Synthesis of Biologically Important Heterocycles from Alkynes and Functional Group Transformations

Thesis

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DOCTOR OF PHILOSPHY

in

Chemistry

by

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Under the Supervision of

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Dedicated
To My Parents and
Family

DELHI TECHNOLOGICAL UNIVERSITY

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CANDIDATE'S DECLARATION

I, **Saurav Kumar,** hereby certify that the work which is being presented in the thesis entitled "**Synthesis of Biologically Important Heterocycles from Alkynes and Functional Group Transformations**" in partial fulfillment of the requirements for the award of the Degree of Doctor of Philosophy, submitted in the Department of Applied Chemistry, Delhi Technological University is an authentic record of my own work carried out during the period from 31/12/2018 to 23/05/2024 under the supervision of **Prof. Anil Kumar** Department of Applied Chemistry, Delhi Technological University, Delhiand **Dr. NityanandaAgasti**, University of Delhi, Delhi.

The matter presented in the thesis has not been submitted by me for the award of any other degree of this or any other institute.

Candidate's Signature

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CERTIFICATE BY THE SUPERVISORS

Certified that **Saurav Kumar** (Roll No. 2K18/PHDAC/503), has carried out his research work presented in this thesis entitled **"Synthesis of Biologically Important Heterocycles from Alkynes and Functional Group Transformations"** for the award of **Doctor of Philosophy** from Department of Applied Chemistry, Delhi Technological University, Delhi, under our supervision. The thesis embodies results of original work, and studies are carried out by the student himself and the contents of the thesis do not form the basis for the award of any other degree to the candidate or to anybody else from this or any other University/Institution.

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Saurav Kumar

ABSTRACT

The thesis describes transition-metal-free synthesis of novel nitroacridinamines, nitrobenzo[c]acridinamines, nitroquinolinamines and late-stage modification of some biologically relevant molecules and natural products. Another base-mediated protocol has been established for the *N*-acetylation of anilines/amines at room temperature. Reaction utilizes acetonitrile as a solvent as well as a surrogate of the acetyl group. Apart from acetonitrile, trifluoroacetonitrile could also be utilized in the reaction. The thesis also describes Potassium *tert*-butoxide mediated a direct one-pot synthesis of diversely substituted nitriles from aldehydes *via* the sequential addition of hydroxylamine and benzoyl chloride. Broad substrate scope, easy operation, quick reactions, tolerance of different functional groups, reactions are the important features of all developed methodology. Various techniques such as ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and mass spectrometry have been used for characterization of those organic compounds

LIST OF PUBLICATIONS

- Saurav Kumar, Nityananda Agasti, Gajendra Singh and Anil Kumar, "Base-Mediated N-Acetylation of Anilines/Amines: Nitriles as a Surrogate of the Acetyl Group" *ChemistrySelect,* **2023**, 8, e202204679.
- Saurav Kumar, Jyoti, Deepak Gupta, Gajendra Singh and Anil Kumar, "A Decade of Exploration of Transition-Metal-Catalyzed Cross-Coupling Reactions: An Overview" *Syn Open*, **2023**, 7, 580-614.
- Saurav Kumar,Ritika Kubba, Nityananda Agasti, Anitha Selvaraj, Anil Kumar, "Potassium *tert*-butoxide promoted a direct one-pot synthesis of nitriles from aldehydes at room temperature" *J. Chem. Sci*, **2024**, 136, 1-6.

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INTRODUCTION

1.1 General Introduction

N-acetylation is commonly employed chemical process in the broader field of organic chemistry, serving to affix an acetyl functional group onto amine compounds[1–4]. The adoption of this acetyl functional group is extensive, spanning applications in drug investigation, pharmaceutical formulation, polymer science, and agricultural endeavors[5–10]. Notably, it finds utility as a protective agent in diverse organic reactions and in the synthesis of peptides[11]. Furthermore, it exerts significant regulatory influence in post-translational protein modification and the control of DNA expression across various life forms[12-13]. Generally, readily available acetylation reagents like acetic anhydride and acetyl chloride are easily obtainable in chemical labs. Even in the most eco-friendly technologies, these reagents are commonly employed either alongside different Lewis acids[14–16] or in their pure form[17]. However, their usage comes with several drawbacks. Acetic anhydride and acetyl chloride compounds are significant irritants, and acetyl chloride is considered as a genotoxic substance[18]. Therefore, there is considerable current interest in phasing out their usage. Although acetonitrile is commonly employed as a solvent and finds widespread use in various fields of chemistry as an eluent[19] and a polar aprotic organic solvent[20], its usage as a reagent in organic chemistry is rare.

Aryl nitriles play crucial roles in medicine, pesticides, liquid crystal materials, and various other fields, making them pivotal intermediates for organic synthesis in the chemical industry[21]. Therefore, the synthesis of aryl nitriles holds fundamental importance in organic chemistry. The synthesis of aryl nitriles include the ammoxidation of methyl aromatics,[22-23] cyanidation of halogenated aromatics,[24-25] dehydration of arylamides,[26] dehydration of arylaldoximes,[27-29] and the Sandmeyer reaction of arylamine diazonium salts.[30-31] Generally, ammoxidation of methyl aromatics is favored for producing large quantities of nitriles. However, the direct cyanidation of halogenated aromatics and the Sandmeyer reaction of arylamine diazonium salts necessitate the use of highly toxic

cyanides. In comparison, the preparation of aromatic nitriles through the dehydration of aromatic amides and aldehyde oximes holds significant importance both in laboratory and industrial applications.

Over the past years, the construction of carbon-carbon and carbon-heteroatom bonds via cross-coupling reactionscatalyzed by transition metals such as Suzuki-Miyaura,[32] Heck,[33] Sonogashira,[34] Stille,[35] Negishi,[36] Kumada,[37] and Hiyama[38] have been remained the most widely employed synthesis protocols of chemical industry. These reations represents the fundamental criteria for a number of basic technologies in modern synthetic organic chemistry and have been widely applied in a variety of academic and industrial process,[39-40] including the synthesis ofnatural products,[41-42] biologically active small molecule, materials science, medicinal, supramolecular catalysis and coordination chemistry. In addition, several of thesereactions have been commercially employed in the field pharmaceutical, agrochemical conjugated polymers,[43-44] crystalline liquids,[45-46] the active components of organic light-emitting diodes (OLEDs),[47-48] and industrial chemicals.[43]*etc*.

The first break through in the direction of cross-coupling was the copper-catalyzed synthesis of biaryl compounds from aryl halides published by F. Ullmann in 1901.[49] This discovery was not limited to a mere presentation of new synthetic methodology, rather brought the realization that carbon-carbon bonds can be made in alaboratory synthetically. After a long gap of nearly seven decades, the discovery by Ullmann gained the recognition and a variety of modifications and new directions emerged consequently. In particular, the discovery of Kumada coupling in 1972, in which reactive chemical halides and alkenyl/aryl halides were combined using Ni or Pd catalysts, paved the way for the discovery of modern TM catalyzed cross-coupling methods.[50-51] These developments were followed by Heck in 1972, where unsaturated halides and olefins are combined with Pd catalysts,[52-53] and Sonogashirain 1975, where terminal alkynes and aryl or vinyl halides were combined with Pd and Cu catalysts.[54-56] In an attempt to extend the outreach of these methodologies, Negishi(1977) used Pd or Ni catalysts to combine organozinc compounds with organic halides or triflates.[57-58] Using similar strategy in 1978, Stille coupled organotin compounds with a variety of organic electrophilesusing Pd[59-60] Suzuki in

1979 presented, the coupling of boric acid and organohalogen compounds using Pd,[61-63] Hiyama 1988, in which organosilanes and organic halides using Pd,[64-66] Buchwald-Hartwig 1994, and with Amines with aryl halides were coupled with Pd[67] and other cross-couplings.[68-70]

The importance of these palladium-catalyzed cross-couplings was finally recognized when the Nobel Prize in Chemistry in 2010 was jointly awarded to A. Suzuki, R. Heck and E. Negishi.[71-73]Since the early developments in the dynamic area ofcross-coupling reactions nearly fifty years ago the diversity, scopes, reactivities, value effectiveness, toxicity, synthetic skillfulness workable applications and limitations of TMs equivalent to palladium,[74-78] iron,[79-82] cobalt,[83-86] nickel,[87-91] copper,[92-94] rhodium,[95-99] ruthenium,[100-101] iridium,[102] *etc*. has led to thousands ofpublications and lots of reviews and books are documented cataloging the advancements. In this area of research, the bottlenecks in cross coupling reactions, have consequentlyencouraged scientists and researchers to formulate novel catalysts primarily based on naturally abundantand environmentally benign elements.Therefore, compared to the widespread applications of late and noble transition metals in TM-catalyzed cross-couplings, much attention is paid to the first-native transition metals such as Fe, Co, Ni, and Cu due to their obvious advantages, such as high earth abundance, low cost, less toxicity, more nucleophilicity, unique catalytic properties and environmental friendliness.[103-105]

In particular, the Pd catalyzed coupling is appear to be one of the most commonly use reaction for producing good quality chemical compounds on a tole scale and are one of the most powerful and diverse techniques available to organic synthesis[106-107] In fact, extensive research has confirmed that nickel-based catalysts are more potent and flexible catalysts for C–C,[108] C-O,[108] [78] C-P,[109] and C-N[110] bond constructions.

Moreover, the past 20 years have encountered an impressive expansion and interest in the advancement of iron-based cross-coupling responses.[111-112]. Kharasch and Field in 1941,Iron-catalyzed cross-coupling responses were first detailed by in which Grignard reagents were combined with arylhalides within the sight of $FeCl_3$.[113] It is intriguing to specify here that it required an additional 30 years for the following report until this

area of research got sped up in which Kochi clarified the cross-coupling of Grignard reagents with alkenyl halides catalyzed by $FeCl_3$.[114] Following Kochi's report, simultaneous work led by the groups of Julia,[115] Molander,[116] Cahiez[117] and Fürstner,[118] in addition toconsiderablecontributions from thegroups of Hayashi,[119] Nakamura,[120] and Itami,[121] Bedford,[122] Knochel,[123] Shi[124] during 90s and early 2000s, dynamically marked the resurgence of Fe-catalyzed alterations. From that point forward, various new iron-catalyzed cross-coupling responses have been discovered and effectively appeal to organic synthesis.[125] Nevertheless, the developmentstowards a viable and economical protocol for iron-mediated cross-coupling catalysis is sluggish in comparison to analogous palladium and nickel-primarily based catalysis.

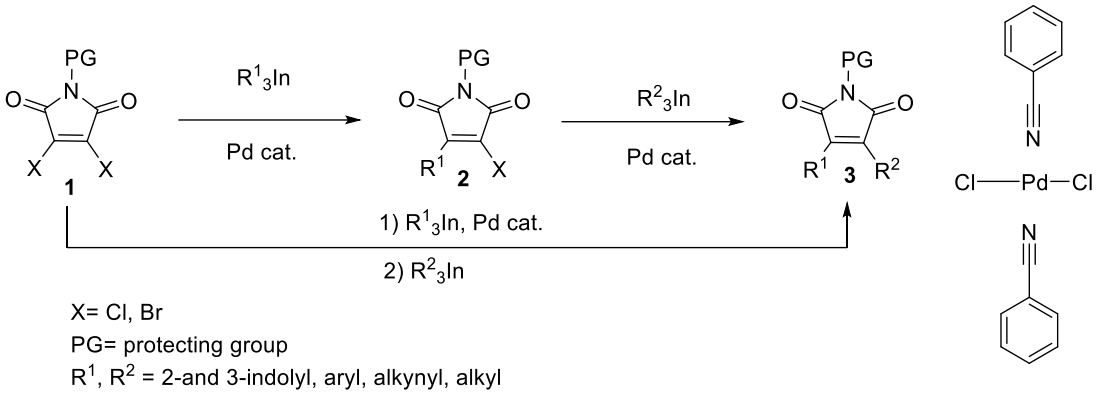
The growing recognition in cross-coupling chemistry, this studyoffers a completeknowledge of the successfulapplications of numerous transition-metals in cross-coupling strategies, that have beencarried out as key steps withinside the Suzuki, Heck,Sonogashira, Stille, Kumada, Kochi, Murahashi, Corriu, and Negishi reactions, in addition to carbonylative, decarboxylative,C-N cross-coupling reactionsand α-arylative, to synthesize heterocycles, organic materials, natural products, and medicinally relevant compounds.

1.2 Pd-Catalyzed Reactions

The discussion in this section is bounded to the use of Palladium catalysis in various cross-coupling reactions and is generally presented in chronological order.

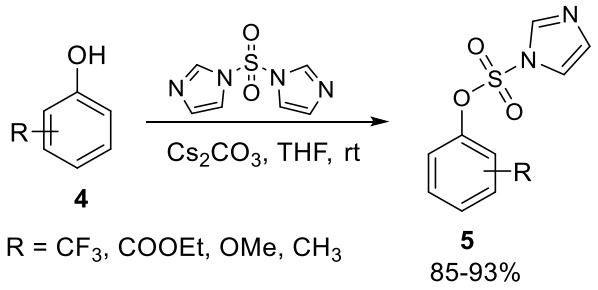
1.2.2 C-C Cross-Coupling Reaction

In 2009, Bouissane and co-workers[126] discovered a palladium-mediated sequential or stepwise one-pot cross-coupling reactions with various triorganoindium reagents (40-50 mol%) with 3,4-dihalomaleimides (**1)** to afford a variety of aryl, heteroaryl, alkyl, alkynyl, 2- and 3- indolyl 3,4-disubstituted maleimides with satisfactory yields with high selectivity and atom economy. (Scheme 1)

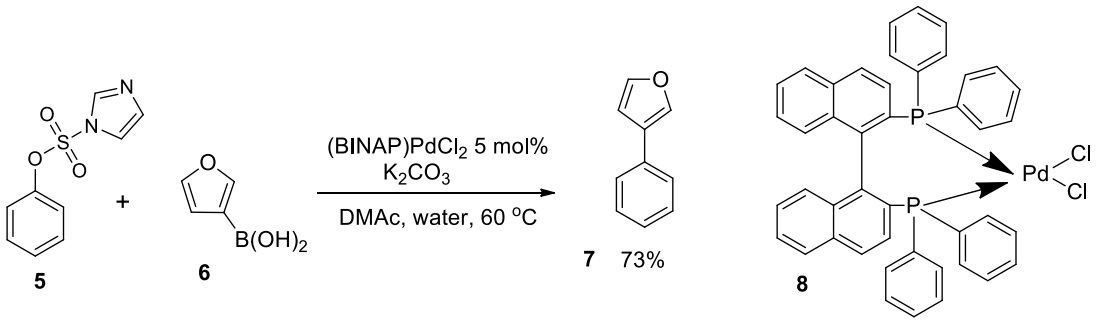


Scheme 1.1: Pd-catalyzed direct and sequential cross-coupling reaction of triorganoindium reagents and 3,4-dihalomaleimides.

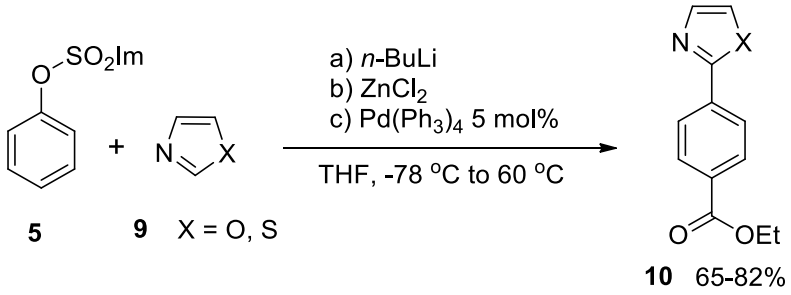
At the same time, Raju and co-workers first synthesized aryl imidazolylsulfonates (**5)** as a cost-effective alternative to triflates which was shown to participate as fully competent electrophilic coupling partners in palladium-catalyzed cross-coupling reactions involving Negishi and Suzuki-Miyaura in excellent reaction yields.[127] (Scheme 1.2-1.4)



Scheme 1.2: Synthesis of imidazolylsulfonates.

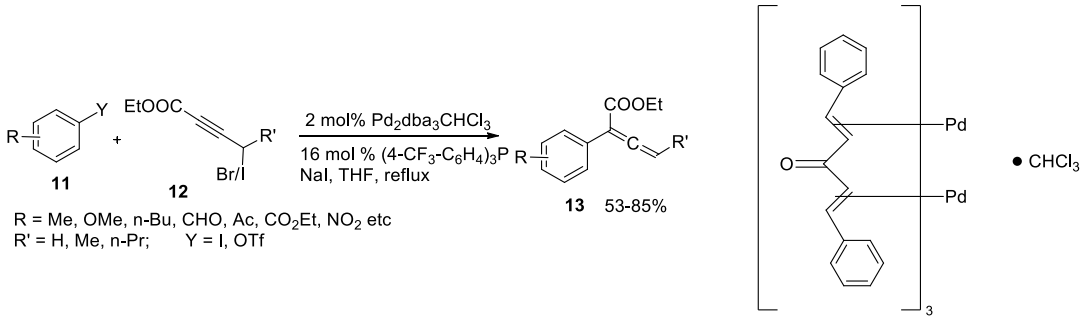


Scheme 1.3: Aryl imidazolyl sulfonates as coupling partner in Pd-catalyzed Suzuki-Miyaura cross-coupling reaction.



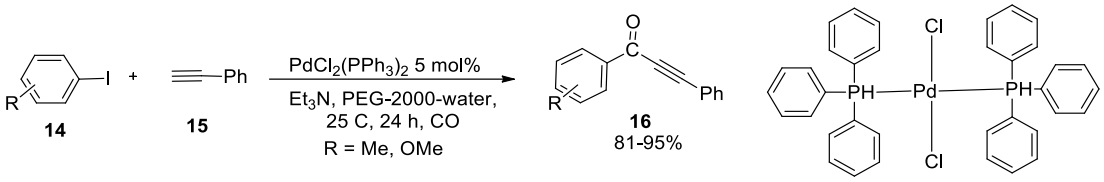
Scheme 1.4: Aryl imidazolylsulfonates as coupling partner in Pd-catalyzed Negishi cross-coupling reaction.

Lee and co-workers[128] published a synthetically valuable process to introduce aryl group to C2-position of 2,3-alkadienoate (**13)** *via Pd*-catalyzed selective allenyl cross-coupling reactions of an electron-withdrawing or electron-donating group containing aromatic iodides with organoindium reagents (**12)**, *i.e* 2-aryl-2,3-alkadienoates and ethyl 4-bromo-2-alkynoates under *insitu* condition with good yield. (Scheme 1.5)



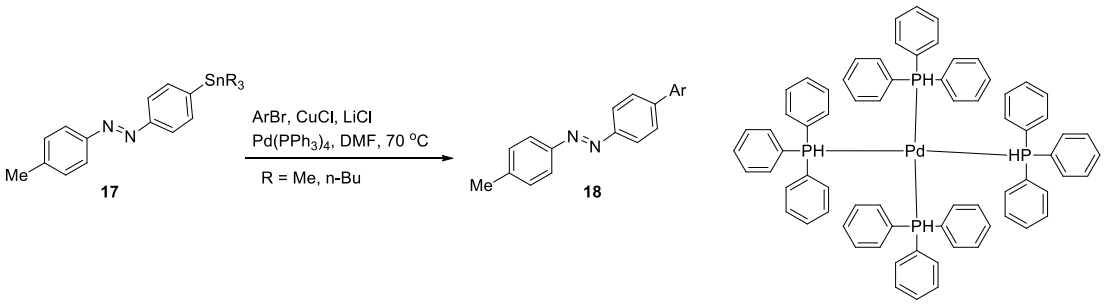
Scheme 1.5: Pd-catalyzed allenylcross-coupling reaction.

In 2014, Liu research team[129] envisioned an efficient, recyclable, green and ligand-free method for the Suzuki coupling of aryl or heteroaryl halides in presence of potassium aryltrifluoroborates with water in air using $Pd(OAc)_2$-H_2O-PEG system yielding the desired products in high reaction yields. The catalytic system was recycled relatively eight times without any appreciable loss in activity. Similarly, the water and PEG-2000 solvent mixture was utilized by the Zhao research group[130] in which they described the carbonylative Sonogashira coupling reaction of terminal alkynes with aryl iodides in presence of $PdCl_2(PPh_3)_2$ and Et_3N as a base under the atmospheric pressure of CO at 25 °C giving a scope of alkynyl ketones giving satisfactory yields (Scheme 1.6). This protocol could be effortlessly extended to the synthesis of 2-substituted flavonesfrom o-iodophenol and terminal alkynes.



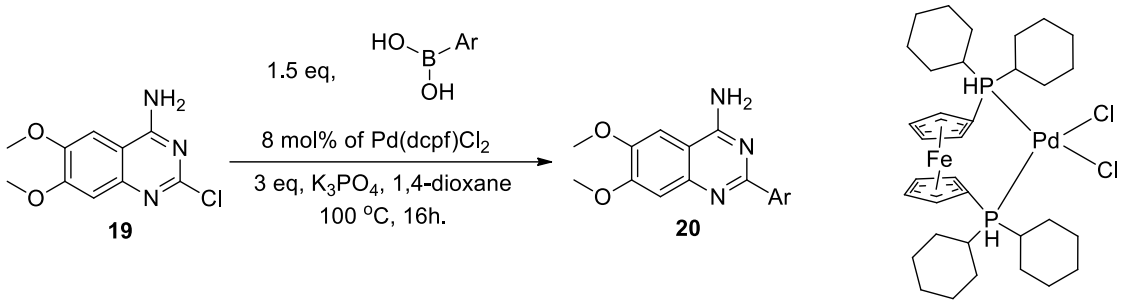
Scheme 1.6: Carbonylative Sonogashira coupling reaction.

In cross-coupling reactions, one of the limitations is that azobenzenes act as electrophiles, when metallated by halogen-metal exchange causes a reduction of azo group yielding hydrazine derivatives in place of the desired metallated azobenzenes. While Strueben[131] provided a solution to this problem and developed a mild method to prepare mono- and distannylated azobenzenes (**17)** which were used as nucleophilic partners in Pd-catalyzed Stille cross-coupling reactions withelectron-deficient andelectron-rich aryl bromides resulted in the formation of the cross-coupled products (**18)** yielding as high as 70 to 93%. (Scheme 1.7)



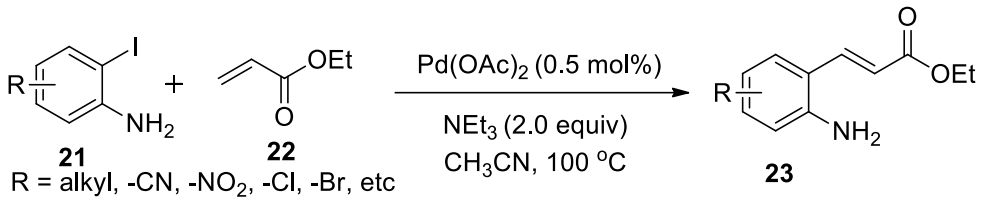
Scheme 1.7: Pd-catalyzed Stille cross-coupling reactions of mono stannylated azobenzenes.

Pulipati and co-workers[132] proposed a vigorous approach for the synthesis of 4-amino quinazoline bi-aryl compounds from arylboronic acids and quinazoline containing an unprotected NH_2 group (**20)** via Suzuki-Miyaura coupling reaction using $Pd(dcpf)Cl_2$. (Scheme 1.8) The synthesized compounds were also assessed for anti-microbial and anti-fungal biological activity.



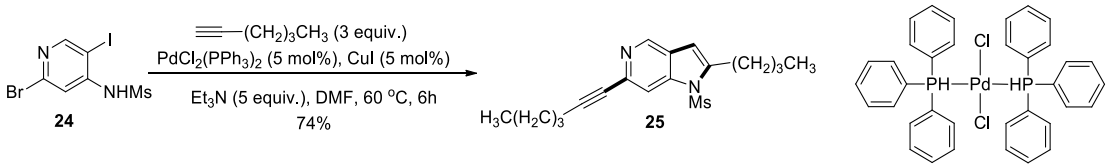
Scheme 1.8: Synthesis of 4-amino quinazoline bi-aryl compound.

Chen and coworkers[133] developed Pd-catalyzed ligand-free Heck reaction between 2-iodoanilines (**21)** and acrylate (**22)** in CH_3CN using $Pd(OAc)_2$ (5.0 mol%) as catalyst and NEt_3 as a base to afford2-alkenylanilines (**23)**in high yield up to 93% yield. (Scheme 1.9)



Scheme 1.9: Pd-catalyzed ligand-free Heck reaction.

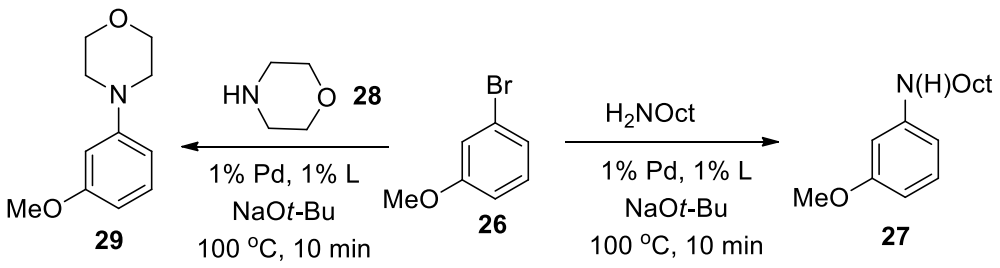
The Balfour research group[134] presented the synthesis of a library of 2,6-disubstituted-azaindoles (**25)** based on tandem Sonogashira coupling/5-endo-dig/Sonogashira coupling sequence. (Scheme 1.10) This protocol tolerated alkynes containing alcohols, aliphatic chains and aromatic substituents.



Scheme 1.10: Pd-catalyzed tandem Sonogashira coupling/5-endo-dig/Sonogashira coupling sequence.

1.2.2 C-N Cross-Coupling Reaction

In 2010, B. P. Fors and co-workers[135] disclosed an alternative approach to catalyst advancement, in which they prepared a multiligand-based Pd catalyst (Scheme 1.11). The designed catalyst was then allowed to catalyze C-N cross-coupling reactions. This catalytic system exhibited the same catalyst activity and substrate scope.



Scheme 1.11: C-N cross-coupling reactions using multiligand-based Pd catalyst.

Similar to the B. P. Fors report, another group led by Dooleweerdt *et al.*[136] also described a palladium catalyst based on biarylphosphine ligands (**30-34)** (Fig. 1) which allowed the coupling of amides and an array of aryl/heteroaryl mesylates (**35)** (electron-rich, -neutral, and -deficient) to afford corresponding N-aryl amides (**37)** in high yields. (Scheme 1.12) Benzamides, aliphatic and heterocyclic amides were also investigated as excellent coupling partners in this protocol.

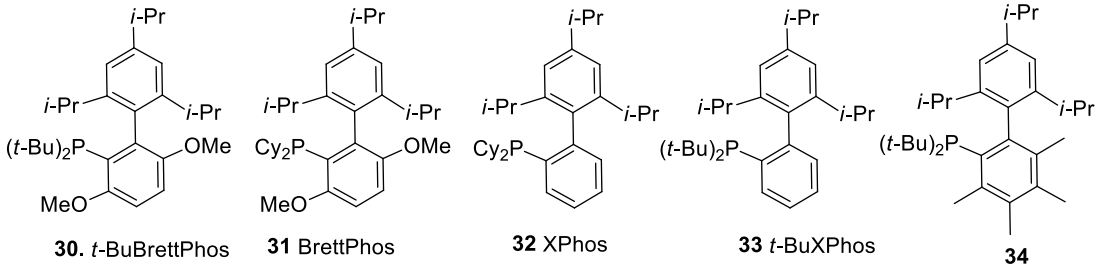
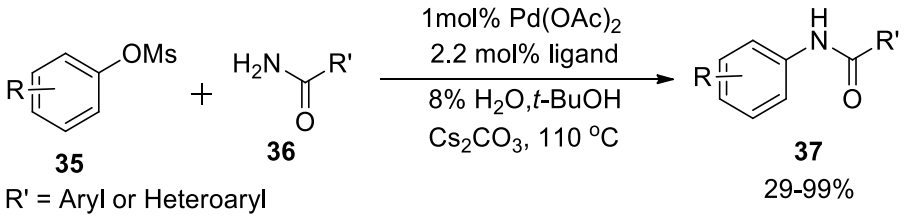
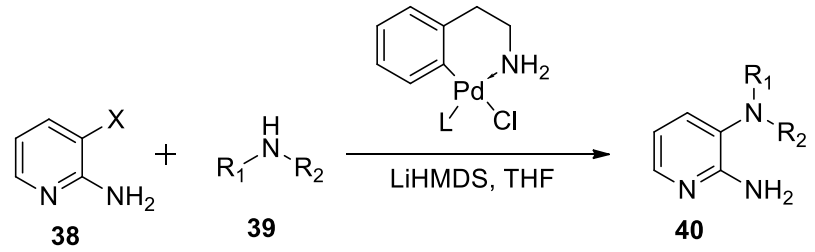


Figure 1.1: Various biarylphosphine ligands used by Dooleweerdt et al.



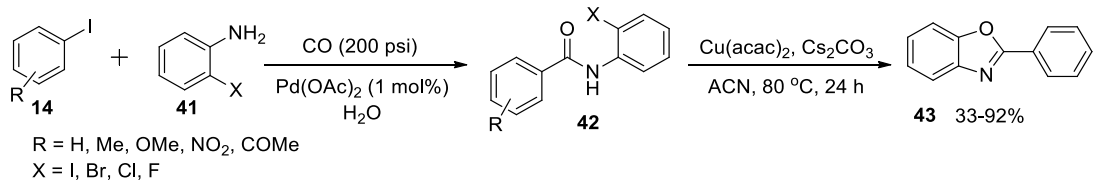
Scheme 1.12: Pd-catalyzedcoupling of amides and aryl mesylates.

In 2011, Perez and coworkers[137] presented an unprecedented approach of Pd-catalyzed C-N cross-coupling of unprotected 3-halo-2-aminopyridines (**38)** with an array of primary and secondary amines yielding N3-substituted-2,3-diaminopyridines (**40)**. (Scheme 1.13) The reaction was performed with BrettPhos- and RuPhos-precatalysts in blend with LiHMDS for this C-N-cross coupling reaction.



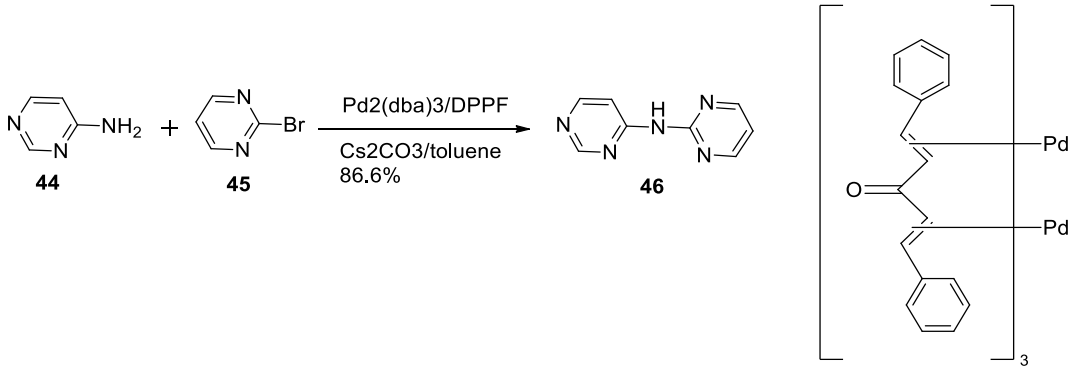
Scheme 1.13: Pd-catalyzed C-N cross-coupling of unprotected 3-halo-2-aminopyridines.

Tambade et al.[138] disclosed phosphine-free $Pd(OAc)_2$ catalyzed procedure for aminocarbonylation or carbonylative cross-coupling which enabled the coupling of a wide range of substituted aryl iodide with ortho-haloaniline to form ortho-haloanilide (**42)** in water affording good yields.(Scheme 1.14) Further, ortho-haloanilides (**42)**were allowed to undergo cyclization for the synthesis of benzoxazoles (**43)**using $Cu(acac)_2$ catalyst.



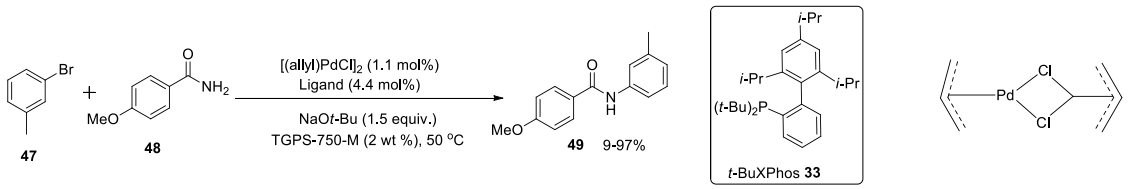
Scheme 1.14: Pd-catalyzed aminocarbonylation cross-coupling.

In 2013, Zhang and co-workers[139] devised a Pd-catalyzed method for the cross-couplings of heteroaryl halides and electron-deficient heteroaromatic amines in the presence of $Pd_2(dba)_3$ as a catalyst, 1,10-bis(diphenylphosphino)ferrocene (DPPF) as ligand, and Cs_2CO_3 as a base. (Scheme 1.15) This methodology allowed the coupling of several rarely reported electron-deficient heteroaromatic amines in good yields.



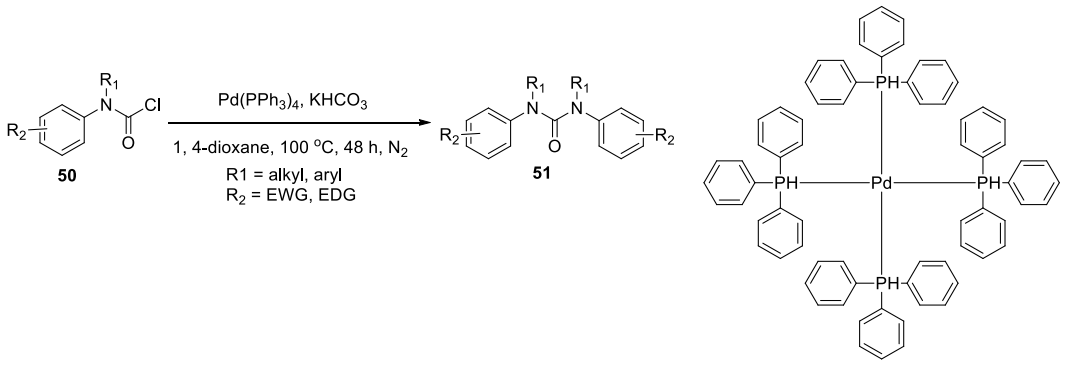
Scheme 1.15: Pd-catalyzed C-N cross-coupling.

In 2014, Wagner *et al.*[140] described a versatile green catalytic system ([(cinnamyl]PdCl]$_2$/t-BuXPhos) **(33)** for coupling of arylbromides or chlorides with a wide range of amines, carbamates, ureas and amides under Buchwald-Hartwig cross-coupling reaction in an aqueous micellar medium. The procedure was functional-group tolerant e.g. for esters and halides and reactions were carried out between 30 to 50 °C providing the target compounds in good to excellent yields. (Scheme 1.16) Compared to the previously reported Takasago's catalyst system (cBRIDP ligand in combination with [(allyl)PdCl]$_2$) this catalytic system was found much efficient for Buchwald-Hartwig reactions with benzamide derivatives or aliphatic primary amines. No racemization was experienced in this method when a substrate with a chiral center was taken.



Scheme 1.16: Pd-catalyzed Buchwald-Hartwig cross-coupling reaction.

In 2020, Fan *et al.*[141] describe the development of a Pd-catalyzed decarbonylative C–N coupling under a nitrogen atmosphere. (Scheme 1.17)



Scheme 1.17: Pd-catalyzed decarbonylative C–N coupling.

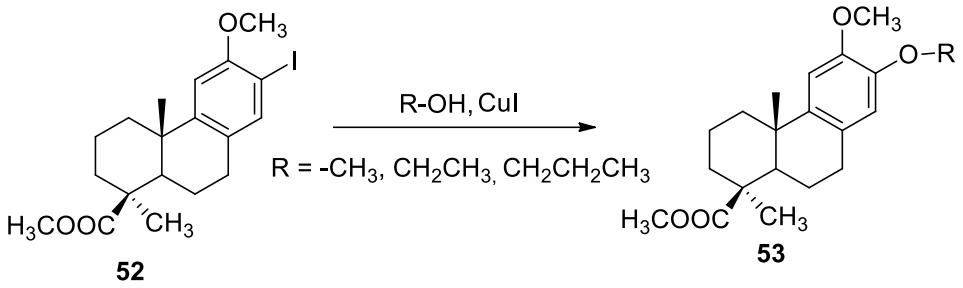
In 2021, Tao and coworkers[142] [165] achieved the direct cross-coupling of NH-sulfoximines through N-benzylation via visible light photocatalysis. Patel *et al.*[143] described Pd-mediated simultaneous CH–CX and CH–NH bond activation followed by intramolecular cyclization reaction to form quinolin-fused benzo[d]azeto[1,2-a] benzimidazole analogs.

1.3 Cu-Catalyzed Cross-Coupling Reactions

We will discuss in this section to limited use of copper catalysis in various cross-coupling reactions and is generally presented in chronological order.

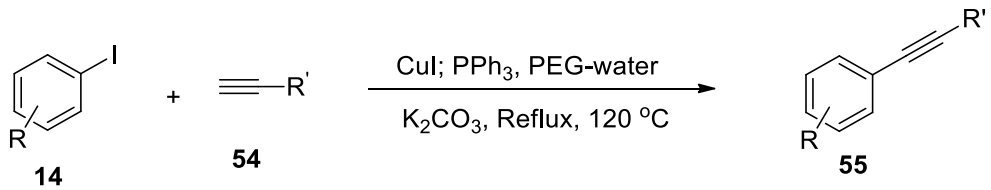
1.3.1 C-C Cross-Coupling Reactions

In 2010, Yalavarty and co-workers[144] found out a new copper-catalyzed method of synthesizing podocarpic acid ether derivatives through the one-step cross-coupling reaction of methyl 13-iodo-O-methylpodocarpate (**52)** with alcohols in excellent yields. (Scheme 1.18) Copper iodide was utilized as an inexpensive catalyst to achieve this transformation.



Scheme 1.18: Cu-catalyzed synthesis of podocarpic acid ether derivatives.

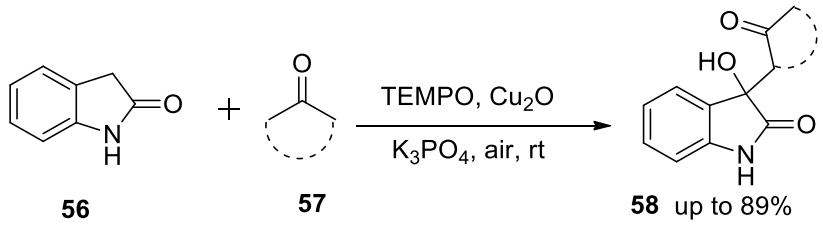
In 2011, Chen research group[145] established an efficient CuI/PPh_3/PEG-H_2O catalytic system for Sonogashira coupling ofelectron-deficientor electron-rich aryl iodides with terminal acetylenes in water-polyethylene glycol under microwave irradiation or reflux to provide good to excellent yields. (Scheme 1.19)



Scheme 1.19: Cu-catalyzed Sonogashira Coupling Reaction.

In 2015, Wang *et al.*[146] developed easy and efficient protocol that allowed the synthesis of a variety of 3-(2-oxoalkyl)-3-hydroxyoxindoles (**58)** through tandem oxidative cross-couplings of oxindoles (180**)** with ketones by using Cu_2O as a catalyst

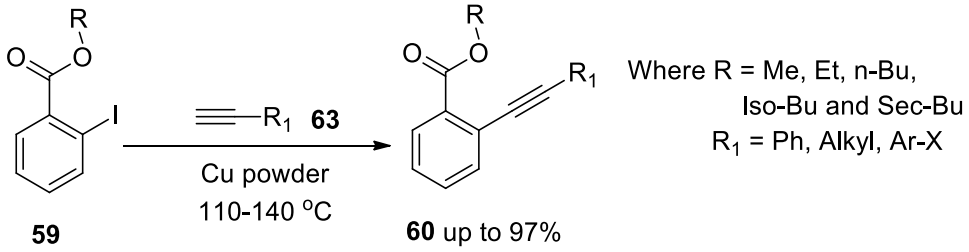
and 2,2,6,6-tetramethylpiperidine N-oxyl (TEMPO) in the air with high reaction yields. (Scheme 1.20) This methodology offers possible approach through generation of all-carbon quaternary centers at the C3 position of oxindoles withoutstanding regioselectivity under mild conditions.



Scheme 1.20: Cu-catalyzed tandem oxidative cross-couplings of oxindoles.

In 2016, Sagadevan and co-workers[147] devised a novel visible-light-initiated Cu-catalysed process for the cross-coupling reaction of terminal alkynes to furnish bio-active 1,3-unsymmetrical conjugated diynes at room temperature. This method did not require pre-functionalized substrates, ligands, bases, additives and costly palladium/gold catalysts.

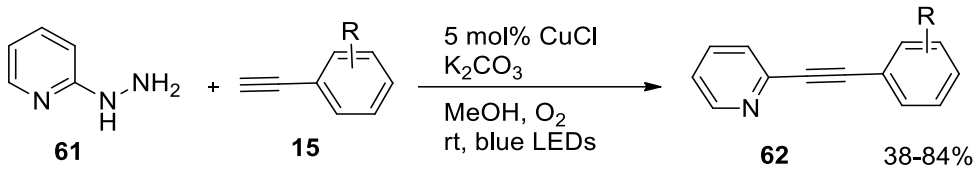
In 2017, Ali and co-workers[148] presented a Cu-catalyzed Sonogashira reaction of alkyl-2-iodobenzoates (**59)** with alkynes under solvent-, co-catalyst-, and base-free conditions providing coupling products yields up to 97%. (Scheme 1.21) According to the authors, the reported compounds may act as anti-phobic, anti-climatic in the future and also have the potential to control Alzheimer's, Schizophrenia, etc. diseases.



Scheme 1.21: Cu-catalyzed Sonogashira reaction of alkyl-2-iodobenzoates.

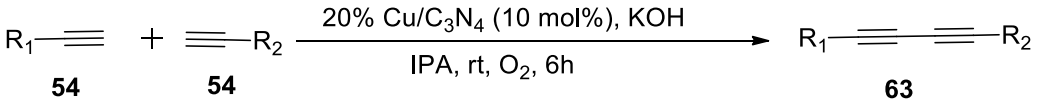
In another report in 2018 by Charpe *et al.*,[149] in which Sagadevan was co-worker, described the first report on visible light-initiated Cu-catalyzed denitrogenative oxidative coupling of 2-hydrazinopyridines (**61)** with terminal alkynes to provide 2-(alkyl/arylethynyl) pyridines (**62)** at room temperature with N_2 and water as the only

byproducts. (Scheme 1.22) The reaction proceeded by an *in-situ* formation of copper(II) superoxo/peroxo complex. This method offered the green synthesis of 2-methyl-6-(phenylethynyl)pyridine (MPEP), mGluR5 receptor antagonists, and 2-((3-methoxyphenyl)ethynyl)-6-methylpyridine (M-MPEP).



Scheme 1.22 Visible light-initiated Cu-catalyzed denitrogenative oxidative coupling.

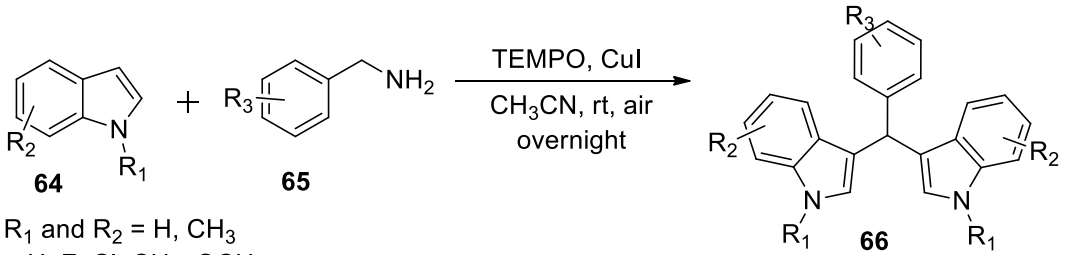
Xu and co-workers[150] prepared an environmentally friendly Cu/C_3N_4 composite and examined it as a highly effective catalyst for the homo- & cross-coupling reaction of terminal alkynes affording symmetrical & unsymmetrical 1,3-diynes (**63)** in good yields. (Scheme 1.23) The reaction was performed with oxygen as an oxidant in an isopropanol solution with excellent functional group tolerance under ambient conditions.



R_1 = *p*-$OMeC_6H_4$-, *m*-$NH_2C_6H_4$-
R_2 = C_6H_5-, *p*-$C_2H_5C_6H_4$-, *p*-$C_5H_{11}C_6H_4$-, *m*-$NH_2C_6H_4$-, *p*-$CF_3C_6H_5$-, *p*-$CH_3C_6H_5$-,*p*-$C_3H_7C_6H_5$-, *m*-$CH_3C_6H_5$-, *p*-FC_6H_5-, *n*-C_4H_9

Scheme 1.23 Cu/C_3N_4 composite-catalyzed coupling of terminal alkynes.

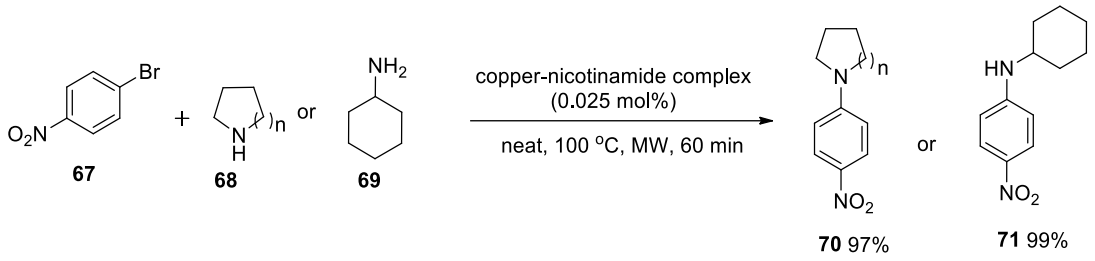
Liao *et al*.[151] found TEMPO/CuI as an effective catalyst for the crosscoupling of benzylic amines (**65)** with indoles (**64)** generating the corresponding bis(indolyl)phenylmethanes (**66)** under air at room temperature in high yields. (Scheme 1.24)



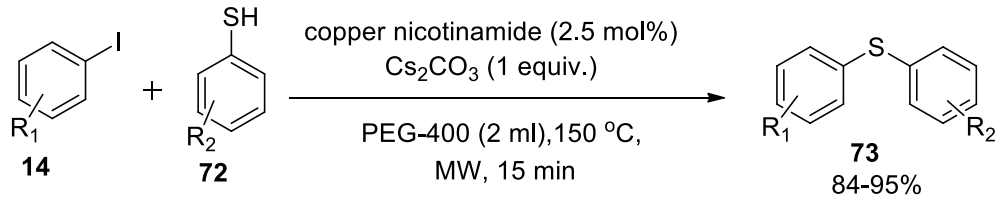
R_1 and R_2 = H, CH_3
R_3 = H, F, Cl, CH_3, OCH_3, CF_3, Ph, NO_2, CN

Scheme 1.24: TEMPO/CuI-catalyzed cross-coupling of benzylic amines with indoles.

A mixed example of a Cu-catalysed coupling reaction was described byBaig and co-workers[152] who synthesized a versatile crystalline copper(II)-nicotinamide complex which efficiently catalyzedthe MW-accelerated C-N,C-S bond-forming and cycloaddition reactions transformations. (Scheme 1.25-1.27)

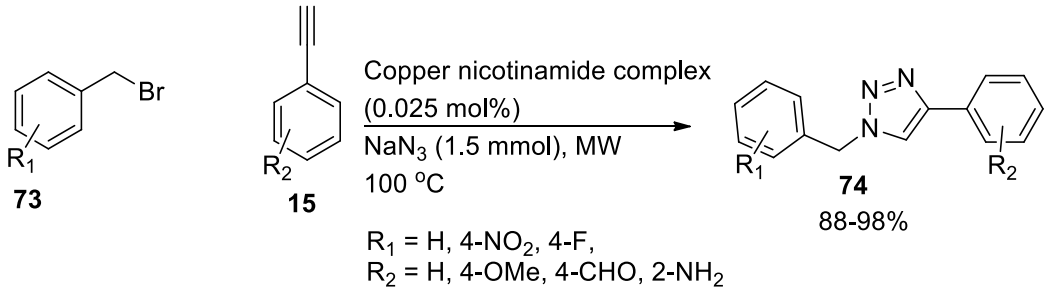


Scheme 1.25: Copper(II)-nicotinamide complex-catalyzed MW-enhanced C-N coupling reaction.



R_1 = H, 4-NO_2, 3-NO_2, 2,4,6 triMe,
4-CH_3CO, 4-CH_3
R_2 = H, 4-Cl, 4-NO_2

Scheme 1.26: Copper(II)-nicotinamide complex-catalyzed MW-enhanced C-S coupling reaction.

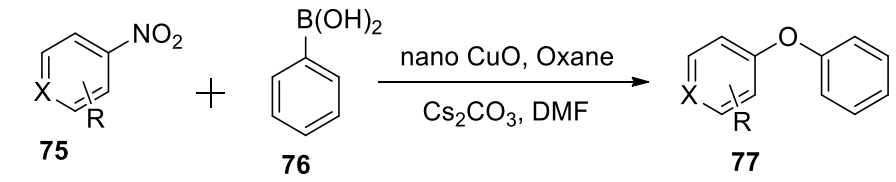


R_1 = H, 4-NO_2, 4-F,
R_2 = H, 4-OMe, 4-CHO, 2-NH_2

Scheme 1.27: Copper(II)-nicotinamide complex-catalyzed MW-enhanced cycloadditionreaction.

1.3.2 C-O Cross-Coupling Reaction

In 2012, Zhang and co-workers[153] developed first example of Cu-catalyzed coupling of nitroarenes with arylboronic acid providing diaryl ethers (**77)** in moderate to excellent yields. (Scheme 1.28) The reaction did not involve any ligand and deuterium labeling in mechanistic studies showed that water was essential for this transformation.

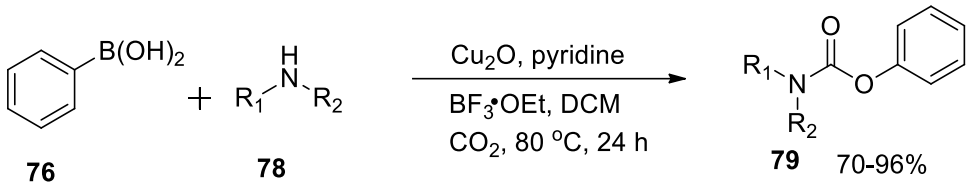


X = CH, N

R = 2-CHO, 4-CN, 4-CF_3, 4-MeCO, 3-Cl-4-CN, 4-NO_2, 4-PhCO, 4-MeOCO, 3-CH_3

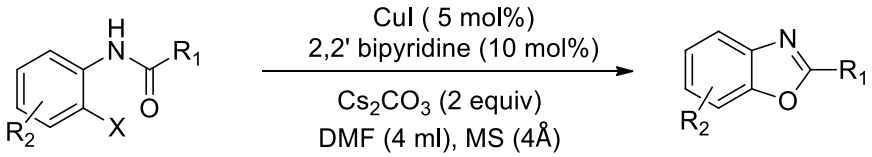
Scheme 1.28: Cu-catalyzed coupling of nitroarenes with arylboronic acid.

In 2017, Xiong and co-workers[154] described the first report on the Cu-catalyzed oxidative coupling reaction ofcarbon dioxide, amines andarylboronic acids to synthesize various *O*-aryl carbamates (**79)** using $BF_3{\cdot}OEt_2$. (Scheme 1.29) A wide range of functional group tolerance could be seen in this transformation.



Scheme 1.29: Cu-catalyzed oxidative coupling reaction.

In 2019, a new method for the synthesis of bioactive 2-substituted benzoxazoleshas been developed by the Saranya research group[155] via Cu-catalyzed intramolecular C-O cross-coupling of 2-haloanilides (**80)** in moderate to good yields. (Scheme 1.30) This transformation occurred by employing CuI (5 mol%)/2,2'-bipyridine (10 mol%) as a catalytic system, Cs_2CO_3 (2 equiv.) as a base and DMF solvent with 4 Å molecular sieves at 140 ^oC. The reaction was observed to be influenced by the amide and aromatic substituents of 2-haloanilides.



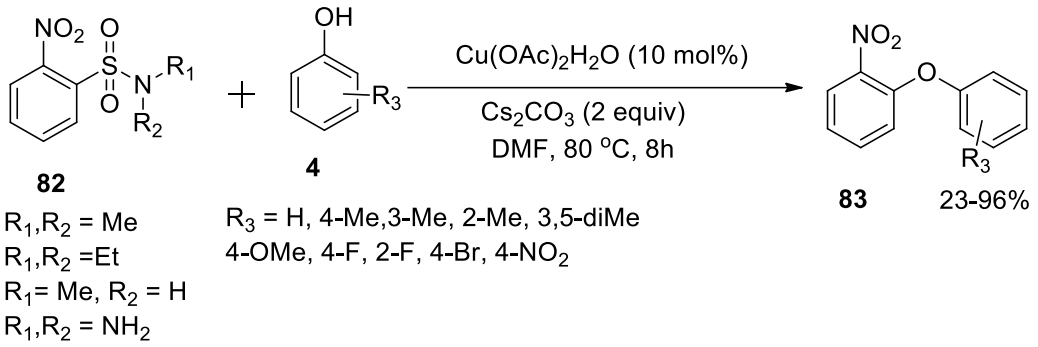
R_1 = ^{t}Bu, ^{i}Pr, Et, Ph

R_2 = H, 4-Me, 4-F, 4-NO_2, 4-OMe, 5-CF_3

X = Br, I, Cl

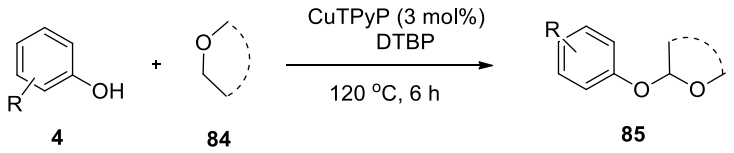
Scheme 1.30: Cu-catalyzed intramolecular C-O cross-coupling reaction.

Chen *et al.*[156] observed an unprecedented ligand-free Cu-catalyzed *O*-arylation of arenesulfonamides (**82)** with phenols generating a range of unsymmetric biaryl ethers (**83)** in excellent yields. (Scheme 1.31) The reaction involved the cleavage of C-S bond with excellent regioselectivity and good functional groups tolerance on phenols.



Scheme 1.31: Cu-catalyzed *O*-arylation of arene sulfonamides.

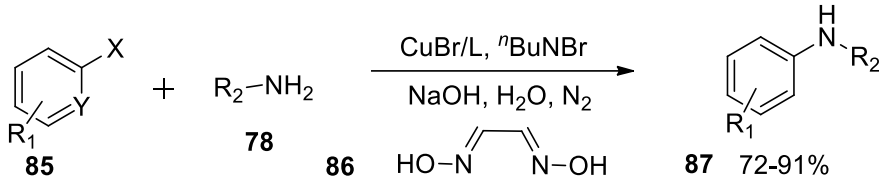
Recently, the Wang group[157] investigated the cross-dehydrogenative coupling (CDC) reaction between the C(sp^3)-H bond and the hydroxyl group of phenol substrates. (Scheme 1.32)



Scheme 1.32: Cu-catalyzed cross-dehydrogenative coupling (CDC) reaction.

1.3.3 C-N Cross-Coupling Reaction

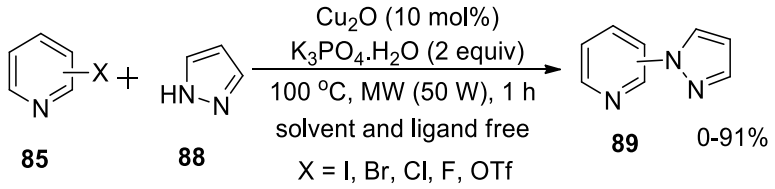
In 2010, the Li group[158] developed a simple Cu-catalyzed method for N-arylations of nitrogen-containing heterocycles and aliphatic amines in wateras a solvent and (1*E*,2*E*)-oxalaldehyde dioxime (**86)** as a ligand at 100 ˚C. (Scheme 1.33)



R_1 = 4-Cl, 4-F, 4-CH_3, 4-OMe, napthyl, 4-Br, 2-NO_2-6-COOH, 4-NO_2-6COOH, 2-Cl
R_2 = $C_{12}H_{25}$, C_3H_6OH, C_2H_4COOH, C_4H_8O, PhC_2H_3COOH, $C_6H_5CH_2$-, C_3H_7, C_6H_{11}, $C_5H_{10}OH$, *p*-$CH_3C_6H4CH_2$, $C_{12}H_{25}$
Y = CH, N

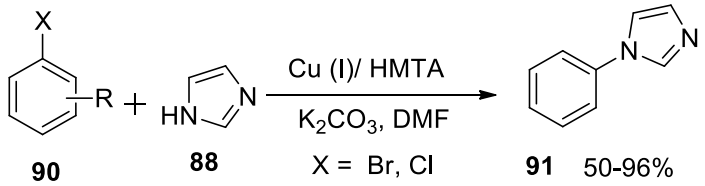
Scheme 1.33: Cu-catalyzed N-arylation of nitrogen-containing heterocycles.

In 2011, Liu and co-workers[159] described a microwave-promoted solvent and ligand-free Cu-catalyzed amination of several halopyridines (**85)** with various nitrogen nucleophiles (**88)** giving corresponding *N*-heteroarylated products (**89)** in good yields. (Scheme 1.34)



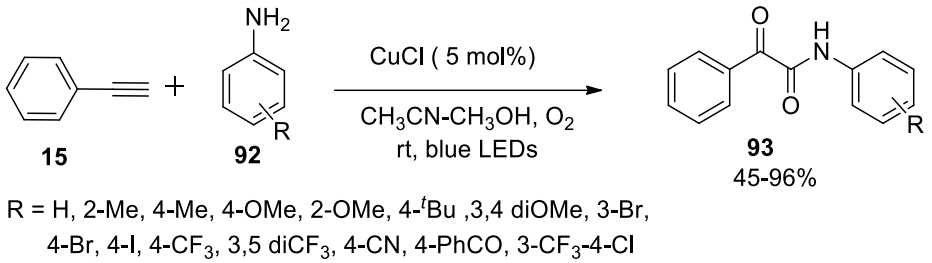
Scheme 1.34: MW-promoted Cu-catalyzed amination of halopyridines.

In 2012, Cao and co-workers[160] reported an efficient C-N cross-coupling reaction which allowed the coupling of imidazole (**88)** with aryl chlorides or bromides by employing a cheap catalytic systemCu(I)/HMTA providing products in moderate to good yields. Moreover, the presence of electron-withdrawing groups or electron-donating groups in aryl halides had no adverse effect on the outcome of the reaction. (Scheme 1.35)



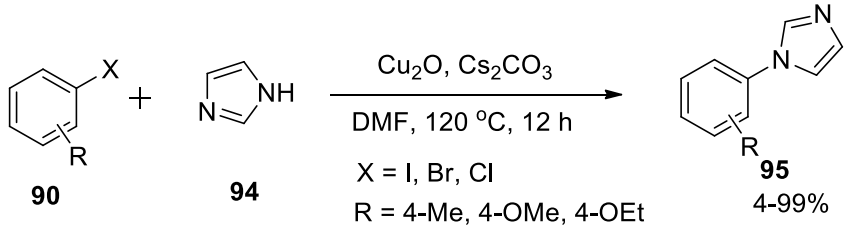
Scheme 1.35: Cu(I)/HMTA-catalyzed C-N cross-coupling of imidazole and aryl halides.

In 2015, Sagadevan and co-workers[161] reported a copper(I) chloride catalyzed green process for direct oxidative C_{sp}-N coupling reactions ofanilinesand alkynes affording biologically important α-ketoamides (**93)** under visible-light irradiation at room temperature without the need for a base, ligands, and an external oxidant. (Scheme 1.36)



Scheme 1.36: Cu-catalyzed direct oxidative C-N coupling reaction.

In 2017, Wang *et al.*[162] established a new Cu-catalyzed ligand-free deal for Ullmann-type N-arylation of N-containing heterocycles with aryl (**90)** or heteroarylbromides oriodides without the protection of an inert gas affording the desired products with high reaction yields. (Scheme 1.37) In 2021, Bai *et al.*[163] reported a simple strategy for the C–N cross-coupling of indazole with a modification of substituted aryl bromides under ligand-free conditions.



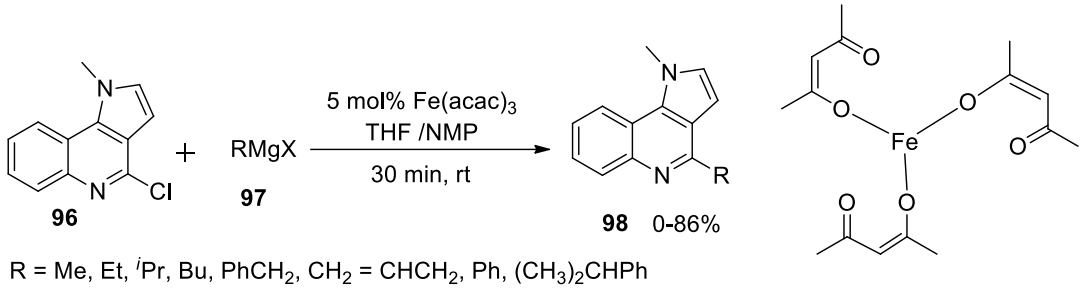
Scheme 1.37: Cu-catalyzed Ullmann-type N-arylation.

1.4 Fe-Catalyzed Reactions

We will discuss in this section to limited use of Iron catalysis in various cross-coupling reactions and is generally presented in chronological order.

1.4.1 C-C Cross-Coupling Reaction

In 2009, Colacino and co-workers[164] developed Fe-catalyzed cross-coupling reaction of 4-chloro-pyrrolo-[3,2-c]quinoline (**96)** witharyl oralkyl magnesium halides in the presence of $Fe(acac)_3$. (Scheme 1.38) The reaction was performed in a mixture of THF and NMP in just 30 min. The coupled products are useful scaffolds for medicinal chemistry which obtained moderate to excellent yields of 52-94%.

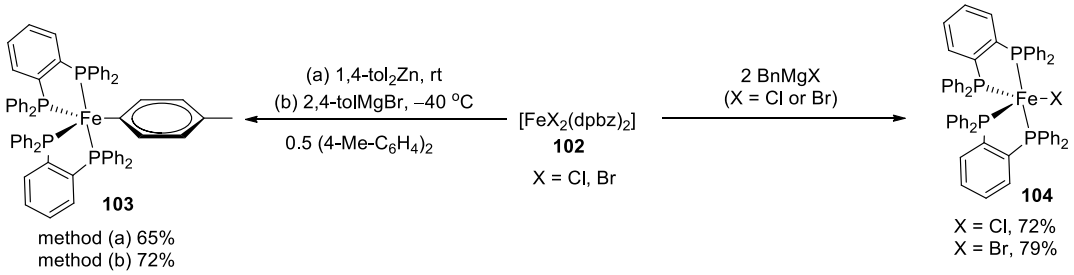


Scheme 1.38: Fe-catalyzed Kumada cross-coupling of 4-chloro-pyrrolo-[3,2-c]quinoline.

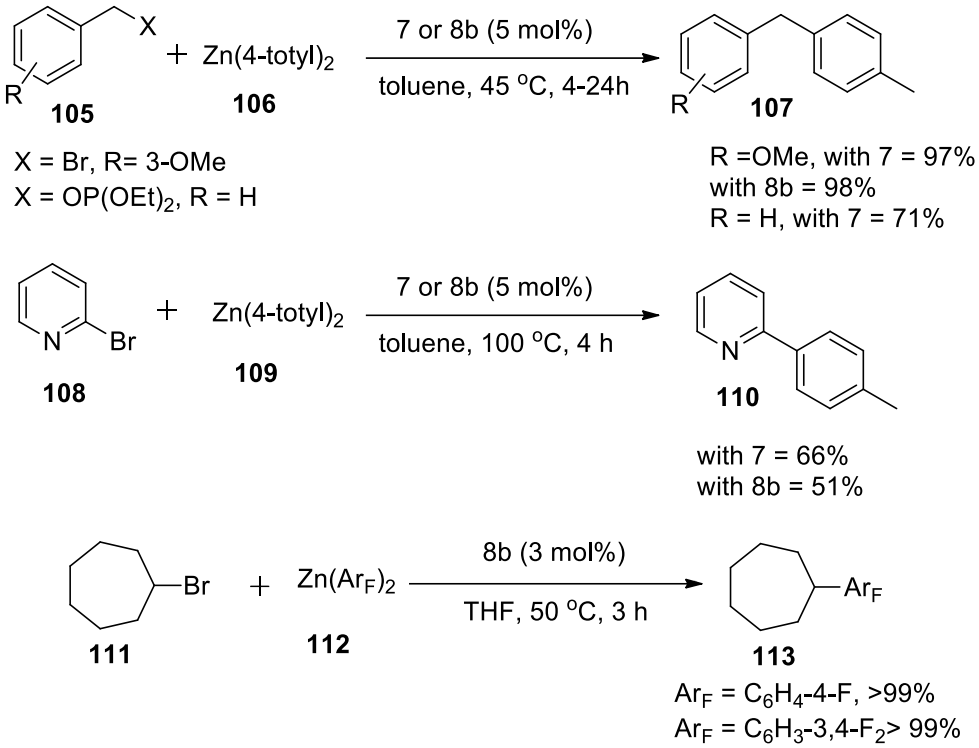
In 2012, Liu *et al.*[165] discovered a Fe-catalyzed arylation of benzoazoles (**99)** with aromatic aldehydes with oxygen as an oxidant in good to excellent yields under base-free conditions. (Scheme 1.39) The reaction was managed by a mixture of water-diglyme instead of organic solvents and better yields were obtained when benzothiazoles were employed as substrates.

Scheme 1.39: Fe-catalyzed arylation of benzoazoles.

Adams and co-workers[166] demonstrated the synthesis of Fe(I) complexes, $[FeX_2(dpbz)_2]$ [X = 4-tolyl, Cl, Br, dpbz = 1,2-bis(diphenylphosphino)benzene] (Scheme 40) and investigated their catalytic efficiency in Negishi cross-coupling reactions with arylzinc reagents. (Scheme 41)

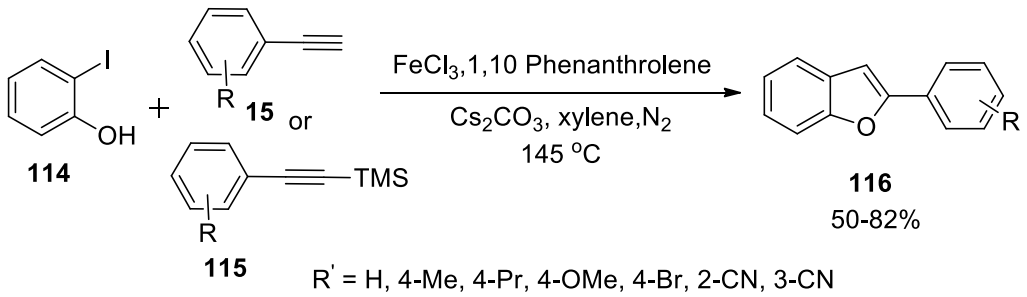


Scheme 1.40: Synthesis of Fe(I) complexes $[FeX\text{-}(dpbz)_2]$.



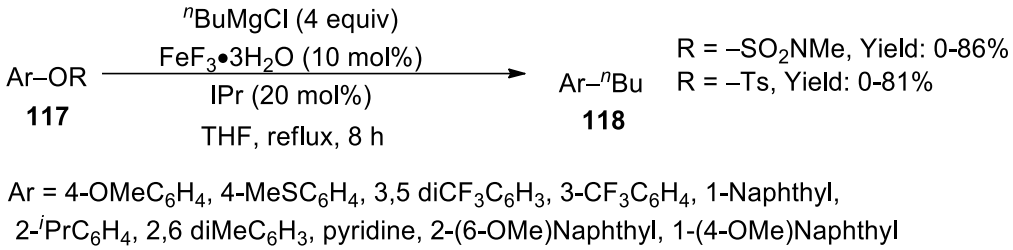
Scheme 1.41: Fe(I) complexes-catalyzed Negishi cross-coupling reactions.

In 2013, Yang and co-workers[167] discovered a Fe-catalyzed method to manage both the intramolecular *O*-arylation of o-iodophenols and Sonogashira cross-coupling and aryl acetylenes/1-substituted-2-trimethylsilyl acetylenes to afford corresponding 2-arylbenzo[b]furans (**116)** in good reaction yields. (Scheme 1.42) The procedure utilized 5% $FeCl_3$ and 10% 1,10-phenanthroline as a catalytic system.



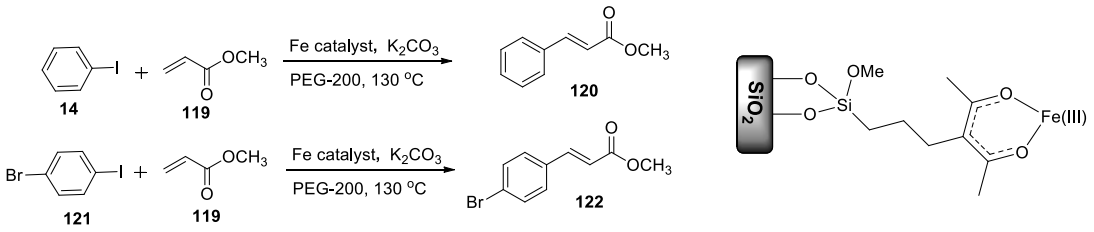
Scheme 1.42: Fe-catalyzed Sonogashiracross-coupling and intramolecular *O*-arylation.

Agrawal *et al.*[168] achieved the Fe-catalyzed cross-coupling of alkyl Grignards using aryl sulfamates or tosylates (**117)** in quantitative yields. (Scheme 1.43)



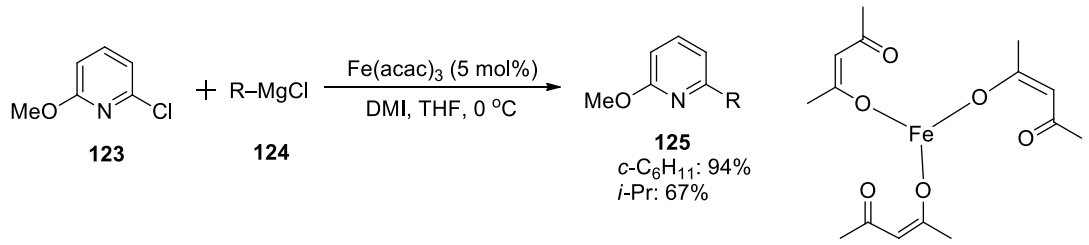
Scheme 1.43: Fe-catalyzed cross-coupling of aryl sulfamates or tosylates with alkyl Grignards.

Hajipour and co-workers[169] prepared heterogeneous Fe-based catalyst supported on acac-functionalized silicawhich was employed as a catalyst in Mizoroki-Heck reaction of aryl iodides and olefins in poly(ethylene glycol) as a green solvent. (Scheme 1.44) Interestingly, this protocol allowed selective coupling reaction of aryl iodides in the appearance of aryl bromides. The catalyst could be recovered well from the reaction mixture and recycled upto five times.

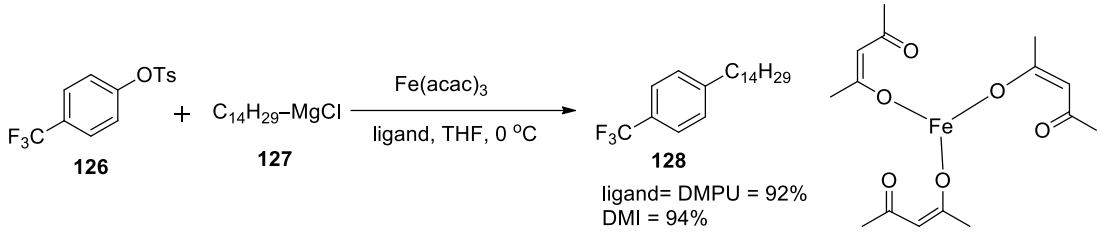


Scheme 1.44: Fe-catalyzed selective coupling reaction of aryl iodides.

In 2017, Bisz and co-workers[170] reported that benign cyclic ureas (DMI, DMPU) are efficient and sustainable ligands instead of hazardous NMP in Fe-catalyzed alkylations of aryl chlorides or tosylates with alkyl Grignard reagents. (Scheme 1.45, 1.46) Moreover, this protocol allowed C(sp^2)-C(sp^3) cross-coupling synthesis of a dual NK1/serotonin receptor antagonist.

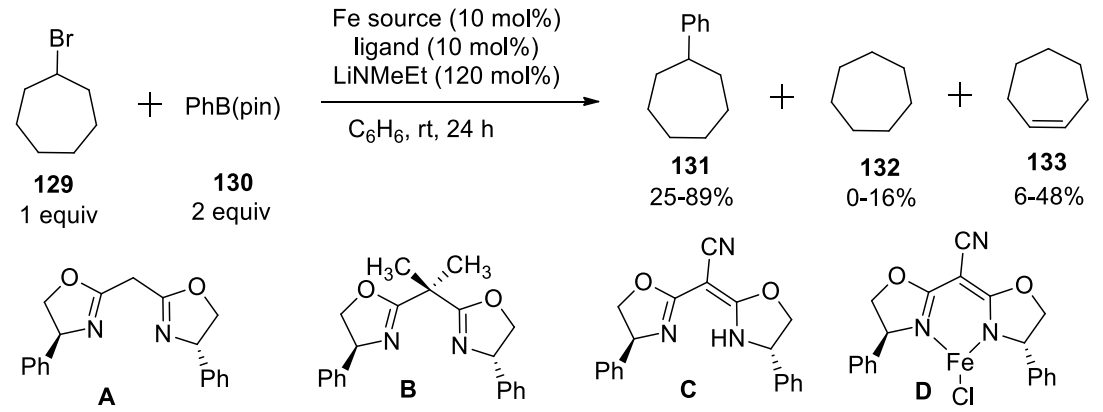


Scheme 1.45: Fe-catalyzed alkylation of aryl chlorides.

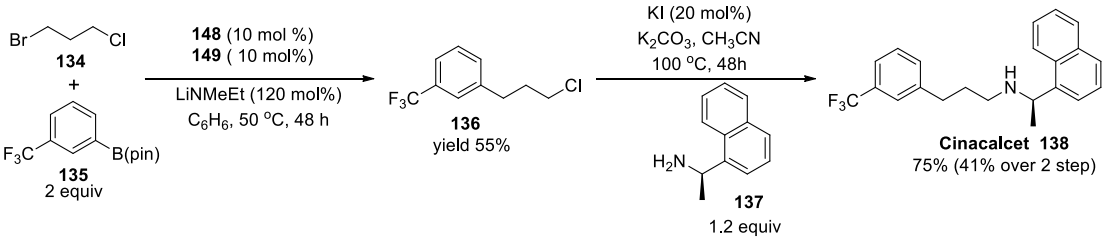


Scheme 1.46: Fe-catalyzed alkylation of aryl tosylates.

In 2018, Crockett and co-workers[171] discovered a Fe-catalyzed cross-coupling reaction between alkyl halides and arylboronic esters by employing lithium amide bases coupled with Fe complexes containing deprotonated cyanobis(oxazoline) ligands (A-D**)** affording up to 89% yields of the coupled products. (Scheme 1.47) Remarkably, the reaction required neither alkyllithium reagents for activation of the boronic ester nor magnesium additives. Moreover, the two-step synthesis of pharmaceutically important Cinacalcet (**138)** was shown by using this protocol. (Scheme 1.48)



Scheme 1.47: Fe-catalyzed cross-coupling reaction between alkyl halides and arylboronic esters. [211]

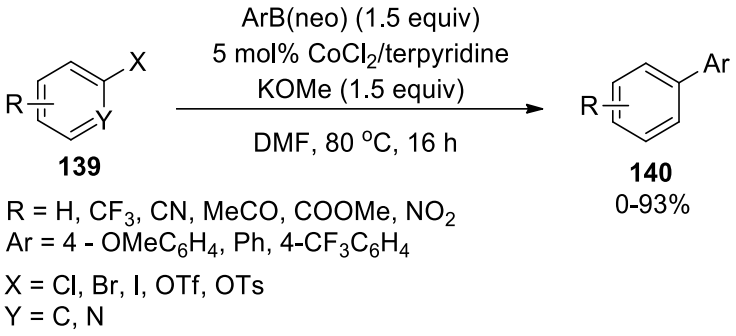


Scheme 1.48: Fe-catalyzed synthesis of pharmaceutical compound Cinacalcet.

1.5 Co-Catalyzed Reactions

We will discuss in this section to limited use of Cobalt catalysis in various cross-coupling reactions and is generally presented in chronological order.

In 2017, Duong and co-workers[172] described a Co-catalyzed Suzuki-Miyaura cross-coupling reaction of aryl halides and arylboronic esters by employing cobalt(II)/terpyridine catalyst and KOMe generating corresponding (hetero)biaryls in moderate to excellent yields. (Scheme 1.49) This procedure well tolerated the πelectron-rich and πelectron-deficient heteroaryl halides and electron-deficient aryl halides.



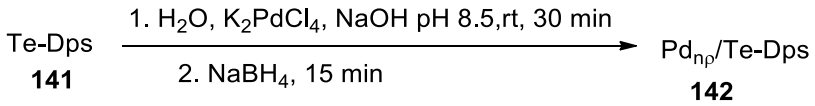
Scheme 1.49: Cobalt(II)/terpyridine-catalyzed SM cross-coupling reaction.

1.6 Transition Metal Nanoparticles-Promoted Reactions

We will discuss in this section to limited use of nanoparticles catalysis in various cross-coupling reactions and is generally presented in chronological order.

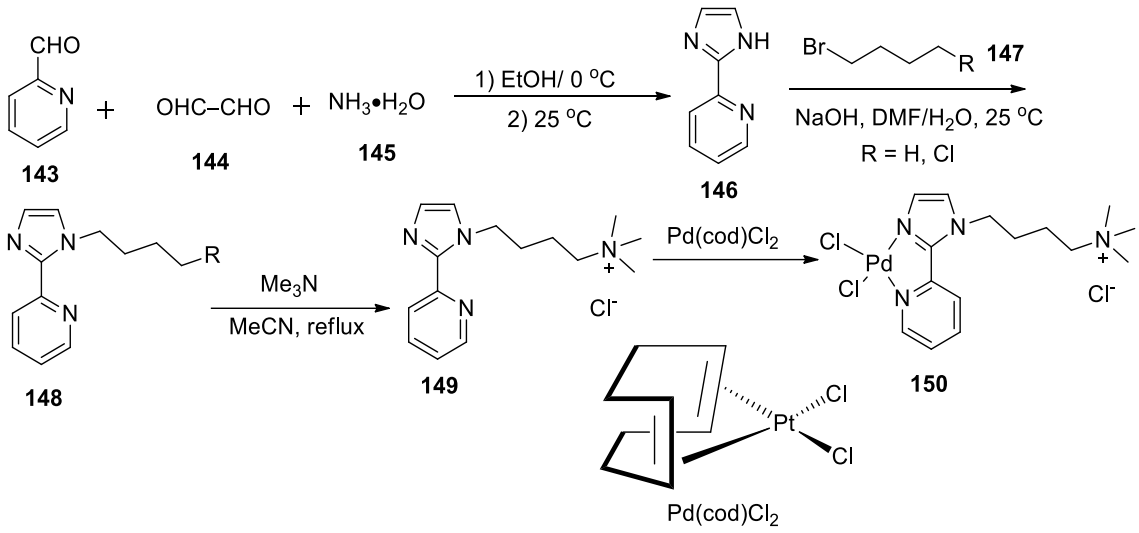
1.6.1 Pd Nanoparticles

In 2009, Prastaro and co-workers[173] prepared a precatalyst to consist of Pd nanoparticles stabilized within the protein cavity of Dps protein (Pdnp/Te-Dps) (**142)** and tested its catalytic ability for Suzuki-Miyaura cross-coupling reactions under phosphine-free, aerobic conditions in the water. (Scheme 1.50)



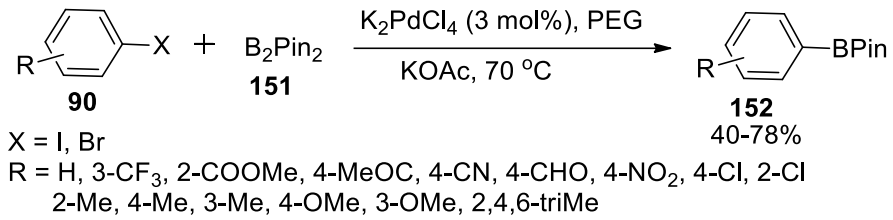
Scheme 1.50: Synthesis of Pd nanoparticles stabilized within the protein cavity of Dps protein.

Based onthe well-known fact that bacteria can recover Pd(0) in the form of nanoparticles, Søbjerg and co-workers[174] decided to investigate the scope of the reactions that could be catalyzed by bio-recovered palladium. They demonstrated that theMizoroki-Heck andSuzuki-Miyaura reactions were catalyzed by bio-Pd(0) nanoparticles set up on the surface of Gram-negative bacteria such as *C.necator* and *P.putida*. In 2011, Zhou and co-workers[175] synthesized a water-soluble ammonium-functionalized bidentate nitrogen-containing ligand (**149)** and its Pd chelating complex (**150)** and utilized this for Suzuki-Miyaura cross-coupling reaction in neat water under aerobic condition. (Scheme 1.51)



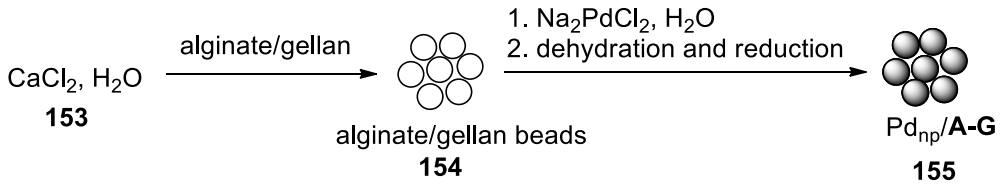
Scheme 1.51: Synthesis of water-soluble ammonium-functionalized bidentate nitrogen-containing ligand and its Pd chelating complex.

Khalafi-Nezhad and co-workers[176] published a report on the synthesis of a recyclable heterogeneous catalyst system in which they managed to immobilize Pd NPs on a silica-starch substrate (PNP-SSS) and found an effective catalyst in Heck and copper-free Sonogashira reactions with water as an eco-friendly solvent. The silica-starch substrate effectively stabilized and provided a platform to Pd NPs and prevented their aggregation and separation from the SSS surface. In 2012, Bej and co-workers[177] made to generate Pd nanoparticles in PEG which catalyzed the reaction of aryl/benzyl halides with bis(pinacolato)diboron to furnish aryl/benzyl boronates in high yield which in turn used as a reaction partner in the solvent- and ligand-free Suzuki-Miyaura coupling reaction with different aryl/benzyl halides in 53-72%. (Scheme 1.52)

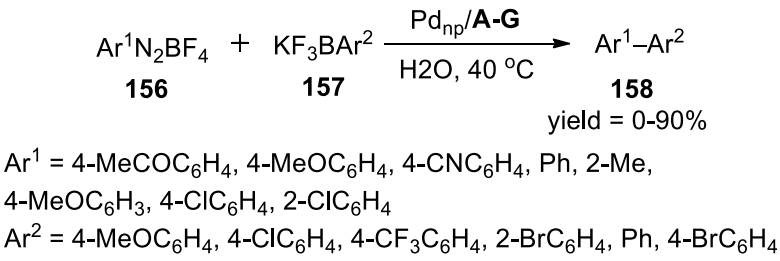


Scheme 1.52: Synthesis of aryl boronates. [218]

Cacchi and co-workers[178] made Pd nanoparticles stabilized by natural beads of an alginate/gellan mixture for the phosphine-, and base-free Suzuki-Miyaura cross-coupling reaction of potassium aryltrifluoroborates and arenediazonium tetrafluoroborates in 1:1 molar ratio with catalyst loading of just 0.01–0.002 mol% under aerobic conditions in the water. (Scheme 1.53, 1.54)

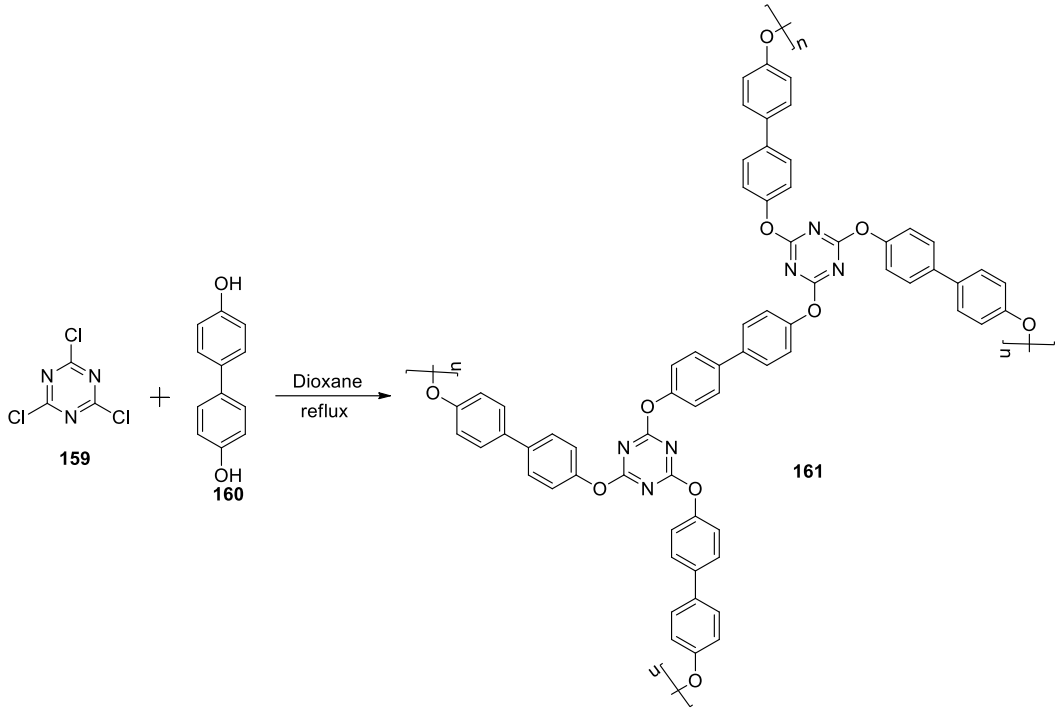


Scheme 1.53: Synthesis of Pd nanoparticles stabilized by natural beads of alginate/gellan mixture.



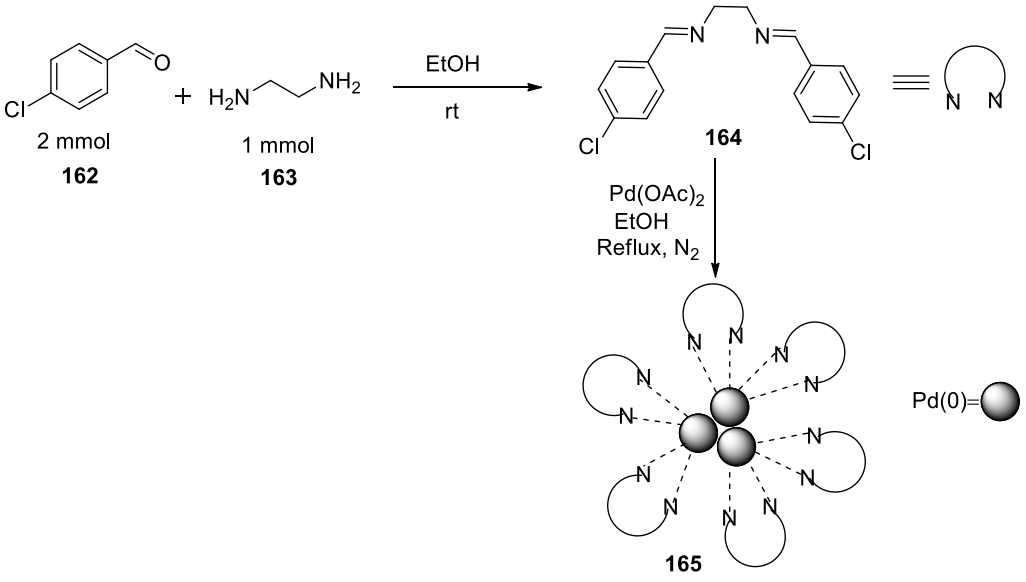
Scheme 1.54: Pdnp/A-Gmediated Suzuki-Miyaura cross-coupling reaction.

In 2014, Huang and co-workers[179] reported a synthetic procedure of Pd nanocomposite by depositing palladium nanoparticles in the micropores of the SBA-15 with hydrophobic triphenylsilyl or trimethylsilyl groups grafted on the mesopores. Then they allowed ligand-free Hiyama cross-couplings of aryl halides and various aryltriethoxysilanes at 100 °C in air. Puthiaraja and co-workers[180] synthesized a novel nitrogen-rich functional mesoporous covalent organic polymer (MCOP) which offered excellent support for Pd nanoparticles (Pd@MCOP) by nucleophilic substitution reaction of cyanuric chloride (**159)** and 4,4'-dihydroxybiphenyl (**160)**. (Scheme 1.55)



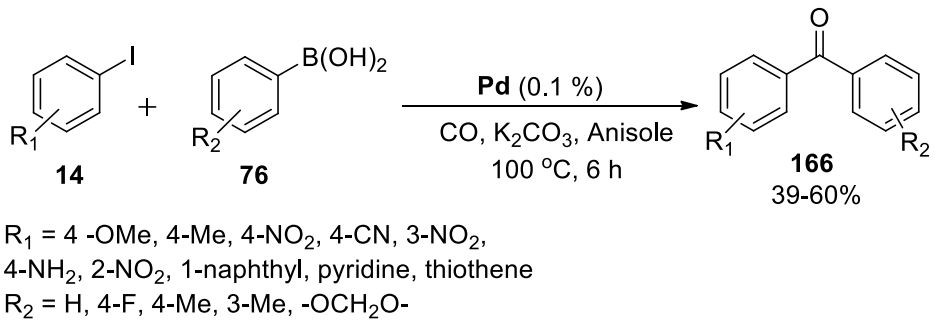
Scheme 1.55: Synthesis of functional mesoporous covalent organic polymer (MCOP).

In 2015, Mandegani and co-workers[181] developed the synthesis of a novel nano tetraimine Pd(0) complex (**165)** with the complexation of $Pd(OAc)_2$ with N,N-bisimine ligand (**164)**. (Scheme 1.56) The catalytic efficiency of this heterogeneous nano-complex was investigated towards the Heck-Mizoroki reaction in water. The catalyst could be reusable and recycled without any loss in catalytic activity.



Scheme 1.56: Synthesis of a novel nano tetraimine Pd(0) complex.

In 2016, Gautam and co-workers[182] investigated the efficiency of PdNPs supported on fibrous nanosilica (KCC-1) towards carbonylative Suzuki-Miyaura cross-coupling reaction with a low Pd loading of 0.1%. (Scheme 1.57) This KCC-1-PEI/Pd catalytic system displayed a TON 28-times and TOF 51-times bigger than already reported supported Pd catalyst in the literature for this reaction probably owing to the fibrous nature of the KCC-1 support and PEI functionalization enhanced the stability.



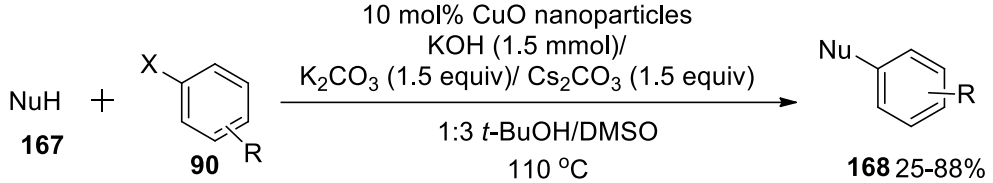
Scheme 1.57: PdNPs/KCC-1mediated carbonylative SM cross-coupling reaction.

In 2019, Yamada and co-workers[183] investigated the effect of a co-existing metal in the ligand-free Suzuki-Miyaura coupling reaction of an aryl chloride under continuous irradiation microwave and a PdNPs catalyst (SGlPd) and established that the co-existing metal such as aluminium foil involves this reaction due to its microwave absorption ability in the reaction system. Mohazzab and co-workers[184] synthesized reusable mesh-GO/Pd catalyst by immobilization of Pd NPs on stainless-steel mesh. Dhara and co-workers[185] prepared glucose-stabilized palladium nanoparticles with recycling and reusing capability up to four times and explored its catalytic potential for both Suzuki and Heck reactions in aqueous medium supported by microwave irradiation. This procedure allowed the coupling of various electron-rich and electron-deficient aryl halides in high reaction yields.

Blanco and co-workers[186] impregnated graphene acid (GA) with $Pd(OAc)_2$ yielding GA-Pd nanohybrids with a size ranging from 1 nm up to 9 nm andapplied in the Suzuki-Miyaura cross-coupling reaction.

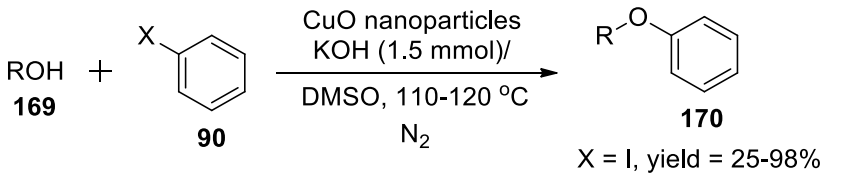
1.6.2 Cu Nanoparticles

In 2009, Jammi and co-workers[187] studied the catalytic behavior of CuO nanoparticles forC-S, C-O, andC-N bond formations through ligand-free cross-coupling reactions of different nucleophiles such asimidazoles, amides, amines, alcohols, thiols and phenols with aryl halides by using a base i.e KOH, K_2CO_3, and Cs_2CO_3 at moderate temperature to afford the cross-coupled products in high yield. (Scheme 1.58-1.60)



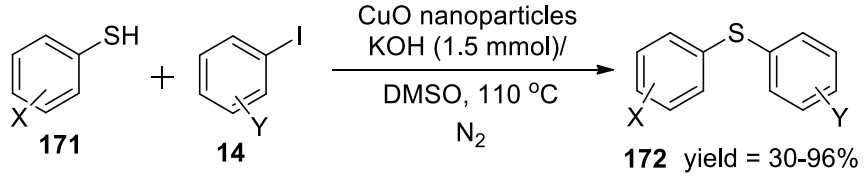
X = I, Br, Cl, OTs, $B(OH)_2$
NuH = $C_6H_5CONH_2$, 4-$MeC_6H_4SO_2NH_2$, cy-$COONHCH_2CH_2$, $C_5H_{11}CONH_2$
R = H, 4-NO_2, 4-OMe,

Scheme 1.58: CuO nanoparticles mediated C-N cross-coupling reaction.



X = I, Br
R = 2-*t*-BuC_6H_4,2-MeC_6H_4, 2-$MeOC_6H_4$, 3-MeC_6H_4, 3-$NO_2C_6H_4$
4-t-BuC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$, 2,4 dit-BuC_6H_3,
2,4-diMeC_6H_3, 1-naphthol, 2-naphthol, n-$C_{10}H_{21}$

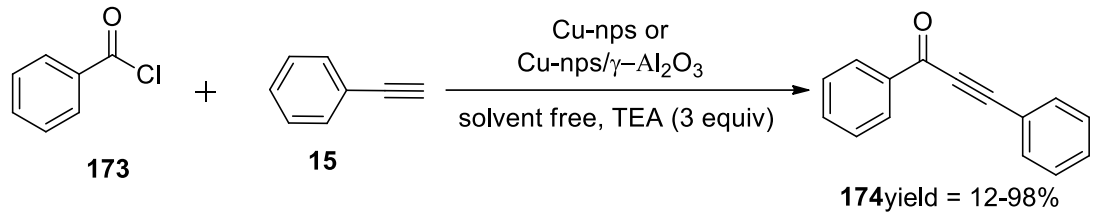
Scheme 1.59: CuO nanoparticles mediated C-O cross-coupling reaction.



X= H, 4-Me,
Y = 3-NO_2, 4-NO_2, 4-Br, 4-Me, 2-OMe,1-naphthyl, 4-OMe, 2,4-diMe

Scheme 1.60: CuO nanoparticles mediated C-S cross-coupling reaction.

In 2013, Sun and co-workers[188] utilized supported copper NPs for the first time Pd-, ligand-, and solvent-free coupling reactions of acyl chlorides with terminal alkynes to generate corresponding ynones in 12-98% yield. (Scheme 1.61)



Scheme 1.61: CuNPs mediated Sonogashira cross-coupling of acyl chlorides.

In 2017, A similar report for the synthesis of ynones via solvent-free Sonogashira reactions was disclosed by Wang and co-workers[189] by employing mesoporous phenol-formaldehyde resin-supported copper nanoparticles catalyst (Cu NPs@MP) having wide surface areas and narrow pore size distributions. The catalyst was synthesized by the melt infiltration of copper nitrate hydrates and the subsequent *in-situ* reductions of Cu(II) by template pyrolysis. This catalyst displayed higher catalytic efficiency than copper powder and mesoporous silica SBA-15-supported Cu NPs.

This chapter documented and showcased an Impressive and elegant overview of the past and recent developments of the various approaches based on the transition metals catalyzed cross-coupling reactions such as Suzuki, Heck, Sonogashira, Stille, Kumada, Kochi, Murahashi, Corriu, Hiyama, and Negishi reactions, as well as decarboxylative, carbonylative, α-arylative, C–O, C–N, C–S bond-forming reactions in the synthesis of natural products and agrochemicals. The past more than 45 years have seen continuous growth in cross-coupling protocols, and plenty of new tools for cross-coupling has been reported by the researchers.

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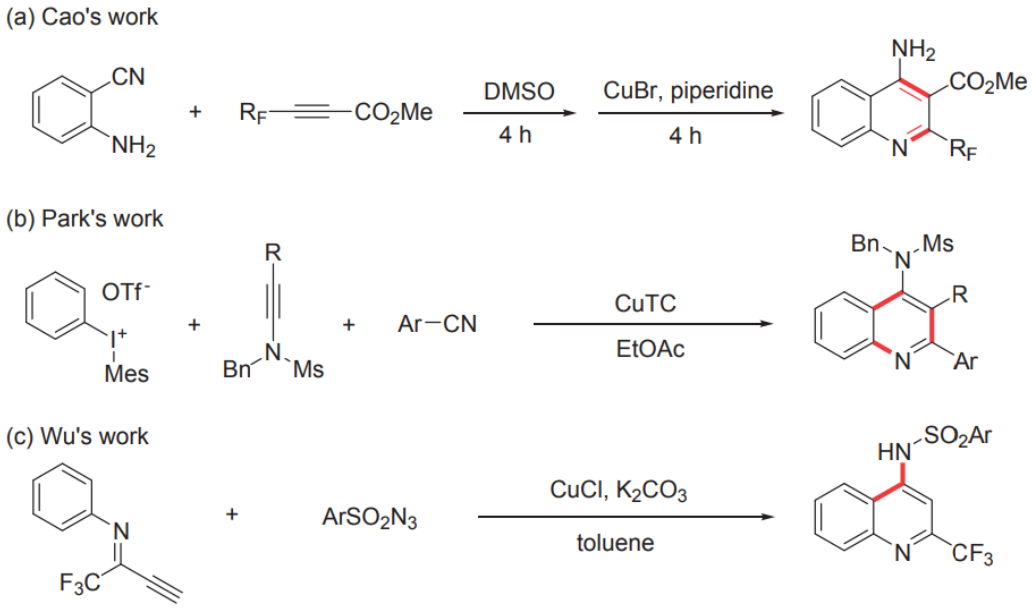
Chapter – 2
Literature

CHAPTER – 2

LITERATURE

Various methods have been developed for constructing 4-aminoquinoline derivatives, with a focus on metal-catalyzed approaches.[1-5] Among these, the Cu-catalyzed synthesis has garnered significant interest due to the cost-effectiveness and abundance of Cu catalysts in organic synthesisFor instance, in 2013, Cao and colleagues introduced a two-step reaction using 2-aminobenzonitrile and methyl perfluoroalk-2-ynoates under copper-catalyzed conditions to yield 4-aminoquinoline derivatives(Scheme 2.1a).[1] Similarly, in 2017, the Park group reported a copper-catalyzed [2+2+2] cyclization of pre-assembled diaryliodoniums, ynamides, and nitriles for synthesizing N-substituted 4-aminoquinolines(Scheme 2.1b).[2] Additionally, Wu and co-workers utilized a copper-catalyzed cycloaddition of fluorinated terminal alkynes with sulfonyl azides to fabricate N-substituted 4-aminoquinolines(Scheme 2.1c).[3] Traditional methods for constructing the quinoline skeleton encompass various named reactions, including the Skraup reaction, Doebner-Von Miller reaction, Combes reaction, and Friedländer reaction.[6] Following these, a modified Friedländer-type reaction has gained prominence. This method employs ortho-acyl anilines and nitroolefins as substrates, leading to the synthesis of the quinoline core through Michael addition and cyclization processes.[7] Despite the advancements made, there remains a strong desire for a direct and practical method to access 4-aminoquinoline derivatives from readily available substrates.



Scheme 2.1: Strategies for the Cu-catalyzed synthesis of 4-aminoquinoline derivatives.

Several methods for synthesizing acridine derivatives have been reported in the past few decades, with these methods including dehydrogenation,[8] metal-catalyzed coupling,[9] C–H functionalization,[10] and inter[11] and intramolecular[12] cyclization. Similarly, radical reactions,[13]metal-catalyzed coupling reactions,[14] cycloaddition reactions[15] and other synthetic methods,[16] mostly involving ortho-functionalized biaryl derivatives as substrates, have been reported for the synthesis of acridine and phenanthridine derivatives. However, these reactions constructed the aza ring of the acridine and phenanthridine moieties. Substrates, in particular quinoline derivatives, affording either acridines or phenanthridines via benzannulation have, in contrast, been less explored.[17]

Numerous examples exist wherein nitriles serve as acyl equivalents.[18] Beginning with the seminal work by Garves,[18a] the synthesis of aryl/heteroaryl ketones via transition metal catalyzed insertion of nitriles into arenes/heteroarenes has been extensively explored by various groups such as Larock,[18b-e] Lu,[18f] Wang,[18l]among others. In these reactions, an aryl metal complex reacts with a nitrile to yield a nitrile addition product. Subsequently, the resulting ketimine undergoes hydrolysis to furnish the ketone. The nucleophilic attack of the aryl metal complex on the relatively inert nitrile is facilitated by the coordination of the transition metal with nitrogen. Although

similar reactions utilizing amine nucleophiles to generate amides have been reported,[19] they suffer from several drawbacks such as the use of expensive catalysts (e.g., Ru,[19a] Pt[19b]), the necessity for costly ligands,[19c] prolonged reaction times,[19d] and other limitations.

The predominant techniques employed in prior studies rely on expensive transition metals either as catalysts, along with necessitating harsh reaction conditions for the synthesis of biologically important heterocycles and functional group transformations.

2.1 Research Gap

- None of the previous work has been explored for the synthesis of nitro-substituted acridinamines/benzo[*c*]acridinamines and quinolinamines. Therefore, there is a high demand for the development of sustainable approaches for the preparation of differently functionalized quinolines and acridines.
- The majority of the previously explored methods for the synthesis of quinoline and acridine utilize expensive transition-metals as a catalyst or stoichiometrically and harsh reaction conditions. So, there is a clear need of transition metal free synthesis of nitro substituted quinoline and acridinamines/benzo[*c*] acridinamines.
- For *N*-acetylation of anilines/amines, the use of expensive transition metals, high reaction temperature, use of the stoichiometric amount of additives and limited substrate scope. Therefore, the development of mild protocols for the use of acetonitrile as an acyl equivalent for *N*-acetylation of anilines/amines is highly desirable.
- Some of the developed methods for the synthesis of benzonitriles suffers due to limited substrate scope, use of strong oxidants and metal catalysts, high reaction temperature, tedious operation procedure, low yields, and poor functional group tolerances. Therefore, the development of a new method for the direct synthesis of nitriles from aldehydes under mild reaction conditions is still desirable.

Objectives

- Transition-Metal-Free Access to Nitroquinolinamines from 2-(Alkynyl)nicotinonitriles through Regeioselective annulations
- Synthesis of Nitro-substituted acridinamines/benzo[*c*] acridinamines via cascade annulations of hetero-2-aklynyl-3-carbonitriles
- Base-Mediated N-Acetylation of Anilines/Amines: Nitriles as a Surrogate of the Acetyl Group
- Potassium tert-butoxide promoted a direct one-pot synthesis of nitriles from aldehydes at room temperature

2.2 References

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Chapter – 3

Transition-metal-free Synthesis of Nitroquinolinamines from 2-(Alkynyl)nicotinonitriles through Regioselective Annulation

CHAPTER – 3

TRANSITION-METAL-FREE SYNTHESIS OF NITROQUINOLINAMINES FROM 2- (ALKYNYL) NICOTINONITRILES THROUGH REGIOSELECTIVE ANNULATION

3.1 Introduction

Amino and nitro-substituted quinolines are especially valuable for their applications in pharmaceuticals and electronic materials.[1-3] aminoquinolines are particularly notable for their significant pharmaceutical activities, including serving as the basis for important drugs such as the anti-Alzheimer's medication tacrine (I),[4] the antimalarial drug chloroquine (II),[5] an antileishmanial agent (III),[6] and an analgesic compound (IV)[7].(Figure.3.1)While numerous strategies exist for synthesizing multifunctional quinolinamines, incorporating nitro groups has proven challenging.[8-9]

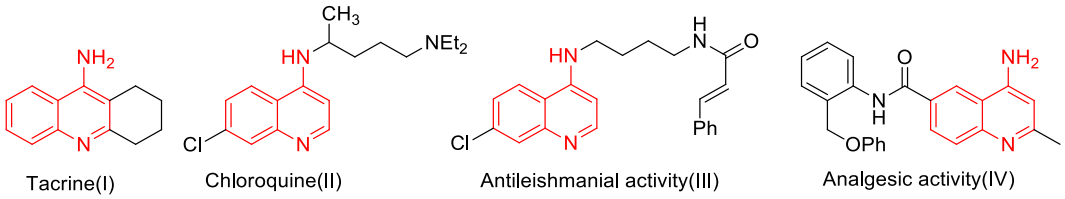
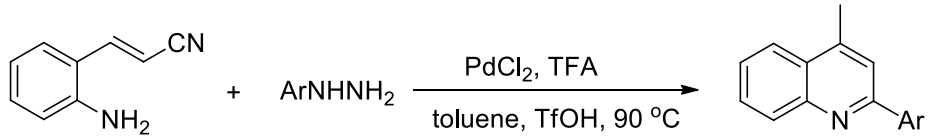


Figure 3.1: Selected biologically active compounds with quinoline moiety.

Traditionally, accessing the quinoline core involved a stepwise process of electrophilic substitution on a quinoline precursor with the required functional groups.[10] However, this method presents challenges such as regioselectivity issues, multistep procedures, harsh reaction conditions, and limited tolerance of existing functional groups, thus constraining its utility in synthetic chemistry.[11] To overcome these limitations, the annulation of functionally diverse quinoline precursors has been successfully developed. This approach eliminates the need for readily available pre-functionalized quinoline substrates.[12] Various strategies have been devised, including annulations involving alkynes, alkenes,[13] allenes,[14] Fischer carbenes,[15] and ynones.[16] Nevertheless, pathways for synthesizing quinolines containing amine or nitro groups are often restricted.

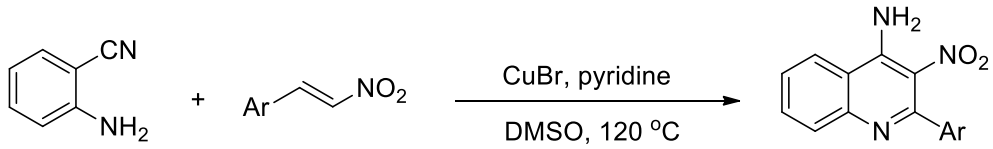
3.2 Review of Literature

In 2016, the group of of Ye[17] has devised a strategy for synthesizing 2-arylquinolines with moderate to satisfactory yields. This method involves a palladium-catalyzed cascade process that combines denitrogenative addition and intramolecular cyclization of o-amino-cinnamonitriles with arylhydrazines.



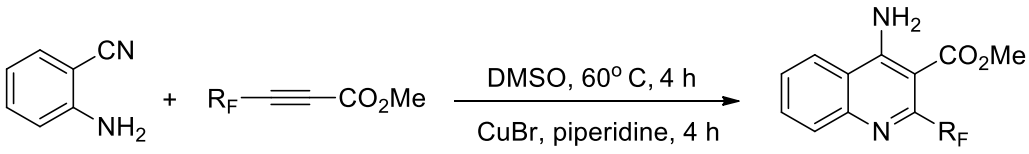
Scheme 3.1: Denitrogenative Pd-catalyzed reaction of o-aminocinnamonitriles with arylhydrazines.

Liu and coworkers[18]have introduced a copper-catalyzed cascade cyclization technique for creating 4-aminoquinoline derivatives. Initial mechanistic investigations suggest that this reaction entails a sequential process of Michael addition, cyclization, and oxidation.



Scheme 3.2: Cu-catalyzed synthesis of 4-aminoquinoline derivatives.

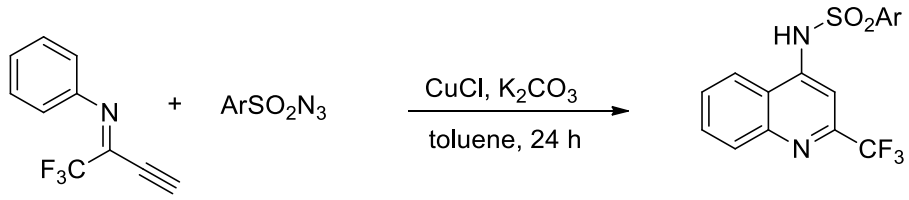
The authors[19] have showcased a copper-catalyzed cyclization approach involving 2-aminobenzonitriles and methyl perfluoroalk-2-ynoates, resulting in the formation of 2-perfluoroalkylated quinolines. This methodology underscores the utilization of copper as a catalyst and perfluoroalk-2-ynoates as the fluorinated building block.



Scheme 3.3: Synthesis of 2-perfluoroalkylated quinolines.

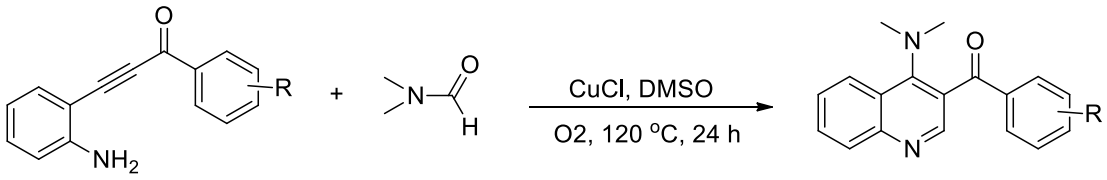
A method has been devised for the synthesis of 2-trifluoromethylquinolines[20] via tandem reactions. The proposed mechanism entails a copper-catalyzedazide–alkyne cycloaddition (CuAAC) reaction followed by cyclization and isomerization steps. Notably, a significant electronic influence of substituents on the N-aromatic moiety of the substrates was

observed, with negligible steric effects. Additionally, this methodology demonstrated the capability to produce 2-trifluoromethyl-4-phosphorylamidoquinolines, thereby offering a versatile route to access 2-trifluoromethylquinolines.



Scheme 3.4: Cu-catalyzed reactions between fluorinated terminal alkynes and sulfonyl azides.

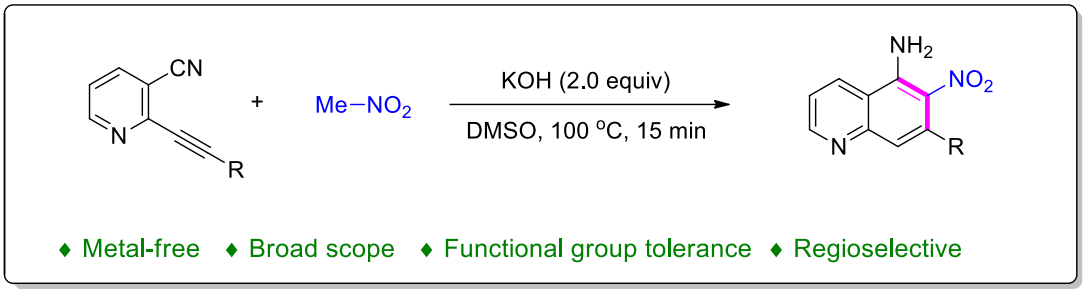
A synthetic procedure has been established for the selective synthesis of 3-acyl-4-aminoquinoline[21] from a specific starting material. The process involves a sequence of steps including the generation of an iminium ion, aza-Michael addition, 6-endo-dig cyclization, and oxidation, all catalyzed by a Cu(I)/DMSO/O_2 system in the presence of DMF. Control experiments indicated that DMF serves as a versatile reagent, providing both methine and *N*,*N*-dimethyl functionalities.



Scheme 3.5: Synthesis of aminoquinolines.

3.3 Designed Strategy

There are no methods for synthesizing quinolines with functionalized benzene rings; all techniques developed are restricted to the synthesis of quinolines with functionalities at the pyridine ring. To the best of our knowledge, there is only one report by Helaja et. al.[22] for the synthesis of quinolines having amino functionality at the benzene ring. However, the reaction requires pre-functionalized nitro-quinolines. Furthermore, the synthesis of nitro-substituted quinolinamines has not been investigated in any of the earlier studies. As a result, there is a great need for the creation of environmentally friendly methods for making variously functionalized quinolines. Therefore, we herein developed an efficient protocol for constructing the diverse range of nitro substituted quinolinamines.



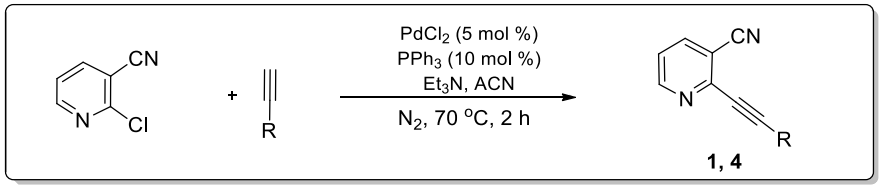
3.4 Experimental Section

General Information and Method

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$/DMSO-d_6. Chemical shifts for protons and carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data has been reported as follows: chemical shift, multiplicity (s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet), coupling constants in Hertz and integration. High-resolution mass spectra were recorded on an electrospray mass spectrometer. Crystal structure analysis was accomplished on single needles X-ray diffractometer. TLC analysis was performed on commercially prepared 60 F_{254} silica gel plates and visualized by either UV irradiation or by staining with I_2. All purchased chemicals were used as received. All melting points are uncorrected.

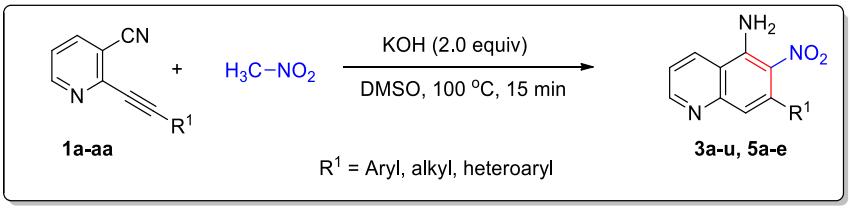
Preparation of 2-alkynylnicotinonitrile (1a-u/4a-e)

To probe the viability of the designed tandem strategy, 2-alkynylnicotinonitrile**1a-u/4a-e** were readily prepared by standard Sonogashira cross-coupling reaction of commercially available and readily accessible 2-chlorohetro-3-carbonitriles with terminal alkynes.[23a,b] This coupling procedure has readily accommodated a large variety of functional groups and provided the coupling products in good to excellent yields. The structure and purity of prepared starting materials **1a-u** and **4a-e** were confirmed by comparison of their physical and spectral data (^{1}H NMR and ^{13}C NMR).



General Procedure for the Synthesis of Functionalized 6-Nitro-7-aryl/alkylquinolin-5-amine (3a-u/5a-e).

In an oven-dried 10 mL round bottom flask, a solution of 2-alkynylnicotinonitrile**1a-u/4a-e** (0.5 mmol), nitromethane (2.0 equiv) and KOH (2.0 equiv) in 2 mL of DMSO was heated at 100 °C for 15 minutes. Progression of the reaction was monitored by TLC analysis; after complete consumption of starting material, the reaction was cooled to room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and water (50 mL). The layers were separated, and the organic layer was washed with aqueous saturated brine solution and dried over Na_2SO_4. Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel (100−200) (hexane:ethyl acetate; 80/20). The structure and purity of products were confirmed by comparison of their physical and spectral data (^{1}H NMR, and ^{13}C NMR).

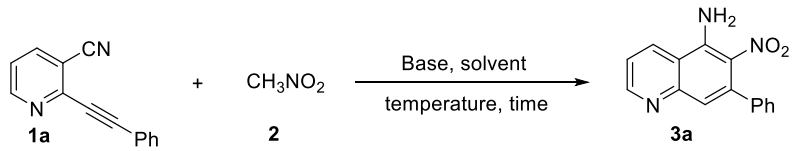


3.5 Results and Discussion

Although, authors have previously optimized the reaction conditions for the annulations of 2-(phenylethynyl)benzonitrile[23] using KOH-DMSO for the synthesis of nitronaphthylamines, in continuation of our ongoing work on synthesis of novel heterocycles we were now motivated to examine the reaction conditions for annulations of 2-(phenylethynyl)nicotinonitrile to access diversified nitroqinolinamines. In order to assess the transformation we conduct the reaction of 2-(phenylethynyl)nicotinonitrile 1a with $MeNO_2$ (2.0 equiv) and KOH (2.0 equiv) in DMSO at 80 °C for 15 min (Table-3.1, entry 1). The desired product 3a was obtained in 64% yield. To our delight, further increment in temperature upto 100 °C enhances the yield of product 3a to 94% (entry 2-3). However, further increase in temperature to 110 °C lead to slight decrease in the yield of product 3a to 92% (entry 4). Use of K^{t}BuO as a base instead of KOH shows a deleterious effect (entry 5). Screening of

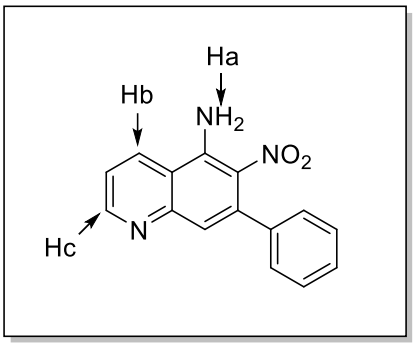
several other bases including, KOAc, K_2CO_3 and Cs_2CO_3 (entries 6-8) and other solvents were not able to proceed with the reaction (entries 9-10).

Table 3.1: Optimization of the Reaction conditions[a]



entry	base	Solvent	T °C	Yield (%)[b] 3a
1	KOH	DMSO	80	64
2	KOH	DMSO	90	86
3	**KOH**	**DMSO**	**100**	**94**
4[c]	KOH	DMSO	110	92
5	K^{t}BuO	DMSO	100	80
6	KOAc	DMSO	100	NR
7	K_2CO_3	DMSO	100	NR
8	Cs_2CO_3	DMSO	100	NR
9	KOH	DMF	100	trace
10	KOH	THF	100	trace

[a]Reactions were performed using 0.5 mmol of **1a**, 2.0 equiv of CH_3NO_2 and 2.0 equiv of base in 2.0 mL of solvent at 100 °C for 15 min. [b]Isolated yield. [c]reaction completed in 5 min only.



6-nitro-7-phenyl-7,8-dihydroquinolin-5-amine (3a)

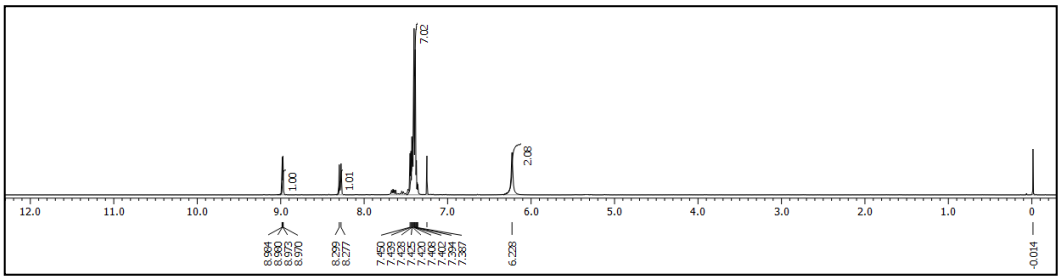
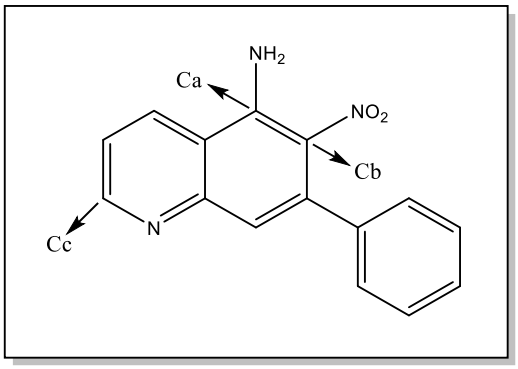


Figure 3.2: ^{1}H NMR of 6-nitro-7-phenyl-7,8-dihydroquinolin-5-amine (3a) in $CDCl_3$ at 400 MHz

In the ^{1}H NMR of **3a (Figure 3.2)** in $CDCl_3$ at 400 MHz, the appearance of a characteristic peak of **NH_2 (Ha)** at δ 6.22 ppm. The appearance of doublet for one proton at 8.28 ppm and 8.97 ppm shows the presence of **Hb** and **Hc** respectively while other protons show multiplet in the range from 7.38 to 7.45 ppm.



6-nitro-7-phenyl-7,8-dihydroquinolin-5-amine (3a)

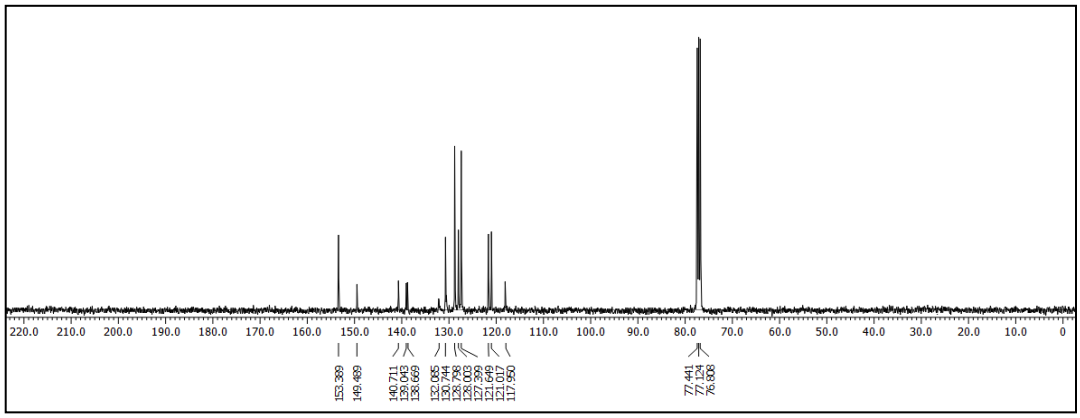


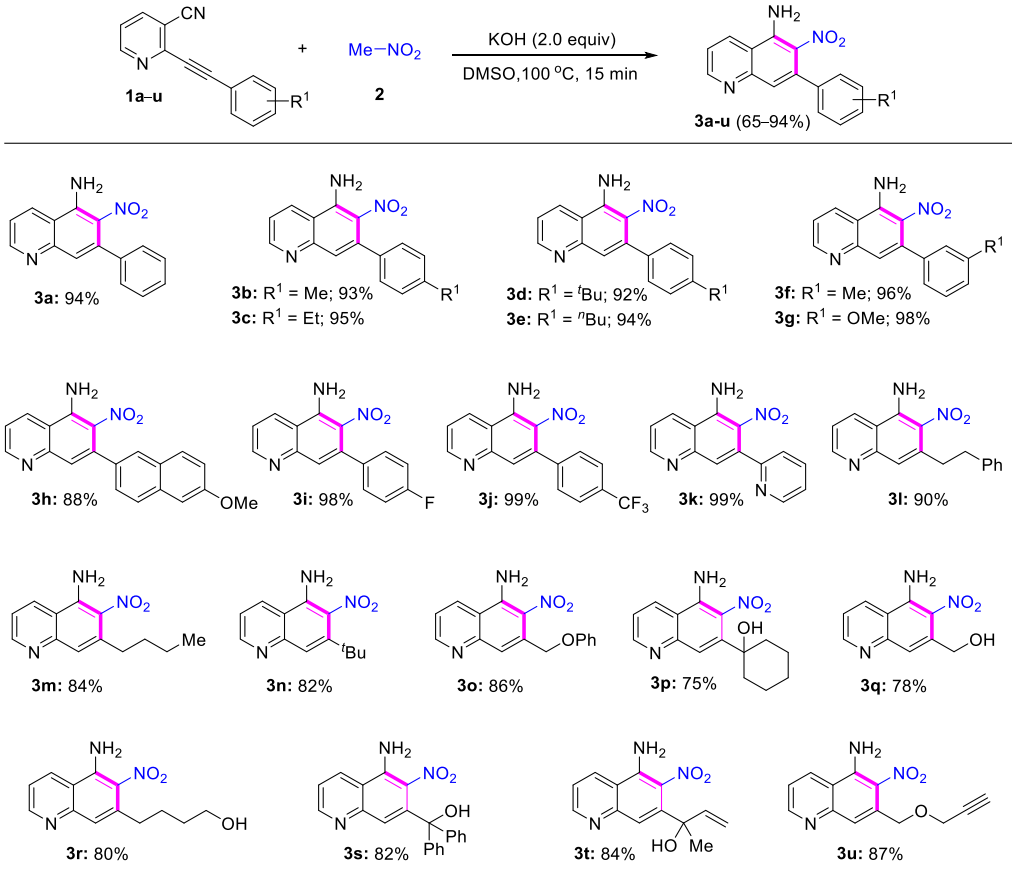
Figure 3.3: ^{13}C NMR of 6-nitro-7-phenyl-7,8-dihydroquinolin-5-amine (3a) in $CDCl_3$ at 100 MHz

Similarly, in ^{13}C NMR spectrum of **3a (Figure 3.3)** in $CDCl_3$ at 100 MHz, the appearance of a characteristic peak at δ 140.7 ppm, 128.7 ppm and 153.3 ppm show the presence of carbon Ca, Cb and Cc respectively.

Having optimal reaction conditions, we first proceed to examine the scope of reaction (Scheme 2) for the endo-dig cyclization of a variety of 2-alkynyl nicotinonitriles 1a-u having differently substituted alkynes with nitromethane **2** for the synthesis of nitro substituted qunolinamine derivatives **3a-u** in good to excellent yields (Scheme 3.6). Substrates **1b-e** bearing electron-rich substituent (-Me, -Et, -tBu and -nBu) at p-position of aryl ring were reacted well to afford the product **3b-e** in 92-95% yields. Electron-rich

substituents (-Me and -OMe) at m-position in substrate **1f** and **1g** also yield the desired product **3f** and **3g** in 96% and 98% yields, respectively. In addition, substrate **1h** and **1i** having bulkier 6-OMe-naphthyl and 4-fluorophenyl ring gave the product **3h** and **3i** in 88% and 98% yields, respectively. Notably, electron-deficient 4-trifluoromethylphenyl and heteroaromatic 2-pyridyl groups in substrate **1j** and **1k** were also reacted smoothly to yield the products **3j** and **3k** in 99% and 99% yields, respectively. The obtained yields were very high without producing any side products. Similarly, aliphatic substituents in substrate **1l-o** were also found to be suitable and quietly converted to the corresponding product **3l-o** in very good yields. The presence of -OH group on aliphatic substituent in substrate **1p-s** was also tolerated under standard reaction conditions and gave the desired products **3p-s** in good yields. Moreover, the free terminal alkene and alkyne groups in substrate **1t** and **1u** can also be well maintained during the reaction and yield the product **3t** and **3u** in 84% and 87% yields, respectively.

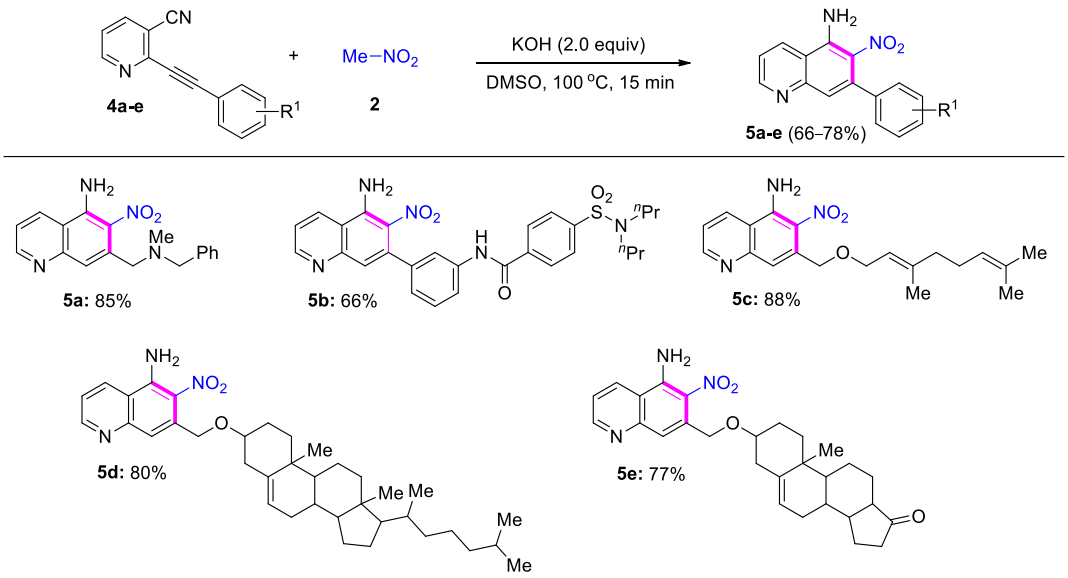
Scheme 3.6: Scope of 2-(arylethynyl)nicotinonitrile[a,b]



[a]Reactions were performed using 0.5 mmol of**1**, 2.0 equiv of CH_3NO_2 and 2.0 equiv of KOH in 2.0 mL of DMSO at 100 °C for 15 min. [b]Isolated yield.

To further explore the versatility of the transformation late-stage modification of various bioactive molecules was also performed (Scheme 3.7). Interestingly, substrate **4a-e** bearing bioactive molecules such as pargyline, probenacid, nerol, cholesterol and estrone were also found to react successfully under optimal reaction conditions to deliver the desired products **5a-e** in 66-88% yields.

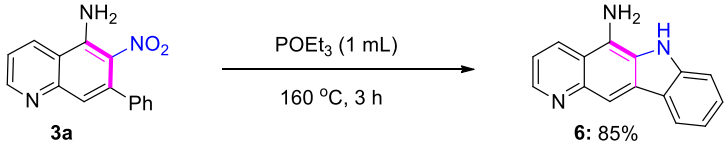
Scheme 3.7: Late-stage modification of bioactive molecules[a,b]



[a]Reactions were performed using 0.5 mmol of **4**, 2.0 equiv of CH_3NO_2 and 2.0 equiv of KOH in 2.0 mL of DMSO at 100 °C for 15 min. [b]Isolated yield.

The synthesized products 6-nitro-7-phenylquinolin-5-amine **3a** could be easily transformed to 6*H*-pyrido[3,2-*b*]carbazol-5-amine **6** with 85% yield by treating it with 1 ml of $POEt_3$ at 160 °C for 3 hours.

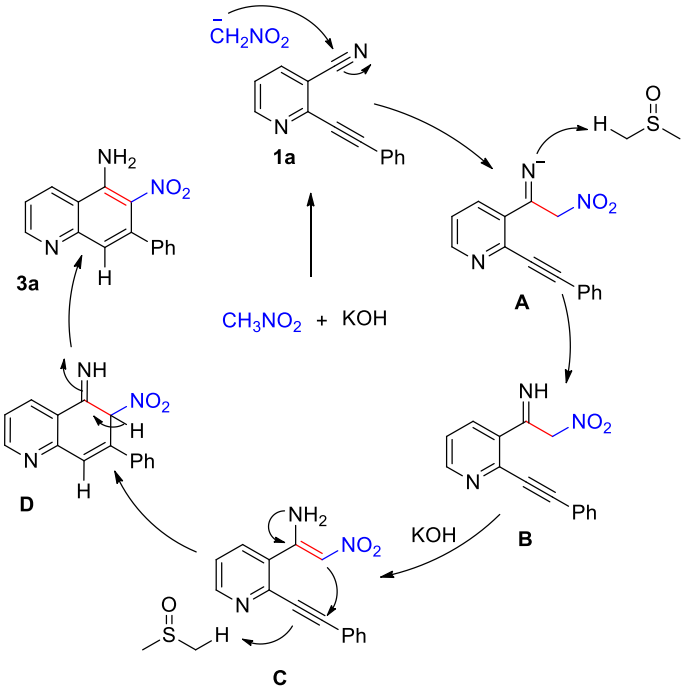
Scheme 3.8: Late-stage modification of synthesized compound 3a



Based on previous findings,[23] a plausible reaction mechanism has been outlined in Scheme 4. Nitromethane in presence of KOH generates an anion that attacks on −CN group of 2-(phenylethynyl)nicotinonitrile**1a** to yield the intermediate **A**. Subsequent protonation of intermediate **A** yield intermediate **B**. In the presence of KOH, the α-

hydrogen of the –NO_2 group in intermediate B is acidic and gets removed, leading to a 6-endo-dig cyclization that forms intermediate **D** through intermediate **C**. Subsequent tautomerization of intermediate **D** results in the formation of the desired product **3a**.

