DEVELOPMENT OF NEW METHODS FOR THE SYNTHESIS OF FIVE-, SIX- AND SEVEN-MEMBERED HETEROCYCLIC COMPOUNDS

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ABSTRACT

DEVELOPMENT OF NEW METHODS FOR THE SYNTHESIS OF FIVE-, SIX- AND SEVEN-MEMBERED HETEROCYCLIC COMPOUNDS

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Synthesis of heterocyclic compounds has become an important area among organic chemists since they occupy a unique position in the design and synthesis of novel biologically active agents that exhibit noteworthy medicinal activities. In this regard, *N*-propargylic β-enaminones have been recognized as valuable substrates in synthesis because they afford a variety of heterocyclic compounds upon treatment with proper reagents. In this study, new reactivity patterns of *N*-propargylic β-enaminones were investigated in order to synthesize different heterocyclic compounds. Accordingly, in the first part of study, 5-iodopyridines were prepared by electrophilic cyclization of *N*-propargylic β-enaminones, and then their Suzuki-Miyaura coupling reaction with boronic acids were investigated to afford 5-aryl-substituted pyridines. Secondly, a facile one-pot method for the synthesis of 2-ferrocenylpyridines has been established. The reaction of α,β-alkynic ketones with propargylamine produced *N*-propargylic β-enaminones in situ, which, in the presence of copper(I) chloride, have underwent electrophilic cyclization to furnish 2-ferrocenylpyridine derivatives. Thirdly, an efficient method for the synthesis of spiro-2*H*-pyrroles has been developed. When reacted with 1-ethynylcyclohexylamine, α,β-alkynic ketones produced cyclohexane-embedded *N*-propargylic β-enaminones, which, upon treatment with cesium carbonate, yielded spiro-2*H*-pyrrole derivatives via nucleophilic cyclization. In addition, cyclohexane-embedded *N*-propargylic β-enaminones were further functionalized with aryl iodides. Subsequently, when these arylated β-enaminones were exposed to cesium carbonate mediated nucleophilic cyclization, they produced spiro-2*H*-pyrroles with two carbonyl groups via further benzylic C-H oxidation. In the last part, a different approach have been employed for the synthesis of spiro-1,4-oxazepines. Upon treatment with zinc iodide and silver hexafluoroantimonate, cyclohexane-embedded *N*-propargylic β-enaminones produced spiro-1,4-oxazepines.

Keywords: Pyridines, Spiro-2H-pyrroles, Spiro-1,4-oxazepines, N-Propargylic β-enaminones

ÖZ

BEŞ, ALTI VE YEDİ ÜYELİ HETEROHALKALI BİLEŞİKLERİN SENTEZİ İÇİN YENİ METOTLARIN GELİŞTİRİLMESİ

Karadeniz, Eda
Doktora, Kimya
Tez Danışmanı: Prof. Dr. Metin Zora

Ekim 2019, 310 sayfa

Önemli tıbbi özellikleri ve biyoaktif bileşiklerin tasarım ve sentezinde eşsiz bir yere sahip olmalarından dolayı heterohalkalı bileşiklerin sentezi organik kimyacılar arasında önemli bir araştırma alanı olmuştur. Bu bakımdan, *N*-proparjilik β-enaminonlar uygun reaktifler ile tepkimeye girdiklerinde çeşitli heterohalkalı bileşikleri üretebildikleri için değerli ara ürünler olarak kabul edilmektedirler. Bu çalışmada, farklı heterohalkalı bileşikler sentezlemek için, *N*-proparjilik β-enaminonların yeni reaktivite özellikleri araştırılmıştır. Çalışmanın ilk bölümünde, *N*-proparjilik β-enaminonların elektrofilik halkalaşmasıyla 5-iyodopiridinler hazırlanmış ve sonrasında boronik asitler kullanılarak Suzuki-Miyaura kenetlenme tepkimesi ile 5-arilpiridinlerin sentezi incelenmiştir. İkinci olarak, 2-ferrosenilpiridinlerin sentezi için tek kapta gerçekleşen kolay bir metot geliştirilmiştir. α,β-Alkinik ketonlar ile proparjilamin tepkimeye girdiğinde tepkime ortamında *N*-proparjilik β-enaminonları oluşturmakta, bunlarda bakır(I) klorür varlığında elektrofilik halkalaşmasına girerek 2-ferrosenilpiridin türevlerini üretmektedir. Üçüncü olarak, spiro-2*H*-pirollerin sentezi için etkili bir yöntem geliştirilmiştir. Bunun için ilk olarak, 1-etinilsiklohekzilamin'in α,β-alkinik ketonlarla tepkimesi sonucu spiro grubu içeren *N*-proparjilik β-enaminonlar hazırlanmış ve sonrasında sezyum karbonat varlığında nükleofilik halkalaşma ile spiro-2*H*-pirol türevlerinin oluşum tepkimeleri araştırılmıştır. Buna ek olarak, spiro grubu içeren *N*-proparjilik β-enaminonlar, aril iyodürler kullanılarak daha da türevlendirilmiştir. Sonrasında, türevlendirilmiş β-enaminonlar, sezyum karbonat ile nükleofilik halkalaşma tepkimesine sokularak iki karbonil grubu içeren spiro-2*H*-piroller elde edilmiştir. Son bölümde ise, spiro-1.4-oksazepinlerin sentezi için farklı bir yaklaşım tarzı araştırılmıştır. Spiro grubu içeren *N*-proparjilik β-enaminonlar, çinko iyodür ve gümüş hekzafloroantimon varlığında tepkimeye sokulduklarında spiro-1,4-oksazepin türevleri elde edilmiştir.

Anahtar Kelimeler: Piridinler, Spiro-2H-piroller, Spiro-1,4-oksazepinler, N-proparjilik β-enaminonlar

To My Dear Family

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ABBREVIATIONS

ATR	attenuated total reflection
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPA	diisopropylamine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
HRMS	high resolution mass spectrometry
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser spectroscopy
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography

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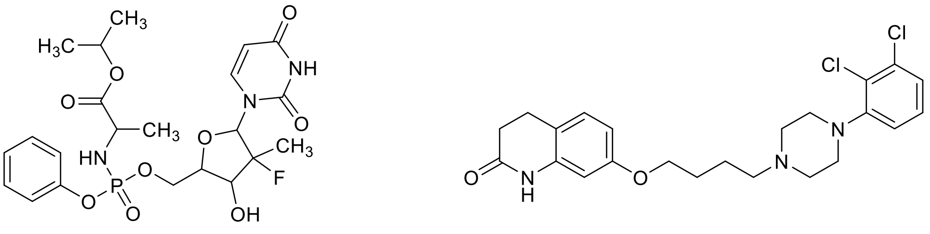
SCHEMES

CHAPTER 1

INTRODUCTION

Organic chemistry is the study of carbon compounds and it is considered as one of the most important branches of chemistry because every living organism is composed of organic compounds.[1] For example, deoxyribonucleic acid (DNA) is the carrier of genetic heritage in all living beings, proteins and enzymes play important role in vital processes of all organisms, and carbohydrates and fats are essential for energy balance of the body. These are all organic compounds and they have great importance for the continuity of life. However, organic chemists are not only interested in the chemistry of life and natural carbon compounds but also sophisticated ability to design and synthesize new organic compounds in medicines, dyes, polymers, pesticides, food additives and a large number of other substances. Therefore, organic chemistry touches the lives of everyone else.[1]

In particular, heterocyclic compounds, which contain at least one heteroatom other than carbon in their ring forming carbon skeletons, occupy unique place in organic chemistry. The most common heteroatoms are nitrogen, oxygen and sulphur.[2] Heterocyclic compounds are widely found in biologically active natural products, organic materials, agrochemicals, additives and modifiers.[3,4] Moreover, heterocycles constitute common structural scaffolds of the most marketed drugs. According to the top of five US small molecule drug retail sales in 2014, four of the five drugs contain heterocyclic units in their structures (Figure 1). These four drugs have brought in approximately 27.4 million U.S. dollars, almost 80% of total income came from the top five drugs.[5] Consequently, development of new and efficient synthetic approaches for the synthesis of heterocyclic compounds and finding specific properties of heterocycles are the main objective for organic chemists. Especially, compounds, which contain five-, six- and seven-membered heterocycles such as pyrroles, pyridines and oxazepines, have gained importance owing to their wide variety of pharmacological properties.[6,7]



Sovaldi (Antiviral)

Aripiprazole (Antipsychotic)

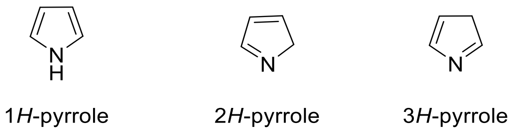
Esomeprazole (Antiulcerant)

Crestor (Cholesterol regulator)

Figure 1. Heterocyclic drugs present in the US top five prescription drugs in 2014.

1.1. Pyrroles

Pyrroles are five-membered heterocyclic aromatic compounds with one nitrogen heteroatom in their ring structure. Three classes of pyrroles are known: the more common aromatic *1H*-pyrroles and the less familiar 2*H*- and 3*H*-pyrroles (Figure 2). The latter two classes, which were defined in early literature examples as isopyrroles and as pyrrolenines, are nonaromatic because of the presence of the tetrahedral carbon atom in their ring.[8] In 1834, pyrrole was first detected by F. F Runge as a constituent of coal tar and it was isolated from the pyrolysate of bone in 1857.[9]



1*H*-pyrrole 2*H*-pyrrole 3*H*-pyrrole

Figure 2. Three classes of pyrroles.

1.1.1. Importance of Pyrroles

Pyrroles are one of the most important class of heterocyclic compounds and emerge in many natural products and synthetic pharmaceuticals.[10] In fact, pyrroles have a wide range of applications in many branches of science including biology, medicine and material science.[11] Pyrrole unit is an essential component of porphyrin rings, which plays a crucial role in biologically important compounds such as chlorophyll, heme, vitamin B_{12} and bile pigments (Figure 3).[12]

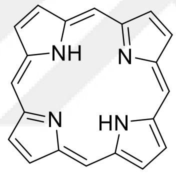
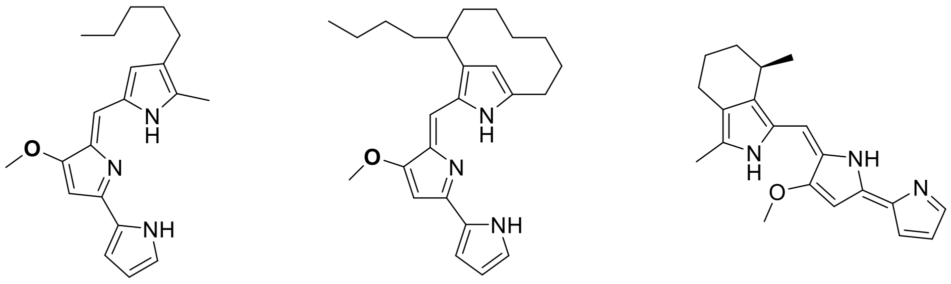


Figure 3. Structure of porphine (the simplest porphyrin ring).

Also, prodigiosin alkaloids, a family of naturally occurring red pigments produced by *Streptomyces*and *Serratia*, include a common pyrrole unit in their structures (Figure 4).[13]



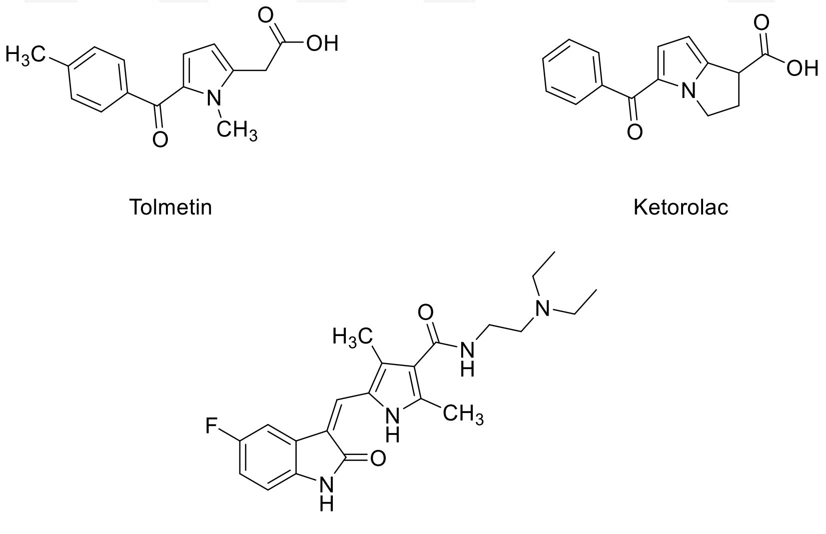
Prodigiosin

Sterptorubin B

Cycloprodigiosin

Figure 4. Representative members of the prodigiosin alkoloids family.

Notably, pyrrole and its derivatives are widely used as building blocks for medicinal research as well,[14] since they are present in the structures of a diverse range of marketed drugs, including neotropic *Aloracetam*, used for the treatment of Alzheimer's disease, anxiolytic *Isamoltane*, non-steroidal antiflammatory *Tolmetin* and *Ketorolac*, cholesterol-lowering *Atorvastatin*, antipsychotic *Elopiprazole* and anticancer *Sunitinib* (Figure 5).[15]



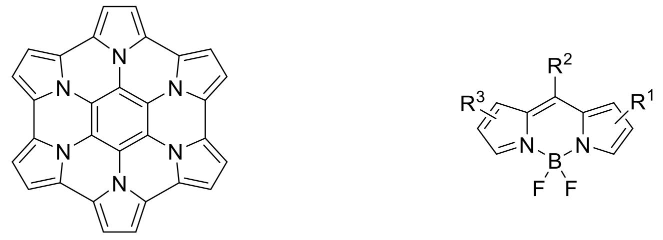
Tolmetin

Ketorolac

Sunitinib

Figure 5. Structures of *Tolmetin, Ketorolac* and *Sunitinib.*

Morover, pyrroles have great importance in material science because of their distinctive potential as components of boron-dipyrromethene (BODIPY) dyes and optoelectronic materials such as organic light emitting diodes (OLEDs), semiconductors and glucose sensors, two examples of which are given in Figure 6.[16]



A pyrrole based semiconductor

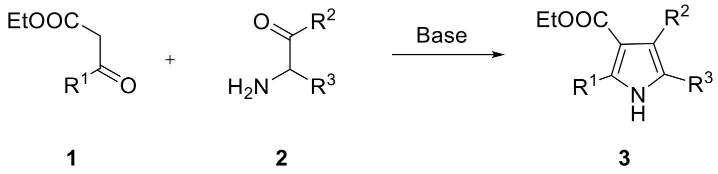
BODIPY dyes

Figure 6. Examples of pyrrole-containing compounds in material science.

1.1.2. Synthesis of Pyrroles

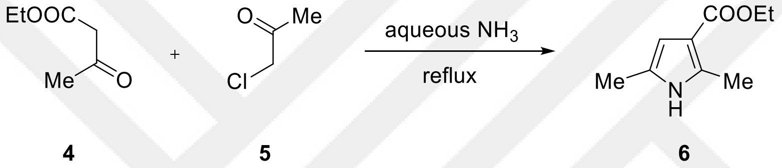
Pyrroles have been a prominent class of heterocyclic molecules in organic research owing to important biological, medicinal and materials science applications.[17] Therefore, development of efficient synthetic routes for their formation have attracted considerable attention from researchers of organic chemistry. A wide variety of methods exist in literature, in which different starting materials have been employed, such as *N*-propargylamines, α-diazoketones, 1,4-dicarbonyls, α-hydroxyketones, isocyanides, nitroalkanes or alkynes.[17] Also traditional approaches for the synthesis of pyrroles include Knorr and Hantzsch reactions.

In 1885, Knorr reported that cyclocondensation of α-aminoketones **2** with β-ketoesters **1** yielded substituted pyrroles **3** as depicted in Scheme 1.[18]



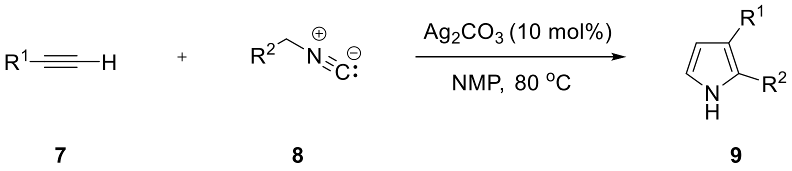
Scheme 1. Knorr pyrrole synthesis.

Then, Hantzsch in 1890 published that the reaction between acetoacetic ester (**4**) and α-chloroacetone (**5**) in the presence of aqueous ammonia afforded pyrrole derivative **6** (Scheme 2).[19]



Scheme 2. Hantzsch pyrrole synthesis.

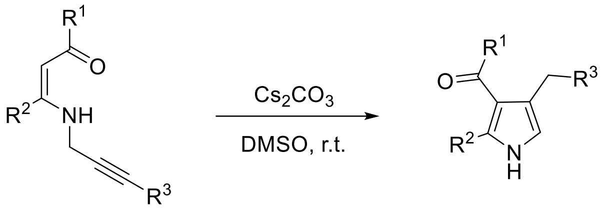
Moreover, Lei research group showed that silver-catalyzed reaction between terminal alkynes **7** and isocyanides **8** yielded substituted pyrroles **9,** as illustrated in Scheme 3.[20]



Scheme 3. Silver-catalyzed pyrrole synthesis.

Notably, cyclization of *N*-propargylic β-enaminones mostly produced pyrrole and pyridine derivatives. In 2008, Cacchi and co-workers described the conversion of *N*-

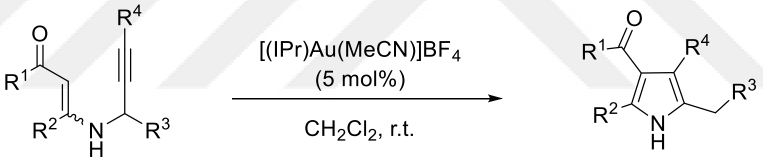
propargylic β-enaminones **10** into pyrroles **11** in the presence of cesium carbonate (Scheme 4).[21]



10 **11**

Scheme 4. Base-mediated synthesis of pyrroles.

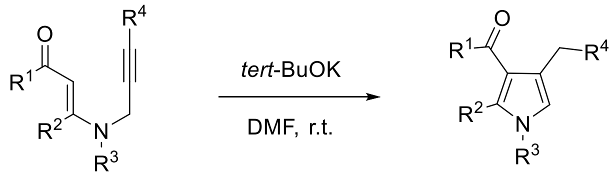
Then, in 2010 Saito, research group found that [(IPr)Au(MeCN)]BF_4-catalyzed amino-Claisen rearrangement of *N*-propargylic β-enaminones **12**, followed by heterocyclization, yielded pyrrole derivatives **13** (Scheme 5).[22]



12 **13**

Scheme 5. Au(I)-catalyzed formation of pyrroles.

Most recently, Hu and Zhang showed that when treated with *tert*-BuOK in DMF at room temperature, *N*-alkyl, *N*-propargylic β-enaminones **14** yielded pyrrole derivatives **15** as well (Scheme 6).[23]



14 **15**

Scheme 6. Base-promoted synthesis of *N*-alkyl pyrroles.

1.2. Pyridines

Pyridines, in which one of carbon of benzene is replaced by nitrogen, are the six-membered heterocyclic aromatic compounds (Figure 7). In 1849, pyridine was discovered as one of the constituents of bone oil by chemist Thomas Anderson.[24] He separated pyridine from oil through fractional distillation. However, the cyclic structure of pyridine was recognized by Wilhelm Körner and James Dewar in 1869.[24]

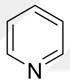
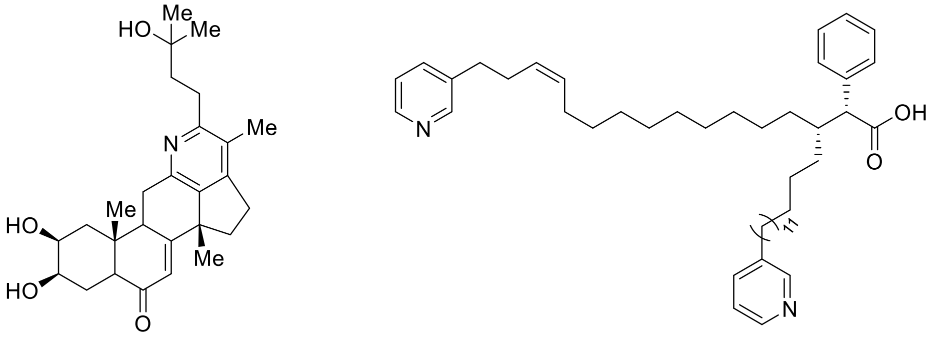


Figure 7. Structure of pyridine.

1.2.1. Importance of Pyridines

Pyridines are one of the most important classes of heterocyclic compounds and found in many natural products and medicinal compounds.[25] In fact, pyridines have a range of applications in many branches of chemistry, such as catalysis, drug design and synthesis, molecular recognition and material science.[26]



Diploclidine

Nakinadine A

Figure 8. Structures of *Diploclidine* and *Nakinadine A.*

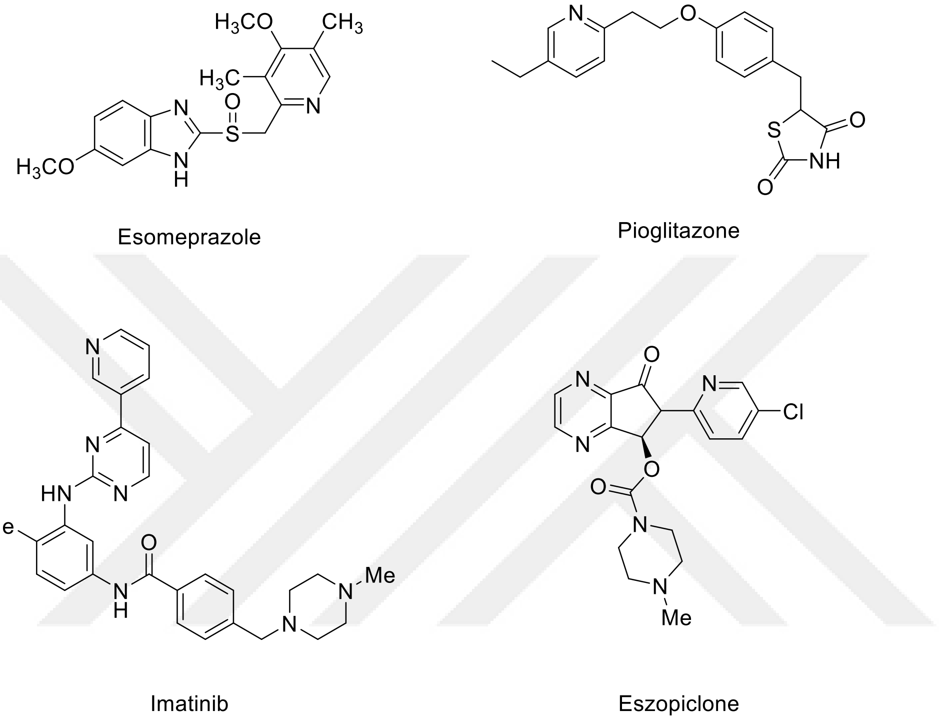
Pyridines are also important structural cores of diverse natural products such as *Diploclidine* and *Nakinadine A*, as depicted in Figure 8.[27] Moreover, there are many pyridine-based alkaloid natural products such as nicotinic acid and pyridoxine (also called vitamin B_3 and vitamin B_6, respectively) (Figure 9).[28] They are found in many multiple vitamins and nutritional supplements. Among them, nicotinic acid is used in NADP/NADPH redox system and lowering cholesterol and triglycerides in the blood. It is also used to lower the risk of heart attack in people with high cholesterol. Moreover, pyridoxine plays an active role in amino acid metabolism.

Nicotinic acid (Vitamin B_3)

Pyridoxine (Vitamin B_6)

Figure 9. Structures of nicotinic acid and pyridoxine.

Notably, pyridines are broadly used in pharmaceutical research because they are found in the structures of a diverse range of pioneering drugs, including anticancer *Imatinib,*[29] antidiabetic *Pioglitazone,*[30] antihistaminic *Desloratadine,*[31]antineoplastic and HIV antiviral *Atazanavir,*[32] bone calcium regulator *Risedronate,*[33] hipnotic and sedative *Eszopiclone*,[34] cholesterol and triglyceride regulator *Niacin*[35] and antiulcerant *Esomeprazole* (Figure 10). Among them, *Esomeprazole*, which is tetrasubstituted pyridine derivative, placed in top twenty pharmaceutical products by sales worldwide in 2015.[36]


Esomeprazole

Pioglitazone

Imatinib

Eszopiclone

Figure 10. Some examples of drugs containing pyridine unit.

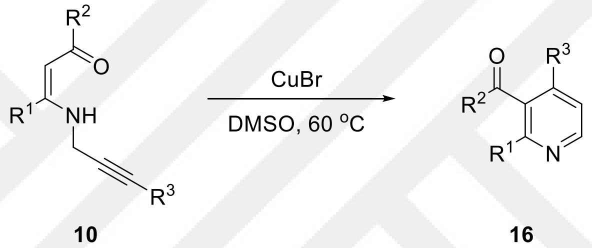
Moreover, pyridines are utilized in preparation of conjugated polymers and functional materials that are employed in the light-emitting devices (LEDs).[37]

1.2.2. Synthesis of Pyridines

Since pyridines are important scaffolds in natural products and pharmaceutical drugs, over many years, many methods have been developed and new ones continue to come out.[38] In this respect, in 1876, first synthesis of pyridine was achieved by William Ramsay via the reaction of acetylene and hydrogen cyanide in hot iron-tube furnace.[38]

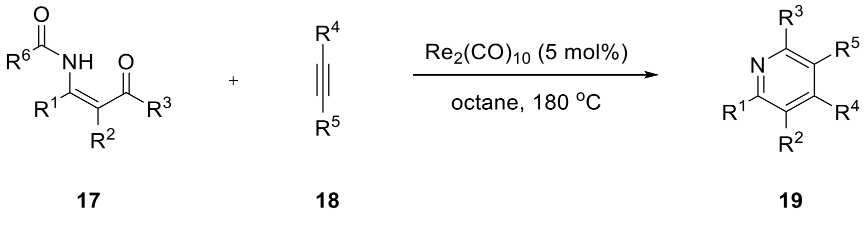
In 1920s, Chichibain synthesized pyridine from the reaction of aldehyde derivatives with ammonia which is one of the most widely used industrial method for the pyridine production.[39] After that, pyridine synthesis was continued with different types of methods, which commonly involve condensation of carbonyl compounds with amines or cycloaddition of azadienes and nitriles with alkane and alkynes.[40]

Recently, Fabrizi and Cacchi have reported that when treated with CuBr in DMSO, *N*-propargylic β-enaminones **10** afforded substituted pyridines **16** via 6-*endo-dig* cyclization (Scheme 7).[21]



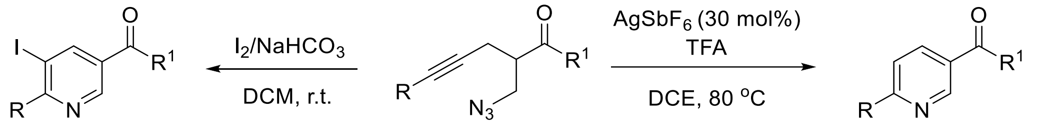
Scheme 7. Cu-catalyzed pyridine synthesis.

In 2012, Takai *et al.* described a different method for the synthesis of multisubstituted pyridine derivatives, which is shown in Scheme 8. When *N*-acetyl β-enamino ketones **17** reacted with alkynes **18** in the presence of the rhenium catalyst, $Re_2(CO)_{10}$, multisubstituted pyridines **19** were obtained (Scheme 8).[41]



Scheme 8. Rhenium-catalyzed synthesis of pyridines.

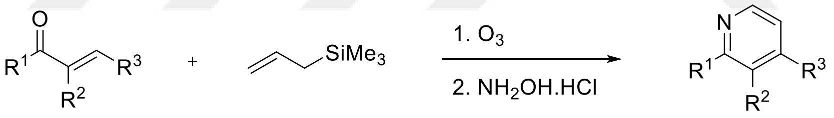
In 2015, Reddy and his co-workers established a method for the synthesis of pyridines through aza-annulation of 2-en-4-ynyl azides **20** (Scheme 9). In this study, Ag-catalyzed cyclization afforded 3,6-disubstituted pyridines **22**. However, in case of I_2-promoted annulation, the reaction gave 5-iodo-3,6-disubstituted pyridines **21**.[42]



21 **20** **22**

Scheme 9. Synthesis of pyridines via aza-annulation of enynyl azides.

Most recently, Rychnovsky and co-workers developed a method for constructing substituted pyridine rings, as illustrated in Scheme 10. This approach first involves the addition of allylsilane (**24**) to enone structure **23**. Then, oxidation and cyclization with hydroxylamine completes the synthesis of pyridine derivatives **25**.[43]

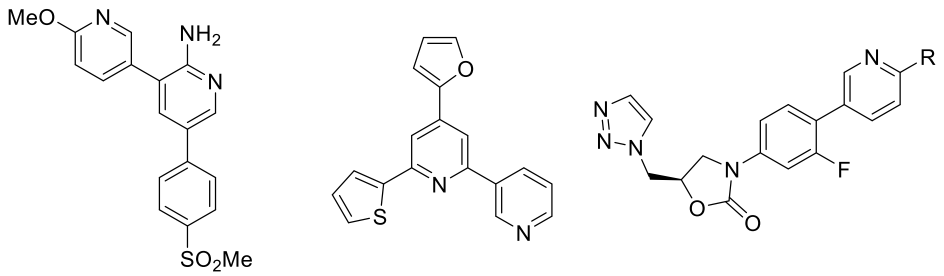


23 **24** **25**

Scheme 10. Synthesis of substituted pyridines.

1.2.3. Aryl-Substituted Pyridines

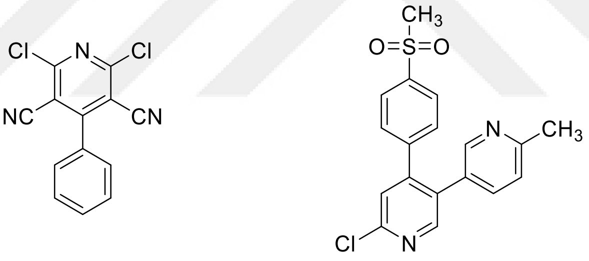
Aryl-substituted pyridines have an important place in pharmaceutical industry. In particular, properly substituted aryl-pyridines exhibit remarkable medicinal properties including antibacterial[44] antifungal,[45] anti-inflammatory,[46] antimalarial,[47] antitumor,[48] high potency calcium-sensing receptor antagonist,[49] and sodium channel inhibitory activities (Figure 11).[50]



Antimalarial Antitumor Antibacterial

Figure 11. Examples of aryl-substituted pyridines showing antimalarial, antitumor and antibacterial activities.

Moreover, *Pyridinitril* is a well known arylpyridine having fungicide activity.[45] *Etoricoxib* is a new class nonsteroidal anti-inflammatory drug. It specifically binds and inhibits the enzyme cyclooxygenase-2 (COX-2), which results in the prevention of conversion of arachidonic acid to prostaglandins.[46]



Pyridinitril Etoricoxib

Figure 12. Structures of *Pyridinitril* and *Etoricoxib.*

Also, arylpyridine-based dipeptyl peptidase-4 (DPP-4) inhibitors are relatively new class of oral diabetes drugs. DPP-4 inhibitors work by blocking the action of DPP-4 enzyme which destroys a group of gastrointestinal hormones. In this way, DPP-4 inhibitors treat the type-2 diabetes mellitus and help other metabolic disorders.[51]

In addition, some terpyridines and the related aryl-substituted pyridines have exhibited strong antitumor cytotoxicities against several human cancer cell lines and topoisomerase I inhibitory activities. Studies also revealed that the number of aryl groups attached to pyridine core plays an important role for their biological activities. When number of aryl substituents on the pyridine ring increases, enhanced biological activities could be observed.[52] Therefore, a large number of studies has been devoted to the synthesis of polyarylated pyridines which could be potential drug substances.

1.2.4. Ferrocenyl-Substituted Pyridines

Ferrocene is the most well-known sandwich-type organometallic compound (Figure 13).[53] The terms like 'sandwich compound' and 'metallocene' are commonly applied to define ferrocene and its derivatives. Ferrocene has obtained considerable importance in medicinal chemistry because it is chemically stable, non-toxic and able to cross cell membranes. Many ferrocene derivatives have displayed antifungal, antibacterial, antimalarial and antitumor activities.[53] For example, ferrocifen, which is a ferrocenyl analog of tamoxifen, shows antiproliferative activity on both hormone-dependent and hormone-independent breast cancer cells, while tamoxifen only displays antiestrogenic activity on hormone-dependent breast cancer cells (Figure 14).[53]

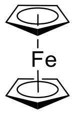
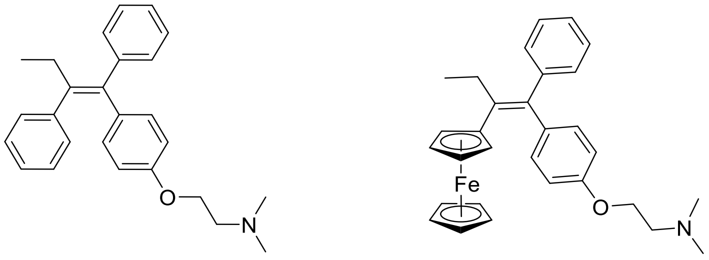


Figure 13. Structure of ferrocene.

Due to the dual effect of ferrocifen, researchers has started to synthesize and investigate further ferrocifen-like complexes. In fact, integration of ferrocene core into potentialy bioactive compounds can introduce new and novel properties. Therefore, development of new methods for their synthesis attracts the attention of organic chemists.



Tamoxifen Ferrocifen

Figure 14. Structures of tamoxifen and ferrocifen.

In particular, ferrocenyl pyridines have gained considerable importance because of their wide variety of applications in nonlinear optic devices, catalysis, self-assembly devices, electrochemical sensors and medicinal chemistry.[54] Ferrocenylpyridines have been also used as ligands for the synthesis of heterobimetallic complexes by the means of metal binding ability of pyridine nitrogen atom. In this manner, different metal complexes of ferrocenylpyridines have been synthesized to facilitate electronic interaction between metal centers.[55] Changing the oxidation state of ferrocenyl unit allows to tune electron density and so reactivity. Moreover, in Heck and Suzuki coupling reactions, carbene adducts of cyclopalladated ferrocenylpyridines have been used as catalyst.[56] In addition, ferrocenylpyridines have been utilized as anticancer agent against human cancer cell lines. Notably, some derivatives of ferrocenylpyridines have exhibited higher activity than cisplatin, which are used as common chemothepautic agents.[54] In brief, ferrocenylpyridines are valuable compounds with a wide range of applications and usage. So the development of new methods for their synthesis of attracts the interest of researchers.

1.3. Oxazepines

Oxazepines are seven-membered unsaturated heterocyclic compounds with one nitrogen and one oxygen heteroatoms. According to the positions of oxygen and nitrogen atoms in the ring, they are named as 1,2-oxazepine, 1,3-oxazepine and 1,4-oxazepine (Figure 15). In 1965, one of oxazepine derivatives, namely benzodiazepine, was first used in mental ease which has been characterized by anxiety and tension.[57]

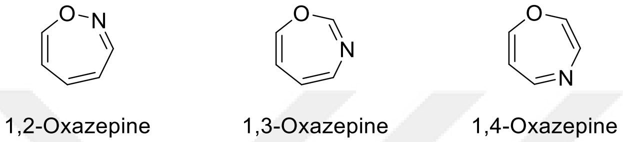


Figure 15. Three types of oxazepines.

1.3.1. Importance of Oxazepines

Seven-membered heterocycles, especially oxazepines, are an important class of molecules in the design and synthesis of bioactive compounds which show extraordinary medicinal activities.[58] Therefore, in recent years, appreciable number of methodologies have been developed for the preparation of oxazepines.[58] Oxazepines could be found in different forms such as partly and fully saturated, benzo-, dibenzo- and oxo derivatives. Notably, all have great importance as pharmaceutical drugs and/or active substances in biological systems.[59]

Oxazepines have exhibited biological activities such as anticonvulsant,[60] antidepressant,[61] antipsychotic[62] and antitumor properties.[63] Moreover, oxazepine derivatives have been used as histone deacetylase inhibitor,[64] progesterone receptor agonist[65] and calcium antagonist.[66] They are also effective against fungi and bacteria.[67]

Oxazepine derivatives have been commonly used to treat symptoms of depression, anxiety and schizophrenia. Therefore, oxazepines are main structural core in medicinally important drugs like antidepressants *Amoxapine*[68] and *Sintamil*[69] and antipsychotic *Loxapine* (Figure 16).[70]

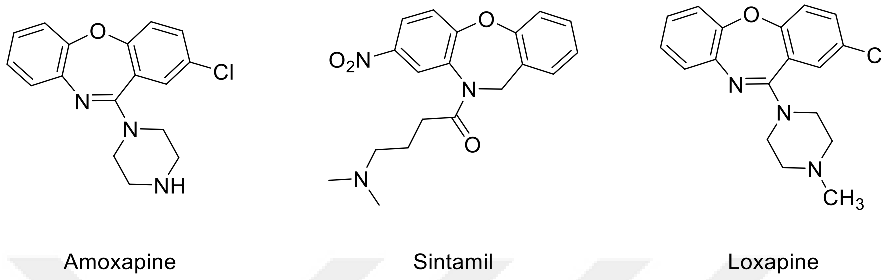


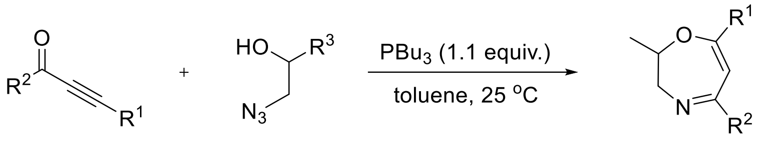
Figure 16. Examples of oxazepine-containing drugs.

In addition, oxazepines are utilized in photostabilization of polymers. Oxazepine containing heterocyclic compounds have been reported as stabilizer of PVC (polyvinylchloride) via different mechanisms like UV adsorber, screener or by radical scavenger. In this way, polymer would have good long-term stability.[71]

1.3.2. Synthesis of Oxazepines

There is an increasing interest for the synthesis of seven-membered rings with two heteroatoms. Among them, partly and fully unsaturated monocyclic 1,4-oxazepines have been less studied, so limited examples could be found in literature. In 1986, Tsuchiya *et al.* reported the first preparation of fully unsaturated 1,4-oxazepines. When irradiated, a tricycloheptene, synthesized from pyridine in five steps, underwent valence isomerization to give the corresponding 1,4-oxazepine derivatives.[72]

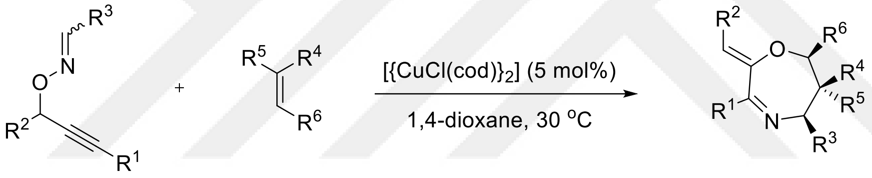
Recently, in 2010, Loreau and Taran published an interesting route for the synthesis of 1,4-oxazepines **28**. The reaction of ynones **26** with 2-azido alcohols **27** via *n*-Bu_3P-mediated tandem aza-Wittig reaction, followed by intramolecular cyclization, afforded 1,4-oxazepines **28** (Scheme 11).[73]



26 **27** **28**

Scheme 11. Phosphine-mediated synthesis of 1,4-oxazepines.

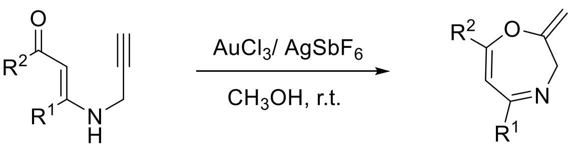
In 2013, Nakamura's research group reported a copper-catalyzed method for the synthesis oxazepines **31** through the reaction of *o*-propargylic oximes **29** with dipolarophiles **30** such as maleimides and fumaric acid esters (Scheme 12).[74]



29 **30** **31**

Scheme 12. Copper-catalyzed synthesis of 1,4-oxazepines.

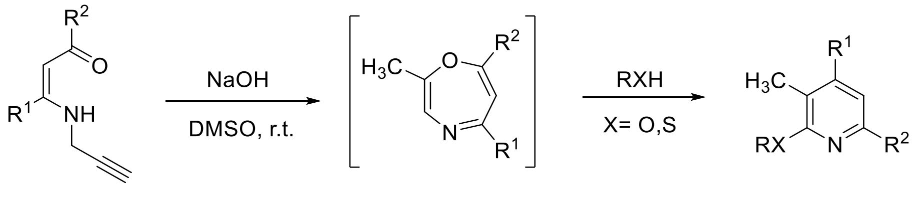
In 2015, Karunakar *et al.* reported an efficient method for the synthesis of 1,4-oxazepines **33** via gold-catalyzed intramolecular cyclization of *N*-propargylic β-enaminones **32,** which is illustrated in Scheme 13.[75]



32 **33**

Scheme 13. Gold-catalyzed synthesis of 1,4-oxazepines.

In 2017, Cui's research group showed that in situ preparation of base-promoted 1,4-oxazepines **34** from the 7-*exo-dig* cyclization of *N*-propargylic β-enaminones **32** (Scheme 14). When alcohols, thiols and aldehydes were added to active intermediate 1,4-oxazepines, pyridine derivatives were formed efficiently.[76]



32 **34** **35**

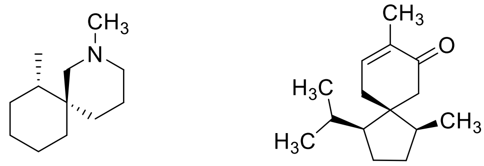
Scheme 14. Base-mediated synthesis of 1,4-oxazepines and their conversion to pyridines.

1.4. Spiro Compounds

Spiro compounds are molecules that combining two rings with one shared atom.[77] The atom connecting the rings is called spiro atom. Carbon atom is most common spiro atom, but other atoms such as nitrogen, phosphorus and boron are also known. It is estimated that the discovery of spirocycles can be traced back to the late 1890s. After a few years, Von Baeyer proposed the name 'spirocylane' for bicyclic hydrocarbons which have two rings with spiro carbon atoms.[77]

1.4.1. Importance of Spiro Compounds

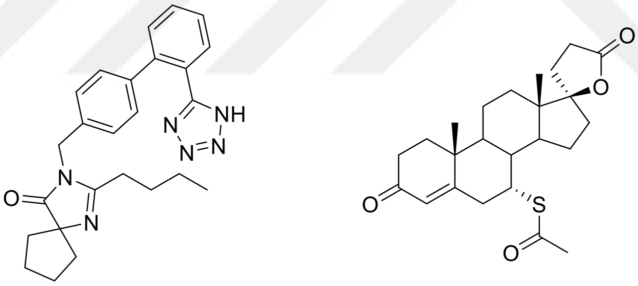
Spiro compounds are a priviliged class of molecules since they are present in the structures of numerous natural and non-natural products. They are widely used as building blocks for medicinal research owing to their presence in pharmacologically important molecules.[78] In fact, spiro compounds are important structural units of diverse natural products such as alkoloid (-)-sibirine, fused tetracyclic lycopodium, alkaloid nankakurine A, several spongistatins and acorenone B (Figure 17).[79]



(-)-Sibirine Acorenone B

Figure 17. Structures of (-)-sibirine and acorenone B.

Spirocycles are found in structures of diverse pioneering drugs such as *Ibersartan*[80] for cardivascular diseases, *Drospirenone*[81] which is used in birth control pills and in menopausal hormone therapy and *Spironolactone*[82] that is used to treat edema and hypokalemia (Figure 18).



Irbesartan Spironolactone

Figure 18. Structures of some drugs containing spirocycles.

Spirocycles have unique structural features with central or axial chirality, so they are useful in asymmetric synthesis as well, in which spiro moiety gives high degree of rigidity to overall structure and reduces the number of rotable bonds. Common examples of chiral ligands are spinol, spirOP and spirobisoxazoline (Figure 19).[83] Moreover, some spiro compounds have homo conjugation because of perpendicular π-electron systems. Due to this property, they could be utilized in light-emitting diodes (OLEDs) and various conjugated polymers.[83]

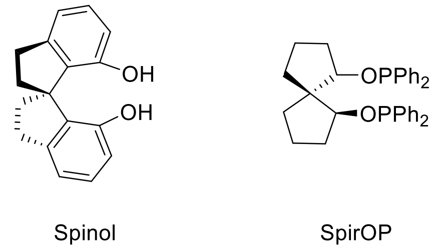
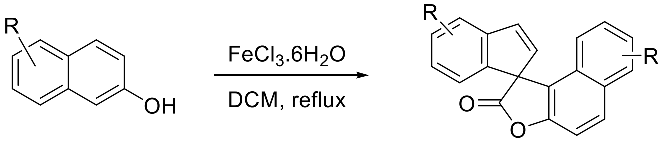


Figure 19. Structures of spinol and spirOP.

1.4.2. Synthesis of Spiro Compounds

Construction of new spirocyclic compounds is one of the chalenges in synthetic organic chemistry. However, design of spirocyclic scaffolds is highly diffucult goal because creation of quaternary centre is needed for this process.[83] Therefore, different strategies have been developed for their synthesis. These methods include cycloadditions, intramolecular substitutions, metal-promoted cyclizations, radical cyclizations and intramolecular arrangements.[77]

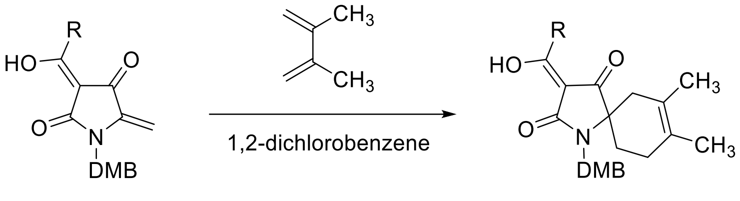
In literature studies, different types of approaches could be observed. For example, in 2010, Tsubaki and his co-workers showed that in the presence of $FeCl_3.6H_2O$, oxidative coupling of 2-naphthols **36** and their rearrangement gave the corresponding spiro compounds **37** (Scheme 15).[84]



36 **37**

Scheme 15. Synthesis of spiro compounds from 2-naphthols.

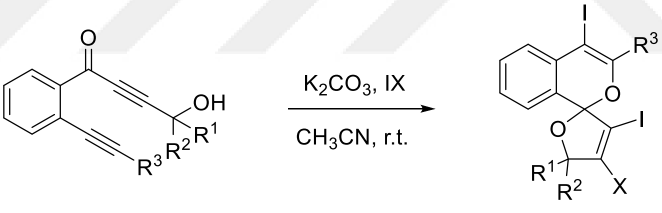
Moody's *et al.* reported an approach for the sythesis of spirocycles **39** through intermolecular Diels-Alder reaction between tetramic acid **38** and 2,3-dimethyl-1,3-butadiene, which is illustrated in Scheme 16.[85]



38 **39**

Scheme 16. Synthesis of spiro compounds via intermolecular Diels-Alder reaction.

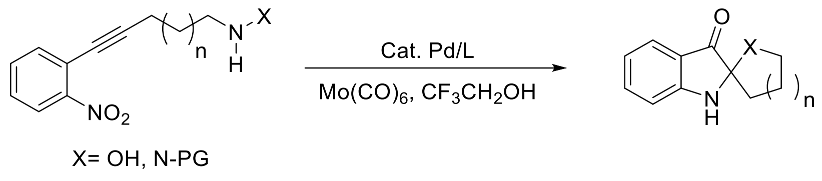
In 2014, Liang research group developed a strategy for synthesis of variety spiroketals **41** via tandem iodocyclization of 1-(2-ethynylphenyl)-4-hydroxybut-2-yn-1-one derivatives **40** (Scheme 17).[86]



40 **41**

Scheme 17. Synthesis of halogenated spiroketals via iodocyclization.

In 2017, Wang and co-workers described an efficient method for the synthesis of spiro-pseudoinoxyls **43** from *o*-alkynylnitrobenzene **42**. This one-pot approach involves Pd-catalyzed cycloisomerization, nucleophilic addition and reduction processes (Scheme 18).[87]

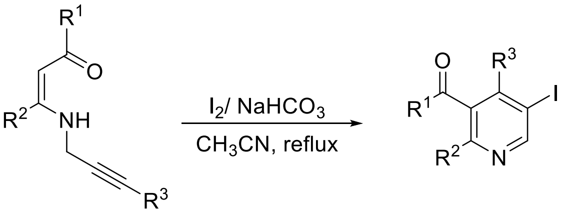


42 **43**

Scheme 18. Synthesis of spiro-pseudoindoxyls.

1.5. Aim of Study

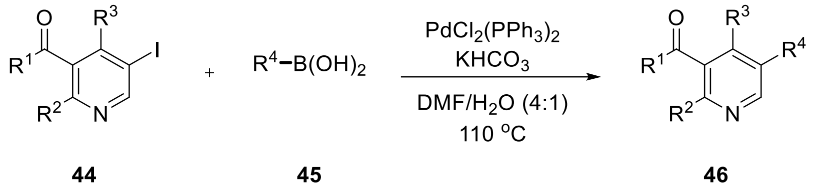
As mentioned before, nitrogen-containing five-, six- and seven-membered heterocyclic compounds have attracted great importance in organic synthesis as a result of their wide range of applications in many branches of chemistry. In this respect, *N*-propargylic β-enaminones have been recognized as the attractive substrates for the preparation of a range of important heterocyclic compounds. Notably, they have a special structure since they contain different fuctional groups like alkene, alkyne, enone, enamine and enaminone. Under proper conditions, *N*-propargylic β-enaminones could afford pyrroles,[22] pyridines,[21] dihydropyridines[88] and oxazepines.[75] The aim of this study is to develop new methodologies for the synthesis of five-, six- and seven-membered heterocyclic compounds by employing the cyclizations of *N*-propargylic β-enaminones. Our research group recently explored their cyclizations. When treated with molecular iodine in the presence of sodium bicarbonate, *N*-propargylic β-enaminones **10** underwent electrophilic cyclization to give 5-iodopyridines **44** (Scheme 19).[89]



10 **44**

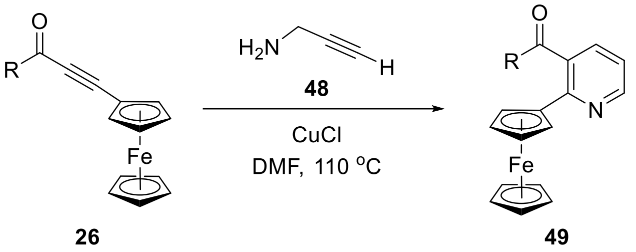
Scheme 19. Synthesis of 5-iodopyridines.

Iodine containing pyridines are desirable building blocks for synthesis of more complex molecules. In fact, they present a platform for metal-catalyzed cross-coupling reactions. Therefore, in the first part of study, Suzuki-Miyaura coupling reaction of 5-iodopyridines **44** with boronic acids **45** has been investigated, which afforded a diverse range of potentially bioactive 5-aryl-substituted pyridines **46** (Scheme 20).[90]



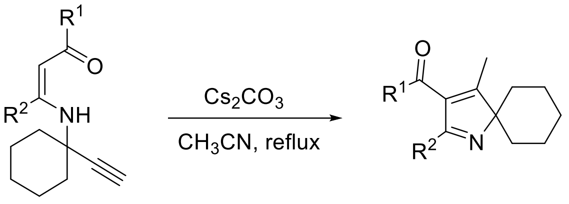
Scheme 20. Synthesis of 5-arylpyridines.

In the second part of the study, a one-pot approach for the synthesis of 2-ferrocenylpyridines has been described. When reacted with propargylamine (**48**), α,β-alkynic ketones **26** yielded *N*-propargylic β-enaminones, which in the presence of copper(I) chloride, underwent electrophilic cyclization to generate 2-ferrocenylpyridine derivatives **49** (Scheme 21).[91]



Scheme 21. One-pot synthesis of 2-ferrocenylpyridines.

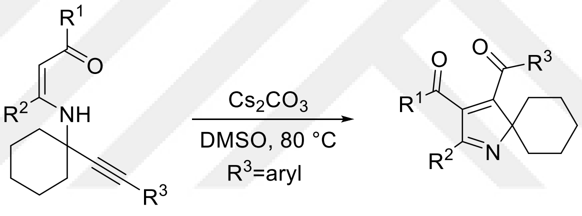
Then, cyclohexane-embedded *N*-propargylic β-enaminones were prepared. In the third part, an efficient methodology has been developed for the synthesis of spiro-2*H*-pyrroles. When treated with cesium carbonate, cyclohexane-embedded *N*-propargylic β-enaminones **50** underwent cyclization to afford spiro-2*H*-pyrrole derivatives **51** in very high yields (Scheme 22).[92]



50 **51**

Scheme 22. Synthesis of spiro-2*H*-pyrroles.

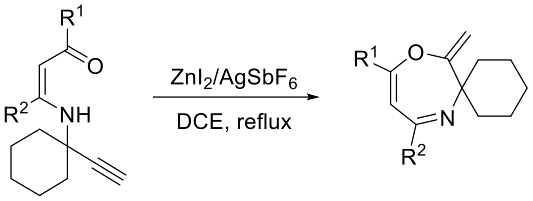
In order to obtain further functionalized spiro-2*H*-pyrroles, cyclohexane-embedded *N*-propargylic β-enaminones were subjected to Sonogashira cross-coupling with aryl iodides. In the fourth part of study, these arylated β-enaminones **52** were exposed to cesium carbonate, which interestingly afforded pyrroles **53** with two carbonyl groups through further benzylic C-H oxidation (Scheme 23).[93]



52 **53**

Scheme 23. Synthesis of spiro-2*H*-pyrroles with two carbonyl groups.

At the final stage, a strategy for the preparation of spiro-1,4-oxazepines was developed. Upon reaction in the presence of zinc iodide and silver hexafluoroantimonate, cyclohexane-embedded *N*-propargylic β-enaminones **50** underwent cyclization to generate spiro-1,4-oxazepines **54** (Scheme 24).



50 **54**

Scheme 24. Synthesis of spiro-1,4-oxazepines.

In summary, scope, limitations and mechanisms for the synthesis of 5-arylpyridines **46**, 2-ferrocenylpyridines **49**, spiro-2*H*-pyrroles **51** and **53** and spiro-1,4-oxazepines **54** will be discussed in detail.

CHAPTER 2

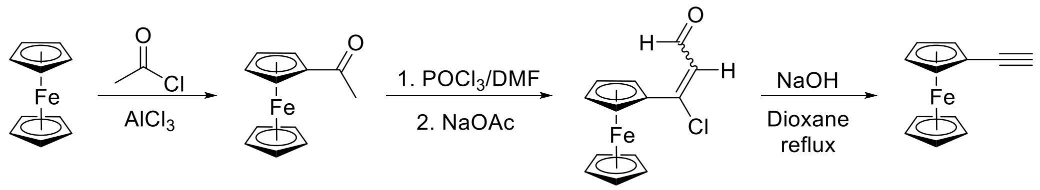
RESULTS AND DISCUSSION

2.1. Synthesis of Starting Materials

2.1.1. Synthesis of α,β-Alkynic Ketones 26

In the first part of the study, Sonogashira cross-coupling reaction of substituted benzoyl chlorides **55** with terminal alkynes **56** was explored for the synthesis of α,β-alkynic ketones **26**. This reaction was performed at room temperature using $PdCl_2(PPh_3)_2$ as a catalyst, combined with CuI as a co-catalyst, and Et_3N in THF under argon atmosphere. By employing Sonogashira approach, we achieved the synthesis of 25 derivatives of α,β-alkynic ketones in 65-99% yields as illustrated in Table 1.

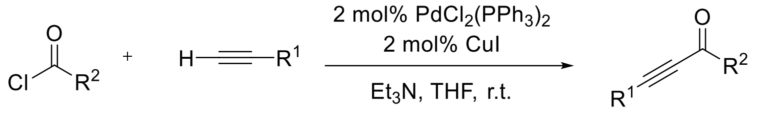
In these Sonogashira cross-coupling reactions, commercially available terminal alkynes were utilized. Only ethynylferrocene (**60**) was synthesized from ferrocene according to a well-known literature procedure as shown in Scheme 25.[94]



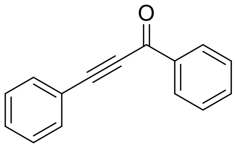
57 **58** **59** **60**

Scheme 25. Synthesis of ethynylferrocene (**60**).

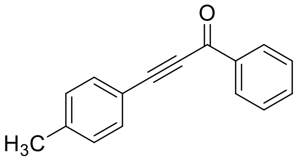
Table 1. Synthesis of α,β-alkynic ketones **26**.[a]



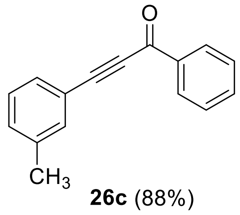
55 **56** **26**



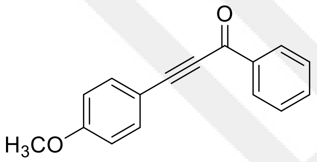
26a (96%)



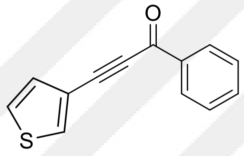
26b (90%)



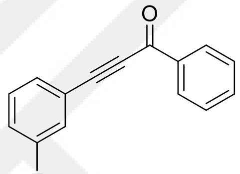
26c (88%)



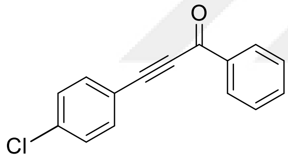
26d (89%)



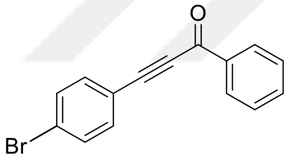
26e (99%)



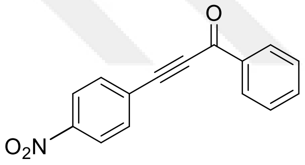
26f (87%)



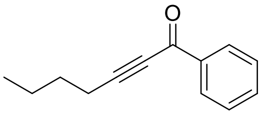
26g (82%)



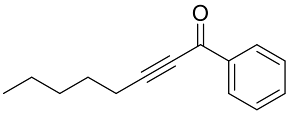
26h (75%)



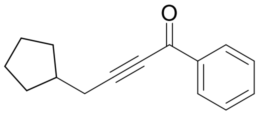
26i (65%)



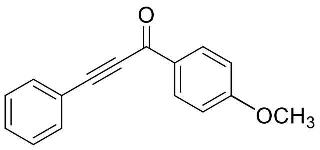
26j (73%)



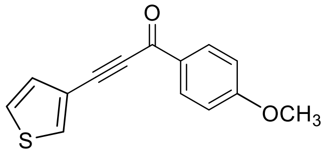
26k (72%)



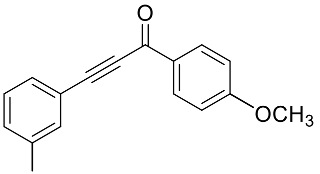
26l (76%)



26m (94%)

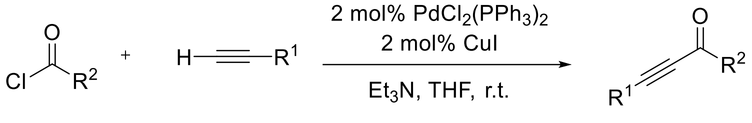


26n (73%)

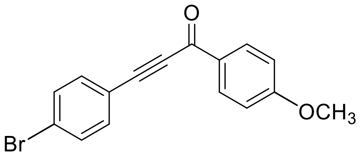


26o (91%)

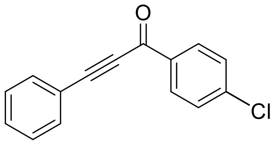
Table 1. Continued.



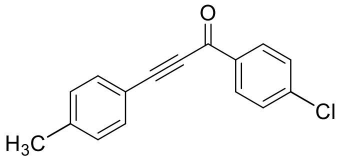
55 **56** **26**



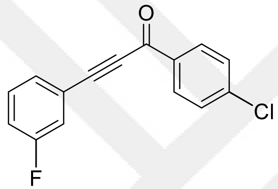
26p (85%)



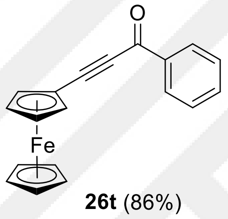
26q (80%)



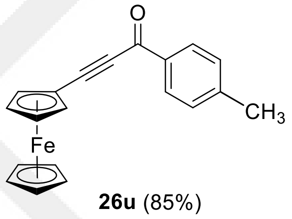
26r (76%)



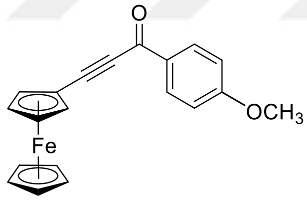
26s (75%)



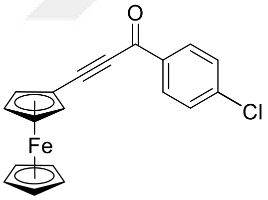
26t (86%)



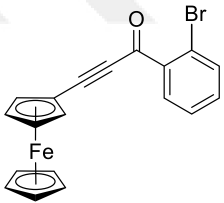
26u (85%)



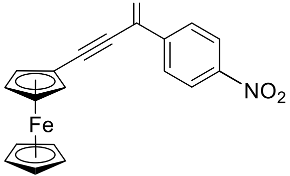
26v (86%)



26w (85%)



26x (75%)



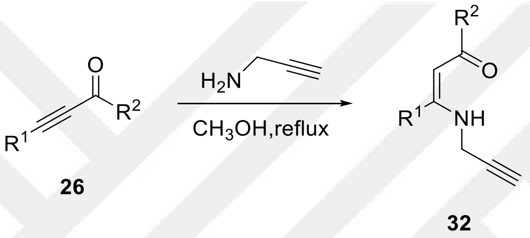
26y (80%)

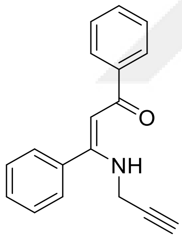
[a] Isolated yields.

2.1.2. Synthesis of *N*-propargylic β-enaminones 32, 50 and 61

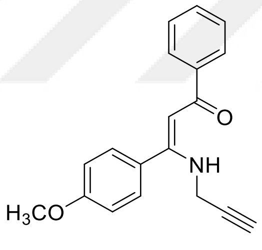
After preparing α,β-alkynic ketones **26**, *N*-propargylic β-enaminone derivatives **32** were synthesized (Table 2). Conjugate addition of propargylamine to α,β-alkynic ketones **26** in refluxing methanol gave *N*-propargylic β-enaminones **32**. By employing this method, 4 derivatives of β-enaminones **32** were obtained in 94-98% yields as shown in Table 2.

Table 2. Synthesis of *N*-propargylic β-enaminones **32**.[a]

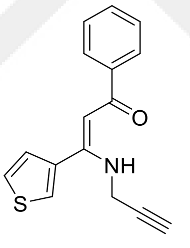




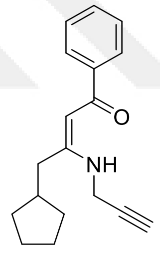
32a (98%)



32b (98%)



32c (94%)

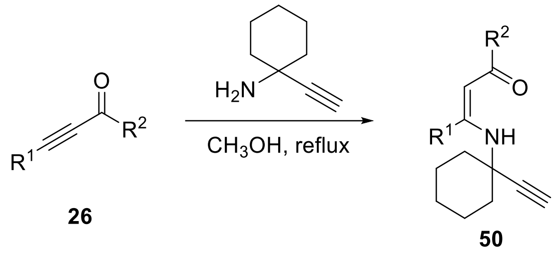


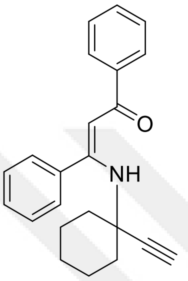
32d (99%)

[a] Isolated yields.

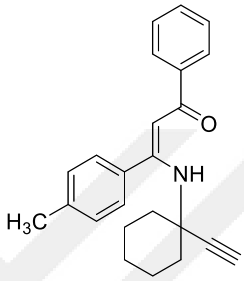
Moreover, previously unknown *N*-propargylic β-enaminone derivatives **50** and **61** were synthesized (Tables 3 and 4). Conjugate addition of 1-ethynylcyclohexylamine to α,β-alkynic ketones **26** in refluxing methanol afforded *N*-propargylic β-enaminones **50** in 51-83% yields (Table 3). By these reactions, 17 derivatives of *N*-propargylic β-enaminones **50** including alkyl and aryl groups with electron-withdrawing and electron-donating substituents were prepared.

Table 3. Synthesis of *N*-propargylic β-enaminones **50**.[a]

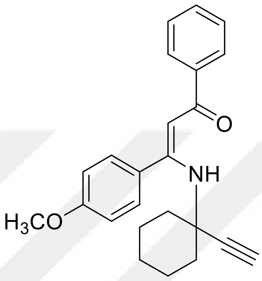




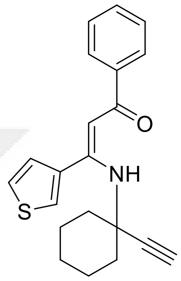
50a (56%)



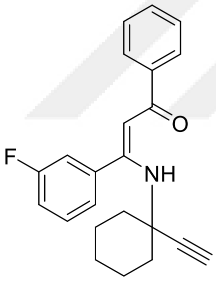
50b (73%)



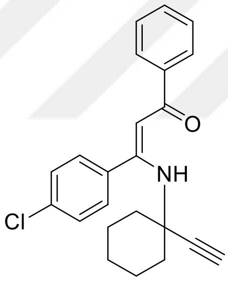
50c (58%)



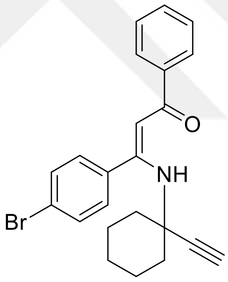
50d (55%)



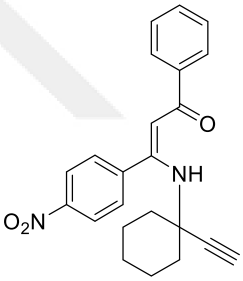
50e (60%)



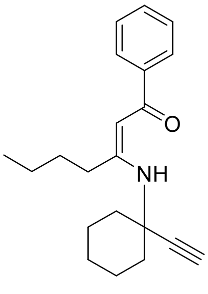
50f (66%)



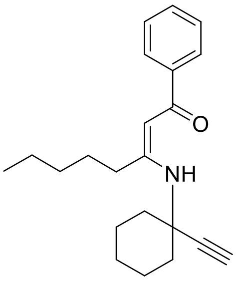
50g (58%)



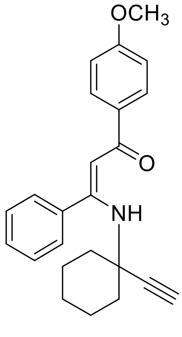
50h (60%)



50i (83%)

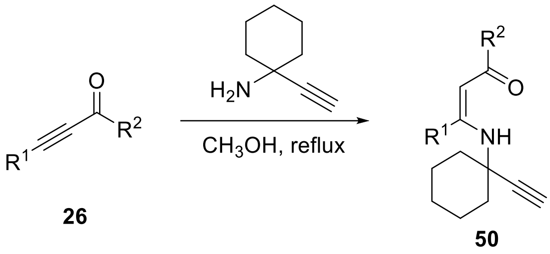


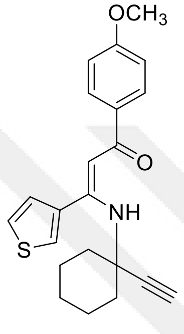
50j (67%)



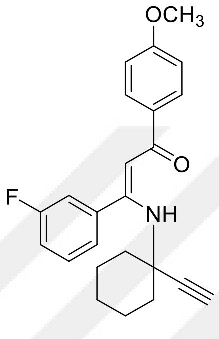
50k (51%)

Table 3. Continued.

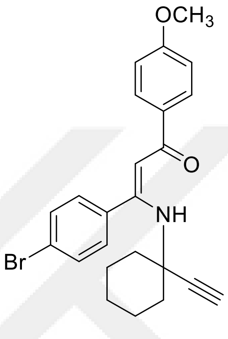




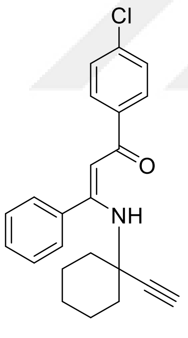
50l (54%)



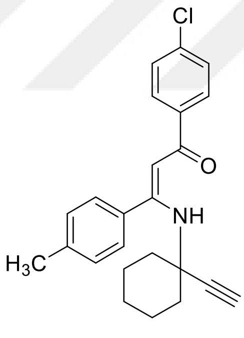
50m (56%)



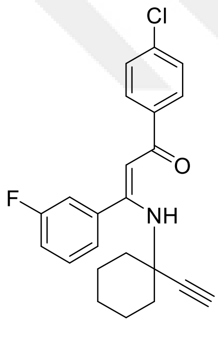
50n (53%)



50o (68%)



50p (63%)

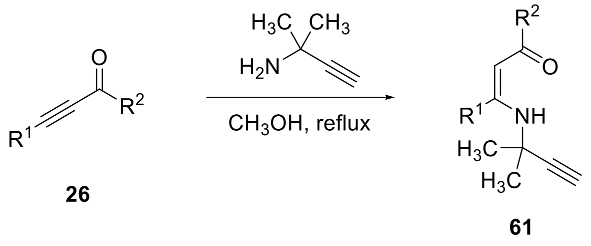


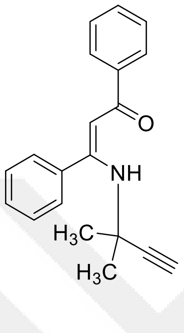
50q (62%)

[a] Isolated yields.

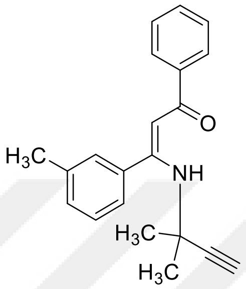
Then, 3 derivatives of *N*-(1,1-dimethyl)propargylic β-enaminones **61** were synthesized as well for comparison purpose. Conjugate addition of 2-methyl-3-butyn-2-amine to α,β-alkynic ketones **26** produced β-enaminones **61** in 60-69% yields (Table 4). In this way, 3 derivatives of *N*-propargylic β-enaminones **61** were prepared.

Table 4. Synthesis of *N*-propargylic β-enaminones **61**.[a]

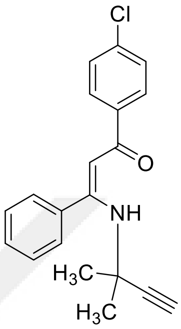




61a (69%)



61b (63%)



61c (60%)

[a] Isolated yields.

Notably, *N*-propargylic β-enaminones were isolated as single isomers. NOESY experiments were done by our[89] and Cacchi[21] research group proved that *N*-propargylic β-enaminones form as (*Z*)-isomers. NOE interactions were observed between the indicated hydrogens of compound **32e** (Figure 20). These signals arise from protons that are close to each other in space even if they are not bonded. Moreover, there is an intramolecular hydrogen bond between amine hydrogen and carbonyl oxygen due to their geometry, which plays an important role in the stability of (*Z*)-isomers.

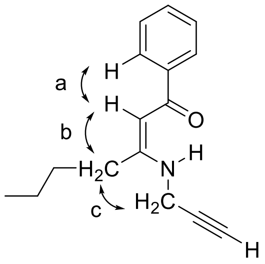


Figure 20. The structure of compound **32e**.

The synthesized *N*-propargylic β-enaminones show some characteristic peaks in their ^{1}H and ^{13}C NMR spectra. As a representative example, ^{1}H and ^{13}C NMR spectra of 1,3-diphenyl-3-(prop-2-ynylamino)prop-2-en-1-one (**32a**) is illustrated in Figures 21 and 22. In case of ^{1}H NMR spectrum (Figure 21), amine hydrogen resonates at 11.34 ppm as a broad singlet peak. The vinylic hydrogen is observed as a singlet at 5.86 ppm. Furthermore, methylene hydrogen atoms resonate at 3.96 ppm. At high field, alkynyl hydrogen gives a resonance signal at 2.32 ppm. Remaining hydrogens, which belong to phenyl groups, appear between 7.94 and 7.38 ppm.

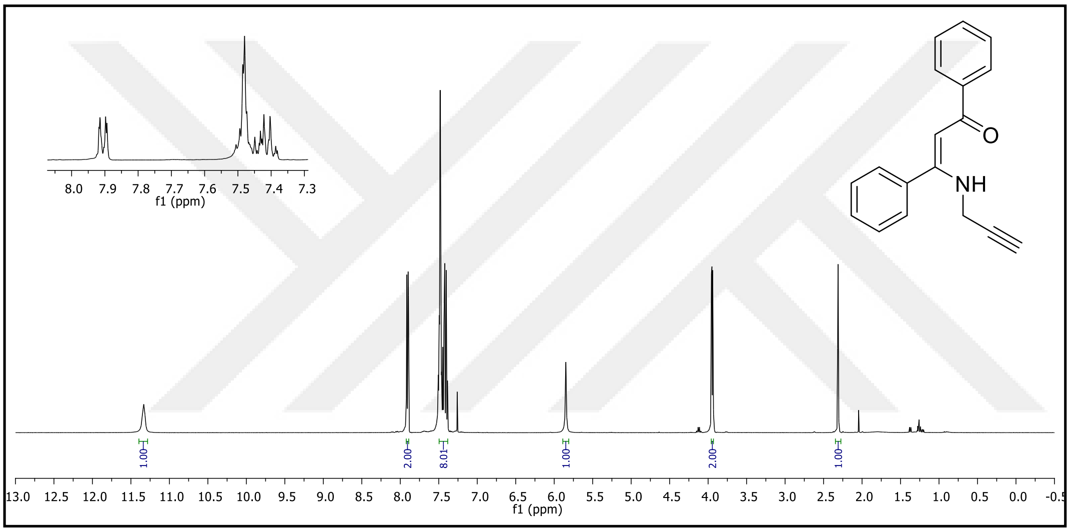


Figure 21. ^{1}H NMR spectrum of compound **32a**.

In the ^{13}C NMR spectrum (Figure 22), compound **32a** displays 14 different resonance signals. Among them, carbonyl carbon and β-carbon resonate at 189.4 and 166.1 ppm, respectively. However, α-carbon is observed at 94.9 ppm. Aromatic carbon atoms appear between 140.2 and 127.4 ppm as expected. Two acetylenic carbons resonate at 80.0 and 72.6 ppm. Methylene carbon signal appears at high field (34.4 ppm). Overall, all NMR data supports the indicated structure of 1,3-diphenyl-3-(prop-2-ynylamino)prop-2-en-1-one (**32a**).

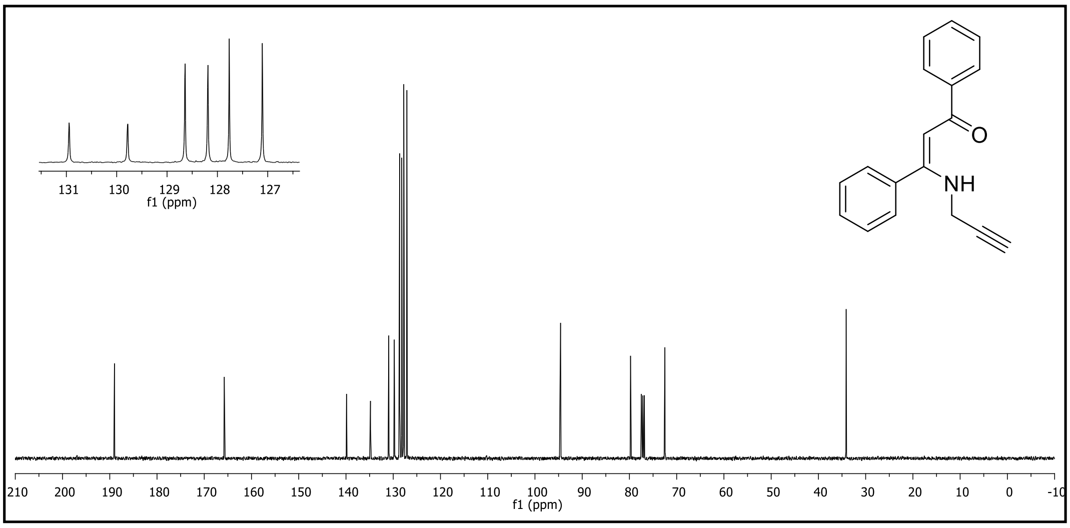


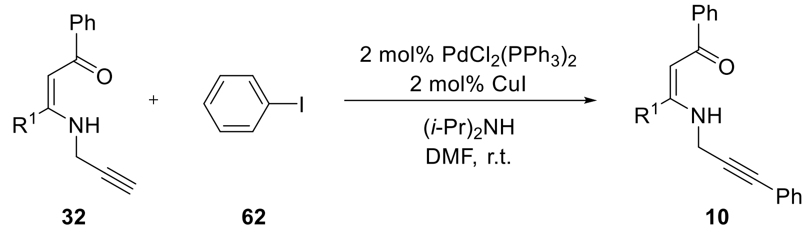
Figure 22. ^{13}C NMR spectrum of compound **32a**.

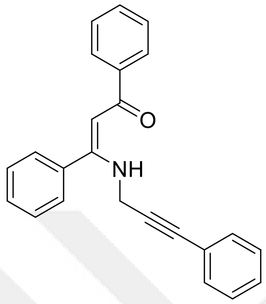
2.1.3. Synthesis of *N*-propargylic β-enaminones 10 and 52

Some of the *N*-propargylic β-enaminones **32** and **50** were subjected to Sonogashira cross-coupling with aryl iodides in order to further functionalize these compounds (Table 5 and 6).

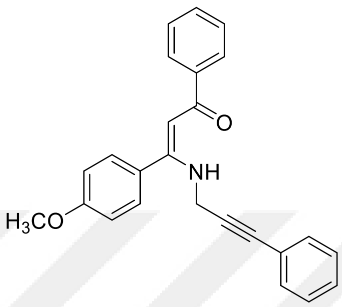
Palladium-catalyzed cross-coupling of β-enaminones was carried out in the presence of (i-Pr)$_2$NH at room temperature. When *N*-propargylic β-enaminones **32** were treated with iodo benzene, arylated β-enaminones **10** were obtained in 77-88% yields as shown in Table 5. On the other hand, the cross-coupling of β-enaminones **50** with aryl iodides provided arylated β-enaminones **52** in 70-89% yields (Table 6).

Table 5. Synthesis of *N*-propargylic β-enaminones **10**.[a]

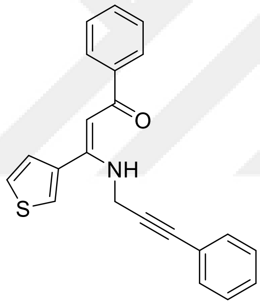




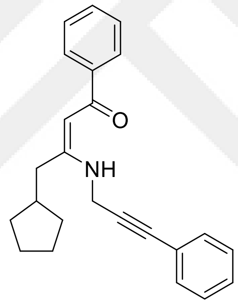
10a (88%)



10b (84%)



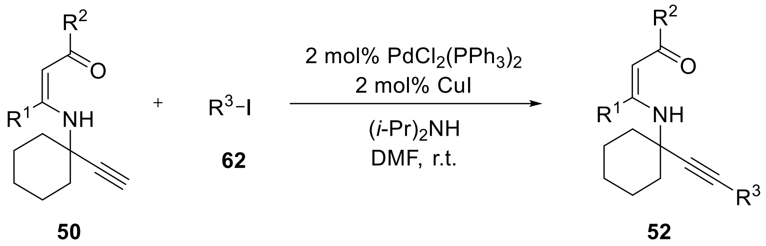
10c (83%)

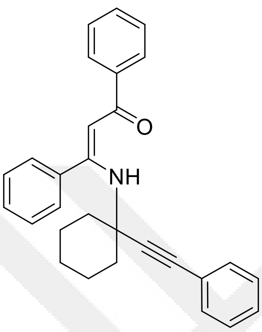


10d (77%)

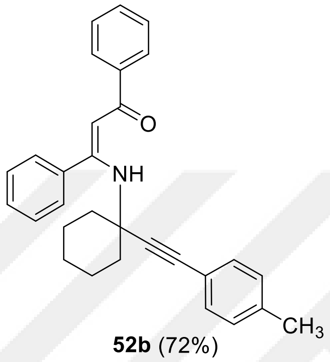
[a] Isolated yields.

Table 6. Synthesis of *N*-propargylic β-enaminones **52**.[a]

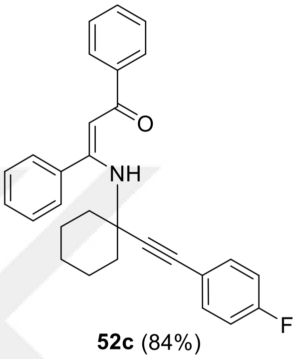




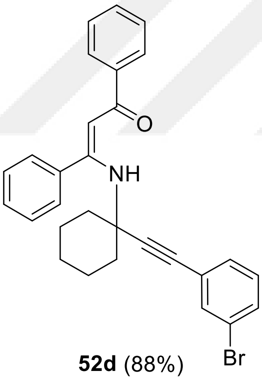
52a (82%)



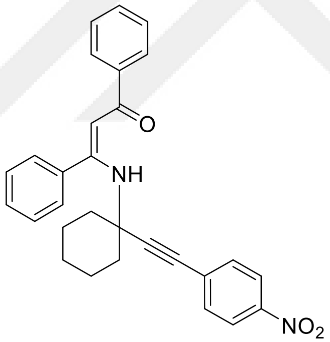
52b (72%)



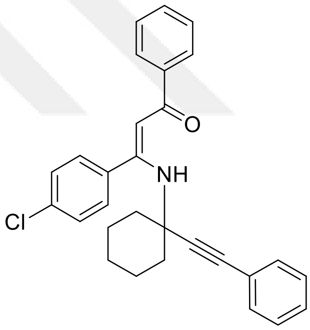
52c (84%)



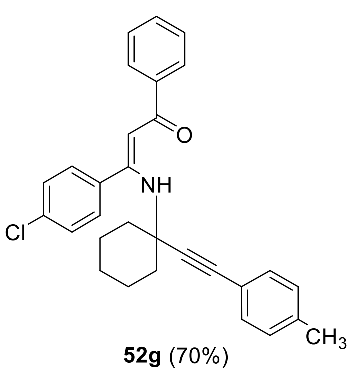
52d (88%)



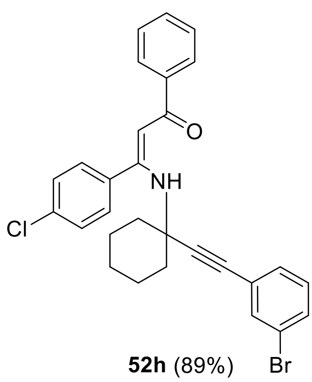
52e (75%)



52f (81%)



52g (70%)



52h (89%)

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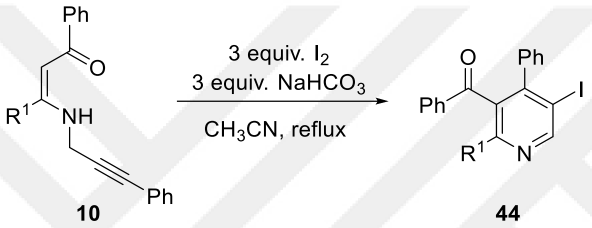
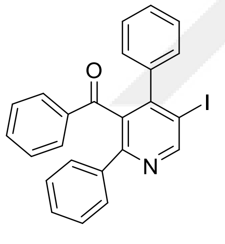
[a] Isolated yields.

2.1.4. Synthesis of 5-Iodopyridines 65

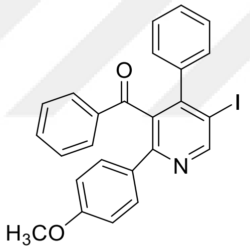
When reacted with excess molecular iodine and sodium bicarbonate in refluxing acetonitrile, *N*-propargylic β-enaminones **10** underwent electrophilic cyclization to provide 5-iodopridines **44**, which were explored by our research group previously.[89] Four different iodo-substituted pyridine derivatives **44** were synthesized from the corresponding *N*-propargylic β-enaminones **10** in 62-80% yields as shown in Table 7.

Table 7. Synthesis of 5-iodopyridines **44**.[a]

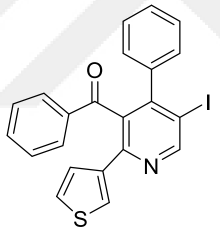




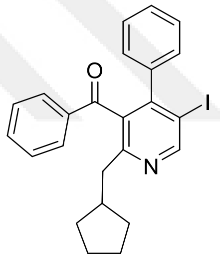
44a (80%)



44b (62%)



44c (75%)



44d (66%)

[a] Isolated yields.

Formation of pyridine ring has been supported by ^{1}H and ^{13}C NMR data. For example, in the ^{1}H NMR spectrum of compound **44a** (Figure 23), α-proton of pyridine ring resonates at 9.28 ppm as singlet. The remaining phenyl hydrogens appear between 7.47-6.78 ppm. In the ^{13}C NMR spectrum (Figure 24), iodine-attached carbon peak was observed around 98.6 ppm. Carbonyl carbon resonates at 195.7 ppm while aromatic carbons were seen between 157.8 and 128.0 ppm.

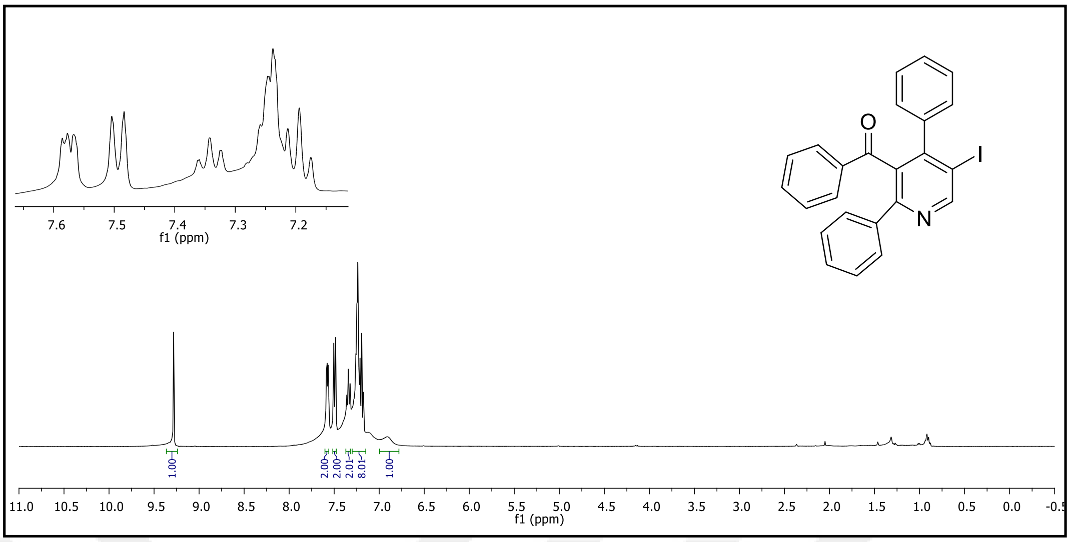


Figure 23. ^{1}H NMR spectrum of compound **44a**.

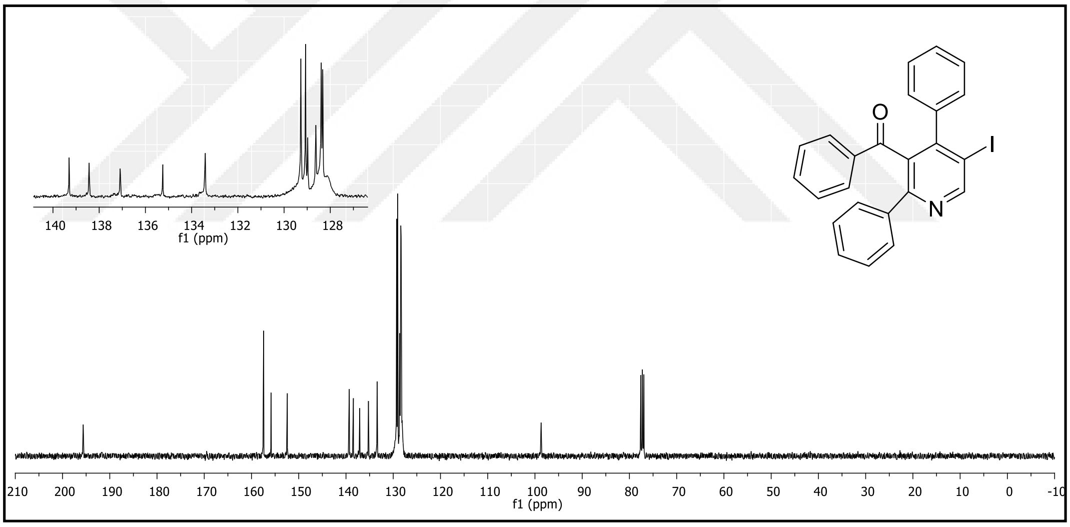
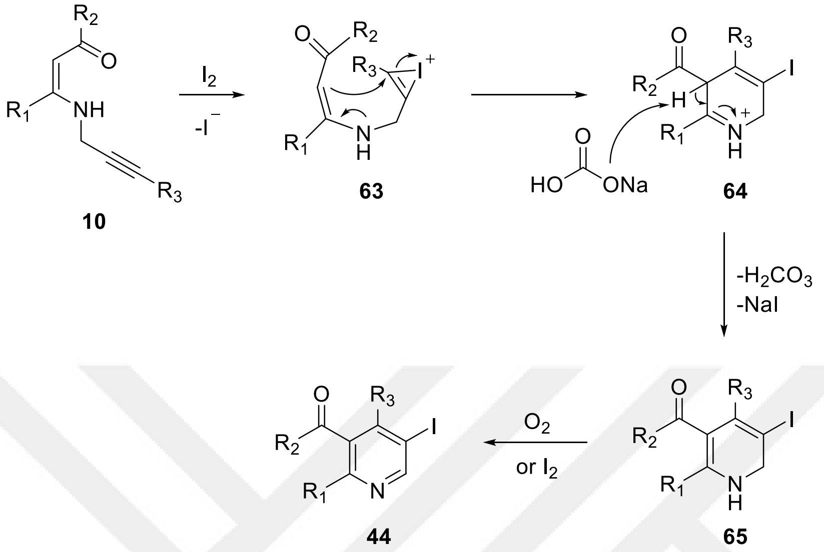


Figure 24. ^{13}C NMR spectrum of compound **44a**.

Proposed mechanism for the formation of 5-iodopyridines **44** is shown in Scheme 26. According to this mechanism, firstly, reaction of alkyne unit of *N*-propargylic β-enaminone **10** with iodine gives iodonium ion **63**. Then, 6-*endo-dig* electrophilic cyclization takes place to afford intermediate **64**. Subsequently, deprotonation with sodium bicarbonate produces dihydropyridine **65**. Finally, aerobic and/or iodine-mediated oxidations yield 5-iodopyridine **44**.



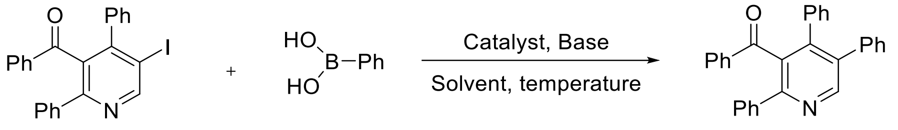
Scheme 26. Proposed mechanism for the formation of 5-iodopyridines **44**.

2.2. Synthesis of Target Compounds

2.2.1. Synthesis of 5-Arylpyridines 46

In this part of the thesis study, Suzuki-Miyaura coupling reaction between 5-iodopyridines **44** and boronic acids **45** were investigated to produce 5-aryl-substituted pyridines **46**. We first examined the reaction of 5-iodopyridine **44a** with phenylboronic acid (**45a**) under different conditions in order to optimize the reaction conditions as illustrated in Table 8. Although Suzuki-Miyaura coupling reactions could be carried out by using different catalysts, bases, and solvents, literature search showed that palladium catalysts with triphenylphosphine ligands and bases in bicarbonate salt form work quite efficiently in such coupling reactions.[95] In this regard, we started our optimization studies by utilizing 5 mol% $PdCl_2(PPh_3)_2$ and 1.4 equiv. of both boronic acid and $KHCO_3$ relative to 5-iodopyridine. Initially, the reaction was carried out in DMF at room temperature and at 110 °C in which expected product 5-arylpyridine (**46a**) was obtained in 60 and 85% yields respectively (Table 8, Entries 1 and 2). Then, the reaction was examined in different solvents such as THF, CH_3CN and dioxane at refluxing conditions, which afforded 5-arylpyridine (**46a**) in 70-80% yields (Table 8, Entries 3-5). All of these reactions went completion in 10-24 h where highest yield was obtained in DMF at 110 °C. At this point, it should be stated that 4:1 ratio of solvent/H_2O combination is widely used in this type of coupling reactions.[95] Then, the reaction was repeated in 4:1 ratio of DMF/H_2O,THF/H_2O, CH_3CN/H_2O and dioxane/H_2O at 110 °C or refluxing conditions (Table 8, Entries 6-9). In DMF/H_2O (4:1) system, the reaction afforded 5-arylpyridine (**46a**) in 94% yield. In addition, this reaction went to completion in 8 h which is shorter reaction time as compared to others (15-18 h). Therefore, DMF/H_2O (4:1) was chosen as the reaction solvent system. After determining solvent system, the reaction was performed with different equivalents of boronic acid. The lower equivalents of boronic acid (1.0 equiv.) decreased the yield of the corresponding product (**46a**) while the higher number of equivalents did not rise the yield (Table 8, Entries 10 and 11). So, the reactions were carried out by using 1.4 equiv. of boronic acid. When the reaction was conducted with different catalyst such as $Pd(OAc)_2$ and $Pd(PPh_3)_4$, 5-arylpyridine was produced in 86 and 89% yields, respectively (Table 8, Entries 12 and 13). When lower number of equivalents of base (1.0 equiv.) was used, the yield of product decreased to 87% (Table 8, Entry 14). The reaction was run with different bases as well but 5-arylpyridine (**46a**) was produced in lower yields (86-89%). As a result of these experiments, we decided to carry out Suzuki coupling reactions of 5-iodopyridines **44** by employing 5 mol% $PdCl_2(PPh_3)$ and 1.4 equiv. of both boronic acids **45** and $KHCO_3$, with respect to iodopyridine **44**, in 4:1 ratio of DMF/H_2O solution at 110 °C (Table 8).

Table 8. Optimization studies for the synthesis of 5-arylpyridines **46**.

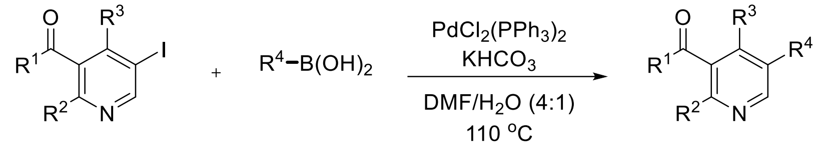


44a **45a** **46a**

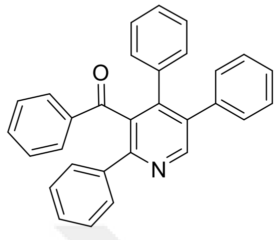
Entry	**Boronic Acid (equiv.)**	**Catalyst (5 mol%)**	**Base (equiv.)**	**Solvent**	**Temp. (°C)**	**Time (h)**	**Yield (%)**[a]
1	1.4	$PdCl_2(PPh_3)_2$	$KHCO_3$ (1.4)	DMF	r.t.	24	60
2	1.4	$PdCl_2(PPh_3)_2$	$KHCO_3$ (1.4)	DMF	110	10	85
3	1.4	$PdCl_2(PPh_3)_2$	$KHCO_3$ (1.4)	THF	reflux	18	70
4	1.4	$PdCl_2(PPh_3)_2$	$KHCO_3$ (1.4)	CH_3CN	reflux	18	76
5	1.4	$PdCl_2(PPh_3)_2$	$KHCO_3$ (1.4)	Dioxane	reflux	12	80
6	**1.4**	**$PdCl_2(PPh_3)_2$**	**$KHCO_3$ (1.4)**	**DMF/H_2O (4:1)**	**110**	**8**	**94**
7	1.4	$PdCl_2(PPh_3)_2$	$KHCO_3$ (1.4)	THF/H_2O (4:1)	reflux	18	74
8	1.4	$PdCl_2(PPh_3)_2$	$KHCO_3$ (1.4)	CH_3CN/H_2O (4:1)	reflux	18	79
9	1.4	$PdCl_2(PPh_3)_2$	$KHCO_3$ (1.4)	Dioxane/H_2O (4:1)	reflux	15	84
10	1.0	$PdCl_2(PPh_3)_2$	$KHCO_3$ (1.4)	DMF/H_2O (4:1)	110	8	88
11	2.0	$PdCl_2(PPh_3)_2$	$KHCO_3$ (1.4)	DMF/H_2O (4:1)	110	8	94
12	1.4	$Pd(OAc)_2$	$KHCO_3$ (1.4)	DMF/H_2O (4:1)	110	8	86
13	1.4	$Pd(PPh_3)_4$	$KHCO_3$ (1.4)	DMF/H_2O (4:1)	110	8	89
14	1.4	$PdCl_2(PPh_3)_2$	$KHCO_3$ (1.0)	DMF/H_2O (4:1)	110	8	87
15	1.4	$PdCl_2(PPh_3)_2$	$NaHCO_3$ (1.4)	DMF/H_2O (4:1)	110	8	86
16	1.4	$PdCl_2(PPh_3)_2$	K_2CO_3 (1.4)	DMF/H_2O (4:1)	110	8	89

[a] Isolated yields.

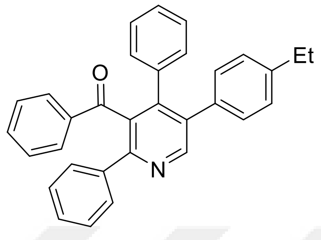
Table 9. Synthesis of 5-arylpyridines via Suzuki-Miyaura reaction.^{a}



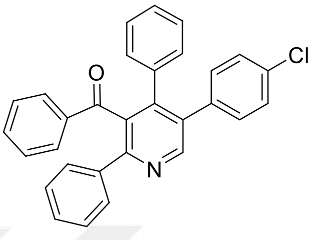
44 **45** **46**



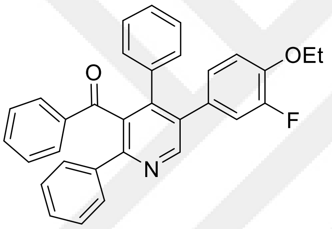
46a (94%)



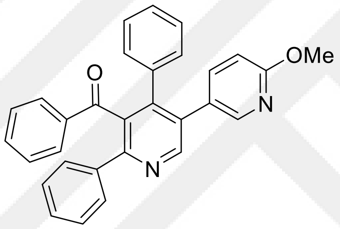
46b (98%)



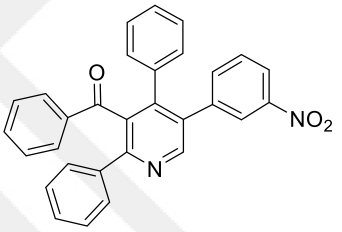
46c (87%)



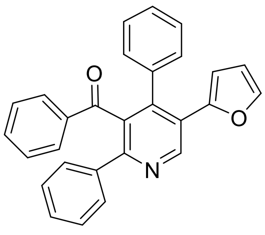
46d (72%)



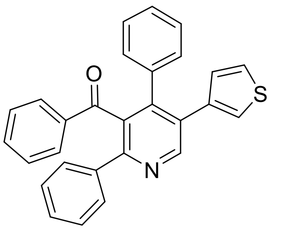
46e (75%)



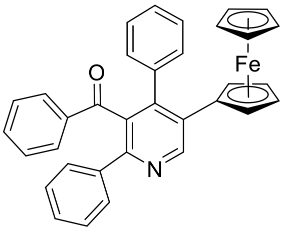
46f (80%)



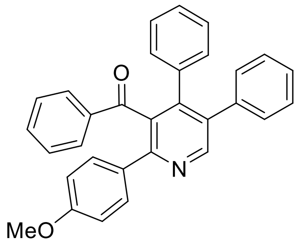
46g (83%)



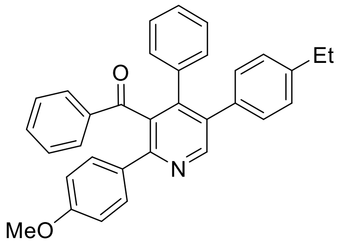
46h (87%)



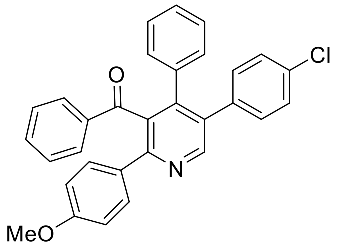
46i (88%)



46j (85%)



46k (82%)



46l (65%)

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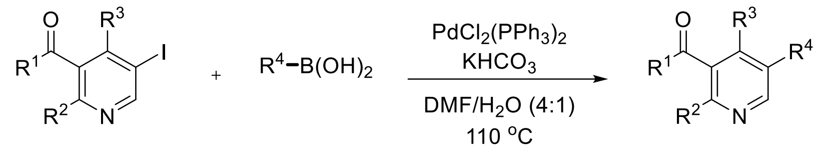
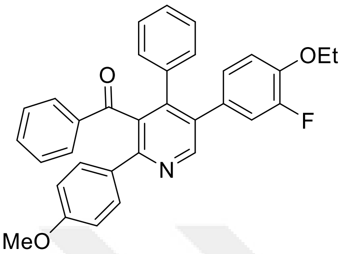
^{a}Isolated yields.

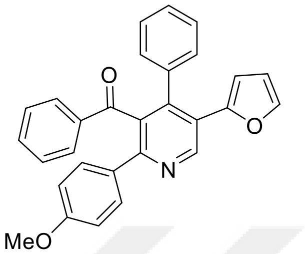
Table 9. Continued.[a]



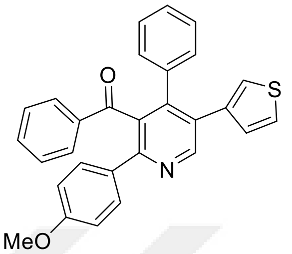
44 **45** **46**



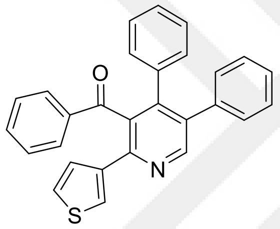
46m (98%)



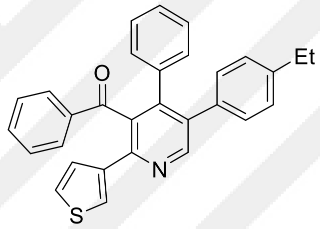
46n (75%)



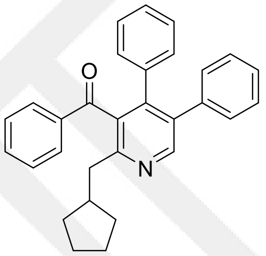
46o (84%)



46p (77%)



46q (78%)



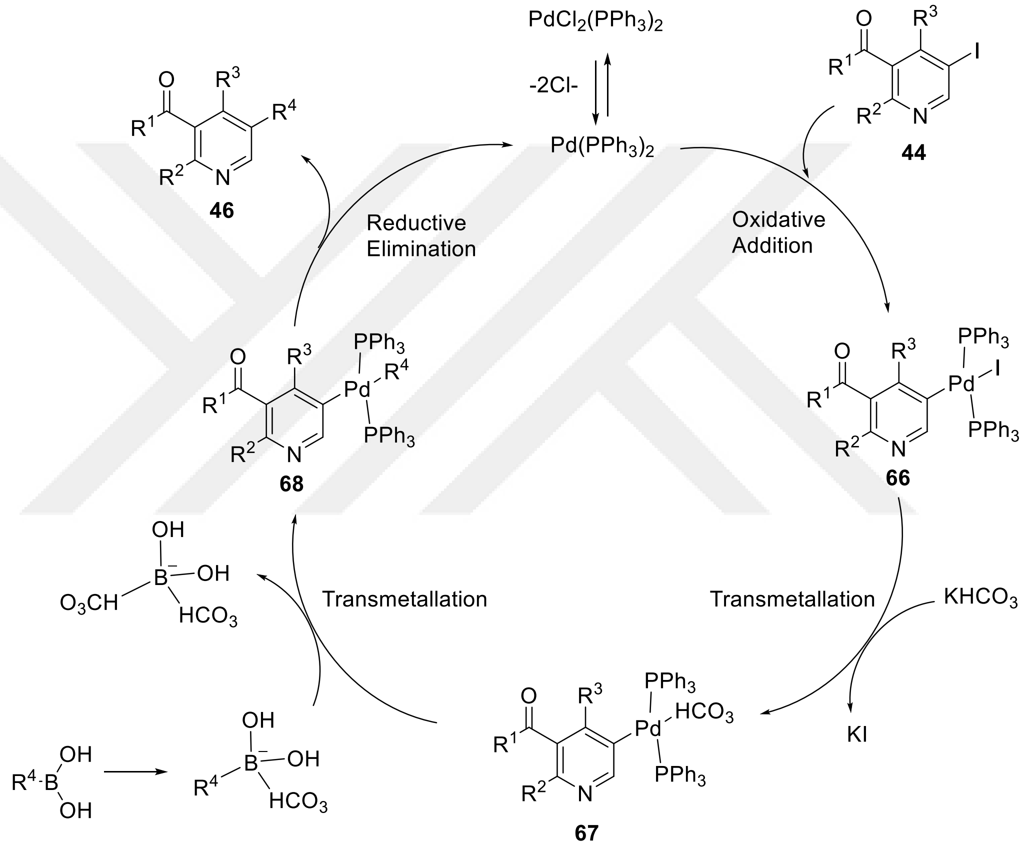
46r (80%)

[a]Isolated yields.

By employing the optimized conditions, 18 novel 5-arylpyridine derivatives **46** were synthesized as shown in Table 9. All coupling reactions proceeded well and the corresponding 5-arylpyridines **46** were obtained in good to excellent yields (65-98%). As a result of these studies, the coupling reactions were found to be general for a wide range of 5-iodopyridines and boronic acids. Moreover, the reactions showed good tolerance for a variety of substituents with different electron-withdrawing and electron-donating groups.

Catalytic cycle for our Suzuki coupling reaction, proposed on the basis of literature studies,[96] is shown in Scheme 27. The cycle begins with oxidative addition of 5-

iodopyridine **44** to Pd(0) catalyst to form Pd(II) complex **66**. Then, transmetallation occurs in which iodine on the palladium complex replaces with bicarbonate to give **67**. Subsequently, bicarbonate also adds to aryl boronic acid to form boronate complex which, initiates the transmetallation between boronate and palladium complex to afford intermediate **68**. Finally, reductive elimination produces the final coupled product **46** and regenerates the palladium catalyst.



Scheme 27. Proposed mechanism for the synthesis of 5-arylpyridines **46.**

Structures of 5-arylpyridines **46** were determined by ^{1}H and ^{13}C NMR spectroscopy. As an example, in the ^{1}H NMR spectrum of phenyl(2,4,5-triphenylpyridin-3-yl)methanone (**46a**), α-proton of pyridine resonates at 8.78 ppm (Figure 25). However, in the ^{1}H NMR spectrum of corresponding starting 5-iodopyridine (see Figure 23), this α-hydrogen appeared at 9.28 ppm. Moreover, the number of aromatic protons increases from 15 to 20 when compared to the corresponding 5-iodopyridine. In ^{13}C NMR spectrum (Figure 26), resonance signal at 98.6 ppm which belongs to carbon atom connected to iodine, disappeared. The carbon atom with hydrogen atom in the pyridine ring resonates at 150.8 ppm. However, in the ^{13}C NMR spectrum of the corresponding starting 5-iodopyridine (see Figure 24), this carbon atom was appeared in relatively lower field (157.5 ppm). Also, the number of aromatic carbon signals rises.

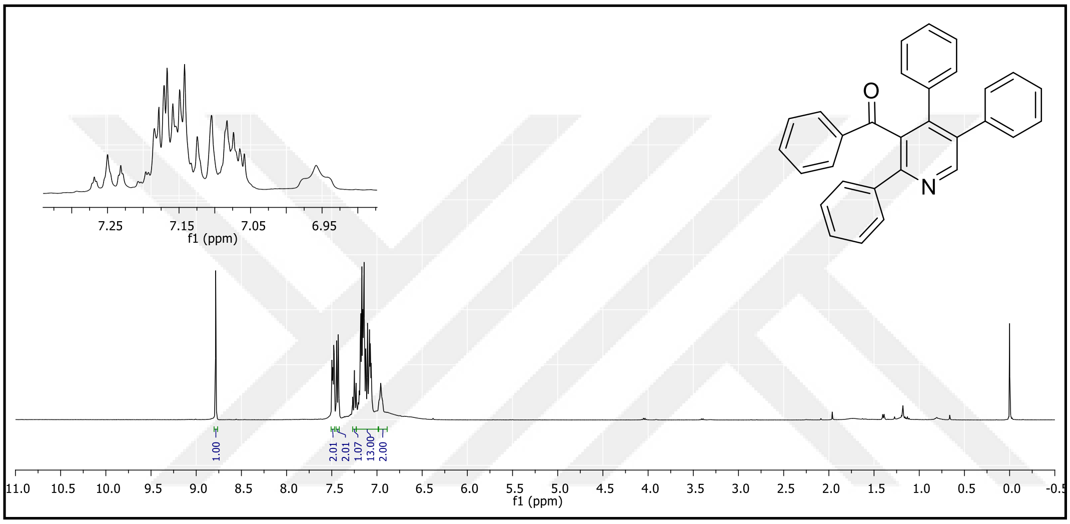


Figure 25. ^{1}H NMR spectrum of compound **46a**.

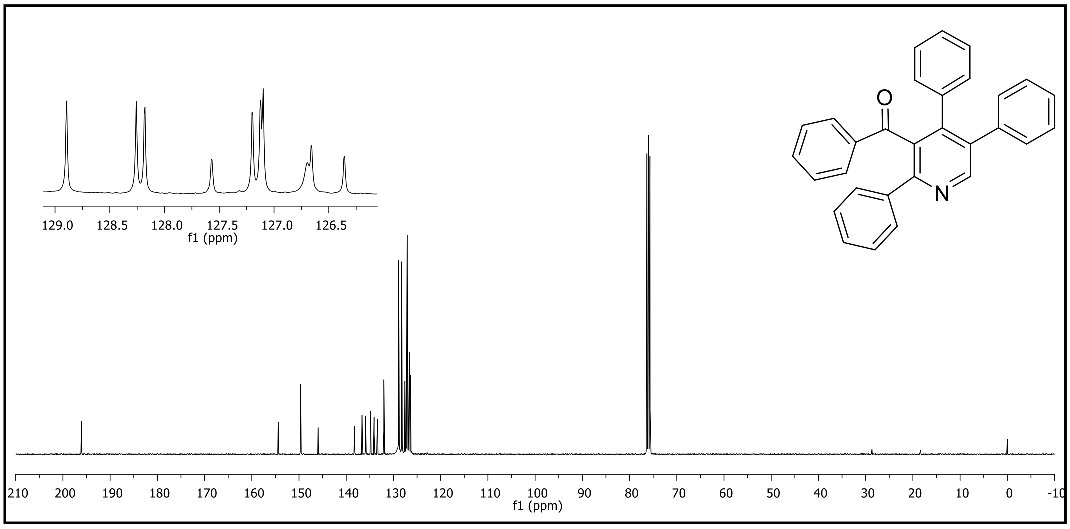
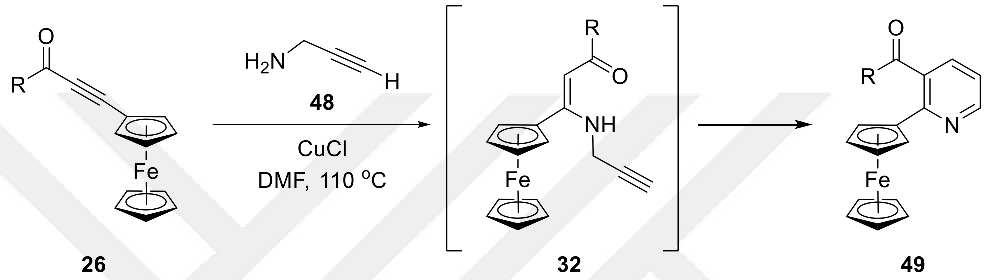


Figure 26. ^{13}C NMR spectrum of compound **46a**.

2.2.2. Synthesis of 2-Ferrocenylpyridines 49

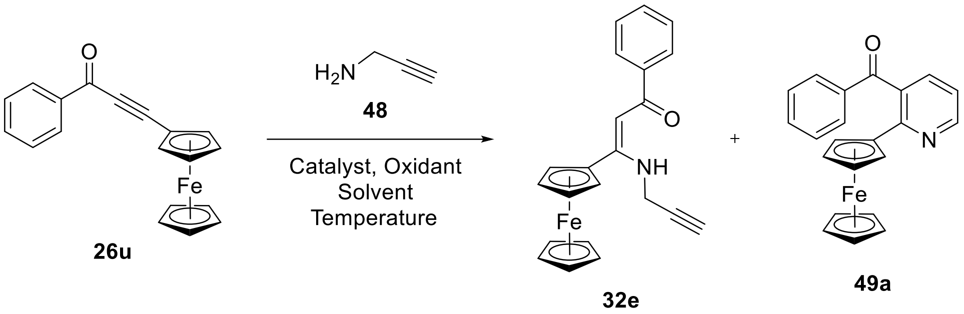
In the second part of the thesis study, we described one-pot method for the synthesis of 2-ferrocenylpyridines **49** from α,β-alkynic ketones **26** and propargyl amine (**48**) via in situ formation of *N*-propargylic β-enaminone **32,** which in the presence of copper (I) chloride, underwent electrophilic cyclization to afford 2-ferrocenyl-substituted pyridine derivatives **49** (Scheme 28).



Scheme 28. One-pot synthesis of 2-ferrocenylpyridines **49.**

Firstly, we synthesized ferrocenly-substituted α,β-alkynic ketones **26** through coupling of ethynylferrocene with aryl chlorides. Then, the reaction of 3-ferrocenyl-1-phenylprop-2-yn-1-one (**26u**) with propargylamine (**48**) was tested under different conditions to find the optimal reaction conditions (Table 10). Initially, the reaction was conducted in CH_3OH and DMF under argon atmosphere at 65 °C and 110 °C, respectively (Table 10, Entries 1 and 2). Interestingly, in CH_3OH, the reaction gave *N*-propargylic β-enaminone in 40% yield. However, in DMF, 2-ferrocenylpyridine **49a** was obtained in 25% yield. Then, when the reaction was performed in the presence of 0.2 equiv. of AuCl and $AuCl_3$ in DMF or THF, a mixture of *N*-propargylic β-enaminone **32e** and 2-ferrocenylpyridine **49a** were produced, where the former was obtained as a major product (Table 10, Entries 3-5). Subsequently, the reaction was conducted in 0.2 equiv. of $InCl_3$ and $AlCl_3$, which also afforded a mixture of *N*-propargylic β-enaminone **32e** and 2-ferrocenylpyridine **49a**, but the latter was obtained as major product (Table 10, Entries 6 and 7).

Table 10. Optimization studies for the formation of 2-ferrocenylpyridines 49.[a]



Entry	Catalyst or additive (equiv)	Atmosphere or oxidant (equiv)	Solvent	Temp. (°C)	32e[b] (%)	49a[b] (%)
1	-	Argon	CH_3OH	reflux	40	-
2	-	Argon	DMF	110	-	25
3	AuCl (0.2)	Argon	DMF	110	28	7
4	$AuCl_3$ (0.2)	Argon	DMF	110	34	16
5	$AuCl_3$ (0.2)	Argon	THF	reflux	30	18
6	$InCl_3$ (0.2)	Argon	DMF	110	7	16
7	$AlCl_3$ (0.2)	Argon	DMF	110	14	20
8	CuI (0.2)	Argon	DMF	110	-	40
9	CuBr (0.2)	Argon	DMF	110	-	43
10	CuCl (0.2)	Argon	DMF	110	-	49
11	CuCl (0.2)	Argon	CH_3OH	reflux	50	16
12	CuCl (0.2)	Argon	THF	reflux	-	30
13	CuCl (0.2)	Argon	CH_3CN	reflux	-	35
14	CuCl (1.0)	Argon	DMF	110	-	60
15	CuCl (2.0)	Argon	DMF	110	-	60
16	**CuCl (1.0)**	**Air**	**DMF**	**110**	**-**	**77**
17	CuCl (1.0)	*p*-Benzoquinone (1.1)	DMF	110	-	72
18	CuCl (1.0)	*p*-Benzoquinone (3.0)	DMF	110	-	61

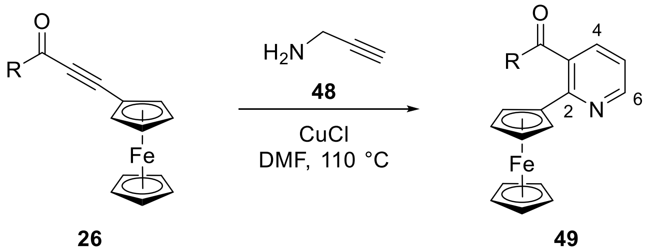
[a] Reactions were carried out using α,β-alkynic ketone **26u** (0.25 mmol), propargylamine **48** (0.30 mmol), solvent (3 mL) under the indicated conditions.

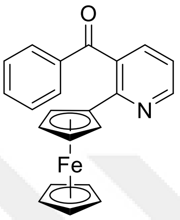
[b] Isolated yields.

When the reactions were carried out with 0.2 equiv. of CuI, CuBr and CuCl, all gave 2-ferrocenylpyridine **49a** as a single product (Table 10, Entries 8-10), where the highest yield (49%) was obtained by using CuCl. Next, we screened the reaction in different solvents such as CH_3OH, THF and CH_3CN by using 0.2 equiv. of CuI (Table 10, Entries 11-13). However, 2-ferrocenylpyridine **49a** was isolated in lower yields (16-35%). Then, the reaction was carried out in the presence of 1.0 equiv. of CuCl. We observed that yield of 2-ferrocenylpyridine **49a** increased to 60% yield (Table 10, Entry 14). The reaction was tested with 2.0 equiv. of CuCl, but increasing number of equivalents of CuCl did not improve the yield (Table 10, Entry 15). Then, we thought that oxidation could be necessary for aromatization. Therefore, the reaction was carried out under air and in the presence of *p*-benzoquinone. The reaction with 1.0 equiv. of CuCl was conducted open to air which afforded 2-ferrocenylpyridine **49a** in 77% yield (Table 10, Entry 16). We tested *p*-benzoquinone as oxidant with 1.1 and 3.0 molar equivalents, but the yield of product did not increase (Table 10, Entries 17 and 18). In summary, the highest yield (77%) of 2-ferrocenylpyridine **49a** was obtained with 1.0 equiv. of CuCl in DMF at 110 ℃ and open to air.

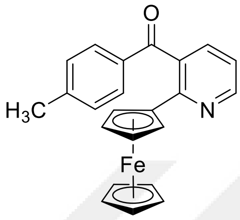
As illustrated in Table 11, a diverse range of 2-ferrocenylpyridine derivatives **49** were synthesized by employing a variety ferrocenly-substituted α,β-alkynic ketones **26** using optimized reaction conditions. In fact, reactions were fast and went completion in 1.5 to 2 hours. Notably, all reactions proceeded well and afforded corresponding 2-ferrocenylpyridines **49** in good yields (69-90%). Moreover, reactions showed good tolerance for both electron-donating and electron-withdrawing groups. α,β-Alkynic ketones with electron-withdrawing groups produced the corresponding ferrocenylpyridines **49** in relatively higher yields (71–90%) (**49d**, **49e** and **49f**) than did those with electron-donating groups (69–70%) (**49b** and **49c**).

Table 11. One-pot synthesis of 2-ferrocenylpyridines **49**.[a]

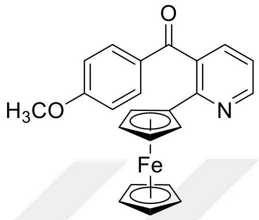




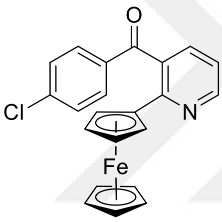
49a (77%)



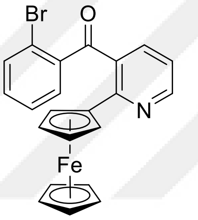
49b (69%)



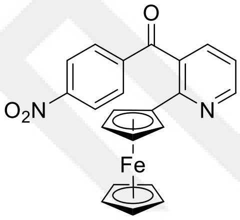
49c (70%)



49d (81%)



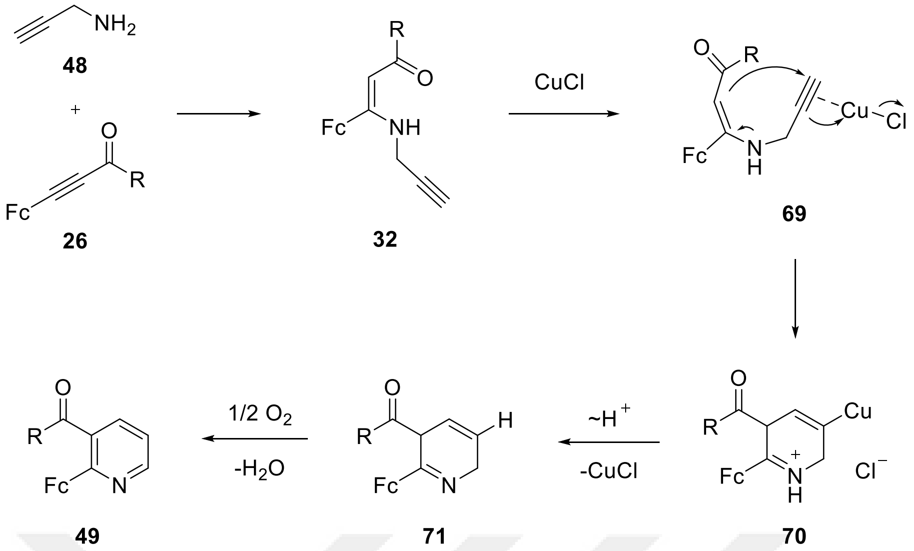
49e (90%)



49f (71%)

[a] Reagents and conditions: α,β-alkynic ketone **26** (0.25 mmol), propargylamine **48** (0.30 mmol), CuCl (0.25 mmol), DMF (3 mL), 110 °C.

