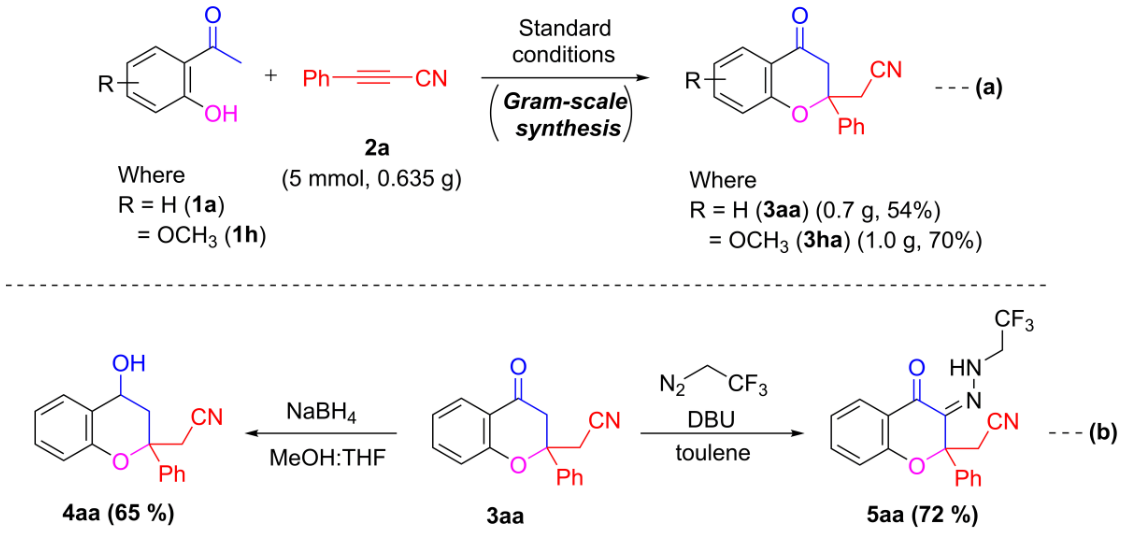
Having established optimal reaction conditions, we examined the substrate scope for the double Michael addition reaction between 2-hydroxyacetophenone **1a** and alkynenitriles **2a-l** with varying electronic character, which afforded the corresponding products **3aa-3al** in moderate to good yields (Scheme 5.2.1). Alkynenitriles with an electron-donating substituent on the aromatic ring showed promising results compared to alkynenitriles with an electron-withdrawing substituent. In addition, alkynenitriles with a heteroaryl group (**3al**) also worked well with 64% yield. However, aliphatic alkynenitriles were ineffective in giving the desired product.



Reagents and conditions: **1** (0.5 mmol), **2** (0.6 mmol), NaH (2.0 mmol), rt, 12 h.

Scheme 5.2.2 Synthesis of compounds **3** using various 2-hydroxyacetophenones.

To further demonstrate the versatility of this approach, a diverse array of 2-hydroxyacetophenones **1a-j** possessing electron-donating or electron-withdrawing groups (methyl, methoxy, bromo, chloro, fluoro, nitro, OH, and acyl groups) at different positions of the aromatic ring, were coupled with phenylacetylenenitrile **2a**. This provided the desired products in moderate to good yields, as shown in Scheme 5.2.2. Interestingly, hydroxyl-bearing substrate **1j** provided the desired products without needing a protection-deprotection strategy, albeit only moderate gains were achieved (**3jc** and **3jk**).



Scheme 5.2.3 Follow up chemistry.

After the successful synthesis of chroman-4-one derivatives, we turned to explore their synthetic potential. Encouragingly, a gram scale reaction produces 0.7 g of **3aa** and 1.0 g of **3ha** with 54% and 70% yields, respectively, when synthesized at a five mmol scale under optimized reaction conditions (Scheme 5.2.3a). Also, **3aa** on reduction with $NaBH_4$ led to 2-(4-hydroxy-2-phenylchroman-2-yl)acetonitrile **4aa** in 65% yield and **3aa** resulted in 72% of 2-(4-oxo-2-phenyl-3-(2-(2,2,2 trifluoroethyl)hydrazono)chroman-2-yl)acetonitrile **5aa** when treated with 2,2,2-Trifluorodiazoethane (Scheme 5.2.3b).

5.3 Conclusions

In conclusion, we have demonstrated a tandem NaH-mediated Michael/intramolecular oxo-Michael addition process to synthesize C2, tetrasubstituted chroman-4-ones from readily accessible starting materials under mild reaction reactions. The transition metal-free, gentle, and operationally simple strategy presented herein using NaH in DMSO for synthesizing tetrasubstituted chroman-4-ones is likely to find potential applications. Studies to expand the scope of this tandem double Michael addition approach to encompass 2-thiol/amino substituted acetophenones are ongoing in our laboratory.

5.4 Experimental section

Reactions were performed in flame-dried glassware under a N_2 atmosphere unless otherwise stated. Solvents used were dried and purified by following standard procedures. Chemicals and reagents were purchased from commercial suppliers and used without further purification. Thin-layer chromatography was performed on Merck precoated silica gel 60 F254 aluminum sheets with detection under UV light at 254 nm. Column chromatography was performed using E. Merck silica gel 60 (100-200 mesh). NMR spectra were recorded in $CDCl_3$, at operating frequencies of 400 MHz (^1H) or 100 MHz (^{13}C) or 376 MHz (^{19}F), on JEOL JNM ECS-400 instrument as indicated in the individual spectrum. Chemical shifts (δ) are given in ppm relative to residual solvent (chloroform, δ = 7.26 for ^1H NMR and 77.16 for proton decoupled ^{13}C NMR) and coupling constants (*J*) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, brs for broad singlet, t for triplet, q for quartet and m for multiplet. The HRMS data was recorded on XEVO G2-XS QTOF. Melting points were taken on Stuart digital melting point apparatus. All the X-ray data were recorded on Bruker D8 venture instrument. All the alkynenitriles used are known compounds and were synthesized according to the reported literature procedure without any modification.[12]

5.4.1 General procedure for the synthesis of chroman-4-ones (3)

In a dried Schlenk flask equipped with a stir bar, a mixture of NaH (4 equiv.) (washed 3 times with dry hexane), alkynenitrile **2** (0.55 mmol) and 2-hydroxyacetophenone **1** (0.5 mmol), and 1 mL of DMSO was stirred for 12 h. After the reaction (monitored reaction by TLC) was completed, the reaction mixture was quinched by ice cooled water and the product was extracted with ethyl acetate three times and the combined organic layers were dried with anhydrous Na_2SO_4 and evaporated. The crude was further purified through column chromatography over silica gel (100-200 mesh) with EtOAc/hexane (20-30%) to give the desired products **3**.

5.4.2 Procedure for gram scale synthesis of 3aa and 3ha

In a dried Schlenk flask equipped with a stir bar, a mixture of phenylacetylenenitrile **2a** (0.635 g, 5.0 mmol, 1 equiv.), 2-hydroxyacetophenone **1a** (1.32 mL, 4.5 mmol, 0.9 equiv.) or 1-(2-hydroxy-6-methoxyphenyl)ethan-1-one **1h** (0.747 g, 4.5 mmol, 0.9 equiv.) and NaH (0.800 g, 20.0 mmol, 4 equiv.), and 10 mL of DMSO was stirred for 12 h. After the reaction (monitored reaction by TLC) was completed, the reaction mixture was quinched by ice cooled water and the product was extracted with ethyl acetate three times and the combined organic layers were dried with anhydrous Na_2SO_4 and evaporated under vacuum. The crude was further purified through column chromatography over silica gel (100-200 mesh) with EtOAc/hexane (20-30%) to give the desired products **3aa** (0.7 g, yield 54%) or **3ha** (1.0 g, yield 70%), respectively.

5.4.3 Procedure for the synthesis of 2-(4-hydroxy-2-phenylchroman-2-yl)acetonitrile (4aa)

In an oven-dried Schlenk round bottom flask equipped with a stir bar, **3aa** (65.8 mg, 0.25 mmol) in MeOH:THF (4:1) 1 mL, at 0 ^{o}C (ice bath), $NaBH_4$ (11.8 mg, 0.3125 mmol) was added and allowed to stirr for 30 minutes at room temperature. After completion of the reaction detected by TLC, the product was extracted with ethyl acetate three times and the combined organic layers were dried with anhydrous Na_2SO_4 and evaporated under vacuum. The crude was further purified through column chromatography over silica gel (100-200 mesh) with EtOAc/hexane (20-30%) to give the desired products **4aa** (43 mg, 65% yield).

5.4.4 Procedure for the synthesis of 2-(4-oxo-2-phenyl-3-(2-(2,2,2-trifluoroethyl)hydrazono)chroman-2-yl)acetonitrile (5aa)

In an oven-dried Schlenk round bottom flask equipped with a stir bar, a mixture of chroman-4-one **3aa** (65.8 mg, 0.25 mmol) and freshly prepared solution of 2,2,2-Trifluorodiazoethane in toluene (0.25 mmol) and DBU (2 mmol) under N_2 atmosphere was stirred for 12 h. After completion of the reaction detected by TLC, reaction mixture was concentrated under reduced pressure and purified by column chromatography and the desired compound was eluted at 15-20% ethyl acetate in hexane to get 2-(4-oxo-2-

phenyl-3-(2-(2,2,2-trifluoroethyl)hydrazono)chroman-2-yl)acetonitrile **5aa** (48 mg, 72% yield).

5.4.5 Characterization data of products

2-(4-oxo-2-phenylchroman-2-yl)acetonitrile (3aa): Light brown crystalline solid (89 mg, 65%); mp 108-109 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.73 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.54-7.49 (m, 1H), 7.44-7.39 (m, 2H), 7.35-7.27 (m, 3H), 7.14 (d, *J* = 8.3 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 3.47 (d, *J* = 16.5 Hz, 1H), 3.38 (d, *J* = 16.5 Hz, 1H), 3.09 (d, *J* = 16.8 Hz, 1H), 2.99 (d, *J* = 16.7 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 189.5, 158.9, 138.2, 136.8, 129.3, 129.2, 126.9, 125.8, 122.2, 121.1, 118.4, 115.5, 81.2, 45.2, 32.97; HRMS: *m*/*z* calculated for $C_{17}H_{14}NO_2$ [M+H]$^+$: 264.1025, found 264.1025

2-(4-oxo-2-(p-tolyl)chroman-2-yl)acetonitrile (3ab): White solid (83 mg, 60%); mp 112-113 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.73 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.53-7.48 (m, 1H), 7.30-7.27 (m, 2H), 7.14-7.11 (m, 3H), 6.99-6.96 (m, 1H), 3.45 (d, *J* = 16.0 Hz, 1H), 3.36 (d, *J* = 16.4 Hz, 1H), 3.08 (d, *J* = 16.8 Hz, 1H), 2.96 (d, *J* = 16.9 Hz, 1H), 2.27 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 189.6, 158.98, 139.2, 136.7, 135.2, 129.99, 126.9, 125.8, 122.2, 121.2, 118.5, 115.6, 81.2, 45.3, 33.1, 21.2; HRMS: *m*/*z* calculated for $C_{18}H_{16}NO_2$ [M+H]$^+$: 278.1181, found 278.1181

2-(2-(4-methoxyphenyl)-4-oxochroman-2-yl)acetonitrile (3ac): Very dense pale yellow liquid (109 mg, 72%); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.74 (dd, *J* = 7.8, 1.9 Hz, 1H), 7.52-7.48 (m, 1H), 7.35-7.31 (m, 2H), 7.11 (d, *J* = 8.4 Hz, 1H), 6.99-6.95 (m, 1H), 6.84-6.80 (m, 2H), 3.74 (S, 3H), 3.44 (d, *J* = 16.2 Hz, 1H), 3.34 (d, *J* = 16.3 Hz, 1H), 3.08 (d, *J* = 16.8 Hz, 1H), 2.96 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 189.73, 160.03, 158.9, 136.7, 129.9, 127.3, 126.8, 122.2, 121.2, 118.4, 115.7, 114.6, 81.0, 55.4, 45.2, 33.3; HRMS: *m*/*z* calculated for $C_{18}H_{16}NO_3$ [M+H]$^+$: 294.1130, found 294.1120

2-(2-(4-chlorophenyl)-4-oxochroman-2-yl)acetonitrile (3ad): White solid (86 mg, 58%); mp 110-111 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.75 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.55-7.50 (m, 1H), 7.38-7.35 (m, 2H), 7.33-7.29 (m, 2H), 7.15-7.12 (m, 1H), 7.03-6.99 (m, 1H), 3.43 (d, *J* = 16.5 Hz, 1H), 3.36 (d, *J* = 16.2 Hz, 1H), 3.07 (d, *J* = 16.8 Hz, 1H), 2.99 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1, 158.6, 136.9, 136.8, 135.5, 129.6, 127.4, 127.0, 122.5, 121.1, 118.4, 115.2, 80.9, 45.3, 32.9; HRMS: *m/z* calculated for $C_{17}H_{13}NO_2Cl$ $[M+H]^+$: 298.0635, found 298.0635

2-(2-(4-fluorophenyl)-4-oxochroman-2-yl)acetonitrile (3ae): Light yellow crystalline solid (77 mg, 55%); mp 133-134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76-7.72 (m, 1H), 7.54-7.49 (m, 1H), 7.44-7.39 (m, 2H), 7.12 (d, *J* = 8.45 Hz, 1H), 7.04-6.97 (m, 3H), 3.44 (d, *J* = 16.4 Hz, 1H), 3.36 (d, *J* = 16.5 Hz, 1H), 3.08 (d, *J* = 16.9 Hz, 1H), 2.99 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.2, 162.9 (d, *J* = 250.0 Hz), 158.6, 138.9, 134.0 (d, *J* = 3.5 Hz), 127.9 (d, *J* = 8.6 Hz), 126.9, 122.4, 121.1, 118.4, 116.4 (d, *J* = 22.0 Hz), 115.5, 80.8, 45.3, 33.0; HRMS: *m/z* calculated for $C_{17}H_{13}NO_2F$ $[M+H]^+$: 282.0930, found 282.0930

2-(2-(4-nitrophenyl)-4-oxochroman-2-yl)acetonitrile (3af): Light brown solid (77 mg, 50%); mp 140-141 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.22-8.15 (m, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.23-7.22 (m, 1H), 7.07-7.00 (m, 1H), 3.59-3.43 (m, 4H); ^{13}C NMR (376 MHz, DMSO-d_6): δ 189.3, 158.2, 147.6, 146.1, 137.2, 127.7, 126.2, 123.9, 122.4, 120.7, 118.4, 116.5, 81.3, 45.1, 30.5; HRMS: *m/z* calculated for $C_{17}H_{13}N_2O_4$ $[M+H]^+$: 309.0875, found 309.0872

2-(2-(4-ethoxyphenyl)-4-oxochroman-2-yl)acetonitrile (3ag): Brownish white solid (115 mg, 75%); mp 83-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.51-7.47 (m, 1H), 7.33-7.29 (m, 2H), 7.10 (d, *J* = 7.9 Hz, 1H), 6.10-6.95 (m, 1H), 6.82-6.78 (m, 2H), 3.95 (q, *J* = 7.1 Hz, 2H), 3.44 (d, *J* = 16.5 Hz, 1H), 3.34 (d, *J* = 16.1 Hz, 1H), 3.08 (d, *J* = 16.5 Hz, 1H), 2.96 (d, *J* = 16.9 Hz, 1H), 1.35 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.8, 159.5, 158.9, 136.7, 129.7, 127.3, 126.9, 122.1, 121.2, 118.4, 115.7, 115.1, 81.1, 63.6, 45.2, 33.3, 14.9; HRMS: *m/z* calculated for $C_{19}H_{18}NO_3$ $[M+H]^+$: 308.1287, found 308.1287

2-(2-(3-methoxyphenyl)-4-oxochroman-2-yl)acetonitrile (3ah): Yellowish white solid (95 mg, 65%); mp 88-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.54-7.49 (m, 1H), 7.28-7.22 (m, 1H), 7.16-7.14 (m, 1H), 7.01-6.95 (m, 3H), 6.82-6.79 (m, 1H), 3.74 (S, 3H), 3.45 (d, *J* = 16.5 Hz, 1H), 3.37 (d, *J* = 16.2 Hz, 1H), 3.11 (d, *J* = 16.9 Hz, 1H), 2.99 (d, *J* = 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.5, 160.1, 158.9, 139.8, 136.7, 130.3, 126.8, 122.2, 121.0, 118.3, 118.1, 115.6, 114.1, 112.1, 81.0, 55.3, 45.2, 32.8; HRMS: *m/z* calculated for $C_{18}H_{16}NO_3$ $[M+H]^+$: 294.1130, found 294.1129

2-(2-(3-chlorophenyl)-4-oxochroman-2-yl)acetonitrile (3ai): Pale yellow solid (89 mg, 60%); mp 75-76 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.57-7.52 (m, 1H), 7.42-7.41 (m, 1H), 7.31-7.27 (m, 3H), 7.17-7.15 (m, 1H), 7.05-7.01 (m, 1H), 3.42 (d, *J* = 16.4 Hz, 1H), 3.36 (d, *J* = 16.4 Hz, 1H), 3.08 (d, *J* = 16.8 Hz, 1H), 2.99 (d, *J* = 16.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.97, 158.6, 140.5, 137.0, 135.5, 130.6, 129.6, 126.99, 126.1, 124.1, 122.6, 120.98, 118.5, 115.2, 80.7, 45.2, 32.7; HRMS: *m/z* calculated for $C_{17}H_{13}NO_2Cl$ $[M+H]^+$: 298.0635, found 298.0635

2-(2-(3-fluorophenyl)-4-oxochroman-2-yl)acetonitrile (3aj): Yellowish white solid (81 mg, 58%); mp 92-93 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 7.9 Hz, 1H), 7.56-7.52 (m, 1H), 7.35-7.29 (m, 1H), 7.19-7.14 (m, 3H), 7.04-6.97 (m, 2H), 3.43 (d, *J* = 16.5 Hz, 1H), 3.37 (d, *J* = 16.5 Hz, 1H), 3.09 (d, *J* = 16.9 Hz, 1H), 2.99 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0, 163.2 (d, *J* = 247.5 Hz), 158.6, 140.98 (d, *J* = 6.85 Hz), 136.99, 131.08 (d, *J* = 7.95 Hz), 126.98, 122.5, 121.6 (d, *J* = 3.1 Hz), 121.0, 118.4, 116.5 (d, *J* = 21.2 Hz), 115.2, 113.3 (d, *J* = 23.0 Hz), 80.7, 45.3, 32.8; HRMS: *m/z* calculated for $C_{17}H_{13}NO_2F$ $[M+H]^+$: 282.0930, found 282.00930

2-(4-oxo-2-(m-tolyl)chroman-2-yl)acetonitrile (3ak): White solid (85 mg, 62%); mp 98-99 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.54-7.49 (m, 1H), 7.21-7.19 (m, 3H), 7.14 (d, *J* = 8.4 Hz, 1H), 7.11-7.07 (m, 1H), 6.99 (t, *J* = 7.8 Hz, 1H), 3.46 (d, *J* = 16.4 Hz, 1H), 3.37 (d, *J* = 16.4 Hz, 1H), 3.09 (d, *J* = 16.9 Hz, 1H), 2.95 (d, *J* = 16.7 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 159.0, 139.1, 138.3, 136.7, 130.0, 129.2, 126.9, 126.4, 122.98, 122.2, 121.2, 118.5, 115.6, 81.2, 45.3, 33.0, 21.7; HRMS: *m/z* calculated for $C_{18}H_{16}NO_2$ $[M+H]^+$: 278.1181, found 278.1181

2-(4-oxo-2-(thiophen-3-yl)chroman-2-yl)acetonitrile (3al): Brownish white solid (86 mg, 64%); mp 139-140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.52-7.48 (m, 1H), 7.30-7.28 (m, 2H), 7.09-7.06 (m, 2H), 7.02-6.98 (m, 1H), 3.35 (s, 2H), 1.25 (d, *J* = 16.9 Hz, 1H), 1.20 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ

189.5, 158.8, 139.8, 136.7, 127.8, 126.9, 125.2, 124.4, 122.3, 120.8, 118.2, 115.5, 79.5, 45.9, 32.5; HRMS: *m/z* calculated for $C_{15}H_{12}NO_2S$ $[M+H]^+$: 270.0587, found 270.0586

2-(6-methyl-4-oxo-2-phenylchroman-2-yl)acetonitrile (3ba): Light yellow solid (99 mg, 65%); mp 97-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, *J* = 2.1 Hz, 1H), 7.43-7.39 (m, 2H), 7.35-7.29 (m, 4H), 7.03 (d, *J* = 8.42 Hz, 1H), 3.44 (d, *J* = 16.4 Hz, 1H), 3.35 (d, *J* = 16.5 Hz, 1H), 3.08 (d, *J* = 16.9 Hz, 1H), 2.97 (d, *J* = 16.9 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.7, 156.98, 138.4, 137.8, 131.8, 129.3, 129.2, 126.6, 125.9, 120.8, 118.3, 115.6, 81.1, 45.3, 32.99, 20.5; HRMS: *m/z* calculated for $C_{18}H_{16}NO_2$ $[M+H]^+$: 278.1181, found 278.1170

2-(6-chloro-4-oxo-2-phenylchroman-2-yl)acetonitrile (3ca): White solid (91 mg, 75%); mp 94-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 2.8 Hz, 1H), 7.44 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.395-7.28 (m, 5H), 7.10(d, *J* = 8.7 Hz, 1H), 3.49 (d, *J* = 16.5 Hz, 1H), 3.37 (d, *J* = 16.5 Hz, 1H), 3.11 (d, *J* = 16.9 Hz, 1H), 2.98 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.4, 157.3, 137.7, 136.6, 129.5, 129.4, 127.9, 126.3, 125.9, 121.95, 120.2, 115.3, 81.6, 44.9, 33.1; HRMS: *m/z* calculated for $C_{17}H_{13}NO_2Cl$ $[M+H]^+$: 298.0635, found 298.0626

2-(6-bromo-4-oxo-2-phenylchroman-2-yl)acetonitrile (3da): Light yellow solid (131 mg, 70%); mp 194-195 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 2.7 Hz, 1H), 7.58 (dd, *J* = 9.3, 2.8 Hz, 1H), 7.39-7.297 (m, 5H), 7.05 (d, *J* = 8.7 Hz, 1H), 3.49 (d, *J* = 16.6 Hz, 1H), 3.37 (d, *J* = 16.6 Hz, 1H), 3.11 (d, *J* = 17.1 Hz, 1H), 2.98 (d, *J* = 17.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.3, 157.8, 139.4, 137.6, 129.5, 129.47, 129.44, 125.9, 122.4, 120.5, 115.3, 115.1, 81.6, 44.9, 33.1; HRMS: *m/z* calculated for $C_{17}H_{13}NO_2Br$ $[M+H]^+$: 342.0130, found 342.0122

2-(6-fluoro-4-oxo-2-phenylchroman-2-yl)acetonitrile (3ea): Yellowish white solid (111 mg, 72%); mp 124-125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41-7.37 (m, 3H),7.36-7.33 (m, 1H), 7.325- 7.27 (m, 2H), 7.25-7.20 (m, 1H), 7.14- 7.10 (m, 1H), 3.49 (d, *J* = 16.5 Hz, 1H), 3.37 (d, *J* = 16.5 Hz, 1H), 3.10 (d, *J* = 17.0 Hz, 1H), 2.98 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8, 157.6 (d, *J* = 243.6 Hz), 155.0, 137.8, 129.4, 125.9, 124.2 (d, *J* = 24.4 Hz), 121.7 (d, *J* = 6.9 Hz), 120.2 (d, *J* = 8.0 Hz), 115.4, 112.2

(d, *J* = 24.0 Hz), 81.5, 44.9, 33.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ -120.0 ppm; HRMS: *m/z* calculated for $C_{17}H_{13}NO_2F$ $[M+H]^+$: 282.0930, found 282.0924

2-(6-methoxy-4-oxo-2-phenylchroman-2-yl)acetonitrile (3fa): Yellowish browm solid (99 mg, 62%); mp 97-98 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.396 (m, 2H), 7.35-7.28 (m, 3H), 7.16-7.15 (m, 1H), 7.12-7.05 (m, 2H), 3.73 (s, 3H), 3.45 (d, *J* = 16.4 Hz, 1H), 3.36 (d, *J* = 16.3 Hz, 1H), 3.08 (d, *J* = 16.7 Hz, 1H), 2.97 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.6, 154.6, 153.4, 138.4, 129.3, 129.2, 125.9, 125.7, 121.0, 119.8, 115.6, 107.4, 81.1, 55.8, 45.1, 32.96; HRMS: *m/z* calculated for $C_{18}H_{16}NO_3$ $[M+H]^+$: 294.1130, found 294.1119

2-(7-methoxy-4-oxo-2-phenylchroman-2-yl)acetonitrile (3ga): Light yellow solid (112 mg, 70%); mp 124-126 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.7 Hz, 1H), 7.44-7.40 (m, 2H), 7.37-7.29 (m, 3H), 6.59 (d, *J* = 2.3 Hz, 1H), 6.54 (dd, *J* = 8.9, 2.3 Hz, 1H), 3.86 (S, 3H), 3.39 (d, *J* = 16.5 Hz, 1H), 3.31 (d, *J* = 16.4 Hz, 1H), 3.07 (d, *J* = 16.5 Hz, 1H), 2.99 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.1, 166.7, 160.9, 138.5, 129.3, 129.2, 128.7, 125.7, 115.6, 114.96, 110.5, 101.7, 81.4, 55.9, 45.0, 32.9; HRMS: *m/z* calculated for $C_{18}H_{16}NO_3$ $[M+H]^+$: 294.1130, found 294.1124

2-(5-methoxy-4-oxo-2-phenylchroman-2-yl)acetonitrile (3ha): White solid (130 mg, 81%); mp 122-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.38 (m, 3H), 7.32-7.23 (m, 3H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.47 (d, *J* = 8.5 Hz, 1H), 3.799 (s, 3H), 3.39-3.30 (m, 2H), 3.04 (d, *J* = 16.9 Hz, 1H), 2.96 (d, *J* = 16.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.1, 160.44, 160.41, 138.2, 136.7, 129.2, 128.99, 125.7, 115.5, 111.3, 110.4, 104.7, 80.5, 56.2, 46.5, 32.7; HRMS: *m/z* calculated for $C_{18}H_{16}NO_3$ $[M+H]^+$: 294.1130, found 294.1127

2-(6,8-dimethyl-4-oxo-2-phenylchroman-2-yl)acetonitrile (3ia): Pale yellow solid (94 mg, 59%); mp 76-77 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.37 (m, 3H), 7.36-7.29 (m, 3H), 7.197-7.19 (m, 1H), 3.41 (d, *J* = 16.4 Hz, 1H), 3.32 (d, *J* = 16.6 Hz, 1H), 3.09-2.99 (m, 2H), 2.39 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.1, 160.44, 160.42, 138.2, 136.7, 129.2, 128.99, 125.7, 115.5, 111.3, 110.4, 104.7, 80.5, 56.2, 46.5, 32.7; HRMS: *m/z* calculated for $C_{19}H_{18}NO_2$ $[M+H]^+$: 292.1338, found 292.1335

