SYNTHESIS OF IODO-SUBSTITUTED SPIRO-FUSED PYRIDINE DERIVATIVES

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SYNTHESIS OF IODO-SUBSTITUTED SPIRO-FUSED PYRIDINE DERIVATIVES

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ABSTRACT

SYNTHESIS OF IODO-SUBSTITUTED SPIRO-FUSED PYRIDINE DERIVATIVES

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Spiro cyclic molecules have gained significance because of their biological activities and electronic properties. Spiro frameworks are present in importance natural products and optoelectronic materials. Moreover, due to steric strain, the presence of a spiro carbon atom induces easy rearrangements that can lead to different cyclic products. Although there are some methods to synthesize spiro compounds, the synthesis of iodo-substituted spiro-fused pyridines have not been studied. Accordingly, in this thesis, a new method for the synthesis of iodo-substituted spiro-fused pyridines have been developed via electrophilic cyclizations. After preparation of 5-alkynyl-4-(4-methoxyphenyl)pyridines, these derivatives were subjected to electrophilic cyclization in the presence of moleculer iodine and $NaHCO_3$, which afforded iodo-substituted spiro-fused pyridines. The reaction conditions have been optimized and the limitations, scope and mechanism of these cyclizations have been studied.

Keywords: Spiro compound, pyridine, *N*-propargylic *β*-enaminone, electrophilic cyclization.

ÖZ

İYOT BAĞLI SPİRO BİRLEŞİK PİRİDİN TÜREVLERİNİN SENTEZİ

Teke, Ecem
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Zora

Şubat 2014, 109 sayfa

Spiro halkalı bileşikler biyolojik aktiviteleri ve elektronik özellikleri açısından önemli bir yere sahiptir. Spiro yapılar doğal ürünlerde ve organik optoelektronik maddelerde bulunmaktadır. Sterik etkiden dolayı spiro karbon atomu kolayca düzenlemelere girebilir, bu da çeşitli halkalı bileşikleri oluşturabilir. Bugüne kadar spiro bileşiklerin sentezi üzerine bir çok çalışma yapılmasına rağmen iyot bağlı spiro birleşik piridin türevleri henüz çalışılmamıştır. Bu tezde iyot bağlı spiro birleşik piridinlerin sentezi için elektrofilik halkalaşma ile yeni bir yöntem geliştirilmiştir. 5-Alkinil-4-(4-metoksifenil)piridin bileşikleri hazırlandıktan sonra bu türevler moleküler iyot ve $NaHCO_3$ varlığında elektrofilik halkalaşma tepkimesine sokularak iyot bağlı spiro birleşik piridin türevleri elde edilmiştir. Bu halkalaşma tepkimelerinin koşulları optimize edilmiş, yöntemin limitleri ve mekanizmaları çalışılmıştır.

Anahtar Kelimeler: Spiro bileşik, piridin, *N*-proparjilik *β*-enaminon, elektrofilik halkalaşma.

To My Dear Family

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ABBREVIATIONS

ACN	acetonitrile
br	broad (spectral)
d	doublet (spectral)
DCM	dichloromethane
dd	doublet of doublet (spectral)
FT	fourier transform
Hz	hertz
J	coupling constant
m	multiplet (spectral)
min	minute(s)
PBD	(2-(4-biphenylyl)-5-(4-tert-butylphenyl)-1,3, 4-oxadiazole)
ppm	parts per million (in NMR)
q	quartet (spectral)
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)
TAD	2,2′,7,7′-tetrakis(*N*,*N*-diphenylamino)-9,9-spirobifluorene
THF	tetrahydrofuran
TLC	thin layer chromatography
δ	chemical shift in parts per million downfield from

CHAPTER 1

INTRODUCTION

Organic chemistry is the study of carbon compounds from a structural property, synthesis and reaction point of view. It intersects with many areas including biochemistry, biology, medicinal chemistry, organometallic chemistry, polymer and material chemistry. Biologically functional molecules are made up by organic compounds as well. Organic compounds are important constituents of many products including drugs, food, explosives, plastics, petrochemicals and paints.[1]

Most of organic compounds contain the rings of carbon atoms.[2] In fact, cyclic compounds occupy one of the important classes of organic compounds. The most common cyclic compounds are those of five and six membered rings, some examples of which are shown in Figure 1.[3]

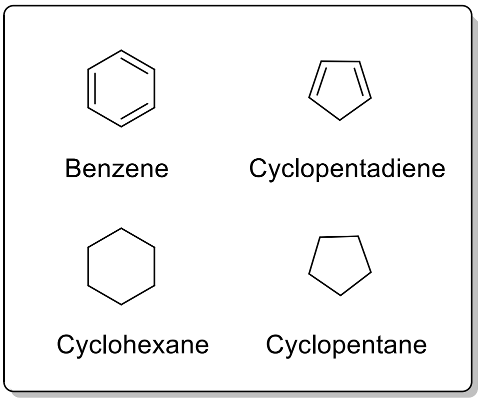


Figure 1. Examples of common cyclic compounds.

1.1 Heterocyclic compounds

Heterocyclic compounds include at least one heteroatom other than carbon in their cyclic skeletons. Heterocyclic compounds mostly contain nitrogen, oxygen and sulfur atoms in their structures.[6]

Heterocyclic compounds play an important role in pharmaceutical industry since they compose a broad range of drugs in human medicine. For instance, many antibiotics such as penicillin contain heterocyclic rings in their structures. Moreover, fundamental necessities of life as the provision of the energy, transmission of nerve impulses, metabolism and the transfer of hereditary information are based on chemical reactions involving the participation of many heterocyclic compounds. Cytosine, thymine, uracil, adenine and guanine derivatives are well known heterocycles on this matter. For instance, adenine and thymine molecules contain imidazole, purine and/or pyrimidine moieties in their structures, which participate the encoding off all genetic information (Figure 2).[4]

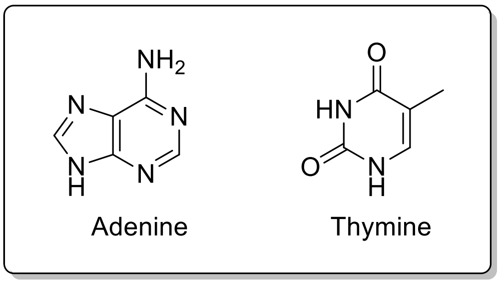


Figure 2. Structures of adenine and thymine heterocycles.

Recently, successful treatments with leaves, fruits, barks and herbs, derived from plants and animals, are frequently triggered by the presence of various types of heterocyclic compounds. One of the most naturally occurring compounds regarding these treatments is quinine (Figure 3), which has curing ability on parasitic diseases.

In fact, quinine is a derivative of quinolone and isoquinoline alkaloids, their structures of which are given in Figure 3.

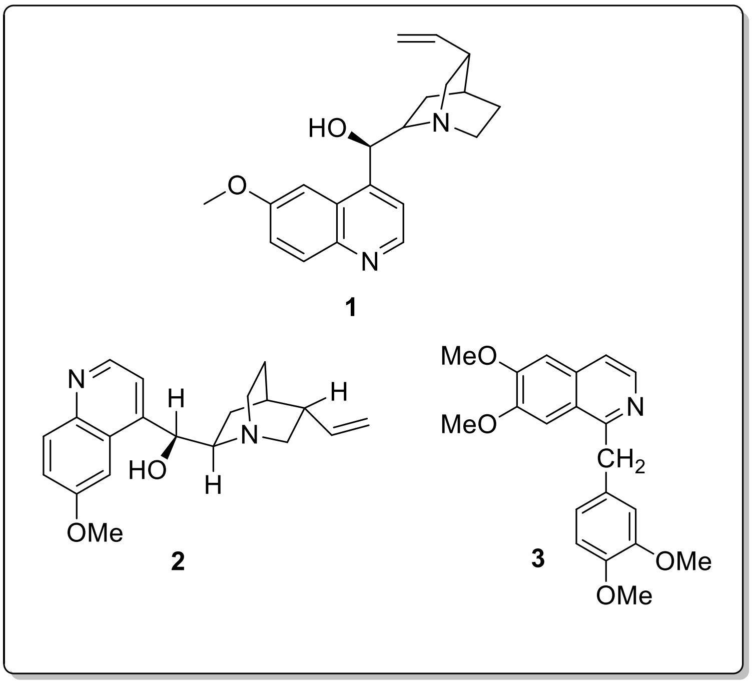


Figure 3. Structures of some quinine, quinoline and isoquinoline alkaloids.

Notably, heterocyclic alkaloids are the active ingredients in many pharmaceuticals.[5] Most of the alkaloids occur in plants.[6] Alkaloids are generally derived from either aromatic or hydrogenated heterocycles. Isoquinoline, pyridine, purine and quinazoline are well known alkaloids in this classification.

Heterocycles undergo many kinds of reactions. The versatile reactivity of heterocycles is related to their electron distributions in their structures. Moreover, the ability of some heterocycles to produce stable complexes with metal ions has attracted biochemical significance.

Heterocycles are critical for numerous applications including electronics, communications and aerospace technology. They also play an important role in more traditional branches of chemical industry such as dye manufacturing. Morover, the contribution of heterocycles to the polychromism is significant.[4]

Since heterocyclic compounds display a wide range of useful biological activities, they are generally designed according to medicinal activity studies and synthesized in the laboratory. Pyridine derivatives are one of such heterocyclic compounds.[6]

1.2 Pyridines

In 1846, pyridine was discovered by Anderson who isolated it in a pure state from bone oil. Pyridine is a six-membered heterocyclic molecule consisting of five carbon atoms and one nitrogen atom on its skeleton. The first synthesis of pyridine was achieved in 1876 from acetylene and hydrogen cyanide.[7] The demand for pyridine and its derivatives has increased significantly over the last fifty years due to the discovery of many pyridine containing bioactive compounds.[8]

Pyridines are often present in the structures of biomolecules including nucleotides and alkaloids. Vitamin B_6 and nicotinamide adenine dinucleotide phosphates have significant importance in biological processes (Figure 4). Pyridines are also present in the structures of many dyes and drugs.[6]

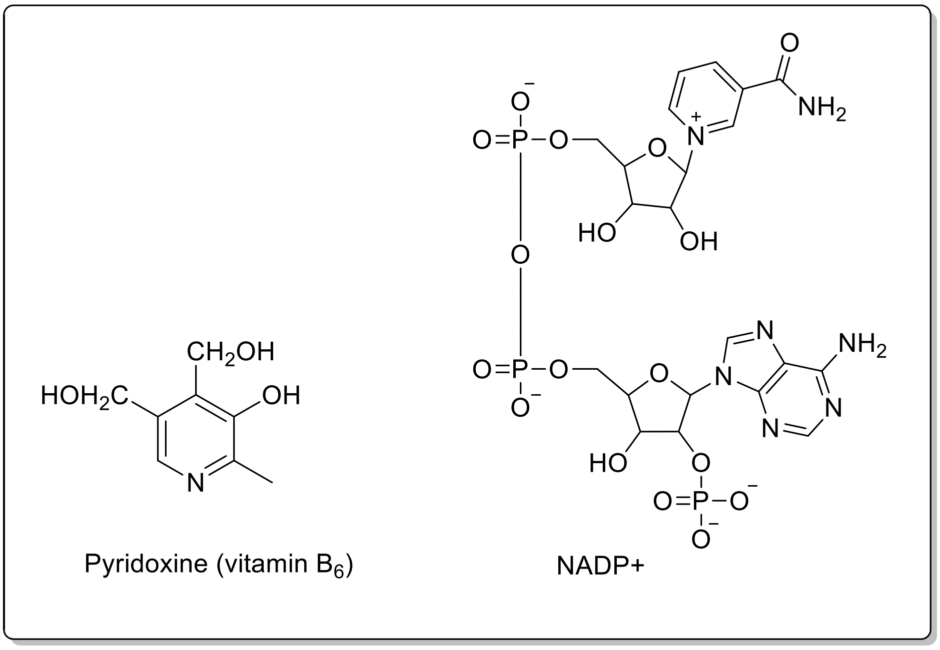
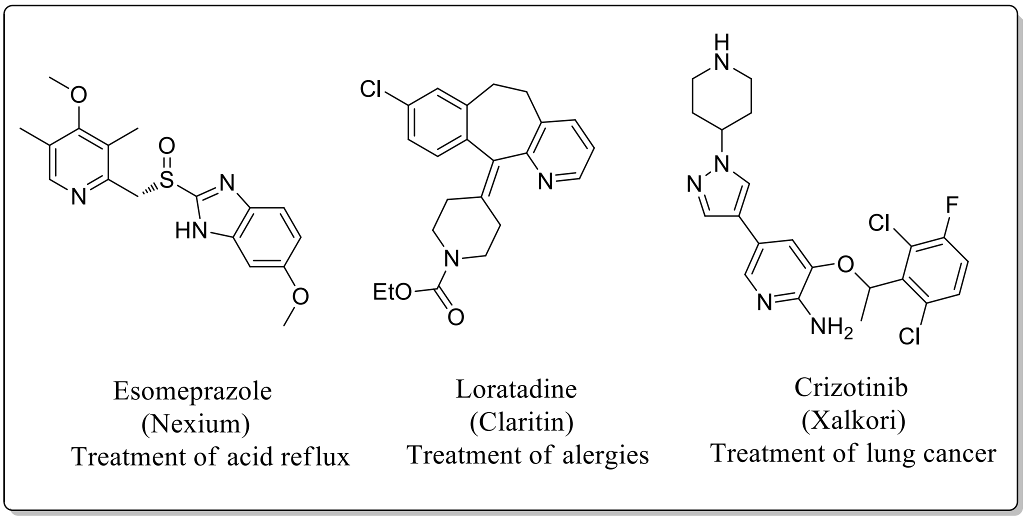


Figure 4. Structures of Vitamin B_6 and NADP+.

Pyridine has an important role in the development of medicines. For instance pyridine-containing *esomeprazole, loratadine* and *crizotinib* are used for the treatment of gastric disease, allergies and lung cancer, respectively (Figure 5).[9]

Accordingly, many researchers have focused on the synthesis of new pyridine derivatives which can display enhanced or totally new biological activities.



Esomeprazole
(Nexium)
Treatment of acid reflux

Loratadine
(Claritin)
Treatment of alergies

Crizotinib
(Xalkori)
Treatment of lung cancer

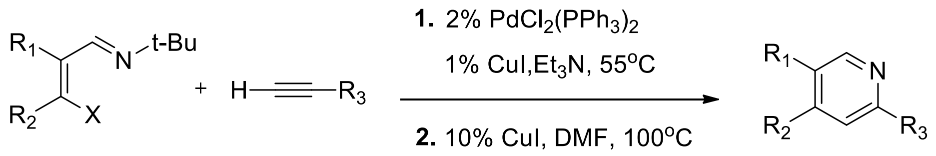
Figure 5. Examples of pyridine-containing drugs.

Over the years, many methods have been developed for the synthesis of pyridines and new variants continue to appear since they have a remarkable impact in the synthesis of various drugs and natural products. In this regard, electrophilic cyclization has recently emerged as a valuable tool in organic synthesis.[10,11] Electrophilic cyclizations generally occur under mild conditions in one-pot manner. Such cyclizations have also been employed in the synthesis of various pyridine derivatives.

1.2.1 Synthesis of pyridines

Pyridines are generally synthesized by the condensation of amines with carbonyl compounds or by the cycloaddition reactions.[12] Transition metals are often used as catalyst in such reactions. Moreover, halo-substituted pyridines can be further functionalized by the metal-catalyzed cross-coupling reactions.[13]

Larock and coworkers employed the Pd-catalyzed reaction of vinylic imines **4** with terminal alkynes **5** to synthesize pyridine derivatives **6** as shown in Scheme 1.[14]

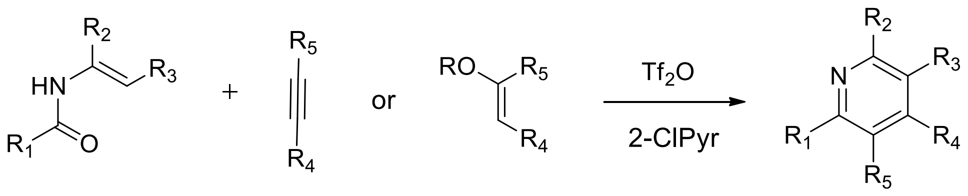


4 **5** **6**

X = Br, I

Scheme 1. Palladium-catalyzed pyridine synthesis.

Movassaghi and coworkers recently reported a one-pot synthesis of pyridines, where the condensation of amides **7** with alkynes **8** or vinyl ethers **9** afforded the corresponding pyridine derivatives **10** (Scheme 2). The reaction was accomplished with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of 2-chloropyridine (2-ClPyr).[12]

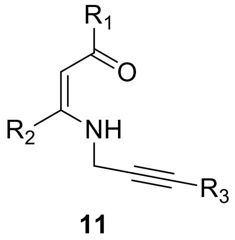


7 **8** **9** **10**

Scheme 2. One-pot synthesis of pyridines.

The presence of both the ambident nucleophilic character of enamine moiety and the electrophilic character of enone moiety make the *β*-enaminones useful synthetic intermediates. Consequently, their usage in organic synthesis have attracted current interest.[15,16]

Cacchi and Fabrizi synthesized polysubstituted pyridine derivatives **12** from *N*-propargylic *β*-enaminones **11** by employing CuBr-mediated electrophilic cyclization (Scheme 3).[17]



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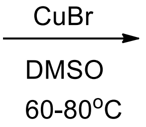

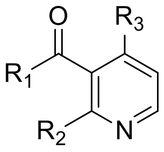

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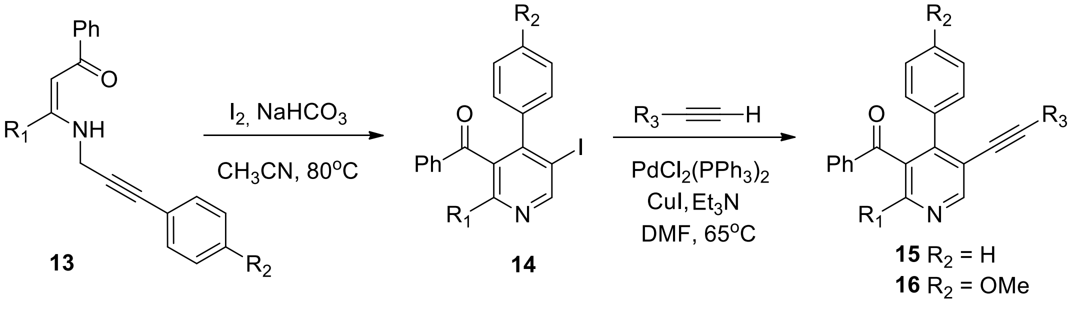
Scheme 3. Synthesis of substituted pyridines.

Zora research group has recently developed a method for the synthesis of iodo-subsituted pyridine derivatives, the initial results of which have been presented.[18] In this study, iodopyridines **14** have been synthesized from *N*-propargylic *β*-enaminones **13** by molecular iodine-mediated electrophilic cyclization as depicted in Scheme 4. In addition, the synthesized iodo-substituted pyridines have been further functionalized by employing their metal-catalyzed cross-couplings with terminal alkynes to generate alkynyl-substituted pyridine derivatives **15** and **16**.[19]



13 **14** **15** R2 = H **16** R2 = OMe

Scheme 4. Synthesis of iodo-substituted pyridines via electrophilic cyclization of *N*-propargylic *β*-enaminones and their further functionalization with terminal alkynes.

1.3 Spiro compounds

Spiro compounds are bicyclic organic molecules with the rings connected through one atom, an example of which is illustrated in Figure 6. Due to steric strain, the presence of a spiro carbon atom induces easy rearrangements that can lead to different cyclic compounds.

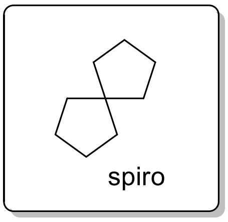


Figure 6. Structure of spiro[4.4]nonane.

The biological activities of spiro based compounds occupied a unique position in the area of organic and pharmaceutical chemistry. One example of such spiro compounds is spirooxindole (Figure 7).[20,21]

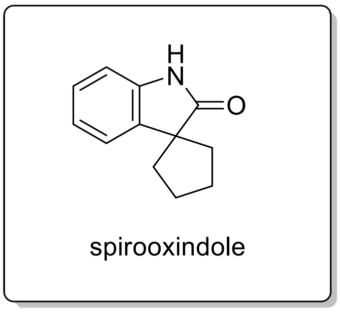
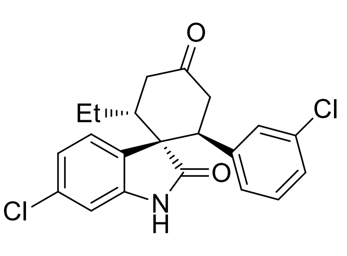


Figure 7. Structure of **s**piro[cyclopentane-1,3'-indolin]-2'-one.

Similarly, 2-oxindoles **17** and **18** have recently attracted the interest of researchers (Figure 8) because these spiro compounds have shown MDM2-p53, non-peptide specific small-molecule, inhibitor[22] and antimalarial activities, respectively.[23]



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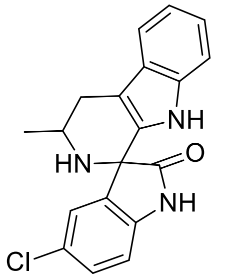

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Figure 8. Structures of some 2-oxindole containing compounds.

Spiro[4,5]decanyl **19** derivatives are also found in several natural products, the basic structure of which is shown in Figure 9.[24] Importantly, (+)-anhydro-*β*-rotunol (**20**) and (+)-dehydro-solanascone (**21**) bear a spiro[4,5]decanyl unit in their structures and display antifungal and antibacterial properties respectively (Figure 10).[25,26]

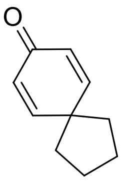

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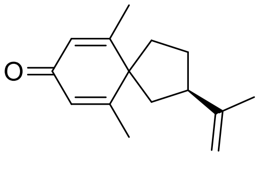
Figure 9. Structure of spiro[4.5]deca-6,9-dien-8-one (**19**).



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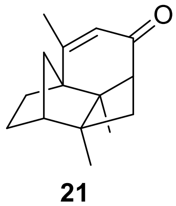

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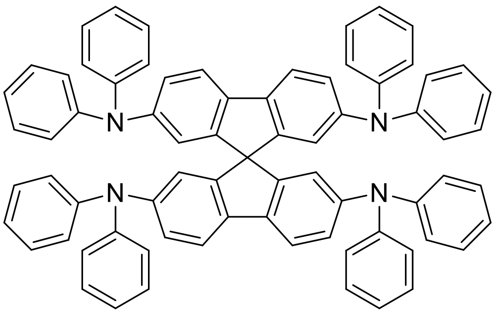
Figure 10. Structures of (+)-anhydro-*β*-rotunol (**20**) and (+)-dehydro-solanascone (**21**).

Spiro compounds are used in the organic semiconductors as well, which are often employed in the production of large area and flexible electronic devices.[27] In fact, organic semiconductors are used in a wide range of devices like light-emitting diodes, field-effect transistors, and solar cells.[27] Spiro compounds constitute the properties of organic optoelectronic devices. The compound known as spiro-TAD (2,2′,7,7′-tetrakis(*N*,*N*-diphenylamino)-9,9-spirobifluorene) hinders the crystallization of the molecules (Figure 11).[27]



spiro-TAD

Figure 11. Structure of spiro-TAD.

The integration of a spirobifluorene linkage into the structure of small molecules leads to a reduction in crystallization tendency, an enhancement in solubility and an increase in glass transition temperature (Figure 12).[28] Such spiro structures have also been applied to polymeric materials, leading to enhancements in both glass transition temperature (Tg) and luminescent stability in alternating polyfluorene copolymers.[29]

Moreover, electron transport materials can also be synthesized by using spiro compounds including the compound spiro-PBD (2-(4-biphenylyl)-5-(4-tert-butylphenyl)-1,3, 4-oxadiazole) (Figure 13). The electronic properties of these kind of compounds have remarkable impact on the electronic devices.[27]

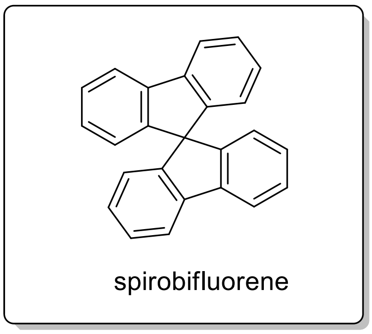


Figure 12. Structure of 9,9'-spirobi[fluorene].

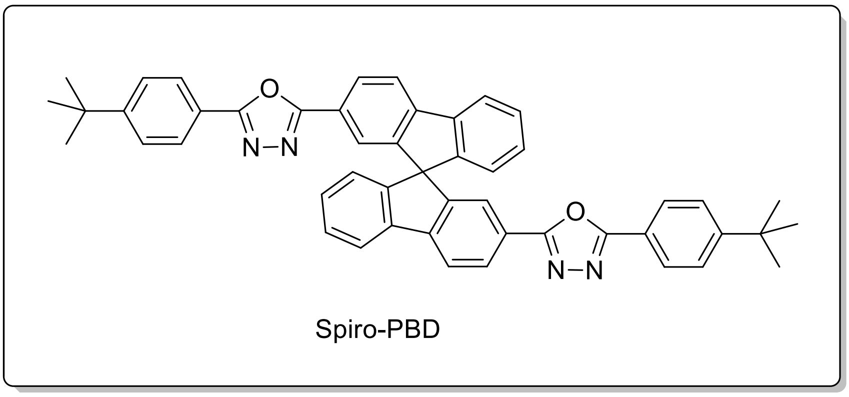


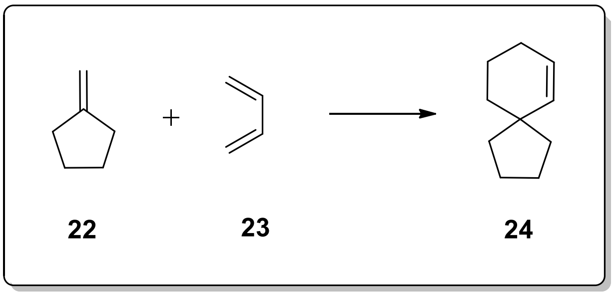
Figure 13. Structure of spiro-PBD.

Furthermore, the contribution of spiro linkages to polymerization have been well documented.[30] In the case of the spiro segment, polymer chain periodically zigzags at each spiro center and this structural feature not only preserves the rigidity of the polymer chain but also prevents the p-stacking of the polymer backbone, which result in an enhancement in both thermal and spectroscopic stabilities.

During the past decades, numerous frameworks have led to successful design and synthesis of diverse types of heterocyclic compounds with a spiro fused ring.[31] In summary, spiro fused cyclic compounds have always been a challenge for synthetic organic chemists and electro chemists.

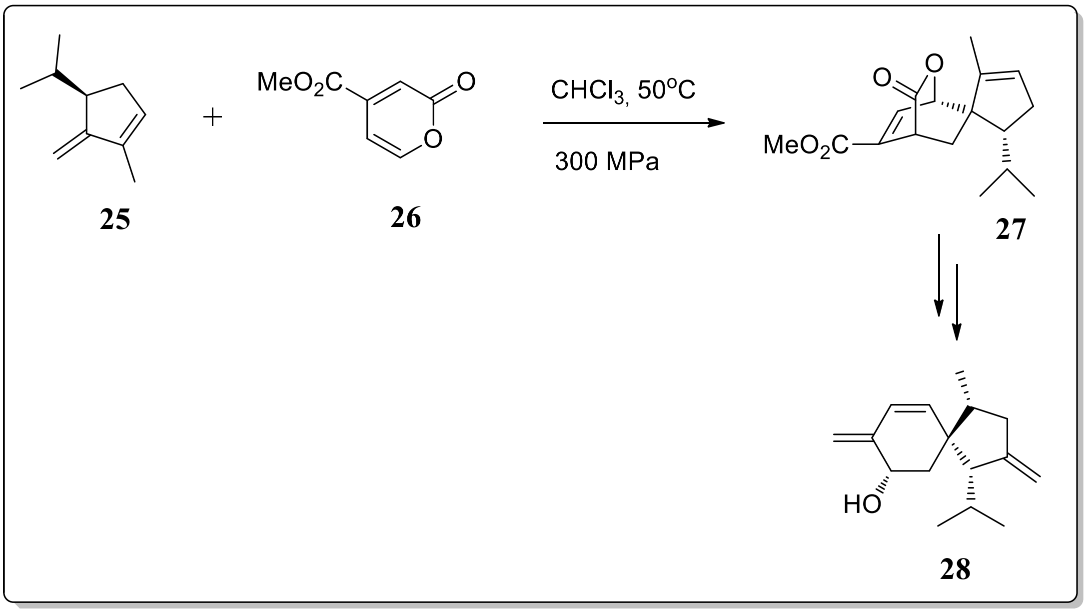
1.3.1 Synthesis of spiro compounds

Spiro compounds are generally synthesized by [4+2] cycloadditions or pinacol-type rearrangements. A schematic synthesis of spiro compouds via [4+2] cycloaddition, i.e., Diels-Alder reaction, is shown in Scheme 5.



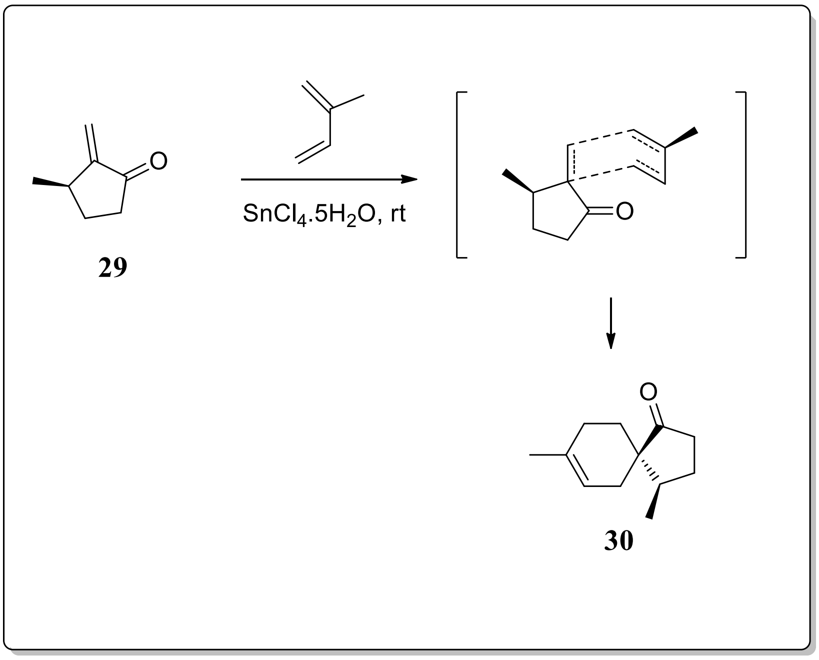
Scheme 5. Synthesis of spiro[4.5]dec-6-ene (**24**) via Diels-Alder reaction.

In the synthesis of Shizukas' acoradienol **28** (Scheme 6), the construction of spiro skeleton was performed by a [4+2] cycloaddition, where oxo-pyran-carboxylate **26** reacted with *exo*-double bond of methylenecyclopentene **25** to afford spiro compound **27**.[32]



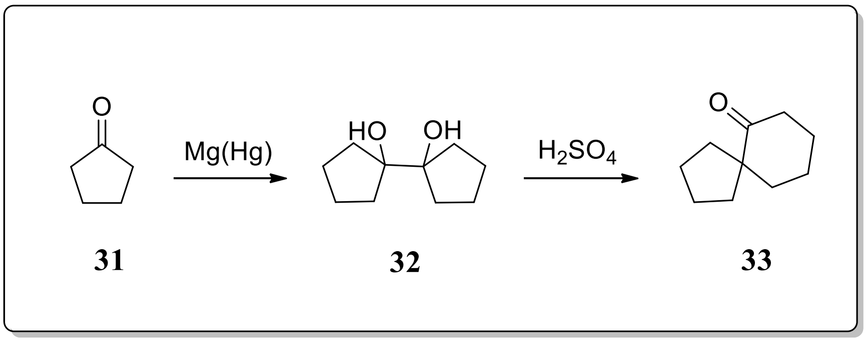
Scheme 6. Diels-alder approach to Shizukas' acoradienol.

Marx research group synthesized spirosesquiterpene **30**, a key intermediate for the synthesis of acorone, by [4 + 2] cycloaddition approach.[33] The Diels-Alder reaction between methylenecyclopentanone **29** and isoprene yielded spirosesquiterpene **30** (Scheme 7).



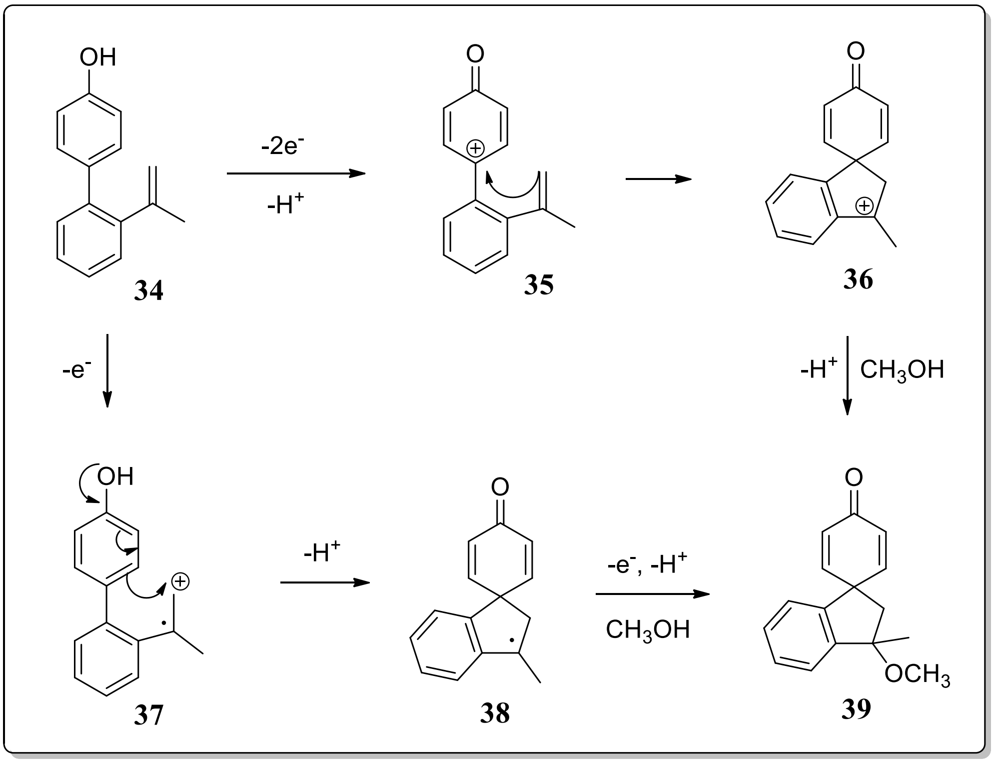
Scheme 7. Synthesis of spirosesquiterpene **30**.

As mentioned before, spiro compounds can also be prepared by pinacol rearrangements. For instance, under acidic conditions, diol **32**, prepared from cyclopentanone (**31**), undergoes pinacol rearrangement to furnish spiro[4,5]decan-6-one (**33**) (Scheme 8).[34]



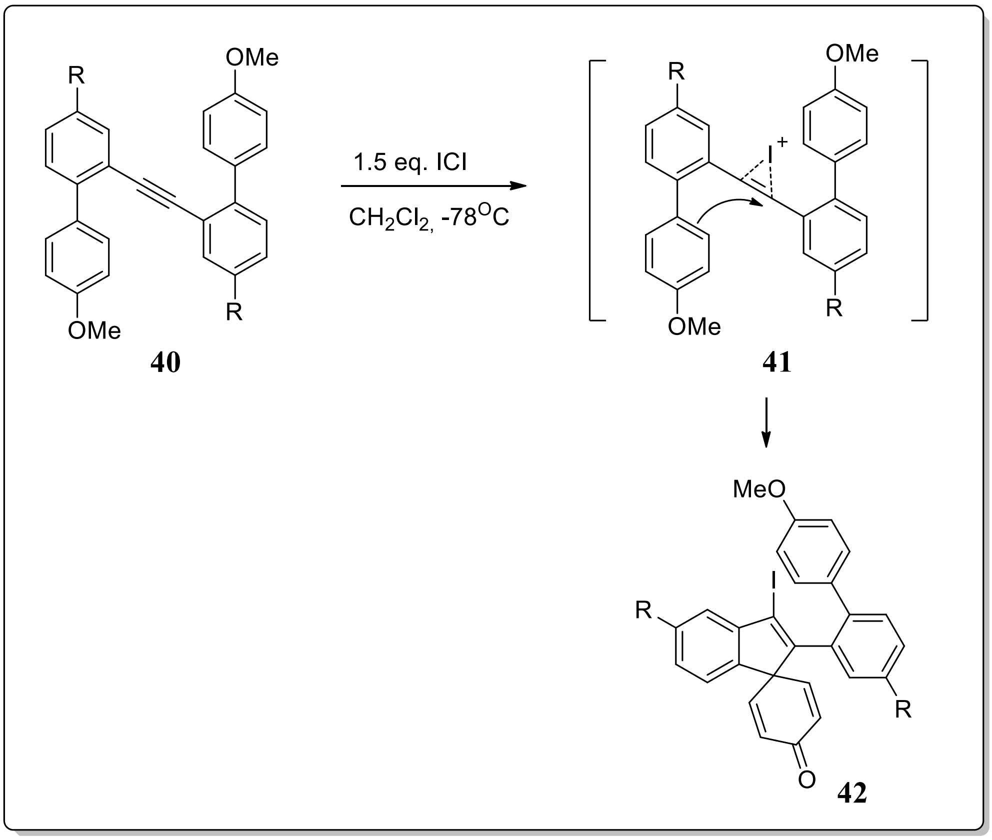
Scheme 8. Synthesis of spiro[4.5]decan-6-one (**33**).

In the study carried out by Swenton and coworkers,[35] intramolecular anodic carbon-carbon bond-forming reactions of oxidized phenol intermediates **35** and **37** led to the formation of spirodienones **39.** Two possible mechanisms were proposed for this reaction. One of these involves the reaction of an olefinic side chain with a phenoxonium intermediate (top mechanism), and the second includes the nucleophilic attack of a phenol on an oxidized styrene double bond (bottom mechanism) as illustrated in Scheme 9.



Scheme 9. Synthesis of spirocyclic 2,5-cyclohexadienones **39** with two proposed mechanisms.

When subjected to electrophilic cyclization, aryl-substituted internal alkynes produce the corresponding spiro compounds. For instance, the treatment of alkyne **40** with ICl has yielded spirocyclohexadienone derivatives **42** via intermediacy of iodonium ion **41** (Scheme 10).[36]

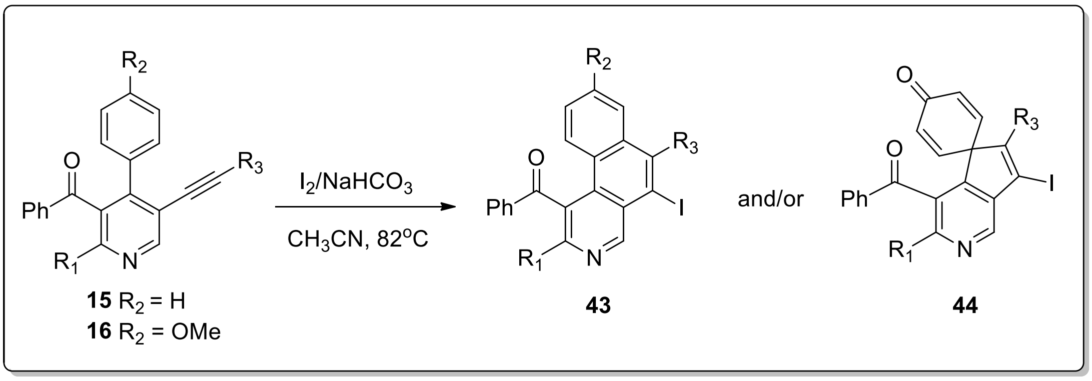


Scheme 10. Synthesis of spirocyclohexadienones with electrophilic cyclization.

After developing a new method for the synthesis of iodo-substituted pyridines, our research group has focused on the synthesis of spiro compounds from alkynyl-substituted pyridines. Accordingly, we have shown that under appropriate conditions, alkynyl-substituted pyridines, obtained from iodopyridines, undergo electrophilic cyclization to afford iodo-substituted spiro-fused pyridine derivatives as it will be discussed below.

1.4 Aim of the study

In this study, the electrophilic cyclizations of 5-alkynylpyridine derivatives **15** and **16** have been investigated as shown in Scheme 11. When treated with molecular iodine in the presence of sodium bicarbonate, 5-alkynylpyridine derivatives **15** and **16** have been expected to undergo electrophilic cyclization to afford iodo-substituted benzo[f]isoquinolines **43** and/or iodo-substituted spiro-fused pyridine derivatives **44**. In the light of our previous studies, 5-alkynylpyridine derivatives **15** (R_2 = H) are expected to mainly produce iodo-substituted benzo[f]isoquinolines **43**. On the other hand, 5-alkynylpyridine derivatives **16**, which bear a methoxy group as the R_2 substituent, are expected to exclusively produce iodo-substituted spiro-fused pyridine derivatives **44**. Initially, the starting materials have been prepared and then subjected to electrophilic cyclization for the synthesis of the above mentioned compounds. In summary, the limitations, scope and the proposed mechanism for these electrophilic cyclizations will be discussed in detail.



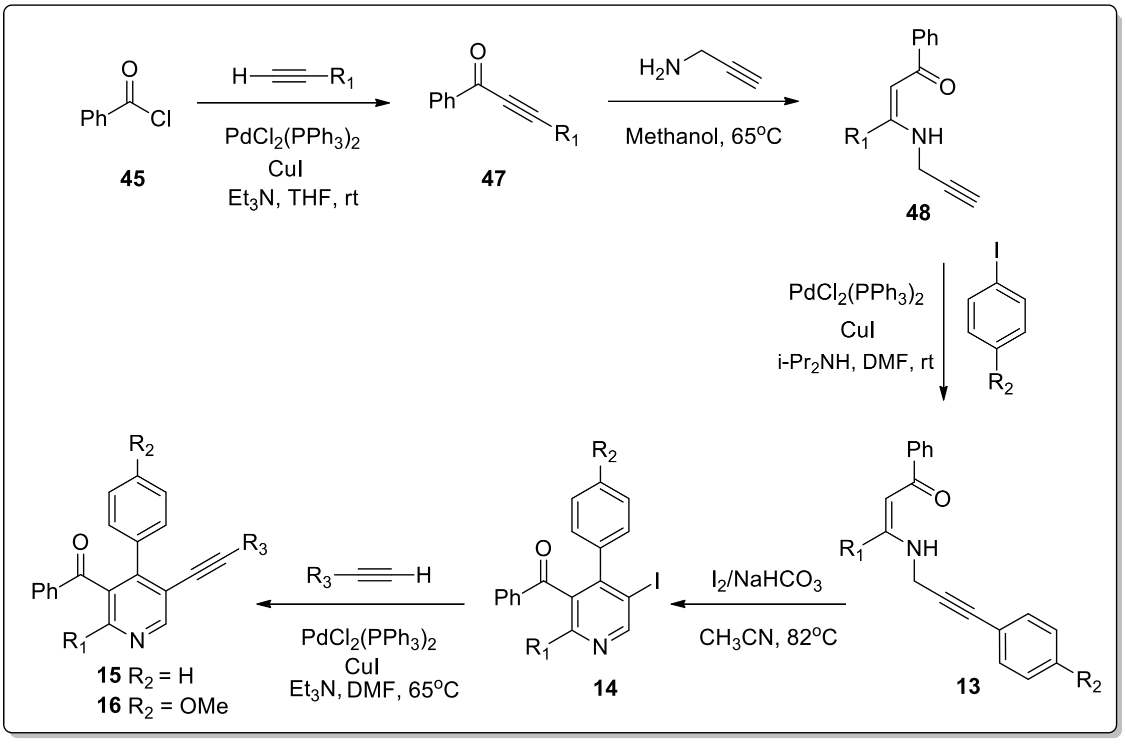
Scheme 11. Electrophilic cyclizations of 5-alkynylpyridine derivatives **15-16**.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of alkynyl-subsituted pyridines

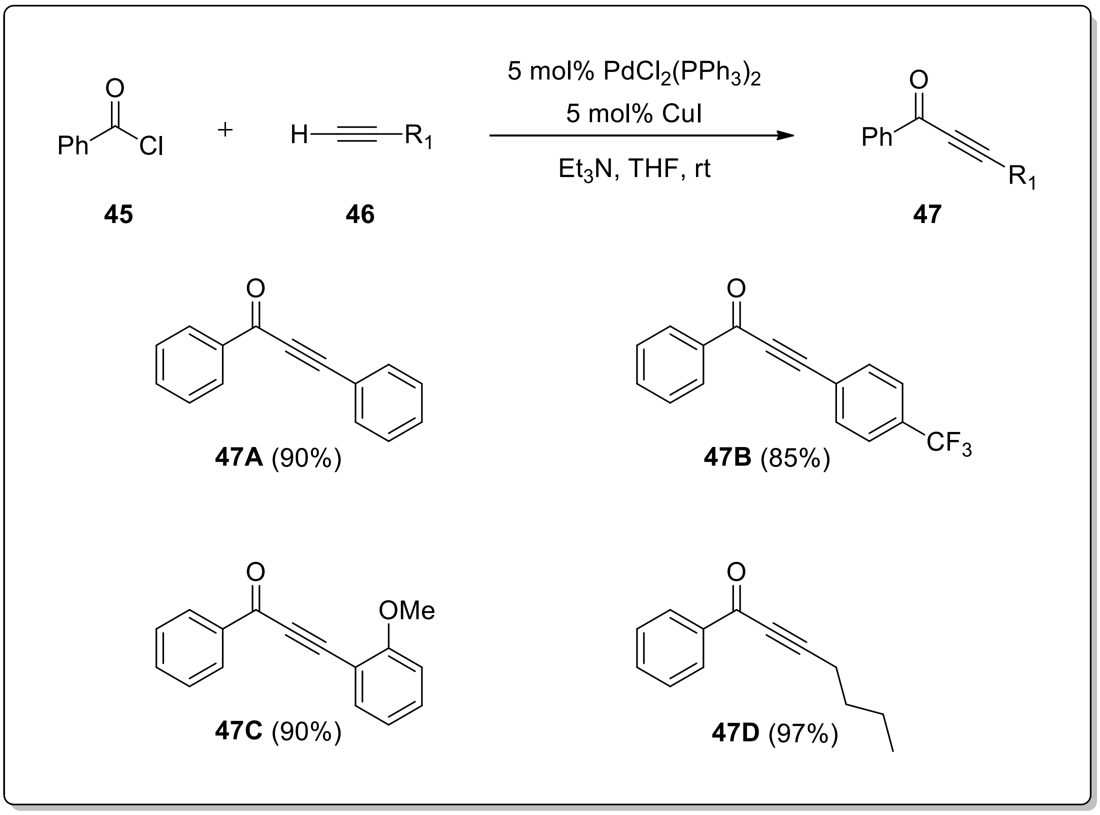
The starting materials of the study, alkynyl-subsituted pyridines **15** and **16**, were synthesized according to the reaction scheme given in Scheme 12. Details of each step of the synthesis will be discussed in the following parts.