Mechanism proposed for the formation of 2-ferrocenylpyridines **49** is outlined in Scheme 29. First, conjugate addition of propargylamine **48** to α,β-alkynic ketone **26** yields *N*-propargylic β-enaminone **32.** Notably, in situ formed β-enaminone **32** was not isolated. Then, copper coordinates to alkyne moiety, which produces complex **69**. Electrophilic cyclization of complex **69** affords intermediate **70**. Hydrogen atom transfer into copper and regeneration of CuCl yields 2,5-dihydropyridine **71** through reductive elimination. Finally, aerobic oxidation of 2,5-dihydropyridine **71** affords 2-ferrocenylpyridines **49**.



Scheme 29. Proposed mechanism for the formation of 2-ferrocenylpyridines **49**.

In the ^{1}H and ^{13}C NMR spectra of the synthesized 2-ferrocenylpyridine derivatives, some characteristic peaks are observed which relates to the formation of pyridine ring. For instance, in the ^{1}H NMR spectrum of compound **49a**, hydrogen atoms at C4, C5 and C6 of the pyridine ring resonate at approximately 7.56-7.50, 7.19 and 8.69 ppm, respectively (Figure 27).

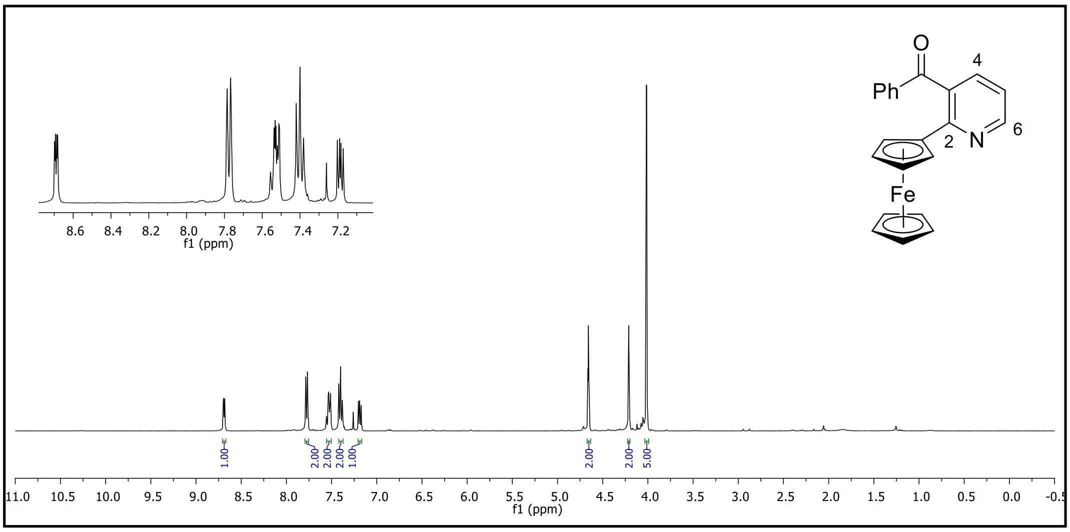


Figure 27. ^{1}H NMR spectrum of compound **49a**.

In the ^{13}C NMR spectrum of compound **49a**, the peaks of C4, C5, and C6 were appeared at approximately 135.5, 119.7 and 150.2 ppm, respectively (Figure 28). Moreover, C2 atom attached to the ferrocenyl group, resonated nearly at 156.6 ppm. C3 atom connected to benzoyl group, appeared around 132.1 ppm. In brief, the combined NMR data clearly support the indicated formation of 2-ferrocenylpyridine ring.

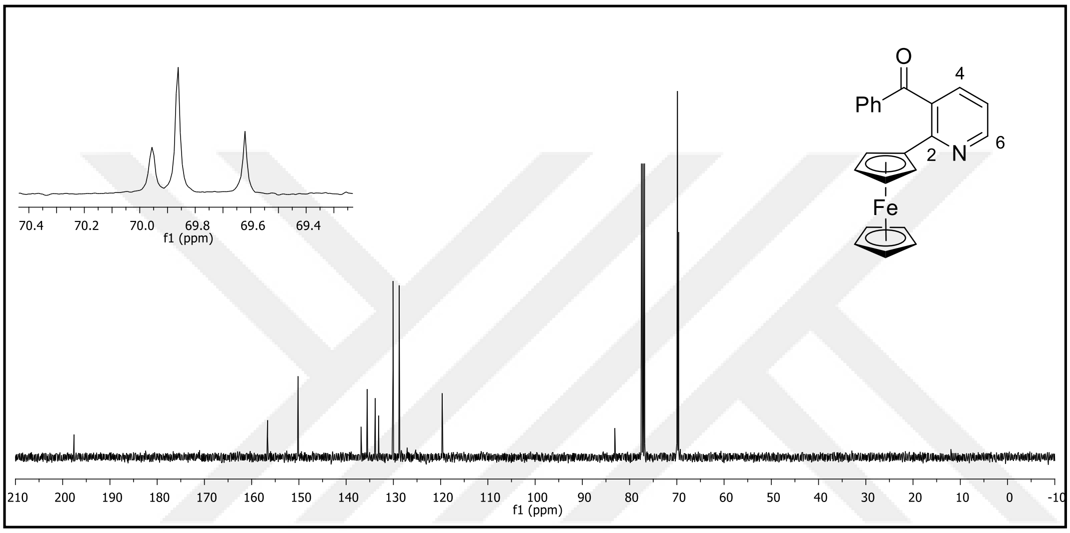
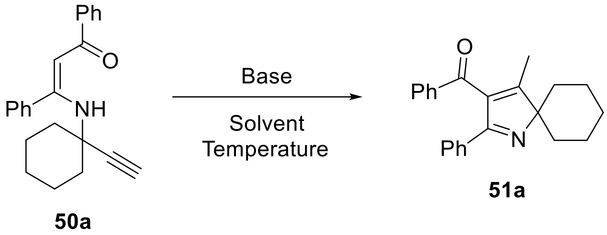


Figure 28. ^{13}C NMR spectrum of compound **49a**.

2.2.3. Synthesis of Spiro-2*H*-pyrroles 51

Investigation of the cyclization of cyclohexane-embedded *N*-propargylic β-enaminones **50** in the presence of cesium carbonate comprises the basis of this section of the thesis study. The cyclohexane-embedded *N*-propargylic β-enaminones **50** were produced from the reaction of α,β-alkynic ketones **26** with 1-ethynylcyclohexylamine. In addition, 3 derivatives of *N*-(1,1-dimethyl)propargylic β-enaminone derivatives **61** were synthesized as well for comparison purpose. Conjugate addition of 2-methyl-3-butyn-2-amine to α,β-alkynic ketones **26** produced β-enaminones **61**. With the synthesized β-enaminones in hand, we next investigated their cyclization to spiro-2*H*-pyrroles **51** and/or 2*H*-pyrroles **72**. In order to optimize the reaction conditions, we first examined the reaction of *N*-propargylic β-enaminone **50a** under different conditions as illustrated in Table 12. Initially, the reaction was performed with 2.0 equiv. of NaH at room temperature in DMF, the corresponding spiro-2*H*-pyrrole **51a** was formed in 69% yield (Table 12, Entry 1). The reaction in the presence of 1.0 and 3.0 molar equivalents of NaH produced (**51a**) in 62 and 68% yields, respectively (Table 12, Entries 2 and 3). Both lower number of equivalents (1.0 equiv.) and higher number of equivalents (3.0 equiv.) of NaH did not improve the yield. Hence, 2.0 equiv. of base was used in the following reactions. Then, the reaction with 2.0 equiv. of NaH at room temperature was performed in CH_3CN, DCM, dioxane, THF, DCE and CH_3OH (Table 12, Entries 4-9). These reactions produced the expected spiro-2*H*-pyrrole **51a** in 47-65% yields. Next, the same reactions were conducted in refluxing conditions and/or high temperatures. The reactions in DMF at 110 °C and in refluxing dioxane yielded **51a** in 12% and 22% yields, respectively (Table 12, Entries 10 and 11). Notably, the reaction at higher temperature such as 100 °C and above did not increase the yield of spiro-2*H*-pyrrole **51a**. Conversely, it drastically decreased the yield of the product. However, the reaction in refluxing DCM, CH_3OH, DCE and CH_3CN afforded spiro-2*H*-pyrrole **51a** in 64-80% yields, (Table 12, Entries 12-15), where the highest yield of spiro-2*H*-pyrrole **51a** was obtained in refluxing CH_3CN (Table 12, Entry 15). Therefore, CH_3CN was choosen as the reaction solvent. In order to improve the yield of product **51a** in refluxing CH_3CN, the reaction was carried out in the presence of various bases. The use of DIPA did not lead to formation of spiro-2*H*-pyrrole **51a** (Table 12, Entry 16). When the reaction was run with NEt_3, compound **51a** was obtained in 5% yield (Table 12, Entry 17). Next, the reaction was tested with in the presence of 2.0 equiv. of DBU, $NaHCO_3$ and $KHCO_3$ (Table 12, Entries 18-20) and spiro-2*H*-pyrrole (**51a**) was obtained in relatively lower yields (71-75%). Subsequently, the reaction was performed by using 2.0 equiv. of Cs_2CO_3, which produced spiro-2*H*-pyrrole **51a** in 92% yield (Table 12, Entry 21).

Table 12. Optimization studies for the synthesis of spiro-2*H*-pyrroles **51**.[a]



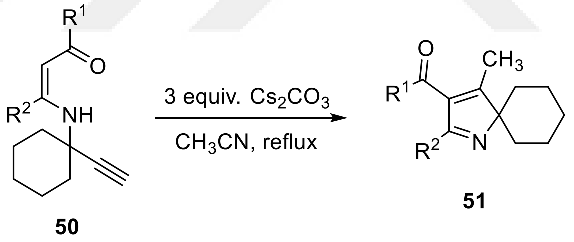
Entry	Base (equiv.)	Solvent	Temp. (°C)	Yield[b] (%)
1	NaH (2.0)	DMF	r.t.	69
2	NaH (1.0)	DMF	r.t.	62
3	NaH (3.0)	DMF	r.t.	68
4	NaH (2.0)	CH_3CN	r.t.	65
5	NaH (2.0)	DCM	r.t.	58
6	NaH (2.0)	Dioxane	r.t.	50
7	NaH (2.0)	THF	r.t.	47
8	NaH (2.0)	DCE	r.t.	53
9	NaH (2.0)	CH_3OH	r.t.	52
10	NaH (2.0)	DMF	110	12
11	NaH (2.0)	Dioxane	reflux	22
12	NaH (2.0)	DCM	reflux	64
13	NaH (2.0)	CH_3OH	reflux	71
14	NaH (2.0)	DCE	reflux	76
15	NaH (2.0)	CH_3CN	reflux	80
16	DIPA(2.0)	CH_3CN	reflux	-
17	Et_3N (2.0)	CH_3CN	reflux	5
18	DBU (2.0)	CH_3CN	reflux	74
19	$NaHCO_3$(2.0)	CH_3CN	reflux	71
20	$KHCO_3$(2.0)	CH_3CN	reflux	75
21	Cs_2CO_3(2.0)	CH_3CN	reflux	92
22	**Cs_2CO_3 (3.0)**	**CH_3CN**	**reflux**	**95**

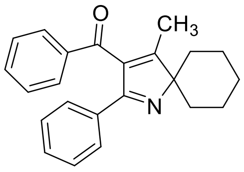
[a] Reaction was carried out using cyclohexane-embedded *N*-propargylic β-enaminone **50a** (0.30 mmol), solvent (3 mL) under indicated conditions.
[b] Isolated yield.

Clearly, the use of Cs_2CO_3 highly improved the yield of **51a**. Finally, we carried out the reaction in the presence of 3.0 equiv. of Cs_2CO_3, which yielded spiro-2*H*-pyrrole **51a** in 95% yield (Table 12, Entry 22). This was the highest yield obtained from these reactions. In brief, cyclization of cyclohexane-embedded *N*-propargylic β-enaminones **50** to spiro-2*H*-pyrroles **51** were performed with 3.0 equiv. of Cs_2CO_3 in refluxing CH_3CN under argon atmosphere.

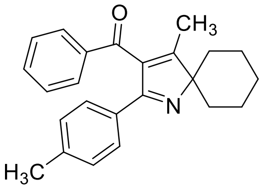
As shown in Table 13, a diverse range of novel spiro-2*H*-pyrroles **51** was synthesized from *N*-propargylic β-enaminone derivatives **50** by emplying the optimized reaction conditions. All cyclizations of β-enaminones **50** proceeded well and afforded corresponding spiro-2*H*-pyrroles **51** in good to excellent yields (82-97%). Notably, the cyclizations were fast and went to completion in very short time (1-2 h). Moreover, cyclizations demonstrated good tolerance for both elecron-donating and electron-withdrawing groups.

Table 13. Synthesis of spiro-2*H*-pyrroles **51**.[a]

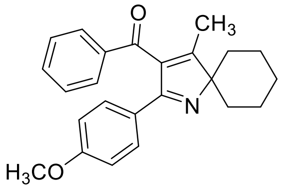




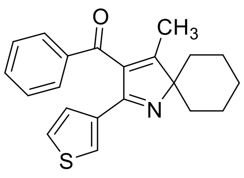
51a (95%)



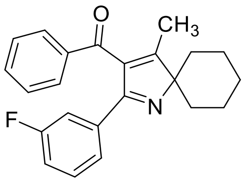
51b (94%)



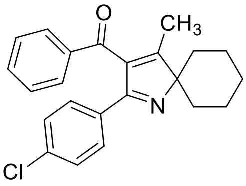
51c (91%)



51d (90%)

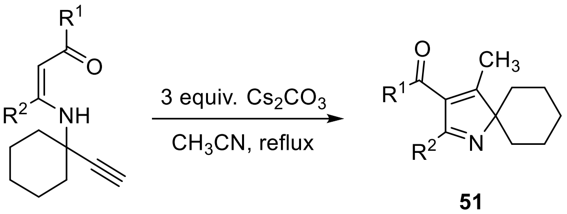


51e (89%)

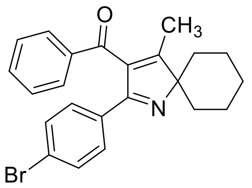


51f (91%)

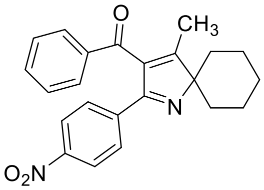
Table 13. Continued.



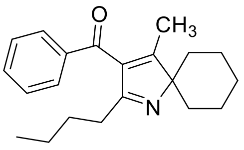
50 **51**



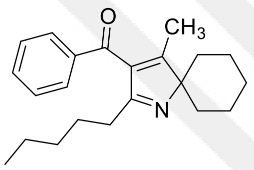
51g (83%)



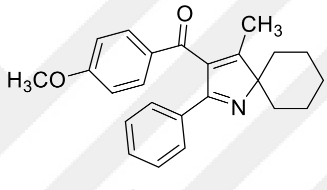
51h (88%)



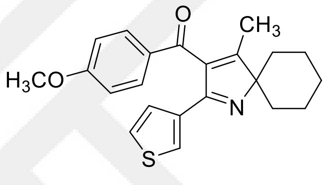
51i (92%)



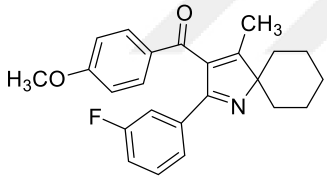
51j (90%)



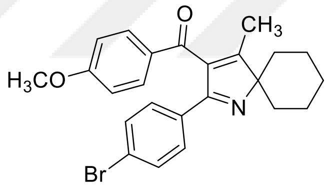
51k (91%)



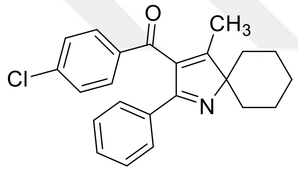
51l (82%)



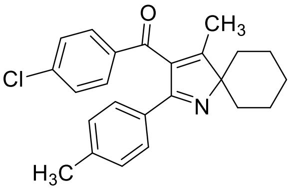
51m (93%)



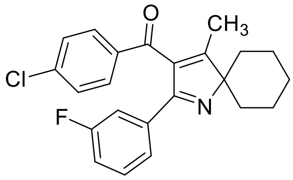
51n (87%)



51o (96%)



51p (97%)



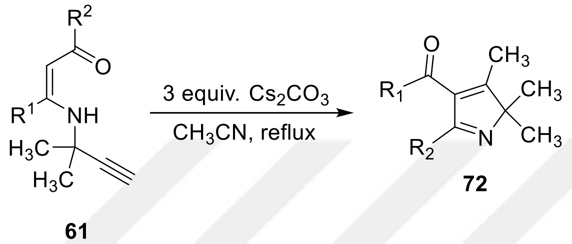
51q (95%)

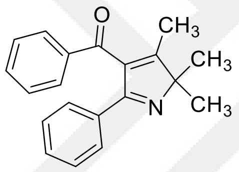
[a] Isolated yields.

As illustrated in Table 14, we also synthesized 3 derivatives of 2,2-dimethyl-2*H*-pyrroles, specifically **72a**, **72b** and **72c**, which contain two methyl groups, instead of a spiro-cyclohexane unit. These 2*H*-pyrrole derivatives **72** were obtained in 85-92%

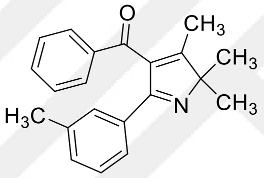
yields, comparable with those of spiro-2*H*-pyrroles **51**. In fact, β-enaminones **50** and **61** with a cyclohexane-embedded or 1,1-dimethyl-substituted propargylamine in the presence of cesium carbonate underwent nucleophilic cyclization smoothly to afford the corresponding spiro-2*H*-pyrroles **51** and 2*H*-pyrroles **72** in good to excellent yields.

Table 14. Synthesis of 2*H*-pyrroles **72.**[a]

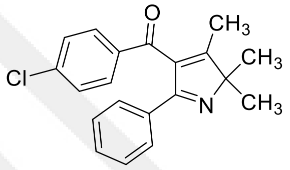




72a (92%)



72b (89%)

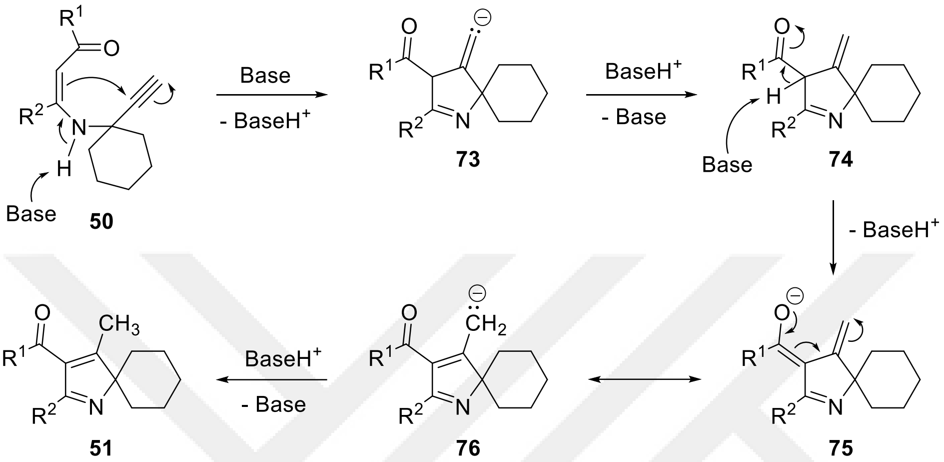


72c (85%)

[a]Isolated yields.

A plausible mechanism for the formation of spiro-2*H*-pyrroles **51** is described in Scheme 30. Initially, abstraction of amine proton with base initiates nucleophilic cyclization giving intermediate **73**. Subsequently, protonation of intermediate **73** yields spiro-1-pyrroline **74**. Then, base takes the acidic α-hydrogen which produces the corresponding enolate **75**, which upon resonance interaction generates intermediate **76**. Finally, protonation of intermediate **76** affords spiro-2*H*-pyrrole derivatives **51**.

The structures of the synthesized spiro-2*H*-pyrroles **51** and 2*H*-pyrroles **72** were proved by the analysis of their corresponding ^{1}H and ^{13}C NMR spectra. Their HRMS data also supported assigned structures of spiro-2*H*-pyrroles and/or 2*H*-pyrroles. As an example, in the ^{1}H NMR spectrum of compound **51a** (Figure 29), aromatic hydrogens which belong to phenyl groups resonate around 7.82-7.19 ppm. 10 aliphatic protons attached to cyclohexyl unit were observed at 2.15-1.33 ppm. Methyl protons appear around 1.94 ppm as a singlet.



Scheme 30. Proposed mechanism for the formation of spiro-2*H*-pyrroles **51**.

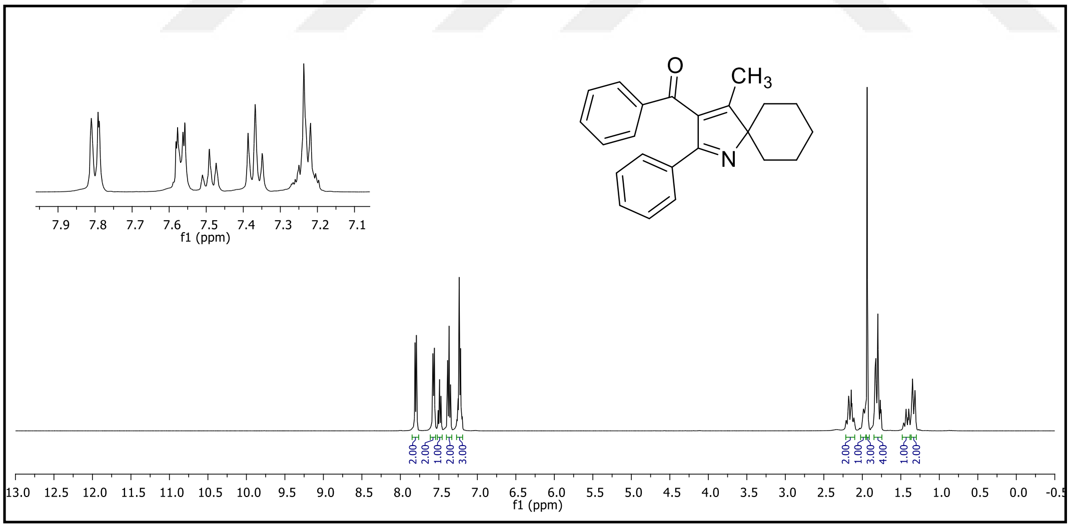


Figure 29. ^{1}H NMR spectrum of compound **51a**.

^{13}C NMR spectra of 3-((1-ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**50a**) and (4-methyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)(phenyl)methanone

(**51a**) are given for comparison in Figures 30 and 31. As it can be seen, the peak of spiro atom (shown by an arrow) in compound **50a** resonates at 53.7 ppm, but in compound **51a**, the peak of spiro atom shifted to downfield and appeared at 82.5 ppm. Moreover, two acetylenic carbon peaks (shown by dashed arrow), which are shown at 86.7 and 73.6 ppm in Figure 30, disappeared in ^{13}C NMR spectrum of compound **51a**. The existence of methyl carbon, which resonates at 12.5 ppm, proves the formation of targeted product **51a**.

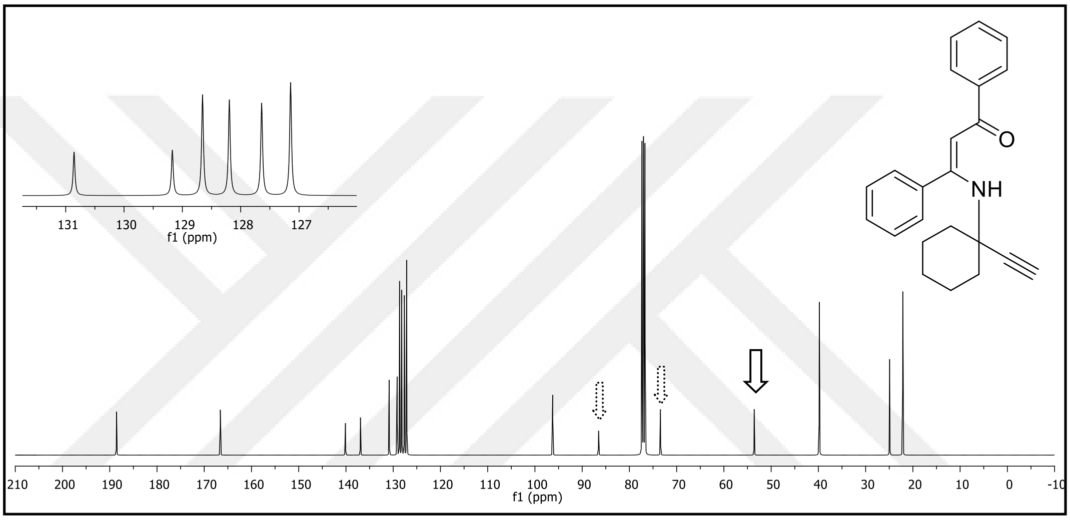


Figure 30. ^{13}C NMR spectrum of compound **50a**.

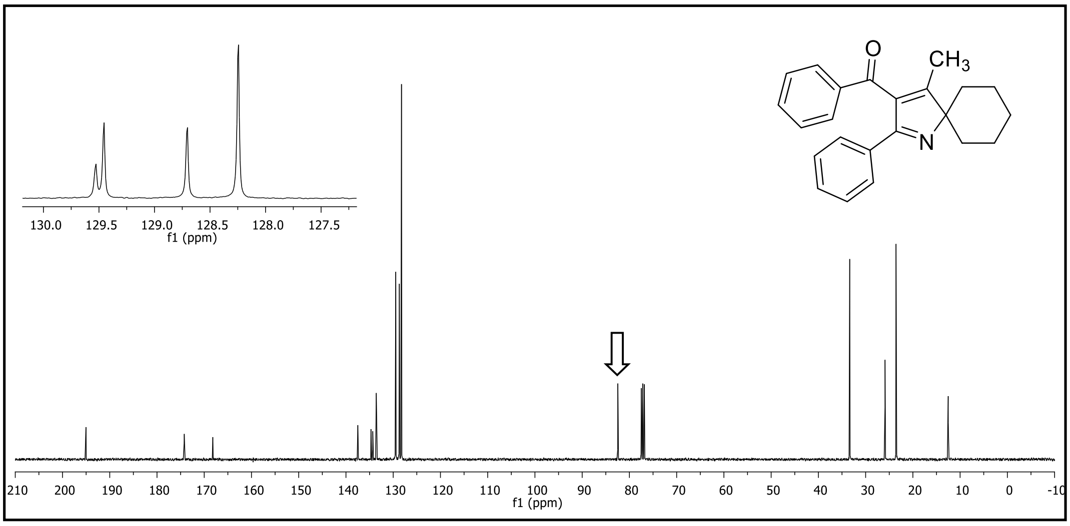
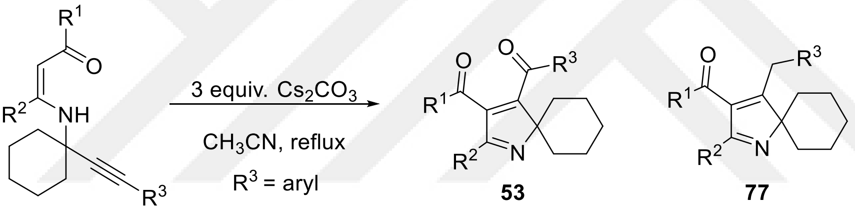


Figure 31. ^{13}C NMR spectrum of compound **51a**.

2.2.4. Synthesis of Spiro-2*H*-pyrroles with Two Carbonyl Groups 53

While synthesizing spiro-2*H*-pyrroles, we also tried to make different derivatives in order to increase the range of products. Then, we subjected to cyclohexane-embedded *N*-propargylic β-enaminones **50** to Sonogashira cross-coupling reactions with aryl iodides in order to further functionalize these compounds. The palladium-catalyzed reaction of β-enaminones **50** with aryl iodides **62** in the presence of CuI and Et_3N at room temperature gave the arylated β-enaminones **52** with internal alkyne functionality in 70-89% yields as shown in Table 6. After preparation of arylated β-enaminones **52**, we carried out their cyclization as illustrated in Scheme 31**.** Surprisingly, this reaction did not produce the expected product **77**; instead, it produced spiro-2*H*-pyrrole **53** with two carbonyl groups via benzylic C-H oxidation.



52

53

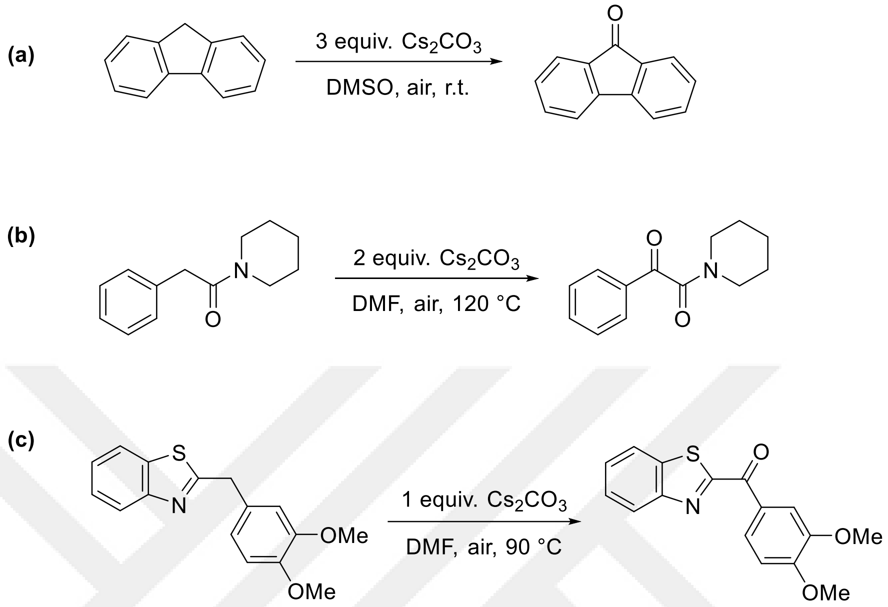
(53% yield)

77

not observed

Scheme 31. Synthesis of spiro-2*H*-pyrrole with two carbonyl groups **53.**

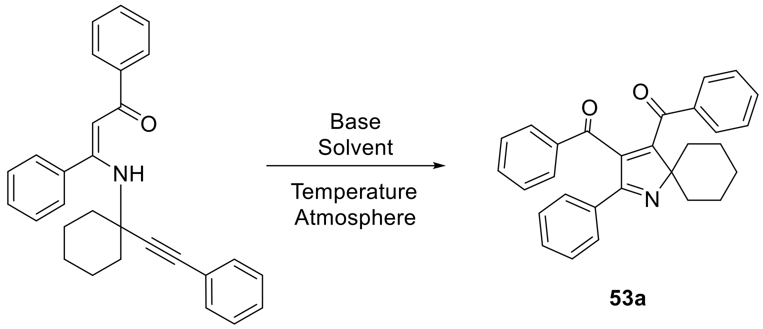
Formation of these oxidized spiro-2*H*-pyrrole **53** was interesting. So, we searched the literature for similar benzylic C-H oxidations. We found similar examples of benzylic oxidations in basic medium, which are shown in Scheme 32.[97] In the first case, fluorenes are effectively transformed into corresponding aryl ketones in the presence of excess cesium carbonate in DMSO at room temperature (Scheme 32a). Secondly, Xu and co-workers provided a route to α-ketoamides from arylacetamides (Scheme 32b). Grimaud and Kaim reported that under air and basic conditions**,** benzothiazoles were easily oxidized to corresponding ketones (Scheme 32c). This literature findings gave brief information about such benzylic C-H oxidations. Notably, in our case, cyclization first produced the corresponding spiro-2*H*-pyrroles **77** in situ, which subsequently underwent benzylic C-H oxidation.



Scheme 32. Examples of benzylic C-H oxidations.

In the light of this literature information about benzylic C-H oxidation, we first examined reaction of 1,3-diphenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one (**52a**) under different conditions in order to find the optimal reaction conditions (Table 15). We already obtained the oxidized spiro-2*H*-pyrrole **53a** in 53% yield in the presence 3.0 equivalents of Cs_2CO_3 in acetonitrile at refluxing condition under argon atmosphere (Table 15, Entry 1). Then, the reaction was performed with 1.0 and 2.0 molar equivalents of Cs_2CO_3, which afforded product **53a** in 5 and 48% yields, respectively (Table 15, Entries 2 and 3). Notably, using 1.0 equivalent of base drastically decreased the yield of product. Moreover, the reaction was carried out at room temperature, which afforded spiro-2*H*-pyrrole **53a** in very low yield (Table 15, Entry 4). When the reaction with 3.0 equivalents of Cs_2CO_3 was conducted open to air, spiro-2*H*-pyrrole **53a** was obtained in 62% yield (Table 15, Entry 5). Then, the

Table 15. Optimization studies for the benzylic C-H oxidation in spiro-2*H*-pyrroles **53**.[a]



52a

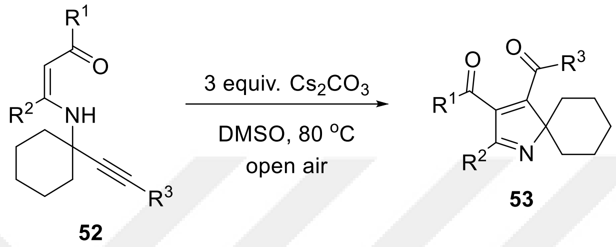
53a

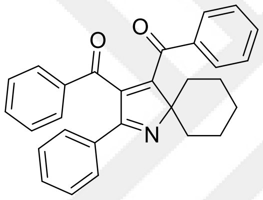
Entry	Base (equiv.)	Atmosphere	Solvent	Temp. (°C)	Yield (%)[b]
1	Cs_2CO_3 (3.0)	Argon	CH_3CN	reflux	53
2	Cs_2CO_3 (2.0)	Argon	CH_3CN	reflux	48
3	Cs_2CO_3 (1.0)	Argon	CH_3CN	reflux	5
4	Cs_2CO_3 (3.0)	Argon	CH_3CN	r.t.	3
5	Cs_2CO_3 (3.0)	Air	CH_3CN	reflux	62
6	Cs_2CO_3 (3.0)	Air	DMF	110	57
7	**Cs_2CO_3 (3.0)**	**Air**	**DMSO**	**80**	**69**
8	Cs_2CO_3 (3.0)	Air	THF	reflux	30
9	Na_2CO_3 (3.0)	Air	DMSO	80	22
10	K_2CO_3 (3.0)	Air	DMSO	80	38
11	NEt_3 (3.0)	Air	DMSO	80	13

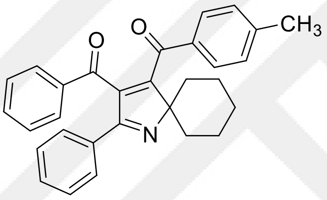
[a] Reaction was carried out using cyclohexane-embedded *N*-propargylic β-enaminone **52a** (0.30 mmol), solvent (3 mL) under indicated conditions.
[b] Isolated yield.

reaction was screened in different solvent such as DMF, DMSO and THF at high temperatures and/or refluxing conditions (Table 15, Entries 6-8). From these reactions, spiro-2*H*-pyrrole **53a** was isolated in 30-69% yields. Notably, the highest yield of **53a** was obtained in DMSO. Finally, the same reaction was carried out in the presence of different bases such as Na_2CO_3, K_2CO_3 and Et_3N, but the corresponding product **53a** was isolated in 13-38% yields (Table 15, Entries 9-11). In summary, the highest yield (69%) was obtained in the presence of 3 equivalents of Cs_2CO_3 in DMSO at 80 °C and open to air (Table 15, Entry 7) and the substrate scope were performed under these conditions. As illustrated in Table 16, different derivatives of spiro-2*H*-pyrroles **53** were synthesized by employing variety of β-enaminone derivatives **52** under optimized conditions via benzylic C-H oxidation.

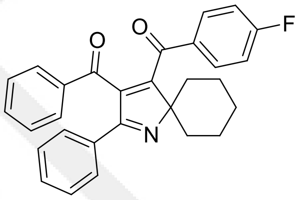
Table 16. Synthesis of spiro-2*H*-pyrroles with two carbonyl groups **53**.[a]



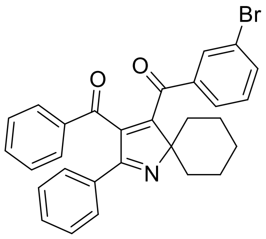

53a (69%)



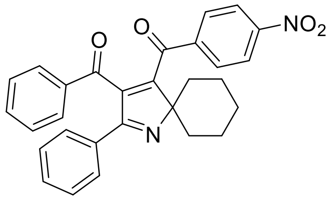
53b (72%)



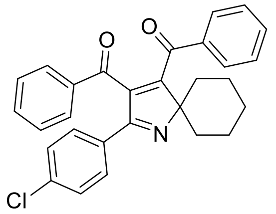
53c (60%)



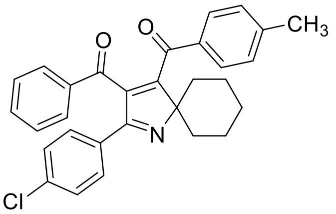
53d (64%)



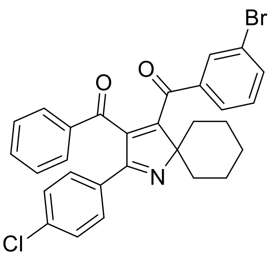
53e (67%)



53f (75%)



53g (69%)

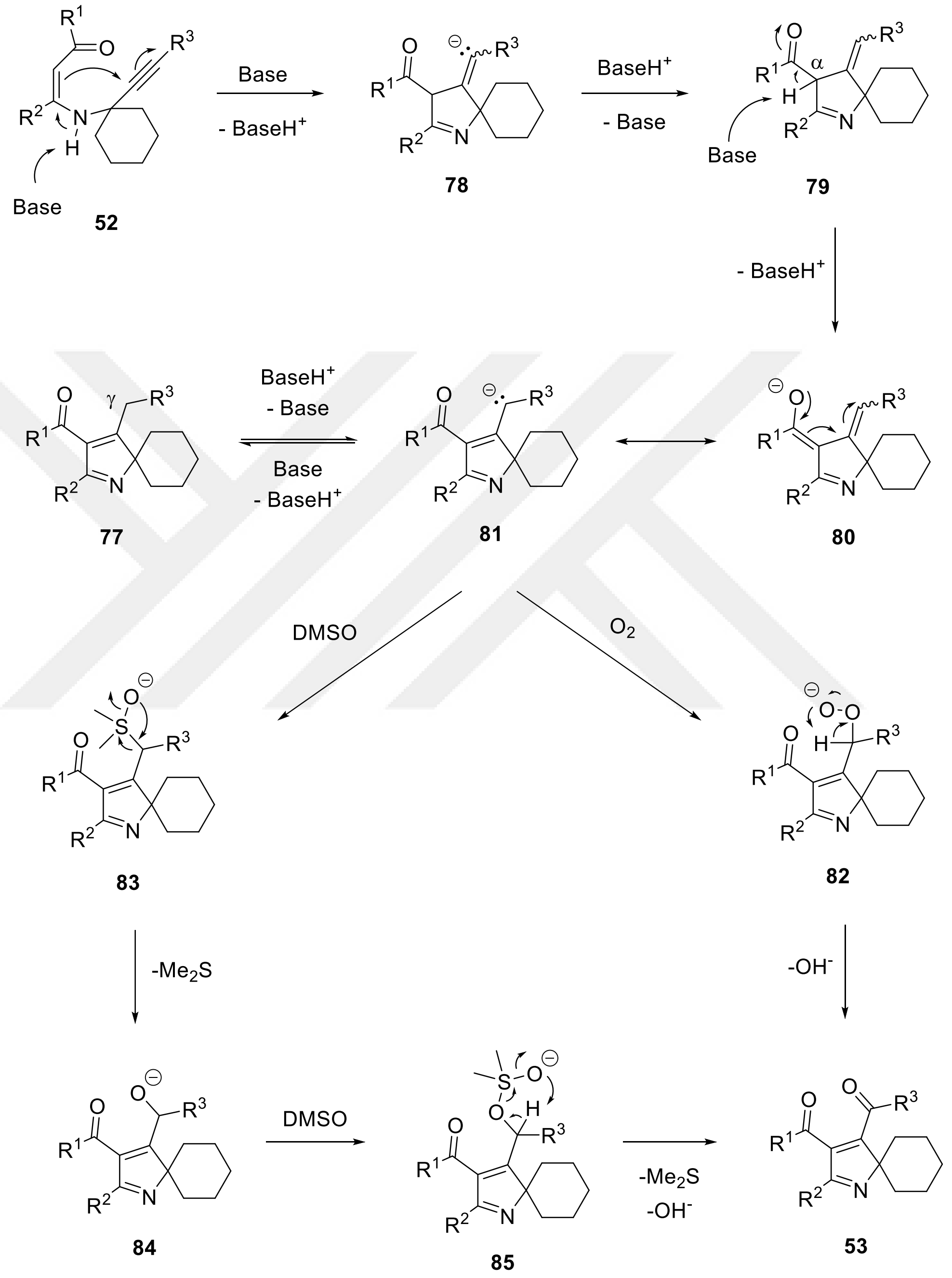


53h (75%)

[a]Isolated yields.

Notably, all reactions proceeded smoothly and afforded corresponding products in good yields (60-75%).

A possible mechanism for the formation of spiro-2*H*-pyrroles **53** is shown in Scheme 33. First, abstraction of the amine proton with base and subsequent vinylogous amido-imido tautomerization initiates nucleophilic cyclization, producing intermediate **78**. Protonation of **78** yields spiro-1-pyrroline **79**. Next, abstraction of the acidic α-hydrogen with base generates enolate **80**, which, upon resonance, produces carbanion **81**. Finally, protonation of **81** affords spiro-2*H*-pyrrole **77**. As previously noted, spiro-2*H*-pyrrole derivatives **77** have not been observed in these reactions. Presumably, under basic conditions, intermediate **77** is converted back into carbanion **81** since γ-hydrogen atoms in **77** are relatively acidic because they are benzylic (R^3 = aryl) and, in **81**, the resulting carbanion at this site is conjugated to the enone functionality. According to literature precedent,[98] at this stage, carbanion **81** undergoes aerobic oxidation and/or DMSO based oxidation to afford spiro-2*H*-pyrrole **53** (Scheme 33). On aerobic oxidation, carbanion **81** reacts with molecular oxygen to generate peroxy anion **82**, which subsequently rearranges to form spiro-2*H*-pyrroles **53** through hydrogen abstraction from the benzylic site, which enables the formation of a carbonyl group with the loss of hydroxide ion. On the other hand, in DMSO-based oxidation, carbanion **81** interacts with DMSO to produce intermediate **83**, which, upon 1,2-sigmatropic rearrangement, forms alkoxide ion **84** with the loss of dimethyl sulfide. Subsequently, alkoxide ion **84** couples with the electrophilic sulfur atom of DMSO to yield intermediate **85**, which finally rearranges to afford spiro-2*H*-pyrrole **53** via proton transfer, followed by E_{1cb} elimination, with the loss of dimethyl sulfide and hydroxide ion (Scheme 33). At present, it is not clear which mechanism is operating, individually or predominantly. However, according to our experimental results, it is most likely that aerobic oxidation is heavily involved in the formation of spiro-2*H*-pyrroles **53** given that the reaction of **52a** with 3.0 equivalents of Cs_2CO_3 in refluxing CH_3CN under air produced spiro-2*H*-pyrrole **53a** in 62% yield (Table 15, entry 5); whereas use of DMSO as solvent under the same conditions did not increase the yield of **53a** significantly (69%; Table 15, entry 7). These results strongly imply that benzylic C–H oxidation of **77** to **53** occurs predominantly by aerobic oxidation.



Scheme 33. Proposed mechanism for the formation of spiro-2*H*-pyrroles **53**.

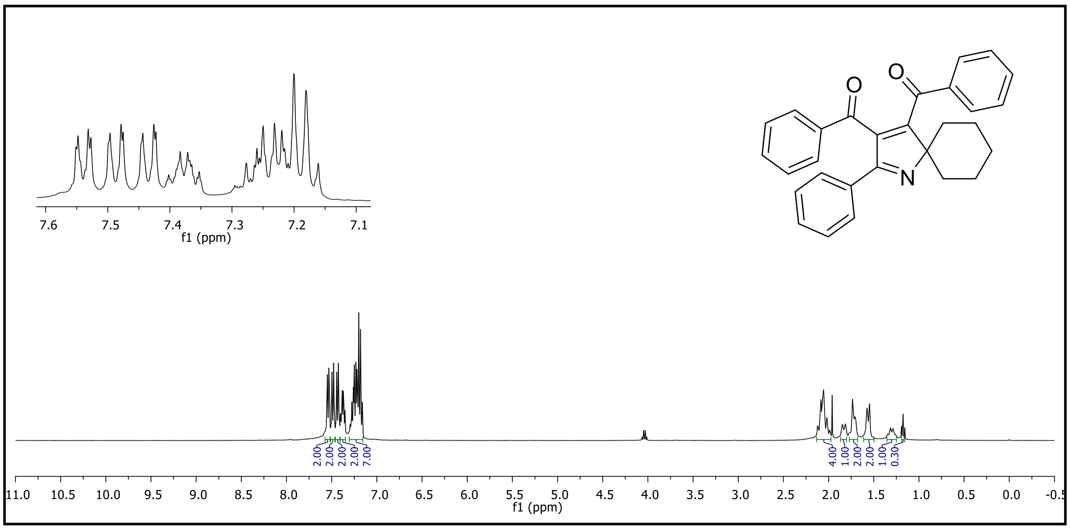


Figure 32. ^{1}H NMR spectrum of compound **53a**.

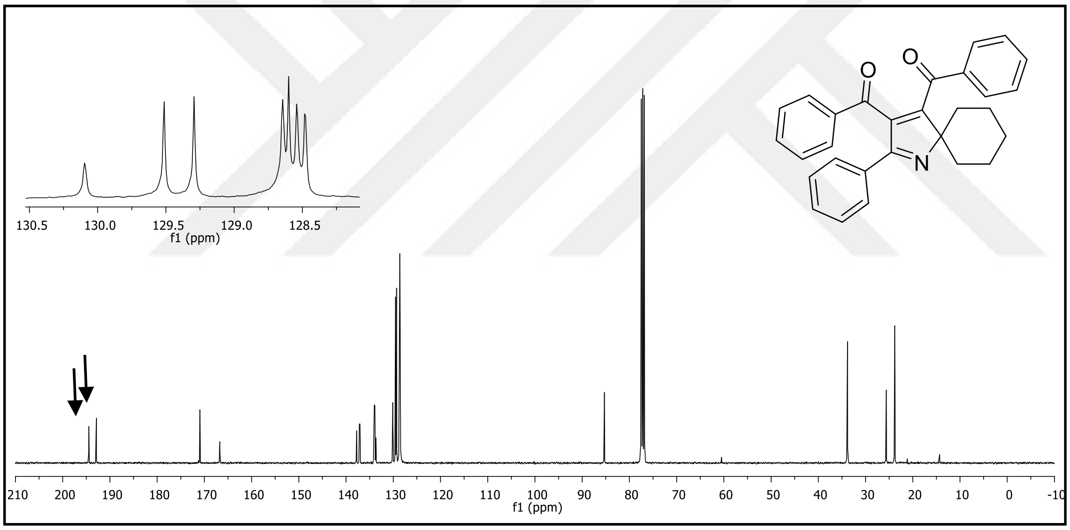


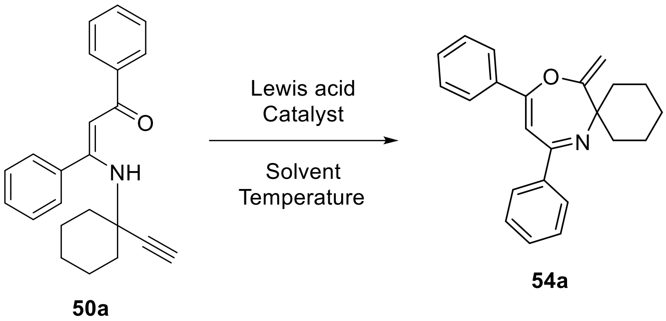
Figure 33. ^{13}C NMR spectrum of compound **53a**.

As an example, ^{1}H and ^{13}C NMR spectra of (2-phenyl-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) (**53a**) are demonstrated in Figures 32 and 33. In the ^{1}H NMR spectrum (Figure 32), all phenyl protons resonate at aromatic region (7.56-7.15 ppm), while 10 aliphatic protons, which belong to cyclohexyl group, appear between 2.13-1.24 ppm. In the ^{13}C NMR spectrum of compound **53a**, two carbonyl carbons resonate at 194.5 and 192.9 ppm (shown by arrows), which are characteristic peaks in order to prove the formation of compound **53a**.

2.2.5. Synthesis of Spiro-1,4-oxazepines 54

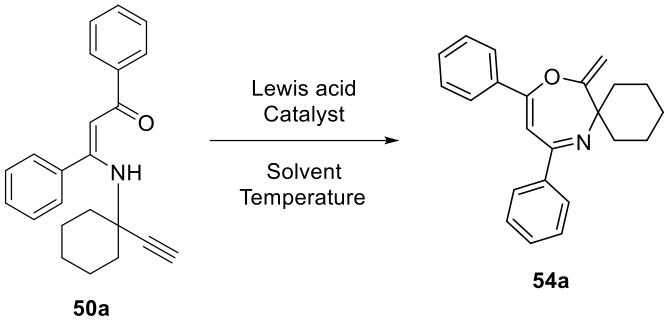
In the last part of the thesis study, cyclization of cyclohexane-embedded *N*-propargylic β-enaminones **50** was described in the presence of zinc iodide and silver hexafluoroantimonate. With the synthesized β-enaminones **50** in hand, we next investigated their Lewis acid promoted electrophilic cyclization to spiro-1,4-oxazepines **54**. In order to optimize reaction conditions, we first examined the representative reaction of *N*-propargylic β-enaminone **50a** under various conditions as illustrated in Table 17. Initially, the reaction was performed with 2.0 equivalents of $ZnCl_2$ and ZnI_2 in DCE at room temperature, which afforded the corresponding spiro-1,4-oxazepine **54a** but in low yields (Table 17, Entries 1 and 2). In order to improve the yield of **54a**, the reaction was conducted in refluxing conditions which produced spiro-1,4-oxazepine **54a** in 41% yield (Table 17, Entry 3). Notably, the reaction with lower number equivalents (1.0 equiv.) and higher number of equivalents (2.0 equiv.) of $ZnCl_2$ at refluxing conditions did not raise the yield (Table 17, Entries 4 and 5). The reaction was carried out in the presence of 0.05 equiv. of silver acetate as an additive, in addition to 1.0 equiv. of $ZnCl_2$, in refluxing DCE. However, the product **54a** was isolated in 35% yield (Table 17, Entry 6). The same reaction was performed in the presence of different equivalents $ZnBr_2$, ZnI_2, $AuCl_3$ and $InCl_3$ (Table 17, Entries 7-12) where the highest yield (48%) was obtained with 2.0 equiv. of ZnI_2. Next, the reaction was tested with AuCl (2.0 equiv.) and $AuCl_3$ (1.0 and 2.0 equiv.) in refluxing chloroform (Table 17, Entries 13-15); however, with these Lewis acids, **54a** was obtained in lower yields (19-32%). When the reaction was conducted with 2.0 equiv. of $AuCl_3$ in refluxing methanol, spiro-1,4-oxazepine **54a** formed in very low yield (Table 18, Entry 16). The reaction was also performed with 0.15 equiv. silver hexafluoroantimonate as an additive together with 0.1 and 1.0 equiv. of $AuCl_3$, but these did not increase the yield (Table 17, Entries 17 and 18). Since the best yield

Table 17. Optimization studies for the synthesis of spiro-1,4-oxazepines **54**.[a]



Entry	Lewis acid /Catalyst (equiv.)	Solvent	Temp. (°C)	Yield (%)[b]
1	$ZnCl_2$ (2.0)	DCE	r.t.	29
2	ZnI_2 (2.0)	DCE	r.t.	28
3	$ZnCl_2$ (2.0)	DCE	84	41
4	$ZnCl_2$ (1.0)	DCE	84	40
5	$ZnCl_2$ (3.0)	DCE	84	40
6	$ZnCl_2$ (1.0)/AgOAc (0.05)	DCE	84	35
7	$ZnBr_2$ (2.0)	DCE	84	43
8	ZnI_2 (2.0)	DCE	84	48
9	ZnI_2 (1.0)	DCE	84	42
10	$InCl_3$ (2.0)	DCE	84	40
11	$InCl_3$ (1.0)	DCE	84	40
12	$AuCl_3$ (2.0)	DCE	84	27
13	AuCl (2.0)	$CHCl_3$	61	19
14	$AuCl_3$ (1.0)	$CHCl_3$	61	30
15	$AuCl_3$ (2.0)	$CHCl_3$	61	32
16	$AuCl_3$ (2.0)	CH_3OH	65	6
17	$AuCl_3$ (0.1)/$AgSbF_6$ (0.15)	CH_3OH	r.t.	12
18	$AuCl_3$ (1.0)/$AgSbF_6$ (0.15)	CH_3OH	65	26
19	ZnI_2 (2.0)	$CHCl_3$	61	44
20	ZnI_2 (2.0)	CH_3CN	82	37
21	ZnI_2 (2.0)	DMF	110	26
22	ZnI_2 (2.0)	DCM	40	32
23	ZnI_2 (2.0)	CH_3OH	65	39

Table 17. Continued.



Entry	Lewis acid /Catalyst (equiv.)	Solvent	Temp. (°C)	Yield (%)[b]
24	ZnI_2 (2.0)/ $AgSbF_6$ (0.05)	DCE	84	60
25	ZnI_2 (2.0)/ $AgSbF_6$ (0.1)	DCE	84	66
26	**ZnI_2 (2.0)/ $AgSbF_6$ (0.15)**	**DCE**	**84**	**73**
27	ZnI_2 (2.0)/ $AgSbF_6$ (0.2)	DCE	84	73

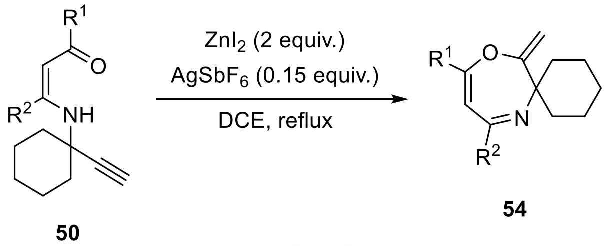
[a] Reactions were carried out on scale of 0.30 mmol of of *N*-propargylic β-enaminones **1a** in 3 mL of solvent under argon with indicated conditions.
[b] Isolated yields.

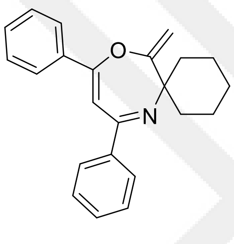
(48%) of **54a** in these reactions was obtained with 2.0 equiv. ZnI_2 in DCE at reflux conditions (Table 17, Entry 8), the same reaction was carried out in $CHCl_3$, CH_3CN, DMF, DCM and CH_3OH as well. From these reactions, spiro-1,4-oxazepine **54a** was isolated in 26-44% yields (Table 17, Entries 19-23). Then, 0.05 equiv. of $AgSbF_6$ was put into reaction medium as an additive, together with 2.0 equiv. ZnI_2, which improved the yield of spiro-1,4-oxazepine **54a** significantly (60%) (Table 17, Entry 24). Finally, when the reaction was tested in the presence of 0.1 and 0.15 equiv. of $AgSbF_6$ (Table 17, Entries 25 and 26), spiro-1,4-oxazepines (**54a**) were isolated in higher yields (66% and 73%). Further increasing the amount of $AgSbF_6$ did not improve the yield of (**54a**) (Table 17, Entry 27). In summary, the highest yield (73%) of spiro-1,4-oxazepine **54a** was obtained with 2.0 equiv. of ZnI_2 and 0.15 equiv. $AgSbF_6$ in refluxing DCE under argon atmosphere, i.e with the conditions present in entry 26.

The generality of reaction and the scope of substrates were performed under these optimized conditions. As depicted in Table 18, a diverse range of spiro-1,4-oxazepines

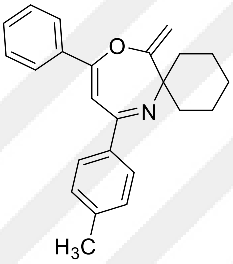
54 were synthesized by employing a variety of *N*-propargylic β-enaminone derivatives **50**. In general, the reaction proceeded smoothly and afforded the corresponding spiro-1,4-oxazepines in good to high yields (60-89%).

Table 18. Synthesis of spiro-1,4-oxazepines **54**.[a]

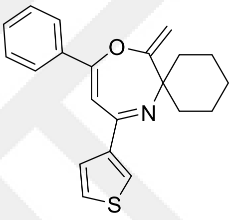




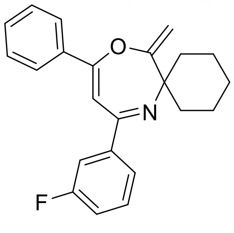
54a (73%)



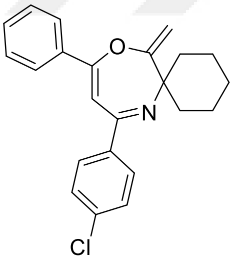
54b (63%)



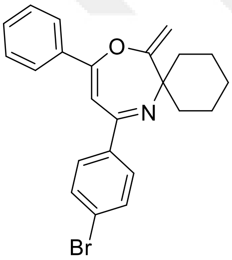
54c (74%)



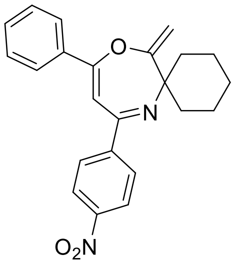
54d (84%)



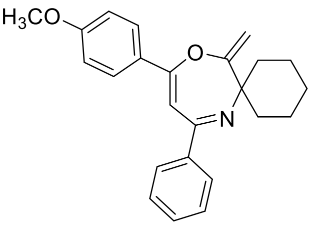
54e (81%)



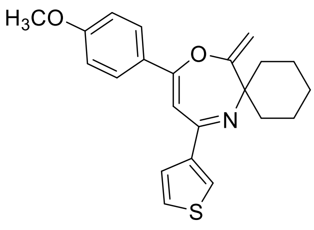
54f (80%)



54g (68%)

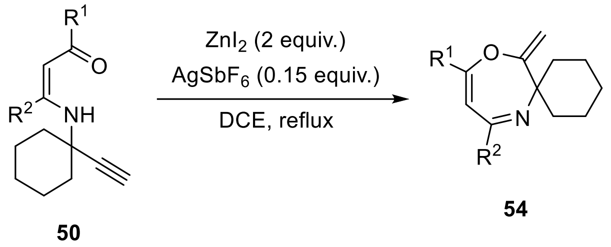


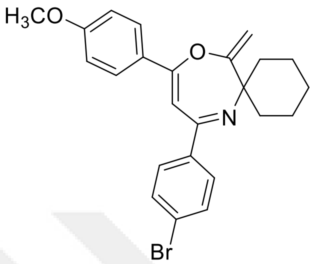
54h (63%)



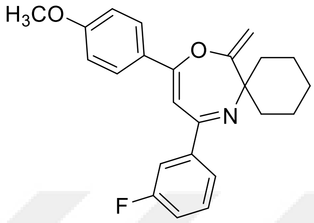
54i (77%)

Table 18. Continued.^{a}

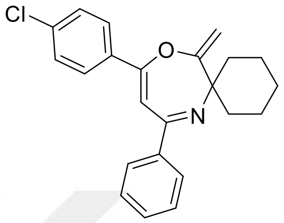




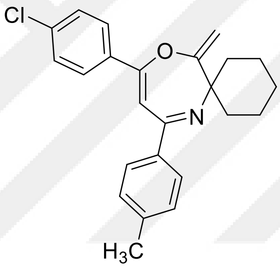
54j (71%)



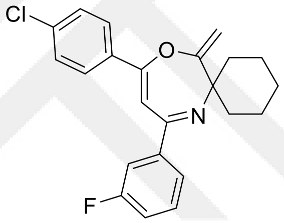
54k (68%)



54l (75%)



54m (73%)



54n (89%)

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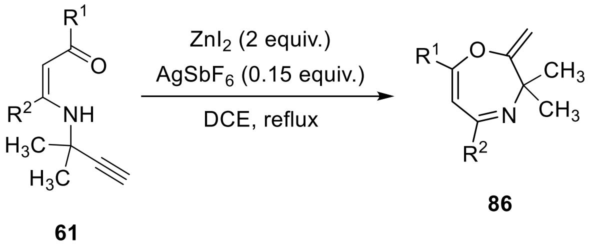
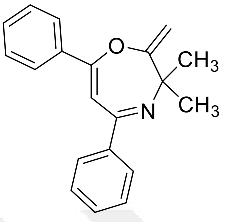
^{a} Isolated yields.

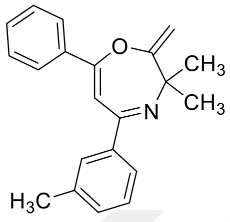
Moreover, the reactions demonstrated good tolerance for both electron-donating and electron-withdrawing groups. As shown in Table 19, we synthesized three derivatives of 3,3-dimethyl-1,4-oxazepines **86** as well, which contain two methyl groups, instead of a spiro-cyclohexane unit. These 1,4-oxazepine derivatives resulted from these reactions in 65-78% yields, comparable with those of spiro-1,4-oxazepines **54**.

Table 19. Synthesis of 1,4-oxazepines **86**.[a]

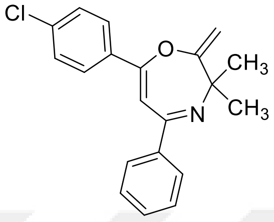




86a (74%)



86b (78%)

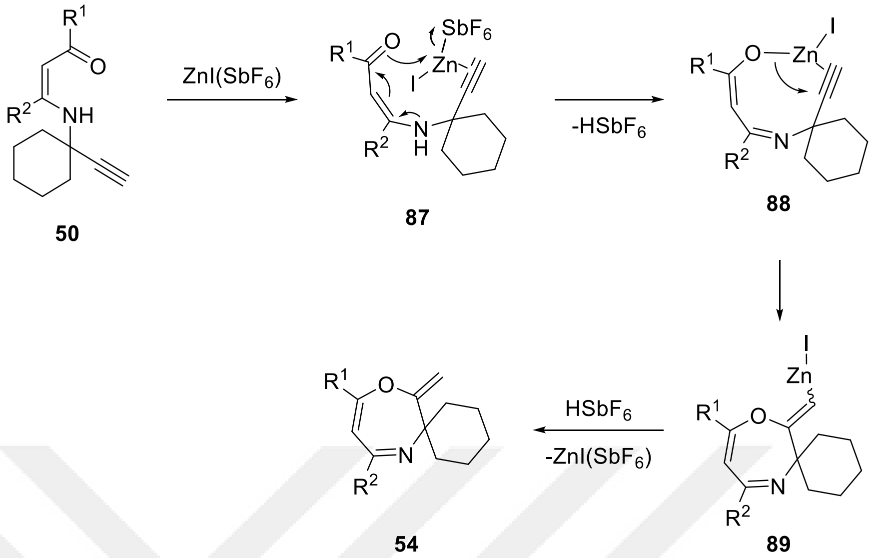


86c (65%)

[a] Isolated yields.

Mechanism proposed for the formation of spiro-1,4-oxazepines **54** is outlined in Scheme 34. First, ZnI_2 reacts with $AgSbF_6$, which affords the more active cationic catalyst system $ZnI(SbF_6)$.[99] Then, interaction of $ZnI(SbF_6)$ with alkyne moiety of **50** gives **87**, which enhances the electrophilicity of alkyne unit. Subsequent coordination of carbonyl oxygen to zinc through vinylogous amido-imido tautomerization produces intermediate **88**, bringing the carbonyl and alkyne functionalities in close proximity. Moreover, intramolecular 7-*exo-dig* electrophilic cyclization occurs to yield vinyl zinc intermediate **89**. Finally, hydrolysis with $HSbF_6$ generated in situ affords spiro-1,4-oxazepine derivatives **54**.[100]

$$ZnI_2 + AgSbF_6 \longrightarrow AgI + ZnI(SbF_6)$$



Scheme 34. Proposed mechanism for the formation of spiro-1,4-oxazepines **54**.

Formation of spiro-1,4-oxazepine derivatives **54** were mainly confirmed by the analysis of their ^{1}H and ^{13}C NMR data. For instance, ^{1}H and ^{13}C NMR spectra of compound **54b** are demonstrated in Figures 34 and 35, respectively. In the ^{1}H NMR spectrum (Figure 34), the protons of *exo*-methylenic carbon give distinct high-field signals at 4.92 and 4.62 ppm as doublets with small coupling constants (J = 1.4 Hz). The other olefinic proton resonates as a singlet at 6.29 ppm. Remaining 10 phenyl hydrogens appear between 7.20 and 7.81 ppm.

In the ^{13}C NMR spectrum (Figure 35), the peaks of C2, C5 and C7 were observed at 159.2, 159.5, and 160.3 ppm. Eight different phenyl carbon peaks appear between 126.6 ppm and 140.2 ppm. The exo-methylenic carbon signal is observed at 96.7 ppm. The peak, which resonates at 97.0 ppm, belongs to olefinic carbon atom at C6. The peak of spiro carbon atom (C3) was observed at 64.7 ppm.

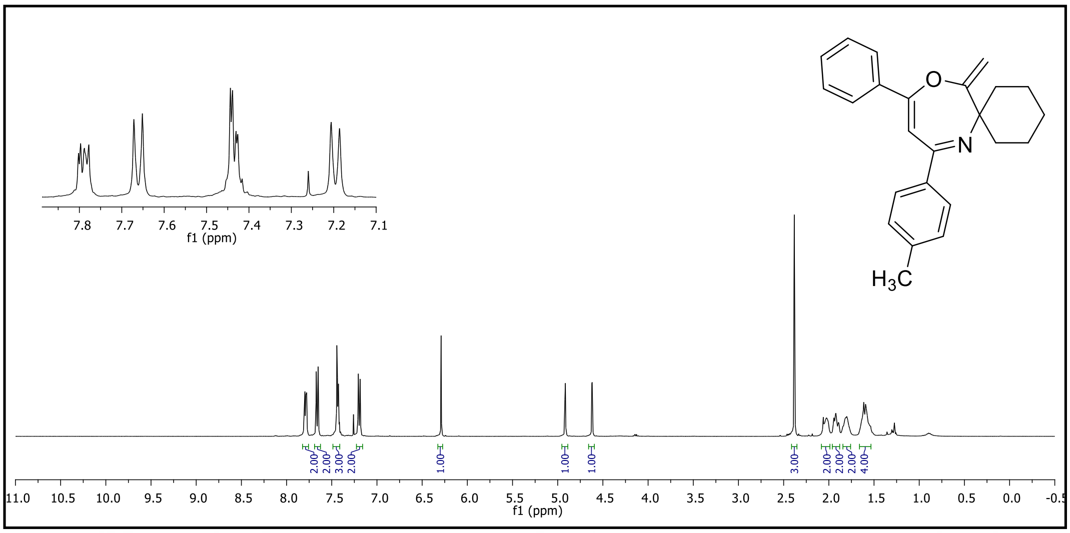


Figure 34. ^{1}H NMR spectrum of compound **54a**.

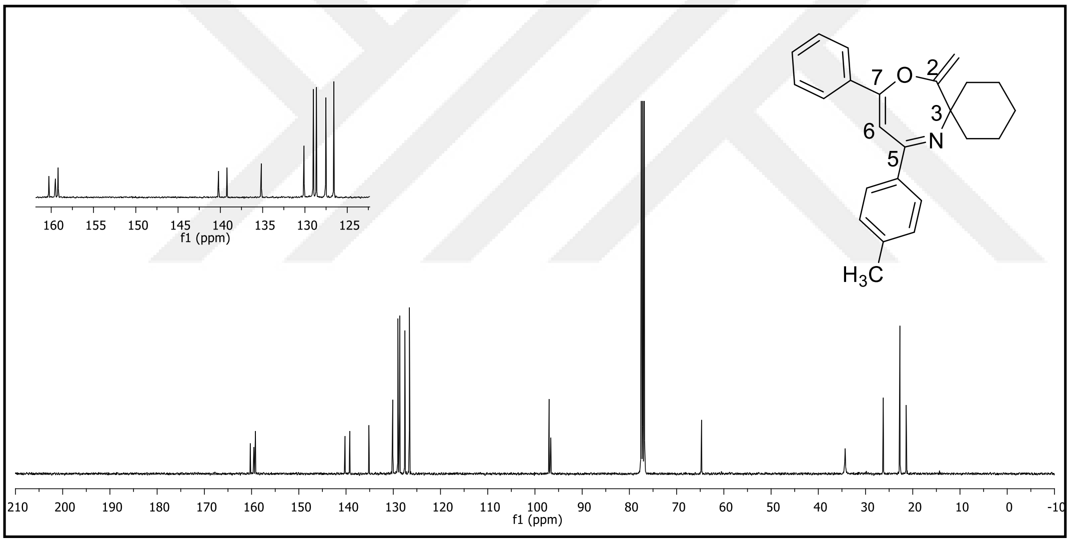


Figure 35. ^{13}C NMR spectrum of compound **54a**.

CHAPTER 3

EXPERIMENTAL

3.1. General Information

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) relative to $CDCl_3$ (7.26 and 77.16 ppm in ^{1}H and ^{13}C NMR, respectively). Coupling constants (*J*) are reported in Hertz (Hz), and spin multiplicities are presented by the following symbols: s (singlet), br s (broad singlet), br t (broad triplet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), tt (triplet of triplet), dt (doublet of triplet), td (triplet of doublet), qt (quartet of triplet), ddd (doublet of doublet of doublet), tdd (triplet of doublet of doublet), pseudo d (pseudo doublet), pseudo t (pseudo triplet), pseudo q (pseudo quartet).Infrared spectra (IR) were recorded by using attenuated total reflection (ATR). Band positions are reported in reciprocal centimeters (cm^{-1}). Mass spectra (MS) and high resolution mass spectra (HRMS) were obtained by using Electrospray Ionization (ESI) with Micro-Tof; *m/z* values are reported (For each measurement, the mass scale was recalibrated with sodium formate clusters, and samples were dissolved and measured in MeOH or CH_3CN). The melting point temperatures of crystalline samples held within capillary tubes were measured and recorded automatically. Flash chromatography was performed using thick-walled glass columns and “flash grade” silica gel (230-400 mesh). Thin layer chromatography (TLC) was performed by using commercially prepared 0.25 mm silica gel or aluminium oxide (neutral) plates and visualization was effected with short wavelength UV lamp (254 nm). The relative proportions of solvents in chromatography solvent mixtures refer to the volume:volume ratio. All commercially available reagents were used directly without purification unless otherwise stated. All solvents used in reactions and chromatography were distilled and/or dried properly for purity. The inert atmosphere was created by slight positive pressure (ca. 0.1 psi) of argon. All glassware was dried in oven prior to use.

3.2. Synthesis of Acetylferrocene (58)

Ferrocene (**57**) (2.0 g, 10.8 mmol) was dissolved in dry CH_2Cl_2 (9 mL) by constant stirring under argon. Then acetyl chloride (0.92mL, 11.8 mmol) was added to the resultant orange/red solution. The flask was immersed in a 0-5 ^oC ice-water bath. Anhydrous aluminum chloride (1.44 g, 10.8 mmol) was slowly added in small portions to the reaction flask. The reaction mixture was stirred at room temperature for 2 h and then it was recooled to 0-5 ^oC by a fresh ice-water bath. By the slow addition of cold water (4 x 0.5 ml), the reaction mixture was hydrolyzed. Then a further 3 mL of cold water was added more rapidly. The hydrolyzed reaction mixture was extracted with CH_2Cl_2 and combined organic extracts were washed with 5% NaOH solution followed by brine solution. The organic phase was dried over magnesium sulfate and filtered off. An orange/red solid was obtained after solvent was removed on rotary evaporator. The resultant solid was purified by flash column chromatography on silica gel using 9:1 hexane/ethylacetate as the eluent to give acetylferrocene (**198**) (1.96 g, 80%). ^1H NMR (400 MHz, $CDCl_3$) δ 4.60 (s, 2H), 4.32 (s, 2H), 4.02 (s, 5H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.2 (C), 72.3 (CH), 69.8 (CH), 69.5 (CH), 27.3 (CH_3). The spectral data is in agreement with those reported previously for this compound.[101]

3.3. Synthesis of (2-Formyl-1-chlorovinyl)ferrocene (59)

In a two necked flask, acetylferrocene (**58**) (2.0 g, 8.8 mmol) and DMF (2.17 ml, 28.2 mmol) were added under argon. The flask was cooled to 0 ^oC by ice-water bath and the brown reaction mixture was stirred for 10 minutes. Separately, in a round-bottom flask, DMF (2.17 mL, 28.2 mmol) was added and cooled to 0 ^oC under argon. Then cautiously phosphorus oxychloride (2.21 mL, 28.2 mmol) was added to DMF with good stirring. The resultant viscous red complex was slowly (over 30 minutes) transferred to the two neck flask containing acetylferrocene (**58**) and DMF by a dropping funnel. After the addition was completed, the contents of the flask were stirred at 0 ^{o}C for approximately 2 h until the color of reaction mixture changed from dark brown to olive green and then to dark blue. A 20 mL portion of diethyl ether was added, and the mixture was stirred vigorously. Then with continued cooling with ice-water bath, sodium acetate trihydrate (10.18 g, 74.6 mmol) was carefully added to the reaction flask in one portion followed by addition of water (2 mL). The ice water bath was removed and a color change in organic layer from colorless to ruby red, indicating the formation of formyl derivative, was observed. After 1 h, additional ether (2 mL) was added and the stirring was continued for 3 h at room temperature for complete quenching. The reaction mixture was extracted with diethyl ether. The organic extracts were combined and washed with saturated sodium bicarbonate solution. After dried by magnesium sulfate and filtered, organic phase was concentrated on rotary evaporator, yielding (2-formyl-1-chlorovinyl)ferrocene (**59**) (2.25 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (d, 1H, *J* = 7.1 Hz), 6.38 (d, 1H, *J* = 7.1 Hz), 4.73 (t, 2H, *J* = 1.68 Hz), 4.54 (t, 2H, *J* = 1.68 Hz), 4.22 (s, 5H). The spectral data is in agreement with those reported previously for this compound.[102]

3.4. Synthesis of Ethynylferrocene (60)

In a dry flask, (2-formyl-1-chlorovinyl)ferrocene (**59**) (1.3 g, 4.75 mmol) was dissolved in anhydrous dioxane (15 mL) by flashing with argon and heated to reflux. After approximately 5 minutes a boiling 1 N solution of sodium hydroxide (12.5 mL) was added rapidly in one portion and the reflux continued for another 25 minutes. Then refluxing was stopped and the mixture was allowed to cool to room temperature. The contents of the flask were poured directly into ice and neutralized with 1 N hydrochloric acid solution. The resultant mixture was extracted with hexane (5 x 5 mL). The organic phase was washed with sodium bicarbonate solution and water. The combined organic parts were dried over magnesium sulfate, filtered and the solvent was removed on rotary evaporator. The crude ethynylferrocene (**60**) was purified by flash chromatography on silica gel by using hexane as the eluent and the clear product was obtained as orange crystals (750 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (s, 2H), 4.21 (s, 5H), 4.19 (s, 2H), 2.71 (s, 1H); ^{13}C NMR (100 MHz,, $CDCl_3$) δ 82.6 (C), 73.6 (C), 71.7 (CH), 70.0 (CH), 68.7 (CH), 63.9 (CH). The spectral data is in agreement with those reported previously for this compound.[102]

3.5. General Procedure for the Synthesis of α,β-Alkynic Ketones 26

A mixture of the corresponding aryloyl/alkanoyl chloride **55** (3.0 mmol), $PdCl_2(PPh_3)_2$ (0.02 mmol) and Et_3N (3.0 mmol) in anhydrous THF (7.5 mL) were stirred for 10 min at room temperature under argon. CuI (0.02 mmol) was then added and the reaction mixture was stirred for another 10 min. After the addition of the appropriate terminal alkyne **56** and/or (**60**) (2.5 mmol) over 15 min, the resulting mixture was stirred at room temperature for approximately 6 h. (Note that the progress of the reaction was monitored by routine TLC). After the reaction was over, ethyl acetate (30 mL) was added, and the resulting solution was washed with 0.1 N HCl (10 mL) and subsequently with a saturated NH_4Cl solution (10 mL) in a separatory funnel. After the layers were separated, organic phase was dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (19:1) as the eluent to afford the corresponding α,β-alkynic ketone **26a-t.**

3.5.1. 1,3-Diphenylprop-2-yn-1-one (26a)

Benzoyl chloride (420.0 mg, 3.00 mmol), $PdCl_2(PPh_3)_2$ (35.1 mg, 0.05 mmol), Et_3N (303.0 mg, 3.00 mmol), CuI (9.5 mg, 0.05 mmol) and phenylacetylene (300.8 mg, 2.50 mmol) were employed to afford 494.4 mg (96%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.14 (m, 2H), 7.59–7.55 (m, 2H), 7.55–7.49 (m, 1H), 7.45–7.40 (m, 2H), 7.39–7.34 (m, 1H), 7.33–7.27 (m, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 177.5 (CO), 136.6 (C), 133.9 (CH), 132.8 (CH), 130.6 (CH), 129.2 (CH), 128.4 (CH), 128.3 (CH), 119.7 (C), 92.8 (C), 86.7 (C); IR (neat) 2195, 1636, 1597, 1580, 1447, 1314, 1282, 1207, 1170, 1010, 994, 756, 687, 535 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[103,104,105,106]

3.5.2. 1-Phenyl-3-(p-tolyl)prop-2-yn-1-one (26b)

Benzoyl chloride (456.4 mg, 3.30 mmol), $PdCl_2(PPh_3)_2$ (46.3 mg, 0.07 mmol), Et_3N (329.3 mg, 3.30 mmol), CuI (12.5 mg, 0.07 mmol) and 1-ethynyl-4-methylbenzene (315.6 mg, 2.70 mmol) were employed to afford 535.3 mg (90%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24–8.19 (m, 2H), 7.64–7.54 (m, 3H), 7.53–7.47 (m, 2H), 7.20 (d, J = 7.9 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.02 (CO), 141.59 (C), 136.99 (C), 134.03 (CH), 133.13 (CH), 129.53 (CH), 128.61 (CH), 116.99 (C), 93.85 (C), 86.83 (C), 21.76 (CH_3) (One CH peak overlaps with each other); IR (neat) 2194, 1627, 1601, 1577, 1448, 1314, 1293, 1168, 1007, 814, 793, 695, 535 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[103,104,106 , 107]

3.5.3. 1-Phenyl-3-(m-tolyl)prop-2-yn-1-one (26c)

Benzoyl chloride (435.0 mg, 3.10 mmol), $PdCl_2(PPh_3)_2$ (36.5 mg, 0.05 mmol), Et_3N (313.1 mg, 3.10 mmol), CuI (9.9 mg, 0.05 mmol) and 1-ethynyl-3-methylbenzene (300.8 mg, 2.60 mmol) were employed to afford 504.0 mg (88%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27–8.20 (m, 2H), 7.63–7.58 (m, 1H), 7.54–7.45 (m, 4H), 7.31–7.24 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (CO), 138.4 (C), 136.8 (C), 134.0 (CH), 133.4 (CH), 131.7 (CH), 130.1 (CH), 129.4 (CH), 128.5 (CH), 128.4 (CH), 119.7 (C), 93.4 (C), 86.6 (C), 21.0 (CH_3); IR (neat) 2190, 1630, 1578, 1451, 1314, 1225, 1164, 1036, 988, 884, 784, 685, 548 cm^{-1}.The spectral data were in agreement with those reported previously for this compound.[107]

3.5.4. 3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (26d)

Benzoyl chloride (387.3 mg, 2.80 mmol), $PdCl_2(PPh_3)_2$ (32.4 mg, 0.05 mmol), Et_3N (279.4 mg, 2.80 mmol), CuI (8.8 mg, 0.05 mmol) and 1-ethynyl-4-methoxybenzene (304.7 mg, 2.30 mmol) were employed to afford 484.9 mg (89%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19–8.15 (m, 2H), 7.60–7.53 (m, 3H), 7.49–7.43 (m, 2H), 6.88–6.84 (m, 2H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (CO), 161.7 (C), 136.9 (C), 135.0 (CH), 133.8 (CH), 129.3 (CH), 128.5 (CH), 114.4 (CH), 111.6 (C), 94.3 (C), 86.8 (C), 55.3 (CH_3); IR (neat) 2183, 1624, 1596, 1510, 1440, 1315, 1252, 1209, 1166, 1005, 834, 793, 695, 605, 507 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[103, 104, 106, 107]

3.5.5. 1-Phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (26e)

Benzoyl chloride (467.8 mg, 3.30 mmol), $PdCl_2(PPh_3)_2$ (39.1 mg, 0.06 mmol), Et_3N (337.5 mg, 3.30 mmol), CuI (10.6 mg, 0.05 mmol) and 3-ethynylthiophene (301.2 mg, 2.80 mmol) were employed to afford 585.2 mg (99%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22–8.17 (m, 2H), 7.81 (dd, J = 3.0, 1.1 Hz, 1H), 7.61–7.56 (m, 1H), 7.47–7.45 (m, 2H), 7.32 (dd, J = 5.0, 3.0 Hz, 1H), 7.27 (dd, J = 5.0, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (CO), 136.6 (C), 134.0 (CH), 133.9 (CH), 130.1 (CH), 129.4 (CH), 128.5 (CH), 126.3 (CH), 119.1 (C), 88.5 (C), 87.1 (C); IR (neat) 2185, 1732, 1630, 1596, 1576, 1448, 1312, 1266, 1217, 1167, 1014, 924, 827, 783, 694, 550 cm^{-1}.The spectral data were in agreement with those reported previously for this compound.[89]

3.5.6. 3-(3-Fluorophenyl)-1-phenylprop-2-yn-1-one (26f)

Benzoyl chloride (434.3 mg, 3.10 mmol), $PdCl_2(PPh_3)_2$ (36.3 mg, 0.05 mmol), Et_3N (313.3 mg, 3.10 mmol), CuI (9.8 mg, 0.05 mmol) and 1-ethynyl-3-fluorobenzene (310.5 mg, 2.60 mmol) were employed to afford 504.2 mg (87%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23–8.18 (m, 2H), 7.67–7.61 (m, 1H), 7.55–7.35 (m, 5H), 7.19 (tdd, J = 8.4, 2.6, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (CO), 162.4 (d, $^1J_{CF}$ = 248.1 Hz, C) 136.8 (C), 134.4 (CH), 130.5 (d, $^3J_{CF}$ = 8.4 Hz, CH), 129.7 (CH), 129.1 (d, $^4J_{CF}$ = 3.0 Hz, CH) , 128.8 (CH), 122.1 (d, $^3J_{CF}$ = 9.5 Hz, C) , 119.8 (d, $^2J_{CF}$ = 23.3 Hz, CH), 118.4 (d, $^2J_{CF}$ = 21.2 Hz, CH), 91.2 (C), 87.3 (C); IR (neat) 2202, 1649, 1579, 1485, 1426, 1299, 1228, 1144, 1015, 922, 867, 781, 691, 516 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[107]

3.5.7. 3-(4-Chlorophenyl)-1-phenylprop-2-yn-1-one (26g)

Benzoyl chloride (424.9 mg, 3.00 mmol), $PdCl_2(PPh_3)_2$ (42.6 mg, 0.06 mmol), Et_3N (306.5 mg, 3.00 mmol), CuI (11.5 mg, 0.06 mmol) and 1-chloro-4-ethynylbenzene (345.4 mg, 2.50 mmol) were employed to afford 499.1 mg (82%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22–8.19 (m, 2H), 7.66–7.60 (m, 3H), 7.55–7.50 (m, 2H), 7.43–7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (CO), 137.2 (C), 136.7 (C), 134.3 (CH), 129.6 (CH), 129.2 (CH), 128.7 (CH), 118.6 (C), 91.6 (C), 87.6 (C) (Two CH peaks overlap with each other); IR (neat) 2197, 1629, 1577, 1477, 1316, 1294, 1205, 1170, 1085, 1030, 820, 791, 692, 530 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[104,108]

3.5.8. 3-(4-Bromophenyl)-1-phenylprop-2-yn-1-one (26h)

Benzoyl chloride (371.2 mg, 2.70 mmol), $PdCl_2(PPh_3)_2$ (37.2 mg, 0.05 mmol), Et_3N (267.8 mg, 2.70 mmol), CuI (10.1 mg, 0.05 mmol) and 1-bromo-4-ethynylbenzene (400.0 mg, 2.20 mmol) were employed to afford 472.5 mg (75%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 7.6 Hz, 1H), 7.67–7.61 (m, 1H), 7.59–7.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (CO), 136.8 (C), 134.5 (CH), 134.4 (CH), 132.2 (CH), 129.7 (CH), 128.8 (CH), 125.7 (C), 119.2 (C), 91.8 (C), 87.8

(C); IR (neat) 2196, 1629, 1577, 1473, 1315, 1292, 1169, 1007, 817, 790, 691, 528 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[106,107]

3.5.9. 3-(4-Nitrophenyl)-1-phenylprop-2-yn-1-one (26i)

Benzoyl chloride (363.0 mg, 3.30 mmol), $PdCl_2(PPh_3)_2$ (46.4 mg, 0.07 mmol), Et_3N (334.1 mg, 3.30 mmol), CuI (12.6 mg, 0.07 mmol) and 1-ethynyl-4-nitrobenzene (405.8 mg, 2.80 mmol) were employed to afford 446.5 mg (65%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.8 Hz, 2H), 8.20 (d, J = 7.7 Hz, 2H), 7.84 (d, J = 8.8 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (CO), 148.7 (C), 136.5 (C), 134.8 (CH), 133.8 (CH), 129.8 (CH), 129.0 (CH), 126.9 (C), 124.0 (CH), 90.0 (C), 89.3 (C); IR (neat) 2199, 1636, 1591, 1512, 1449, 1341, 1314, 1283, 1168, 1005, 856, 749, 695, 525 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[104]

3.5.10. 1-Phenylhept-2-yn-1-one (26j)

Benzoyl chloride (512.1 mg, 3.60 mmol), $PdCl_2(PPh_3)_2$ (42.8 mg, 0.06 mmol), Et_3N (369.4 mg, 3.60 mmol), CuI (11.6 mg, 0.06 mmol) and hex-1-yne (250.4 mg, 3.00 mmol) were employed to afford 414.4 mg (73%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, J = 8.2, 0.9 Hz, 2H), 7.51–7.47 (m, 1H), 7.40–7.34 (m, 2H), 2.39 (t, J = 7.1 Hz, 2H), 1.55 (pentet, J = 7.3 Hz, 2H), 1.40 (sextet, J = 7.3 Hz, 2H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.8 (CO), 136.8 (C), 133.7 (CH), 129.3 (CH), 128.3 (CH), 96.5 (C), 79.5 (C), 29.7 (CH_2), 21.9 (CH_2), 18.6 (CH_2), 13.3 (CH_3); IR (neat) 2958, 2932, 2871, 2236, 2199, 1640, 1580, 1449, 1312, 1262, 1174, 910, 698 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[104,105]

3.5.11. 1-Phenyloct-2-yn-1-one (26k)

Benzoyl chloride (524.1 mg, 3.70 mmol), $PdCl_2(PPh_3)_2$ (43.8 mg, 0.06 mmol), Et_3N (378.1 mg, 3.70 mmol), CuI (11.9 mg, 0.06 mmol) and hept-1-yne (300.0 mg, 3.10 mmol) were employed to afford 449.8 mg (72%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13–8.04 (m, 2H), 7.55–7.47 (m, 1H), 7.44–7.35 (m, 2H), 2.46–2.37 (m, 2H), 1.67–1.53 (m, 2H), 1.45–1.22 (m, 4H), 0.91–0.81 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (CO), 136.8 (C), 133.7 (CH), 129.3 (CH), 128.3 (CH), 96.6 (C), 79.6 (C), 30.9 (CH_2), 27.4 (CH_2), 22.0 (CH_2), 19.0 (CH_2), 13.7 (CH_3); IR (neat) 2955, 2930, 2860, 2235, 2200, 1640, 1580, 1449, 1312, 1261, 1174, 918, 699 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[108,109]

3.5.12. 4-Cyclopentyl-1-phenylbut-2-yn-1-one (26l)

Benzoyl chloride (824.4 mg, 5.89 mmol), $PdCl_2(PPh_3)_2$ (68.9 mg, 0.10 mmol), Et_3N (595.0 mg, 5.89 mmol), CuI (18.6 mg, 0.10 mmol) and 3-cyclopentyl-1-propyne (530.0 mg, 4.91 mmol) were employed to afford 787.0 mg (76%) of the indicated product as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.13-8.08 (m, 2H), 7.56–7.51 (m, 1H), 7.45–7.39 (m, 2H), 2.45 (d, *J*= 6.9 Hz, 2H), 2.14 (septet, *J* = 7.5 Hz, 1H), 1.89–1.77 (m, 2H), 1.69–1.47 (m, 4H), 1.36–1.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9 (CO), 136.8 (C), 133.7 (C), 129.3 (CH), 128.4 (CH), 96.2 (C), 79.6 (C), 38.3 (CH), 32.1 (CH_2), 25.1 (CH_2), 24.8 (CH_2); IR (neat): 2948, 2865, 2232, 2197, 1640, 1596, 1579, 1448, 1261, 904, 698 cm^{-1}; MS (ESI, m/z): 213.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{17}O$: 213.1274 $[M+H]^+$, found: 213.1278.

3.5.13. 1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-one (26m)

4-Methoxybenzoyl chloride (634.6 mg, 3.70 mmol), $PdCl_2(PPh_3)_2$ (43.5 mg, 0.06 mmol), Et_3N (375.7 mg, 3.70 mmol), CuI (11.8 mg, 0.06 mmol) and phenylacetylene

(316.2 mg, 3.10 mmol) were employed to afford 688.5 mg (94%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27–8.12 (m, 2H), 7.70–7.64 (m, 2H), 7.50–7.45 (m, 1H), 7.44–7.39 (m, 2H), 7.01–6.96 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (CO), 164.6 (C), 133.1 (CH), 132.1 (CH), 130.7 (CH), 130.3 (C), 128.8 (CH), 120.4 (C), 114.0 (CH), 92.4 (C), 87.0 (C), 55.7 (CH_3); IR (neat) 2195, 1627, 1594, 1567, 1420, 1305, 1258, 1157, 1030, 993, 838, 760, 682, 598 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[103-106]

3.5.14. 1-(4-Methoxyphenyl)-3-(thiophen-3-yl)prop-2-yn-1-one (26n)

4-Methoxybenzoyl chloride (598.5 mg, 3.50 mmol), $PdCl_2(PPh_3)_2$ (41.0 mg, 0.06 mmol), Et_3N (354.3 mg, 3.50 mmol), CuI (11.1 mg, 0.06 mmol) and 3-ethynylthiophene (316.2 mg, 2.90 mmol) were employed to afford 517.1 mg (73%) of the indicated product as a light yellow solid (R_f = 0.58 in 9:1 hexane/ethyl acetate; mp 101.2-103.1 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20–8.14 (m, 2H), 7.82 (dd, J = 3.0, 1.2 Hz, 1H), 7.37 (dd, J = 5.0, 3.0 Hz, 1H), 7.31 (dd, J = 5.0, 1.2 Hz, 1H), 7.00–6.96 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (CO), 164.4 (C), 133.5 (CH), 131.8 (CH), 130.1 (CH), 130.0 (C), 126.2 (CH), 119.4 (C), 113.8 (CH), 87.7 (C), 87.0 (C), 55.5 (CH_3); IR (neat) 2186, 1625, 1597, 1570, 1506, 1421, 1361, 1280, 1157, 1087, 1004, 839, 791, 676, 535 cm^{-1}; MS (ESI, m/z): 243.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{11}SO_2$: 243.0474 $[M+H]^+$, found: 243.0477.

3.5.15. 3-(3-Fluorophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-one (26o)

4-Methoxybenzoyl chloride (621.2 mg, 3.60 mmol), $PdCl_2(PPh_3)_2$ (42.6 mg, 0.06 mmol), Et_3N (367.8 mg, 3.60 mmol), CuI (11.5 mg, 0.06 mmol) and 1-ethynyl-3-fluorobenzene (364.5 mg, 3.00 mmol) were employed to afford 702.1 mg (91%) of the indicated product as a yellow solid (R_f = 0.60 in 9:1 hexane/ethyl acetate; mp 91.9-93.7 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.14 (m, 2H), 7.46–7.42 (m, 1H), 7.41–

7.32 (m, 2H), 7.17 (tdd, *J* = 8.5, 2.5, 1.2 Hz, 1H), 7.00–6.95 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.4 (CO), 164.8 (C), 162.4 (d, $^{1}J_{CF}$ = 248.2 Hz, C), 132.1 (CH), 130.5 (d, $^{3}J_{CF}$ = 8.3 Hz, CH), 130.2 (C), 128.9 (d, $^{4}J_{CF}$ = 3.0 Hz, CH), 122.3 (d, $^{3}J_{CF}$ = 9.0 Hz, C), 119.7 (d, $^{2}J_{CF}$ = 23.2 Hz, CH) , 118.1 (d, $^{2}J_{CF}$ = 21.4 Hz, CH), 114.1 (CH), 90.4 (C), 87.3 (C), 55.7 (CH_3); IR (neat) 2200, 1637, 1592, 1579, 1484, 1316, 1296, 1232, 1165, 1145, 1021, 998, 870, 839, 777, 674, 540 cm^{-1}; MS (ESI, m/z): 255.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{12}FO_2$: 255.0816 $[M+H]^+$, found: 255.0823.

3.5.16. 3-(4-Bromophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-one (26p)

4-Methoxybenzoyl chloride (458.8 mg, 2.70 mmol), $PdCl_2(PPh_3)_2$ (31.4 mg, 0.04 mmol), Et_3N (271.6 mg, 2.70 mmol), CuI (8.5 mg, 0.04 mmol) and 1-bromo-4-ethynylbenzene (405.7 mg, 2.20 mmol) were employed to afford 600.3 mg (85%) of the indicated product as a light yellow solid (R_f = 0.62 in 9:1 hexane/ethyl acetate; mp 114.5-116.7 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–8.13 (m, 2H), 7.58–7.49 (m, 4H), 7.00–6.95 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (CO), 164.7 (C), 134.4 (CH), 132.2 (CH), 132.1 (CH), 130.3 (C), 125.5 (C), 119.4 (C), 114.1 (CH), 91.0 (C), 87.9 (C), 55.8 (CH_3); IR (neat) 2199,1627, 1602, 1578, 1474, 1392, 1295, 1249, 1162, 1061, 1007, 820, 748, 679, 529 cm^{-1}; MS (ESI, m/z): 315.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{12}BrO_2$: 315.0015 $[M+H]^+$, found: 315.0017.

3.5.17. 1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one (26q)

4-Chlorobenzoyl chloride (617.6 mg, 3.5 mmol), $PdCl_2(PPh_3)_2$ (41.3 mg, 0.06 mmol), Et_3N (356.5 mg, 3.50 mmol), CuI (11.2 mg, 0.06 mmol) and phenylacetylene (300.0 mg, 2.90 mmol) were employed to afford 566.3 mg (80%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.13 (m, 2H), 7.70–7.66 (m, 2H), 7.53–7.47 (m, 3H), 7.45–7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (CO), 140.8 (C), 135.4 (C), 133.2 (CH), 131.1 (CH), 131.0 (CH), 129.1 (CH), 128.9 (CH), 120.0 (C), 93.8

(C), 86.7 (C); IR (neat) 2196, 1648, 1582, 1480, 1300, 1276, 1168, 1089, 993, 812, 750, 680, 527 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[103, 107, 110]

3.5.18. 1-(4-Chlorophenyl)-3-(p-tolyl)prop-2-yn-1-one (26r)

4-Chlorobenzoyl chloride (560.2 mg, 3.20 mmol), $PdCl_2(PPh_3)_2$ (37.5 mg, 0.05 mmol), Et_3N (323.3 mg, 3.20 mmol), CuI (10.1 mg, 0.05 mmol) and 1-ethynyl-4-methylbenzene (310.0 mg, 2.70 mmol) were employed to afford 516.4 mg (76%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (CO), 141.9 (C), 140.7 (C), 135.6 (C), 133.3 (CH), 131.0 (CH), 129.7 (CH), 129.1 (CH), 116.9 (C), 94.5 (C), 86.6 (CH), 21.9 (CH_3); IR (neat) 2191, 1628, 1583, 1481, 1398, 1298, 1180, 1163, 1087, 1005, 814, 741, 672, 535 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[103]

3.5.19. 1-(4-Chlorophenyl)-3-(p-tolyl)prop-2-yn-1-one (26s)

4-Chlorobenzoyl chloride (560.2 mg, 3.20 mmol), $PdCl_2(PPh_3)_2$ (37.5 mg, 0.05 mmol), Et_3N (323.3 mg, 3.20 mmol), CuI (10.1 mg, 0.05 mmol) and 1-ethynyl-4-methylbenzene (310.0 mg, 2.70 mmol) were employed to afford 516.4 mg (76%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (CO), 141.9 (C), 140.7 (C), 135.6 (C), 133.3 (CH), 131.0 (CH), 129.7 (CH), 129.1 (CH), 116.9 (C), 94.5 (C), 86.6 (CH), 21.9 (CH_3); IR (neat) 2191, 1628, 1583, 1481, 1398, 1298, 1180, 1163, 1087, 1005, 814, 741, 672, 535 cm^{-1}. The spectral data were in agreement with those reported previously for this compound.[103]

3.5.20. 3-Ferrocenyl-1-phenylprop-2-yn-1-one (26t)

Benzoyl chloride (152.6 mg, 1.09 mmol), $PdCl_2(PPh_3)_2$ (12.6 mg, 0.02 mmol), Et_3N (110.0 mg, 1.09 mmol), CuI (3.42 mg, 0.02 mmol) and ethynylferrocene (190.0 mg, 0.90 mmol) were employed to afford 243.1 mg (86%) of the indicated product as a red solid (R_f = 0.52 in 9:1 hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 7.2 Hz, 2H), 7.62 (t, J = 7.3 Hz, 1H), 7.52 (t, J = 7.6 Hz, 2H), 4.69 (t, J = 1.7 Hz, 2H), 4.43 (t, J = 1.7 Hz, 2H), 4.29 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (CO), 137.4 (C), 133.8 (CH) , 129.5 (CH), 128.7 (CH), 96.7 (C), 85.7 (C), 73.3 (CH), 71.0 (CH), 70.6 (CH), 60.5 (C); IR (neat) 3087, 2213, 2169, 1617, 1596, 1573, 1452, 1315, 1291, 1224, 1169, 948, 821, 795, 702, 633 cm^{-1}; MS (ESI, m/z): 314.04 $[M]^+$; HRMS (ESI) calcd. for $C_{19}H_{14}OFe$: 314.0394 $[M]^+$, found: 314.0407. The spectral data are in agreement with those reported previously for this compound.[111,112]

3.5.21. 3-Ferrocenyl-1-(p-tolyl)prop-2-yn-1-one (26u)

4-Methylbenzoyl chloride (182.3 mg, 1.18 mmol), $PdCl_2(PPh_3)_2$ (14.0 mg, 0.02 mmol), Et_3N (119.2 mg, 1.18 mmol), CuI (3.8 mg, 0.02 mmol) and ethynylferrocene (205.8 mg, 0.98 mmol) were employed to afford 273.3 mg (85%) of the indicated product as a orange-red solid (R_f = 0.50 in 9:1 hexane/ethyl acetate; mp 155-156 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.1 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 4.70 (t, J = 1.7 Hz, 2H), 4.43 (t, J = 1.7 Hz, 2H), 4.30 (s, 5H), 2.46 (s, 3H): ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4 (CO), 144.8 (C), 135.0 (C) , 129.6 (CH), 129.3 (CH), 96.0 (C), 85.6 (C), 73.2 (CH), 70.8 (CH), 70.5 (CH), 60.6 (C), 21.9 (CH_3); IR (neat) 3089, 2185, 2167, 1618, 1597, 1564, 1410, 1285, 1221, 1169, 1109, 1006, 823, 740, 678, 600, 524 cm^{-1}; MS (ESI, m/z): 328.06 $[M]^+$; HRMS (ESI) calcd. for $C_{20}H_{16}OFe$: 328.0551 $[M]^+$, found: 328.0562.

3.5.22. 3-Ferrocenyl-1-(4-methoxyphenyl)prop-2-yn-1-one (26v)

4-Methoxybenzoyl chloride (214.9 mg, 1.26 mmol), $PdCl_2(PPh_3)_2$ (14.7 mg, 0.02 mmol), Et_3N (127.3 mg, 1.26 mmol), CuI (4.0 mg, 0.02 mmol) and ethynylferrocene (205.8 mg, 1.05 mmol) were employed to afford 310.7 mg (86%) of the indicated product as a red solid (R_f = 0.47 in 9:1 hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.6 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 4.66 (br s, 2H), 4.40 (br s, 2H), 4.27 (s, 5H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (CO), 164.3 (C), 131.8 (CH) , 130.7 (C), 113.9 (CH), 95.5 (C), 85.5 (C), 73.1 (CH), 70.7 (CH), 70.5 (CH), 60.8 (C), 55.7 (CH_3); IR (neat) 3085, 2173, 1613, 1593, 1566, 1506, 1421, 1290, 1263, 1227, 1158, 1108, 1029, 1010, 823, 756, 684, 604 cm^{-1}; MS (ESI, m/z): 344.05 $[M]^+$; HRMS (ESI) calcd. for $C_{20}H_{16}O_2Fe$: 344.0500 $[M]^+$, found: 344.0516. The spectral data are in agreement with those reported previously for this compound.[111, 112]

3.5.23. 1-(4-Chlorophenyl)-3-ferrocenylprop-2-yn-1-one (26w)

4-Chlorobenzoyl chloride (217.0 mg, 1.24 mmol), $PdCl_2(PPh_3)_2$ (14.5 mg, 0.02 mmol), Et_3N (125.2 mg, 1.03 mmol), CuI (3.9 mg, 0.02 mmol) and ethynylferrocene (217.0 mg, 1.03 mmol) were employed to afford 305.2 mg (85%) of the indicated product as a reddish violet solid (R_f = 0.55 in 9:1 hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 4.67 (br s, 2H), 4.42 (br s, 2H), 4.27 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2 (CO), 140.2 (C), 135.6 (C) , 130.7 (CH), 128.9 (CH), 97.4 (C), 85.4 (C), 73.2 (CH), 71.0 (CH), 70.6 (CH), 60.0 (C); IR (neat) 2979, 1734, 1668, 1577, 1554, 1478, 1410, 1372, 1283, 1238, 1105, 1044, 1029, 925, 817, 779, 740, 646, 630, 520 cm^{-1}; MS (ESI, m/z): 348.00 $[M]^+$; HRMS (ESI) calcd. for $C_{19}H_{13}OClFe$: 348.0005 $[M]^+$, found: 347.9999. The spectral data are in agreement with those reported previously for this compound.[111]

3.5.24. 1-(2-Bromophenyl)-3-ferrocenylprop-2-yn-1-one (26x)

2-Bromobenzoyl chloride (259.1 mg, 1.18 mmol), $PdCl_2(PPh_3)_2$ (13.8 mg, 0.02 mmol), Et_3N (119.2 mg, 1.18 mmol), CuI (3.7 mg, 0.02 mmol) and ethynylferrocene (205.0 mg, 0.98 mmol) were employed to afford 288.9 mg (75%) of the indicated product as a dark red solid (R_f = 0.53 in 9:1 hexane/ethyl acetate; mp 82-83°C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 7.7, 1.6 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.35 (td, J = 7.6, 1.6 Hz, 1H), 4.63 (pseudo t, J = 1.7 Hz, 2H), 4.41 (pseudo t, J = 1.7 Hz, 2H), 4.27 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (CO), 138.2 (C), 134.8 (CH), 133.0 (CH), 132.3 (CH), 127.4 (CH), 121.0 (C), 98.6 (C), 86.9 (C), 73.2 (CH), 71.1 (CH), 70.5 (CH), 60.1 (C); IR (neat) 3098, 2172, 1622, 1582, 1560, 1459, 1432, 1295, 1204, 1135, 1055, 1033, 996, 896, 828, 730, 673, 629, 513 cm^{-1}; MS (ESI, m/z): 391.95 $[M]^+$; HRMS (ESI) calcd. for $C_{19}H_{13}BrOFe$: 391.9501 $[M]^+$, found: 391.9493.

3.5.25. 3-Ferrocenyl-1-(4-nitrophenyl)prop-2-yn-1-one (26y)

4-Nitrobenzoyl chloride (202.3 mg, 1.09 mmol), $PdCl_2(PPh_3)_2$ (12.8 mg, 0.02 mmol), Et_3N (110.1 mg, 1.09 mmol), CuI (3.5 mg, 0.02 mmol) and ethynylferrocene (191.2 mg, 0.91 mmol) were employed to afford 261.2 mg (80%) of the indicated product as a dark violet solid (R_f = 0.44 in 9:1 hexane/ethyl acetate; mp 182-183 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (pseudo q, J = 8.8 Hz, 4H), 4.72 (pseudo t, J = 1.8 Hz, 2H), 4.49 (pseudo t, J = 1.8 Hz, 2H), 4.30 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.4 (CO), 150.8 (C), 141.6 (C) , 130.4 (CH), 123.9 (CH), 99.9 (C), 85.8 (C), 73.6 (CH), 71.5 (CH), 70.8 (CH), 59.5 (C); IR (neat) 3091, 2179, 1629, 1598, 1519, 1457, 1409, 1341, 1321, 1213, 1104, 1003, 915, 868, 819, 708, 679, 635 cm^{-1}; MS (ESI, m/z): 359.02 $[M]^+$; HRMS (ESI) calcd. for $C_{19}H_{13}NO_3Fe$: 359.0245 $[M]^+$, found: 359.0232. The spectral data are in agreement with those reported previously for this compound.[111, 112]

3.6. General Procedure for the Synthesis of *N*-Propargylic β-Enaminones 32, 50 and 61

To a stirred solution of the corresponding α,β-alkynic ketone **26** (2.5 mmol) in absolute MeOH (10 mL) under argon was added propargylamine (**48**), 1-ethynylcyclohexylamine or 2-methylbut-3-yn-2-amine (3.0 mmol). The resulting mixture was heated at 65 °C for approximately 6 h for propargylamine and 18-24 h for 1-ethynylcyclohexylamine or 2-methylbut-3-yn-2-amine (Note that the progress of the reaction was monitored by routine TLC for the completion of the reaction). After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (50 mL) and a saturated NaCl solution (50 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding β-enaminone**32a-d, 50a-q** and **61a-c**.

3.6.1. 1,3-Diphenyl-3-(prop-2-ynylamino)prop-2-en-1-one (32a)

1,3-Diphenylprop-2-yn-1-one (**26a**) (515.6 mg, 2.50 mmol) and propargylamine (165.3 mg, 3.00 mmol) were employed to afford 640.3 mg (98%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.34 (br s, 1H), 7.94-7.89 (m, 2H), 7.54-7.38 (m, 8H), 5.86 (br s, 1H), 3.96 (dd, *J* = 6.3 and 2.5 Hz, 2H), 2.32 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4 (CO), 166.1 (C), 140.2 (C), 135.1 (C), 131.2 (CH), 130.0 (CH), 128.9 (CH), 128.4 (CH), 128.1 (CH), 127.4 (CH), 94.9 (CH), 80.0 (C), 72.6 (CH), 34.4 (CH_2). The spectral data were in agreement with those reported previously for this compound.[21]

3.6.2. 3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-ynylamino)prop-2-en-1-one (32b)

3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (**26d**) (590.7 mg, 2.50 mmol) and propargylamine (165.3 mg, 3.00 mmol) were employed to afford 713.8 mg (98%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.37 (br s, 1H), 7.94-7.88 (m, 2H), 7.49-7.38 (m, 5H), 7.02-6.97 (m, 2H), 5.85 (s, 1H), 3.99 (dd, *J* = 6.3 and 2.5 Hz, 2H), 3.87 (s, 3H), 2.33 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1 (CO), 166.1 (C), 161.1 (C), 140.3 (C), 131.1 (CH), 129.6 (CH), 128.4 (CH), 127.3 (CH), 114.3 (CH), 94.8 (CH), 80.2 (C), 72.6 (CH), 55.6 (CH_3), 34.5 (CH_2) (Two C peaks overlap with each other); IR (neat): 3285, 3056, 2931, 2837, 1593, 1559, 1497, 1247, 1173, 1142, 1023, 836, 757, 689 cm^{-1}; MS (ESI, m/z): 292.13 $[M+H]^+$; HRMS (ESI): calcd. for $C_{19}H_{18}NO_2$: 292.1338 $[M+H]^+$, found: 292.1337.

3.6.3. 1-Phenyl-3-(prop-2-ynylamino)-3-(thiophen-3-yl)prop-2-en-1-one (32c)

1-Phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (**26e**) (530.7 mg, 2.50 mmol) and propargylamine (165.3 mg, 3.00 mmol) were employed to afford 628.3 mg (94%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.44 (br t, *J* = 6.1 Hz, 1H), 7.95-7.87 (m, 2H), 7.59 (dd, *J* = 2.8 and 1.0 Hz, 1H), 7.44-7.33 (m, 4H), 7.24 (dd, *J* = 5.0 and 1.0 Hz, 1H), 5.92 (s, 1H), 3.97 (dd, *J* = 6.4 and 2.4 Hz, 2H), 2.38 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6 (CO), 160.3 (C), 139.7 (C), 135.2 (C), 130.8 (CH), 128.1 (CH), 127.1 (CH), 126.9 (CH), 126.5 (CH), 126.2 (CH), 94.0 (CH), 79.9 (C), 72.6 (CH), 34.0 (CH_2); IR (neat): 3249, 3214, 1653, 1593, 1577, 1290, 1247, 1227, 1079, 1057, 799, 754, 720 cm^{-1}; MS (ESI, m/z): 268.08 $[M+H]^+$; HRMS (ESI): calcd. for $C_{16}H_{14}NOS$: 268.0796 $[M+H]^+$, found: 268.0775.

3.6.4. 4-Cyclopentyl-1-phenyl-3-(prop-2-yn-1-ylamino)but-2-en-1-one (32d)

4-Cyclopentyl-1-phenylbut-2-yn-1-one (**26l**) (637.0 mg, 3.00 mmol) and propargylamine (198.0 mg, 3.60 mmol) were employed to afford 801.0 mg (99%) of the indicated product as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.51 (d, *J* = 5.5 Hz, 1H), 7.95–7.79 (m, 2H), 7.52–7.29 (m, 3H), 5.76–5.68 (m, 1H), 4.12–3.98 (m, 2H), 2.43–2.27 (m, 2H), 2.19–2.01 (m, 1H), 1.94–1.74 (m, 2H), 1.72–1.45 (m, 4H), 1.36–1.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9 (CO), 167.1 (C), 140.13 (C), 130.4 (CH), 127.9 (CH), 126.7 (CH), 92.5 (CH), 79.0 (C), 72.3 (C), 38.2 (CH_2), 37.6 (CH), 32.4 (CH_2), 32.1 (CH_2), 24.6 (CH_2). IR (neat): 3289, 2947, 2865, 1732, 1594, 1549, 1516, 1328, 1289, 1176, 1061, 1025, 742, 698, 661 cm^{-1}; MS (ESI, m/z): 254.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{18}H_{22}NO$: 254.1540 $[M+H]^+$, found: 254.1551.

3.6.5. 3-((1-Ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (50a)

1,3-Diphenylprop-2-yn-1-one (**26a**) (312.6 mg, 1.52 mmol) and 1-ethynylcyclohexylamine (221.8 mg, 1.82 mmol) were employed to afford 286.6 mg (56%) of the indicated product as a light yellow solid (R_f = 0.41 in 4:1 hexane/ethyl acetate; mp 107.5-109.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.75 (s, 1H), 7.92–7.87 (m, 2H), 7.61–7.54 (m, 2H), 7.47–7.36 (m, 6H), 5.73 (s, 1H), 2.30 (t, *J* = 1.8 Hz, 1H), 1.90–1.84 (m, 2H), 1.76–1.60 (m, 4H), 1.58–1.45 (m, 3H), 1.36–1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7 (CO), 166.7 (C), 140.3 (C), 137.1 (C), 131.0 (CH), 129.3 (CH), 128.8 (CH), 128.3 (CH), 127.8 (CH), 127.3 (CH), 96.4 (CH), 86.7 (C), 73.6 (CH), 53.7 (C), 40.0 (CH_2), 25.1 (CH_2), 22.3 (CH_2); IR (neat) 3231, 2932, 2855, 1607, 1546, 1440, 1327, 1294, 1258, 1146, 1055, 748, 688 cm^{-1}; MS (ESI, m/z): 330.19 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{24}NO$: 330.1852 $[M+H]^+$, found: 330.1849.

3.6.6. 3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(p-tolyl)prop-2-en-1-one (50b)

1-Phenyl-3-(p-tolyl)prop-2-yn-1-one (**26b**) (295.4 mg, 1.34 mmol) and 1-ethynylcyclohexylamine (198.3 mg, 1.61 mmol) were employed to afford 325.9 mg (73%) of the indicated product as a light brown solid (R_f = 0.52 in 4:1 hexane/ethyl acetate; mp 91.4-93.8 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 11.76 (s, 1H), 7.90 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.44–7.35 (m, 3H), 7.19 (d, *J* = 7.9 Hz, 2H), 5.73 (s, 1H), 2.40 (s, 3H), 2.33 (s, 1H), 1.88 (dd, *J* = 9.6, 4.3 Hz, 2H), 1.75–1.60 (m, 4H), 1.58–1.42 (m, 3H), 1.36–1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4 (CO), 166.9 (C) , 140.1 (C), 139.2 (C), 134.1 (C), 130.8 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.1 (CH), 96.2 (CH), 86.8 (C), 73.3 (CH), 53.5 (C), 39.7 (CH_2), 25.0 (CH_2), 22.1 (CH_2), 21.4 (CH_3); IR (neat) 3221, 2934, 2856, 1550, 1501, 1446, 1330, 1303, 1259, 1147, 1058, 1025, 826, 732, 695 cm^{-1}; MS (ESI, m/z): 344.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{26}NO$: 344.2009 $[M+H]^+$, found: 344.2007.

3.6.7. 3-((1-Ethynylcyclohexyl)amino)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (50c)

3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-one (**26d**) (332.0 mg, 1.40 mmol) and 1-ethynylcyclohexylamine (209.4 mg, 1.69 mmol) were employed to afford 292.2 mg (58%) of the indicated product as an orangish-yellow solid (R_f = 0.54 in 4:1 hexane/ethyl acetate); mp 140.5 °C.) ^1H NMR (400 MHz, $CDCl_3$) δ 11.69 (s, 1H), 7.88 dd, (J = 7.6, 1.4 Hz, 2H), 7.52 (J = 8.5 Hz, 2H), 7.44–7.35 (m, 3H), 6.90 (J = 8.5 Hz, 2H), 5.72 (s, 1H), 3.84 (s, 3H), 2.34 (s, 1H), 1.86 (dd, J = 11.1, 4.6 Hz, 2H), 1.74–1.59 (m, 4H), 1.57–1.43 (m, 3H), 1.34–1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4 (CO), 166.7 (C), 160.5 (C), 140.3 (C), 130.9 (CH), 130.1 (CH), 129.5 (C), 128.3 (CH), 127.2 (CH), 113.2 (CH), 96.4 (CH), 86.9 (C), 73.4 (CH), 55.4 (C), 53.6 (CH_3), 39.8 (CH_2), 25.0 (CH_2), 22.2 (CH_2); IR (neat) 3228, 2939, 2958, 1612, 1577, 1501, 1482, 1332, 1292, 1245, 1173, 1058, 1030, 834, 763, 698 cm^{-1}; MS (ESI, m/z): 360.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{26}NO_2$: 360.1958 $[M+H]^+$, found: 360.1963.

3.6.8. 3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(thiophen-3-yl)prop-2-en-1-one (50d)

1-Phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (**26e**) (340.8 mg, 1.61 mmol) and 1-ethynylcyclohexylamine (237.4 mg, 1.93 mmol) were employed to afford 296.2 mg (55%) of the indicated product as a dark yellow solid (R_f = 0.55 in 4:1 hexane/ethyl acetate; mp 88.0-90.7 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.76 (s, 1H), 7.91–7.86 (m, 2H), 7.63 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.43–7.36 (m, 3H), 7.35 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.30 (dd, *J* = 5.0, 3.0 Hz, 1H), 5.81 (s, 1H), 2.40 (s, 1H), 1.93–1.85 (m, 2H), 1.70 (ddd, *J* = 12.9, 9.7, 3.4 Hz, 2H), 1.65–1.52 (m, 4H), 1.51–1.42 (m, 1H), 1.35–1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4 (CO), 161.3 (C), 140.1 (C), 137.2 (C), 130.9 (CH), 128.7 (CH), 128.3 (CH), 127.1 (CH), 126.2 (CH), 125.1 (CH), 95.9 (CH), 86.9 (C), 73.2 (CH), 53.4 (C), 39.4 (CH_2), 25.0 (CH_2), 22.2 (CH_2); IR (neat) 3219, 2942, 2854, 1580, 1544, 1499, 1444, 1317, 1296, 1245, 1161, 1146, 1055, 996, 891, 749, 687, 568 cm^{-1}; MS (ESI, m/z): 336.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{22}NOS$: 336.1417 $[M+H]^+$, found: 336.1416.

3.6.9. 3-((1-Ethynylcyclohexyl)amino)-3-(3-fluorophenyl)-1-phenylprop-2-en-1-one (50e)

3-(3-Fluorophenyl)-1-phenylprop-2-yn-1-one (**26f**) (337.5 mg, 1.51 mmol) and 1-ethynylcyclohexylamine (222.5 mg, 1.81 mmol) were employed to afford 313.8 mg (60%) of the indicated product as a dark yellow solid (R_f = 0.61 in 4:1 hexane/ethyl acetate; mp 68.2-70.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.65 (s, 1H), 7.90–7.86 (m, 2H), 7.46–7.30 (m, 6H), 7.16–7.09 (m, 1H), 5.72 (s, 1H), 2.33 (s, 1H), 1.92–1.82 (m, 2H), 1.74–1.60 (m, 4H), 1.59–1.44 (m, 3H), 1.35–1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (CO), 164.9 (C), 162.0 (d, $^1J_{CF}$ = 246.9 Hz, C) , 139.9 (C), 138.8 (d, $^3J_{CF}$ = 7.8 Hz, C), 131.1 (CH), 129.5 (d, $^3J_{CF}$ = 8.2 Hz, CH), 128.3 (CH), 127.2 (CH), 124.5 (d, $^4J_{CF}$ = 3.0 Hz, CH), 116.3 (d, $^2J_{CF}$ = 20.8 Hz, CH), 116.1 (d, $^4J_{CF}$ = 22.9 Hz, CH), 96.2 (CH), 86.3 (C), 73.9 (CH), 53.7 (C), 39.9 (CH_2), 24.9 (CH_2), 22.2 (CH_2);

IR (neat) 3255, 2931, 2857, 1580, 1551, 1443, 1331, 1260, 1232, 1126, 1055, 923, 886, 750, 686 cm^{-1}; MS (ESI, m/z): 348.18 [M+H]$^+$; HRMS (ESI) calcd. for $C_{23}H_{23}FNO$: 348.1758 [M+H]$^+$, found: 348.1761.

3.6.10. 3-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one (50f)

3-(4-Chlorophenyl)-1-phenylprop-2-yn-1-one (**26g**) (360.8 mg, 1.50 mmol) and 1-ethynylcyclohexylamine (221.6 mg, 1.80 mmol) were employed to afford 360.0 mg (66%) of the indicated product as a yellow solid (R_f = 0.58 in 4:1 hexane/ethyl acetate; mp 132.9-135.2 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.64 (s, 1H), 7.88 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.52 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.46–7.35 (m, 5H), 5.67 (s, 1H), 2.31 (s, 1H), 1.91–1.82 (m, 2H), 1.73–1.61 (m, 4H), 1.57–1.46 (m, 3H), 1.34–1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (CO), 165.3 (C), 140.0 (C), 135.4 (C), 131.2 (C), 130.2 (CH), 128.4 (CH), 128.1 (CH), 127.3 (CH), 96.4 (C), 86.5 (CH), 74.0 (CH), 53.7 (C), 40.0 (CH_2), 25.0 (CH_2), 22.2 (CH_2) (Two CH peaks overlap with each other.); IR (neat) 3280, 2932, 2850, 1575, 1559, 1474, 1327, 1296, 1144, 1089, 1055, 1015, 832, 758, 648, 573 cm^{-1}; MS (ESI, m/z): 364.15 [M+H]$^+$; HRMS (ESI) calcd. for $C_{23}H_{23}ClNO$: 364.1463 [M+H]$^+$, found: 364.1469.