2-(2-(4-(tert-butyl)phenyl)-5-methoxy-4-oxochroman-2-yl)acetonitrile (3hm): Pale yellow solid (129 mg, 68%); mp 84-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (t, *J* = 8.5 Hz, 1H), 7.30 (s, 4H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.47 (d, *J* = 8.5 Hz, 1H), 3.82 (s, 3H), 3.35 (s, 2H), 3.03 (d, *J* = 16.9 Hz, 1H), 2.93 (d, *J* = 16.9 Hz, 1H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.4, 160.6, 160.5, 151.9, 136.6, 135.0, 126.2, 125.4, 115.7, 111.3, 110.4, 104.5, 80.5, 56.3, 46.5, 34.6, 32.9, 31.2; HRMS: *m/z* calculated for $C_{22}H_{24}NO_3$ $[M+H]^+$: 350.1758, found 350.1758

2-(6-acetyl-7-hydroxy-2-(4-methoxyphenyl)-4-oxochroman-2-yl)acetonitrile (3jc): Yellowish white solid (111 mg, 58%); mp 83-84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.32-7.28 (m, 2H), 6.86-6.82 (m, 2H), 6.61 (s, 1H), 3.75 (s, 3H), 3.47 (d, *J* = 16.6 Hz, 1H), 3.34 (d, *J* = 16.6 Hz, 1H), 3.12 (d, *J* = 16.8 Hz, 1H), 2.95 (d, *J* = 16.9 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.9, 187.7, 169.1, 164.2, 160.3, 132.2, 129.5., 127.2, 116.0, 115.4, 114.8, 114.3, 105.8, 82.0, 55.4, 44.8, 33.4, 26.6; HRMS: *m/z* calculated for $C_{20}H_{18}NO_5$ $[M+H]^+$: 352.1185, found 352.1180

2-(6-acetyl-7-hydroxy-4-oxo-2-(m-tolyl)chroman-2-yl)acetonitrile (3jk): Yellowish white solid (103 mg, 56%); mp 216-217 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.25-7.21 (m, 1H), 7.19-7.16 (m, 2H), 7.12-7.098 (m, 1H), 6.64 (s, 1H), 3.48 (d, *J* = 16.6 Hz, 1H), 3.36 (d, *J* = 16.7 Hz, 1H), 3.13 (d, *J* = 17.1 Hz, 1H), 2.96 (d, *J* = 17.1 Hz, 1H), 2.57 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.9, 187.6, 169.1, 164.3, 139.4, 137.8, 132.2, 130.3, 129.3, 126.2, 122.8, 116.0, 115.3, 114.2, 105.8, 82.1, 44.8, 33.3, 26.6, 21.8; HRMS: *m/z* calculated for $C_{20}H_{18}NO_4$ $[M+H]^+$: 336.1236, found 336.1226

2-(4-hydroxy-2-phenylchroman-2-yl)acetonitrile (4aa): White solid (43 mg, 65%); mp 78-79 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.46 (m, 2H), 7.37-7.27 (m, 5H), 7.12-7.099 (m, 1H), 7.00-6.96 (m, 1H), 4.76 (t, *J* = 4.3 Hz, 1H), 2.98-2.89 (m, 2H), 2.83 (dd, *J* = 14.7, 3.7 Hz, 1H), 2.61 (dd, *J* = 14.6, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.99, 140.1, 130.3, 129.9, 129.0, 128.6, 125.8, 123.8, 121.9, 117.6, 116.1, 76.6, 62.9, 39.1, 32.99; HRMS: *m/z* calculated for $C_{17}H_{16}NO_2$ $[M+H]^+$: 266.1181, found 266.1179

2-(4-oxo-2-phenyl-3-(2-(2,2,2-trifluoroethyl)hydrazono)chroman-2-yl)acetonitrile (5aa): Yellowish white solid (48 mg, 72%); ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.87-7.84 (m, 1H), 7.58-7.53 (m, 1H), 7.42-7.33 (m, 3H), 7.23-7.20 (m, 2H), 7.03-6.99 (m, 1H), 6.91-6.92 (m, 1H), 6.78 (s, 1H), 3.71 (bs, 5H), 2.10 (s, 2H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 194.0, 175.0, 163.9, 155.9, 141.5, 140.1, 137.7, 134.3, 133.3, 129.7, 129.14, 129.1, 127.3, 125.3, 122.8, 119.3, 118.8, 51.4 (q, *j* = 35.2), 20.6; HRMS: *m/z* calculated for $C_{19}H_{15}N_3O_2F_3$ $[M+H]^+$: 374.1116, found 374.1114

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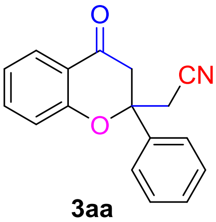
5.6 NMR spectra of compounds



3aa

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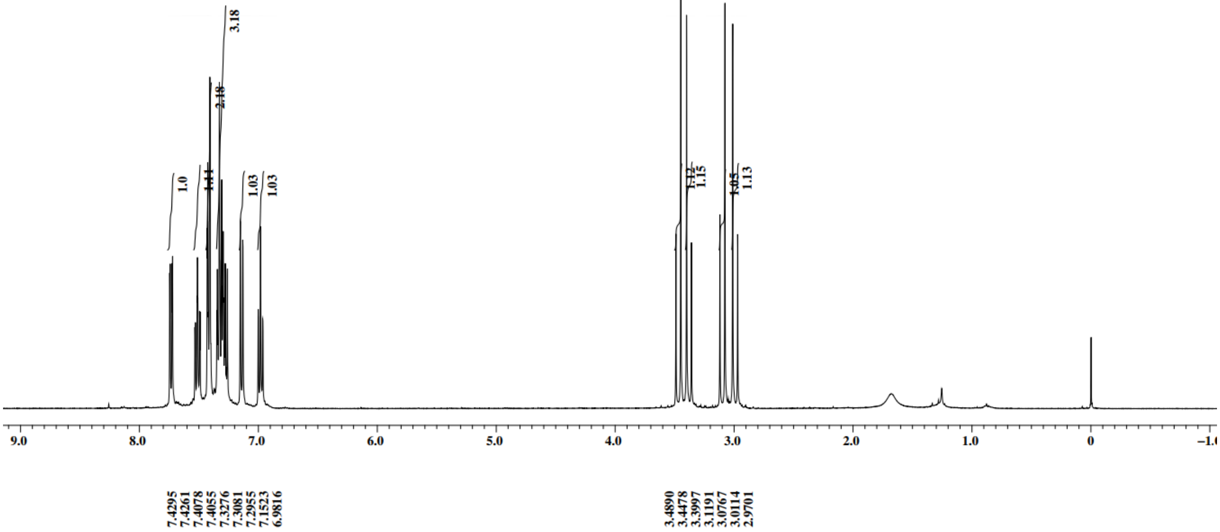

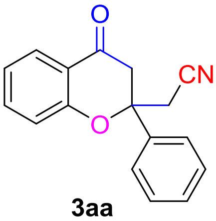

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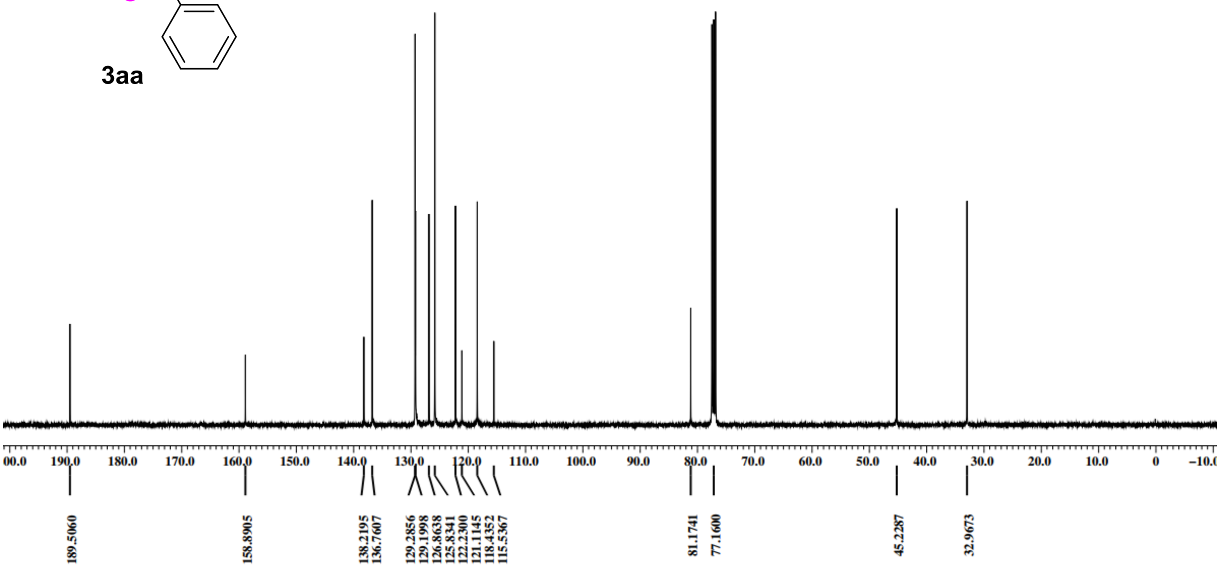

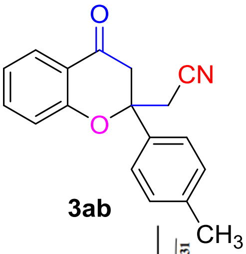

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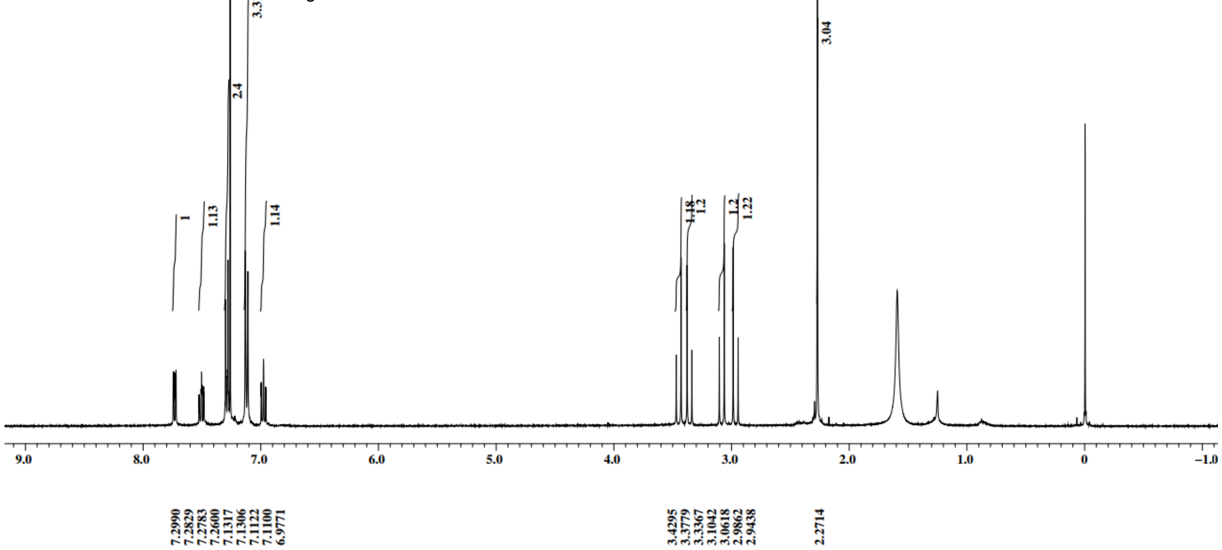

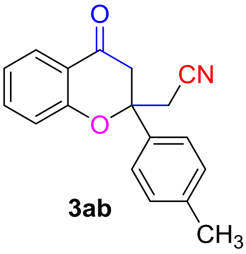

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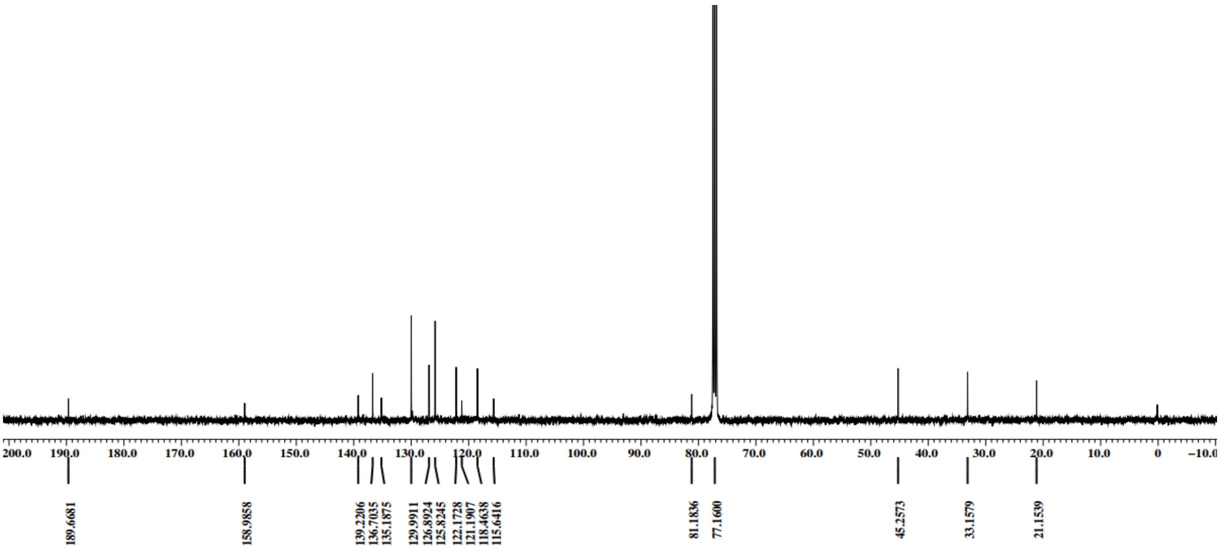

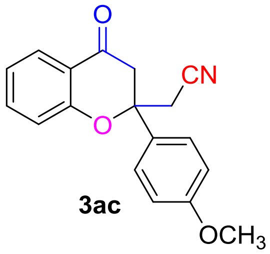

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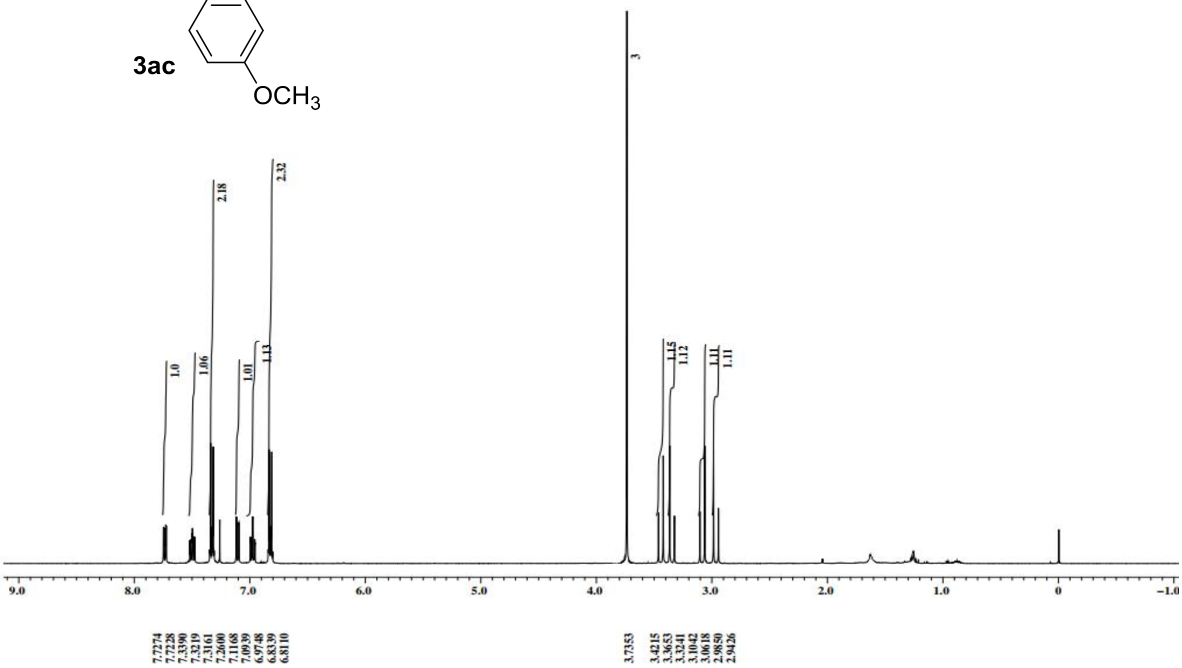

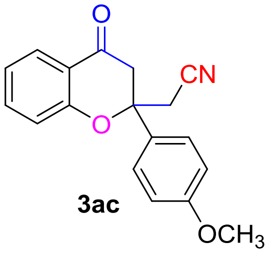

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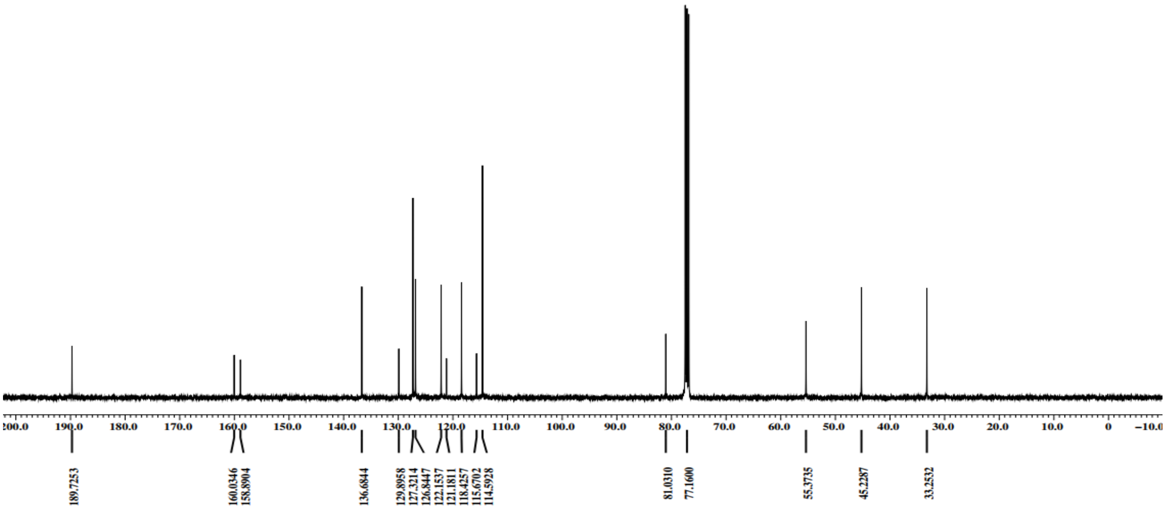

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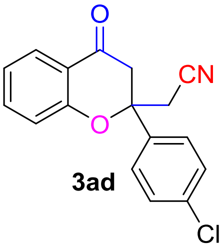

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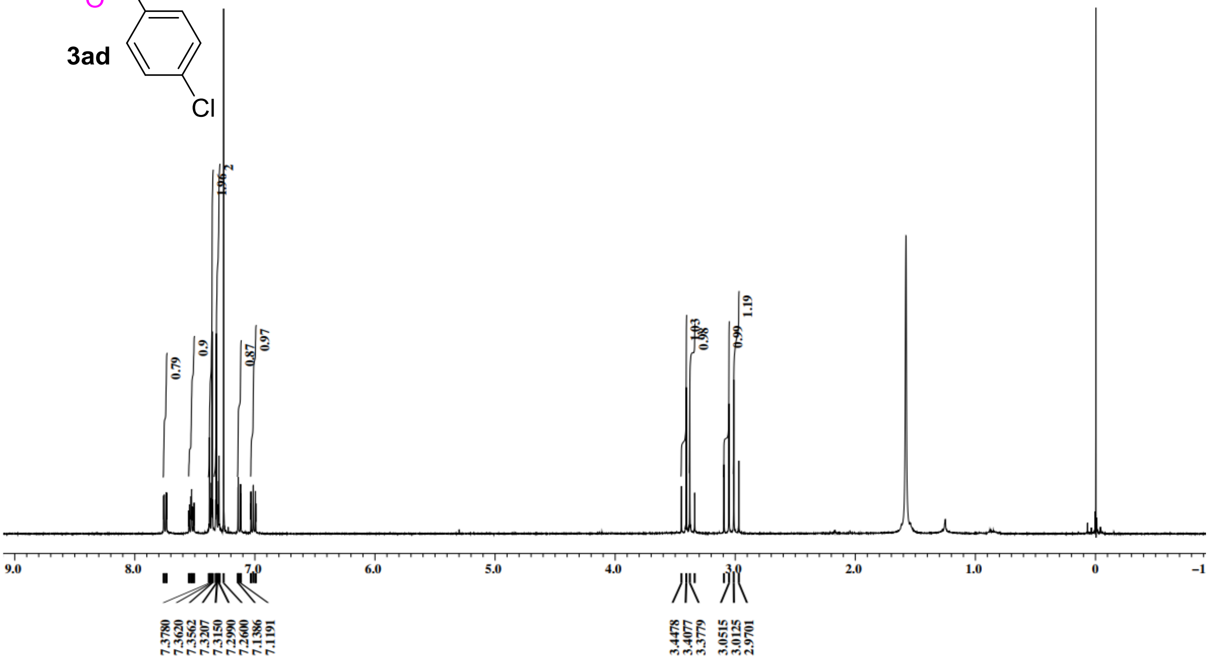

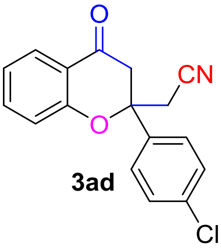

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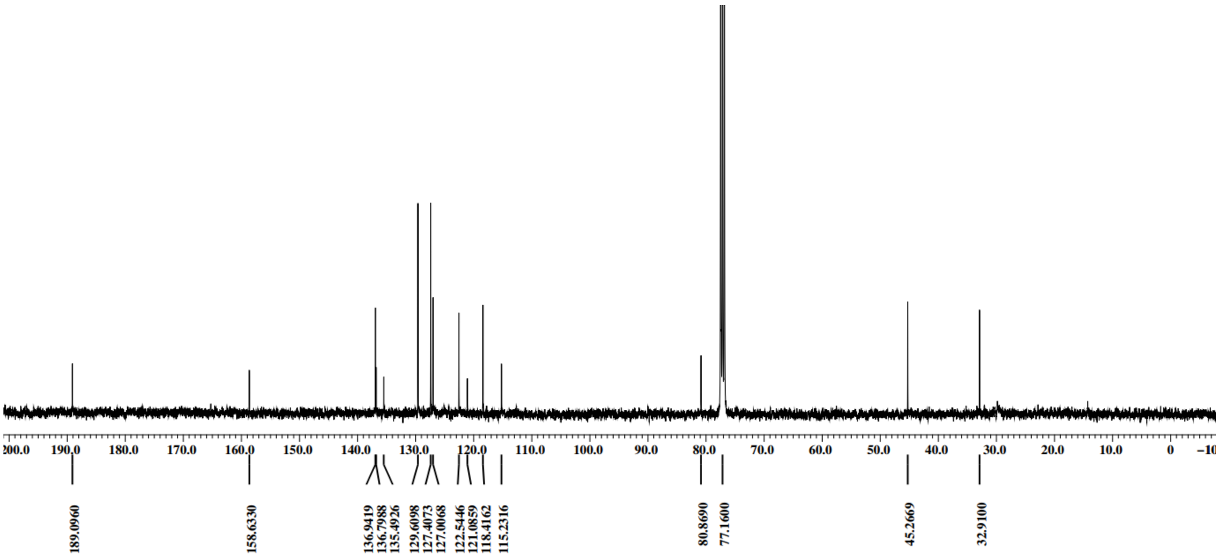

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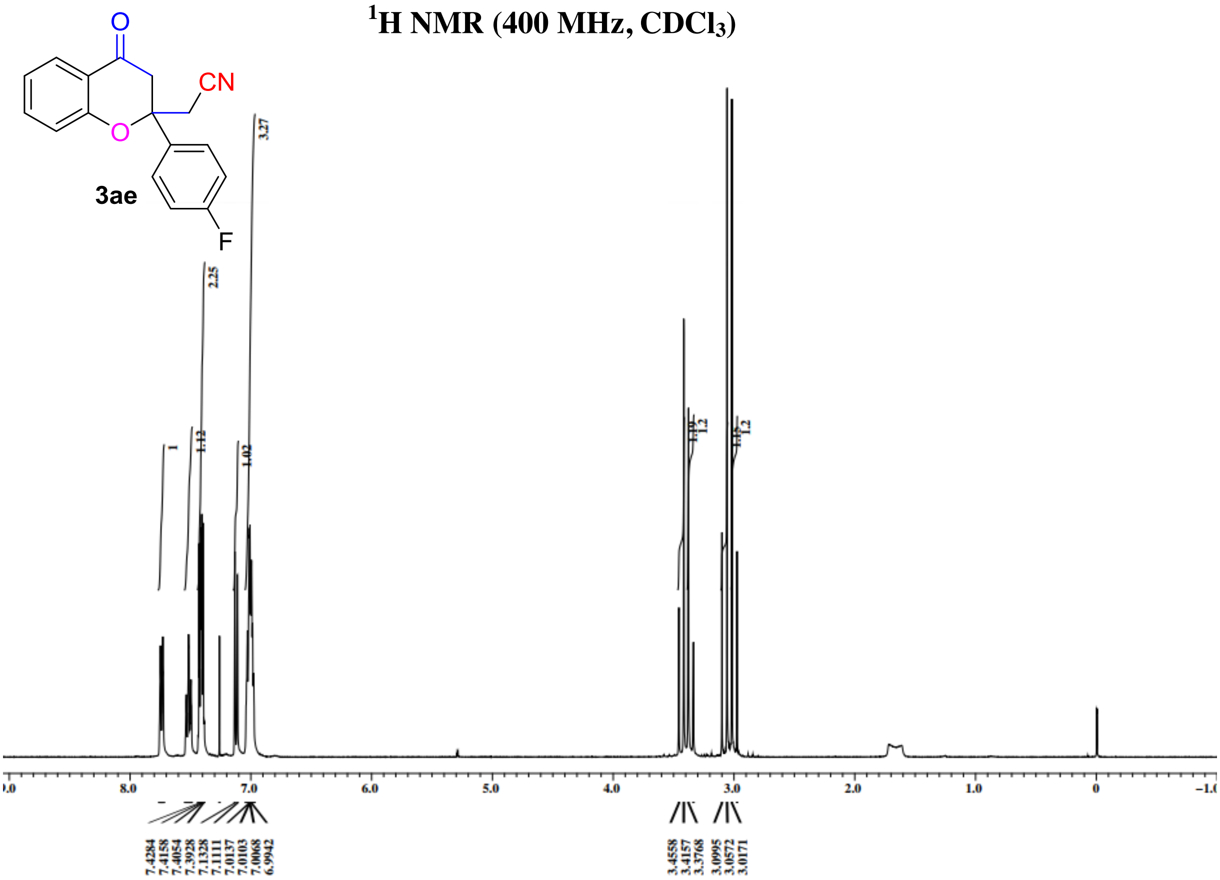

