

SYNTHESIS OF SPIRO-PYRROLOPYRIDAZINES

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ABSTRACT

SYNTHESIS OF SPIRO-PYRROLOPYRIDAZINES

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Heterocyclic molecules have great importance in organic chemistry due to their significant functions in very wide areas. Scientists tend to work on them because they exhibit excellent properties from medicine to material science. Especially, spiro class of heterocyclic molecules also have unique character among biological active compounds. Additon to spiro unit of molecules, fused systems also provide significant features to them. That's why, spiro and fused systems are always popular subjects among organic chemists.

In this thesis, the synthesis of a new family of heterotricyclic hybrids, spiro-pyrrolopyridazines, has been invetigated since such hybrid molecule may provide benefits for biological studies. With this aim, totally five steps were followed and 21 new derivatives of fused spiro-pyrrolopyridazines were synthesized with different electron-withdrawing and electron-donating groups.

Firstly, synthesis of α,β -alkynic ketones by Sonogashira cross coupling of terminal alkynes with benzoyl chlorides were performed. Secondly, cyclohexane-embedded

N-propargylic β -enaminones were obtained via conjugate addition of 1-ethynylcyclohexylamine to α,β -alkynic ketones. Thirdly, cyclohexane-embedded *N*-propargylic β -enaminones were exposed to second Sonogashira cross coupling reaction with the corresponding aryl iodides to yield arylated β -enaminone derivatives. Forthly, spiro-2*H*-pyrroles, which are the starting compounds for the last step, were produced by the reaction between arylated cyclohexane-embedded *N*-propargylic β -enaminones and Cs₂CO₃ in DMSO.

In the last step, a novel approach was enhanced for the synthesis of spiro-pyrrolopyridazines. For this purpose, spiro-2*H*-pyrroles with a 1,4-diketone group were treated with hydrazine monohydrate in refluxing *n*-butyl alcohol. At the final, 21 novel derivatives of previously unknown spiro-pyrrolopyridazine were synthesized in good to high yields.

Keywords: Pyrrolopyridazine, Pyridazine, Spiro-2*H*-pyrrole, *N*-Propargylic β -Enaminone

ÖZ

SPIRO-PIROLOPİRİDAZİNLERİN SENTEZİ

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Heterosiklik moleküller, çok geniş alanlardaki önemli işlevleri nedeniyle organik kimyada büyük öneme sahiptir. Bilim adamları, tıptan malzeme bilimine kadar mükemmel özellikler sergiledikleri için bunlar üzerine çalışma eğilimindedirler. Özellikle spiro sınıfı heterosiklik moleküller, biyolojik olarak aktif bileşikler arasında benzersiz bir karaktere sahiptir. Moleküllerin spiro birimlerine ek olarak, kaynaşmış sistemler de onlara önemli özellikler sağlar. Bu nedenle spiro ve kaynaşmış sistemler organik kimyacılar arasında her zaman popüler konulardır.

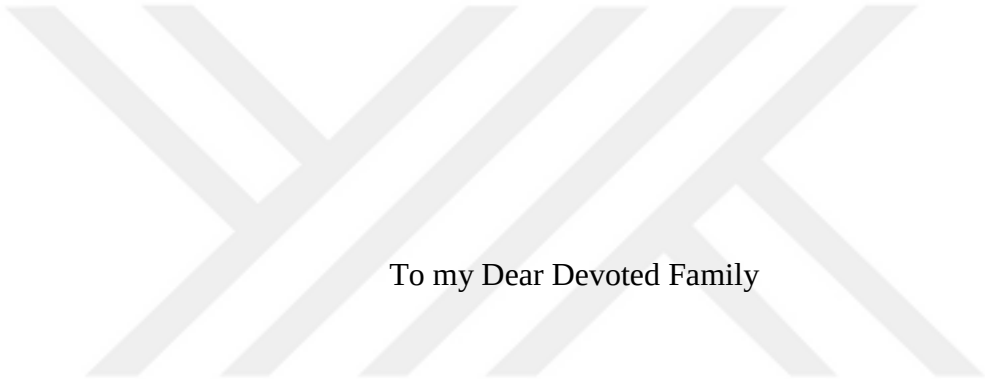
Bu projede, spiro-pirolopiridazinin sentezlenmesine odaklanıldı. Bu amaçla toplam beş adım izlendi ve spiro-pirolopiridazinin 21 yeni türevi, farklı elektron çeken ve elektron veren gruplarla birlikte sentezlendi.

İlk olarak, terminal alkinlerin benzoil klorür ile Sonogashira çapraz bağlanma reaksiyonu ile α,β -alkinik ketonların sentezi gerçekleştirildi. İkinci olarak, sikloheksan-gömülü *N*-propargilik β -enaminonlar, 1-etilnilsikloheksilaminin konjuge katılma reaksiyonu ile elde edildi. Üçüncü olarak, arillenmiş sikloheksan-gömülü *N*-propargilik β -enaminon türevlerini elde etmek için sikloheksan-gömülü *N*-propargilik β -enaminonlar çeşitli aril iyodürler ile ikinci Sonogashira çapraz

bağlanma reaksiyonuna maruz bırakıldı. Dördüncü olarak, arillenmiş β -enaminonlar ile Cs_2CO_3 , DMSO içinde reaksiyona sokularak, son aşamanın başlangıç maddeleri olan spiro-2*H*-piroller üretildi.

Projenin son aşamasında, spiro-pirolopiridazinlerin sentezi için yeni bir yaklaşım geliştirildi. Bu amaçla, 1,4-diketon gruplu spiro-2*H*-piroller, *n*-bütil alkol içinde kaynatılarak hidrazin monohidrat ile reaksiyona sokuldu. Final olarak, 21 yeni spiro-pirolopiridazin türevi iyi verimlerle elde edildi.

Anahtar Kelimeler: Pirolopiridazin, Piridazin, Spiro-2*H*-pirol, *N*-proparjilik β -enaminon



To my Dear Devoted Family

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LIST OF ABBREVIATIONS

ABBREVIATIONS

ATR	attenuated total reflection
NOESY	nuclear overhauser spectroscopy
IBX	2-iodobenzoic acid



CHAPTER 1

INTRODUCTION

Organic chemistry which concerns with carbon-containing molecules is one of the most important branch of chemistry. Although there are many elements in the periodic table, this field of chemistry focuses on compounds including carbon element. This is because carbon-containing molecules matters for living organisms.¹ For instance, DNA, RNA, aminoacids, enzymes that are significant for continuity of life include organic compounds. In addition to the natural neccesities of organic molecules, organic chemistry also plays very important role on everyone's lives from their clothing, computer screen to food preservation and drug that heal them.^{1,2} Thus, organic chemists have a wide range of subjects to work on. Organic molecules synthesized by them is placed in a wide variety of products such as dyes, drugs, poylmers, agrichemicals and many more. Therefore, organic chemistry concerns with many fields such as biochemistry, organometallic chemistry, material and polymer chemistry, and medicinal science.³

Organic chemistry can be classified into several sub-branches such as heterocyclic chemistry and organometallic chemistry. Heterocyclic chemistry investigates heterocyclic compounds which consist of at least one heteroatom in their ring skeleton. The most common heterocyclic compounds have five- or six-membered ring systems with nitrogen, oxygen and sulphur atoms.⁴ Heterocyclic compounds are very abundant in nature and many living organisms have them naturally.⁴ Nucleic acid bases of DNA and RNA, or chlorophyll and heme which are vital component for oxygen transportation in plants and animal, or aminoacids consist heterocyclic units.⁴ In Figure 1, some natural compounds include heterocyclic units are given.

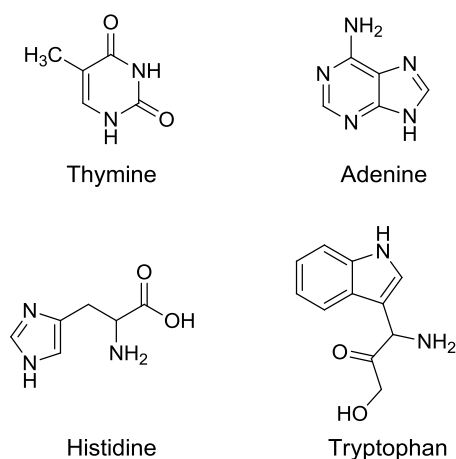


Figure 1. Examples of heterocyclic units present in natural compounds.

Besides heterocyclic compounds found in many natural compounds, they can be also synthesized in laboratory for application areas such as medicine, agriculture and material science. For example, according to the literature, more than 85% of biologically active compounds used in medicines include heterocyclic units in their systems.⁵ This fact shows us that heterocyclic compounds have central role in drug chemistry.

In Figure 2, some drugs containing heterocycles are given. For example, *Ganciclovir*,⁴ is used to treatment of cytomegalovirus infection, whereas *Cladribine*⁴ and *Pentostatin*⁴ is employed for the treatment of hairy cell leukaemia and multiple sclerosis.

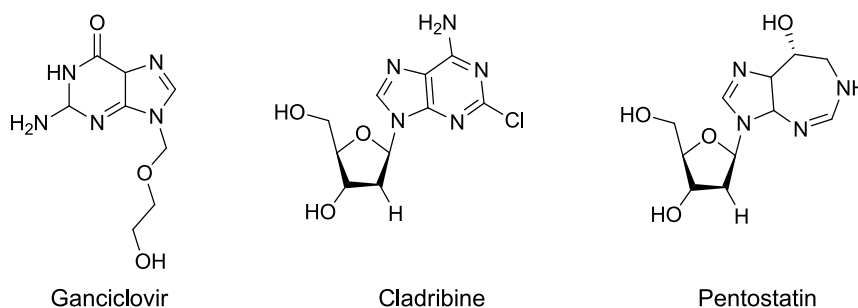


Figure 2. Examples of biologically active heterocyclic compounds.

In the light of some studies, it can be said that heterocyclic compounds made contribution to material science as well. For example, especially nitrogen containing ones show significant efficiency and operating voltage for creation of PHOLEDs (phosphorescent organic light-emitting diodes) to improve device performance.⁶

1.1 *N*-Propargylic β -Enaminones

N-Propargylic β -enaminones are key intermediates for synthesis of many heterocyclic compounds due to their high reactivity (Figure 3).⁷ These high reactivity comes from their enaminone conjugation. Enaminone conjugation provides to *N*-propargylic β -enaminones both electrophilic and nucleophilic character. Enone groups show electrophilic character, while enamine groups show nucleophilic character.⁸ That's why, they attract significant attention in synthesis of many organic compounds.

In fact, *N*-propargylic β -enaminones have a fascinating chemical structure since they consist of several functional groups such as alkene, alkyne, enone, enamine and enaminone (Figure 3). For this reason, *N*-propargylic β -enaminones have been used as a building blocks in many synthesis.⁹

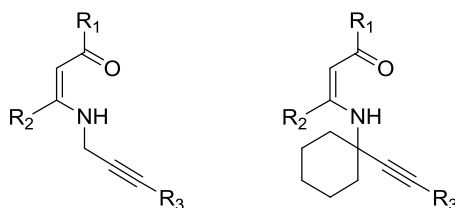


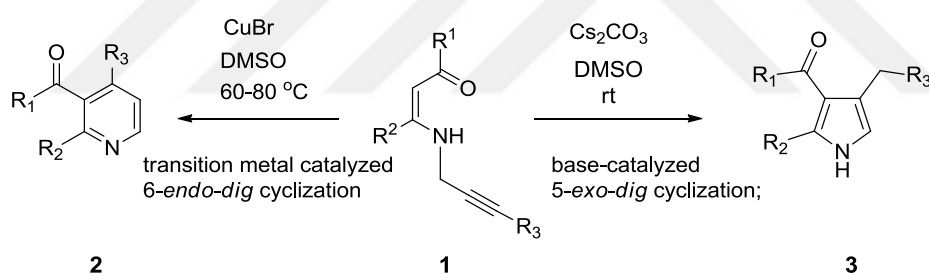
Figure 3. Structures of *N*-propargylic β -enaminones.

On the other hand, cyclohexane-embedded *N*-propargylic β -enaminones have been used to synthesize spiro compounds. Due to importance of spiro compounds, which will be explained in the later chapters of this thesis, cyclohexane-embedded *N*-propargylic β -enaminones are also preferable intermediates for organic synthesis.¹⁰

1.1.1 Reactions of *N*-Propargylic β -Enaminones

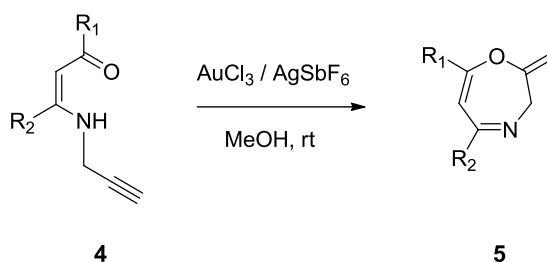
As mentioned before, *N*-propargylic β -enaminones are important intermediates for synthesis of many heterocyclic compounds such as pyrroles, 1-pyrroline, pyridines and 1,4-oxazepines.³ If literature is scanned, many studies, which are about transformation of *N*-propargylic β -enaminones to the corresponding heterocyclic compounds can be found. Some examples are given below.

In 2008, Cacchi and his research group worked on two important reactions of *N*-propargylic β -enaminones (Scheme 1).⁷ Treating *N*-propargylic β -enaminones with CuBr in DMSO, they obtained pyridine derivative through metal-catalyzed 6-*endo-dig* cyclization. On the other hand, using Cs₂CO₃ in DMSO, they synthesized the corresponding pyrrole derivative via base catalyzed 5-*exo-dig* cyclization. In fact, these reactions wide scientists' horizons about heterocyclic chemistry (Scheme 1).⁷



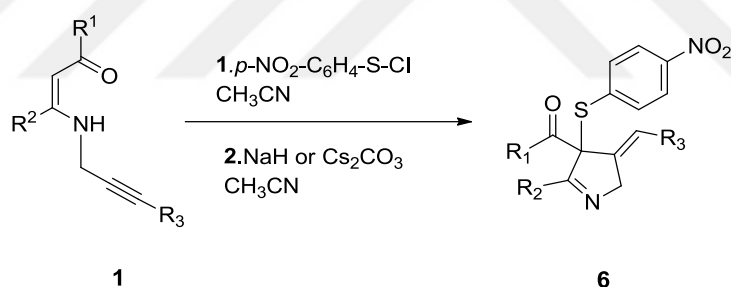
Scheme 1. Synthesis of the substituted pyridines and pyrroles.

Another important study were performed by Karunakar and co-workers in 2015 (Scheme 2).⁹ They introduced a new method to synthesize 1,4-oxazepines from *N*-propargylic β -enaminones. This method provided 1,4-oxazepines through a gold-catalyzed 7-*exo-dig* cyclization regioselectively (Scheme 2).⁹



Scheme 2. Synthesis of poly-substituted 1,4-oxazepines.

In 2020, Zora and his research group developed a new strategy for the synthesis of 1-pyrroline derivatives (Scheme 3).¹¹ After *N*-propargylic β-enaminones was treated with 4-nitrobenzenesulfonyl chloride in refluxing ACN, they obtained α-sulfonylated *N*-propargylic β-enaminones. Then, in the presence of appropriate bases such as sodium hydride and cesium carbonate, α-sulfonylated β-enaminones gave 4-methylene-3-[(4-nitrophenyl)thio]-1-pyrrolines by nucleophilic cyclization (Scheme 3).¹¹



Scheme 3. Synthesis of 4-methylene-3-[(4-nitrophenyl)thio]-1-pyrrolines.

1.2 Pyrroles

Pyrroles are one of the most important class of five-membered heterocyclic compounds consisting of one nitrogen atom in their ring skeleton. Their general formula is $\text{C}_4\text{H}_5\text{N}$. Pyrroles can be found in three different tautomeric forms; 1*H*-, 2*H*- and 3*H*-pyrroles (Figure 4). 1*H*-Pyrroles are aromatic compounds but the others not. In the earlier literature, 2*H*- and 3*H*-pyrroles named as isopyrroles and

pyrrolenines. Due to presence of the tetrahedral carbon in the ring, these two type pyrroles are not aromatic compounds.¹²

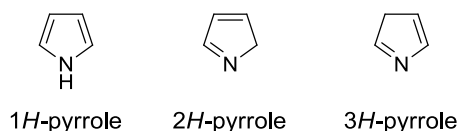
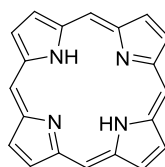


Figure 4. Three tautomers of pyrroles.

1.2.1 Importance of Pyrroles

Pyrrole-containing heterocycles have attracted great attention as consequence of their important role in biological systems and drug discovery.¹³ Of these heterocyclic compounds, the synthesis, reactions and biological activities of pyrrole-containing compounds have a wide range of research areas in heterocyclic chemistry. These molecules were found in many pharmaceutical and natural products¹⁴ such as vitamin B12, heme, chlorophyll, bacteriochlorin and porphine ring (Figure 5).¹⁵



Porphine

Figure 5. Structure of basic porphine ring.

Although pyrrole rings are found in many natural products,¹³ they also play active roles in numerous pharmaceuticals, which are served in market. For instance, *Calcimcyn* shows antibiotic properties against Gram positive bacteria and fungi, while *Ageliferin* has antibacterial properties (Figure 6). On the other hand, *Aloracetam* and *Atorvastatin* are used for treatment of Alzheimer's disease and dyslipidemia, respectively (Figure 6).¹⁵

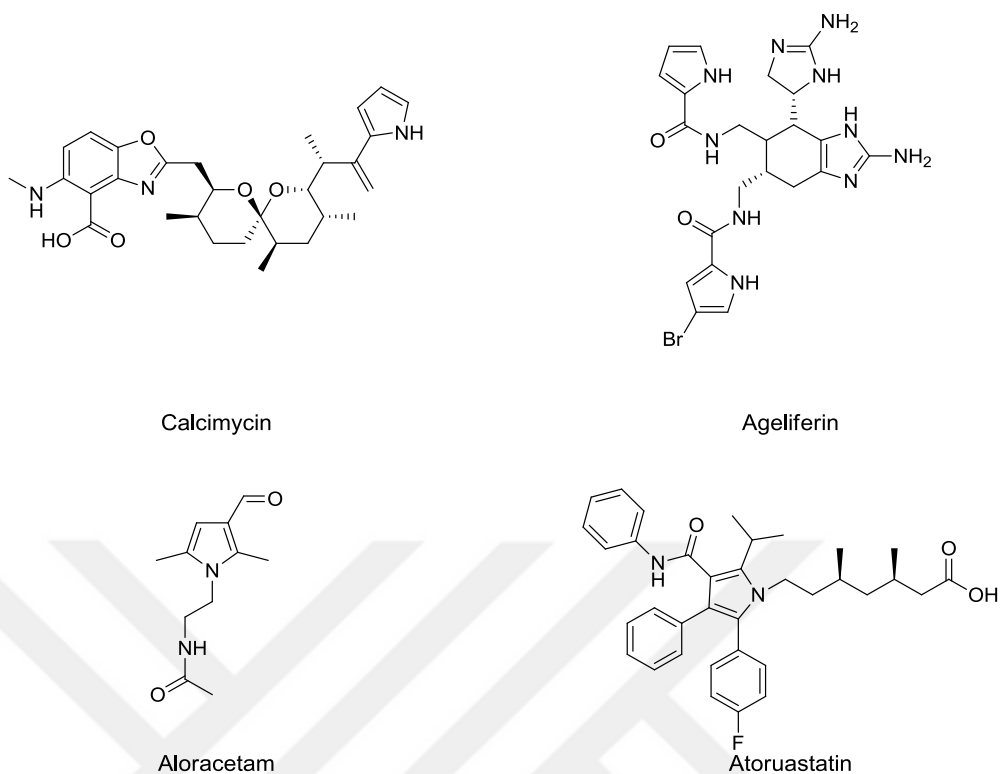


Figure 6. Examples of pyrrole-containing pharmaceuticals.

1.2.2 Spiro-Based Heterocyclic Compounds

In spiro-based heterocyclic systems, two different rings share one carbon atom, which has attracted great attention. Due to their asymmetric nature, they carry significant criteria for the biological activities.¹⁶

In fact, they show unique 3D structural properties and this provide to them rigidity. These intrinsic properties of spiro systems offer several advantages to drug development process. Also, rigidity of spiro compounds is beneficial for designing 3D orientation of the core with maximum H-bonding, hydrophobic and π -stacking interactions.¹⁷

Examples of some drugs that contain spiro parts are given in Figure 7. *Buspirone*¹⁸ has antianxiolytic role while *Ibesartan*¹⁹ is used for cardiovascular disease.

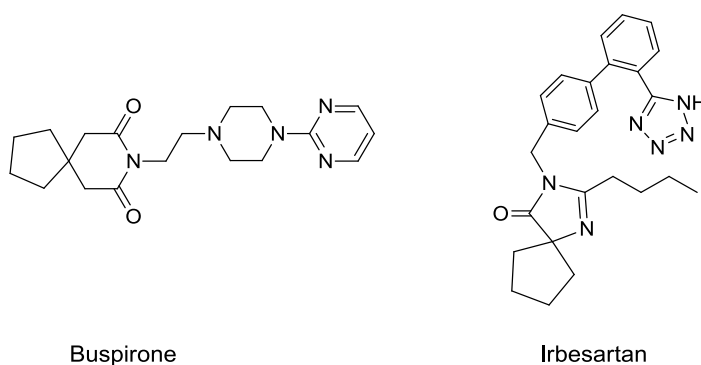
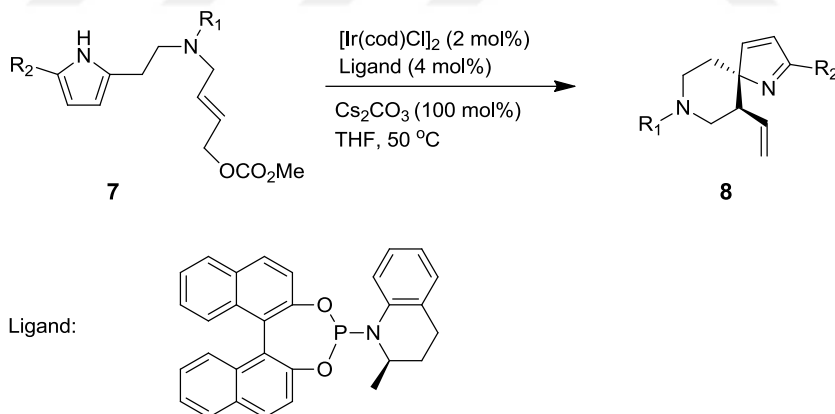


Figure 7. Structures of some medicines including spiro units.

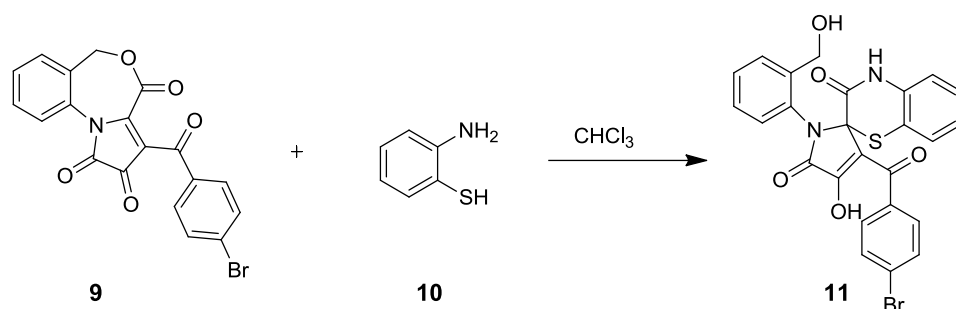
1.2.3. Synthesis of Spiro Pyrroles

In literature, there are many methods for the synthesis of spiro-pyrroles, such as You's work. In the study of You and his co-workers, it was shown that from allylic carbonate-tethered pyrrole, spiro-2*H*-pyrrole derivatives were obtained by using $[\text{Ir}(\text{cod})\text{Cl}]_2$ and a BINOL-derived phosphoramidite ligand.²⁰



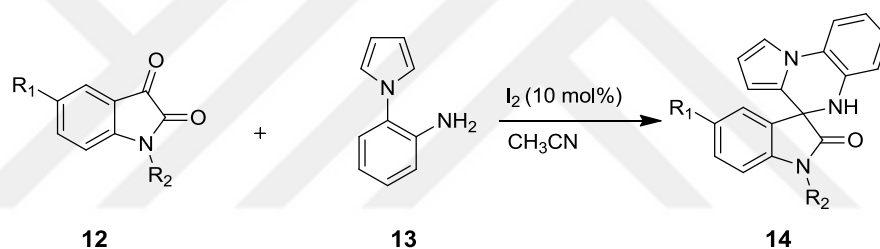
Scheme 4. Synthesis of a spiro compound from allylic carbonate-tethered pyrroles.

Another study was performed by Maslivets and his group. To synthesize 2*H*-spiro pyrroles, they treated the corresponding pyrrole compounds with 2-aminobenzenethiol in chloroform, which was shown in Scheme 5.²¹



Scheme 5. Synthesis of spiro-2*H* pyrrole derivatives

In 2013, Alizadeh and his colleagues developed a new method to synthesize spiro[indoline-3,4-pyrrolo[1,2-*a*]quinoxalin]-2-ones.²² In this strategy, different isatins and *N*-(2-aminophenyl)pyrrole that are mediated by iodine were used in CH₃CN as shown in Scheme 6.²²



Scheme 6. Synthesis of spiro[indoline-3,4-pyrrolo[1,2-*a*]quinoxalin]-2-ones.

1.3 Pyridazines

Pyridazines are important six-membered heterocyclic compounds. They are also aromatic compounds. Pyridazines are members of the diazine groups that are formed by replacement of two carbon atoms of benzene with nitrogen atoms. Three different isomeric forms of diazines exist as depicted shown in Figure 8. There are 1,2, 1,3 and 1,4 relationship among them with respect to the position of nitrogen atoms. They are named as like pyridazine (1,2-diazine), pyrimidine (1,3-diazine), pyrazine (1,4-diazine), respectively.²³

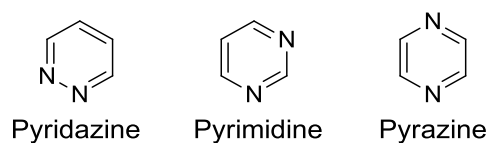


Figure 8. Three isomeric forms of diazine.

Moreover, pyridazine has planarity and it shows two resonance hybrid structures. They are represented as 1a and 1b (Figure 9). Among these two structure, 1a has greater contribution than 1b. This result supported by studies in microwave spectroscopy, electron diffraction and X-ray crystallography and it indicates that bond between two nitrogen atoms has single bond character.²³



Figure 9. Two resonance hybrid structure of pyridazine.

1.3.1 Importance of Pyridazines

Heterocyclic compounds that have pyridazine as a core unit attract significant attention because pyridazine provides them varies types of properties from medicinal chemistry²⁴ to agricultural fields.²⁵ Pyridazines present many different priviledges for using them as a main scaffold⁴ when they are compared with their carbon analogues. In fact, pyridazine patterns are most commonly used instead of phenyl units²⁶.

According to GlaxoSmithKline researchers, compounds contain pyridazine are one of the most improvable heterocyclic compound for drug design because pyridazines offer excellent biological activities due to its features such as H-bonding and solubility.^{26,27} For instance, moiety of two nitrogen atoms in pyridazine ring can perform H-bonding effectively by comparison with same carbocycles.^{26,28}

Another possibility that is provided by pyridazine is an isosteric replacement by phenyl or pyridines.²⁶ By this way, biological activity or toxicity can be changed positively for drug development.²⁶ In industry, several drug molecules found as free bases and this situation made them oily with low melting point.²⁶ Due to this, they are not water-soluble molecules. However, by applying isosteric replacement, it is possible that obtaining water-soluble and solid biological active molecules.²⁶ One example is given in Figure 10.



Figure 10. Replacement of pyridine moiety with pyridazine unit.

For instance, as shown in above Figure 10, if pyridine is replaced with pyridazine unit, solubility of the molecule increases.^{26,28} Another example shows that using pyridazine unit in bioactive molecules makes them more developable²⁶. *Minaprine*^{24,26}, used as antidepressant, is a base with oily, water-insoluble form. But, thanks to pyridazine part of it, it can be converted salt form to make water-soluble solid.^{26,28} (Figure 11).

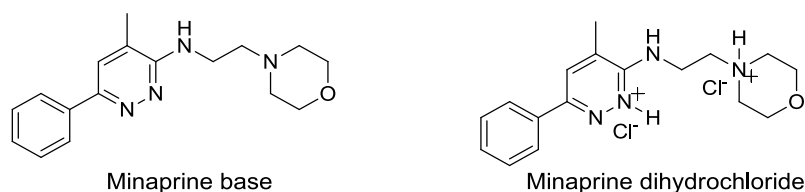


Figure 11. Difference between base and salt form of *Minaprine*.

Heterocyclic molecules that contain nitrogen atom, especially pyridazine, present in both natural and synthetic compounds commonly owing to its biological activity.^{27,29} Thus, it is significant molecule for medicinal scientists.²⁹

Moreover, these molecules have several roles in drug chemistry²⁷ and medicinal chemistry as building blocks.³⁰ For example, *Cadralazine*^{24,31} is used to regulate blood pressure while *Hydralazine*^{24,32} is used for treatment of chronic congestive heart failure (Figure 12).

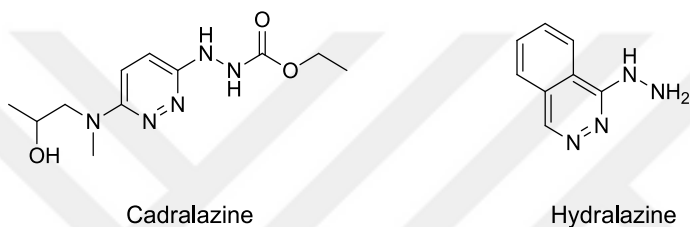


Figure 12. Pyridazine-containing drugs.

Although pyridazine frameworks are employed in drug development as key structure, they are also very commonly used in agricultural field.³⁰ According literature, *Norflurazon*³⁰ and *Chloridazon*³⁰ are important chemicals for crop protection (Figure 13). They are used for mono- and dicotyledonous weeds in cotton and used as pre-emergent herbicides, respectively. With the same way, another beneficial product that has been improved is *Propyrisulfuron*.³⁰ which is significant for controlling sulfenylurea-resistant weeds in rice (Figure 13).

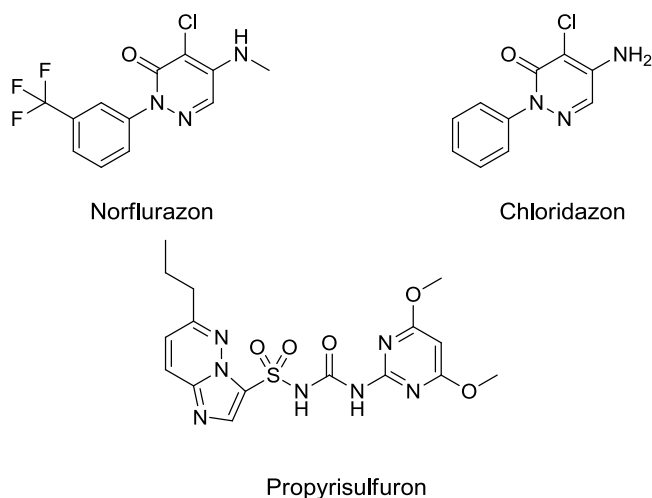


Figure 13. Agricultural compounds with pyridazine moieties.

1.3.2 Fused Pyridazines

Heterocyclic compounds that include nitrogen atoms are significant intermediates for the synthesis of fused molecules.²⁷ That's why, many scientists have focuses on synthesizing fused heterocycles due to their excellent features such as biological activity²⁷ and fluorescent activity.³³

In the literature, pyrrolo- and pyridazine-fused molecules are very common separately. However, fused pyrrolo-pyridazine skeleton is not very widespread, although it is also very important unit for medicinal research.³⁴ For example, they offer anti-cancer activities³⁴. In Figure 14, two of them are exemplified.

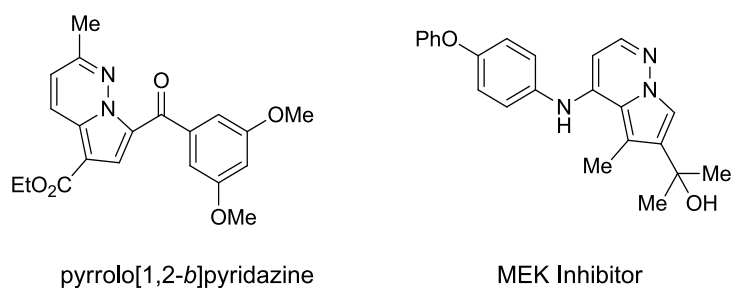


Figure 14. Biologically active fused-pyridazine compounds.

Moreover, fused pyrrolopyridazines have fluorescent activities so they can be used in sensors, lasers, and semiconductor devices.³³ For instance, pyrrolo[1,2-*b*]cinnolines shows excellent luminiscence properties (Figure 15).³³



Figure 15. Structure of pyrrolo[1,2-*b*]cinnolines.

Furthermore, fused pyridazines can be classified into two groups²⁷. The first class contains bridgeshead nitrogen atom (Figure 16).²⁷ On the other hand, second class has fused 5- or 6-membered ring without bridgehead nitrogen atom.²⁷ Generally, 5-membered ring are fused to pyridazine ring (Figure 16).²⁷

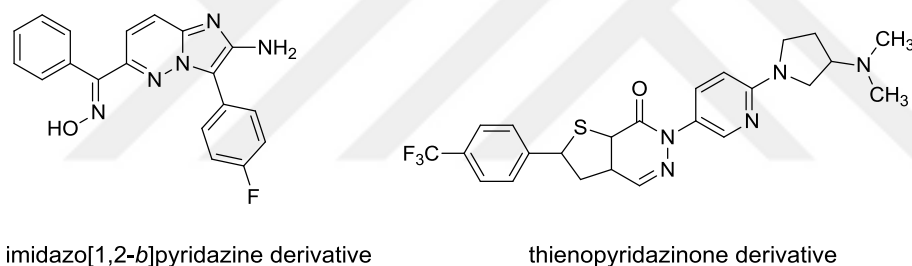


Figure 16. Different fused pyridazine molecules.

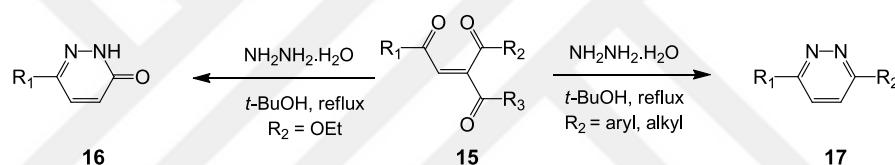
As depicted in Figure 16, imidazo[1,2-*b*]pyridazine and thienopyridazinone derivatives can be given as examples for these two groups. The first one is active molecule against human picornaviruses and the other one is used as anorectic agents.²⁶

All of these remarkable specialities offer to study in several fields and these results are adequate to work with pyridazine.

1.3.3 Synthesis of Pyridazines

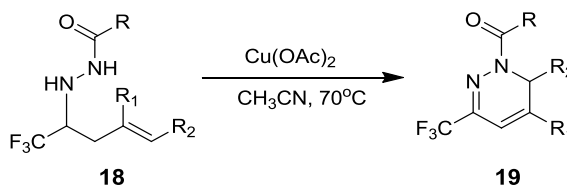
Among organic chemists, exploring new methods for the synthesis of pyridazine derivative is very challenging due to its important properties and utility in many different fields. In literature, there are many examples about how pyridazine or fused-pyridazine systems can be obtained.

As our precursor study, in 2012, Wu and his research group investigated C-C cleavage surprisingly during the reactions of 1,3-dicarbonyl compounds and methyl ketones with hydrazine hydrate and *t*-BuOH at reflux (Scheme 7).³⁵ In the result of reaction, they got 3,6-diarylpyridazines and 6-arylpyridazin-3-ones as condensation products after cleavage of benzoyl group without using metal.³⁵



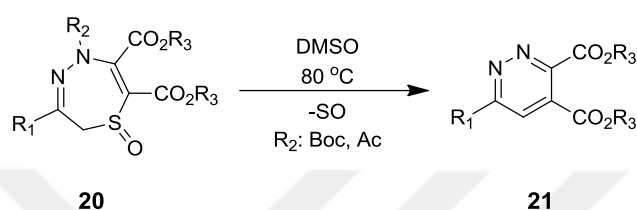
Scheme 7. C-C cleavage and synthesis of pyridazine and pyridazinone derivatives

In 2020, Hu and their colleagues worked on the transformation of trifluoromethylated *N*-acylhydrazines to 1,6-dihydropyridazines in the presence of $\text{Cu}(\text{OAc})_2$ (Scheme 8).³⁶ Their goal in this study was to synthesize target product with aggregation-induced emission properties.³⁶



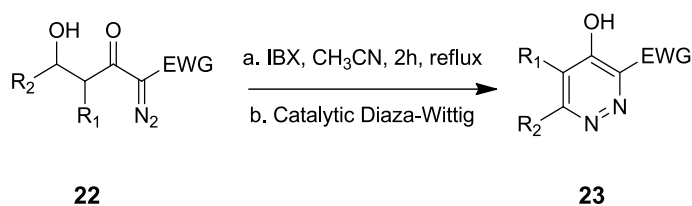
Scheme 8. Cyclization of trifluoromethylated *N*-acylhydrazines

Another study was performed by Zhai and his research group in 2020 by employing ring contraction of 2,5-dihydro-1,4,5-thiadiazepine S-oxides (Scheme 9).³⁷ During the course of reaction, they only used heat and an appropriate solvent that gave the best yield.³⁷ In the result of reaction, they obtained pyridazine derivative with ring contraction, an important way to get small rings.³⁷



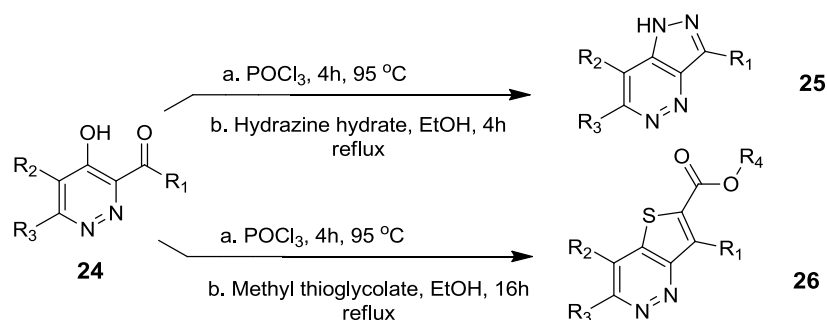
Scheme 9. Ring contraction of 2,5-dihydro-1,4,5-thiadiazepine S-oxides.

In 2014, Herdewijn and members of his research group designed an interesting strategy for the synthesis of pyridazine derivatives by using intramolecular Diaza-Wittig reaction.³⁷ They achieved getting their target molecule by using catalytic amount of organophosphorus reagent with innovative and safe way (Scheme 10).³⁸



Scheme 10. Diaza-Wittig reaction with organophosphorus reagent.

After synthesizing functionalized pyridazine derivative, Herdewijn research group developed other alternatives for the synthesis of fused pyridazine derivatives.²⁷ They achieved to obtain a variety of fused pyridazine derivatives with different heterocyclic rings (Scheme 11).²⁷



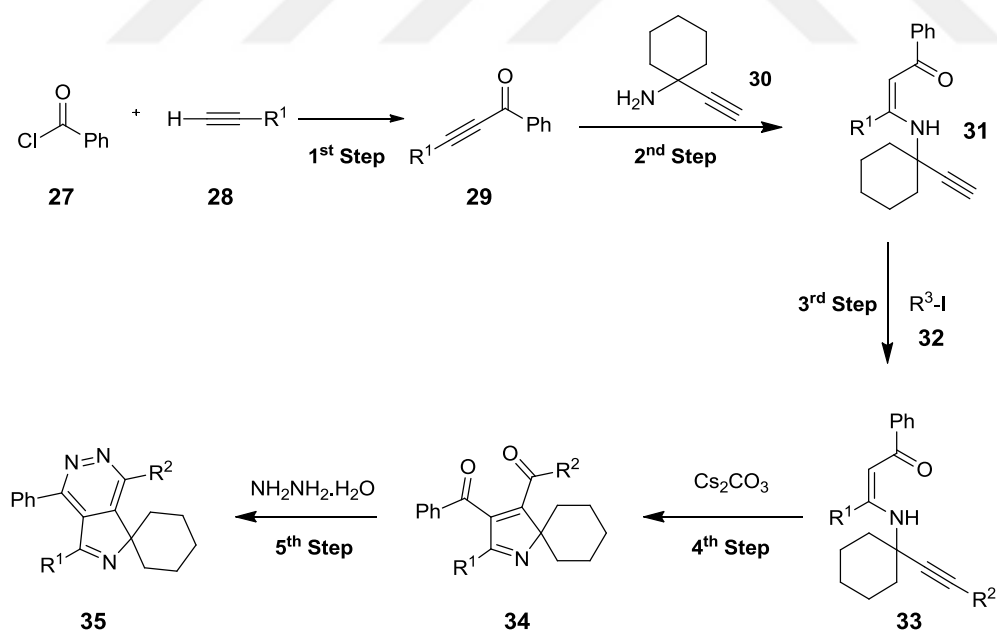
Scheme 11. Two example methods for the synthesis of fused pyridazine derivatives.

Notably, in Scheme 11, two strategies were shown to obtain biheterocyclic pyridazine molecules. In the first way, they used POCl_3 and then hydrazine hydrate to get pyrazolo[4,3-*c*]pyridazine derivative.²⁷ On the other hand, in the second alternative, they treated starting compound with POCl_3 and methyl thioglycolate, respectively and finally, they reached to their another target compound which is a thieno[3,2-*c*]pyridazine derivative.²⁷

1.4 Aim of Study

As mentioned before, five- and six-membered nitrogen containing heterocyclic compounds have great significance for organic synthesis due to their privileged properties. In fact, especially, *N*-propargylic β -enaminones are key starting materials to obtain many heterocyclic molecules. They can be used to yield pyrroles, pyridines, dihydropyridines and 1,4-oxazepines and many more under appropriate conditions.³⁹ These synthesized molecules can be functionalized with different substituted groups. After using *N*-propargylic β -enaminones as intermediates for obtaining pyrroles for example, they can be also used for further functionalization. The aim of this study is to create new approaches for synthesis of five- and six-membered fused heterocyclic compounds by intramolecular cyclizations and condensation reaction of 2*H*-pyrroles.

In this study, our goal is to synthesize fused spiro-pyrrolopyridazine **35** derivatives starting from spiro-2*H*-pyrroles **34** with 1,4-diketone unit. For this purpose, we have planned several steps. The first step was synthesis of α,β -alkynic ketones **29** by Sonogashira cross coupling of benzyl chlorides **27** with terminal alkynes **28**. In the second step of study, our aim was synthesis of cyclohexane embedded *N*-propargylic β -enaminones **31** by the reaction of 1-ethynylcyclohexylamine **30** and ketones **29** in methanol. In the third step, we thought performing Sonogashira cross coupling reaction of **31** with aryl iodides to obtain arylated β -enaminones **33**. This step has allowed further functionalization of β -enaminones **33**. Then, in the fourth step, our aim was to get spiro-2*H*-pyrroles **34** with 1,4-diketone group by reaction between arylated β -enaminones **33** and Cs_2CO_3 in DMSO. In the final step, using hydrazine monohydrate, it was planned that developing new methodology for the synthesis of novel class of fused spiro-pyrrolopyridazine **35** molecules from spiro-2*H*-pyrroles **34** (Scheme 12).