3.6.11. 3-(4-Bromophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one (50g)

3-(4-Bromophenyl)-1-phenylprop-2-yn-1-one (**26h**) (378.3 mg, 1.34 mmol) and 1-ethynylcyclohexylamine (196.1 mg, 1.60 mmol) were employed to afford 314.0 mg (58%) of the indicated product as a yellow solid (R_f = 0.62 in 4:1 hexane/ethyl acetate; mp 126.0-128.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (s, 1H), 7.87 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.54–7.51 (m, 2H), 7.46–7.36 (m, 5H), 5.68 (s, 1H), 2.31 (s, 1H), 1.92–1.83 (m, 2H), 1.73–1.60 (m, 4H), 1.58–1.45 (m, 3H), 1.34–1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (CO), 165.2 (C), 139.9 (C), 135.9 (C), 131.2 (CH), 131.0

(CH), 130.5 (CH), 128.4 (CH), 127.2 (CH), 123.6 (C), 96.4 (CH), 86.5 (C), 74.0 (CH), 53.7 (C), 40.0 (CH_2), 25.0 (CH_2), 22.2 (CH_2); IR (neat) 3282, 2932, 2850, 1592, 1557, 1472, 1326, 1296, 1170, 1055, 1022, 830, 759, 650 cm^{-1}; MS (ESI, m/z): 408.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{23}BrNO$: 408.0958 $[M+H]^+$, found: 408.0949.

3.6.12. 3-((1-Ethynylcyclohexyl)amino)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (50h)

3-(4-Nitrophenyl)-1-phenylprop-2-yn-1-oneone (**26i**) (317.0 mg, 1.26 mmol) and 1-ethynylcyclohexylamine (186.5 mg, 1.51 mmol) were employed to afford 283.5 mg (60%) of the indicated product as a dark yellow solid (R_f = 0.40 in 4:1 hexane/ethyl acetate; mp 134.8-136.0 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 11.58 (s, 1H), 8.25 (d, *J* = 8.6 Hz, 2H), 7.87 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 7.47–7.37 (m, 3H), 5.68 (s, 1H), 2.29 (s, 1H), 1.91–1.83 (m, 2H), 1.74–1.61 (m, 4H), 1.59–1.46 (m, 3H), 1.34–1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.2 (CO), 163.6 (C), 148.3 (C), 143.2 (C), 139.6 (C), 131.5 (CH), 130.1 (CH), 128.5 (CH), 127.3 (CH), 123.0 (CH), 96.5 (CH), 86.1 (C), 74.8 (CH), 53.9 (C), 40.2 (CH_2), 24.9 (CH_2), 22.2 (CH_2); IR (neat) 3221, 2935, 2852, 1574, 1510, 1477, 1306, 1231, 1145, 1055, 1023, 849, 750, 687 cm^{-1}; MS (ESI, m/z): 375.17 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{23}N_2O_3$: 375.1703 $[M+H]^+$, found: 375.1711.

3.6.13. 3-((1-Ethynylcyclohexyl)amino)-1-phenylhept-2-en-1-one (50i)

1-Phenylhept-2-yn-1-one (**26j**) (296.5 mg, 1.6 mmol) and 1-ethynylcyclohexylamine (235.4 mg, 1.91 mmol) were employed to afford 408.9 mg (83%) of the indicated product as a light orange solid (R_f = 0.58 in 4:1 hexane/ethyl acetate; mp 67.5-69.8 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 12.07 (s, 1H), 7.87–7.84 (m, 2H), 7.42–7.36 (m, 3H), 5.73 (s, 1H), 2.70 (pseudo t, *J* = 8.1 Hz, 2H), 2.52 (s, 1H), 2.17–2.08 (m, 2H), 1.87–1.78 (m, 2H), 1.77–1.63 (m, 6H), 1.61–1.53 (m, 1H), 1.45 (sextet, *J* =7.4 Hz, 2H), 1.38–1.29 (m, 1H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8

(CO), 170.4 (C), 140.6 (C), 130.5 (CH), 128.2 (CH), 127.0 (CH), 92.4 (CH), 85.8 (C), 73.7 (CH), 52.5 (C), 39.7 (CH_2), 32.2 (CH_2), 31.7 (CH_2), 25.0 (CH_2), 22.9 (CH_2), 22.3 (CH_2), 14.0 (CH_3); IR (neat) 3286, 2933, 2852, 1589, 1554, 1514, 1443, 1348, 1290, 1253, 1167, 1095, 895, 741, 634 cm^{-1}; MS (ESI, m/z): 310.22 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{28}NO$: 310.2165 $[M+H]^+$, found: 310.2165.

3.6.14. 3-((1-Ethynylcyclohexyl)amino)-1-phenyloct-2-en-1-one (50j)

1-Phenyloct-2-yn-1-one (**26k**) (310.7 mg, 1.55 mmol) and 1-ethynylcyclohexylamine (229.4 mg, 1.86 mmol) were employed to afford 336.2 mg (67%) of the indicated product as an orange oil (R_f = 0.49 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.07 (s, 1H), 7.87–7.82 (m, 2H), 7.40–7.34 (m, 3H), 5.73 (s, 1H), 2.70–2.65 (m, 2H), 2.51 (s, 1H), 2.14–2.08 (m, 2H), 1.85–1.77 (m, 2H), 1.74–1.64 (m, 6H), 1.56–1.52 (m, 1H), 1.41–1.29 (m, 5H), 0.91 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7 (CO), 170.3 (C), 140.6 (C), 130.4 (CH), 128.1 (CH), 126.9 (CH), 92.3 (CH), 85.7 (C), 73.6 (CH), 52.4 (C), 39.6 (CH_2), 32.4 (CH_2), 31.9 (CH_2), 29.3 (CH_2), 24.9 (CH_2), 22.5 (CH_2), 22.2 (CH_2), 14.0 (CH_2); IR (neat) 3295, 2930, 2856, 1584, 1555, 1445, 1320, 1257, 1169, 1094, 899, 744, 648 cm^{-1}; MS (ESI, m/z): 324.23 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{30}NO$: 324.2322 $[M+H]^+$, found: 324.2325.

3.6.15. 3-((1-Ethynylcyclohexyl)amino)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (50k)

1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-one (**26m**) (329.4 mg, 1.39 mmol) and 1-ethynylcyclohexylamine (206.1 mg, 1.67 mmol) were employed to afford 255.6 mg (51%) of the indicated product as a yellow solid (R_f = 0.40 in 4:1 hexane/ethyl acetate; mp 119.2-121.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.63 (s, 1H), 7.87 (d, J = 8.9 Hz, 2H), 7.58–7.54 (m, 2H), 7.43–7.34 (m, 3H), 6.88 (d, J = 8.9 Hz, 2H), 5.69 (s, 1H), 3.81 (s, 3H), 2.29 (s, 1H), 1.88–1.80 (m, 2H), 1.73–1.58 (m, 4H), 1.56–1.42 (m, 3H), 1.32–1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8 (CO), 166.1 (C), 162.0 (C), 137.1 (C), 132.8 (C), 129.2 (CH), 129.1 (CH), 128.7 (CH), 127.7 (CH), 113.5 (CH), 95.9 (CH), 86.7 (C), 73.4 (CH), 55.4 (CH_3), 53.5 (C), 39.8 (CH_2), 25.0 (CH_2), 22.2 (CH_2); IR (neat) 3241, 2936, 1573, 1545, 1443, 1415, 1321, 1255, 1233, 1185, 1146, 1062, 1023, 847, 785, 692 cm^{-1}; MS (ESI, m/z): 360.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{26}NO_2$: 360.1958 $[M+H]^+$, found: 360.1968.

3.6.16. 3-((1-Ethynylcyclohexyl)amino)-1-(4-methoxyphenyl)-3-(thiophen-3-yl)prop-2-en-1-one (50l)

1-(4-Methoxyphenyl)-3-(thiophen-3-yl)prop-2-yn-1-one (**26n**) (305.8 mg, 1.26 mmol) and 1-ethynylcyclohexylamine (186.6 mg, 1.51 mmol) were employed to afford 249.1 mg (54%) of the indicated product as a yellow oil (R_f = 0.41 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ 11.62 (s, 1H), 7.87 (d, J = 8.9 Hz, 2H), 7.61 (dd, J = 2.9, 1.2 Hz, 1H), 7.34 (dd, J = 5.0, 1.2 Hz, 1H), 7.30 (dd, J = 5.0, 2.9 Hz, 1H), 6.89 (d, J = 8.9 Hz, 2H), 5.76 (s, 1H), 3.83 (s, 3H), 2.38 (s, 1H), 1.91–1.83 (m, 2H), 1.73–1.65 (m, 2H), 1.64–1.52 (m, 4H), 1.50–1.43 (m, 1H), 1.33–1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8 (CO), 162.0 (C), 160.8 (C), 137.5 (C), 132.8 (C), 129.1 (CH), 128.8 (CH), 126.1 (CH), 125.0 (CH), 113.5 (CH), 95.6 (CH), 87.1 (C), 73.1 (CH), 55.4 (CH_3), 53.4 (C), 39.5 (CH_2), 25.1 (CH_2), 22.2 (CH_2); IR (neat) 3235, 2934, 1580, 1541, 1472, 1439, 1320, 1238, 1175, 1123, 1021, 925, 854, 780, 689 cm^{-1}; MS (ESI, m/z): 366.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{24}NO_2S$: 366.1522 $[M+H]^+$, found: 366.1518.

3.6.17. 3-((1-Ethynylcyclohexyl)amino)-3-(3-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (50m)

3-(3-Fluorophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-one (**26o**) (319.4 mg, 1.26 mmol) and 1-ethynylcyclohexylamine (185.7 mg, 1.51 mmol) were employed to afford 265.5 mg (56%) of the indicated product as an orangish-yellow solid (R_f = 0.46 in 4:1 hexane/ethyl acetate; mp 147.2-149.3 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 11.51

(s, 1H), 7.87 (d, J = 8.9 Hz, 2H), 7.38–7.29 (m, 3H), 7.14–7.08 (m, 1H), 6.89 (d, J = 8.9 Hz, 2H), 5.68 (s, 1H), 3.83 (s, 3H), 2.31 (s, 1H), 1.90–1.82 (m, 2H), 1.74–1.59 (m, 4H), 1.58–1.43 (m, 3H), 1.35–1.21 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 188.2 (CO), 164.4 (d, $^{4}J_{CF}$ =1.8 Hz, C), 162.3 (C), 162.1 (d, $^{1}J_{CF}$ =246.7 Hz, C),139.2 (d, $^{3}J_{CF}$ =7.9 Hz, C), 132.8 (C), 129.4 (d, $^{3}J_{CF}$ =8.2 Hz, CH), 129.2 (CH), 124.7 (d, $^{4}J_{CF}$ =3.1 Hz, CH), 116.3 (d, $^{2}J_{CF}$ =22.7 Hz, CH), 116.2 (d, $^{2}J_{CF}$ =20.8 Hz, CH), 113.6 (CH), 96.1 (CH), 86.7 (C), 73.8 (CH), 55.5 (CH$_3$), 53.7 (C), 40.0 (CH$_2$) , 25.0 (CH$_2$), 22.3 (CH$_2$); IR (neat) 3241, 2933, 1578, 1544, 1477, 1438, 1322, 1235, 1174, 1126, 1020, 923, 853, 783, 683 cm^{-1}; MS (ESI, m/z): 378.19 [M+H]$^+$; HRMS (ESI) calcd. for $C_{24}H_{25}FNO_2$: 378.1864 [M+H]$^+$, found: 378.1854.

3.6.18. 3-(4-Bromophenyl)-3-((1-ethynylcyclohexyl)amino)-1-(4-methoxyphenyl)prop-2-en-1-one (50n)

3-(4-Bromophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-one (**26p**) (480.2 mg, 1.52 mmol) and 1-ethynylcyclohexylamine (225.3 mg, 1.83 mmol) were employed to afford 354.0 mg (53%) of the indicated product as a light yellow solid (R_f = 0.47 in 4:1 hexane/ethyl acetate: mp 86.5-89.8 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.50 (s, 1H), 7.85 (d, J = 8.9 Hz, 2H), 7.51–7.47 (m, 2H), 7.45–7.41 (m, 2H), 6.87 (d, J = 8.9 Hz, 2H), 5.64 (s, 1H), 3.80 (s, 3H), 2.30 (s, 1H), 1.88–1.81 (m, 2H), 1.71–1.57 (m, 4H), 1.57–1.41 (m, 3H), 1.33–1.20 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 187.9 (CO), 164.6 (C), 162.1 (C), 136.1 (C), 132.6 (C), 130.9 (CH), 130.5 (CH), 129.1 (CH), 123.4 (C), 113.5 (CH), 96.1 (CH), 86.6 (C), 73.8 (CH), 55.3 (CH$_3$), 53.5 (C), 40.0 (CH$_2$), 24.9 (CH$_2$), 22.2 (CH$_2$); IR (neat) 3225, 2934, 1570, 1544, 1475, 1327, 1301, 1253, 1228, 1160, 1145, 1059, 1023, 827, 782, 662 cm^{-1}; MS (ESI, m/z): 438.11 [M+H]$^+$; HRMS (ESI) calcd. for $C_{24}H_{25}BrNO_2$: 438.1063 [M+H]$^+$, found: 438.1051.

3.6.19. 1-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-3-phenylprop-2-en-1-one (50o)

1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one (**26q**) (336.5 mg, 1.40 mmol) and 1-ethynylcyclohexylamine (206.7 mg, 1.68 mmol) were employed to afford 345.9 mg (68%) of the indicated product as a brownish-yellow solid (R_f = 0.54 in 4:1 hexane/ethyl acetate; mp 100.0-102.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.76 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.57–7.52 (m, 2H), 7.44–7.30 (m, 5H), 5.65 (s, 1H), 2.30 (s, 1H), 1.90–1.81 (m, 2H), 1.71–1.42 (m, 7H), 1.28 (dd, *J* = 8.6, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9 (CO), 167.0 (C), 138.5 (C), 137.0 (C), 136.7 (C), 129.3 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 95.8 (CH), 86.4 (C), 73.7 (CH), 53.7 (C), 39.8 (CH_2), 24.9 (CH_2), 22.2 (CH_2). (Two CH peaks overlap with each other); IR (neat) 3287, 2935, 2860, 1588, 1570, 1474, 1445, 1324, 1256, 1166, 1146, 1060, 1005, 847, 759, 628 cm^{-1}; MS (ESI, m/z): 364.15 [M+H]$^+$; HRMS (ESI) calcd. for $C_{23}H_{23}ClNO$: 364.1463 [M+H]$^+$, found: 364.1455.

3.6.20. 1-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-3-(p-tolyl)prop-2-en-1-one (50p)

1-(4-Chlorophenyl)-3-(p-tolyl)prop-2-yn-1-one (**26r**) (306.1 mg, 1.20 mmol) and 1-ethynylcyclohexylamine (177.7 mg, 1.44 mmol) were employed to afford 286.1 mg (63%) of the indicated product as a light yellow solid (R_f = 0.41 in 4:1 hexane/ethyl acetate; mp 109.6-111.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.74 (s, 1H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.65 (s, 1H), 2.40 (s, 3H), 2.32 (s, 1H), 1.91–1.82 (m, 2H), 1.75–1.59 (m, 4H), 1.56–1.42 (m, 3H), 1.35–1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9 (CO), 167.3 (C), 139.4 (C), 138.7 (C), 136.9 (C), 134.0 (C), 128.6 (CH), 128.5 (CH), 128.47 (CH), 128.45 (CH), 95.9 (CH), 86.7 (C), 73.5 (CH), 53.7 (C), 39.7 (CH_2), 25.0 (CH_2), 22.2 (CH_2), 21.5 (CH_3); IR (neat) 3299, 2935, 2861, 1582, 1551, 1494, 1476, 1322, 1258, 1170, 1145, 1061, 1005, 826, 778, 631 cm^{-1}; MS (ESI, m/z): 378.16 [M+H]$^+$; HRMS (ESI) calcd. for $C_{24}H_{25}ClNO$: 378.1619 [M+H]$^+$, found: 378.1625.

3.6.21. 1-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-3-(3-fluorophenyl)prop-2-en-1-one (50q)

1-(4-Chlorophenyl)-3-(3-fluorophenyl)prop-2-yn-1-one (**26s**) (314.3 mg, 1.22 mmol) and 1-ethynylcyclohexylamine (179.6 mg, 1.46 mmol) were employed to afford 287.7 mg (62%) of the indicated product as an orangish-yellow solid (R_f = 0.52 in 4:1 hexane/ethyl acetate; mp 99.0-101.9°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.65 (s, 1H), 7.82 (d, J = 8.6 Hz, 2H), 7.37–7.28 (m, 5H), 7.16–7.10 (m, 1H), 5.65 (s, 1H), 2.33 (s, 1H), 1.92–1.83 (m, 2H), 1.73–1.59 (m, 4H), 1.58–1.46 (m, 3H), 1.36–1.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.4 (CO), 165.3 (d, $^4J_{CF}$ =1.8 Hz, C), 162.1(d, $^1J_{CF}$ =246.7 Hz, C), 138.7 (d, $^3J_{CF}$ =7.9 Hz, C), 138.3 (C), 137.3 (C), 129.6 (d, $^3J_{CF}$ =8.2 Hz, CH), 128.7 (CH), 128.6 (CH), 124.6 (d, $^4J_{CF}$ =3.1 Hz, CH), 116.4 (d, $^2J_{CF}$ =21.0 Hz, CH), 116.2 (d, $^2J_{CF}$ =22.8 Hz, CH), 95.8 (CH), 86.3 (C), 74.1 (CH), 53.9 (C), 40.0 (CH_2), 25.0 (CH_2), 22.3 (CH_2); IR (neat) 3287, 2936, 2856, 1577, 1552, 1470, 1324, 1256, 1232, 1166, 1060, 1006, 886, 777, 628 cm^{-1}; MS (ESI, m/z): 382.14 [M+H]$^+$; HRMS (ESI) calcd. for $C_{23}H_{22}ClFNO$: 382.1369 [M+H]$^+$, found: 382.1363.

3.6.22. 3-((2-Methylbut-3-yn-2-yl)amino)-1,3-diphenylprop-2-en-1-one (61a)

1,3-Diphenylprop-2-yn-1-one (**26a**) (300.2 mg, 1.46 mmol) and 2-methylbut-3-yn-2-amine (145.2 mg, 1.75 mmol) were employed to afford 290.3 mg (69%) of the indicated product as a pale orange solid (R_f = 0.49 in 4:1 hexane/ethyl acetate; mp 127.2-129.1°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.78 (s, 1H), 7.89 (dd, J = 8.0, 1.6 Hz, 2H), 7.56 (dd, J = 7.8, 1.6 Hz, 2H), 7.43–7.34 (m, 6H), 5.75 (s, 1H), 2.26 (s, 1H), 1.51 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5 (CO), 166.4 (C), 139.9 (C), 136.4 (C), 130.9 (CH), 129.2 (CH), 128.7 (CH), 128.2 (CH), 127.7 (CH), 127.1 (CH), 96.2 (CH), 87.6 (C), 71.3 (CH), 49.3 (C), 32.2 (CH_3); IR (neat) 3243, 2986, 1572, 1549, 1476, 1441, 1328, 1282, 1218, 1174, 1053, 1023, 998, 811, 783, 672 cm^{-1}; MS (ESI, m/z): 290.15 [M+H]$^+$; HRMS (ESI) calcd. for $C_{20}H_{20}NO$: 290.1539 [M+H]$^+$, found: 290.1539.

3.6.23. 3-((2-Methylbut-3-yn-2-yl)amino)-1-phenyl-3-(m-tolyl)prop-2-en-1-one (61b)

1-Phenyl-3-(m-tolyl)prop-2-yn-1-one (**26c**) (308.3 mg, 1.40 mmol) and 2-methylbut-3-yn-2-amine (139.6 mg, 1.68 mmol) were employed to afford 267.5 mg (63%) of the indicated product as a pinkish orange solid (R_f = 0.44 in 4:1 hexane/ethyl acetate; mp 75.2-77.9 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.81 (s, 1H), 7.97–7.94 (m, 2H), 7.49–7.41 (m, 5H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.30 (d, *J* = 7.7 Hz, 1H), 5.81 (s, 1H), 2.45 (s, 3H), 2.34 (s, 1H), 1.57 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6 (CO), 166.8 (C), 140.0 (C), 137.4 (C), 136.4 (C), 130.9 (CH), 130.0 (CH), 129.5 (CH), 128.2 (CH), 127.7 (CH), 127.1 (CH), 125.8 (CH), 96.1 (CH), 88.0 (C), 71.0 (CH), 49.4 (C), 32.2 (CH_3), 21.4 (CH_3); IR (neat) 3221, 2980, 1574, 1549, 1473, 1445, 1330, 1290, 1221, 1174, 1154, 1055, 999, 757, 695 cm^{-1}; MS (ESI, m/z): 304.17 [M+H]$^+$; HRMS (ESI) calcd. for $C_{21}H_{22}NO$: 304.1696 [M+H]$^+$, found: 304.1700.

3.6.24. 1-(4-Chlorophenyl)-3-((2-methylbut-3-yn-2-yl)amino)-3-phenylprop-2-en-1-one (61c)

1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-one (**26q**) (324.1 mg, 1.35 mmol) and 2-methylbut-3-yn-2-amine (134.3 mg, 1.62 mmol) were employed to afford 261.6 mg (60%) of the indicated product as a light yellow solid (R_f = 0.54 in 4:1 hexane/ethyl acetate; mp 82.6-84.9 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.77 (s, 1H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.54 (dd, *J* = 7.9, 1.6 Hz, 2H), 7.42–7.35 (m, 3H), 7.33 (d, *J* = 8.6 Hz, 2H), 5.66 (s, 1H), 2.25 (s, 1H), 1.50 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.0 (CO), 166.8 (C), 138.4 (C), 137.0 (C), 136.3 (C), 129.4 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 127.8 (CH), 95.8 (CH), 87.5 (C), 71.5 (CH), 49.5 (C), 32.2 (CH_3); IR (neat) 3291, 3208, 2980, 1583, 1567, 1474, 1443, 1326, 1295, 1216, 1090, 1056, 1010, 850, 761, 661 cm^{-1}; MS (ESI, m/z): 324.12 [M+H]$^+$; HRMS (ESI) calcd. for $C_{20}H_{19}ClNO$: 324.1150 [M+H]$^+$, found: 324.1143.

3.7. General Procedure for the Synthesis of *N*-Propargylic β-enaminones 10 and 52

To a stirred solution of the corresponding β-enaminone **32** or **50** (1.8 mmol) in DMF (0.45 mL) at room temperature under argon was added (i-Pr)$_2$NH (3.6 mL), $PdCl_2(PPh_3)_2$ (0.036 mmol) and CuI (0.036 mmol) in turn and the reaction mixture was stirred for 10 min. The appropriate aryl iodide (2.8 mmol) was then added and the resulting mixture was stirred at room temperature for approximately 3-5 h (Note that stirring was continued until β-enaminone **32** or **50** was completely consumed as monitored by routine TLC). After the reaction was over, ethyl acetate (50 mL) was added, and the resulting solution was washed with 0.1 N HCl (10 mL) and subsequently with a saturated NH_4Cl solution (10 mL) in a separatory funnel. After the layers were separated, organic phase was dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding β-enaminone **10a-d** and **52a-h**.

3.7.1. 1,3-Diphenyl-3-(3-phenylprop-2-ynylamino)prop-2-en-1-one (10a)

1,3-Diphenyl-3-(prop-2-ynylamino)prop-2-en-1-one (**32a**) (470.8 mg, 1.80 mmol), (i-Pr)$_2$NH (3.6 mL), $PdCl_2(PPh_3)_2$ (25.8 mg, 0.036 mmol), CuI (6.9 mg, 0.036 mmol) and iodobenzene (571.3 mg, 2.79 mmol) were employed to afford 534.5 mg (88%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.43 (br s, 1H), 7.96-7.90 (m, 2H), 7.59-7.53 (m, 2H), 7.52-7.47 (m, 3H), 7.47-7.39 (m, 5H), 7.35-7.28 (m, 3H), 5.88 (s, 1H), 4.19 (d, J = 6.2 Hz, 2H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 189.1 (CO), 166.0 (C), 140.1 (C), 135.1 (C), 131.8 (CH), 131.0 (CH), 129.8 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.9 (CH), 127.2 (CH), 122.6 (C), 94.6 (CH), 85.2 (C), 84.2 (C), 35.1 (CH_2); IR (neat): 3056, 3031, 2922, 2853, 1594, 1582, 1559, 1476, 1293, 1224, 1139, 1054, 1023, 747, 688 cm^{-1}; MS (ESI, m/z): 338.15 $[M+H]^+$; HRMS (ESI): calcd. for $C_{24}H_{20}NO$: 338.1545 $[M+H]^+$, found: 338.1548.

3.7.2. 3-(4-Methoxyphenyl)-1-phenyl-3-(3-phenylprop-2-ynylamino)prop-2-en-1-one (10b)

3-(4-Methoxyphenyl)-1-phenyl-3-(prop-2-ynylamino)prop-2-en-1-one (**32b**) (524.5 mg, 1.80 mmol), (i-Pr)$_2$NH (3.6 mL), $PdCl_2(PPh_3)_2$ (25.8 mg, 0.036 mmol), CuI (6.9 mg, 0.036 mmol) and iodobenzene (571.3 mg, 2.79 mmol) were employed to afford 555.6 mg (84%) of the indicated product. ^1H NMR (400 MHz, $CDCl_3$) δ 11.49 (br t, J = 6.0 Hz, 1H), 7.96-7.91 (m, 2H), 7.54-7.49 (m, 2H), 7.48-7.39 (m, 5H), 7.35-7.30 (m, 3H), 7.04-6.99 (m, 2H), 5.88 (s, 1H), 4.22 (d, J = 6.3 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (CO), 166.1 (C), 161.0 (C), 140.3 (C), 131.9 (CH), 131.0 (CH), 129.6 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 127.5 (C), 127.3 (CH), 122.7 (C), 114.2 (CH), 94.6 (CH), 85.5 (C), 84.2 (C), 55.5 (CH_3), 35.3 (CH_2); IR (neat): 3057, 3003, 2934, 2838, 1667, 1594, 1582, 1560, 1498, 1295, 1250, 1176, 837, 760, 699 cm^{-1}; MS (ESI, m/z): 368.16 $[M+H]^+$; HRMS (ESI): calcd. for $C_{25}H_{22}NO_2$: 368.1651 $[M+H]^+$, found: 368.1644.

3.7.3. 1-Phenyl-3-(3-phenylprop-2-ynylamino)-3-(thiophen-3-yl)prop-2-en-1-one (10c)

1-Phenyl-3-(prop-2-ynylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**32c**) (481.3 mg, 1.80 mmol), (i-Pr)$_2$NH (3.6 mL), $PdCl_2(PPh_3)_2$ (25.3 mg, 0.036 mmol), CuI (6.9 mg, 0.036 mmol) and iodobenzene (571.3 mg, 2.79 mmol) were employed to afford 513.1 mg (83%) of the indicated product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.62 (br s, 1H), 8.00 (d, *J* = 7.5 Hz, 2H), 7.68 (br s, 1H), 7.53-7.38 (m, 6H), 7.37-7.27 (m, 4H), 6.01 (s, 1H), 4.26 (d, *J* = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (CO), 160.5 (C), 140.0 (C), 135.5 (C), 131.6 (CH), 130.9 (CH), 128.4 (CH), 128.2 (CH), 128.1 (CH), 127.3 (CH), 127.0 (CH), 126.6 (CH), 126.2 (CH), 122.4 (C), 94.1 (CH), 85.3 (C), 84.2 (C), 35.0 (CH_2); IR (neat): 3095, 3063, 2922, 1559, 1507, 1273, 1226, 1174, 1068, 1022, 754, 688 cm^{-1}; MS (ESI, m/z): 344.11 $[M+H]^+$; HRMS (ESI): calcd. for $C_{22}H_{18}NOS$: 344.1109 $[M+H]^+$, found: 344.1107.

3.7.4. 4-Cyclopentyl-1-phenyl-3-((3-phenylprop-2-yn-1-yl)amino)but-2-en-1-one (10d)

4-Cyclopentyl-1-phenyl-3-(prop-2-yn-1-ylamino)but-2-en-1-one (**32d**) (323.0 mg, 1.21 mmol), (*i*-Pr)$_2$NH (2.4 mL), $PdCl_2(PPh_3)_2$ (16.9 mg, 0.024 mmol),CuI(4.6 mg, 0.024 mmol) and iodobenzene (382.0 mg, 1.87 mmol) were employed to afford 415.0 mg (77%) of the indicated product as a brownish orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.65 (t, *J* = 5.6 Hz, 1H), 7.99–7.88 (m, 2H), 7.54–7.40 (m, 5H), 7.38–7.29 (m, 3H), 5.80 (s, 1H), 4.35 (d, *J* = 6.1 Hz, 2H), 2.48 (d, *J* = 7.4 Hz, 2H), 2.24 (septet, *J* = 7.7 Hz, 1H), 1.98–1.86 (m, 2H), 1.78–1.53 (m, 4H), 1.38–1.23 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.4 (CO), 167.5 (C), 140.5 (C), 131.72 (CH), 130.6 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.0 (CH), 122.5 (C), 92.9 (CH), 84.6 (C), 84.1 (C), 38.6 (CH_2), 38.0 (CH_2), 33.2 (CH), 32.8 (CH_2), 24.8 (CH_2); IR (neat): 2948, 2865, 1734, 1594, 1578, 1551, 1238, 1175, 1061, 1025, 753, 690 cm^{-1}; MS (ESI, m/z): 330.19 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{26}NO$: 330.1852 $[M+H]^+$, found: 330.1864.

3.7.5. 1,3-Diphenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one (52a)

3-((1-Ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**50a**) (266.0 mg, 0.81 mmol), (i-Pr)$_2$NH (1.6 mL), PdCl$_2$(PPh$_3$)$_2$ (11.5 mg, 0.016 mmol), CuI (3.1 mg, 0.016 mmol) and iodobenzene (255.2 mg, 1.25 mmol) were employed to afford 268.4 mg (82%) of the indicated product as a yellow oil (R_f = 0.65 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.78 (s, 1H), 7.82–7.78 (m, 2H), 7.52–7.48 (m, 2H), 7.35–7.22 (m, 6H), 7.21–7.13 (m, 5H), 5.64 (s, 1H), 1.95–1.85 (m, 2H), 1.70 (td, J= 9.9, 3.3 Hz, 2H), 1.63–1.37 (m, 5H), 1.29–1.16 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 188.5 (CO), 166.9 (C), 140.2 (C), 137.0 (C), 131.6 (CH), 130.9 (CH), 129.1 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.7 (CH), 127.2 (CH), 123.0 (C), 96.2 (CH), 92.2 (C), 85.8 (C), 54.3 (C), 40.2 (CH$_2$), 25.1 (CH$_2$), 22.5 (CH$_2$); IR (neat) 3058, 2931, 2855, 1736, 1584, 1567, 1475, 1443, 1327, 1299, 1258, 1157, 1054, 1024,752, 689 cm^{-1}; MS (ESI, m/z): 406.22 [M+H]$^+$; HRMS (ESI) calcd. for C$_{29}$H$_{28}$NO: 406.2165 [M+H]$^+$, found: 406.2175.

3.7.6. 1,3-Diphenyl-3-((1-(p-tolylethynyl)cyclohexyl)amino)prop-2-en-1-one (52b)

3-((1-Ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**50a**) (269.2 mg, 0.82 mmol), (i-Pr)$_2$NH (1.63 mL), PdCl$_2$(PPh$_3$)$_2$ (11.5 mg, 0.016 mmol), CuI (3.1 mg, 0.016 mmol) and 1-iodo-4-methylbenzene (276.1 mg, 1.27 mmol) were employed to afford 246.8 mg (72%) of the indicated product as a yellow oil (R_f = 0.61 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.90 (s, 1H), 7.96–7.90 (m, 2H), 7.64–7.59 (m, 2H), 7.46–7.33 (m, 6H), 7.19 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 5.75 (s, 1H), 2.36 (s, 3H), 2.05–1.98 (m, 2H), 1.82 (td, J= 9.9, 3.3 Hz, 2H), 1.74–1.58 (m, 4H), 1.55–1.48 (m, 1H), 1.41–1.30 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 188.4 (CO), 166.9 (C), 140.2 (C), 138.2 (C), 137.1 (C), 131.5 (CH), 130.9 (CH), 129.1 (CH), 129.0 (CH), 128.6 (CH), 128.2 (CH), 127.7 (CH), 127.2 (CH), 120.0 (C), 96.1 (CH), 91.5 (C), 85.9 (C), 54.3 (C), 40.3 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 21.5 (CH_3); IR (neat) 3057, 2931, 2855, 1736, 1584, 1567, 1509, 1475, 1443, 1327, 1298, 1259, 1226, 1157, 1076, 1054, 815, 748, 691 cm^{-1}; MS (ESI, m/z): 420.23 $[M+H]^+$; HRMS (ESI) calcd. for $C_{30}H_{30}NO$: 420.2322 $[M+H]^+$, found: 420.2323.

3.7.7. 3-((1-((4-Fluorophenyl)ethynyl)cyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (52c)

3-((1-Ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**50a**) (240.4 mg, 0.73 mmol), (*i*-Pr)$_2$NH (1.46 mL), $PdCl_2(PPh_3)_2$ (10.2 mg, 0.015 mmol), CuI (2.8 mg, 0.015 mmol) and 1-fluoro-4-iodobenzene (251.2 mg, 1.13 mmol) were employed to afford 259.7 mg (84%) of the indicated product as a yellow oil (R_f = 0.64 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$) δ 11.76 (s, 1H), 7.84–7.77 (m, 2H), 7.50–7.45 (m, 2H), 7.35–7.22 (m, 6H), 7.16–7.10 (m, 2H), 6.92–6.84 (m, 2H), 5.64 (s, 1H), 1.93–1.86 (m, 2H), 1.75–1.67 (m, 2H), 1.63–1.55 (m, 2H), 1.54–1.37 (m, 3H), 1.29–1.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5 (CO), 166.7 (C), 162.4 (d, $^1J_{CF}$ = 249.4 Hz, C), 140.1 (C), 137.0 (C), 133.4 (d, $^3J_{CF}$ = 8.4Hz, CH), 130.9 (CH), 129.1 (CH), 128.6 (CH), 128.2 (CH), 127.7 (CH), 127.1 (CH), 119.1 (d, $^4J_{CF}$ = 3.5 Hz, C), 115.4 (d, $^2J_{CF}$ = 22.0 Hz, CH), 96.2 (CH), 91.8 (C), 84.8 (C), 54.2 (C), 40.2 (CH_2), 25.0 (CH_2), 22.4 (CH_2); IR (neat) 3059, 2931, 2855, 1736, 1584, 1567, 1504, 1475, 1327, 1299, 1260, 1219, 1153, 1054, 1024, 834, 748, 691 cm^{-1}; MS (ESI, m/z): 424.21 $[M+H]^+$; HRMS (ESI) calcd. for $C_{29}H_{27}FNO$: 424.2071 $[M+H]^+$, found: 424.2075.

3.7.8. 3-((1-((3-Bromophenyl)ethynyl)cyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (52d)

3-((1-Ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**50a**) (227.5 mg, 0.69 mmol), (*i*-Pr)$_2$NH (1.38 mL), $PdCl_2(PPh_3)_2$ (9.7 mg, 0.014 mmol), CuI (2.6 mg, 0.014 mmol) and 1-bromo-3-iodobenzene (303.0 mg, 1.07 mmol) were employed to afford 294.0 mg (88%) of the indicated product as a yellow solid (R_f = 0.57 in 4:1

hexane/ethyl acetate; mp 98.2-99.7 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.87 (s, 1H), 7.94–7.89 (m, 2H), 7.60–7.55 (m, 2H), 7.44–7.34 (m, 8H), 7.20–7.12 (m, 2H), 5.76 (s, 1H), 2.04–1.98 (m, 2H), 1.87–1.78 (m, 2H), 1.75–1.67 (m, 2H), 1.65–1.50 (m, 3H), 1.40–1.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6 (CO), 166.6 (C), 140.1 (C), 137.0 (C), 134.4 (CH), 131.3 (CH), 130.9 (CH), 130.1 (CH), 129.7 (CH), 129.2 (CH), 128.6 (CH), 128.3 (CH), 127.8 (CH), 127.2 (CH), 124.9 (C), 122.0 (C), 96.4 (CH), 93.5 (C), 84.5 (C), 54.2 (C), 40.3 (CH_2), 25.0 (CH_2), 22.5 (CH_2); IR (neat) 3068, 2936, 2854, 1738, 1585, 1551, 1471, 1404, 1259, 1229, 1150, 1056, 1025, 812, 792, 749, 680 cm^{-1}; MS (ESI, m/z): 484.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{29}H_{27}BrNO$: 484.1271 $[M+H]^+$, found: 484.1282.

3.7.9. 3-((1-((4-Nitrophenyl)ethynyl)cyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (52e)

3-((1-Ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**50a**) (308.9 mg, 0.94 mmol), (i-Pr)$_2$NH (1.88 mL), $PdCl_2(PPh_3)_2$ (13.2 mg, 0.019 mmol), CuI (3.6 mg, 0.019 mmol) and 1-iodo-4-nitrobenzene (362.0 mg, 1.45 mmol) were employed to afford 316.9 mg (75%) of the indicated product as an orange solid (R_f = 0.62 in 4:1 hexane/ethyl acetate; mp 129.1-131.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.82 (s, 1H), 8.15 (d, J= 8.8 Hz, 2H), 7.92–7.87 (m, 2H), 7.58–7.52 (m, 2H), 7.46–7.30 (m, 8H), 5.75 (s, 1H), 2.07–1.98 (m, 2H), 1.89–1.80 (m, 2H), 1.78–1.69 (m, 2H), 1.63–1.48 (m, 3H), 1.43–1.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (CO), 166.5 (C), 147.1 (C), 140.0 (C), 137.0 (C), 132.4 (CH), 131.1 (CH), 129.9 (C), 129.4 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 127.3 (CH), 123.6 (CH), 97.7 (C), 96.7 (CH), 84.4 (C), 54.3 (C), 40.2 (CH_2), 25.0 (CH_2), 22.5 (CH_2); IR (neat) 3077, 2932, 2857, 1737, 1578, 1555, 1521, 1475, 1442, 1346, 1325, 1295, 1257, 1161, 1145, 1054, 1023, 854, 749, 689 cm^{-1}; MS (ESI, m/z): 451.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{29}H_{27}N_2O_3$: 451.2016 $[M+H]^+$, found: 451.2029.

3.7.10. 3-(4-Chlorophenyl)-1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one (52f)

3-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one (**50f**) (377.5 mg, 1.04 mmol), (*i*-Pr)$_2$NH (2.07 mL), PdCl$_2$(PPh$_3$)$_2$ (14.6 mg, 0.021 mmol), CuI (3.9 mg, 0.021 mmol) and iodobenzene (327.9 mg, 1.61 mmol) were employed to afford 369.6 mg (81%) of the indicated product as a yellow oil (R_f = 0.64 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.84 (s, 1H), 7.95–7.91 (m, 2H), 7.57–7.52 (m, 2H), 7.48–7.39 (m, 3H), 7.36–7.30 (m, 5H), 7.30–7.26 (m, 2H), 5.74 (s, 1H), 2.09–2.01 (m, 2H), 1.87–1.78 (m, 2H), 1.75–1.51 (m, 5H), 1.41–1.29 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 188.6 (CO), 165.3 (C), 139.9 (C), 135.4 (C), 135.2 (C), 131.5 (CH), 131.0 (CH), 130.0 (CH), 128.3 (CH), 128.0 (CH), 127.1 (CH), 122.7 (C), 96.2 (CH), 91.8 (C), 86.4 (C), 54.3 (C), 40.4 (CH$_2$), 25.0 (CH$_2$), 22.5 (CH$_2$) (2 x Two CH peaks overlap with each other); IR (neat) 3058, 2931, 2855, 1736, 1578, 1560, 1473, 1443, 1326, 1298, 1259, 1226, 1157, 1090, 1053, 1023, 833, 752, 689 cm^{-1}; MS (ESI, m/z): 440.18 [M+H]$^+$; HRMS (ESI) calcd. for $C_{29}H_{27}ClNO$: 440.1776 [M+H]$^+$, found: 440.1785.

3.7.11. 3-(4-Chlorophenyl)-1-phenyl-3-((1-(p-tolylethynyl)cyclohexyl)amino)prop-2-en-1-one (52g)

3-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one (**50f**) (331.3 mg, 0.91 mmol), (*i*-Pr)$_2$NH (1.82 mL), PdCl$_2$(PPh$_3$)$_2$ (12.8 mg, 0.018 mmol), CuI (3.5 mg, 0.018 mmol) and1-iodo-4-methylbenzene (307.9 mg, 1.41 mmol) were employed to afford 289.2 mg (70%) of the indicated product as a yellow oil (R_f = 0.59 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.81 (s, 1H), 7.94–7.86 (m, 2H), 7.55–7.51 (m, 2H), 7.45–7.38 (m, 3H), 7.34–7.30 (m, 2H), 7.17–7.10 (m, 4H), 5.70 (s, 1H), 2.36 (s, 3H), 2.05–1.98 (m, 2H), 1.84–1.76 (m, 2H), 1.73–1.59 (m, 4H), 1.56–1.50 (m, 1H), 1.38–1.30 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 188.6 (CO), 165.4 (C), 140.0 (C), 138.4 (C), 135.5 (C), 135.2 (C), 131.5 (CH), 131.0 (CH), 130.1 (CH), 129.1 (CH), 128.3 (CH), 128.0 (CH), 127.2 (CH), 119.8 (C), 96.1 (CH), 91.2 (C), 86.5 (C), 54.4 (C), 40.5 (CH_2), 25.0 (CH_2), 22.5 (CH_2), 21.5 (CH_3); IR (neat) 3056, 2931, 2856, 1737, 1578, 1560, 1473, 1326, 1298, 1259, 1226, 1157, 1090, 1053, 1015, 814, 753, 690 cm^{-1}; MS (ESI, m/z): 454.19 $[M+H]^+$; HRMS (ESI) calcd. for $C_{30}H_{29}ClNO$: 454.1932 $[M+H]^+$, found: 454.1934.

3.7.12. 3-((1-((3-Bromophenyl)ethynyl)cyclohexyl)amino)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (52h)

3-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one (**50f**) (346.4 mg, 0.95 mmol), (*i*-Pr)$_2$NH (1.90 mL), $PdCl_2(PPh_3)_2$ (13.4 mg, 0.019 mmol), CuI (3.6 mg, 0.019 mmol) and 1-bromo-3-iodobenzene (417.4 mg, 1.48 mmol) were employed to afford 439.6 mg (89%) of the indicated product as a yellow oil (R_f = 0.65 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.77 (s, 1H), 7.93–7.86 (m, 2H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.45–7.36 (m, 5H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.18–7.12 (m, 2H), 5.72 (s, 1H), 2.06–1.98 (m, 2H), 1.84–1.76 (m, 2H), 1.74–1.66 (m, 2H), 1.64–1.49 (m, 3H), 1.39–1.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7 (CO), 165.1 (C), 139.9 (C), 135.4 (C), 135.3 (C), 134.3 (CH), 131.5 (CH), 131.1 (CH), 130.1 (CH), 130.0 (CH), 129.7 (CH), 128.3 (CH), 128.0 (CH), 127.2 (CH), 124.7 (C), 122.1 (C), 96.4 (CH), 93.1 (C), 85.0 (C), 54.32 (C), 40.4 (CH_2), 24.9 (CH_2), 22.5 (CH_2); IR (neat) 3060, 2931, 2855, 1736, 1578, 1556, 1471, 1325, 1299, 1257, 1226, 1158, 1090, 1053, 1023, 833, 781, 680 cm^{-1}; MS (ESI, m/z): 518.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{29}H_{26}BrClNO$: 518.0881 $[M+H]^+$, found: 518.0890.

3.8. General Procedure for the Synthesis of Iodopyridines 44

To a stirred solution of the corresponding *N*-propargylic β-enaminone **10** (0.25 mmol) in acetonitrile (10 mL) were added iodine (0.75 mmol) and $NaHCO_3$ (0.75 mmol). The resulting mixture was then refluxed at 82 °C under air for approximately 8-10 h (Note that stirring was continued until β-enaminone **10** was completely consumed as monitored by routine TLC). After the reaction was over, the solventwas removed on a rotary evaporator, and ethylacetate (30 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (30 mL) were added (Note that the treatment of the reaction mixture with a saturated $Na_2S_2O_3$ solution removes the unreacted/excess I_2). After the layers were separated, the aqueous layer was extracted with ethyl acetate (3x30 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatographyon silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding iodopyridine **44a-d**.

3.8.1. (5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (44a)

1,3-Diphenyl-3-(3-phenylprop-2-ynylamino)prop-2-en-1-one (**10a**) (84.4 mg, 0.25 mmol), I_2 (190.4 mg, 0.75 mmol) and $NaHCO_3$ (63.0 mg, 0.75 mmol) were employed to afford 92.3 mg (80%) of the indicated product as an off-white solid; mp 166.9-167.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.28 (s, 1H), 7.47-7.41(m, 2H), 7.40-7.35 (m, 2H), 7.27 (tt, *J* =7.4 and 1.1 Hz, 2H), 7.22-6.92(m, 8H), 6.78 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8 (CO),157.5 (CH), 156.0 (C), 152.6 (C), 139.4 (C), 138.5 (C), 137.2 (C), 135.4(C), 133.5 (CH), 129.4 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 128.5 (CH), 128.4 (CH), 128.0 (CH), 128.0 (CH), 98.6 (C); IR (neat): 3066,1667, 1503, 1443, 1421, 1311, 1279, 1225, 945, 762, 698, 683, 653, 570 cm^{-1}; MS (ESI, m/z): 462.03 $[M+H]^+$; HRMS (ESI): calcd. for $C_{24}H_{17}INO$: 462.0349 $[M+H]^+$, found: 462.0345.

3.8.2. (5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (44b)

3-(4-Methoxyphenyl)-1-phenyl-3-(3-phenylprop-2-ynylamino)prop-2-en-1-one (**10b**) (91.9 mg, 0.25 mmol), I_2 (190.4 mg, 0.75 mmol) and $NaHCO_3$ (63.0 mg, 0.75 mmol) were employed to afford 76.2 mg (62%) of the indicated product as a yellow solid; mp 175.2-176.4 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.12 (s, 1H), 7.44-7.34 (m, 4H), 7.27 (tt, *J* =7.4 and 1.1 Hz, 2H), 7.19-7.07 (m, 4H), 6.99 (br s, 1H), 6.74 (br s, 1H), 6.70-6.64 (m, 2H), 3.62 (s,3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.0 (CO), 160.3 (C), 157.4 (CH), 155.5 (C), 152.5 (C), 139.5 (C), 137.2 (C), 134.9 (C), 133.5 (CH), 131.0 (C), 130.6 (CH), 129.4 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.1(CH), 114.0 (CH), 98.0 (C), 55.3 (CH$_3$); IR (neat): 2963, 2839, 1658, 1535, 1471, 1411, 1327, 1228, 1160, 1012, 837, 777, 633, 614, 582 cm^{-1}; MS(ESI, m/z): 492.05 [M+H]$^+$; HRMS (ESI): calcd. for $C_{25}H_{19}INO_2$:492.0460 [M+H]$^+$, found: 492.0454.

3.8.3. (5-Iodo-4-phenyl-2-(thiophen-3-yl)pyridin-3-yl)(phenyl)methanone (44c)

1-Phenyl-3-(3-phenylprop-2-ynylamino)-3-(thiophen-3-yl)prop-2-en-1-one (**10c**) (85.9 mg, 0.25 mmol), I$_2$ (190.4 mg, 0.75 mmol) and NaHCO$_3$ (63.0 mg, 0.75 mmol) were employed to afford 87.3 mg (75%) of the indicated product as a light yellow solid; mp 154.8-155.7 °C. ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.20 (s, 1H), 7.57-7.51 (m, 3H), 7.46-7.34 (m, 3H), 7.30-7.22 (m, 4H), 7.19 (dd, *J* =5.0 and 3.0 Hz, 1H), 7.09 (br s, 1H), 6.85 (br s, 1H); ^{13}CNMR (100 MHz, CDCl$_3$) δ 196.2 (CO), 157.4 (CH), 152.3 (C), 150.5 (C), 139.5 (C), 139.2 (C), 137.0 (C), 134.5 (C), 133.7 (CH), 129.3 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.0 (CH), 126.9 (CH), 126.0 (CH), 98.0 (C); IR (neat): 2963, 1652, 1590, 1540, 1514, 1493,1431, 1310, 1285, 1229, 940, 782, 759, 695, 666 cm^{-1}; MS (ESI, m/z):467.99 [M+H]$^+$; HRMS (ESI): calcd. for $C_{22}H_{15}INOS$: 467.9919 [M+H]$^+$, found: 467.9913.

3.8.4. (2-(Cyclopentylmethyl)-5-iodo-4-phenylpyridin-3-yl)(phenyl)methanone (44d)

4-Cyclopentyl-1-phenyl-3-((3-phenylprop-2-yn-1-yl)amino)but-2-en-1-one (**10d**) (345.0 mg, 1.05 mmol), I$_2$ (799.1 mg, 3.10 mmol) and NaHCO$_3$ (264.3 mg, 3.10 mmol) were employed to afford 323.9 mg (66%) of the indicated product as an orange oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 9.08 (s, 1H), 7.52 (d, *J* = 7.3 Hz, 2H), 7.48–7.41 (m, 1H), 7.29 (t, *J* = 7.6 Hz, 3H), 7.18 (t, *J* = 6.2 Hz, 2H), 7.14–6.81 (m, 2H), 2.65 (d, *J* = 6.8 Hz, 2H), 2.37 (septet, *J* = 7.7 Hz, 1H), 1.76–1.62 (m, 2H), 1.60–1.37 (m, 4H), 1.13 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1 (CO), 158.0 (CH), 157.0 (CH), 150.9 (C), 139.1 (CH), 137.0 (C), 135.7 (C), 133.7 (CH), 129.3 (CH), 128.5 (CH), 128.5 (CH), 128.0 (C), 127.9 (C), 96.4 (C), 41.3 (CH_2), 39.9 (CH), 32.4 (CH_2), 24.9 (CH_2); IR (neat): 2945, 2862, 1735, 1668, 1595, 1520, 1425, 1372, 1227, 1175, 880, 757, 696, 665, 546 cm^{-1}; MS (ESI, m/z): 468.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{23}INO$: 468.0819 $[M+H]^+$, found: 468.0862.

3.9. General Procedure for the Synthesis of 5-Aryl-substituted Pyridines 46

To a stirred solution of 5-iodopyridines **44** (0.25 mmol) and boronic acid **45** (0.35 mmol) in DMF/H_2O (4 ml:1 ml) under argon was added $KHCO_3$ (0.35 mmol) and $PdCl_2(PPh_3)_2$ (0.0125 mmol) and resulting solution was allowed to stir under reflux at 110 °C for approximately 8 h. The reaction was monitored by TLC to establish completion. When the reaction was over, the mixture was quenched by adding saturated aqueous NaCl solution (30 mL) and extracted twice with ethyl acetate (2x30 mL). The combined ethyl acetate fractions were dried over $MgSO_4$ and removed under reduced pressure. The residue was purified by flash column chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding 5-arylpyridines **46a-r.**

3.9.1. Phenyl(2,4,5-triphenylpyridin-3-yl)methanone(46a)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**44a**) (140.7 mg, 0.31 mmol), phenylboronic acid (52.1 mg, 0.43 mmol), $KHCO_3$ (42.7 mg, 0.43 mmol) and $PdCl_2(PPh_3)_2$ (14.0 mg, 0.02 mmol) were employed to afford 117.5 mg (94%) of the indicated product as an off-white solid (R_f = 0.24 in 9:1 hexane/ethyl acetate; mp 169-170 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.51–7.46 (m, 2H), 7.44 (d, *J* = 7.9 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 7.21–7.04 (m, 13H), 6.99–6.92 (m, 2H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 197.2 (CO), 155.6 (C), 150.8 (CH), 147.1 (C), 139.4 (C), 137.8 (C), 137.1 (C), 136.0 (C), 135.3 (C), 134.5 (C), 133.2 (CH), 130.1 (CH), 129.4 (CH), 129.3 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.26 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH) (Two C peaks overlap with each other); IR (neat) 3049, 1672, 1595, 1529, 1433, 1371, 1317, 1217, 1172, 1024, 948, 753, 722, 695, 578, 516 cm^{-1}; MS (ESI, m/z): 412.17 $[M+H]^+$; HRMS (ESI) calcd. for $C_{30}H_{22}NO$: 412.1696 $[M+H]^+$, found: 412.1707.

3.9.2. (5-(4-Ethylphenyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (46b)

5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**44a**) (83.0 mg, 0.18 mmol), 4-ethylphenylboronic acid (37.7 mg, 0.25 mmol), $KHCO_3$ (25.2 mg, 0.25 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were employed to afford 77.0 mg (98%) of the indicated product as a yellowish white solid (R_f = 0.26 in 9:1 hexane/ethyl acetate; mp 164-165 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.78 (s, 1H), 7.50–7.45 (m, 2H), 7.45–7.41 (m, 2H), 7.27–7.21 (m, 1H), 7.21–7.14 (m, 4H), 7.13–7.06 (m, 2H), 7.03–6.57 (m, 8H), 2.51 (q, J= 7.6 Hz, 2H), 1.12 (m, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3 (CO), 155.3 (C), 150.9 (CH), 147.0 (C), 143.6 (CH), 139.5 (C), 137.8 (C), 136.2 (C), 135.2 (C), 134.5 (C), 134.2 (C), 133.1 (CH), 130.0 (CH), 129.4 (CH), 129.3 (CH), 128.6 (C), 128.3 (CH), 128.25 (CH), 127.8 (CH), 127.77 (CH), 127.7 (CH), 28.5 (CH_2), 15.4 (CH_3) (Two C peaks overlap with each other); IR (neat) 3050, 1670, 1557, 1524, 1435, 1315, 1285, 1215, 1019, 949, 833, 807, 752, 688, 544, 520 cm^{-1}; MS (ESI, m/z): 440.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{32}H_{26}NO$: 440.2009 $[M+H]^+$, found: 440.2007.

3.9.3. (5-(4-Chlorophenyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (46c)

5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**44a**) (78.4 mg, 0.17 mmol), 4-chlorophenylboronic acid (37.9 mg, 0.24 mmol), $KHCO_3$ (24.2 mg, 0.24 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were employed to afford 67.0 mg (87%) of the indicated product as a yellowish white solid (R_f = 0.3 in 9:1 hexane/ethyl acetate; mp 224-225 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 7.61–7.55 (m, 2H), 7.54–7.50 (m, 2H), 7.39–7.33 (m, 1H), 7.31–7.18 (m, 8H), 7.14–6.54 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0 (CO), 155.9 (C), 150.6 (CH), 147.1 (C), 139.3 (C), 137.7 (CH), 135.7 (C), 135.6 (C), 134.6 (C), 134.1 (C), 133.9 (C), 133.3 (CH), 131.3 (CH), 129.4 (CH), 129.3 (CH), 128.8 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.1 (C), 128.0 (CH) (Two C peaks overlap with each other);IR (neat) 3051, 1671, 1578, 1557, 1440, 1322, 1217, 1093, 1011, 947, 832, 807, 762, 697, 585, 527 cm^{-1}; MS (ESI, m/z): 446.13 [M+H]$^+$; HRMS (ESI) calcd. for $C_{30}H_{21}ClNO$:446.1306 [M+H]$^+$, found: 446.1318.

3.9.4. (5-(4-Ethoxy-3-fluorophenyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (46d)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**44a**) (73.8 mg, 0.16 mmol), 4-ethoxy-3-fluorophenylboronic acid (40.7 mg, 0.22 mmol), $KHCO_3$ (22.1 mg, 0.22 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were employed to afford 53.0 mg (72%) of the indicated product as a brown solid (R_f = 0.16 in 9:1 hexane/ethyl acetate; mp 117-119 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.50–7.45 (m, 2H), 7.44–7.39 (m, 2H), 7.25 (t, J = 7.4 Hz, 1H), 7.21–7.14 (m, 4H), 7.10 (t, J = 7.7 Hz, 3H), 6.98 (t, J = 7.1 Hz, 2H), 6.82–6.50 (m, 4H), 3.97 (q, J= 7.0 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1 (CO) , 155.5 (CH), 152.1 (d, $^1J_{CF}$= 246.6 Hz, C) , 150.6 (CH) , 147.0 (CH) , 146.5 (d, $^2J_{CF}$= 10.8 Hz, C), 139.2 (C), 137.7 (CH), 135.8 (CH), 134.6 (C), 133.9 (C), 133.2 (CH), 129.7 (d, $^3J_{CF}$= 6.9 Hz, C), 129.4 (CH), 129.3 (CH), 128.8 (C), 128.4 (CH), 128.3 (CH), 128.0 (C), 127.8 (CH), 125.9 (d, $^4J_{CF}$= 3.4 Hz, CH), 117.8 (d, $^2J_{CF}$= 19.5 Hz, CH), 114.3 (CH), 114.2 (C), 64.9 (CH_2), 14.8 (CH_3); IR (neat) 2980, 1736, 1666, 1595, 1513, 1440, 1390, 1298, 1243, 1139, 1042, 976, 922, 754, 692, 606, 523 cm^{-1}; MS (ESI, m/z): 474.19 [M+H]$^+$;HRMS (ESI) calcd. for $C_{32}H_{25}FNO_2$: 474.1864 [M+H]$^+$, found: 474.1874.

3.9.5. (6'-Methoxy-4,6-diphenyl-[3,3'-bipyridin]-5-yl)(phenyl)methanone (46e)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**44a**) (73.8 mg, 0.16 mmol), 6-methoxy-3-pyridinylboronic acid (33.7 mg, 0.22 mmol), $KHCO_3$ (22.1 mg, 0.22 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were employed to afford 52.0 mg (75%) of the indicated product as a yellowish brown solid (R_f = 0.1 in 9:1 hexane/ethyl acetate; mp 152-154 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (s, 1H), 8.10 (d, J = 2.3 Hz, 1H), 7.60–7.55 (m, 2H), 7.55–7.50 (m, 2H), 7.38–7.32 (m, 1H), 7.29–7.25 (m, 3H), 7.24–7.17 (m, 4H), 7.14– 6.66 (m, 4H), 6.57 (d, J = 8.6 Hz, 1H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0(CO), 163.5 (CH), 155.9 (C), 150.4 (CH), 147.4 (C), 147.2 (CH), 140.0 (CH), 139.2 (C), 139.1 (C), 137.6 (C), 135.6 (CH), 134.7 (C), 133.3 (CH), 131.8 (C), 129.4 (CH), 129.3 (CH), 128.9 (C), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.9 (C), 126.0 (CH), 110.4 (CH), 53.6 (CH_3); IR (neat) 2979, 1666, 1602, 1580, 1490, 1439, 1382, 1356, 1249, 1213, 1160, 1024, 947, 816, 751, 691, 582, 524 cm^{-1}; MS (ESI, m/z): 443.18 [M+H]$^+$; HRMS (ESI) calcd. for $C_{30}H_{23}N_2O_2$: 443.1754 [M+H]$^+$, found: 443.1769.

3.9.6. (5-(3-Nitrophenyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (46f)

5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**44a**) (92.2 mg, 0.20 mmol), 3-nitrophenylboronic acid (46.1 mg, 0.28 mmol), $KHCO_3$ (27.6 mg, 0.28 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were employed to afford 72.0 mg (80%) of the indicated product as a white solid (R_f = 0.13 in 9:1 hexane/ethyl acetate; mp 168-169 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.03–7.99 (m, 2H), 7.52–7.47 (m, 2H), 7.45–7.40 (m, 2H), 7.37 (dt, J = 7.7, 1.4 Hz, 1H), 7.34–7.30 (m, 1H), 7.29–7.24 (m, 1H), 7.23–7.16 (m, 4H), 7.14–7.09 (m, 2H), 6.99 (t, J = 7.2 Hz, 2H), 6.94–6.42 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ196.7 (CO), 156.7 (C), 150.3 (CH), 148.2 (C), 147.4 (C), 139.0 (C) , 138.9 (CH), 137.49 (C), 135.92 (CH), 135.07 (C), 134.70 (CH), 133.40 (CH), 132.93 (C), 129.35 (CH), 129.30 (CH), 129.25 (CH), 129.01 (CH), 128.43 (CH), 128.37 (CH), 128.34 (CH), 128.21 (C), 128.20 (C), 124.80 (CH), 122.51

(CH); IR (neat) 3059, 1672, 1557, 1535, 1447, 1346, 1321, 1216, 1176, 968, 881, 758, 737, 694, 582, 518 cm^{-1}; MS (ESI, m/z): 457.16 [M+H]$^+$;HRMS (ESI) calcd. for $C_{30}H_{21}N_2O_3$: 457.1547 [M+H]$^+$, found: 457.1560.

3.9.7. (5-(Furan-2-yl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone (46g)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**44a**) (96.9 mg, 0.21 mmol), 2-furanylboronic acid (32.8 mg, 0.29 mmol), $KHCO_3$ (29.3 mg, 0.29 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were employed to afford 70.0 mg (83%) of the indicated product as an orange solid (R_f = 0.31 in 9:1 hexane/ethyl acetate; mp 175-176 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.64–7.58 (m, 2H), 7.52–7.47 (m, 2H), 7.46–7.44 (m, 1H), 7.36 (tt, J = 7.4, 1.7, 1.3 Hz, 2H), 7.31–6.75 (m, 9H), 6.24 (dd, J = 3.5, 1.8 Hz, 1H), 5.36 (dd, J = 3.5, 0.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8 (CO), 154.3 (C), 149.5 (C), 147.8 (CH), 144.5 (C), 142.7 (CH), 139.2 (CH), 137.7 (C), 136.1 (CH), 134.5 (C), 133.3 (CH), 129.3 (CH), 129.27 (CH), 128.8 (CH), 128.6 (C), 128.5 (C), 128.4 (CH), 128.3 (CH), 128.28 (CH), 124.4 (C), 111.8 (CH), 111.4 (CH); IR (neat) 2914, 1668, 1558, 1540, 1436, 1385, 1315, 1229, 1161, 1027, 960, 900, 768, 743, 698, 585, 523 cm^{-1}; MS (ESI, m/z): 402.15 [M+H]$^+$;HRMS (ESI) calcd. for $C_{28}H_{20}NO_2$: 402.1489 [M+H]$^+$, found: 402.1497.

3.9.8. (2,4-Diphenyl-5-(thiophen-3-yl)pyridin-3-yl)(phenyl)methanone (46h)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**44a**) (92.2 mg, 0.20 mmol), 3-thienylboronic acid (36.4 mg, 0.28 mmol), $KHCO_3$ (27.6 mg, 0.28 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were employed to afford 74.0 mg (87%) of the indicated product as an off-white solid (R_f = 0.26 in 9:1 hexane/ethyl acetate; mp 191-192 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.48 (d, J = 3.9 Hz, 2H), 7.43 (d, J = 7.4 Hz, 2H), 7.26 (t, J = 7.2 Hz, 1H), 7.21–6.83 (m, 12H), 6.65 (d, J = 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ197.1 (CO), 155.3 (C), 150.4 (CH), 146.7 (C), 139.4 (C), 137.8 (C), 137.3 (C), 136.2 (CH), 134.6 (C), 133.2 (CH) , 133.2 (CH), 130.2 (C), 129.4 (CH), 129.3 (CH), 128.7 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 128.06 (C), 125.5 (CH), 124.6 (CH) (Two C peaks overlap with each other); IR (neat) 2980, 1736, 1666, 1595, 1529, 1440, 1390, 1372, 1243, 1139, 1042, 976, 922, 754, 692, 637, 523 cm^{-1}; MS (ESI, m/z): 418.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{28}H_{20}NOS$:418.1260 $[M+H]^+$, found: 418.1264.

3.9.9. (5-(Ferrocenyl)-2,4-diphenylpyridin-3-yl)(phenyl)methanone(46i)

(5-Iodo-2,4-diphenylpyridin-3-yl)(phenyl)methanone (**44a**) (96.9 mg, 0.21 mmol), ferrocene boronic acid (66.9 mg, 0.291 mmol), $KHCO_3$ (29.3 mg, 0.29 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were employed to afford 71.0 mg (88%) of the indicated product as an orange solid (R_f = 0.36 in 9:1 hexane/ethyl acetate; mp 146-148 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.68–7.52 (m, 2H), 7.50–7.41 (m, 2H), 7.38–7.08 (m, 9H), 6.95 (br s, 1H), 6.67 (br s, 1H), 4.35 (br s, 1H), 4.29–3.95 (m, 7H), 3.73 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4 (CO), 153.0 (C), 151.8 (CH), 145.9 (C), 139.5 (C), 137.8 (CH), 136.5 (C), 134.0 (C), 133.1 (CH), 132.8 (C), 129.4 (CH), 129.2 (CH), 128.7 (C), 128.6 (CH), 128.3 (CH), 128.2 (CH), 128.0 (C), 127.9 (CH), 81.2 (CH), 69.9 (CH), 68.9 (CH) (Two C peaks overlap with each other); IR (neat) 2925, 1669, 1615, 1593, 1557, 1443, 1427, 1363, 1250, 1046, 988, 894, 857, 758, 698, 572, 524 cm^{-1}; MS (ESI, m/z): 520.14 $[M+H]^+$;HRMS (ESI) calcd. for $C_{34}H_{26}NOFe$: 520.1359 $[M+H]^+$, found: 520.1370.

3.9.10. (2-(4-Methoxyphenyl)-4,5-diphenylpyridin-3-yl)(phenyl)methanone (46j)

(5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (**44b**) (172.0 mg, 0.35 mmol), phenylboronic acid (59.7 mg, 0.49 mmol), $KHCO_3$ (49.0 mg, 0.49 mmol) and $PdCl_2(PPh_3)_2$ (14.0 mg, 0.02 mmol) were employed to afford 130.0 mg (85%) of the indicated product as a beige solid (R_f = 0.24 in 9:1 hexane/ethyl acetate; mp 178-179 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 7.51–7.38 (m, 4H), 7.28–7.21 (m, 1H), 7.20– 6.99 (m, 9H), 6.94 (t, *J* = 7.0 Hz, 2H), 6.76–6.38 (m, 3H), 3.64

(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5 (CO), 160.0 (C), 155.1 (CH), 150.7 (CH), 147.0 (C), 137.8 (C), 137.1 (C), 136.0 (C), 134.7 (CH), 134.1 (C), 133.2 (CH), 131.9 (C), 130.7 (CH), 130.0 (CH), 129.4 (CH), 128.3 (CH), 128.2 (CH), 127.9 (C), 127.8 (C), 127.7 (CH), 127.4 (CH), 113.8 (CH), 55.3 (CH_3); IR (neat) 2927, 1668, 1606, 1513, 1432, 1316, 1253, 1214, 1176, 1030, 947, 837, 760, 698, 578, 518 cm^{-1}; MS (ESI, m/z): 442.18 $[M+H]^+$; HRMS (ESI) calcd. for $C_{31}H_{24}NO_2$: 442.1802 $[M+H]^+$, found: 442.1817.

3.9.11. (5-(4-Ethylphenyl)-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (46k)

(5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (**44b**) (157.2 mg, 0.32 mmol), 4-ethylphenylboronic acid (66.1 mg, 0.44 mmol), $KHCO_3$ (44 mg, 0.44 mmol) and $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol) were employed to afford 121.0 mg (82%) of the indicated product as a pale yellow solid (R_f = 0.32 in 9:1 hexane/ethyl acetate; mp 179-180 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.58–7.52 (m, 4H), 7.38–7.32 (m, 1H), 7.21 (t, J = 7.7 Hz, 3H), 7.11–6.90 (m, 7H), 6.86–6.53 (m, 3H), 3.75 (s, 3H), 2.61 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ197.5 (CO), 160.0 (C), 154.8 (C), 150.8 (CH), 147.0 (C), 143.5 (CH), 137.8 (C), 136.2 (CH), 134.7 (CH), 134.3 (C), 134.1 (C), 133.1 (CH), 132.0 (C), 130.7 (CH), 129.9 (CH), 129.4 (CH), 128.3 (CH), 127.9 (C), 127.8 (C), 127.7 (CH), 127.6 (C), 113.8 (CH), 55.3 (CH_3), 28.5 (CH_2), 15.3 (CH_3); IR (neat) 2961, 1662, 1606, 1576, 1511, 1437, 1308, 1248, 1215, 1174, 1045, 948, 832, 763, 698, 682, 536 cm^{-1}; MS (ESI, m/z): 470.22 $[M+H]^+$; HRMS (ESI) calcd. for $C_{33}H_{28}NO_2$: 470.2115 $[M+H]^+$, found: 470.2132.

3.9.12. (5-(4-Chlorophenyl)-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (46l)

(5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (**44b**) (117.9 mg, 0.242 mmol), 4-chlorophenylboronic acid (53.2 mg, 0.34 mmol), $KHCO_3$ (34.0 mg, 0.34 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.012 mmol) were employed to afford 74.0 mg (65%) of the indicated product as a dark beige solid (R_f = 0.41 in 9:1 hexane/ethyl acetate; mp 213-214 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.55–7.48 (m, 4H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.24–7.15 (m, 6H), 7.06 (d, *J* = 8.5 Hz, 4H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.66 (br s, 1H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3 (CO), 160.2 (CH) , 155.4 (C), 150.5 (CH), 147.1 (C), 137.7 (C), 135.8 (CH), 135.7 (C), 134.2 (C), 133.7 (C), 133.6 (C), 133.3 (CH), 131.8 (C), 131.3 (CH), 130.8 (CH), 130.1 (C), 129.4 (CH), 128.6 (CH), 128.4 (CH), 128.0 (C), 127.9 (CH), 113.9 (CH), 55.3 (CH_3); IR (neat) 2928, 1670, 1605, 1514, 1436, 1371, 1250, 1213, 1175, 1094, 1029, 947, 828, 763, 698, 576, 523 cm^{-1}; MS (ESI, m/z): 476.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{31}H_{23}ClNO_2$: 476.1412 $[M+H]^+$, found: 476.1420.

3.9.13. (5-(4-Ethoxy-3-fluorophenyl)-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (46m)

(5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (**44b**) (108.1 mg, 0.22 mmol), 4-ethoxy-3-fluorophenylboronic acid (57.0 mg, 0.31 mmol), $KHCO_3$ (31.0 mg, 0.31 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were employed to afford 108.0 mg (98%) of the indicated product as a pale yellow solid (R_f = 0.46 in 9:1 hexane/ethyl acetate; mp 175-176 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.61–7.48 (m, 4H), 7.42–7.29 (m, 1H), 7.26–7.15 (m, 3H), 7.13–6.96 (m, 2H), 6.95–6.54 (m, 7H), 4.05 (q, *J* = 7.0 Hz, 2H), 3.73 (s, 3H), 1.42 (t, *J* = 7.0 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3 (CO), 160.0 (CH), 155.0 (CH), 153.3 (C), 152.1 (d, $^1J_{CF}$= 245.9 Hz, C), 150.5 (CH), 146.9(CH), 146.4 (d, $^2J_{CF}$= 10.0 Hz, C) , 137.7 (C) , 135.8 (C), 134.1 (C), 133.3 (C), 133.2 (CH), 131.8 (C), 130.7 (CH), 129.8 (d, $^3J_{CF}$= 6.6 Hz, C), 129.3 (CH), 128.3 (CH), 127.9 (C), 127.85 (CH), 125.9 (d, ${}^4J_{CF}$= 3.4 Hz, CH) , 117.7 (d, ${}^2J_{CF}$= 19.5 Hz, CH), 114.2 (C), 113.8 (CH), 64.8 (CH_2), 55.2 (CH_3), 14.8 (CH_3);IR (neat) 2933, 1666, 1528, 1518, 1426, 1395, 1267, 1219, 1179, 1029, 970, 884, 809, 765, 687, 543 cm^{-1}; MS (ESI, m/z): 504.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{33}H_{27}FNO_3$: 504.1970 $[M+H]^+$, found: 504.1974.

3.9.14. (5-(Furan-2-yl)-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (46n)

(5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (**44b**) (122.8 mg, 0.25 mmol), 2-furanylboronic acid (39.2 mg, 0.35 mmol), $KHCO_3$ (35.0 mg, 0.35 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were employed to afford 80.0 mg (75%) of the indicated product as a brownish red solid (R_f = 0.39 in 9:1 hexane/ethyl acetate; mp 150-151 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (s, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 2H), 7.44 (d, *J* = 1.4 Hz, 1H), 7.37 (t, *J* = 7.3 Hz, 2H), 7.30–7.16 (m, 4H), 7.07 (br s, 1H), 6.79 (d, *J* = 8.5 Hz, 3H), 6.22 (dd, *J* = 3.4, 1.7 Hz, 1H), 5.32 (d, *J* = 3.4 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.0 (CO), 160.1 (CH), 153.7 (C), 149.5 (C), 147.6 (CH), 144.6 (C), 142.6 (CH), 137.7 (C), 136.1 (CH), 134.1 (C), 133.3 (CH), 131.6 (C), 130.7 (CH), 129.3 (CH), 128.5 (C), 128.48 (C), 128.4 (CH), 128.3 (CH), 124.0 (C), 113.9 (CH), 111.7 (CH), 111.2 (CH), 55.3 (CH_3); IR (neat) 2918, 1662, 1607, 1579, 1513, 1489, 1437, 1306, 1249, 1226, 1174, 1026, 956, 898, 839, 747, 698, 688, 574 cm^{-1}; MS (ESI, m/z): 432.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{29}H_{22}NO_3$: 432.1594 $[M+H]^+$, found: 432.1596.

3.9.15. (2-(4-Methoxyphenyl)-4-phenyl-5-(thiophen-3-yl)pyridin-3-yl)(phenyl)methanone (46o)

(5-Iodo-2-(4-methoxyphenyl)-4-phenylpyridin-3-yl)(phenyl)methanone (**44b**) (147.4 mg, 0.30 mmol), 3-thienylboronic acid (53.7 mg, 0.42 mmol), $KHCO_3$ (42.0 mg, 0.42 mmol) and $PdCl_2(PPh_3)_2$ (14.0 mg, 0.02 mmol) were employed to afford 99.0 mg

(84%) of the indicated product as a beige solid (R_f = 0.35 in 9:1 hexane/ethyl acetate; mp 197-198 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.56–7.48 (m, 4H), 7.37–7.30 (m, 1H), 7.23–7.16 (m, 3H), 7.15–7.07 (m, 3H), 7.03 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.00–6.87 (m, 1H), 6.85–6.74 (m, 3H), 6.71 (dd, *J* = 5.0, 1.3 Hz, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3 (CO), 160.1 (C), 154.7 (C), 150.2 (CH), 146.8 (C), 137.8 (C), 137.3 (CH), 136.2 (CH), 134.2 (C), 133.2 (CH), 131.8 (C), 130.7 (CH), 129.7 (C), 129.4 (CH), 128.6 (CH), 128.3 (CH), 128.2 (C), 128.0 (CH), 127.9 (C), 125.4 (CH), 124.4 (CH), 113.9 (CH), 55.3 (CH_3); IR (neat) 3050, 1667, 1605, 1575, 1511, 1438, 1375, 1294, 1250, 1227, 1177, 1028, 971, 895, 837, 771, 699, 563 cm^{-1}; MS (ESI, m/z): 448.14 [M+H]$^+$; HRMS (ESI) calcd. for $C_{29}H_{22}NO_2S$: 448.1366 [M+H]$^+$, found: 448.1359.

3.9.16. (4,5-Diphenyl-2-(thiophen-3-yl)pyridin-3-yl)(phenyl)methanone (46p)

5-Iodo-4-phenyl-2-(thiophen-3-yl)pyridin-3-yl)(phenyl)methanone (**44c**) (107.5 mg, 0.23 mmol), phenylboronic acid (39.0 mg, 0.32 mmol), $KHCO_3$ (32.0 mg, 0.32 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were employed to afford 74.0 mg (77%) of the indicated product as a yellow solid (R_f = 0.37 in 9:1 hexane/ethyl acetate; mp 172-174 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.50–7.46 (m, 2H), 7.45 (dd, *J* = 3.0, 1.3 Hz, 1H), 7.34 (dd, *J*= 5.0, 1.2 Hz, 1H), 7.30 (t, *J*= 7.4 Hz, 1H), 7.19–7.10 (m, 7H), 7.06 (m, 2H), 7.00–6.43 (m, 4H);^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7 (CO), 150.8 (CH), 150.2 (C), 146.9 (C), 140.4 (C), 137.6 (C), 137.0 (C), 135.9 (CH), 135.0 (C), 133.8 (C), 133.4 (CH), 130.0 (CH), 129.4 (CH), 128.6 (CH), 128.5 (CH), 128.3 (CH), 127.9 (C), 127.8 (CH) 127.5 (CH), 126.5 (CH), 125.7 (CH) (Two C peaks overlap with each other); IR (neat) 2920, 1672, 1594, 1556, 1528, 1438, 1316, 1220, 1174, 1023, 949, 813, 760, 698, 571, 520cm^{-1}; MS (ESI, m/z): 418.13 [M+H]$^+$;HRMS (ESI) calcd. for $C_{28}H_{20}NOS$: 418.1260 [M+H]$^+$, found: 418.1262.

3.9.17. (5-(4-Ethylphenyl)-4-phenyl-2-(thiophen-3-yl)pyridin-3-yl)(phenyl)methanone (46q)

(5-Iodo-4-phenyl-2-(thiophen-3-yl)pyridin-3-yl)(phenyl)methanone (**44c**) (112.2 mg, 0.24 mmol), 4-ethylphenylboronic acid (51.0 mg, 0.34 mmol), $KHCO_3$ (34.0 mg, 0.34 mmol) and $PdCl_2(PPh_3)_2$ (7.0 mg, 0.01 mmol) were employed to afford 84.0 mg (78%) of the indicated product as a yellow solid (R_f = 0.25 in 9:1 hexane/ethyl acetate; mp 145-147 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.60–7.56 (m, 2H), 7.55 (dd, *J*= 2.9, 1.2 Hz, 1H), 7.43 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.39 (d, *J*= 7.4 Hz, 1H), 7.30–7.19 (m, 4H), 7.11–6.83 (m, 7H), 6.75 (d, *J* = 8.4 Hz, 1H), 2.61 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J*= 7.6 Hz, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8 (CO), 150.9 (CH), 149.9 (C), 146.8 (C) 143.6 (C), 140.4 (C), 137.6 (CH), 136.0 (CH), 135.0 (C), 134.2 (C), 133.8 (C), 133.4 (CH), 129.9 (CH), 129.4 (CH), 128.9 (C), 128.6 (CH), 128.4 (CH), 127.8 (CH), 127.76 (CH), 126.5 (CH), 125.7 (CH), 115.3 (C), 28.6 (CH_2), 15.4 (CH_3);IR (neat) 2966, 1670, 1593, 1514, 1442, 1314, 1206, 1171, 1020, 930, 834, 808, 761, 701, 680, 606, 545 cm^{-1}; MS (ESI, m/z): 446.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{30}H_{24}NOS$:446.1573 $[M+H]^+$, found: 446.1567.

3.9.18. (4'-(Cyclopentylmethyl)-[1,1':2',1''-terphenyl]-3'-yl)(phenyl)methanone (46r)

(3-(Cyclopentylmethyl)-6-iodo-[1,1'-biphenyl]-2-yl)(phenyl)methanone (**44d**) (229.0 mg, 0.49 mmol), phenylboronic acid(84.1 mg, 0.69 mmol), $KHCO_3$ (69.0 mg, 0.69 mmol) and $PdCl_2(PPh_3)_2$ (21.0 mg, 0.03 mmol) were employed to afford 164.0 mg (80%) of the indicated product as a brownish white solid (R_f = 0.34 in 9:1 hexane/ethyl acetate; mp 117-118 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.59–7.54 (m, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.27 (t, *J* = 7.7 Hz, 2H), 7.23–7.16 (m, 3H), 7.15–7.10 (m, 3H), 6.99 (t, *J* = 6.4 Hz, 2H), 6.94–6.52 (m, 3H), 2.88–2.53 (m, 2H), 2.45 (septet, *J* = 7.7 Hz, 1H), 1.82–1.35 (m, 6H), 1.33–1.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9 (CO), 157.4 (CH), 150.3 (CH), 145.8 (C), 137.5 (C), 137.1 (C), 136.1 (CH), 134.6 (C), 133.8 (C), 133.4 (CH), 129.9 (CH), 129.3 (CH), 128.4 (CH), 128.2 (CH), 127.7 (C), 127.72 (C), 127.6 (CH), 127.2 (CH), 41.7 (CH_2), 40.1 (CH), 32.6 (CH_2), 24.9 (CH_2); IR (neat) 2943, 1667, 1578, 1559, 1439, 1316, 1273, 1213, 1027, 951, 758, 699, 568 cm^{-1}; MS (ESI, m/z): 418.22 $[M+H]^+$; HRMS (ESI) calcd. for $C_{30}H_{28}NO$: 418.2165 $[M+H]^+$, found: 418.2162.

3.10. General Procedure for the Synthesis of 2-Ferrocenyl-Substituted Pyridines 49

To a stirred solution of ferrocenyl-substituted α,β-alkynic ketone **26** (0.25 mmol) and propargylamine (**48**) (0.30 mmol) in DMF (3 mL) under air was added CuCl (0.25 mmol) and the resulting solution was allowed to stir at 110 °C for approximately 2 h (Note that the progress of the reaction was monitored by routine TLC for the completion of the reaction). When the reaction was over, a saturated NaCl solution (10 mL) and ethyl acetate (10 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding 2-ferrocenyl-substituted pyridines **49a-f**.

3.10.1. (2-Ferrocenylpyridin-3-yl)(phenyl)methanone (49a)

3-Ferrocenyl-1-phenylprop-2-yn-1-one (**26t**) (103.4 mg, 0.33 mmol), propargylamine (21.7 mg, 0.39 mmol) and CuCl (32.7 mg, 0.33 mmol) were employed to afford 93.3 mg (77%) of indicated product as an orangish brown solid (R_f = 0.55 in 4:1 hexane/ethyl acetate; mp 125-126 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (dd, *J* = 4.7, 1.7 Hz, 1H), 7.79–7.76 (m, 2H), 7.56–7.50 (m, 2H), 7.42-7.38 (m, 2H), 7.19 (dd, *J* = 7.7, 4.8 Hz, 1H), 4.66 (t, *J* = 1.9 Hz, 2H), 4.21 (t, *J* = 1.9 Hz, 2H), 4.02 (s, 5H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6 (CO), 156.6 (C), 150.2 (CH), 136.9 (C), 135.5 (CH), 133.8 (CH), 133.1 (C), 130.1 (CH), 128.8 (CH), 119.7 (CH), 83.1 (C), 70.0 (CH), 69.9 (CH), 69.6 (CH); IR (neat) 2919, 2173, 1735, 1665, 1623, 1578, 1482, 1411, 1272, 1202, 1135, 1032, 997, 926, 823, 776, 712, 671, 508 cm^{-1}; MS (ESI, m/z): 367.07 [M]$^+$; HRMS (ESI) calcd. for $C_{22}H_{17}ONFe$: 367.0660 [M]$^+$, found: 367.0657.

3.10.2. (2-Ferrocenylpyridin-3-yl)(p-tolyl)methanone (49b)

3-Ferrocenyl-1-(p-tolyl)prop-2-yn-1-one (**26u**) (112.4 mg, 0.34 mmol), propargylamine (22.6 mg, 0.41 mmol) and CuCl (33.7 mg, 0.34 mmol) were employed to afford 89.4 mg (69%) of indicated product as a dark brown solid (R_f = 0.47 in 4:1 hexane/ethyl acetate; mp 122-123 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (dd, J = 4.6, 1.4 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.49 (dd, J = 7.6, 1.4 Hz, 1H), 7.23–7.15 (m, 3H), 4.68 (t, J = 1.8 Hz, 2H), 4.22 (t, J = 1.8 Hz, 2H), 4.01 (s, 5H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3 (CO), 156.5 (C), 150.1 (CH), 145.0 (C), 135.6 (CH), 134.5 (C), 133.4 (C), 130.3 (CH), 129.6 (CH), 119.7 (CH), 83.0 (C), 70.1 (CH), 69.9 (CH), 69.7 (CH), 22.0 (CH_3); IR (neat) 3032, 2172, 1660, 1598, 1576, 1557, 1411, 1278, 1241, 1203, 1150, 1119, 1059, 1033, 997, 926, 839, 815, 776, 756, 672, 608, 524 cm^{-1}; MS (ESI, m/z): 381.08 [M]$^+$; HRMS (ESI) calcd. for $C_{23}H_{19}ONFe$: 381.0816 [M]$^+$, found: 381.0808.

3.10.3. (2-Ferrocenylpyridin-3-yl)(4-methoxyphenyl)methanone (49c)

3-Ferrocenyl-1-(4-methoxyphenyl)prop-2-yn-1-one (**26v**) (108.7 mg, 0.32 mmol), propargylamine (20.9 mg, 0.38 mmol) and CuCl (31.3 mg, 0.32 mmol) were employed to afford 87.9 mg (70%) of indicated product as an orangish brown oil (R_f = 0.41 in 4:1 hexane/ethyl acetate): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (pseudo d, J = 3.2 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 7.3 Hz, 1H), 7.17 (dd, J = 7.0, 4.4 Hz, 1H), 6.88 (d, J = 8.6 Hz, 2H), 4.70 (br s, 2H), 4.23 (br s, 2H), 4.02 (s, 5H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1 (CO), 164.1 (C), 156.2 (C) , 150.0 (CH), 135.4

(CH), 133.4 (C), 132.5 (CH), 130.0 (C), 119.6 (CH), 114.0 (CH), 82.9 (C), 70.0 (CH), 69.9 (CH), 69.6 (CH), 55.6 (CH_3); IR (neat) 2931, 1734, 1657, 1593, 1508, 1410, 1258, 1175, 1148, 1106, 1083, 1028, 927, 844, 816, 781, 765, 608, 514 cm^{-1}; MS (ESI, m/z): 397.08 $[M]^+$; HRMS (ESI) calcd. for $C_{23}H_{19}O_2NFe$: 397.0765 $[M]^+$, found: 397.0761.

3.10.4. (4-Chlorophenyl)(2-ferrocenylpyridin-3-yl)methanone (49d)

1-(4-Chlorophenyl)-3-ferrocenylprop-2-yn-1-one (**26w**) (103.4 mg, 0.30 mmol), propargylamine (19.6 mg, 0.36 mmol) and CuCl (29.4 mg, 0.30 mmol) were employed to afford 96.5 mg (81%) of indicated product as a reddish violet solid ($R_f = 0.58$ in 4:1 hexane/ethyl acetate; mp 153-154 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.69 (dd, J = 4.7, 1.8 Hz, 1H), 7.68–7.64 (m, 2H), 7.51 (dd, J = 7.7, 1.8 Hz, 1H), 7.35–7.31 (m, 2H), 7.19 (dd, J = 7.7, 4.8 Hz, 1H), 4.61 (t, J = 1.9 Hz, 2H), 4.21 (t, J = 1.9 Hz, 2H), 4.02 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.4 (CO), 156.7 (C), 150.4 (CH), 140.2 (C), 135.6 (CH), 135.2 (C), 132.6 (C), 131.3 (CH), 129.1 (CH), 119.8 (CH), 83.2 (C), 70.0 (CH), 69.9 (CH), 69.6 (CH); IR (neat) 3029, 2174, 1657, 1580, 1556, 1557, 1412, 1276, 1240, 1083, 998, 924, 893, 839, 812, 778, 756, 673, 630, 513 cm^{-1}; MS (ESI, m/z): 401.03 $[M]^+$; HRMS (ESI) calcd. for $C_{22}H_{16}ONClFe$: 401.0270 $[M]^+$, found: 401.0264.

3.10.5. (2-Bromophenyl)(2-ferrocenylpyridin-3-yl)methanone (49e)

1-(2-Bromophenyl)-3-ferrocenylprop-2-yn-1-one (**26x**) (98.2 mg, 0.25 mmol), propargylamine (16.5 mg, 0.30 mmol) and CuCl (24.7 mg, 0.25 mmol) were employed to afford 100.3 mg (90%) of indicated product as an orange-red oil ($R_f = 0.56$ in 4:1 hexane/ethyl acetate): ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (dd, J = 4.8, 1.9 Hz, 1H), 7.66 (dd, J = 7.8, 1.9 Hz, 1H), 7.58 (dd, J = 7.5, 1.7 Hz, 1H), 7.39–7.15 (m, 4H), 4.69 (pseudo t, J = 1.8 Hz, 2H), 4.22 (pseudo t, J = 1.8 Hz, 2H), 4.08 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.3 (CO), 158.3 (C), 150.8 (CH), 138.3 (C), 136.9 (CH), 134.6

(CH), 133.4 (C), 132.9 (CH), 132.1 (CH), 127.1 (CH), 121.8 (C), 119.9 (CH), 84.1 (C), 70.2 (CH), 69.9 (CH), 69.6 (CH); IR (neat) 2980, 1734, 1668, 1577, 1554, 1478, 1411, 1284, 1238, 1157, 1105, 1044, 1029, 1004, 925, 892, 817, 779, 740, 679, 631, 520 cm^{-1}; MS (ESI, m/z): 444.98 [M]$^+$; HRMS (ESI) calcd. for $C_{22}H_{16}ONBrFe$: 444.9766 [M]$^+$, found: 444.9767.

3.10.6. (2-Ferrocenylpyridin-3-yl)(4-nitrophenyl)methanone (49f)

3-Ferrocenyl-1-(4-nitrophenyl)prop-2-yn-1-one (**26y**) (101.4 mg, 0.28 mmol), propargylamine (18.6 mg, 0.34 mmol) and CuCl (27.9 mg, 0.28 mmol) were employed to afford 82.6 mg (71%) of indicated product as a dark brown solid (R_f = 0.52 in 4:1 hexane/ethyl acetate; mp 173-174 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.7, 1.7 Hz, 1H), 8.16 (d, *J* = 8.9 Hz, 2H), 7.83 (d, *J* = 8.9 Hz, 2H), 7.65 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.28 (dd, *J* = 7.6, 4.9 Hz, 1H), 4.55 (t, *J* = 1.8 Hz, 2H), 4.19 (t, *J* = 1.8 Hz, 2H), 4.06 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0 (CO), 157.4 (C), 151.2 (CH), 150.4 (C), 141.4 (C), 136.2 (CH), 132.1 (C), 130.6 (CH), 123.8 (CH), 120.2 (CH), 83.9 (C), 70.1 (CH), 70.0 (CH), 69.9 (CH); IR (neat) 2978, 1677, 1599, 1578, 1520, 1477, 1410, 1345, 1269, 1237, 1146, 1104, 1083, 1031, 999, 925, 867, 809, 782, 714, 692, 639, 595 cm^{-1}; MS (ESI, m/z): 412.05 [M]$^+$; HRMS (ESI) calcd. for $C_{22}H_{16}O_3N_2Fe$: 412.0511 [M]$^+$, found: 412.0516.

3.11. General Procedure for the Synthesis of Spiro-2*H*-Pyrroles 51 and 2*H*-Pyrroles 72

To a stirred solution of *N*-propargylic β-enaminones **50** and **61** (0.30 mmol) in acetonitrile (3 mL) under argon was added Cs_2CO_3 (0.90 mmol) and the resulting solution was allowed to stir at 82 °C for 1-2 h (Note that the progress of the reaction was monitored by routine TLC for the completion of the reaction). When the reaction was over, a saturated NH_4Cl solution (10 mL) and ethyl acetate (10 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding spiro-2*H*-pyrroles **51a-q** and 2*H*-pyrroles **72a-c**.

3.11.1. (4-Methyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)(phenyl)methanone (51a)

3-((1-Ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**50a**) (123.8 mg, 0.38 mmol) and Cs_2CO_3 (371.4 mg, 1.14 mmol) were employed to afford 118.9 mg (95%) of indicated product as an orangish-red solid (R_f = 0.64 in 4:1 hexane/ethyl acetate; mp 118.4-120.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.78 (m, 2H), 7.58–7.55 (m, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.26–7.19 (m, 3H), 2.15 (qt, *J* = 13.2, 3.4 Hz, 2H), 1.97 (d, *J* = 13.6 Hz, 1H), 1.94 (s, 3H), 1.86–1.74 (m, 4H), 1.43 (tt, *J* = 13.2, 3.4 Hz, 1H), 1.33 (d, *J* = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0 (CO), 174.2 (C), 168.2 (C), 137.5 (C), 134.7 (C), 134.3 (C), 133.6 (CH), 129.5 (CH), 129.4 (CH), 128.7 (CH), 128.3 (CH), 82.5 (C), 33.4 (CH_2), 25.9 (CH_2), 23.6 (CH_2), 12.5 (CH_3) (Two CH peaks overlap with each other); IR (neat) 2932, 2856, 1645, 1619, 1577, 1444, 1341, 1261, 1227, 1158, 1072, 974, 873, 739, 695 cm^{-1}; MS (ESI, m/z): 330.19 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{24}NO$: 330.1852 $[M+H]^+$, found: 330.1861.

3.11.2. (4-Methyl-2-(p-tolyl)-1-azaspiro[4.5]deca-1,3-dien-3-yl)(phenyl)methanone (51b)

3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(p-tolyl)prop-2-en-1-one (**50b**) (126.4 mg, 0.37 mmol) and Cs_2CO_3 (368.1 mg, 1.11 mmol) were employed to afford 119.5 mg (94%) of indicated product as a light orange oil (R_f = 0.53 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 2.26 (s, 3H), 2.15 (qt, *J* = 13.2, 3.4 Hz, 2H), 1.97 (d, *J* = 12.8 Hz, 1H), 1.92 (s, 3H), 1.85–1.73 (m, 4H), 1.42 (tt, *J* = 13.2, 3.4 Hz, 1H), 1.33 (d, *J* = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.3 (CO), 173.8 (C), 168.0 (C), 139.6 (C), 137.5 (C), 134.4 (C), 133.6 (CH), 131.9 (C), 129.5 (CH), 129.0 (CH), 128.8 (CH), 128.2 (CH), 82.3 (C), 33.4 (CH_2), 25.9 (CH_2), 23.6 (CH_2), 21.4 (CH_3), 12.5 (CH_3); IR (neat) 2926, 2852, 1659, 1616, 1508, 1446, 1328, 1258, 1233, 1181, 966, 898, 823, 733, 688 cm^{-1}; MS (ESI, m/z): 344.20 [M+H]$^+$; HRMS (ESI) calcd. for $C_{24}H_{26}NO$: 344.2009 [M+H]$^+$, found: 344.2020.

3.11.3. (2-(4-Methoxyphenyl)-4-methyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)(phenyl)methanone (51c)

3-((1-Ethynylcyclohexyl)amino)-3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (**50c**) (104.2 mg, 0.29 mmol) and Cs_2CO_3 (283.5 mg, 0.87 mmol) were employed to afford 94.9 mg (91%) of indicated product as a reddish-orange oil (R_f = 0.57 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.56–7.48 (m, 3H), 7.38 (t, *J* = 7.7 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 3.72 (s, 3H), 2.14 (qt, *J* = 13.2, 3.4 Hz, 2H), 1.96 (d, *J*= 12.7 Hz, 1H), 1.91 (s, 3H), 1.85–1.73 (m, 4H), 1.42 (tt, *J* = 13.2, 3.4 Hz, 1H), 1.32 (d, *J* = 12.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4 (CO), 173.7 (C), 167.4 (C), 160.8 (C), 137.5 (C), 134.4 (C), 133.7 (CH), 129.9 (CH), 129.5 (CH), 128.8 (CH), 127.3 (C), 113.7 (CH), 82.1 (C), 55.3 (CH_3), 33.5 (CH_2), 26.0 (CH_2), 23.6 (CH_2), 12.5 (CH_3); IR (neat) 2929, 2850, 1659, 1607, 1504, 1446, 1303, 1248, 1174, 1026, 965, 898, 835, 732, 688 cm^{-1}; MS (ESI, m/z): 360.20 [M+H]$^+$; HRMS (ESI) calcd. for $C_{24}H_{26}NO_2$: 360.1959 [M+H]$^+$, found: 360.1967.

3.11.4. (4-Methyl-2-(thiophen-3-yl)-1-azaspiro[4.5]deca-1,3-dien-3-yl)(phenyl)methanone (51d)

3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(thiophen-3-yl)prop-2-en-1-one (**50d**) (138.0 mg, 0.41 mmol) and Cs$_2$CO$_3$ (402.1 mg, 1.23 mmol) were employed to afford 124.2 mg (90%) of indicated product as an orangish-brown solid (R_f = 0.62 in 4:1 hexane/ethyl acetate; mp 120.2-122.6 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.87–7.83 (m, 2H), 7.54 (tt, J = 7.4, 1.4 Hz, 1H), 7.48–7.44 (m, 2H), 7.44–7.39 (m, 2H), 7.17 (dd, J = 5.0, 3.0 Hz, 1H), 2.12 (qt, J = 13.2, 3.4 Hz, 2H), 1.95 (d, J = 12.8 Hz, 1H), 1.88 (s, 3H), 1.83–1.71 (m, 4H), 1.41 (tt, J = 13.2, 3.4 Hz, 1H), 1.31 (d, J = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 195.5 (CO), 173.2 (C), 162.4 (C), 137.4 (C), 136.7 (C), 134.1 (C), 133.8 (CH), 129.5 (CH), 128.8 (CH), 127.8 (CH), 126.7 (CH), 125.4 (CH), 82.1 (C), 33.4 (CH$_2$), 25.9 (CH$_2$), 23.5 (CH$_2$), 12.4 (CH$_3$); IR (neat) 2926, 2853, 1653, 1623, 1577, 1445, 1330, 1258, 1197, 1070, 910, 874, 804, 742, 692 cm^{-1}; MS (ESI, m/z): 336.14 [M+H]$^+$; HRMS (ESI) calcd. for C$_{21}$H$_{22}$NOS: 336.1417 [M+H]$^+$, found: 336.1413.

3.11.5. (2-(3-Fluorophenyl)-4-methyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)(phenyl)methanone (51e)

3-((1-Ethynylcyclohexyl)amino)-3-(3-fluorophenyl)-1-phenylprop-2-en-1-one (**50e**) (122.0 mg, 0.35 mmol) and Cs$_2$CO$_3$ (343.2 mg, 1.05 mmol) were employed to afford 108.6 mg (89%) of indicated product as an orange solid (R_f = 0.50 in 4:1 hexane/ethyl acetate; mp 131.1-133.9 °C). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.83–7.80 (m, 2H), 7.55 (tt, J = 7.4, 1.5 Hz, 1H), 7.44–7.38 (m, 3H), 7.29–7.26 (m, 1H), 7.19 (td, J = 7.9, 5.7 Hz, 1H), 6.98 (tdd, J = 8.4, 2.6, 1.0 Hz, 1H), 2.16 (qt, J = 13.3, 3.5 Hz, 2H), 2.00 (d, J = 9.6 Hz, 1H), 1.96 (s, 3H), 1.88–1.77 (m, 4H), 1.44 (tt, J = 13.3, 3.5 Hz, 1H), 1.34 (d, J = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.8 (CO), 174.9 (C), 167.3 (d, $^4J_{CF}$ = 2.3 Hz, C), 162.7 (d, $^1J_{CF}$ = 246.0 Hz, C), 137.4 (C), 136.8 (d, $^3J_{CF}$ = 7.5 Hz, C), 134.0 (C), 133.8 (CH), 129.8 (d, $^3J_{CF}$ = 8.2 Hz, CH), 129.5 (CH), 128.9 (CH), 124.1 (d, $^4J_{CF}$ = 2.8 Hz, CH), 116.6 (d, $^2J_{CF}$ = 21.3 Hz, CH), 115.3 (d, $^2J_{CF}$ = 22.7 Hz, CH), 82.7 (C), 33.4 (CH_2), 25.9 (CH_2), 23.5 (CH_2), 12.7 (CH_3); IR (neat) 2933, 2855, 1660, 1582, 1442, 1309, 1260, 1206, 1158, 1074, 912, 854, 829, 787, 684 cm^{-1}; MS (ESI, m/z): 348.18 $[M+H]^+$; HRMS (ESI) calcd. for$C_{23}H_{23}FNO$: 348.1758 $[M+H]^+$, found: 348.1763.

3.11.6. (2-(4-Chlorophenyl)-4-methyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)(phenyl)methanone (51f)

3-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one (**50f**) (138.6 mg, 0.38 mmol) and Cs_2CO_3 (371.4 mg, 1.14 mmol) were employed to afford 126.1 mg (91%) of indicated product as a reddish-orange oil (R_f = 0.69 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.2, 1.1 Hz, 2H), 7.55–7.49 (m, 3H), 7.39 (t, J = 7.7 Hz, 2H), 7.21 (d, J = 8.5 Hz, 2H), 2.12 (qt, J = 13.2, 3.4 Hz, 2H), 1.96 (d, J = 12.0 Hz, 1H), 1.93 (s, 3H), 1.86–1.74 (m, 4H), 1.42 (tt, J = 13.2, 3.4 Hz, 1H), 1.31 (d, J = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9 (CO), 174.8 (C), 167.2 (C), 137.4 (C), 135.7 (C), 134.0 (C), 133.9 (CH), 133.1 (C), 129.7 (CH), 129.5 (CH), 128.9 (CH), 128.5 (CH), 82.7 (C), 33.4 (CH_2), 25.9 (CH_2), 23.6 (CH_2), 12.7 (CH_3); IR (neat) 2929, 2852, 1736, 1658, 1596, 1401, 1313, 1233, 1159, 1092, 1014, 965, 836, 746, 688 cm^{-1}; MS (ESI, m/z): 364.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{23}ClNO$: 364.1463 $[M+H]^+$, found: 364.1452.

3.11.7. (2-(4-Bromophenyl)-4-methyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)(phenyl)methanone (51g)

3-(4-Bromophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one (**50g**) (155.0 mg, 0.38 mmol) and Cs_2CO_3 (371.4 mg, 1.14 mmol) were employed to afford 128.7 mg (83%) of indicated product as an orangish-brown oil (R_f = 0.47 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.76 (m, 2H), 7.53 (t, J = 7.4 Hz, 1H), 7.46 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 7.39–7.35 (m, 2H), 2.19–2.07 (m, 2H), 1.96 (d, *J* = 13.3 Hz, 1H), 1.93 (s, 3H), 1.85–1.74 (m, 4H), 1.41 (tt, *J* = 13.2, 3.4 Hz, 1H), 1.32 (d, *J* = 12.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8 (CO), 174.9 (C), 167.5 (C), 137.3 (C), 133.9 (C), 133.8 (C), 131.5 (CH), 130.0 (CH), 129.5 (CH), 128.9 (CH), 124.3 (CH), 82.7 (C), 33.3 (CH_2), 25.8 (CH_2), 23.5 (CH_2), 12.7 (CH_3) (Two CH peak overlap with each other); IR (neat) 2928, 2852, 1664, 1649, 1595, 1446, 1342, 1231, 1175, 1009, 876, 831, 743, 695 cm^{-1}; MS (ESI, m/z): 408.10 [M+H]$^+$; HRMS (ESI) calcd. for $C_{23}H_{23}BrNO$: 408.0958 [M+H]$^+$, found: 408.0953.

3.11.8. (4-Methyl-2-(4-nitrophenyl)-1-azaspiro[4.5]deca-1,3-dien-3-yl)(phenyl)methanone (51h)

3-((1-Ethynylcyclohexyl)amino)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (**50h**) (103.4 mg, 0.28 mmol) and Cs_2CO_3 (270.4 mg, 0.83 mmol) were employed to afford 91.0 mg (88%) of indicated product as a reddish-brown oil (R_f = 0.42 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.6 Hz, 2H), 7.81–7.76 (m, 2H), 7.73 (d, *J* = 8.6 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 2.11–2.05 (m, 2H), 1.98 (d, *J* = 11.5 Hz, 1H), 1.95 (s, 3H), 1.88–1.78 (m, 4H), 1.44 (tt, *J* = 13.2, 3.3 Hz, 1H), 1.33 (d, *J* = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.3 (CO), 176.0 (C), 166.8 (C), 148.4 (C), 140.8 (C), 137.3 (C), 134.1 (CH), 133.6 (C), 129.5 (CH), 129.3 (CH), 129.0 (CH), 123.5 (CH), 83.4 (C), 33.4 (CH_2), 25.8 (CH_2), 23.5 (CH_2), 12.9 (CH_3); IR (neat) 2930, 2852, 1656, 1597, 1518, 1446, 1343, 1232, 1108, 1045, 974, 850, 735, 690 cm^{-1}; MS (ESI, m/z): 375.17 [M+H]$^+$; HRMS (ESI) calcd. for $C_{23}H_{23}N_2O_3$: 375.1703 [M+H]$^+$, found: 375.1694.

3.11.9. (2-Butyl-4-methyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)(phenyl)methanone (51i)

3-((1-Ethynylcyclohexyl)amino)-1-phenylhept-2-en-1-one (**50i**) (128.3 mg, 0.41 mmol) and Cs_2CO_3 (400.8 mg, 1.23 mmol) were employed to afford 118.0 mg (92%)

of indicated product as a reddish-brown oil (R_f = 0.53 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.72 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 2.50 (t, *J* = 7.8 Hz, 2H), 1.98 (qt, *J* = 13.2, 3.5 Hz, 2H), 1.87 (d, *J* = 13.0 Hz, 1H), 1.75 (s, 3H), 1.74–1.69 (m, 2H), 1.63 (td, *J* = 13.0, 3.9 Hz, 2H), 1.43–1.35 (m, 2H), 1.34–1.26 (m, 1H), 1.21 (q, *J* = 7.4 Hz, 2H), 1.13 (d, *J* = 12.2 Hz, 2H), 0.74 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8 (CO), 173.5 (C), 171.6 (C), 138.0 (C), 134.1 (C), 133.5 (CH), 129.2 (CH), 128.8 (CH), 81.5 (C), 33.2 (CH_2), 31.5 (CH_2), 29.6 (CH_2), 25.7 (CH_2), 23.4 (CH_2), 22.4 (CH_2), 13.8 (CH_3), 12.8 (CH_3); IR (neat) 2928, 2857, 1655, 1597, 1447, 1343, 1231, 1175, 1093, 898, 850, 733, 693 cm^{-1}; MS (ESI, m/z): 310.22 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{28}NO$: 310.2165 $[M+H]^+$, found: 310.2157.

3.11.10. (4-Methyl-2-pentyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)(phenyl)methanone (51j)

3-((1-Ethynylcyclohexyl)amino)-1-phenyloct-2-en-1-one (**50j**) (104.8 mg, 0.32 mmol) and Cs_2CO_3 (312.8 mg, 0.96 mmol) were employed to afford 94.3 mg (90%) of indicated product as a reddish-orange oil (R_f = 0.54 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.74 (m, 2H), 7.58 (tt, *J* = 7.4, 1.2 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 2.52 (t, *J* = 7.8 Hz, 2H), 2.02 (qt, *J* = 13.2, 3.5 Hz, 2H), 1.90 (d, *J* = 13.0 Hz, 1H), 1.79 (s, 3H), 1.77–1.72 (m, 2H), 1.66 (td, *J* = 13.0, 3.9 Hz, 2H), 1.48–1.39 (m, 2H), 1.33 (qt, *J* = 13.2, 3.7 Hz, 1H), 1.24–1.12 (m, 6H), 0.78–0.72 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8 (CO), 173.4 (C), 171.6 (C), 138.0 (C), 134.2 (C), 133.5 (CH), 129.3 (CH), 128.8 (CH), 81.6 (C), 33.2 (CH_2), 31.7 (CH_2), 31.5 (CH_2), 27.2 (CH_2), 25.7 (CH_2), 23.4 (CH_2), 22.3 (CH_2), 13.9 (CH_3), 12.8 (CH_3); IR (neat) 2928, 2855, 1657, 1595, 1449, 1341, 1235, 1178, 1097, 896, 851, 736, 695 cm^{-1}; MS (ESI, m/z): 324.23 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{30}NO$: 324.2322 $[M+H]^+$, found: 324.2316.

3.11.11. (4-Methoxyphenyl)(4-methyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)methanone (51k)

3-((1-Ethynylcyclohexyl)amino)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (**50k**) (118.2 mg, 0.33 mmol) and Cs_2CO_3 (322.6 mg, 0.99 mmol) were employed to afford 107.6 mg (91%) of indicated product as a light yellow solid (R_f = 0.49 in 4:1 hexane/ethyl acetate; mp 138.2-140.8 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.9 Hz, 2H), 7.62 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.31–7.23 (m, 3H), 6.88 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H), 2.24–2.11 (m, 2H), 1.98 (d, *J* = 12.1 Hz, 1H), 1.94 (s, 3H), 1.86–1.75 (m, 4H), 1.43 (tt, *J* = 13.2, 3.3 Hz, 1H), 1.35 (d, *J* = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6 (CO), 173.1 (C), 168.4 (C), 164.0 (C), 134.5 (C), 134.4 (C), 131.9 (CH), 130.6 (C), 129.7 (CH), 128.3 (CH), 128.2 (CH), 114.0 (CH), 82.2 (C), 55.5 (CH_3), 33.4 (CH_2), 25.9 (CH_2), 23.6 (CH_2), 12.5 (CH_3); IR (neat) 2928, 2849, 1650, 1594, 1571, 1445, 1342, 1257, 1237, 1174, 1144, 1027, 882, 780, 699 cm^{-1}; MS (ESI, m/z): 360.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{26}NO_2$: 360.1958 $[M+H]^+$, found: 360.1949.

3.11.12. (4-Methoxyphenyl)(4-methyl-2-(thiophen-3-yl)-1-azaspiro[4.5]deca-1,3-dien-3-yl)methanone (51l)

3-((1-Ethynylcyclohexyl)amino)-1-(4-methoxyphenyl)-3-(thiophen-3-yl)prop-2-en-1-one (**50l**) (118.2 mg, 0.33 mmol) and Cs_2CO_3 (322.6 mg, 0.99 mmol) were employed to afford 96.9 mg (82%) of indicated product as a light brown solid (R_f = 0.57 in 4:1 hexane/ethyl acetate; mp 119.4-121.8 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.9 Hz, 2H), 7.48 (d, *J* = 4.5 Hz, 2H), 7.16 (dd, *J* = 4.5, 3.4 Hz, 1H), 6.90 (d, *J* = 8.9 Hz, 2H), 3.84 (s, 3H), 2.12 (qt, *J* = 13.2, 3.5 Hz, 2H), 1.94 (d, *J* = 12.8 Hz, 1H), 1.88 (s, 3H), 1.82–1.71 (m, 4H), 1.41 (tt, *J* = 13.2, 3.5 Hz, 1H), 1.30 (d, *J* = 12.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2 (CO), 172.1 (C), 164.3 (C), 162.5 (C), 136.9 (C), 134.4 (C), 132.0 (CH), 130.7 (CH), 127.9 (CH), 126.9 (C), 125.3 (CH), 114.2 (CH), 82.0 (C), 55.6 (CH_3), 33.5 (CH_2), 26.0 (CH_2), 23.6 (CH_2), 12.3 (CH_3); IR (neat) 2928, 2852, 1648, 1589, 1562, 1423, 1330, 1255, 1236, 1171, 1136, 1026, 913, 850, 774, 627 cm^{-1}; MS (ESI, m/z): 366.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{24}NO_2S$: 366.1522 $[M+H]^+$, found: 366.1517.

3.11.13. (2-(3-Fluorophenyl)-4-methyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)(4-methoxyphenyl)methanone (51m)

3-((1-Ethynylcyclohexyl)amino)-3-(3-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**50m**) (136.7 mg, 0.36 mmol) and Cs_2CO_3 (351.9 mg, 1.08 mmol) were employed to afford 127.1 mg (93%) of indicated product as a light orange solid (R_f = 0.58 in 4:1 hexane/ethyl acetate; mp 98.1-100.9 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.9 Hz, 2H), 7.40 (ddd, *J* = 9.8, 2.5, 1.6 Hz, 1H), 7.29 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.17 (td, *J* = 8.0, 5.8 Hz, 1H), 6.95 (tdd, *J* = 8.5, 2.5, 0.8 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H), 2.12 (qt, *J* = 13.5, 3.5 Hz, 2H), 1.95 (d, *J* = 12.9 Hz, 1H), 1.91 (s, 3H), 1.84–1.73 (m, 4H), 1.41 (tt, *J* = 13.2, 3.4 Hz, 1H), 1.30 (d, *J* = 12.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4 (CO), 173.5 (C), 167.1 (C), 164.2 (C) 162.7 (d, $^1J_{CF}$ = 245.9 Hz, C), 137.0 (d, $^3J_{CF}$ = 7.6 Hz, C), 134.2 (C), 131.9 (CH), 130.6 (C), 129.8 (d, $^3J_{CF}$ = 8.0 Hz, CH) , 124.0 (d, $^4J_{CF}$ = 2.8 Hz, CH), 116.5 (d, $^2J_{CF}$ = 21.3 Hz, CH), 115.2 (d, $^2J_{CF}$ = 22.7 Hz, CH), 114.1 (CH), 82.5 (C), 55.6 (CH_3), 33.4 (CH_2), 25.9 (CH_2), 23.6 (CH_2), 12.5 (CH_3); IR (neat) 2931, 2852, 1649, 1593, 1571, 1487, 1343, 1257, 1171, 1028, 909, 858, 780, 682 cm^{-1}; MS (ESI, m/z): 378.19 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{25}FNO_2$: 378.1864 $[M+H]^+$, found: 378.1853.

3.11.14. (2-(4-Bromophenyl)-4-methyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)(4-methoxyphenyl)methanone (51n)

3-(4-Bromophenyl)-3-((1-ethynylcyclohexyl)amino)-1-(4-methoxyphenyl)prop-2-en-1-one (**50n**) (106.0 mg, 0.24 mmol) and Cs_2CO_3 (234.6 mg, 0.72 mmol) were employed to afford 92.2 mg (87%) of indicated product as a yellow oil (R_f = 0.52 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.9 Hz, 2H), 7.47

(d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 3.83 (s, 3H), 2.10 (qt, *J* = 13.1, 3.4 Hz, 2H), 1.95 (d, *J* = 12.7 Hz, 1H), 1.91 (s, 3H), 1.84–1.71 (m, 4H), 1.41 (tt, *J* = 13.1, 3.4 Hz, 1H), 1.29 (d, *J* = 12.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5 (CO), 173.5 (C), 167.2 (C), 164.2 (C), 134.2 (C), 133.7 (C), 131.9 (CH), 131.5 (CH), 130.5 (C), 129.9 (CH), 124.1 (C), 114.2 (CH), 82.5 (C), 55.6 (CH_3), 33.4 (CH_2), 25.9 (CH_2), 23.6 (CH_2), 12.5 (CH_3); IR (neat) 2928, 2845, 1650, 1593, 1571, 1485, 1307, 1255, 1238, 1141, 1108, 1010, 965, 864, 782, 623 cm^{-1}; MS (ESI, m/z): 438.11 [M+H]$^+$; HRMS (ESI) calcd. for $C_{24}H_{25}BrNO_2$: 438.1063 [M+H]$^+$, found: 438.1058.

3.11.15. 4-Chlorophenyl)(4-methyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)methanone (51o)

1-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-3-phenylprop-2-en-1-one (**50o**) (112.3 mg, 0.31 mmol) and Cs_2CO_3 (303.0 mg, 0.93 mmol) were employed to afford 107.8 mg (96%) of indicated product as a brown solid (R_f = 0.53 in 4:1 hexane/ethyl acetate; mp 138.0-140.2 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.5 Hz, 2H), 7.53 (dd, *J* = 7.7, 1.5 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.26–7.19 (m, 3H), 2.13 (qt, *J* = 13.2, 3.4 Hz, 2H), 1.97 (s, 1H), 1.94 (s, 3H), 1.85–1.73 (m, 4H), 1.41 (tt, *J* = 13.2, 3.4 Hz, 1H), 1.30 (d, *J* = 12.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7 (CO), 174.9 (C), 167.9 (C), 140.1 (C), 135.8 (C), 134.6 (C), 134.0 (C), 130.8 (CH), 129.7 (CH), 129.1 (CH), 128.4 (CH), 128.2 (CH), 82.6 (C), 33.4 (CH_2), 25.9 (CH_2), 23.5 (CH_2), 12.6 (CH_3); IR (neat) 2927, 2842, 1645, 1584, 1568, 1440, 1329, 1225, 1158, 1085, 974, 876, 773, 699 cm^{-1}; MS (ESI, m/z): 363.14 [M+H]$^+$; HRMS (ESI) calcd. for $C_{23}H_{23}ClNO$: 364.1463 [M+H]$^+$, found: 364.1455.

3.11.16. (4-Chlorophenyl)(4-methyl-2-(p-tolyl)-1-azaspiro[4.5]deca-1,3-dien-3-yl)methanone (51p)

1-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-3-(p-tolyl)prop-2-en-1-one (**50p**) (135.9 mg, 0.36 mmol) and Cs_2CO_3 (351.9 mg, 1.08 mmol) were employed to afford 131.8 mg (97%) of indicated product as a brownish-orange solid (R_f = 0.52 in 4:1 hexane/ethyl acetate; mp 119.5-121.2 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.6 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.04 (d, *J* = 7.9 Hz, 2H), 2.27 (s, 3H), 2.15 (qt, *J* = 13.2, 3.5 Hz, 2H), 1.96 (d, *J* = 9.9 Hz, 1H), 1.93 (s, 3H), 1.84–1.73 (m, 4H), 1.41 (tt, *J* = 13.2, 3.5 Hz, 1H), 1.30 (d, *J* = 12.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9 (CO), 174.5 (C), 167.7 (C), 140.1 (C), 139.8 (C), 135.9 (C), 134.1 (C), 131.8 (C), 130.9 (CH), 129.1 (CH), 129.0 (CH), 128.2 (CH), 82.5 (C), 33.4 (CH_2), 25.9 (CH_2), 23.6 (CH_2), 21.4 (CH_3), 12.5 (CH_3); IR (neat) 2937, 2847, 1658, 1629, 1584, 1435, 1399, 1322, 1279, 1229, 1086, 965, 889, 820, 767 cm^{-1}; MS (ESI, m/z): 378.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{25}ClNO$: 378.1619 $[M+H]^+$, found: 378.1614.

3.11.17. (4-Chlorophenyl)(2-(3-fluorophenyl)-4-methyl-1-azaspiro[4.5]deca-1,3-dien-3-yl)methanone (51q)

1-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-3-(3-fluorophenyl)prop-2-en-1-one (**50q**) (99.6 mg, 0.26 mmol) and Cs_2CO_3 (254.1 mg, 0.78 mmol) were employed to afford 94.6 mg (95%) of indicated product as an orange solid (R_f = 0.54 in 4:1 hexane/ethyl acetate; mp 107.0-109.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.6 Hz, 2H), 7.39–7.32 (m, 3H), 7.25–7.14 (m, 2H), 6.98 (ddd, *J* = 9.4, 2.5, 1.4 Hz, 1H), 2.19–2.06 (m, 2H), 1.97 (d, *J* = 9.9 Hz, 1H), 1.94 (s, 3H), 1.86–1.73 (m, 4H), 1.41 (tt, *J* = 13.2, 3.3 Hz, 1H), 1.30 (d, *J* = 12.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5 (CO), 175.5 (C), 166.9 (C), 162.7 (d, $^1J_{CF}$ = 246.9 Hz, C), 140.4 (C), 136.8 (d, $^3J_{CF}$ = 5.6 Hz, C), 135.8 (C), 133.6 (C), 130.8 (CH), 130.0 (d, $^3J_{CF}$ = 8.0 Hz, CH), 129.3 (CH), 124.0 (d, $^4J_{CF}$ = 2.8 Hz, CH), 116.8 (d, $^2J_{CF}$ = 21.4 Hz, CH), 115.3 (d, $^2J_{CF}$

= 22.3 Hz, CH), 82.9 (C), 33.4 (CH_2), 25.9 (CH_2), 23.6 (CH_2), 12.7 (CH_3); IR (neat) 2927, 2855, 1649, 1584, 1483, 1442, 1329, 1228, 1198, 1088, 908, 845, 771, 677 cm^{-1}; MS (ESI, m/z): 382.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{22}ClFNO$: 382.1369 $[M+H]^+$, found: 382.1362.

3.11.18. Phenyl(2,2,3-trimethyl-5-phenyl-2*H*-pyrrol-4-yl)methanone (72a)

3-((2-Methylbut-3-yn-2-yl)amino)-1,3-diphenylprop-2-en-1-one (**61a**) (112.6 mg, 0.39 mmol) and Cs_2CO_3 (381.2 mg, 1.17 mmol) were employed to afford 103.6 mg (92%) of indicated product as a dark red solid (R_f = 0.54 in 4:1 hexane/ethyl acetate; mp 84.6-87.8 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.81–7.77 (m, 2H), 7.55–7.51 (m, 2H), 7.49 (tt, J = 7.4, 1.4 Hz, 1H), 7.36 (t, J = 7.7 Hz, 2H), 7.25–7.18 (m, 3H), 1.94 (s, 3H), 1.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6 (CO), 173.8 (C), 168.4 (C), 137.3 (C), 134.1 (C), 133.9 (C), 133.7 (CH), 129.8 (CH), 129.4 (CH), 128.7 (CH), 128.3 (CH), 128.1 (CH), 79.4 (C), 23.3 (CH_3), 12.4 (CH_3); IR (neat) 2974, 2929, 1655, 1625, 1579, 1445, 1320, 1252, 1176, 1073, 914, 880, 747 cm^{-1}; MS (ESI, m/z): 290.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{20}H_{20}NO$: 290.1539 $[M+H]^+$, found: 290.1533.