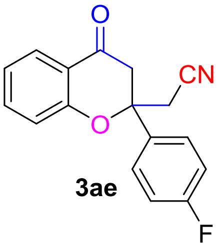

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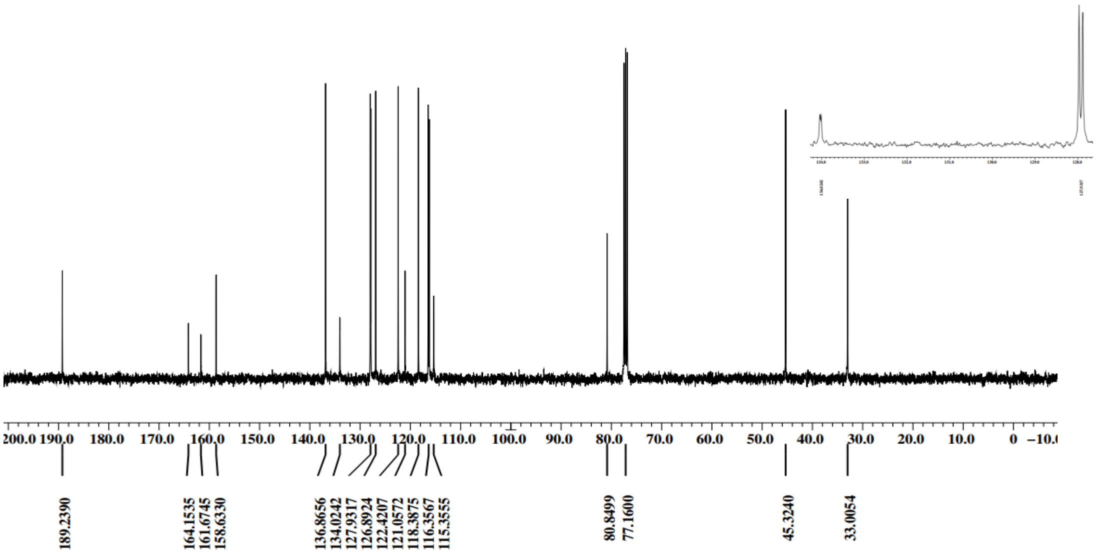

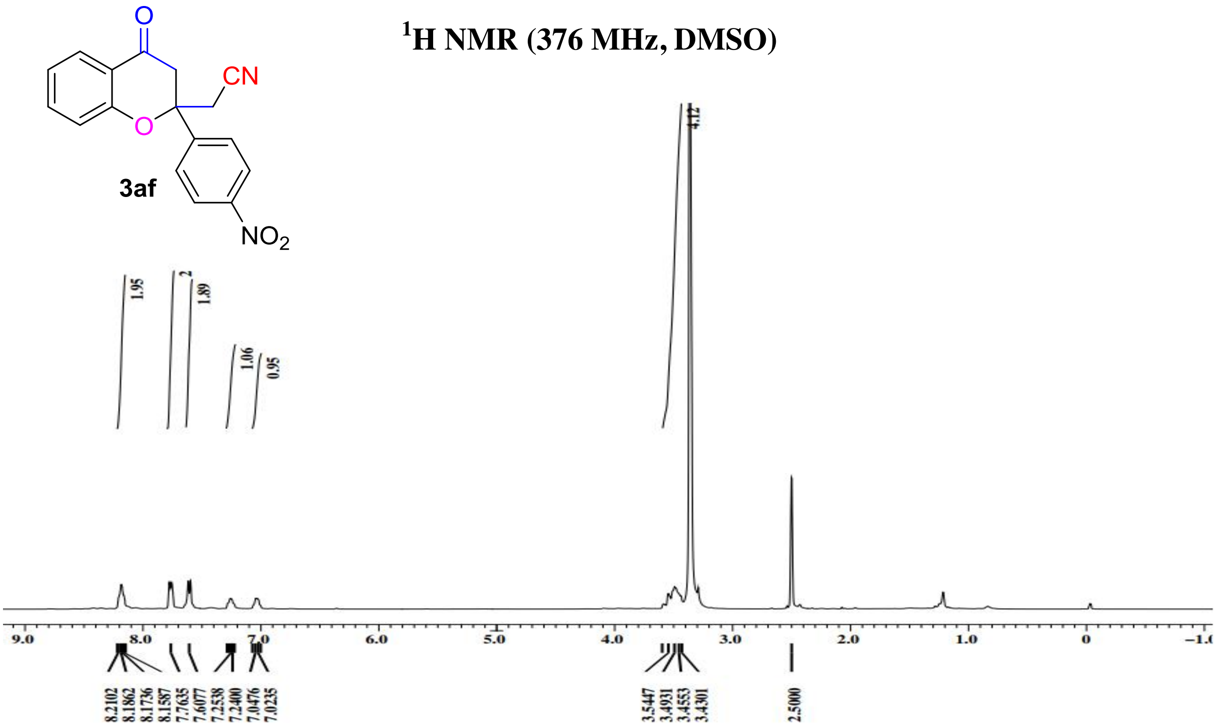

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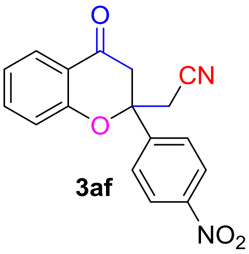

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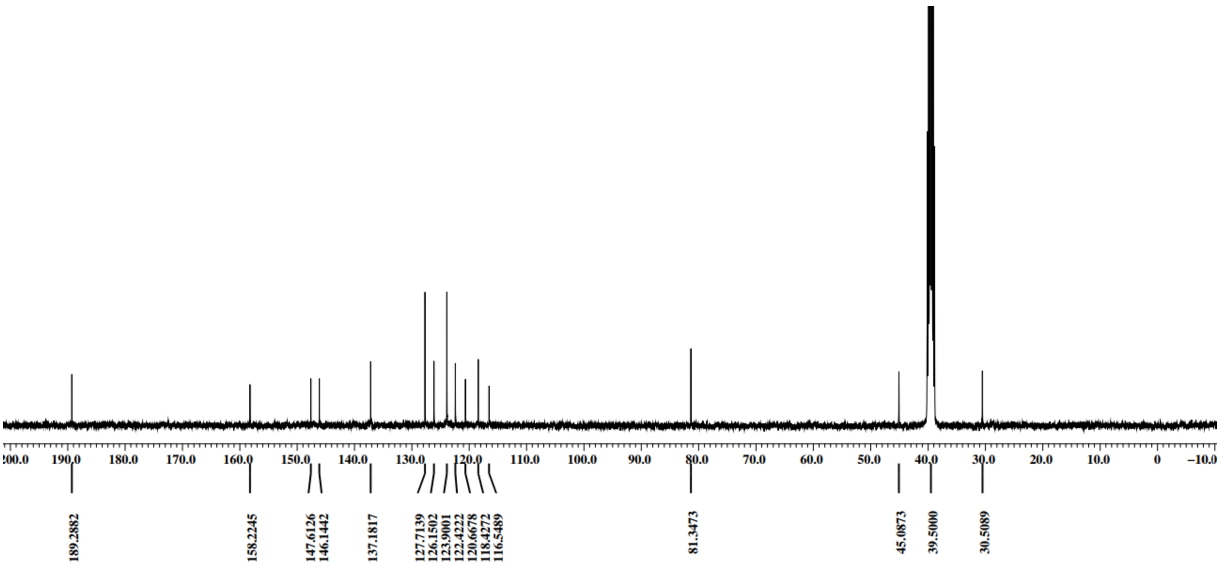

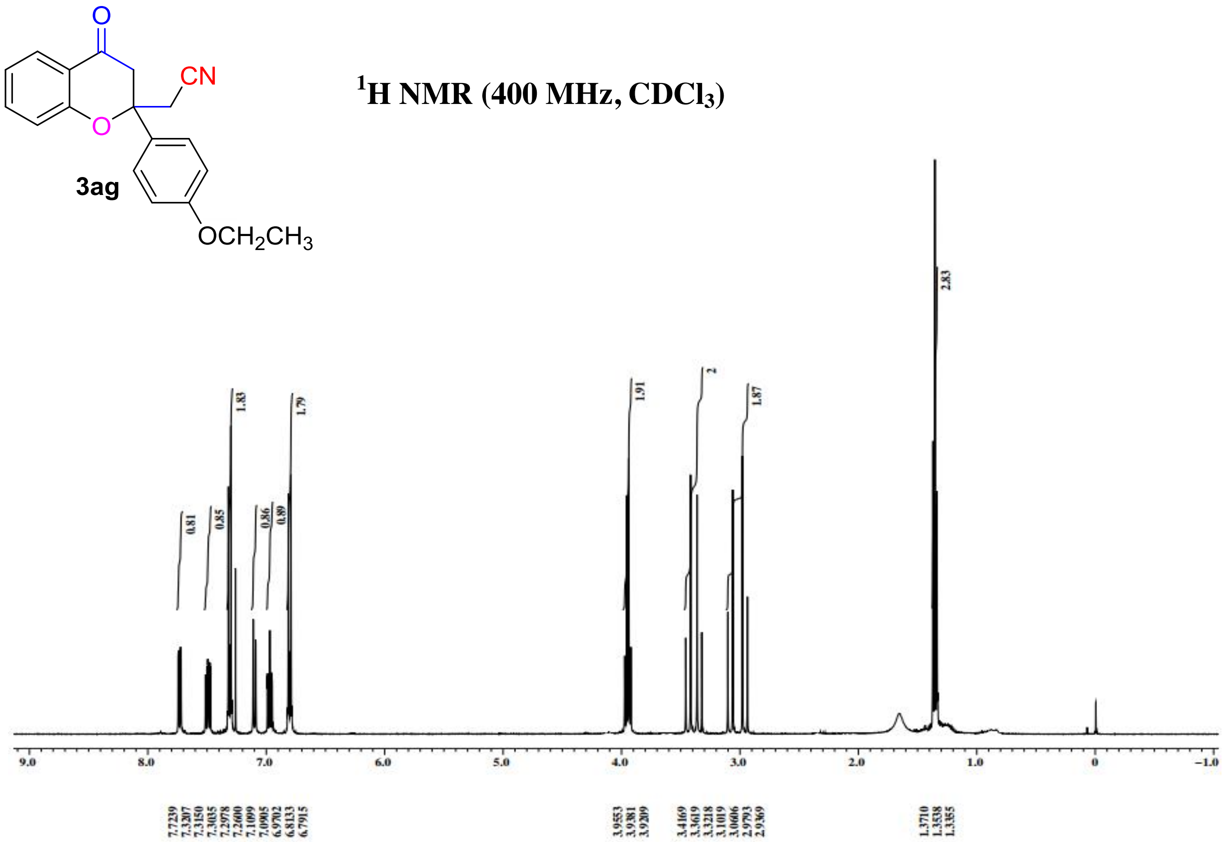
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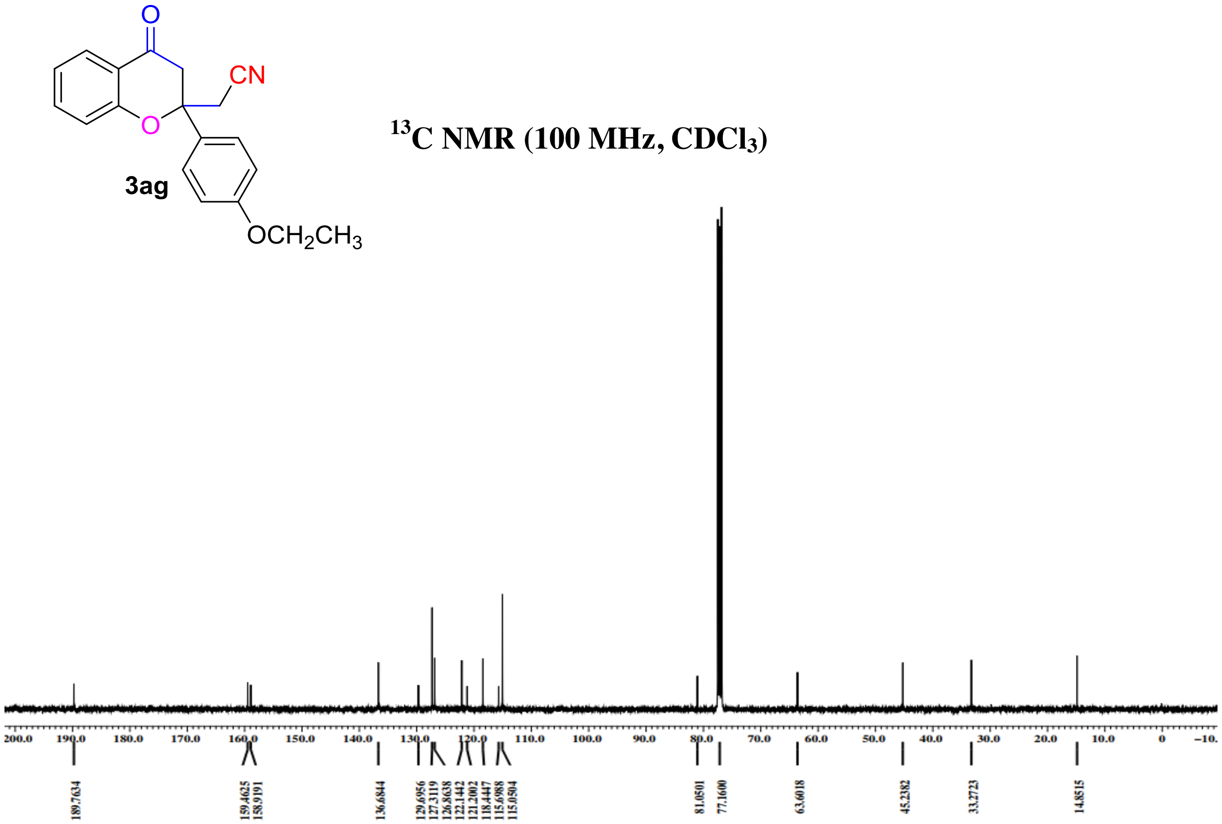
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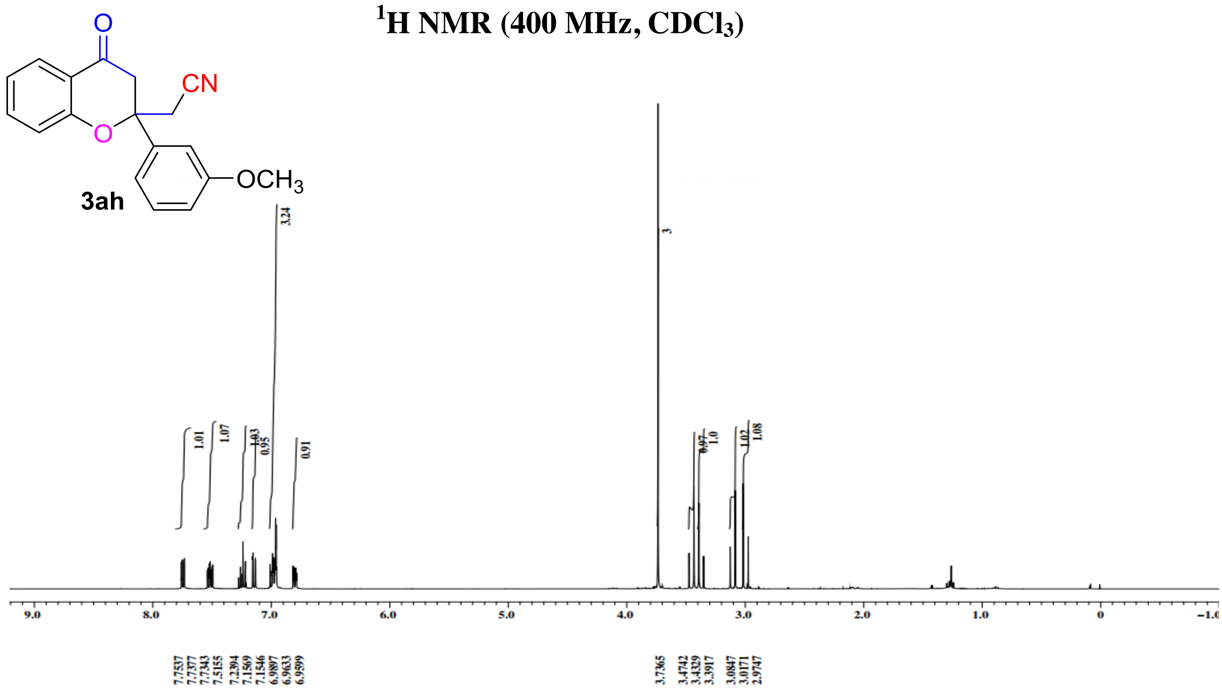
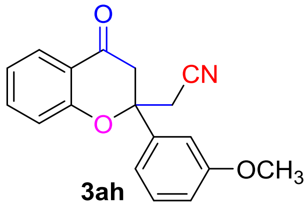
^{1}H NMR (400 MHz, $CDCl_3$)





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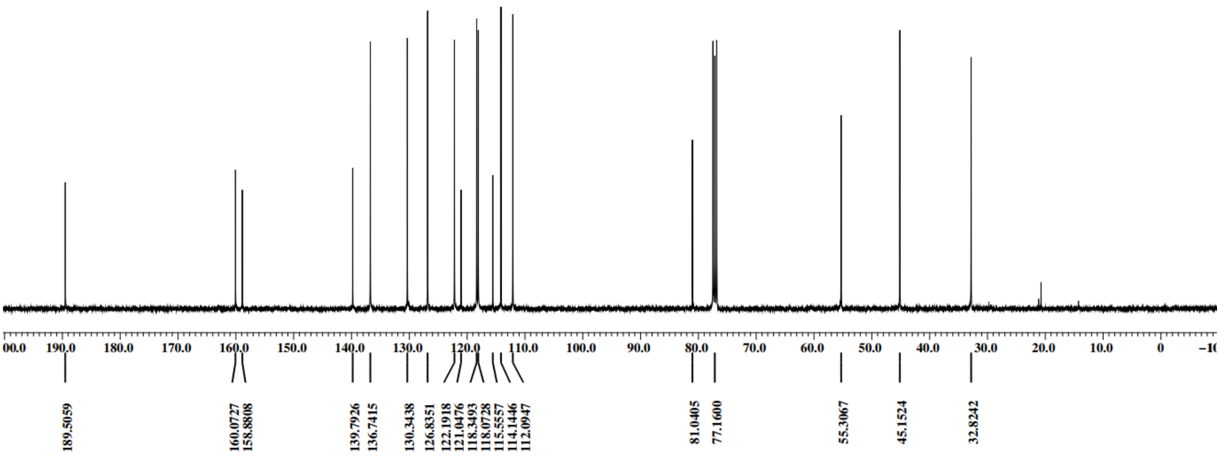

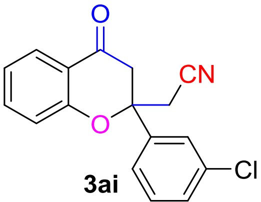

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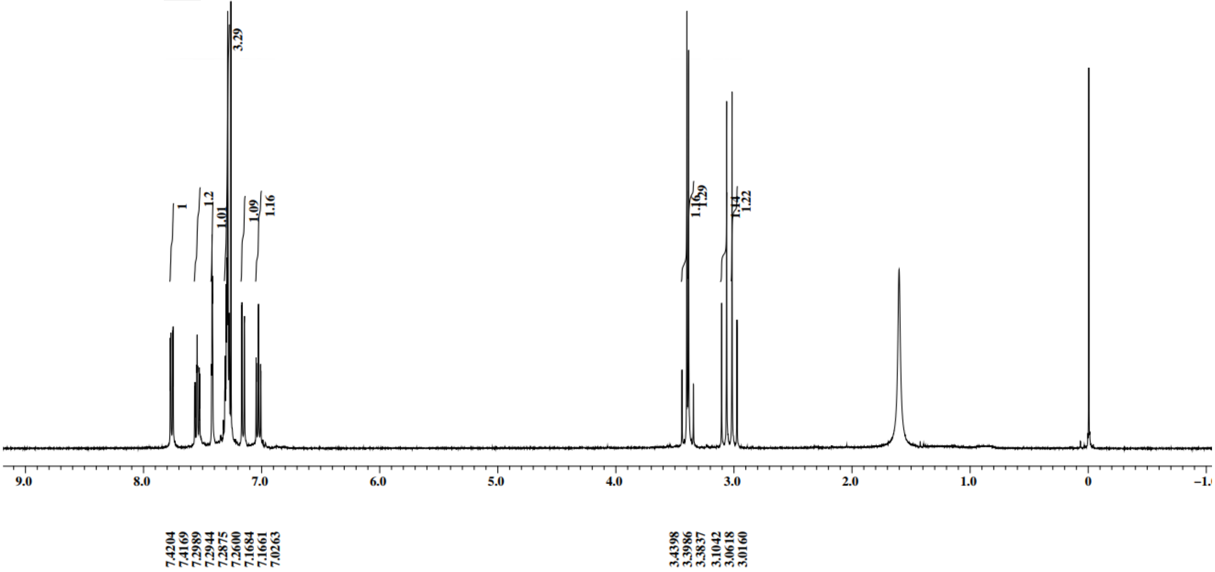

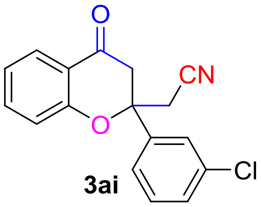

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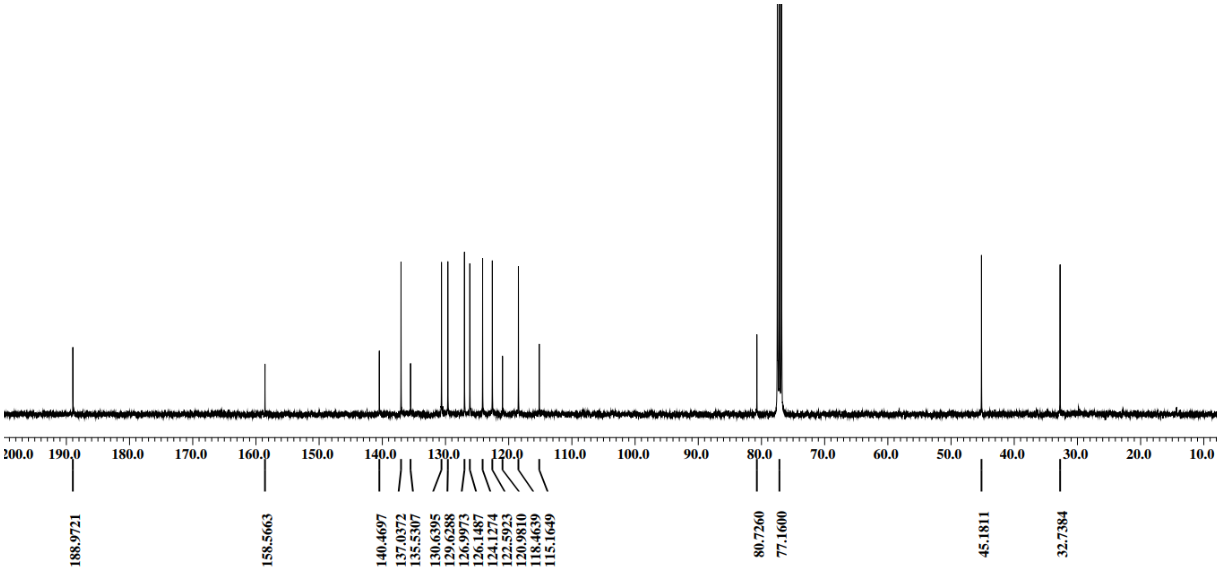

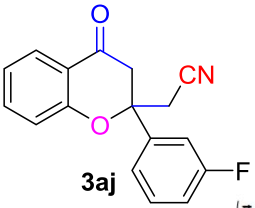

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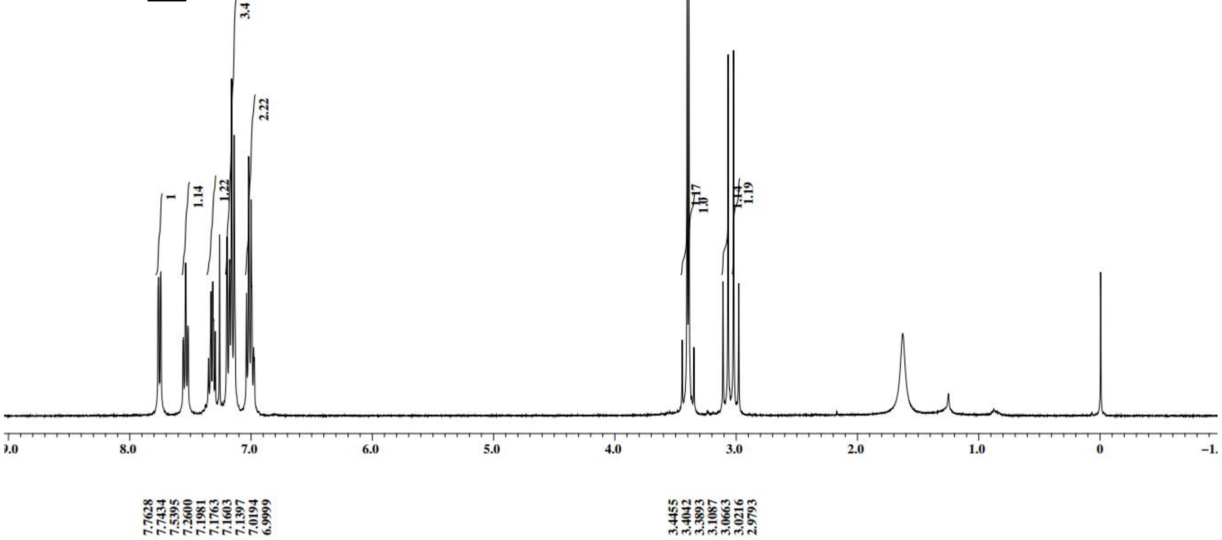