Scheme 12. Reaction pathway for the synthesis of alkynyl-subsituted pyridines.

2.1.1 Synthesis of *N*-propargylic *β*-enaminone derivatives

In the first phase of the study, *N*-propargylic *β*-enaminones derivatives **48** were synthesized. Initially, alkynyl ketones **47** were prepared by Sonogashira cross-coupling[37] of benzoyl chloride (**45**) with terminal alkynes **46** (Scheme 13).

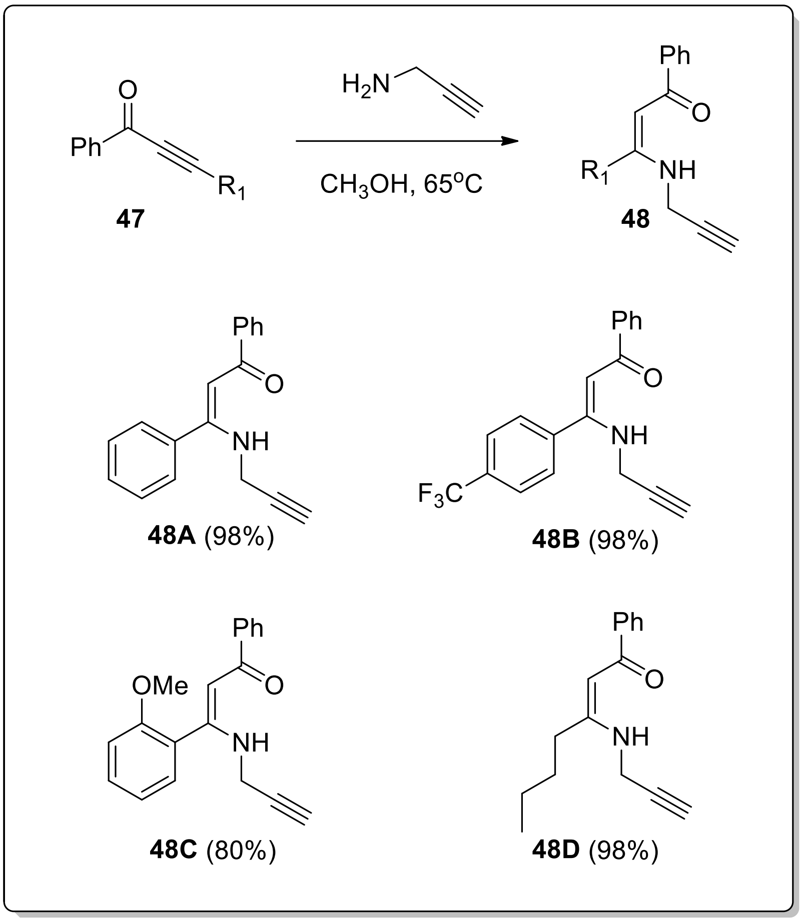


Scheme 13. Synthesis of alkynyl ketones **47**.

By employing these coupling reactions, four derivatives of alkynyl ketones **47**, namely 1,3-diphenylprop-2-yn-1-one (**47A**), 1-phenyl-3-(4-(trifluoromethyl)-phenyl)prop-2-yn-1-one (**47B**), 3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-one (**47C**) and 1-phenylhept-2-yn-1-one (**47D**), were synthesized in high yields (Scheme 13).

Next we carried out their reactions with propargylamine. For this purpose, alkynyl ketones **47** and propargylamine were refluxed in methanol at 65 °C for approximately 2 h. During the course of the reactions, propargylamine undergoes conjugate addition with alkynyl ketones **47** to give *N*-propargylic *β*-enaminones **48** (Scheme 14).

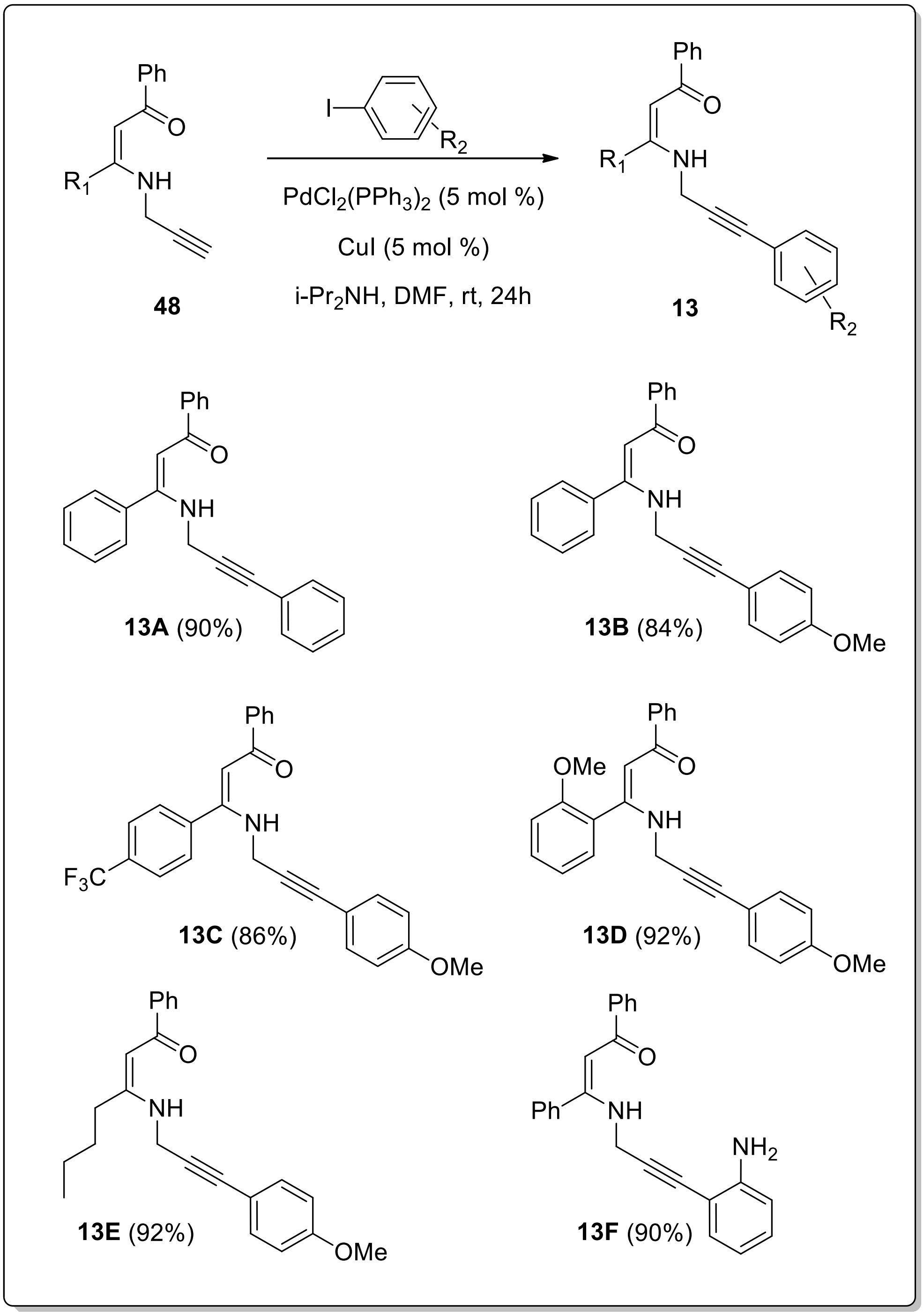
By utilizing these reactions, four derivatives of *N*-propargylic *β*-enaminones **48** were prepared in high yields (Scheme 14).



Scheme 14. Synthesis of *N*-propargylic *β*-enaminones **48**.

Finally, the synthesized *N*-propargylic *β*-enaminones **48** were subjected to Sonagashira coupling with iodoaryl derivatives (Scheme 15). By this way, alkynyl moieties of *β*-enaminones **48** were further functionalized.

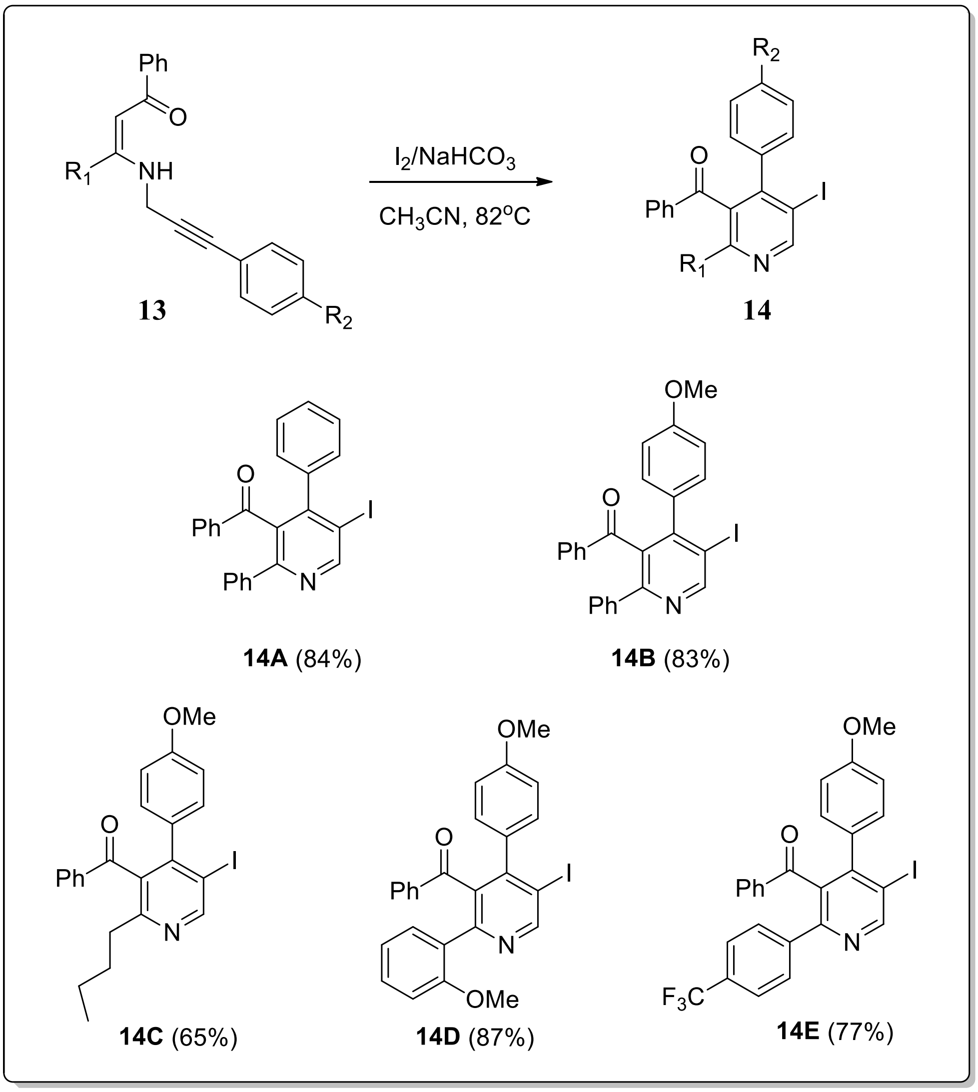
In the presence of palladium catalyst, CuI and amine base, *β*-enaminones **48** reacted with iodoaryl derivatives, such as iodobenzene, 4-iodoanisole and 2-iodoaniline furnished the arylated *N*-propargylic *β*-enaminone derivatives **13** in high yields (Scheme 15).



Scheme 15. Synthesis of arylated *N*-propargylic *β*-enaminones **13**.

2.1.2 Synthesis of iodo-substituted pyridine derivatives via electrophilic cyclization

In the second phase of the study, we synthesized iodo-substituted pyridine derivatives **14** from *N*-propargylic β-enaminones **13** (Scheme 16). The syntheses of iodopyridines were achieved under the optimized conditions which were developed by our research group.[18] In the presence of molecular iodine, *N*-propargylic β-enaminones **13** underwent electrophilic cyclization in refluxing acetonitrile to produce iodopyridines in good to high yields (Scheme 16).



Scheme 16. Synthesis of iodo-pyridine derivatives **14**.

Structural assignments of iodo-substituted pyridines **14** were made by ^{1}H and ^{13}C NMR spectroscopy. As a representative example, ^{1}H and ^{13}C NMR **s**pectra of compound **14A** are given in Figures 14 and 15, respectively. As seen in ^{1}H NMR spectrum of **14A** (Figure 14), the proton of pyridine at α position resonates around 9.30 ppm, which is a characteristic proton peak for such compounds. As expected, phenyl protons appear between 6.7 and 7.6 ppm of aromatic region. On the other hand, in ^{13}C NMR **s**pectrum of **14A** (Figure 15), iodine-attached carbon resonates around 95 ppm, a specific carbon peak for iodo-substituted pyridines. In the spectrum, the peak around 190 ppm belongs to carbonyl group. Within 130-160 ppm, the peaks of phenyl carbons are observed.

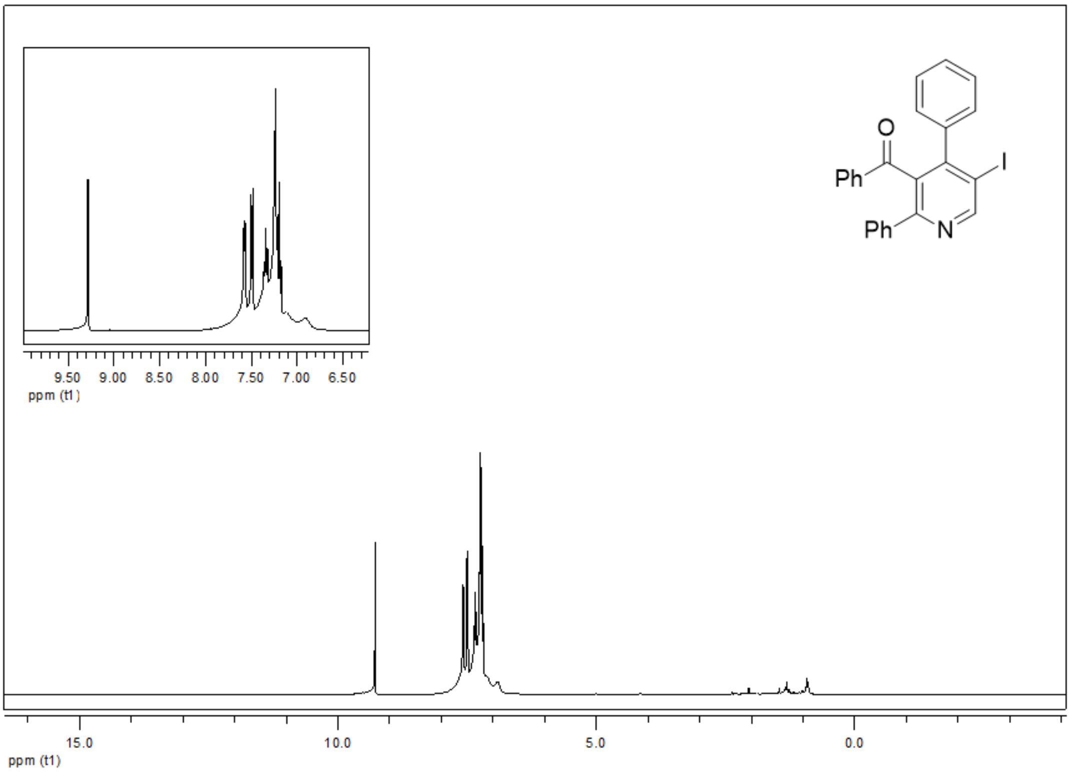


Figure 146. ^{1}H NMR spectrum of iodopyridine **14A**.

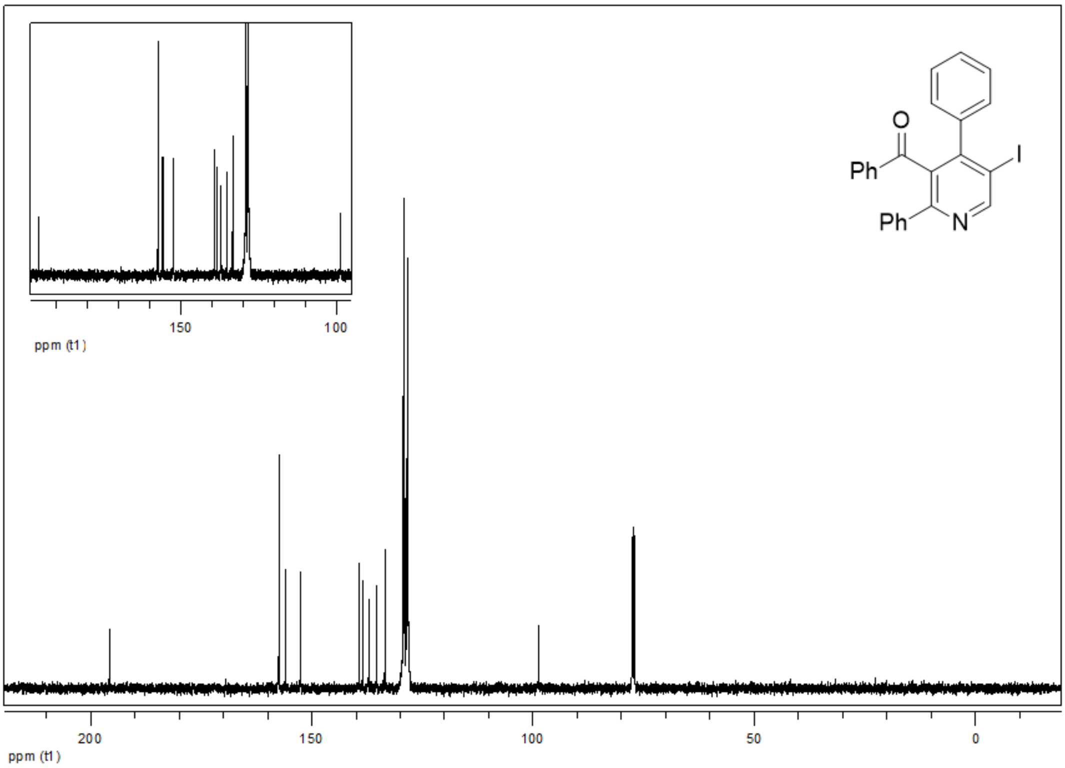
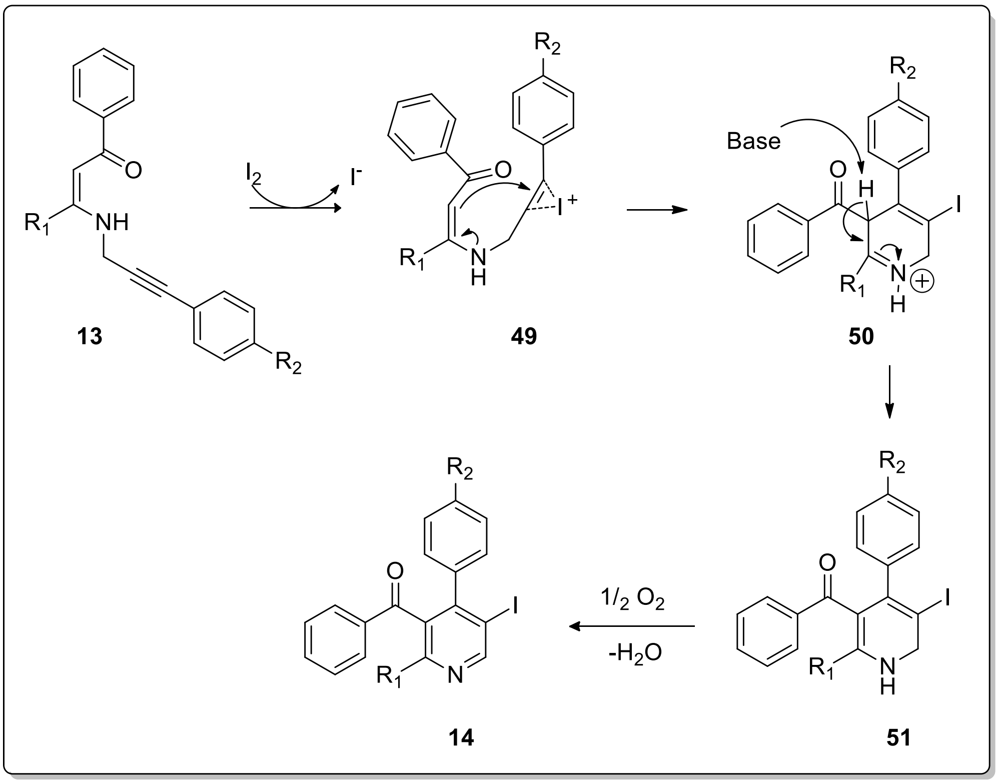


Figure 157. ^{13}C NMR spectrum of iodopyridine **14A**.

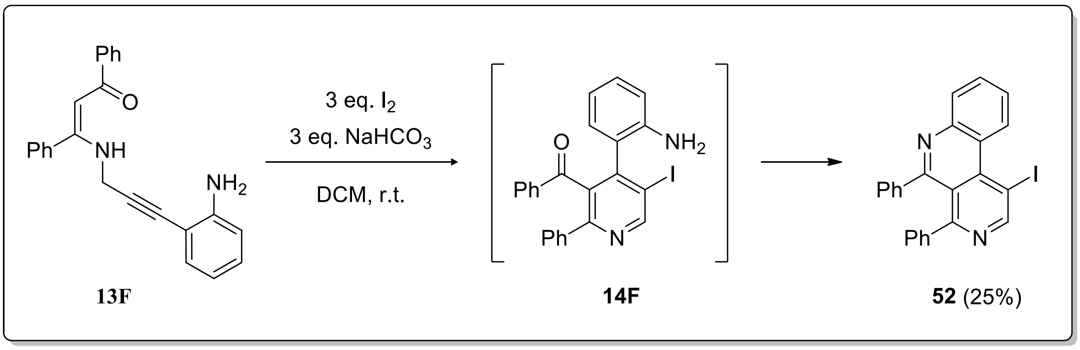
Proposed mechanism for the formation of iodo-substituted pyridines **14** is depicted in Scheme 17. First, moleculer iodine reacts with alkyne moiety of *β*-enaminones **13**, giving iodonium ion **49**. Nucleophilic attack of enamine moiety then takes place to give intermediate **50**. Subsequently, hydrogen abstraction with base yields dihydropyridine **51**. Finally, aerobic oxidation affords iodo-substituted pyridine derivatives **14** (Scheme 17).



Scheme 17. Proposed mechanism for the formation of iodo-substituted pyridines **14**.

2.1.3 Electrophilic cyclization of *β*-enaminone 13F

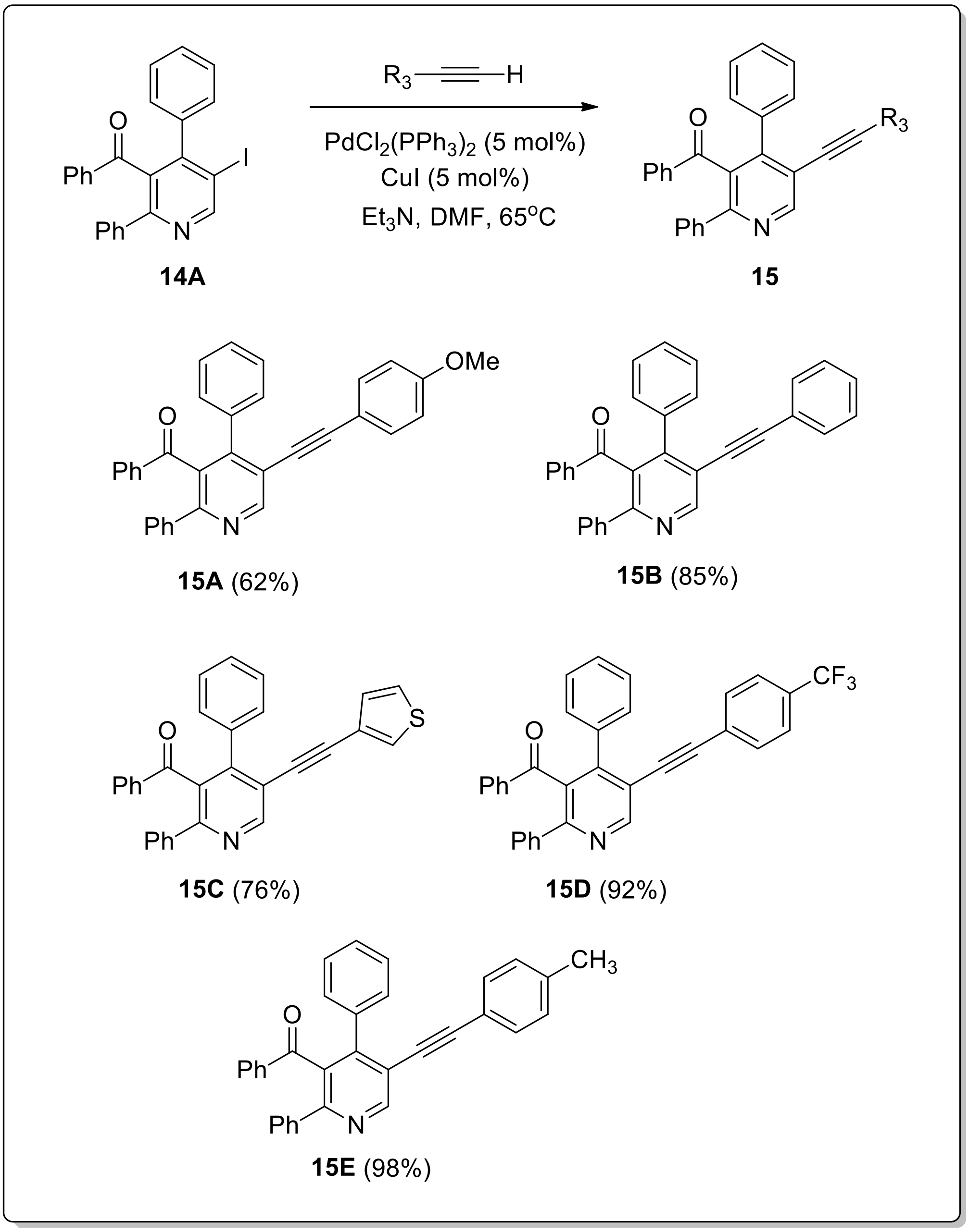
Initially, we also examined electrophilic cyclization of *β*-enaminone **13F** under the same conditions (Scheme 18). Surprisingly, this reaction produced iodo-substituted benzo[c]naphthyridine derivative **52** in 25% yield, without formation of the expected iodopyridine **14F**. In fact, benzo[c]naphthyridine **52** is a secondary product of the reaction and results from the initially formed iodopyridine derivative **14F** via a condensation reaction between amino and carbonyl groups (Scheme 18). Importantly, electrophilic cyclizations of *β*-enaminones bearing 2-aminophenyl group on the alkynyl moiety (such as **13F**) can provide a rapid entry to benzo[c]naphthyridine ring systems. We also tried to improve the yield of benzo[c]naphthyridine **52** by performing the electrophilic cyclizations with $ZnCl_2$ and $AuCl_3$; unfortunately these reactions afforded benzo[c]naphthyridine **52** in trace amounts, which requires further investigation.



Scheme 18. Synthesis of benzo[c]naphthyridine **52** via intermediacy of iodopyridine **14F**.

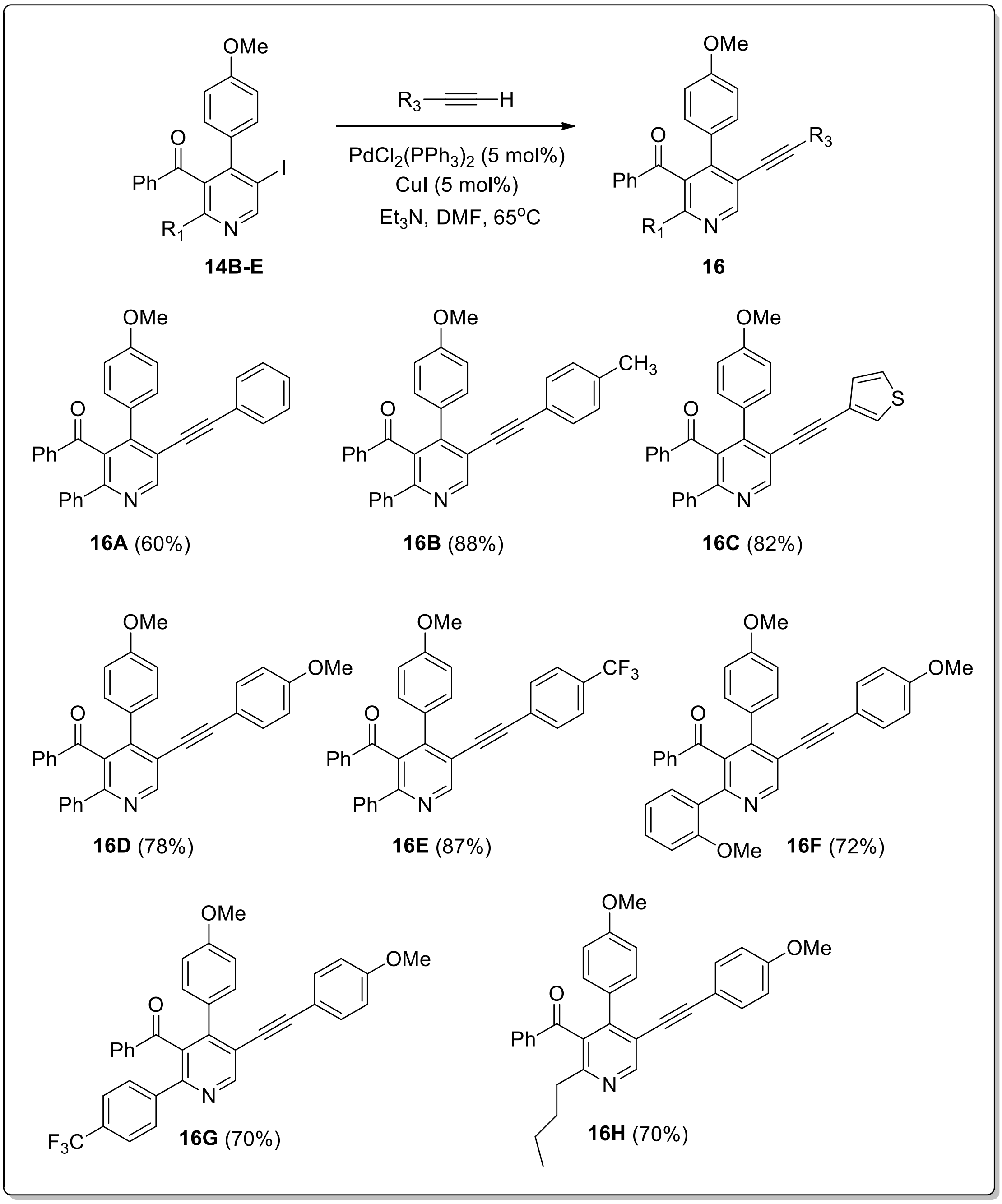
2.1.4 Synthesis of alkynyl-substituted pyridines

Finally, we functionalized iodo-substituted pyridines **14** by palladium-catalyzed Sonogashira coupling as shown in Scheme 19 and 20. Initially, the coupling of 5-iodo-4-phenylpyridine **14A** was performed with five kinds of terminal alkynes. In the presence of palladium catalyst, CuI and triethylamine, iodopyridine **14A** reacted with a variety of terminal alkynes to give 5-alkynyl-4-phenylpyridines **15** in good to high yields (Scheme 19).



Scheme 19. Synthesis of 5-alkynyl-4-phenylpyridine derivatives **15**.

Subsequently, Sonogashira couplings of 5-iodo-4-(4-methoxyphenyl)pyridines **14B-E** with five kinds of terminal alkynes were carried out (Scheme 20). Iodopyridines **14B-E** underwent coupling with a variety of alkynes in the presence of palladium catalyst, CuI and triethylamine to afford 5-alkynyl-4-(4-methoxyphenyl)pyridines **16** in good yields (Scheme 20).



Scheme 20. Synthesis of 5-alkynyl-4-(4-methoxyphenyl)pyridine derivatives **16**.

Structures of 5-alkynylpyridine derivatives **15** and **16** were determined by ^{1}H and ^{13}C NMR spectroscopy. As a representative example, ^{1}H and ^{13}C NMR **s**pectra of compound **16D** are given in Figures 16 and 17, respectively. As seen in the ^{1}H NMR spectrum of **16D** (Figure 16), the peaks of two methoxy groups are observed at 3.76 and 3.80 ppm. The α-proton of pyridine appears around 9.0 ppm as expected. Phenyl protons resonate between 6.7 and 7.6 ppm of aromatic region. On the other hand, in ^{13}C NMR **s**pectrum of **16D** (Figure 17), alkyne carbons appear at 84.5 and 96.5 ppm while methoxy carbons resonate at 55.2 and 55.3 ppm. The peak around 195 ppm belongs to carbonyl group. Between 115 and 160 ppm of the spectrum, phenyl carbons are observed.

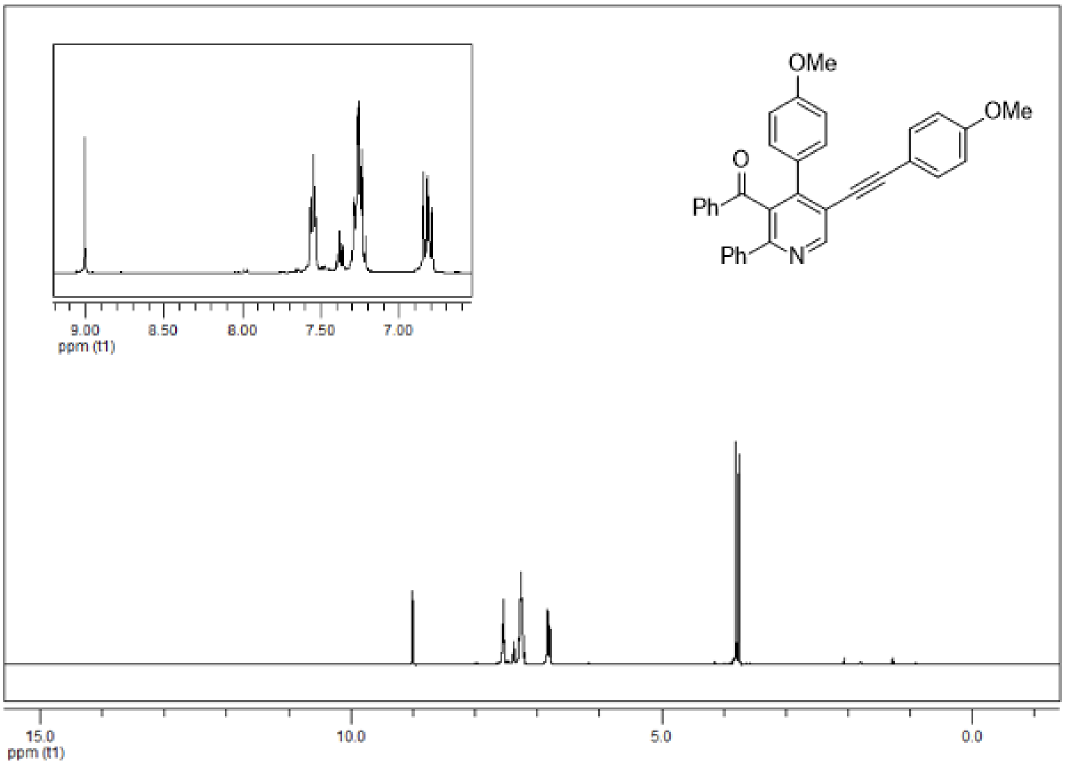


Figure 8. ^{1}H NMR spectrum of 5-alkynyl-4-(4-methoxyphenyl)pyridine **16D**.

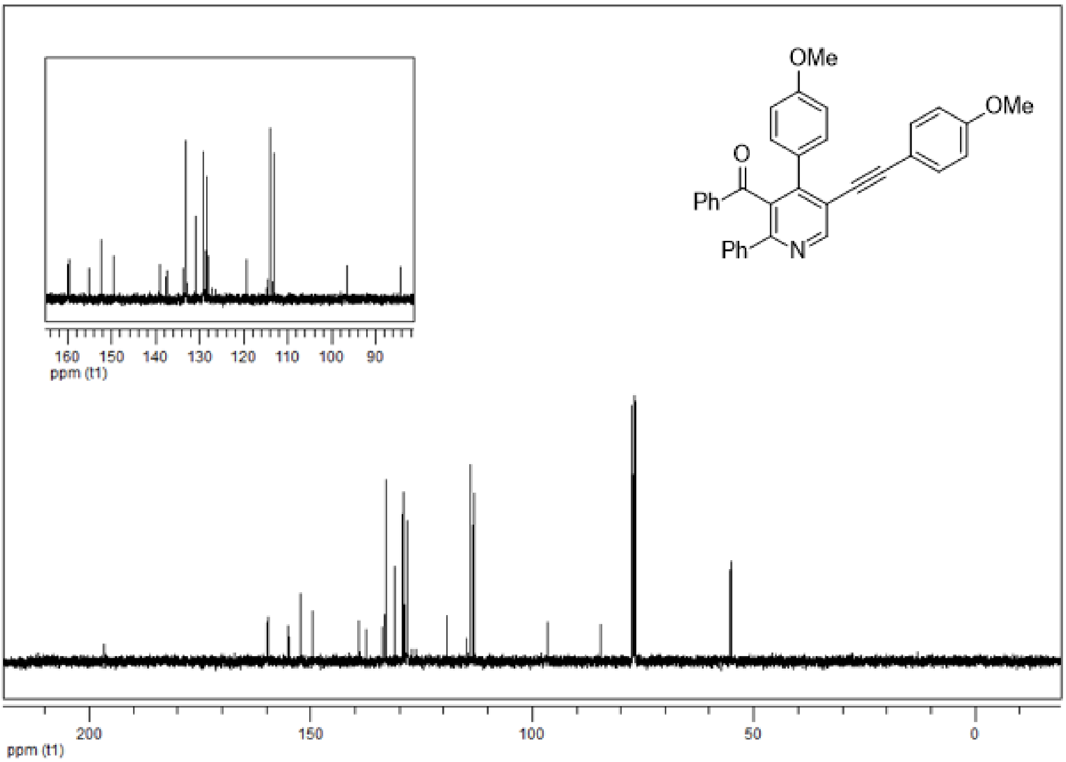
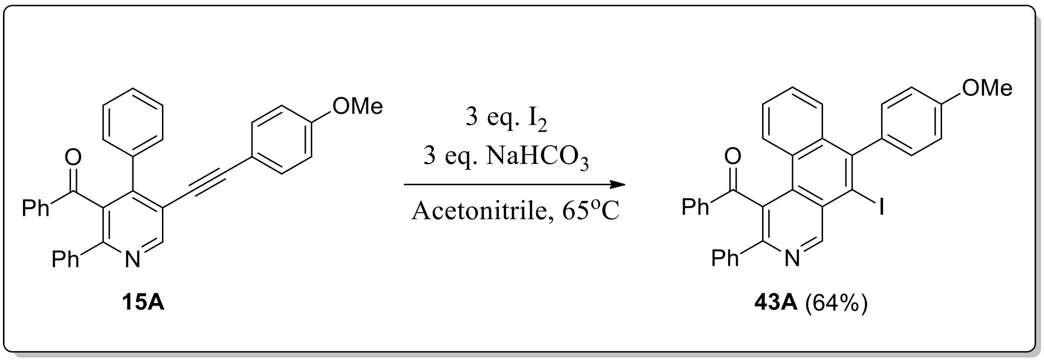


Figure 9. ^{13}C NMR spectrum of 5-alkynyl-4-(4-methoxyphenyl)pyridine **16D**.

2.2 Investigation of electrophilic cyclization of alkynyl phenylpyridines 16: Synthesis of benzo[f]isoquinolines 43

Following the synthesis of 5-alkynyl-4-phenylpyridine derivatives **15A-E**, we investigated their electrophilic cyclizations under our previous conditions with moleculer iodine in the presence of $NaHCO_3$.[18] Alkynyl-substituted pyridines **15A-E** were all tested, but only pyridine derivative **15A** underwent electrophilic cyclization to afford iodo-substituted benzo[f]isoquinoline **43A** (Scheme 21). Unfortunately, from the reactions with alkynyl-substituted pyridines **15B-E,** starting compounds were recovered with some decomposition; these reactions did not produced any desired new products. Briefly, in **15A**, strong electron donating effect of *p*-methoxy group via resonance has an effect on the outcome of the reaction. It can be concluded from these results that the initial reaction of iodine requires a rich alkyne moiety.



Scheme 21. Synthesis of iodo-substituted benzo[f]isoquinoline **43A**.

^{1}H and ^{13}C spectra of benzo[f]isoquinolines **43A** are shown in Figures 18 and 19, respectively. As seen in ^{1}H NMR spectrum (Figure 18), the peak at 9.9 ppm belongs to α-proton of pyridine. Methoxy group gives a peak around 3.8 ppm. The remaining aromatic protons resonate between 7.01 and 8.26 ppm. On the other hand, in the^{13}C spectrum of benzo[f]isoquinoline **43A** (Figure 19), there is no alkyne carbon peaks around 85.00 ppm which implies that alkyne moiety underwent reaction. Importantly, the carbon connected to iodine appears at 103.4 ppm. The rest of aromatic carbons resonate between 105 and 160 ppm while the carbonyl carbon appears at 199 ppm.

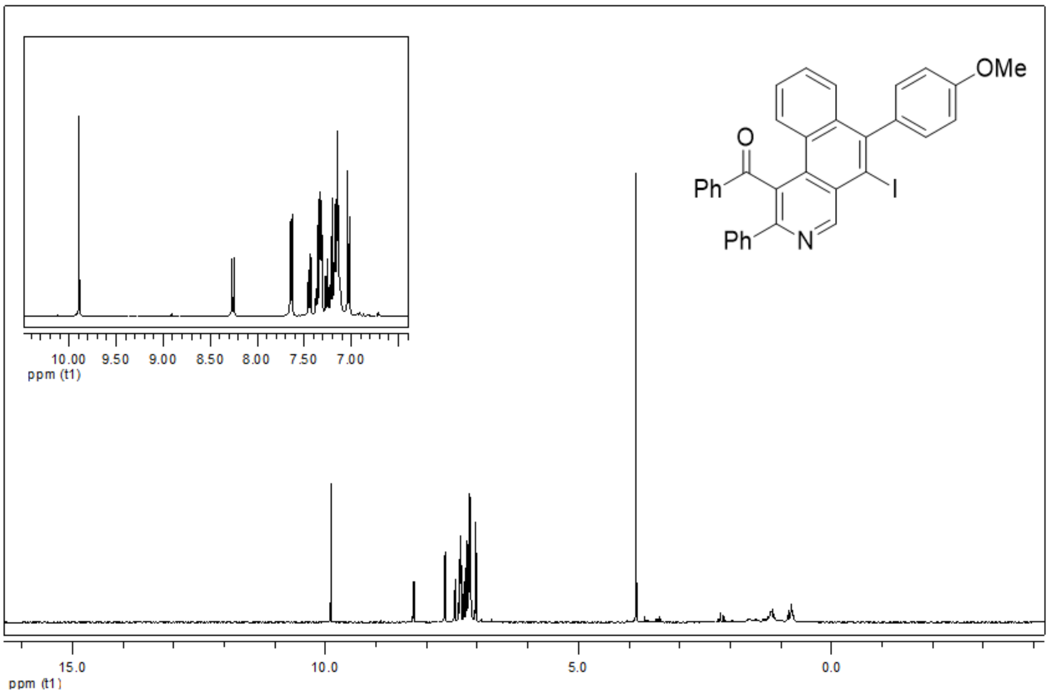


Figure 18. ^{1}H NMR spectrum of benzo[f]isoquinoline **43A**.

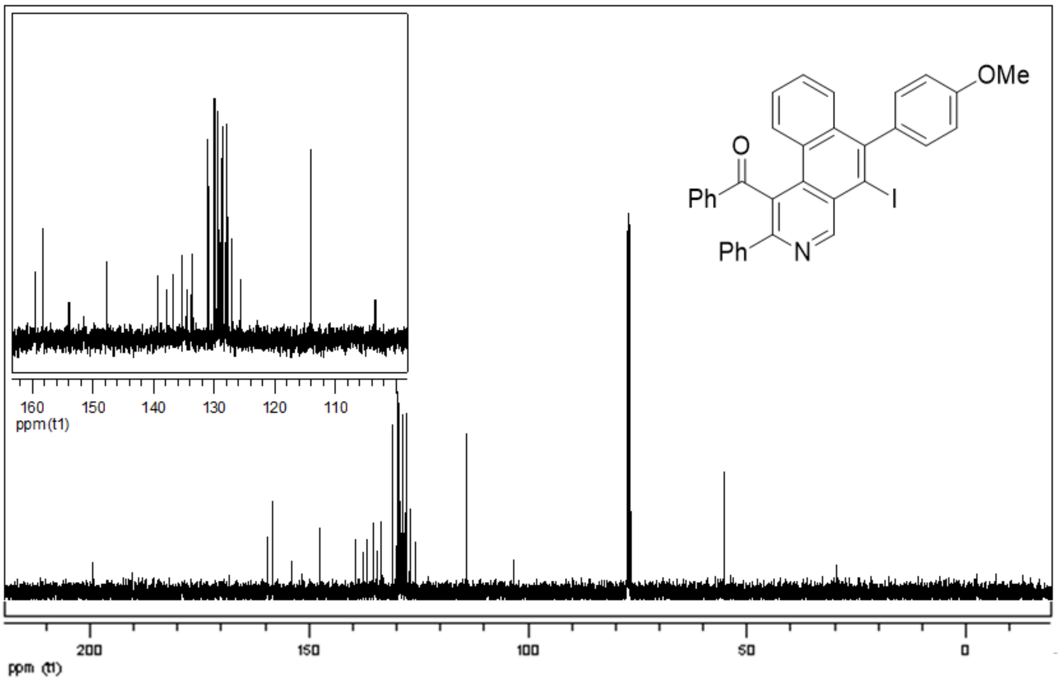
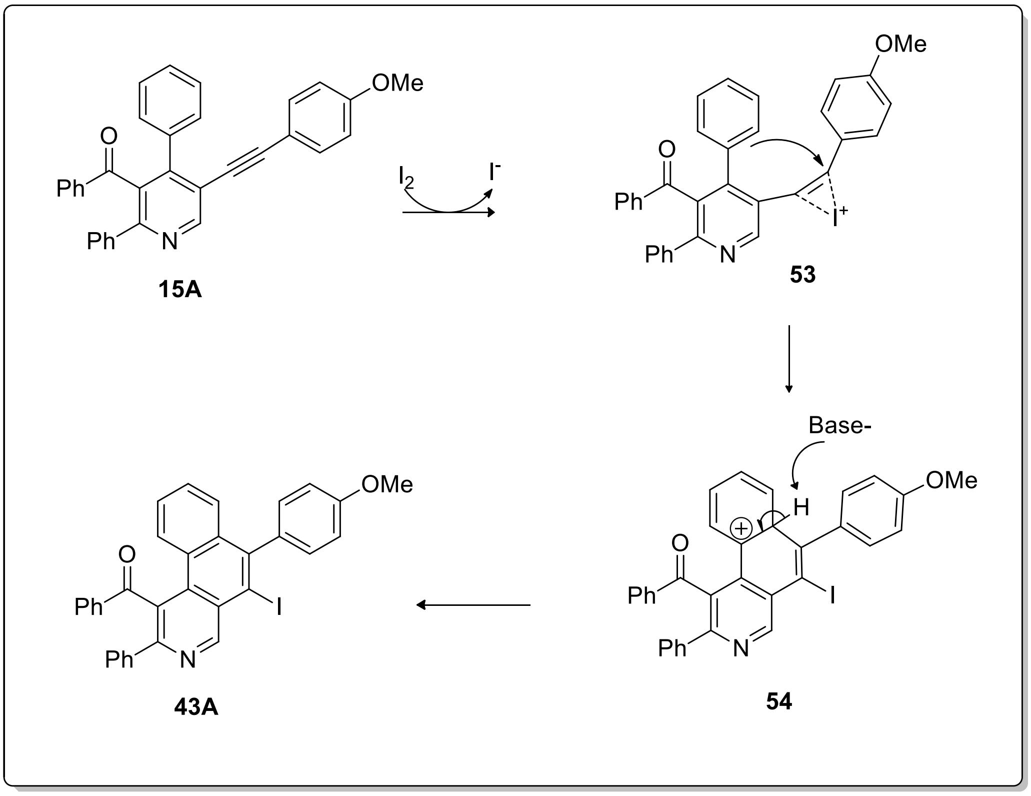


Figure 19. ^{13}C NMR spectrum of benzo[f]isoquinoline **43A**.

