# SYNTHESIS OF PYRROLOQUINOXALINO-FUSED BENZOXAZEPINES AND ESTER-CONTAINING IODOPYRIDINES

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**SYNTHESIS OF PYRROLOQUINOXALINO-FUSED BENZOXAZEPINES AND ESTER-CONTAINING IODOPYRIDINES**

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## ABSTRACT

SYNTHESIS OF PYRROLOQUINOXALINO-FUSED BENZOXAZEPINES AND ESTER-CONTAINING IODOPYRIDINES

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August 2013, 96 pages

Heterocyclic fused compounds have gained considerable attention for pharmaceutical applications since they show remarkable biological activities such as antitumor and/or anticancer activities. In particular, the synthesis of seven-membered ring embedded molecules is a challenging issue among organic chemists. Therefore, we have aimed to develop one-pot reaction for the synthesis of seven-membered-fused heterocyclic compounds. We have developed a new methodology for the synthesis of pyrrolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepine derivatives starting from pyrrolo-substituted anilines and *o*-propargyloxybenzaldehydes. First of all, the synthesis of pyrrolo-substituted anilines was accomplished. Then, *o*-propargylation of benzaldehyde derivatives was performed. The reaction between pyrrolo-substituted anilines and *o*-propargyloxybenzaldehydes have afforded pentacyclic pyrroloquinoxalino-fused benzoxazepine molecules in one pot manner. For the synthesis of benzoxazepine derivatives, $InCl_3$ was used as a Lewis acid catalyst in order to initiate electrophilic cyclization.

In the second part of the study, the synthesis of ester-containing iodopyridines was performed in the presence of molecular iodine. In the course of this study, the synthesis of 5-iodopyridine-2,3-dicarboxylate was achieved through electrophilic cyclization of dimethyl 2-(prop-2-ynylamino)maleate in the presence of $I_2$ and $NaHCO_3$. The synthesized iodopyridine molecule was further functionalized by the Sonogashira coupling using terminal alkynes.



**Keywords:** Benzoxazepine, Aniline, *o*-Propargyloxybenzaldehyde, Electrophilic Cylization, Pyridine

# ÖZ

PİROLOKİNOKSALİN İÇEREN BENZOKSAZEPİNLERİN VE ESTER İÇEREN İYODOPİRİDİNLERİN SENTEZİ

Yazıcı, Nuray Esra

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Zora

Ağustos 2013, 96 sayfa

Heterosiklik yapıların biyolojik ve tıbbi aktiviteye sahip olması, bu yapıların farmasötik uygulamalar için giderek artan bir ilgi ile çalışılmasını sağlamıştır. Bu nedenle, bu projede tek kap yöntemi ile yedili halka içeren moleküllerin sentezi üzerinde çalışılmıştır. Pirolo[2',1':3,4]kinoksalin[1,2-*d*][1,4]benzoksazepin türevlerinin sentezi için yeni bir metod geliştirilmiştir. İlk olarak, pirol bağlı anilin türevlerinin sentezi, daha sonra ise *o*-proparjil benzaldehit türevlerinin sentezi gerçekleştirilmiştir. Sentezlenen anilin ve *o*-proparjil benzaldehit türevleri arasında gerçekleşen reaksiyon sonucu beş halkalı bir yapı olan, pirolokinoksalin içeren benzoksazepin molekülü tek kap yöntemi ile sentezlenmiştir. Benzoksazepin türevlerinin sentezi için, elektrofilik halkalaşma tepkimelerinin gerçekleşmesinde $InCl_3$, Lewis asit katalizörü olarak kullanılmıştır.

Çalışmanın ikinci kısmında, ester içeren iyodopiridin türevlerinin sentezi moleküler iyot yardımı ile gerçekleştirilmiştir. Proje süresince 5-iyodopiridin-2,3-dikarboksilat molekülü dimetil 2-(prop-2-inilamino)maleat molekülünün $I_2$ ve $NaHCO_3$ varlığında elektrofilik halkalaşma tepkimesi sonucunda sentezlenmiştir. Sentezlenen iyodopiridin molekülünün türevlendirilmesi Sonogashira eşleşme tepkimesi ile gerçekleştirilmiştir.

**Anahtar kelimeler:** Benzoksazepin, Anilin, *o*-Proparjil Benzaldehit, Elektrofilik Halkalaşma, Piridin

*Aileme*

*To My Parents and Sister*

If a molecule used to be made in 20 steps,
but you can now make it in three then that changes the world.

-H. Yamamoto

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I would like to express my sincere thanks to Prof. Dr. Metin Zora for his endless guidance and support throughout my thesis study. In the light of his encouragement and suggestions, I could easily carry out my Master study at METU. Also, his efforts in my career will never be forgotten.

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## ABBREVIATIONS

| | |
|---|---|
| br | broad (spectral) |
| δ | chemical shift in parts per million downfield from |
| d | doublet (spectral) |
| dd | doublet of doublet (spectral) |
| td | triplet of doublet (spectral) |
| m | multiplet (spectral) |
| FT | fourier transform |
| Hz | hertz |
| *J* | coupling constant |
| ppm | parts per million (in NMR) |
| q | quartet (spectral) |
| RT | room temperature |
| s | singlet (spectral) |
| t | triplet (triplet) |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| DCM | dichloromethane |
| DCE | dichloroethane |
| IBX | 2-iodoxybenzoicacid |
| ICI | iodine monochloride |
| HOAC | acetic acid |
| DMEDA | N,N'-dimethylethylenediamine |
| TFE | tetrafluoroethylene |

# CHAPTER 1

## INTRODUCTION

Organic chemistry is defined as the study of carbon compounds in all means. In fact, we live in the age of organic chemistry because, as a scientific discipline, it has opened a new era in human development. Advances arise from the development of compounds and materials. So far, more than thirty five millions of organic compounds have been prepared by the combination of carbon with hydrogen, oxygen, nitrogen, sulfur, phosphor and/or halogen atoms.[1] Organic compounds are commonly found in nature and living organisms as well. Recently the synthesis of new organic compounds in the laboratory has attracted great attention for potential pharmaceutical, material and agricultural benefits. In fact, organic chemistry is a broad discipline which intersects with biology, medicine, pharmacology, polymer technology, agriculture, and petroleum engineering.[1]

In a cyclic organic compound, if at least one carbon of ring skeleton is replaced by a heteroatom, it refers to a heterocyclic compound. Mostly, this heteroatom is nitrogen, sulfur or oxygen element. Notably, antibiotics, amino acids, coenzymes, vitamins, hormones and many synthetic drugs are the examples of heterocyclic compounds. Heterocyclic chemistry is important for biosynthesis and drug metabolism as well.[2] Heterocyclic compounds form the major part of living organisms such as DNA and RNA, which are based on pyrimidine and purine bases, including cytosine, adenine and thymine (Figure 1).[3]

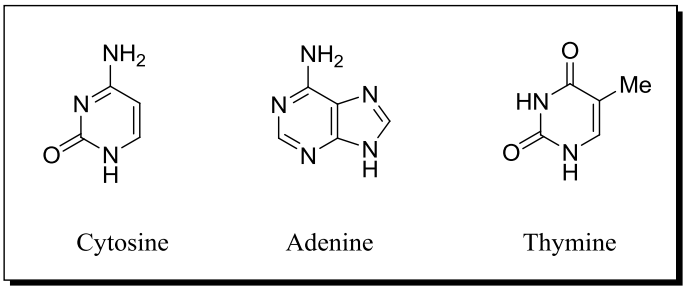



**Figure 1.** Structures of some pyrimidine and purine bases.

Pharmaceutical products are produced by mimicking natural products with biological activity, having heterocyclic moieties. Many essential drugs are designed by deriving and testing such heterocyclic compounds. There are many heterocyclic products for human and animal health like antibiotics such as penicillins and alkaloids such as vinblastine, ellipticine, anabasine, morphine, reserpine, and cardiac glycosides (Figure 2).

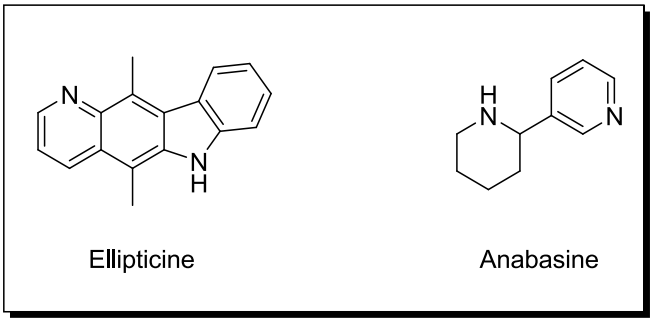



**Figure 2.** Structures of some alkaloid derivatives.

Inspired by these molecules, researchers in academia and pharmaceutical companies developed better drugs.[3] Two of the most selling pharmaceutical products are shown in Figure 3.

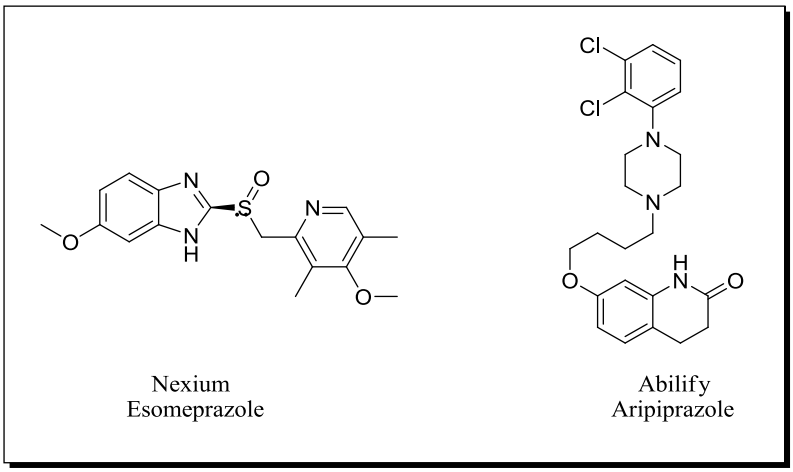



**Figure 3.** Two examples of most selling pharmaceutical products.

Among heterocyclic compounds, quinoxalines and quinolines, which have the fused ring systems, constitute remarkable place due to wide range of biological activities they showed. (Figure 4).

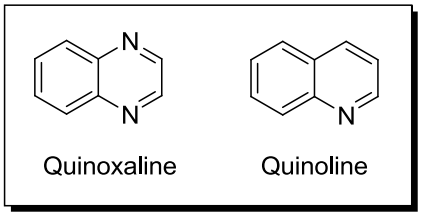



**Figure 4.** Structures of quinoxaline and quinoline.

Recently, heterocyclic compounds having ring systems larger than six-membered ring gained much attention of organic chemists.[4] Notably, seven-membered heterocyclic compounds are among the popular ring systems. Depending on the kind of the heteroatom, different types of seven-membered heterocyclic compounds can be derived.[4] Oxepins, azepines and thiepins are some examples of seven-membered heterocyclic compounds containing oxygen, nitrogen and sulfur, respectively, the structures of which are shown in Figure 5.[5]

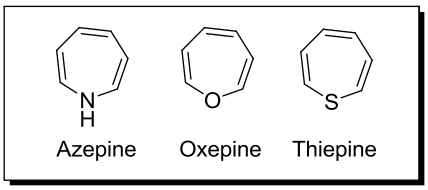



**Figure 5.** Some examples of seven-membered heterocyclic compounds.

In the synthesis of these compounds, Lewis acids play an important role. Recently, Lewis acid catalyzed reactions have become very popular for chemists. For this reason, different kinds of Lewis acids were developed to affect the organic reactions. Some metals, such as aluminum, antimony, boron, cobalt, copper, iron, indium, nickel, palladium, silver, tin and zinc, and their derivatives were frequently used as Lewis acids in syntheses.[6]

Carbon-carbon bond formation in the presence of Lewis acid catalysts is one of the most important reactions of organic chemistry. Classical Lewis acids, such as $AlCl_3$, $BF_3$ and $SnCl_4$, catalyze Friedel-Crafts, ene, Diels-Alder, and Mukaiyama aldol reactions. During our research we have focused on the electrophilic cyclizations which are catalyzed by Indium Lewis acids.[6]

## 1.1 Indium Catalysts

Early in the 20th century, indium metal was used for a little while in organic syntheses.[7]

Recently, many indium salts were developed and used intensely as Lewis acid catalyst in organic transformations.[8] Indium salts have high potential since they are unaffected by air or oxygen, and they have low toxicity. In general, organoindium reagents tolerate nitrogen-containing functional groups because indium metal has low heterophilicity. Indium-promoted reactions show a low nucleophilicity, thus permitting chemoselective transformations of similar reactivity groups.[9]

Regioselective allylation of alkynes, homocoupling of alkyl and aryl halides, chemoselective reduction of α-halocarbonyl compounds and benzyl halides and stereoselective debromination of vic-dibromides can be given as examples of indium mediated reactions.[9]

In(III) salts are milder as compared to $AlCl_3$, $BF_3$ and other Lewis acids. In(III) Lewis acids have gained importance due to its stability in the presence of water as well as its tolerance toward air. These catalysts are also important in terms of atom-conserving reactions. In short, In(III) salts are crucial for 'green chemistry' concept.[1]

Along with the studies of indium metal chemistry, indium trichloride ($InCl_3$) has gained much attention due to the fact that it is effective in both organic solvents and aqueous media.[9] $InCl_3$ has catalyst activity towards many reactions. It is a white, odorless, and highly deliquescent powder. Its particles are flake or plate-shaped and highly soluble in water and mineral acids. It is also used as starting compound for the synthesis of other inorganic and organic indium compounds, such as tri-methyl indium (TMI). Indium trichloride is used in alkaline batteries, LED technology, lighting and the semiconductor component manufacturing.[11]

### 1.1.1 Indium Catalyzed Reactions

As mentioned before, indium catalysts have received considerable attention as a Lewis acid in recent years. There exists many In(III) catalyzed reactions in literature. One of these examples is 1,2-addition to aldehydes and ketones. Most of the 1,2-addition to carbonyl compounds in the presence of In(III) salts are in the class of allylation reactions.[10] Marshall and coworkers reported that allylstannanes **2** readily add to aldehydes **1** in the presence of $InCl_3$ in acetone (Figure 6).[12]

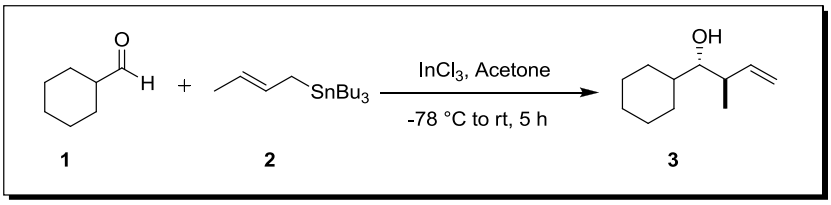



**Figure 6**. Allylation of aldehydes by In(III) catalyst.

A similar work was published by Baba and coworkers (Figure 7).[13] In this study, both alkynylation and allylation of aldehydes take place. They found that $InCl_3$ mainly works as a Lewis acid, activating the carbonyl group.

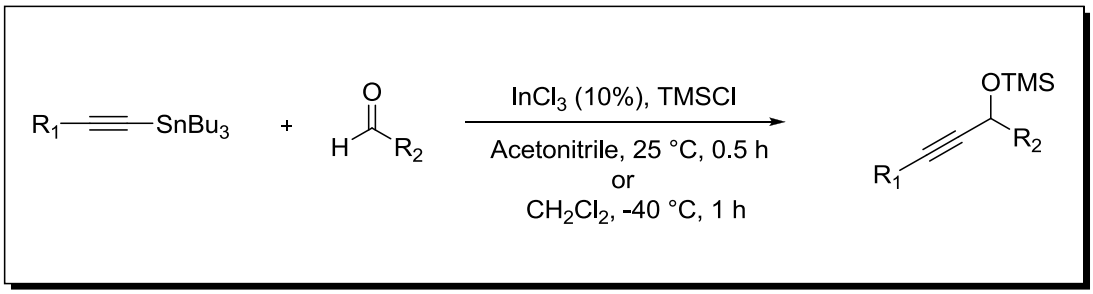



**Figure 7.** Alkynylation of aldehydes by $InCl_3$.

$InCl_3$ was also employed in the synthesis of quinolines. A microwave-assisted one-pot procedure for the synthesis of alkylquinolines **6** has been developed from the amines **4** and alkyl vinyl ketones **5** on the surface of silica gel using $InCl_3$ as catalyst (Figure 8).[14]

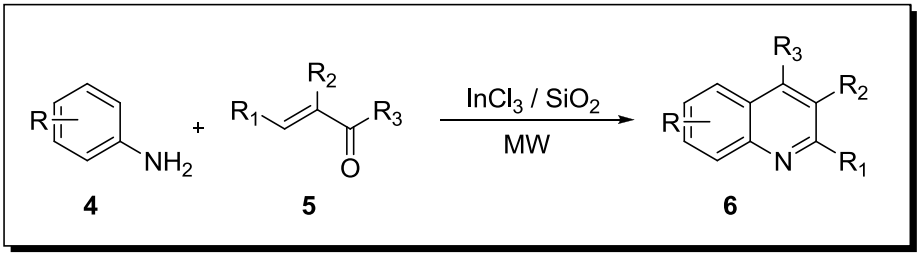



**Figure 8.** $InCl_3$-catalyzed synthesis of quinolines from anilines and alkyl vinyl ketones.

Synthesis of α-aminophosphonates demonstrates another example for applicability of indium trichloride as a Lewis acid catalyst. α-Aminophosphonates have attracted

considerable attention due to their structural resemblance to α -amino acids. α-Aminophosphonates are quite crucial because of their potential usage as peptide mimetics, enzyme inhibitors, antibiotics, and pharmacological agents. It was found that a mixture of a carbonyl compound, an amine, and diethyl phosphate in the presence of $InCl_3$ under ultrasound conditions yielded α-aminophosphonate derivatives (Figure 9).[9]

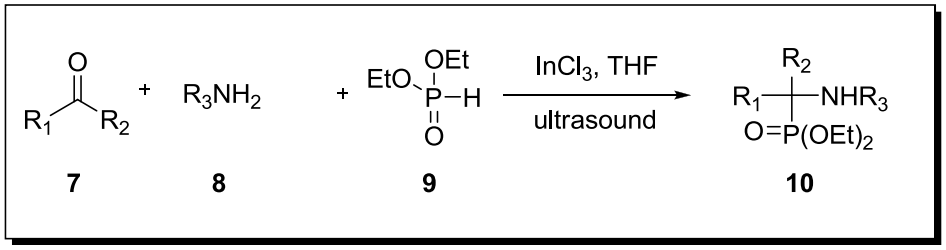



**Figure 9.** $InCl_3$-catalyzed synthesis of α-aminophosphonates from aldehydes/ketones and amines.

One of the other important reactions catalyzed by $InCl_3$ is the addition to C=N bonds.[10] As shown in Figure 10, the Mannich-type reaction between resulting imines and silyl enol ethers afforded β-aminoketones (**13**) (Figure 10).

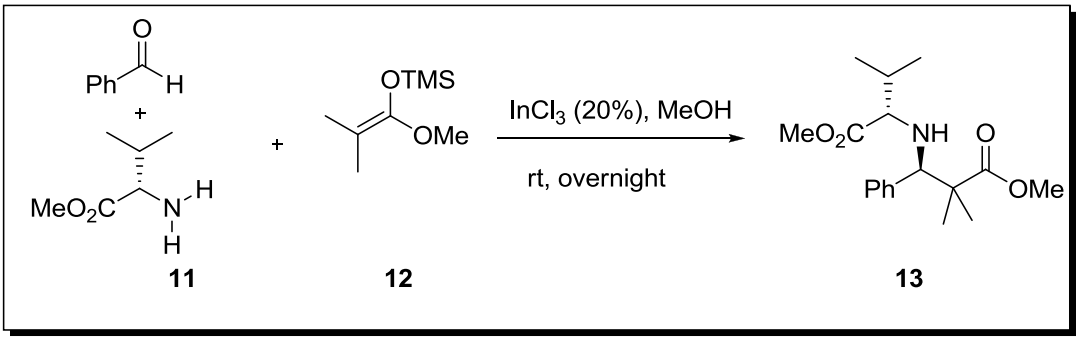



**Figure 10.** $InCl_3$-catalyzed one-pot Mannich reaction.

1,4-Additions were also catalyzed by In(III) Lewis acids. Loh and coworkers reported a study including Michael-type additions of silyl enol ethers (**15**) to α,β-unsaturated ketones (**14**) (Figure 11).[15]

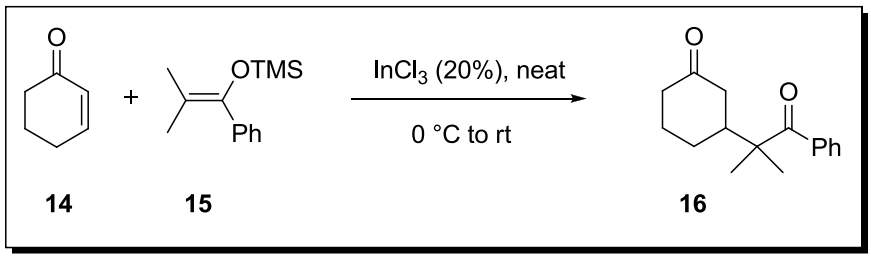



**Figure 11.** An example of Michael-type reaction catalyzed by $InCl_3$.

Polycyclic heteroarene synthesis is also possible by using In(III) catalysts. One of the most important roles of Indium catalyst is to activate alkyne triple bond as shown in the reaction of Figure 12.[10] Tsuchimoto and Shirakawa reported that 2-arylindoles **(17)** reacted with propargyl ethers **(18)** in the presence of $In(ONf)_3$ (nonaflate= $C_4F_9SO_3$) to form product **19**.[16]

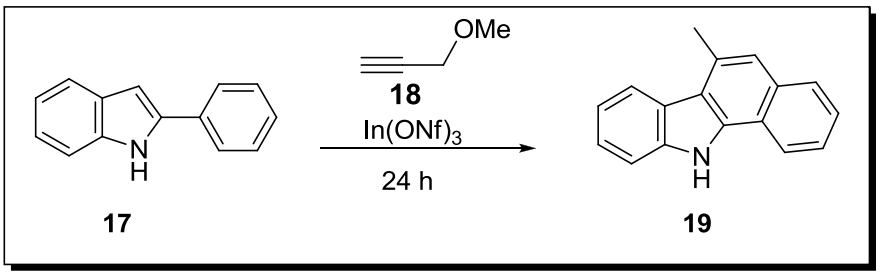



**Figure 12.** $In(ONf)_3$-catalyzed formation of polycyclic heteroarenes.

There are many other reactions which are catalyzed by In(III) salts, including oxidation, reduction, protection, deprotection and cyclization reactions. To conclude, Lewis acid behavior of In(III) catalysts are important for their catalytic influence and contribution to 'green chemistry'.[10]

### 1.2 Quinoxalines

Quinoxalines are one of the most important heterocyclic compounds in organic chemistry. Quinoxaline derivatives have various biological properties for pharmaceutical applications. Especially, substituted examples of quinoxalines constitute an important class of benzoheterocycles, which are the building blocks of wide range of pharmacologically active compounds, having antibacterial, antifungal, anticancer, antimalarial and antidepressant activities.[17] Some examples are given in Figure 13.

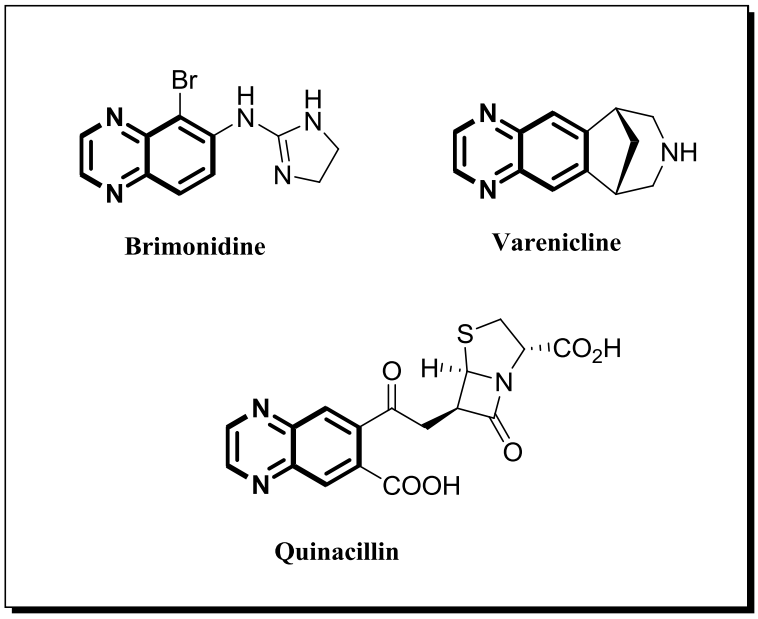



**Figure 13**. Structures of some biologically important drugs and molecules having a quinoxaline moiety.

Quinoxaline is the bioisoster of quinoline, naphthalene, benzothiophene and other aromatic rings (Figure 14). There is a considerable similarity between some antitubercular drugs and quinoxalines. Quinoxaline derivatives form many insecticides, fungicides and herbicides. Synthetic quinoxaline derivatives are the part of some antibiotics such as echinomycin, levomycin and actinomycin, which are known to inhibit the growth of Grampositive bacteria and also active against various transplantable tumors. Moreover, quinoxaline derivatives are known as for their applicability in dyes, efficient electroluminescent materials, organic semiconductors and DNA cleaving agents.[17]

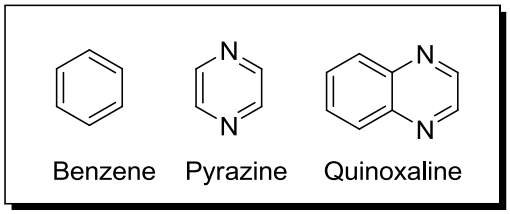



**Figure 14.** Structures of benzene, pyrazine and quinoxaline

Quinoxalines are also known as benzopyrazines. Pyrazines are colorless, stable and watersoluble molecules. The pyrazine ring system exists in the fungal metabolite aspergillic acid and in luciferin of several bettles.[17]

During last decade, several methods have been developed for the synthesis of quinoxalines. Basu and coworkers reported a method based on the reactions between α-hydroxy and α-bromo ketones in the presence of KF-alumina to synthesize quinoxalines (**22**) (Figure 15).[18]

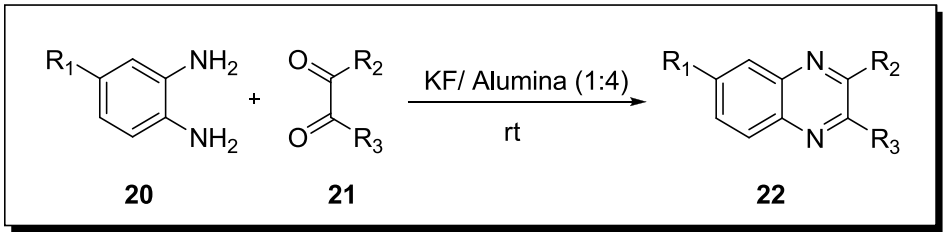



**Figure 15.** KF-alumina mediated condensation reactions of 1,2-dicarbonyl compounds with 1,2-diamines.

In the study conducted by the research group of Chen, quinoxaline derivatives were synthesized from o-phenyldiamines in the presence of Cu(II) catalyst (Figure 16). During the study, a wide range of substituted nitroolefins gave the desired products in moderate to good yields.[19]

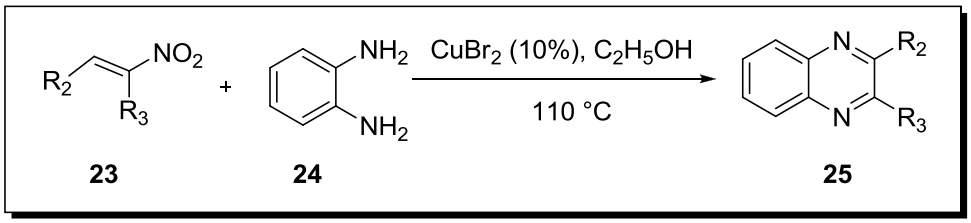



**Figure 16.** Reaction of nitroolefins (**23**) with o-phenylenediamine **24**.

Another convenient method for the synthesis of quinoxalines has been developed by Heravi and his research group. In their methodology, 1,2-diketones **(26)** and *o*-phenylenediamines **(27)** reacted in the presence of *o*-Iodoxybenzoic acid (IBX) at room temperature to give quinoxaline derivative **28** (Figure 17).[20]

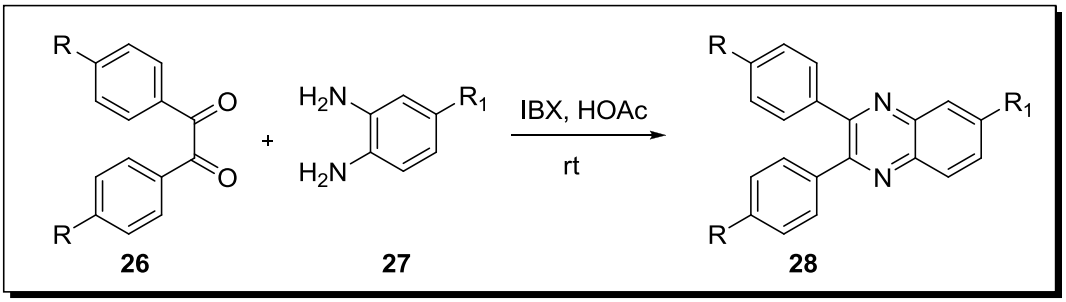



**Figure 17.** Synthesis of quinoxaline derivatives by using IBX.

### 1.2.1 Pyrroloquinoxalines

Pyrroloquinoxaline compound is formed by the fusion of a pyrrole ring with a quinoxaline moiety, the structure of which is illustrated in Figure 18. Pyrrolo[1,2-a]quinoxalines have been subjected to considerable interest because of their potential bioactivities. Properly substituted derivatives are used to hinder microbial resistance for antibiotics.[21] They are also employed as antitumor[22] and antileishmanial[23] agents, as well as specific high-affinity receptor ligands.[24]

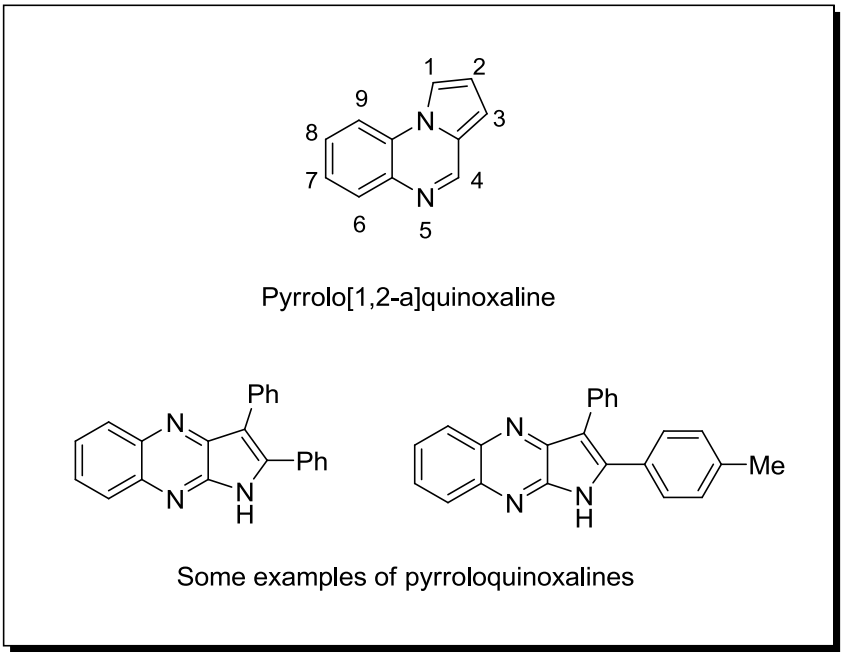



**Figure 18**. Pyrrolo[1,2-a]quinoxaline and its some examples.

### 1.2.2 Synthesis of pyrroloquinoxalines

In general, methods for the synthesis of pyrrolo[1,2-a]quinoxalines are based on the further functionalization of quinoxaline and pyrrole compounds, recyclization of other heterocycles and cyclization of non-heterocyclic compounds.[20] Here, only the synthesis from quinoxalines will be mentioned.

One of the most successful methods for the synthesis of pyrrolo[1,2-a]quinoxalines has been achieved by the intramolecular cyclization of quinoxalines containing at least three carbon atoms with a reaction center capable of nucleophilic attack (Figure 19). Quinoxalines **29**, bearing a γ-carbonylalkyl substituent as the part of ketone, carboxylic acid or ester functionality, undergo intramolecular cyclization in the presence of acids in order to form pyrroloquinoxalines **30**.[20]

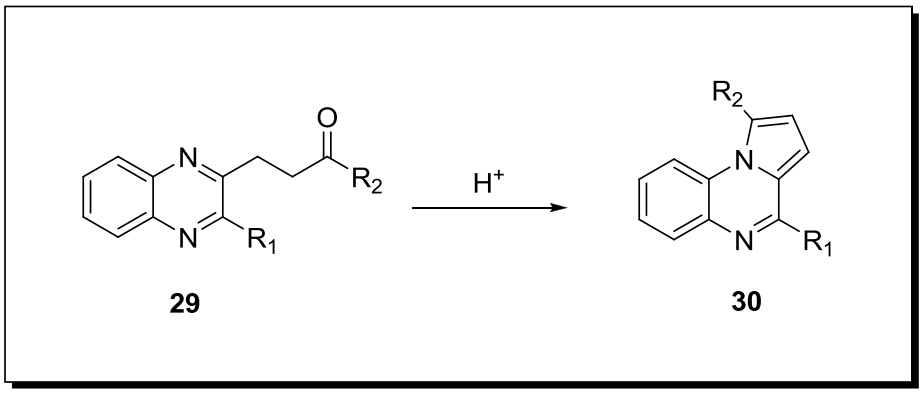



**Figure 19.** Synthesis of quinoxalines in the presence of acids.

Pereira and coworkers developed a new route for the construction of substituted pyrrolo[1,2-a]quinoxaline derivatives by iron-mediated aryl nitro reduction and aerobic oxidation of alcohols in one-pot manner (Figure 20).[25]

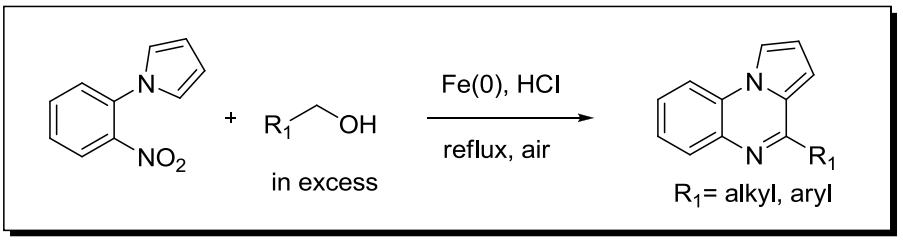



**Figure 20.** Pyrrolo[1,2-a]quinoxaline synthesis via iron-promoted aryl nitro reduction.

Liu and coworkers reported an efficient method for the synthesis of pyrrolo[1,2-a]quinoxalines using a gold catalyst (Figure 21).[26] Substituted pyrrolo[1,2-a]quinoxalines were isolated in moderate to excellent yields.

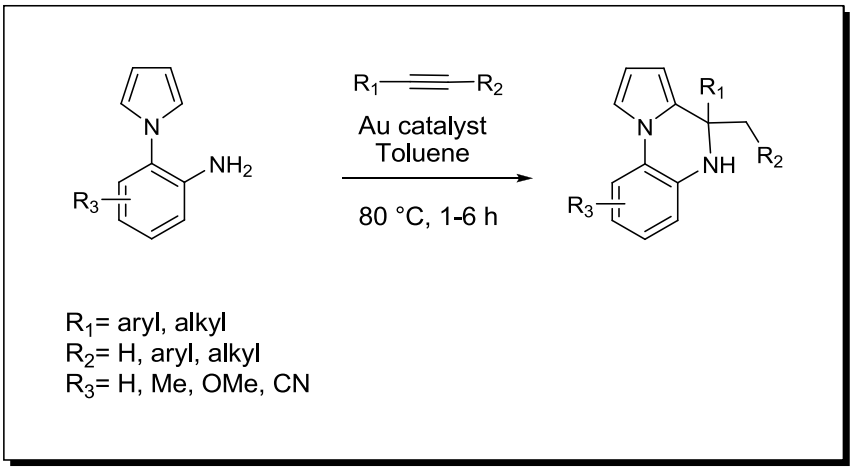



**Figure 21.** Synthesis of pyrrolo[1,2-a]quinoxalines via gold(I)-mediated reactions.

In another study, after the palladium-catalyzed coupling of 2-haloquinoxalines with functionally substituted alkynes, the addition of bromine to 2-alkynylquinoxalines gave the corresponding pyrrolo[1,2-a]quinoxalines (Figure 22).[27]

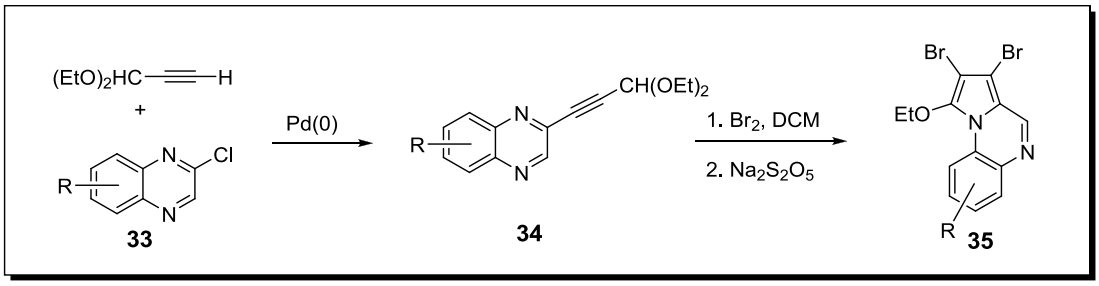



**Figure 22.** Synthesis of pyrrolo[1,2-*a*]-quinoxalines from 2-haloquinoxalines.

Beside these studies, a new route for the synthesis of pyrroloquinoxalines was investigated by the Zora research group, the initial results of which were presented.[28] The reactions of 1-(2-aminophenyl)pyrroles **36** with aldehydes and ketones **37** in the presence of $InCl_3$ afforded 4,5-dihydropyrrolo[1,2-a]quinoxalines **38** and/or pyrrolo[1,2-a]quinoxalines **39** in good to excellent yields (Figure 23).

In fact, these reactions produced exclusively 4,5-dihydropyrrolo[1,2-a]quinoxalines **38** and pyrrolo[1,2-a]quinoxalines **39** were obtained as minor products. However, when the same reactions were carried out in the presence of *p*-benzoquinone, only the pyrrolo[1,2-a]quinoxaline derivatives **39** were obtained from these reactions.

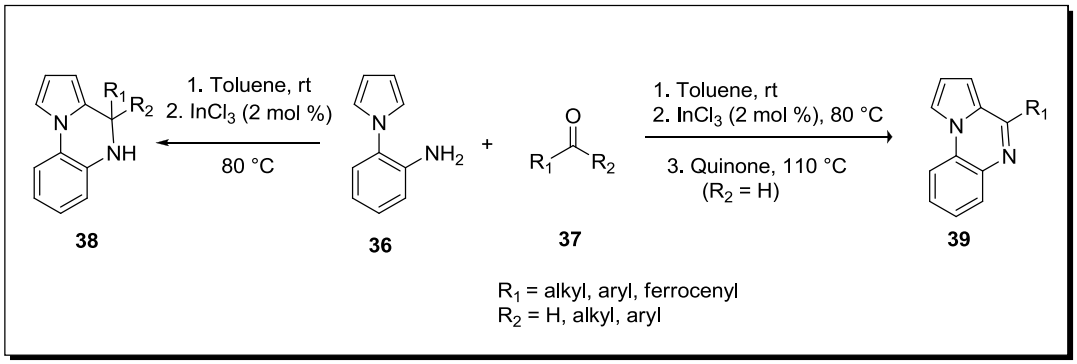



**Figure 23.** Synthesis of 4,5-dihydropyrrolo[1,2-a]quinoxalines and pyrrolo[1,2-a]quinoxalines.

Zora and coworkers utilized this methodology for the synthesis of pyrroloquinoxaline-embedded complex molecules (Figure 24), the initial results of which were also presented.[29] When the same reactions were performed with functionally substituted aldehydes **41**, pentacyclic complex molecules **42** were resulted from these one-pot reactions in good to high yields.

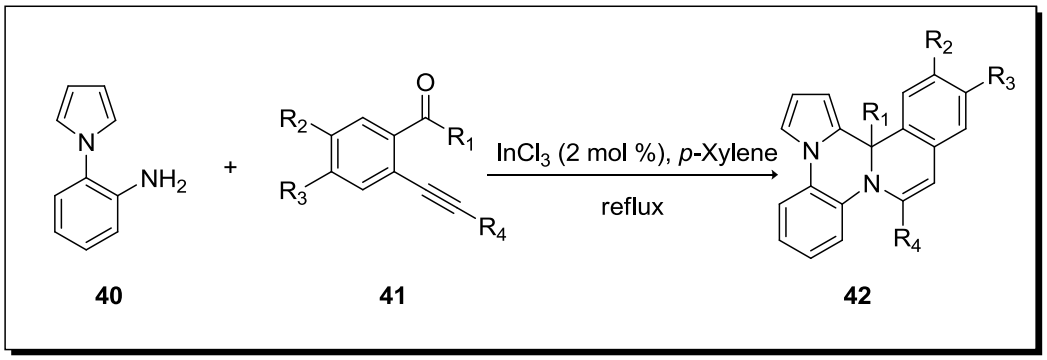



**Figure 24.** One-pot synthesis of pyrroloquinoxaline-embedded pentacyclic molecules.

It should be mentioned that during these studies, Verma [30] and Patil [31] and research groups

reported the synthesis of such complex molecules by employing Ag(I)- and Au(I)-catalyzed versions of these reactions, respectively (Figure 25).

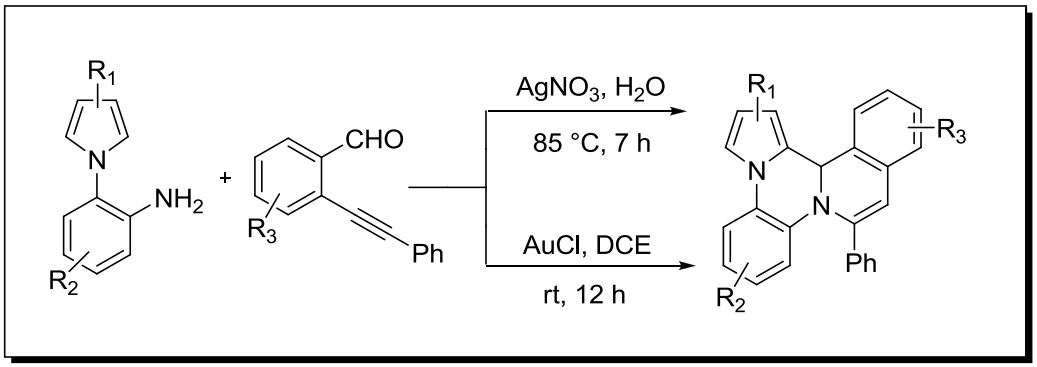



**Figure 25.** Ag(I)- and Au(I)-catalyzed syntheses of pyrroloquinoxaline-embedded molecules.

### 1.3 Pyridines

Pyridine is a six-membered heterocyclic compound having a nitrogen atom instead of a CH group (Figure 26). Properly substituted derivatives are commonly used for pharmaceutical and agrochemical applications. They catalyze both chemical and biological reactions such that in various living organisms, many oxidation and reduction processes are done by prosthetic pyridine nucleotide (NADP).[32]

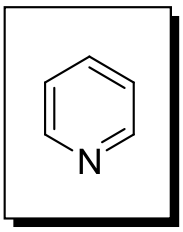



**Figure 26.** Structure of pyridine.

Another potential of pyridines in biological systems is that they exist in the structure of important vitamins such as niacin and pyridoxine (vitamin B6). Moreover, in the pharmaceutical industry, pyridine is found in the nucleus of many existing drugs, two of which are shown in Figure 27.[28]

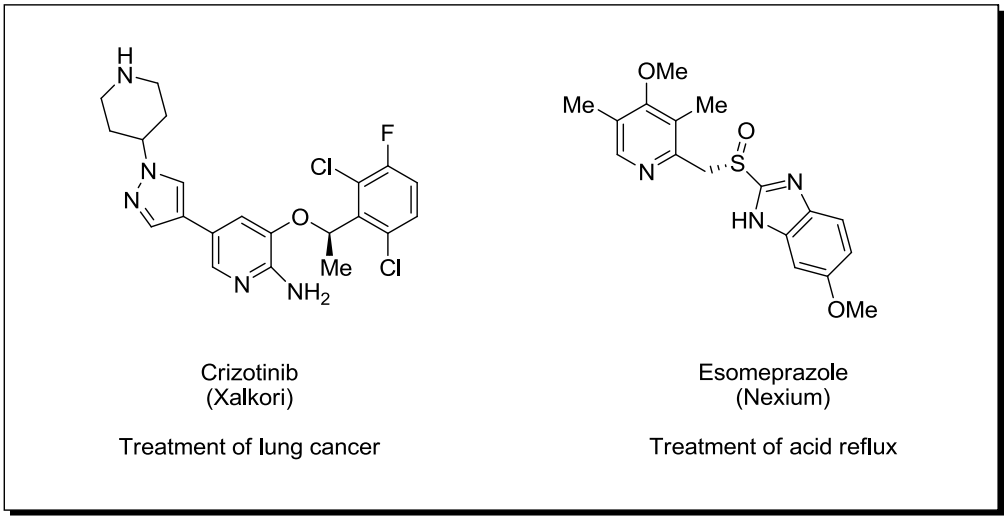



**Figure 27. S**tructures of some pyridine containing drugs.

As a result, the biological activities of pyridines can be listed as antiviral,[33] anticancer,[34] antioxidant,[35] antibacterial,[36] antidiabetic [37] and antifungal [38] properties.