Scheme 3.9: Proposed reaction mechanism



Spectroscopic Data

*2-(Phenylethynyl)nicotinonitrile***(1a).** Brown needles (163.2 mg, 80%):mp 108–109 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J = 4.1 Hz, 1H), 7.97 (d, J = 7.7 Hz, 1H), 7.68 (d, J = 7.0 Hz, 2H), 7.32-7.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 146.0, 140.0, 132.6, 130.0, 128.7, 122.2, 121.0, 116.1, 112.9, 96.2, 85.8; (Figure 3.4) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{14}H_9N_2$ 205.0766, found 205.0758. (Figure 3.5)

*2-(p-Tolylethynyl)nicotinonitrile***(1b).** Brown needles (185.3 mg, 85%): mp 113-114 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72-8.71 (m, 1H), 7.92 (dd, J = 7.9, 1.7 Hz, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.30-7.25 (m, 1H), 7.16 (d, J = 7.8 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 146.2, 140.7, 140.0, 132.5, 129.4, 122.0, 117.9, 116.2, 112.7, 96.7, 85.5, 21.8; (Figure 3.6) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{15}H_{11}N_2$ 219.0917, found 219.0920. (Figure 3.7)

*2-((4-Ethylphenyl)ethynyl)nicotinonitrile***(1c).** Brownneedles (204.2 mg, 88%): mp 114-115 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ8.66 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.23 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 2.58 (q, *J* = 7.6 Hz, 2H), 1.14 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 146.9, 146.1, 140.0, 132.6, 128.2, 122.0, 118.1, 116.2, 112.6, 96.6, 85.5, 29.0, 15.3; (Figure 3.8) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{16}H_{13}N_2$ 233.1073, found 233.1066. (Figure 3.9)

*2-((4-(tert-Butyl)phenyl)ethynyl)nicotinonitrile***(1d).** Brown needles (234.0 mg, 90%):mp 119–120 °C: ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.81 (d, *J* = 9.2 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 7.18 (dd, *J* = 7.9, 4.9 Hz, 1H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 152.9, 145.9, 140.0, 132.3, 125.7, 122.1, 117.9, 116.1, 112.7, 96.4, 85.6, 35.0, 31.1; (Figure 3.10) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{18}H_{17}N_2$ 261.1386, found 261.1383. (Figure 3.11)

*2-((4-Butylphenyl)ethynyl)nicotinonitrile***(1e).**Brown needles (226.2 mg, 87%):mp 116–117 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71-8.72 (m, 1H), 7.92 (d, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.27-7.30 (m, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 1.52-1.59 (m, 2H), 1.30 (td, *J* = 14.8, 7.3 Hz, 2H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ152.9, 146.3, 145.7, 140.0, 132.5, 128.8, 121.9, 118.1, 116.2, 112.9, 96.7, 85.4, 35.8, 33.3, 22.4, 14.0; (Figure 3.12) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{18}H_{17}N_2$ 261.1386, found 261.1383. (Figure 3.13)

*2-(m-Tolylethynyl)nicotinonitrile***(1f).** Brown needles (181.0 mg, 83%):mp 117–118 °C: ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.96 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.33 (dd, *J* = 8.0, 4.9 Hz, 1H), 7.29-7.22 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 146.2, 140.0, 138.4, 133.1, 131.1, 129.8, 128.5, 122.0, 120.9, 116.1, 112.8, 96.7, 85.4, 21.3; (Figure 3.14) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{15}H_{11}N_2$ 219.0917, found 219.0920. (Figure 3.15)

*2-((3-Methoxyphenyl)ethynyl)nicotinonitrile***(1g).** Brown needles (175.5 mg, 75%): mp 122-123 °C: ^{1}HNMR (400 MHz, DMSO-d_6) δ8.82 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.36 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.58 (dd, *J* = 8.1, 4.9 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 1.1 Hz, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 7.08 (dd, *J* = 8.3, 2.7 Hz, 1H), 3.77 (s,

3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.8, 154.0, 144.9, 141.4, 130.9, 124.9, 123.9, 121.8, 117.4, 117.1, 116.8, 112.7, 94.7, 86.2, 55.9; (Figure 3.16) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{15}H_{11}N_2O$ 235.0866, found235.0887. (Figure 3.17)

*2-((6-Methoxynaphthalen-2-yl)ethynyl)nicotinonitrile***(1h).** Brown needles (204.5 mg, 72%): mp 132–133 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ8.77 (d, J = 4.8 Hz, 1H), 8.14 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.73 (t, J = 8.6 Hz, 2H), 7.65 (d, J = 8.5 Hz, 1H), 7.30-7.33 (m, 1H), 7.17 (dd, J = 8.8, 2.3 Hz, 1H), 7.11 (s, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 153.0, 146.3, 140.0, 135.3, 133.3, 129.9, 129.1, 128.3, 127.2, 121.8, 119.9, 116.3, 115.8, 112.7, 106.0, 97.4, 85.7, 55.5; (Figure 3.18) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{19}H_{13}N_2O$ 285.1022, found 285.1023. (Figure 3.19)

*2-((4-Fluorophenyl)ethynyl)nicotinonitrile***(1i).** Brown needles (173.2 mg, 78%):mp 121–122 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (dd, J = 4.9, 1.7 Hz, 1H), 7.95 (dd, J = 8.0, 1.8 Hz, 1H), 7.66-7.62 (m, 2H), 7.33 (dd, J = 7.9, 4.9 Hz, 1H), 7.09-7.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 162.4, 153.0, 146.0, 140.0, 134.8, 122.2, 117.2, 117.2, 116.3, 116.1, 116.0, 112.9, 95.2, 85.6; (Figure 3.20) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{14}H_8FN_2$ 223.0666, found 223.0663. (Figure 3.21)

*2-((4-(Trifluoromethyl)phenyl)ethynyl)nicotinonitrile***(1j).** Brown needles (272.2 mg, 75%):mp 127–128 °C: ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.77 (dd, J = 4.9, 1.6 Hz, 1H), 7.97 (dd, J = 8.0, 1.6 Hz, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 7.36 (dd, J = 8.0, 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 145.5, 140.0, 132.8, 131.8, 131.4, 125.6, 124.8, 122.7, 115.9, 113.3, 94.0, 87.4; (Figure 3.22) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{15}H_8F_3N_2$ 273.0634, found 273.0633. (Figure 3.23)

*2-(Pyridin-2-ylethynyl)nicotinonitrile***(1k).** Dark brownneedles (151.7 mg, 74%):mp 143–144 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J = 4.8 Hz, 1H), 8.62 (d, J = 4.8 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.61-7.64 (m, 2H), 7.29 (t, J = 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 150.5, 145.2, 141.6, 136.2, 132.1, 128.5, 124.2, 122.9, 115.9, 113.4, 93.9, 84.3; (Figure 3.24) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{13}H_8N_3$ 206.0713, found 206.0700. (Figure 3.25)

*2-(4-Phenylbut-1-yn-1-yl)nicotinonitrile***(1l).** Brown needles (167.0 mg, 72%): mp 115–116 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ8.65 (s, 1H), 7.84 (t, J = 3.9 Hz, 1H), 7.28-7.31 (m, 4H), 7.21 (s, 2H), 2.98 (t, J = 7.3 Hz, 2H), 2.80 (t, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ152.7, 146.0, 140.0, 139.9, 128.5, 128.5, 126.5, 121.9, 116.2, 112.3, 97.6, 78.4, 34.3, 21.9; (Figure 3.26) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{16}H_{13}N_2$ 233.1073, found 233.1066. (Figure 3.27)

*2-(Hex-1-yn-1-yl)nicotinonitrile***(1m).** Brown needles (125.1 mg, 68%):mp 102–103 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, J = 4.9, 1.6 Hz, 1H), 7.90 (dd, J = 7.9, 1.6 Hz, 1H), 7.29 (dd, J = 7.8, 5.0 Hz, 1H), 2.50 (t, J = 7.1 Hz, 2H), 1.60-1.67 (m, 2H), 1.49 (td, J = 14.9, 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 146.2, 139.8, 121.7, 116.1, 112.5, 98.9, 77.7, 30.0, 21.9, 19.0, 13.4; (Figure 3.28) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{12}H_{13}N_2$ 185.1073, found 185.1072. (Figure 3.29)

*2-(3,3-Dimethylbut-1-yn-1-yl)nicotinonitrile***(1n).** Brown needles (114.0 mg, 62%):mp 97–97 °C: ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.57 (dd, J = 4.9, 1.8 Hz, 1H), 7.81 (dq, J = 8.0, 1.4 Hz, 1H), 7.16-7.22 (1H), 1.23 (t, J = 2.0 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 146.3, 139.8, 121.8, 116.1, 112.8, 106.3, 76.5, 30.3, 28.2; (Figure 3.30) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{12}H_{13}N_2$ 185.1073, found 185.1072. (Figure 3.31)

*2-(3-Phenoxyprop-1-yn-1-yl)nicotinonitrile***(1o).**Brown needles (161.5 mg, 69%): mp 106–107 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, J = 4.9, 1.6 Hz, 1H), 7.90 (dd, J = 8.0, 1.6 Hz, 1H), 7.34-7.28 (m, 3H), 7.04 (d, J = 8.0 Hz, 2H), 6.99 (t, J = 7.4 Hz, 1H), 4.99 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 152.9, 145.0, 140.0, 129.7, 122.8, 121.9, 115.8, 115.1, 113.2, 90.8, 83.0, 56.1; (Figure 3.32) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{15}H_{11}N_2O$ 235.0866, found 235.0887. (Figure 3.33)

*2-((1-Hydroxycyclohexyl)ethynyl)nicotinonitrile***(1p).** Brown needles(144.6 mg, 64%):mp 117–118 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, J = 4.9, 1.8 Hz, 1H), 7.91 (dd, J = 8.0, 1.8 Hz, 1H), 7.31 (dd, J = 8.0, 4.9 Hz, 1H), 3.81 (s, 1H), 2.07-2.01 (m, 2H), 1.71-1.53 (m, 7H), 1.25-1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 145.6, 140.1, 122.4, 116.0, 112.9, 101.0, 80.4, 68.9, 39.5, 25.1, 23.2; (Figure 3.34) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{14}H_{15}N_2O$ 227.1179, found 227.1188. (Figure 3.35)

2-(3-Hydroxyprop-1-yn-1-yl)nicotinonitrile**(1q).** Brown needles (94.8 mg, 60%): mp 102–103 °C:^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 4.9 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H), 7.55 (dd, J = 7.8, 4.9 Hz, 1H), 5.57 (t, J = 6.0 Hz, 1H), 4.38 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.7, 149.5, 146.3, 128.6, 121.4, 116.9, 100.8, 85.6, 54.5; (Figure 3.36) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_9H_7N_2O$ 159.0553, found 159.0551. (Figure 3.37)

*2-(6-Hydroxyhex-1-yn-1-yl)nicotinonitrile***(1r).** Brown needles (128.0 mg, 64%):mp 113–114 °C: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.56 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.82 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.21 (dd, *J* = 8.0, 4.9 Hz, 1H), 3.54 (t, *J* = 5.8 Hz, 2H), 2.43 (t, *J* = 6.3 Hz, 2H), 1.63 (t, *J* = 3.1 Hz, 4H);^{13}C NMR (100 MHz, $CDCl_3$) *δ* 152.7, 146.1, 139.6, 122.0, 116.2, 112.5, 98.5, 77.9, 61.7, 31.7, 24.2, 19.1; (Figure 3.38) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{12}H_{13}N_2O$ 201.1022, found 201.1020. (Figure 3.39)

*2-(3-Hydroxy-3,3-diphenylprop-1-yn-1-yl)nicotinonitrile***(1s).** Brown needles (220.1 mg, 71%):mp 135–136 °C: ^{1}HNMR (400 MHz, $CDCl_3$) *δ* 8.33 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.81 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.75-7.73 (m, 4H), 7.35-7.31 (m, 4H), 7.28-7.24 (m, 2H), 7.16 (dd, *J* = 8.0, 5.1 Hz, 1H), 5.32 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 152.7, 145.2, 144.2, 140.1, 128.5, 128.0, 126.4, 122.7, 116.0, 112.9, 99.1, 82.8, 74.8; (Figure 3.40) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{21}H_{15}N_2O$ 311.1179, found 311.1176. (Figure 3.41)

*2-(3-Hydroxy-3-methylpent-4-en-1-yn-1-yl)nicotinonitrile***(1t).** Brown needles (134.6 mg, 68%):mp 107–108 °C:^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.66 (dd, *J* = 4.9, 1.5 Hz, 1H), 7.89 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.31 (dd, *J* = 7.9, 5.0 Hz, 1H), 5.96 (dd, *J* = 17.1, 10.4 Hz, 1H), 5.55 (d, *J* = 17.2 Hz, 1H), 5.08 (d, *J* = 10.4 Hz, 1H), 4.56 (s, 1H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 152.8, 145.2, 141.0, 140.3, 122.8, 115.9, 114.6, 112.8, 98.8, 80.5, 68.3, 29.9; (Figure 3.42) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{12}H_{11}N_2O$ 199.0866, found 199.0888. (Figure 3.43)

*2-(3-(Prop-2-yn-1-yloxy)prop-1-yn-1-yl)nicotinonitrile***(1u).** Brown needles (121.5 mg, 62%):mp 93–94 °C: ^{1}HNMR (400 MHz, $CDCl_3$) *δ* 8.76 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.37 (dd, *J* = 8.0, 4.9 Hz, 1H), 4.60 (s, 2H), 4.40 (d, *J* = 2.3 Hz, 2H), 2.48 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 153.1, 145.4,

139.7, 122.6, 115.9, 113.0, 91.5, 83.0, 78.5, 75.4, 57.0, 56.7; (Figure 3.44) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{12}H_9N_2O$ 197.0709, found 197.0738. (Figure 3.45)

*2-(3-(Benzyl(methyl)amino)prop-1-yn-1-yl)nicotinonitrile***(4a).** Brown needles (195.7 mg, 75%):mp 113–114 °C: ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 6.5 Hz, 1H), 7.95 (dt, J = 8.0, 1.6 Hz, 1H), 7.39-7.23 (m, 6H), 3.73 (s, 2H), 3.65 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 145.9, 140.0, 137.9, 129.5, 128.5, 127.5, 122.3, 116.3, 112.9, 92.3, 82.7, 59.9, 45.3, 41.9; (Figure 3.46) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{17}H_{16}N_3$ 262.1339, found 262.1338. (Figure 3.47)

*N-(3-((3-cyanopyridin-2-yl)ethynyl)phenyl)-4-(N,N-diisopropyl sulfamoyl)benzamide***(4b).** Brown needles (306.2 mg, 63%):mp 153–154 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (dd, J = 4.9, 1.7 Hz, 1H), 8.53 (s, 1H), 7.94-7.98 (m, 3H), 7.89 (d, J = 8.1 Hz, 1H), 7.85 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 6.6 Hz, 1H), 7.34-7.39 (m, 2H), 3.06 (t, J = 7.7 Hz, 4H), 1.47-1.55 (m, 4H), 0.84 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 153.0, 145.9, 143.1, 140.0, 138.4, 138.2, 129.5, 128.8, 128.2, 127.4, 123.9, 122.4, 122.3, 121.7, 116.0, 113.1, 95.6, 85.8, 50.0, 22.0, 11.2; (Figure 3.48) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{27}H_{27}N_4O_3S$ 487.1798, found 487.1780. (Figure 3.49)

*(E)-2-(3-((3,7-dimethylocta-2,6-dien-1-yl)oxy)prop-1-yn-1-yl) nicotinonitrile***(4c).** Brown needles (176.4 mg, 60%):mp 113–114 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, J = 4.9, 1.6 Hz, 1H), 7.92 (dd, J = 8.0, 1.8 Hz, 1H), 7.33 (dd, J = 8.0, 4.9 Hz, 1H), 5.32 (t, J = 6.9 Hz, 1H), 5.02-5.05 (m, 1H), 4.40 (s, 2H), 4.13 (d, J = 6.7 Hz, 2H), 2.07-2.11 (m, 2H), 1.99-2.05 (m, 2H), 1.71 (s, 3H), 1.58 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ152.9, 145.4, 142.5, 140.0, 131.9, 123.8, 122.2, 120.8, 115.9, 112.9, 92.5, 82.0, 65.4, 57.2, 32.3, 26.8, 25.5, 22.8, 17.7; (Figure 3.50) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{19}H_{23}N_2O$ 295.1805, found 295.1806. (Figure 3.51)

*2-(3-((10,13-Dimethyl-17-(6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)prop-1-yn-1-yl)nicotinonitrile***(4d).** Brown needles (294.6 mg, 56%):mp 134–135 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, J = 4.9, 1.9 Hz, 1H), 8.01 (dd, J = 7.7, 1.9 Hz, 1H), 7.39 (dd, J = 7.7, 4.9 Hz, 1H), 5.37 (d, J = 5.1 Hz, 1H), 4.51 (s, 2H), 3.48-3.56 (m, 1H), 2.44 (dq, J =

13.1, 2.3 Hz, 1H), 2.22-2.28 (m, 1H), 1.93-2.00 (m, 3H), 1.76-1.89 (m, 2H), 1.41-1.59 (m, 9H), 1.19-1.38 (m, 5H), 1.04-1.17 (m, 7H), 0.99 (s, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.84 (dd, *J* = 6.7, 1.7 Hz, 6H), 0.66 (s, 3H); (Figure 3.52) ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 145.5, 142.6, 139.9, 122.4, 122.3, 122.1, 115.9, 112.9, 93.4, 78.8, 56.9, 56.4, 55.6, 50.2, 42.4, 40.0, 39.6, 38.8, 37.3, 36.9, 36.2, 35.7, 32.0, 31.9, 28.3, 28.2, 28.1, 24.4, 23.9, 22.9, 22.4, 21.2, 19.3, 18.8, 11.9; (Figure 3.53) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{36}H_{51}N_2O$ 527.3996, found 527.3988. (Figure 3.54)

*2-(3-((10,13-Dimethyl-17-oxo-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)prop-1-yn-1-yl)nicotinonitrile***(4e).**Brown needles (248.2 mg, 58%):mp 144–145 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.93 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.34 (dd, *J* = 8.0, 4.9 Hz, 1H), 5.39-5.40 (m, 1H), 4.51 (s, 2H), 3.49-3.57 (m, 1H), 2.40-2.49 (m, 2H), 2.22-2.28 (m, 1H), 1.99-2.15 (m, 3H), 1.80-1.95 (m, 3H), 1.59-1.69 (m, 3H), 1.42-1.56 (m, 3H), 1.22-1.31 (m, 3H), 1.10 (td, *J* = 13.7, 3.8 Hz, 1H), 1.02-1.00 (3H), 0.86 (s, 3H); (Figure 3.55) ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.6, 152.9, 145.5, 140.8, 139.8, 122.6, 121.2, 116.1, 113.0, 93.5, 81.9, 78.3, 55.6, 52.0, 50.3, 47.8, 38.7, 37.0, 37.0, 35.9, 31.6, 31.5, 30.9, 28.1, 22.0, 20.4, 19.5, 13.6; (Figure 3.56) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{28}H_{33}N_2O_2$ 429.2533, found 429.2555. (Figure 3.57)

6-Nitro-7-phenylquinolin-5-amine(3a).Orange needles (132.5 mg, 94%):mp 134–135 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ7.92 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.64 (t, J = 7.1 Hz, 1H), 7.56 (t, J = 7.8 Hz, 1H), 7.35-7.44 (m, 5H), 7.10 (s, 1H), 6.26 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0, 139.7, 134.9, 134.7, 130.3, 129.9, 129.1, 128.6, 127.51, 127.47, 126.7, 122.8, 122.1, 120.5; (Figure 3.58) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{16}H_{13}N_2O_2$ 265.0977, found 265.0965. (Figure 3.59)

*6-Nitro-7-(p-tolyl)quinolin-5-amine***(3b).**Orange needles (129.7 mg, 93%): mp 138–139 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ9.01 (s, 1H), 8.30 (d, J = 8.5 Hz, 1H), 7.43-7.48 (m, 2H), 7.30 (dd, J = 26.8, 7.5 Hz, 4H), 6.13 (s, 2H), 2.42 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 149.4, 140.2, 138.7, 137.8, 135.9, 130.9, 130.6, 129.5, 127.2, 121.4, 120.8, 117.9, 21.2; (Figure 3.60) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{16}H_{14}N_3O_2$ 280.1081, found 280.1073. (Figure 3.61)

*7-(4-Ethylphenyl)-6-nitroquinolin-5-amine***(3c**). Orange needles (139.2 mg, 95%):mp 134–135 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (d, J = 4.0 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H), 7.43-7.46 (m, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.29 (d, J = 4.5 Hz, 2H), 6.17 (s, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ153.2, 149.4, 144.1, 140.3, 138.7, 136.1, 130.9, 130.6, 128.3, 127.1, 121.4, 120.8, 117.9, 28.8, 15.3; (Figure 3.62) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{17}H_{16}N_3O_2$294.1237, found 294.1232. (Figure 3.63)

7-(4-(tert-Butyl)phenyl)-6-nitroquinolin-5-amine(3d).Orange needles (147.7 mg, 92%): mp 143–144 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ8.96 (s, 1H), 8.27 (d, J = 8.4 Hz, 1H), 7.44-7.39 (m, 4H), 7.33 (d, J = 8.2 Hz, 2H), 6.18 (s, 2H), 1.34 (s, 9H); 13C-NMR (100 MHz, $CDCl_3$) δ 153.3, 150.9, 149.2, 140.1, 138.5, 135.9, 130.8, 130.8, 127.2, 125.8, 121.4, 120.7, 117.9, 34.7, 31.6; (Figure 3.64) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{19}H_{20}N_3O_2$ 322.1550, found 322.1566. (Figure 3.65)

*7-(4-Butylphenyl)-6-nitroquinolin-5-amine***(3e).**Orange needles (150.9 mg, 94%): mp 140–141 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, J = 3.4 Hz, 1H), 8.27 (d, J = 8.5 Hz, 1H), 7.47 – 7.35 (m, 2H), 7.31 (d, J = 8.0 Hz, 2H), 7.24 (t, J = 7.6 Hz, 2H), 6.24 (s, 2H), 2.70 – 2.56 (m, 2H), 1.68 – 1.55 (m, 2H), 1.44 – 1.31 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H); (Figure 3.66) ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 149.4, 142.8, 140.6, 138.7, 136.1, 130.8, 130.6, 128.8, 127.2, 121.2, 120.8, 118.0, 35.4, 33.5, 22.5, 14.0; (Figure 3.67) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{19}H_{20}N_3O_2$ 322.1550, found 322.1566. (Figure 3.68)

*6-Nitro-7-(m-tolyl)quinolin-5-amine***(3f).**Orange needles (134.0 mg, 96%):mp 130–131 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ8.99 (d, J = 3.5 Hz, 1H), 8.33 (d, J = 8.5 Hz, 1H), 7.45 (q, J = 4.3 Hz, 1H), 7.40 (s, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.21-7.25 (m, 3H), 6.29 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ153.1, 149.2, 140.7, 138.9, 138.9, 138.4, 131.0, 130.4, 128.8, 128.6, 128.0, 124.2, 121.2, 120.9, 118.1, 21.5; (Figure 3.69) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{16}H_{14}N_3O_2$ 280.1081, found 280.1073. (Figure 3.70)

*7-(3-Methoxyphenyl)-6-nitroquinolin-5-amine***(3g).**Orange needles (144.6 mg, 98%): mp 128–129 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 3.5 Hz, 1H), 8.32 (d, J = 8.5 Hz, 1H), 7.46 (q, J = 4.3 Hz, 1H), 7.43 (d, J = 7.0 Hz, 1H), 7.35 (t, J = 8.0 Hz,

1H), 6.94-6.98 (m, 3H), 6.23 (s, 2H), 3.85 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 159.7, 152.9, 148.8, 140.8, 140.2, 138.9, 131.3, 130.6, 129.7, 120.9, 120.8, 119.8, 118.3, 113.5, 113.0, 55.1; (Figure 3.71) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{16}H_{14}N_3O_3$ 296.1030, found 296.1030. (Figure 3.72)

*7-(6-Methoxynaphthalen-2-yl)-6-nitroquinolin-5-amine***(3h).** Orange needles (151.8 mg, 88%): mp 147–148 °C:^{1}H NMR (400 MHz, DMSO-d_6) δ8.92-8.88 (m, 2H), 7.86-7.78 (m, 3H), 7.60 (s, 2H), 7.51 (q, J = 4.3 Hz, 1H), 7.37 (dd, J = 8.5, 1.4 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.15 (dd, J = 8.7, 2.7 Hz, 2H), 3.81-3.87 (3H);^{13}C NMR (100 MHz, $CDCl_3$) δ158.1, 153.2, 149.5, 141.0, 138.6, 134.4, 134.0, 130.9, 130.4, 129.7, 128.9, 127.0, 126.0, 125.8, 121.6, 120.8, 119.3, 118.1, 105.5, 55.5; (Figure 3.73)HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{20}H_{16}N_3O_3$ 346.1186, found 346.1181. (Figure 3.74)

7-(4-Fluorophenyl)-6-nitroquinolin-5-amine(3i).Orange needles (138.7 mg, 98%): mp 131–132 °C:^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (d, J = 22.4 Hz, 2H), 7.58-7.34 (m, 5H), 7.19 (s, 2H), 6.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO- d_6) δ162.24 (d, J = 243.7 Hz, 1C), 153.7, 149.3, 142.9, 137.0, 136.0, 133.1, 129.6, 128.8, 121.4, 119.3, 118.7, 115.9 (d, J = 21.2 Hz, 1C); (Figure 3.75) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{15}H_{11}FN_3O_2$ 284.0830, found 284.0825. (Figure 3.76)

*6-Nitro-7-(4-(trifluoromethyl)phenyl)quinolin-5-amine***(3j).**Orange needles (164.8 mg, 99%): mp 129–130 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ9.04 (d, J = 3.8 Hz, 1H), 8.35 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 3H), 7.38 (s, 1H), 6.48 (s, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 149.6, 142.9, 141.4, 137.6, 130.7, 130.0, 129.5, 127.7, 125.7 (q, J = 10.9, 3.6 Hz, 2H), 121.8, 121.3, 118.3; (Figure 3.77) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{16}H_{11}F_3N_3O_2$ 334.0798, found 334.0791. (Figure 3.78)

*6-Nitro-7-(pyridin-2-yl)quinolin-5-amine***(3k).** Orange needles (131.7 mg, 99%): mp 141–142 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92-8.87 (m, 2H), 8.52 (d, J = 4.5 Hz, 1H), 7.87 (t, J = 7.6 Hz, 1H), 7.71 (d, J = 7.7 Hz, 1H), 7.59-7.53 (m, 3H), 7.33-7.30 (m, 1H), 7.23 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.4, 153.8, 149.3, 142.9, 137.9, 133.2, 128.4, 123.1, 122.8, 121.8, 119.6, 119.4; (Figure 3.79) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{14}H_{11}N_4O_2$ 267.0877, found 267.0872. (Figure 3.80)

*6-Nitro-7-phenethylquinolin-5-amine***(3l)**. Orange needles (131.8 mg, 90%): mp 125–126 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ8.95 (d, J = 5.3 Hz, 1H), 8.25 (d, J = 8.5 Hz, 1H), 7.39 (q, J = 4.3 Hz, 1H), 7.27-7.33 (m, 5H), 7.22 (t, J = 6.9 Hz, 1H), 6.37 (s, 2H), 3.23-3.27 (m, 2H), 3.01 (t, J = 8.1 Hz, 2H)**;** ^{13}C NMR (100 MHz, $CDCl_3$) δ153.1, 149.3, 141.3, 141.2, 138.3, 131.3, 130.9, 128.5, 126.4, 120.5, 120.5, 117.5, 37.1, 36.6; (Figure 3.81) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{17}H_{16}N_3O_2$ 294.1237, found 294.1232. (Figure 3.82)

*7-Butyl-6-nitroquinolin-5-amine***(3m).**Orange needles (102.9 mg, 84%): mp 120–121 °C**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, J = 4.1 Hz, 1H), 8.25 (d, J = 8.7 Hz, 1H), 7.40-7.43 (m, 1H), 7.29 (d, J = 14.2 Hz, 1H), 6.15 (s, 2H), 2.96 (t, J = 7.8 Hz, 2H), 1.64 (q, J = 7.6 Hz, 2H), 1.37-1.44 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H)**;** ^{13}C NMR (100 MHz, $CDCl_3$) δ152.9, 149.4, 140.6, 139.2, 131.9, 130.6, 120.2, 120.2, 117.3, 33.8, 32.4, 22.8, 13.7; (Figure 3.83) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{13}H_{16}N_3O_2$ 246.1237, found 279.0933. (Figure 3.84)

*7-(tert-Butyl)-6-nitroquinolin-5-amine***(3n).**Orange needles (100.5 mg, 82%): mp 118–119 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ8.93 (d, J = 4.0 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.66 (s, 1H), 7.39 (q, J = 4.2 Hz, 1H), 4.84 (s, 2H), 1.49 (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ152.1, 148.4, 144.2, 135.9, 135.5, 129.9, 120.6, 118.9, 117.2, 36.4, 31.1; (Figure 3.85) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{13}H_{16}N_3O_2$ 246.1237, found 279.0933. (Figure 3.86)

*6-Nitro-7-(phenoxymethyl)quinolin-5-amine***(3o).**Orange needles (126.8 mg, 86%): mp 118–119 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ9.01 (d, J = 3.8 Hz, 1H), 8.31 (d, J = 8.3 Hz, 1H), 7.78 (s, 1H), 7.47 (q, J = 4.2 Hz, 1H), 7.31 (t, J = 7.9 Hz, 2H), 6.97-7.04 (m, 3H), 6.89 (s, 2H), 5.51 (s, 2H)**;** ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 153.5, 149.8, 143.1, 134.9, 130.4, 129.5, 128.2, 121.3, 121.0, 118.4, 118.1, 115.0, 68.1; (Figure 3.87) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{16}H_{14}N_3O_3$ 296.1030, found 296.1030. (Figure 3.88)

*1-(5-Amino-6-nitroquinolin-7-yl)cyclohexanol***(3p).** Orange needles (107.7 mg, 75%): mp 146–147 °C**:**^{1}H NMR (400 MHz, DMSO-d_6) δ8.88 (d, J = 3.0 Hz, 1H), 8.74 (d, J = 8.3 Hz, 1H), 7.46 (q, J = 4.2 Hz, 1H), 7.29 (s, 1H), 6.24 (s, 2H), 5.08 (s, 1H), 2.01-

2.08 (m, 2H), 1.60-1.83 (m, 5H), 1.48 (d, *J* = 11.3 Hz, 2H), 1.20-1.26 (m, 1H);^{13}C NMR (100 MHz, DMSO-d_6) δ 152.3, 148.1, 145.2, 137.7, 132.9, 132.1, 120.6, 117.5, 114.1, 73.3, 38.2, 25.5, 21.9; (Figure 3.89) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{15}H_{18}N_3O_3$ 288.1343, found 288.1330. (Figure 3.90)

(5-Amino-6-nitroquinolin-7-yl)methanol(3q).Orange needles (85.4 mg, 78%): mp 140–141 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (dd, J = 4.3, 1.4 Hz, 1H), 8.84 (d, J = 8.5 Hz, 1H), 7.80 (s, 2H), 7.49 (q, J = 4.3 Hz, 1H), 7.35 (s, 1H), 5.39 (t, J = 5.6 Hz, 1H), 4.75 (d, J = 5.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.6, 149.9, 144.1, 139.8, 133.1, 127.7, 121.1, 118.5, 115.6, 61.8; (Figure 3.91) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{10}H_{10}N_3O_3$ 220.0717, found 220.0733. (Figure 3.92)

4-(5-Amino-6-nitroquinolin-7-yl)butan-1-ol**(3r).**Orange needles (104.4 mg, 80%): mp 132–133 °C**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, J = 3.0 Hz, 1H), 8.23 (d, J = 8.5 Hz, 1H), 7.41 (dd, J = 8.5, 4.3 Hz, 1H), 7.31 (s, 1H), 6.16 (s, 2H), 3.75 (s, 1H), 3.70 (t, J = 6.3 Hz, 2H), 2.99 (t, J = 7.6 Hz, 2H), 2.17 (s, 1H), 1.78 (dd, J = 10.4, 5.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 149.5, 140.8, 138.7, 130.4, 120.5, 120.4, 117.4, 62.5, 33.9, 32.5, 26.5**;** (Figure 3.93) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{13}H_{16}N_3O_3$ 262.1186, found 262.1178. (Figure 3.94)

(5-Amino-6-nitroquinolin-7-yl)diphenylmethanol(3s). Orange needles (152.1 mg, 82%): mp 151–152 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92-8.91 (m, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.46 (q, J = 4.3 Hz, 1H), 7.42-7.39 (m, 4H), 7.32-7.25 (m, 6H), 7.00 (s, 1H), 5.67 (s, 2H), 4.88 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.7, 147.3, 141.2, 138.9, 132.4, 128.2, 128.1, 127.5, 121.2, 119.1, 118.3, 82.2; (Figure 3.95) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{22}H_{18}N_3O_3$ 372.1343, found 372.1335. (Figure 3.96)

2-(5-Amino-6-nitroquinolin-7-yl)but-3-en-2-ol(3t).Orange needles (108.8 mg, 84%):mp 133–133 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, J = 3.8 Hz, 1H), 8.24 (d, J = 8.5 Hz, 1H), 7.70 (s, 1H), 7.49 (q, J = 4.3 Hz, 1H), 7.28 (s, 1H), 6.22-6.30 (m, 1H), 5.43 (s, 2H), 5.18-5.29 (m, 2H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 143.8, 142.1, 140.6, 130.3, 123.7, 121.2, 119.2, 113.3, 75.0, 29.7; (Figure 3.97)

HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{13}H_{14}N_3O_3$ 260.1030, found 260.1033. (Figure 3.98)

6-Nitro-7-((prop-2-yn-1-yloxy)methyl)quinolin-5-amine(3u).Orange needles (111.8 mg, 87%): mp 124–125 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (dd, J = 4.3, 1.2 Hz, 1H), 8.86 (d, J = 8.4 Hz, 1H), 7.87 (s, 2H), 7.52 (q, J = 4.3 Hz, 1H), 7.23 (s, 1H), 4.80 (s, 2H), 4.20 (d, J = 2.5 Hz, 2H), 3.47 (t, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 153.9, 149.6, 144.4, 134.8, 133.2, 127.4, 121.5, 119.0, 116.7, 80.5, 78.2, 69.7, 58.0; (Figure 3.99) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{13}H_{12}N_3O_3$ 258.0873, found 258.0880. (Figure 3.100)

7-((Benzyl(methyl)amino)methyl)-6-nitroquinolin-5-amine(5a).Orange needles (136.8 mg, 85%): mp 140–141 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (d, J = 3.0 Hz, 1H), 8.26 (d, J = 8.3 Hz, 1H), 7.52 (s, 1H), 7.43 (q, J = 4.2 Hz, 1H), 7.30 (d, J = 4.0 Hz, 4H), 7.22 (d, J = 4.0 Hz, 1H), 5.97 (s, 2H), 3.98 (s, 2H), 3.53 (s, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 149.1, 140.0, 139.2, 136.4, 131.4, 130.5, 128.7, 127.9, 126.8, 120.6, 120.5, 118.5, 62.1, 61.1, 41.8; (Figure 3.101) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{18}H_{19}N_4O_2$ 323.1503, found 323.1500. (Figure 3.102)

N-(3-(5-amino-6-nitroquinolin-7-yl)phenyl)-4-(N,N-diisopropylsulfamoyl)benzamide (5b).Orange needles (180.5 mg, 66%): mp 208–209 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ8.96 (s, 1H), 8.56-8.62 (m, 1H), 8.36 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 8.3 Hz, 2H), 7.79 (d, J = 7.0 Hz, 2H), 7.71 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 26.8 Hz, 2H), 7.30 (s, 1H), 7.17 (d, J = 6.5 Hz, 1H), 6.47 (s, 2H), 3.08 (t, J = 7.6 Hz, 4H), 1.54 (td, J = 15.0, 7.4 Hz, 4H), 0.87 (t, J = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 153.1, 149.1, 142.8, 141.5, 141.3, 139.9, 138.4, 138.1, 137.9, 132.0, 131.2, 131.1, 129.4, 128.5, 127.8, 127.2, 123.8, 121.3, 121.0, 119.8, 119.2, 118.3, 50.1, 21.9, 11.2; (Figure 3.103) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{28}H_{30}N_5O_5S$548.1962,found 548.1993. (Figure 3.104)

(E)-7-(((3,7-Dimethylocta-2,6-dien-1-yl)oxy)methyl)-6-nitroquinolin-5-amine(5c). Orange needles (156.2 mg, 88%): mp 146–147 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (d, J = 3.4 Hz, 1H), 8.27 (d, J = 8.4 Hz, 1H), 7.61 (s, 1H), 7.41 (dd, J = 8.4, 4.2 Hz, 1H), 6.68 (s, 2H), 5.43 (t, J = 6.5 Hz, 1H), 5.08 (s, 1H), 4.88 (s, 2H), 4.10 (d, J =

6.7 Hz, 2H), 2.17 (s, 1H), 2.09 (d, J = 10.0 Hz, 3H), 1.76 (s, 3H), 1.65 (s, qw3H), 1.57 (s, 3H); (Figure 3.105) ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 149.7, 142.4, 140.8, 136.3, 131.9, 130.5, 128.8, 123.8, 121.4, 120.7, 118.6, 118.1, 70.1, 67.2, 32.2, 26.6, 25.6, 23.4, 17.6; (Figure 3.106) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{20}H_{26}N_3O_3$ 356.1969, found 356.1955. (Figure 3.107)

7-(((10,13-Dimethyl-17-(6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-3-yl)oxy)methyl)-6-nitro-2,3-dihydroquinolin-5-amine(5d).Orange needles (235.6 mg, 80%):mp 152–153 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ9.01 (d, J = 4.0 Hz, 1H), 8.28 (d, J = 8.5 Hz, 1H), 7.69 (s, 1H), 7.47 (q, J = 4.3 Hz, 1H), 6.63 (s, 2H), 5.39 (s, 1H), 4.97 (s, 2H), 3.32-3.39 (m, 1H), 2.49 (d, J = 10.8 Hz, 1H), 2.29-2.35 (m, 1H), 1.97-2.04 (m, 3H), 1.79-1.91 (m, 2H), 1.45-1.62 (m, 7H), 1.31-1.42 (m, 4H), 1.27 (s, 2H), 1.09-1.21 (m, 7H), 1.00 (d, J = 27.0 Hz, 6H), 0.93 (d, J = 6.5 Hz, 3H), 0.88 (dd, J = 6.6, 1.4 Hz, 6H), 0.69 (s, 3H); (Figure 3.108) ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 149.8, 142.1, 140.7, 136.8, 130.5, 129.0, 121.8, 120.7, 118.6, 118.0, 79.6, 68.2, 56.7, 56.1, 50.1, 42.3, 39.8, 39.5, 39.0, 37.2, 36.9, 36.2, 35.8, 31.9, 31.8, 28.4, 28.2, 28.0, 24.3, 23.8, 22.8, 22.6, 21.0, 19.4, 18.7, 11.8; (Figure 3.109) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{37}H_{56}N_3O_3$ 590.4316, found 590.4338. (Figure 3.110)

3-((5-Amino-6-nitro-2,3-dihydroquinolin-7-yl)methoxy)-10,13-dimethyl 3,4,7,8,9,10,11,12,13,14,15,16-dodecahydro-1H-cyclopenta[a]phenanthren-17(2H)-one(5e).Orange needles (189.0 mg, 77%):mp 165–166 °C: ^{1}H NMR (400 MHz, DMSO–d_6) δ8.88 (d, J = 3.7 Hz, 1H), 8.83 (d, J = 8.5 Hz, 1H), 7.68 (s, 2H), 7.49 (q, J = 4.2 Hz, 1H), 7.27 (s, 1H), 5.28 (s, 1H), 4.76 (s, 2H), 3.14 (t, J = 10.9 Hz, 1H), 2.32-2.37 (m, 2H), 2.11 (t, J = 11.9 Hz, 1H), 1.89-1.98 (m, 2H), 1.73-1.85 (m, 3H), 1.60 (d, J = 12.2 Hz, 1H), 1.48-1.52 (m, 3H), 1.28-1.44 (m, 3H), 1.06-1.16 (m, 3H), 0.91 (s, 4H), 0.85 (d, J = 11.5 Hz, 2H), 0.73 (s, 3H); (Figure 3.111) ^{13}C NMR (100 MHz, DMSO–d_6) δ220.0, 154.0, 149.5, 143.7, 141.0, 135.9, 132.8, 128.1, 121.3, 121.3, 118.9, 116.7, 78.5, 68.0, 51.3, 50.0, 47.3, 39.1, 37.0, 36.9, 35.7, 31.6, 31.4, 30.5, 28.4, 21.9, 20.4, 19.4, 13.6; (Figure 3.112) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{29}H_{38}N_3O_4$ 492.2857, found 492.2887. (Figure 3.113)

6H-pyrido[3,2-b]carbazol-5-amine(6).Brown needles (90.9 mg, 78%):mp 172–173 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ9.44 (d, J = 6.3 Hz, 1H), 8.62 (s, 1H), 7.88-7.91 (m, 1H), 7.79-7.82 (m, 2H), 7.69-7.77 (m, 3H), 7.30-7.34 (m, 4H), 7.23 (t, J = 6.3 Hz, 1H), 6.26 (s, 2H), 4.09 (s, 2H), 3.58 (s, 2H), 2.15 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 143.8, 139.3, 139.2, 138.0, 137.5, 137.4, 135.4, 131.2, 129.7, 128.8, 128.3, 123.0, 101.0, 99.3; (Figure 3.114) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{15}H_{12}N_3$ 234.1026, found 234.1032. (Figure 3.115)

3.6 Conclusion

In summary, by integrating the regioselective annulation, our study has unveiled the inaugural synthesis of polyfunctional nitroquinolinamines. This synthetic strategy shows great potential, offering an atom-economic pathway for the efficient assembly of a diverse array of heterocyclic scaffolds previously difficult to access. The versatility of our transition-metal-free approach is evidenced by its broad applicability to various 2-(Alkynyl)nicotinonitriles and nucleophiles. Furthermore, we have expanded this methodology to enable the late-stage modification of complex bioactive molecules.

3.7 References

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Chapter – 4

Synthesis of Novel Nitro-substituted Acridinamines/Benzo[c]acridinamines via Cascade Annulation of Hetero-2-alkynyl-3-carbonitriles

CHAPTER – 4

SYNTHESIS OF NOVEL NITRO-SUBSTITUTED ACRIDINAMINES/BENZO[*C*]ACRIDINAMINES VIA CASCADE ANNULATION OF HETERO-2-ALKYNYL-3-CARBONITRILES

4.1 Introduction

Acridines represent a significant category of heteroaromatic compounds with diverse applications[1-3] spanning medicinal chemistry,[4-5] fluorescent organic dyes,[6-8] chemosensors,[9-11] photocatalysis,[12] and as materials for solar cells and photovoltaic systems.[13-15]Among them, acridines are an important class of heterocyclic compounds displaying a wide range of biological activities including antibacterial, antileukemic, antiviral, antitumor, inhibitory activities towards EGFR-TK etc (Figure 4.1).[16]

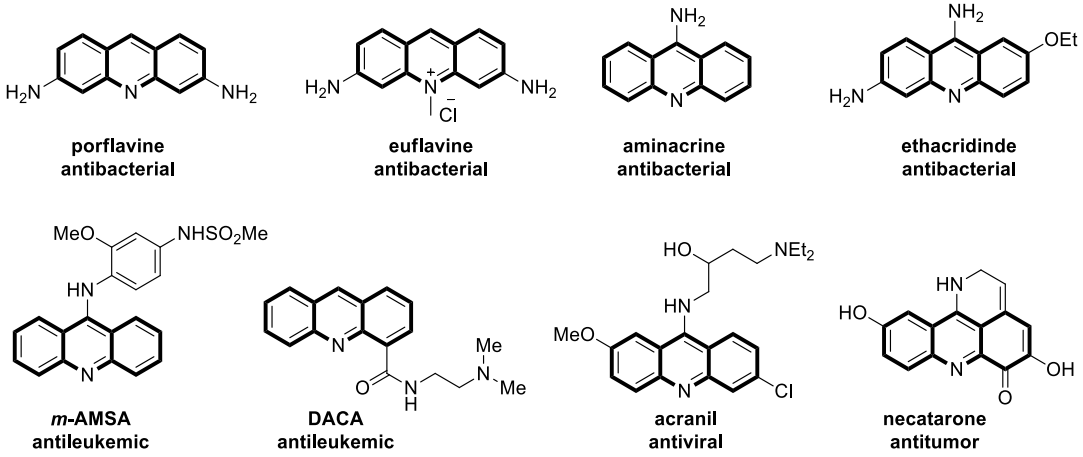


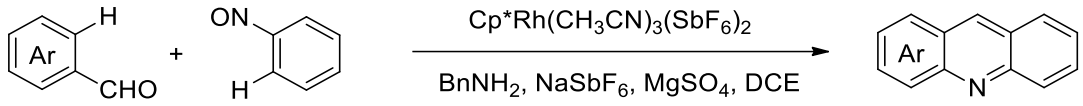
Figure 4.1: Representative bioactive acridines.

Acridinium ions, owing to their extended excited state lifetime and adjustable redox potential, have emerged as efficient visible light single electron transfer (SET) organic photocatalysts for various organic transformations.[17-20] Given their historical significance and utility, acridines have garnered substantial scientific interest, leading to the development of numerous synthetic routes.[21-24] However, these methods typically involve the formation of a new 6-membered ring by modifying appropriately substituted functional groups within the existing aromatic system, followed by

aromatization to yield acridines.[25] Often, the aromatic precursors required for these procedures are not commercially available, rendering the synthesis challenging, multi-step, and resource-intensive, thereby posing environmental concerns. Moreover, many of these synthetic approaches necessitate high temperatures and harsh acidic or basic conditions, limiting their tolerance towards functional groups and consequently reducing the reaction's generality and versatility.

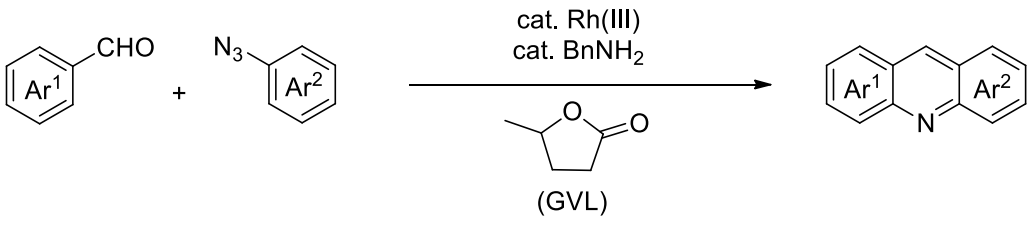
4.2 Review of Literature

A number of traditional approaches have been reported in the literature for the synthesis of acridines derivatives. However, these methods having the use of catalyst with limited substrate scope. The Nitro-substituted acridinamines/benzo[*c*] acridinamines are synthetically challenging frameworks which have not been much explored. In 2017, Cheng and its coworkers[26] reported the Rh(III)-catalyzed bilateral cyclization for the synthesis of acridines using aromatic aldehydes and aryl nitrosos . The presence of catalytic amount of $BnNH_2$ is required for the removal of in situ formed imino group as a transient intermediate. The reaction involves amination, cyclization, and aromatization reaction in sequential manner.



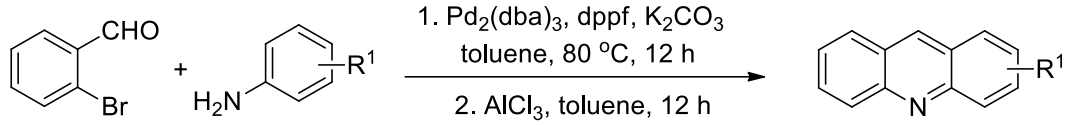
Scheme 4.1: Rh(III)-catalyzed bilateral cyclization for the synthesis of acridines.

Again, in 2018, utilizing the similar concept He and co-workers[27] have developed a Rh(III)-catalyzed synthesis of unsymmetrical acridines from aldehydes and azides utilizing inexpensive $BnNH_2$ as a transient directing group and GVL as the green reaction medium. The reaction involved the transient imino directing group (in situ generated) from aldehyde and $BnNH_2$ used in a catalytic amount.



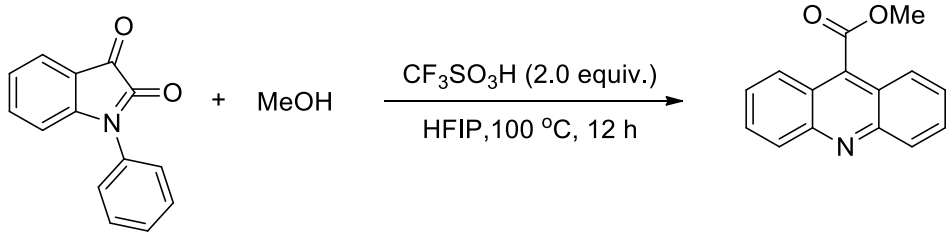
Scheme 4.2: Rh(III)-catalyzed synthesis of unsymmetrical acridines.

An effortless and effective method is detailed for producing diverse acridines[28] through the sequential coupling and cyclization of substituted 2-bromobenzaldehydes and anilines. This process is facilitated by the presence of catalytic quantities of $Pd_2(dba)_3$ and the diphosphine ligand dppf. Additionally, the inclusion of the Lewis acid, $AlCl_3$, is necessary to facilitate cyclization, especially for anilines with lower electron density.



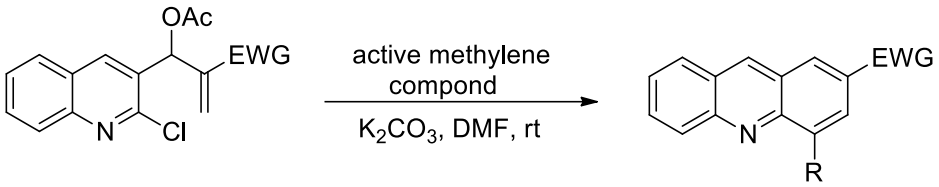
Scheme 4.3: Reaction of 2-bromobenzaldehydes with aniline.

A methodical procedure for synthesizing acridinium[29] esters and amides has been developed, involving the cyclization and subsequent esterification or amidation of isatins with alcohols or amines serving as nucleophiles. This process is conducted in the presence of CF_3SO_3H. Subsequently, the photophysical characteristics of these synthesized acridines were examined.



Scheme 4.4: Preparation of acridinium esters and amides through the cyclization and esterification or amidation of isatins with alcohols.

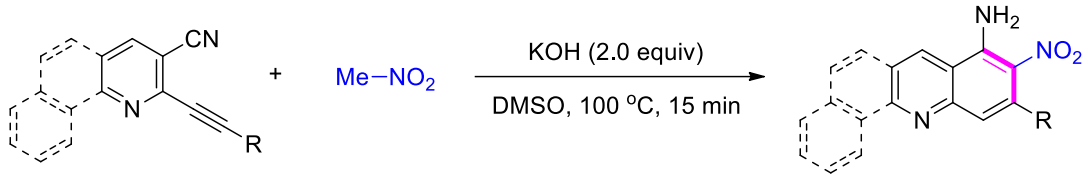
The authors conducted syntheses of acridines and phenanthridines[30] utilizing MBH acetates of 2-chloro-quinoline-3-carbaldehydes in conjunction with active methylene compounds (AMCs). The product formation was observed to vary depending on the functional group present in the AMC. For instance, ethylcyanoacetate and malononitrile favored the production of acridines and cyanoacetamide, while ethyl nitroacetate and malonic esters favored the formation of angularly-fused phenanthridines. The reactions leading to the generation of phenanthridines proceeded via single bond rotation of SN2 intermediates, which was attributed to electronic/steric repulsion between the functional groups of AMCs and the nitrogen of quinoline.



Scheme 4.5: Syntheses of acridines and phenanthridines from MBH acetates of 2- chloro-quinoline-3-carbaldehydes with active methylene compounds (AMCs)

4.3 Designed Strategy

All the devised strategies are limited only to the synthesis of acridines having functionalities, there are no approaches for the synthesis of nitro substituted acrdinamines and benzo[c]acridinamines. Therefore, there is a high demand for the development of sustainable approaches for the preparation of differently functionalized acridines and benzo[c]acridinamines. Intrigued by the notable lack of procedures for the construction of versatile multisubstituted acridines and benzo[c]acridinamines, we herein report the synthesis of nitro substituted acridinamines and benzo[c]acridinamines. Generally, installation of amino and nitro group on the *N*-heterocycles remains a difficult task as the direct nitration of these motifs lead to the formation of a multiple number of products.



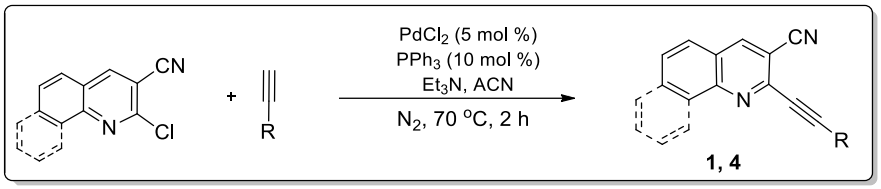
4.4 Experimental Section

General information and method

Preparation of 2-alkynylquinoline-3-carbonitrile (1a-h) and 2-alkynylbenzo[*h*]quinoline-3-carbonitrile (4a-e)

To probe the viability of the designed tandem strategy, 2-alkynylquinoline-3-carbonitrile **1a-h** and 2-alkynylbenzo[*h*]quinoline-3-carbonitrile **4a-e** were readily prepared by standard Sonogashira cross-coupling reaction of commercially available and readily accessible 2-chlorohetro-3-carbonitriles with terminal alkynes. This coupling procedure has readily accommodated a large variety of functional groups

and provided the coupling products in good to excellent yields. The structure and purity of prepared starting materials **1a-h, 4a-e** were confirmed by comparison of their physical and spectral data (^{1}H NMR and ^{13}C NMR).



General Procedure for the Synthesis of 2-Nitro-3-aryl/alkylacridin-1-amine (3a-h).

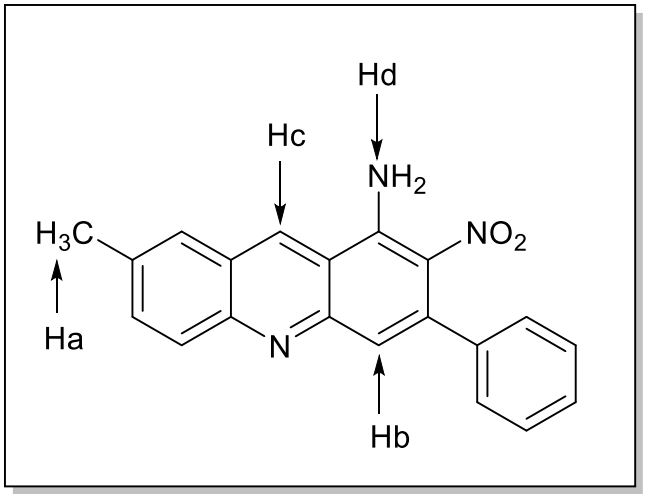
In an oven-dried 10 mL round bottom flask, a solution of 2-alkynylquinoline-3-carbonitrile **1a-h** (0.5 mmol), nitromethane (2.0 equiv) and KOH (2.0 equiv) in 2 mL of DMSO was heated at 100 °C for 15 minutes. Progression of the reaction was monitored by TLC analysis; after complete consumption of starting material, the reaction was cooled to room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and water (50 mL). The layers were separated, and the organic layer was washed with aqueous saturated brine solution and dried over Na_2SO_4. Organic layer was concentrated under reduced pressure (150 mbar). The crude material so obtained was purified by column chromatography on silica gel (100−200) (hexane:ethyl acetate; 80/20). The structure and purity of products were confirmed by comparison of their physical and spectral data (^{1}H NMR, and ^{13}C NMR).

General Procedure for the Synthesis of 9-Nitro-10-phenylbenzo[c]acridin-8-amine (5a-e)

In an oven-dried 10 mL round bottom flask, a solution of 2-alkynylbenzo[*h*]quinoline-3-carbonitrile **4a-e** (0.5 mmol), nitromethane (2.0 equiv) and KOH (2.0 equiv) in 2 mL of DMSO was heated at 100 °C for 15 minutes. Progression of the reaction was monitored by TLC analysis; after complete consumption of starting material, the reaction was cooled to room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and water (50 mL). The layers were separated, and the organic layer was washed with aqueous saturated brine solution and dried over Na_2SO_4. Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel (100−200) (hexane:ethylacetate;

80/20). The structure and purity of products were confirmed by comparison of their physical and spectral data (^{1}H NMR, and ^{13}C NMR).

4.5 Results and Discussion



7-methyl-2-nitro-3-phenylacridin-1-amine (3a)

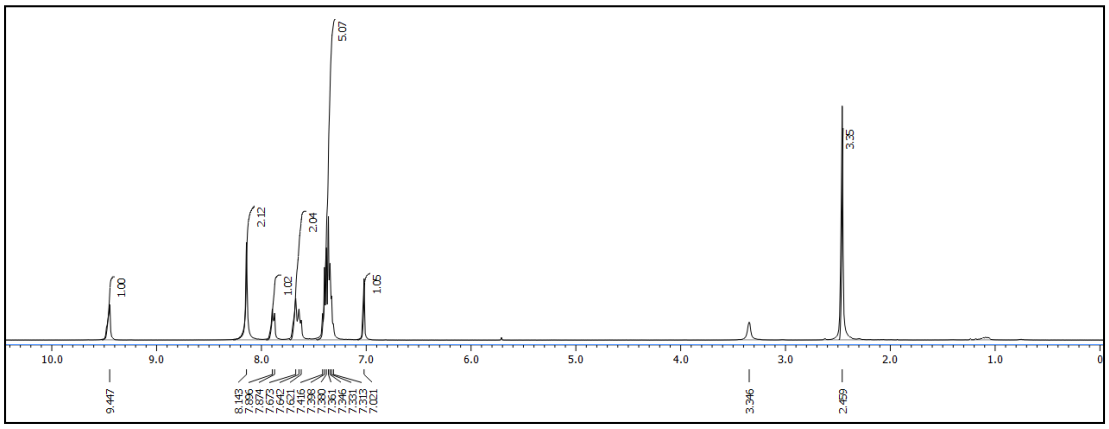
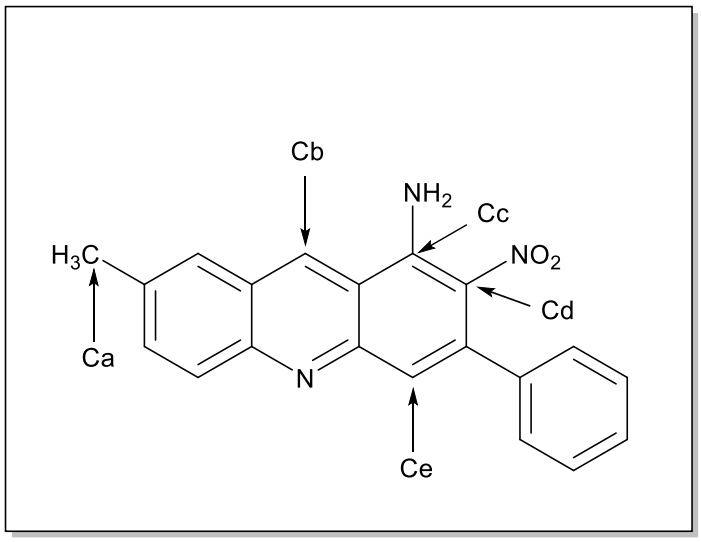


Figure 4.1a: ^{1}H NMR of 7-methyl-2-nitro-3-phenylacridin-1-amine (3a) in $CDCl_3$ at 400 MHz

In the ^{1}H NMR of **3a (Figure 4.1a)** in $CDCl_3$ at 400 MHz, the appearance of a characteristic peak of NH2(Hd) at 7.62 ppm and aliphatic proton of methyl group (Ha) shows at 2.45 ppm. The appearance for one proton at 9.44 ppm and 8.14 ppm shows the presence of Hb and Hc respectively while other protons shows multiplet in the range from 7.89 to 7.02 ppm.



7-methyl-2-nitro-3-phenylacridin-1-amine (3a)

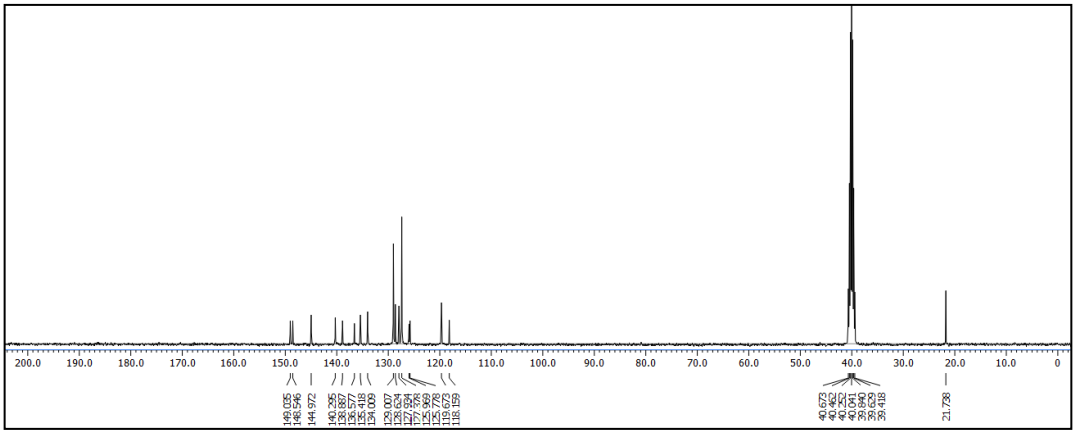


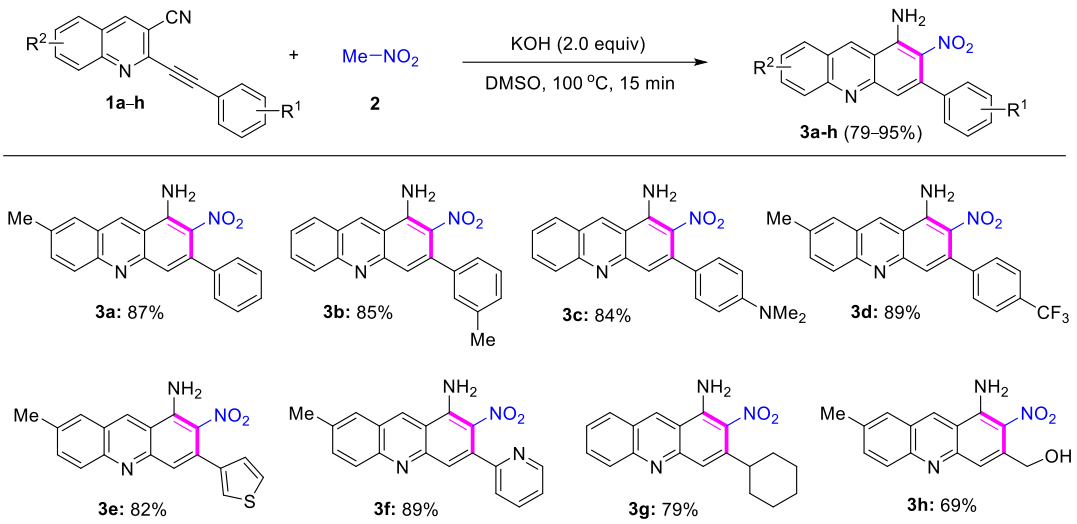
Figure 4.2: ^{13}C NMR of 7-methyl-2-nitro-3-phenylacridin-1-amine (3a) in $CDCl_3$ at 100 MHz

Similarly, in ^{13}C NMR spectrum of **3a (Figure 4.2)** in $CDCl_3$ at 100 MHz, the appearance of a characteristic peak at δ 21.7 ppm, 140.2 ppm and 118.1 ppm show the presence of carbon Ca (aliphatic carbon of methyl group), Cb and Ce respectively. While peaks at 144.9 ppm, and 128.6 ppm confirms the presence of carbon Cc (carbon attached to NH_2 group) and Cd (carbon attached to NO_2 group) respectively.

To enhance the scope of reaction towards the synthesis of nitroacridinamines, a variety of substituted 2-(arylethynyl)quinoline-3-carbonitrile were eventually evaluated under optimized reaction conditions (Scheme 4.6). Reactions proceed efficiently with both the substrates having electron-rich as well as an electron-deficient substituent. Substrate **1a-d** when reacted with nitromethane **2** gave the

desired products **3a-d** in 84-89% yields. The reaction also proceeds with substrate **1e** and **1f** bearing heteroaromatic electron-rich 3-thienyl and electron-deficient 2-pyridyl functionalities yielding the desired product **3e** and **3f** in 82% and 89% yields, respectively. The substrate **1g-h** bearing aliphatic substituents group also yield the corresponding products **3g-h** in 79-69% yields leaving the free hydroxy group intact.

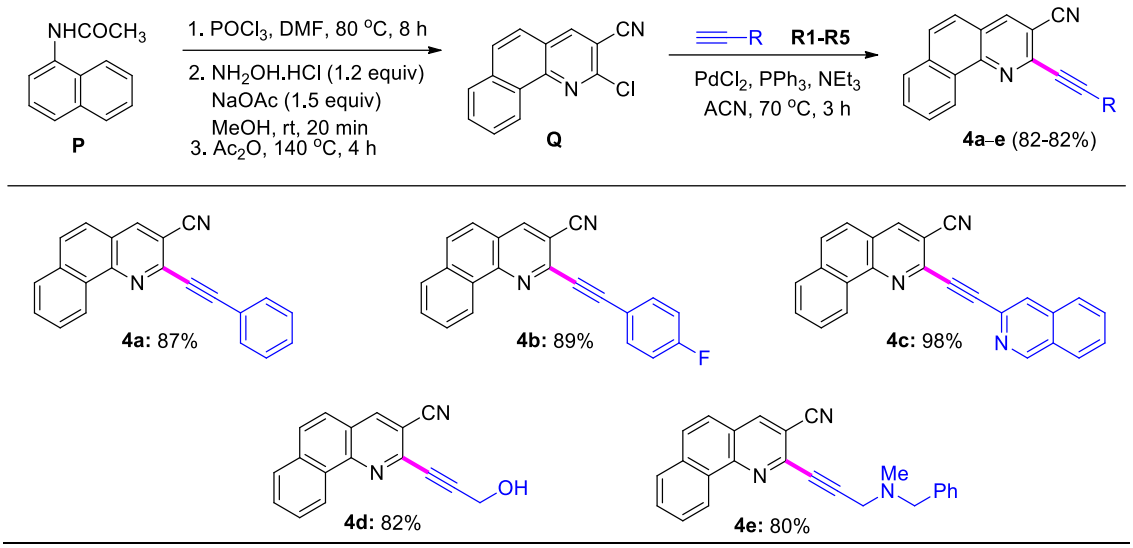
Scheme 4.6: Scope of 2-(arylethynyl)quinoline-3-carbonitrile[a,b]



[a]Reactions were performed using 0.5 mmol of **4**, 2.0 equiv of CH_3NO_2 and 2.0 equiv of KOH in 2.0 mL of DMSO at 100 °C for 15 min. [b]Isolated yield.

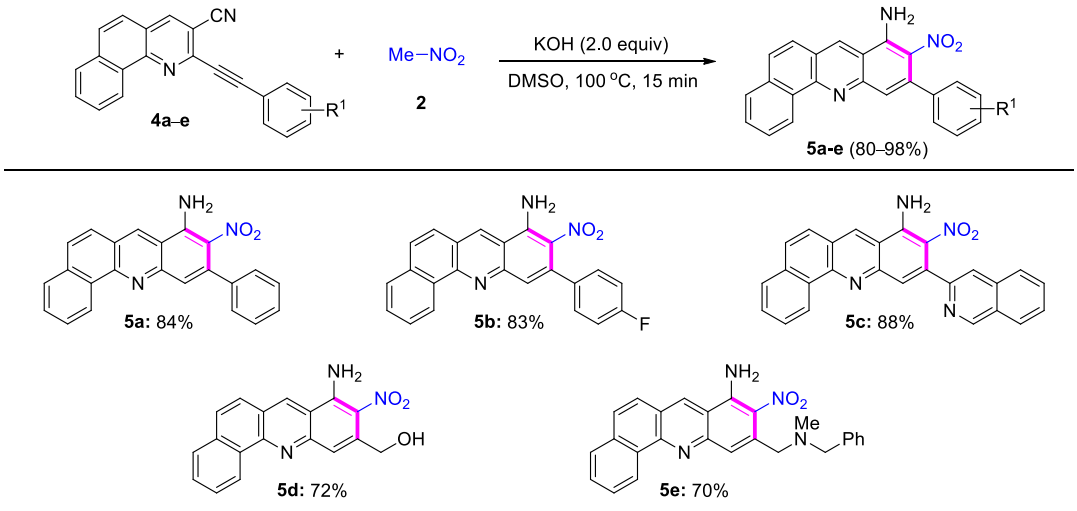
Next, to enhance the substrate scope we have synthesized a series of novel 2-(aryl/alkylethynyl)benzo[*h*]quinoline-3-carbonitrile derivatives **4a-e** that enables the synthesis of various substituted nitrobenzo[*c*]acridinamines (Scheme 4.7). Substrates **4a-e** was prepared using the procedures reported in our previous reports.[10a,g] Substrate **Q** on reaction with phenylacetylene **R1** and 4-fluorophenylacetylene **R2** yields the product **4a** and **4b** in 87% and 89% yields, respectively. Heteroaromatic 3-ethynylisoquinoline **R3** also yield product **6c** in 98% yield. Furthermore, aliphatic propargylalcohol**R4** and pargyline **R5** also reacts with substrate **Q** to furnish the corresponding products **4d** and **4e** in good yields.

Scheme 4.7: Synthesis of novel 2-(aryl/alkylethynyl)benzo[*h*]quinoline-3-carbonitrile derivatives [a,b]



Using the synthesized 2-(aryl/alkylethynyl)benzo[*h*]quinoline-3-carbonitriles (Scheme 4.7), we explore the substrate scope of the reaction for the synthesis of nitrobenzo[*c*]acridinamines (Scheme 4.8). Substrates **4a-d** having aromatic, aliphatic and heteroaromatic substituents gave the corresponding product **5a-d** in 72-88% yields. Furthermore, substrate **4e** having biologically active pargyline also yields the product **5e** successfully in 70% yield.

Scheme 4.8: Scope of 2-(aryl/alkylethynyl)benzo[*h*]quinoline-3-carbonitrile[a,b]



[a]Reactions were performed using 0.5 mmol of **6**, 2.0 equiv of CH_3NO_2 and 2.0 equiv of KOH in 2.0 mL of DMSO at 100 °C for 15 min. [b]Isolated yield.

Spectroscopic Data

*6-Methyl-2-(phenylethynyl)quinoline-3-carbonitrile***(1a).** Brown needles (209.0 mg, 78%):mp 120–121 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.92 (d, J = 8.7 Hz, 1H), 7.67-7.65 (m, 2H), 7.60 (dd, J = 8.7, 1.9 Hz, 1H), 7.46 (s, 1H), 7.38-7.32 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 141.9, 141.2, 139.3, 135.6, 132.6, 130.0, 129.2, 128.6, 126.8, 125.0, 121.3, 116.6, 109.5, 95.1, 86.4, 21.8; (Figure 4.3) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{19}H_{13}N_2$ 269.1073, found 269.1077. (Figure 4.4)

*2-(m-Tolylethynyl)quinoline-3-carbonitrile***(1b).** Brown needles (222.4 mg, 83%):mp 122–123 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.89-7.84 (m, 2H), 7.67-7.63 (m, 1H), 7.54 (d, J = 7.4 Hz, 2H), 7.30-7.23 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 143.1, 142.2, 138.4, 133.3, 133.2, 131.1, 129.9, 129.6, 128.8, 128.5, 128.1, 125.0, 121.0, 116.6, 109.7, 96.0, 86.0, 21.3; (Figure 4.5) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{19}H_{13}N_2$ 269.1073, found 269.1077. (Figure 4.6)

*2-((4-(Dimethylamino)phenyl)ethynyl)quinoline-3-carbonitrile***(1c).** Brown needles (244.4 mg, 74%):mp 128–129 °C: ^{1}H NMR (400 MHz, DMSO–d_6) δ 8.85 (d, J = 4.7 Hz, 2H), 8.40 (d, J = 8.0 Hz, 2H), 7.71-7.83 (m, 3H), 7.54-7.65 (m, 3H); ^{13}C NMR (100 MHz, DMSO–d_6) δ 154.1, 144.6, 141.5, 135.2, 134.2, 130.7, 124.2, 121.8, 116.7, 113.0, 93.1, 87.2; (Figure 4.7) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{22}H_{11}N_4$ 331.0984, found 331.0964. (Figure 4.8)

*6-Methyl-2-((4-(trifluoromethyl)phenyl)ethynyl)quinoline-3-carbonitrile***(1d).** Brown needles (242.0 mg, 72%):mp 132–133 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.58-7.52 (m, 3H), 7.43 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 141.2, 141.1, 139.7, 135.7, 132.8, 131.3 (q, J = 65.5, 32.7 Hz, 1C), 129.2, 126.8, 125.4 (d, J = 2.9 Hz, 1C), 125.1, 125.0, 122.4, 116.4, 109.6, 92.8, 88.1, 21.7; (Figure 4.9) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{20}H_{12}F_3N_2$ 337.0947, found 337.0977. (Figure 4.10)

*6-Methyl-2-(thiophen-3-ylethynyl)quinoline-3-carbonitrile***(1e).** Brown needles (235.6 mg, 86%):mp 122–123 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.94 (d, J =

8.7 Hz, 1H), 7.75 (t, *J* = 2.0 Hz, 1H), 7.63 (dd, *J* = 8.7, 1.7 Hz, 1H), 7.51 (s, 1H), 7.28-7.33 (2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 142.0, 141.3, 139.3, 135.6, 132.1, 130.2, 129.2, 126.8, 126.0, 125.0, 120.5, 116.6, 109.4, 90.4, 86.2, 21.8; (Figure 4.11) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{17}H_{11}N_2S$ 275.0637, found 275.0666. (Figure 4.12)

6-Methyl-2-(pyridin-2-ylethynyl)quinoline-3-carbonitrile(1f).Brown needles (183.0 mg, 68%):mp 136–137 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 4.8 Hz, 1H), 8.35 (s, 1H), 7.94 (d, J = 8.7 Hz, 1H), 7.70-7.62 (m, 3H), 7.55 (s, 1H), 7.29-7.25 (m, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 147.3, 141.9, 141.3, 141.1, 139.8, 136.3, 135.7, 129.4, 128.5, 126.8, 125.3, 124.1, 116.4, 109.6, 92.8, 85.0, 21.8; (Figure 4.13) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{18}H_{12}N_3$ 270.1026,found 270.1035. (Figure 4.14)

2-(Cyclohexylethynyl)quinoline-3-carbonitrile(1g).Brown needles(163.8 mg, 63%): mp 118–119 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ8.34 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.76-7.70 (m, 2H), 7.53-7.49 (m, 1H), 2.70-2.66 (m, 1H), 1.88-1.85 (m, 2H), 1.76-1.70 (m, 2H), 1.64-1.56 (m, 2H), 1.48-1.43 (m, 1H), 1.31-1.28 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.4, 143.3, 141.9, 133.0, 129.4, 128.4, 128.0, 124.8, 116.6, 109.7, 102.1, 78.3, 31.9, 29.8, 25.8, 24.7; (Figure 4.15) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{18}H_{17}N_2$ 261.1386,found 261.1370. (Figure 4.16)

2-(3-Hydroxyprop-1-yn-1-yl)-6-methylquinoline-3-carbonitrile(1h). Brown needles (137.6 mg, 62%): mp 120–121 °C:^{1}H NMR (400 MHz, DMSO-d_6) δ 8.84 (s, 1H), 7.79 (d, J = 48.5 Hz, 2H), 7.53 (d, J = 30.5 Hz, 1H), 5.59 (s, 1H), 4.42 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.9, 143.4, 141.2, 139.6, 136.2, 129.4, 127.8, 125.3, 117.0, 108.5, 94.9, 81.2, 49.8, 21.3; (Figure 4.17) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{14}H_{11}N_2O$ 223.0866,found 223.0888. (Figure 4.18)

2-(Phenylethynyl)benzo[h]quinoline-3-carbonitrile(4a). Brown needles (231.0 mg, 76%): mp 133–134 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (dt, J = 9.6, 3.5 Hz, 1H), 8.42 (s, 1H), 7.91-7.85 (m, 2H), 7.80-7.76 (m, 4H), 7.62 (d, J = 8.8 Hz, 1H), 7.47-7.40 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 142.5, 140.5, 134.9, 132.7, 130.2, 130.0, 128.6, 128.1, 128.1, 125.7, 124.1, 123.8, 121.5, 116.8, 110.3, 95.5, 86.9;

(Figure 4.19) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{22}H_{13}N_2$ 305.1073, found 305.1067. (Figure 4.20)

2-((4-Fluorophenyl)ethynyl)benzo[h]quinoline-3-carbonitrile(4b). Brown needles (225.4 mg, 70%): mp 137–138 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.27 (s, 1H), 8.39 (s, 1H), 7.88-7.59 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (d, J = 293.8 Hz, 1C), 148.1, 142.3, 140.5, 134.8 (d, J = 8.7 Hz, 1C), 130.2, 127.9, 125.6, 124.1, 123.8, 117.6, 116.8, 116.1 (d, J = 22.2 Hz, 1C), 110.2, 94.5, 86.6; (Figure 4.21) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{22}H_{12}FN_2$ 323.0979, found 323.0980. (Figure 4.22)

2-(Isoquinolin-3-ylethynyl)benzo[h]quinoline-3-carbonitrile(4c). Brown needles (237.8 mg, 67%): mp 154–155 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.39 (s, 1H), 9.10 (s, 2H), 8.33 (s, 1H), 8.07-8.18 (m, 4H), 7.76-7.89 (m, 4H), 7.48-7.59 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 154.1, 147.6, 142.6, 141.1, 135.4, 135.3, 135.1, 134.4, 132.0, 130.9, 130.8, 129.9, 129.3, 129.2, 128.9, 128.7, 128.4, 127.4, 126.8, 125.2, 124.6, 117.2, 110.0, 93.9, 85.6; (Figure 4.23) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{25}H_{14}N_3$ 356.1182, found 356.1150. (Figure 4.24)

2-(3-Hydroxyprop-1-yn-1-yl)benzo[h]quinoline-3-carbonitrile(4d). Brown needles (160.0 mg, 62%): mp 140–141 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92-9.05 (m, 1H), 7.95-8.08 (m, 2H), 7.66-7.86 (m, 3H), 7.42-7.50 (m, 1H), 5.64-5.77 (m, 1H), 4.50 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.1, 142.5, 141.5, 134.2, 130.7, 128.8, 128.6, 126.5, 125.5, 125.0, 123.3, 122.1, 116.8, 109.5, 95.8, 81.7, 50.1; (Figure 4.25) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{17}H_{11}N_2O$ 259.0866, found 259.0863. (Figure 4.26)

2-(3-(Benzyl(methyl)amino)prop-1-yn-1-yl)benzo[h]quinoline-3-carbonitrile(4e). Brown needles (231.0 mg, 64%): mp 134–135 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (d, J = 4.8 Hz, 1H), 8.37-8.35 (m, 1H), 7.88 (t, J = 3.6 Hz, 1H), 7.83 (dd, J = 8.7, 3.5 Hz, 1H), 7.76 (t, J = 4.1 Hz, 2H), 7.58-7.54 (m, 1H), 7.46 (d, J = 7.1 Hz, 2H), 7.37-7.32 (m, 2H), 7.28 (t, J = 7.3 Hz, 1H), 3.82 (s, 2H), 3.74 (s, 2H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 142.2, 140.6, 138.3, 134.8, 130.2, 129.5, 128.5, 128.1, 128.0, 127.4, 125.6, 124.1, 123.8, 117.1, 110.0, 91.5, 83.5, 60.2, 45.8, 42.3;

(Figure 4.27) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{25}H_{20}N_3$ 362.1652, found 362.1650. (Figure 4.28)

7-Methyl-2-nitro-3-phenylacridin-1-amine**(3a).** Orange needles (143.1 mg, 87%):mp 140–141 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.45 (s, 1H), 8.14 (s, 2H), 7.89 (d, J = 8.7 Hz, 1H), 7.62-7.67 (m, 2H), 7.31-7.42 (m, 5H), 7.02 (s, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.0, 148.5, 145.0, 140.3, 138.9, 136.6, 135.4, 134.0, 129.0, 128.6, 127.9, 127.4, 126.0, 125.8, 119.7, 118.2, 21.7; (Figure 4.29) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{20}H_{16}N_3O_2$ 330.1237, found 330.1236. (Figure 4.30)

2-Nitro-3-(m-tolyl)acridin-1-amine**(3b).** Orange needles (139.8 mg, 85%): mp 145–146 °C: ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.29-7.23 (m, 2H), 7.14 (dd, J = 12.7, 7.6 Hz, 2H), 7.07-7.04 (m, 2H), 7.00 (t, J = 7.5 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.58 (d, J = 2.2 Hz, 1H), 6.12 (s, 1H), 5.90 (s, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 142.1, 141.1, 139.3, 138.3, 137.2, 129.4, 128.7, 128.6, 128.5, 127.7, 124.2, 123.6, 123.1, 118.1, 114.5, 108.0, 21.6; (Figure 4.31) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{20}H_{16}N_3O_2$ 330.1237, found 330.1236. (Figure 4.32)

N,N-dimethyl-2-nitroacridine-1,3-diamine(3c).Orange needles (118.4 mg, 84%): mp 135–136 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1 H), 8.17 (d, J = 8.7 Hz, 1 H), 7.98 (d, J = 8.2 Hz, 1 H), 7.84 (t, J = 7.6 Hz, 1 H), 7.56 (t, J = 7.6 Hz, 1 H), 7.49 (s, 1 H), 7.35 (d, J = 8.7 Hz, 2 H), 6.77 (d, J = 8.8 Hz, 2 H), 6.52 (s, 2 H), 3.01 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 150.2, 149.3, 141.6, 139.4, 132.3, 132.1, 129.0, 128.6, 128.1, 126.6, 126.5, 125.5, 120.4, 117.2, 112.4, 40.4; (Figure 4.33) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{21}H_{19}N_4O_2$ 359.1508, found 359.1515. (Figure 4.34)

7-Methyl-2-nitro-3-(4-(trifluoromethyl)phenyl)acridin-1-amine(3d).Orange needles (176.7 mg, 89%): mp 147–148 °C:^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 8.08 (d, J = 8.8 Hz, 1H), 7.74-7.66 (m, 4H), 7.51 (d, J = 8.1 Hz, 2H), 7.40 (s, 1H), 6.96 (s, 2H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 148.3, 143.4, 137.6, 131.1, 128.9, 127.5, 126.8, 126.0, 125.6, 122.3, 117.6, 21.9; (Figure 4.35) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{21}H_{15}F_3N_3O_2$ 398.1111, found 398.1103. (Figure 4.36)

7-Methyl-2-nitro-3-(thiophen-3-yl)acridin-1-amine(3e).Orange needles (137.3 mg, 82%): mp 139–140 °C:^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.02 (s, 2H), 7.86 (d, J = 8.7 Hz, 1H), 7.64-7.54 (m, 4H), 7.12-7.08 (m, 2H), 2.45 (d, J = 4.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 148.8, 148.4, 144.3, 140.1, 136.5, 135.5, 134.1, 133.5, 128.4, 127.5, 126.8, 126.3, 125.7, 122.7, 118.7, 118.1, 21.7; (Figure 4.37) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{18}H_{14}N_3O_2S$ 336.0801, found 336.0811. (Figure 4.38)

7-Methyl-2-nitro-3-(pyridin-2-yl)acridin-1-amine(3f).Brown needles (146.8 mg, 89%): mp 149–150 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (d, J = 19.7 Hz, 1H), 8.53 (d, J = 4.7 Hz, 1H), 8.21 (s, 2H), 7.89-8.01 (m, 2H), 7.73-7.80 (m, 3H), 7.33-7.36 (m, 1H), 7.25 (d, J = 13.2 Hz, 1H), 2.51 (d, J = 16.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.8, 149.2, 148.7, 148.1, 144.9, 138.5, 137.8, 137.0, 135.9, 134.4, 128.4, 127.6, 126.0, 125.5, 123.0, 122.6, 119.8, 118.6, 21.7; (Figure 4.39) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{19}H_{15}N_4O_2$ 331.1190, found 331.1182. (Figure 4.40)

3-Cyclohexyl-2-nitroacridin-1-amine(3g). Orange needles (126.8 mg, 79%): mp 138–139 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.14 (d, J = 8.7 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.80-7.84 (m, 1H), 7.52-7.56 (m, 1H), 7.48 (s, 1H), 6.31 (s, 2H), 3.02-3.09 (m, 1H), 2.02 (d, J = 11.1 Hz, 1H), 1.85 (d, J = 12.8 Hz, 2H), 1.77 (d, J = 9.9 Hz, 1H), 1.47-1.57 (m, 2H), 1.40-1.44 (m, 2H), 1.23-1.31 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 149.3, 145.0, 140.5, 132.2, 131.9, 130.17, 129.0, 128.5, 126.5, 125.3, 117.5, 116.6, 40.3, 34.4, 27.0, 26.3; (Figure 4.41) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{19}H_{20}N_3O_2$ 322.1550, found 322.1544. (Figure 4.42)

(1-Amino-7-methyl-2-nitroacridin-3-yl)methanol(3h).Orange needles (97.6 mg, 69%):mp 154–155 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.65 (s, 1H), 8.58 (s, 1H), 7.97-8.00 (m, 1H), 7.78 (s, 1H), 7.58 (dd, J = 11.7, 7.1 Hz, 2H), 7.52 (dd, J = 6.7, 3.1 Hz, 1H), 7.43 (s, 1H), 4.81 (s, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 146.5, 132.7, 132.5, 132.1, 131.9, 129.3, 129.2, 127.6, 125.5, 118.3, 62.1, 21.6; (Figure 4.43) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{15}H_{14}N_3O_3$ 284.1030, found 284.1033. (Figure 4.44)

9-Nitro-10-phenylbenzo[c]acridin-8-amine(5a). Orange needles (153.3 mg, 84%):mp 169–170 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ9.62 (s, 1H), 9.26 (d, J = 7.7 Hz, 1H), 8.00-8.04 (m, 3H), 7.91 (d, J = 8.9 Hz, 1H), 7.76-7.85 (m, 3H), 7.43 (t, J = 5.8 Hz, 4H), 7.35-7.39 (m, 1H), 7.28 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.0, 148.2, 144.0, 140.0, 139.1, 134.7, 134.0, 130.5, 130.5, 129.1, 128.8, 128.5, 128.1, 128.0, 127.5, 127.2, 126.4, 125.2, 124.2, 119.7, 118.2; (Figure 4.45) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{23}H_{16}N_3O_2$ 366.1237, found 366.1240. (Figure 4.46)

10-(4-Fluorophenyl)-9-nitrobenzo[c]acridin-8-amine(5b). Orange needles (159.0 mg, 83%):mp 175–176 °C: ^{1}H NMR (400 MHz, DMSO-d_6) δ9.86 (d, J = 7.1 Hz, 1H), 9.48 (d, J = 6.2 Hz, 1H), 8.26-8.31 (m, 3H), 8.15 (dd, J = 8.7, 4.9 Hz, 1H), 8.02-8.09 (m, 3H), 7.71 (dd, J = 7.6, 5.4 Hz, 2H), 7.50-7.53 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ162.2 (d, J = 218.6 Hz, 1C), 149.0, 148.1, 144.4, 138.0, 136.4, 134.7, 133.9, 130.5, 129.6(d, J = 8.7 Hz, 1H), 128.8, 128.4, 128.1, 127.1, 126.3, 125.2, 124.4, 119.7, 118.3, 116.1, 115.8; (Figure 4.47) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{23}H_{15}FN_3O_2$ 384.1143, found 384.1142. (Figure 4.48)

10-(Isoquinolin-3-yl)-9-nitrobenzo[c]acridin-8-amine(5c).Light-brown needles (144.5 mg, 88%):mp 192–193 °C: ^{1}H NMR (400 MHz, DMSO–d_6) δ9.65 (s, 1H), 9.25 (s, 1H), 8.41 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.00 (s, 1H), 7.87 (d, J = 6.3 Hz, 1H), 7.77-7.83 (m, 2H), 7.66-7.70 (m, 1H), 7.51-7.54 (m, 2H), 7.26 (d, J = 8.4 Hz, 1H), 6.90 (s, 1H), 6.81 (s, 2H); ^{13}C NMR (100 MHz, DMSO–d_6) δ152.1, 144.1, 143.8, 138.8, 136.4, 133.9, 133.6, 131.3, 128.7, 128.4, 128.0, 127.6, 127.1, 126.9, 126.7, 126.2, 122.1, 121.6, 120.1, 118.7, 118.0, 112.9, 109.2, 101.6; (Figure 4.49) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{26}H_{17}N_4O_2$ 417.1346, found 417.1343. (Figure 4.50)

(8-Amino-9-nitrobenzo[c]acridin-10-yl)methanol(5d).Orange needles (114.8 mg, 72%):mp 185–186 °C: ^{1}H NMR (400 MHz, DMSO–d_6) δ9.60 (s, 1H), 9.30 (d, J = 7.0 Hz, 1H), 8.37 (s, 2H), 8.05 (d, J = 7.8 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.81-7.85 (m, 2H), 7.66 (s, 1H), 7.54 (t, J = 3.6 Hz, 1H), 5.47 (t, J = 5.5 Hz, 1H), 4.90 (d, J = 5.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO–d_6) δ149.0, 148.5, 145.7, 140.7, 134.7, 133.9, 130.3, 128.7, 127.9, 126.2, 126.0, 125.1, 124.0, 123.1, 121.8, 118.0, 115.8, 62.2;

(Figure 4.51) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{18}H_{14}N_3O_3$ 320.1030, found 320.1028. (Figure 4.52)

10-((Benzyl(methyl)amino)methyl)-9-nitrobenzo[c]acridin-8-amine(5e).Brown needles (147.7 mg, 70%):mp 165–166 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ9.44 (d, J = 6.3 Hz, 1H), 8.62 (s, 1H), 7.88-7.91 (m, 1H), 7.79-7.82 (m, 2H), 7.69-7.77 (m, 3H), 7.30-7.34 (m, 4H), 7.23 (t, J = 6.3 Hz, 1H), 6.26 (s, 2H), 4.09 (s, 2H), 3.58 (s, 2H), 2.15 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 147.8, 140.8, 139.1, 136.4, 134.4, 130.8, 130.1, 129.8, 129.8, 128.8, 128.3, 128.1, 128.0, 127.5, 126.8, 125.4, 125.1, 124.2, 121.1, 117.6, 62.1, 61.5, 41.9; (Figure 4.53) HRMS (ESI-TOF) $[M+H]^+$ Calcd for $C_{26}H_{23}N_4O_2$ 423.1816, found 423.1822. (Figure 4.54)

4.6 Conclusion

In summary, we have developed an efficient and transition-metal-free protocol for the synthesis of highly functionalized nitro substituted acridinamines and benzo[c]acrdinamines in excellent yields. It was established that developed transformation tolerates a wide range of the functional group. The chemistry is general and expected to find wide application in diverse fields of organic synthesis.

4.7 References

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Chapter – 5

Base-mediated N-acetylation of Anilines/Amines using Nitriles as a Surrogate of the Acetyl Group

CHAPTER – 5

BASE-MEDIATED N-ACETYLATION OF ANILINES/AMINES USING NITRILES AS A SURROGATE OF THE ACETYL GROUP

5.1 Introduction

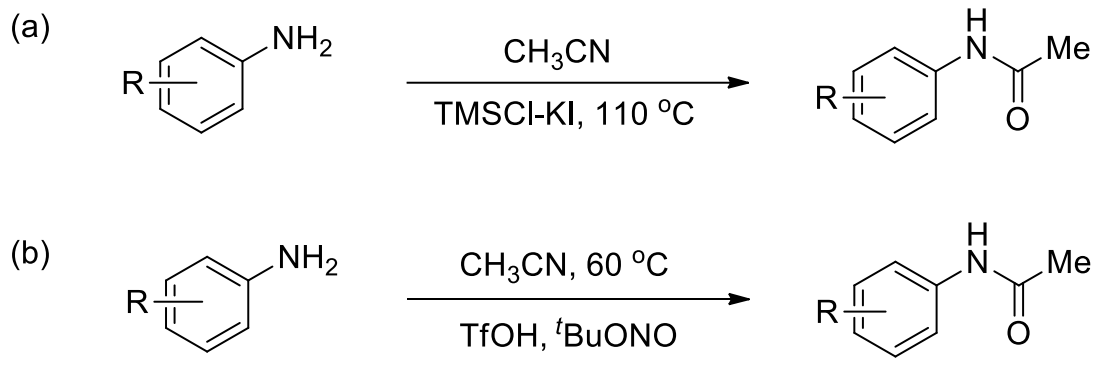
Amides are one of the most ubiquitous substructure in natural products, peptides, polymer chemistry, agrochemical industries and pharmaceutical preparations.[1] The pivotal role of amide-containing scaffolds is evident from their presence in several top-selling active pharmaceutical ingredients (APIs).[2] In addition, they have served as key intermediates in asymmetric catalysis and biological stains and indicators in chemical laboratories.[3] Due to their significance, considerable interest has been aroused in developing reliable methods for the construction of amide-containing scaffolds.

Early routes to access these motifs include the coupling of amines with carboxylic acid and its derivatives.[4] However, this reaction requires a coupling reagent, the use of which is always associated with the production of a stoichiometric amount of waste. Later, more reactive and activated carboxylic acid derivatives such as, acetic anhydrides and acyl chlorides were employed to avoid the use of coupling reagents but their hygroscopic nature and their tendency to react with water readily again restrict their use as coupling partners.[5] Therefore, the development of more efficient and sustainable approaches remains challenging and are in great need.

To overcome these issues several other procedures were developed that avoid the use of stoichiometric coupling reagents. It includes some traditional well-known reactions such as Ritter, Beckmann, Schmidt reaction etc.[6] Alongside various other catalytic procedures were developed such as oxidative amidation of carbonyl compounds, transamidation of amides, aminocarbonylation of aryl halides etc.[7] Recently, nitriles have gained significant attention as an amide synthon, although it has not been much explored yet. The coupling of nitriles with amines represents an effective method for the synthesis of amides.[8-9]

5.2 Review of Literature

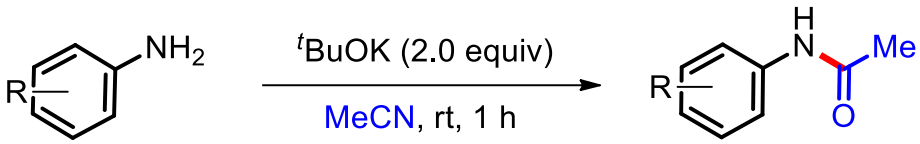
The first coupling of nitriles with amines was reported by Murashahi*et. al.* using ruthenium catalyst for the synthesis of polyamides.[8a] Later, Vries, Zhou and Williams have reported this coupling reaction using copper and iron catalyst independently.[8b-d] Recently, Pahari *et. al.*have carried out trimethylsilyl iodide catalyzed coupling of aromatic amines with acetonitrile (Scheme 5.1a).[9a] Subsequently, Wen *et. al.*have reported that triflic acid and *tert.* Butyl nitrite catalyzed coupling of anilines with acetonitrile (Scheme 5.1b).[9b]



Scheme 5.1: Approaches for the *N*-acetylation of anilines.

5.3 Designed Strategy

However, the use of all these procedures was impacted by the use of expensive transition metals, high reaction temperature, use of the stoichiometric amount of additives and limited substrate scope. Therefore, the development of mild protocols for the use of acetonitrile as an acyl equivalent for *N*-acetylation of anilines/amines is highly desirable. So we have developed a base-mediated protocol for *N*-acetylation of anilines/amines at room temperature using acetonitrile as a solvent as well as a surrogate of the acetyl group.



5.4 Experimental section

General Information

Chemicals and solvents utilized for the organic reactions were procured from the commercial sources and used as received. Substituted anilines and amines, acetonitrile, trifluoroacetonitrile, and bases were obtained from Sigma-Aldrich, and TCI. All the reactions were carried out in oven-dried glassware. The melting points of the isolated compounds were measured in open glass capillary tubes on "BUCHI Labortechnik AG CH-9230". Nuclear magnetic resonance (NMR), ^{1}H, and ^{13}C spectra were recorded on JEOL ECX-400P NMR spectrometer with TMS as an internal standard. The splitting pattern of the peaks were described as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). The SAG reactions were carried out at room temperature.

General Procedure for the Synthesis of Compounds 3, 4, 6, 7 and 9

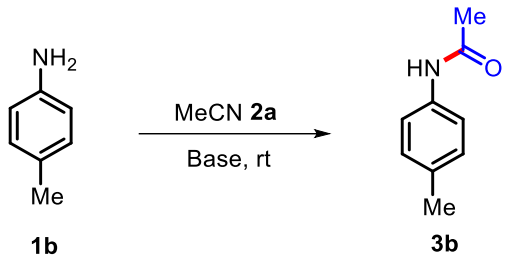
In a 25 mL oven-dried round bottom flask add substituted amine (1.0 mmol, 1.0 equiv) in 2.0 mL of acetonitrile as a solvent and the anhydrous potassium tertiary butoxide (2.0 equiv) was addedat room temperature. The reaction was stirred for 1 hour and the progress of the reaction was monitor by thin layer chromatography. Progression of the reaction was monitored by TLC analysis; after complete consumption of starting material, the reaction mixture was diluted with ethyl acetate (10 mL) and water (10 mL). The layers were separated, and the organic layer was washed with aqueous saturated brine solution and dried over Na_2SO_4. Organic layer was concentrated under reduced pressure. The crude material so obtained was purified by column chromatography on silica gel (100−200) (hexane: ethyl acetate; 90/10). The structure and purity of products were confirmed by comparison of their physical and spectral data (^{1}H NMR, ^{13}C NMR, and HRMS).

5.5 Results and Discussion

Considering the broad significance of amide scaffolds, we herein report the base-promoted *N*-acetylation of aromatic as well as aliphatic amines at room temperature under the transition-metal-free condition in a short reaction time (Scheme 1c). To

initiate the optimization studies, 4-methylaniline 1b was taken as the model substrate and acetonitrile (MeCN) 2a as acyl equivalent as well as a reaction solvent. Initially, the reaction of 1b was conducted in MeCN using 1.0 equiv of NaOH as a base at rt but there was no reaction even after 24 h (entry 1). Screening of other bases such as KOH, K_2CO_3 and Cs_2CO_3 also not led to the formation of product 3b (entry 2-4). Further, conducting the reaction with K_3PO_4 and K_2HPO_4 gives the desired product 3b in 22% and 18% yield, respectively with incomplete consumption of starting material even after 24 h (entry 5-6). To our delight using ^{t}BuONa afford the desired product 3b in 34% yield(entry 7).

Table 5.1: Optimization of reaction condition[a]

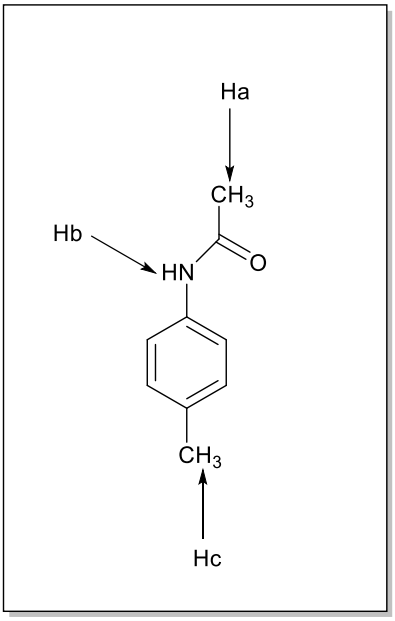


1b **3b**

entry	base (equiv)	time(h)	yield (%)[b] 3a
1	NaOH (1.0)	24	NR
2	KOH (1.0)	24	NR
3	K_2CO_3 (1.0)	24	NR
4	Cs_2CO_3 (1.0)	24	NR
5	K_3PO_4 (1.0)	24	22
6	K_2HPO_4 (1.0)	24	18
7	^{t}BuONa (1.0)	3	34
8	^{t}BuOK (1.0)	1	54
9	**^{t}BuOK (2.0)**	**1**	**78**
10	^{t}BuOK (3.0)	1	76

[a]Reactions were performed using 1.0 mmol of 1b, and 2.0 equiv of base in 2.0 mL of solvent at rt. [b]Isolated yield.

Interestingly, the use of^{t}BuOKas a base provided the desired product **3b** in 54% yield in 1 hour (entry 8). Increasing the loading of ^{t}BuOK to 2.0 equiv furnished the desired product **3b** in 78% yield with complete consumption of starting material (entry 9). Further, an increment in the loading of ^{t}BuOK did not lead to an increase in the product yield (entry 10). Therefore, entry 9 was found to be the optimal reaction condition for the transformation.



N-(p-tolyl)acetamide (3b)

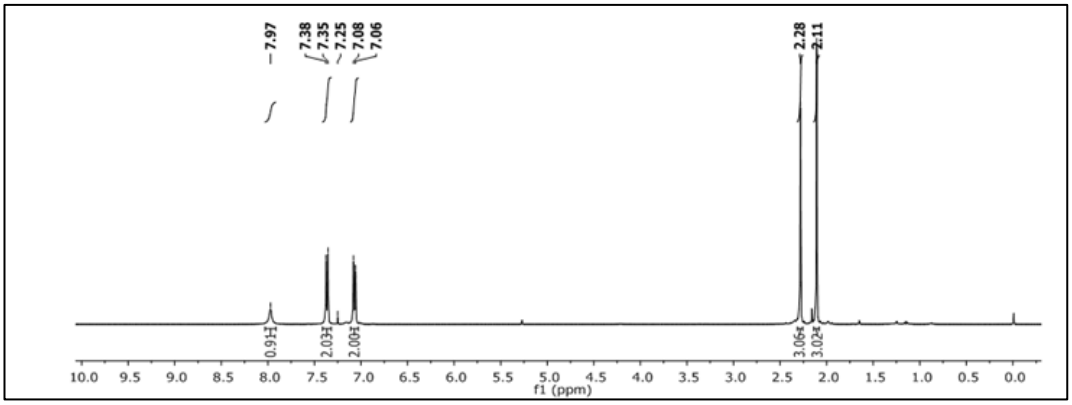
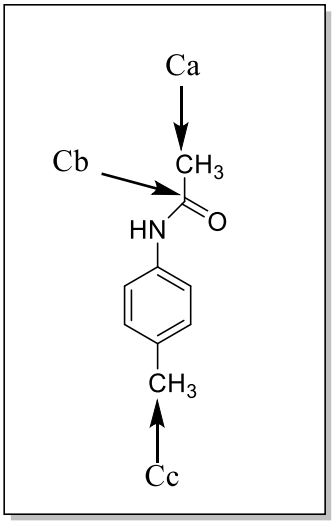


Figure 5.1: ^{1}H NMR of N-(p-tolyl)acetamide (3b) in $CDCl_3$ at 400 MHz

In the ^{1}H NMR of **3b (Figure 5.1)** in $CDCl_3$ at 400 MHz, the appearance of a characteristic peak of NH (Hb) displays at δ 7.97 ppm. The appearance of aliphatic

protons at 2.11 ppm and 2.28 ppm shows the presence of Ha and Hc respectively while aromatic protons shows in the range from 7.38 to 7.06 ppm.



N-(p-tolyl)acetamide (3b)

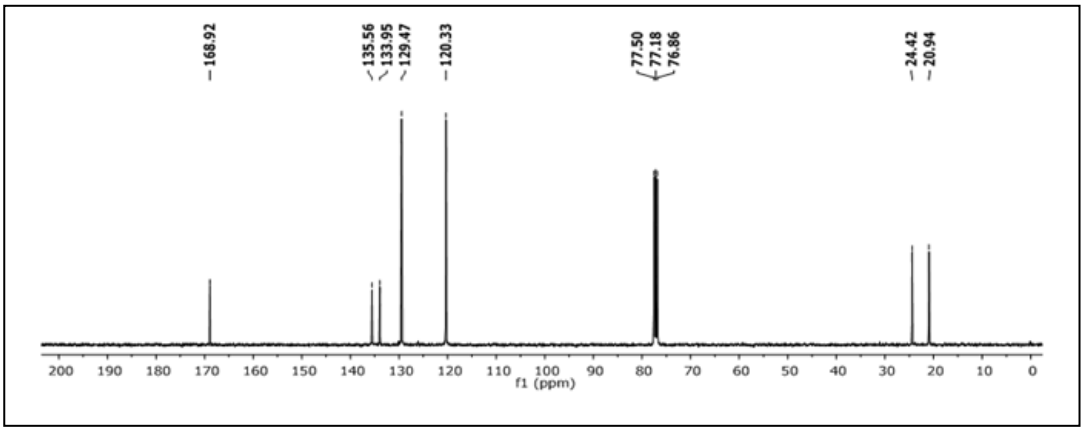
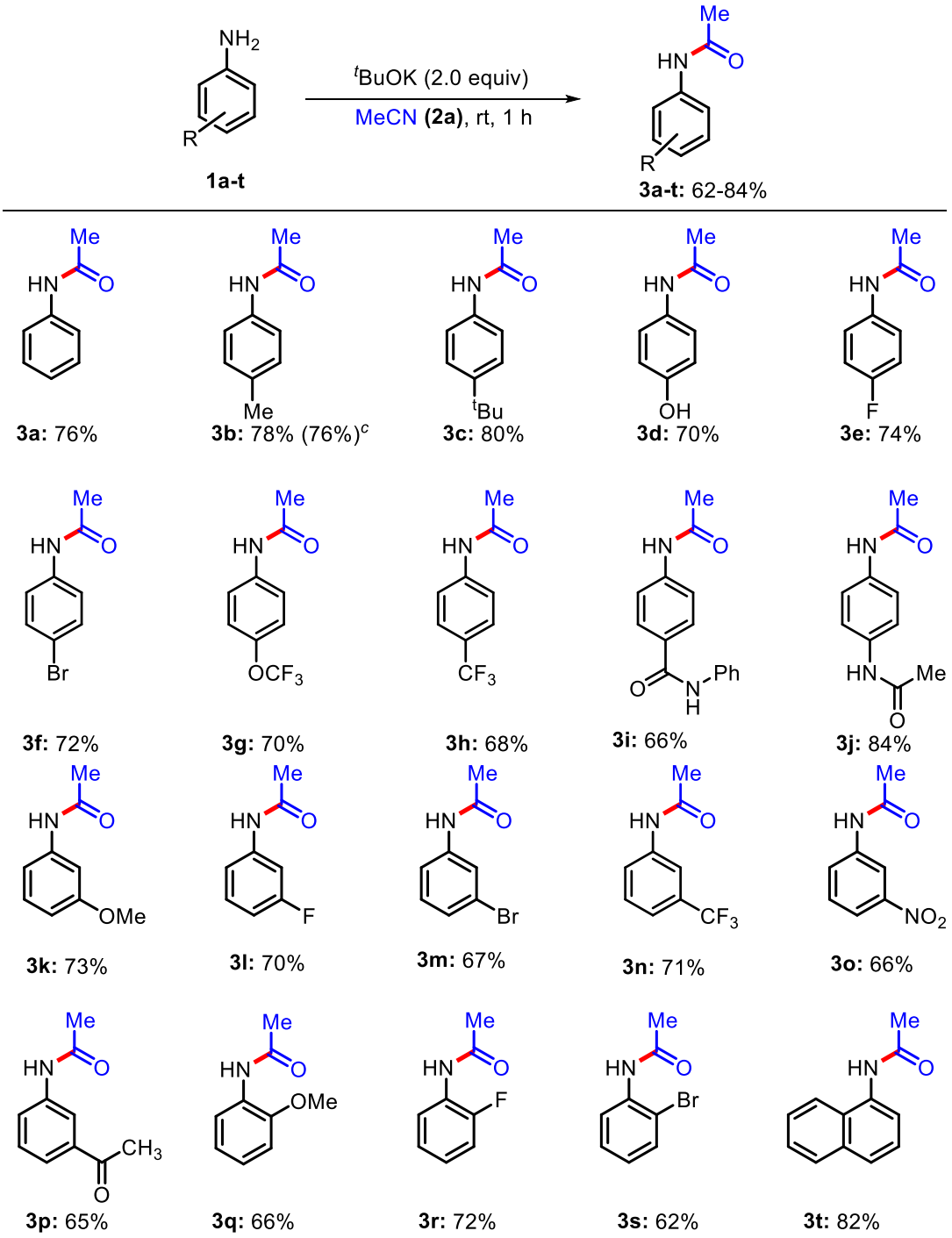


Figure 5.2: ^{13}C NMR of N-(p-tolyl)acetamide (3b) in $CDCl_3$ at 100 MHz

Similarly, in ^{13}C NMR spectrum of **3b (Figure 5.2)** in $CDCl_3$ at 100 MHz, the appearance of a characteristic peak at δ 24.4 ppm, 168.9 ppm and 20.9 ppm show the presence of carbon Ca, Cb and Cc respectively.

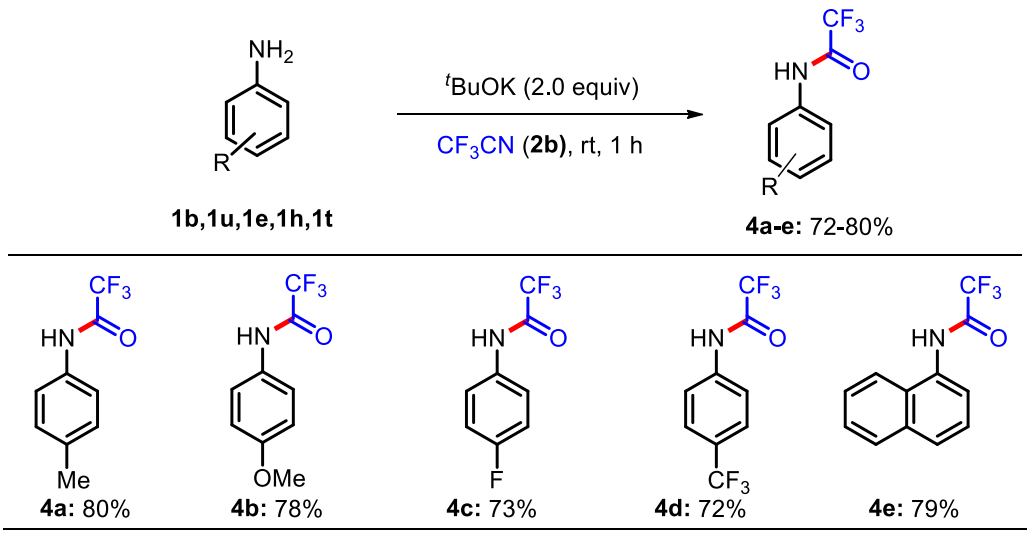
Scheme 5.2: Scope for substitutedanilines[a,b]



[a]1.0 mmol and 2.0 equiv of ^{t}BuOK in 2.0 mL of ACN at rt for 1 h. [b]Isolated yield. [c]Gram-scale in 10 mL solvent.

After having the optimal reaction conditions (Table 5.1, entry 9) for the *N*-acetylation of amines, we test the scope of various substituted anilines with MeCN (Scheme 5.2). Under optimized reaction conditions, aniline **1a** gave 76% yield of product**3a**. Anilines **1b**and **1c** having electron releasing groups *i.e.* -Me and -^{t}Bu at *para* position gave the desired product**3b** and **3c** in 78% and 80% yields, respectively. The reaction of Aniline **1b**also found to be efficient at gram-scale giving the desired product in 76% yield. Notably, 4-aminophenol **1d** selectively provided the *N*-acetylated product **3d** in 70% yield. halogenatedand electron-deficient anilines **1e-h** having –F, -Br -OCF_3, and -CF_3at *para* position yield the products **3e-h** in 68-74% yield. Notably, anilines **1i**and **1j** having amide substitution well tolerated the reaction condition provided the products **3i** and **3j** with 66% and 84% yields, respectively. Electron-deficient meta-substituted anilines **1k-p** having electron-withdrawing groups also reacted well to give the corresponding product **3k-p** in 65-73% yield. Moreover, *ortho*-substituted anilines **1q-s** having –OMe, -F, and –Br reacted to give desired products **3q-s**in 62-72% yield. Furthermore, 1-naphthylamine **1t** also underwent the reaction smoothly provided the product **3t** in 80% yield. Moreover, the reaction was also compatible on a gram scale providing the product **3b** in 76% yield.

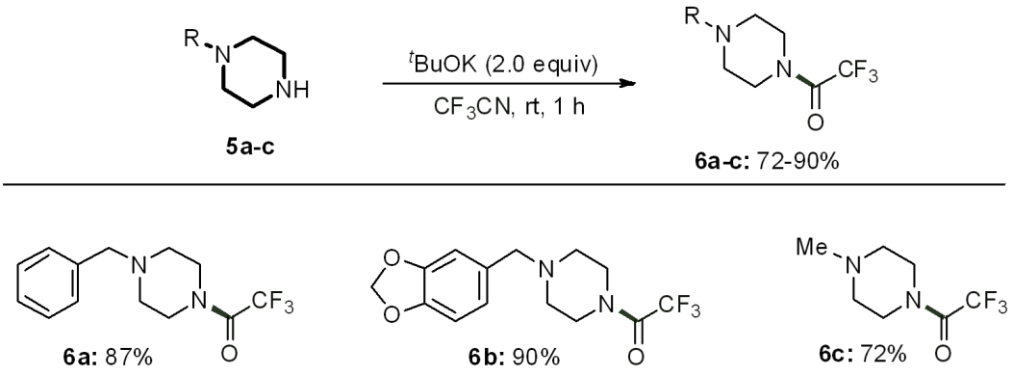
Scheme 5.3: Scope for substituted anilines with trifluoroacetonitrile[a,b]



[a]1.0 mmol and 2.0 equiv of ^{t}BuOKin 2.0 mL of CF_3CN at rt for 1 h. [b]Isolated yield.

The methodology was next extended towards the use of 2,2,2-trifluoroacetonitrile (CF_3CN) **2b** under standard reaction conditions (Table 5.1, entry 9) for the synthesis of 2,2,2-trifluoro-N-phenylacetamide derivatives (Scheme 5.3). The reaction of 4-Me, and 4-OMe, substituted aniline **1b**and **1u** with **2b** gave the desired product **4a**and **4b** in 80% and 78% yields, respectively. Similarly, electron-deficient 4-fluoroaniline **1e** and 4-trifluoromethyl **1h** gave the products **4c** and **4d** in 73% and 72% yields, respectively. Moreover, 1-naphthylamine **1t** also afforded the corresponding products **4e** in 79% yield.

Scheme 5.4: Substrate scope of cyclic secondary amine with trifluoroacetonitrile[a,b]

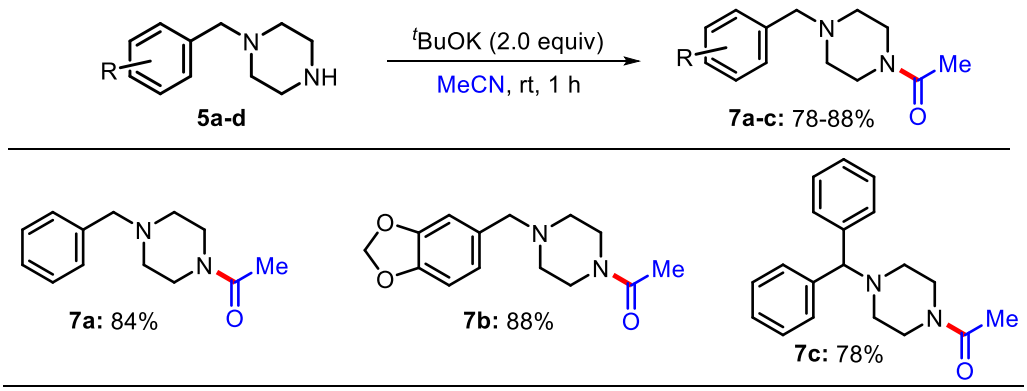


[a]Reactions were performed using 1.0mmol of aminesand 2.0 equivof ^{t}BuOK in 2.0 mL of ACN at rt for 1 h.[b]Isolated yield.

Further, we extended the substrate scope of cyclic secondary amine **5a-c** with 2,2,2-trifluoroacetonitrile (CF_3CN) **2b** under optimal reaction condition (Table 5.1, entry 9) and we got the corresponding products**6a-c** in good yields. (Scheme-5.4)

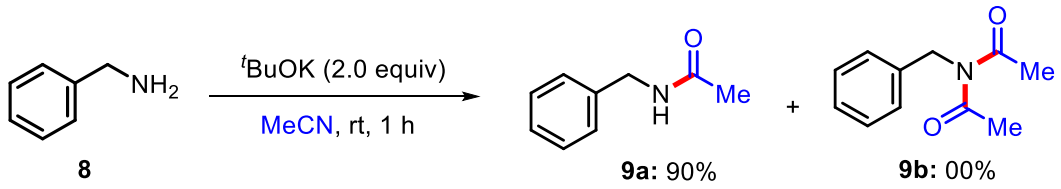
The developed protocol was next used to explore the substrate scope of aliphatic amines which have not been explored yet. (Scheme 5.5) To our desire, the reaction of mono-substituted piperazines *i.e.*1-benzylpiperazine**5a**1-(benzo[*d*][1,3]dioxol-5-ylmethyl)piperazine **5b** and1-benzhydrylpiperazine **5d** with acetonitrile **2b** gave the corresponding products **7a-c** in 78-88% yields.

Scheme 5.5: substrate scope of aliphatic amines.



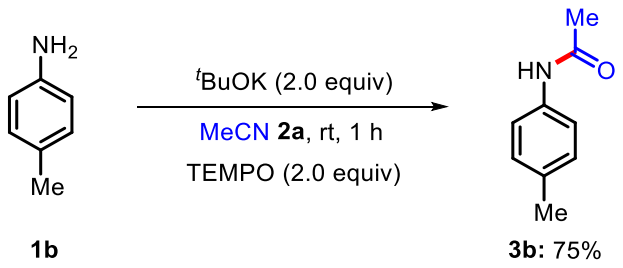
[a]Reactions were performed using 1.0 mmol of aminesand 2.0 equivof^{t}BuOK in 2.0 mL of ACN at rt for 1 h. [b]Isolated yield.

Further extending the scope of the developed protocol, the reaction of benzylamine **8** was conducted with acetonitrile **2b** under standard reaction conditions (Table 5.1, entry 9) which yields the selective mono-acetylated product **9a** in 90% yield (Scheme 5.6). However, when the reaction was performed with aliphatic amines the reaction did not proceed at all.



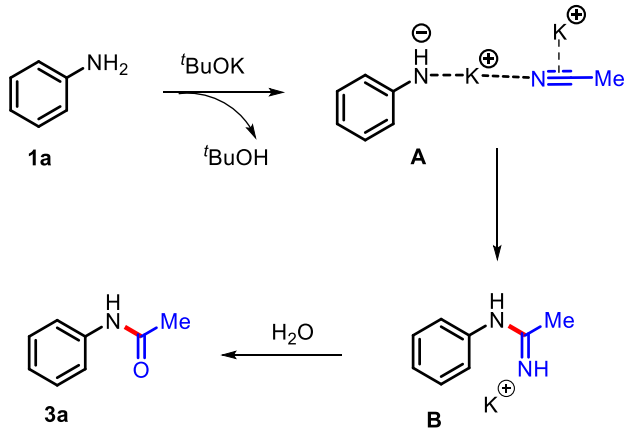
Scheme 5.6: Synthesis of *N*-benzylacetamide.

To understand the reaction pathway a control reaction of 4-methylaniline **1b** was performed with acetonitrile **2a** under standard reaction conditions(Table 5.1, entry9)in presence of 2.0 equiv of TEMPO (Scheme 5.7). No significant change in the yield of product**3b** indicates that the reaction proceeds *via*anionic pathway instead of a radical pathway.



Scheme 5.7: Control experiments.

On the basis of control reaction (Scheme 5.7) and precedents,[8-10] we herein proposed a reasonable mechanistic pathway for the reaction (Scheme5.8). Initially, in presence of K^{t}BuO, the aniline **1a** and nitrile **2a** get activated by the coordination of lone pair of their nitrogen with potassium and subsequent removal of ^{t}BuOH to give transient species **A**. Coordination of potassium ion makes the nitrile carbon electrophilic and the nucleophilic attack of aniline onto that carbon yields amidine **B** which is followed by hydrolysis to provide the desired *N*-phenylacetamide**3a**.



Scheme 5.8: Proposed reaction mechanism

Spectroscopic Data

*N-phenylacetamide***(3a).** White solid (103.3 mg, 76%): mp 113–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.9 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 2.12 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 169.34, 138.2, 128.9, 124.3, 120.3, 24.4; (Figure 5.3) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_8H_{10}NO$ 136.0757; found 136.0756.

*N-(p-Tolyl)acetamide***(3b)**. White solid (116.2 mg, 78%): mp 149–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 2.28 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) 168.9, 135.6, 133.9, 129.5, 120.3, 24.42, 21.0; (Figure 5.4) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_9H_{12}NO$ 150.0913; found 150.0917.

*N-(4-(Tert-butyl)phenyl)acetamide***(3c)**. White solid (152.8 mg, 80%): mp 172–173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.40 (d, *J* = 8.7 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 2.14 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 147.3, 135.3, 125.8, 119.9, 34.4, 31.4, 24.6; (Figure 5.5) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{12}H_{18}NO$ 192.1383; found 192.1377.

*N-(4-Hydroxyphenyl)acetamide***(3d)**. White solid (105.7 mg, 70%): mp 166–167 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ δ 9.62 (s, 1H), 9.11 (s, 1H), 7.31 (d, *J* = 6.7 Hz, 2H), 6.65 (d, *J* = 8.9 Hz, 2H), 1.95 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.0, 153.6, 131.5, 121.3, 115.5, 24.2; (Figure 5.6) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_8H_{10}NO_2$ 152.0706; found 152.0710.

*N-(4-Fluorophenyl)acetamide***(3e)**. White solid (113.2 mg, 74%): mp 151–152 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 7.56 (dd, *J* = 7.0, 5.2 Hz, 2H), 7.07 (t, *J* = 8.8 Hz, 2H), 2.00 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.7, 159.5, 157.1, 136.2, 121.2, 121.1, 115.8, 115.5, 24.3; (Figure 5.7) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_8H_9FNO 154.0663; found 154.0667.

*N-(4-Bromophenyl)acetamide***(3f)**. Light-brown solid (152.6 mg, 72%): mp 165–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 2H), 7.41 (d, *J* = 6.7 Hz, 2H), 2.00 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.0, 139.2, 132.0, 121.3, 115.0, 24.5; (Figure 5.8) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_8H_9BrNO 213.9862; found 213.9873.

*N-(4-(Trifluoromethoxy)phenyl)acetamide***(3g)**. Brown solid (153.3 mg, 70%): mp 114–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 6.7 Hz, 2H), 2.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 145.3,

136.8, 121.7, 121.3, 24.3; (Figure 5.9) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_9H_9F_3NO_2$ 220.0580; found 220.0583.

*N-(4-(Trifluoromethyl)phenyl)acetamide***(3h)**. Brown solid (138.0 mg, 68%): mp 149–150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.26 (s, 1H), 7.67 (d, J = 64.7 Hz, 4H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.5, 143.3, 126.5, (q, J_{C-F} = 3.6 Hz), 123.7, (q, J_{C-F} = 31.4 Hz), 123.5, (q, J_{C-F} = 270 Hz), 119.2, 24.6; (Figure 5.10) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_9H_9F_3NO$ 204.0631; found 204.0638.

*4-Acetamido-N-phenylbenzamide***(3i)**. Brown solid (167.6 mg, 66%): mp 132–133 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.16 (s, 1H), 9.90 (s, 1H), 7.91 (d, J = 7.0 Hz, 2H), 7.65 (d, J = 8.9 Hz, 2H), 7.50 (dt, J = 15.9, 6.5 Hz, 5H), 2.00 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.6, 165.8, 135.7, 135.5, 134.8, 132.0, 128.9, 128.1, 121.3, 119.7, 24.4; (Figure 5.11) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{15}H_{15}N_2O_2$ 255.1128; found 255.1134.

*N,N'-(1,4-Phenylene)diacetamide***(3j)**. Brown solid (161.3 mg, 84%): mp 165–166 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.85 (s, 2H), 7.43 (s, 4H), 1.97 (s, 6H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.9, 135.3, 120.1, 24.4; (Figure 5.12) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{10}H_{13}N_2O_2$ 193.0972; found 193.0977.

*(3-Methoxyphenyl)acetamide***(3k)**. Brown solid (120.4 mg, 73%): mp 81–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 7.23 (s, 1H), 7.09 (d, J = 7.2 Hz, 1H), 7.02 (d, J = 6.7 Hz, 1H), 6.58 (d, J = 7.6 Hz, 1H), 3.65 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 139.5, 129.6, 112.8, 109.9, 106.4, 55.2, 24.2; (Figure 5.13) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_9H_{12}NO_2$ 166.0863; found 166.0866.

*N-(3-Fluorophenyl)acetamide***(3l)**. Brown solid (107.1 mg, 70%): mp 82–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 7.47 (d, J = 10.7 Hz, 1H), 7.13 (t, J = 9.5 Hz, 2H), 6.70 (d, J = 7.6 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.0, 161.5, 140.1, 130.5, 116.0, 110.8, 107.8, 24.5; (Figure 5.14) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_8H_9FNO 154.0663; found 154.0667.

*N-(3-Bromophenyl)acetamide***(3m)**. Brown solid (142.0 mg, 67%): mp 69–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.77 (s, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.14

(d, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.9 Hz, 1H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 139.5, 130.2, 127.3, 123.3, 122.4, 118.9, 24.2; (Figure 5.15) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_8H_9BrNO 213.9862; found 213.9873.

*N-(3-(Trifluoromethyl)phenyl)acetamide***(3n)**. Brown solid (133.6 mg, 61%): mp 109–110 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.23 (s, 1H), 8.07 (s, 1H), 7.73 (d, *J* = 8.2 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 2.04 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 169.3, 140.6, 130.5, 130.0, 129.9, 129.6, 128.6, 125.9, 123.2, 122.8, 120.5, 119.6, 115.5, 24.3; (Figure 5.16) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_9H_9F_3NO_2$ 220.0580; found 220.0583.

*N-(3-Nitrophenyl)acetamide***(3o)**. Brown solid (118.8 mg, 66%): mp 154–155 °C; ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 10.38 (s, 1H), 8.57 (s, 1H), 7.83 (d, *J* = 12.6 Hz, 2H), 7.53 (t, *J* = 8.2 Hz, 1H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, DMSO-*d*$_6$) δ 169.6, 148.4, 140.9, 130.6, 125.3, 118.0, 113.4, 24.6; (Figure 5.17) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_8H_9N_2O_3$ 181.0608; found 181.0610.

*N-(3-Acetylphenyl)acetamide***(3p)**. Brown solid (115.0 mg, 65%): mp 112–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.07 (s, 1H), 7.89 (d, *J* = 9.3 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 2.53 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.7, 169.9, 139.0, 137.4, 129.2, 124.9, 124.0, 119.6, 26.8, 24.4; (Figure 5.18) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{10}H_{12}NO_2$ 178.0863; found 178.0865.

*N-(2-Methoxyphenyl)acetamide***(3q)**. Brown solid (108.9 mg, 66%): mp 90–91 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 7.8 Hz, 1H), 7.85 (s, 1H), 6.98 (t, *J* = 7.7 Hz, 1H), 6.89 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.80 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 147.8, 127.7, 123.7, 121.1, 119.8, 109.9, 55.7, 25.0; (Figure 5.19) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_9H_{12}NO_2$ 166.0863; found 166.0860.

*N-(2-Fluorophenyl)acetamide***(3r)**. Brown solid (110.2 mg, 72%): mp 78–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (s, 1H), 7.88 (s, 1H), 6.91 (d, *J* = 7.1 Hz, 2H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 154.8, 152.4, 125.9, 125.2, 124.2,

123.6, 115.2, 115.0, 23.7; (Figure 5.20) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_8H_9FNO 154.0663; found 154.0667.

*N-(2-Bromophenyl)acetamide***(3s)**. Brown solid (131.4 mg, 62%): mp 97–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.1 Hz, 1H), 7.68 (s, 1H), 7.47 (d, *J* = 9.1 Hz, 1H), 7.24 (t, *J* = 8.4 Hz, 1H), 6.92 (t, *J* = 7.3 Hz, 1H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 135.8, 132.3, 128.4, 125.4, 122.4, 113.7, 24.8; (Figure 5.21) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_8H_9BrNO 213.9862; found 213.9873.

*N-(Naphthalen-1-yl)acetamide***(3t)**. Brown solid (151.7 mg, 82%): mp 106–107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 25.2, 6.8 Hz, 4H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.49 – 7.36 (m, 3H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 134.1, 132.4, 128.7, 126.3, 126.1, 126.0, 125.7, 121.6, 121.0, 24.0. (Figure 5.22) ^{19} F NMR (376 MHz,) δ -75.56; HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{12}H_{12}NO$ 186.0913; found 186.0912.

*2,2,2-Trifluoro-N-(p-tolyl)acetamide***(4a)**. Brown solid (162.4 mg, 80%): mp 106–107 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.34 (s, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.8, 155.4, 155.0, 154.7, 136.4, 132.6, 129.8, 120.9, 117.4, 114.5, 111.6, 21.0 ((Figure 5.23) ^{19}F NMR (376 MHz,) δ -75.56; (Figure 5.24) HRMS (ESI) m/z: $[M+H]^+$ Calcd. for $C_9H_9F_3NO$ 204.0631; found 204.0638.

*2,2,2-Trifluoro-N-(4-methoxyphenyl)acetamide***(4b)**. Brown solid (170.8 mg, 78%): mp 117–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 2.25 (s, 3H). (Figure 5.25) ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.5, 155.1, 154.7, 154.4, 135.2, 134.5, 129.6, 121.4, 117.9, 115.0, 112.2, 20.6 ^{19}F NMR (376 MHz,) δ -74.57; (Figure 5.26) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_9H_9F_3NO_2$ 220.0580; found 220.0587.

*2,2,2-Trifluoro-N-(4-fluorophenyl)acetamide***(4c)**. Brown solid (151.1 mg, 73%): mp 108–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.57 – 7.46 (m, 2H), 7.10 – 6.99 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 159.3, 155.7, 155.3, 154.9, 154.6, 131.1, 122.7, 122.7, 117.2, 116.3, 116.1, 114.3. (Figure 5.27) ^{19}F NMR (376

MHz,) δ -75.56, -114.62; (Figure 5.28) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_8H_6F_4NO$ 208.0380; found 208.0384.

*2,2,2-Trifluoro-N-(4-(trifluoromethyl)phenyl)acetamide***(4d)**. Brown solid (185.0 mg, 72%): mp 124–125 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (t, *J* = 7.0 Hz, 2H), 7.61 (t, *J* = 6.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.8, 160.5, 160.1, 159.7, 144.9, 132.9, 131.7, 131.4, 130.8, 130.2, 127.5, 125.7, 122.1, 119.2, 83.2, 82.9, 82.6, 82.3. (Figure 5.29) ^{19}F NMR (376 MHz,) δ -56.91, -69.36; (Figure 5.30) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_9H_6F_6NO$ 258.0348; found 258.0344.

*2,2,2-Trifluoro-N-(naphthalen-1-yl)acetamide***(4e)**. Brown solid (188.8 mg, 79%): mp 95–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.87 – 7.80 (m, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.70 – 7.59 (m, 2H), 7.54 – 7.43 (m, 2H), 7.36 (td, *J* = 8.1, 2.2 Hz, 1H). (Figure 5.31) ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 156.3, 155.9, 155.6, 134.0, 129.2, 128.8, 127.9, 127.1 (d, *J* = 19.0 Hz), 126.6, 125.4, 122.1, 120.4, 117.6, 114.7, 111.8. ^{19} F NMR (376 MHz,)δ -75.08; ((Figure 5.32) HRMS (ESI) m/z: $[M+H]^+$ Calcd. for $C_{12}H_9F_3NO$ 240.0631; found 240.0642.

*1-(4-benzylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one***(6a)**. Semi-solid (236.6 mg, 87%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.26 (m, 5H), 3.69 (t, *J* = 4.9 Hz, 2H), 3.60 (t, *J* = 4.6 Hz, 2H), 3.54 (s, 2H), 2.50 (q, *J* = 4.9 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.2, 129.1, 128.4, 127.4, 62.6, 52.8, 52.3, 45.8, 43.3. (Figure 5.33) ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.6; HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{13}H_{16}F_3N_2O$ 273.1209; found 273.1215.