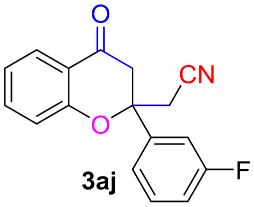

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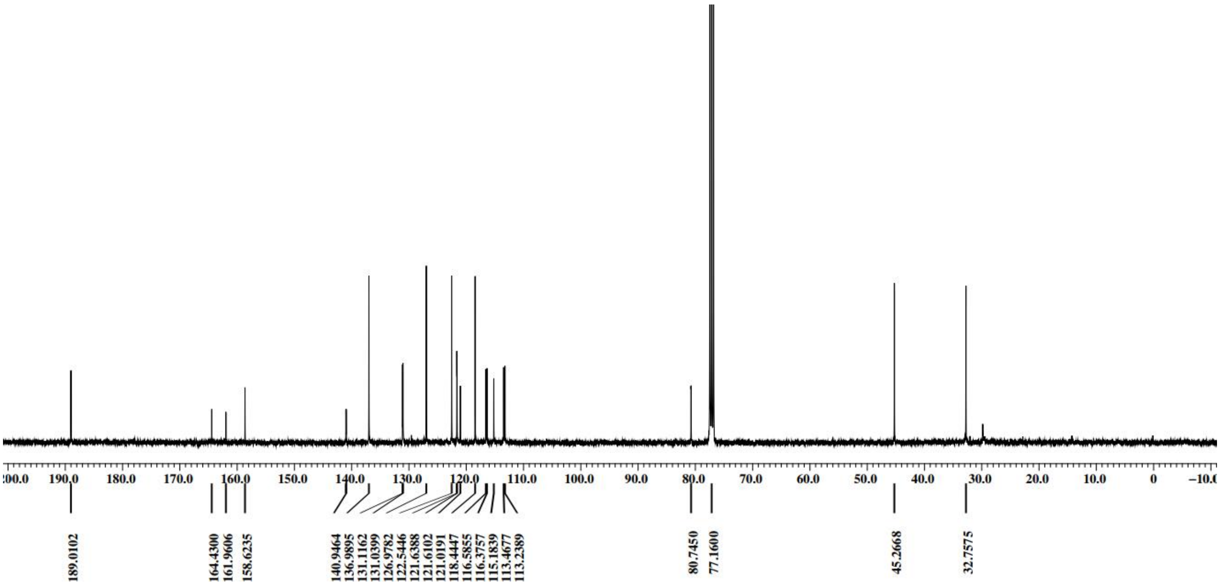

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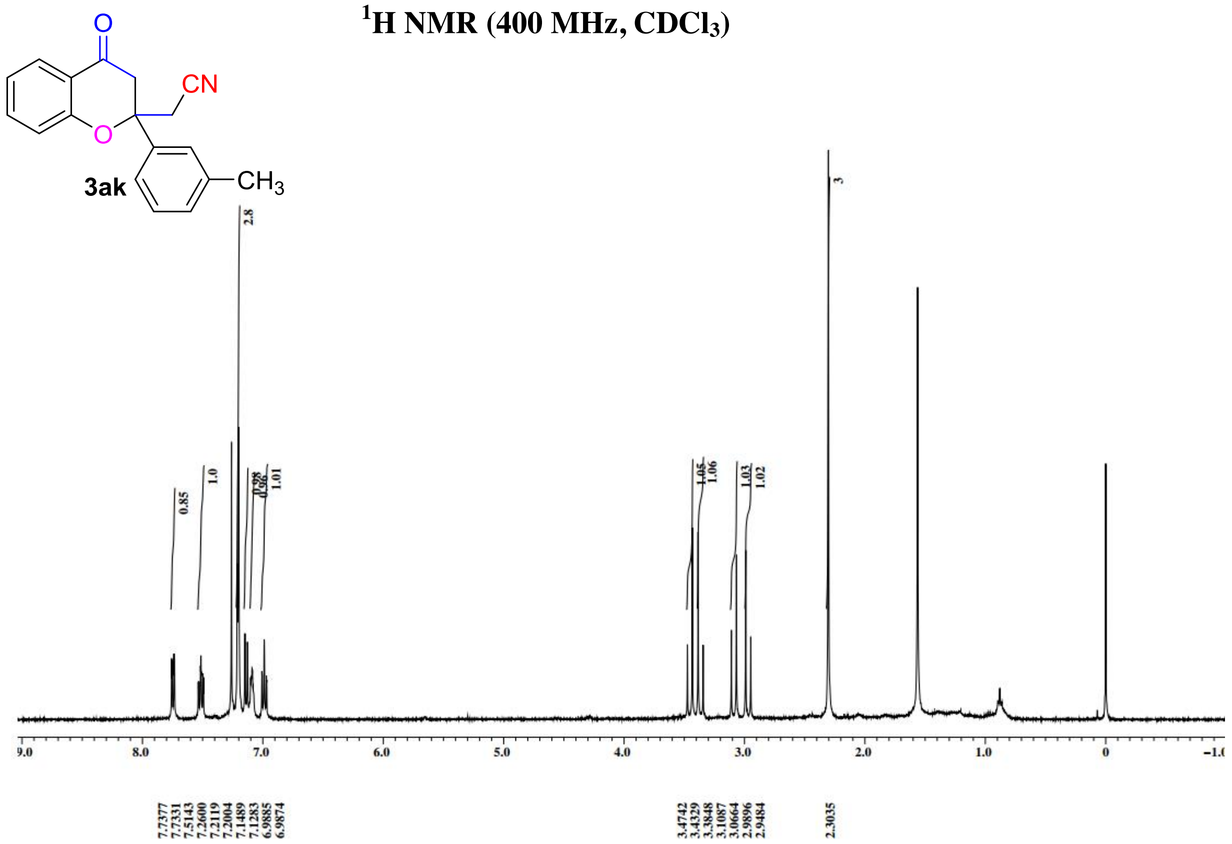

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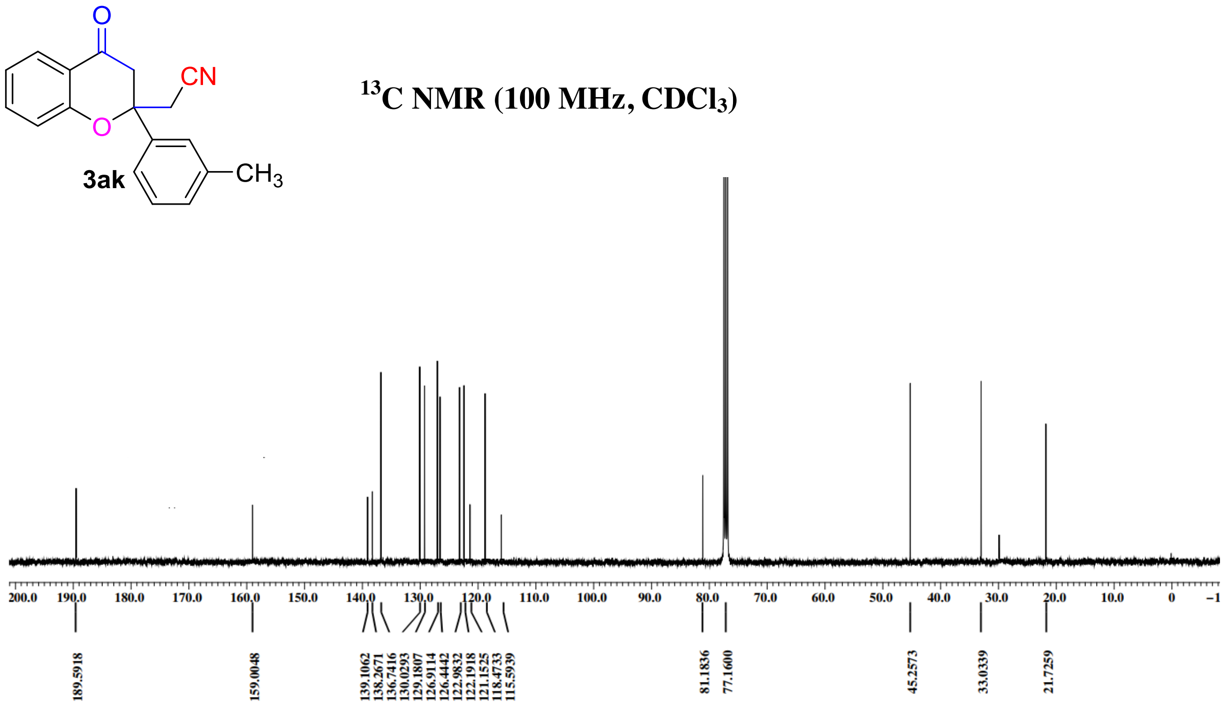

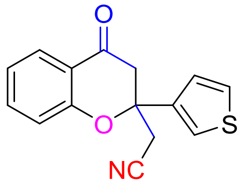

3al

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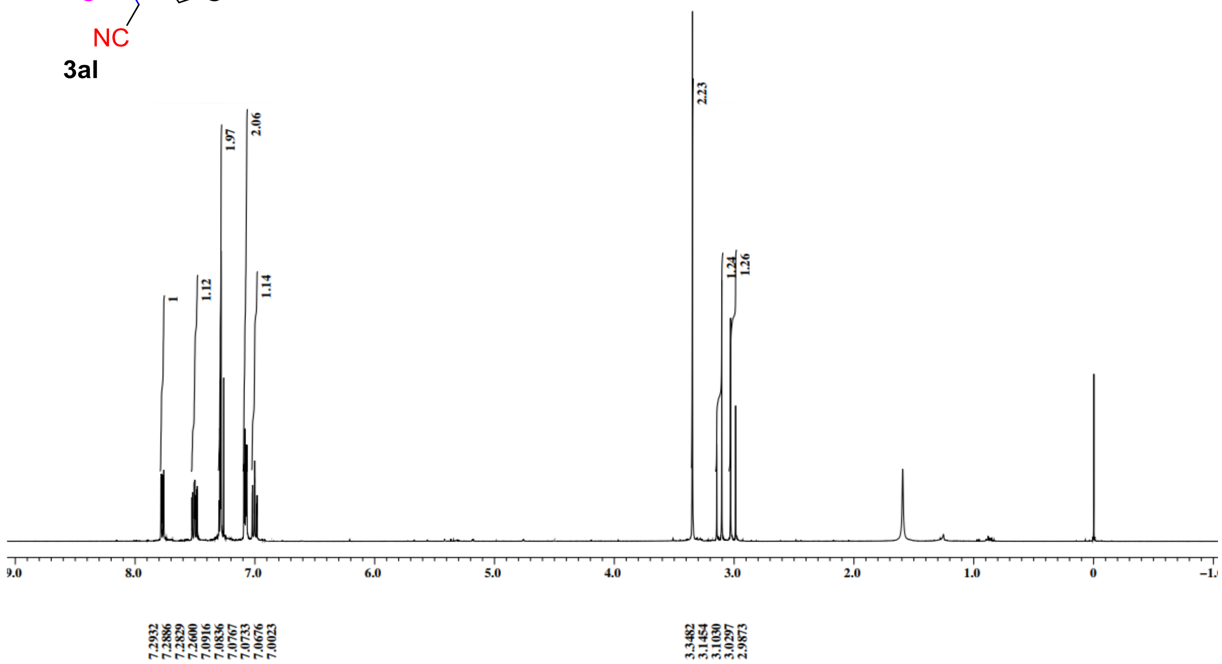
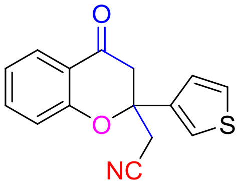
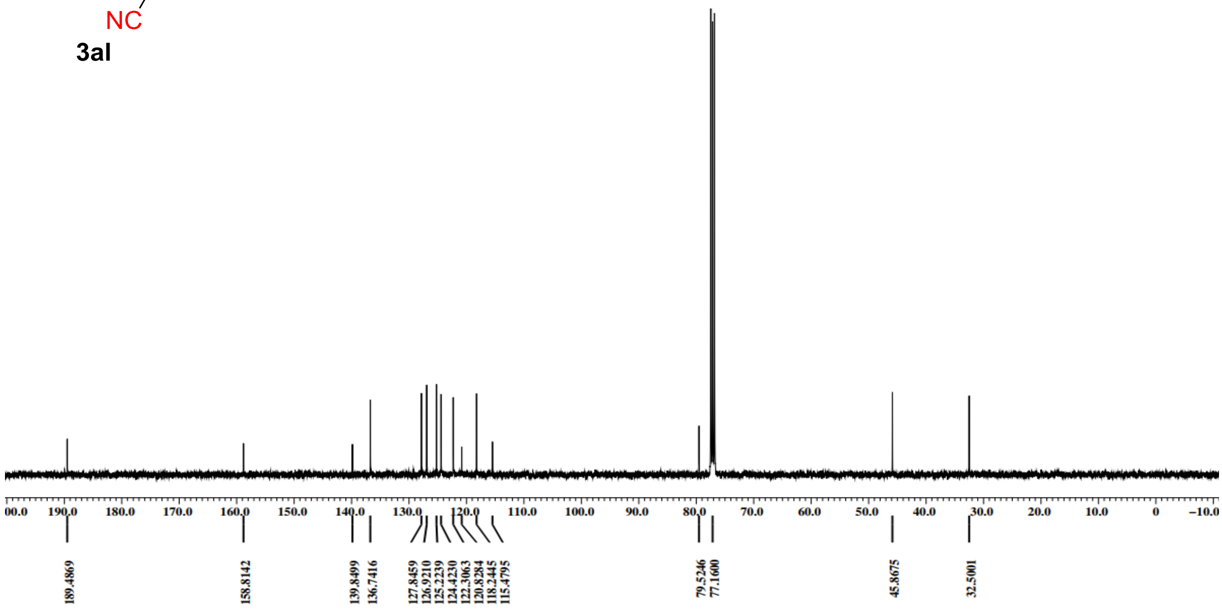
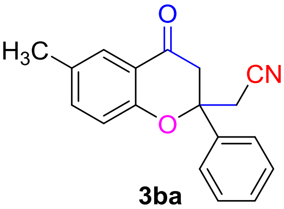




3al

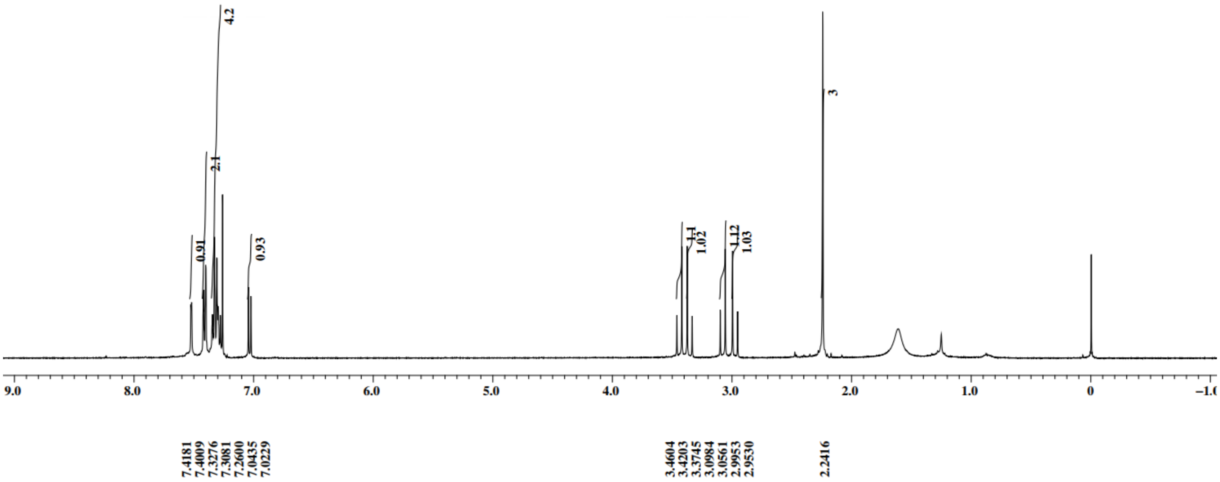
^{13}C NMR (100 MHz, CDCl$_3$)

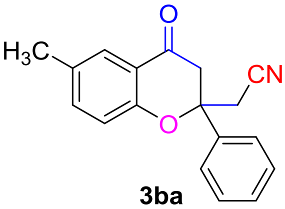




3ba

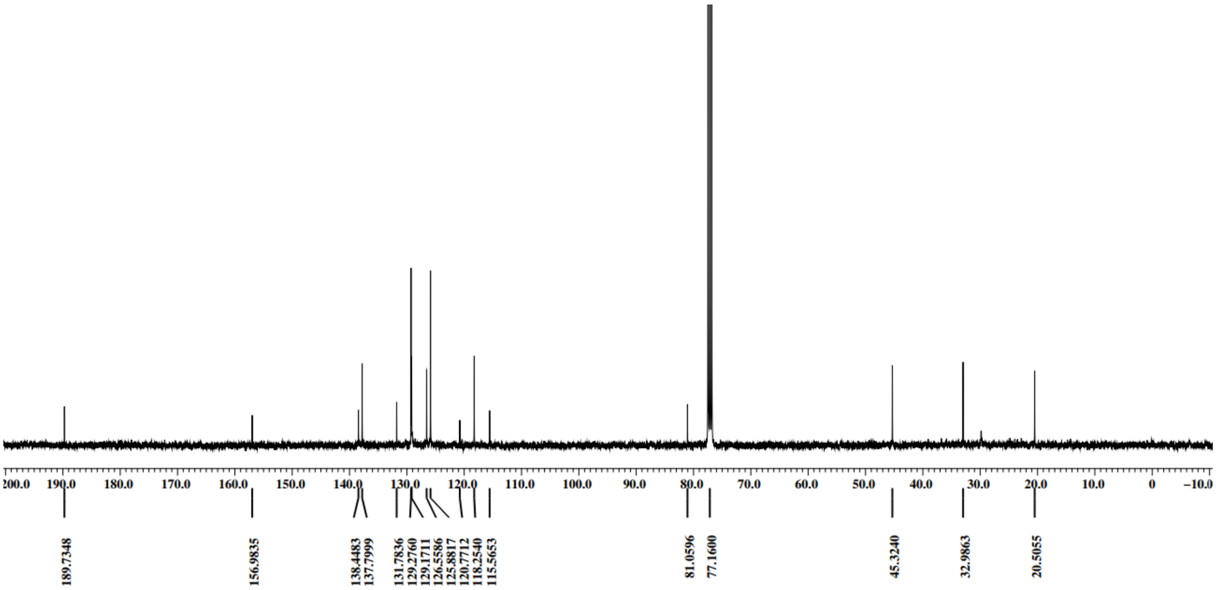
^{1}H NMR (400 MHz, CDCl$_3$)

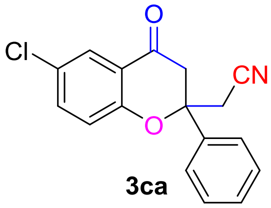




3ba

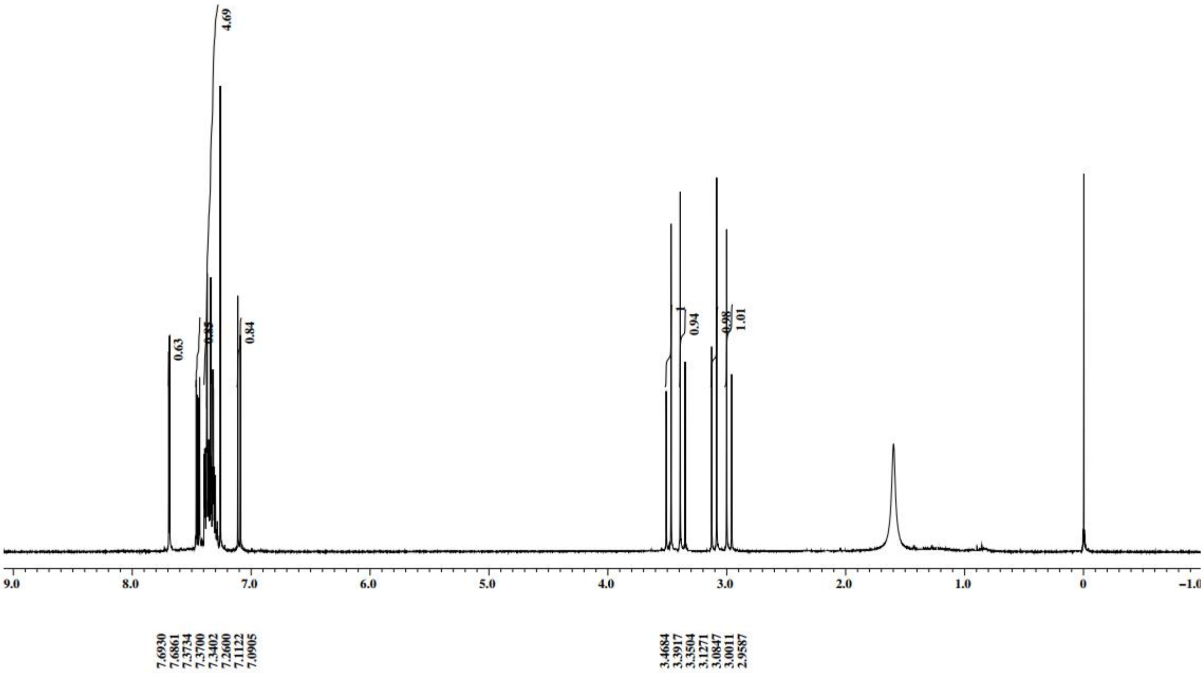
^{13}C NMR (100 MHz, CDCl$_3$)

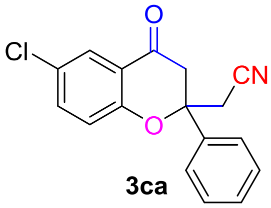




3ca

^{1}H NMR (400 MHz, CDCl$_3$)





3ca

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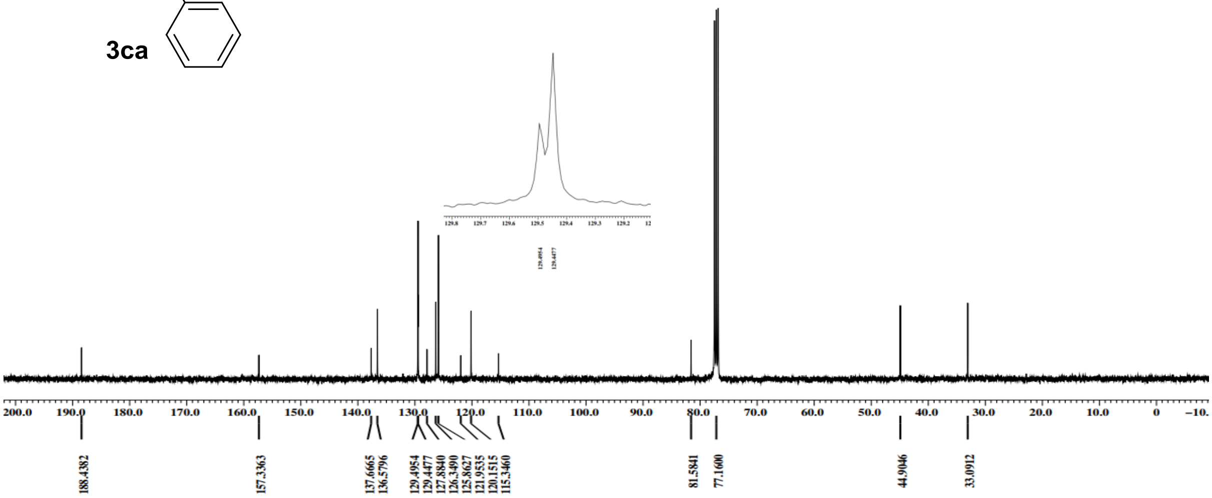
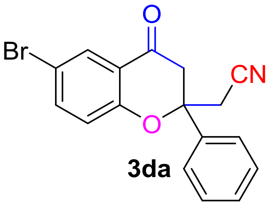
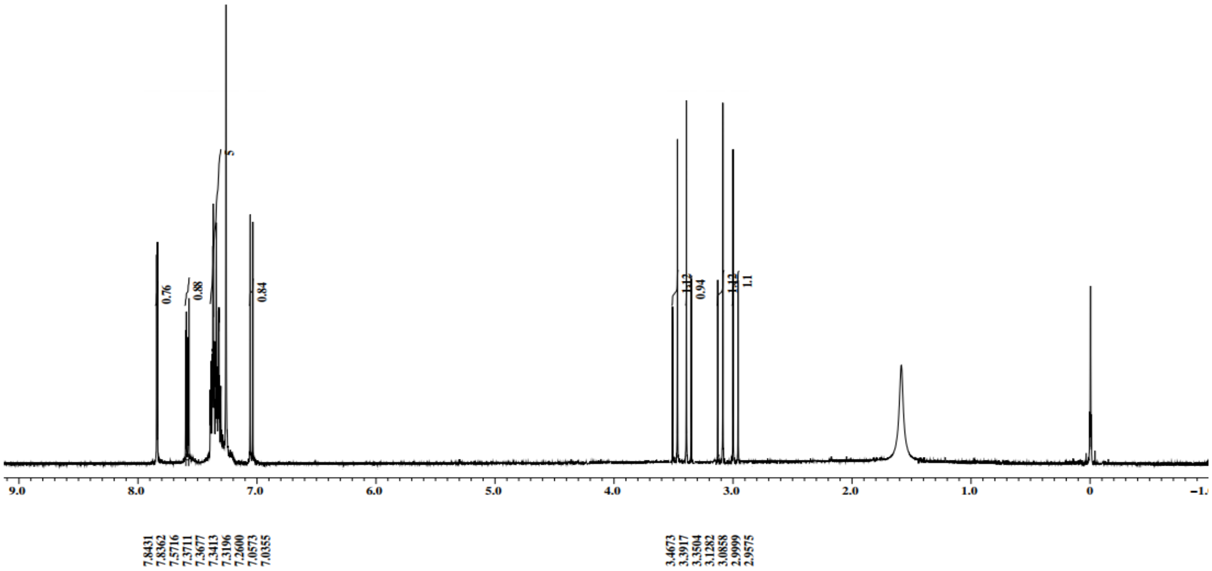
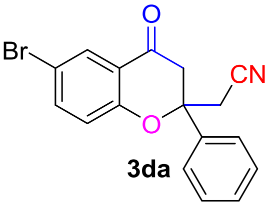




3da

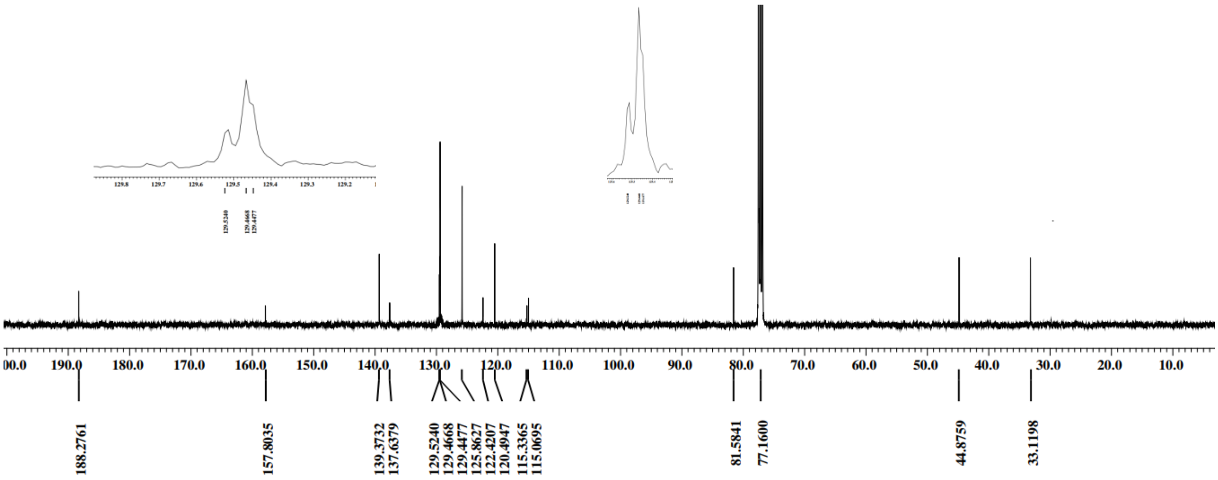
^{1}H NMR (400 MHz, $CDCl_3$)