Scheme 12. Steps for the synthesis of fused spiro-pyrrolopyridazines.

In summary, in this thesis, the synthesis of the necessary starting materials spiro-2*H*-pyrroles **34** via intermediary of compounds **29**, **31** and **33**, and the condensation reactions of spiro-2*H*-pyrroles **34** with hydrazine hydrate leading to a new family of previously unknown heterotricyclic hybrids, namely spiro-pyrrolopyridazines **35**, will be discussed in detailed. Moreover, optimization studies, substrate scope and mechanism of the spiro-pyrrolopyridazine-producing reaction will be examined in detail.

It is hoped that these heterocyclic hybrids may show potential for enhanced and totally new biological activities, as compared to parent heterocyclic compounds which form these hybrids. Biological activity studies of spiro-pyrrolopyridazines **35** are out of the subject of this thesis.

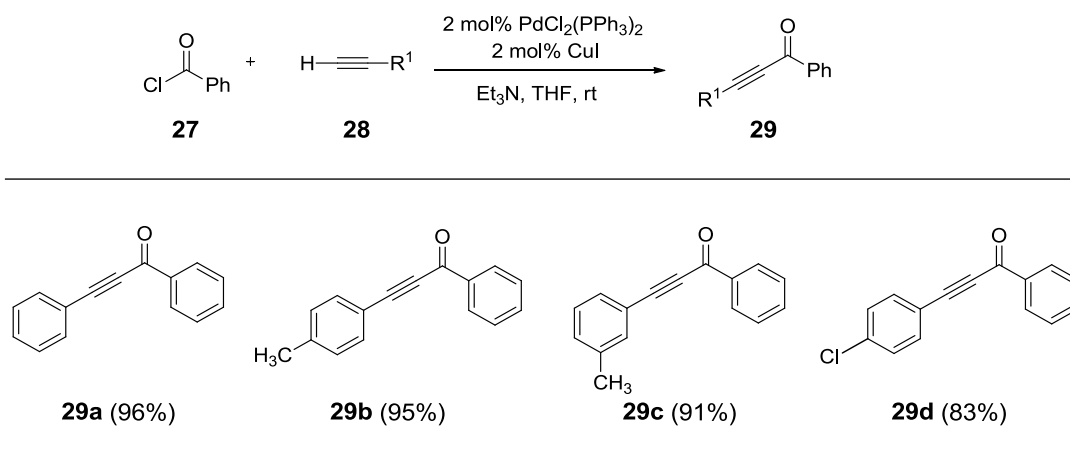
CHAPTER 2

RESULT AND DISCUSSION

2.1 Synthesis of α,β -Alkynic Ketones **27**

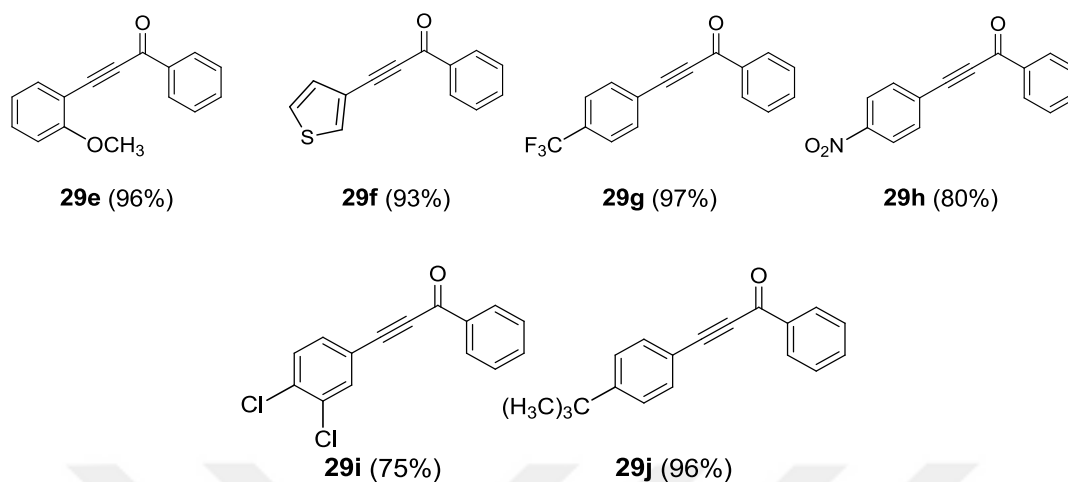
In the first part of the thesis, α,β -alkynic ketones **27** were synthesized by Sonogahira cross-coupling between benzoyl chlorides and terminal alkynes **28** (Table 1).^{41,42,43} This reaction was performed by Et₃N in THF using PdCl₂(PPh₃)₂, CuI and reaction was carried out at room temperature under argon atmosphere. As a result of this coupling reaction, we obtained 10 derivatives of α,β -alkynic ketones **27** with different yields that range from 75% to 97%, which are shown in Table 1. To diversify derivatives, different electron-withdrawing and electron-donating groups were used as substituent.

Table 1. Synthesis of α,β -alkynic ketones **27**.^a



^aIsolated yields.

Table 1. Continued.^a



^aIsolated yields.

The structures of the synthesized α,β -alkynic ketones were proven by their ^1H and ^{13}C NMR spectra. As an example, ^1H and ^{13}C NMR spectra of compound **29a** are shown in Figures 17 and 18, respectively. ^1H spectrum of 1,3-diphenylprop-2-yn-1-one (**29a**) shows that aromatic ten hydrogens of two phenyl groups are seen between 7.42 and 8.27 ppm (Figure 17). In Figure 18, ^{13}C NMR spectrum of **29a** indicates that aromatic carbons of phenyls give peaks between 120.11 and 136.89 ppm, while signal of carbonyl carbon appears at 178.00 ppm. Also, peaks of two alkynic carbons are clearly seen at 86.94 and 93.15 ppm.

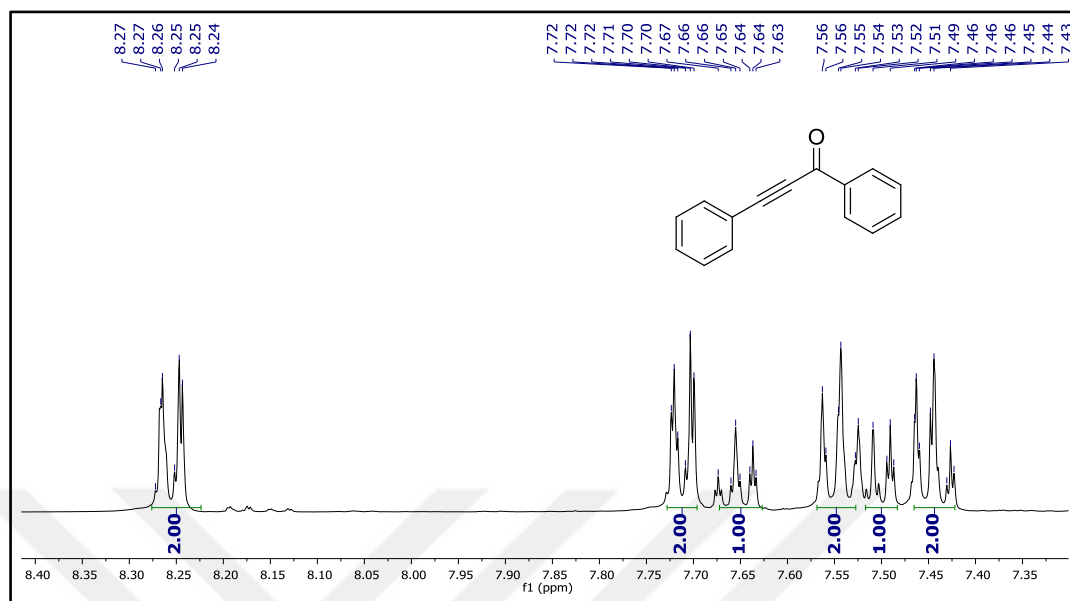


Figure 17. ¹H NMR spectrum of compound 29a.

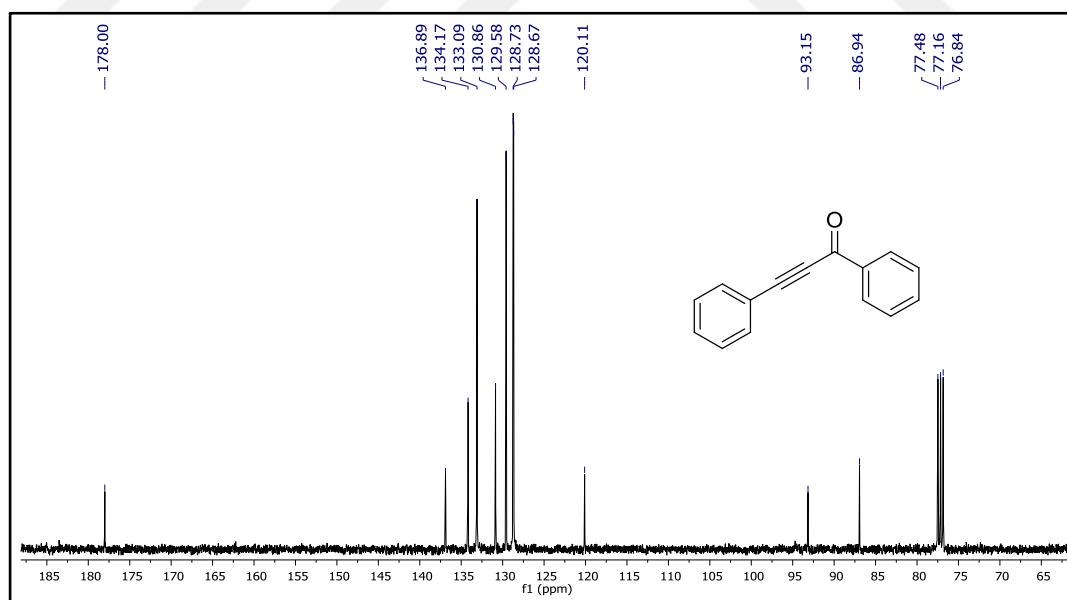


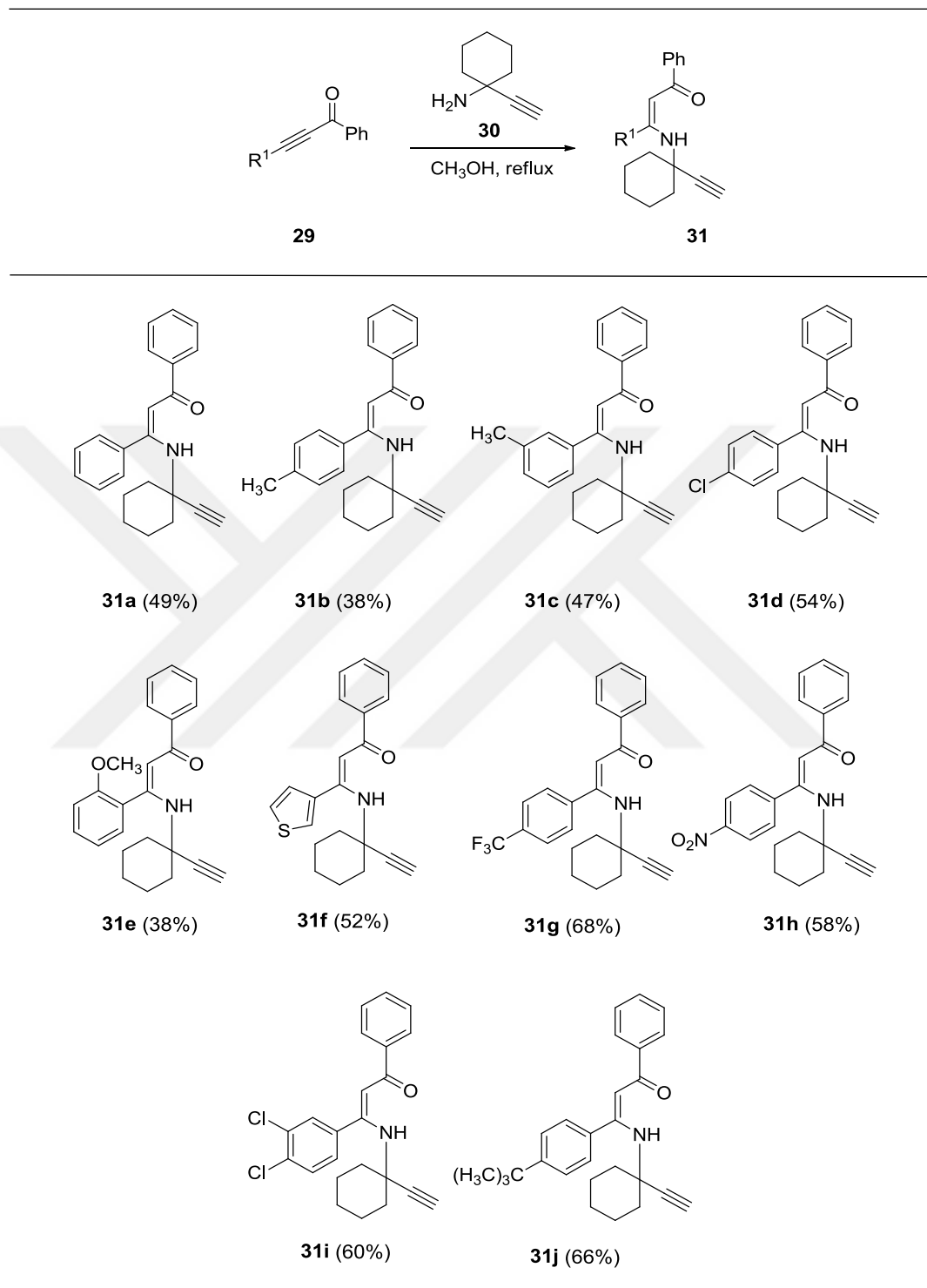
Figure 18. ¹³C NMR spectrum of compound 29a.

2.2 Synthesis of Cyclohexane-Embedded *N*-Propargylic β -Enaminones **31**

After synthesizing α,β -alkynic ketones **29**, we prepared *N*-propargylic β -enaminone derivatives **31** (Table 2).⁴⁰ Conjugate addition of 1-ethynylcyclohexylamine (**30**) to α,β -alkynic ketones **29** afforded the expected cyclohexane-embedded *N*-propargylic β -enaminones **31**. Reaction was performed in refluxing methanol under argon for approximately 17-18 hours. From this reaction, 10 derivatives of cyclohexane-embedded *N*-propargylic β -enaminones **31** were obtained in 38-68% yields (Table 2).⁴⁰

The significant point to mention here is that only single isomers of *N*-propargylic β -enaminone have been obtained. Cacchi⁷ and Zora⁴¹ research groups have proved the formation of only (*Z*) isomer of β -enaminones **31** with NOESY experiments. These experiments have indicated that there is an intramolecular H-bonding between amine hydrogen and carbonyl oxygen. That's why, throughout this step, only *Z*-isomers of cyclohexane-embedded *N*-propargylic β -enaminones **31** have been synthesized.

Table 2. Synthesis of cyclohexane-embedded *N*-propargylic β -enaminones **31**.^a



^aIsolated yields.

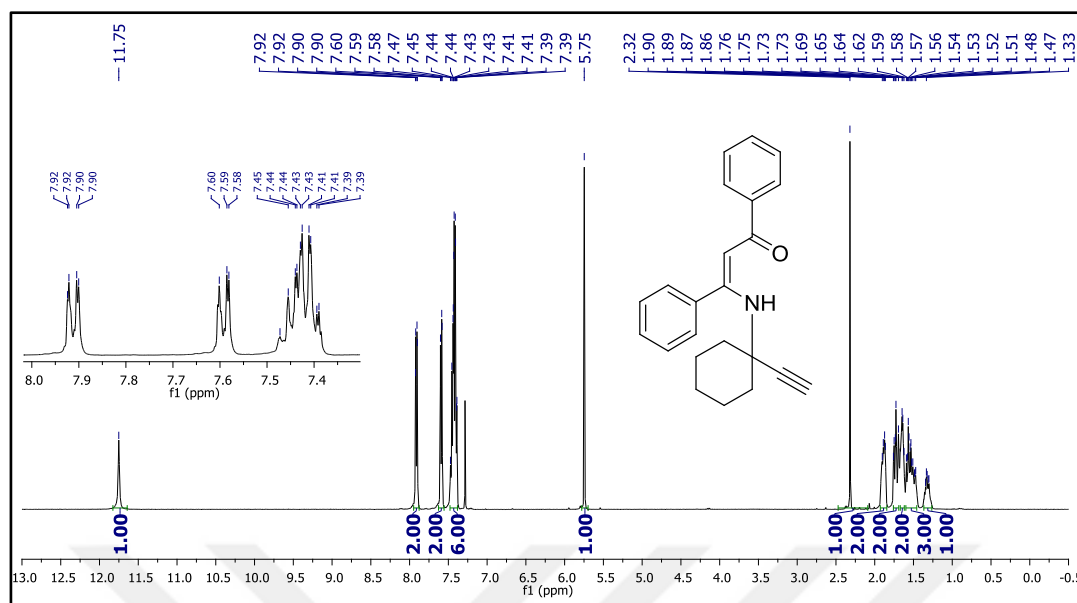


Figure 19. ^1H NMR spectrum of compound **31a**.

^1H NMR spectrum of 3-((1-ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**31a**) is shown in Figure 19. According to this spectrum, we can see that hydrogens of cyclohexyl group give peaks between 1.33-1.90 ppm, whereas aromatic hydrogens of phenyl groups appear at 7.39-7.92 ppm. Moreover, amine hydrogen gives a singlet peak at 11.75 ppm, while vinylic hydrogen resonates at 5.75 ppm and alkynyl hydrogen gives signal at 2.32 ppm (Figure 19).

In Figure 20, ^{13}C NMR spectrum of compound **31a** shows that carbon signals of cyclohexyl part appear at high field (22.21 25.00, 39.85 and 53.64 ppm). Also, β -carbon and carbonyl carbon gives peak at 166.70 and 188.61 ppm, respectively. Signals of two alkynyl carbons appear at 73.55 and 86.58 ppm while α -carbon resonates at 96.29 ppm. Remaining aromatic peaks are belong to phenyl groups which ranges from 127.22 to 140.15 ppm (Figure 20). All of these data clearly proves the formation of 3-((1-ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**31a**).

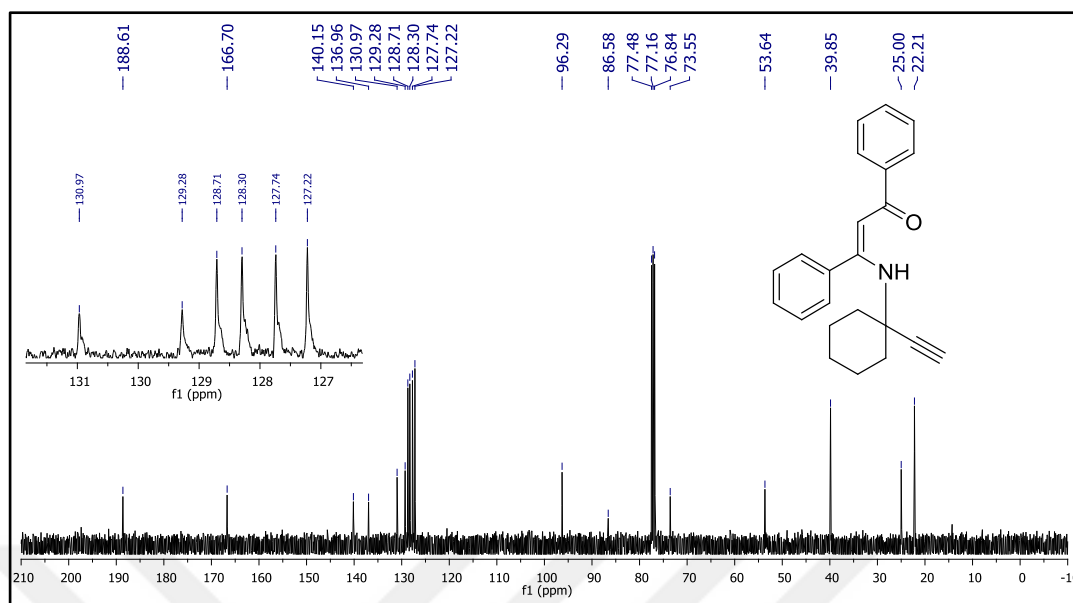


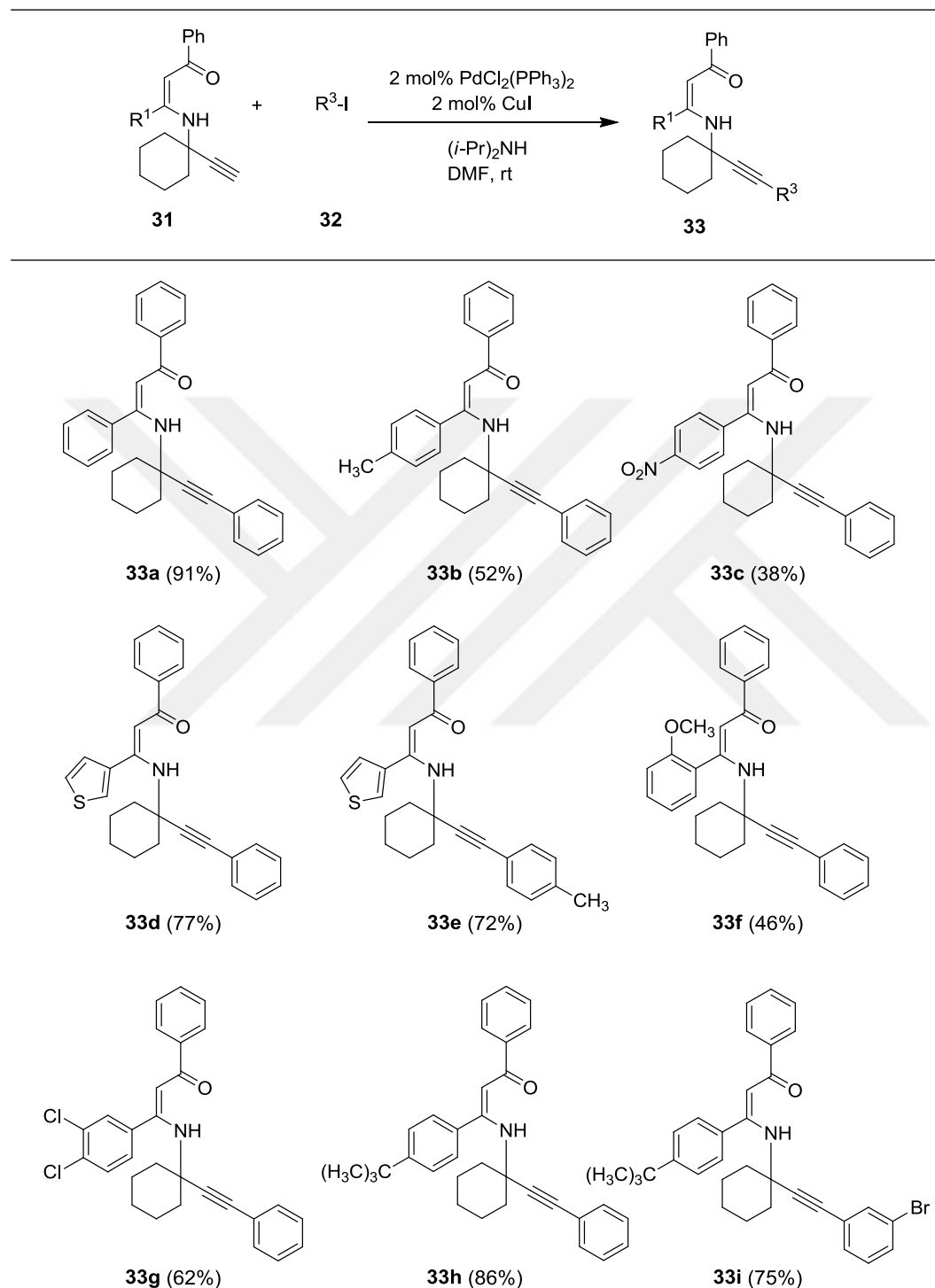
Figure 20. ¹³C NMR spectrum of compound **31a**.

2.3 Synthesis of Arylated Cyclohexane-Embedded *N*-Propargylic β -Enaminones **33**

For the further functionalization, all of the synthesized cyclohexane-embedded *N*-propargylic β -enaminones **31** were reacted with aryl iodides according to Sonogashira cross-coupling reaction (Table 3).^{10,41,42,43} Coupling reaction was carried out in the presence of Pd and Cu catalysts at room temperature. Also, (*i*-Pr)₂NH was used as a base in DMF and reaction was performed under argon. As a result of this reaction, totally 21 (16 of them are new) derivatives of arylated cyclohexane-embedded *N*-propargylic β -enaminones **33** were synthesized in 38-86% yields which is given in Table 3.

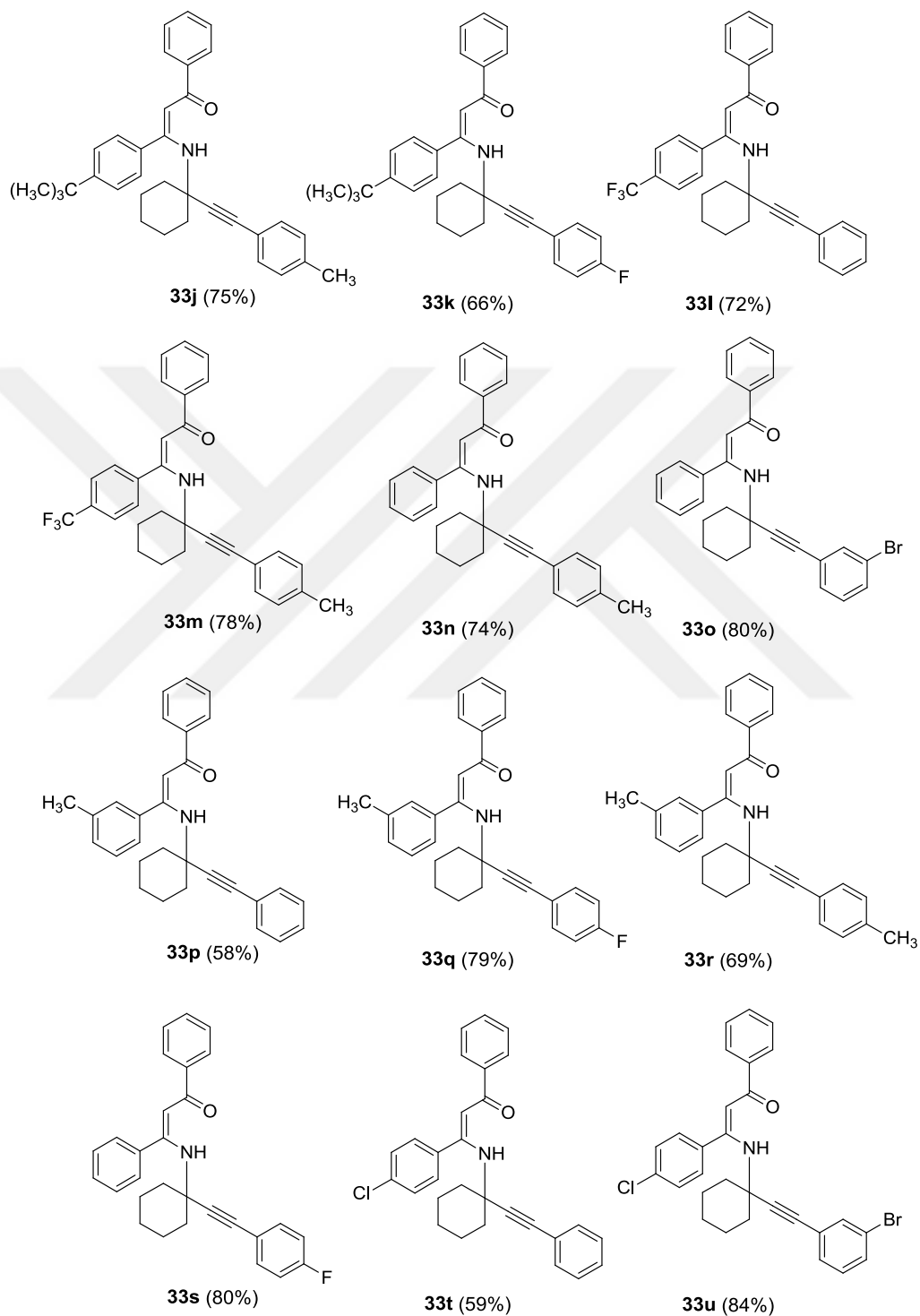
Table 3. Synthesis of arylated cyclohexane-embedded *N*-propargylic β -enaminones

33.^a



^aIsolated yields.

Table 3. Continued.^a



^aIsolated yields.

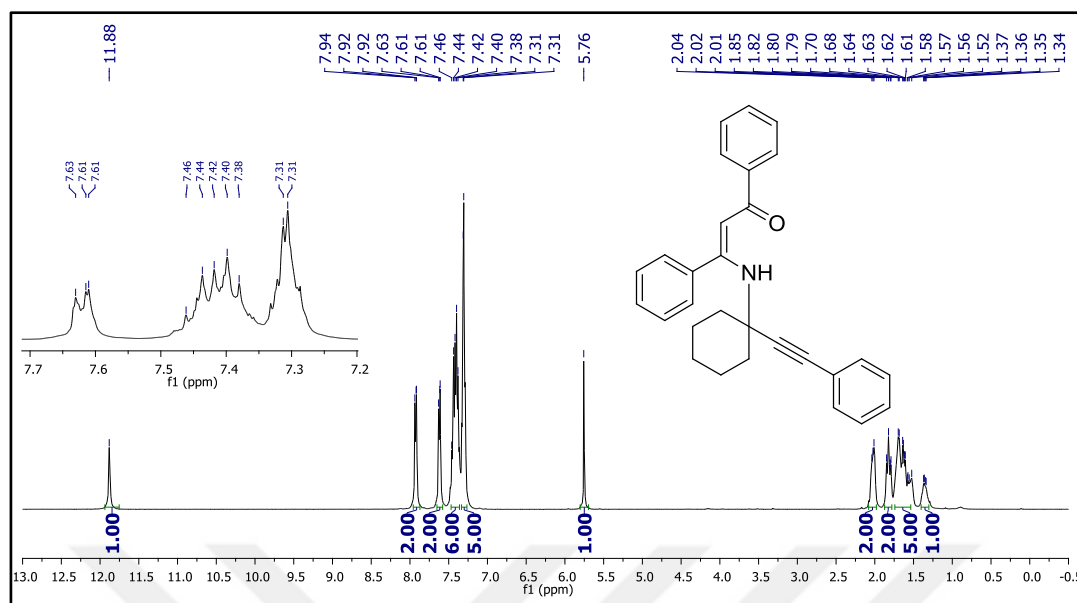


Figure 21. ¹H NMR spectrum of compound **33a**.

In Figure 21, ¹H NMR spectra of 1,3-diphenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one (**33a**) is given. When it was examined, there is only one difference from previous β-enaminones. In this spectrum, there is no alkynic hydrogen due to phenyl coupling. Other hydrogen peaks resonate at similar region. For example, amine hydrogen gives singlet at 11.88 ppm while peak of α-hydrogen appears at 5.76 ppm. Other aromatic hydrogens and cyclohexyl part resonate at 7.31 – 7.94 and 1.34 – 2.04 ppm, respectively (Table 20).

In Figure 22, ¹³C NMR spectrum of 1,3-diphenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one (**33a**) is shown. Like its ¹H NMR spectrum, in ¹³C NMR spectrum, there is only a few difference as compared to non-coupled β-enaminones **31**. One acetylenic carbon gives peak at lower field (85.80 ppm) when it was compared with previous one. Also, there are more carbon peaks in aromatic field because of the third phenyl group. Furthermore, carbonyl carbon gives singlet at 188.46 ppm as expected and the peak of β-carbon is observed at 166.85 ppm. Four

carbon peaks, which appear at high fields, are belong to cyclohexyl moiety (Figure 22).

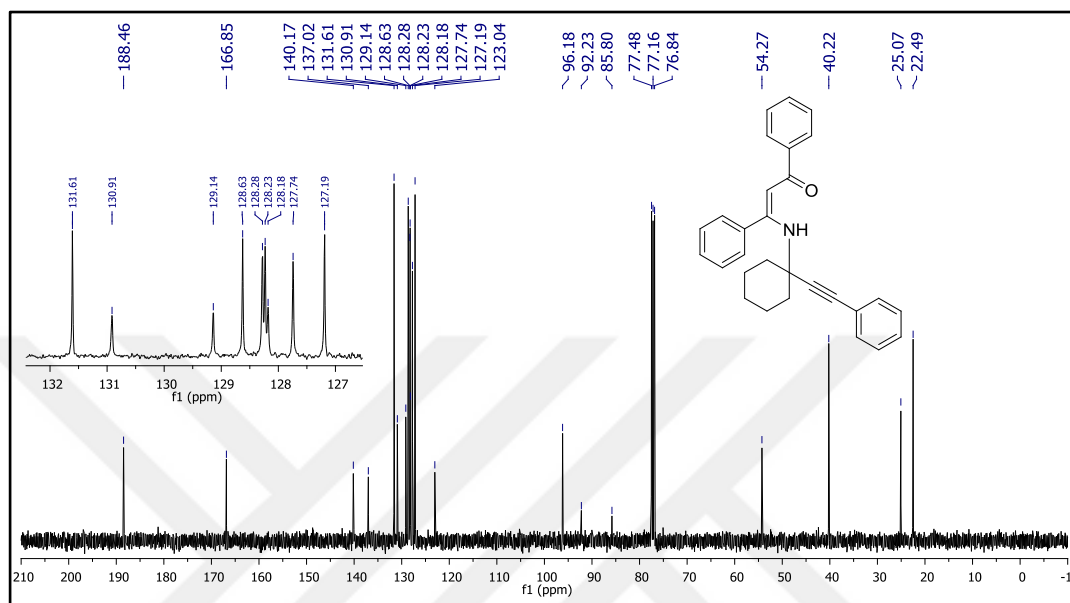
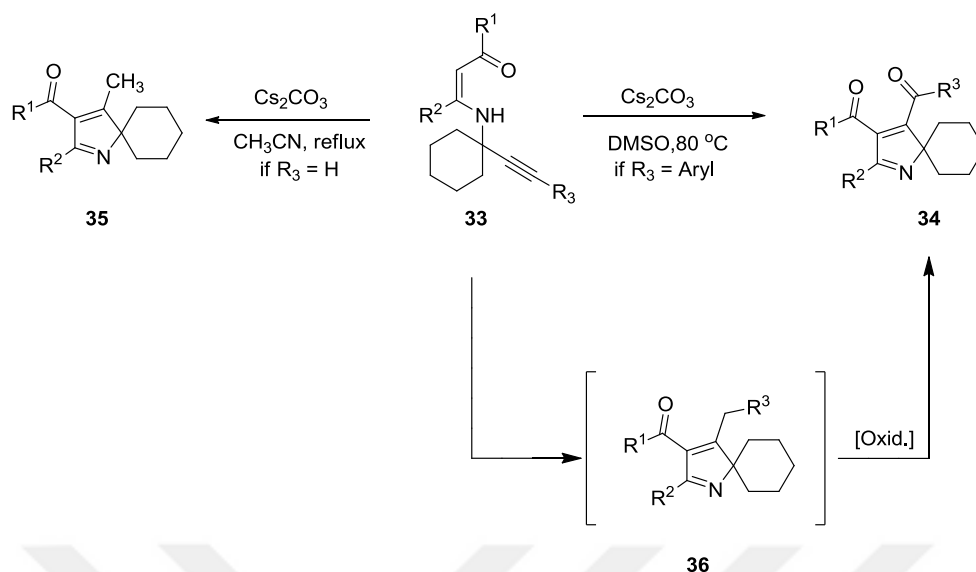


Figure 22. ^{13}C NMR spectrum of compound **33a**.

2.4 Synthesis of Spiro-2*H*-pyrroles with 1,4-Diketone Group **34**

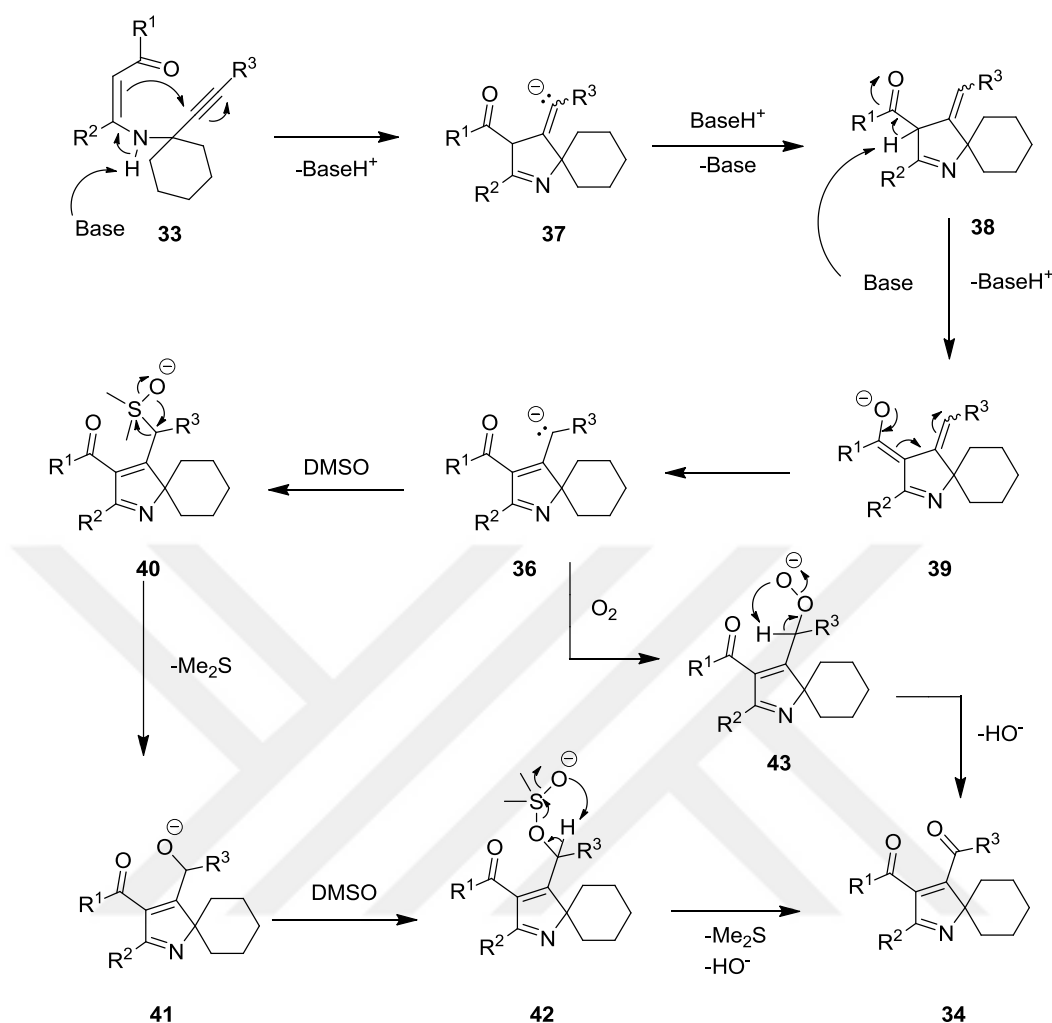
After performing second Sonogashira cross coupling of cyclohexane-embedded *N*-propargylic β -enaminones **31**, all of resulting β -enaminones derivatives **33** were reacted with Cs_2CO_3 in DMSO at 80 °C and open to air (Table 4) according to previous our group's studies.¹⁰ In fact, our group has already worked on the synthesis of different spiro-2*H*-pyrroles **34** and **35** from cyclohexane-embedded *N*-propargylic β -enaminones **33** (Scheme 13).^{10,40}



Scheme 13. Synthesis of 2*H*-pyrroles.

As shown in scheme 13, two methods were developed by our research group to obtain spiro-2*H*-pyrroles **34** and **35** in the presence of Cs_2CO_3 .^{10,40} R_3 groups make difference between the formation of these pyrroles. If it is aryl group, spiro-2*H*-pyrroles **34** are formed in situ via nucleophilic cyclization followed by C-H benzylic oxidation, which results in the formation of spiro-2*H*-pyrroles **34** with 1,4-diketone group.¹⁰ This part of pyrroles **34** can allow us their further functionalization owing to their reactivity.¹⁰

In literature, 1,4-diketones are generally used as starting material for the synthesis of several heterocyclic compound such as thiophenes, furans, pyrroles and pyridazines via cyclization reaction. Moreover, this like 1,4-diketone functionality which is found in heterocyclic molecules also present a chance for the synthesis of novel familia of previously unknown heterocyclic systems.

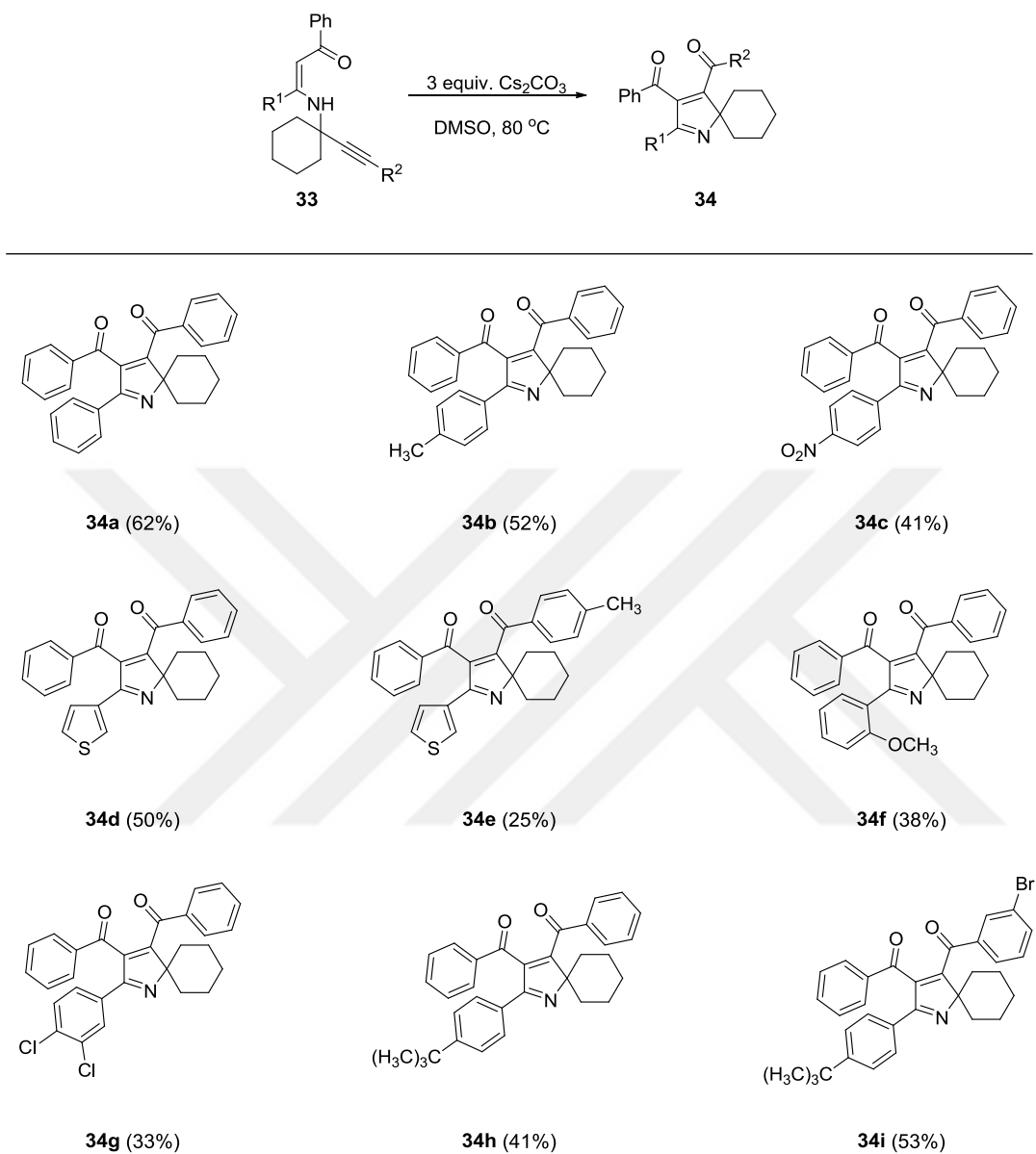


Scheme 14. Proposed mechanism for the formation of spiro-2H-pyrroles.