Proposed mechanism for the formation of benzo[f]isoquinoline **43A** is illustrated in Scheme 22. First, moleculer iodine reacts with alkyne moiety of 5-alkynyl-4-phenylpyridine **15A** giving iodonium ion **53**. Nucleophilic attack of phenyl group then occurs to give intermediate **54**. Finally, hydrogen abstraction with base yields benzo[f]isoquinoline **43A** (Scheme 22).



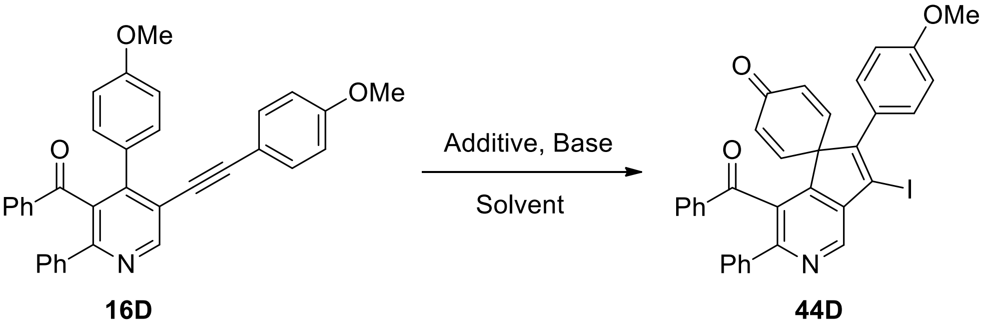
Scheme 22. Proposed mechanism for the synthesis of benzo[f]isoquinoline **43A**.

2.3 Investigation of electrophilic cyclizations of alkynyl phenylpyridine 16: Synthesis of iodo-substituted spiro-fused pyridine derivatives 44

As mentioned before, in the electrophilic cyclizations of 5-alkynyl-4-phenylpyridine derivatives **15A-E**, only compound **15A** containing a 4-methoxyphenyl group as one of the alkyne substituents underwent the reaction to give the cyclized product **43A** (Scheme 21). These results inspired us to study electrophilic cyclizations of 5-alkynyl-4-(4-methoxyphenyl)pyridine derivatives **16A-H**. It was thought that the presence of 4-methoxyphenyl group at the para position of pyridine can also initiate the electrophilic cyclization. Electrophilic cyclization of 5-alkynyl-4-(4-methoxy-phenyl)pyridine **16D** was first examined. Interestingly, from this reaction, a spiro compound was isolated (Table 1). Accordingly, we optimized reaction conditions. As seen in entries 1 and 2 of Table 1, the electrophilic cyclizations carried out with CuI and AuCl yielded the spiro compound **44D** in trace amounts and starting compounds were recovered with some decomposition. The reaction was also performed with

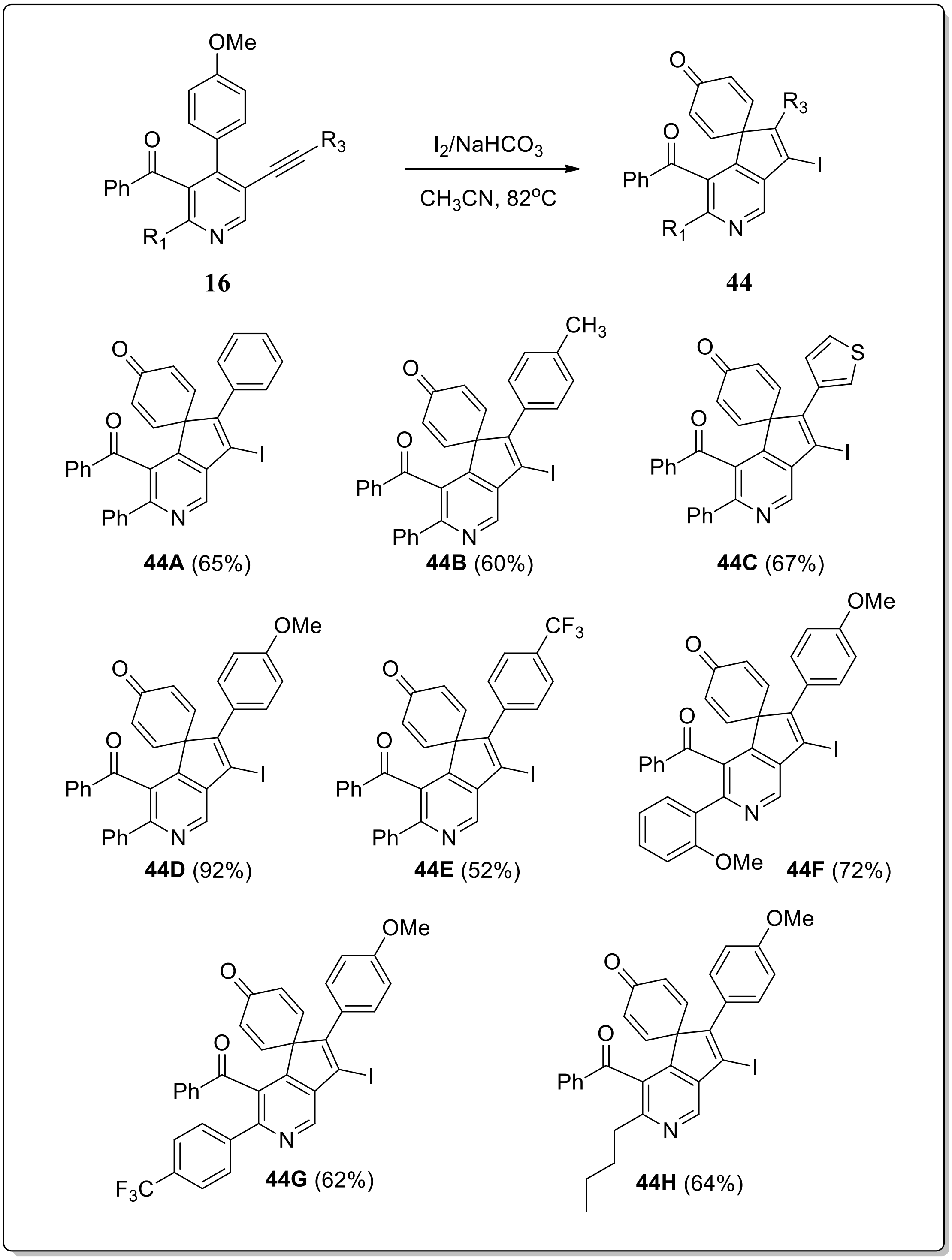
Cs_2CO_3, but this reaction did not produce any products (Table 1, entry 3). Then electrophilic cyclizations were conducted in the presence of molecular iodine and $NaHCO_3$ (Table 1, entries 4 and 5). The best yield (92%) of iodo-substituted spiro-fused pyridine **44D** was obtained in the presence 3 molar equivalents of I_2 and $NaHCO_3$ in refluxing acetonitrile (Table 1, entry 5). The effect of $NaHCO_3$ might be related to ionic strength of the reaction.

Table 1. Optimization studies for the synthesis of iodo-substituted spiro-fused pyridine **44D**.



Entry	Additive	Base	Solvent	Temperature	Time	Yield
1	1 eq.CuI	1 eq. NEt_3	ACN	82 °C	10 h	trace amount
2	5 mol% AuCl	-	DCM	25 °C	36 h	trace amount
3	3 eq. I_2	3 eq. Cs_2CO_3	ACN	82 °C	6 h	-
4	2 eq. I_2	2 eq. $NaHCO_3$	ACN	82 °C	4 h	62%
5	3 eq. I_2	3 eq. $NaHCO_3$	ACN	82 °C	2.5 h	92%

Next we carried out the electrophilic cyclizations of a variety of 5-alkynl-4-(4-methoxyphenyl)pyridines **16** under optimized conditions. The results from a systematic study are given in Scheme 23. By employing these reactions, we synthesized eight kinds of iodo-substituted spiro-fused pyridine derivatives **44** in good to high yields.



Scheme 23. Synthesis of iodo-substituted spiro-fused pyridine derivatives **44**.

Structures of iodo-substituted spiro-fused pyridine derivatives **44** were elucidated by ^{1}H and ^{13}C NMR spectroscopy. As representative examples, ^{1}H and ^{13}C NMR spectra of both spiro compound **44F** and its starting material 5-alkynyl-4-(4-methoxyphenyl)pyridine **16F** for comparison are given in Figures 20 and 21. As seen in the ^{1}H NMR spectrum of **16F**, methoxy groups appear at 3.1, 3.5 and 3.7 ppm. Conversely, in the ^{1}H NMR spectrum of **44F**, the methoxy group which resonates at 3.1 ppm are not seen because this methoxy group initiates the cyclization and is converted to a carbonyl group. Moreover, protons of cyclohexa-2,5-dienone moiety resonate at around 5.9 and 6.2 ppm (shown by arrows); the each peak represents 2 protons. The remaining phenyl hydrogens show up between 6.5 and 7.3 ppm.

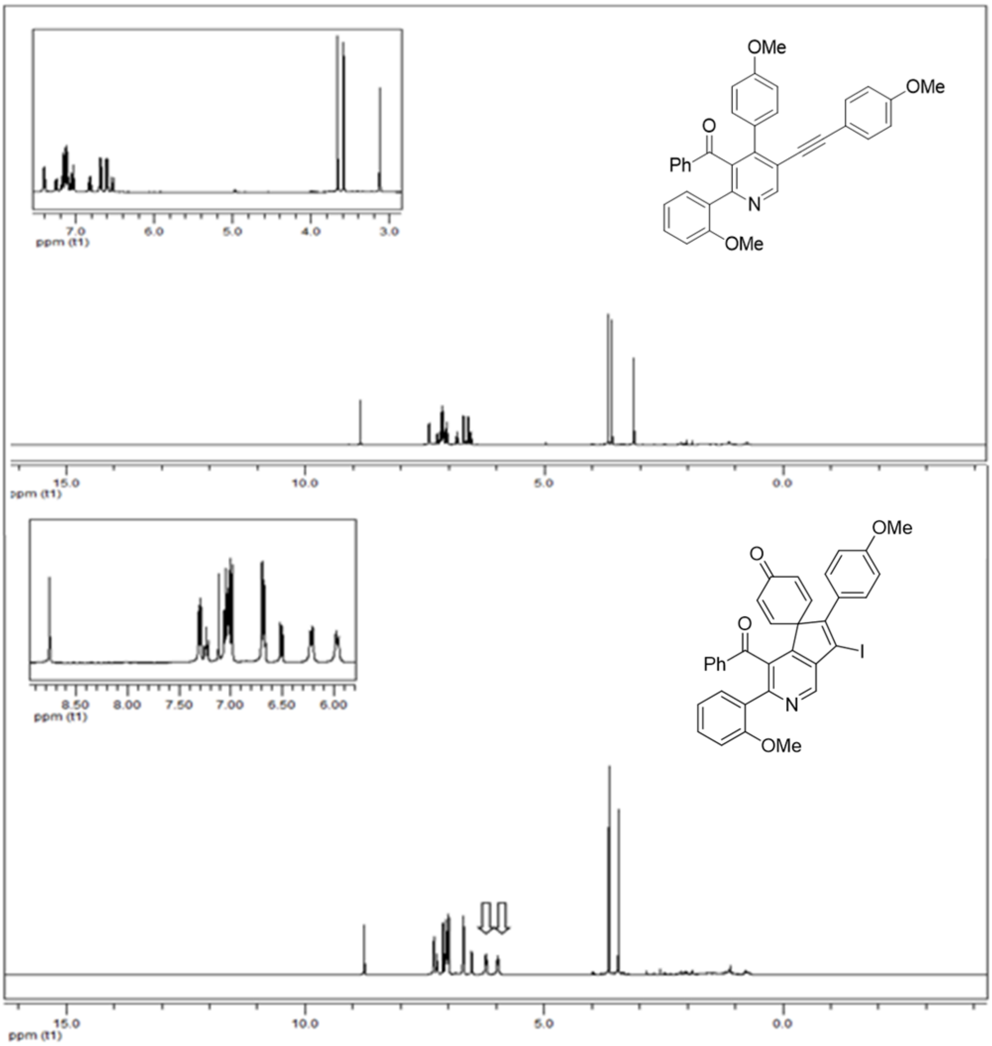


Figure 20. ^{1}H NMR spectrum of 5-alkynyl-4-(4-methoxyphenyl)pyridine **16F** (top) and iodo-substituted spiro-fused pyridine **44F** (bottom).

^{13}C NMR spectra of iodo-substituted spiro-fused pyridine **44F** and its starting material 5-alkynyl-4-(4-methoxyphenyl)pyridine **16F** for comparison are shown in Figure 21. As expected, the alkyne peaks at 84.6 and 96.0 ppm and, particularly, the methoxy peak at 55.3 ppm in starting compound **16F** disappear in the spectrum of product **44F**. Prominently, in the product spectrum, another carbonyl peak appears at 184.7 ppm as shown by an arrow. Briefly, one of the methoxy group of **16F** is converted to carbonyl group during spiro cyclization. Furthermore, in the spectrum of compound **44F**, the existence of the new peak at 62.8 ppm (shown with an arrow), which belongs to spiro carbon, clearly proves the formation of this spiro compound. The peak at 94.4 ppm shows the iodine connected carbon atom.

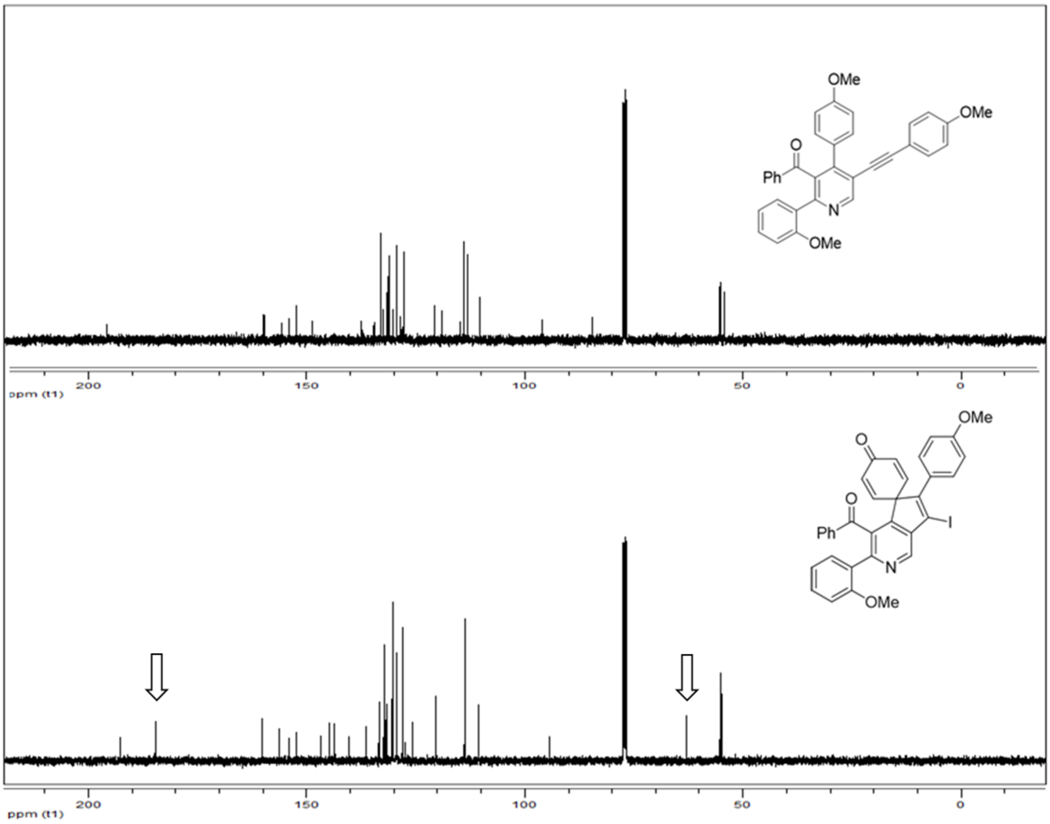
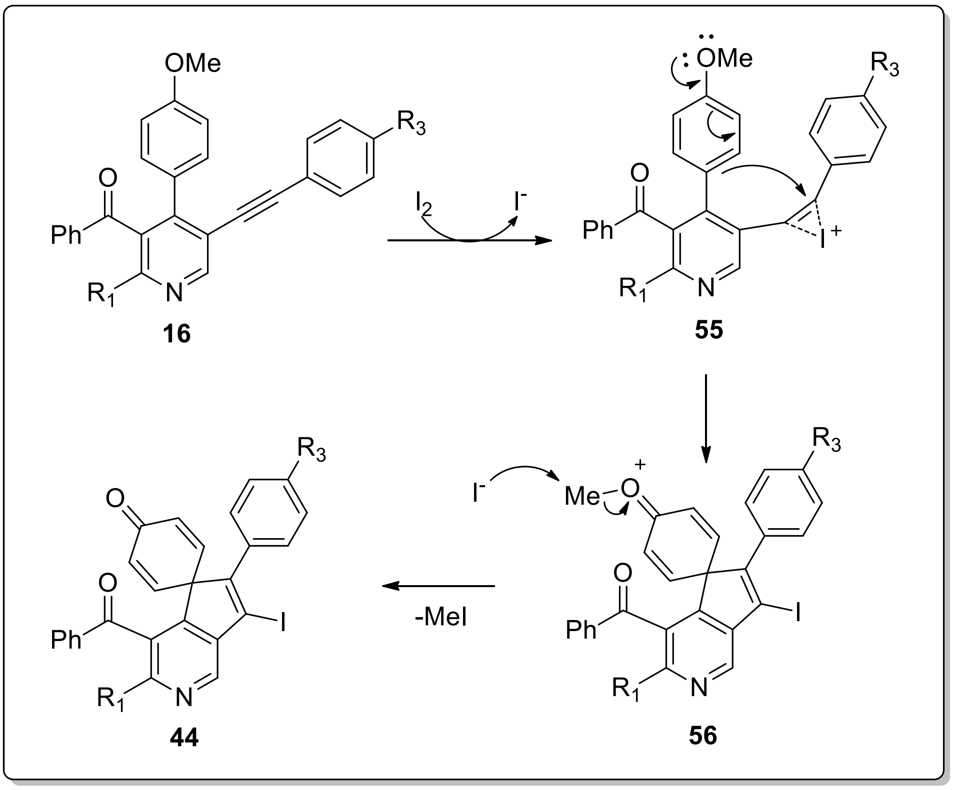


Figure 21. ^{13}C NMR spectra of 5-alkynyl-4-(4-methoxyphenyl)pyridine **16F** (top) and iodo-substituted spiro-fused pyridine **44F** (bottom).

Proposed mechanism for the formation of iodo-substituted spiro-fused pyridine derivatives **44** is illustrated in Scheme 24. Firstly, molecular iodine reacts with alkyne moiety of 5-alkynyl-4-(4-methoxy-phenyl)pyridine **16**, yielding in situ iodonium ion **55**, which initiates nucleophilic attack of 4-methoxyphenyl group to afford spiro compound **56**. Finally, elimination of methyl iodide from **56** leads to the formation of iodo-substituted spiro-fused pyridine **44** (Scheme 24).



Scheme 24. Proposed mechanism for the formation of iodo-substituted spiro-fused pyridine derivatives **44**.

In order to get some information about three dimensional structures of iodo-substituted spiro-fused pyridine derivatives **44**, the structure of compound **44A** was optimized at semi-empirical AM1 (Austin Method) level.[38] The optimized ground state structure of **44A** is given in Figure 22. Most importantly, the conjugation between 5*H*-cyclopenta[c]pyridine unit and its substituents (cyclohexadienone, benzoyl and phenyl groups) is severely interrupted because these substituents adopt approximately a perpendicular orientation.

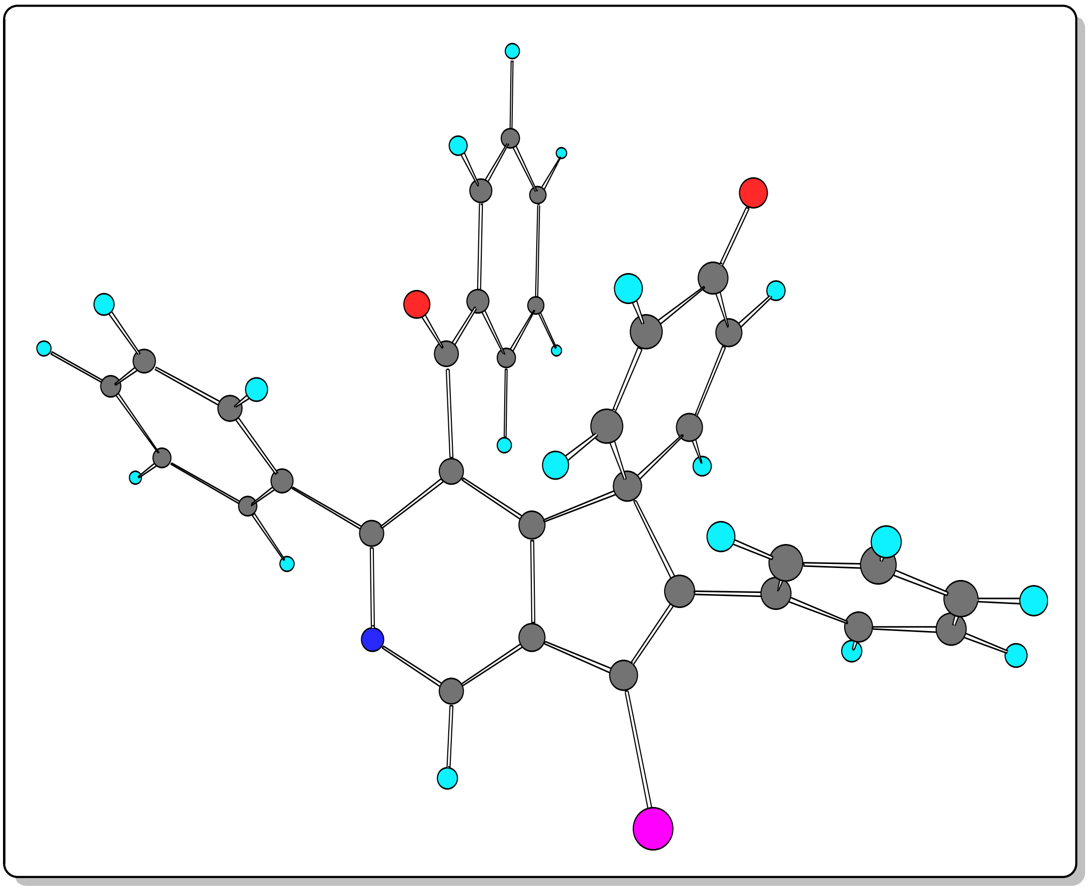


Figure 22. AM1-optimized structure of iodo-substituted spiro-fused pyridine **44A**.

CHAPTER 3

CONCLUSION

In summary, we investigated electrophilic cyclizatons of 5-alkynyl-4-phenylpyridines **15** and 5-alkynyl-4-(4-methoxyphenyl)pyridines **16**.

In the first part of the study, we prepared iodo-substituted pyridines via electrophilic cyclization of *N*-propargylic *β*-enaminones **13**. Continuously, we functionalized these iodo-substituted pyridines **14** by palladium-catalyzed Sonogashira coupling with terminal alkynes to produce a broad range of 5-alkynyl-4-phenylpyridines **15** and 5-alkynyl-4-(4-methoxyphenyl)pyridines **16**.

Accordingly, we examined electrophilic cyclizations of 5-alkynyl-4-phenylpyridines **15**. The reactions were carried out in the presence of molecular iodine and $NaHCO_3$ in acetonitrile at 82 ^{o}C. Unfortunately, only alkynyl-pyridine **15A** underwent electrophilic cyclization to produce the corresponding iodo-substituted benzo[f]-isoquinolines **43**.

On the other hand, when treated with molecular iodine and $NaHCO_3$ in refluxing acetonitrile, 5-alkynyl-4-(4-methoxyphenyl)pyridines **16** afforded a variety of iodo-substituted spiro-fused pyridine derivatives **44**.

Spiro structural motifs are present in some natural products as well as in some organic optoelectronic materials. Subsequently, eight different iodospiro-cyclopenta[c]-pyridine derivatives **44** were synthesized in good yields. Both the biological activities and other properties of these derivatives will be carried out by a collaborative work.

CHAPTER 4

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, by a Bruker Spectrospin Avance DPX400 Ultrashield spectrometer. The chemical shifts are reported in ppm (parts per million) downfield from an internal TMS (trimethylsilane) reference. Coupling constants (*J*) are given in Hz (Hertz), and the spin multiplicities are presented by the following symbols: br (broad), m (multiplet), q (quartet), t (triplet), d (doublet), dd (doublet of doublet) and s (singlet). Infrared Spectra (IR) were recorded on a Nicolet IS10 FTIR Spectrometer using attenuated total reflection (ATR). Band positions were counted in reciprocal centimeters (cm^{-1}). The reactions were accomplished by using Flash chromatography involving thick-walled glass columns using silica gel (Merck 230-400). Mass spectra (MS) were obtained on Bruker Daltonics spectrometer, using electrospray ionization (ESI) with Micro-Tof. Thin layer chromatography (TLC) was performed by using commercially available 0.25 mm silica gel plates and visualizing was effected with short wavelength UV lamp. Ethyl acetate-hexane solvent mixtures were used as eluent in Flash chromatography and their polarities were employed according to volume:volume ratio. In case of necessity, solvents used in reactions were distilled for purity. The inert atmosphere for the reactions was provided by slightly positive pressure (ca. 0.1 psi) of argon gas. All glassware was dried in oven before use.

4.1 General Procedure 1. Synthesis of alkynyl ketones 47

In a round-bottomed flask, the corresponding benzoyl chloride (**45**) (0.70 mmol) was dissolved in THF (1.0 mL) and to the solution, $PdCl_2(PPh_3)_2$ (0.02 mmol) and Et_3N (0.5 mL), and CuI (0.02 mmol) were added, respectively, and stirred at room temperature under argon atmosphere. After 20 min later, terminal alkyne **46** (0.58 mmol) was added slowly and the resulting mixture was continued to be stirred for additional 40 min. When the reaction was over, water (50 mL) was added to the flask and the organic layer was extracted with ethyl acetate (2 x 25 mL). The separated organic phase was washed with water (2 x 50 mL) and then dried over $MgSO_4$ and filtered. The obtained crude product was purified by flash chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent.

4.1.1 Synthesis of 1,3-diphenylprop-2-yn-1-one (47A)

General Procedure 1 was followed by using benzoyl chloride (**45**) (100 mg, 0.70 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and ethynylbenzene (59 mg, 0.58 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1,3-diphenylprop-2-yn-1-one (**47A**) (yellow oil, 129 mg, 90% yield).

47A: ^1H NMR (400 MHz, $CDCl_3$): δ 8.26-8.24 (m, 2H), 7.7-7.4 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 136.9, 134.2, 133.1, 130.9, 129.6, 128.7, 128.6, 120.1, 93.1, 87.0. The spectral data are matching for this compound with those reported previously.[40]

4.1.2 Synthesis of 1-phenyl-3-(4-(trifluoromethyl)-phenyl)prop-2-yn-1-one (47B)

General Procedure 1 was followed by using benzoyl chloride (**45**) (100 mg, 0.70 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and 1-ethynyl-4-(trifluoromethyl)benzene (98 mg, 0.58 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1-phenyl-3-(4-(trifluoromethyl)-phenyl)prop-2-yn-1-one (**47B**) (brown-yelow oil, 162 mg, 85% yield).

47B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24-8.22 (m, 2H), 7.8-7.5 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 136.6, 134.4, 133.2, 129.6, 128.8, 125.6, 124.0, 90.4, 88.1. The spectral data are matching for this compound with those reported previously.[39]

4.1.3 Synthesis of 3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-one (47C)

General Procedure 1 was followed by using benzoyl chloride (**45**) (100 mg, 0.70 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and 1-ethynyl-2-methoxybenzene (76 mg, 0.58 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-one (**47C**) (brown solid, 148 mg, 90% yield).

47C: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85-6.96 (m, 9H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 160.9, 134.5, 134.3, 129.2, 128.7, 124.0, 121.0, 111.2, 96.1, 88.2, 55.4. The spectral data are matching for this compound with those reported previously.[40]

4.1.4 Synthesis of 1-phenylhept-2-yn-1-one (47D)

General Procedure 1 was followed by using benzoyl chloride (**45**) (100 mg, 0.70 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and hex-1-yne (47 mg, 0.58 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1-phenylhept-2-yn-1-one (**47D**) (yellow oil, 126 mg, 97% yield).

47D: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16-8.14 (m, 2H), 7.61-7.47 (m, 3H), 2.52 (t, J = 7.2 Hz, 2H), 1.72-1.50 (m, 4H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 136.9, 133.8, 129.5, 128.5, 96.8, 79.7, 29.8, 22.0, 18.8, 13.4. The spectral data are matching for this compound with those reported previously.[40]

4.2 General Procedure 2. Synthesis of *N*-propargylic ***β***-enaminones derivatives 48

In a round-bottomed flask, the corresponding alkynyl ketone **47** (0.50 mmol) was dissolved in methanol (2.0 mL) and to the solution, propargylamine (0.60 mmol) was added. The resulting reaction mixture was refluxed in methanol at 65 ^{o}C for approximately 2 h under argon atmosphere. When the reaction was over, methanol was evaporated and the resulting crude product was purified by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent.

4.2.1 Synthesis of 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (48A)

General Procedure 2 was followed by using 1,3-diphenylprop-2-yn-1-one (**47A**) (103 mg, 0,50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**48A**) (brown-yellow solid, 128 mg, 98% yield).

48A: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.25 (br s, 1H), 7.80-7.33 (m, 10H), 5.85 (s, 1H), 3.88 (dd *J* = 6.4, 2.4 Hz, 2H), 2.35 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.2, 165.6, 136.5, 134.2, 129.9, 128.2, 94.4, 72.4, 68.3, 34.2. The spectral data are matching for this compound with those reported previously.[17]

4.2.2 Synthesis of 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)-phenyl)prop-2-en-1-one (48B)

General Procedure 2 was followed by using 1-phenyl-3-(4-(trifluoromethyl)-phenyl)prop-2-yn-1-one (**47B**) (137 mg, 0,50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1-phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)-phenyl)prop-2-en-1-one (**48B**) (yellow solid, 161 mg, 98% yield).

48B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.29 (br s, 1H), 7.93-7.40 (m, 9H), 5.85 (s, 1H), 3.89 (dd, *J* = 6.4, 2.4 Hz, 2H), 2.35 (t, *J* = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.4, 162.9, 138.5, 137.4, 130.3, 127.4, 127.3, 126.1, 124.7, 124.6, 93.9, 78.5, 71.7, 33.1. MS (ESI, *m/z*): 330.11 $[M+H]^+$; HRMS (ESI): calc. for $C_{19}H_{14}F_3NO$: 330.1100 $[M+H]^+$, found: 330.1160.

4.2.3 Synthesis of 3-(2-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (48C)

General Procedure 2 was followed by using 3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-one (**47C**) (118 mg, 0,50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-(2-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**48C**) (red oil, 116 mg, 80% yield).

48C: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.50 (br s, 1H), 7.95-7.86 (m, 2H), 7.52-7.26 (m, 5H), 7.03 (m, 2H), 5.91-5.65 (m, 1H), 3.97-3.81 (m, 2H), 3.85 (s, 3H), 2.27 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 163.3, 156.1, 140.2, 131.3, 130.8, 129.9, 128.2, 127.1, 123.7, 121.0, 110.9, 94.1, 79.5, 72.2, 55.6, 33.9; MS (ESI, *m/z*): 292.13 $[M+H]^+$; HRMS (ESI): calc. for $C_{19}H_{17}NO_2$: 292.1332 $[M+H]^+$, found: 292.1347.

4.2.4 Synthesis of 1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (48D)

General Procedure 2 was followed by using 1-phenylhept-2-yn-1-one (**47D**) (41 mg, 0,50 mmol) and propargylamine (33 mg, 0.60 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1-phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (**48D**) (yellow oil, 118 mg, 98% yield).

48D: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.5 (br s, 1H), 7.90-7.87 (m, 2H), 7.43-7.41 (m, 3H), 5.77 (s, 1H), 4.10 (dd, *J* = 6.0, 2.8 Hz, 2H), 2.40 (t, *J* = 8.0 Hz, 2H), 2.34 (t, *J* = 2.4 Hz, 1H), 1.66-1.42 (m, 4H), 0.99 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 188.7, 168.1, 140.3, 130.6, 128.2, 127.0, 92.2, 79.2, 72.4, 32.2, 31.9, 30.1, 22.6, 13.8; MS (ESI, *m/z*): 242.15 $[M+H]^+$; HRMS (ESI): calc. for $C_{16}H_{19}NO$: 242.1545 $[M+H]^+$, found: 242.1524.

4.3 General Procedure 3. Synthesis of arylated *N*-propargylic *β*-enaminone derivatives 13

In a round-bottomed flask, the corresponding *N*-propargylic *β*-enaminone **48** (0.40 mmol) was dissolved in DMF (2.0 mL) and to the solution, $PdCl_2(PPh_3)_2$ (5% mmol) and diisopropylamine (1.0 mL), and CuI (5% mmol) were added, respectively. Finally, iodobenzene derivative (4-iodoanisole or 2-iodoaniline) (0.40 mmol) was added and the resulting reaction mixture was stirred at room temperature for 20 h under argon atmosphere. When the reaction was over, water (50 mL) was added to the flask and the organic layer was exracted with ethyl acetate (2 x 25 mL). The separated organic phase was washed with water (2 x 50 mL) and then dried over $MgSO_4$ and filtered. The obtained crude product was purified by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent.

4.3.1 Synthesis of 1,3-diphenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-en-1-one (13A)

General Procedure 3 was followed by using 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**48A**) (104 mg, 0.40 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and iodobenzene (81 mg, 0.40 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 1,3-diphenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-en-1-one (**13A**) (brown-yellow oil, 121 mg, 90% yield).

13A: ^1H NMR (400 MHz, $CDCl_3$): δ 11.43 (br s, 1H), 7.98-7.88 (m, 2H), 7.58-7.48 (m, 5H), 7.47-7.38 (m, 5H), 7.34-7.30 (m, 3H), 5.87 (s, 1H), 4.18 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.1, 166.0, 140.0, 135.1, 131.7, 131.0, 129.8, 128.7, 128.5, 128.3, 127.9, 127.2, 122.6, 94.6, 85.1, 84.1, 35.1; IR (neat): 1554, 1477, 1324, 1139, 1053, 1024, 747, 688, 567, 526; MS (ESI, *m/z*): 338.15 $[M+H]^+$; HRMS (ESI): calc. for $C_{24}H_{19}NO$: 338.1545 $[M+H]^+$, found: 338.1548.

4.3.2 Synthesis of 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1,3-diphenyl-prop-2-en-1-one (13B)

General Procedure 3 was followed by using 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**48A**) (104 mg, 0.40 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02mmol) and 4-iodoanisole (93 mg, 0.40 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1,3-diphenylprop-2-en-1-one (**13B**) (brown-red oil, 123 mg, 84% yield).

13B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.48 (br s, 1H), 8.96-7.94 (m, 2H), 7.58-7.38 (m, 10H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.89 (s, 1H), 4.18 (d, *J* = 6.0 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0, 166.0, 159.8, 140.1, 135.2, 133.2, 131.0, 129.8, 128.7, 128.3, 128.0, 127.2, 114.7, 114.0, 94.5, 84.1, 83.7, 55.3, 35.2; IR (neat): 1733, 1563, 1508, 1243, 1172, 1025, 831, 748, 692, 535; MS (ESI, *m/z*): 368.16 $[M+H]^+$; HRMS (ESI): calc. for $C_{25}H_{21}NO_2$: 368.1645 $[M+H]^+$, found: 368.1648.

4.3.3 Synthesis of 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (13C)

General Procedure 3 was followed by using phenyl-3-(prop-2-yn-1-ylamino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**48B**) (132 mg, 0.40 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02mmol), CuI (4 mg, 0.02mmol) and 4-iodoanisole (93 mg, 0.40 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**13C**) (brown solid, 149 mg, 86% yield).

13C: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.35 (br s, 1H), 7.98-7.89 (m, 2H), 7.79-7.69 (m, 3H), 7.50-7.42 (m, 4H), 7.37-7.34 (m, 2H), 6.87-6.85 (m, 2H), 5.85 (s, 1H), 4.14 (d, *J* = 6.4 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.4, 164.1, 159.8, 139.8, 138.7, 133.2, 131.2, 128.5, 128.4, 128.3, 127.2, 125.7, 114.4, 114.0, 94.8, 84.5, 83.4, 55.3, 36.2; IR (neat): 1596, 1508, 1321, 1247, 1165, 1109, 1066, 1016, 831, 688; MS (ESI, *m/z*): 436.15 $[M+H]^+$; HRMS (ESI): calc. for $C_{26}H_{20}F_3NO_2$: 436.1519 $[M+H]^+$, found: 436.1515.

4.3.4 Synthesis of 3-(2-methoxyphenyl)-3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenylprop-2-en-1-one (13D)

General Procedure 3 was followed by using 3-(2-methoxyphenyl)-1-phenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**48C**) (116 mg, 0.40 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02mmol), CuI (4 mg, 0.02 mmol) and 4-iodoanisole (93 mg, 0.40 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-(2-methoxyphenyl)-3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenylprop-2-en-1-one (**13D**) (brown oil, 146 mg, 92% yield).

13D: ^1H NMR (400 MHz, $CDCl_3$): δ 11.53 (br s, 1H), 7.97-7.88 (m, 2H), 7.54-7.31 (m, 7H), 7.14-6.97 (m, 2H), 6.87-6.78 (m, 2H), 5.79 (s, 1H), 4.25-4.14 (m, 2H), 3.89 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8, 163.4, 159.6, 156.2, 140.3, 133.1, 131.1, 130.7, 129.9, 128.1, 127.1, 124.1, 120.9, 114.9, 113.9, 110.8, 93.4, 83.7, 83.4, 55.6, 55.3, 34.8; IR (neat): 1733, 1566, 1508, 1239, 1171, 1020, 832, 752, 691, 538; MS (ESI, *m/z*): 398.18 $[M+H]^+$; HRMS (ESI): calc. for $C_{26}H_{23}NO_3$: 398.1751 $[M+H]^+$, found: 398.1754.

4.3.5 Synthesis of 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenylhept-2-en-1-one (13E)

General Procedure 3 was followed by using phenyl-3-(prop-2-yn-1-ylamino)hept-2-en-1-one (**48D**) (96 mg, 0.40 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and 4-iodoanisole (93 mg, 0.40 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenylhept-2-en-1-one (**13E**) (yellow-brown solid, 127 mg, 92% yield).

13E: ^1H NMR (400 MHz, $CDCl_3$): δ 11.59 (br s, 1H), 7.98-7.84 (m, 2H), 7.51-7.33 (m, 5H), 6.93-6.77 (m, 2H), 5.78 (s, 1H), 4.33 (d, *J* = 6.0 Hz, 2H), 3.82 (s, 3H), 2.52-2.43 (t, *J* = 8.0, 2H), 1.74-1.66 (m, 2H), 1.54-1.45 (m, 2H), 1.00 (t, *J* = 7.6, 3H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 188.5, 168.3, 159.8, 140.5, 133.2, 130.6, 128.2, 127.0, 114.6, 113.9, 92.0, 84.0, 83.0, 55.3, 33.2, 32.0, 30.3, 22.7, 13.9; IR (neat): 1583, 1544, 1507, 1288, 1246, 1171, 1090, 1025, 832, 746, 690, 601, 539; MS (ESI, *m/z*): 348.20 $[M+H]^+$; HRMS (ESI): calc. for $C_{23}H_{26}NO_2$: 348.1964 $[M+H]^+$, found: 348.1984.

4.3.6 Synthesis of 3-((3-(2-aminophenyl)prop-2-yn-1-yl)amino)-1,3-diphenyl-prop-2-en-1-one (13F)

General Procedure 3 was followed by using 1,3-diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one (**48A**) (104 mg, 0.40 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), CuI (4 mg, 0.02 mmol) and 2-iodoaniline (87 mg, 0.4 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded 3-((3-(2-aminophenyl)prop-2-yn-1-yl)amino)-1,3-diphenylprop-2-en-1-one (**13F**) (yellow-brown liquid, 126 mg, 90% yield).

13F: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.54 (br s, 1H), 7.98 (d, *J* = 6.0 Hz, 2H), 7.62-7.38 (m, 10H), 7.29-7.27 (dd, *J* = 5.6, 7.6 Hz, 1H), 7.15 (m, 1H), 6.70 (m, 2H), 5.88 (s, 1H), 4.32 (d, *J* = 6.0 Hz, 3H), 3.66 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.7, 166.7, 144.2, 140.1, 130.9, 129.7, 128.9, 128.8, 128.7, 127.1, 122.6, 126.3, 119.1, 116.4, 112.7, 94.2, 35.2.

4.4 General Procedure 4. Synthesis of iodo-subsituted pyridines 14

In a round-bottomed flask, arylated *N*-propargylic *β*-enaminone derivative **13** (100 mg, 0.40 mmol) was dissolved in acetonitrile (10 mL) and to this solution, I_2 (303 mg, 1.20 mmol) and $NaHCO_3$ (100 mg, 1.20 mmol) were added, respectively. The resulting reaction mixture was then refluxed at 82 ^oC for 5 h under air. When the reaction was over, saturated aqueous solution of $Na_2S_2O_3$ (35 mL) was added to remove unreacted excess I_2. Subsequently, the mixture was extracted with ethyl acetate (2 x 20 mL). The separated organic phase was washed with water (50 mL) and dried over $MgSO_4$ and filtered. The obtained crude product was purified by flash chromatography on silica gel using hexane/ethyl acetate as the eluent.

4.4.1. Synthesis of (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (14A)

General Procedure 4 was followed by using 1,3-diphenyl-3-((3-phenylprop-2-yn-1-yl)amino)prop-2-en-1-one (**13A**) (134 mg, 0.40 mmol), I_2 (303 mg, 1.20 mmol) and $NaHCO_3$ (100 mg, 1.20 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**14A**) (black solid, 155 mg, 84% yield).

14A: ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR ($CDCl_3$): δ 9.07 (s, 1H), 7.36-7.34 (m, 2H), 7.28 (dd, *J* = 8.0, 6.4 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 2H), 7.10-7.02 (m, 8H), 6.85 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 157.4, 155.8, 152.4, 139.3, 138.3, 133.3, 131.9, 129.2, 129.0, 128.9, 128.6, 128.3, 128.2, 91.1; IR (neat): 1707, 1674, 1594, 1577, 1447, 1374, 1316, 1257, 1229, 1042, 954, 757, 720, 697, 653, 531; MS (ESI, *m/z*): 462.03 $[M+H]^+$; HRMS (ESI): calc. for $C_{24}H_{16}INO$: 462.0349 $[M+H]^+$, found: 462.0345.

4.4.2 Synthesis of (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl) methanone (14B)

General Procedure 4 was followed by using 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1,3-diphenylprop-2-en-1-one (**13B**) (146 mg, 0.40 mmol), I_2 (303 mg, 1.20 mmol) and $NaHCO_3$ (100 mg, 1.20 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl) methanone (**14B**) (brown solid, 163 mg, 83% yield).

14B: ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR ($CDCl_3$): δ 9.30 (s, 1H), 7.59-7.47 (m, 4H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.33-7.20 (m, 6H), 6.96-6.80 (br m, 2H), 6.69 (br s, 1H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 159.6, 157.4, 155.9, 152.2, 138.4, 137.1, 135.5, 133.3, 131.6, 129.2, 129.0, 128.9, 128.3, 113.5, 99.4, 55.1; IR (neat): 1733, 1664, 1605, 1540, 1507, 1419, 1287, 1244, 1173, 1027, 940, 827, 787, 760, 697, 573, 532, 419; MS (ESI, *m/z*): 492.05 $[M+H]^+$; HRMS (ESI): calc. for $C_{25}H_{18}INO_2$: 492.0460 $[M+H]^+$, found: 492.0470.

4.4.3 Synthesis of (2-butyl-5-iodo-4-(4-methoxyphenyl)pyridin-3-yl)(phenyl) methanone (14C)

General Procedure 4 was followed by using 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenylhept-2-en-1-one (**13E**) (138 mg, 0.40 mmol), I_2 (303 mg, 1.20 mmol) and $NaHCO_3$ (100 mg, 1.20 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2-butyl-5-iodo-4-(4-methoxyphenyl)pyridin-3-yl)(phenyl) methanone (**14C**) (yellow-brown oil, 122 mg, 65% yield).

14C: ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR ($CDCl_3$): δ 8.98 (s, 1H), 7.49-7.43 (m, 2H), 7.39 (t, *J* = 6.4 Hz, 1H), 7.22 (dd, *J* = 16.0, 8.0 Hz, 2H), 6.85 (br s, 2H), 6.35 (br s, 2H), 3.64 (s, 3H), 2.51 (t, *J* = 8.0 Hz, 2H), 1.58 (s, 2H), 1.25-1.13 (m, 2H), 0.73 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 159.5, 158.4, 157.1, 150.8, 136.9, 135.8, 133.7, 131.4, 129.2, 128.5, 113.4, 97.1, 55.1, 35.5, 31.6, 22.6, 13.8; IR (neat): 2956, 1734, 1668, 1608, 1510, 1428, 1246, 1175, 1029, 942, 832, 799, 729, 708, 554; MS (ESI, *m/z*): 472.08 $[M+H]^+$; HRMS (ESI): calc. for $C_{23}H_{22}INO_2$: 472.0773 $[M+H]^+$, found: 472.0779.