### 1.3.1 Synthesis of pyridines

There is a rich history of pyridine syntheses; however, old methodologies are still valuable. Some of these methodologies involved direct condensation of amine and carbonyl groups. Also many transition-metal catalysts were employed during the synthesis of pyridines over the past several decades.[39]

Larock research group developed a method for the synthesis of pyridines, which involved a transition metal catalyzed route to 2,4-di- and 2,4,5-trisubstituted pyridines (**43**) (Figure 28).[40]

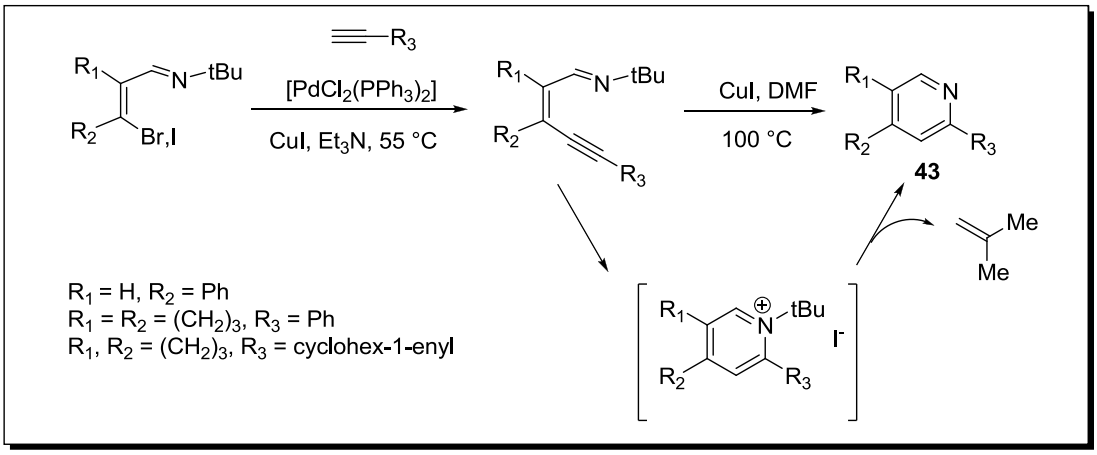



**Figure 28.** A palladium-catalyzed route to pyridines.

Cheng and coworkers also reported a method for the synthesis of pyridines.[41] They developed a rhodium-catalyzed one-pot synthesis of alkyl, aromatic, and heteroaromatic-substituted pyridines (**44**) (Figure 29).

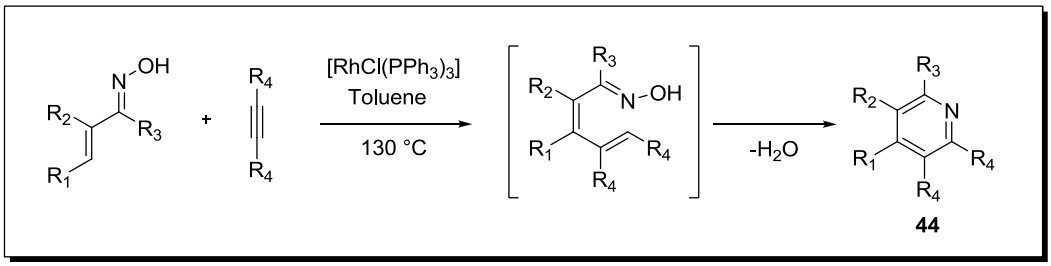



**Figure 29.** Synthesis of pyridines via a rhodium catalyst.

A similar study was reported by Rovis and coworkers.[42] In their method, α,β-unsaturated oximes reacted with alkynes under mild conditions and low temperatures in the presence of an Rh(III) catalyst to afford pyridines (Figure 30).

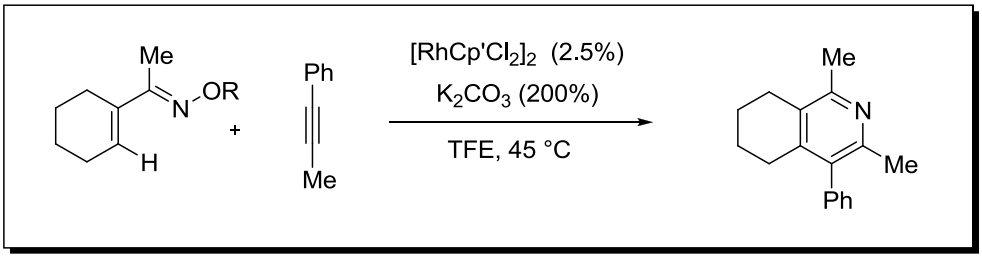



**Figure 30. S**ynthesis of pyridines from oximes and alkynes via a rhodium(III) catalyst.

Another interesting study was published by Cacchi and coworkers.[43] In their work, *N*-propargylic β-enaminones were cyclized to pyridines in the presence of CuBr in DMSO in good to high yields as shown in the Figure 31.

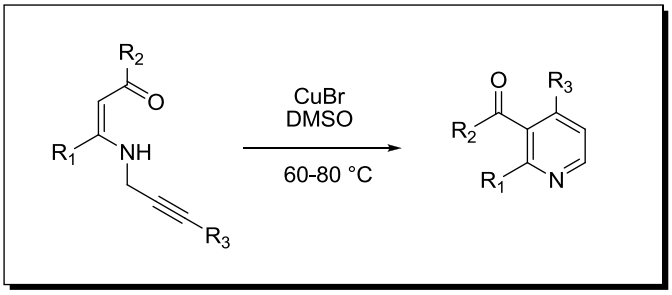



**Figure 31.** Synthesis of pyridines from *N*-propargylic β-enaminones.

Zora research group has reported a convenient way for the synthesis of iodo-substituted pyridine derivatives (**45**) from *N*-propargylic β-enaminones in the presence of molecular iodine, the initial results of which were presented (Figure 32).[44] In this method, iodine has initiated electrophilic cyclization of *N*-propargylic β-enaminones and yielded iodopyridines, which are very important precursors since they could be elaborated to more complex structures by metal-catalyzed coupling reactions.[45]

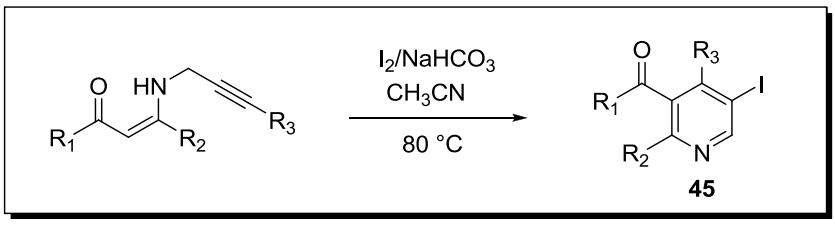



**Figure 32.** Synthesis of pyridines from β-enaminones using iodine.

A nickel-catalyzed cycloaddition of dialkynes with nitriles was reported to produce a variety of pyridine derivatives (Figure 33).[46] In this study, $Ni(COD)_2$ was used as the nickel catalyst.

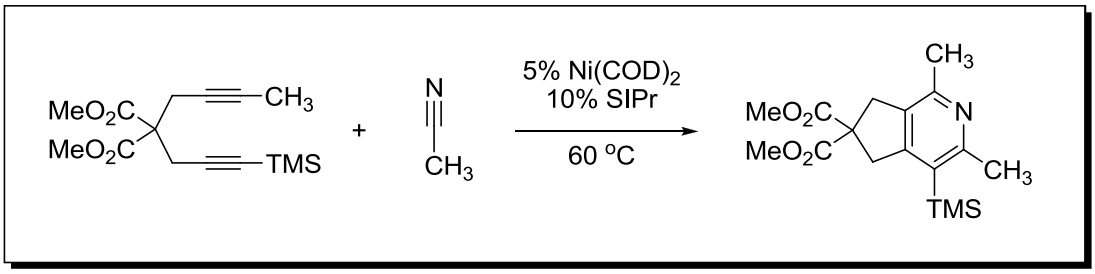



**Figure 33.** A nickel-catalyzed pyridine synthesis.

Recently, Wan and coworkers studied the cyclization of 3-aza-1,5-enynes.[47] They described the synthesis of 1,2-dihydropyridines (**46**) and 3-iodo-1,2-dihydropyridines (**47**) via cyclization and electrophilic iodocyclizations of 3-aza-1,5-enynes, respectively (Figure 34).

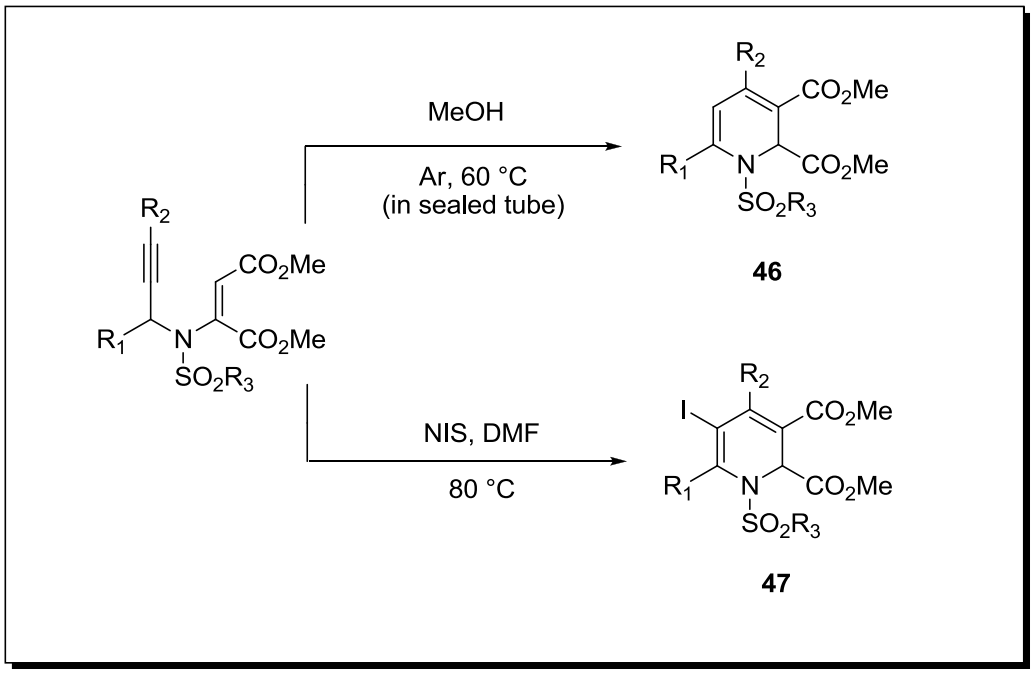



**Figure 34.** Synthesis of 1,2-dihydropyridines (**46**) and 3-iodo-1,2-dihydropyridines (**47**) from 3-aza-1,5-enynes.

## 1.4 Electrophilic cyclization

Cyclization reactions in which electrophiles play an activation role is called as electrophilic cyclization reactions. In fact, electrophilic species bearing substituents that can behave as nucleophiles undergo cyclization reaction. Substituents that can participate as internal nucleophiles contain carboxy and carboxylate, hydroxyl and hydroxylate, amino and amido groups. On the other hand, electrophiles accept electrons, and they are considered as Lewis acids. Some examples of electrophiles are $I_2$, $Br_2$, ICI, NBS, NIS, PhSeCl and PhSeBr. Electrophilic cyclization reactions are convenient for occurrence of a variety of oxygen-, nitrogen and sulfur-containing ring systems. Final product conformation is based on the ring size and the endo-exo selectivity (Figure 35).[48]

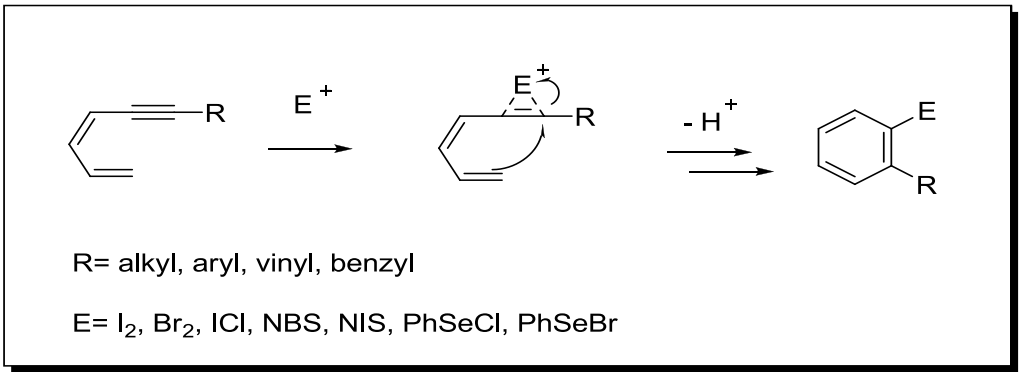



**Figure 35**. A representation of an electrophilic cyclization.

## 1.5 Aim of the Study

As mentioned before, pyrroloquinoxaline derivatives have important biological properties such antitumor, antibacterial and antimalarial activities. The synthesis of seven-membered ring systems is also very crucial for heterocyclic and bioorganic chemistry because of the scarcity of these compounds. Although pyrroloquinoxalines have many essential bioactivities, there are very few studies for the synthesis of such molecules. Our research group has recently synthesized 4,5-dihydropyrrolo[1,2-a]quinoxaline and pyrrolo[1,2-a]quinoxaline derivatives.[29] In the light of these studies, we have investigated one-pot synthesis of pyrroloquinoxalino-fused benzoxazepine molecules (**59**-**68**) by employing reaction between pyrrole-substituted anilines (**48**-**53**) and *o*-propargyloxy-substituted benzaldehydes (**54**-**58**) in the presence of $InCl_3$ Lewis acid (Figure 36). As anticipated, these reactions afforded the expected benzoxazepine molecules.

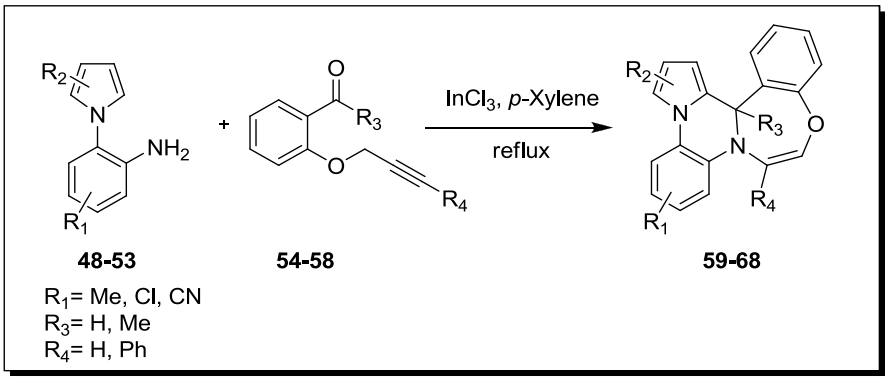



**Figure 36.** Synthesis of 10-methyl-16b*H*-pyrrolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepine derivatives (**59**-**68**).

In the second part of our study, we have investigated the synthesis of ester-containing iodopyridine derivatives. First, the synthesis of dimethyl 5-iodopyridine-2,3-dicarboxylate (**70**) have been studied by employing electrophilic cyclization of dimethyl 2-(prop-2-ynylamino)maleate (**69**) with molecular iodine (Figure 37). Then, dimethyl 5-iodopyridine-2,3-dicarboxylate (**70**) was subjected to Sonagashira coupling with terminal alkynes to synthesize a variety of dimethyl 5-alkynylpyridine-2,3-dicarboxylate derivatives (**79**-**86**).

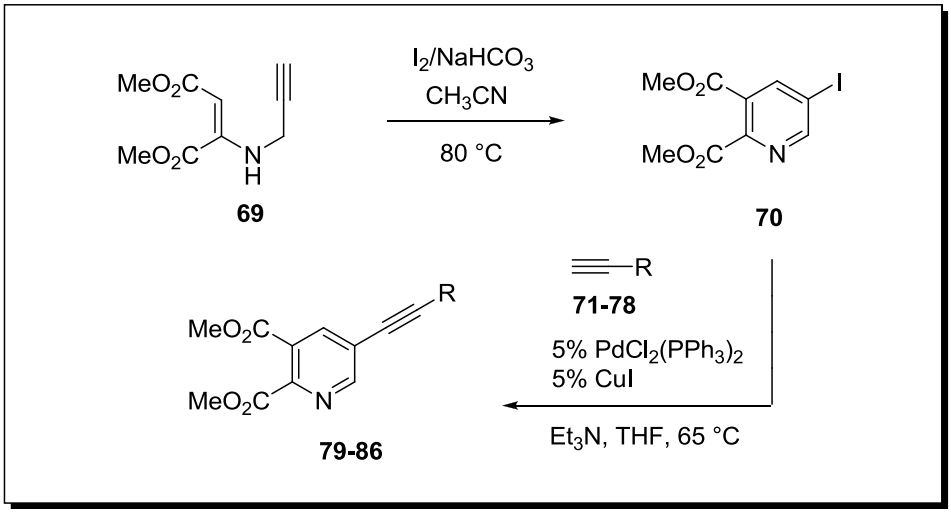



**Figure 37.** Synthesis of dimethyl 5-iodopyridine-2,3-dicarboxylate (**70**) and its further derivatization with Sonagashira coupling.

In summary, in this thesis, the results concerning the scope, limitations and mechanisms of the above mentioned reactions will be discussed.

# CHAPTER 2

# RESULTS AND DISCUSSION

## 2.1 Synthesis of pyrroloquinoxalino-fused benzoxazepines

### 2.1.1 Synthesis of pyrrole-substituted anilines

In the first part of the study, the synthesis of starting compounds, namely, 2-(1*H*-indol-1-yl)aniline **(49)**, 5-chloro-2-(1*H*-pyrrol-1-yl)aniline (**50**), 4-methyl-2-(1*H*-pyrrol-1-yl)aniline (**51**), 5-methyl-2-(1*H*-pyrrol-1-yl)aniline (**52**) and 4-amino-3-(1H-pyrrol-1-yl)benzonitrile (**53**), were carried out. For the synthesis of these derivatives, a standard procedure was used (Figure 38).[49]

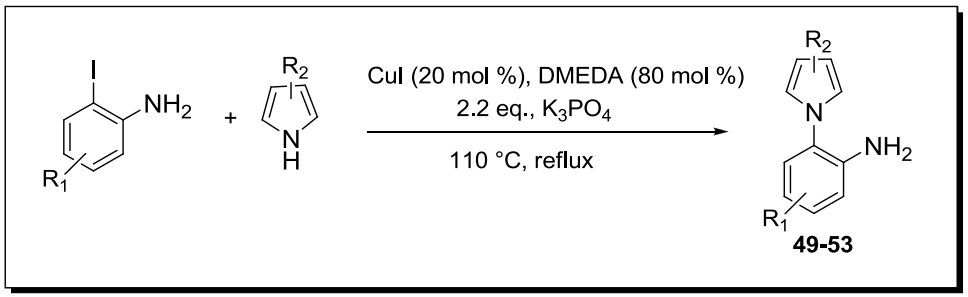



**Figure 38.** Synthesis of pyrrole-substituted aniline derivatives.

In the synthesis, we used commercially available 2-iodoaniline derivatives along with pyrrole and indole. During the course of the reaction, iodoaniline derivatives underwent CuI-catalyzed coupling with pyrrole and indole in the presence of DMEDA at 110 °C (Figure 38), which yielded the corresponding pyrrole- and indole-substituted aniline derivatives.[49] By applying this procedure, we synthesized five different aniline derivatives as depicted in Figure 39. It should be mentioned that along with these five derivatives, we used commercially available 2-(1*H*-pyrrol-1-yl)aniline (**48**) in the reactions as well.

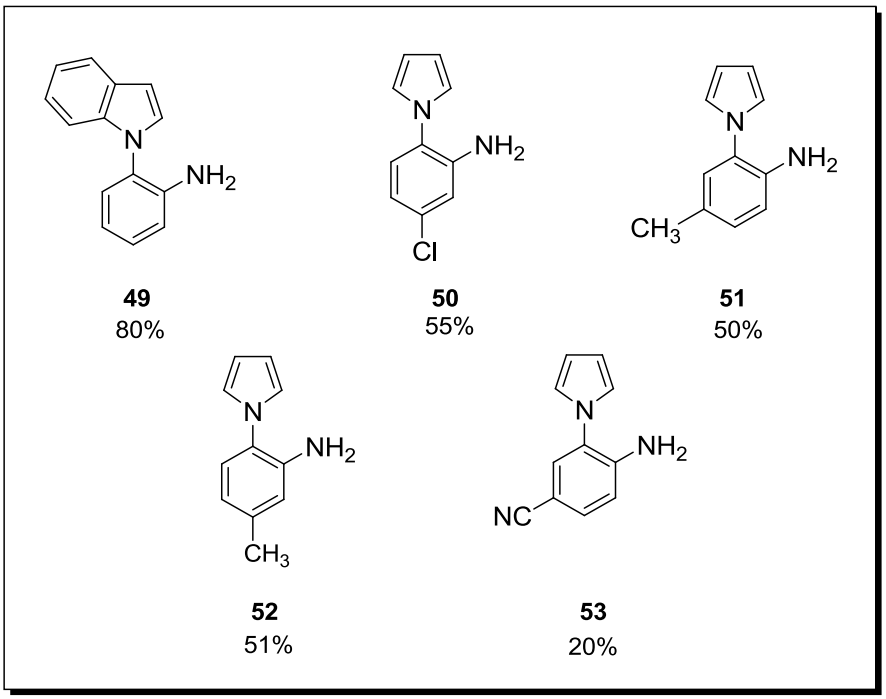



**Figure 39.** Structures of the synthesized pyrrolo-substituted aniline derivatives **49**-**53**.

### 2.1.2 Synthesis of *o*-propargyloxybenzaldehydes

After the synthesis of pyrrole-susbtituted aniline derivatives, we synthesized *o*-propargyloxy-benzaldehydes (**54**-**58**) starting from commercially available benzaldehyde derivatives and propargyl bromide. For this purpose, 2-hydroxybenzaldehyde (salicylaldehyde) (**87**), 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (**88**), 5-bromo-2-hydroxybenzaldehyde (**89**), 2-hydroxy-4-methoxy-benzaldehyde (**90**) and 2-hydroxy-3-methoxybenzaldehyde (**91)** were used, the structures of which are shown in Figure 40.

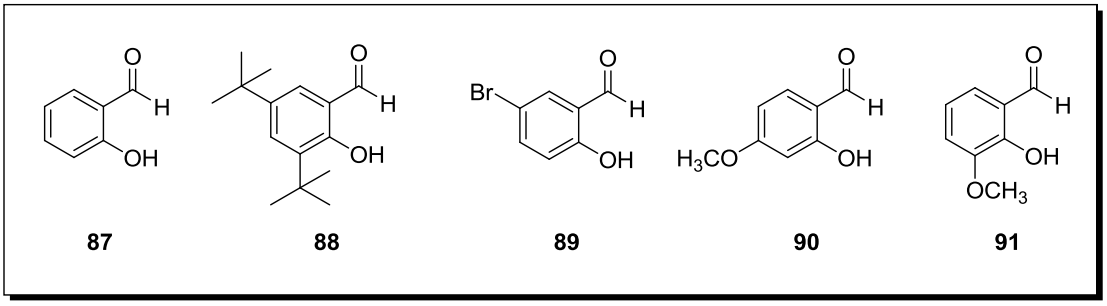



**Figure 40.** Structures of the substituted salicylaldehyde derivatives used for the synthesis of *o*-propargyloxybenzaldehydes.

We carried out the reactions of benzaldehyde derivatives with propargyl bromide in DMF using $K_2CO_3$ at room temperature (Figure 41).[50]

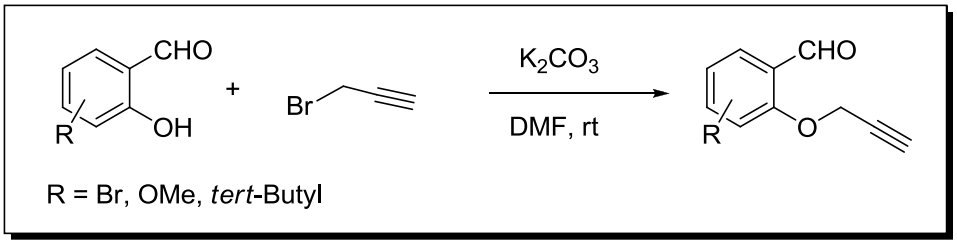



**Figure 41.** Synthesis of *o*-propargyloxy-benzaldehyde derivatives.

By employing this standard $S_N2$ reaction procedure, we prepared five kinds of *o*-propargyloxy-benzaldehyde derivatives (**54**-**58**) (Figure 42). Yields were found above 80% for each benzaldehyde derivative.

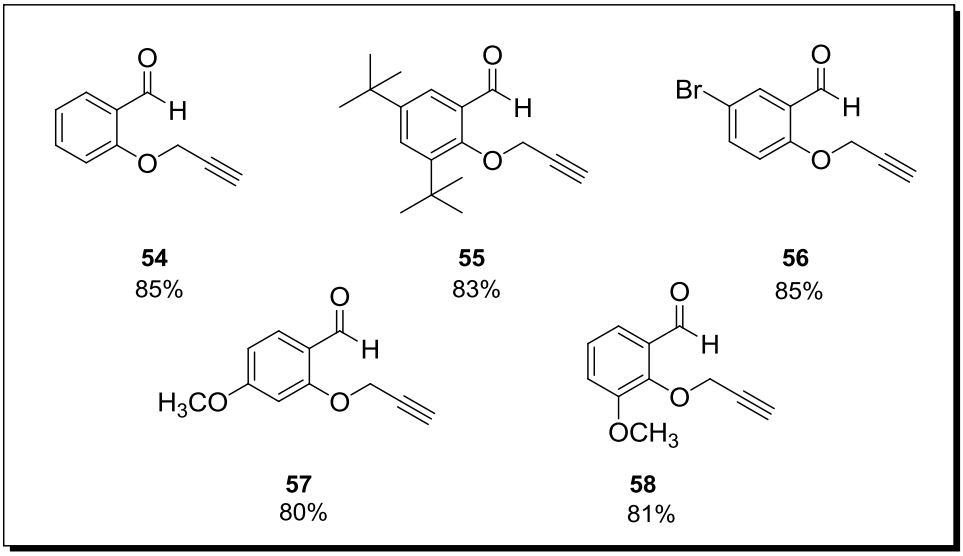



**Figure 42.** Structures of the synthesized *o*-propargylated benzaldehydes **54**-**58**.

### 2.1.3 Synthesis of 2-(3-phenylprop-2-ynyloxy)benzaldehyde

As a starting material, we also synthesized 2-(3-phenylprop-2-ynyloxy)benzaldehyde (**92**) by employing Sonagashira coupling reaction of *o*-propargylated benzaldehyde **54** with iodobenzene (Figure 43).

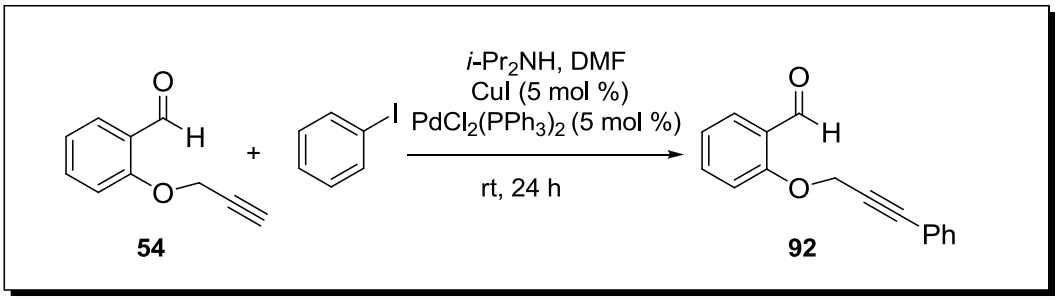



**Figure 43.** Synthesis of 2-(3-phenylprop-2-ynyloxy)benzaldehyde (**92**).

### 2.1.4 Synthesis of 1-(2-(prop-2-ynyloxy)phenyl)ethanone

In addition to *o*-propargyloxybenzaldehydes, we prepared *o*-propargylated acetophenone **94** by following same $S_N2$ procedure with 1-(2-hydroxyphenyl)ethanone (**93**) (Figure 44).

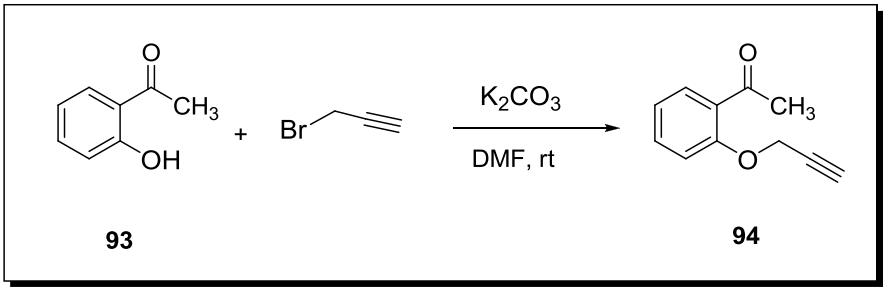



**Figure 44.** Synthesis of 1-(2-(prop-2-ynyloxy)phenyl)ethanone (**94**).

### 2.1.5 Synthesis of 1-(2-(3-phenylprop-2-ynyloxy)phenyl)ethanone

After the synthesis of 1-(2-(prop-2-ynyloxy)phenyl)ethanone (**94**), we carried out Sonagashira coupling with iodobenzene to synthesize acetophenone derivative **95** as depicted in Figure 45.

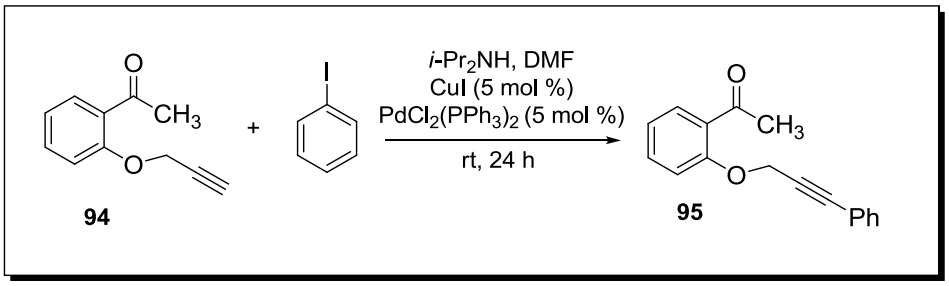
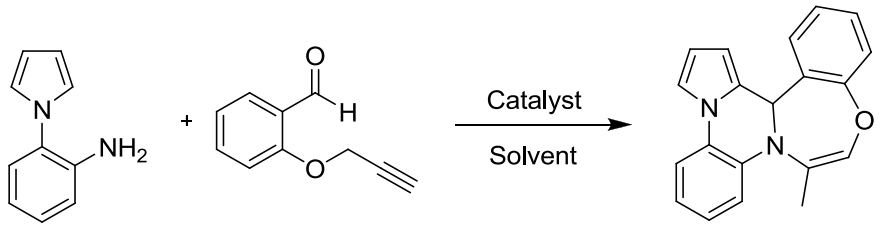



**Figure 45.** Synthesis of 1-(2-(3-phenylprop-2-ynyloxy)phenyl)ethanone (**95**).

### 2.1.6 Synthesis of pyrrolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepines via the reactions between pyrrole-substituted anilines and *o*-propargyloxybenzaldehydes

Following the preparation of starting materials, we investigated the synthesis of targeted pyrroloquinoxalino-fused benzoxazepine derivatives by studying Lewis acid catalyzed reactions between pyrrole-substituted anilines and *o*-propargyloxybenzaldehydes. These reactions yielded the expected pyrrolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepines. Accordingly, we carried out some reactions in order to find the optimal conditions. Table 1 shows how the variables, such as catalyst, solvent, temperature and time, affected the yield. As seen in the table, $InCl_3$ was found to be more efficient catalyst when compared to AuCl in the same period of time. The effect of solvent and temperature was examined by using toluene and *p*-xylene. As seen in entries 1 and 2, better result was obtained in refluxing *p*-xylene as compared to that in refluxing toluene. For this reason, *p*-xylene was chosen as the reaction solvent. Reaction times changed from 2 to 24 hours; however it is obvious that longer reaction times did not improve the yields significantly. To sum up, optimum reaction condition for the synthesis of pyrrolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepine derivatives was adapted from entry 2. In other words, the reactions were performed in refluxing *p*-xylene using 2 mol % $InCl_3$ over 2 h.

**Table 1.** Optimization studies for the synthesis of pyrrolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepines.




| **Entry** | **Catalyst** | **Solvent** | **Temp.** ($^{o}$C) | **Time** (h) | **Yield** (%) |
|---|---|---|---|---|---|
| **1** | 2 mol % $InCl_3$ | toluene | 110 | 4 | 26 |
| **2** | 2 mol % $InCl_3$ | *p*-xylene | 140 | 2 | 68 |
| **3** | 2 mol % $InCl_3$ | *p*-xylene | 140 | 8 | 70 |
| **4** | 2 mol % $InCl_3$ | *p*-xylene | 140 | 12 | 70 |
| **5** | 2 mol % $InCl_3$ | *p*-xylene | 140 | 24 | 68 |
| **6** | 2 mol % $InCl_3$ | *p*-xylene | 140 | 2 | 26 |

After the determination of optimum condition, the synthesis of targeted benzoxazepine molecules was carried out. It should be noted that, while conducting reactions, $InCl_3$ was added half an hour later to the reaction medium after the addition of starting materials and solvent. The reason was to increase the efficiency of imine formation during the reaction. After applying the procedure with determined condition, ten derivatives of benzoxazepines (**59-68**) were synthesized in moderate to high yields. The structures of the corresponding benzoxazepine derivatives are shown in Figure 46. The yields of pyrroloquinoxalino-fused benzoxazepines were changed from 47 to 83% while the yields of indoloquinoxalino-fused benzoxazepines were altered from 25 to 40%. Notably, indole-containing derivatives were obtained in lower yields. This might be due to that in electrophilic aromatic substitution reactions, 2-positions of indoles are not so reactive as compared to 2-positions of pyrroles because of aromaticity and resonance interactions.

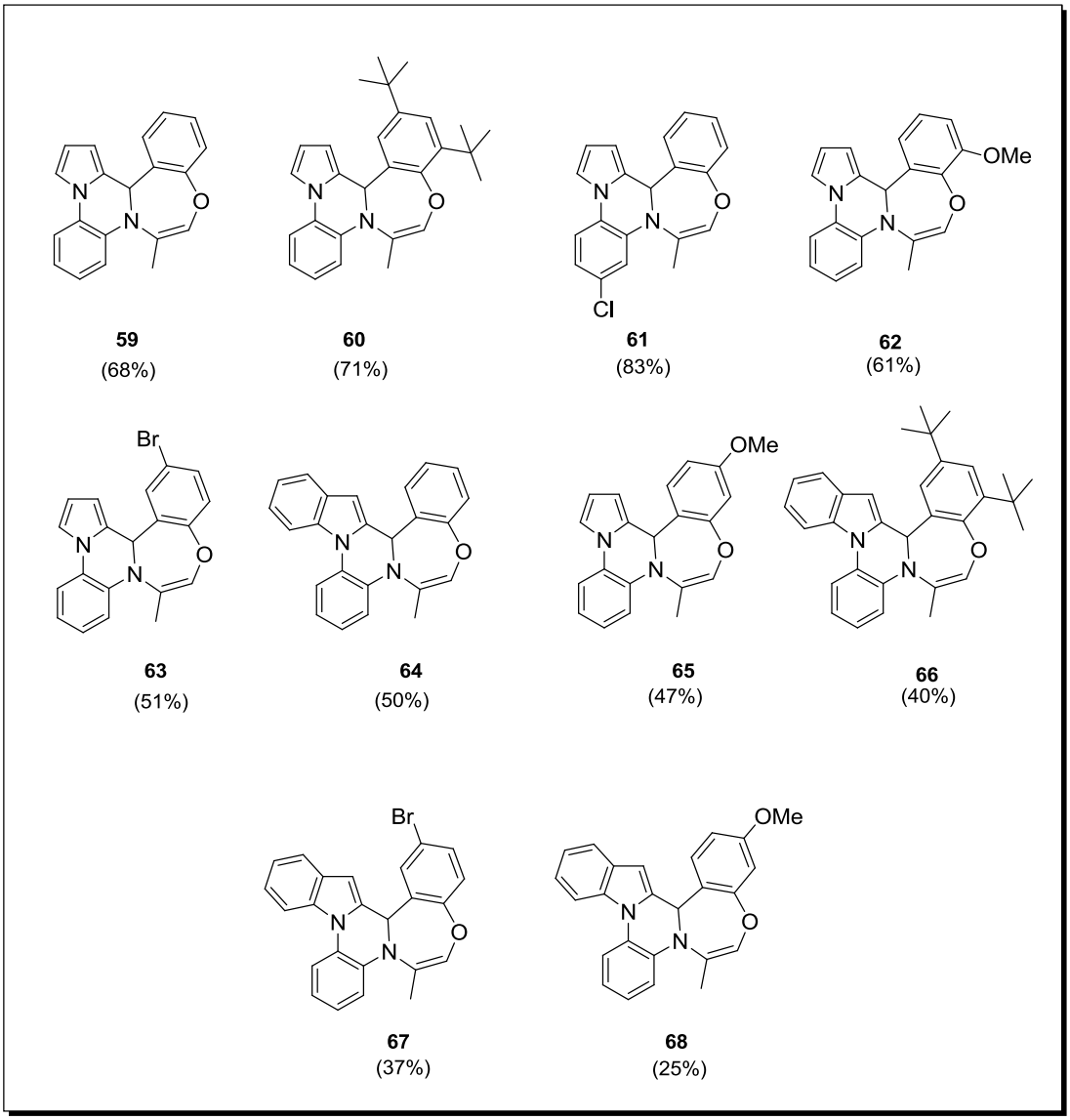



**Figure 46.** Structures of the synthesized benzoxazepine derivatives.

The structures of benzoxazepines have been analyzed by NMR spectroscopy. As an illustration, $^{1}$H NMR spectrum of benzoxazepine derivative **59** is given in Figure 47. As noted, methyl hydrogens appear as doublet at 1.84 ppm region of the spectrum. The hydrogen of tertiary carbon at the ring junction gives a singlet peak at 6.43 ppm. The observation of this peak in the low field is mainly due to its existence in the deshielding zone of both pyrrole and phenyl groups. The peaks of eleven phenyl and pyrrole hydrogens are observed between 6.18-7.39 ppm. The specific olefinic hydrogen peak that is near to oxygen appears as doublet of doublet at 6.19 ppm.

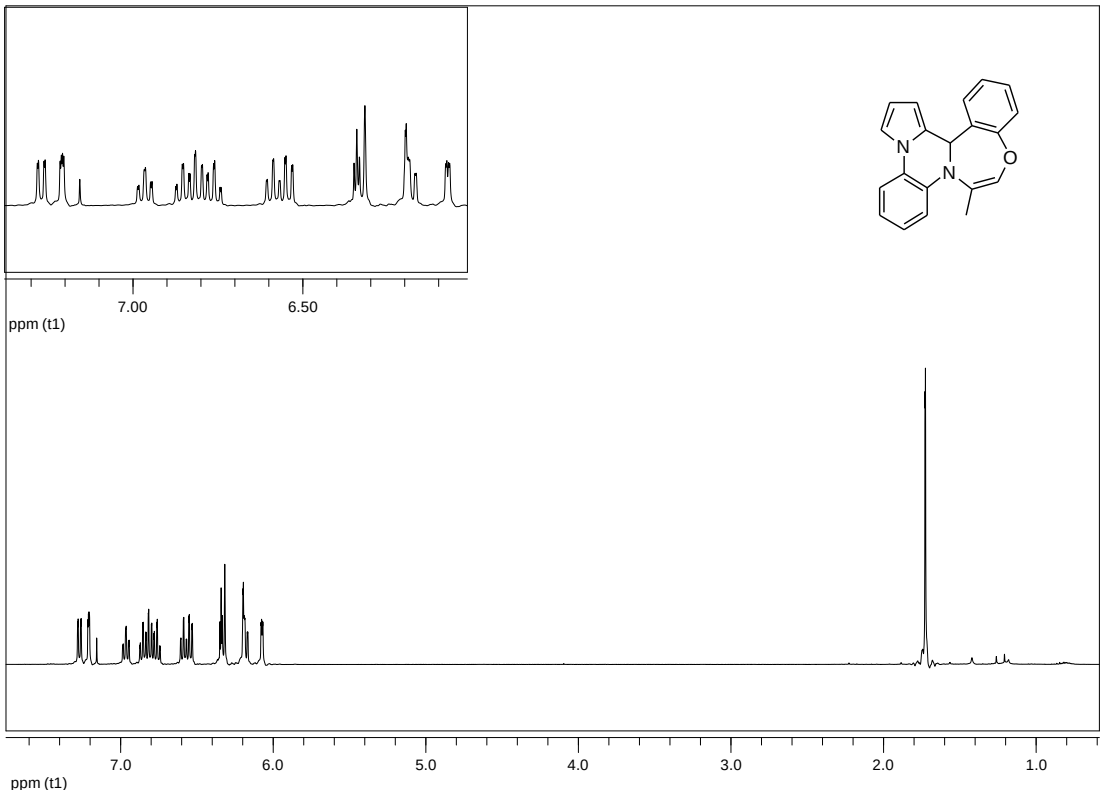



**Figure 47.** $^{1}$H NMR spectrum of benzoxazepine **59**.

$^{13}$C NMR spectrum of benzoxazepine derivative **59** is shown in Figure 48. The methyl carbon peak appears at 17.0 ppm while the tertiary carbon peak at the ring junction comes around 57.7 ppm. The specific olefinic carbon near to the oxygen atom comes at 105.9 ppm. Other olefinic and aromatic carbons resonate between 106.0-155.6 ppm.