*1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-2,2,2-trifluoroethan-1-one***(6b)**. Semi-solid (284.4 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84-6.73 (m, 3H), 5.95 (s, 2H), 3.69-3.44 (m, 6H), 2.47 (d, *J* = 3.7 Hz, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 155.3 (q, *J* = 107.0 MHz, 1C), 147.7, 146.8, 130.9, 122.1, 109.2, 107.9, 100.9, 62.2, 52.5, 52.0, 45.7, 43.2. (Figure 5.34) ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.7; HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{14}H_{16}F_3N_2O_3$317.1108; found 317.1112.

*2,2,2-trifluoro-1-(4-methylpiperazin-1-yl)ethan-1-one***(6c)**. Semi-solid (141.1 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (d, *J* = 4.1 Hz, 2H), 3.36 (d, *J* = 4.1 Hz,

2H), 2.22 (t, J = 2.4 Hz, 4H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6 (q, *J* = 107 MHz, 1C), 54.0, 53.4, 52.9, 48.8, 44.8, 42.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.8; (Figure 5.35) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{17}H_{12}F_3N_2O$197.0896; found 197.0890.

*1-(4-Benzylpiperazin-1-yl)ethan-1-one***(7a)**. Semi-solid (183.1 mg, 84%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.18 (m, 5H), 3.50 (s, 2H), 3.25 – 3.13 (m, 4H), 2.50 – 2.38 (m, 4H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ δ 169.3, 135.7, 129.5, 128.3, 127.8, 62.1, 52.3, 52.0, 45.5, 40.8, 20.9; (Figure 5.36) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{13}H_{19}N_2O$ 219.1492; found 219.1497.

*1-(4-(Benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)ethan-1-one***(7b)**. Semi-solid (230.5 mg, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.65 (s, 1H), 6.55 (s, 2H), 5.74 (s, 2H), 3.49 – 3.42 (m, 2H), 3.38 (s, 2H), 3.36 – 3.30 (m, 2H), 2.43 – 2.36 (m, 2H), 2.36 – 2.30 (m, 2H), 1.88 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 147.7, 147.2, 128.7, 123.1, 109.9, 107.9, 101.0, 61.6, 52.0, 51.6, 45.3, 40.5, 21.5; (Figure 5.37) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{14}H_{19}N_2O_3$ 263.1390; found 263.1399.

*1-(4-Benzhydrylpiperazin-1-yl)ethan-1-one***(7c)**. Semi-solid (229.3 mg, 78%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.8 Hz, 4H), 7.26 (t, *J* = 7.5 Hz, 4H), 7.17 (dd, *J* = 11.6, 4.3 Hz, 2H), 4.22 (s, 1H), 3.62 – 3.56 (m, 2H), 3.50 – 3.37 (m, 2H), 2.36 (dd, *J* = 10.3, 5.3 Hz, 4H), 2.03 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 169.4, 142.1, 128.7, 127.9, 127.2, 76.0, 52.0, 51.5, 46.5, 41.7, 21.2; (Figure 5.38) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{19}H_{23}N_2O$ 295.1805; found 295.1800.

*N-Benzylacetamide***(9a).** Colorless liquid (134.1 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ NMR (400 MHz,) δ 7.30 (ddd, *J* = 28.0, 14.7, 6.7 Hz, 5H), 4.90 (s, 1H), 4.11 (d, *J* = 5.2 Hz, 2H), 2.11 (s, H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 136.5, 128.9, 128.0, 127.7, 122.0, 47.69, 20.24; (Figure 5.39) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_9H_{12}NO$ 150.0913; found 150.0910.

5.6 Conclusion

In conclusion, we have developed an efficient and operationally simple approach for the synthesis of differently substituted *N*-acetamides in good yields using readily available and cheap anilines/amines and acetonitrile. Acetonitrile here acts as an acyl equivalent as well as solvent. Apart from acetonitrile, 2,2,2-trifluoroacetonitrile could also be used in the reaction as an acyl surrogate. Therefore, the reaction shows high generality in terms of substrate scope. Further, the short reaction time at room temperature makes the developed strategy more useful in terms of synthetic aspects.

5.7 References

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Chapter – 6

Potassium tert-butoxide Promoted a Direct one-pot Synthesis of Nitriles from Aldehydes at Room Temperature

CHAPTER – 6

POTASSIUM TERT-BUTOXIDE PROMOTED A DIRECT ONE-POT SYNTHESIS OF NITRILES FROM ALDEHYDES AT ROOM TEMPERATURE

6.1 Introduction

Nitrile (cyano) is one of the key functional groups in organic synthesis.[1] Nitrile groups are found in many natural products, drugs, and bioactive molecules (Figure 6.1).[2] For instance, anastrozole is used against breast cancer while verapamil and tofacitinib are used for treating high blood pressure and arthritis, respectively. On the other hand, functional group transformation of nitrile with different reagents allows easy access to primary amines, amides, carboxylic acid, ketones, etc.[3] Hence, compounds with nitrile functional group have been used as a precursor for preparing various bioactive molecules, natural products, pharmaceuticals, agrochemicals, polymers, dyes, etc.[1-4]

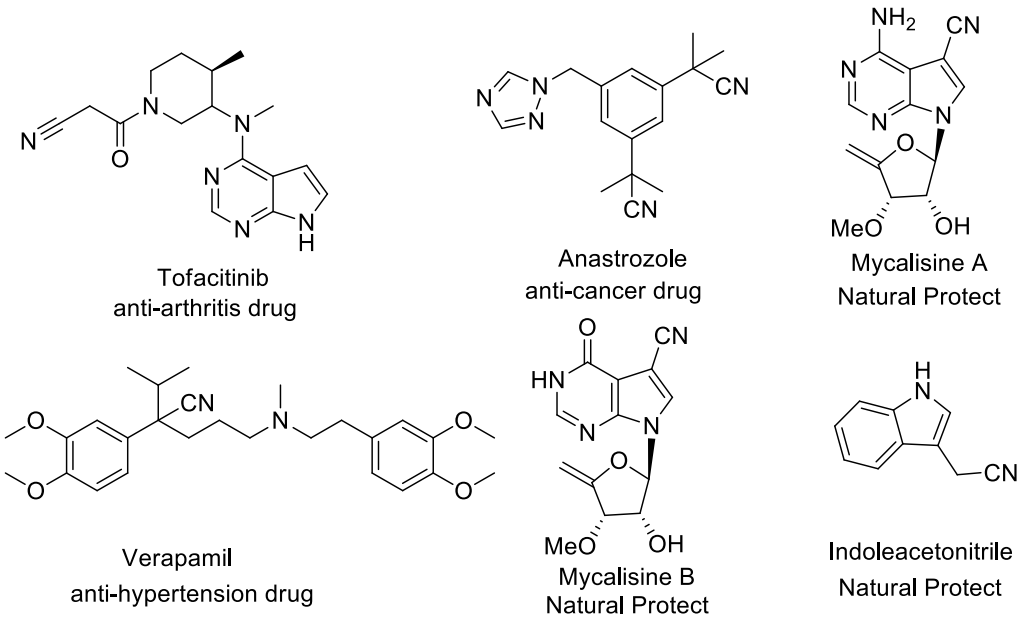


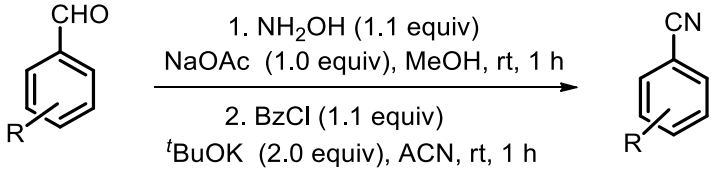
Figure 6.1: Nitrile groups on natural products and bioactive molecules

Considering the importance of nitrile groups in organic synthesis, numerous methods have been developed for their preparation.[5] The conventional approaches for synthesizing nitriles include Kolbe's nitrile synthesis, Sandmeyer reaction,

Rosenmund-von Braun reaction, dehydration of amides, cyanide-halide exchange reactions, etc.[6] However, this approach requires complex operations, toxic metal and metal-free reagents, harsh reaction conditions, etc. In this context, the synthesis of nitriles from aldehydes received considerable attention owing to their commercial availability and inexpensiveness.[7] A diverse range of nitrogen sources has been employed in the transformation of aldehydes into nitriles.[5,7] However, some of the developed methods under this approach suffer due to limited substrate scope, use of strong oxidants and metal catalysts, high reaction temperature, tedious operation procedure, low yields, and poor functional group tolerances. Therefore, the development of a new method for the direct synthesis of nitriles from aldehydes under mild reaction conditions is still desirable.

6.2 Designed Strategy

In this context, here we disclosed ^{t}BuOK-mediated one-pot synthesis of nitriles from aldehydes via the sequential addition of hydroxylamine and benzoyl chloride at room temperature. This method relies on the generation of aldoxime *in situ* from aldehyde, and the sequent transformation of aldoxime into the nitrile group using benzoyl chloride and potassium *tert*-butoxide at room temperature (Scheme 1).



Scheme 6.1: Synthesis of nitrile to aldehyde.

6.3 Experimental Section

General Information

Chemicals and solvents utilized for the organic reactions were procured from commercial sources and used as received. Substituted benzaldehyde, hydroxylamine, benzoyl chloride, acetonitrile, and bases were obtained from Sigma-Aldrich, and TCI. All the reactions were carried out in oven-dried glassware. The melting points of the isolated compounds were measured in open glass capillary tubes on "BUCHI

Labortechnik AG CH-9230". Nuclear magnetic resonance (NMR), ^{1}H, and ^{13}C spectra were recorded on JEOL ECX-400P NMR spectrometer with TMS as an internal standard. The splitting pattern of the peaks were described as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). The SAG reactions were carried out at room temperature.

General Procedure for the Synthesis of Compounds 2, 4

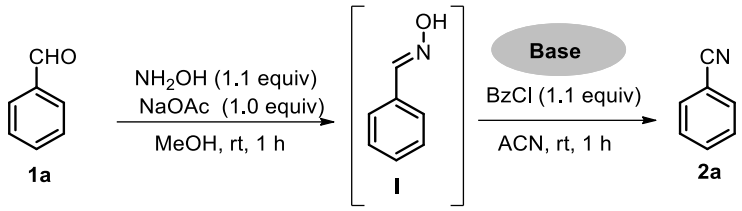
Methanol (2.0 mL) was added to 25 mL oven-dried round bottom flask containingbenzaldehyde (1.0 mmol, 1.0 equiv.), hydroxylamine hydrochloride (1.1 equiv.) and anhydrous sodium acetate (1.0 equiv.). The reaction was stirredat room temperature for 1 hour and the progress of the reaction was monitored by thin layer chromatography. After that, the methanol was removed under reduced pressure and co-evaporated with acetonitrile. To the concentrated round bottom flask,2.0 mL dry acetonitrile was addedfollowed by benzoyl chloride (1.1 equiv.) and potassium tert-butoxide. The resulting reaction mixture was further stirred for 1 hourat room temperature. The progress of the reaction was monitored by TLC analysis. After complete consumption of aldoxime, the reaction mixture was diluted with ethyl acetate (10 mL), washed with water andbrineand dried over Na_2SO_4. The organic layer was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel (100−200) (hexane: ethyl acetate; 95/05). The structure and purity of products were confirmed by comparison of their physical and spectral data (^{1}H NMR, ^{13}C NMR, and HRMS).

6.4 Results and Discussion

At the beginning, optimization of the reaction conditions was investigated using benzaldehyde as the model substrate. Initially, the benzaldehyde **1a** was converted into benzaldoxime **I** in the presence of hydroxylamine hydrochloride and sodium acetate in methanol. The reaction was carried out at room temperature for one hour to obtain quantitative yield aldoxime **I**. After that, the methanol was evaporated to dryness and the crude mixture was dissolved in acetonitrile. The resulting mixture was treated with benzoyl chloride (1.1 equiv.) followed by base (1.0 equiv.). Various organic and inorganic bases including Et_3N, DBU, DABCO, KOH, NaOH, K_2CO_3,

Cs_2CO_3, K_3PO_4, K_2HPO_4, ^tBuONa and ^tBuOK were investigated. The desired product **2a** was not obtained with Et_3N, DABCO, KOH, NaOH, K_2CO_3 and Cs_2CO_3. However, DBU, K_3PO_4 and K_2HPO_4 gave the product **2a** in 16-24% yields. On the other hand, sodium *tert*-butoxide gave the desired nitrile **2a** in 36% yield in 3 h while 46% was obtained with potassium *tert*-butoxide in 1 h. Further, we investigated the reaction with additional equiv. of potassium *tert*-butoxide. To our delight, the desired product **2a** was obtained in 78% yield with two equiv. of potassium *tert*-butoxide at room temperature. However, a further increase in the equiv. of potassium *tert*-butoxide did not improve the yield of the product.

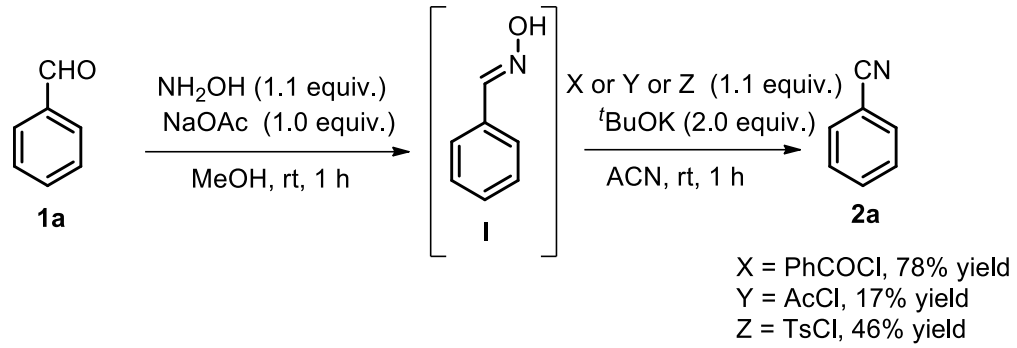
Table 6.1: Optimization of reaction conditions[a,b]



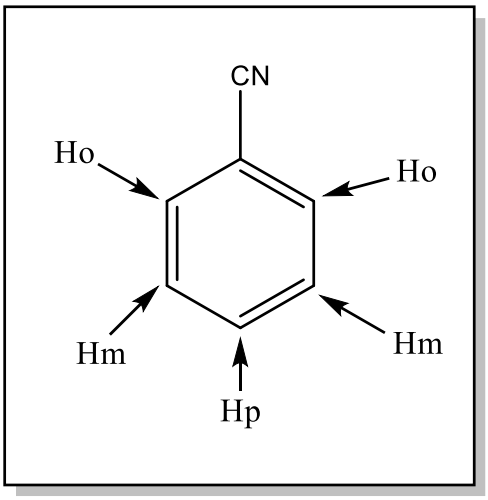
entry	base (equiv)	time(h)	yield (%)[b]2a
1	Et_3N	24	NR
2	DBU	24	16
3	DABCO	24	NR
4	KOH (1.0)	24	NR
5	NaOH (1.0)	24	NR
6	K_2CO_3 (1.0)	24	NR
7	Cs_2CO_3 (1.0)	24	NR
8	K_3PO_4 (1.0)	24	24
9	K_2HPO_4 (1.0)	24	20
10	^tBuONa (1.0)	3	36
11	^tBuOK (1.0)	1	46
12	**^tBuOK (2.0)**	**1**	**78**
13	^tBuOK (3.0)	1	76

[a]Reactions were performed using 1.0 mmol of 1a, 1.1 equiv of NH_2OH and 1.0 equiv of sodium acetate in 2.0 mL of methanol at rt. Then methanol was removed under reduced pressure. For the secondstep,reactions were carried out using 1.1 equiv of BzCl and 2.0 equivof base in 2.0mL of ACN at rt.[b]Isolated yield.

The optimization study was further continued by screening acyl chlorides in the presence of potassium *tert*-butoxide (Scheme 6.2). The reaction provided **2a** only in 17% yield when acetyl chloride was used instead of benzoyl chloride. On the other hand, the reaction with sulfonyl chloride gave the product in 46% yield, indicating the superiority of benzoyl chloride over other acyl chlorides. Reason of sulfonyl chloride gave low yield might be due to the potassium ion coordinate with nitrogen atom of imine and oxygen atom of carbonyl group, which accelerate the reaction.



Scheme 6.2: Screening of acyl chlorides.



Benzonitrile (2a)

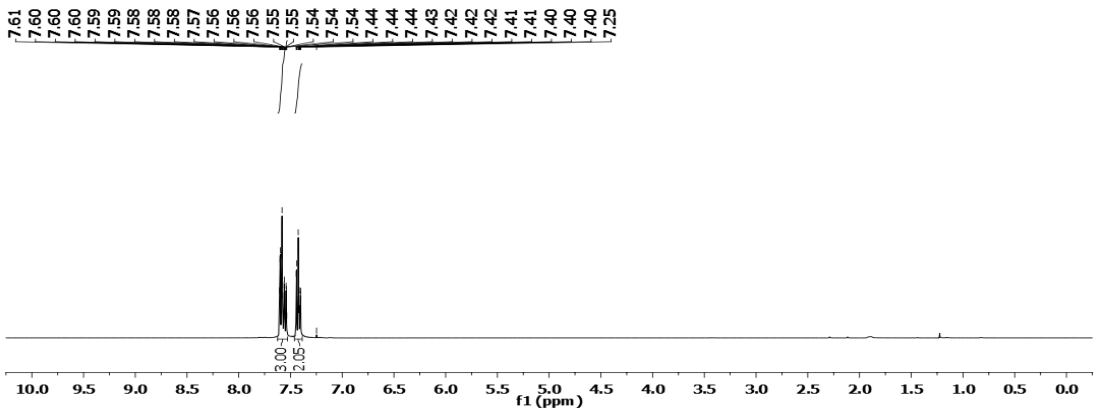
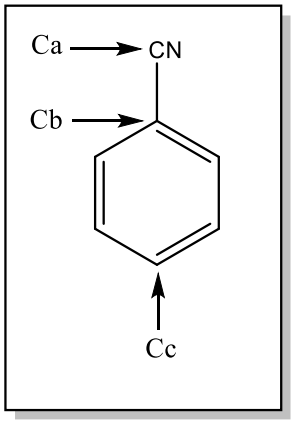


Figure 6.1a: ^{1}H NMR of benzonitrile (2a) in $CDCl_3$ at 400 MHz

In the ^{1}H NMR of **2a (Figure 6.1a)** in $CDCl_3$ at 400 MHz, ortho aromatic protons (Ho) shows chemical shift in the range from 7.61 to 7.55 ppm while meta and para aromatic protons (Hm and Hp) shows chemical shift in the range from 7.54 to 7.40 ppm.



Benzonitrile (2a)

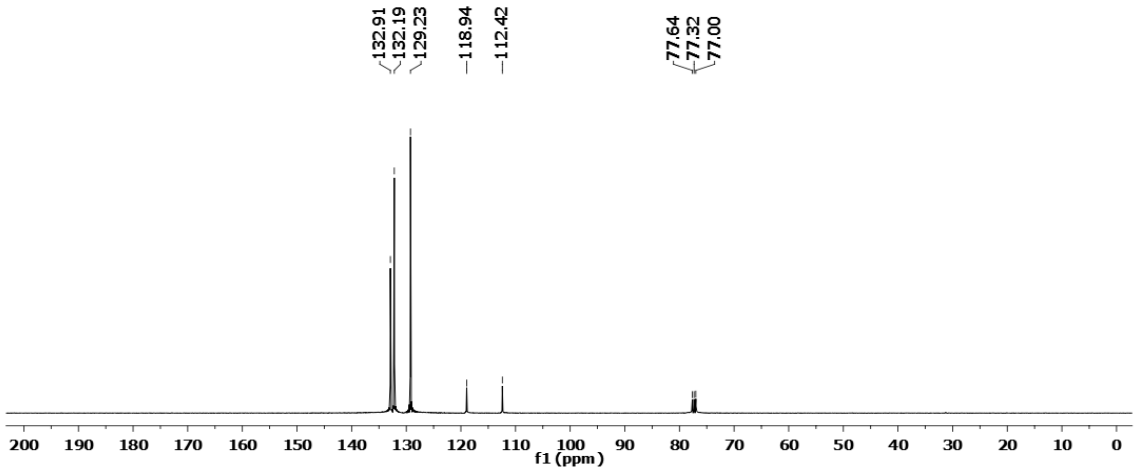
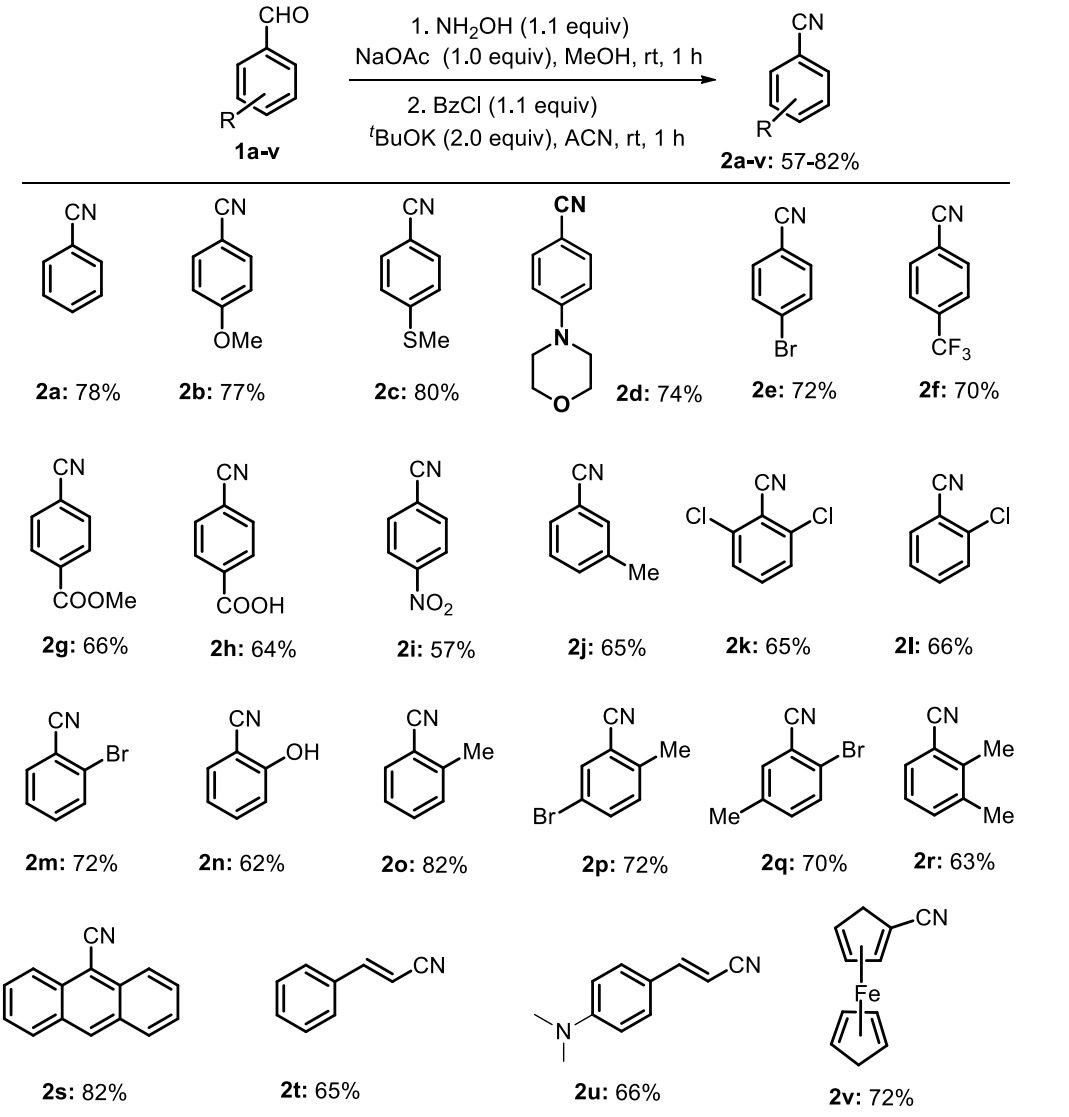


Figure 6.2: ^{13}C NMR of benzonitrile (2a) in $CDCl_3$ at 100 MHz

Similarly, in ^{13}C NMR spectrum of **2a (Figure 6.2)** in $CDCl_3$ at 100 MHz, characteristic peak of CN (Ca) appears at 118.9 ppm while peaks at 112.4 ppm and 132.9 ppm show the presence of carbon Cb and Cc respectively.

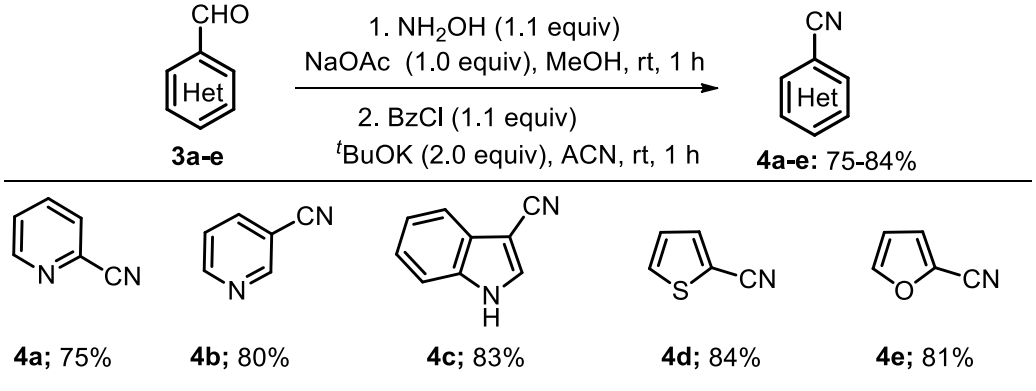
After identifying optimized reaction conditions (Table 6.1, entry 12),the scope of the methodology was studied using different aromatic, heteroaromatic, and vinyl aldehydes 1a-v (Scheme 3). Initially, aromatic aldehydes bearing functional groups at the *para*-position were investigated to understand the electronic effects of subtituents on the reaction progress.



Scheme 6.3: Scope for substituted aromatic and vinyl aldehydes.

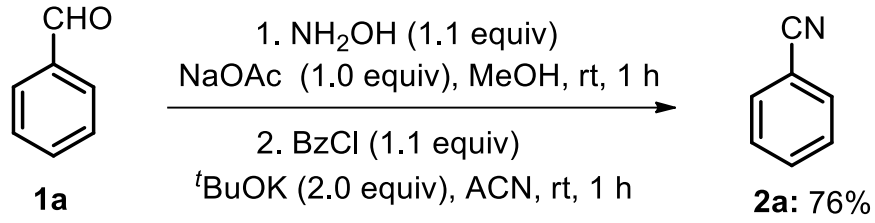
Benzaldehydes bearing electron-donating groups such as OMe and SCH_3 (**1b** and **1c**) gave the desired products **2b** and **2c** with yields of 77% and 80%, respectively. Notably, a heterocyclic compound such as morpholine functionalized benzaldehyde **1d** gave the desired product **2d** in 74% yield. On the other hand, halogens such as Br and CF_3 functionalized benzaldehydes **1e** and **1f** were successfully converted to corresponding nitriles **2e** and **2f** in 70% and 72% yields, respectively. Moreover, carboxylic esters and carboxylic acid functionalized benzaldehydes **1g** and **1h** delivered the desired products **2g** and **2h** in 66% and 64% yields, respectively. Interestingly, the strong electron deficient group such as NO_2-functionalized aldehyde **1i** gave the corresponding nitrile compound **2i** in 57% yield. On the other hand, the substrate bearing functional groups at the *meta*-position of benzaldehyde **1j** proceeded well under optimized reaction conditions to afford **2j** in 65% yields. Further, we investigated various aldehydes bearing Cl, Br, OH and Me substituents at the *ortho*-position (**1k-r)**. These substrates successfully converted into corresponding nitriles **2k-r** with 62-82% yields. Notably, 1-naphthylbenzaldehyde **1s**, cinnamaldehyde **1t**, and dimethylamino cinnamaldehyde **1u** also gave desired products **2s-u** in 65-82% yields under the optimized conditions. More interestingly, the inorganic compound, ferrocene carboxaldehyde **1v** was successfully converted into **2v** in 72% yield.

Considering the important role of heterocyclic scaffolds in medicinal and pharmaceutical chemistry, we further examined the transformation of heteroaromatic aldehydes into corresponding nitriles (Scheme 4). A range of nitrogen, sulfur and oxygen-containing heteroaromatic aldehydes **3a-e** weresmoothly converted into the corresponding nitriles **4a-e** in 75-84% yields.



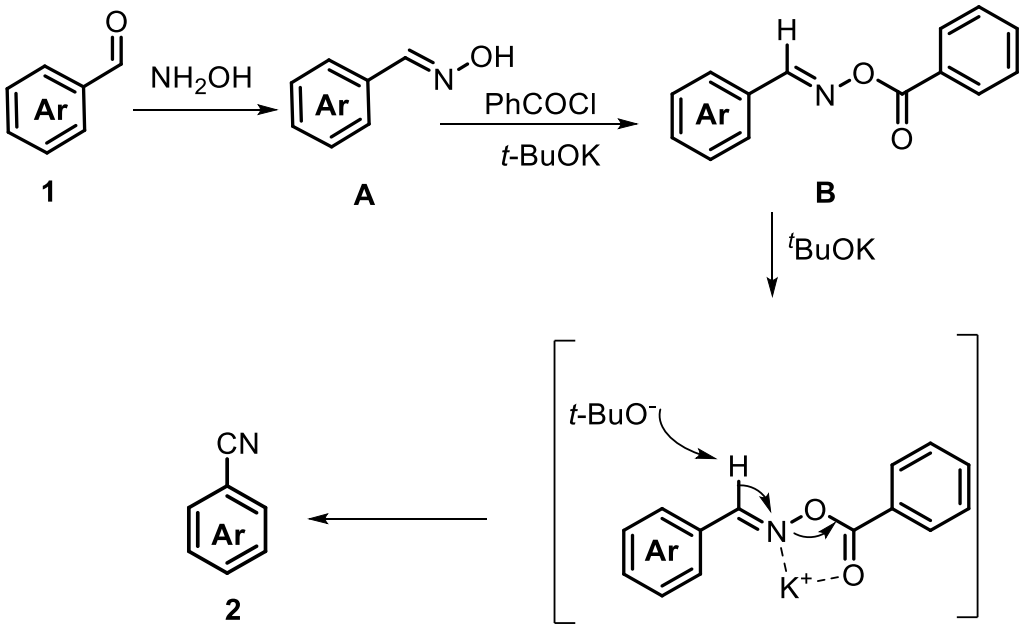
Scheme 6.4: Scope for substituted heteroaromatic aldehydes.

To demonstrate the practicality of the protocol, a gram-scale reaction was performed using model substrate **1a** under the optimized reaction conditions (Scheme 6.5). The reaction proceeded very well to give the product **2a** in 76% yield.



Scheme 6.5: Gram-scale synthesis.

Based on the observed results and the available literature,[5-8] a plausible mechanism for the reaction has been proposed as shown in Scheme 6.6. Initially, aldehyde **1** reacts with hydroxylamine to afford the aldoxime **A**. *O*-Acylation of aldoxime **A** in the presence of benzoyl chloride and ^{t}BuOK leads to the formation of compound **B.** The intermediate **B** is converted into desired compound **2** in the presence of ^{t}BuOK via an elimination reaction.



Scheme 6.6: Proposed reaction mechanism.

Spectroscopic Data

Benzonitrile **(2a)**.[9]Colorless liquid (80 mg, 78%);^{1}H NMR (400 MHz, $CDCl_3$)δ 7.62 – 7.53 (m,3H), 7.46 – 7.39 (m,2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 132.9, 132.2, 129.2, 118.9, 112.4; (Figure 6.3) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_7H_6N104.0495; found 104.0498.

4-Methoxybenzonitrile **(2b).**[9]White solid (102mg, 77%): mp 58–60 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.53 (m,2H), 6.96 – 6.90 (m,2H), 3.84 (s,3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.9, 134.1, 119.3, 114.8, 104.0, 55.6; (Figure 6.4) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_8H_8NO 134.0600; found 134.0601.

4-(methylthio)benzonitrile **(2c).**[10]Brown solid (119 mg, 80%): mp62-64 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.47 (m,2H), 7.25 – 7.20 (m,2H), 2.49 – 2.47 (m,3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2 , 132.2, 125.5, 119.1, 107.7, 14.8; (Figure 6.5) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_8H_8NS150.0372; found 150.0376.

4-Morpholinobenzonitrile **(2d).**[10]White solid (139 mg, 74%): mp 84–86 °C;^{1}H NMR (400 MHz$CDCl_3$) δ 7.55 – 7.46 (m,1H), 6.88 – 6.81 (m,1H), 3.84 (dd, *J*= 9.5, 4.6 Hz,2H), 3.30 – 3.21 (m,2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 133.6, 120.0, 114.1, 101.00, 66.5, 47.3; (Figure 6.6) HRMS (ESI) m/z: $[M+H]^+$ Calcd. for $C_{11}H_{13}N_2O$ 189.1022; found 189.1017.

4-Bromobenzonitrile **(2e)**.[9]Light yellow solid (131 mg, 72%): mp 54-56 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.60 (m,2H), 7.54 – 7.49 (m,2H). ^{13}C NMR (101 MHz, $CDCl_3$) NMR (101 MHz,) δ 133.5, 132.7, 128.1, 118.2, 111.3; (Figure 6.7) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_7H_5BrN 183.9600; found 183.9610.

4-(trifluoromethyl)benzonitrile **(2f).**[11]Semi solid (119 mg, 70%);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.72 (m,4H).^{13}C NMR (101 MHz, $CDCl_3$) δ 135.1, 134.8, 134.5, 134.1, 132.8, 127.2, 126.3, 126.3, 126.3, 126.2, 124.5, 121.8, 119.0, 117.6, 116.1; (Figure 6.8) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_8H_5F_3N$172.0369; found 172.0372.

Methyl 4-cyanobenzoate **(2g).**[9]Off white solid (106 mg, 66%): mp 67-69 °C; ^{1}H NMR (400 MHz, $CDCl_3$)δ 8.12 (dt, *J* = 3.7, 1.6 Hz,2H), 7.73 (dt, *J* = 3.7, 1.5 Hz,2H), 3.94

(s,3H).[13]C NMR (101 MHz, $CDCl_3$) δ 165.5, 134.0, 132.3 , 130.2, 118.0, 116.5, 52.8; (Figure 6.9) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_9H_8NO_2$162.0550; found 162.0559.

4-cyanobenzoic acid **(2h).**[9]White solid (94 mg, 64%): mp218–220 °C; [1]H NMR (400 MHz, $CDCl_3$)δ 8.21 (dt, *J* = 3.6, 1.5 Hz,2H), 7.86 – 7.71 (m,2H).[13]C NMR (101 MHz, $CDCl_3$) δ 169.4, 133.0, 132.4, 130.8, 117.9, 117.4; (Figure 6.10) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_8H_6NO_2$148.0393; found 148.0397.

4-Nitrobenzonitrile **(2i).**[9]Light Yellow solid (84 mg, 57%): mp 144–146 °C;[1]H NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.30 (m,2H), 7.92 – 7.84 (m,2H).[13]C NMR (101 MHz, $CDCl_3$) δ 150.1 (s), 133.6, 124.4, 118.4, 116.9; (Figure 6.11) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_7H_5N_2O_2$149.0346; found 149.0352.

3-Methylbenzonitrile **(2j).**[12]Pale yellow liquid (76 mg, 65%);[1]H NMR (400 MHz, $CDCl_3$)δ 7.41 – 7.33 (m,3H), 7.32 – 7.27 (m,1H), 2.34 – 2.31 (m,3H). [13]C NMR (101 MHz, $CDCl_3$) δ 139.3, 133.8, 132.5, 129.3, 129.1, 119.1, 112.2, 21.8.; (Figure 6.12) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_8H_8N118.0651; found 118.0658.

2,6-Dichlorobenzonitrile **(2k).**[9]White solid (112 mg, 65%): mp 144–146 °C;[1]H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.41 (m,1H), 7.49 – 7.40 (m,1H), 7.49 – 7.39 (m,1H).[13]C NMR (101 MHz, $CDCl_3$) δ 138.6, 133.9, 128.2, 114.5, 113.4; (Figure 6.13) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_7H_4Cl_2N$171.9715; found 171.9708.

2-Chlorobenzonitrile ***(2l).***[13]Light-yellow solid (91 mg, 66%): mp 44–46 °C; [1]H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.63 (m,1H), 7.56 – 7.47 (m,2H), 7.39 – 7.33 (m,1H). [13]C NMR (101 MHz, $CDCl_3$) δ 136.9, 134.10, 134.03,130.1, 127.3, 116.1, 113.4; (Figure 6.14) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_7H_5ClN138.0105; found 138.0111.

2-Bromobenzonitrile **(2m).**[9]White solid (131 mg, 72%): mp 52–54 °C; [1]H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.60 (m,2H), 7.48 – 7.38 (m,2H). [13]C NMR (101 MHz, $CDCl_3$)δ 134.4, 134.0, 133.3, 127.8, 125.4, 117.2, 115.9; (Figure 6.15) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_7H_5BrN181.9600; found 181.9608.

*2-Hydroxybenzonitrile***(2n).**[14]Brown solid (74 mg, 62%): mp 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.41 (m,2H), 7.22 (d, *J* = 19.3 Hz,1H), 7.03 (d, *J* = 8.3 Hz,1H), 6.98 – 6.91 (m,1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 134.1, 133.1, 120.9, 116.7, 116.6, 99.3; (Figure 6.16) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_7H_6NO120.0444; found 120.0438.

*2-Methylbenzonitrile***(2o).**[12]Colourless liquid (96 mg, 82%); ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.58 (dd, *J* = 7.7, 1.2 Hz,1H), 7.46 (td, *J* = 7.7, 1.4 Hz,1H), 7.33 – 7.23 (m,2H), 2.53 (s,3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 142.0, 132.7, 132.6, 130.3, 126.3, 118.3, 112.8, 20.6; (Figure 6.17) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_8H_8N118.0651; found 118.0656.

*5-Bromo-2-Methylbenzonitrile***(2p).**[18]Light Orange solid (141 mg, 72%): mp 47–49 °C; ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.70 (d, *J* = 2.1 Hz,1H), 7.58 (dd, *J* = 8.3, 2.1 Hz,1H), 7.18 (d, *J* = 8.3 Hz,1H), 2.49 (s,3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1, 135.9, 134.9, 131.9, 119.4, 116.7, 114.7, 20.1; (Figure 6.18) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C8H7BrN195.9756; found 195.9762.

*2-Bromo-5-Methylbenzonitrile***(2q).**[19]Light yellow solid (137 mg, 70%): mp 64–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.3 Hz,1H), 7.44 (d, *J* = 2.2 Hz,1H), 7.27 – 7.22 (m,1H), 2.33 (s,3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 135.0, 134.7, 132.0, 121.9, 117.4, 115.6, 20.8; (Figure 6.19) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_8H_7BrN195.9756; found 195.9762.

2,3-Dimethylbenzonitrile **(2r).**[20]Light yellow liquid (83 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.7 Hz,1H), 7.33 (d, *J* = 7.5 Hz,1H), 7.15 (t, *J* = 7.7 Hz,1H), 2.45 (s,3H), 2.30 (s,3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 138.0, 134.1, 130.4, 118.9, 113.1, 20.2, 18.0; (Figure 6.20) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_9H_{10}N$132.0808; found 132.0801.

*Anthracene-9-carbonitrile(***2s).**[18]Light yellow solid (167 mg, 82%): mp 176–178 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s,1H), 8.39 (dd, *J* = 8.7, 0.8 Hz,2H), 8.04 (d, *J* = 8.5 Hz,2H), 7.76 – 7.64 (m,2H), 7.61 – 7.53 (m,2H).^{13}C NMR (101 MHz,

$CDCl_3$)δ 133.4, 132.8, 130.7, 128.0, 128.9, 126.5, 125.4, 117.3, 105.5; (Figure 6.21) HRMS (ESI) m/z:$[M+H]^+$Calcd. for $C_{15}H_{10}N$204.0808;found 204.0814.

*Cinnamonitrile***(2t).**[11]Semi solid (103 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.31 (m,5H), 7.31 – 7.10 (m,1H), 5.88 (d, *J* = 16.7 Hz,1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 133.6, 131.3, 129.2, 127.5, 118.3, 96.4; (Figure 6.22) HRMS (ESI) m/z: $[M+H]^+$Calcd. for C_9H_8N130.0651; found 130.0655.

*4-dimethylamino Cinnamonitrile***(2u).**[19]Brown solid (114 mg, 66%): mp 166-168 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.22 (m,3H), 6.69 – 6.60 (m,2H), 5.56 (d, *J* = 16.5 Hz,1H), 3.02 (s,6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 150.7, 129.1, 121.5, 119.9, 111.7, 89.5, 40.2; (Figure 6.23) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{11}H_{13}N_2$173.1073; found 173.1079.

*Cyanoferrocene***(2v).** [20]Brown solid (152 mg, 72%): mp 107–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 – 4.63 (m.2H), 4.39 – 4.37 (m,2H), 4.33 (s,5H).^{13}C NMR (101 MHz, $CDCl_3$) δ 120.4, 71.8, 70.8, 70.7, 51.9; (Figure 6.24) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_{11}H_{10}FeN$ 212.0157; found 212.0149.

*Picolinonitrile***(4a).**[9]Semi solid (78 mg, 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (ddd, *J* = 3.1, 2.5, 1.6 Hz,1H), 7.79 (tt, *J* = 7.8, 1.5 Hz,1H), 7.68 – 7.58 (m,1H), 7.53 – 7.41 (m,1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 137.4, 133.7, 128.7, 127.3, 117.4; (Figure 6.25) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_6H_5N_2$105.0447; found 105.0442.

*Nicotinonitrile***(4b).**[21]White solid (83 mg, 80%):mp 48–52; °C^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (ddd, *J* = 6.7, 3.5, 1.2 Hz,2H), 8.03 – 7.87 (m,1H), 7.43 (ddd, *J* = 8.0, 5.0, 0.9 Hz,1H).^{13}C NMR (101 MHz, $CDCl_3$)δ 153.1, 152.6, 139.4, 123.7, 116.6, 110.2; (Figure 6.26) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_6H_5N_2$105.0447; found 105.0453.

*1H-indole-3-carbonitrile***(4c).**[11]White solid (118 mg, 83%): mp 179–182 °C;^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s,1H), 8.22 (s,1H), 7.64 – 7.49 (m,2H), 7.22 (dddd, *J* = 8.9, 8.2, 7.1, 1.2 Hz,2H).^{13}C NMR (101 MHz, DMSO-d_6) δ 135.7, 135.1, 127.2, 123.9, 122.2, 118.9, 116.0, 113.5, 84.7; (Figure 6.27) HRMS (ESI) m/z: $[M+H]^+$Calcd. for $C_9H_7N_2$143.0604; found 143.0611.

*Thiophene-2-carbonitrile***(4d).**[9]White solid (92 mg, 84%): mp128–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (ddd, *J* = 6.2, 4.4, 1.2 Hz,2H), 7.12 (dd, *J* = 5.1, 3.8 Hz,1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 137.6, 132.7, 127.8, 114.4, 109.9; (Figure 6.28) HRMS (ESI) m/z: $[M+H]^+$ Calcd. for C_5H_4NS110.0059; found 110.0064.

*Furan-2-carbonitrile****(4e).***[21]white solid (75 mg, 81%): mp 147–149 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.56 (m,1H), 7.11 – 7.08 (m,1H), 6.54 – 6.51 (m,1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ147.5, 126.3, 122.2, 111.6; (Figure 6.29) HRMS (ESI) m/z: $[M+H]^+$ Calcd. for C_5H_4NO94.0287; found 94.0292.

6.5 Conclusion

An efficient base-mediated a direct synthesis of aromatic and heteroaromatic nitriles from corresponding aldehydes was reported. As the starting ingredients for the synthesis, aldehyde, and hydroxylamine were combined with benzoyl chloride in a series of reactions. Notably, this process may be carried out at room temperature without the need for transition metal catalysts, making it a practical and effective process. A wide variety of aromatic and heteroaromatic aldehydes gave the products in good to excellent yields. Broad substrate scope, easy operation, quick reactions, tolerance of different functional groups, and room temperature reactions are the important features of the developed methodology.

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Chapter – 7

Summary and Future Prospects

CHAPTER – 7

SUMMARY AND FUTURE PROSPECTS

- An efficient metal-free protocol for the synthesis of Nitro Substituted quinolinamines through regeoseletive annulation of 2-(akynyl)nicotinonitriles with nitromethane in excellent yields(upto 99%). The designed strategy, late-stage modification of various bioactive molecules was carried out successfully to synthesize various biactive molecules containing nitroquinolinamines in good yields.

- This study disclosed transition-metal-free synthesis of novel nitroacridinamines, nitrobenzo[*c*]acridinamines. This transformation is compatible with aliphatic, aromatic as well as heteroaromatic functionalities on alkynes. The chemistry is general and expected to find wide application in diverse fields of organic synthesis.

- We have also developed an efficient and operationally simple approach for the synthesis of differently substituted N-acetamides in good yields using readily available and cheap anilines/amines and acetonitrile. Acetonitrile here acts as an acyl equivalent as well as solvent. Apart from acetonitrile, 2,2,2-trifluoroacetonitrile could also be used in the reaction as an acyl surrogate.

- A base-mediated direct synthesis of aromatic and heteroaromatic nitriles from corresponding aldehydes has been established reported. As the starting ingredients for the synthesis, aldehyde, and hydroxylamine were combined with benzoyl chloride in a series of reactions. Notably, this process may be carried out at room temperature without the need for transition metal catalysts, making it a practical and effective process.

- All the presented protocols for the metal free synthesis of avoids the use of expensive catalysts and ligands. Based on this we could develop more efficient routes for the construction of more challenging molecular complexities.

- Broad substrate scope, easy operation, quick reactions, tolerance of different functional groups, reactions are the important features of all developed methodology.

- In Future, our synthesized compound can be explored biological activities such as anti-inflammatory, antifungal, antimalarial, antibacterial, antiviral, antitumor, and antilukemic effects within various field of organic synthesis.

Appendix

APPENDIX

- **Nuclear Magnetic Resonance (NMR)**

Nuclear Magnetic Resonance (NMR) is a powerful analytical technique used to determine the structure, dynamics, reaction state, and chemical environment of molecules. It exploits the magnetic properties of certain atomic nuclei. When a sample is placed in a strong magnetic field, the nuclei of specific isotopes (like ^{1}H, ^{13}C, ^{15}N, and ^{31}P) resonate at characteristic frequencies when exposed to a radiofrequency (RF) pulse. By analyzing these resonances, it is possible to infer molecular structures and interactions.

- **Common NMR Techniques**

1. **^{1}H-NMR (Proton NMR)**: Focuses on hydrogen atoms (protons). It provides information on the number of hydrogen atoms in different chemical environments and their connectivity.
2. **^{13}C-NMR (Carbon-13 NMR)**: Used for analyzing carbon atoms in a molecule. Since ^{13}C is less abundant (about 1%), ^{13}C-NMR is less sensitive but provides detailed information on the carbon skeleton of molecules.
3. **^{19}F-NMR (Fluorine-19 Nuclear Magnetic Resonance):** It is an NMR technique that focuses on detecting the fluorine-19 isotope. With 100% natural abundance and a high sensitivity similar to proton (^{1}H) NMR, ^{19}F-NMR is a powerful tool for studying fluorine-containing compounds.

NMR protocols begin with dissolving the sample in a deuterated solvent, such as D_2O or $CDCl_3$, to prevent interference from solvent peaks, with typical concentrations ranging from 1-10 mg/mL depending on the nuclei's sensitivity. The sample is then placed in a strong magnetic field to align nuclear spins. A short radiofrequency (RF) pulse disturbs the aligned spins, and as the nuclei return to equilibrium, they emit energy that is detected as the NMR signal. The emitted signals are collected and processed into spectra, representing chemical shifts and coupling constants, which are then analyzed to deduce molecular structure and bonding.

- **Advantages of NMR**

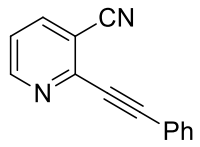
1. **Non-destructive**: NMR analysis does not damage or alter the sample, making it ideal for studying biological and synthetic compounds.
2. **Detailed Structural Information**: NMR gives comprehensive information about molecular structure, including functional groups, molecular symmetry, and 3D configurations.
3. **Quantitative Analysis**: NMR can quantify the number of nuclei in different environments, which is useful for determining compound purity and concentration.
4. **Versatile**: It can be used for both small organic molecules and large biological macromolecules, including proteins and nucleic acids.
5. **No Special Labeling Needed**: Unlike some techniques, NMR does not require radioactive or fluorescent labeling.

- **Limitations of NMR**

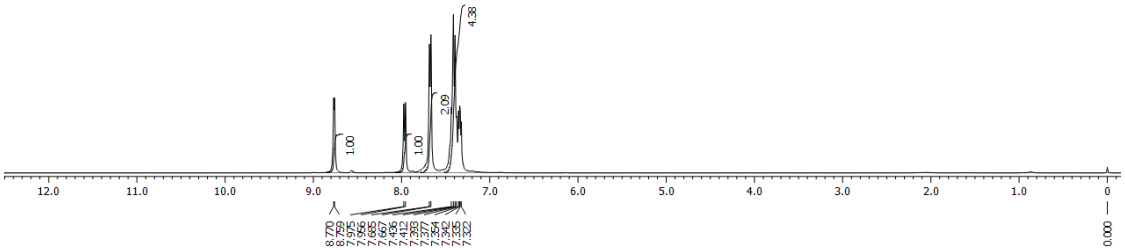
1. **Low Sensitivity**: NMR is relatively insensitive compared to techniques like mass spectrometry. This is particularly true for nuclei with low natural abundance (e.g., ^{13}C, ^{15}N).
2. **High Sample Concentration Required**: NMR generally requires higher concentrations of the sample (typically in milligrams), which may not always be feasible for limited samples.
3. **Expensive Equipment**: NMR instruments are costly to purchase and maintain due to the need for strong superconducting magnets and liquid helium.
4. **Time-Consuming**: Some NMR experiments, especially 2D or 3D NMR for macromolecules, can be time-intensive, requiring hours to days of data collection.
5. **Limited for Complex Mixtures**: While NMR can provide detailed information on pure compounds, complex mixtures or overlapping peaks can make interpretation difficult without extensive deconvolution methods.

Appendix – A
^{1}H NMR, ^{13}C NMR and HRMS Spectra of Chapter 3

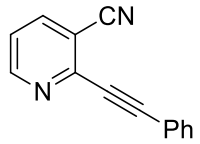
^{1}H NMR



2-(Phenylethynyl)nicotinonitrile (1a)



^{13}C NMR



2-(Phenylethynyl)nicotinonitrile(1a)

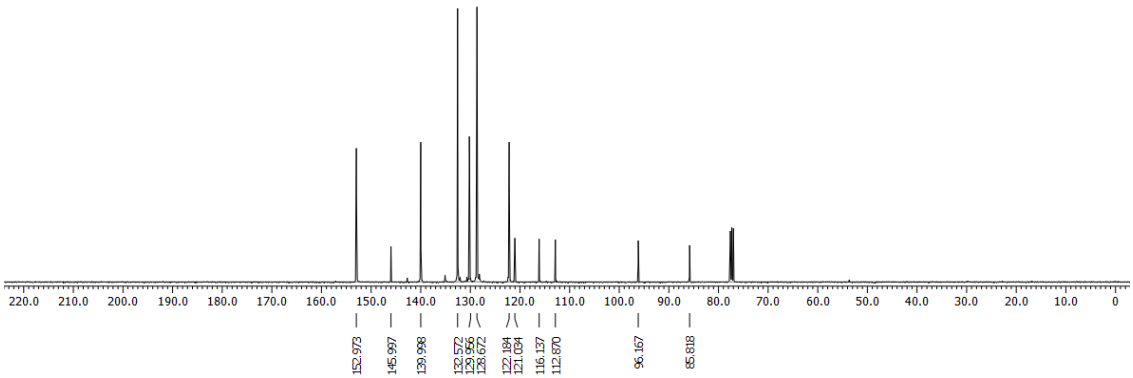
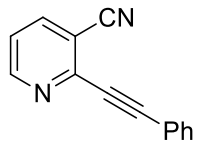


Figure 3.4

HRMS



2-(Phenylethynyl)nicotinonitrile(1a)

Qualitative Compound Report

Data File	SV-699.d	**Sample Name**	SV-699
Sample Type	Sample	**Position**	P1-D7
Instrument Name	Instrument 1	**User Name**	
Acq Method	Damo JK.m	**Acquired Time**	07-05-2019 16:47:11
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

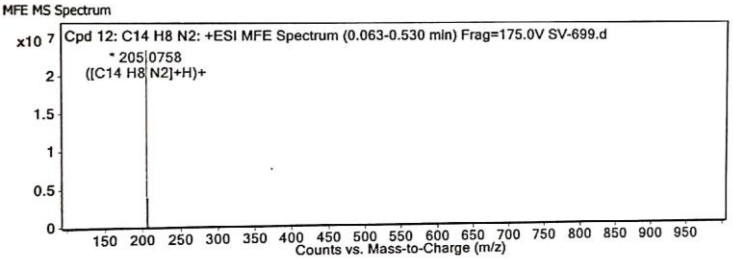
Sample Group **Info.**
Acquisition SW 6200 series TOF/6500 series
Version Q-TOF B.05.01 (B5125.1)

Compound Table

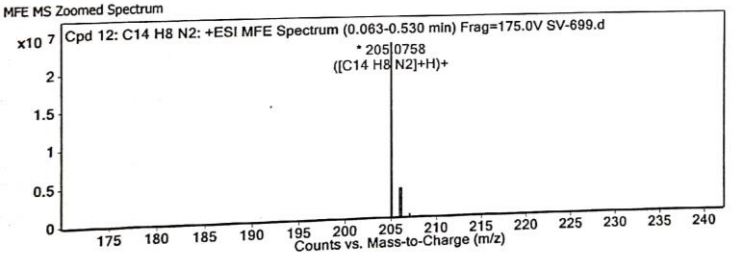
Compound Label	RT	Mass	Formula	MFG Formula	MFG Diff (ppm)	DB Formula
Cpd 12: C14 H8 N2	0.136	204.0686	C14 H8 N2	C14 H8 N2	0.92	C14 H8 N2

Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 12: C14 H8 N2	205.0758	0.136	Find by Molecular Feature	204.0686

MFE MS Spectrum



MFE MS Zoomed Spectrum



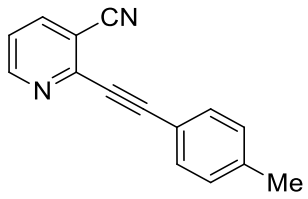
MS Spectrum Peak List

m/z	z	Abund	Formula	Ion
205.0758	1	23471526	C14 H8 N2	(M+H)+
206.0791	1	3852442.65	C14 H8 N2	(M+H)+
207.0822	1	278191.6	C14 H8 N2	(M+H)+

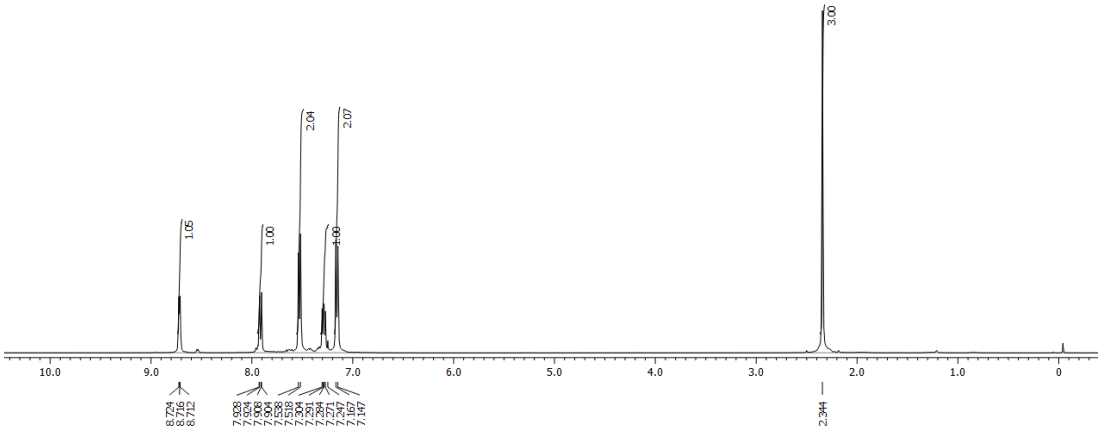
--- End Of Report ---

Figure 3.5

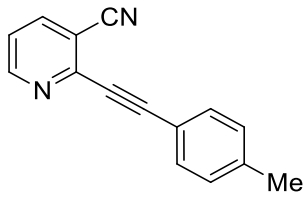
^{1}H NMR



2-(*p*-Tolylethynyl)nicotinonitrile(1b)



^{13}C NMR



2-(*p*-Tolylethynyl)nicotinonitrile(1b)

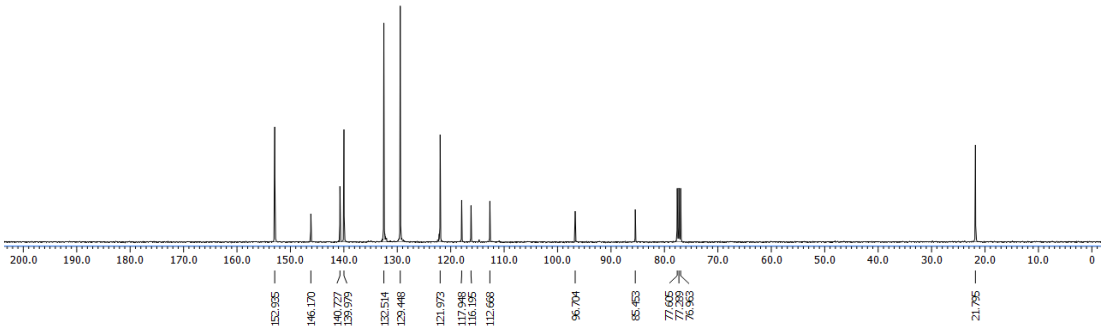
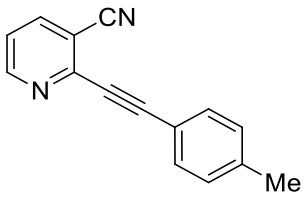


Figure 3.6

HRMS



2-(*p*-Tolylethynyl)nicotinonitrile(1b)

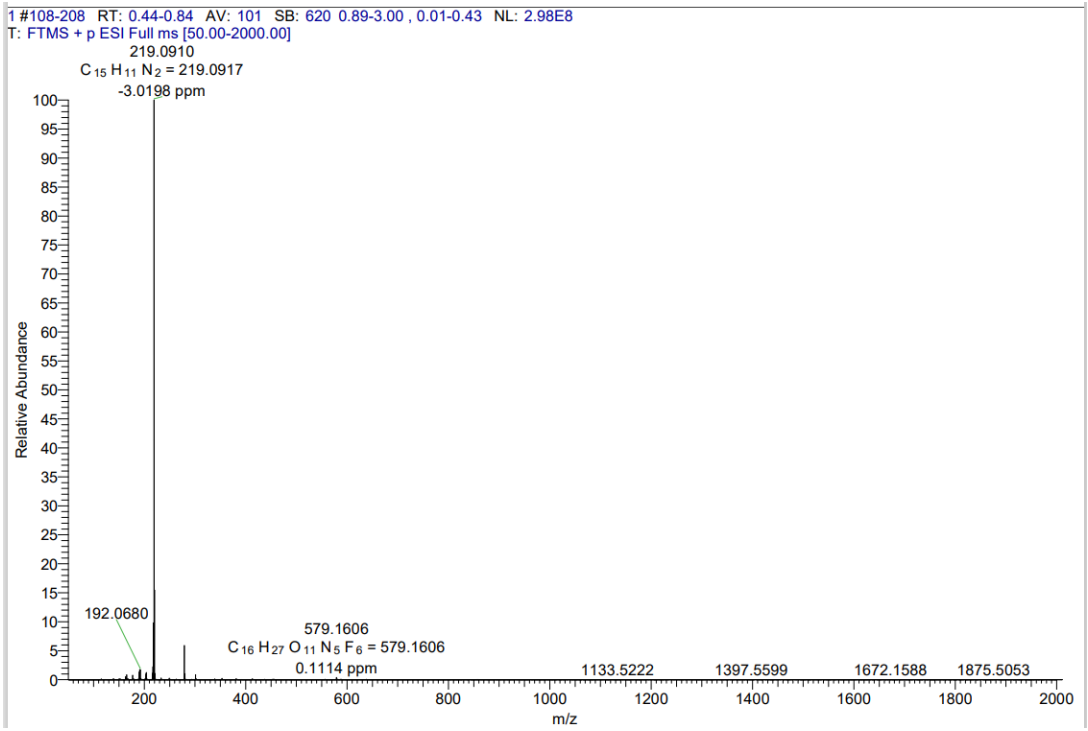
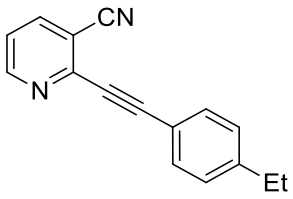
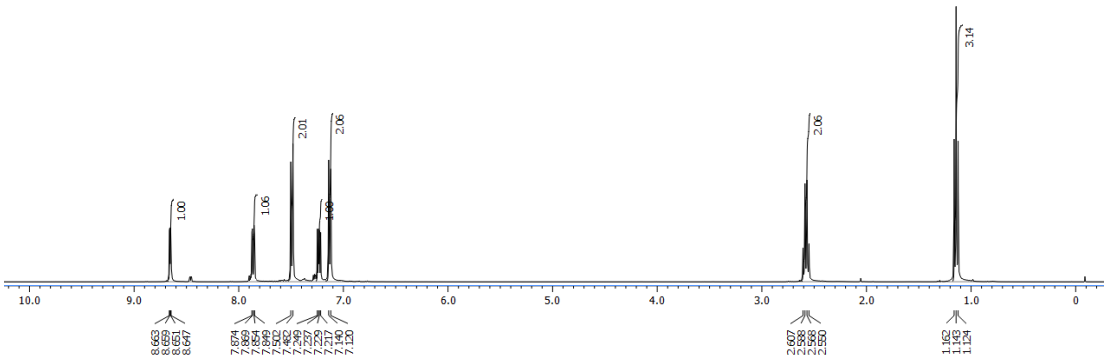


Figure 3.7

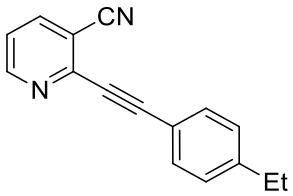
^{1}H NMR



2-((4-Ethylphenyl)ethynyl)nicotinonitrile (1c)



^{13}C NMR



2-((4-Ethylphenyl)ethynyl)nicotinonitrile (1c)

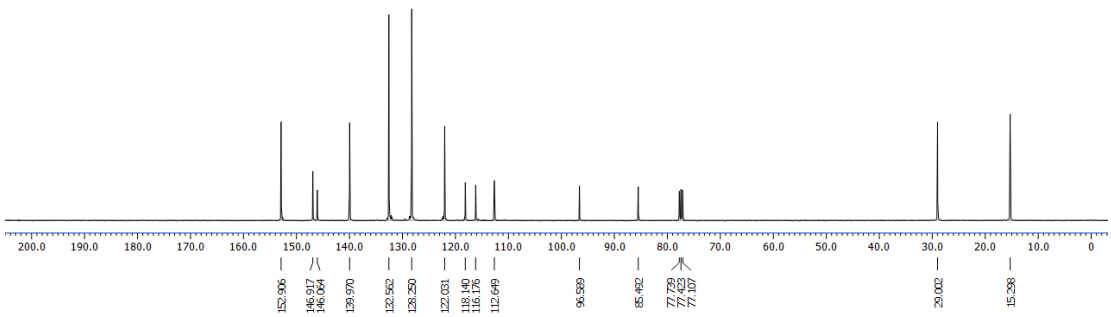
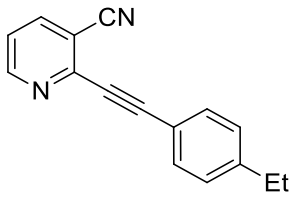


Figure 3.8

HRMS



2-((4-Ethylphenyl)ethynyl)nicotinonitrile (1c)

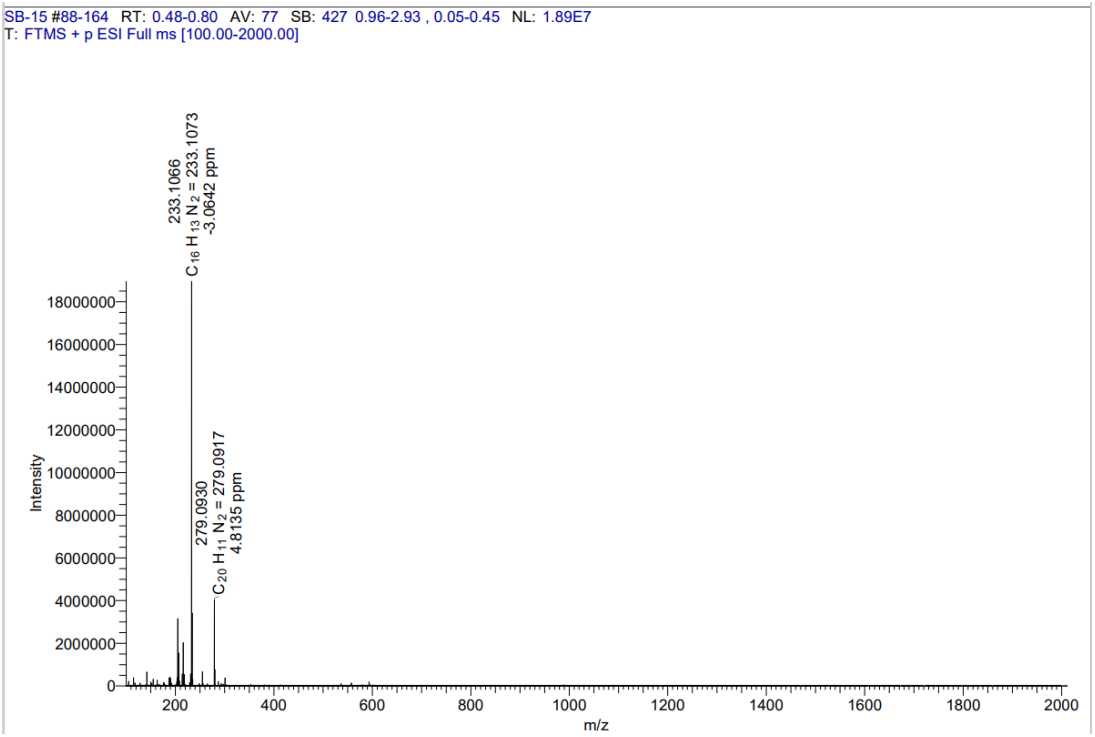
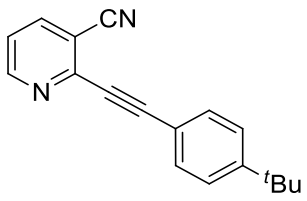
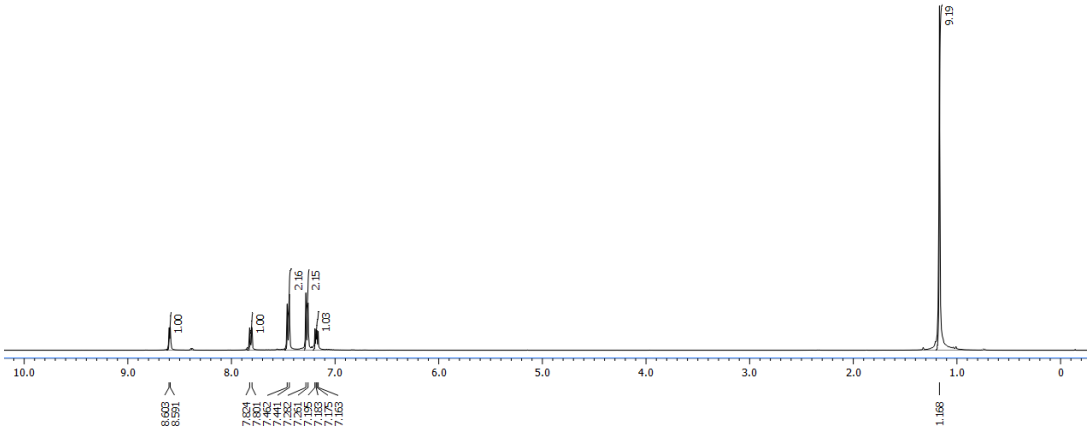


Figure 3.9

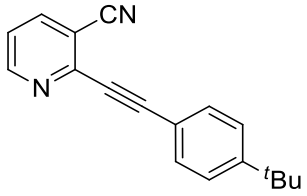
^{1}H NMR



2-((4-(*tert*-Butyl)phenyl)ethynyl)nicotinonitrile(1d)



^{13}C NMR



2-((4-(*tert*-Butyl)phenyl)ethynyl)nicotinonitrile(1d)

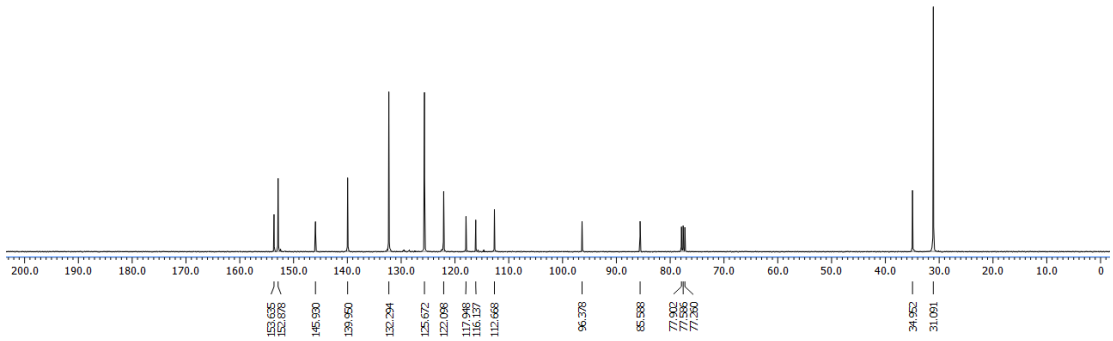
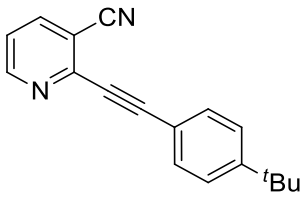


Figure 3.10

HRMS



2-((4-(*tert*-Butyl)phenyl)ethynyl)nicotinonitrile(1d)

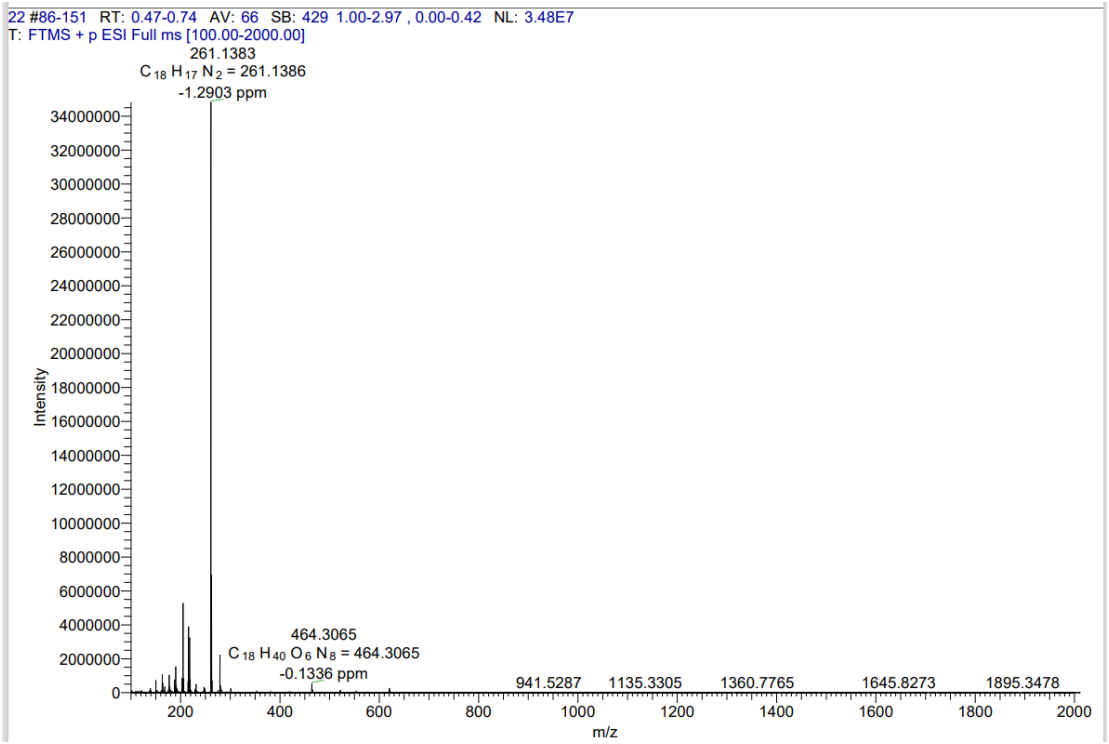
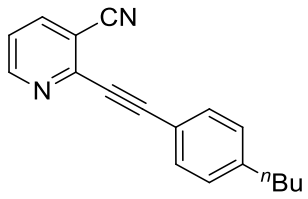
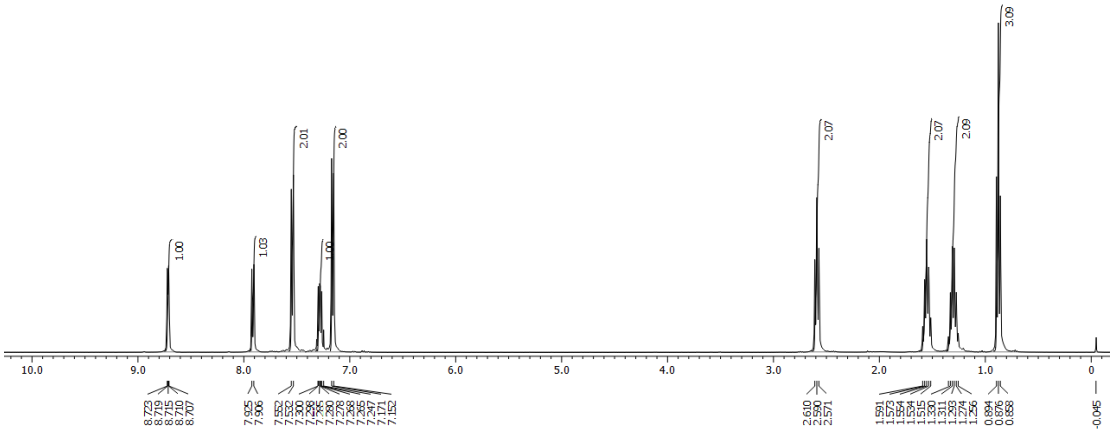


Figure 3.11

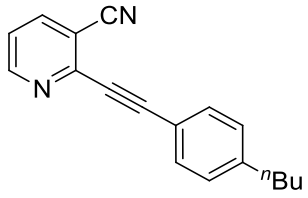
^{1}H NMR



2-((4-Butylphenyl)ethynyl)nicotinonitrile(1e)



^{13}C NMR



2-((4-Butylphenyl)ethynyl)nicotinonitrile(1e)

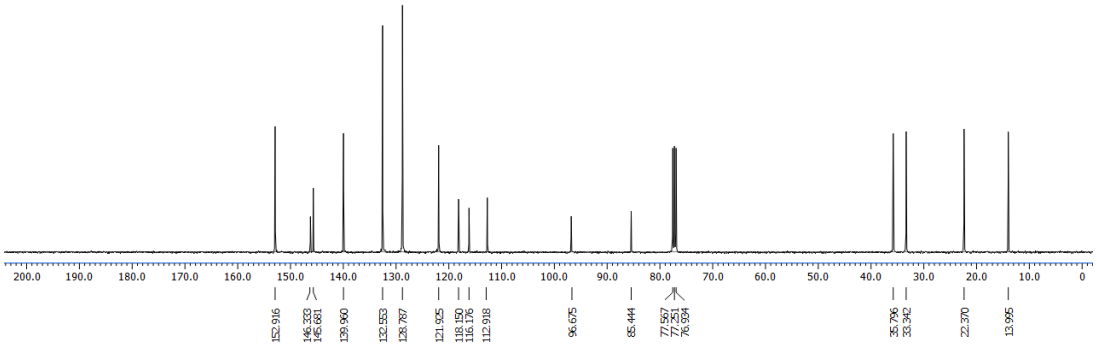
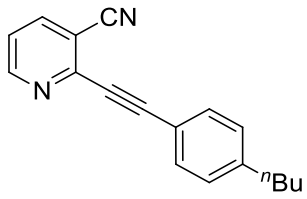


Figure 3.12

HRMS



2-((4-Butylphenyl)ethynyl)nicotinonitrile(1e)

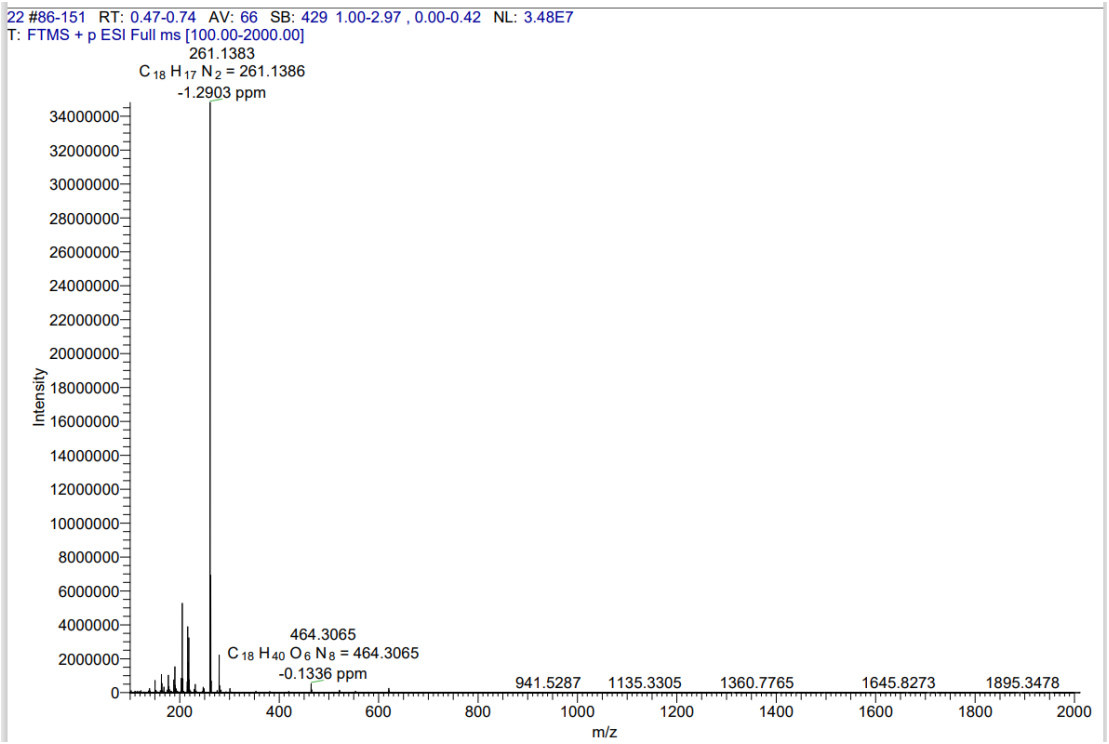
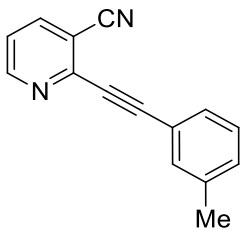
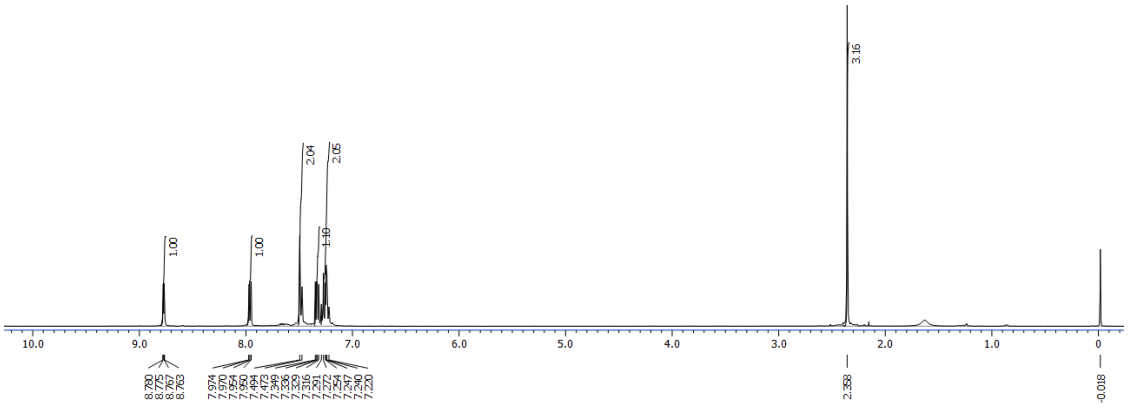


Figure 3.13

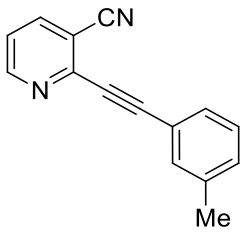
^{1}H NMR



2-(*m*-Tolylethynyl)nicotinonitrile(1f)



^{13}C NMR



2-(*m*-Tolylethynyl)nicotinonitrile(1f)

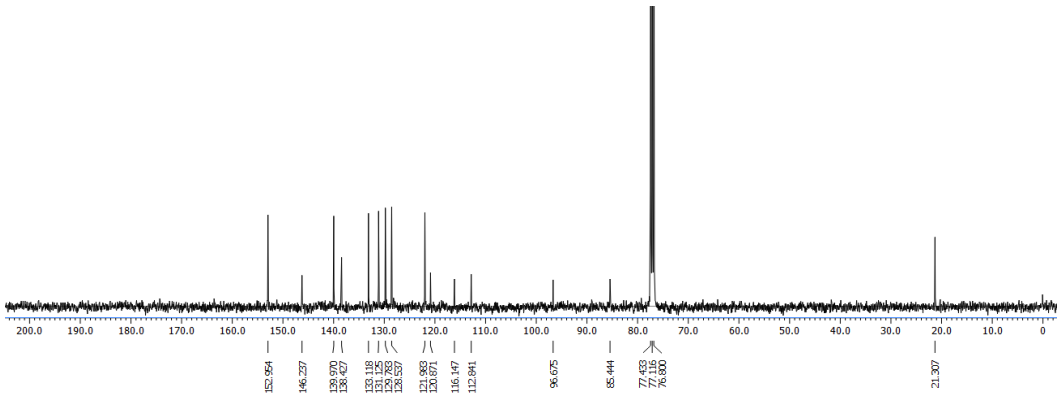
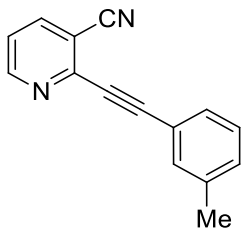


Figure 3.14

HRMS



2-(*m*-Tolylethynyl)nicotinonitrile(1f)

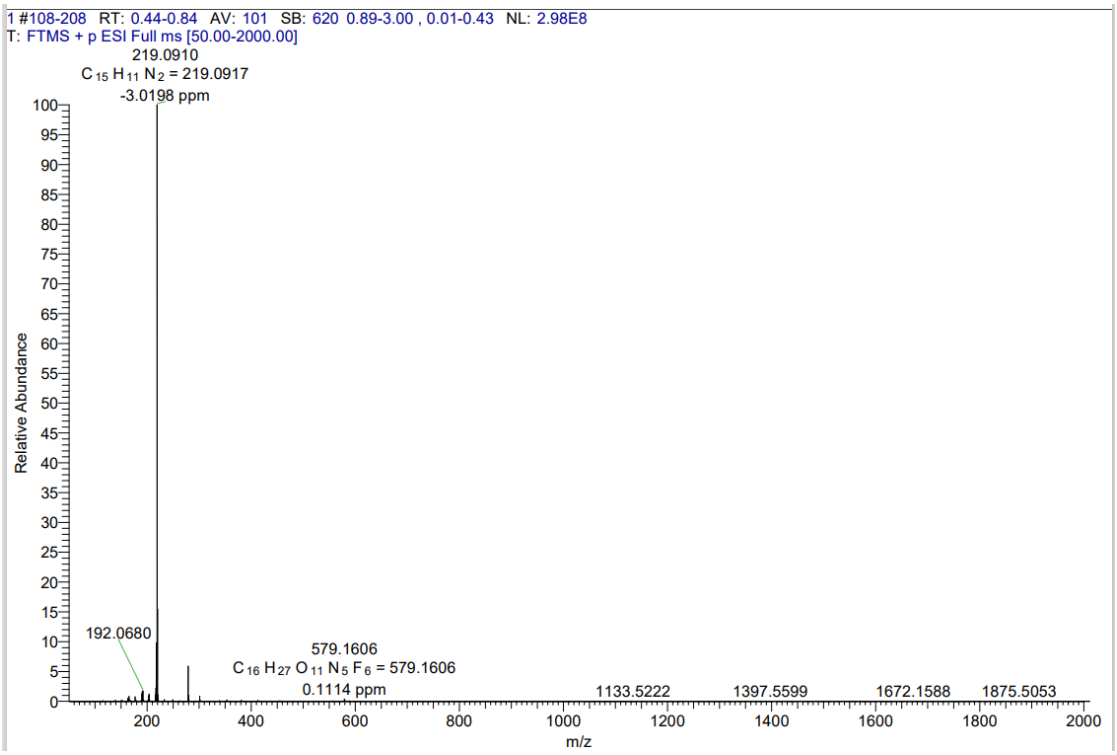
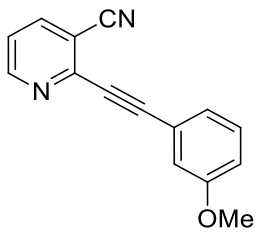
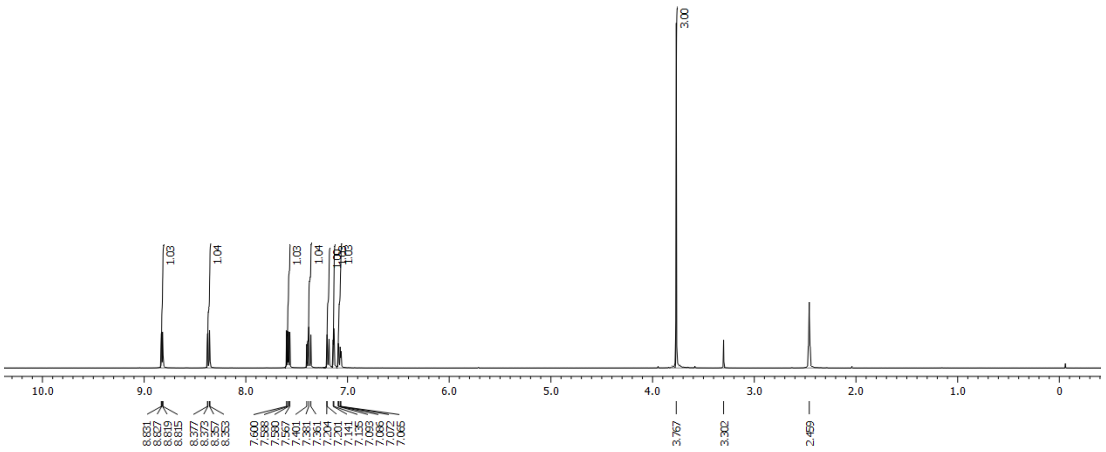


Figure 3.15

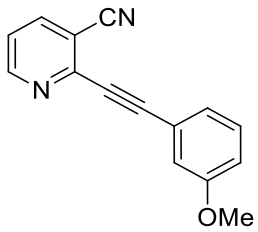
^{1}H NMR



2-((3-Methoxyphenyl)ethynyl)nicotinonitrile(1g)



^{13}C NMR



2-((3-Methoxyphenyl)ethynyl)nicotinonitrile(1g)

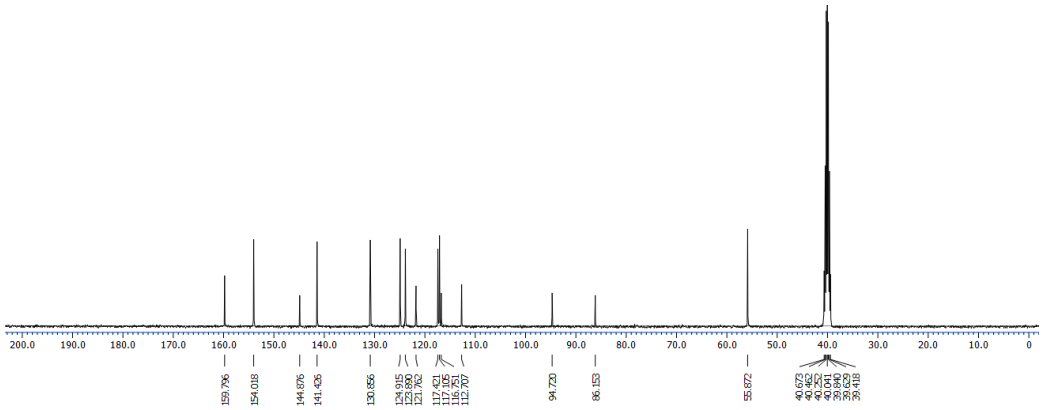
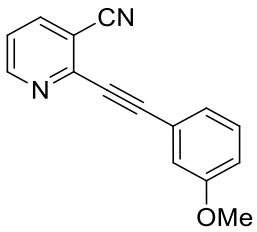


Figure 3.16

HRMS



2-((3-Methoxyphenyl)ethynyl)nicotinonitrile(1g)

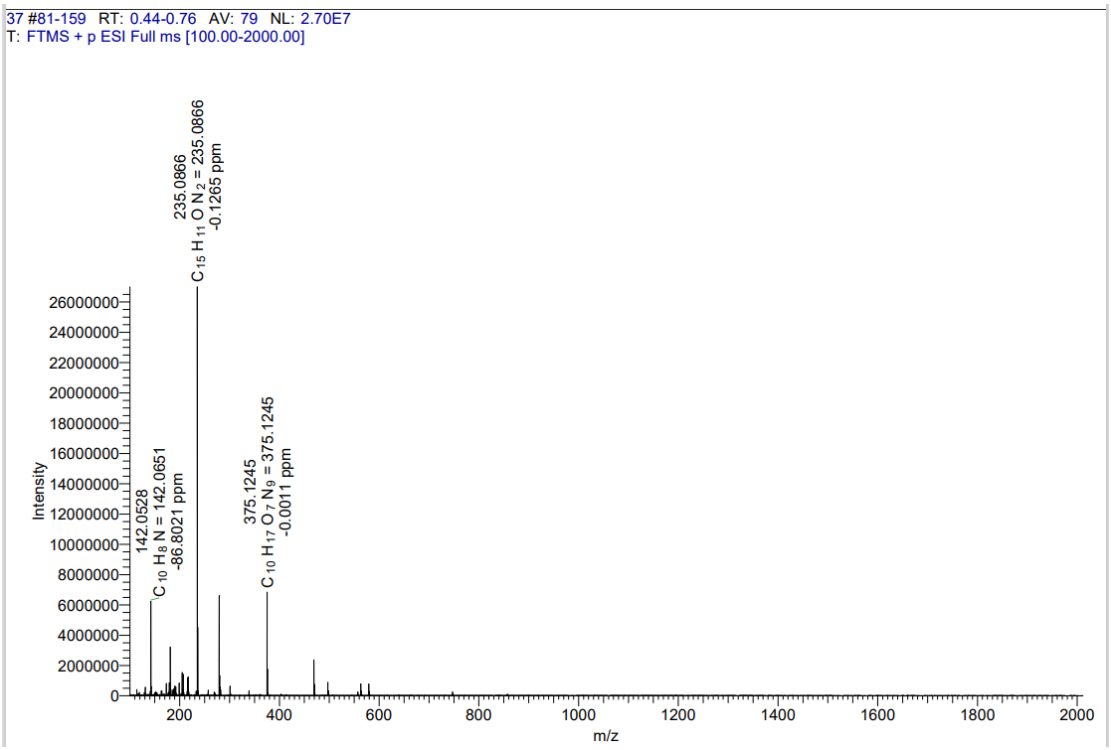
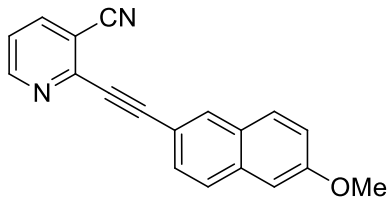
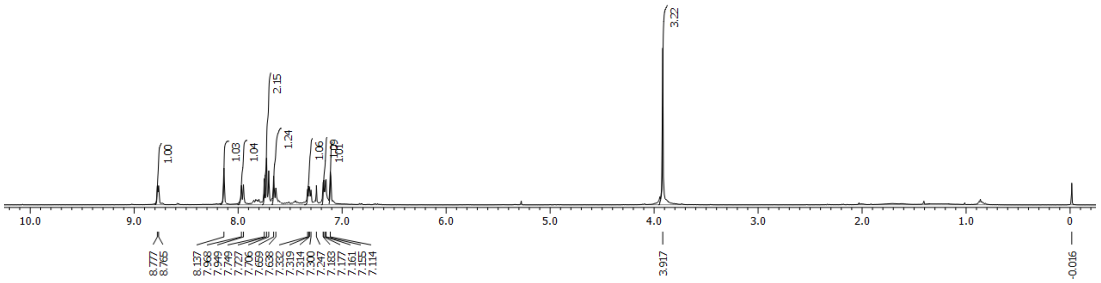


Figure 3.17

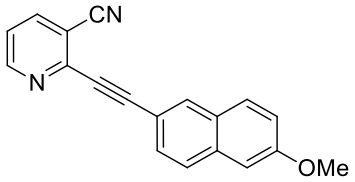
^{1}H NMR



2-((6-Methoxynaphthalen-2-yl)ethynyl)nicotinonitrile(1h)



^{13}C NMR



2-((6-Methoxynaphthalen-2-yl)ethynyl)nicotinonitrile(1h)

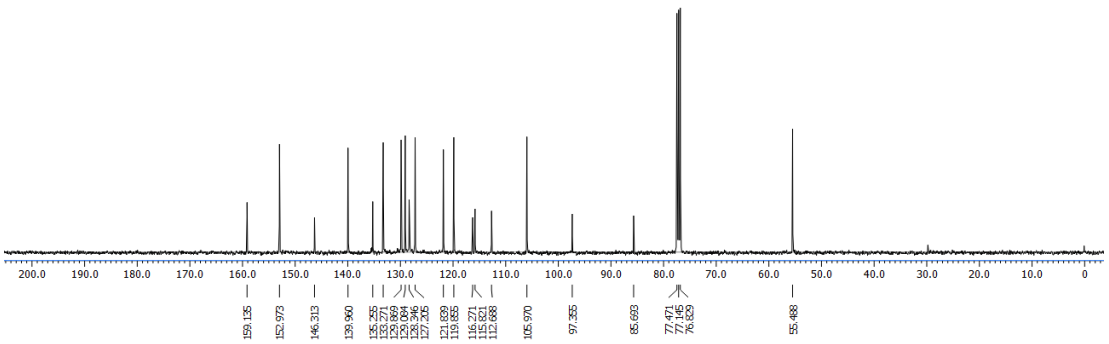
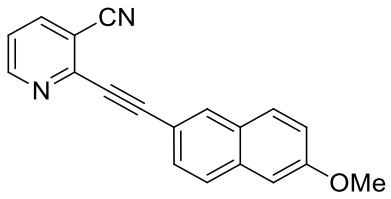


Figure 3.18

HRMS



2-((6-Methoxynaphthalen-2-yl)ethynyl)nicotinonitrile(1h)

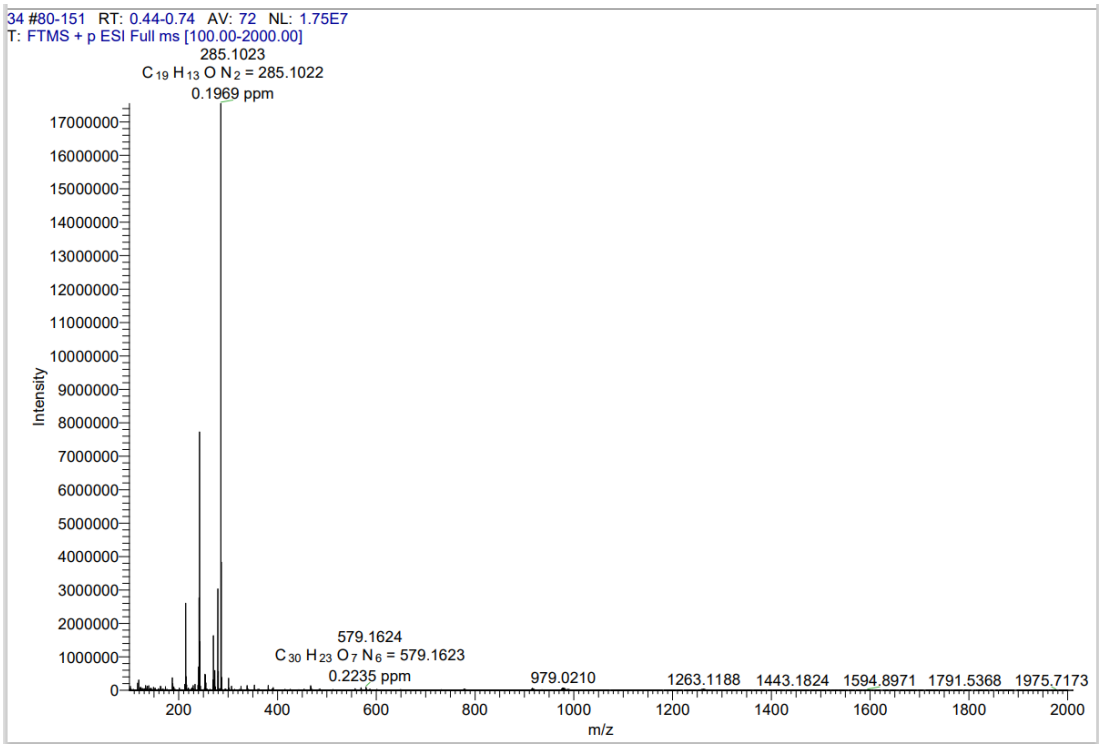
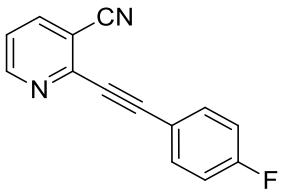
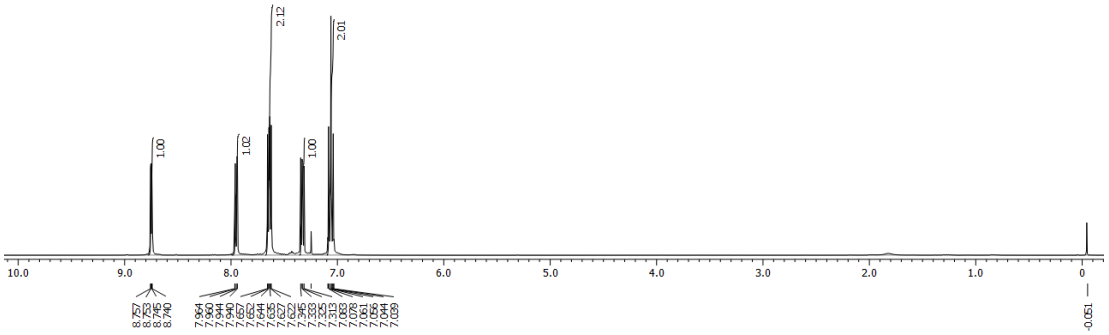


Figure 3.19

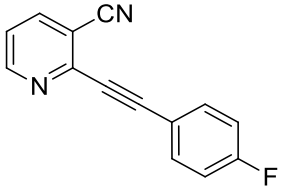
^{1}H NMR



2-((4-fluorophenyl)ethynyl)nicotinonitrile(1i)



^{13}C NMR



2-((4-fluorophenyl)ethynyl)nicotinonitrile(1i)

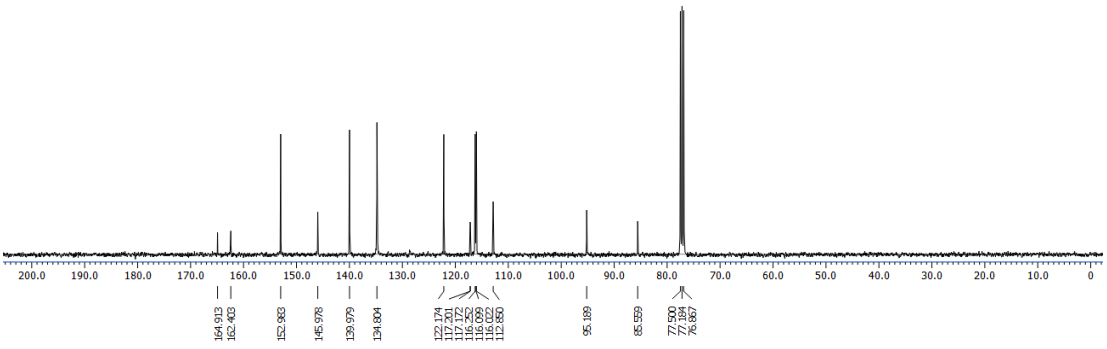
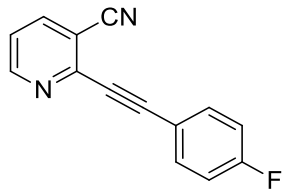


Figure 3.20

HRMS



2-((4-fluorophenyl)ethynyl)nicotinonitrile(1i)

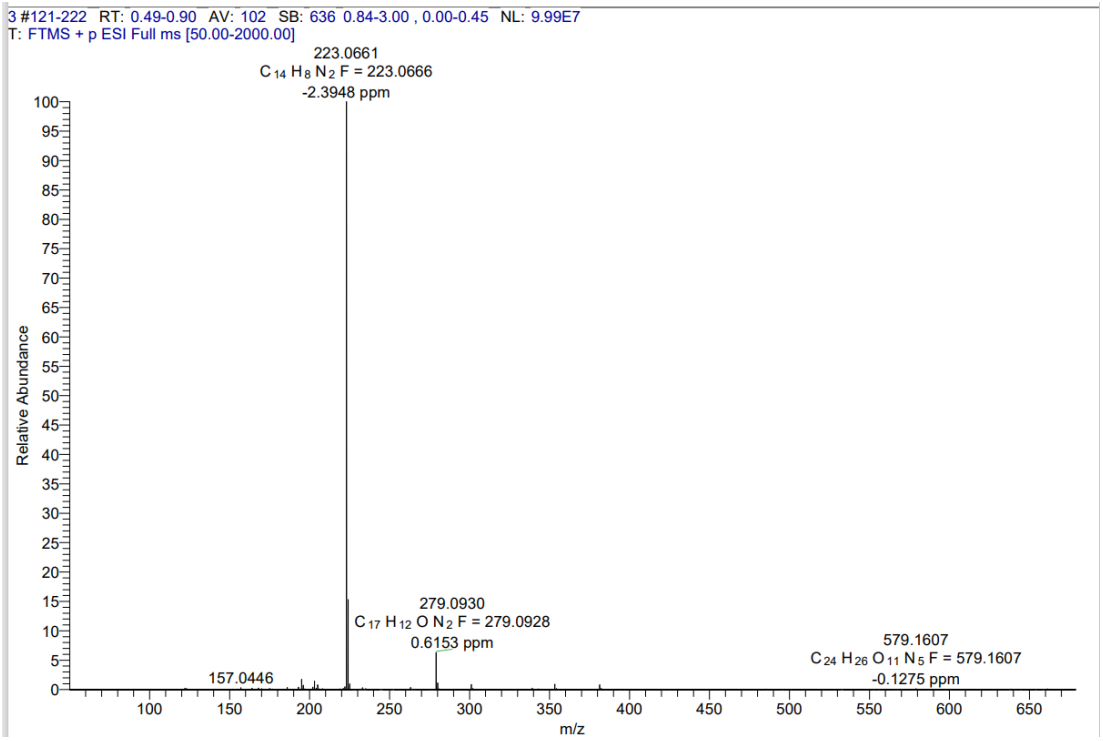
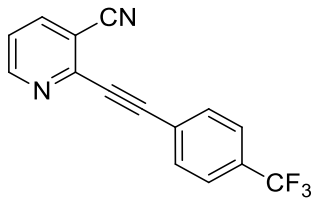
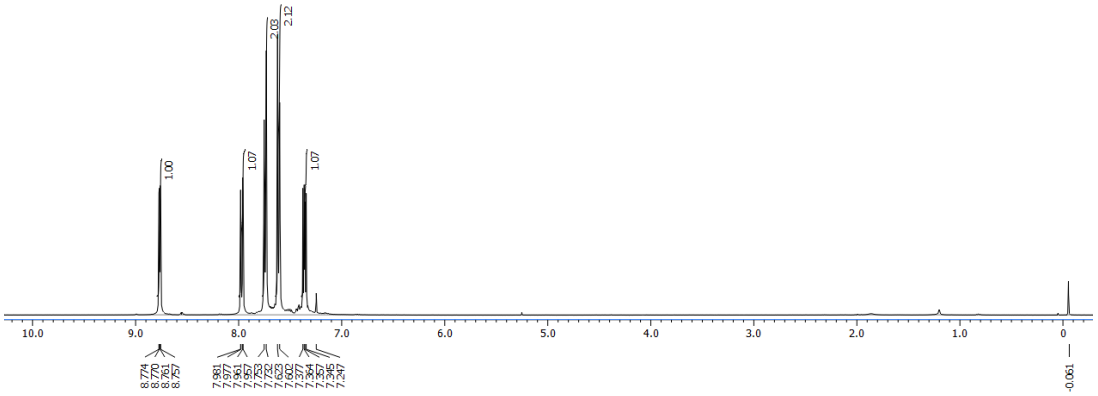


Figure 3.21

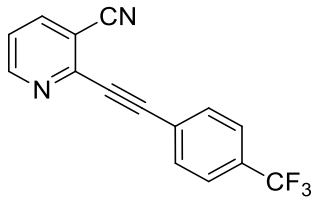
^{1}H NMR



2-((4-(Trifluoromethyl)phenyl)ethynyl)nicotinonitrile (1j)



^{13}C NMR



2-((4-(Trifluoromethyl)phenyl)ethynyl)nicotinonitrile (1j)

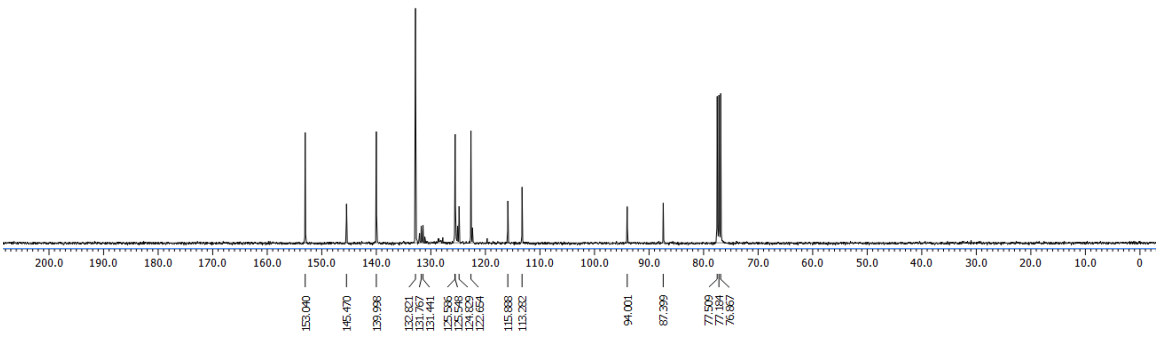
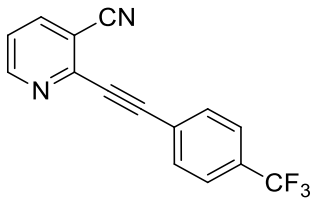


Figure 3.22

HRMS



2-((4-(Trifluoromethyl)phenyl)ethynyl)nicotinonitrile (1j)

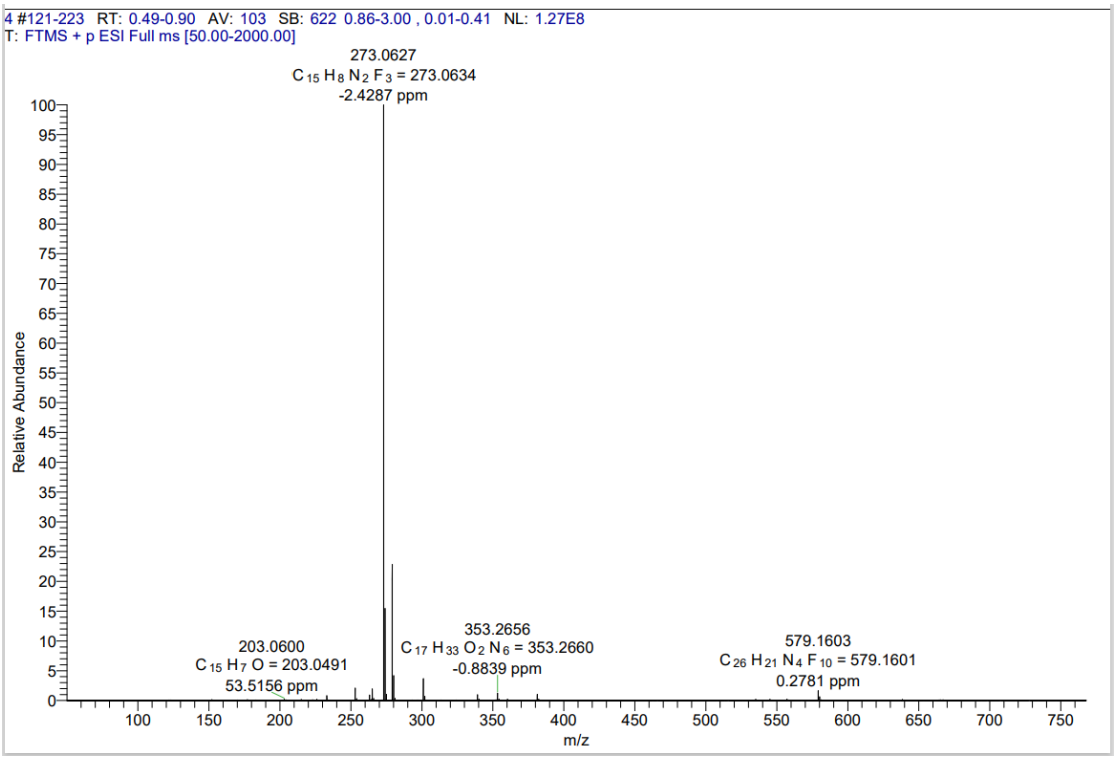
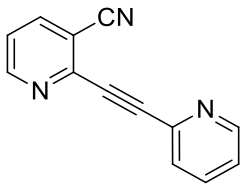
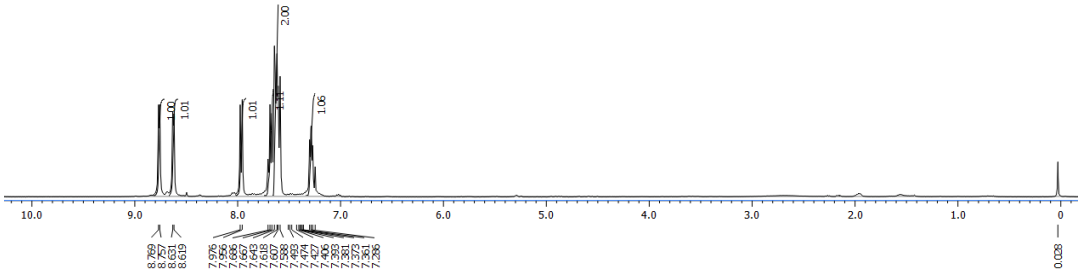


Figure 3.23

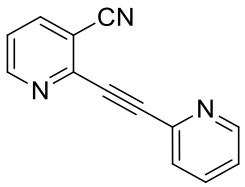
^{1}H NMR



2-(Pyridin-2-ylethynyl)nicotinonitrile(1k)



^{13}C NMR



2-(Pyridin-2-ylethynyl)nicotinonitrile (1k)

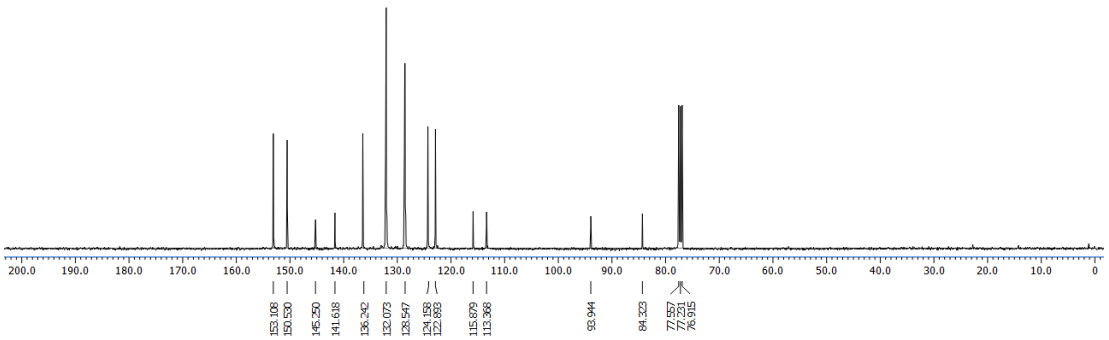
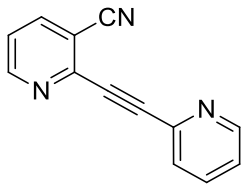


Figure 3.24

HRMS



2-(Pyridin-2-ylethynyl)nicotinonitrile (1k)

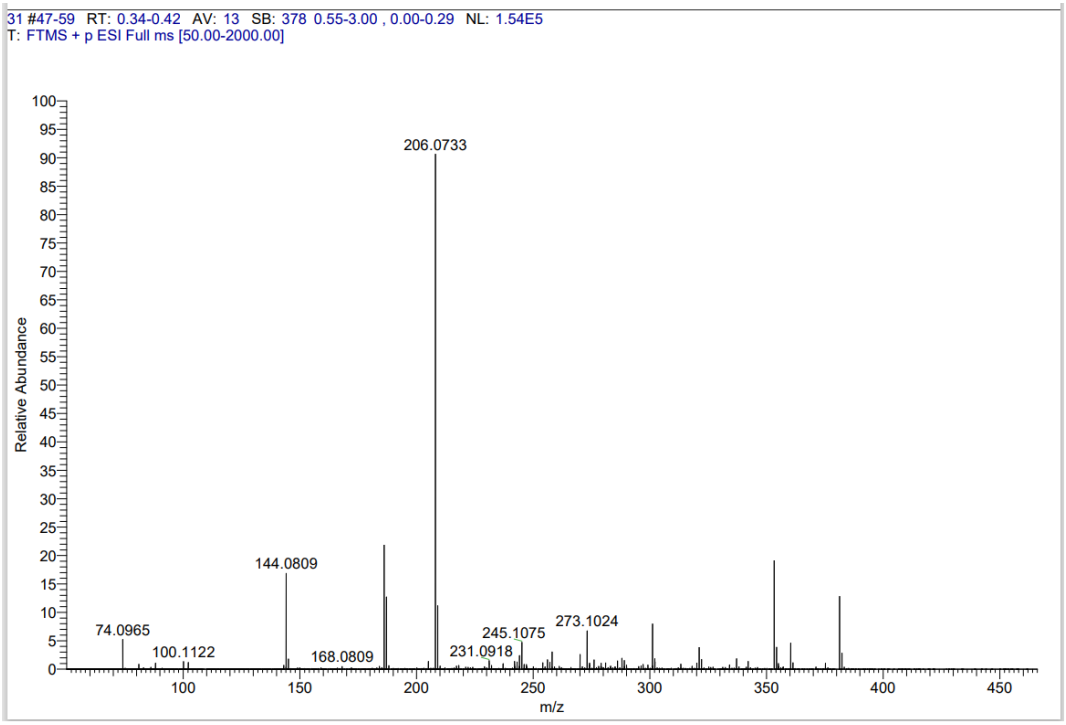
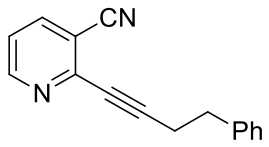
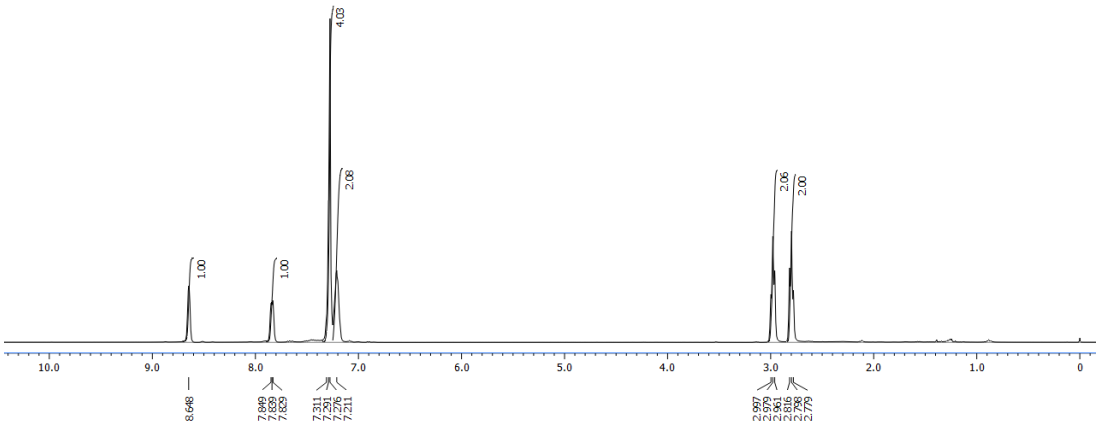


Figure 3.25

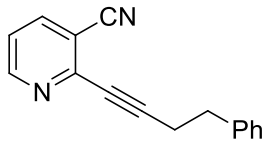
^{1}H NMR



2-(4-Phenylbut-1-yn-1-yl)nicotinonitrile (1l)



^{13}C NMR



2-(4-Phenylbut-1-yn-1-yl)nicotinonitrile (1l)

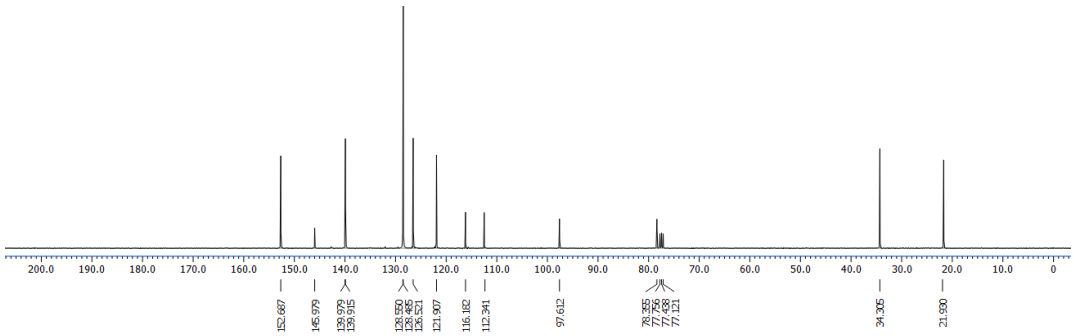
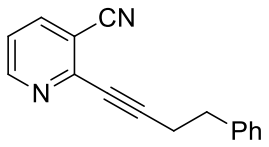


Figure 3.26

HRMS



2-(4-Phenylbut-1-yn-1-yl)nicotinonitrile (1l)

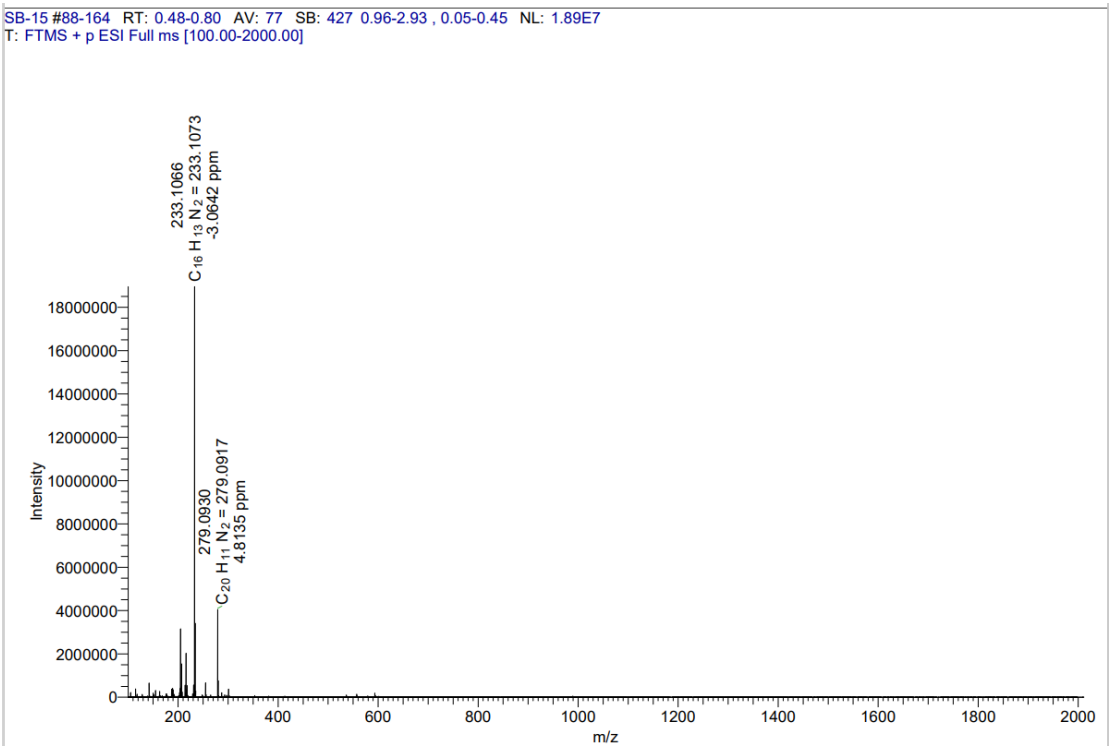
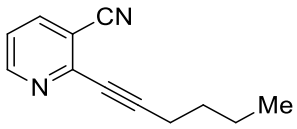
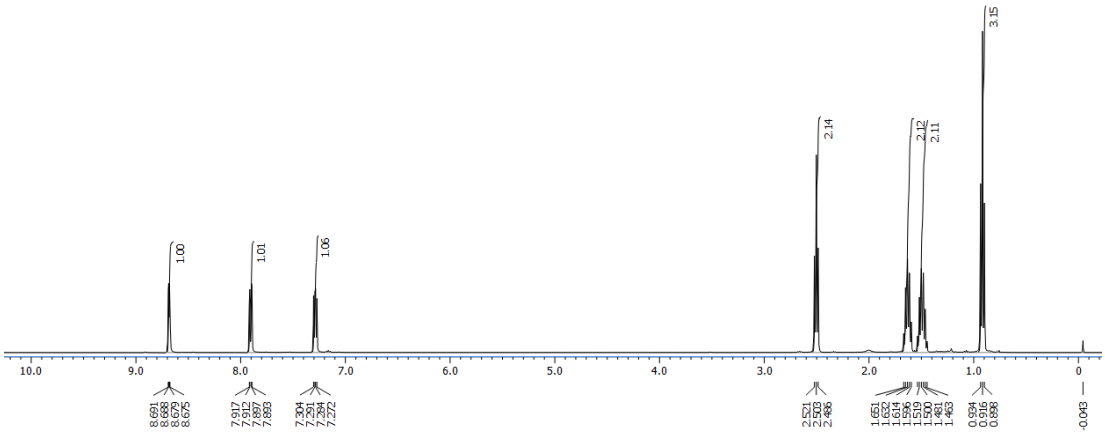


Figure 3.27

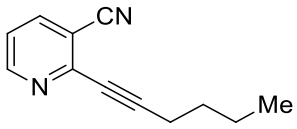
^{1}H NMR



2-(Hex-1-yn-1-yl)nicotinonitrile(1m)



^{13}C NMR



2-(Hex-1-yn-1-yl)nicotinonitrile(1m)

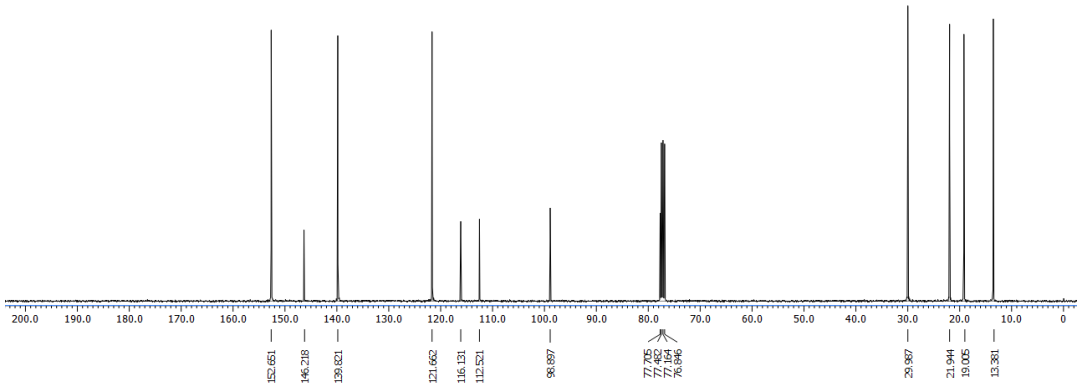
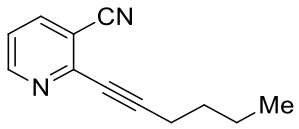


Figure 3.28

HRMS



2-(Hex-1-yn-1-yl)nicotinonitrile(1m)

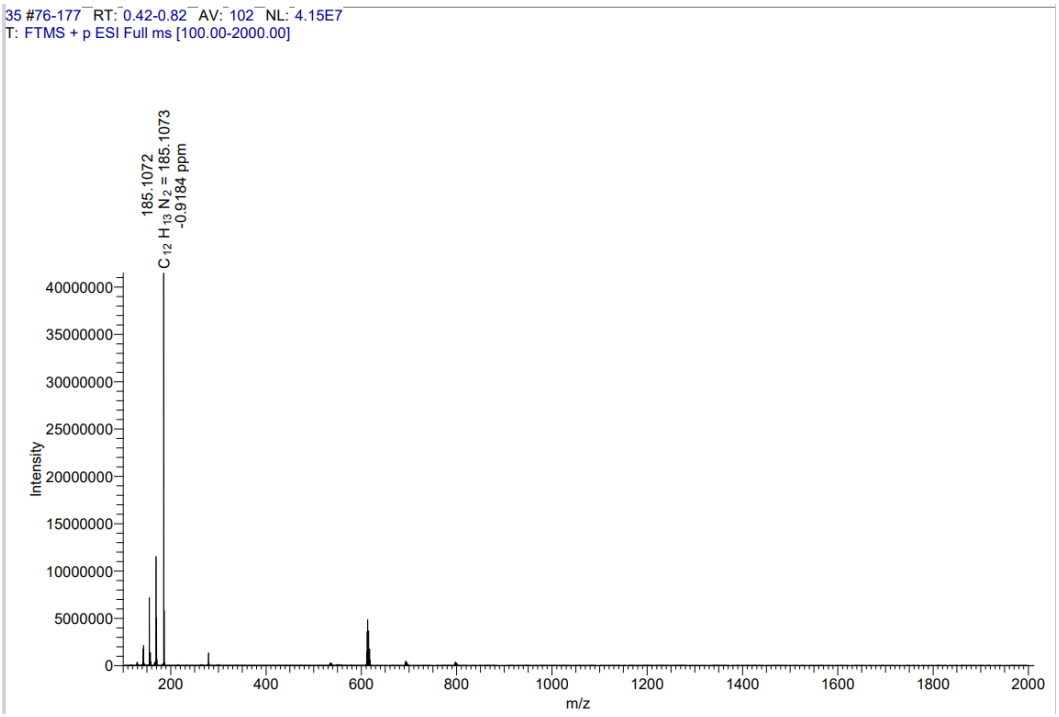
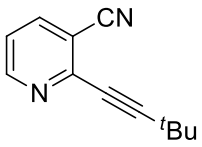
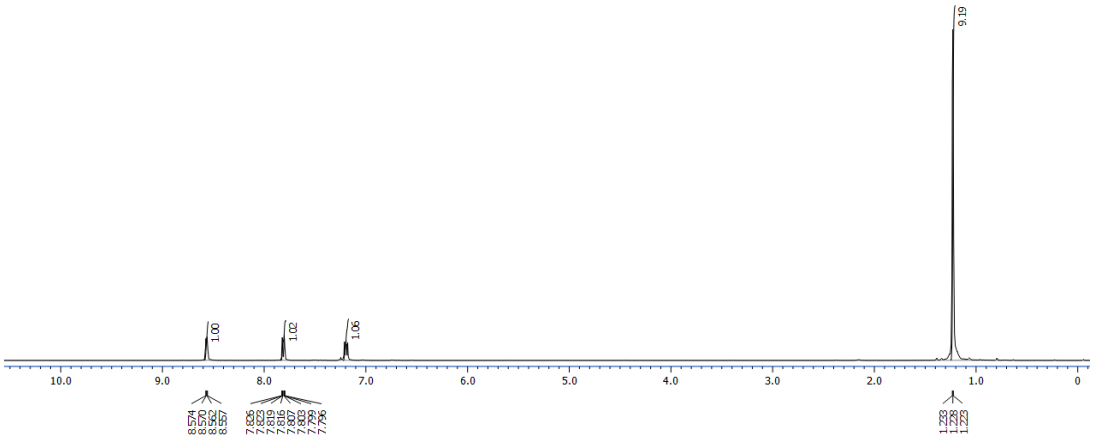


Figure 3.29

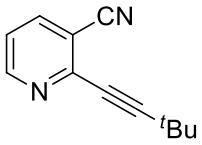
^{1}H NMR



2-(3,3-Dimethylbut-1-yn-1-yl)nicotinonitrile (1n)



^{13}C NMR



2-(3,3-Dimethylbut-1-yn-1-yl)nicotinonitrile (1n)

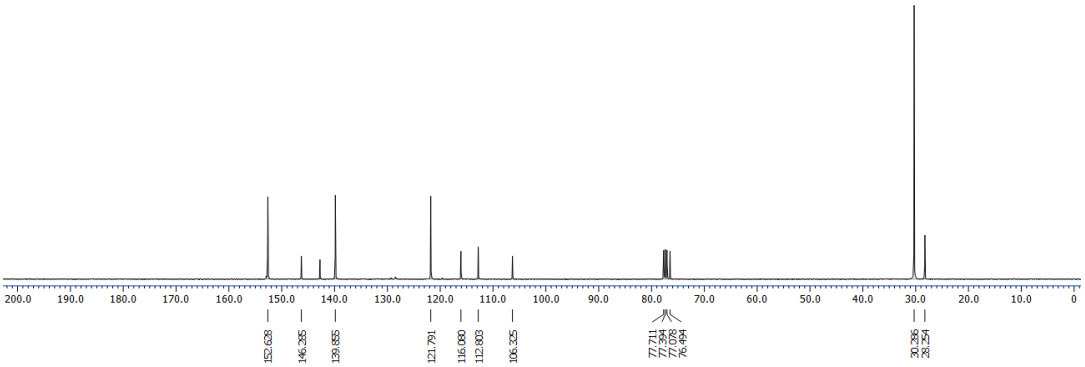
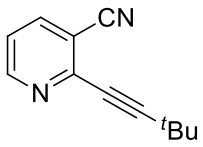


Figure 3.30

HRMS



2-(3,3-Dimethylbut-1-yn-1-yl)nicotinonitrile (1n)