Moreover, the proposed mechanism of the formation of spiro-2H-pyrroles **34** is given in Scheme 14.¹⁰ According to mechanism, it can be say that both DMSO and O₂ favor the reaction to form target spiro-2H-pyrroles **34**.

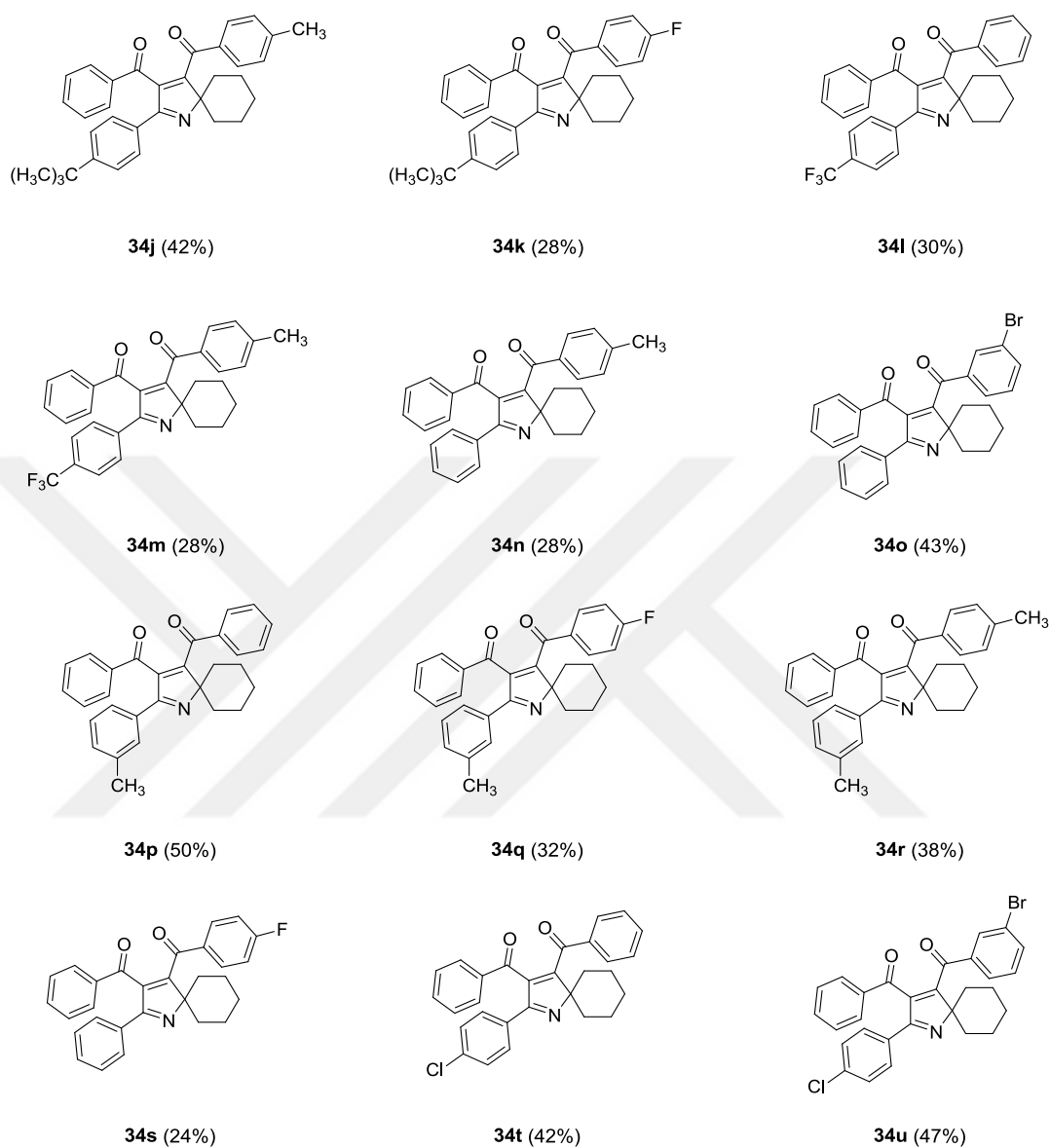
From result of this reaction, 21 (15 of them is new) derivatives of spiro-pyrroles **34** with a 1,4-diketone functionality were synthesized. Their yields ranges between 24% and 69%. The presence of 1,4-dicarbonyl group can allow further improvement of these derivatives.

Table 4. Synthesis of spiro-2*H*-pyrroles with 1,4-dicarbonyl unit **34**.^a



^aIsolated yields.

Table 4. Continued.^a



^aIsolated yields.

With the ¹H and ¹³C NMR spectra of (2-phenyl-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) (**34a**), which are shown in Figures 23 and 24, respectively, formation of these compounds have been proven. In ¹H NMR spectrum (Figure 23), it can be seen that aromatic hydrogen peaks of phenyl rings are placed

between 7.17 – 7.55 ppm, whereas ten aliphatic hydrogen of cyclohexyl group give signal at 1.29 – 2.13 ppm (Figure 23).

On the other hand, in ^{13}C NMR spectrum of (2-phenyl-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) (**34a**), there is a distinctive peak when it was compared with previous compound. This spiro-2*H*-pyrrole compound gives two carbonyl peaks at 194.47 and 192.86 ppm. The peaks which are placed at high fields belong to cyclohexyl carbons at 23.79, 25.58, 33.78 and 85.29 ppm. The remaining peaks are phenyl carbon signals (Figure 24).

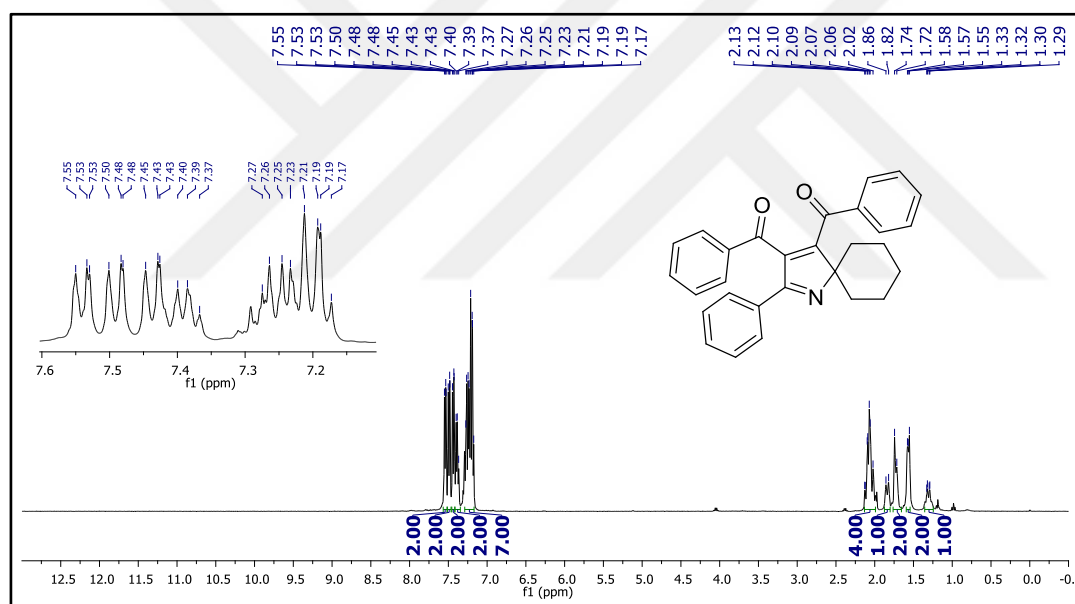


Figure 23. ^1H NMR spectrum of compound **34a**.

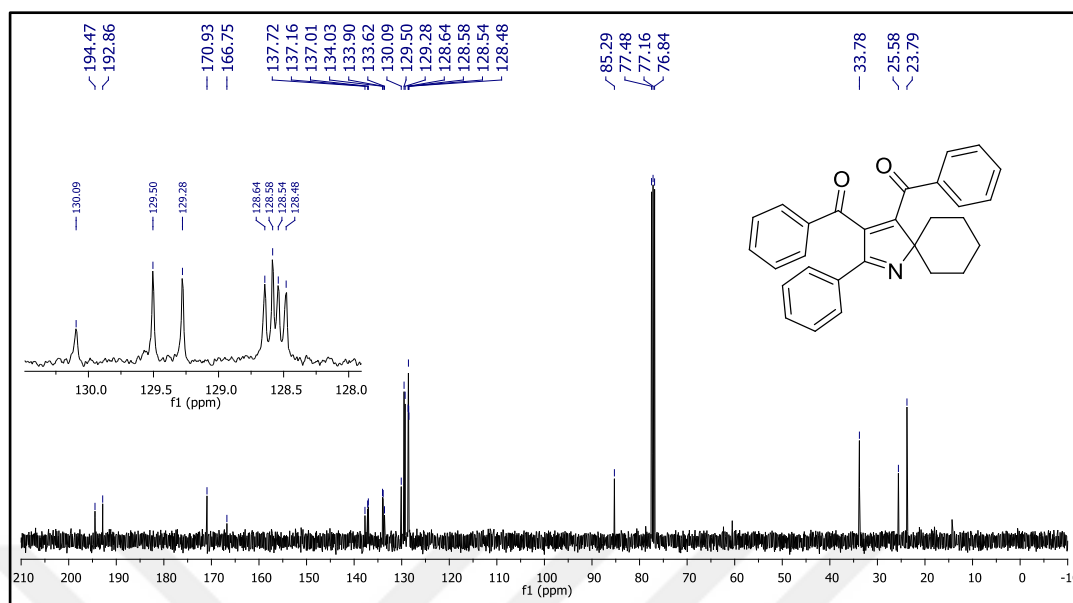
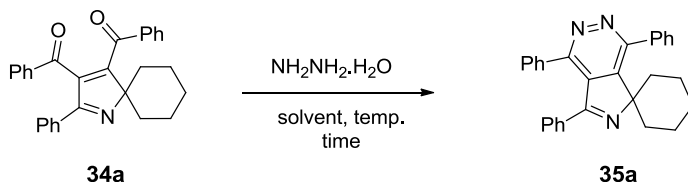


Figure 24. ¹³C NMR spectrum of compound **34a**.

2.5 Synthesis of Pyridazines

After preparation of spiro-2*H*-pyrroles **34**, we have planned to utilize their reactive 1,4-dicarbonyl unit because such compounds can be used as starting material for the synthesis of important heterocyclic molecules. So we have investigated the condensation reactions with hydrazine hydrate, which can give rise to the formation of spiro-pyrrolopyridazines. For this reason, we have tested the reaction (Table 5). Test reaction afforded the expected spiro-pyrrolopyridazine derivative **35a**, a novel family of heterotricyclic hybrids, which may have potential for medicinal purpose. Next, we have optimized the reaction conditions, as depicted in Table 5, for the higher yields of the product **35**.

Table 5. Optimization of the reaction conditions for the synthesis of spiro-pyrrolopyridazines **35**.



Entry	NH ₂ NH ₂ ·H ₂ O (Equiv)	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	30	EtOH	Reflux	1.5	47
2	30	MeOH	Reflux	1.5	63
3	30	DMSO	80 °C	1.5	54
4	30	1-propanol	Reflux	2	64
5	30	2-propanol	Reflux	2.5	67
6	30	CH ₃ Cl	Reflux	4.5	-
7	30	1-butanol	Reflux	2	72
8	40	1-butanol	Reflux	2.5	72
9	20	1-butanol	Reflux	2.5	72
10	10	1-butanol	Reflux	2.5	74

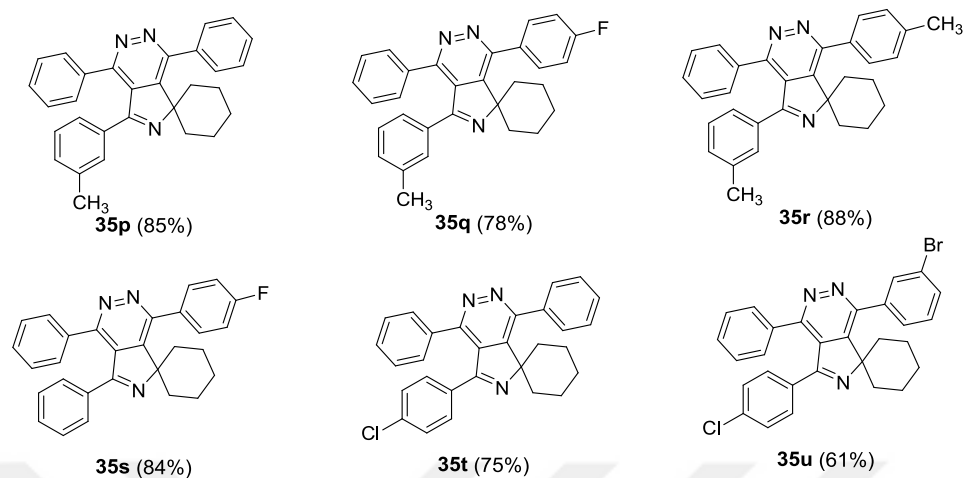
Firstly, we started with changing the solvent (Table 5). At the first synthesis of spiro-pyrrolopyridazine compound, solvent was EtOH in refluxing condition, equivalent of hydrazine monohydrate was 30 and reaction was in about 1.5h with a yield of 47% (Table 5, Entry 1). The progress of the reaction was followed by TLC for the disappearance of spiro-2*H*-pyrrole **34**. Secondly, MeOH and DMSO were tried as the solvent. Reaction was completed at the same time but higher yields were obtained 63% and 54%, respectively (Table 5, Entry 2 and 3). After that, 1- and 2-propanol were tested during optimization and they gave better yields (64% and 67%, respectively) than previous solvents (Table 5, Entry 4 and 5). Then CH₃Cl was tried but formation of any product was not observed (Table 5, Entry 6). And then,

1-butanol was tested and within 2 hours, it formed spiro-pyrrolopyridazine **35a** in 72% yield. Then, the equivalency of nucleophile was tested. Firstly, we increased equivalent of hydrazine monohydrate to 40, then decreased proportionally to 20 and 10, which provided **35a** in 72%, 72% and 74% yields, respectively (Table 5, Entry 8-10). By using 10 equivalent of nucleophile, we obtained the best yield of **35a** as 74%. So, we decided to use the conditions of Entry 10 for derivation studies.

After we optimized the reaction conditions, we started to derivatization part. For this reason, a variety of spiro-2*H*-pyrroles **34** were treated with hydrazine monohydrate under optimized conditions, to get a diverse range of new target products spiro-pyrrolopyridazines **35** as illustrated in Table 6. The starting spiro-2*H*-pyrroles **34** reacted well with hydrazine monohydrate through their highly reactive 1,4-diketone moiety and afforded the expected spiro-pyrrolopyridazine **35** generally in good to high yields. Yields were changed between 43% and 96%. Among them, the best yield belongs to trifluoro-substituted derivative **35i** (96%), meanwhile 3,4-dichloro substituted one **35g** has the lowest yield (43%). Totally, 21 new derivatives of novel class of spiro-pyrrolopyridazines were synthesized for the first time. Importantly, the synthesized spiro-pyrrolopyridazines may display potential in pharmaceutical and medicinal chemistry.

During the derivatization studies, the starting materials containing electron-withdrawing and electron-donating groups were used and the reactions showed a good tolerance to such substituents. Moreover, 8 halogens, 2 thiophenes, 10 methyls and 1 nitro-containing derivatives were synthesized.

Table 6. Continued.^a



^aIsolated yields.

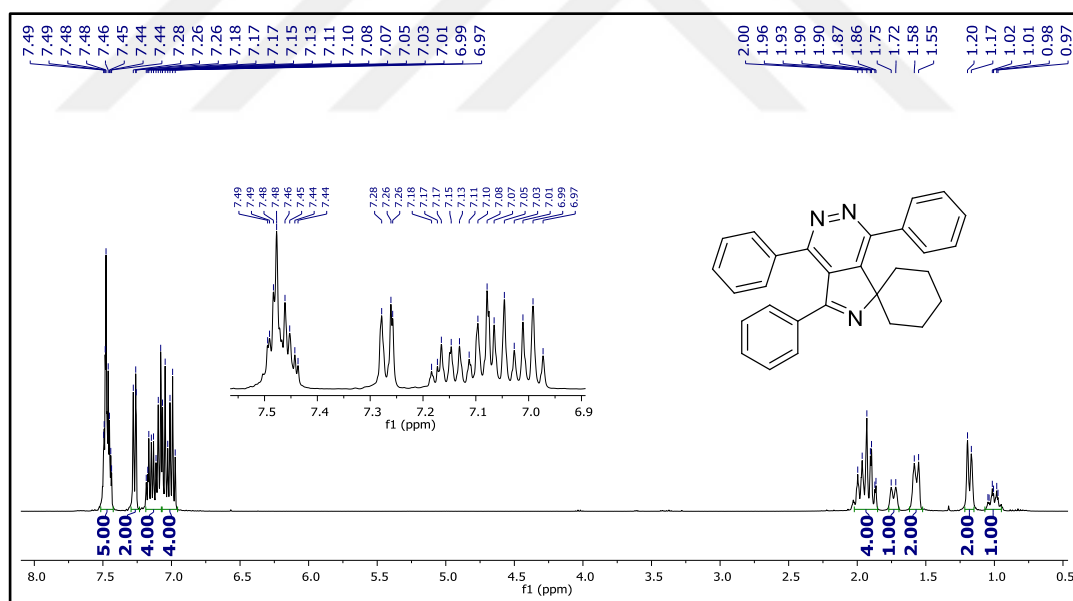


Figure 25. ¹H NMR spectrum of compound 35a.

As an example, ^1H and ^{13}C NMR spectra of 1',4',7'-triphenylspiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] **35a** are given in Figures 25 and 26. It is examined, there will be seen that there is no difference between that of spiro-2*H*-pyrrole **34a** because numbers of hydrogens in the molecule do not change as well as their chemical shifts (Figure 25). Therefore, determinative spectrum is ^{13}C NMR (Figure 26). Importantly, two carbonyl peaks in the spectrum of **35a** disappear. Also, the signals of three C-N bonds is observed at 157.01, 157.38 and 166.73 ppm. Other aromatic carbon peaks appear between 132.29 and 156.58 ppm. Other peaks in aromatic region belong to CH peaks of phenyl groups. C and CH_2 peaks of cyclohexyl group resonate at 23.36, 25.64, 34.19 and 80.42 ppm, respectively (Figure 26).

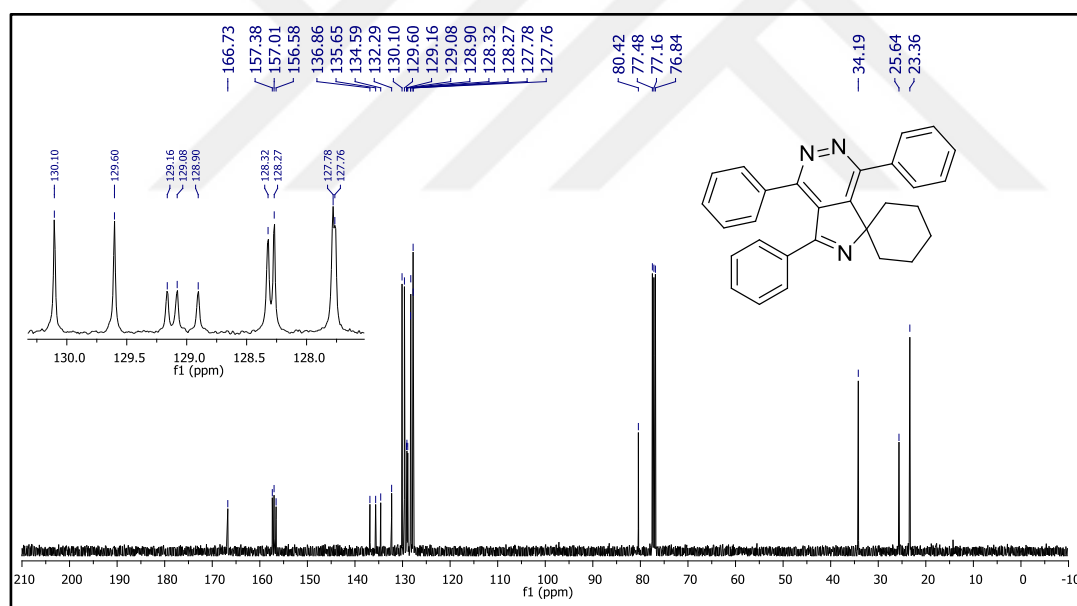
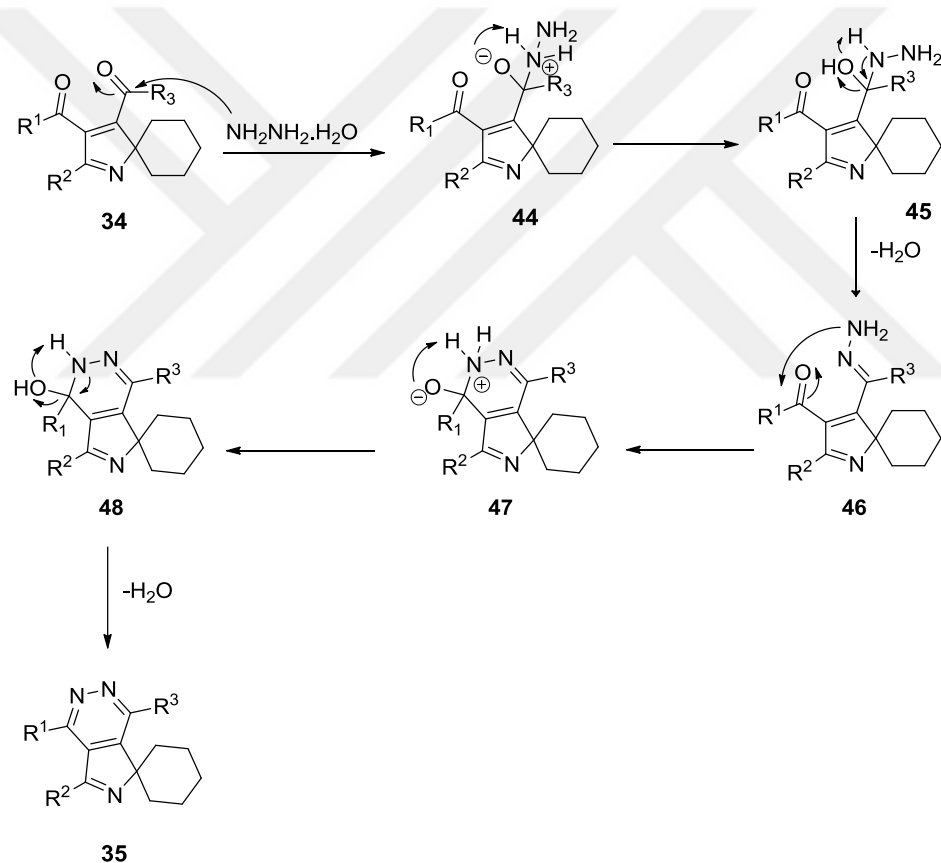


Figure 26. ^{13}C NMR spectrum of compound **35a**.

The proposed mechanism of the formation of spiro-pyrrolopyridazines **35** is given in Scheme 15. First step is the generation of hydrazone **46** in situ with elimination of water through the intermediates **44** and **45**. Next, same mechanism is repeated and second condensation reaction happen. At least, the target spiro-pyrrolopyridazine **35** form via intermediacy of **46**, **47** and **48** (Scheme 15). In summary, tandem condensation reactions of spiro-2*H*-pyrroles **34** with hydrazine monohydrate furnish a pyridazine ring fused to spiro-2*H*-pyrrole unit. At final, a novel family of heterocyclic hybrids, namely spiro-pyrrolopyridazines are obtained.



Scheme 15. Proposed mechanism of fused pyrrolopyridazine compound **35**.

CHAPTER 3

CONCLUSION

In summary, we developed a novel approach for the synthesis of spiro-pyrrolopyridazines via condensation reaction between hydrazine monohydrate and spiro-2*H*-pyrroles with a 1,4-diketone group.

In the first part of the study, α,β -alkynic ketones were synthesized by Sonogashira cross-coupling reaction of terminal alkyne with benzoyl chloride in the presence of Pd and Cu. They were obtained with yields of 75-96%. Secondly, α,β -alkynic ketones were reacted with 1-ethynylcyclohexylamine in refluxing methanol to produce cyclohexane-embedded *N*-propargylic β -enaminones, the yields of which ranged 38 to 68%. Then, these *N*-propargylic β -enaminones were treated with the corresponding aryl iodides under Sonogashira cross-coupling conditions. As a result of second Sonogashira coupling reaction, totally 21 derivative of arylated *N*-propargylic β -enaminones were synthesized with the yields between 38 and 86%. Next, arylated *N*-propargylic β -enaminones were subjected to Cs₂CO₃ in DMSO, which afforded spiro-2*H*-pyrroles with 1,4-diketone group as a result of C-H oxidation. By this step, we synthesized the starting compounds for the last step.

Finally, previously synthesized spiro-2*H*-pyrroles with 1,4-diketone group were treated with hydrazine monohydrate which underwent condensation reaction twice and yielded spiro-pyrrolopyridazine derivatives in good to high yields (43-96%). The reaction was carried out in refluxing *n*-butyl alcohol with 10 equivalent of hydrazine monohydrate according to optimized conditions. By employing this strategy, 21 new derivatives of spiro-pyrrolopyridazine were synthesized for the first time. It is hoped that this new family of heterotricyclic hybrids may show great potential in terms of

biological activity and they can be used in the development of new and novel molecular entities and structural leads.



CHAPTER 4

EXPERIMENTAL

General Information

^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz by using Bruker Spectrospin Avance DPX400 Ultrashield spectrometer. The chemical shifts are represented as parts per million (ppm) with respect to CDCl_3 (7.26 and 77.16 ppm in ^1H and ^{13}C NMR, respectively). Coupling constants (J) are reported in hertz (Hz) and spin multiplicities are represented as singlet (s), doublet (d), triplet (t), doublet of doublet (dd), doublet of triplet (dt), triplet of doublet (td), doublet of doublet of doublet (ddd), quartet (q). After reactions were completed, flash chromatography was used with silica gel (Merck 230-400) for purification step. Moreover, TLC (thin layer chromatography) was applied by using 0.25 mm commercially available silica gel plates to observe completion of reaction and visualization was performed with short wavelength UV lamp (254 nm). Flash chromatography was achieved by using different volumes of hexane-ethyl acetate solvent mixture. These solvents were purified by distillation. Attenuated total reflection (ATR) was run for recording infrared spectra (IR). Band positions were recorded as reciprocal centimeters (cm^{-1}). Detecting of melting points of crystalline compounds, capillary tubes were used and their values were recorded automatically. For creation of inert atmosphere, argon gas (ca. 0.1 psi) was used. Reagents which are commercially available were used directly without any purification process unless stated. All glassware and laboratory materials were dried in oven.

4.1 General Procedure for the Synthesis of α,β -Alkynic Ketones 29 (Table 1)

A mixture of benzoyl chloride, $\text{PdCl}_2(\text{PPh}_3)_2$ (0.02 mmol), Et_3N (1.2 mmol) and CuI (0.02 mmol) in anhydrous THF were stirred for 10 min. After addition of appropriate terminal alkyne (1.0 mmol), resulting mixture was stirred at room temperature under argon for approximately 4h. While reaction was carried out, the process was followed by TLC (19:1 hexane/ethyl acetate). Note that reaction was completed when all terminal alkyne was consumed. After reaction was over, solvent was removed by rotary evaporator. After that, extraction was performed to separate organic phase from aqueous phase by using ethyl acetate (30 mL) and saturated NH_4Cl solution (30 mL). Separation of organic phase was completed, it was dried over MgSO_4 and evaporated on a rotary to give the crude product. Flash chromatography on silica gel was used to purify the crude product by using 19:1 hexane-ethyl acetate as the eluent, which afforded corresponding α,β -alkynic ketones.^{41,42,43}

4.1.1 Synthesis of 1,3-diphenylprop-2-yn-1-one (29a)

General procedure was followed by using benzoyl chloride (420.0 mg, 3.00 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (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), which afforded 494.4 mg (96%) of the indicated product **29a** as a yellow oil (R_f = 0.54 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 8.26 (dt, J = 8.5, 1.8 Hz, 2H), 7.73 – 7.69 (m, 2H), 7.68 – 7.63 (m, 1H), 7.54 (td, J = 7.1, 1.4 Hz, 2H), 7.52 – 7.48 (m, 1H), 7.47 – 7.42 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.0 (CO), 136.9 (C), 134.2 (CH), 133.1 (CH), 130.9 (CH), 129.6 (CH), 128.7 (CH), 128.7 (CH), 120.1 (C), 93.2 (C), 86.9 (C). The spectral data were in agreement with those reported previously for this compound.⁴²

4.1.2 Synthesis of 1-phenyl-3-(*p*-tolyl)prop-2-yn-1-one (**29b**)

General procedure was followed by using benzoyl chloride (500.0 mg, 3.84 mmol), PdCl₂(PPh₃)₂ (42.1 mg, 0.06 mmol), Et₃N (391.3 mg, 3.84 mmol), CuI (12.0 mg, 0.06 mmol) and 4-ethynyltoluene (369.4 mg 3.18 mmol), which afforded 667.3 mg (95%) of the indicated product **29b** as a yellow solid (*R*_f = 0.56 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 8.38 – 8.15 (m, 2H), 7.69 – 7.57 (m, 3H), 7.54 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 178.1 (CO), 141.7 (C), 137.1 (C), 134.1 (CH), 133.2 (CH), 129.61 (CH), 129.58 (CH), 128.7 (CH), 117.1 (C), 93.9 (C), 86.9 (C), 21.8 (CH₃). The spectral data were in agreement with those reported previously for this compound.⁴³

4.1.3 Synthesis of 1-phenyl-3-(*m*-tolyl)prop-2-yn-1-one (**29c**)

General procedure was followed by using benzoyl chloride (534.8 mg, 3.82 mmol), PdCl₂(PPh₃)₂ (42.2 mg, 0.06 mmol), Et₃N (389.3 mg, 3.82 mmol), CuI (11.4 mg, 0.06 mmol) and 3-ethynyltoluene (369.4 mg 3.18 mmol), which afforded 635.0 mg (91%) of the indicated product **29c** as a yellow solid (*R*_f = 0.64 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 8.07 – 8.01 (m, 2H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.35 – 7.25 (m, 4H), 7.12 – 7.04 (m, 2H), 2.16 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 177.7 (CO), 138.3 (C), 136.8 (C), 133.9 (CH), 133.4 (CH), 131.7 (CH), 130.1 (CH), 129.4 (CH), 128.5 (CH), 128.5 (CH), 119.7 (C), 93.3 (C), 86.6 (C), 21.0 (CH₃). The spectral data were in agreement with those reported previously for this compound.⁴³

4.1.4 Synthesis of 3-(4-chlorophenyl)-1-phenylprop-2-yn-1-one (**29d**)

General procedure was followed by using benzoyl chloride (350.0 mg, 2.50 mmol), PdCl₂(PPh₃)₂ (28.1 mg, 0.04 mmol), Et₃N (254.8 mg, 2.50 mmol), CuI (7.6 mg, 0.04 mmol) and 1-chloro-4-ethynylbenzene (284.1 mg 2.08 mmol), which afforded 414.7 mg (83%) of the indicated product **29d** as a light yellow solid (*R*_f = 0.64 in 4:1

hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 8.14 – 8.08 (m, 2H), 7.57 – 7.49 (m, 3H), 7.43 (t, J = 7.6 Hz, 2H), 7.32 – 7.29 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.6 (CO), 137.1 (C), 136.6 (C), 134.2 (CH), 129.5 (CH), 129.1 (CH), 128.6 (CH), 118.5 (C), 91.5 (C), 87.6 (C) (Note that two CH peaks overlap with each others). The spectral data were in agreement with those reported previously for this compound.⁴¹

4.1.5 Synthesis of 3-(2-methoxyphenyl)-1-phenylprop-2-yn-1-one (29e)

General procedure was followed by using benzoyl chloride (569.8 mg, 4.07 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (49.1 mg, 0.07 mmol), Et_3N (414.7 mg, 4.07 mmol), CuI (13.3 mg, 0.07 mmol) and 2-ethynylanisole (448.0 mg, 3.39 mmol), which afforded 771.8 mg (96%) of the indicated product **29e** as an orange solid (R_f = 0.45 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 8.34 (d, J = 7.4 Hz, 2H), 7.66 – 7.61 (m, 2H), 7.56 – 7.42 (m, 3H), 6.99 (dd, J = 17.5, 8.0 Hz, 2H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.7 (CO), 161.6 (C), 136.9 (C), 134.6 (CH), 133.7 (CH), 132.6 (CH), 129.4 (CH), 128.3 (CH), 120.4 (CH), 110.7 (CH), 108.9 (C), 91.1 (C), 90.5 (C), 55.6 (OCH_3); IR (neat) 3064, 2199, 1643, 1592, 1578, 1488, 1448, 1426, 1314, 1297, 1277, 1251, 1228, 1204, 1173, 1114, 1041, 1026, 1008, 854, 827, 744, 694, 623, 581 cm^{-1} . The spectral data were in agreement with those reported previously for this compound.⁴²

4.1.6 Synthesis of 1-phenyl-3-(thiophen-3-yl)prop-2-yn-1-one (29f)

General procedure was followed by using benzoyl chloride (554.4 mg, 3.96 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (49.1 mg, 0.07 mmol), Et_3N (403.5 mg, 3.96 mmol), CuI (13.3 mg, 0.07 mmol) and 3-ethynylthiophene (356.9 mg, 3.30 mmol), which afforded 649.7 mg (93%) of the indicated product **29f** as brown oil (R_f = 0.68 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 8.24 – 8.21 (m, 2H), 7.86 (dd, J = 2.9, 1.1 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.38 (dd, J = 5.0, 3.0 Hz,

1H), 7.33 (dd, $J = 5.0, 1.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.7 (CO), 136.7 (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). The spectral data were in agreement with those reported previously for this compound.⁴²

4.1.7 Synthesis of 1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one (29g)

General procedure was followed by using benzoyl chloride (428.4 mg, 3.06 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (35.1 mg, 0.05 mmol), Et_3N (311.8 mg, 3.06 mmol), CuI (9.5 mg, 0.05 mmol) and 4-ethynyl- α,α,α -trifluorotoluene (443.8 mg, 2.55 mmol), which afforded 677.3 mg (97%) of the indicated product **29g** as a light yellow solid ($R_f = 0.77$ in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 8.06 – 8.01 (m, 2H), 7.58 (d, $J = 8.1$ Hz, 2H), 7.50 – 7.44 (m, 3H), 7.34 (t, $J = 7.7$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.5 (CO), 136.6 (C), 134.4 (CH), 133.2 (CH), 132.1 (q, $^2J = 32.9$ Hz, C), 129.5 (CH), 128.7 (CH), 125.5 (q, $^3J = 3.7$ Hz, CH), 123.9 (C), 123.6 (q, $^1J = 272.6$ Hz, CF_3), 90.4 (C), 88.1 (C); IR (neat) 3052, 2206, 1638, 1596, 1449, 1405, 1312, 1292, 1213, 1166, 1153, 1105, 1067, 1029, 1009, 845, 792, 695, 598, 527 cm^{-1} ; MS (ESI, m/z): 275.06 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{16}\text{H}_{10}\text{F}_3\text{O}$: 275.06783 $[\text{M}+\text{H}]^+$, found: 275.06850.

4.1.8 Synthesis of 3-(4-nitrophenyl)-1-phenylprop-2-yn-1-one (29h)

General procedure was followed by using benzoyl chloride (469.0 mg, 3.35 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (42.1 mg, 0.06 mmol), Et_3N (341.4 mg, 3.35 mmol), CuI (11.4 mg, 0.06 mmol) and 1-ethynyl-nitrobenzene (410.5 mg, 2.79 mmol), which afforded 560.1 mg (80%) of the indicated product **29h** as a light yellow solid ($R_f = 0.48$ in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 8.31 (d, $J = 8.9$ Hz, 2H), 8.22 (dd, $J = 8.6, 1.0$ Hz, 2H), 7.86 (d, $J = 8.9$ Hz, 2H), 7.70 (t, $J = 7.4$ Hz, 1H), 7.57 (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). The spectral data were in agreement with those reported previously for this compound.⁴¹

4.1.9 Synthesis of 3-(3,4-dichlorophenyl)-1-phenylprop-2-yn-1-one (29i)

General procedure was followed by using benzoyl chloride (366.8 mg, 2.62 mmol), PdCl₂(PPh₃)₂ (28.1 mg, 0.04 mmol), Et₃N (270.0 mg, 2.62 mmol), CuI (7.6 mg, 0.04 mmol) and 3,4-dichlorophenylacetylene (372.8 mg, 2.18 mmol), which afforded 450.0 mg (75%) of the indicated product **29i** as a light yellow solid (*R*_f = 0.66 in 4:1 hexane/ethyl acetate; mp = 111.5-112.0 °C). ¹H NMR (400 MHz, CDCl₃) δ 8.03 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.56 – 7.54 (m, 1H), 7.52 – 7.46 (m, 1H), 7.41 – 7.30 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 177.3 (CO), 136.4 (C), 135.5 (C), 134.4 (CH), 134.3 (C), 133.1 (CH), 131.9 (CH), 130.8 (CH), 129.5 (CH), 128.7 (CH), 119.9 (C), 89.7 (C), 87.9 (C); IR (neat) 3734, 2203, 2182, 1634, 1596, 1578, 1448, 1375, 1313, 1295, 1252, 1208, 1168, 1126, 1028, 1013, 874, 824, 789, 739, 690, 648, 586 cm⁻¹; MS (ESI, *m/z*): 275.00 [M+H]⁺; HRMS (ESI) calcd. for C₁₅H₉Cl₂O: 275.0025 [M+H]⁺, found: 275.00198.

4.1.10 Synthesis of 3-(4-(*tert*-butyl)phenyl)-1-phenylprop-2-yn-1-one (29j)

General procedure was followed by using benzoyl chloride (448.0 mg, 3.20 mmol), PdCl₂(PPh₃)₂ (35.1 mg, 0.05 mmol), Et₃N (326.1 mg, 3.20 mmol), CuI (9.5 mg, 0.05 mmol) and 4-*tert*-butylphenylacetylene (422.5 mg, 2.67 mmol), which afforded 673.2 mg (96%) of the indicated product **29j** as yellow oil (*R*_f = 0.55 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 8.14 – 8.08 (m, 2H), 7.49 (t, *J* = 9.3 Hz, 3H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.30 (d, *J* = 7.7 Hz, 2H), 1.19 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 178.0 (CO), 154.6 (C), 137.0 (C), 134.0 (CH), 133.0 (CH), 129.5 (CH), 128.6 (CH), 125.8 (CH), 117.0 (C), 93.8 (C), 86.8 (C), 35.1 (C), 31.0 (CH₃); IR (neat) 3063, 2961, 2905, 2193, 1637, 1598, 1579, 1504, 1449, 1395, 1364, 1314, 1288, 1212, 1171, 1108, 1029, 1007, 834, 793, 696, 650, 563, 524

cm⁻¹; MS (ESI, m/z): 263,14 [M+H]⁺; HRMS (ESI) calcd. for C₁₉H₁₉O: 263,14304 [M+H]⁺, found: 263,14298.

4.2 General Procedure for the Synthesis of *N*-Propargylic β -Enaminones **31** (Table 2)

To stirred solution of the corresponding α,β -alkynic ketones (1.00 mmol) in MeOH (10 mL) was added 1-ethynylcyclohexylamine (1.20 mmol) under argon and the resulting mixture was then heated to reflux at 65 °C for approximately 18 h. The progress of the reaction was monitored by routine TLC for the disappearance of α,β -alkynic ketone **29** using hexane/ethyl acetate (19:1) as the eluent. After the reaction was over, MeOH was removed by rotary evaporator and ethyl acetate (30 mL) and a saturated NH₄Cl (30 mL) were added to perform extraction. After the layers were separated, the aqueous phase was extracted with ethyl acetate (2 $\times$ 30 mL). After obtaining organic phase from extraction process, it was dried with MgSO₄ and solvents were evaporated on a rotary to give the crude product. The crude product was purified with flash chromatography on silica gel by using hexane/ethyl acetate (hexane followed by 19:1) as the eluent to afford the corresponding cyclohexane embedded *N*-propargylic β -enaminones.⁴⁰

4.2.1 Synthesis of 3-((1-ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**31a**)

1,3-Diphenylprop-2-yn-1-one **29a** (598.8 mg, 2.91 mmol) and 1-ethynylcyclohexylamine (430.0 mg, 3.49 mmol) were employed to afford 467.4 mg (49%) of the indicated product **31a** as a light yellow solid (R_f = 0.43 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.75 (s, 1H), 7.92 (dt, J = 8.3, 2.1 Hz, 2H), 7.62 – 7.55 (m, 2H), 7.48 – 7.37 (m, 6H), 5.75 (s, 1H), 2.32 (s, 1H), 1.93 – 1.84 (m, 2H), 1.77 – 1.69 (m, 2H), 1.68 – 1.61 (m, 2H), 1.60 – 1.46 (m, 3H), 1.37 – 1.27 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.6 (CO), 166.7 (C), 140.2 (C), 137.0 (C), 131.0

(CH), 129.3 (CH), 128.7 (CH), 128.3 (CH), 127.7 (CH), 127.2 (CH), 96.3 (CH), 86.6 (C), 73.6 (CH), 53.6 (C), 39.9 (CH₂), 25.0 (CH₂), 22.2 (CH₂); IR (neat) 3231, 2933, 2850, 1607, 1570, 1547, 1476, 1440, 1328, 1294, 1258, 1225, 1172, 1146, 1074, 1056, 1023, 998, 894, 814, 788, 749, 697, 580 cm⁻¹. The spectral data were in agreement with those reported previously for this compound.⁴⁰

4.2.2 Synthesis of 3-((1-ethynylcyclohexyl)amino)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-one (31b)

1-Phenyl-3-(*p*-tolyl)prop-2-yn-1-one **29b** (600.0 mg, 2.73 mmol) and 1-ethynylcyclohexylamine (404.1 mg, 3.28 mmol) were employed to afford 355.0 mg (38%) of the indicated product **31b** as a light brown solid (*R*_f = 0.55 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.80 (s, 1H), 7.93 (d, *J* = 6.6 Hz, 2H), 7.51 (d, *J* = 7.9 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 3H), 7.22 (d, *J* = 7.7 Hz, 2H), 5.77 (s, 1H), 2.42 (d, *J* = 2.5 Hz, 3H), 2.36 (d, *J* = 3.0 Hz, 1H), 1.89 (s, 2H), 1.78 – 1.63 (m, 4H), 1.59 – 1.45 (m, 3H), 1.32 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.3 (CO), 166.8 (C), 140.1 (C), 139.2 (C), 134.1 (C), 130.8 (CH), 128.5 (CH), 128.3 (CH), 128.2 (CH), 127.1 (CH), 96.2 (CH), 86.8 (C), 73.3 (CH), 53.6 (C), 39.6 (CH₃), 24.9 (CH₂), 22.1 (CH₂), 21.4 (CH₂); IR (neat) 3030, 2929, 2852, 1581, 1561, 1496, 1479, 1442, 1327, 1297, 1259, 1224, 1169, 1145, 1078, 1055, 1022, 894, 825, 805, 755, 695, 651, 577 cm⁻¹. The spectral data were in agreement with those reported previously for this compound.⁴⁰

4.2.3 Synthesis of 3-((1-ethynylcyclohexyl)amino)-1-phenyl-3-(*m*-tolyl)prop-2-en-1-one (31c)

1-Phenyl-3-(*m*-tolyl)prop-2-yn-1-one **29c** (529.8 mg, 2.41 mmol) and 1-ethynylcyclohexylamine (356.0 mg, 2.89 mmol) were employed to afford 385 mg (47%) of the indicated product **31c** as orange oil (*R*_f = 0.63 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.78 (s, 1H), 7.93 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.46 – 7.38 (m,

5H), 7.32 – 7.23 (m, 2H), 5.77 (s, 1H), 2.41 (s, 3H), 2.36 (s, 1H), 1.76 – 1.62 (m, 2H), 1.60 – 1.52 (m, 4H), 1.60 – 1.53 (m, 2H), 1.50 – 1.45 (m, 1H), 1.35 – 1.29 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.4 (CO), 166.8 (C), 140.1 (C), 137.2 (C), 136.7 (C), 130.8 (CH), 129.9 (CH), 129.3 (CH), 128.2 (CH), 127.6 (CH), 127.1 (CH), 125.6 (CH), 96.0 (CH), 86.8 (C), 73.2 (CH), 53.5 (C), 39.6 (CH_3), 24.9 (CH_2), 22.1 (CH_2), 21.4 (CH_2); IR (neat) 3058, 2931, 2856, 1572, 1474, 1327, 1256, 1230, 1163, 1055, 1024, 999, 897, 793, 751, 689 cm^{-1} .