4.4.4 Synthesis of (5-iodo-2-(2-methoxyphenyl)-4-(4-methoxyphenyl)pyridin-3-yl)(phenyl)methanone (14D)

General Procedure 4 was followed by using 3-(2-methoxyphenyl)-3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenylprop-2-en-1-one (**13D**) (159 mg, 0.40 mmol), I_2 (303 mg, 1.20 mmol) and $NaHCO_3$ (100 mg, 1.20 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (5-iodo-2-(2-methoxyphenyl)-4-(4-methoxyphenyl)pyridin-3-yl)(phenyl)methanone (**14D**) (yellow solid, 181 mg, 87% yield).

14D: ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR ($CDCl_3$): δ 9.14 (s, 1H), 7.43-7.35 (m, 2H), 7.29-7.05 (m, 6H), 6.92 (br s, 2H), 6.83 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.64 (br s, 1H), 6.60 (t, *J* = 10.4 Hz, 1H), 3.65 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9, 159.5, 157.3, 155.8, 154.8, 151.5, 137.0, 136.6, 132.6, 131.9, 131.4, 130.3, 129.2, 127.7, 120.5, 113.4, 110.4, 99.2, 55.1, 54.5; IR (neat): 3649, 1661, 1606, 1507, 1420, 1285, 1246, 1176, 117, 1015, 937, 836, 810, 758, 700, 651, 546; MS (ESI, *m/z*): 522.06 $[M+H]^+$; HRMS (ESI): calc. for $C_{26}H_{20}INO_3$: 522.0561 $[M+H]^+$, found: 522.0562.

4.4.5 Synthesis of (5-iodo-4-(4-methoxyphenyl)-2-(4-(trifluoromethyl) phenyl)pyridin-3-yl)(phenyl)methanone (14E)

General Procedure 4 was followed by using 3-((3-(4-methoxyphenyl)prop-2-yn-1-yl)amino)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**13C**) (174 mg, 0.40 mmol), I_2 (303 mg, 1.20 mmol) and $NaHCO_3$ (100 mg, 1.20 mmol). Final purification of the crude product using 19:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (5-iodo-4-(4-methoxyphenyl)-2-(4-(trifluoromethyl) phenyl)pyridin-3-yl)(phenyl)methanone (**14E**) (brown solid, 172 mg, 77% yield).

14E: ^1H NMR (400 MHz, $CDCl_3$): δ 9.16 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.47-7.27 (m, 6H), 7.15 (dd, *J* = 16.0, 6.4 Hz, 2H), 6.73 (br s, 3H), 3.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 157.4, 155.3, 152.1, 150.1, 139.6, 134.6, 131.4, 128.9, 127.1, 126.9, 126.2, 123.0, 111.3, 52.9; IR (neat): 1717, 1671, 1615, 1541, 1508, 1420, 1321, 1248, 1159, 1120, 1067, 1014, 942, 844, 798, 710, 688, 661, 559; MS (ESI, *m/z*): 560.03 $[M+H]^+$; HRMS (ESI): calc. for $C_{26}H_{17}F_3INO_2$: 560.0329 $[M+H]^+$, found: 560.0327.

4.5 Synthesis of 1-iodo-4,5-diphenylbenzo[c][2,7]naphthyridine (52)

3-((3-(2-Aminophenyl)prop-2-yn-1-yl)amino)-1,3-diphenylprop-2-en-1-one (**13F**) (100 mg, 0.30 mmol) was dissolved in DCM (2.0 mL), and to this solution, I_2 (303 mg, 1.2 mmol) and $NaHCO_3$ (100 mg, 1.2 mmol) were added, respectively. The resulting reaction mixture was then stirred at room temperature for 20 h under argon atmosphere. When the reaction was over, saturated aqueous solution of $Na_2S_2O_3$ (35 mL) was added to remove unreacted excess I_2. Subsequently, the mixture was extracted with ethyl acetate (2 x 20 mL). The separated organic phase was washed with water (50 mL) and dried over $MgSO_4$ and filtered. The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 1-iodo-4,5-diphenylbenzo[c][2,7]naphthyridine (**52**) (brown oil, 34 mg, 25% yield).

52: ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.07 (s, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.99-7.86 (m, 1H), 7.69 (s, 1H), 7.57-7.35 (m, 8H), 7.23-7.13 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 165.4, 157.7, 151.7, 137.5, 134.5, 134.3, 133.0, 132.0, 130.1, 129.9, 129.2, 129.0, 128.9, 126.8, 125.0, 122.7, 122.6, 96.9; IR (neat): 1653, 1576, 1508, 1457, 1437, 1360, 1298, 1073, 999, 758, 689, 624, 584.

4.6 General Procedure 5. Synthesis of alkynyl-substituted pyridines 15 and 16

The corresponding iodo-substituted pyridine derivative **14** (100 mg, 0.20 mmol) was dissolved in DMF (2 mL) and to this solution, Et$_3$N (1.5 ml), PdCl$_2$(PPh$_3$)$_2$ (7 mg, 5% mmol) and CuI (2 mg, 5% mmol) were added. Finally, terminal alkyne (25 mg, 0.24 mmol) was added to the solution and the resulting reaction mixture was heated at 65 ^{o}C for 10 h under argon atmosphere. When the reaction was over, water (50 mL) was added to the flask and the organic layer was exracted with ethyl acetate (2 x 25 ml). The separated organic phase was washed with water (2 x 50 mL) and then dried over MgSO$_4$ and filtered. The obtained crude product was purified by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent.

4.6.1 Synthesis of (5-((4-methoxyphenyl)ethynyl)-2,4-diphenylpyridin-3-yl)-(phenyl)methanone (15A)

General Procedure 5 was followed by using (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**14A**) (100 mg, 0.20 mmol), PdCl$_2$(PPh$_3$)$_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynylanisole (32 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (5-((4-methoxyphenyl)ethynyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**15A**) (brown solid, 57 mg, 62% yield).

15A: ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.92 (s, 1H), 7.45 (m, 4H), 7.33-7.25 (m, 1H), 7.24-7.05 (m, 12H), 6.72 (m, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 198.0, 160.0, 152.2, 149.9, 141.4, 133.2, 133.0, 129.3, 129.1, 128.8, 128.3, 127.8, 119.2, 114.0, 96.8, 86.8, 55,3; IR (neat): 2216, 1672, 1602, 1508, 1445, 1291, 1253, 1226, 1162, 1030, 992, 876, 833, 807, 757, 697, 575, 535, 509; MS (ESI, *m/z*): 466.18 [M+H]$^+$; HRMS (ESI): calc. for $C_{33}H_{23}NO_2$: 466.1802 [M+H]$^+$, found: 466.1802.

4.6.2 Synthesis of (2,4-diphenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl) methanone (15B)

General Procedure 5 was followed by using (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**14A**) (100 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and phenylacetylene (25 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2,4-diphenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl) methanone (**15B**) (white-yellow solid, 74 mg, 85% yield).

15B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.92 (s, 1H), 7.56-7.34 (m, 4H), 7.30-7.05 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 142.0, 136.4, 134.7, 132.2, 130.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.4, 127.3, 126.8, 92.6, 92.5, 88.7; IR (neat): 1669, 1592, 1489, 1434, 1322, 1258, 1220, 1002, 873, 754, 717, 701, 685, 591, 514; MS (ESI, *m/z*): 436.17 [M+H]$^+$; HRMS (ESI): calc. for $C_{32}H_{21}NO$: 436.1695 [M+H]$^+$, found: 436.1692.

4.6.3 Synthesis of (2,4-diphenyl-5-(thiophen-3-ylethynyl)pyridin-3-yl)(phenyl) methanone (15C)

General Procedure 5 was followed by using (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**14A**) (100 mg, 0.20mmol), $PdCl_2(PPh_3)_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 3-ethynylthiophene (26 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2,4-diphenyl-5-(thiophen-3-yl-ethynyl)pyridin-3-yl)(phenyl) methanone (**15C**) (white-yellow oil, 67 mg, 76% yield).

15C: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (s, 1H), 7.61-7.52 (m, 4H), 7.37 (t, J = 7.2 Hz, 1H), 7.34-7.19 (m, 12H), 6.93 (dd, J = 4.8, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 155.3, 152.3, 150.2, 139.0, 137.5, 135.8, 133.7, 133.3, 129.6, 129.5, 129.3, 129.1, 128.9, 128.4, 128.3, 127.8, 125.5, 121.6, 118.9, 91.8, 85.0; IR (neat): 1730, 1710, 1698, 1683, 1653, 1635, 1558, 1541, 1520, 1507, 1489, 1436, 1027, 694, 419; MS (ESI, *m/z*): 442.13 $[M+H]^+$; HRMS (ESI): calc. for $C_{30}H_{19}NOS$: 442.1260 $[M+H]^+$, found: 442.1262.

4.6.4 Synthesis of (2,4-diphenyl-5-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (15D)

General Procedure 5 was followed by using (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**14A**) (100 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynyl-alpha,alpha,alpha-trifluorotoluene (40 mg, 0.24 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2,4-diphenyl-5-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (**15D**) (yellow solid, 92 mg, 92% yield).

15D: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08 (s, 1H), 7.67-7.50 (m, 6H), 7.40-7.22 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 155.9, 152.5, 150.7, 138.9, 137.4, 135.7, 133.8, 133.4, 131.7, 130.5, 130.2, 129.5, 129.4, 129.3, 129.2, 129.0, 128.6, 128.3, 127.9, 126.3, 125.3, 122.5, 118.2, 94.9, 87.8; IR (neat): 1663, 1558, 1521, 1437, 1316, 1226, 1161, 1118, 1064, 1016, 874, 833, 756, 716, 698, 597, 520; MS (ESI, *m/z*): 504.16 $[M+H]^+$; HRMS (ESI): calc. for $C_{33}H_{20}F_3NO$: 504.1570 $[M+H]^+$, found: 504.1564.

4.6.5 Synthesis of (2,4-diphenyl-5-(*p*-tolylethynyl)pyridin-3-yl)(phenyl) methanone (15E)

General Procedure 5 was followed by using (5-iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**14A**) (100 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynyltoluene (28 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2,4-diphenyl-5-(*p*-tolylethynyl)pyridin-3-yl)(phenyl) methanone (**15E**) (yellow solid, 86 mg, 96% yield).

15E: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (s, 1H), 7.51-7.41 (m, 4H), 7.35-7.09 (m, 11H), 7.08-6.96 (m, 4H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 152.2, 150.3, 139.1, 138.9, 137.5, 135.8, 133.2, 131.4, 129.5, 129.3, 129.2, 129.1, 128.9, 128.4, 128.3, 127.8, 119.4, 119.2, 96.9, 84.7, 21.5; IR (neat): 1733, 1670, 1558, 1507, 1437, 1225, 1174, 992, 875, 813, 755, 696, 577, 529, 507; MS (ESI, *m/z*): 450.18 $[M+H]^+$; HRMS (ESI): calc. for $C_{33}H_{23}NO$: 450.1852 $[M+H]^+$, found: 450.1847.

4.6.6 Synthesis of (4-(4-methoxyphenyl)-2-phenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl)methanone (16A)

General Procedure 5 was followed by using (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl)methanone (**14B**) (100 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 5% mmol), CuI (2 mg 5% mmol) and phenylacetylene (25 mg, 0.24 mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (4-(4-methoxyphenyl)-2-phenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl)methanone (**16A**) (yellow oil, 56 mg, 60% yield).

16A: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (s, 1H), 7.62-7.48 (m, 4H), 7.32 (m, 13H), 6.81 (d, J = 8.0 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 159.6, 152.6, 149.9, 131.5, 131.0, 129.3, 129.1, 128.8, 128.4, 128.3, 122.6, 119.0, 113.3, 96.4, 85.6, 55.2; IR (neat): 1733, 1716, 1683, 1558, 1507, 1457, 1009, 911, 669, 535, 471, 419; MS (ESI, *m/z*): 466.18 $[M+H]^+$; HRMS (ESI): calc. for $C_{33}H_{23}NO_2$: 466.1802 $[M+H]^+$, found: 466.1808.

4.6.7 Synthesis of (4-(4-methoxyphenyl)-2-phenyl-5-(p-tolylethynyl)pyridin-3-yl)(phenyl)methanone (16B)

General Procedure 5 was followed by using (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl) methanone (**14B**) (100 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynyltoluene (28 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (4-(4-methoxyphenyl)-2-phenyl-

5-(p-tolylethynyl)pyridin-3-yl)(phenyl)methanone (**16B**) (brown solid, 84 mg, 88% yield).

16B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (s, 1H), 7.55 (dd, *J* = 6.4, 3.2 Hz, 4H), 7.43-7.33 (m, 2H), 7.32-7.18 (m, 8H), 7.13 (t, *J* = 6.4 Hz, 2H), 6.82 (t, *J* = 10.0 Hz, 2H), 3.76 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 159.6, 155.2, 152.6, 149.7, 139.1, 139.0, 137.5, 133.8, 133.2, 131.4, 131.0, 129.3, 129.1, 128.8, 128.3, 128.2, 128.0, 119.6, 119.2, 113.3, 96.6, 85.1, 55.2, 21.54; IR (neat): 2210, 1732, 1668, 1607, 1507, 1437, 1248, 1177, 1030, 876, 846, 817, 763, 699, 595, 528, 504; MS (ESI, *m/z*): 480.20 $[M+H]^+$; HRMS (ESI): calc. for $C_{34}H_{15}NO_2$: 480.1958 $[M+H]^+$, found: 480.1959.

4.6.8 Synthesis of (4-(4-methoxyphenyl)-2-phenyl-5-(thiophen-3-ylethynyl) pyridin-3-yl)(phenyl)methanone (16C)

General Procedure 5 was followed by using (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl) methanone (**14B**) (100 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (0.01mmol), CuI (0.01mmol) and 3-ethynylthiophene (25 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (4-(4-methoxyphenyl)-2-phenyl-5-(thiophen-3-ylethynyl) pyridin-3-yl)(phenyl)methanone (**16C**) (yellow solid, 77 mg, 82% yield).

16C: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (s, 1H), 7.59-7.51 (m, 4H), 7.42-7.34 (m, 2H), 7.31-7.20 (m, 8H), 7.03-6.97 (dd, *J* = 4.8, 0.8 Hz, 1H) 6.80 (d, *J* = 8.0 Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 159.7, 155.3, 152.4, 149.8, 139.0, 137.5, 133.9, 133.3, 130.9, 129.6, 129.3, 129.1, 128.8, 128.3, 128.0, 125.5, 121.7, 119.0, 113.3, 91.5, 85.2, 55.2; IR (neat): 1733, 1716, 1699, 1668, 1607, 1576, 1541, 1507, 1435, 1249, 1175, 1029, 927, 840, 816, 784, 694, 670, 620, 420; MS (ESI, *m/z*): 472.14 $[M+H]^+$; HRMS (ESI): calc. for $C_{31}H_{21}NO_2S$: 472.1366 $[M+H]^+$, found: 472.1363.

4.6.9 Synthesis of (4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-2-phenylpyridin-3-yl)(phenyl)methanone (16D)

General Procedure 5 was followed by using (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl)methanone (**14B**) (100 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynylanisole (32 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-2-phenylpyridin-3-yl)(phenyl)methanone (**16D**) (bright yellow solid, 77 mg, 78% yield).

16D: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (s, 1H), 7.53 (m, 4H), 7.42-7.34 (m, 1H), 7.33-7.20 (m, 9H), 6.84 (m, 4H), 3.81 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.7, 160.0, 159.6, 155.0, 152.4, 149.5, 139.1, 137.5, 133.8, 133.2, 133.0, 131.0, 129.3, 129.1, 128.7, 128.3, 128.1, 119.3, 114.7, 114.0, 113.3, 96.5, 84.5, 55.3, 55.2; IR (neat): 2205, 1671, 1604, 1507, 1438, 1289, 1247, 1172, 1019, 877, 829, 768, 701, 533; MS (ESI, *m/z*): 496.19 $[M+H]^+$; HRMS (ESI): calc. for $C_{34}H_{15}NO_3$: 496.1907 $[M+H]^+$, found: 496.1908.

4.6.10 Synthesis of (4-(4-methoxyphenyl)-2-phenyl-5-((4-(trifluoromethyl) phenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (16E)

General Procedure 5 was followed by using (5-iodo-4-(4-methoxyphenyl)-2-phenylpyridin-3-yl)(phenyl)methanone (**14B**) (100 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynyl-alpha,alpha,alpha-trifluorotoluene (40 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (4-(4-methoxyphenyl)-2-phenyl-5-((4-(trifluoromethyl) phenyl)ethynyl)-pyridin-3-yl)(phenyl)methanone (**16E**) (yellow-brown solid, 93 mg, 87% yield).

16E: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (s, 1H), 7.56 (d, J = 5.6 Hz, 7H), 7.45-7.34 (m, 3H), 7.33-7.19 (m, 6H), 6.82 (d, J = 8.0 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 159.8, 156.0, 152.7, 150.3, 138.9, 137.4, 134.0, 133.4, 131.7, 130.9, 129.3, 129.2, 129.0, 128.4, 128.3, 127.8, 125.3, 118.3, 113.3, 94.6, 88.0, 55.2; IR (neat): 1734, 1669, 1607, 1507, 1437, 1320, 1246, 1172, 1106, 1061, 1017, 875, 840, 760, 698, 593, 563, 524; MS (ESI, *m/z*): 534.17 [M+H]$^+$; HRMS (ESI): calc. for $C_{34}H_{22}F_3NO$: 534.1675 [M+H]$^+$, found: 534.1673.

4.6.11 Synthesis of (2-(2-methoxyphenyl)-4-(4-methoxyphenyl)-5-((4-methoxy phenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (16F)

General Procedure 5 was followed by using (5-iodo-2-(2-methoxyphenyl)-4-(4-methoxyphenyl)pyridin-3-yl)(phenyl)methanone (**14D**) (100 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynylanisole (32 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2-(2-methoxyphenyl)-4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)pyridin-3-yl)-(phenyl)methanone (**16F**) (yellow-brown solid, 75 mg, 72% yield).

16F: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (s, 1H), 7.45-7.37 (m, 2H), 7.26 (dt, *J* = 8.0, 8.0, 2.0 Hz, 1H), 7.21-7.00 (m, 8H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.69 (dd, *J* = 8.0, 2.0 Hz, 2H), 6.61 (t, *J* = 8.0 Hz, 2H), 6.53 (d, *J* = 8.0 Hz, 1H), 3.67 (s, 3H), 3.60 (s, 3H), 3.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 160.0, 159.6, 155.8, 154.0, 152.4, 148.7, 137.4, 134.5, 133.0, 132.4, 131.5, 131.2, 130.1, 129.3, 128.6, 128.1, 127.7, 120.6, 119.0, 114.8, 114.0, 113.2, 110.3, 96.0, 84.6, 55.3, 55.2, 54.2; IR (neat): 1733, 1654, 1602, 1507, 1437, 1288, 1246, 1174, 1107, 1031, 876, 835, 758, 703, 593, 534; MS (ESI, *m/z*): 526.20 [M+H]$^+$; HRMS (ESI): calc. for $C_{35}H_{27}NO_4$: 526.2013 [M+H]$^+$, found: 526.2013.

4.6.12 Synthesis of (4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-2-(4-(trifluoromethyl)phenyl)pyridin-3-yl)(phenyl)methanone (16G)

General Procedure 5 was followed by using (5-iodo-4-(4-methoxyphenyl)-2-(4-(trifluoromethyl) phenyl)pyridin-3-yl)(phenyl)methanone (**14E**) (100 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynylanisole (32 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-2-(4-(trifluoromethyl)phenyl)-pyridin-3-yl)(phenyl)methanone (**16G**) (yellow-brown solid, 79 mg, 70% yield).

16G: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.54 (dd, *J* = 6.4, 1.6 Hz, 4H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.34-7.19 (m, 6H), 6.82 (dd, *J* = 16.0, 8.0 Hz, 4H), 3.82 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 160.1, 159.7, 153.4, 152.5, 149.5, 142.6, 137.3, 134.0, 133.6, 131.0, 129.5, 129.2, 128.5, 127.8, 125.2, 120.0, 114.5, 114.1, 113.3, 97.1, 84.2, 55.3, 55.2; IR (neat): 2215, 1664, 1605, 1507, 1441, 1321, 1292, 1247, 1157, 1110, 1066, 1028, 875, 822, 707, 660, 591, 528; MS (ESI, *m/z*): 564.18 $[M+H]^+$; HRMS (ESI): calc. for $C_{35}H_{24}F_3NO_3$: 564.1781 $[M+H]^+$, found: 564.1782.

4.6.13 Synthesis of (2-butyl-4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl) pyridin-3-yl)(phenyl)methanone (16H)

General Procedure 5 was followed by using (2-butyl-5-iodo-4-(4-methoxyphenyl)pyridin-3-yl)(phenyl)methanone (**14C**) (100 mg, 0.20 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 5% mmol), CuI (2 mg, 5% mmol) and 4-ethynylanisole (32 mg, 0.24mmol). Final purification of the crude product using 9:1 hexane/ethyl acetate as the eluent by flash column chromatography on silica gel afforded (2-butyl-4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (**16H**) (white-yellow solid, 66 mg, 70% yield).

16H: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 7.63-7.56 (m, 2H), 7.47 (t, *J* = 8.0 Hz, 1H), 7.36-7.19 (m, 6H), 6.80 (m, 4H), 3.80 (s, 3H), 3.75 (s, 3H), 2.68 (t, *J* = 8.0 Hz, 2H), 1.69 (s, 2H), 1.35-1.25 (m, 2H), 0.84 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.3, 159.9, 159.6, 157.8, 152.3, 148.2, 137.2, 133.8, 133.5, 132.9, 131.1, 129.3, 128.4, 128.2, 117.7, 114.8, 114.0, 113.2, 95.3, 84.4, 55.3, 55.2, 36.0, 31.8, 22.7, 13.8; IR (neat): 2218, 1656, 1605, 1510, 1446, 1289, 1247, 1185, 1027, 889, 834, 808, 713, 536; MS (ESI, *m/z*): 476.22 $[M+H]^+$; HRMS (ESI): calc. for $C_{32}H_{29}NO_3$: 476.2220 $[M+H]^+$, found: 476.2218.

4.7 Synthesis of (5-iodo-6-(4-methoxyphenyl)-2-phenylbenzo[f]isoquinolin-1-yl)(phenyl)methanone (43A)

(5-((4-Methoxyphenyl)ethynyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**15A**) (100 mg, 0.22 mmol) was dissolved in acetonitrile (10 mL) and to this solution, I_2

(166 mg, 0.66 mmol) and $NaHCO_3$ (55 mg, 0.66 mmol) were added. The resulting reaction mixture was then refluxed at 82 ^{o}C for 10 h under air. When the reaction was over, saturated aqueous solution of $Na_2S_2O_3$ (35 mL) was added to remove unreacted excess I_2. Subsequently, the mixture was extracted with ethyl acetate (2 x 20 mL). The separated organic phase was washed with water (50 mL) and dried over $MgSO_4$ and filtered. The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford (5-iodo-6-(4-methoxyphenyl)-2-phenylbenzo[f]isoquinolin-1-yl)(phenyl)methanone (**43A**) (white-yellow solid, 83 mg, 64% yield).

43A: ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.68-7.60 (m, 2H), 7.44 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.39-7.30 (m, 4H), 7.30-7.09 (m, 8H), 7.04-7.02 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.5, 159.5, 158.3, 153.9, 147.7, 139.4, 137.8, 136.8, 135.4, 134.6, 133.7, 131.0, 129.9, 129.5, 129.3, 129.1, 128.9, 128.7, 128.2, 127.9, 127.8, 127.0, 125.7, 114.1, 103.4, 55.4; IR (neat): 2919, 1668, 1605, 1508, 1447, 1409, 1287, 1243, 1211, 1174, 1028, 945, 884, 837, 767, 744, 694, 632, 568, 512, 438; MS (ESI, *m/z*): 592.08 $[M+H]^+$; HRMS (ESI): calc. for $C_{33}H_{22}INO_2$: 592.0768 $[M+H]^+$, found: 592.0756.

4.8 General Procedure 6. Synthesis of iodo-substituted spiro-fused pyridine derivatives 44

The corresponding 5-alkynyl-4-(4-methoxyphenyl)pyridine derivative **16** (100 mg, 0.4 mmol) was dissolved in acetonitrile (10 mL) and to this solution, I_2 (303 mg, 1.2 mmol) and $NaHCO_3$ (100 mg, 1.2 mmol) were added. The resulting reaction mixture was then refluxed at 82 ^{o}C for 2 h under air. When the reaction was over, saturated aqueous solution of $Na_2S_2O_3$ (35 mL) was added to remove unreacted excess I_2. Subsequently, the mixture was extracted with ethyl acetate (2 x 20 mL). The separated organic phase was washed with water (50 mL) and dried over $MgSO_4$ and filtered. The obtained crude product was purified by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent.

4.8.1 Synthesis of 4'-benzoyl-7'-iodo-3',6'-diphenylspiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44A)

General Procedure 6 was followed by using (4-(4-methoxyphenyl)-2-phenyl-5-(phenylethynyl)pyridin-3-yl)(phenyl)methanone (**16A**) (100 mg, 0.2 mmol) and $NaHCO_3$ (50 mg, 0.6mmol), I_2 (151 mg, 0.6mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4'-benzoyl-7'-iodo-3',6'-diphenylspiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (**44A**) (light yellow solid, 75 mg, 65% yield).

44A: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (s, 1H), 7.39-7.22 (m, 6H), 7.48 (dd, *J* = 8.0, 2.0 Hz, 2H), 7.14 (m, 7H), 6.45-5.94 (br m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.5, 184.6, 155.5, 152.9, 147.4, 145.0, 140.2, 138.6, 136.2, 133.8, 133.5, 132.4, 131.1, 129.4, 129.3, 129.1, 128.8, 128.5, 128.4, 94.6, 62.8; IR (neat): 1660, 1558, 1421, 1388, 1237, 1159, 1042, 916, 871, 851, 764, 694, 671, 591, 542, 443, 420; MS (ESI, *m/z*): 578.06 $[M+H]^+$; HRMS (ESI): calc. for $C_{32}H_{20}INO_2$: 578.0612 $[M+H]^+$, found: 578.0603.

4.8.2 Synthesis of 4'-benzoyl-7'-iodo-3'-phenyl-6'-(p-tolyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44B)

General Procedure 6 was followed by using (4-(4-methoxyphenyl)-2-phenyl-5-(p-tolylethynyl)pyridin-3-yl)(phenyl)methanone (**16B**) (100 mg, 0.2 mmol) and $NaHCO_3$ (50 mg, 0.6mmol), I_2 (151 mg, 0.6mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4'-benzoyl-7'-iodo-3'-phenyl-6'-(p-tolyl)spiro[cyclohexa [2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (**44B**) (yellow solid, 70 mg, 60% yield).

44B: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 7.58-7.55 (m, 2H), 7.49-7.37 (m, 4H), 7.30-7.19 (m, 4H), 7.15-7.07 (m, 4H), 6.52-6.00 (br m, 4H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 184.7, 155.5, 152.9, 147.2, 145.1, 140.2, 139.3, 138.8, 136.3, 133.8, 132.3, 131.1, 130.5, 129.4, 129.3, 129.1, 129.0, 128.6, 128.5, 128.4, 94.3, 62.8, 21.4; IR (neat): 1733, 1660, 1558, 1507, 1419, 1396, 1239, 1174, 917, 873, 854, 822, 756, 695, 672; MS (ESI, *m/z*): 592.08 $[M+H]^+$; HRMS (ESI): calc. for $C_{33}H_{22}INO_2$: 592.0768 $[M+H]^+$, found: 592.0757.

4.8.3 Synthesis of 4'-benzoyl-7'-iodo-3'-phenyl-6'-(thiophen-3-yl)spiro [cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44C)

General Procedure 6 was followed by using (4-(4-methoxyphenyl)-2-phenyl-5-(thiophen-3-ylethynyl)pyridin-3-yl)(phenyl)methanone (**16C**) (100 mg, 0.2 mmol) and $NaHCO_3$ (50 mg, 0.6mmol), I_2 (151 mg, 0.6mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4'-benzoyl-7'-iodo-3'-phenyl-6'-(thiophen-3-yl)spiro [cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (**44C**) (yellow solid, 78 mg, 67% yield).

44C: ^1H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 7.50-7.41 (m, 3H), 7.32 (dd, *J* = 7.2, 6.0 Hz, 3H), 7.22 (d, *J* = 2.0 Hz, 2H), 7.15 (m, 5H), 6.45-5.90 (br m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 184.7, 184.6, 155.5, 146.4, 145.2, 140.4, 138.7, 136.3, 133.8, 133.4, 130.9, 129.4, 129.3, 129.0, 128.5, 128.4, 127.0, 125.7, 92.9, 62.5; IR (neat): 1658, 1620, 1550, 1421, 1397, 1314, 1236, 1182, 1034, 901, 858, 797, 753, 694, 672, 624, 593, 559, 443; MS (ESI, *m/z*): 584.02 $[M+H]^+$; HRMS (ESI): calc. for $C_{30}H_{18}INO_2S$: 584.0176 $[M+H]^+$, found: 584.0170.

4.8.4 Synthesis of 4'-benzoyl-7'-iodo-6'-(4-methoxyphenyl)-3'-phenylspiro [cyclohexa[2,5] diene-1,5'-cyclopenta[c]pyridin]-4-one (44D)

General Procedure 6 was followed by using (4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-2-phenylpyridin-3-yl)(phenyl)methanone (**16D**) (100 mg, 0.20 mmol) and $NaHCO_3$ (50 mg, 0.60 mmol), I_2 (151 mg, 0.6 mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4'-benzoyl-7'-iodo-6'-(4-methoxyphenyl)-3'-phenylspiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (**44D**) (yellow solid, 110 mg, 92% yield).

44D: ^1H NMR (400 MHz, $CDCl_3$): δ 8.94 (s, 1H), 7.62-7.49 (m, 2H), 7.42 (dd, *J* = 16.0, 7.6 Hz, 2H), 7.32-7.11 (m, 8H), 6.83 (m, 2H), 6.47-6.08 (br m, 4H) 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.6, 184.7, 160.2, 147.1, 145.0, 138.8, 136.3, 133.8, 131.1, 130.1, 129.4, 129.3, 129.0, 128.5, 125.6, 113.8, 94.1, 62.8, 55.2; IR (neat): 1733, 1660, 1504, 1419, 1248, 1175, 1030, 874, 833, 759, 697, 577, 515, 444;

MS (ESI, *m/z*): 608.07 $[M+H]^+$; HRMS (ESI): calc. for $C_{33}H_{22}INO_3$: 608.0717 $[M+H]^+$, found: 608.0710.

4.8.5 Synthesis of 4'-benzoyl-7'-iodo-3'-phenyl-6'-(4-(trifluoromethyl) phenyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44E)

General Procedure 6 was followed by using (4-(4-methoxyphenyl)-2-phenyl-5-((4-(trifluoromethyl)phenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (**16E**) (100 mg, 0.2 mmol) and $NaHCO_3$ (50 mg, 0.6mmol), I_2 (151 mg, 0.6mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4'-benzoyl-7'-iodo-3'-phenyl-6'-(4-(trifluoromethyl) phenyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (**44E**) (white-yellow solid, 67 mg, 52% yield).

44E: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H), 7.64-7.54 (m, 4H), 7.42 (dd, *J* = 12.8, 7.2 Hz, 3H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.27-7.18 (m, 5H), 6.54-6.20 (br m 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 184.34, 156.0, 151.2, 147.2, 145.4, 139.8, 138.6, 137.2, 136.1, 133.9, 132.5, 131.1, 129.4, 129.3, 129.2, 128.6, 128.5, 125.5, 125.4, 95.9, 62.8; IR (neat): 1667, 1653, 1395, 1322, 1244, 1158, 1124, 1063, 1015, 909, 879, 845, 761, 709, 697, 670, 600, 504, 450; MS (ESI, *m/z*): 646.05 $[M+H]^+$; HRMS (ESI): calc. for $C_{33}H_{19}F_3INO_2$: 646.0485 $[M+H]^+$, found: 646.0476.

4.8.6 Synthesis of 4'-benzoyl-7'-iodo-3'-(2-methoxyphenyl)-6'-(4-methoxyphenyl) spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44F)

General Procedure 6 was followed by using (2-(2-methoxyphenyl)-4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (**16F**) (100 mg, 0.2 mmol) and $NaHCO_3$ (50 mg, 0.6mmol), I_2 (151 mg, 0.6mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4'-benzoyl-7'-iodo-3'-(2-methoxyphenyl)-6'-(4-methoxyphenyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]-pyridin]-4-one (**44F**) (yellow-brown solid, 92 mg, 72% yield).

44F: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (s, 1H), 7.30 (d, *J* = 7.2 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.09-6.96 (m, 6H), 6.69-6.66 (m, 3H), 6.51 (d, *J* = 8.26 Hz, 1H), 6.22 (d, *J* = 9.6 Hz, 2H), 5.96 (d, *J* = 9.6 Hz, 2H), 3.64 (s, 3H), 3.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 184.7, 160.1, 156.3, 154.1, 152.3, 146.9, 144.7, 143.6, 140.3, 136.4, 133.4, 132.1, 131.6, 130.5, 130.1, 129.3, 128.0, 125.7, 120.3, 113.8, 110.6, 94.4, 62.8, 55.2, 54.9; IR (neat): 1660, 1558, 1498, 1437, 1393, 1237, 1174, 1019, 880, 855, 835, 754, 709, 673, 637, 583, 521, 450, 412; MS (ESI, *m/z*): 638.08 $[M+H]^+$; HRMS (ESI): calc. for $C_{34}H_{24}INO_4$: 638.0822 $[M+H]^+$, found: 638.0811.

4.8.7 Synthesis of 4'-benzoyl-7'-iodo-6'-(4-methoxyphenyl)-3'-(4-(trifluoro methyl)phenyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44G)

General Procedure 6 was followed by using (4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)-2-(4-(trifluoromethyl)phenyl)pyridin-3-yl)(phenyl)-methanone (**16G**) (100 mg, 0.2 mmol) and $NaHCO_3$ (50 mg, 0.6mmol), I_2 (151 mg, 0.6mmol). The obtained crude product was purified by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford 4'-benzoyl-7'-iodo-6'-(4-methoxyphenyl)-3'-(4-(trifluoro methyl)phenyl)spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (**44G**) (yellow solid, 84 mg, 62% yield).

44G: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 8.4 Hz, 2H), 7.32-7.24 (m, 3H), 7.21-7.13 (m, 2H), 6.87 (dd, *J* = 6.8, 4.8 Hz, 2H), 6.47-5.98 (br m, 4H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 184.5, 160.3, 147.4, 145.1, 141.0, 136.2, 134.2, 132.4, 131.4, 130.0, 129.6, 129.4, 128.7, 125.4, 125.3, 113.9, 97.6, 93.7, 62.7, 55.2; IR (neat): 1733, 1716, 1699, 1662, 1558, 1541, 1506, 1457, 1323, 1250, 1174, 1123, 1066, 851, 705, 419; MS (ESI, *m/z*): 676.06 $[M+H]^+$; HRMS (ESI): calc. for $C_{34}H_{21}F_3INO_3$: 676.0591 $[M+H]^+$, found: 676.0581.

4.8.8 Synthesis of 4'-benzoyl-3'-butyl-7'-iodo-6'-(4-methoxyphenyl)spiro-[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (44H)

General Procedure 6 was followed by using (2-butyl-4-(4-methoxyphenyl)-5-((4-methoxyphenyl)ethynyl)pyridin-3-yl)(phenyl)methanone (**16H**) (100 mg, 0.2 mmol) and $NaHCO_3$ (50 mg, 0.6 mmol), I_2 (151 mg, 0.6mmol). The obtained crude product using 9:1 hexane/ethyl acetate as the eluent was purified by flash column chromatography on silica gel to afford 4'-benzoyl-3'-butyl-7'-iodo-6'-(4-methoxyphenyl) spiro[cyclohexa[2,5]diene-1,5'-cyclopenta[c]pyridin]-4-one (**44H**) (yellow solid, 75 mg, 64% yield).

44H: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (s, 1H), 7.59 (t, *J* = 7.2 Hz, 3H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.16-7.08 (m, 2H), 6.83-6.80 (m, 2H), 6.26 (br s, 2H), 6.05 (br s, 2H), 3.78 (s, 3H), 2.72-2.61 (m, 2H), 1.68 (m, 2H), 1.32-1.23 (m, 2H), 0.82 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 184.5, 160.1, 151.2, 145.5, 144.6, 143.8, 136.8, 134.4, 132.1, 130.0, 128.9, 125.7, 121.9, 121.1, 119.9, 113.8, 94.3, 62.4, 55.2, 31.9, 22.6, 19.4, 13.8; IR (neat): 1661, 1559, 1504, 1457, 1395, 1290, 1248, 1175, 1031, 833, 745, 706, 519; MS (ESI, *m/z*): 588.10 $[M+H]^+$; HRMS (ESI): calc. for $C_{31}H_{26}INO_3$: 588.1030 $[M+H]^+$, found: 588.1027.

REFERENCES

[1] Clayden, J.; Greeves, N.; Warren, S. *Organic Chemistry*, Oxford University Press, **2012**.

[2] Mcmurry, J**.** *Organic Chemistry*, 7th Ed. Thomson Books/Cole, **2008**.

[3] Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 5th Ed. **2007**.

[4] Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*, 2nd Ed. Wiley, **2011**.

[5] Joule, J. A.; Mills K. *Heterocyclic Chemistry*, 5th Ed. Wiley, **2010**.

[6] Acheson, R. M. *An Introduction to the Chemistry of Heterocyclic Compounds*, 2nd Ed. **1967**.

[7] Henry, G. D. *Tetrahedron Lett.* **2004**, 6043.

[8] Behbehani, H.; Ibrahim, H. M.; Elnagdi, M. H. *Tetrahedron Lett.* **2013**, *69*, 6176.

[9] Goetz, A. E.; Garg, N. K. *Nat. Chem.* **2013**, *5*, 54.

[10] Majumdar, K. C.; Ansary, I.; Samanta, S.; Roy, B. *Tetrahedron Lett.* **2011**, *52*, 411.

[11] Fei, N.; Hou, Q.; Wang, S.; Wang, H.; Yaoa, Z. *Org. Biomol. Chem.* **2010**, *8*, 4096.

[12] Movassaghi, M.; Hill, M. D.; Ahmad, O. K. *J. Am. Chem. Soc.* **2007**, *129*, 10096.

[13] Chinchilla, R.; Najera, C.; Yus, M. *Chem. Rev.* **2004**, *104*, 2667.

[14] Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86.

[15] Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463.

[16] Stanovnik, B.; Svete, J. *Chem. Rev.* **2004**, *104*, 2433.

[17] Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2629.

[18] Zora, M.; Karabiyoglu, S. Abstracts of Papers. 243th National Meeting of American Chemical Society, San Diego, California, March 25-29, 2012; American Chemical Society; Washington, DC, 2012; ORGN 844.

[19] Zora, M.; Kelgokmen, Y. Abstracts of Papers, 243th National Meeting of American Chemical Society, San Diego, California; March 25-29, 2012; American Chemical Society: Washington, DC, 2012; ORGN 846.

[20] Bazgir, A.; Noroozi Tisseh, Z.; Mirzaei, P. *Tetrahedron Lett.* **2008**, *49*, 5165.

[21] Sun, Y.; Sun J.; Yan, C. *Beilstein J. Org. Chem.* **2013**, *9*, 8.

[22] Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stukey, J.; Krajewski, K.; Roller, P. P.; Wang, S. *J. Med. Chem*. **2006**, *49*, 3432.

[23] Badillo, J. J.; Hanhan, N. V.; Franz, A. K. *Curr. Opin. Drug Disc.* **2010**, *13*, 758.

[24] Coxon, D. T.; Price, K. R.; Howard, B.; Osman, S. F.; Kalan, E. B.; Zacharius, R. M. *Tetrahedron Lett.* **1974**, *15*, 2921.

[25] Nishikawaji, S.; Fujimori, T.; Matsushima, S.; Kato, K. *Phytochemistry* **1983**, *22*, 1819.

[26] Beaulieu, M. A.; Guérard, K. C.; Maertens, G.; Sabot, C.; Canesi, S. *J. Org. Chem.* **2011**, *76*, 9460.

[27] Mahns, B.; Roth, F.; Grobosch, M.; Lindner, S.; Knupfer, M.; Saragi, T. P. I.; Reichert, T.; Salbeck, J.; Hahn, T. *J. Chem. Phys.* **2012,** *10*, 1063.

[28] Salbeck, J.; Yu, N.; Bauer, J.; Weissortel, F.; Bestgen, H. *Synth. Met.* **1997**, *91*, 209.

[29] Yu, W. L.; Pei, J.; Huang W.; Heeger, A. *J. Adv. Mater.* **2000**, *12*, 828.

[30] Wu, F.; Dodda, R.; Reddy, D. S.; Shu, C. *J. Mater. Chem.* **2002,** 2893.

[31] Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104.

[32] Hatsui, T.; Hashiguchi, T.; Takeshita. H. *Chem. Express* **1993**, *8*, 581.

[33] Marx, J. N.; Norman, L. R. *J. Org. Chem*. **1975**, *40*, 1602.

[34] Naro, P. A.; Dixon, J. A. *J. Am. Chem. Soc.* **1959**, *81*, 1681.

[35] Swenton, J. S.; Carpenter, K.; Chen, Y.; Kerns, M. L.; Morrow, G. W. *J. Org. Chem*. **1993**, *58*, 3308.

[36] Li, C.; Wang, C.; Liao, H.; Chaudhuri, R.; Liu, R. *J. Org. Chem.* **2007**, *72*, 9203.

[37] Karpov, A. S.; Müller, T. J. *J. Org. Lett.* **2003**, *5*, 3451.

[38] a) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. b) Dewar, M. J. S.; Jie, C.; Yu, J. *Tetrahedron* **1993**, *49*, 5003.

[39] Atobe, S.; Masuno, H.; Sonoda M.; Suzuki Y.; Shinohara H.; Shilbata S.; Ogawa, A. *Tetrahedron Lett.* **2012**, *53*, 1764.

[40] Chen, J.; Lin, T.; Chen, S.; Chen, A.; Mou, C.; Tsai, F. *Tetrahedron Lett.* **2009**, *65*, 10134.

APPENDICES A

NMR DATA

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker Spectrospin Avance DPX400 Ultrashield spectrometer.

^{1}H and ^{13}C NMR spectra of products are given below.

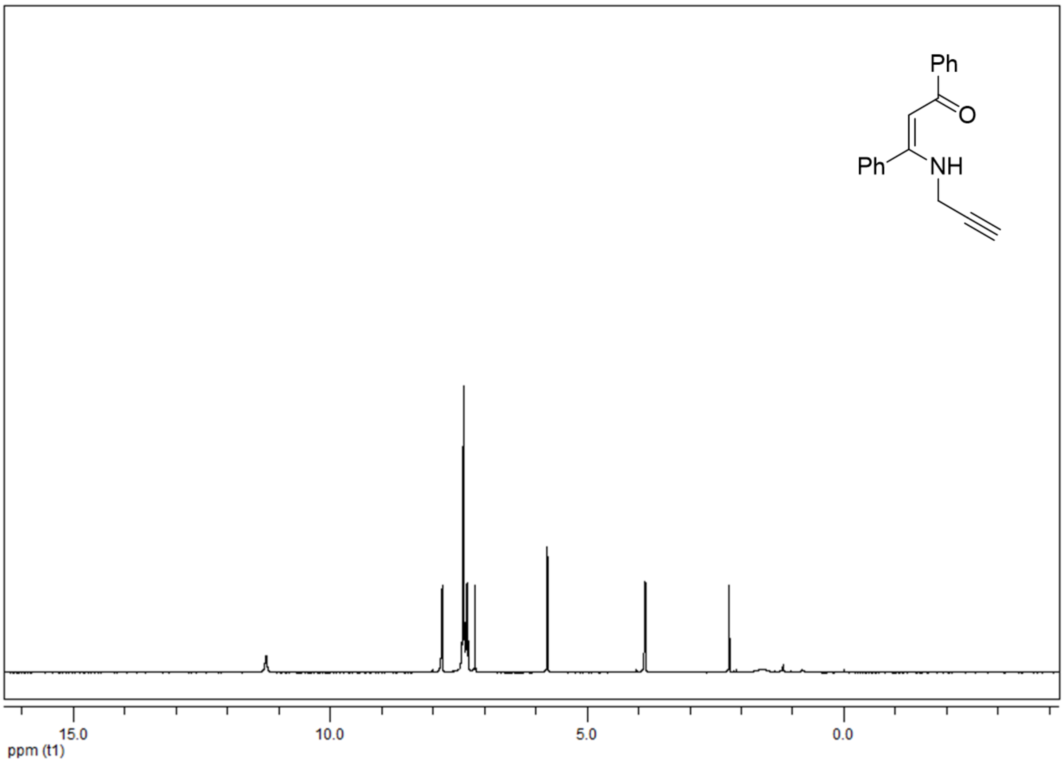


Figure 23A. ^{1}H NMR Spectrum of compound **48A**.

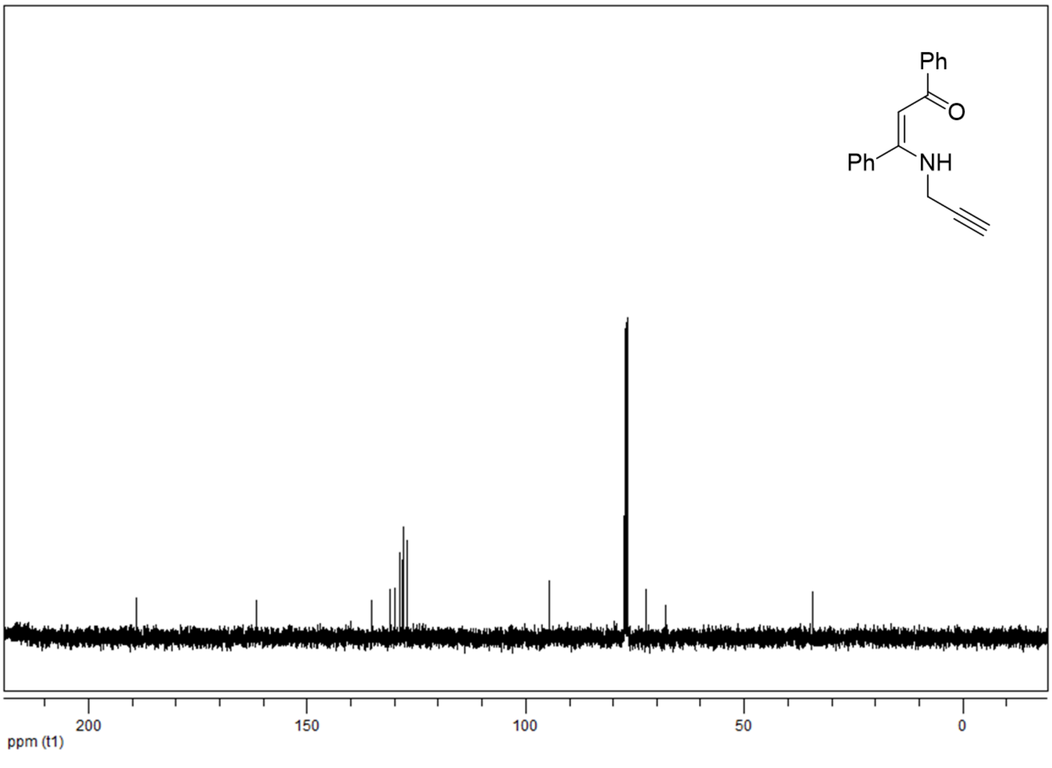


Figure 24A. ^{13}C NMR Spectrum of compound **48A**.