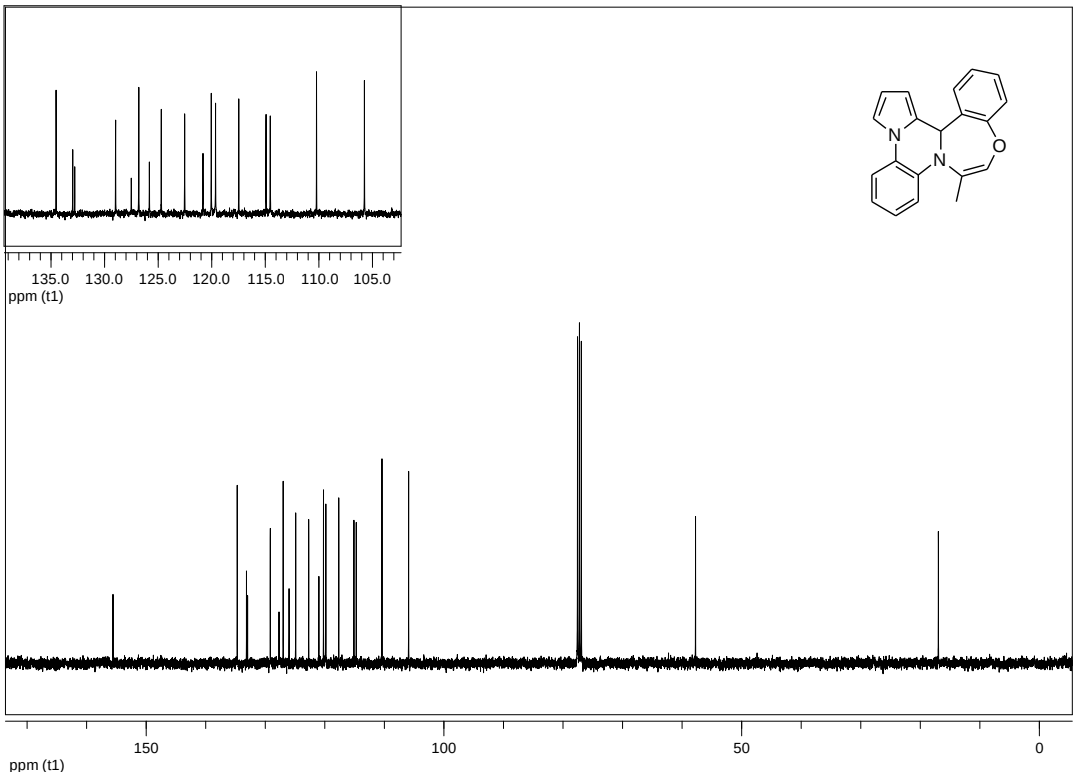



**Figure 48.** $^{13}$C NMR spectrum of benzoxazepine **59**.

### 2.1.7 Proposed mechanism for the formation of benzoxazepines 59-68

Proposed mechanism for the formation of pyrroloquinoxalino-fused benzoxazepines is shown in Figure 49. The reaction of pyrrole-substituted aniline with proper *o*-propargylated benzaldehyde produces the corresponding imine, which is then activated by $InCl_3$, giving intermediate **96**. Subsequently, electrophilic aromatic substitution reaction of pyrrole moiety with imine functionality gives intermediate **97**. In fact, such cyclization reactions can be considered as Pictet-Spengler type cyclization reaction.[51] Hydrogen exchange and the departure of $InCl_3$ yields pyrroloquinoxaline derivative **98**. Next $InCl_3$ activates alkyne moiety and initiates the nucleophilic attack of secondary nitrogen to give seven-membered compound **100**. Hydrogen exchange and the leave of $InCl_3$ then yields exo-double bond containing pentacyclic compound **101**. Finally, H-shift produces thermodynamically more stable pyrroloquinoxalino-fused benzoxazepine derivatives **59**-**68** depending upon the identity of R groups (Figure 50).

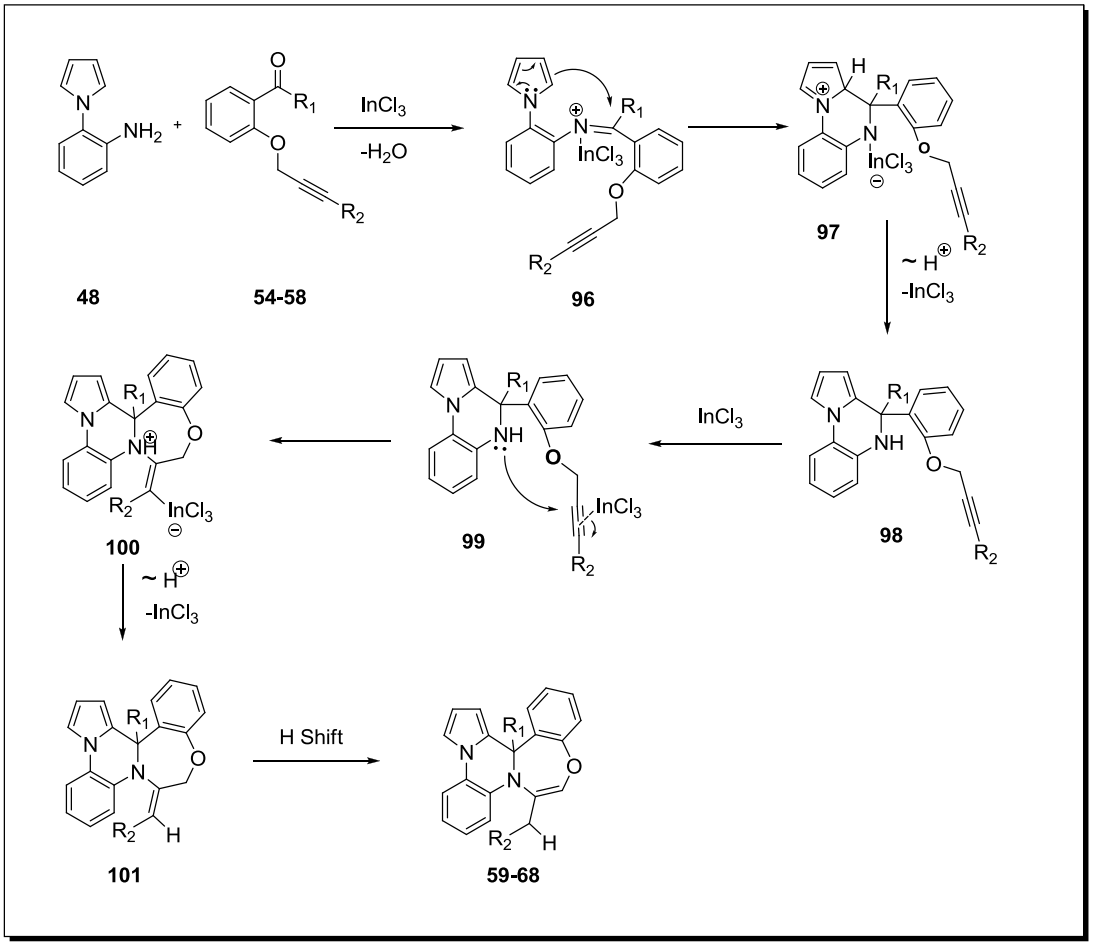



**Figure 49.** Proposed mechanism for the formation of pyrroloquinoxalino-fused benzoxazepines.

### 2.1.8 Reaction of pyrrole-substituted aniline 48 with *o*-propargylated benzaldehyde 92

Following the syntheses of benzoxazepines, we examined the reaction of pyrrole-substituted aniline **48** with *o*-propargyloxy-benzaldehyde **92**. However, the desired final pentacyclic product could not be obtained from this reaction. The reaction stopped at the formation step of dihydropyrroloquinoxaline derivative **102** (Figure 50). Presumably due to conformational and steric effects, dihydropyrrolo-quinoxaline **102** did not undergo electrophilic cyclization with alkyne moiety. Subsequently, dihydropyrroloquinoxaline **102** was subjected to the reaction with $InCl_3$ in order to initiate electrophilic cyclization, but no reaction was observed. However, when it was treated with iodine, dihydropyrroloquinoxaline **102** was oxidized to pyrroloquinoxaline **103** without further cyclization.

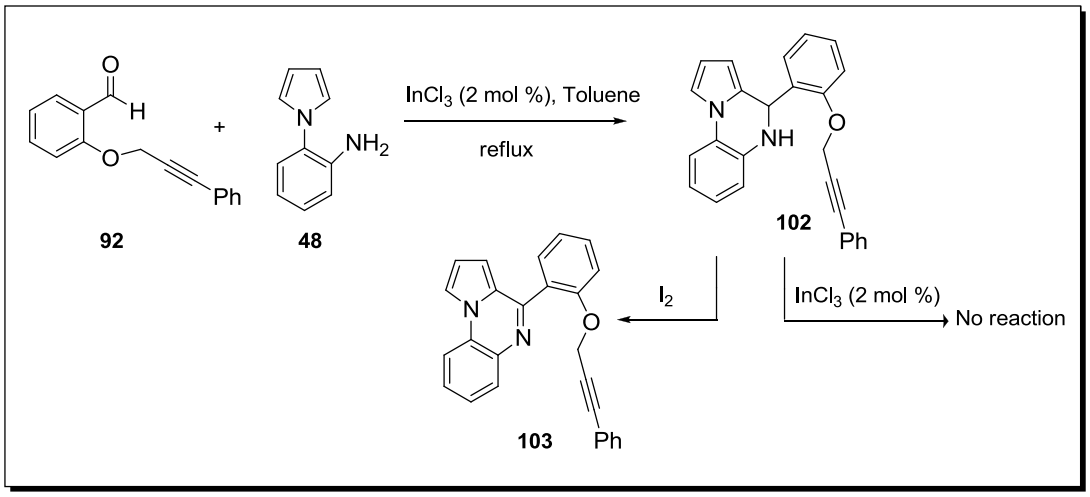



**Figure 50.** Reaction of pyrrole-substituted aniline **48** with *o*-propargyloxy-benzaldehyde **92**.

### 2.1.9 Reaction of pyrrole-substituted aniline 48 with *o*-propargylated acetophenone 94

Next, we tried the reaction of pyrrole-substituted aniline **48** with *o*-propargylated acetophenone **94**. Unfortunately, this reaction also did not yield the expected pentacyclic product and only the corresponding dihydropyrroloquinoxaline derivative **104** was obtained in very low yield (5%) (Figure 51). After its formation, dihydropyrroloquinoxaline **104** did not undergo electrophilic cyclization with alkyne moiety possibly as a result of conformational effects.

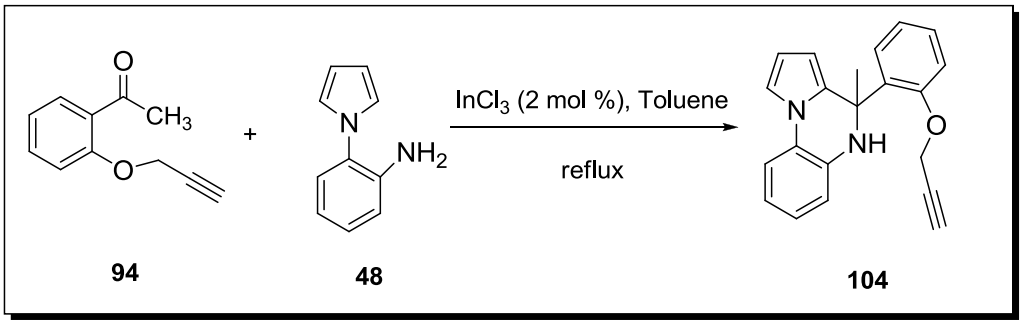



**Figure 51.** Reaction of pyrrole-substituted aniline **48** with *o*-propargylated acetophenone **94**.

### 2.1.10 Reaction of pyrrole-substituted aniline 48 with *o*-propargylated acetophenone 95

We also investigated the reaction of pyrrole-substituted aniline **48** with *o*-propargylated acetophenone **95**. Interestingly, this reaction produced chromenyldihydropyrroloquinoxaline derivative **105** instead of the desired benzoxazepine product (Figure 52). The final product **105** was isolated in 98% yield. Interestingly, after the formation of dihydropyrroloquinoxaline **108**, electrophilic cyclization took place between phenyl and alkyne moiety, giving chromenyldihydropyrroloquinoxaline derivative **105**.

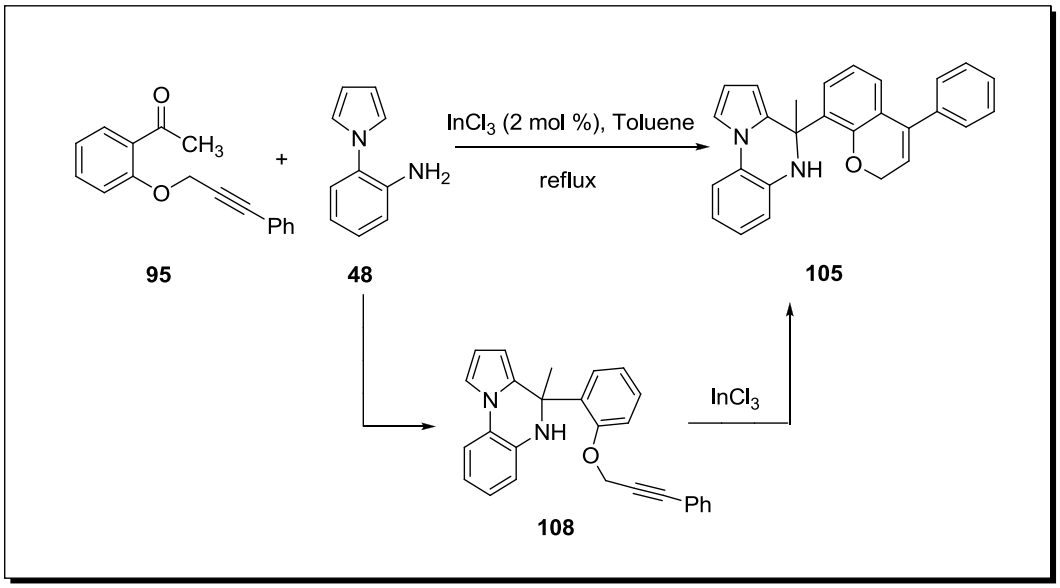



**Figure 52.** Synthesis of 4-methyl-4-(4-phenyl-2H-chromen-8-yl)-4,5-dihydropyrrolo[1,2-a]quinoxaline (**105**).

$^{1}$H NMR spectrum of chromenyldihydropyrroloquinoxaline derivative **105** is given in Figure 53. Distinctly, as seen in the spectrum, methyl H singlet peak appears at 2.15 ppm while H singlet peak of NH group comes at 5.85 ppm. Two methylene protons give a triplet peak at 5.00 ppm. Olefinic hydrogen that is near to the methylene protons gives a triplet at 5.91 ppm.

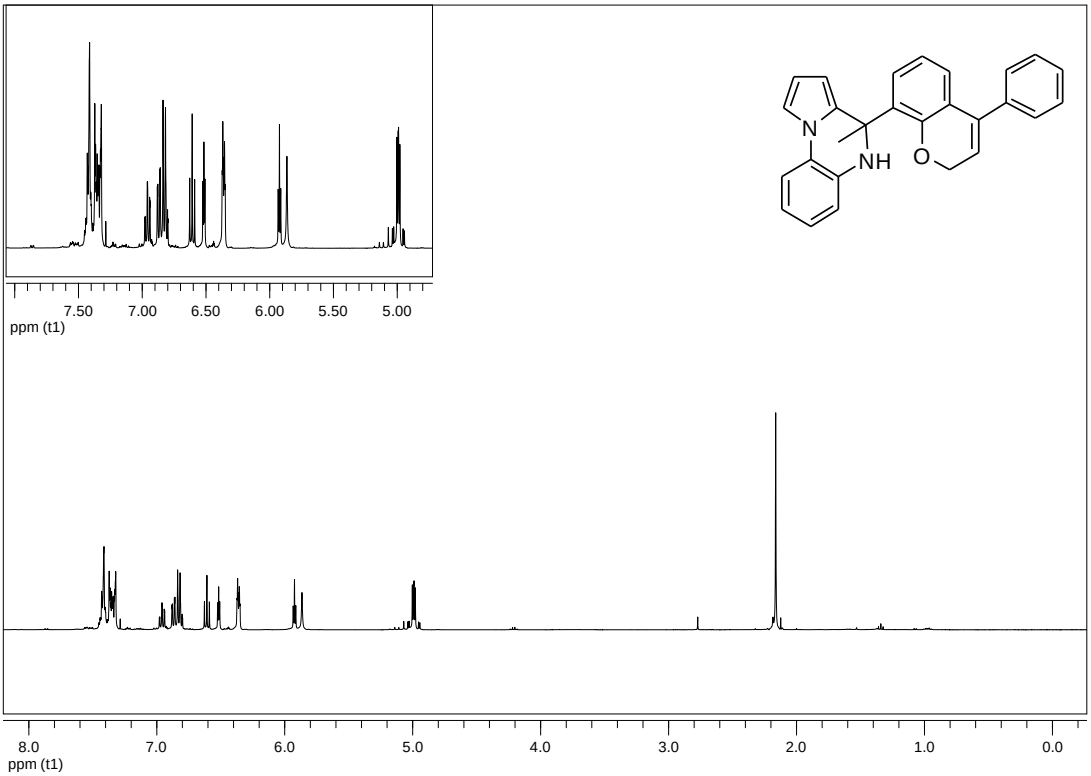



**Figure 53.** $^{1}$H NMR Spectrum of 4-methyl-4-(4-phenyl-2H-chromen-8-yl)-4,5-dihydropyrrolo[1,2-a]quinoxaline (**105**).

$^{13}$C NMR Spectrum of compound **105** is demonstrated in Figure 54. The carbon peak that belongs to methyl group appears at 26.3 ppm. The specific peak that belongs to quaternary carbon is seen at 57.5 ppm. The carbon of methylene peak is observed at 65.0 ppm. All the other olefinic and aromatic carbon signals resonate between 105.7-151.5 ppm region of the spectrum. Specific olefinic carbon near to the methylene group gives peak at 119.4 ppm.

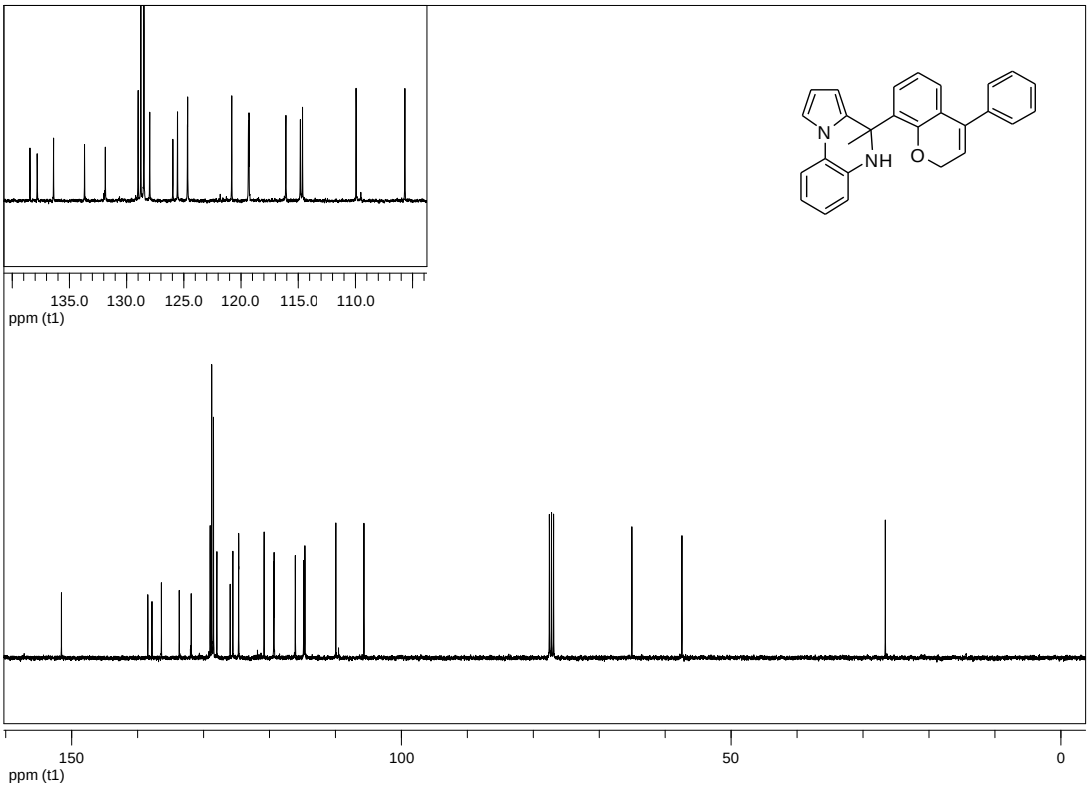



**Figure 54.** $^{13}$C NMR Spectrum of 4-methyl-4-(4-phenyl-2H-chromen-8-yl)-4,5-dihydropyrrolo[1,2-a]quinoxaline (**105**).

### 2.1.11 Proposed mechanism for the formation of chromenyldihydropyrroloquinoxaline 105

The mechanism proposed for the formation of chromenyldihydropyrroloquinoxaline **105** is depicted in Figure 55. First of all, $InCl_3$-catalyzed reaction between pyrrolo-substituted aniline **48** and *o*-propargylated acetophenone **95** forms dihydropyrroloquinoxaline **108** by a similar mechanism shown in Figure 50, involving imine formation and electrophilic aromatic substitution reaction, respectively. After the activation of alkyne moiety with $InCl_3$ in **109**, propargyloxyphenyl group undergoes electrophilic cyclization to produce **110**. Finally, hydrogen exchange followed by $InCl_3$ removal yields chromenyldihydropyrroloquinoxaline derivative **105** (Figure 55).

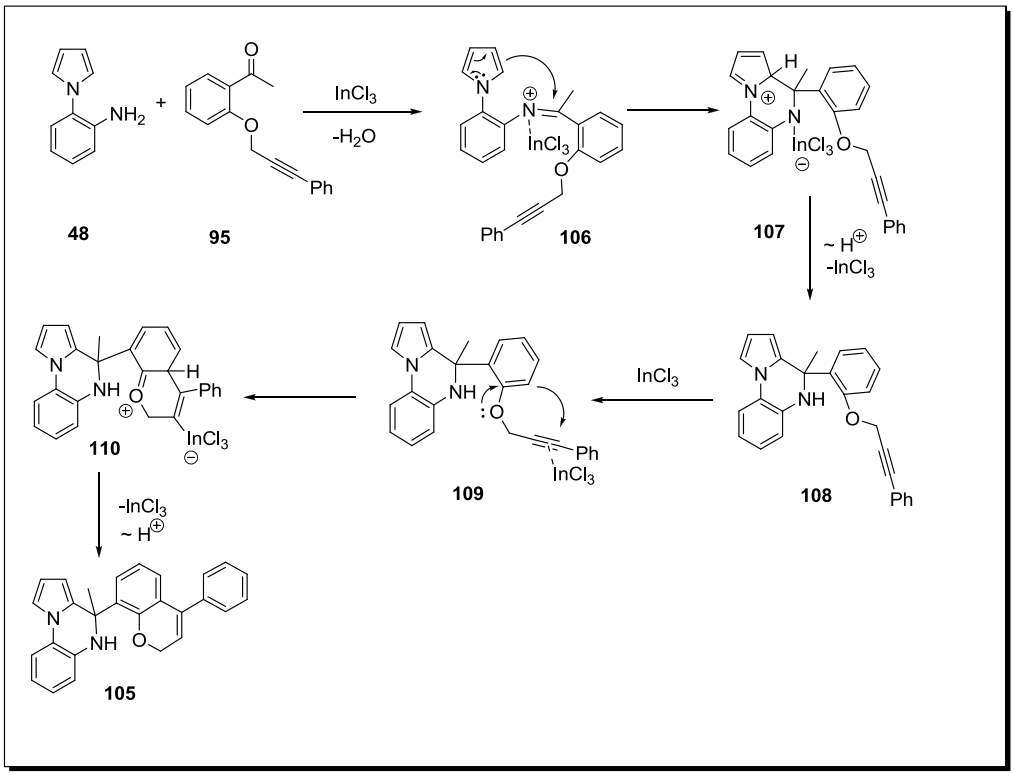



**Figure 55.** Proposed mechanism for the formation of chromenyldihydropyrroloquinoxaline **105**.

### 2.2 Synthesis of ester-containing iodopyridines

#### 2.2.1 Synthesis of dimethyl 2-(prop-2-ynylamino)maleate (69)

We also investigated the synthesis of ester-bearing pyridines. For this purpose, we first synthesized the starting material, namely 2-(prop-2-ynylamino)maleate (**69**) (Figure 56). The reaction of dimethyl acetylenedicarboxylate with propargylamine in acetonitrile at room temperature afforded the targeted dimethyl 2-(prop-2-ynylamino)maleate (**69**) in 70% yield.

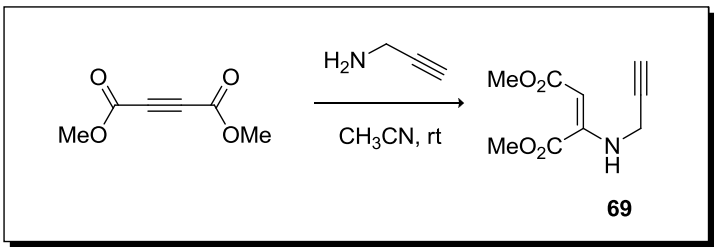
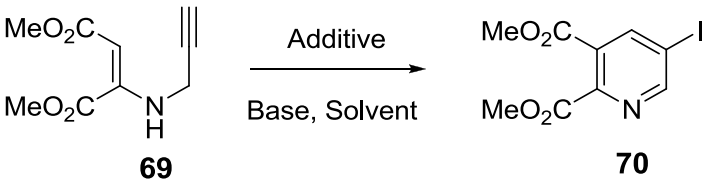



**Figure 56.** Synthesis of dimethyl 2-(prop-2-ynylamino)maleate (69).

### 2.2.2 Synthesis of 5-iodopyridine-2,3-dicarboxylate (70)

Following the synthesis of maleate **69**, we examined its reaction with molecular iodine, which afforded 5-iodopyridine-2,3-dicarboxylate (**70**) via electrophilic cyclization. Accordingly, we carried out some reactions in order to optimize the reaction conditions. In Table 3, the effects of variables such as solvent, temperature, electrophile and time on the yield are shown. As solvent, DCM, acetonitrile and toluene were used. Reactions were performed at room temperature and in refluxing conditions with different time periods. The reaction conditions in Entry 3 appeared as the optimal conditions for the synthesis of 5-iodopyridine-2,3-dicarboxylate (**70**), which was obtained in 54% yield. Longer reaction times did not improve the yields significantly (Entry 3). As a result, the reactions were carried out in the presence of 3 equivalents of $I_2$ and $NaHCO_3$ in refluxing acetonitrile for overnight.

**Table 2.** Optimization reactions for the synthesis of -iodopyridine-2,3-dicarboxylate (**70**).




**69** **70**

| Entry | Reagent | Solvent | Temp. ($^{o}$C) | Time (h) | Base | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | $I_2$ (3 eq.) | $CH_3CN$ | rt | 24 | $NaHCO_3$ (3 eq.) | 14 |
| 2 | $I_2$ (3 eq.) | $CH_3CN$ | 82 | 2 | $NaHCO_3$ (3 eq.) | 38 |
| 3 | $I_2$ (3 eq.) | $CH_3CN$ | 82 | 21 | $NaHCO_3$ (3 eq.) | 54 |
| 4 | $I_2$ (3 eq.) | $CH_3CN$ | 82 | 40 | $NaHCO_3$ (3 eq.) | 55 |
| 5 | $I_2$ (3 eq.) | DCM | rt | 24 | $NaHCO_3$ (3 eq.) | 28 |
| 6 | $I_2$ (3 eq.) | DCM | 40 | 20 | $NaHCO_3$ (3 eq.) | 38 |
| 7 | ICl (3 eq.) | $CH_3CN$ | 82 | 8 | $NaHCO_3$ (3 eq.) | -- |
| 8 | $I_2$ (3 eq.) | Toluene | 110 | 6 | $NaHCO_3$ (3 eq.) | -- |
| 9 | $ZnCl_2$ (3 eq.) | DCM | 40 | 6 | --- | -- |

The structure of 5-iodopyridine-2,3-dicarboxylate (**70**) has been analyzed by NMR spectroscopy, $^{1}$H NMR spectrum of which is given in Figure 57. Methyl groups give singlet peaks at 3.94 and 3.99 ppm. As seen in the spectrum, there are only two aromatic hydrogen signals. One appears as doublet at 8.48 ppm while the other singlet peak comes at 8.97 ppm.

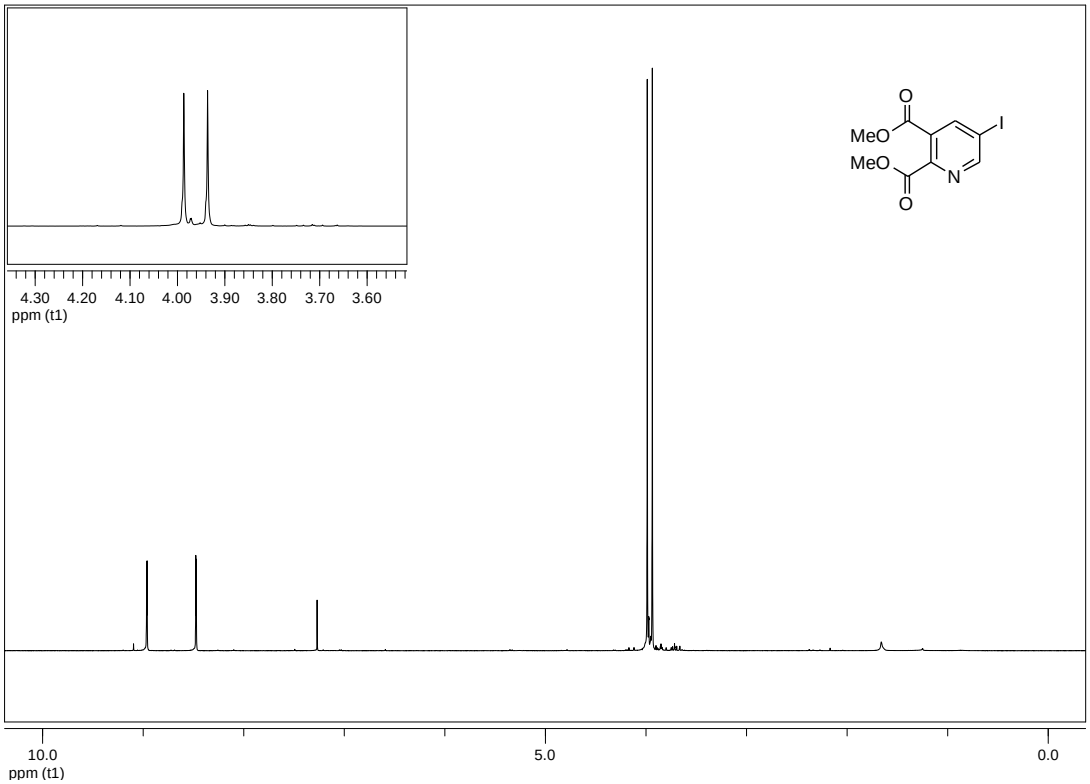



**Figure 57.** $^{1}$H NMR Spectrum of 5-iodopyridine-2,3-dicarboxylate (**70**).

$^{13}$C NMR spectrum of 5-iodopyridine-2,3-dicarboxylate (**70**) is shown in Figure 58. Methyl carbon peaks overlap to some extent and appear at 53.4 ppm. Notably, the carbon bearing iodine atom gives a peak at 95.0 ppm. The remaining aromatic carbons resonate between 128.2 and 157.9 ppm. Two carbonyl groups resonate at 164.2 and 166.8 ppm.

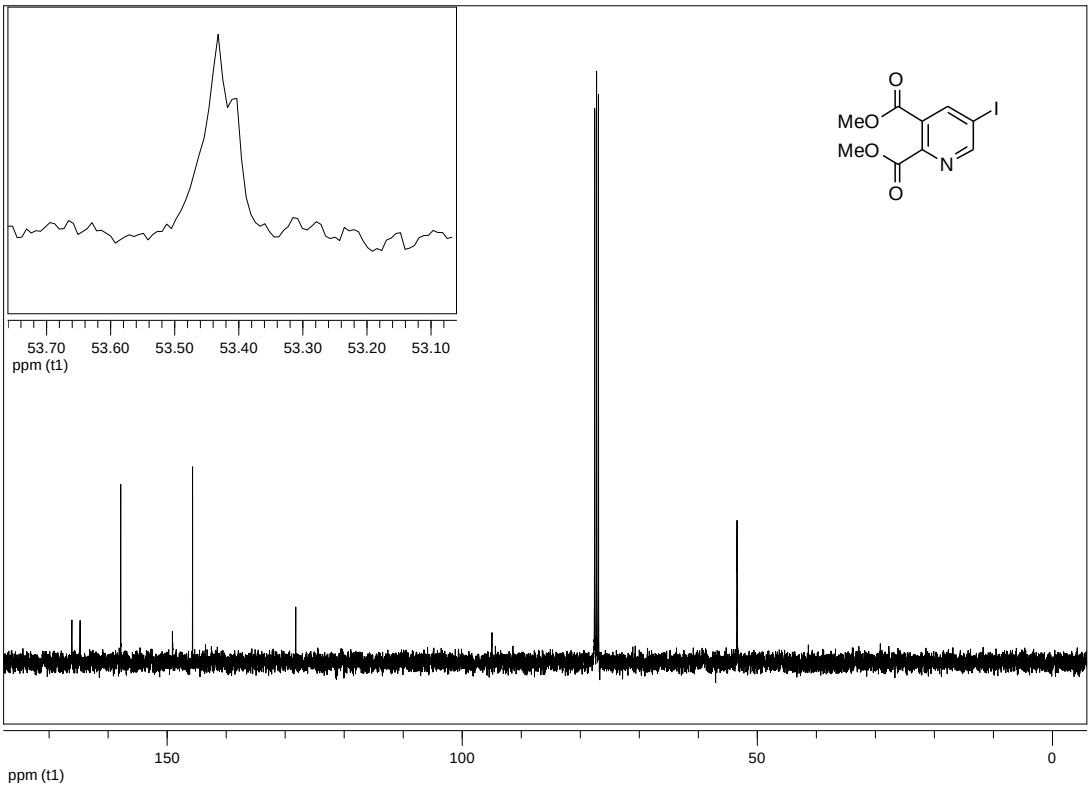



**Figure 58.** $^{13}$C NMR Spectrum of 5-iodopyridine-2,3-dicarboxylate (**70**).

### 2.2.3 Proposed mechanism for the formation of 5-iodopyridine-2,3-dicarboxylate (70)

The mechanism proposed for the formation of 5-iodopyridine-2,3-dicarboxylate (**70**) is demonstrated in Figure 59. First, the reaction of compound **69** with iodine yields iodonium ion **111**, which initiates electrophilic cyclization via nucleophilic attack of secondary nitrogen atom to give protonated dihydropyridine **112**. Subsequently, deprotonation with base affords 1,2-dihydropyridine **113**. Finally, air oxidation of **113** yields 5-iodopyridine-2,3-dicarboxylate (**70**) (Figure 59).

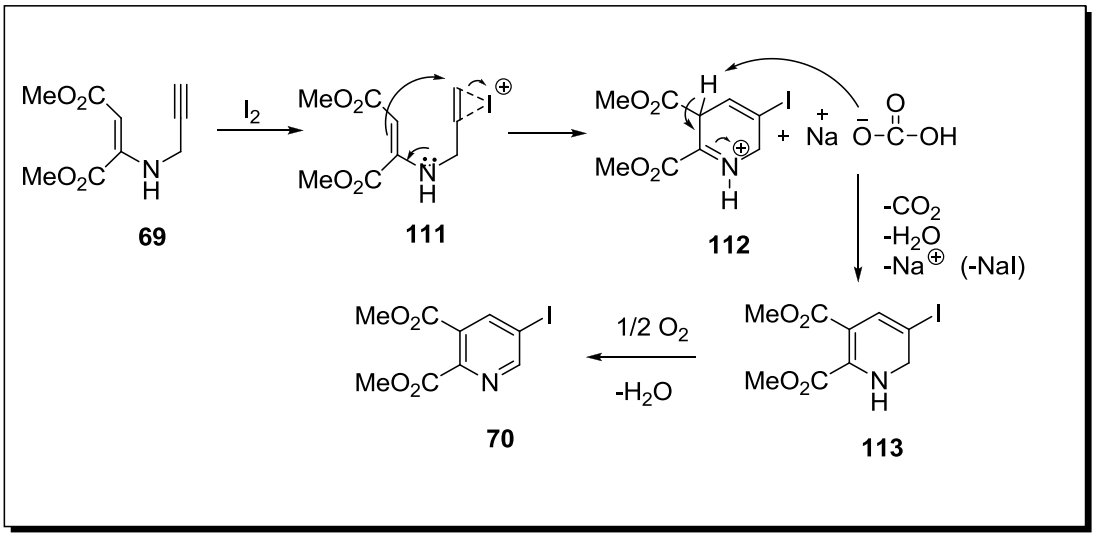



**Figure 59.** Proposed mechanism for the formation of 5-iodopyridine-2,3-dicarboxylate (**70**)

### 2.2.4 Synthesis of dimethyl 5-alkynylpyridine-2,3-dicarboxylate derivatives

In order to further functionalize iodopyridine-2,3-dicarboxylate (**70**), it was subjected to Sonogashira coupling with terminal alkynes (Figure 60). The reaction was performed in refluxing THF in the presence of $PdCl_2(PPh_3)_2$ and CuI over 4 h, yielding dimethyl 5-alkynylpyridine-2,3-dicarboxylate derivatives **79-86**.

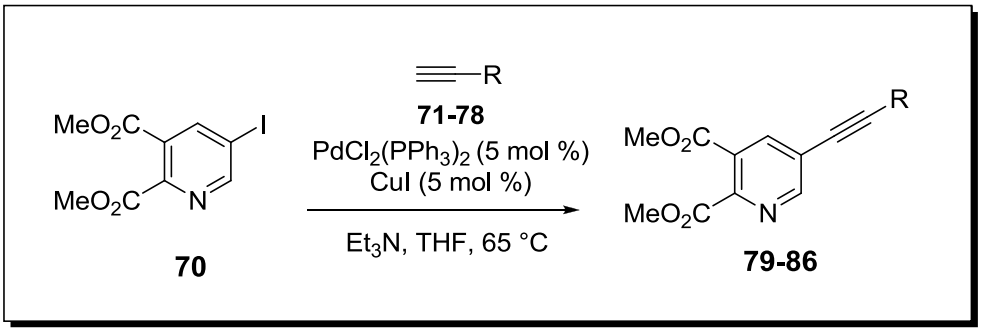



**Figure 60.** Synthesis of dimethyl 5-alkynylpyridine-2,3-dicarboxylate derivatives (**79-86**).

Applying this procedure, eight derivatives of dimethyl 5-alkynylpyridine-2,3-dicarboxylates were synthesized in good yields, which changed from 63 to 82%. The structures of the synthesized 5-alkynylpyridine derivatives are shown in Figure 61.

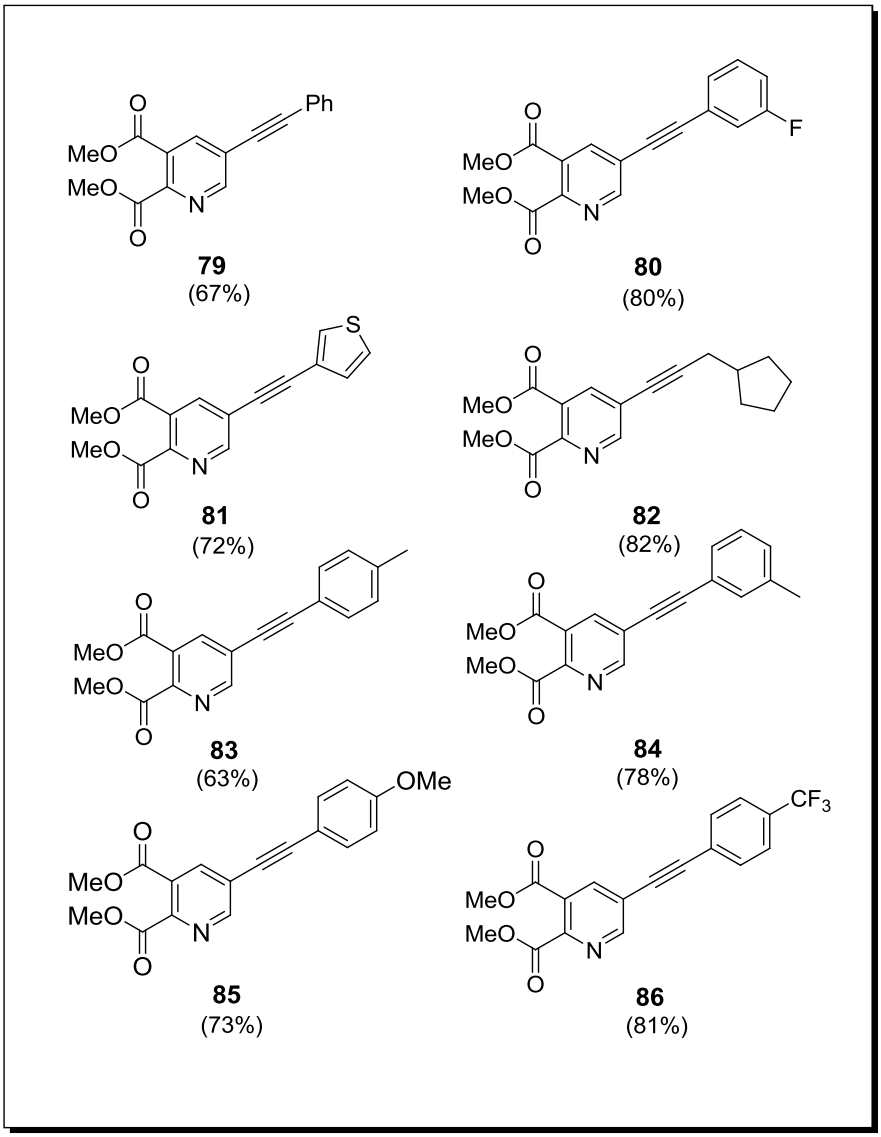



**Figure 61.** Structures of the synthesized 5-alkynylpyridine derivatives.

As an example, $^{1}$H NMR spectrum of pyridine derivative **79** is shown in Figure 62. Methyl protons of methoxy groups appears as singlet at 3.94 and 4.00 ppm. The remaining seven aromatic hydrogen signals appear between 7.37-8.84 ppm.

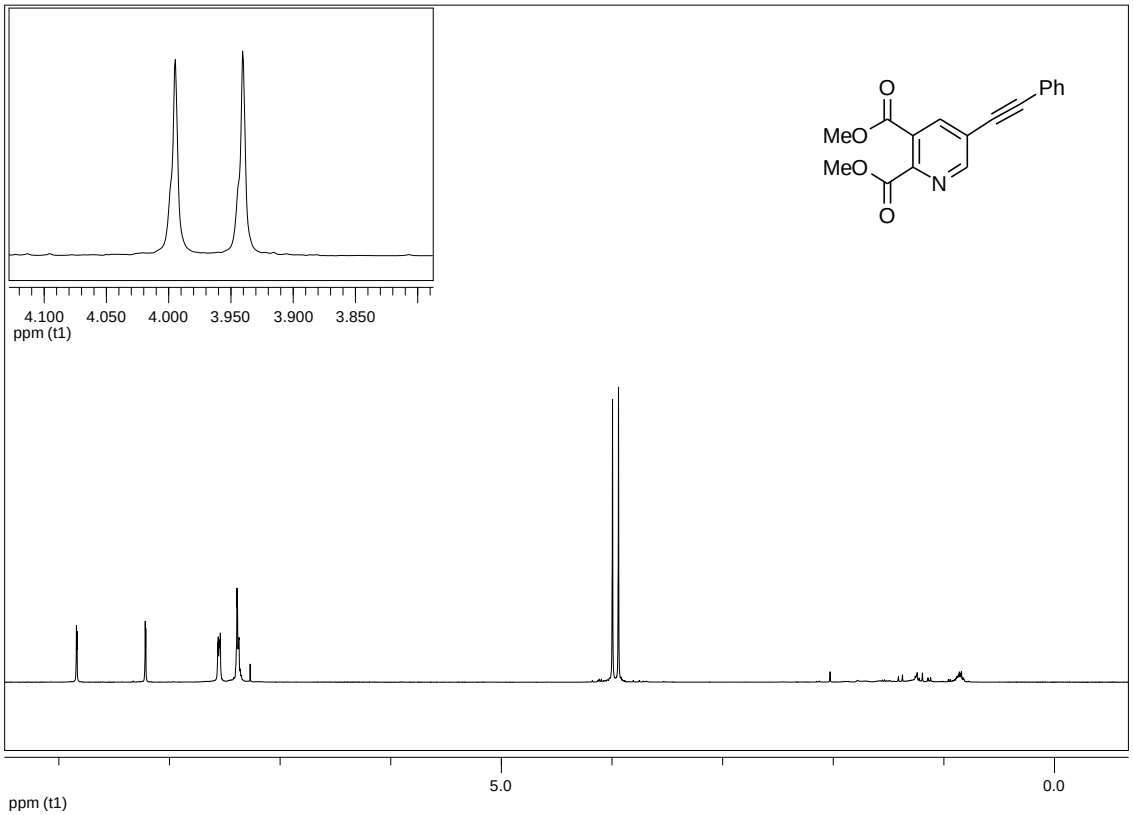



**Figure 62.** $^{1}$H NMR Spectrum of pyridine derivative **79**.

$^{13}$C NMR spectrum of pyridine **79** is shown in Figure 63. Methyl carbon peaks of methoxy groups appear at 53.2 and 53.1 ppm. Specific alkynyl carbons resonate at 95.8 and 84.3 ppm. Other signals of olefinic carbons come between 153.4 and 121.7 ppm. . Carbonyl group signals give peaks at 166.0 and 165.4 ppm.