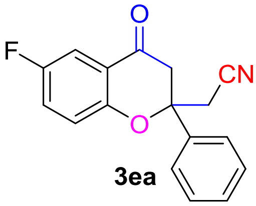




3da

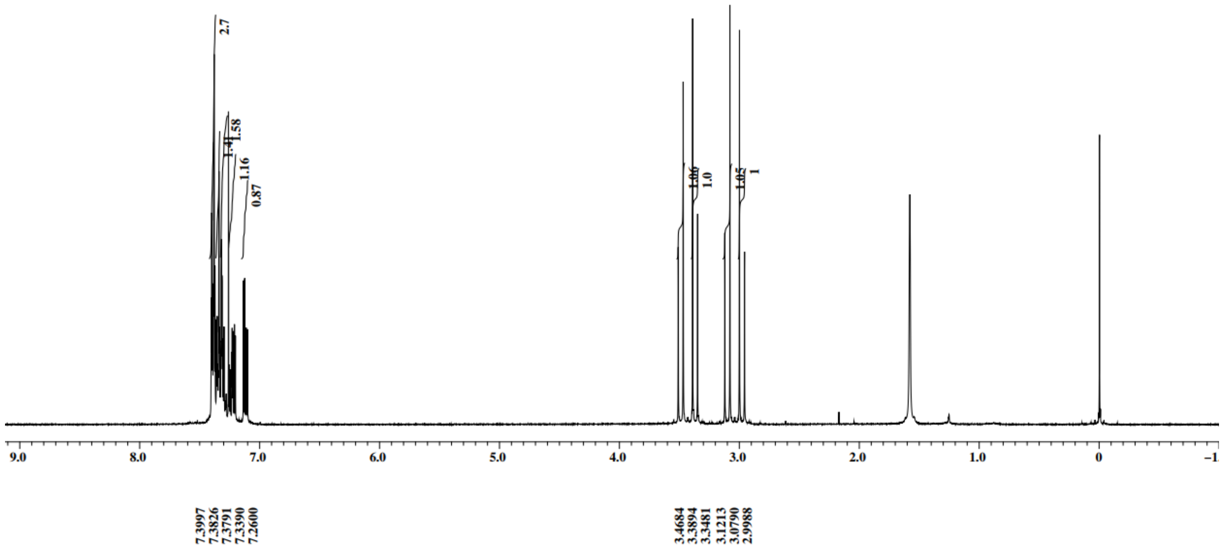
^{13}C NMR (100 MHz, $CDCl_3$)

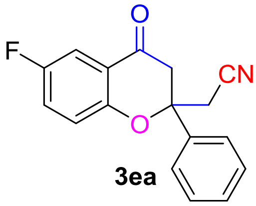




3ea

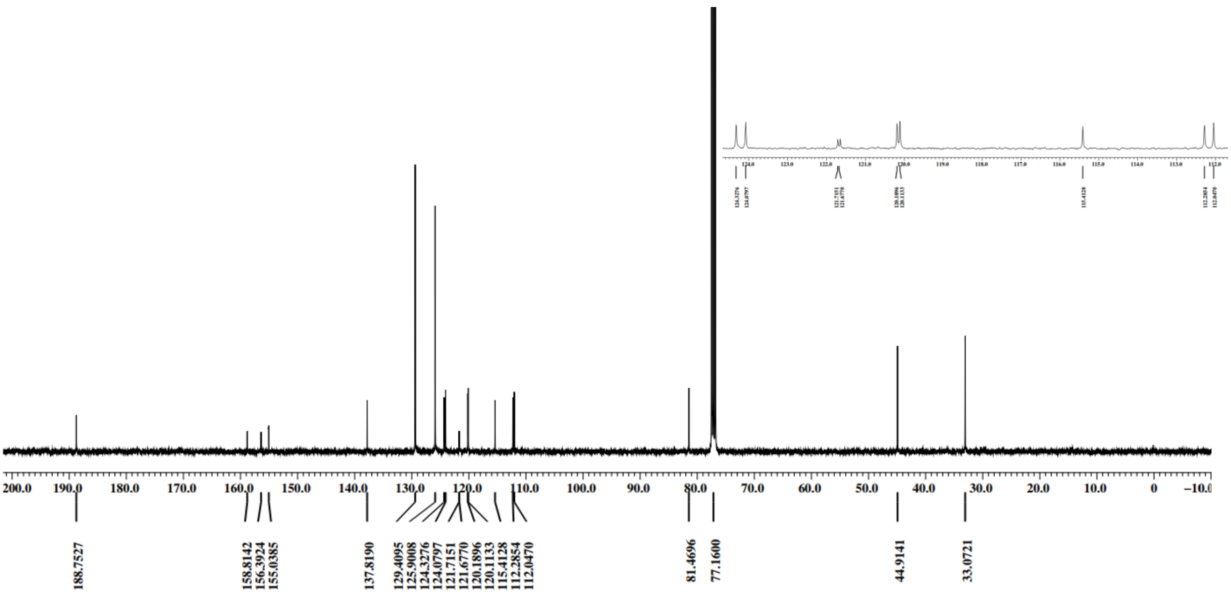
^{1}H NMR (400 MHz, CDCl$_3$)

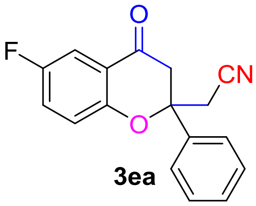




3ea

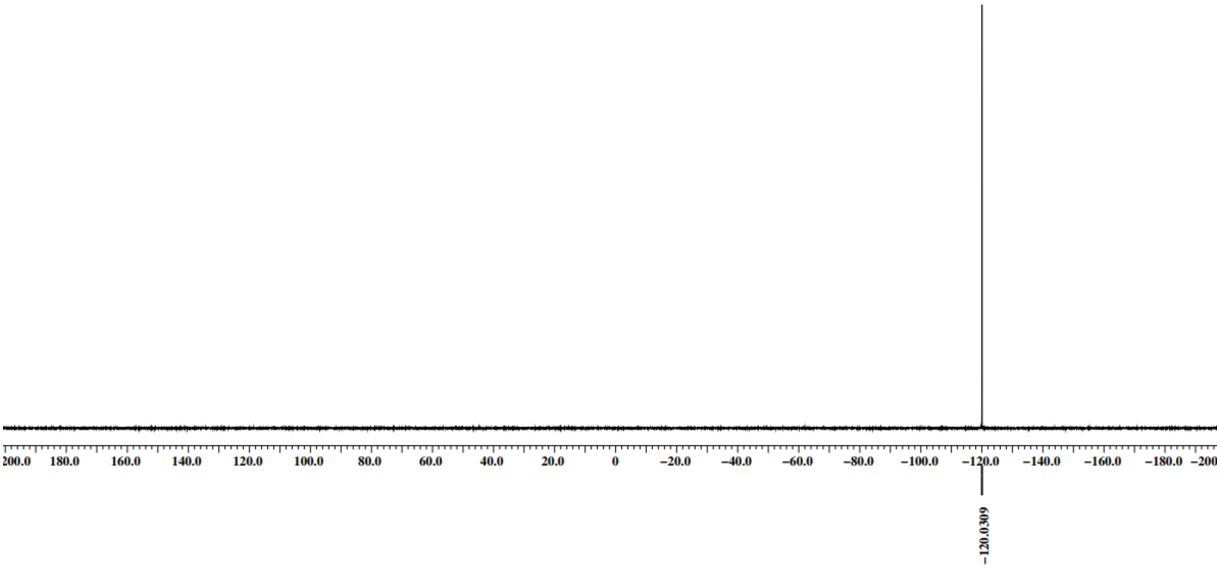
^{13}C NMR (100 MHz, CDCl$_3$)

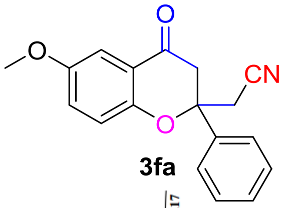




3ea

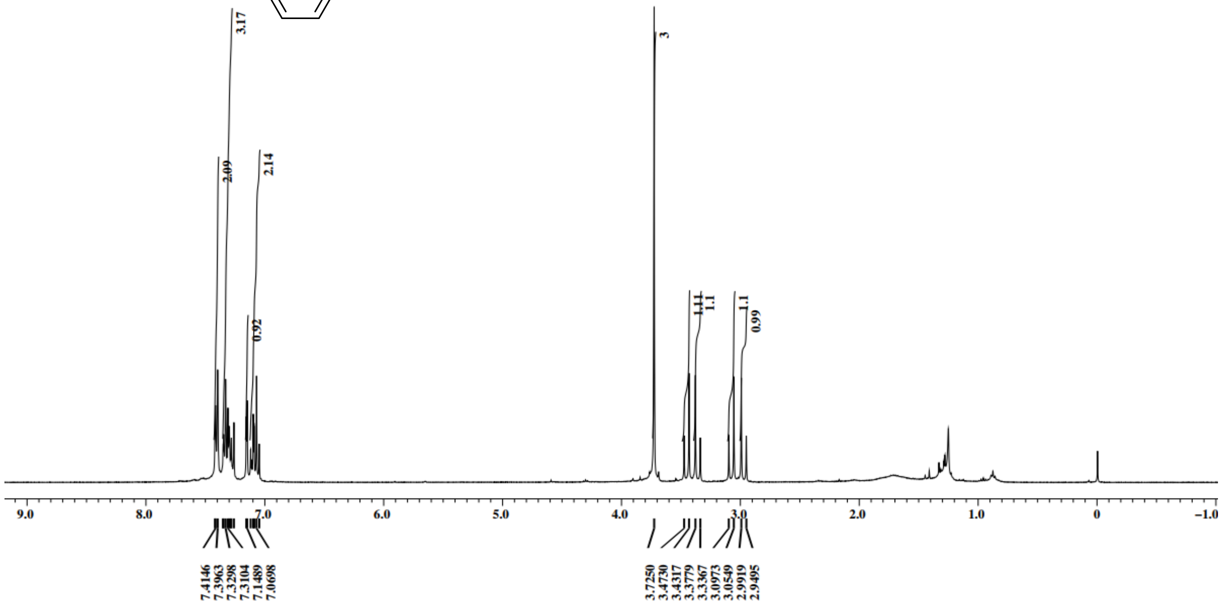
^{19}F NMR (376 MHz, CDCl$_3$)

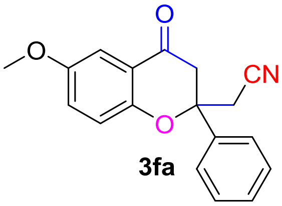




3fa

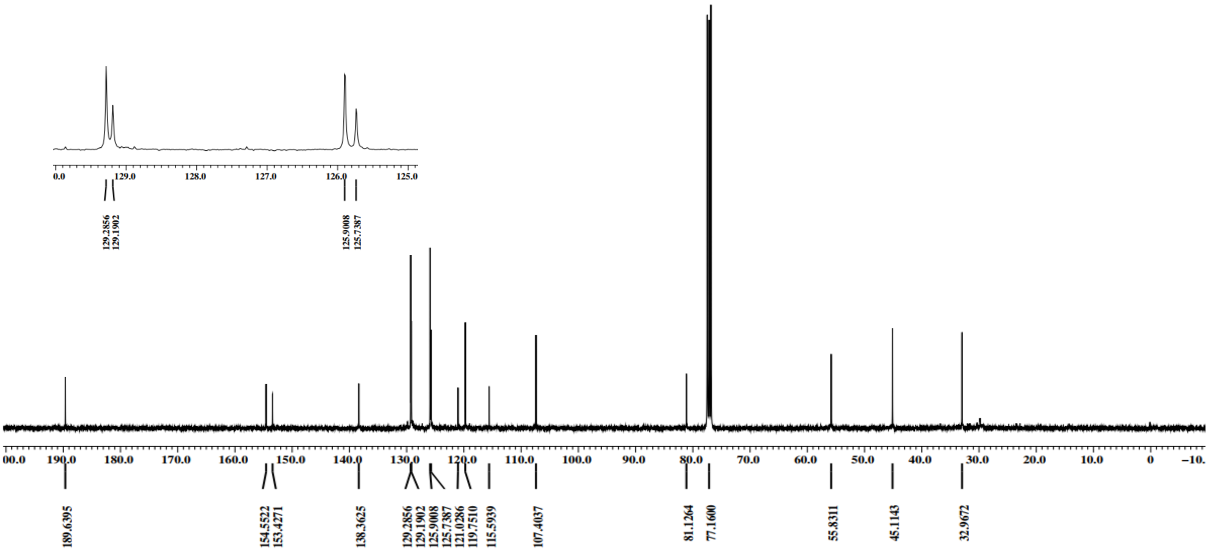
^{1}H NMR (400 MHz, CDCl$_3$)

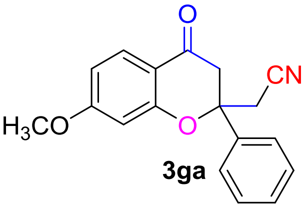




3fa

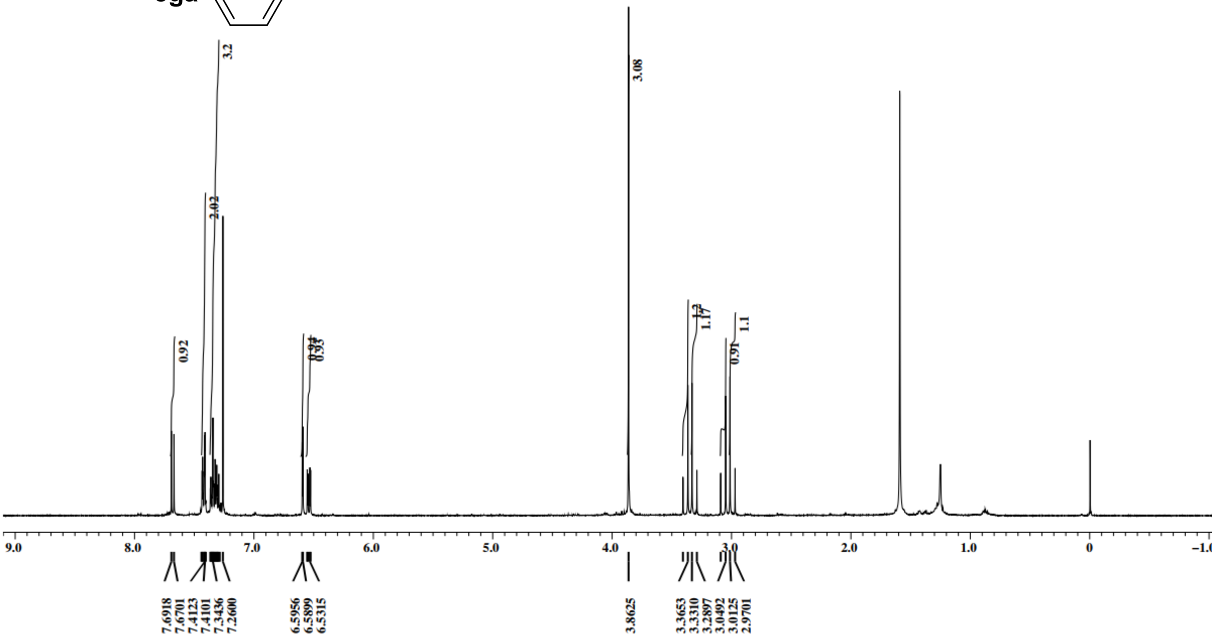
^{13}C NMR (100 MHz, CDCl$_3$)

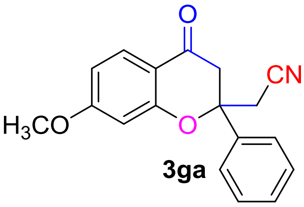




3ga

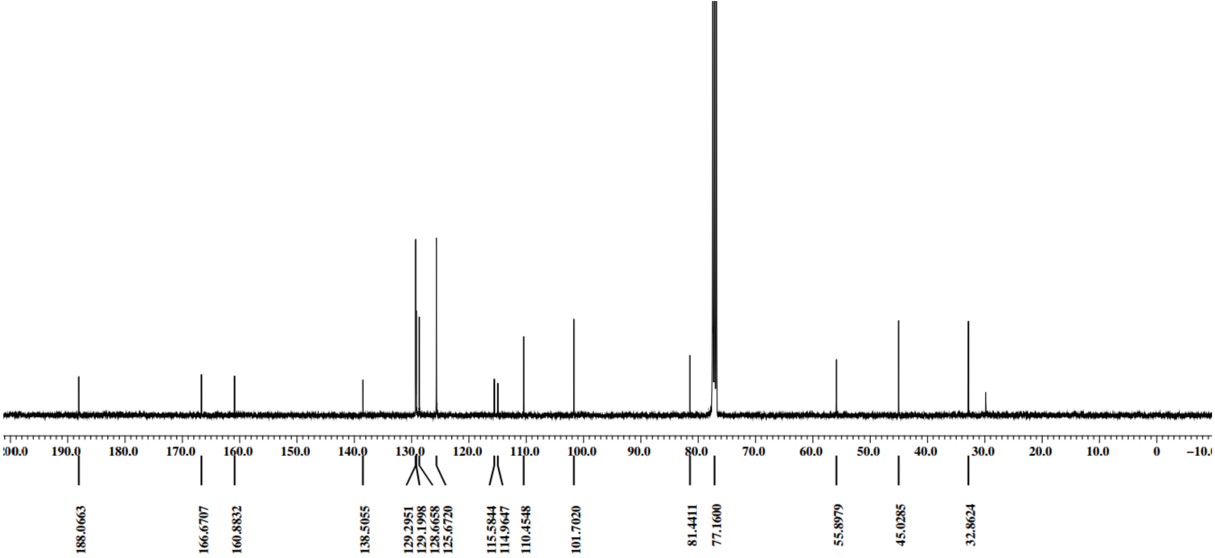
^{1}H NMR (400 MHz, CDCl$_3$)

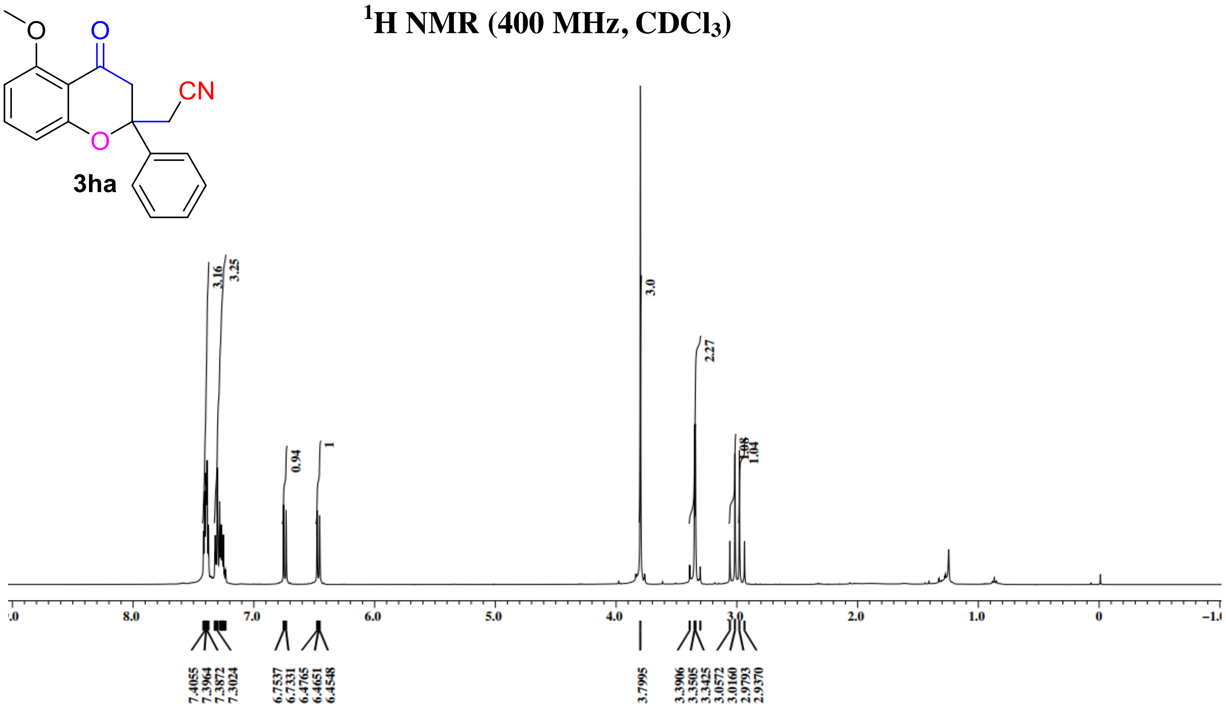




3ga

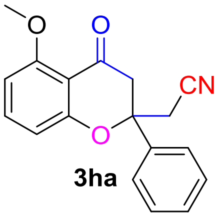
^{13}C NMR (100 MHz, CDCl$_3$)





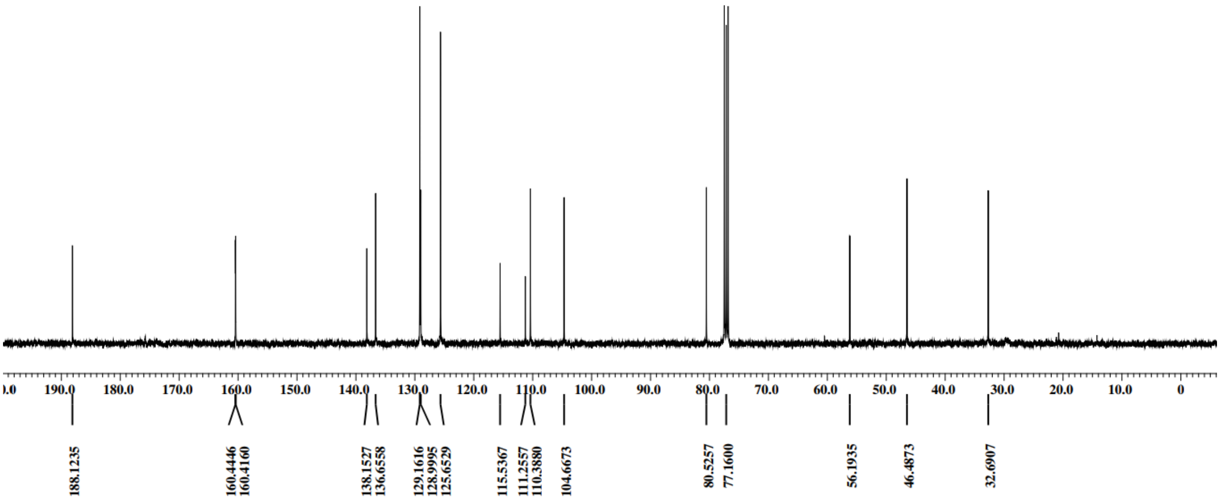
3ha

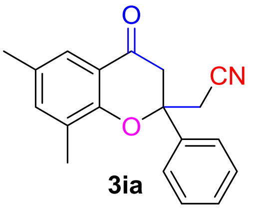
^{1}H NMR (400 MHz, CDCl$_3$)



3ha

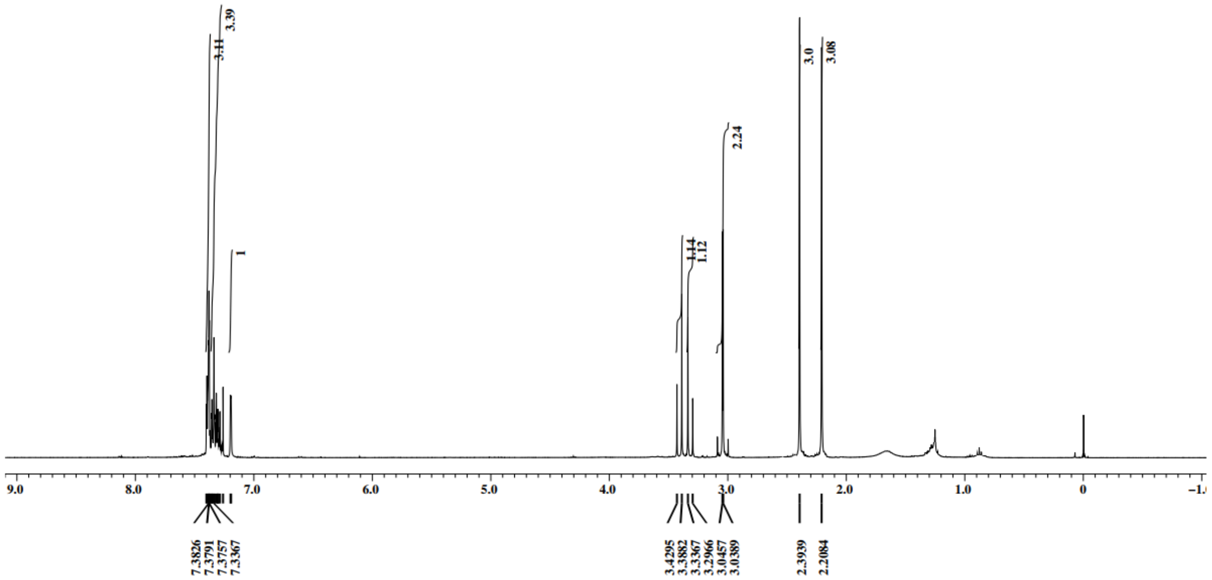
^{13}C NMR (100 MHz, CDCl$_3$)