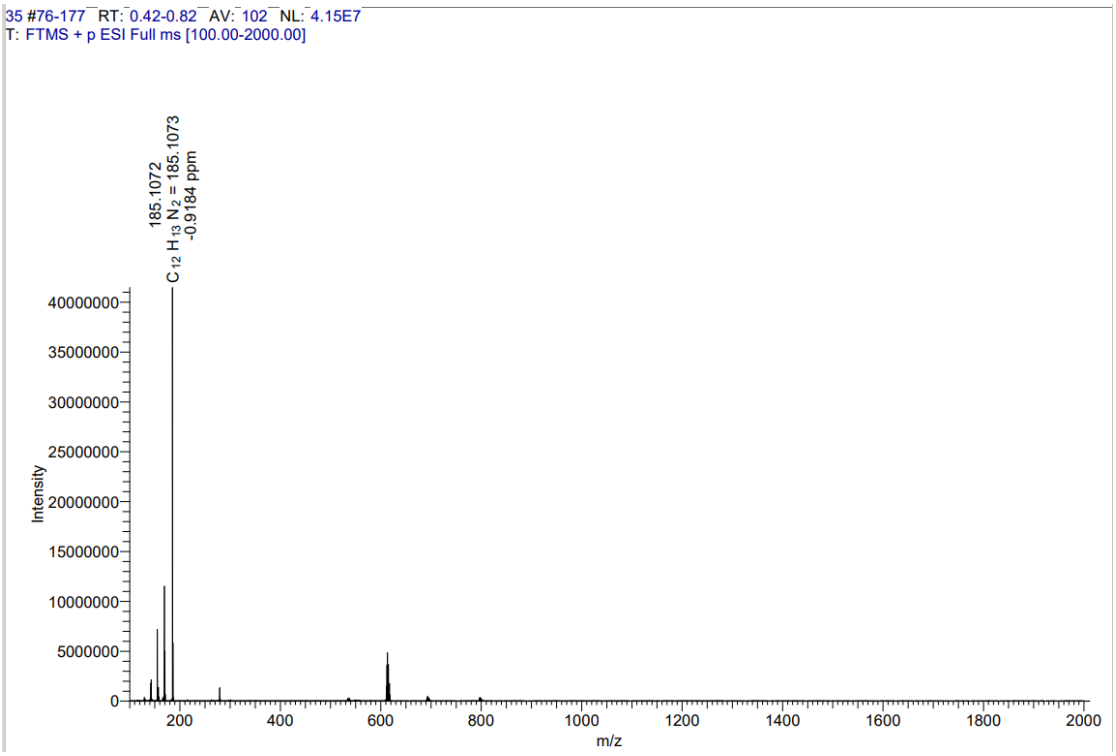
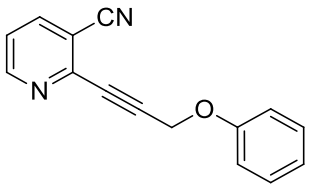
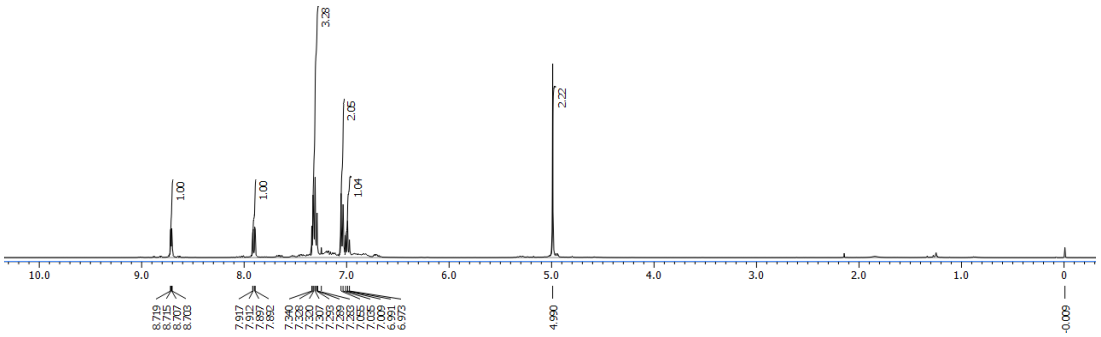


Figure 3.31

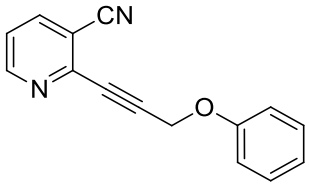
^{1}H NMR



2-(3-Phenoxyprop-1-yn-1-yl)nicotinonitrile(1o)



^{13}C NMR



2-(3-Phenoxyprop-1-yn-1-yl)nicotinonitrile(1o)

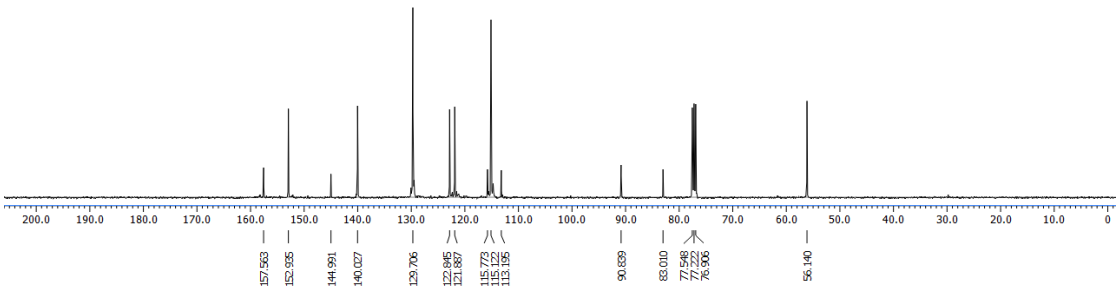
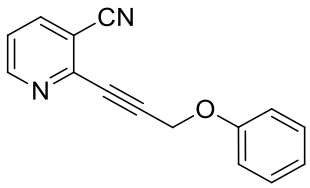


Figure 3.32

HRMS



2-(3-Phenoxyprop-1-yn-1-yl)nicotinonitrile(1o)

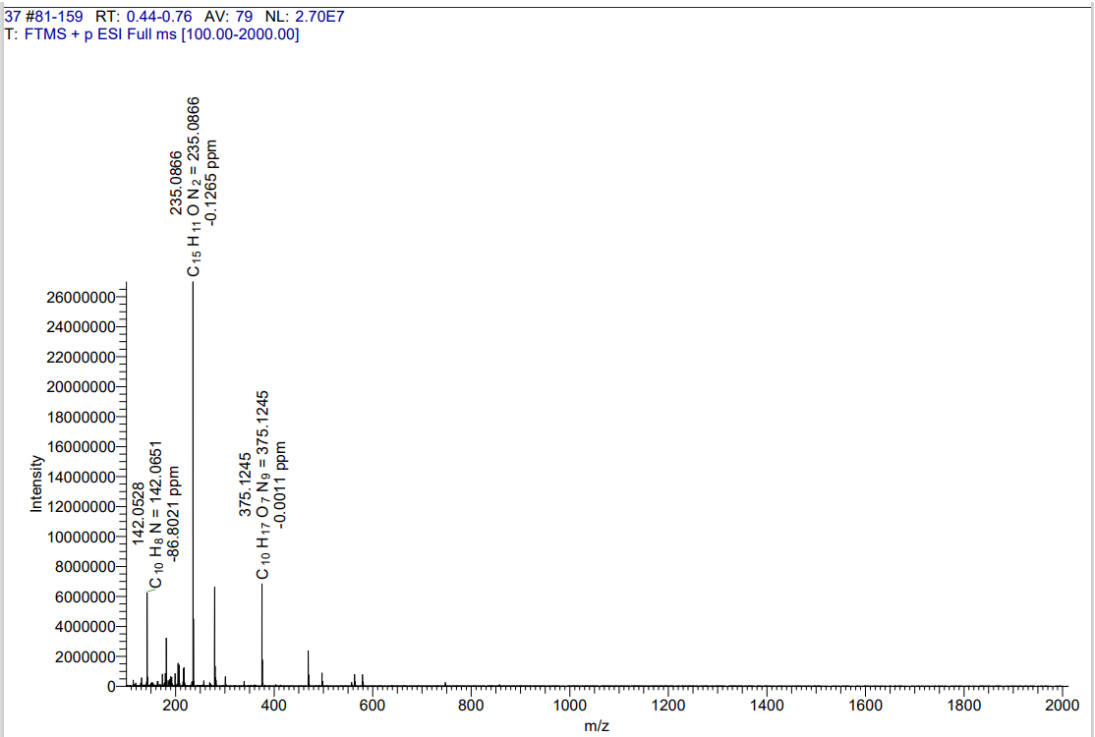
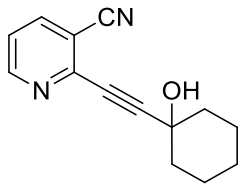
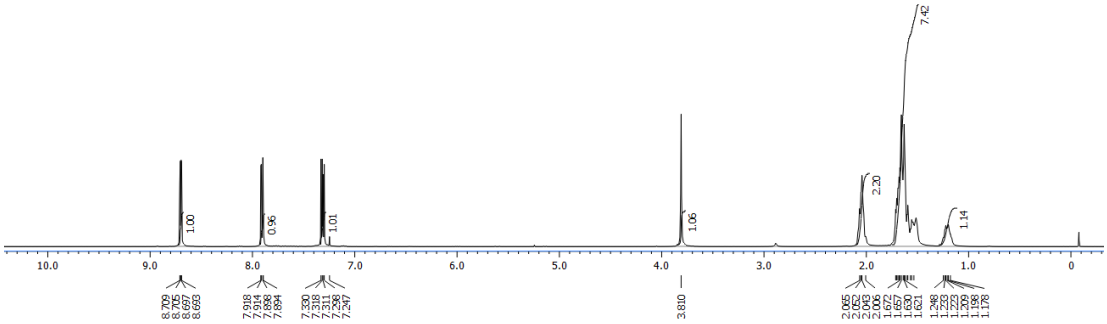


Figure 3.33

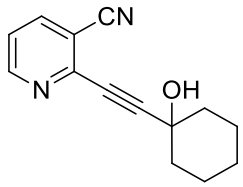
^{1}H NMR



2-((1-Hydroxycyclohexyl)ethynyl)nicotinonitrile(1p)



^{13}C NMR



2-((1-Hydroxycyclohexyl)ethynyl)nicotinonitrile(1p)

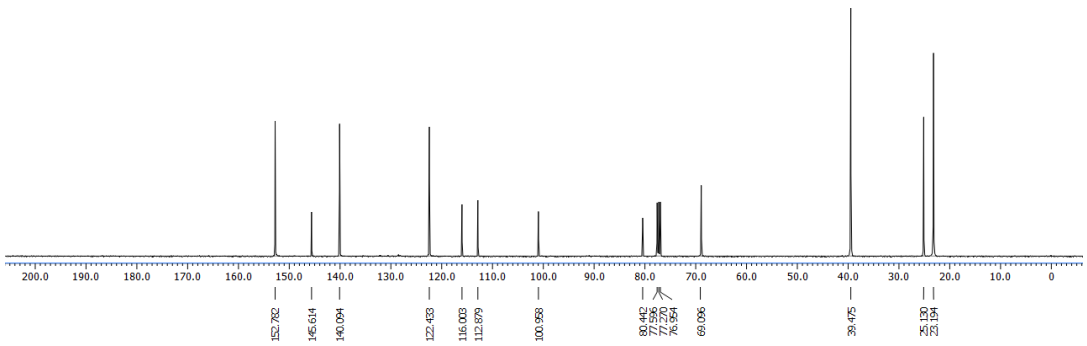
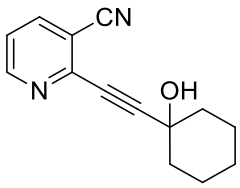


Figure 3.34

HRMS



2-((1-Hydroxycyclohexyl)ethynyl)nicotinonitrile(1p)

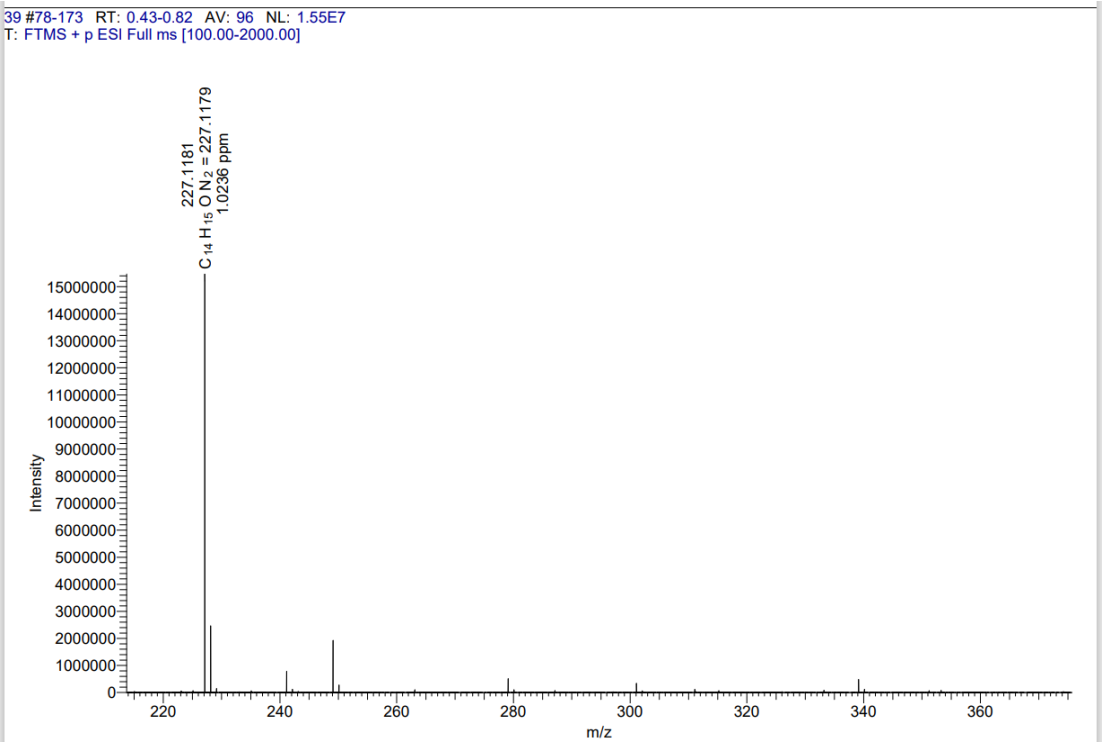
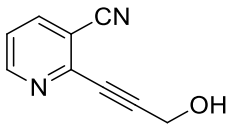
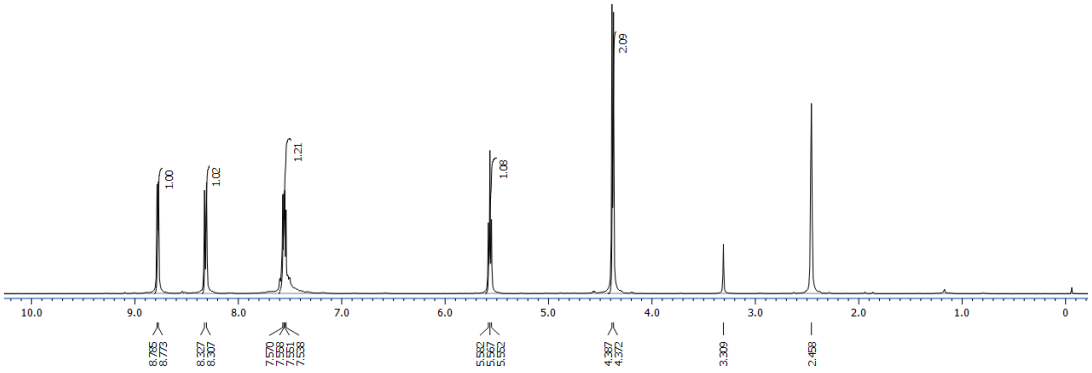


Figure 3.35

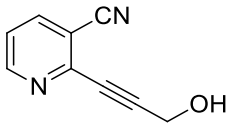
^{1}H NMR



2-(3-Hydroxyprop-1-yn-1-yl)nicotinonitrile(1q)



^{13}C NMR



2-(3-Hydroxyprop-1-yn-1-yl)nicotinonitrile(1q)

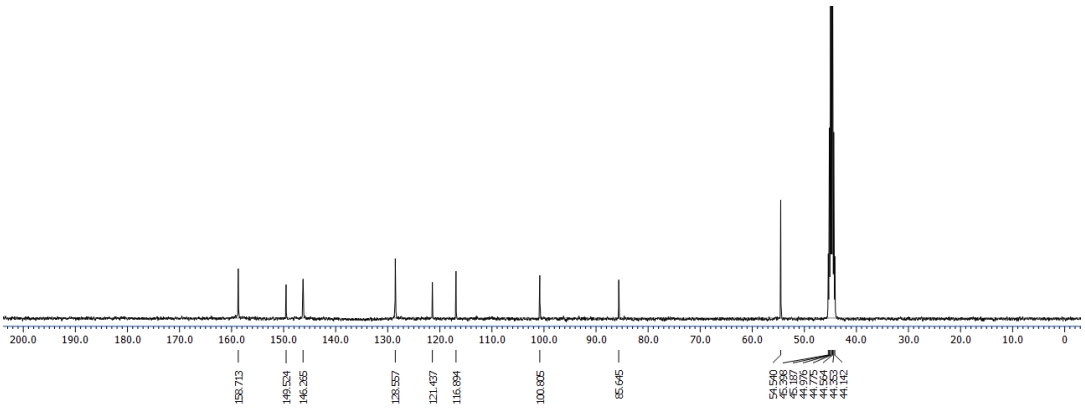
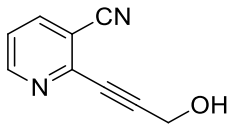


Figure 3.36

HRMS



2-(3-Hydroxyprop-1-yn-1-yl)nicotinonitrile(1q)

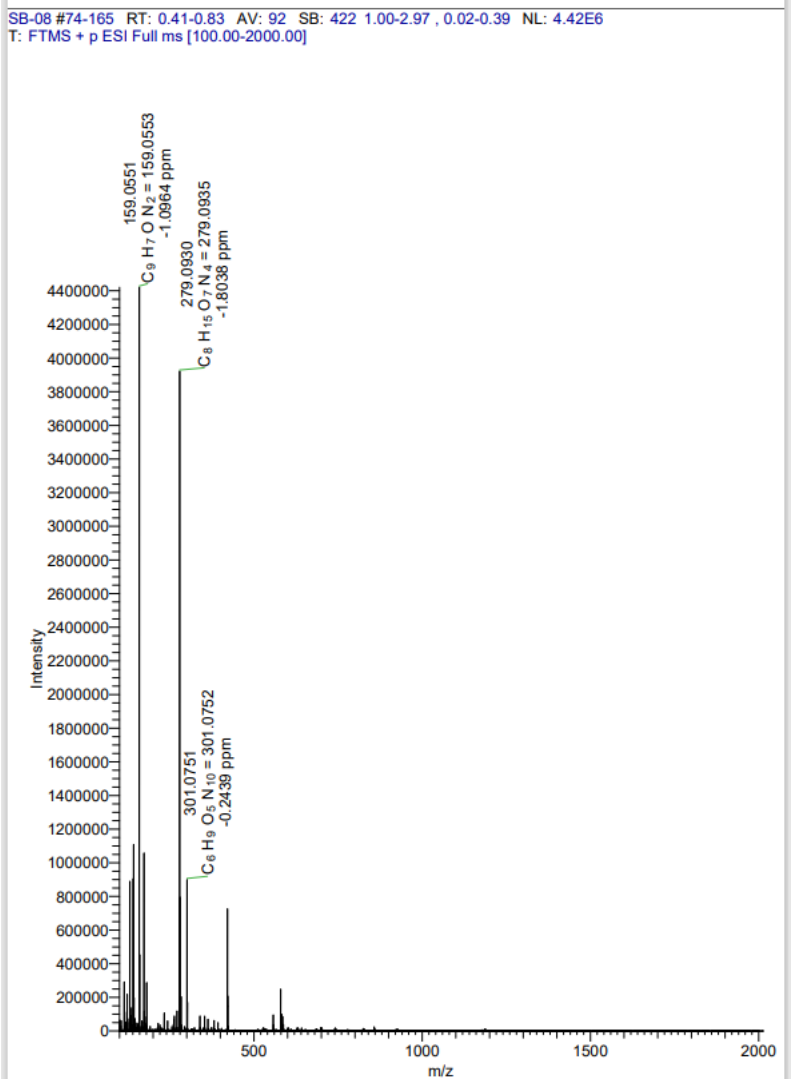
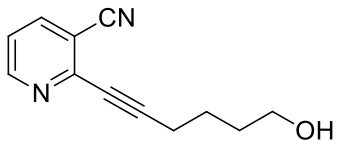
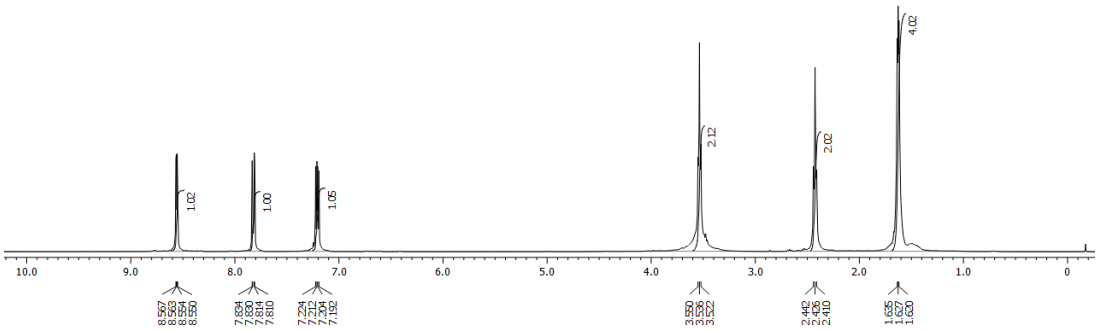


Figure 3.37

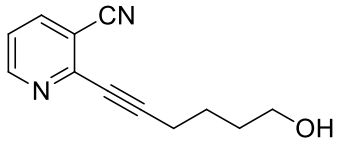
^{1}H NMR



2-(6-Hydroxyhex-1-yn-1-yl)nicotinonitrile(1r)



^{13}C NMR



2-(6-Hydroxyhex-1-yn-1-yl)nicotinonitrile(1r)

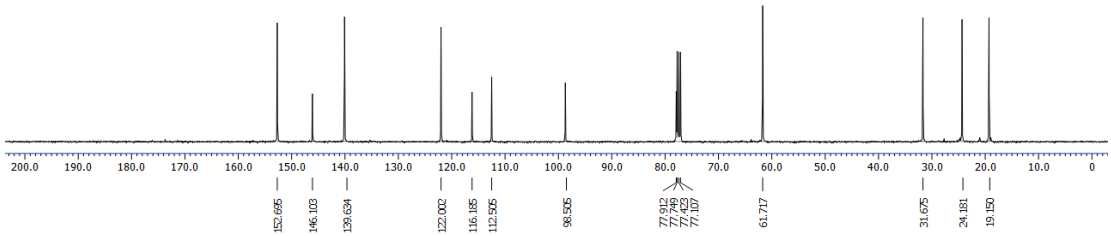
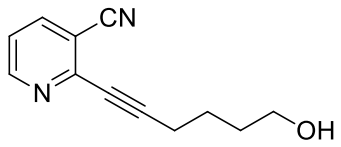


Figure 3.38

HRMS



2-(6-Hydroxyhex-1-yn-1-yl)nicotinonitrile(1r)

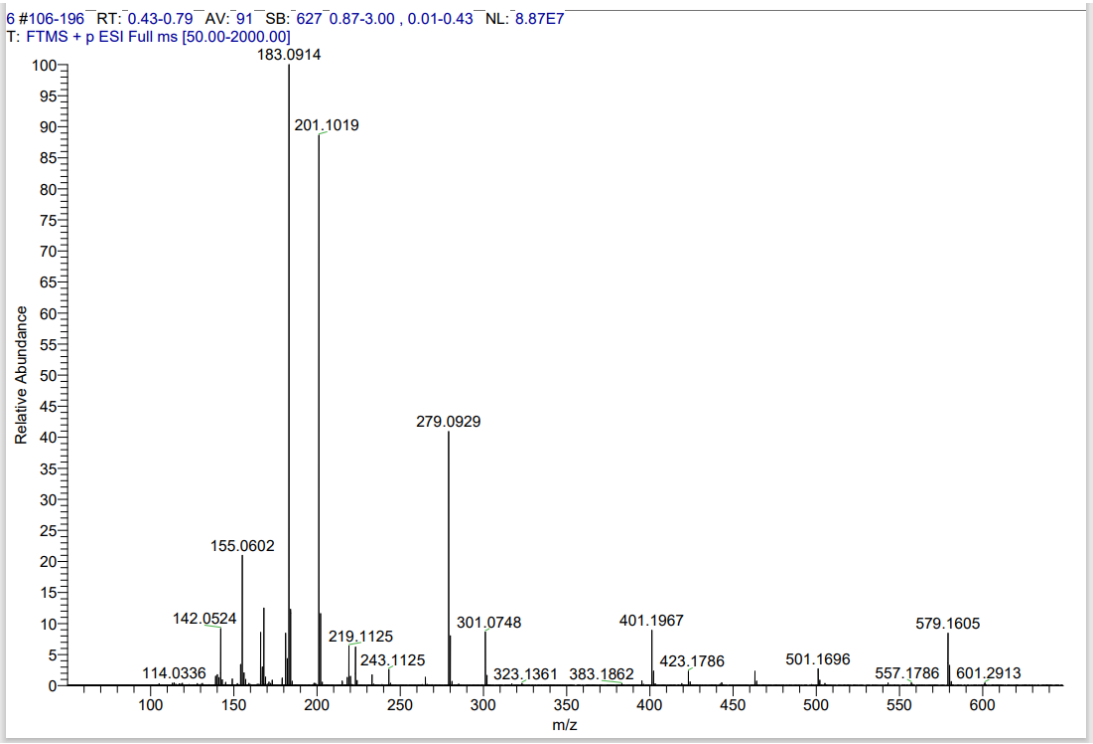
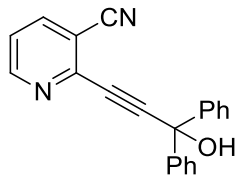
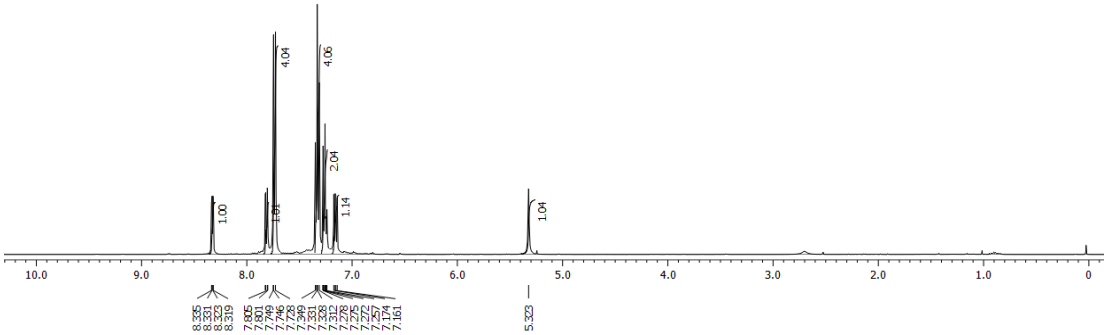


Figure 3.39

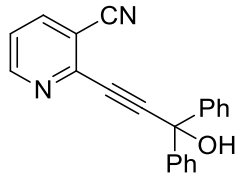
^{1}H NMR



2-(3-Hydroxy-3,3-diphenylprop-1-yn-1-yl)nicotinonitrile(1s)



^{13}C NMR



2-(3-Hydroxy-3,3-diphenylprop-1-yn-1-yl)nicotinonitrile(1s)

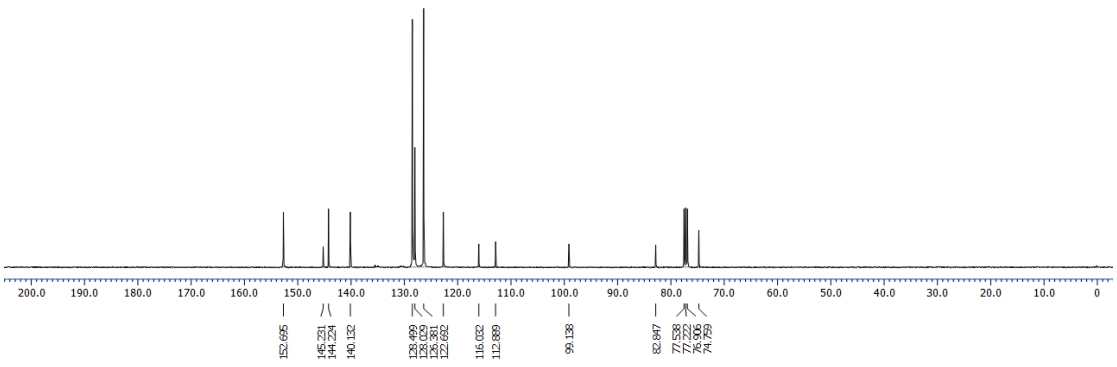
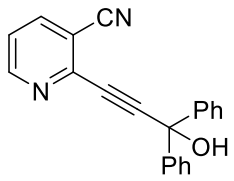


Figure 3.40

HRMS



2-(3-Hydroxy-3,3-diphenylprop-1-yn-1-yl)nicotinonitrile(1s)

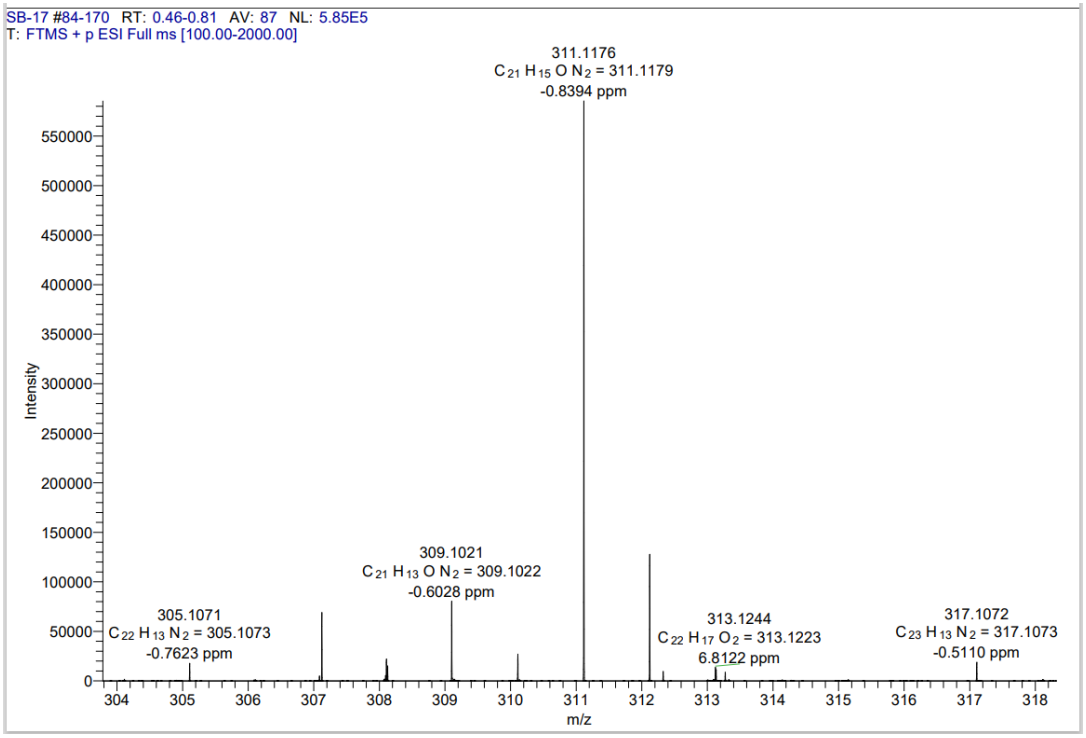
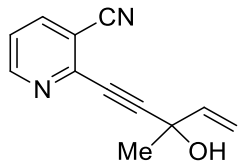
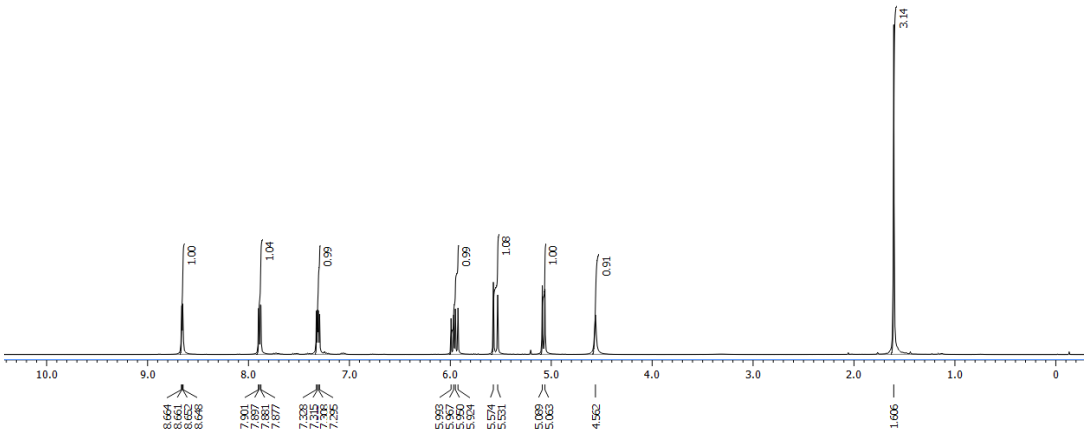


Figure 3.41

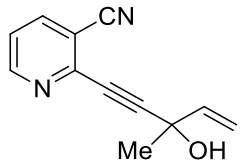
^{1}H NMR



2-(3-Hydroxy-3-methylpent-4-en-1-yn-1-yl)nicotinonitrile(1t)



^{13}C NMR



2-(3-Hydroxy-3-methylpent-4-en-1-yn-1-yl)nicotinonitrile(1t)

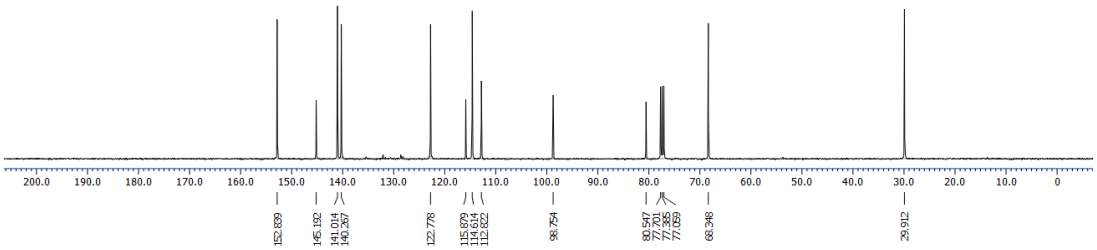
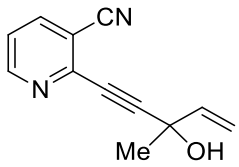


Figure 3.42

HRMS



2-(3-Hydroxy-3-methylpent-4-en-1-yn-1-yl)nicotinonitrile(1t)

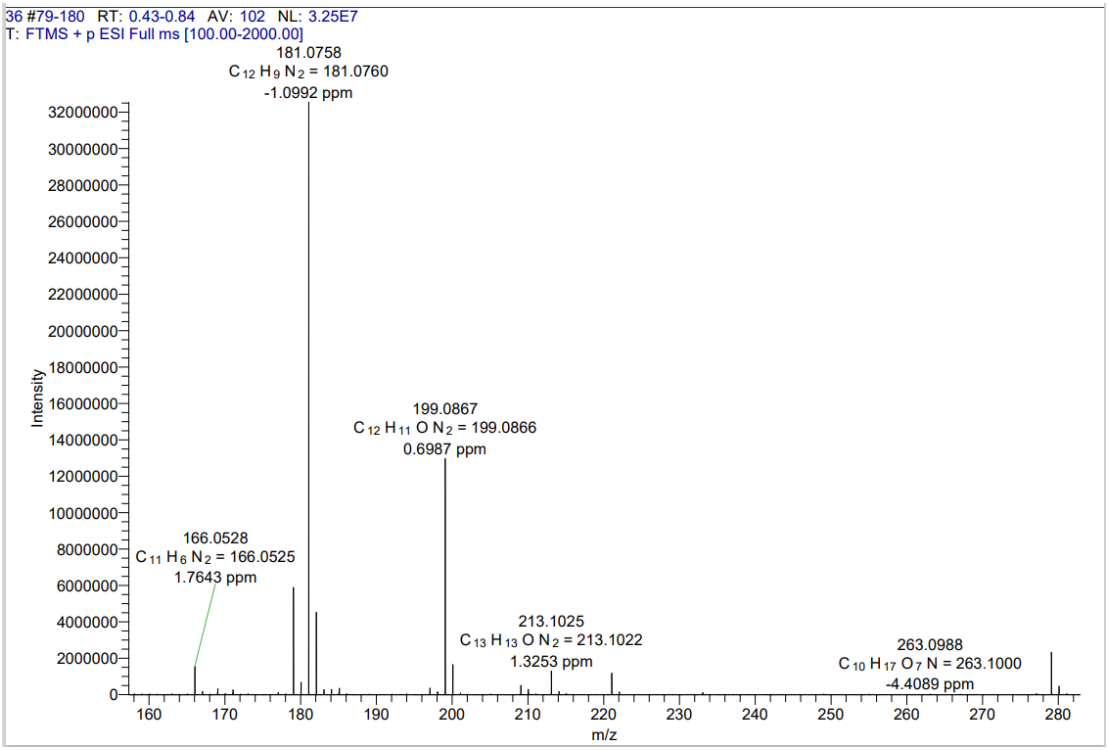
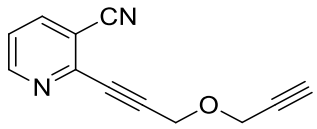
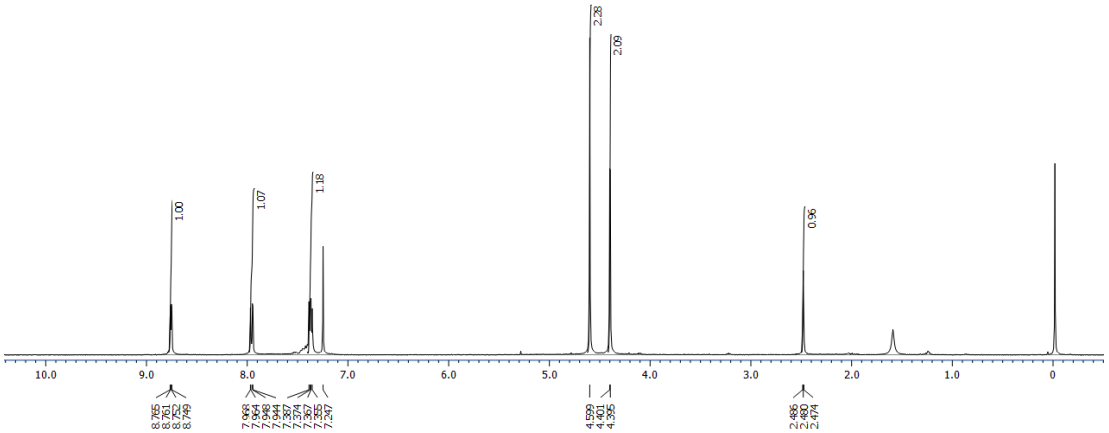


Figure 3.43

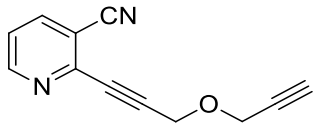
^{1}H NMR



2-(3-(Prop-2-yn-1-yloxy)prop-1-yn-1-yl)nicotinonitrile (1u)



^{13}C NMR



2-(3-(Prop-2-yn-1-yloxy)prop-1-yn-1-yl)nicotinonitrile (1u)

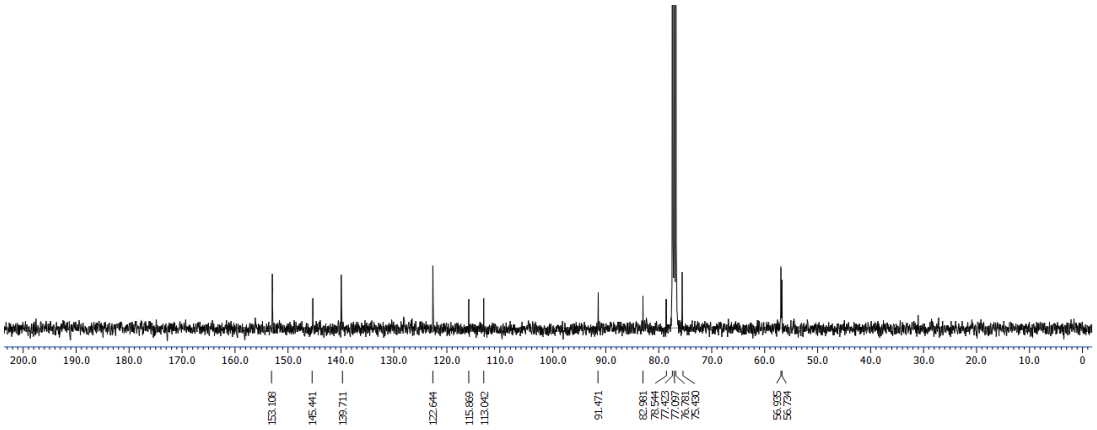
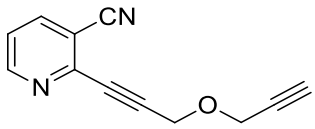


Figure 3.44

HRMS



2-(3-(Prop-2-yn-1-yloxy)prop-1-yn-1-yl)nicotinonitrile (1u)

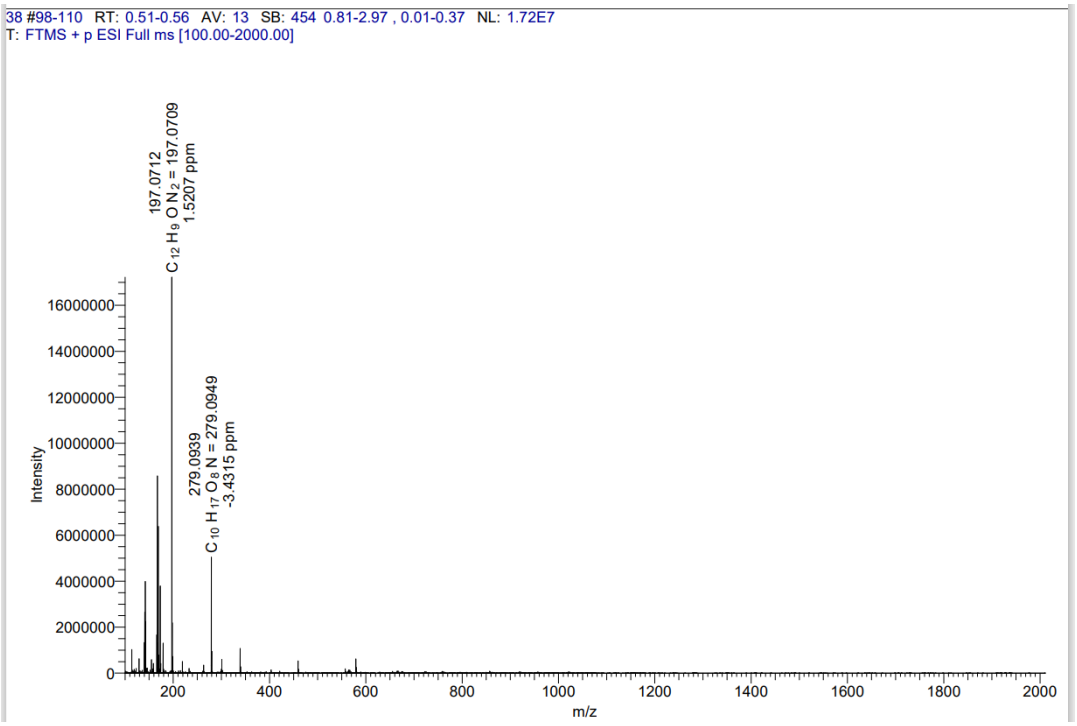
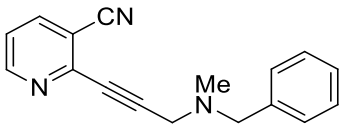
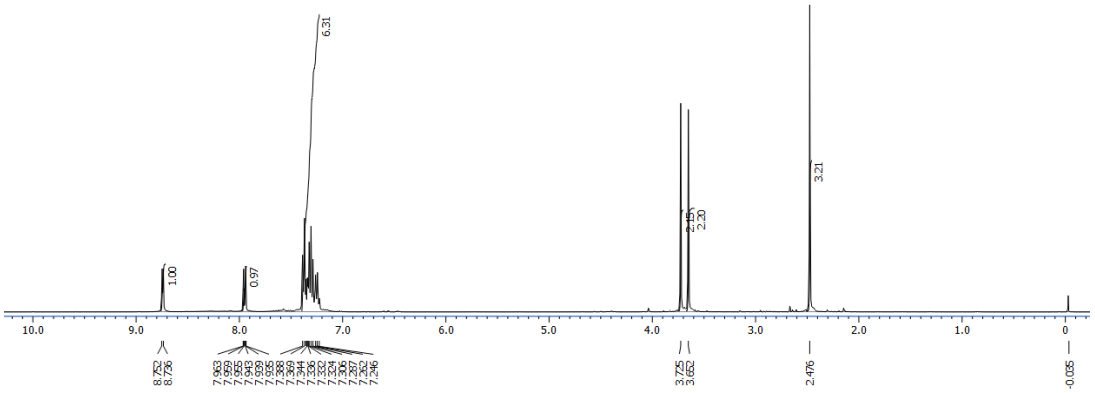


Figure 3.45

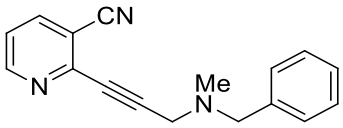
^{1}H NMR



2-(3-(Benzyl(methyl)amino)prop-1-yn-1-yl)nicotinonitrile (4a)



^{13}C NMR



2-(3-(Benzyl(methyl)amino)prop-1-yn-1-yl)nicotinonitrile (4a)

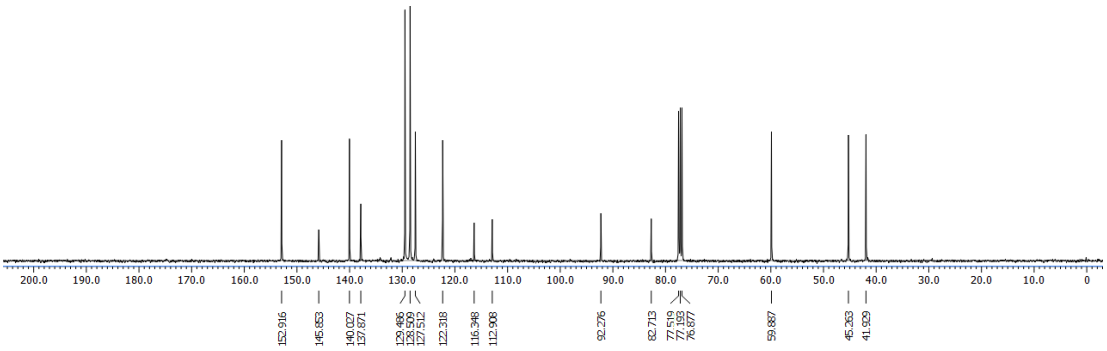
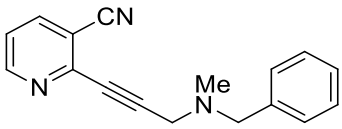


Figure 3.46

HRMS



2-(3-(Benzyl(methyl)amino)prop-1-yn-1-yl)nicotinonitrile (4a)

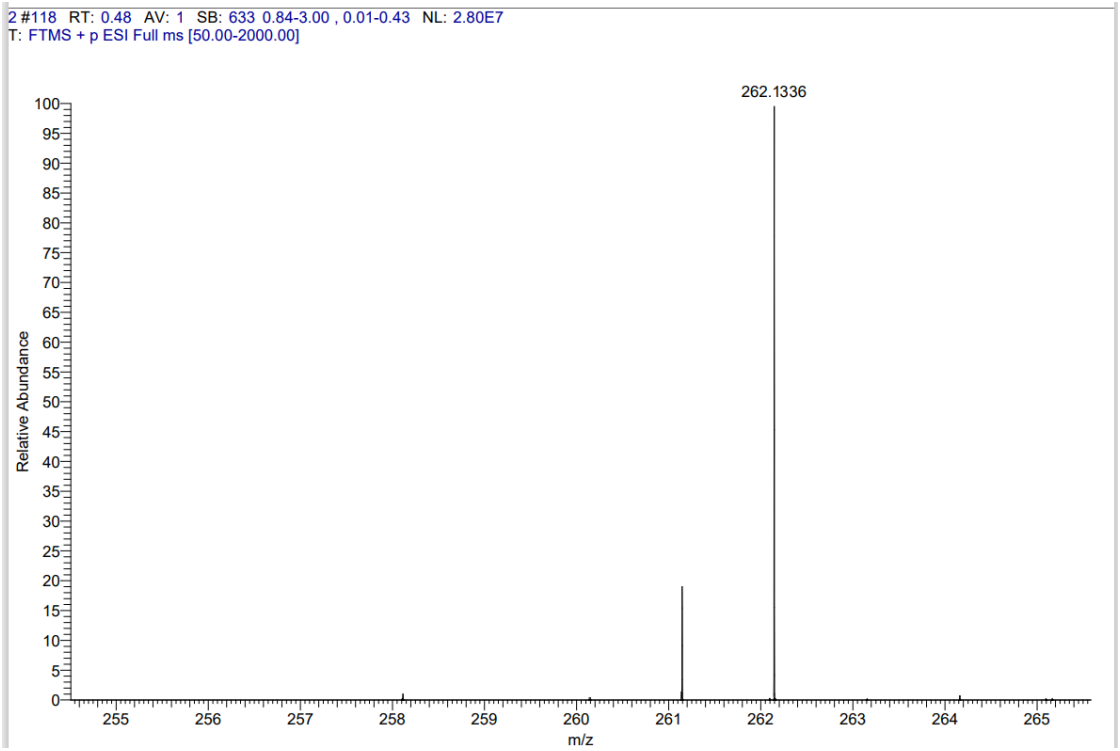
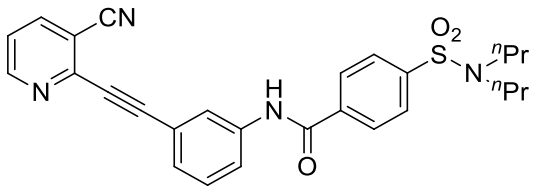
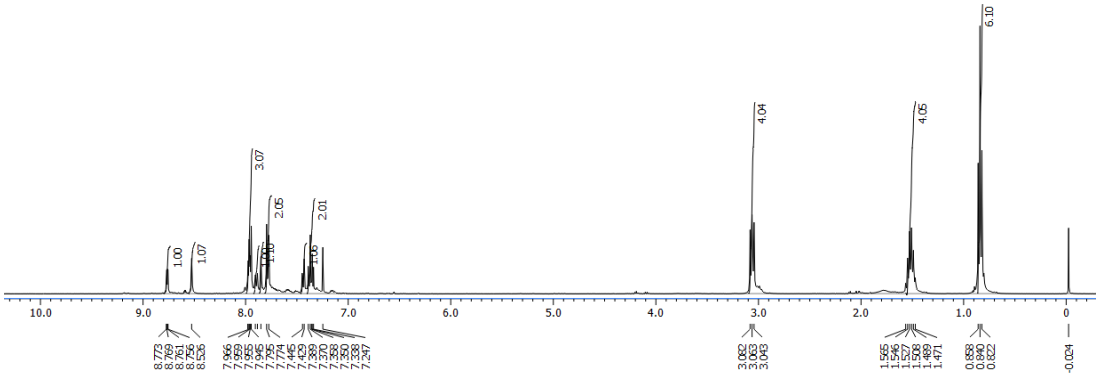


Figure 3.47

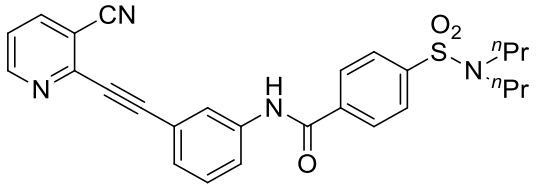
^{1}H NMR



***N*-(3-((3-cyanopyridin-2-yl)ethynyl)phenyl)-4-(*N*,*N*-dipropylsulfamoyl)benzamide (4b)**



^{13}C NMR



***N*-(3-((3-cyanopyridin-2-yl)ethynyl)phenyl)-4-(*N*,*N*-dipropylsulfamoyl)benzamide (4b)**

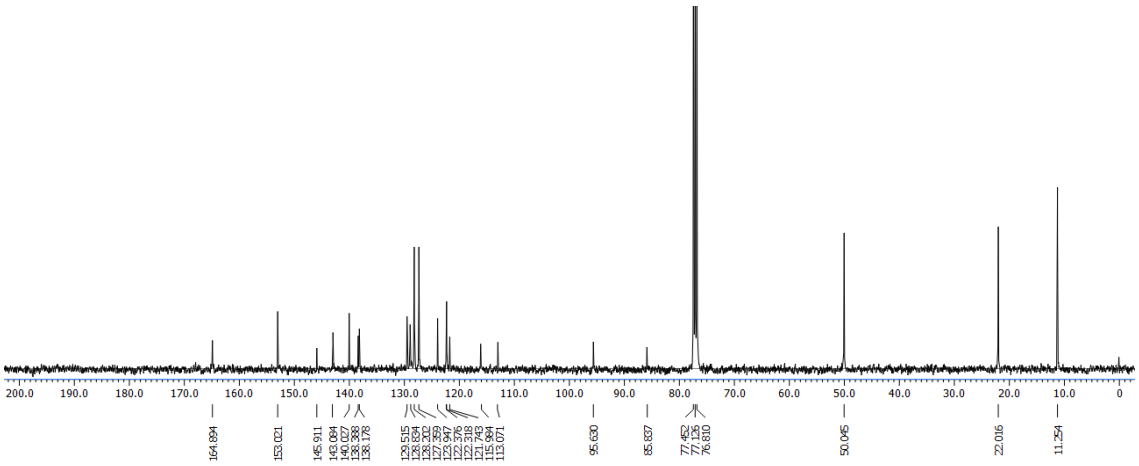
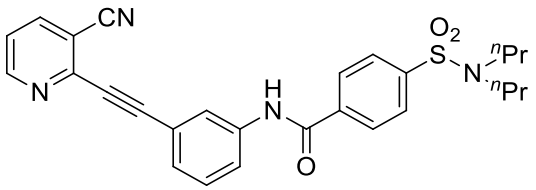


Figure 3.48

HRMS



***N*-(3-((3-cyanopyridin-2-yl)ethynyl)phenyl)-4-(*N*,*N*-dipropylsulfamoyl)benzamide (4b)**

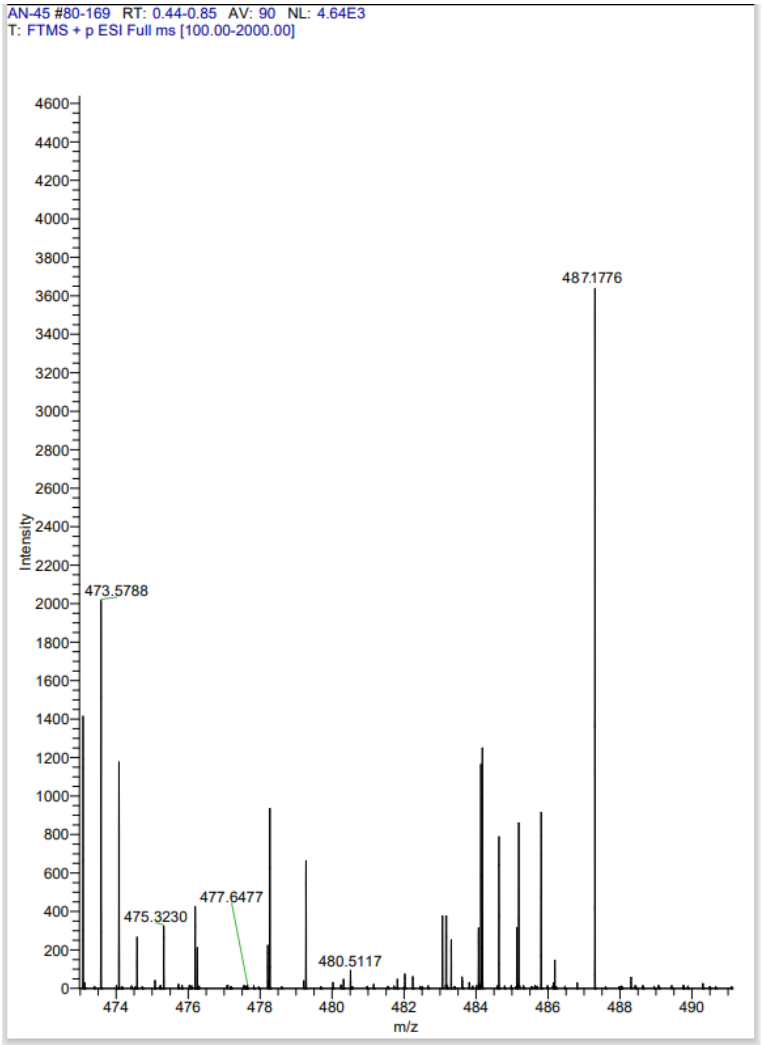
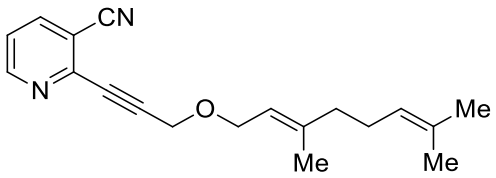
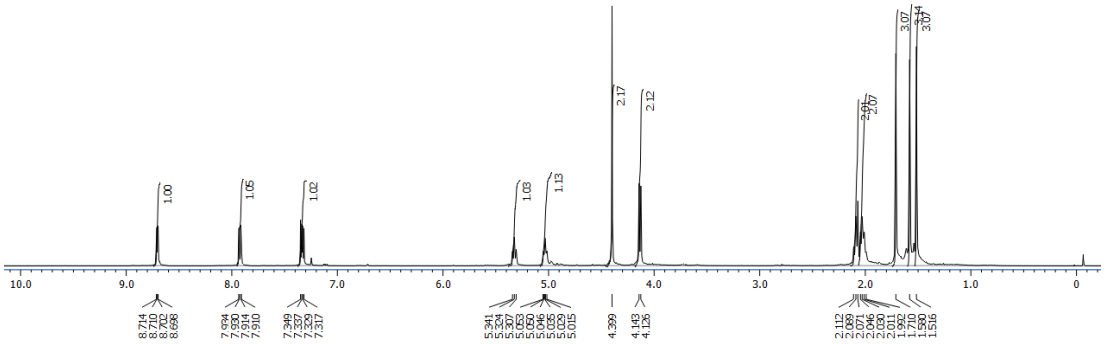


Figure 3.49

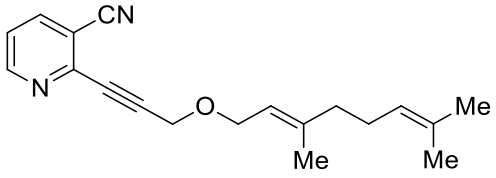
^{1}H NMR



(*E*)-2-(3-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)prop-1-yn-1-yl)nicotinonitrilele(4c)



^{13}C NMR



(*E*)-2-(3-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)prop-1-yn-1-yl)nicotinonitrilele(4c)

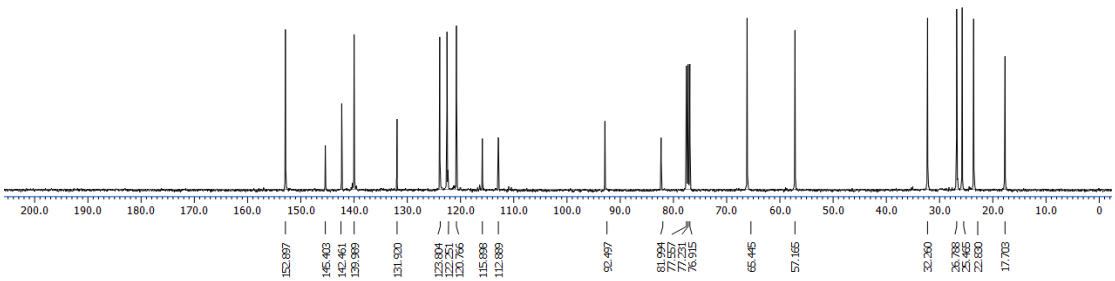
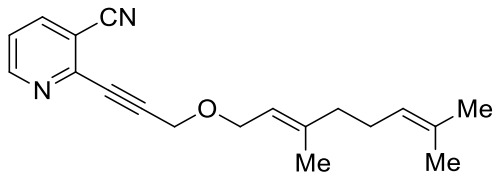


Figure 3.50

HRMS



(*E*)-2-(3-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)prop-1-yn-1-yl)nicotinonitrilele(4c)

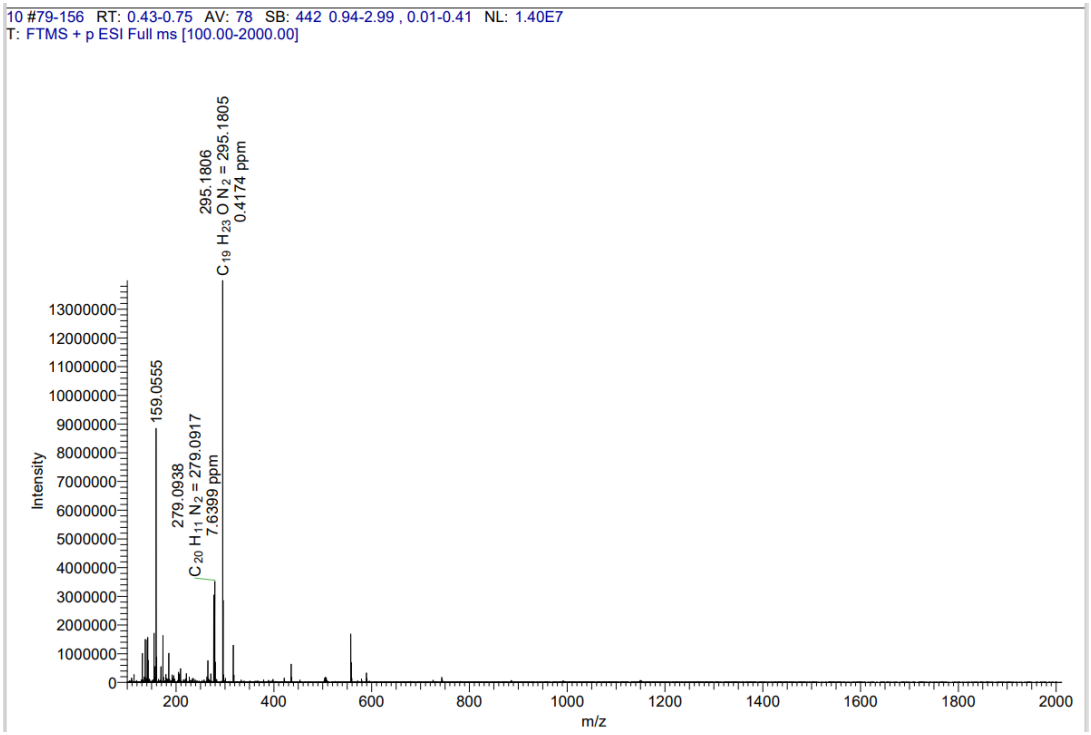
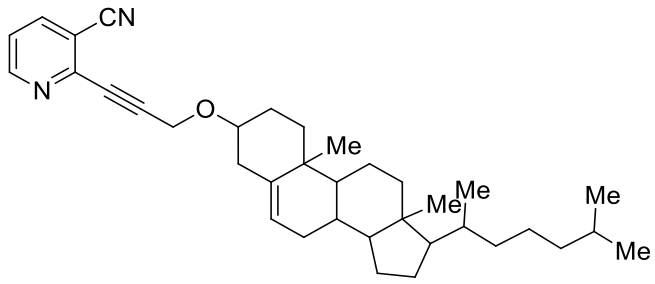


Figure 3.51

^{1}H NMR



2-(3-((10,13-Dimethyl-17-(6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)oxy)prop-1-yn-1-yl)nicotinonitrile (4d)

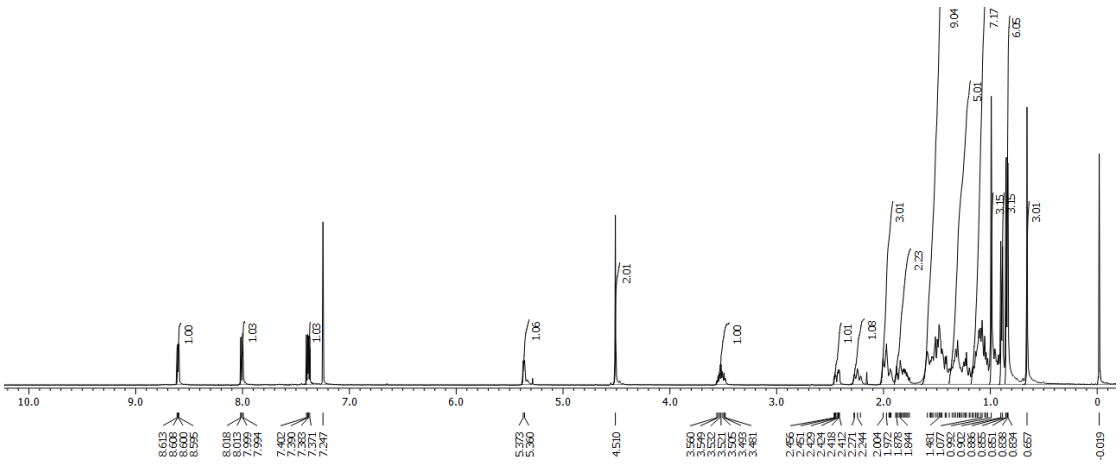
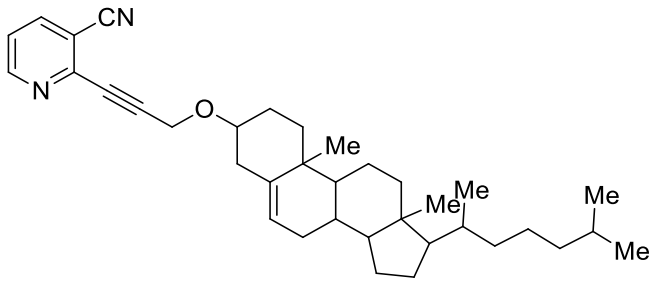


Figure 3.52

^{13}C NMR



2-(3-((10,13-Dimethyl-17-(6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)oxy)prop-1-yn-1-yl)nicotinonitrile (4d)

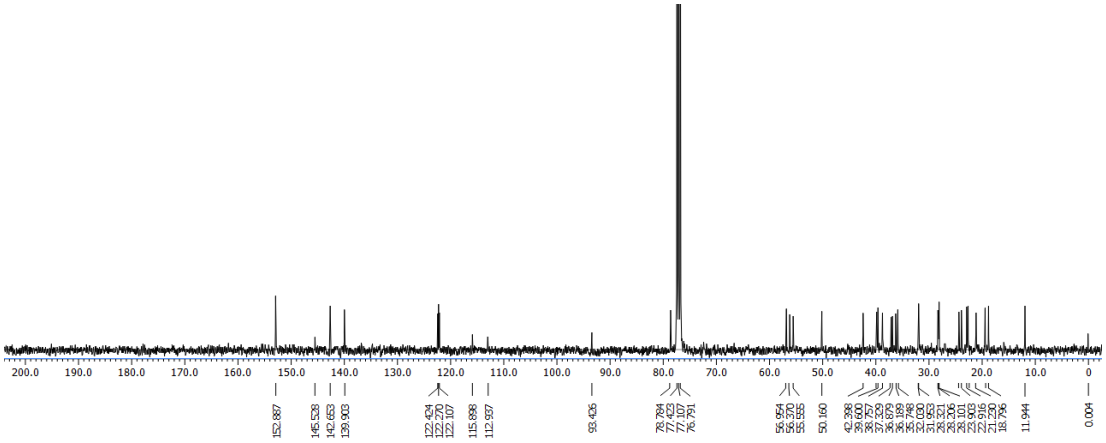
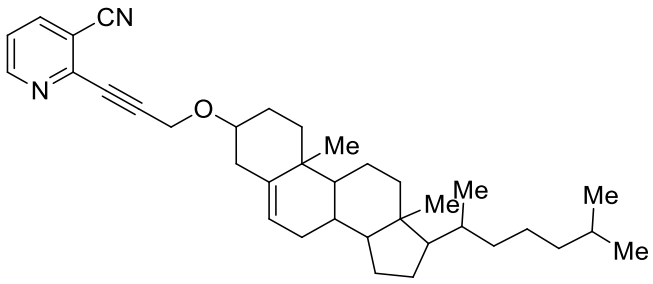


Figure 3.53

HRMS



2-(3-((10,13-Dimethyl-17-(6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)oxy)prop-1-yn-1-yl)nicotinonitrile (4d)

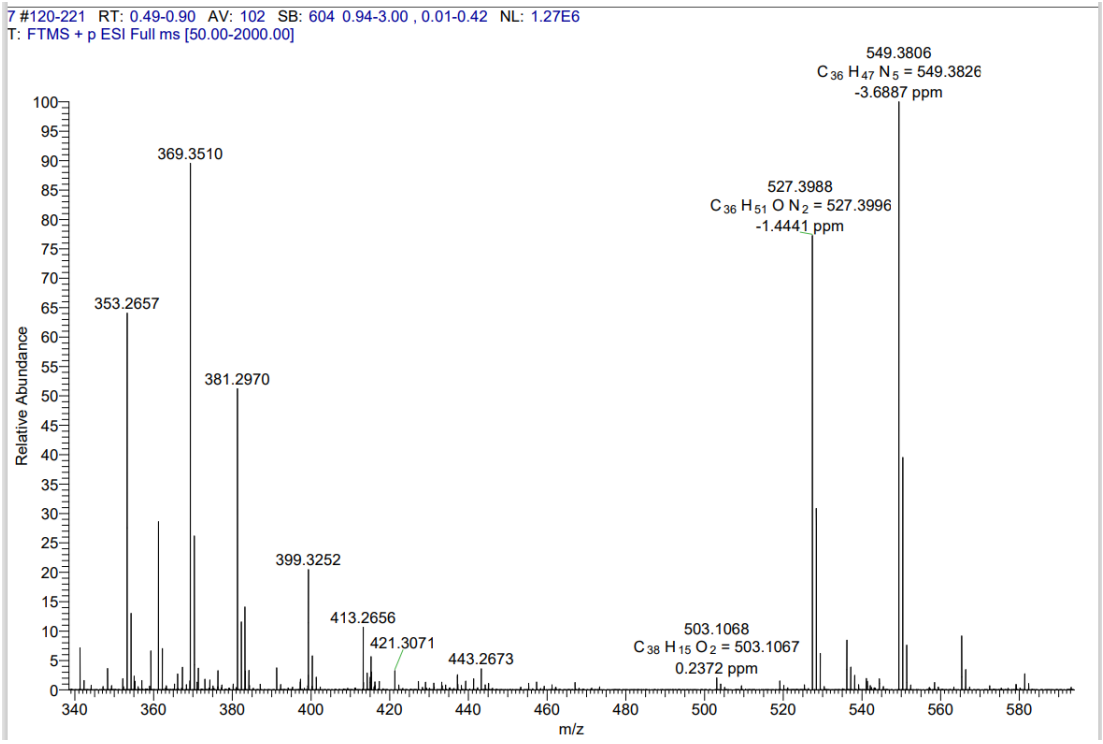
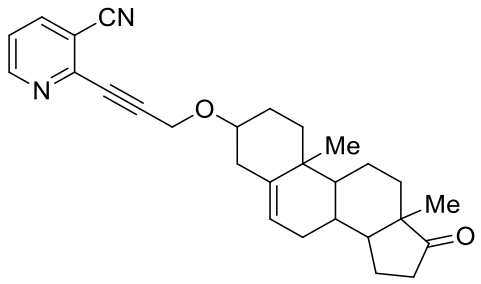


Figure 3.54

^{1}H NMR



2-(3-((10,13-Dimethyl-17-oxo-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)prop-1-yn-1-yl)nicotinonitrile (4e)

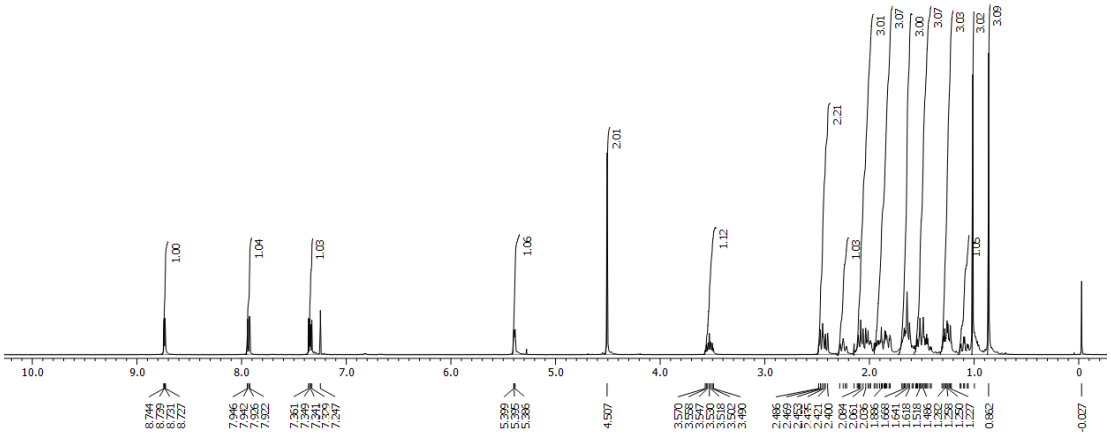
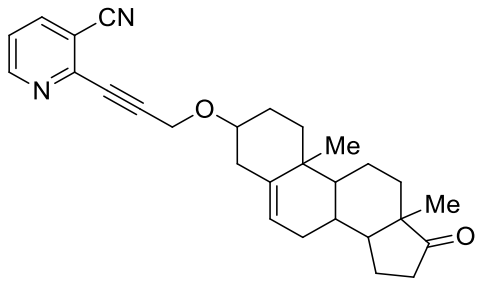


Figure 3.55

^{13}C NMR



2-(3-((10,13-Dimethyl-17-oxo-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)prop-1-yn-1-yl)nicotinonitrile (4e)

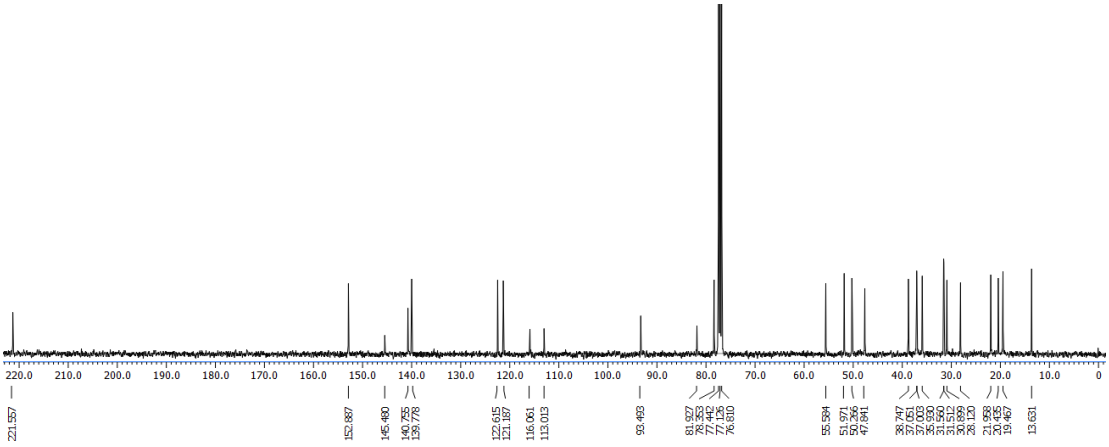
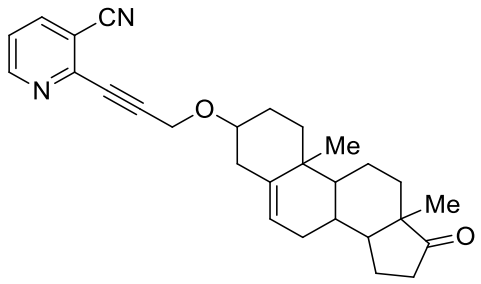


Figure 3.56

HRMS



2-(3-((10,13-Dimethyl-17-oxo-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)prop-1-yn-1-yl)nicotinonitrile (4e)

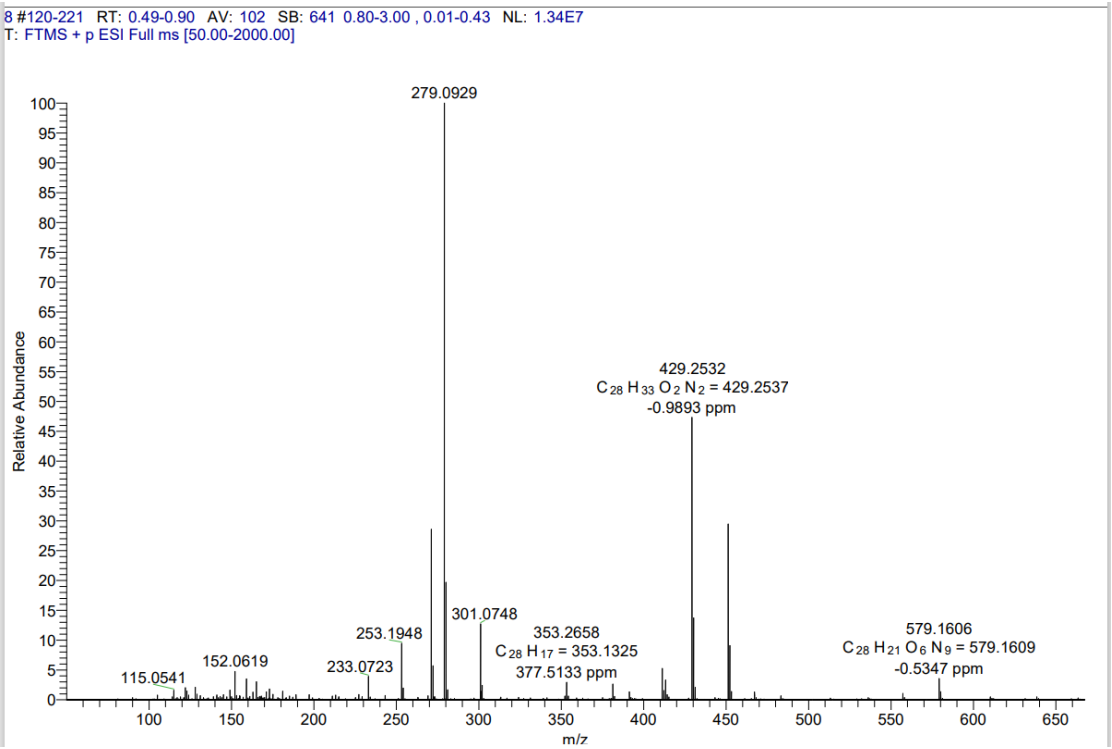
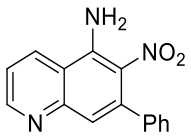
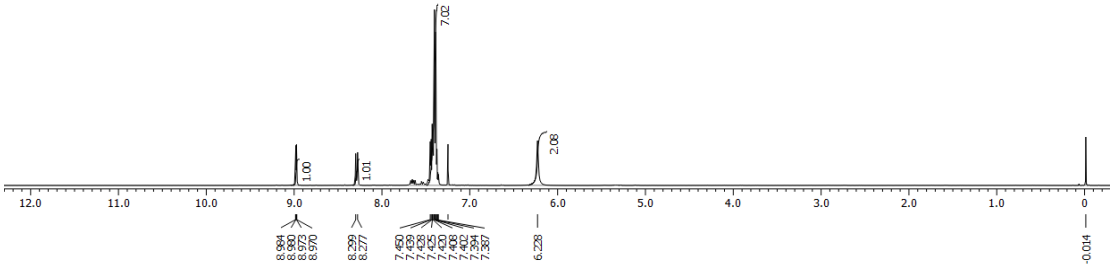


Figure 3.57

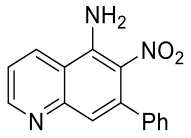
^{1}H NMR



6-Nitro-7-phenylquinolin-5-amine (3a)



^{13}C NMR



6-Nitro-7-phenylquinolin-5-amine (3a)

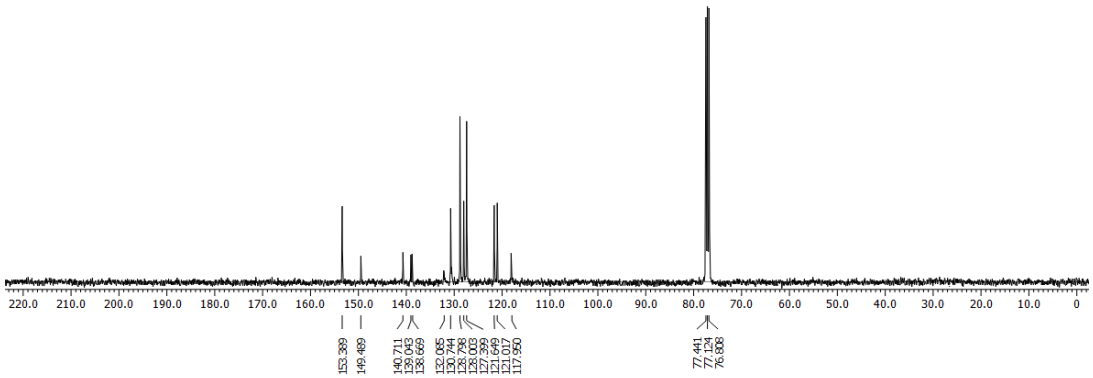
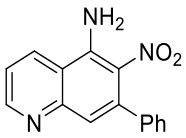


Figure 3.58

HRMS



6-Nitro-7-phenylquinolin-5-amine (3a)

Qualitative Compound Report

Data File	SV-814.d	**Sample Name**	SV-814
Sample Type	Sample	**Position**	P1-E5
Instrument Name	Instrument 1	**User Name**	
Acq Method	Damo JK.m	**Acquired Time**	02-05-2019 16:02:13
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

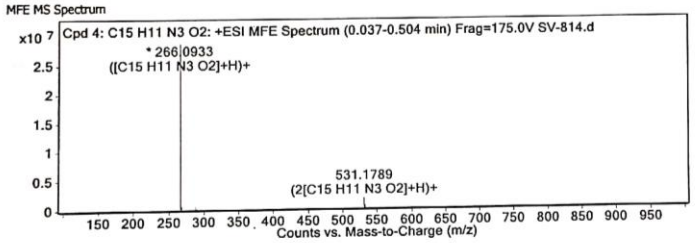
Sample Group **Info.**
Acquisition SW Version 6200 series TOF/6500 series Q-TOF B.05.01 (B5125.1)

Compound Table

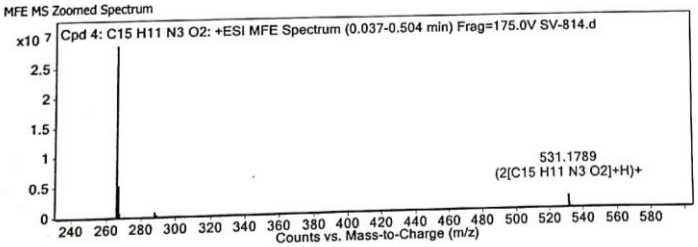
Compound Label	RT	Mass	Formula	MFG Formula	MFG Diff (ppm)	DB Formula
Cpd 4: C15 H11 N3 O2	0.102	265.0861	C15 H11 N3 O2	C15 H11 N3 O2	-3.59	C15 H11 N3 O2

Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 4: C15 H11 N3 O2	266.0933	0.102	Find by Molecular Feature	265.0861

MFE MS Spectrum



MFE MS Zoomed Spectrum



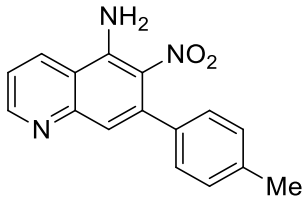
MS Spectrum Peak List

m/z	z	Abund	Formula	Ion
266.0933	1	28697120	C15 H11 N3 O2	(M+H)+
267.0965	1	5393556.09	C15 H11 N3 O2	(M+H)+
268.0991	1	544195.77	C15 H11 N3 O2	(M+H)+
269.1013	1	34599.35	C15 H11 N3 O2	(M+H)+
288.0753	1	553538.5	C15 H11 N3 O2	(M+Na)+
289.0782	1	95556.88	C15 H11 N3 O2	(M+Na)+
531.1789	1	1708551.38	C15 H11 N3 O2	(2M+H)+
532.1819	1	608271.54	C15 H11 N3 O2	(2M+H)+
533.1841	1	108411.29	C15 H11 N3 O2	(2M+H)+
534.1854	1	16418.73	C15 H11 N3 O2	(2M+H)+

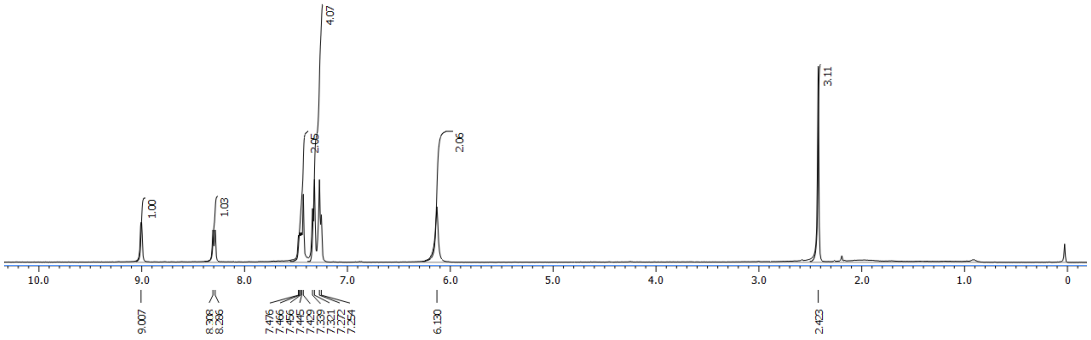
--- End Of Report ---

Figure 3.59

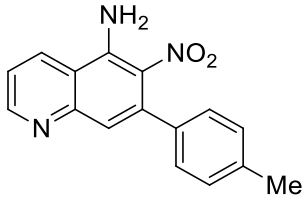
^{1}H NMR



6-Nitro-7-(*p*-tolyl)quinolin-5-amine (3b)



^{13}C NMR



6-Nitro-7-(*p*-tolyl)quinolin-5-amine (3b)

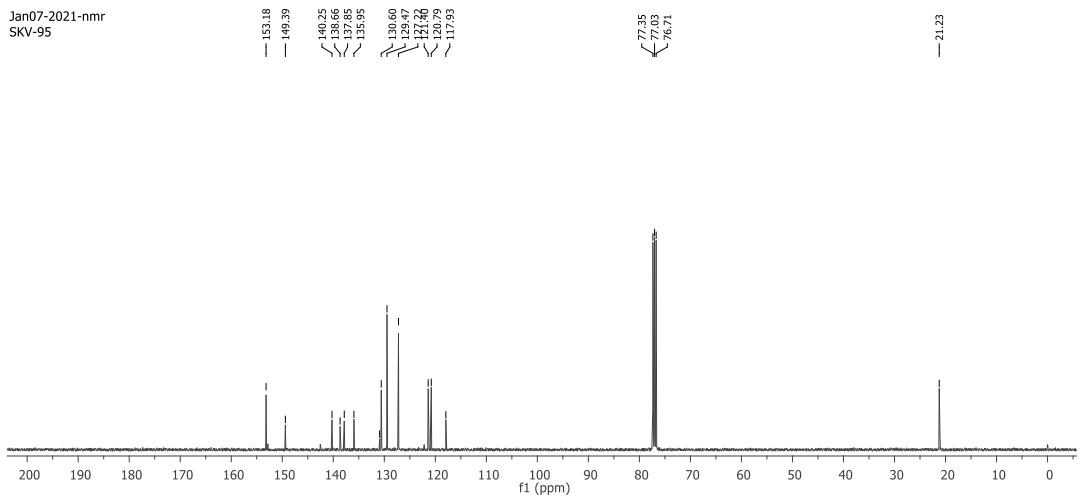
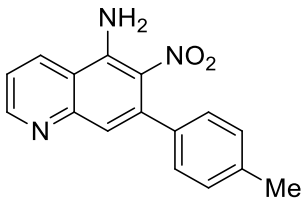


Figure 3.60

HRMS



6-Nitro-7-(*p*-tolyl)quinolin-5-amine (3b)

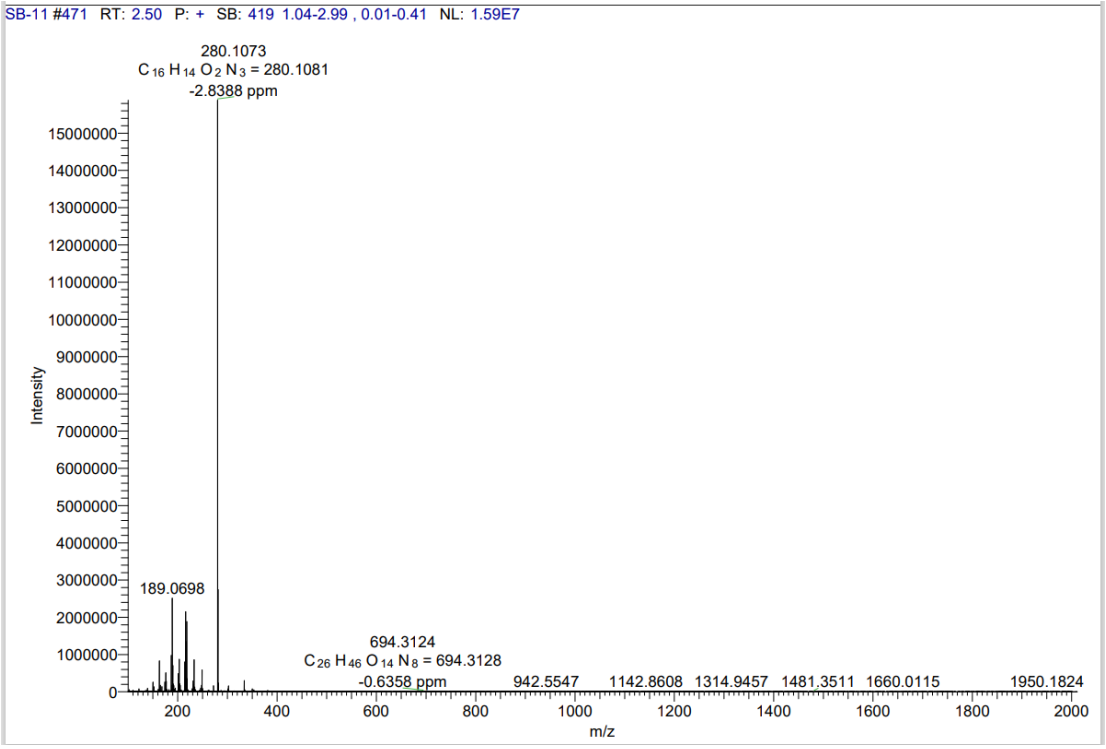
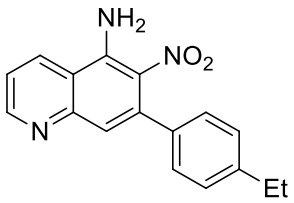
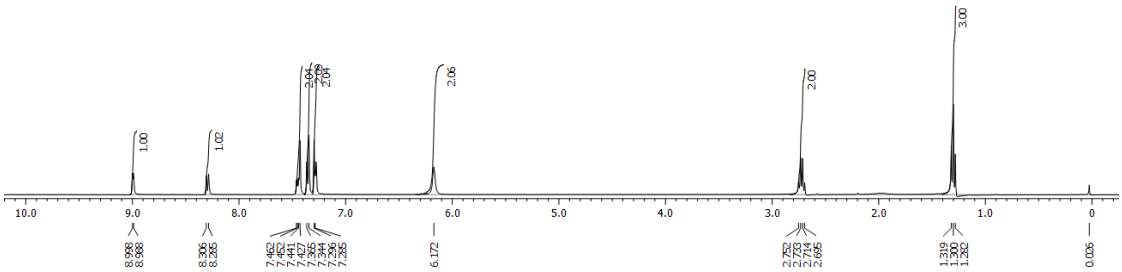


Figure 3.61

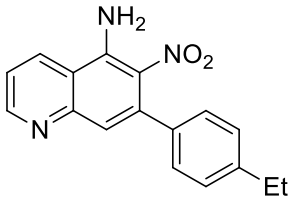
^{1}H NMR



7-(4-Ethylphenyl)-6-nitroquinolin-5-amine (3c)



^{13}C NMR



7-(4-Ethylphenyl)-6-nitroquinolin-5-amine (3c)

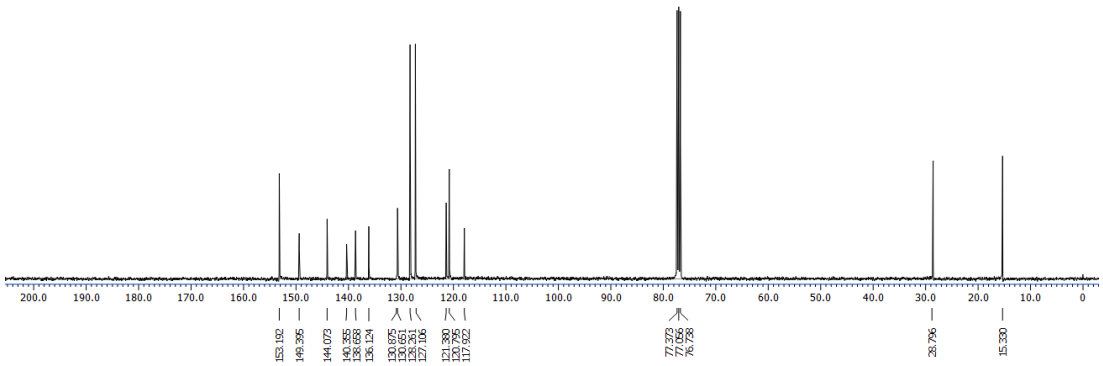
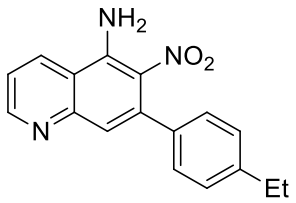


Figure 3.62

HRMS



7-(4-Ethylphenyl)-6-nitroquinolin-5-amine (3c)

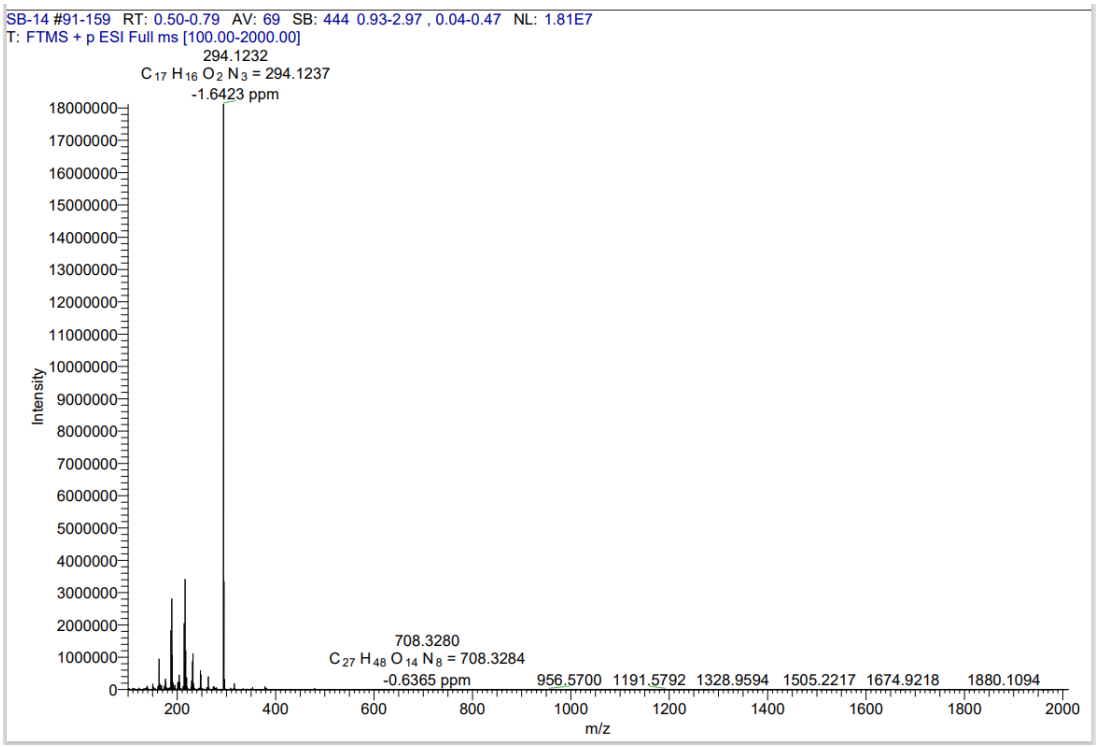
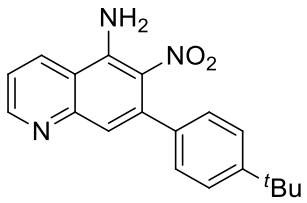
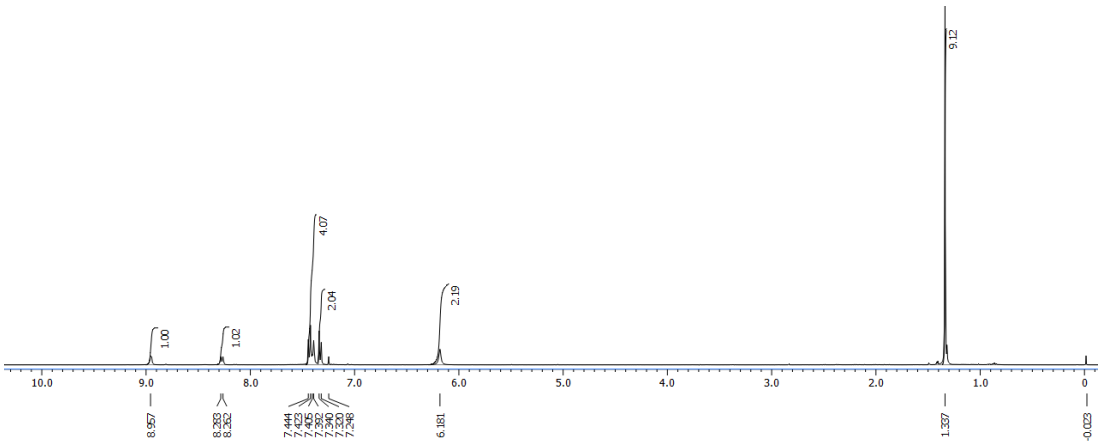


Figure 3.63

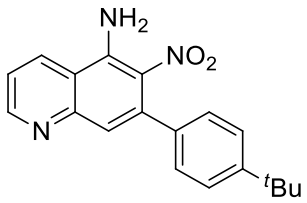
^{1}H NMR



7-(4-(*tert*-Butyl)phenyl)-6-nitroquinolin-5-amine (3d)



^{13}C NMR



7-(4-(*tert*-Butyl)phenyl)-6-nitroquinolin-5-amine (3d)

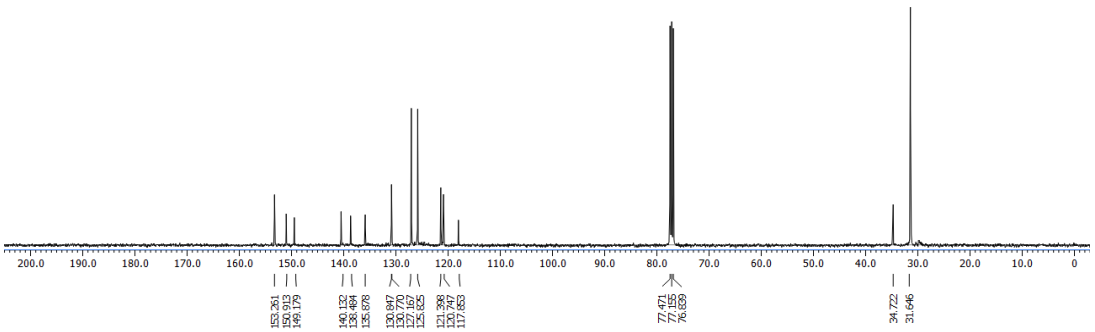
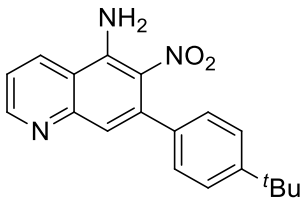


Figure 3.64

HRMS



7-(4-(*tert*-Butyl)phenyl)-6-nitroquinolin-5-amine (3d)

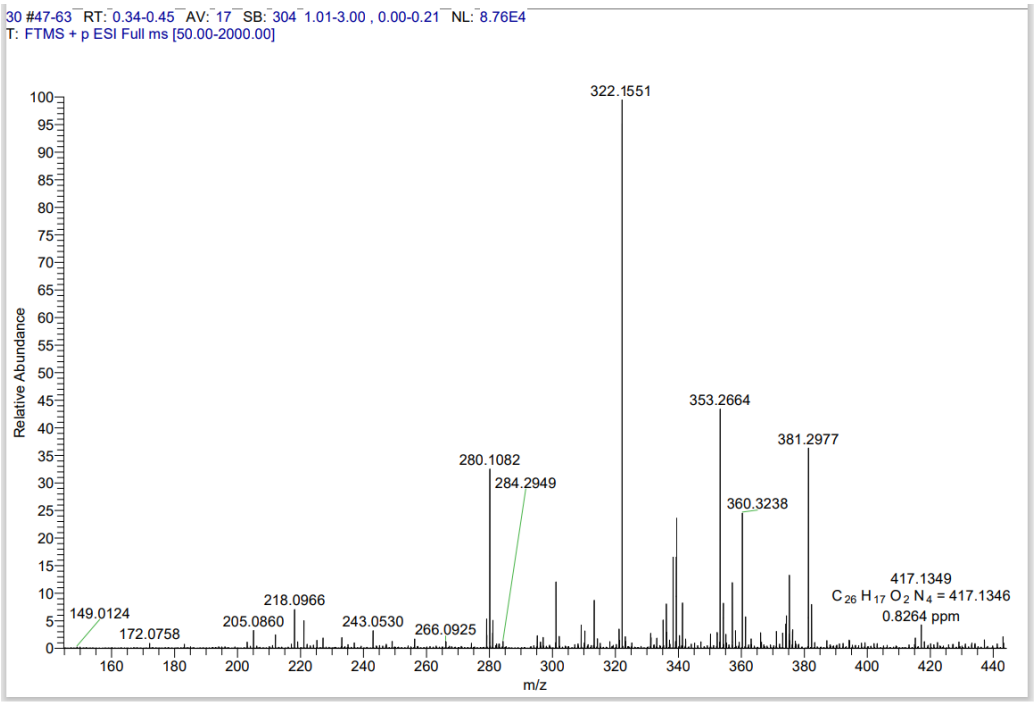
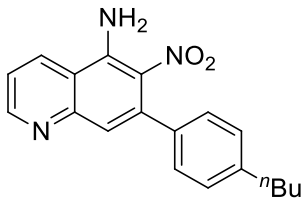


Figure 3.65

^{1}H NMR



7-(4-Butylphenyl)-6-nitroquinolin-5-amine (3e)

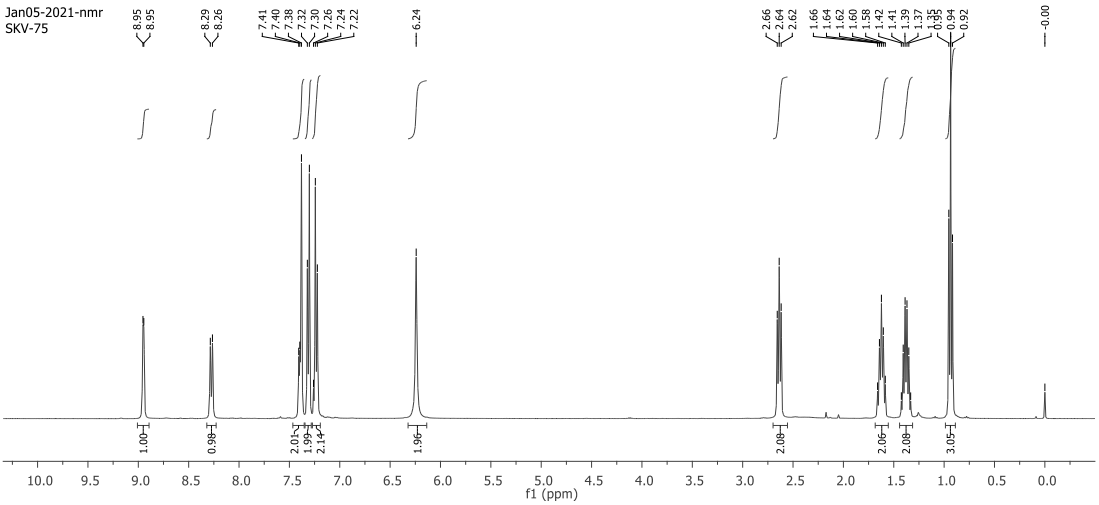
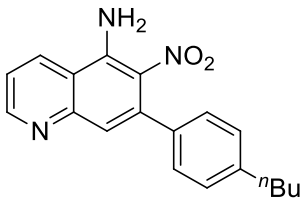


Figure 3.66

^{13}C NMR



7-(4-Butylphenyl)-6-nitroquinolin-5-amine (3e)

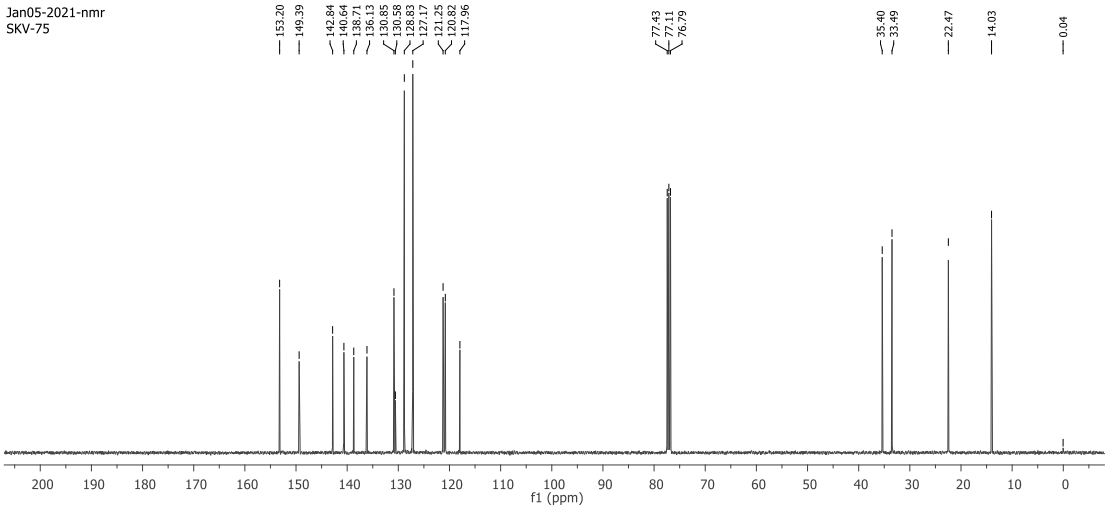
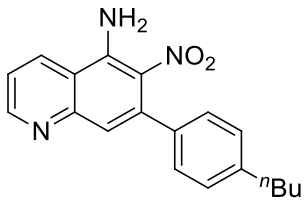


Figure 3.67

HRMS



7-(4-Butylphenyl)-6-nitroquinolin-5-amine (3e)

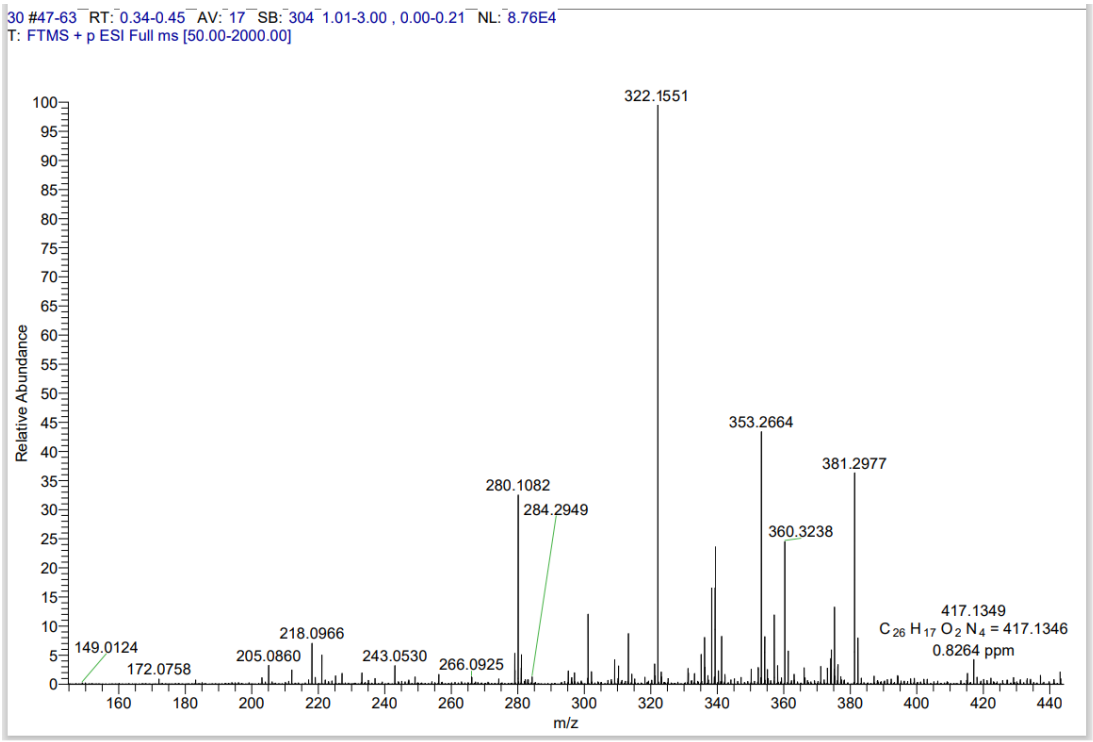
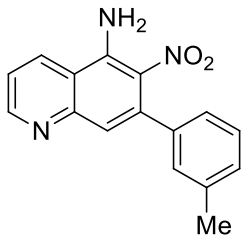
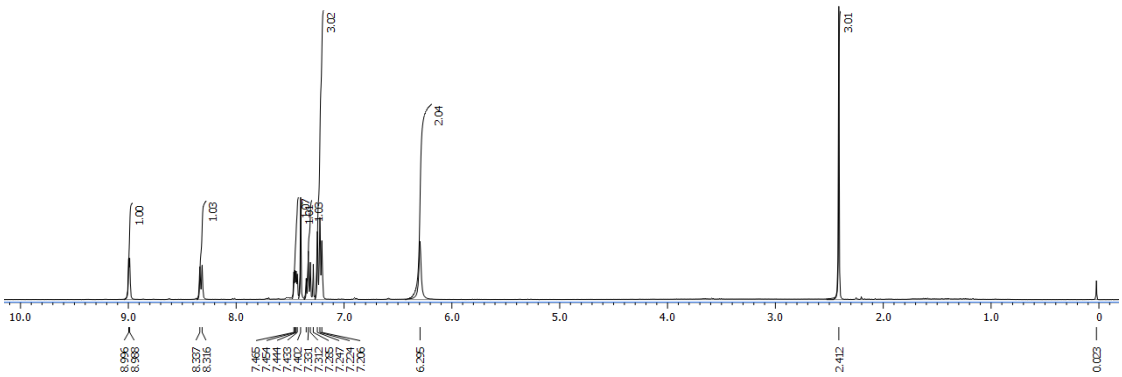


Figure 3.68

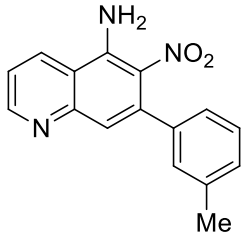
^{1}H NMR



6-Nitro-7-(m-tolyl)quinolin-5-amine (3f)



^{13}C NMR



6-Nitro-7-(m-tolyl)quinolin-5-amine (3f)

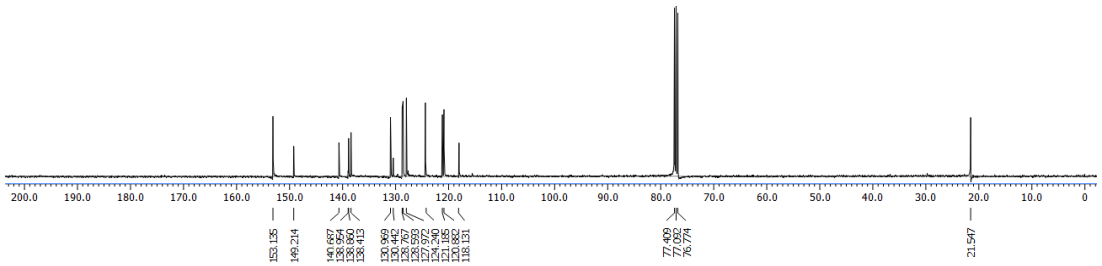
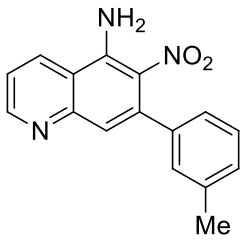


Figure 3.69

HRMS



6-Nitro-7-(m-tolyl)quinolin-5-amine (3f)

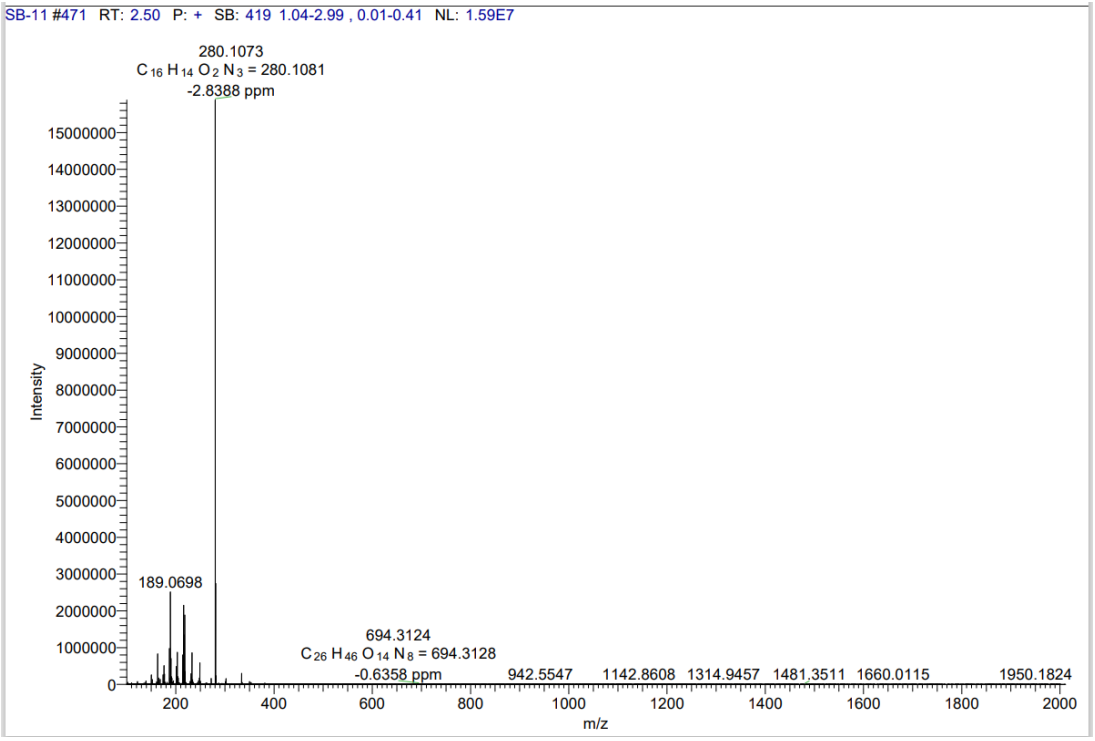
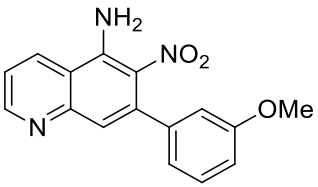
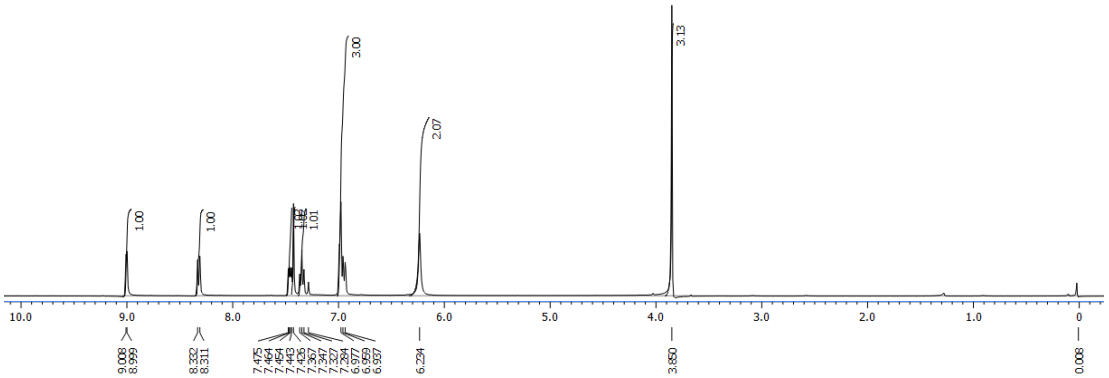


Figure 3.70

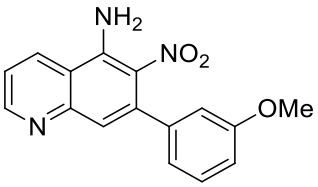
^{1}H NMR



7-(3-Methoxyphenyl)-6-nitroquinolin-5-amine (3g)



^{13}C NMR



7-(3-Methoxyphenyl)-6-nitroquinolin-5-amine (3g)

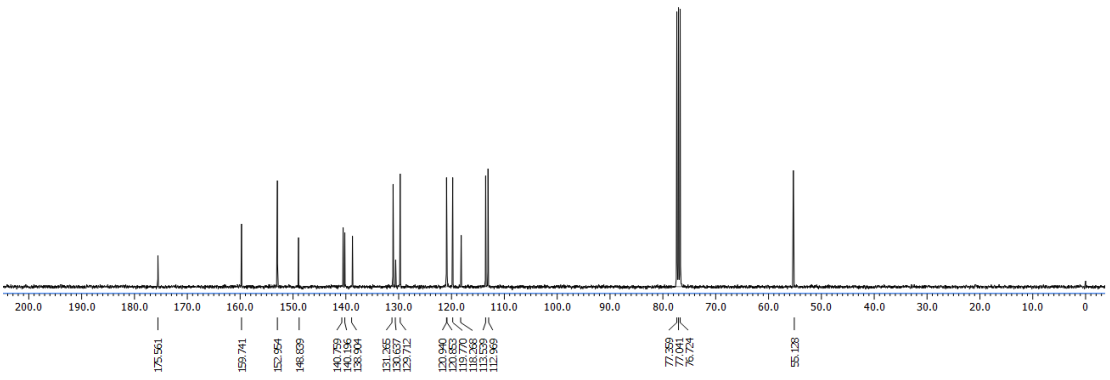
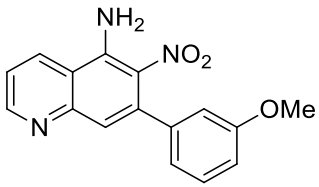


Figure 3.71

HRMS



7-(3-Methoxyphenyl)-6-nitroquinolin-5-amine (3g)

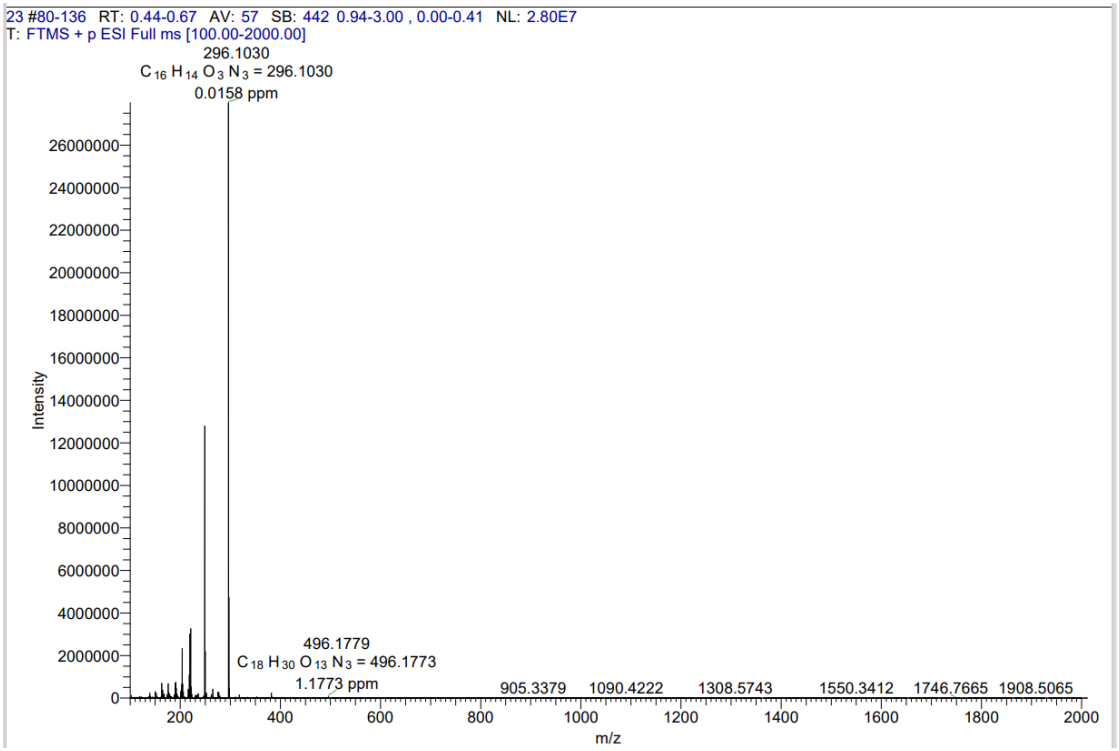
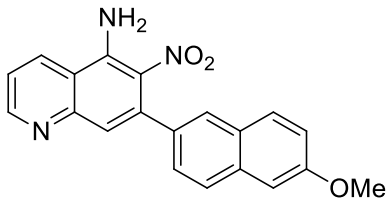
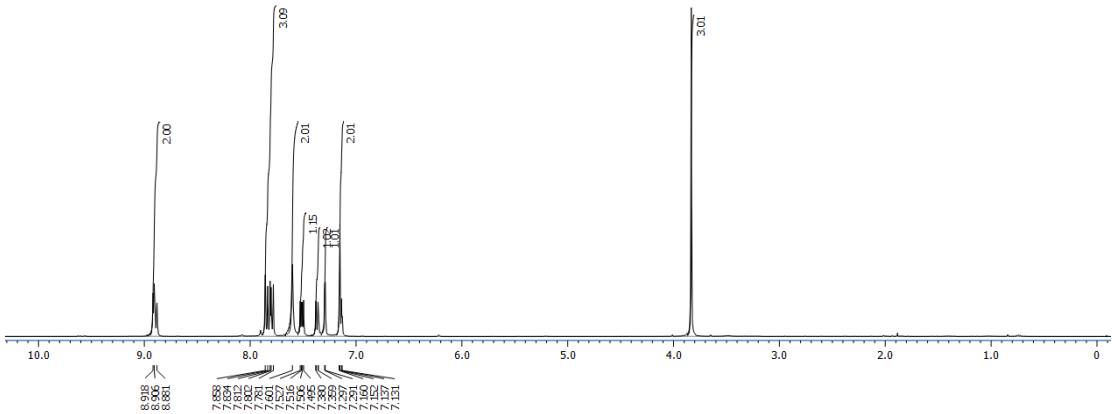


Figure 3.72

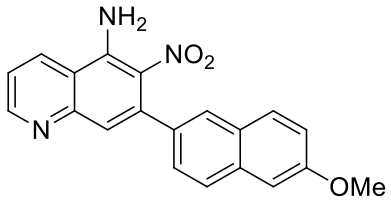
^{1}H NMR



7-(6-Methoxynaphthalen-2-yl)-6-nitroquinolin-5-amine (3h)



^{13}C NMR



7-(6-Methoxynaphthalen-2-yl)-6-nitroquinolin-5-amine (3h)

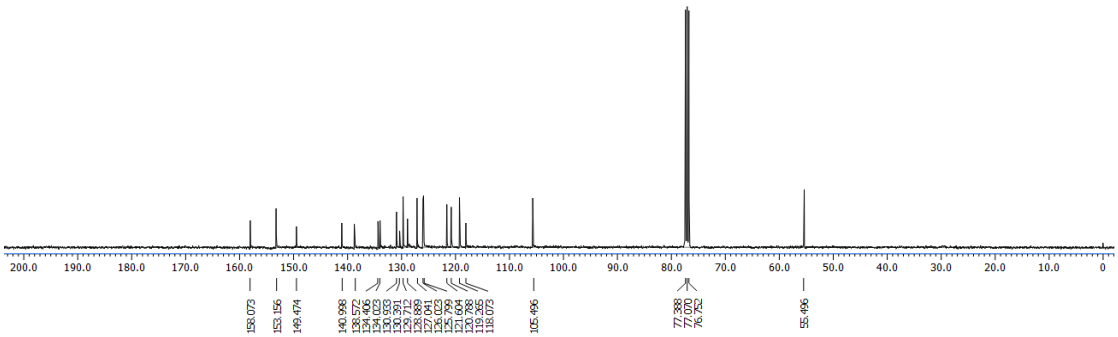
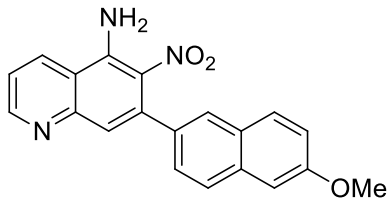


Figure 3.73

HRMS



7-(6-Methoxynaphthalen-2-yl)-6-nitroquinolin-5-amine (3h)

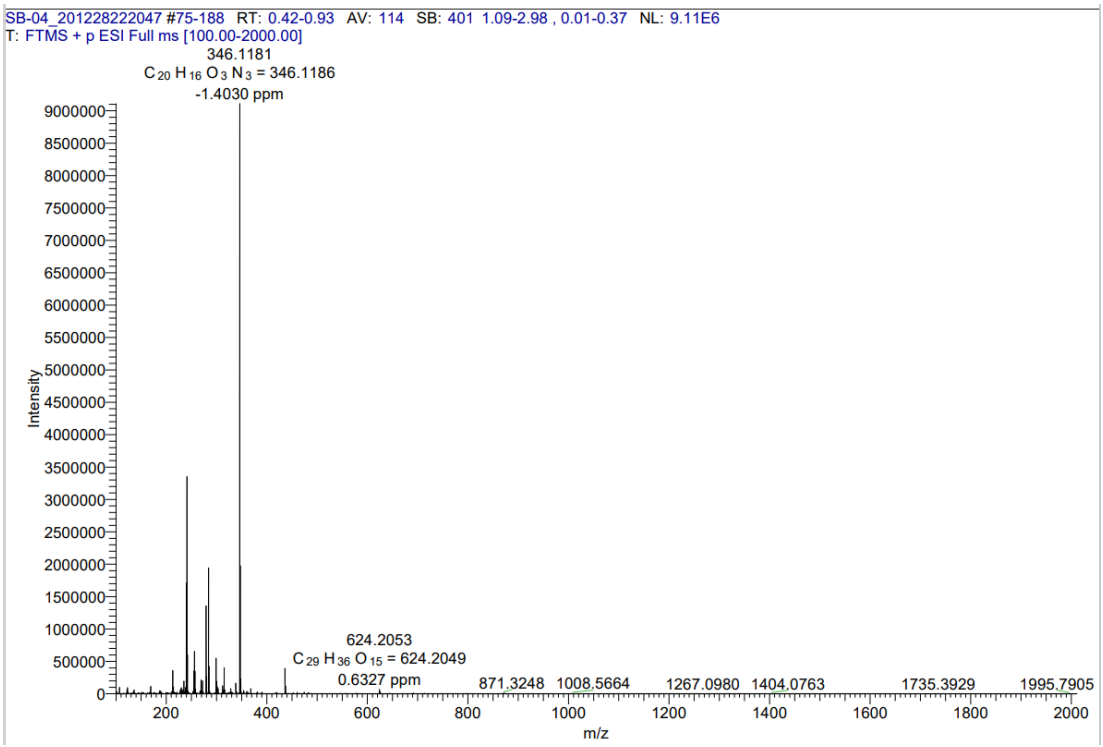
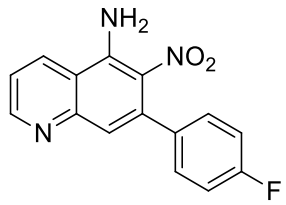
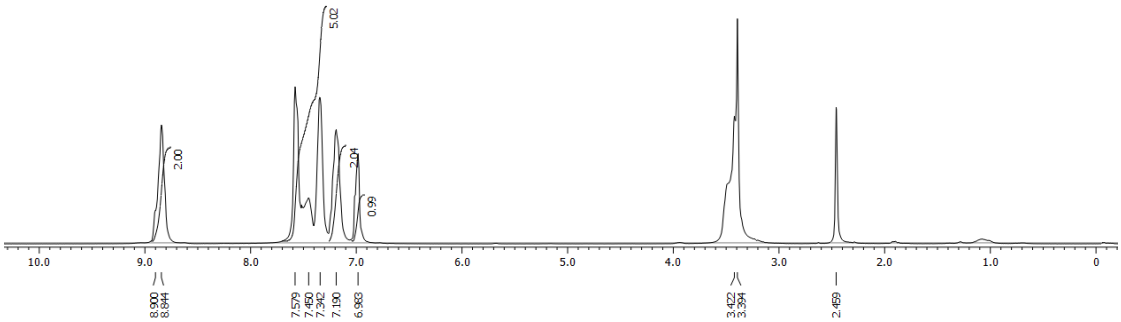


Figure 3.74

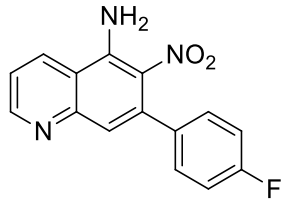
^{1}H NMR



7-(4-Fluorophenyl)-6-nitroquinolin-5-amine (3i)



^{13}C NMR



7-(4-Fluorophenyl)-6-nitroquinolin-5-amine (3i)

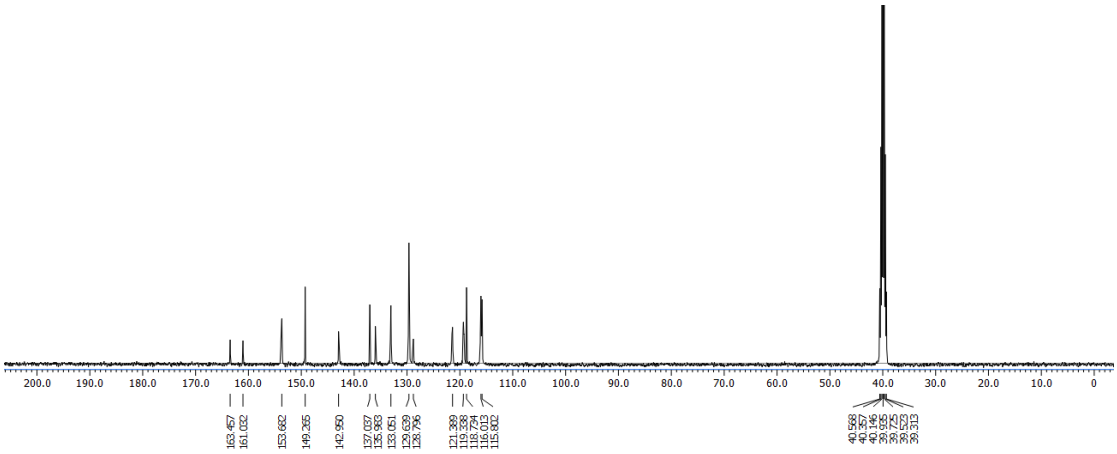
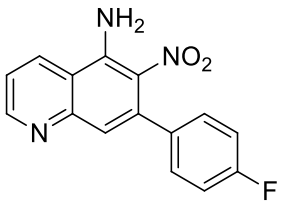


Figure 3.75

HRMS



7-(4-Fluorophenyl)-6-nitroquinolin-5-amine (3i)

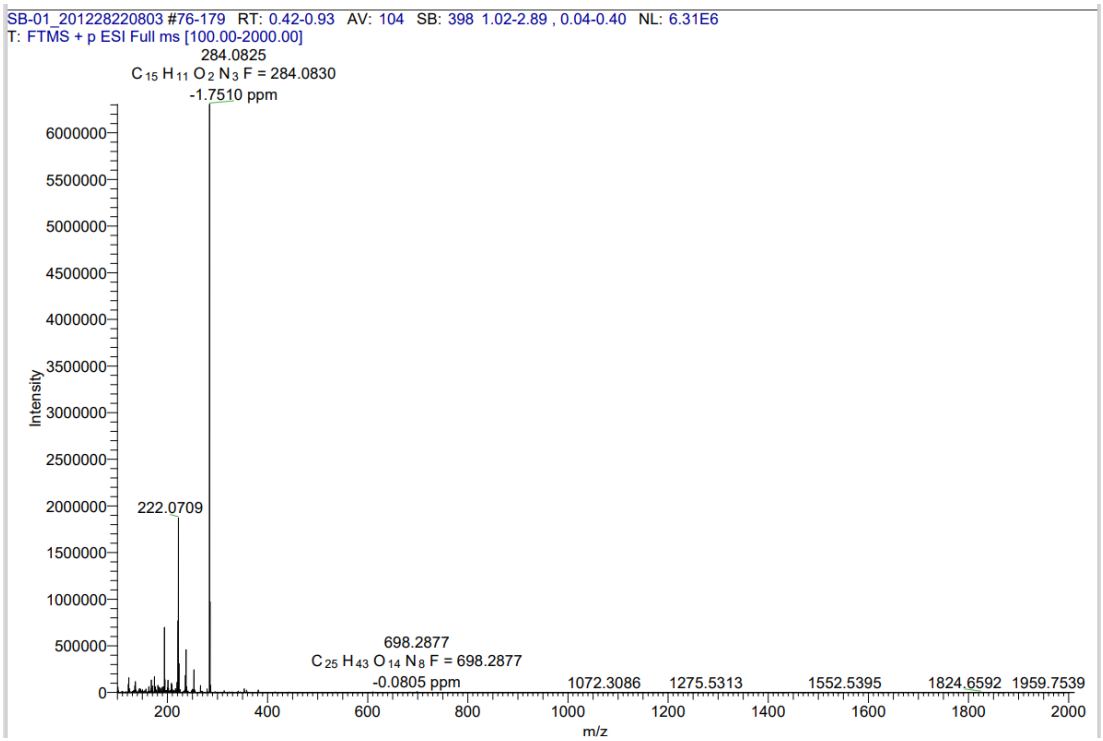
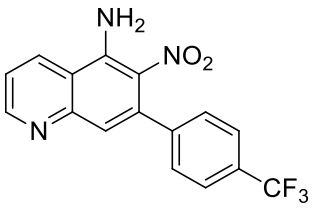
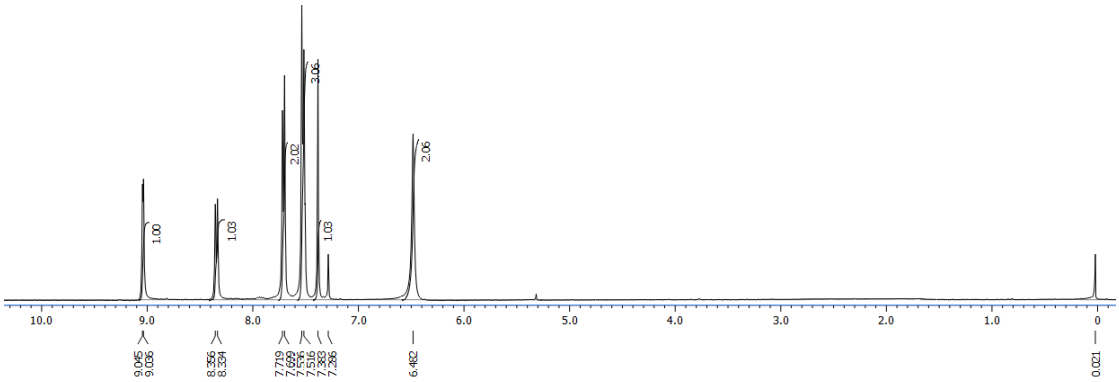