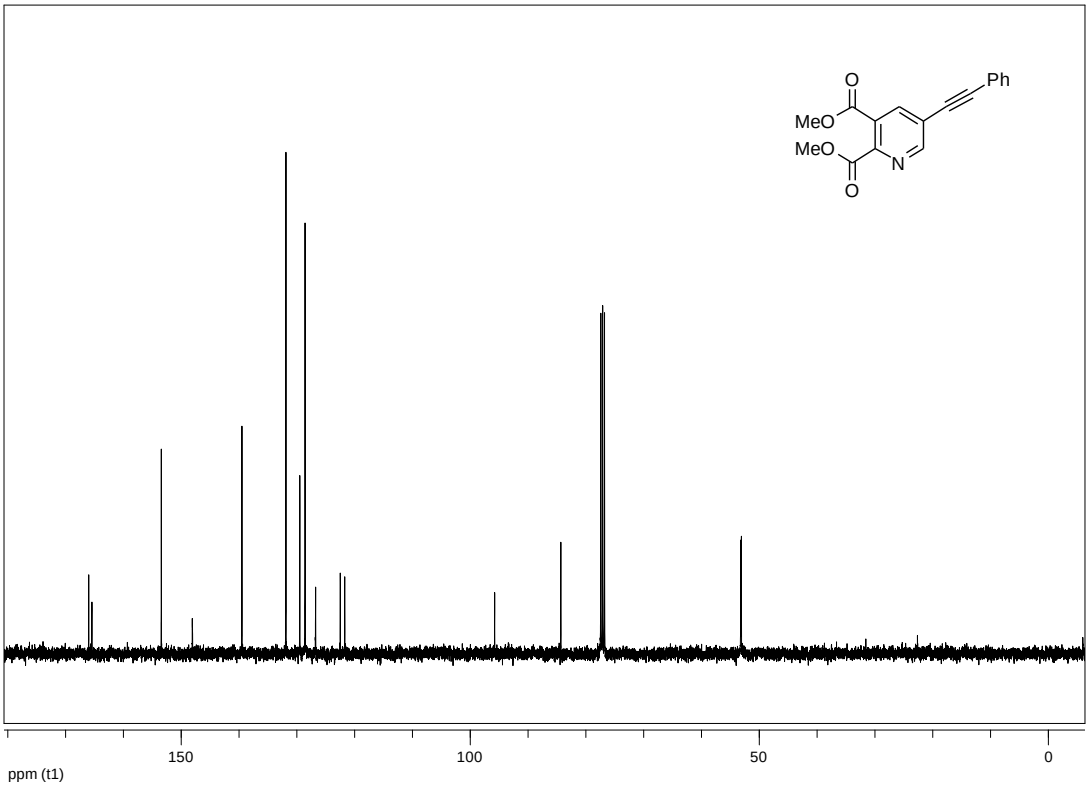



**Figure 63.** $^{13}$C NMR Spectrum of pyridine derivative **79**.

The proposed mechanism for the formation of pyridine derivatives **79**-**86** is shown in Figure 64. This mechanism starts with the oxidative addition of iodopyridine **70** to Pd(0) to form compound **114**. Next, transmetallation between organocopper compound and complex **114** occurs to give complex **115**. At the final step, reductive elimination gives the final coupled product **79**-**86** and regenerates the palladium catalyst.

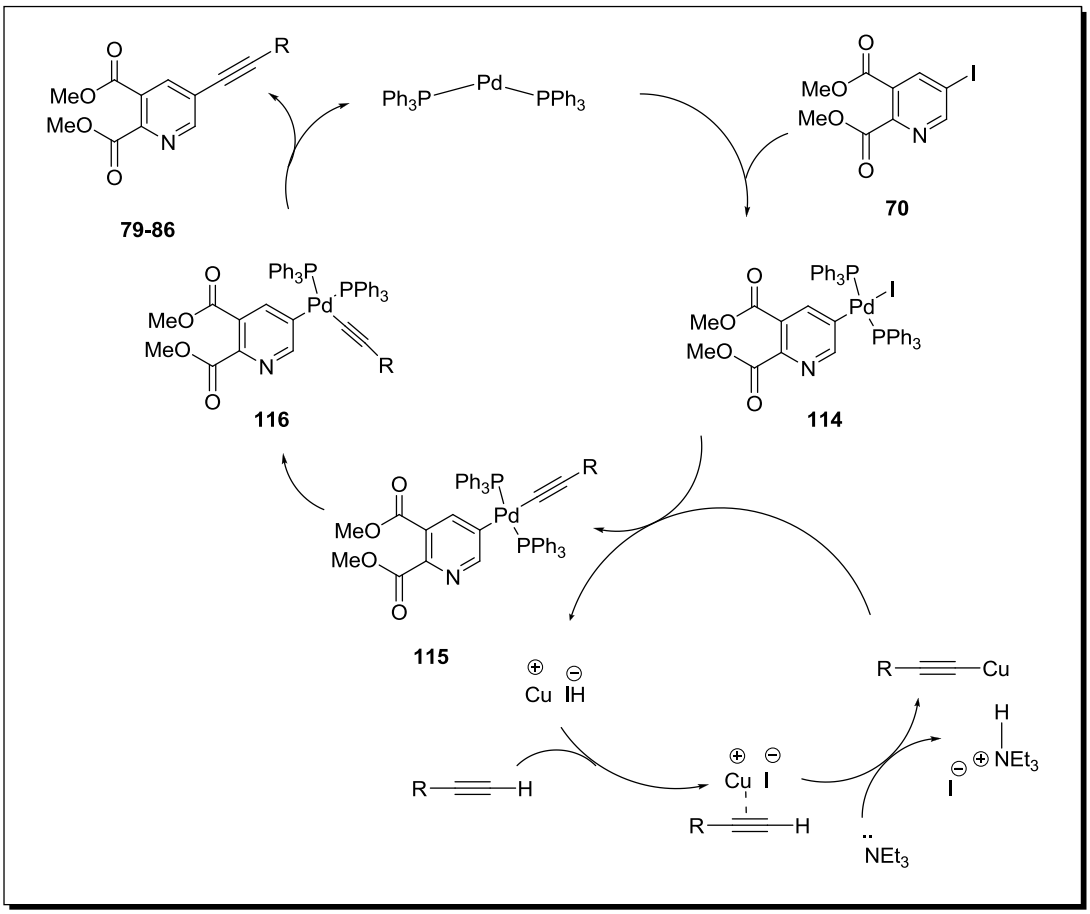



**Figure 64.** Proposed mechanism for the synthesis of pyridines **79**-**86**.

# CHAPTER 3

# CONCLUSION

In summary, one-pot synthesis of pyrrolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepine compounds from pyrrole-substituted anilines and *o*-propargyloxybenzaldehydes was investigated in the presence of an Indium Lewis acid catalyst.

In the first step of the study, pyrrole-substituted anilines were prepared by using copper-catalyzed coupling reaction. Following this procedure, five derivatives of pyrrole-substituted anilines were synthesized. Then, six *o*-propargyloxybenzaldehyde derivatives were prepared by employing the $S_N2$ reaction of *o*-hydroxybenzaldehyde and acetophenone derivatives with propargyl bromide in the presence of $K_2CO_3$.

Next, optimization reactions were conducted between the synthesized *o*-propargyloxybenzaldehydes and pyrrole-substituted anilines and it was found that the reactions were done in refluxing *p*-xylene using 2% $InCl_3$ over 2 h.

Finally, a series of pentacyclic pyrroloquinoxalino-fused benzoxazepine derivatives were synthesized in one-pot manner via electrophilic cyclization using $InCl_3$ as a Lewis acid catalyst. Although the yields of benzoxazepine derivatives were altered between 25 and 85%, they were in moderate to good yields in most cases.

In the second part of the study, we investigated the synthesis of ester-containing iodopyridine from 2-(prop-2-ynylamino)maleate in the presence of molecular iodine. The reaction was carried out in the presence of 3 equivalents of $I_2$ and $NaHCO_3$ in refluxing acetonitrile. Then this iodopyridine was further functionalized by Sonogashira coupling with terminal alkynes. Finally, we have synthesized eight alkynylpyridine derivatives in high yields.

The biological activity tests of the synthesized benzoxazepines and pyridines, which may have some potential for pharmaceutical benefit, will be carried out by a collaborative work.

# CHAPTER 4

## EXPERIMENTAL

The record of $^{1}H$ and $^{13}C$ NMR spectra were made on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz) spectrometer. The chemical shifts of structures are reported in parts per million (ppm) downfield from an internal TMS (trimethlsilane) reference. Coupling constants (*J)* are reported in hertz (Hz), and the spin multiplicities are presented by the following symbols: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Infrared Spectra (IR) were recorded on a NICOLET IS10 FTIR Spectrometer using attenuated total reflection (ATR). Band positions were adjusted to reciprocal centimeters ($cm^{-1}$). Band intensities of the corresponding bands were represented according to the most intense band, and expressed as: br (broad), vs (very strong), s (strong), m (medium), w (weak) and vw (very weak). The progress of the reactions was followed by Thin Layer Chromatography (TLC) on commercially available 0.25 mm silica gel plates, using ethyl acetate-hexane solvent mixtures with relative polarity. The polarity of these solvents was employed as volume to volume ratio. If necessary, solvents were purified by distillation or according to standard literature procedures. When appropriate, inert atmosphere for the reactions was provided by slightly positive pressure (ca. 0.1 psi) of argon gas. All equipments and glassware were dried in oven before use.

### 4.1. General Procedure 1. Synthesis of pyrrole-substituted anilines (49-53)

The corresponding aniline (0,5 mmol) was dissolved in toluene (10-15 ml). Then pyrrole (0.6 mmol) was added to the solution under argon. Next, *N*,*N*-dimethylethylenediamine (0.4 mmol), CuI (0.1 mmol) and $K_3PO_4$ (0.2 mol) were added to the flask, respectively. The resulting solution was refluxed at 110 °C for 24 h. After the reaction was over, solvent was evaporated under reduced pressure. Finally, the desired pyrrole-substituted aniline molecule was isolated by flash column chromatography on silica gel using hexane/ethyl acetate as the eluent.

#### 4.1.1 Synthesis of 2-(1*H*-indol-1-yl)aniline (49)

General Procedure 1 was employed using 2-iodoaniline (100 mg, 0.5 mmol), indole (64.1 mg, 0.6 mmol), *N*,*N*-dimethylethylenediamine (26.5 mg, 0.4 mmol), CuI (16.0 mg, 0.1 mmol) and $K_3PO_4$ (214.5 mg, 1.0 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 76.5 mg (80%) of the indicated product.

**49:** $^1$H NMR (400 MHz, $CDCl_3$): δ 7.85 (m, 1H), 7.31 (m, 6H), 6.94 (td, *J* = 7.6, 1.2 Hz, 1H), 6.84 (d, *J* = 1.2 Hz, 1H), 6.82 (d, *J* = 3.2 Hz, 1H), 3.56 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 143.2, 136.4, 129.2, 128.7, 128.63, 123.61, 124.8, 122.3, 121.0, 120.3, 118.5, 116.3, 110.8, 103.2; IR (neat): 3367, 1617, 1500, 1452, 1329, 1305, 1228, 1135, 1009, 954, 739, 494, 425 $cm^{-1}$. The spectral data are in agreement with those reported previously for this compound.[52]

#### 4.1.2 Synthesis of 5-chloro-2-(1H-pyrrol-1-yl)aniline (50)

General Procedure 1 was employed using 5-chloro-2-iodoaniline (100 mg, 0.4 mmol), pyrrole (31.8 mg, 0.5 mmol), *N*,*N*-dimethylethylenediamine (23.0 mg, 0.3 mmol), CuI (15.2 mg, 0.1 mmol) and $K_3PO_4$ (186.6 mg, 0.9 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 42.2 mg (55%) of the indicated product.

**50:** $^1$H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, *J* = 8.4 Hz, 1H), 6.83 (t, *J* = 2.4 Hz, 2H), 6.79 (m, 2H), 6.39 (t, *J* = 2.4 Hz, 2H), 3.79 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 143.3, 134.1, 128.3, 126.1, 121.8, 118.3, 115.8, 109.9; IR (neat): 3312, 1618, 1507, 1321, 1243, 1069, 927, 854, 800, 738, 636, 537, 485, 456 $cm^{-1}$.

#### 4.1.3 Synthesis of 4-methyl-2-(1H-pyrrol-1-yl)aniline (51)

General Procedure 1 was employed using 2-bromo-4-methylaniline (100 mg, 0.5 mmol), pyrrole (43.2 mg, 0.7 mmol), *N*,*N*-dimethylethylenediamine (31.1 mg, 0.4 mmol), CuI (20.5 mg, 0.1 mmol) and $K_3PO_4$ (251.9 mg, 1.2 mmol). Purification of the crude product by

flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 46.5 mg (50%) of the indicated product.

**51:** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.00 (m, 2H), 6.85 (t, *J* = 2.0 Hz, 2H), 6.77 (dd, *J* = 6.8, 2.0 Hz, 1H), 6.34 (t, 2.4 Hz, 2H), 3.54 (s, 2H), 2.28 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 153.5, 141.8, 129.2, 127.8, 121.9, 116.7, 109.5, 20.5; IR (neat): 3376, 1627, 1513, 1487, 1330, 1262, 1155, 1067, 1026, 947, 815, 725, 631, 480 cm$^{-1}$. The spectral data are in agreement with those reported previously for this compound.[49]

### 4.1.4 Synthesis of 5-methyl-2-(1H-pyrrol-1-yl)aniline (52)

General Procedure 1 was employed using 2-bromo-5-methylaniline (100 mg, 0.5 mmol), pyrrole (43.2 mg, 0.7 mmol), *N*,*N*-dimethylethylenediamine (31.1 mg, 0.4 mmol), CuI (20.5 mg, 0.1 mmol) and $K_3PO_4$ (251.9 mg, 1.2 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 48.4 mg (52%) of the indicated product.

**52:** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.0 Hz, 1H), 6.83 (t, *J* = 2.0 Hz, 2H), 6.67 (s, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.34 (t, *J* = 2.0 Hz, 2H), 3.78 (s, 2H), 2.32 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 154.1, 150.8, 138.9, 127.2, 122.1, 119.7, 117.0, 109.5, 21.4; IR (neat): 3382, 2921, 1623, 1584, 1522, 1452, 1326, 1299, 1272, 1071, 1018, 951, 911, 857, 804, 729, 640, 561, 478 cm$^{-1}$. The spectral data are in agreement with those reported previously for this compound.[49]

### 4.1.5 Synthesis of 4-amino-3-(1H-pyrrol-1-yl)benzonitrile (53)

General Procedure 1 was employed using 4-amino-3-iodobenzonitrile (100 mg, 0.4 mmol), pyrrole (31.7 mg, 0.5 mmol), *N*,*N*-dimethylethylenediamine (22.5 mg, 0.3 mmol), CuI (14.8 mg, 0.1 mmol) and $K_3PO_4$ (181.9 mg, 0.9 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 17.8 mg (25%) of the indicated product.

**53:** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 1.6 Hz, 1H), 7.38 (m, 2H), 6.8 (d, *J* = 8.4 Hz, 1H), 6.79 (t, *J* = 2.0 Hz, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.37 (t, *J* = 2.0 Hz, 1H), 4.65 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.9, 146.7, 142.8, 133.3, 132.8, 131.2, 121.5, 115.8, 113.6, 110.5, 81.9; IR (neat): 3455, 3349, 2213, 1985, 1618, 1512, 1494, 1404, 1343, 1195, 1163, 1068, 1029, 885, 814, 732, 627 cm$^{-1}$.

## 4.2 General Procedure 2. Synthesis of o-propargyloxybenzaldehydes (54-58)

The corresponding benzaldehyde (0.8 mmol) was dissolved in approximately 20 ml of dry DMF and then $K_2CO_3$ (113.1 mg, 0.8 mmol) was added to the solution under argon. Following the addition of base, propargyl bromide (87.7 μl, 1.0 mmol) was added in one portion. Reaction was stirred at room temperature overnight. Then, the content of reaction

mixture was poured into separatory funnel. Layers were separated and organic phase is washed with water (20 ml). Aqueous phase was further extracted with dichloromethane (3 x 20 ml). The collected organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator. Purification of the obtained crude product by flash chromatography on silica gel by using hexane/ethyl acetate as the eluent afforded the corresponding *o*-propargyloxybenzaldehyde.

### 4.2.1 Synthesis of 2-(prop-2-ynyloxy)benzaldehyde (54)

General Procedure 2 was employed using 2-hydroxybenzaldehyde (**87**) (100 mg, 0.8 mmol), $K_2CO_3$ (113.1 mg, 0.8 mmol) and propargyl bromide (87.7 µl, 01.0 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 111.5 mg (85%) of 2-prop-2-ynyloxy-benzaldehyde (**54**).

**54:** $^1$H NMR (400 MHz, $CDCl_3$): δ 10.48 (s, 1H), 7.85 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.57 (td, *J* = 7.2, 1.2 Hz, 1H), 7.10 (m, 2H), 4.83 (d, *J* = 2.4 Hz, 2H), 2.58 (t, *J* = 2.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 189.7, 159.9, 135.5, 128.7, 125.7, 121.8, 113.4, 77.8, 76.7, 56.6; IR (neat): 3268, 3873, 2116, 1679, 1595, 1480, 1456, 1398, 1286, 1263, 1192, 1104, 1044, 1006, 925, 832, 755, 675, 610, 526, 461, 441 $cm^{-1}$. The spectral data are in agreement with those reported previously for this compound.[53]

### 4.2.2 Synthesis of 3,5-di-tert-butyl-2-(prop-2-ynyloxy)benzaldehyde (55)

General Procedure 2 was employed using ,5-di-tert-butyl-2-hydroxybenzaldehyde (**88**) (100 mg, 0.4 mmol), $K_2CO_3$ (59.0 mg, 0.4 mmol) and propargyl bromide (46.0 µl, 0.5 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 97.1 mg (83%) of 3,5-di-tert-butyl-2-(prop-2-ynyloxy)benzaldehyde (**55**).

**55**: $^1$H NMR (400 MHz, $CDCl_3$): δ 10.38 (s, 1H), 7.72 (d, *J* = 2.4 Hz, 1H), 7.65 (d, *J* = 2.8 Hz, 1H), 4.64 (d, *J* = 2.4 Hz, 2H), 2.62 (t, *J* = 2.4 Hz, 1H), 1.46 (s, 9H), 1.33 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 191.0, 158.6, 147.3, 143.5, 131.2, 129.8, 124.8, 78.4, 76.9, 65.2, 35.6, 35.0, 31.5, 31.2; IR (neat): 3287, 2958, 1738, 1689, 1593, 1441, 1361, 1234, 1199, 1161, 1113, 989, 961, 892, 814, 750, 686, 647, 600, 548 $cm^{-1}$. The spectral data are in agreement with those reported previously for this compound.[50]

### 4.2.3 Synthesis of 5-bromo-2-(prop-2-ynyloxy)benzaldehyde (56)

General Procedure 2 was employed using 5-bromo-2-hydroxybenzaldehyde (**89**) (100 mg, 0.5 mmol), $K_2CO_3$ (68.7 mg, 0.5 mmol) and propargyl bromide (53.5 µl, 0.6 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 101.2 mg (85%) of 5-bromo-2-(prop-2-ynyloxy)benzaldehyde (**56**).

**56:** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 10.4 (s, 1H), 7.95 (m, 1H), 7.65 (m, 1H), 7.04 (d, *J* = 8.8 Hz, 1H), 4.83 (d, *J* = 2.4 Hz, 2H), 2.6 (t, *J* = 2.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 188.2, 158.8, 138.3, 131.4, 127.0, 115.6, 114.8, 77.4, 77.2, 56.9; IR (neat): 3283, 2865, 1681, 1588, 1471, 1394, 1274, 1215, 1182, 1123, 1009, 927, 875, 816, 783, 684, 645, 588, 532, 486, 440 $cm^{-1}$. The spectral data are in agreement with those reported previously for this compound.[54]

### 4.2.4 Synthesis of 4-methoxy-2-(prop-2-ynyloxy)benzaldehyde (57)

General Procedure 2 was employed using 2-hydroxy-4-methoxybenzaldehyde (**90**) (100 mg, 0.7 mmol), $K_2CO_3$ (91.1 mg, 0.7 mmol) and propargyl bromide (70.4 µl, 0.8 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 100.3 mg (80%) of 4-methoxy-2-(prop-2-ynyloxy)benzaldehyde (**57**).

**57:** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 10.31 (s, 1H), 7.84 (d, *J* = 9.2 Hz, 1H), 6.60 (m, 2H), 4.81 (d, *J* = 2.4 Hz, 2H), 3.89 (s, 3H), 2.59 (t, *J* = 2.4 Hz, 1H) ; $^{13}$C NMR (100 MHz, $CDCl_3$): δ 188.3, 166.1, 161.7, 130.9, 119.8, 107.1, 99.7, 77.8, 76.8, 56.6, 55.9; IR (neat): 3228, 2123, 1665, 1600, 1504, 1444, 1398, 1371, 1314, 1293, 1264, 1196, 1168, 1106, 1048, 1008, 938, 850, 821, 782, 750, 691, 636, 603, 561, 463, 425 $cm^{-1}$. The spectral data are in agreement with those reported previously for this compound.[55]

### 4.2.5 Synthesis of 3-methoxy-2-(prop-2-ynyloxy)benzaldehyde (58)

General Procedure 2 was employed using 2-hydroxy-3-methoxybenzaldehyde (**91**) (100 mg, 0.7 mmol), $K_2CO_3$ (91.1 mg, 0.7 mmol) and propargyl bromide (70.4 µl, 0.8 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 101.6 mg (81%) of 3-methoxy-2-(prop-2-ynyloxy)benzaldehyde (**58**).

**58:** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 10.51 (s, 1H), 7.47 (dd, *J* = 6.4, 2.0 Hz, 1H), 7.19 (m, 2H), 4.9 (d, *J* = 2.4 Hz, 2H), 3.92 (s, 3H), 2.49 (t, *J* = 2.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 190.8, 153.1, 149.7, 131.4, 125.1, 119.1, 118.0, 78.5, 77.1, 61.1, 56.3; IR (neat): 3266, 2939, 2889, 1682, 1583, 1478, 1437, 1383, 1248, 1202, 1178, 1066, 981, 910, 782, 749, 649, 529 $cm^{-1}$.

## 4.3 General Procedure 3. Synthesis of pyrroloquinoxalino-fused benzoxazepine derivatives (59-68)

The corresponding *o*-propargyloxybenzaldehyde (0.5 mmol) was dissolved in p-xylene (10 ml) and the proper pyrrole-substituted aniline (0.6 mmol) was added in one portion under argon. After reaction was stirred for half an hour, $InCl_3$ (0.01 mmol) was added. The resulting reaction mixture was then refluxed at 140 °C for 2 h. After the reaction was over,

*p*-xylene was removed under reduced pressure. Purification of the obtained crude product by flash column chromatography on silica gel using hexane/ethyl acetate as the eluent afforded the corresponding benzoxazepine derivative.

### 4.3.1 Synthesis of 10-methyl-16b*H*-pyrrolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepine (59)

General Procedure 3 was followed using 2-(prop-2-ynyloxy)benzaldehyde (**54**) (0.1g, 0.6 mmol), 2-(1H-pyrrol-1-yl)aniline (**48**) (120 mg, 0.8 mmol) and $InCl_3$ (2.2 mg, 0.01 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 128.5 mg (68%) of benzoxazepine **59**.

**59:** $^1$H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.33 (m, 1H), 7.08 (td, *J* = 7.8, 1.2 Hz, 1H), 6.92 (m, 3H), 6.70 (t, 7.2 Hz, 1H), 6.66 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.46 (t, 3.2 Hz, 1H), 6.43 ( s, 1H), 6.30 (m, 2H), 6.19 (dd, *J* = 3.6, 1.6 Hz, 1H), 1.84 (d, 1.2 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.6, 134.7, 133.1, 132.9, 129.2, 127.7, 127.0, 126.0, 124.9, 122.7, 121.0, 120.2, 119.8, 117.7, 115.1, 114.7, 110.4, 105.9, 57.7, 17.0 ($CH_3$); IR (neat): 3855, 3651, 2240, 2144, 2069, 2031, 1965, 1751, 1509, 1213, 1123, 761, 693, 562, 493, 459, 426, 406 cm$^{-1}$; MS (ESI, *m/z*): 299.12 $[M-H]^+$; HRMS (ESI): calc. for $C_{20}H_{15}N_2O$: 299.1184 $[M-H]^+$, found: 299.1162.

### 4.3.2 Synthesis of 13,15-di-tert-butyl-10-methyl-16b*H*-pyrrolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepine (60)

General Procedure 3 was followed using 2-(prop-2-ynyloxy)benzaldehyde (**54**) (0.1g, 0.4 mmol), 2-(1H-pyrrol-1-yl)aniline (**48**) (69.5 mg, 0.4 mmol) and $InCl_3$ (2.2 mg, 0.01 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 108.8 mg (71%) of benzoxazepine (**60**).

**60:** $^1$H NMR (400 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 8.0,1.6 Hz, 1H), 7.32 (dd, *J* = 2.8, 1.6 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 6.93 (td, *J* = 8.0, 1.6 Hz, 1H), 6.86 (td, *J* = 7.6, 1.2 Hz, 1H), 6.57 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.47 ( s, 1H), 6.44 (t, *J* = 3.2 Hz, 1H), 6.35 (d, *J* = 1.2 Hz, 1H), 6.18 (dd, *J* = 3.2, 1.2 Hz, 1H), 6.05 (d, *J* = 2.4 Hz, 1H), 1.84 (d, *J* = 0.8 Hz, 3H), 1.39 (s, 9H), 1.01 (s, 9H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 152.0, 144.6, 139.8, 134.1, 133.9, 133.1, 128.1, 127.1, 124.7, 123.2, 122.0, 121.8, 120.3, 118.0, 114.9, 114.3, 110.5, 105.6, 57.4, 34.9, 34.4, 31.3, 30.4, 17.0 ($CH_3$); IR (neat): 2960, 1508, 1475, 1334, 1253, 1215, 1138, 1088, 794, 773, 747, 697 cm$^{-1}$; MS (ESI, *m/z*): 411.24 $[M-H]^+$; HRMS (ESI): calc. for $C_{28}H_{31}N_2O$: 411.2436 $[M-H]^+$, found: 411.2427.

### 4.3.3 Synthesis of 7-chloro-10-methyl-16b*H*-pyrrolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepine (61)

General Procedure 3 was followed using 2-(prop-2-ynyloxy)benzaldehyde (**54**) (0.1g, 0.6

mmol), 5-chloro-2-(1H-pyrrol-1-yl)aniline (**50**) (100.1 mg, 0.5 mmol) and $InCl_3$ (2.2 mg, 0.01 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 174.6 mg (83%) of benzoxazepine (**61**).

**61:** $^1$H NMR (400 MHz, $CDCl_3$): δ 7.44 (m, 2H), 7.28 (td, *J* = 7.6, 1.6 Hz, 1H), 7.11 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.00 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.91 (*J* = 7.6, 1.2 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 6.63 ( t, *J* = 3.2 Hz, 1H), 6.57 (s, 1H), 6.49 (d, *J* = 1.2 Hz, 1H), 6.45 ( dd, *J* = 7.6, 1.2 Hz, 1H), 6.36 ( dd, *J* = 3.6, 1.2 Hz, 1H), 2.01 ( d, *J* = 1.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.3, 135.3, 134.1, 132.7, 130.1, 129.4, 126.9, 126.3, 125.6, 122.9, 120.3, 120.0, 119.9, 117.4, 116.0, 114.8, 110.8, 106.3, 57.9, 16.7 ($CH_3$); IR (neat): 3855, 1664, 1604, 1509, 1480, 1449, 1386, 1341, 1267, 1212, 1116, 990, 874, 810, 794, 765, 723, 695, 632, 550, 453 $cm^{-1}$; MS (ESI, *m/z*): 333.08 $[M-H]^+$; HRMS (ESI): calc. for $C_{20}H_{14}ClN_2O$: 333.0795 $[M-H]^+$, found: 333.0781.

### 4.3.4 Synthesis of 13-methoxy-10-methyl-16b*H*-pyrrolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepine (62)

General Procedure 3 was followed using 2 methoxy-2-(prop-2-ynyloxy)benzaldehyde **58** **(**0.1g, 0.5 mmol), 2-(1H-pyrrol-1-yl)aniline (**48**) (99.8 mg, 0.6 mmol) and $InCl_3$ (2.2 mg, 0.01 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 106.7 mg (61%) of benzoxazepine (**62**).

**62:** $^1$H NMR (400 MHz, $CDCl_3$): δ 7.38 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.31 (m, 1H), 6.96 (td, *J* = 7.6, 1.2 Hz, 1H), 6.88 (td, *J* = 7.6, 1.2 Hz, 1H), 6.72 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.64 (m, 2H), 6.48 (s, 1H), 6.44 (t, *J* = 3.2 Hz, 1H), 6.43 (d, *J* = 1.2 Hz, 1H), 6.18 (dd, *J* = 7.6, 1.2 Hz, 1H), 5.89 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.83 (s, 3H), 1.83 (d, *J* = 0.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 149.8, 144.2, 134.8, 134.5, 132.8, 127.8, 126.2, 124.8, 122.7, 121.4, 120.3, 118.7, 117.8, 115.0, 114.6, 112.2, 110.4, 105.9, 57.5, 56.3, 16.9 ($CH_3$); IR (neat): 2836, 1671, 1583, 1507, 1474, 1381, 1337, 1255, 1205, 1179, 1123, 1070, 987, 928, 811, 777, 753, 670, 607 $cm^{-1}$; MS (ESI, *m/z*): 329.13 $[M-H]^+$; HRMS (ESI): calc. for $C_{21}H_{17}N_2O_2$: 329.1290 $[M-H]^+$, found: 329.1267.

### 4.3.5 Synthesis of 15-bromo-10-methyl-16b*H*-pyrrolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepine (63)

General Procedure 3 was followed using 5-bromo-2-(prop-2-ynyloxy)benzaldehyde **(56**) **(**0.1g, 0.4 mmol), 2-(1H-pyrrol-1-yl)aniline (**48**) (79.7 mg, 0.5 mmol) and $InCl_3$ (2.2 mg, 0.01 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 81.2 mg (51%) of benzoxazepine (**63**).

**63:** $^1$H NMR (400 MHz, $CDCl_3$): δ 7.41 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.33 (m, 1H), 7.18 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.99 (td, *J* = 7.6, 1.2 Hz, 1H), 6.91 (td, *J* = 8.0, 1.2 Hz, 1H), 6.79

(d, J = 8.4 Hz, 1H), 6.67 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.45 (s, 1H), 6.39 (m, 2H), 6.28 (d, *J* = 1.2 Hz, 1H), 6.19 (dd, *J* = 7.6, 2.8 Hz, 1H), 1.83 (d, *J* = 1.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 154.7, 135.3, 134.5, 132.5, 132.1, 129.7, 127.5, 125.0, 124.8, 121.7, 121.4, 120.6, 117.6, 115.4, 115.3, 115.1, 110.6, 106.3, 57.5, 16.8 ($CH_3$); IR (neat): 1668, 1608, 1509, 1471, 1399, 1336, 1292, 1258, 1216, 1189, 1163, 1124, 1095, 871, 831, 784, 770, 741, 700, 605, 543, 516, 496, 462 cm$^{-1}$; MS (ESI, *m/z*): 377.03 $[M-H]^+$; HRMS (ESI): calc. for $C_{20}H_{15}BrN_2O$: 377.0290 $[M-H]^+$, found: 377.0278.

### 4.3.6 Synthesis of 7-methyl-18b*H*-indolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepine (64)

General Procedure 3 was followed using 2-(prop-2-ynyloxy)benzaldehyde (**54**) (0.1g, 0.6 mmol), and 2-(1H-indol-1-yl)aniline (**49**) (108.3 mg, 0.5 mmol)and $InCl_3$ (2.2 mg, 0.01 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 110.3 mg (50%) of benzoxazepine (**64**).

**64:** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.0 Hz, 1H), 7.99 (m, 1H), 7.79 (d, *J* = 7.6 Hz, 1H), 7.41 (m, 1H), 7.33 (m, 1H), 7.12 (td, *J* = 8.0, 1.6 Hz, 1H), 7.05 (m, 2H), 7.00 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.78 (m, 1H), 6.69 (td, *J* = 7.2, 1.2 Hz, 1H), 6.63 (s, 1H), 6.61 (s, 1H), 6.47 (dd, *J* =7.6, 1.6 Hz, 1H), 6.41 (d, *J* = 1.2 Hz, 1H), 1.88 (d, *J* = 1.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.8, 134.7, 134.4, 134.3, 133.9, 131.9, 129.7, 129.3, 129.0, 127.1, 124.6, 122.8, 121.5, 121.4, 121.0, 120.9, 119.9, 118.2, 117.1, 112.0, 100.2, 58.4, 22.9, 17.3 ($CH_3$); IR (neat): 2922, 1590, 1500, 1452, 1384, 1214, 1122, 744 cm$^{-1}$; MS (ESI, *m/z*): 349.13 $[M-H]^+$; HRMS (ESI): calc. for $C_{24}H_{18}N_2O$: 349.1341 $[M-H]^+$, found: 349.1329.

### 4.3.7 Synthesis of 14-methoxy-10-methyl-16bH-pyrrolo[2',1':3,4]quinoxalino[1,2-d][1,4]benzoxazepine (65)

General Procedure 3 was followed using -methoxy-2-(prop-2-ynyloxy)benzaldehyde (**57**) **(**0.1g, 0.5 mmol), 2-(1H-pyrrol-1-yl)aniline (**48**) (99.8 mg, 0.6 mmol) and $InCl_3$ (2.2 mg, 0.01 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 82.2 mg (47%) of benzoxazepine (**65**).

**65:** $^1$H NMR (400 MHz, $CDCl_3$): δ 7.37 (dd, *J* =8.0, 1.2 Hz, 1H), 7.29 (m, 1H), 6.97 (td, *J* = 7.6, 1.6 Hz, 1H), 6.86 (td, *J* = 7.6, 1.2 Hz, 1H), 6.64 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.43 (t, *J* = 3.2 Hz, 1H), 6.33 (s, 1H), 6.28 (d, *J* = 1.2 Hz, 1H), 6.21 (m, 2H), 6.15 (dd, *J* = 7.6, 1.6 Hz, 1H), 3.67 (s, 3H), 1.83 (d, *J* = 0.8 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 160.1, 156.1, 134.4, 132.9, 127.48, 127.46, 126.1, 125.3, 124.7, 120.9, 120.0, 117.4, 114.9, 114.4, 110.2, 107.7, 105.7, 105.6, 57.3, 55.3, 16.8 ($CH_3$); IR (neat): 1669, 1611, 1503, 1423, 1377, 1338, 1282, 1241, 1187, 1164, 1131, 1085, 1036, 980, 852, 801, 771, 749, 708, 637, 567, 487, 546 cm$^{-1}$; MS (ESI, *m/z*): 329.13 $[M-H]^+$; HRMS (ESI): calc. for $C_{21}H_{17}N_2O_2$: 329. 1290 $[M-H]^+$, found: 329. 1273.

### 4.3.8 Synthesis of 7-methyl-2,4-di-tert-butyl-5,18b-dihydroindolo[2',1':3,4]quinoxalino[2,1-*a*][2]benzazepine (66)

General Procedure 3 was followed using 3,5-di-tert-butyl-2-(prop-2-ynyloxy)benzaldehyde (**55**) **(**0.1g, 0.4 mmol), 2-(1H-indol-1-yl)aniline (**49**) (91.8 mg, 0.4 mmol) and $InCl_3$ (2.2 mg, 0.01 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 68.4 mg (40%) of benzoxazepine (**66**).

**66:** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.91 (dd, *J* = 7.6, 2.0 Hz, 1H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.35 (td, *J* = 8.4, 1.2 Hz, 1H), 7.27 (t, *J* = 6.0 Hz, 1H), 7.1 (d, *J* = 2.4 Hz, 1H), 6.98 (m, 2H), 6.61 (m, 2H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.40 (d, *J* = 1.2 Hz, 1H), 6.20 (d, *J* = 2.4 Hz, 1H), 1.82 (d, *J* = 1.2 Hz, 3H), 1.4 (s, 9H), 0.94 (s, 9H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 152.3, 145.0, 140.0, 132.9, 135.6, 134.6, 134.0, 130.0, 124.6, 123.2, 122.6, 122.4, 121.9, 121.6, 121.2, 121.0, 118.6, 117.0, 111.9, 100.1, 58.1, 34.9, 34.5, 31.3, 30.5, 17.3 ($CH_3$); IR (neat): 2954, 1591, 1501, 1452, 1380, 1380, 1360, 1285, 1243, 1214, 1132, 881, 795, 772, 745, 726, 680, 435 cm$^{-1}$; MS (ESI, *m/z*): 461.26 $[M-H]^+$; HRMS (ESI): calc. for $C_{32}H_{33}N_2O$: 461.2593 $[M-H]^+$, found: 461.2569.

### 4.3.9 Synthesis of 2-bromo-7-methyl-18b*H*-indolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepine (67)

General Procedure 3 was followed using 25-bromo-2-(prop-2-ynyloxy)benzaldehyde (**56**) **(**0.1g, 0.4 mmol), 2-(1H-indol-1-yl)aniline (**49**) (104.9 mg, 0.5 mmol) and $InCl_3$ (2.2 mg, 0.01 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 66.7 mg (37%) of benzoxazepine (**67**).

**67:** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.97 (m, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.39 ( td, *J* = 7.0, 1.2 Hz, 1H), 7.29 (s, 1H), 7.18 (dd, *J* = 8.8, 2.4, 1H), 7.05 (m, 2H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.75 (m, 1H), 6.57 (s, 1H), 6.52 (m, 2H), 6.33 (d, *J* = 1.2 Hz, 1H), 1.83 (d, *J* = 1.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 155.0, 134.5, 134.03, 134.0, 133.9, 133.3, 132.3, 129.7, 129.6, 128.8, 124.7, 123.0, 121.9, 121.6, 121.5, 121.44, 121.4, 118.2, 117.4, 115.5, 112.1, 100.7, 58.1, 17.1 ($CH_3$); IR (neat): 1669, 1589, 1500, 1452, 1391, 1257, 1216, 1165, 1121, 1094, 825, 786, 743, 730, 665, 610, 521, 431 cm$^{-1}$; MS (ESI, *m/z*): 427.04 $[M-H]^+$; HRMS (ESI): calc. for $C_{24}H_{17}BrN_2O$: 427.0446 $[M-H]^+$, found: 427.0423.

### 4.3.10 Synthesis of 3-methoxy-7-methyl-18b*H*-indolo[2',1':3,4]quinoxalino[1,2-*d*][1,4]benzoxazepine (68)

General Procedure 3 was followed using -methoxy-2-(prop-2-ynyloxy)benzaldehyde (**57**) **(**0.1g, 0.5 mmol), 2-(1H-indol-1-yl)aniline (**49**) (132.3 mg, 0.6 mmol) and $InCl_3$ (2.2 mg,

0.01 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 50.4 mg (25%) of benzoxazepine (**68**).

**68:** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.92 (m, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.34 (m, 1H), 7.25 (m, 1H), 7.01 (m, 2H), 6.73 (m, 1H), 6.53 (s, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 6.47 (s, 1H), 6.33 (m, 1H), 6.29 (d, *J* = 8.8 Hz, 1H), 6.17 ( dd, *J* = 8.4, 2.4 Hz, 1H), 3.66 (s, 3H), 1.83 ( d, *J* = 1.2 Hz, 3H). $^{13}$C NMR (100 MHz, $CDCl_3$): δ 156.6, 134.62, 134.6, 134.5, 133.9, 129.7, 127.8, 124.6, 124.2, 122.7, 121.5, 121.3, 121.2, 120.8, 118.2, 117.1, 112.0, 108.0, 105.9, 100.1,58.1, 55.5, 17.4 ($CH_3$); IR (neat): 3333, 2929, 1731, 1611, 1500, 1454, 1358, 1240, 1195, 1160, 1120, 1040, 734 $cm^{-1}$.

### 4.3.11 Synthesis of 4-methyl-4-(4-phenyl-2H-chromen-8-yl)-4,5-dihydropyrrolo[1,2-a]quinoxaline (105)

General Procedure 3 was followed using 1-(2-(3-phenylprop-2-ynyloxy)phenyl)ethanone (**95**) **(**0.1g, 0.4 mmol), 2-(1H-pyrrol-1-yl)aniline (**48**) (75.8 mg, 0.5 mmol) and $InCl_3$ (2.2 mg, 0.01 mmol). Purification of the crude product by flash column chromatography on silica gel using 19:1 hexane/ethyl acetate as the eluent afforded 240.8 mg (98%) of benzoxazepine (**105**).

**105:** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.41 (m, 3H), 7.33 (m, 4H), 6.94 (td, *J* = 9.2, 1.2 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.81 (d, *J* = 8.0 Hz, 2H), 6.59 (t, *J* = 8.0 Hz, 1H), 6.50 (t, *J* = 3.6 Hz, 1H), 6.35 ( dt, *J* = 5.2, 2.0 Hz, 2H), 5.91 (t, *J* = 4.0 Hz, 1H), 5.85 (s, 1H), 4.98 (t, *J* = 4.0 Hz, 2H), 2.15 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 151.5, 138.4, 137.8, 136.4, 133.7, 131.9, 129.0, 128.8, 128.5, 128.0, 126.0, 125.6, 124.7, 120.8, 119.4, 119.34, 119.3, 116.1, 114.8, 114.6, 109.9, 105.7, 65.0, 57.5, 26.6 ($CH_3$); IR (neat): 3378, 2840, 1599, 1513, 1484, 1415, 1335, 1295, 1185, 1090, 920, 799, 740, 696, 663, 611, 563, 461 $cm^{-1}$.

## 4.4 Synthesis of dimethyl 2-(prop-2-ynylamino)maleate (69)

Dimethyl acetylenedicarboxylate (0.1 g, 0.7 mmol) was dissolved in acetonitrile (10 ml) and propargyl amine (0.1 g, 1.8 mmol) was added slowly to the mixture. Reaction was stirred half an hour at room temperature. After the reaction was over, acetonitrile was removed on a rotary evaporator. Purification of the obtained crude product by flash column chromatography on silica gel by using 4:1 hexane/ethyl acetate as the eluent afforded 96.6 mg (70%) of dimethyl 2-(prop-2-ynylamino)maleate (**69**).

**69:** $^{1}$H NMR (400 MHz, $CDCl_3$): δ 6.03 (s, 1H), 5.25 (s, 1H), 4.13 (dd, *J* = 6.4, 2.4 Hz, 2H), 3.77 (s, 3H), 3.61 (s, 3H), 2.52 (t, *J* = 2.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 170.0, 163.7, 150.0, 90.8, 90.2, 72.1, 52.7, 50.9, 34.0.

### 4.5 Synthesis of 5-iodopyridine-2,3-dicarboxylate (70)

A mixture of dimethyl 2-(prop-2-ynylamino)maleate (**69**), $NaHCO_3$ (127.8 mg, 1.5 mmol) and $I_2$ (386.1 mg, 1.5 mmol) was refluxed in acetonitrile at 82 °C for 21 h. After the reaction was over, acetonitrile was removed on a rotary evaporator. The crude product was dissolved in ethyl acetate (15 ml) and washed with a saturated aqueous solution of $Na_2S_2O_3$ (30 ml) in a separatory funnel to remove the excess $I_2$. The aqueous solution was then extracted with
ethyl acetate (3 x 15 ml). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator. Purification of the obtained crude product by flash column chromatography on silica gel using 9:1 hexane/ ethyl acetate as the eluent afforded 87.9 mg (54%) of dimethyl 5-iodopyridine-2,3-dicarboxylates (**70**).

**70:** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.96 (d, *J* = 2.0 Hz, 1H), 8.47 (d, *J* = 2.0 Hz, 1H), 3.99 (s, 3H), 3.94 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.2, 164.8, 157.9, 149.1, 145.7, 128.2, 95.0, 53.44, 53.41; IR (neat): 2954, 1731, 1428, 1277, 1137, 1076, 771 $cm^{-1}$.

### 4.6 General Procedure 4. Synthesis of 5-alkynylpyridines (79-86)

To a stirred solution of dimethyl 5-iodopyridine-2,3-dicarboxylate (**70**) (0.7 mmol) in THF (1.5 ml) under argon was added $Et_3N$ (0,01 mol, 1.5 ml), $PdCl_2(PPh_3)_2$ (0.04 mmol), CuI (0.04 mmol) and the corresponding terminal alkyne (1.1 mmol) were added in turn. The resulting reaction mixture was heated at 65 °C over 4 h. After the removal of THF under reduced pressure, purification of the obtained crude product by flash column chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent afforded the corresponding 5-alkynylpyridine derivative.

#### 4.6.1 Synthesis of dimethyl 5-(phenylethynyl)pyridine-2,3-dicarboxylate (79)

General Procedure 4 was employed using dimethyl 5-iodopyridine-2,3-dicarboxylate (**70**) (0.1 g, 0.3 mmol), $Et_3N$ (0.01 mol, 1.5 ml), $PdCl_2(PPh_3)_2$ (10.5 mg, 0.02 mmol), CuI (2.9 mg, 0.02 mmol) and phenylacetylene (**71**) (45.9 mg, 0.5 mmol). Purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 59.3 mg (67%) of the corresponding 5-alkynylpyridine **79**.