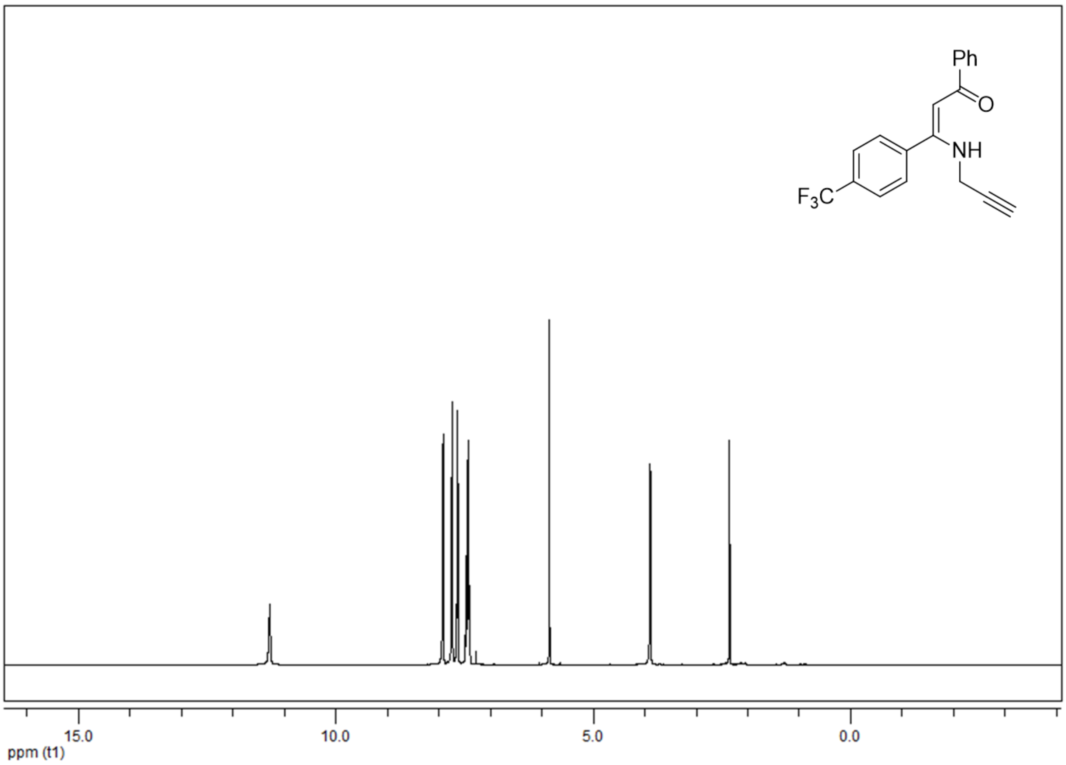


Figure 25A. ^{1}H NMR Spectrum of compound **48B**.

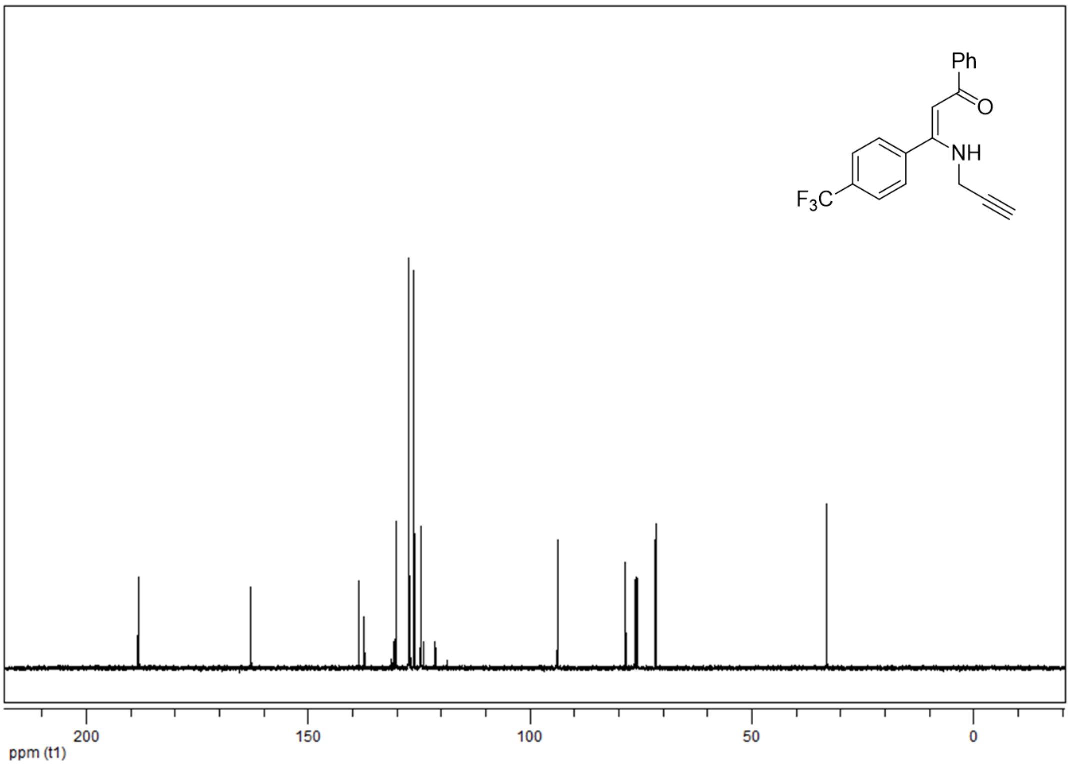


Figure 26A. ^{13}C NMR Spectrum of compound **48B**.

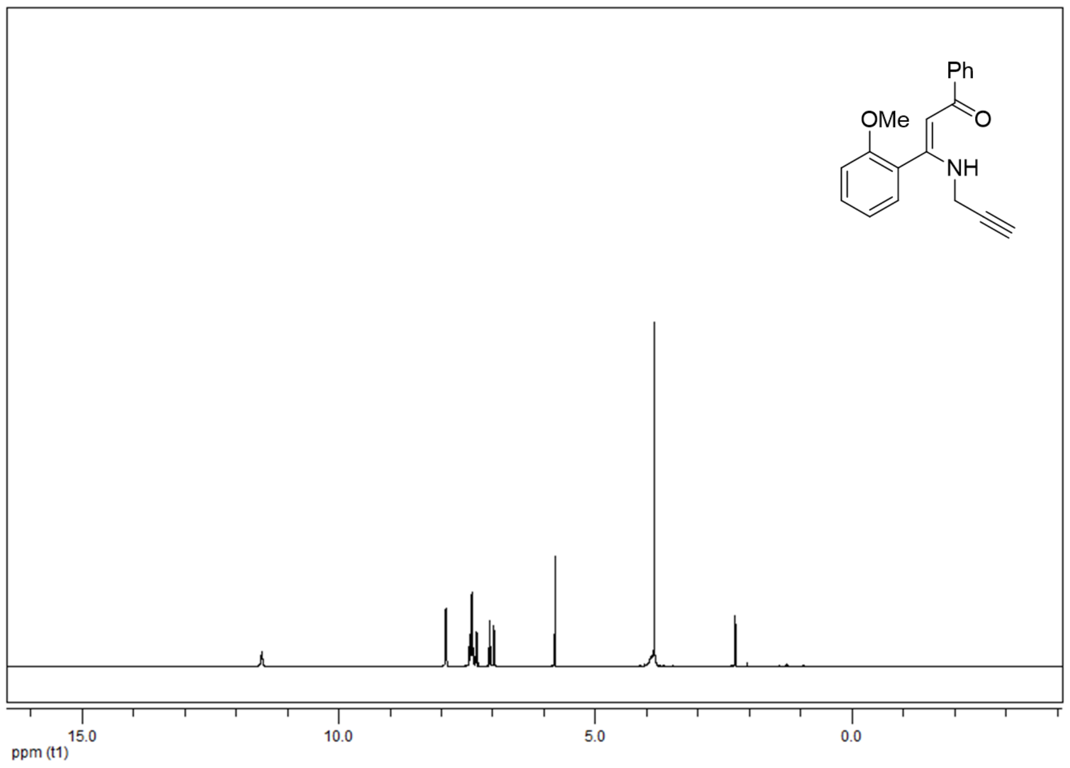


Figure 27A. ^{1}H NMR Spectrum of compound **48C**.

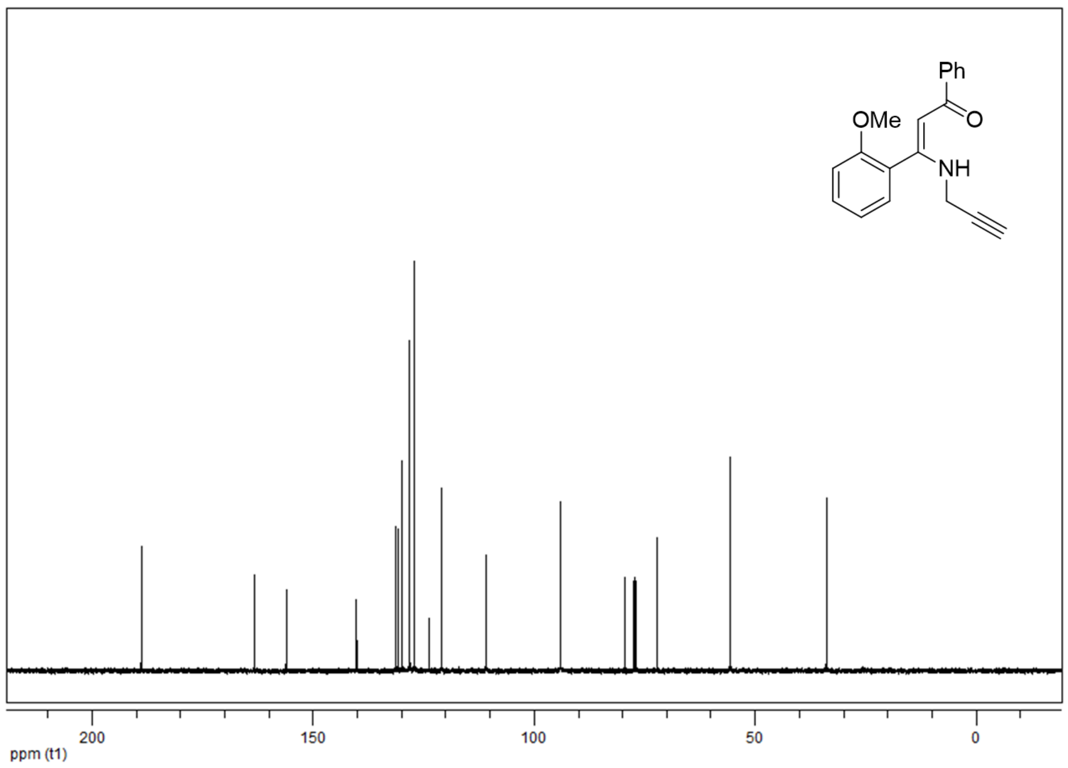


Figure 28A. ^{13}C NMR Spectrum of compound **48C**.

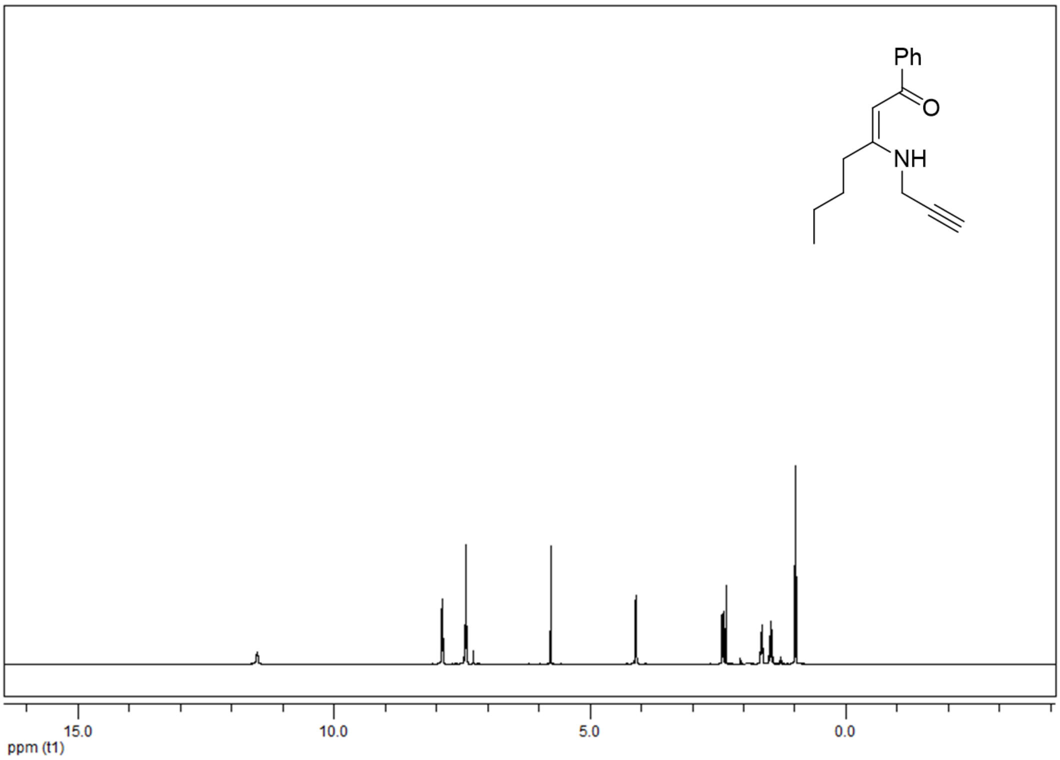


Figure 29A. ^{1}H NMR Spectrum of compound **48D**.

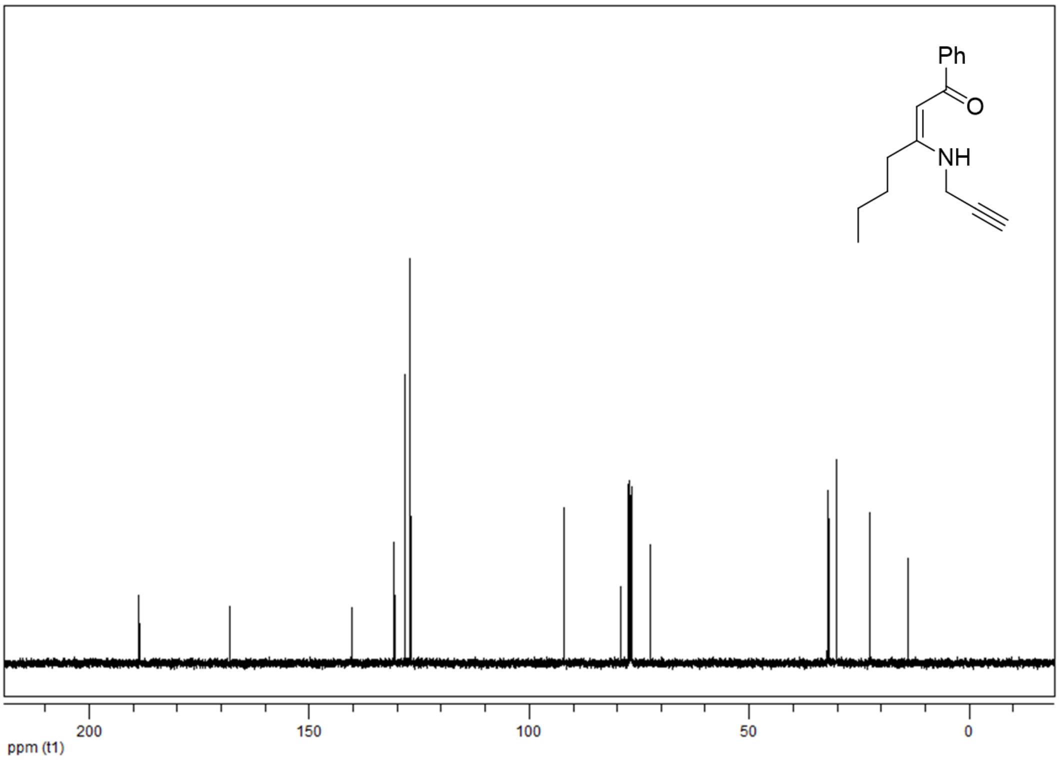


Figure 30A. ^{13}C NMR Spectrum of compound **48D**.

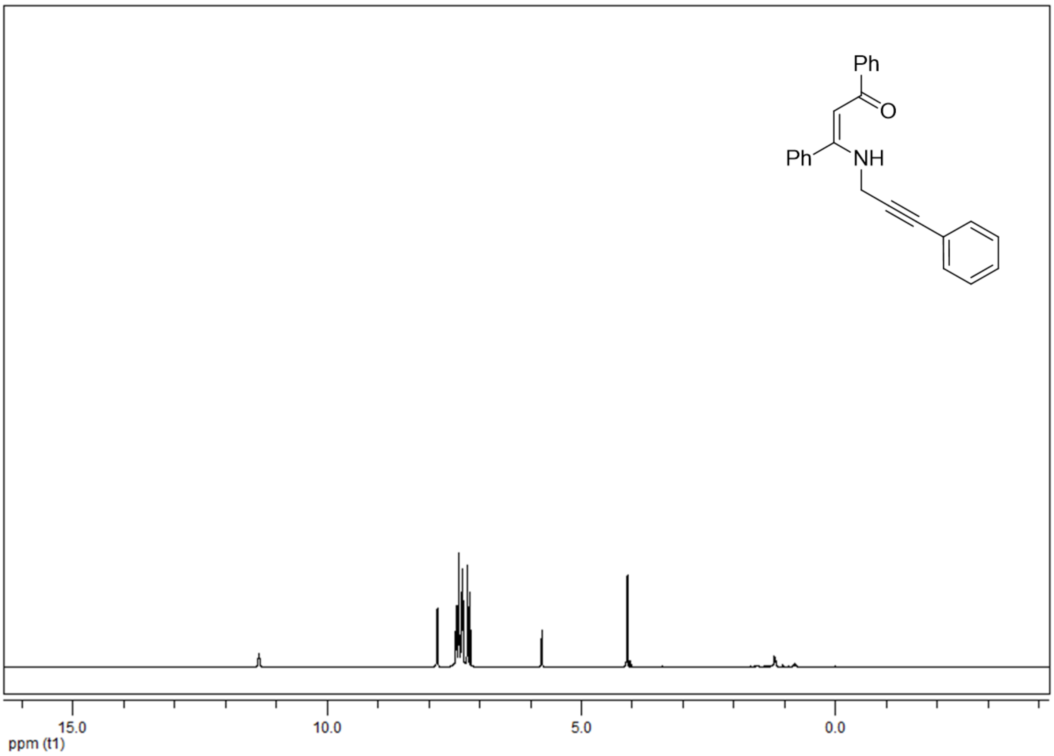


Figure 31A. ^{1}H NMR Spectrum of compound **13A.**

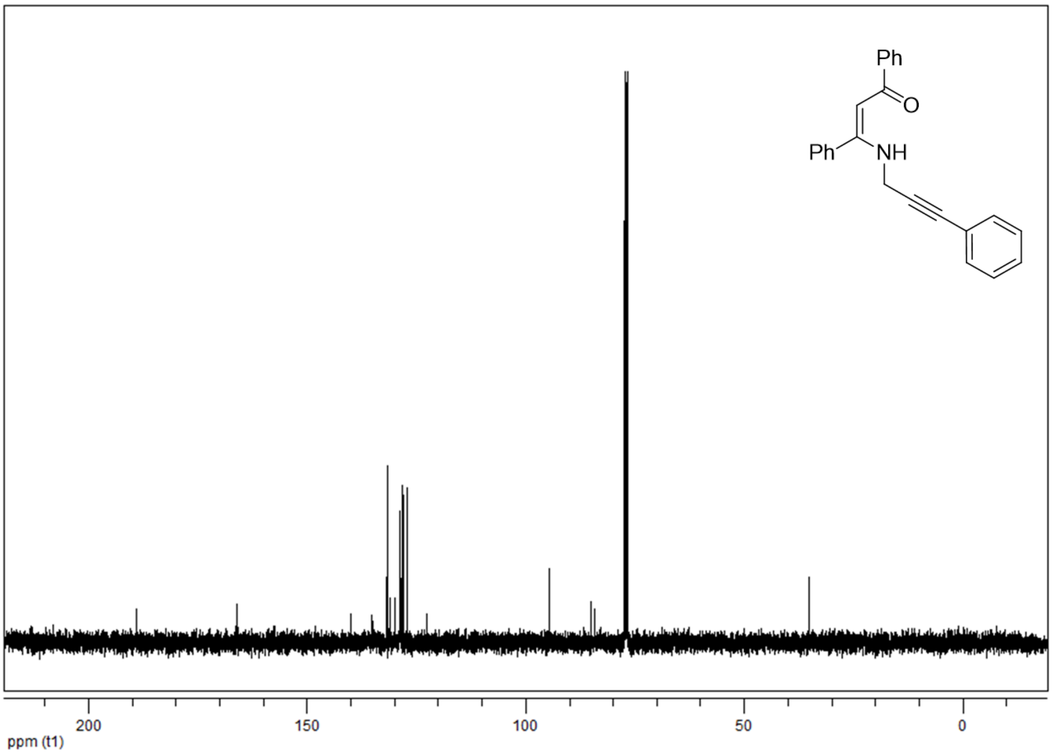


Figure 32A. ^{13}C NMR Spectrum of compound **13A.**

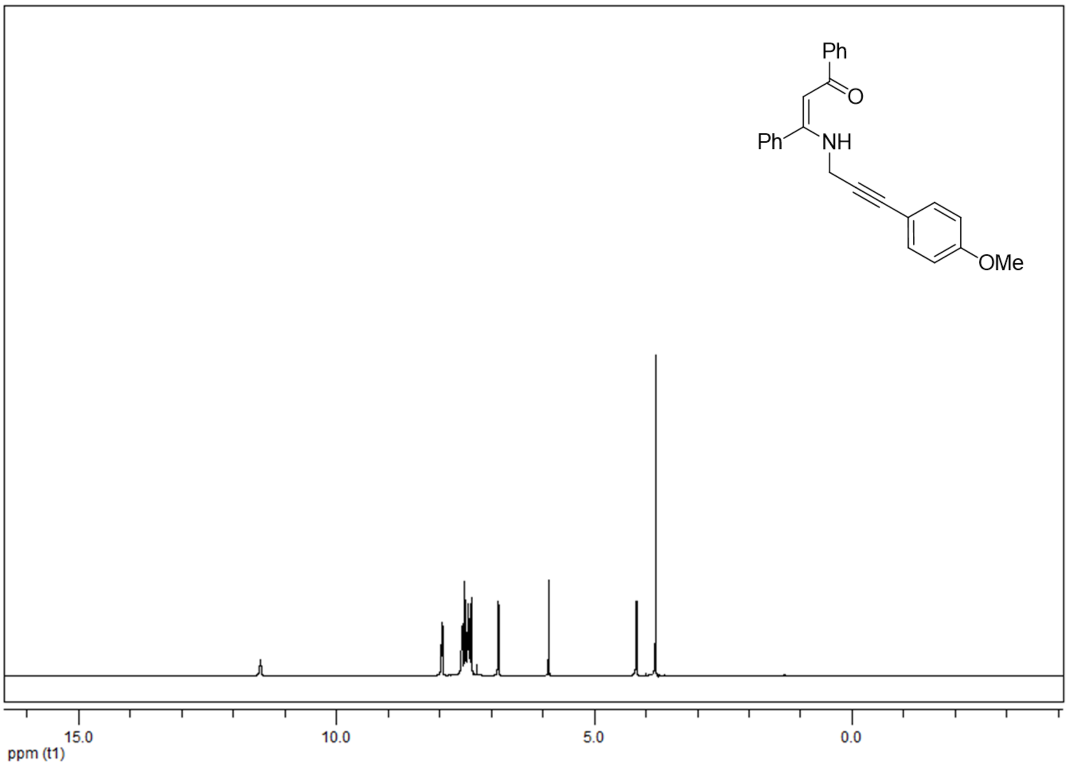


Figure 33A. ^{1}H NMR Spectrum of compound **13B**.

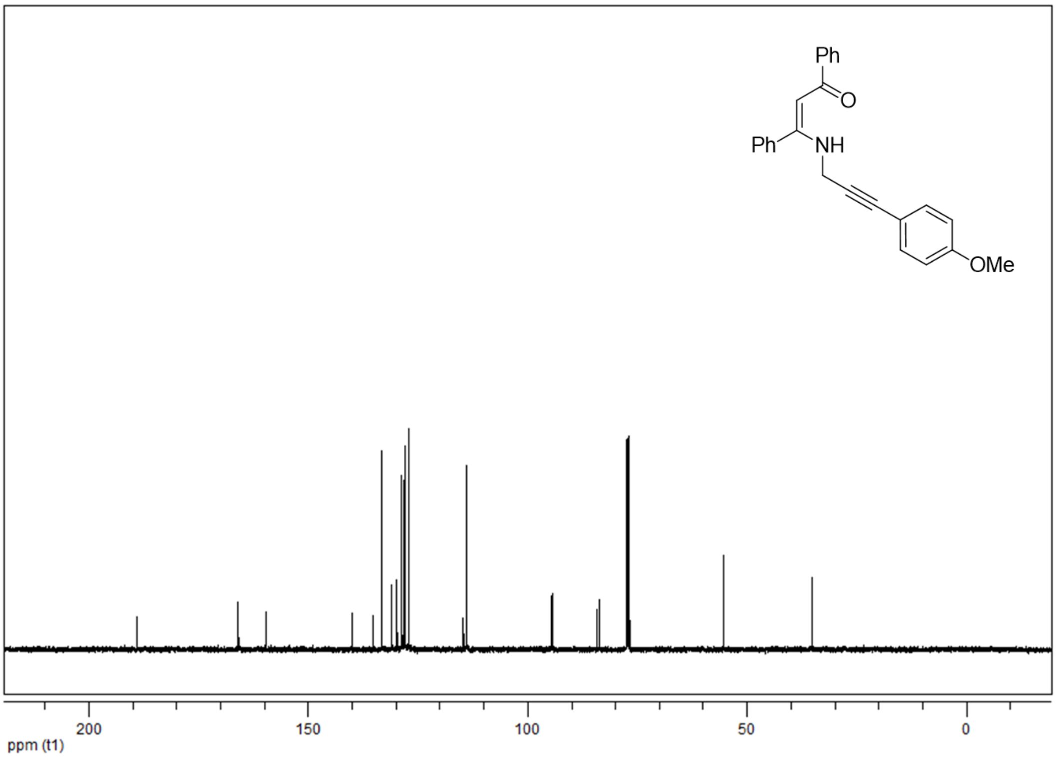


Figure 34A. ^{13}C NMR Spectrum of compound **13B**.

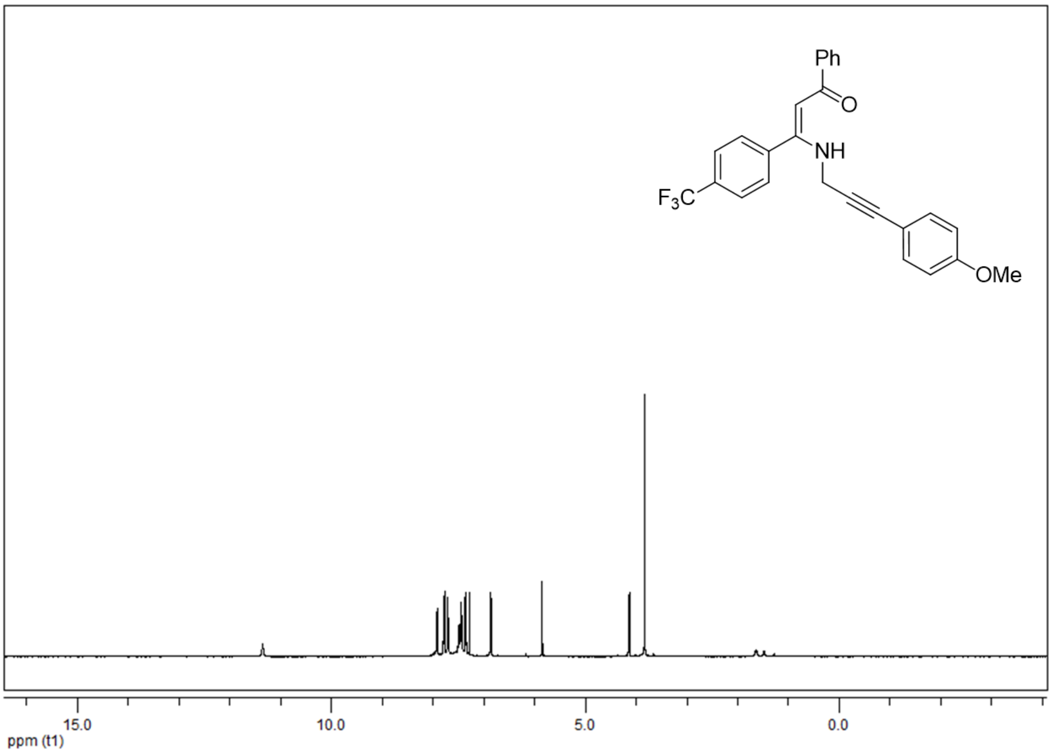


Figure 35A. ^{1}H NMR Spectrum of compound **13C**.

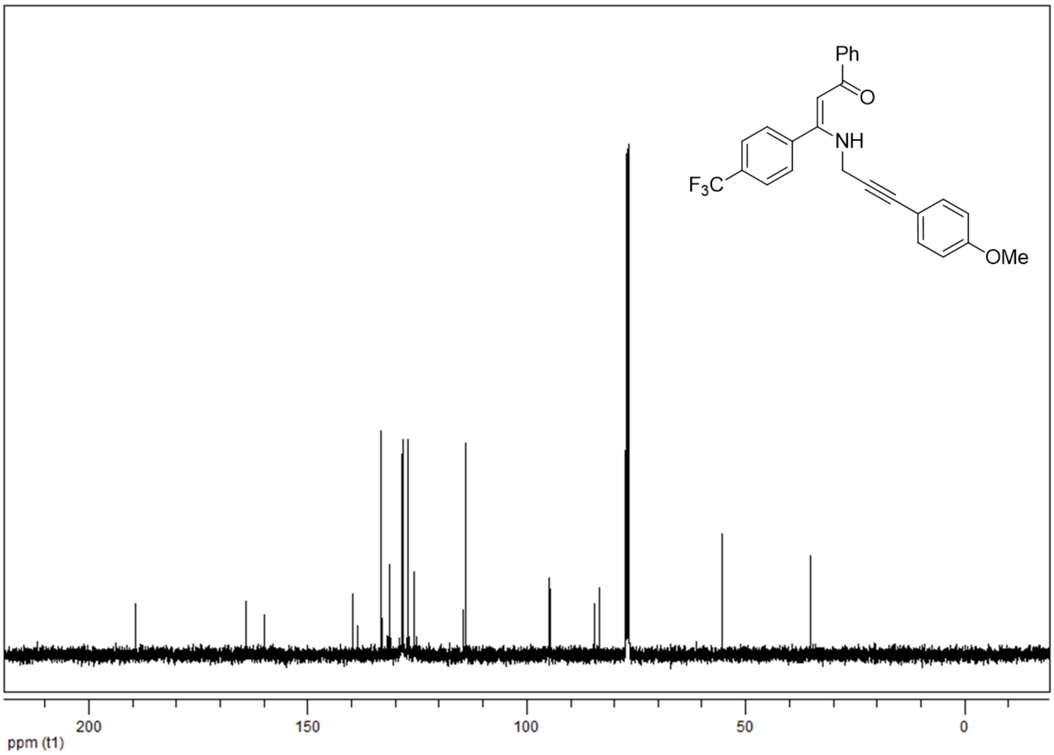


Figure 36A. ^{13}C NMR Spectrum of compound **13C**.

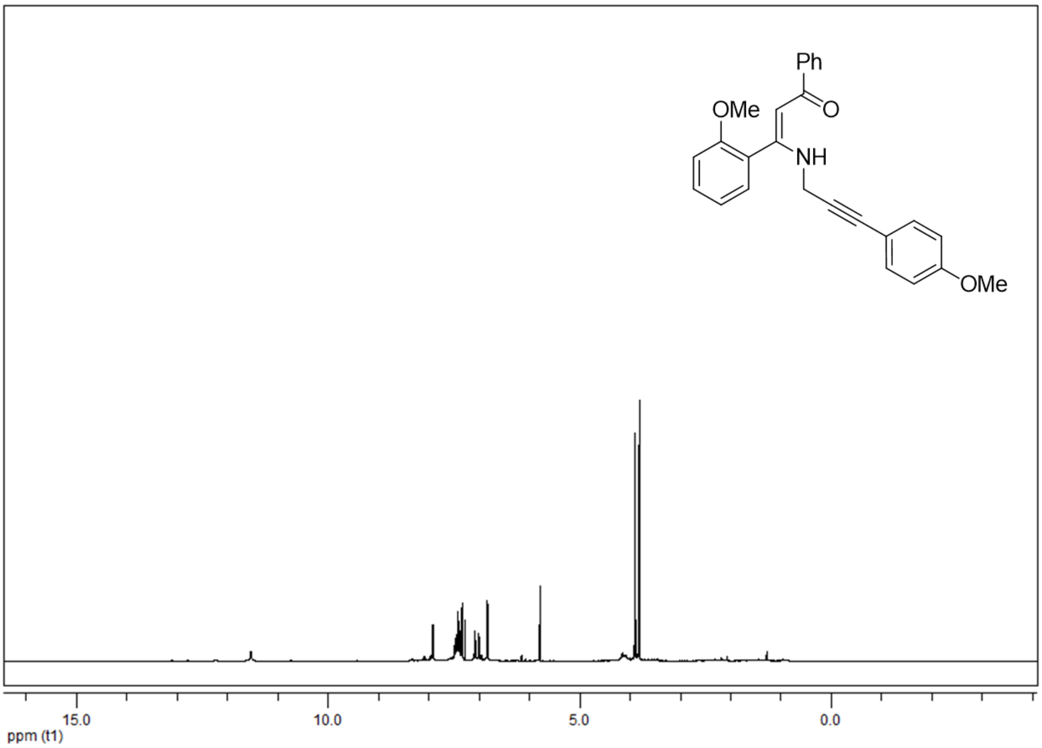


Figure 37A. ^{1}H NMR Spectrum of compound **13D**.

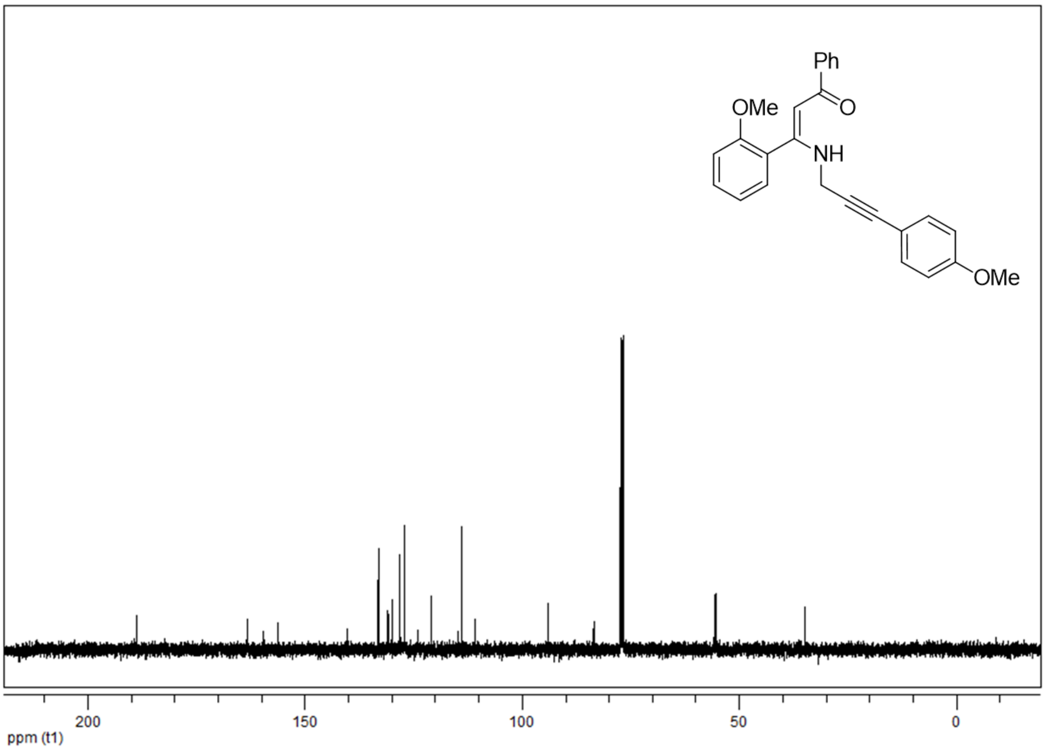


Figure 38A. ^{13}C NMR Spectrum of compound **13D**.

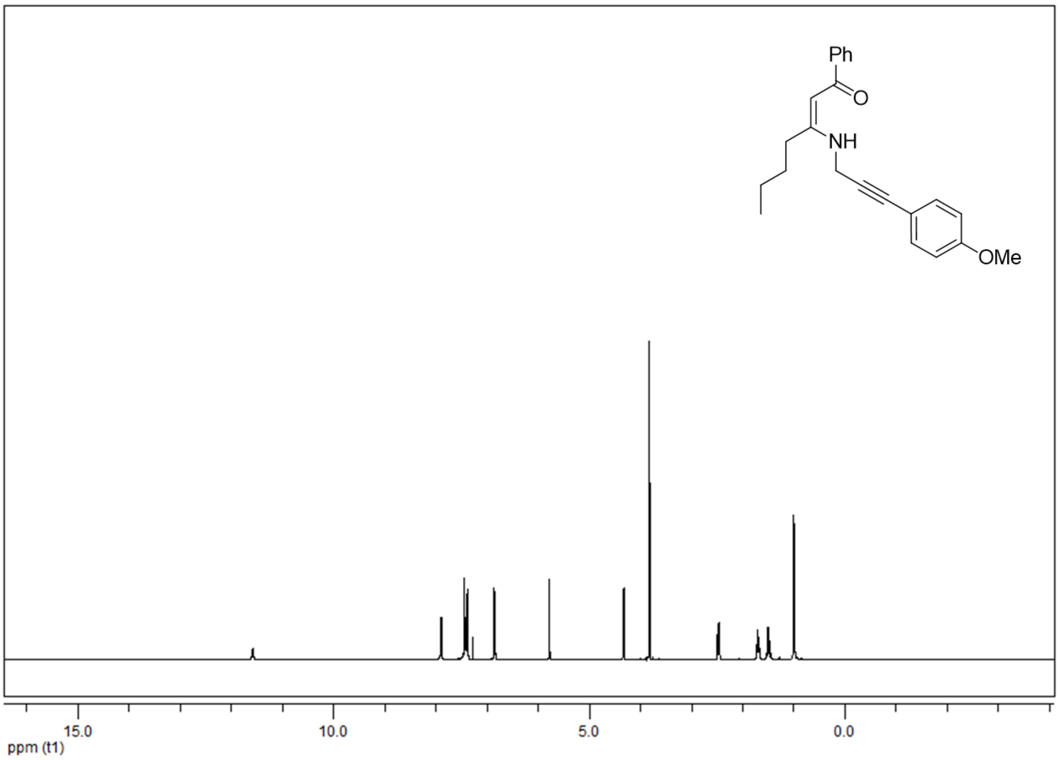


Figure 39A. ^{1}H NMR Spectrum of compound **13E**.

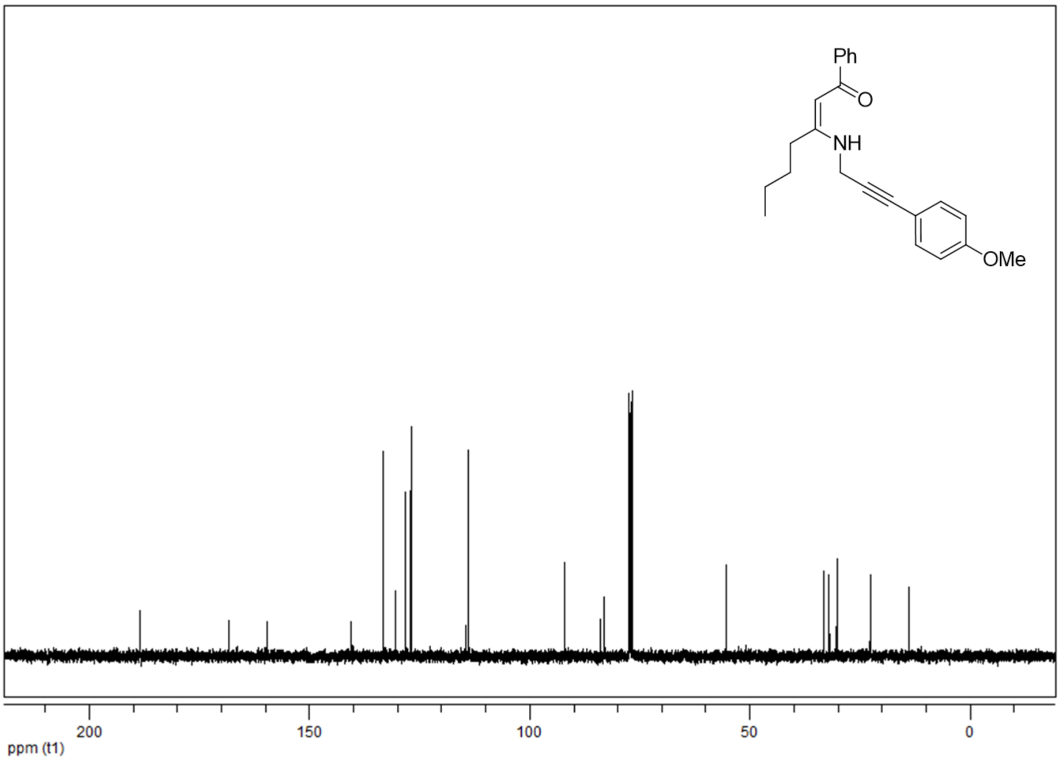


Figure 40A. ^{13}C NMR Spectrum of compound **13E**.

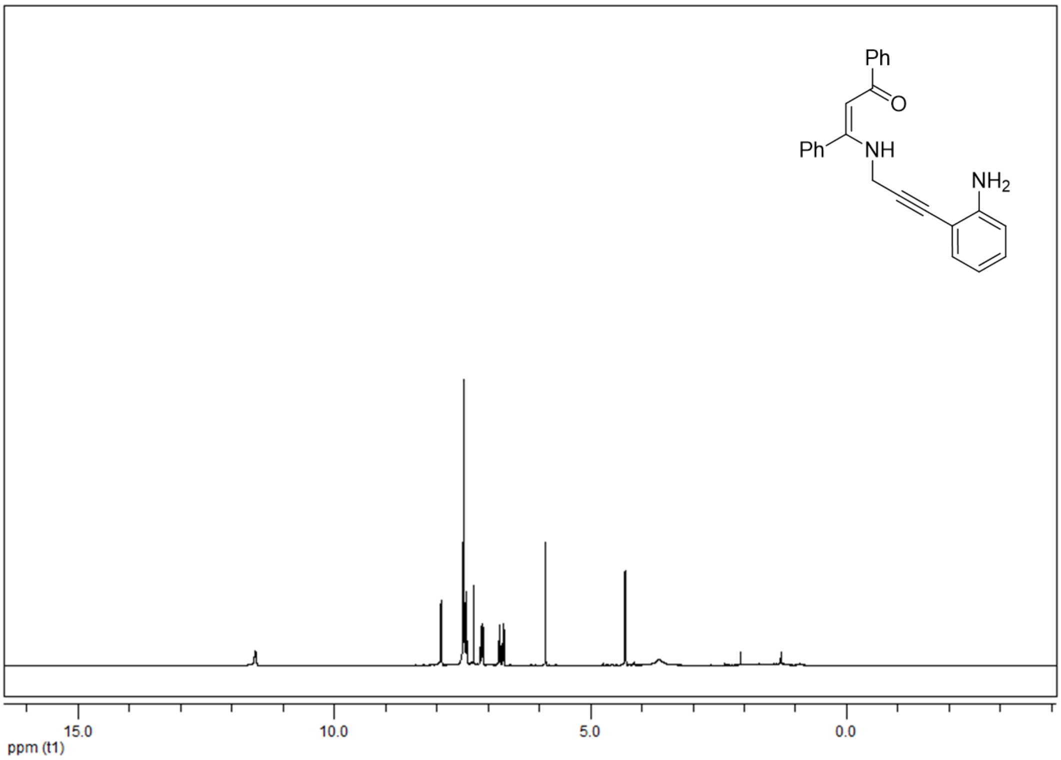


Figure 41A. ^{1}H NMR Spectrum of compound **13F**.