3.11.19. Phenyl(2,2,3-trimethyl-5-(m-tolyl)-2*H*-pyrrol-4-yl)methanone (72b)

3-((2-Methylbut-3-yn-2-yl)amino)-1-phenyl-3-(m-tolyl)prop-2-en-1-one (**61b**) (106.2 mg, 0.35 mmol) and Cs_2CO_3 (342.1 mg, 1.05 mmol) were employed to afford 94.5 mg (89%) of indicated product as a brown solid (R_f = 0.45 in 4:1 hexane/ethyl acetate; mp 105.1-107.2 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.51–7.43 (m, 2H), 7.39–7.32 (m, 2H), 7.23–7.18 (m, 1H), 7.08–7.03 (m, 2H), 2.22 (s, 3H), 1.94 (s, 3H), 1.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.6 (CO), 173.8 (C), 168.6 (C), 138.0 (C), 137.3 (C), 134.0 (C), 133.9 (C), 133.6 (CH), 130.6 (CH), 129.3 (CH), 128.7 (CH), 128.0 (CH), 125.2 (CH), 79.2 (C), 23.2 (CH_3), 21.2 (CH_3), 12.4 (CH_3) (Two CH peaks overlap with each other); IR (neat) 2967, 2925, 1656, 1626, 1594, 1445, 1308, 1254, 1202, 1171, 1072, 913, 899, 736, 688, 609 cm^{-1}; MS

(ESI, m/z): 304.17 [M+H]$^+$; HRMS (ESI) calcd. for $C_{21}H_{22}NO$: 304.1696 [M+H]$^+$, found: 304.1696.

3.11.20. (4-Chlorophenyl)(2,2,3-trimethyl-5-phenyl-2*H*-pyrrol-4-yl)methanone (72c)

1-(4-Chlorophenyl)-3-((2-methylbut-3-yn-2-yl)amino)-3-phenylprop-2-en-1-one (**61c**) (86.6 mg, 0.27 mmol) and Cs_2CO_3 (263.9 mg, 0.81 mmol) were employed to afford 73.6 mg (85%) of indicated product as a light yellow solid (R_f = 0.40 in 4:1 hexane/ethyl acetate; mp 168.7-171.9 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.6 Hz, 2H), 7.55–7.51 (m, 1H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.33–7.24 (m, 4H), 2.00 (s, 3H), 1.48 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3 (CO), 174.6 (C), 168.3 (C), 140.3 (C), 135.7 (C), 134.0 (C), 133.6 (C), 130.9 (CH), 130.1 (CH), 129.2 (CH), 128.5 (CH), 128.2 (CH), 79.6 (C), 23.3 (CH_3), 12.6 (CH_3); IR (neat) 2974, 2928, 1655, 1626, 1582, 1569, 1400, 1306, 1288, 1257, 1199, 1088, 964, 879, 776, 692, 546 cm^{-1}; MS (ESI, m/z): 324.12 [M+H]$^+$; HRMS (ESI) calcd. for $C_{20}H_{19}ClNO$: 324.1150 [M+H]$^+$, found: 324.1146.

3.12. General Procedure for the Synthesis of Spiro-2*H*-Pyrroles with Two Carbonyl Groups 53

To a stirred solution of spiro-containing *N*-propargylic β-enaminone **52** (0.30 mmol) in DMSO (3 mL) under air was added Cs_2CO_3 (0.90 mmol) and the resulting solution was allowed to stir at 80 °C for approximately 30-75 min (Note that the progress of the reaction was monitored by routine TLC for the completion of the reaction). After completion of the reaction, the reaction mixture was cooled to room temperature and diluted with chloroform (30 mL). To the diluted reaction mixture, equal volume of ice was added, stirred for 10 minutes and separated the organic layer. The aqueous layer was extracted twice with chloroform (2x15 mL) to minimize the loss of product. The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding spiro-2*H*-pyrroles **53a-h**.

3.12.1. (2-Phenyl-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) (53a)

1,3-Diphenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one (**52a**) (106.5 mg, 0.26 mmol) and Cs_2CO_3 (256.7 mg, 0.79 mmol) were employed to afford 76.1 mg (69%) of indicated product as a yellow solid ($R_f = 0.44$ in 4:1 hexane/ethyl acetate; mp 172.4-174.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.52 (m, 2H), 7.51–7.47 (m, 2H), 7.45–7.42 (m, 2H), 7.41–7.34 (m, 2H), 7.30–7.15 (m, 7H), 2.13–1.97 (m, 4H), 1.83 (d, $J = 13.2$ Hz, 1H), 1.78–1.67 (m, 2H), 1.56 (d, $J = 11.0$ Hz, 2H), 1.35–1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.5 (CO), 192.9 (CO), 170.9 (C), 166.7 (C), 137.8 (C), 137.2 (C), 137.1 (C), 134.0 (CH), 133.9 (CH), 133.7 (C), 130.1 (CH), 129.5 (CH), 129.3 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 128.5 (CH), 85.3 (C), 33.8 (CH_2), 25.6 (CH_2), 23.8 (CH_2); IR (neat) 3057, 2913, 2857, 1657, 1597, 1578, 1445, 1337, 1315, 1296, 1258, 1154, 1071, 866, 744, 720, 688 cm^{-1}; MS (ESI, m/z): 420.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{29}H_{26}NO_2$: 420.1958 $[M+H]^+$, found: 420.1968.

3.12.2. (3-Benzoyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-4-yl)(p-tolyl)methanone (53b)

1,3-Diphenyl-3-((1-(p-tolylethynyl)cyclohexyl)amino)prop-2-en-1-one (**52b**) (175.2 mg, 0.42 mmol) and Cs_2CO_3 (408.2 mg, 1.25 mmol) were employed to afford 130.5 mg (72%) of indicated product as a yellow oil ($R_f = 0.47$ in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.62 (m, 4H), 7.52–7.46 (m, 3H), 7.41–7.28 (m, 5H), 7.11 (d, $J = 8.0$ Hz, 2H), 2.35 (s, 3H), 2.20–2.09 (m, 4H), 1.93 (d, $J = 12.3$ Hz, 1H), 1.82 (br s, 2H), 1.67 (d, $J = 8.5$ Hz, 2H), 1.44–1.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1 (CO), 193.0 (CO), 171.2 (C), 166.7 (C), 145.1 (C), 137.1 (C), 137.0

(C), 134.6 (C), 134.0 (CH), 133.7 (C), 130.0 (CH), 129.6 (CH), 129.5 (CH), 129.3 (CH), 128.6 (CH), 128.5 (CH), 128.4 (CH), 85.2 (C), 33.8 (CH_2), 25.6 (CH_2), 23.8 (CH_2), 21.8 (CH_3); IR (neat) 3059, 2928, 2854, 1736, 1652, 1600, 1446, 1314, 1289, 1241, 1169, 1044, 1018, 872,764, 744, 690 cm^{-1}; MS (ESI, m/z): 434.21 $[M+H]^+$; HRMS (ESI) calcd. for $C_{30}H_{28}NO_2$: 434.2115 $[M+H]^+$, found: 434.2122.

3.12.3. (3-Benzoyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-4-yl)(4-fluorophenyl)methanone (53c)

3-((1-((4-Fluorophenyl)ethynyl)cyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**52c**) (152.7 mg, 0.36 mmol) and Cs_2CO_3 (352.4 mg, 1.08 mmol) were employed to afford 94.8 mg (60%) of indicated product as a yellow oil (R_f = 0.53 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.54 (m, 6H), 7.51–7.45 (m, 1H), 7.39–7.28 (m, 5H), 6.98–6.91 (m, 2H), 2.20–2.06 (m, 4H), 1.91 (d, J = 12.1 Hz, 1H), 1.85–1.76 (m, 2H), 1.63 (d, J = 9.4 Hz, 2H), 1.43–1.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9 (CO), 192.88 (CO), 170.5 (C), 166.6 (C), 166.2 (d, $^1J_{CF}$ = 256.9 Hz, C), 137.8 (C), 136.9 (C), 134.2 (CH), 133.6 (d, $^4J_{CF}$ = 2.6 Hz, C), 133.5 (C), 132.1 (d, $^3J_{CF}$ = 9.7 Hz, CH), 130.2 (CH), 129.5 (CH), 128.7 (CH), 128.6 (CH), 128.5 (CH), 115.8 (d, $^2J_{CF}$ = 22.1 Hz, CH), 85.3 (C), 33.8 (CH_2), 25.6 (CH_2), 23.8 (CH_2); IR (neat) 3062, 2930, 2855, 1736, 1656, 1593, 1446, 1410, 1295, 1237, 1150, 1045, 1019, 969, 873, 848,768, 745, 632 cm^{-1}; MS (ESI, m/z): 438.19 $[M+H]^+$; HRMS (ESI) calcd. for $C_{29}H_{25}FNO_2$: 438.1864 $[M+H]^+$, found: 438.1876.

3.12.4. (3-Benzoyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-4-yl)(3-bromophenyl)methanone (53d)

3-((1-((3-Bromophenyl)ethynyl)cyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**52d**) (168.3 mg, 0.35 mmol) and Cs_2CO_3 (339.6 mg, 1.04 mmol) were employed to afford 110.7 mg (64%) of indicated product as a yellow oil (R_f = 0.49 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.61 (m, 2H), 7.58–7.53

(m, 4H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.38–7.27 (m, 5H), 7.14 (t, *J* = 7.8 Hz, 1H), 2.23–2.06 (m, 4H), 1.92 (d, *J* = 13.2 Hz, 1H), 1.87–1.77 (m, 2H), 1.62 (d, *J* = 10.4 Hz, 2H), 1.47–1.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9 (CO), 192.6 (CO), 170.1 (C), 166.6 (C), 139.0 (C), 138.7 (C), 136.9 (C), 136.5 (CH), 134.1 (CH), 133.5 (C), 131.5 (CH), 130.2 (CH), 130.1 (CH), 129.4 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 128.1 (CH), 122.9 (C), 85.4 (C), 33.8 (CH_2), 25.6 (CH_2), 23.8 (CH_2); IR (neat) 3061, 2929, 2854, 1736, 1656, 1596, 1446, 1291, 1239, 1171, 1068, 1045, 1019, 873, 746, 714, 691 cm^{-1}; MS (ESI, m/z): 498.11 [M+H]$^{+}$; HRMS (ESI) calcd. for $C_{29}H_{25}BrNO_2$: 498.1063 [M+H]$^{+}$, found: 498.1075.

3.12.5. (3-Benzoyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-4-yl)(4-nitrophenyl)methanone (53e)

3-((1-((4-Nitrophenyl)ethynyl)cyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**52e**) (141.7 mg, 0.32 mmol) and Cs_2CO_3 (307.4 mg, 0.94 mmol) were employed to afford 98.7 mg (67%) of indicated product as an orangish-yellow solid (R_f = 0.48 in 4:1 hexane/ethyl acetate; mp 139.1-140.3 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.7 Hz, 2H), 7.65–7.58 (m, 4H), 7.56–7.47 (m, 3H), 7.38–7.27 (m, 5H), 2.25–2.07 (m, 4H), 1.94 (d, *J* = 13.7 Hz, 1H), 1.88–1.79 (m, 2H), 1.63 (d, *J* = 10.9 Hz, 2H), 1.46–1.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7 (CO), 192.5 (CO), 169.3 (C), 166.4 (C), 150.4 (C), 141.6 (C), 139.4 (C), 136.7 (C), 134.5 (CH), 133.2 (C), 130.3 (CH), 130.0 (CH), 129.4 (CH), 128.9 (CH), 128.5 (CH), 123.6 (CH), 85.6 (C), 33.8 (CH_2), 25.5 (CH_2), 23.7 (CH_2) (Two CH peaks overlap with each other); IR (neat) 3067, 2920, 2855, 1651, 1596, 1521, 1444, 1345, 1301, 1260, 1167, 1072, 1019, 876, 840, 746, 725, 687 cm^{-1}; MS (ESI, m/z): 465.18 [M+H]$^{+}$; HRMS (ESI) calcd. for $C_{29}H_{25}N_2O_4$: 465.1809 [M+H]$^{+}$, found: 465.1822.

3.12.6. (2-(4-Chlorophenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) (53f)

3-(4-Chlorophenyl)-1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one (**52f**) (151.8 mg, 0.35 mmol) and Cs_2CO_3 (337.2 mg, 1.04 mmol) were employed to afford 117.5 mg (75%) of indicated product as a yellow solid (R_f = 0.46 in 4:1 hexane/ethyl acetate; mp 148.8-150.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.57 (m, 4H), 7.54–7.45 (m, 4H), 7.35–7.25 (m, 6H), 2.25–2.05 (m, 4H), 1.94 (d, *J*= 13.5 Hz, 1H), 1.88–1.76 (m, 2H), 1.65 (d, *J* = 10.9 Hz, 2H), 1.46– 1.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2 (CO), 192.7 (CO), 171.3 (C), 165.6 (C), 137.3 (C), 137.1 (C), 136.9 (C), 136.2 (C), 134.1 (CH), 133.9 (CH), 132.1 (C), 130.0 (CH), 129.5 (CH), 129.2 (CH), 128.7 (CH), 128.5 (CH), 85.4 (C), 33.7 (CH_2), 25.5 (CH_2), 23.7 (CH_2) (Two CH peaks overlap with each other); IR (neat) 3061, 2922, 2855, 1654, 1595, 1492, 1445, 1402,1316, 1294, 1255, 1155, 1093, 1015, 867, 833, 764, 726, 687 cm^{-1}; MS (ESI, m/z): 454.16 [M+H]$^+$; HRMS (ESI) calcd. for $C_{29}H_{25}ClNO_2$: 454.1568 [M+H]$^+$, found: 454.1579.

3.12.7. (3-Benzoyl-2-(4-chlorophenyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(p-tolyl)methanone (53g)

3-(4-Chlorophenyl)-1-phenyl-3-((1-(p-tolylethynyl)cyclohexyl)amino)prop-2-en-1-one (**52g**) (142.9 mg, 0.32 mmol) and Cs_2CO_3 (307.7 mg, 0.94 mmol) were employed to afford 101.7 mg (69%) of indicated product as an orangish-yellow oil (R_f = 0.41 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.56 (m, 4H), 7.51–7.46 (m, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.33–7.27 (m, 4H), 7.08 (d, *J*= 8.1 Hz, 2H), 2.33 (s, 3H), 2.16–2.05 (m, 4H), 1.90 (d, *J* = 12.9 Hz, 1H), 1.84–1.76 (m, 2H), 1.62 (d, *J* = 10.0 Hz, 2H), 1.43–1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9 (CO), 192.9 (CO), 171.6 (C), 165.6 (C), 145.2 (C), 136.9 (C), 136.7 (C), 136.2 (C), 134.6 (C), 134.2 (CH), 132.2 (C), 130.0 (CH), 129.6 (CH), 129.5 (CH), 129.3 (CH), 128.7 (CH), 128.6 (CH), 85.3 (C), 33.8 (CH_2), 25.6 (CH_2), 23.8 (CH_2), 21.8 (CH_3); IR (neat)

3061, 2927, 2853, 1655, 1599, 1488, 1447, 1401, 1311, 1291, 1260, 1169, 1091, 1012, 872, 835, 752, 741, 689 cm^{-1}; MS (ESI, m/z): 468.17 [M+H]$^+$; HRMS (ESI) calcd. for $C_{30}H_{27}ClNO_2$: 468.1725 [M+H]$^+$, found: 468.1736.

3.12.8. (3-Benzoyl-2-(4-chlorophenyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(3-bromophenyl)methanone (53h)

3-((1-((3-Bromophenyl)ethynyl)cyclohexyl)amino)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (**52h**) (165.4 mg, 0.32 mmol) and Cs_2CO_3 (311.6 mg, 0.96 mmol) were employed to afford 127.5 mg (75%) of indicated product as an orange oil (R_f = 0.53 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.49 (m, 6H), 7.48–7.42 (m, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.35–7.27 (m, 4H), 7.14 (t, *J* = 7.8 Hz, 1H), 2.23–2.06 (m, 4H), 1.92 (d, *J* = 13.7 Hz, 1H), 1.83–1.77 (m, 2H), 1.60 (d, *J* = 11.5 Hz, 2H), 1.45–1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.8 (CO), 192.6 (CO), 170.5 (C), 165.5 (C), 139.0 (C), 138.3 (C), 136.9 (C), 136.6 (CH), 136.4 (C), 134.4 (CH), 132.0 (C), 131.5 (CH), 130.1 (CH), 130.0 (CH), 129.4 (CH), 128.9 (CH), 128.8 (CH), 128.1 (CH), 123.0 (C), 85.5 (C), 33.8 (CH_2), 25.5 (CH_2), 23.8 (CH_2); IR (neat) 3062, 2927, 2853, 1658, 1596, 1487, 1447, 1401, 1292, 1246, 1172, 1091, 1012, 873, 835, 740, 713, 687 cm^{-1}; MS (ESI, m/z): 532.07 [M+H]$^+$; HRMS (ESI) calcd. for $C_{29}H_{24}BrClNO_2$: 532.0674 [M+H]$^+$, found: 532.0674

3.13. General Procedure for the Synthesis of Spiro-1,4-Oxazepines 54 and 1,4-Oxazepines 86

To a stirred solution of *N*-propargylic β-enaminones **50** or **61** (0.30 mmol) in DCE (3 mL) under argon was added ZnI_2 (0.60 mmol) and $AgSbF_6$ (0.045mmol). The resulting solution was allowed to stir at 84 °C. (Note that reaction was continued until *N*-propargylic β-enaminone was completely consumed as monitored by routine TLC). After the reaction was over, ethyl acetate (20 mL) and a saturated aqueous solution of NH_4Cl (15 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 15 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (9:1 followed by 4:1) as the eluent to afford the corresponding spiro-1,4-oxazepines **54a-n** and1,4-oxazepines **78a-c**.

3.13.1. 12-Methylene-8,10-diphenyl-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54a)

3-((1-Ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**50a**) (113.5 mg, 0.35 mmol), ZnI_2 (220.0 mg, 0.69 mmol) and $AgSbF_6$ (17.8 mg, 0.05 mmol) were employed to afford 82.9 mg (73%) of indicated product as a yellow solid (R_f = 0.62 in 4:1 hexane/ethyl acetate; mp 94.2-95.7 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.75 (m, 4H), 7.45 (dd, J = 5.1, 1.8 Hz, 3H), 7.42–7.38 (m, 3H), 6.31 (s, 1H), 4.94 (d, J = 1.4 Hz, 1H), 4.64 (d, J = 1.4 Hz, 1H), 2.07 (br s, 2H), 1.98–1.90 (m, 2H), 1.88–1.79 (m, 2H), 1.68–1.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5 (C), 159.4 (C), 142.6 (C), 135.1 (C), 130.2 (CH), 129.2 (CH), 128.7 (CH), 128.4 (CH), 127.6 (CH), 126.6 (CH), 96.9 (CH), 96.8 (CH_2), 64.8 (C), 34.3 (CH_2), 26.2 (CH_2), 22.7 (CH_2) (Two C peaks overlap with each other.); IR (neat) 2924, 2847, 1636, 1588, 1569, 1492, 1446, 1369, 1359, 1288, 1257, 1220, 1191, 1179, 1113, 1020, 915, 884, 762, 690 cm^{-1}; MS (ESI, m/z): 330.19 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{24}NO$: 330.1852 $[M+H]^+$, found: 330.1862.

3.13.2. 12-Methylene-10-phenyl-8-(p-tolyl)-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54b)

3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(p-tolyl)prop-2-en-1-one (**50b**) (180.7 mg, 0.53 mmol), ZnI_2 (335.9 mg, 1.05 mmol) and $AgSbF_6$ (27.1 mg, 0.079 mmol) were employed to afford 113.8 mg (63%) of indicated product as ayellow solid (R_f = 0.57 in 4:1 hexane/ethyl acetate; mp 107.2-109.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.81–7.77 (m, 2H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.45–7.41 (m, 3H), 7.20 (d, *J* = 8.0 Hz, 2H), 6.29 (s, 1H), 4.92 (d, *J* = 1.4 Hz, 1H), 4.62 (d, *J* = 1.4 Hz, 1H), 2.38 (s, 3H), 2.03 (br s, 2H), 1.96–1.88 (m, 2H), 1.86–1.76 (m, 2H), 1.67–1.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3 (C), 159.5 (C), 159.2 (C), 140.2 (C), 139.2 (C), 135.1 (C), 130.1 (CH), 129.0 (CH), 128.6 (CH), 127.5 (CH), 126.6 (CH), 97.0 (CH), 96.7 (CH_2), 64.7 (C), 34.3 (CH_2), 26.2 (CH_2), 22.7 (CH_2), 21.4 (CH_3); IR (neat) 2933, 2853, 1635, 1585, 1493, 1445, 1369, 1290, 1255, 1179, 1144, 1062, 1048, 964, 886, 811, 766, 690 cm^{-1}; MS (ESI, m/z): 344.20 [M+H]$^+$; HRMS (ESI) calcd. for $C_{24}H_{26}NO$: 344.2009 [M+H]$^+$, found: 344.2016.

3.13.3. 12-Methylene-10-phenyl-8-(thiophen-3-yl)-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54c)

3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(thiophen-3-yl)prop-2-en-1-one (**50d**) (114.8 mg, 0.34 mmol), ZnI_2 (218.5 mg, 0.68 mmol) and $AgSbF_6$ (17.7 mg, 0.05 mmol) were employed to afford 85.0 mg (74%) of indicated product as a yellow solid (R_f = 0.64 in 4:1 hexane/ethyl acetate; mp 103.5-105.4 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 6.5, 2.9 Hz, 2H), 7.65 (d, *J* = 2.9 Hz, 1H), 7.56 (d, *J* = 5.0 Hz, 1H), 7.49–7.43 (m, 3H), 7.29 (dd, *J*= 5.0, 2.9 Hz, 1H), 6.33 (s, 1H), 4.93 (d, *J* = 0.9 Hz, 1H), 4.64 (d, *J* = 0.9 Hz, 1H), 2.00 (br s, 2H), 1.96–1.89 (m, 2H), 1.85–1.74 (m, 2H), 1.66–1.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (C), 159.0 (C), 155.4 (C), 145.6 (C), 135.0 (C), 130.2 (CH), 128.7 (CH), 127.7 (CH), 126.6 (CH), 125.6 (CH), 124.6 (CH), 96.9 (CH), 96.6 (CH_2), 64.8 (C), 34.3 (CH_2), 26.2 (CH_2), 22.7 (CH_2); IR (neat) 2927, 2852, 1632, 1577, 1493, 1448, 1358, 1276, 1222, 1112, 1062, 981, 939, 849, 788, 688 cm^{-1}; MS (ESI, m/z): 336.14 [M+H]$^+$; HRMS (ESI) calcd. for $C_{21}H_{22}NOS$: 336.1417 [M+H]$^+$, found: 336.1426.

3.13.4. 8-(3-Fluorophenyl)-12-methylene-10-phenyl-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54d)

3-((1-Ethynylcyclohexyl)amino)-3-(3-fluorophenyl)-1-phenylprop-2-en-1-one (**50e**) (124.3 mg, 0.36 mmol), ZnI_2 (228.4 mg, 0.72 mmol) and $AgSbF_6$ (18.6 mg, 0.05 mmol) were employed to afford 104.4 mg (84%) of indicated product as a yellow solid (R_f = 0.60 in 4:1 hexane/ethyl acetate; mp 93.8-95.7 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.78 (m, 2H), 7.57–7.50 (m, 2H), 7.48–7.42 (m, 3H), 7.37 (td, J = 8.0, 5.9 Hz, 1H), 7.10 (tdd, J = 8.4, 2.5, 0.7 Hz, 1H), 6.27 (s, 1H), 4.96 (d, J = 1.6 Hz, 1H), 4.66 (d, J = 1.6 Hz, 1H), 2.04 (br s, 2H), 1.98–1.89 (m, 2H), 1.88–1.77 (m, 2H), 1.69–1.54 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (d, $^1J_{CF}$ = 245.4 Hz, C), 159.9 (C), 159.3 (d, $^4J_{CF}$ = 2.5 Hz, C), 159.2 (C), 145.1 (d, $^3J_{CF}$ = 7.0 Hz, C), 134.8 (C), 130.3 (CH), 129.8 (d, $^3J_{CF}$ = 8.0 Hz, CH), 128.7 (CH), 126.6 (CH), 123.2 (d, $^4J_{CF}$ = 2.3 Hz, CH), 116.1 (d, $^2J_{CF}$ = 21.2 Hz, CH), 114.6 (d, $^2J_{CF}$ = 22.5 Hz, CH), 97.0 (CH), 96.3 (CH_2), 65.0 (C), 34.2 (CH_2), 26.1 (CH_2), 22.7 (CH_2); IR (neat) 2924, 2847, 1635, 1573, 1483, 1439, 1369, 1360, 1248, 1174, 1103, 1062, 971, 891, 768, 691 cm^{-1}; MS (ESI, m/z): 348.18 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{23}FNO$: 348.1758 $[M+H]^+$, found: 348.1763.

3.13.5. 8-(4-Chlorophenyl)-12-methylene-10-phenyl-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54e)

3-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one (**50f**) (122.1 mg, 0.34 mmol), ZnI_2 (214.2 mg, 0.67 mmol) and $AgSbF_6$ (17.3 mg, 0.05 mmol) were employed to afford 98.9 mg (81%) of indicated product as an orangish-yellow solid (R_f = 0.41 in 4:1 hexane/ethyl acetate; mp 121.7-123.1 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.75 (m, 2H), 7.73–7.67 (m, 2H), 7.48–7.41 (m, 3H), 7.39–7.32 (m, 2H), 6.23 (s, 1H), 4.94 (d, J = 1.6 Hz, 1H), 4.64 (d, J = 1.6 Hz, 1H), 2.03 (br s, 2H), 1.97–1.88 (m, 2H), 1.85–1.74 (m, 2H), 1.67–1.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8 (C), 159.4 (C), 159.3 (C), 141.3 (C), 135.3 (C), 134.9 (C), 130.3 (CH), 129.0 (CH), 128.7 (CH), 128.5 (CH), 126.6 (CH), 97.0 (CH), 96.3 (CH_2), 65.0 (C), 34.2 (CH_2), 26.2 (CH_2), 22.7 (CH_2); IR (neat) 2923, 2858, 1620, 1592, 1571, 1489, 1397, 1284, 1190, 1076, 1009, 940, 892, 878, 764, 685 cm^{-1}; MS (ESI, m/z): 364.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{23}ClNO$: 364.1463 $[M+H]^+$, found: 364.1466.

3.13.6. 8-(4-Bromophenyl)-12-methylene-10-phenyl-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54f)

3-(4-Bromophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one (**50g**) (125.9 mg, 0.31 mmol), ZnI_2 (196.8 mg, 0.62 mmol) and $AgSbF_6$ (15.9 mg, 0.05 mmol) were employed to afford 100.7 mg (80%) of indicated product as an orangish-yellow solid (R_f = 0.64 in 4:1 hexane/ethyl acetate; mp 105.1-107.8 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.80–7.76 (m, 2H), 7.66–7.62 (m, 2H), 7.53–7.49 (m, 2H), 7.47–7.42 (m, 3H), 6.22 (s, 1H), 4.93 (d, J = 1.6 Hz, 1H), 4.63 (d, J = 1.6 Hz, 1H), 2.00 (br s, 2H), 1.96–1.87 (m, 2H), 1.84–1.74 (m, 2H), 1.67–1.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9 (C), 159.5 (C), 159.2 (C), 141.7 (C), 134.8 (C), 131.4 (CH), 130.4 (CH), 129.3 (CH), 128.7 (CH), 126.6 (CH), 123.7 (C), 97.1 (CH), 96.3 (CH_2), 65.0 (C), 34.2 (CH_2), 26.1 (CH_2), 22.7 (CH_2); IR (neat) 2923, 2857, 1652, 1620, 1569, 1556, 1486, 1445, 1372, 1283, 1190, 1071, 1007, 940, 876, 764, 686 cm^{-1}; MS (ESI, m/z): 408.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{23}BrNO$: 408.0958 $[M+H]^+$, found: 408.0964.

3.13.7. 12-Methylene-8-(4-nitrophenyl)-10-phenyl-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54g)

3-((1-Ethynylcyclohexyl)amino)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one (**50h**) (103.2 mg, 0.28 mmol), ZnI_2 (176.0 mg, 0.56 mmol) and $AgSbF_6$ (14.2 mg, 0.04 mmol) were employed to afford 70.2 mg (68%) of indicated product as a brownish-orange solid (R_f = 0.61 in 4:1 hexane/ethyl acetate; mp 127.2-128.8 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.26–8.21 (m, 2H), 7.94–7.88 (m, 2H), 7.81–7.77 (m, 2H), 7.48–7.42

(m, 3H), 6.21 (s, 1H), 4.97 (br s, 1H), 4.66 (br s, 1H), 2.05–1.98 (m, 2H), 1.96–1.88 (m, 2H), 1.83–1.73 (m, 2H), 1.67–1.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8 (C), 158.9 (C), 158.8 (C), 148.7 (C), 148.4 (C), 134.6 (C), 130.7 (CH), 128.8 (CH), 128.6 (CH), 126.7 (CH), 123.6 (CH), 97.6 (CH), 95.8 (CH_2), 65.6 (C), 34.2 (CH_2), 26.1 (CH_2), 22.7 (CH_2); IR (neat) 2912, 2852, 1629, 1567, 1507, 1446, 1343, 1288, 1225, 1106, 1047, 964, 857, 823, 770, 692 cm^{-1}; MS (ESI, m/z): 375.17 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{23}N_2O_3$: 375.1703 $[M+H]^+$, found: 375.1707.

3.13.8. 10-(4-Methoxyphenyl)-12-methylene-8-phenyl-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54h)

3-((1-Ethynylcyclohexyl)amino)-1-(4-methoxyphenyl)-3-phenylprop-2-en-1-one (**50k**) (104.0 mg, 0.29 mmol), ZnI_2 (184.7 mg, 0.58 mmol) and $AgSbF_6$ (14.9 mg, 0.04 mmol) were employed to afford 65.5 mg (63%) of indicated product as a yellow oil (R_f = 0.46 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.70 (m, 4H), 7.40–7.36 (m, 3H), 6.96–6.91 (m, 2H), 6.20 (s, 1H), 4.90 (d, *J* = 1.4 Hz, 1H), 4.61 (d, *J* = 1.4 Hz, 1H), 3.86 (s, 3H), 2.06–1.98 (m, 2H), 1.95–1.87 (m, 2H), 1.84–1.75 (m, 2H), 1.65–1.52 (m, 4H); ^{13}CNMR (100 MHz, $CDCl_3$) δ 161.4 (C), 160.7 (C), 159.5 (C), 159.4 (C), 143.2 (C), 129.2 (CH), 128.3 (CH), 128.2 (CH), 127.6 (CH), 127.4 (C), 114.0 (CH), 96.7 (CH), 95.6 (CH_2), 64.7 (C), 55.6 (CH_3), 34.3 (CH_2), 26.2 (CH_2), 22.7 (CH_2); IR (neat) 2929, 2852, 1623, 1606, 1560, 1509, 1443, 1373, 1254, 1226, 1176, 1027, 821, 767, 696 cm^{-1}; MS (ESI, m/z): 360.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{26}NO_2$: 360.1958 $[M+H]^+$, found: 360.1961.

3.13.9. 10-(4-Methoxyphenyl)-12-methylene-8-(thiophen-3-yl)-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54i)

3-((1-Ethynylcyclohexyl)amino)-1-(4-methoxyphenyl)-3-(thiophen-3-yl)prop-2-en-1-one (**50l**) (131.6 mg, 0.36 mmol), ZnI_2 (230.0 mg, 0.72 mmol) and $AgSbF_6$ (18.6 mg, 0.05 mmol) were employed to afford 101.3 mg (77%) of indicated product as a brownish-yellow solid (R_f = 0.56 in 4:1 hexane/ethyl acetate; mp 91.2-92.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67–7.62 (m, 2H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.45 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.18 (dd, *J* = 5.0, 3.0 Hz, 1H), 6.88–6.82 (m, 2H), 6.14 (s, 1H), 4.80 (d, *J*= 1.4 Hz, 1H), 4.52 (d, *J*= 1.4 Hz, 1H), 3.77 (s, 3H), 1.88 (br s, 2H), 1.85–1.76 (m, 2H), 1.72–1.63 (m, 2H), 1.54–1.41 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (C), 159.5 (C), 159.1 (C), 155.5 (C), 145.8 (C), 128.2 (CH), 127.8 (CH), 127.4 (C), 125.5 (CH), 124.5 (CH), 114.0 (CH), 96.8 (CH), 95.2 (CH_2), 64.7 (C), 55.5 (CH_3), 34.4 (CH_2), 26.2 (CH_2), 22.7 (CH_2); IR (neat) 2923, 2853, 1619, 1604, 1563, 1509, 1452, 1359, 1253, 1229, 1171, 1070, 974, 822, 785, 694 cm^{-1}; MS (ESI, m/z): 366.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{24}NO_2S$: 366.1522 $[M+H]^+$, found: 366.1528.

3.13.10. 8-(3-Fluorophenyl)-10-(4-methoxyphenyl)-12-methylene-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54j)

3-((1-Ethynylcyclohexyl)amino)-3-(3-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**50m**) (152.1 mg, 0.40 mmol), ZnI_2 (257.3 mg, 0.81 mmol) and $AgSbF_6$ (20.8 mg, 0.06 mmol) were employed to afford 103.4 mg (68%) of indicated product as a yellow oil (R_f = 0.52 in 4:1 hexane/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.71 (m, 2H), 7.52 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.50–7.45 (m, 1H), 7.34 (td, *J* = 8.0, 5.9 Hz, 1H), 7.07 (tdd, *J* = 8.4, 2.5, 0.7 Hz, 1H), 6.96–6.92 (m, 2H), 6.15 (s, 1H), 4.91 (d, *J* = 1.4 Hz, 1H), 4.62 (d, *J* = 1.4 Hz, 1H), 3.86 (s, 3H), 2.00–1.96 (m, 2H), 1.94–1.85 (m, 2H), 1.83–1.73 (m, 2H), 1.66–1.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (d, $^1J_{CF}$ = 245.5 Hz, C), 161.5 (C), 159.8 (C), 159.5 (C), 159.3 (C), 145.5 (d, $^3J_{CF}$ = 6.9 Hz, C), 129.8 (d, $^3J_{CF}$ = 8.1 Hz, CH), 128.2 (CH), 127.2 (C), 123.2 (d, $^4J_{CF}$ = 2.0 Hz, CH), 116.0 (d, $^2J_{CF}$ = 21.4 Hz, CH), 114.7 (d, $^2J_{CF}$ = 22.4 Hz, CH), 114.1 (CH), 96.9 (CH), 95.0 (CH_2), 64.9 (C), 55.6 (CH_3), 34.2 (CH_2), 26.2 (CH_2), 22.7 (CH_2); IR (neat) 2931, 2854, 1623, 1607, 1562, 1509, 1440, 1372, 1246, 1177, 1032, 977, 881, 785, 710, 586cm^{-1}; MS (ESI, m/z): 378.19 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{25}FNO_2$: 378.1864 $[M+H]^+$, found: 378.1868.

3.13.11. 8-(4-Bromophenyl)-10-(4-methoxyphenyl)-12-methylene-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54k)

3-((1-Ethynylcyclohexyl)amino)-3-(3-fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**50n**) (110.0 mg, 0.25 mmol), ZnI_2 (160.2 mg, 0.50 mmol) and $AgSbF_6$ (12.9 mg, 0.04 mmol) were employed to afford 78.1 mg (71%) of indicated product as a yellow solid (R_f = 0.57 in 4:1 hexane/ethyl acetate; mp 104.7-106.8 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.75–7.70 (m, 2H), 7.64–7.60 (m, 2H), 7.52–7.48 (m, 2H), 6.96–6.91 (m, 2H), 6.12 (s, 1H), 4.90 (d, *J* = 1.5 Hz, 1H), 4.61 (d, *J*= 1.5 Hz, 1H), 3.86 (s, 3H), 1.98 (br s, 2H), 1.94–1.85 (m, 2H), 1.82–1.72 (m, 2H), 1.64–1.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (C), 159.9 (C), 159.7 (C), 159.3 (C), 142.0 (C), 131.4 (CH), 129.3 (CH), 128.2 (CH), 127.2 (C), 123.6 (C), 114.0 (CH), 96.9 (CH), 94.9 (CH_2), 64.9 (C), 55.6 (CH_3), 34.2 (CH_2), 26.2 (CH_2), 22.7 (CH_2); IR (neat) 2937, 2847, 1632, 1588, 1509, 1484, 1417, 1367, 1251, 1225, 1117, 1030, 1008, 916, 804, 720, 641 cm^{-1}; MS (ESI, m/z): 438.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{24}H_{25}BrNO_2$: 438.1063 $[M+H]^+$, found: 438.1068.

3.13.12. 10-(4-Chlorophenyl)-12-methylene-8-phenyl-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54l)

1-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-3-phenylprop-2-en-1-one (**50o**) (124.8 mg, 0.34 mmol), ZnI_2 (219.0 mg, 0.69 mmol) and $AgSbF_6$ (17.7 mg, 0.05 mmol) were employed to afford 93.6 mg (75%) of indicated product as an orange solid (R_f = 0.54 in 4:1 hexane/ethyl acetate; mp 125.5-127.9 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.67 (m, 4H), 7.43–7.33 (m, 5H), 6.27 (s, 1H), 4.92 (brs, 1H), 4.64 (brs, 1H), 2.02 (br s, 2H), 1.94–1.85 (m, 2H), 1.84–1.75 (s, 2H), 1.65–1.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.3 (C), 159.3 (C), 158.2 (C), 142.8 (C), 136.2 (C), 133.5 (C), 129.3 (CH), 128.9 (CH), 128.4 (CH), 127.9 (CH), 127.5 (CH), 97.0 (CH_2), 96.9 (CH), 64.9 (C), 34.3 (CH_2), 26.2 (CH_2), 22.7 (CH_2); IR (neat) 2927, 2852, 1637, 1592, 1572, 1487, 1403, 1359, 1221, 1191, 1114, 1090, 1010, 915, 867, 767, 695 cm^-

^{1}; MS (ESI, m/z): 364.15 [M+H]$^{+}$; HRMS (ESI) calcd. for $C_{23}H_{23}ClNO$: 364.1463 [M+H]$^{+}$, found: 364.1464.

3.13.13. 10-(4-Chlorophenyl)-12-methylene-8-(p-tolyl)-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54m)

1-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-3-(p-tolyl)prop-2-en-1-one (**50p**) (135.4 mg, 0.36 mmol), ZnI_2 (228.7 mg, 0.72 mmol) and $AgSbF_6$ (18.6 mg, 0.05 mmol) were employed to afford 98.9 mg (73%) of indicated product as a light yellow solid (R_f = 0.60 in 4:1 hexane/ethyl acetate; mp 147.2-149.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.69 (m, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.41–7.36 (m, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.25 (s, 1H), 4.90 (d, *J* = 1.3 Hz, 1H), 4.62 (d, *J* = 1.3 Hz, 1H), 2.38 (s, 3H), 2.01 (br s, 2H), 1.94–1.85 (m, 2H), 1.84–1.75 (m, 2H), 1.64–1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0 (C), 159.5 (C), 158.0 (C), 140.1 (C), 139.3 (C), 136.2 (C), 133.6 (C), 129.1 (CH), 128.9 (CH), 127.9 (CH), 127.5 (CH), 97.1 (CH), 96.8 (CH_2), 64.8 (C), 34.3 (CH_2), 26.2 (CH_2), 22.7 (CH_2), 21.4 (CH_3); IR (neat) 2937, 2852, 1621, 1575, 1556, 1487, 1402, 1369, 1285, 1178, 1088, 1010, 950, 864, 807, 678 cm^{-1}; MS (ESI, m/z): 378.16 [M+H]$^{+}$; HRMS (ESI) calcd. for $C_{24}H_{25}ClNO$: 378.1619 [M+H]$^{+}$, found: 378.1625.

3.13.14. 10-(4-Chlorophenyl)-8-(3-fluorophenyl)-12-methylene-11-oxa-7-azaspiro[5.6]dodeca-7,9-diene (54n)

1-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-3-(3-fluorophenyl)prop-2-en-1-one (**50q**) (119.7 mg, 0.31 mmol), ZnI_2 (200.1 mg, 0.63 mmol) and $AgSbF_6$ (16.2 mg, 0.05 mmol) were employed to afford 106.5 mg (89%) of indicated product as a light orange solid (R_f = 0.63 in 4:1 hexane/ethyl acetate; mp 116.6-118.9 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74–7.70 (m, 2H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.50–7.45 (m, 1H), 7.42–7.39 (m, 2H), 7.35 (td, *J* = 8.0, 5.9 Hz, 1H), 7.09 (td, *J* = 8.3, 2.1 Hz, 1H), 6.21 (s, 1H), 4.93 (d, *J* = 1.5 Hz, 1H), 4.64 (d, *J*= 1.5 Hz, 1H), 2.00 (br s, 2H), 1.93–1.85 (m, 2H), 1.84–1.73 (m, 2H), 1.65–1.51 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (d, $^1J_{CF}$ = 245.8 Hz, C), 159.1 (C), 158.7 (C), 145.0 (d, $^3J_{CF}$ = 6.9 Hz, C), 136.4 (C), 133.2 (C), 129.9 (d, $^3J_{CF}$ = 8.1 Hz, CH), 128.9 (CH), 127.9 (CH), 123.1 (d, $^4J_{CF}$ = 2.5 Hz, CH), 116.2 (d, $^2J_{CF}$= 21.4 Hz, CH), 114.6 (d, $^2J_{CF}$ = 22.5 Hz, CH), 97.2 (CH), 96.4 (CH_2), 65.0 (C), 34.2 (CH_2), 26.1 (CH_2), 22.6 (CH_2) (Two C peaks overlap with each other); IR (neat) 2926, 2848, 1634, 1575, 1484, 1439, 1361, 1292, 1249, 1196, 1064, 1044, 939, 819, 784, 676 cm^{-1}; MS (ESI, m/z): 382.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{22}ClFNO$: 382.1369 $[M+H]^+$, found: 382.1378.

3.13.15. 3,3-Dimethyl-2-methylene-5,7-diphenyl-2,3-dihydro-1,4-oxazepine (86a)

3-((2-Methylbut-3-yn-2-yl)amino)-1,3-diphenylprop-2-en-1-one (**61a**) (102.0 mg, 0.35 mmol), ZnI_2 (225.0 mg, 0.71 mmol) and $AgSbF_6$ (18.2 mg, 0.05 mmol) were employed to afford 75.5 mg (74%) of indicated product as a yellow solid (R_f = 0.59 in 4:1 hexane/ethyl acetate; mp 90.7-92.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.80 (m, 2H), 7.78–7.74 (m, 2H), 7.49–7.44 (m, 3H), 7.43–7.39 (m, 3H), 6.34 (s, 1H), 4.87 (d, J = 1.5 Hz, 1H), 4.71 (d, J = 1.5 Hz, 1H), 1.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0 (C), 160.8 (C), 159.2 (C), 142.8 (C), 135.0 (C), 130.2 (CH), 129.2 (CH), 128.6 (CH), 128.4 (CH), 127.4 (CH), 126.6 (CH), 97.2 (CH), 95.5 (CH_2), 61.7 (C), 26.5 (CH_3); IR (neat) 2973, 2934, 1627, 1562, 1492, 1446, 1373, 1287, 1234, 1145, 1045, 868, 765, 676 cm^{-1}; MS (ESI, m/z): 290.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{20}H_{20}NO$: 290.1539 $[M+H]^+$, found: 290.1542.

3.13.16. 3,3-Dimethyl-2-methylene-7-phenyl-5-(m-tolyl)-2,3-dihydro-1,4-oxazepine (86b)

3-((2-Methylbut-3-yn-2-yl)amino)-1-phenyl-3-(m-tolyl)prop-2-en-1-one (**61b**) (109.3 mg, 0.36 mmol), ZnI_2 (230.0 mg, 0.72 mmol) and $AgSbF_6$ (18.6 mg, 0.05 mmol) were employed to afford 85.3 mg (78%) of indicated product as a yellow solid (R_f = 0.65 in 4:1 hexane/ethyl acetate; mp 91.6-93.3 °C). ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.83–7.80 (m, 2H), 7.57 (br s, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.48–7.43 (m, 3H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 6.33 (s, 1H), 4.86 (d, *J* = 1.5 Hz, 1H), 4.71 (d, *J* = 1.5 Hz, 1H), 2.42 (s, 3H), 1.63 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3 (C), 160.8 (C), 159.1 (C), 142.8 (C), 138.0 (C), 135.0 (C), 130.2 (CH), 129.9 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 126.6 (CH), 124.5 (CH), 97.4 (CH), 95.4 (CH_2), 61.7 (C), 26.5 (CH_2), 21.6 (CH_3); IR (neat) 2978, 2921, 1637, 1573, 1492, 1448, 1363, 1285, 1251, 1169, 1140, 1054, 881, 786, 688 cm^{-1}; MS (ESI, m/z): 304.17 [M+H]$^+$; HRMS (ESI) calcd. for $C_{21}H_{22}NO$: 304.1696 [M+H]$^+$, found: 304.1705.

3.13.17. 7-(4-Chlorophenyl)-3,3-dimethyl-2-methylene-5-phenyl-2,3-dihydro-1,4-oxazepine (86c)

1-(4-Chlorophenyl)-3-((2-methylbut-3-yn-2-yl)amino)-3-phenylprop-2-en-1-one (**61c**) (101.8 mg, 0.31 mmol), ZnI_2 (200.7 mg, 0.63 mmol) and $AgSbF_6$ (16.2 mg, 0.05 mmol) were employed to afford 66.2 mg (65%) of indicated product as a yellow solid (R_f = 0.48 in 4:1 hexane/ethyl acetate; mp 126.3-128.2 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.68 (m, 4H), 7.43–7.36 (m, 5H), 6.27 (s, 1H), 4.82 (d, *J* = 1.7 Hz, 1H), 4.68 (d, *J* = 1.7 Hz, 1H), 1.58 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9 (C), 160.7 (C), 158.2 (C), 142.7 (C), 136.4 (C), 133.5 (C), 129.3 (CH), 128.9 (CH), 128.4 (CH), 127.9 (CH), 127.5 (CH), 97.4 (CH), 95.8 (CH_2), 61.8 (C), 26.6 (CH_3); IR (neat) 2984, 2927, 1626, 1581, 1561, 1487, 1405, 1371, 1286, 1231, 1177, 1149, 1090, 1010, 867, 821, 768, 697, 604 cm^{-1}; MS (ESI, m/z): 324.11 [M+H]$^+$; HRMS (ESI) calcd. for $C_{20}H_{19}ClNO$: 324.1150 [M+H]$^+$, found: 324.1155.

CHAPTER 4

CONCLUSION

In summary, many novel and potentially bioactive 5-arylpyridines **46**, 2-ferrocenylpyridines **49**, spiro-2*H*-pyrroles **51** and **53** and spiro-1,4-oxazepines **54** were synthesized in good to high yields. Efficient methodologies for the synthesis of each class of heterocyclic molecules were developed successfully.

Firstly, starting materials were prepared by Pd- and Cu-catalyzed Sonogashira cross-coupling reaction of aryl chlorides with terminal alkynes. As a result of Sonogashira approach, we achieved the synthesis of twenty five α,β-alkynic ketone derivatives **26** in 65-99% yields. Conjugate addition of propargylamine, 1-ethynylcyclohexylamine and 2-methyl-3-butyn-2-amine to α,β-alkynic ketones **26** in refluxing methanol gave *N*-propargylic β-enaminone derivatives **32**, **50** and **61** in 94-98%, 51-83% and 60-69% yields, respectively. Some of the *N*-propargylic β-enaminones were subjected to Sonogashira cross-coupling with aryl iodides in order to further functionalize these compounds. Therefore, arylated β-enaminone derivatives **10** and **52** were obtained in 77-88% and 70-89% yields. Then, when treated with 3.0 equiv. of molecular iodine and sodium bicarbonate in refluxing acetonitrile, *N*-propargylic β-enaminones **10** underwent electrophilic cyclization to provide 5-iodopridines **44** in 62-80% yields.

After preparation of starting materials, suitable reaction conditions were explored for the facile synthesis of final compounds. In first part of the synthesis, a series of optimization reactions were carried out to synthesize 5-arylpyridines **46** by using model reaction of 5-iodopyridine derivative **44a**. As a result of these reactions, the best yield (94%) was achieved by using 5 mol% $PdCl_2(PPh_3)$ and 1.4 equiv. of both boronic acids and $KHCO_3$ in 4:1 ratio of DMF/H_2O solution at 110 °C. These optimized reaction conditions were employed for Suzuki-Miyaura coupling reaction of 5-iodopyridines **44** with boronic acids **45**. As a result, eighteen novel 5-arylpyridines derivatives **46** were synthesized in good to excellent yields (65-98%).

Secondly, one-pot method for the synthesis of 2-ferrocenylpyridines **49** from α,β-alkynic ketones **26** and propargylamine **48** via in situ formation of *N*-propargylic β-enaminone was described. After optimization studies, the highest yield (77%) of 2-ferrocenylpyridine **49** was obtained with 1.0 equiv. of CuCl in DMF at 110 °C and open to air. By employing the optimized reaction conditions, six novel 2-ferrocenylpyridines **49** were synthesized in good yields (69-90%).

The basis of third section of the thesis study comprises investigation of cyclization of cyclohexane-embedded *N*-propargylic β-enaminones **50** in basic medium. In order optimize the reaction conditions, the representative reaction of cyclohexane-embedded *N*-propargylic β-enaminone **50a** under different conditions was examined. Depending on optimization studies, the best yield (95%) of cyclization reactions of cyclohexane-embedded *N*-propargylic β-enaminones to the spiro-2*H*-pyrroles was afforded by using 3.0 equiv. of Cs_2CO_3 in refluxing CH_3CN under argon atmosphere. Seventeen spiro-2*H*-pyrroles **51** were synthesized in good to excellent yields (82-97%). In addition to these spiro-2*H*-pyrroles **51**, three derivatives of 2,2-dimethyl-2*H*-pyrroles **72** were prepared in 85-92% yields for comparison.

In the same manner, in order to obtain further functionalized spiro-2*H*-pyrroles, cyclohexane-embedded *N*-propargylic β-enaminones **50** were subjected to Sonogashira cross-coupling with aryl iodides. These arylated β-enaminones **52** with internal alkyne functionality were exposed to base and the oxidized spiro-2*H*-pyrroles were obtained unexpectedly. Then, we proceeded a series of optimization reactions and the highest yield (69%) of product **53** was obtained when treated with 3 equivalents Cs_2CO_3 in DMSO at 80 °C and open to air. By employing these conditions, eight spiro-2*H*-pyrroles **53** with two carbonyl groups via benzylic C-H oxidation were obtained in good yields (60-75%).

In the last part of this thesis study, we investigated Lewis acid promoted electrophilic cyclization of cyclohexane-embedded *N*-propargylic β-enaminones **50** to spiro-1,4-oxazepines **54**. By using 2.0 equiv. of ZnI_2 and 0.15 equiv. $AgSbF_6$ in refluxing DCE under argon atmosphere, the highest yield of spiro-1,4-oxazepine **54** (73%) was obtained from corresponding cyclohexane-embedded *N*-propargylic β-enaminone **50** in optimization studies. According to the results, reaction proceeded smoothly and afforded fourteen spiro-1,4-oxazepines **54** in good to high yields (60-89%). In addition, we synthesized three derivatives of 3,3-dimethyl-1,4-oxazepines **86** as well, which contain two methyl groups, instead of a spiro-cyclohexane unit. These 1,4-oxazepine derivatives were obtained in 65-78% yields, the yields of which are comparable with those of spiro-1,4-oxazepines **54**.

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APPENDIX A

NMR SPECTRA

Bruker Spectrospin Avance DPX400 Ultrashield spectromer was used for the records of ^{1}H and ^{13}CNMR spectra. Chemical shifts are reported in parts per million (ppm) relative to $CDCl_3$ (7.26 and 77.16 ppm in ^{1}H and ^{13}C NMR, respectively).

NMR spectra of synthesized starting materials and products are given below.

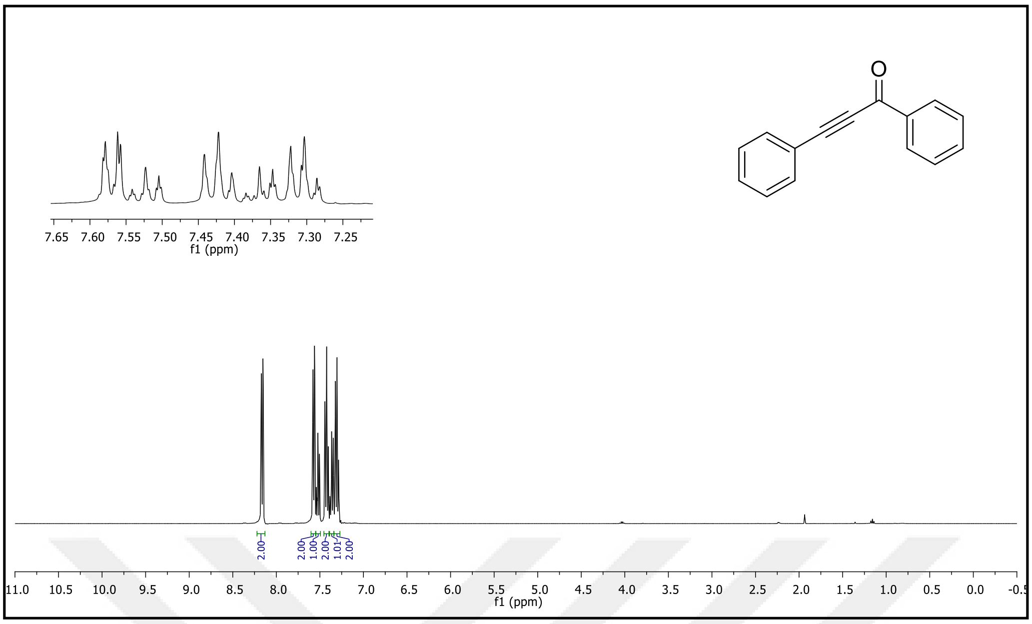

Figure A1. ^{1}H NMR spectrum of compound **26a.**

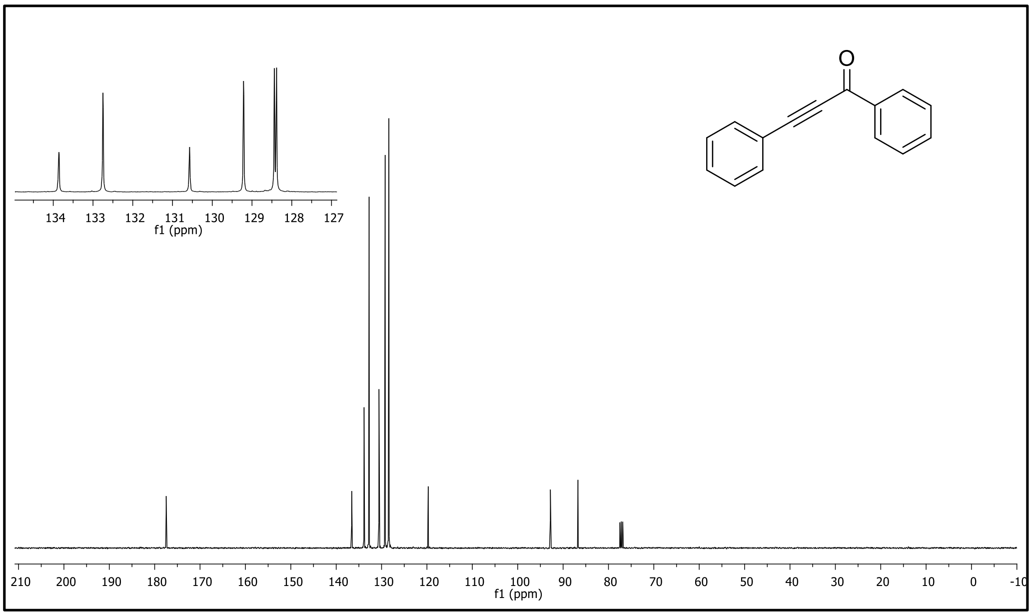

Figure A2. ^{13}C NMR spectrum of compound **26a**.

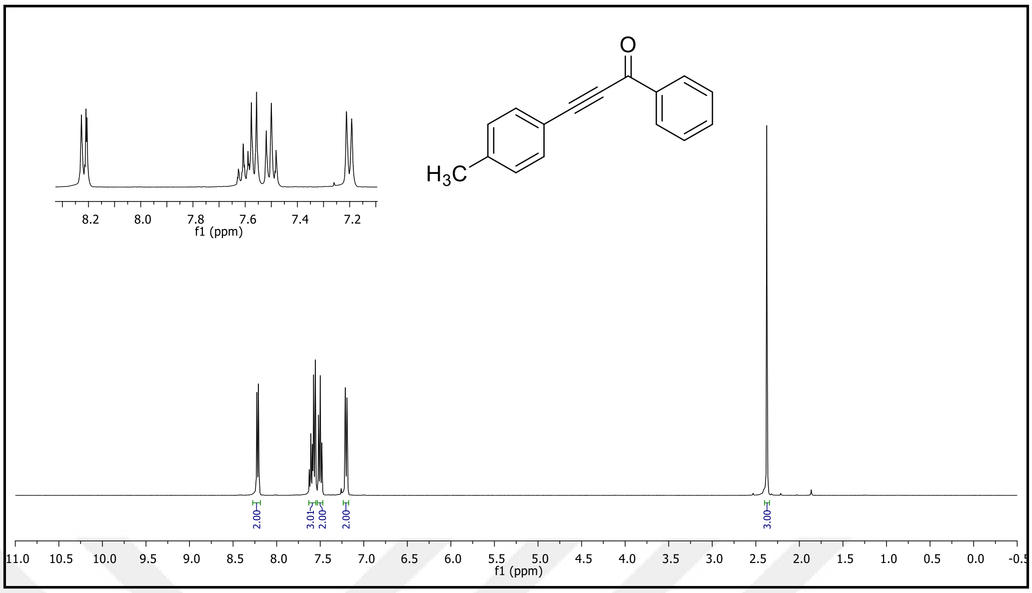

Figure A3. ^{1}H NMR spectrum of compound **26b.**

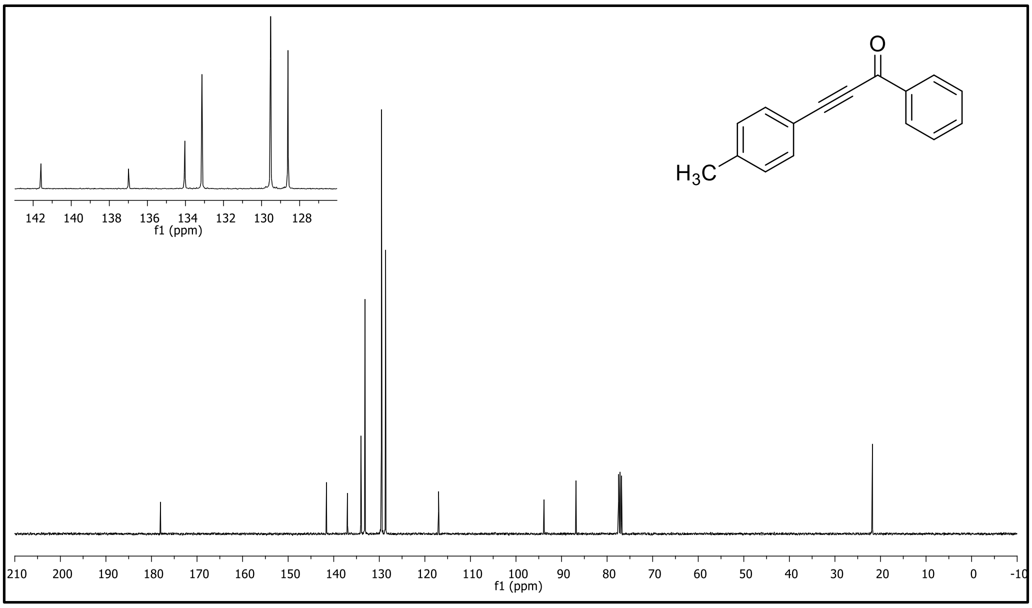

Figure A4. ^{13}C NMR spectrum of compound **26b.**

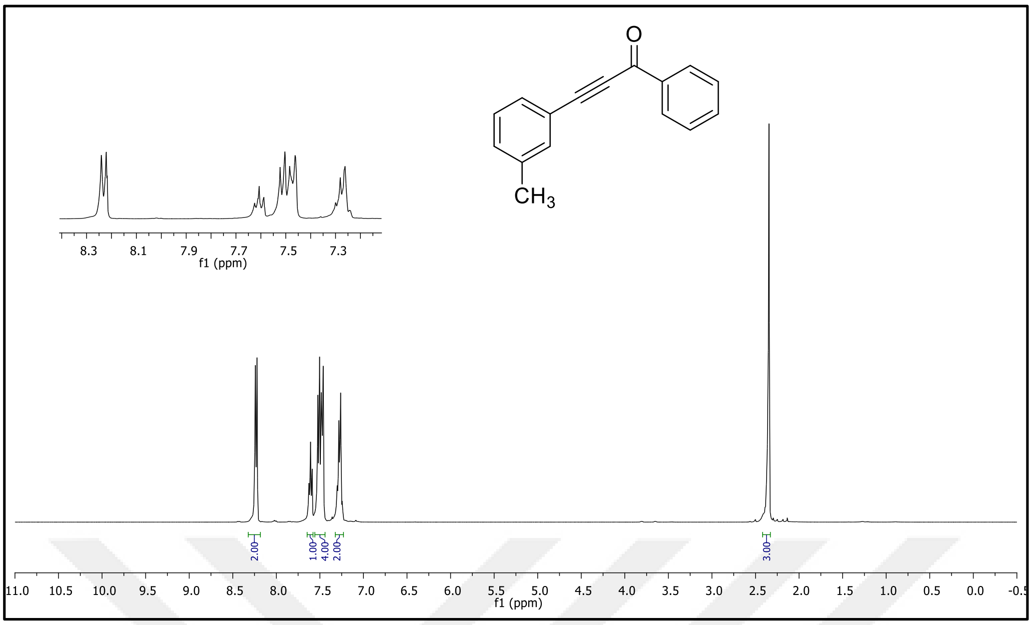

Figure A5. ^{1}H NMR spectrum of compound **26c.**

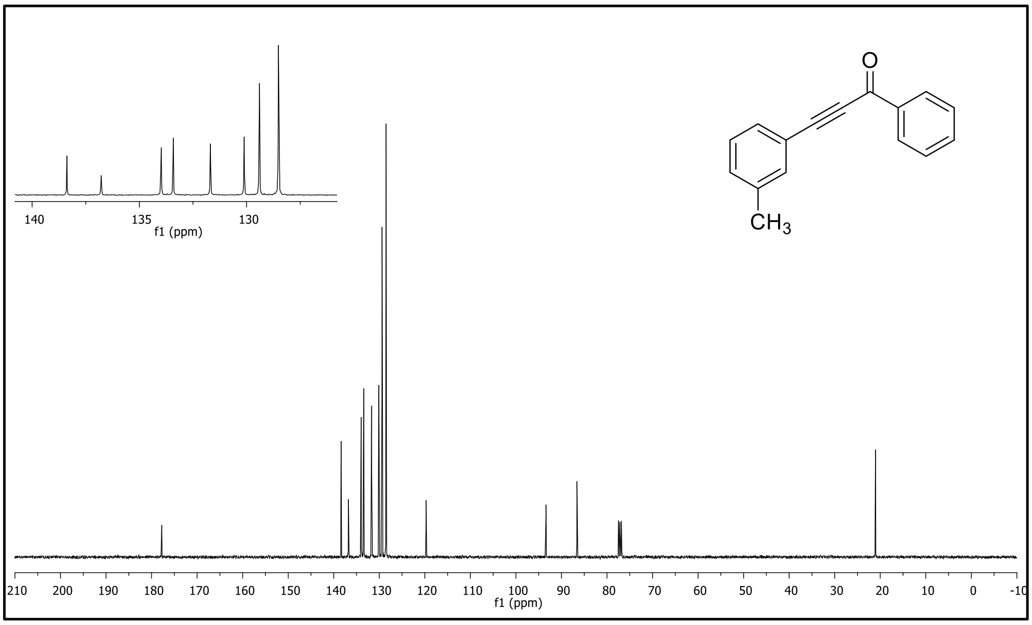

Figure A6. ^{13}C NMR spectrum of compound **26c.**

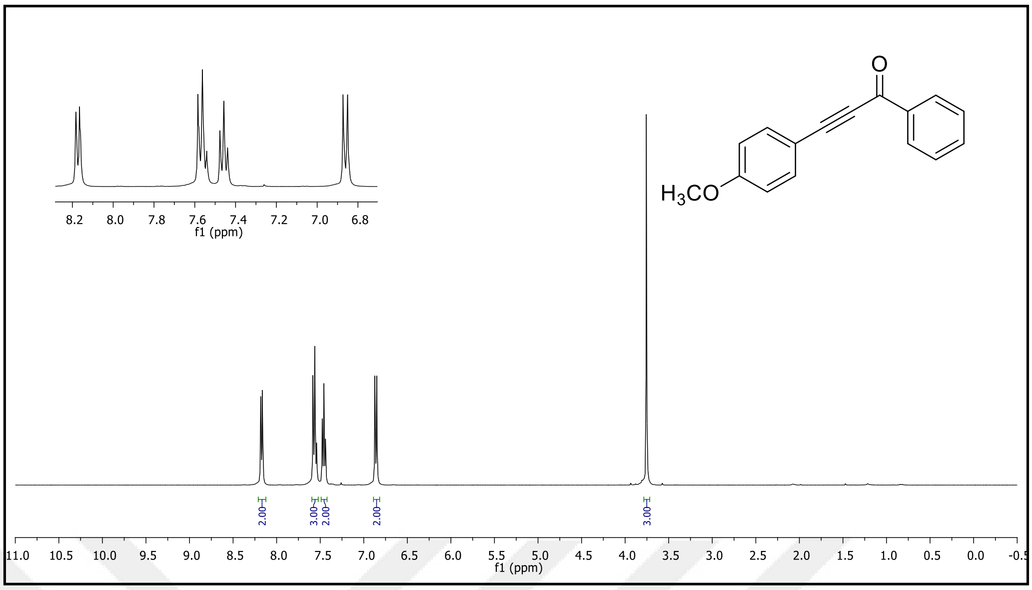

Figure A7. ^{1}H NMR spectrum of compound **26d.**

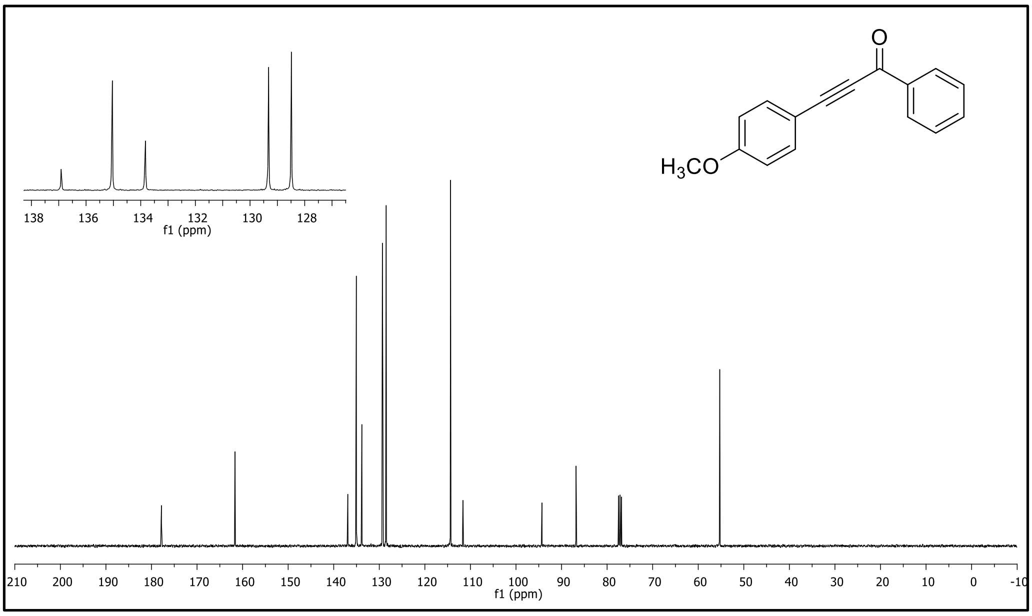

Figure A8.^{13}C NMR spectrum of compound **26d**.

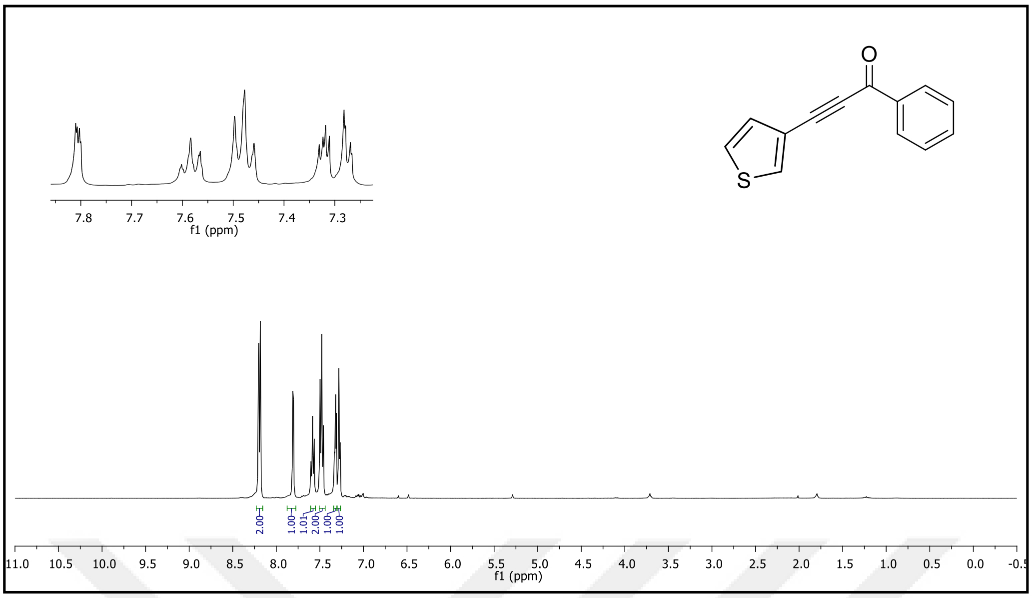

Figure A9. ^{1}H NMR spectrum of compound **26e.**

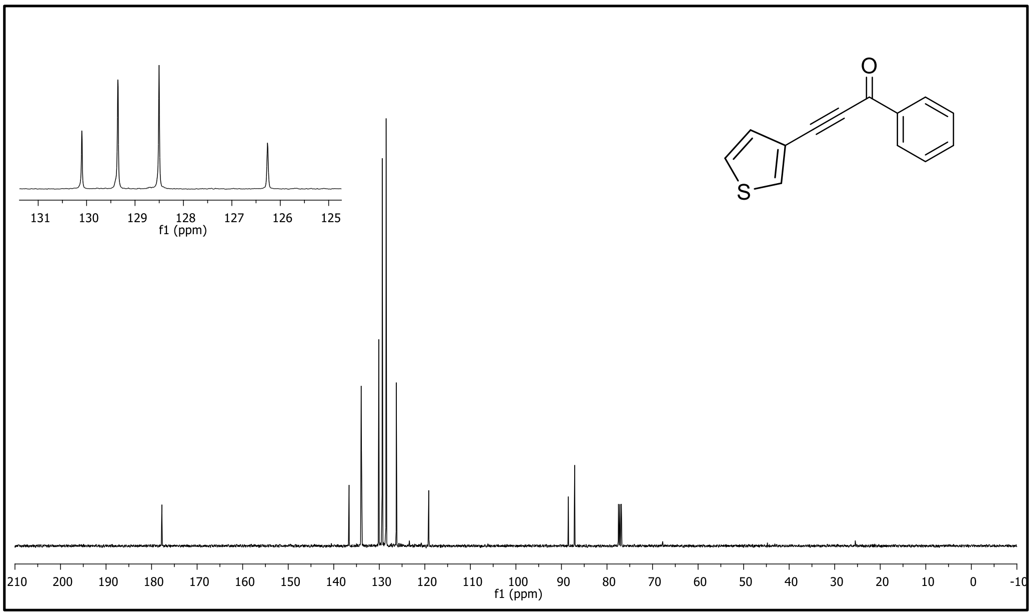

Figure A10. ^{13}C NMR spectrum of compound **26e**

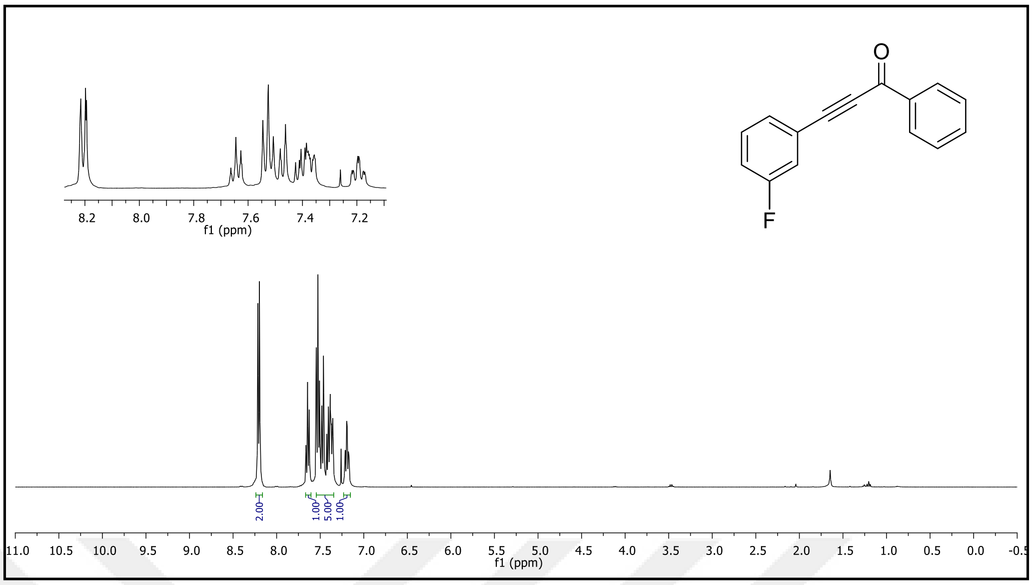

Figure A11. ^{1}H NMR spectrum of compound **26f**.