Figure 3.76

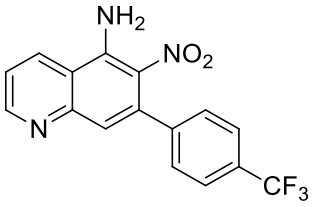
^{1}H NMR



6-Nitro-7-(4-(trifluoromethyl)phenyl)quinolin-5-amine (3j)



^{13}C NMR



6-Nitro-7-(4-(trifluoromethyl)phenyl)quinolin-5-amine (3j)

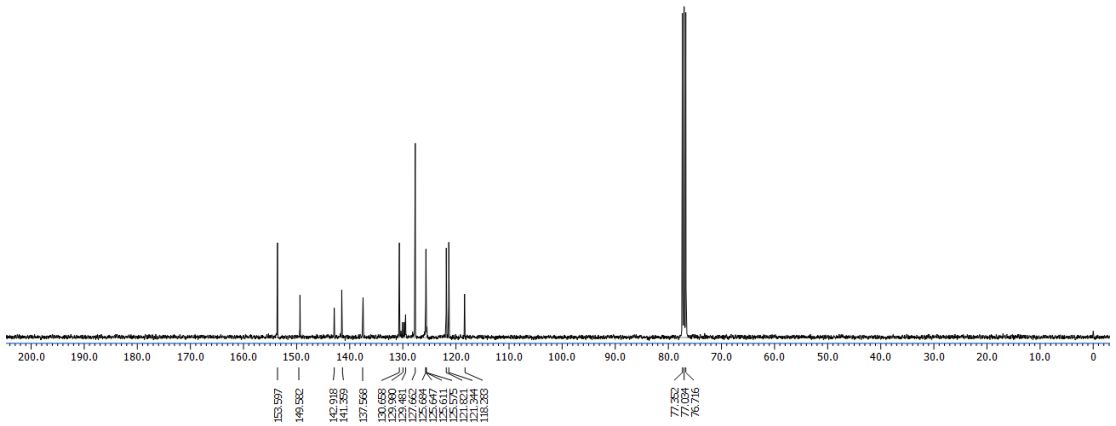
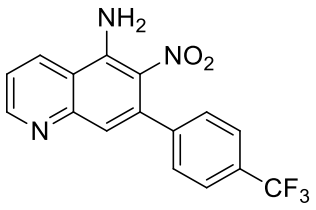


Figure 3.77

HRMS



6-Nitro-7-(4-(trifluoromethyl)phenyl)quinolin-5-amine (3j)

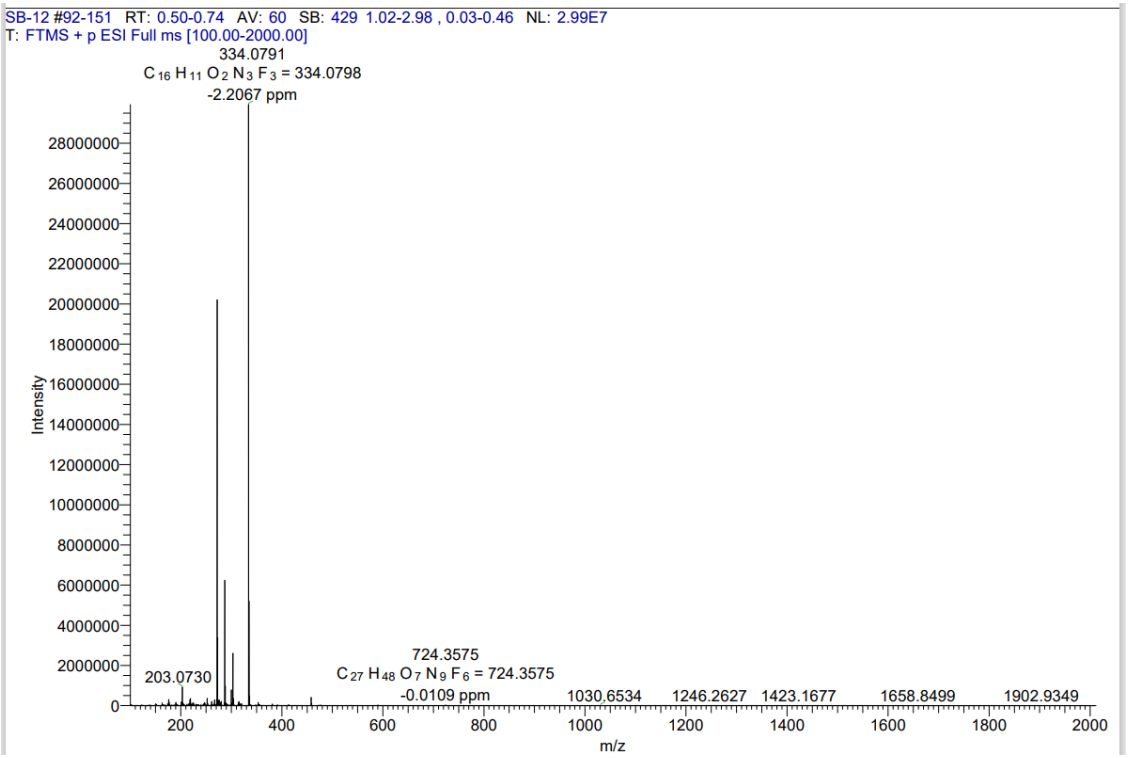
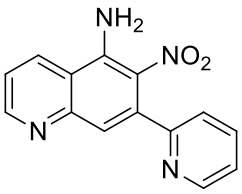
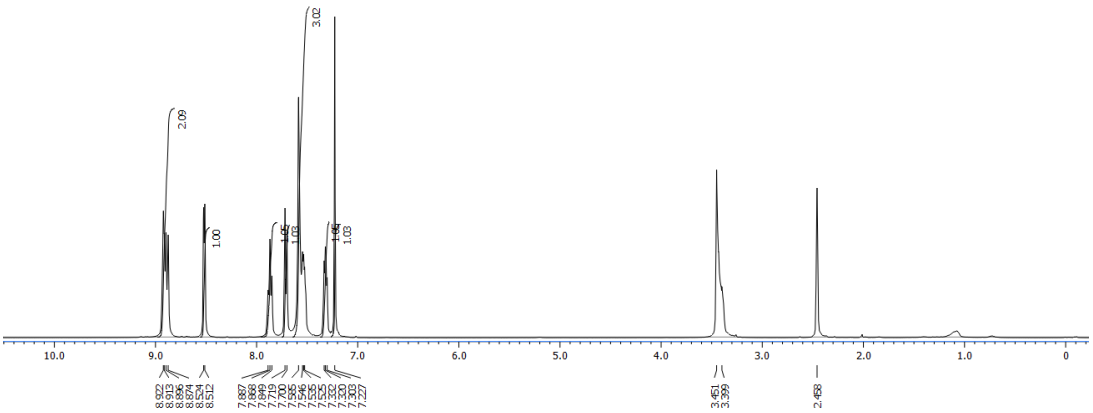


Figure 3.78

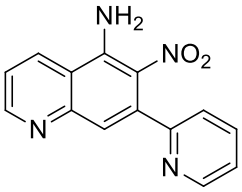
^{1}H NMR



6-Nitro-7-(pyridin-2-yl)quinolin-5-amine (3k)



^{13}C NMR



6-Nitro-7-(pyridin-2-yl)quinolin-5-amine (3k)

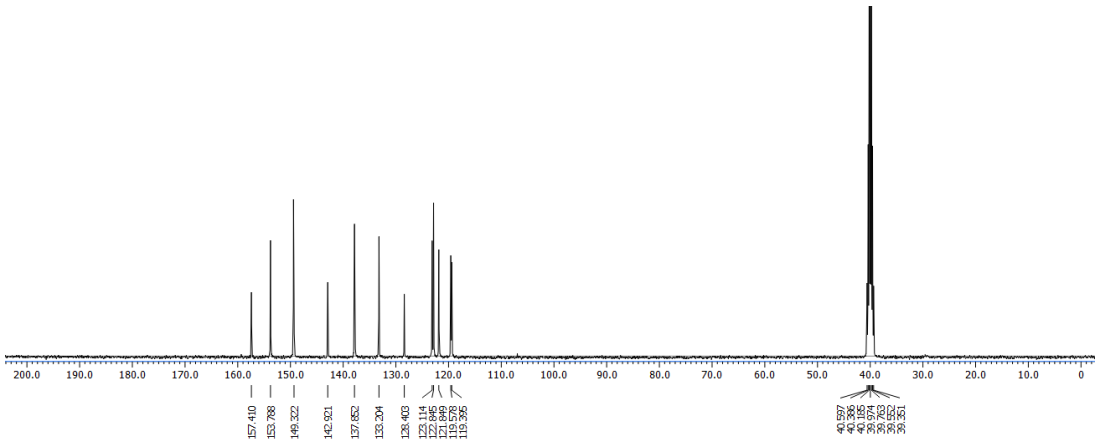
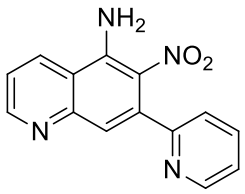


Figure 3.79

HRMS



6-Nitro-7-(pyridin-2-yl)quinolin-5-amine (3k)

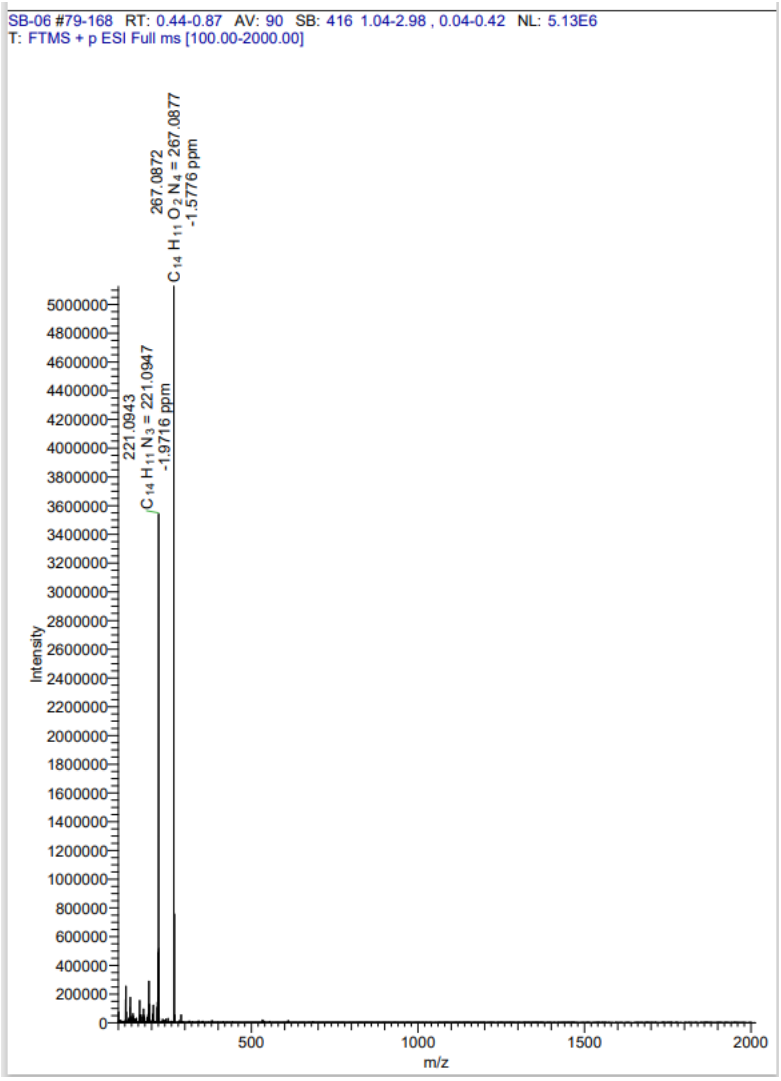
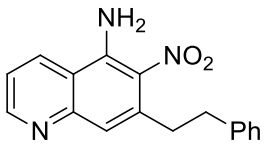
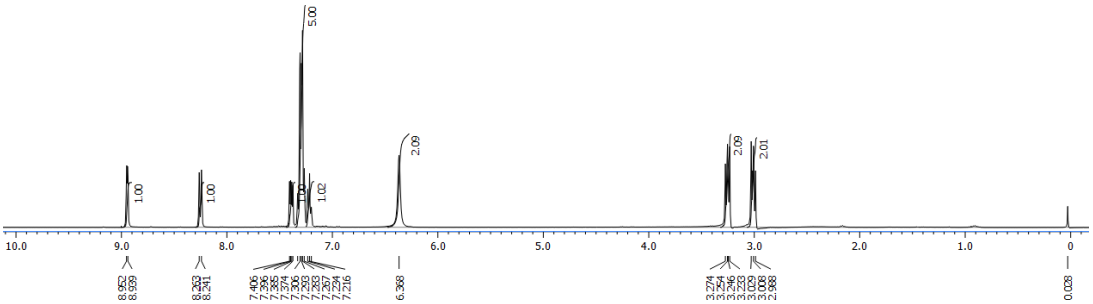


Figure 3.80

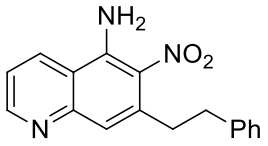
^{1}H NMR



6-Nitro-7-phenethylquinolin-5-amine (3l)



^{13}C NMR



6-Nitro-7-phenethylquinolin-5-amine (3l)

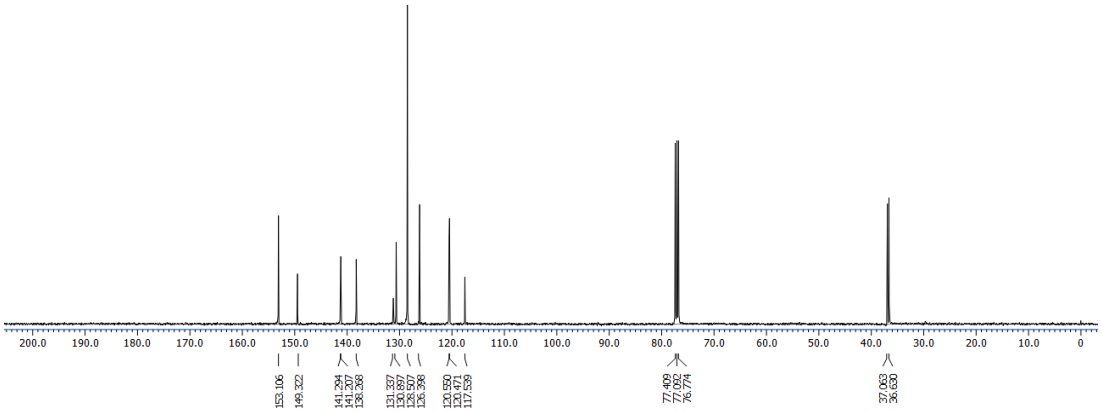
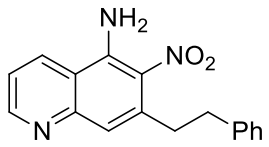


Figure 3.81

HRMS



6-Nitro-7-phenethylquinolin-5-amine (3l)

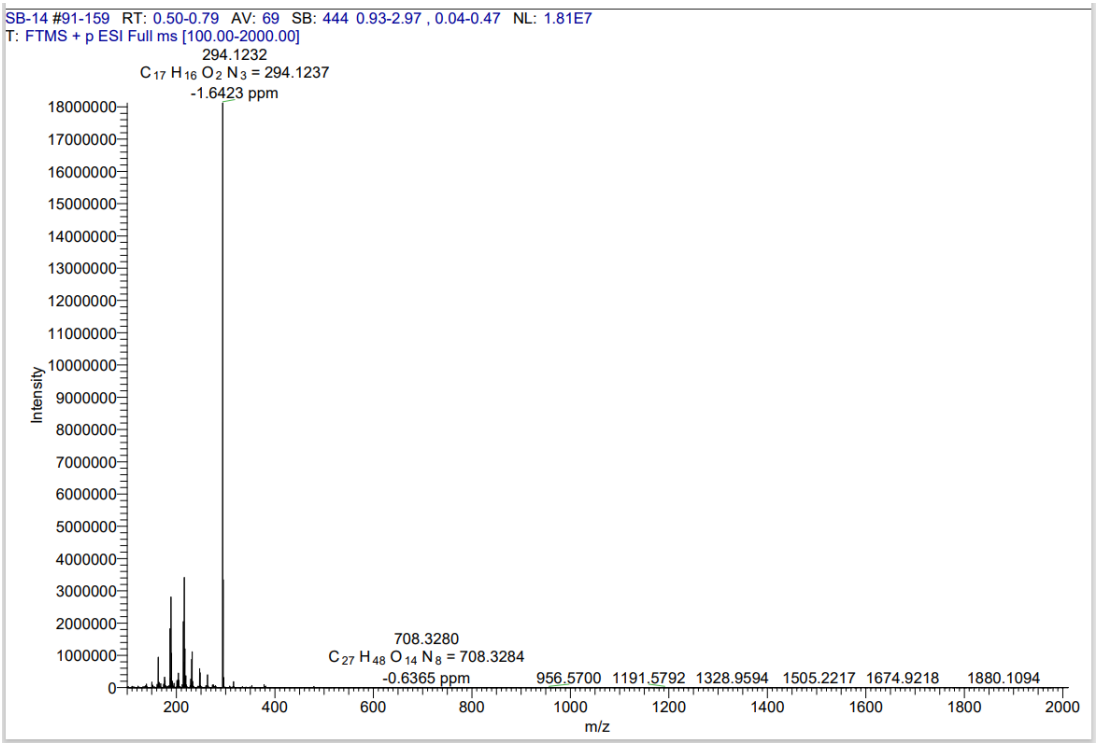
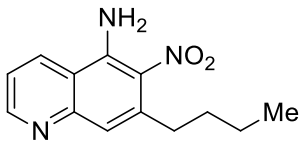
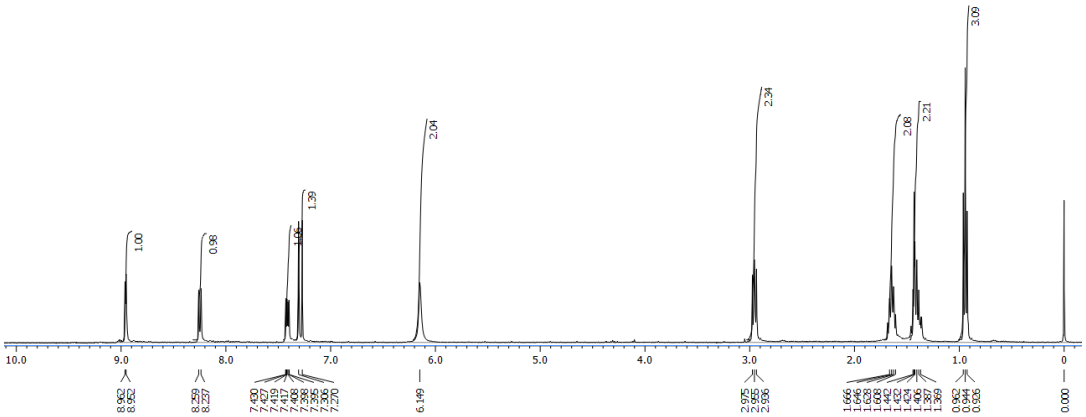


Figure 3.82

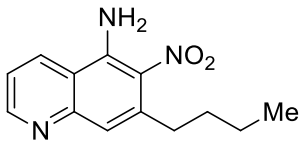
^{1}H NMR



7-Butyl-6-nitroquinolin-5-amine (3m)



^{13}C NMR



7-Butyl-6-nitroquinolin-5-amine (3m)

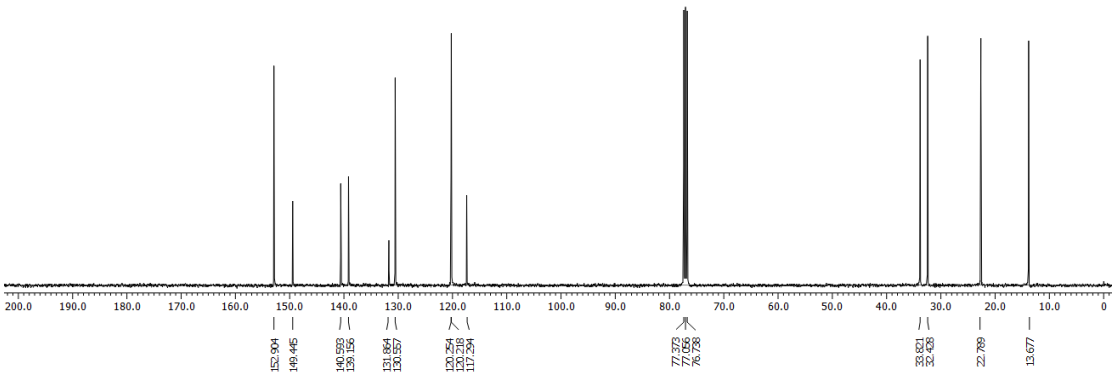
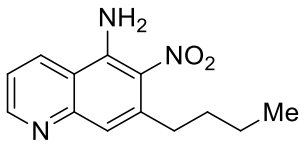


Figure 3.83

HRMS



7-Butyl-6-nitroquinolin-5-amine (3m)

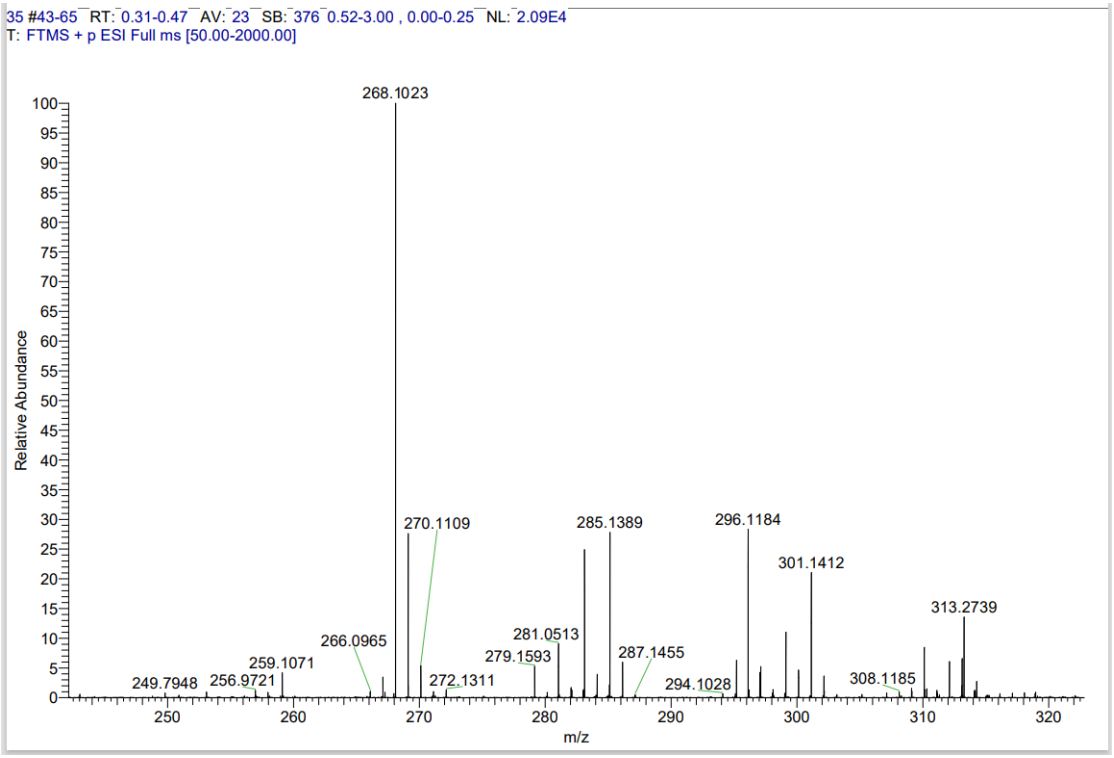
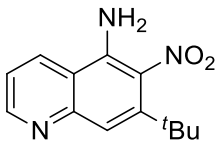
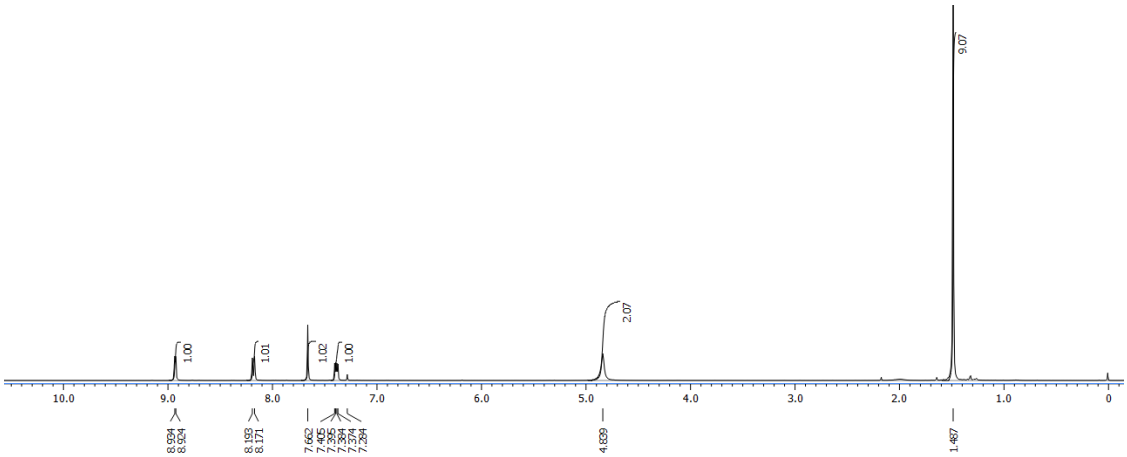


Figure 3.84

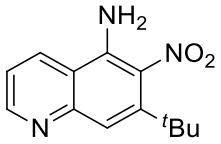
^{1}H NMR



7-(*tert*-Butyl)-6-nitroquinolin-5-amine (3n)



^{13}C NMR



7-(*tert*-Butyl)-6-nitroquinolin-5-amine (3n)

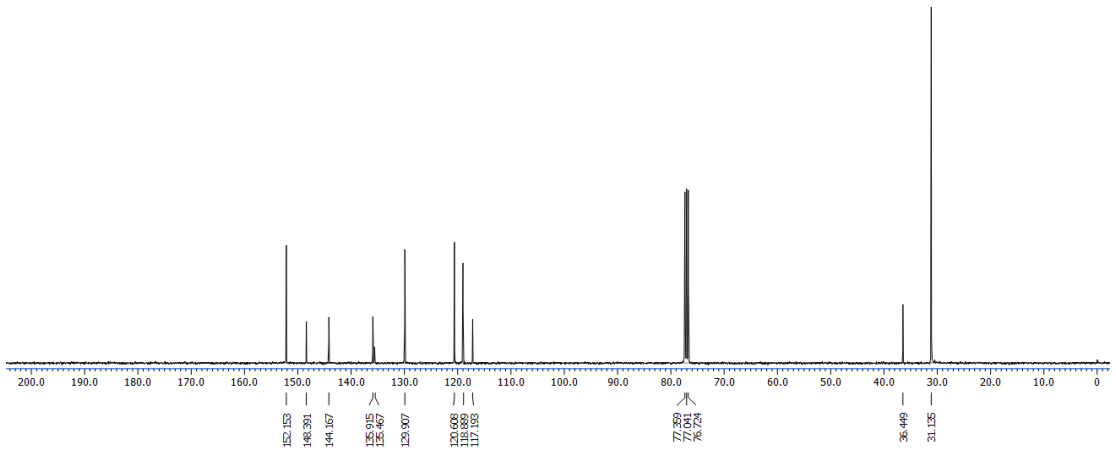
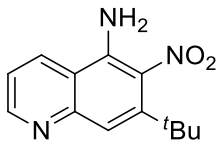


Figure 3.85

HRMS



7-(*tert*-Butyl)-6-nitroquinolin-5-amine (3n)

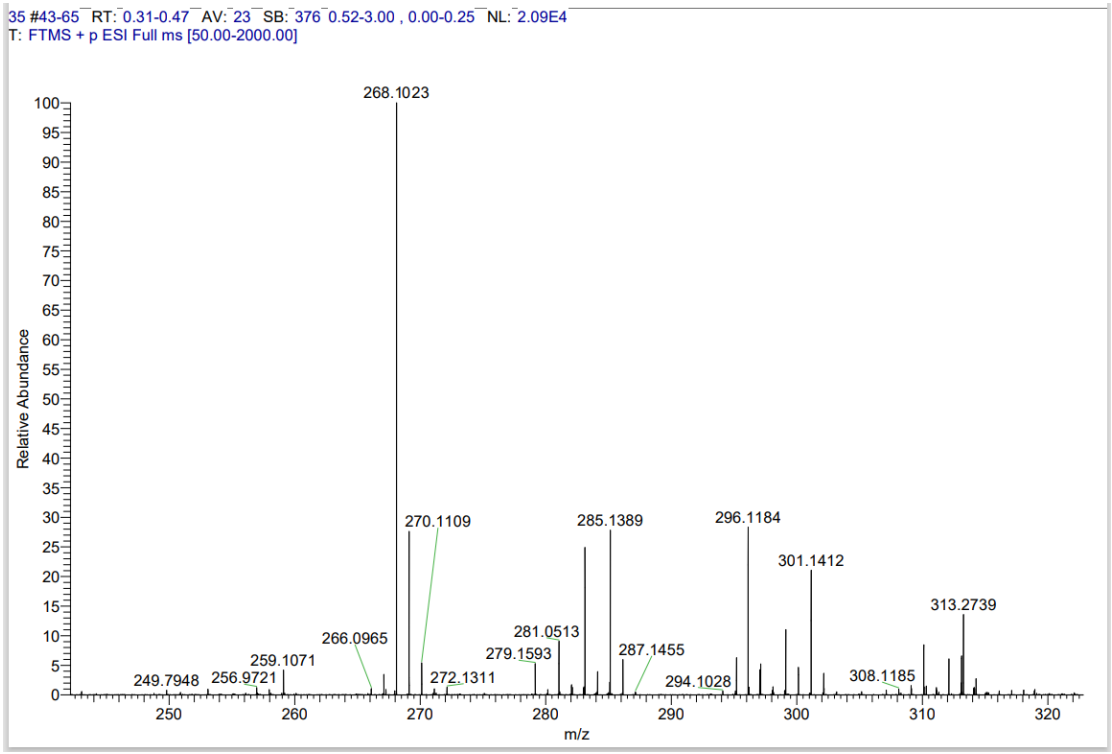
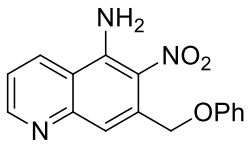
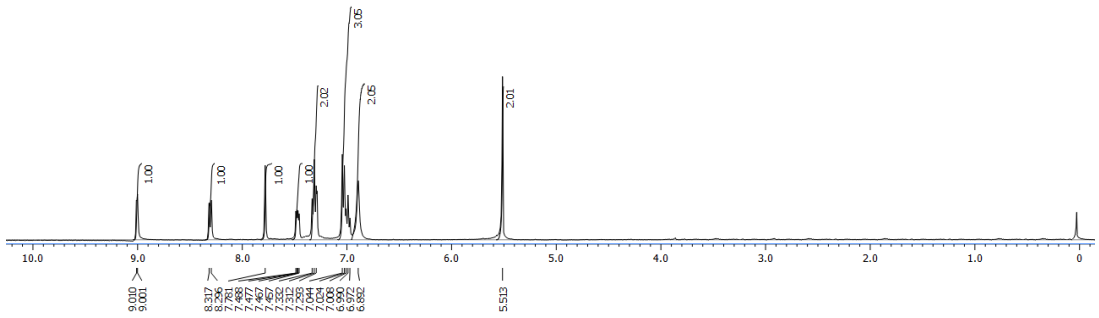


Figure 3.86

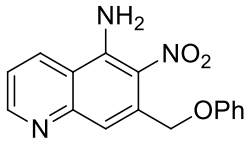
^{1}H NMR



6-Nitro-7-(phenoxymethyl)quinolin-5-amine (3o)



^{13}C NMR



6-Nitro-7-(phenoxymethyl)quinolin-5-amine (3o)

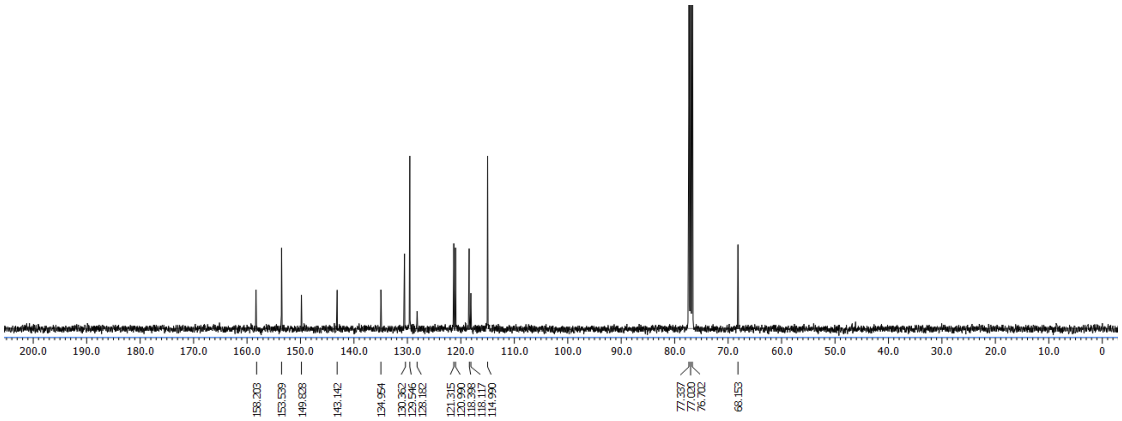
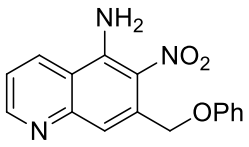


Figure 3.87

HRMS



6-Nitro-7-(phenoxymethyl)quinolin-5-amine (3o)

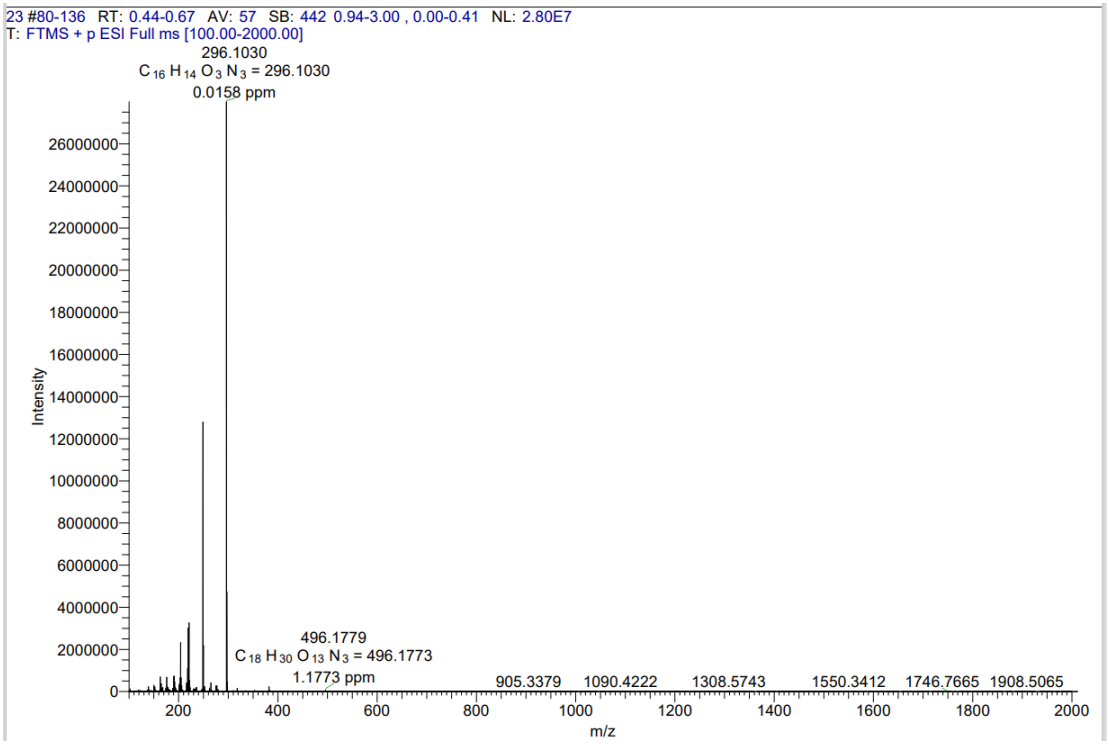
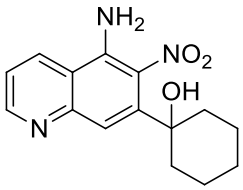
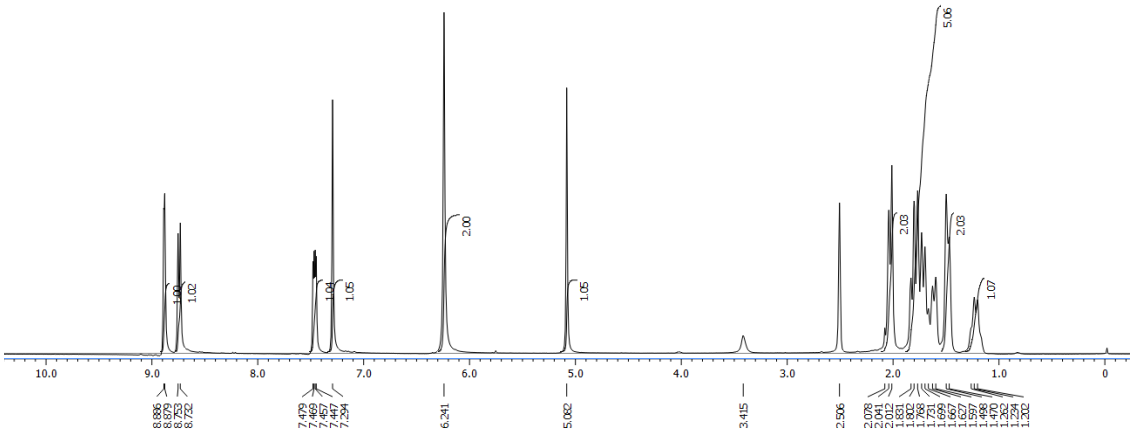


Figure 3.88

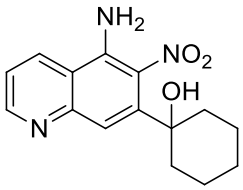
^{1}H NMR



1-(5-Amino-6-nitroquinolin-7-yl)cyclohexanol (3p)



^{13}C NMR



1-(5-Amino-6-nitroquinolin-7-yl)cyclohexanol (3p)

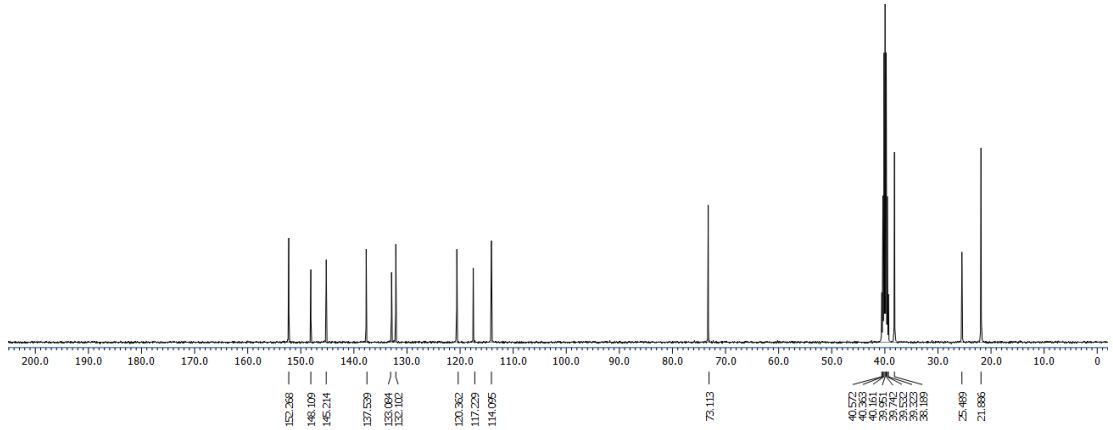
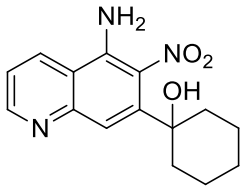


Figure 3.89

HRMS



1-(5-Amino-6-nitroquinolin-7-yl)cyclohexanol (3p)

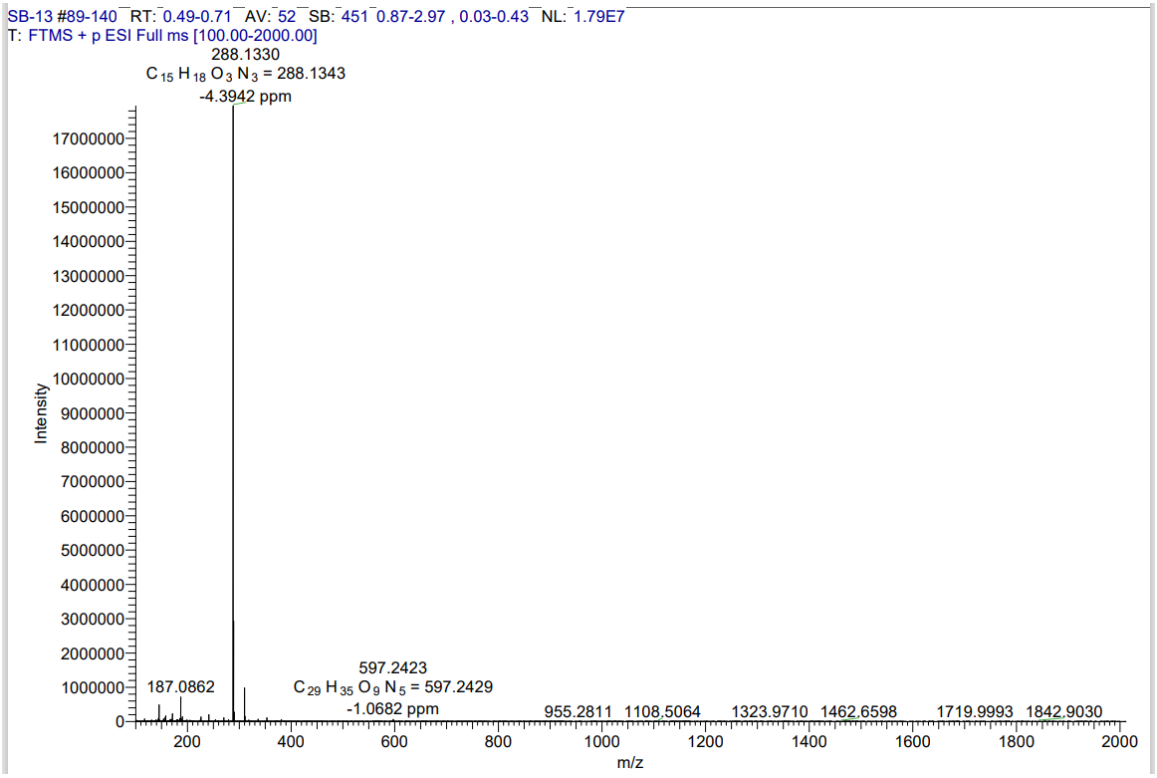
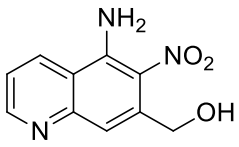
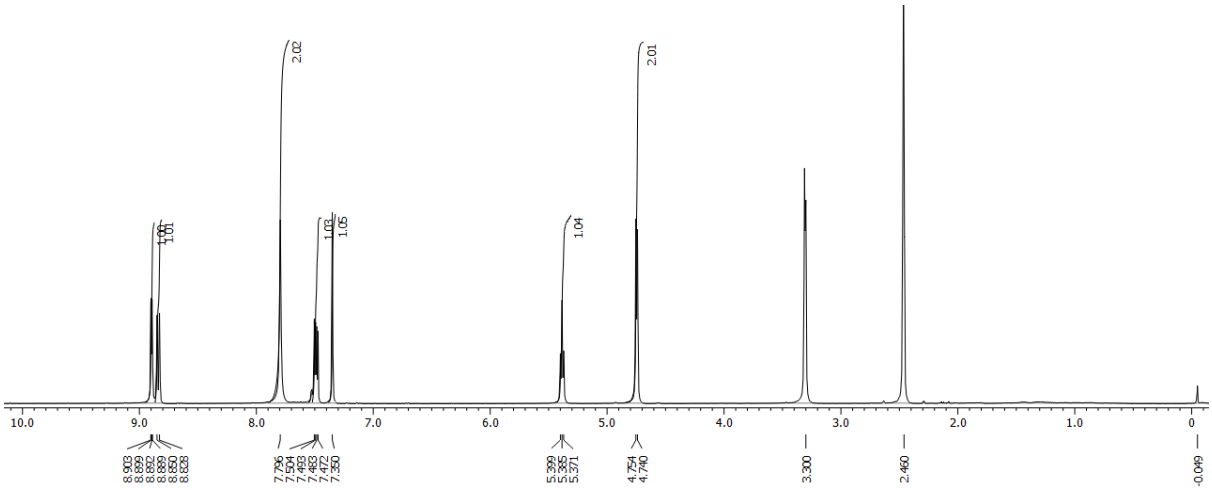


Figure 3.90

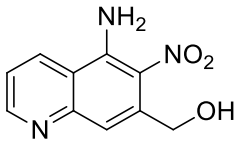
^{1}H NMR



(5-Amino-6-nitroquinolin-7-yl)methanol (3q)



^{13}C NMR



(5-Amino-6-nitroquinolin-7-yl)methanol (3q)

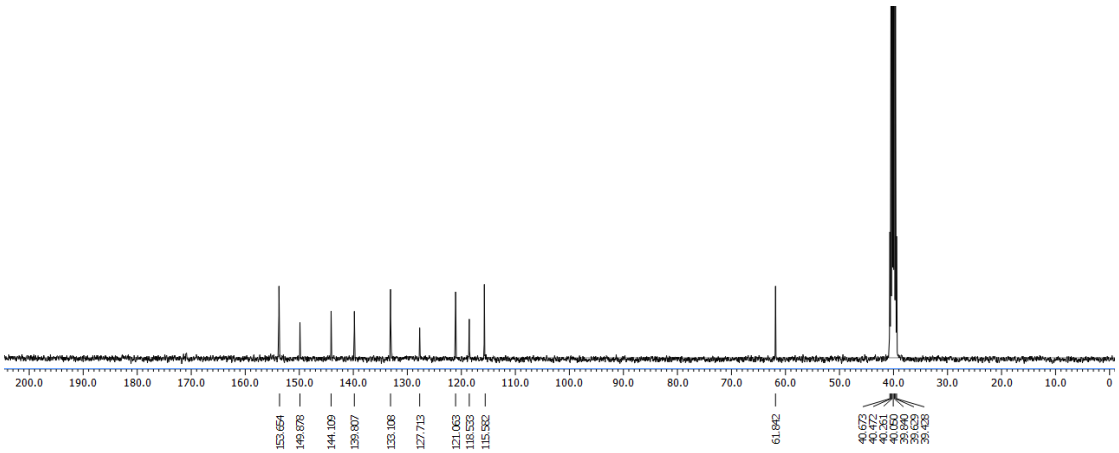
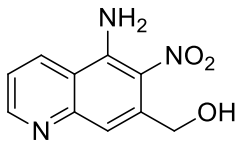


Figure 3.91

HRMS



(5-Amino-6-nitroquinolin-7-yl)methanol (3q)

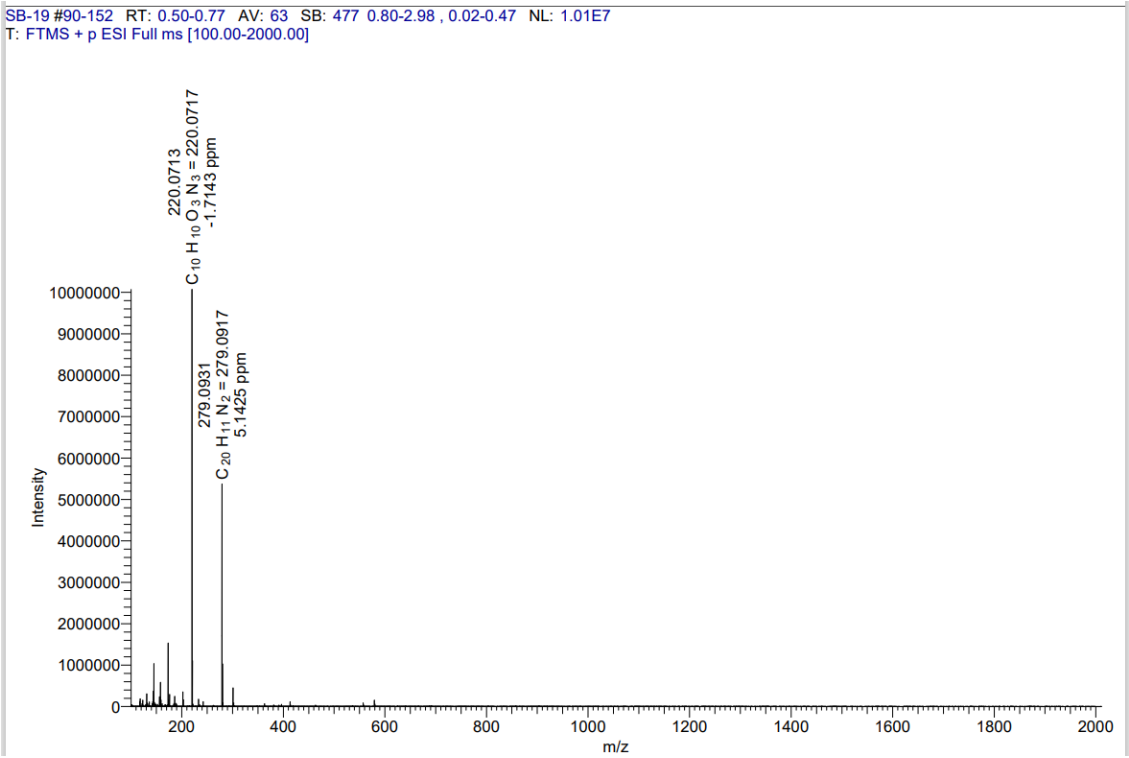
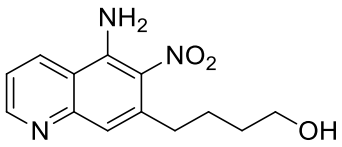
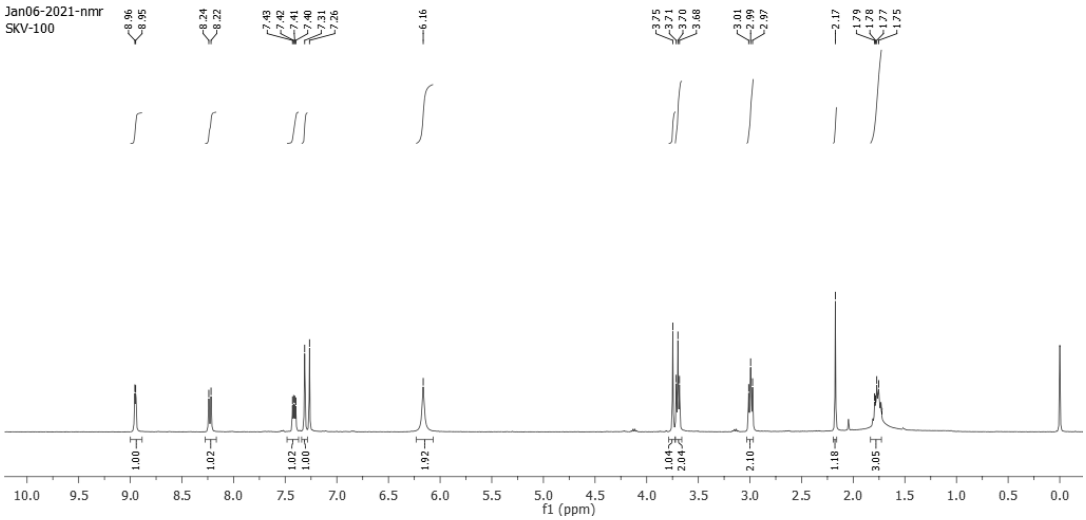


Figure 3.92

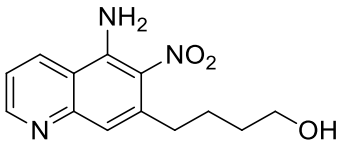
^{1}H NMR



4-(5-Amino-6-nitroquinolin-7-yl)butan-1-ol (3r)



^{13}C NMR



4-(5-Amino-6-nitroquinolin-7-yl)butan-1-ol (3r)

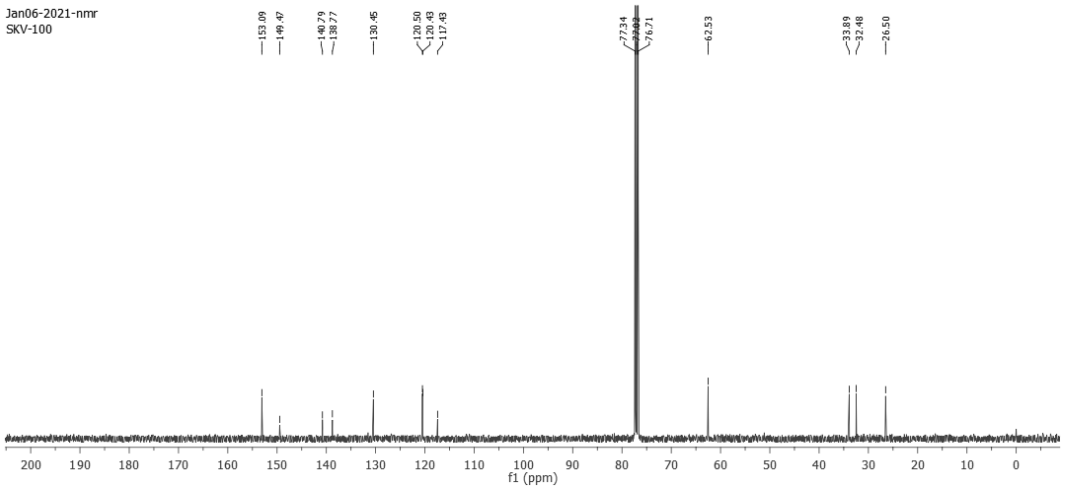
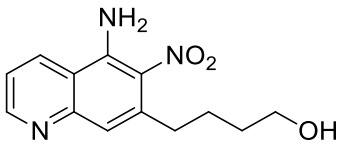


Figure 3.93

HRMS



4-(5-Amino-6-nitroquinolin-7-yl)butan-1-ol (3r)

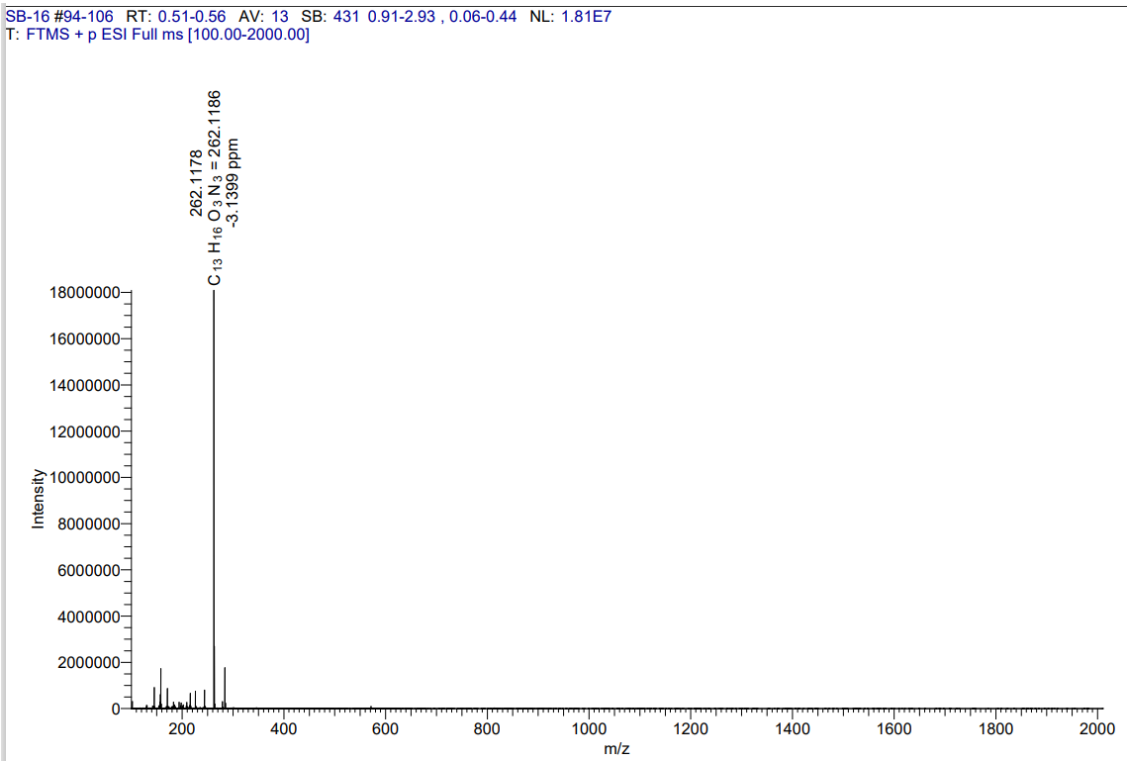
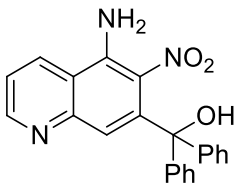
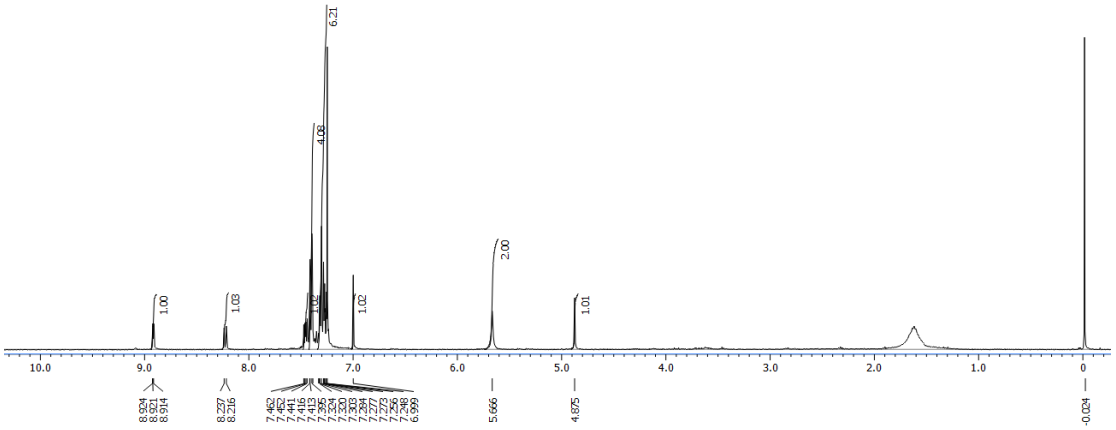


Figure 3.94

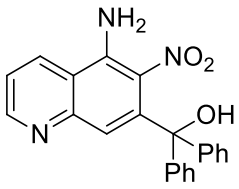
^{1}H NMR



(5-Amino-6-nitroquinolin-7-yl)diphenylmethanol(3s)



^{13}C NMR



(5-Amino-6-nitroquinolin-7-yl)diphenylmethanol(3s)

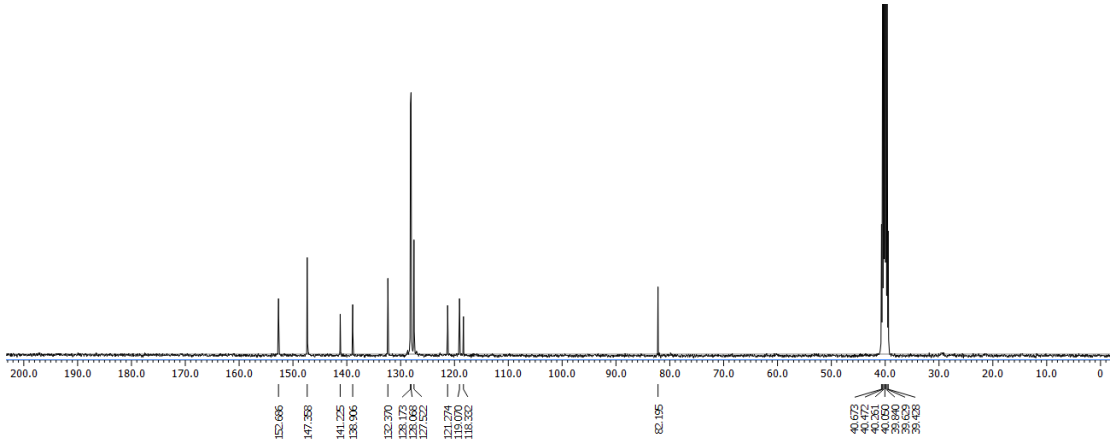
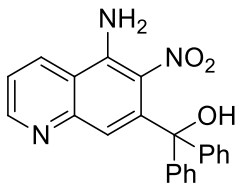


Figure 3.95

HRMS



(5-Amino-6-nitroquinolin-7-yl)diphenylmethanol(3s)

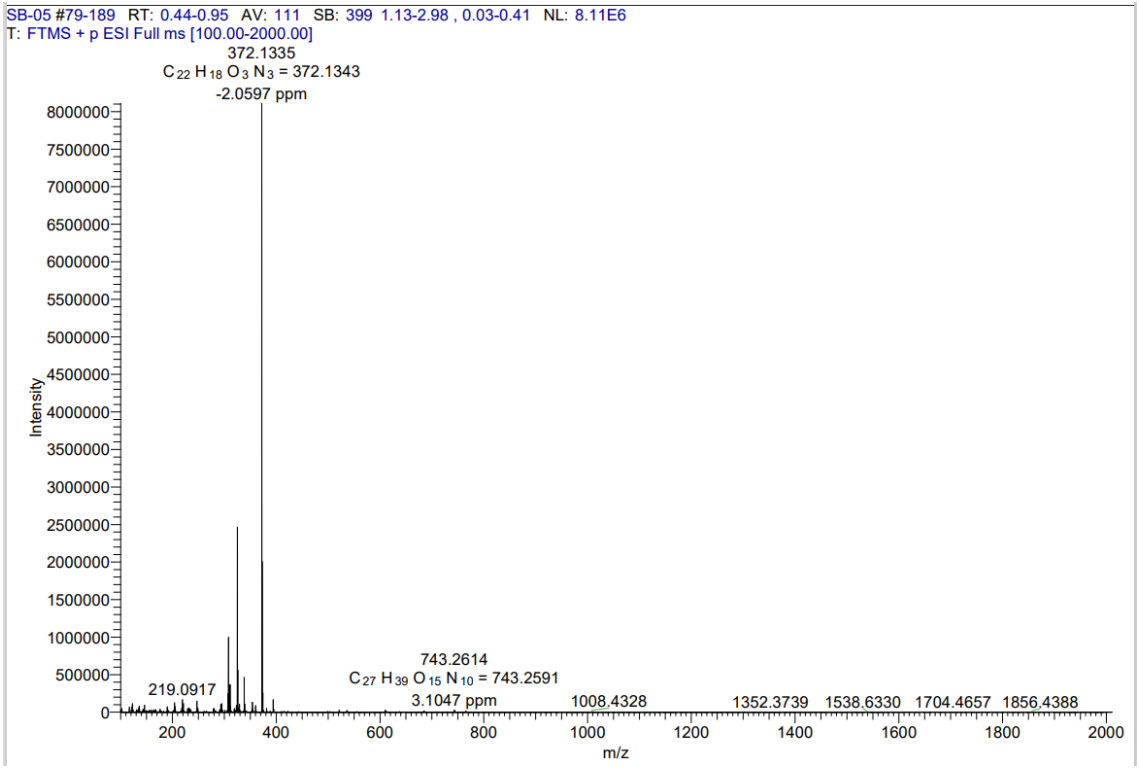
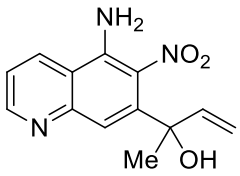
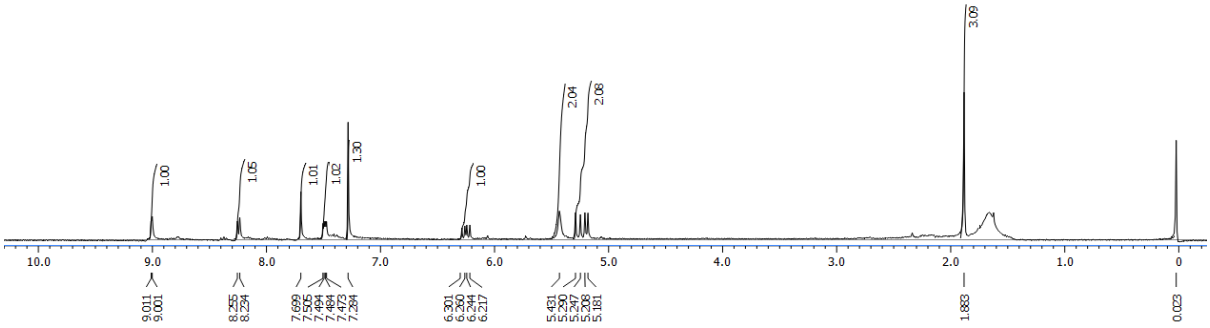


Figure 3.96

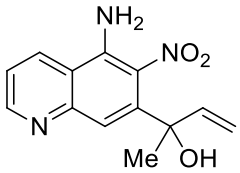
^{1}H NMR



2-(5-Amino-6-nitroquinolin-7-yl)but-3-en-2-ol (3t)



^{13}C NMR



2-(5-Amino-6-nitroquinolin-7-yl)but-3-en-2-ol (3t)

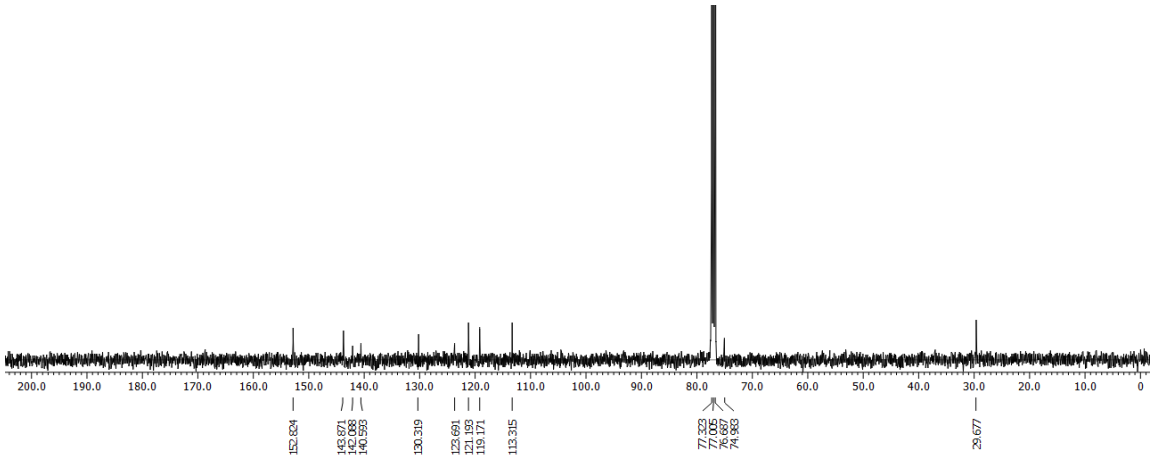
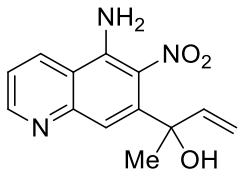


Figure 3.97

HRMS



2-(5-Amino-6-nitroquinolin-7-yl)but-3-en-2-ol (3t)

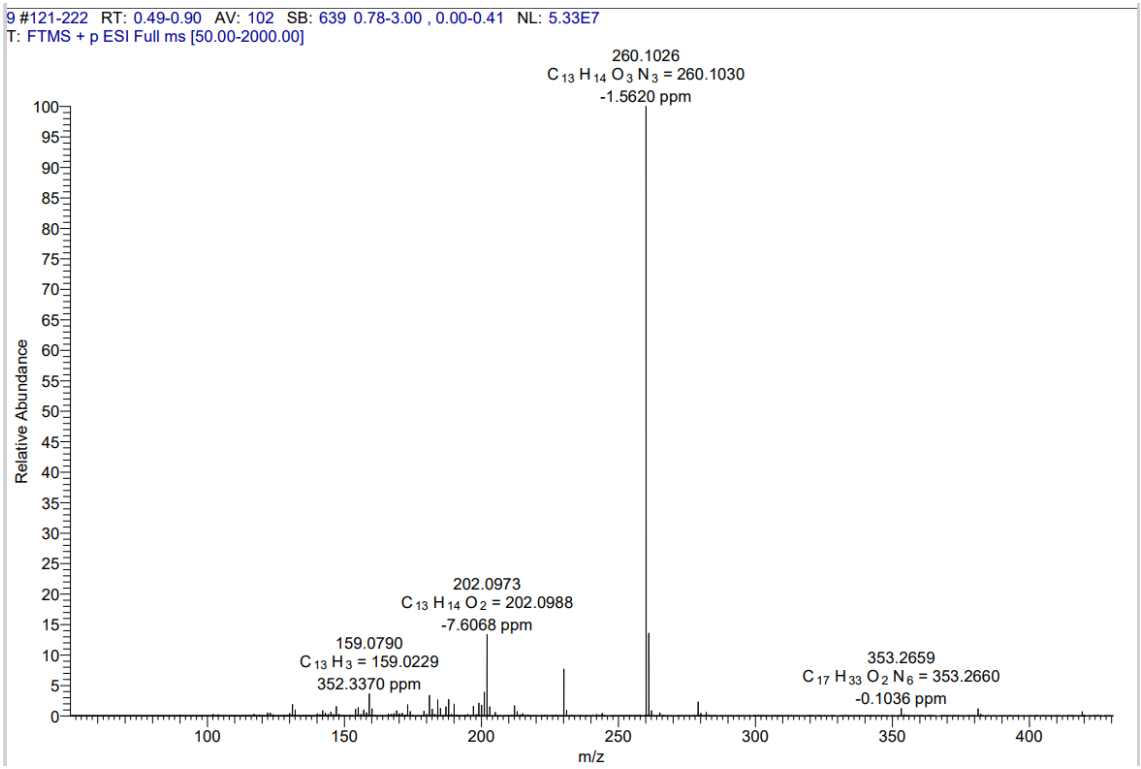
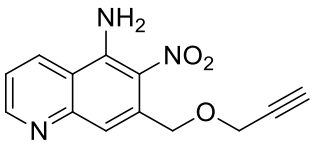
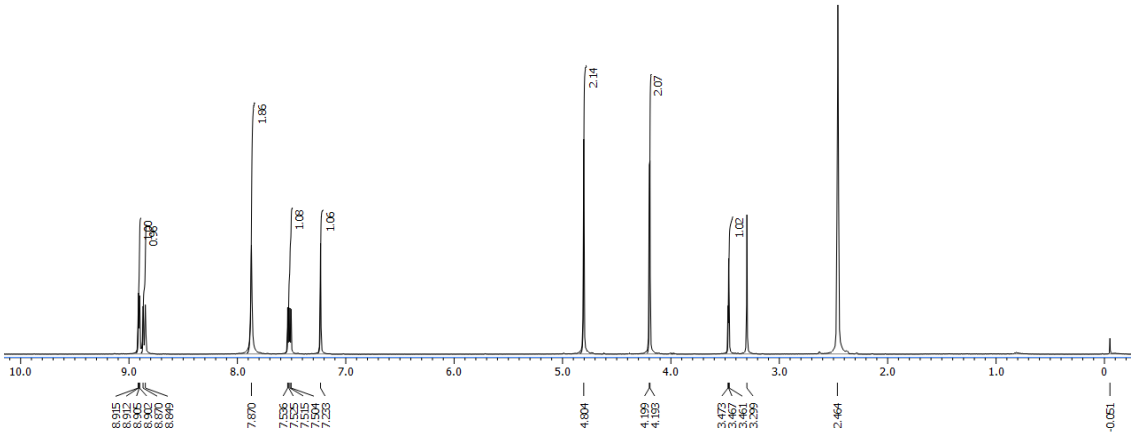


Figure 3.98

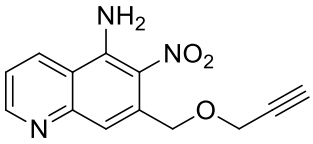
^{1}H NMR



6-Nitro-7-((prop-2-yn-1-yloxy)methyl)quinolin-5-amine (3u)



^{13}C NMR



6-Nitro-7-((prop-2-yn-1-yloxy)methyl)quinolin-5-amine (3u)

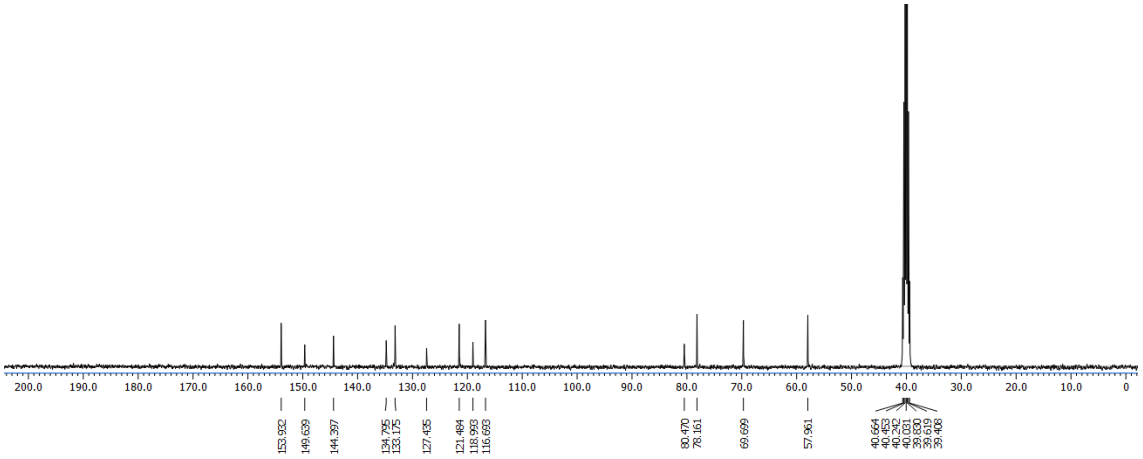
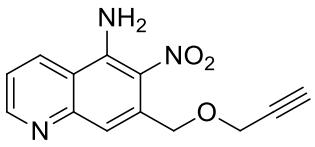


Figure 3.99

HRMS



6-Nitro-7-((prop-2-yn-1-yloxy)methyl)quinolin-5-amine (3u)

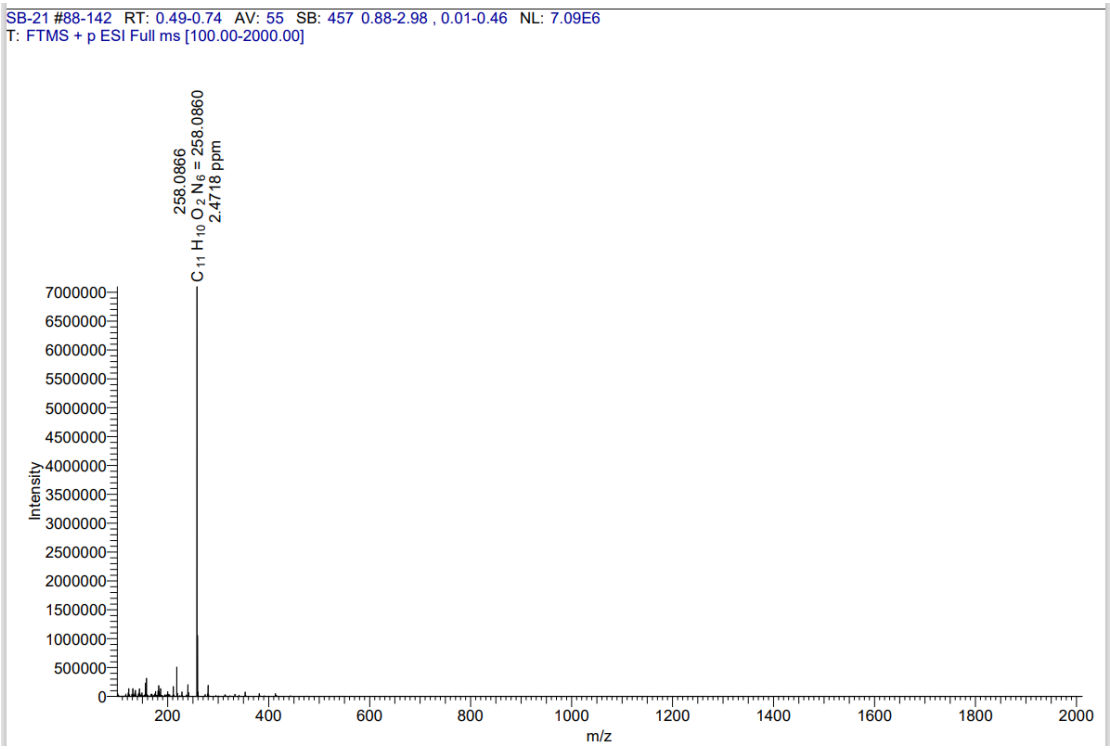
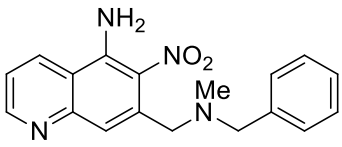
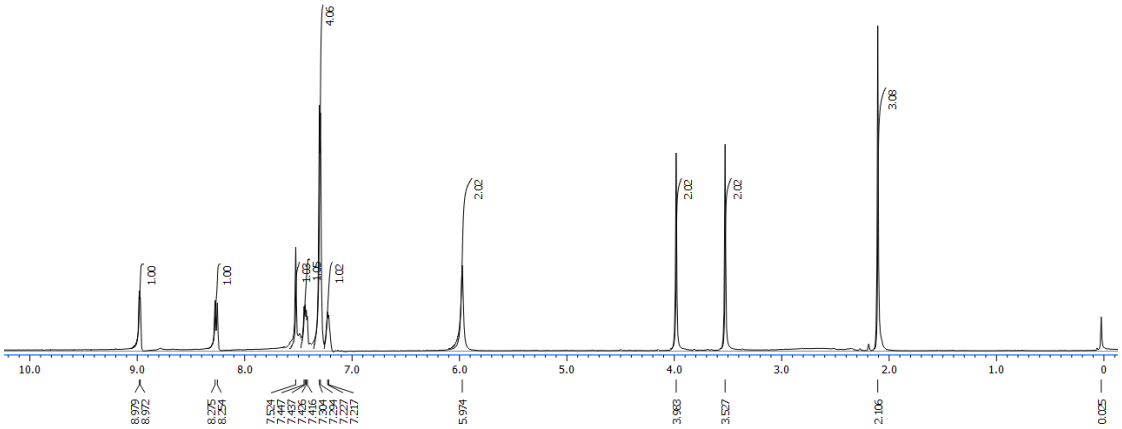


Figure 3.100

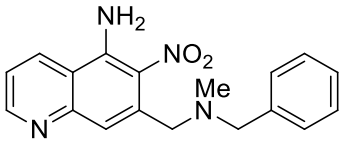
^{1}H NMR



7-((Benzyl(methyl)amino)methyl)-6-nitroquinolin-5-amine (5a)



^{13}C NMR



7-((Benzyl(methyl)amino)methyl)-6-nitroquinolin-5-amine (5a)

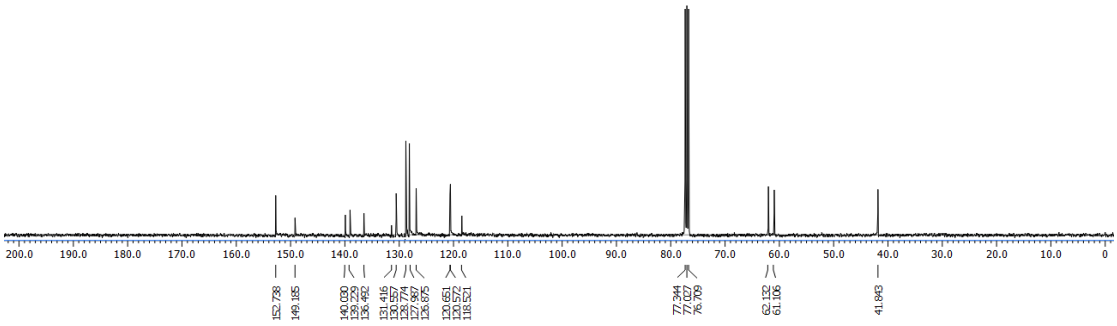
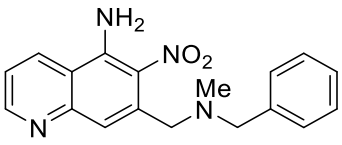


Figure 3.101

HRMS



7-((Benzyl(methyl)amino)methyl)-6-nitroquinolin-5-amine (5a)

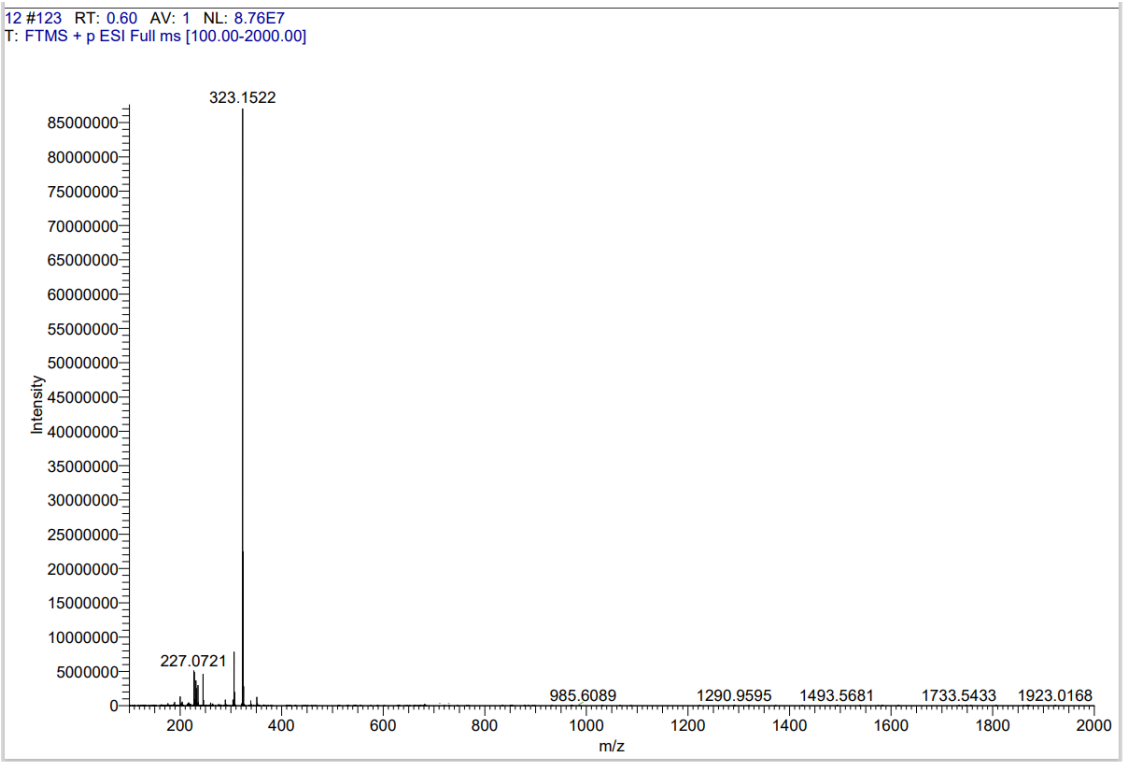
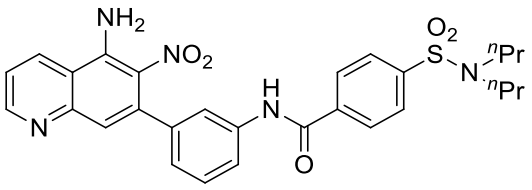
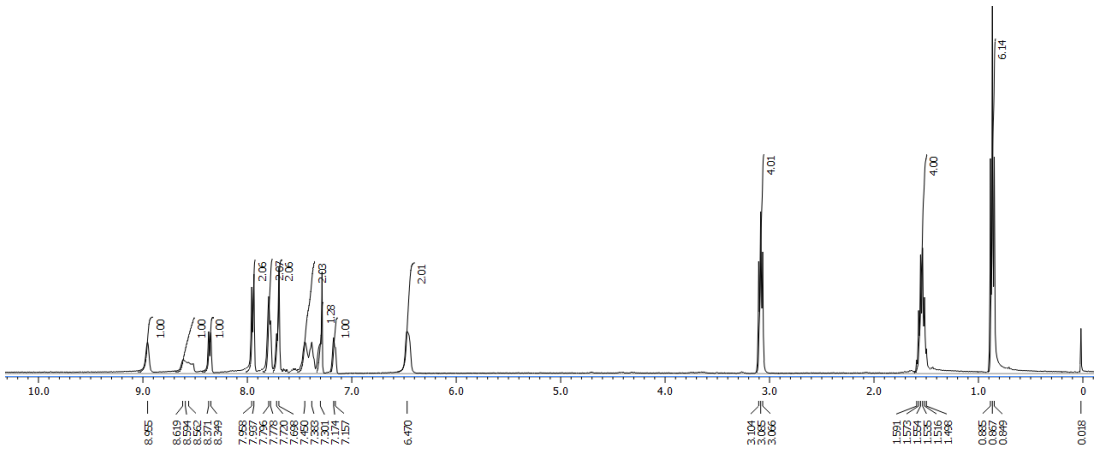


Figure 3.102

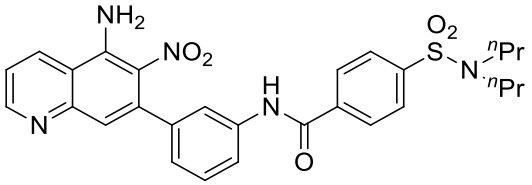
^{1}H NMR



***N*-(3-(5-amino-6-nitroquinolin-7-yl)phenyl)-4-(*N*,*N*-dipropylsulfamoyl)benzamide (5b)**



^{13}C NMR



***N*-(3-(5-amino-6-nitroquinolin-7-yl)phenyl)-4-(*N*,*N*-dipropylsulfamoyl)benzamide (5b)**

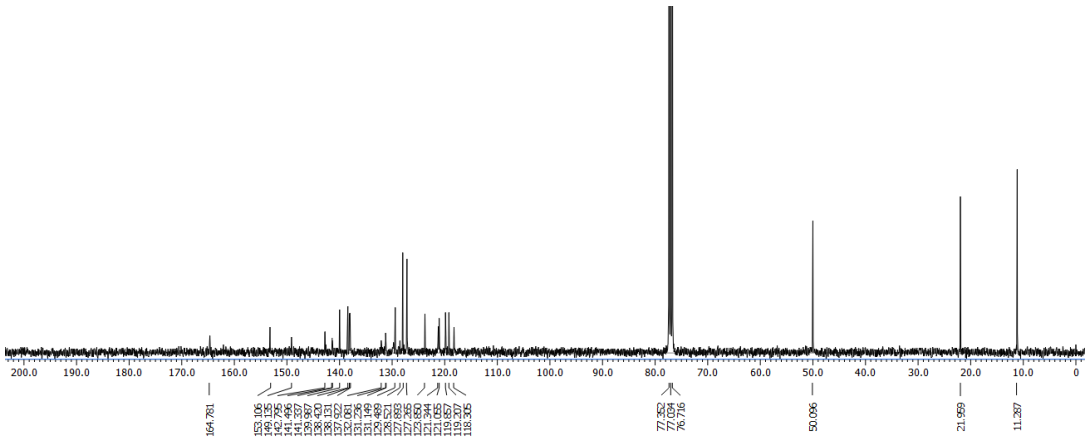
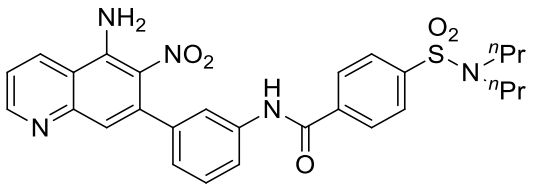


Figure 3.103

HRMS



***N*-(3-(5-amino-6-nitroquinolin-7-yl)phenyl)-4-(*N*,*N*-dipropylsulfamoyl)benzamide (5b)**

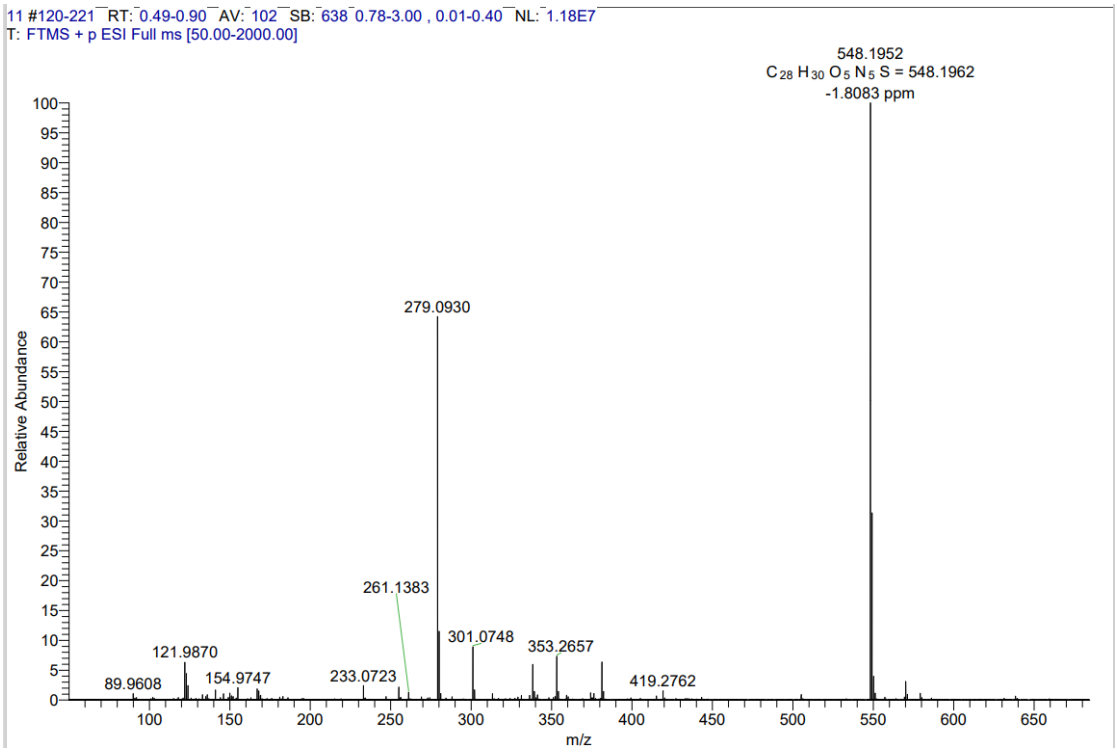
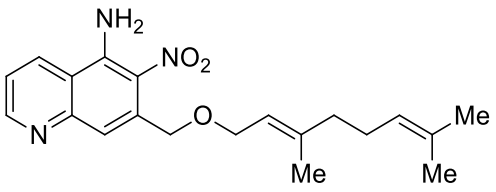


Figure 3.104

^{1}H NMR



(*E*)-7-(((3,7-Dimethylocta-2,6-dien-1-yl)oxy)methyl)-6-nitroquinolin-5-amine (5c)

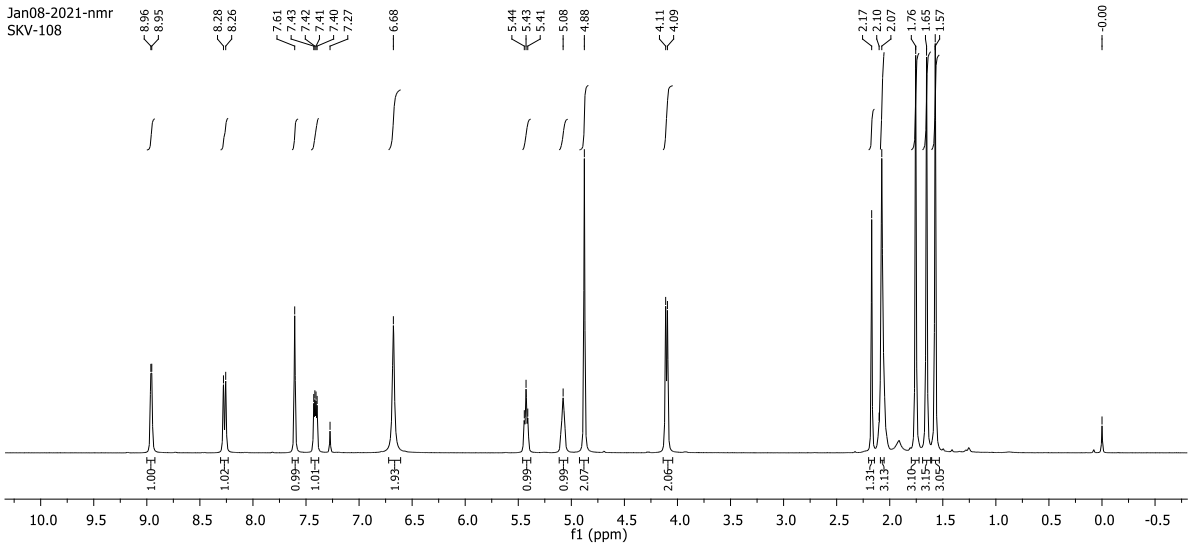
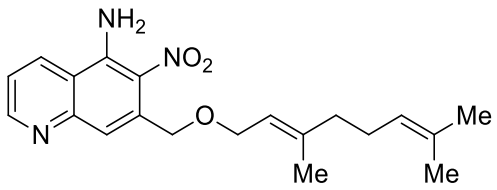


Figure 3.105

^{13}C NMR



(*E*)-7-(((3,7-Dimethylocta-2,6-dien-1-yl)oxy)methyl)-6-nitroquinolin-5-amine (5c)

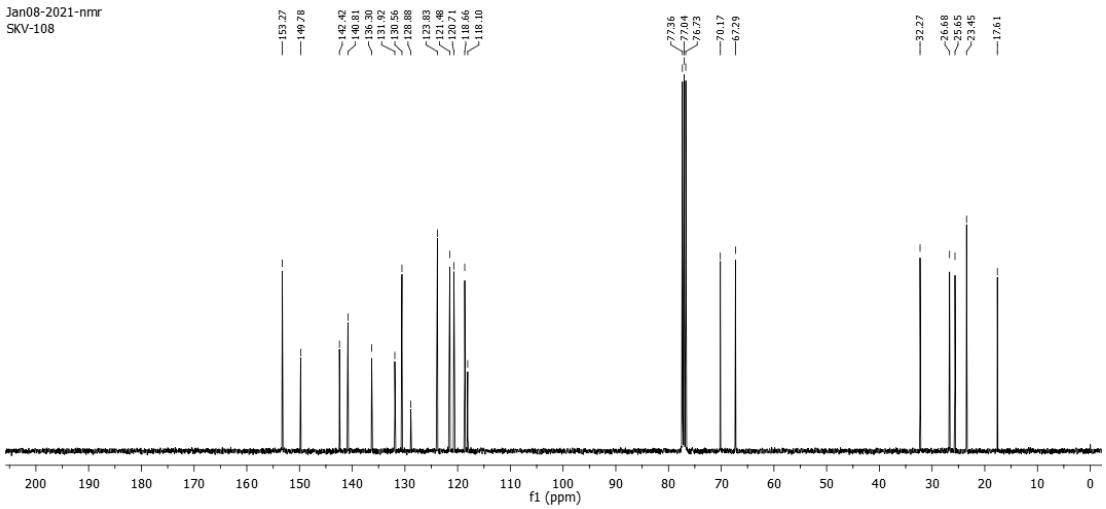
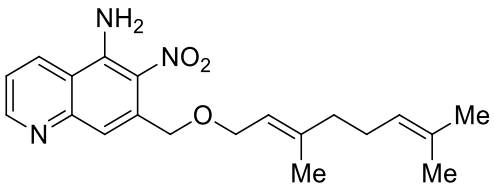


Figure 3.106

HRMS



(*E*)-7-(((3,7-Dimethylocta-2,6-dien-1-yl)oxy)methyl)-6-nitroquinolin-5-amine (5c)

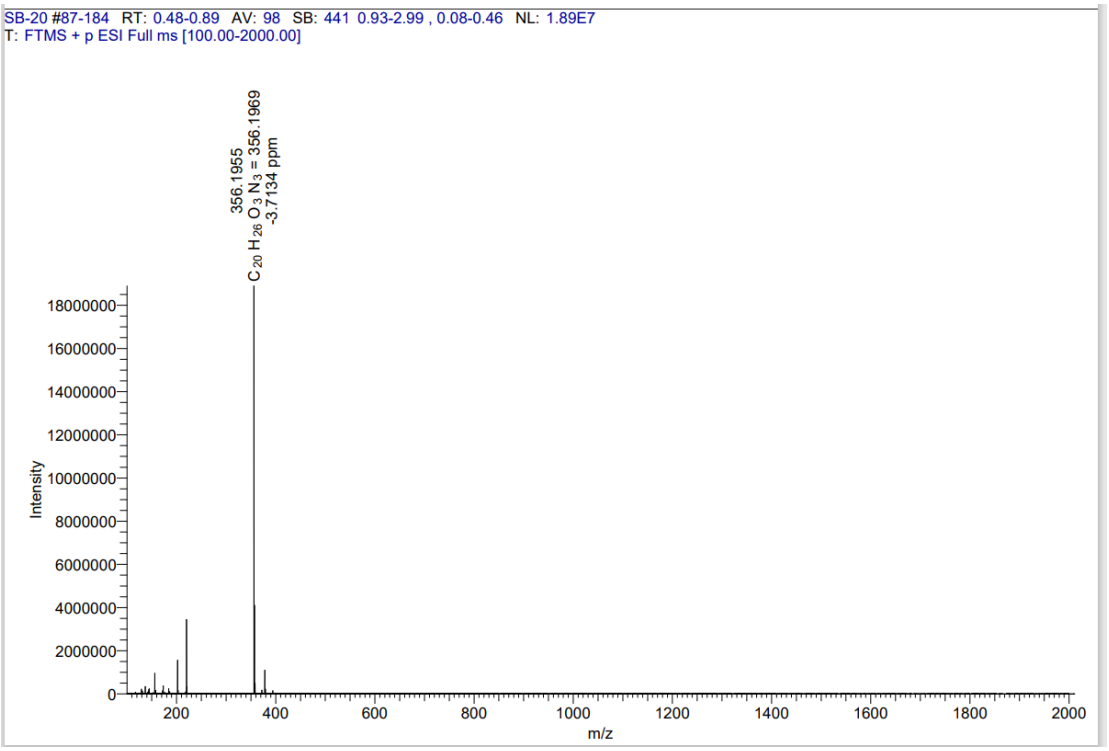
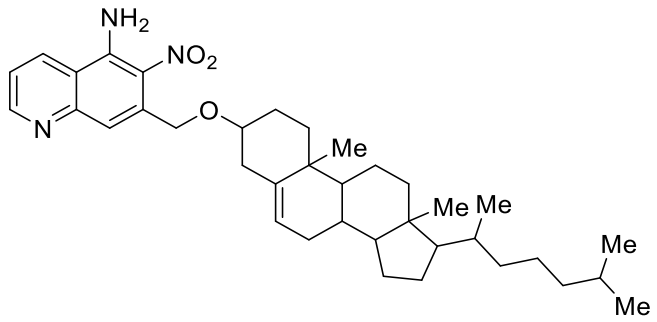


Figure 3.107

^{1}H NMR



7-(((10,13-Dimethyl-17-(6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)oxy)methyl)-6-nitroquinolin-5-amine (5d)

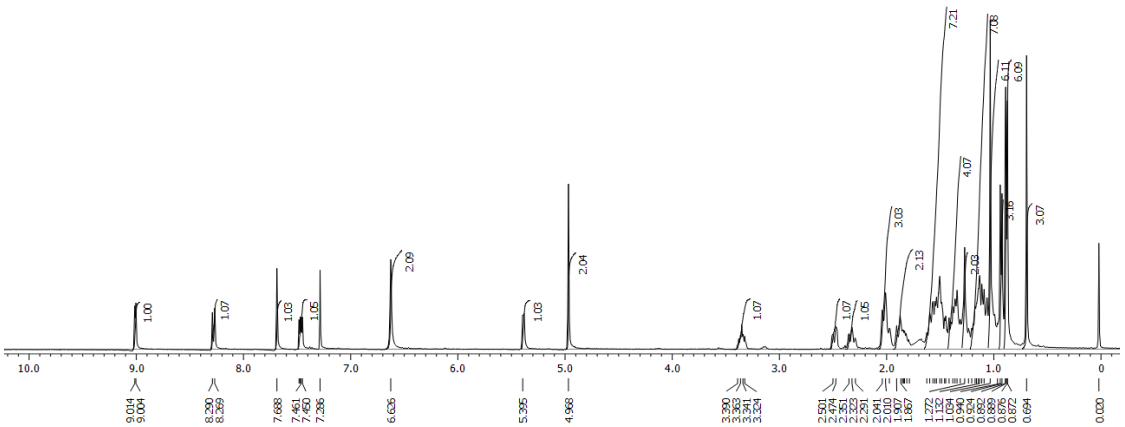
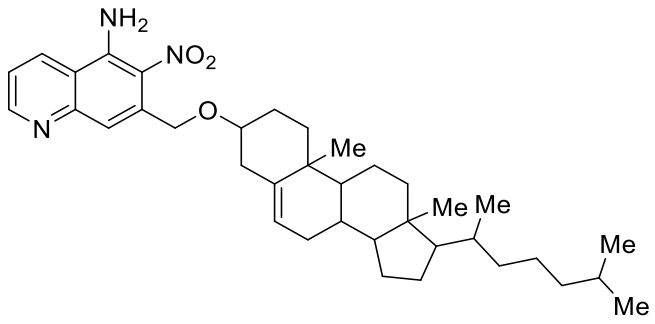


Figure 3.108

^{13}C NMR



7-(((10,13-Dimethyl-17-(6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)oxy)methyl)-6-nitroquinolin-5-amine (5d)

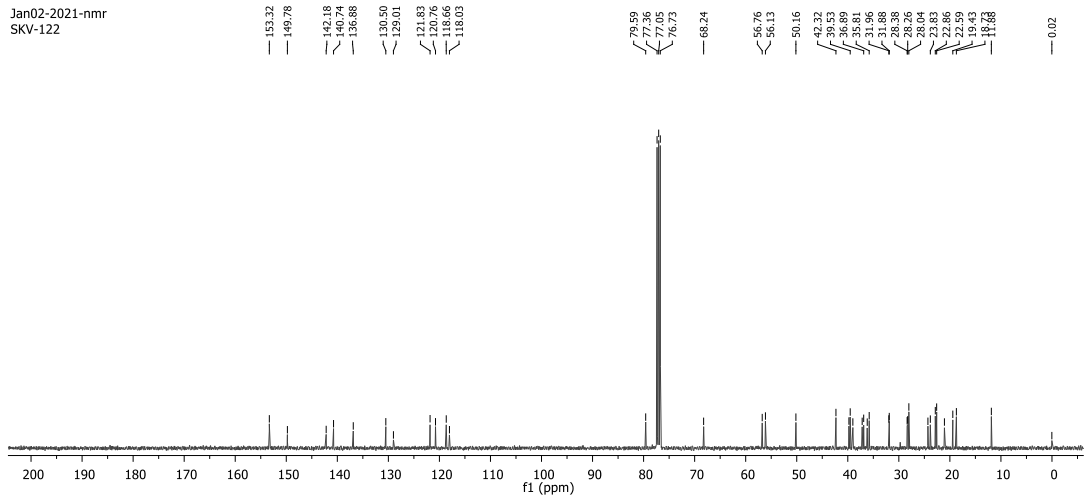
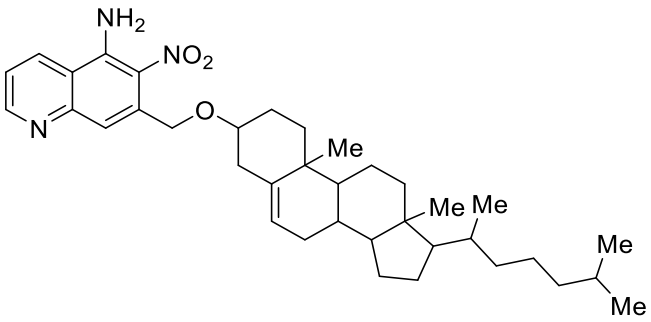


Figure 3.109

HRMS



7-(((10,13-Dimethyl-17-(6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-yl)oxy)methyl)-6-nitroquinolin-5-amine (5d)

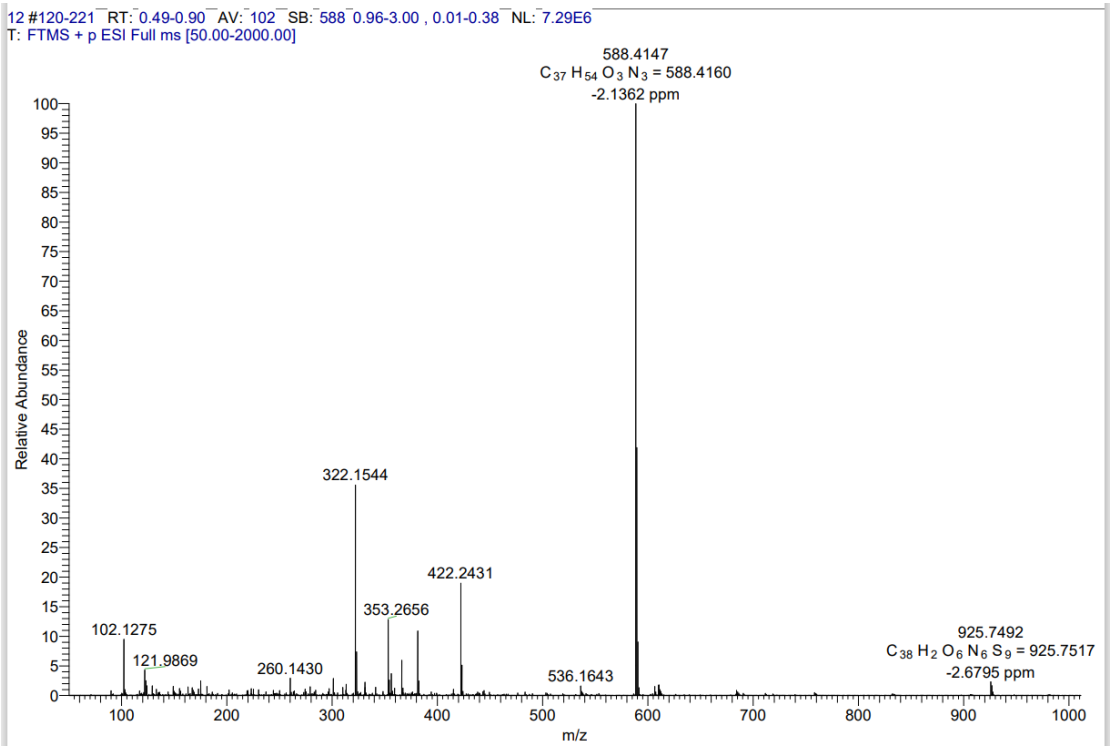
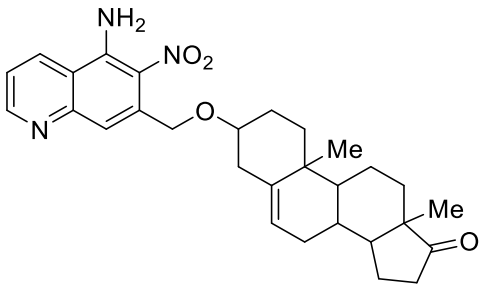


Figure 3.110

^{1}H NMR



3-((5-Amino-6-nitroquinolin-7-yl)methoxy)-10,13-dimethyl-1,2,3,4,7,8,9,10,11,12,13,14,15,16-tetradecahydro-17H-cyclopenta[a]phenanthren-17-one (5e)

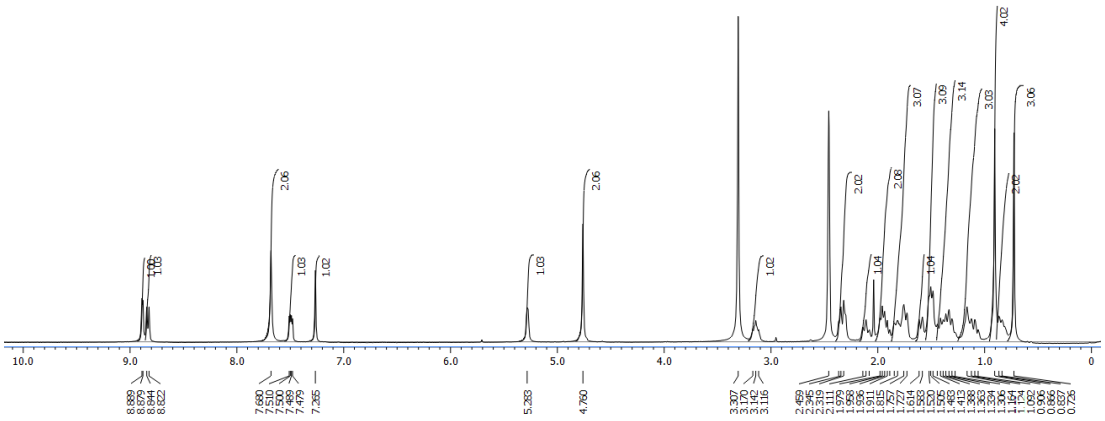
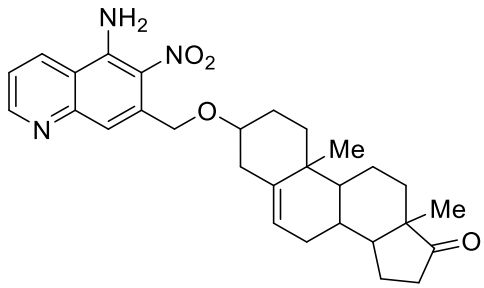


Figure 3.111

^{13}C NMR



3-((5-Amino-6-nitroquinolin-7-yl)methoxy)-10,13-dimethyl-1,2,3,4,7,8,9,10,11,12,13,14,15,16-tetradecahydro-17H-cyclopenta[a]phenanthren-17-one (5e)

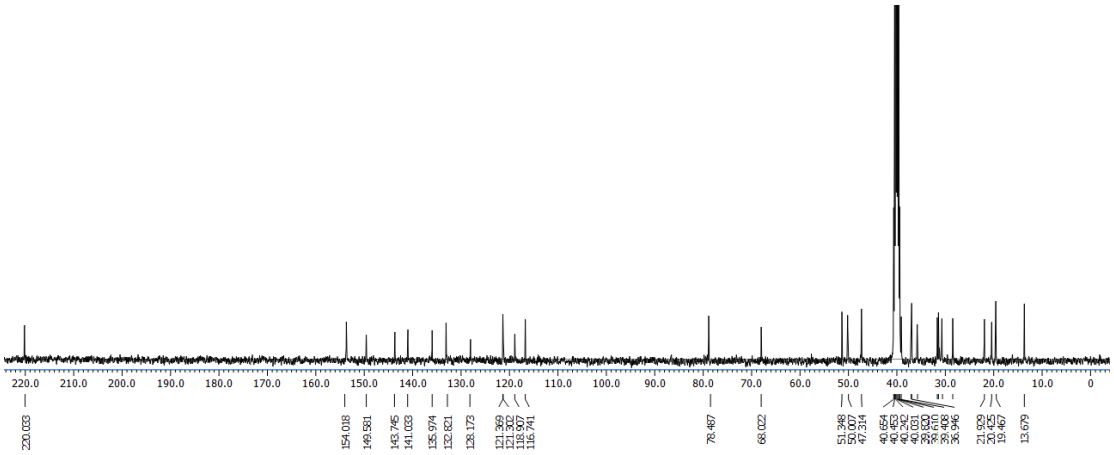
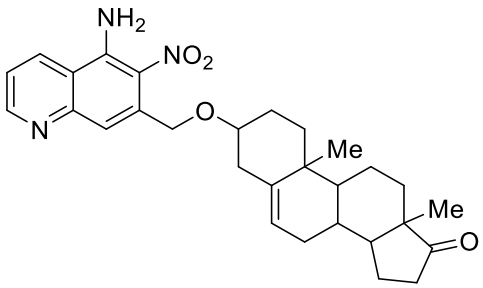


Figure 3.112

HRMS



3-((5-Amino-6-nitroquinolin-7-yl)methoxy)-10,13-dimethyl-1,2,3,4,7,8,9,10,11,12,13,14,15,16-tetradecahydro-17H-cyclopenta[a]phenanthren-17-one (5e)

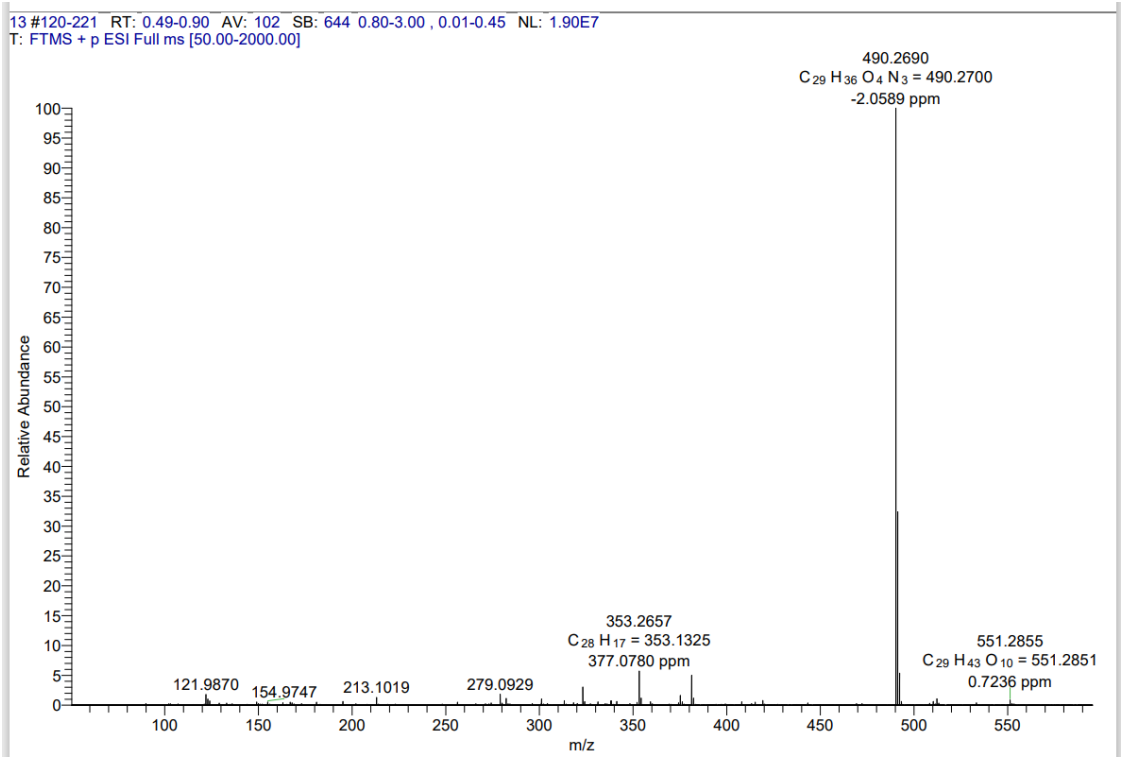
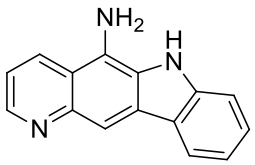
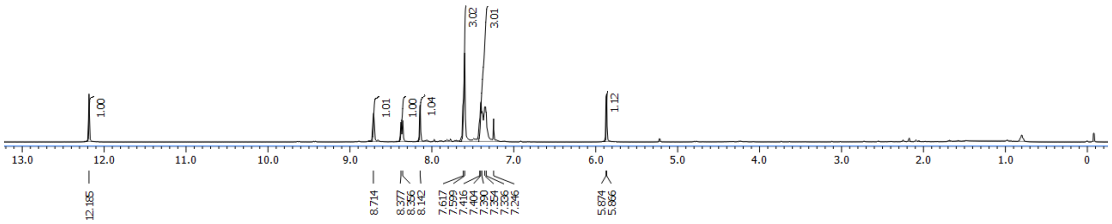


Figure 3.113

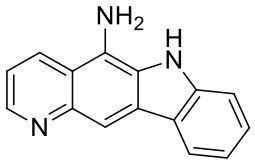
^{1}H NMR



6*H*-pyrido[3,2-*b*]carbazol-5-amine (6)



^{13}C NMR



6*H*-pyrido[3,2-*b*]carbazol-5-amine (6)

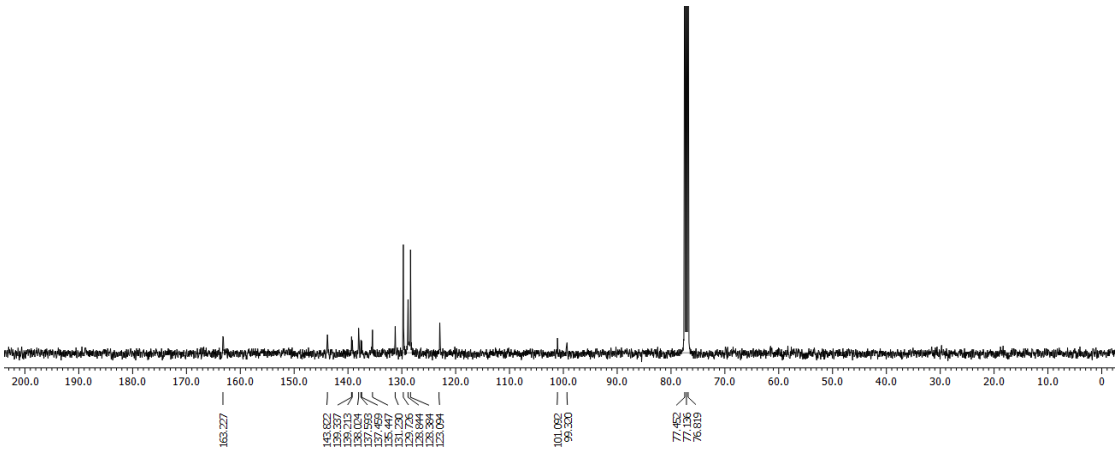
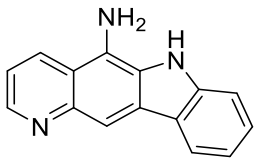


Figure 3.114

HRMS



6*H*-pyrido[3,2-*b*]carbazol-5-amine (6)

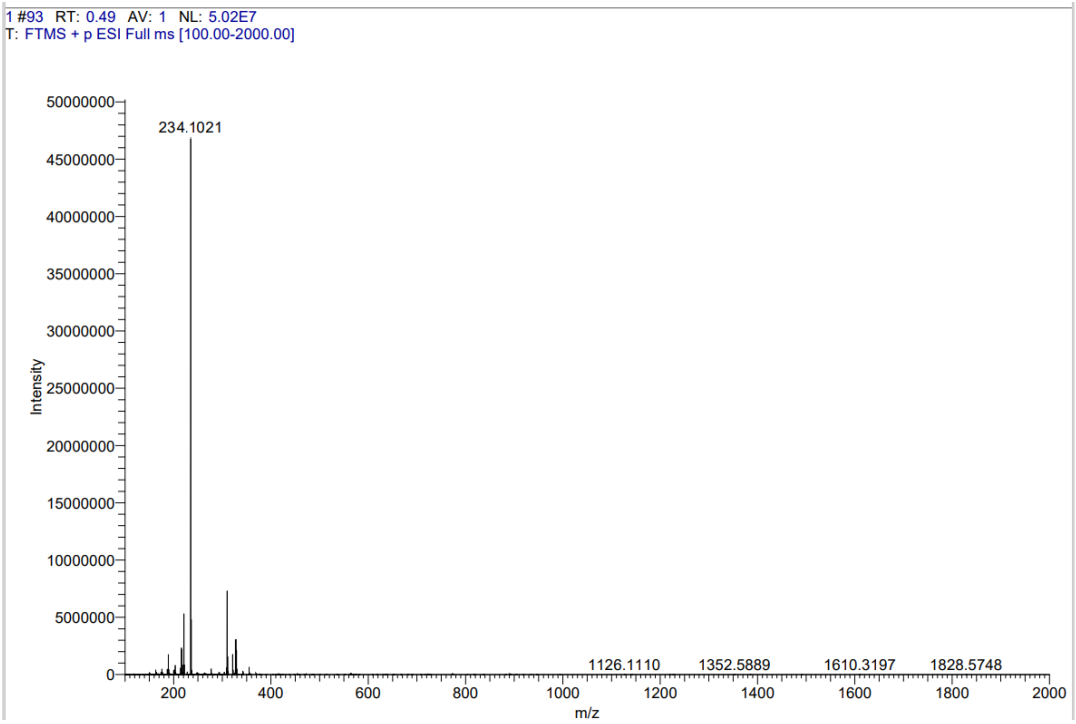
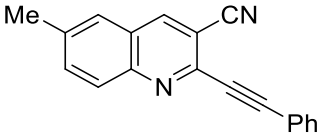


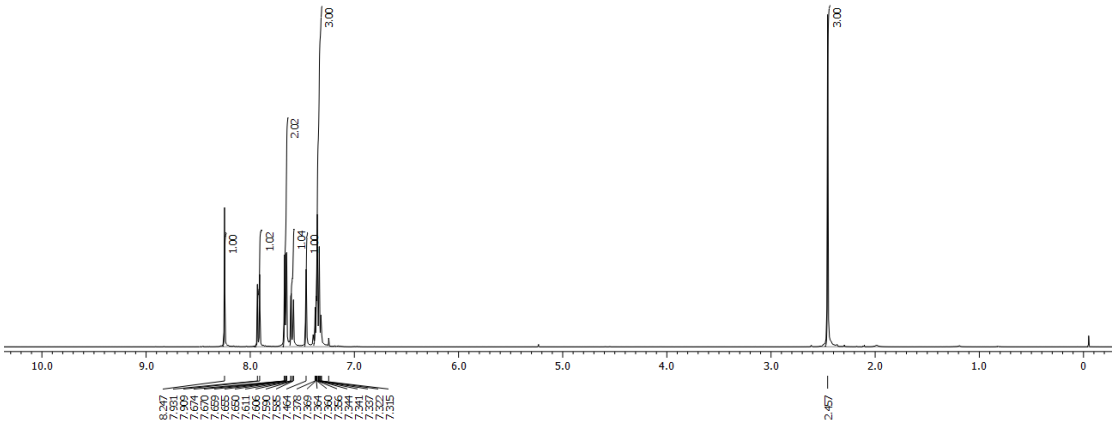
Figure 3.115

Appendix – B
^{1}H NMR, ^{13}C NMR and HRMS Spectra of Chapter 4

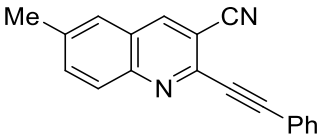
^{1}H NMR



6-Methyl-2-(phenylethynyl)quinoline-3-carbonitrile (1a)



^{13}C NMR



6-Methyl-2-(phenylethynyl)quinoline-3-carbonitrile (1a)

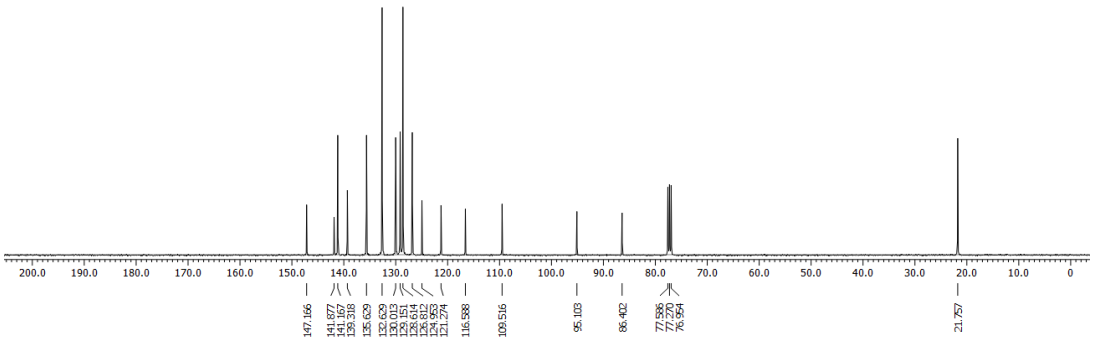
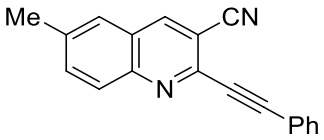


Figure 4.3

HRMS



6-Methyl-2-(phenylethynyl)quinoline-3-carbonitrile (1a)

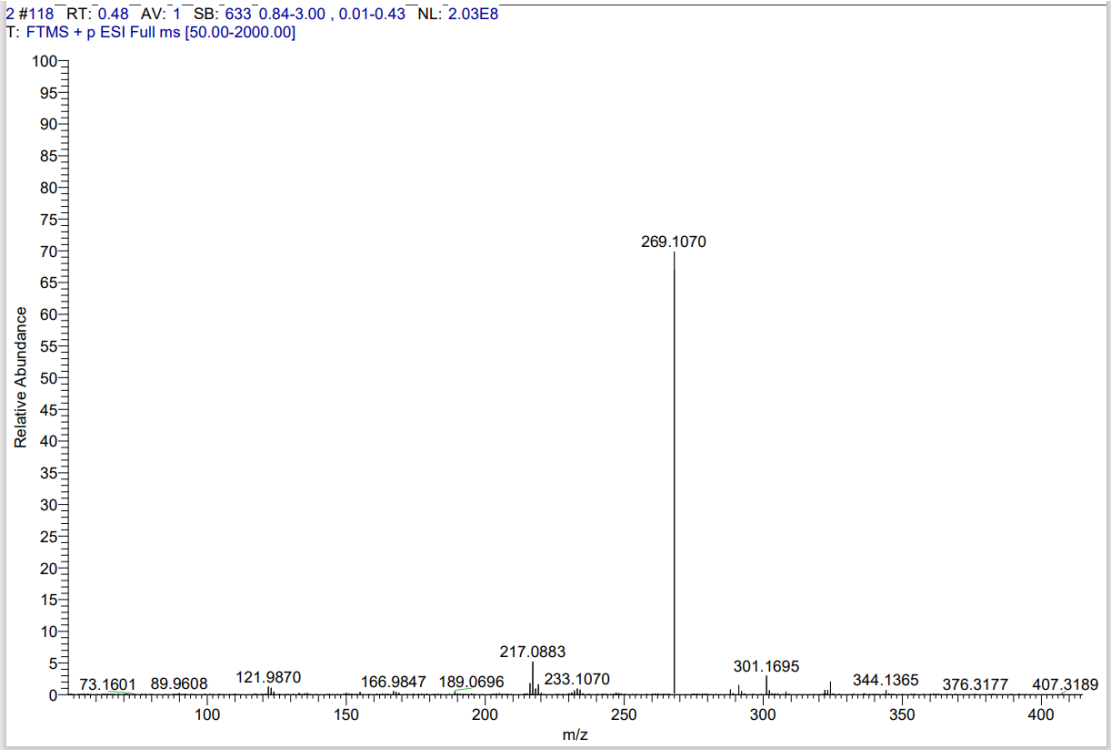
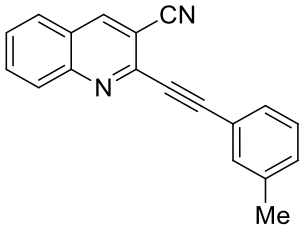
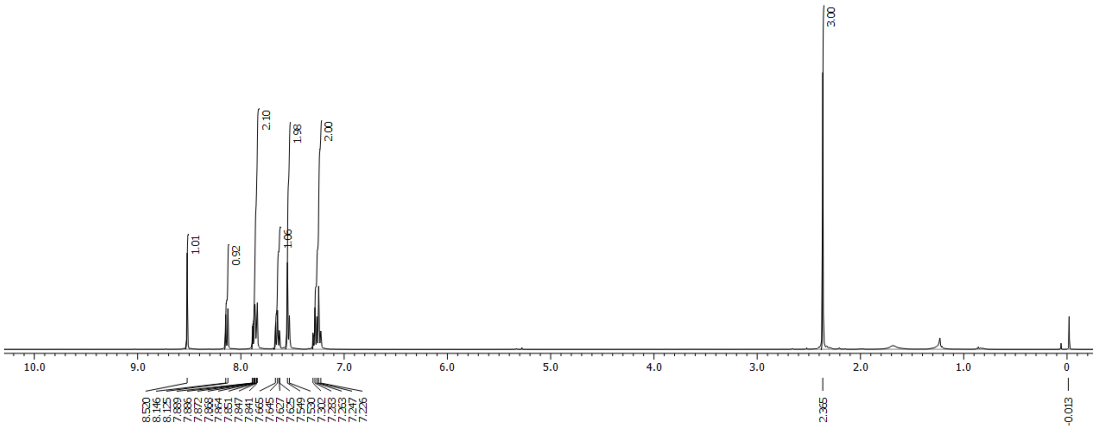


Figure 4.4

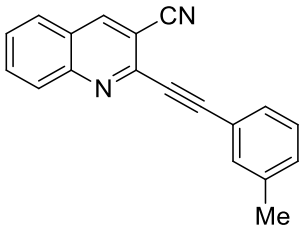
^{1}H NMR



2-(*m*-Tolylethynyl)quinoline-3-carbonitrile (1b)



^{13}C NMR



2-(*m*-Tolylethynyl)quinoline-3-carbonitrile (1b)

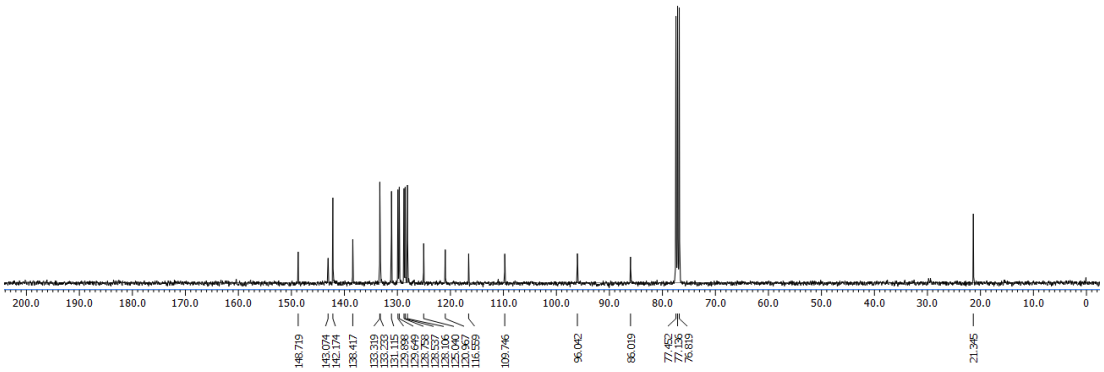
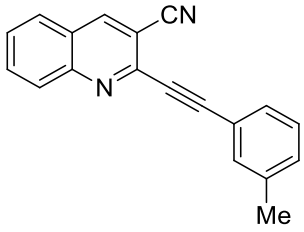


Figure 4.5

HRMS



2-(*m*-Tolylethynyl)quinoline-3-carbonitrile (1b)