4.2.4 Synthesis of 3-(4-chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one (31d)

3-(4-Chlorophenyl)-1-phenylprop-2-yn-1-one **29d** (376.2 mg, 1.56 mmol) and 1-ethynylcyclohexylamine (230.4 mg, 1.87 mmol) were employed to afford 309.2 mg (54%) of the indicated product **31d** as a yellow solid (R_f = 0.63 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 11.56 (s, 1H), 7.83 – 7.76 (m, 2H), 7.47 – 7.41 (m, 2H), 7.40 – 7.25 (m, 5H), 5.61 (s, 1H), 2.23 (s, 1H), 1.84 – 1.75 (m, 2H), 1.68 – 1.52 (m, 4H), 1.51 – 1.36 (m, 3H), 1.26 – 1.14 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.7 (CO), 165.2 (C), 139.8 (C), 135.3 (C), 135.2 (C), 131.1 (CH), 130.1 (CH), 128.3 (CH), 128.0 (CH), 127.1 (CH), 96.3 (CH), 86.4 (C), 74.0 (CH), 53.6 (C), 39.9 (CH_2), 24.9 (CH_2), 22.1 (CH_2); IR (neat) 3299, 2933, 2850, 1562, 1474, 1394, 1328, 1261, 1227, 1171, 1145, 1089, 1055, 1015, 894, 833, 805, 759, 693, 649, 605 cm^{-1} . The spectral data were in agreement with those reported previously for this compound.⁴⁰

4.2.5 Synthesis of 3-((1-ethynylcyclohexyl)amino)-3-(2-methoxyphenyl)-1-phenylprop-2-en-1-one (31e)

3-(2-Methoxyphenyl)-1-phenylprop-2-yn-1-one **29e** (615.4 mg, 2.60 mmol) and 1-ethynylcyclohexylamine (384.4 mg, 3.21 mmol) were employed to afford 357.0 mg (38%) of the indicated product **31e** as orange oil (R_f = 0.43 in 4:1 hexane/ethyl

acetate). ^1H NMR (400 MHz, CDCl_3) δ 11.88 (s, 1H), 7.82 – 7.77 (m, 2H), 7.34 – 7.25 (m, 5H), 6.87 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 5.60 (s, 1H), 3.72 (s, 3H), 2.06 (s, 1H), 1.87 (s, 1H), 1.72 (d, J = 11.6 Hz, 2H), 1.60 (s, 4H), 1.46 – 1.31 (m, J = 14.8, 8.6 Hz, 2H), 1.28 – 1.19 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.1 (CO), 163.6 (C), 156.7 (C), 140.2 (C), 130.7 (CH), 130.5 (CH), 128.1 (CH), 127.1 (CH), 125.3 (CH), 119.4 (CH), 110.3 (CH), 95.8 (CH), 85.5 (C), 72.9 (CH), 55.2 (OCH_3), 53.4 (C), 40.5 (C), 38.6 (CH_2), 24.9 (CH_2), 22.1 (CH_2); IR (neat) 3062, 2933, 2857, 1735, 1605, 1572, 1479, 1451, 1326, 1276, 1243, 1163, 1111, 1055, 1023, 896, 809, 751, 691 cm^{-1} .

4.2.6 Synthesis of 3-((1-ethynylcyclohexyl)amino)-1-phenyl-3-(thiophen-3-yl)prop-2-en-1-one (**31f**)

1-Phenyl-3-(thiophen-3-yl)prop-2-yn-1-one **29f** (649.7 mg, 3.06 mmol) and 1-ethynylcyclohexylamine (452.4 mg, 3.67 mmol) were employed to afford 521.1 mg (52%) of the indicated product **31f** as dark orange oil (R_f = 0.53 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 11.76 (s, 1H), 7.92 – 7.89 (m, 2H), 7.66 (dd, J = 2.9, 1.3 Hz, 1H), 7.46 – 7.33 (m, 5H), 5.83 (s, 1H), 2.42 (s, 1H), 1.92 (dd, J = 12.3, 5.2 Hz, 2H), 1.77 – 1.66 (m, 3H), 1.66 – 1.52 (m, 4H), 1.34 (td, J = 8.9, 4.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.5 (CO), 161.4 (C), 140.1 (C), 137.2 (C), 131.0 (CH), 128.7 (CH), 128.3 (CH), 127.2 (CH), 126.2 (CH), 125.1 (CH), 95.9 (CH), 86.9 (C), 73.3 (CH), 53.5 (C), 39.4 (CH_2), 25.0 (CH_2), 22.2 (CH_2); IR (neat) 3286, 2931, 2855, 11582, 1499, 1479, 1444, 1366, 1316, 1255, 1225, 1161, 1077, 1055, 1023, 999, 890, 863, 796, 749, 690, 563 cm^{-1} . The spectral data were in agreement with those reported previously for this compound.⁴⁰

4.2.7 Synthesis of 3-((1-ethynylcyclohexyl)amino)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (**31g**)

1-Phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-yn-1-one **29g** (626.4 mg, 2.28 mmol) and 1-ethynylcyclohexylamine (337.6 mg, 2.74 mmol) were employed to afford 620.0 mg (68%) of the indicated product **31g** as an orange solid (R_f = 0.63 in 4:1 hexane/ethyl acetate; mp = 91.1-92.7 °C). ^1H NMR (400 MHz, CDCl_3) δ 11.70 (s, 1H), 7.91 (d, J = 8.1 Hz, 2H), 7.70 (dd, J = 18.4, 8.0 Hz, 4H), 7.49 – 7.38 (m, 3H), 5.72 (d, J = 1.2 Hz, 1H), 2.37 – 2.25 (m, 1H), 1.93 – 1.85 (m, 2H), 1.77 – 1.61 (m, 4H), 1.61 – 1.44 (m, 3H), 1.33 (dd, J = 10.7, 7.4 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.0 (CO), 164.7 (C), 140.4 (C), 139.8 (C), 131.3 (q, 2J = 21.7 Hz, C), 129.3 (CH), 128.4 (CH), 127.2 (CH), 125.4 (CH), 124.7 (q, 3J = 3.6 Hz, CH), 124.0 (q, 1J = 136.2 Hz, CF_3), 96.5 (CH), 86.2 (C), 74.2 (CH), 53.8 (C), 40.1 (CH_2), 24.9 (CH_2), 22.2 (CH_2); IR (neat) 3055, 2941, 2852, 1561, 1445, 1405, 1323, 1227, 1161, 1123, 1107, 1065, 1054, 1019, 854, 843, 805, 754, 740, 694, 650, 609 cm^{-1} .

4.2.8 Synthesis of 3-((1-ethynylcyclohexyl)amino)-3-(4-nitrophenyl)-1-phenyl prop-2-en-1-one (**31h**)

3-(4-Nitrophenyl)-1-phenylprop-2-yn-1-one **29h** (560.0 mg, 2.23 mmol) and 1-ethynylcyclohexylamine (330.2 mg, 2.68 mmol) were employed to afford 577.0 mg (58%) of the indicated product **31h** as a dark yellow solid (R_f = 0.45 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 11.61 (s, 1H), 8.22 (d, J = 8.7 Hz, 2H), 7.87 (d, J = 6.8 Hz, 2H), 7.73 (d, J = 8.7 Hz, 2H), 7.46 – 7.35 (m, 3H), 5.70 (s, 1H), 2.33 (s, 1H), 1.89 – 1.82 (m, 2H), 1.72 – 1.60 (m, 4H), 1.56 – 1.44 (m, 3H), 1.32 – 1.24 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.9 (CO), 163.5 (C), 148.1 (C), 142.9 (C), 139.4 (C), 131.3 (CH), 129.9 (CH), 128.3 (CH), 127.1 (CH), 122.8 (CH), 96.3 (CH), 85.9 (C), 74.7 (CH), 53.7 (C), 40.0 (CH_2), 24.7 (CH_2), 22.0 (CH_2); IR (neat) 3284, 2958, 2858, 1568, 1519, 1475, 1445, 1346, 1327, 1310, 1231, 1172, 1145, 1080, 1056, 1023, 854, 806, 753, 693, 650, 618, 596 cm^{-1} . The spectral data were in agreement with those reported previously for this compound.⁴⁰

4.2.9 Synthesis of 3-(3,4-dichlorophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one (31i)

3-(3,4-Dichlorophenyl)-1-phenylprop-2-yn-1-one **29i** (450.8 mg, 1.64 mmol) and 1-ethynylcyclohexylamine (242.7 mg, 1.97 mmol) were employed to afford 390.8 mg (60%) of the indicated product **31i** as dark orange oil (R_f = 0.63 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 11.56 (s, 1H), 7.93 – 7.88 (m, 2H), 7.73 (d, J = 1.9 Hz, 1H), 7.49 – 7.38 (m, 5H), 5.71 (s, 1H), 2.38 (s, 1H), 1.89 (dd, J = 11.5, 5.4 Hz, 2H), 1.69 (ddd, J = 17.2, 10.0, 3.6 Hz, 4H), 1.61 – 1.45 (m, 3H), 1.35-1.27 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 189.0 (CO), 163.5 (C), 139.7 (C), 136.6 (C), 133.5 (C), 132.0 (C), 131.2 (CH), 131.0 (CH), 129.8 (CH), 128.3 (CH), 128.1 (CH), 127.2 (CH), 96.5 (CH), 86.4 (C), 74.2 (CH), 53.7 (C), 40.0 (CH_2), 24.8 (CH_2), 22.1 (CH_2); IR (neat) 3064, 2933, 2857, 1595, 1575, 1458, 1376, 1325, 1256, 1226, 1155, 1076, 1054, 1024, 890, 826, 753, 732, 694, 645 cm^{-1} .

4.2.10 Synthesis of 3-(4-(*tert*-butyl)phenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one (31j)

3-(4-(*tert*-Butyl)phenyl)-1-phenylprop-2-yn-1-one **29j** (670.0 mg, 2.55 mmol) and 1-ethynylcyclohexylamine (377.0 mg, 3.06 mmol) were employed to afford 650.0 mg (66%) of the indicated product **31j** as a light orange solid (R_f = 0.65 in 4:1 hexane/ethyl acetate; mp = 127.0-128.0 $^\circ\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 11.78 (s, 1H), 7.94 – 7.89 (m, 2H), 7.53 (dd, J = 6.5, 1.9 Hz, 2H), 7.45 – 7.39 (m, 5H), 5.76 (s, 1H), 2.32 (s, 1H), 1.88 (d, J = 6.8 Hz, 2H), 1.78 – 1.70 (m, 3H), 1.66 – 1.52 (m, 5H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.4 (CO), 167.0 (C), 152.6 (C), 140.3 (C), 134.2 (C), 130.9 (CH), 128.4 (CH), 128.3 (CH), 127.2 (CH), 124.7 (CH), 96.3 (CH), 86.8 (C), 73.4 (CH), 53.6 (C), 39.8 (C), 34.9 (CH_2), 31.4 (CH_3), 25.1 (CH_2), 22.2 (CH_2); IR (neat) 3262, 2933, 2858, 1586, 1546, 1498, 1481, 1328, 1292, 1254, 1226, 1167, 1107, 1077, 1057, 1023, 989, 843, 760, 728, 691, 664, 630, 592 cm^{-1} .

4.3 General Procedure for the Synthesis of Arylated *N*-Propargylic β -Enaminones 27 (Table 3)

To a stirred solution of the corresponding *N*-propargylic β -enaminone **35** (1.00 mmol) in DMF (0.30 mL) at room temperature under argon was added (*i*-Pr)₂NH (2.00 mL), PdCl₂(PPh₃)₂ (0.02 mmol) and CuI (0.02 mmol) and aryl iodide (1.55 mmol). The resulting mixture was then stirred at room temperature for approximately 4 h (The progress of the reaction was followed by routine TLC for the disappearance of *N*-propargylic β -enaminone **31** using hexane/ethyl acetate (19:1) as the eluent). After the reaction was over, without removing DMF, ethyl acetate (30 mL) and saturated aqueous NH₄Cl solution (30 mL) were added to perform extraction. After the layers were separated, the aqueous phase was extracted with ethyl acetate (2 $\times$ 30 mL). The combined organic phases were dried over MgSO₄ and evaporated on a rotary evaporator to give a crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (hexane followed by 19:1) as the eluent to afford the corresponding arylated *N*-propargylic β -enaminones **33**.¹⁰

4.3.1 Synthesis of 1,3-diphenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one (**33a**)

3-((1-Ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one **31a** (472.7 mg, 1.43 mmol), (*i*-Pr)₂NH (1.43 mL), PdCl₂(PPh₃)₂ (21.0 mg, 0.030 mmol), CuI (5.70 mg, 0.030 mmol) and iodobenzene (450.0 mg, 2.22 mmol) were employed to afford 530.1 mg (91%) of the indicated product **33a** as yellow oil (*R*_f = 0.60 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.88 (s, 1H), 7.95 – 7.89 (m, 2H), 7.64 – 7.59 (m, 2H), 7.47 – 7.36 (m, 6H), 7.31 (d, *J* = 2.7 Hz, 5H), 5.76 (s, 1H), 2.07 – 1.98 (m, 2H), 1.87 – 1.77 (m, 2H), 1.73 – 1.51 (m, 5H), 1.35 (dd, *J* = 9.0, 3.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) 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), 128.23 (CH), 128.18 (CH), 127.7 (CH), 127.2 (CH), 123.0 (C), 96.2 (CH), 92.2 (C), 85.8 (C), 54.3

(C), 40.2 (CH₂), 25.1 (CH₂), 22.5 (CH₂). The spectral data were in agreement with those reported previously for this compound.¹⁰

4.3.2 Synthesis of 1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)-3-(*p*-tolyl)prop-2-en-1-one (33b)

3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(*p*-tolyl)prop-2-en-1-one **31b** (307.0 mg, 0.89 mmol), (i-Pr)₂NH (1.8 mL), PdCl₂(PPh₃)₂ (12.64 mg, 0.018 mmol), CuI (3.42 mg, 0.018 mmol) and iodobenzene (281.5 mg, 1.38 mmol) were employed to afford 197.0 mg (52%) of the indicated product **33b** as light yellow oil (*R*_f = 0.71 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.93 (s, 1H), 7.98 – 7.92 (m, 2H), 7.54 (t, *J* = 6.8 Hz, 2H), 7.47 – 7.40 (m, 3H), 7.35 – 7.31 (m, 5H), 7.19 (t, *J* = 6.7 Hz, 2H), 5.78 (d, *J* = 5.8 Hz, 1H), 2.40 (d, *J* = 5.7 Hz, 3H), 2.06 (d, *J* = 5.8 Hz, 2H), 1.90 – 1.81 (m, 2H), 1.76 – 1.52 (m, 5H), 1.44 – 1.33 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.3 (CO), 167.1 (C), 140.3 (C), 139.1 (C), 134.3 (C), 131.6 (CH), 130.8 (CH), 128.5 (CH), 128.4 (CH), 128.23 (CH), 128.18 (CH), 128.1 (CH), 127.2 (CH), 123.1 (C), 96.1 (CH), 92.3 (C), 85.9 (C), 54.3 (C), 40.3 (CH₂), 25.1 (CH₂), 22.5 (CH₃), 21.4 (CH₂); IR (neat) 3023, 2930, 2855, 1613, 1581, 1497, 1442, 1327, 1297, 1259, 1225, 1157, 1054, 1023, 894, 819, 752, 689 cm⁻¹.

4.3.3 Synthesis of 3-(4-nitrophenyl)-1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one (33c)

3-((1-Ethynylcyclohexyl)amino)-3-(4-nitrophenyl)-1-phenylprop-2-en-1-one **31h** (481.0 mg, 1.07 mmol), (i-Pr)₂NH (2.0 mL), PdCl₂(PPh₃)₂ (15.02 mg, 0.021 mmol), CuI (3.99 mg, 0.021 mmol) and iodobenzene (338.3 mg, 1.66 mmol) were employed to afford 183.8 mg (38%) of the indicated product **33c** as a yellow solid (*R*_f = 0.49 in 4:1 hexane/ethyl acetate, mp = 121.0-124.7 °C). ¹H NMR (400 MHz, CDCl₃) δ 11.79 (s, 1H), 8.17 (d, *J* = 8.6 Hz, 2H), 7.92 (d, *J* = 7.0 Hz, 2H), 7.76 (d, *J* = 8.6 Hz, 2H), 7.50 – 7.40 (m, 3H), 7.34 – 7.27 (m, 3H), 7.20 (dd, *J* = 7.5, 1.8 Hz, 2H), 5.73

(s, 1H), 2.04 (d, $J = 12.4$ Hz, 2H), 1.86 – 1.78 (m, 2H), 1.76 – 1.54 (m, 5H), 1.37 – 1.31 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.9 (CO), 163.7 (C), 148.0 (C), 143.2 (C), 139.6 (C), 131.3 (CH), 129.8 (CH), 128.6 (CH), 128.4 (CH), 127.2 (CH), 122.9 (CH), 122.3 (C), 96.1 (CH), 91.4 (C), 87.2 (C), 54.6 (C), 40.6 (CH_2), 24.8 (CH_2), 22.5 (CH_2) (Note that two CH peaks overlap with each others); IR (neat) 3018, 2924, 2858, 1561, 1513, 1478, 1344, 1332, 1258, 1152, 1057, 1026, 984, 895, 865, 854, 754, 688 cm^{-1} .

4.3.4 Synthesis of 1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)-3-(thiophen-3-yl)prop-2-en-1-one (33d)

3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(thiophen-3-yl)prop-2-en-1-one **31f** (212.1 mg, 0.63 mmol), (*i*-Pr) $_2$ NH (1.2 mL), $\text{PdCl}_2(\text{PPh}_3)_2$ (9.13 mg, 0.013 mmol), CuI (2.47 mg, 0.013 mmol) and iodobenzene (199.9 mg, 0.98 mmol) were employed to afford 200.7 mg (77%) of the indicated product **33d** as a orange oil ($R_f = 0.56$ in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 11.78 (s, 1H), 7.84 – 7.78 (m, 2H), 7.54 (dd, $J = 2.8, 0.9$ Hz, 1H), 7.35 – 7.27 (m, 5H), 7.26 – 7.19 (m, 5H), 5.72 (s, 1H), 1.95 (s, 1H), 1.92 (d, $J = 6.1$ Hz, 1H), 1.74 – 1.67 (m, 2H), 1.57 (dtd, $J = 17.6, 9.6, 3.8$ Hz, 4H), 1.47 – 1.40 (m, 1H), 1.24 (dq, $J = 13.0, 4.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.4 (CO), 161.5 (C), 140.1 (C), 137.3 (C), 131.6 (CH), 130.9 (CH), 128.7 (CH), 128.3 (CH), 128.3 (CH), 127.1 (CH), 125.8 (CH), 125.0 (CH), 123.0 (C), 95.8 (CH), 92.3 (C), 85.6 (C), 54.1 (C), 39.9 (CH_2), 25.1 (CH_2), 22.5 (CH_2) (Note that two CH peaks overlap with each others); IR (neat) 3057, 2930, 2854, 1736, 1582, 1480, 1442, 1369, 1316, 1258, 1225, 1157, 1054, 1023, 913, 890, 826, 787, 751, 688 cm^{-1} .

4.3.5 Synthesis of 1-phenyl-3-(thiophen-3-yl)-3-((1-(*p*-tolylethynyl)cyclohexyl)amino)prop-2-en-1-one (**33e**)

3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(thiophen-3-yl)prop-2-en-1-one **31f** (223.0 mg, 0.66 mmol), (*i*-Pr)₂NH (1.2 mL), PdCl₂(PPh₃)₂ (9.13 mg, 0.013 mmol), CuI (2.47 mg, 0.013 mmol) and 1-iodo-4-methylbenzene (223.1 mg, 1.02 mmol) were employed to afford 202.4 mg (72%) of the indicated product **33e** as an orange solid (*R*_f = 0.63 in 4:1 hexane/ethyl acetate; mp = 98.0-99.8 °C). ¹H NMR (400 MHz, CDCl₃) δ 11.78 (s, 1H), 7.83 – 7.78 (m, 2H), 7.55 (dd, *J* = 2.9, 1.2 Hz, 1H), 7.37-7.26 (m, 4H), 7.19 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.15 (d, *J* = 8.1 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 2H), 5.72 (s, 1H), 2.26 (s, 3H), 1.97 – 1.87 (m, 2H), 1.74 – 1.66 (m, 2H), 1.61 – 1.50 (m, 4H), 1.43 (dd, *J* = 9.0, 3.8 Hz, 1H), 1.30-1.18 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.3 (CO), 161.6 (C), 140.2 (C), 138.3 (C), 137.3 (C), 131.5 (CH), 130.9 (CH), 129.1 (CH), 128.7 (CH), 128.3 (CH), 127.2 (CH), 125.9 (CH), 125.0 (CH), 119.9 (C), 95.8 (CH), 91.6 (C), 85.7 (C), 54.2 (C), 39.9 (CH₂), 25.1 (CH₂), 22.5 (CH₂), 21.5 (CH₃); IR (neat) 3102, 2935, 2853, 1582, 1551, 1502, 1483, 1442, 1395, 1372, 1322, 1294, 1260, 1228, 1159, 1075, 1057, 1025, 922, 891, 868, 811, 800, 750, 724, 697 cm⁻¹.

4.3.6 Synthesis of 3-(2-methoxyphenyl)-1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one (**33f**)

3-((1-Ethynylcyclohexyl)amino)-3-(2-methoxyphenyl)-1-phenylprop-2-en-1-one **31e** (257.8 mg, 0.72 mmol), (*i*-Pr)₂NH (1.4 mL), PdCl₂(PPh₃)₂ (9.83 mg, 0.014 mmol), CuI (2.66 mg, 0.014 mmol) and iodobenzene (228.5 mg, 1.12 mmol) were employed to afford 142.0 mg (46%) of the indicated product **33f** as green oil (*R*_f = 0.49 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 12.10 (s, 1H), 7.91 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.48 – 7.33 (m, 6H), 7.32 – 7.27 (m, 3H), 7.25 – 7.23 (m, 1H), 6.98 – 6.91 (m, 1H), 6.86 (d, *J* = 8.3 Hz, 1H), 5.70 (s, 1H), 3.73 (s, 3H), 1.94 (s, 2H), 1.87 – 1.66 (m, 5H), 1.63 – 1.49 (m, 2H), 1.42 – 1.34 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.2 (CO), 163.9 (C), 156.6 (C), 140.4 (C), 131.8 (C), 130.71

(CH), 130.66 (CH), 130.4 (CH), 128.2 (CH), 128.14 (CH), 128.08 (CH), 127.2 (CH), 125.6 (CH), 123.2 (CH), 119.6 (CH), 110.6 (C), 95.8 (CH), 91.5 (C), 85.2 (C), 55.4 (CH₃), 54.2 (C), 39.0 (CH₂), 25.2 (CH₂), 22.6 (CH₂); IR (neat) 3032, 2930, 2855, 1736, 1570, 1479, 1325, 1299, 1243, 1157, 1111, 1055, 1023, 895, 806, 750, 689 cm⁻¹.

4.3.7 Synthesis of 3-(3,4-dichlorophenyl)-1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino) prop-2-en-1-one (33g)

3-(3,4-Dichlorophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one **31i** (300.0 mg, 0.75 mmol), (i-Pr)₂NH (1.5 mL), PdCl₂(PPh₃)₂ (10.5 mg, 0.015 mmol), CuI (2.85 mg, 0.015 mmol) and iodobenzene (236.6 mg, 1.16 mmol) were employed to afford 222.0 mg (62%) of the indicated product **33g** as yellow oil (*R*_f = 0.66 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.61 (s, 1H), 7.79 (dd, *J* = 8.1, 1.4 Hz, 2H), 7.61 (s, 1H), 7.37 – 7.26 (m, 5H), 7.22 – 7.14 (m, 5H), 5.59 (s, 1H), 1.97 – 1.88 (m, 2H), 1.74 – 1.65 (m, 2H), 1.64 – 1.49 (m, 4H), 1.48 – 1.40 (m, 1H), 1.27 – 1.18 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.9 (CO), 163.7 (C), 139.8 (C), 136.9 (C), 133.5 (C), 132.2 (C), 131.6 (CH), 131.2 (CH), 130.7 (CH), 129.8 (CH), 128.41 (CH), 128.37 (CH), 128.3 (CH), 128.0 (CH), 127.2 (CH), 122.5 (C), 96.3 (CH), 91.5 (C), 87.0 (C), 54.6 (C), 40.6 (CH₂), 25.0 (CH₂), 22.5 (CH₂); IR (neat) 3034, 2931, 2855, 1594, 1573, 1458, 1325, 1259, 1225, 1155, 1054, 1023, 991, 887, 824, 752, 732, 689 cm⁻¹.

4.3.8 Synthesis of 3-(4-(*tert*-butyl)phenyl)-1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one (33h)

3-(4-(*tert*-Butyl)phenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one **31j** (190.7 mg, 0.49 mmol), (i-Pr)₂NH (1.0 mL), PdCl₂(PPh₃)₂ (7.0 mg, 0.010 mmol), CuI (1.9 mg, 0.010 mmol) and iodobenzene (155.0 mg, 0.76 mmol) were employed to afford 196.8 mg (86%) of the indicated product **33h** as orange oil (*R*_f = 0.66 in 4:1

hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 11.81 (s, 1H), 7.80 (dd, J = 8.0, 1.6 Hz, 2H), 7.41 (dd, J = 6.6, 1.8 Hz, 2H), 7.32 – 7.22 (m, 5H), 7.18 – 7.13 (m, 3H), 7.12 – 7.07 (m, 2H), 5.64 (s, 1H), 1.96 (dd, J = 11.5, 4.8 Hz, 2H), 1.78 – 1.70 (m, 2H), 1.69 – 1.46 (m, 5H), 1.42 (dd, J = 8.2, 3.9 Hz, 1H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.2 (CO), 167.2 (C), 152.0 (C), 140.3 (C), 134.2 (C), 131.6 (CH), 130.8 (CH), 128.3 (CH), 128.2 (CH), 128.14 (CH), 128.09 (CH), 127.2 (CH), 124.7 (CH), 123.1 (C), 96.3 (CH), 91.8 (C), 86.4 (C), 54.4 (C), 40.6 (C), 34.7 (CH_2), 31.3 (CH_3), 25.1 (CH_2), 22.6 (CH_2); IR (neat) 3034, 2931, 2857, 1737, 1613, 1581, 1497, 1443, 1328, 1259, 1226, 1157, 1105, 1054, 1023, 894, 834, 754, 689 cm^{-1} .

4.3.9 Synthesis of 3-((1-((3-bromophenyl)ethynyl)cyclohexyl)amino)-3-(4-(*tert*-butyl)phenyl)-1-phenylprop-2-en-1-one (33i)

3-(4-(*tert*-Butyl)phenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one **31j** (650.0 mg, 1.69 mmol), (*i*-Pr) $_2$ NH (3.4 mL), $\text{PdCl}_2(\text{PPh}_3)_2$ (23.9 mg, 0.034 mmol), CuI (6.46 mg, 0.034 mmol) and 1-bromo-3-iodobenzene (741.2 mg, 2.62 mmol) were employed to afford 684.8 mg (75%) of the indicated product **33i** as an orange solid (R_f = 0.63 in 4:1 hexane/ethyl acetate; mp = 71.4-75.1 $^\circ\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 11.77 (s, 1H), 7.78 (d, J = 7.8 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.23 (t, J = 9.6 Hz, 7H), 6.97 (d, J = 6.6 Hz, 2H), 5.63 (s, 1H), 1.96 – 1.89 (m, 2H), 1.77 – 1.68 (m, 3H), 1.52 – 1.37 (m, 5H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.3 (CO), 166.9 (C), 152.1 (C), 140.1 (C), 134.13 (C), 134.09 (C), 131.2 (CH), 130.8 (CH), 130.1 (CH), 129.6 (CH), 128.3 (CH), 128.2 (CH), 127.1 (CH), 125.0 (CH), 124.6 (CH), 121.9 (C), 96.4 (CH), 93.1 (C), 84.9 (C), 54.2 (C), 40.5 (C), 34.7 (CH_2), 31.2 (CH_3), 25.0 (CH_2), 22.5 (CH_2); IR (neat) 3057, 2928, 2856, 1736, 1664, 1578, 1546, 1498, 1475, 1444, 1400, 1329, 1297, 1258, 1229, 1150, 1105, 1057, 1023, 992, 893, 836, 785, 756, 731, 682 cm^{-1} .

4.3.10 Synthesis of 3-(4-(*tert*-butyl)phenyl)-1-phenyl-3-((1-(*p*-tolylethynyl)cyclohexyl)amino) prop-2-en-1-one (**33j**)

3-(4-(*Tert*-butyl)phenyl)-3-((1-ethynlycyclohexyl)amino)-1-phenylprop-2-en-1-one **31j** (318.0 mg, 0.82 mmol), (i-Pr)₂NH (1.66 mL), PdCl₂(PPh₃)₂ (11.23 mg, 0.016 mmol), CuI (3.04 mg, 0.016 mmol) and 1-iodo-4-methylbenzene (276.9 mg, 1.27 mmol) were employed to afford 294.0 mg (75%) of the indicated product **33j** as yellow oil (*R_f* = 0.68 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.97 (t, *J* = 2.9 Hz, 1H), 7.98 – 7.92 (m, 2H), 7.56 (td, *J* = 8.4, 4.8 Hz, 2H), 7.47 – 7.36 (m, 5H), 7.18 – 7.07 (m, 4H), 5.79 (t, *J* = 4.8 Hz, 1H), 2.40 – 2.31 (m, 3H), 2.09 (s, 2H), 1.93 – 1.85 (m, 2H), 1.78 – 1.65 (m, 4H), 1.56 (s, 1H), 1.41 (s, 1H), 1.36 (t, *J* = 4.8 Hz, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 188.2 (CO), 167.2 (C), 152.0 (C), 140.3 (C), 138.1 (C), 134.3 (C), 131.5 (CH), 130.8 (CH), 128.9 (CH), 128.3 (CH), 128.2 (CH), 127.2 (CH), 124.6 (CH), 120.1 (C), 96.2 (CH), 91.1 (C), 86.4 (C), 54.4 (C), 40.6 (C), 34.7 (CH₃), 31.3 (CH₂), 25.1 (CH₂), 22.6 (CH₂), 21.5 (CH₃); IR (neat) 3029, 2931, 2857, 1738, 1580, 1498, 1478, 1327, 1300, 1260, 1226, 1158, 1106, 1054, 1023, 990, 894, 836, 815, 758, 742, 692 cm⁻¹.

4.3.11 Synthesis of 3-(4-(*tert*-butyl)phenyl)-3-((1-((4-fluorophenyl)ethynyl)cyclohexyl)amino)-1-phenylprop-2-en-1-one (**33k**)

3-(4-(*tert*-Butyl)phenyl)-3-((1-ethynlycyclohexyl)amino)-1-phenylprop-2-en-1-one **31j** (301.0 mg, 0.78 mmol), (i-Pr)₂NH (1.56 mL), PdCl₂(PPh₃)₂ (11.2 mg, 0.016 mmol), CuI (3.0 mg, 0.016 mmol) and 1-fluoro-4-iodobenzene (268.6 mg, 1.21 mmol) were employed to afford 247.0 mg (66%) of the indicated product **33k** as orange oil (*R_f* = 0.71 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.93 (s, 1H), 7.93 (t, *J* = 5.8 Hz, 2H), 7.54 – 7.50 (m, 2H), 7.40 (tdd, *J* = 8.4, 6.5, 4.9 Hz, 5H), 7.22 – 7.16 (m, 2H), 7.01 – 6.94 (m, 2H), 5.79 – 5.76 (m, 1H), 2.08 – 2.05 (m, 2H), 1.87 (t, *J* = 11.3 Hz, 2H), 1.73 (s, 2H), 1.67 – 1.61 (m, 2H), 1.51 (d, *J* = 21.6 Hz, 1H), 1.37 (s, 1H), 1.34 – 1.32 (m, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 188.3 (CO), 167.1 (C), 162.4 (d, ¹*J* = 249.0 Hz, C), 152.1 (C), 140.3 (C), 134.3 (C),

133.5 (d, $^3J = 8.3$ Hz, CH), 130.8 (CH), 128.3 (CH), 128.2 (CH), 127.2 (CH), 124.6 (CH), 119.2 (d, $^4J = 3.1$ Hz, C), 115.4 (d, $^2J = 22.0$ Hz, CH), 96.3 (CH), 91.5 (C), 85.4 (C), 54.4 (C), 40.6 (C), 34.7 (CH₂), 31.3 (CH₃), 25.1 (CH₂), 22.6 (CH₂); IR (neat) 3060, 2933, 2858, 1738, 1580, 1504, 1478, 1328, 1302, 1260, 1220, 1153, 1106, 1055, 1023, 895, 834, 759, 743, 692 cm⁻¹.

4.3.12 Synthesis of 1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (33l)

3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **31g** (427.0 mg, 1.07 mmol), (i-Pr)₂NH (2.14 mL), PdCl₂(PPh₃)₂ (14.7 mg, 0.021 mmol), CuI (4.0 mg, 0.021 mmol) and iodobenzene (338.6 mg, 1.66 mmol) were employed to afford 364.4 mg (72%) of the indicated product **33l** as yellow oil ($R_f = 0.56$ in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.84 (s, 1H), 7.94 – 7.88 (m, 2H), 7.71 (d, $J = 8.0$ Hz, 2H), 7.61 (d, $J = 8.1$ Hz, 2H), 7.45 (td, $J = 14.1, 7.0$ Hz, 3H), 7.36 – 7.27 (m, 3H), 7.18 (dd, $J = 7.7, 1.5$ Hz, 2H), 5.72 (s, 1H), 2.06 (d, $J = 9.9$ Hz, 2H), 1.89 – 1.80 (m, 2H), 1.78 – 1.53 (m, 5H), 1.29 (t, $J = 7.1$ Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.9 (CO), 164.9 (C), 140.6 (C), 139.9 (C), 131.6 (C), 131.2 (CH), 131.1 (q, $^2J = 27.0$ Hz, C), 129.2 (CH), 128.5 (CH), 128.4 (CH), 128.3 (CH), 127.3 (CH), 124.8 (q, $^3J = 5.8$ Hz, CH), 121.4 (q, $^1J = 258.9$ Hz, CF₃), 96.3 (CH), 91.5 (C), 87.1 (C), 54.6 (C), 40.7 (CH₂), 25.0 (CH₂), 22.6 (CH₂) (Note that two CH peaks overlap with each others); IR (neat) 3022, 2934, 2857, 1566, 1489, 1444, 1404, 1320, 1260, 1227, 1162, 1125, 1054, 1021, 907, 851, 754, 733, 690 cm⁻¹.

4.3.13 Synthesis of 1-phenyl-3-((1-(p-tolylethynyl)cyclohexyl)amino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one (33m)

3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **31g** (513.0 mg, 1.29 mmol), (i-Pr)₂NH (2.6 mL), PdCl₂(PPh₃)₂ (18.3 mg, 0.026

mmol), CuI (4.9 mg, 0.026 mmol) and 1-iodo-4-methylbenzene (436.0 mg, 2.00 mmol) were employed to afford 493.0 mg (78%) of the indicated product **33m** as yellow oil (R_f = 0.54 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 11.90 (s, 1H), 7.99 – 7.92 (m, 2H), 7.73 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 6.8 Hz, 2H), 7.49 – 7.40 (m, 3H), 7.16 – 7.08 (m, 4H), 5.75 (d, J = 2.0 Hz, 1H), 2.53 – 2.25 (m, 3H), 2.12 – 2.04 (m, 2H), 1.87 (t, J = 9.9 Hz, 2H), 1.66 (dd, J = 39.3, 29.1 Hz, 5H), 1.39 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.7 (CO), 164.9 (C), 140.6 (C), 139.9 (C), 138.5 (C), 131.4 (C), 131.1 (CH), 130.9 (q, 2J = 38.2 Hz, C), 129.1 (CH), 129.0 (CH), 128.3 (CH), 127.2 (CH), 124.6 (q, 3J = 3.5 Hz, CH), 124.0 (q, 1J = 272.4 Hz, CF_3), 119.5 (CH), 96.2 (CH), 90.7 (C), 87.2 (C), 54.5 (C), 40.7 (CH_3), 24.9 (CH_2), 22.5 (CH_2), 21.4 (CH_2); IR (neat) 3031, 2933, 2857, 1738, 1563, 1509, 1445, 1404, 1320, 1226, 1161, 1124, 1107, 1052, 1019, 839, 815, 755, 690 cm^{-1} .

4.3.14 Synthesis of 1,3-diphenyl-3-((1-(p-tolylethynyl)cyclohexyl)amino)prop-2-en-1-one (**33n**)

3-((1-Ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one **31a** (287.3 mg, 0.87 mmol), (i-Pr) $_2$ NH (1.8 mL), $\text{PdCl}_2(\text{PPh}_3)_2$ (11.9 mg, 0.017 mmol), CuI (3.2 mg, 0.017 mmol) and 1-iodo-4-methylbenzene (294.4 mg, 1.35 mmol) were employed to afford 271.9 mg (74%) of the indicated product **33n** as yellow oil (R_f = 0.60 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 11.91 (s, 1H), 7.94 (dd, J = 8.1, 1.5 Hz, 2H), 7.63 (dd, J = 7.8, 1.6 Hz, 2H), 7.47 – 7.36 (m, 6H), 7.17 (dd, J = 30.1, 8.1 Hz, 4H), 5.76 (s, 1H), 2.38 (s, 3H), 2.07 – 2.00 (m, 2H), 1.87 – 1.79 (m, 2H), 1.73 – 1.61 (m, 4H), 1.54 (dd, J = 8.5, 4.2 Hz, 1H), 1.41 – 1.32 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.5 (CO), 166.9 (C), 140.2 (C), 138.2 (C), 137.0 (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), 40.2 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 21.5 (CH_3); IR (neat) 3025, 2920, 2859, 1736, 1552, 1508, 1476, 1442, 1327, 1304, 1274, 1260, 1228, 1151, 1054, 1025, 985, 929, 897, 849, 822,

790, 758, 693 cm^{-1} . The spectral data were in agreement with those reported previously for this compound.¹⁰

4.3.15 Synthesis of 3-((1-((3-bromophenyl)ethynyl)cyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**33o**)

3-((1-Ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one **31a** (360.0 mg, 1.9 mmol), (i-Pr)₂NH (2.0 mL), PdCl₂(PPh₃)₂ (15.4 mg, 0.022 mmol), CuI (4.2 mg, 0.022 mmol) and 1-bromo-3-iodobenzene (478.1 mg, 1.69 mmol) were employed to afford 420.8 mg (80%) of the indicated product **33o** as a yellow solid (R_f = 0.55 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.75 (s, 1H), 7.84 – 7.79 (m, 2H), 7.50 – 7.45 (m, 2H), 7.36 – 7.24 (m, 8H), 7.07 (dt, J = 15.3, 7.7 Hz, 2H), 5.65 (s, 1H), 1.97 – 1.87 (m, 2H), 1.76 – 1.67 (m, 2H), 1.61 (dd, J = 9.9, 3.6 Hz, 2H), 1.54 – 1.40 (m, 3H), 1.24 (dd, J = 9.5, 3.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.5 (CO), 166.6 (C), 140.1 (C), 137.0 (C), 134.4 (C), 131.3 (CH), 130.9 (CH), 130.0 (CH), 129.6 (CH), 129.2 (CH), 128.6 (CH), 128.3 (CH), 127.8 (CH), 127.2 (CH), 124.9 (CH), 122.0 (C), 96.3 (CH), 93.5 (C), 84.5 (C), 54.2 (C), 40.2 (CH₂), 25.0 (CH₂), 22.5 (CH₂); IR (neat) 3020, 2935, 2855, 1688, 1605, 1585, 1552, 1472, 1441, 1328, 1294, 1259, 1228, 1151, 1077, 1056, 1026, 982, 891, 792, 767, 750, 714, 699 cm^{-1} . The spectral data were in agreement with those reported previously for this compound.¹⁰

4.3.16 Synthesis of 1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)-3-(*m*-tolyl)prop-2-en-1-one (**33p**)

3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(*m*-tolyl)prop-2-en-1-one **31c** (335.0 mg, 0.98 mmol), (i-Pr)₂NH (2.0 mL), PdCl₂(PPh₃)₂ (14.04 mg, 0.020 mmol), CuI (3.8 mg, 0.020 mmol) and iodobenzene (310.1 mg, 1.52 mmol) were employed to afford 242.0 mg (58%) of the indicated product **33p** as yellow oil (R_f = 0.49 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.96 (s, 1H), 8.01-7.91 (m,

2H), 7.48 – 7.41 (m, 5H), 7.34 – 7.32 (m, 6H), 7.23 (d, $J = 5.5$ Hz, 1H), 5.80 (t, $J = 4.6$ Hz, 1H), 2.29 (t, $J = 4.5$ Hz, 3H), 2.06 (s, 2H), 1.92 – 1.81 (m, 2H), 1.74 – 1.63 (m, 4H), 1.56 (s, 1H), 1.41 – 1.36 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.3 (CO), 167.0 (C), 140.2 (C), 137.4 (C), 136.9 (C), 131.6 (CH), 130.8 (CH), 129.8 (CH), 129.2 (CH), 128.2 (CH), 128.1 (CH), 127.6 (CH), 127.1 (CH), 125.5 (CH), 123.0 (C), 96.0 (CH), 92.2 (C), 85.7 (C), 54.2 (C), 40.1 (CH_2), 25.0 (CH_2), 22.4 (CH_2), 21.3 (CH_3) (Note that two CH peaks overlap with each others); IR (neat) 3022, 2930, 2855, 1737, 1570, 1507, 1473, 1443, 1327, 1299, 1259, 1230, 1157, 1054, 1024, 999, 895, 787, 753, 688 cm^{-1} .