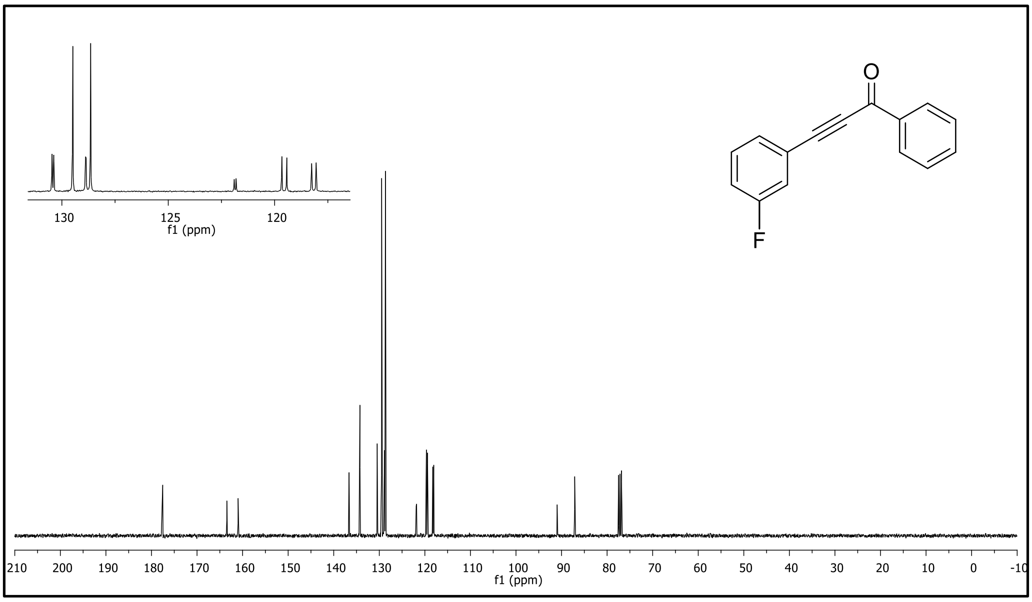

Figure A12.^{13}C NMR spectrum of compound **26f.**

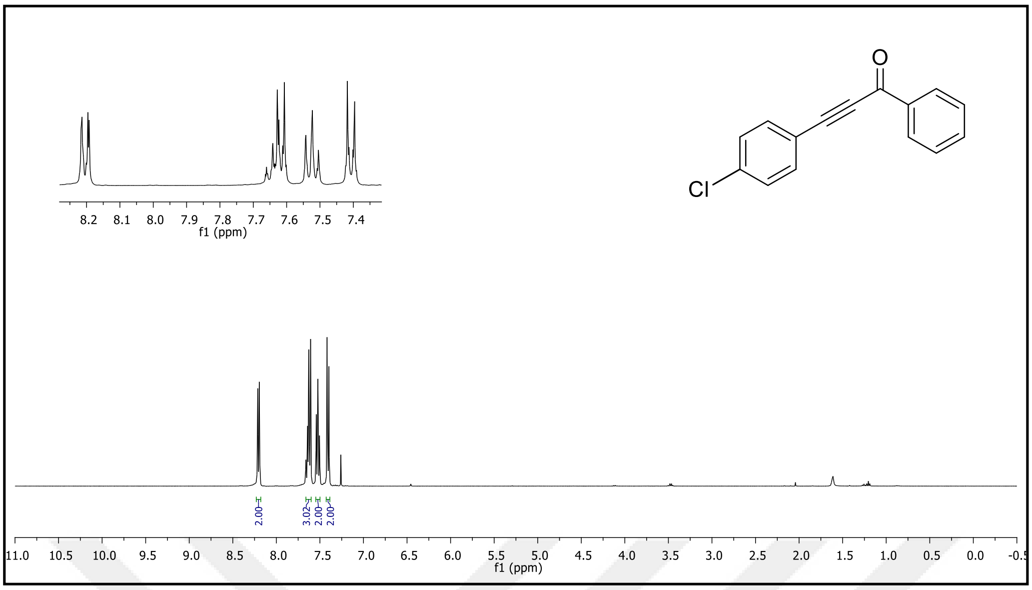

Figure A13. ^{1}H NMR spectrum of compound **26g.**

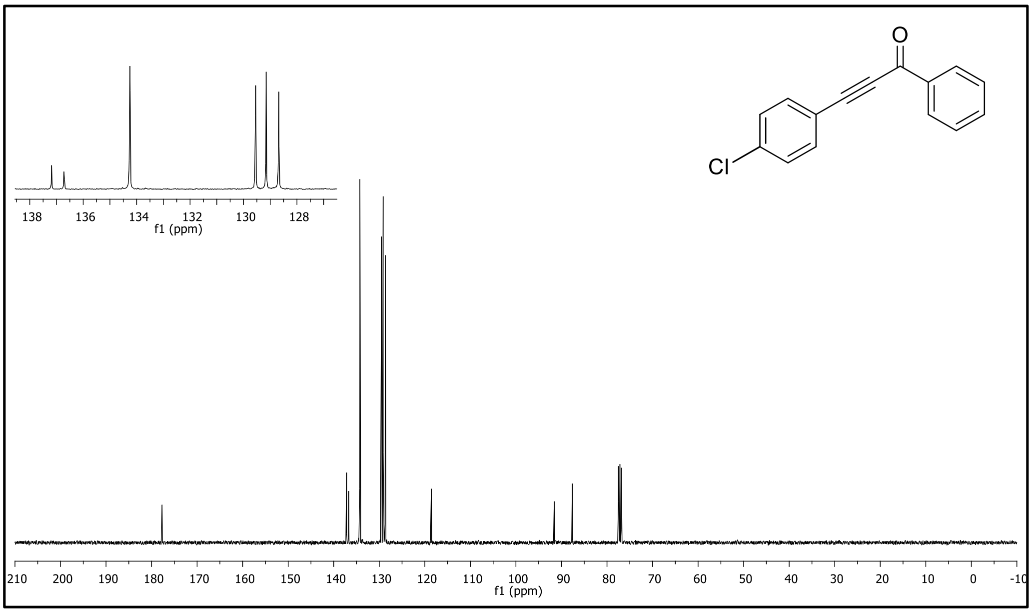

Figure A14. ^{13}C NMR spectrum of compound **26g.**

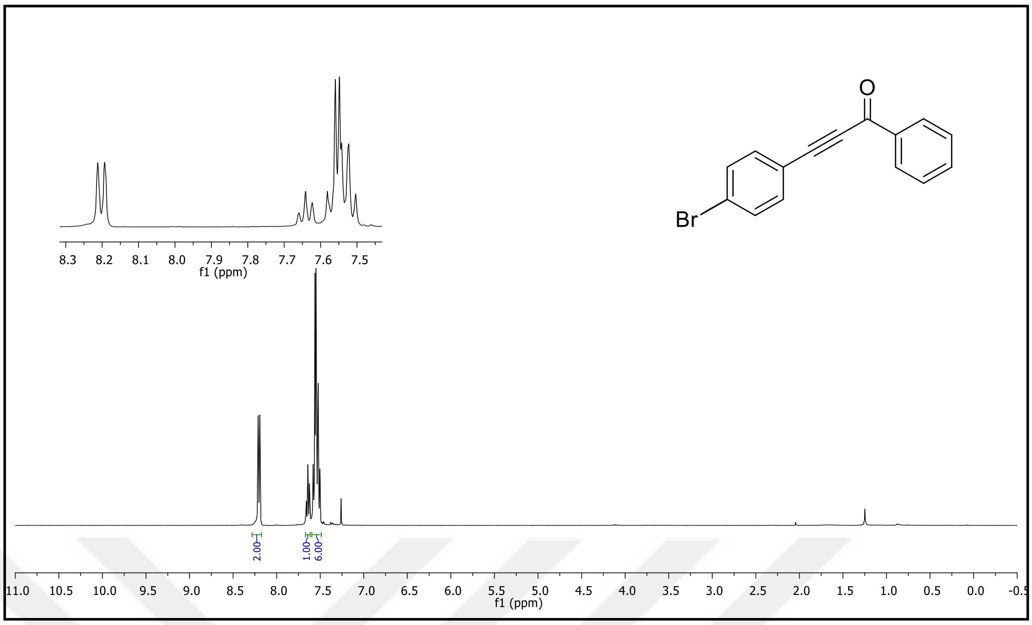

Figure A15. ^{1}H NMR spectrum of compound **26h.**

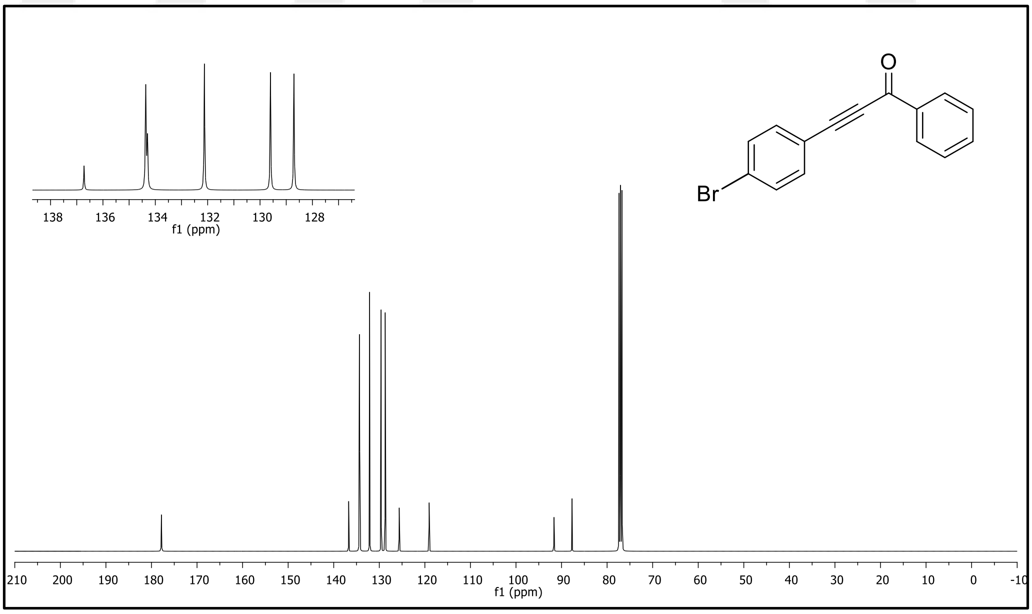

Figure A16. ^{13}C NMR spectrum of compound **26h.**

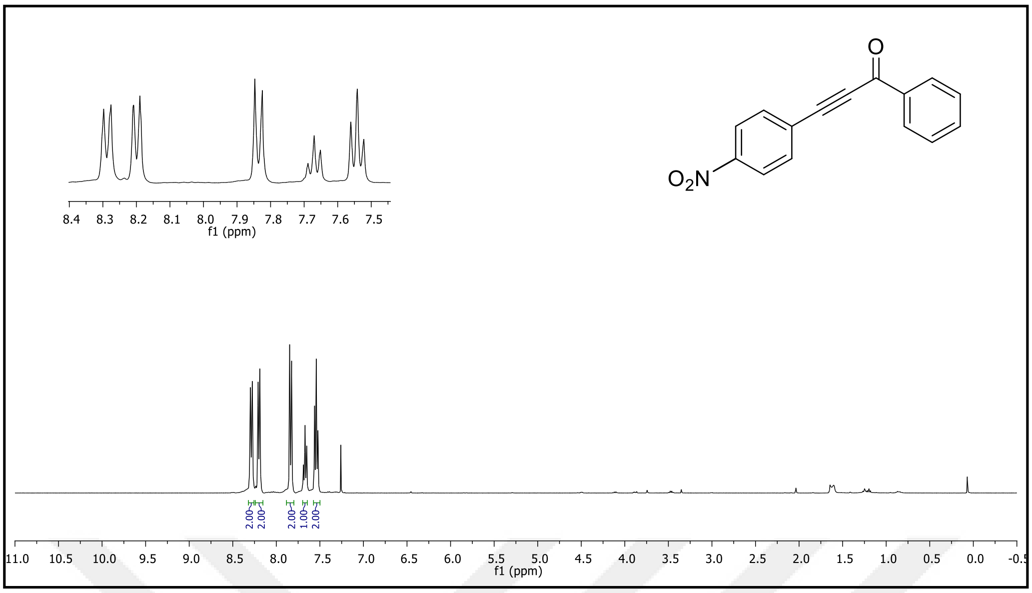

Figure A17. ^{1}H NMR spectrum of compound **26i.**

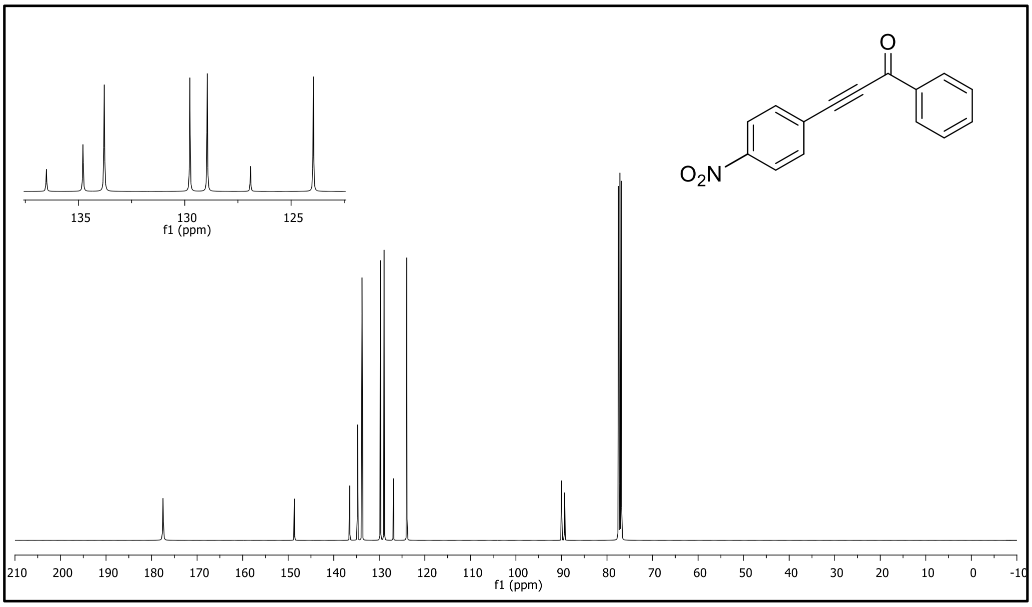

Figure A18. ^{13}C NMR spectrum of compound **26i.**

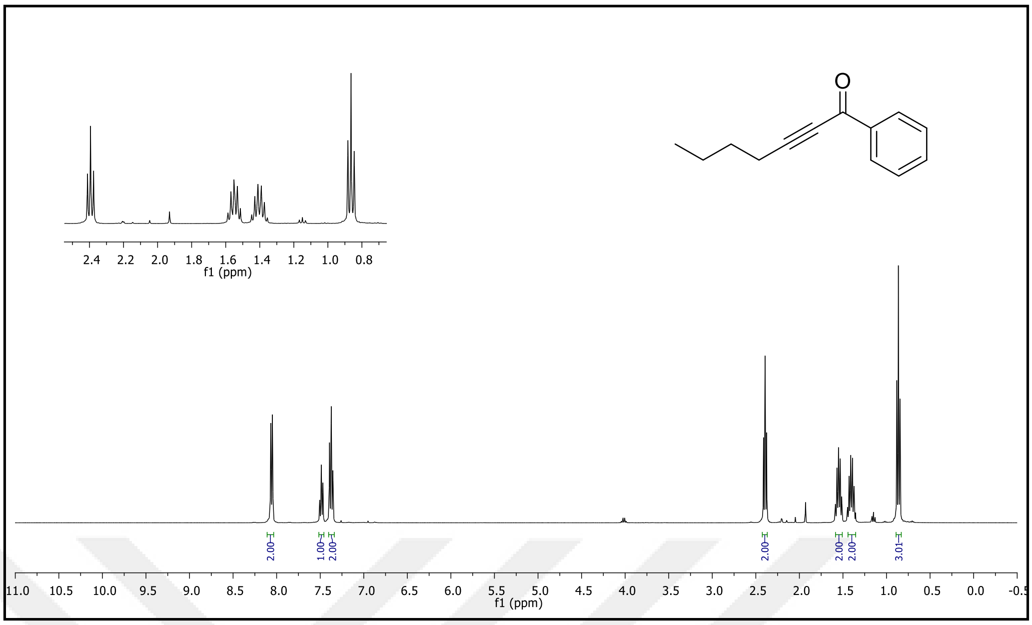

Figure A19. ^{1}H NMR spectrum of compound **26j.**

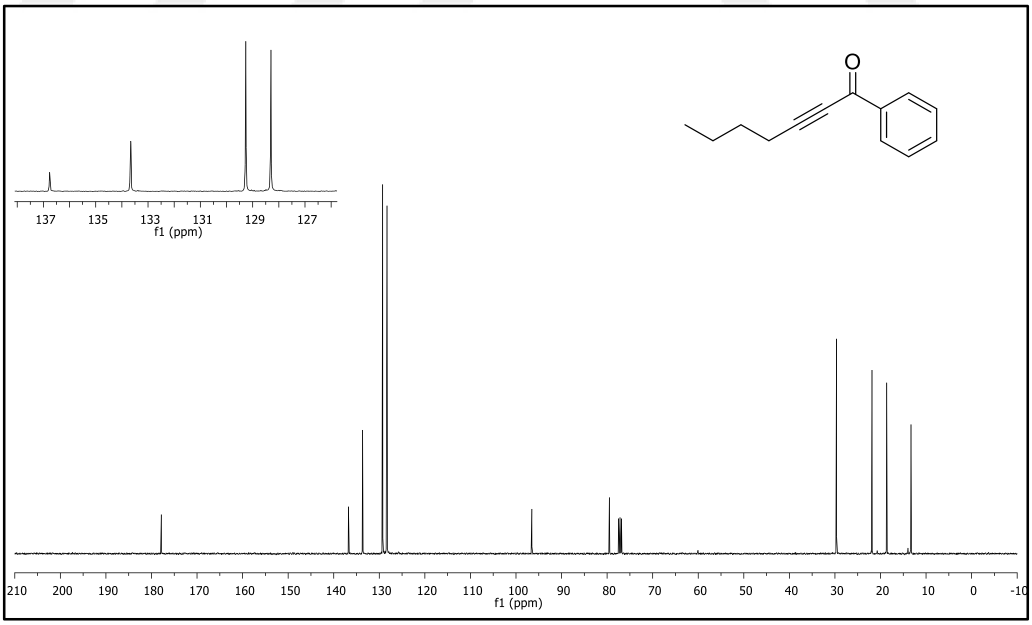

Figure A20. ^{13}C NMR spectrum of compound **26j.**

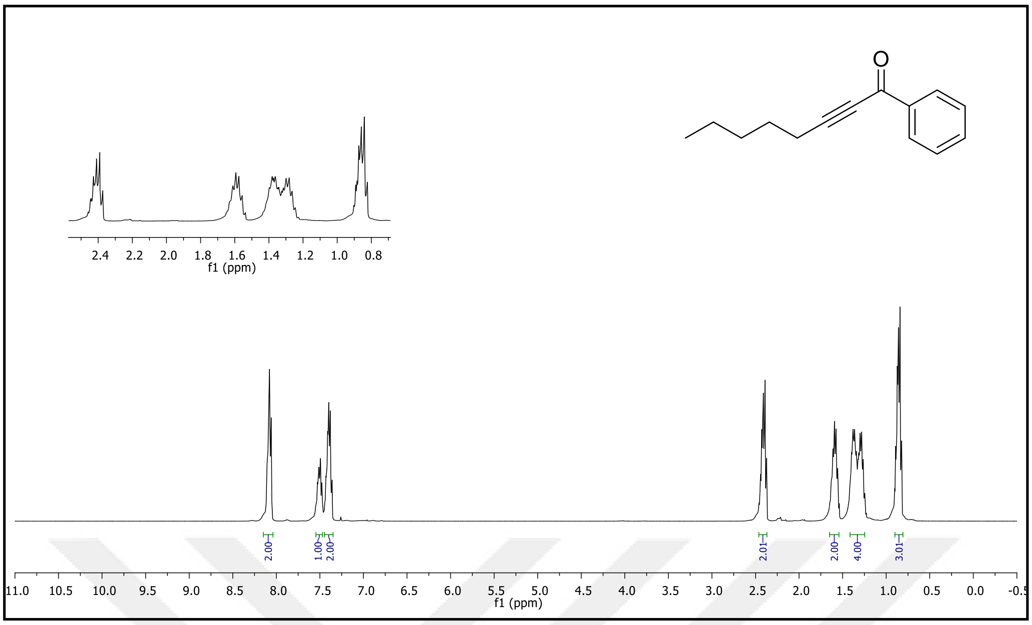

Figure A21. ^{1}H NMR spectrum of compound **26k.**

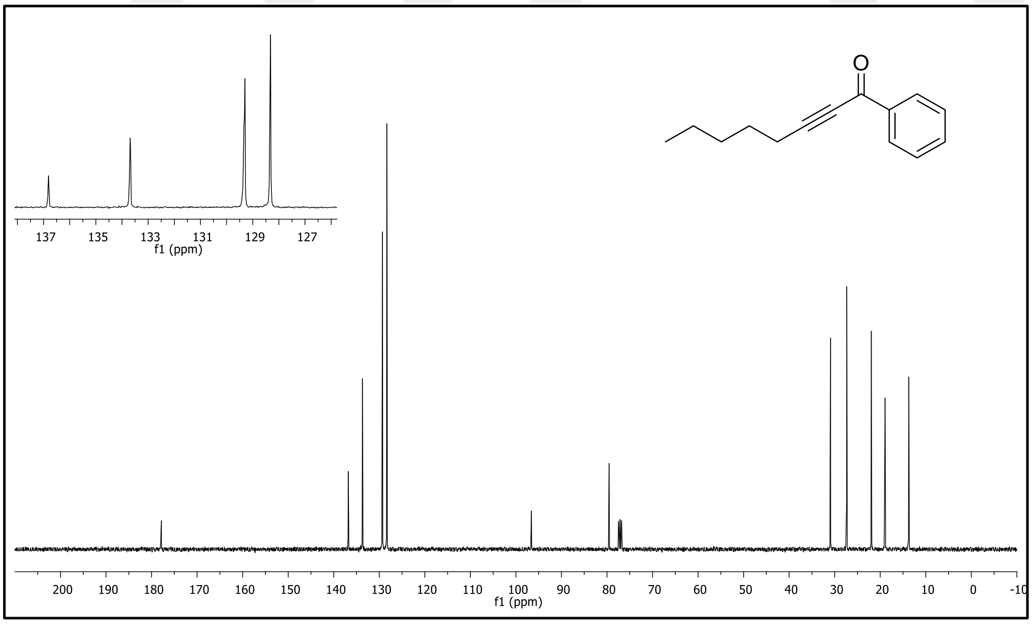

Figure A22. ^{13}C NMR spectrum of compound **26k.**

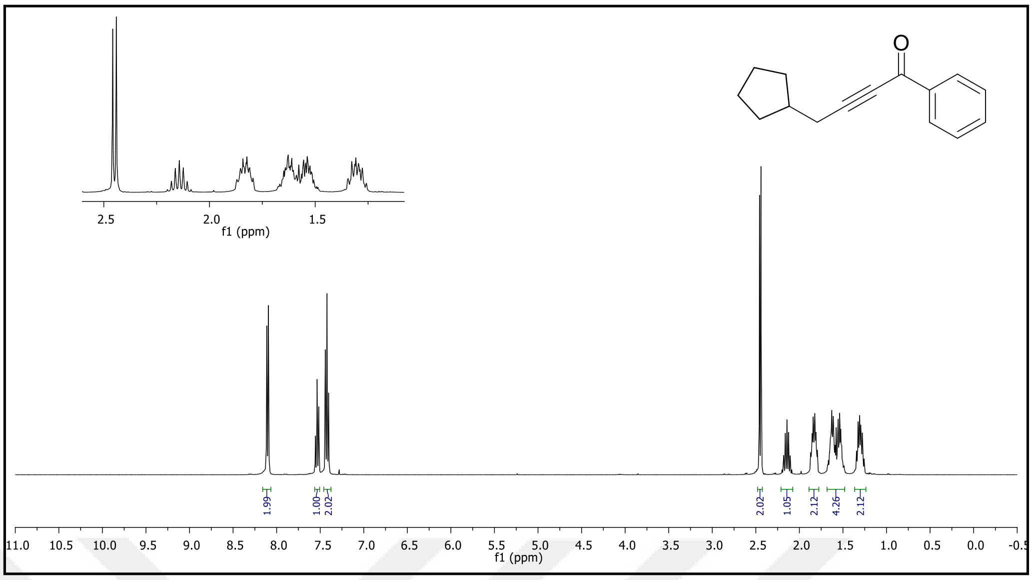

Figure A23. ^{1}H NMR spectrum of compound **26l.**

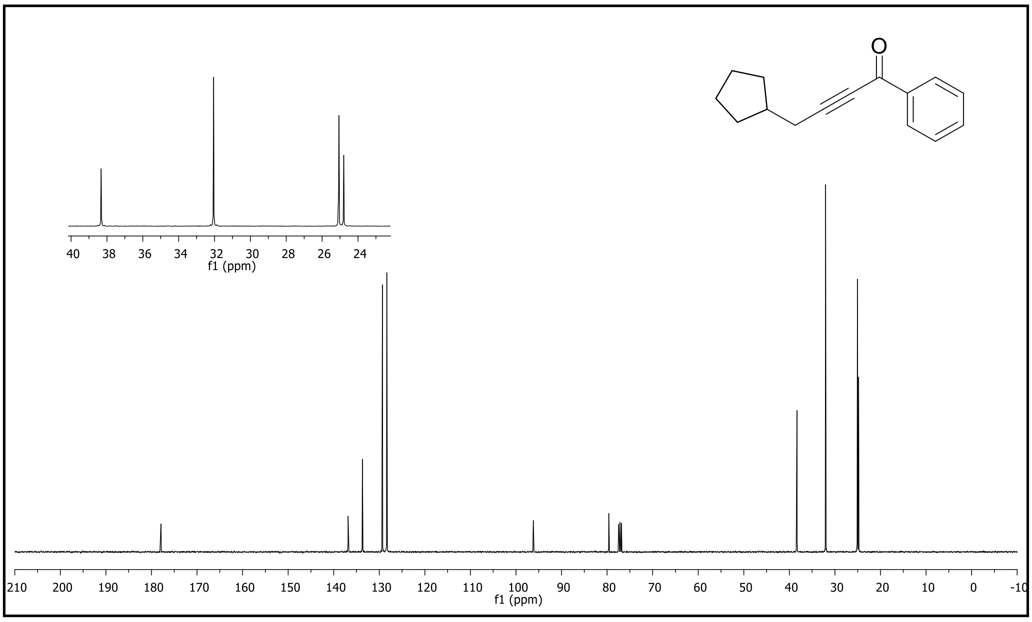

Figure A24. ^{13}C NMR spectrum of compound **26l.**

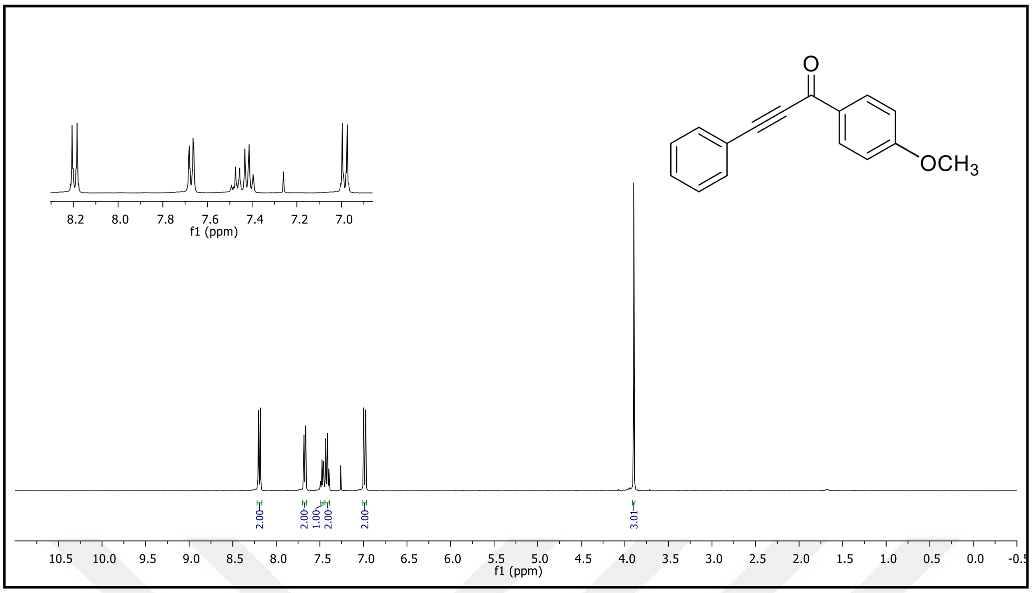

Figure A25. ^{1}H NMR spectrum of compound **26m.**

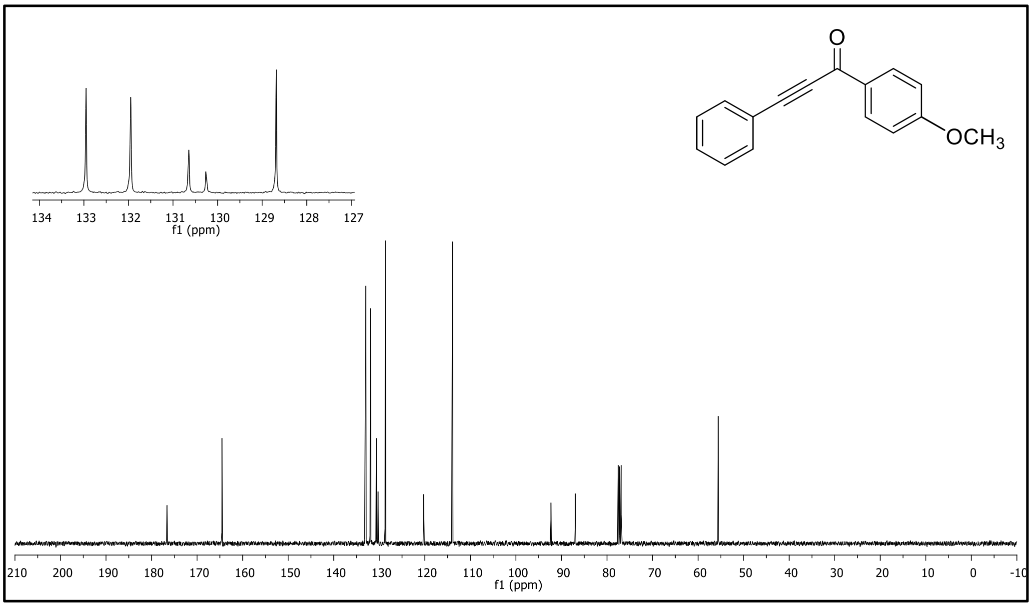

Figure A26. ^{13}C NMR spectrum of compound **26m.**

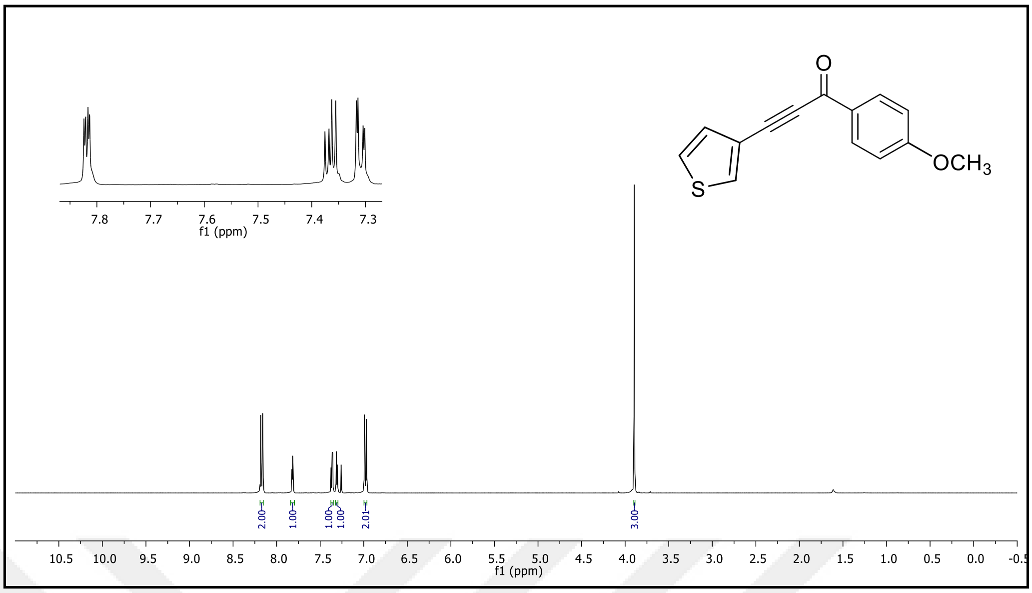

Figure A27. ^{1}H NMR spectrum of compound **26n.**

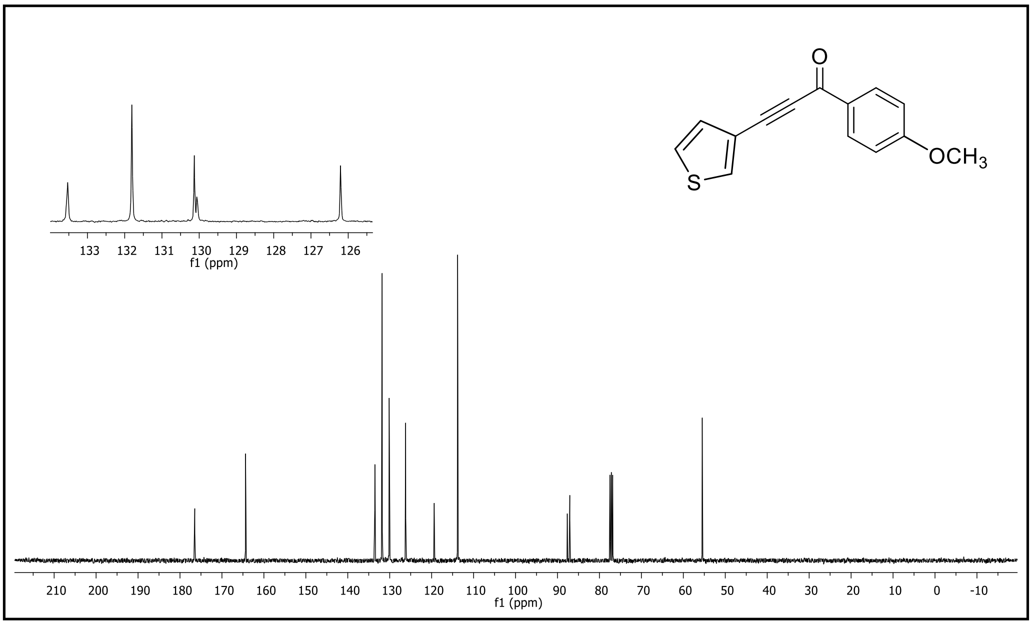

Figure A28. ^{13}C NMR spectrum of compound **26n.**

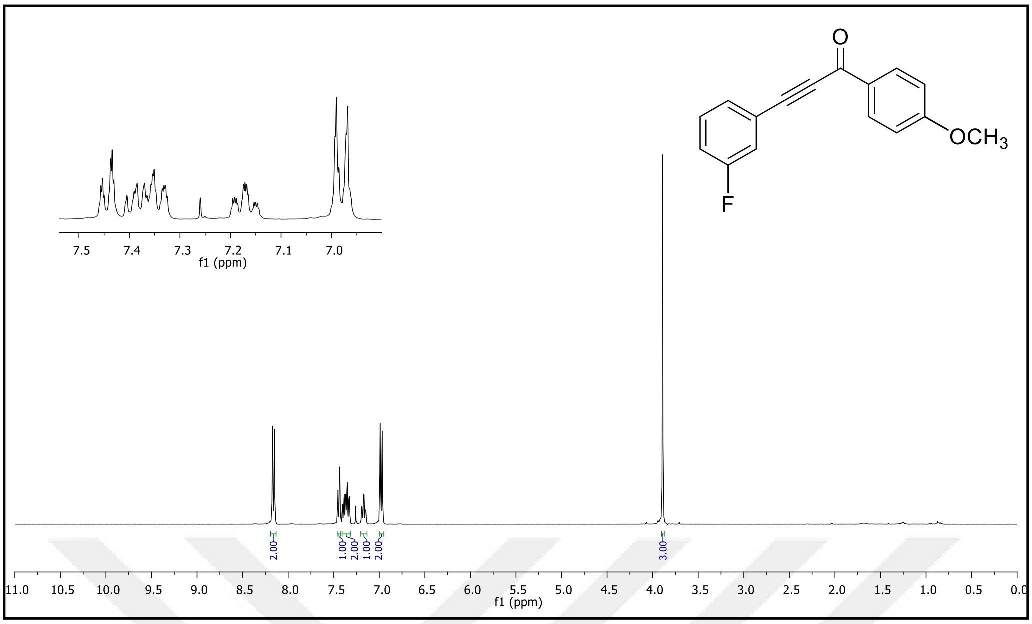

Figure A29. ^{1}H NMR spectrum of compound **26o.**

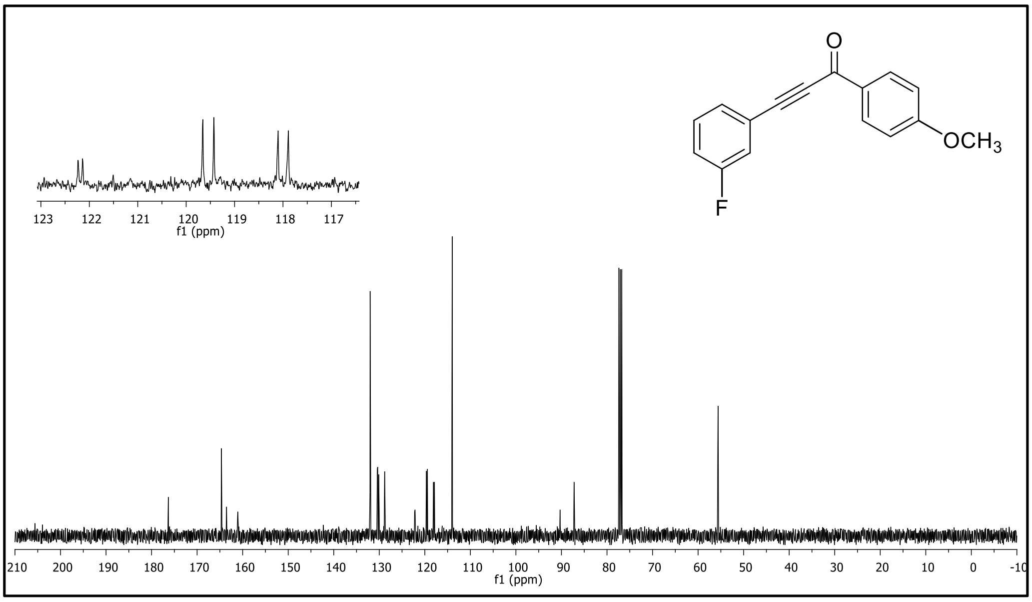

Figure A30. ^{13}C NMR spectrum of compound **26o.**

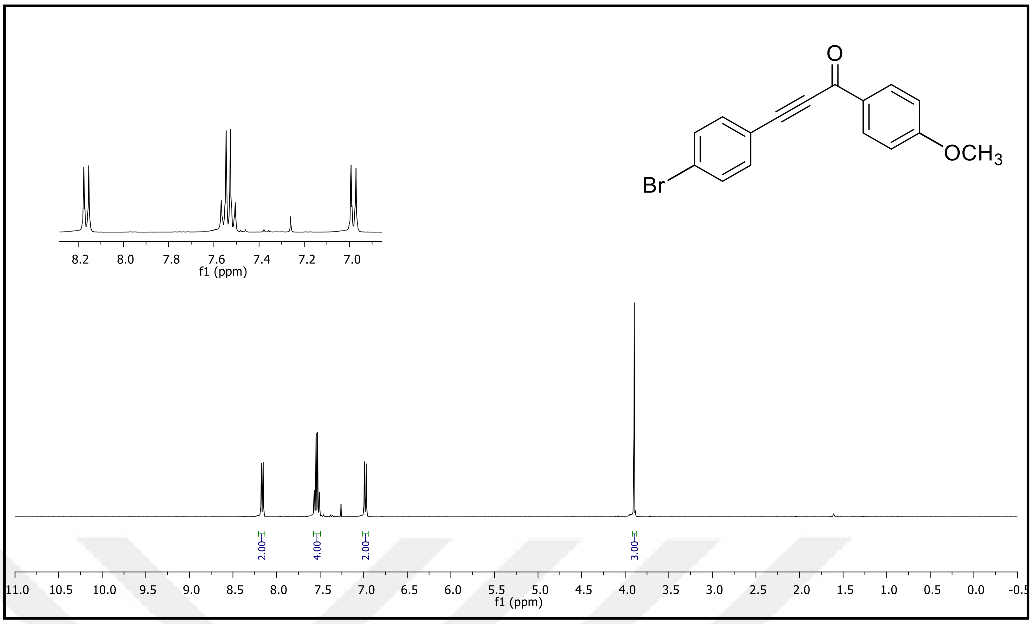

Figure A31. ^{1}HNMR spectrum of compound **26p.**

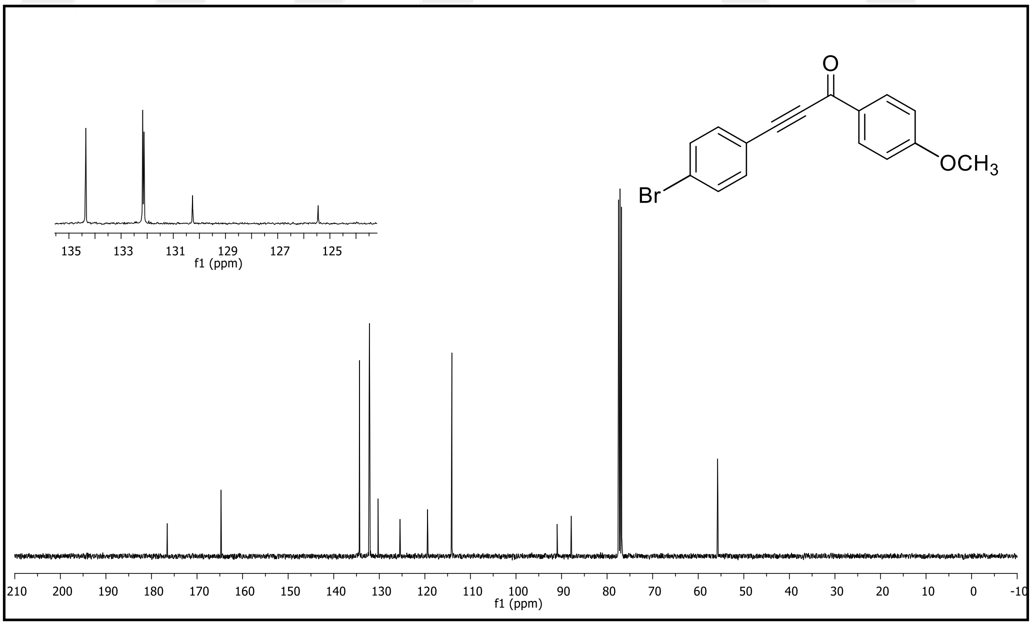

Figure A32. ^{13}C NMR spectrum of compound **26p.**

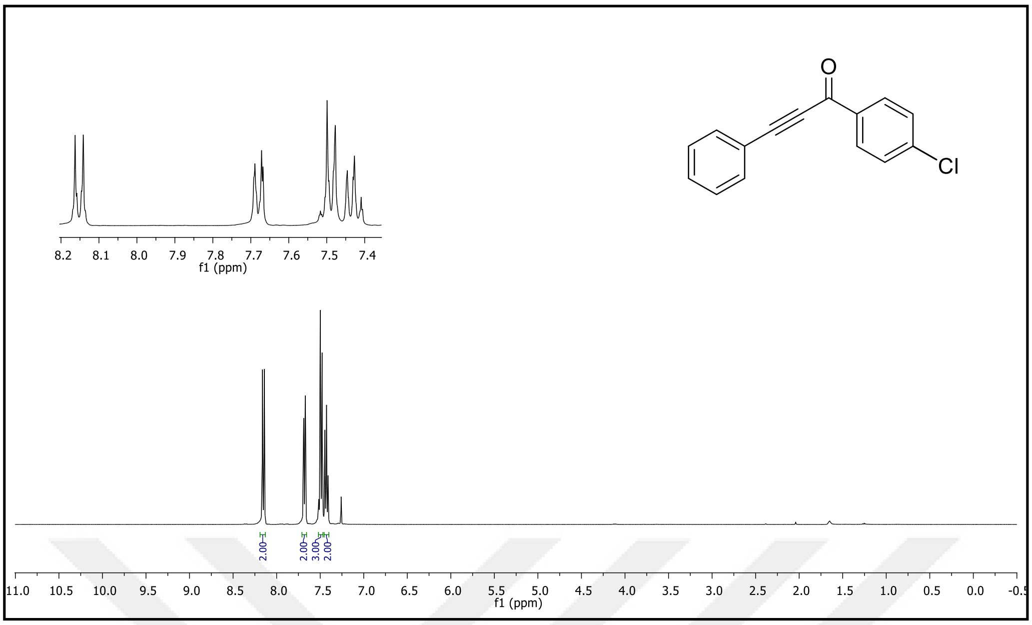

Figure A33. ^{1}H NMR spectrum of compound **26q.**

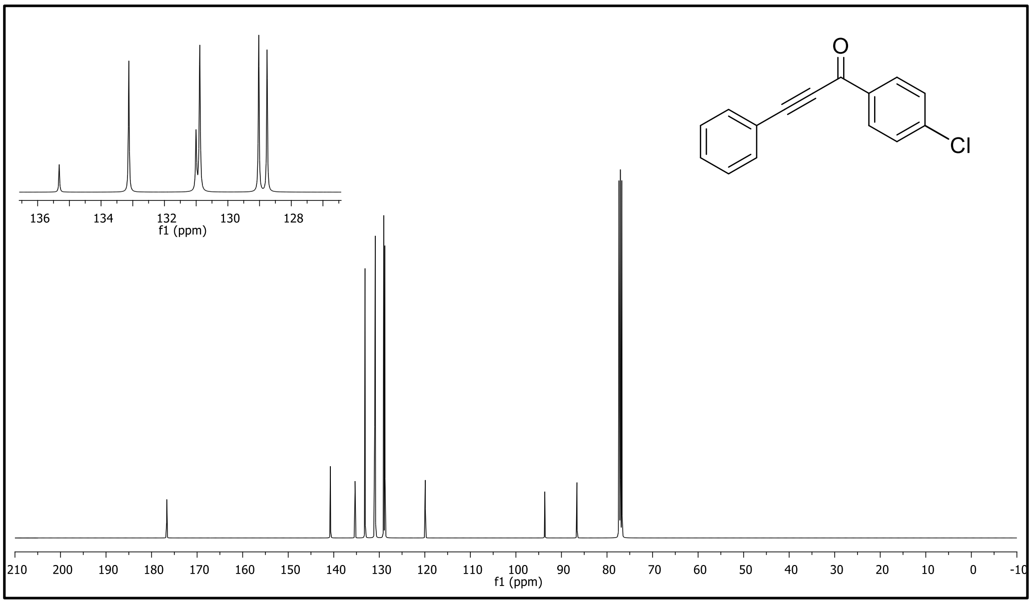

Figure A34. ^{13}C NMR spectrum of compound **26q.**

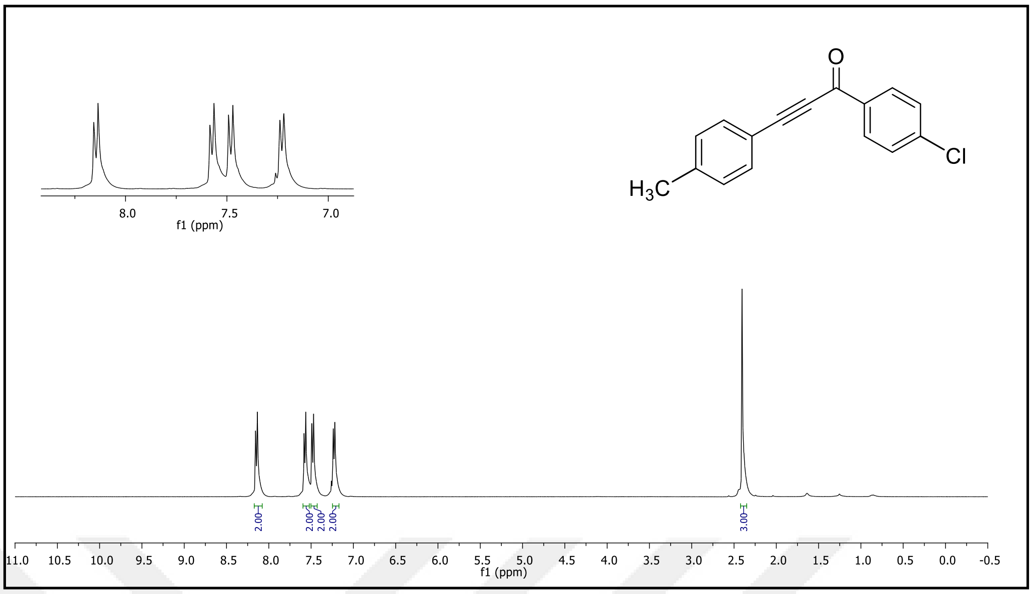

Figure A35. ^{1}H NMR spectrum of compound **26r.**

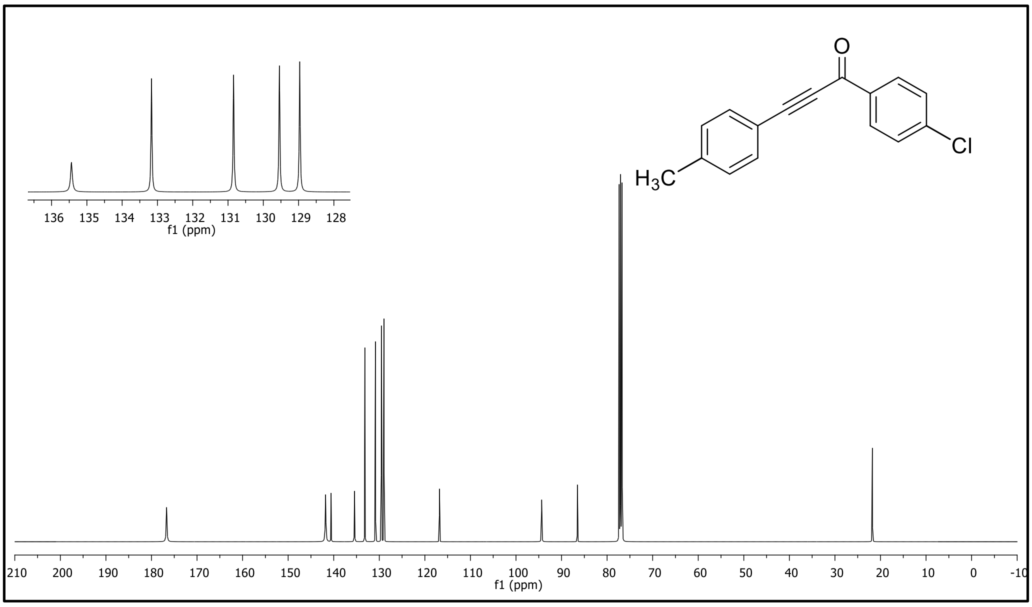

Figure A36. ^{13}C NMR spectrum of compound **26r**

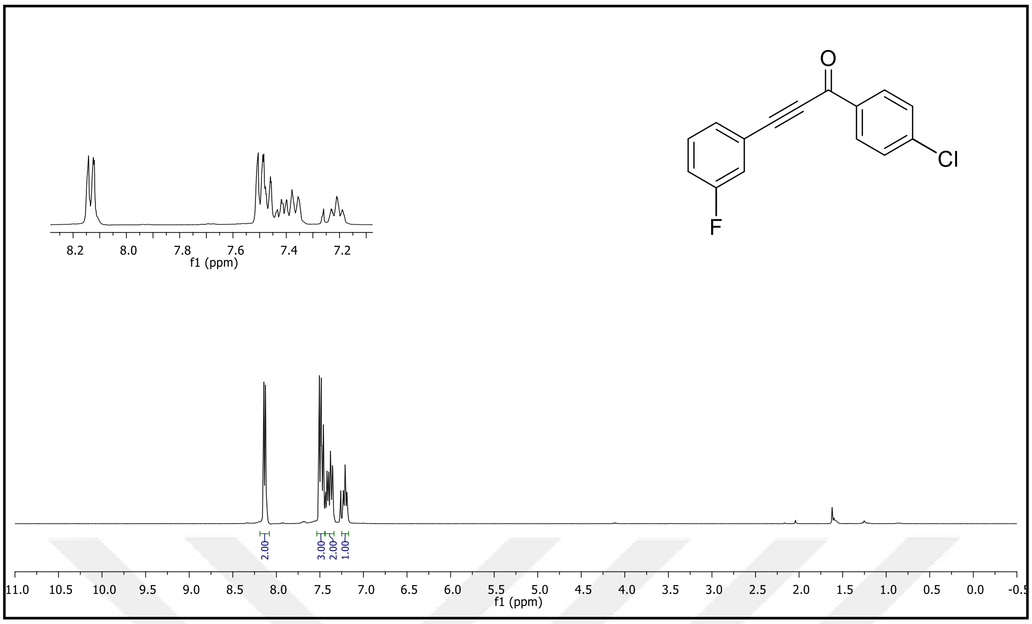

Figure A37. ^{1}H NMR spectrum of compound **26s.**

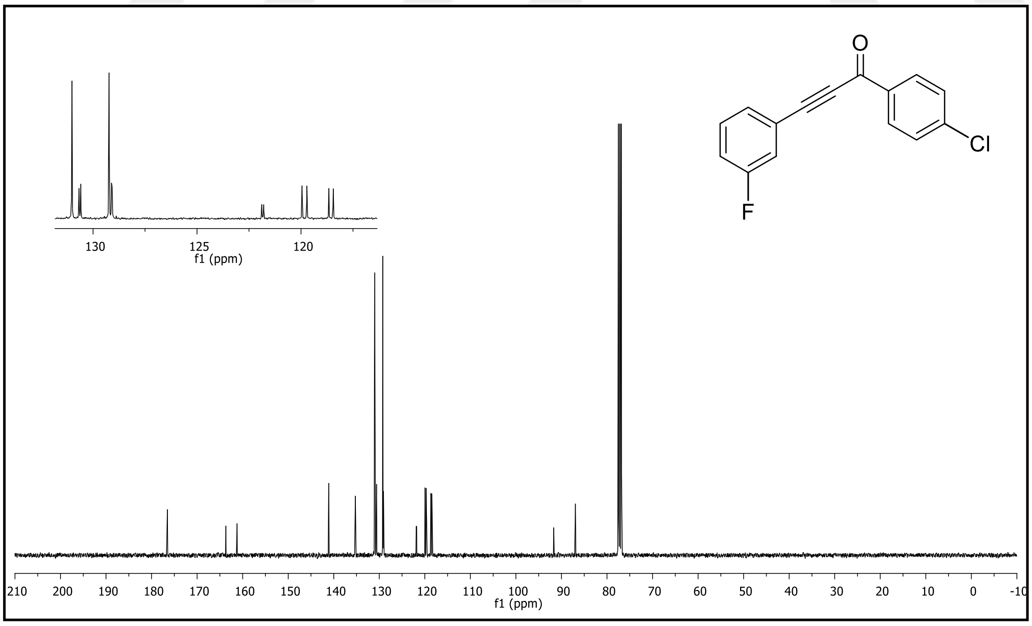

Figure A38. ^{13}C NMR spectrum of compound **26s.**

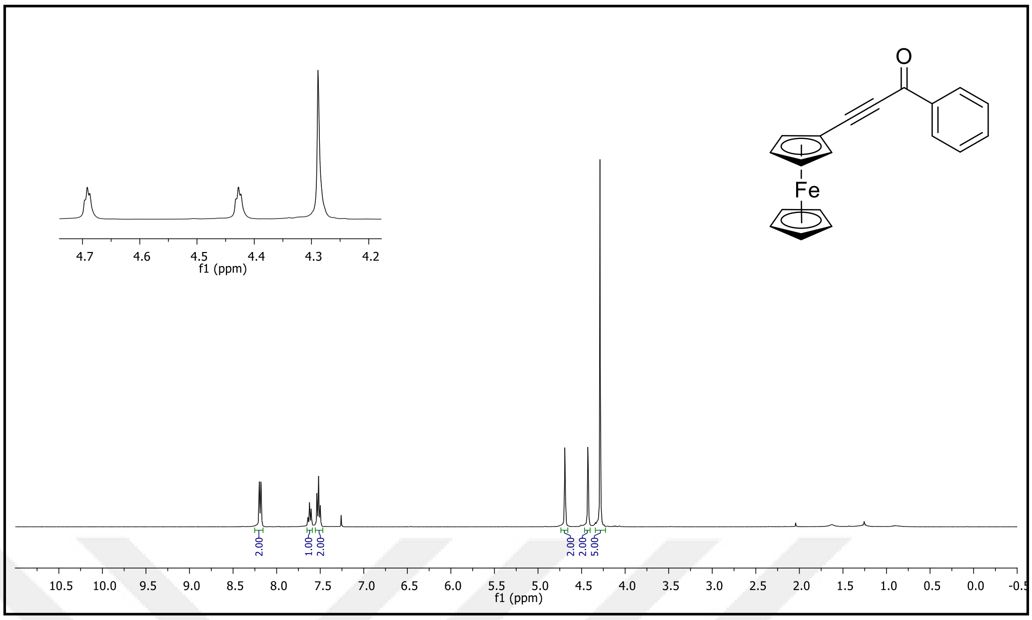

Figure A39. ^{1}H NMR spectrum of compound **26t.**

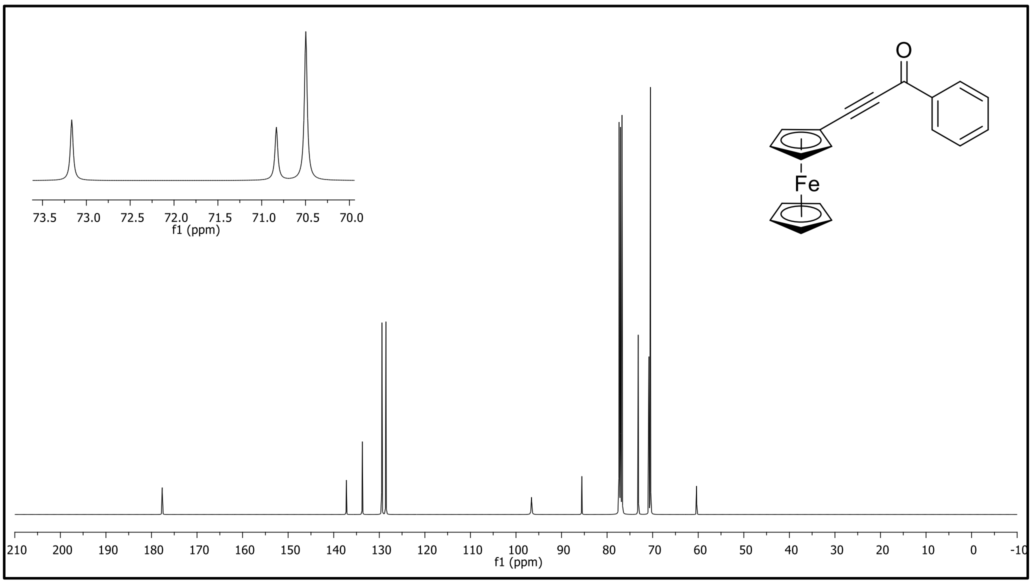

Figure A40. ^{13}C NMR spectrum of compound **26t.**

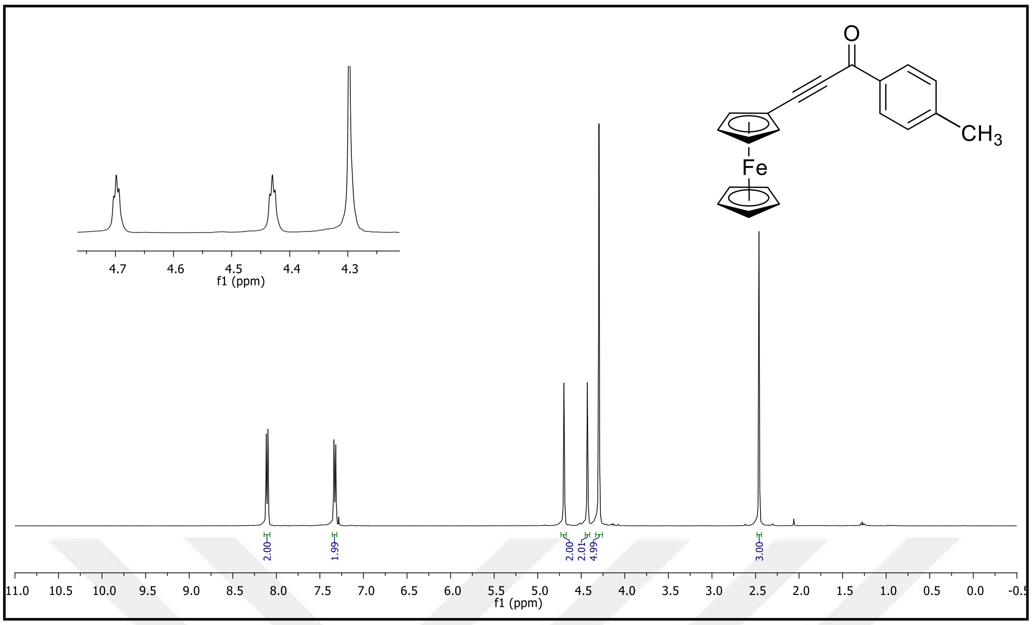

Figure A41. ^{1}H NMR spectrum of compound **26u.**

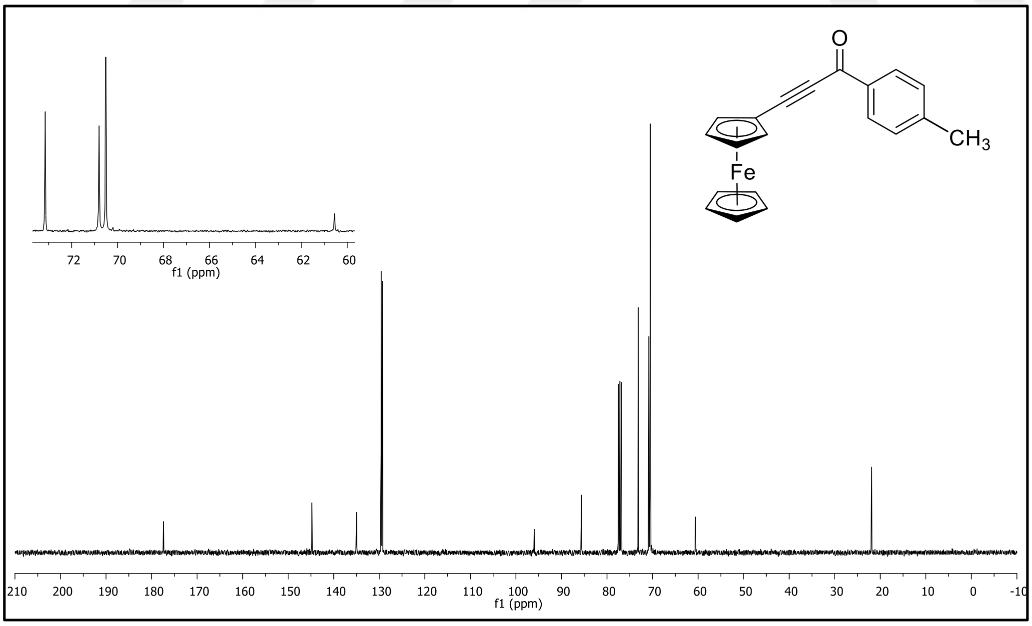

Figure A42. ^{13}C NMR spectrum of compound **26u.**

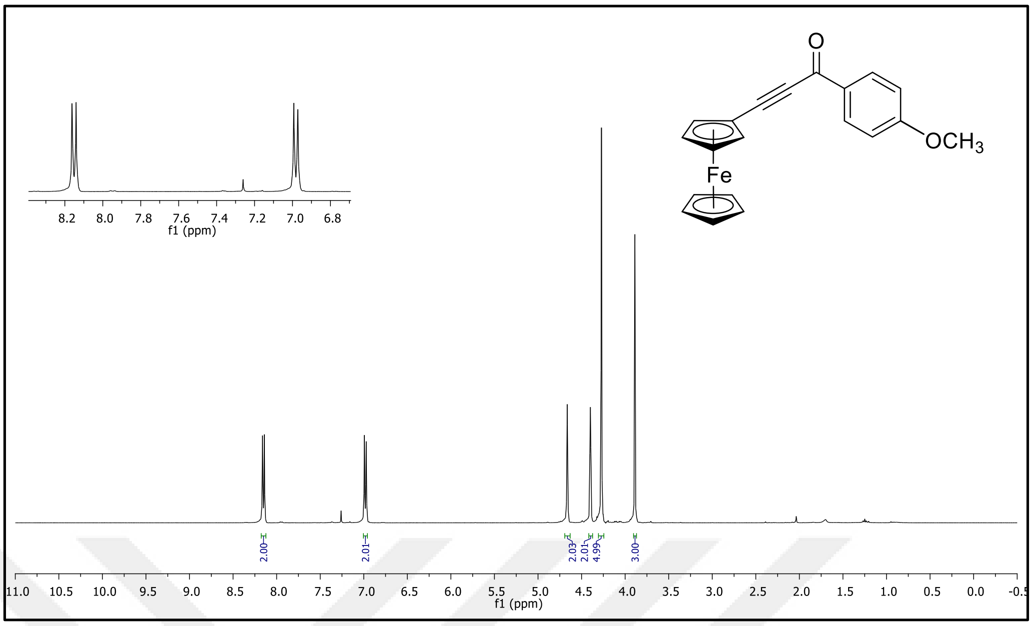

Figure A43. ^{1}H NMR spectrum of compound **26v.**

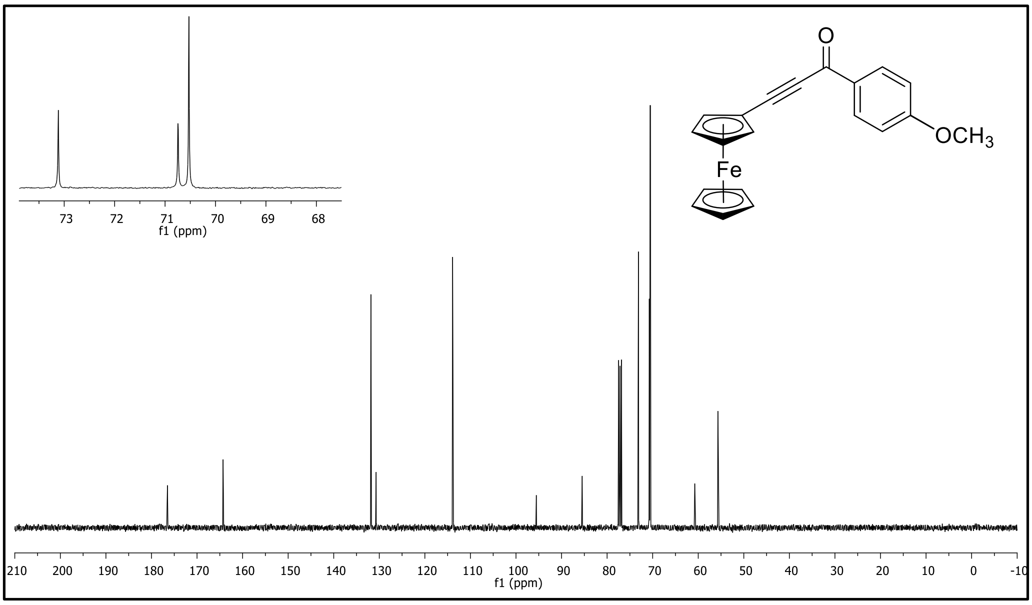

Figure A44. ^{13}C NMR spectrum of compound **26v.**

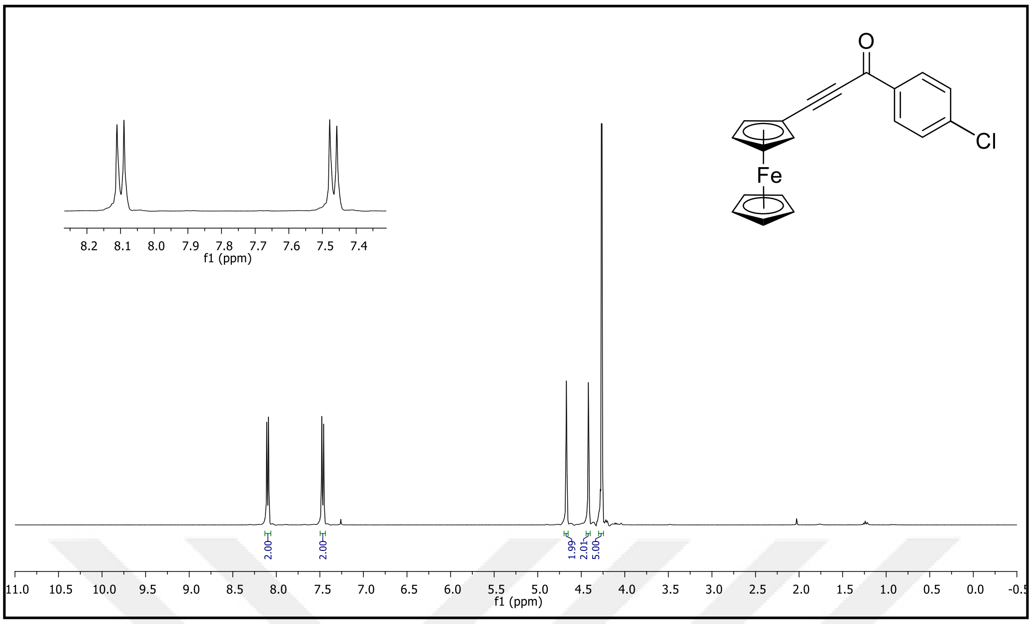

Figure A45. ^{1}H NMR spectrum of compound **26w.**

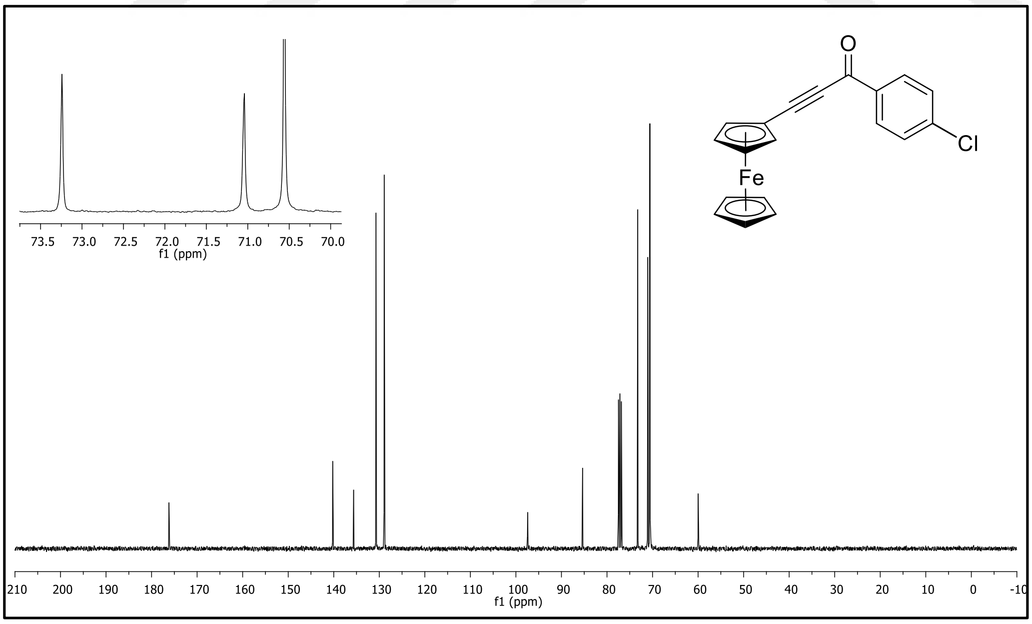

Figure A46. ^{13}C NMR spectrum of compound **26w.**

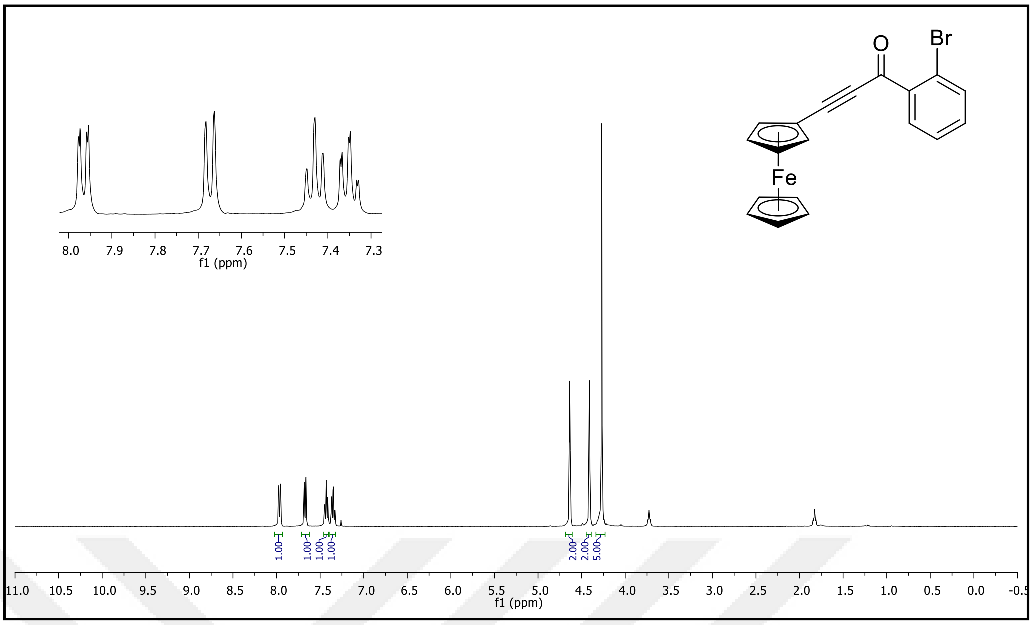

Figure A47. ^{1}H NMR spectrum of compound **26x.**

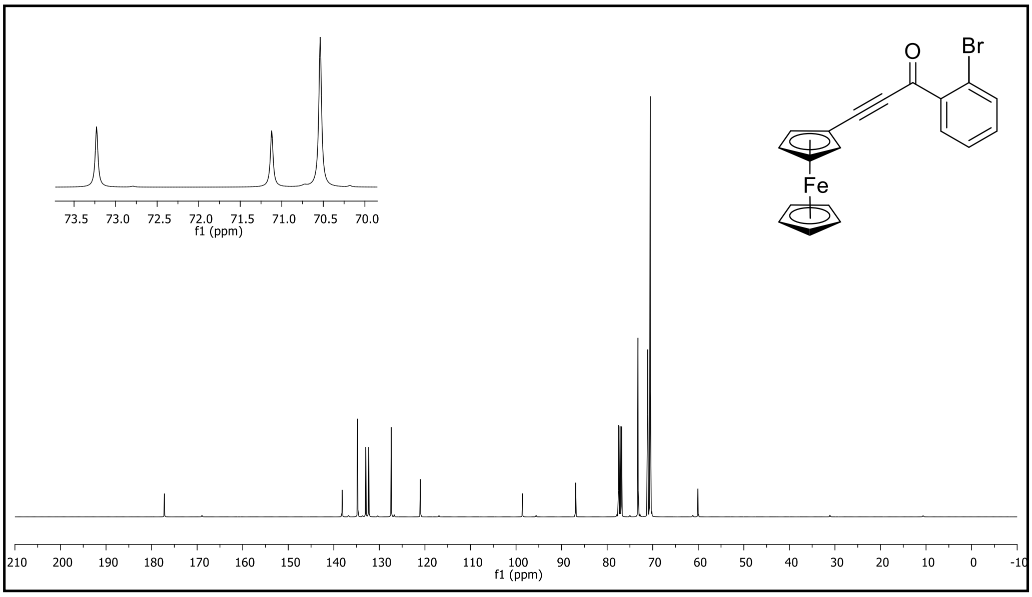

Figure A48. ^{13}C NMR spectrum of compound **26x.**

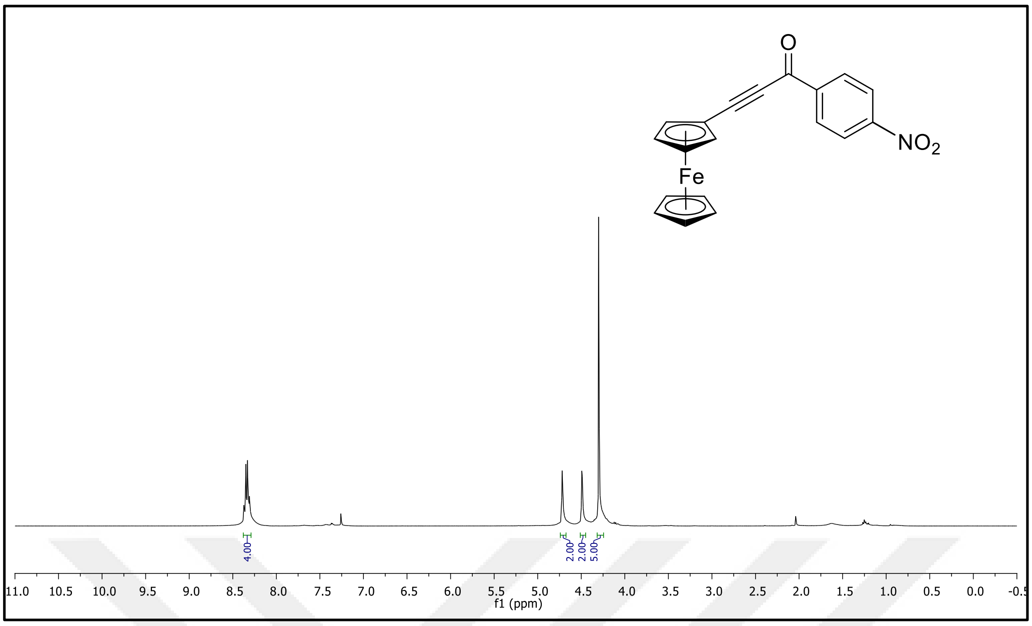

Figure A49. ^{1}H NMR spectrum of compound **26y.**

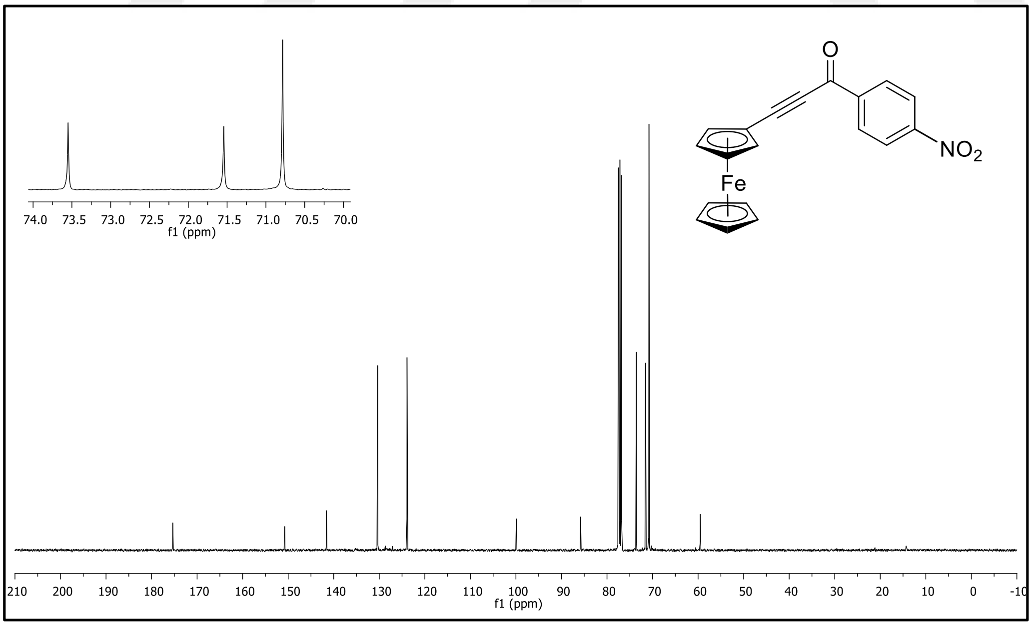

Figure A50. ^{13}C NMR spectrum of compound **26y.**

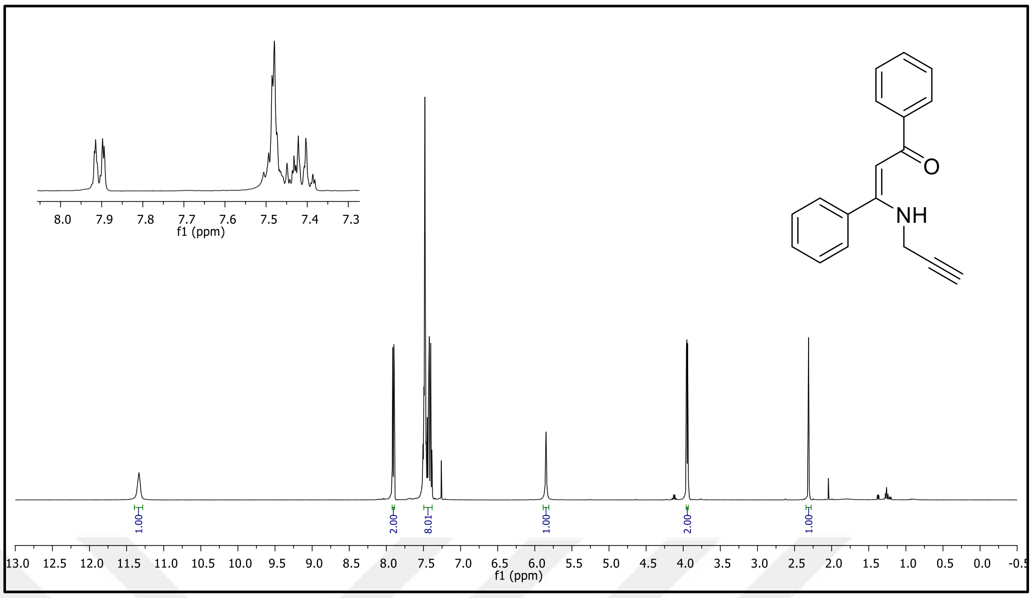

Figure A51. ^{1}H NMR spectrum of compound **32a.**

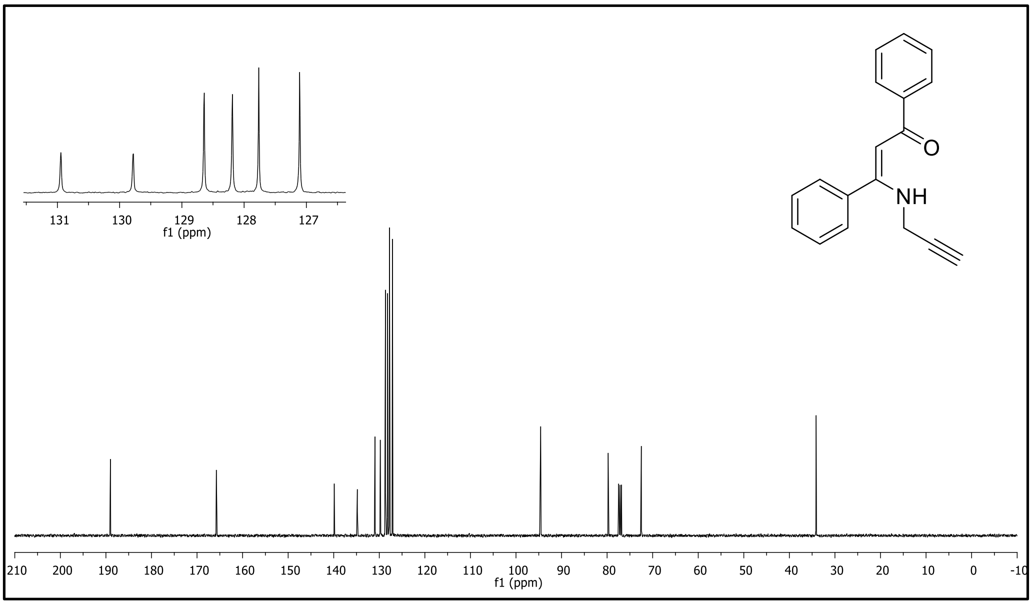

Figure A52. ^{13}C NMR spectrum of compound **32a.**

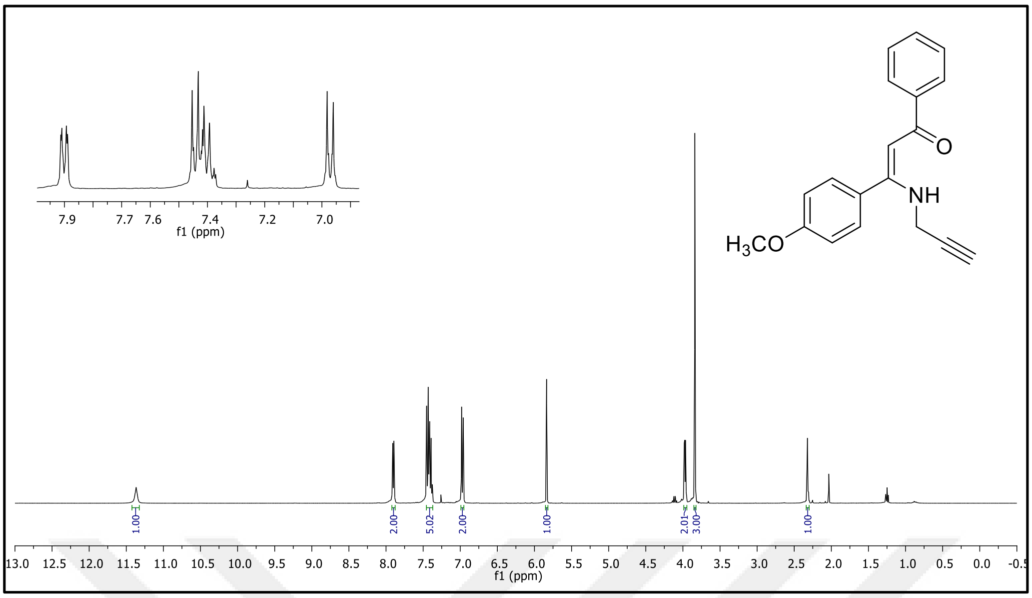

Figure A53. ^1H NMR spectrum of compound **32b.**

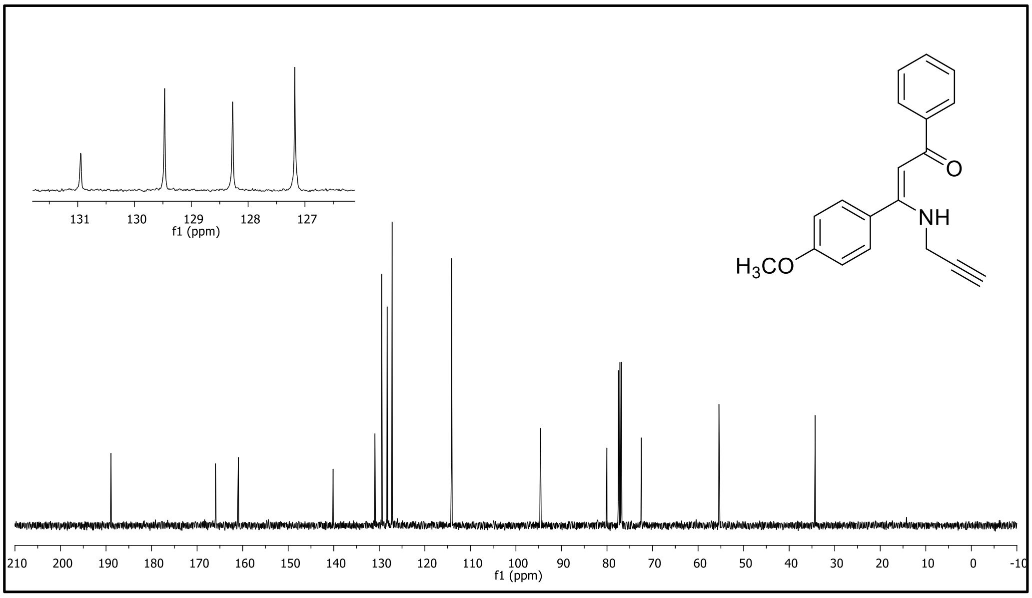

Figure A54. ^{13}C NMR spectrum of compound **32b.**

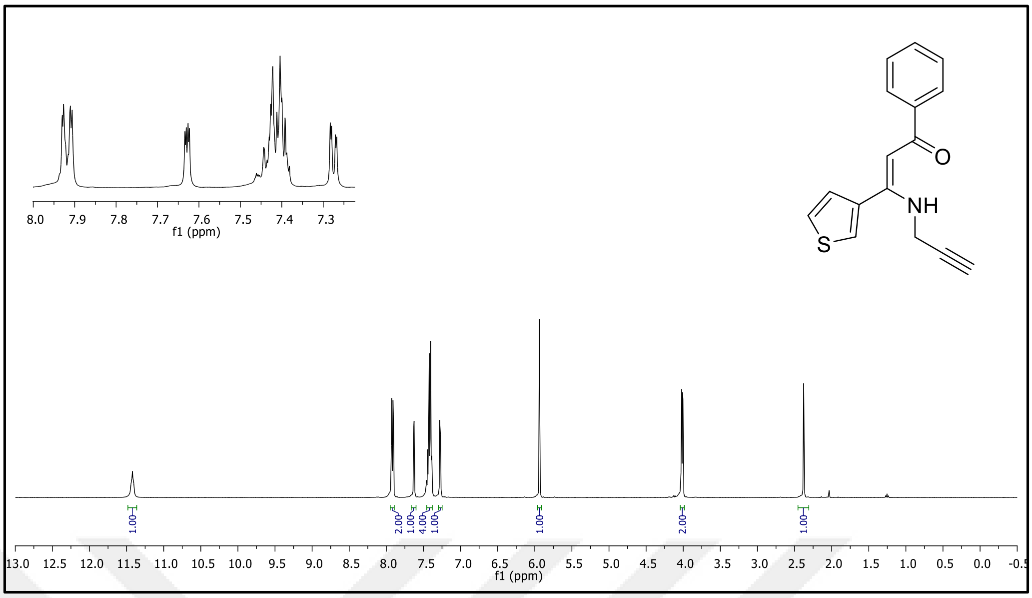

Figure A55. ^{1}H NMR spectrum of compound **32c.**

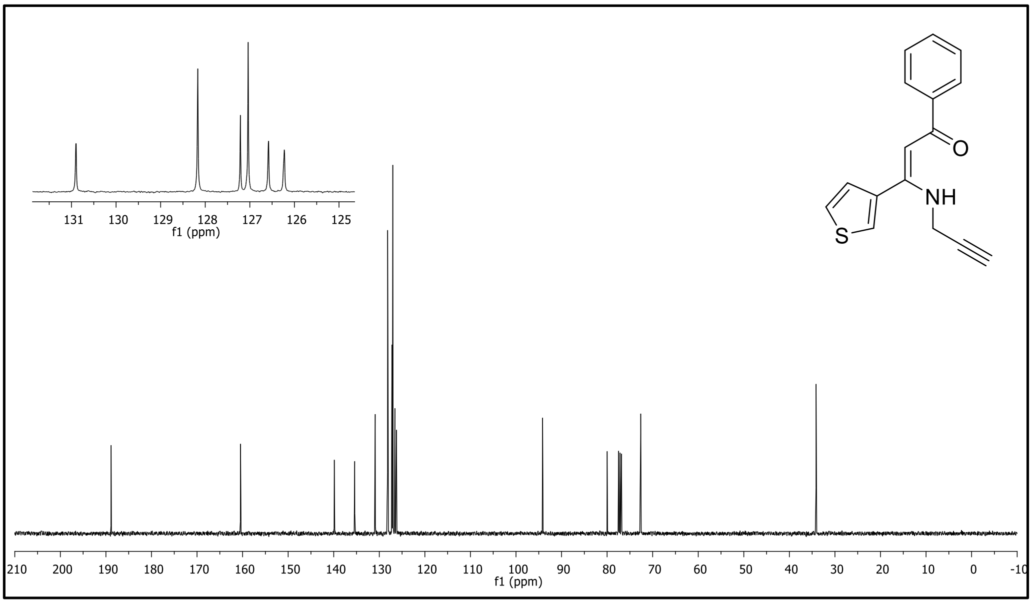

Figure A56. ^{13}C NMR spectrum of compound **32c.**

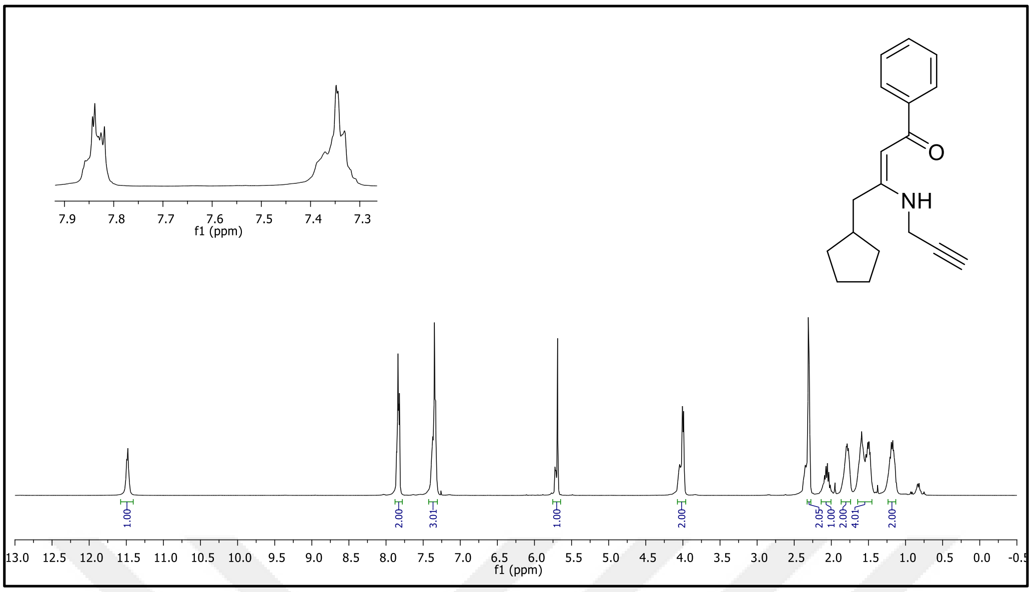

Figure A57. ^{1}H NMR spectrum of compound **32d.**

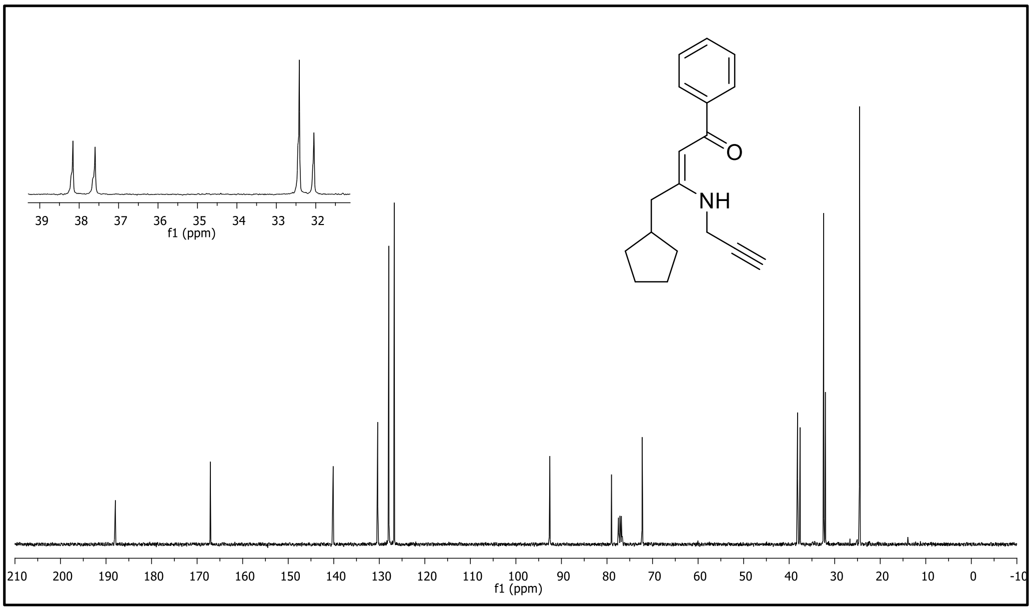

Figure A58. ^{13}C NMR spectrum of compound **32d.**

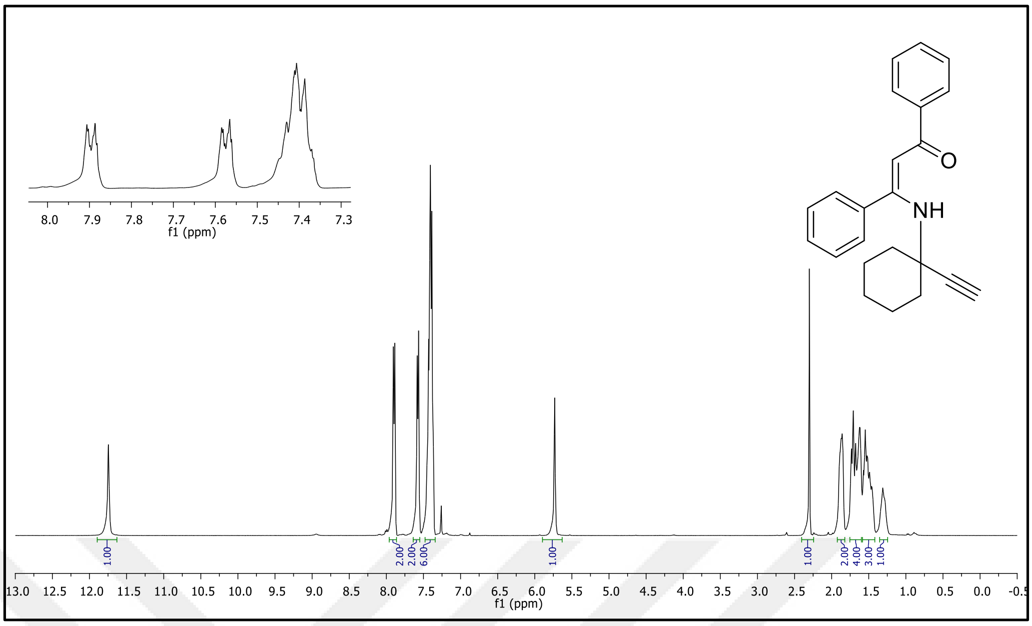

Figure A59. ^{1}H NMR spectrum of compound **50a.**

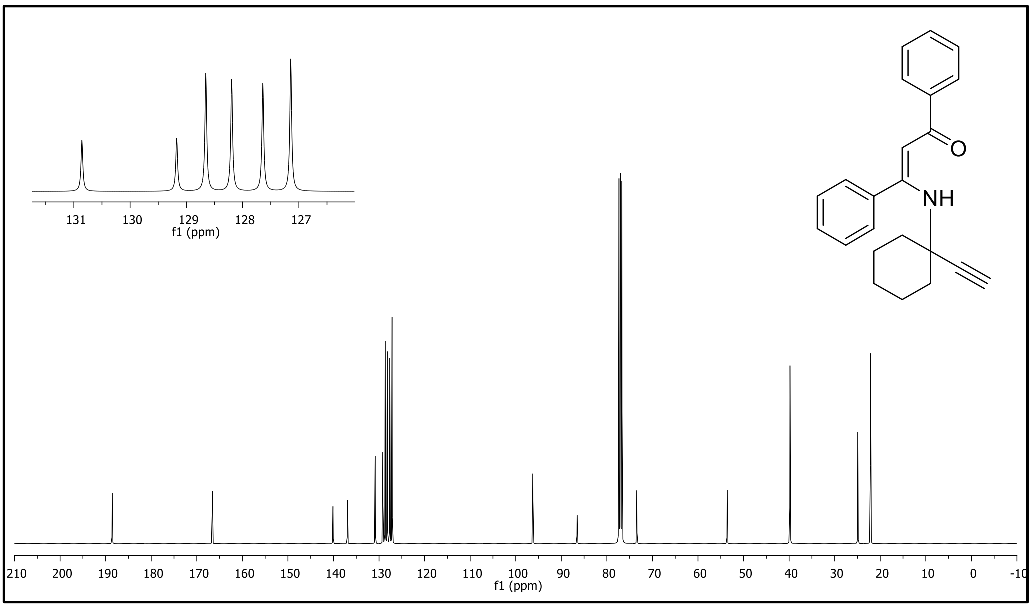

Figure A60. ^{13}C NMR spectrum of compound **50a.**

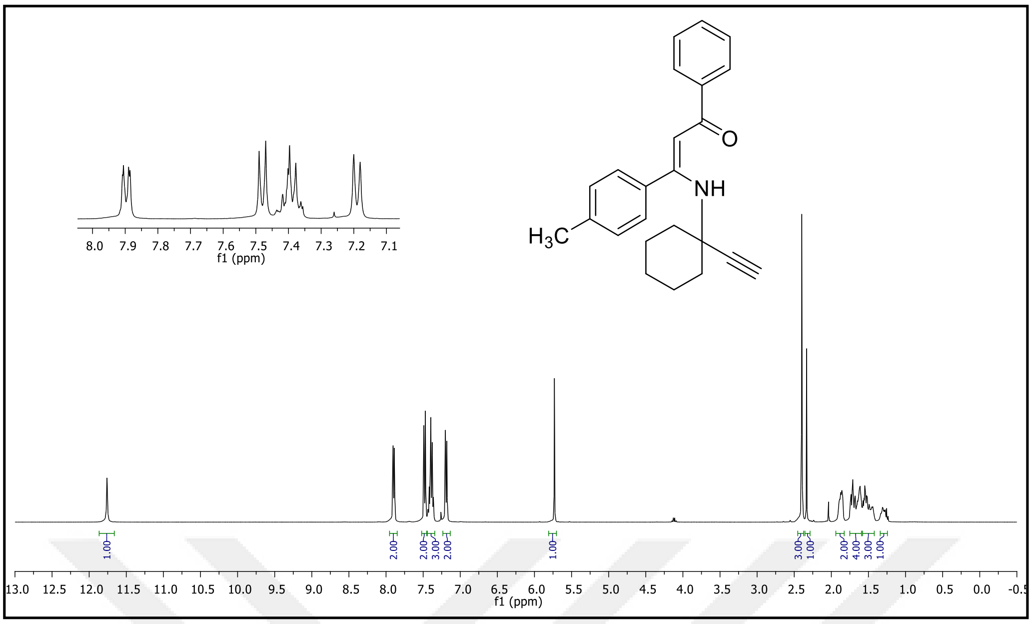

Figure A61. ^{1}H NMR spectrum of compound **50b.**

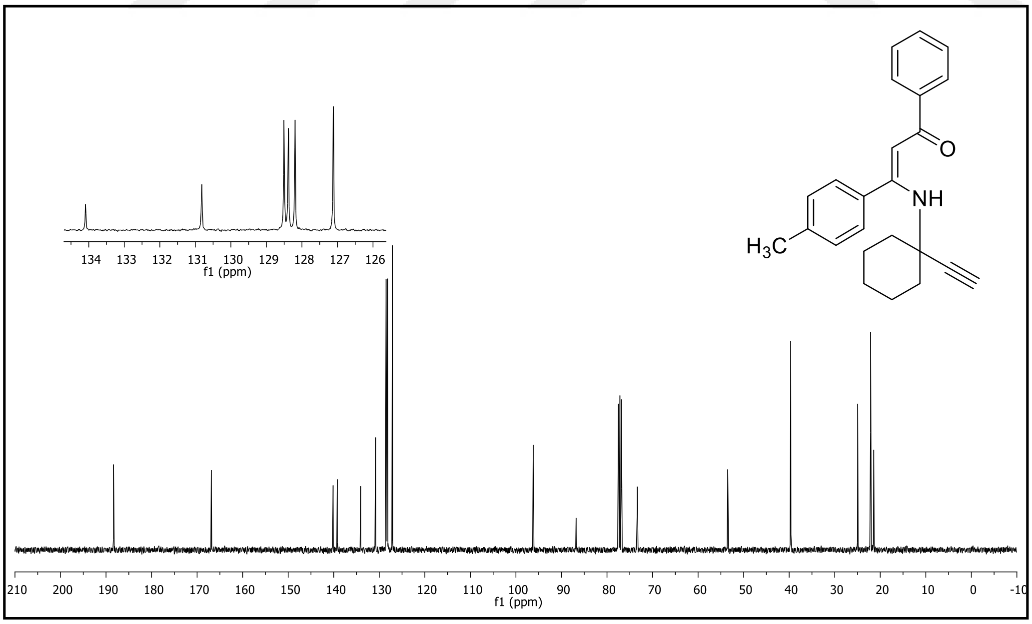

Figure A62. ^{13}C NMR spectrum of compound **50b.**

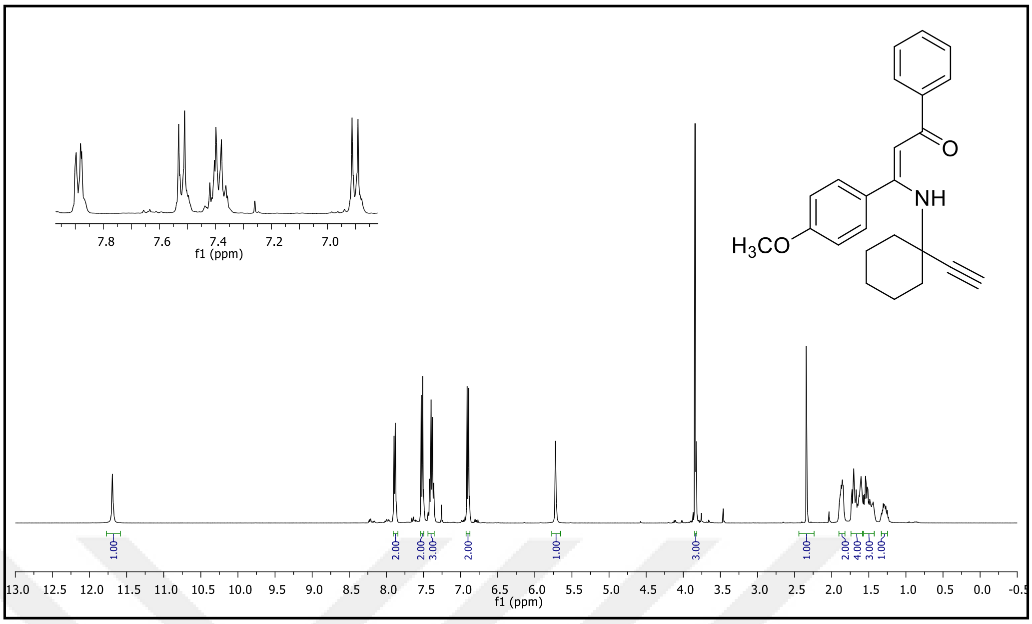

Figure A63. ^{1}H NMR spectrum of compound **50c.**

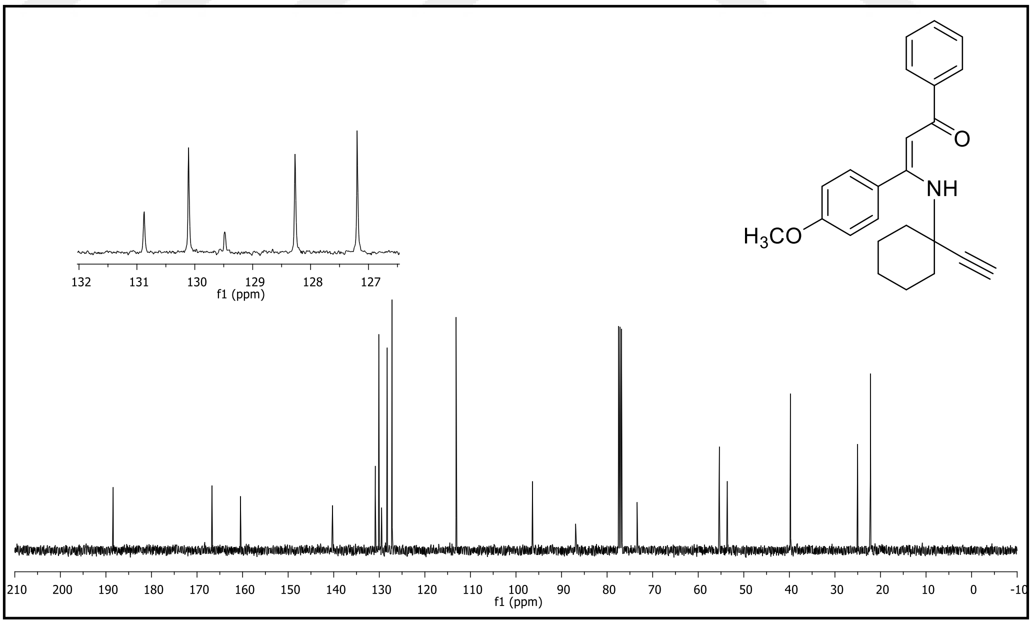

Figure A64. ^{13}C NMR spectrum of compound **50c.**

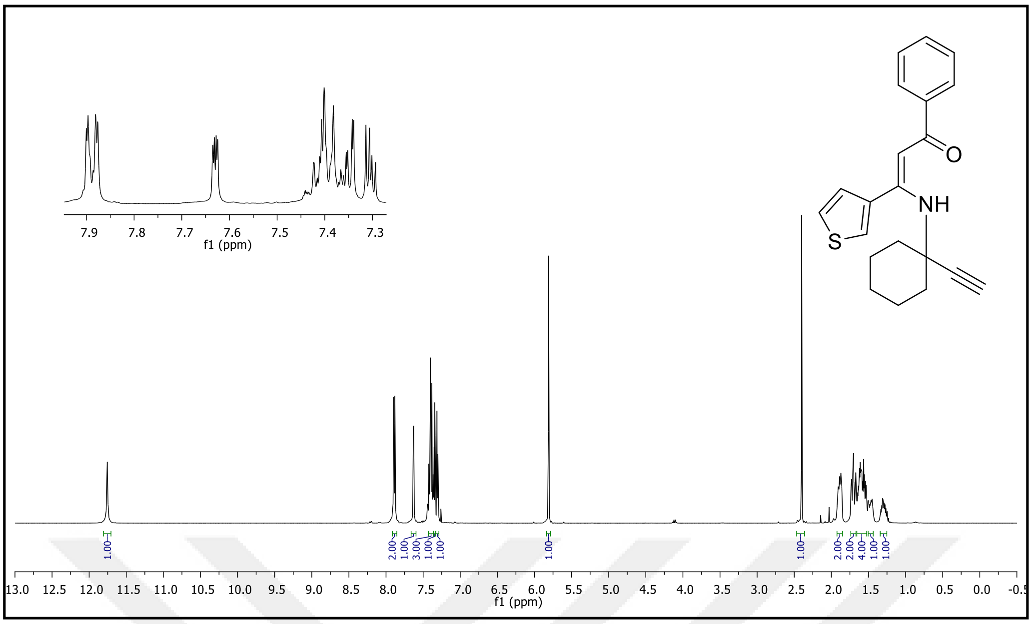

Figure A65. ^{1}H NMR spectrum of compound **50d.**

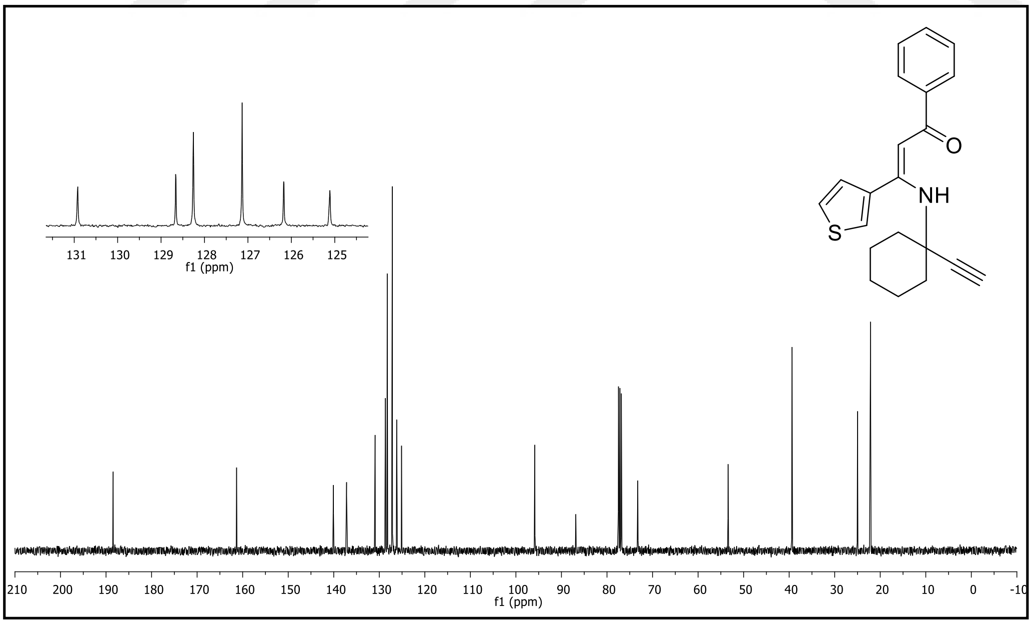

Figure A66. ^{13}C NMR spectrum of compound **50d.**

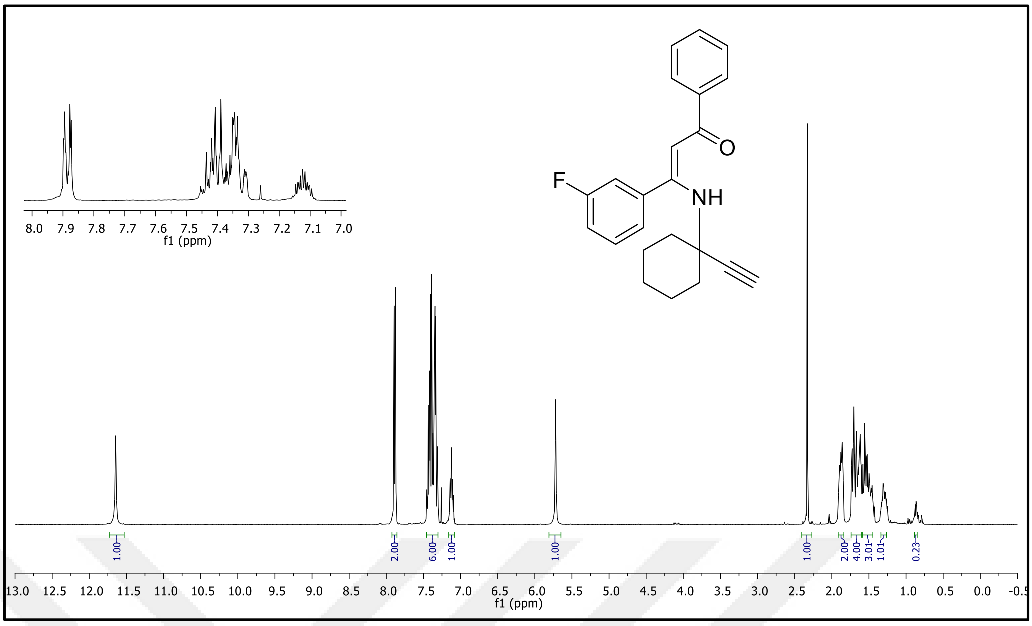

Figure A67. ^{1}H NMR spectrum of compound **50e.**

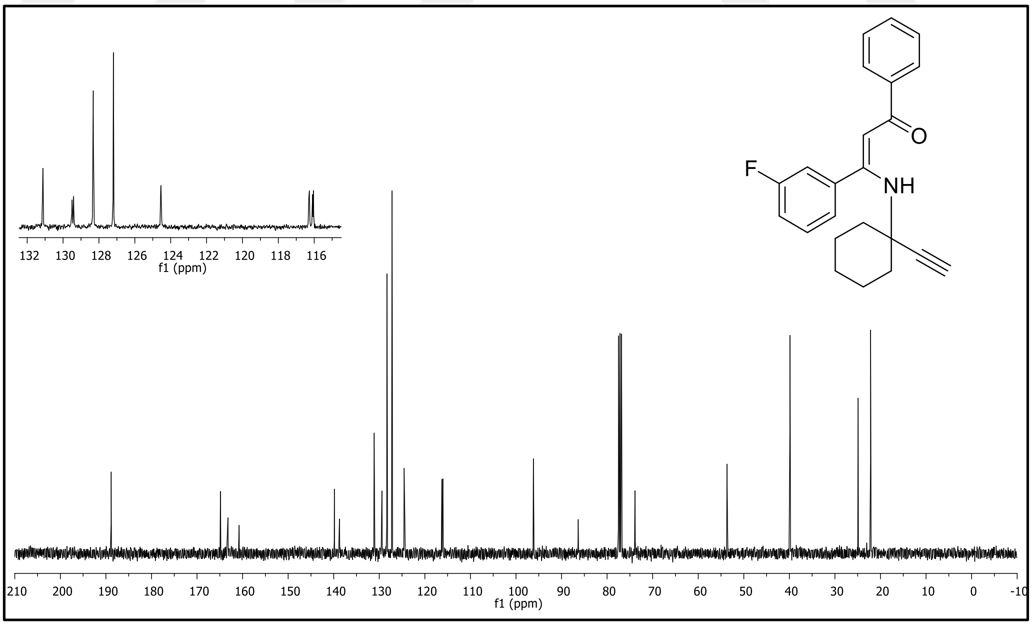

Figure A68. ^{13}C NMR spectrum of compound **50e.**

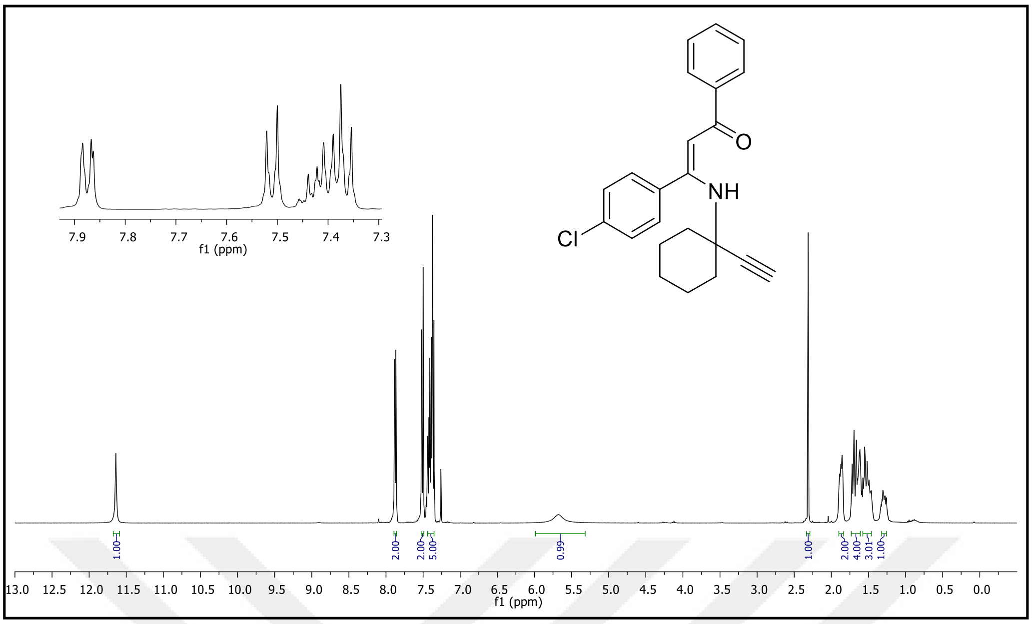

Figure A69. ^{1}H NMR spectrum of compound **50f.**

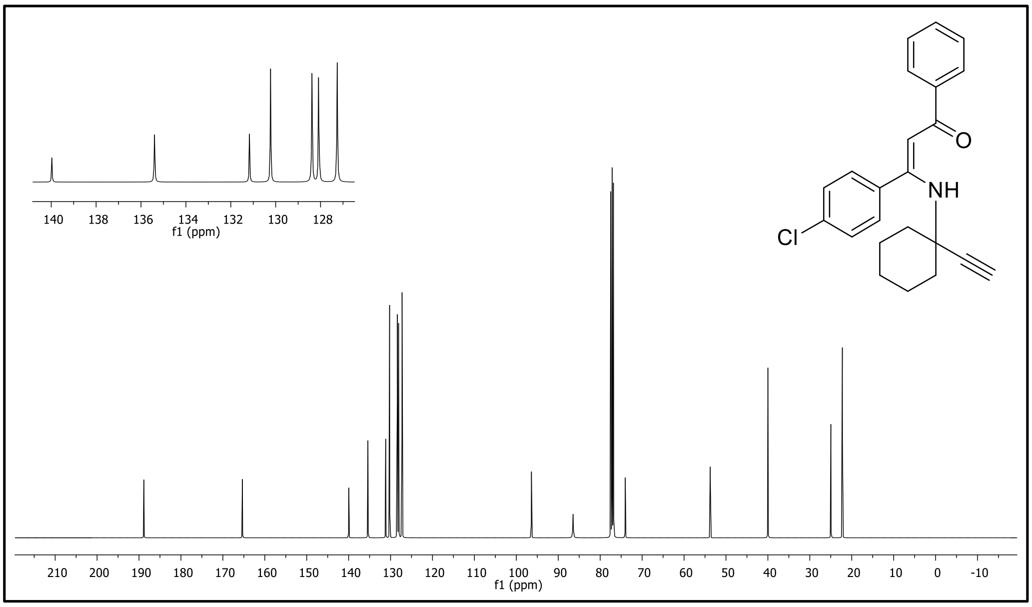

Figure A70. ^{13}C NMR spectrum of compound **50f.**

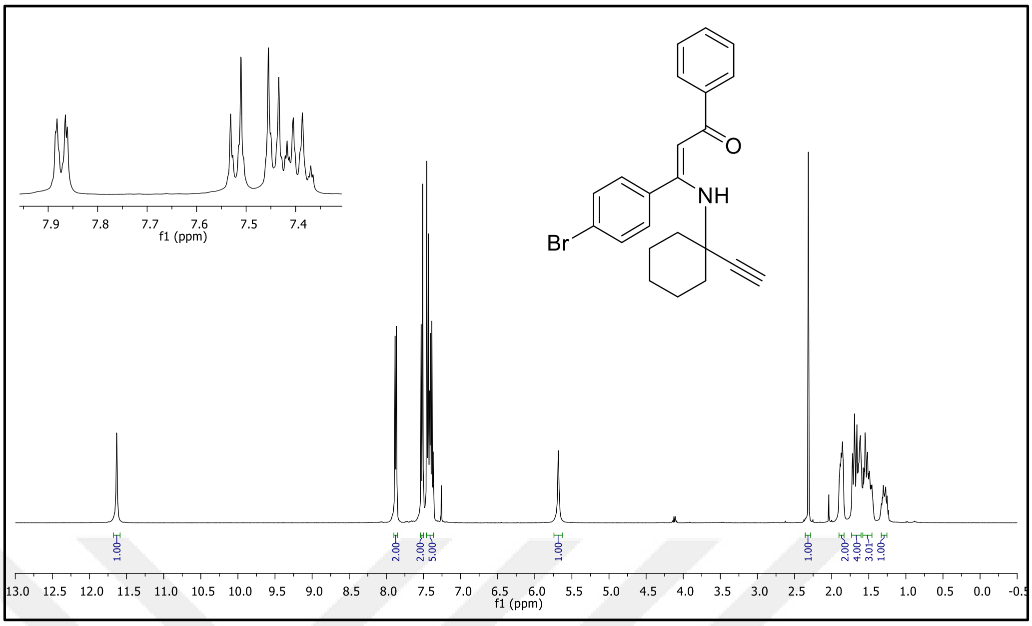

Figure A71. ^{1}H NMR spectrum of compound **50g.**

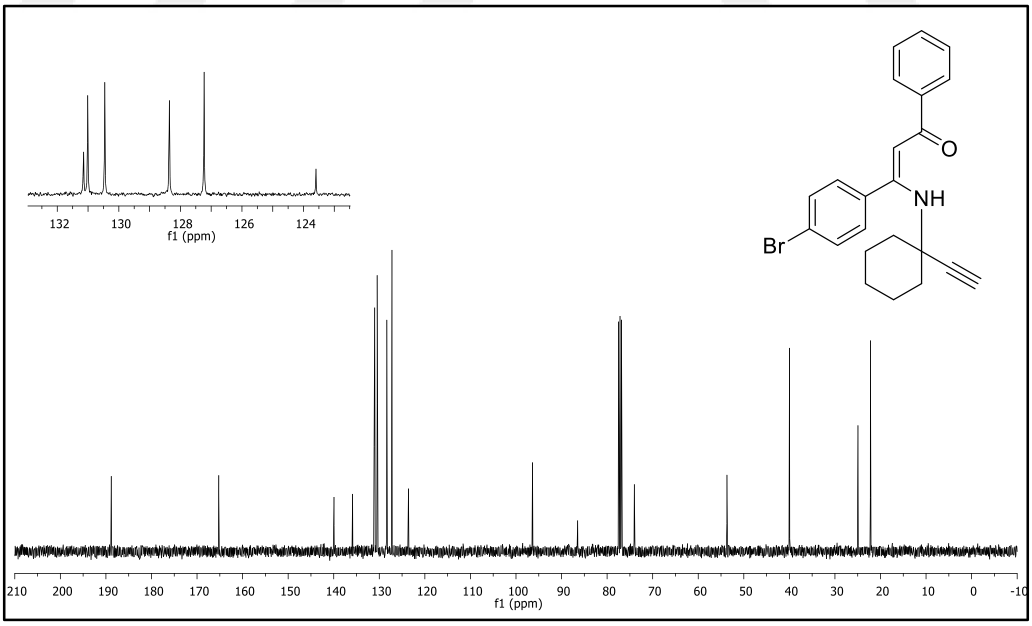

Figure A72. ^{13}C NMR spectrum of compound **50g.**

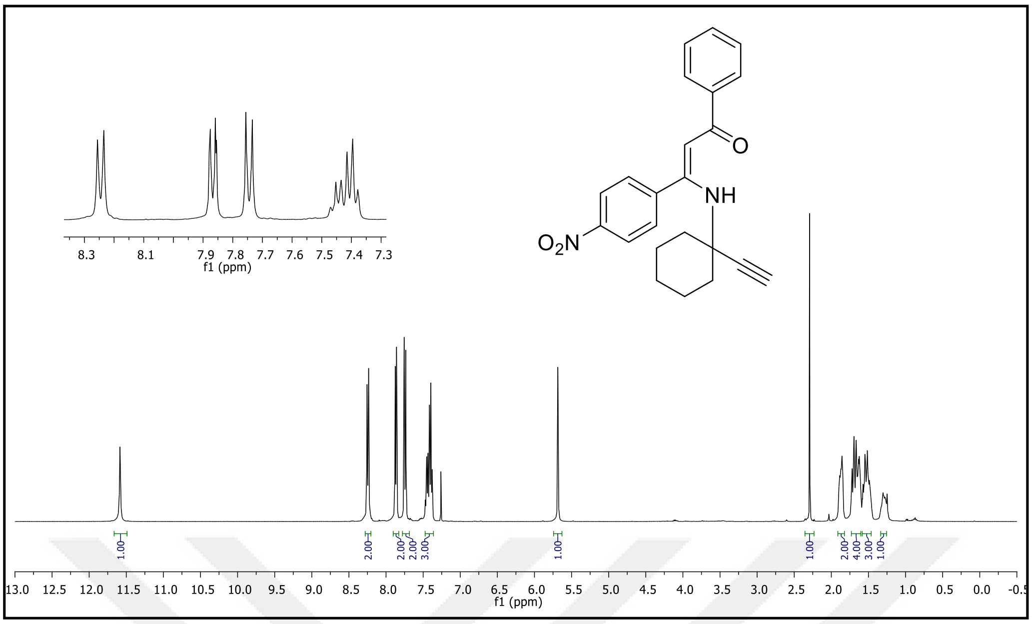

Figure A73. ^{1}H NMR spectrum of compound **50h.**

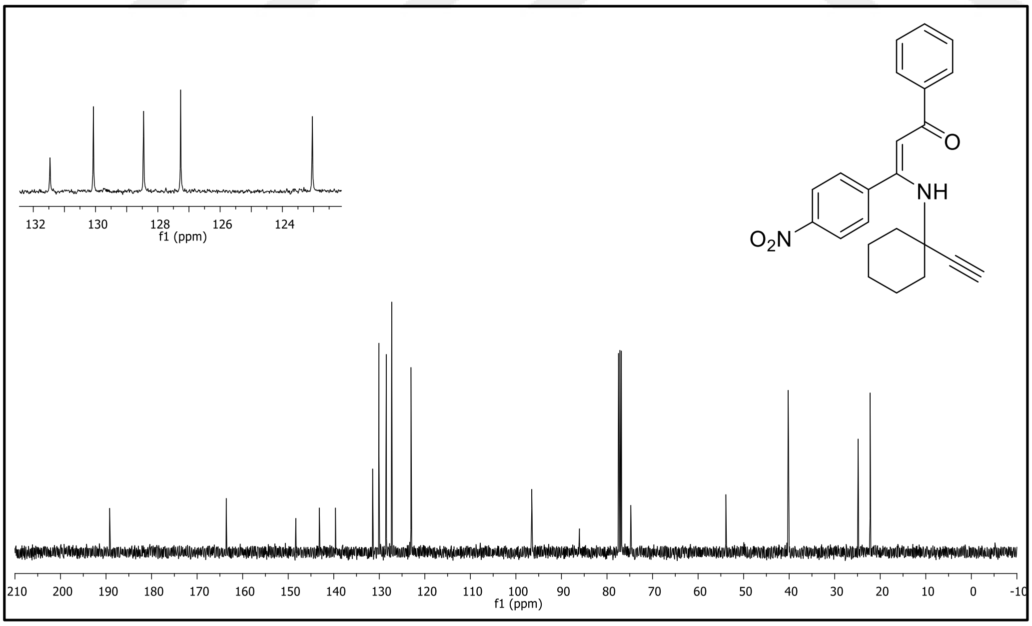

Figure A74. ^{13}C NMR spectrum of compound **50h.**

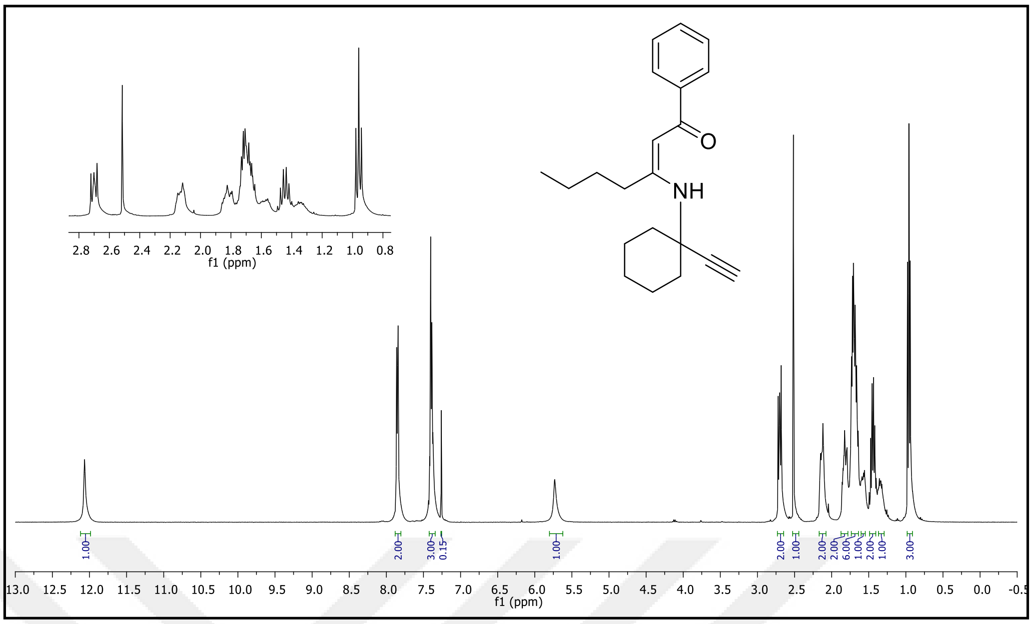

Figure A75. ^{1}H NMR spectrum of compound **50i.**

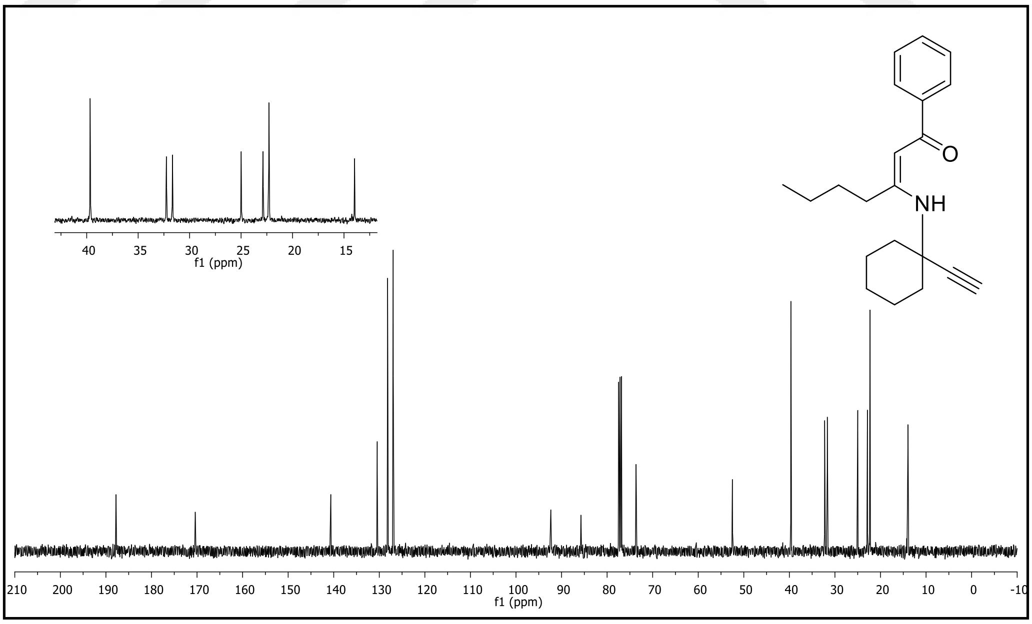

Figure A76. ^{13}C NMR spectrum of compound **50i.**

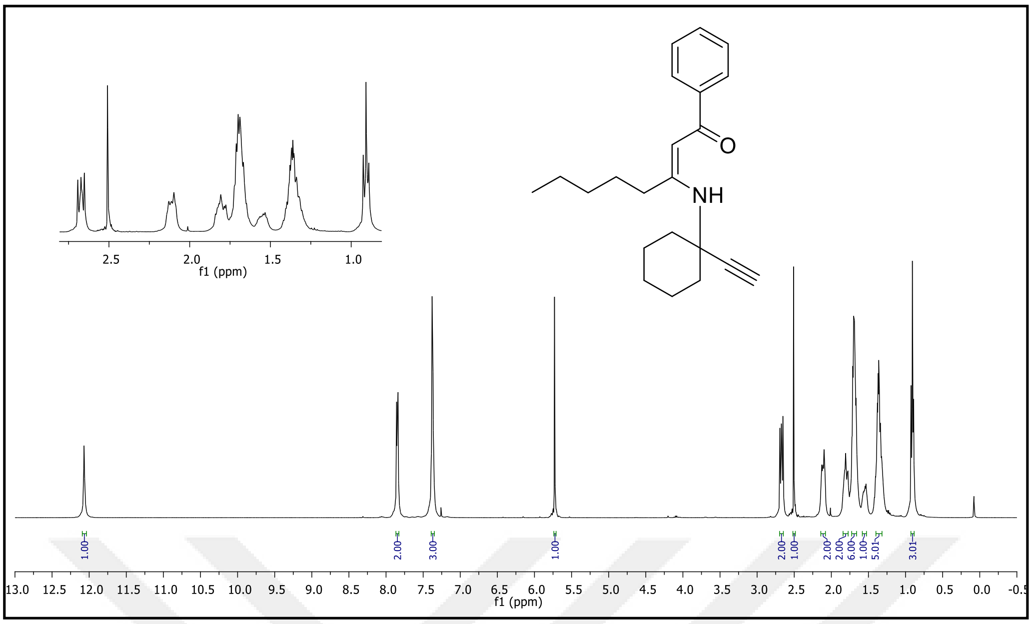

Figure A77. ^{1}H NMR spectrum of compound **50j.**

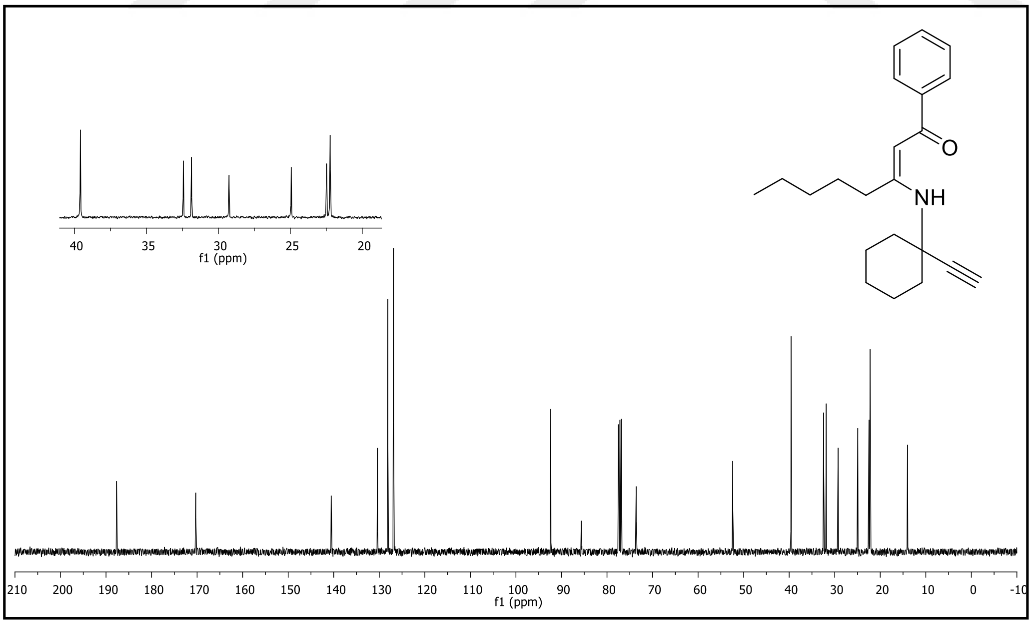

Figure A78. ^{13}C NMR spectrum of compound **50j.**

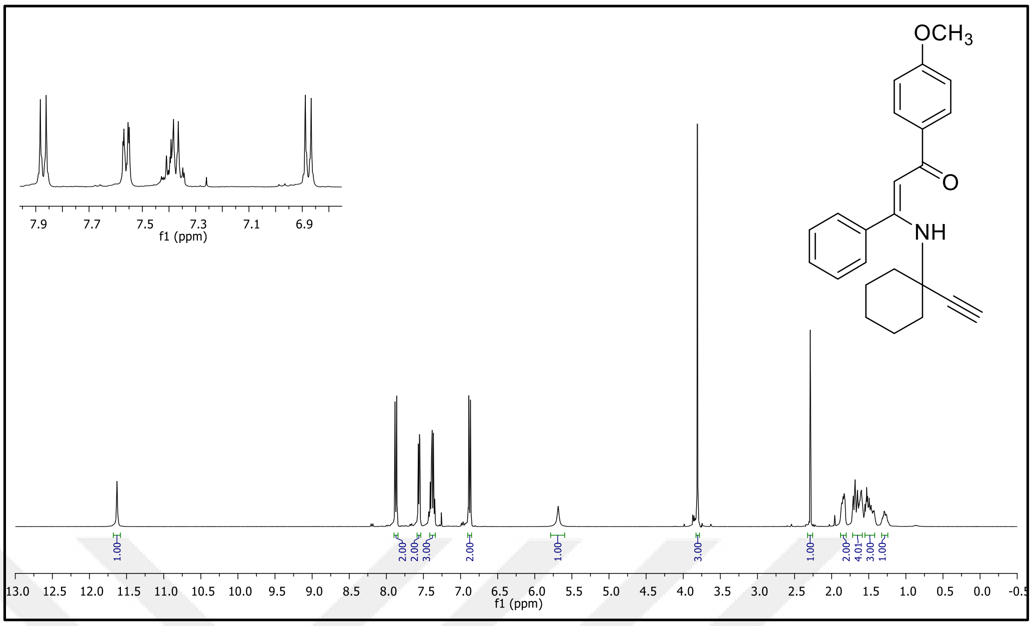

Figure A79. ^{1}H NMR spectrum of compound **50k.**

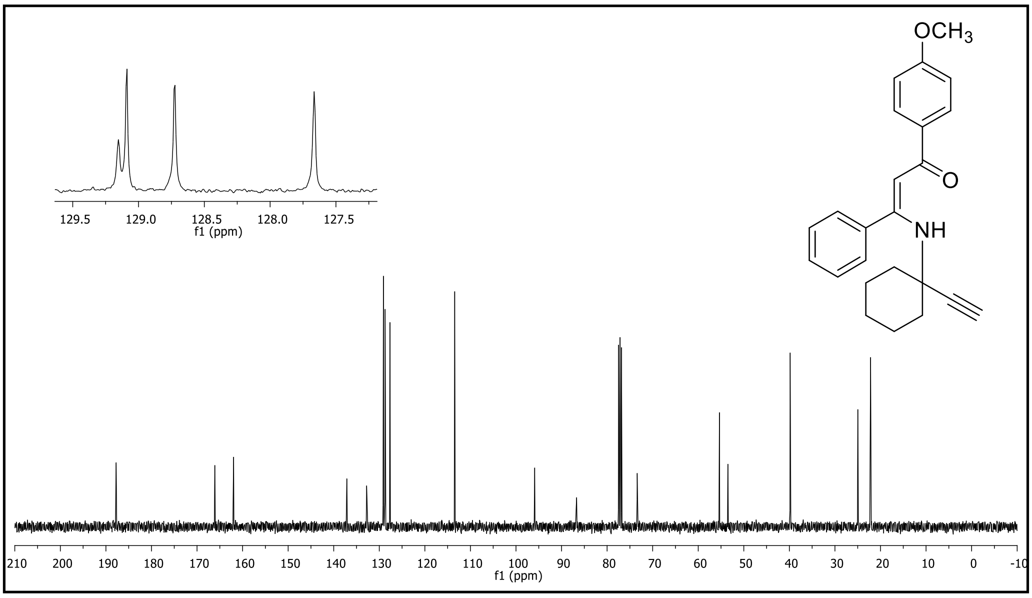

Figure A80. ^{13}C NMR spectrum of compound **50k.**

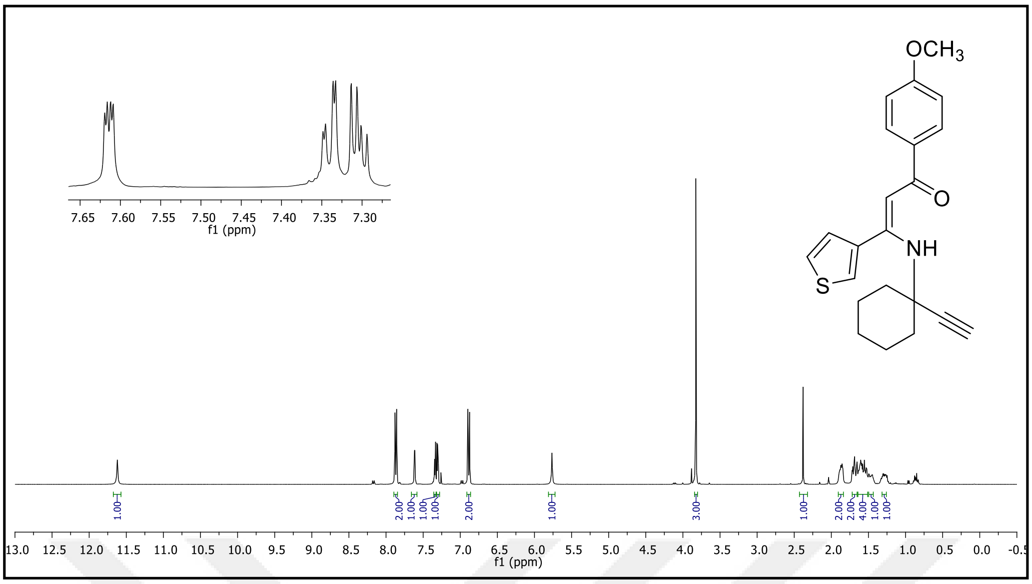

Figure A81. ^{1}H NMR spectrum of compound **50l.**