**79:** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, *J* = 1.6 Hz, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 7.55 (m, 2H), 7.38 (m, 3H), 4.00 (s, 3H), 3.94 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.1, 165.6, 153.6, 148.2, 139.6, 132.0, 129.6, 128.7, 126.9, 122.6, 121.9, 95.9, 84.5, 53.3, 53.2; IR (neat): 2210, 1717, 1542, 1433, 1304, 1265, 1138, 1066, 949, 909, 832, 805, 773, 757, 688, 665, 529, 477 $cm^{-1}$.

#### 4.6.2 Synthesis of dimethyl 5-((3-fluorophenyl)ethynyl)pyridine-2,3-dicarboxylate (80)

General Procedure 4 was employed using dimethyl 5-iodopyridine-2,3-dicarboxylate (**70**)

(0.1 g, 0.3 mmol), $Et_3N$ (0.01 mol, 1.5 ml), $PdCl_2(PPh_3)_2$ (10.5 mg, 0.02 mmol), CuI (2.9 mg, 0.02 mmol) and 1-ethynyl-3-fluorobenzene (**72**) (54.1 mg, 0.5 mmol). Purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl

acetate as the eluent afforded 75.1 mg (80%) of the corresponding 5-alkynylpyridine **80**.

**80:** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, *J* = 2.0 Hz, 1H), 8.24 (d, *J* = 2.0 Hz, 1H), 7.25 (m, 2H), 7.11 (m, 1H), 7.06 (m, 1H), 4.01 (s, 3H), 3.95 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.1, 165.5, 162.6 (d, *J* = 246.1 Hz), 153.7, 148.7, 139.8, 130.4 (d, *J* = 8,5 Hz), 128.0 (d, *J* = 3.0 Hz), 126.9, 123.7 (d, *J* = 9.6 Hz), 122.1, 118.8 (d, *J* = 22.9 Hz), 117.1 (d, *J* = 21.0 Hz), 94.4 (d, *J* = 2.7 Hz), 85.2, 53.4, 53.3; IR (neat): 2948, 1732, 1541, 1427, 1306, 1272, 1133, 1076, 964, 887, 825, 790, 684, 524 $cm^{-1}$.

### 4.6.3 Synthesis of dimethyl dimethyl 5-(thiophen-3-ylethynyl)pyridine-2,3-dicarboxylate (81)

General Procedure 4 was employed using dimethyl 5-iodopyridine-2,3-dicarboxylate (**70**) (0.1 g, 0.3 mmol), $Et_3N$ (0.01 mol, 1.5 ml), $PdCl_2(PPh_3)_2$ (10.5 mg, 0.02 mmol), CuI (2.9 mg, 0.02 mmol) and 3-ethynylthiophene (**73**) (48.6 mg, 0.5 mmol). Purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 65.0 mg (72%) of the corresponding 5-alkynylpyridine **81**.

**81:** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, *J* = 2.0 Hz, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 7.64 (dd, *J* = 2.8, 1.2 Hz, 1H), 7.35 (dd, *J* = 6.4, 2.8 Hz, 1H), 7.23 (dd, *J* = 4.8, 1.2 Hz, 1H), 4.01 (s, 3H), 3.95 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.2, 165.6, 153.5, 148.1, 139.5, 130.7, 129.9, 127.0, 126.1, 122.7, 121.0, 91.2, 84.2, 53.4, 53.3; IR (neat): 3853, 3839, 3735, 3689, 3675, 3649, 3567, 2369, 1717, 1684, 1653, 1558, 1541, 1507, 1473, 1457, 1434, 1308, 1261, 1132, 1069, 947, 915, 797, 780, 703, 624, 457, 420 $cm^{-1}$.

### 4.6.4 Synthesis of dimethyl 5-(3-cyclopentylprop-1-ynyl)pyridine-2,3-dicarboxylate (82)

General Procedure 4 was employed using dimethyl 5-iodopyridine-2,3-dicarboxylate (**70**) (0.1 g, 0.3 mmol), $Et_3N$ (0.01 mol, 1.5 ml), $PdCl_2(PPh_3)_2$ (10.5 mg, 0.02 mmol), CuI (2.9 mg, 0.02 mmol) and 3-cyclopentyl-1-propyne (**74**) (48.6 mg, 0.5 mmol. Purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 74.0 mg (82%) of the corresponding 5-alkynylpyridine **82**.

**82:** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, *J* = 2.0 Hz, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 3.97 (s, 3H), 3.91 (s, 3H), 2.44 (d, *J* = 2.8 Hz, 2H), 2.13 (m, 1H), 1.84 (m, 2H), 1.60 (m, 4H), 1.33 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.2, 165.9 ,153.8, 139.7, 127.0, 123.5, 97.7, 76.3, 53.3, 53.2, 39.0 ,32.3, 25.5, 25.4; IR (neat): 2952, 2225, 1728, 1543, 1434, 1299, 1240, 1134, 1076, 960, 919, 775, 730 $cm^{-1}$.

### 4.6.5 Synthesis of dimethyl 5-(p-tolylethynyl)pyridine-2,3-dicarboxylate (83)

General Procedure 4 was employed using dimethyl 5-iodopyridine-2,3-dicarboxylate (**70**) (0.1 g, 0.3 mmol), $Et_3N$ (0.01 mol, 1.5 ml), $PdCl_2(PPh_3)_2$ (10.5 mg, 0.02 mmol), CuI (2.9 mg, 0.02 mmol) and 4-ethynyltoluene (**75**) (52.2 mg, 0.5 mmol). Purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 58.4 mg (63%) of the corresponding 5-alkynylpyridine **83**.

**83:** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, *J* = 2.0 Hz, 1H), 8.22 (d, *J* = ‘.0 Hz, 1H), 7.47 (s, 1H), 7.45 (s, 1H), 7.21 (s, 1H), 7.19 (s, 1H), 4.01 (s, 3H), 3.96 (s, 3H), 2.4 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.2, 153.6, 140.1, 139.6, 132.0, 129.6, 127.0, 123.0, 118.9, 96.4, 84.0, 53.4, 53.3, 21.8; IR (neat): 2214, 1732, 1542, 1508, 1430, 1306, 1267, 1132, 1077, 959, 918, 823, 771, 662, 533, 418 $cm^{-1}$.

### 4.6.6 Synthesis of dimethyl 5-(m-tolylethynyl)pyridine-2,3-dicarboxylate (84)

General Procedure 4 was employed using dimethyl 5-iodopyridine-2,3-dicarboxylate (**70**) (0.1 g, 0.3 mmol), $Et_3N$ (0.01 mol, 1.5 ml), $PdCl_2(PPh_3)_2$ (10.5 mg, 0.02 mmol), CuI (2.9 mg, 0.02 mmol) and 3-ethynyltoluene (**76**) (52.2 mg, 0.5 mmol).). Purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 72.3 mg (78%) of the corresponding 5-alkynylpyridine **84**.

**84:** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, *J* = 2.0 Hz, 1H), 8.22 (d, *J* = 2.0 Hz, 1H), 7.38 (m, 2H), 7.27 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 4.01 (s, 3H), 3.95 (s, 3H), 2.37 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.2, 165.7, 153.6, 139.6, 138.5, 132.6, 130.6, 129.2, 128.6, 127.0, 122.8, 121.7, 96.2, 84.2, 53.4, 53.3, 21.4; IR (neat): 3853, 3735, 3675, 3649, 2214, 1737, 1653, 1541, 1507, 1457, 1309, 1273, 1131, 1076, 955, 920, 787, 692, 666, 419 $cm^{-1}$.

### 4.6.7 Synthesis of dimethyl 5-((4-methoxyphenyl)ethynyl)pyridine-2,3-dicarboxylate (85)

General Procedure 4 was employed using dimethyl 5-iodopyridine-2,3-dicarboxylate (**70**) (0.1 g, 0.3 mmol), $Et_3N$ (0.01 mol, 1.5 ml), $PdCl_2(PPh_3)_2$ (10.5 mg, 0.02 mmol), CuI (2.9 mg, 0.02 mmol) and 4-ethynylanisole (**77**) (59.4 mg, 0.5 mmol). Purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 71.2 mg (73%) of the corresponding 5-alkynylpyridine **85**.

**85: :** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.82 (d, *J* = 2.0 Hz, 1H), 8.19 ( d, *J* = 2.0 Hz, 1H), 7.51 (s, 1H), 7.49 (s, 1H), 6.92 (s, 1H), 6.90 (s, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 3.84 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 166.2, 165.8, 160.8, 153.4, 147.7, 139.4, 133.7, 127.1, 123.1, 114.4, 113.9, 96.4, 83.6, 55.6, 53.4, 53.3; IR (neat): 3853, 3735, 3675, 3649, 2208, 1720, 1653, 1605, 1541, 1508, 1457, 1436, 1305, 1248, 1140, 1072, 1027, 955, 830, 808, 770, 662, 537, 420 $cm^{-1}$.

### 4.6.8 Synthesis of dimethyl 5-((4-(trifluoromethyl)phenyl)ethynyl)pyridine-2,3-dicarboxylate (86)

General Procedure 4 was employed using dimethyl 5-iodopyridine-2,3-dicarboxylate (**70**) (0.1 g, 0.3 mmol), $Et_3N$ (0.01 mol, 1.5 ml), $PdCl_2(PPh_3)_2$ (10.5 mg, 0.02 mmol), CuI (2.9 mg, 0.02 mmol) and 4-ethynyl-alpha,alpha,alpha-trifluorotoluene (**78**) (76.5 mg, 0.5 mmol). Purification of the crude product by flash column chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent afforded 88.3 mg (81%) of the corresponding 5-alkynylpyridine **86**.

**86:** $^1$H NMR (400 MHz, $CDCl_3$): δ 8.88 (m, 1H), 8.27 (m, 1H), 7.66 (m, 4H), 4.01 (s, 3H), 3.96 (s, 3H); NMR (100 MHz, $CDCl_3$): δ 166.1, 165.4, 153.8, 149.0, 140.0, 132.3, 126.8, 125.7 (d, $J$ = 3.7 Hz), 125.3, 122.6, 121.9, 94.1, 86.6, 53.4, 53.3; IR (neat): 3735, 3649, 1722, 1610, 1541, 1436, 1400, 1320, 1168, 1103, 1077, 1062, 1013, 960, 918, 842, 797, 772, 729, 624, 598 $cm^{-1}$.

## REFERENCES


**[1]** McMurry J.; Simanek E. E. *Fundamentals of Organic Chemistry*, 6th Ed., Thomson Brooks/Cole: New York, 2007.

**[2]** Bansa R. K., *Heterocyclic Chemistry,* 3rd Ed., New Age International Ltd.: New Delhi, 1999.

**[3]** Balaban, A. T.; Oniciu, D. C.; Katritzky, A. R. *Chem. Rev.* **2004**, *104,* 2777−2812.

**[4]** Builla J. A.; Vaguero J. J.; Barluenga J. *Modern Heterocyclic Chemistry*, Volume 4, Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2011.

**[5]** Rosowski A. *The Chemistry of Heterocyclic Compounds, Seven-Membered Heterocyclic Compounds Containing Oxygen and Sulfur,* John Wiley & Sons: New York, 2009.

**[6]** Lin, S. K. Lewis Acids in Organic Synthesis By Yamamoto, Hisashi. *Molecules* 2000, *5*, 1522-1523.

**[7]** Gilman, H., Jones, R. G. *J. Am. Chem. Soc.* **1940**, *62*, 2353-2357.

**[8]** Cintas, P. *Synlett* **1995**, 1087-1096.

**[9]** Ranu, B. C. *Eur. J. Org. Chem*. **2000**, *2000*, 2347-2356.

**[10]** Yamamoto H., Ishihara K. *Acid Catalysis in Modern Organic Synthesis*, Volume 1,Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2008.

**[11]** Mikolajczak, C.; Jackson, B., *Availability of Indium and Gallium,* Indium Corporation TechPaper, 2012.

**[12]** Marshall J. A.; HinMe K. W. *J. Org. Chem.* **1995**, *60*, 1920-1921.

**[13]** Yasuda, M.; Miyai, T.; Shibata, I.; Baba, A.; Nomura, R.; Matsuda, H. *Tetrahedron Lett.* **1995**, *36*, 9497-9500.

**[14]** Ranu, B. C.; Hajra, A.; Jana, U. *Tetrahedron Lett.* **2000**, *41*, 531-533.

**[15]** Miles, R. B.; Davis, C. E.; Coates, R. M. *J. Org. Chem.* **1996**, *71*, 1493-501.

**[16]** Nagase, Y.; Shirai, H.; Kaneko, M.; Shirakawa, E.; Tsuchimoto, T. *Org. Biomol. Chem.,* **2013**, *11*, 1456–1459.

**[17]** Patidar, A. K.; Jeyakandan, M.; Mobiya, A. K.; Selvam, G. *Int. J. Pharm. Tech. Res*. **2011**, *3*, 386-392.

**[18]** Paul, S.; Basu, B.; *Tetrahedron Lett.* **2011**, *52*, 6597–6602.

**[19]** Chen, Y.; Li, K.; Zhao, M.; Li, Y.; Chen, B. *Tetrahedron Lett.* **2013**, *54*, 1627-1630.

**[20]** Mamedov, V. A.; Kalinin, A. *Chem. Heterocycl. Com*. **2011**, *46*, 1423-1442.

**[21]** Vidaillac, C.; Guillon, J.; Arpin, C.; Forfar-Bares, I.; Ba, B. B.; Grellet, J.; Moreau, S.; Caignard, D. H.; Jarry, C.; Quentin, C. *Antimicrob. Agents Ch.* **2007**, *51*, 831–838.

**[22]** Grande, F.; Aiello, F.; De Grazia, O.; Brizzi, A.; Garofalo, A.; Neamati, N. *Bioorgan. Med. Chem*. **2007**, *15*, 288–294.

**[23]** Guillon, J.; Forfar, I.; Mamani-Matsuda, M.; Desplat, V.; Saliege, M.;Thiolat, D.; Massip, S.;Tabourier, A.; Leger, J.-M.; Dufaure, B.; Haumont, G.; Jarry, C.; Mossalayi, D. *Bioorgan. Med. Chem*. **2007**, *15*, 194–210.

**[24]** Campiani, G.; Morelli, E.; Gemma, S.; Nacci, V.; Butini, S.; Hamon, M.; Novellino, E.; Greco, G.; Cagnotto, A.; Goegan, M.; Cervo, L.; Dalla Valle, F.; Fracasso, C.; Caccia, S.; Mennini, T. *J. Med. Chem.* **1999**, *42*, 4362–4379.

**[25]** Pereira, M. F.; Thiery V. *Org. Lett.* **2012**, *14*, 4754-4757.

**[26]** Liu, G.; Zhou, Y.; Lin, D.; Wang, J.; Zhang, L; Jiang, H.; Liu, H. *ACS Comb. Sci.* **2011**, *13*, 209–213.

**[27]** Armengol, M.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 978-984.

**[28]** Zora M.; Kivrak A. Abstracts of Papers. 243th National Meeting of American Chemical Society, San Diego, California; March 25-29, 2012; American Chemical Society; Washington, DC, 2012; ORGN 608.

**[29]** Zora M.; Kivrak A.; Yazc N. E. Abstracts of Papers. 243th National Meeting of American Chemical Society, San Diego, California; March 25-29, 2012; American Chemical Society; Washington, DC, 2012; ORGN 348.

**[30]** Rustagi, V.; Aggarwal T.; Verma A. K. *Green Chem.* **2011**, *13*, 1640.

**[31]** Patil, N. T.; Mutyala, A. K.; Lakshmi, P. G. V.; Raju, P. V: K.; Sridhar, B. *Eur. J. Org. Chem.* **2010**, *2010*, 1999–2007.

**[32]** Chaubey A.; Pandeya S. N. *Asian J. Pharm. Clin. Res*. **2011**, *4*, 5-8.

**[33]** Bernardino, A. M. R.; Castro, H. C. *Bioorgan. Med. Chem.* **2006**, *14*, 5765–5770.

**[34]** Nicolaou, K. C. *Chem. Biol.* **2000**, *7*, 593-599.

**[35]** Shi, F; Ning Ma, S. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5565–5568.

**[36]** Ivachtchenko, A. V.; Kovalenko, S. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5483–5487.

**[37]** Bahekar, R. H.; Jain, M. R.; Jadav, P. A.; Prajapati, V. M.; Patel, D. N.; Gupta, A. A.; Sharma, A.; Tom, R.; Bandyopadhya, D.; Modi H.; Patel, P. R. *Bioorgan. Med. Chem.* **2007**, *15*, 6782–6795.

**[38]** Ozdemir, A.; Demirci, F. *Eur. J. Med. Chem.* **2010,** *45*, 2080-2084.

**[39]** Hill, M. D. *Chem. Eur. J.* **2010**, *16*, 12052–12062.

**[40]** Roesch, K. R.; Larock R. C., *J. Org. Chem*. **2002**, *67*, 86–94.

**[41]** Parthasarathy, K.; Jeganmohan, M.; Cheng, C. H. *Org. Lett*. **2008**, *10*, 325–328.

**[42]** Hyster, T. K.; Rovis, T. *Chem. Commun*. **2011**, *47*, 11846–11848.

**[43]** Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008,** *10*, 2629-2632.

**[44]** 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.

**[45]** 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.

**[46]** McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie J. *J. Am. Chem. Soc*. **2005**, *127*, 5030-5031.

**[47]** Xin, X.; Wang, D.; Wu, F.; Li, X.; Wan, B. *J. Org. Chem*. **2013**, *78*, 4065−4074.

**[48]** Carey F. A., Sundberg R. J., *Advanced Organic Chemistry: Part B: Reaction and Syntheses*, 5th Ed., LLC: New York, 2007.