4.3.17 Synthesis of 3-((1-((4-fluorophenyl)ethynyl)cyclohexyl)amino)-1-phenyl-3-(*m*-tolyl)prop-2-en-1-one (33q)

3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(*m*-tolyl)prop-2-en-1-one **31c** (390.0 mg, 1.14 mmol), (i-Pr) $_2$ NH (2.3 mL), $\text{PdCl}_2(\text{PPh}_3)_2$ (16.1 mg, 0.023 mmol), CuI (4.37 mg, 0.023 mmol) and 1-fluoro-4-iodobenzene (392.9 mg, 1.77 mmol) were employed to afford 398.0 mg (79%) of the indicated product **33q** as yellow oil ($R_f = 0.46$ in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 11.94 (s, 1H), 7.96 (dd, $J = 7.9, 1.6$ Hz, 2H), 7.42 (dd, $J = 12.5, 4.9$ Hz, 5H), 7.31 – 7.25 (m, 3H), 7.21 (d, $J = 7.6$ Hz, 1H), 7.01 (t, $J = 8.7$ Hz, 2H), 5.79 (s, 1H), 2.28 (s, 3H), 2.05 (d, $J = 11.1$ Hz, 2H), 1.85 (dd, $J = 16.2, 6.5$ Hz, 2H), 1.77 – 1.70 (m, 2H), 1.68 – 1.61 (m, 2H), 1.58 – 1.51 (m, 1H), 1.37 (dd, $J = 9.2, 3.8$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.3 (CO), 166.9 (C), 162.4 (d, $^1J = 249.4$ Hz, C), 140.1 (C), 137.3 (C), 137.0 (C), 133.4 (d, $^3J = 8.2$ Hz, CH), 130.8 (CH), 129.8 (CH), 129.2 (CH), 128.2 (CH), 127.5 (CH), 127.1 (CH), 125.5 (CH), 119.1 (d, $^4J = 3.5$ Hz, C), 115.4 (d, $^2J = 22.0$ Hz, CH), 96.1 (CH), 91.9 (C), 84.6 (C), 54.1 (C), 40.2 (CH_2), 25.0 (CH_2), 22.4 (CH_2), 21.3 (CH_3); IR (neat) 3023, 2930, 2856, 1571, 1504, 1474, 1444, 1327, 1260, 1229, 1154, 1054, 1024, 895, 834, 795, 753, 689 cm^{-1} .

4.3.18 Synthesis of 1-phenyl-3-(*m*-tolyl)-3-((1-(*p*-tolylethynyl)cyclohexyl)amino)prop-2-en-1-one (**33r**)

3-((1-Ethynylcyclohexyl)amino)-1-phenyl-3-(*m*-tolyl)prop-2-en-1-one **31c** (417.0 mg, 1.21 mmol), (i-Pr)₂NH (2.4 mL), PdCl₂(PPh₃)₂ (16.8 mg, 0.024 mmol), CuI (4.6 mg, 0.024 mmol) and 1-iodo-4-methylbenzene (409.8 mg, 1.88 mmol) were employed to afford 360.6 mg (69%) of the indicated product **33r** as a light yellow solid (*R*_f = 0.51 in 4:1 hexane/ethyl acetate, mp = 103.6-104.3°C). ¹H NMR (400 MHz, CDCl₃) δ 11.98 (s, 1H), 7.98 (d, *J* = 7.4 Hz, 2H), 7.49 (s, 1H), 7.44 (d, *J* = 7.1 Hz, 4H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 7.9 Hz, 3H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.81 (s, 1H), 2.38 (s, 3H), 2.32 (s, 3H), 2.10 – 2.04 (m, 2H), 1.86 (dd, *J* = 16.0, 6.4 Hz, 2H), 1.78 – 1.62 (m, 4H), 1.55 (d, *J* = 3.6 Hz, 1H), 1.39 (dd, *J* = 8.9, 3.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.2 (CO), 167.1 (C), 140.2 (C), 138.1 (C), 137.3 (C), 137.0 (C), 131.4 (CH), 130.7 (CH), 129.8 (CH), 129.2 (CH), 128.9 (CH), 128.2 (CH), 127.5 (CH), 127.1 (CH), 125.5 (CH), 119.9 (C), 95.9 (CH), 91.5 (C), 85.8 (C), 54.2 (C), 40.2 (CH₃), 25.1 (CH₂), 22.4 (CH₃), 21.4 (CH₂), 21.3 (CH₂); IR (neat) 3021, 2922, 2856, 1449, 1507, 1476, 1445, 1330, 1303, 1259, 1231, 1152, 1054, 1025, 898, 819, 796, 756, 691 cm⁻¹.

4.3.19 Synthesis of 3-((1-((4-fluorophenyl)ethynyl)cyclohexyl)amino)-1,3-diphenylprop-2-en-1-one (**33s**)

3-((1-Ethynylcyclohexyl)amino)-1,3-diphenylprop-2-en-1-one **31a** (496.0 mg, 1.51 mmol), (i-Pr)₂NH (3.0 mL), PdCl₂(PPh₃)₂ (21.1 mg, 0.030 mmol), CuI (5.7 mg, 0.030 mmol) and 1-fluoro-4-iodobenzene (519.5 mg, 2.34 mmol) were employed to afford 512.8 mg (80%) of the indicated product **33s** as yellow oil (*R*_f = 0.49 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.76 (s, 1H), 7.80 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.48 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.29 (ddd, *J* = 17.3, 9.9, 7.0 Hz, 6H), 7.13 (dd, *J* = 8.7, 5.4 Hz, 2H), 6.88 (t, *J* = 8.7 Hz, 2H), 5.64 (s, 1H), 1.93 – 1.85 (m, 2H), 1.75 – 1.67 (m, 2H), 1.60 (dd, *J* = 9.8, 3.8 Hz, 2H), 1.54 – 1.38 (m, 3H), 1.31-1.19 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.6 (CO), 166.8 (C), 162.4 (d, ¹*J* =

249.4 Hz, C), 140.2 (C), 137.1 (C), 133.5 (d, $^3J = 8.4$ Hz, CH), 131.0 (CH), 129.1 (CH), 128.6 (CH), 128.3 (CH), 127.7 (CH), 127.2 (CH), 119.1 (d, $^4J = 3.1$ Hz, C), 115.5 (d, $^2J = 22.0$ Hz, CH), 96.3 (CH), 91.9 (C), 84.9 (C), 54.3 (C), 40.3 (CH₂), 25.1 (CH₂), 22.5 (CH₂); IR (neat) 3059, 2918, 2853, 1763, 1555, 1503, 1443, 1327, 1260, 1224, 1150, 1053, 1025, 985, 927, 897, 841, 794, 759, 691 cm⁻¹. The spectral data were in agreement with those reported previously for this compound.¹⁰

4.3.20 Synthesis of 3-(4-chlorophenyl)-1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one (33t)

3-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one **31d** (277.0 mg, 0.76 mmol), (i-Pr)₂NH (1.6 mL), PdCl₂(PPh₃)₂ (10.5 mg, 0.015 mmol), CuI (2.9 mg, 0.015 mmol) and iodobenzene (240.7 mg, 1.18 mmol) were employed to afford 196.4 mg (59%) of the indicated product **33t** as yellow oil (*R*_f = 0.60 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 11.69 (s, 1H), 7.80 (dt, *J* = 6.8, 1.5 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.38 – 7.29 (m, 3H), 7.25 – 7.20 (m, 5H), 7.18 – 7.14 (m, 2H), 5.61 (s, 1H), 1.95 – 1.89 (m, 2H), 1.76 – 1.66 (m, 2H), 1.61 – 1.50 (m, 4H), 1.48 – 1.42 (m, 1H), 1.27 – 1.23 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 188.7 (CO), 165.4 (C), 140.0 (C), 135.5 (C), 135.2 (C), 131.6 (CH), 131.1 (CH), 130.1 (CH), 128.3 (CH), 128.0 (CH), 127.2 (CH), 122.8 (C), 96.2 (CH), 91.9 (C), 86.4 (C), 54.4 (C), 40.4 (CH₂), 25.0 (CH₂), 22.5 (CH₂) (Note that three CH peaks overlap with each other); IR (neat) 3056, 2930, 2855, 1737, 1577, 1559, 1473, 1443, 1325, 1258, 1225, 1157, 1090, 1053, 1023, 893, 752, 688, 620 cm⁻¹. The spectral data were in agreement with those reported previously for this compound.¹⁰

4.3.21 Synthesis of 3-((1-((3-bromophenyl)ethynyl)cyclohexyl)amino)-3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (33u)

3-(4-Chlorophenyl)-3-((1-ethynylcyclohexyl)amino)-1-phenylprop-2-en-1-one **31d** (252.8 mg, 1.44 mmol), (i-Pr)₂NH (1.4 mL), PdCl₂(PPh₃)₂ (20.4 mg, 0.029 mmol),

CuI (5.5 mg, 0.029 mmol) and 1-bromo-3-iodobenzene (630.9 mg, 2.23 mmol) were employed to afford 307.7 mg (84%) of the indicated product **33u** as orange oil ($R_f = 0.63$ in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 11.67 (s, 1H), 7.80 (dd, $J = 8.1, 1.3$ Hz, 2H), 7.41 (d, $J = 8.4$ Hz, 2H), 7.37 – 7.27 (m, 5H), 7.26 – 7.15 (m, 2H), 7.12 – 7.03 (m, 2H), 5.62 (s, 1H), 1.98 – 1.88 (m, 2H), 1.76 – 1.67 (m, 2H), 1.65 – 1.58 (m, 2H), 1.49 (dt, $J = 13.4, 10.1$ Hz, 3H), 1.29 – 1.21 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 188.7 (CO), 165.2 (C), 139.8 (C), 135.4 (C), 135.3 (C), 134.3 (C), 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 (CH), 122.1 (C), 96.3 (CH), 93.1 (C), 85.0 (C), 54.3 (C), 40.4 (CH_2), 24.9 (CH_2), 22.5 (CH_2); IR (neat) 3077, 2934, 2856, 1743, 1578, 1556, 1474, 1327, 1298, 1259, 1228, 1148, 1090, 1076, 1055, 1014, 984, 892, 831, 784, 756, 713, 679, 606 cm^{-1} . The spectral data were in agreement with those reported previously for this compound.¹⁰

4.4 General Procedure for the Synthesis of Spiro-2*H*-Pyrroles with 1,4-Dicarbonyl Groups **34** (Table 4)

To a stirred solution of spiro-containing *N*-propargylic β -enaminone **33** (0.30 mmol) in DMSO (5 mL) was added Cs_2CO_3 (0.90 mmol) under air and the solution was allowed to stir at 80 °C for approximately 1.5 h. (The progress of the reaction was monitored by routine TLC for the disappearance of *N*-propargylic β -enaminone **33** using hexane/ethyl acetate (9:1) as the eluent. After completion of the reaction, the reaction mixture was cooled to room temperature. After cooling, 30 mL of chloroform and ice obtained from 30 mL distilled water were added to reaction mixture. The resulting mixture was stirred for 10 minutes and the aqueous layer was extracted with chloroform (2 x 15 mL). And then, the organic layer was dried over MgSO_4 and evaporated on the rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (15:1 followed by 9:1) as the eluent to afford the corresponding spiro-2*H*-pyrroles **34**.¹⁰

4.4.1 Synthesis of (2-phenyl-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenyl methanone) (34a)

1,3-Diphenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one **33a** (123.1 mg, 0.30 mmol) and Cs₂CO₃ (293.2 mg, 0.90 mmol) were employed to afford 77.4 mg (62%) of indicated product **34a** as a yellow solid (*R_f* = 0.40 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 7.56 – 7.52 (m, 2H), 7.51 – 7.47 (m, 2H), 7.46 – 7.42 (m, 2H), 7.41 – 7.35 (m, 2H), 7.29 – 7.17 (m, 7H), 2.13 – 1.99 (m, 4H), 1.84 (d, *J* = 13.6 Hz, 1H), 1.73 (d, *J* = 11.6 Hz, 2H), 1.60 – 1.54 (m, 2H), 1.31 (dd, *J* = 12.5, 3.4 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 194.5 (CO), 192.9 (CO), 170.9 (C), 166.8 (C), 137.7 (C), 137.2 (C), 137.0 (C), 134.0 (C), 133.9 (CH), 133.6 (CH), 130.1 (CH), 129.5 (CH), 129.3 (CH), 128.64 (CH), 128.58 (CH), 128.54 (CH), 128.48 (CH), 85.3 (C), 33.8 (CH₂), 25.6 (CH₂), 23.8 (CH₂); IR (neat) 2998, 2926, 2858, 1657, 1596, 1578, 1445, 1337, 1266, 1153, 1070, 964, 866, 756, 745, 720, 689 cm⁻¹. The spectral data were in agreement with those reported previously for this compound.¹⁰

4.4.2 Synthesis of (2-(*p*-tolyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenyl methanone) (34b)

1-Phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)-3-(*p*-tolyl)prop-2-en-1-one **33b** (177.0 mg, 0.42 mmol) and Cs₂CO₃ (410.5 mg, 1.26 mmol) were employed to afford 95.0 mg (52%) of indicated product **34b** as a bright yellow solid (*R_f* = 0.63 in 4:1 hexane/ethyl acetate; mp = 159.5-160.7 °C) ¹H NMR (400 MHz, CDCl₃) δ 7.63 – 7.59 (m, 2H), 7.57 – 7.53 (m, 4H), 7.50 – 7.47 (m, 3H), 7.33 – 7.28 (m, 3H), 7.17 – 7.13 (m, 2H), 2.34 (d, *J* = 4.0 Hz, 3H), 2.16 (t, *J* = 10.3 Hz, 4H), 1.93 (d, *J* = 11.4 Hz, 1H), 1.82 (d, *J* = 8.7 Hz, 2H), 1.67 (d, *J* = 8.6 Hz, 2H), 1.43 – 1.37 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 194.6 (CO), 193.0 (CO), 170.6 (C), 166.5 (C), 140.2 (C), 137.8 (C), 137.2 (C), 137.0 (C), 134.0 (C), 133.8 (CH), 130.8 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 128.6 (CH), 128.5 (CH), 85.1 (C), 33.8 (CH₂), 25.6 (CH₂), 23.8 (CH₃), 21.5 (CH₂) (Note that two CH peaks overlap with each others); IR (neat)

3032, 2921, 2856, 1657, 1595, 1577, 1510, 1445, 1331, 1315, 1294, 1255, 1164, 1070, 1018, 967, 906, 867, 825, 760, 737, 715, 687 cm^{-1} ; MS (ESI, m/z): 434.21 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{28}\text{NO}_2$: 434.2115 $[\text{M}+\text{H}]^+$, found: 434.2116.

4.4.3 Synthesis of (2-(4-nitrophenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) (34c)

3-(4-Nitrophenyl)-1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one **33c** (181.0 mg, 0.40 mmol) and Cs_2CO_3 (390.8 mg, 1.20 mmol) were employed to afford 38.0 mg (41%) of indicated product **34c** as yellow oil (R_f = 0.50 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 8.12 (d, J = 8.8 Hz, 2H), 7.72 (d, J = 8.8 Hz, 2H), 7.49 – 7.36 (m, 6H), 7.20 (dt, J = 14.0, 8.1 Hz, 4H), 2.16 – 2.09 (m, 2H), 2.04 – 1.98 (m, 2H), 1.86 (d, J = 13.1 Hz, 1H), 1.75 (d, J = 12.9 Hz, 2H), 1.56 (d, J = 12.4 Hz, 2H), 1.32 (dd, J = 15.6, 2.5 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.9 (CO), 192.3 (CO), 172.1 (C), 165.3 (C), 148.7 (C), 139.7 (C), 137.0 (C), 136.83 (C), 136.79 (C), 134.4 (CH), 134.1 (CH), 129.7 (CH), 129.5 (CH), 129.1 (CH), 128.8 (CH), 128.6 (CH), 123.6 (CH), 86.1 (C), 33.7 (CH_2), 25.5 (CH_2), 23.7 (CH_2); IR (neat) 3063, 2928, 2854, 1734, 1651, 1595, 1519, 1447, 1340, 1314, 1289, 1258, 1169, 1109, 1069, 1014, 957, 904, 850, 768, 745, 720, 688 cm^{-1} ; MS (ESI, m/z): 465.78 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{25}\text{N}_2\text{O}_4$: 465.1809 $[\text{M}+\text{H}]^+$, found: 465.1777.

4.4.4 Synthesis of (2-(thiophen-3-yl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) (34d)

1-Phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)-3-(thiophen-3-yl)prop-2-en-1-one **33d** (96.7 mg, 0.23 mmol) and Cs_2CO_3 (224.8 mg, 0.69 mmol) were employed to afford 48.5 mg (50%) of indicated product **34d** as a brown solid (R_f = 0.58 in 4:1 hexane/ethyl acetate; mp = 122.1-124.5 $^\circ\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 7.54 – 7.51 (m, 2H), 7.48 (dd, J = 5.5, 1.0 Hz, 2H), 7.44 (s, 1H), 7.43 (d, J = 1.3 Hz, 1H),

7.41 – 7.36 (m, 2H), 7.23 (d, $J = 8.1$ Hz, 2H), 7.20 – 7.17 (m, 3H), 2.08 – 1.98 (m, 4H), 1.82 (d, $J = 13.8$ Hz, 1H), 1.70 (d, $J = 11.9$ Hz, 2H), 1.54 (d, $J = 11.2$ Hz, 2H), 1.33-1.25 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.4 (CO), 193.5 (CO), 170.4 (C), 160.7 (C), 137.4 (C), 137.1 (C), 137.0 (C), 135.7 (C), 134.2 (CH), 133.9 (CH), 129.6 (CH), 129.3 (CH), 128.7 (CH), 128.5 (CH), 128.2 (CH), 127.7 (CH), 125.7 (CH), 84.9 (C), 33.9 (CH_2), 25.6 (CH_2), 23.8 (CH_2); IR (neat) 3005, 2923, 2849, 1647, 1610, 1585, 1430, 1346, 1263, 1225, 1157, 1026, 978, 880, 780, 754, 724, 705, 692 cm^{-1} .

4.4.5 Synthesis of (3-benzoyl-2-(thiophen-3-yl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(*p*-tolyl)methanone (34e)

1-Phenyl-3-(thiophen-3-yl)-3-((1-(*p*-tolylethynyl)cyclohexyl)amino)prop-2-en-1-one **33e** (137.0 mg, 0.32 mmol) and Cs_2CO_3 (312.8 mg, 0.96 mmol) were employed to afford 48.7 mg (25%) of indicated product **34e** as a yellow solid ($R_f = 0.55$ in 4:1 hexane/ethyl acetate; mp = 134.3-137.1 $^\circ\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 7.65 (dd, $J = 8.3, 1.2$ Hz, 2H), 7.59 (dd, $J = 5.1, 1.1$ Hz, 1H), 7.53 – 7.46 (m, 3H), 7.38 – 7.31 (m, 3H), 7.31 – 7.27 (m, 1H), 7.12 (d, $J = 8.1$ Hz, 2H), 2.37 (s, 3H), 2.12 (d, $J = 8.8$ Hz, 4H), 1.91 (d, $J = 12.3$ Hz, 2H), 1.80 (s, 2H), 1.64 (d, $J = 9.0$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.1 (CO), 193.7 (CO), 170.6 (C), 160.7 (C), 145.2 (C), 136.9 (C), 136.8 (C), 135.8 (C), 134.6 (C), 134.2 (CH), 129.7 (CH), 129.6 (CH), 129.3 (CH), 128.7 (CH), 128.2 (CH), 127.6 (CH), 125.7 (CH), 84.9 (C), 33.9 (CH_2), 25.6 (CH_2), 23.8 (CH_2), 21.9 (CH_3); IR (neat) 3044, 2919, 2852, 1649, 1599, 1552, 1445, 1328, 1269, 1191, 1170, 1074, 974, 906, 871, 854, 837, 807, 745, 689 cm^{-1} .

4.4.6 Synthesis of (2-(2-methoxyphenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) (34f)

3-(2-Methoxyphenyl)-1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one **33f** (114.1 mg, 0.26 mmol) and Cs_2CO_3 (254.1 mg, 0.78 mmol) were employed

to afford 44.3 mg (38%) of indicated product **34f** as a light orange solid (R_f = 0.48 in 4:1 hexane/ethyl acetate; mp = 167.1-170.3 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.83 (dd, J = 7.5, 1.7 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.46 – 7.34 (m, J = 4.9, 4.1 Hz, 5H), 7.30 – 7.18 (m, 4H), 7.11 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H), 3.13 (s, 3H), 2.31 – 2.10 (m, J = 29.2, 13.0, 6.7 Hz, 4H), 1.92 (d, J = 13.1 Hz, 1H), 1.82 (dd, J = 9.6, 3.2 Hz, 2H), 1.64 (d, J = 12.2 Hz, 2H), 1.39 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.5 (CO), 191.1 (CO), 167.7 (C), 166.1 (C), 156.6 (C), 139.4 (C), 137.8 (C), 137.2 (C), 133.5 (C), 133.0 (CH), 131.4 (CH), 130.8 (CH), 129.2 (CH), 129.0 (CH), 128.4 (CH), 128.2 (CH), 123.1 (CH), 121.5 (CH), 110.4 (CH), 84.8 (C), 54.0 (OCH₃), 33.6 (CH₂), 25.6 (CH₂), 23.8 (CH₂); IR (neat) 3062, 2924, 2841, 1656, 1597, 1579, 1487, 1440, 1338, 1315, 1255, 1162, 1115, 1072, 1050, 1020, 958, 905, 878, 865, 740, 715, 688 cm^{-1} ; MS (ESI, m/z): 450.20 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{28}\text{NO}_3$: 450.2064 $[\text{M}+\text{H}]^+$, found: 450.2019.

4.4.7 Synthesis of (2-(3,4-dichlorophenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) (**34g**)

3-(3,4-Dichlorophenyl)-1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one **33g** (174.0 mg, 0.37 mmol) and Cs_2CO_3 (361.7 mg, 1.11 mmol) were employed to afford 65.0 mg (33%) of indicated product **34g** as a bright orange solid (R_f = 0.60 in 4:1 hexane/ethyl acetate; mp = 118.6-119.1 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.90 (d, J = 1.4 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.50 (d, J = 8.3 Hz, 4H), 7.39 – 7.33 (m, 3H), 7.33 – 7.27 (m, 3H), 2.24 – 2.05 (m, 5H), 1.94 (d, J = 13.0 Hz, 1H), 1.87 – 1.81 (m, 2H), 1.63 (d, J = 11.7 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.1 (CO), 192.6 (CO), 171.8 (C), 164.7 (C), 137.1 (C), 137.0 (C), 136.9 (C), 134.4 (C), 134.3 (C), 134.0 (C), 133.7 (CH), 133.0 (CH), 130.7 (CH), 130.3 (CH), 129.5 (CH), 129.2 (CH), 128.8 (CH), 128.6 (CH), 127.8 (CH), 85.6 (C), 33.7 (CH₂), 25.5 (CH₂), 23.8 (CH₂); IR (neat) 3034, 2924, 2855, 1953, 1657, 1595, 1447, 1389, 1292, 1259, 1171, 1071, 1031, 962, 866, 826, 757, 730, 688 cm^{-1} ; MS (ESI, m/z): 488.11

[M+H]⁺; HRMS (ESI) calcd. for C₂₉H₂₄Cl₂NO₂: 488.1179 [M+H]⁺, found: 488.1128.

4.4.8 Synthesis of (2-(4-(*tert*-butyl)phenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) (34h)

3-(4-(*tert*-Butyl)phenyl)-1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one **33h** (64.8 mg, 0.14 mmol) and Cs₂CO₃ (136.8 mg, 0.42 mmol) were employed to afford 27.5 mg (41%) of indicated product **34h** as an orange solid (*R*_f = 0.65 in 4:1 hexane/ethyl acetate; mp = 131.3-134.5 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.48 (dd, *J* = 4.7, 3.6 Hz, 3H), 7.43 – 7.32 (m, 5H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.22 – 7.15 (m, 4H), 2.12 – 1.96 (m, 5H), 1.81 (d, *J* = 12.8 Hz, 1H), 1.71 (t, *J* = 4.5 Hz, 2H), 1.54 (d, *J* = 10.0 Hz, 2H), 1.18 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 194.5 (CO), 193.1 (CO), 170.5 (C), 166.4 (C), 153.3 (C), 137.7 (C), 137.2 (C), 137.1 (C), 134.0 (C), 133.8 (CH), 130.7 (CH), 129.5 (CH), 129.3 (CH), 128.5 (CH), 128.3 (CH), 128.1 (CH), 125.4 (CH), 85.1 (C), 34.8 (C), 33.8 (CH₂), 31.2 (CH₃), 25.6 (CH₂), 23.8 (CH₂); IR (neat) 3001, 2932, 1655, 1596, 1503, 1446, 1294, 1262, 1171, 1110, 1071, 1013, 966, 903, 879, 865, 838, 800, 753, 720, 687 cm⁻¹; MS(ESI, *m/z*): 476.25 [M+H]⁺; HRMS (ESI) calcd. for C₃₃H₃₄NO₂: 476.2548 [M+H]⁺, found: 476.2547.

4.4.9 Synthesis of (3-benzoyl-2-(4-(*tert*-butyl)phenyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(3-bromophenyl)methanone (34i)

3-((1-((3-Bromophenyl)ethynyl)cyclohexyl)amino)-3-(4-(*tert*-butyl)phenyl)-1-phenylprop-2-en-1-one **33i** (170.0 mg, 0.31 mmol) and Cs₂CO₃ (303.0 mg, 0.93 mmol) were employed to afford 90.0 mg (53%) of indicated product **34i** as a light orange solid (*R*_f = 0.68 in 4:1 hexane/ethyl acetate; mp = 180.4-181.7 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.48 (dd, *J* = 8.9, 1.9 Hz, 6H), 7.41 (t, *J* = 6.2 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.23 (dd, *J* = 14.7, 8.0 Hz, 4H), 7.07 – 7.02 (m, 1H), 2.07 (d, *J* =

10.5 Hz, 3H), 1.83 (d, J = 12.8 Hz, 1H), 1.72 (d, J = 9.5 Hz, 2H), 1.52 (d, J = 10.2 Hz, 2H), 1.27 (d, J = 4.3 Hz, 2H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.0 (CO), 192.9 (CO), 169.7 (C), 166.3 (C), 153.5 (C), 139.1 (C), 138.7 (C), 137.0 (C), 136.5 (C), 134.1 (C), 131.5 (CH), 130.6 (CH), 130.0 (CH), 129.4 (CH), 128.8 (CH), 128.4 (CH), 128.1 (CH), 125.5 (CH), 122.9 (CH), 85.2 (C), 34.9 (C), 33.8 (CH_2), 31.2 (CH_3), 25.6 (CH_2), 23.8 (CH_2); IR (neat) 3060, 2944, 2924, 1652, 1595, 1564, 1503, 1455, 1411, 1339, 1301, 1258, 1178, 1110, 1067, 1013, 967, 900, 874, 838, 805, 777, 758, 742, 730, 688 cm^{-1} ; MS (ESI, m/z): 554.17 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{33}\text{H}_{33}\text{BrNO}_2$: 554.1689 $[\text{M}+\text{H}]^+$, found: 554.1695.

4.4.10 Synthesis of (3-benzoyl-2-(4-(*tert*-butyl)phenyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(*p*-tolyl)methanone (**34j**)

3-(4-(*tert*-Butyl)phenyl)-1-phenyl-3-((1-(*p*-tolylethynyl)cyclohexyl)amino)prop-2-en-1-one **33j** (251.0 mg, 0.53 mmol) and Cs_2CO_3 (518.1 mg, 1.59 mmol) were employed to afford 108.0 mg (42%) of indicated product **34j** as yellow oil (R_f = 0.65 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 7.70 – 7.56 (m, 4H), 7.49 (td, J = 8.2, 5.0 Hz, 3H), 7.40 – 7.29 (m, 4H), 7.14 – 7.06 (m, 2H), 2.35 (t, J = 4.9 Hz, 3H), 2.14 (s, 4H), 1.92 (s, 1H), 1.81 (s, 2H), 1.65 (s, 2H), 1.37 (s, 1H), 1.30 (t, J = 5.1 Hz, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.1 (CO), 193.2 (CO), 170.8 (C), 166.3 (C), 153.3 (C), 145.0 (C), 137.0 (C), 134.6 (C), 134.0 (C), 130.7 (C), 129.6 (CH), 129.5 (CH), 129.3 (CH), 128.6 (CH), 128.3 (CH), 125.4 (CH), 85.0 (C), 34.8 (C), 33.8 (CH_2), 31.2 (CH_3), 25.6 (CH_2), 23.8 (CH_2), 21.8 (CH_3) (Note that two CH peaks overlap with each others); IR (neat) 3031, 2929, 2856, 1738, 1652, 1602, 1504, 1447, 1407, 1291, 1262, 1169, 1109, 1071, 1045, 1013, 959, 905, 872, 839, 789, 755, 739, 687 cm^{-1} ; MS (ESI, m/z): 490.27 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{34}\text{H}_{36}\text{NO}_2$: 490.2741 $[\text{M}+\text{H}]^+$, found: 490.2704.

4.4.11 Synthesis of (3-benzoyl-2-(4-(*tert*-butyl)phenyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(4-fluorophenyl)methanone (**34k**)

3-(4-(*tert*-Butyl)phenyl)-3-((1-((4-fluorophenyl)ethynyl)cyclohexyl)amino)-1-phenylprop-2-en-1-one **33k** (219.0 mg, 0.46 mmol) and Cs₂CO₃ (449.6 mg, 1.38 mmol) were employed to afford 63.0 mg (28%) of indicated product **34k** as a dark orange solid (*R*_f = 0.63 in 4:1 hexane/ethyl acetate; mp = 148.5-150.0 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, *J* = 6.7 Hz, 1H), 7.61 – 7.47 (m, 6H), 7.40 – 7.32 (m, 4H), 7.01 – 6.91 (m, 2H), 2.15 (s, 4H), 1.94 (d, *J* = 12.6 Hz, 1H), 1.82 (s, 1H), 1.64 (d, *J* = 7.6 Hz, 2H), 1.38 (s, 2H), 1.30 (d, *J* = 2.9 Hz, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 193.2 (CO), 193.0 (CO), 170.1 (C), 166.3 (C), 166.2 (d, ¹*J* = 256.7 Hz, C), 153.4 (C), 137.7 (C), 137.0 (C), 134.2 (C), 133.7 (d, ⁴*J* = 3.1 Hz, C), 132.1 (d, ³*J* = 9.6 Hz, CH), 130.6 (CH), 129.6 (CH), 128.7 (CH), 128.4 (CH), 125.51 (CH), 115.8 (d, ²*J* = 22.2 Hz, CH), 85.2 (C), 34.9 (C), 33.8 (CH₂), 31.2 (CH₃), 25.6 (CH₂), 23.8 (CH₂); IR (neat) 3071, 2932, 2856, 1654, 1593, 1503, 1447, 1407, 1294, 1237, 1173, 1150, 1070, 1014, 968, 905, 877, 847, 777, 757, 717, 688 cm⁻¹; MS (ESI, *m/z*): 494.25 [M+H]⁺; HRMS (ESI) calcd. for C₃₃H₃₃FNO₂: 494.2490 [M+H]⁺, found: 494.2454.

4.4.12 Synthesis of (2-(4-(trifluoromethyl)phenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis (phenylmethanone) (**34l**)

1-Phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **33l** (289.0 mg, 0.61 mmol) and Cs₂CO₃ (596.3 mg, 1.83 mmol) were employed to afford 87.8 mg (30%) of indicated product **34l** as orange oil (*R*_f = 0.51 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 7.77 (d, *J* = 8.1 Hz, 2H), 7.64 – 7.56 (m, 4H), 7.54 – 7.45 (m, 4H), 7.35 – 7.26 (m, 4H), 2.27 – 2.07 (m, 4H), 1.95 (d, *J* = 13.3 Hz, 1H), 1.85 (d, *J* = 12.7 Hz, 2H), 1.66 (d, *J* = 12.2 Hz, 2H), 1.48 – 1.38 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 194.1 (CO), 192.6 (CO), 171.6 (C), 165.8 (C), 137.2 (C), 137.1 (C), 136.9 (C), 134.3 (C), 134.0 (CH), 131.8 (q, ²*J* = 32.6 Hz, C), 129.5 (CH), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 126.8

(q, $^1J = 196.2$ Hz, CF_3), 125.4 (q, $^3J = 3.2$ Hz, CH), 85.8 (C), 33.7 (CH_2), 25.5 (CH_2), 23.8 (CH_2) (Note that two CH peaks overlap with each others); IR (neat) 3016, 2929, 2852, 1653, 1597, 1447, 1411, 1317, 1265, 1168, 1124, 1067, 1016, 904, 880, 866, 845, 763, 740, 718, 689 cm^{-1} ; MS (ESI, m/z): 488.18 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{25}\text{F}_3\text{NO}_2$: 488.1832 $[\text{M}+\text{H}]^+$, found: 488.1817.

4.4.13 Synthesis of (3-benzoyl-2-(4-(trifluoromethyl)phenyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(*p*-tolyl)methanone (34m)

1-Phenyl-3-((1-(*p*-tolylethynyl)cyclohexyl)amino)-3-(4-(trifluoromethyl)phenyl)prop-2-en-1-one **33m** (441.0 mg, 0.91 mmol) and Cs_2CO_3 (889.5 mg, 2.73 mmol) were employed to afford 59.0 mg (28%) of indicated product **34m** as orange oil ($R_f = 0.51$ in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 7.77 (d, $J = 8.1$ Hz, 2H), 7.62 (d, $J = 7.8$ Hz, 4H), 7.51 (t, $J = 7.4$ Hz, 1H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.33 (t, $J = 7.7$ Hz, 2H), 7.10 (d, $J = 8.1$ Hz, 2H), 2.36 (s, 3H), 2.21 – 2.08 (m, 4H), 1.94 (d, $J = 13.3$ Hz, 1H), 1.86 – 1.80 (m, 2H), 1.65 (d, $J = 10.6$ Hz, 2H), 1.45 – 1.35 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.8 (CO), 192.7 (CO), 171.9 (C), 165.8 (C), 145.3 (C), 137.2 (C), 136.9 (C), 136.6 (C), 134.6 (C), 134.3 (CH), 131.7 (q, $^2J = 32.3$ Hz, C), 129.6 (CH), 129.5 (CH), 129.4 (CH), 129.0 (CH), 128.8 (CH), 125.4 (q, $^3J = 4.2$ Hz, CH), 121.3 (q, $^1J = 281.1$ Hz, CF_3), 85.7 (C), 33.8 (CH_2), 25.6 (CH_2), 23.8 (CH_2), 21.8 (CH_3); IR (neat) 3031, 2931, 2856, 1738, 1653, 1603, 1448, 1409, 1314, 1291, 1264, 1166, 1124, 1066, 1015, 957, 905, 872, 843, 786, 753, 741 cm^{-1} ; MS (ESI, m/z): 502.20 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{27}\text{F}_3\text{NO}_2$: 502.1988 $[\text{M}+\text{H}]^+$, found: 502.1962.

4.4.14 Synthesis of (3-benzoyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-4-yl)(*p*-tolyl)methanone (34n)

1,3-Diphenyl-3-((1-(*p*-tolylethynyl)cyclohexyl)amino)prop-2-en-1-one **33n** (103.5 mg, 0.24 mmol) and Cs_2CO_3 (240.0 mg, 0.75 mmol) were employed to afford 29.1.0

mg (28%) of indicated product **34n** as yellow oil (R_f = 0.45 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 7.67 – 7.60 (m, 4H), 7.49 (d, J = 8.0 Hz, 3H), 7.39 – 7.29 (m, 5H), 7.10 (d, J = 8.0 Hz, 2H), 2.36 (s, 3H), 2.14 (d, J = 8.7 Hz, 4H), 1.92 (d, J = 12.8 Hz, 1H), 1.82 (s, 2H), 1.66 (d, J = 8.6 Hz, 2H), 1.39 (d, J = 12.3 Hz, 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), 136.9 (C), 134.6 (C), 134.0 (C), 133.7 (CH), 130.1 (CH), 129.6 (CH), 129.5 (CH), 129.3 (CH), 128.62 (CH), 128.58 (CH), 128.5 (CH), 85.2 (C), 33.8 (CH_2), 25.6 (CH_2), 23.8 (CH_2), 21.8 (CH_3); IR (neat) 3058, 2927, 2852, 1744, 1652, 1600, 1446, 1289, 1259, 1446, 1289, 1259, 1169, 1071, 1018, 872, 1018, 872, 838, 790, 764, 744, 690 cm^{-1} . The spectral data were in agreement with those reported previously for this compound.¹⁰

4.4.15 Synthesis of (3-benzoyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-4-yl)(3-bromophenyl)methanone (**34o**)

3-((1-((3-Bromophenyl)ethynyl)cyclohexyl)amino)-1,3-diphenylprop-2-en-1-one **33o** (195.0 mg, 0.40 mmol) and Cs_2CO_3 (391.0 mg, 1.20 mmol) were employed to afford 94.6 mg (43%) of indicated product **34o** as light orange oil (R_f = 0.51 in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 7.64 (d, J = 6.7 Hz, 2H), 7.58 (d, J = 9.3 Hz, 4H), 7.52 (t, J = 7.4 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.39 – 7.31 (m, 5H), 7.17 (t, J = 8.2 Hz, 1H), 2.24 – 2.13 (m, 4H), 1.95 (d, J = 13.3 Hz, 1H), 1.84 (d, J = 11.6 Hz, 2H), 1.65 (d, J = 11.0 Hz, 2H), 1.47 – 1.38 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 193.0 (CO), 192.7 (CO), 170.1 (C), 166.6 (C), 139.0 (C), 138.6 (C), 136.9 (C), 136.5 (C), 134.2 (C), 133.5 (CH), 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 (CH), 85.4 (C), 33.8 (CH_2), 25.6 (CH_2), 23.8 (CH_2); IR (neat) 3060, 2922, 2853, 1737, 1656, 1596, 1563, 1491, 1445, 1418, 1290, 1243, 1170, 1068, 1019, 969, 873, 820, 783, 764, 745, 713, 687 cm^{-1} . The spectral data were in agreement with those reported previously for this compound.¹⁰

4.4.16 Synthesis of (2-(*m*-tolyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) (**34p**)

1-Phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)-3-(*m*-tolyl)prop-2-en-1-one **33p** (207.0 mg, 0.49 mmol) and Cs₂CO₃ (479.0 mg, 1.47 mmol) were employed to afford 108.0 mg (50%) of indicated product **34p** as a yellow solid (*R*_f = 0.44 in 4:1 hexane/ethyl acetate; mp = 136.1-136.5 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.76 – 7.52 (m, 5H), 7.51 – 7.43 (m, 2H), 7.36 – 7.25 (m, 5H), 7.23 – 7.14 (m, 2H), 2.33 (s, 3H), 2.24 – 2.13 (m, 4H), 1.94 (d, *J* = 12.8 Hz, 1H), 1.87 – 1.79 (m, 2H), 1.67 (d, *J* = 9.1 Hz, 2H), 1.41 (d, *J* = 11.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 194.5 (CO), 192.8 (CO), 170.8 (C), 166.9 (C), 138.2 (C), 137.9 (C), 137.1 (C), 137.0 (C), 133.9 (C), 133.8 (CH), 133.6 (CH), 130.8 (CH), 129.4 (CH), 129.3 (CH), 129.1 (CH), 128.6 (CH), 128.5 (CH), 128.2 (CH), 125.6 (CH), 85.2 (C), 33.8 (CH₂), 25.5 (CH₂), 23.8 (CH₂), 21.4 (CH₃); IR (neat) 3063, 2915, 2854, 1655, 1596, 1446, 1314, 1295, 1268, 1169, 1073, 965, 888, 865, 848, 805, 790, 764, 735, 720, 706, 688 cm⁻¹; MS (ESI, *m/z*): 434.21 [M+H]⁺; HRMS (ESI) calcd. for C₃₀H₂₈NO₂: 434.2115 [M+H]⁺, found: 434.2082.

4.4.17 Synthesis of (3-benzoyl-2-(*m*-tolyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(4-fluorophenyl)methanone (**34q**)

3-((1-((4-Fluorophenyl)ethynyl)cyclohexyl)amino)-1-phenyl-3-(*m*-tolyl)prop-2-en-1-one **33q** (354.0 mg, 0.81 mmol) and Cs₂CO₃ (791.7 mg, 2.43 mmol) were employed to afford 117.8 mg (32%) of indicated product **34q** as yellow oil (*R*_f = 0.49 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 7.68 – 7.58 (m, 4H), 7.51 (dd, *J* = 18.1, 10.8 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 3H), 7.22 – 7.17 (m, 2H), 6.97 (t, *J* = 8.6 Hz, 2H), 2.33 (s, 3H), 2.16 (d, *J* = 7.9 Hz, 4H), 1.94 (d, *J* = 11.6 Hz, 1H), 1.83 (s, 2H), 1.66 (d, *J* = 6.4 Hz, 2H), 1.47 – 1.35 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 192.88 (CO), 192.85 (CO), 170.4 (C), 166.8 (C), 166.2 (d, ¹*J* = 257.0 Hz, C), 138.2 (C), 137.8 (C), 136.9 (C), 134.1 (C), 133.5 (d, ⁴*J* = 15.3 Hz, C), 132.1 (d, ³*J* = 9.6 Hz, CH), 130.9 (CH), 129.4 (CH), 129.1 (CH), 128.7 (CH), 128.2 (CH),

125.6 (CH), 115.8 (d, $^2J = 22.0$ Hz, CH), 85.2 (C), 33.8 (CH₂), 25.5 (CH₂), 23.7 (CH₂), 21.4 (CH₃) (Note that two CH peaks overlap with each others); IR (neat) 3064, 2929, 2855, 1737, 1656, 1594, 1504, 1447, 1296, 1237, 1173, 1150, 1073, 1044, 968, 906, 873, 850, 795, 776, 749, 728, 690 cm⁻¹; MS (ESI, m/z): 452.20 [M+H]⁺; HRMS (ESI) calcd. for C₃₀H₂₇FNO₂: 452.2020 [M+H]⁺, found: 452.19977.