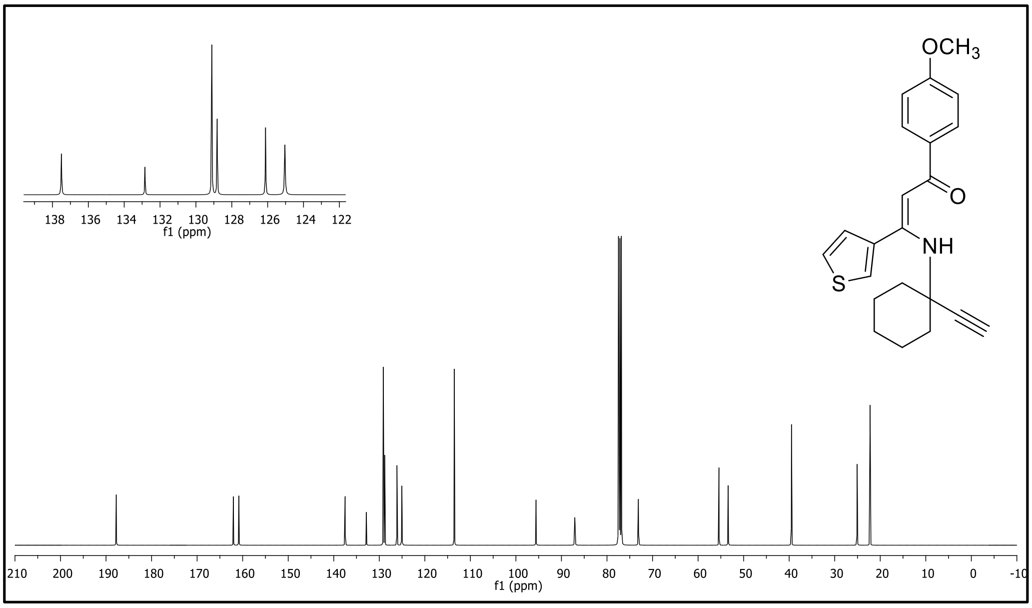

Figure A82. ^{13}C NMR spectrum of compound **50l.**

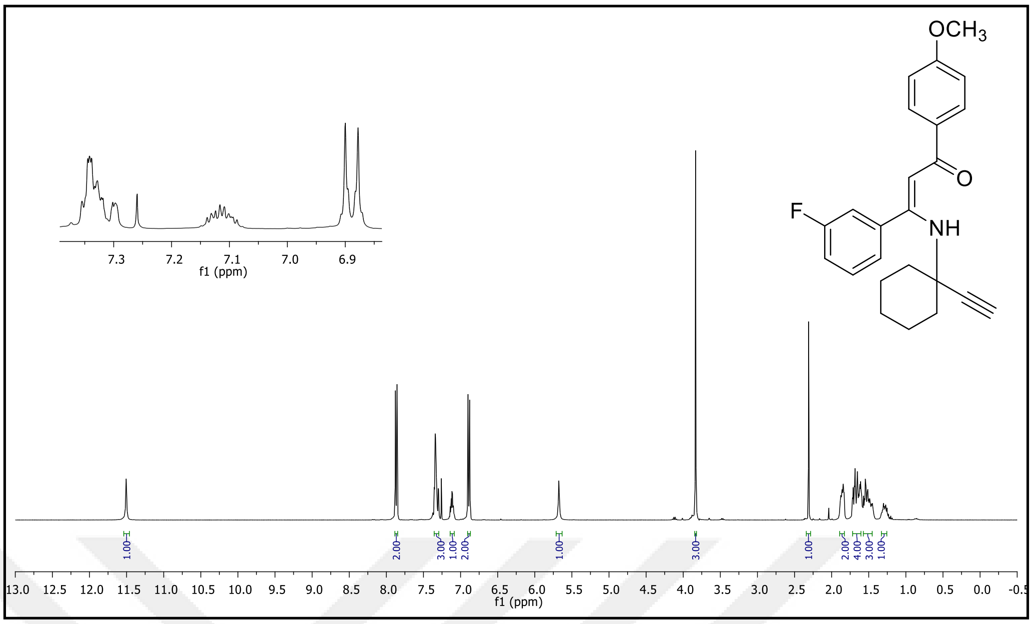

Figure A83. ^{1}H NMR spectrum of compound **50m.**

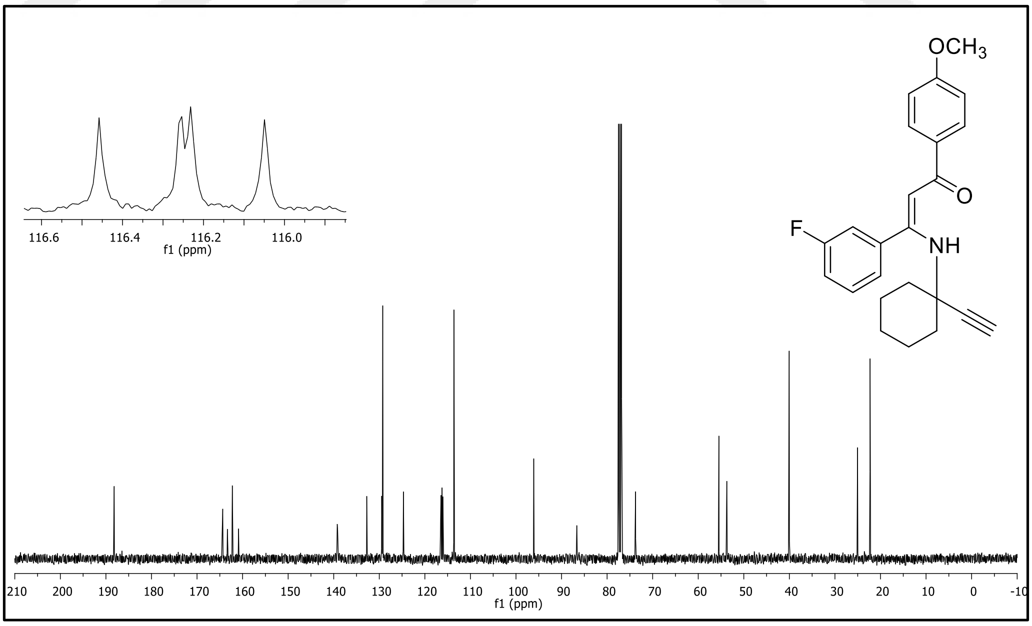

Figure A84. ^{13}C NMR spectrum of compound **50m.**

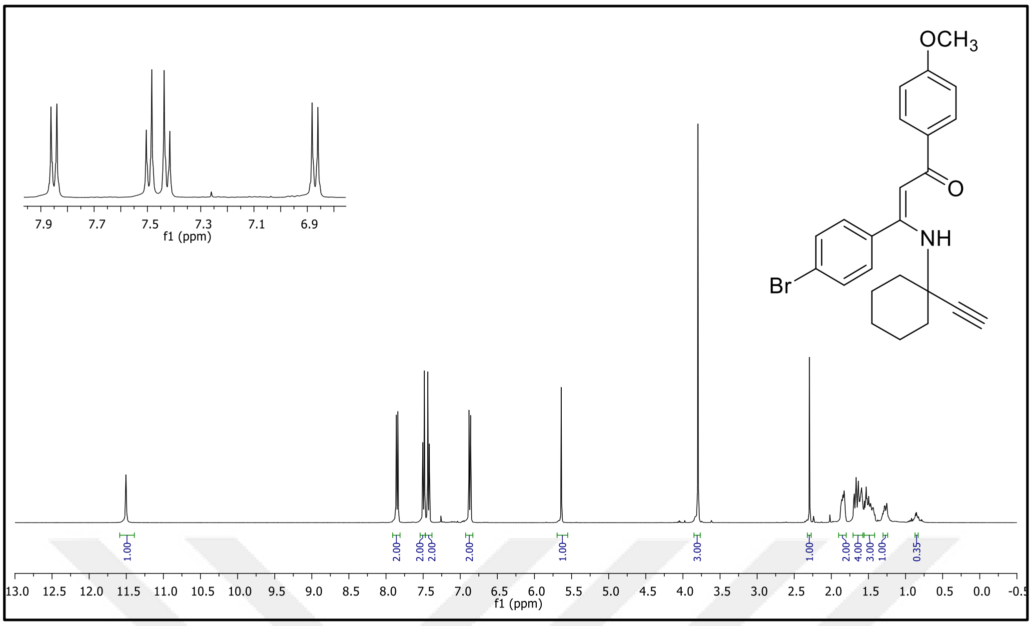

Figure A85. ^{1}H NMR spectrum of compound **50n.**

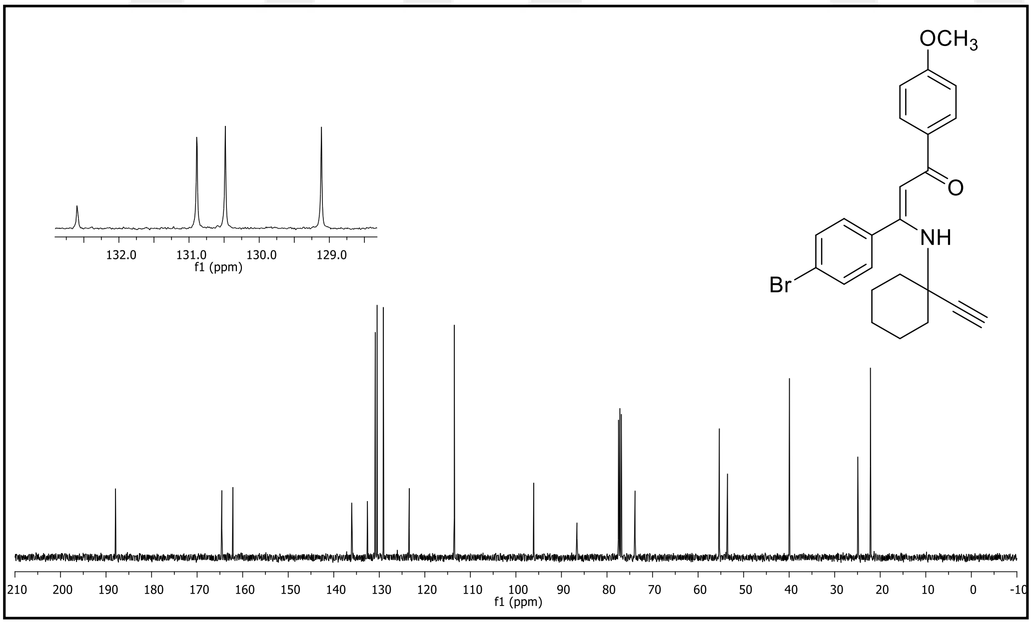

Figure A86. ^{13}C NMR spectrum of compound **50n.**

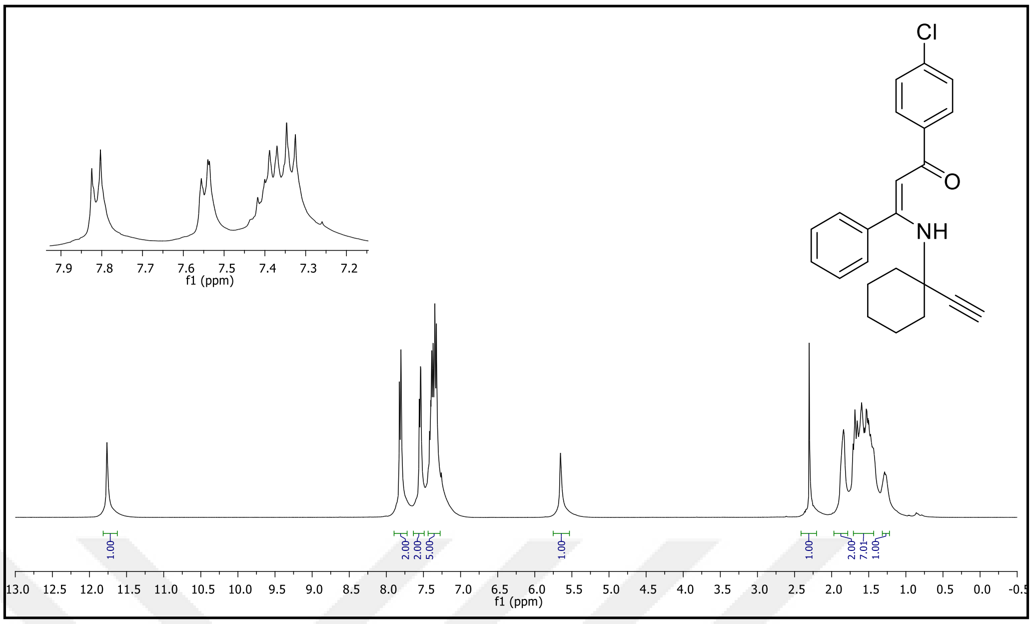

Figure A87. ^{1}H NMR spectrum of compound **50o.**

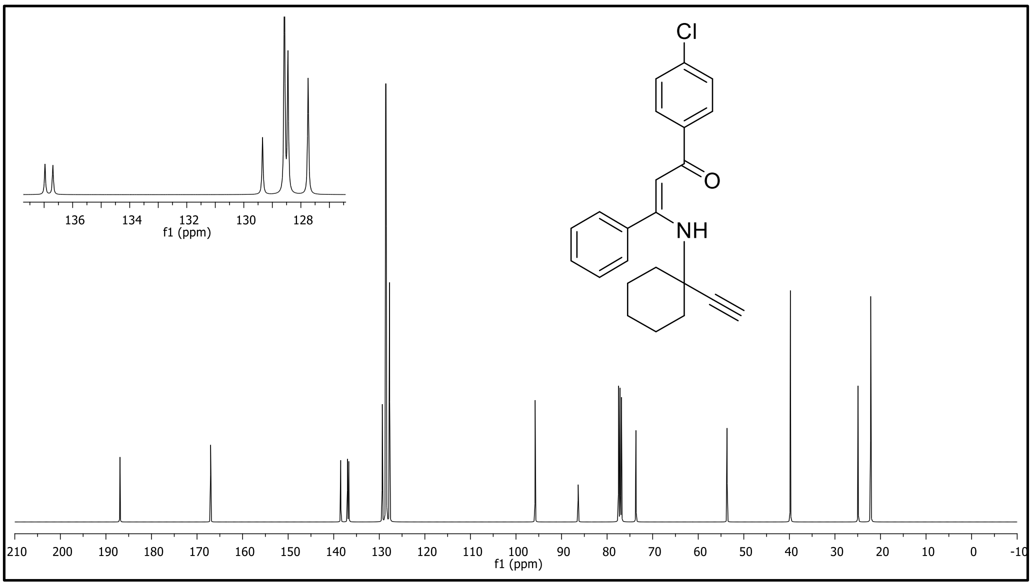

Figure A88. ^{13}C NMR spectrum of compound **50o.**

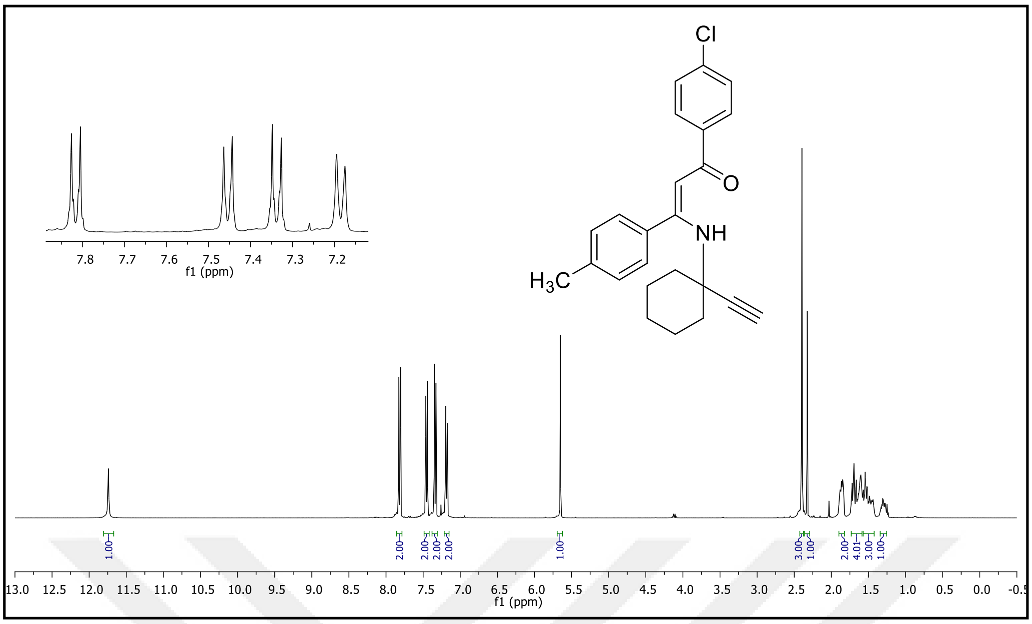

Figure A89. ^{1}H NMR spectrum of compound **50p.**

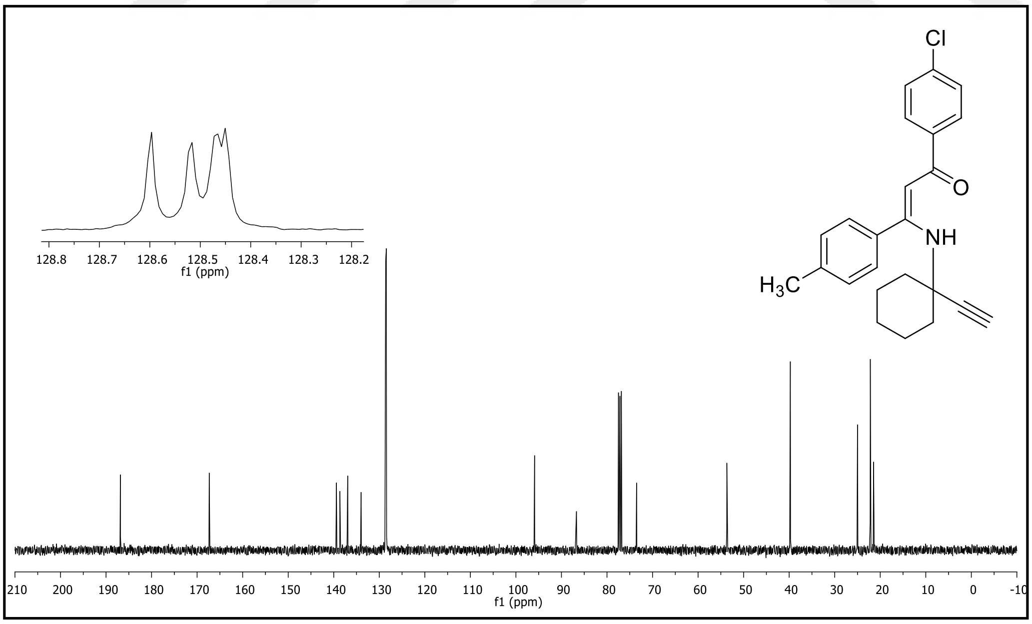

Figure A90. ^{13}C NMR spectrum of compound **50p.**

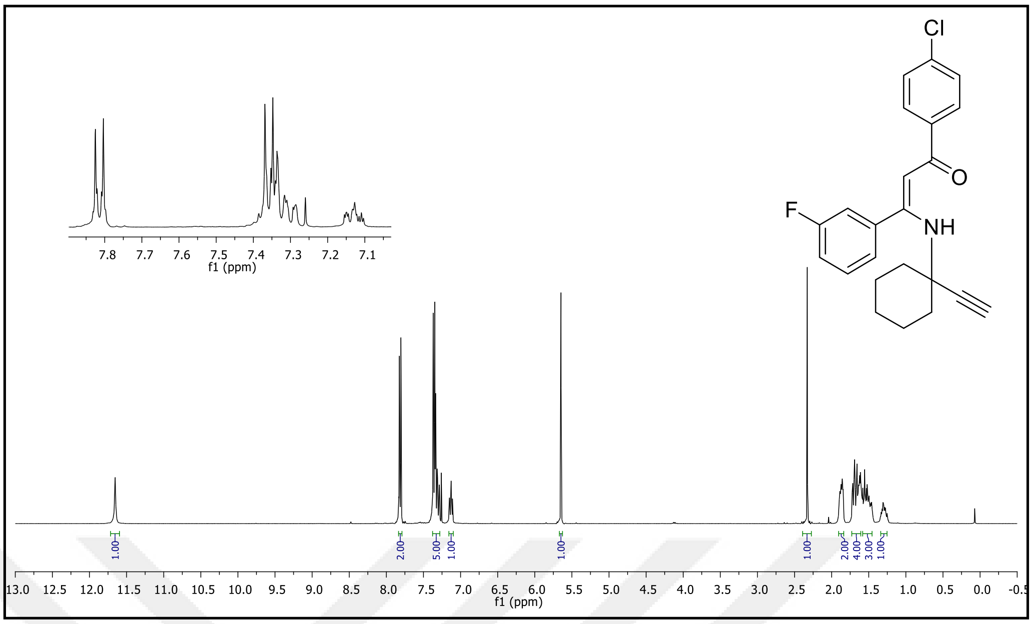

Figure A91. ^{1}H NMR spectrum of compound **50q.**

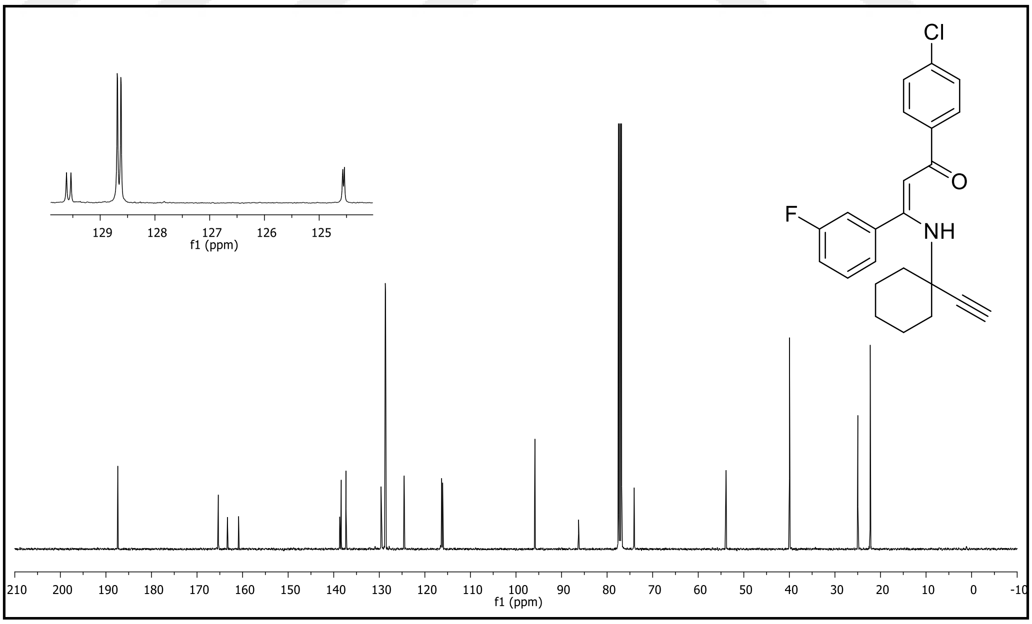

Figure A92. ^{13}C NMR spectrum of compound **50q.**

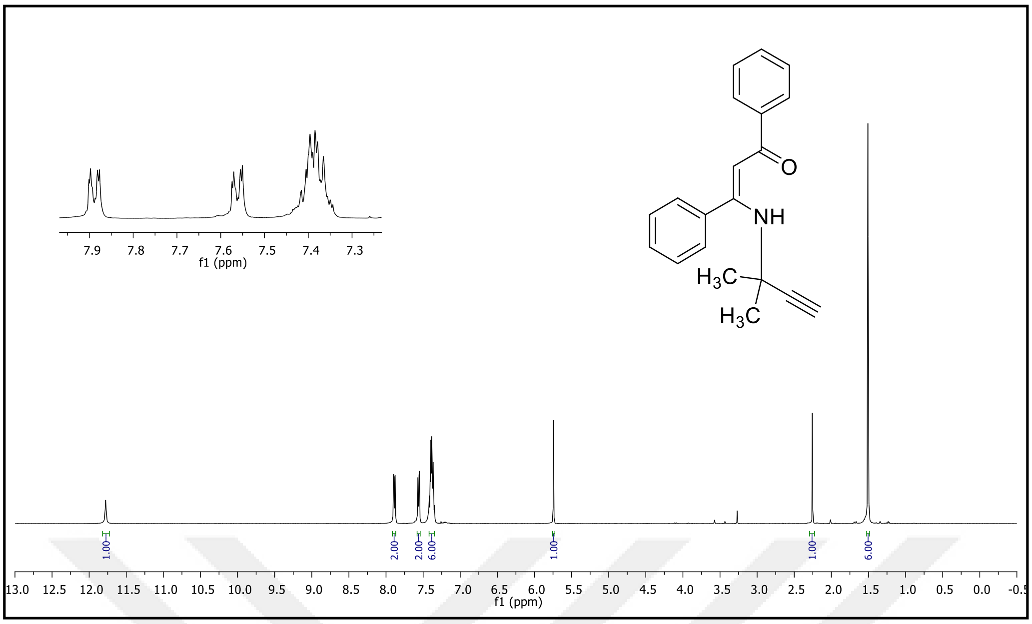

Figure A93. ^{1}H NMR spectrum of compound **61a.**

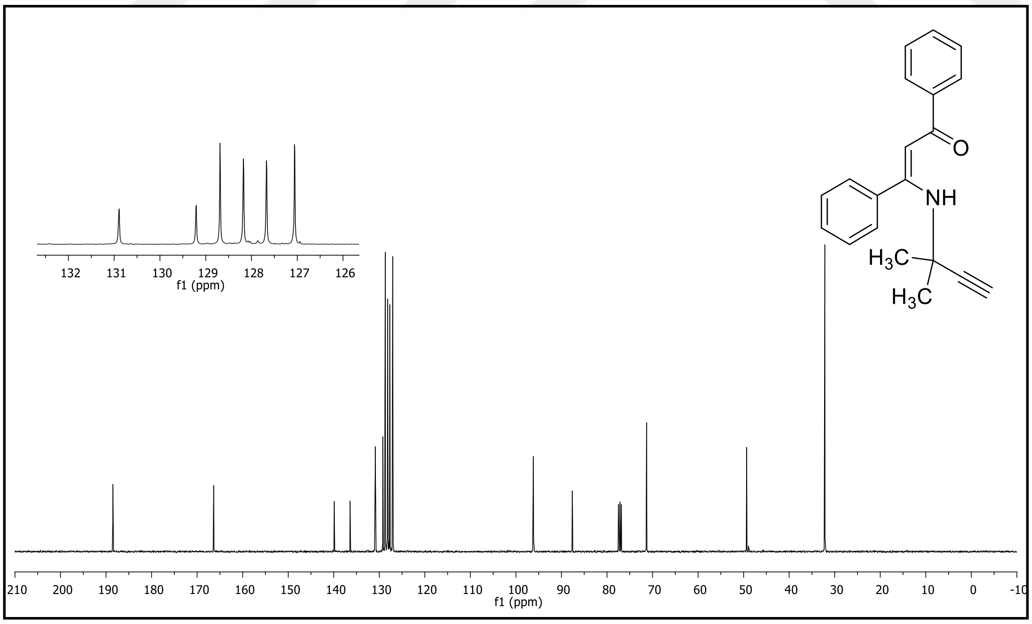

Figure A94. ^{13}C NMR spectrum of compound **61a.**

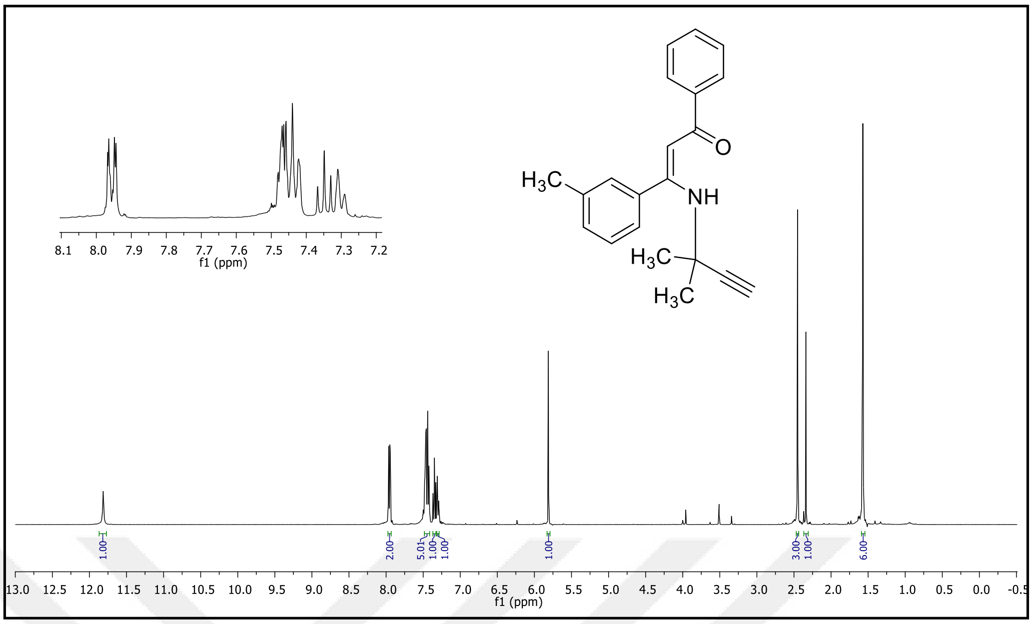

Figure A95. ^{1}H NMR spectrum of compound **61b.**

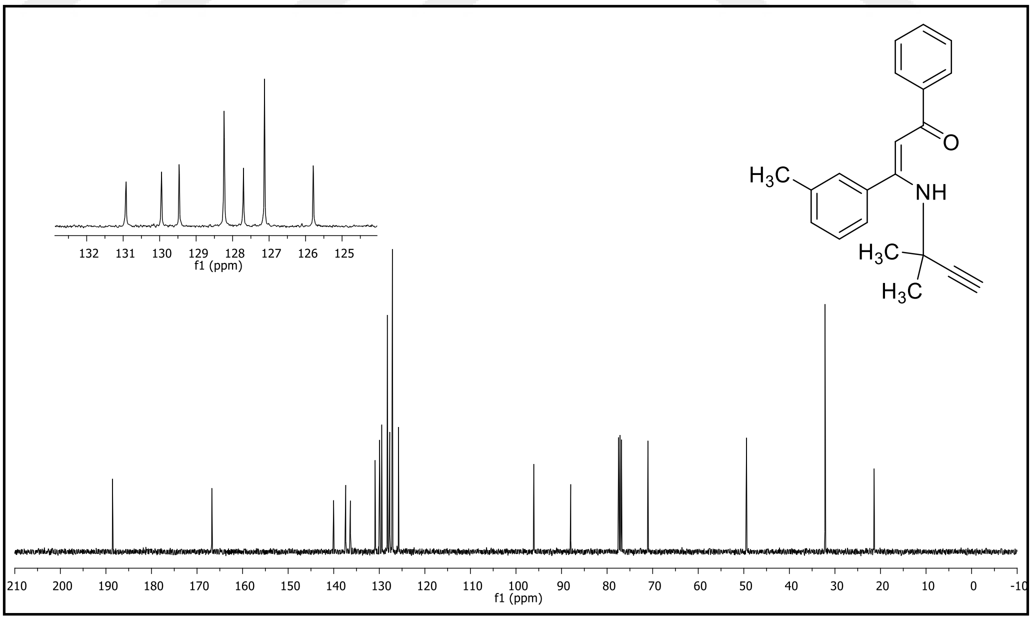

Figure A96. ^{13}C NMR spectrum of compound **61b.**

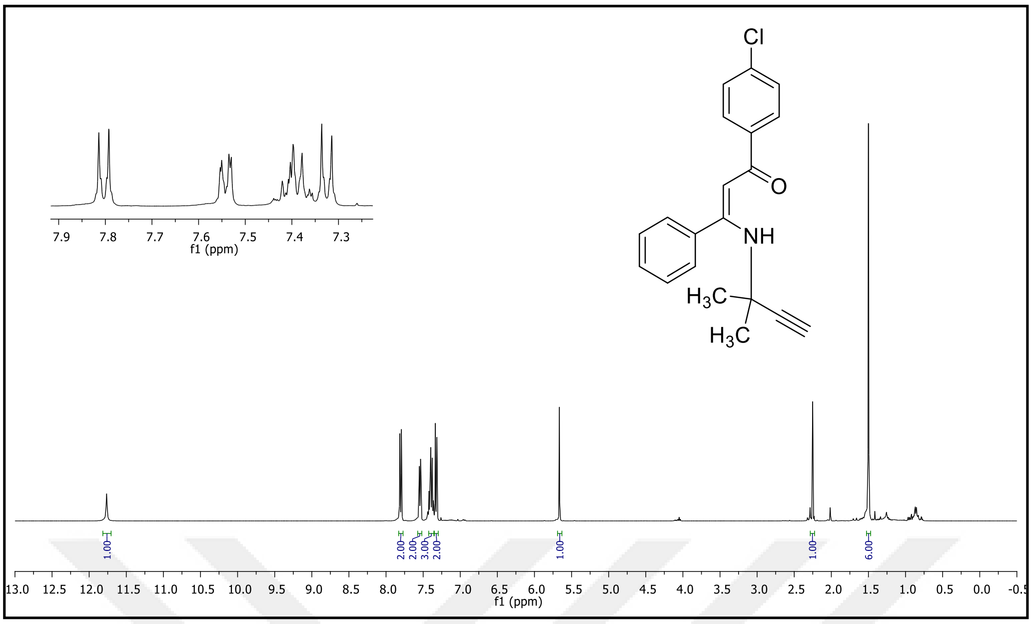

Figure A97. ^{1}H NMR spectrum of compound **61c.**

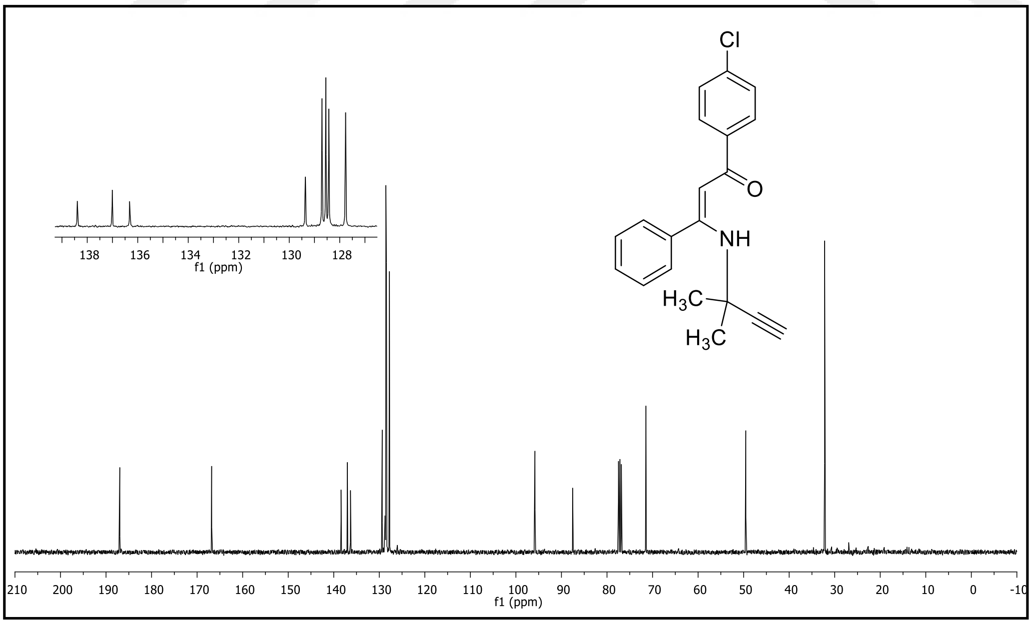

Figure A98. ^{13}C NMR spectrum of compound **61c.**

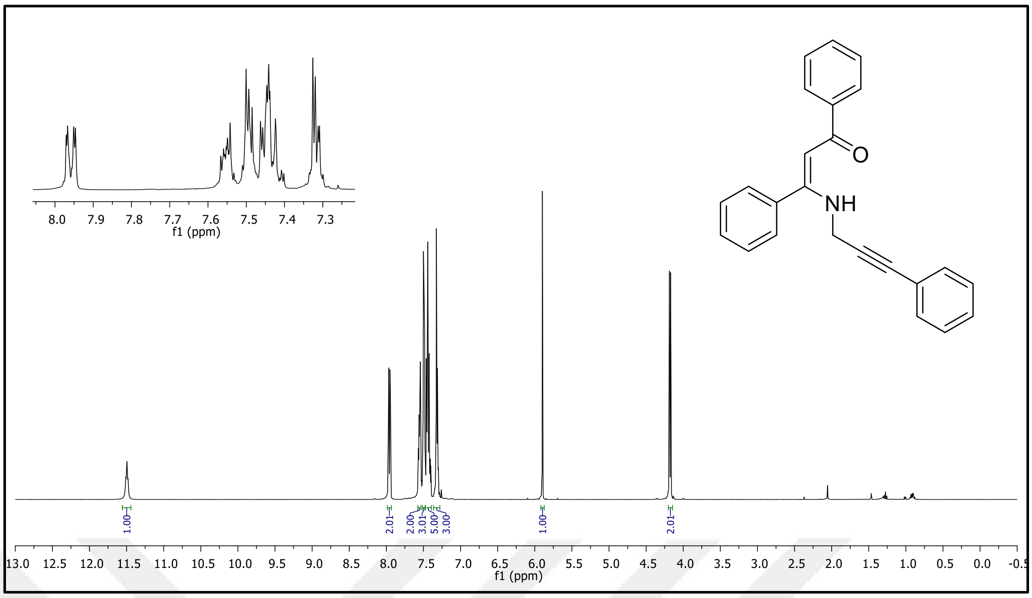

Figure A99. ^{1}H NMR spectrum of compound **10a.**

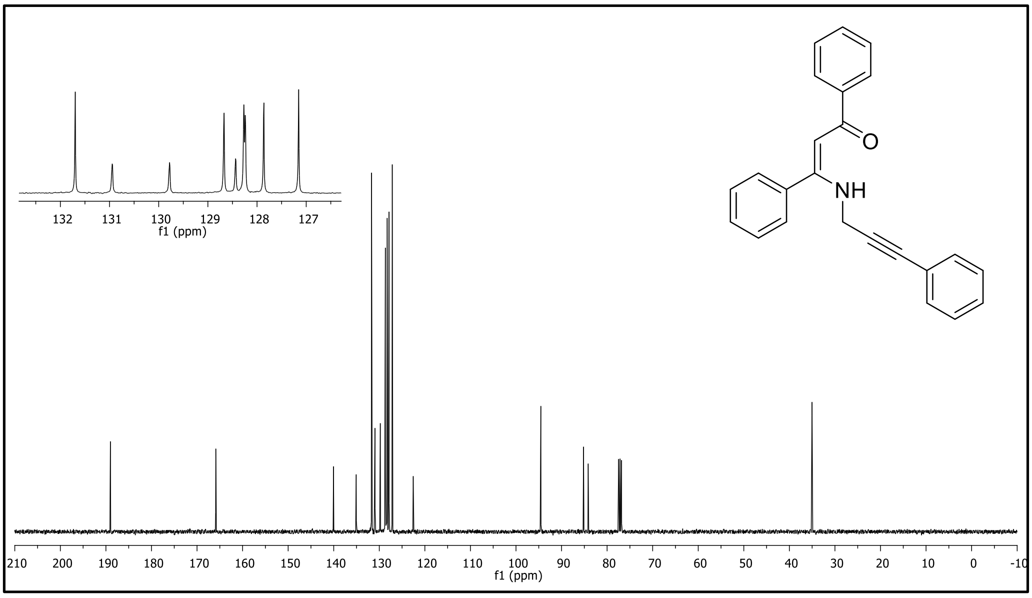

Figure A100. ^{13}C NMR spectrum of compound **10a.**

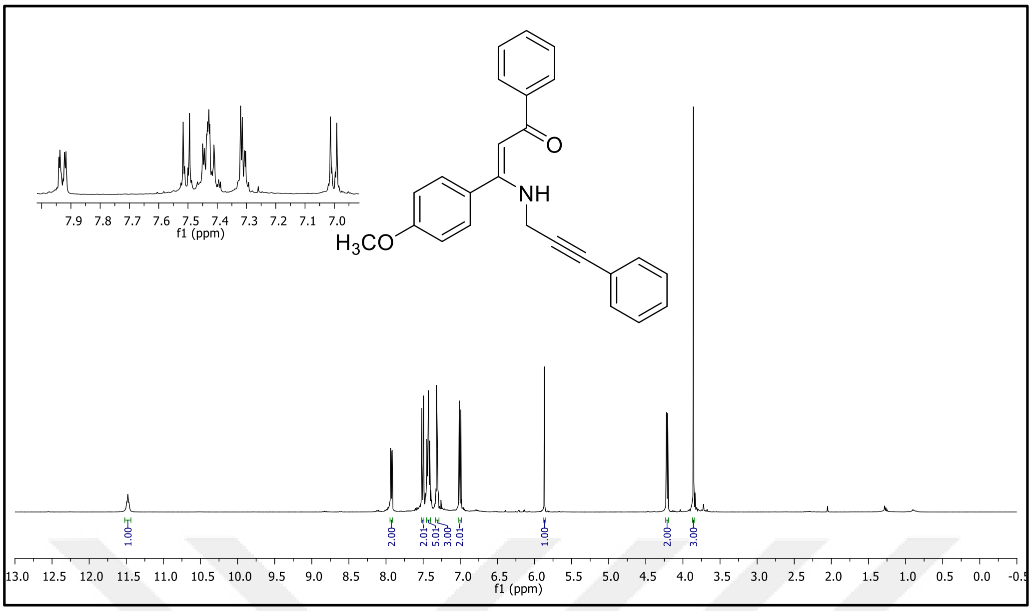

Figure A101. ^{1}H NMR spectrum of compound **10b.**

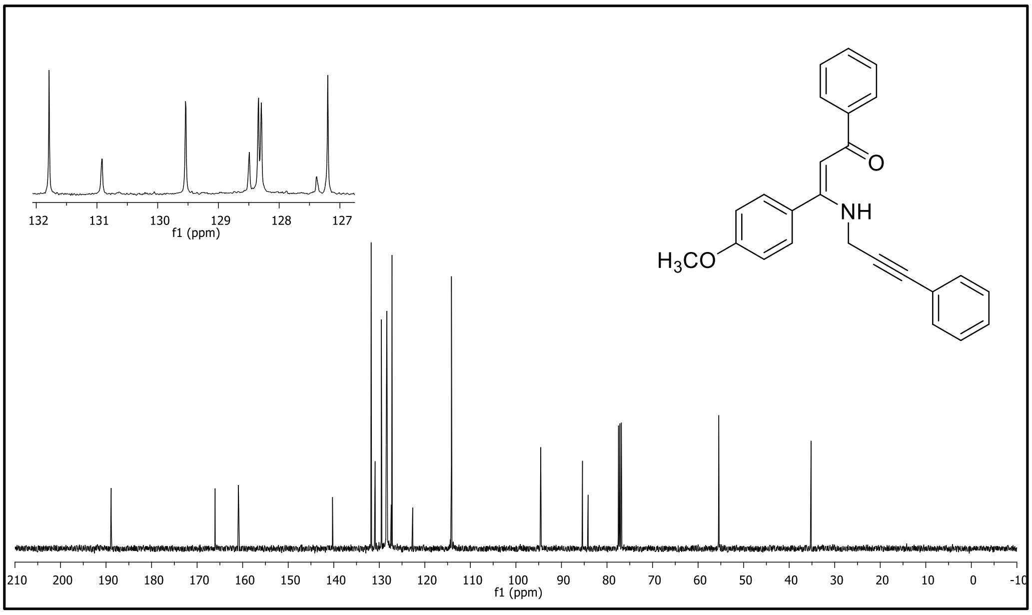

Figure A102. ^{13}C NMR spectrum of compound **10b.**

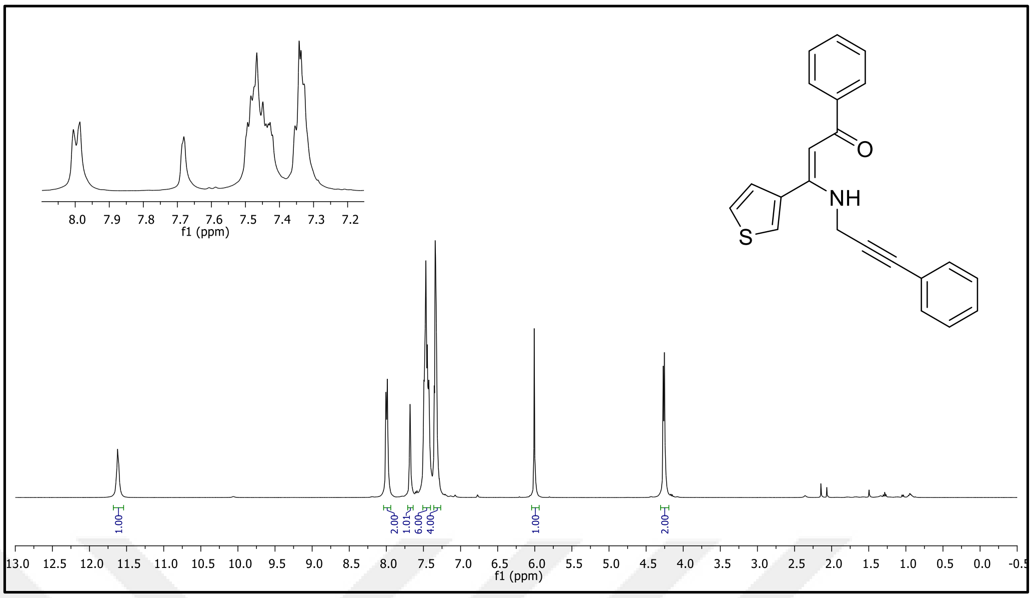

Figure A103. ^{1}H NMR spectrum of compound **10c.**

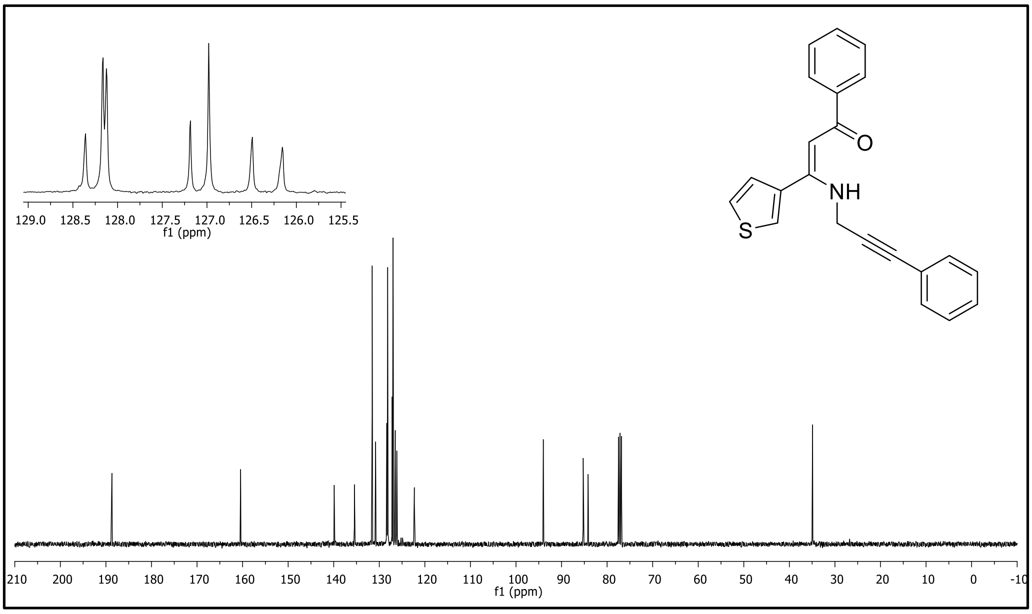

Figure A104. ^{13}C NMR spectrum of compound **10c.**

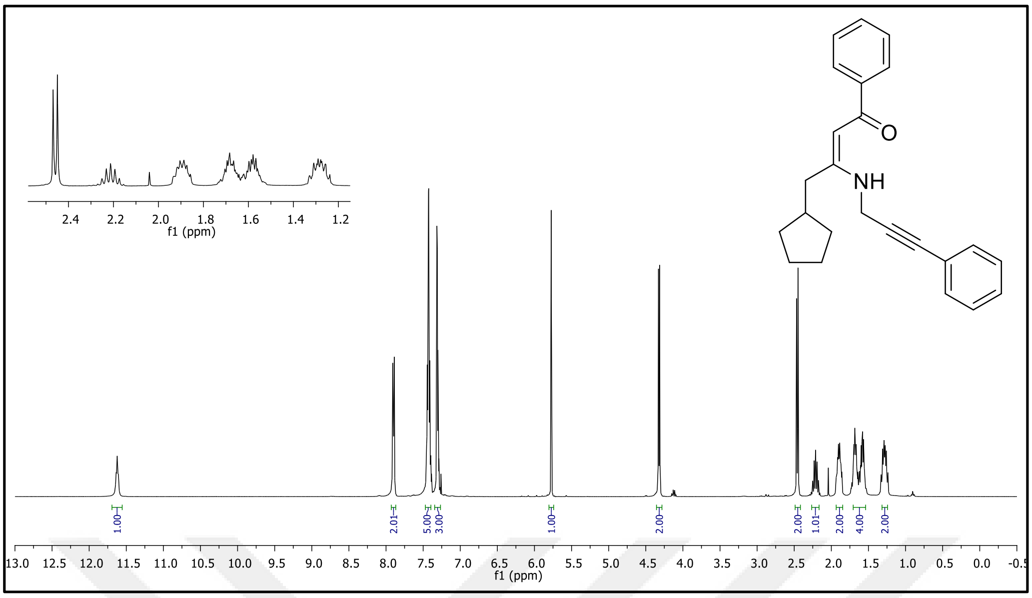

Figure A105. ^{1}H NMR spectrum of compound **10d.**

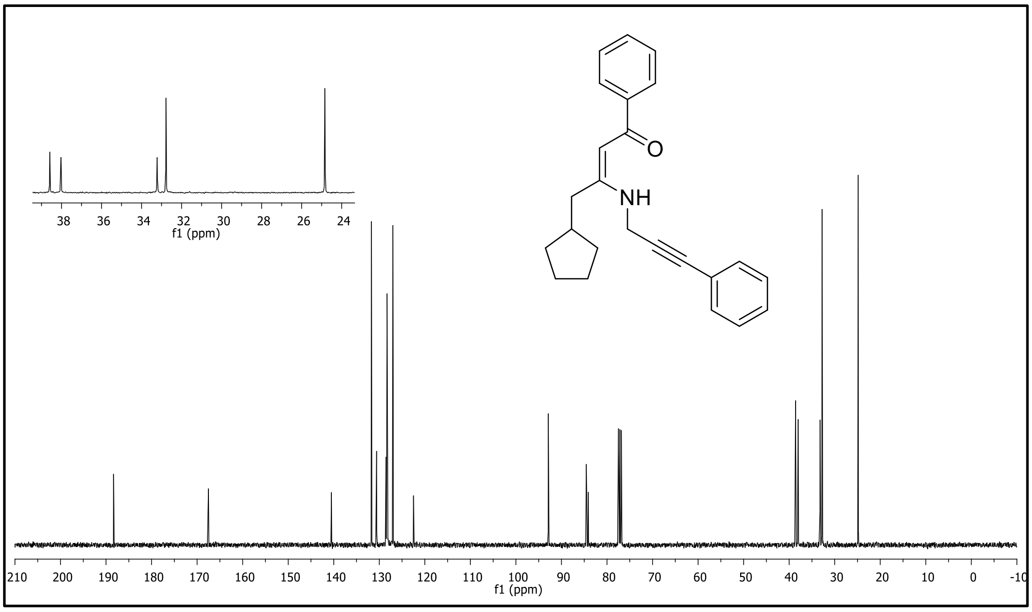

Figure A106. ^{13}C NMR spectrum of compound **10d.**

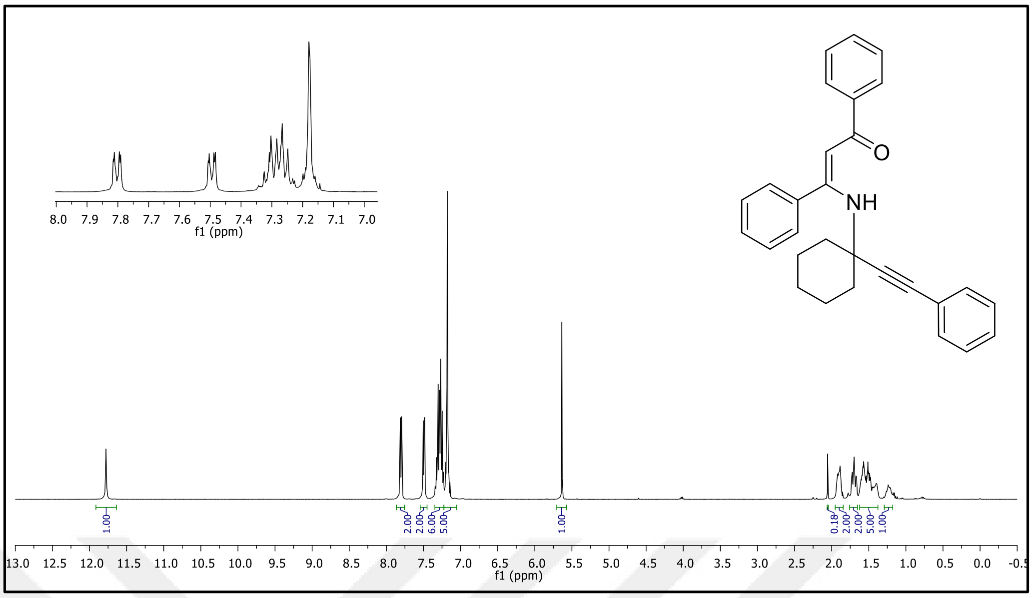

Figure A107. ^{1}H NMR spectrum of compound **52a.**

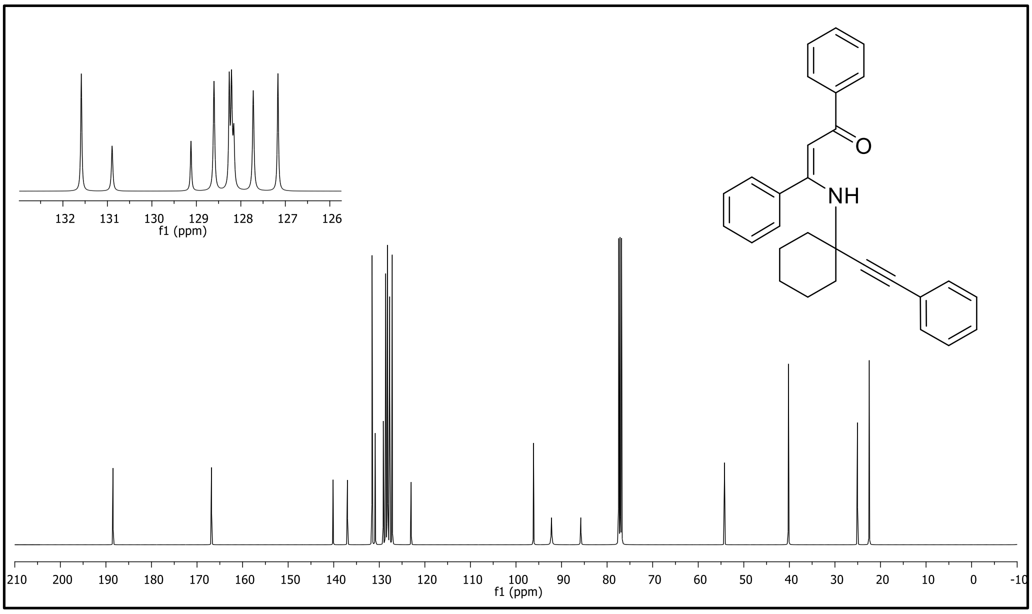

Figure A108. ^{13}C NMR spectrum of compound **52a.**

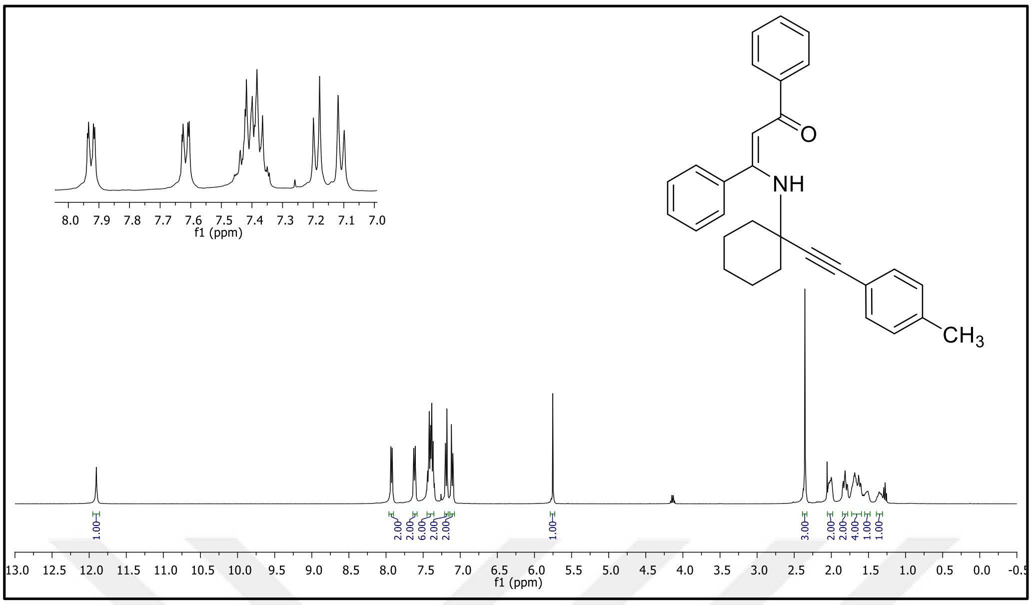

Figure A109. ^{1}H NMR spectrum of compound **52b.**

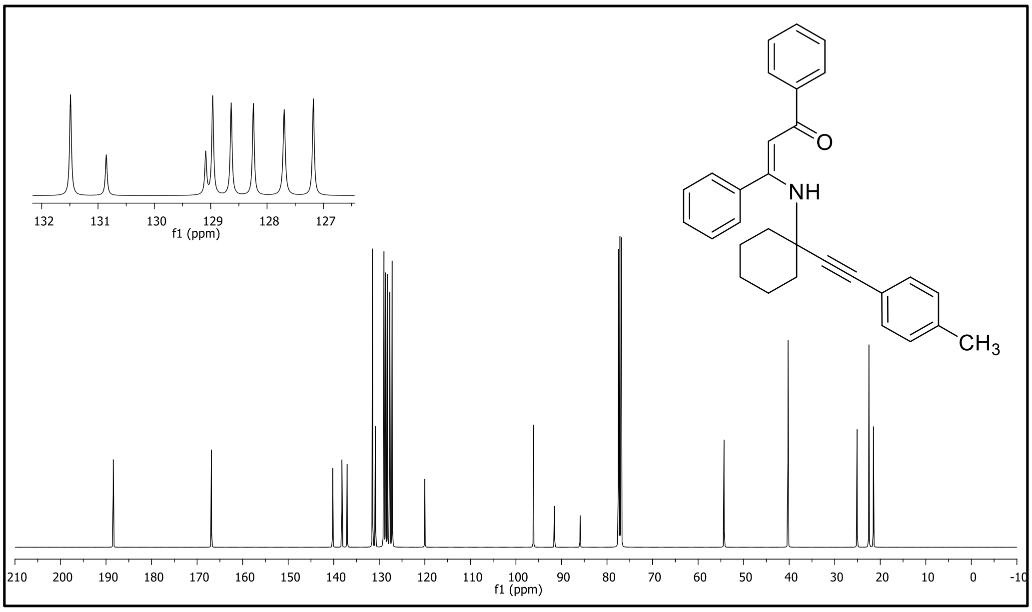

Figure A110. ^{13}C NMR spectrum of compound **52b.**

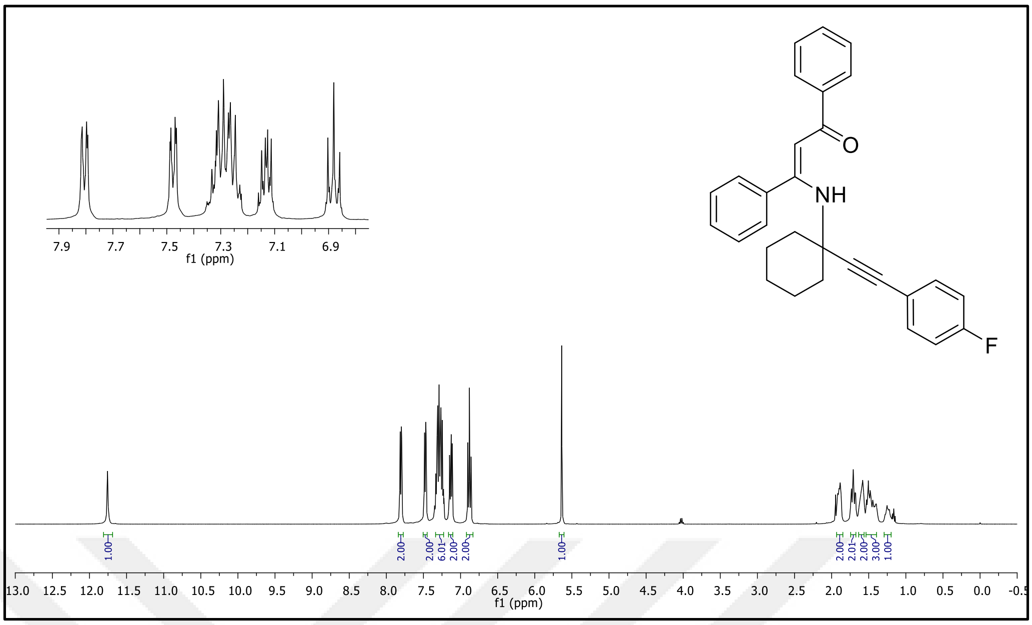

Figure A111. ^{1}H NMR spectrum of compound **52c.**

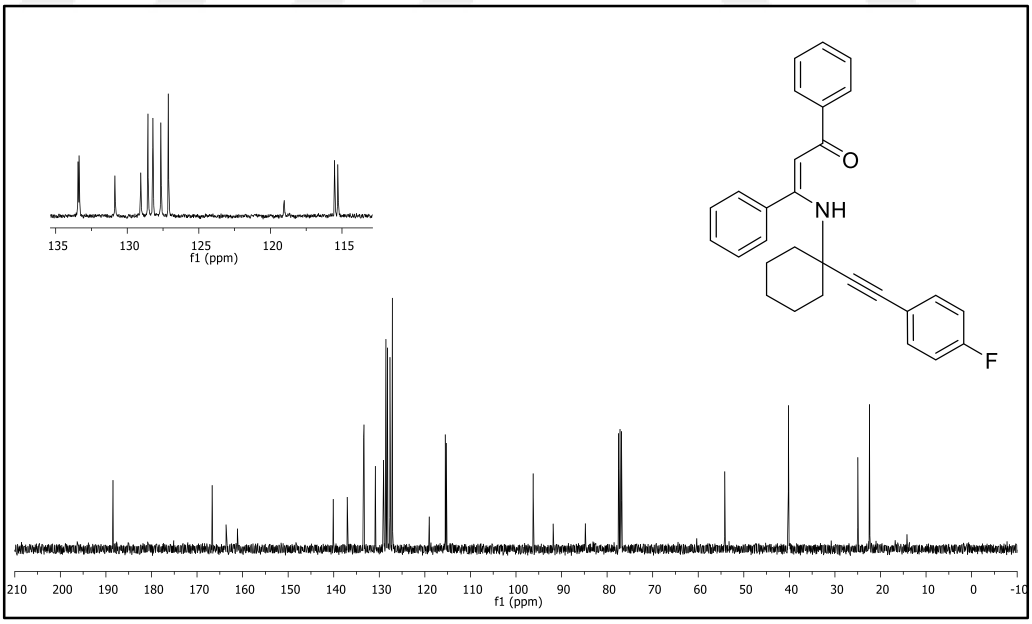

Figure A112. ^{13}C NMR spectrum of compound **52c.**

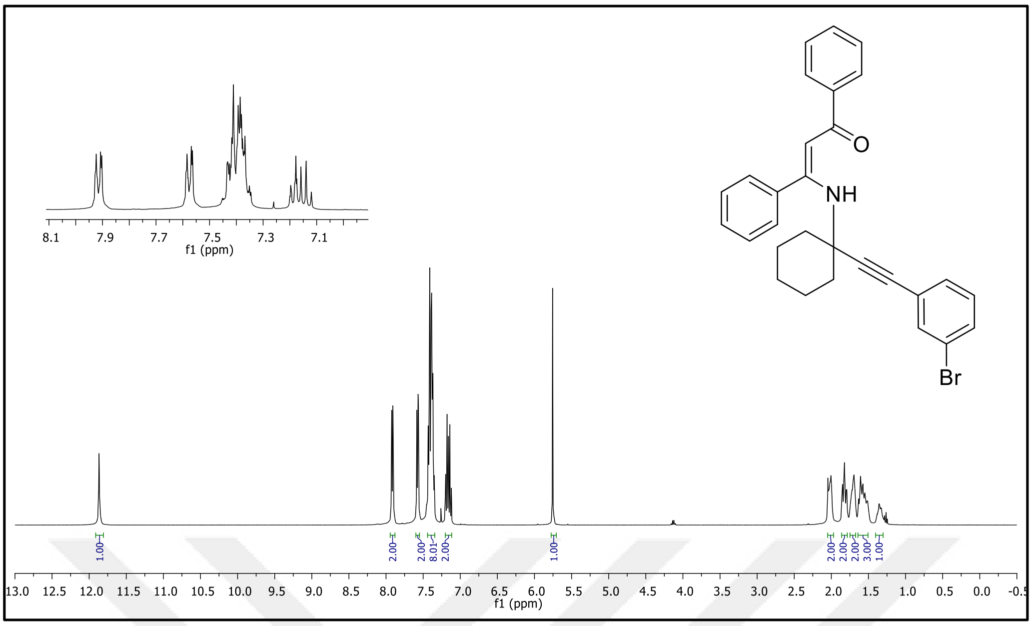

Figure A113. ^{1}H NMR spectrum of compound **52d.**

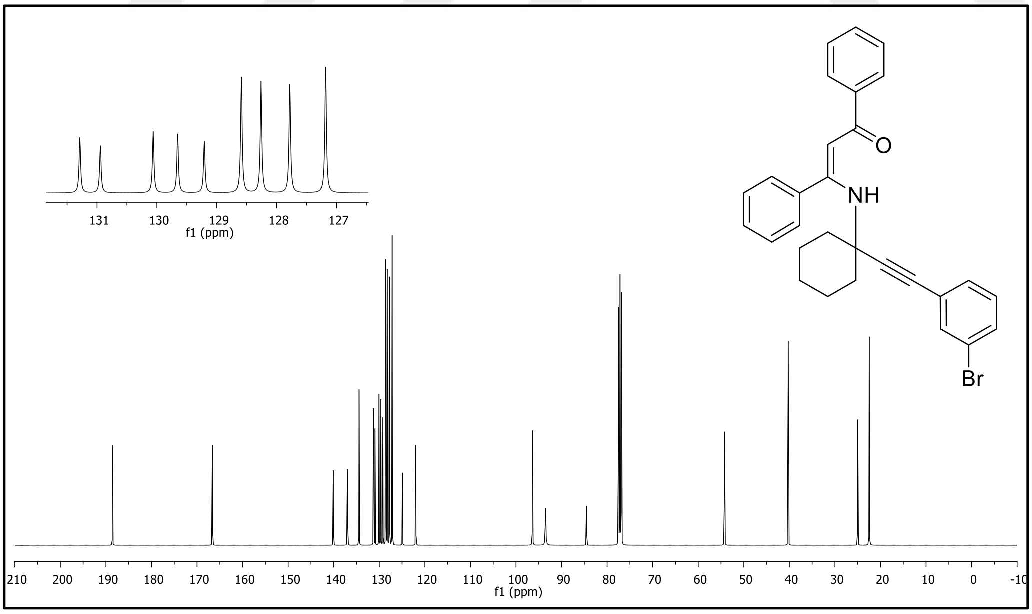

Figure A114. ^{13}C NMR spectrum of compound **52d.**

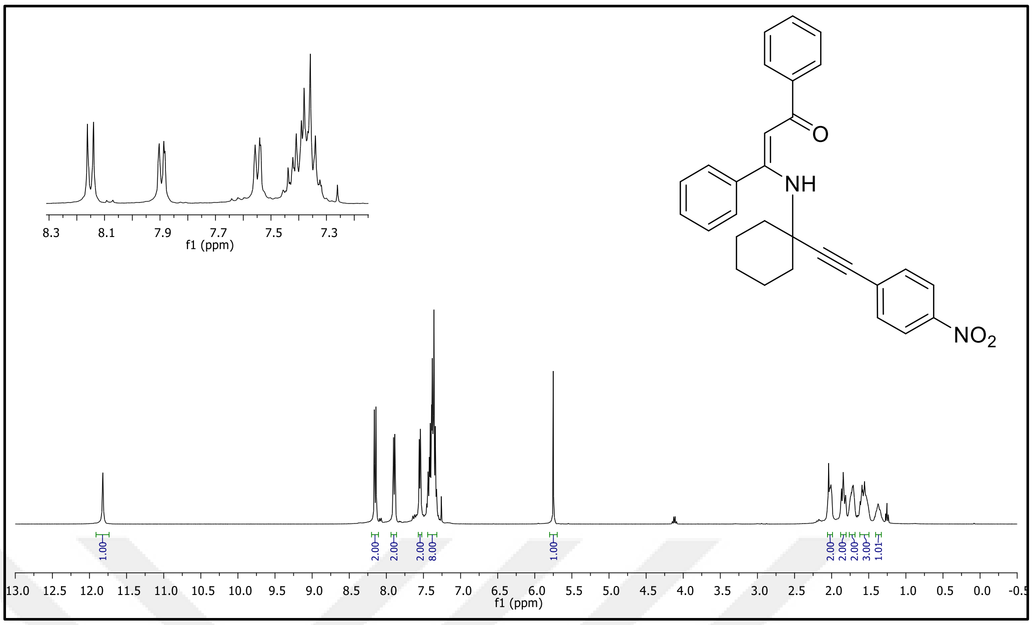

Figure A115. ^{1}H NMR spectrum of compound **52e.**

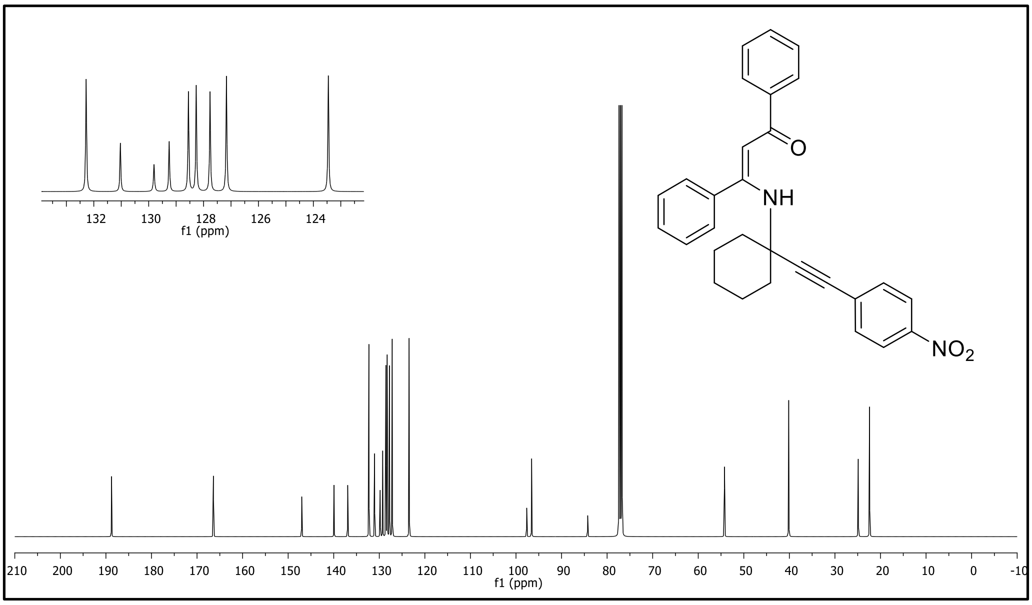

Figure A116. ^{13}C NMR spectrum of compound **52e.**

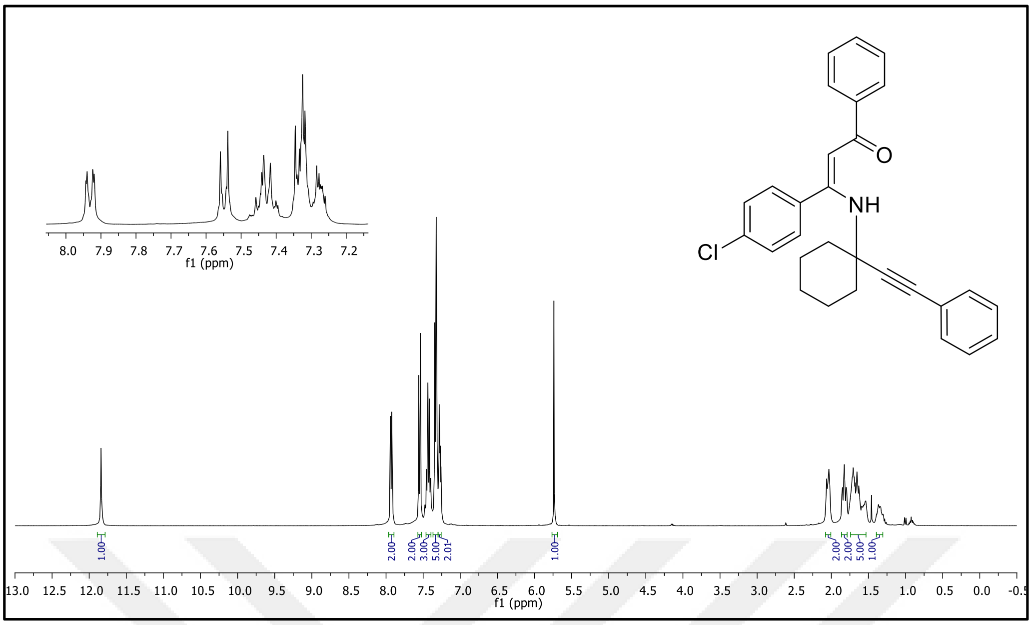

Figure A117. ^{1}H NMR spectrum of compound **52f.**

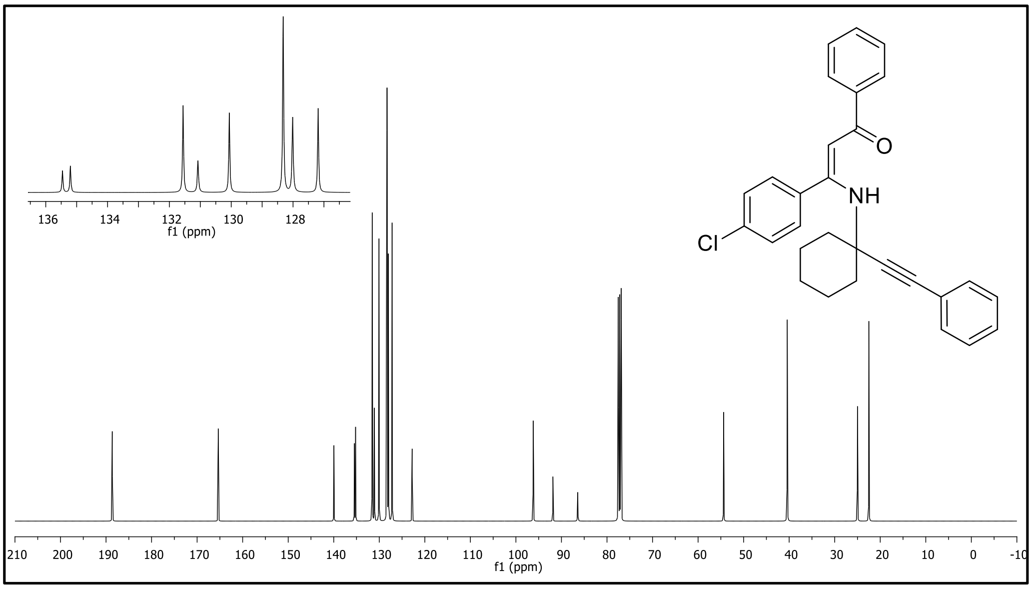

Figure A118. ^{13}C NMR spectrum of compound **52f.**

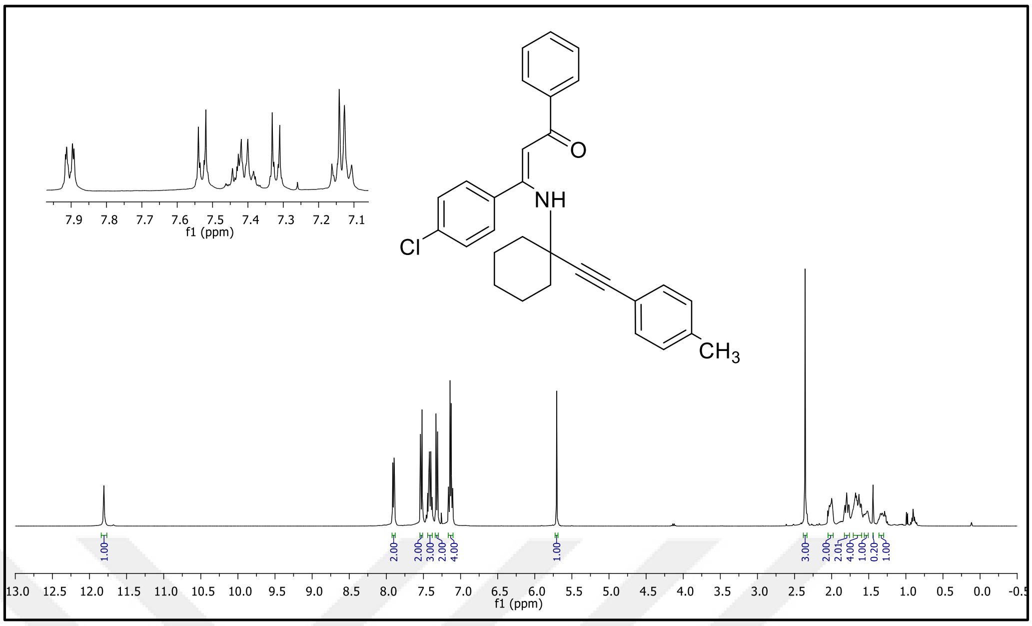

Figure A119. ^{1}H NMR spectrum of compound **52g.**

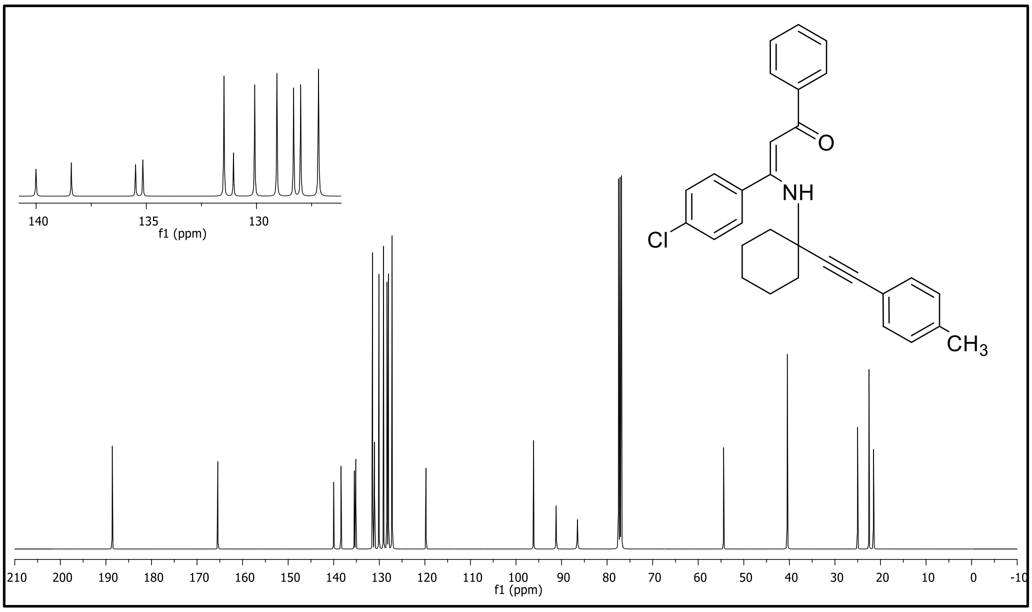

Figure A120. ^{13}C NMR spectrum of compound **52g.**

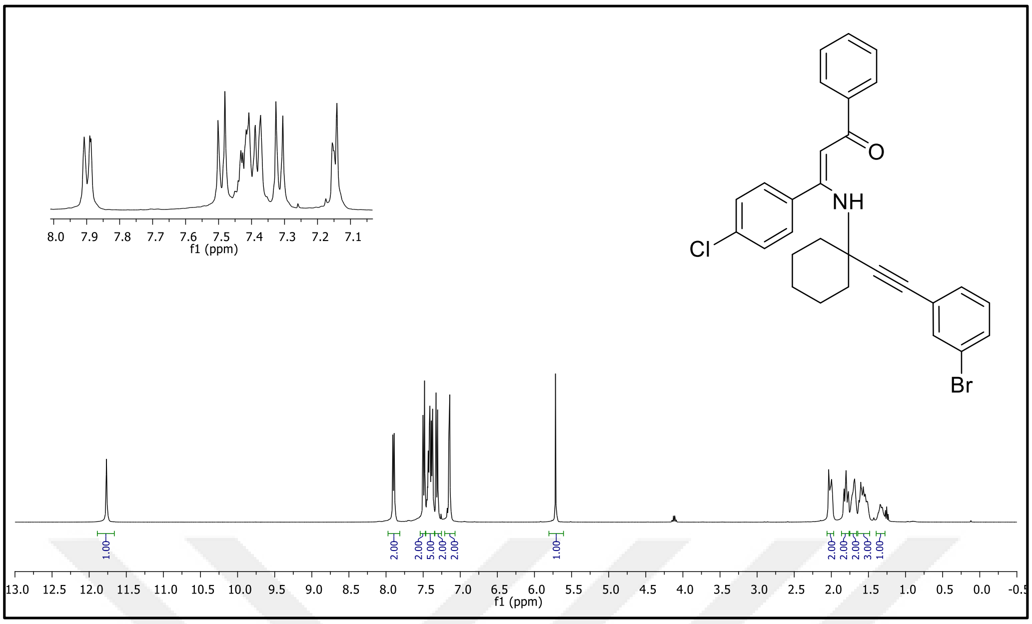

Figure A121. ^{1}H NMR spectrum of compound **52h.**

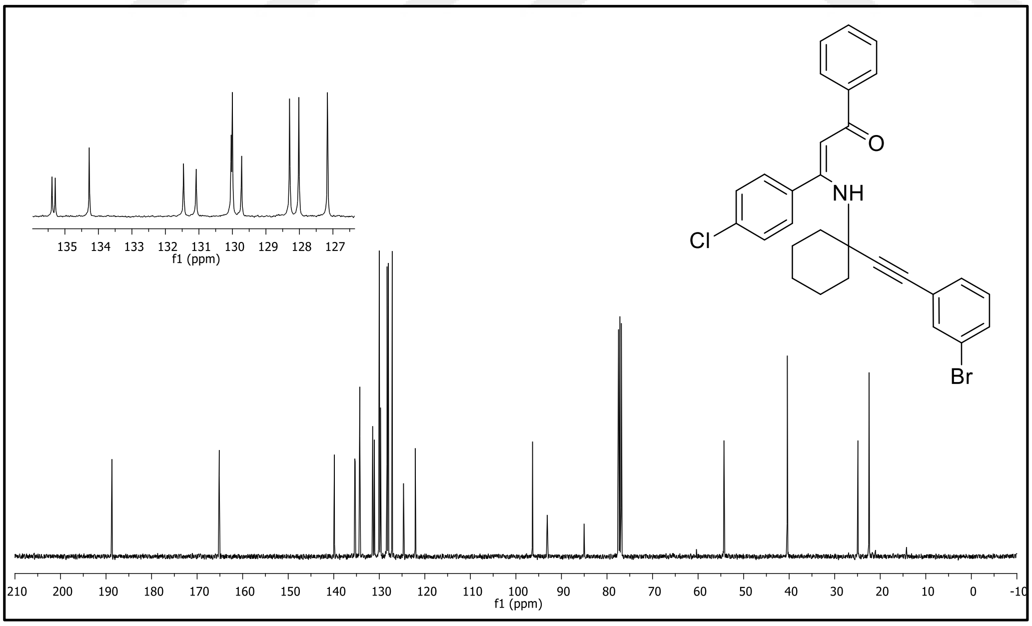

Figure A122. ^{13}C NMR spectrum of compound **52h.**

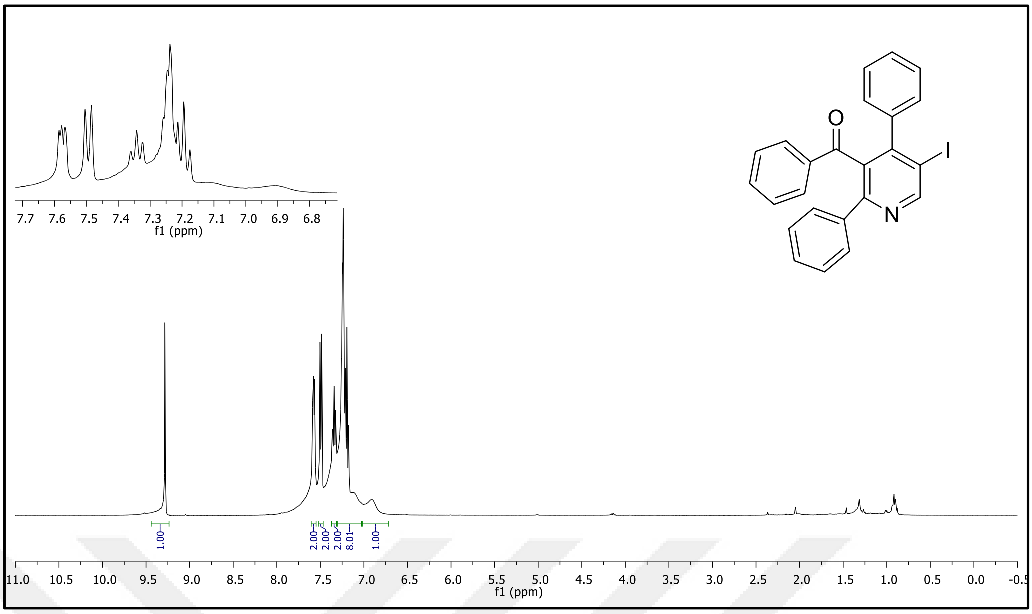

Figure A123. ^{1}H NMR spectrum of compound **44a.**

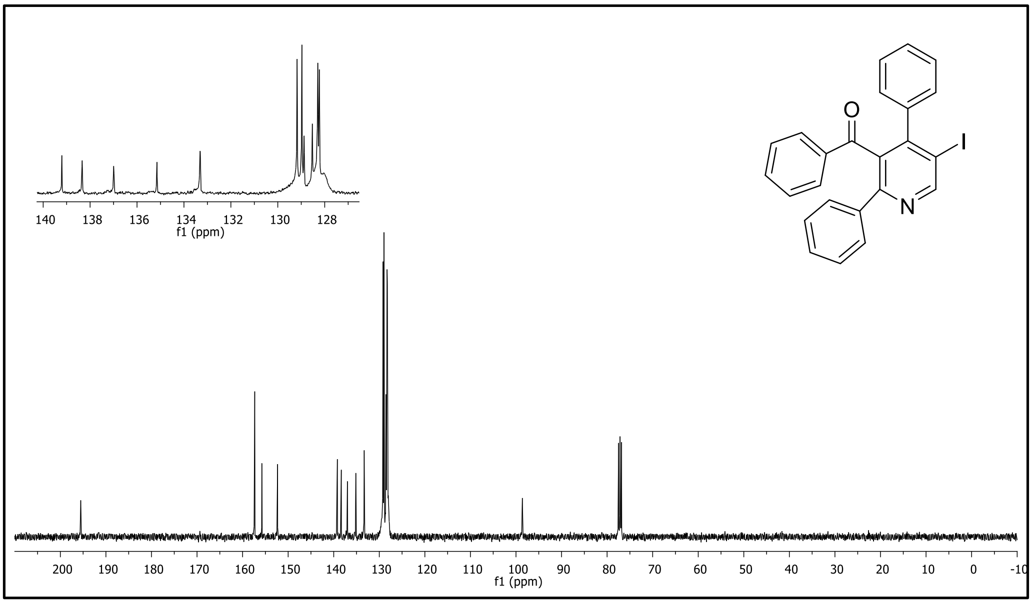

Figure A124. ^{13}C NMR spectrum of compound **44a.**

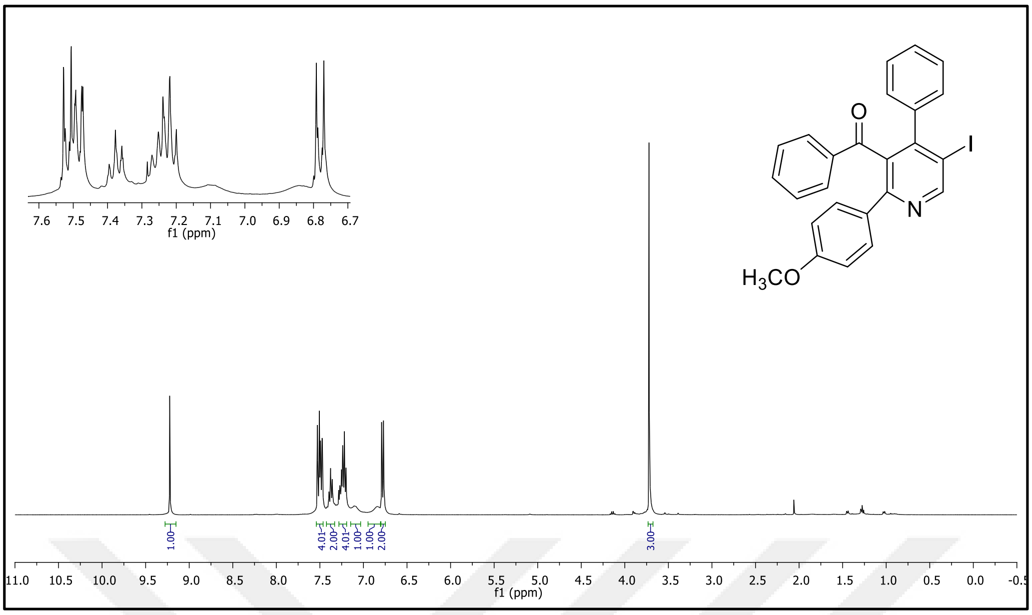

Figure A125. ^{1}H NMR spectrum of compound **44b.**

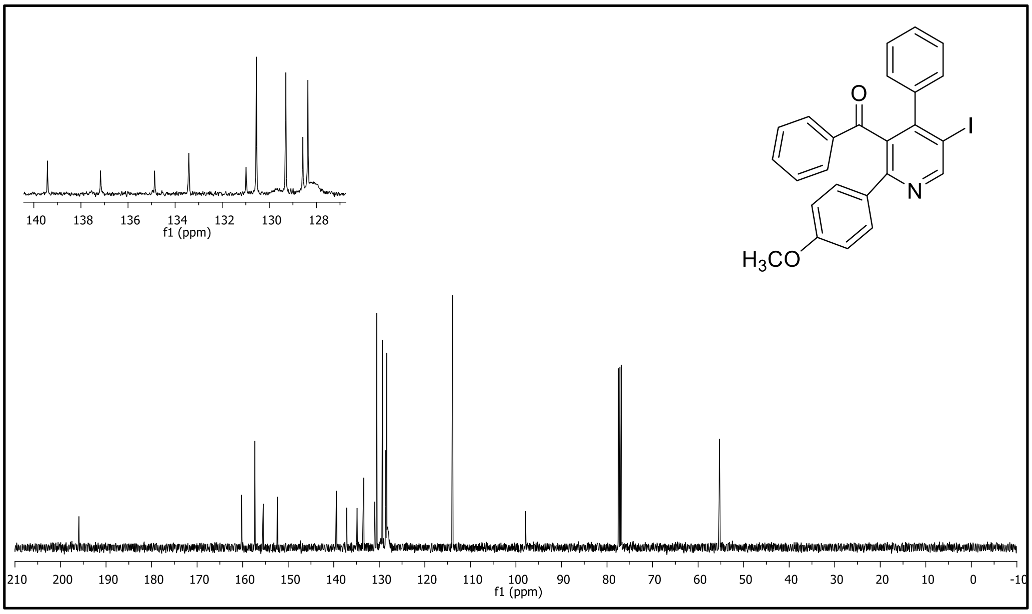

Figure A126. ^{13}C NMR spectrum of compound **44b.**

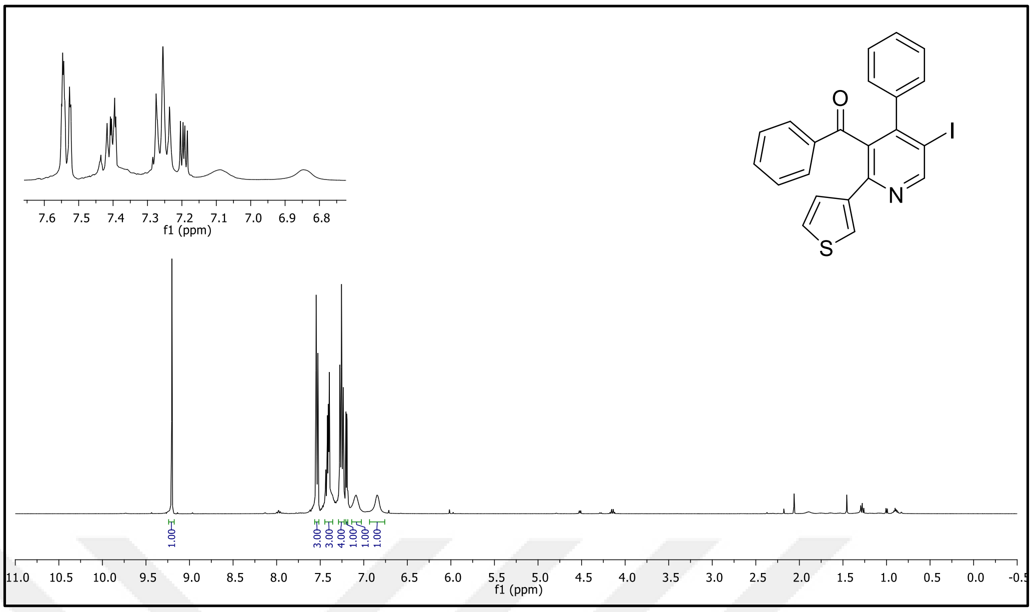

Figure A127. ^{1}H NMR spectrum of compound **44c.**

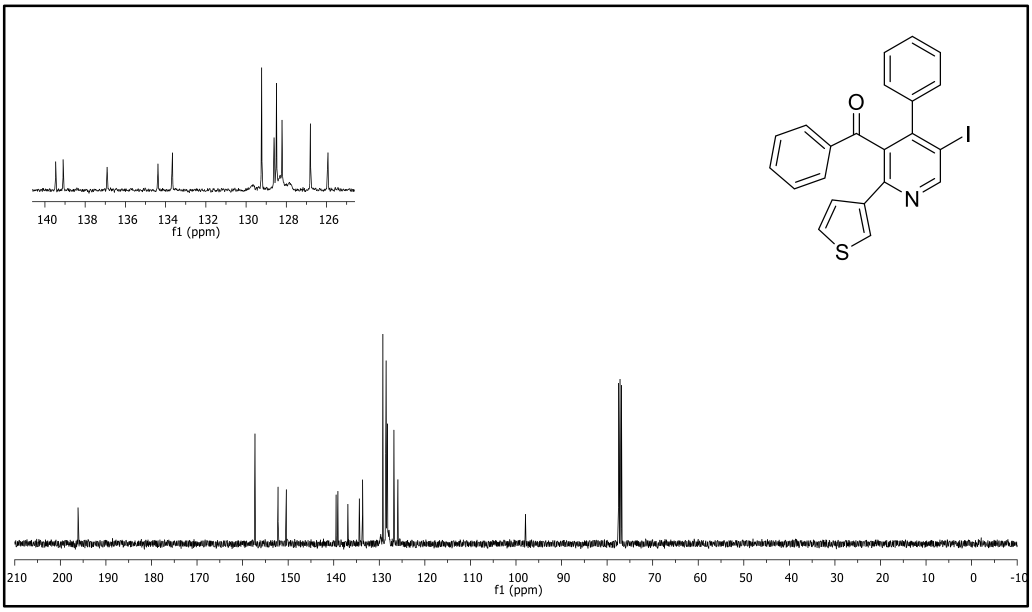

Figure A128. ^{13}C NMR spectrum of compound **44c.**

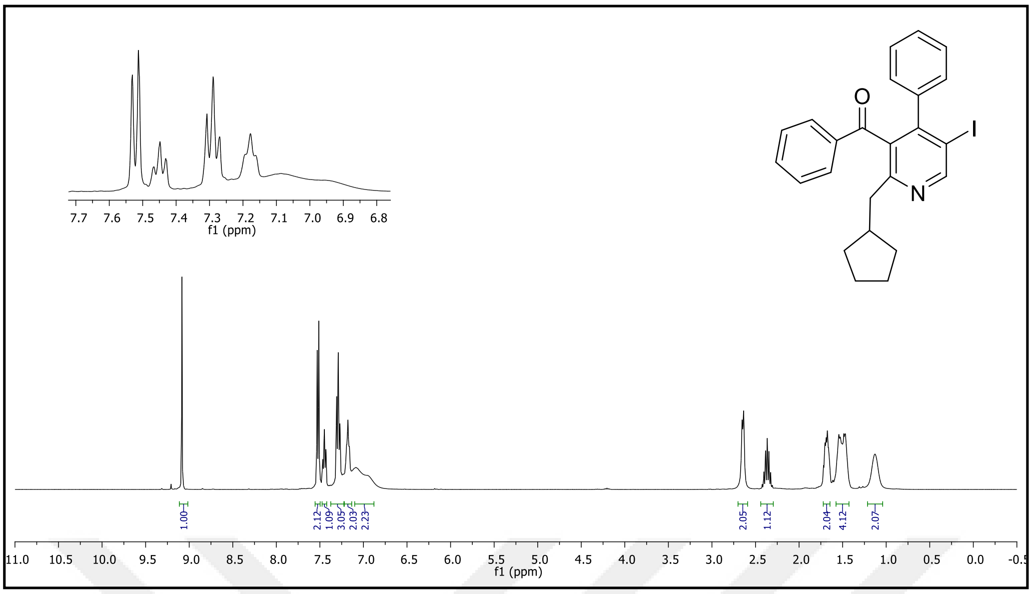

Figure A129. ^{1}H NMR spectrum of compound **44d.**

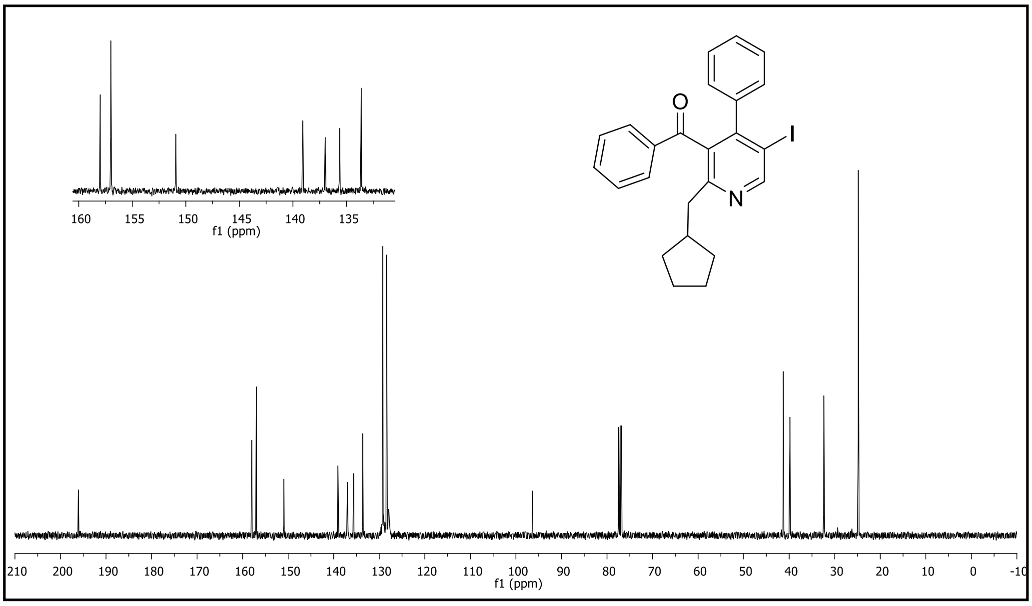

Figure A130. ^{13}C NMR spectrum of compound **44d.**

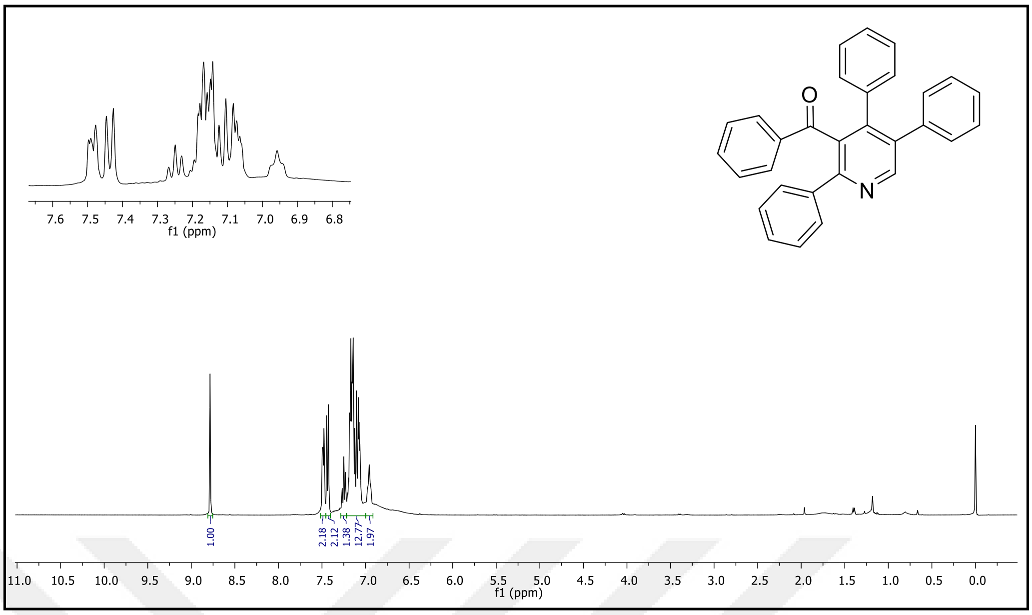

Figure A131. ^{1}H NMR spectrum of compound **46a.**

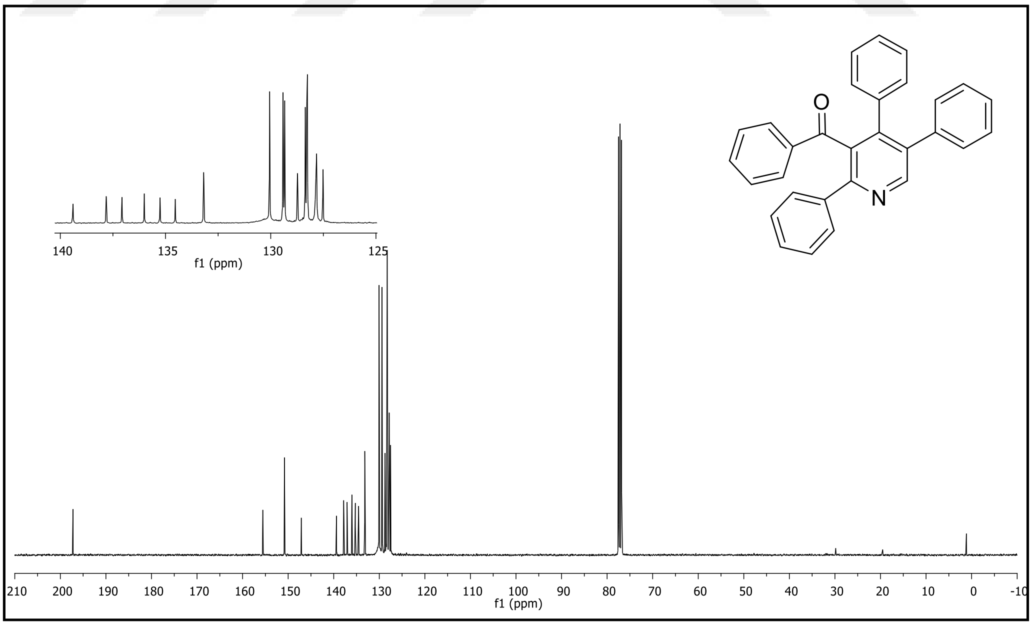

Figure A132. ^{13}C NMR spectrum of compound **46a.**

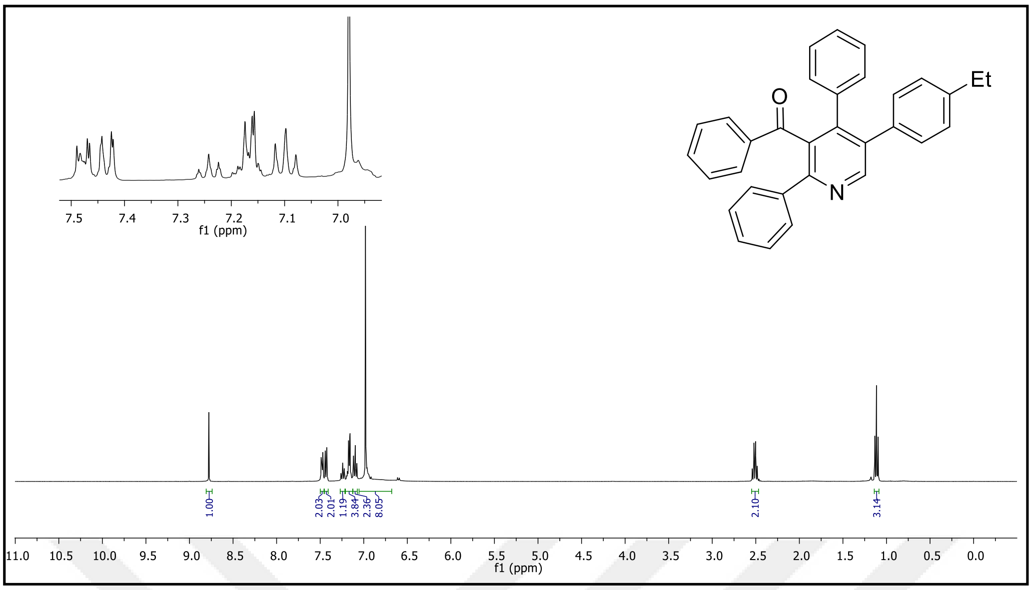

Figure A133. ^{1}H NMR spectrum of compound **46b.**

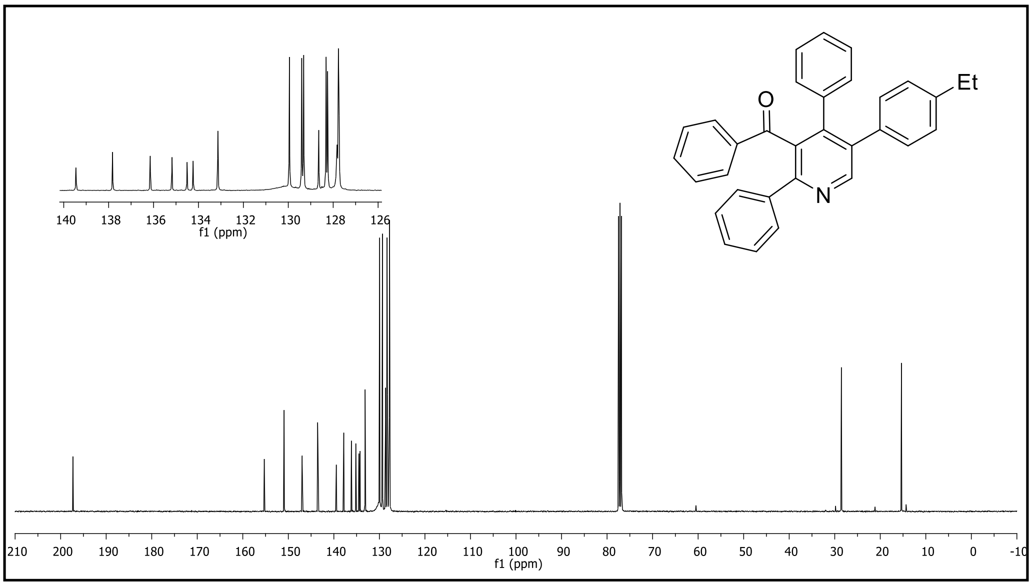

Figure A134. ^{13}C NMR spectrum of compound **46b.**

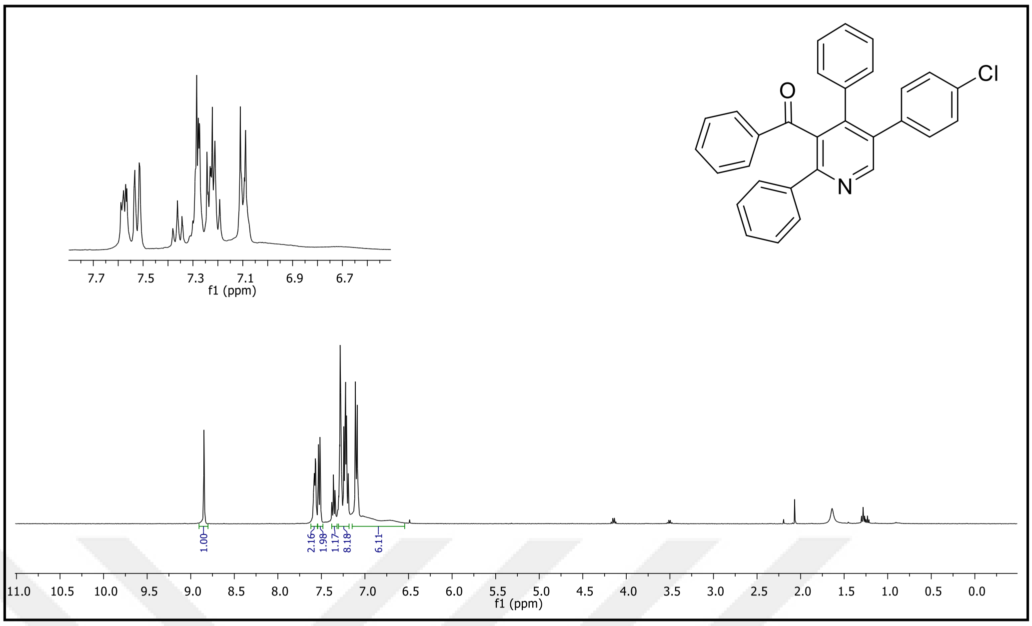

Figure A135. ^{1}H NMR spectrum of compound **46c.**

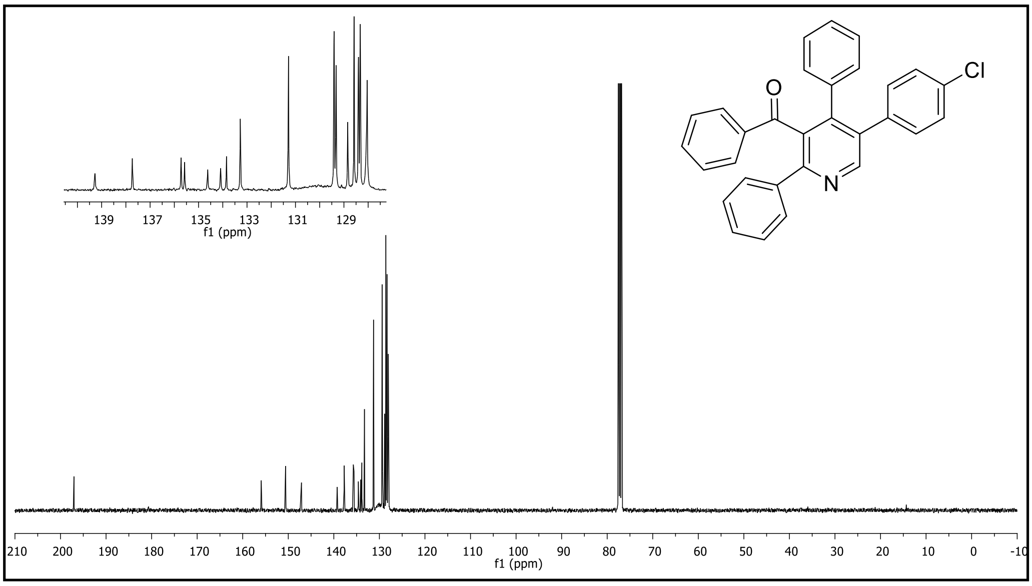

Figure A136. ^{13}C NMR spectrum of compound **46c.**

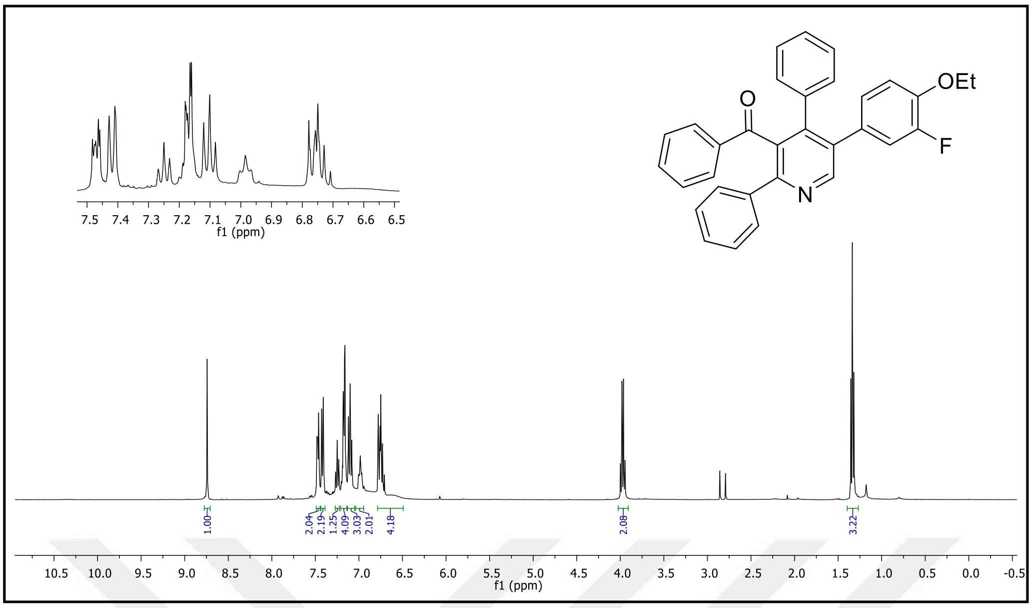

Figure A137. ^{1}H NMR spectrum of compound **46d.**

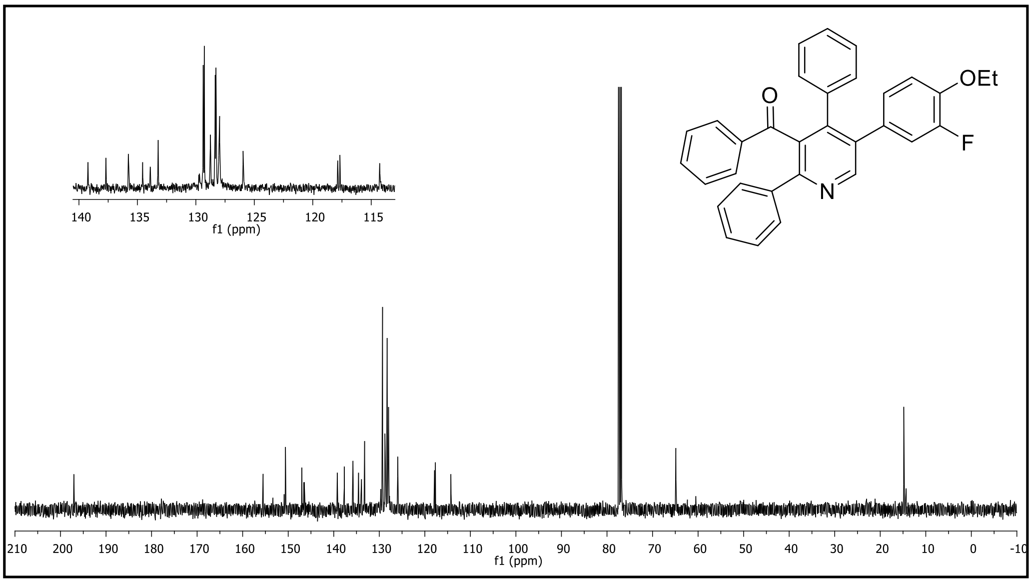

Figure A138. ^{13}C NMR spectrum of compound **46d.**

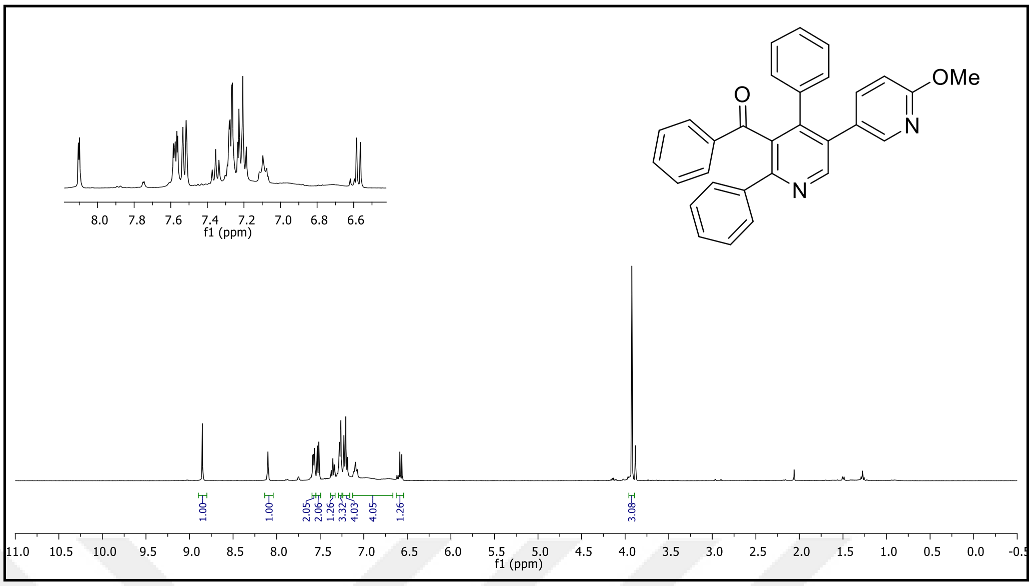

Figure A139. ^{1}H NMR spectrum of compound **46e.**

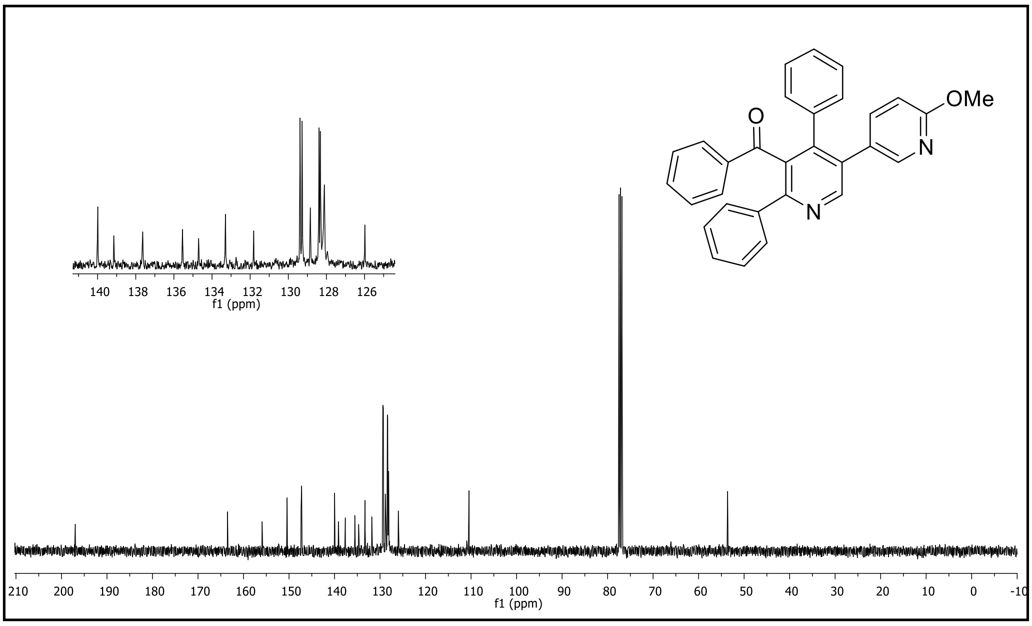

Figure A140. ^{13}C NMR spectrum of compound **46e.**

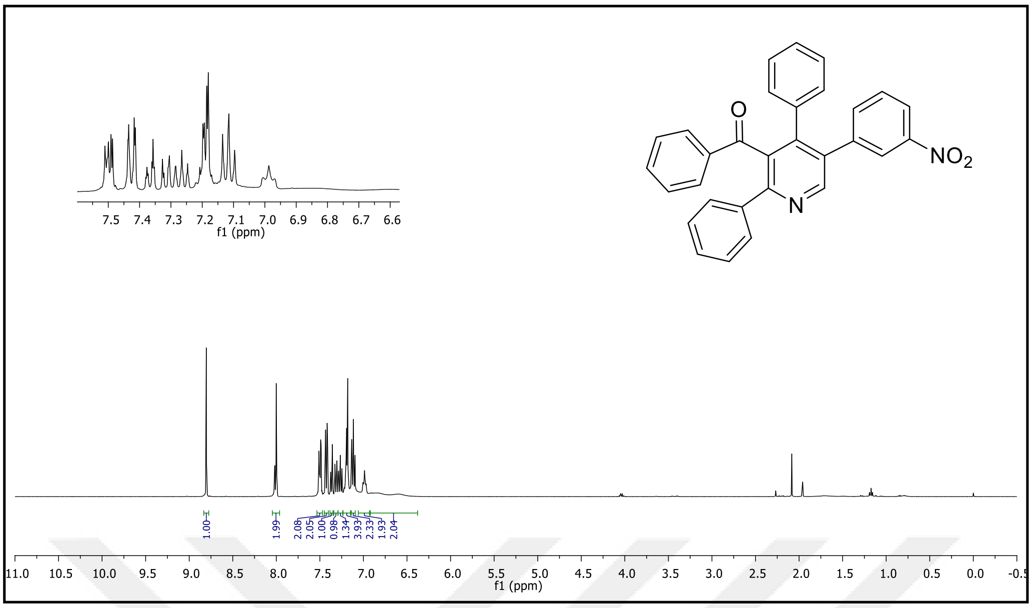

Figure A141. ^{1}H NMR spectrum of compound **46f.**

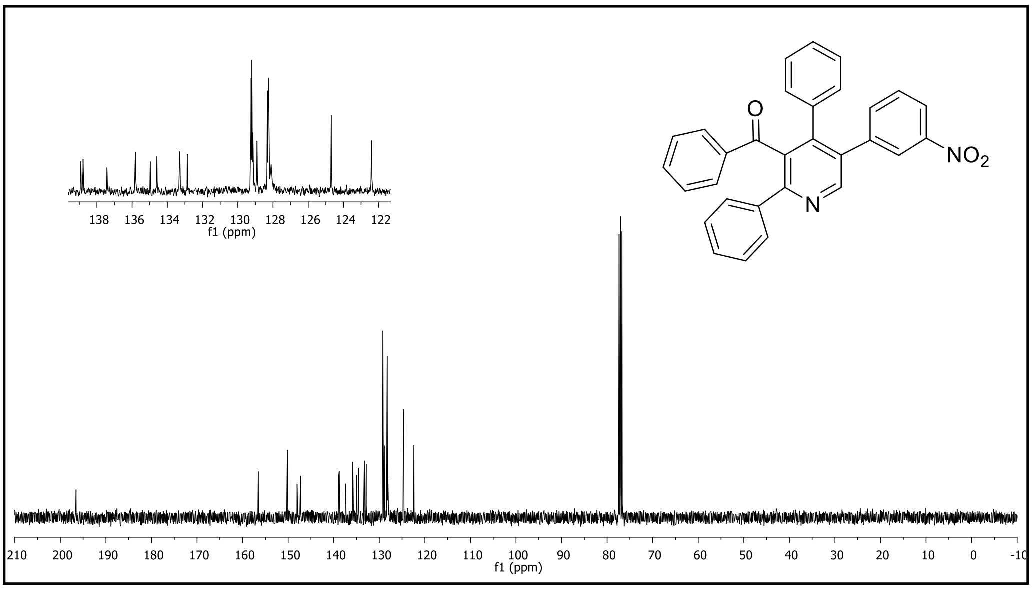

Figure A142. ^{13}C NMR spectrum of compound **46f.**

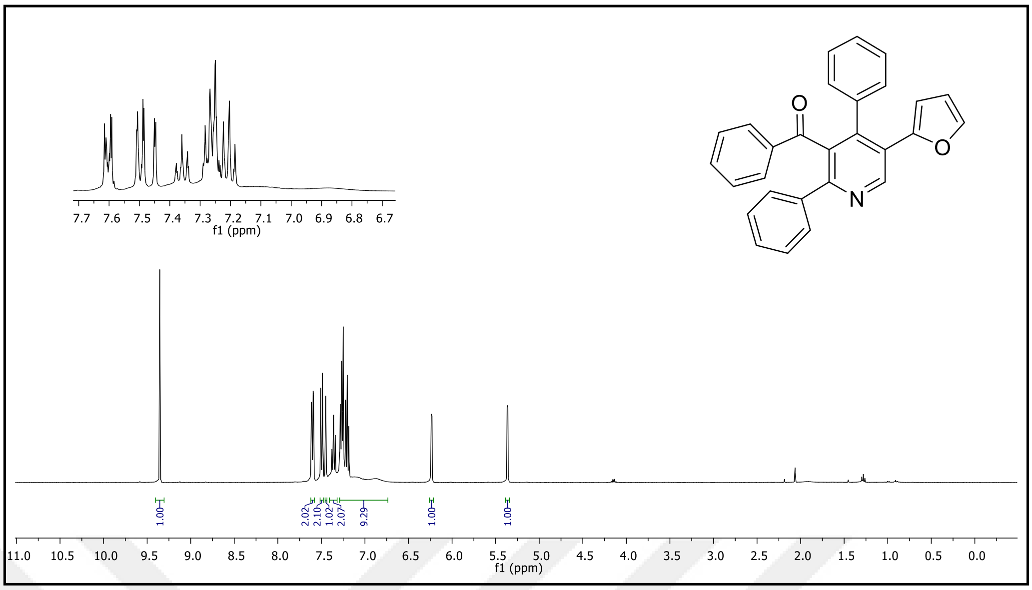

Figure A143. ^{1}H NMR spectrum ofcompound **46g.**

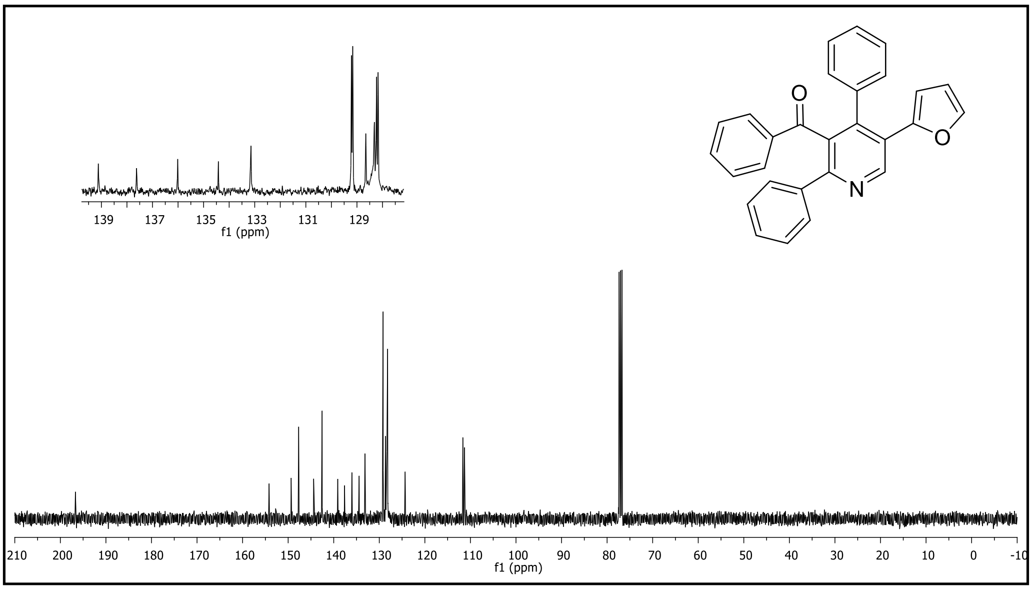

Figure A144. ^{13}C NMR spectrum of compound **46g.**

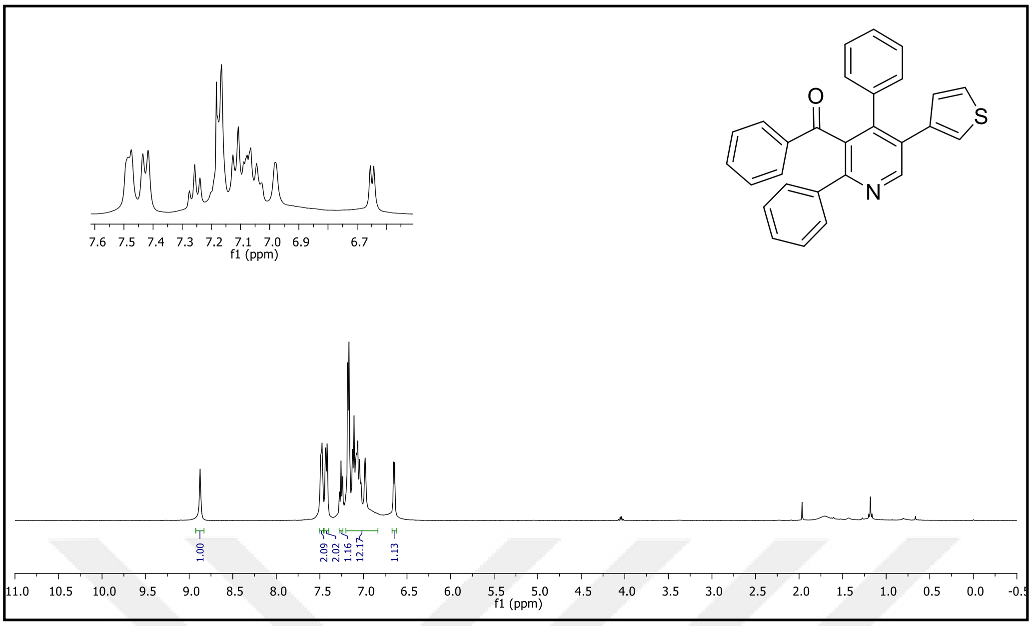

Figure A145. ^{1}H NMR spectrum of compound **46h.**

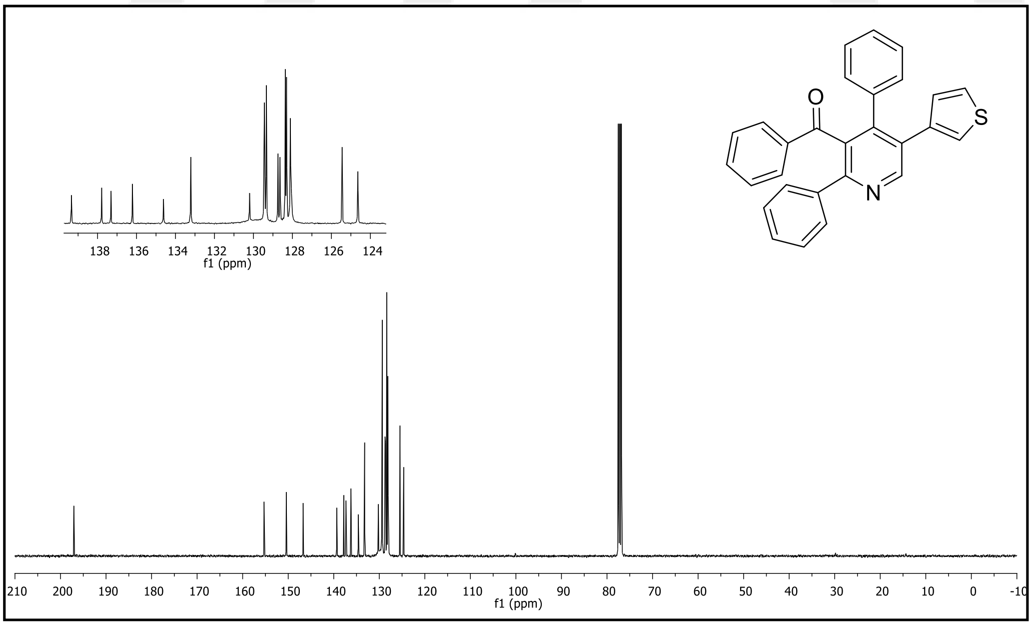

Figure A146. ^{13}C NMR spectrum of compound **46h.**

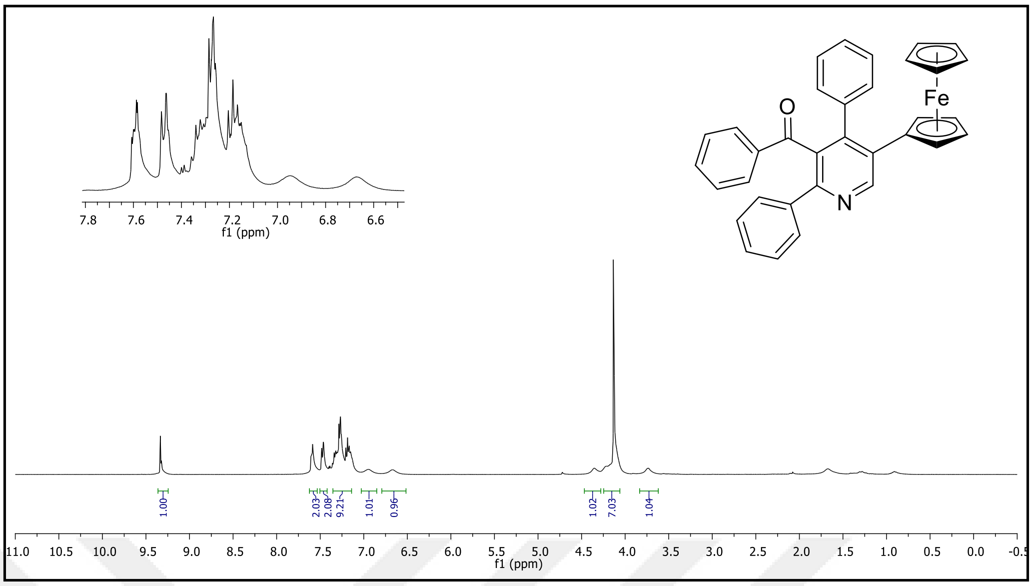

Figure A147. ^{1}H NMR spectrum of compound **46i.**

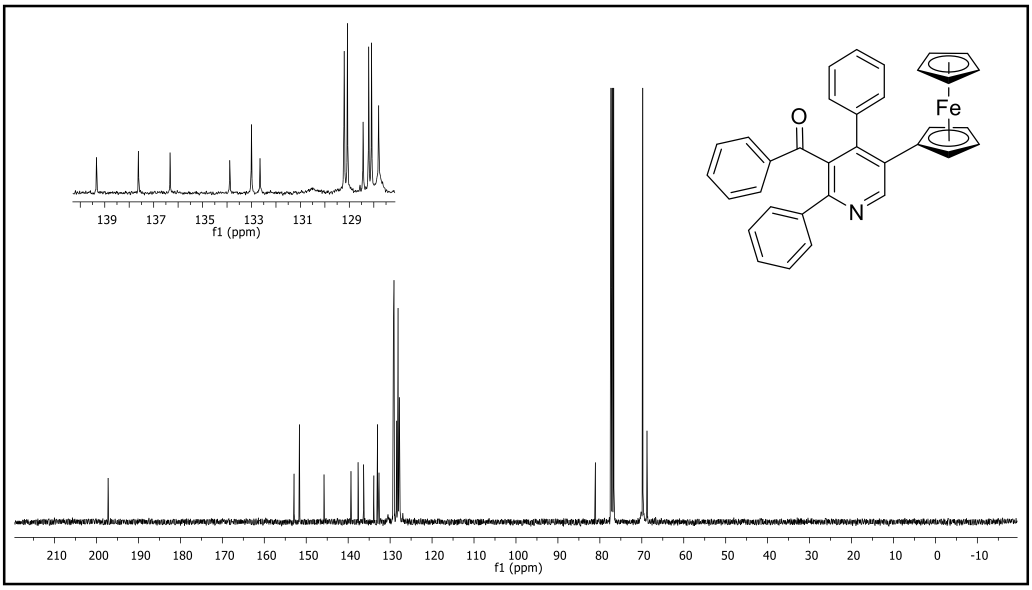

Figure A148. ^{13}C NMR spectrum of compound **46i.**

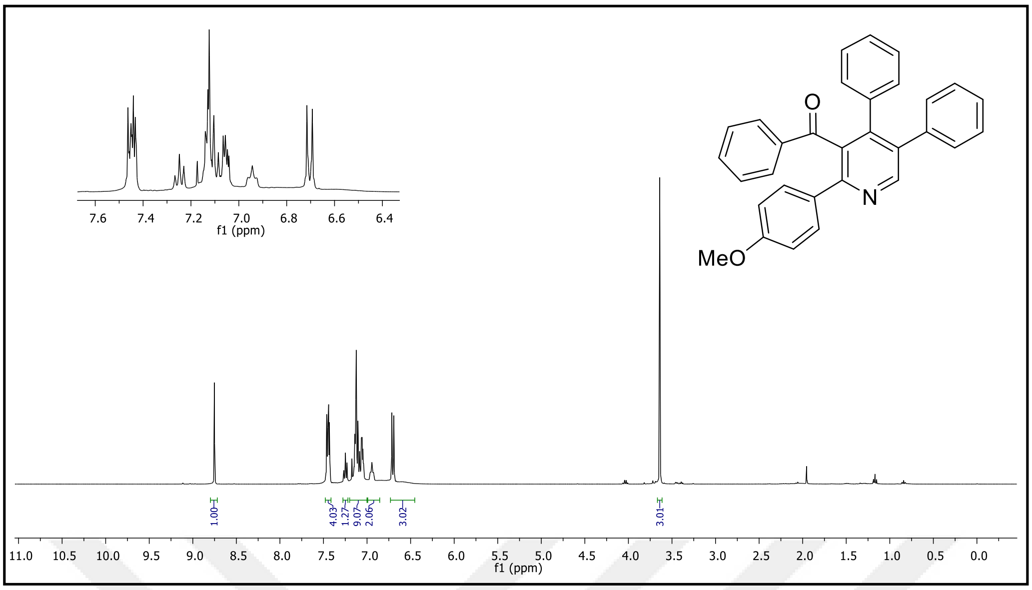

Figure A149. ^{1}H NMR spectrum of compound **46j.**

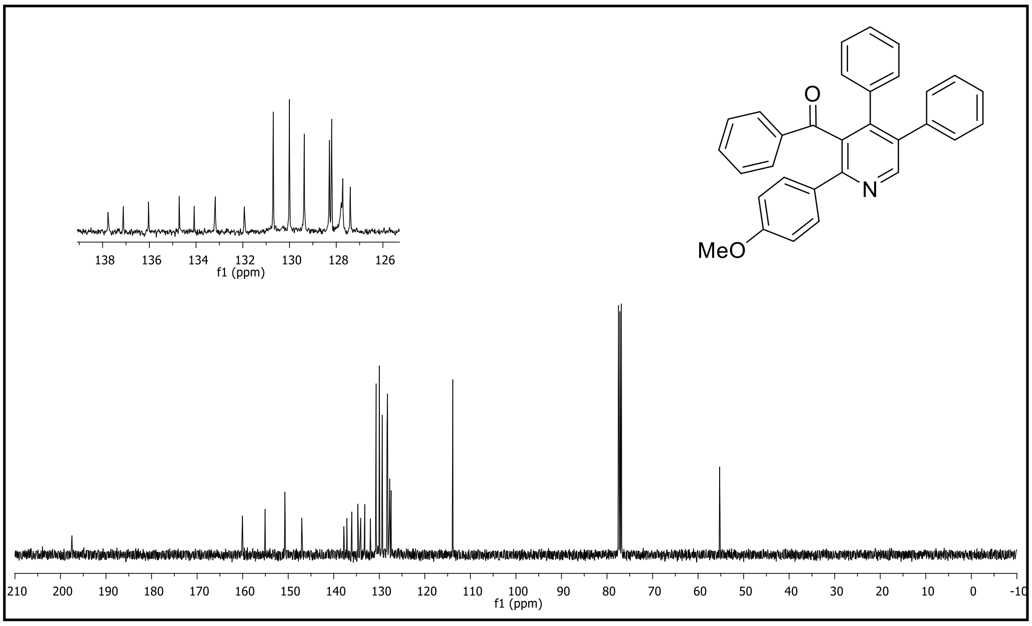

Figure A150. ^{13}C NMR spectrum of compound **46j.**