**[49]** Patil, N. T.; Kavthe, R. D.; Raut, V. S.; Reddy, V. V. N. *J. Org. Chem*. **2009**, *74*, 6315–6318.

**[50]** Khoshkholgh, M. J.; Balalaie, S.; Bijanzadeh, H. R.; Gross, J. H. *ARKIVOC* **2008**, *2009*, 114-121.

**[51]** Lee, Y.; Klausen, R. S.; Jacobsen E. N. *Org. Lett.* **2011**, *13*, 5564.

**[52]** Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem.* Soc. **2002**, *124*, 11684-11688.

**[53]** Morita, M.; Obora, Y.; Ishii, Y. *Chem. Commun*. **2007**, 2850-2852.

**[54]** Ueura, K.; Satoh, T.; Miura, M. *J. Org. Chem*. **2007**, *72*, 5362-5367.

**[55]** Padmanaban, M.; Biju, A. T.; Glorius, F. *Org Lett.* **2011**, *13*, 5624-5627.

# APPENDIX A

## NMR DATA

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

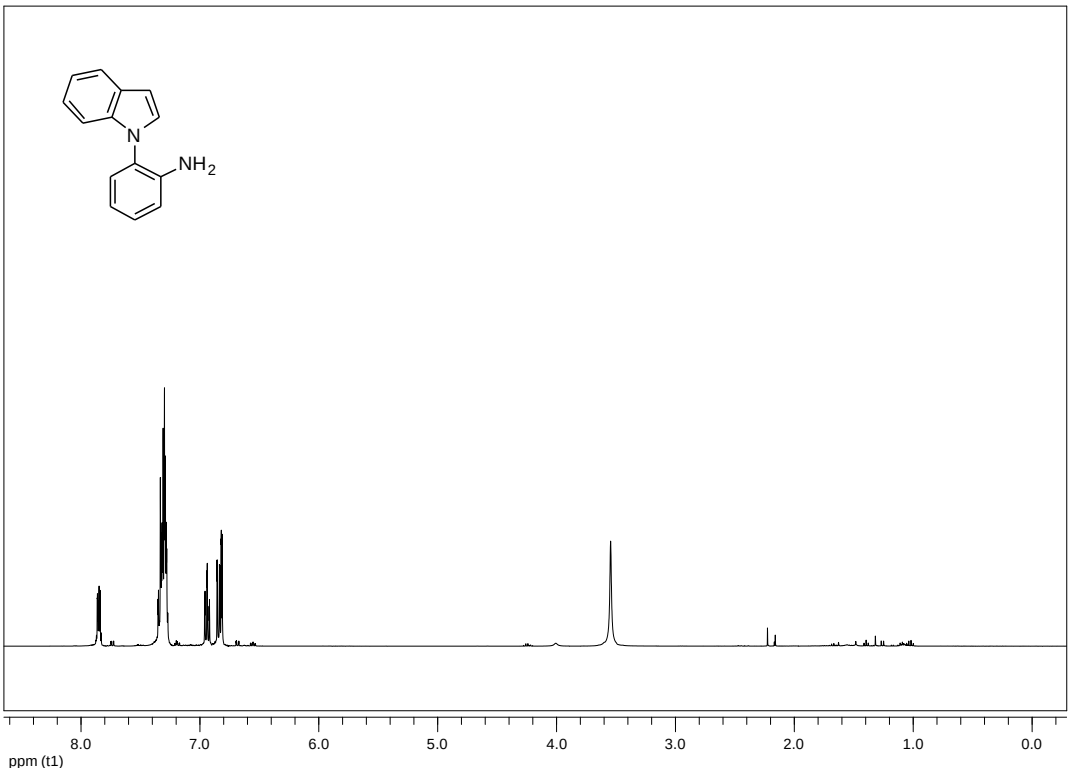



**Figure A1.** $^{1}$H NMR Spectrum of compound **49**.

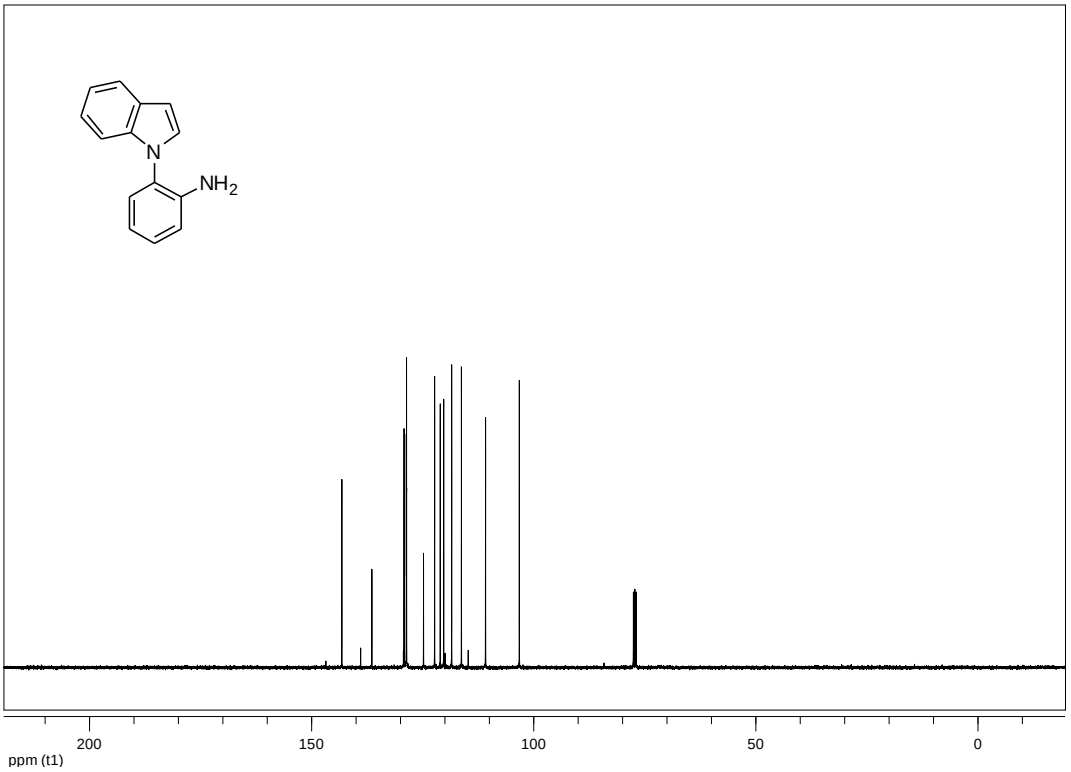



**Figure A2.** $^{13}$C NMR Spectrum of compound **49**.

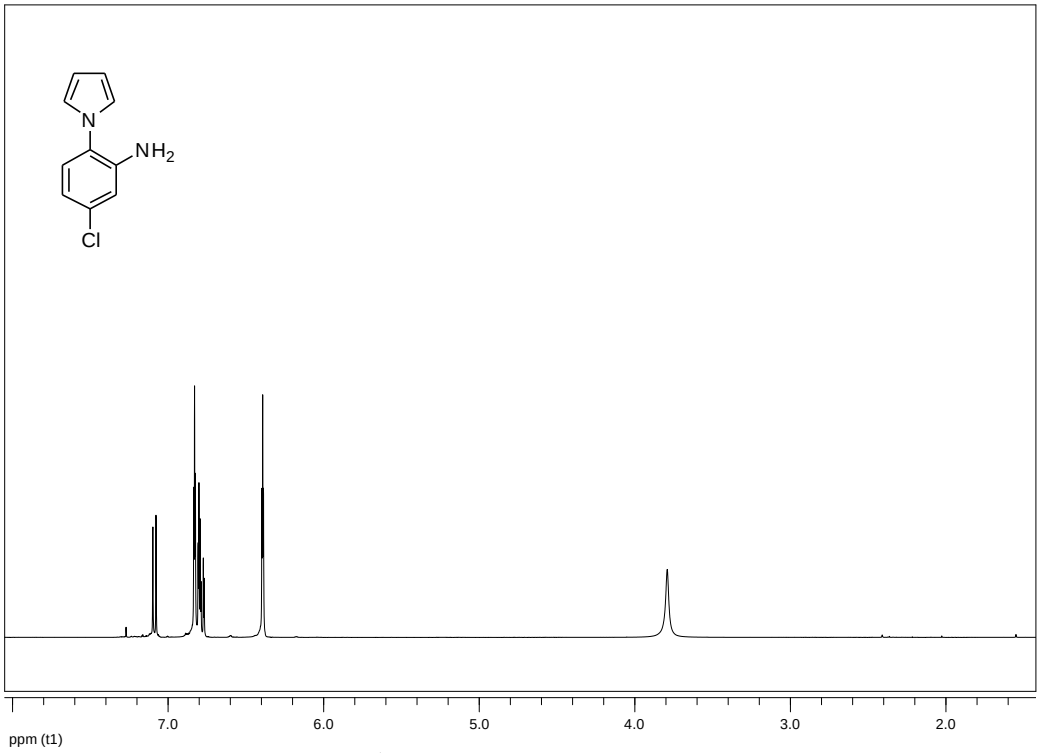



**Figure A3.** $^{1}$H NMR Spectrum of compound **50**.

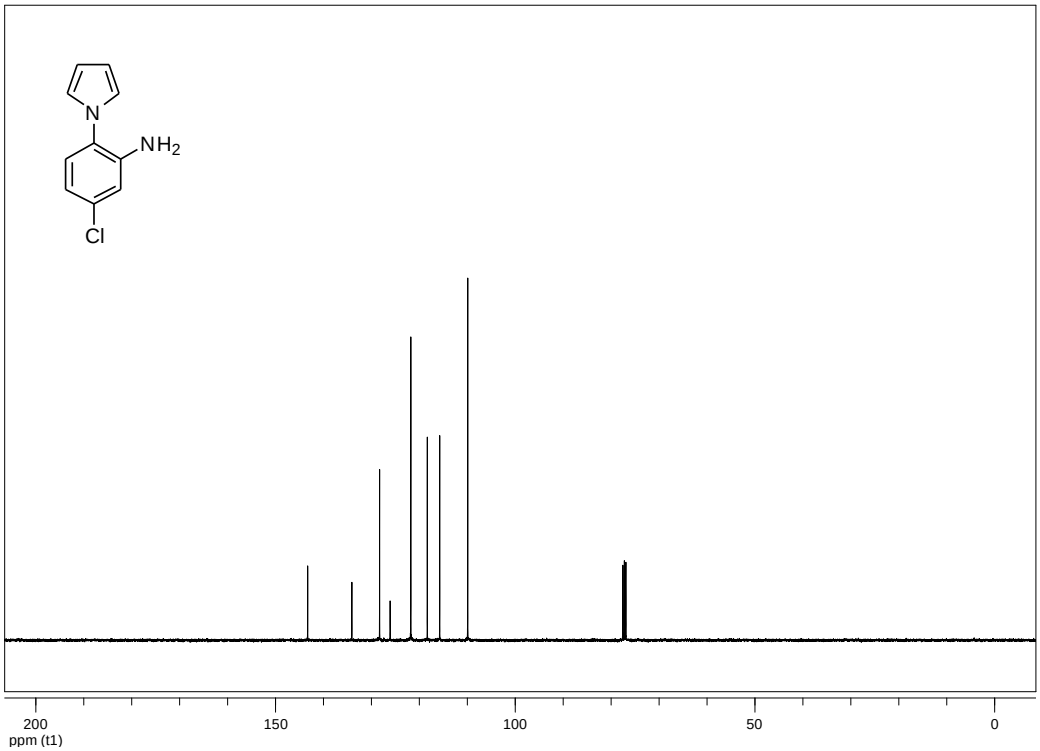



**Figure A4.** $^{13}$C NMR Spectrum of compound **50**.

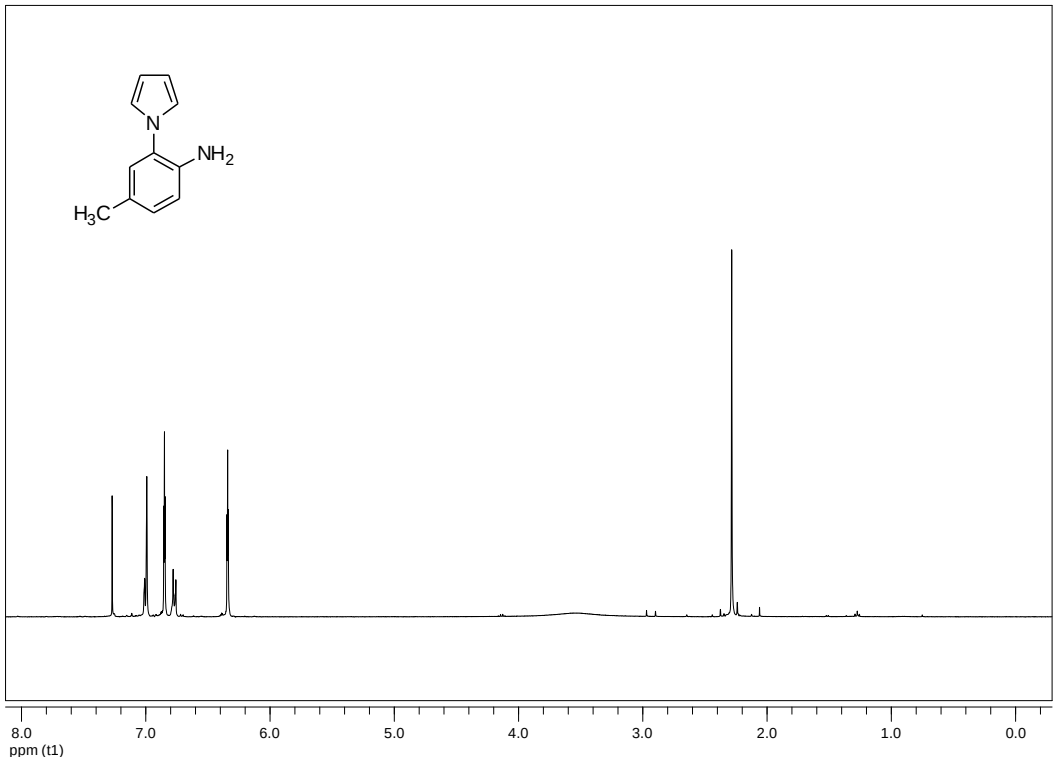



**Figure A5.** $^{1}$H NMR Spectrum of compound **51**.

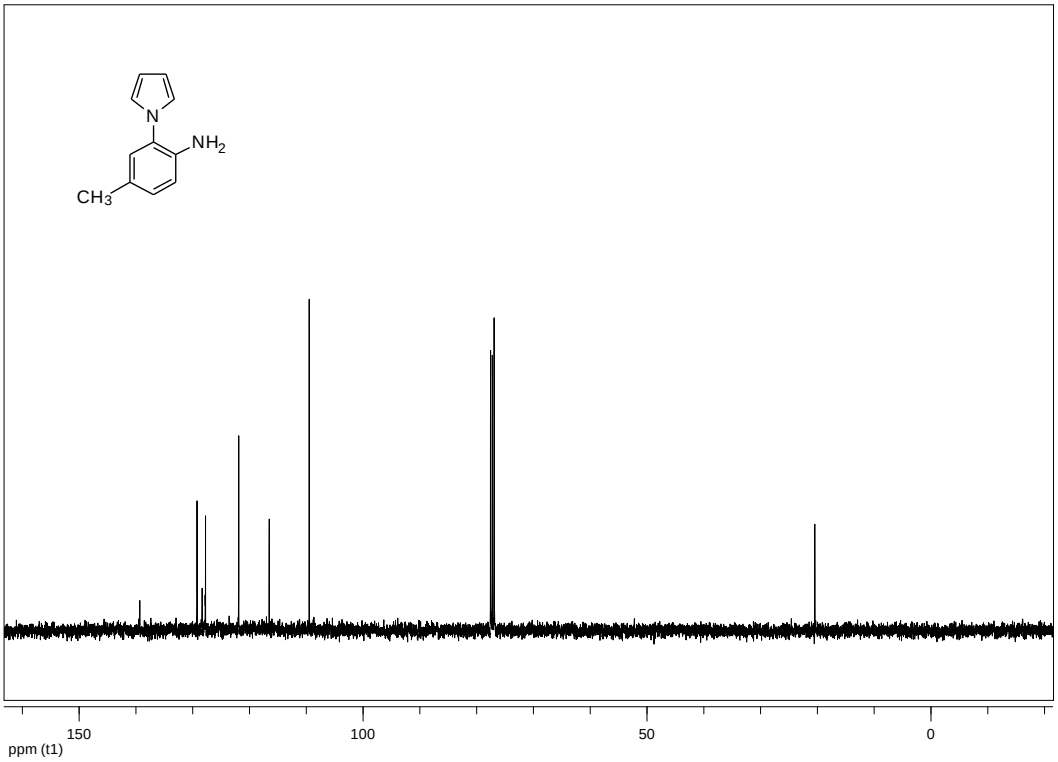



**Figure A6.** $^{13}$C NMR Spectrum of compound **51**.

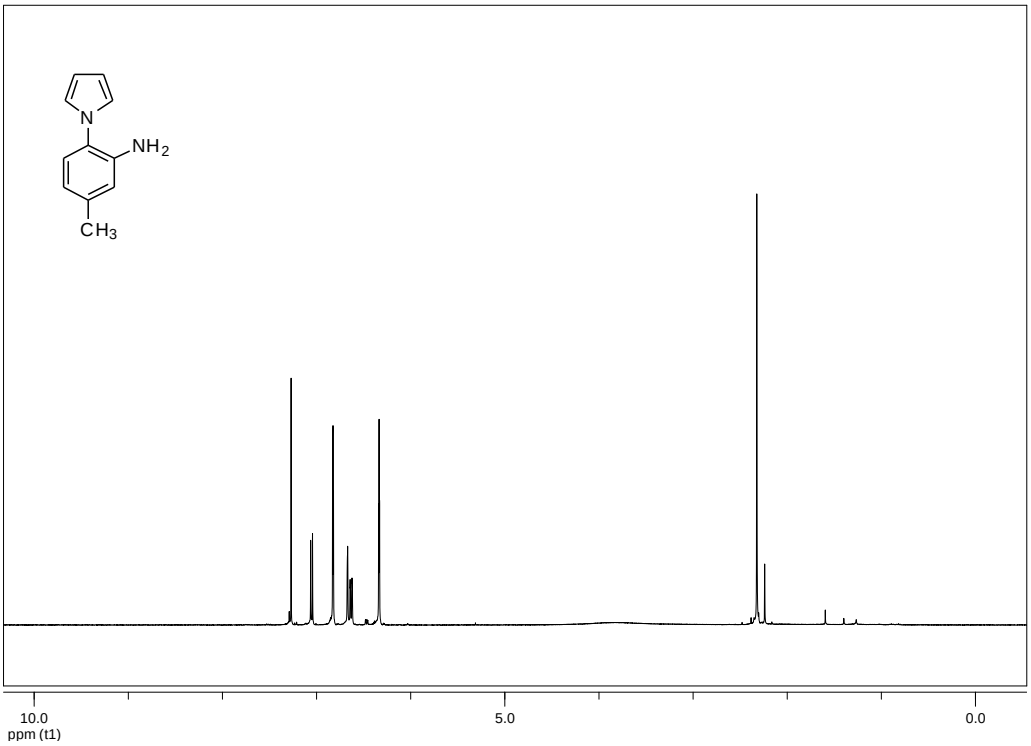



**Figure A7.** $^{1}$H NMR Spectrum of compound **52**.

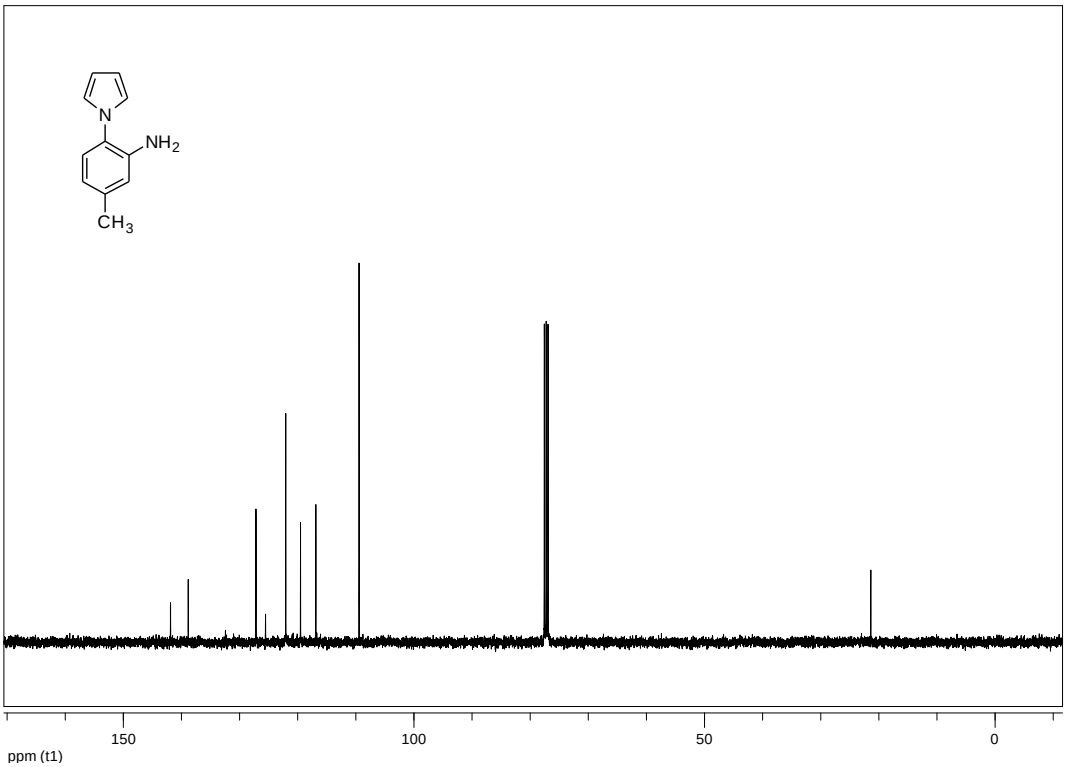



**Figure A8.** $^{13}$C NMR Spectrum of compound **52**.

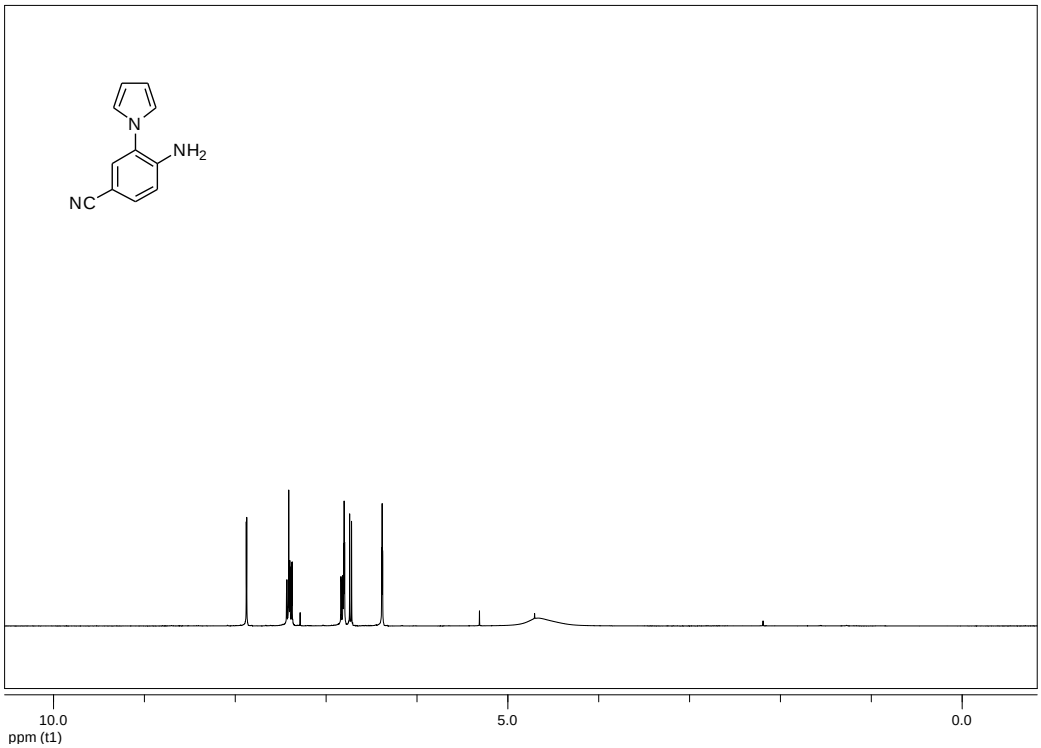



**Figure A9.** $^{1}$H NMR Spectrum of compound **53**.

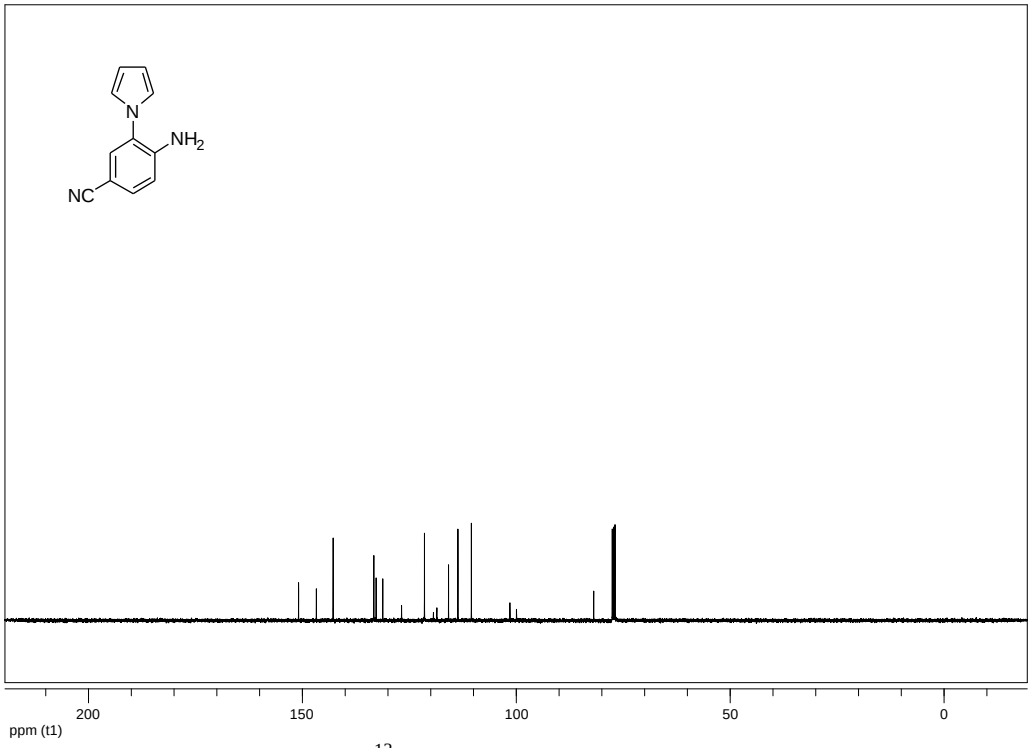



**Figure A10.** $^{13}$C NMR Spectrum of compound **53**.

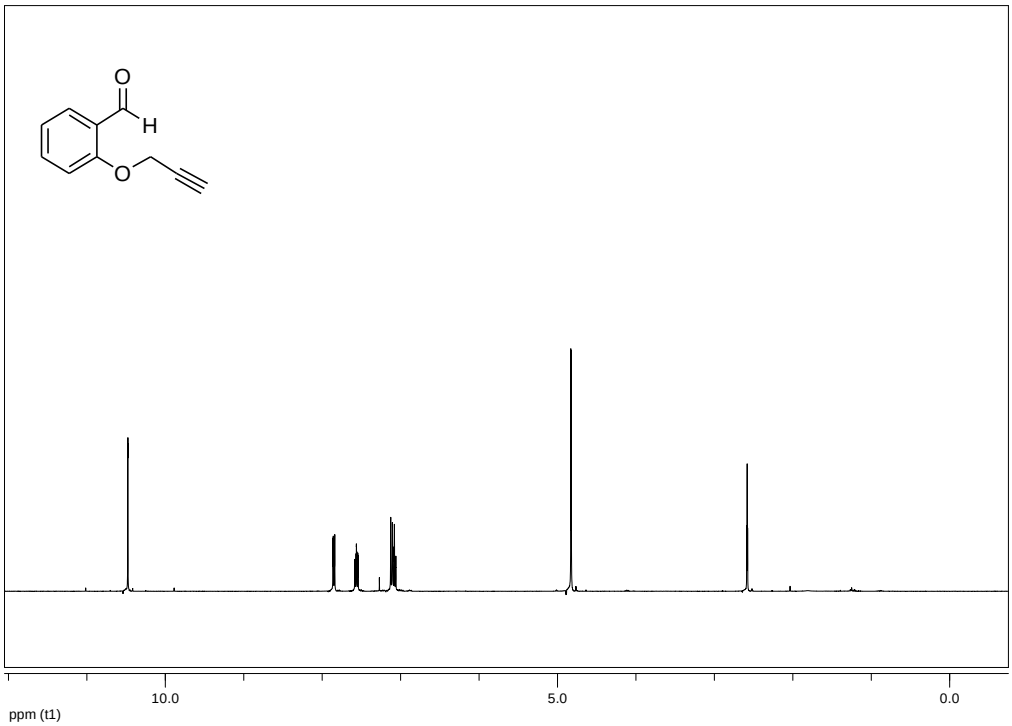



**Figure A11.** $^{1}$H NMR Spectrum of compound **54**.

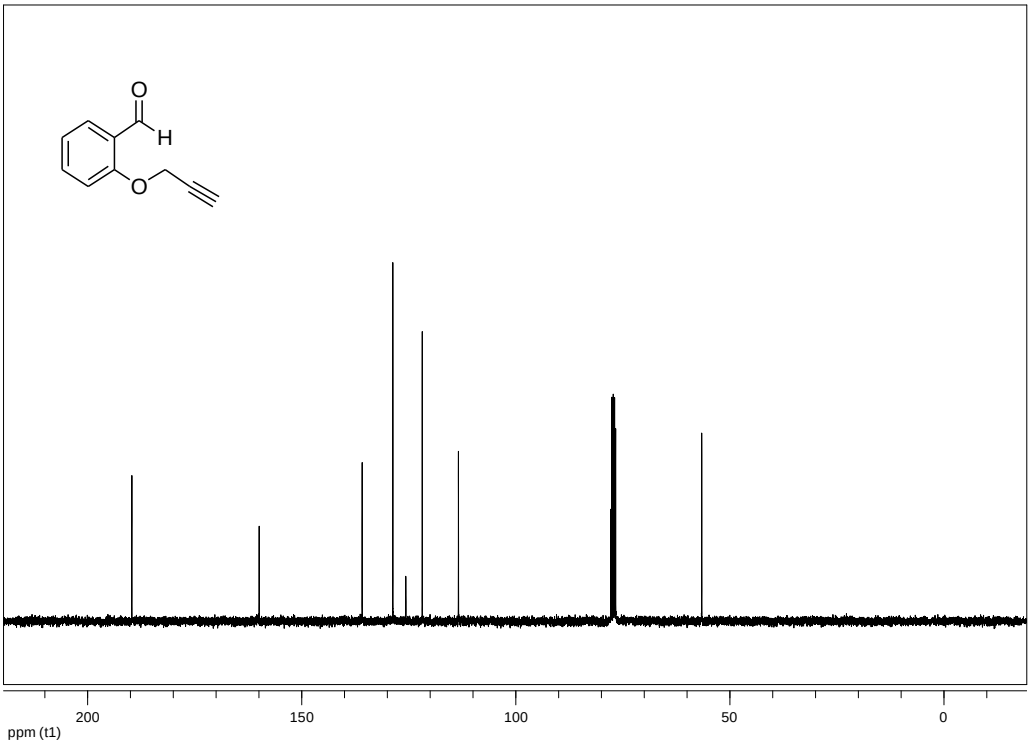



**Figure A12.** $^{13}$C NMR Spectrum of compound **54**.

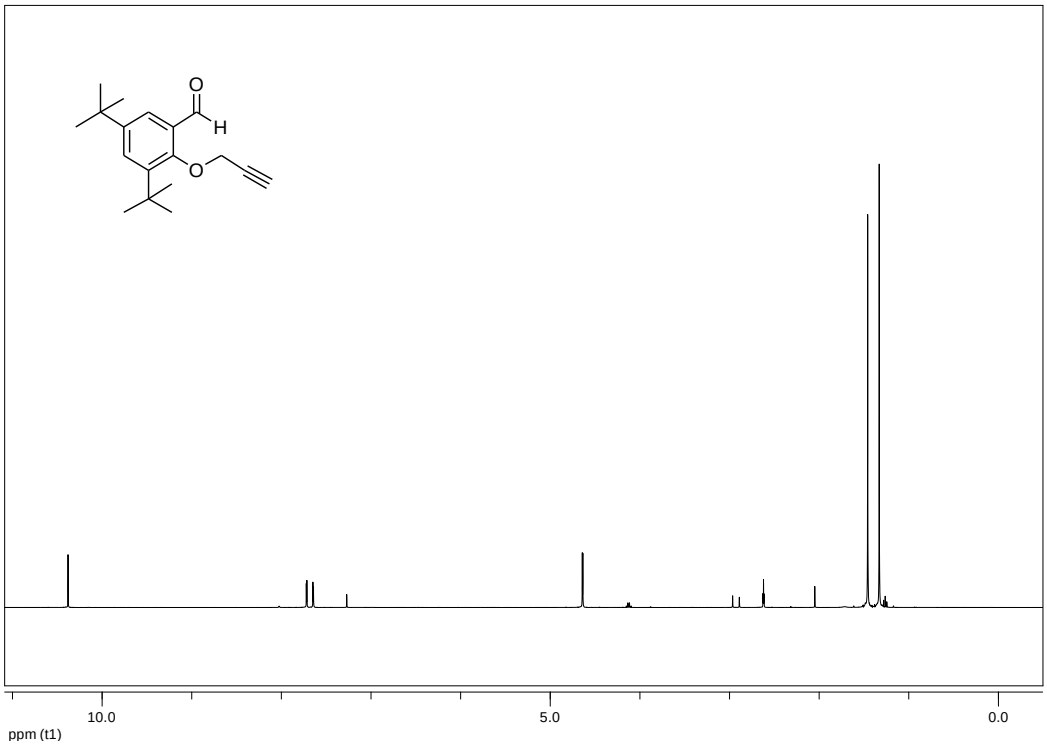



**Figure A13.** $^{1}$H NMR Spectrum of compound **55**.

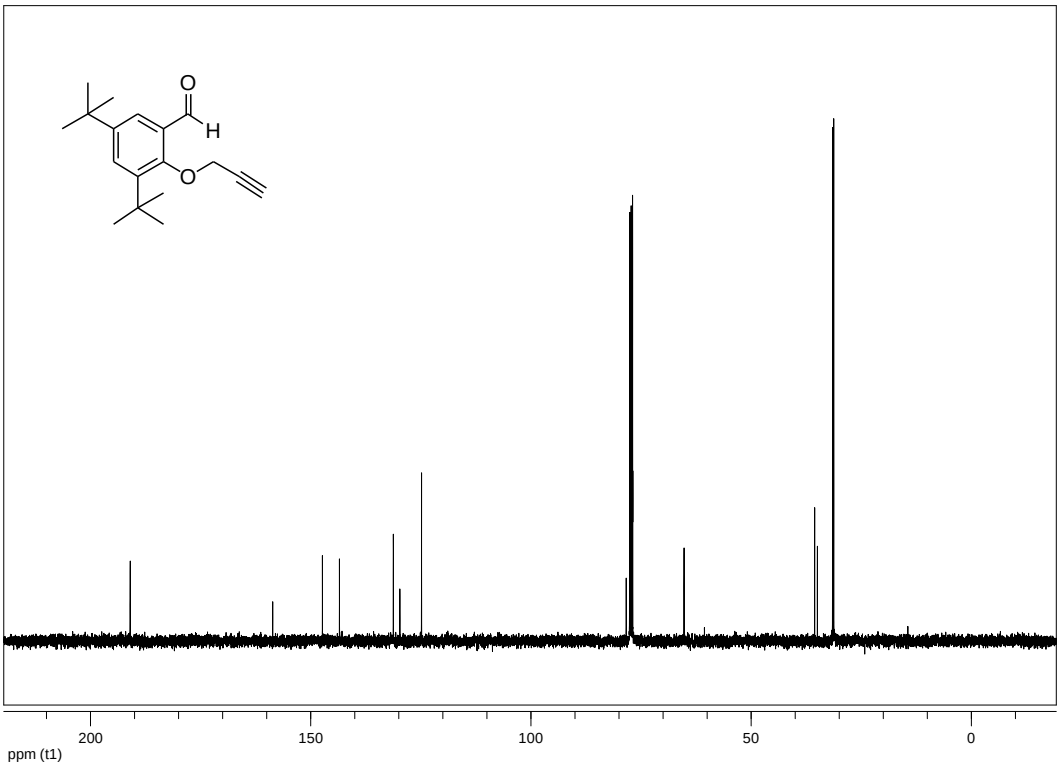



**Figure A14.** $^{13}$C NMR Spectrum of compound **55**.

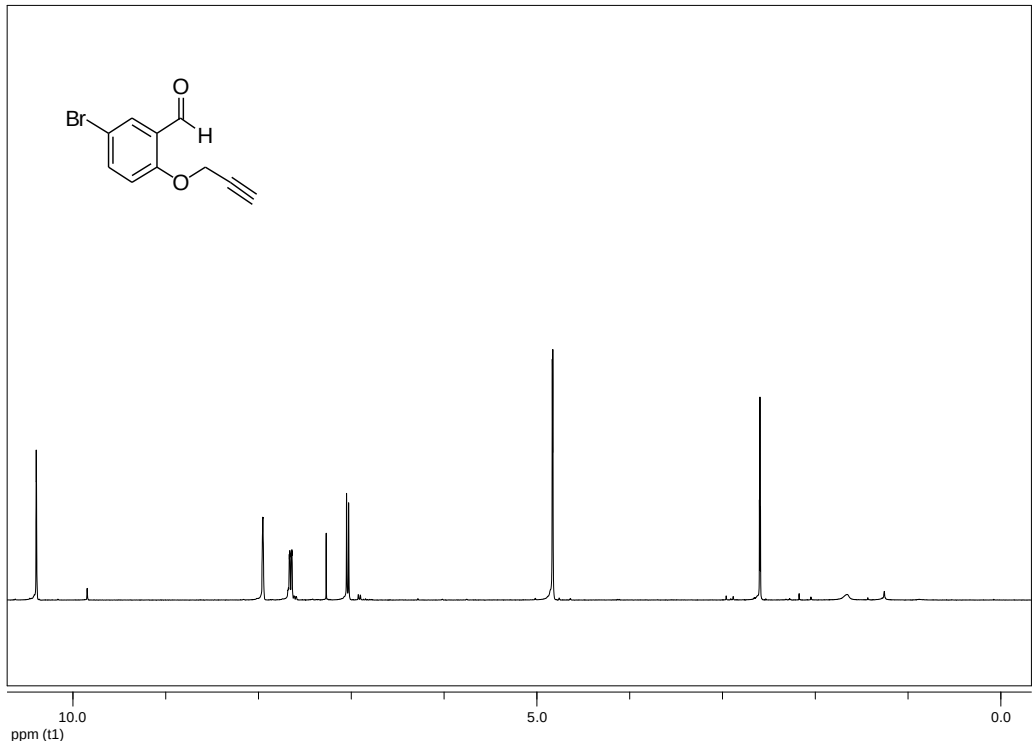



**Figure A15.** $^{1}$H NMR Spectrum of compound **56**.

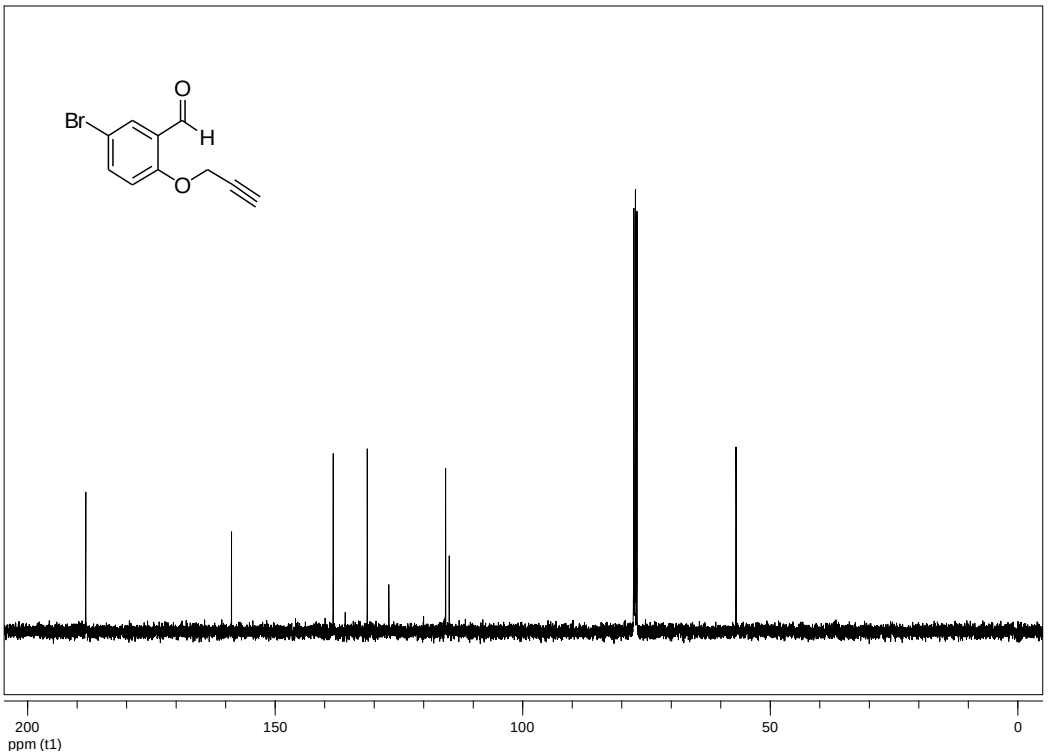