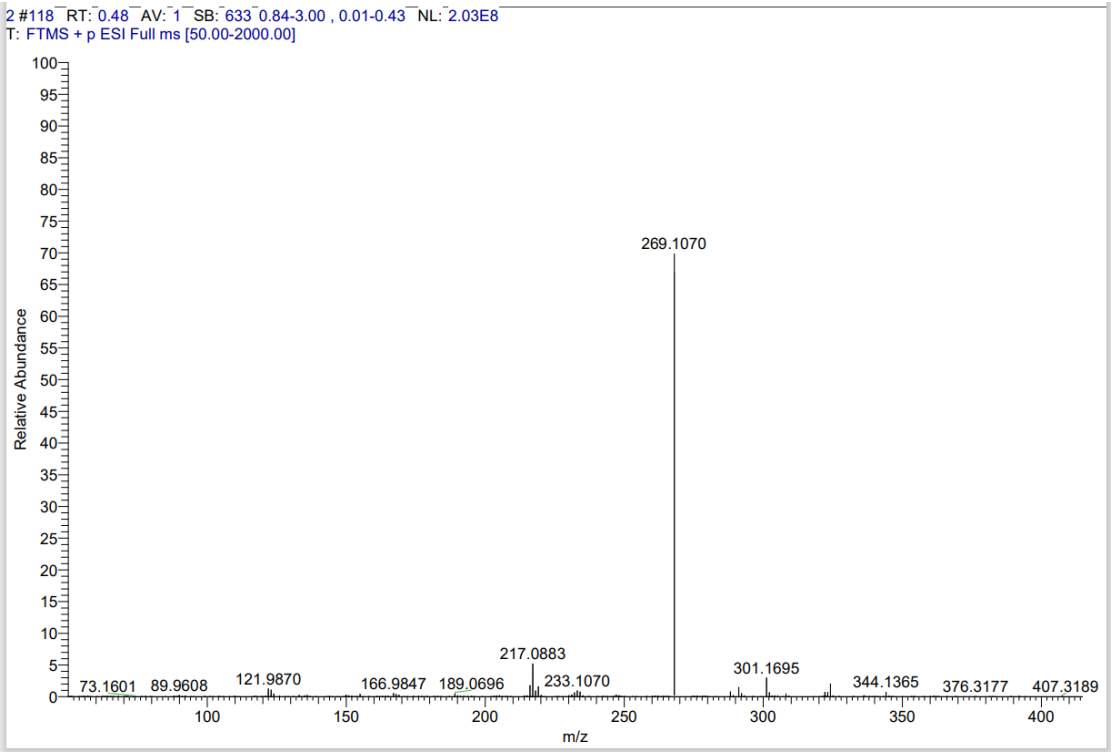
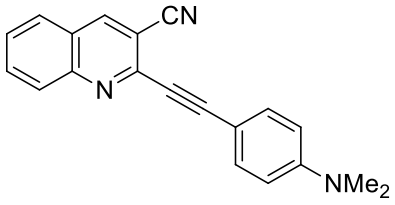
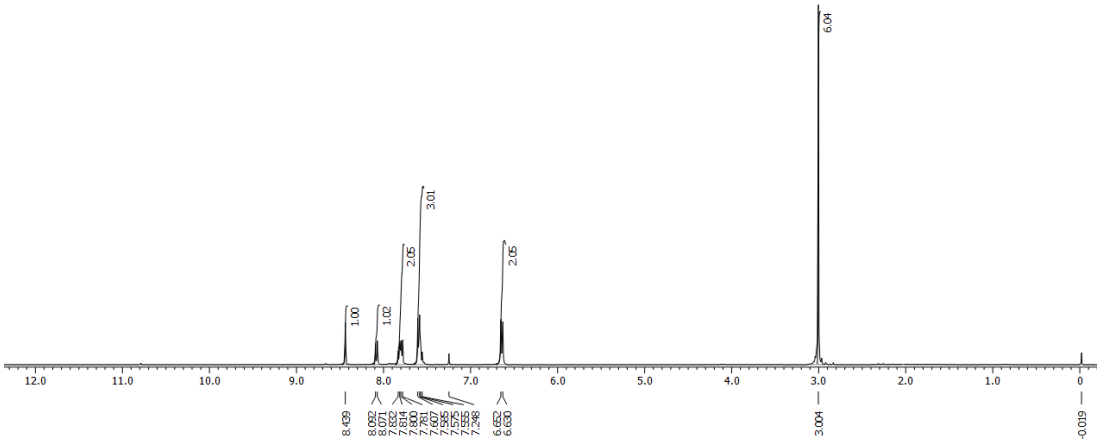


Figure 4.6

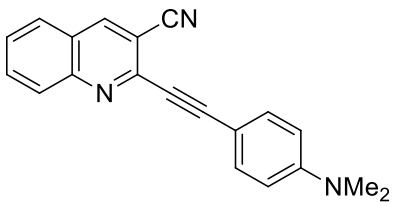
^{1}H NMR



2-((4-(Dimethylamino)phenyl)ethynyl)quinoline-3-carbonitrile (1c)



^{13}C NMR



2-((4-(Dimethylamino)phenyl)ethynyl)quinoline-3-carbonitrile (1c)

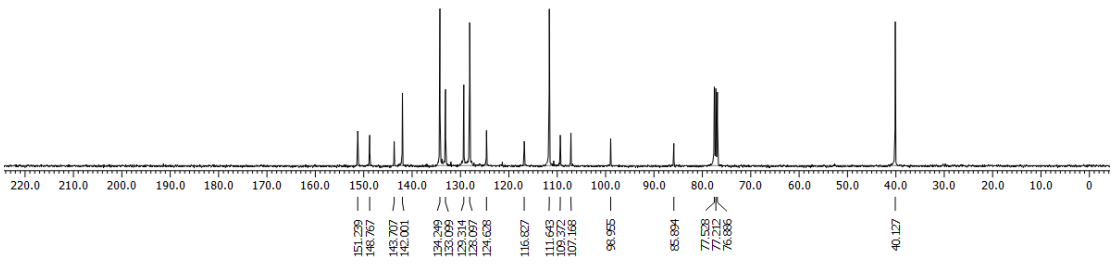
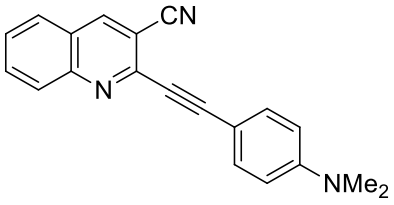


Figure 4.7

HRMS



2-((4-(Dimethylamino)phenyl)ethynyl)quinoline-3-carbonitrile (1c)

Qualitative Compound Report

Data File	SV-786.d	**Sample Name**	SV-786
Sample Type	Sample	**Position**	P1-B3
Instrument Name	Instrument 1	**User Name**	
Acq Method	Damo JK.m	**Acquired Time**	28-03-2019 13:27:52
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

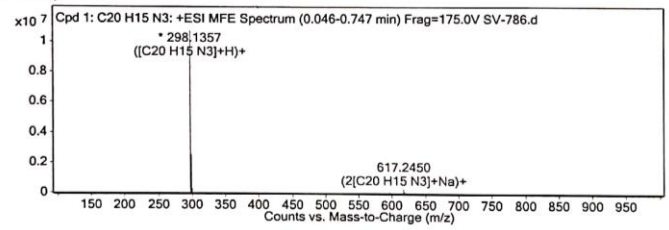
Sample Group	**Info.**
Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.01 (B5125.1)

Compound Table

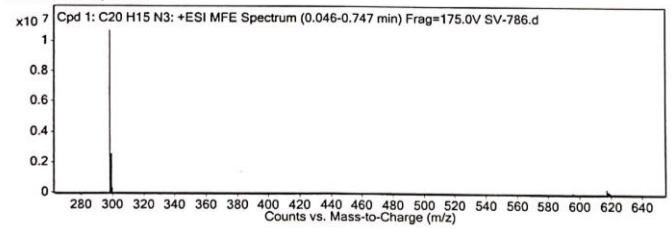
Compound Label	RT	Mass	Formula	MFG Formula	MFG Diff (ppm)	DB Formula
Cpd 1: C20 H15 N3	0.152	297.1271	C20 H15 N3	C20 H15 N3	-1.6	C20 H15 N3

Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C20 H15 N3	298.1357	0.152	Find by Molecular Feature	297.1271

MFE MS Spectrum



MFE MS Zoomed Spectrum



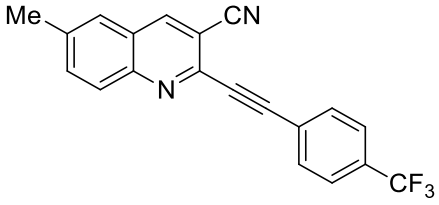
MS Spectrum Peak List

m/z	z	Abund	Formula	Ion
298.1357	1	10718903	C20 H15 N3	(M+H)+
299.1394	1	2540100.81	C20 H15 N3	(M+H)+
300.1421	1	267366.11	C20 H15 N3	(M+H)+
595.2613	1	58454.59	C20 H15 N3	(2M+H)+
596.2634	1	27717.05	C20 H15 N3	(2M+H)+
597.2662	1	7350.13	C20 H15 N3	(2M+H)+
617.245	1	292611.91	C20 H15 N3	(2M+Na)+
618.248	1	129449.95	C20 H15 N3	(2M+Na)+
619.251	1	28892.2	C20 H15 N3	(2M+Na)+

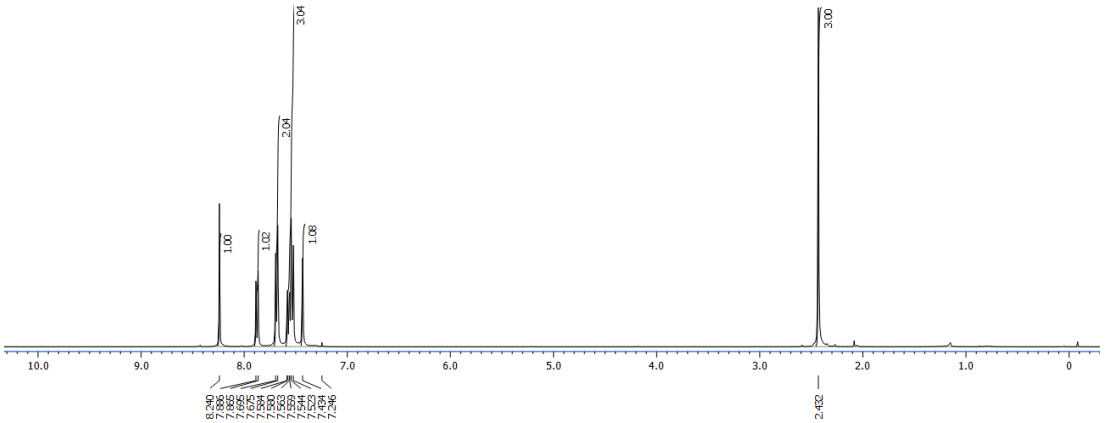
--- End Of Report ---

Figure 4.8

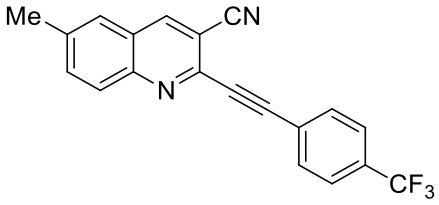
^{1}H NMR



6-Methyl-2-((4-(trifluoromethyl)phenyl)ethynyl)quinoline-3-carbonitrile (1d)



^{13}C NMR



6-Methyl-2-((4-(trifluoromethyl)phenyl)ethynyl)quinoline-3-carbonitrile (4d)

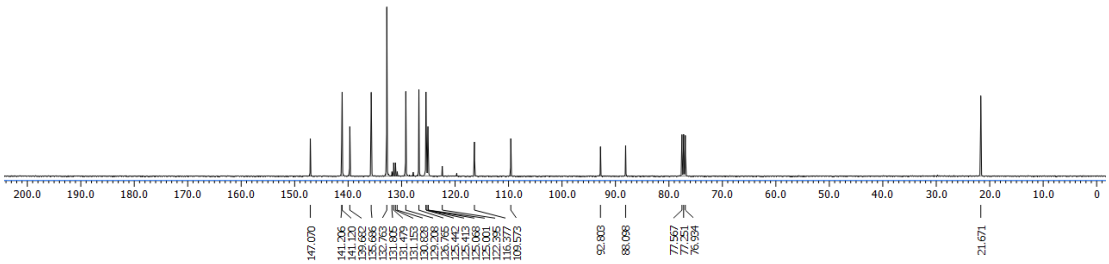
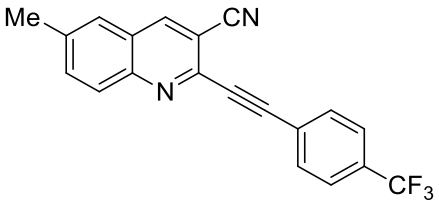


Figure 4.9

HRMS



6-Methyl-2-((4-(trifluoromethyl)phenyl)ethynyl)quinoline-3-carbonitrile (1d)

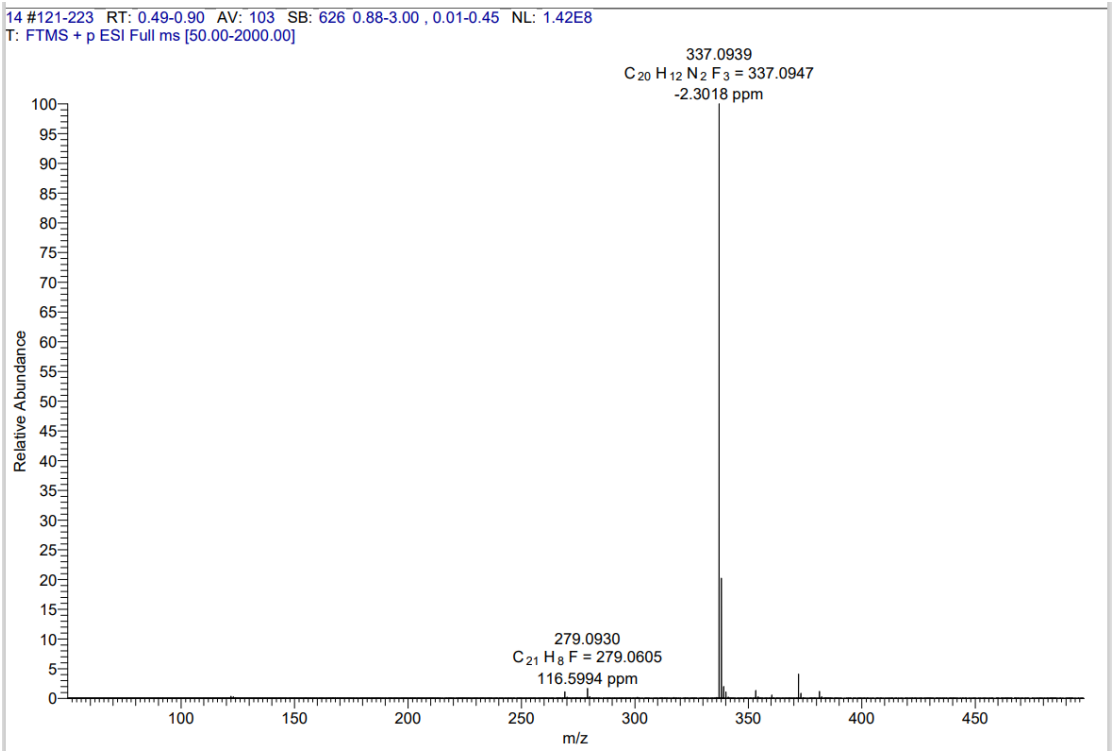
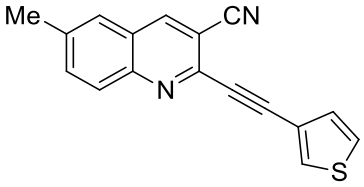
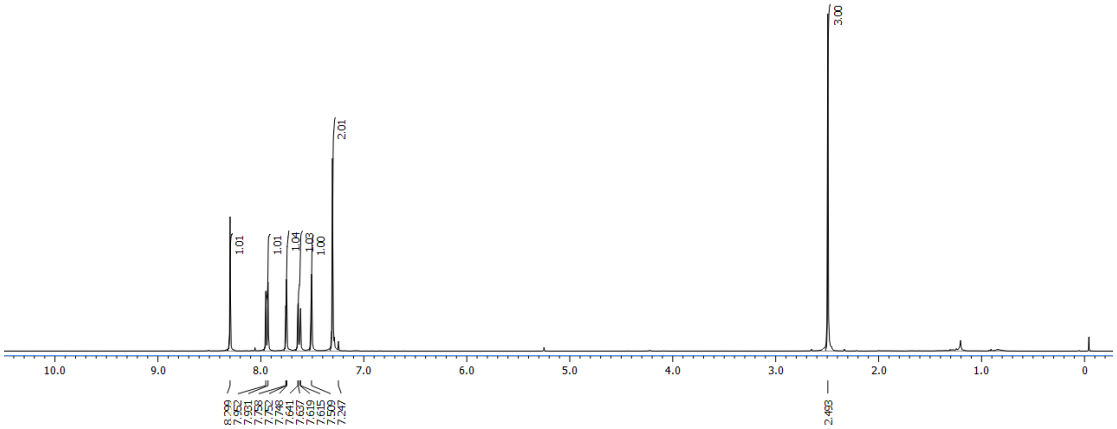


Figure 4.10

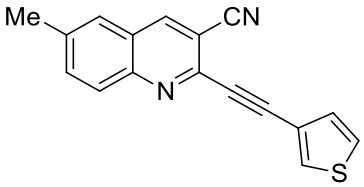
^{1}H NMR



6-Methyl-2-(thiophen-3-ylethynyl)quinoline-3-carbonitrile(1e)



^{13}C NMR



6-Methyl-2-(thiophen-3-ylethynyl)quinoline-3-carbonitrile(1e)

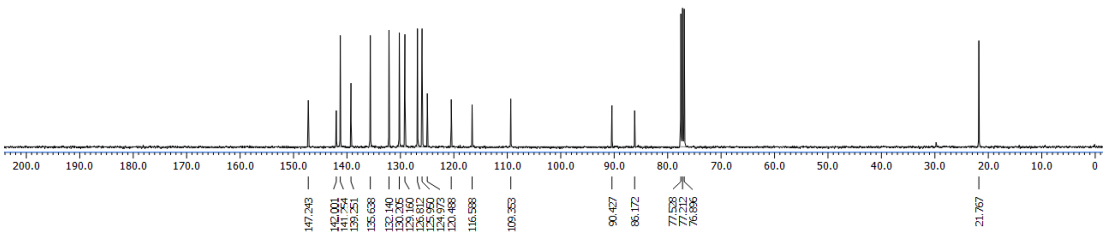
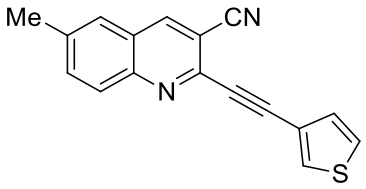


Figure 4.11

HRMS



6-Methyl-2-(thiophen-3-ylethynyl)quinoline-3-carbonitrile(1e)

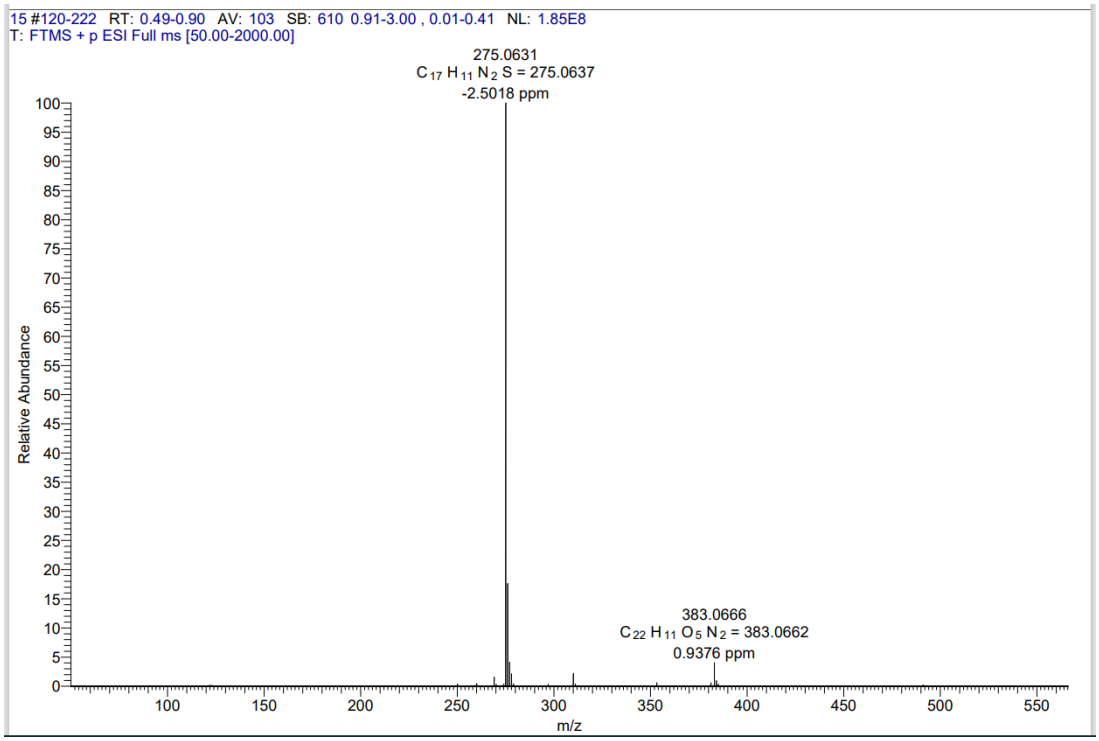
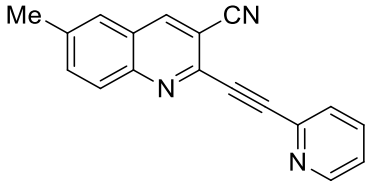
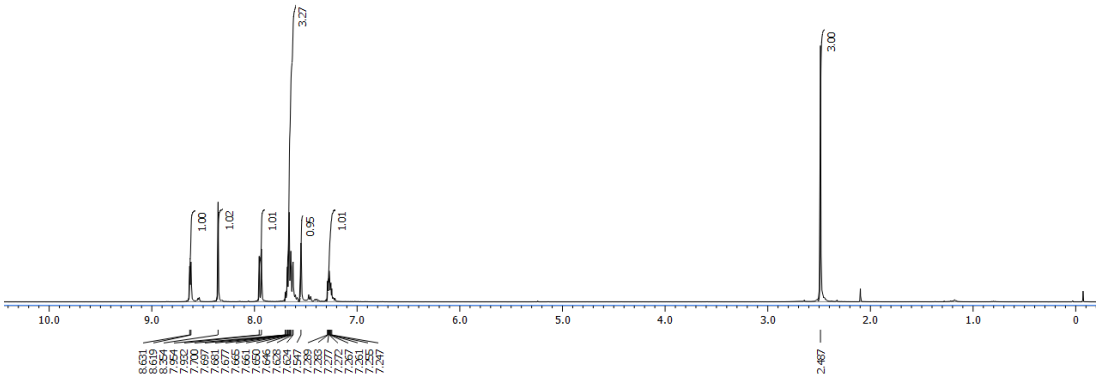


Figure 4.12

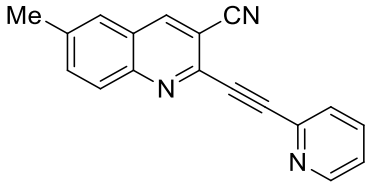
^{1}H NMR



6-Methyl-2-(pyridin-2-ylethynyl)quinoline-3-carbonitrile (1f)



^{13}C NMR



6-Methyl-2-(pyridin-2-ylethynyl)quinoline-3-carbonitrile (1f)

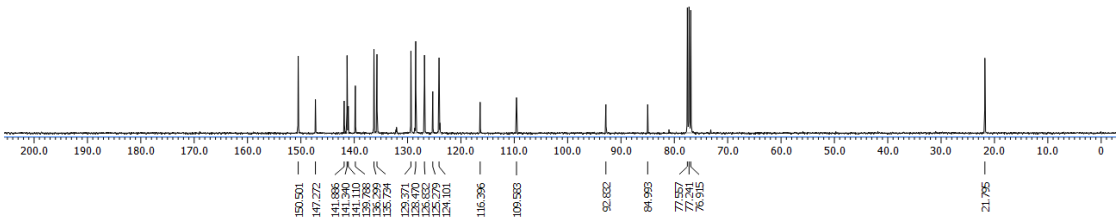
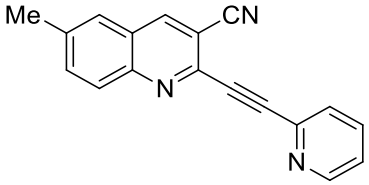


Figure 4.13

HRMS



6-Methyl-2-(pyridin-2-ylethynyl)quinoline-3-carbonitrile (1f)

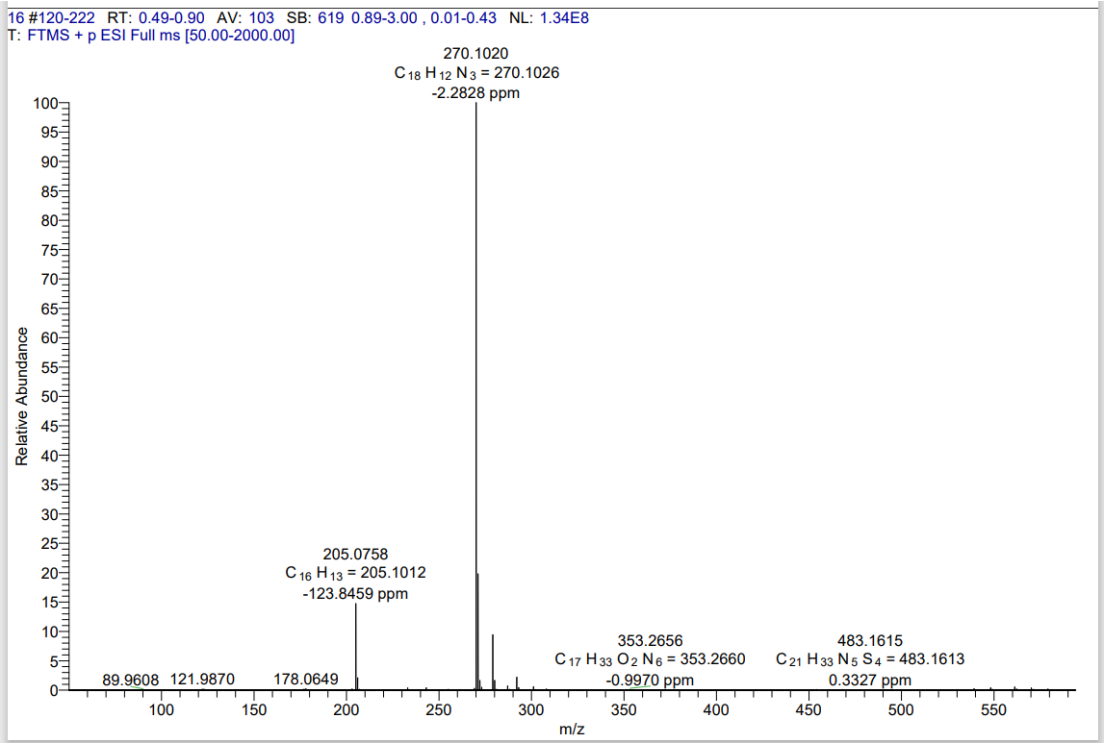
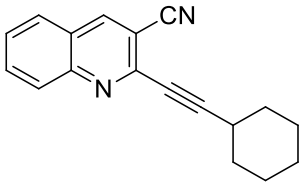
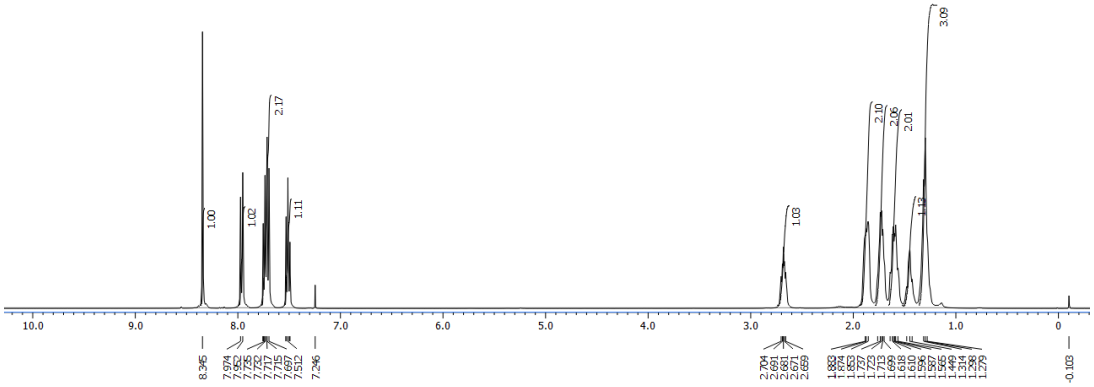


Figure 4.14

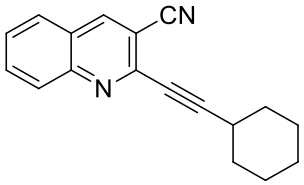
^{1}H NMR



2-(Cyclohexylethynyl)quinoline-3-carbonitrile (1g)



^{13}C NMR



2-(Cyclohexylethynyl)quinoline-3-carbonitrile (1g)

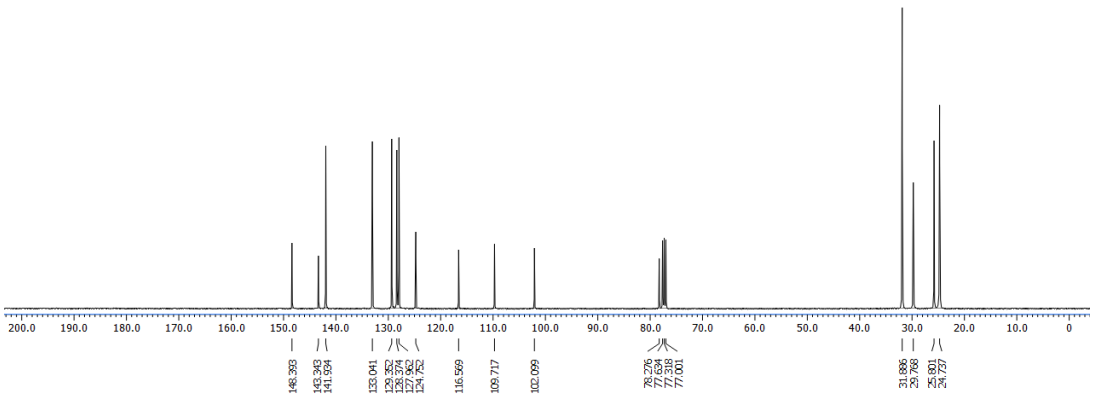
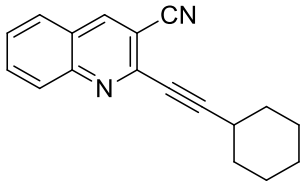


Figure 4.15

HRMS



2-(Cyclohexylethynyl)quinoline-3-carbonitrile (1g)

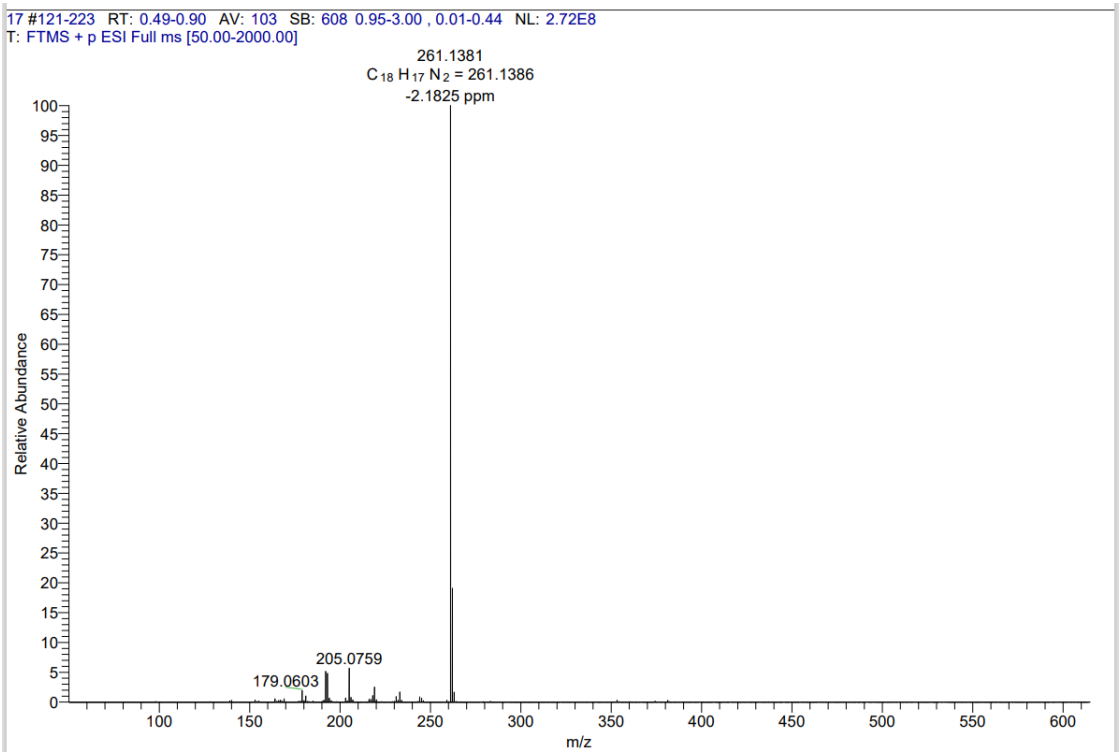
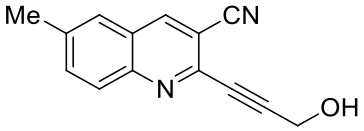
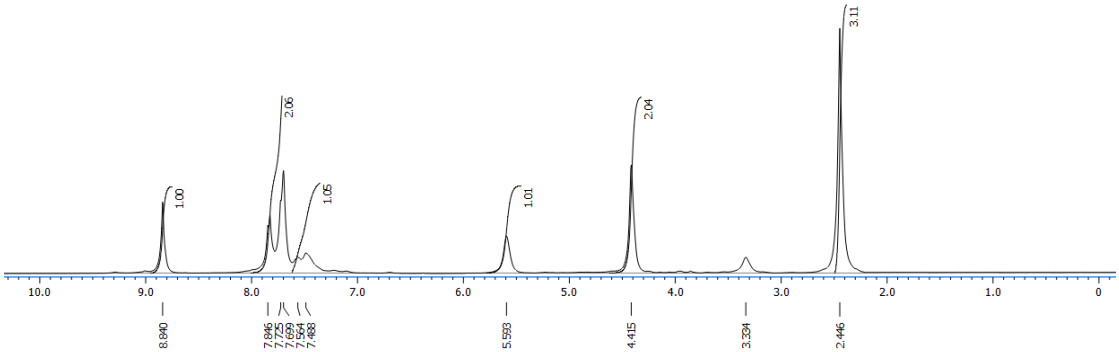


Figure 4.16

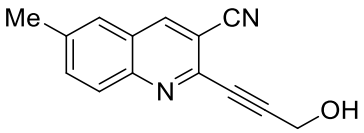
^{1}H NMR



2-(3-Hydroxyprop-1-yn-1-yl)-6-methylquinoline-3-carbonitrile (1h)



^{13}C NMR



2-(3-Hydroxyprop-1-yn-1-yl)-6-methylquinoline-3-carbonitrile (1h)

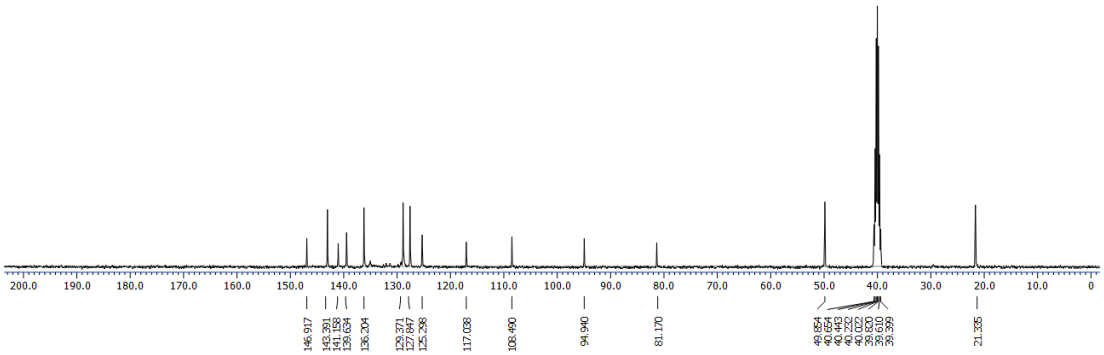
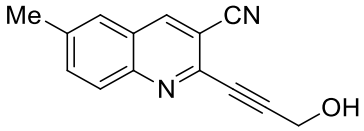


Figure 4.17

HRMS



2-(3-Hydroxyprop-1-yn-1-yl)-6-methylquinoline-3-carbonitrile (1h)

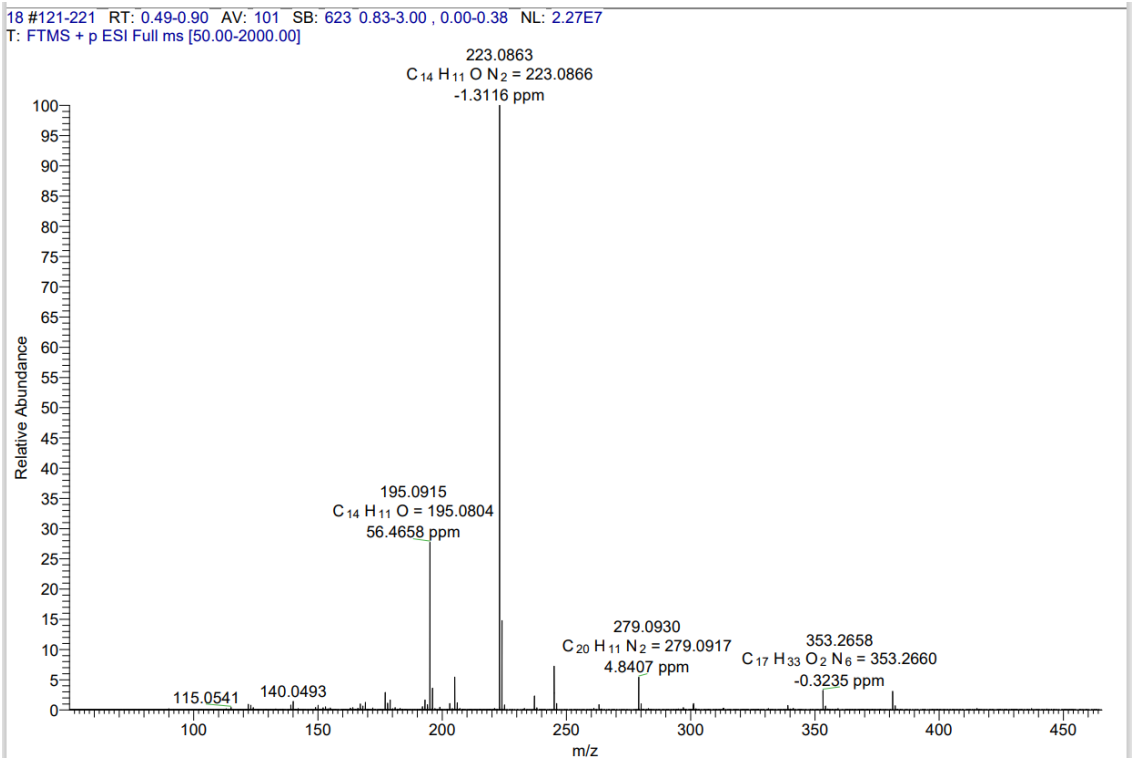
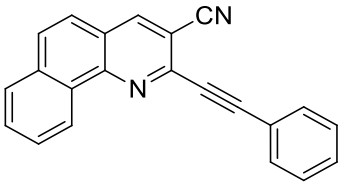
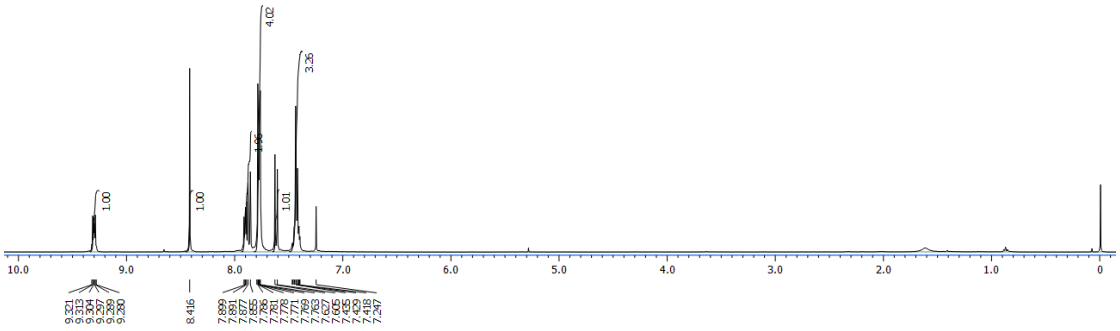


Figure 4.18

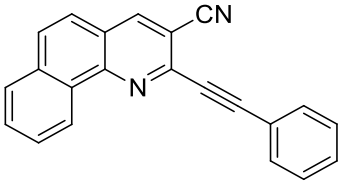
^{1}H NMR



2-(Phenylethynyl)benzo[*h*]quinoline-3-carbonitrile (4a)



^{13}C NMR



2-(Phenylethynyl)benzo[*h*]quinoline-3-carbonitrile (4a)

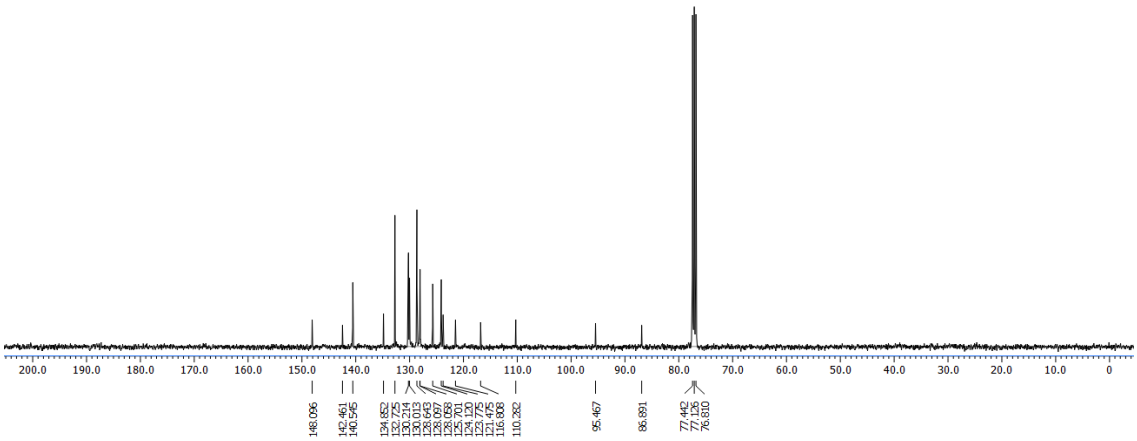
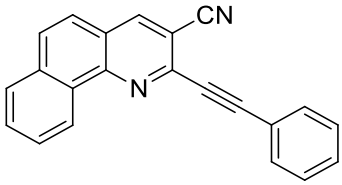


Figure 4.19

HRMS



2-(Phenylethynyl)benzo[*h*]quinoline-3-carbonitrile (4a)

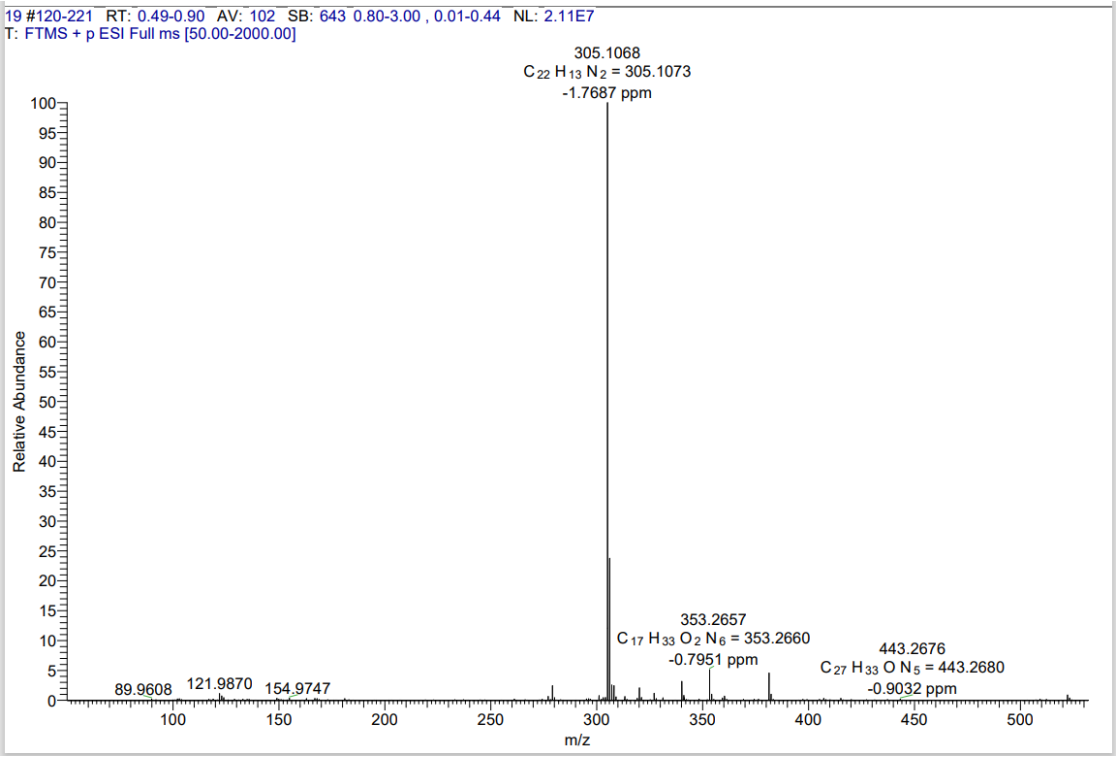
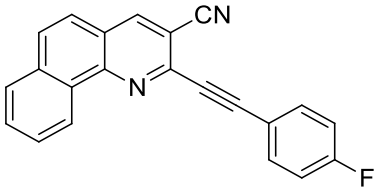
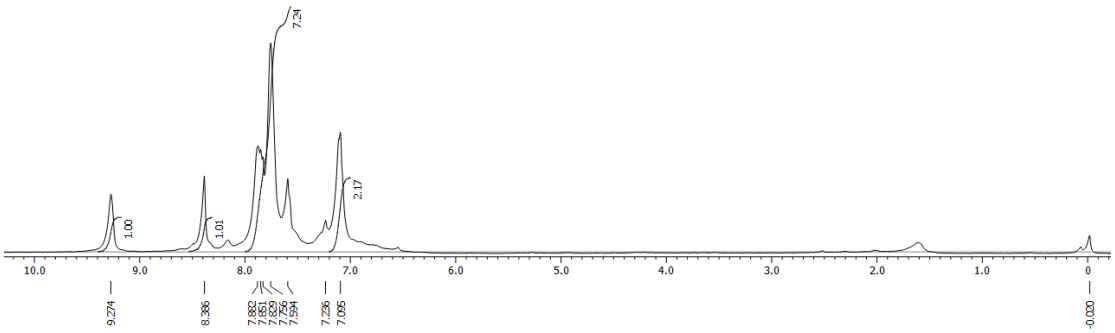


Figure 4.20

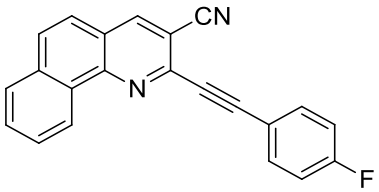
^{1}H NMR



2-((4-Fluorophenyl)ethynyl)benzo[*h*]quinoline-3-carbonitrile (4b)



^{13}C NMR



2-((4-Fluorophenyl)ethynyl)benzo[*h*]quinoline-3-carbonitrile (4b)

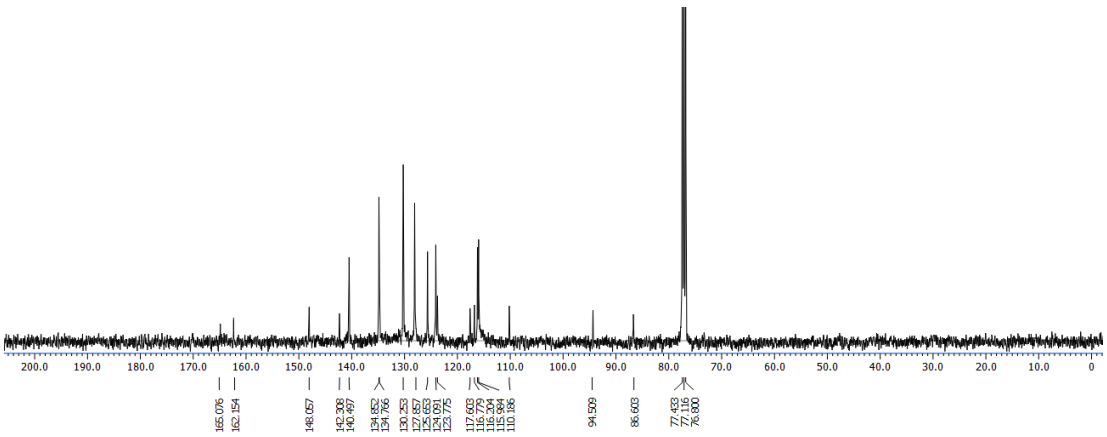
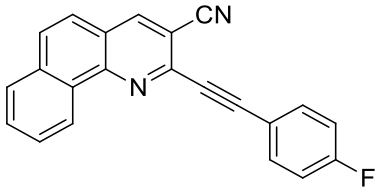


Figure 4.21

HRMS



2-((4-Fluorophenyl)ethynyl)benzo[*h*]quinoline-3-carbonitrile (4b)

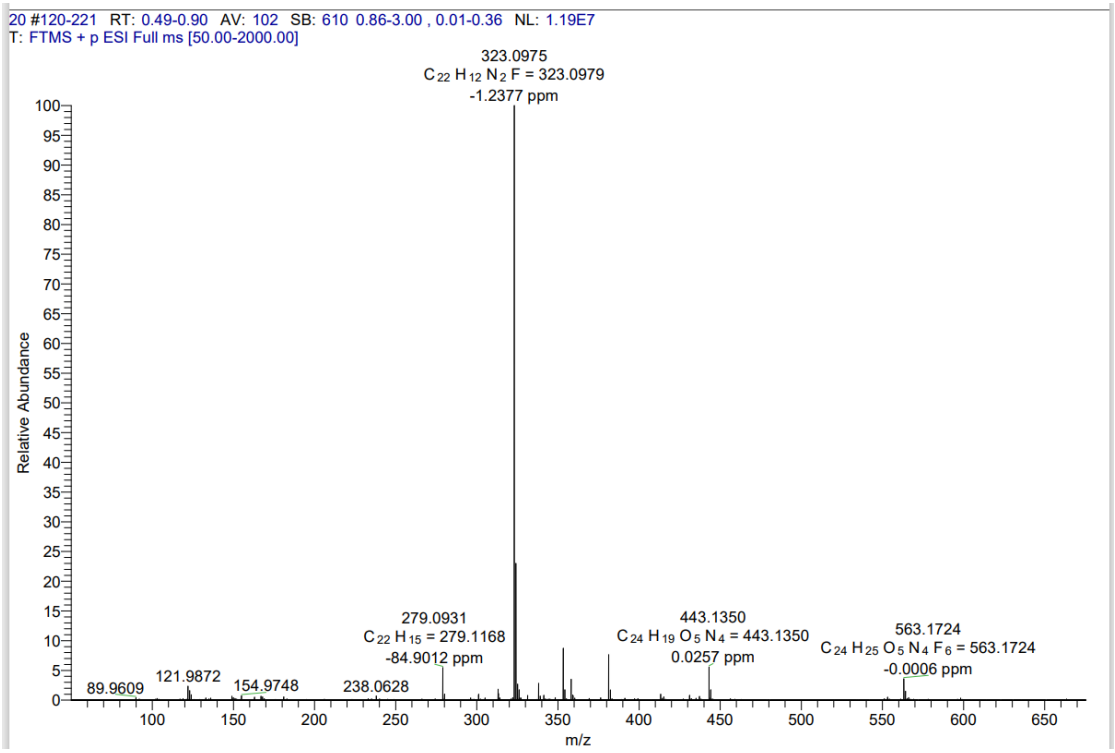
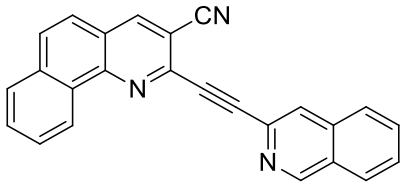
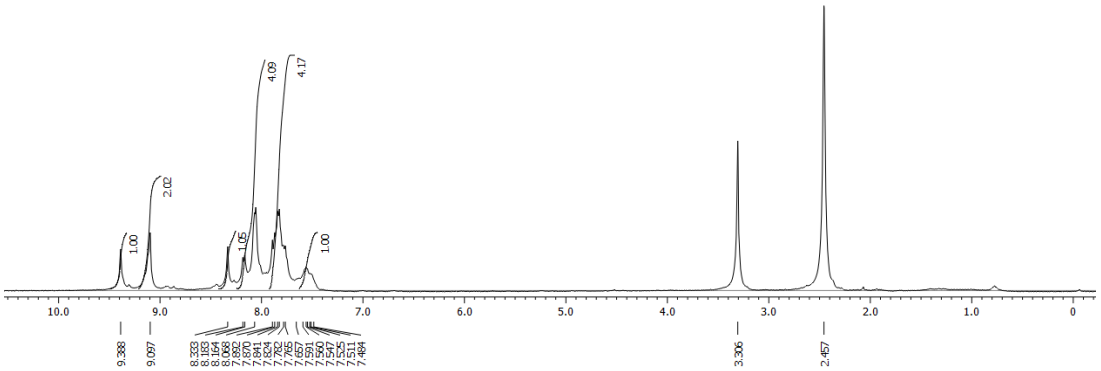


Figure 4.22

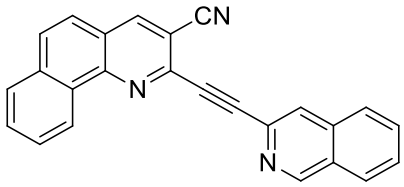
^{1}H NMR



2-(Isoquinolin-3-ylethynyl)benzo[*h*]quinoline-3-carbonitrile (4c)



^{13}C NMR



2-(Isoquinolin-3-ylethynyl)benzo[*h*]quinoline-3-carbonitrile (4c)

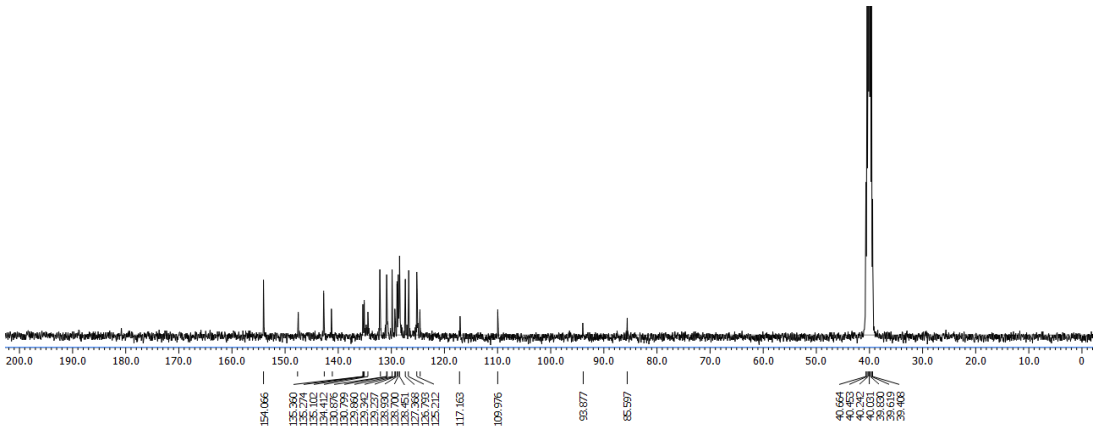
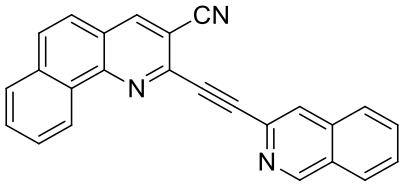


Figure 4.23

HRMS



2-(Isoquinolin-3-ylethynyl)benzo[*h*]quinoline-3-carbonitrile (4c)

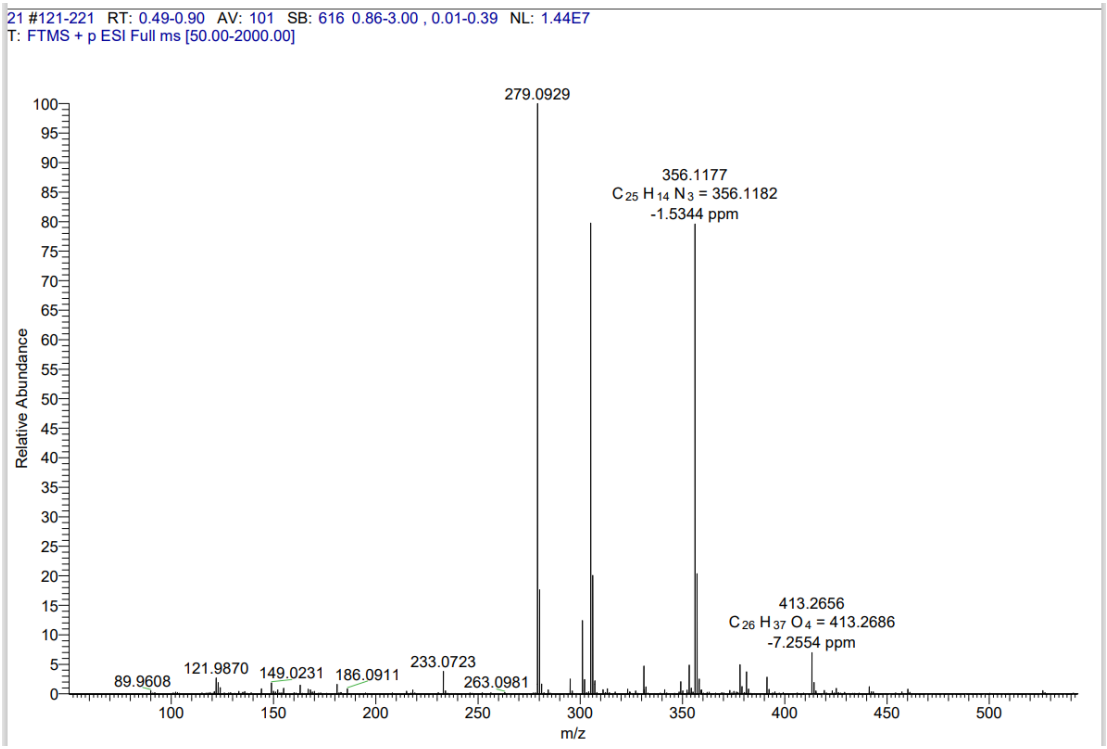
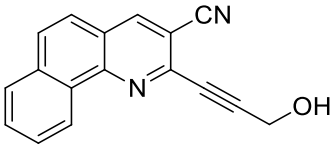
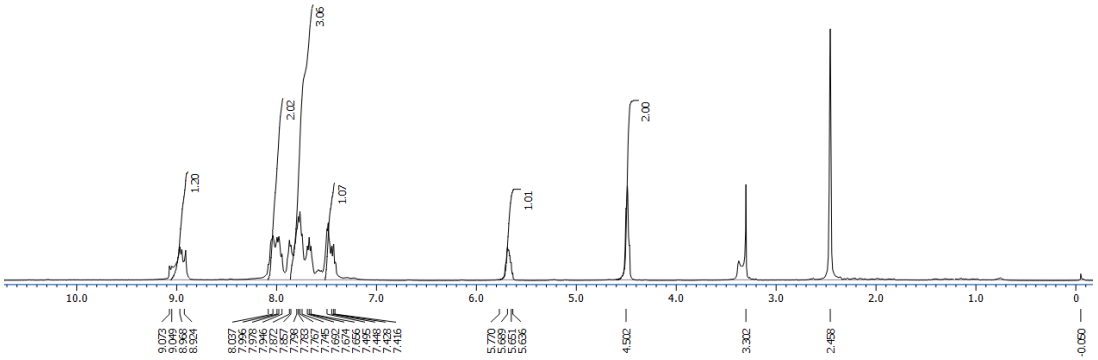


Figure 4.24

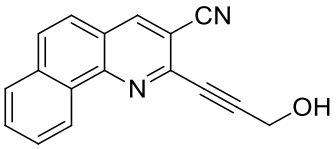
^{1}H NMR



2-(3-Hydroxyprop-1-yn-1-yl)benzo[*h*]quinoline-3-carbonitrile (4d)



^{13}C NMR



2-(3-Hydroxyprop-1-yn-1-yl)benzo[*h*]quinoline-3-carbonitrile (4d)

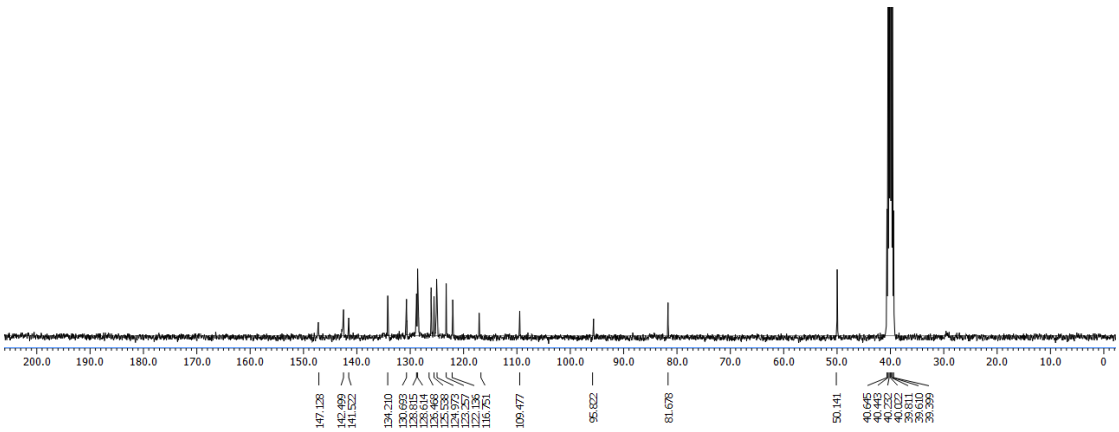
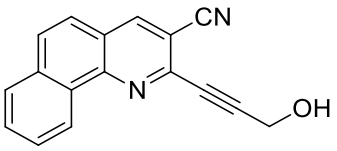


Figure 4.25

HRMS



2-(3-Hydroxyprop-1-yn-1-yl)benzo[*h*]quinoline-3-carbonitrile (4d)

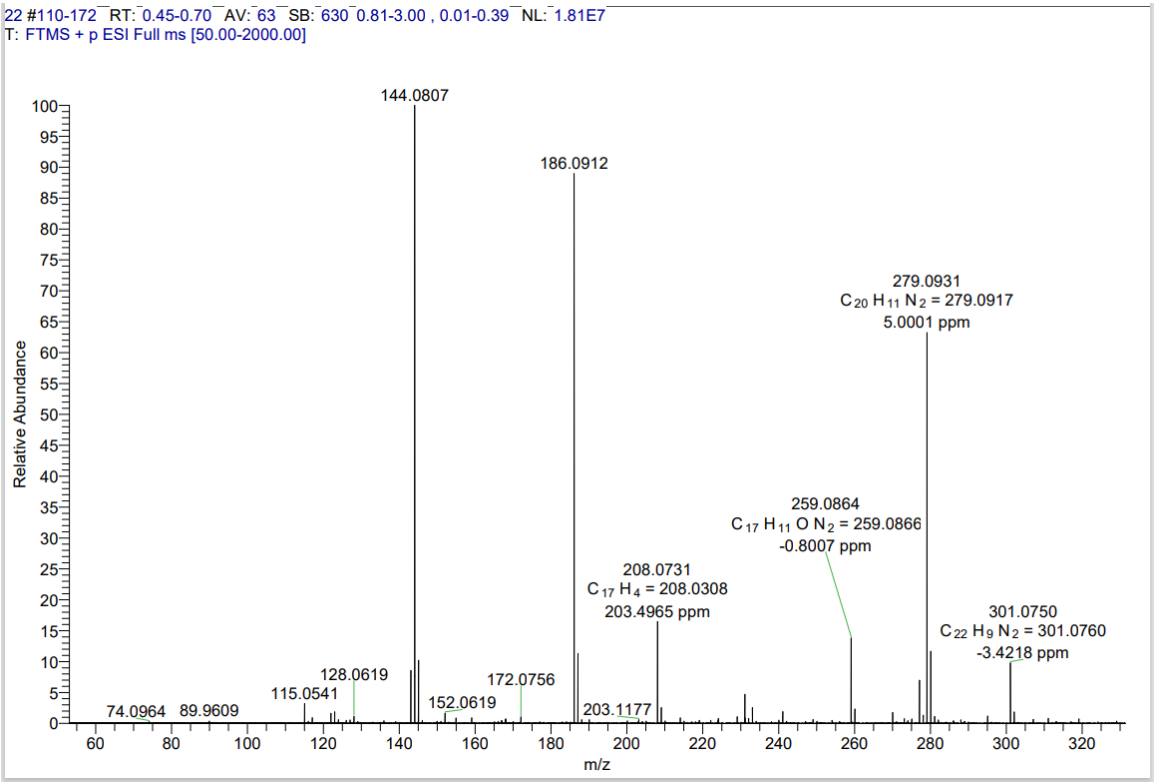
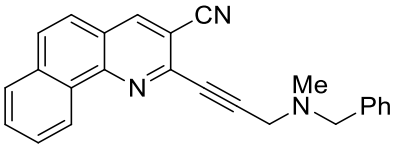
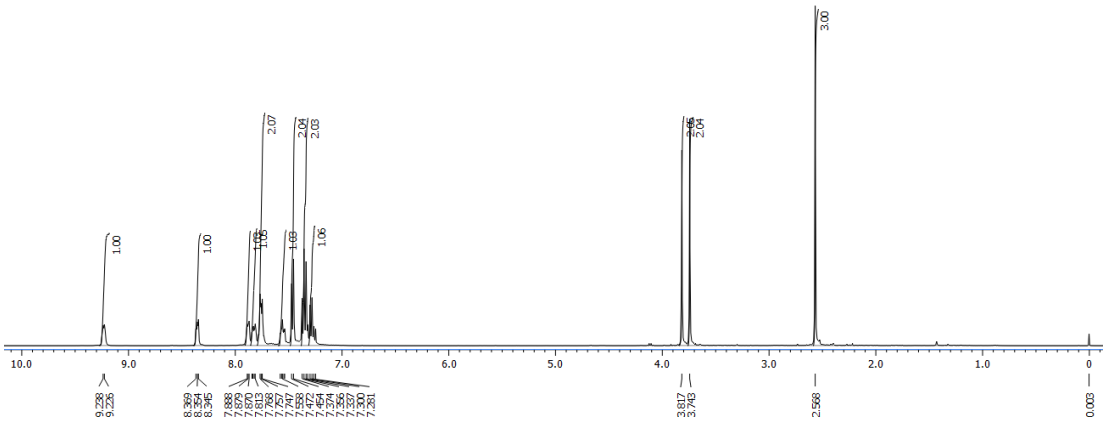


Figure 4.26

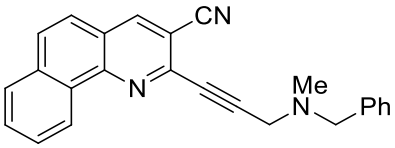
^{1}H NMR



2-(3-(Benzyl(methyl)amino)prop-1-yn-1-yl)benzo[*h*]quinoline-3-carbonitrile (4e)



^{13}C NMR



2-(3-(Benzyl(methyl)amino)prop-1-yn-1-yl)benzo[*h*]quinoline-3-carbonitrile (4e)

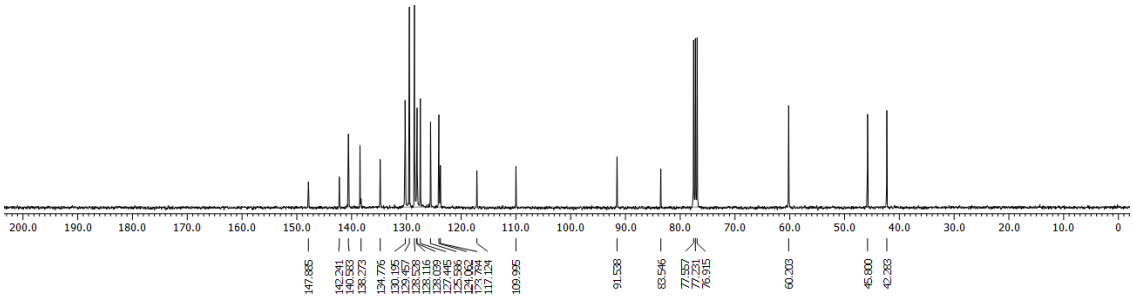
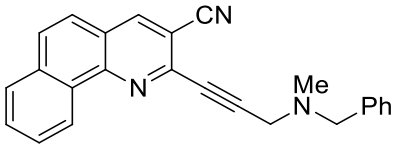


Figure 4.27

HRMS



2-(3-(Benzyl(methyl)amino)prop-1-yn-1-yl)benzo[*h*]quinoline-3-carbonitrile (4e)

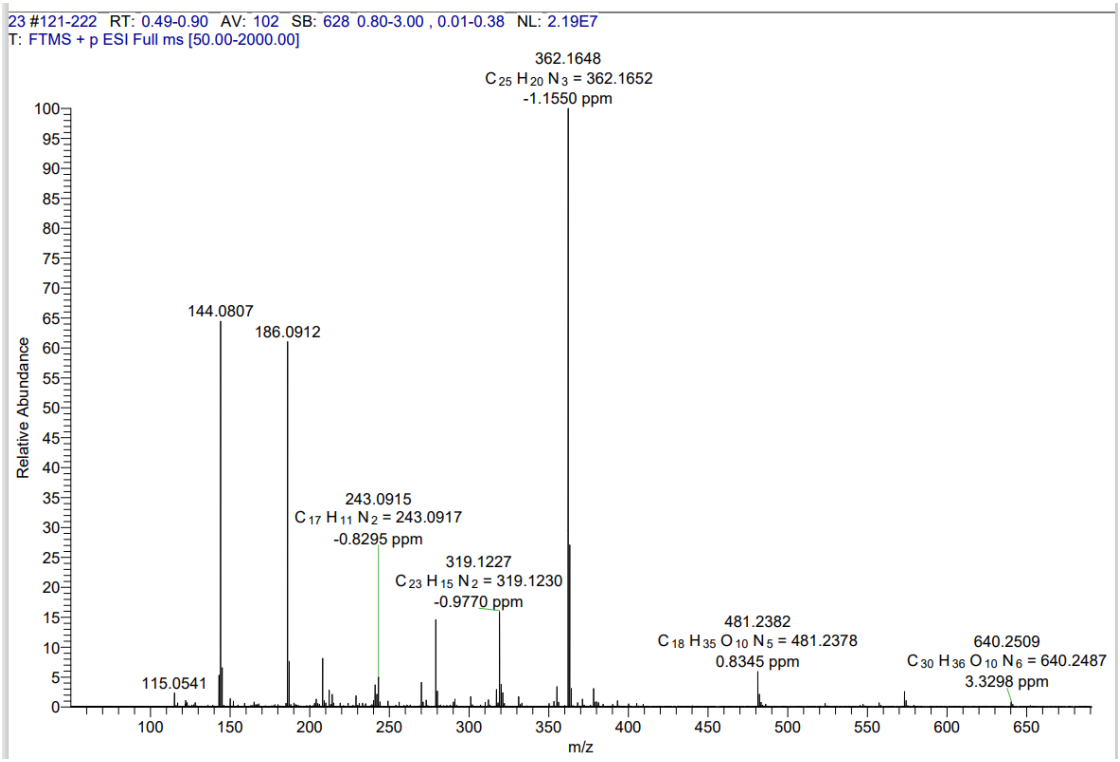
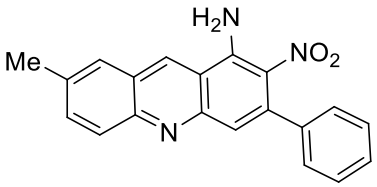
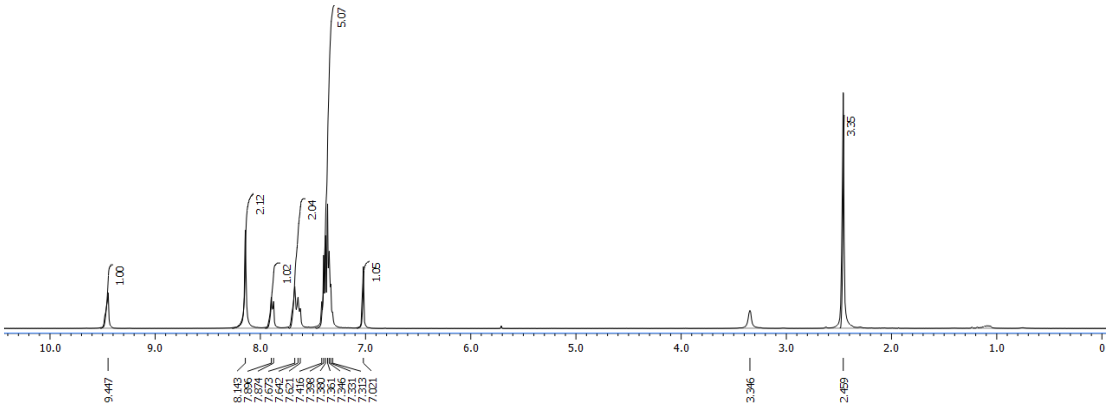


Figure 4.28

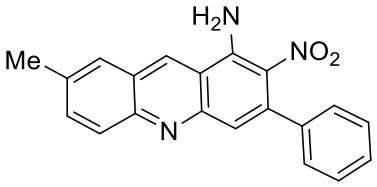
^{1}H NMR



7-Methyl-2-nitro-3-phenylacridin-1-amine (3a)



^{13}C NMR



7-Methyl-2-nitro-3-phenylacridin-1-amine (3a)

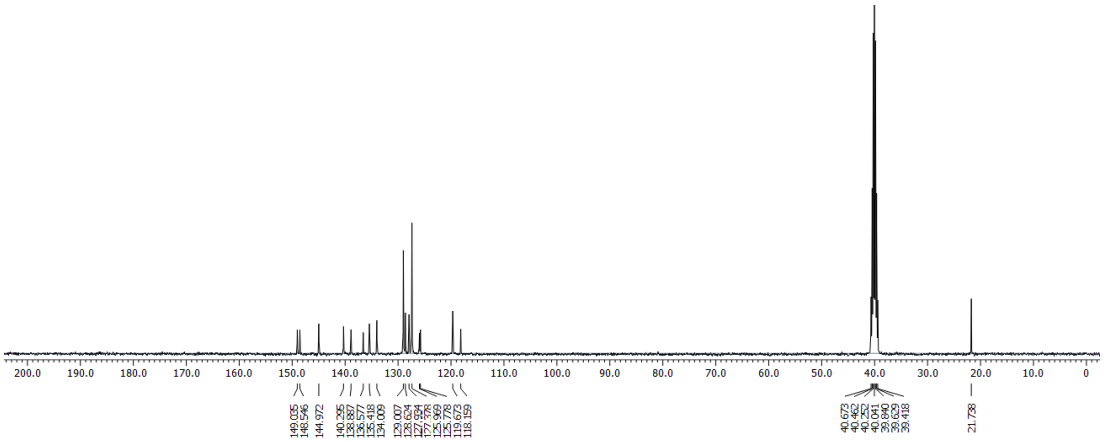
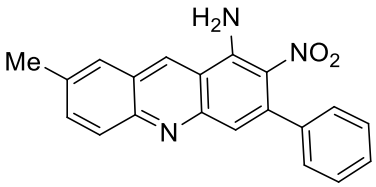


Figure 4.29

HRMS



7-Methyl-2-nitro-3-phenylacridin-1-amine (3a)

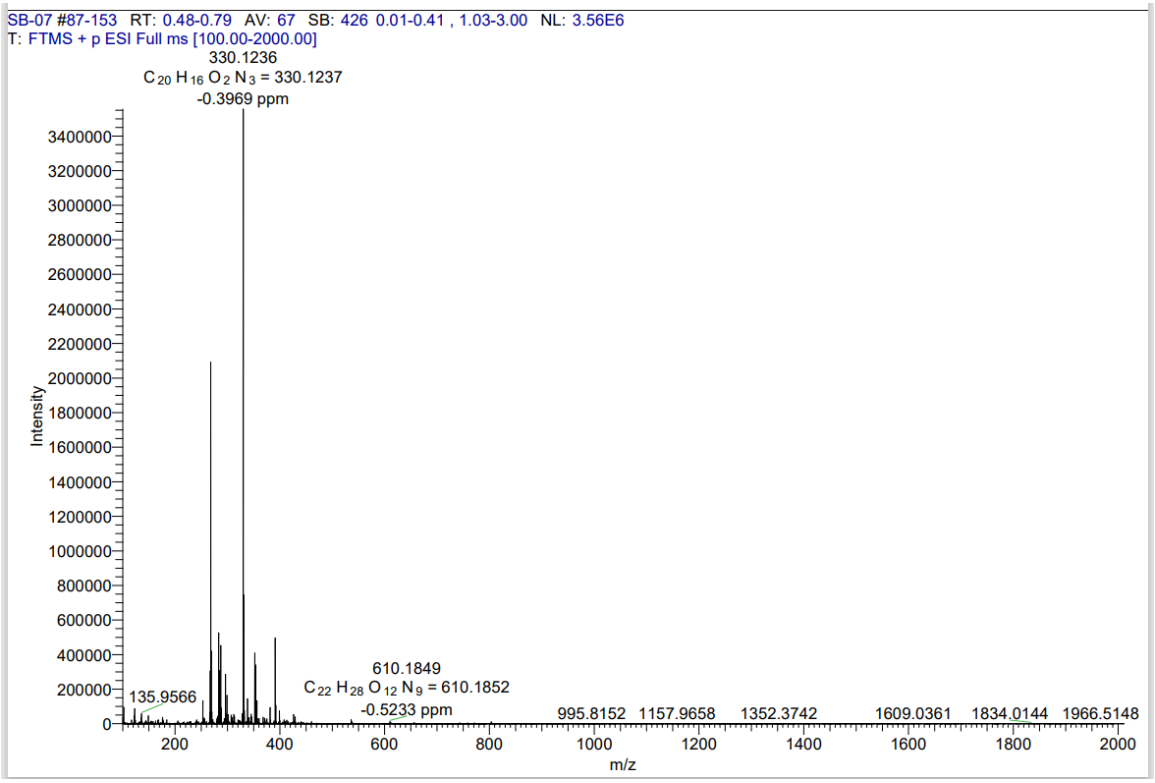
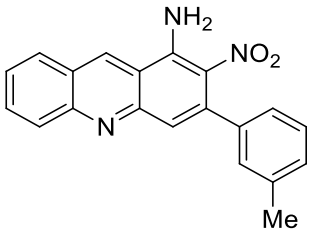
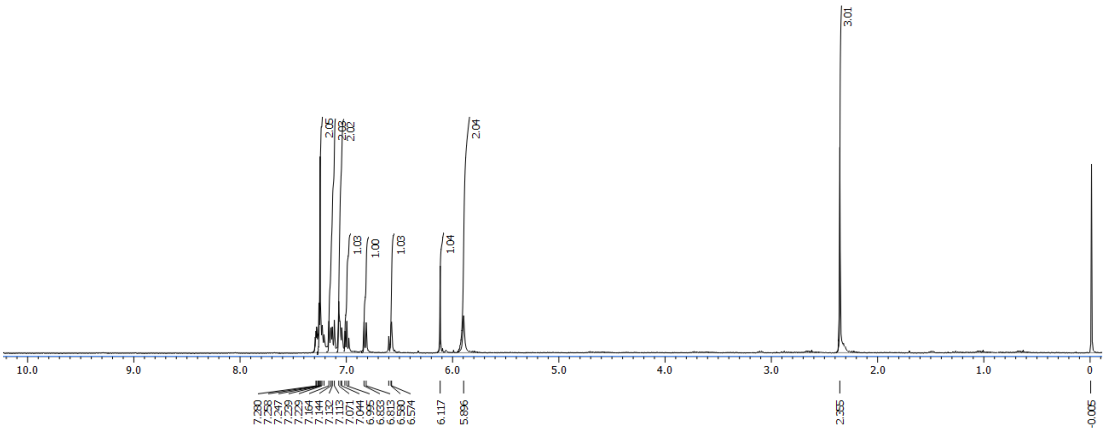


Figure 4.30

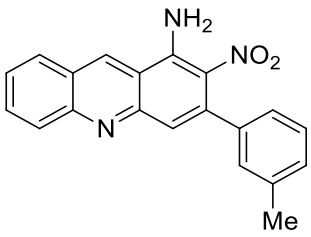
^{1}H NMR



2-Nitro-3-(*m*-tolyl)acridin-1-amine (3b)



^{13}C NMR



2-Nitro-3-(*m*-tolyl)acridin-1-amine (3b)

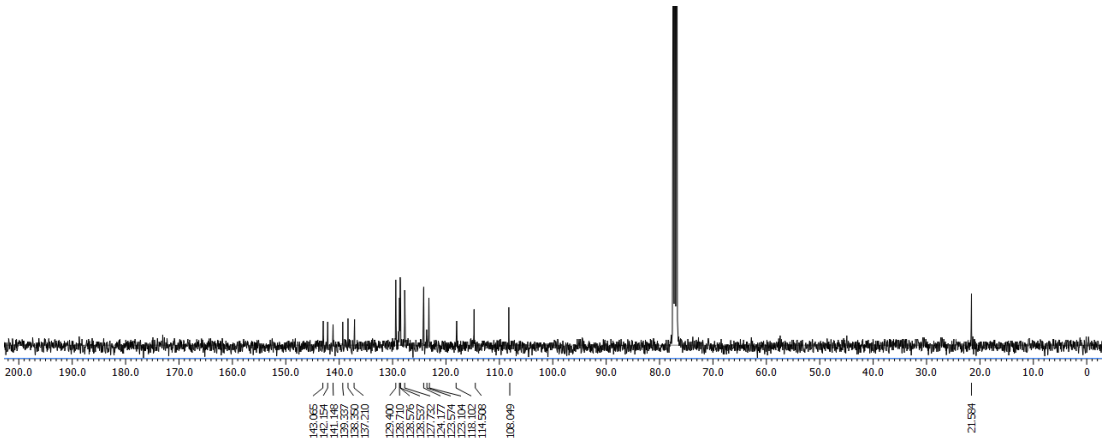
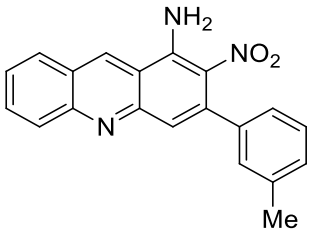


Figure 4.31

HRMS



2-Nitro-3-(*m*-tolyl)acridin-1-amine (3b)

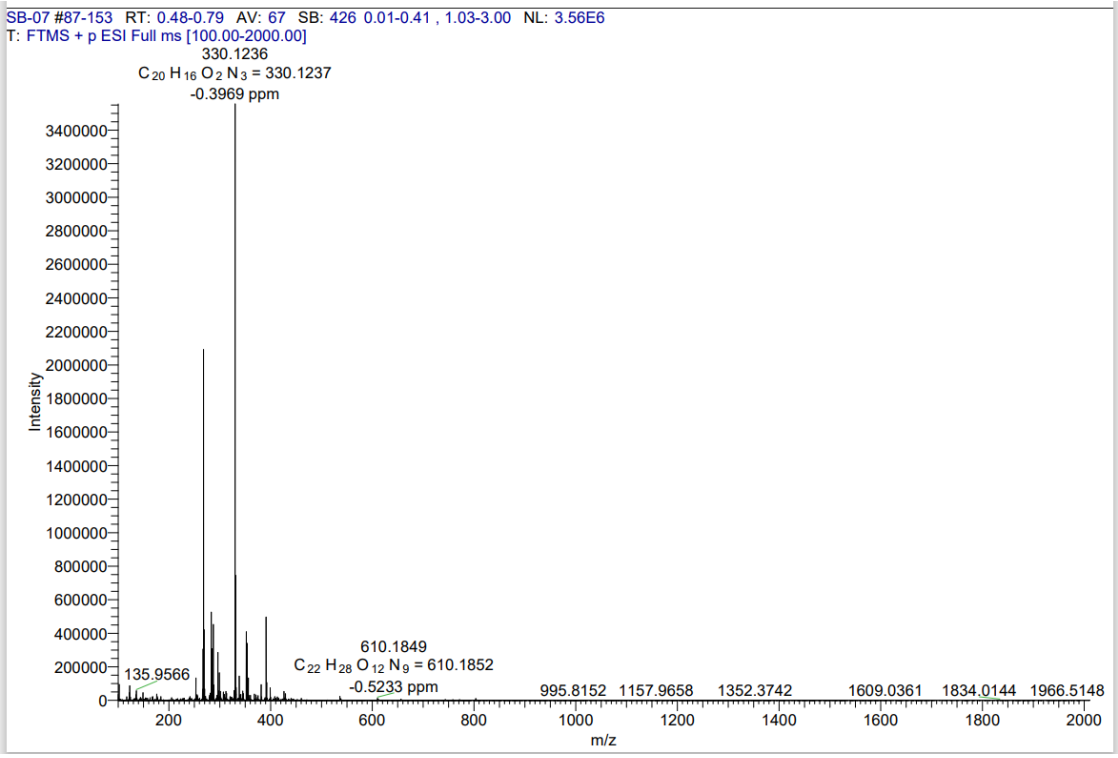
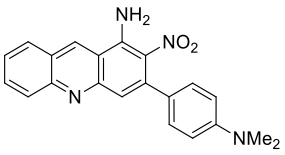
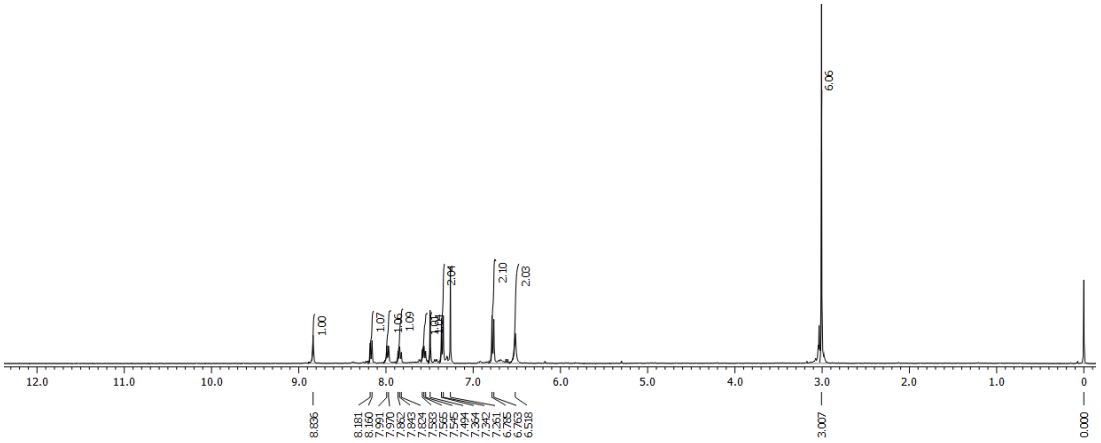


Figure 4.32

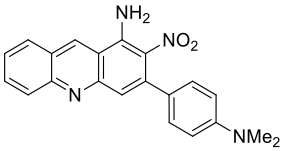
^{1}H NMR



3-(4-(Dimethylamino)phenyl)-2-nitroacridin-1-amine (3c)



^{13}C NMR



3-(4-(Dimethylamino)phenyl)-2-nitroacridin-1-amine (3c)

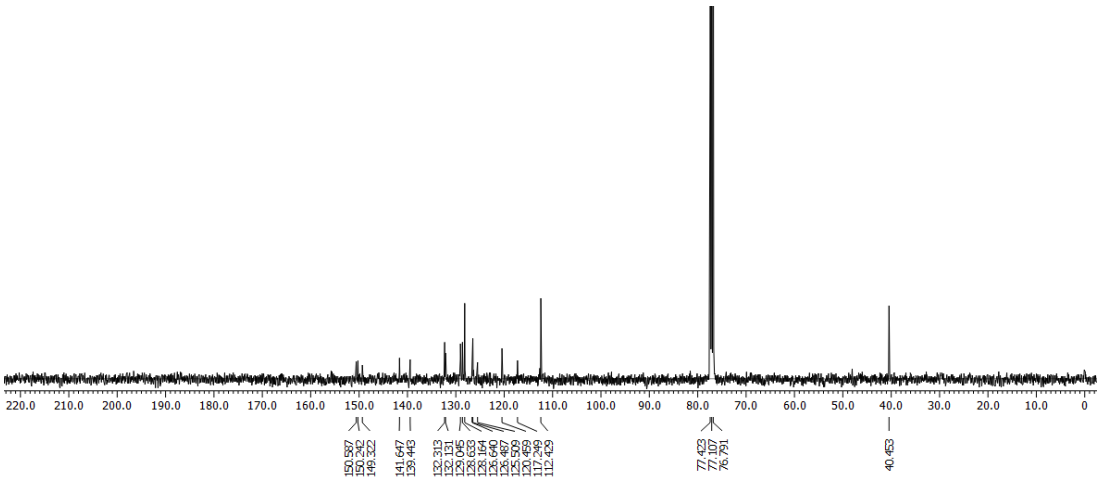
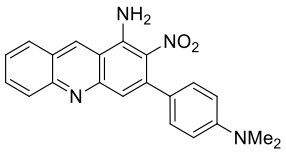


Figure 4.33

HRMS



3-(4-(Dimethylamino)phenyl)-2-nitroacridin-1-amine (3c)

Qualitative Compound Report

Data File	SV-811.d	**Sample Name**	SV-811
Sample Type	Sample	**Position**	P1-F1
Instrument Name	Instrument 1	**User Name**	
Acq Method	Damo JK.m	**Acquired Time**	02-05-2019 16:11:56
IRM Calibration Status	Success	**DA Method**	Default.m
Comment			

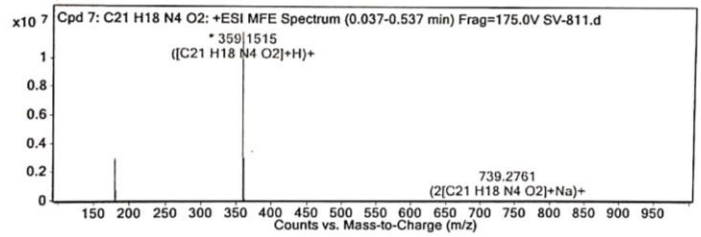
Sample Group	**Info.**
Acquisition SW Version	6200 series TOF/6500 series Q-TOF B.05.01 (B5125.1)

Compound Table

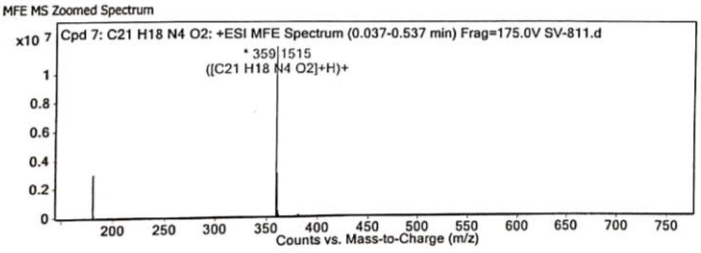
Compound Label	RT	Mass	Formula	MFG Formula	MFG Diff (ppm)	DB Formula
Cpd 7: C21 H18 N4 O2	0.101	358.1443	C21 H18 N4 O2	C21 H18 N4 O2	-3.69	C21 H18 N4 O2

Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 7: C21 H18 N4 O2	359.1515	0.101	Find by Molecular Feature	358.1443

MFE MS Spectrum



MFE MS Zoomed Spectrum



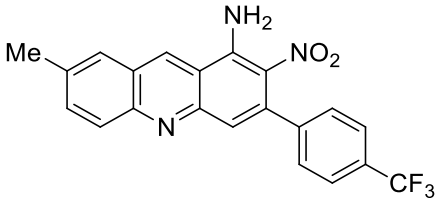
MS Spectrum Peak List

m/z	z	Abund	Formula	Ion
180.0794	2	3002752.5	C21 H18 N4 O2	(M+2H)+2
180.581	2	733756.51	C21 H18 N4 O2	(M+2H)+2
181.0817	2	105199.65	C21 H18 N4 O2	(M+2H)+2
359.1515	1	11879504	C21 H18 N4 O2	(M+H)+
360.1545	1	2972658.88	C21 H18 N4 O2	(M+H)+
361.1572	1	365482.34	C21 H18 N4 O2	(M+H)+
362.1468	1	102264.98	C21 H18 N4 O2	(M+H)+
363.1471	1	26341.81	C21 H18 N4 O2	(M+H)+
381.1339	1	37205.11	C21 H18 N4 O2	(M+Na)+
739.2761	1	50616.88	C21 H18 N4 O2	(2M+Na)+

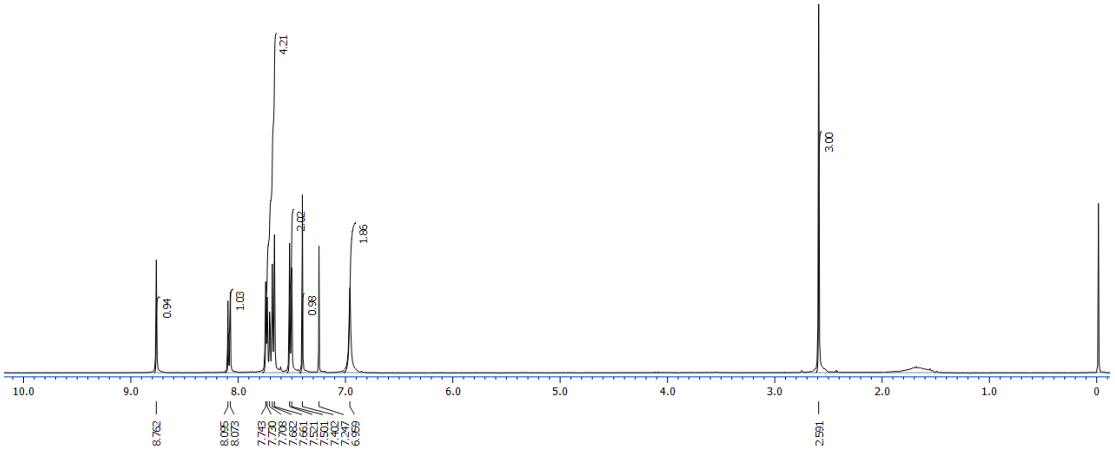
--- End Of Report ---

Figure 4.34

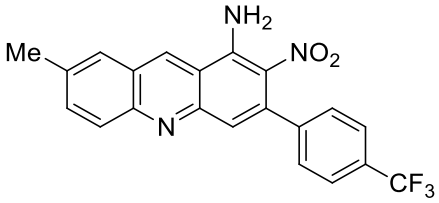
^{1}H NMR



7-Methyl-2-nitro-3-(4-(trifluoromethyl)phenyl)acridin-1-amine (3d)



^{13}C NMR



7-Methyl-2-nitro-3-(4-(trifluoromethyl)phenyl)acridin-1-amine (3d)

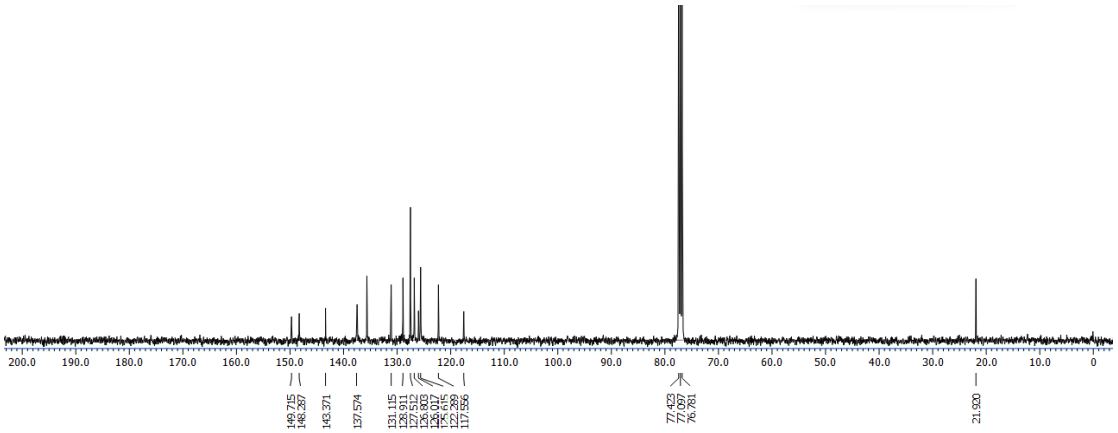
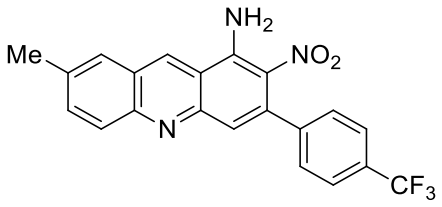


Figure 4.35

HRMS



7-Methyl-2-nitro-3-(4-(trifluoromethyl)phenyl)acridin-1-amine (3d)

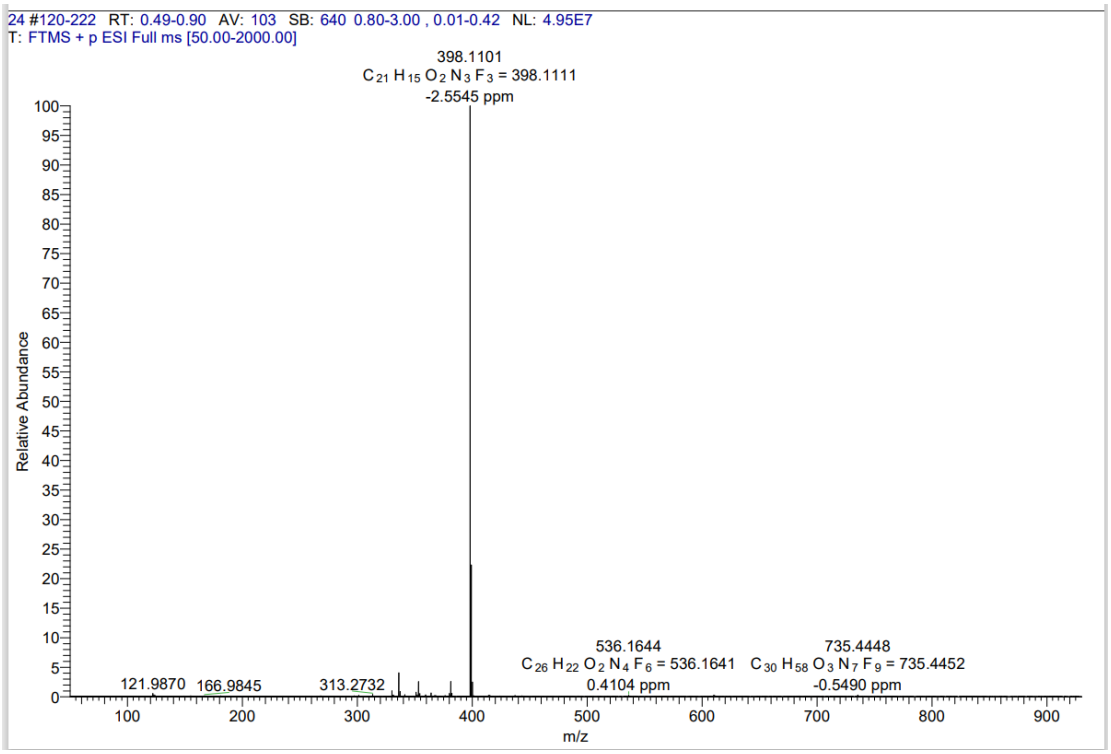
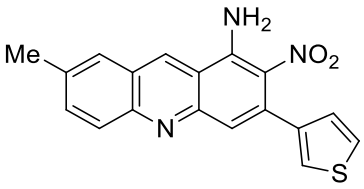
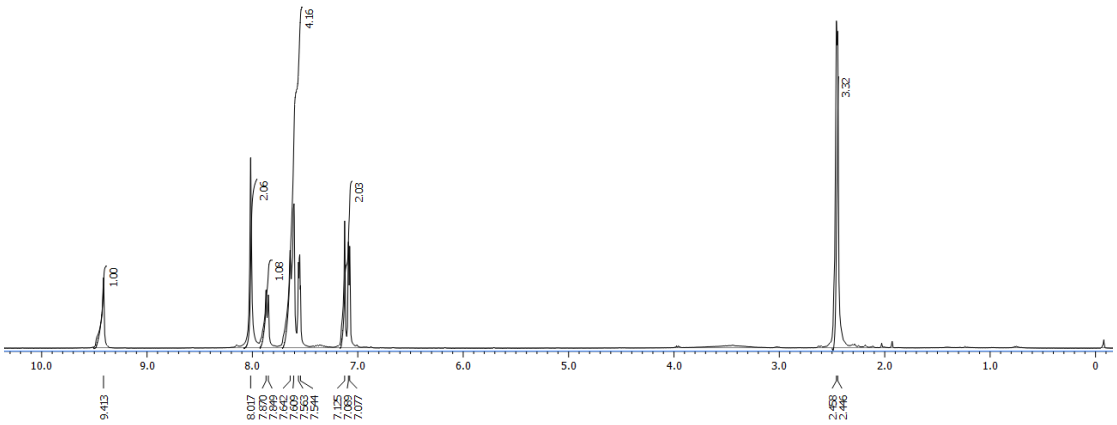


Figure 4.36

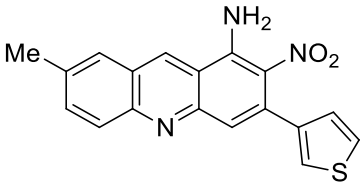
^{1}H NMR



7-Methyl-2-nitro-3-(thiophen-3-yl)acridin-1-amine (3e)



^{13}C NMR



7-Methyl-2-nitro-3-(thiophen-3-yl)acridin-1-amine (3e)

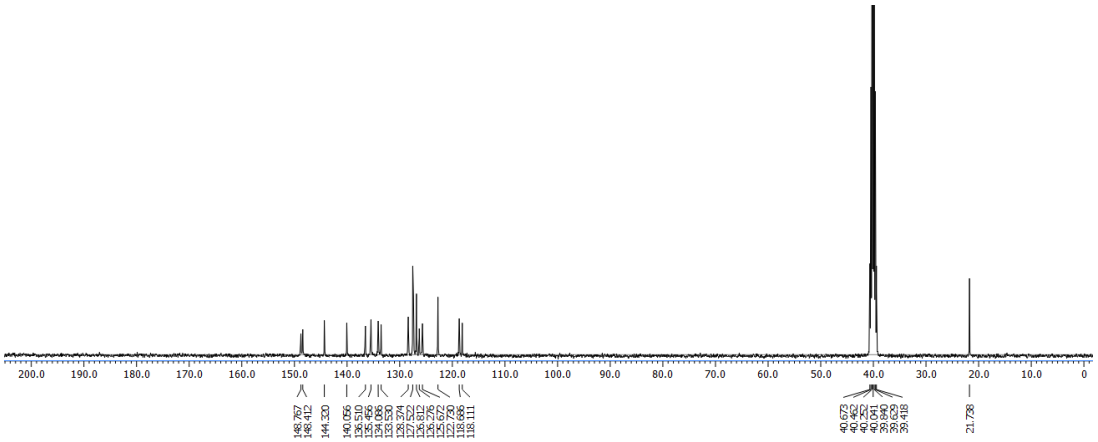
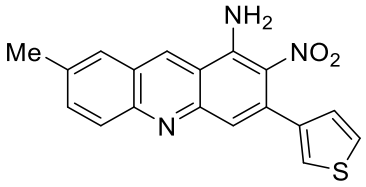


Figure 4.37

HRMS



7-Methyl-2-nitro-3-(thiophen-3-yl)acridin-1-amine (3e)

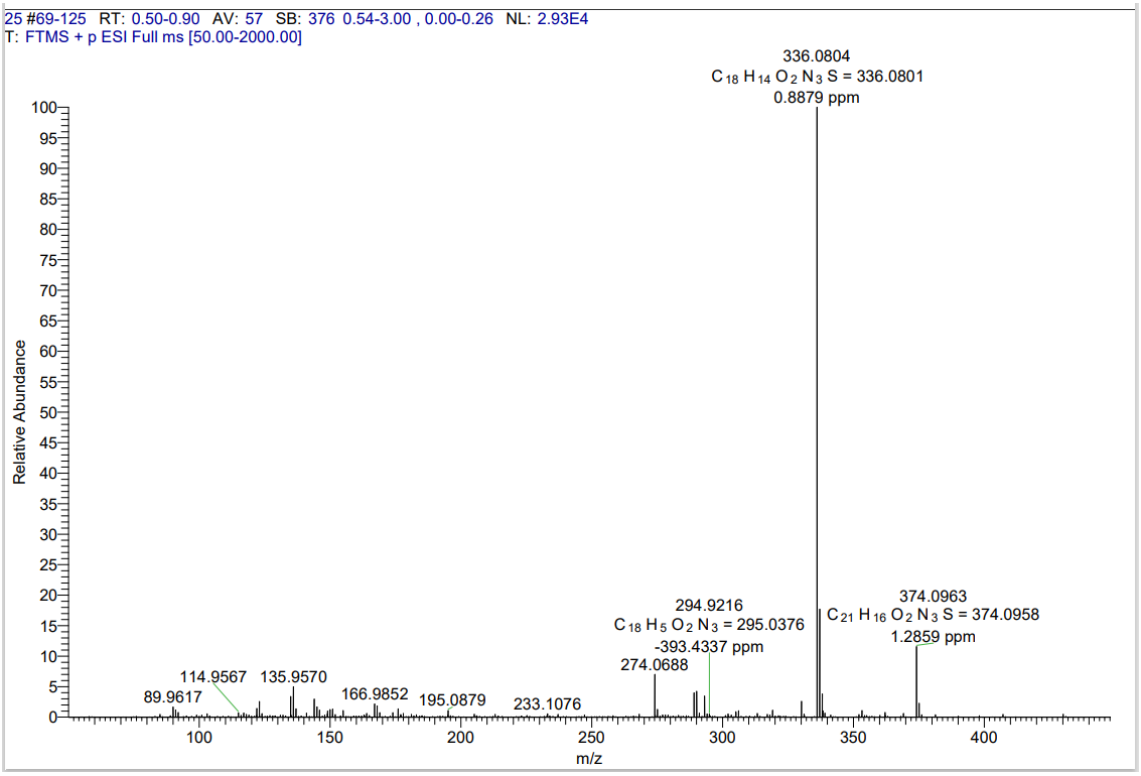
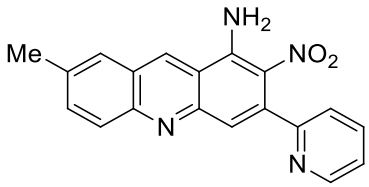
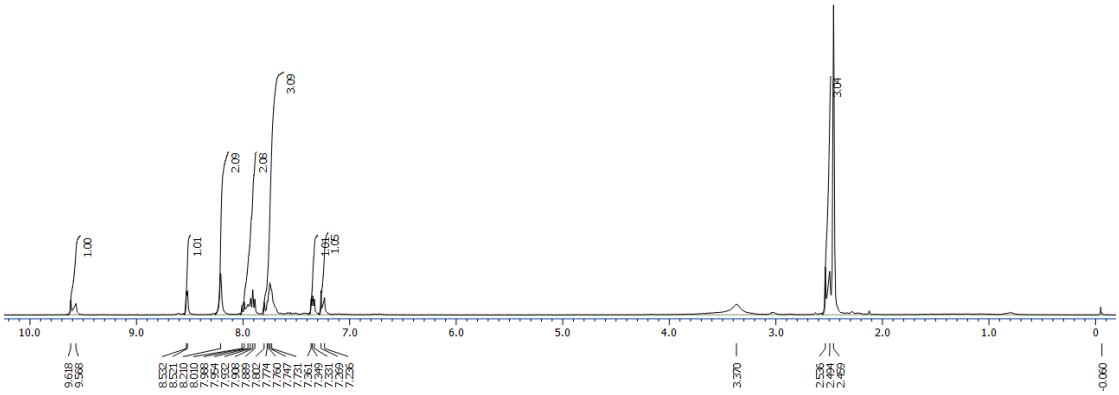


Figure 4.38

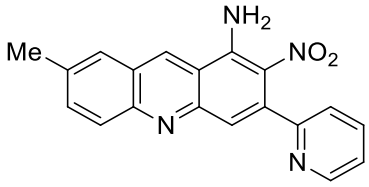
^{1}H NMR



7-Methyl-2-nitro-3-(pyridin-2-yl)acridin-1-amine (3f)



^{13}C NMR



7-Methyl-2-nitro-3-(pyridin-2-yl)acridin-1-amine (3f)

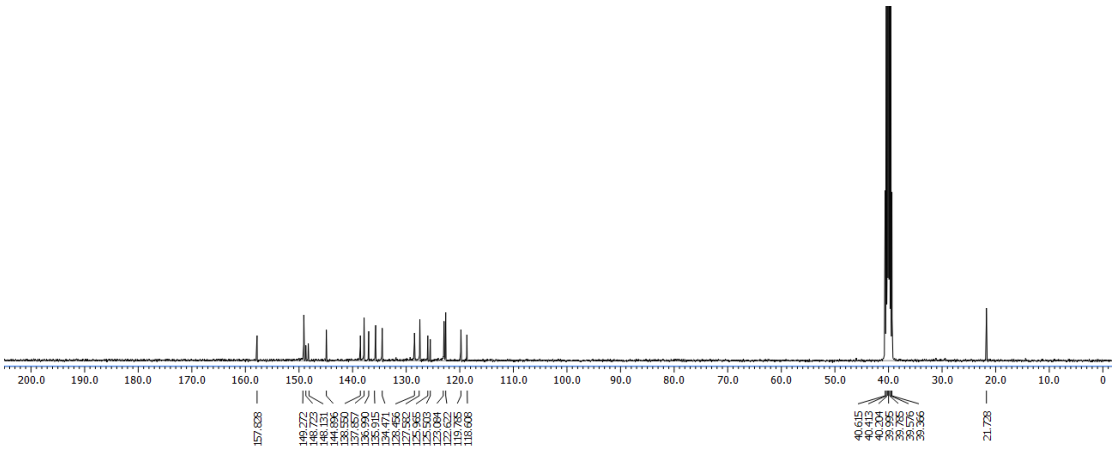
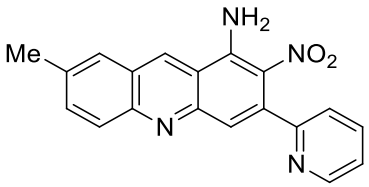


Figure 4.39

HRMS



7-Methyl-2-nitro-3-(pyridin-2-yl)acridin-1-amine (3f)

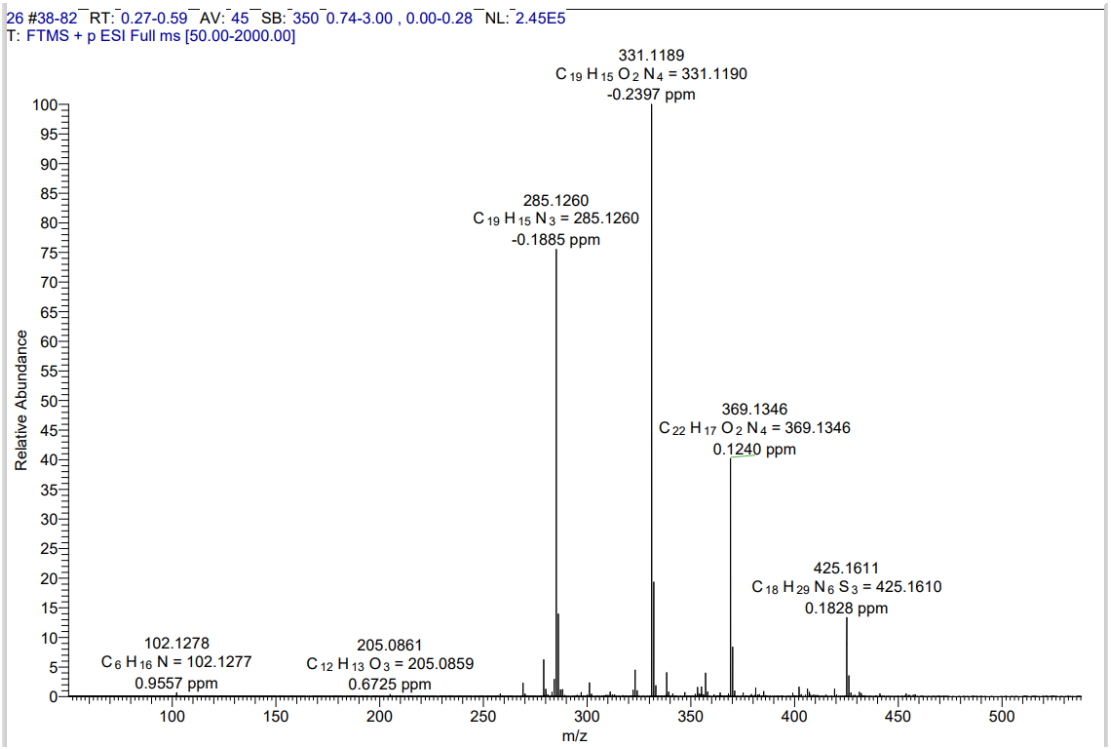
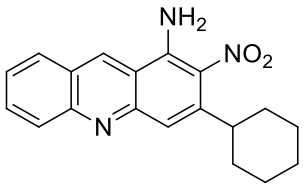
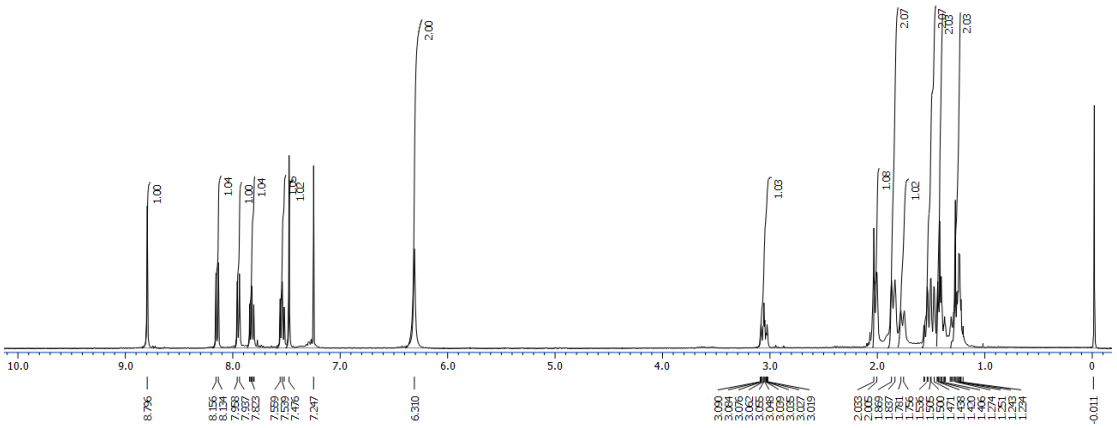


Figure 4.40

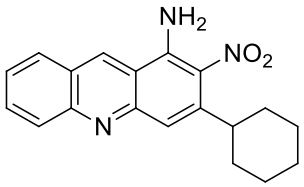
^{1}H NMR



3-Cyclohexyl-2-nitroacridin-1-amine (3g)



^{13}C NMR



3-Cyclohexyl-2-nitroacridin-1-amine (3g)

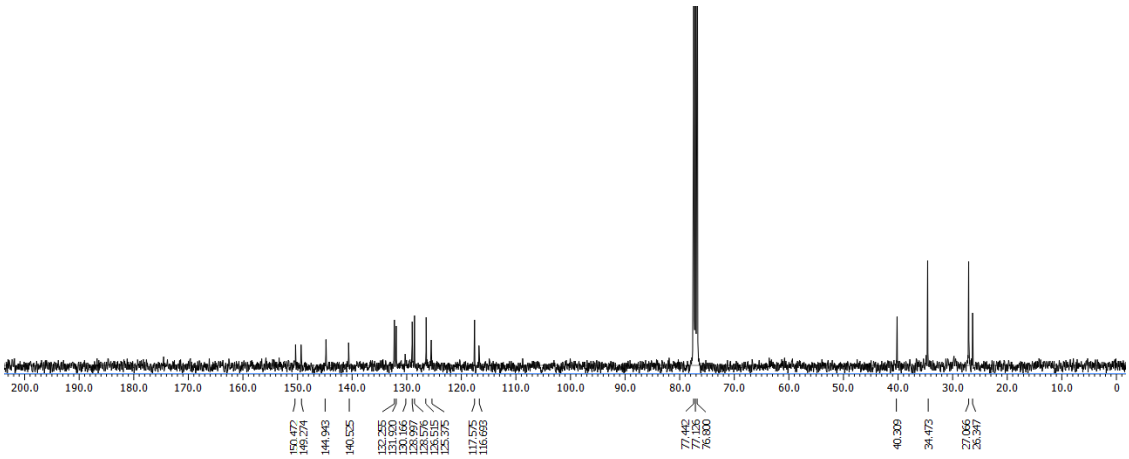
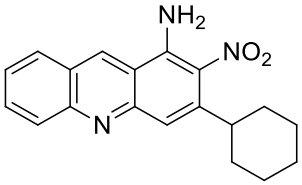


Figure 4.41

HRMS



3-Cyclohexyl-2-nitroacridin-1-amine (3g)

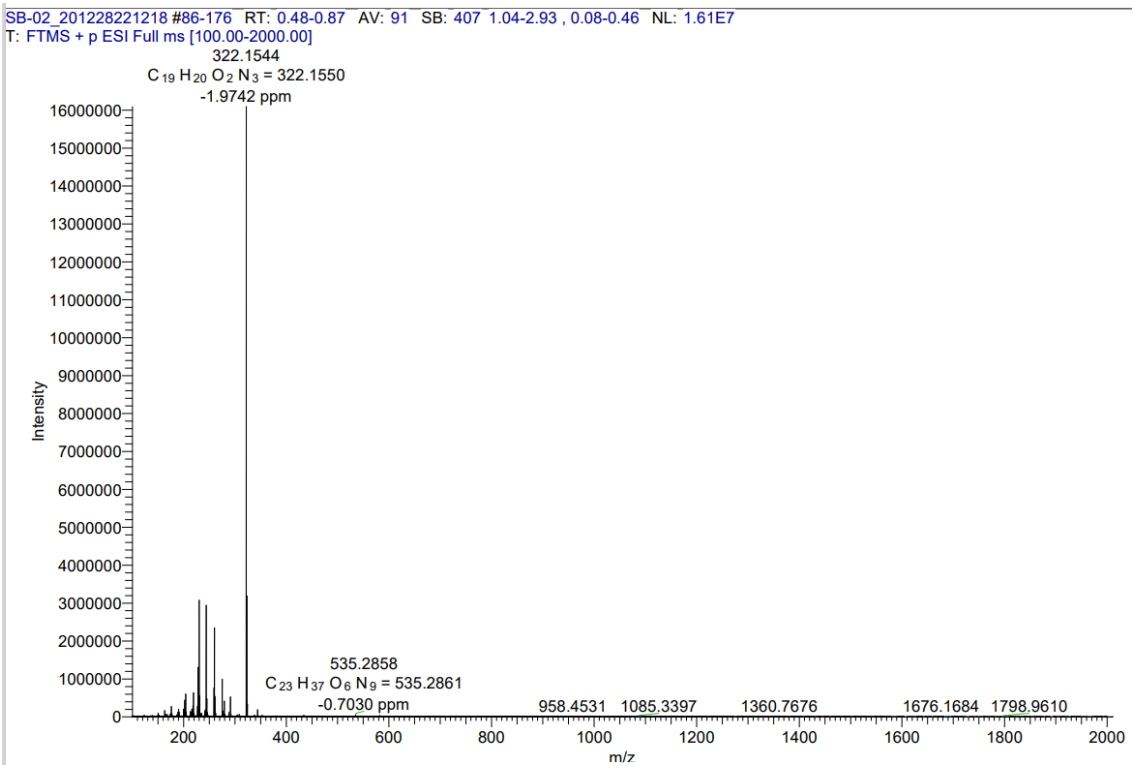
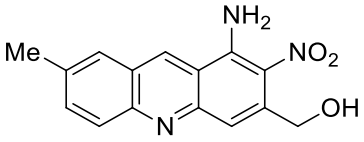
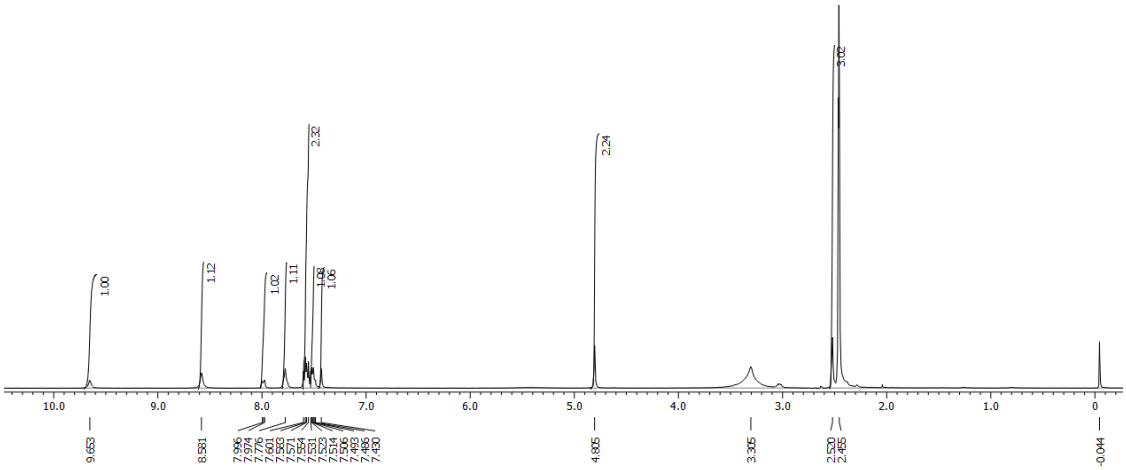


Figure 4.42

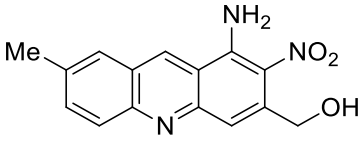
^{1}H NMR



(1-Amino-7-methyl-2-nitroacridin-3-yl)methanol(3h)



^{13}C NMR



(1-Amino-7-methyl-2-nitroacridin-3-yl)methanol(3h)

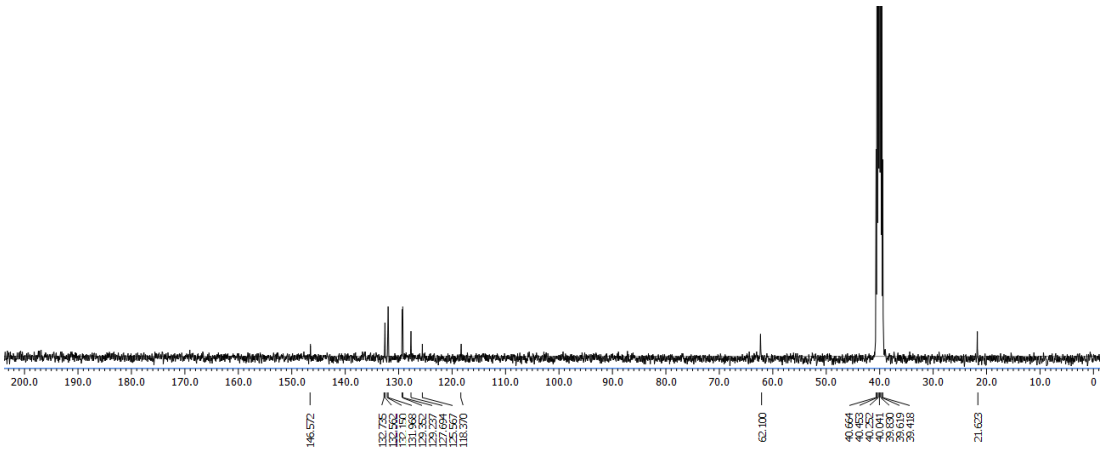
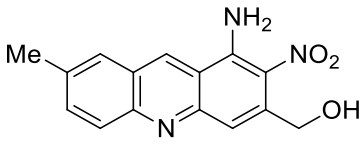


Figure 4.43

HRMS



(1-Amino-7-methyl-2-nitroacridin-3-yl)methanol(3h)

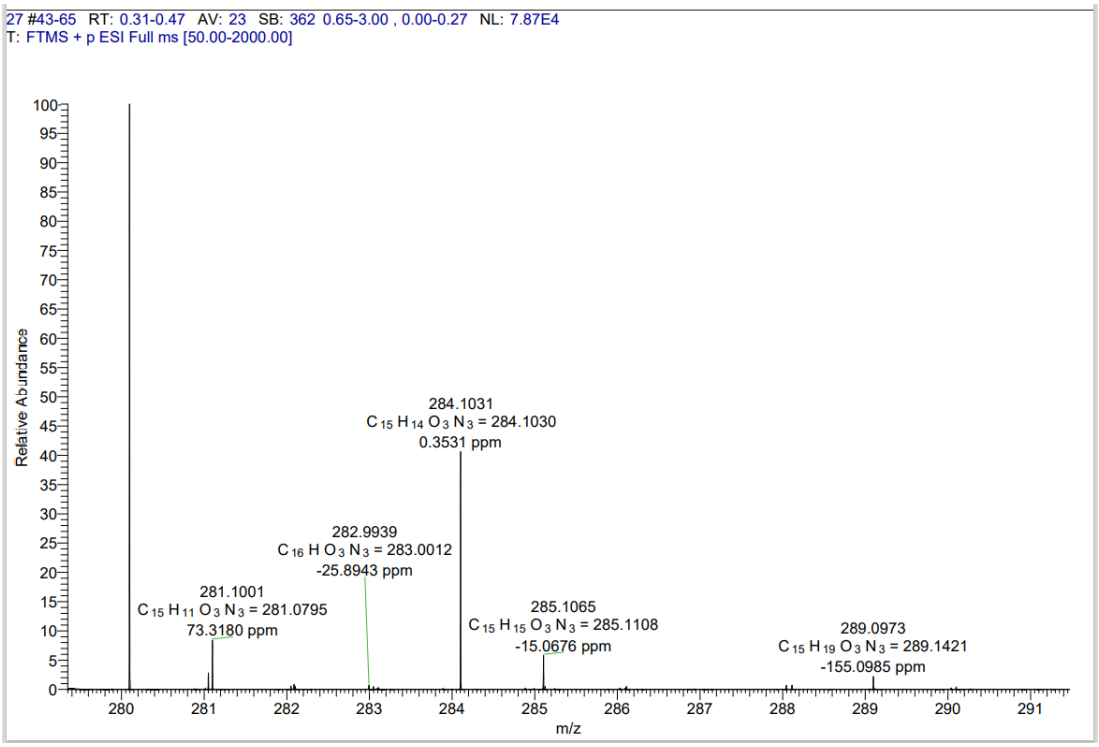
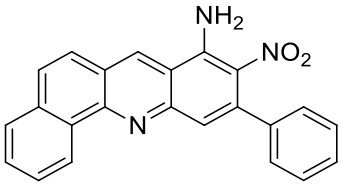
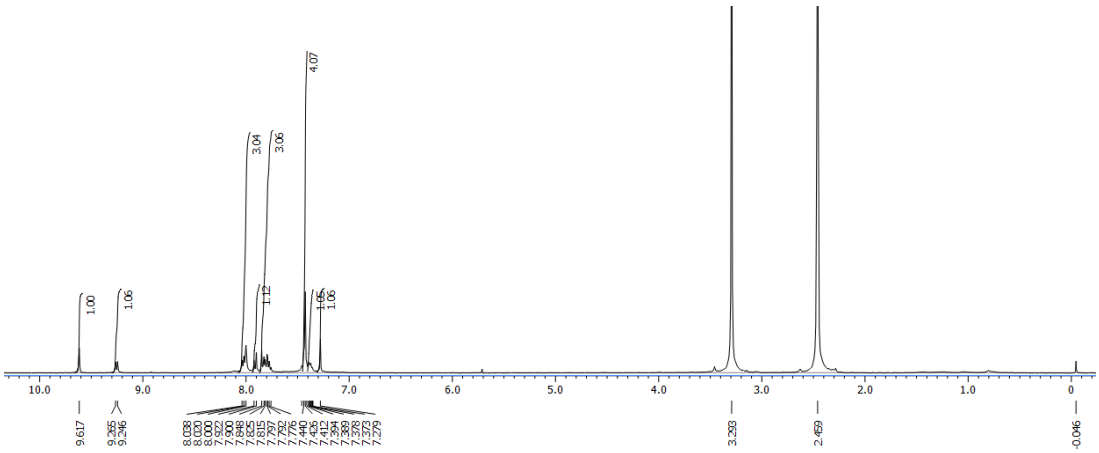


Figure 4.44

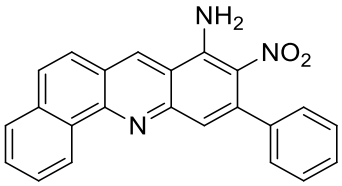
^{1}H NMR



9-Nitro-10-phenylbenzo[*c*]acridin-8-amine(5a)



^{13}C NMR



9-Nitro-10-phenylbenzo[*c*]acridin-8-amine(5a)

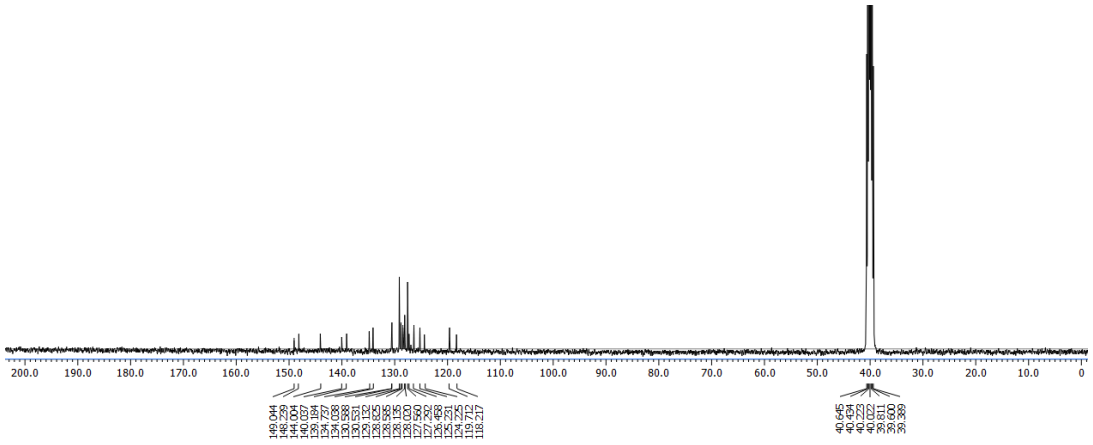
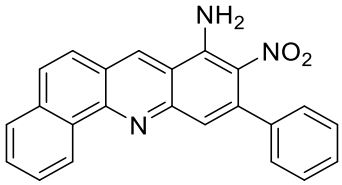


Figure 4.45

HRMS



9-Nitro-10-phenylbenzo[*c*]acridin-8-amine(5a)