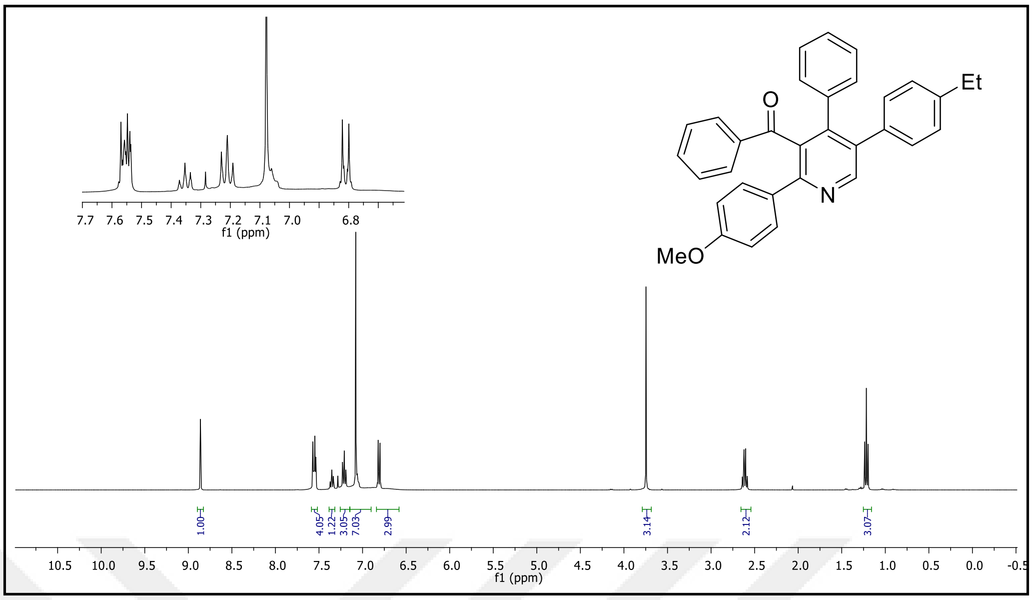

Figure A151. ^{1}H NMR spectrum of compound **46k.**

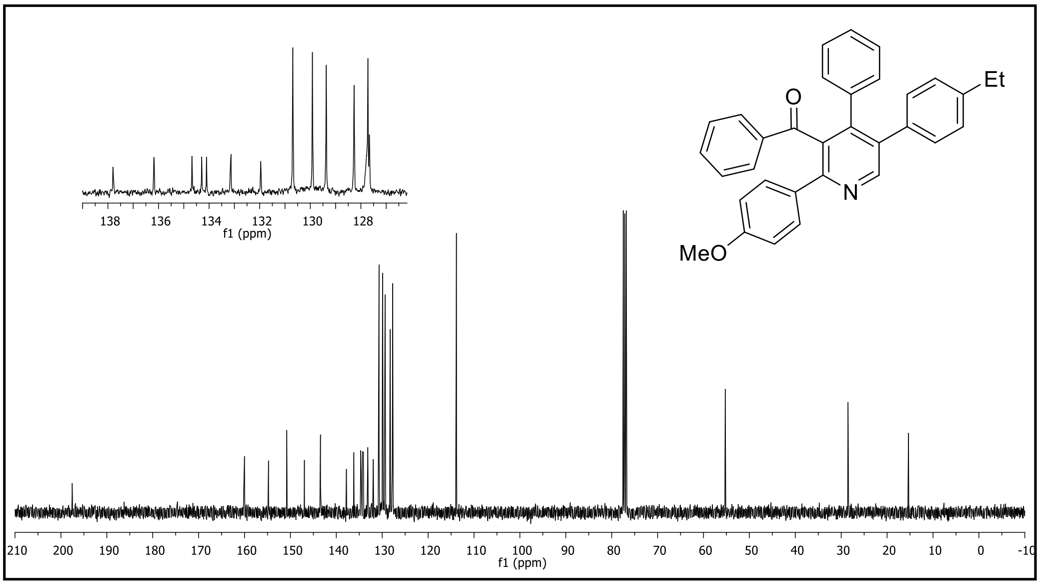

Figure A152. ^{13}C NMR spectrum of compound **46k.**

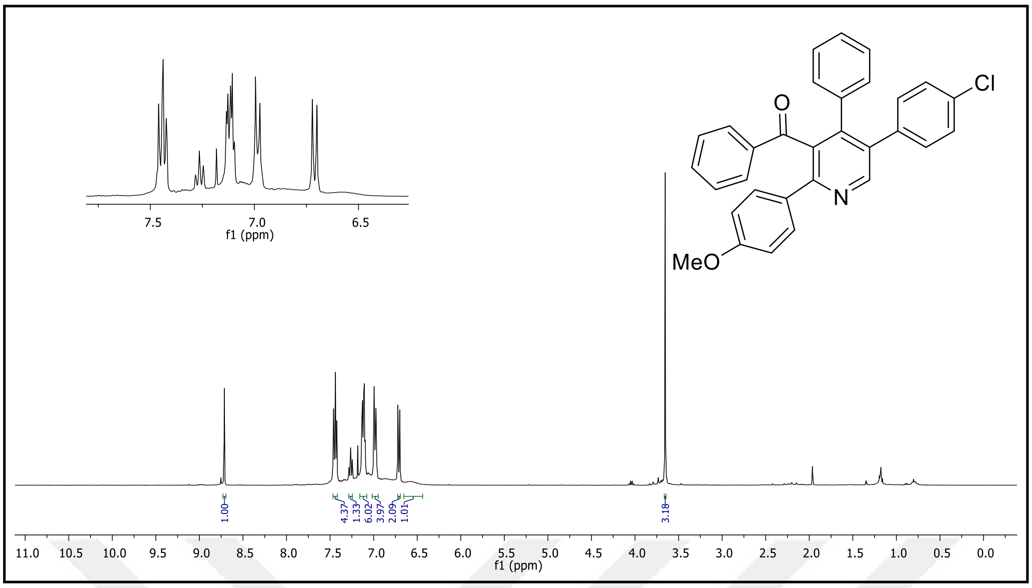

Figure A153. ^{1}H NMR spectrum of compound **46l.**

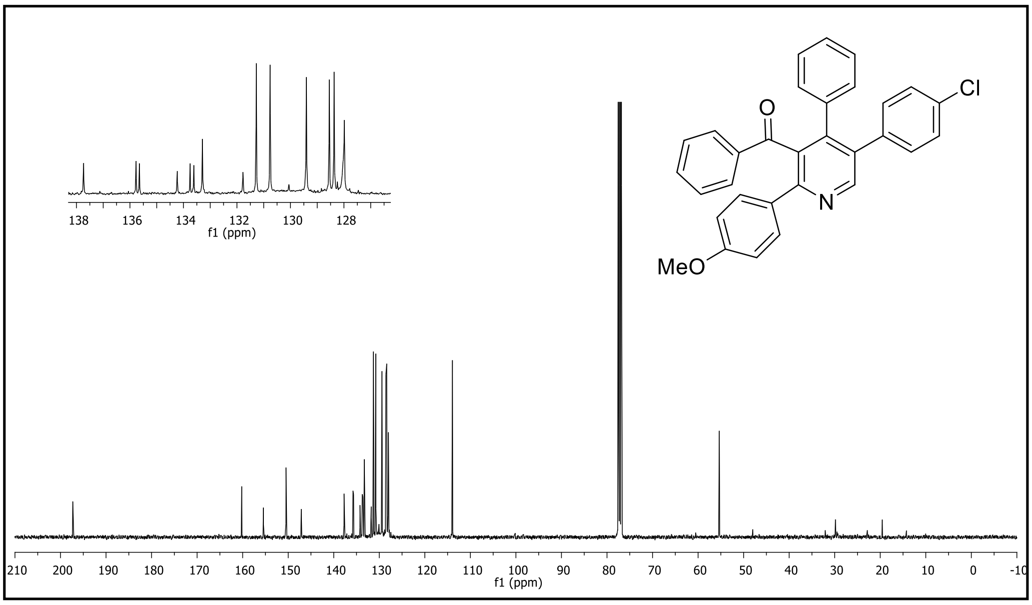

Figure A154. ^{13}C NMR spectrum of compound **46l.**

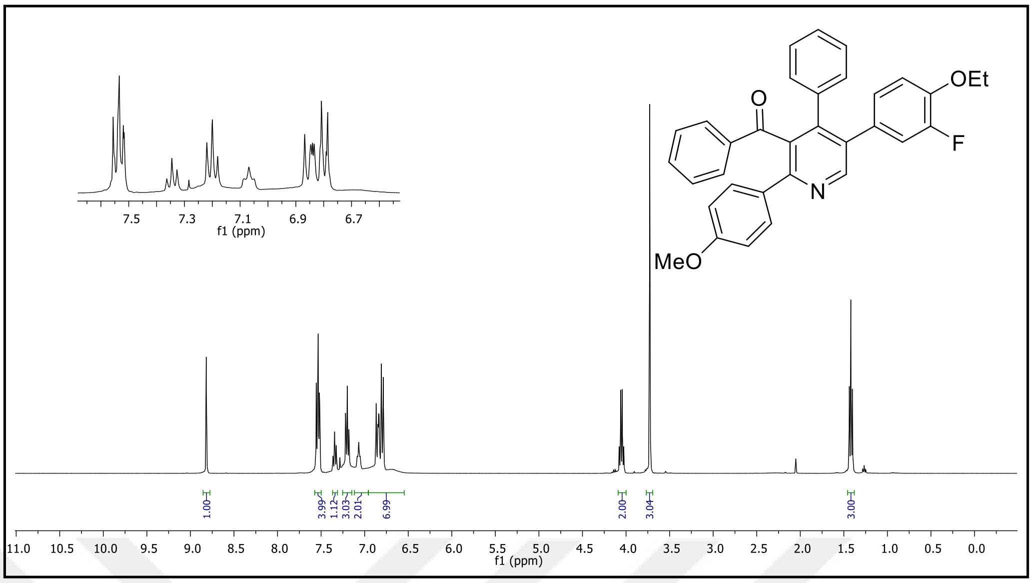

Figure A155. ^{1}H NMR spectrum of compound **46m.**

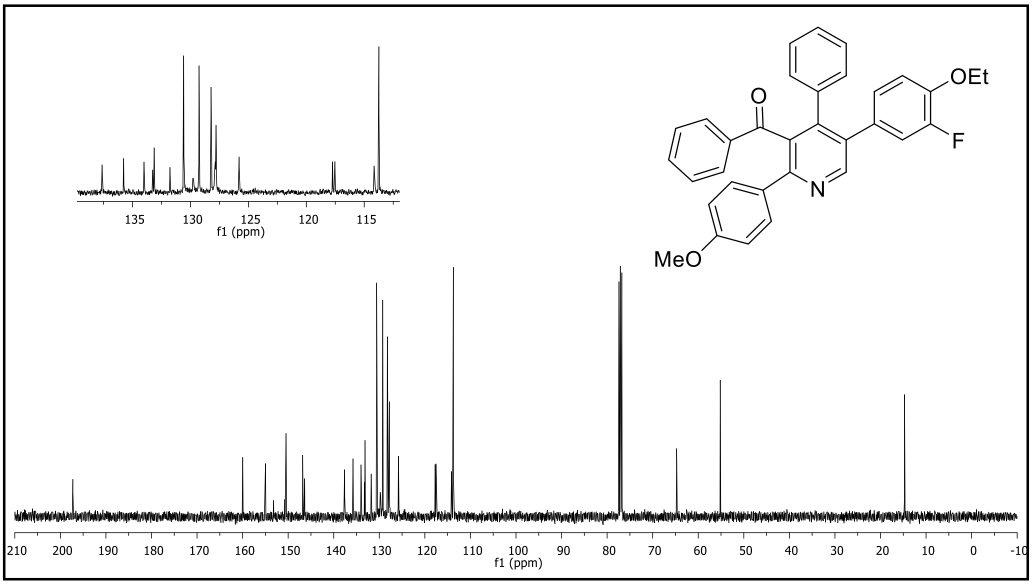

Figure A156. ^{13}C NMR spectrum of compound **46m.**

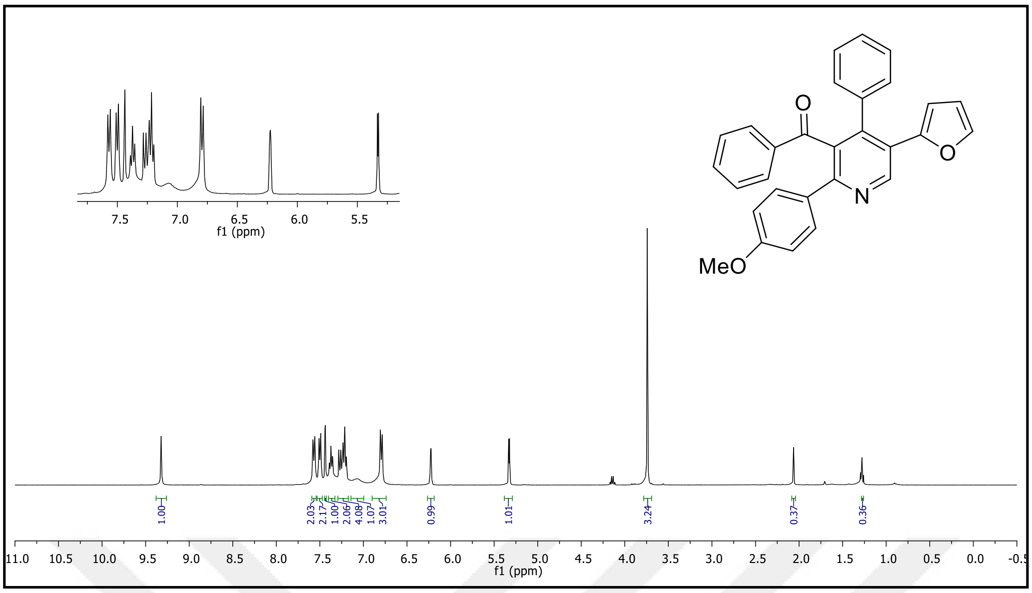

Figure A157. ^{1}H NMR spectrum of compound **46n.**

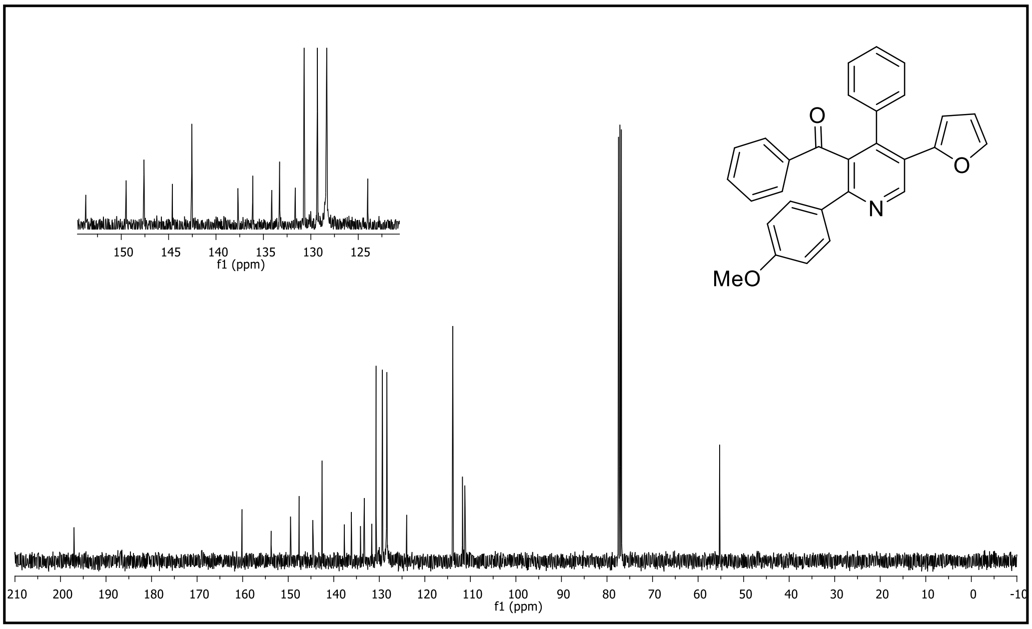

Figure A158. ^{13}C NMR spectrum of compound **46n.**

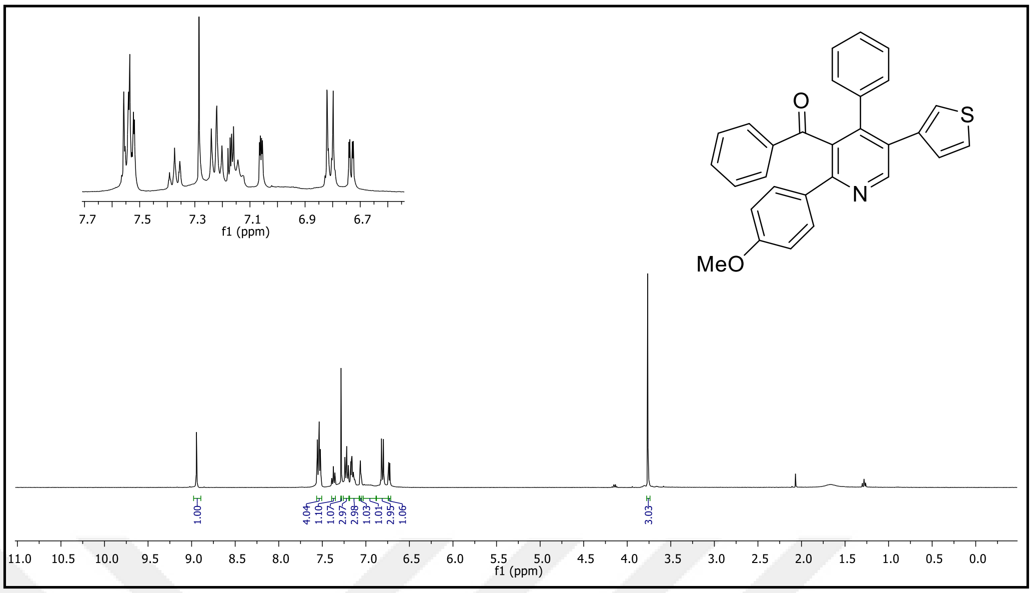

Figure A159. ^{1}H NMR spectrum of compound **46o.**

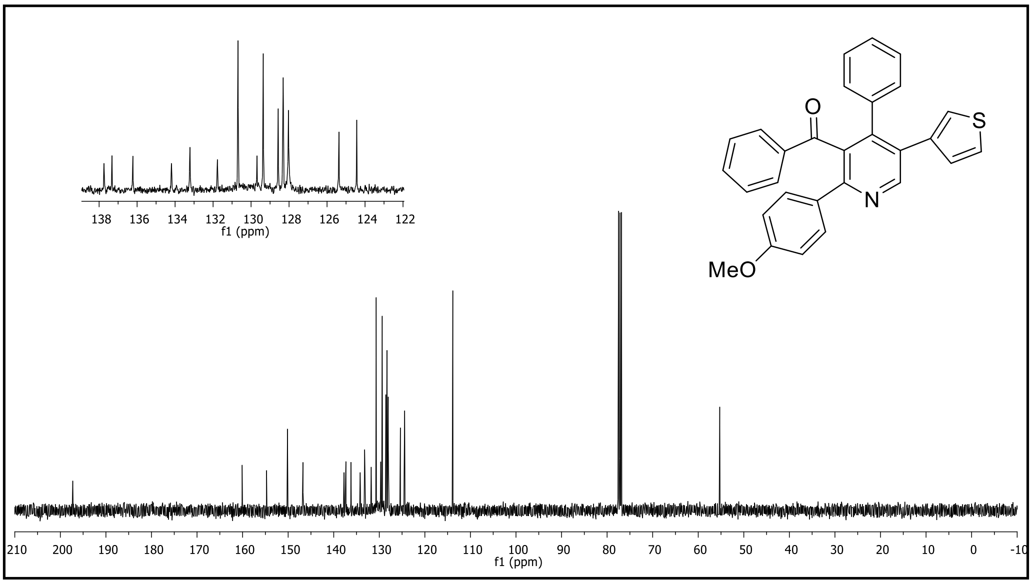

Figure A160. ^{13}C NMR spectrum of compound **46o.**

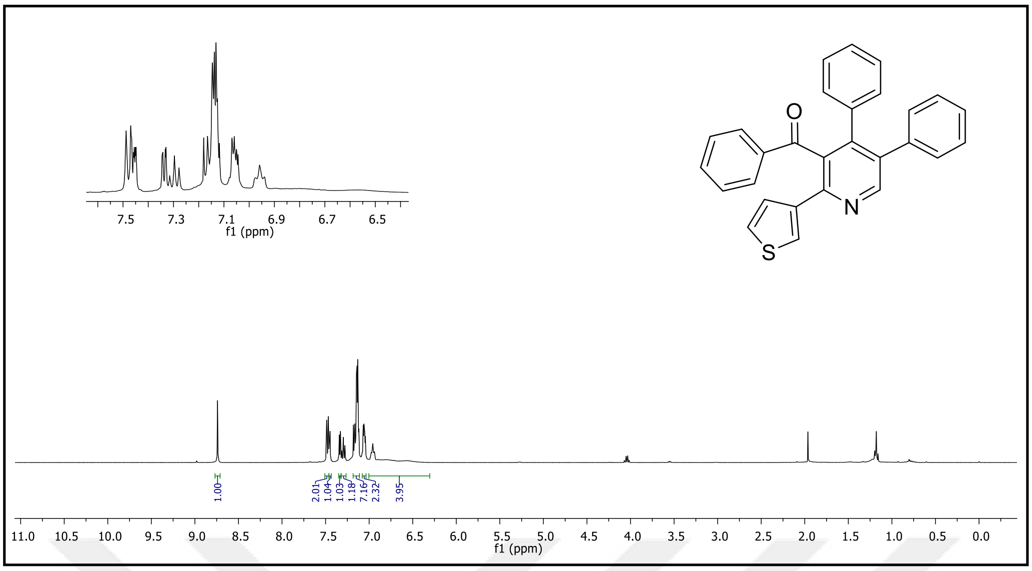

Figure A161. ^{1}H NMR spectrum of compound **46p.**

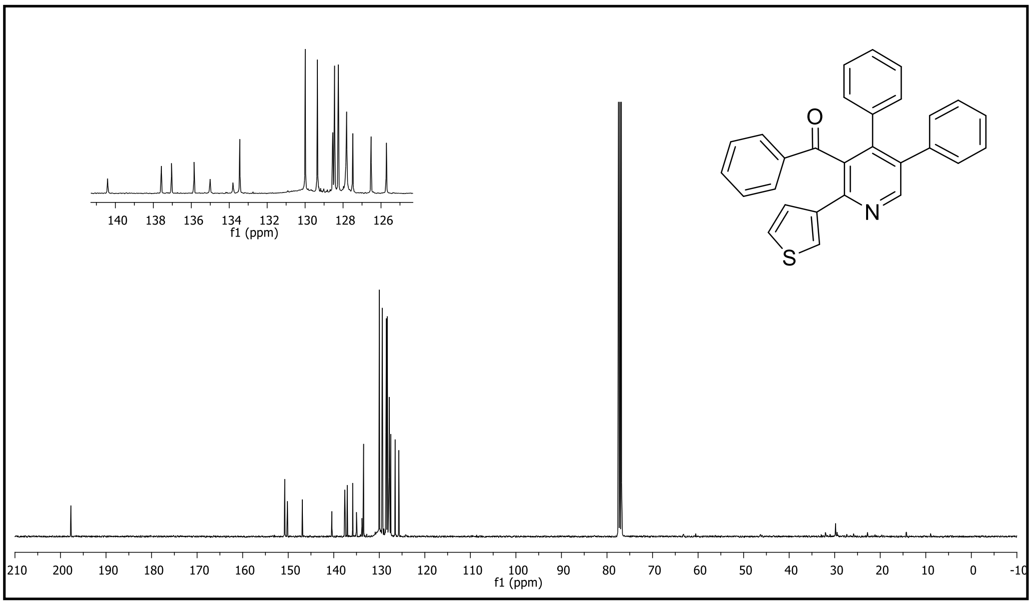

Figure A162. ^{13}C NMR spectrum of compound **46p.**

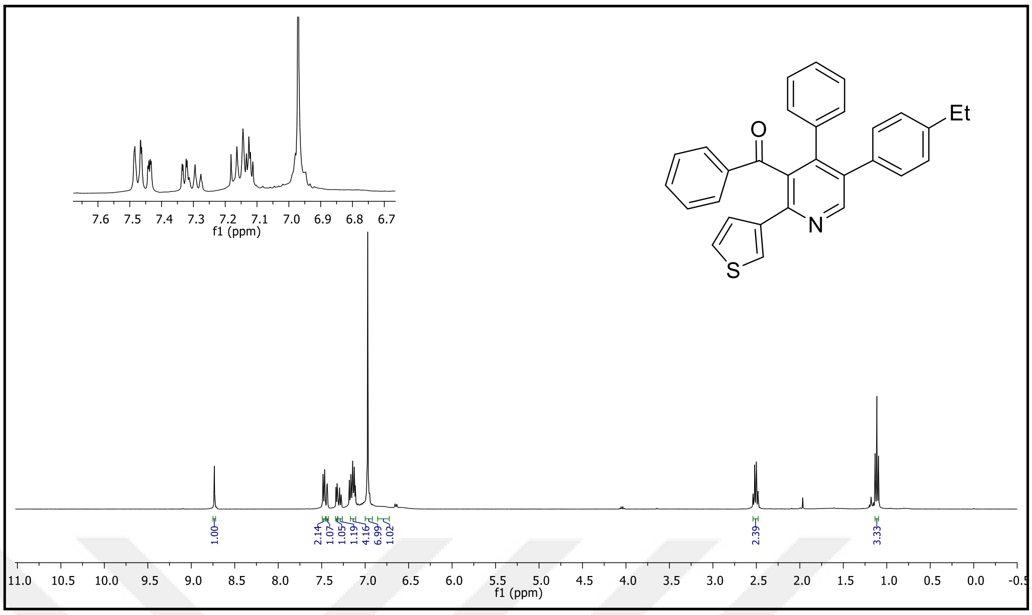

Figure A163. ^{1}H NMR spectrum of compound **46q.**

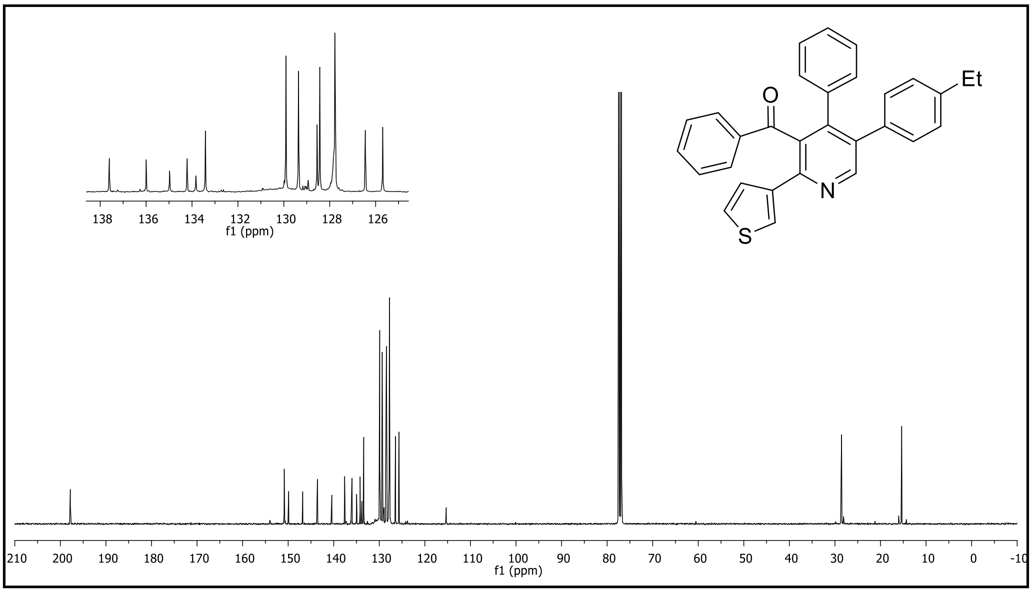

Figure A164. ^{13}C NMR spectrum of compound **46q.**

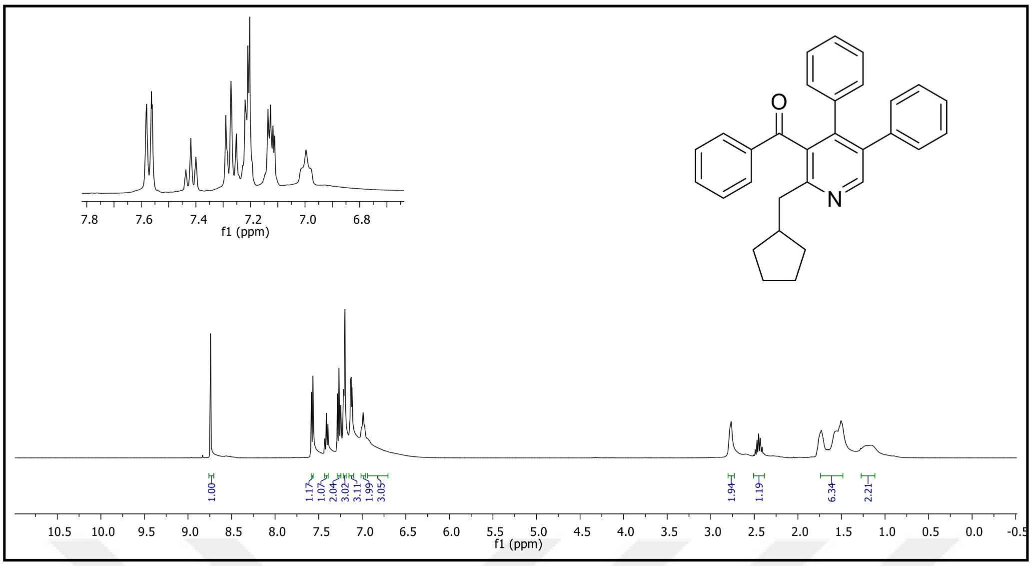

Figure A165. ^{1}H NMR spectrum of compound **46r.**

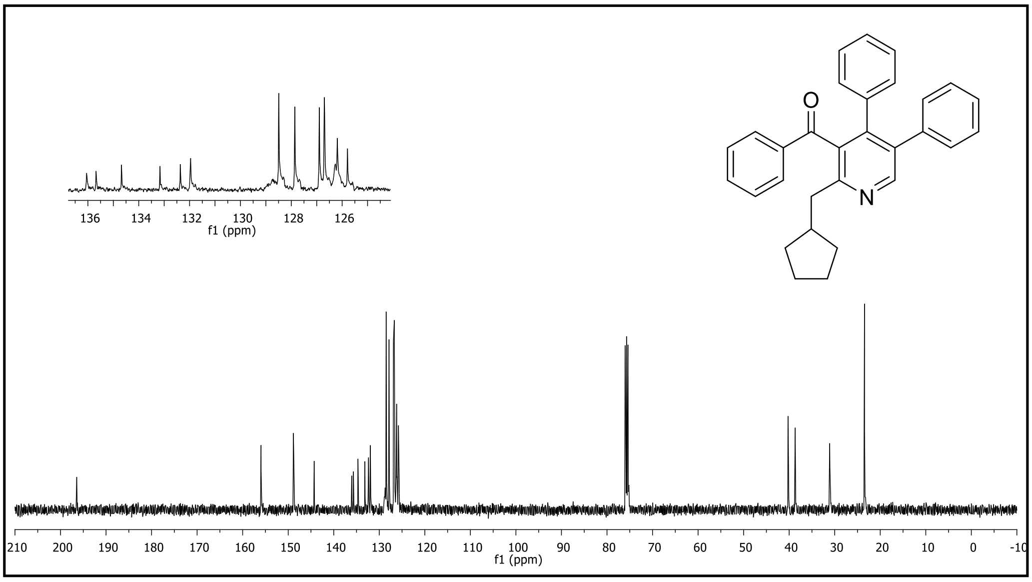

Figure A166. ^{13}C NMR spectrum of compound **46r.**

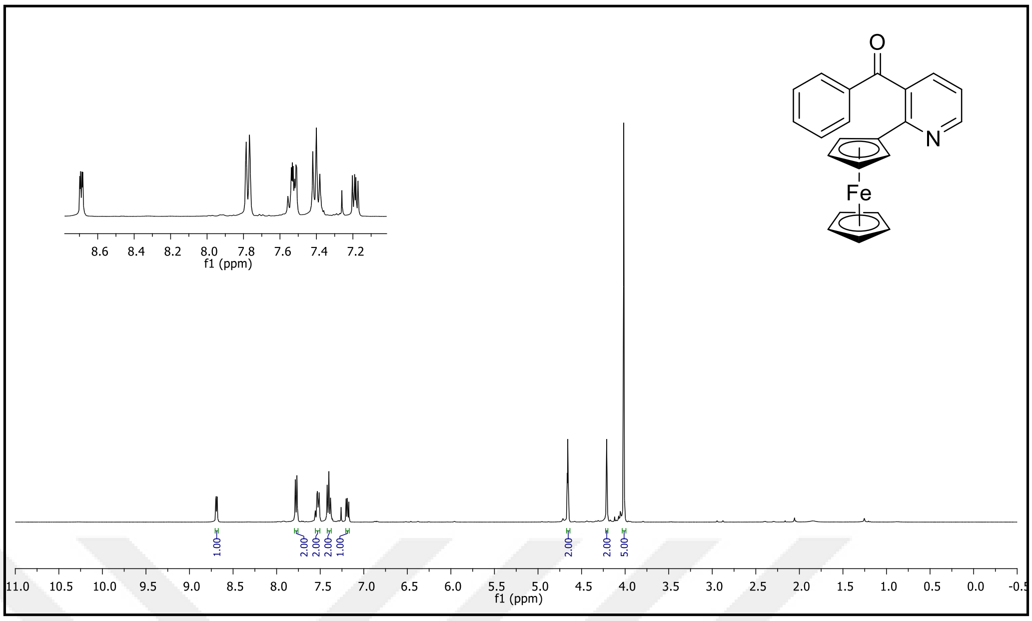

Figure A167. ^{1}H NMR spectrum of compound **49a.**

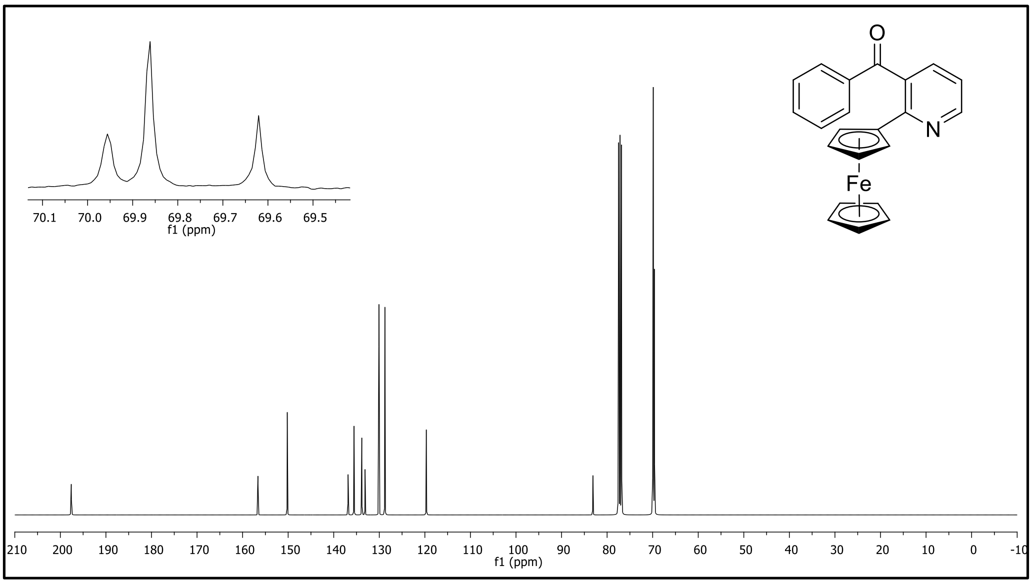

Figure A168. ^{13}C NMR spectrum of compound **49a.**

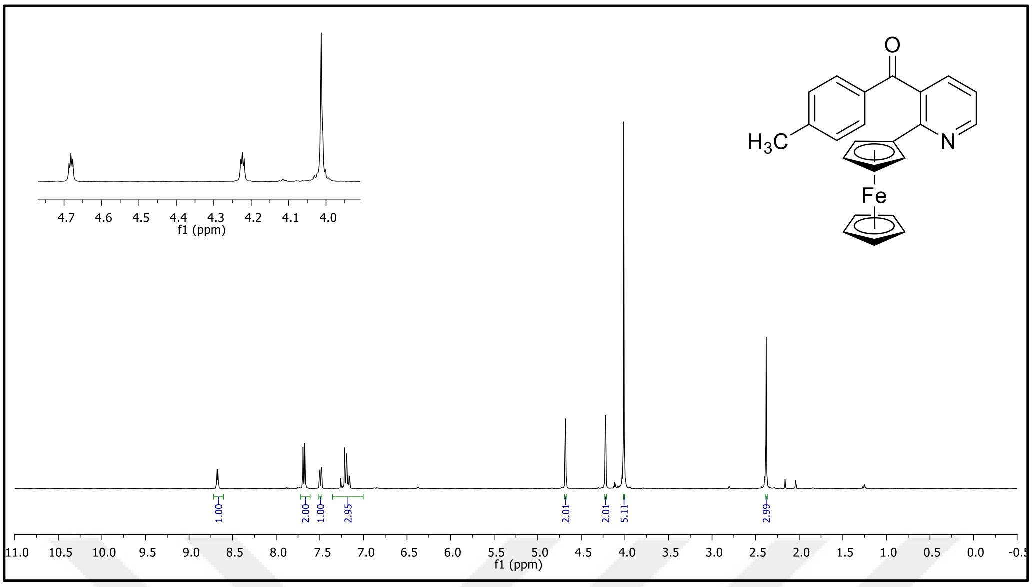

Figure A169. ^{1}H NMR spectrum of compound **49b.**

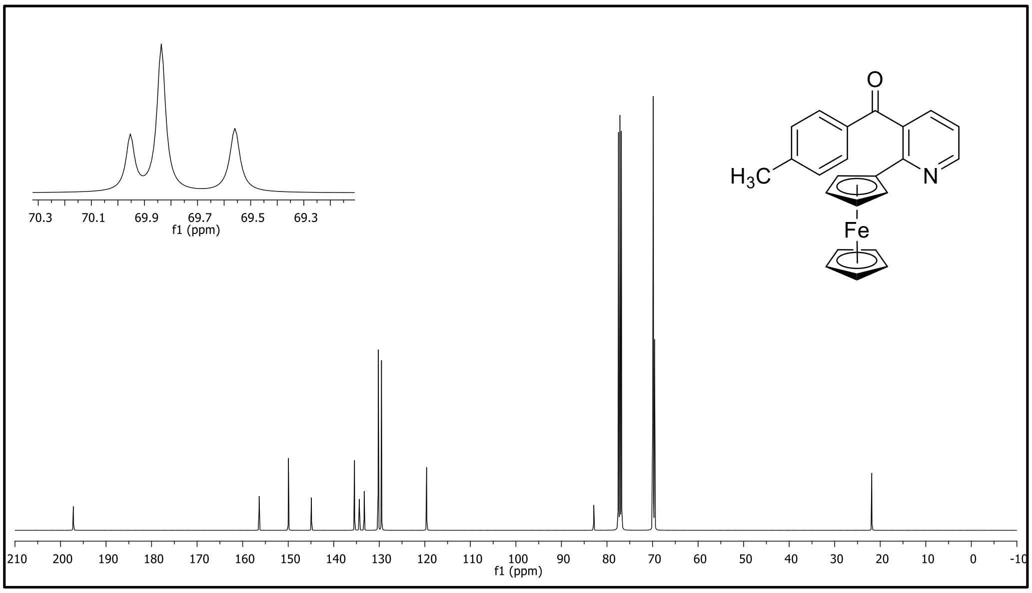

Figure A170. ^{13}C NMR spectrum of compound **49b.**

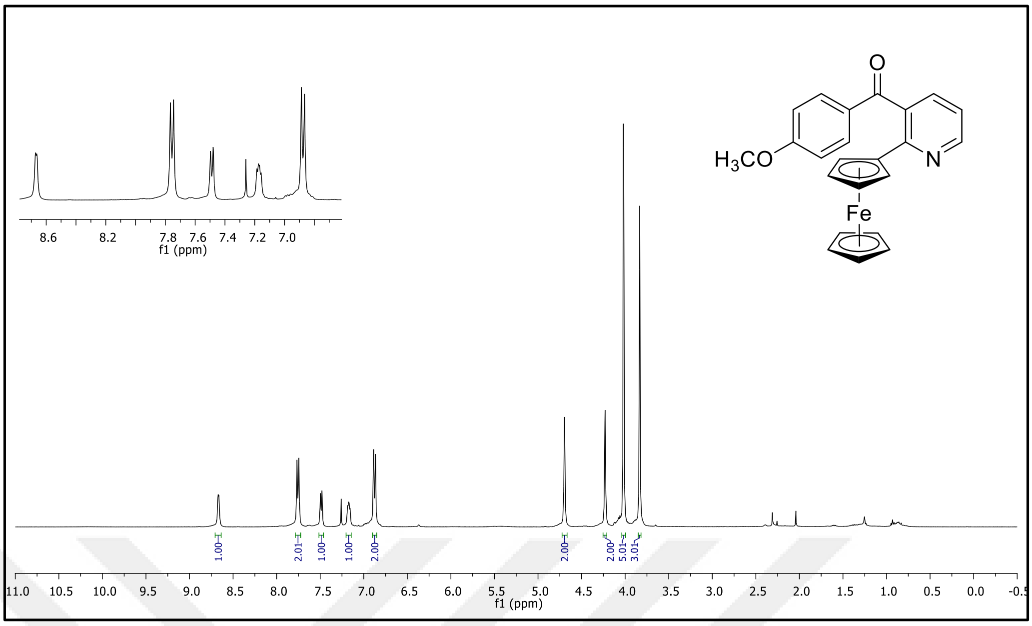

Figure A171. ^{1}H NMR spectrum of compound **49c.**

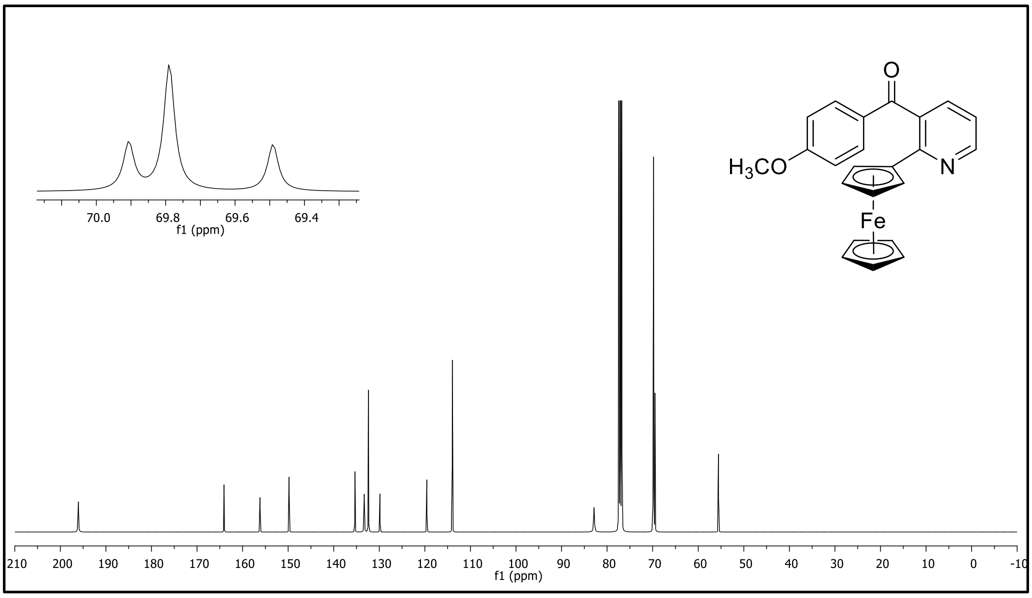

Figure A172. ^{13}C NMR spectrum of compound **49c.**

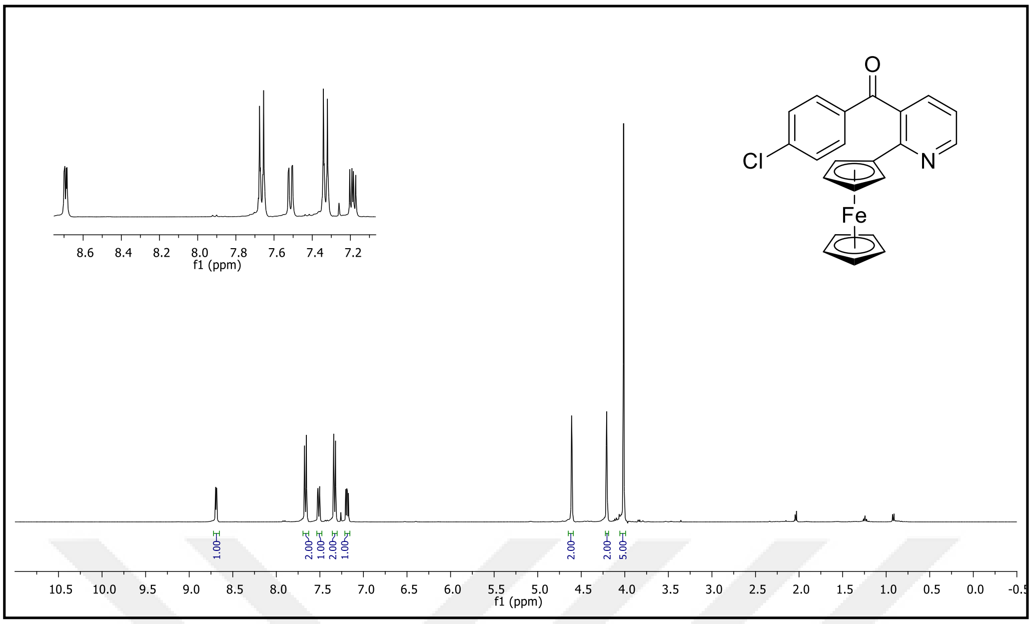

Figure A173. ^{1}H NMR spectrum of compound **49d.**

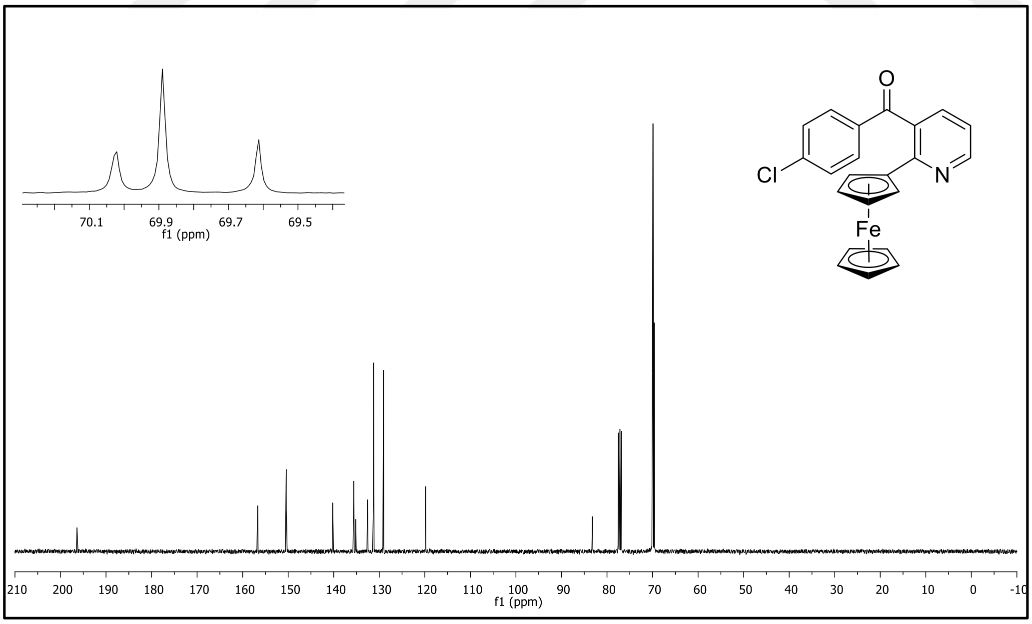

Figure A174. ^{13}C NMR spectrum of compound **49d.**

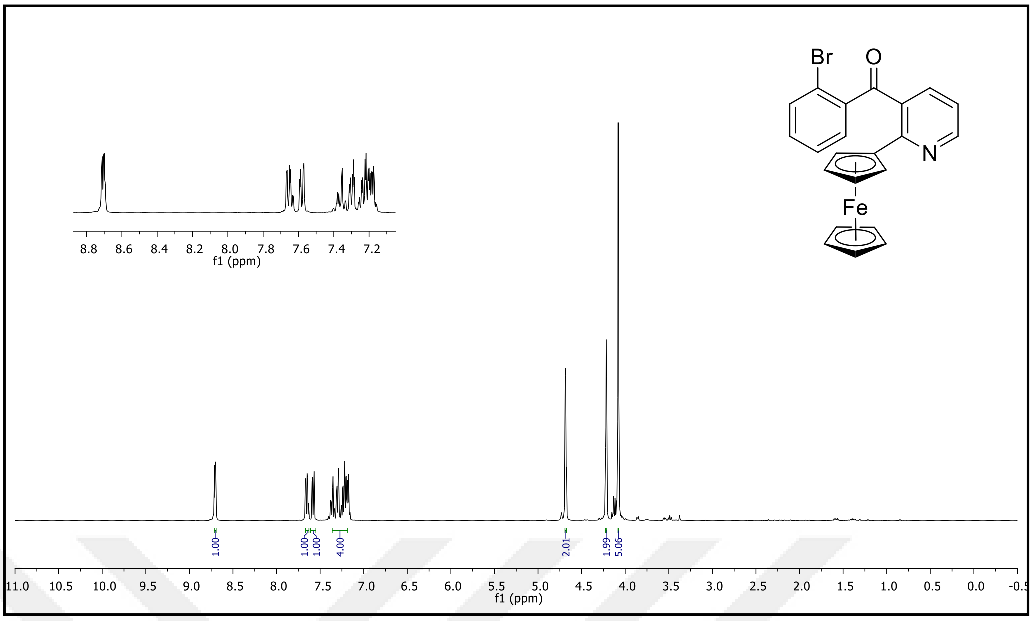

Figure A175. ^{1}H NMR spectrum of compound **49e.**

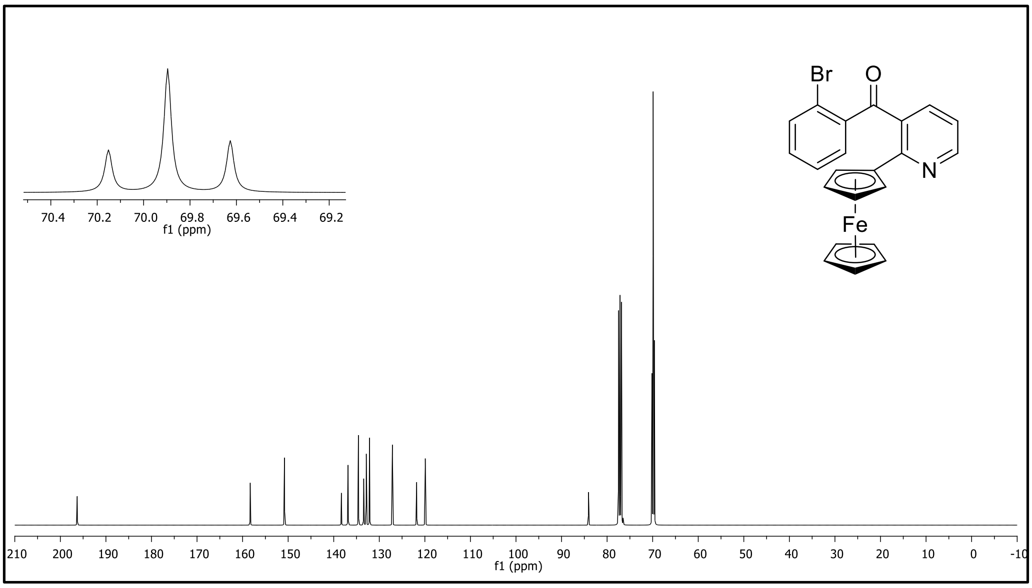

Figure A176. ^{13}C NMR spectrum of compound **49e.**

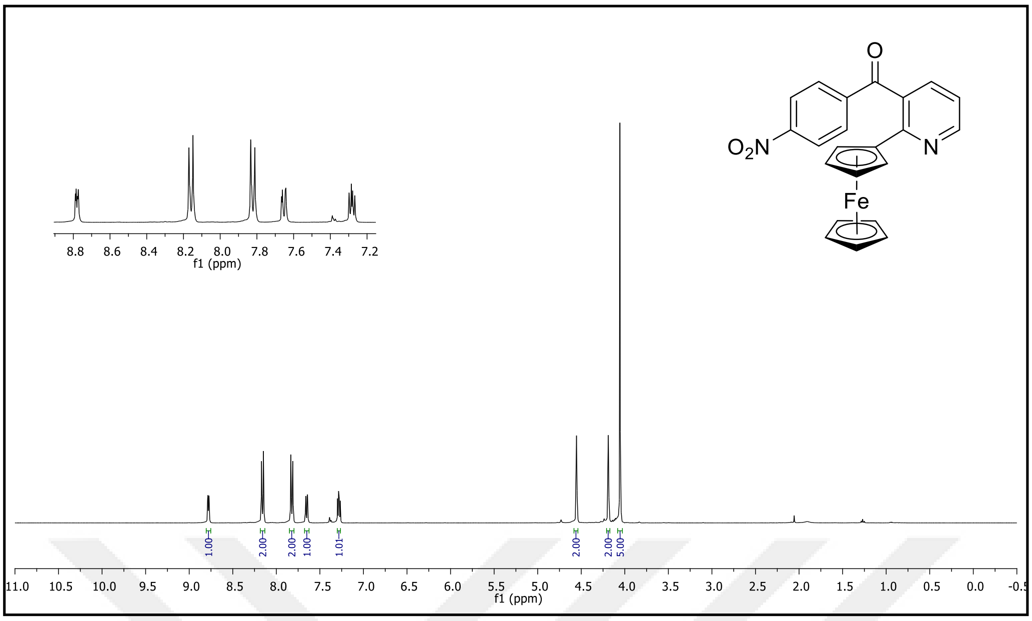

Figure A177. ^{1}H NMR spectrum of compound **49f.**

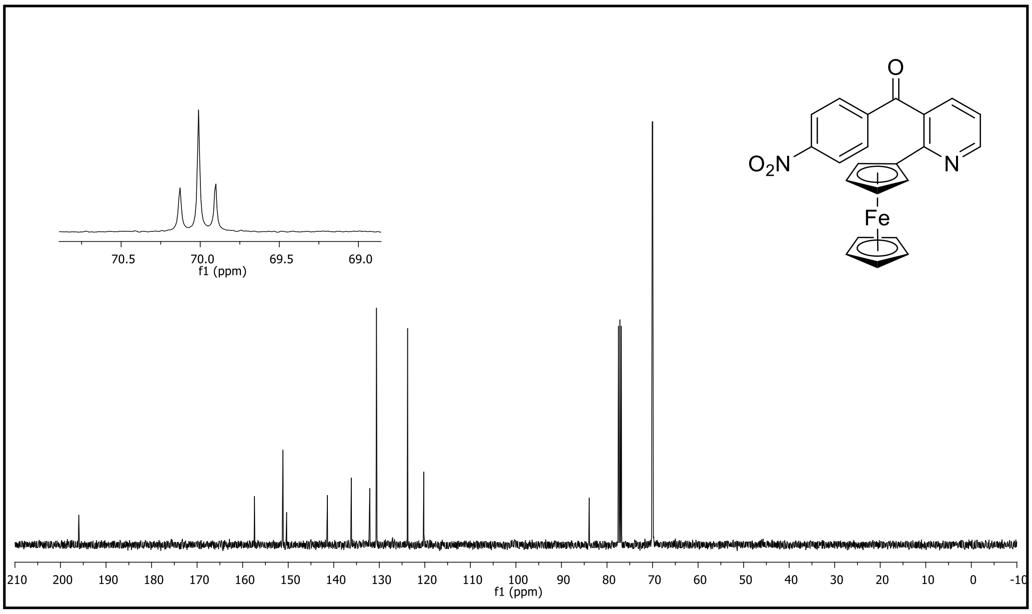

Figure A178. ^{13}C NMR spectrum of compound **49f.**

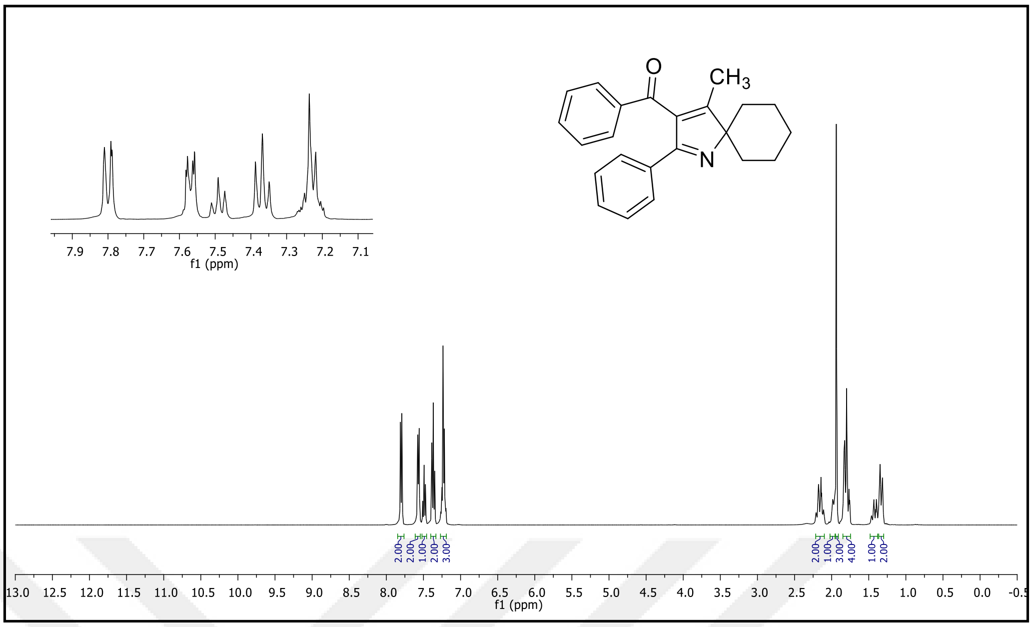

Figure A179. ^{1}H NMR spectrum of compound **51a.**

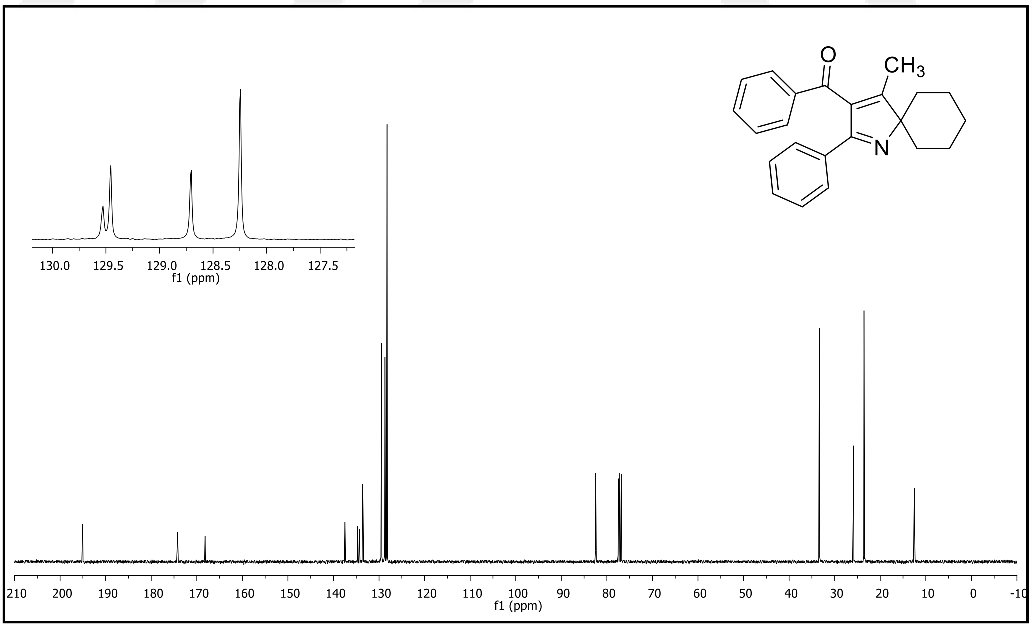

Figure A180. ^{13}C NMR spectrum of compound **51a.**

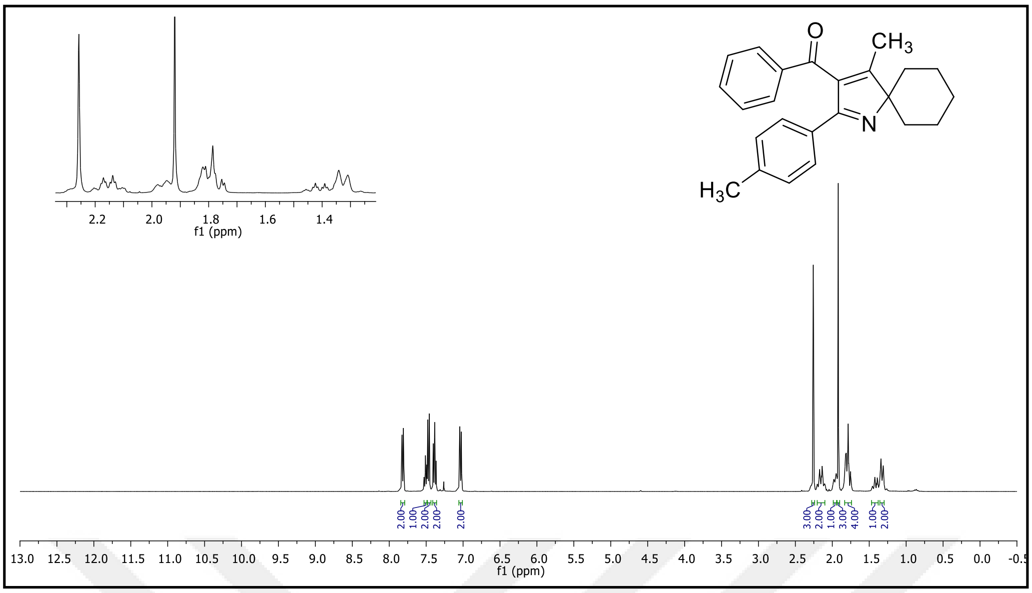

Figure A181. ^{1}H NMR spectrum of compound **51b.**

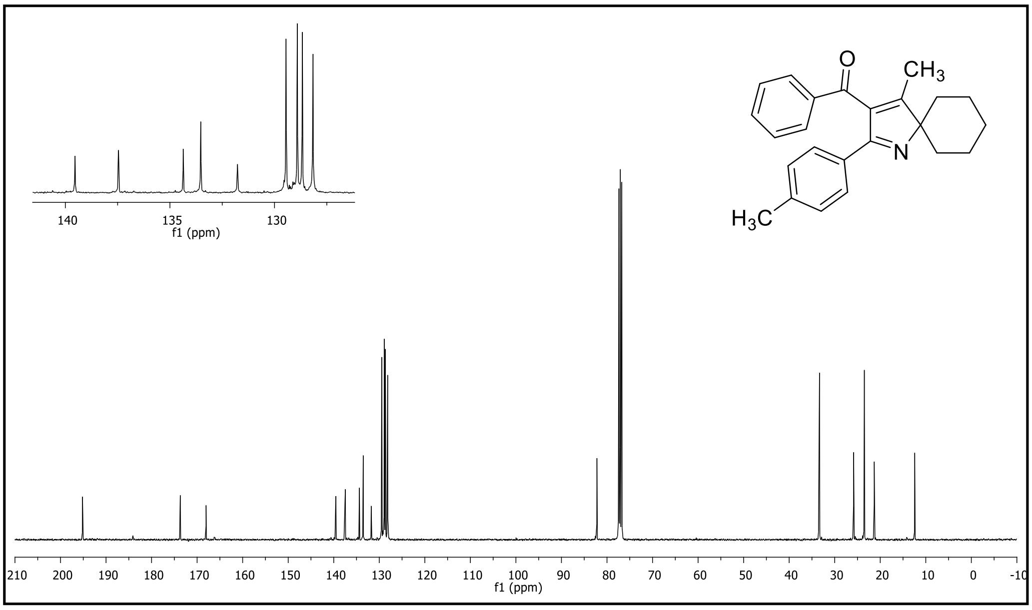

Figure A182. ^{13}C NMR spectrum of compound **51b.**

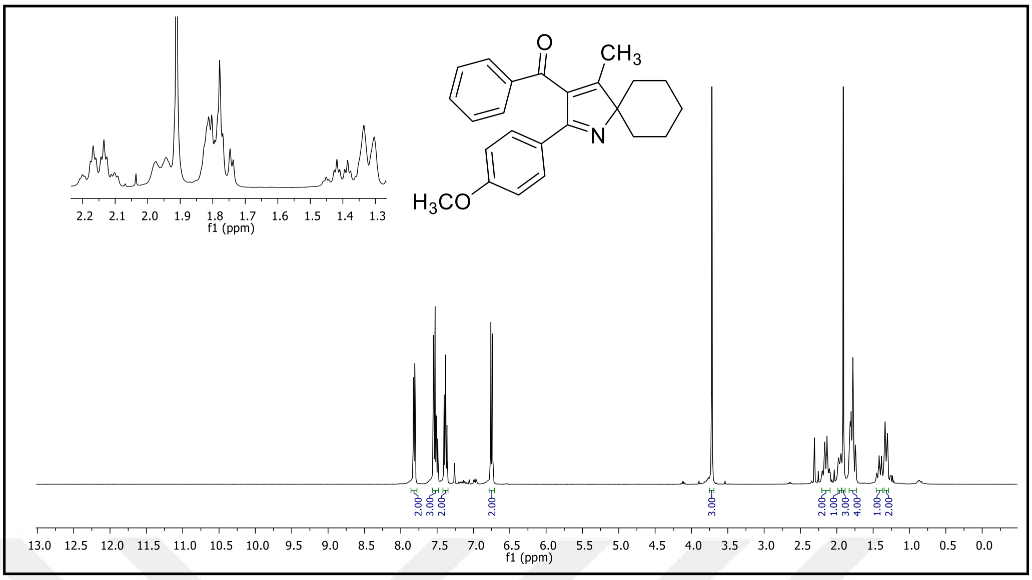

Figure A183. ^{1}H NMR spectrum of compound **51c.**

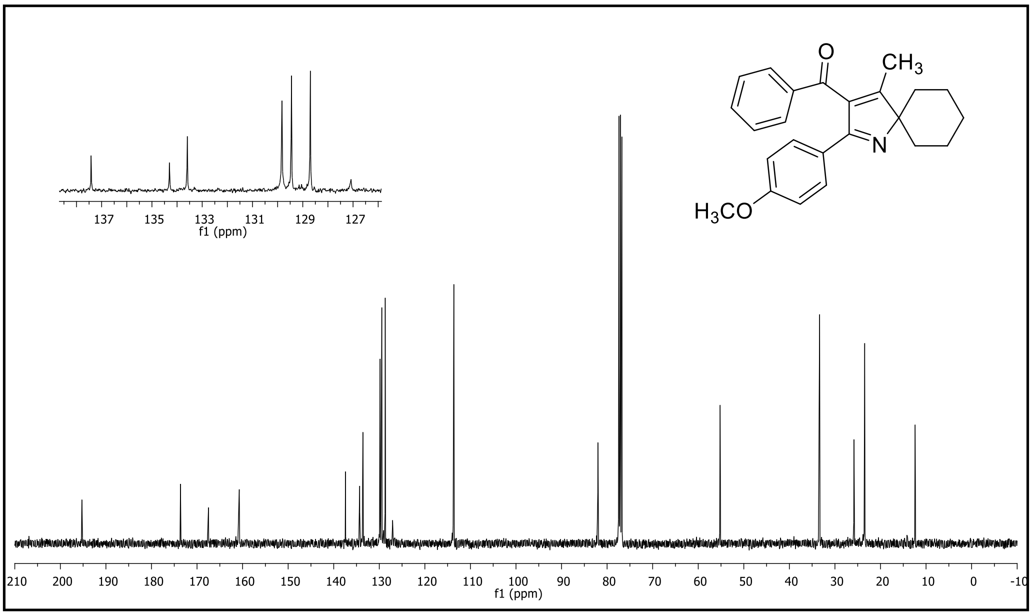

Figure A184. ^{13}C NMR spectrum of compound **51c.**

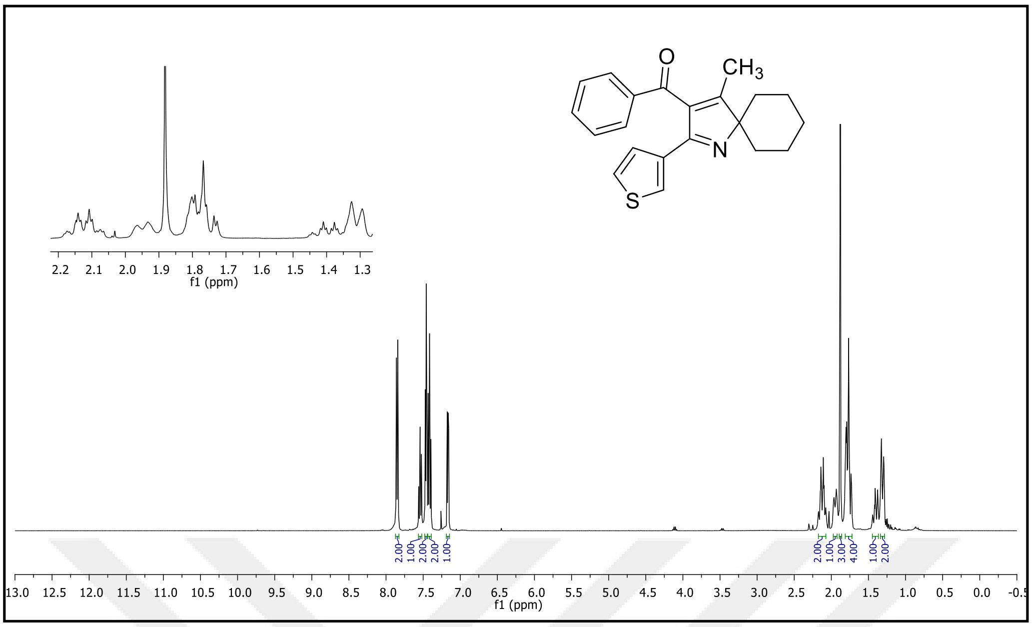

Figure A185. ^{1}H NMR spectrum of compound **51d.**

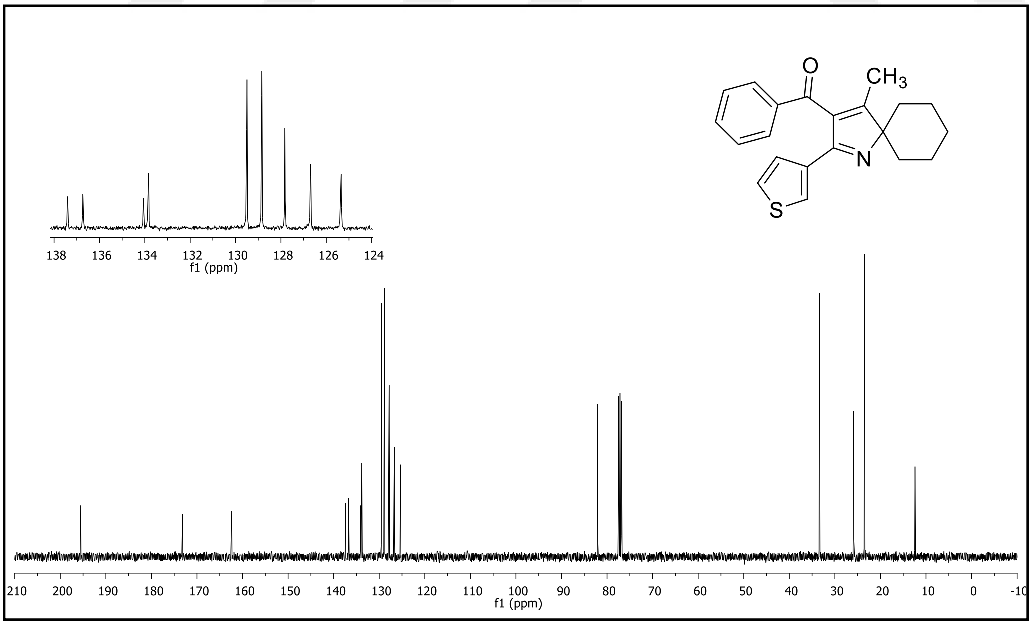

Figure A186. ^{13}C NMR spectrum of compound **51d.**

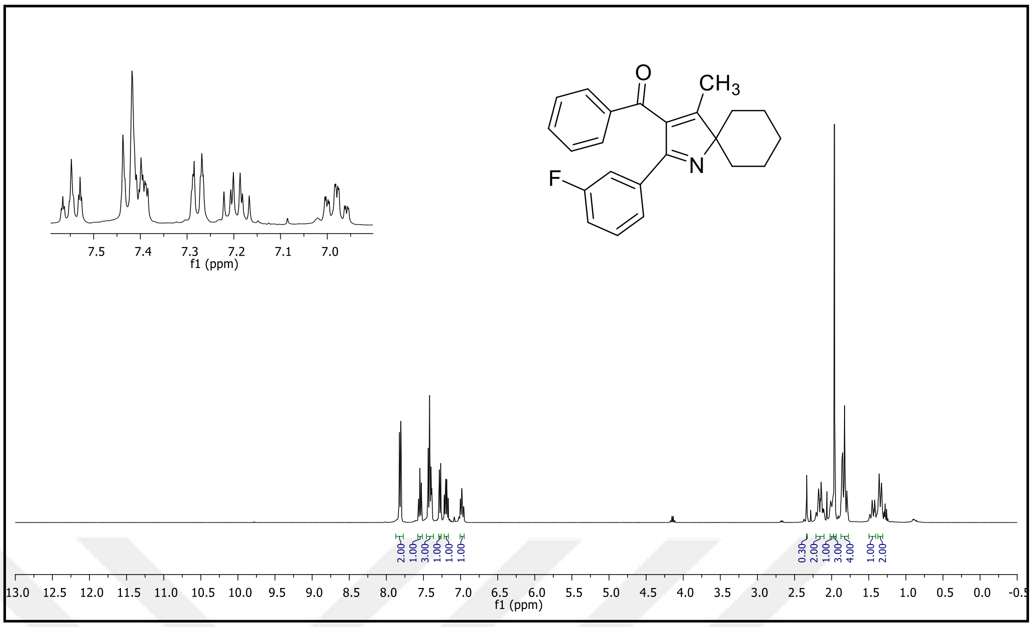

Figure A187. ^{1}H NMR spectrum of compound **51e.**

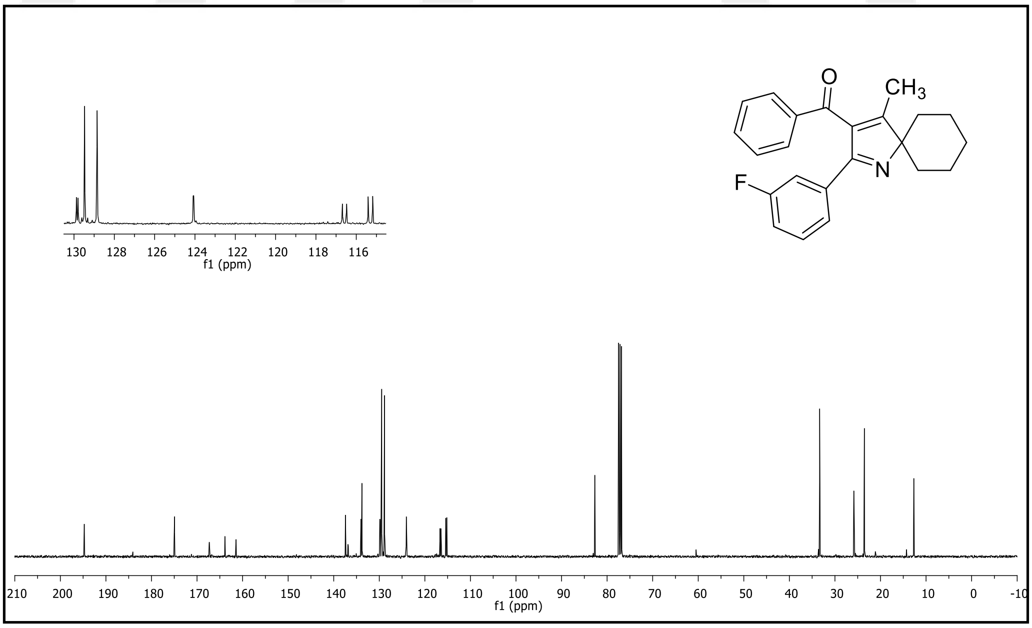

Figure A188. ^{13}C NMR spectrum of compound **51e.**

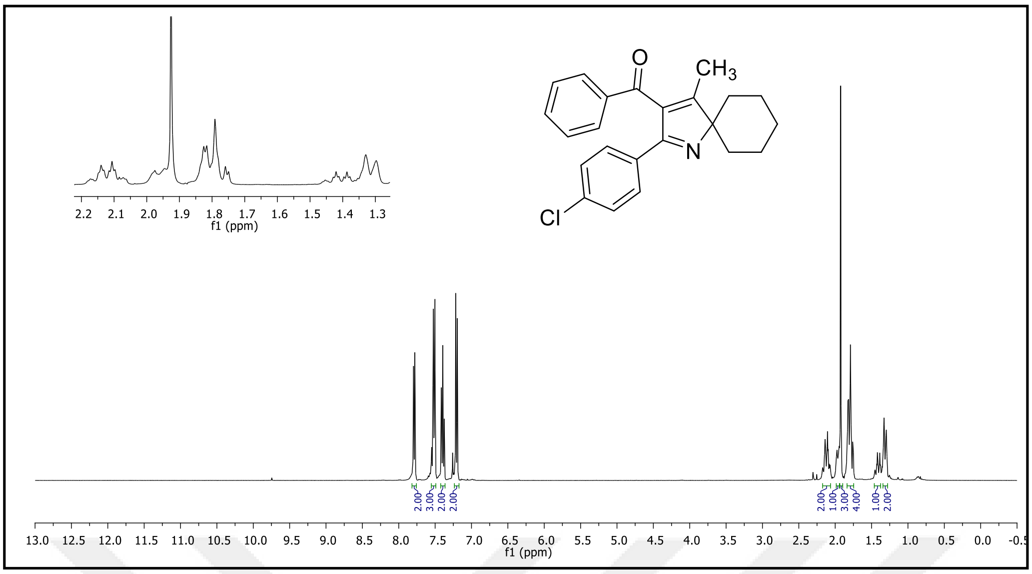

Figure A189. ^{1}H NMR spectrum of compound **51f.**

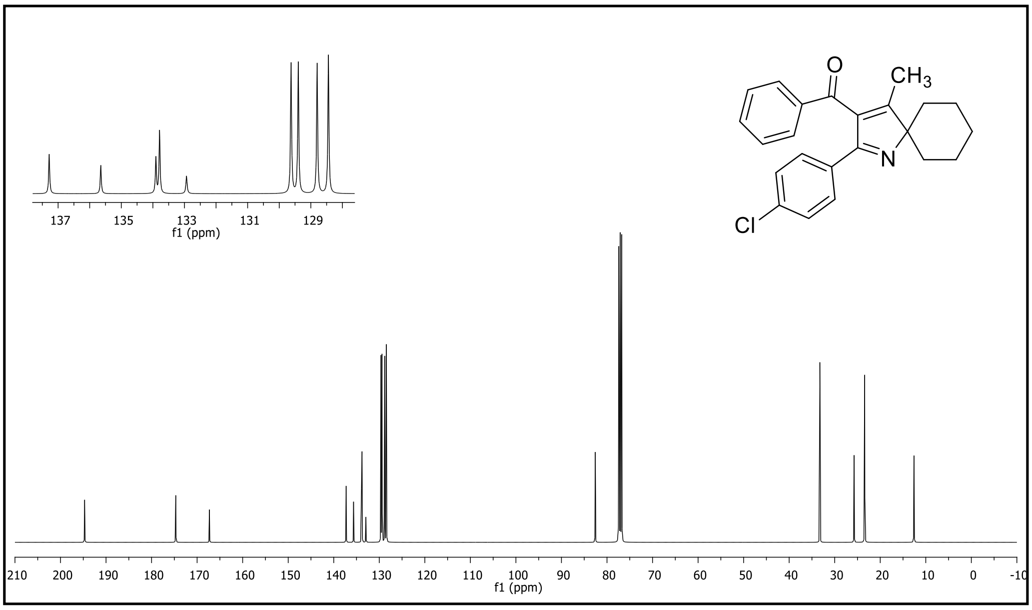

Figure A190. ^{13}C NMR spectrum of compound **51f.**

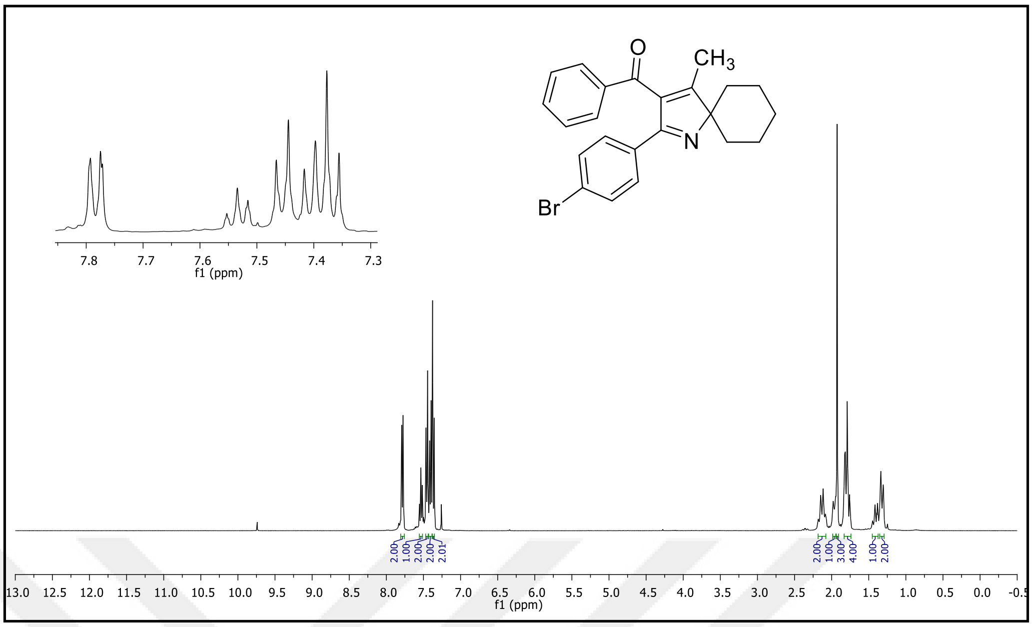

Figure A191. ^{1}H NMR spectrum of compound **51g.**

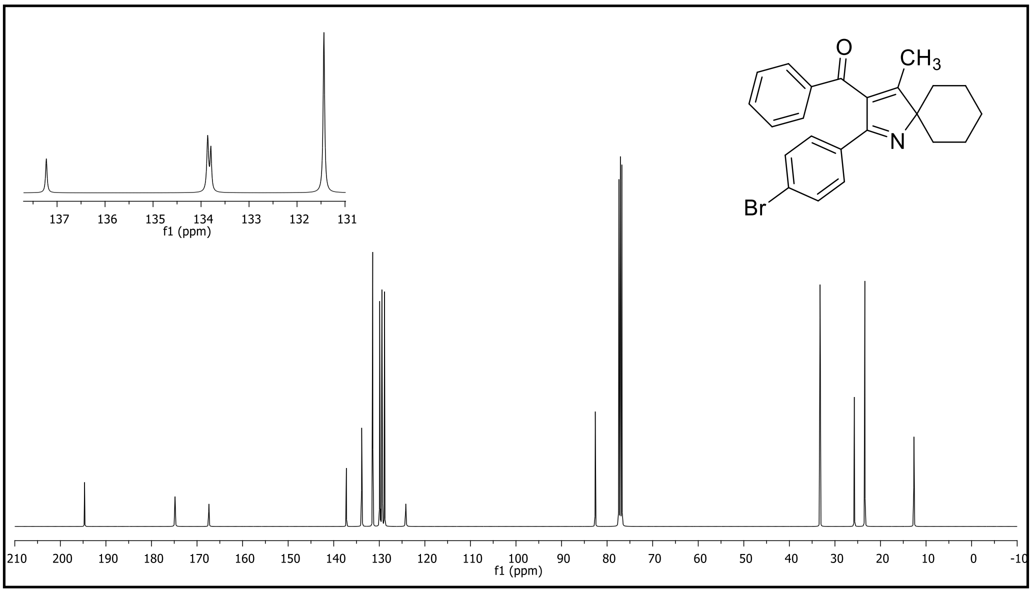

Figure A192. ^{13}C NMR spectrum of compound **51g.**

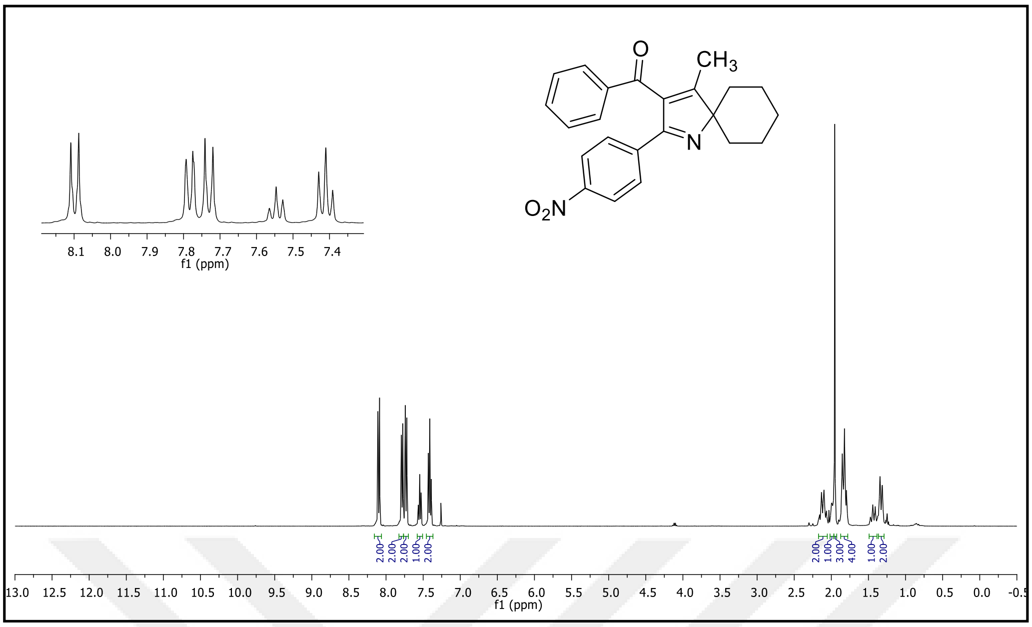

Figure A193. ^{1}H NMR spectrum of compound **51h.**

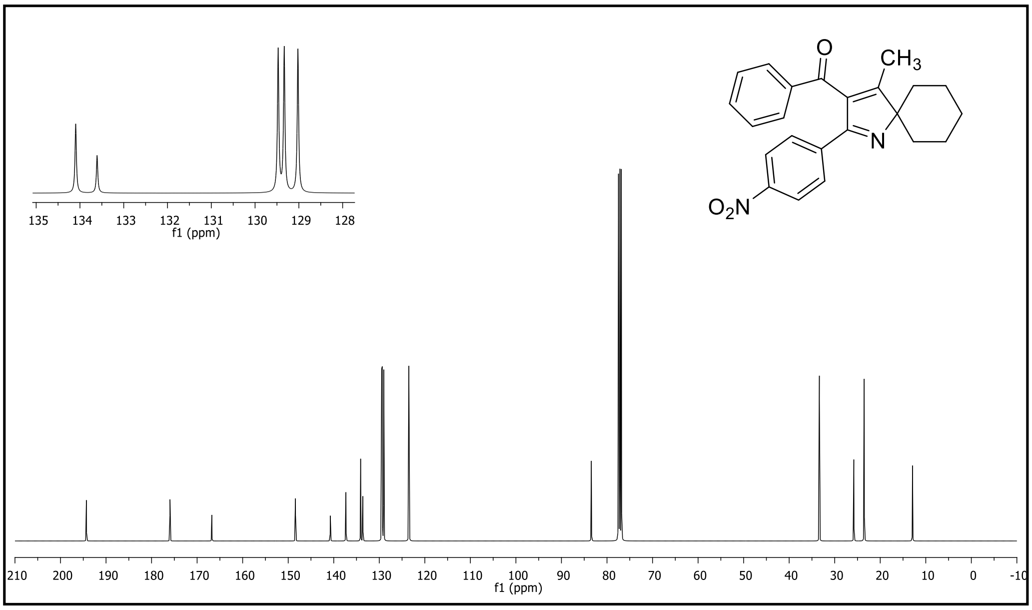

Figure A194. ^{13}C NMR spectrum of compound **51h.**

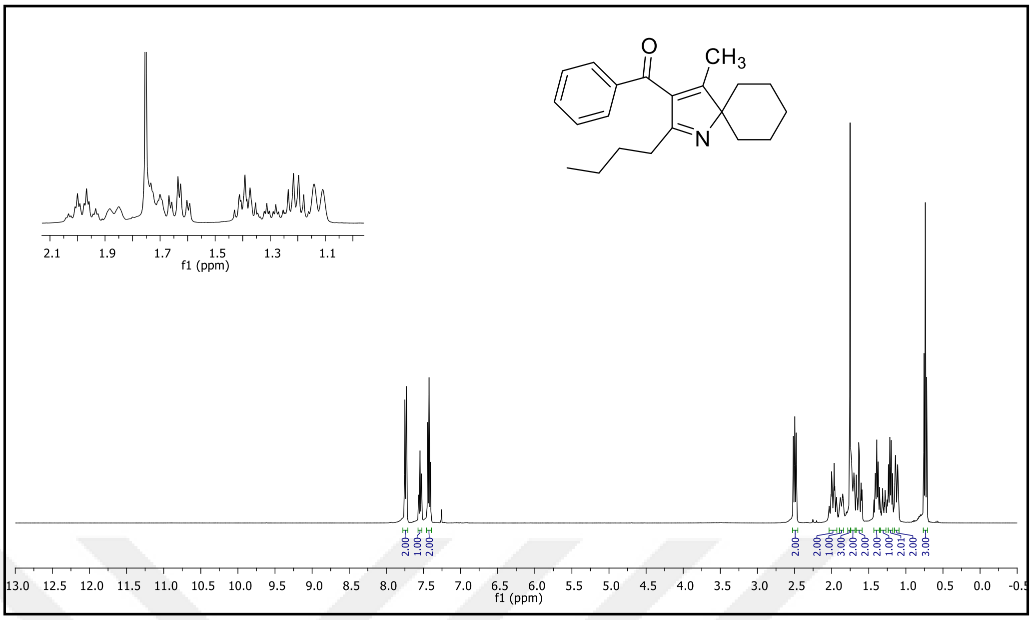

Figure A195. ^{1}H NMR spectrum of compound **51i.**

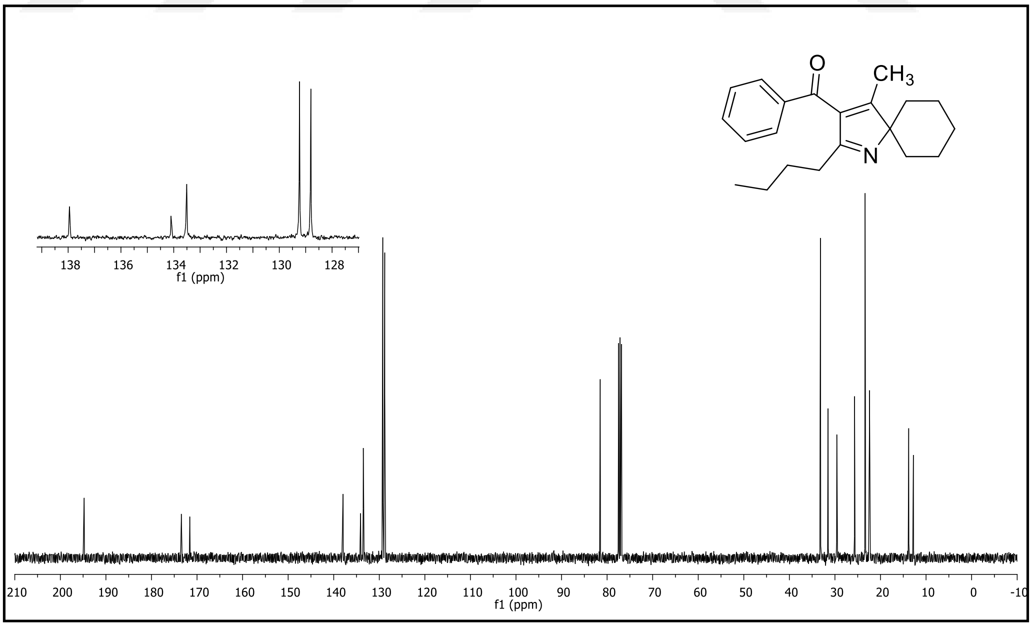

Figure A196. ^{13}C NMR spectrum of compound **51i.**

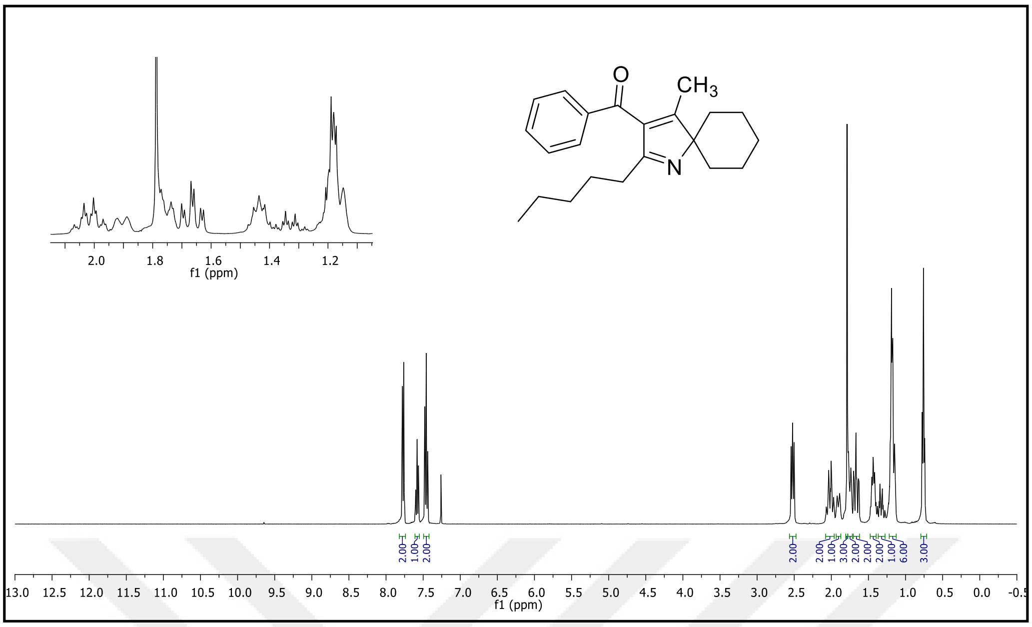

Figure A197. ^{1}H NMR spectrum of compound **51j.**

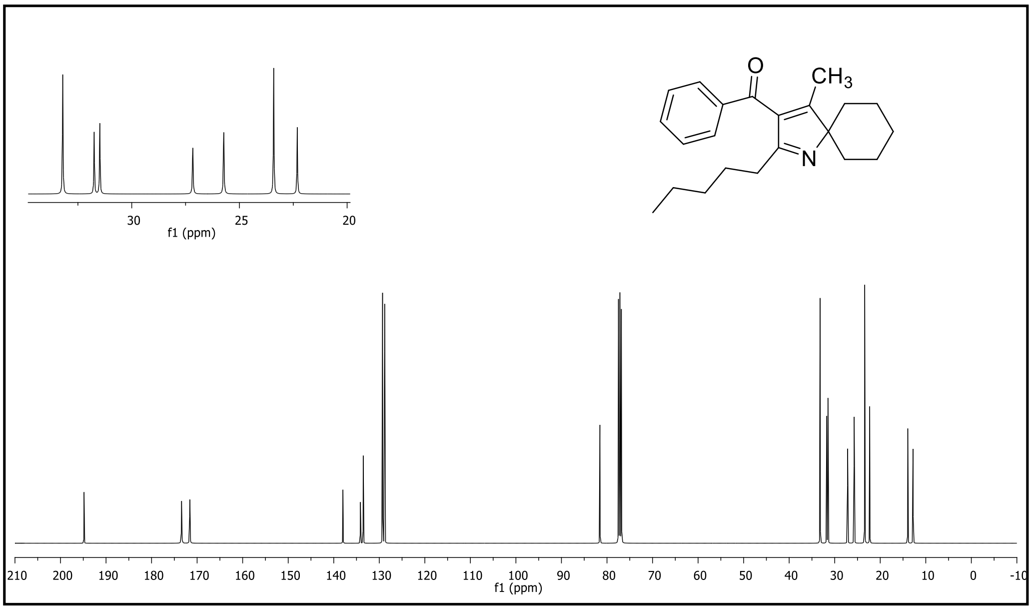

Figure A198. ^{13}C NMR spectrum of compound **51j.**

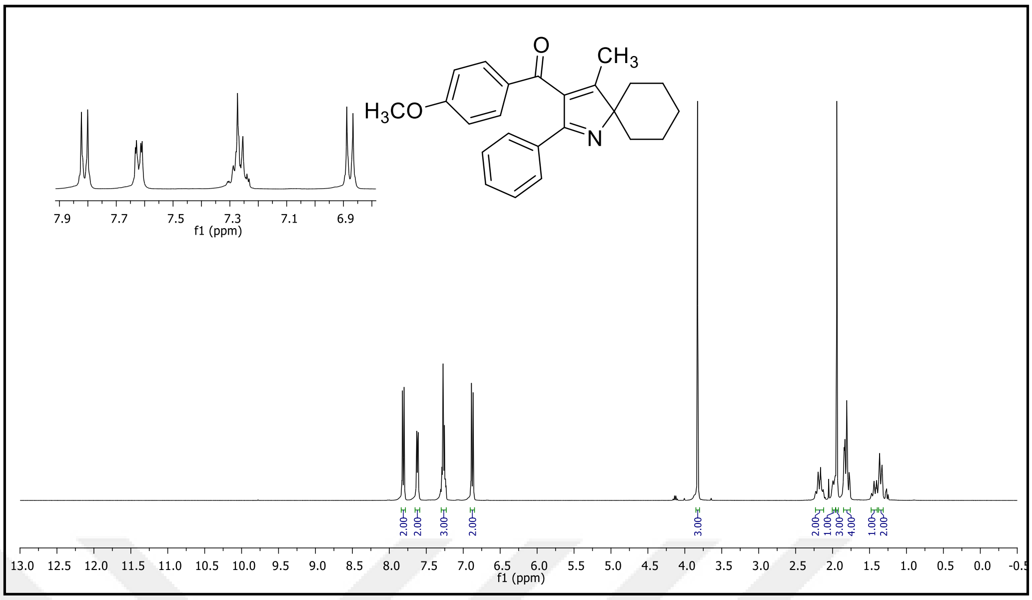

Figure A199. ^{1}H NMR spectrum of compound **51k.**

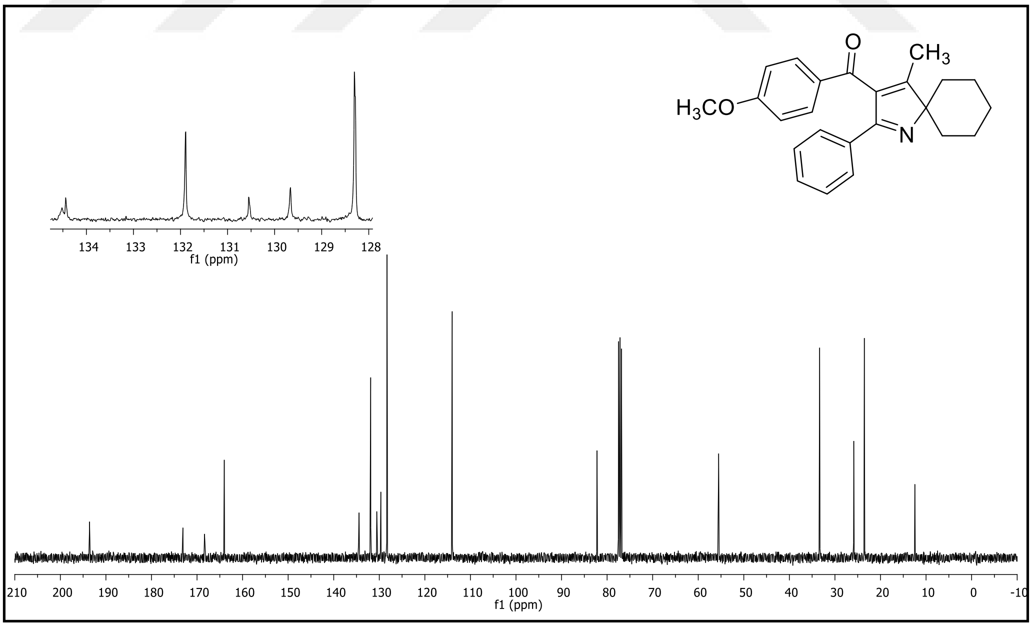

Figure A200. ^{13}C NMR spectrum of compound **51k.**

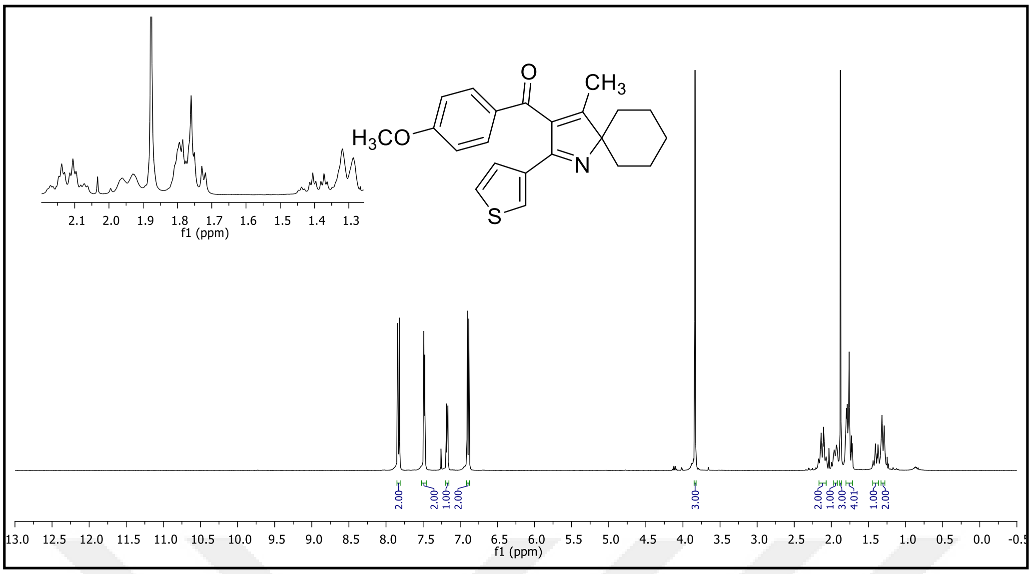

Figure A201. ^{1}H NMR spectrum of compound **51l.**

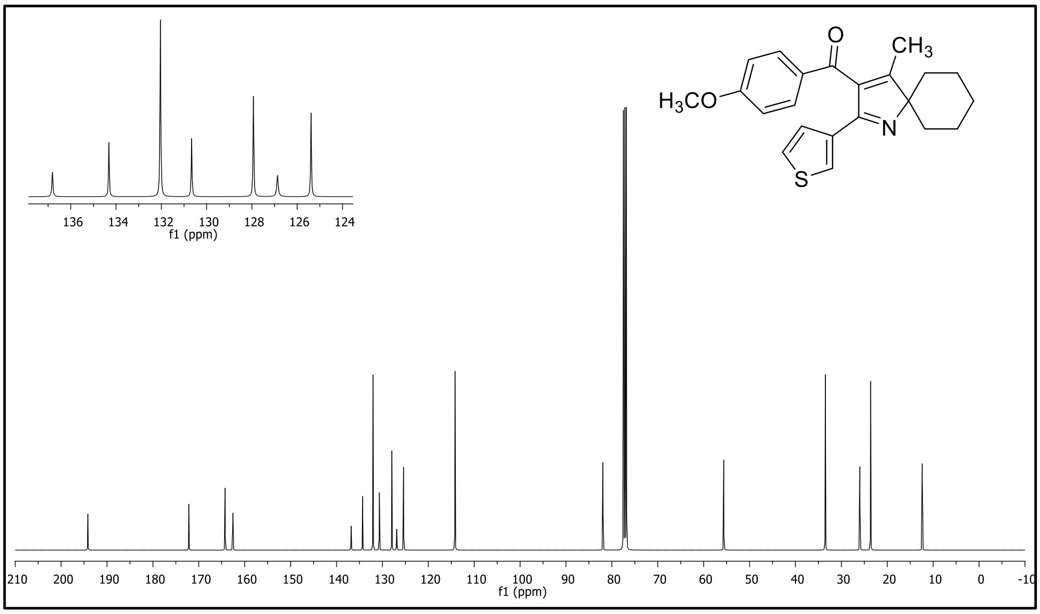

Figure A202. ^{13}C NMR spectrum of compound **51l.**

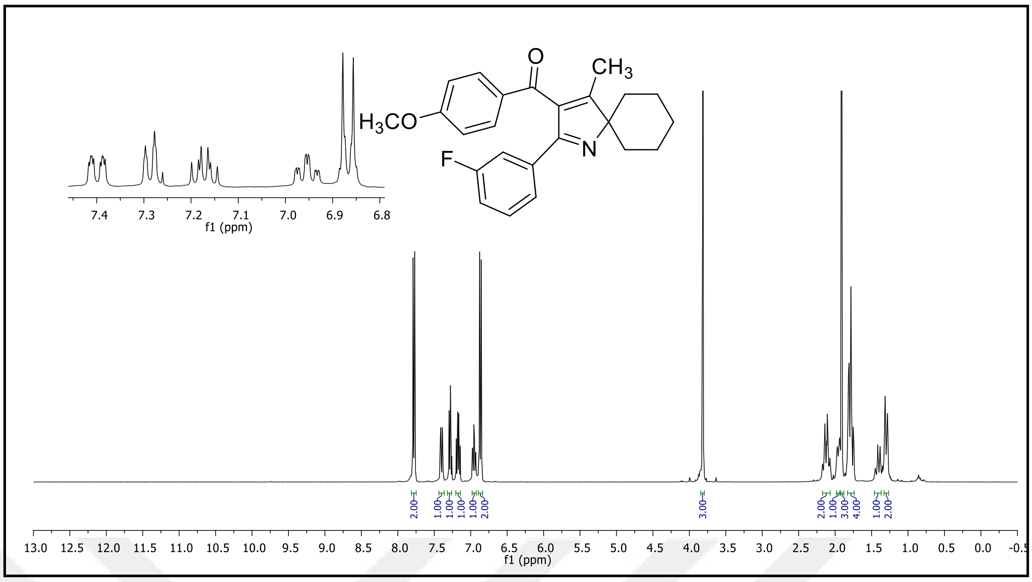

Figure A203. ^{1}H NMR spectrum of compound **51m.**

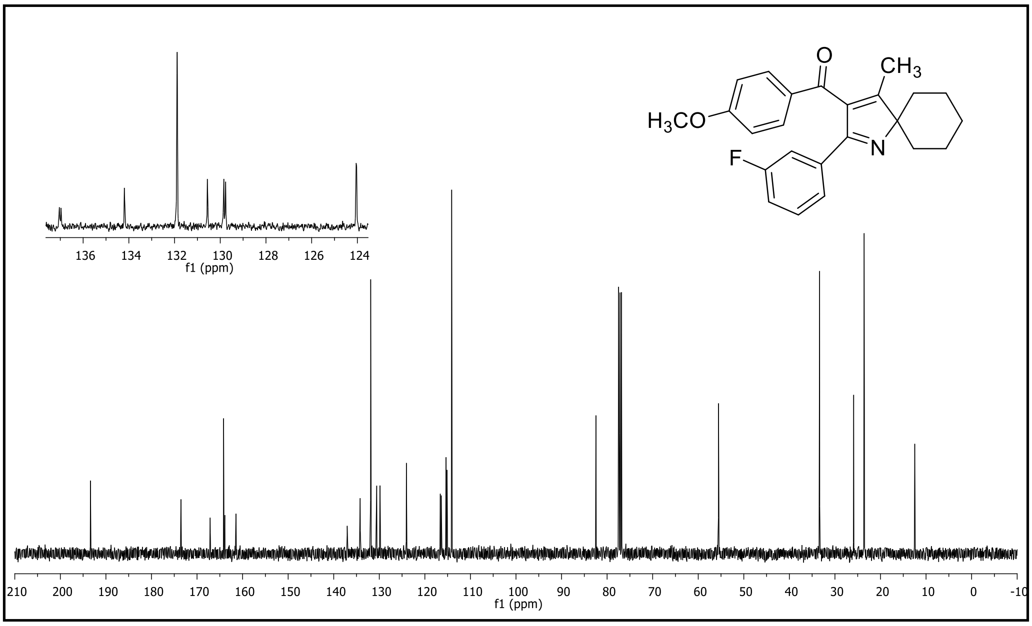

Figure A204. ^{13}C NMR spectrum of compound **51m.**

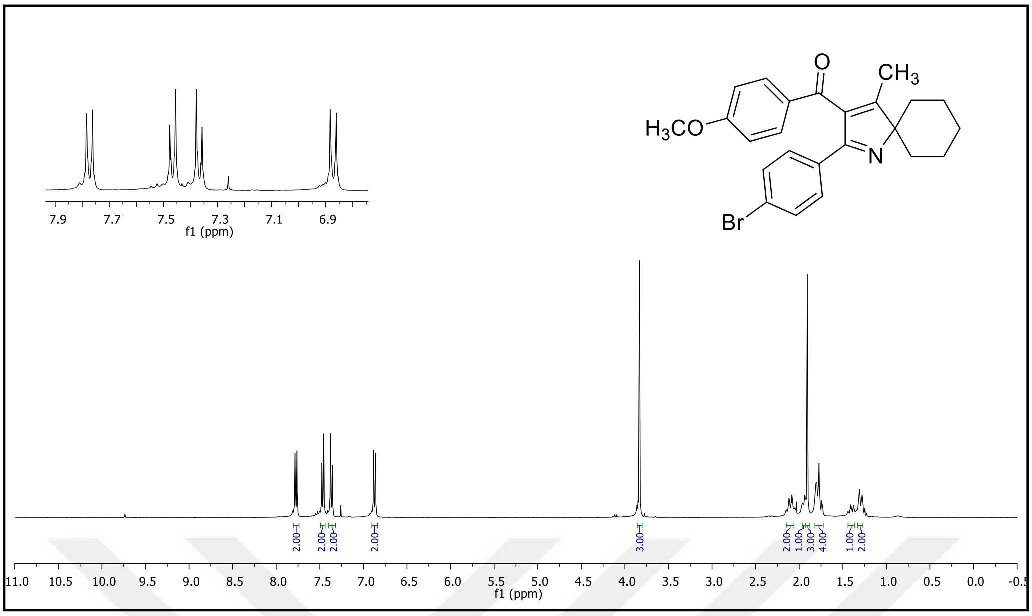

Figure A205. ^{1}H NMR spectrum of compound **51n.**

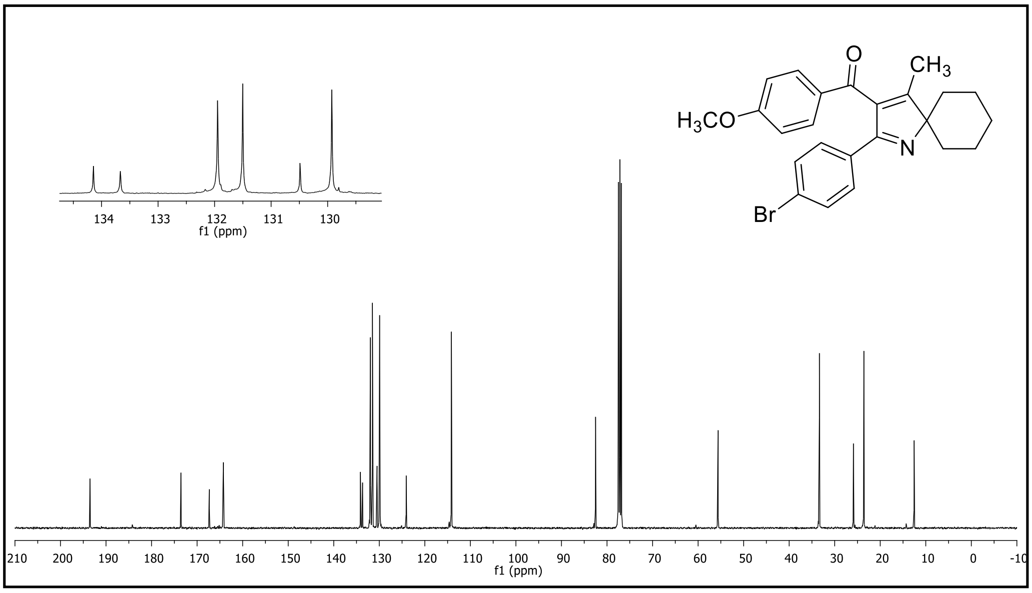

Figure A206. ^{13}C NMR spectrum of compound **51n.**

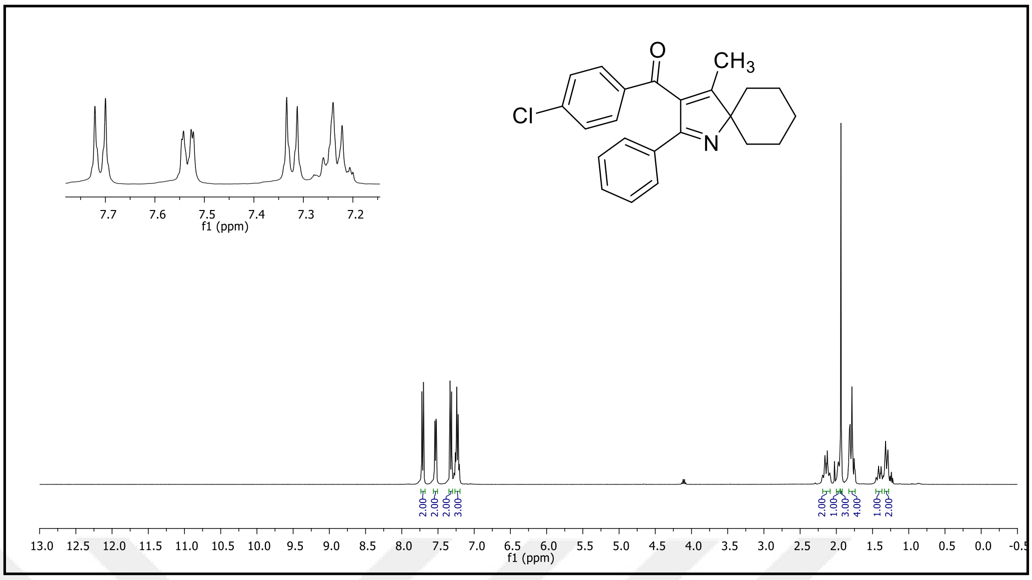

Figure A207. ^{1}H NMR spectrum of compound **51o.**

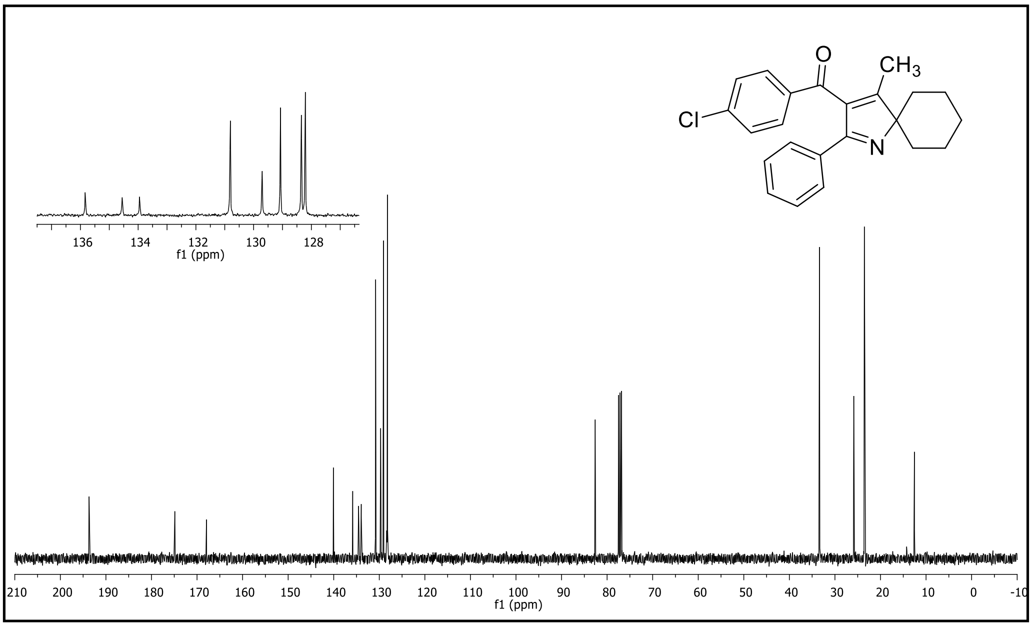

Figure A208. ^{13}C NMR spectrum of compound **51o.**

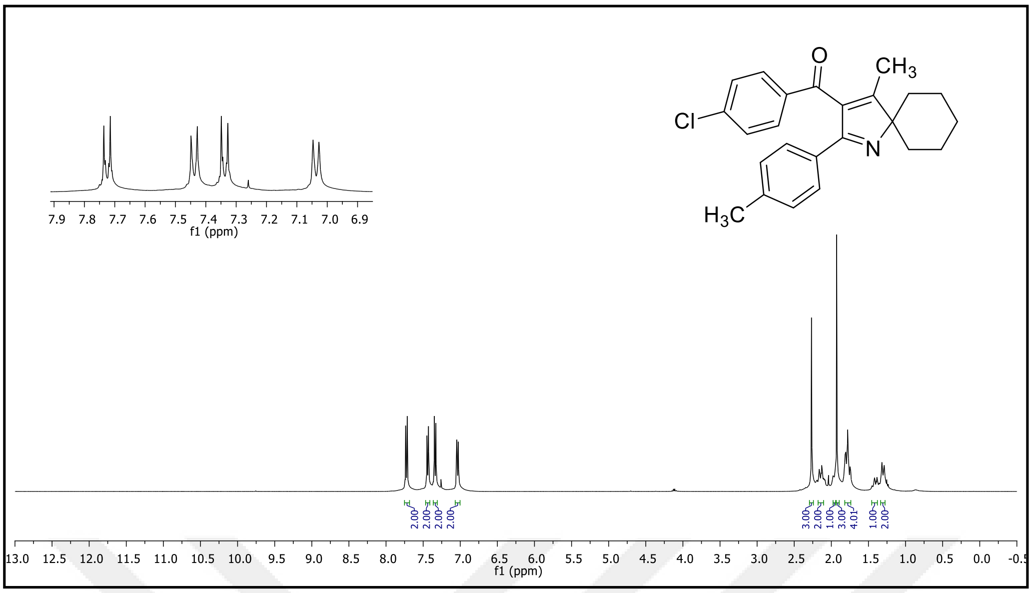

Figure A209. ^{1}H NMR spectrum of compound **51p.**

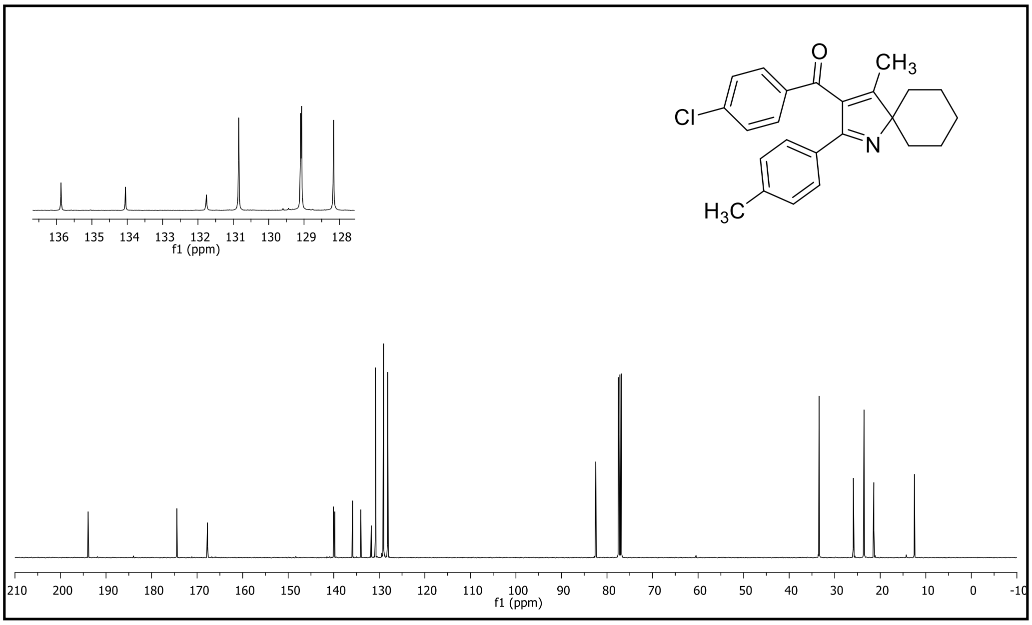

Figure A210. ^{13}C NMR spectrum of compound **51p.**

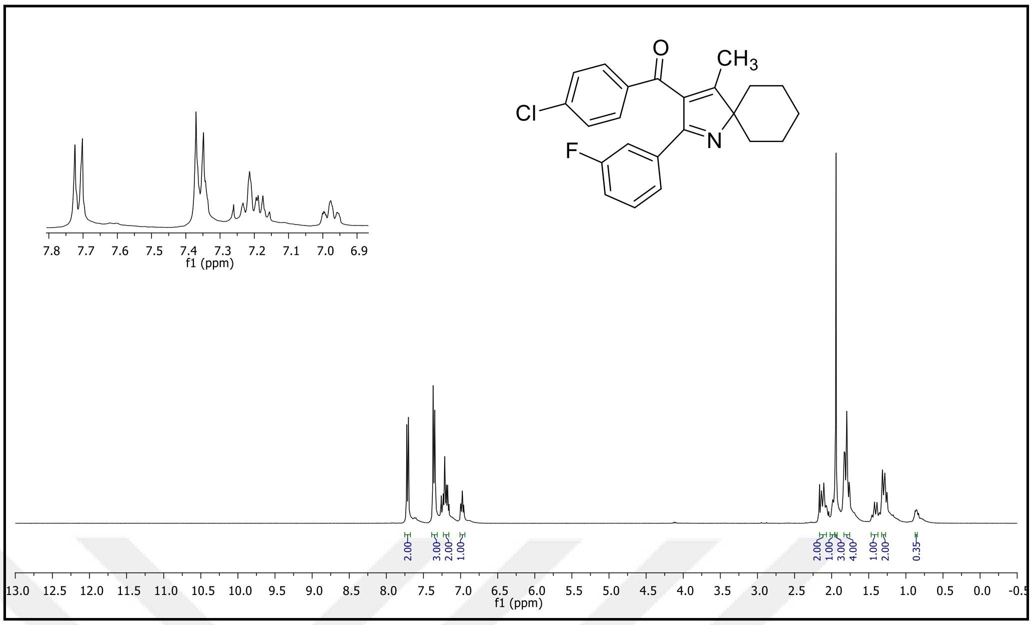

Figure A211. ^{1}H NMR spectrum of compound **51q.**

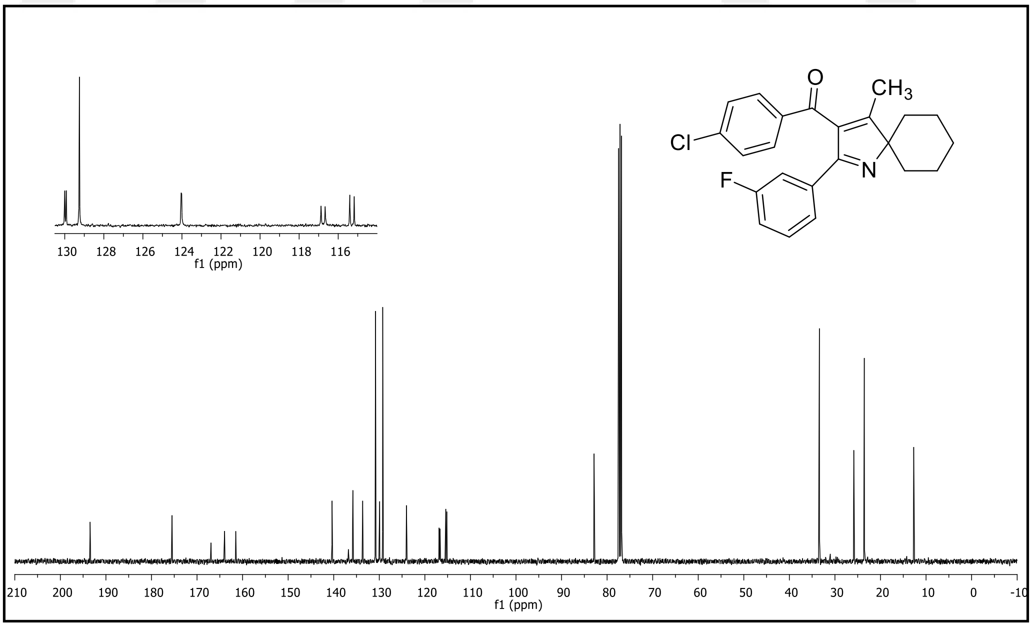

Figure A212. ^{13}C NMR spectrum of compound **51q.**

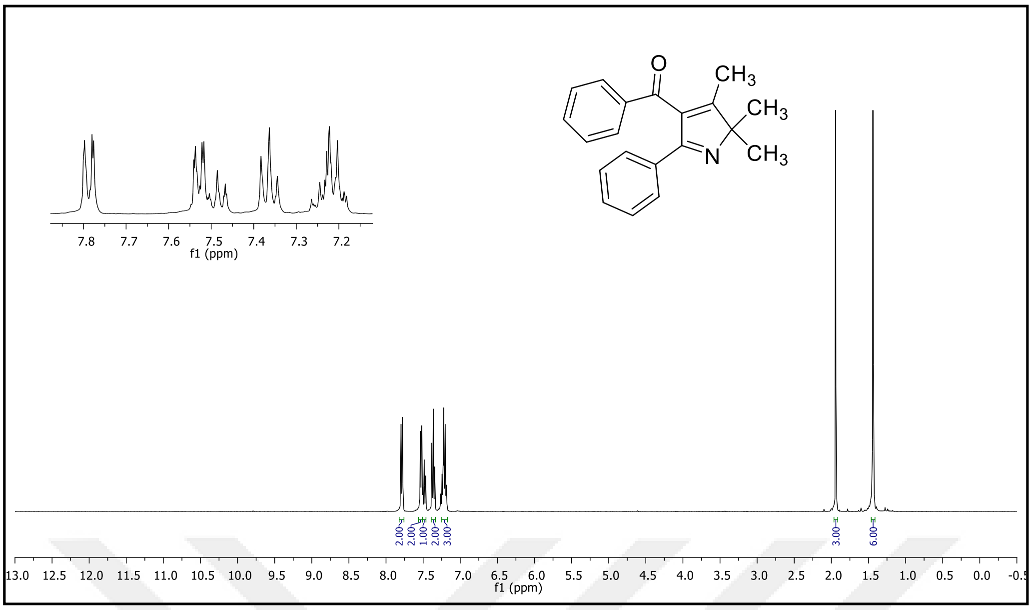

Figure A213. ^{1}H NMR spectrum of compound **72a.**

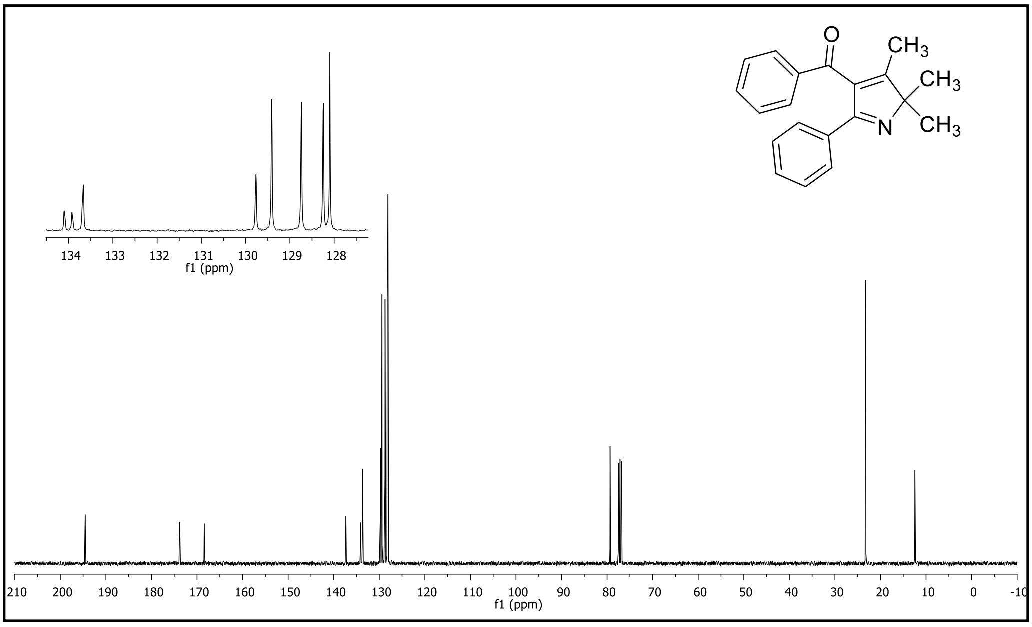

Figure A214. ^{13}C NMR spectrum of compound **72a.**

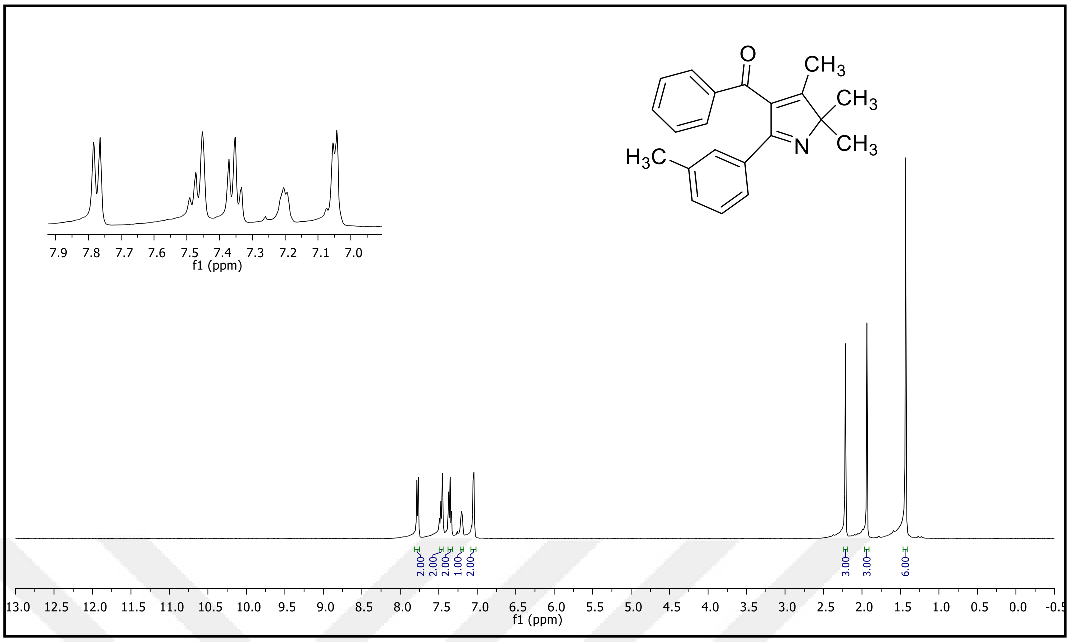

Figure A215. ^{1}H NMR spectrum of compound **72b.**

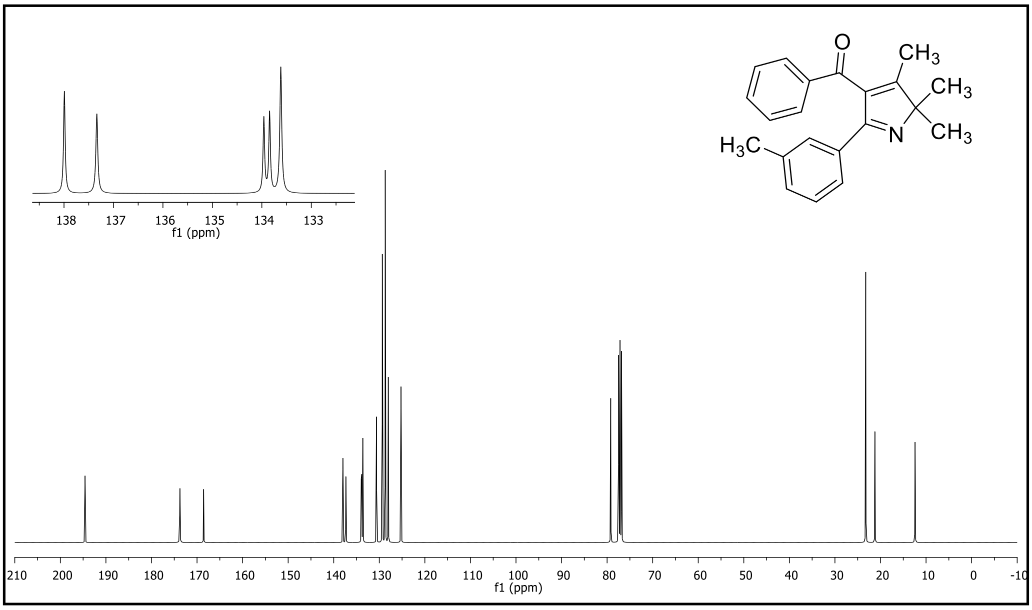

Figure A216. ^{13}C NMR spectrum of compound **72b.**

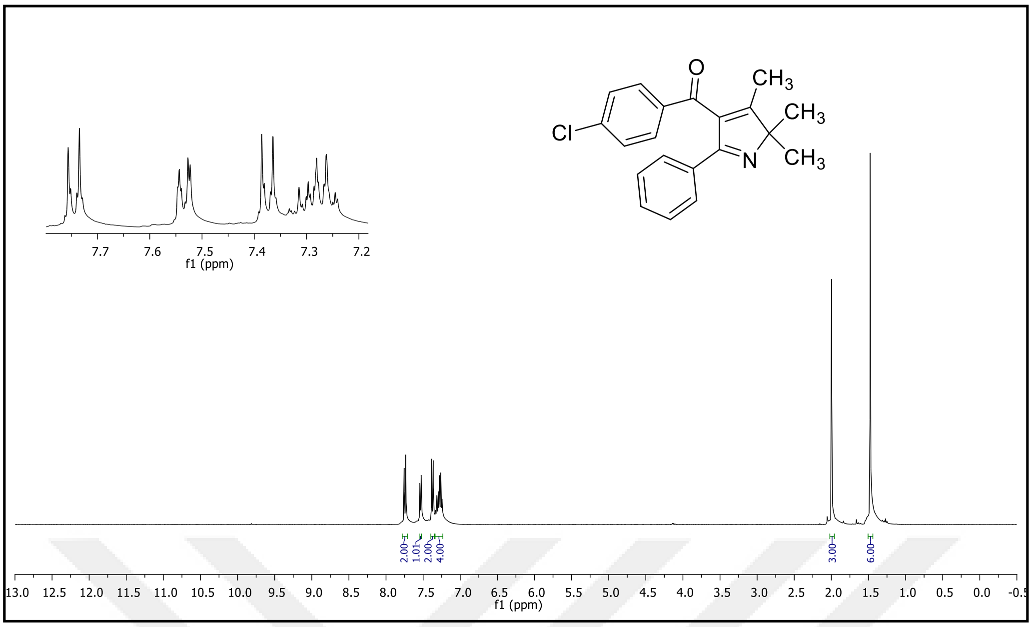

Figure A217. ^{1}H NMR spectrum of compound **72c.**

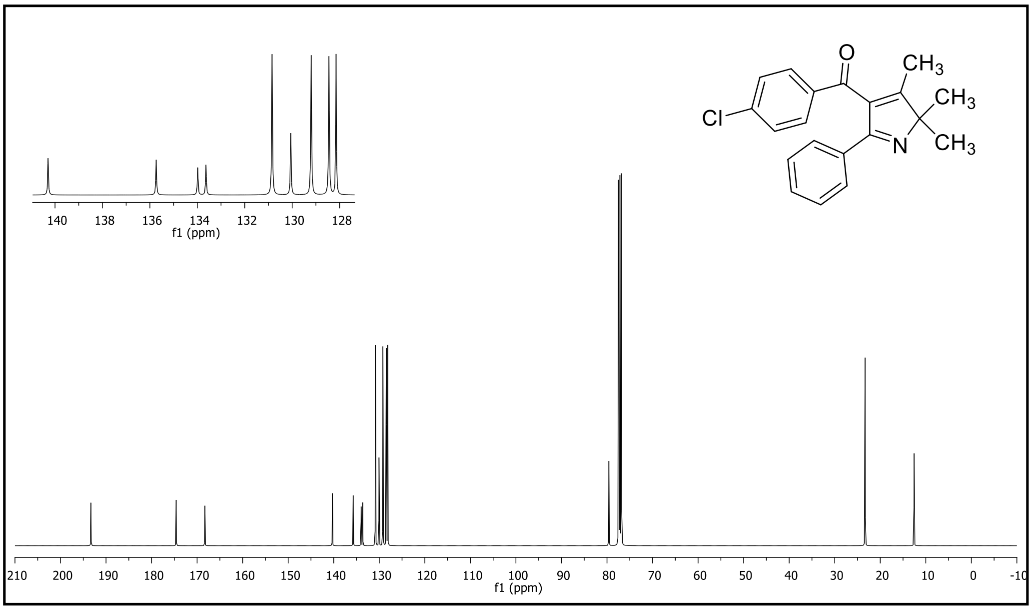

Figure A218. ^{13}C NMR spectrum of compound **72c.**

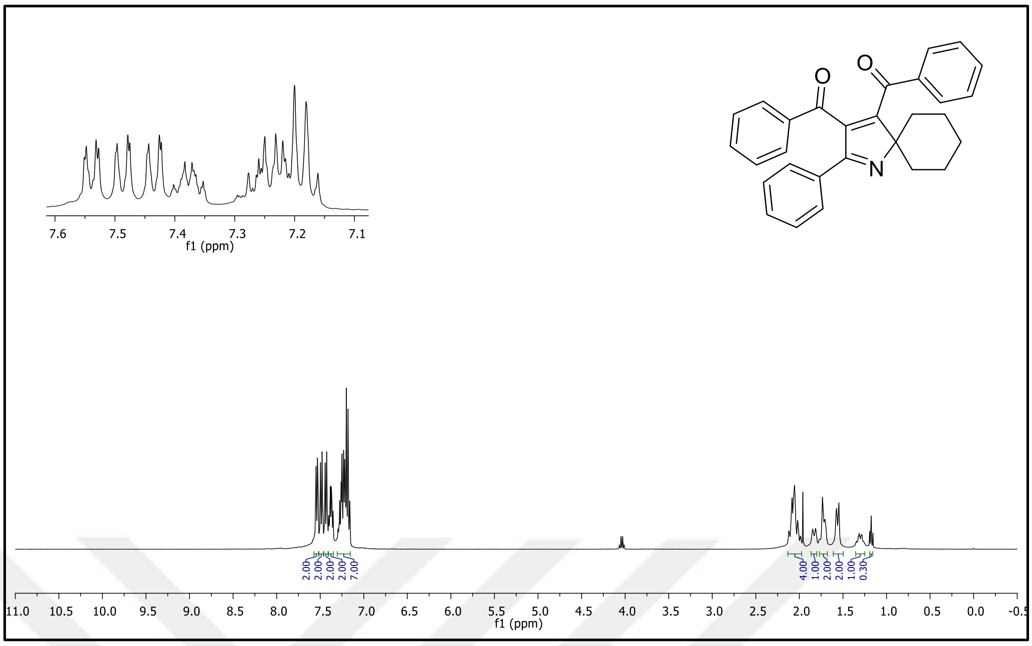

Figure A219. ^{1}H NMR spectrum of compound **53a.**

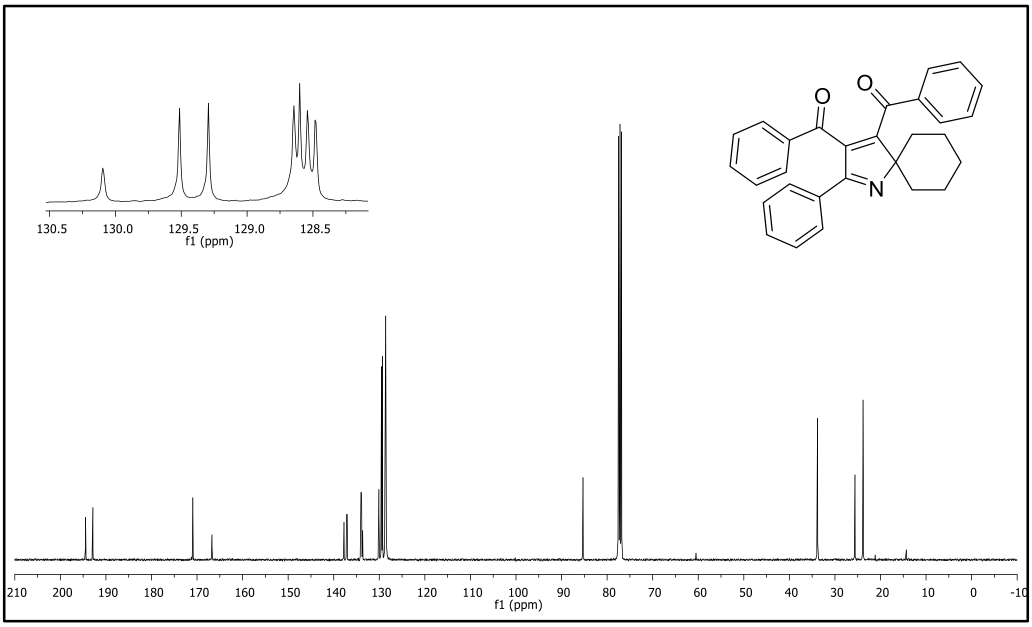