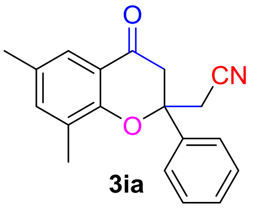




3ia

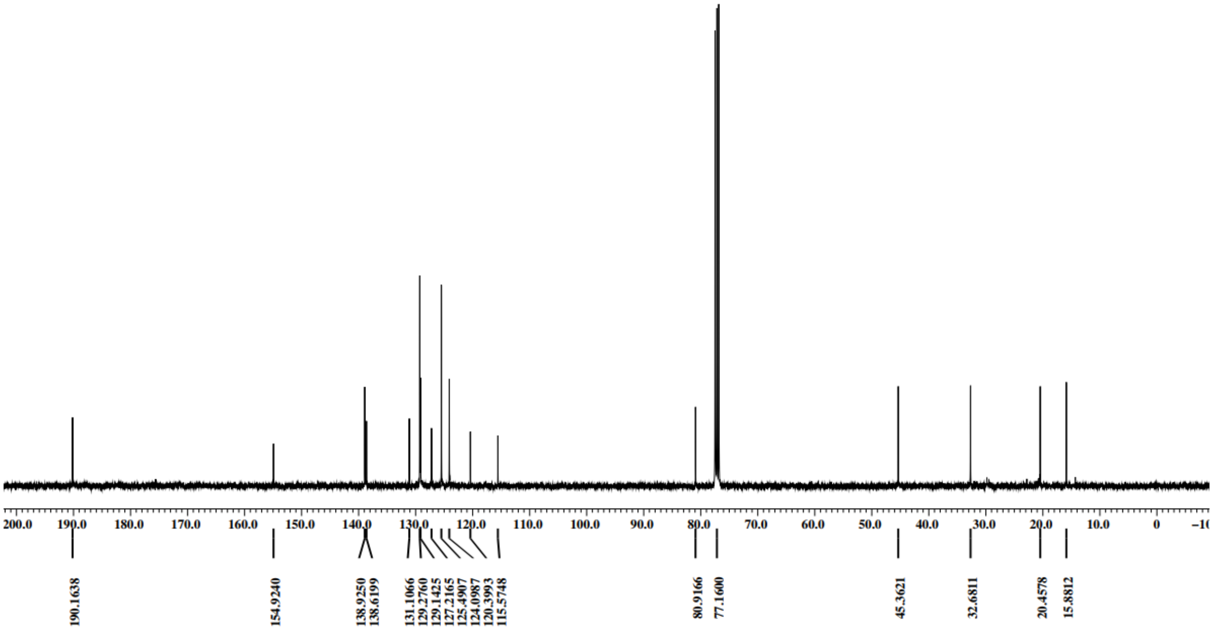
^{1}H NMR (400 MHz, $CDCl_3$)



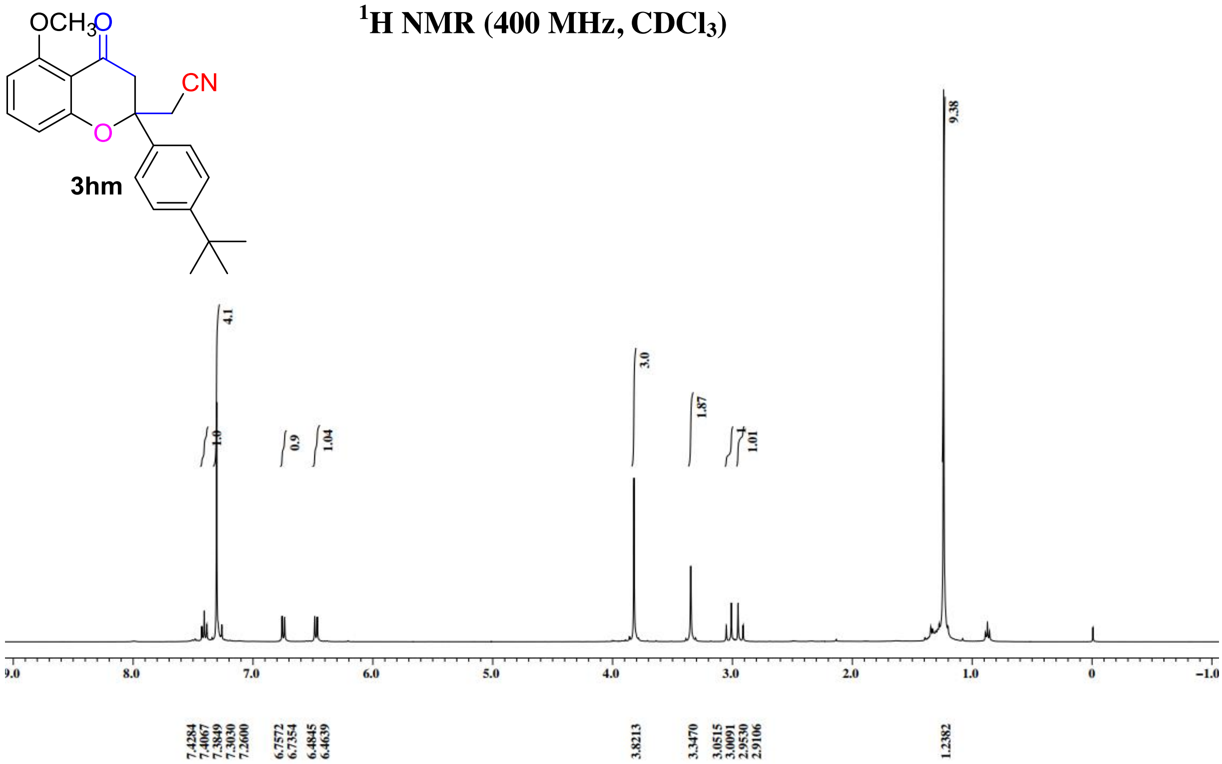


3ia

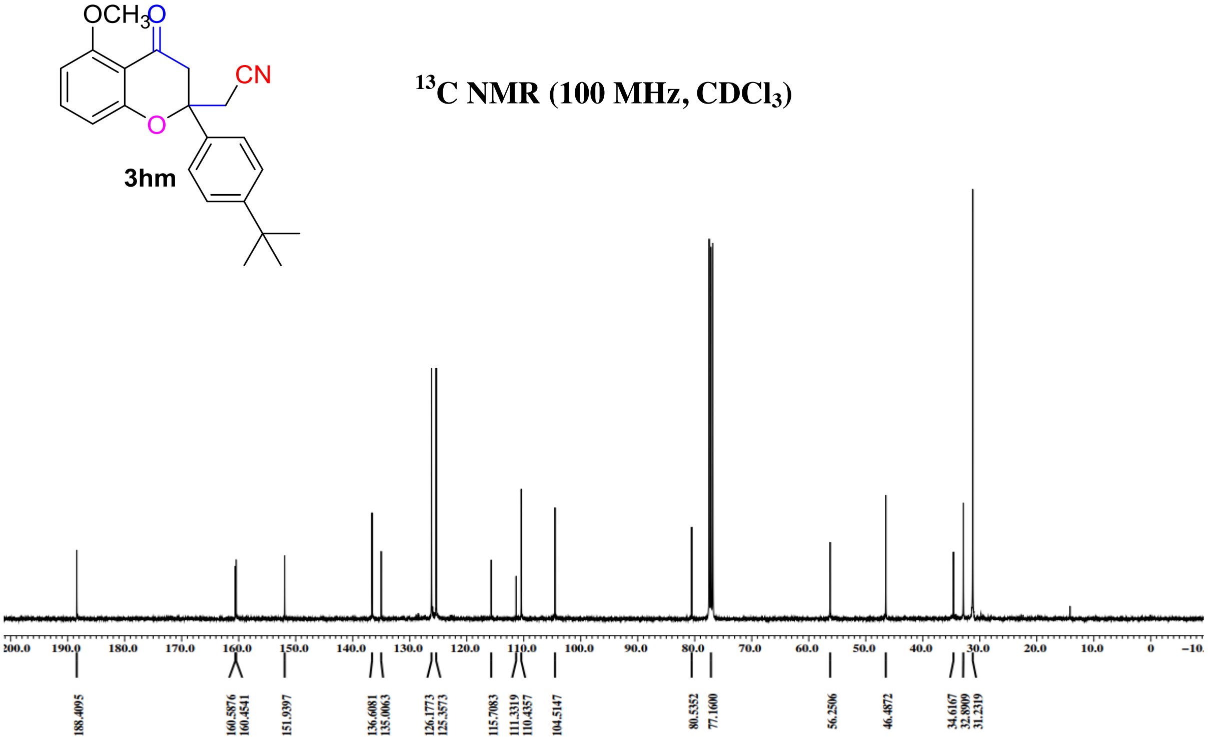
^{13}C NMR (100 MHz, $CDCl_3$)



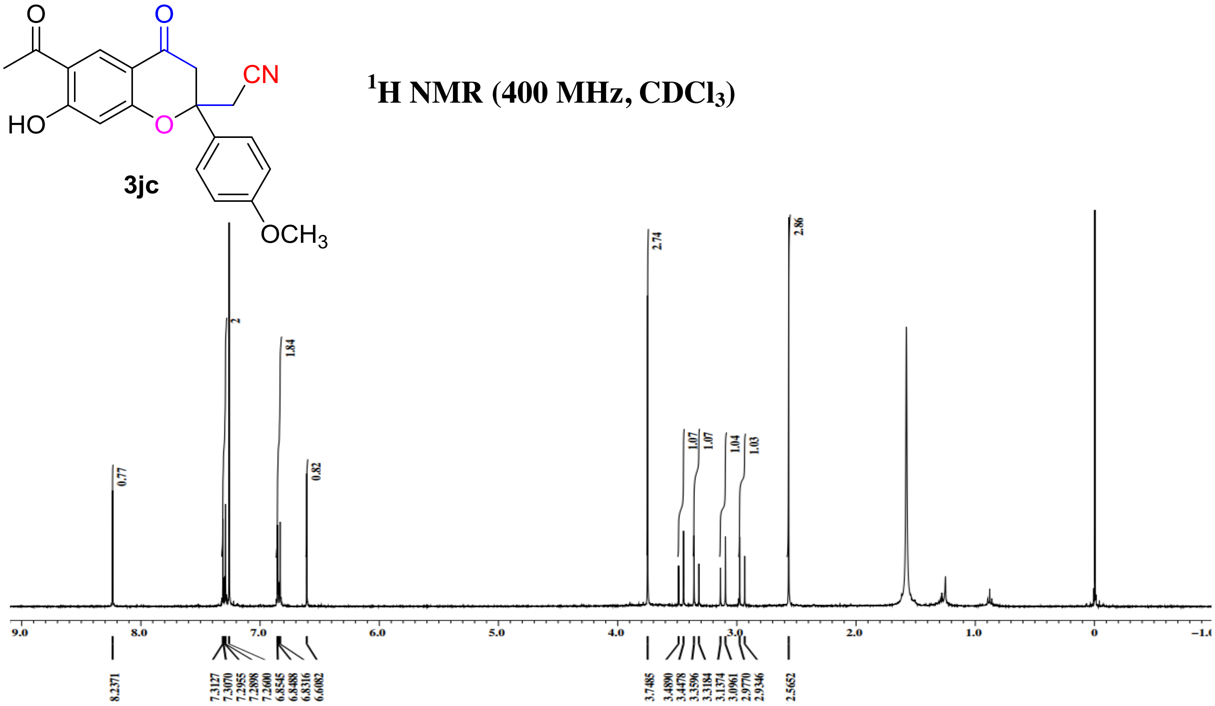
^{1}H NMR (400 MHz, CDCl$_3$)


3hm

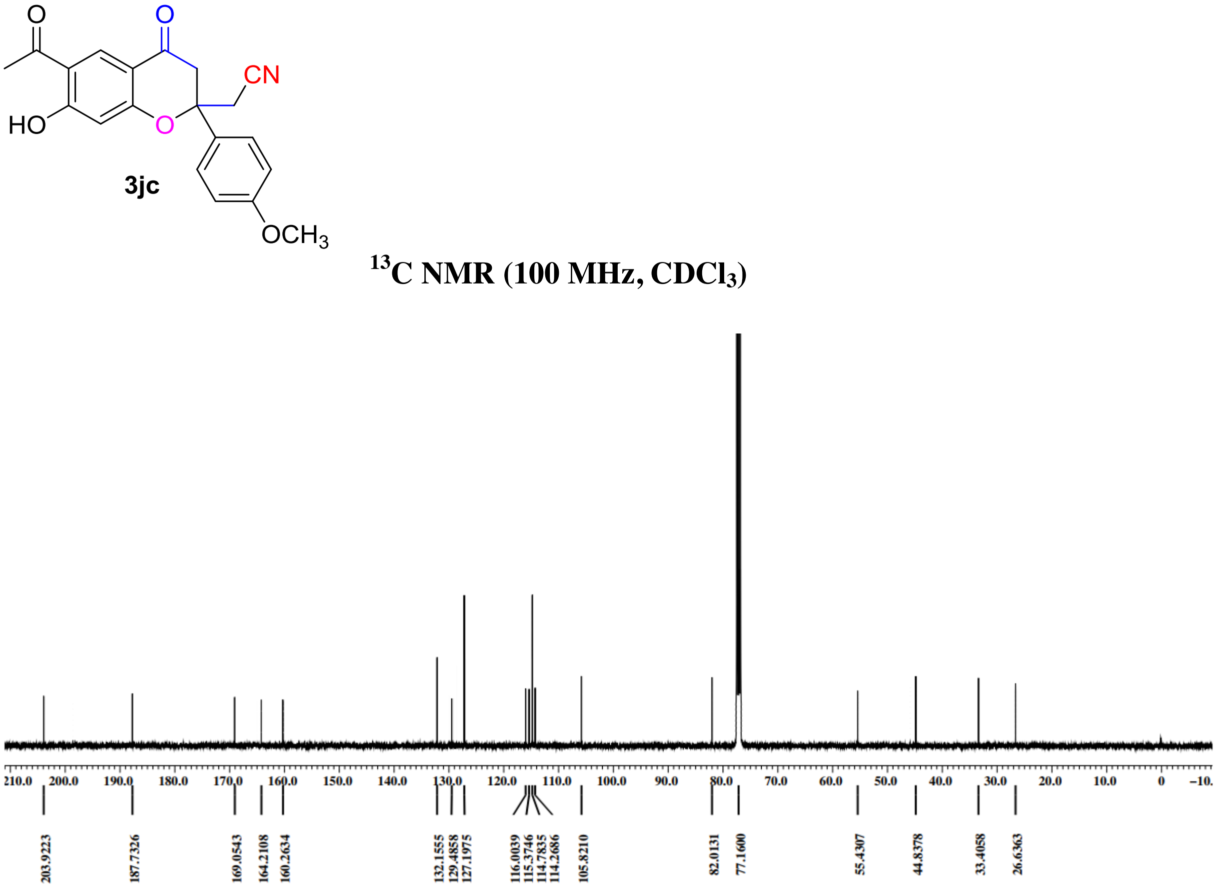
^{13}C NMR (100 MHz, CDCl$_3$)

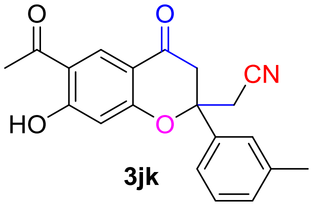

3hm

^{1}H NMR (400 MHz, CDCl$_3$)



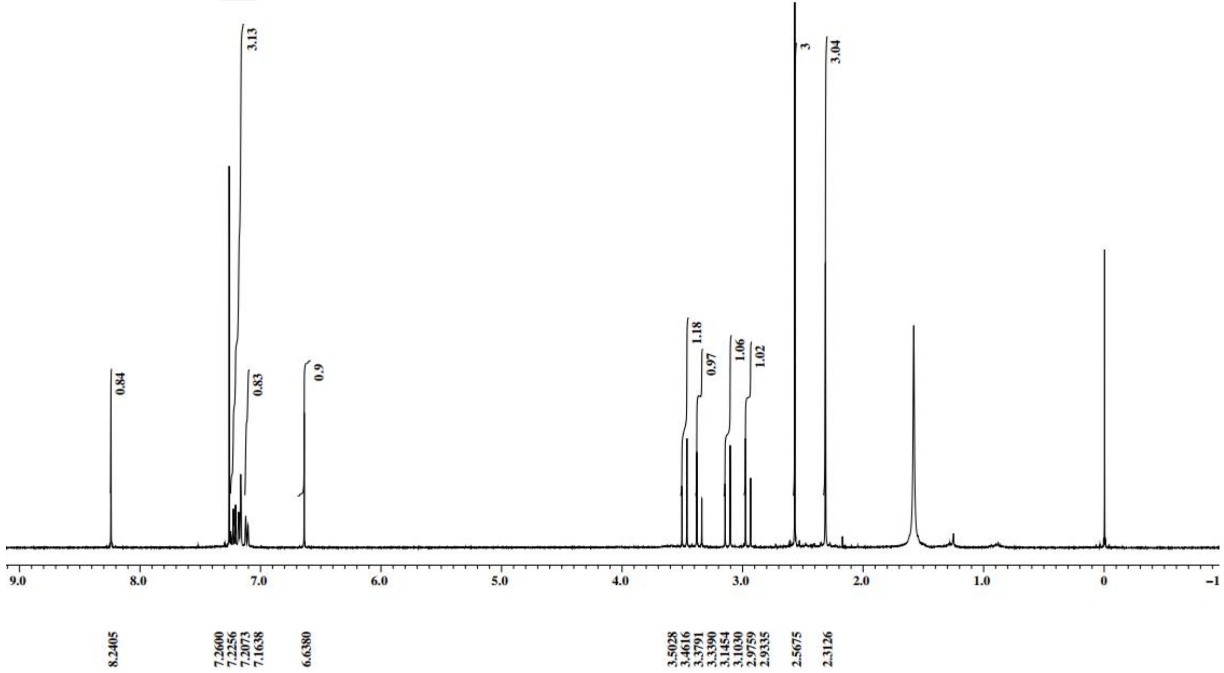
^{13}C NMR (100 MHz, CDCl$_3$)

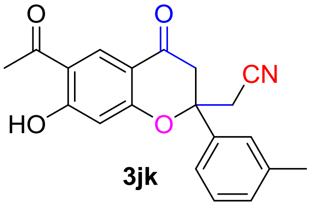




3jk

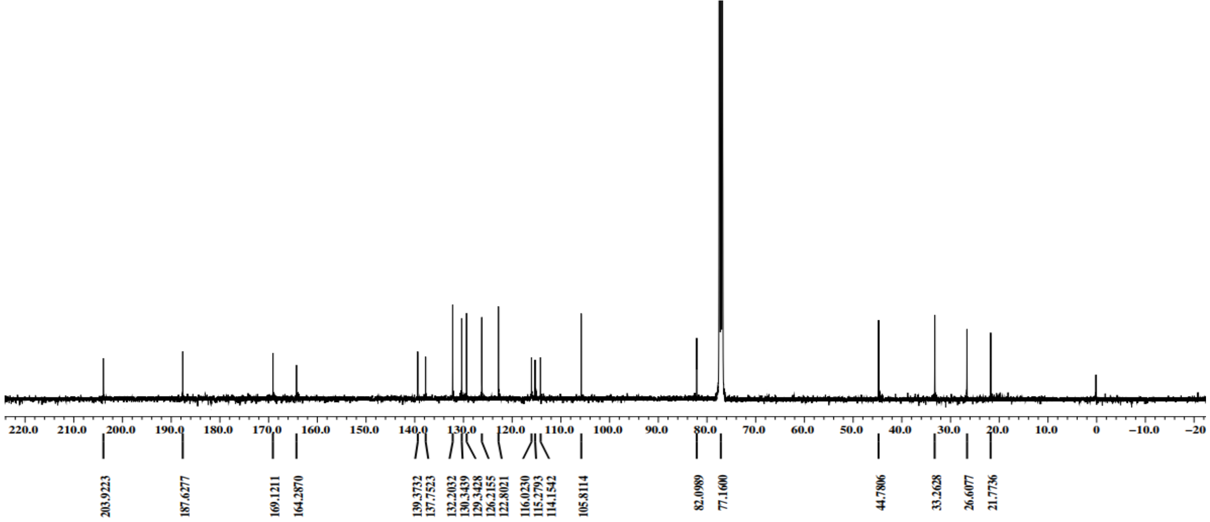
^{1}H NMR (400 MHz, CDCl$_3$)



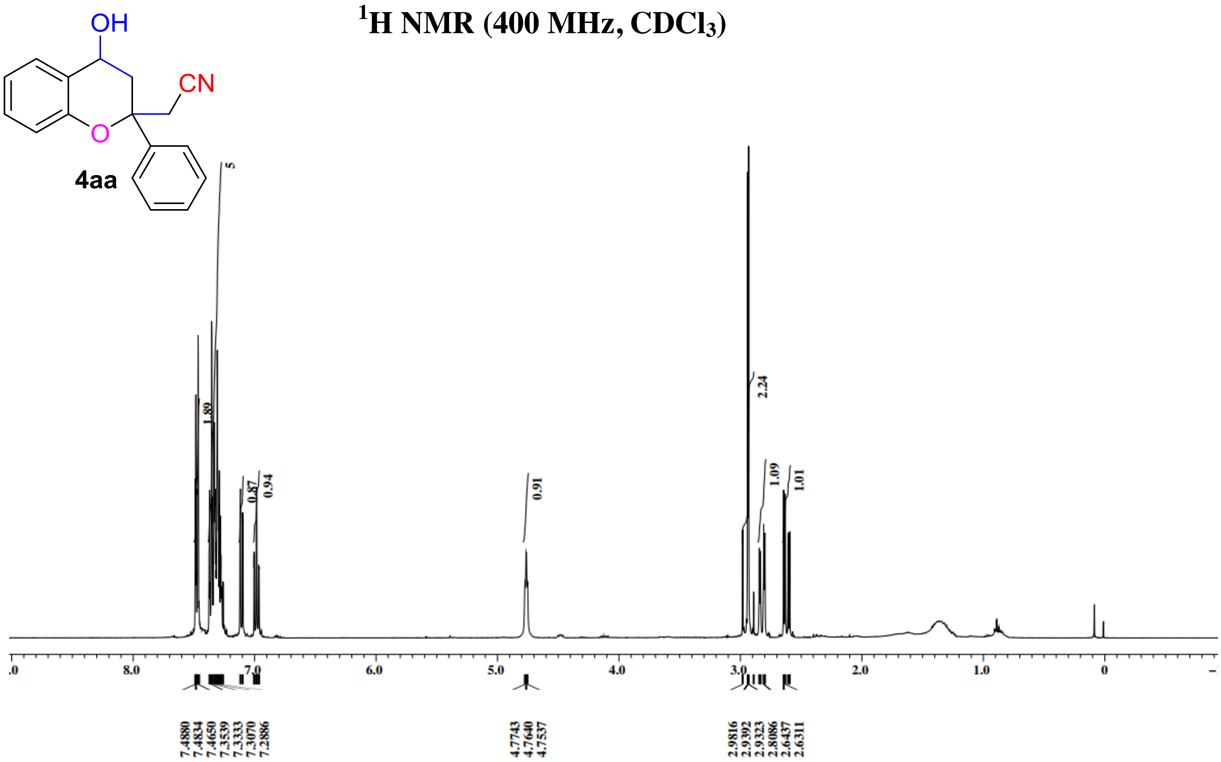


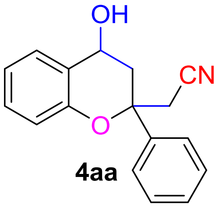
3jk

^{13}C NMR (100 MHz, CDCl$_3$)



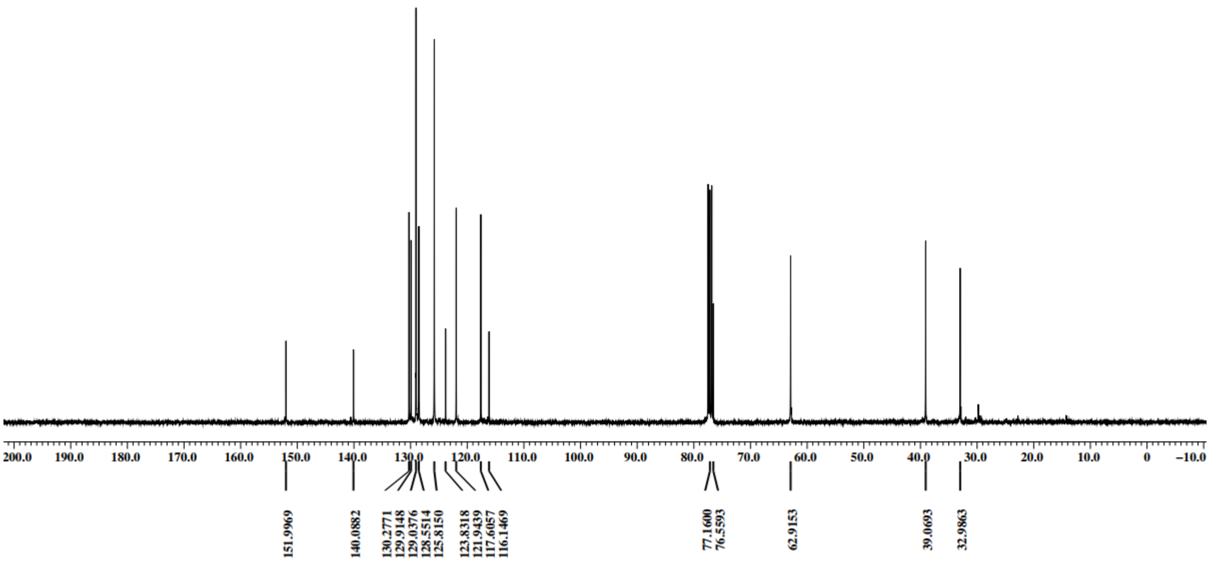
^{1}H NMR (400 MHz, CDCl$_3$)

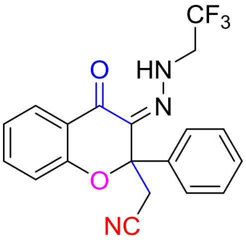




4aa

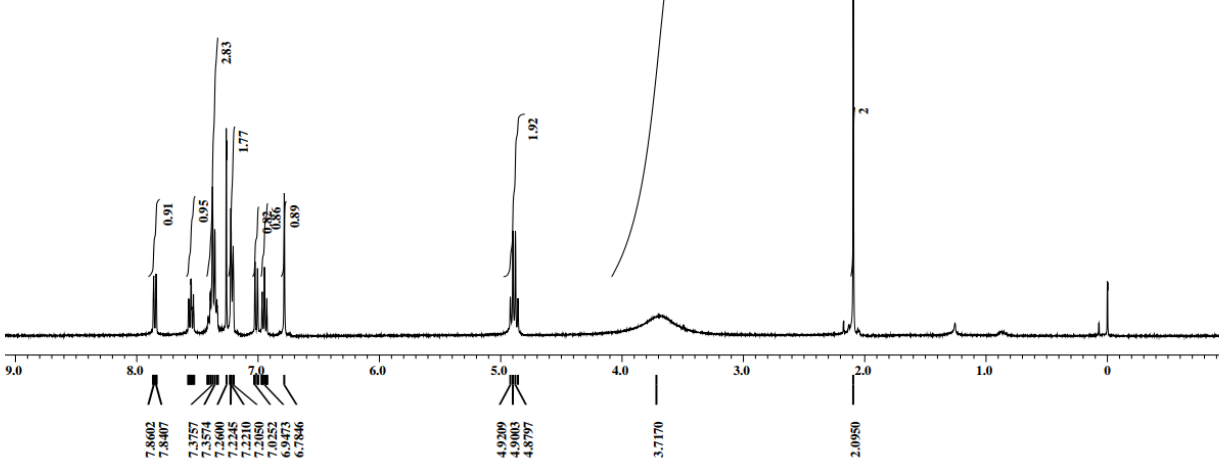
^{13}C NMR (100 MHz, CDCl$_3$)