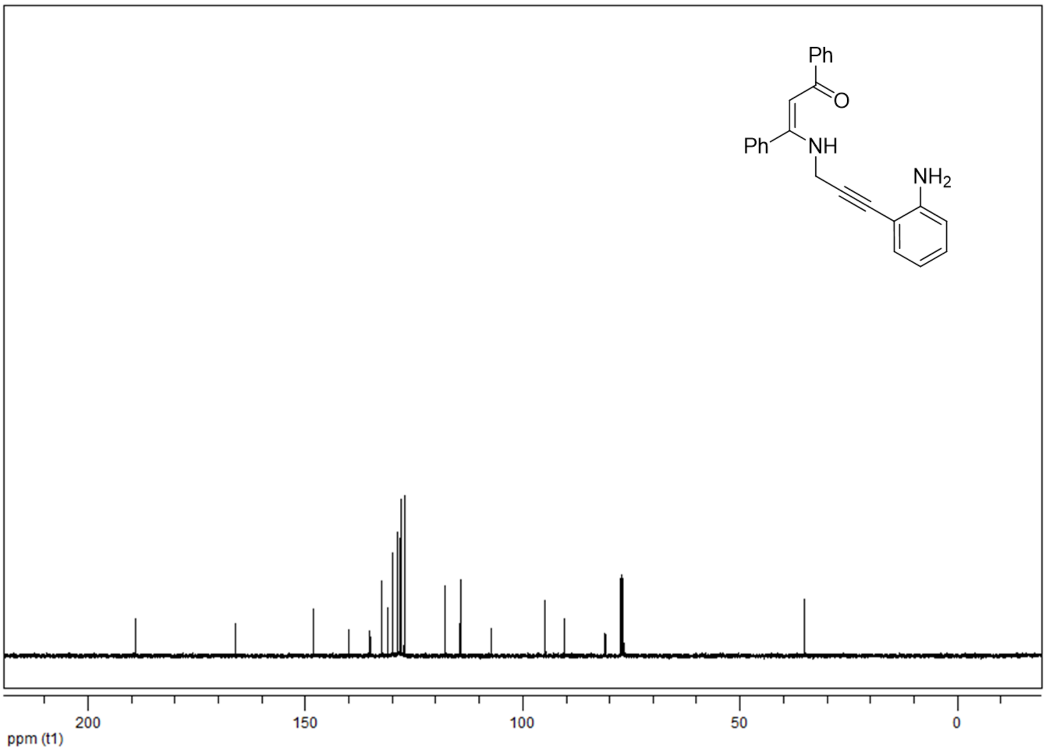


Figure 42A. ^{13}C NMR Spectrum of compound **13F**.

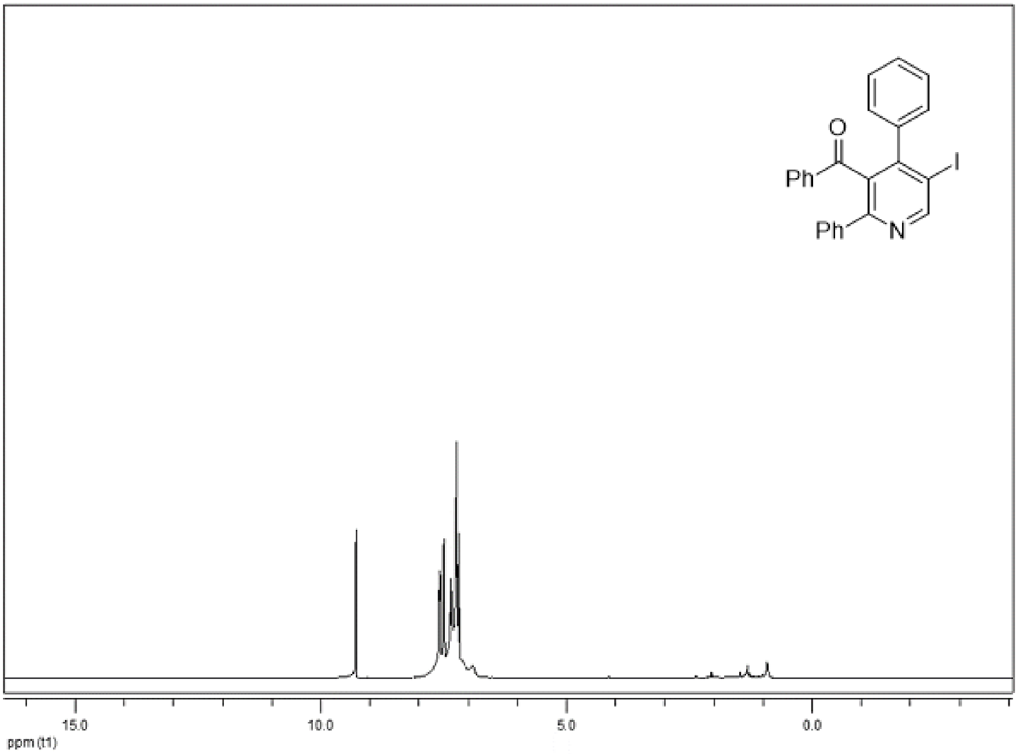


Figure 43A. ^{1}H NMR Spectrum of compound **14A**.

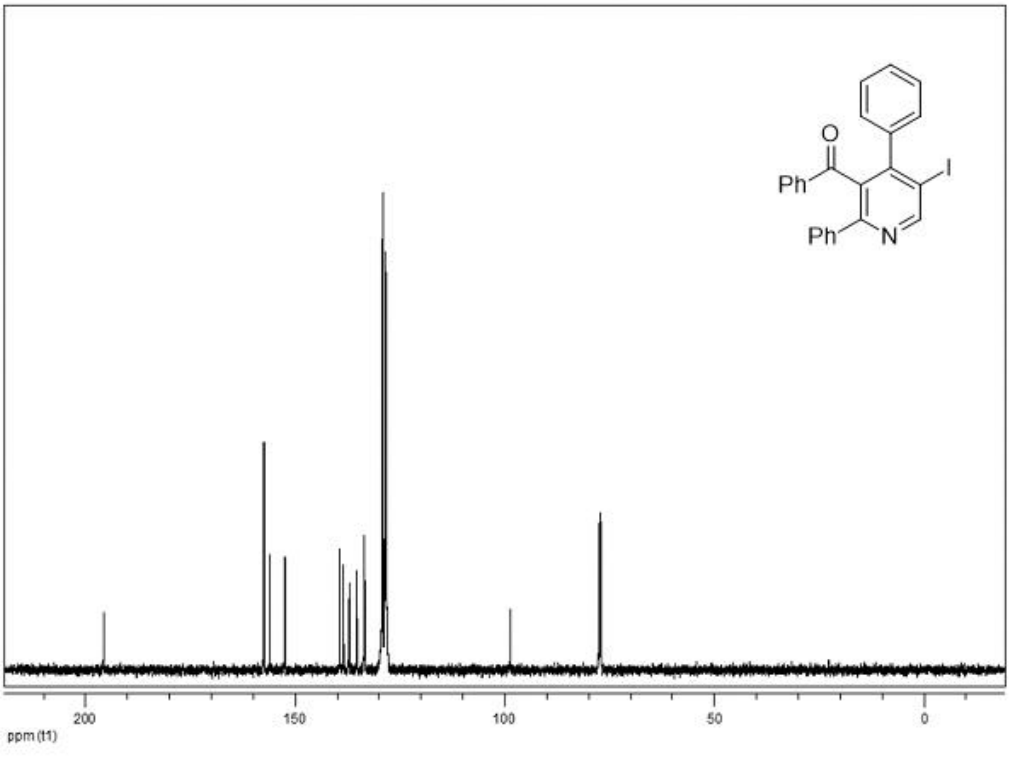


Figure 44A. ^{13}C NMR Spectrum of compound **14A**.

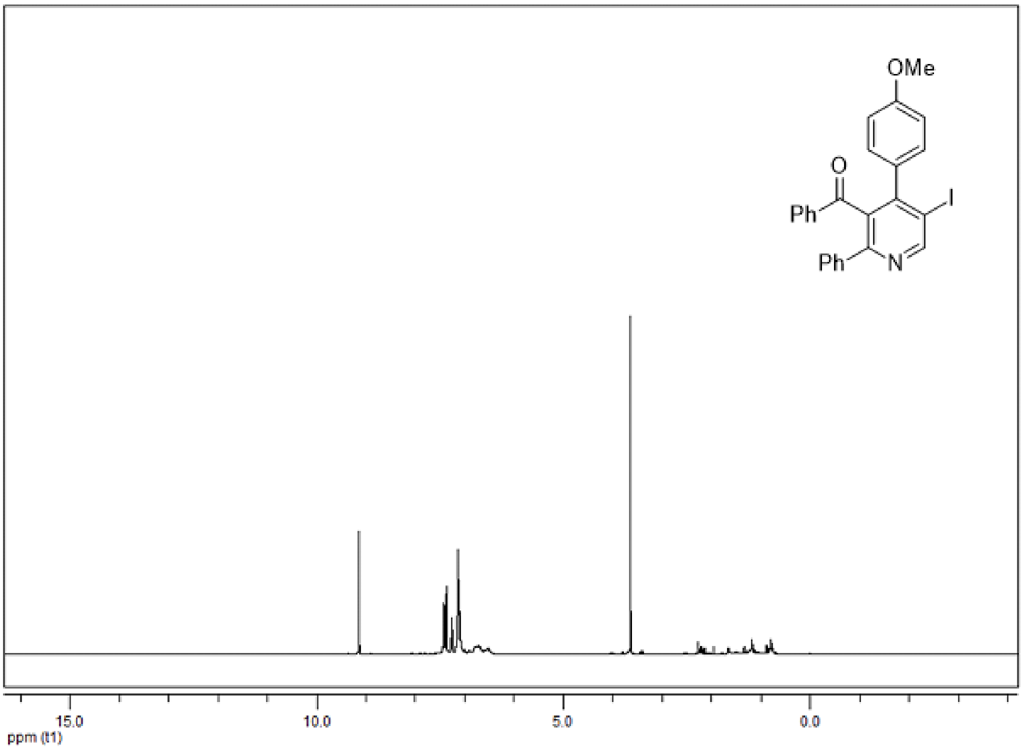


Figure 45A. ^{1}H NMR Spectrum of compound **14B**.

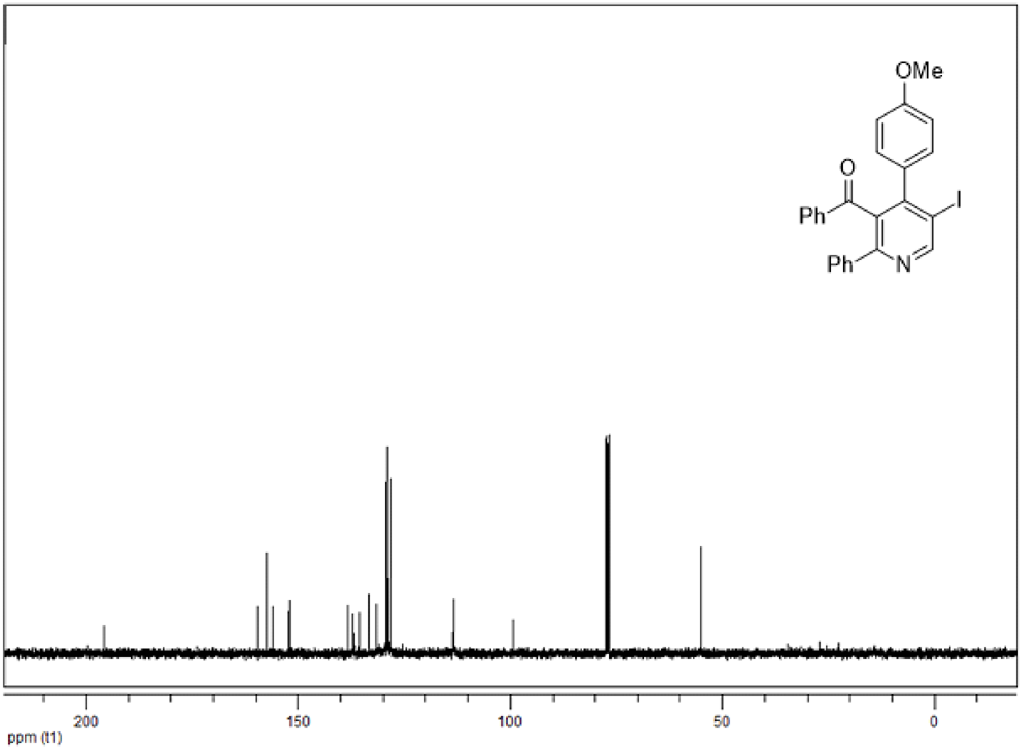


Figure 46A. ^{13}C NMR Spectrum of compound **14B**.

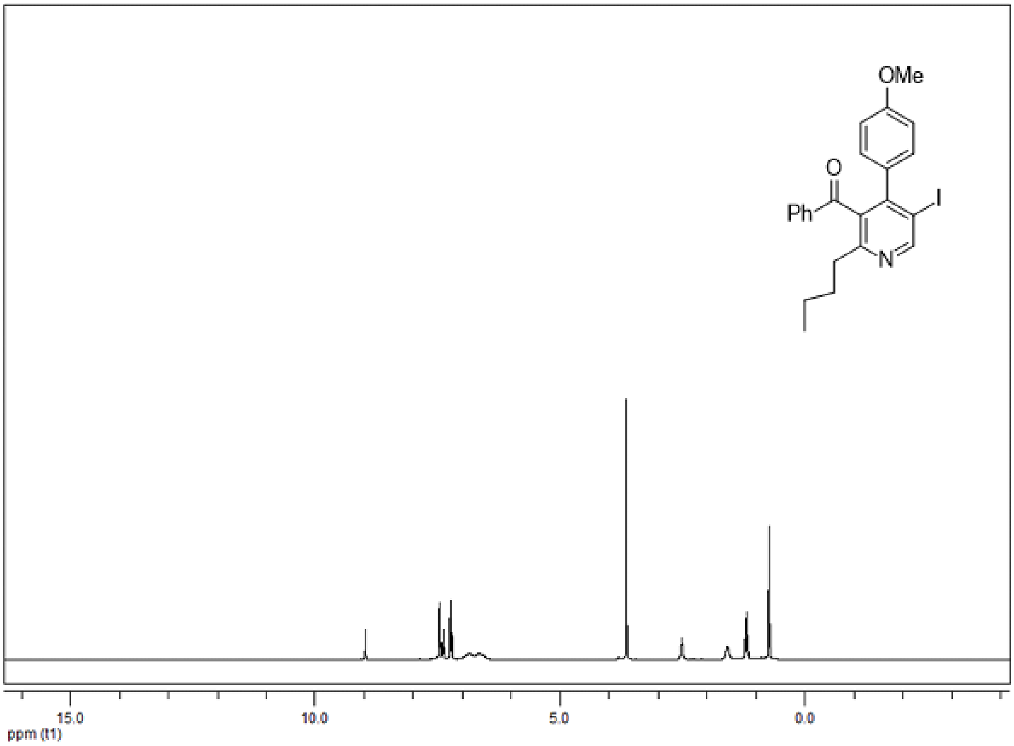


Figure 47A. ^{1}H NMR Spectrum of compound **14C**.

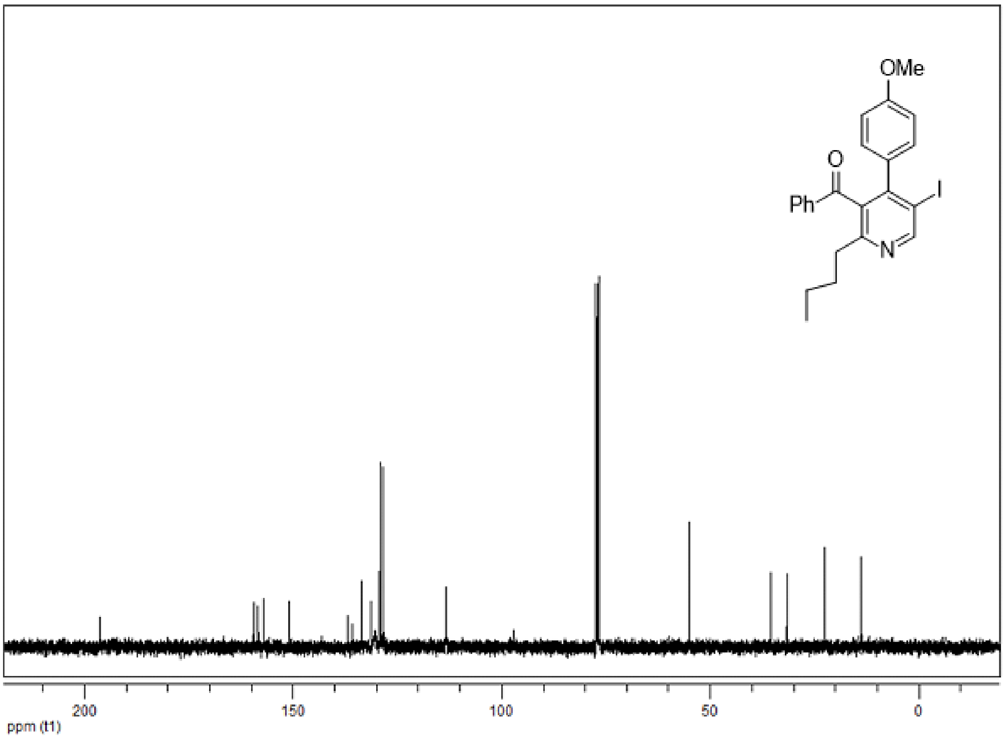


Figure 48A. ^{13}C NMR Spectrum of compound **14C**.

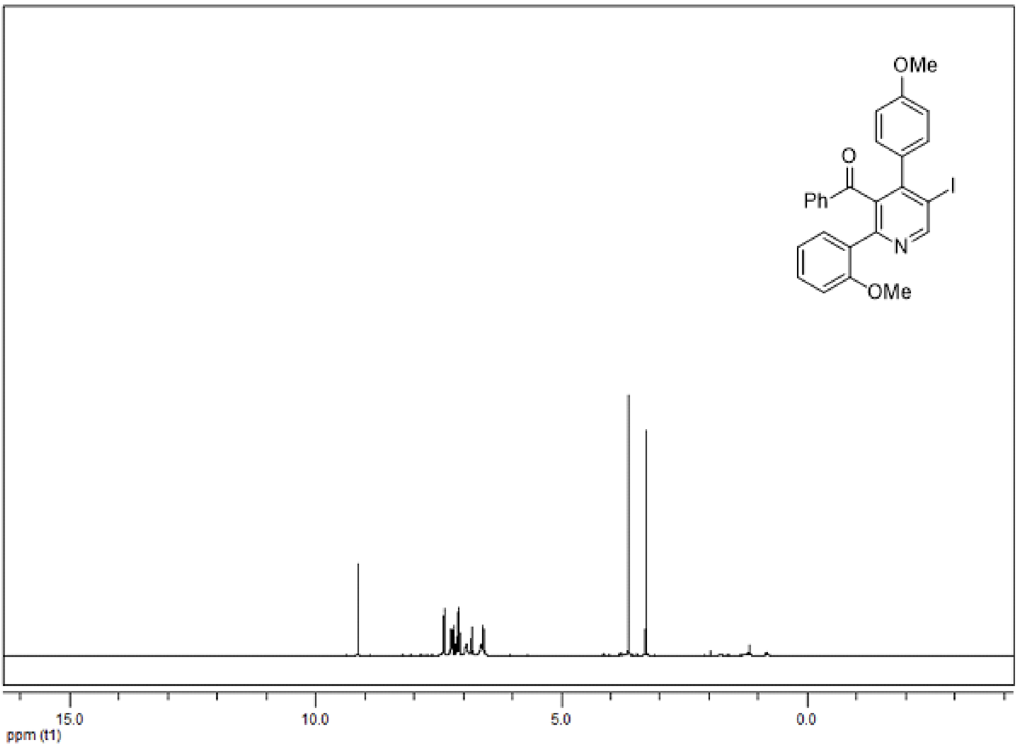


Figure 49A. ^{1}H NMR Spectrum of compound **14D**.

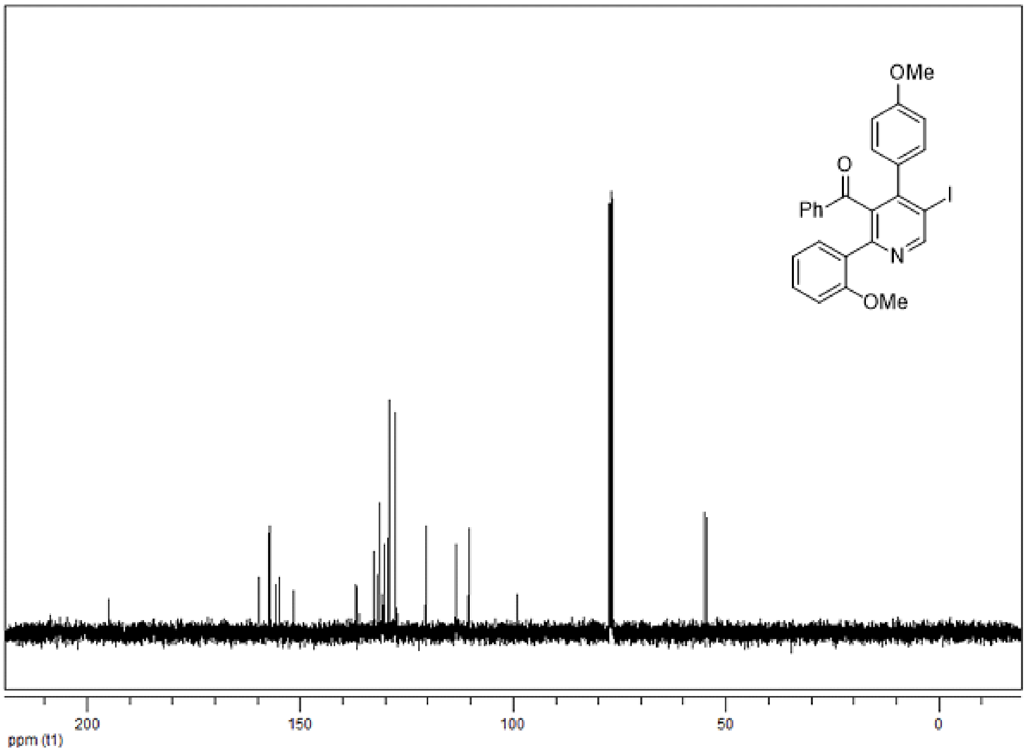


Figure 50A. ^{13}C NMR Spectrum of compound **14D**.

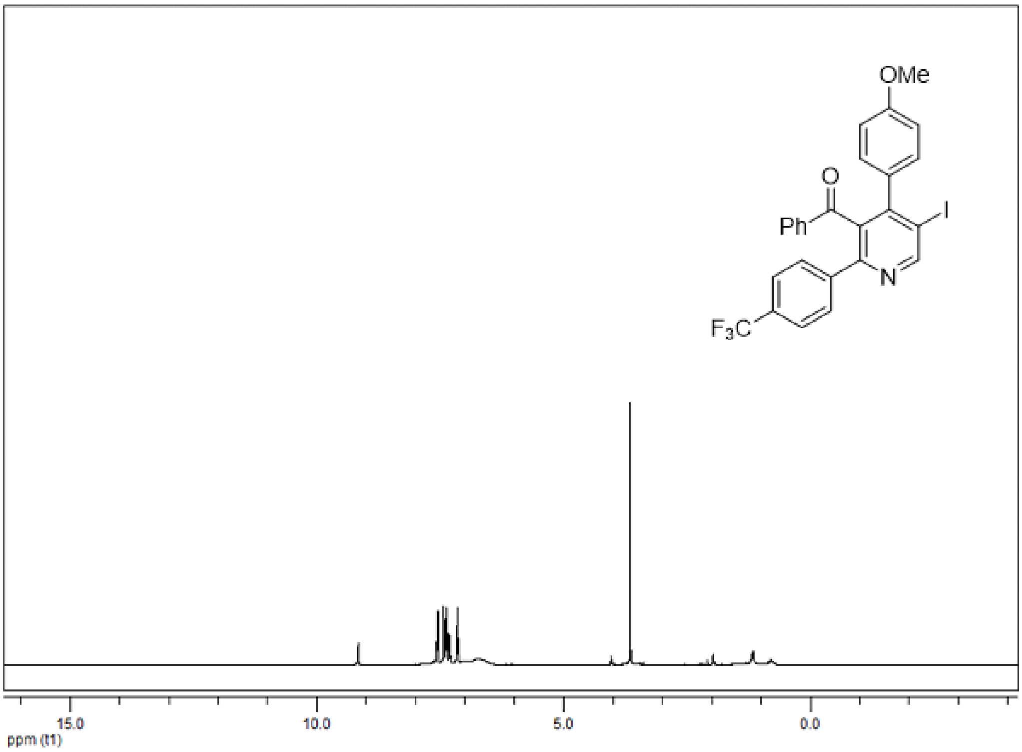


Figure 51A. ^{1}H NMR Spectrum of compoun **14E**.

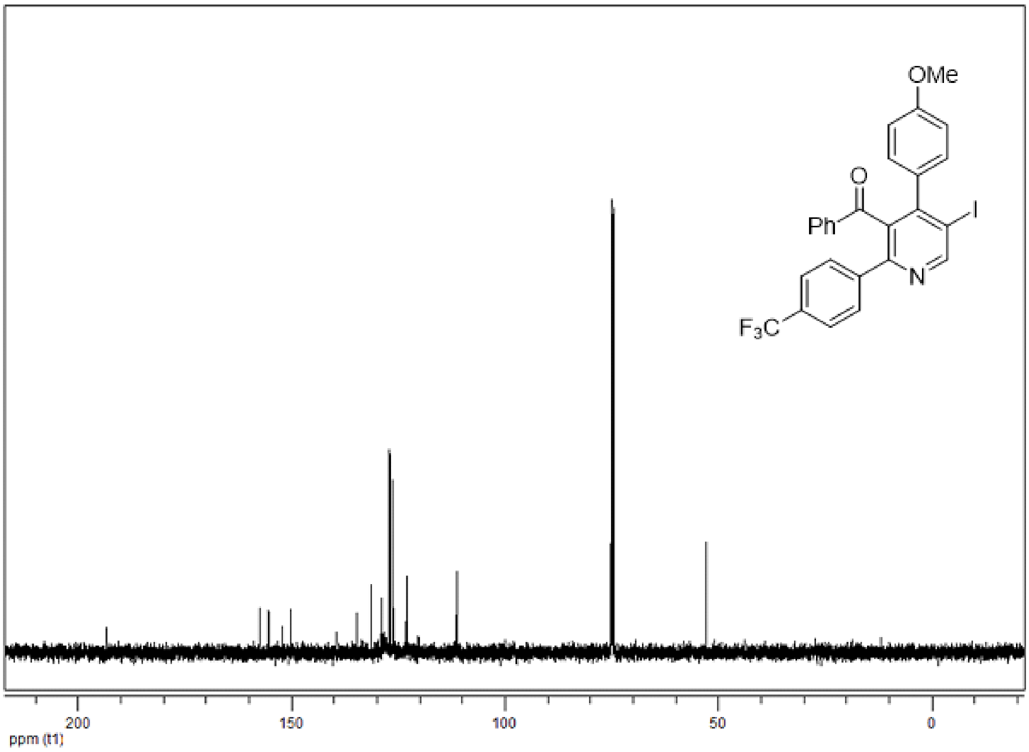


Figure 52A. ^{13}C NMR Spectrum of compound **14E**.

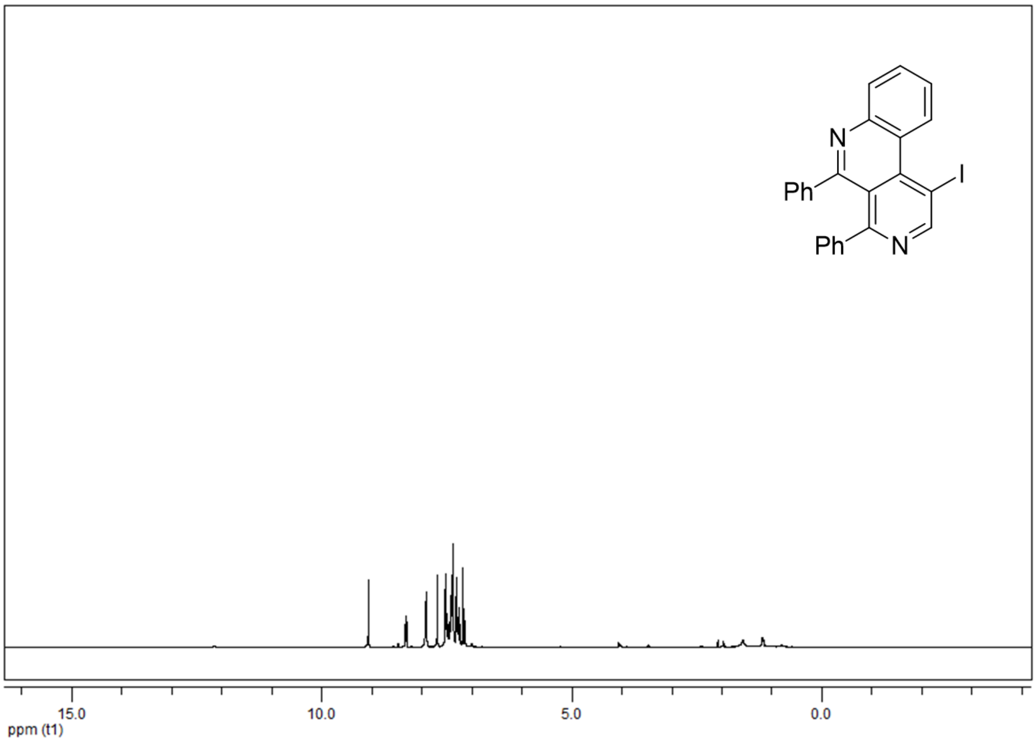


Figure 53A. ^{1}H NMR Spectrum of compound **52**.

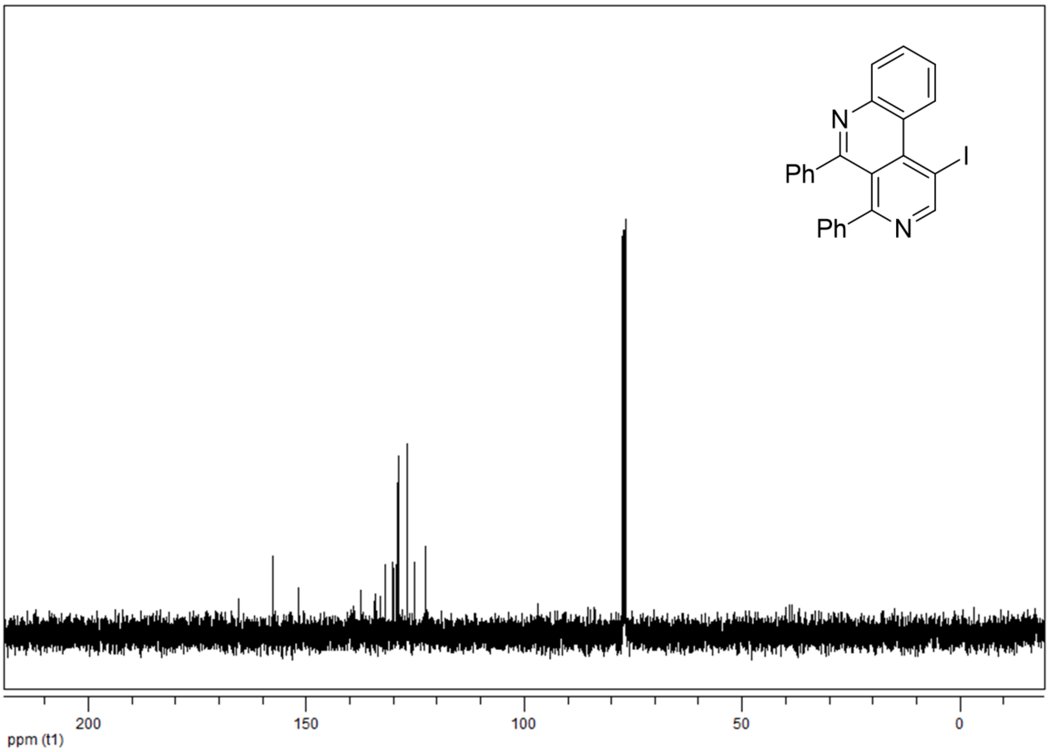


Figure 54A. ^{13}C NMR Spectrum of compound **52**.

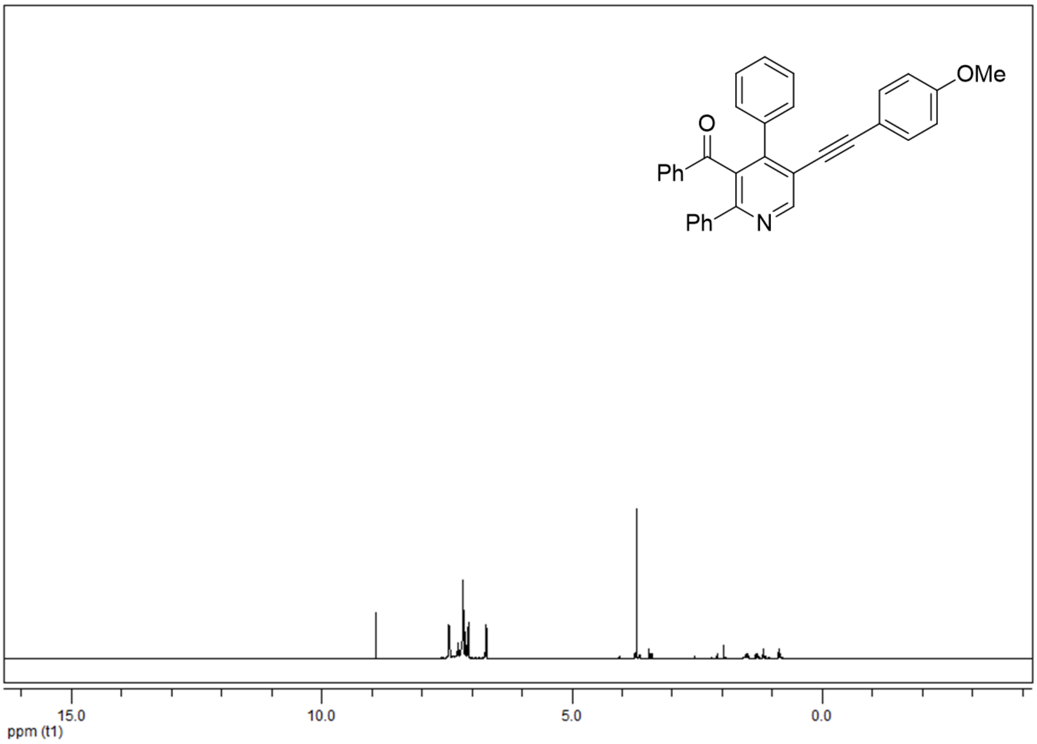


Figure 55A. ^{1}H NMR Spectrum of compound **15A**.

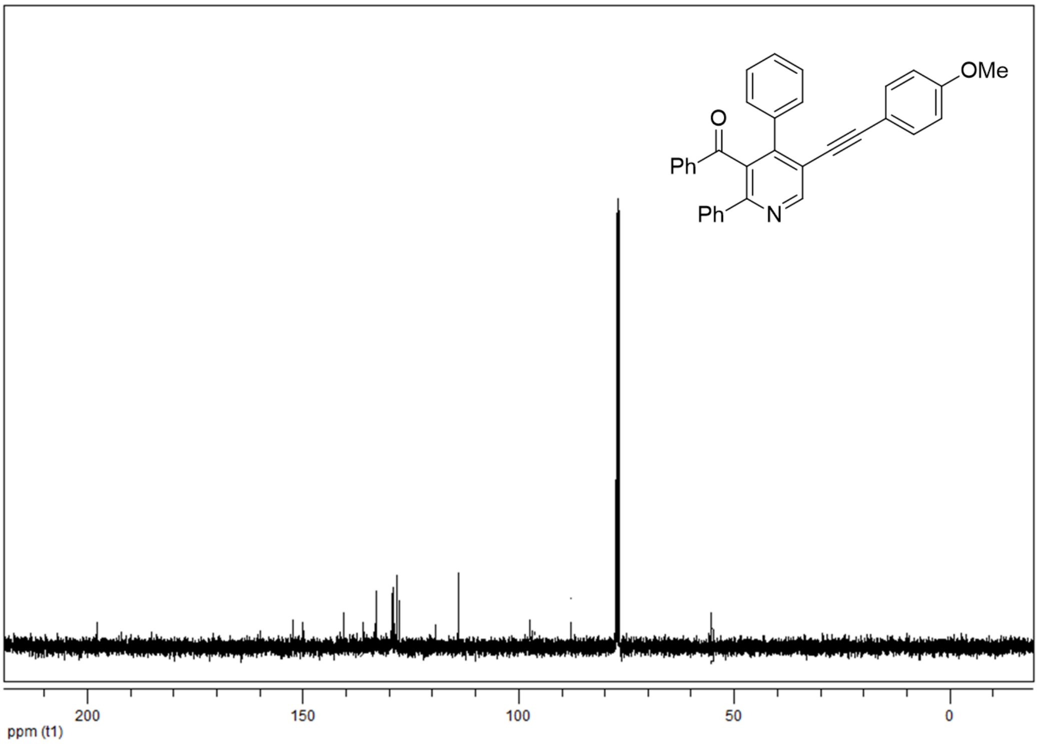


Figure 56A. ^{13}C NMR Spectrum of compound **15A**.

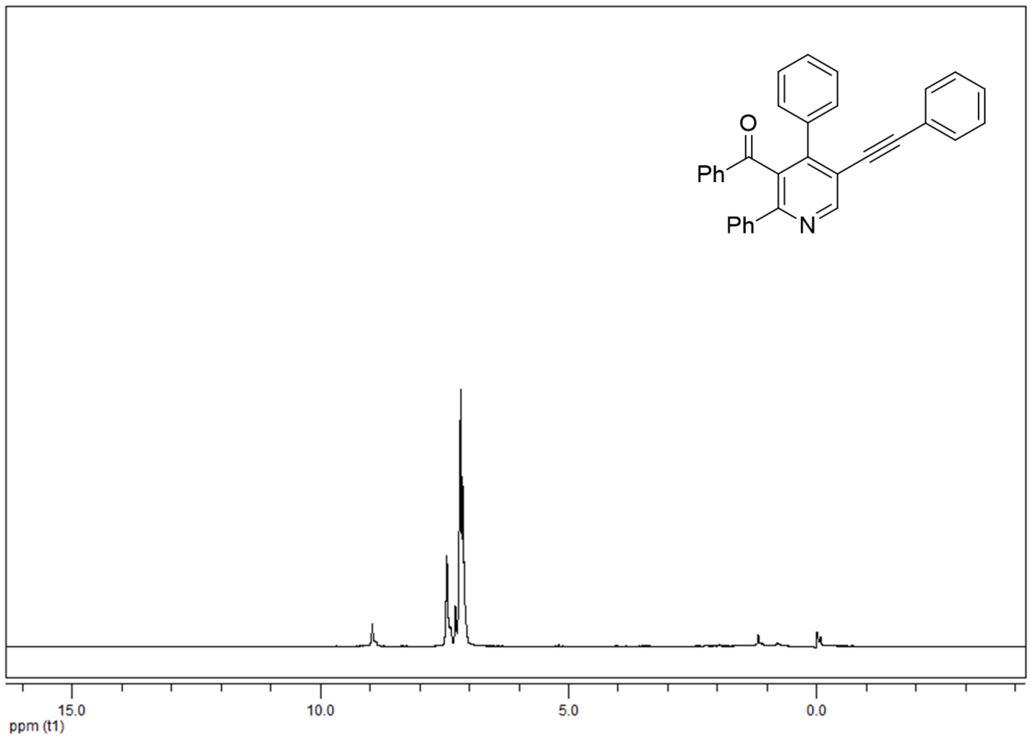


Figure 57A. ^{1}H NMR Spectrum of compound **15B**.

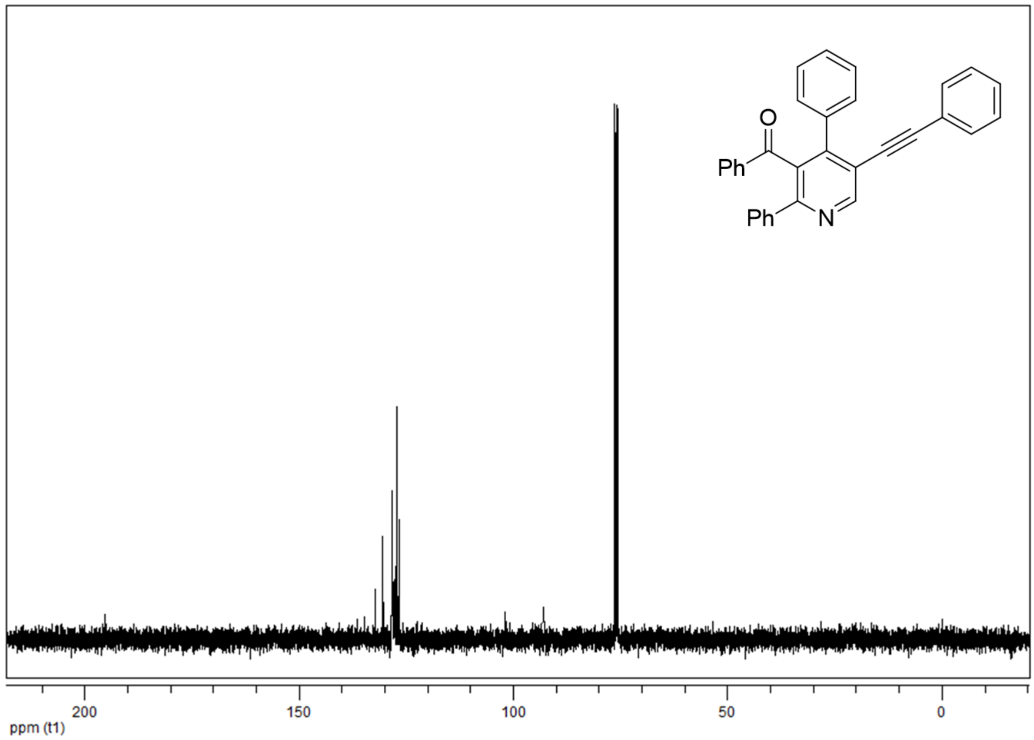


Figure 58A. ^{13}C NMR Spectrum of compound **15B**.

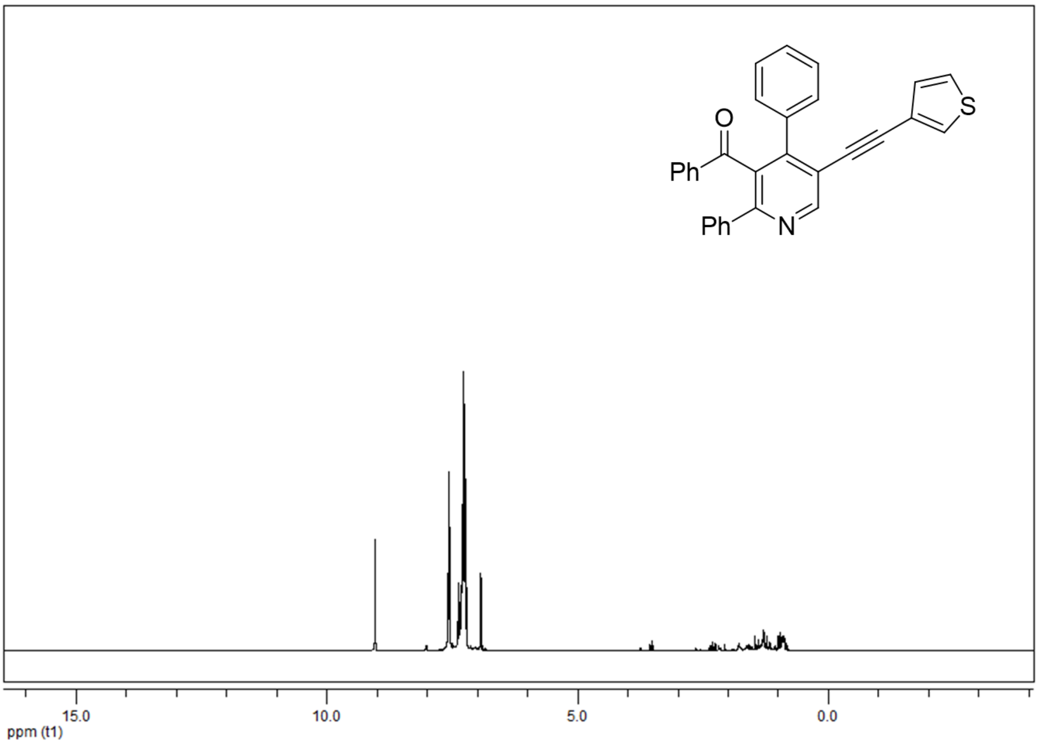


Figure 59A. ^{1}H NMR Spectrum of compound **15C**.

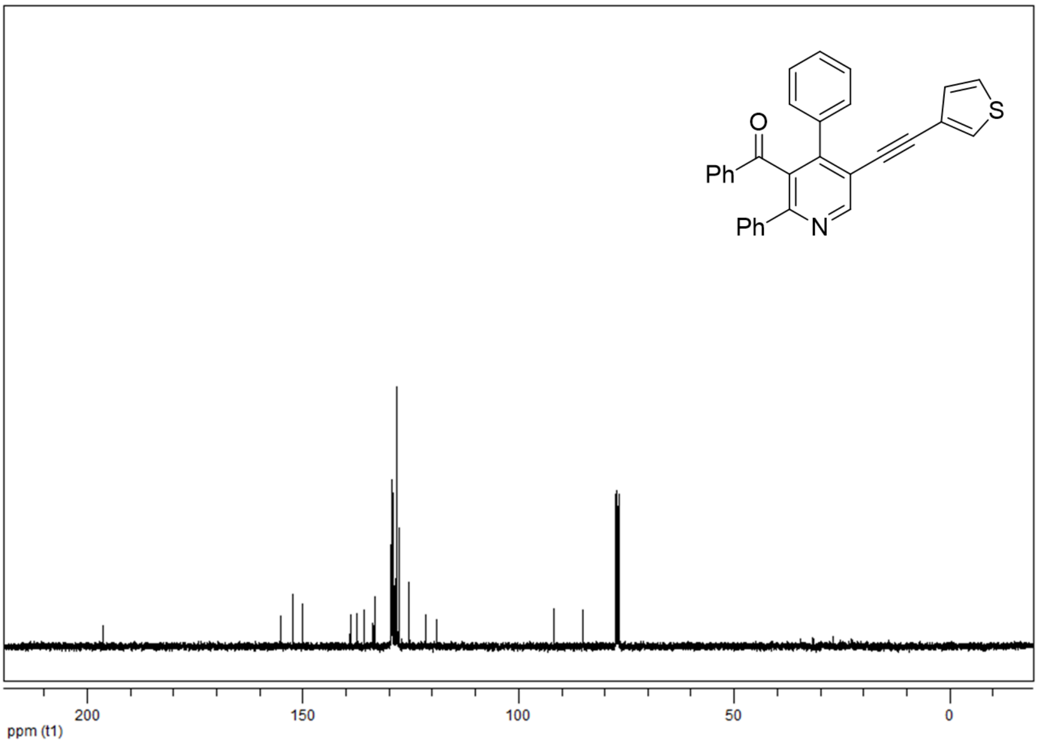


Figure 60A. ^{13}C NMR Spectrum of compound **15C**.