Figure A220. ^{13}C NMR spectrum of compound **53a.**

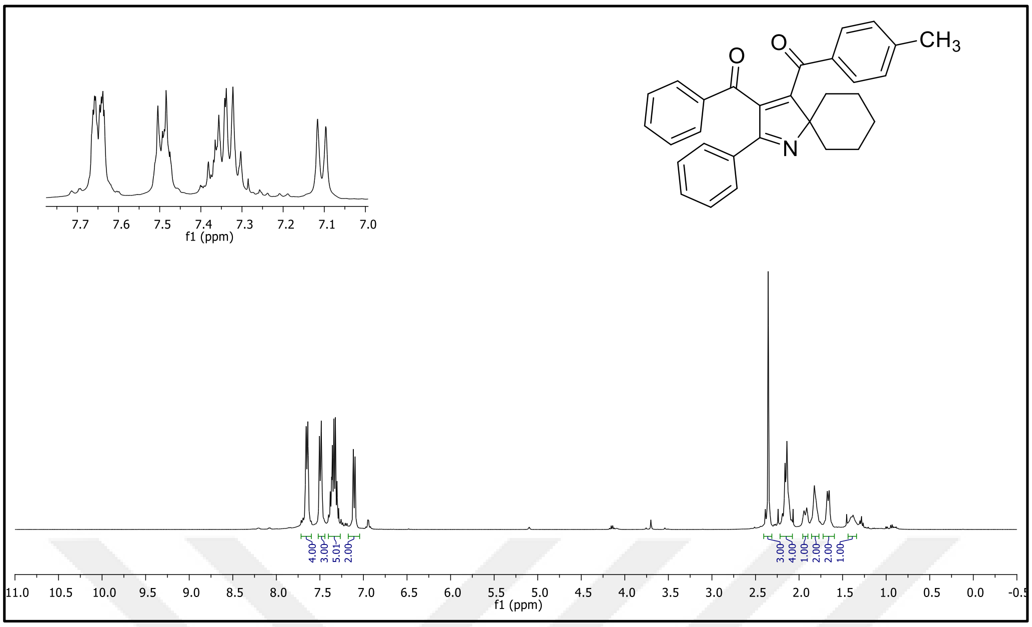

Figure A221. ^{1}H NMR spectrum of compound **53b.**

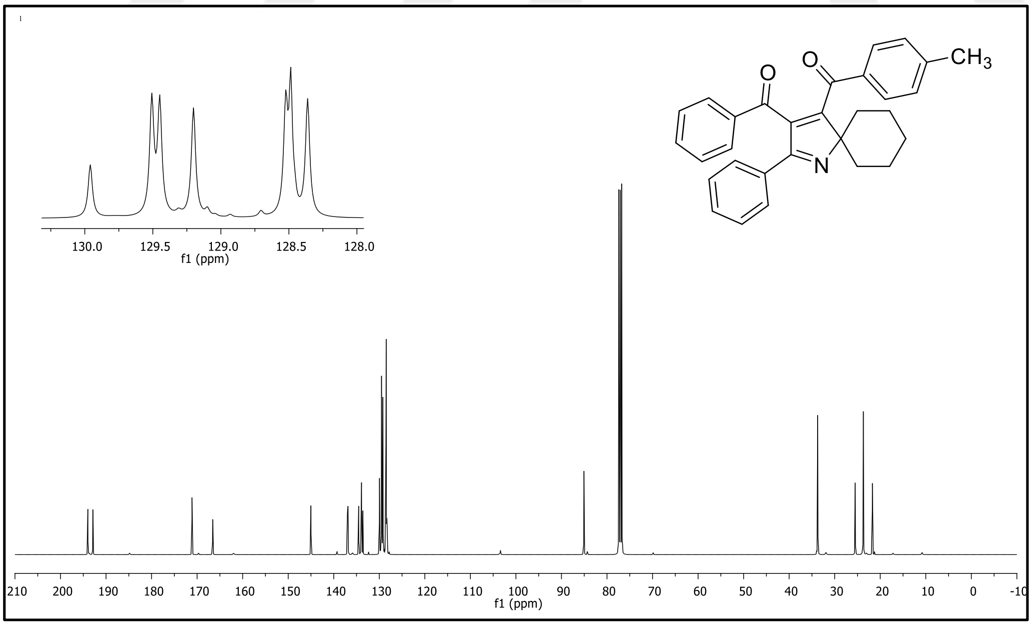

Figure A222. ^{13}C NMR spectrum of compound **53b.**

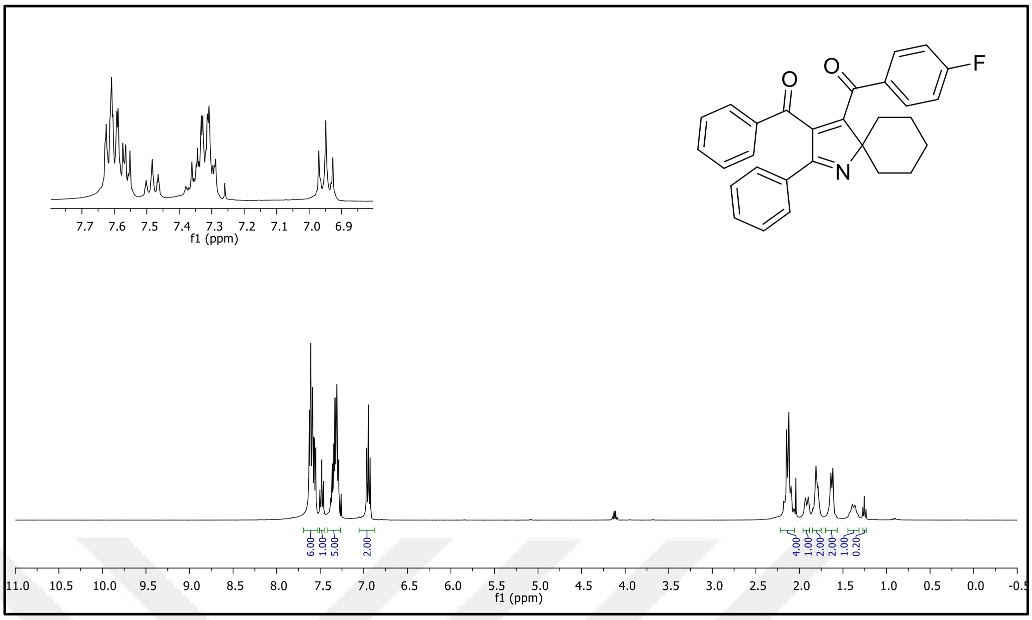

Figure A223. ^{1}H NMR spectrum of compound **53c.**

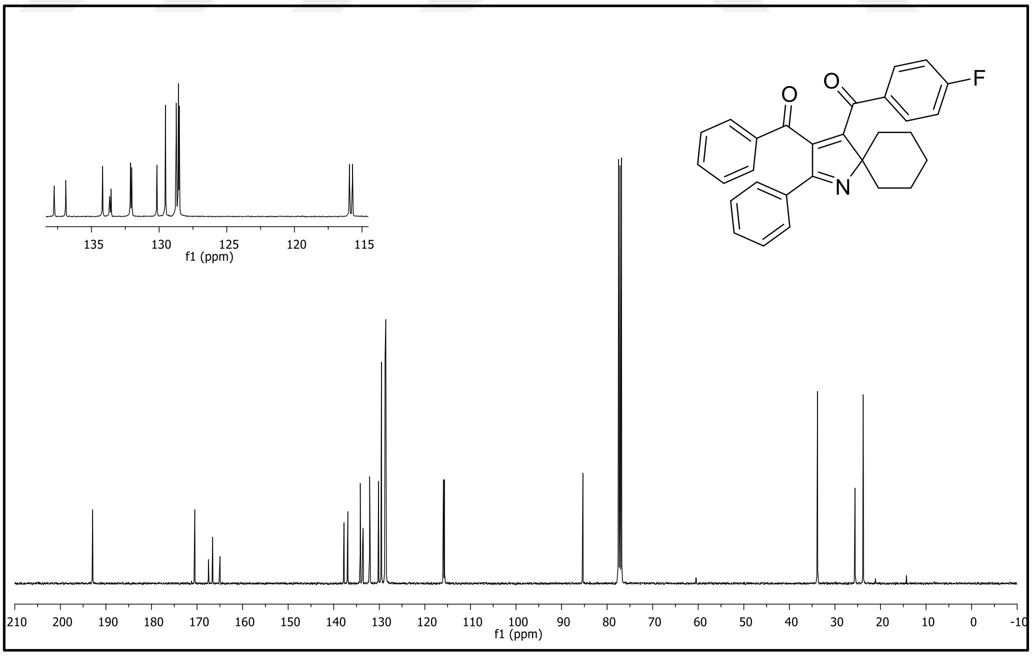

Figure A224. ^{13}C NMR spectrum of compound **53c.**

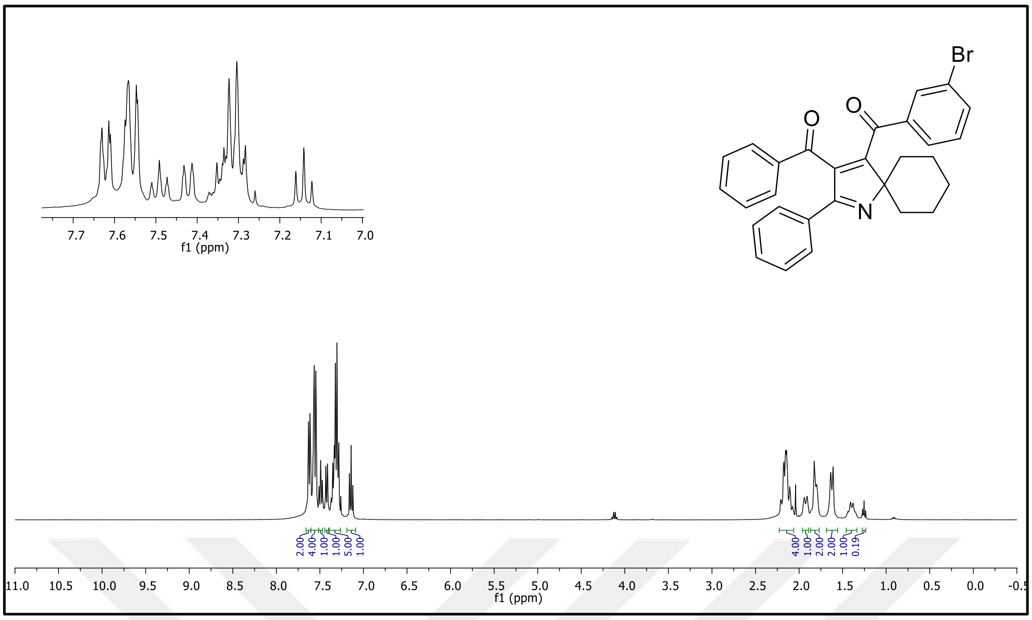

Figure A225. ^{1}H NMR spectrum of compound **53d.**

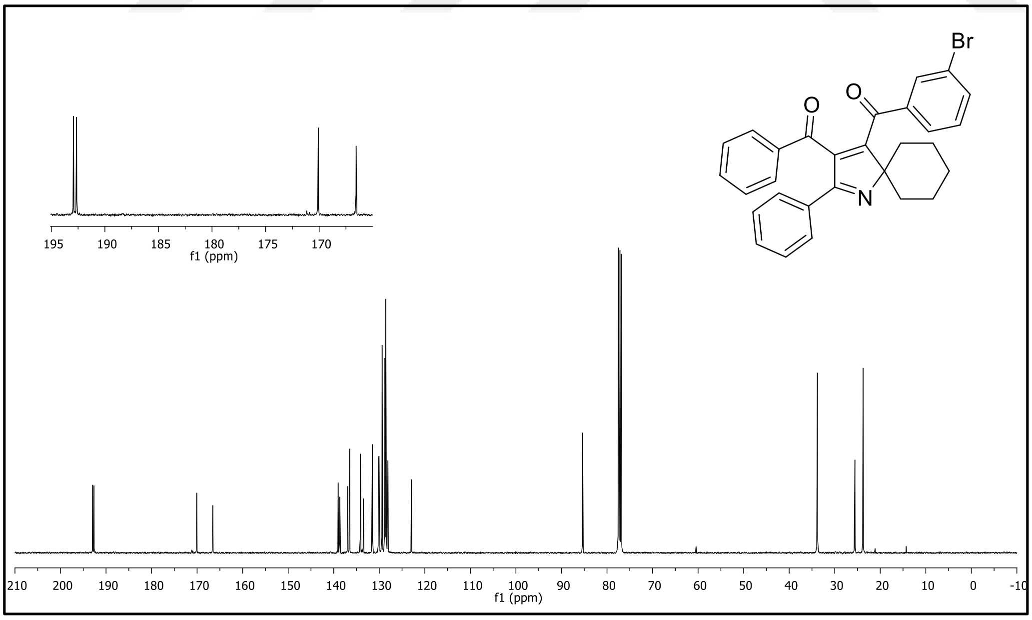

Figure A226. ^{13}C NMR spectrum of compound **53d.**

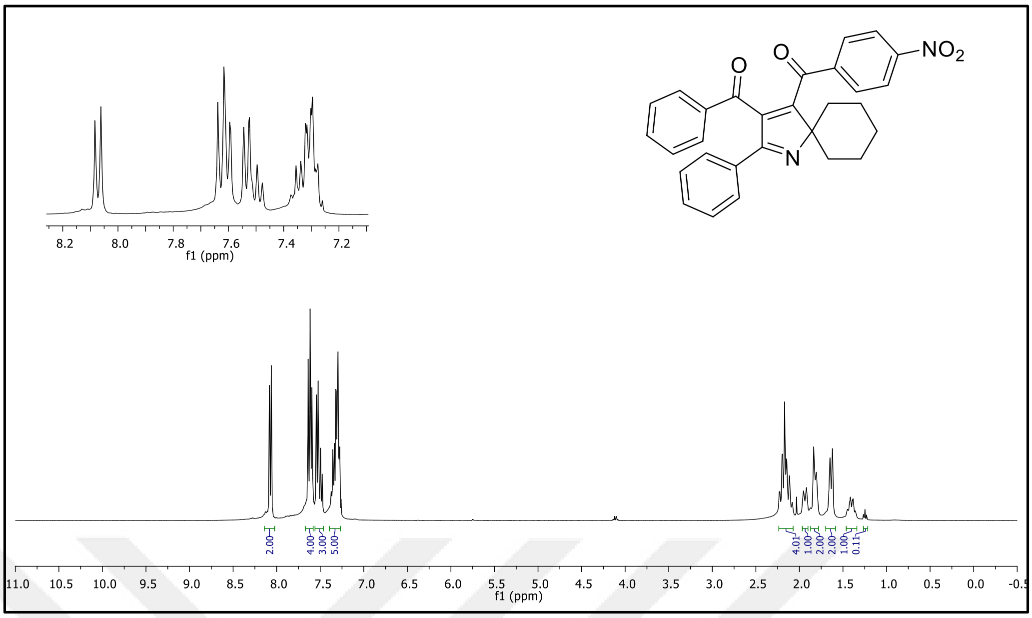

Figure A227. ^{1}H NMR spectrum of compound **53e.**

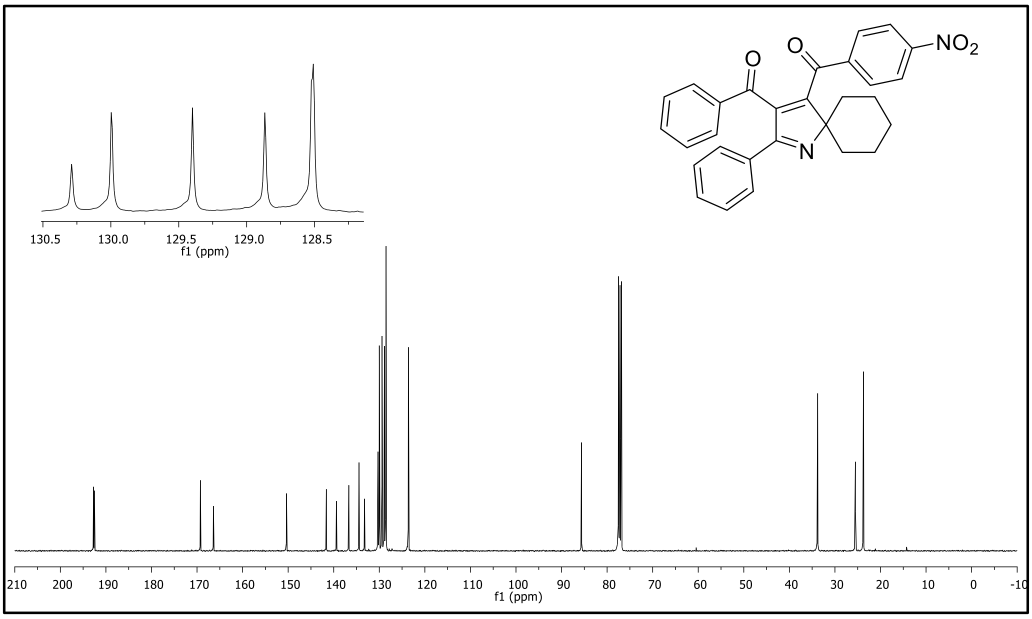

Figure A228. ^{13}C NMR spectrum of compound **53e.**

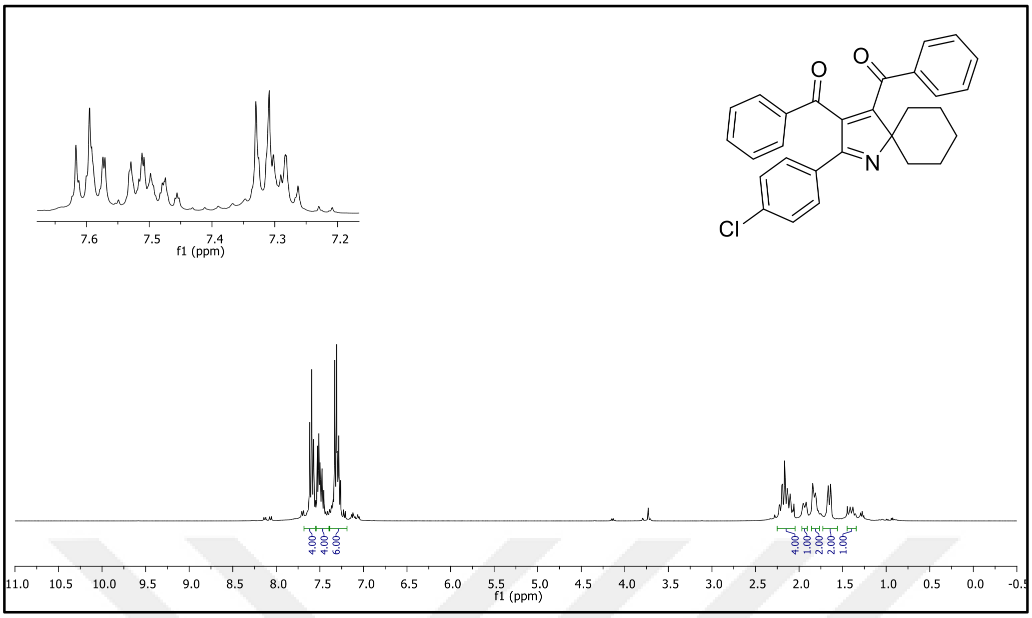

Figure A229. ^{1}H NMR spectrum of compound **53f.**

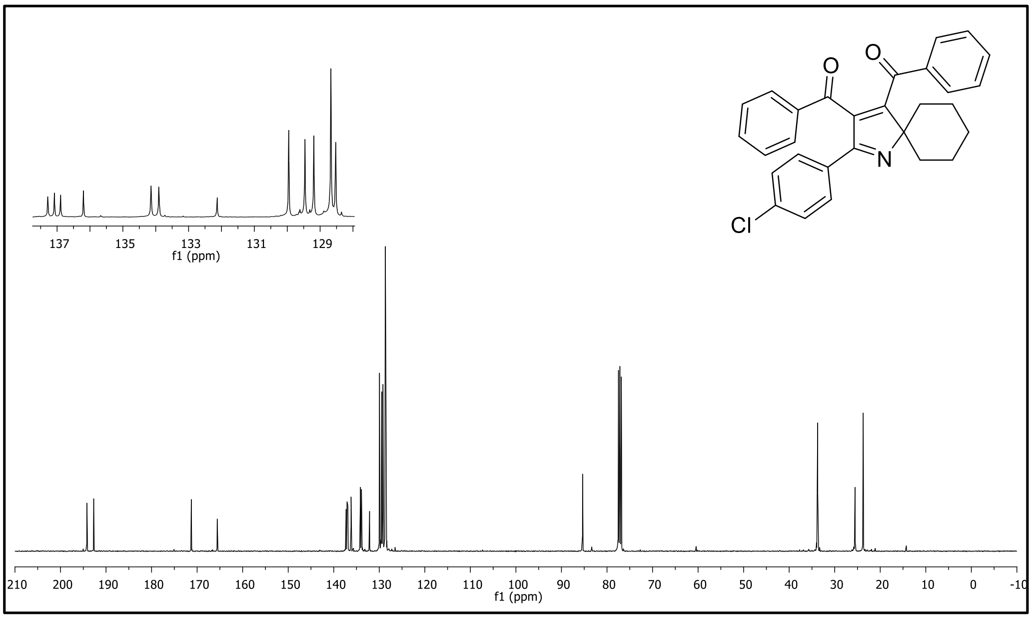

Figure A230. ^{13}C NMR spectrum of compound **53f.**

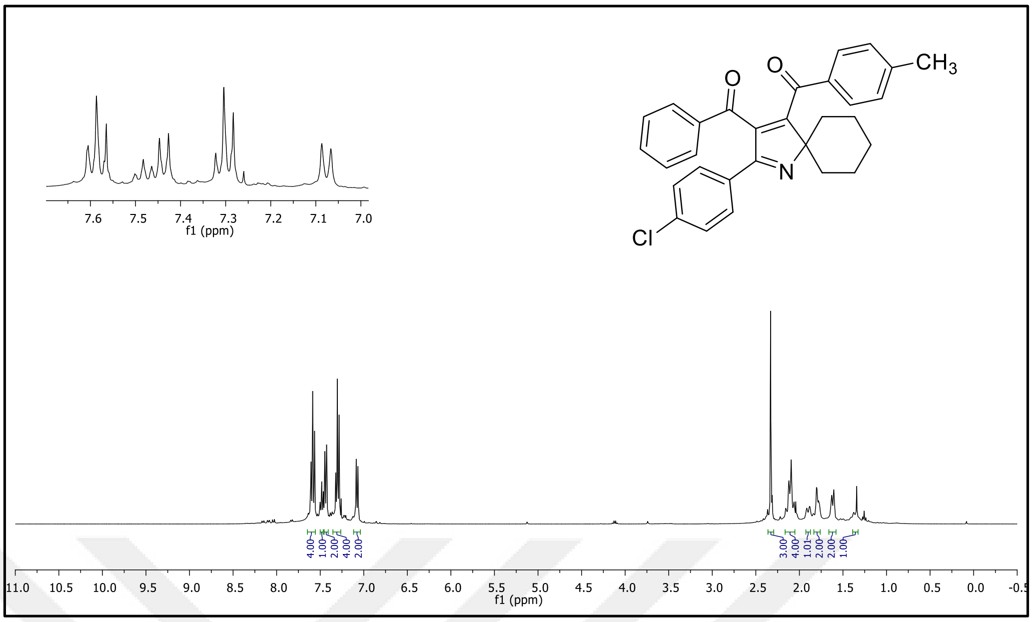

Figure A231. ^{1}H NMR spectrum of compound **53g.**

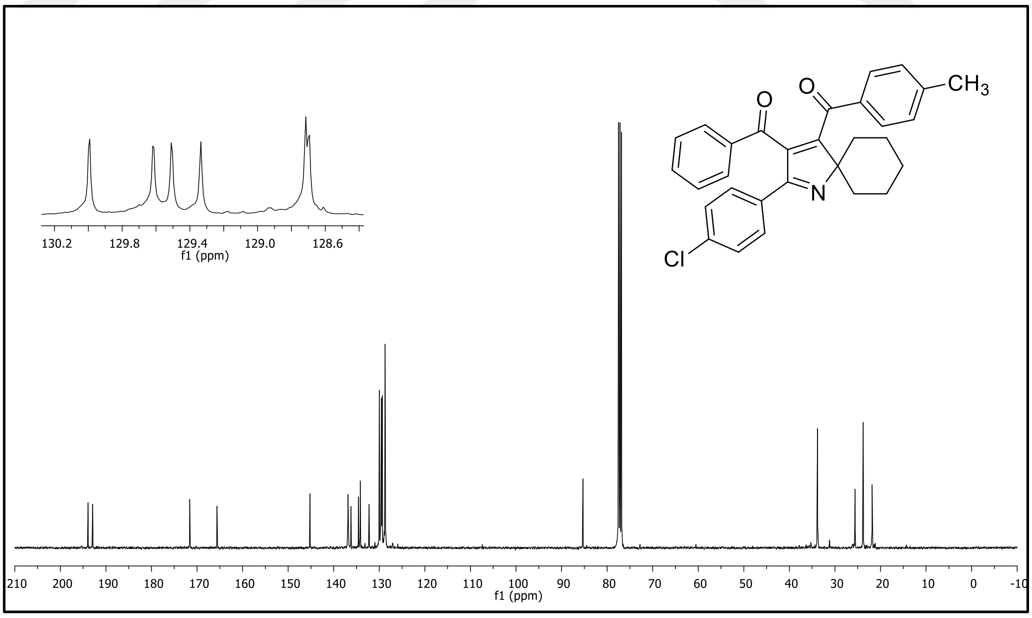

Figure A232. ^{13}C NMR spectrum of compound **53g.**

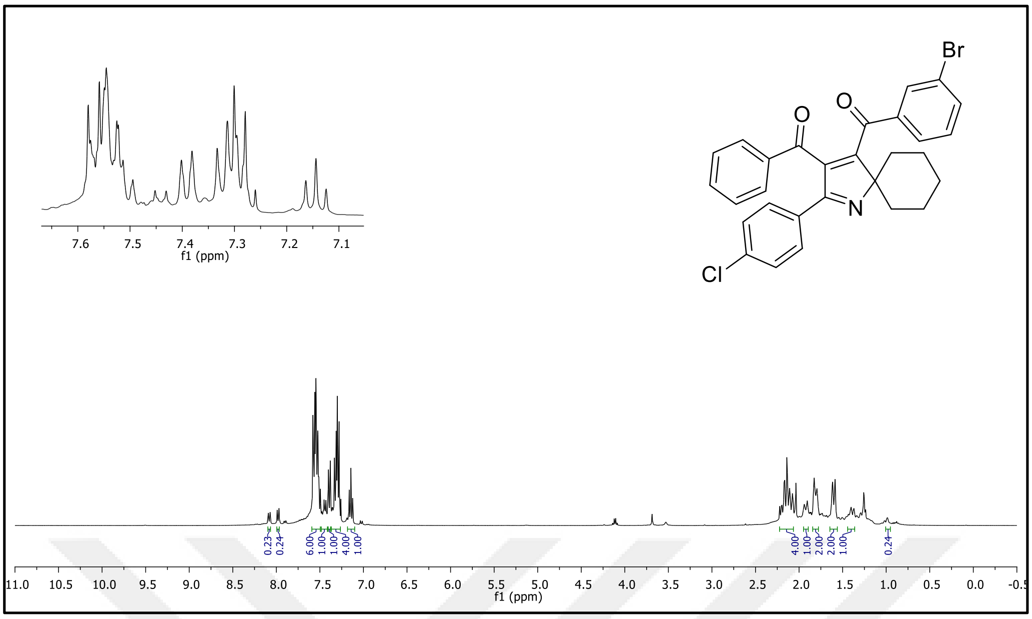

Figure A233. ^{1}H NMR spectrum of compound **53h.**

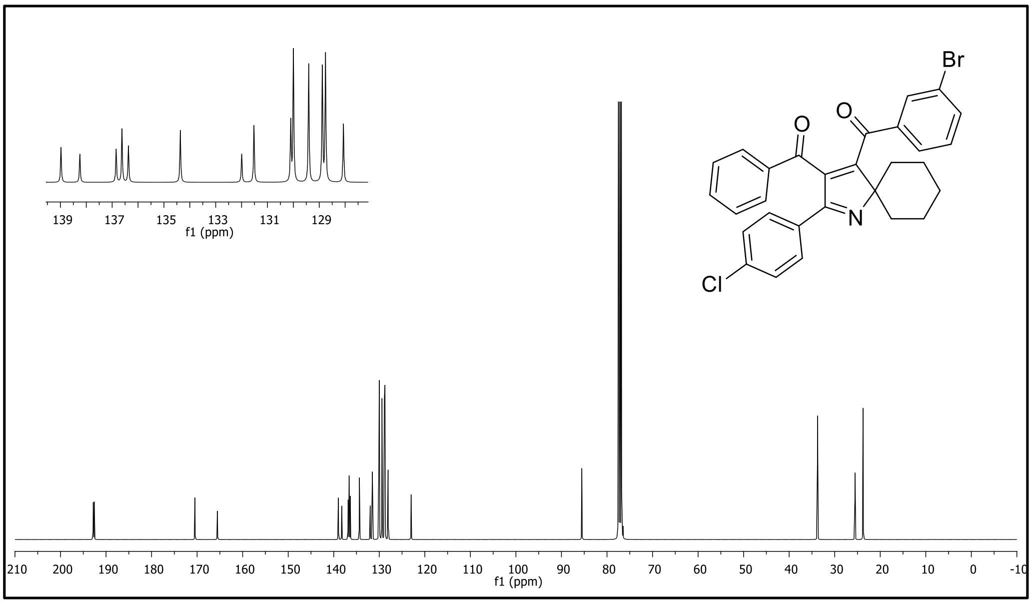

Figure A234. ^{13}C NMR spectrum of compound **53h.**

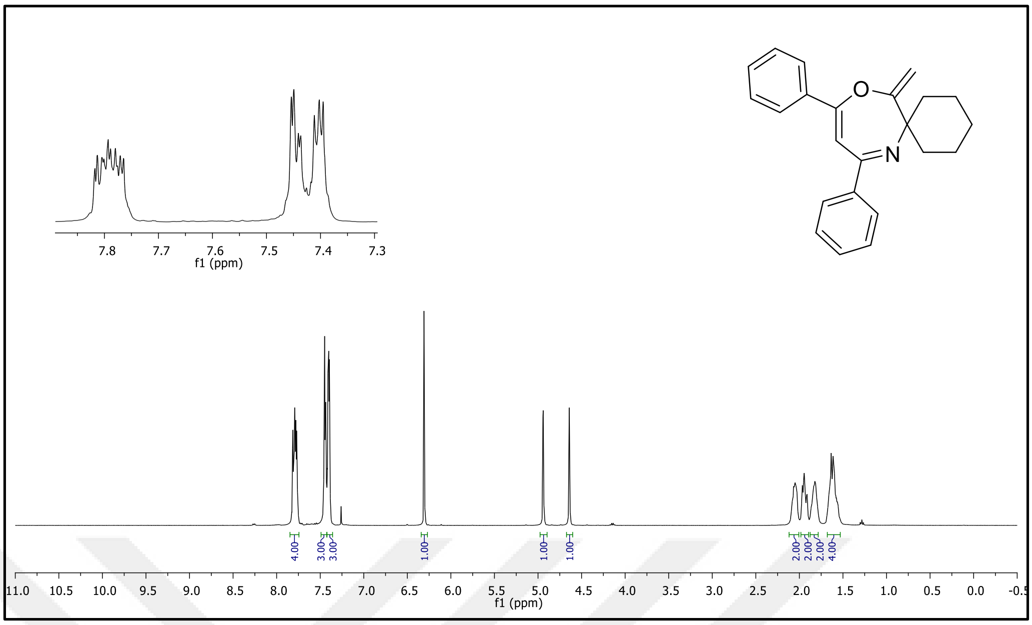

Figure A235. ^{1}H NMR spectrum of compound **54a.**

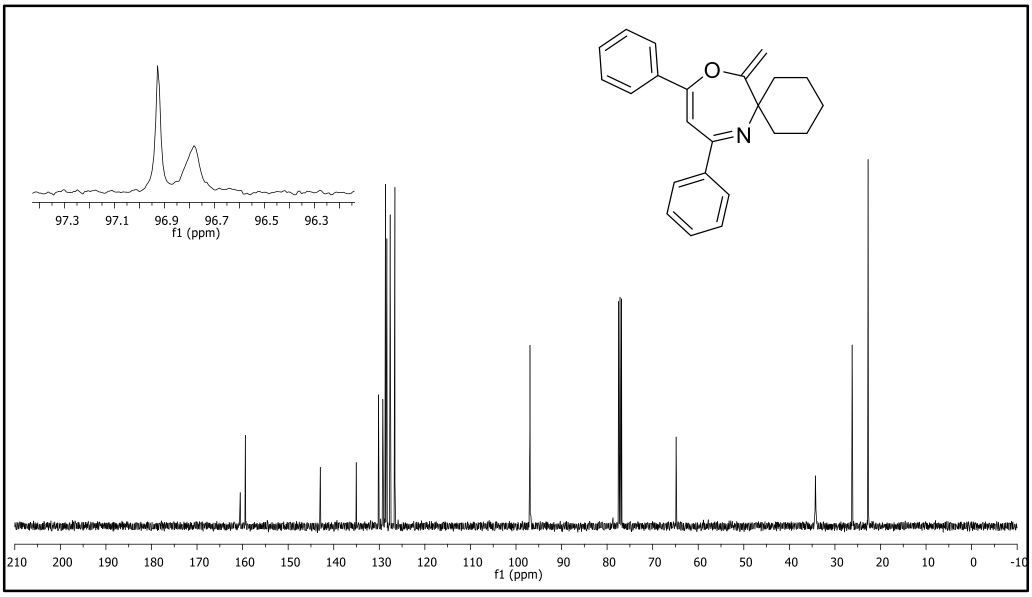

Figure A236. ^{13}C NMR spectrum of compound **54a.**

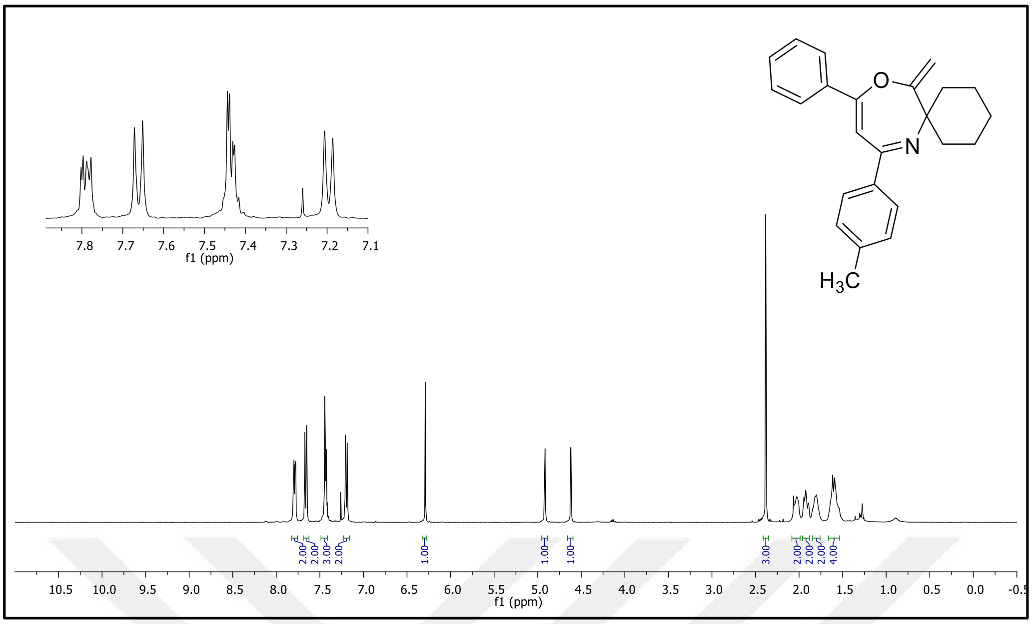

Figure A237. ^{1}H NMR spectrum of compound **54b.**

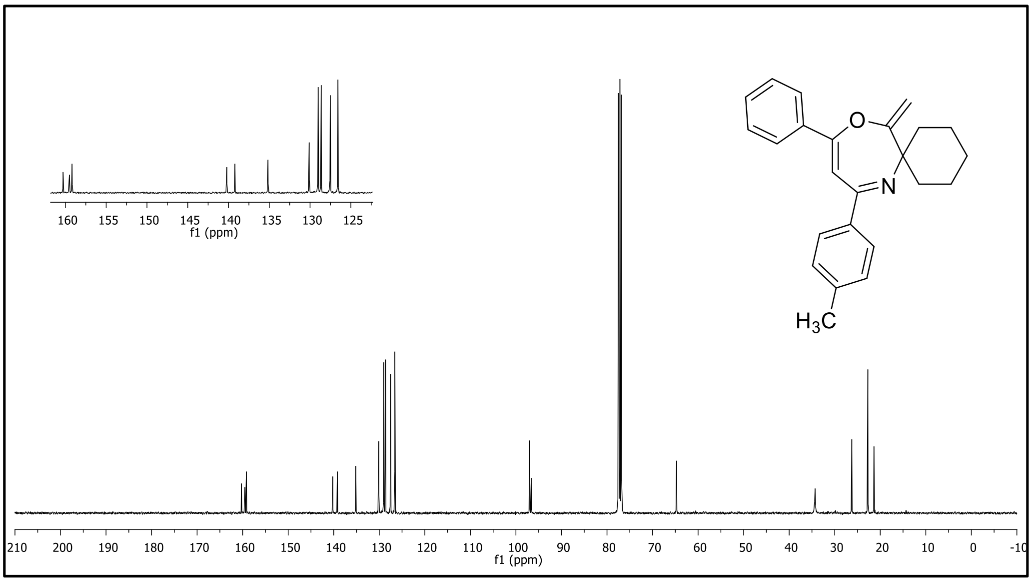

Figure A238. ^{13}C NMR spectrum of compound **54b.**

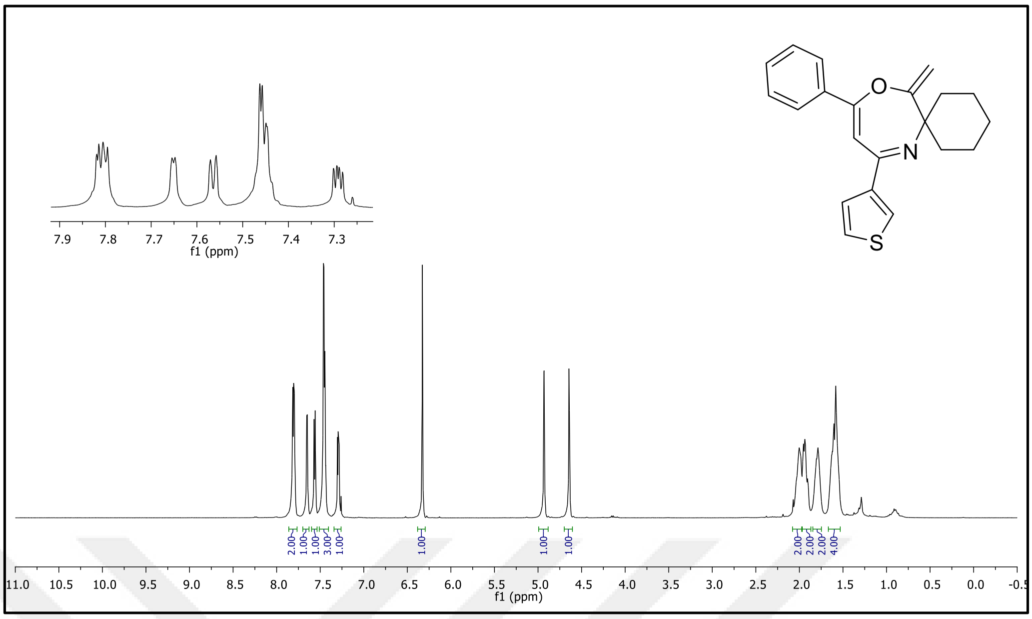

Figure A239. ^{1}H NMR spectrum of compound **54c.**

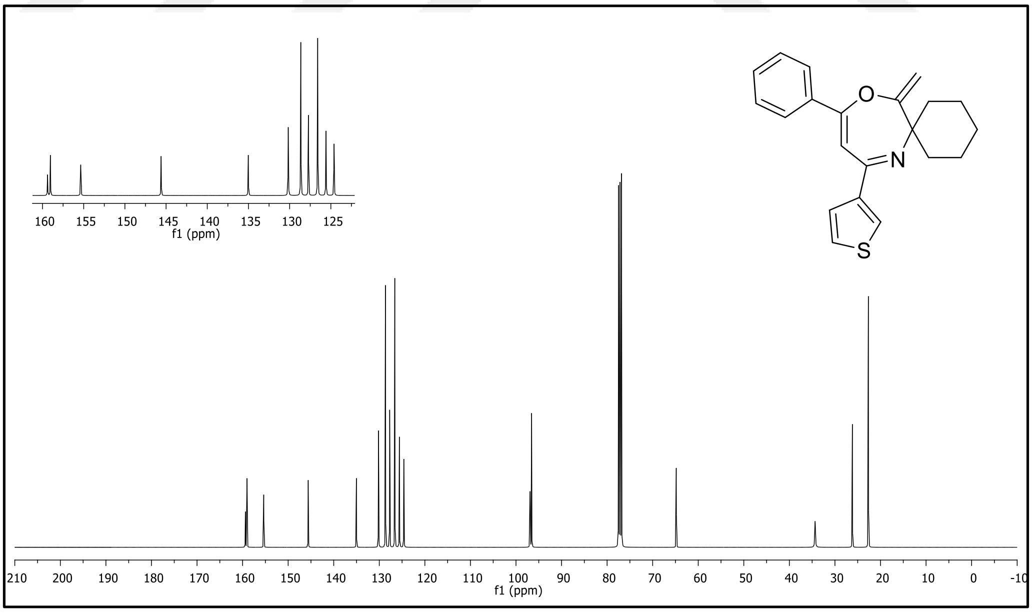

Figure A240. ^{13}C NMR spectrum of compound **54c.**

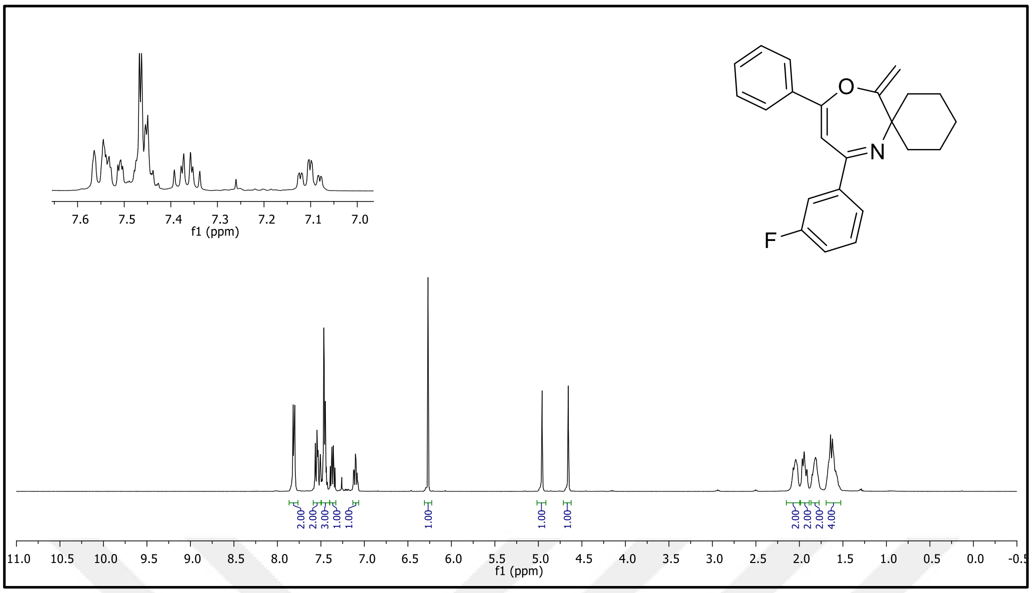

Figure A241. ^{1}H NMR spectrum of compound **54d.**

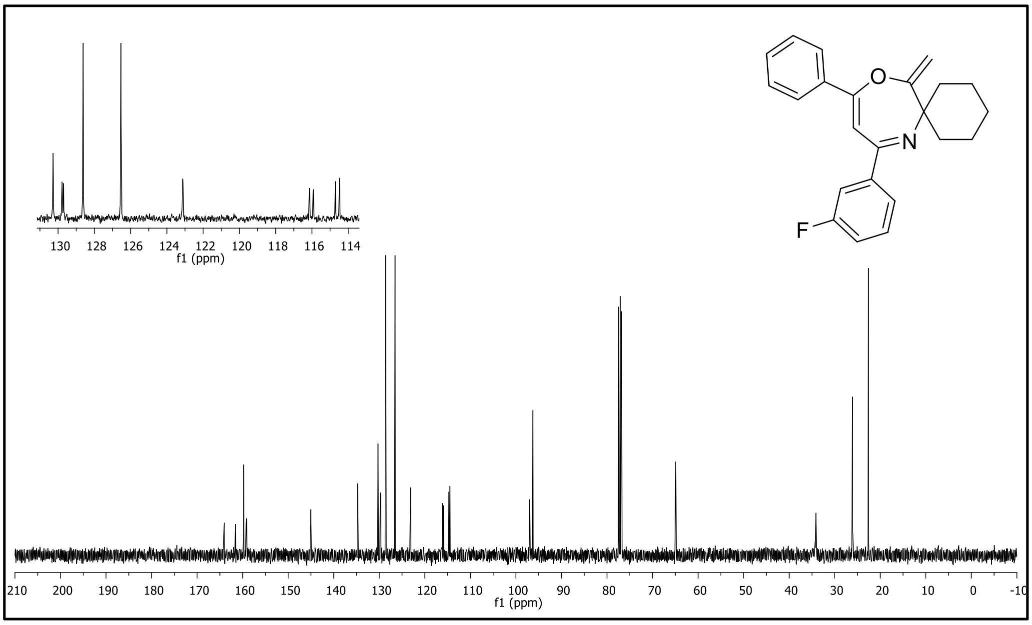

Figure A242. ^{13}C NMR spectrum of compound **54d.**

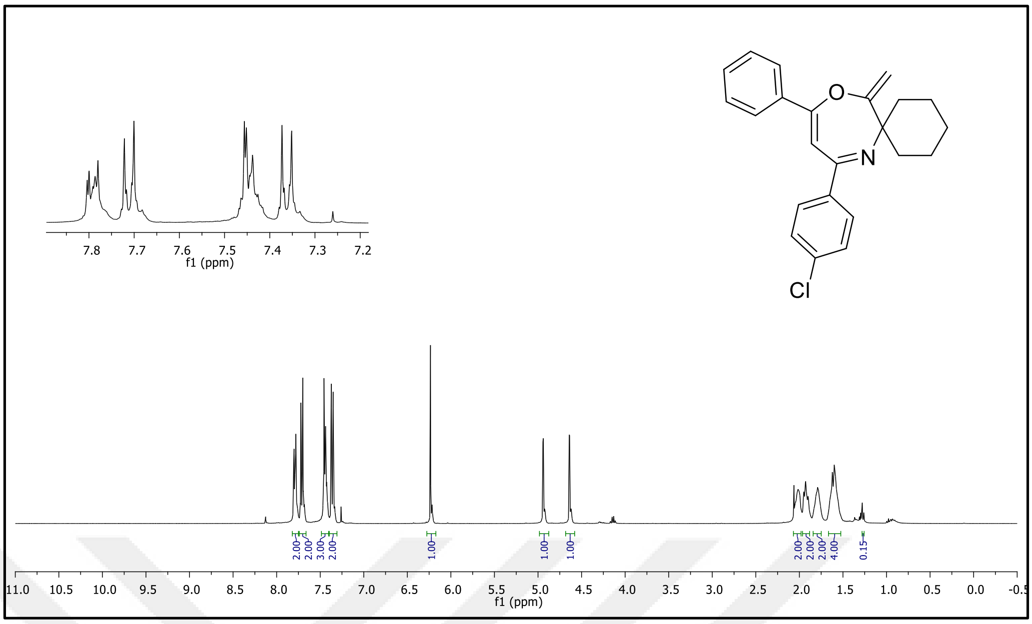

Figure A243. ^{1}H NMR spectrum of compound **54e.**

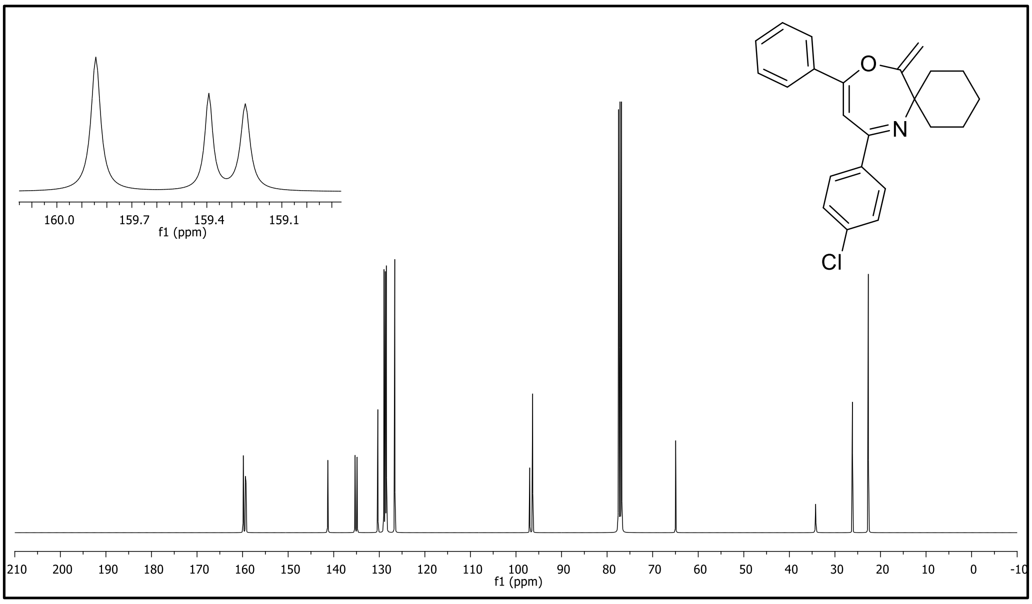

Figure A244. ^{13}C NMR spectrum of compound **54e.**

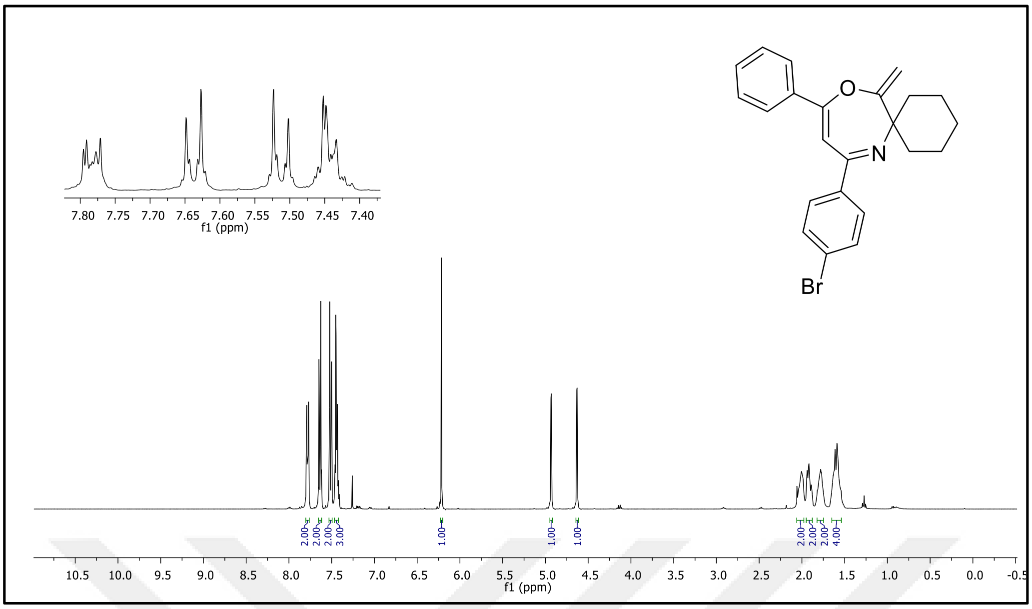

Figure A245. ^{1}H NMR spectrum of compound **54f.**

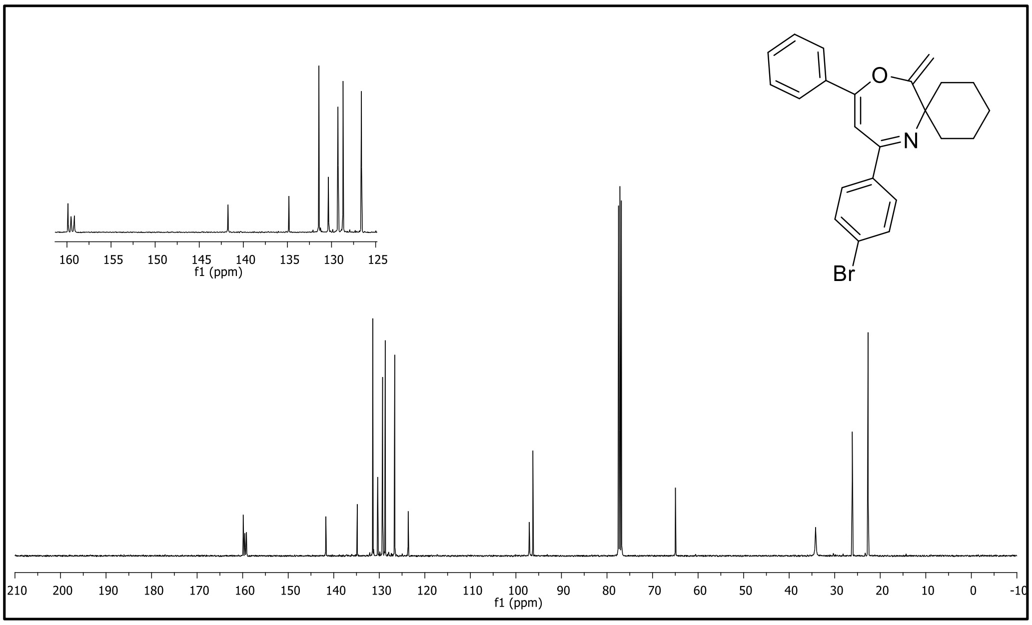

Figure A246. ^{13}C NMR spectrum of compound **54f.**

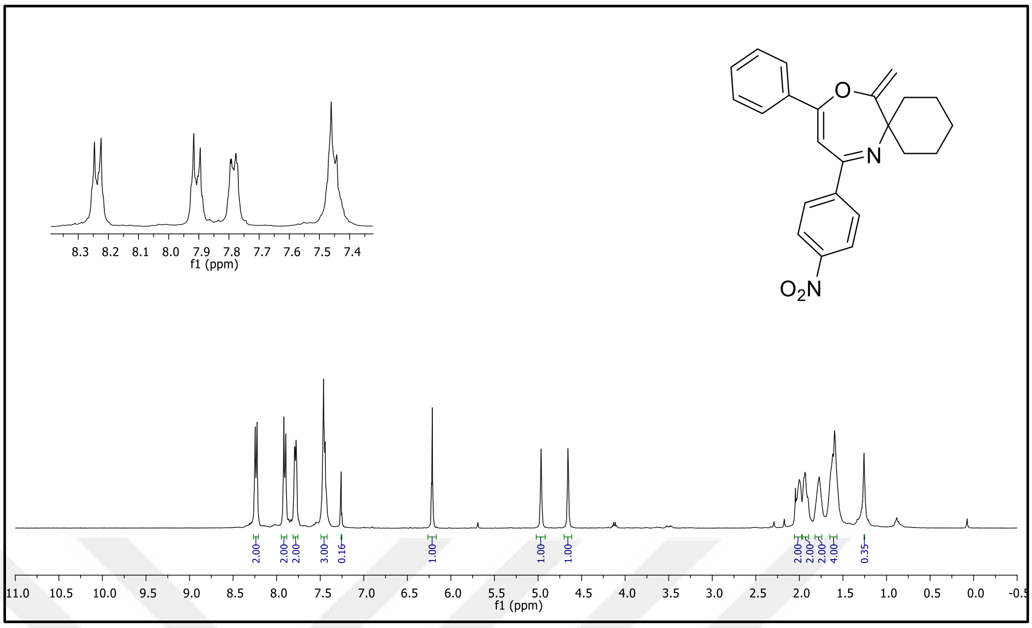

Figure A247. ^{1}H NMR spectrum of compound **54g.**

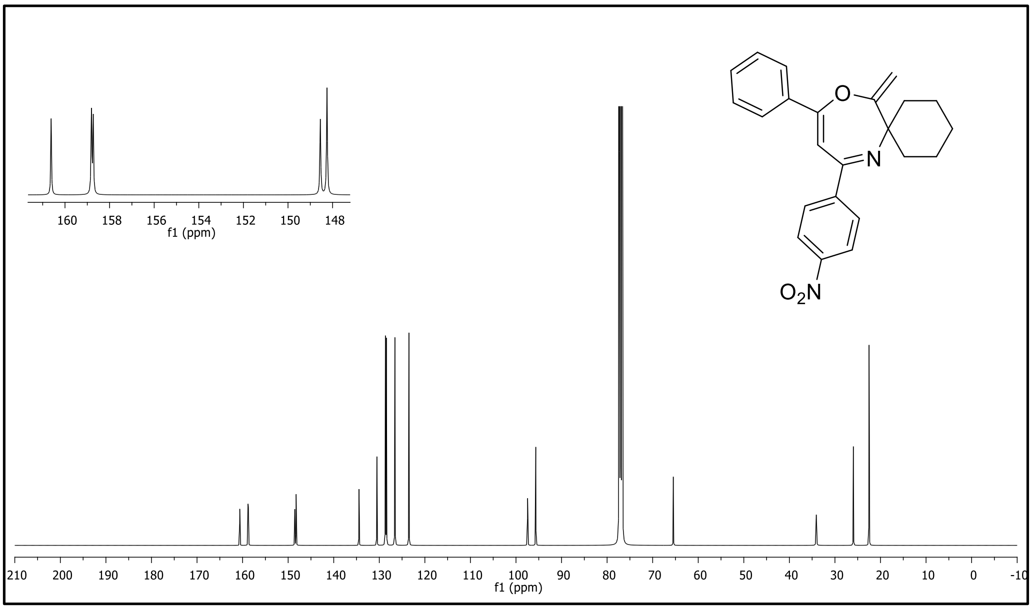

Figure A248. ^{13}C NMR spectrum of compound **54g.**

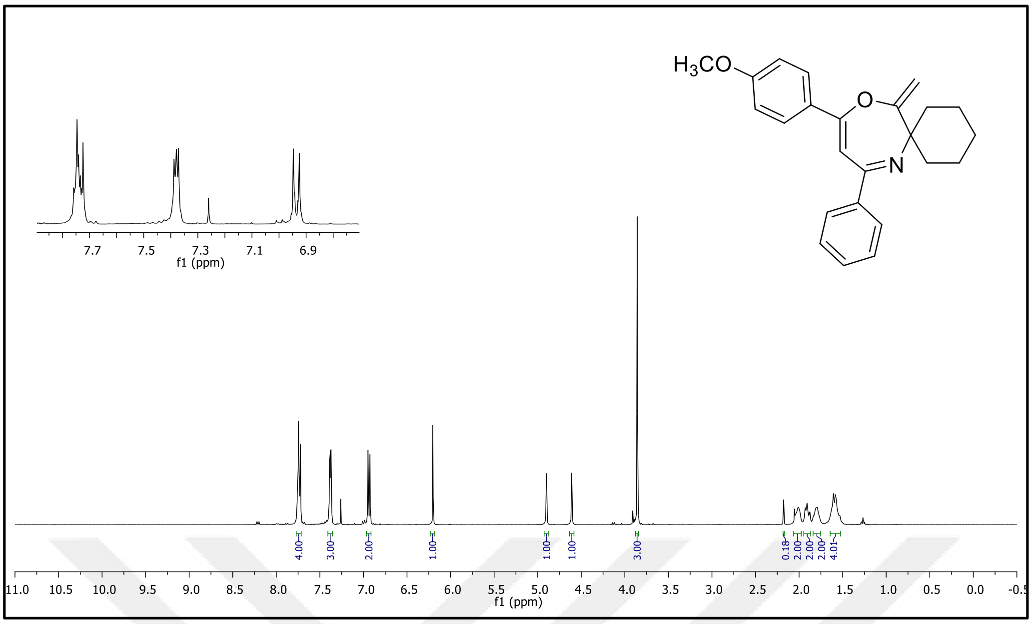

Figure A249. ^{1}H NMR spectrum of compound **54h.**

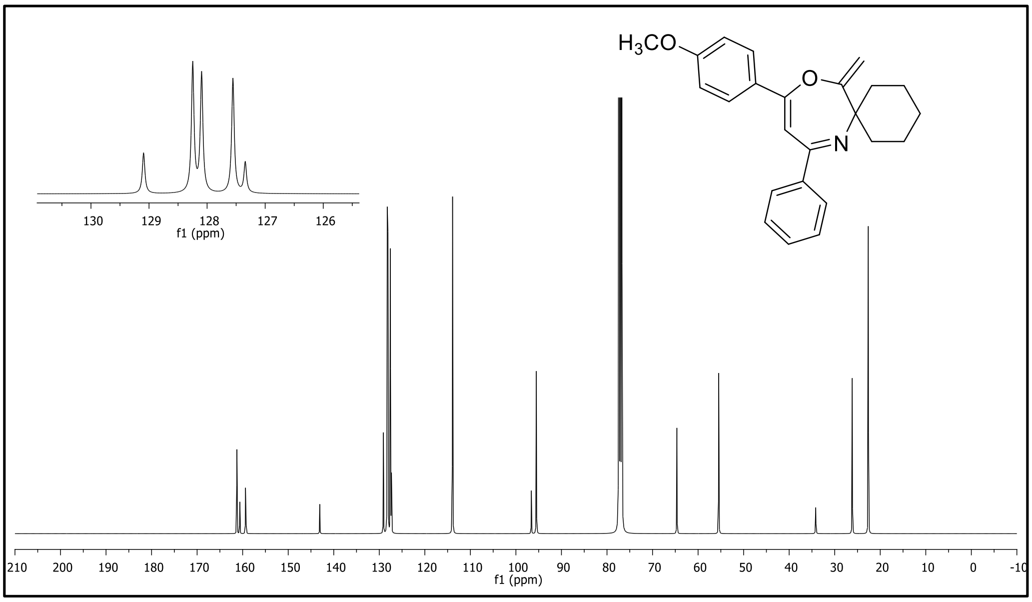

Figure A250. ^{13}C NMR spectrum of compound **54h.**

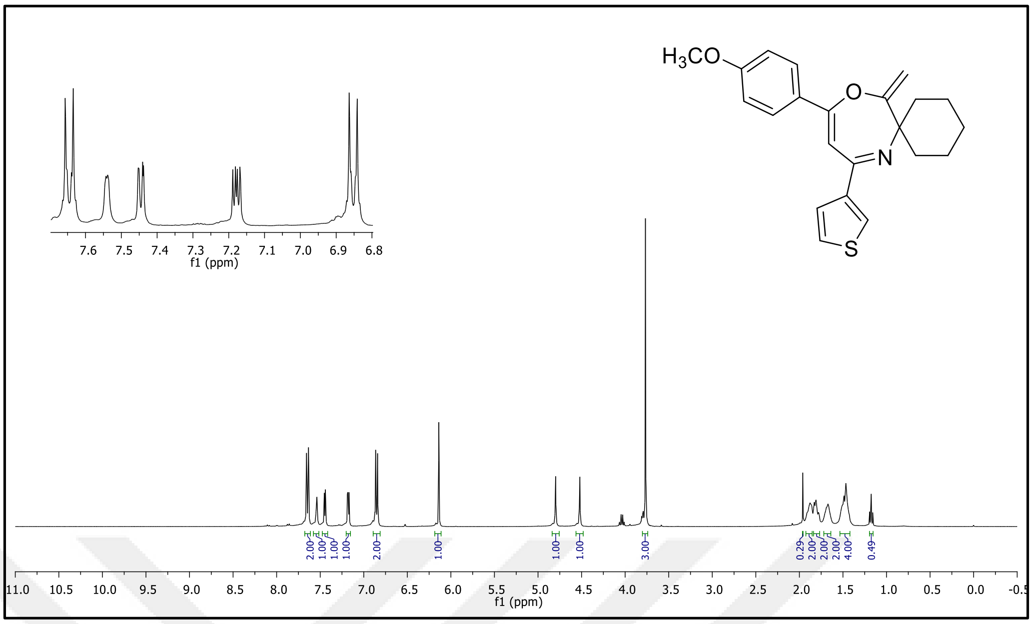

Figure A251. ^{1}H NMR spectrum of compound **54i.**

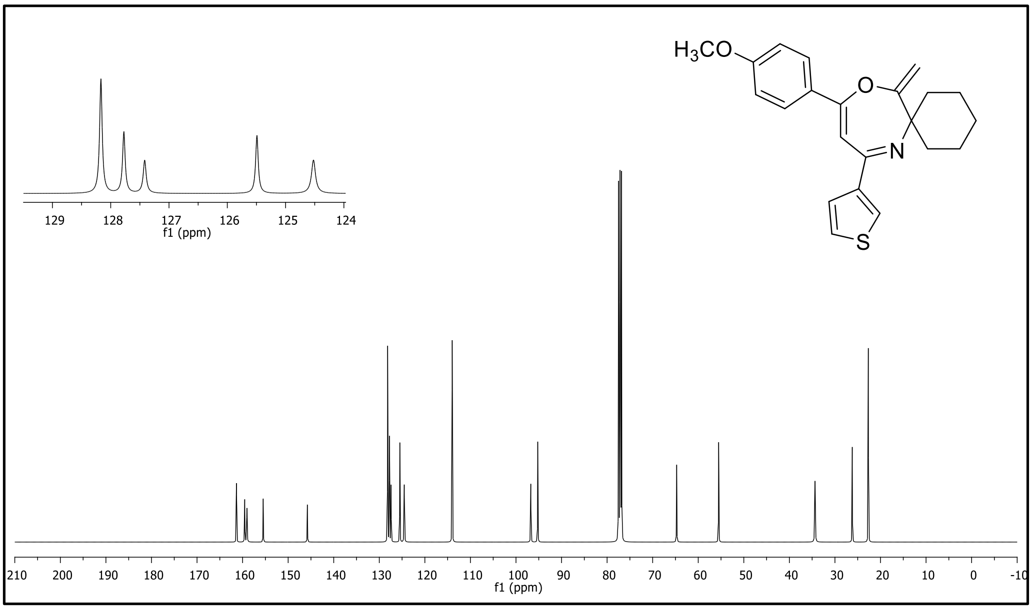

Figure A252. ^{13}C NMR spectrum of compound **54i.**

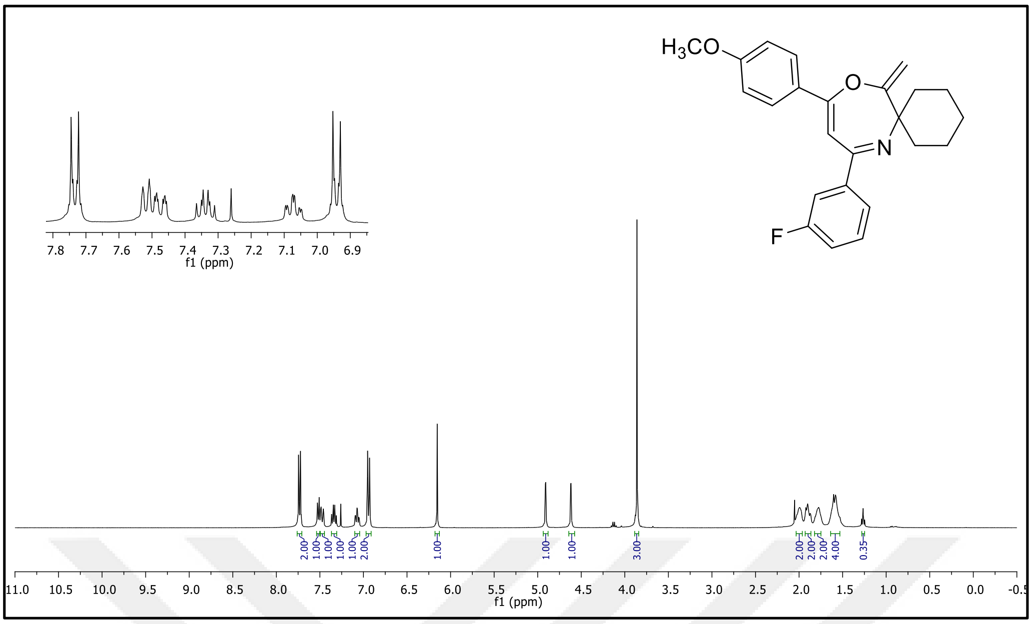

Figure A253. ^{1}H NMR spectrum of compound **54j.**

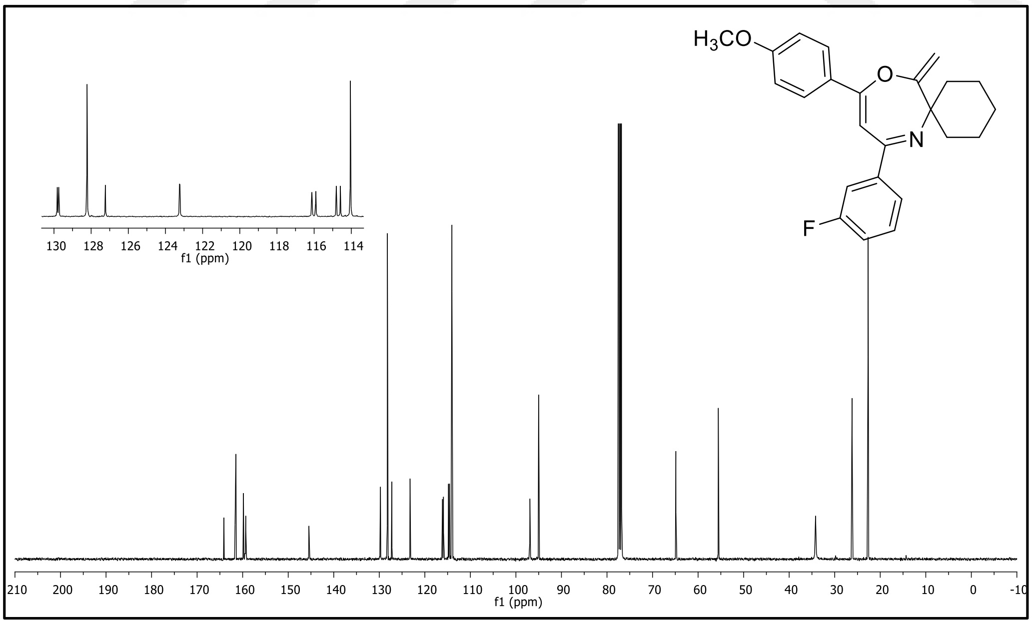

Figure A254. ^{13}C NMR spectrum of compound **54j.**

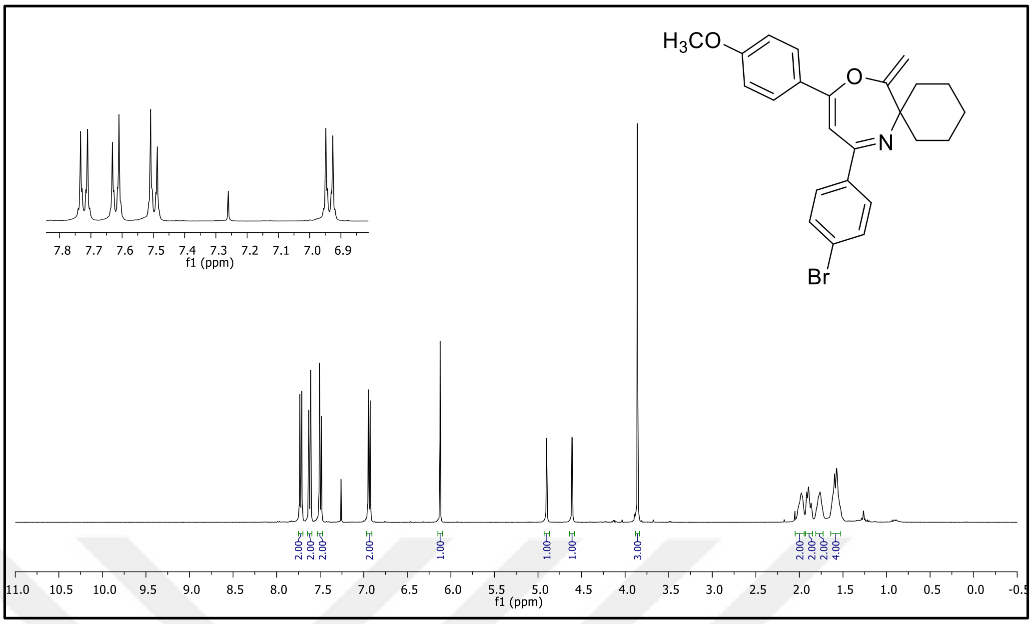

Figure A255. ^{1}H NMR spectrum of compound **54k.**

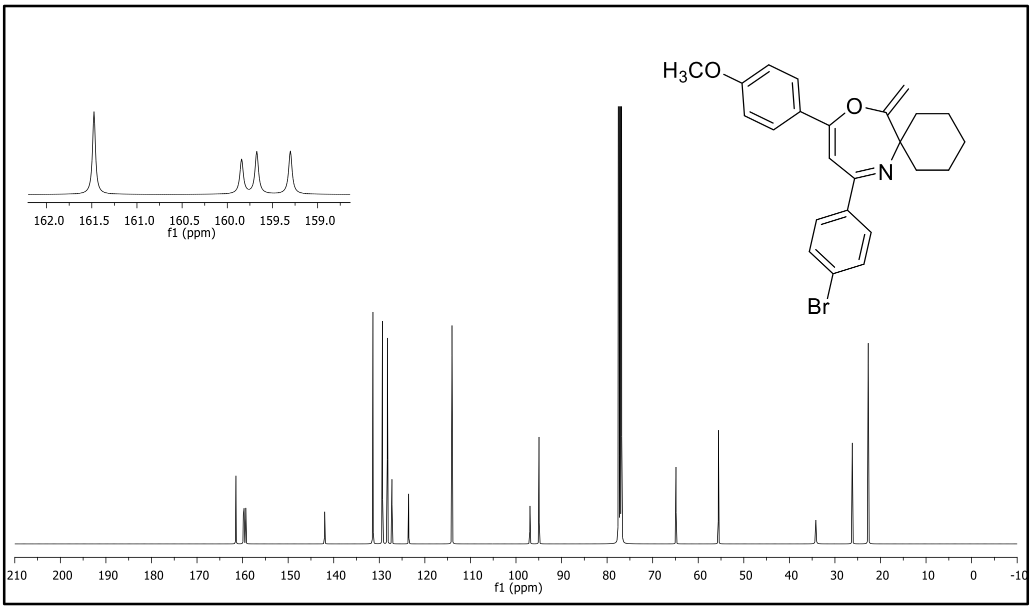

Figure A256. ^{13}C NMR spectrum of compound **54k.**

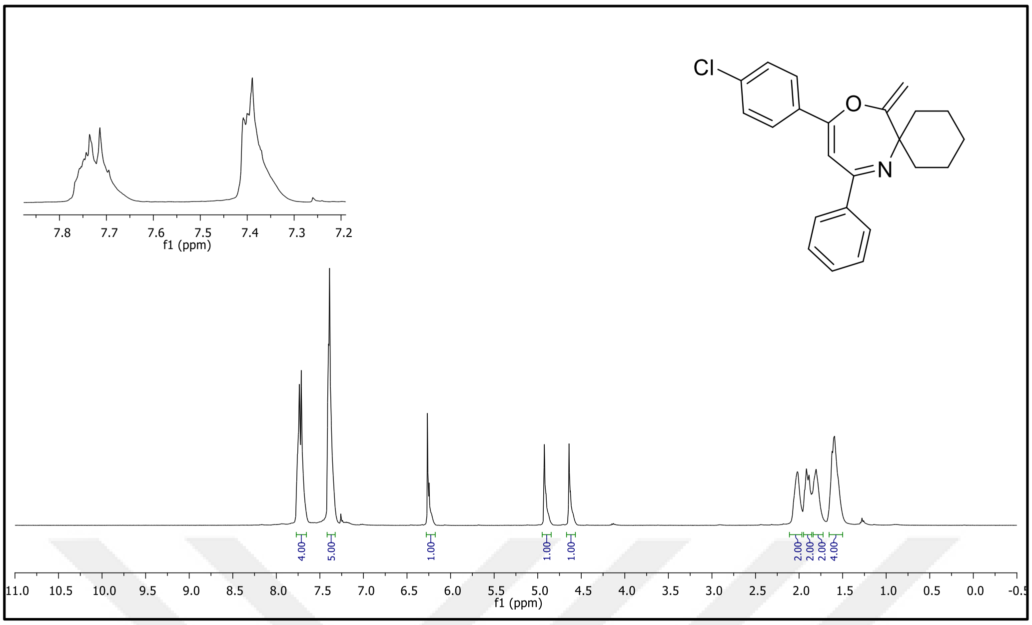

Figure A257. ^{1}H NMR spectrum of compound **54l.**

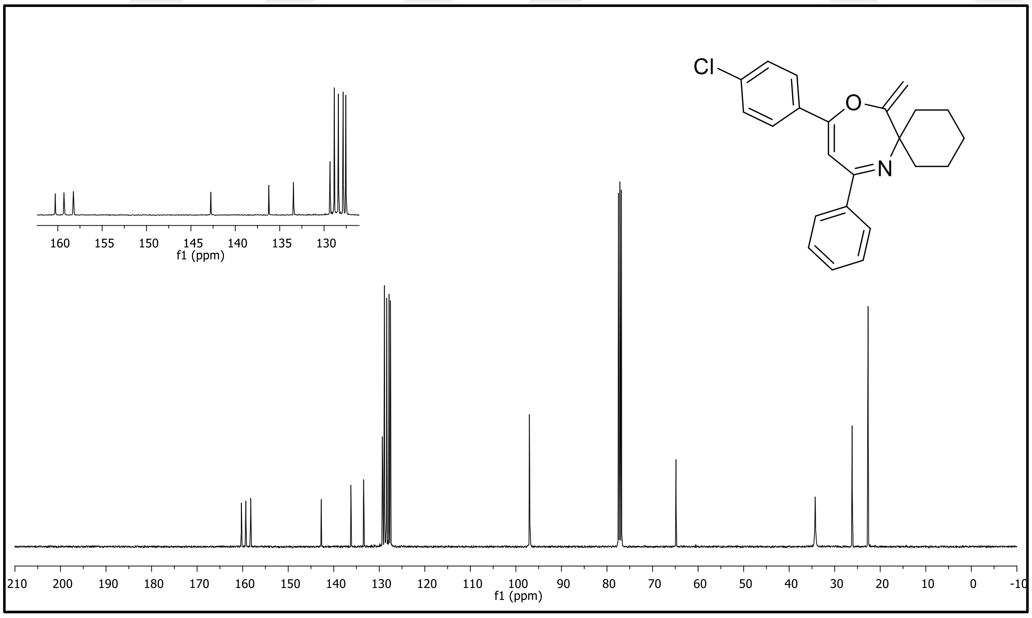

Figure A258. ^{13}C NMR spectrum of compound **54l.**

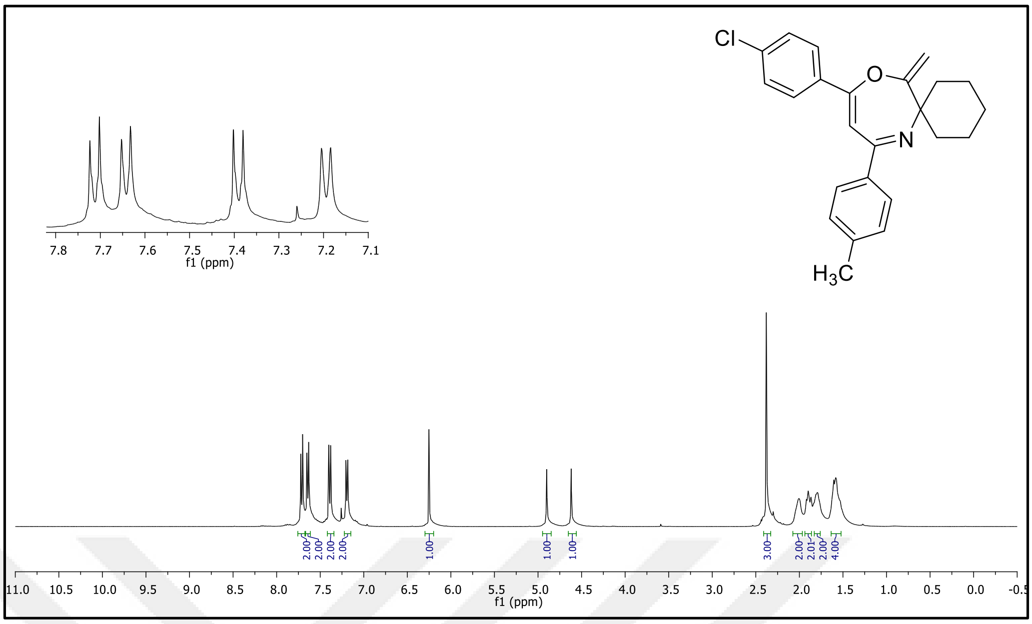

Figure A259. ^{1}H NMR spectrum of compound **54m.**

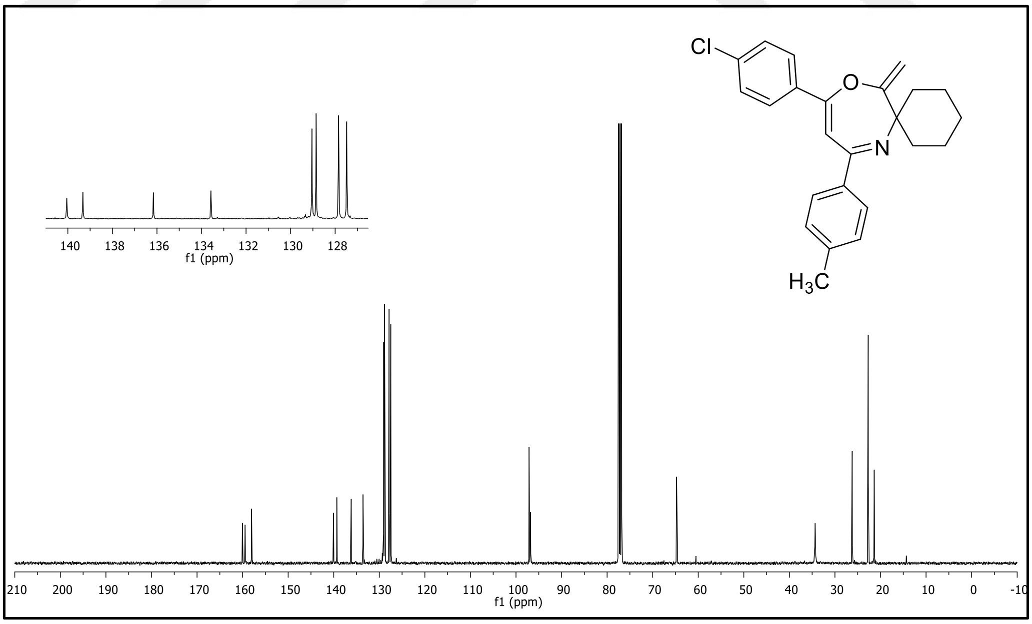

Figure A260. ^{13}C NMR spectrum of compound **54m.**

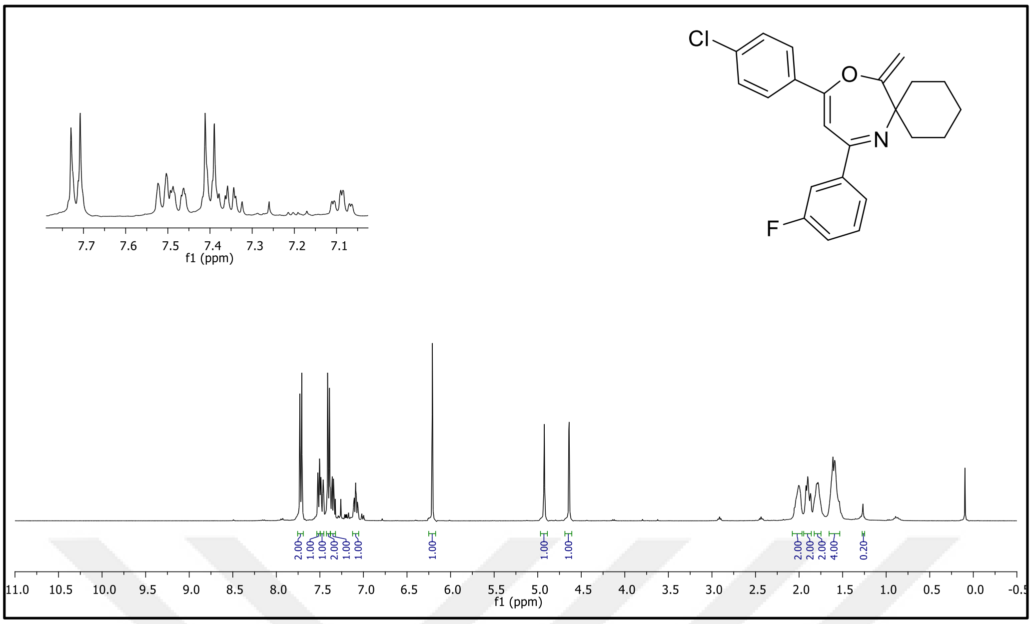

Figure A261. ^{1}H NMR spectrum of compound **54n.**

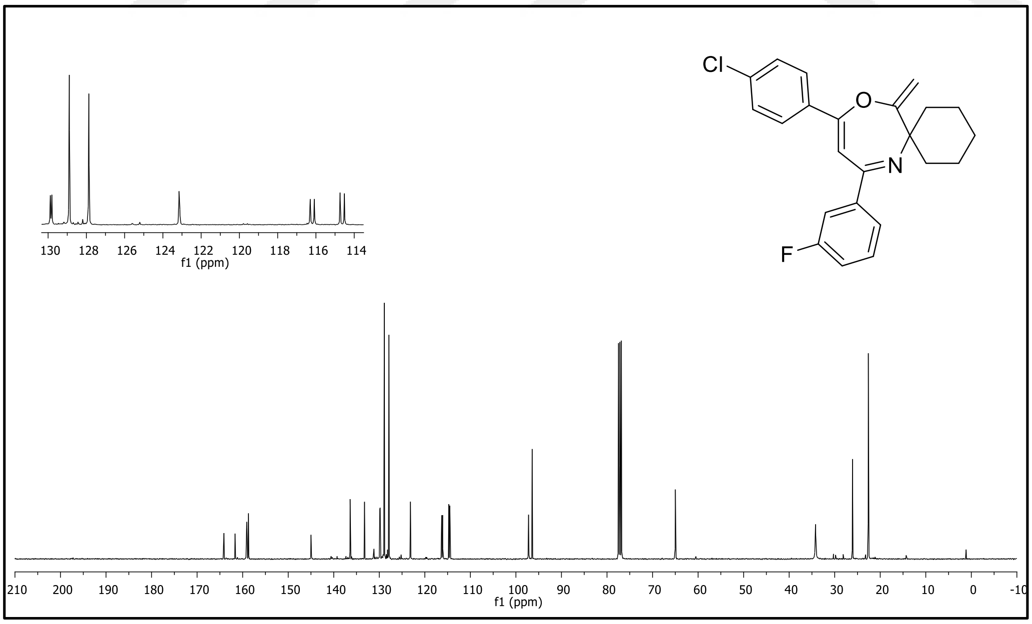

Figure A262. ^{13}C NMR spectrum of compound **54n.**

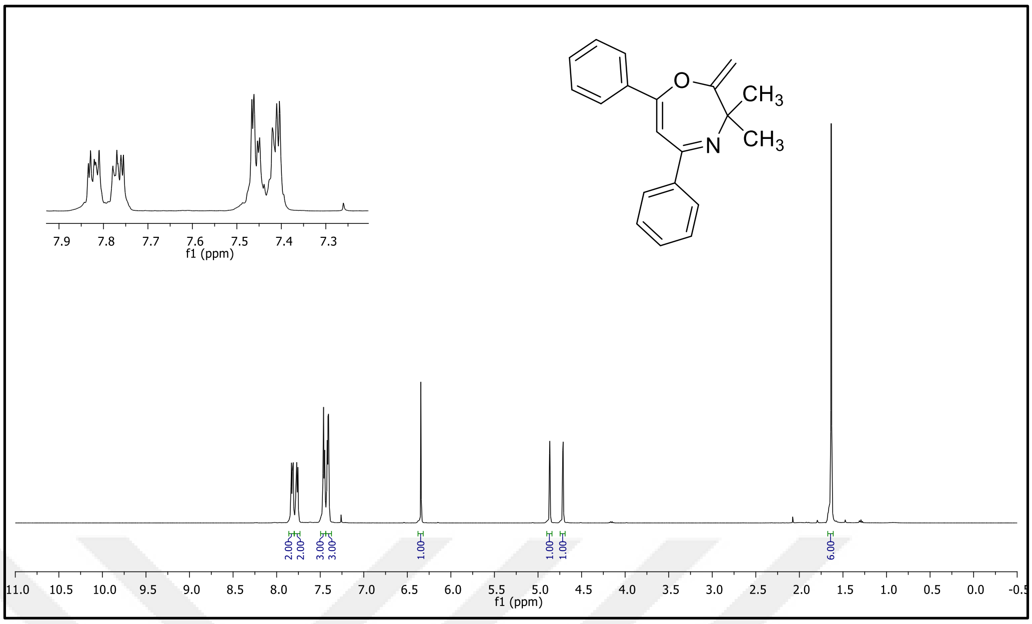

Figure A263. ^{1}H NMR spectrum of compound **86a.**

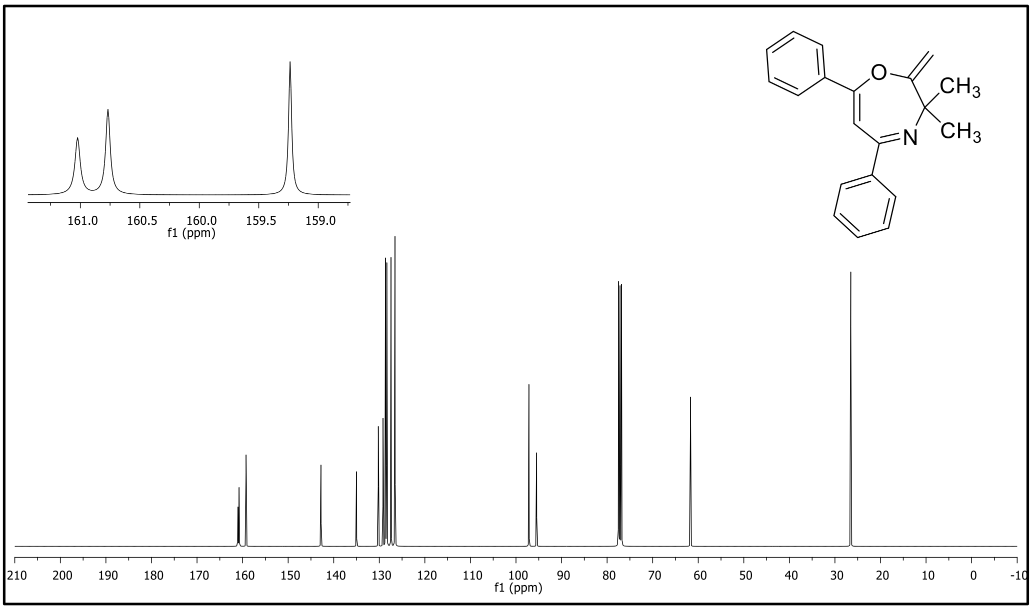

Figure A264. ^{13}C NMR spectrum of compound **86a.**

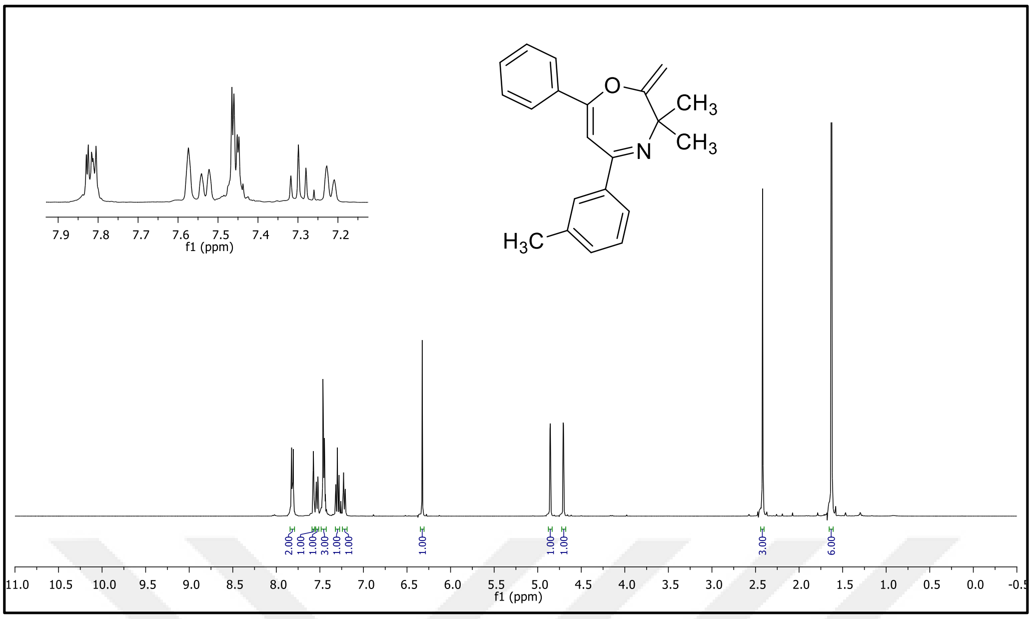

Figure A265. ^{1}H NMR spectrum of compound **86b.**

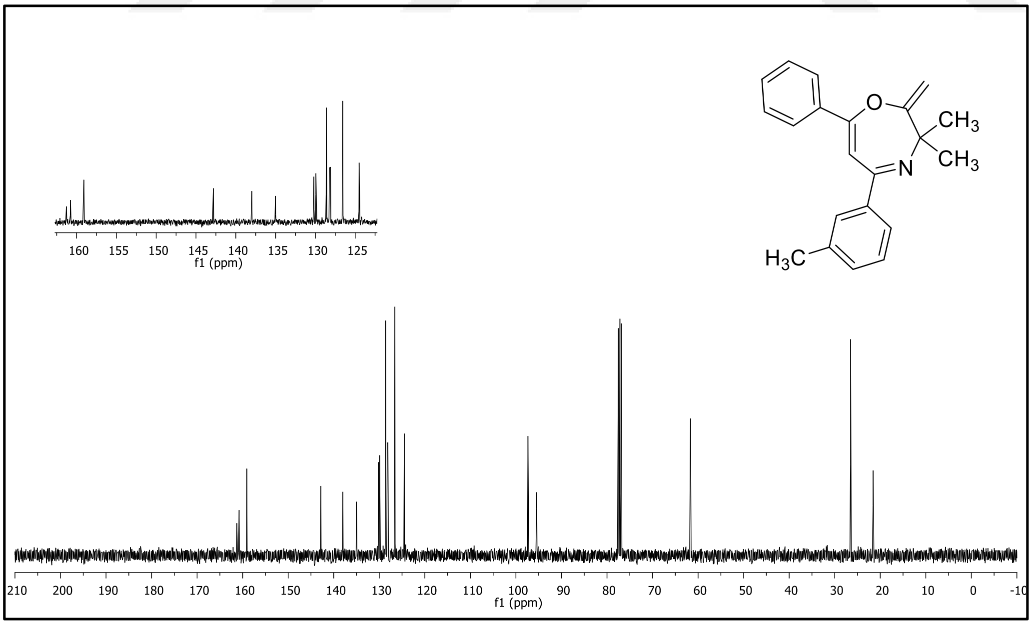

Figure A266. ^{13}C NMR spectrum of compound **86b.**

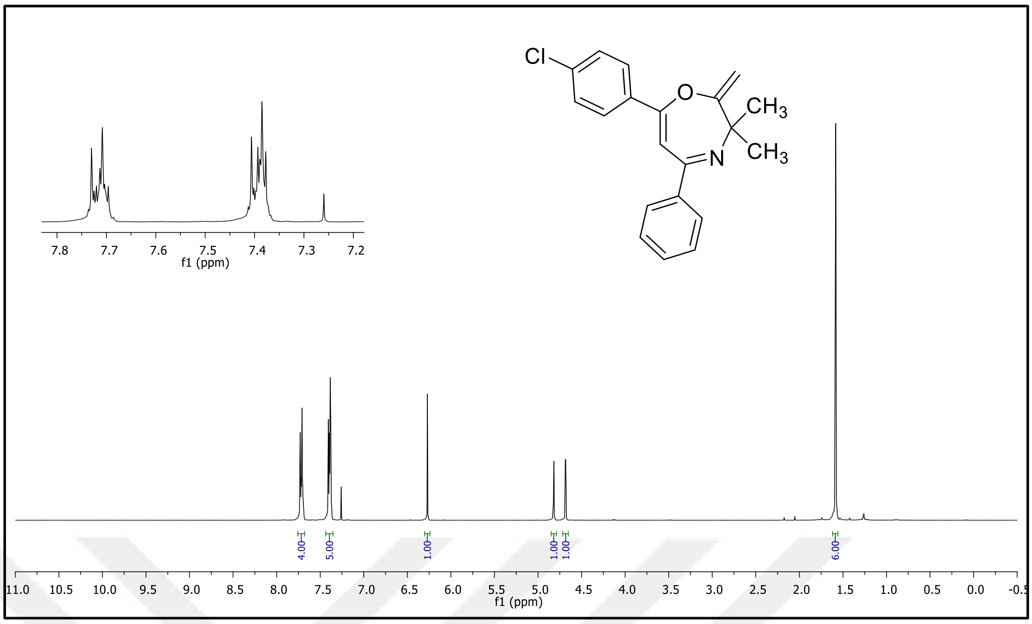

Figure A267. ^{1}H NMR spectrum of compound **86c.**

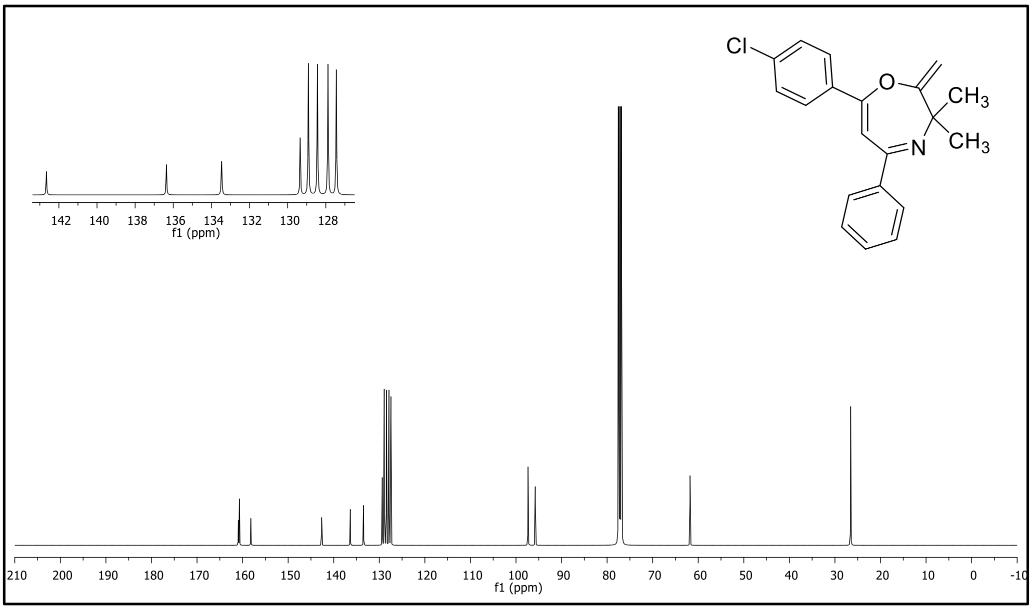

Figure A268. ^{13}C NMR spectrum of compound **86c.**

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PUBLICATIONS

1. Karadeniz, E.; Zora, M. One-Pot Synthesis of Spiro-2*H*-pyrroles from *N*-Propargylic β-Enaminones. *Synlett* **2019**, *30*, 1231. (DOI: 10.1055/s-0037-1611816)

2. Karadeniz, E.; Zora, M. Synthesis of 1-Azaspiro[4.5]deca-1,3-dienes from *N*-Propargylic β-Enaminones in Basic Medium**.** *Synthesis* **2019**, *51*, 2157. (DOI: 10.1055/s-0037- 1611723)

3. Karadeniz, E.; Zora, M. One-Pot Synthesis of 2-Ferrocenyl-substituted Pyridines. *Tetrahedron Lett.* **2016**, *57*, 4930. (DOI: 10.1016/j.tetlet.2016.09.080)

4. Karadeniz, E.; Kilicaslan, N.; Zora, M. Facile Synthesis of Aryl-substituted Pyridines via Suzuki-Miyaura Approach. *Tetrahedron*, **2015**, *47*, 8943. (DOI: 10.1016/j.tet.2015.09.063)

INTERNATIONAL CONFERENCE PROCEEDINGS

1. 255th American Chemical Society National Meeting, Synthesis of Spiro-Containing 1,4-Oxazepines from *N*-Propargylic β-Enaminones. 18-22 March 2018, New Orleans, USA. (*Poster presentation*)

2. 253rd American Chemical Society National Meeting, Synthesis of 1-Azaspiro[4.5]deca-1,3-dienes from *N*-Propargylic β-Enaminones. 2-6 April 2017, San Francisco, USA. (*Poster presentation*)

3. Anatolian Conference on Synthetic Organic Chemistry, ACSOC II, An Efficient and Single-Step Approach for the Synthesis of Ferrocenylpyridines. 21-24 March 2016, Kuşadası, Turkey. (*Poster presentation*)

4. Trans Mediterranean Colloquium on Heterocyclic Chemistry, TRAMECH VIII, One-Pot Synthesis of Ferrocenyl-Substituted Pyridines. 11-15 November 2015, Antalya, Turkey. (*Poster presentation*)

NATIONAL CONFERENCE PROCEEDING

1. 29. Ulusal Kimya Kongresi, Spiro-2*H*-pirol Türevlerinin Yeni Bir Metotla Sentezi. 10-14 September 2017, Ankara, Turkey. (*Poster presentation*)

2. 26. Ulusal Kimya Kongresi, Synthesis of 5-Iodopyridines via Electrophilic Cyclization of *N*-propargylic β-Enaminones. 1-6 October 2012, Muğla, Turkey. (*Poster presentation*)