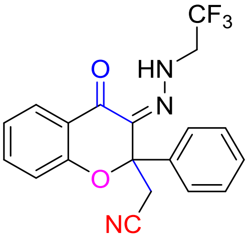




5aa

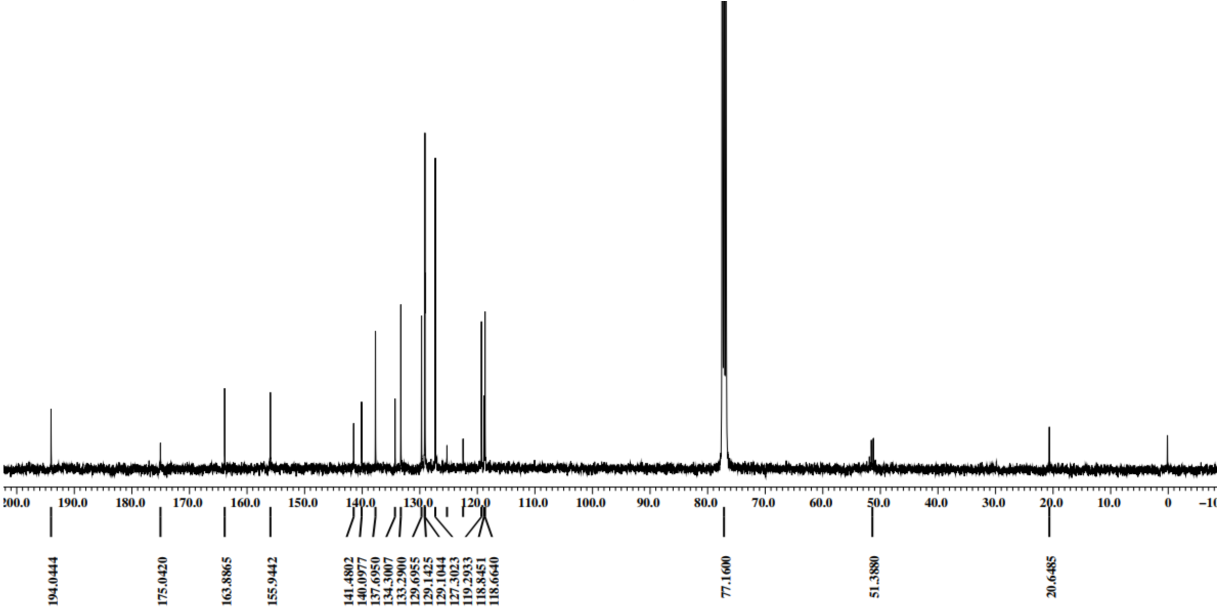
^{1}H NMR (400 MHz, CDCl$_3$)





5aa

^{13}C NMR (100 MHz, CDCl$_3$)



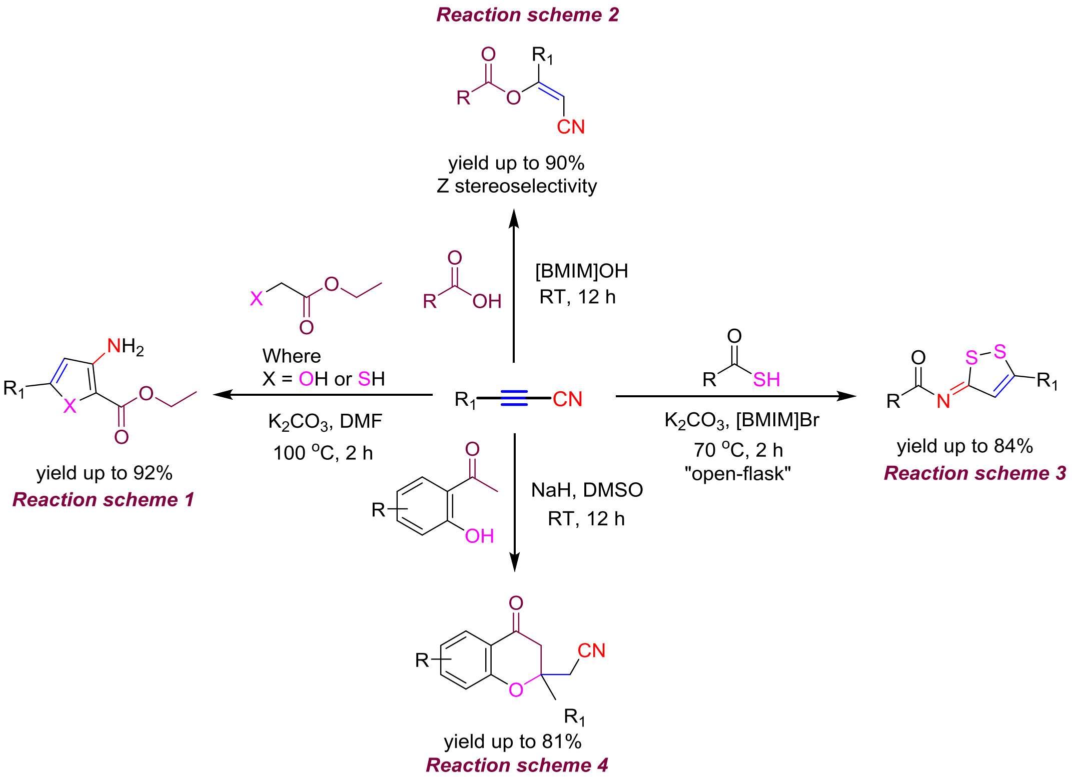
CHAPTER 6

Conclusions

Chapter 6: Conclusions

Bifunctional alkynenitriles with the alkyne-π system (acetylene) and a nitrile moiety in the same molecule offers opportunities for constructing various chemically and biologically important carbo- and heterocycles. Inspired by their unique chemistry, in our lab, multiple attempts are being made to exploit these bifunctional compounds to synthesize important heterocyclic structural scaffolds. This thesis aims to delineate the results and observations based on the experimental work performed on synthetically important scaffolds and heterocyclic ring construction from these readily available, bifunctional alkynenitriles employing transition metal-free reaction conditions. Five and six-membered heterocyclic compounds are frequently found in various natural products, pharmaceuticals, agrochemicals, and dyes. These primary ring cores play a significant role in constructing different drug molecules. Over the last few decades, the general synthetic routes to prepare these compounds mainly relied on the transition metal-catalyzed reactions, all of which involve the derivatization of the already available aromatic/heteroaromatic ring, elevated temperatures, and significant reaction times. Herein, we have developed facile synthetic protocols for constructing molecular architectures often found as core structures of various biologically active and pharmaceutically important molecules.

The work, presented in the thesis emphasizes the exploitation of alkynenitriles, the bifunctional compounds to construct aromatic/heteroaromatic ring by means of using atom-economical and straight forward conjugate addition approach. In this respect, one methodology has been developed for synthesizing different furans and thiophenes (Reaction scheme 1). Here, 3-aminofurans have been synthesized through K_2CO_3 mediated conjugate addition reactions between ethyl glycolates and alkynenitriles. The reaction employed K_2CO_3/DMF as a base/solvent system. 3 equiv. of base generates 3-amino substituted, furan heterocycle via *in situ* generation of cyanovinyl ether from the reaction of heteronucleophile having EWG at α-position with alkynenitrile, which subsequently could undergo modified intramolecular Thorpe-Ziegler cyclization. The methodology also provides an efficient one-pot access to 3-aminothiophenes in good to



Scheme 6.1.1 A quick view of transition metal-free routes to some synthetically important structural scaffolds, presented in the thesis.

excellent yields. The reaction system consisting of [BMIM]OH as the catalyst as well as the reaction medium furnished *Z*-stereoselective enol esters within 12 h via conjugate addition reaction between carboxylic acids and alkynenitriles (Reaction scheme 2).

Furthermore, a simple approach to furnish 1,2-dithiols in moderate to good yields was developed employing solvent-free ionic liquid mediated addition reactions between thiobenzoic acids and alkynenitriles using [BMIM]Br as the reaction medium and K_2CO_3 as the base (Reaction scheme 3). The method has broad substrate scope w.r.t thiocarboxylic acids as well as alkynenitriles. It was anticipated that the disulfide, generated *in situ* by aerial oxidation of thiocarboxylic acids is acting as an important reaction intermediate. After that, oxygen based biologically important six membered heterocycles 4-chromanones were synthesized in good to excellent yields from the one-pot double conjugate addition reactions between 2-hydroxyacetophenones and alkynenitriles employing NaH as a base in DMSO solvent (Reaction scheme 4).

Appendix A: Chapter 2

Single Crystal X-Ray

For the determination of X-ray crystal structures, single crystals were selected and mounted with paratone oil on a glass fiber using gum. The data were collected at 293 K on a CMOS based Bruker D8 Venture PHOTON 100 diffractometer equipped with a INCOATEC micro-focus source with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) operating at 50 kV and 30 mA. For the integration of diffraction profiles SAINT program[1] was used. Adsorption correction was done applying SADABS program[2]. The crystal structure was solved by SIR 92[3] and refined by full matrix least square method using SHELXL-97[4] WinGX system, Ver 1.70.01[5]. All the non-hydrogen atoms in the structure were located from the Fourier map and refined anisotropically. The hydrogen atoms were fixed by HFIX in their ideal positions and refined using riding model with isotropic thermal parameters.

Single Crystal X-Ray Data of **3ba**, **3cd**, **4ab'**, **4bb'**, **4eb'** and **5**

CCDC-2153824, 2103735, 2153841, 2153870, 2103732 and 2153873 contains the supplementary crystallographic data for **3ba**, **3cd**, **4ab'**, **4bb'**, **4eb'** and **5** respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal structure of 3ba

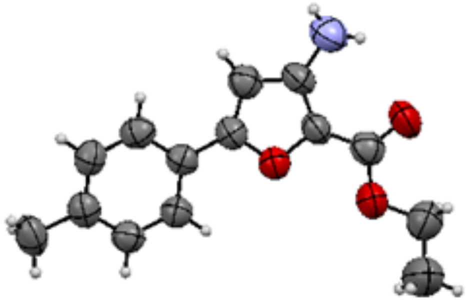


Table 1 Crystal data and structure refinement for 3ba

CCDC No.	2153824
Empirical formula	$C_{14}H_{15}NO_3$
Formula weight	245.27
Temperature/K	298.00

Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	5.458(2)
b/Å	32.021(13)
c/Å	15.119(6)
α/°	90
β/°	90.192(10)
γ/°	90
Volume/Å^3	2642.3(18)
Z	8
ρ_{calc}g/cm^3	1.233
μ/mm^{-1}	0.087
F(000)	1040.0
Crystal size/mm^3	0.386 × 0.078 × 0.045
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.672 to 50.138
Index ranges	$-6 \leq h \leq 6$, $-38 \leq k \leq 32$, $-17 \leq l \leq 18$
Reflections collected	19815
Independent reflections	4689 [R_{int} = 0.1373, R_{sigma} = 0.1518]
Data/restraints/parameters	4689/0/331
Goodness-of-fit on F^2	0.951
Final R indexes [I>=2σ (I)]	R_1 = 0.0743, wR_2 = 0.1728
Final R indexes [all data]	R_1 = 0.2497, wR_2 = 0.2685
Largest diff. peak/hole/e Å^{-3}	0.22/-0.20

Crystal structure of 3cd

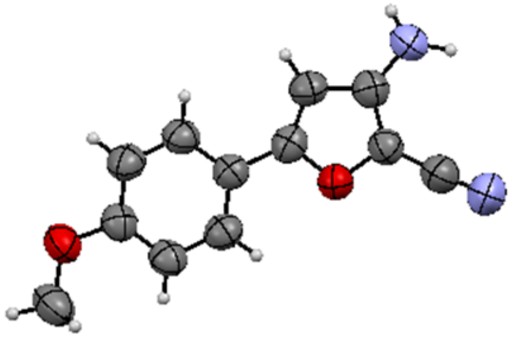


Table 2 Crystal data and structure refinement for 3cd

CCDC No.	2103735
Empirical formula	$C_{24}H_{20}N_4O_4$
Formula weight	428.44
Temperature/K	293.15
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	23.86(2)
b/Å	6.256(5)
c/Å	14.809(11)
α/°	90
β/°	95.40(4)
γ/°	90
Volume/Å^3	2201(3)
Z	4
ρ_{calc}g/cm^3	1.293
μ/mm^{-1}	0.090
F(000)	896.0
2Θ range for data collection/°	5.144 to 52.744
Index ranges	$-29 \leq h \leq 29$, $-7 \leq k \leq 7$, $-18 \leq l \leq 18$

Reflections collected	24989
Independent reflections	4493 [R_{int} = 0.1737, R_{sigma} = 0.1142]
Data/restraints/parameters	4493/0/308
Final R indexes [I>=2σ (I)]	R_1 = 0.0692, wR_2 = 0.1381
Final R indexes [all data]	R_1 = 0.1989, wR_2 = 0.1865

Crystal structure of 4ab'

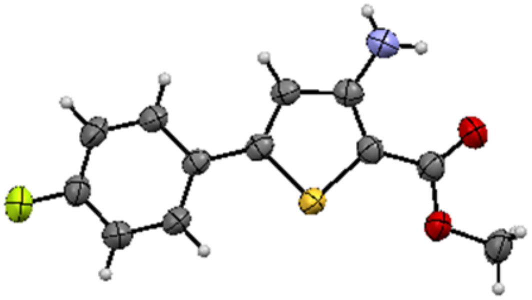


Table 3 Crystal data and structure refinement for 4ab'

CCDC No.	2153841
Empirical formula	$C_{12}H_{11}NO_2S$
Formula weight	233.28
Temperature/K	298
Crystal system	monoclinic
Space group	$P2_1$
a/Å	8.701(2)
b/Å	5.6233(14)
c/Å	11.886(4)
α/°	90
β/°	103.905(11)
γ/°	90
Volume/Å^3	564.5(3)
Z	2

ρ_{calc}g/cm^3	1.372
μ/mm^{-1}	0.270
F(000)	244.0
Crystal size/mm^3	0.356 × 0.256 × 0.048
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.824 to 56.948
Index ranges	$-11 \leq h \leq 11$, $-7 \leq k \leq 7$, $-15 \leq l \leq 15$
Reflections collected	12647
Independent reflections	2806 [R_{int} = 0.0500, R_{sigma} = 0.0372]
Data/restraints/parameters	2806/1/154
Final R indexes [I>=2σ (I)]	R_1 = 0.0331, wR_2 = 0.0758
Final R indexes [all data]	R_1 = 0.0520, wR_2 = 0.0855
Largest diff. peak/hole/e Å^{-3}	0.20/-0.21

Crystal structure of 4bb'

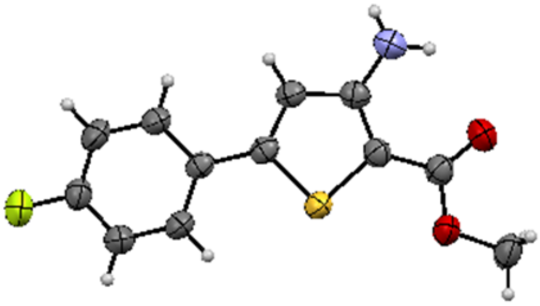


Table 4 Crystal data and structure refinement for 4bb'

CCDC No.	2153870
Empirical formula	$C_{13}H_{13}NO_2S$
Formula weight	247.30
Temperature/K	298
Crystal system	monoclinic
Space group	$P2_1/c$

a/Å	13.112(8)
b/Å	5.823(3)
c/Å	16.148(10)
α/°	90
β/°	98.40(2)
γ/°	90
Volume/Å^3	1219.6(12)
Z	4
ρ_{calc}g/cm^3	1.347
μ/mm^{-1}	0.254
F(000)	520.0
Crystal size/mm^3	0.256 × 0.154 × 0.089
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.1 to 52.378
Index ranges	$-16 \leq h \leq 16$, $-7 \leq k \leq 7$, $-20 \leq l \leq 20$
Reflections collected	25557
Independent reflections	2435 [R_{int} = 0.0624, R_{sigma} = 0.0310]
Data/restraints/parameters	2435/0/164
Final R indexes [I>=2σ (I)]	R_1 = 0.0410, wR_2 = 0.1039
Final R indexes [all data]	R_1 = 0.0631, wR_2 = 0.1223
Largest diff. peak/hole/e Å^{-3}	0.23/-0.20

Crystal structure of 4eb'

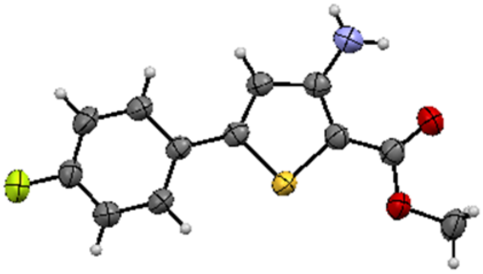


Table 5 Crystal data and structure refinement for 4eb'

CCDC No.	2103732
Empirical formula	$C_{12}H_{10}FNO_2S$
Formula weight	251.27
Temperature/K	293.15
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	12.230(12)
b/Å	5.594(5)
c/Å	16.719(16)
α/°	90
β/°	91.29(3)
γ/°	90
Volume/Å^3	1143.5(18)
Z	4
ρ_{calc}g/cm^3	1.459
μ/mm^{-1}	0.284
F(000)	520.0
Crystal size/mm^3	0.359 × 0.321 × 0.078
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.874 to 52.734
Index ranges	$-15 \leq h \leq 15, -6 \leq k \leq 6, -20 \leq l \leq 20$
Reflections collected	12176
Independent reflections	2294 [R_{int} = 0.0515, R_{sigma} = 0.0379]
Data/restraints/parameters	2294/0/163
Goodness-of-fit on F^2	1.039
Final R indexes [I>=2σ (I)]	R_1 = 0.0403, wR_2 = 0.0919
Final R indexes [all data]	R_1 = 0.0562, wR_2 = 0.1006

Largest diff. peak/hole/e Å^{-3}	0.22/-0.18

Crystal structure of 5

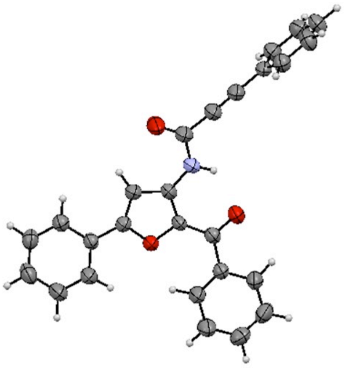


Table 6 Crystal data and structure refinement for 5

CCDC No.	2153873
Empirical formula	$C_{26}H_{17}NO_3$
Formula weight	391.40
Temperature/K	298
Crystal system	triclinic
Space group	P-1
a/Å	5.8957(13)
b/Å	12.609(3)
c/Å	14.233(4)
α/°	110.451(8)
β/°	91.406(8)
γ/°	95.505(7)
Volume/Å^3	984.9(4)
Z	2
ρ_{calc}g/cm^3	1.320
μ/mm^{-1}	0.087

F(000)	408.0
Crystal size/mm^3	0.256 × 0.125 × 0.045
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.378 to 50.854
Index ranges	$-7 \le h \le 7$, $-15 \le k \le 15$, $-17 \le l \le 17$
Reflections collected	14936
Independent reflections	3604 [R_{int} = 0.1063, R_{sigma} = 0.0950]
Data/restraints/parameters	3604/0/340
Goodness-of-fit on F^2	1.011
Final R indexes [I>=2σ (I)]	R_1 = 0.0591, wR_2 = 0.1325
Final R indexes [all data]	R_1 = 0.1408, wR_2 = 0.1810
Largest diff. peak/hole/e Å^{-3}	0.21/-0.20

Appendix B: Chapter 3

Single Crystal X-Ray Data of **3aa, 3ab, 3ah, 3al, 3ch, 3am, 3aq, 3ai,** and **3aj**

Compounds **3aa, 3ab, 3ah, 3al, 3ch, 3am, 3aq, 3ai,** and **3aj** were isolated as pure single crystals. The crystal structures have been deposited to Cambridge Crystallographic Data Centre and allotted deposition numbers are 1955826, 1956366, 1956367, 1955829, 1955825, 1955831, 1955836, 1955838 and 1955847 respectively.

Crystal structure of 3aa

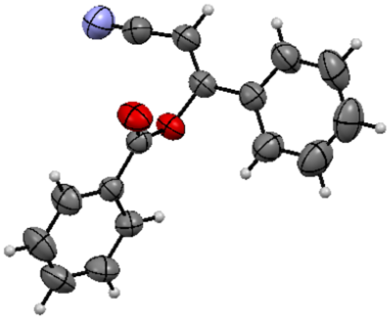


Table 1 Crystal data and structure refinement of 3aa

CCDC No.	1955826
Formula	$C_{16}H_{11}NO_2$
Formula weight	249.26
Crystal system	Monoclinic
Space group	P21/c
a, b, c (Å)	13.4056(9), 9.5884(6), 10.4878(7)
α, β, γ (°)	90, 102.493(2), 90
V (Å^3)	1316.16(15)
Z	4
Calculated density (g/cm^3)	1.258
Absorption coefficient (mm^{-1})	0.084
F(000)	520
Theta range for data collection:	2.9 to 28.3
Data set	-17: 14 ; -12: 12 ; -13: 13

Reflection	11280
Independent refl.	3199, (R(int) = 0.032)
data [I > 2σ(I)]	2293
R indices (all data)	R = 0.0618, wR_2 = 0.1722
S	1.06
Min. and Max. Resd. Dens. (e/$Å^3$)	-0.16 and 0.17

Crystal structure of 3ab

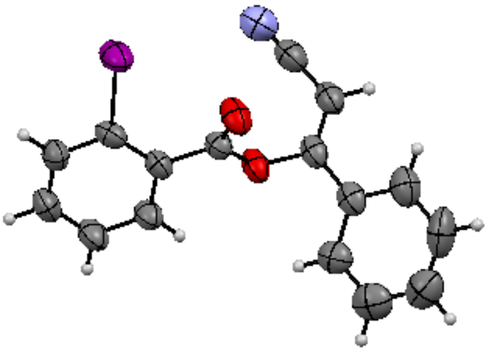


Table 2 Crystal data and structure refinement of 3ab

CCDC No.	1956366
Formula	$C_{16}H_{10}INO_2$
Formula weight	375.15
Crystal system	Monoclinic
Space group	P21/c
a, b, c (Å)	9.6440(7), 15.2393(9), 9.9287(5)
α, β, γ (°)	90, 97.574(2), 90
V ($Å^3$)	1446.47(15)
Z	4
Calculated density (g/cm^3)	1.723
Absorption coefficient (mm^{-1})	2.214
F(000)	728

Theta range for data collection:	2.5 to 26.4
Data set	-12: 8; -19: 14; -12: 11
Reflection	6101
Independent refl.	2925, (R(int) = 0.045)
data [I > 2σ(I)]	2339
R indices (all data)	R = 0.0647, wR_2 = 0.2159
S	1.04
Min. and Max. Resd. Dens. (e/Å^3)	-0.75 and 0.92

Crystal structure of 3ah

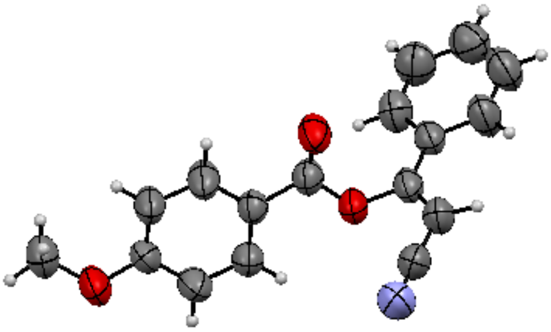


Table 3 Crystal data and structure refinement of 3ah

CCDC No.	1956367
Formula	$C_{17}H_{13}NO_3$
Formula weight	279.28
Crystal system	Triclinic
Space group	P-1
a, b, c (Å)	4.501(3), 10.175(6), 15.909(9)
α, β, γ (°)	87.196(19), 84.330(17), 80.128(18)
V (Å^3)	713.9(8)
Z	2
Calculated density (g/cm^3)	1.299
Absorption coefficient (mm^{-1})	0.090
F(000)	292

Theta range for data collection:	2.4 to 26.6
Data set	-4: 5 ; -12: 12 ; -19: 20
Reflection	7142
Independent refl.	2925, (R(int) = 0.085)
data [$I > 2\sigma(I)$]	1206
R indices (all data)	R = 0.0894, wR_2 = 0.3155
S	0.98
Min. and Max. Resd. Dens. (e/Å^3)	-0.22 and 0.27

Crystal structure of 3al

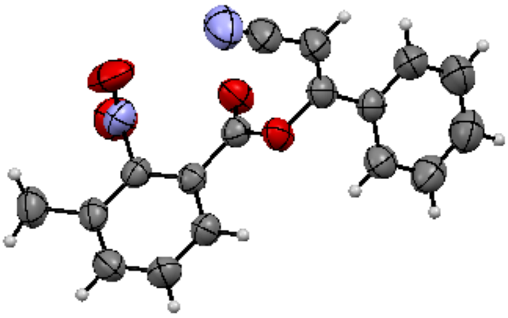


Table 4 Crystal data and structure refinement of 3al

CCDC No.	1955829
Formula	$C_{17}H_{12}N_2O_4$
Formula weight	308.29
Crystal system	Monoclinic
Space group	C2/c
a, b, c (Å)	26.827(4), 7.8444(10), 14.910(2)
α, β, γ (°)	90, 91.997(5), 90
V (Å^3)	3135.8(7)
Z	8
Calculated density (g/cm^3)	1.306
Absorption coefficient (mm^{-1})	0.095
F(000)	1280

Theta range for data collection:	2.7 to 28.0
Data set	-35: 35 ; -10: 10 ; -19: 19
Reflection	20640
Independent refl.	3761, (R(int) = 0.098)
data [$I > 2\sigma(I)$]	2086
R indices (all data)	R = 0.0693, wR_2 = 0.2327
S	1.03
Min. and Max. Resd. Dens. (e/Å^3)	-0.28 and 0.27

Crystal structure of 3ch

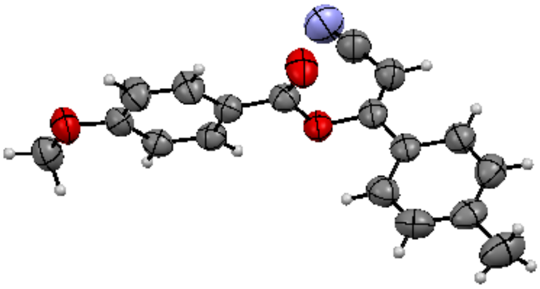


Table 5 Crystal data and structure refinement of 3ch

CCDC No.	1955825
Formula	$C_{18}H_{15}NO_3$
Formula weight	293.31
Crystal system	Monoclinic
Space group	P21/n
a, b, c (Å)	8.7829(8), 9.4702(8), 18.8436(18)
α, β, γ (°)	90, 99.941(3), 90
V (Å^3)	1543.8(2)
Z	4
Calculated density (g/cm^3)	1.262
Absorption coefficient (mm^{-1})	0.086
F(000)	616

Theta range for data collection:	2.2 to 26.4
Data set	-10: 10 ; -11: 9 ; -23: 23
Reflection	15308
Independent refl.	3094, (R(int) = 0.032)
data $[I > 2\sigma(I)]$	2184
R indices (all data)	$R = 0.0533$, $wR_2 = 0.1514$
S	1.12
Min. and Max. Resd. Dens. (e/Å^3)	-0.16 and 0.20