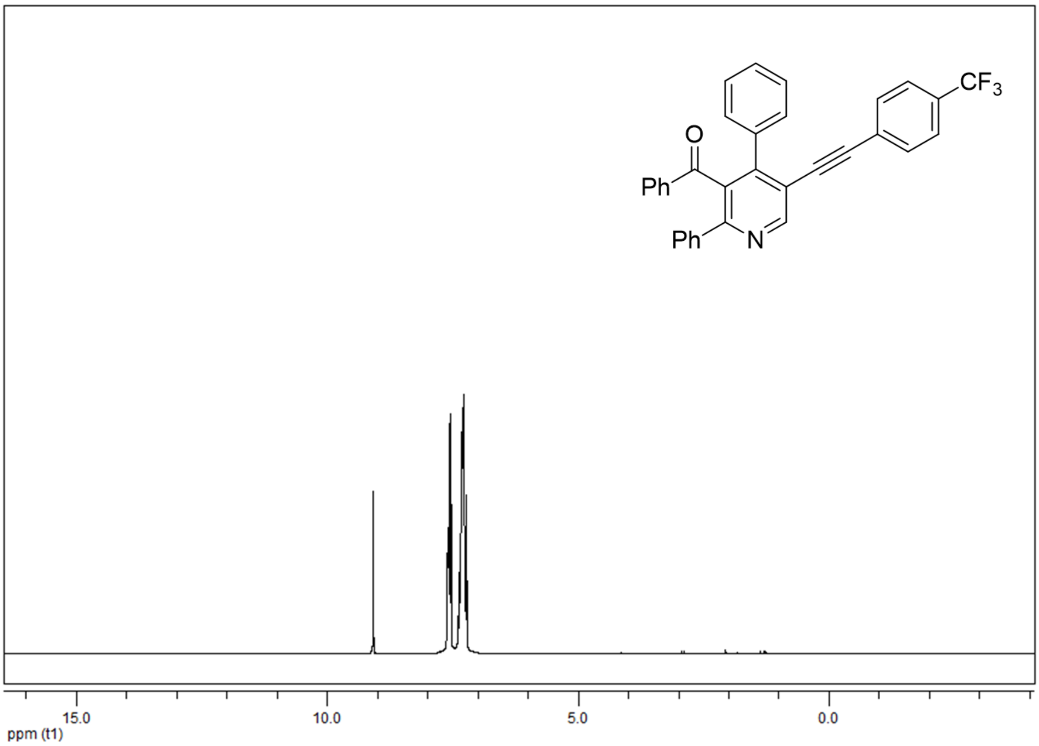


Figure 61A. ^{1}H NMR Spectrum of compound **15D**.

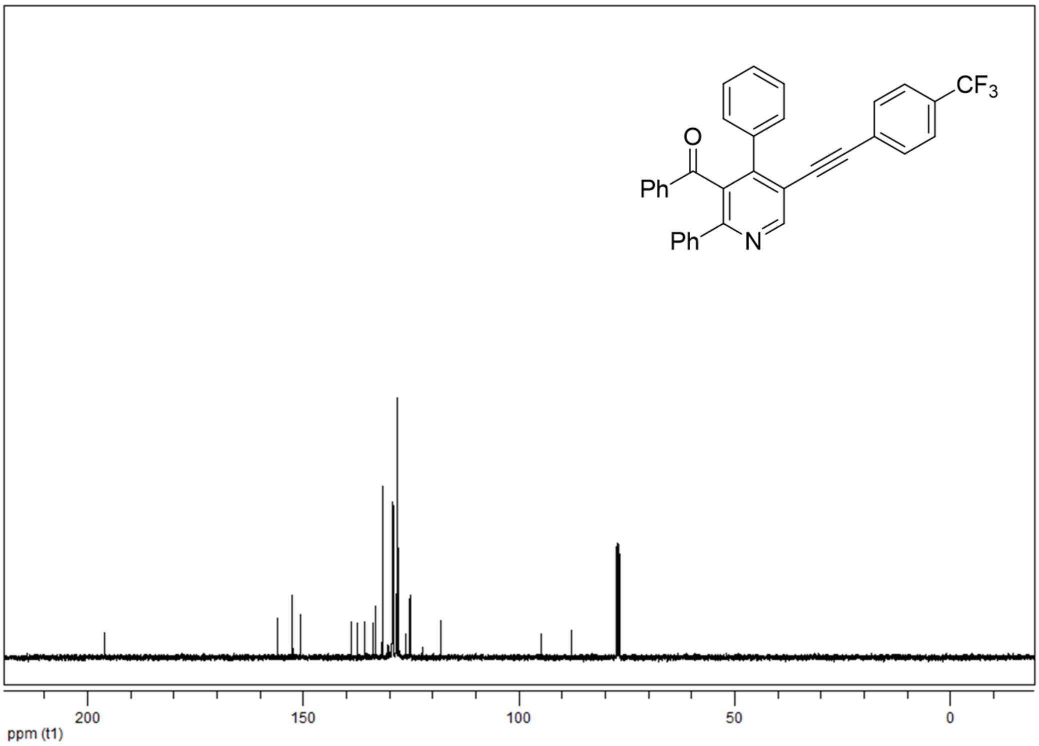


Figure 62A. ^{13}C NMR Spectrum of compound **15D**.

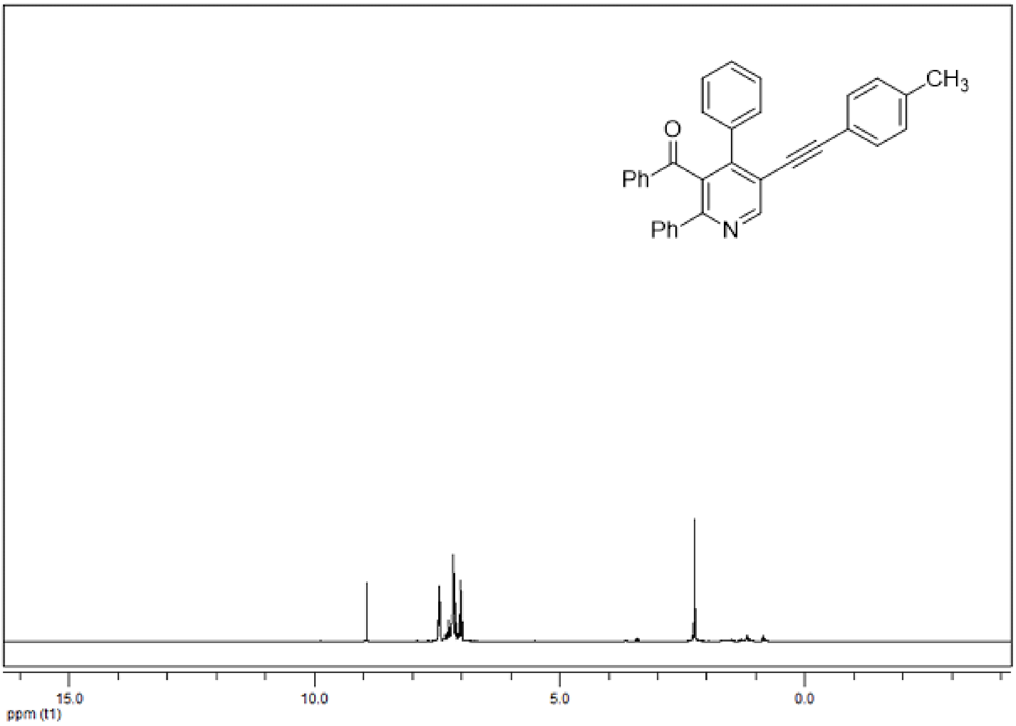


Figure 63A. ^{1}H NMR Spectrum of compound **15E**.

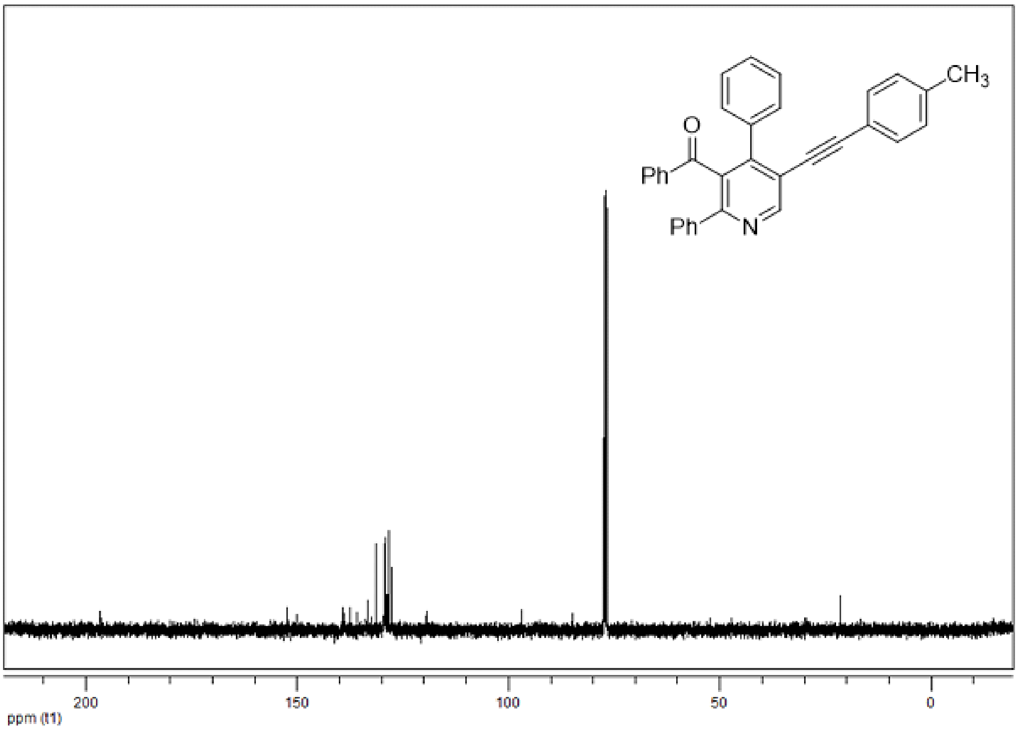


Figure 64A. ^{13}C NMR Spectrum of compound **15E**.

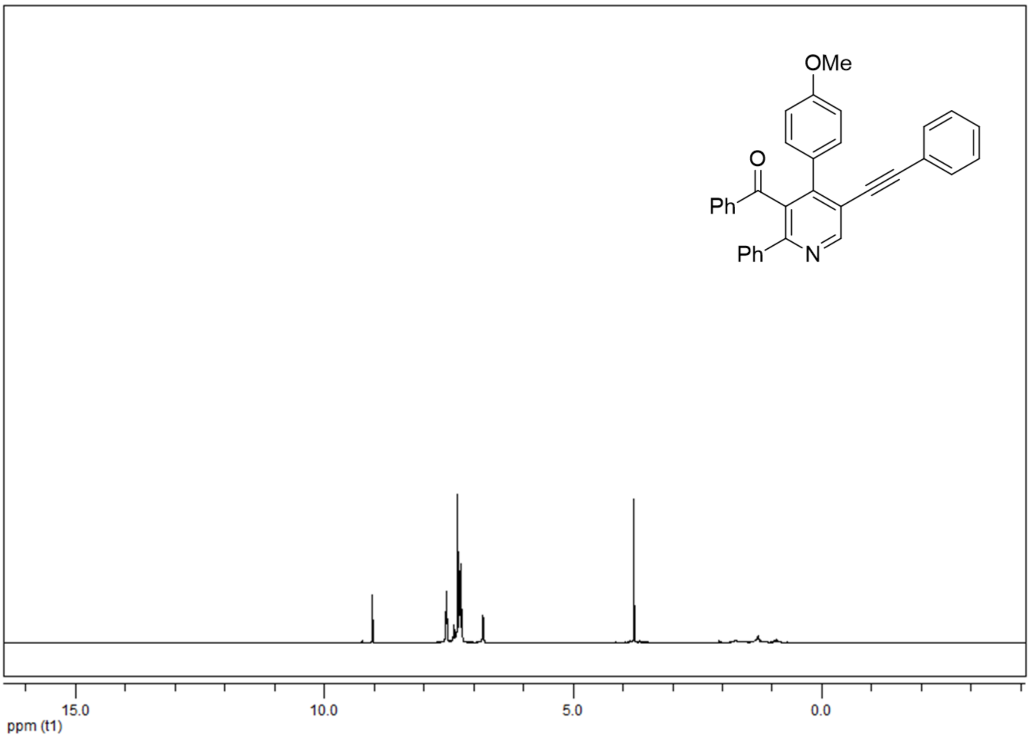


Figure 65A. ^{1}H NMR Spectrum of compound **16A**.

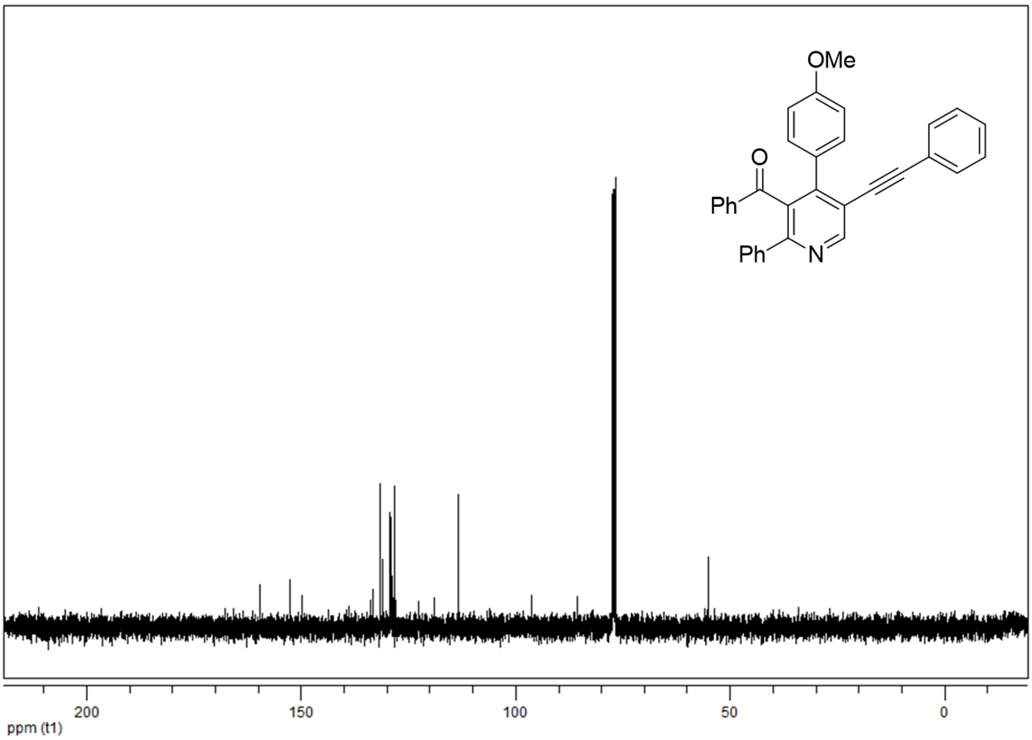


Figure 66A. ^{13}C NMR Spectrum of compound **16A**.

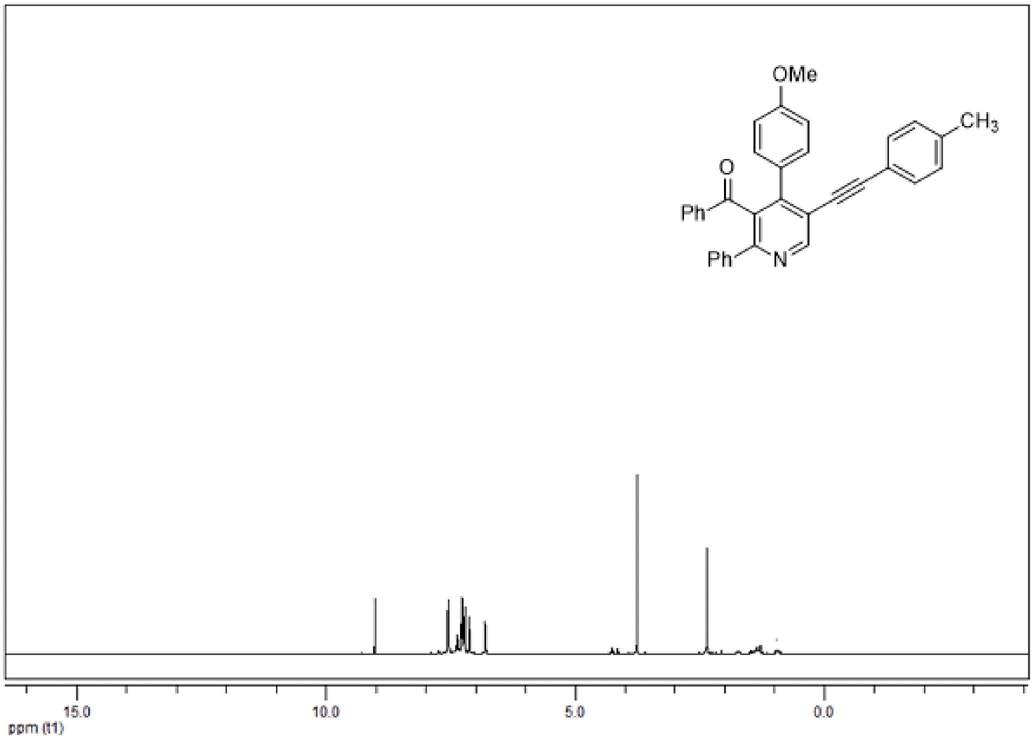


Figure 67A. ^{1}H NMR Spectrum of compound **16B**.

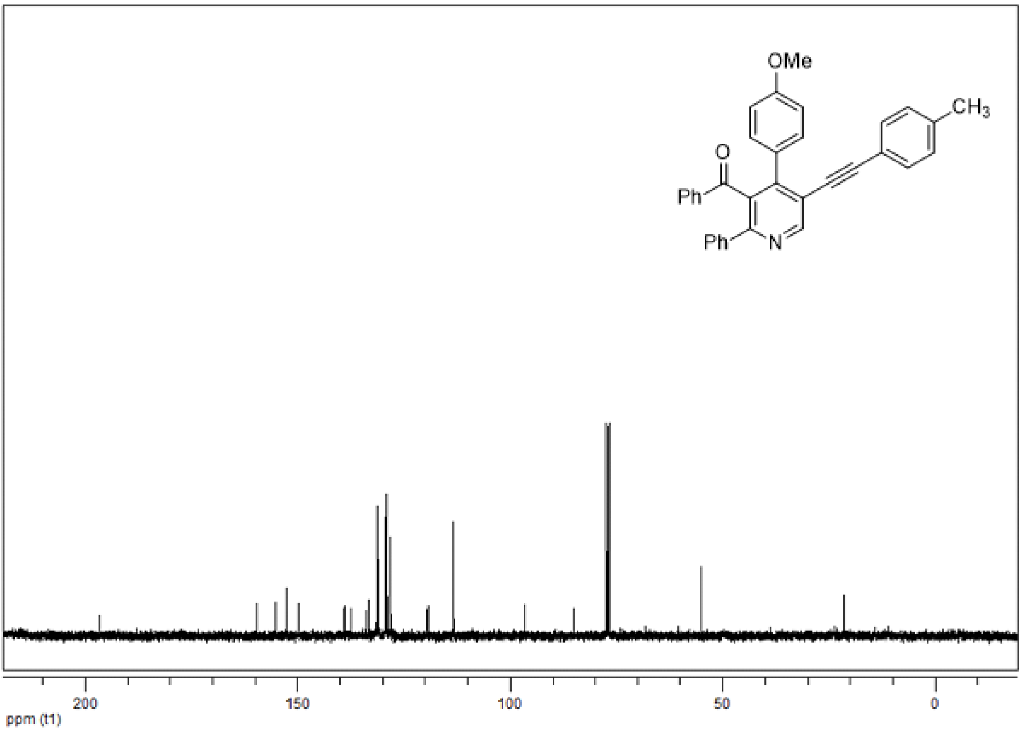


Figure 68A. ^{13}C NMR Spectrum of compound **16B**.

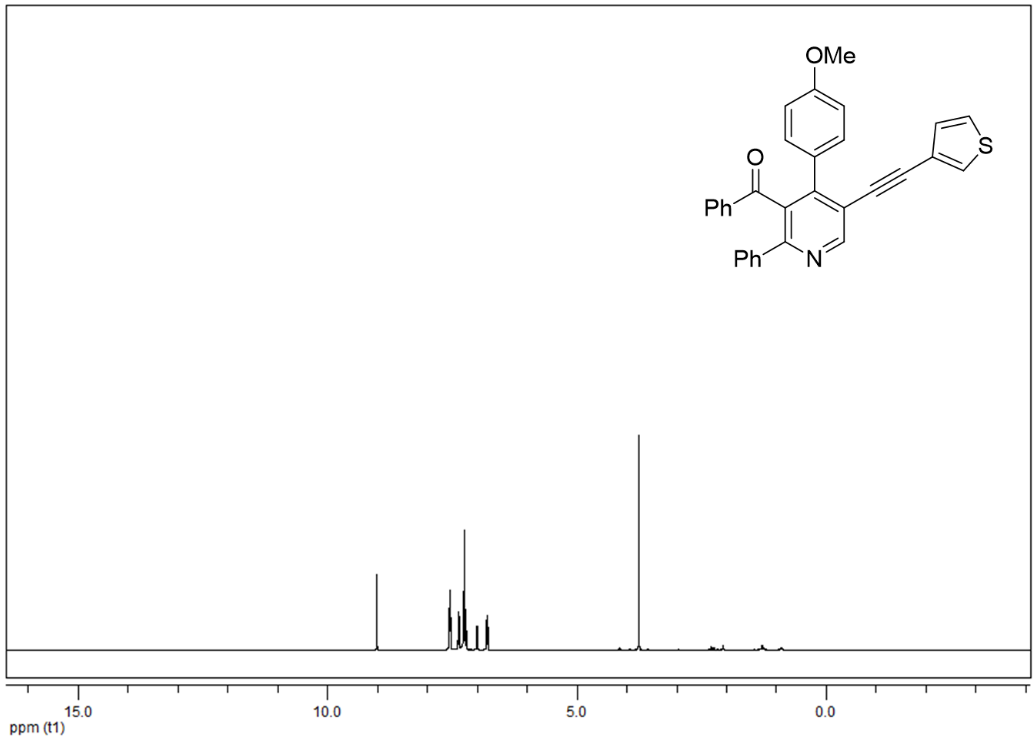


Figure 69A. ^{1}H NMR Spectrum of compound **16C**.

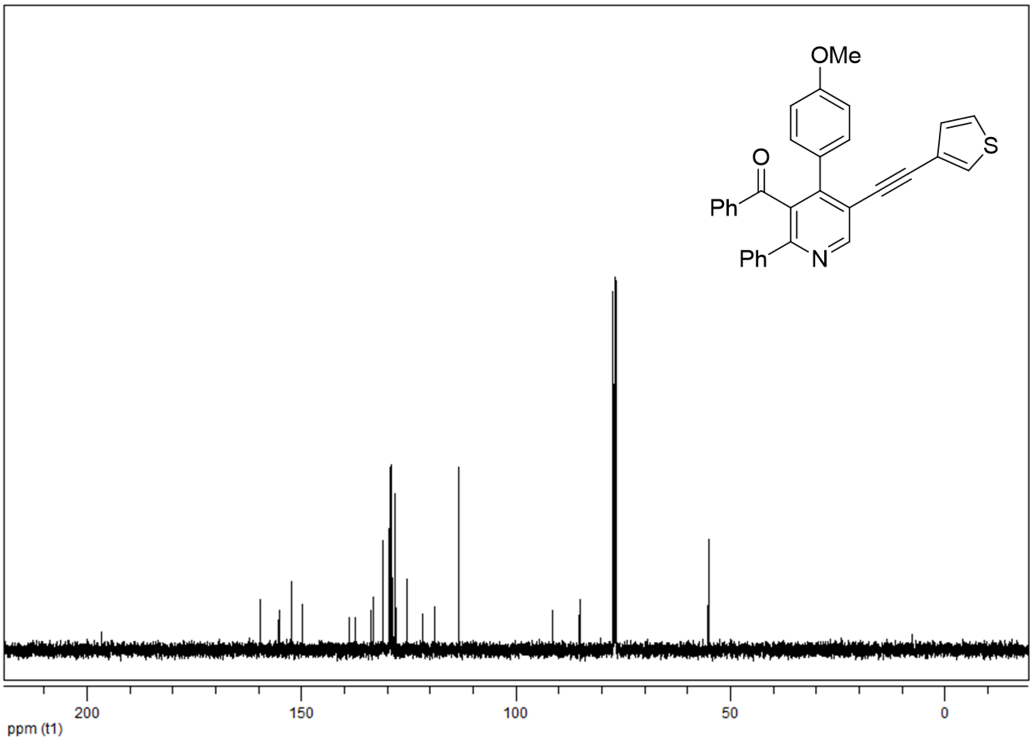


Figure 70A. ^{13}C NMR Spectrum of compound **16C**.

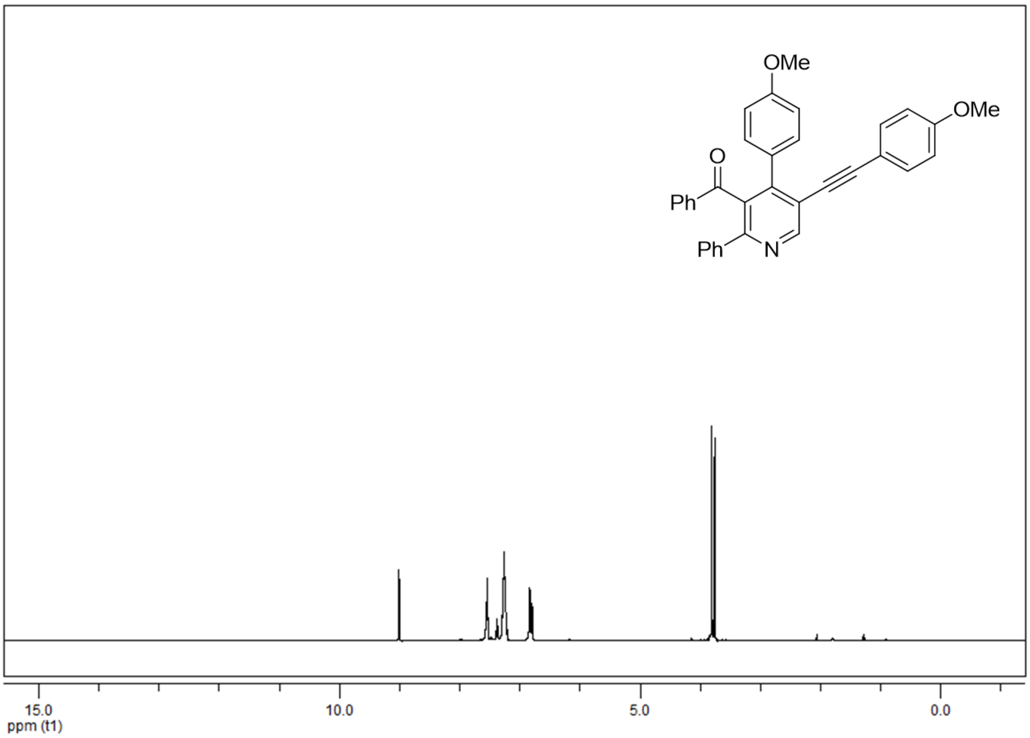


Figure 71A. ^{1}H NMR Spectrum of compound **16D**.

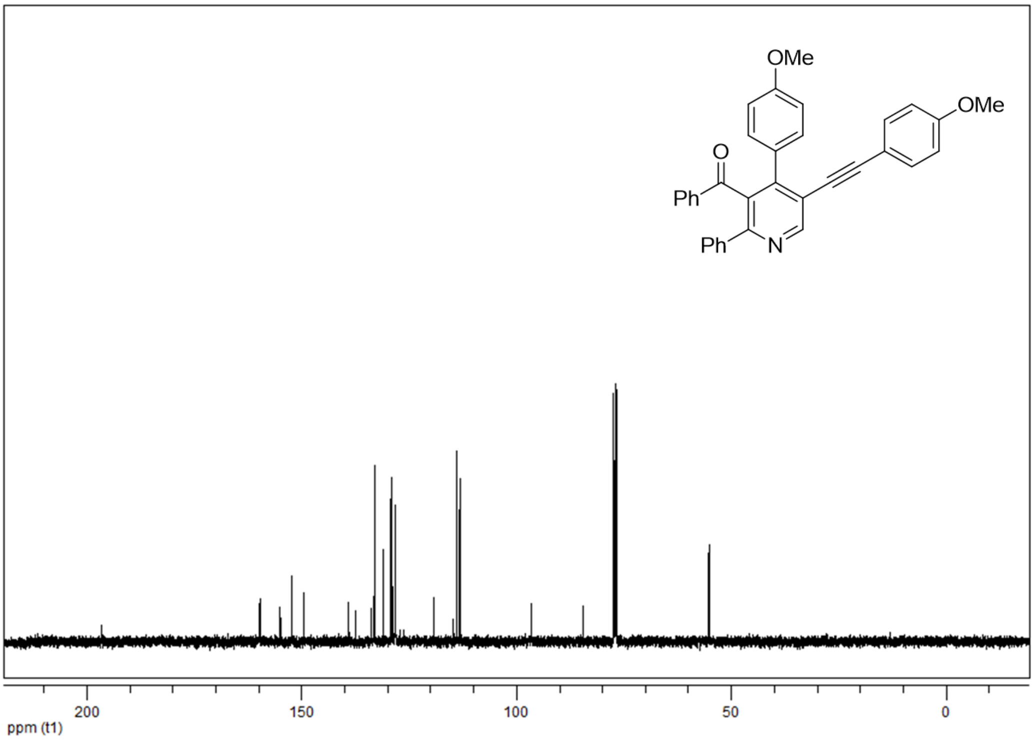


Figure 72A. ^{13}C NMR Spectrum of compound **16D**.

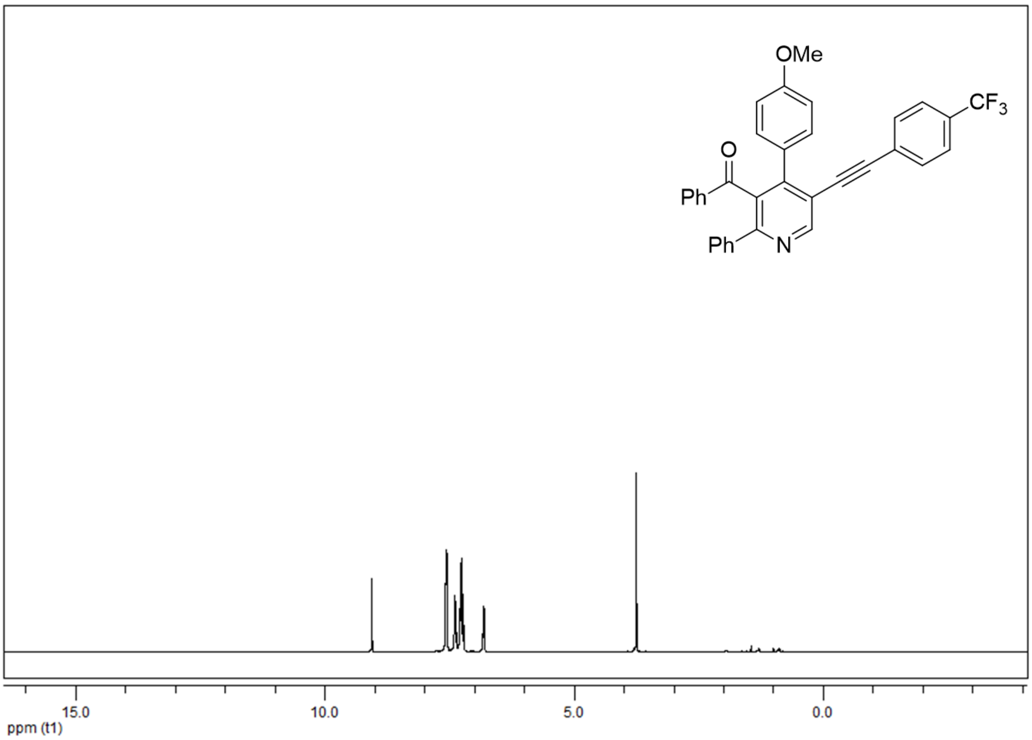


Figure 73A. ^{1}H NMR Spectrum of compound **16E**.

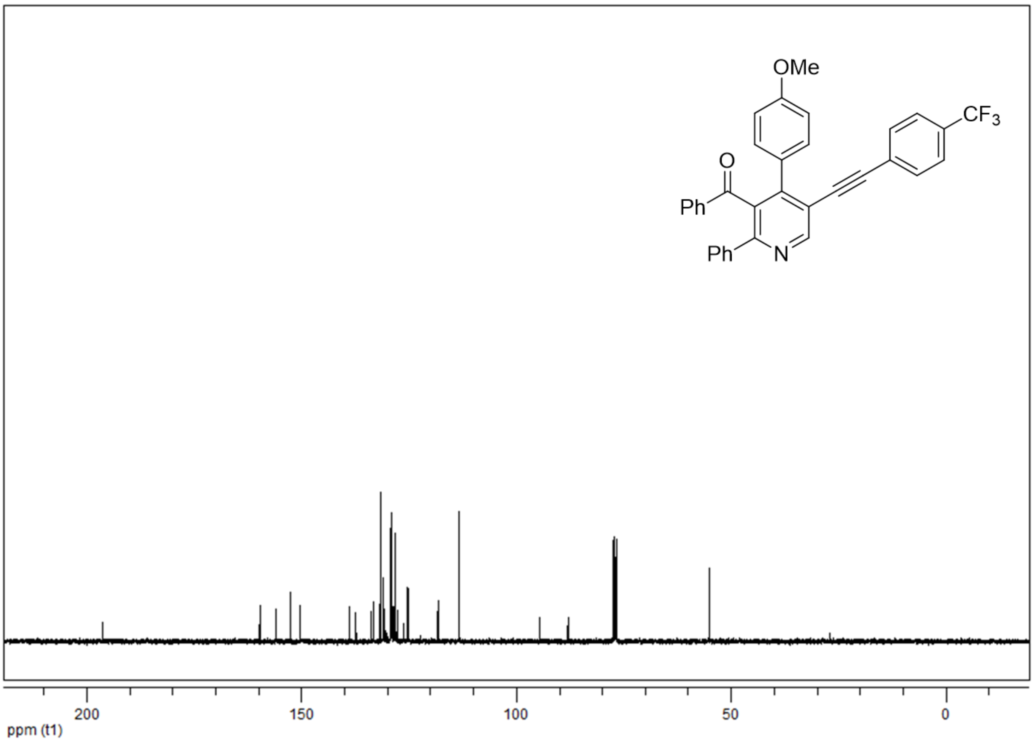


Figure 74A. ^{13}C NMR Spectrum of compound **16E**.

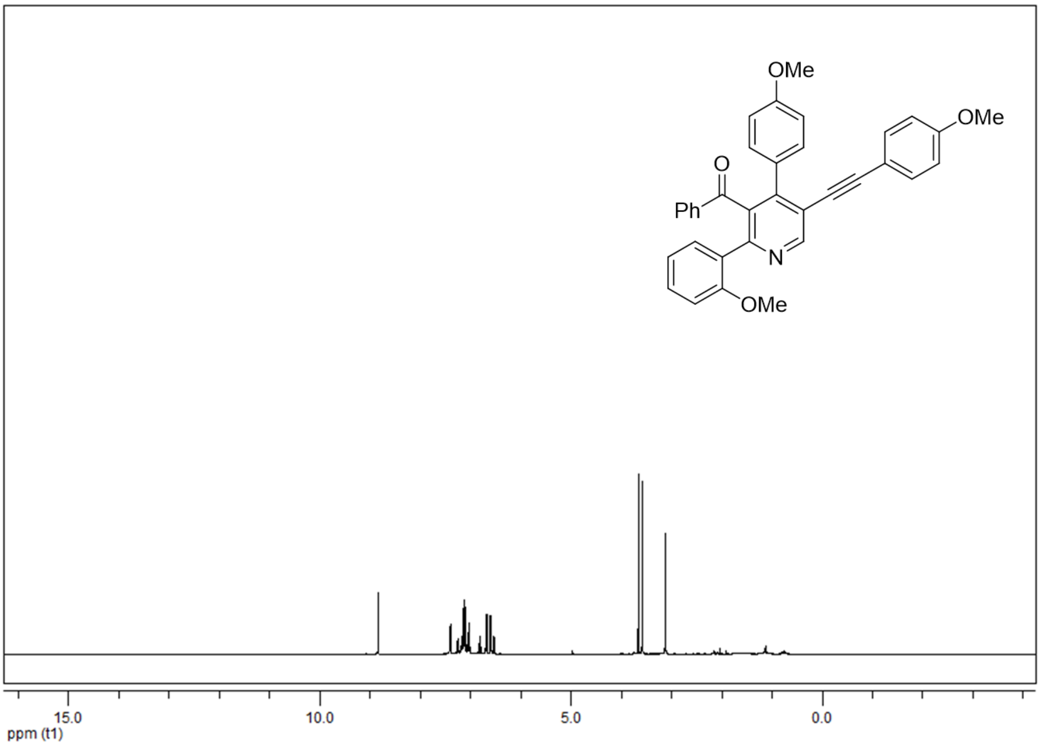


Figure 75A. ^{1}H NMR Spectrum of compound **16F**.

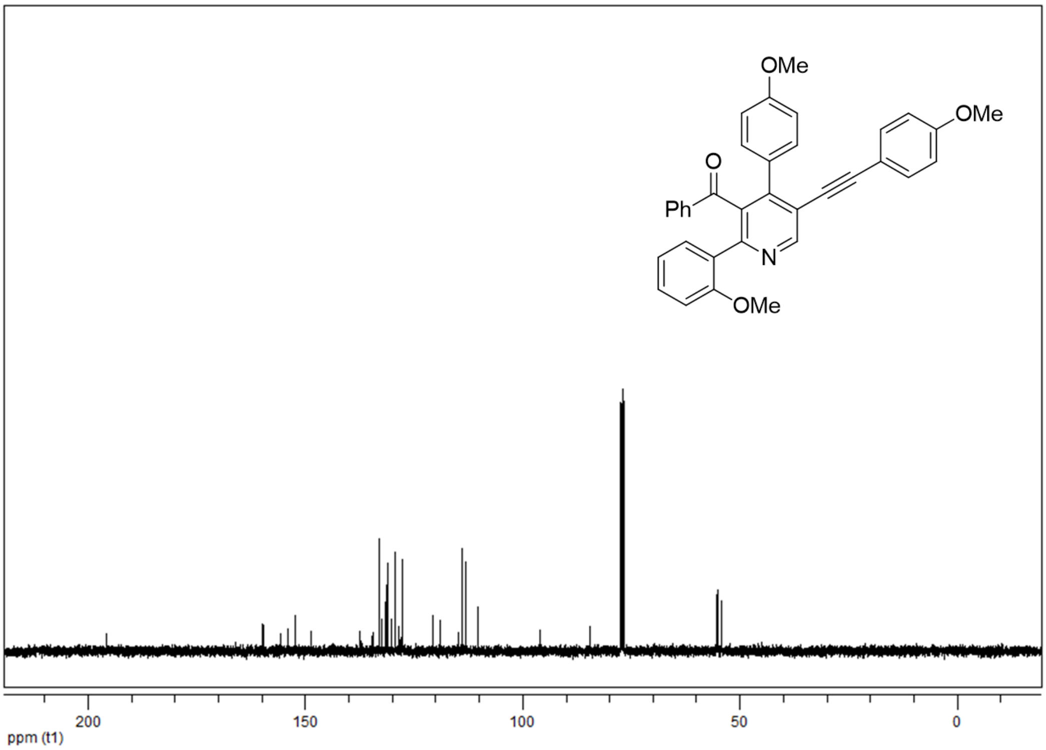


Figure 76A. ^{13}C NMR Spectrum of compound **16F**.

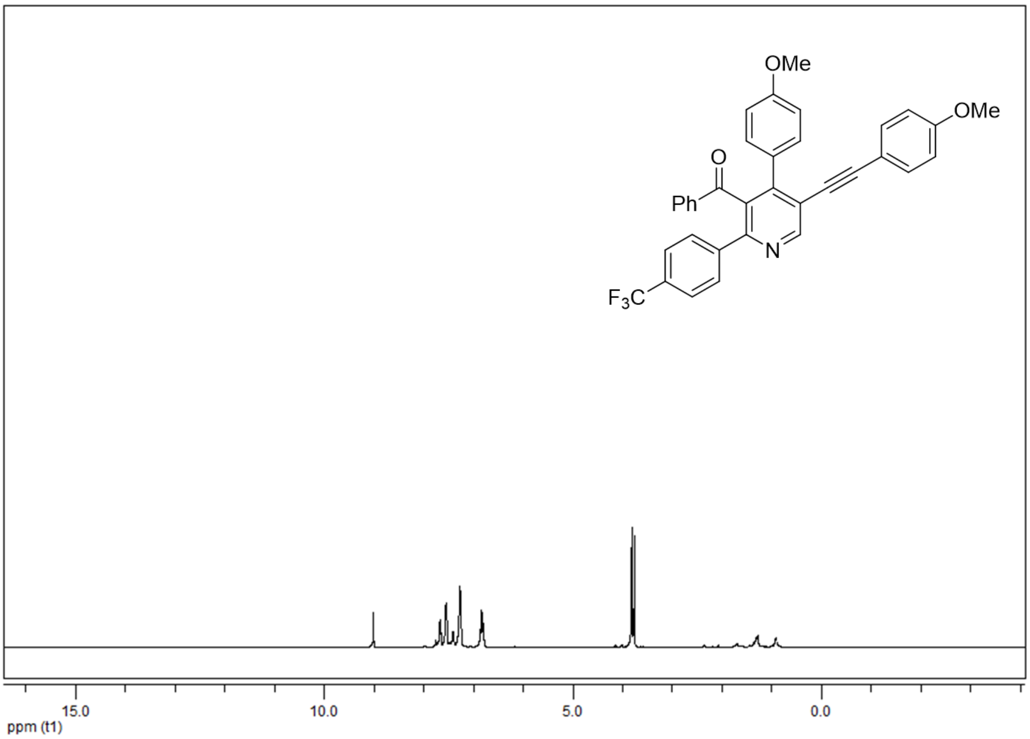


Figure 77A. ^{1}H NMR Spectrum of compound **16G**.

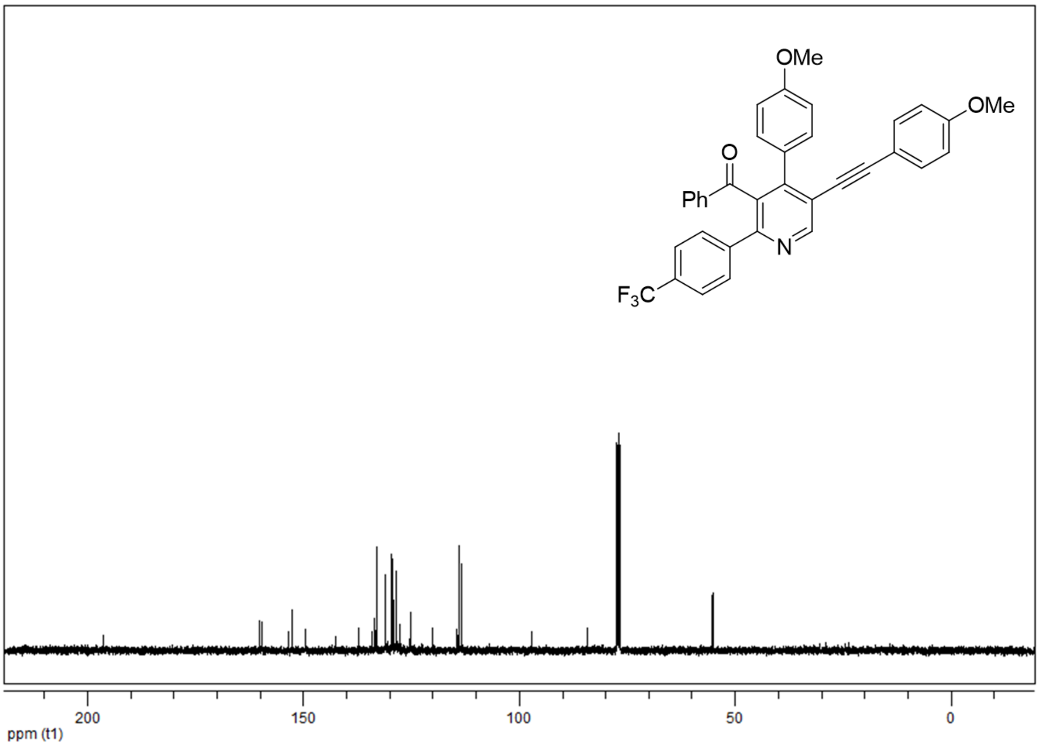


Figure 78A. ^{13}C NMR Spectrum of compound **16G**.

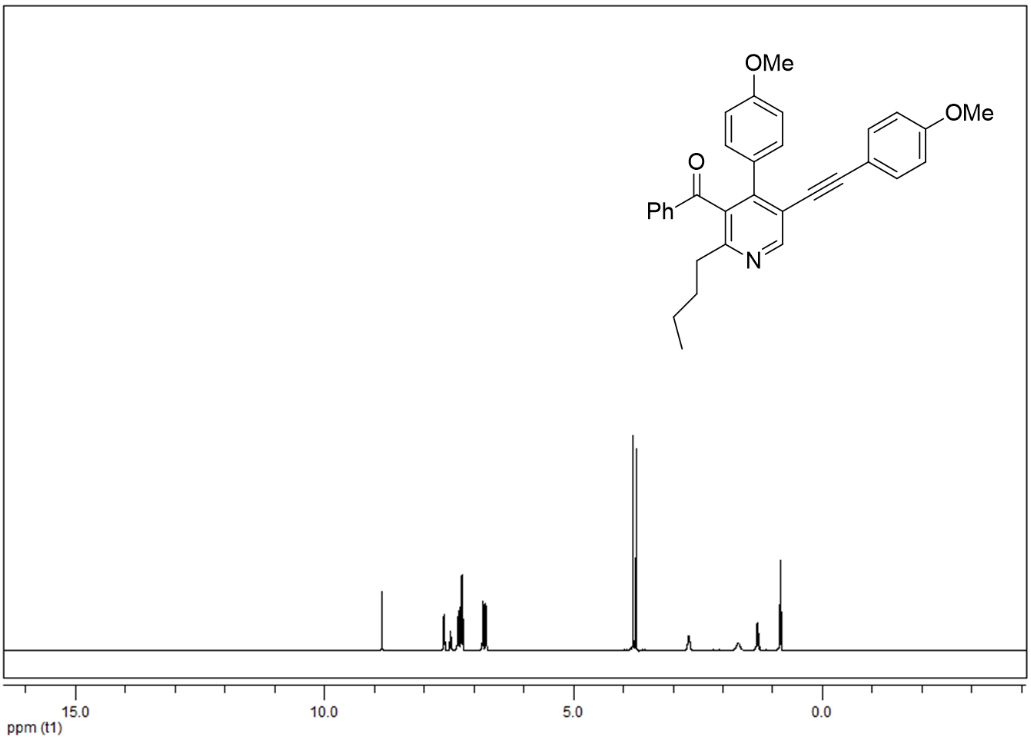


Figure 79A. ^{1}H NMR Spectrum of compound **16H**.