4.4.18 Synthesis of (3-benzoyl-2-(*m*-tolyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(*p*-tolyl)methanone (34r)

1-Phenyl-3-(*m*-tolyl)-3-((1-(*p*-tolylethynyl)cyclohexyl)amino)prop-2-en-1-one **33r** (288.0 mg, 0.66 mmol) and Cs₂CO₃ (645.1 mg, 1.98 mmol) were employed to afford 119.0 mg (38%) of indicated product **34r** as yellow oil ($R_f = 0.44$ in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 7.64 (d, $J = 6.8$ Hz, 2H), 7.56 (s, 1H), 7.49 (dd, $J = 14.2, 6.8$ Hz, 4H), 7.31 (dd, $J = 14.0, 6.3$ Hz, 3H), 7.19 (d, $J = 3.2$ Hz, 1H), 7.11 (d, $J = 6.3$ Hz, 2H), 2.35 (d, $J = 2.2$ Hz, 3H), 2.34 (d, $J = 2.3$ Hz, 3H), 2.14 (s, 3H), 1.92 (d, $J = 12.6$ Hz, 1H), 1.82 (s, 3H), 1.67 (d, $J = 7.3$ Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 194.1 (CO), 193.0 (CO), 171.1 (C), 166.9 (C), 145.1 (C), 138.2 (C), 137.2 (C), 137.0 (C), 134.6 (C), 133.9 (C), 133.6 (CH), 130.8 (CH), 129.5 (CH), 129.3 (CH), 129.2 (CH), 128.6 (CH), 128.2 (CH), 125.6 (CH), 85.1 (C), 33.8 (CH₂), 25.6 (CH₂), 23.8 (CH₂), 21.8 (CH₃), 21.4 (CH₃) (Note that two CH peaks overlap each others); IR (neat) 3030, 2926, 2854, 1737, 1652, 1601, 1447, 1293, 1257, 1168, 1073, 1043, 968, 871, 848, 790, 769, 746, 690 cm⁻¹; MS (ESI, m/z): 448.22 [M+H]⁺; HRMS (ESI) calcd. for C₃₁H₃₀NO₂: 448.2271 [M+H]⁺, found: 448.2241.

4.4.19 Synthesis of (3-benzoyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-4-yl)(4-fluorophenyl) methanone (34s)

3-((1-((4-Fluorophenyl)ethynyl)cyclohexyl)amino)-1,3-diphenylprop-2-en-1-one **33s** (86.6 mg, 0.20 mmol) and Cs₂CO₃ (195.5 mg, 0.60 mmol) were employed to afford 21.1 mg (24%) of indicated product **34s** as yellow oil ($R_f = 0.50$ in 4:1

hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 7.56 – 7.47 (m, 6H), 7.41 (t, $J = 7.4$ Hz, 1H), 7.26 (dq, $J = 10.3, 7.7$ Hz, 5H), 6.87 (t, $J = 8.6$ Hz, 2H), 2.10 – 2.01 (m, 4H), 1.84 (d, $J = 12.5$ Hz, 1H), 1.72 (d, $J = 9.5$ Hz, 2H), 1.55 (d, $J = 9.6$ Hz, 2H), 1.30 (d, $J = 9.1$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 192.93 (CO), 192.90 (CO), 170.5 (C), 167.5 (C), 165.8 (d, $^1J = 256.9$ Hz, C), 137.7 (C), 136.9 (C), 134.2 (CH), 133.6 (d, $^4J = 2.6$ Hz, C), 133.5 (C), 132.1 (d, $^3J = 9.7$ Hz, CH), 130.2 (CH), 129.5 (CH), 128.8 (CH), 128.6 (CH), 128.5 (CH), 115.9 (d, $^2J = 22.1$ Hz, CH), 85.3 (C), 33.8 (CH_2), 25.6 (CH_2), 23.8 (CH_2); IR (neat) 3049, 2928, 2913, 1744, 1657, 1596, 1504, 1445, 1411, 1337, 1297, 1266, 1235, 1176, 1148, 1075, 1018, 964, 906, 871, 848, 808, 768, 749, 695, 672 cm^{-1} . The spectral data were in agreement with those reported previously for this compound.¹⁰

4.4.20 Synthesis of (2-(4-chlorophenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis (phenylmethanone) (34t)

3-(4-Chlorophenyl)-1-phenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one **33t** (160.0 mg, 0.36 mmol) and Cs_2CO_3 (351.9 mg, 1.08 mmol) were employed to afford 68.0 mg (42%) of indicated product **34t** as a light orange solid ($R_f = 0.53$ in 4:1 hexane/ethyl acetate). ^1H NMR (400 MHz, CDCl_3) δ 7.49 (t, $J = 8.0$ Hz, 4H), 7.44–7.35 (m, 4H), 7.25 – 7.16 (m, 6H), 2.14 – 2.00 (m, 3H), 1.84 (d, $J = 13.3$ Hz, 1H), 1.73 (d, $J = 12.4$ Hz, 2H), 1.55 (d, $J = 13.2$ Hz, 2H), 1.37 – 1.26 (m, 1H), 1.25 – 1.07 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 194.3 (CO), 192.8 (CO), 171.3 (C), 165.7 (C), 137.3 (C), 137.1 (C), 136.9 (C), 136.2 (C), 134.2 (C), 134.0 (CH), 132.1 (CH), 130.0 (CH), 129.5 (CH), 129.2 (CH), 128.7 (CH), 128.6 (CH), 85.4 (C), 33.8 (CH_2), 25.6 (CH_2), 23.8 (CH_2) (Note that two CH peaks overlap with each others); IR (neat) 3061, 2922, 2855, 1654, 1595, 1492, 1445, 1402, 1316, 1294, 1255, 1155, 1093, 1015, 867, 833, 764, 726, 687 cm^{-1} . The spectral data were in agreement with those reported previously for this compound.¹⁰

4.4.21 Synthesis of (3-benzoyl-2-(4-chlorophenyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(3-bromophenyl)methanone (**34u**)

3-((1-((3-Bromophenyl)ethynyl)cyclohexyl)amino)-3-(4-chlorophenyl)-1-phenyl prop-2-en-1-one **33u** (128.7 mg, 0.25 mmol) and Cs₂CO₃ (244.4 mg, 0.75 mmol) were employed to afford 63.2 mg (47%) of indicated product **34u** as orange oil (*R_f* = 0.46 in 4:1 hexane/ethyl acetate). ¹H NMR (400 MHz, CDCl₃) δ 7.52 – 7.41 (m, 7H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.26 – 7.17 (m, 4H), 7.06 (t, *J* = 7.8 Hz, 1H), 2.14 – 1.94 (m, 4H), 1.84 (d, *J* = 13.5 Hz, 1H), 1.73 (d, *J* = 12.5 Hz, 2H), 1.52 (d, *J* = 11.2 Hz, 2H), 1.35 – 1.27 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 192.8 (CO), 192.6 (CO), 170.5 (C), 165.5 (C), 139.0 (C), 138.2 (C), 136.8 (C), 136.6 (C), 136.3 (C), 134.4 (C), 132.0 (CH), 131.5 (CH), 130.1 (CH), 130.0 (CH), 129.4 (CH), 128.9 (CH), 128.7 (CH), 128.0 (CH), 123.0 (CH), 85.5 (C), 33.7 (CH₂), 25.5 (CH₂), 23.8 (CH₂); IR (neat) 3062, 2927, 2853, 1735, 1656, 1595, 1565, 1487, 1446, 1400, 1291, 1241, 1171, 1090, 1012, 958, 873, 834, 778, 753, 740, 712, 685 cm⁻¹. The spectral data were in agreement with those reported previously for this compound.¹⁰

4.5 General Procedure for the Synthesis of Spiro-Pyrrolopyridazines **35** (Table 6)

To a stirred solution of spiro-2*H*-pyrroles **34** (0.10 mmol) in *n*-butyl alcohol (5 mL) was added NH₂NH₂·H₂O (1.00 mmol) for approximately 2-5 h open to air. The resulting mixture was heated to reflux at 117 °C. (The progress of the reaction was followed by routine TLC for the disappearance of spiro-2*H*-pyrrole **34** using hexane/ethyl acetate (4:1) as the eluent). After the reaction was over, 1-butanol was removed on a rotary evaporator, and ethyl acetate (30 mL) and distilled water (30 mL) were added. After the layers were separated, the aqueous phase was extracted with ethyl acetate (2 × 15 mL). The combined organic phases were dried over MgSO₄ and evaporated on a rotary evaporator to give a 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-pyrrolopyridazine **35**.

4.5.1 Synthesis of 1',4',7'-triphenylspiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35a)

1,3-Diphenyl-3-((1-(phenylethynyl)cyclohexyl)amino)prop-2-en-1-one **34a** (67.0 mg, 0.16 mmol) and $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (80.1 mg, 1.60 mmol) were employed to afford 49.2 mg (74%) of indicated product **35a** as a white solid (R_f = 0.20 in 4:1 hexane/ethyl acetate; mp = 194.7-196.0 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.50 – 7.43 (m, 5H), 7.29 – 7.24 (m, 2H), 7.19 – 7.08 (m, 4H), 7.06 – 6.95 (m, 4H), 2.02 – 1.85 (m, 4H), 1.74 (d, J = 13.3 Hz, 1H), 1.57 (d, J = 12.5 Hz, 2H), 1.18 (d, J = 11.2 Hz, 2H), 1.07 – 0.95 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7 (C), 157.4 (C), 157.0 (C), 156.6 (C), 136.9 (C), 135.7 (C), 134.6 (C), 132.3 (C), 130.1 (CH), 129.6 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.32 (CH), 128.27 (CH), 127.78 (CH), 127.76 (CH), 80.4 (C), 34.2 (CH_2), 25.6 (CH_2), 23.4 (CH_2); IR (neat) 2933, 1584, 1445, 1381, 1282, 1091, 1078, 1023, 899, 852, 784, 761, 712, 695, 623 cm^{-1} ; MS (ESI, m/z): 416.21 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{26}\text{N}_3$: 416.2121 $[\text{M}+\text{H}]^+$, found: 416.2120.

4.5.2 Synthesis of 1',4'-diphenyl-7'-(*p*-tolyl)spiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35b)

(2-(*p*-Tolyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) **34b** (56.0 mg, 0.13 mmol) and $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (65.1 mg, 1.30 mmol) were employed to afford 53.0 mg (96%) of indicated product **35b** as a light yellow solid (R_f = 0.22 in 4:1 hexane/ethyl acetate; mp = 205.6-207.8 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.62 – 7.54 (m, 5H), 7.41 – 7.37 (m, 2H), 7.32 – 7.27 (m, 1H), 7.17 (t, J = 7.5 Hz, 2H), 7.09 (d, J = 7.9 Hz, 2H), 6.91 (d, J = 7.6 Hz, 2H), 2.30 (s, 3H), 2.13 – 1.98 (m, 4H), 1.84 (d, J = 13.2 Hz, 1H), 1.67 (d, J = 12.6 Hz, 2H), 1.28 (d, J = 11.7 Hz, 2H), 1.11 (d, J = 12.9 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.6 (C), 157.3 (C), 157.0 (C), 156.6 (C), 139.1 (C), 136.9 (C), 135.8 (C), 132.4 (C), 131.7 (C), 130.2 (CH), 129.6 (CH), 129.1 (CH), 128.8 (CH), 128.4 (CH), 128.30 (CH), 128.25 (CH), 127.7 (CH), 80.2 (C), 34.2 (CH_2), 25.7 (CH_2), 23.4 (CH_2), 21.4 (CH_3); IR (neat) 2936, 1537,

1443, 1371, 1095, 1020, 897, 829, 816, 775, 761, 730, 699, 667, 624 cm^{-1} ; MS (ESI, m/z): 430.23 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{28}\text{N}_3$: 430.2278 $[\text{M}+\text{H}]^+$, found: 430.2271.

4.5.3 Synthesis of 7'-(4-nitrophenyl)-1',4'-diphenylspiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35c)

(2-(4-Nitrophenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) **34c** (28.0 mg, 0.06 mmol) and $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (30.0 mg, 0.60 mmol) were employed to afford 21.7 mg (79%) of indicated product **35c** as a light orange solid (R_f = 0.10 in 4:1 hexane/ethyl acetate; mp = 285.3-286.6 $^\circ\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 7.88 (d, J = 8.8 Hz, 2H), 7.54 – 7.50 (m, 3H), 7.48 – 7.44 (m, 2H), 7.30 – 7.25 (m, 4H), 7.24 – 7.19 (m, 1H), 7.10 (t, J = 7.6 Hz, 2H), 2.01 – 1.87 (m, 5H), 1.77 (d, J = 12.6 Hz, 1H), 1.61 (d, J = 5.1 Hz, 2H), 1.20 (dd, J = 7.8, 4.3 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.1 (C), 157.7 (C), 157.0 (C), 156.1 (C), 148.1 (C), 140.9 (C), 136.6 (C), 135.5 (C), 131.8 (C), 130.1 (CH), 129.6 (CH), 129.43 (CH), 129.40 (CH), 128.5 (CH), 128.1 (CH), 122.9 (CH), 81.4 (C), 34.2 (CH_2), 25.6 (CH_2), 23.4 (CH_2) (Note that two CH peaks overlap with each others); IR (neat) 2937, 1582, 1519, 1444, 1381, 1350, 1105, 1015, 992, 899, 865, 847, 760, 721, 703 cm^{-1} ; MS (ESI, m/z): 461.20 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{25}\text{N}_4\text{O}_2$: 461.1972 $[\text{M}+\text{H}]^+$, found: 461.1965.

4.5.4 Synthesis of 1',4'-diphenyl-7'-(thiophen-3-yl)spiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35d)

(2-(Thiophen-3-yl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) **34d** (66.1 mg, 0.16 mmol) and $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (80.1 mg, 1.60 mmol) were employed to afford 58.1 mg (86%) of indicated product **35d** as a white solid (R_f = 0.17 in 4:1 hexane/ethyl acetate; mp = 185.5-188.0 $^\circ\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 7.60-7.57 (m, 3H), 7.54 (dd, J = 6.7, 3.0 Hz, 2H), 7.48 (d, J = 7.1 Hz, 2H), 7.39 (t, J = 7.4

Hz, 1H), 7.29 (t, $J = 7.5$ Hz, 2H), 7.09 – 7.02 (m, 2H), 6.92 (d, $J = 4.6$ Hz, 1H), 2.08 – 1.97 (m, 4H), 1.84 (d, $J = 12.8$ Hz, 1H), 1.66 (d, $J = 12.3$ Hz, 2H), 1.27 (d, $J = 10.7$ Hz, 2H), 1.14 – 1.07 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.9 (C), 157.3 (C), 156.8 (C), 156.4 (C), 136.9 (C), 136.0 (C), 135.7 (C), 132.4 (C), 130.1 (CH), 129.6 (CH), 129.2 (CH), 128.3 (CH), 128.1 (CH), 127.7 (CH), 126.9 (CH), 124.9 (CH), 80.2 (C), 34.3 (CH_2), 25.7 (CH_2), 23.4 (CH_2) (Note that two CH peaks overlap with each others); IR (neat) 2933, 1586, 1447, 1376, 1025, 945, 905, 856, 797, 761, 693, 661, 625 cm^{-1} ; MS (ESI, m/z): 422.17 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{27}\text{H}_{24}\text{N}_3\text{S}$: 422.1685 $[\text{M}+\text{H}]^+$, found: 422.1685.

4.5.5 Synthesis of 1'-phenyl-7'-(thiophen-3-yl)-4'-(*p*-tolyl)spiro[cyclohexane-1,5'-pyrrolo[3,4-*d*] pyridazine] (35e)

(3-Benzoyl-2-(thiophen-3-yl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(*p*-tolyl) methanone **34e** (34.0 mg, 0.08 mmol) and $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (40.0 mg, 1.80 mmol) were employed to afford 29.0 mg (87%) of indicated product **35e** as a light orange solid ($R_f = 0.20$ in 4:1 hexane/ethyl acetate; mp = 202.7-203.6 $^\circ\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 7.49 – 7.42 (m, 5H), 7.40 – 7.37 (m, 2H), 7.28 (t, $J = 7.5$ Hz, 2H), 7.09 – 7.03 (m, 2H), 6.92 (dd, $J = 4.9, 1.0$ Hz, 1H), 2.52 (s, 3H), 2.11 – 1.99 (m, 5H), 1.85 (d, $J = 12.7$ Hz, 1H), 1.68 (d, $J = 10.3$ Hz, 2H), 1.26 (d, $J = 10.8$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.0 (C), 157.4 (C), 156.9 (C), 156.3 (C), 139.0 (C), 136.0 (C), 135.7 (C), 134.0 (C), 132.4 (C), 130.1 (CH), 129.5 (CH), 129.2 (CH), 129.0 (CH), 128.1 (CH), 127.7 (CH), 126.9 (CH), 124.9 (CH), 80.2 (C), 34.2 (CH_2), 25.7 (CH_2), 23.4 (CH_2), 21.6 (CH_3); IR (neat) 2919, 2847, 1572, 1503, 1443, 1379, 1276, 1072, 1021, 945, 904, 865, 825, 799, 766, 722, 699, 637, 622 cm^{-1} ; MS (ESI, m/z): 436.18 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{28}\text{H}_{26}\text{N}_3\text{S}$: 436.1842 $[\text{M}+\text{H}]^+$, found: 436.1845.

4.5.6 Synthesis of 7'-(2-methoxyphenyl)-1',4'-diphenylspiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35f)

(2-(2-Methoxyphenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenyl methanone) **34f** (30.5 mg, 0.07 mmol) and $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (34.0 mg, 0.68 mmol) were employed to afford 26.2 mg (87%) of indicated product **35f** as a beige solid (R_f = 0.07 in 4:1 hexane/ethyl acetate; mp = 217.5-218.7 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.49 (tt, J = 5.0, 2.6 Hz, 5H), 7.42 (dd, J = 7.4, 1.7 Hz, 1H), 7.27 (d, J = 7.0 Hz, 2H), 7.18 – 7.09 (m, 2H), 7.01 (t, J = 7.5 Hz, 2H), 6.93 (t, J = 7.4 Hz, 1H), 6.20 (d, J = 8.3 Hz, 1H), 3.10 (s, 3H), 1.98 (d, J = 4.9 Hz, 3H), 1.84 – 1.69 (m, 2H), 1.58 (d, J = 39.8 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.5 (C), 157.3 (C), 157.2 (C), 157.1 (C), 156.0 (C), 137.1 (C), 135.5 (C), 133.6 (C), 131.1 (C), 129.7 (CH), 129.6 (CH), 129.3 (CH), 129.1 (CH), 128.6 (CH), 128.3 (CH), 127.1 (CH), 125.0 (CH), 120.6 (CH), 109.8 (CH), 80.3 (C), 60.5 (CH_3), 54.6 (CH_2), 25.7 (CH_2), 14.3 (CH_2); IR (neat) 2919, 1737, 1602, 1586, 1490, 1469, 1436, 1382, 1274, 1250, 1188, 1159, 1090, 1020, 991, 938, 890, 852, 763, 750, 706, 698, 667, 622 cm^{-1} ; MS (ESI, m/z): 446.22 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{28}\text{N}_3\text{O}$: 446.2227 $[\text{M}+\text{H}]^+$, found: 446.2226.

4.5.7 Synthesis of 7'-(3,4-dichlorophenyl)-1',4'-diphenylspiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35g)

(2-(3,4-Dichlorophenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenyl methanone) **34g** (45.0 mg, 0.09 mmol) and $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (46.1 mg, 0.92 mmol) were employed to afford 20.6 mg (43%) of indicated product **35g** as a white solid (R_f = 0.15 in 4:1 hexane/ethyl acetate; mp = 247.7-248.9 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.64 – 7.58 (m, 3H), 7.57 – 7.53 (m, 2H), 7.39 (t, J = 7.9 Hz, 3H), 7.29 (dd, J = 12.3, 4.5 Hz, 3H), 7.18 (d, J = 8.3 Hz, 1H), 7.03 (dd, J = 8.2, 2.0 Hz, 1H), 2.08 – 1.99 (m, 4H), 1.86 (d, J = 12.6 Hz, 1H), 1.69 (d, J = 9.5 Hz, 2H), 1.28 (s, 2H), 1.13 (dt, J = 12.6, 6.2 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 164.7 (C), 157.6 (C), 157.0 (C), 156.3 (C), 136.7 (C), 135.6 (C), 134.4 (C), 133.6 (C), 132.3 (C), 131.9

(C), 130.6 (CH), 130.1 (CH), 129.7 (CH), 129.62 (CH), 129.58 (CH), 129.3 (CH), 128.4 (CH), 128.2 (CH), 127.7 (CH), 80.9 (C), 34.2 (CH₂), 25.6 (CH₂), 23.4 (CH₂); IR (neat) 2946, 1551, 1467, 1386, 1133, 1028, 1003, 942, 903, 833, 805, 758, 735, 696, 680, 662 cm⁻¹; MS (ESI, m/z): 484.13 [M+H]⁺; HRMS (ESI) calcd. for C₂₉H₂₄Cl₂N₃: 484.1342 [M+H]⁺, found: 484.1339.

4.5.8 Synthesis of 7'-(4-(*tert*-butyl)phenyl)-1',4'-diphenylspiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35h)

(2-(4-(*tert*-Butyl)phenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenyl methanone) **34h** (58.3 mg, 0.12 mmol) and NH₂NH₂.H₂O (60.1 mg, 1.2 mmol) were employed to afford 44.0 mg (78%) of indicated product **35h** as a light yellow solid (*R*_f = 0.24 in 4:1 hexane/ethyl acetate; mp = 238.9-240.1 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.51 – 7.44 (m, 5H), 7.25 – 7.21 (m, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.05 – 6.95 (m, 6H), 2.02 – 1.88 (m, 4H), 1.74 (d, *J* = 13.1 Hz, 1H), 1.57 (d, *J* = 12.5 Hz, 2H), 1.23 (s, 2H), 1.18 (s, 9H), 1.00 (d, *J* = 12.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 166.8 (C), 157.4 (C), 156.9 (C), 156.7 (C), 152.2 (C), 136.9 (C), 135.6 (C), 132.6 (C), 131.7 (C), 130.1 (CH), 129.6 (CH), 129.2 (CH), 128.7 (CH), 128.3 (CH), 127.9 (CH), 127.7 (CH), 124.7 (CH), 80.4 (C), 34.7 (C), 34.2 (CH₂), 31.3 (CH₃), 25.7 (CH₂), 23.4 (CH₂); IR (neat) 2939, 1616, 1582, 1532, 1445, 1374, 1269, 1175, 1112, 1080, 1025, 989, 896, 839, 821, 764, 710, 694, 666, 622 cm⁻¹; MS (ESI, m/z): 472.27 [M+H]⁺; HRMS (ESI) calcd. for C₃₃H₃₄N₃: 472.2747 [M+H]⁺, found: 472.2748.

4.5.9 Synthesis of 4'-(3-bromophenyl)-7'-(4-(*tert*-butyl)phenyl)-1'-phenylspiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35i)

(3-Benzoyl-2-(4-(*tert*-butyl)phenyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(3-bromo phenyl)methanone **34i** (198.2 mg, 0.36 mmol) and NH₂NH₂.H₂O (180.0 mg, 3.6 mmol) were employed to afford 145.8 mg (74%) of indicated product **35i** as bright

a yellow solid ($R_f = 0.37$ in 4:1 hexane/ethyl acetate; mp = 227.8-228.9 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.64 – 7.59 (m, 2H), 7.41 – 7.32 (m, 2H), 7.23 – 7.20 (m, 2H), 7.13 (t, $J = 7.5$ Hz, 1H), 7.03 – 6.95 (m, 6H), 2.03 – 1.93 (m, 2H), 1.86 (td, $J = 12.9, 3.4$ Hz, 2H), 1.76 (d, $J = 13.1$ Hz, 1H), 1.59 (d, $J = 12.9$ Hz, 2H), 1.21 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.6 (C), 156.9 (C), 156.8 (C), 155.8 (C), 152.3 (C), 138.9 (C), 135.4 (C), 132.7 (C), 132.2 (C), 131.5 (C), 130.1 (CH), 129.8 (CH), 128.7 (CH), 128.3 (CH), 127.8 (CH), 127.7 (CH), 124.7 (CH), 122.4 (CH), 80.3 (C), 34.6 (C), 34.4 (CH_2), 31.2 (CH_3), 25.7 (CH_2), 23.3 (CH_2) (Note that two CH peaks overlap with each others); IR (neat) 2943, 1610, 1584, 1560, 1461, 1445, 1409, 1371, 1267, 1113, 1023, 997, 907, 889, 837, 795, 767, 745, 718, 695, 650 cm^{-1} ; MS (ESI, m/z): 550.19 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{33}\text{H}_{33}\text{BrN}_3$: 550.1852 $[\text{M}+\text{H}]^+$, found: 550.1851.

4.5.10 Synthesis of 7'-(4-(*tert*-butyl)phenyl)-1'-phenyl-4'-(*p*-tolyl)spiro[cyclohexane-1,5'-pyrrolo [3,4-*d*]pyridazine] (35j)

(3-Benzoyl-2-(4-(*tert*-butyl)phenyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(*p*-tolyl) methanone **34j** (84.0 mg, 0.17 mmol) and $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (85.1 mg, 1.7 mmol) were employed to afford 71.3 mg (86%) of indicated product **35j** as a light yellow solid ($R_f = 0.22$ in 4:1 hexane/ethyl acetate; mp = 250.4-252.7 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.45 (d, $J = 7.9$ Hz, 2H), 7.39 (d, $J = 7.8$ Hz, 2H), 7.33 (d, $J = 7.1$ Hz, 2H), 7.24 (t, $J = 7.2$ Hz, 1H), 7.14 – 7.06 (m, 6H), 2.52 (s, 3H), 2.14 – 1.98 (m, 5H), 1.85 (d, $J = 13.0$ Hz, 1H), 1.68 (d, $J = 11.6$ Hz, 2H), 1.34 (d, $J = 3.2$ Hz, 1H), 1.29 (d, $J = 2.2$ Hz, 9H), 1.14 (d, $J = 12.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7 (C), 157.5 (C), 156.9 (C), 156.5 (C), 152.1 (C), 138.9 (C), 135.7 (C), 134.0 (C), 132.5 (C), 131.7 (C), 130.1 (CH), 129.5 (CH), 129.0 (CH), 128.6 (CH), 127.8 (CH), 127.6 (CH), 124.7 (CH), 80.4 (C), 34.6 (C), 34.1 (CH_2), 31.3 (CH_3), 25.7 (CH_2), 23.4 (CH_2), 21.6 (CH_3); IR (neat) 2922, 2853, 1739, 1611, 1584, 1505, 1445, 1406, 1379, 1267, 1112, 1041, 1017, 992, 934, 900, 840, 823, 769, 728, 714, 703, 662, 635, 601

cm⁻¹; MS (ESI, m/z): 486.29 [M+H]⁺; HRMS (ESI) calcd. for C₃₄H₃₆N₃: 486.2904 [M+H]⁺, found: 486.2905.

4.5.11 Synthesis of 7'-(4-(*tert*-butyl)phenyl)-4'-(4-fluorophenyl)-1'-phenylspiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35k)

(3-Benzoyl-2-(4-(*tert*-butyl)phenyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(4-fluorophenyl)methanone **34k** (42.0 mg, 0.09 mmol) and NH₂NH₂.H₂O (42.6 mg, 0.9 mmol) were employed to afford 25.3 mg (61%) of indicated product **35k** as a yellow solid (*R*_f = 0.16 in 4:1 hexane/ethyl acetate; mp = 202.1-205.2 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.55 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.34 – 7.28 (m, 4H), 7.24 (d, *J* = 7.4 Hz, 1H), 7.15 – 7.06 (m, 6H), 2.08 (dd, *J* = 16.2, 9.8 Hz, 2H), 1.97 (td, *J* = 12.9, 3.4 Hz, 2H), 1.87 (d, *J* = 12.5 Hz, 1H), 1.69 (d, *J* = 12.7 Hz, 2H), 1.29 (s, 2H), 1.28 (s, 9H), 1.18 – 1.09 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 166.8 (C), 163.4 (d, ¹*J* = 248.6 Hz, C), 157.1 (C), 156.9 (C), 156.5 (C), 152.4 (C), 135.6 (C), 133.1 (d, ⁴*J* = 3.4 Hz, C), 132.7 (C), 131.6 (d, ³*J* = 8.2 Hz, CH), 130.1 (CH), 128.8 (CH), 127.9 (CH), 127.7 (CH), 124.8 (CH), 115.5 (d, ²*J* = 21.8 Hz, CH), 80.4 (C), 34.7 (C), 34.3 (CH₂), 31.3 (CH₃), 25.7 (CH₂), 23.4 (CH₂) (Note that one C peak overlap with CH peak.); IR (neat) 2937, 1589, 1504, 1445, 1379, 1268, 1221, 1156, 1114, 1016, 994, 900, 844, 765, 727, 697, 676, 660 cm⁻¹; MS (ESI, m/z): 490.27 [M+H]⁺; HRMS (ESI) calcd. for C₃₃H₃₃FN₃: 490.2653 [M+H]⁺, found: 490.2654.

4.5.12 Synthesis of 1',4'-diphenyl-7'-(4-(trifluoromethyl)phenyl)spiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35l)

(2-(4-(Trifluoromethyl)phenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) **34l** (68.0 mg, 0.14 mmol) and NH₂NH₂.H₂O (70.1 mg, 1.40 mmol) were employed to afford 56.4 mg (96%) of indicated product **35l** as a light yellow solid (*R*_f = 0.08 in 4:1 hexane/ethyl acetate; mp = 222.0-224.3 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.65 – 7.55 (m, 5H), 7.33 (dt, *J* = 14.2, 8.1 Hz, 7H), 7.16 (dd, *J* = 10.6, 4.7

Hz, 2H), 2.12 – 1.98 (m, 4H), 1.86 (d, $J = 12.5$ Hz, 1H), 1.70 (d, $J = 9.1$ Hz, 2H), 1.30 (d, $J = 9.3$ Hz, 2H), 1.12 (d, $J = 10.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.7 (C), 157.6 (C), 156.9 (C), 156.3 (C), 138.2 (C), 136.7 (C), 135.4 (C), 132.1 (C), 130.6 (q, $^2J = 34.1$ Hz, C), 130.1 (CH), 129.6 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 126.6 (q, $^1J = 225.9$ Hz, CF_3), 124.7 (q, $^3J = 3.4$ Hz, CH), 122.6 (CH), 81.0 (C), 34.2 (CH_2), 25.6 (CH_2), 23.4 (CH_2) (Note that two CH peaks overlap with each others); IR (neat) 2940, 1594, 1540, 1440, 1409, 1375, 1326, 1162, 1124, 1108, 1065, 1020, 896, 843, 774, 758, 723, 701, 666, 605 cm^{-1} ; MS (ESI, m/z): 484.20 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{25}\text{F}_3\text{N}_3$: 484.1995 $[\text{M}+\text{H}]^+$, found: 484.1998.

4.5.13 Synthesis of 1'-phenyl-4'-(*p*-tolyl)-7'-(4-(trifluoromethyl)phenyl)spiro[cyclohexane-1,5'-pyrrolo[3,4 *d*]pyridazine] (35m)

(3-Benzoyl-2-(4-(trifluoromethyl)phenyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(*p*-tolyl)methanone **34m** (40.0 mg, 0.08 mmol) and $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (40.1 mg, 0.80 mmol) were employed to afford 38.0 mg (95%) of indicated product **35m** as a light yellow solid ($R_f = 0.14$ in 4:1 hexane/ethyl acetate; mp = 244.5-246.7 $^\circ\text{C}$). ^1H NMR (400 MHz, CDCl_3) δ 7.43 (dd, $J = 19.2, 8.0$ Hz, 4H), 7.39 – 7.27 (m, 7H), 7.16 (t, $J = 7.6$ Hz, 2H), 2.53 (s, 3H), 2.07 (s, 4H), 1.87 (d, $J = 12.2$ Hz, 1H), 1.71 (s, 2H), 1.29 (d, $J = 7.1$ Hz, 2H), 1.17 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.8 (C), 157.7 (C), 157.0 (C), 156.2 (C), 139.2 (C), 138.2 (C), 135.5 (C), 133.8 (C), 132.0 (C), 131.1 (q, $^2J = 32.5$ Hz, C), 130.1 (CH), 129.5 (CH), 129.2 (CH), 129.1 (CH), 128.7 (CH), 128.0 (CH), 124.7 (q, $^3J = 3.64$ Hz, CH), 123.9 (q, $^1J = 272.2$ Hz, CF_3), 81.1 (C), 34.2 (CH_2), 25.6 (CH_2), 23.4 (CH_2), 21.6 (CH_3); IR(neat) 2934, 1595, 1445, 1407, 1382, 1326, 1161, 1122, 1064, 1021, 993, 901, 858, 820, 766, 727, 701, 661 cm^{-1} ; MS (ESI, m/z): 498.22 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{31}\text{H}_{27}\text{F}_3\text{N}_3$: 498.2152 $[\text{M}+\text{H}]^+$, found: 498.2152.

4.5.14 Synthesis of 1',7'-diphenyl-4'-(*p*-tolyl)spiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35n)

(3-Benzoyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-4-yl)(*p*-tolyl)methanone **34n** (40.0 mg, 0.09 mmol) and $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (45.1 mg, 0.90 mmol) were employed to afford 32.2 mg (83%) of indicated product **35n** as a light yellow solid (R_f = 0.16 in 4:1 hexane/ethyl acetate; mp = 249.7-251.3 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.45 (d, J = 7.8 Hz, 2H), 7.41 – 7.35 (m, 4H), 7.26 (dd, J = 12.5, 5.4 Hz, 2H), 7.22 – 7.14 (m, 4H), 7.11 (dd, J = 13.9, 6.3 Hz, 2H), 2.52 (s, 3H), 2.15 – 2.00 (m, 4H), 1.85 (d, J = 12.9 Hz, 1H), 1.69 (d, J = 10.1 Hz, 2H), 1.29 (d, J = 6.6 Hz, 2H), 1.16 (dd, J = 18.2, 9.3 Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.8 (C), 157.5 (C), 157.1 (C), 156.4 (C), 139.0 (C), 135.8 (C), 134.7 (C), 134.0 (C), 132.3 (C), 130.1 (CH), 129.5 (CH), 129.1 (CH), 129.0 (CH), 128.9 (CH), 128.3 (CH), 127.8 (CH), 80.5 (C), 34.2 (CH_2), 25.7 (CH_2), 23.4 (CH_2), 21.6 (CH_3) (Note that two CH peaks overlap with each others); IR (neat) 2931, 1566, 1542, 1491, 1445, 1373, 1096, 1021, 992, 898, 830, 819, 764, 727, 710, 694, 664, 634 cm^{-1} ; MS (ESI, m/z): 430.23 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{30}\text{H}_{28}\text{N}_3$: 430.2278 $[\text{M}+\text{H}]^+$, found: 430.2278.

4.5.15 Synthesis of 4'-(3-bromophenyl)-1',7'-diphenylspiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35o)

(3-Benzoyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-4-yl)(3-bromophenyl)methanone **34o** (82.3 mg, 0.17 mmol) and $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$ (85.1 mg, 1.70 mmol) were employed to afford 68.5 mg (82%) of indicated product **35o** as a yellow solid (R_f = 0.16 in 4:1 hexane/ethyl acetate; mp = 184.4-186.7 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.74 (dd, J = 6.7, 1.5 Hz, 2H), 7.53 – 7.45 (m, 2H), 7.39 – 7.35 (m, 2H), 7.26 (dd, J = 15.0, 7.5 Hz, 2H), 7.21 – 7.07 (m, 6H), 2.15 – 2.05 (m, 2H), 1.98 (td, J = 12.9, 3.4 Hz, 2H), 1.88 (d, J = 12.9 Hz, 1H), 1.72 (d, J = 12.9 Hz, 2H), 1.32 (d, J = 12.4 Hz, 2H), 1.19 – 1.12 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7 (C), 157.0 (C), 156.9 (C), 155.8 (C), 138.8 (C), 135.4 (C), 134.4 (C), 132.7 (C), 132.4 (C), 132.3 (CH), 130.1 (CH), 129.9 (CH), 129.2 (CH), 129.1 (CH), 128.30 (CH), 128.26 (CH),

127.83 (CH), 127.78 (CH), 122.5 (CH), 80.4 (C), 34.4 (CH₂), 25.7 (CH₂), 23.3 (CH₂); IR (neat) 2928, 1737, 1562, 1444, 1371, 1237, 1042, 996, 905, 848, 793, 764, 745, 713, 696, 679, 651 cm⁻¹; MS (ESI, m/z): 494.12 [M+H]⁺; HRMS (ESI) calcd. for C₂₉H₂₅BrN₃: 494.1226 [M+H]⁺, found: 494.1227.

4.5.16 Synthesis of 1',4'-diphenyl-7'-(*m*-tolyl)spiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35p)

(2-(*m*-Tolyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) **34p** (81.3 mg, 0.19 mmol) and NH₂NH₂.H₂O (95.1 mg, 1.90 mmol) were employed to afford 69.0 mg (85%) of indicated product **35p** as a light yellow solid (*R*_f = 0.14 in 4:1 hexane/ethyl acetate; mp = 178.5-180.3 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.64-7.52 (m, 5H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.28 (dd, *J* = 8.1, 6.7 Hz, 1H), 7.20 – 6.99 (m, 5H), 6.91 (s, 1H), 2.10 (s, 3H), 2.05 – 1.96 (m, 3H), 1.84 (d, *J* = 12.2 Hz, 1H), 1.67 (d, *J* = 11.8 Hz, 2H), 1.29 (t, *J* = 10.2 Hz, 3H), 1.16 – 1.08 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 166.7 (C), 157.3 (C), 156.9 (C), 156.6 (C), 137.4 (C), 136.9 (C), 135.8 (C), 134.3 (C), 132.4 (C), 130.0 (CH), 129.8 (CH), 129.6 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 125.4 (CH), 80.3 (C), 34.2 (CH₂), 25.6 (CH₂), 23.3 (CH₂), 21.1 (CH₃); IR (neat) 2938, 1570, 1485, 1444, 1374, 1313, 1191, 1093, 1021, 939, 903, 853, 790, 777, 763, 724, 711, 694, 656, 623 cm⁻¹; MS (ESI, m/z): 430.23 [M+H]⁺; HRMS (ESI) calcd. for C₃₀H₂₈N₃: 430.2278 [M+H]⁺, found: 430.2278.

4.5.17 Synthesis of 4'-(4-fluorophenyl)-1'-phenyl-7'-(*m*-tolyl)spiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35q)

(3-Benzoyl-2-(*m*-tolyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(4-fluorophenyl) methanone **34q** (78.0 mg, 0.17 mmol) and NH₂NH₂.H₂O (85.1 mg, 1.70 mmol) were employed to afford 60.0 mg (78%) of indicated product **35q** as a light yellow solid (*R*_f = 0.16 in 4:1 hexane/ethyl acetate; mp = 186.5-186.8 °C). ¹H NMR (400 MHz,

CDCl₃) δ 7.55 (t, J = 6.9 Hz, 2H), 7.41 – 7.36 (m, 2H), 7.30 (dd, J = 11.8, 5.1 Hz, 3H), 7.17 (t, J = 7.5 Hz, 2H), 7.08 (dd, J = 16.3, 2.1 Hz, 3H), 6.90 (s, 1H), 2.11 (s, 3H), 2.06 (s, 1H), 1.97 (t, J = 12.9 Hz, 2H), 1.87 (d, J = 12.5 Hz, 1H), 1.69 (d, J = 12.2 Hz, 3H), 1.29 (d, J = 12.1 Hz, 2H), 1.21 – 1.10 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 166.8 (C), 163.4 (d, 1J = 248.7 Hz, C), 157.2 (C), 156.8 (C), 156.5 (C), 137.5 (C), 135.7 (C), 134.3 (C), 133.2 (d, 4J = 3.3 Hz, C), 132.5 (C), 131.6 (d, 3J = 8.3 Hz, CH), 130.1 (CH), 129.9 (CH), 129.2 (CH), 129.0 (CH), 127.8 (CH), 127.7 (CH), 125.4 (CH), 115.5 (d, 2J = 21.7 Hz, CH), 80.3 (C), 34.3 (CH₂), 25.7 (CH₂), 23.3 (CH₂), 21.1 (CH₃); IR (neat) 2919, 2853, 1605, 1574, 1503, 1445, 1376, 1221, 1157, 1097, 1023, 940, 904, 851, 842, 822, 804, 764, 733, 717, 693, 663, 601 cm⁻¹; MS (ESI, m/z): 448.22 [M+H]⁺; HRMS (ESI) calcd. for C₃₀H₂₇FN₃: 448.2184 [M+H]⁺, found: 448.2184.

4.5.18 Synthesis of 1'-phenyl-7'-(*m*-tolyl)-4'-(*p*-tolyl)spiro[cyclohexane-1,5'-pyrrolo[3,4-*d*] pyridazine] (35r)

(3-Benzoyl-2-(*m*-tolyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(*p*-tolyl)methanone **34r** (97.2 mg, 0.22 mmol) and NH₂NH₂.H₂O (110.1 mg, 2.20 mmol) were employed to afford 86.0 mg (88%) of indicated product **35r** as a yellow solid (R_f = 0.22 in 4:1 hexane/ethyl acetate; mp = 231.0-233.6 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.45 (s, 1H), 7.39 (d, J = 8.2 Hz, 4H), 7.28 (d, J = 7.4 Hz, 1H), 7.17 (t, J = 7.5 Hz, 3H), 7.10 (d, J = 3.3 Hz, 1H), 7.05 (s, 2H), 6.91 (s, 1H), 2.53 (s, 3H), 2.11 (d, J = 2.7 Hz, 3H), 2.07 (s, 4H), 1.85 (d, J = 12.7 Hz, 1H), 1.69 (d, J = 9.3 Hz, 2H), 1.28 (dd, J = 7.1, 3.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.8 (C), 157.5 (C), 157.0 (C), 156.5 (C), 138.9 (C), 137.4 (C), 135.9 (C), 134.4 (C), 134.0 (C), 132.3 (C), 130.0 (CH), 129.8 (CH), 129.5 (CH), 129.2 (CH), 129.0 (CH), 128.8 (CH), 127.8 (CH), 127.7 (CH), 125.4 (CH), 80.4 (C), 34.2 (CH₂), 25.7 (CH₂), 23.4 (CH₂), 21.5 (CH₃), 21.1 (CH₃); IR (neat) 2950, 2912, 1571, 1508, 1433, 1372, 1189, 1097, 1040, 1000, 940, 904, 851, 818, 790, 768, 729, 718, 695, 664, 637, 602 cm⁻¹; MS (ESI, m/z): 444.24 [M+H]⁺; HRMS (ESI) calcd. for C₃₁H₃₀N₃: 444.2434 [M+H]⁺, found: 444.2440.