Crystal structure of 3am

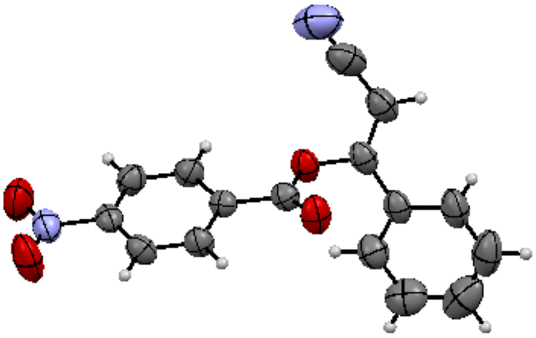


Table 6 Crystal data and structure refinement of 3am

CCDC No.	1955831
Formula	$C_{16}H_{10}N_2O_4$
Formula weight	294.26
Crystal system	Monoclinic
Space group	P21/n
a, b, c (Å)	7.2849(5), 27.990(2), 7.0362(6)
α, β, γ (°)	90, 100.301(3), 90
V (Å^3)	1411.59(19)
Z	4
Calculated density (g/cm^3)	1.385
Absorption coefficient (mm^{-1})	0.102

F(000)	608
Theta range for data collection:	2.9 to 28.3
Data set	-9: 9 ; -37: 26 ; -9: 8
Reflection	12595
Independent refl.	3433, (R(int) = 0.047)
data [I > 2σ(I)]	2465
R indices (all data)	R = 0.0562, wR_2 = 0.1437
S	1.03
Min. and Max. Resd. Dens. (e/Å^3)	-0.16 and 0.16

Crystal structure of 3aq

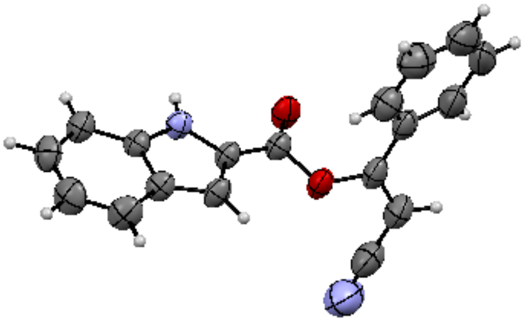


Table 7 Crystal data and structure refinement of 3aq

CCDC No.	1955836
Formula	$C_{18}H_{12}N_2O_2$
Formula weight	288.30
Crystal system	Monoclinic
Space group	P21/n
a, b, c (Å)	7.1790(9), 26.849(3), 7.5558(11)
α, β, γ (°)	90, 95.998(5), 90
V (Å^3)	1448.4(3)
Z	4
Calculated density (g/cm^3)	1.322

Absorption coefficient (mm^{-1})	0.088
F(000)	600
Theta range for data collection:	2.8 to 26.4
Data set	-8: 8; -31: 33; -9: 9
Reflection	11531
Independent refl.	2840, (R(int) = 0.040)
data [I > 2σ(I)]	2114
R indices (all data)	R = 0.0570, wR$_2$ = 0.1358
S	1.11
Min. and Max. Resd. Dens. (e/Å^3)	-0.19 and 0.17

Crystal structure of 3ai

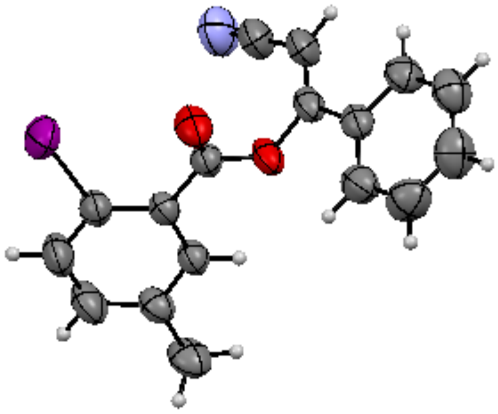


Table 8 Crystal data and structure refinement of 3ai

CCDC No.	1955838
Formula	$C_{17}H_{12}INO_2$
Formula weight	389.18
Crystal system	Monoclinic
Space group	P21/n
a, b, c (Å)	13.0663(7), 15.0648(8), 8.1922(4)
α, β, γ (°)	90, 104.548(2), 90
V (Å^3)	1560.86(14)

Z	4
Calculated density (g/cm^3)	1.656
Absorption coefficient (mm^{-1})	2.055
F(000)	760
Theta range for data collection:	2.7 to 26.7
Data set	-15: 16 ; -19: 19 ; -10: 9
Reflection	17318
Independent refl.	3157, (R(int) = 0.024)
data [$I > 2\sigma(I)$]	2493
R indices (all data)	R = 0.0311, wR_2 = 0.0675
S	1.05
Min. and Max. Resd. Dens. (e/Å^3)	-0.68 and 0.57

Crystal structure of 3aj

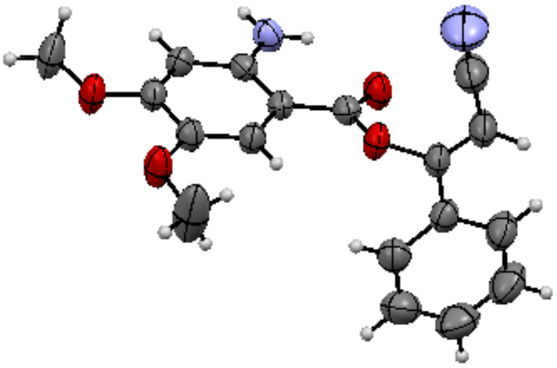


Table 9 Crystal data and structure refinement of 3aj

CCDC No.	1955847
Formula	$C_{18}H_{16}N_2O_4$
Formula weight	324.33
Crystal system	Monoclinic
Space group	P21/n
a, b, c (Å)	10.4120(4), 13.5033(5), 11.9276(5)

α, β, γ (°)	90, 94.684(1), 90
V (Å^3)	1671.38(11)
Z	4
Calculated density (g/cm^3)	1.289
Absorption coefficient (mm^{-1})	0.092
F(000)	680
Theta range for data collection:	2.5 to 28.3
Data set	-13: 13 ; -17: 18 ; -12: 15
Reflection	17116
Independent refl.	4093, (R(int) = 0.026)
data [$I > 2\sigma(I)$]	2828
R indices (all data)	R = 0.0466, wR$_2$ = 0.1349
S	1.03
Min. and Max. Resd. Dens. (e/Å^3)	-0.16 and 0.16

Appendix C: Chapter 4

Single Crystal X-Ray Data of **3aa, 3ca, 3ab, 3lf, 3ai, 3ak, 3ea,** and **5aa**

The crystal structures of **3aa, 3ca, 3ab, 3lf, 3ai, 3ak, 3ea,** and **5aa** has been deposited to Cambridge Crystallographic Data Centre and allotted deposition numbers are 2063591, 1982944, 2064242, 2065019, 2064530, 2063782 2103019 and 2103423 respectively.

Crystal structure of 3aa

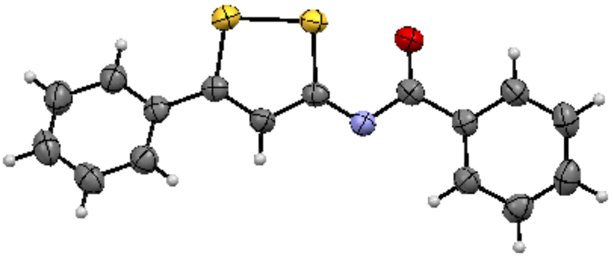


Table 1 Crystal data and structure refinement of 3aa

CCDC No.	2063591
Formula	$C_{16}H_{11}NOS_2$
Formula weight	297.38
Crystal system	Orthorhombic
Space group	Pbca (No. 61)
a, b, c (Å)	8.7341(2), 16.7204(4), 19.2030(4)
α, β, γ (°)	90, 90, 90
V (Å^3)	2804.36(11)
Z	8
Calculated density (g/cm^3)	1.409
Absorption coefficient (mm^{-1})	0.373
F(000)	1232
Theta range for data collection:	2.7 to 27.7
Data set	-11: 11; -21: 21; -25: 24
Reflection	34619
Independent refl.	3266, (R(int) = 0.039)

data [I > 2σ(I)]	2690
R indices (all data)	R = 0.0306, wR$_2$ = 0.0869
S	1.04
Min. and Max. Resd. Dens. (e/Å^3)	-0.23 and 0.19

Crystal structure of 3ca

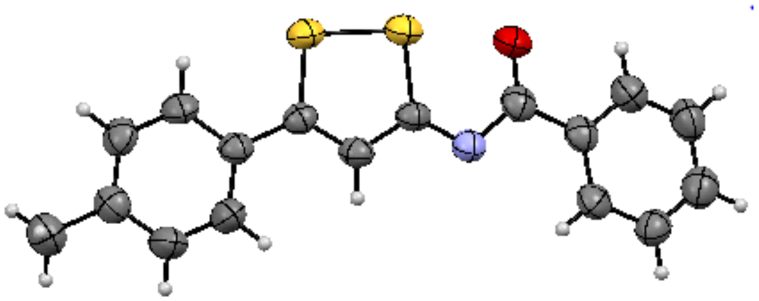


Table 2 Crystal data and structure refinement of 3ca

CCDC No.	1982944
Formula	$C_{17}H_{13}NOS_2$
Formula weight	311.405
Crystal system	Triclinic
Space group	P-1 (No. 2)
a, b, c (Å)	11.210(3), 12.059(3), 12.241(4)
α, β, γ (°)	73.839(9), 82.341(9), 69.593(8)
V (Å^3)	1488.4(7)
Z	2
Calculated density (g/cm^3)	1.390
Absorption coefficient (mm^{-1})	0.355
F(000)	648
Theta range for data collection:	2.2 to 26.4
Data set	-13: 13 ; -14: 15 ; -15: 15
Reflection	14987
Independent refl.	5959, (R(int) = 0.070)

data [I > 2σ(I)]	2978
R indices (all data)	R = 0.0598, wR_2 = 0.1938
S	0.93
Min. and Max. Resd. Dens. (e/Å^3)	0.06 and 0.00

Crystal structure of 3ab

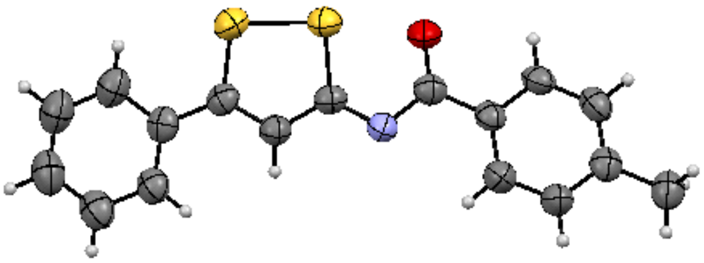


Table 3 Crystal data and structure refinement of 3ab

CCDC No.	2064242
Formula	$C_{17}H_{13}NOS_2$
Formula weight	311.40
Crystal system	Orthorhombic
Space group	Pbca (No. 61)
a, b, c (Å)	7.7674(5), 11.6512(10), 32.430(3)
α, β, γ (°)	90, 90, 90
V (Å^3)	2934.9(4)
Z	8
Calculated density (g/cm^3)	1.410
Absorption coefficient (mm^{-1})	0.360
F(000)	1296
Theta range for data collection:	2.5 to 27.1
Data set	-9: 8 ; -13: 14 ; -36: 41
Reflection	19254
Independent refl.	3229, (R(int) = 0.127)
data [I > 2σ(I)]	1468

R indices (all data)	R = 0.0591, wR_2 = 0.1962
S	1.02
Min. and Max. Resd. Dens. (e/Å^3)	-0.32 and 0.25

Crystal structure of 3lf

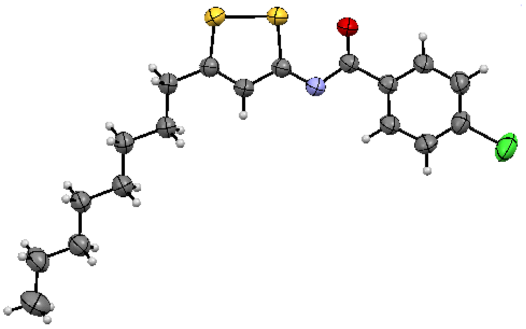


Table 4 Crystal data and structure refinement of 3lf

CCDC No.	2065019
Formula	$C_{18}H_{22}ClNOS_2$
Formula weight	367.93
Crystal system	Triclinic
Space group	P-1 (No. 2)
a, b, c (Å)	6.8464(7), 9.489(1), 15.5282(17)
α, β, γ (°)	81.120(4), 85.432(4), 70.588(3)
V (Å^3)	939.61(17)
Z	2
Calculated density (g/cm^3)	1.300
Absorption coefficient (mm^{-1})	0.429
F(000)	388
Theta range for data collection:	2.3 to 28.4
Data set	-9: 9 ; -12: 12 ; -20: 20
Reflection	22981
Independent refl.	4658, (R(int) = 0.043)
data [I > 2σ(I)]	3607

R indices (all data)	R = 0.0374, wR_2 = 0.1061
S	1.03
Min. and Max. Resd. Dens. (e/Å^3)	-0.20 and 0.23

Crystal structure of 3ai

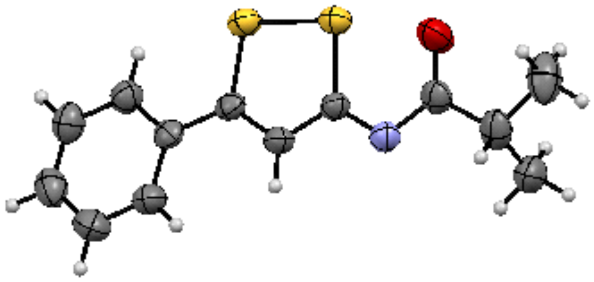


Table 5 Crystal data and structure refinement of 3ai

CCDC No.	2064530
Formula	$C_{13}H_{13}NOS_2$
Formula weight	263.36
Crystal system	orthorhombic
Space group	Fdd2 (No. 43)
a, b, c (Å)	22.599(3), 41.351(5), 5.4325(6)
α, β, γ (°)	90, 90, 90
V (Å^3)	5076.6(11)
Z	16
Calculated density (g/cm^3)	1.378
Absorption coefficient (mm^{-1})	0.401
F(000)	2208
Theta range for data collection:	0.0, 0.0
Data set	999:-99 ; 999:-99 ; 999:-99
Reflection	0.0000
Independent refl.	0.0000, (R(int) = 0.00)
data [I > 2σ(I)]	0
R indices (all data)	R = 0, wR_2 = 0

S	0
Min. and Max. Resd. Dens. (e/Å^3)	-0 and 0

Crystal structure of 3ak

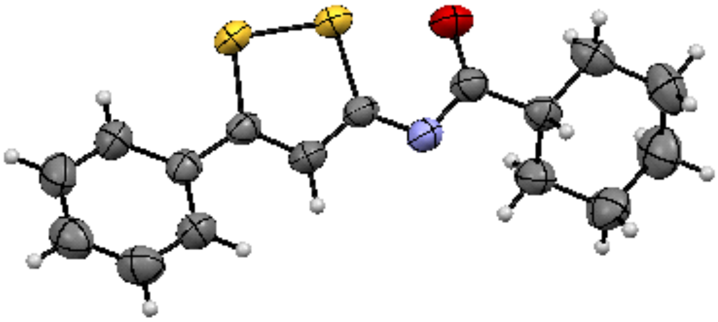


Table 6 Crystal data and structure refinement of 3ak

CCDC No.	2063782
Formula	$C_{16}H_{17}NOS_2$
Formula weight	303.42
Crystal system	Monoclinic
Space group	P21/c (No. 14)
a, b, c (Å)	12.1161(6), 11.3642(4), 12.2311(5)
α, β, γ (°)	90, 115.824(2), 90
V (Å^3)	1515.92(11)
Z	4
Calculated density (g/cm^3)	1.329
Absorption coefficient (mm^{-1})	0.346
F(000)	640
Theta range for data collection:	2.6 to 28.3
Data set	-16: 16 ; -15: 15 ; -16: 16
Reflection	24773
Independent refl.	3749, (R(int) = 0.034)
data [I > 2σ(I)]	3147
R indices (all data)	R = 0.0382, wR_2 = 0.1000

S	1.06
Min. and Max. Resd. Dens. (e/Å^3)	-0.16 and 0.23

Crystal structure of 3ea

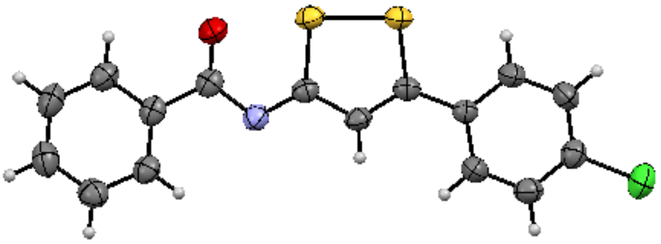


Table 7 Crystal data and structure refinement of 3ea

CCDC No.	2103019
Formula	$C_{16}H_{10}ClNOS_2$
Formula weight	331.82
Crystal system	Monoclinic
Space group	P21/c (No. 14)
a, b, c (Å)	3.9565(3), 11.3236(10), 31.927(3)
α, β, γ (°)	90, 91.875(3), 90
V (Å^3)	1429.6(2)
Z	4
Calculated density (g/cm^3)	1.542
Absorption coefficient (mm^{-1})	0.555
F(000)	680
Theta range for data collection:	2.2 to 26.4
Data set	-4: 4 ; -14: 14 ; -39: 36
Reflection	10988
Independent refl.	2899, (R(int) = 0.095)
data [I > 2σ(I)]	1988
R indices (all data)	R = 0.0470, wR_2 = 0.1194
S	1.03

Min. and Max. Resd. Dens. (e/Å^3)	-0.25 and 0.29

Crystal structure of 5aa

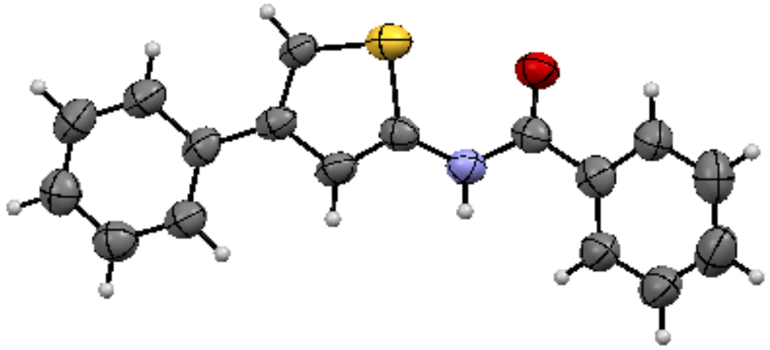


Table 8 Crystal data and structure refinement of 5aa

CCDC No.	2103423
Formula	$C_{34}H_{26}N_2O_2S_2$
Formula weight	558.69
Crystal system	Orthorhombic
Space group	Pca21 (No. 29)
a, b, c (Å)	9.121(4), 11.020(5), 28.365(16)
α, β, γ (°)	90, 90, 90
V (Å^3)	2851(2)
Z	4
Calculated density (g/cm^3)	1.302
Absorption coefficient (mm^{-1})	0.221
F(000)	1168
Theta range for data collection:	2.3 to 26.4
Data set	-11: 11 ; -13: 12 ; -35: 35
Reflection	20613
Independent refl.	5678, (R(int) = 0.151)
data [I > 2σ(I)]	2622
R indices (all data)	R = 0.0622, wR2 = 0.1736
S	0.98
Min. and Max. Resd. Dens. (e/Å^3)	-0.26 and 0.22

Appendix D: Chapter 5

Single Crystal X-Ray Data of **3ae,** and **3al**

Compounds **3ae** and **3al** were isolated as pure single crystals. The crystal structure has been deposited to Cambridge Crystallographic Data Centre and allotted deposition numbers are 2190267 and 2190268 respectively.

Crystal structure of 3ae

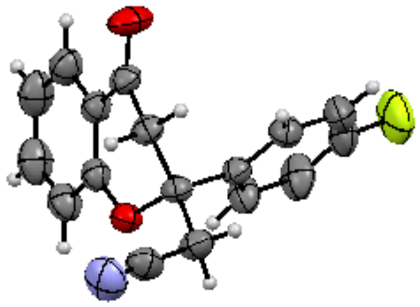


Table 1 Crystal data and structure refinement of 3ae

CCDC No.	2190267
Empirical formula	$C_{17}H_{12}FNO_2$
Formula weight	281.28
Temperature/K	298
Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	12.4174(10)
b/Å	14.7059(10)
c/Å	7.7773(6)
α/°	90
β/°	94.520(3)
γ/°	90
Volume/Å^3	1415.79(19)
Z	4

ρ_{calc}g/cm^3	1.320
μ/mm^{-1}	0.096
F(000)	584.0
Crystal size/mm^3	0.302 × 0.235 × 0.075
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	5.94 to 50.852
Index ranges	$-14 \le h \le 14$, $-17 \le k \le 17$, $-9 \le l \le 9$
Reflections collected	24574
Independent reflections	2592 [R_{int} = 0.0700, R_{sigma} = 0.0324]
Data/restraints/parameters	2592/0/190
Goodness-of-fit on F^2	1.068
Final R indexes [I>=2σ (I)]	R_1 = 0.0417, wR_2 = 0.1005
Final R indexes [all data]	R_1 = 0.0558, wR_2 = 0.1127
Largest diff. peak/hole / e Å^{-3}	0.14/-0.17

Crystal structure of 3al

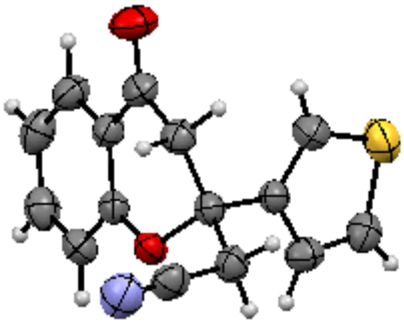


Table 2 Crystal data and structure refinement of 3al

CCDC No.	2190268
Empirical formula	$C_{2.31}H_{1.69}N_{0.15}O_{0.31}S_{0.15}$
Formula weight	41.43
Temperature/K	298

Crystal system	monoclinic
Space group	$P2_1/c$
a/Å	8.5919(16)
b/Å	16.471(3)
c/Å	9.0797(14)
α/°	90
β/°	93.347(6)
γ/°	90
Volume/Å^3	1282.7(4)
Z	26
ρ_{calc}g/cm^3	1.395
μ/mm^{-1}	0.248
F(000)	560.0
Crystal size/mm^3	0.215 × 0.156 × 0.123
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	4.75 to 51.438
Index ranges	$-10 \leq h \leq 10$, $-20 \leq k \leq 20$, $-11 \leq l \leq 11$
Reflections collected	19042
Independent reflections	2441 [R_{int} = 0.1187, R_{sigma} = 0.0630]
Data/restraints/parameters	2441/0/173
Goodness-of-fit on F^2	1.056
Final R indexes [I>=2σ (I)]	R_1 = 0.0477, wR_2 = 0.1077
Final R indexes [all data]	R_1 = 0.0963, wR_2 = 0.1345
Largest diff. peak/hole / e Å^{-3}	0.24/-0.23

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List of publications

1. Divya Bhatt**,** Chandresh Kumari and Avijit Goswami, Synthesis and applications of 2-alkynylnitriles, *Asian J. Org. Chem*. **2019**, *8*, 1985-2001.

2. Chandresh Kumari and Avijit Goswami, A Facile Transition Metal-free Ionic Liquid [BMIM]OH Mediated Regio- and Stereoselective Hydrocarboxylation of Alkynylnitriles, *Eur. J. Org. Chem*. **2021**, *2021*, 429-435.

3. Chandresh Kumari and Avijit Goswami, Ionic liquid mediated one-pot 3-acylimino-3*H*-1,2-dithioles synthesis from thiocarboxylic acids and alkynylnitriles *via* in situ generation of disulfide intermediate, *J. Org. Chem.* **2022**, *87*, 8396-8405.

4. Chandresh Kumari and Avijit Goswami, Access to 5-Substituted 3-Aminofuran/thiophene-2-carboxylates from Bifunctional Alkynenitriles, *Adv. Synth. Catal.* **2022**, *364*, 2254-2259.

5. Chandresh Kumari and Avijit Goswami, NaH mediated One-Pot Tandem Michael/oxa-Michael Addition of 2-Hydroxyacetophenones with Alkynenitriles, *Manuscript under preparation.*

Conferences attended

1. Oral presentation

   International Conference on Chemistry and Allied Sciences (ICCAS-2022), Organised by Department of Chemistry, Pingle Government College for Women (Autonomous), Hanumakonda, Warangal, in August, 2022, at NIT, Warangal, India.

2. Poster presentation

    1. **Recent Advances in Organic & Bio-organic Chemistry (RAOBC-2019)**, Organised by IISER Mohali in March, 2019 at IISER Mohali, Punjab, India.

    2. **Chemical Research Society of India (27th CRSI-NSC-2021**), National Symposium in Chemistry, online national conference organized by IISER Kolkata in September 2021, West Bengal, India.

    3. **RSC-IISER Desktop Seminar with Organic & Biomolecular Chemistry**, jointly organized by Organic & Biomolecular Chemistry (OBC) and IISER Mohali (virtually) in Nov, 2021 at IISER Mohali, Punjab, India.

    4. **RSC-IISER Desktop Seminar with Dalton Transactions,** jointly organized by Dalton Transactions and IISER Thiruvananthapuram (virtually) in May, 2022 at IISER Thiruvananthapuram, India.

    5. **Recent Advances in Chemical Sciences (RACS-2022)**, International Conference organized by Central University of Jammu in Nov, 2022, J & K, India.

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- 2001: Secondary; Sen. Sec. Sch. Pandoh (H.P), H.P.B.S.E, 76%
- 2003: Senior secondary (Medical); BSNL Sen. Sec. Sch. Pandoh (H.P), Pb Board, 76%
- 2006: B. Sc. (Medical); Vallabh Govt. College, Mandi (HP), Himachal Pradesh University, Shimla, 68.8%
- 2007: B. Ed.; Noble College of Education, Pandoh, Mandi (HP), Himachal Pradesh University, Shimla, 65.5%
- 2009: M. Sc. (Chemistry); Lovely School of Technology and Science, Jalandhar (PB), 80%
- 2018: Joined Ph.D.; IIT Ropar, Punjab

Awards and Honours:

- Qualified National Eligibility Test (NET)-2010.
- Qualified GATE, 2017, with **AIR 426**.
- Qualified CSIR-JRF, June 2017 with **AIR 67**.
- Qualified CSIR-JRF, Dec 2017 with **AIR 62**.
- Awarded a one-time incentive of INR 75,000 under Mukhyamantri Protsahan Yojna from H.P. government.
- Received certificate for the Best Project & Best Performer of the batch from "DNA Research Centre, Chandigarh during summer training from 27-06-2008 to 14-08-2008.
- Awarded merit certificate for 79th position in matriculation examination by the Himachal Pradesh Board of School Education, Dharamshala.