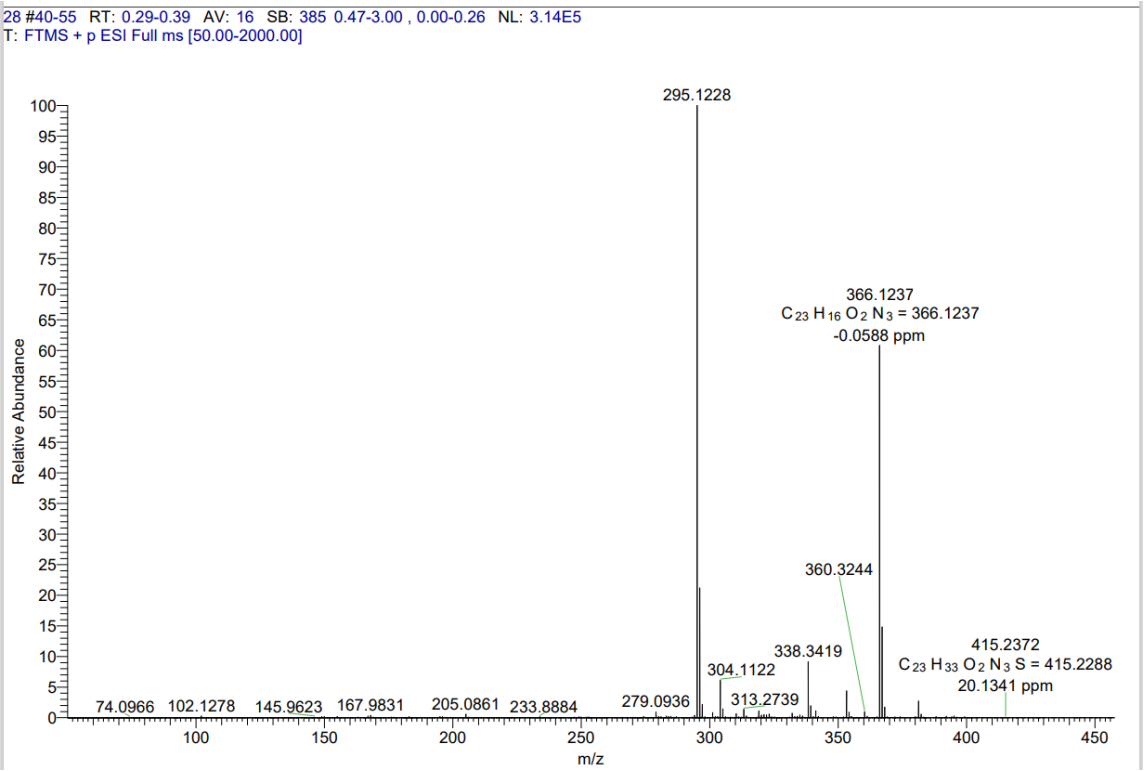
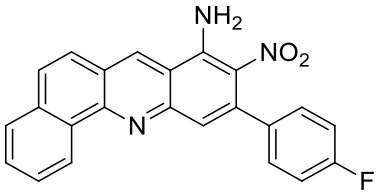
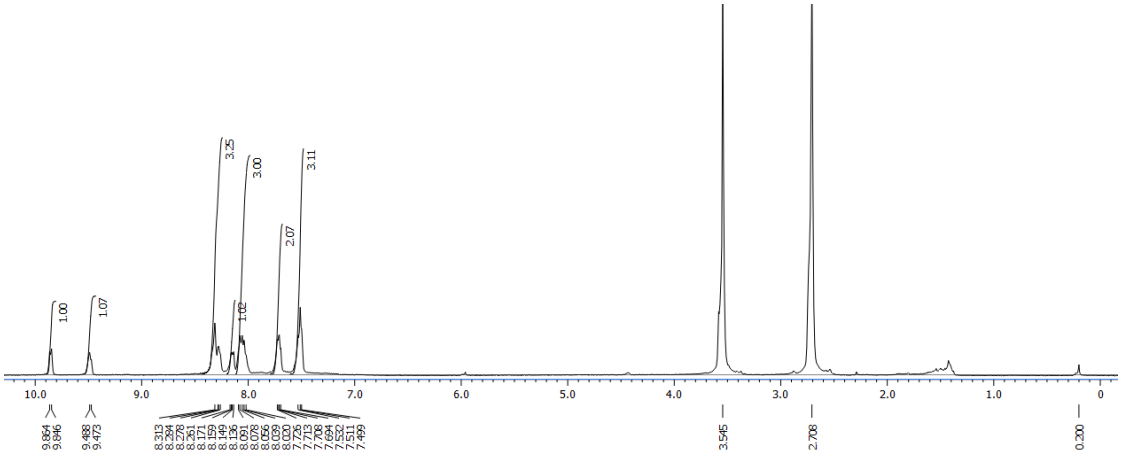


Figure 4.46

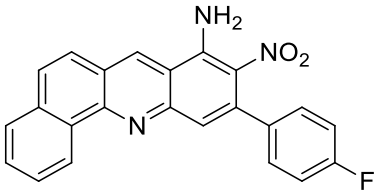
^{1}H NMR



10-(4-Fluorophenyl)-9-nitrobenzo[*c*]acridin-8-amine (5b)



^{13}C NMR



10-(4-Fluorophenyl)-9-nitrobenzo[*c*]acridin-8-amine (5b)

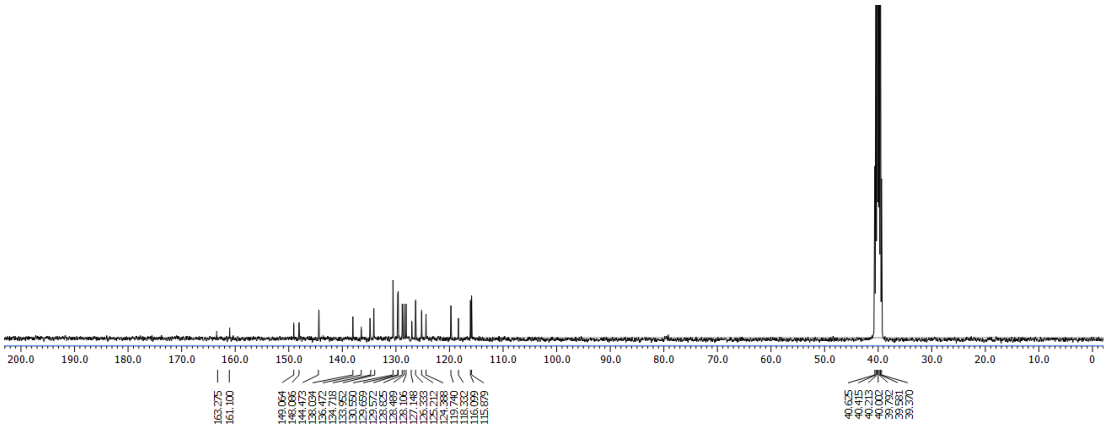
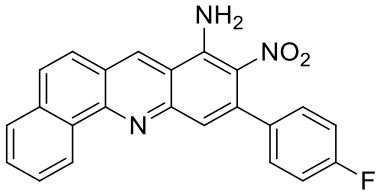


Figure 4.47

HRMS



10-(4-Fluorophenyl)-9-nitrobenzo[*c*]acridin-8-amine (5b)

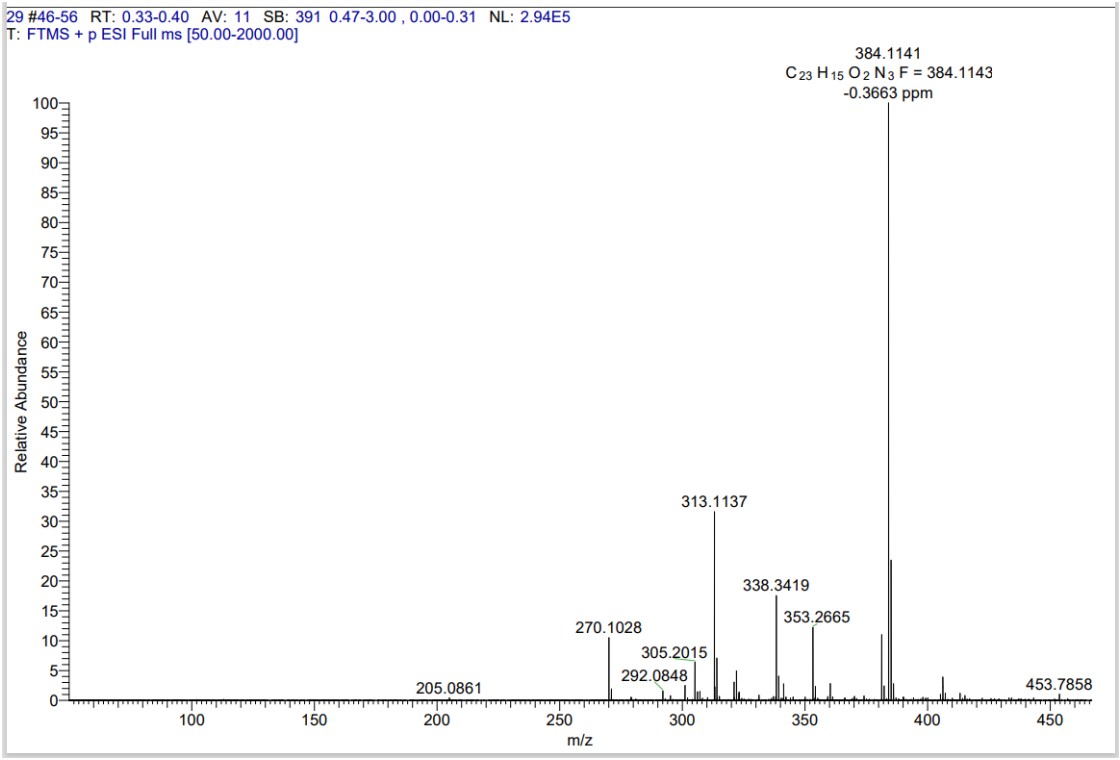
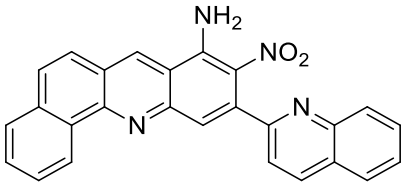
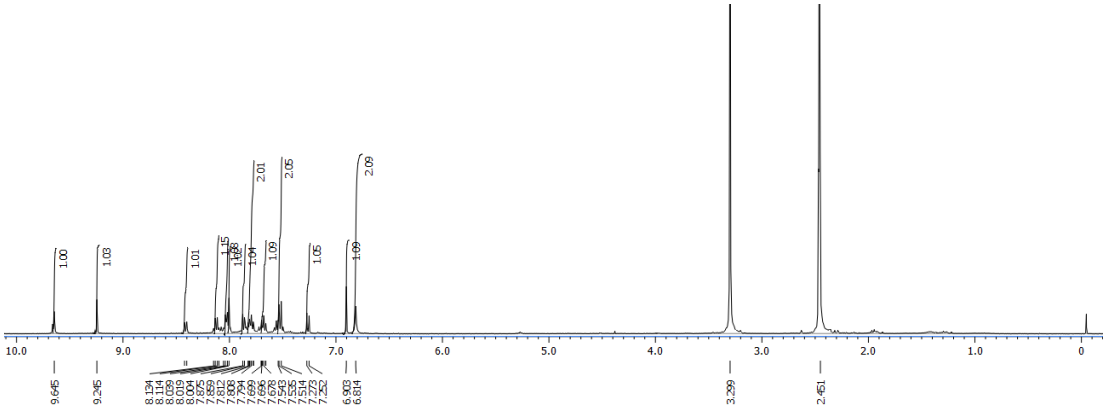


Figure 4.48

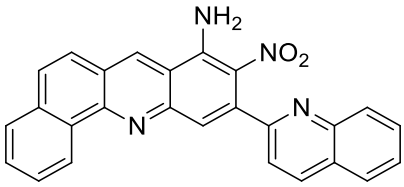
^{1}H NMR



9-Nitro-10-(quinolin-2-yl)benzo[*c*]acridin-8-amine (5c)



^{13}C NMR



9-Nitro-10-(quinolin-2-yl)benzo[*c*]acridin-8-amine (5c)

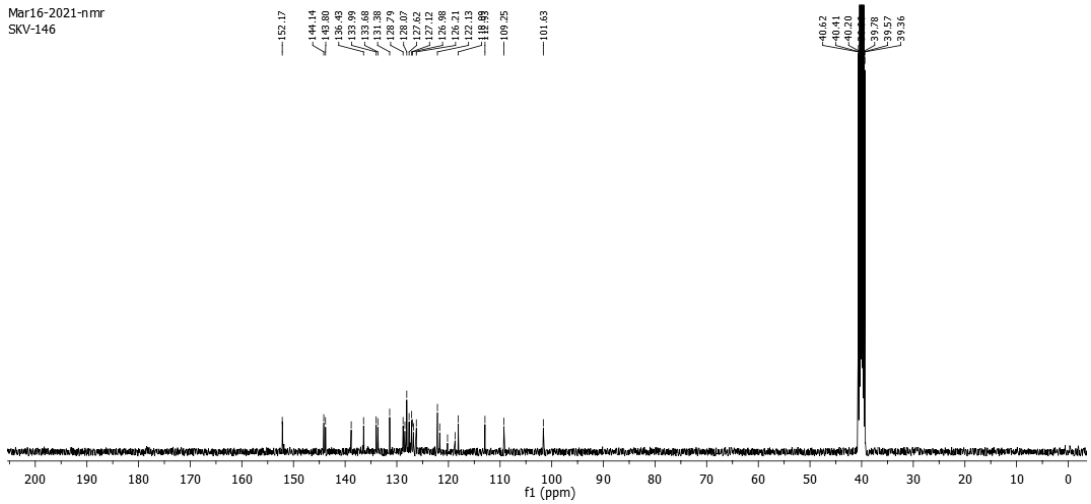
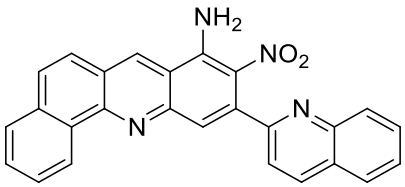


Figure 4.49

HRMS



9-Nitro-10-(quinolin-2-yl)benzo[*c*]acridin-8-amine (5c)

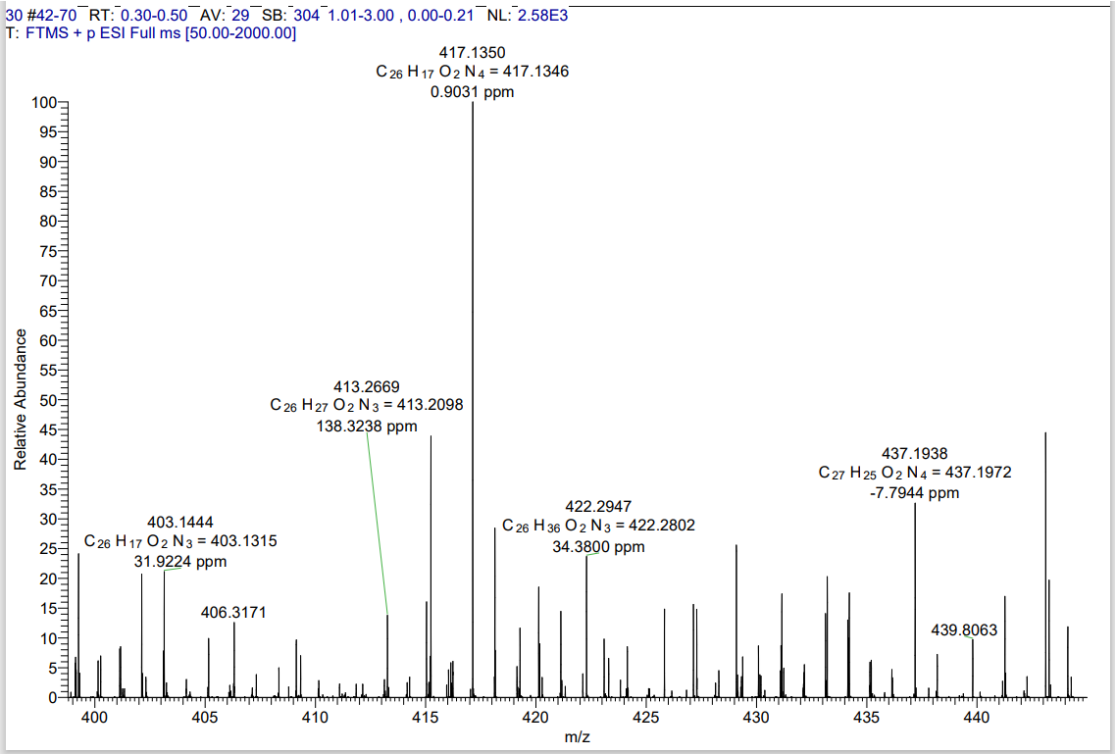
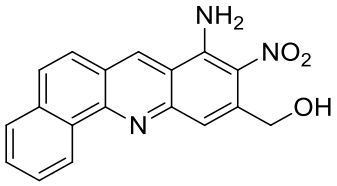
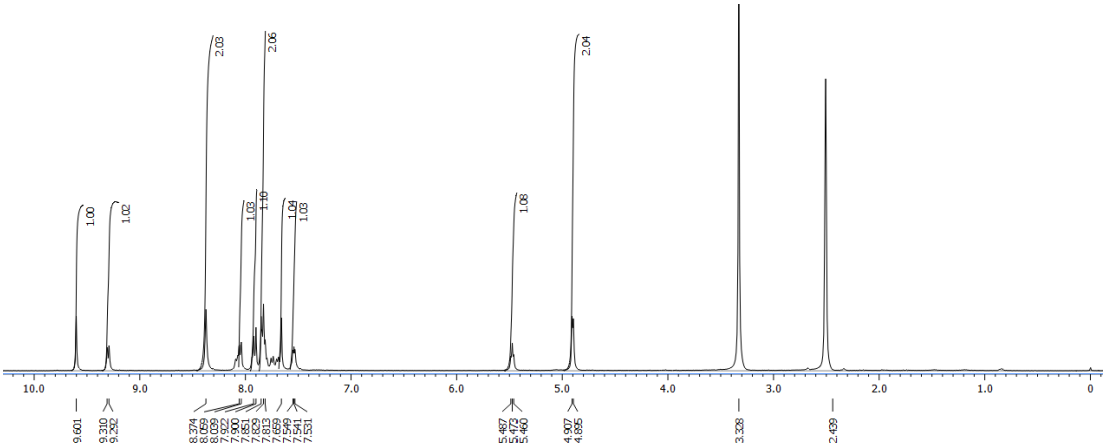


Figure 4.50

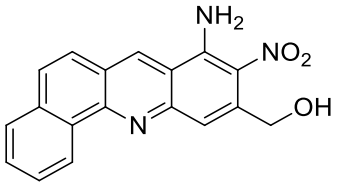
^{1}H NMR



(8-Amino-9-nitrobenzo[*c*]acridin-10-yl)methanol(5d)



^{13}C NMR



(8-Amino-9-nitrobenzo[*c*]acridin-10-yl)methanol(5d)

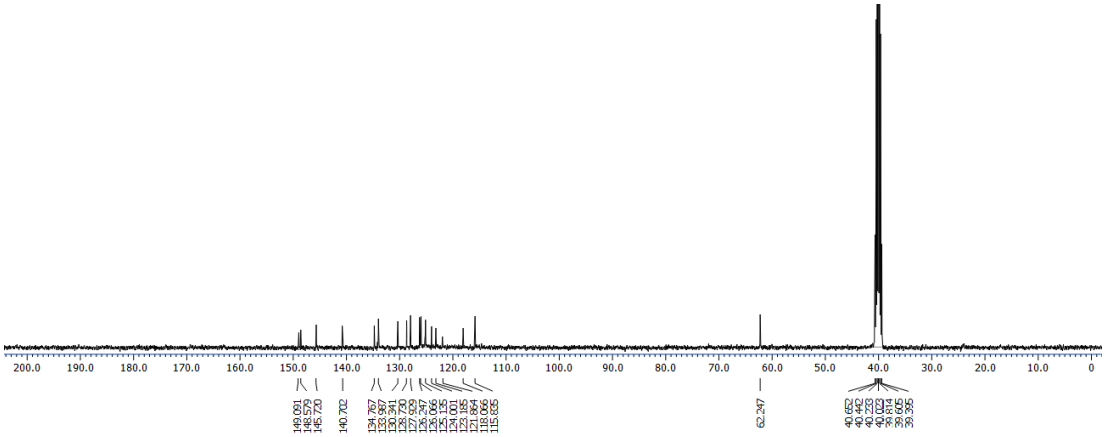
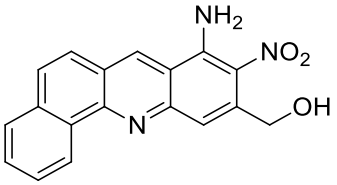


Figure 4.51

HRMS



(8-Amino-9-nitrobenzo[*c*]acridin-10-yl)methanol(5d)

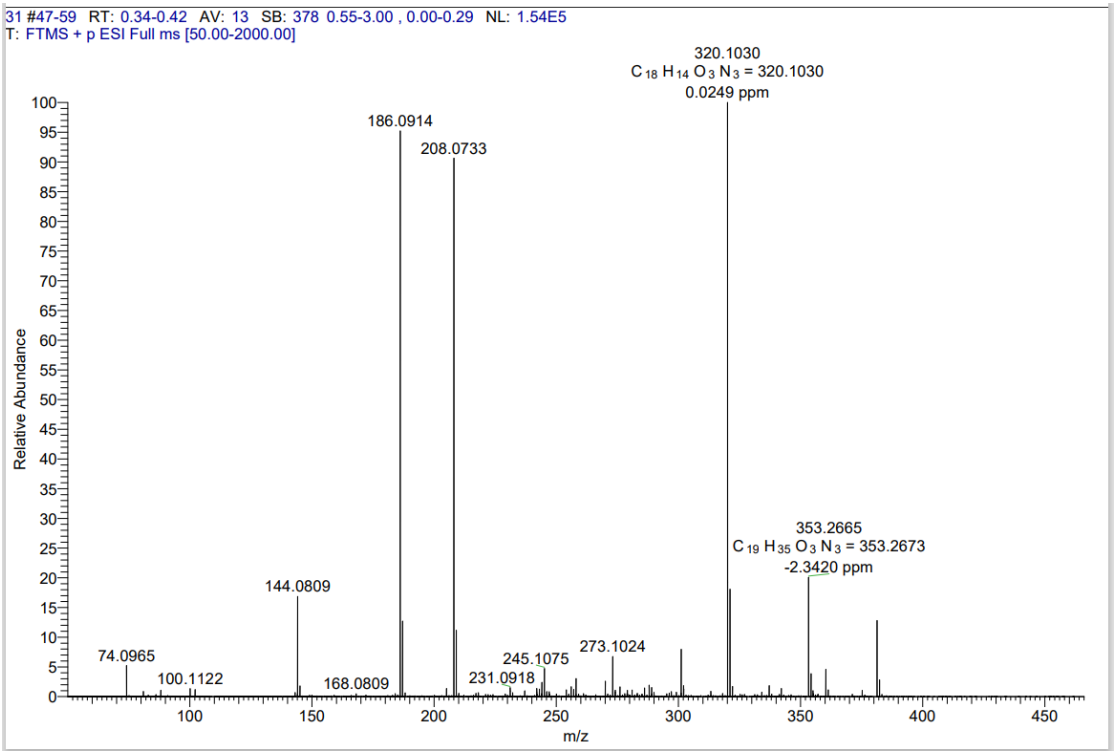
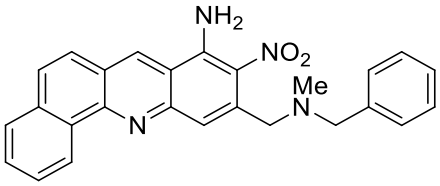
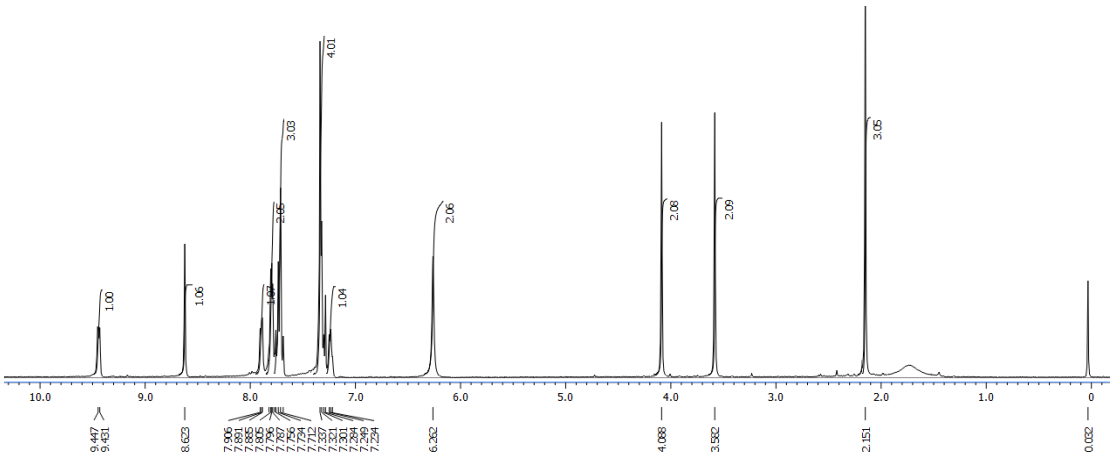


Figure 4.52

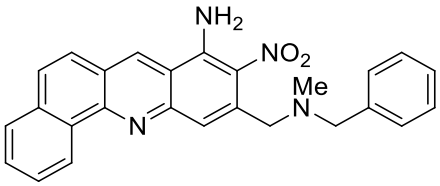
^{1}H NMR



10-((Benzyl(methyl)amino)methyl)-9-nitrobenzo[*c*]acridin-8-amine (5e)



^{13}C NMR



10-((Benzyl(methyl)amino)methyl)-9-nitrobenzo[*c*]acridin-8-amine (5e)

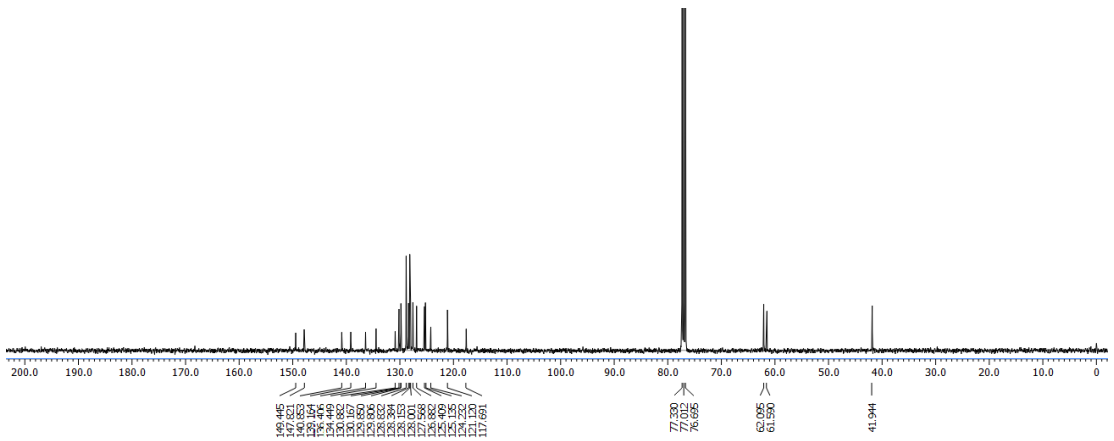
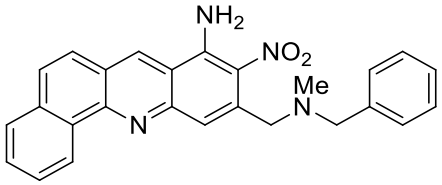


Figure 4.53

HRMS



10-((Benzyl(methyl)amino)methyl)-9-nitrobenzo[*c*]acridin-8-amine (5e)

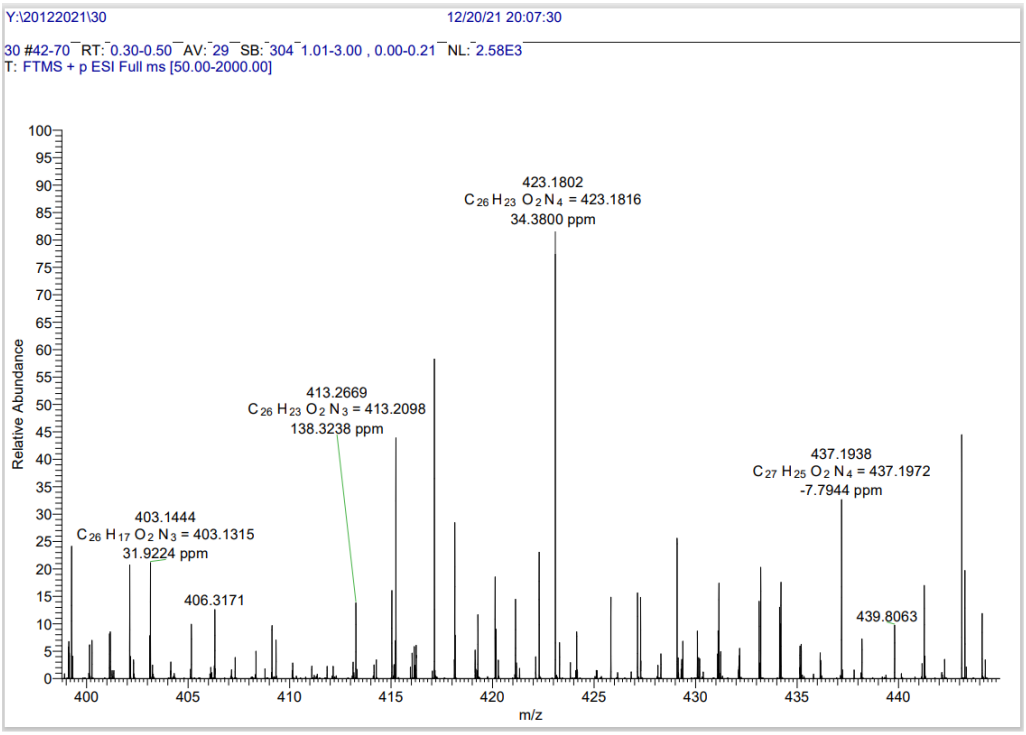
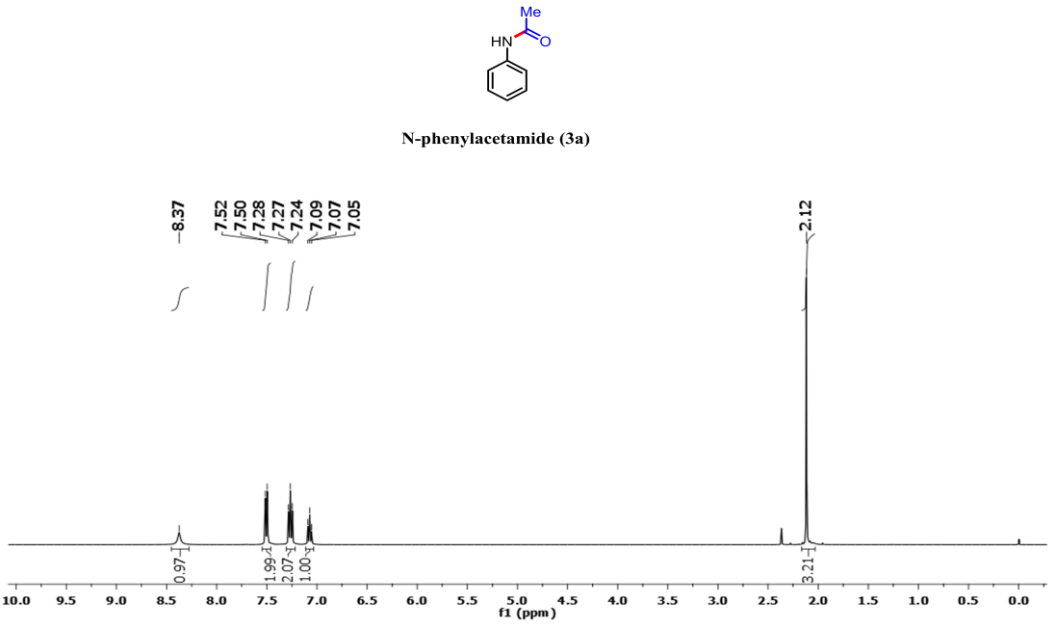


Figure 4.54

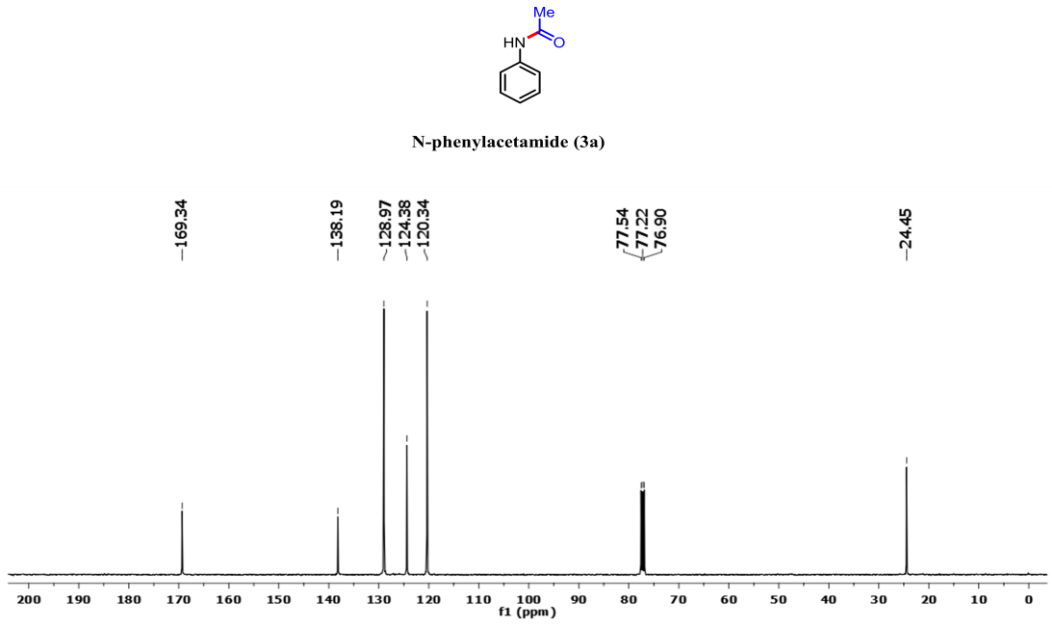
Appendix – C
^{1}H NMR, ^{13}C NMR Spectra of Chapter 5

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



N-phenylacetamide (3a)

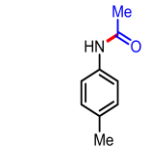
^{13}C NMR (100 MHz, $CDCl_3$)



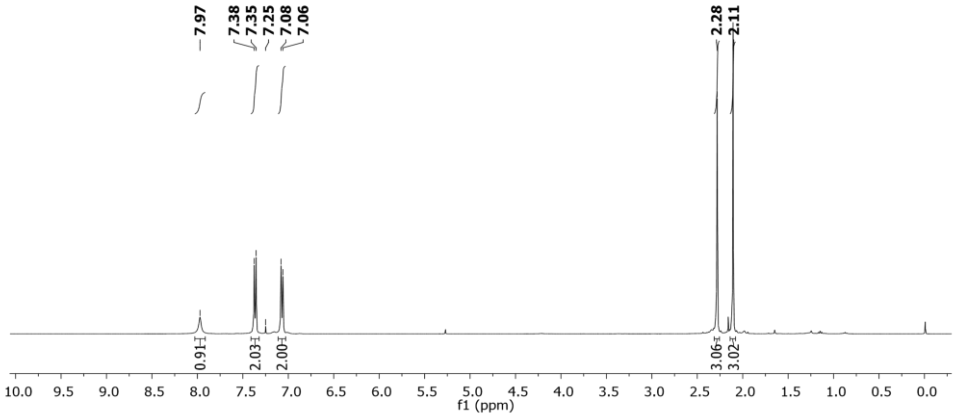
N-phenylacetamide (3a)

Figure 5.3

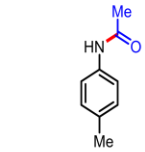
^{1}H NMR (400 MHz, $CDCl_3$)



N-(p-tolyl)acetamide (3b)



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



N-(p-tolyl)acetamide (3b)

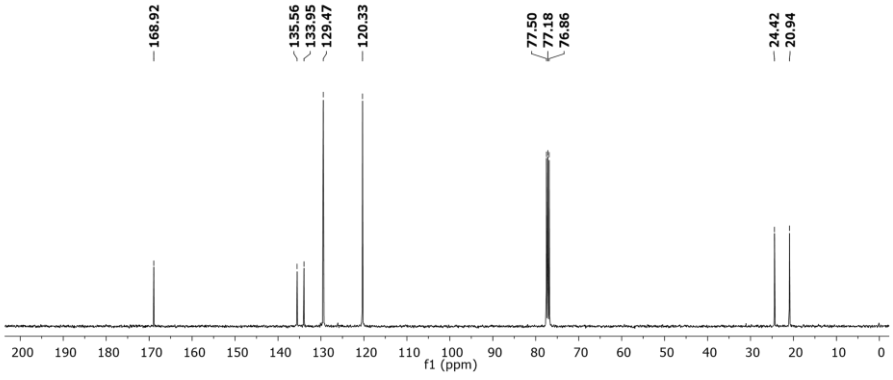
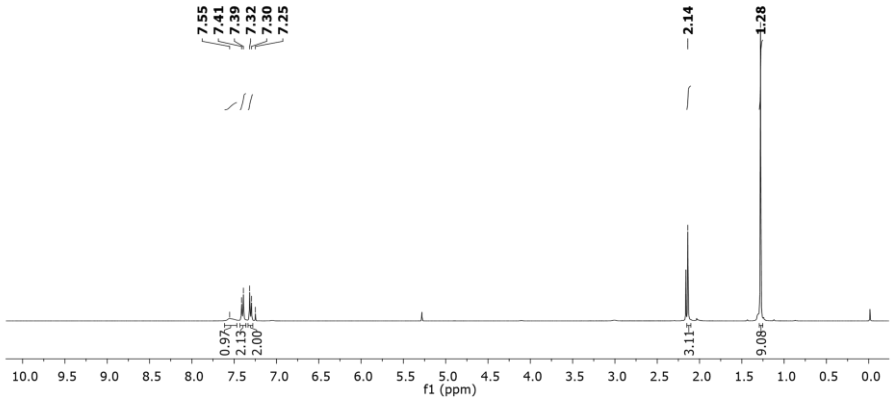


Figure 5.4

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

N-(4-(tert-butyl)phenyl)acetamide (3c)



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

N-(4-(tert-butyl)phenyl)acetamide (3c)

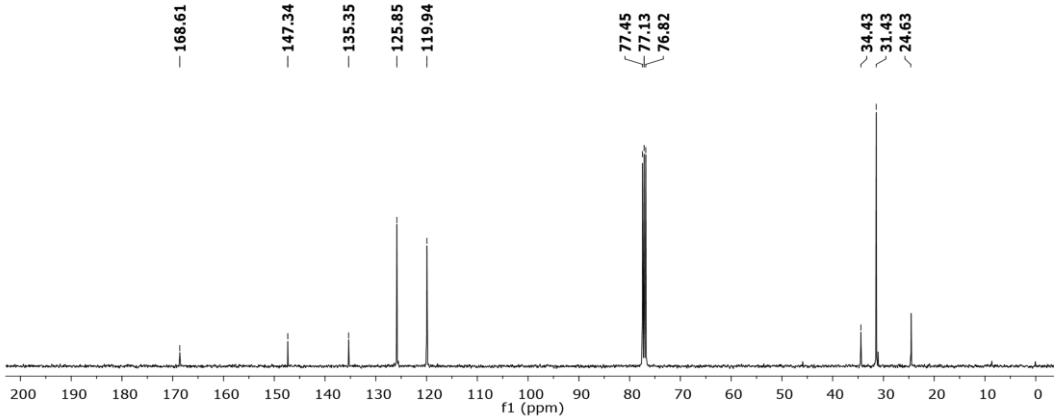
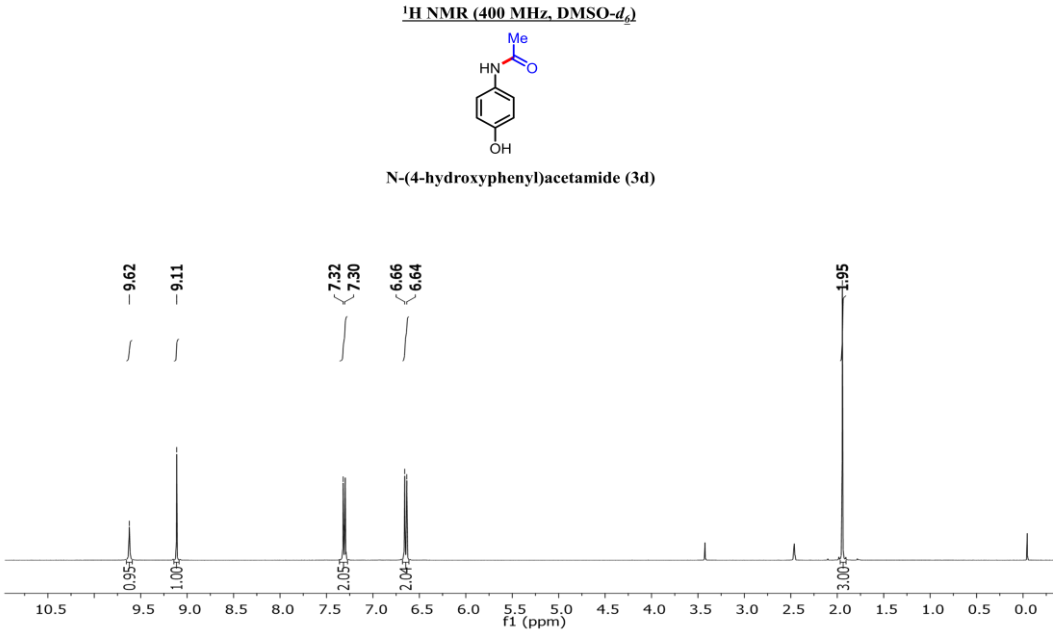


Figure 5.5


^{1}H NMR (400 MHz, DMSO-d_6)
Me
HN
O
OH
N-(4-hydroxyphenyl)acetamide (3d)
9.62
9.11
7.32
7.30
6.66
6.64
1.95
0.95
1.00
2.05
2.04
3.00
f1 (ppm)

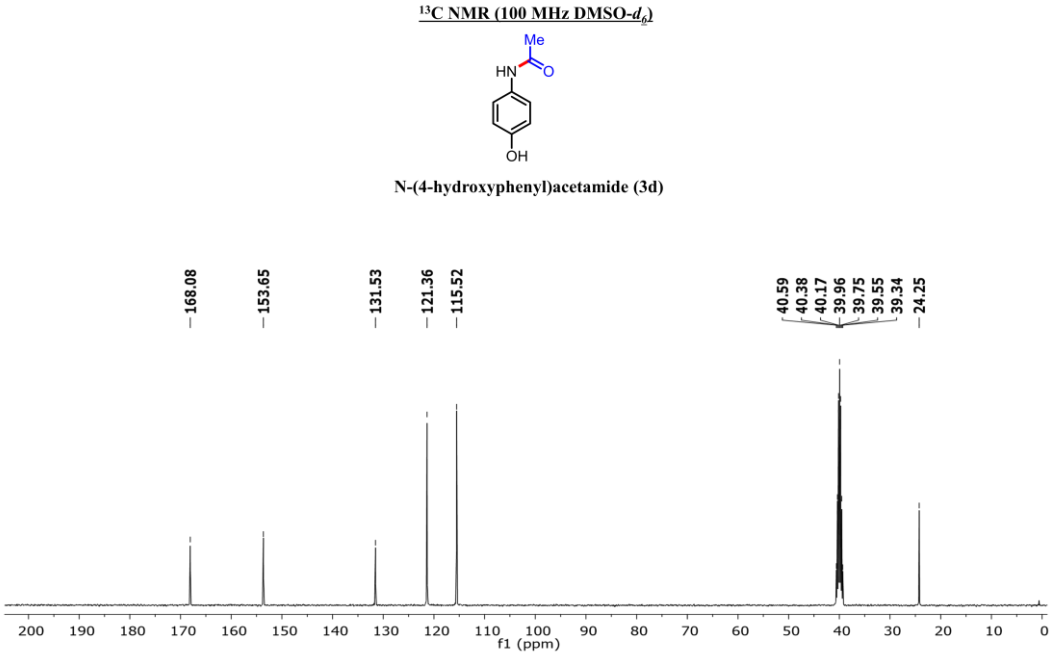

^{13}C NMR (100 MHz DMSO-d_6)
Me
HN
O
OH
N-(4-hydroxyphenyl)acetamide (3d)
168.08
153.65
131.53
121.36
115.52
40.59
40.38
40.17
39.96
39.75
39.55
39.34
24.25
f1 (ppm)

Figure 5.6

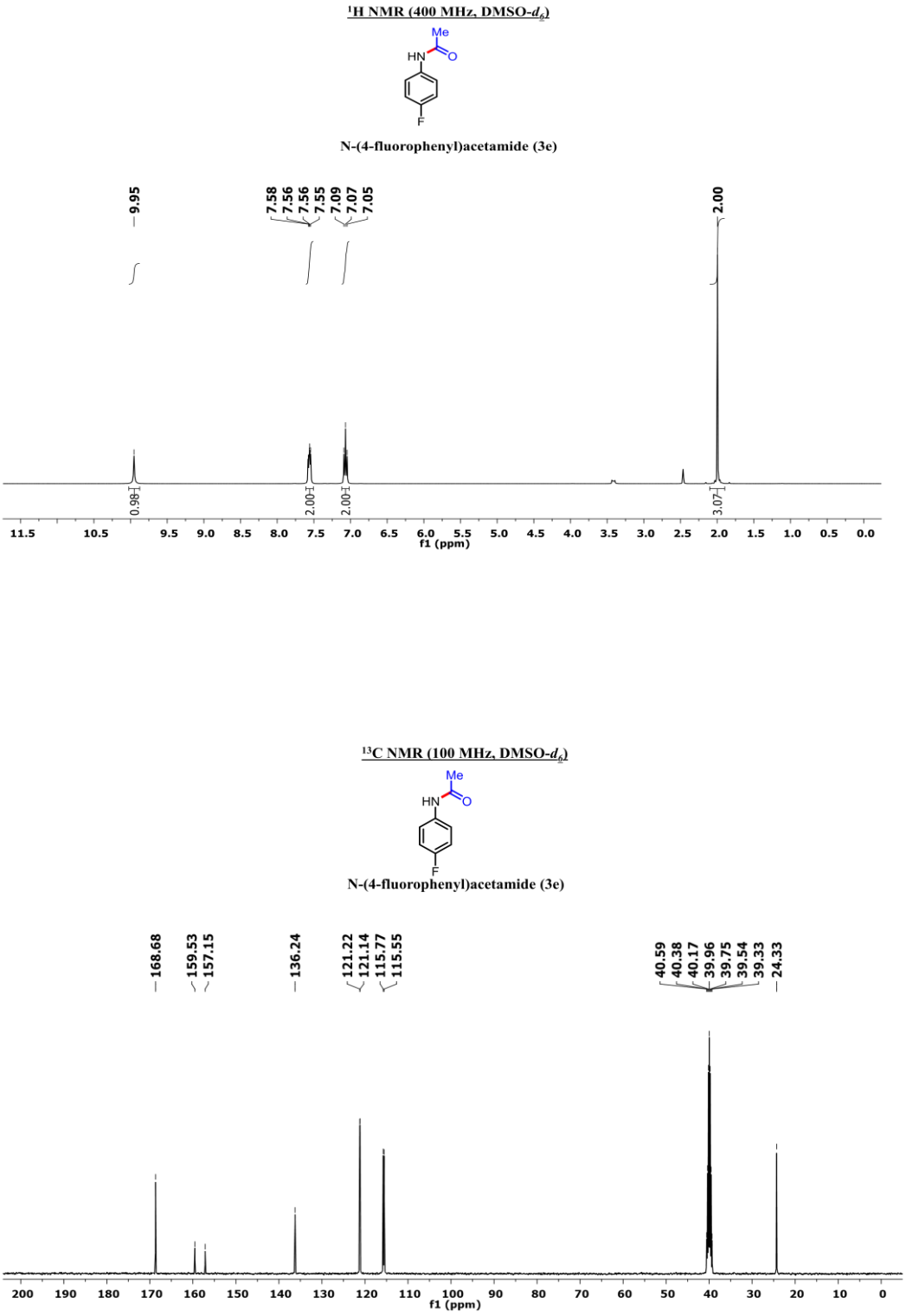
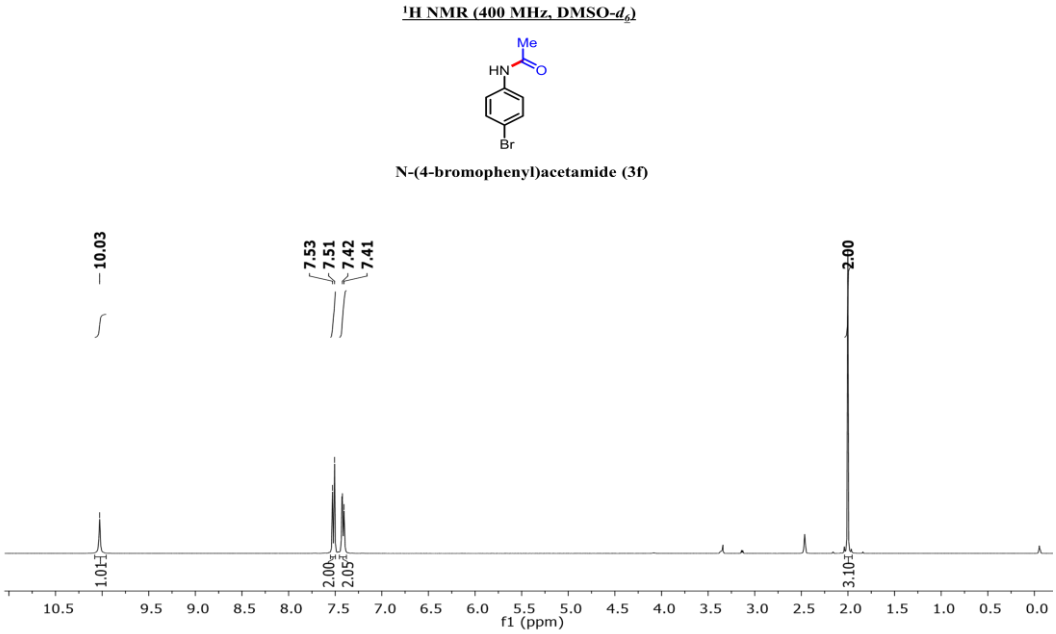

^{1}H NMR (400 MHz, DMSO-d_6)
Me
HN
O
F
N-(4-fluorophenyl)acetamide (3e)
9.95
7.58
7.56
7.56
7.55
7.09
7.07
7.05
2.00
0.98
2.00
2.00
3.07
f1 (ppm)
^{13}C NMR (100 MHz, DMSO-d_6)
N-(4-fluorophenyl)acetamide (3e)
168.68
159.53
157.15
136.24
121.22
121.14
115.77
115.55
40.59
40.38
40.17
39.96
39.75
39.54
39.33
24.33
f1 (ppm)

Figure 5.7


¹H NMR (400 MHz, DMSO-d_6)
Me
HN
O
Br
N-(4-bromophenyl)acetamide (3f)
10.03
7.53
7.51
7.42
7.41
2.00
1.01
2.00
2.05
3.10
10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

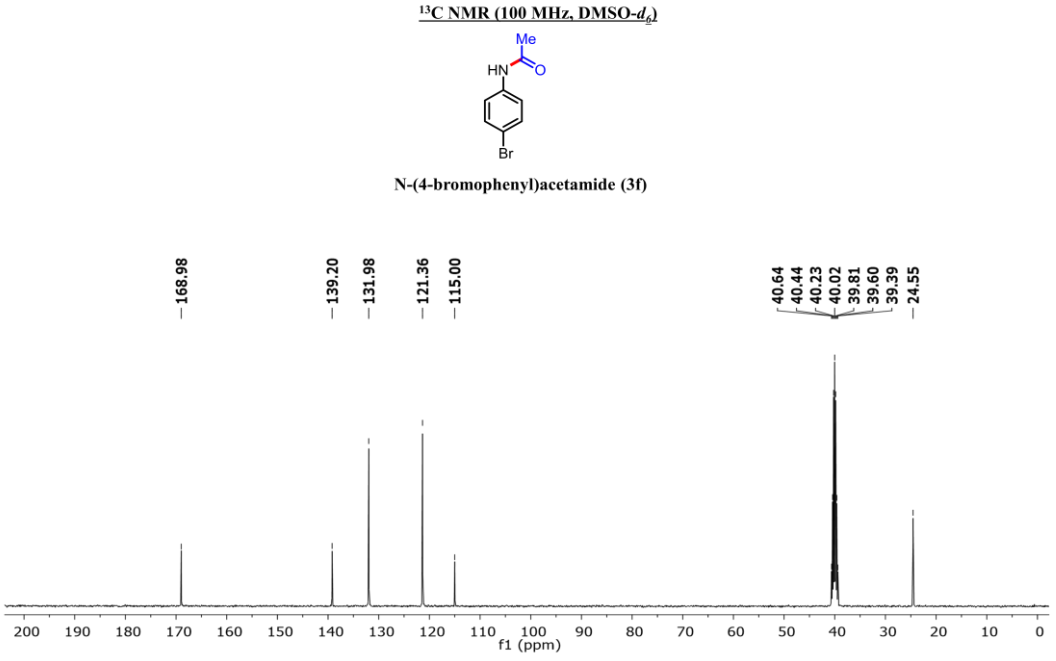
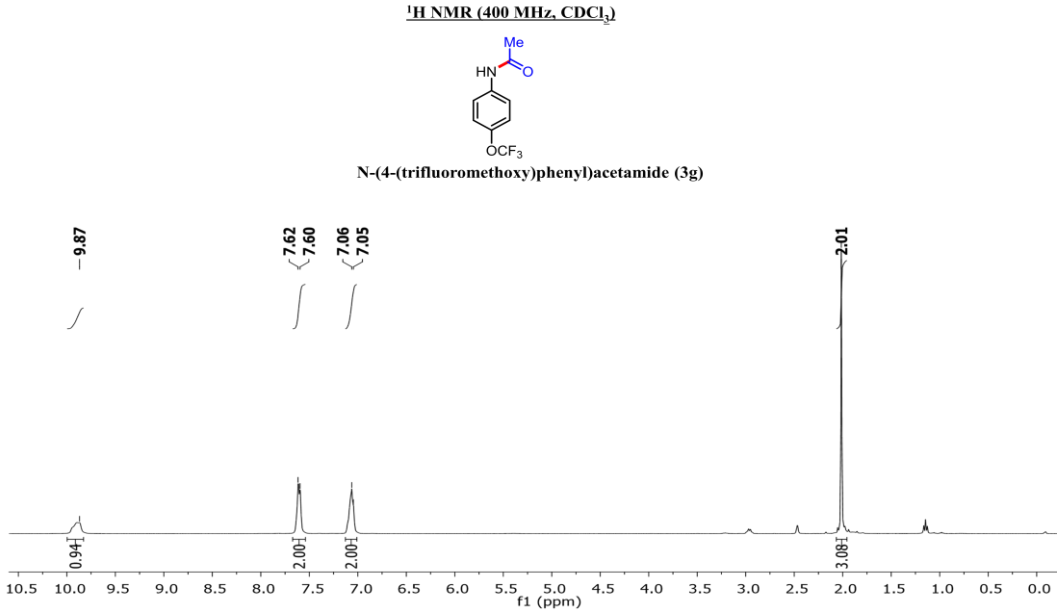

¹³C NMR (100 MHz, DMSO-d_6)
Me
HN
O
Br
N-(4-bromophenyl)acetamide (3f)
168.98
139.20
131.98
121.36
115.00
40.64
40.44
40.23
40.02
39.81
39.60
39.39
24.55
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Figure 5.8


^{1}H NMR (400 MHz, CDCl$_3$)
Me
HN
O
OCF$_3$
N-(4-(trifluoromethoxy)phenyl)acetamide (3g)
9.87
7.62
7.60
7.06
7.05
2.01
0.94
2.00
2.00
3.08
f1 (ppm)

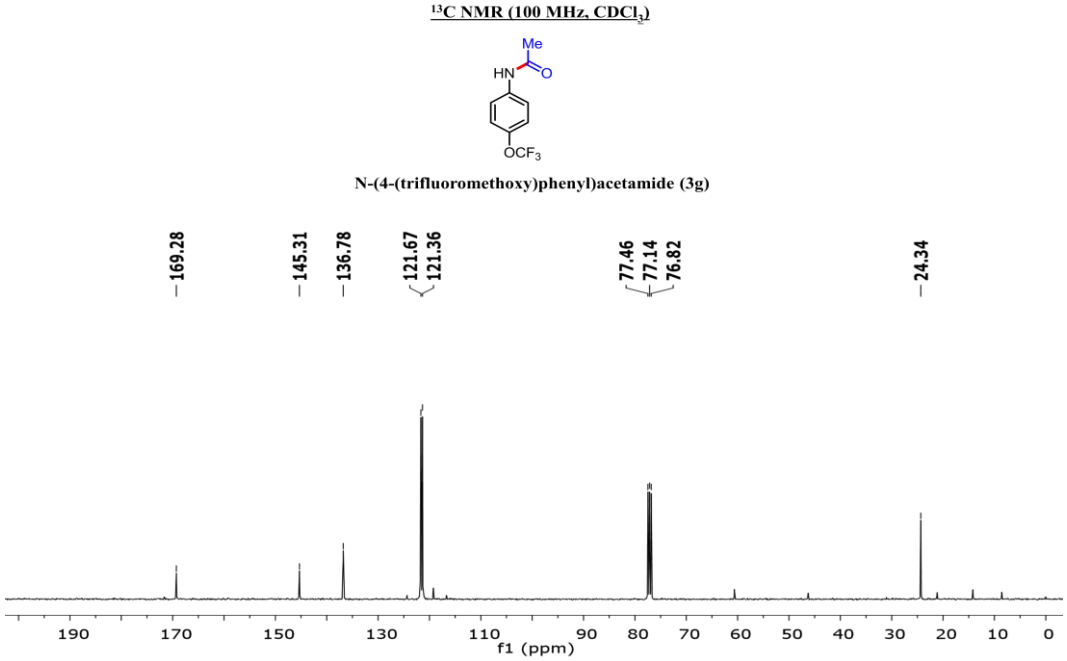
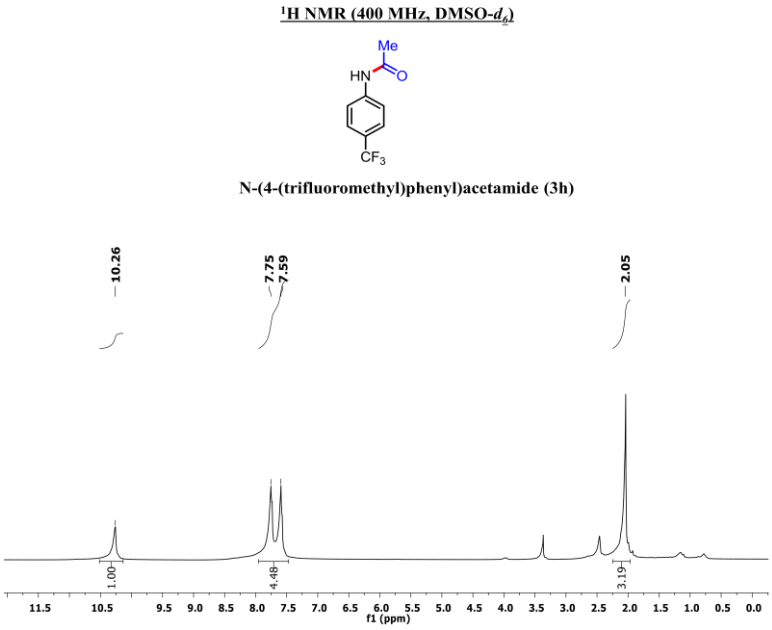

^{13}C NMR (100 MHz, CDCl$_3$)
Me
HN
O
OCF$_3$
N-(4-(trifluoromethoxy)phenyl)acetamide (3g)
169.28
145.31
136.78
121.67
121.36
77.46
77.14
76.82
24.34
f1 (ppm)

Figure 5.9


^{1}H NMR (400 MHz, DMSO-d_6)
Me
HN
O
CF3
N-(4-(trifluoromethyl)phenyl)acetamide (3h)
10.26
7.75
7.59
2.05
1.00
4.48
3.19
11.5 10.5 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

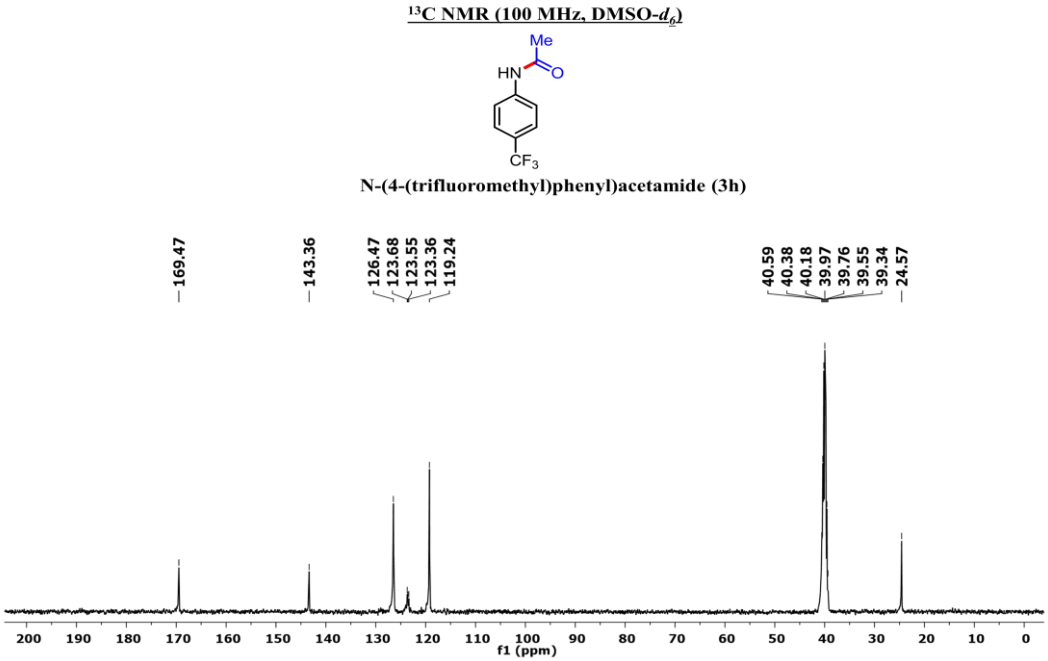
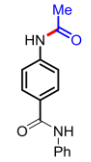
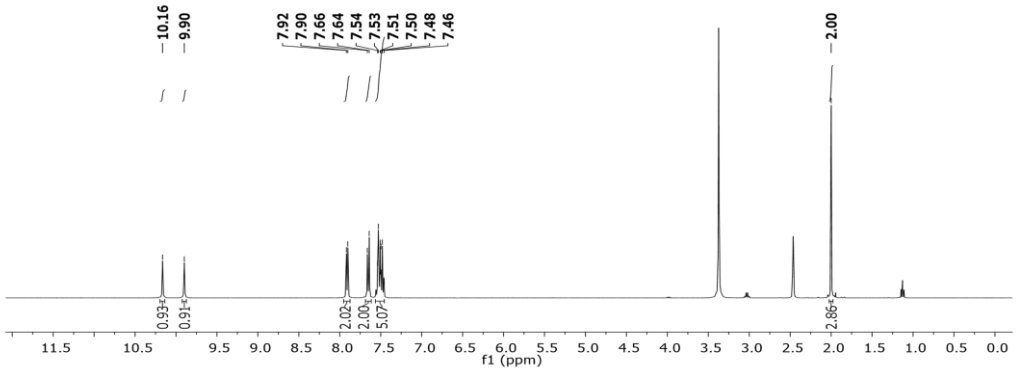

^{13}C NMR (100 MHz, DMSO-d_6)
Me
HN
O
CF3
N-(4-(trifluoromethyl)phenyl)acetamide (3h)
169.47
143.36
126.47
123.68
123.55
123.36
119.24
40.59
40.38
40.18
39.97
39.76
39.55
39.34
24.57
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Figure 5.10

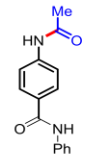
^{1}H NMR (400 MHz, DMSO-d_6)



4-acetamido-N-phenylbenzamide (3i)



^{13}C NMR (100 MHz, DMSO-d_6)



4-acetamido-N-phenylbenzamide (3i)

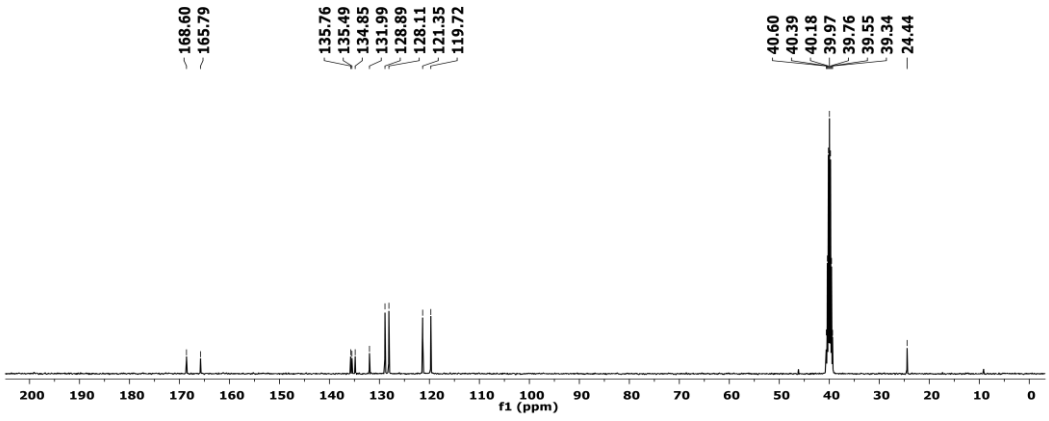


Figure 5.11

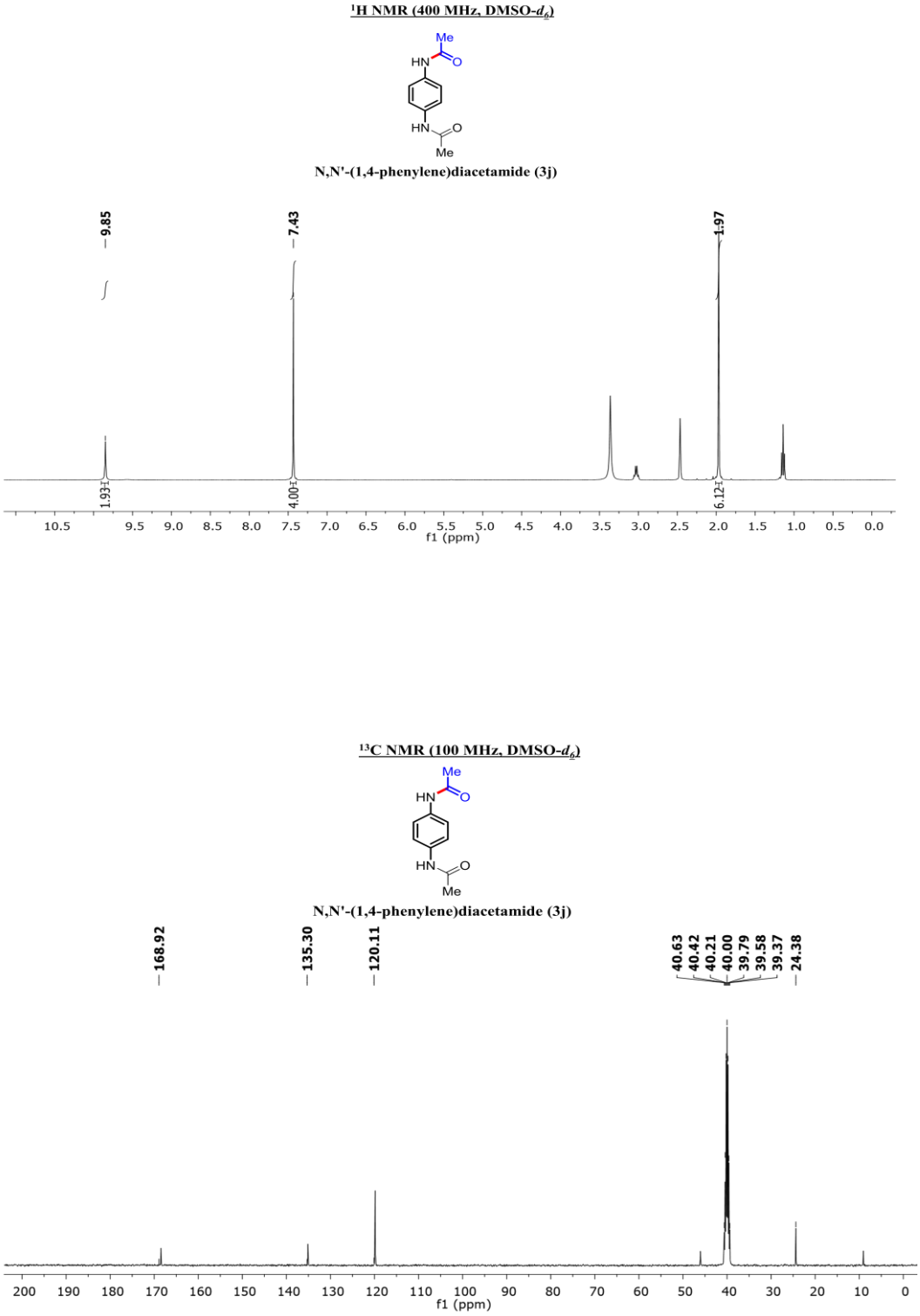
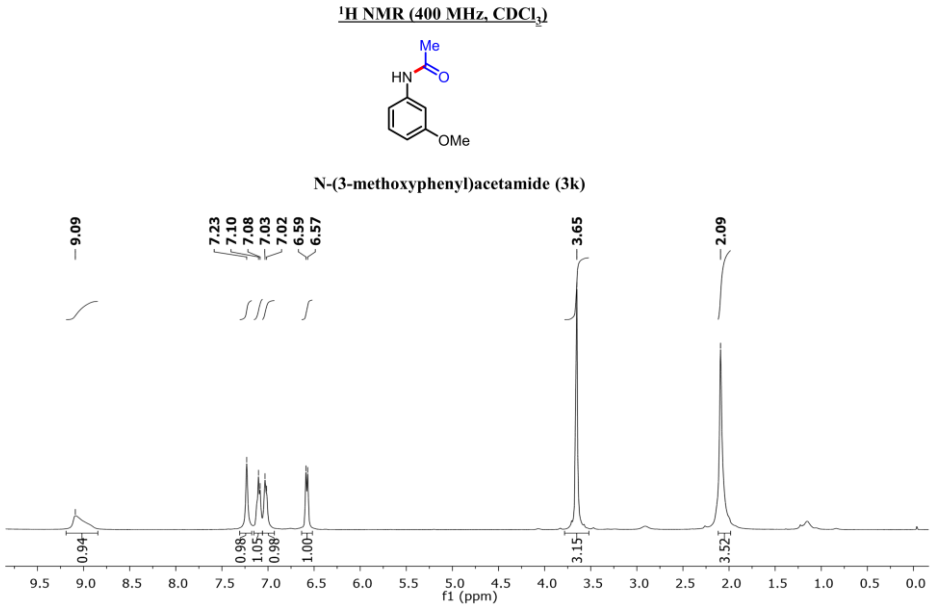

¹H NMR (400 MHz, DMSO-d_6)
N,N'-(1,4-phenylene)diacetamide (3j)
9.85
7.43
1.97
1.93
4.00
6.12
f1 (ppm)
¹³C NMR (100 MHz, DMSO-d_6)
N,N'-(1,4-phenylene)diacetamide (3j)
168.92
135.30
120.11
40.63
40.42
40.21
40.00
39.79
39.58
39.37
24.38
f1 (ppm)

Figure 5.12


^{1}H NMR (400 MHz, CDCl$_3$)
Me
HN
O
OMe
N-(3-methoxyphenyl)acetamide (3k)
9.09
7.23
7.10
7.08
7.03
7.02
6.59
6.57
3.65
2.09
0.94
0.98
1.05
0.98
1.00
3.15
3.52
f1 (ppm)

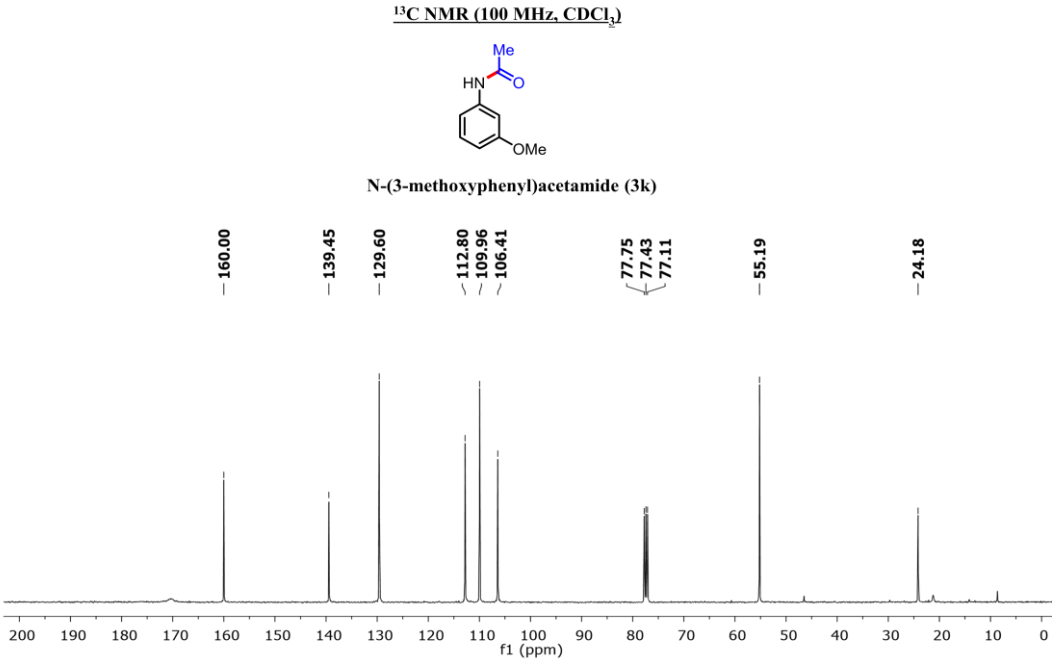
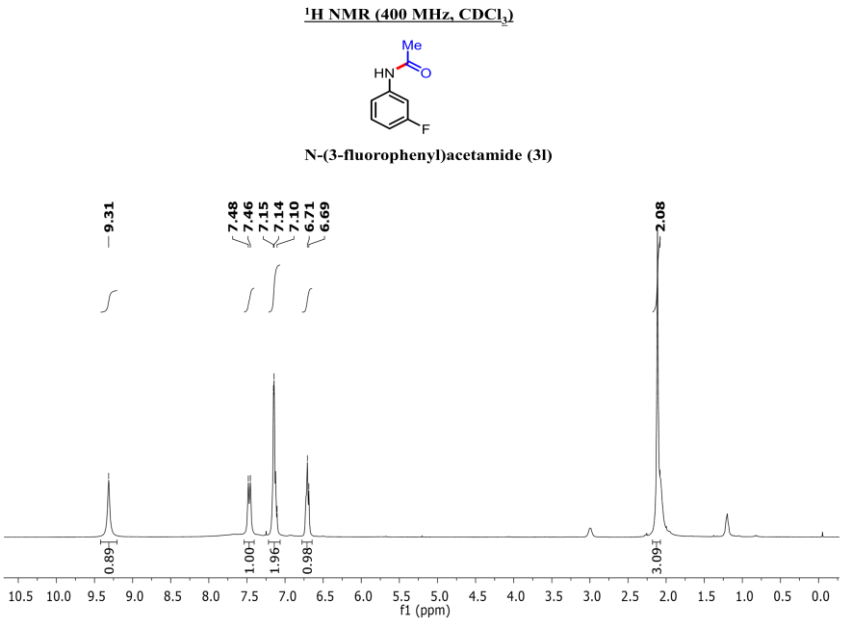

^{13}C NMR (100 MHz, CDCl$_3$)
Me
HN
O
OMe
N-(3-methoxyphenyl)acetamide (3k)
160.00
139.45
129.60
112.80
109.96
106.41
77.75
77.43
77.11
55.19
24.18
f1 (ppm)

Figure 5.13


^{1}H NMR (400 MHz, CDCl$_3$)
Me
HN
O
F
N-(3-fluorophenyl)acetamide (3l)
9.31
7.48
7.46
7.15
7.14
7.10
6.71
6.69
2.08
0.89
1.00
1.96
0.98
3.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

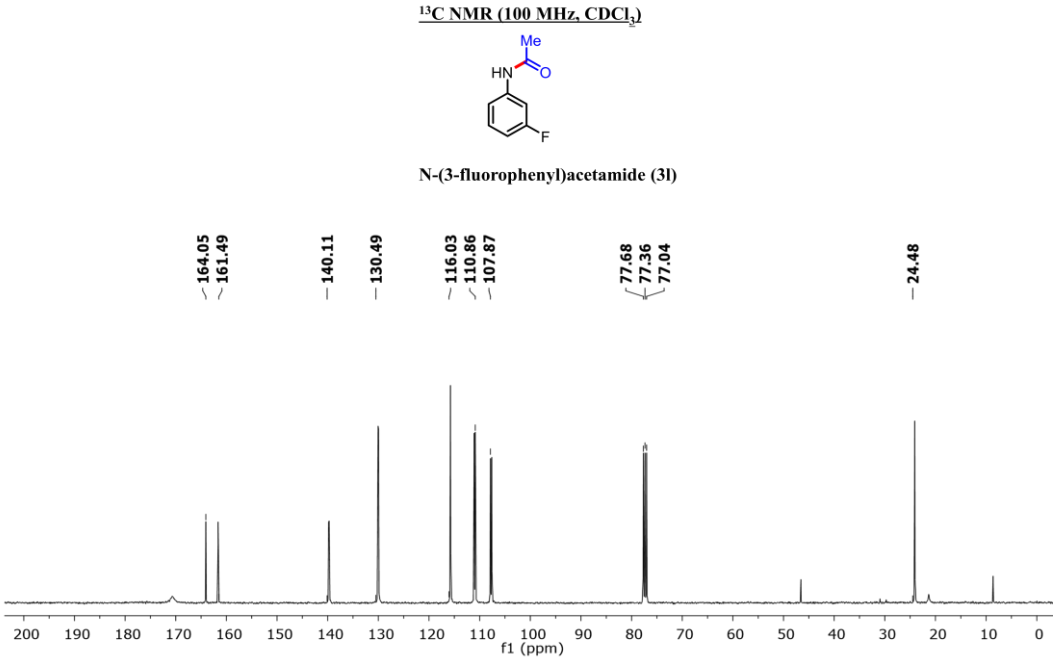
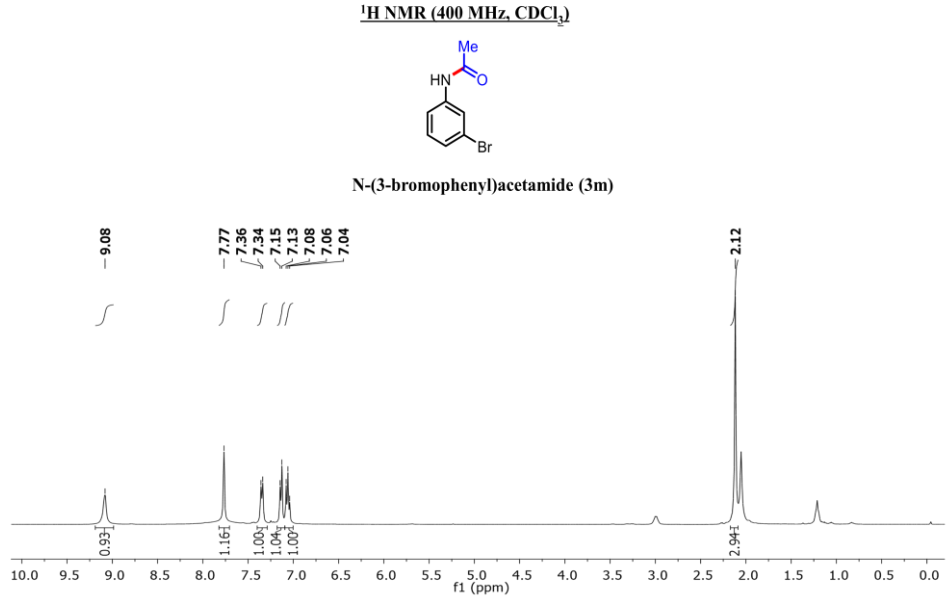

^{13}C NMR (100 MHz, CDCl$_3$)
Me
HN
O
F
N-(3-fluorophenyl)acetamide (3l)
164.05
161.49
140.11
130.49
116.03
110.86
107.87
77.68
77.36
77.04
24.48
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Figure 5.14


^{1}H NMR (400 MHz, CDCl$_3$)
Me
HN
O
Br
N-(3-bromophenyl)acetamide (3m)
9.08
7.77
7.36
7.34
7.15
7.13
7.08
7.06
7.04
2.12
0.93
1.16
1.00
1.04
1.00
2.94
f1 (ppm)

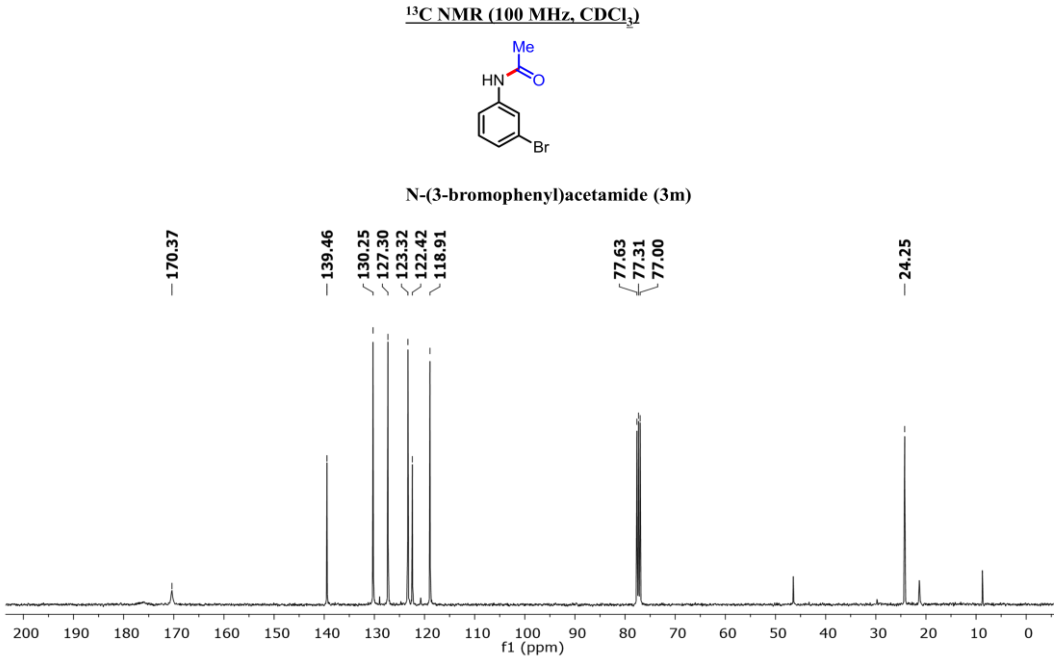
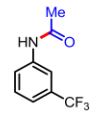
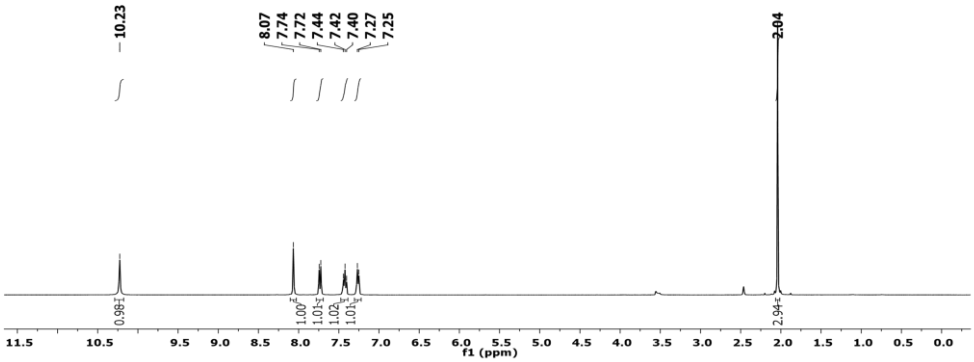

^{13}C NMR (100 MHz, CDCl$_3$)
Me
HN
O
Br
N-(3-bromophenyl)acetamide (3m)
170.37
139.46
130.25
127.30
123.32
122.42
118.91
77.63
77.31
77.00
24.25
f1 (ppm)

Figure 5.15

^{1}H NMR (400 MHz, DMSO-d_6)



N-(3-(trifluoromethyl)phenyl)acetamide (3n)



^{13}C NMR (100 MHz, DMSO-d_6)

N-(3-(trifluoromethyl)phenyl)acetamide (3n)

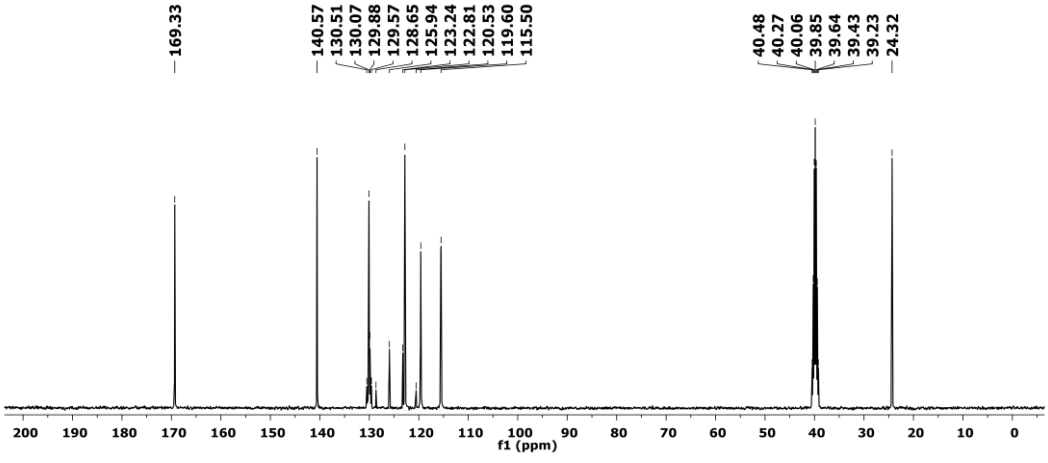
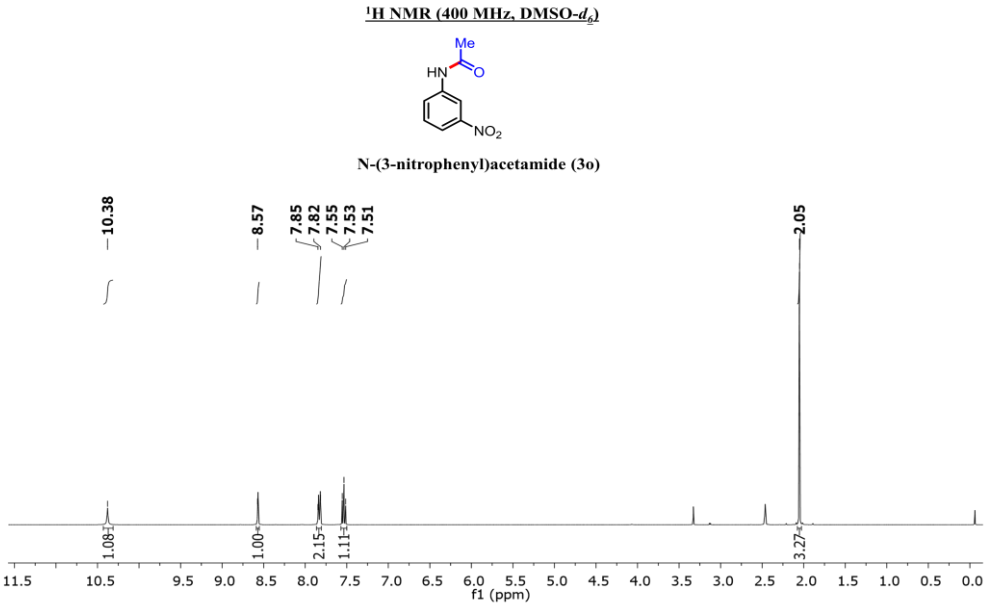


Figure 5.16


^{1}H NMR (400 MHz, DMSO-d_6)
Me
HN
O
NO2
N-(3-nitrophenyl)acetamide (3o)
10.38
8.57
7.85
7.82
7.55
7.53
7.51
2.05
1.08
1.00
2.15
1.11
3.27
f1 (ppm)

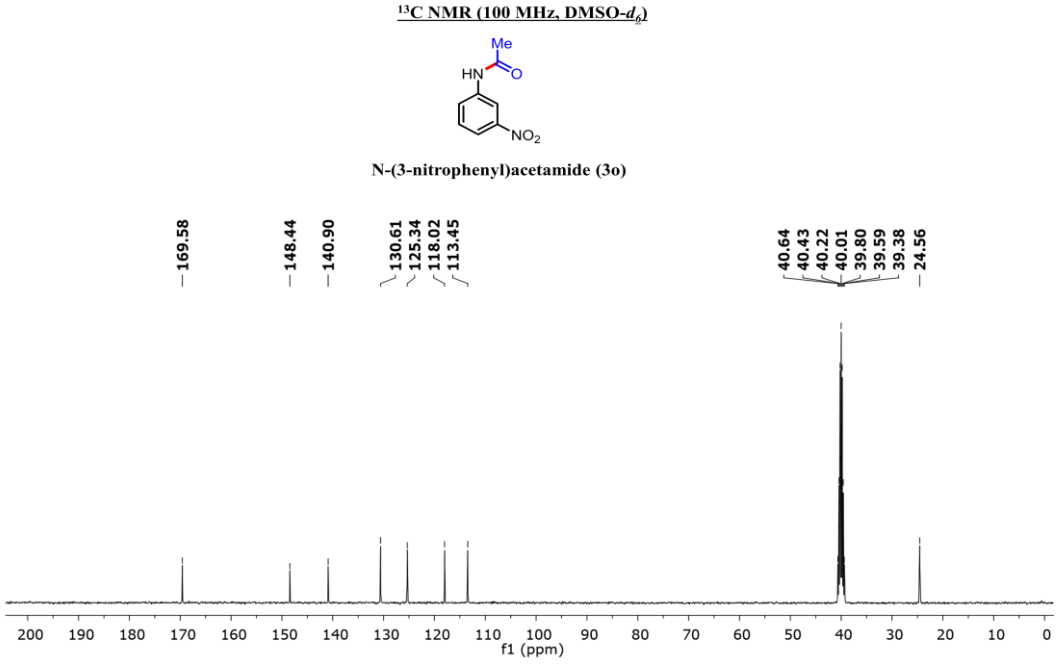
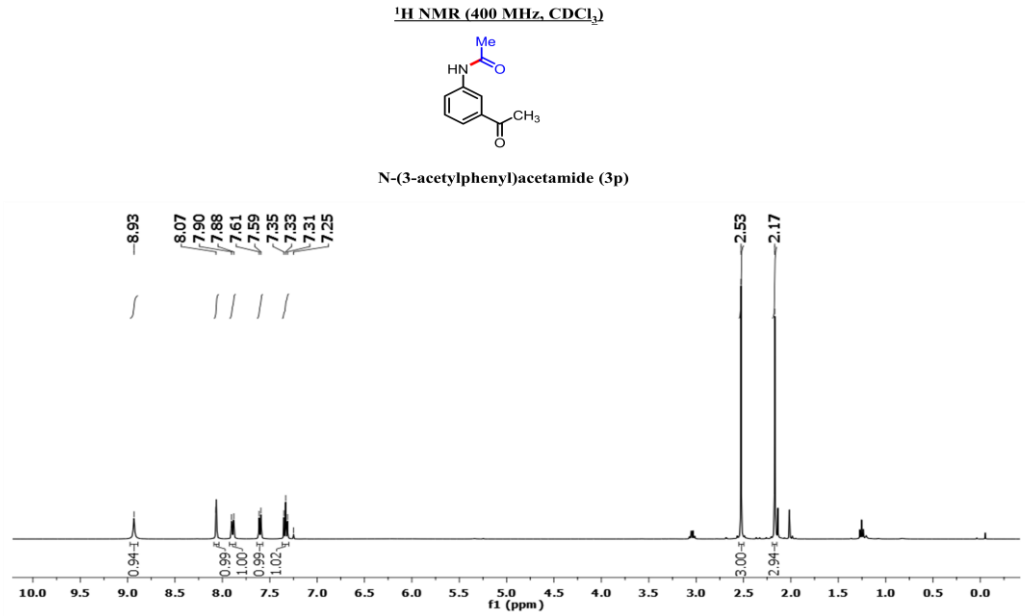

^{13}C NMR (100 MHz, DMSO-d_6)
Me
HN
O
NO2
N-(3-nitrophenyl)acetamide (3o)
169.58
148.44
140.90
130.61
125.34
118.02
113.45
40.64
40.43
40.22
40.01
39.80
39.59
39.38
24.56
f1 (ppm)

Figure 5.17


^{1}H NMR (400 MHz, CDCl$_3$)
Me
HN
O
CH$_3$
O
N-(3-acetylphenyl)acetamide (3p)
8.93
8.07
7.90
7.88
7.61
7.59
7.35
7.33
7.31
7.25
2.53
2.17
0.94
0.99
1.00
0.99
1.02
3.00
2.94
f1 (ppm)

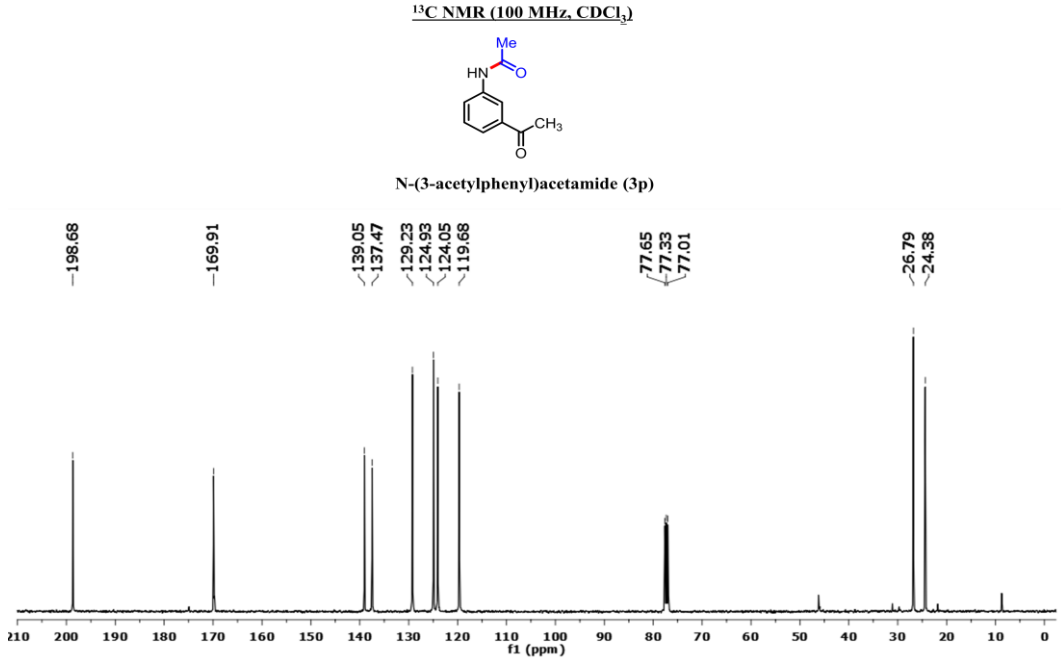
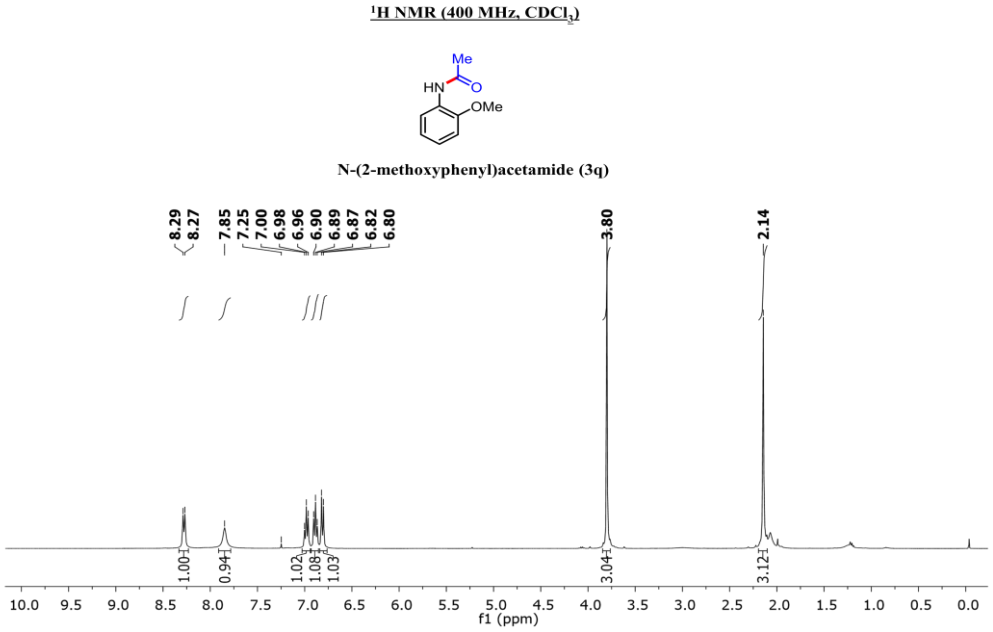

^{13}C NMR (100 MHz, CDCl$_3$)
Me
HN
O
CH$_3$
O
N-(3-acetylphenyl)acetamide (3p)
198.68
169.91
139.05
137.47
129.23
124.93
124.05
119.68
77.65
77.33
77.01
26.79
24.38
f1 (ppm)

Figure 5.18


^{1}H NMR (400 MHz, CDCl$_3$)
Me
HN
O
OMe
N-(2-methoxyphenyl)acetamide (3q)
8.29
8.27
7.85
7.25
7.00
6.98
6.96
6.90
6.89
6.87
6.82
6.80
3.80
2.14
1.00
0.94
1.02
1.08
1.03
3.04
3.12
f1 (ppm)

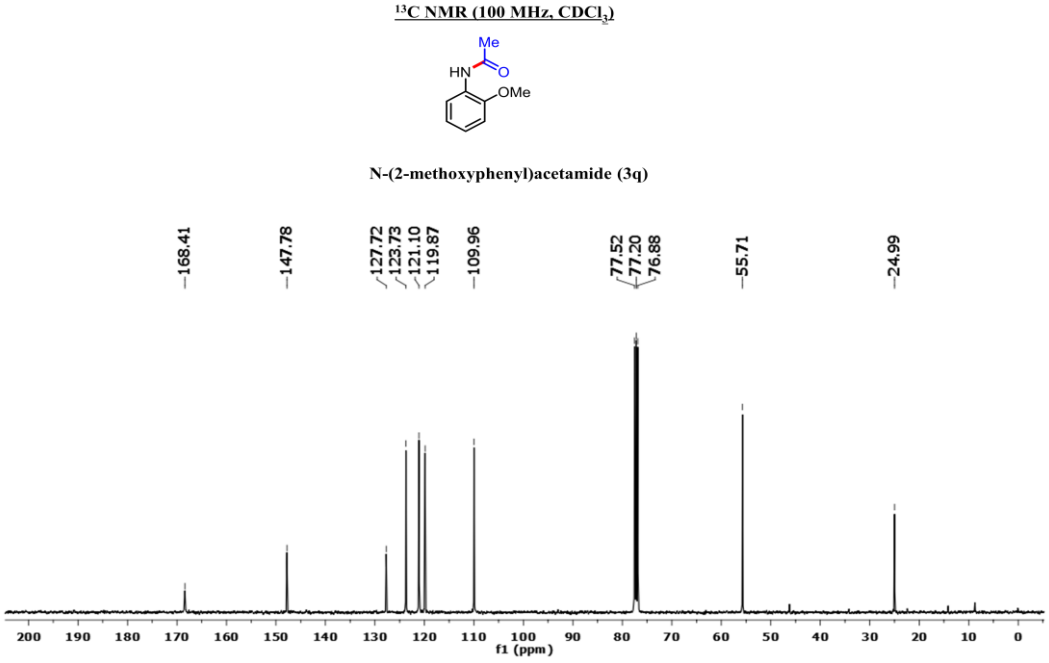
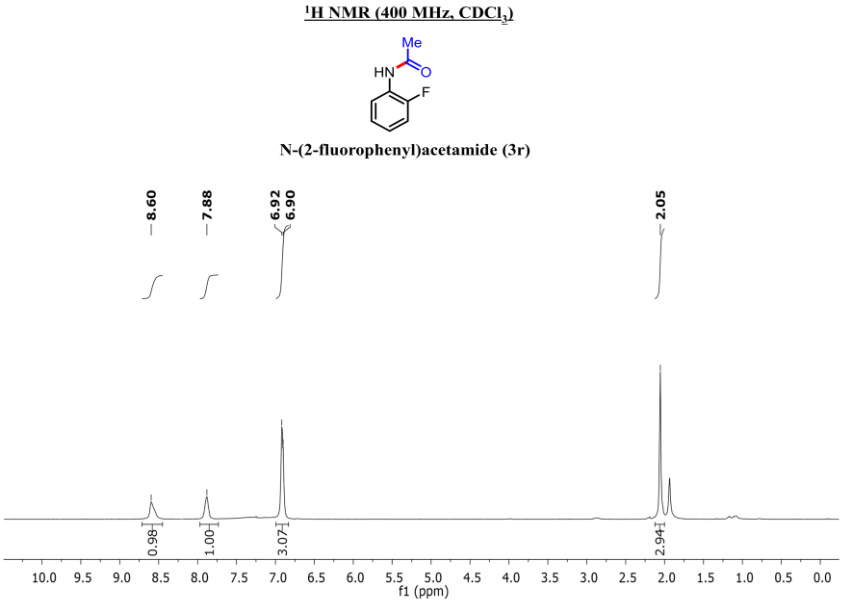

^{13}C NMR (100 MHz, CDCl$_3$)
Me
HN
O
OMe
N-(2-methoxyphenyl)acetamide (3q)
168.41
147.78
127.72
123.73
121.10
119.87
109.96
77.52
77.20
76.88
55.71
24.99
f1 (ppm)

Figure 5.19


^{1}H NMR (400 MHz, CDCl$_3$)
Me
HN
O
F
N-(2-fluorophenyl)acetamide (3r)
8.60
7.88
6.92
6.90
2.05
0.98
1.00
3.07
2.94
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

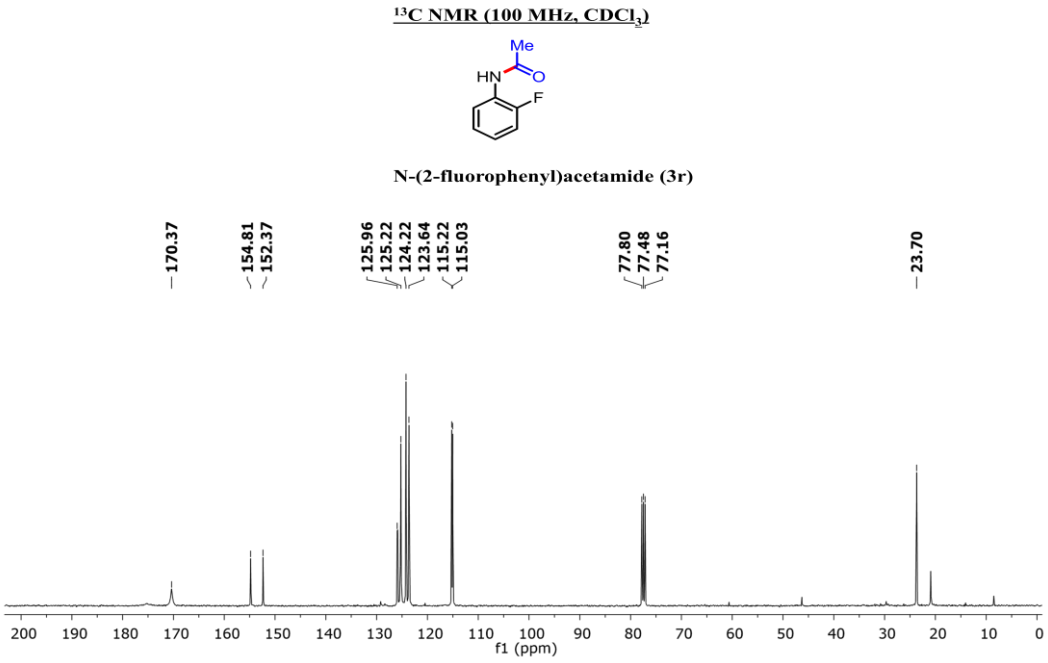
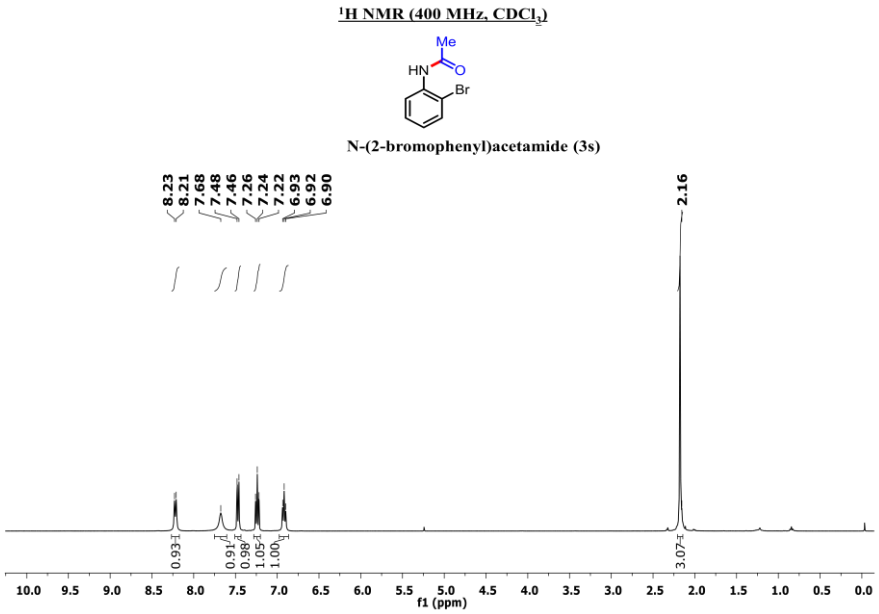

^{13}C NMR (100 MHz, CDCl$_3$)
Me
HN
O
F
N-(2-fluorophenyl)acetamide (3r)
170.37
154.81
152.37
125.96
125.22
124.22
123.64
115.22
115.03
77.80
77.48
77.16
23.70
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Figure 5.20


^{1}H NMR (400 MHz, CDCl$_3$)
Me
HN
O
Br
N-(2-bromophenyl)acetamide (3s)
8.23
8.21
7.68
7.48
7.46
7.26
7.24
7.22
6.93
6.92
6.90
2.16
0.93
0.91
0.98
1.05
1.00
3.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

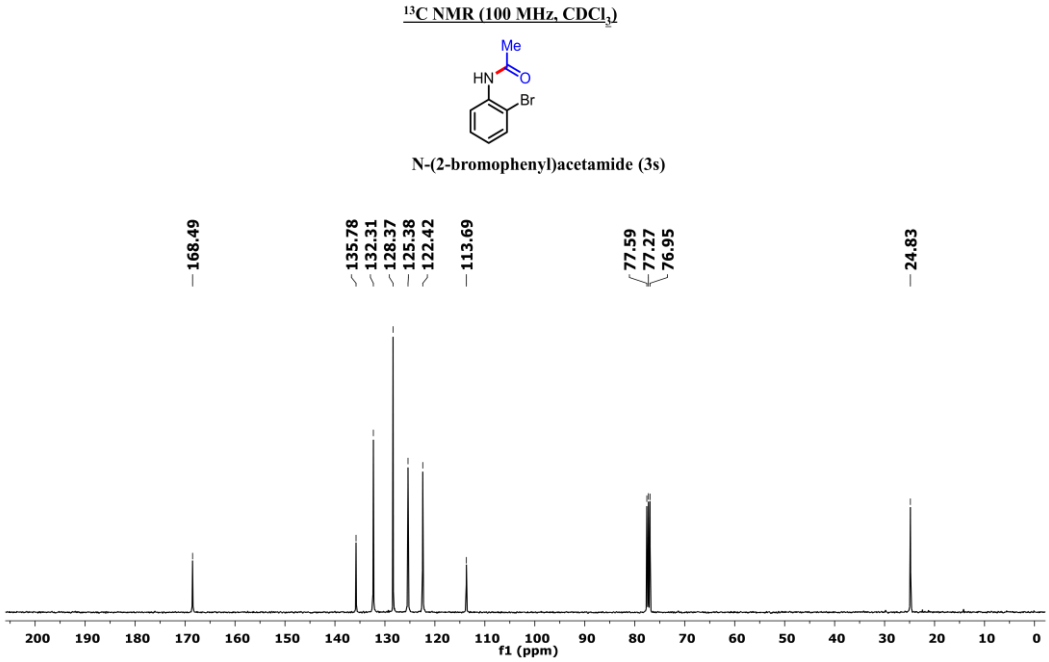
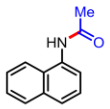
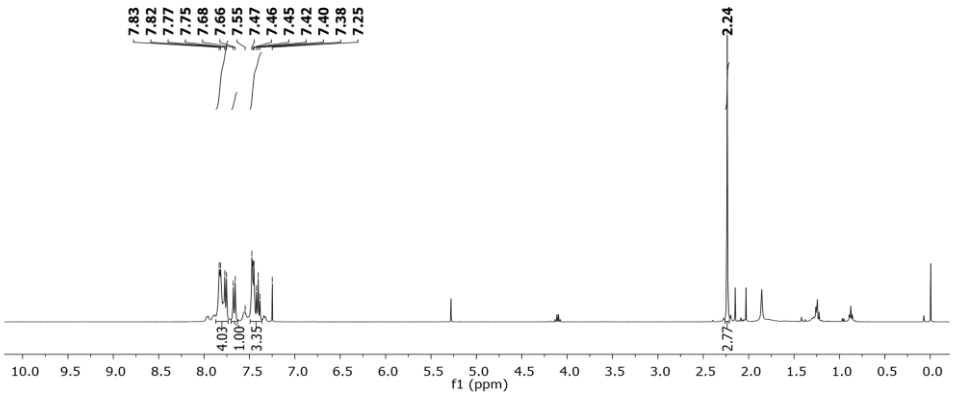

^{13}C NMR (100 MHz, CDCl$_3$)
Me
HN
O
Br
N-(2-bromophenyl)acetamide (3s)
168.49
135.78
132.31
128.37
125.38
122.42
113.69
77.59
77.27
76.95
24.83
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

Figure 5.21

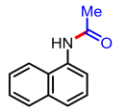
^{1}H NMR (400 MHz, $CDCl_3$)



N-(naphthalen-1-yl)acetamide (3t)



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



N-(naphthalen-1-yl)acetamide (3t)

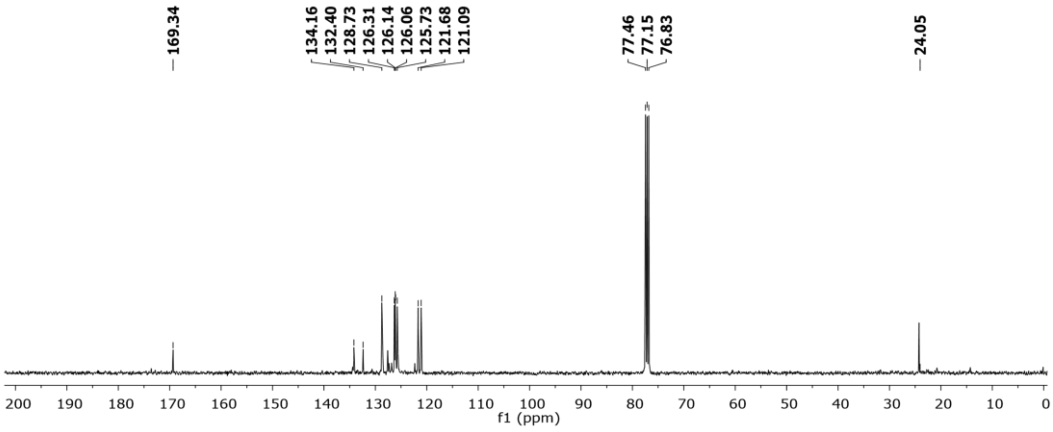
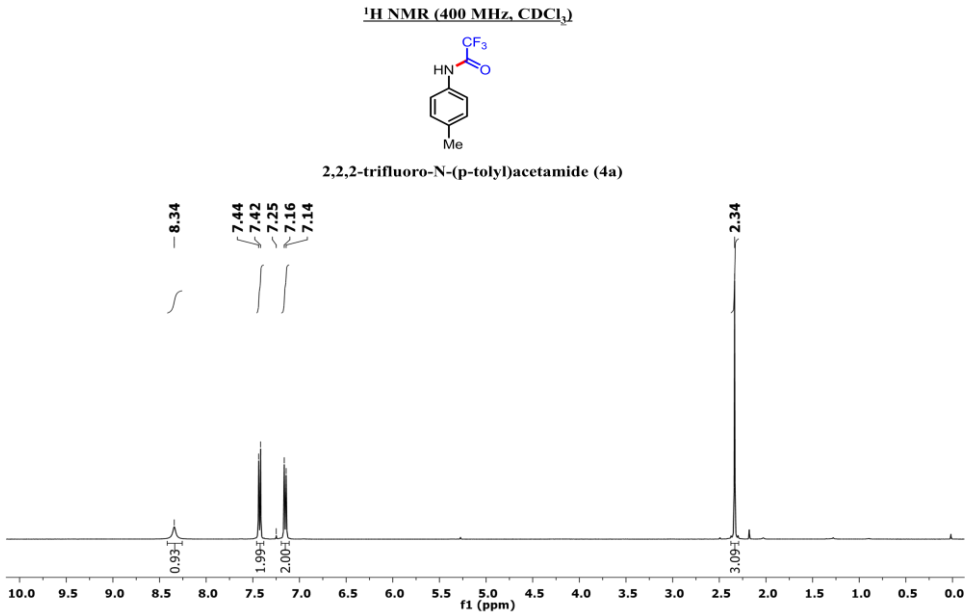


Figure 5.22


^{1}H NMR (400 MHz, CDCl$_3$)
CF3
HN
O
Me
2,2,2-trifluoro-N-(p-tolyl)acetamide (4a)
8.34
7.44
7.42
7.25
7.16
7.14
2.34
0.93
1.99
2.00
3.09
f1 (ppm)

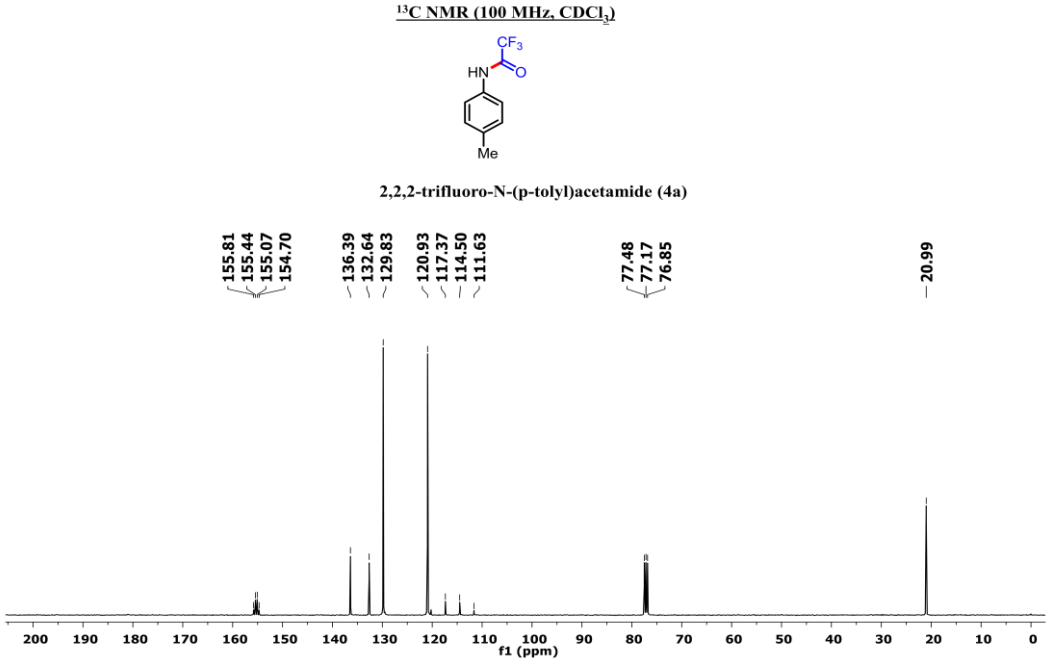

^{13}C NMR (100 MHz, CDCl$_3$)
CF3
HN
O
Me
2,2,2-trifluoro-N-(p-tolyl)acetamide (4a)
155.81
155.44
155.07
154.70
136.39
132.64
129.83
120.93
117.37
114.50
111.63
77.48
77.17
76.85
20.99
f1 (ppm)

Figure 5.23

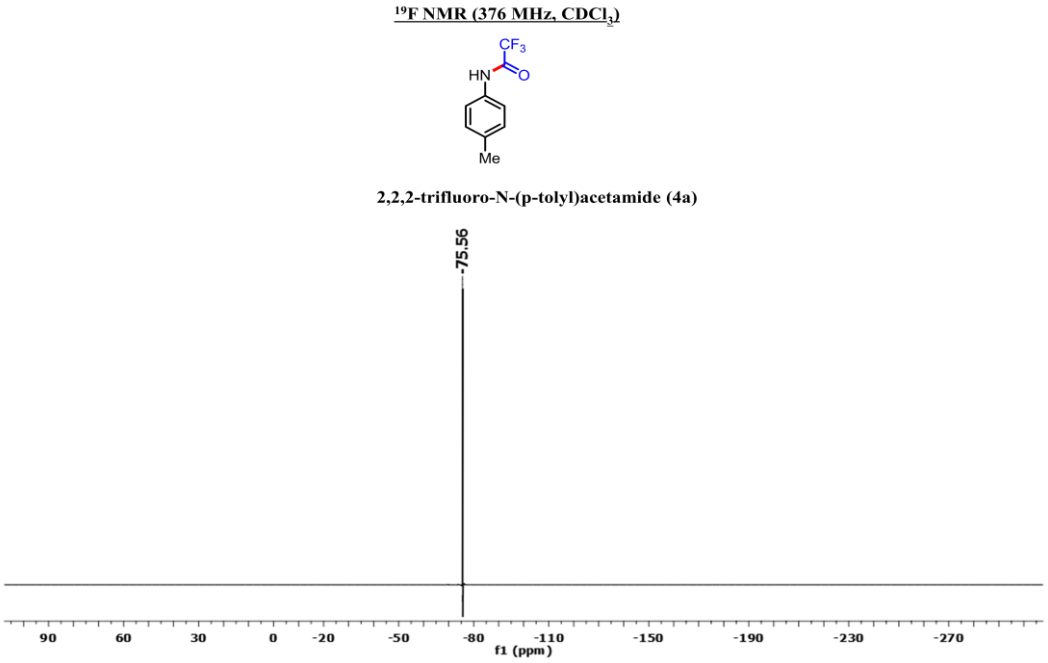


Figure 5.24

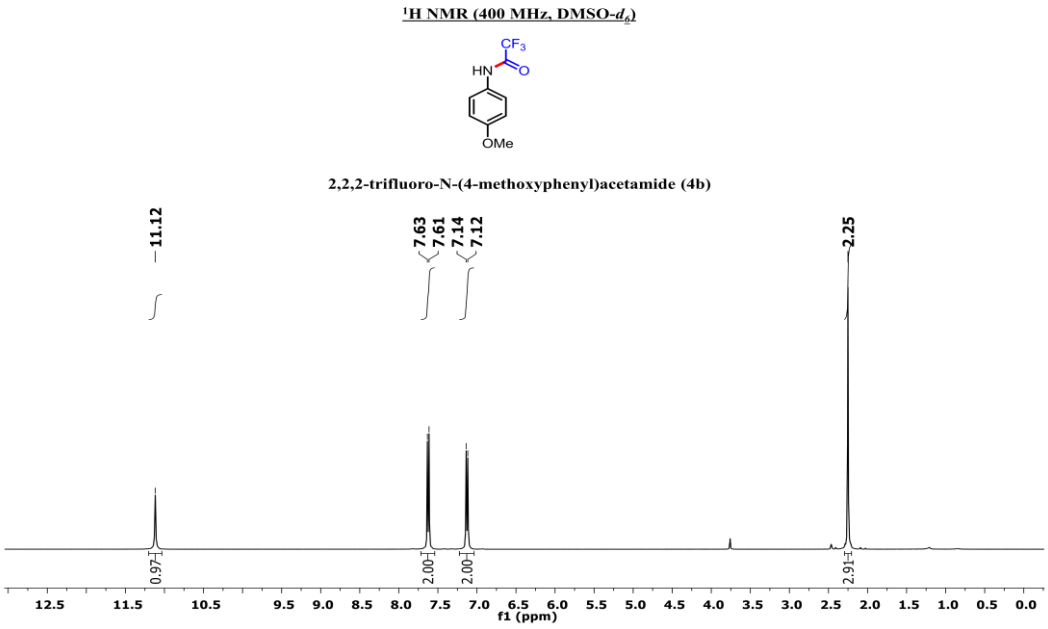
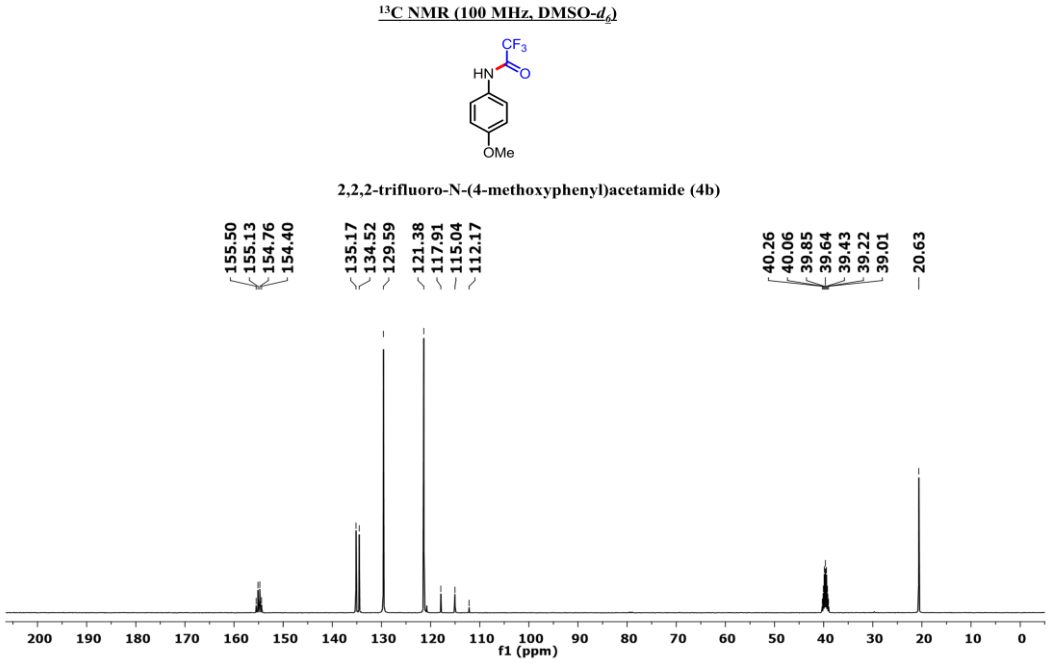


Figure 5.25


^{13}C NMR (100 MHz, DMSO-d_6)
CF3
HN
O
OMe
2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide (4b)
155.50
155.13
154.76
154.40
135.17
134.52
129.59
121.38
117.91
115.04
112.17
40.26
40.06
39.85
39.64
39.43
39.22
39.01
20.63
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

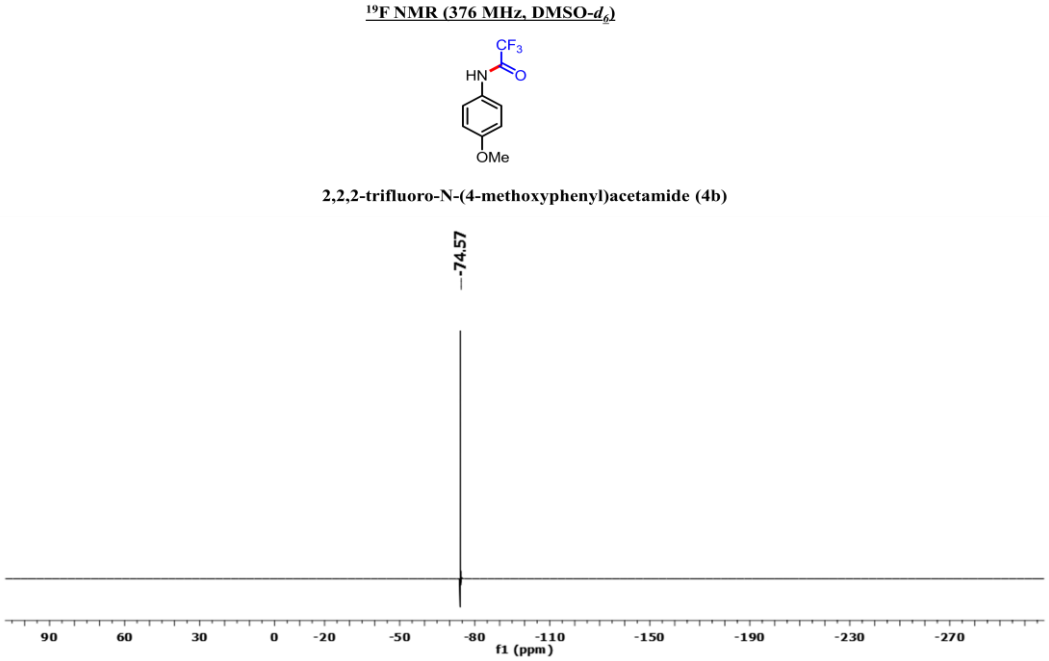
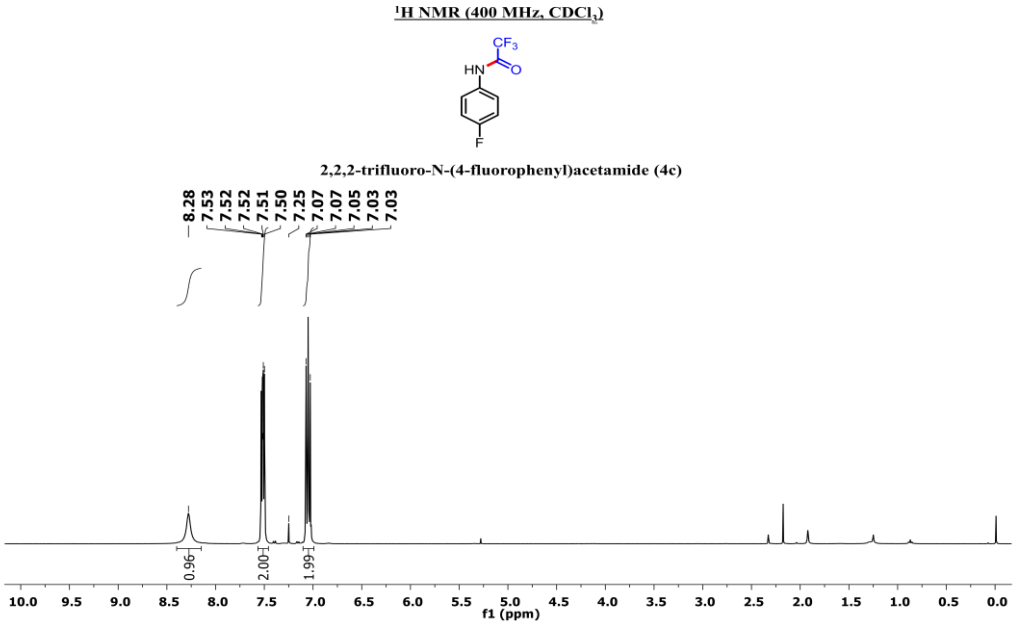

^{19}F NMR (376 MHz, DMSO-d_6)
CF3
HN
O
OMe
2,2,2-trifluoro-N-(4-methoxyphenyl)acetamide (4b)
-74.57
90 60 30 0 -20 -50 -80 -110 -150 -190 -230 -270
f1 (ppm)

Figure 5.26


^{1}H NMR (400 MHz, CDCl$_3$)
2,2,2-trifluoro-N-(4-fluorophenyl)acetamide (4c)
8.28
7.53
7.52
7.52
7.51
7.50
7.25
7.07
7.07
7.05
7.03
7.03
0.96
2.00
1.99
f1 (ppm)

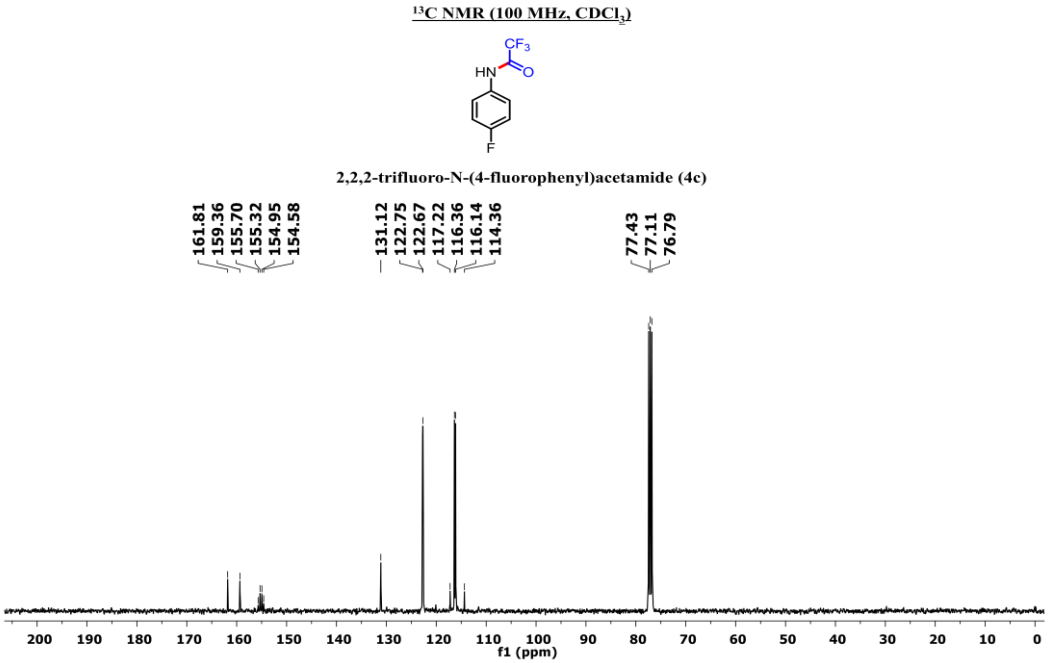
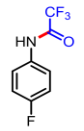

^{13}C NMR (100 MHz, CDCl$_3$)
2,2,2-trifluoro-N-(4-fluorophenyl)acetamide (4c)
161.81
159.36
155.70
155.32
154.95
154.58
131.12
122.75
122.67
117.22
116.36
116.14
114.36
77.43
77.11
76.79
f1 (ppm)

Figure 5.27

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



2,2,2-trifluoro-N-(4-fluorophenyl)acetamide (4c)

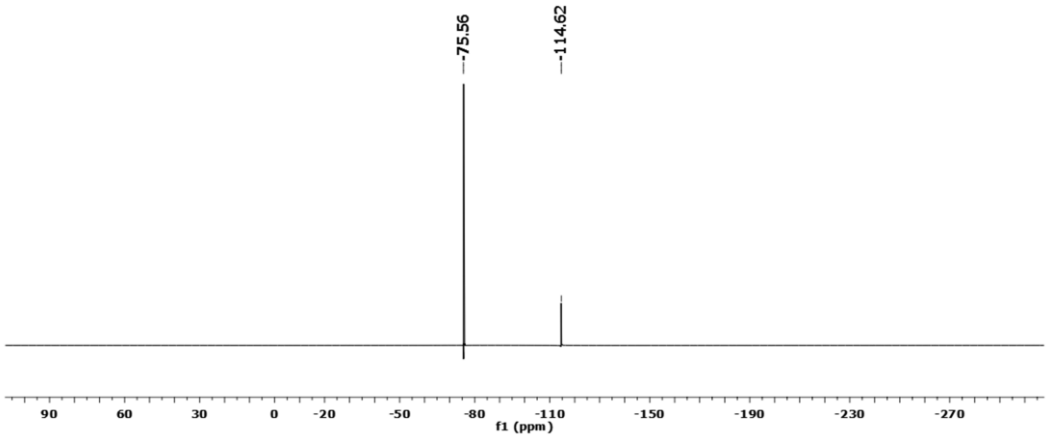
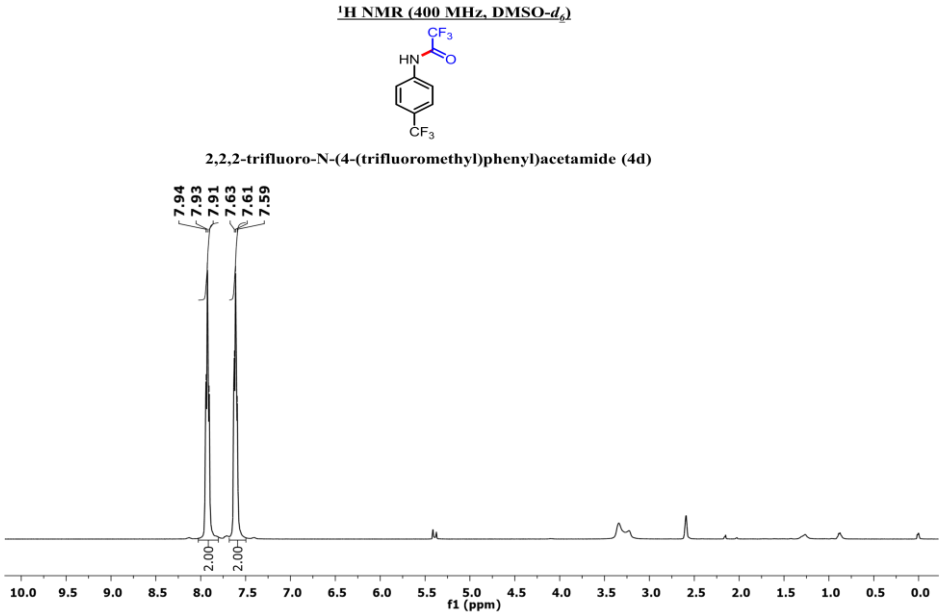