4.5.19 Synthesis of 4'-(4-fluorophenyl)-1',7'-diphenylspiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35s)

(3-Benzoyl-2-phenyl-1-azaspiro[4.5]deca-1,3-dien-4-yl)(4-fluorophenyl) methanone **34s** (84.1 mg, 0.19 mmol) and $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (95.1 mg, 1.90 mmol) were employed to afford 69.0 mg (84%) of indicated product **35s** as a light orange solid ($R_f = 0.17$ in 4:1 hexane/ethyl acetate; mp = 195.5-195.9 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.47 (dd, $J = 8.4, 5.4$ Hz, 2H), 7.28 (d, $J = 7.2$ Hz, 2H), 7.24 – 7.15 (m, 4H), 7.12 – 6.99 (m, 6H), 1.99 (dd, $J = 17.2, 8.8$ Hz, 2H), 1.89 (td, $J = 12.9, 3.2$ Hz, 2H), 1.79 (d, $J = 12.9$ Hz, 1H), 1.61 (d, $J = 12.8$ Hz, 2H), 1.21 (d, $J = 12.8$ Hz, 2H), 1.06 (d, $J = 13.4$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 166.7 (C), 163.3 (d, $^1J = 248.8$ Hz, C), 157.2 (C), 156.7 (C), 156.5 (C), 135.5 (C), 134.4 (C), 132.9 (d, $^4J = 2.4$ Hz, C), 132.4 (C), 131.6 (CH), 131.5 (CH), 130.1 (CH), 129.1 (d, $^3J = 15.1$ Hz, CH), 128.2 (CH), 127.80 (CH), 127.76 (CH), 115.5 (d, $^2J = 21.7$ Hz, CH), 80.4 (C), 34.2 (CH_2), 25.6 (CH_2), 23.3 (CH_2); IR (neat) 2927, 1737, 1604, 1567, 1505, 1445, 1378, 1219, 1156, 1095, 1043, 1014, 993, 900, 846, 824, 812, 763, 730, 708, 696, 663, 632 cm^{-1} ; MS (ESI, m/z): 434.20 $[\text{M}+\text{H}]^+$; HRMS (ESI) calcd. for $\text{C}_{29}\text{H}_{25}\text{FN}_3$: 434.2027 $[\text{M}+\text{H}]^+$, found: 434.2028.

4.5.20 Synthesis of 7'-(4-chlorophenyl)-1',4'-diphenylspiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35t)

(2-(4-Chlorophenyl)-1-azaspiro[4.5]deca-1,3-diene-3,4-diyl)bis(phenylmethanone) **34t** (70.0 mg, 0.15 mmol) and $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$ (75.1 mg, 1.5 mmol) were employed to afford 50.5 mg (75%) of indicated product **35t** as a bright orange solid ($R_f = 0.11$ in 4:1 hexane/ethyl acetate; mp = 253.4-256.1 °C). ^1H NMR (400 MHz, CDCl_3) δ 7.53 – 7.42 (m, 5H), 7.31 – 7.22 (m, 3H), 7.13 (t, $J = 7.6$ Hz, 2H), 7.02 (dd, $J = 21.6, 8.6$ Hz, 4H), 1.96 – 1.89 (m, 3H), 1.76 (d, $J = 11.7$ Hz, 1H), 1.59 (d, $J = 10.5$ Hz, 3H), 1.20 – 1.13 (m, 2H), 1.07 – 0.96 (m, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ 165.7 (C), 157.5 (C), 157.0 (C), 156.4 (C), 136.8 (C), 135.6 (C), 135.3 (C), 133.1 (C), 132.1 (C), 130.2 (CH), 129.7 (CH), 129.6 (CH), 129.3 (CH), 129.2 (CH), 128.4 (CH),

128.0 (CH), 128.0 (CH), 80.7 (C), 34.2 (CH₂), 25.6 (CH₂), 23.4 (CH₂); IR (neat) 2935, 2849, 2028, 1990, 1968, 1607, 1540, 1489, 1444, 1380, 1108, 1089, 1015, 992, 899, 838, 757, 701, 620 cm⁻¹; MS (ESI, m/z): 450.17 [M+H]⁺; HRMS (ESI) calcd. for C₂₉H₂₅ClN₃: 450.1732 [M+H]⁺, found: 450.1736.

4.5.21 Synthesis of 4'-(3-bromophenyl)-7'-(4-chlorophenyl)-1'-phenylspiro[cyclohexane-1,5'-pyrrolo[3,4-*d*]pyridazine] (35u)

(3-Benzoyl-2-(4-chlorophenyl)-1-azaspiro[4.5]deca-1,3-dien-4-yl)(3-bromophenyl) methanone **34u** (70.5 mg, 0.13 mmol) and NH₂NH₂.H₂O (65.1 mg, 1.3 mmol) were employed to afford 42.0 mg (61%) of indicated product **35u** as a beige solid (*R*_f = 0.17 in 4:1 hexane/ethyl acetate; mp = 219.2 -221.0 °C). ¹H NMR (400 MHz, CDCl₃) δ 7.73 (dd, *J* = 5.4, 1.8 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.40 – 7.33 (m, 3H), 7.22 (t, *J* = 7.7 Hz, 2H), 7.10 (dd, *J* = 21.0, 8.6 Hz, 4H), 2.11 – 1.93 (m, 4H), 1.88 (d, *J* = 12.7 Hz, 1H), 1.72 (d, *J* = 12.4 Hz, 2H), 1.30 (d, *J* = 12.2 Hz, 2H), 1.19 (dd, *J* = 17.7, 8.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 165.6 (C), 157.0 (C), 156.7 (C), 155.9 (C), 138.7 (C), 135.4 (C), 132.9 (C), 132.7 (C), 132.4 (C), 132.2 (C), 130.2 (CH), 129.9 (CH), 129.7 (CH), 129.3 (CH), 128.3 (CH), 127.99 (CH), 127.95 (CH), 122.5 (CH), 80.6 (C), 34.3 (CH₂), 25.7 (CH₂), 23.4 (CH₂) (Note that two CH peaks overlap with each others); IR (neat) 2933, 1609, 1490, 1445, 1398, 1374, 1090, 1017, 998, 907, 884, 839, 789, 768, 730, 701 cm⁻¹; MS (ESI, m/z): 528.08 [M+H]⁺; HRMS (ESI) calcd. for C₂₉H₂₄BrClN₃: 528.0837 [M+H]⁺, found: 528.0838.

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APPENDIX A

NMR SPECTRA

Bruker Spectrospin Avance DPX400 Ultrashield spectrometer was used for analyzing ^1H and ^{13}C NMR spectra. Chemical shifts are represented in parts per million (ppm) relative to CDCl_3 (7.26 and 77.16 ppm in ^1H and ^{13}C NMR, respectively).

^1H and ^{13}C NMR spectra of all synthesized compounds are shown in below.

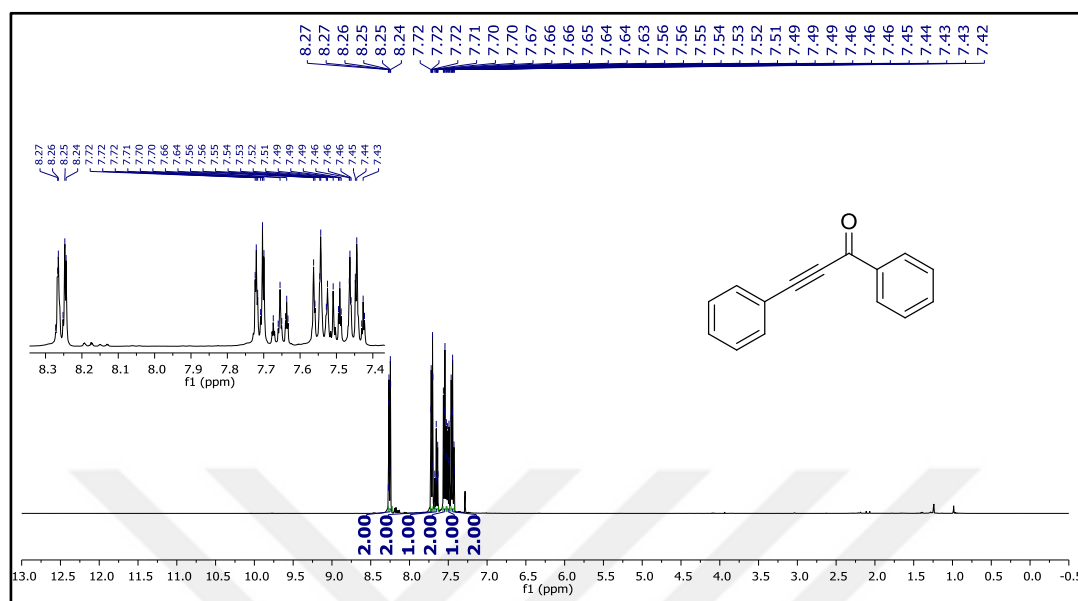


Figure 27. ¹H NMR spectrum of compound 29a.

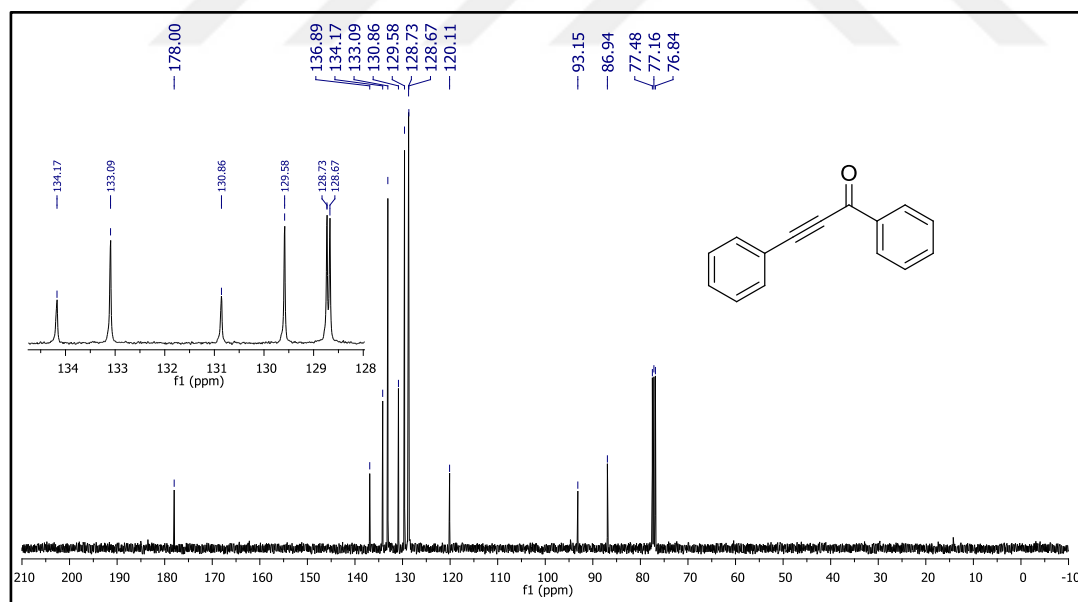


Figure 28. ¹³C NMR spectrum of compound 29a.

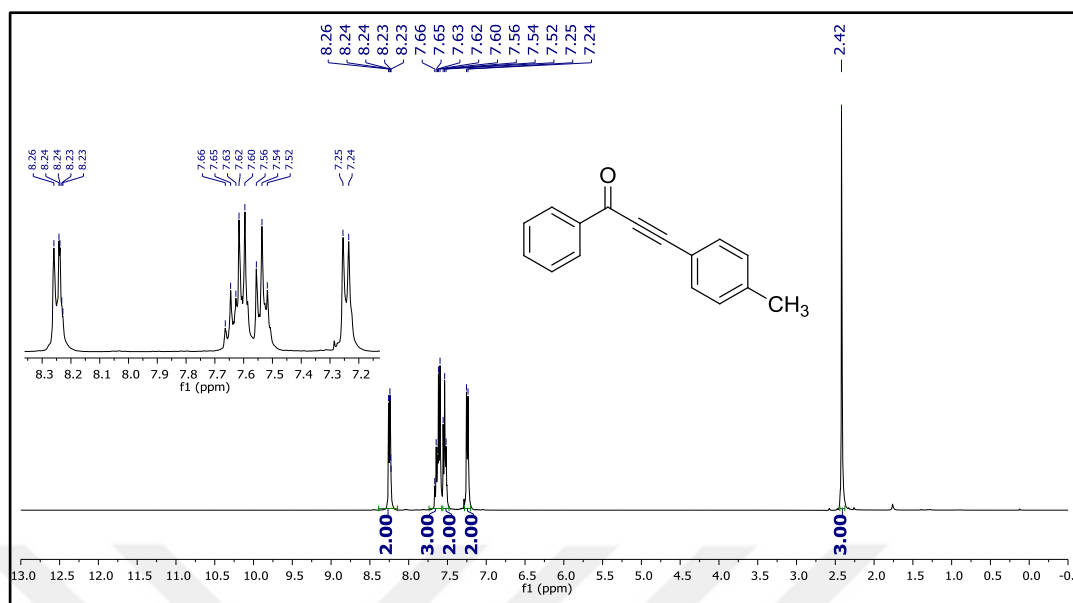


Figure 29. ^1H NMR spectrum of compound **29b**.

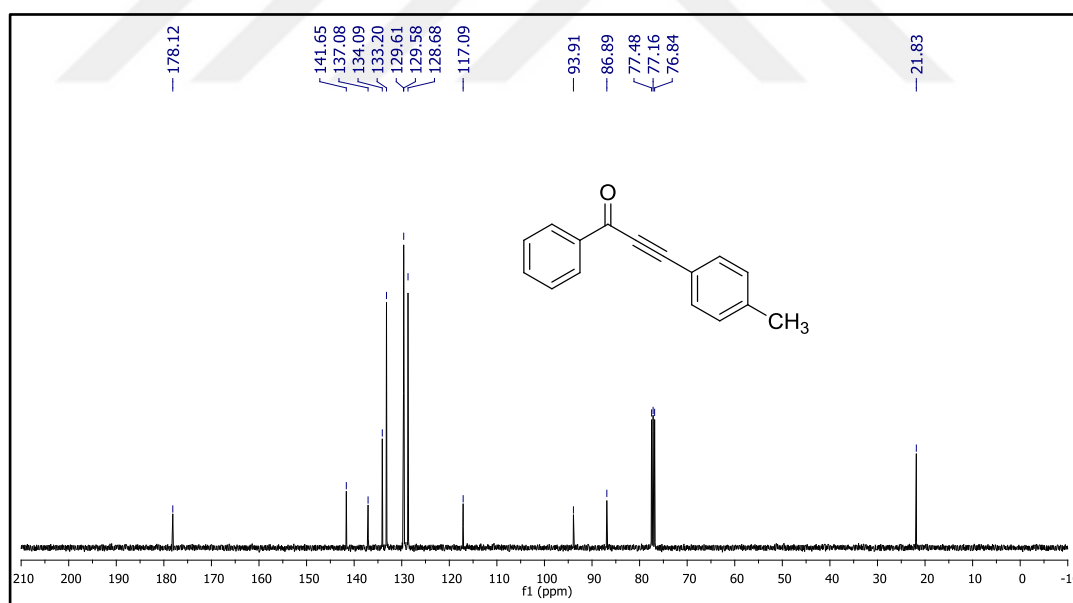


Figure 30. ^{13}C NMR spectrum of compound **29b**.

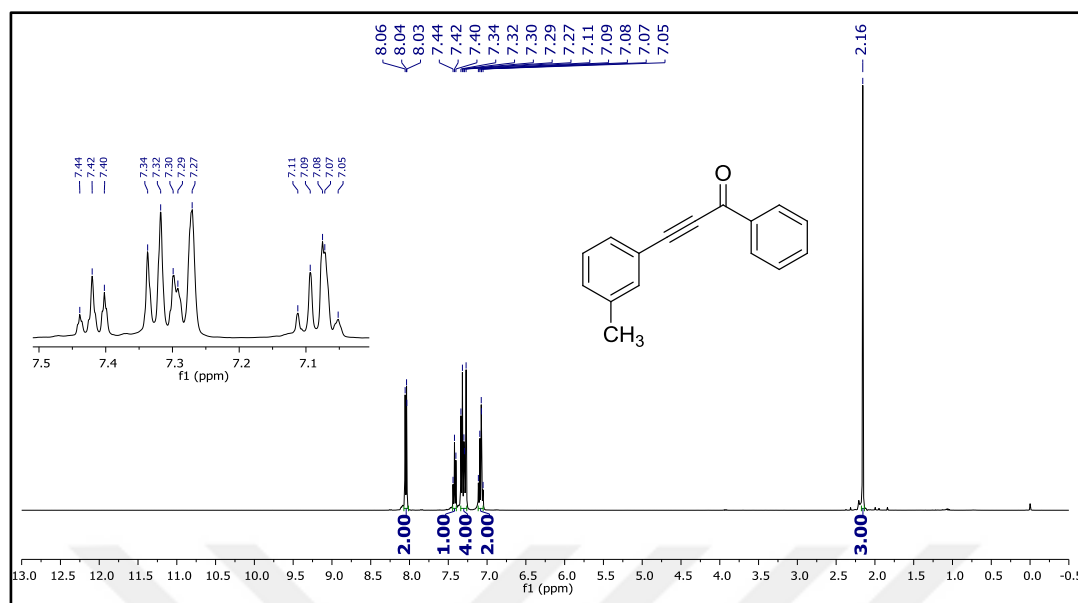


Figure 31. ^1H NMR spectrum of compound **29c**.

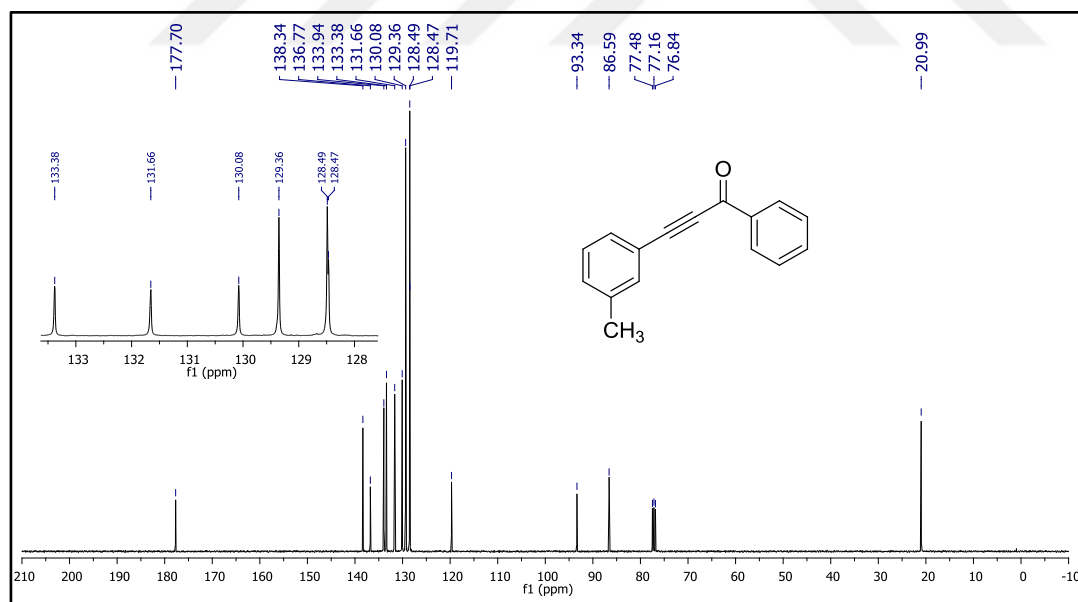


Figure 32. ^{13}C NMR spectrum of compound **29c**.

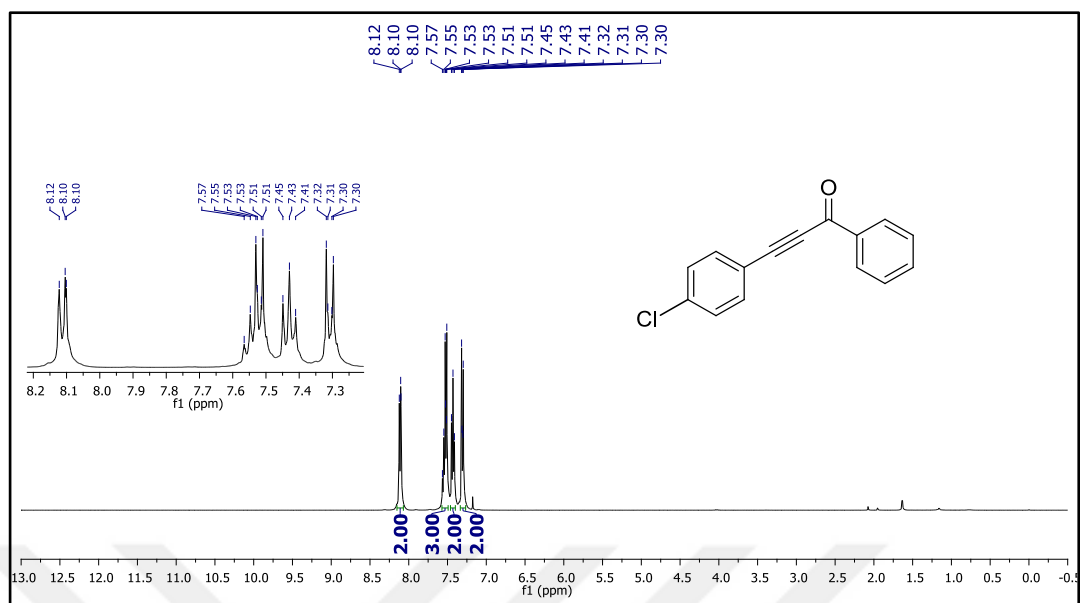


Figure 33. ^1H NMR spectrum of compound **29d**.

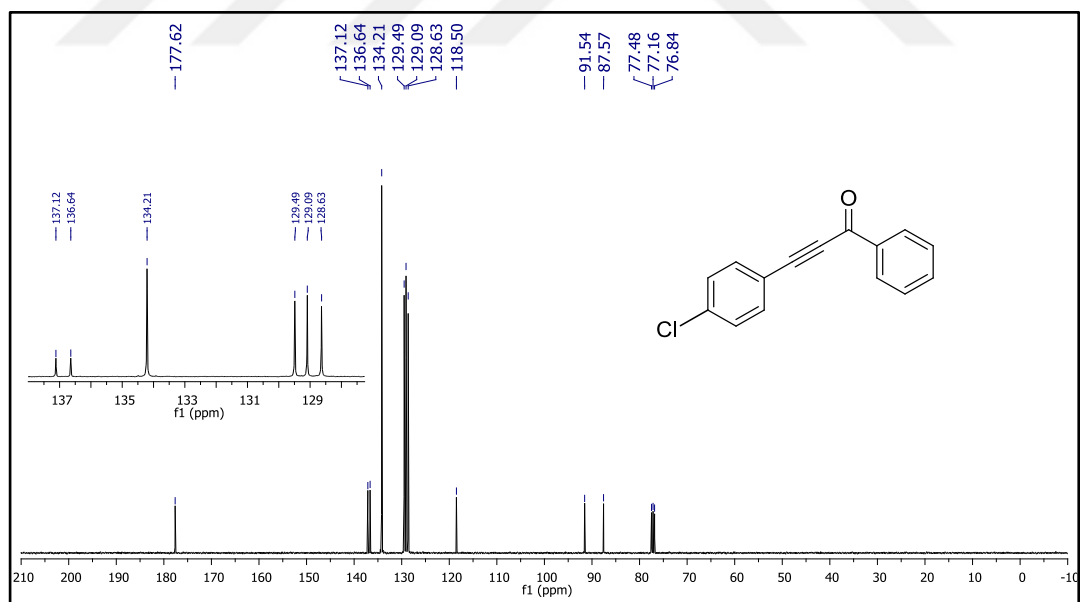


Figure 34. ^{13}C NMR spectrum of compound **29d**.

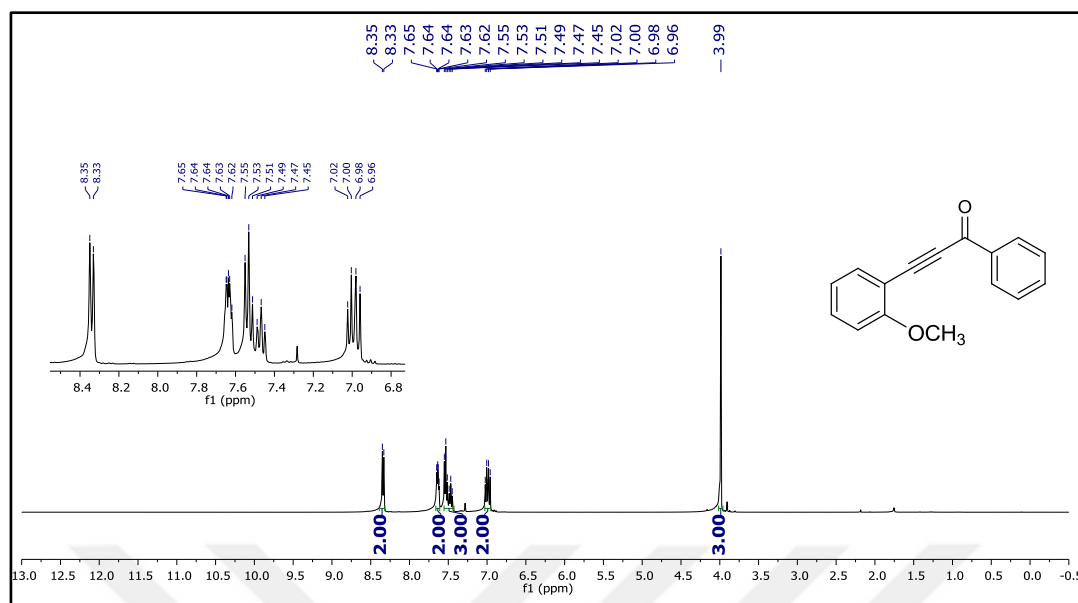


Figure 35. ¹H NMR spectrum of compound **29e**.

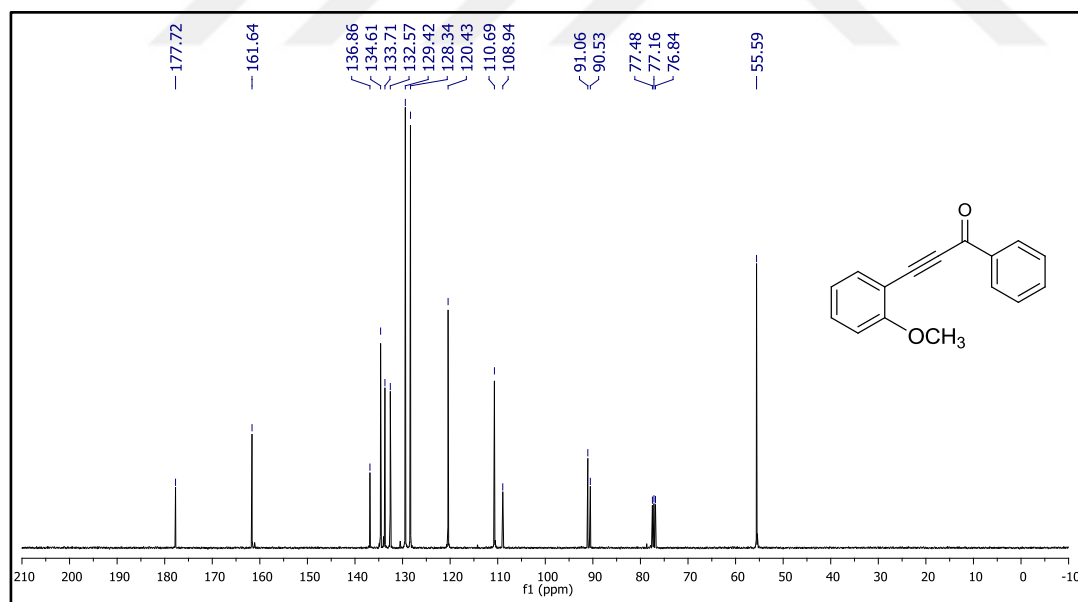


Figure 36. ¹³C NMR spectrum of compound **29e**.

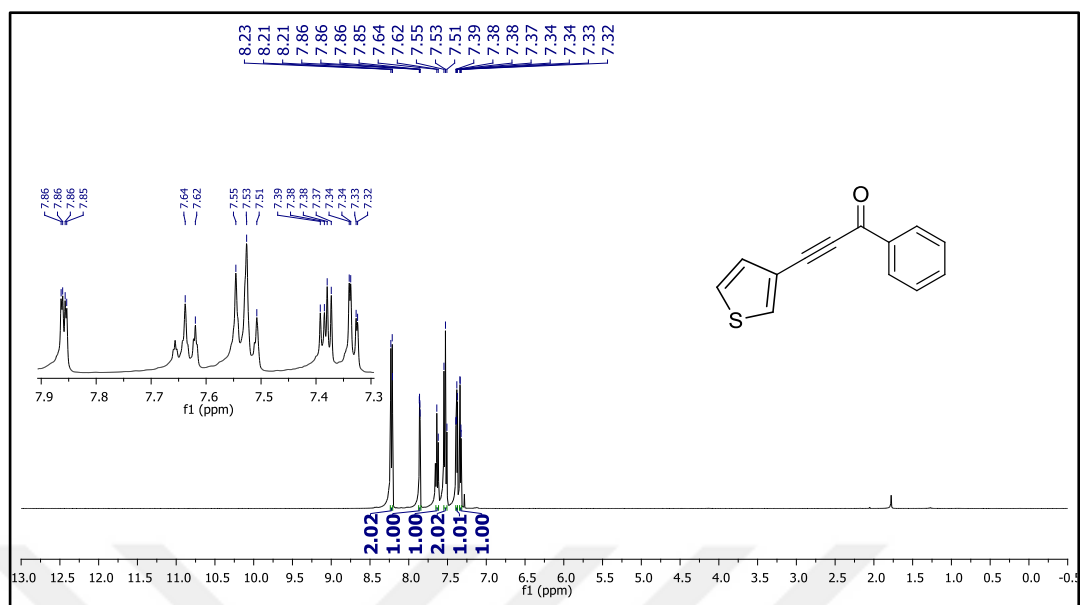


Figure 37. ¹H NMR spectrum of compound 29f.

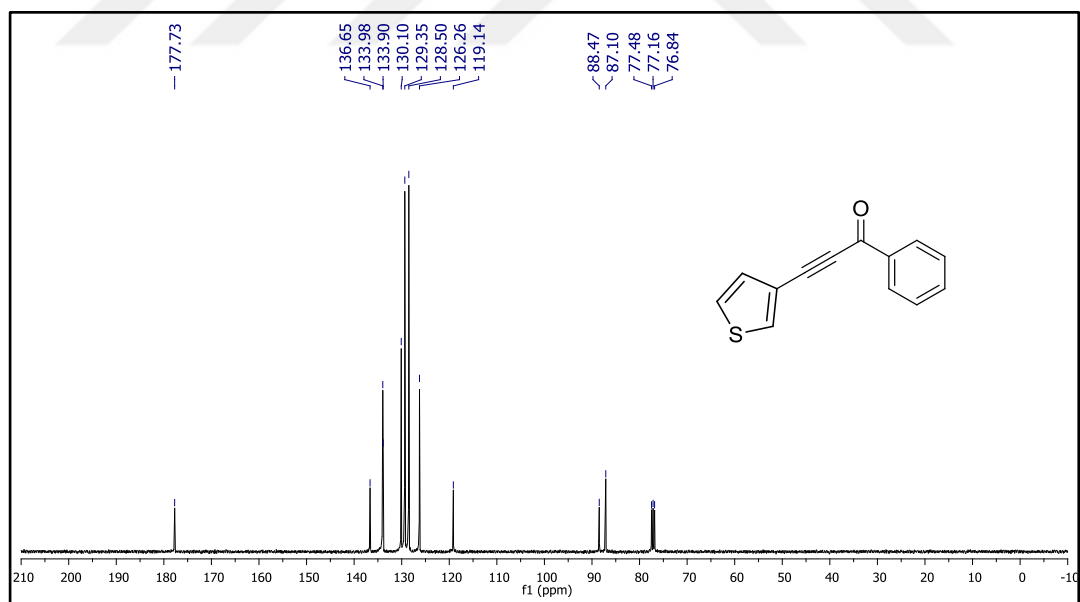


Figure 38. ¹³C NMR spectrum of compound 29f.

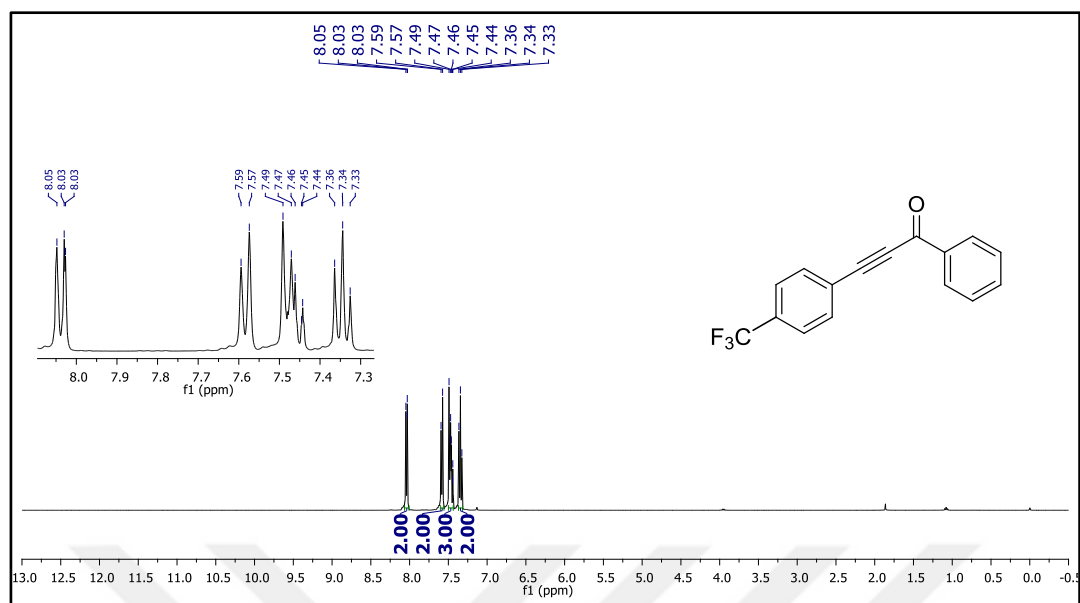


Figure 39. ¹H NMR spectrum of compound 29g.

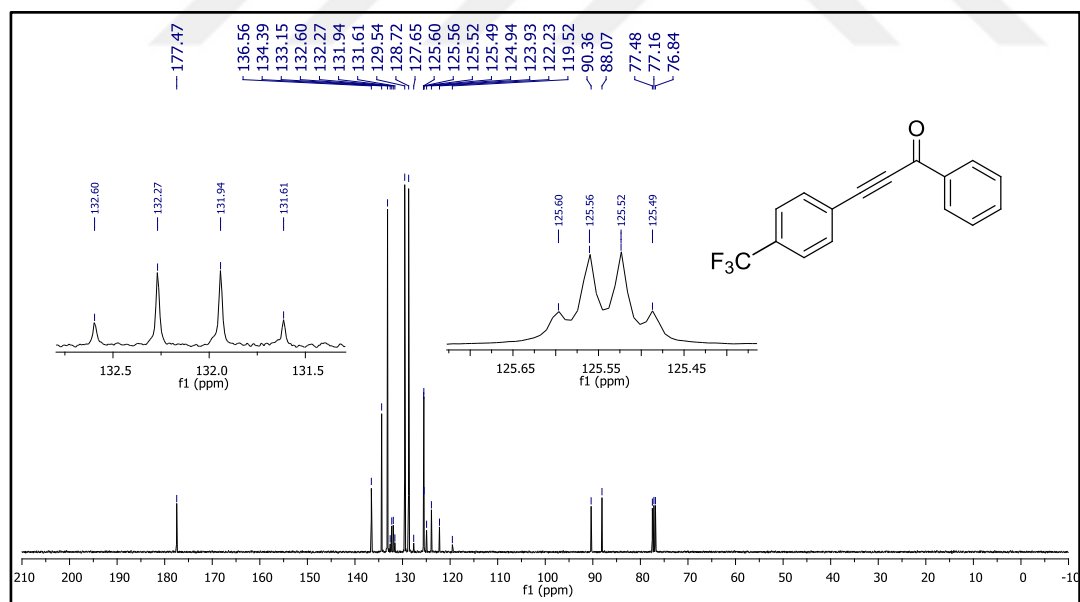


Figure 40. ¹³C NMR spectrum of compound 29g.

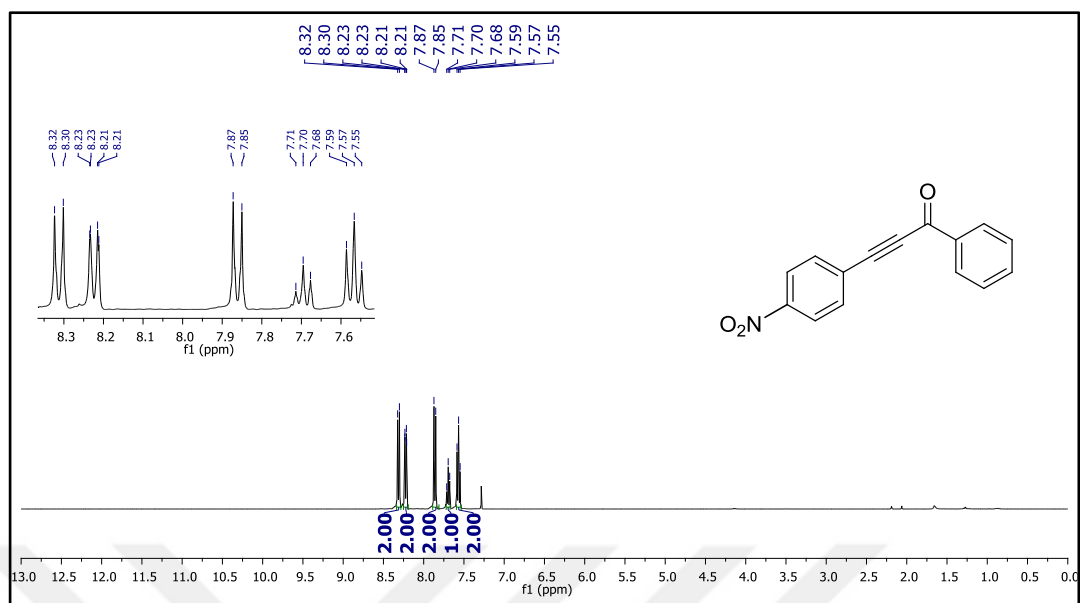


Figure 41. ^1H NMR spectrum of compound **29h**.

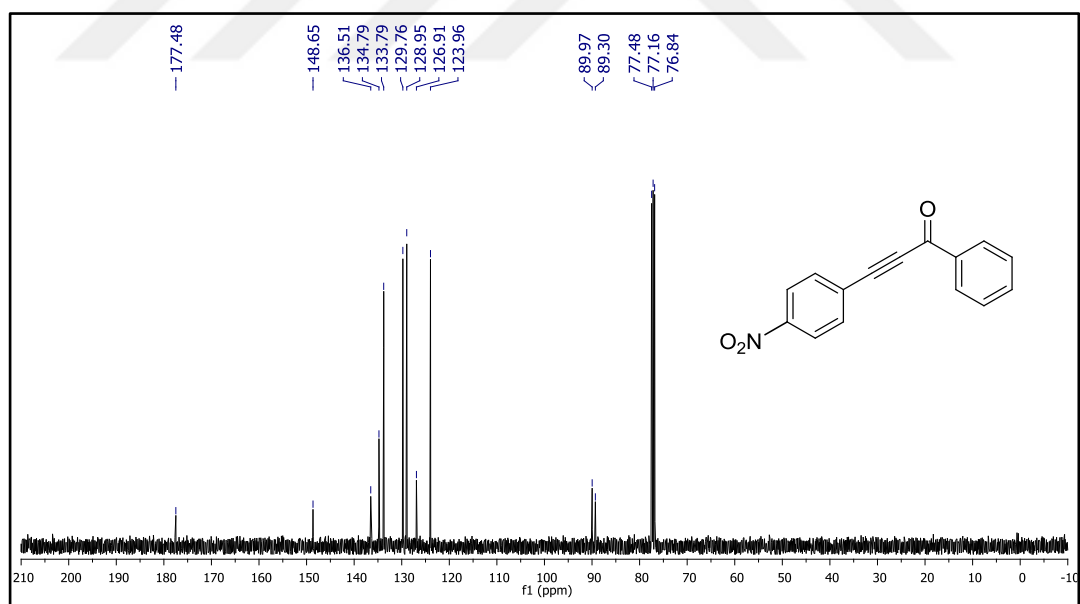


Figure 42. ^{13}C NMR spectrum of compound **29h**.

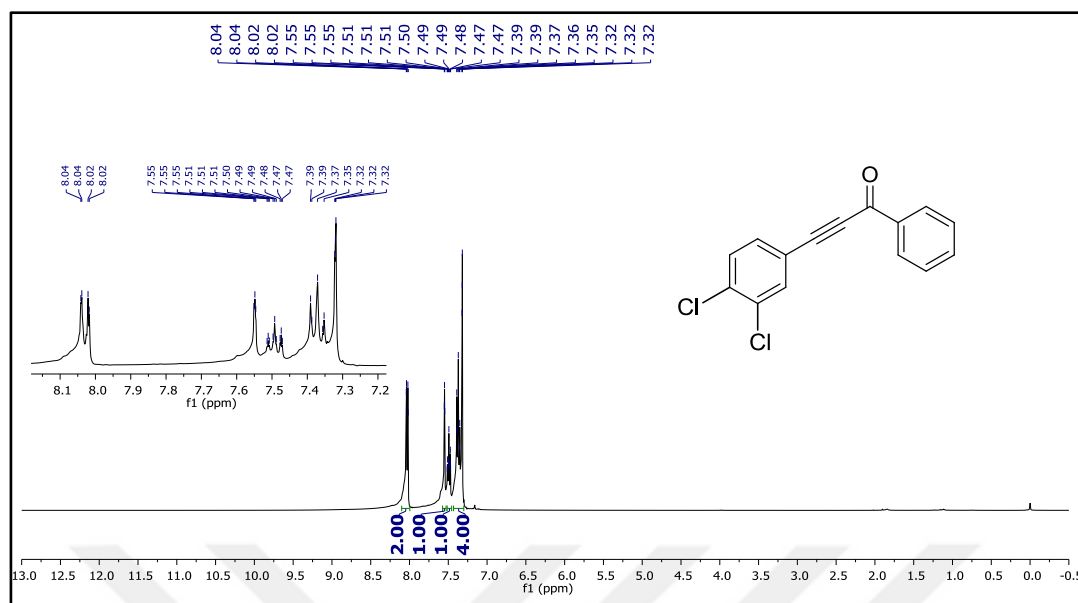


Figure 43. ^1H NMR spectrum of compound **29i**.

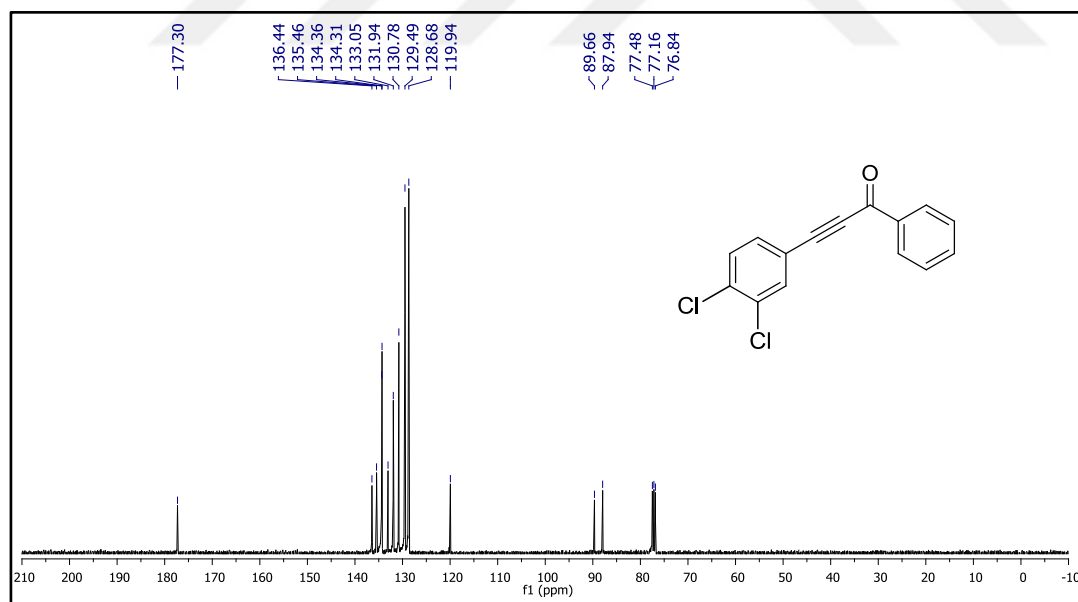


Figure 44. ^{13}C NMR spectrum of compound **29i**.