**Figure A16.** $^{13}$C NMR Spectrum of compound **56**.

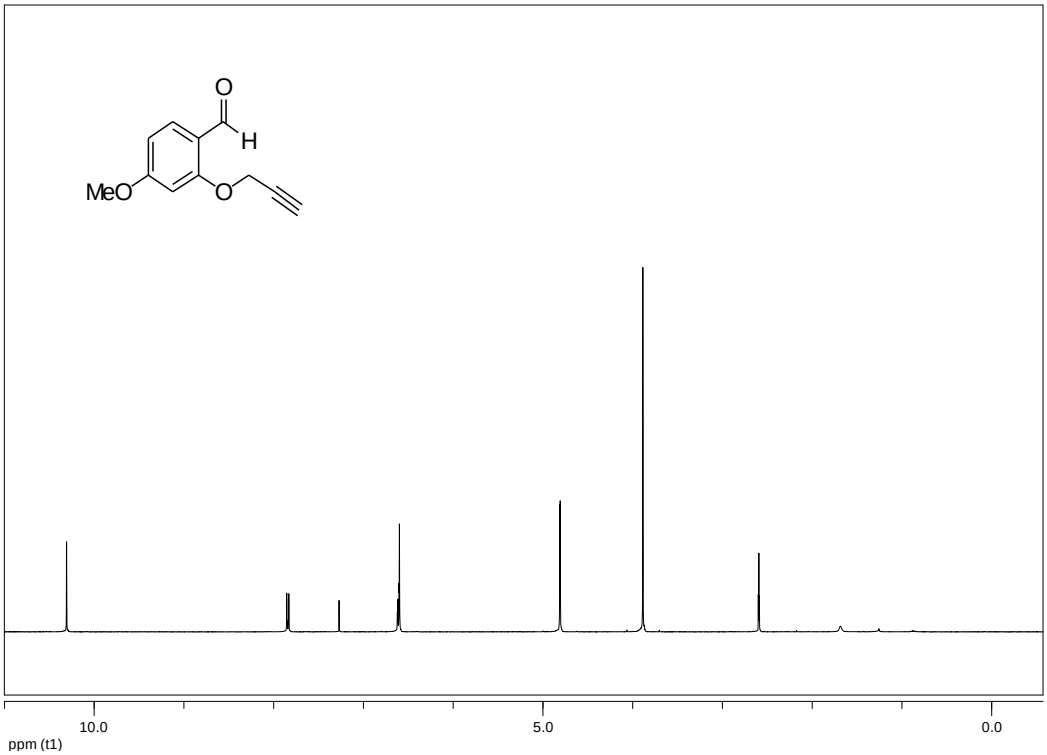



**Figure A17.** $^{1}$H NMR Spectrum of compound **57**.

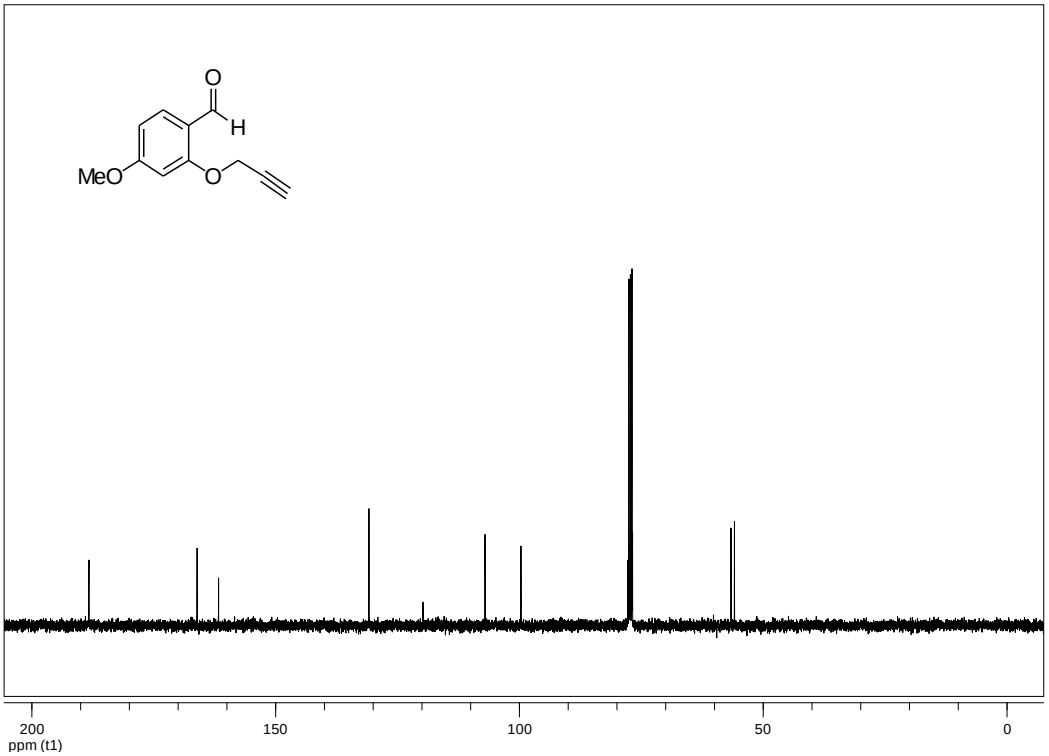



**Figure A18.** $^{13}$C NMR Spectrum of compound **57**.

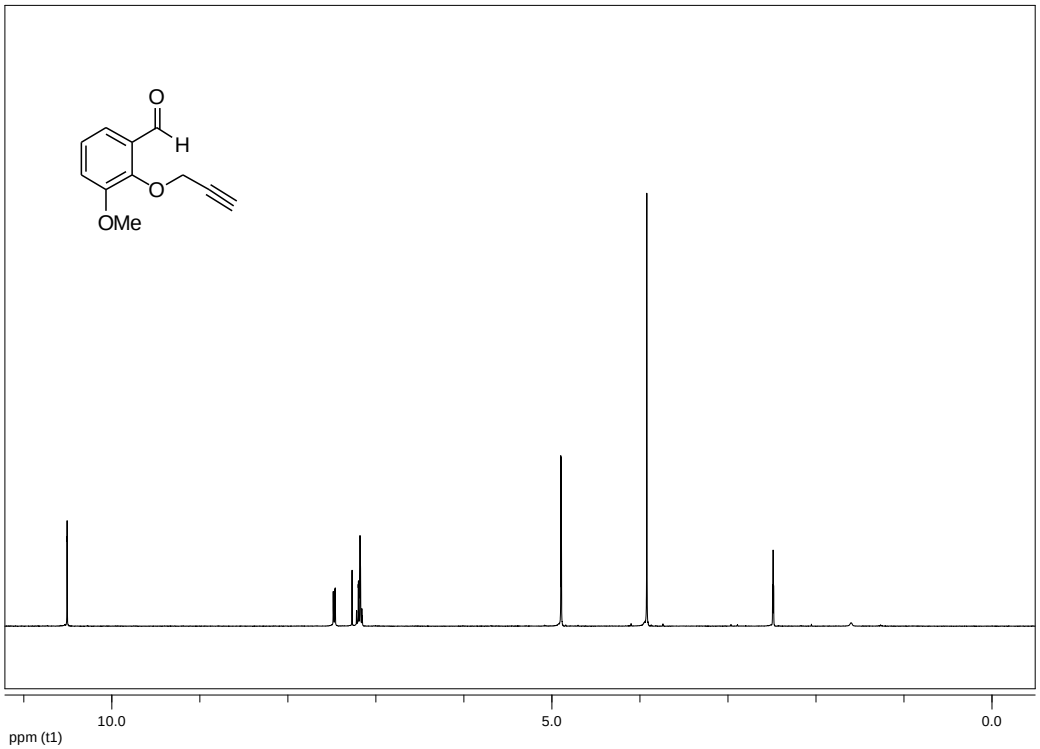



**Figure A19.** $^{1}$H NMR Spectrum of compound **58**.

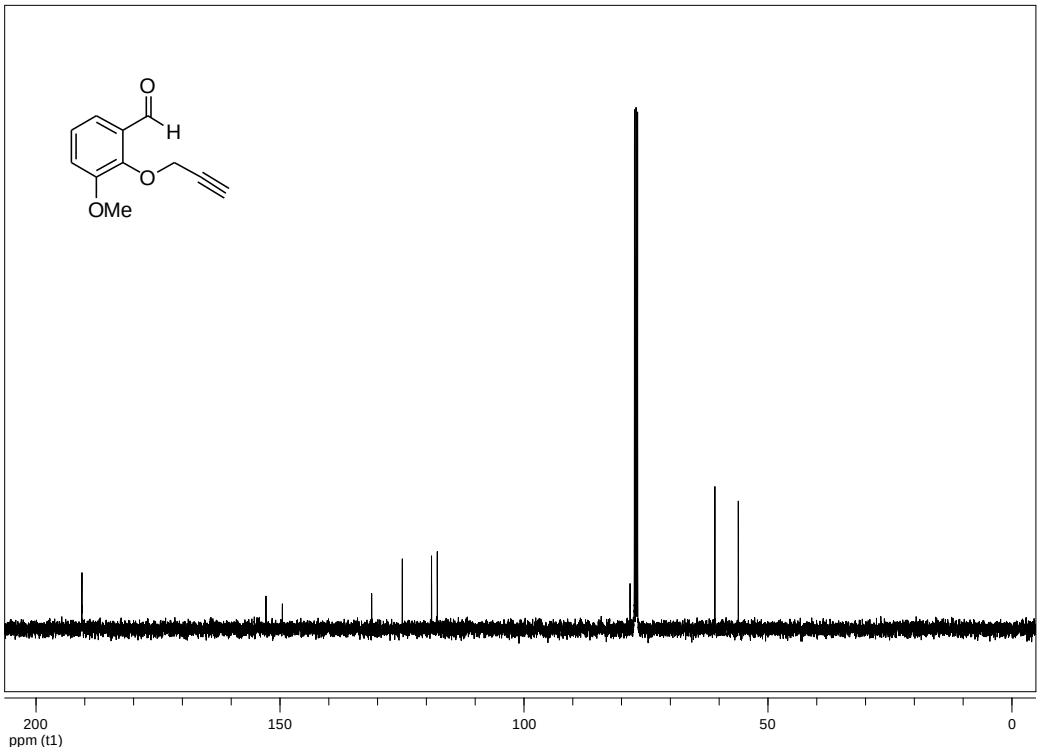



**Figure A20.** $^{13}$C NMR Spectrum of compound **58**.

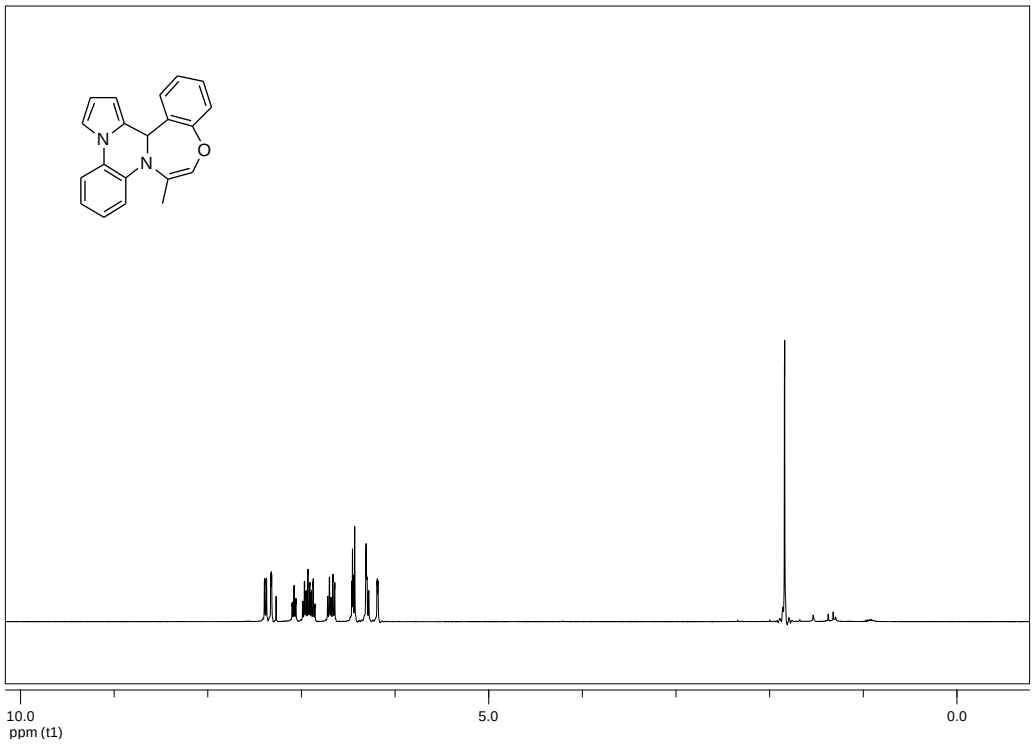



**Figure A21.** $^{1}$H NMR Spectrum of compound **59**.

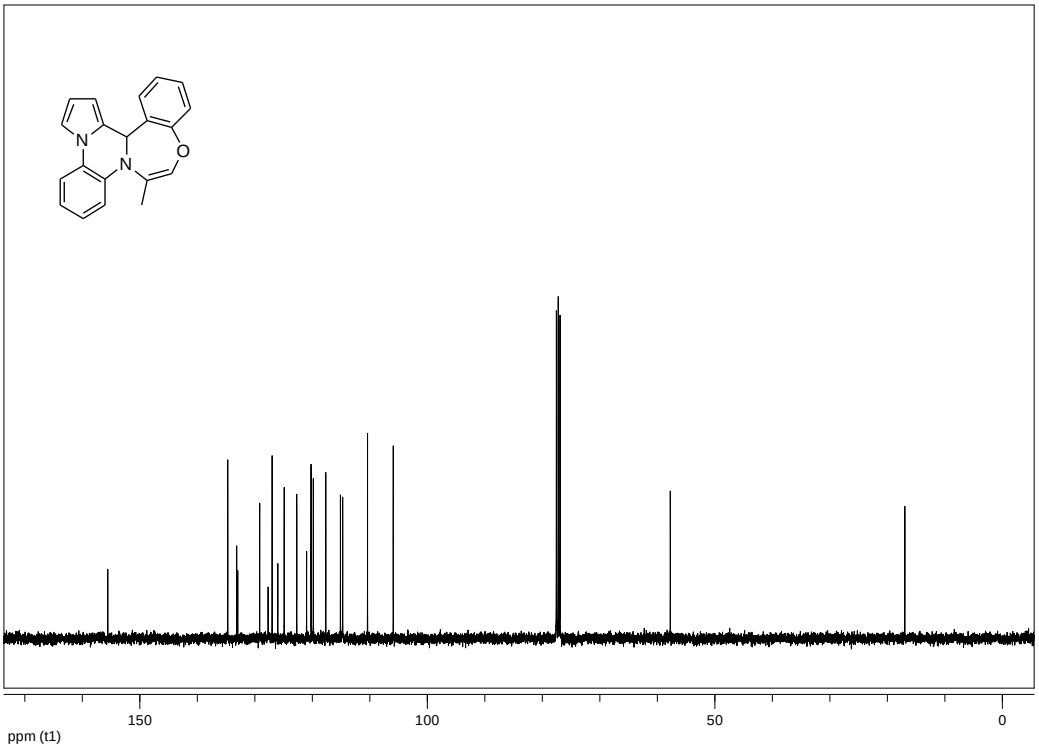



**Figure A22.** $^{13}$C NMR Spectrum of compound **59**.

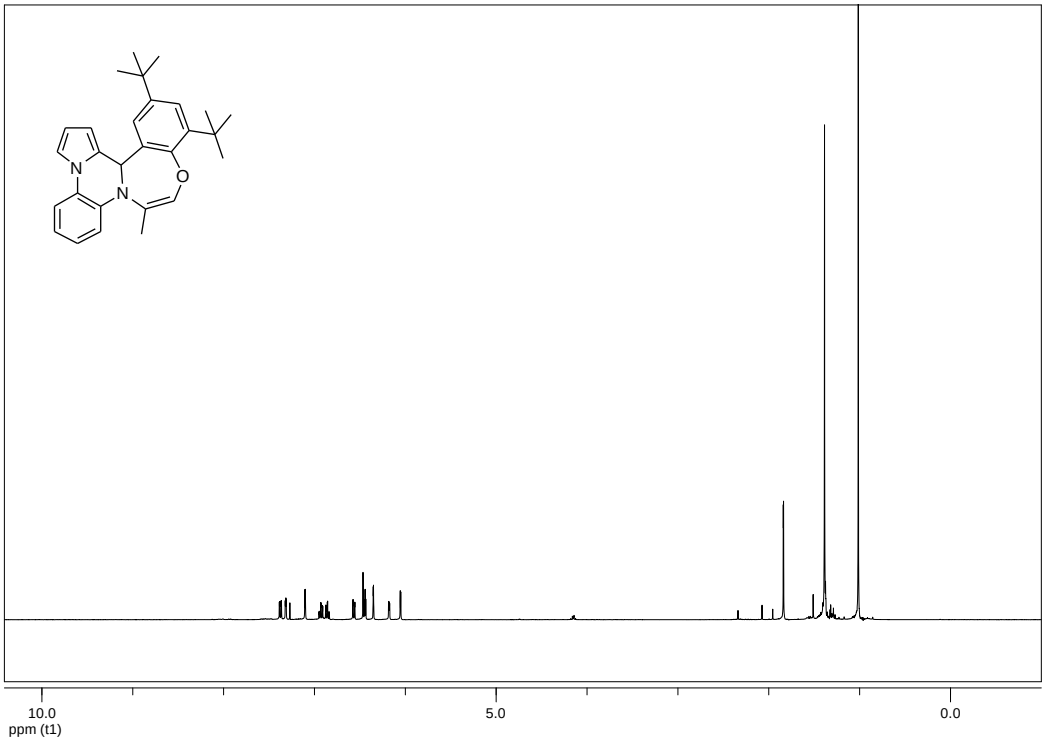



**Figure A23.** $^{1}$H NMR Spectrum of compound **60**.

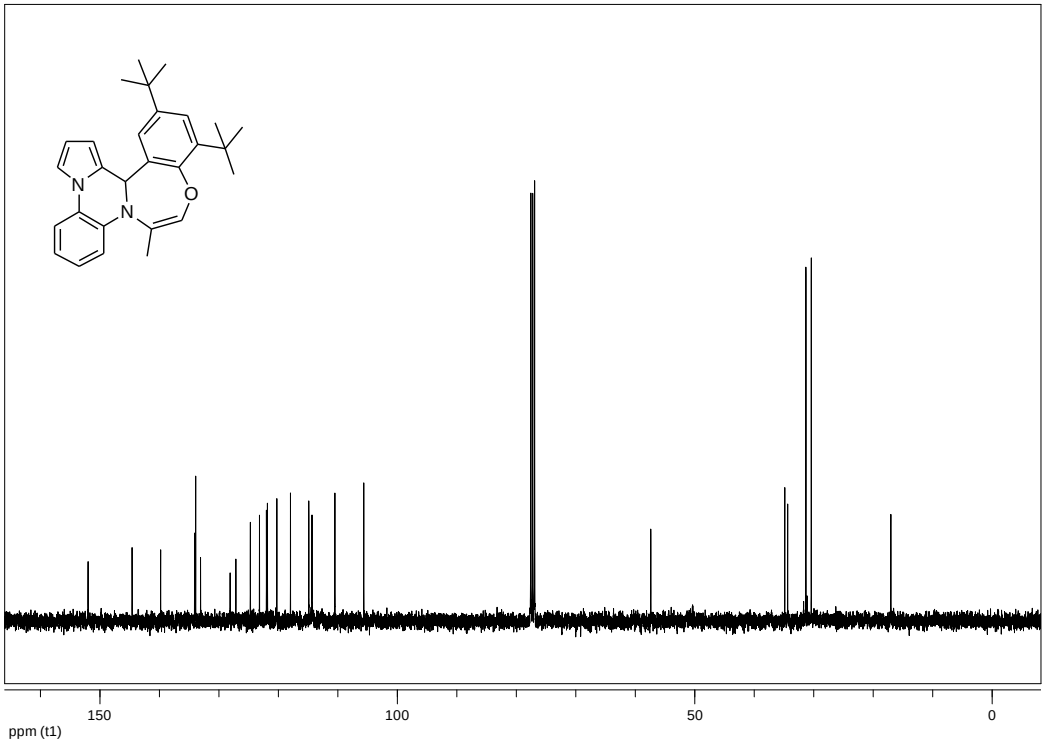



**Figure A24.** $^{13}$C NMR Spectrum of compound **60**.

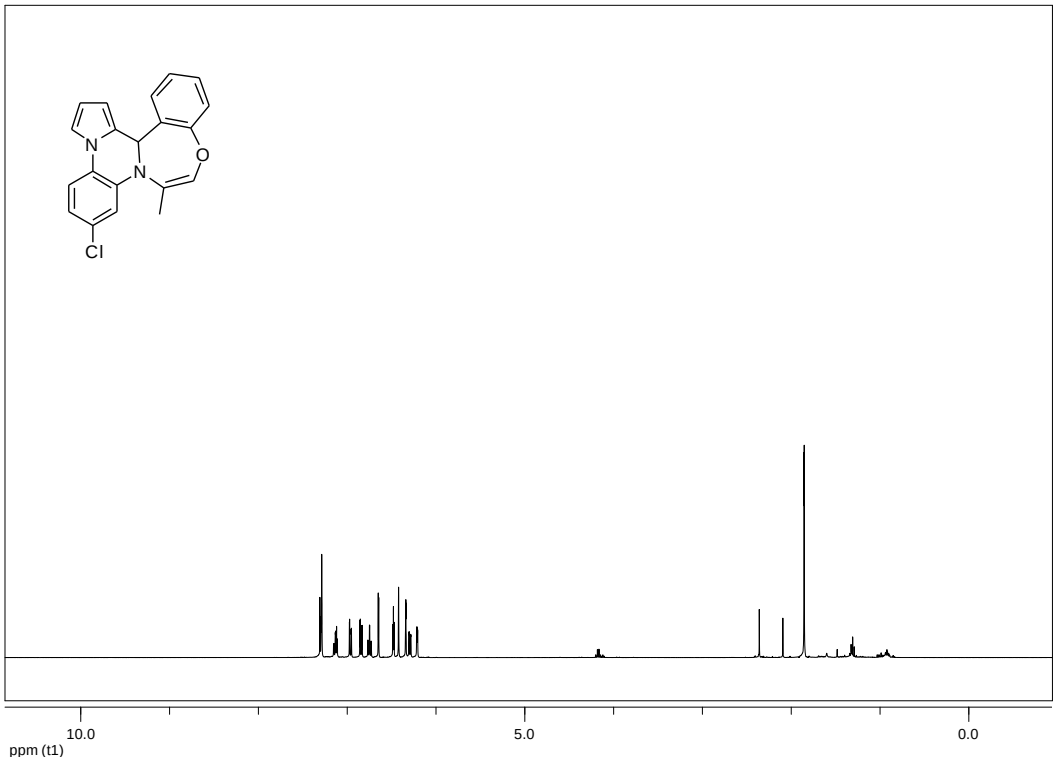



**Figure A25.** $^{1}$H NMR Spectrum of compound **61**.

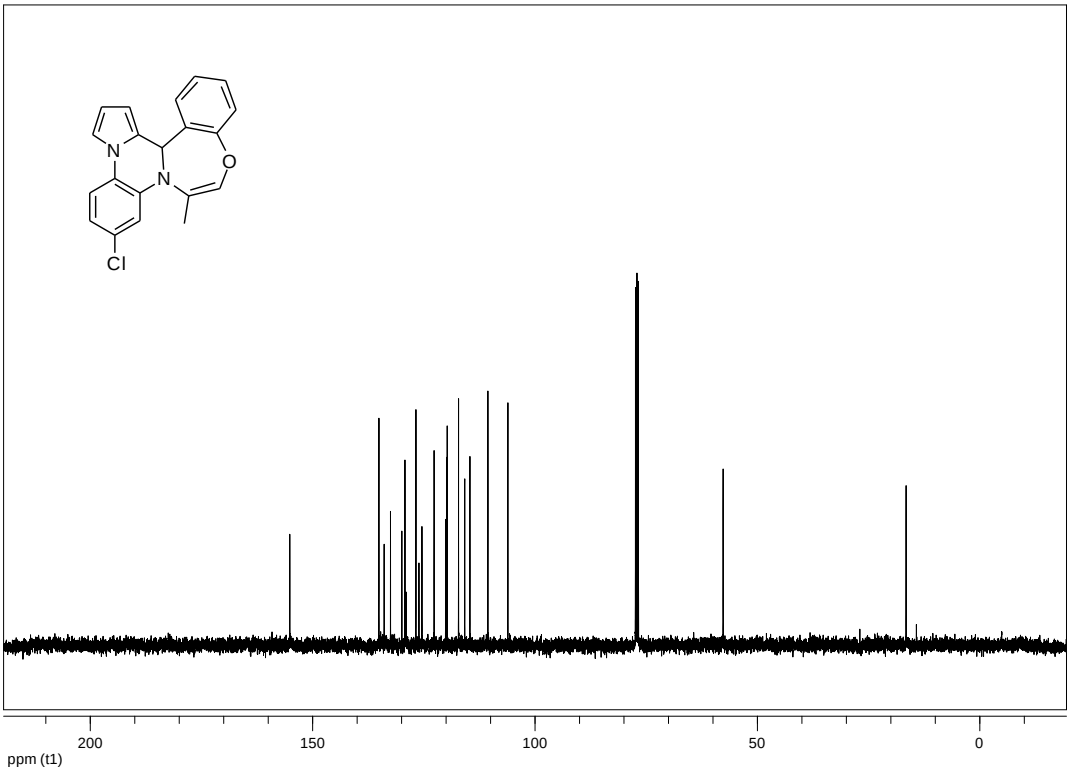



**Figure A26.** $^{13}$C NMR Spectrum of compound **61**.

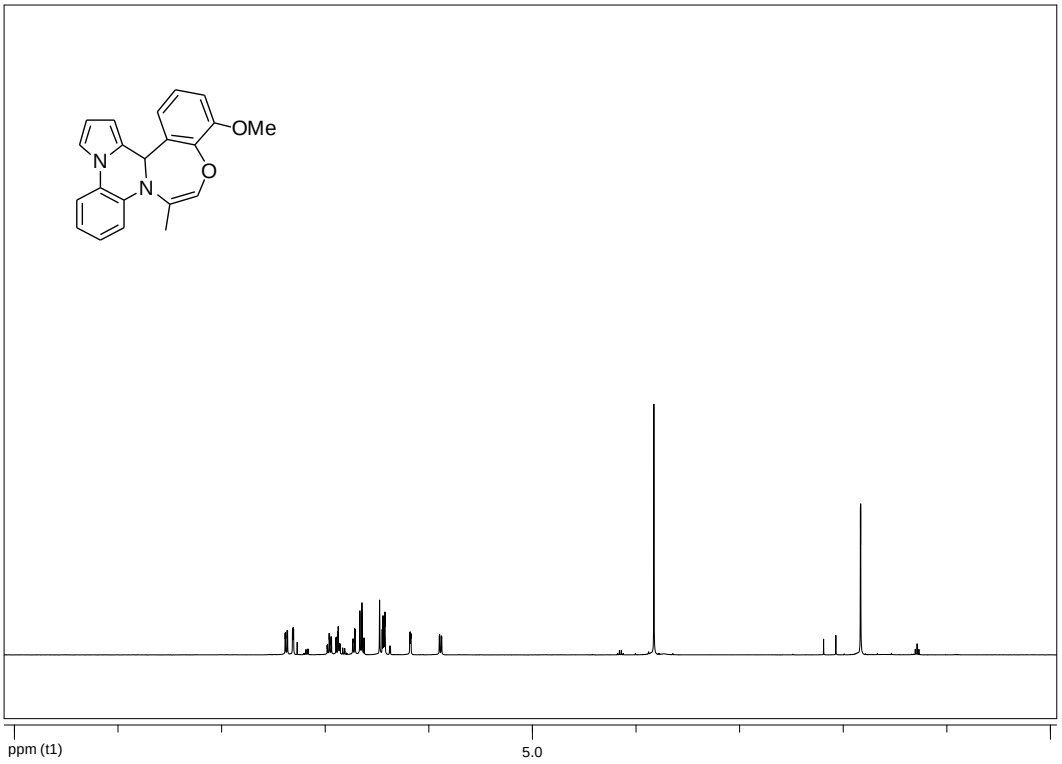



**Figure A27.** $^{1}$H NMR Spectrum of compound **62**.

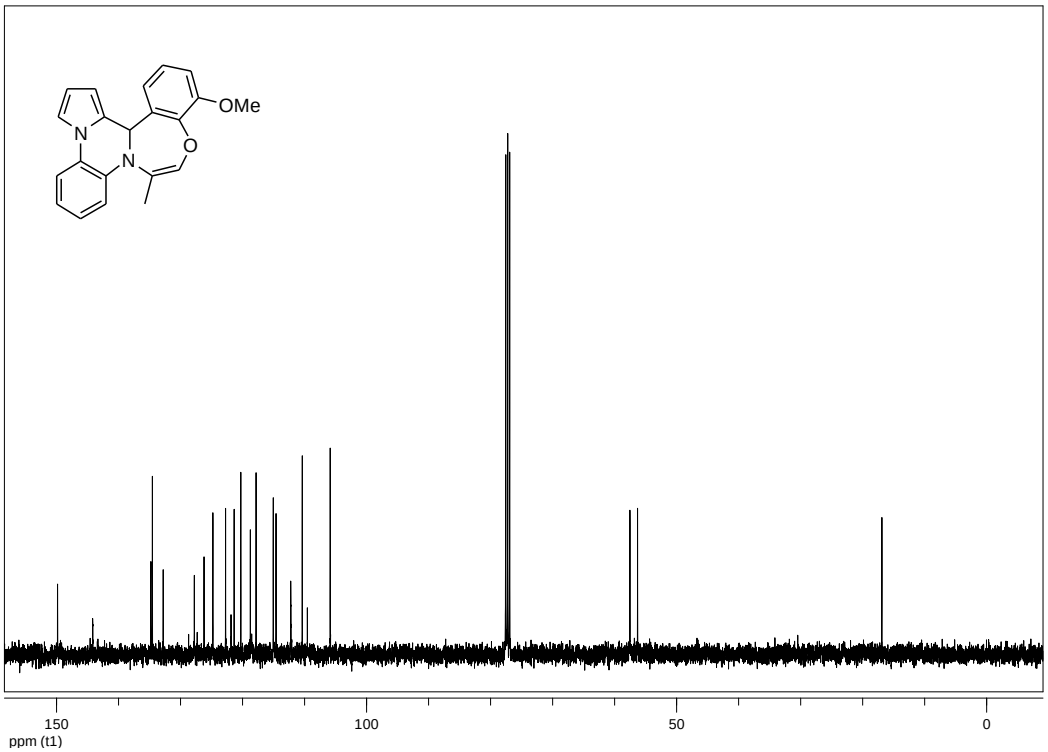



**Figure A28.** $^{13}$C NMR Spectrum of compound **62**.

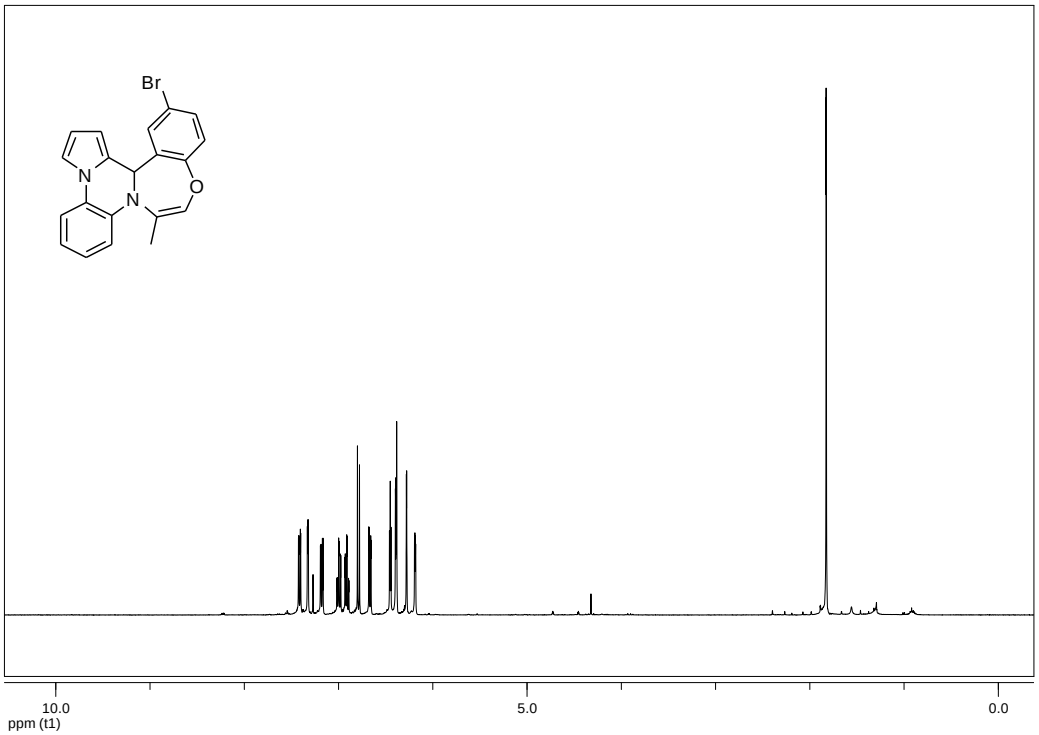



**Figure A29.** $^{1}$H NMR Spectrum of compound **63**.

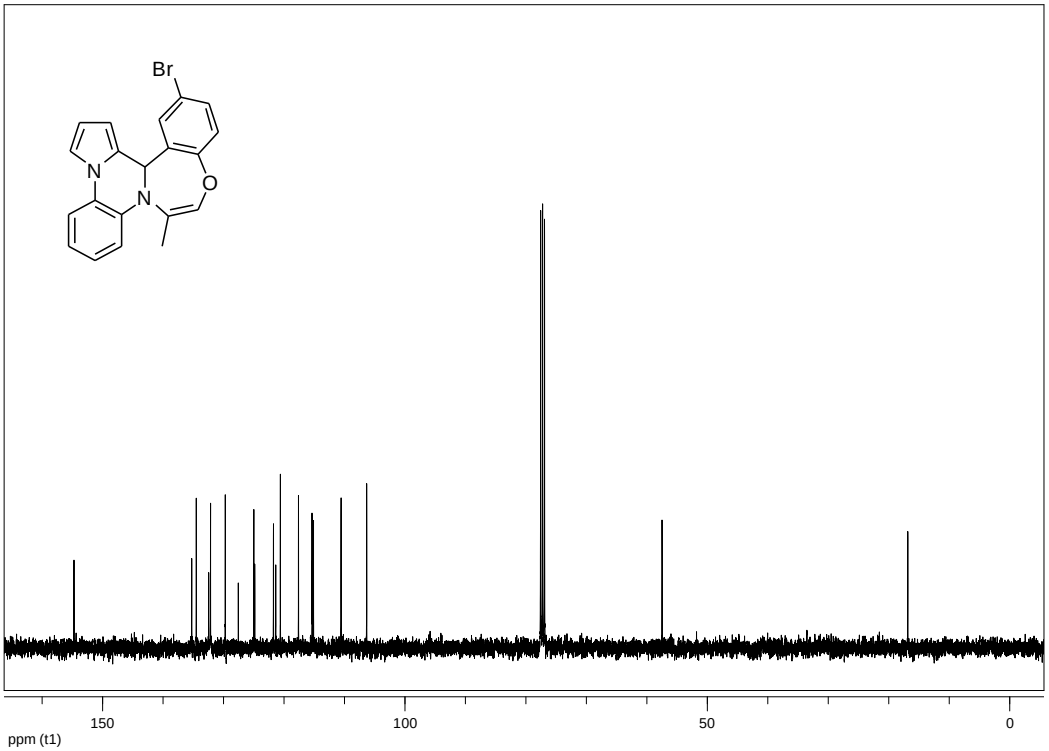



**Figure A30.** $^{13}$C NMR Spectrum of compound **63**.

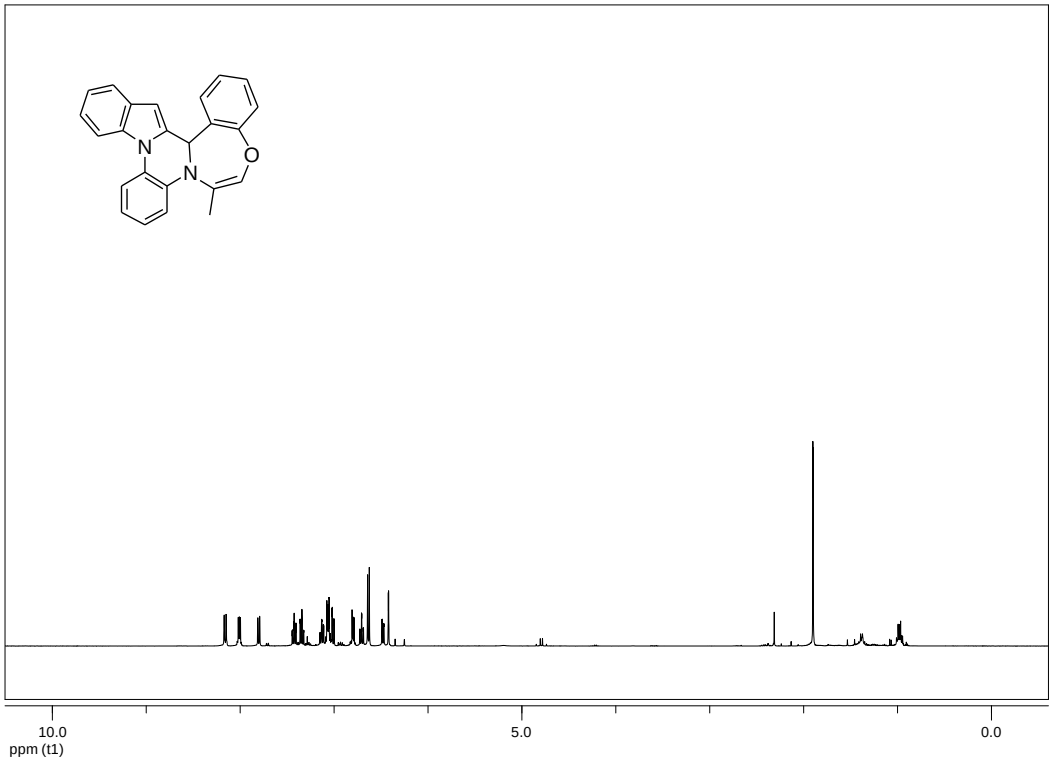



**Figure A31.** $^{1}$H NMR Spectrum of compound **64**.

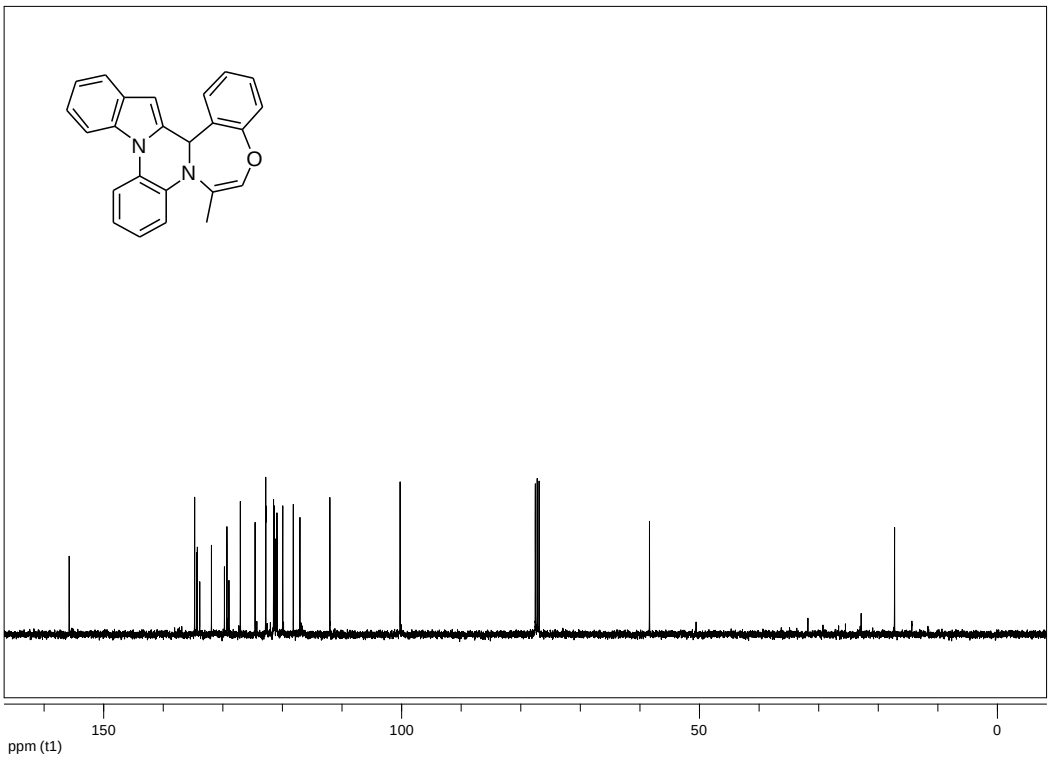



**Figure A32.** $^{13}$C NMR Spectrum of compound **64**.

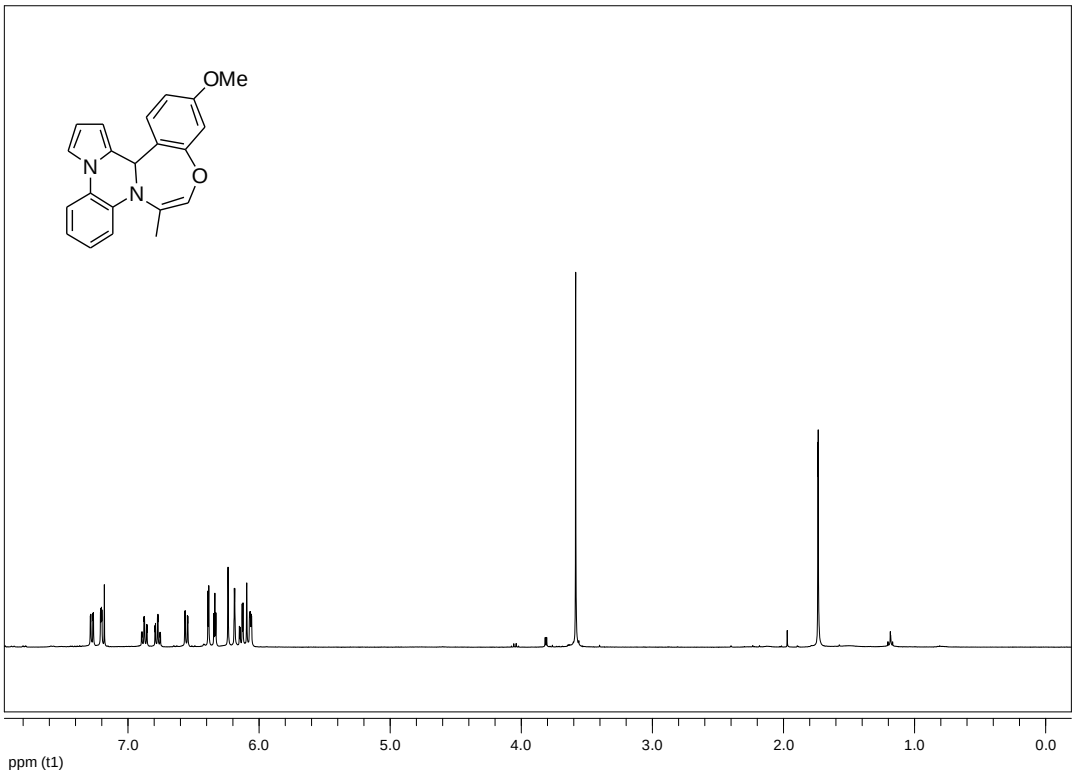



**Figure A33.** $^{1}$H NMR Spectrum of compound **65**.

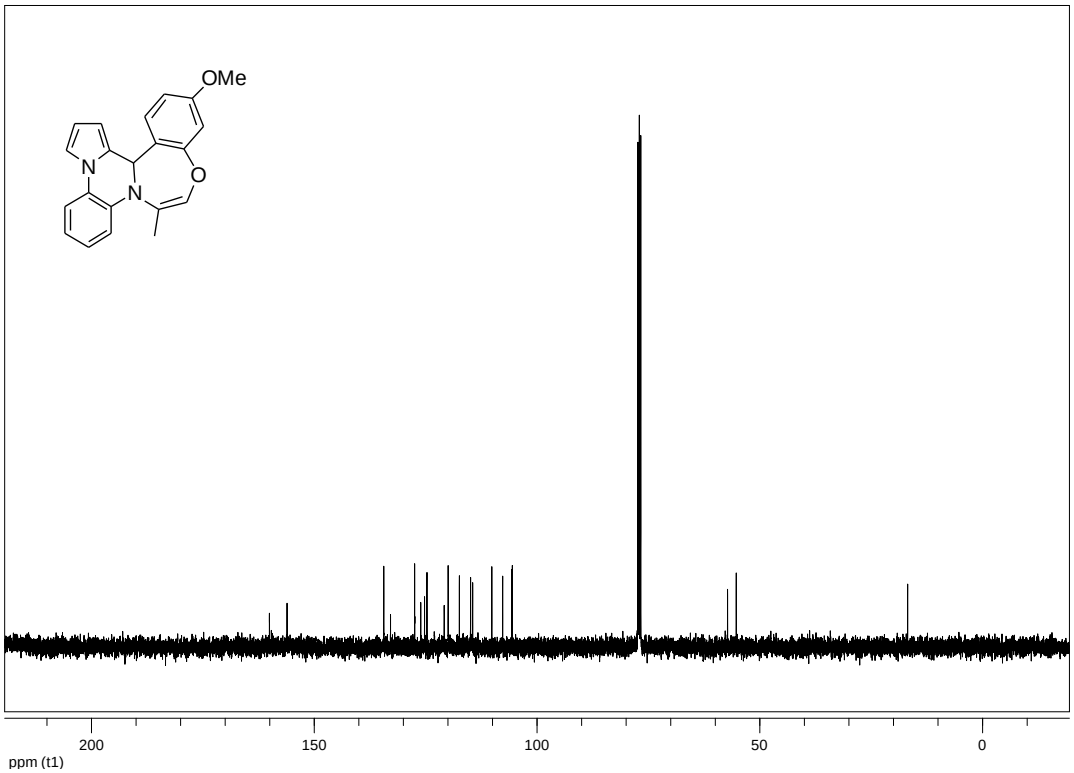



**Figure A34.** $^{13}$C NMR Spectrum of compound **65**.

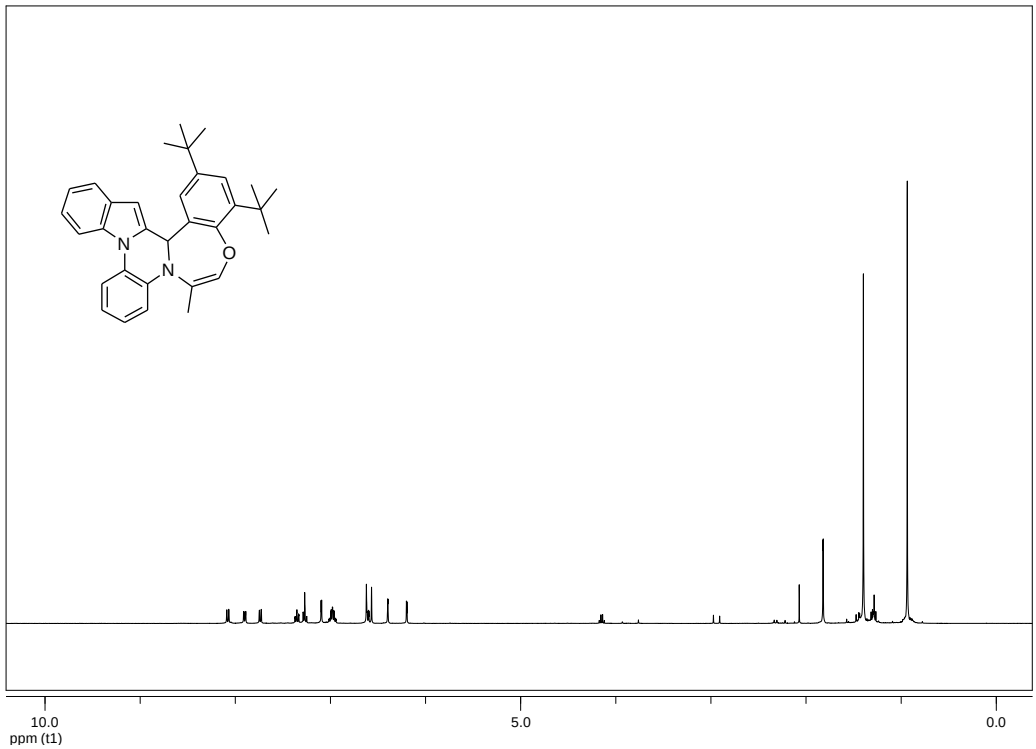



**Figure A35.** $^{1}$H NMR Spectrum of compound **66**.

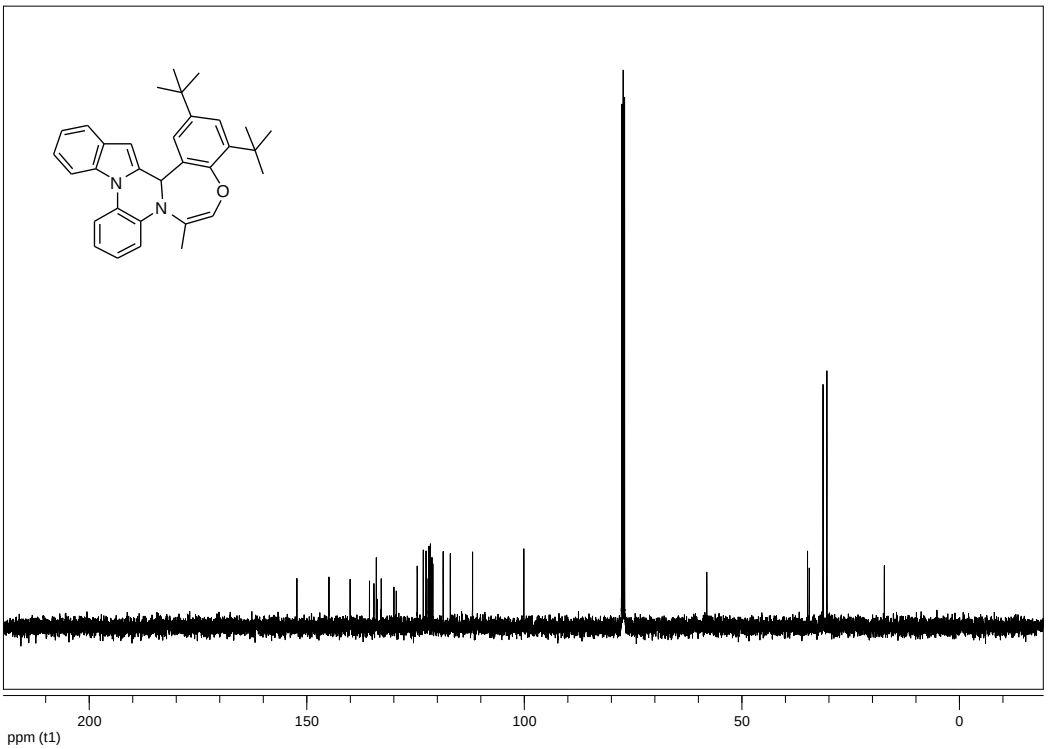



**Figure A36.** $^{13}$C NMR Spectrum of compound **66**.

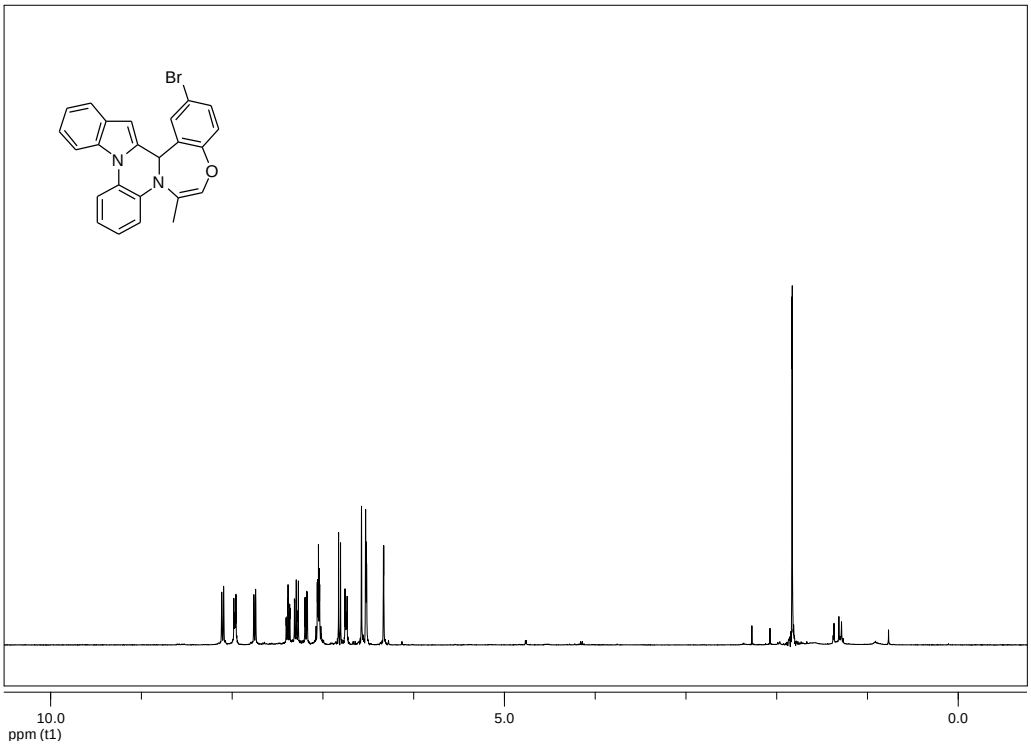



**Figure A37.** $^{1}$H NMR Spectrum of compound **67**.

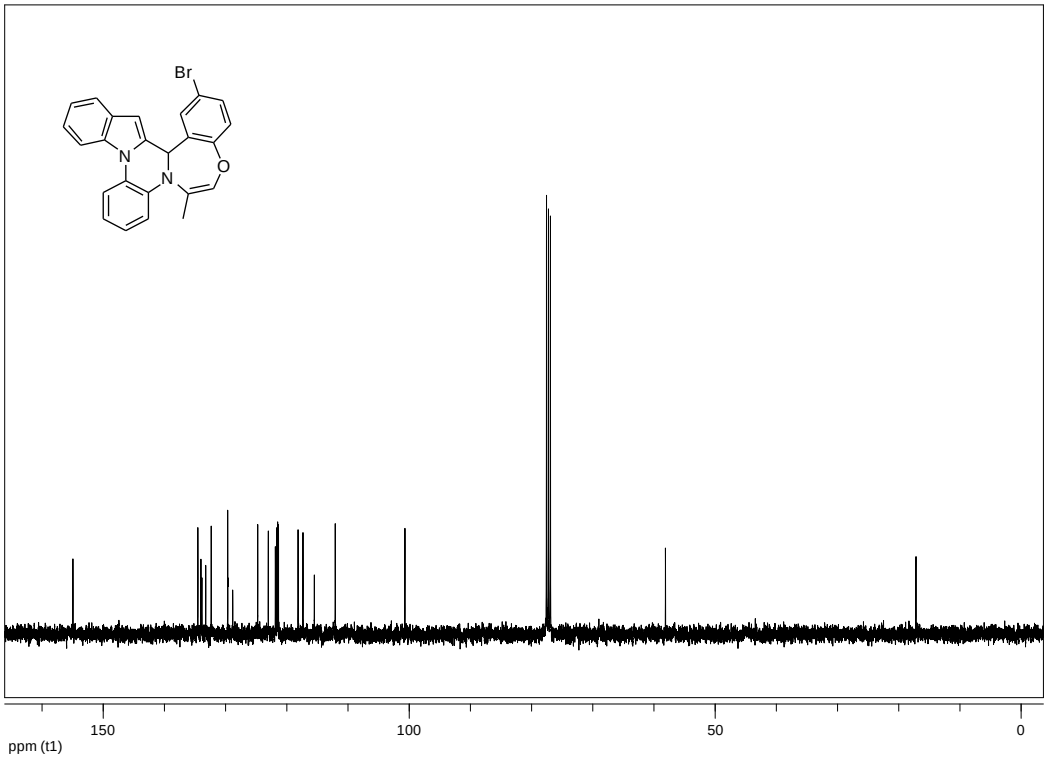



**Figure A38.** $^{13}$C NMR Spectrum of compound **67**.

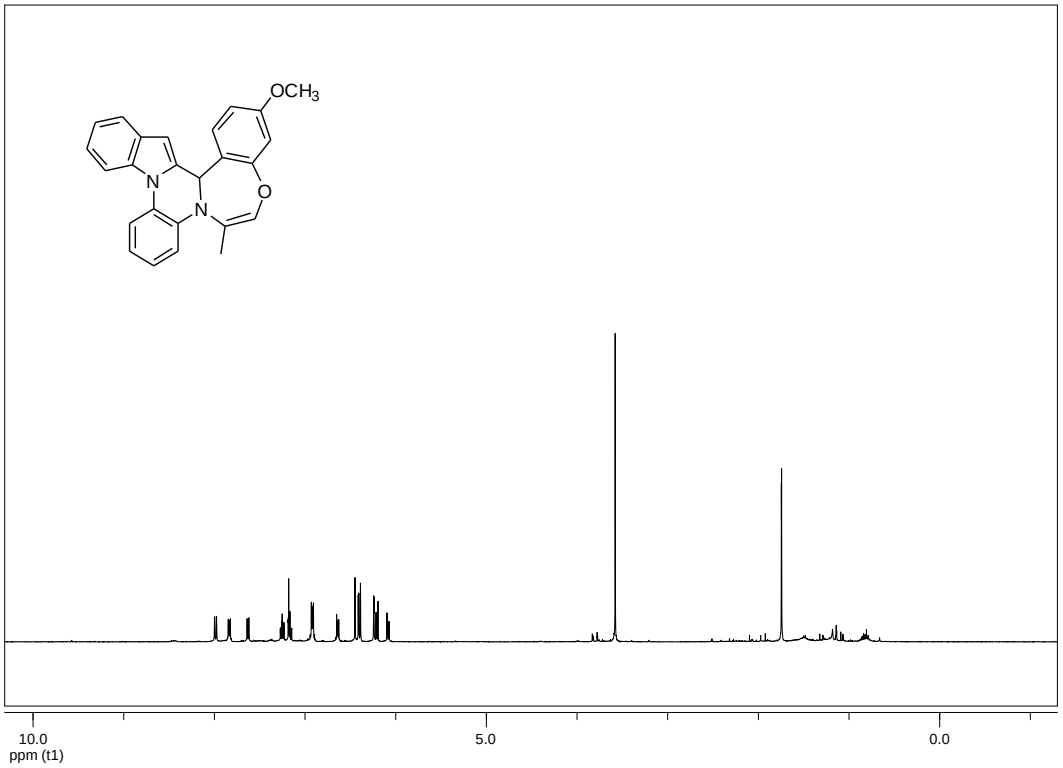



**Figure A39.** $^{1}$H NMR Spectrum of compound **68**.

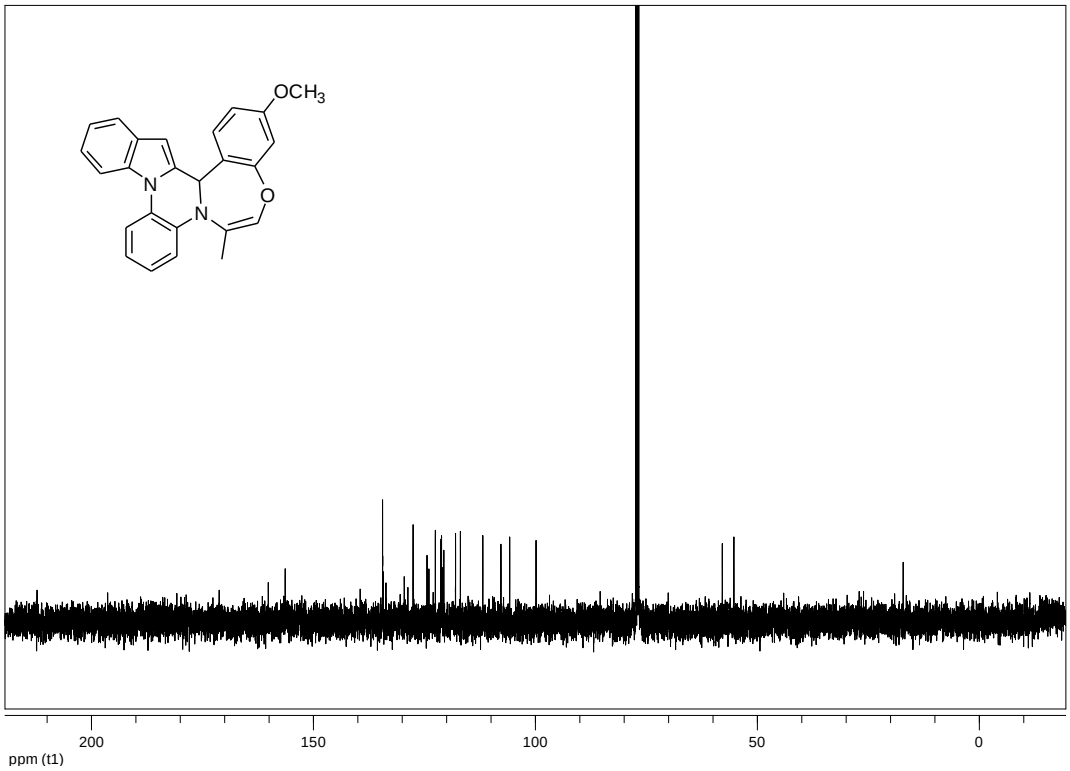