Figure 5.28


^{1}H NMR (400 MHz, DMSO-d_6)
2,2,2-trifluoro-N-(4-(trifluoromethyl)phenyl)acetamide (4d)
7.94
7.93
7.91
7.63
7.61
7.59
2.00
2.00
f1 (ppm)

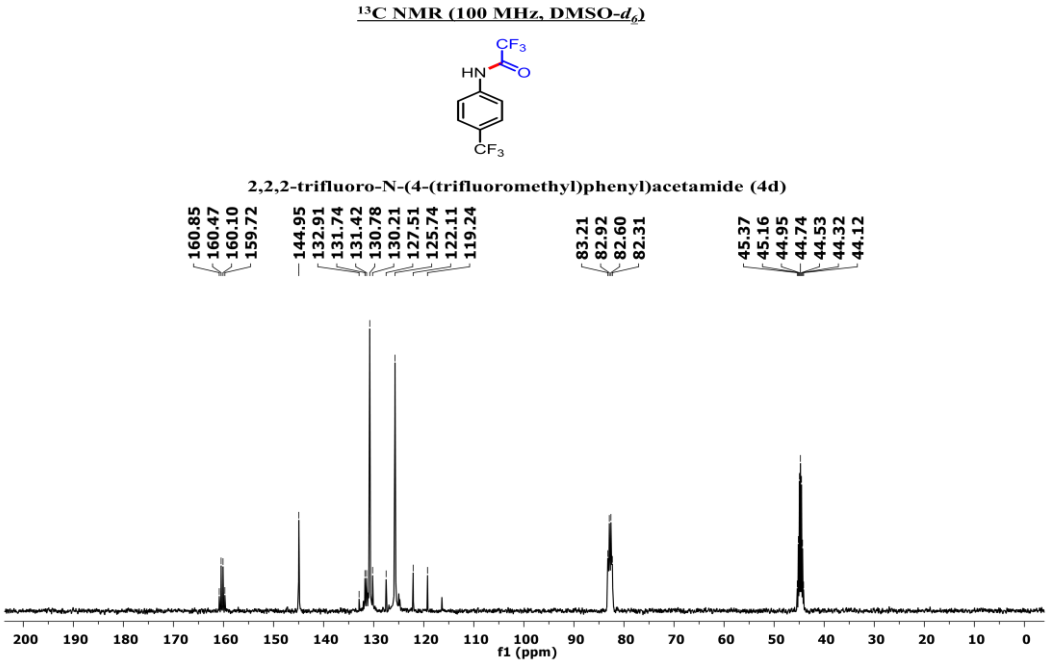

^{13}C NMR (100 MHz, DMSO-d_6)
2,2,2-trifluoro-N-(4-(trifluoromethyl)phenyl)acetamide (4d)
160.85
160.47
160.10
159.72
144.95
132.91
131.74
131.42
130.78
130.21
127.51
125.74
122.11
119.24
83.21
82.92
82.60
82.31
45.37
45.16
44.95
44.74
44.53
44.32
44.12
f1 (ppm)

Figure 5.29

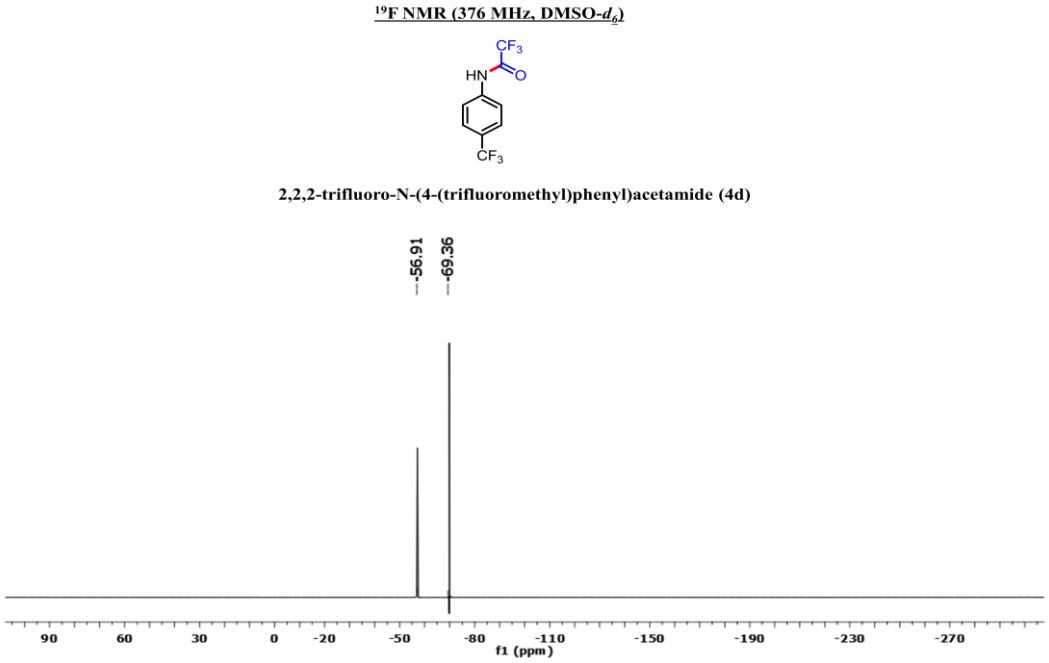


Figure 5.30

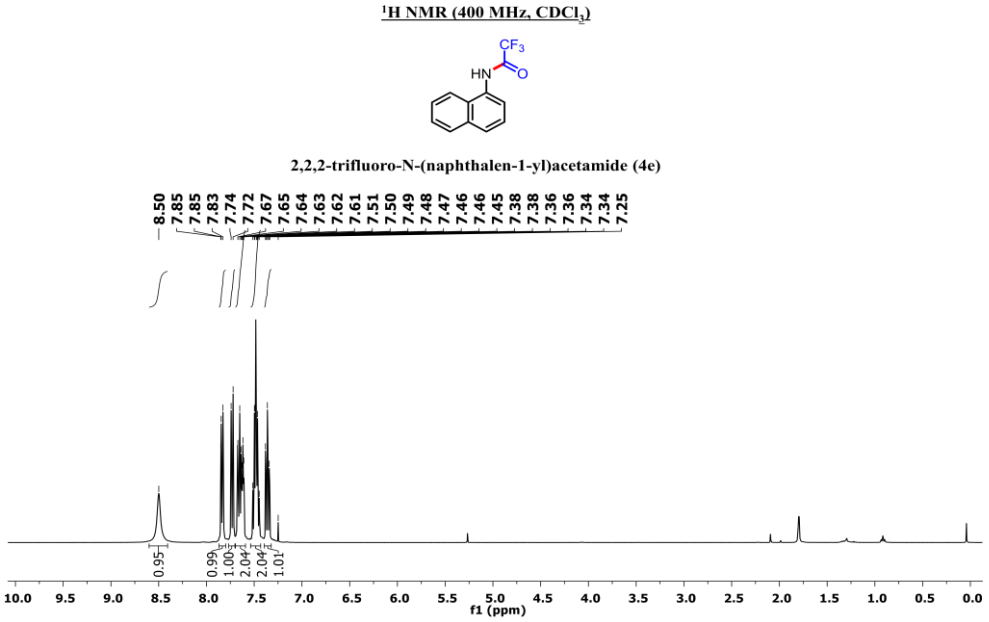
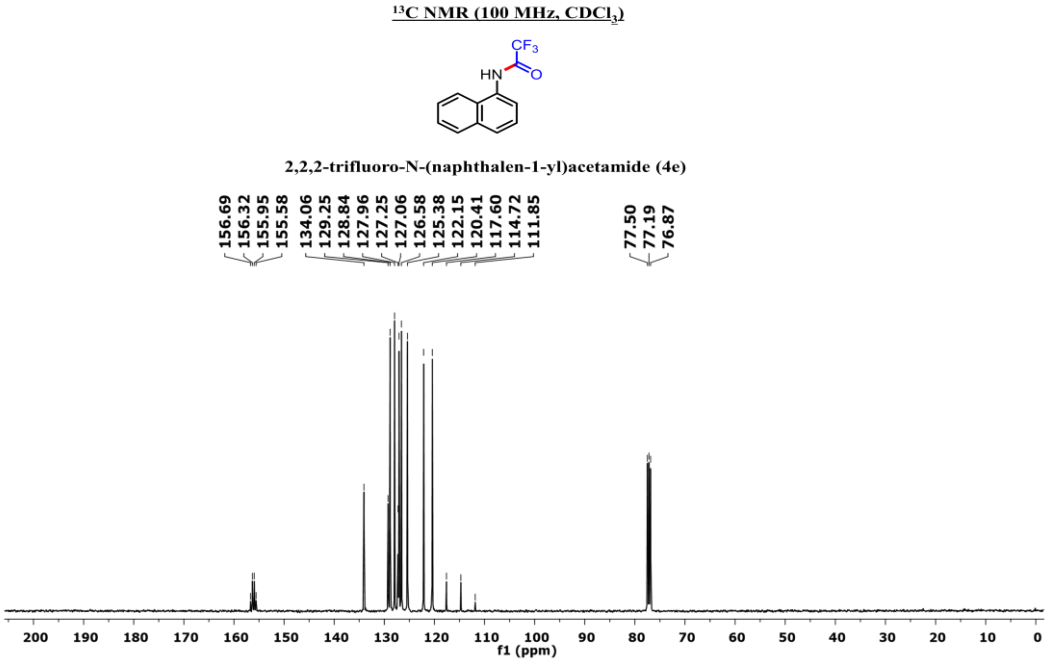


Figure 5.31


^{13}C NMR (100 MHz, CDCl$_3$)
CF3
HN
O
2,2,2-trifluoro-N-(naphthalen-1-yl)acetamide (4e)
156.69
156.32
155.95
155.58
134.06
129.25
128.84
127.96
127.25
127.06
126.58
125.38
122.15
120.41
117.60
114.72
111.85
77.50
77.19
76.87
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

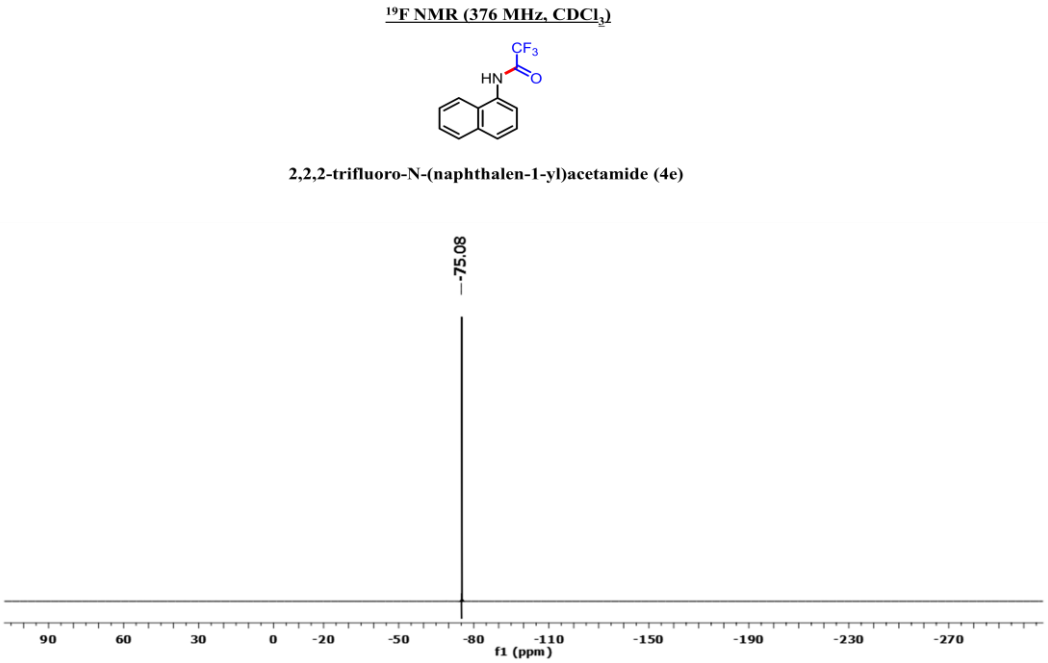
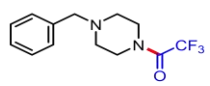
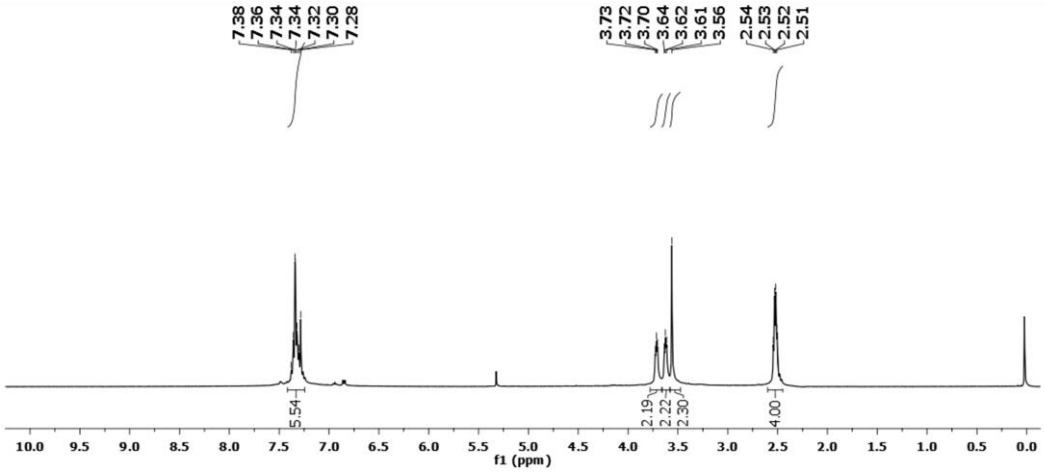

^{19}F NMR (376 MHz, CDCl$_3$)
CF3
HN
O
2,2,2-trifluoro-N-(naphthalen-1-yl)acetamide (4e)
-75.08
90 60 30 0 -20 -50 -80 -110 -150 -190 -230 -270
f1 (ppm)

Figure 5.32

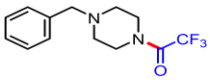
^{1}H NMR (400 MHz, $CDCl_3$)



1-(4-benzylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one (6a)



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



1-(4-benzylpiperazin-1-yl)-2,2,2-trifluoroethan-1-one (6a)

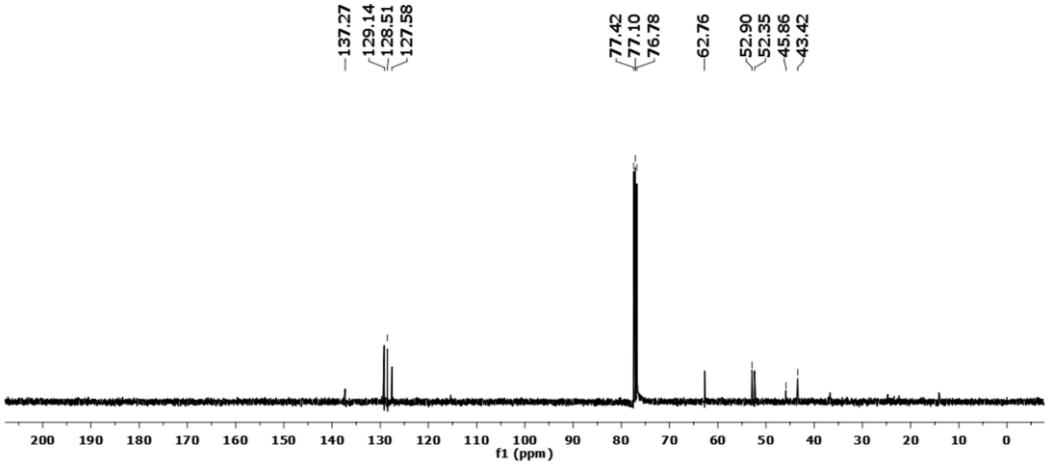
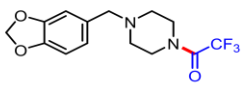
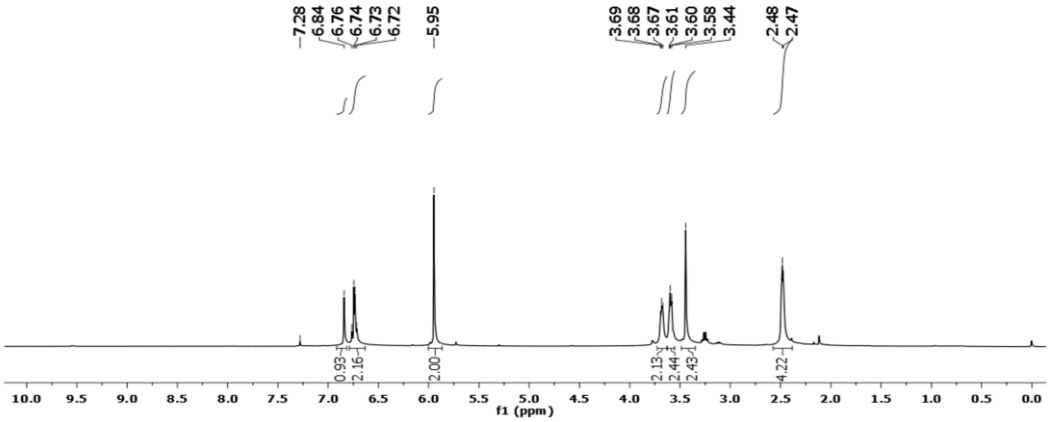


Figure 5.33

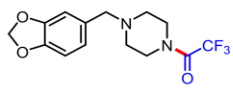
^{1}H NMR (400 MHz, $CDCl_3$)



1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-2,2,2-trifluoroethan-1-one (6b)



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



1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)-2,2,2-trifluoroethan-1-one (6b)

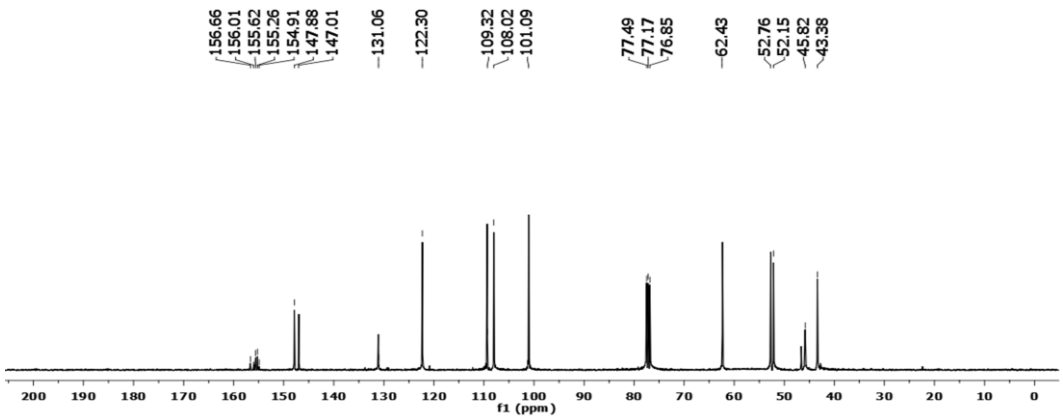
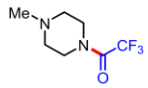
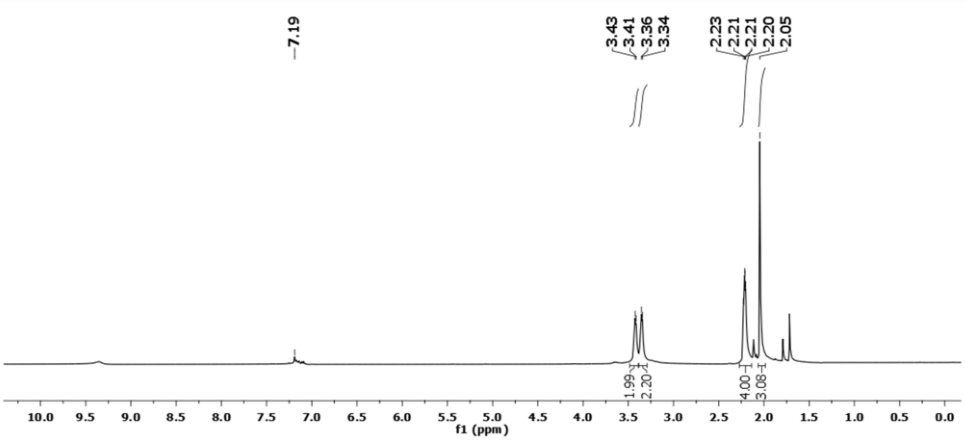


Figure 5.34

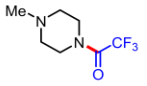
^{1}H NMR (400 MHz, $CDCl_3$)



2,2,2-trifluoro-1-(4-methylpiperazin-1-yl)ethan-1-one(6c)



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



2,2,2-trifluoro-1-(4-methylpiperazin-1-yl)ethan-1-one(6c)

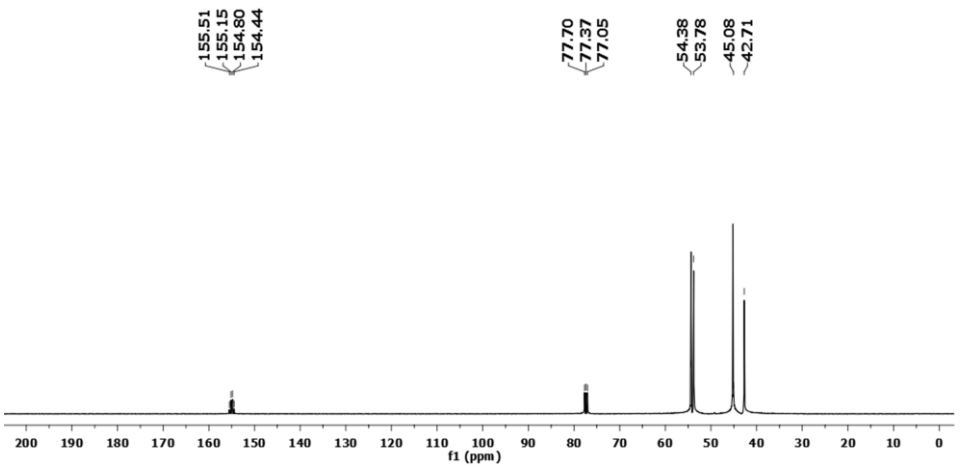
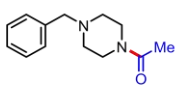
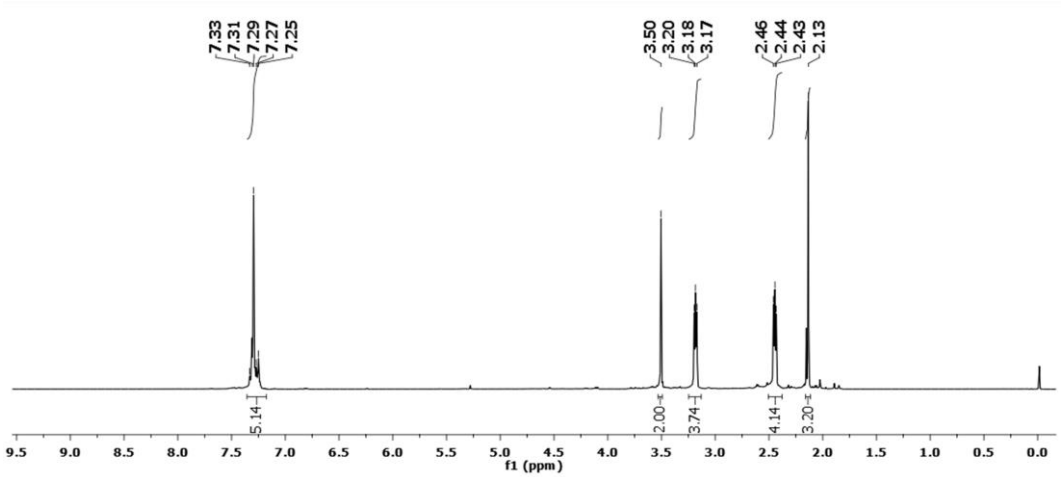


Figure 5.35

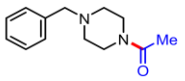
^{1}H NMR (400 MHz, $CDCl_3$)



1-(4-benzylpiperazin-1-yl)ethan-1-one (7a)



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



1-(4-benzylpiperazin-1-yl)ethan-1-one (7a)

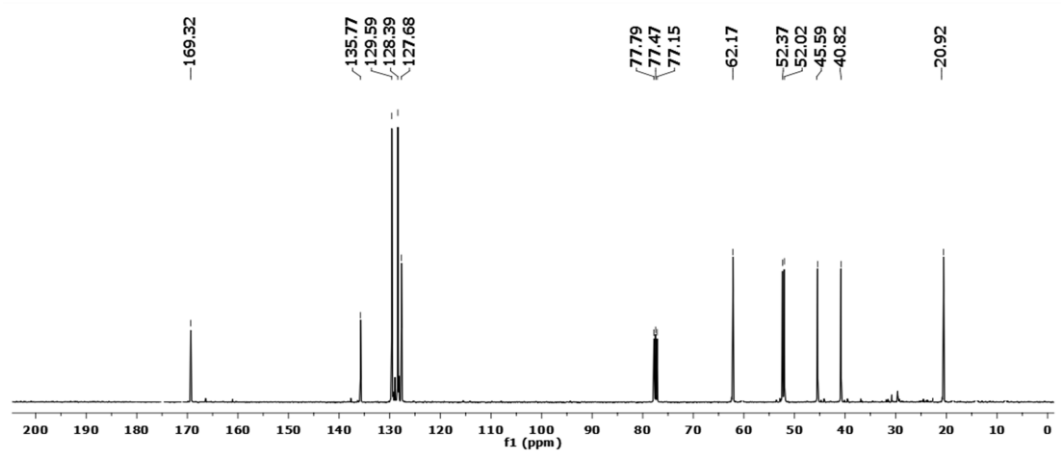
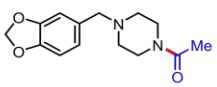
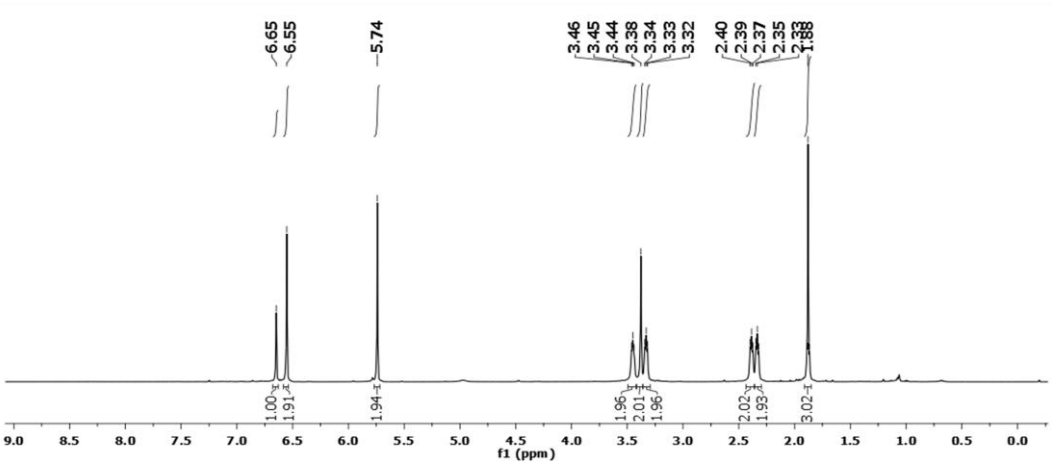


Figure 5.36

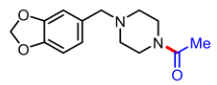
^{1}H NMR (400 MHz, $CDCl_3$)



1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)ethan-1-one (7b)



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



1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)ethan-1-one (7b)

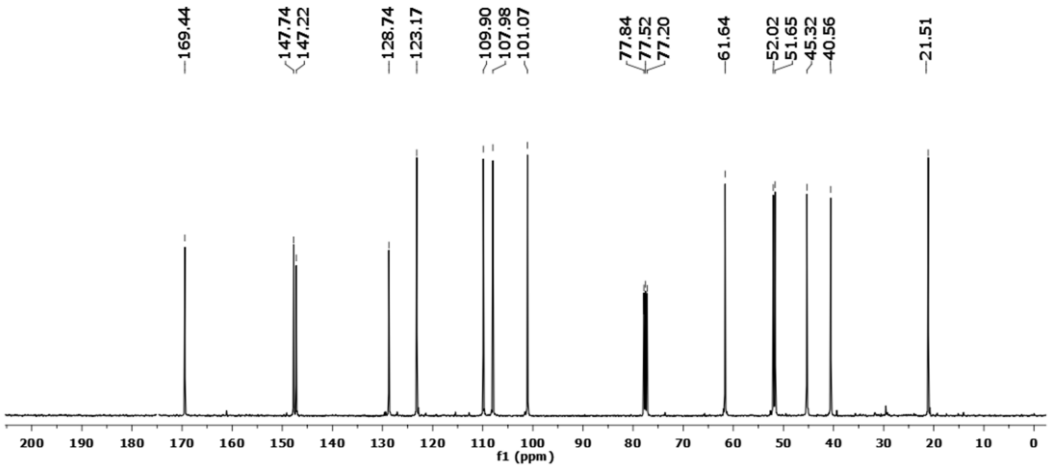
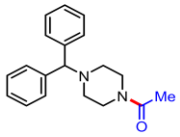
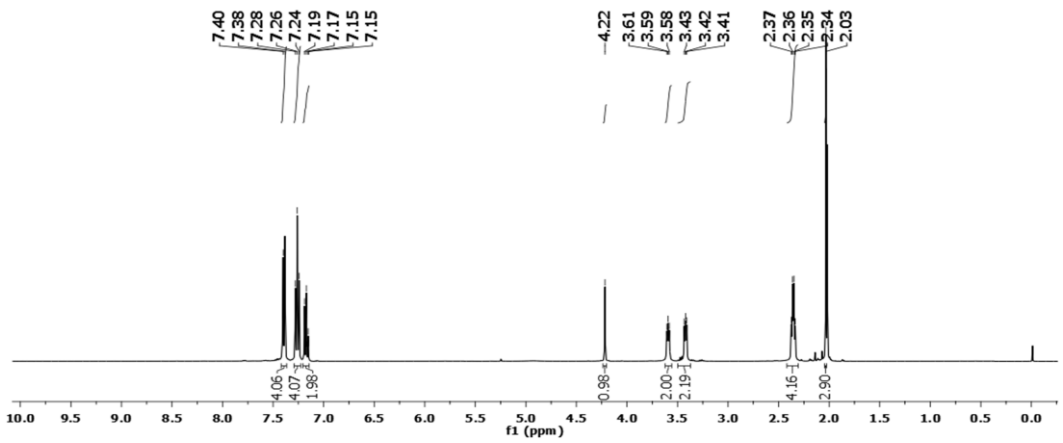


Figure 5.37

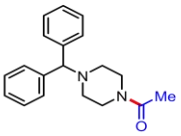
^{1}H NMR (400 MHz, $CDCl_3$)



1-(4-benzhydrylpiperazin-1-yl)ethan-1-one (7c)



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



1-(4-benzhydrylpiperazin-1-yl)ethan-1-one (7c)

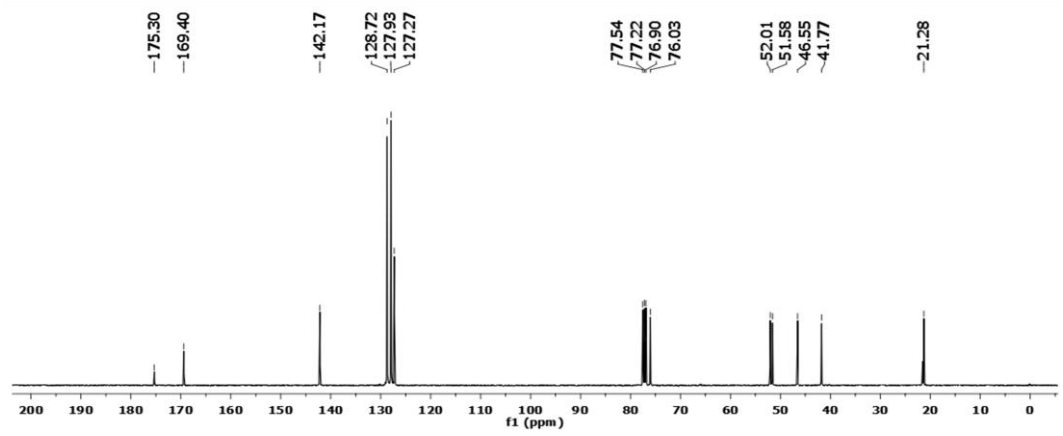
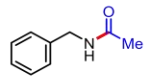
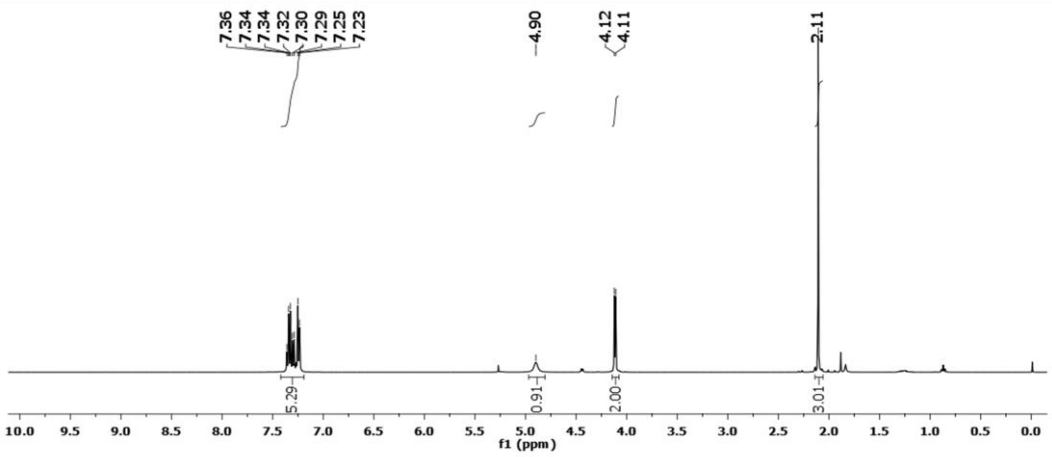


Figure 5.38

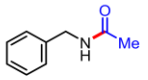
^{1}H NMR (400 MHz, $CDCl_3$)



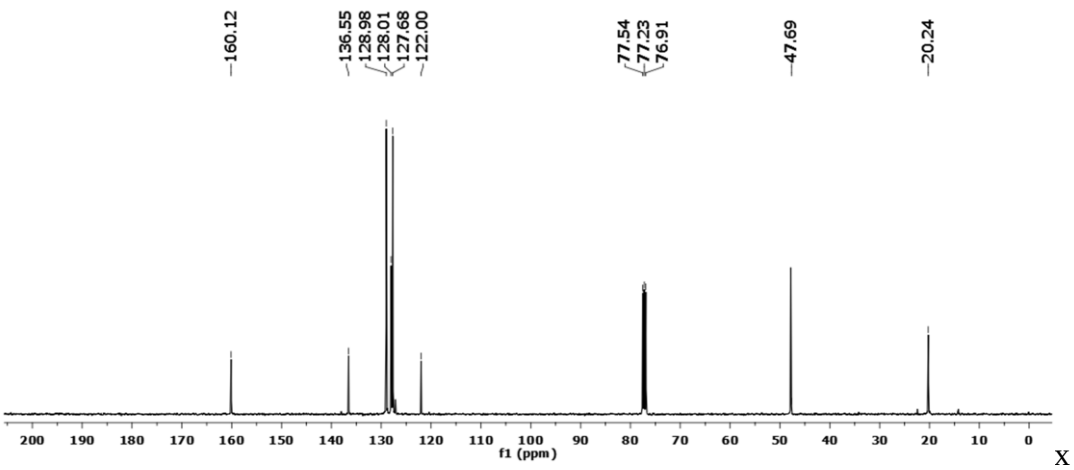
N-benzylacetamide (9a)



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



N-benzylacetamide (9a)

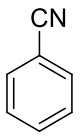


X

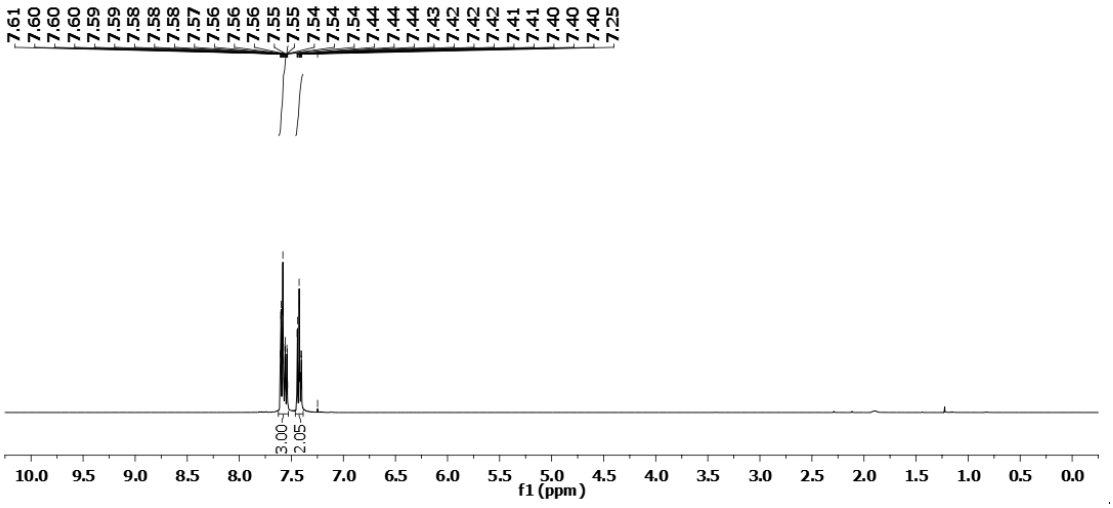
Figure 5.39

Appendix – D
^{1}H NMR, ^{13}C NMR Spectra of Chapter 6

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



Benzonitrile (2a)



^{13}C NMR (100 MHz CDCl

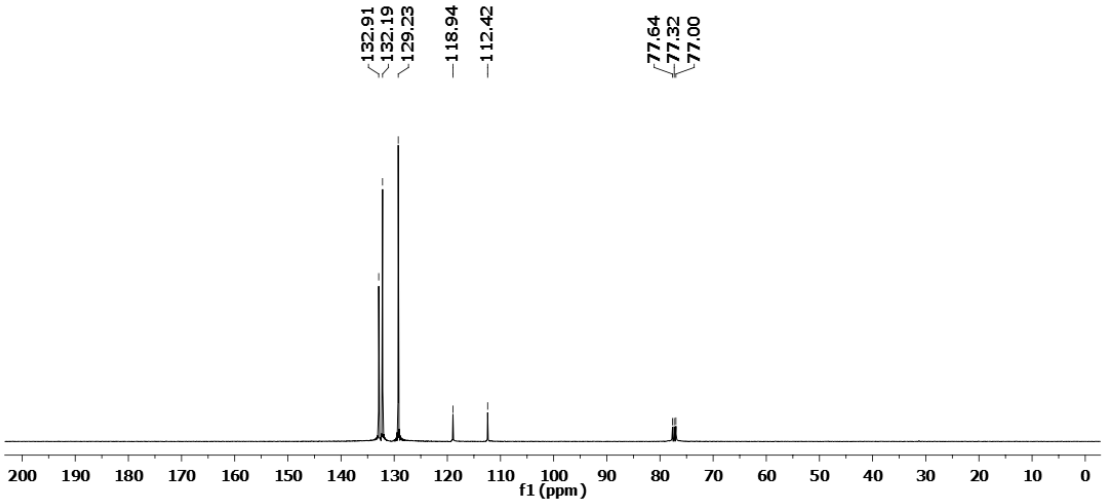
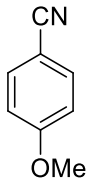
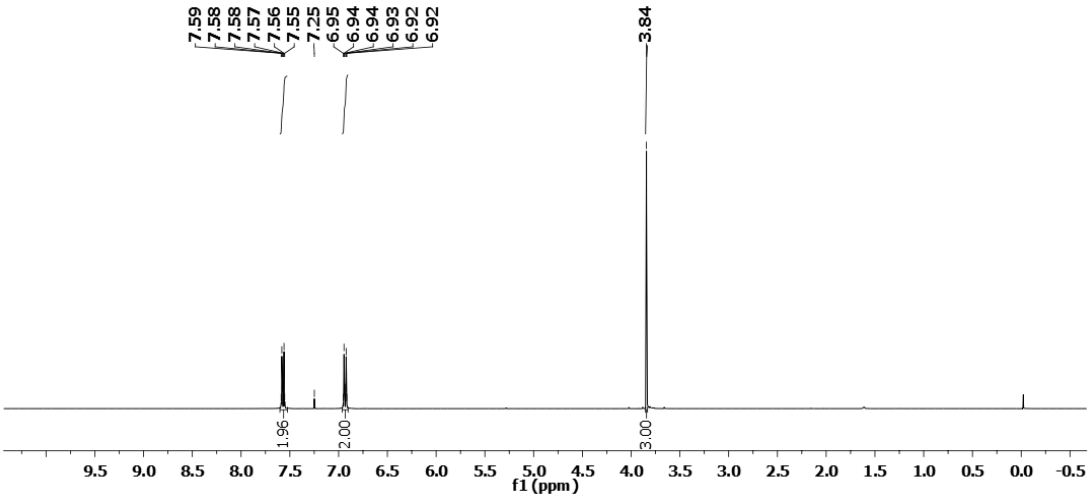


Figure 6.3

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



4-Methoxybenzonitrile (2b)



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

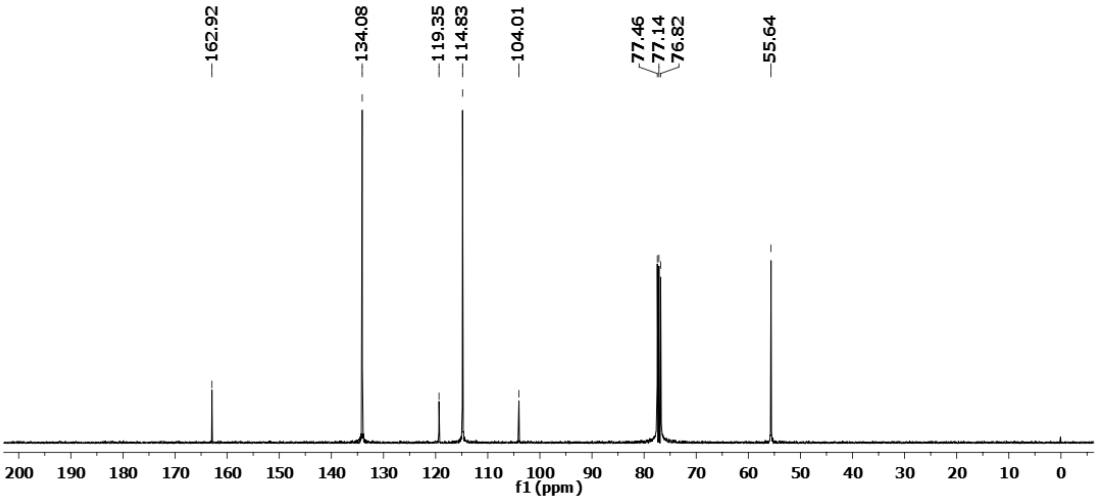
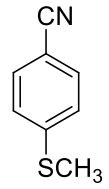
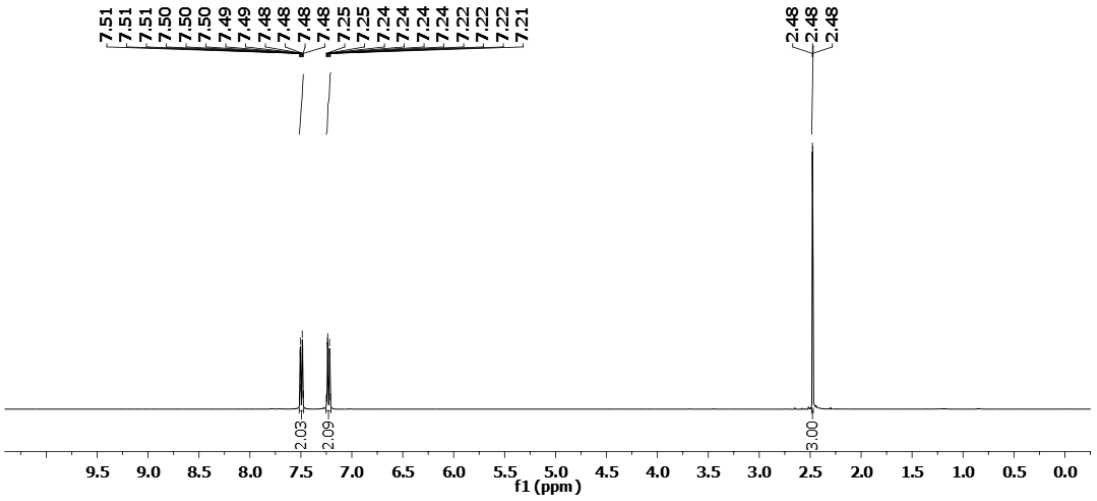


Figure 6.4

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



4-(methylthio)benzonitrile (2c)



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

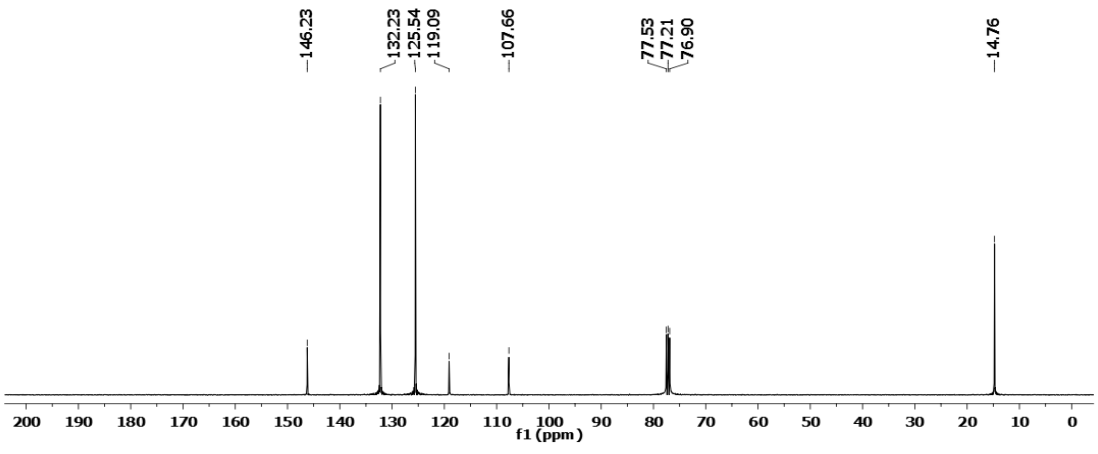
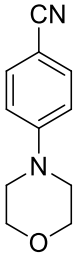
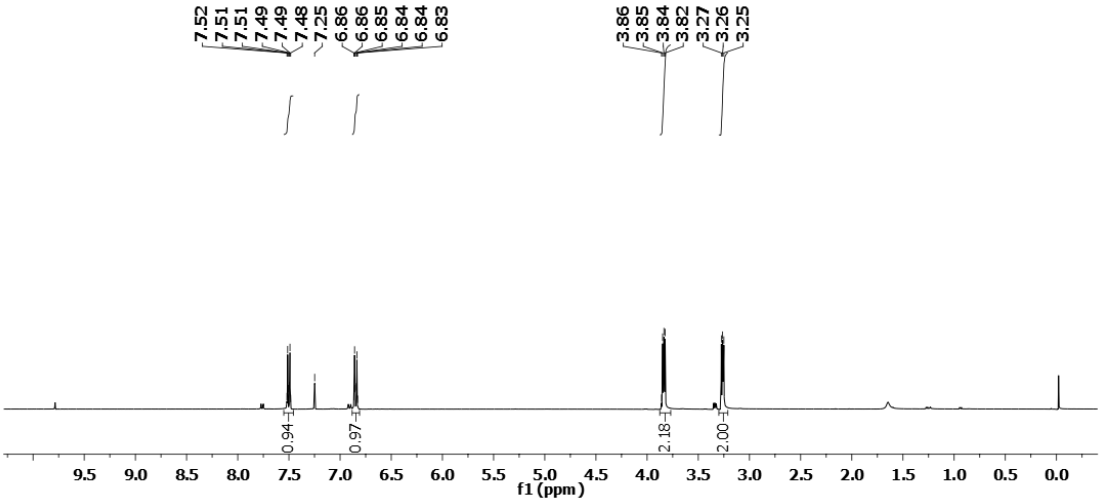


Figure 6.5

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



4-Morpholinobenzonitrile (2d)



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

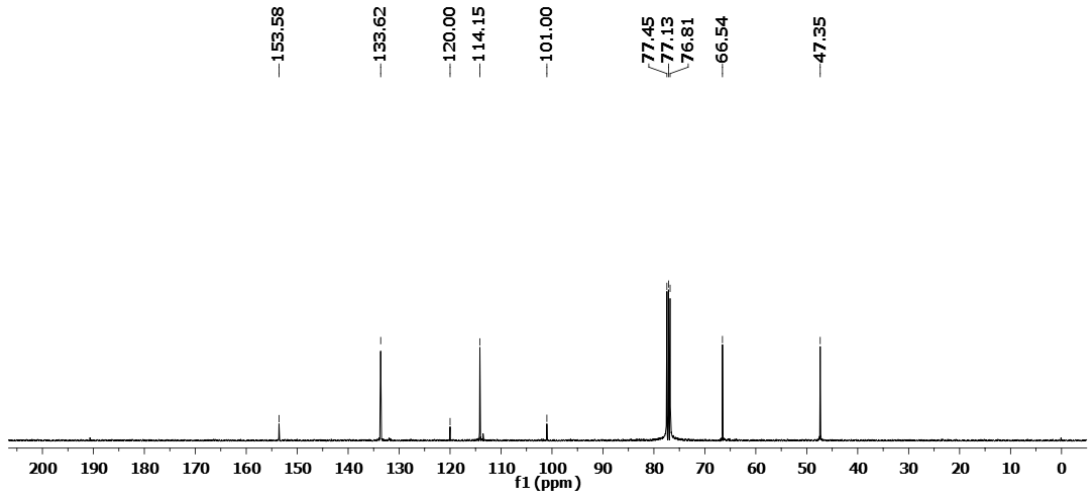
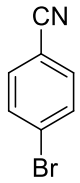
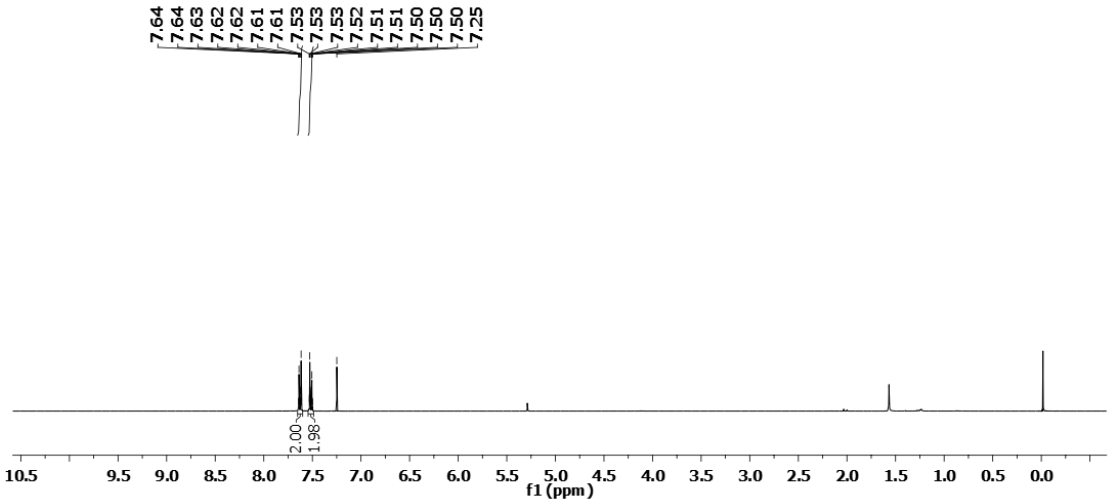


Figure 6.6

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



4-Bromobenzonitrile(2e)



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

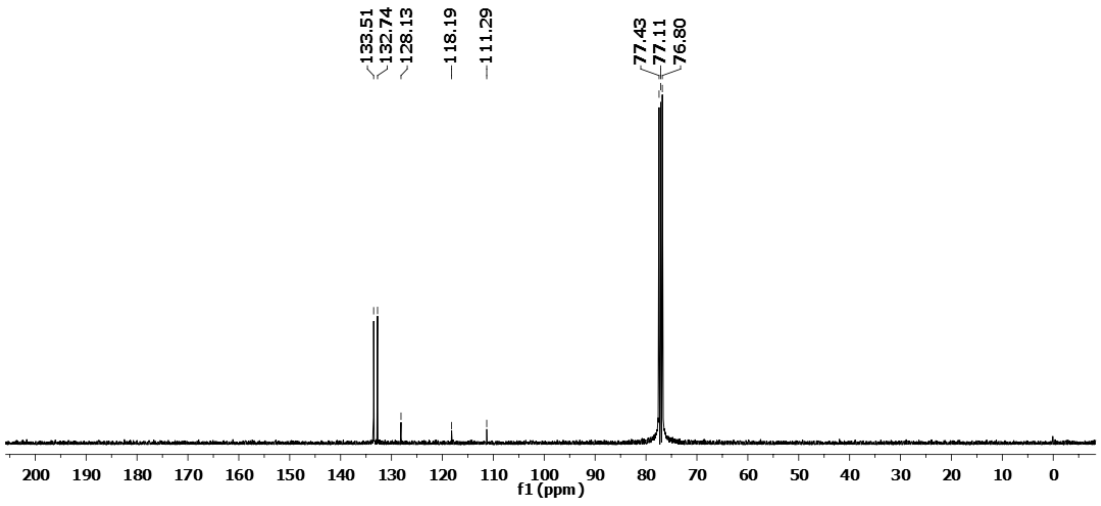
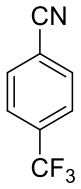


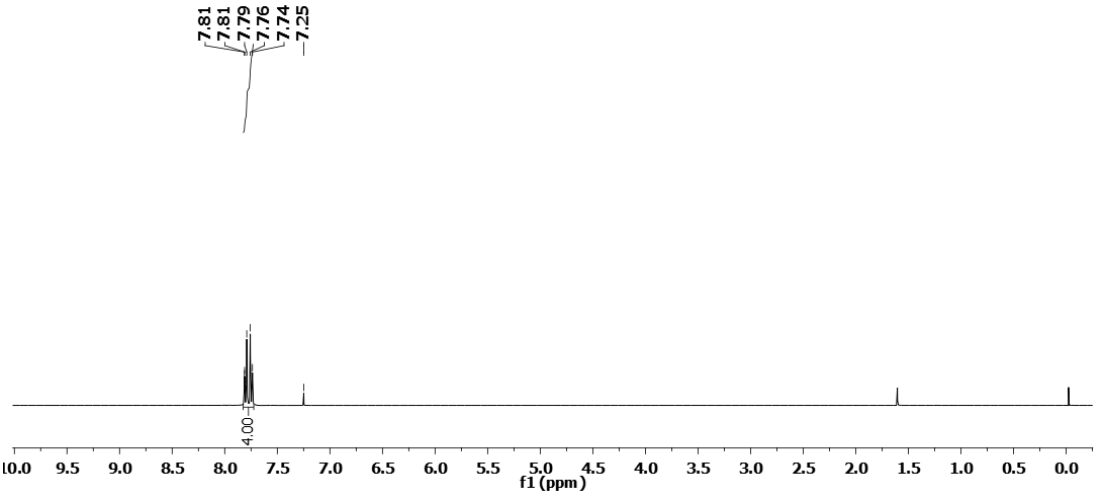
Figure 6.7

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



4-(trifluoromethyl)benzonitrile(2f)

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



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

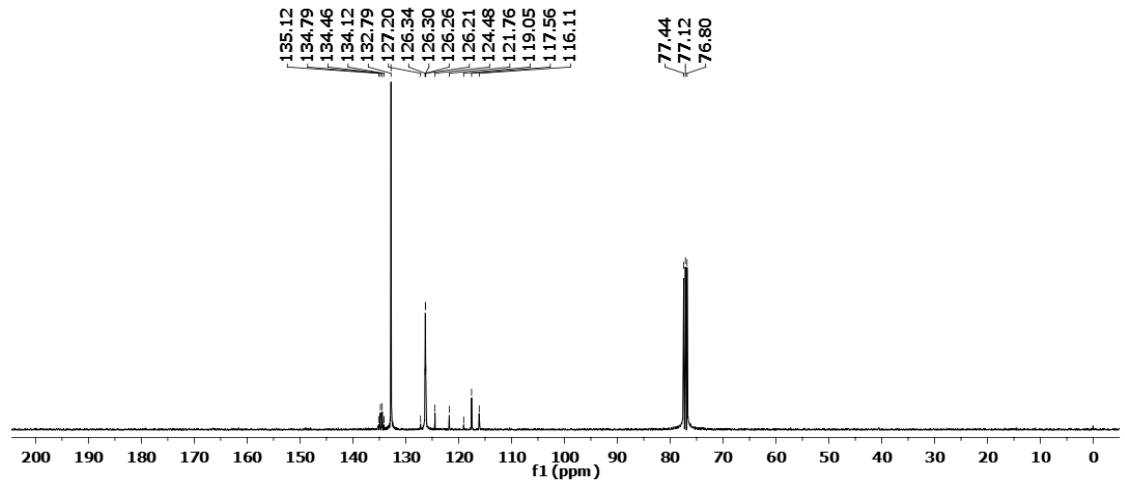
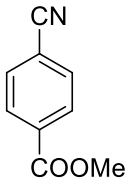


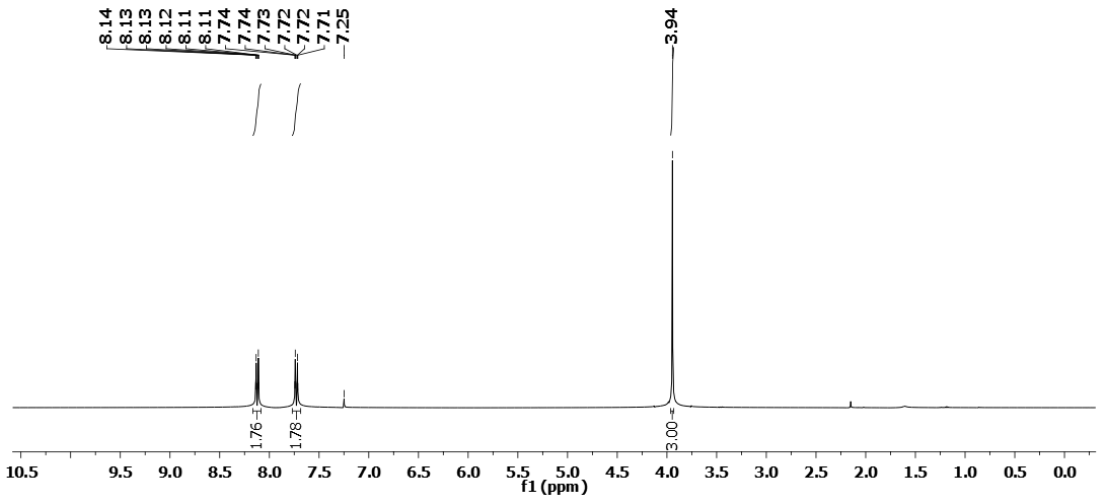
Figure 6.8

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



Methyl 4-cyanobenzoate(2g)

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



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

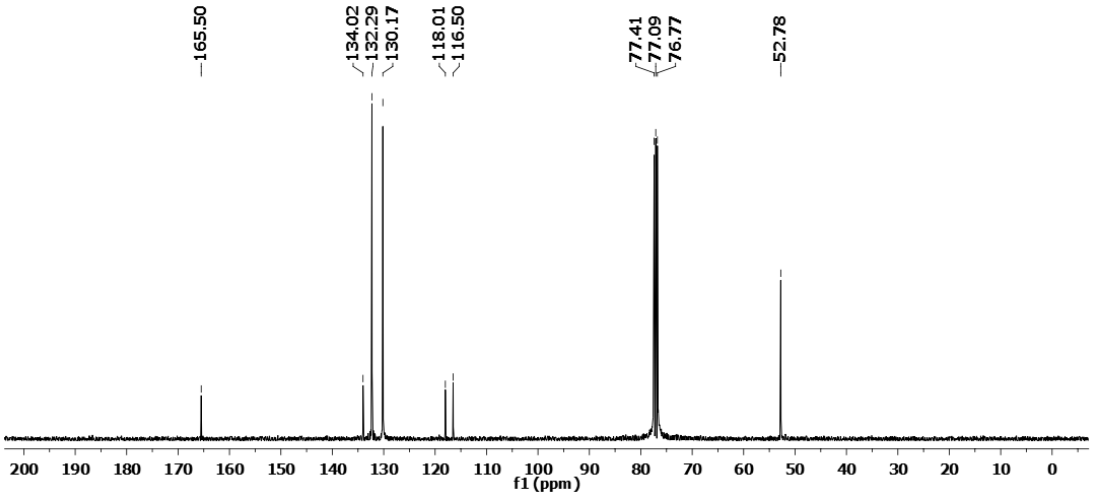
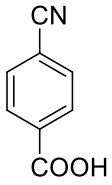
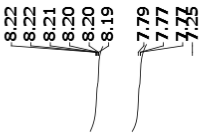


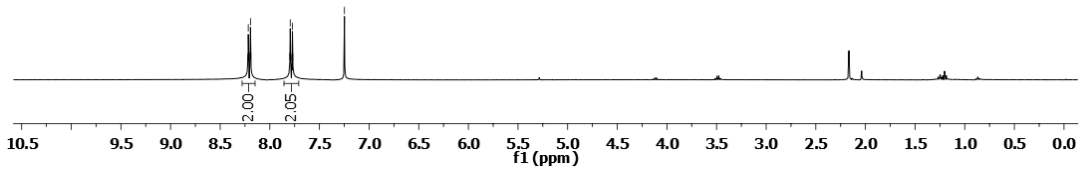
Figure 6.9

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



4-Cyanobenzoic acid(2h)





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

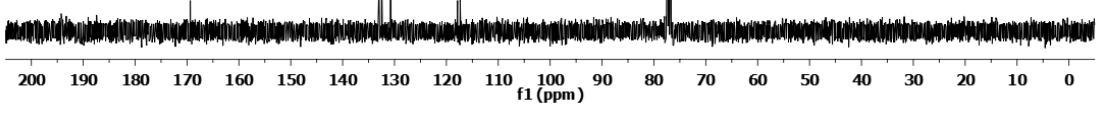
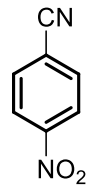
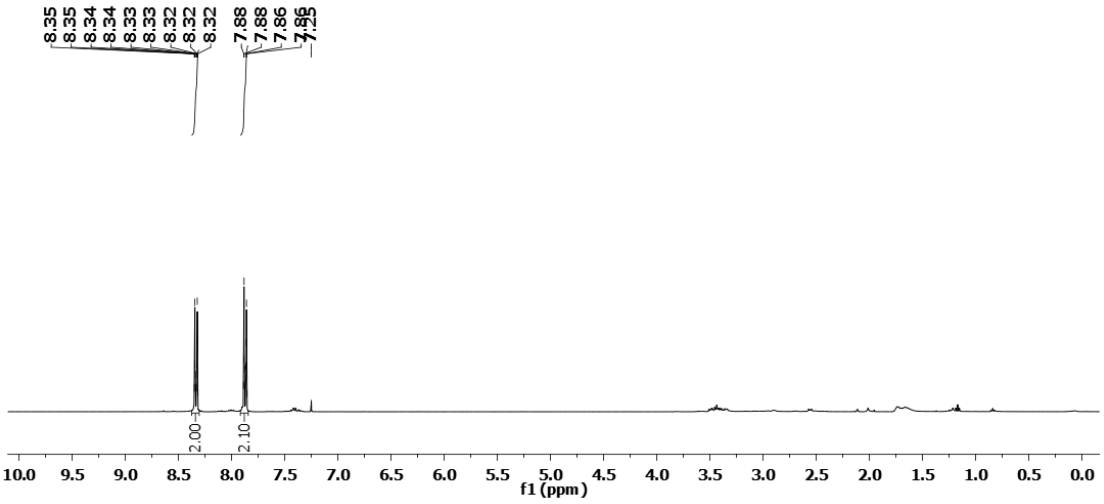


Figure 6.10

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



4-Nitrobenzonitrile (2i)



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

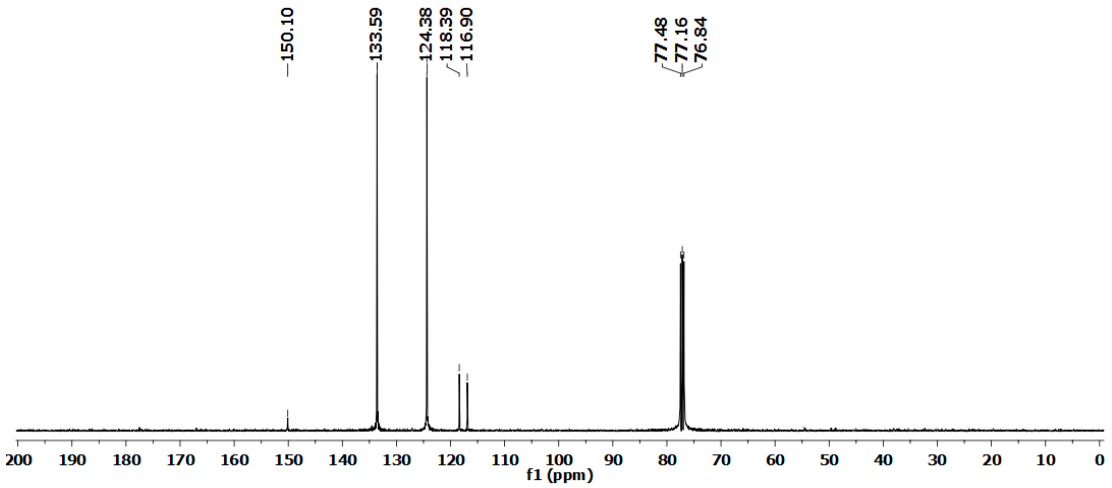
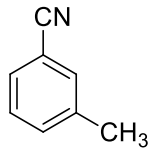
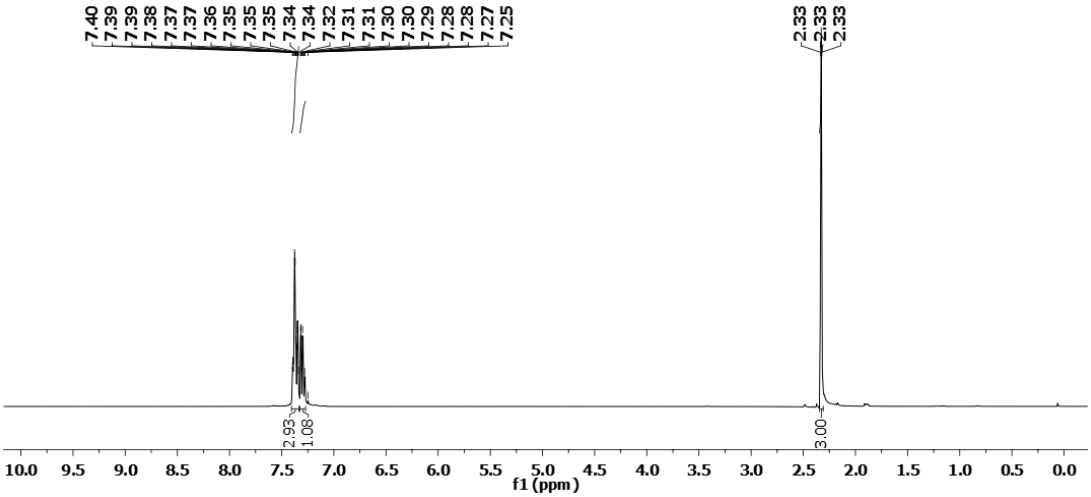


Figure 6.11

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



3-Methylbenzonitrile (2j)



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

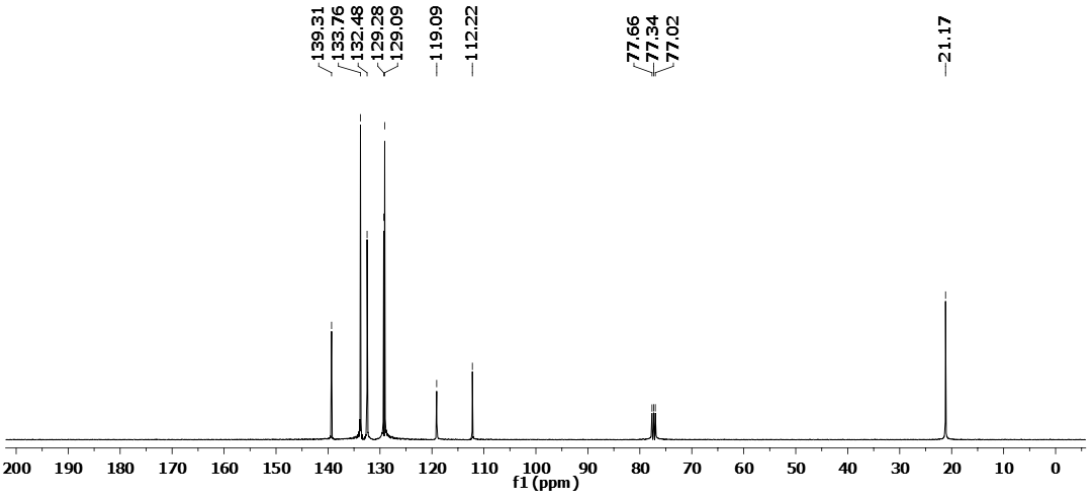
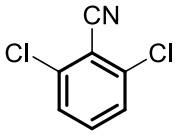
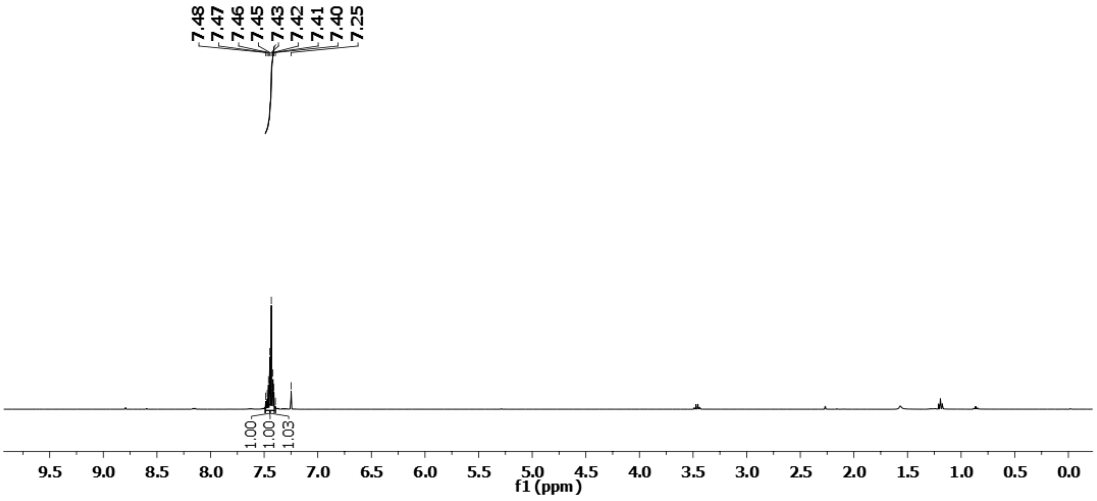


Figure 6.12

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



2,6-Dichlorobenzonitrile (2k)



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

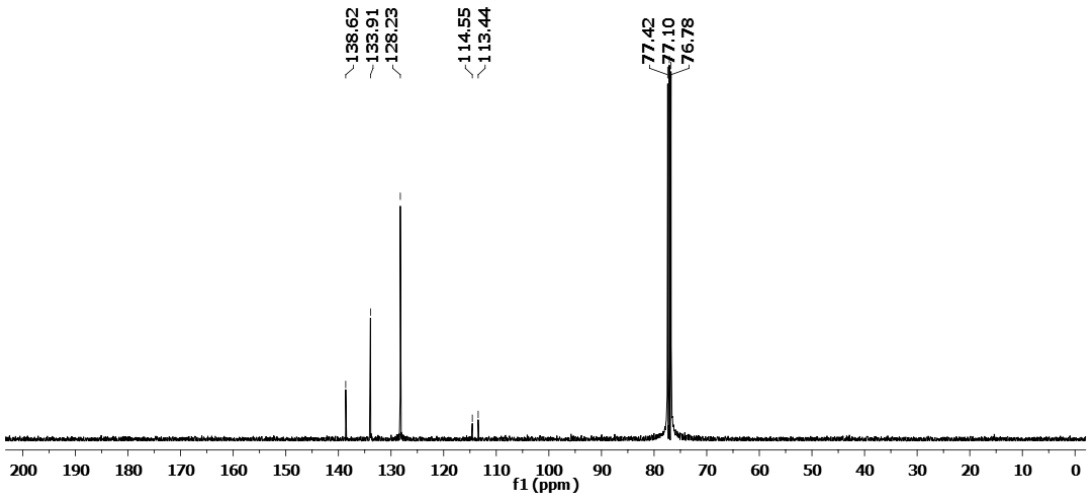
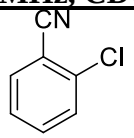
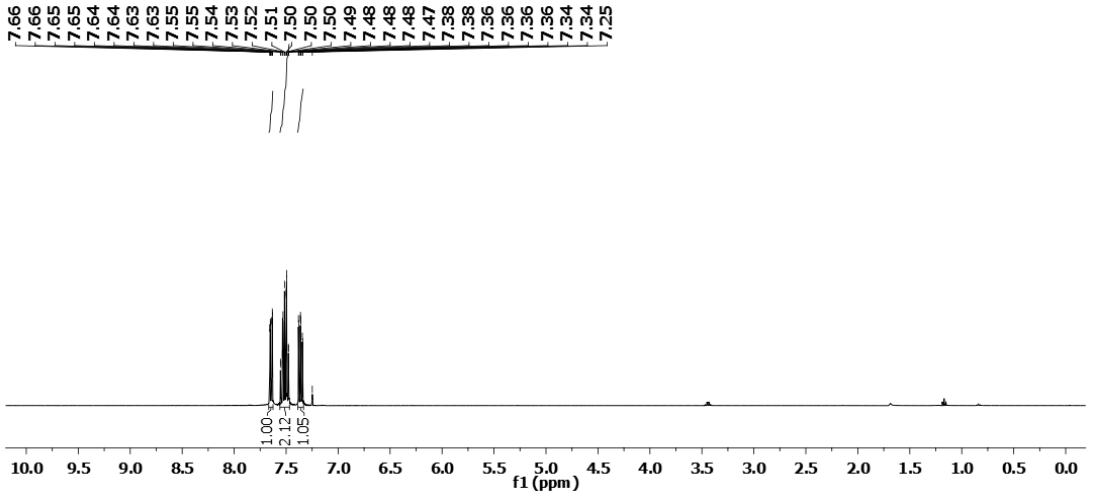


Figure 6.13

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



2-Chlorobenzonitrile (2l)



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

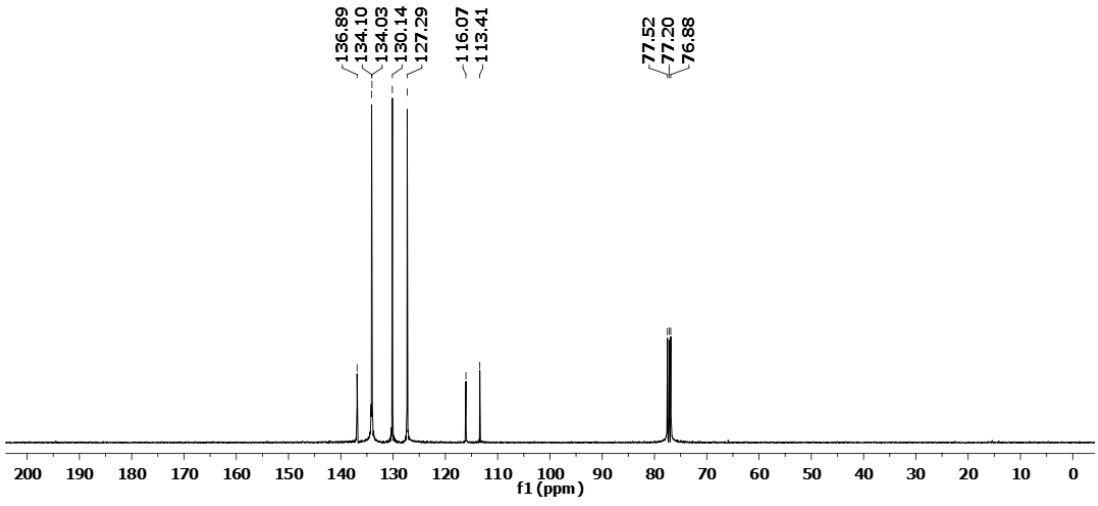
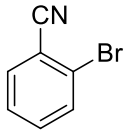
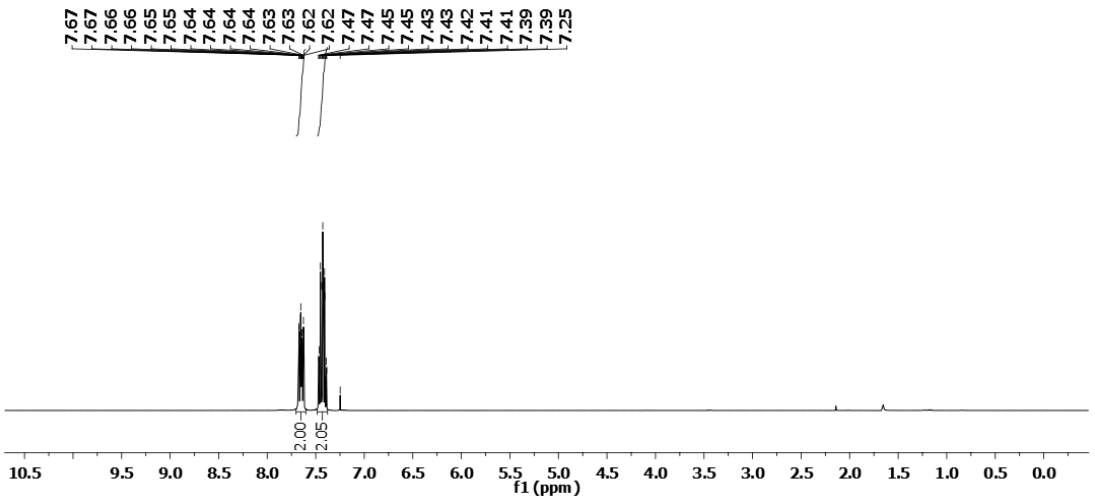


Figure 6.14

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



2-Bromobenzonitrile (2m)



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

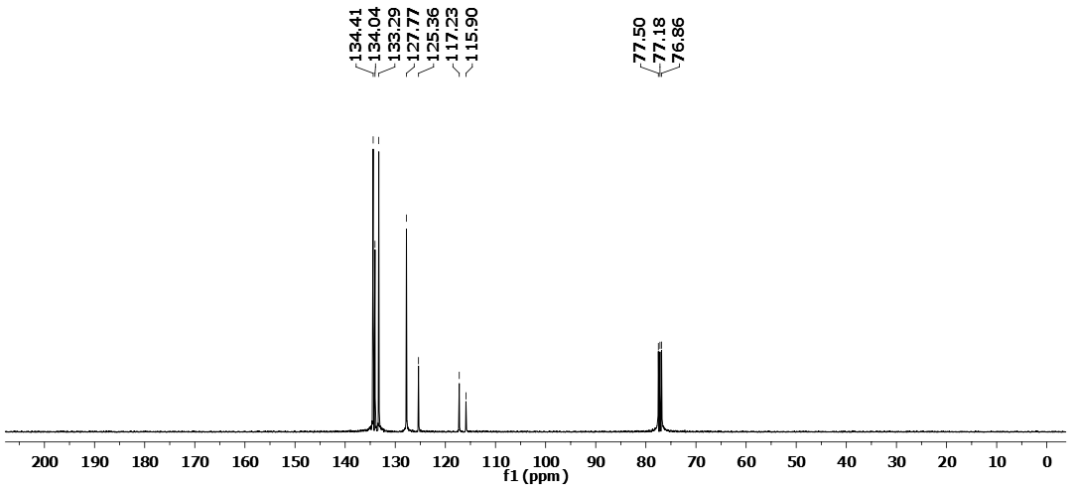
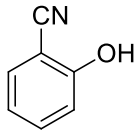
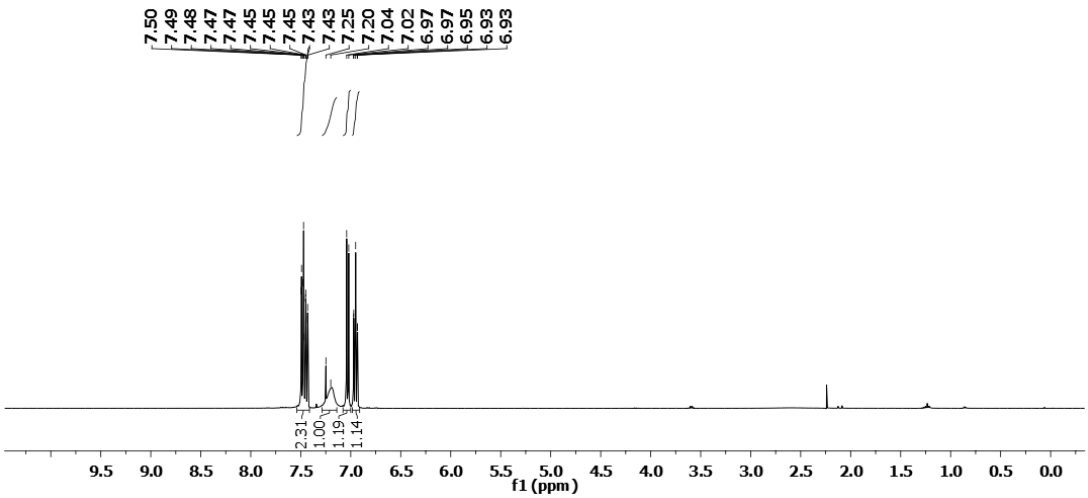


Figure 6.15

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



2-Hydroxybenzonitrile(2n)



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

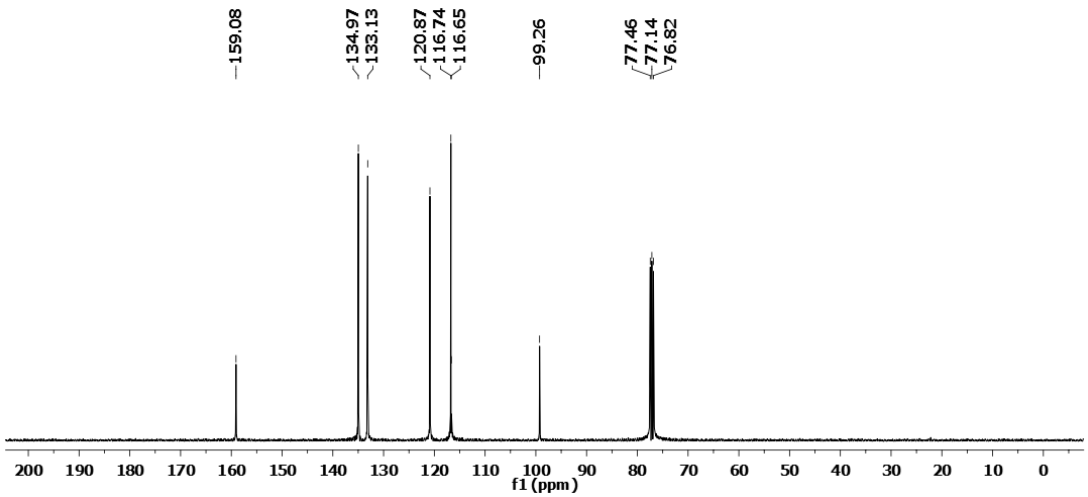
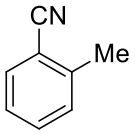
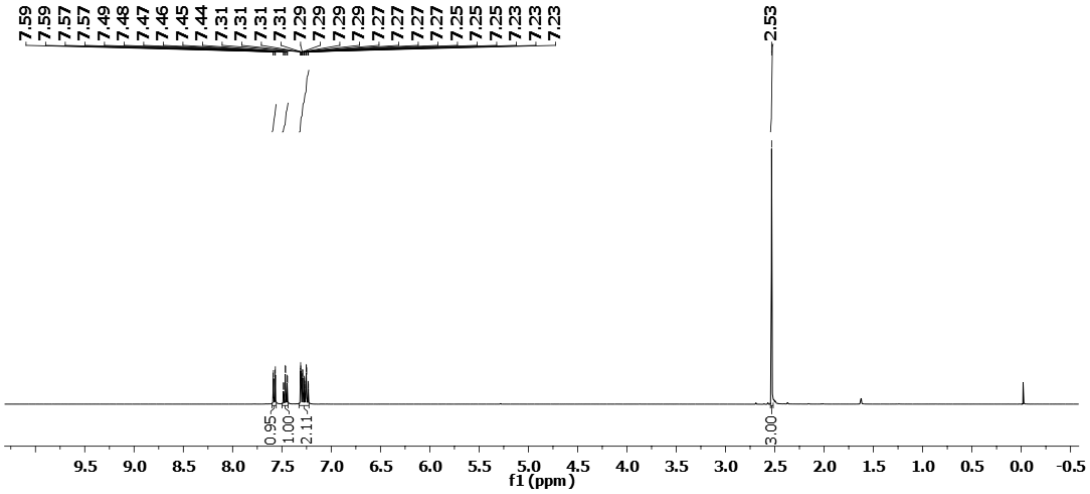


Figure 6.16

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



2-Methylbenzonitrile(2o)



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

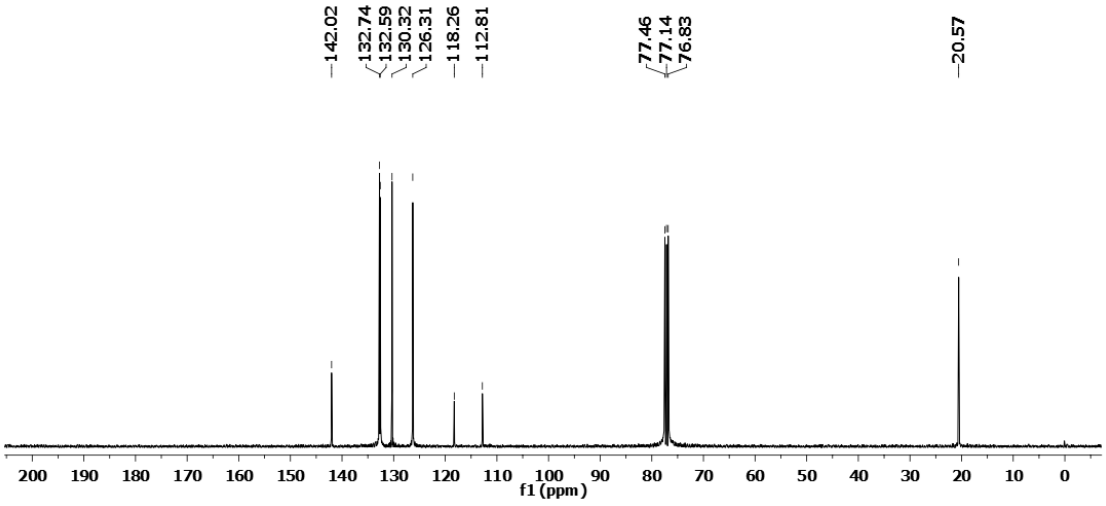
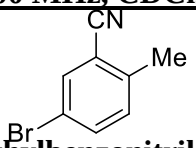
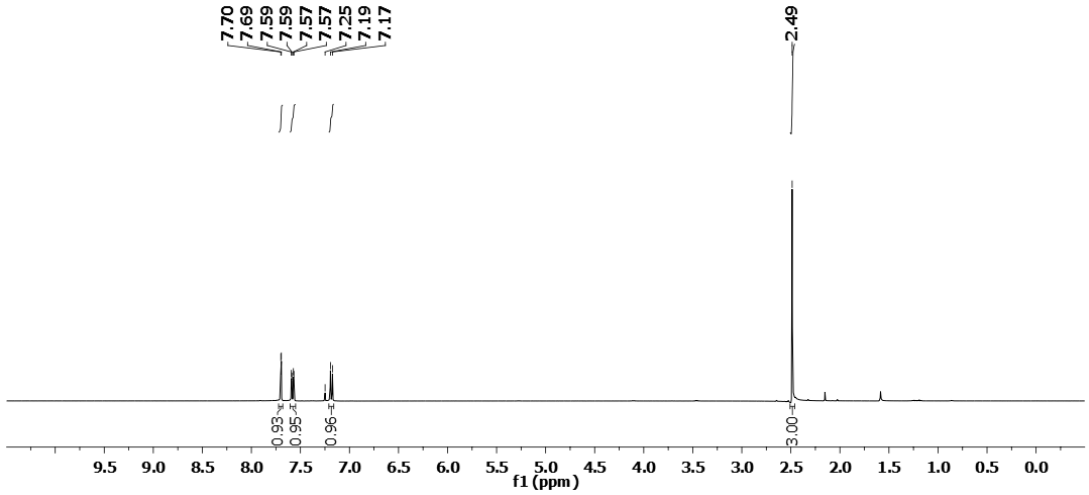


Figure 6.17

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



5-Bromo-2-Methylbenzonitrile(2p)



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

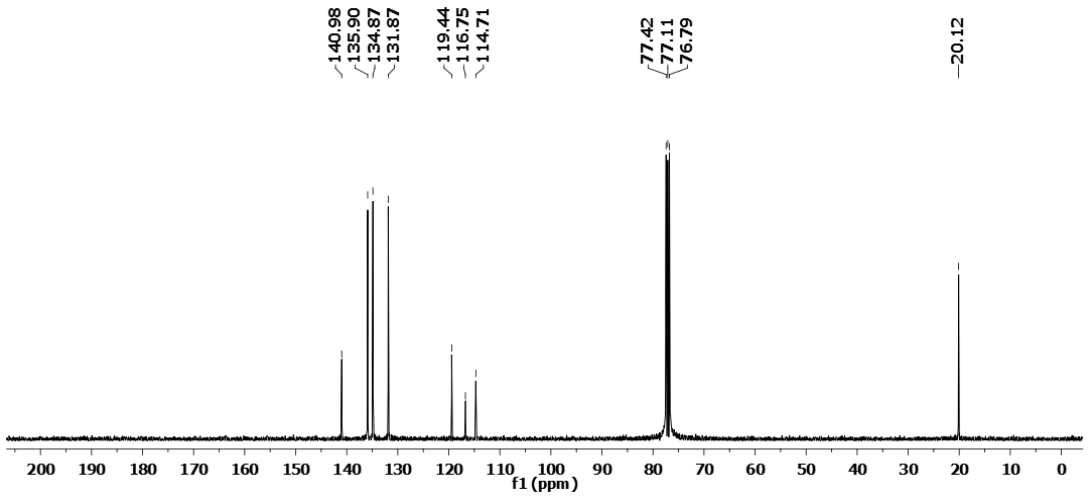
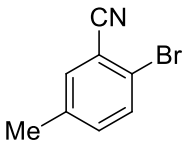
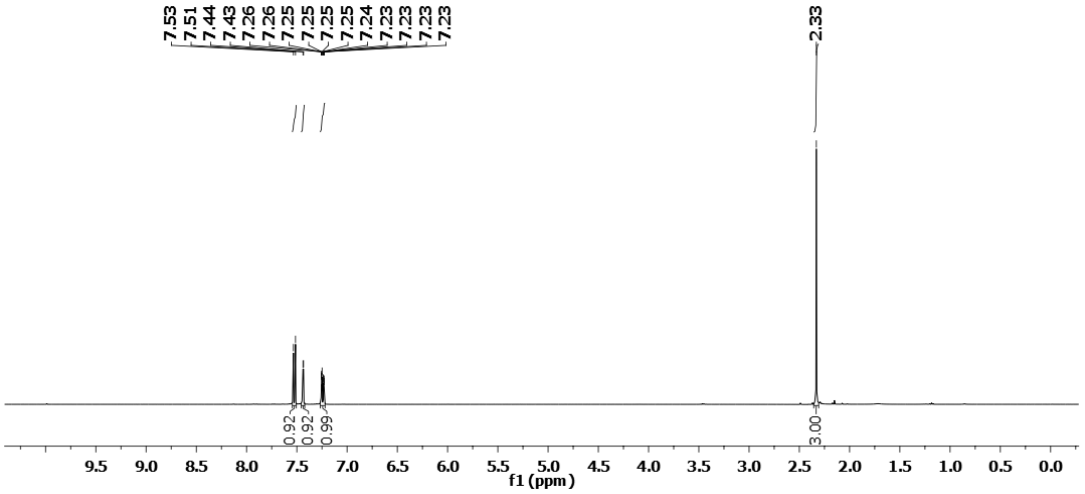


Figure 6.18

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



2-Bromo-5-Methylbenzonitrile(2q)



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

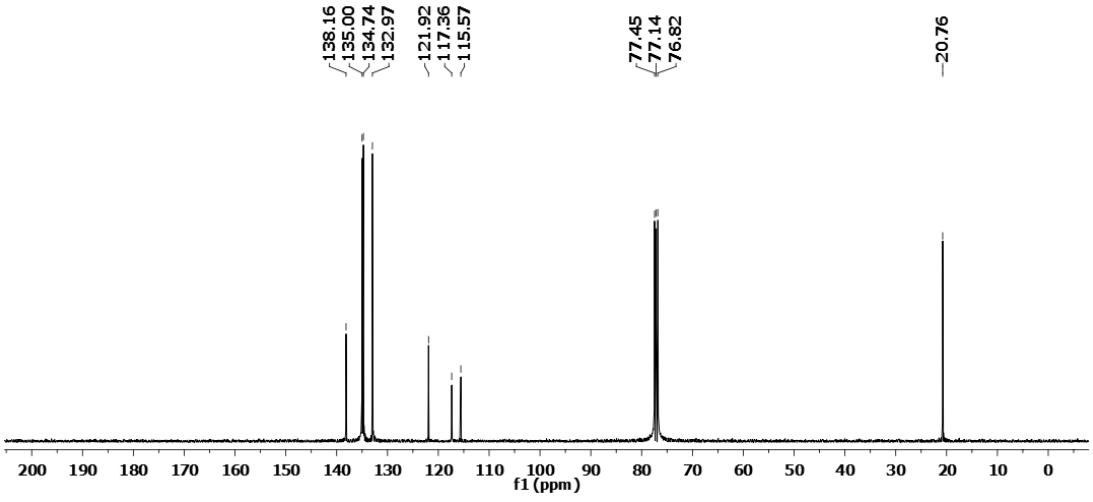
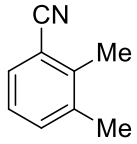
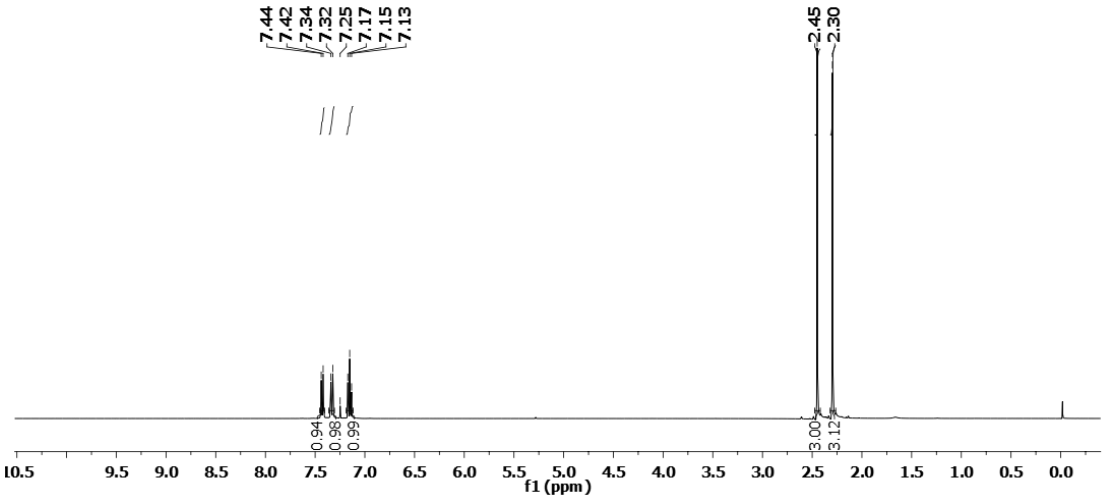


Figure 6.19

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



2,3-Dimethylbenzonitrile(2r)



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

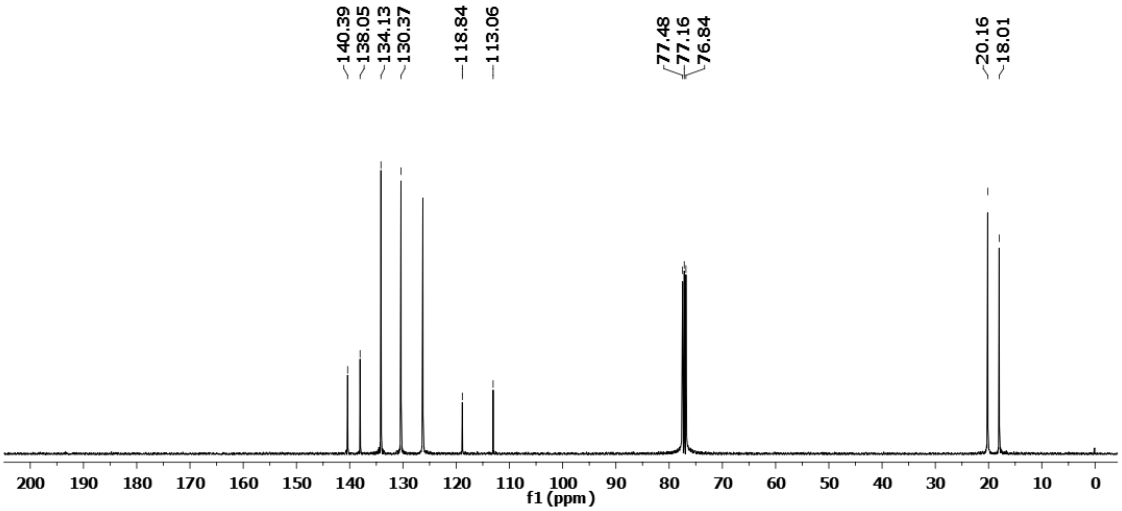
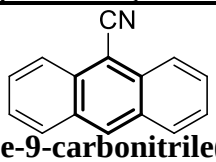
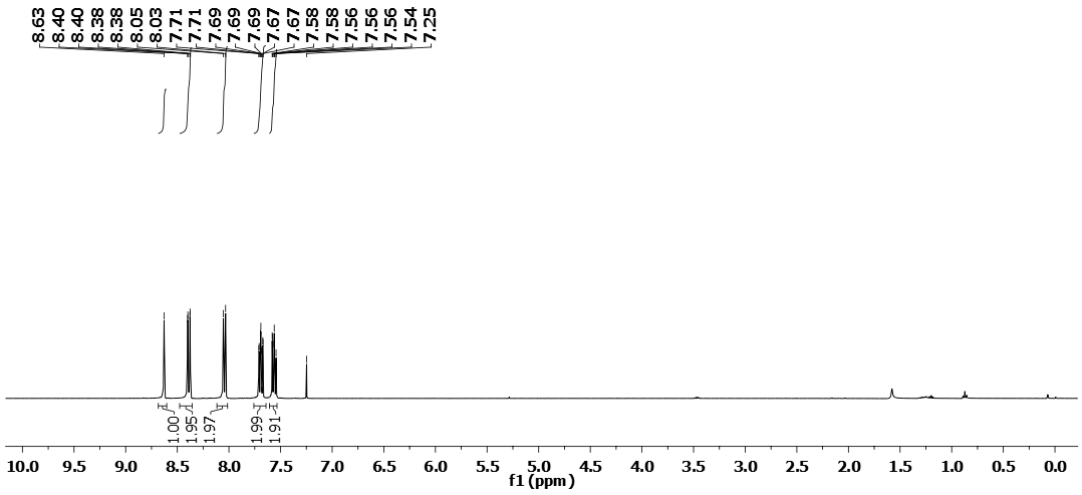


Figure 6.20

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



Anthracene-9-carbonitrile(2s)



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

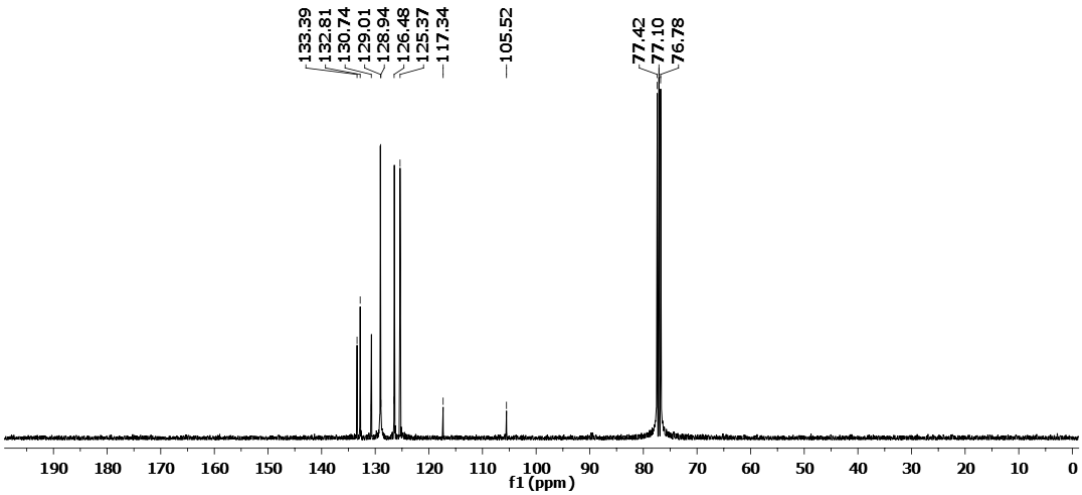
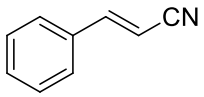
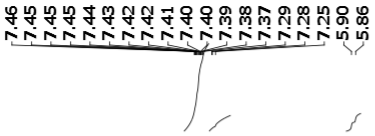


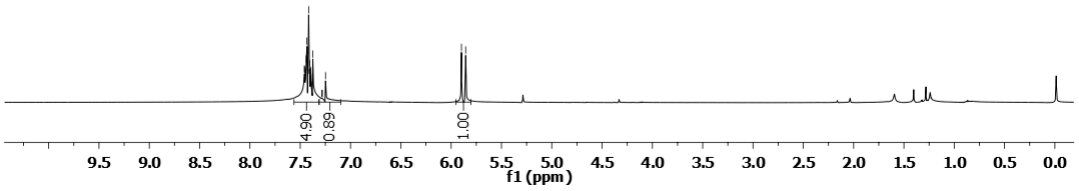
Figure 6.21

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



Cinnamonitrile(2t)





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

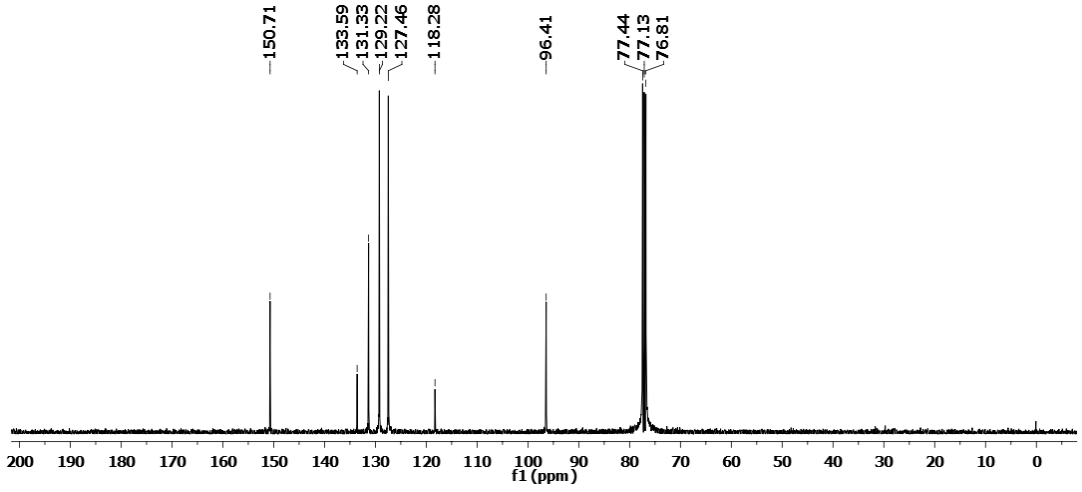
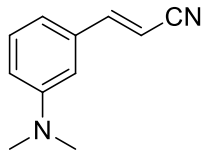
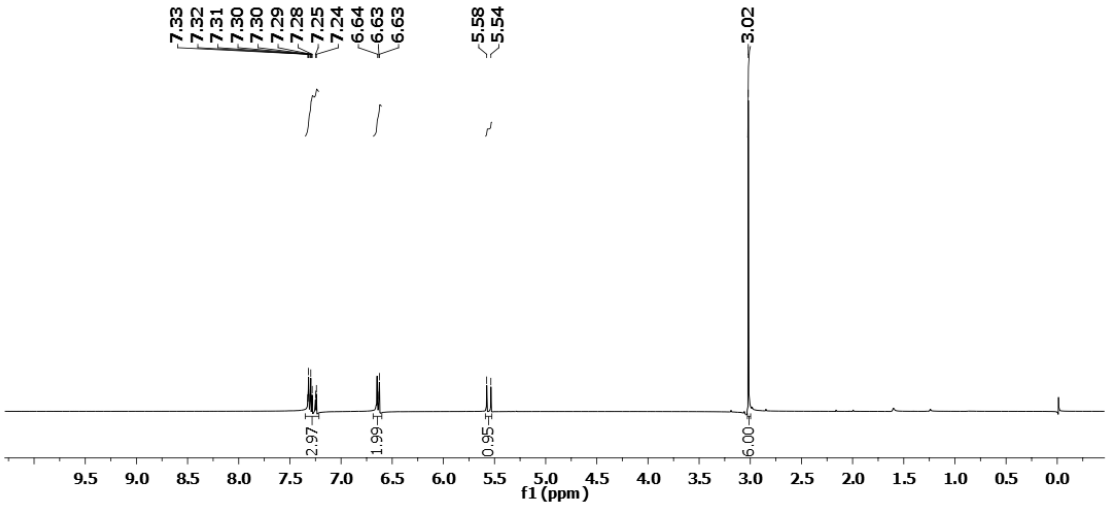


Figure 6.22

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



4-Dimethylamino Cinnamonitrile(2u)



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

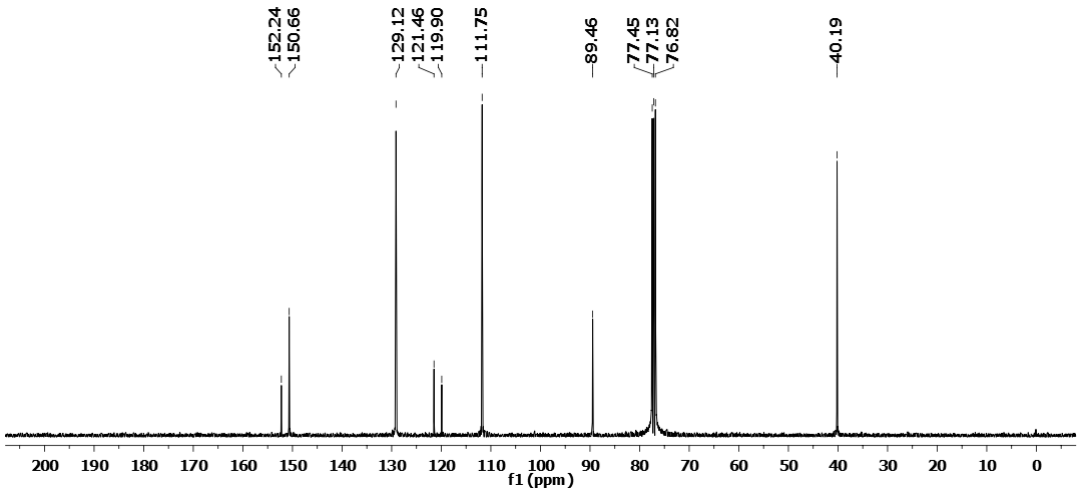
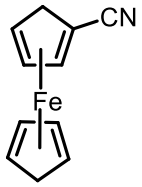
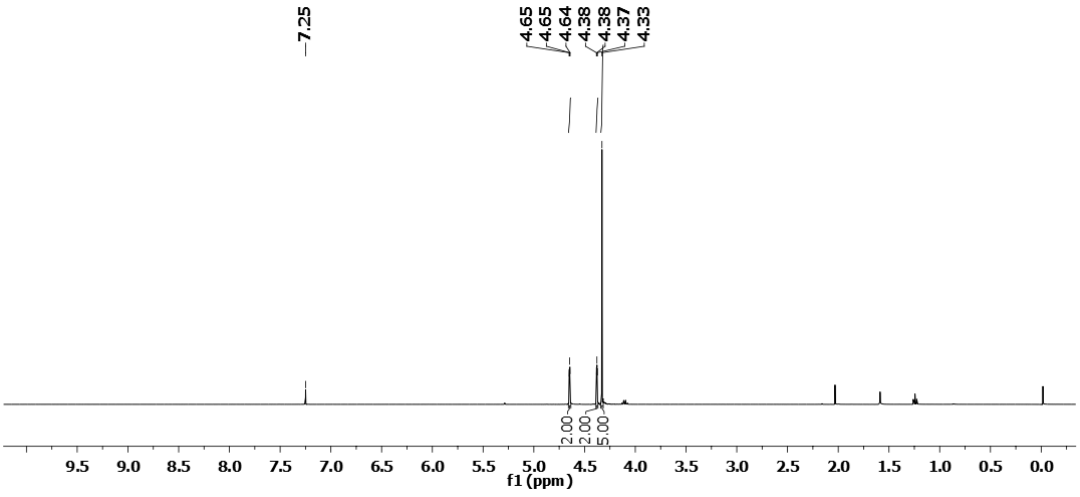


Figure 6.23

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



Cyanoferrocene(2v)



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

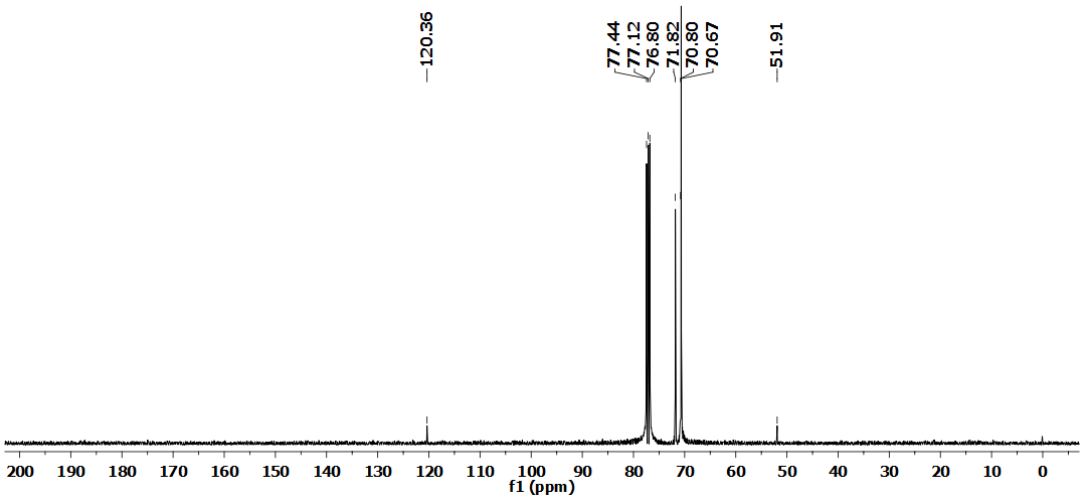
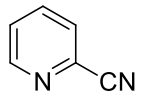
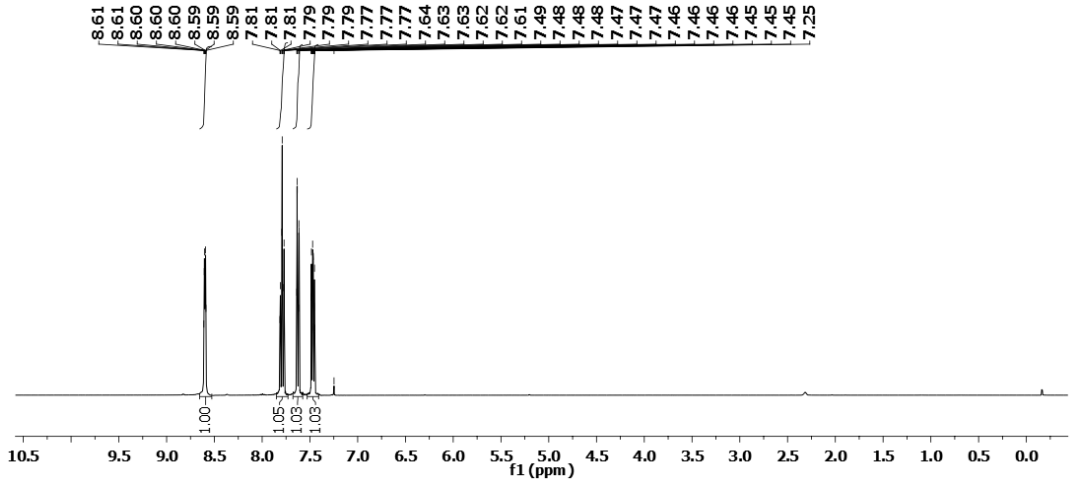


Figure 6.24

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



Picolinonitrile(4a)



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

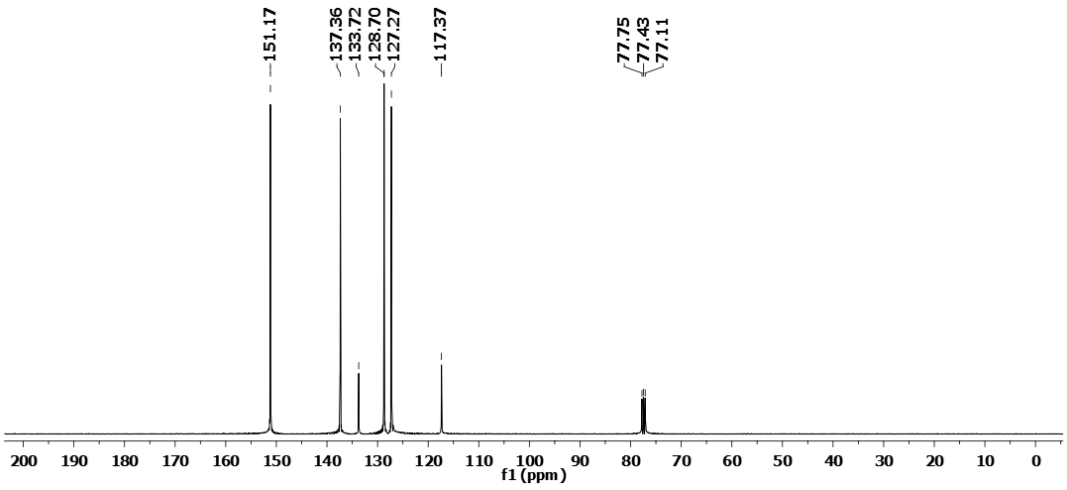
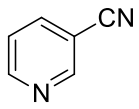
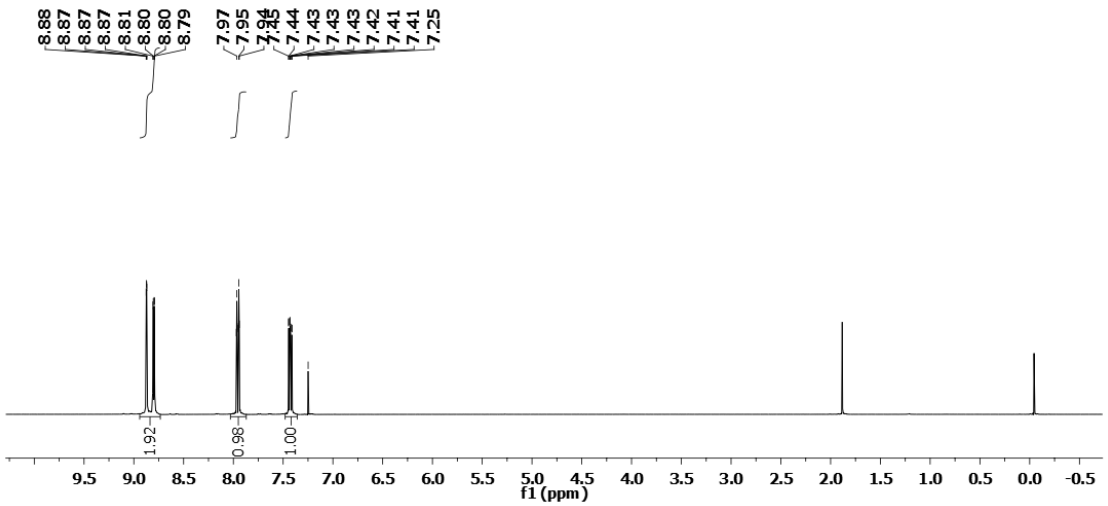


Figure 6.25

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



Nicotinonitrile(4b)



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

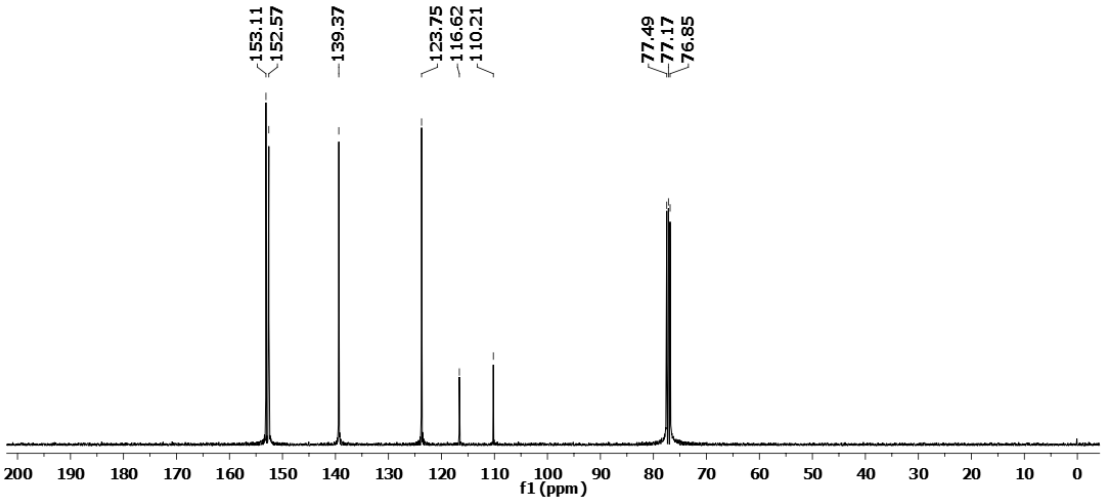
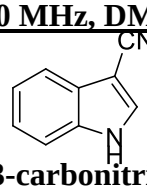
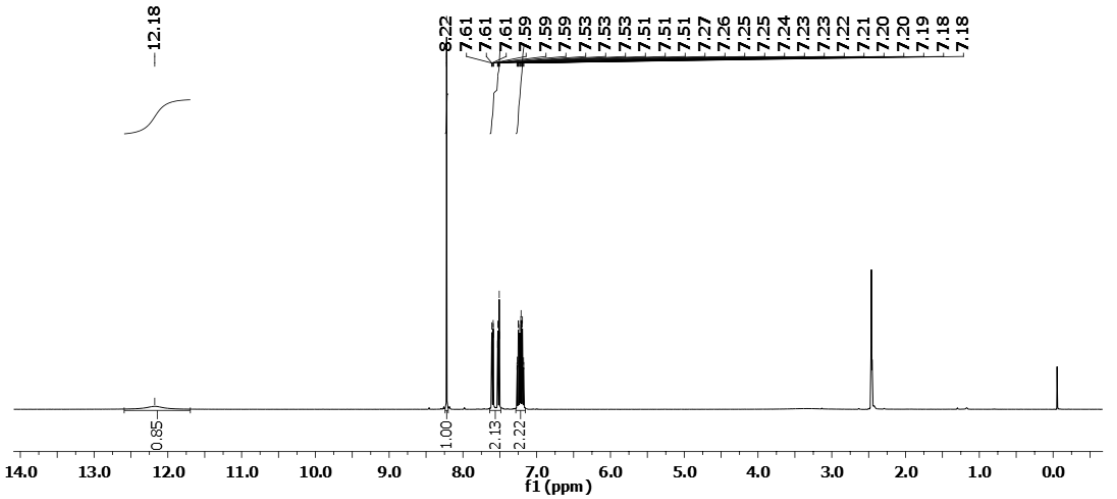


Figure 6.26

^{1}H NMR (400 MHz, DMSO-d_6)



1H-indole-3-carbonitrile(4c)



^{13}C NMR (100 MHz, DMSO-d_6)

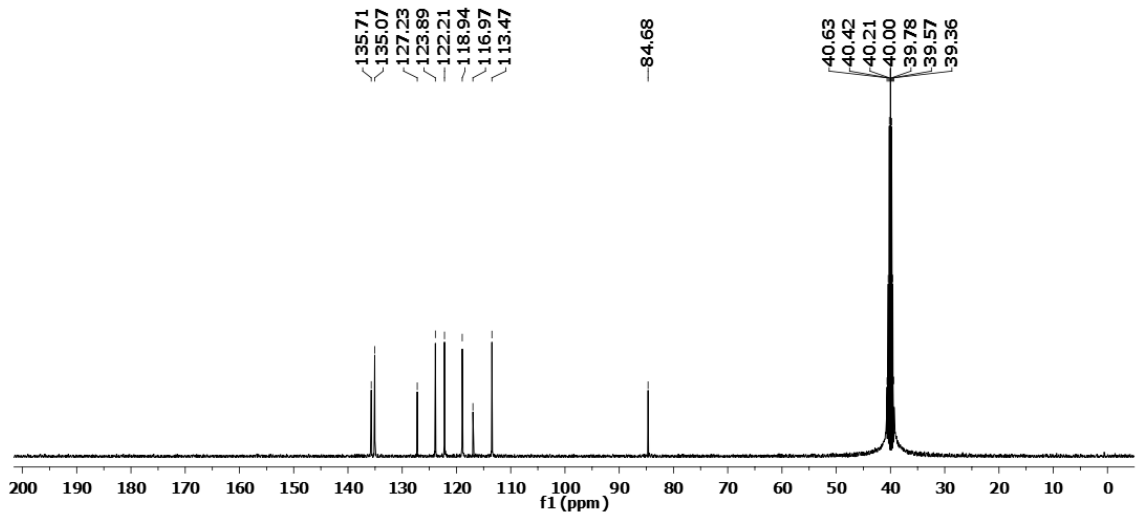
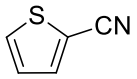
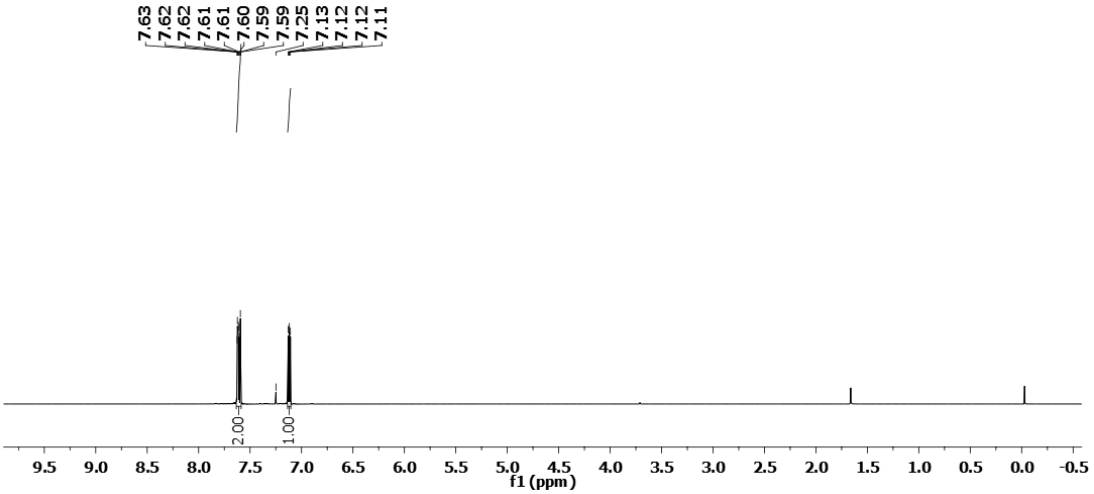


Figure 6.27

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



Thiophene-2-carbonitrile(4d)



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

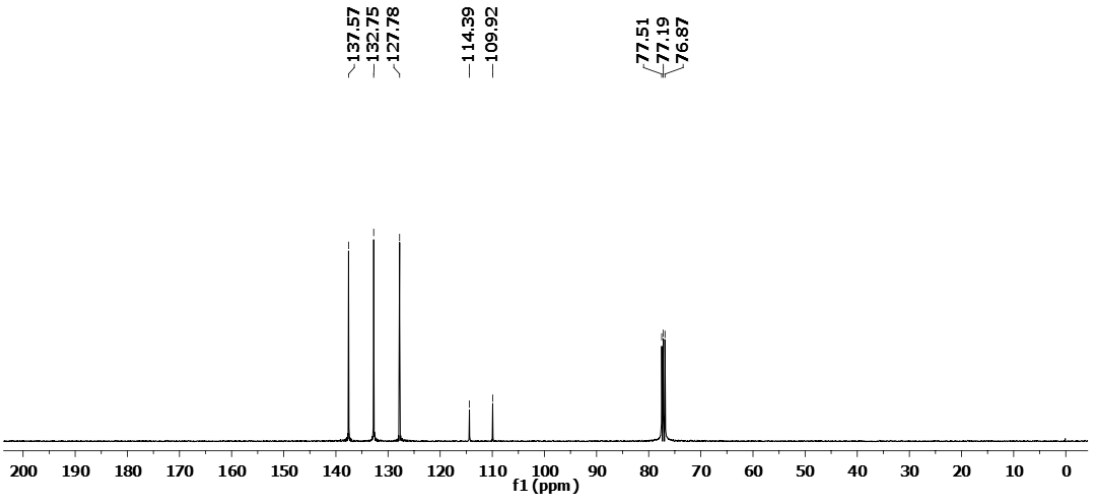
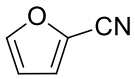
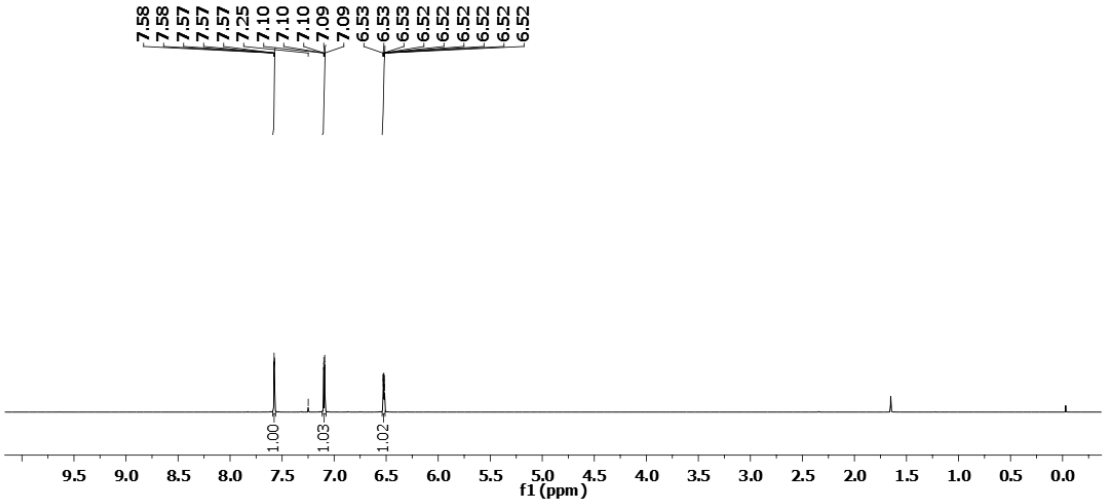


Figure 6.28

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



Furan-2-carbonitrile(4e)



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

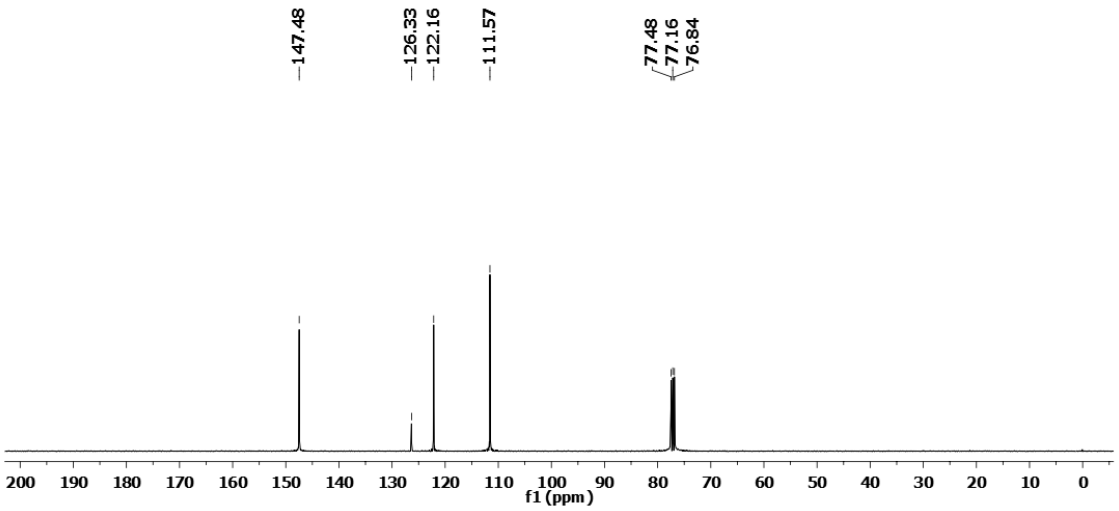


Figure 6.29

List of Publications

LIST OF PUBLICATIONS

- Saurav Kumar, Nityananda Agasti, Gajendra Singh and Anil Kumar, "Base-Mediated N-Acetylation of Anilines/Amines: Nitriles as a Surrogate of the Acetyl Group" *ChemistrySelect,* **2023**, 8, e202204679.

- Saurav Kumar, Jyoti, Deepak Gupta, Gajendra Singh and Anil Kumar, "A Decade of Exploration of Transition-Metal-Catalyzed Cross-Coupling Reactions: An Overview" *Syn Open*, **2023**, 7, 580-614.

- Saurav Kumar, Ritika Kubba, Nityananda Agasti, Anitha Selvaraj, Anil Kumar, "Potassium *tert*-butoxide promoted a direct one-pot synthesis of nitriles from aldehydes at room temperature" *J. Chem. Sci*, **2024**, 136, 1-6.

PROOFS OF PUBLICATIONS

ChemistrySelect | Research Article
doi.org/10.1002/slct.202204679
Chemistry Europe
European Chemical Societies Publishing
www.chemistryselect.org

Base-Mediated *N*-Acetylation of Anilines/Amines: Nitriles as a Surrogate of the Acetyl Group

Saurav Kumar,[a] Nityananda Agasti,[b] Gajendra Singh,[c] and Anil Kumar*[a]

A base-mediated protocol has been established for the *N*-acetylation of anilines/amines at room temperature. Reaction utilizes acetonitrile as a solvent as well as a surrogate of the acetyl group. Apart from acetonitrile, trifluoroacetonitrile could also be utilized in the reaction. The advantages of the reactions are simple operation, transition-metal-free approach, short reaction time, high functional group tolerance, and gram-scale synthesis, which show the reaction's utility. The developed strategy represents a valuable approach in synthetic organic chemistry.

SynOpen | S. Kumar et al. | THIEME OPEN ACCESS | Review

A Decade of Exploration of Transition-Metal-Catalyzed Cross-Coupling Reactions: An Overview

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Jyoti[a]
Deepak Gupta[a]
Gajendra Singh[b]
Anil Kumar*[a]

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X = H, Halogen, BR_2, SiR_3, SO_2R, NR_2, COOH etc.
Y = H, NH, OH, SH, PH, CH, RM, BR_2 etc.
R^1 = Alkyl, Aryl, Heteroaryl
R^2 = Alkyl, Aryl, Heteroaryl

J. Chem. Sci. (2024) 136:39
https://doi.org/10.1007/s12039-024-02282-6

REGULAR ARTICLE

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Potassium *tert*-butoxide promoted a direct one-pot synthesis of nitriles from aldehydes at room temperature

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MS received 4 March 2024; revised 8 April 2024; accepted 9 April 2024

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