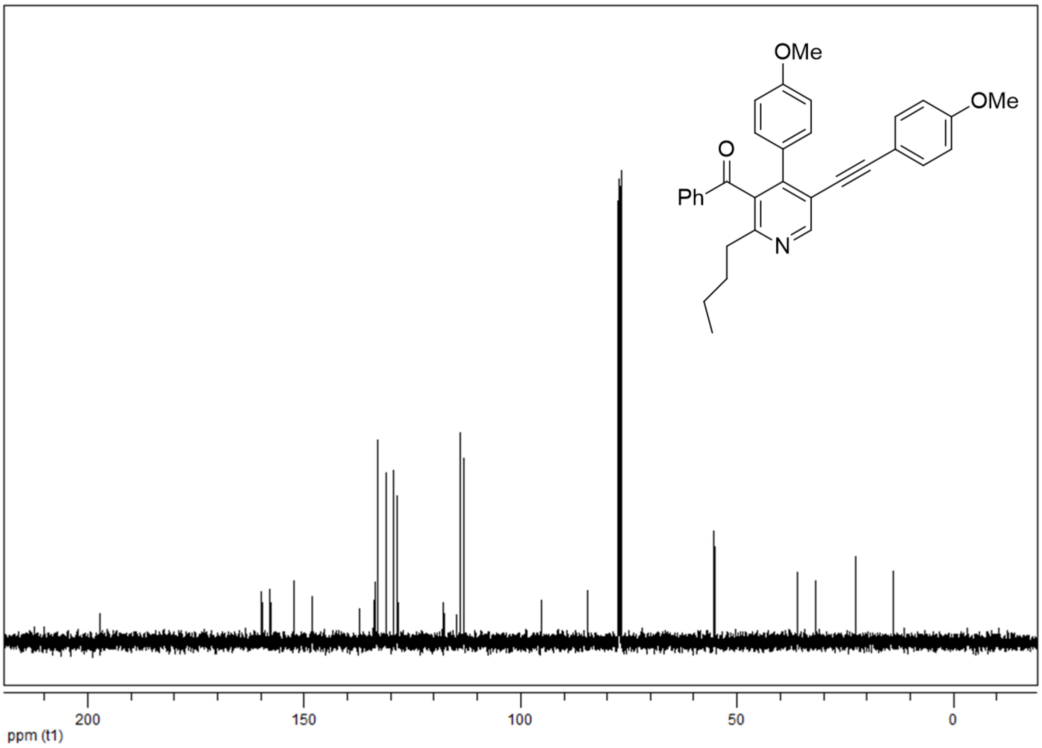


Figure 80A. ^{13}C NMR Spectrum of compound **16H**.

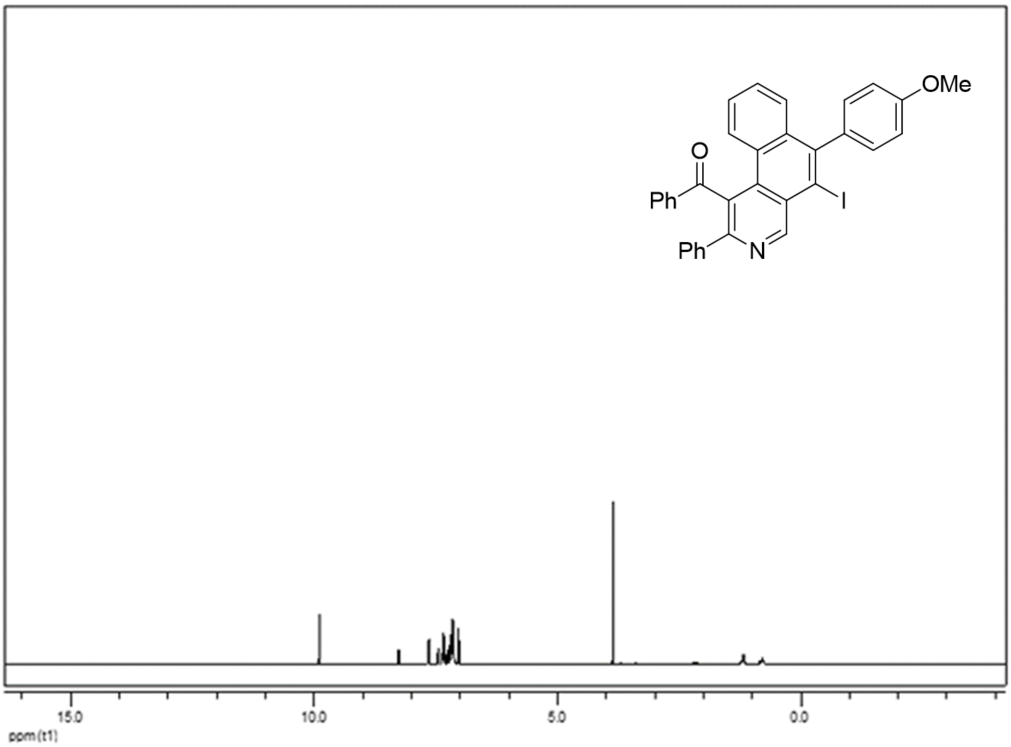


Figure 81A. ^{1}H NMR Spectrum of compound **43A**.

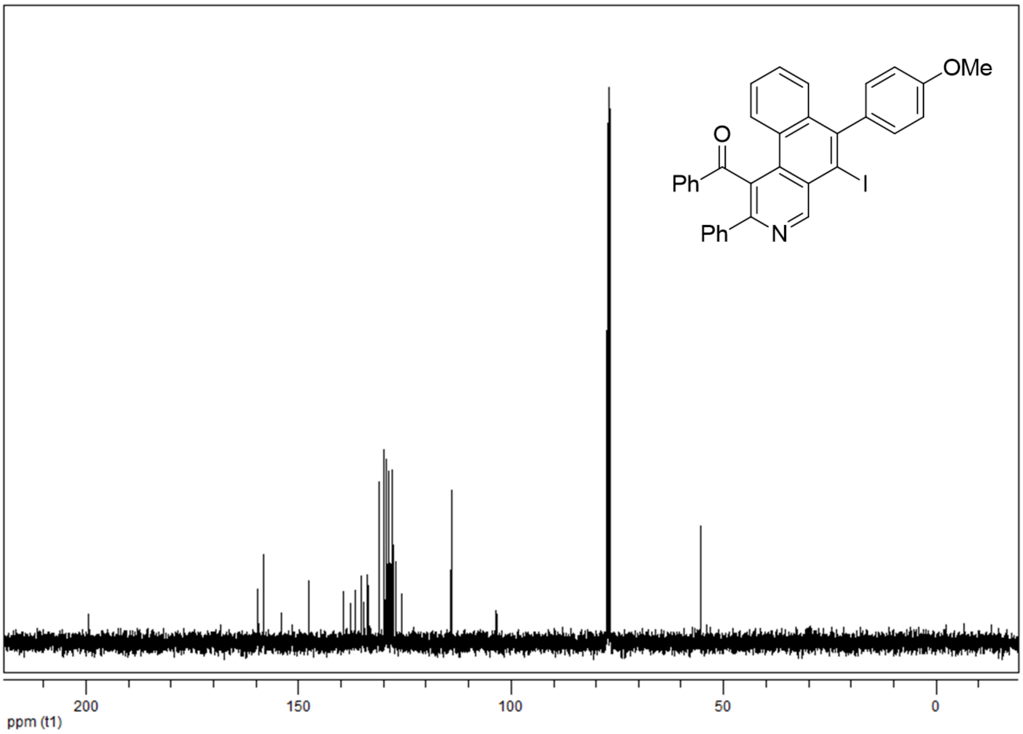


Figure 82A. ^{13}C NMR Spectrum of compound **43A.**

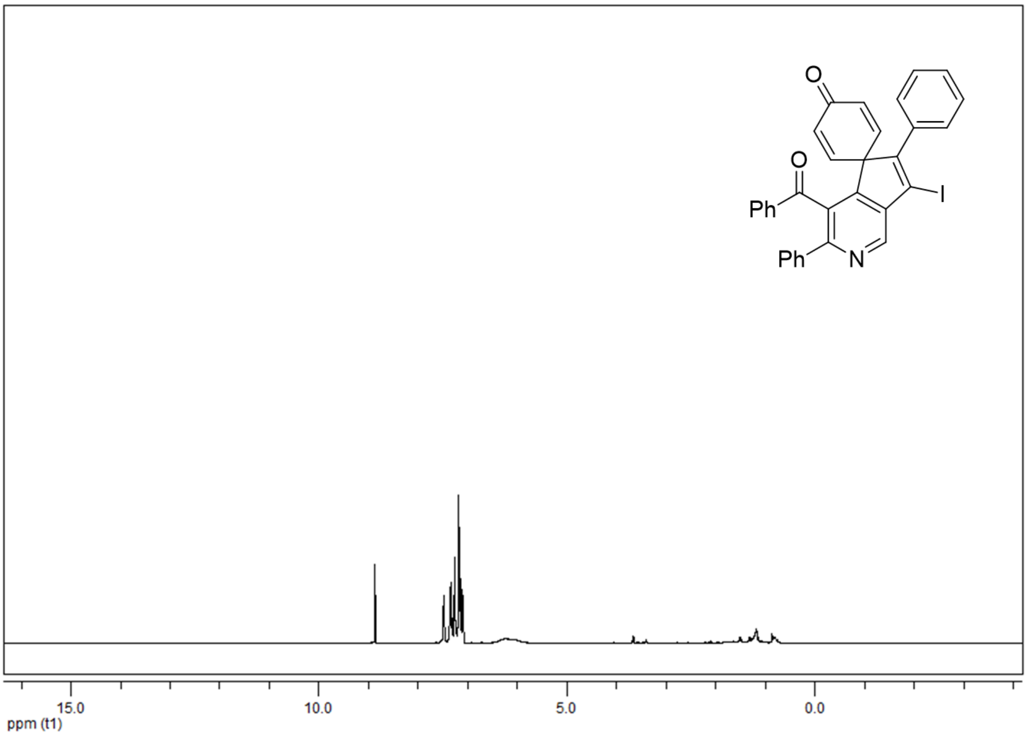


Figure 83A. ^{1}H NMR Spectrum of compound **44A**.

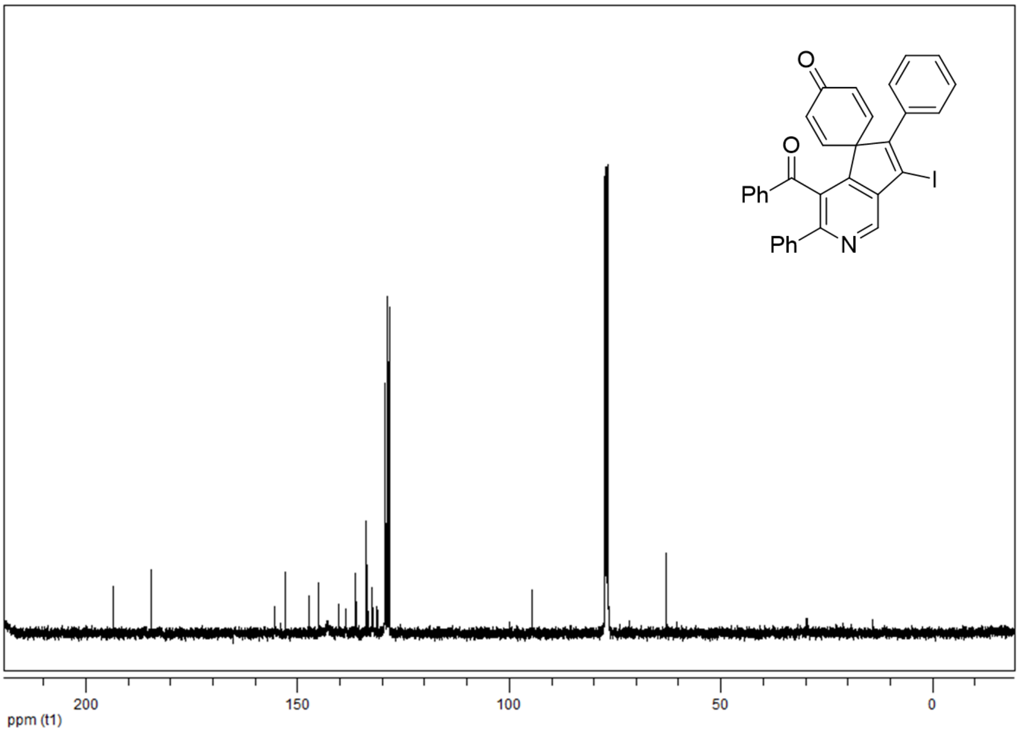


Figure 84A. ^{13}C NMR Spectrum of compound **44A**.

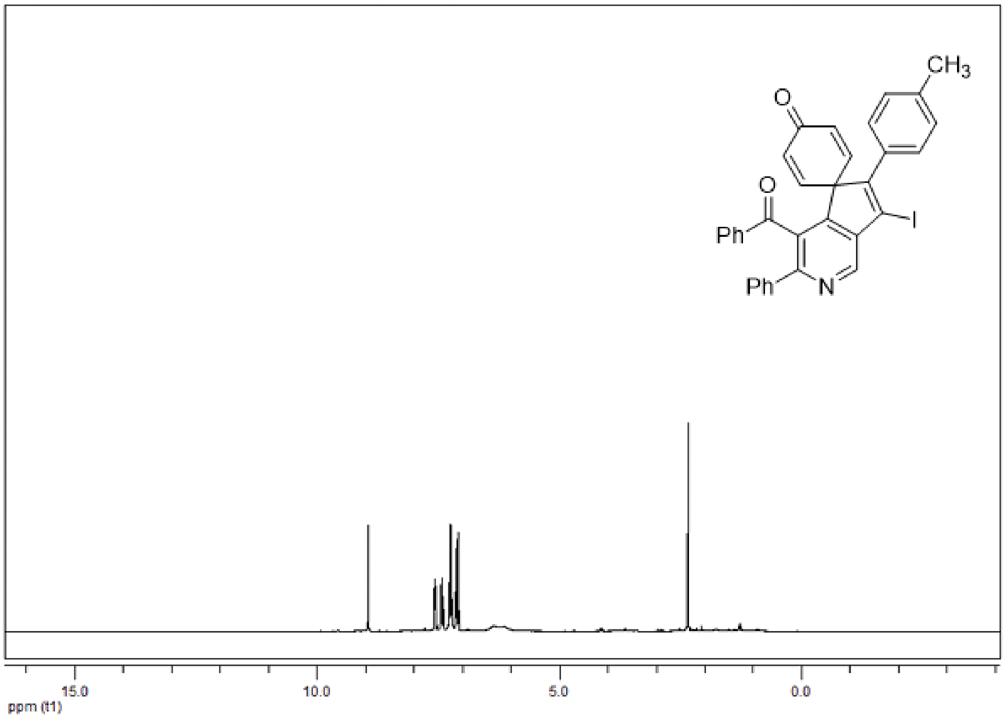


Figure 85A. ^{1}H NMR Spectrum of compound **44B**.

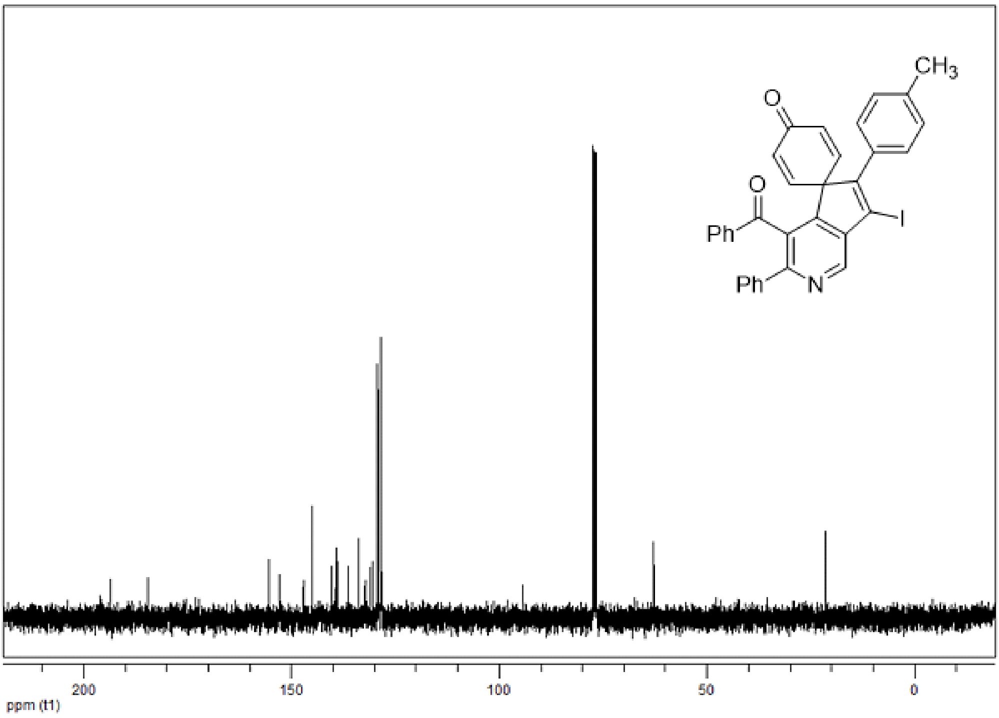


Figure 86A. ^{13}C NMR Spectrum of compound **44B**.

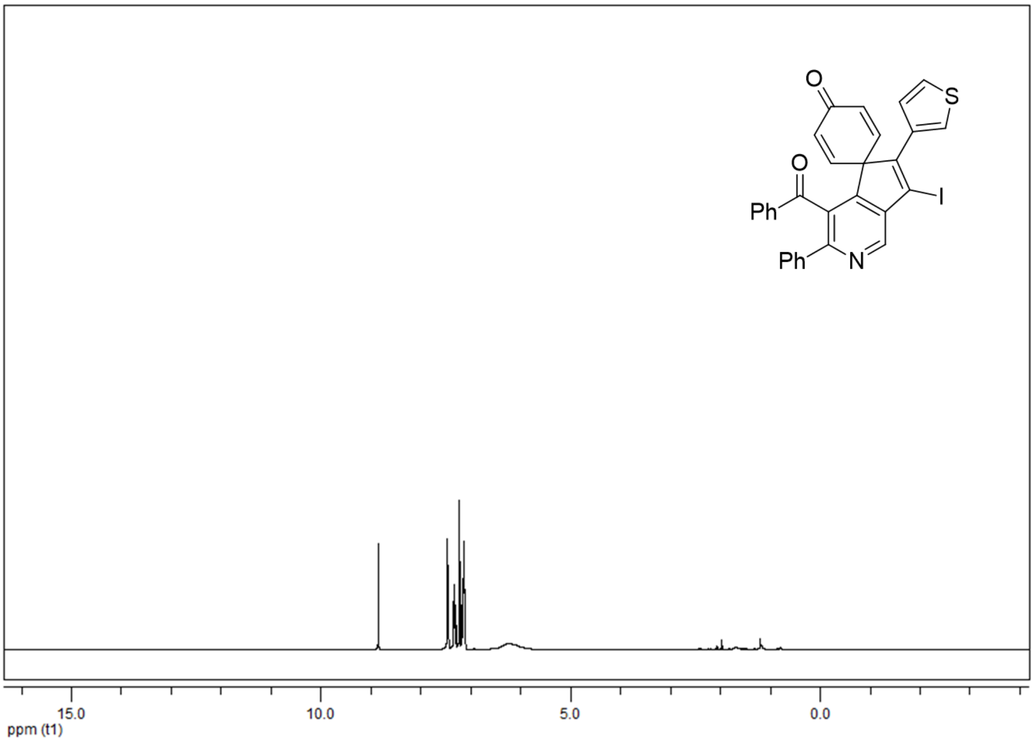


Figure 87A. ^{1}H NMR Spectrum of compound **44C**.

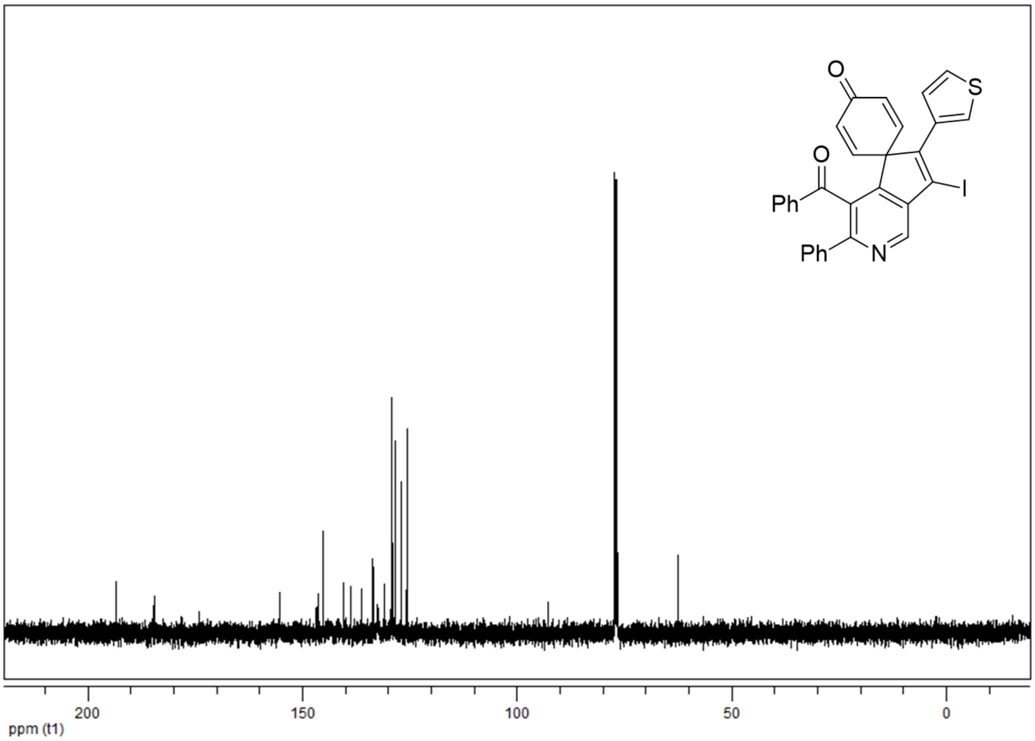


Figure 88A. ^{13}C NMR Spectrum of compound **44C**.

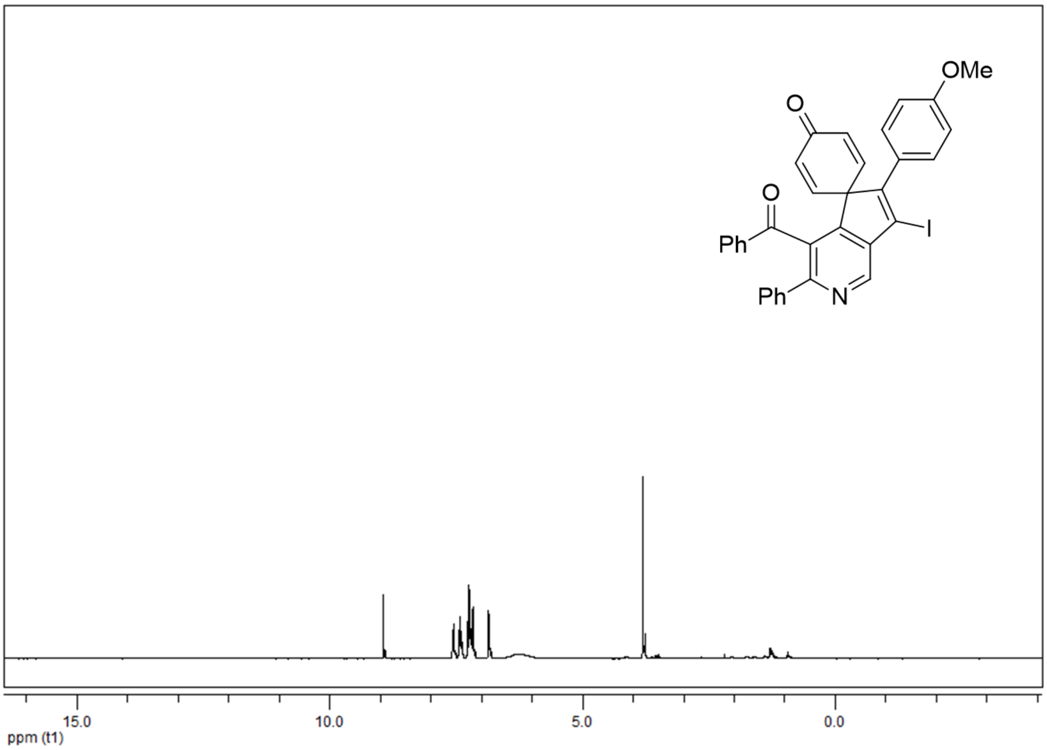


Figure 89A. ^{1}H NMR Spectrum of compound **44D**.

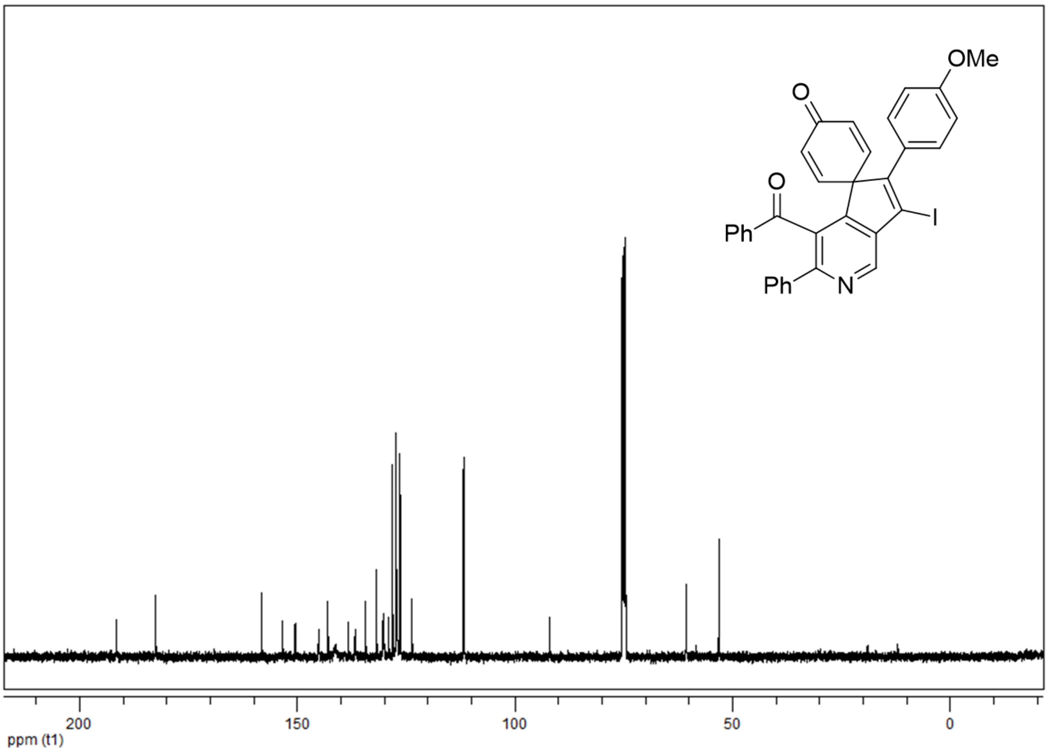


Figure 90A. ^{13}C NMR Spectrum of compound **44D**.

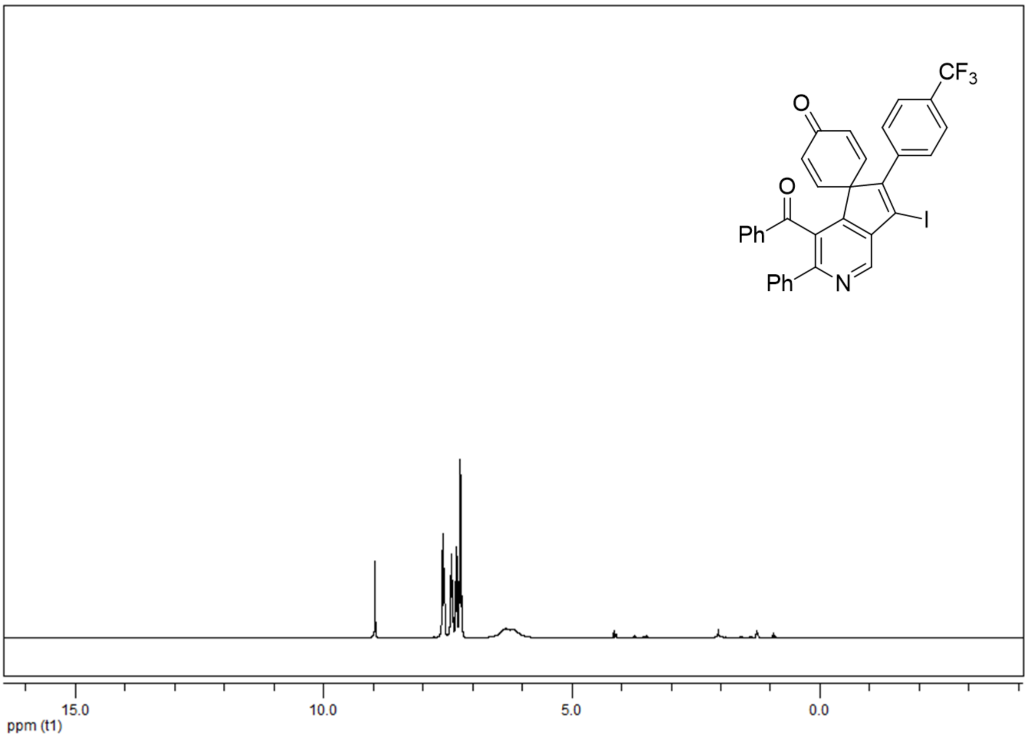


Figure 91A. ^{1}H NMR Spectrum of compound **44E**.

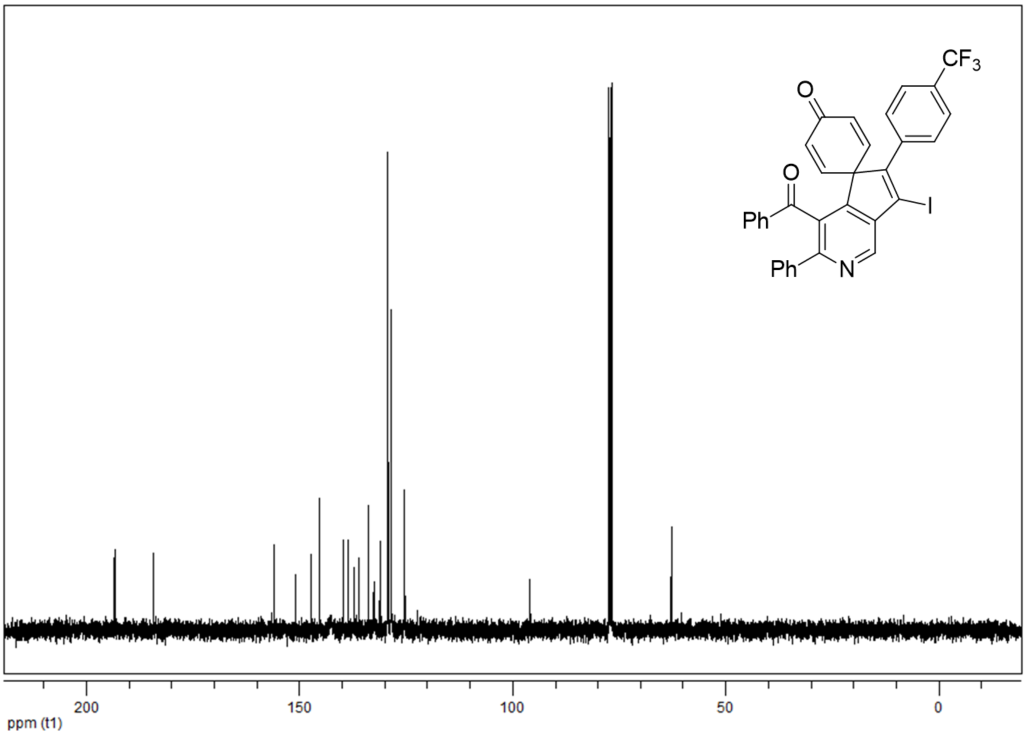


Figure 92A. ^{13}C NMR Spectrum of compound **44E**.

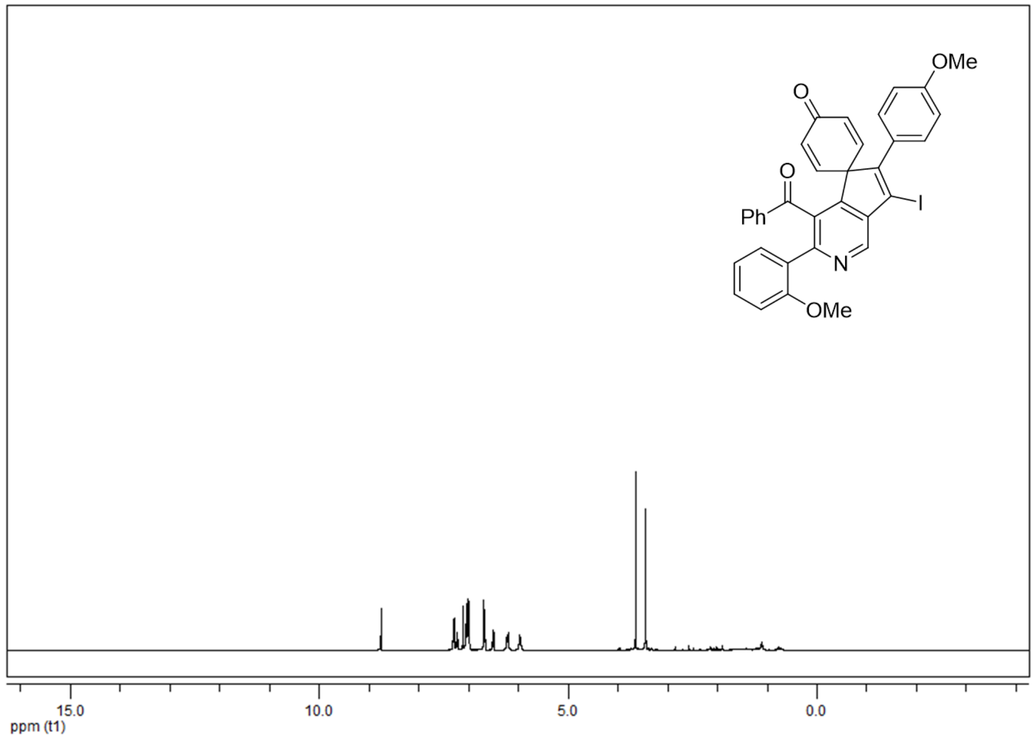


Figure 93A. ^{1}H NMR Spectrum of compound **44F**.

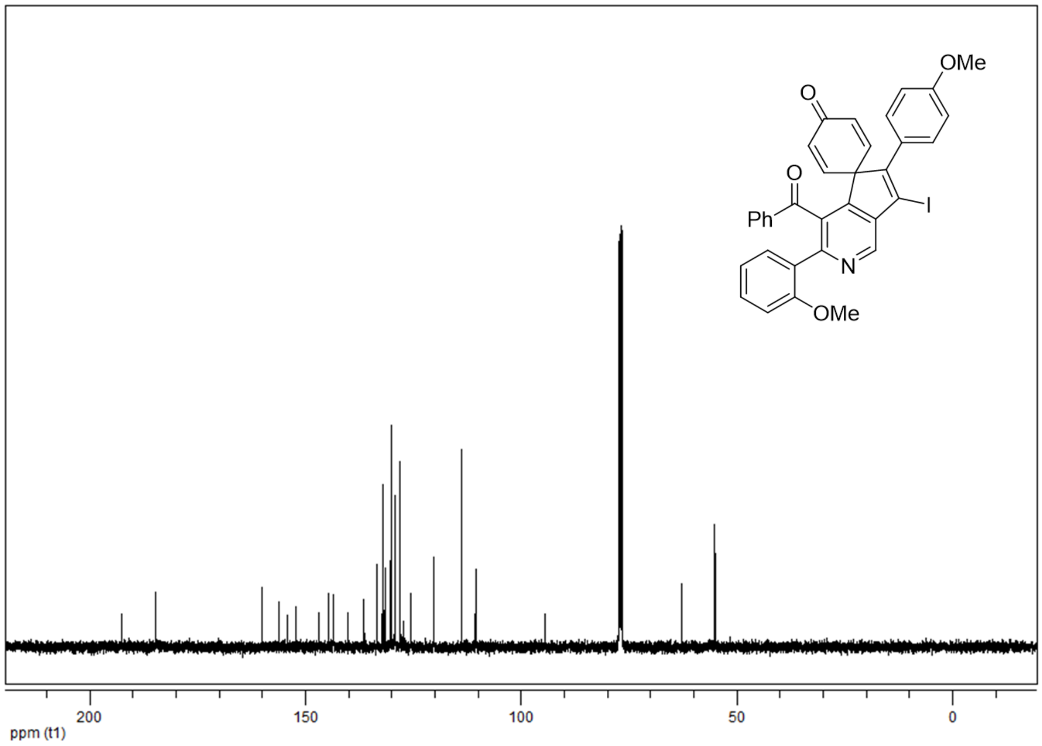


Figure 94A. ^{13}C NMR Spectrum of compound **44F**.

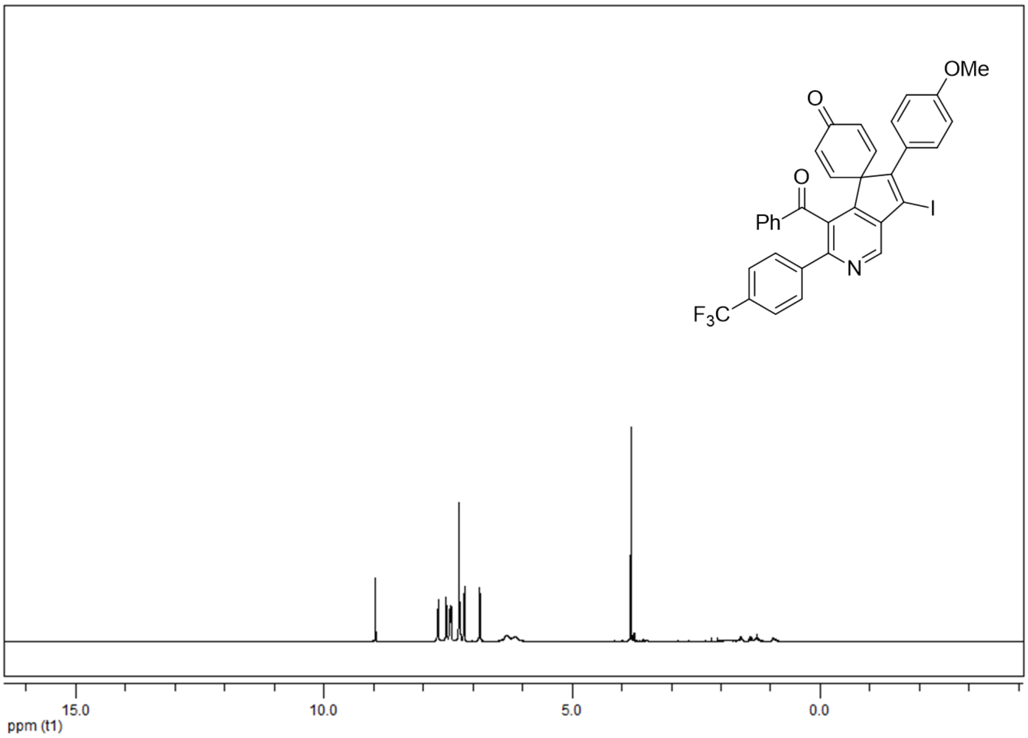


Figure 95A. ^{1}H NMR Spectrum of compound **44G**.

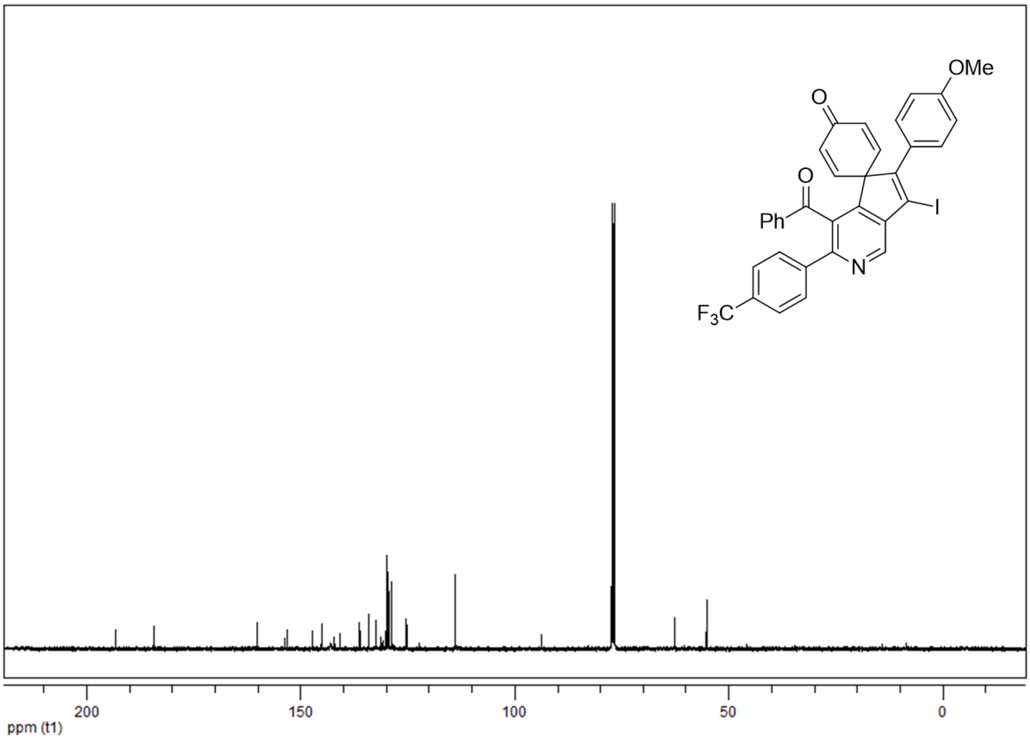


Figure 96A. ^{13}C NMR Spectrum of compound **44G**.

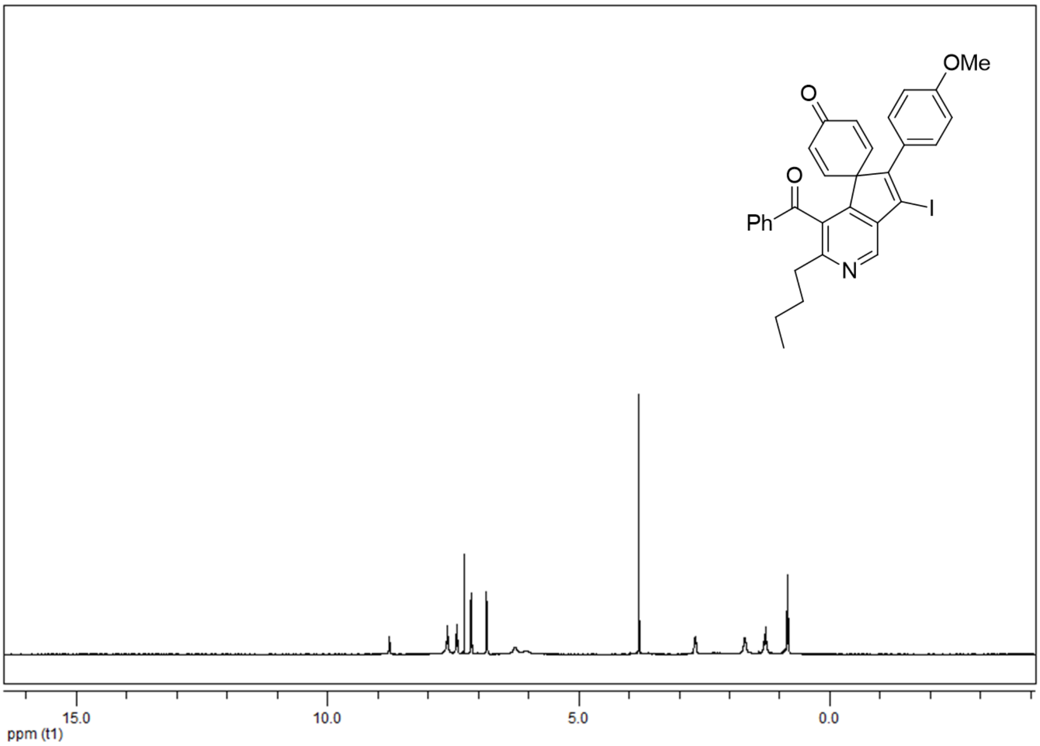


Figure 97A. ^{1}H NMR Spectrum of compound **44H**.

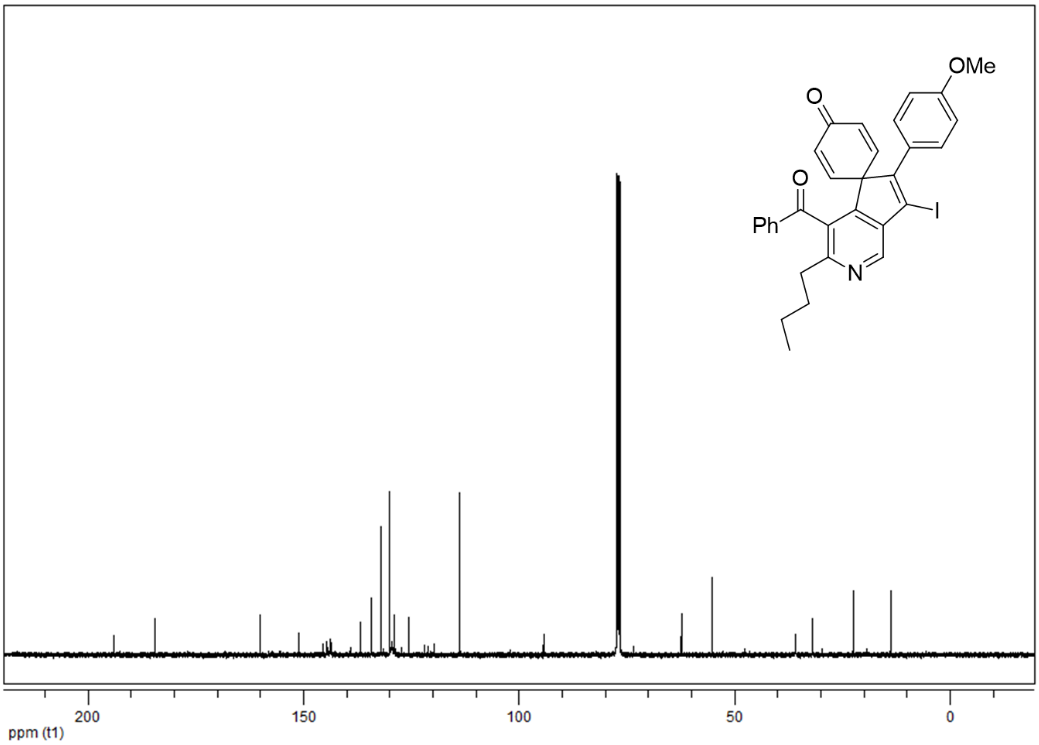


Figure 98A. ^{13}C NMR Spectrum of compound **44H**.