**Figure A40.** $^{13}$C NMR Spectrum of compound **68**.

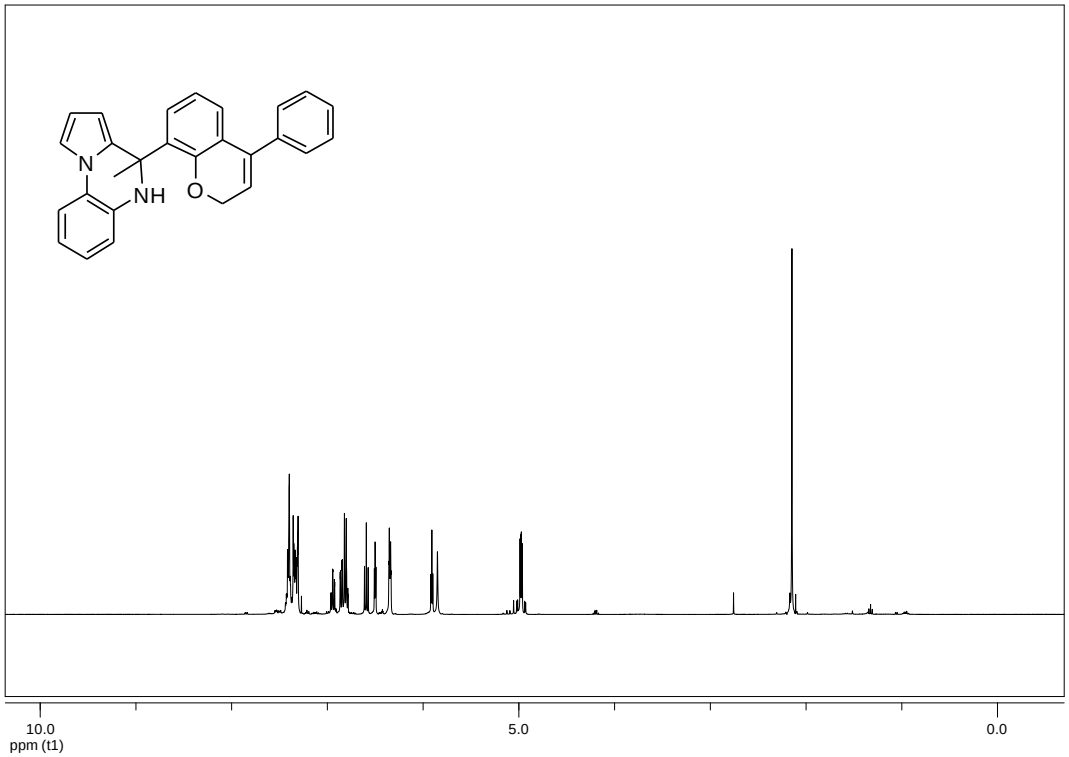



**Figure A41.** $^{1}$H NMR Spectrum of compound **105**.

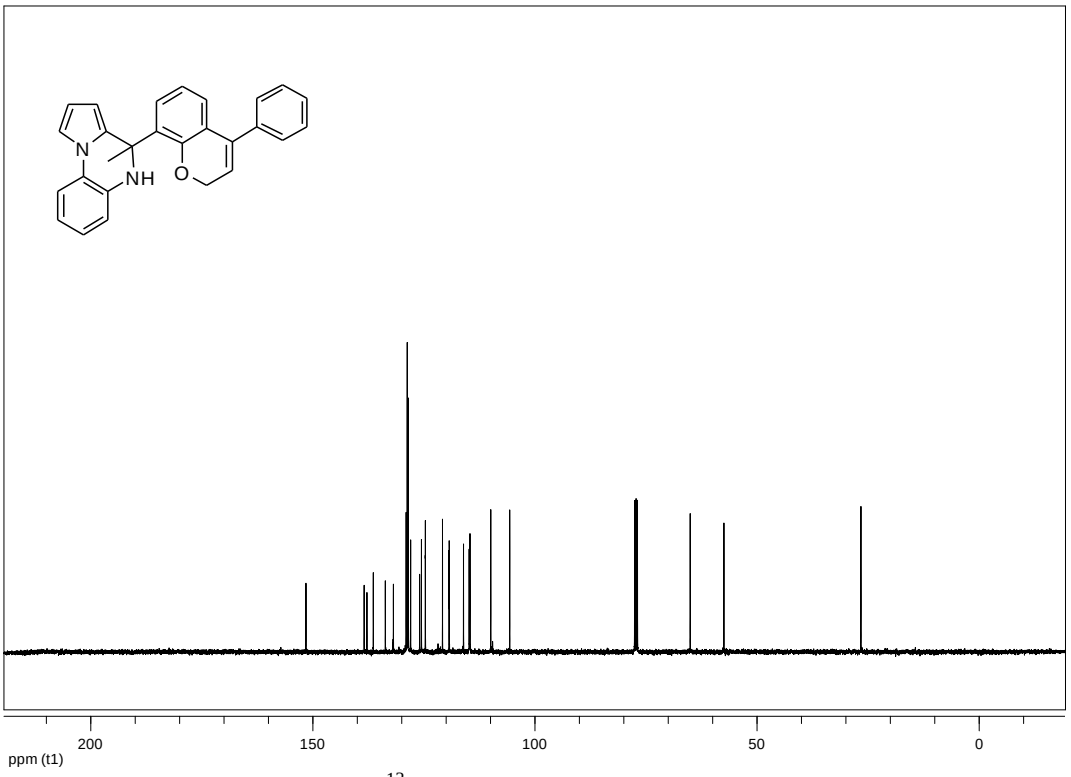



**Figure A42.** $^{13}$C NMR Spectrum of compound **105**.

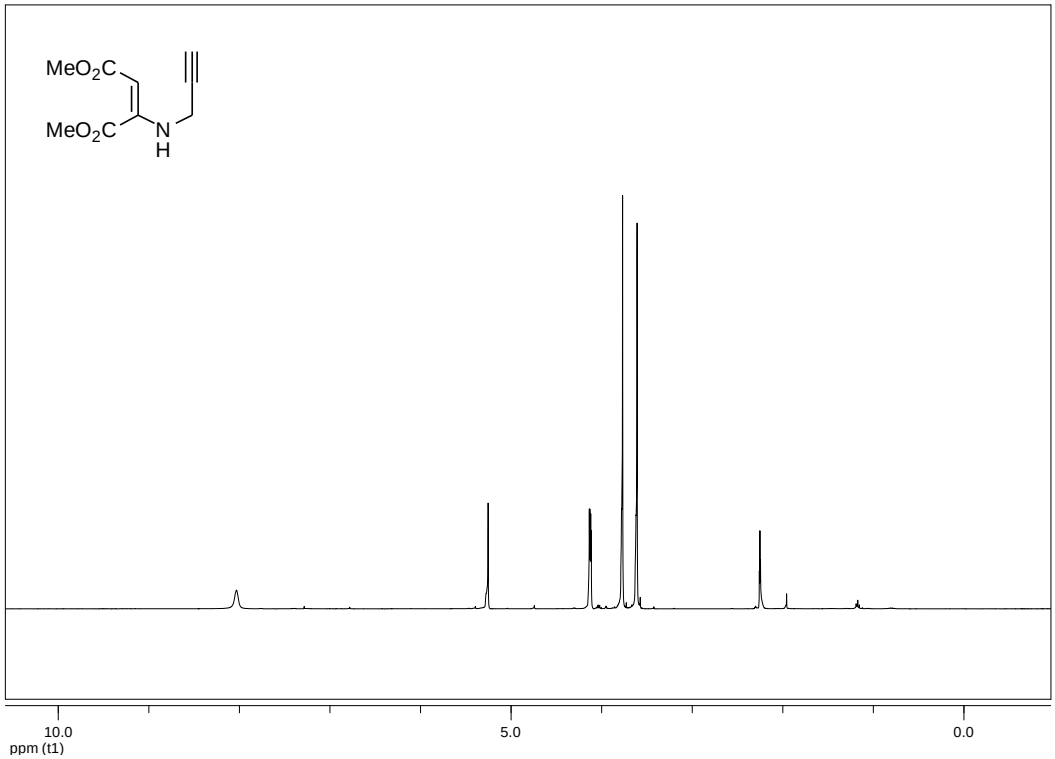



**Figure A43.** $^{1}$H NMR Spectrum of compound **69**.

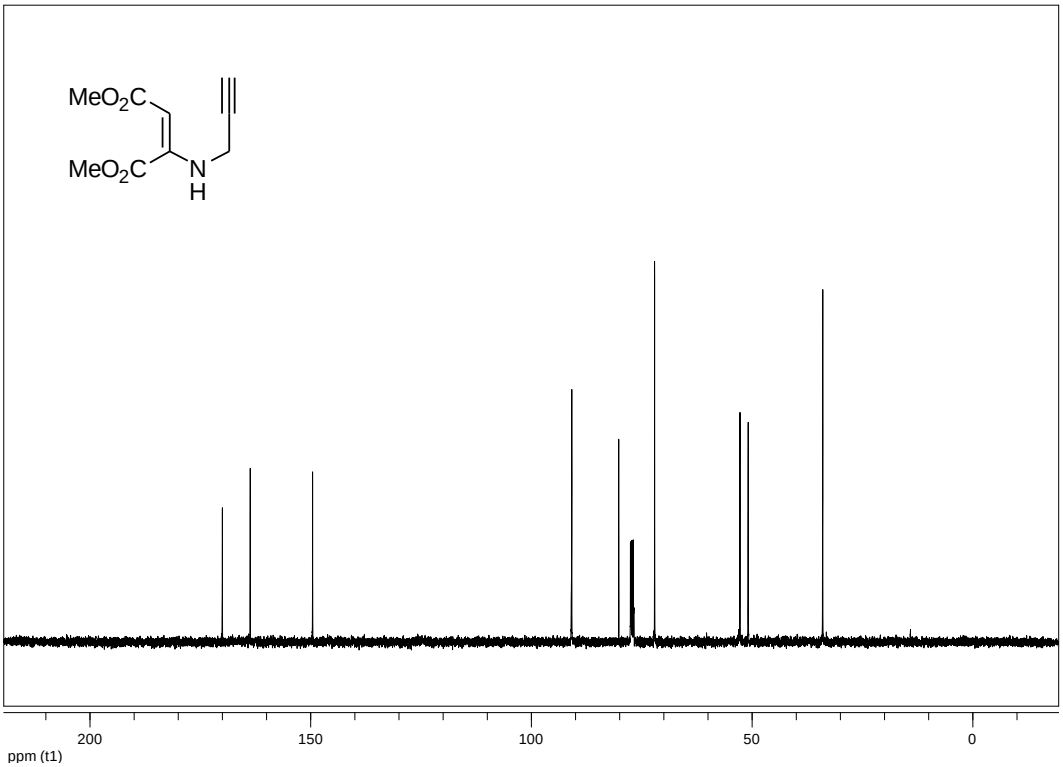



**Figure A44.** $^{13}$C NMR Spectrum of compound **69**.

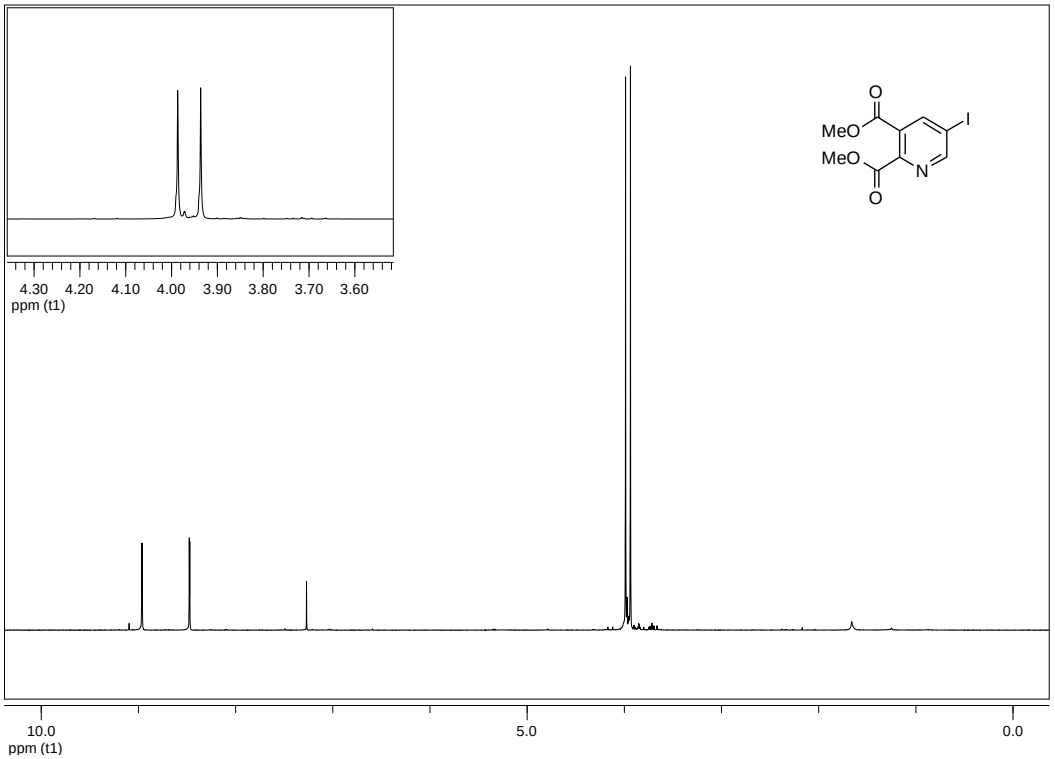



**Figure A45.** $^{1}$H NMR Spectrum of compound **70**.

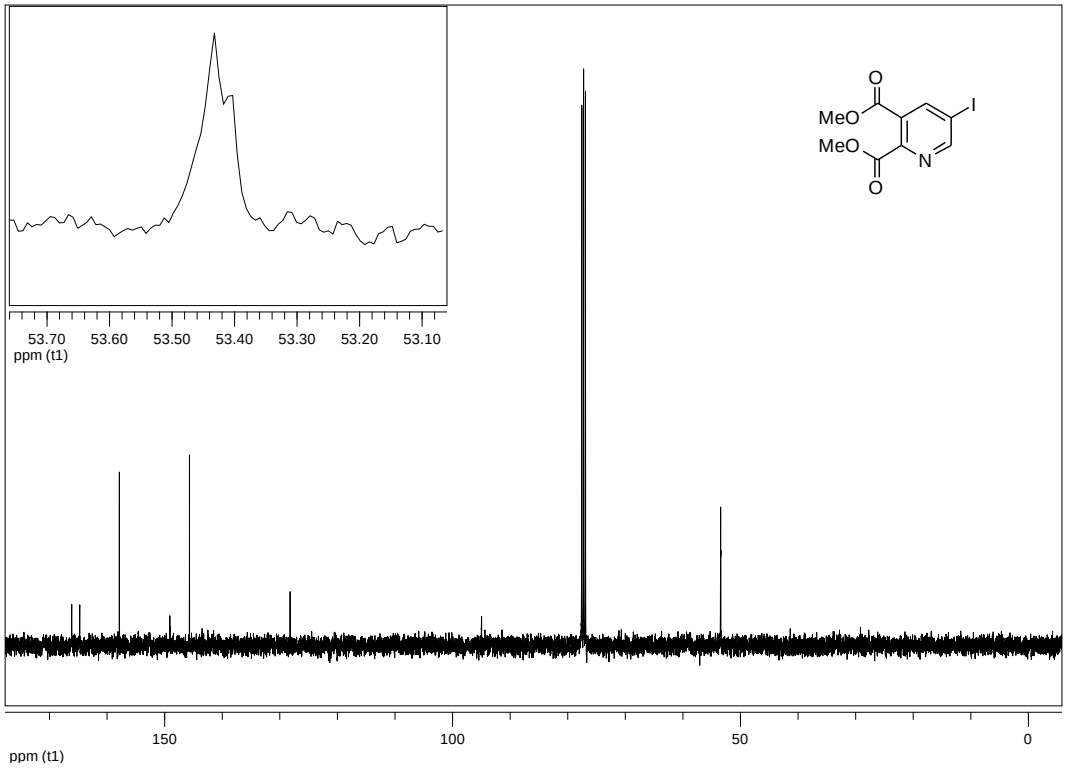



**Figure A46.** $^{13}$C NMR Spectrum of compound **70**.

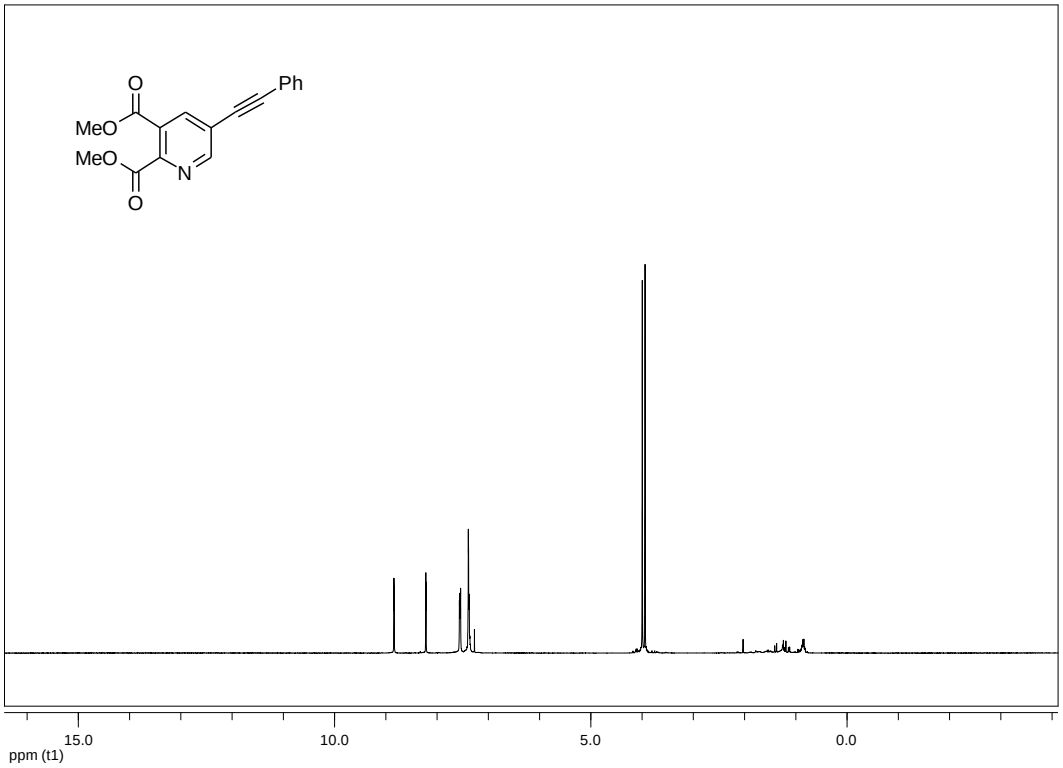



**Figure A47.** $^{1}$H NMR Spectrum of compound **79**.

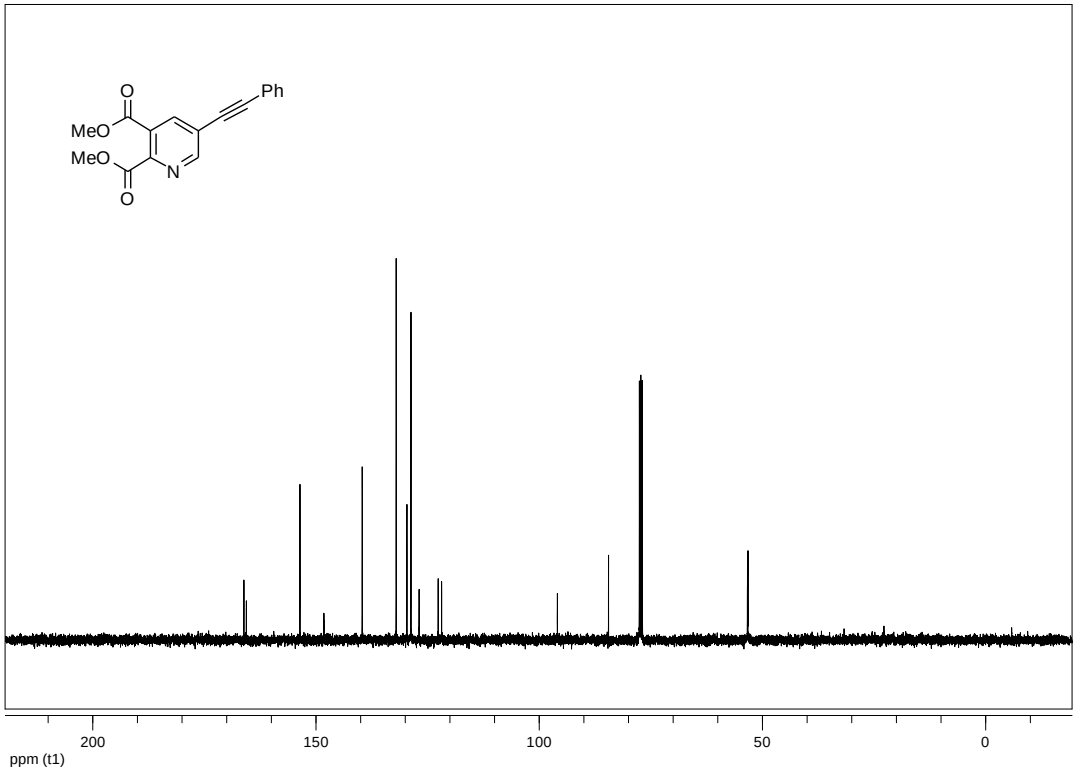



**Figure A48.** $^{13}$C NMR Spectrum of compound **79**.

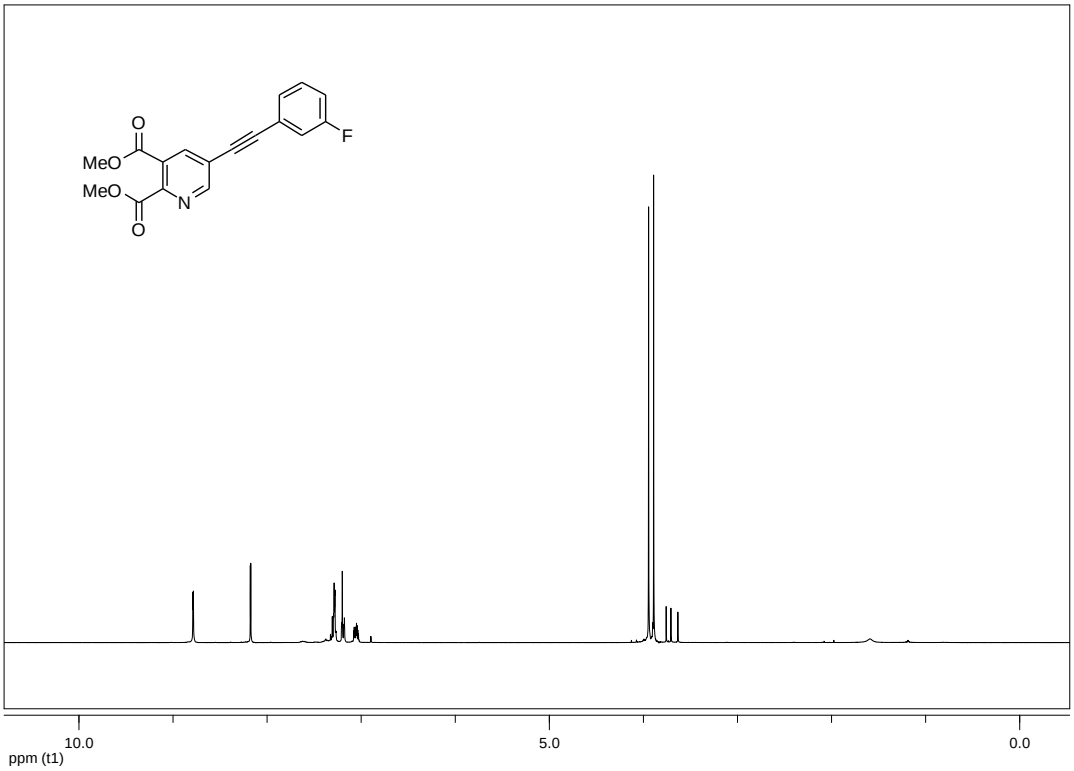



**Figure A49.** $^{13}$C NMR Spectrum of compound **80**.

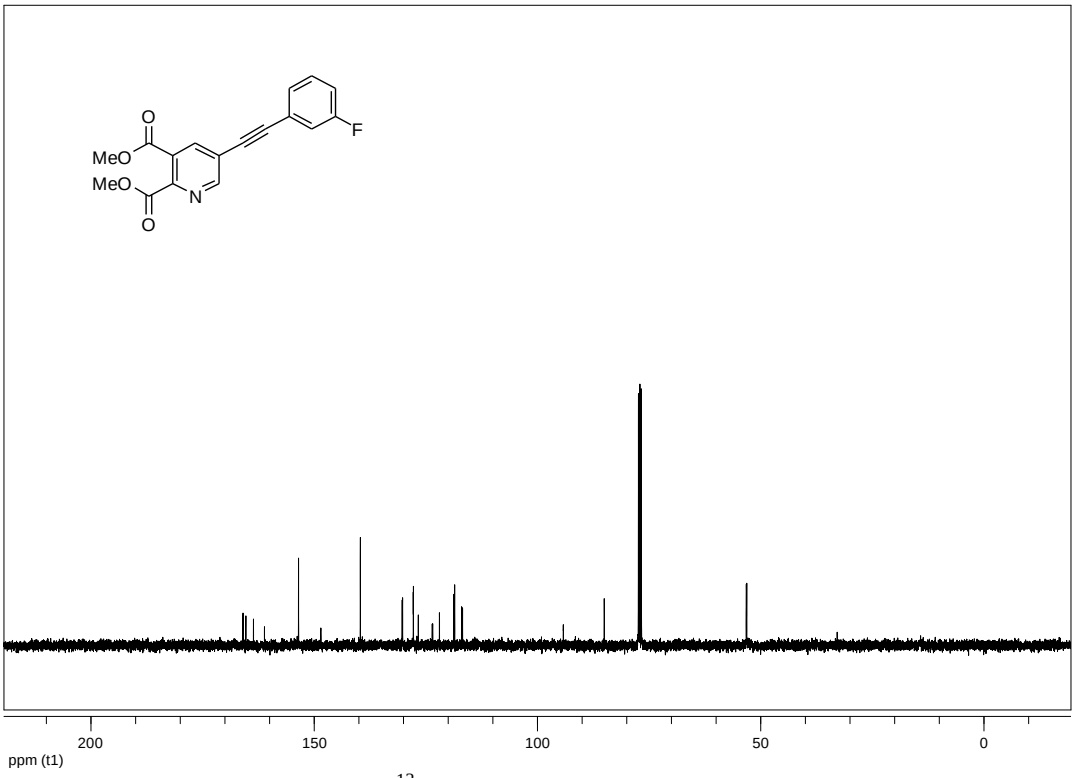



**Figure A50.** $^{13}$C NMR Spectrum of compound **80**.

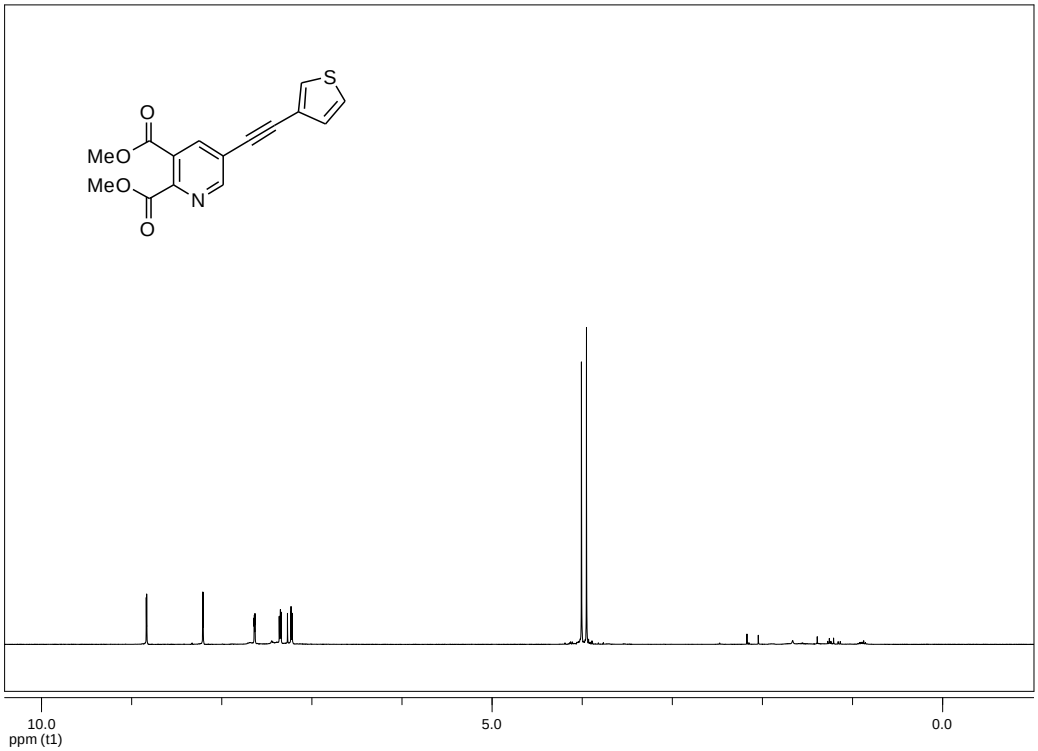



**Figure A51.** $^{1}$H NMR Spectrum of compound **81**.

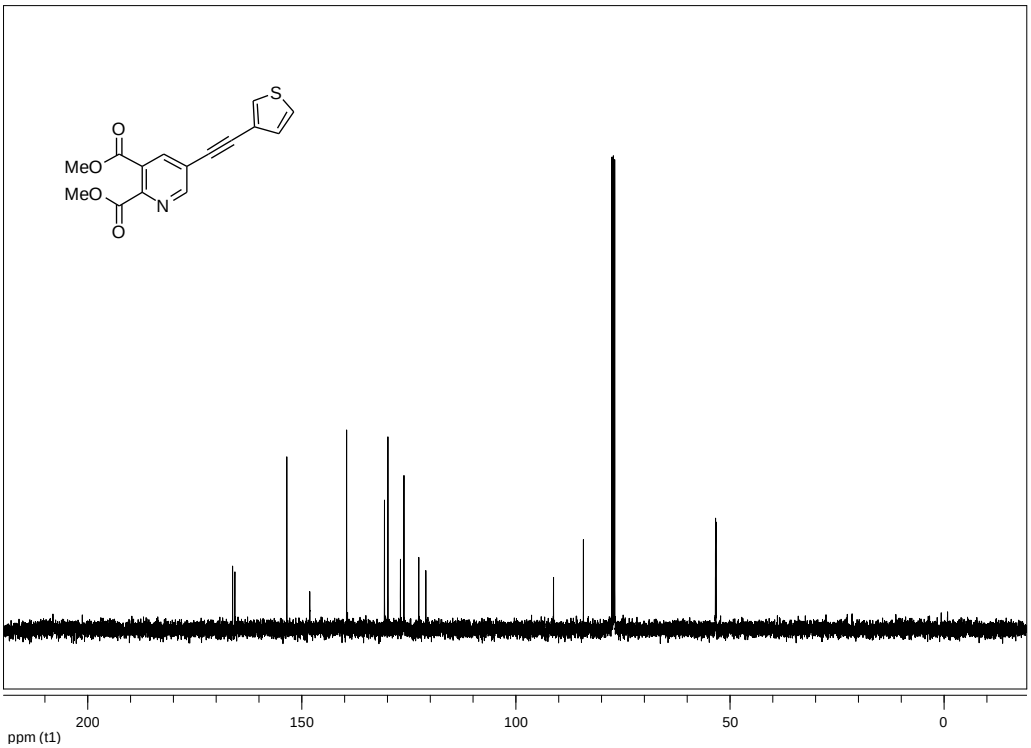



**Figure A52.** $^{13}$C NMR Spectrum of compound **81**.

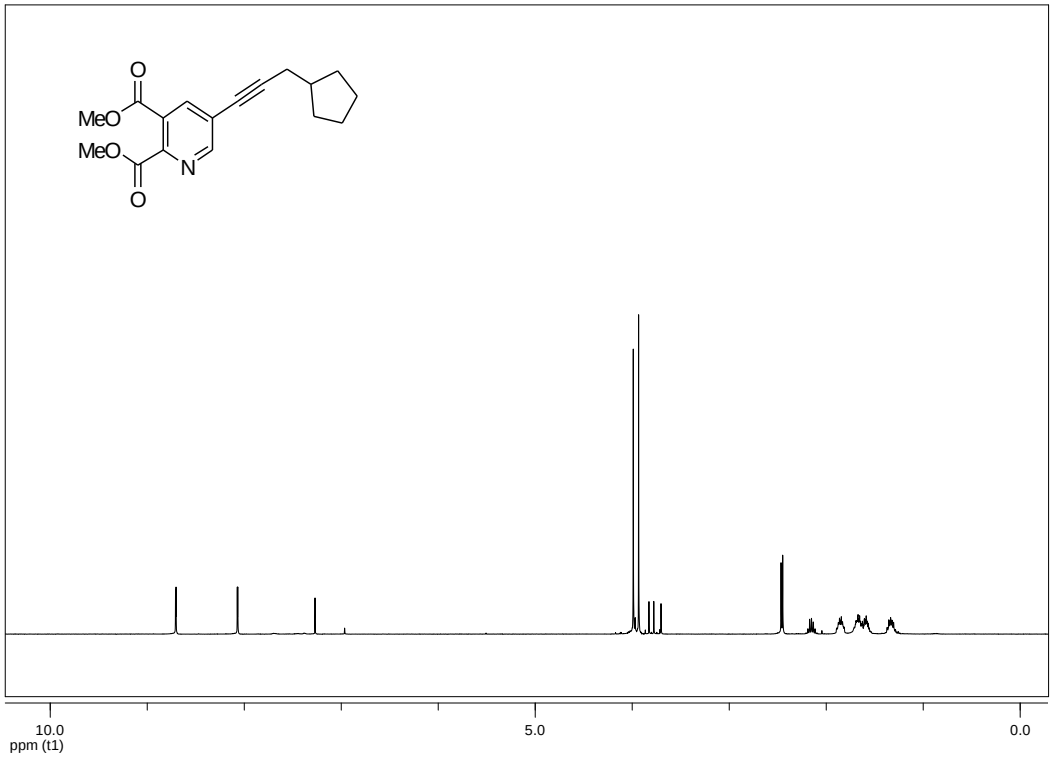



**Figure A53.** $^{13}$C NMR Spectrum of compound **82**.

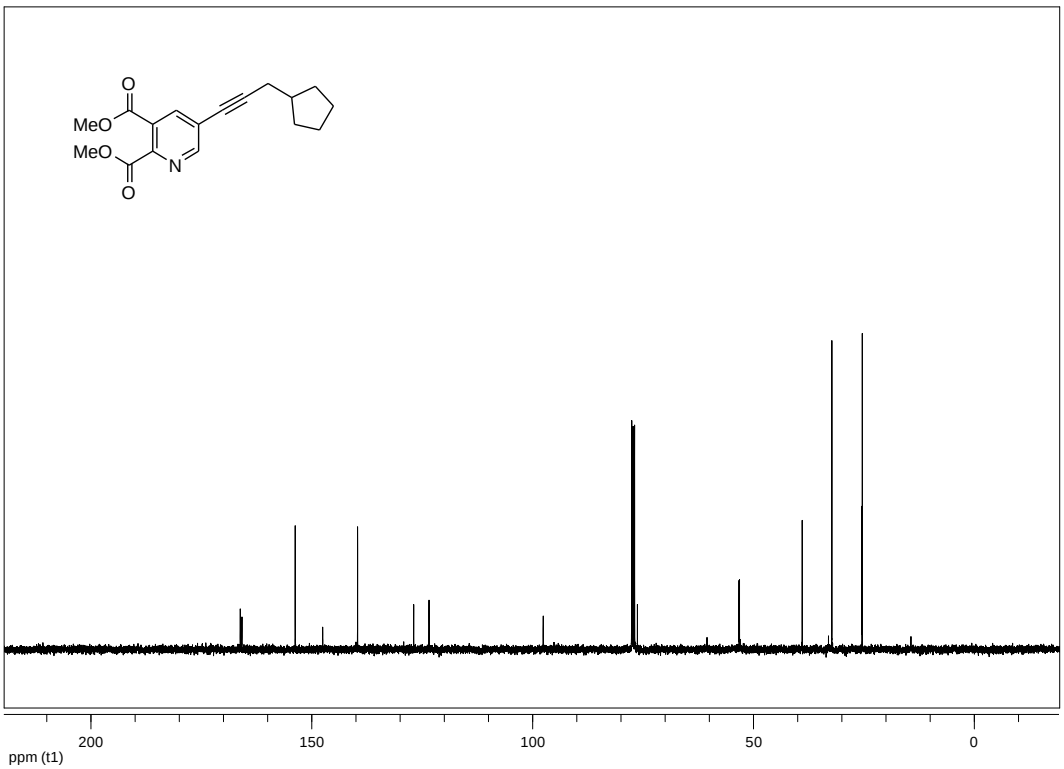



**Figure A54.** $^{13}$C NMR Spectrum of compound **82**.

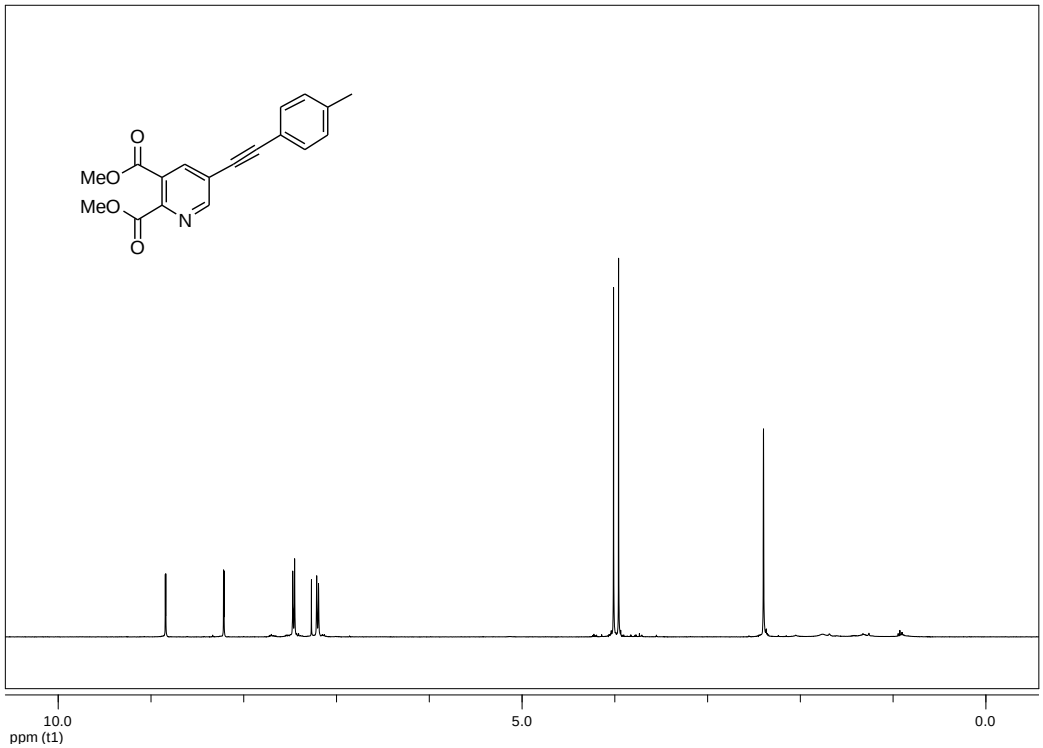



**Figure A55.** $^{13}$C NMR Spectrum of compound **83**.

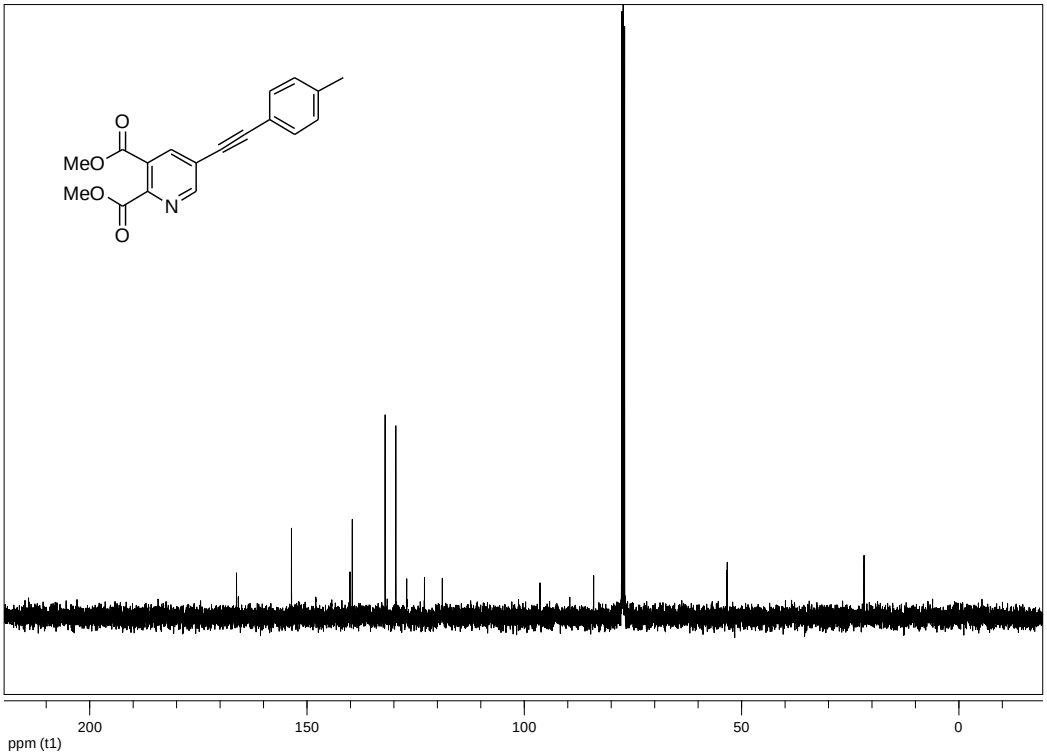



**Figure A56.** $^{13}$C NMR Spectrum of compound **83**.

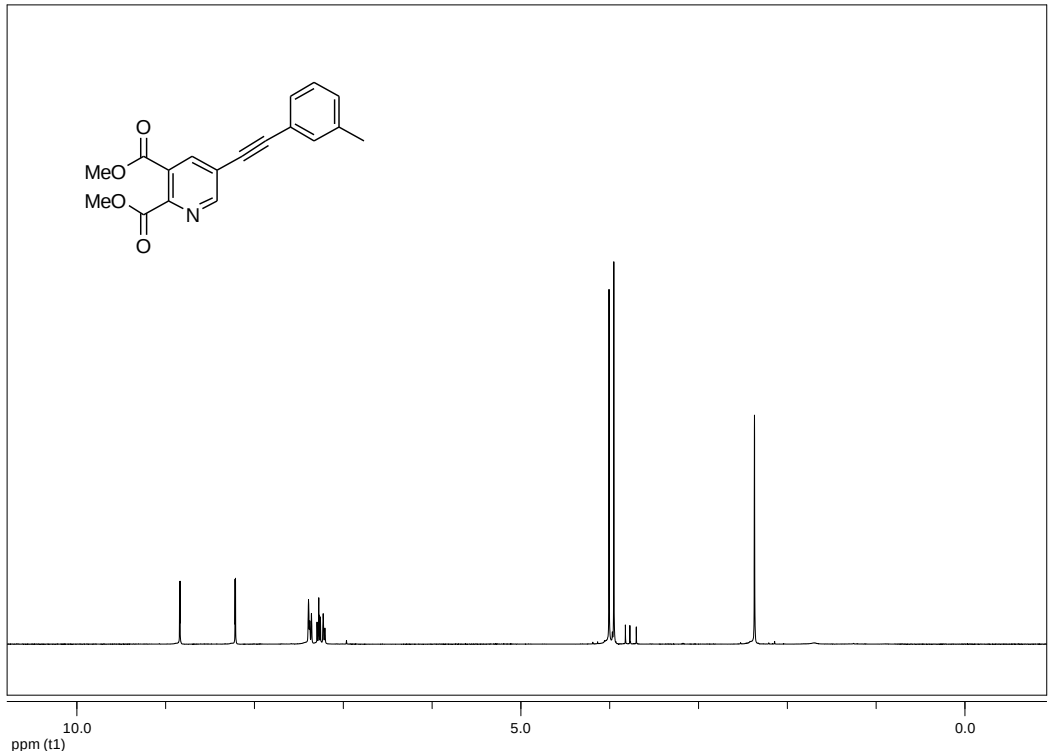



**Figure A57.** $^{1}$H NMR Spectrum of compound **84**.

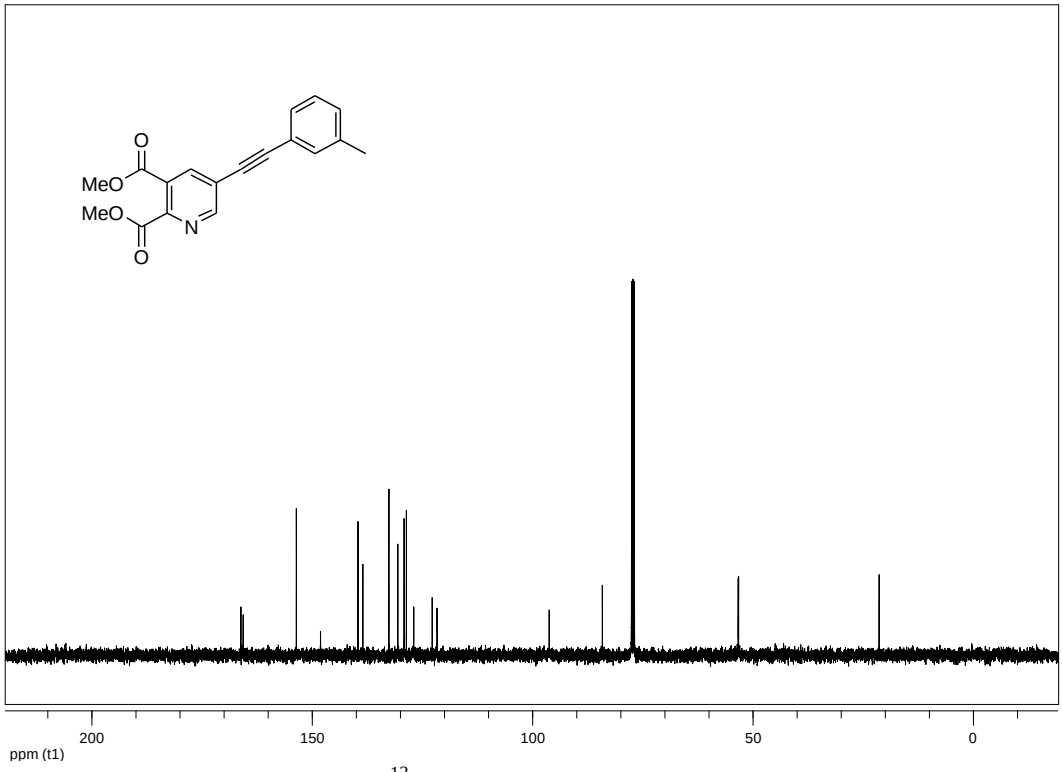



**Figure A58.** $^{13}$C NMR Spectrum of compound **84**.

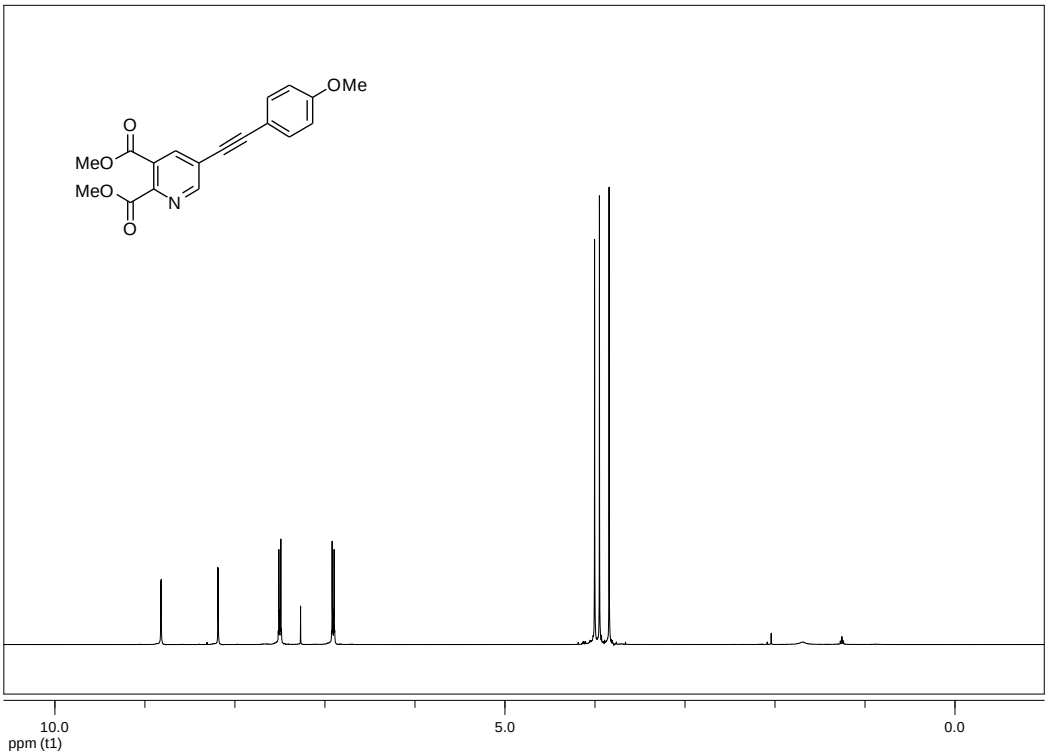



**Figure A59.** $^{1}$H NMR Spectrum of compound **85**.

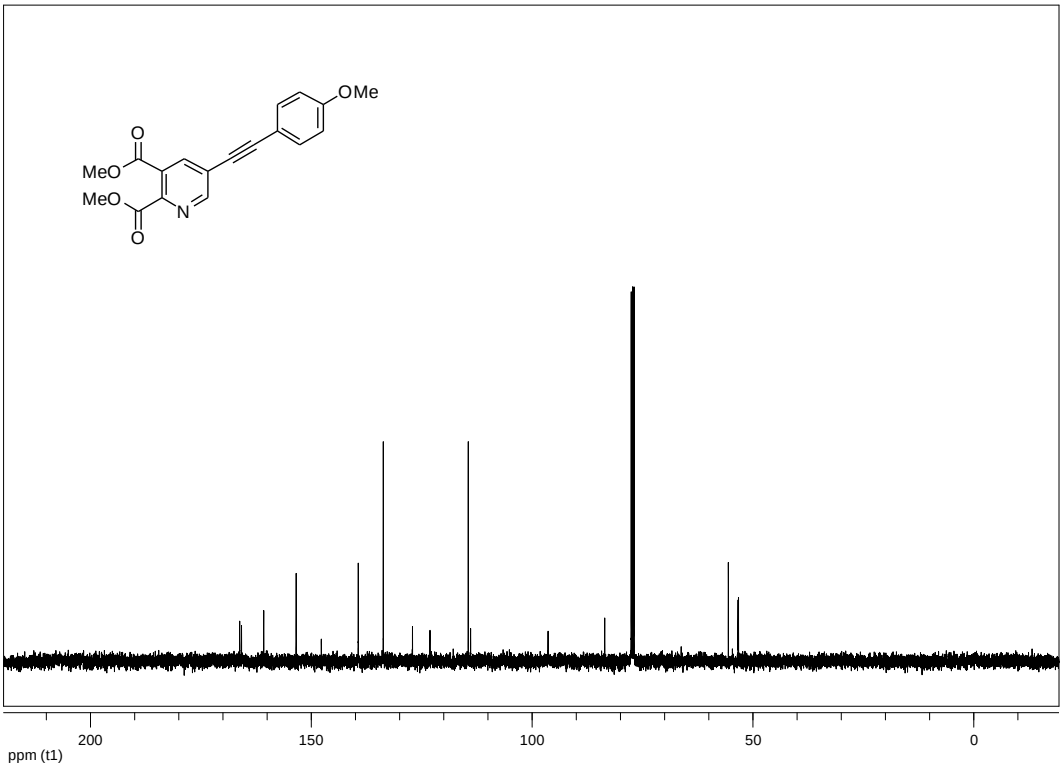



**Figure A60.** $^{13}$C NMR Spectrum of compound **85**.

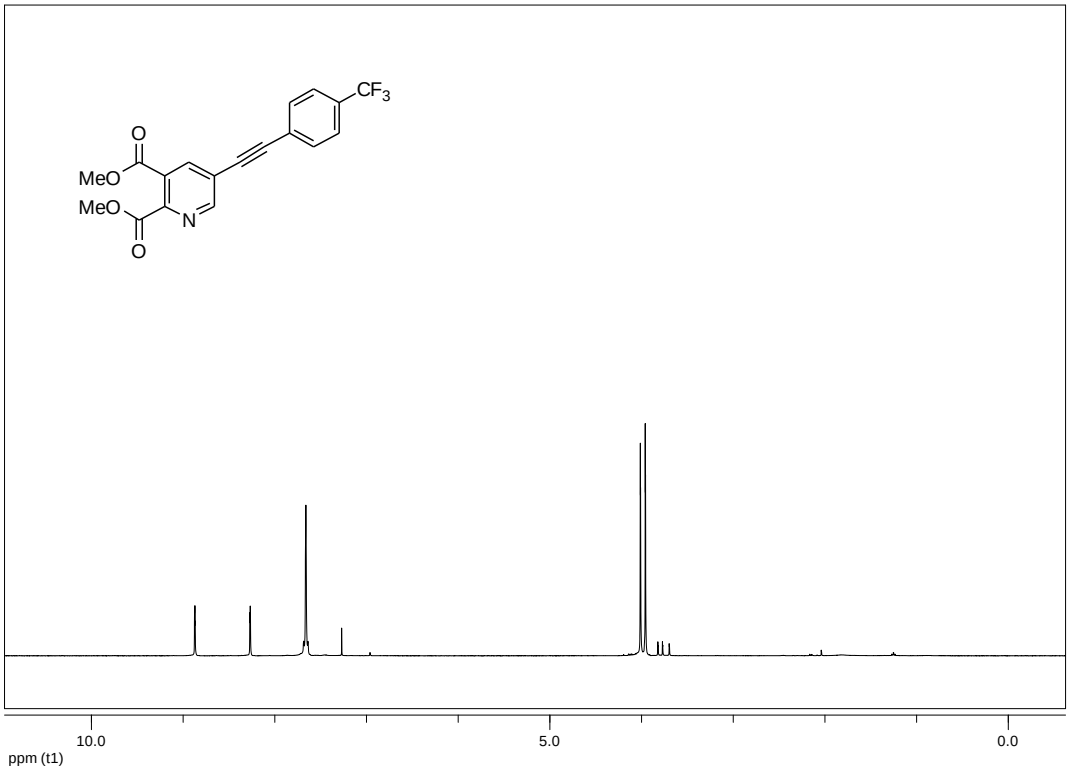



**Figure A61.** $^{1}$H NMR Spectrum of compound **86**.

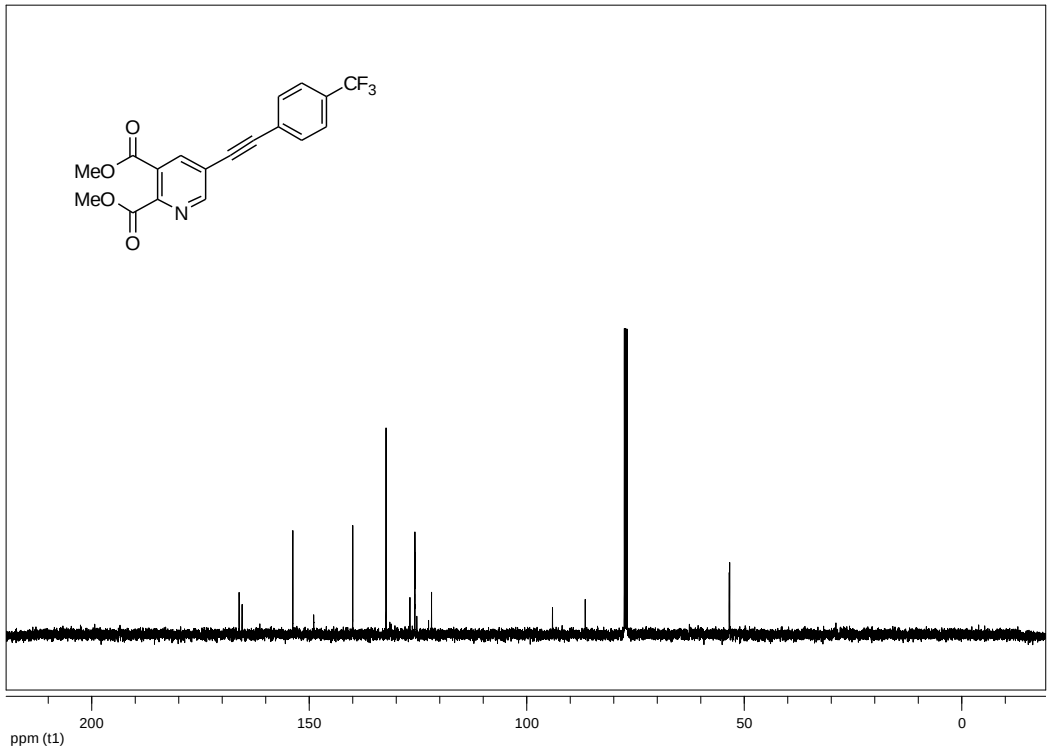



**Figure A62.** $^{13}$C NMR Spectrum of compound **86**.