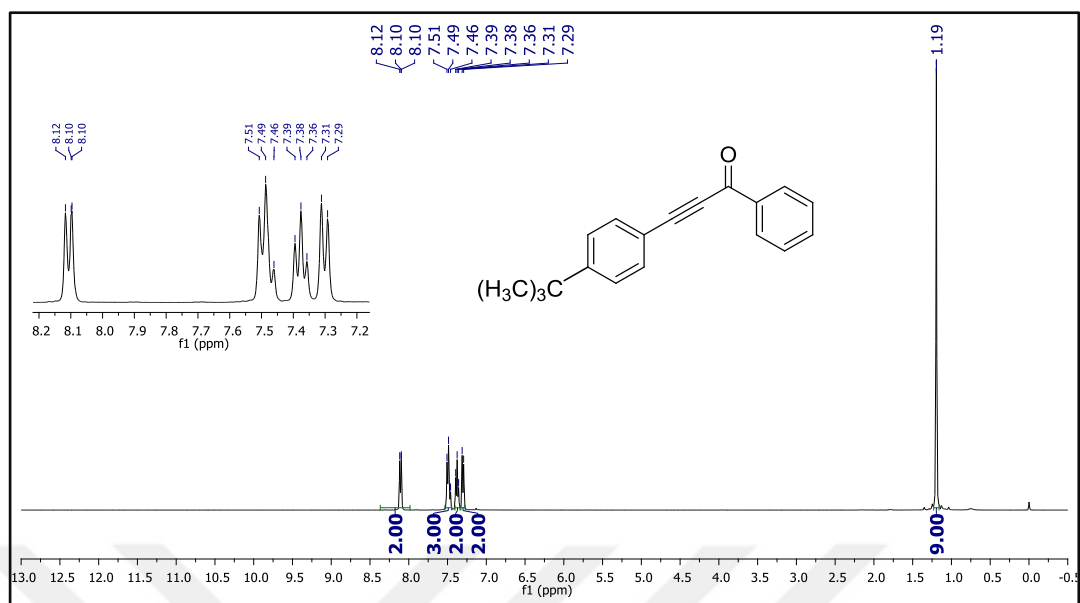


Figure 45. ^1H NMR spectrum of compound **29j**.

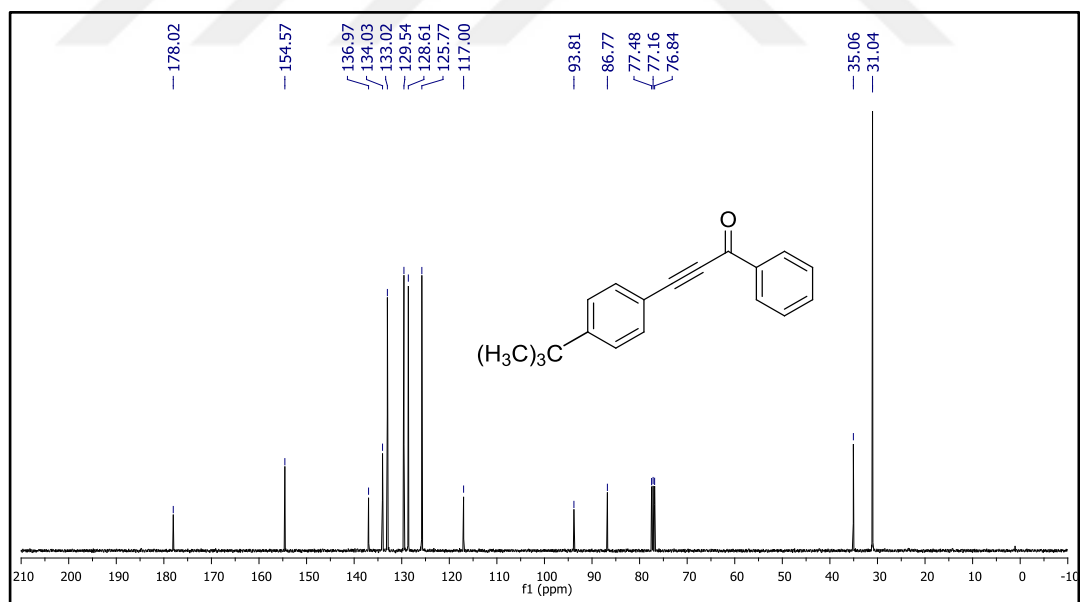


Figure 46. ^{13}C NMR spectrum of compound **29j**.

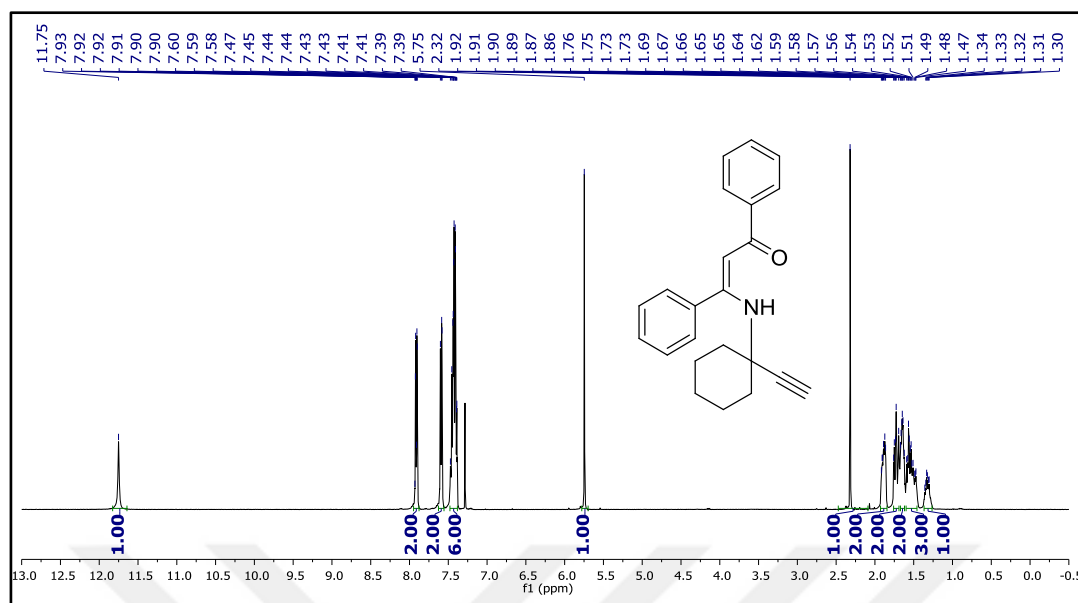


Figure 47. ^1H NMR spectrum of compound 31a.

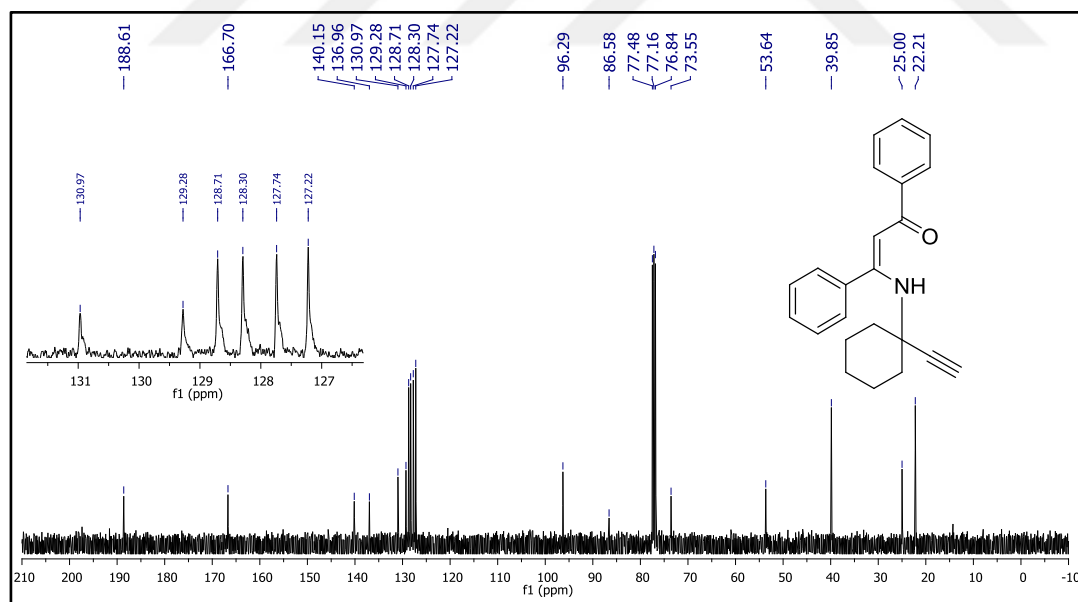


Figure 48. ^{13}C NMR spectrum of compound 31a.

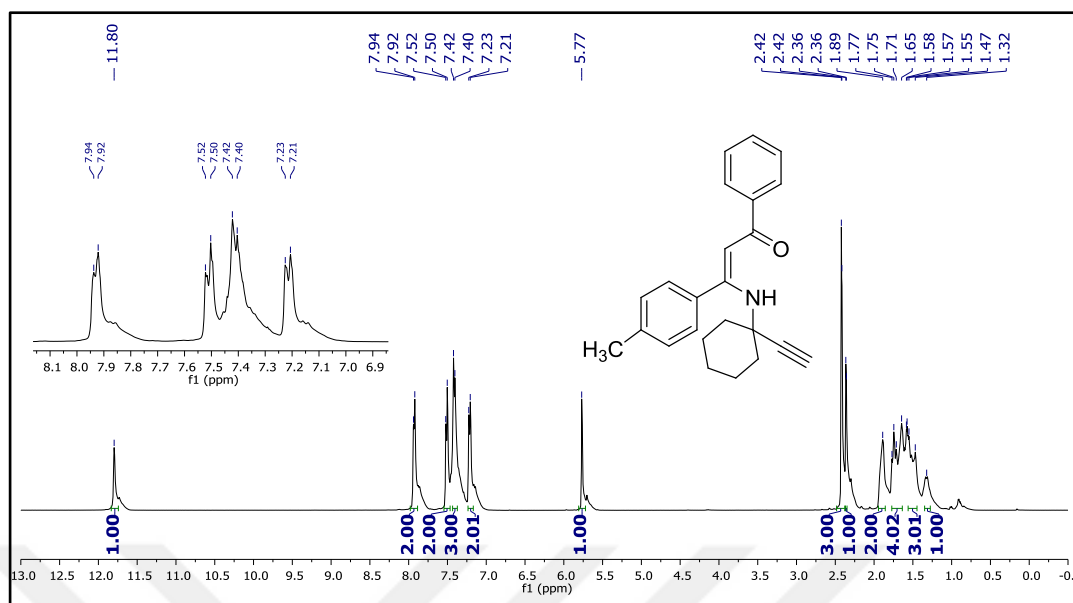


Figure 49. ¹H NMR spectrum of compound 31b.

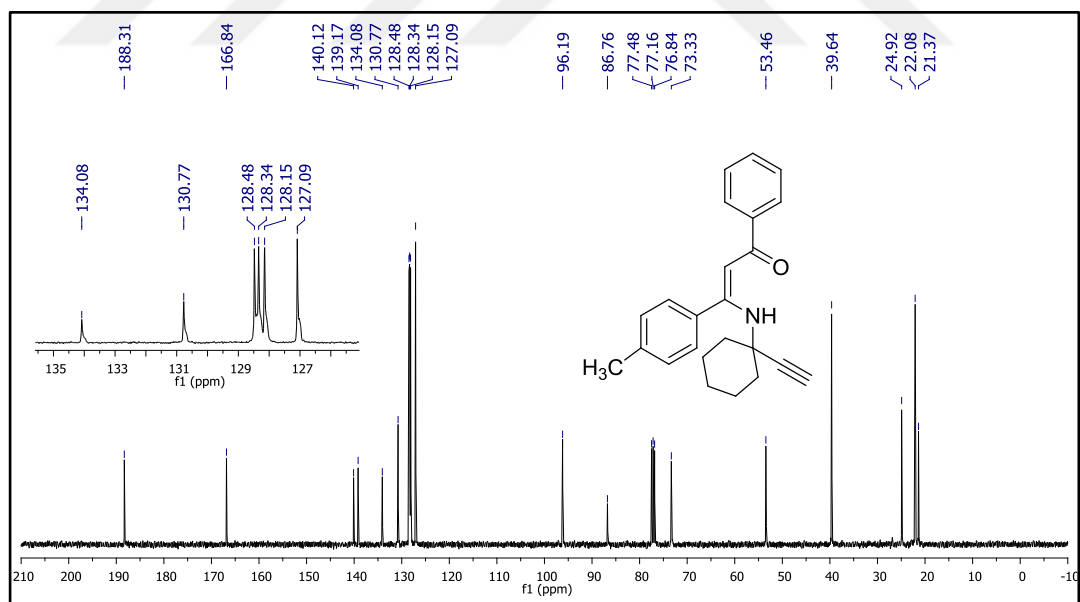


Figure 50. ¹³C NMR spectrum of compound 31b.

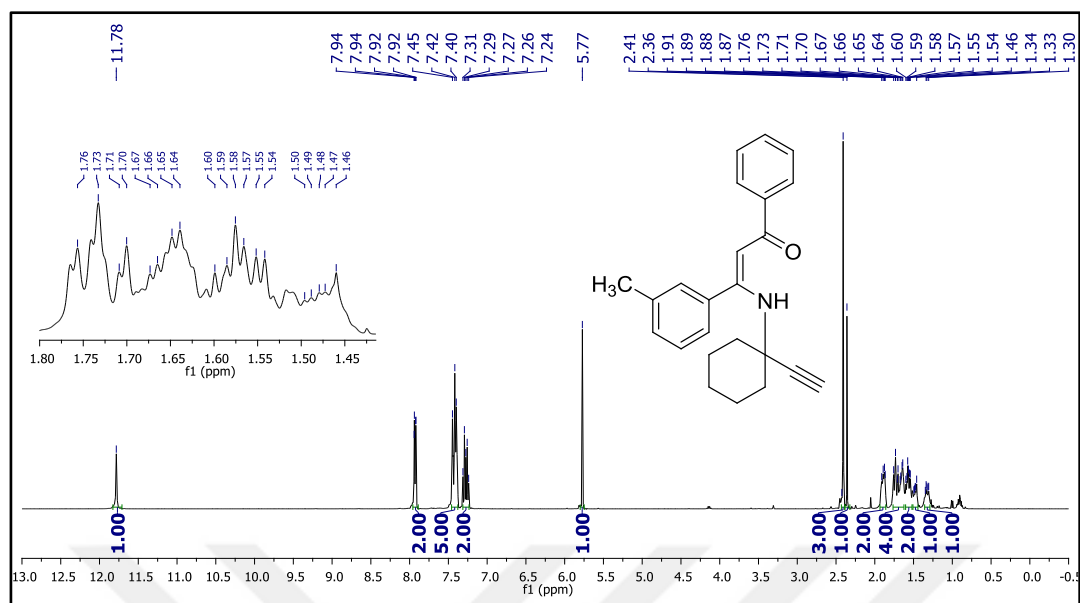


Figure 51. ^1H NMR spectrum of compound 31c.

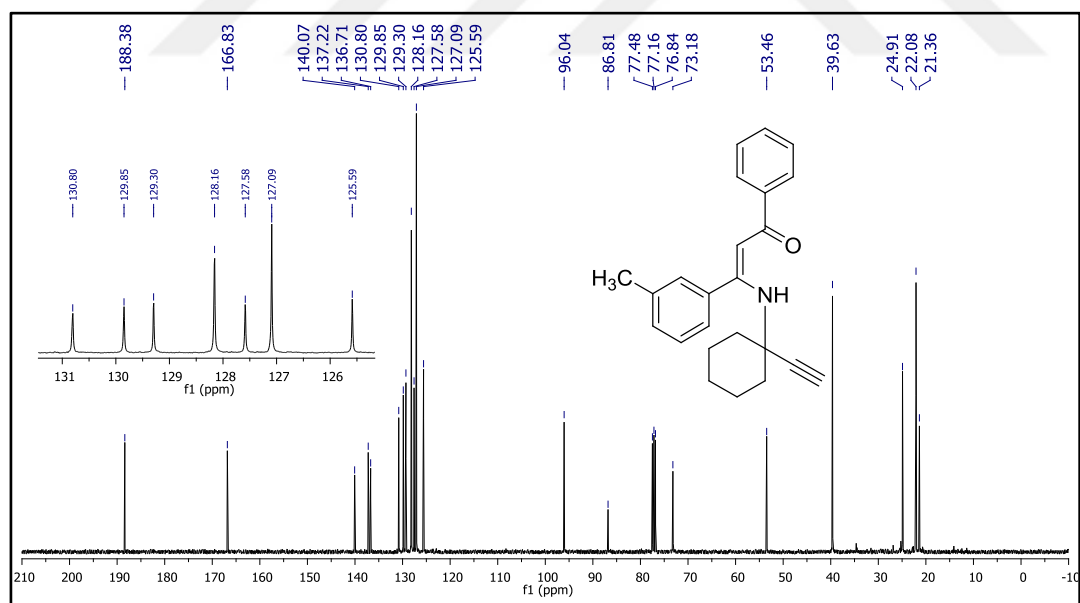


Figure 52. ^{13}C NMR spectrum of compound 31c.

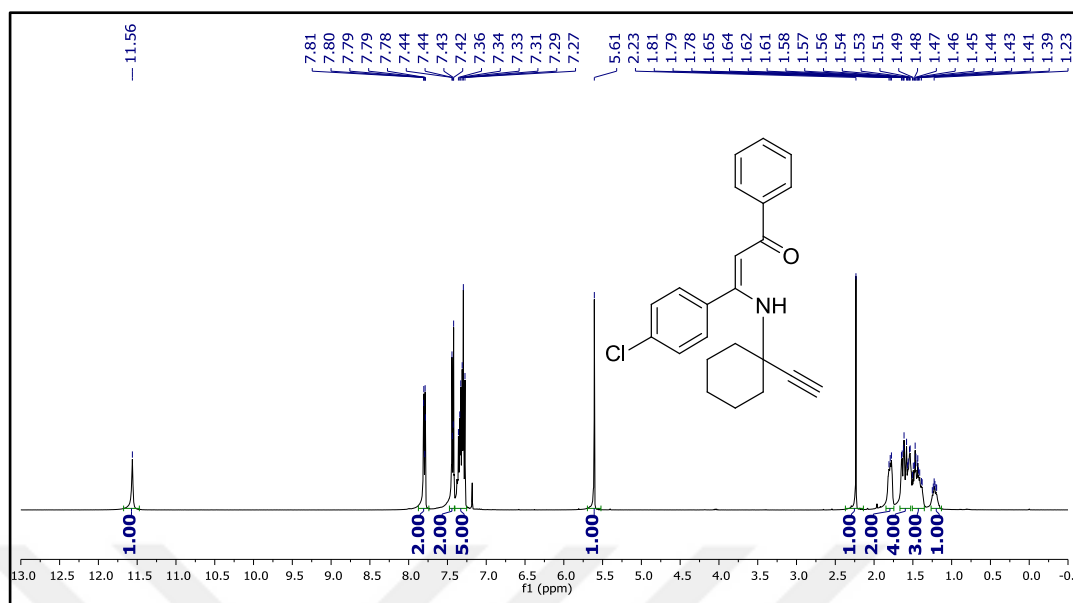


Figure 53. ¹H NMR spectrum of compound 31d.

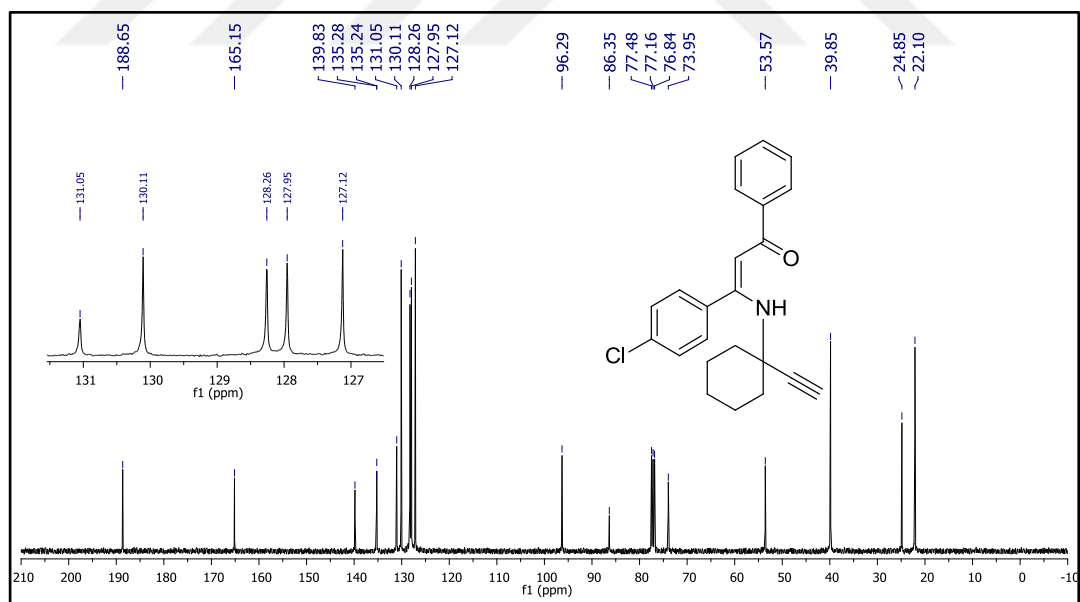


Figure 54. ¹³C NMR spectrum of compound 31d.

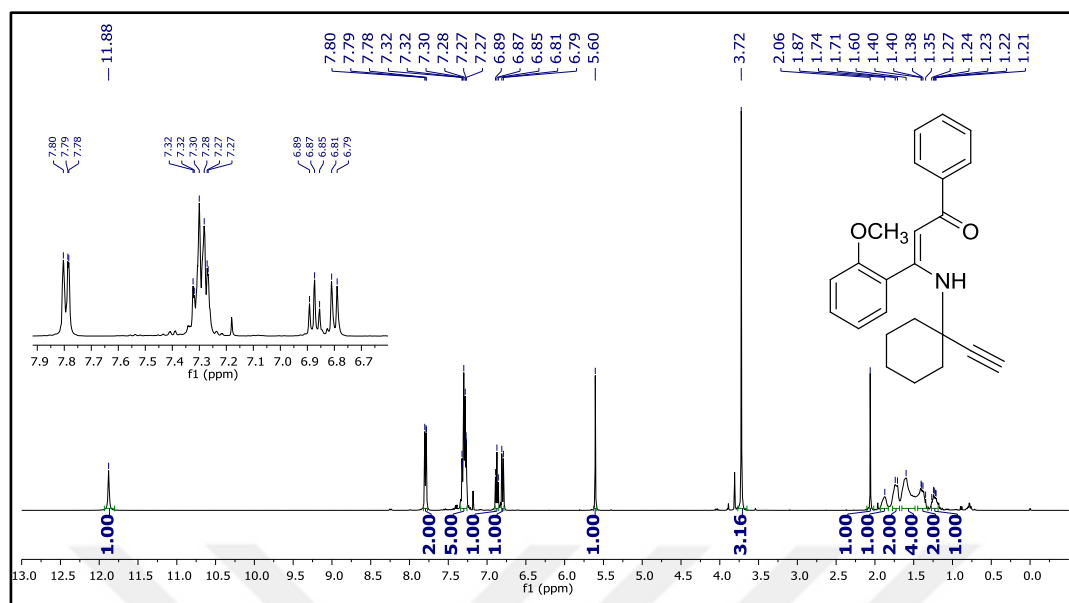


Figure 55. ^1H NMR spectrum of compound 31e.

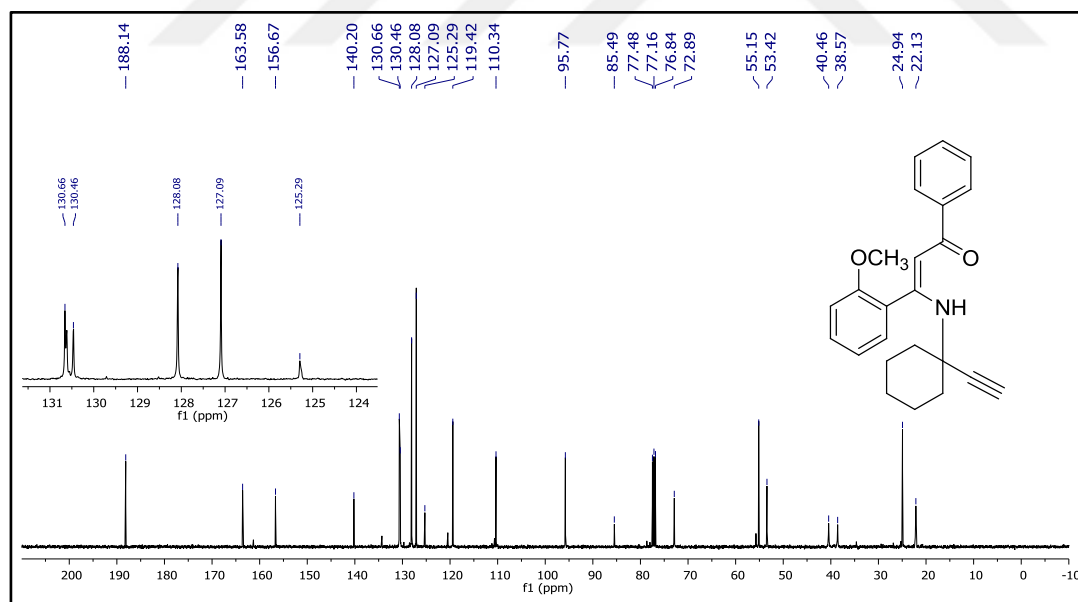


Figure 56. ^{13}C NMR spectrum of compound 31e.

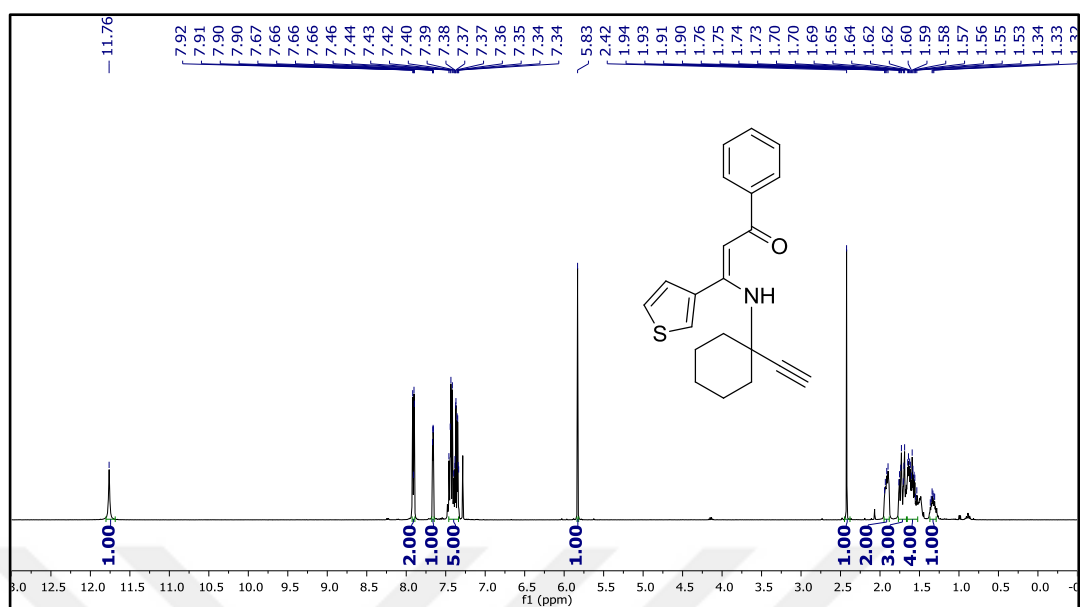


Figure 57. ¹H NMR spectrum of compound 31f.

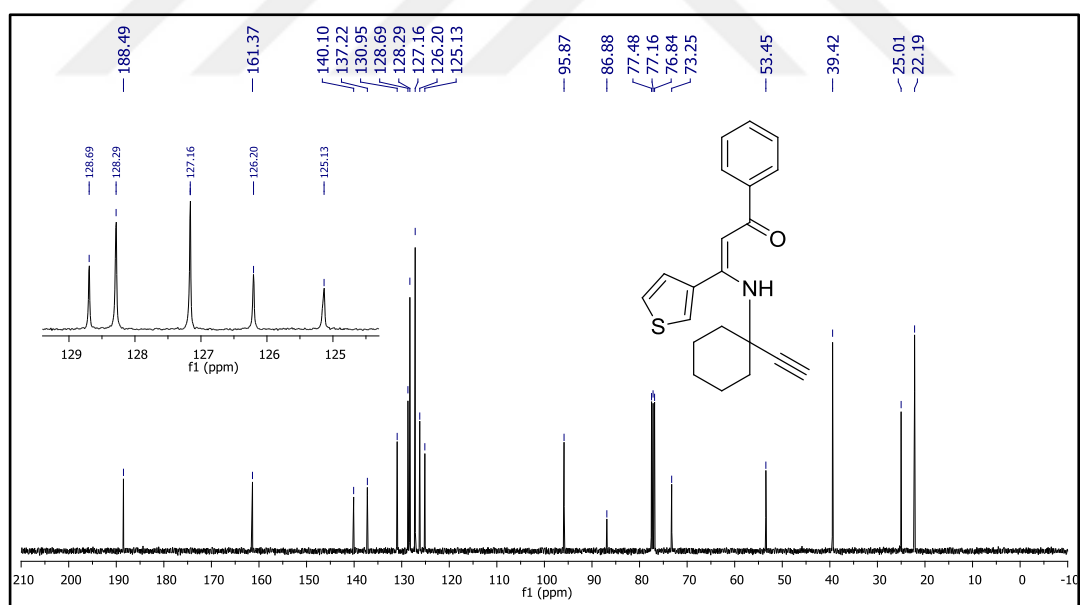


Figure 58. ¹³C NMR spectrum of compound 31f.

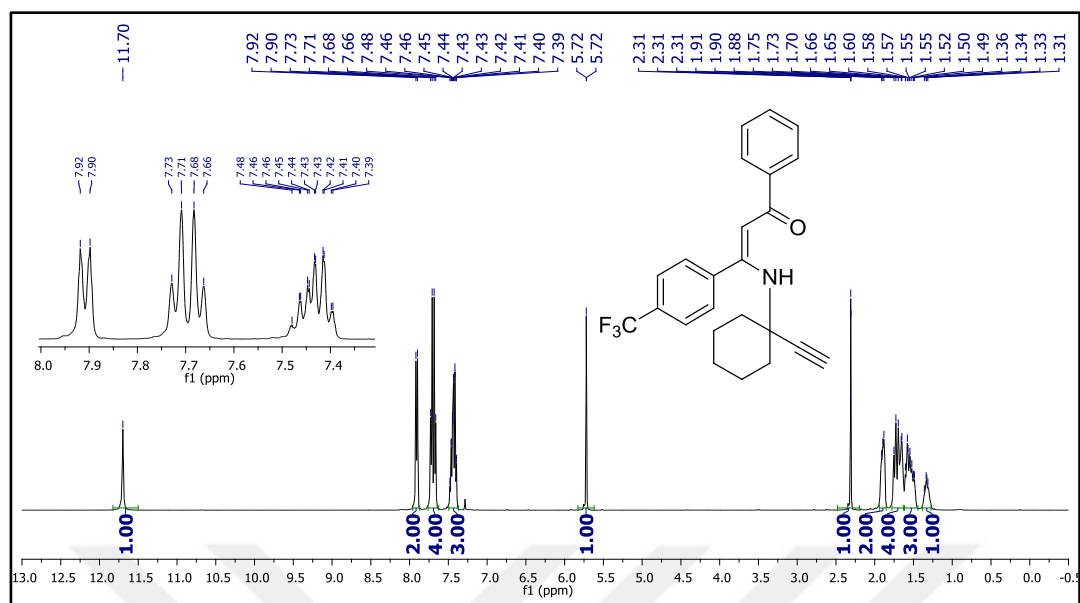


Figure 59. ^1H NMR spectrum of compound **31g**.

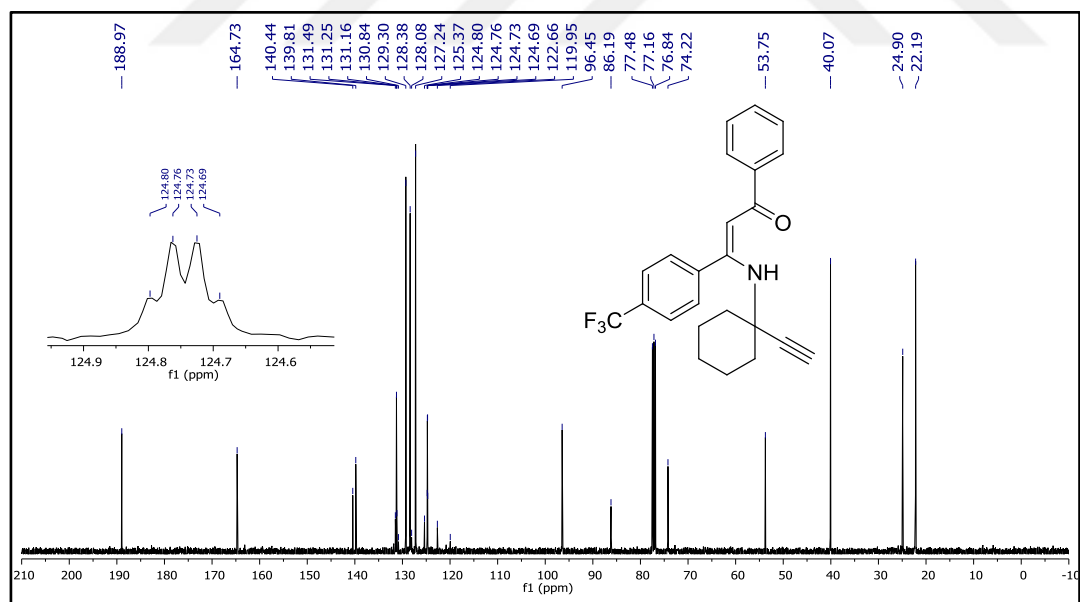
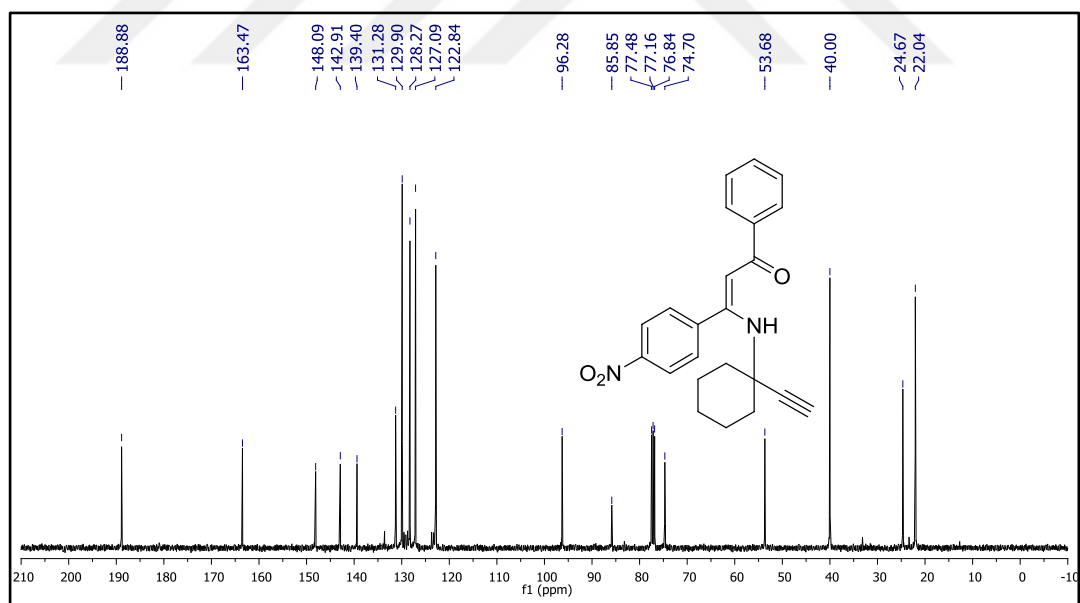
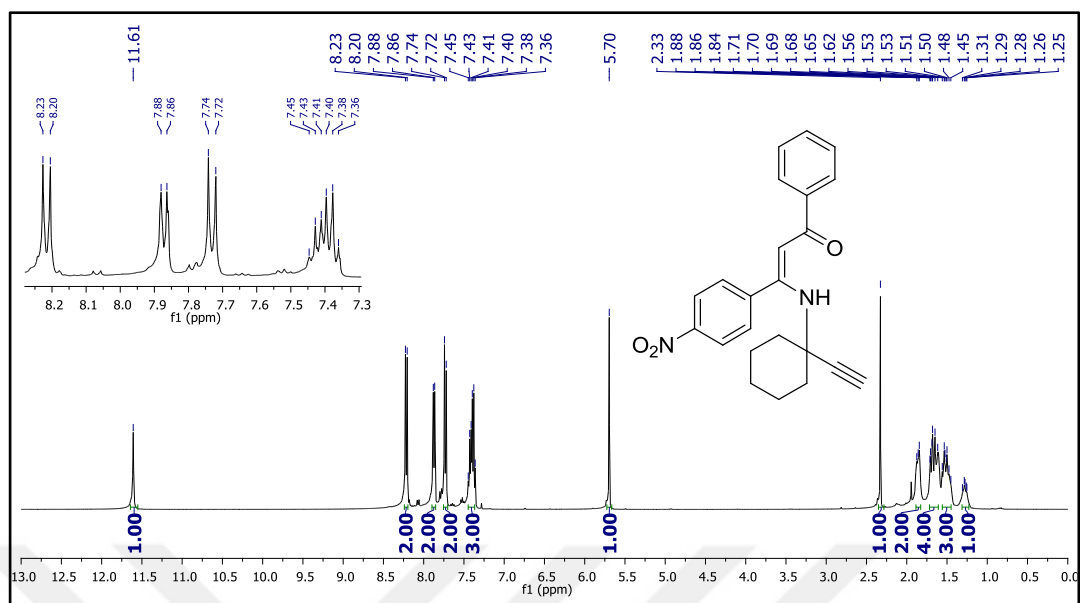


Figure 60. ^{13}C NMR spectrum of compound **31g**.



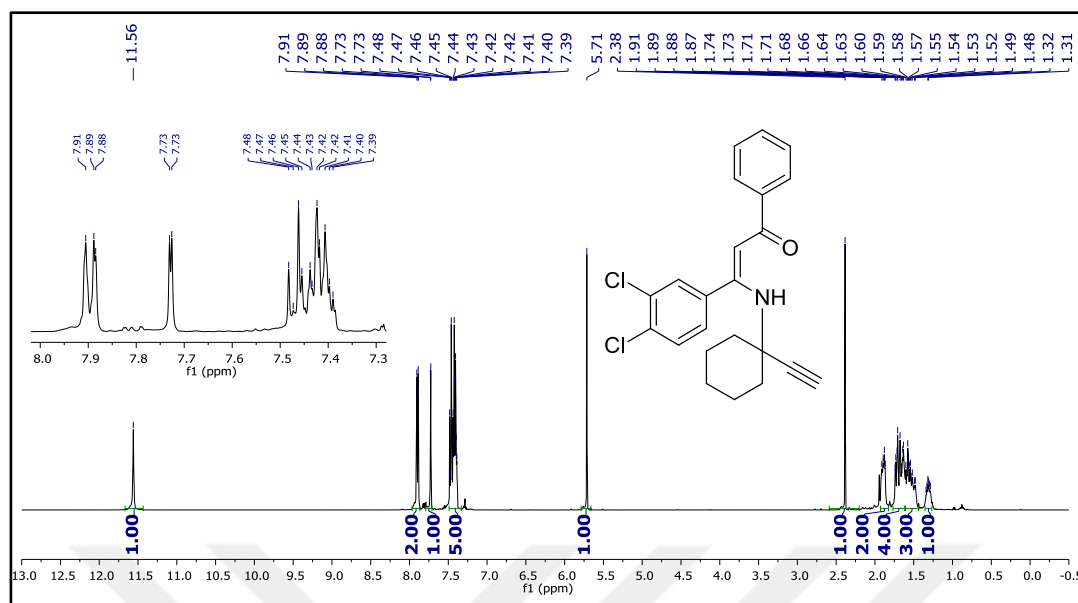


Figure 63. ¹H NMR spectrum of compound 31i.

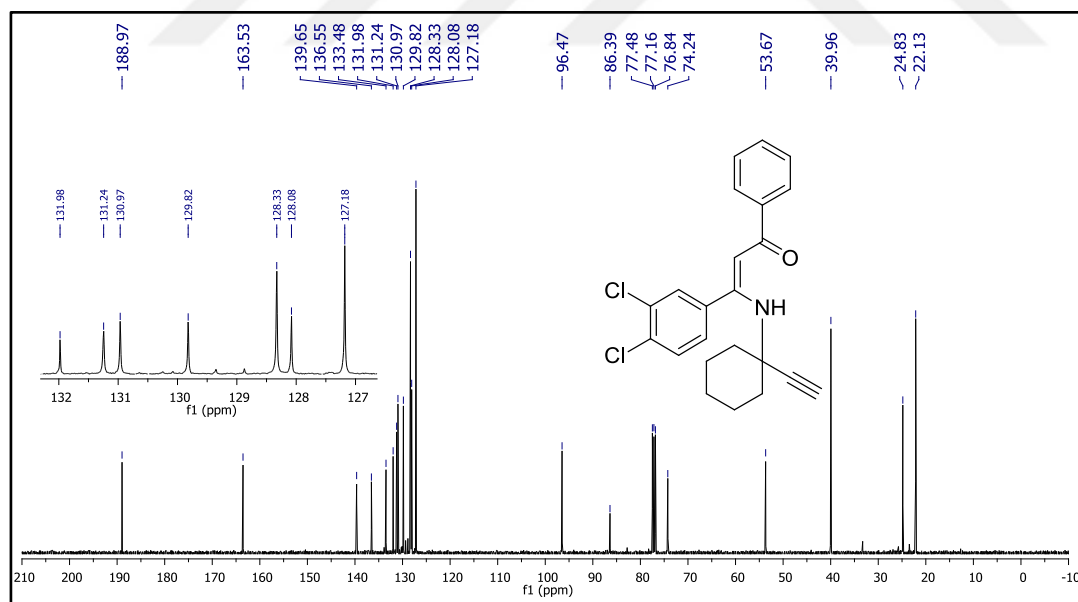


Figure 64. ¹³C NMR spectrum of compound 31i.

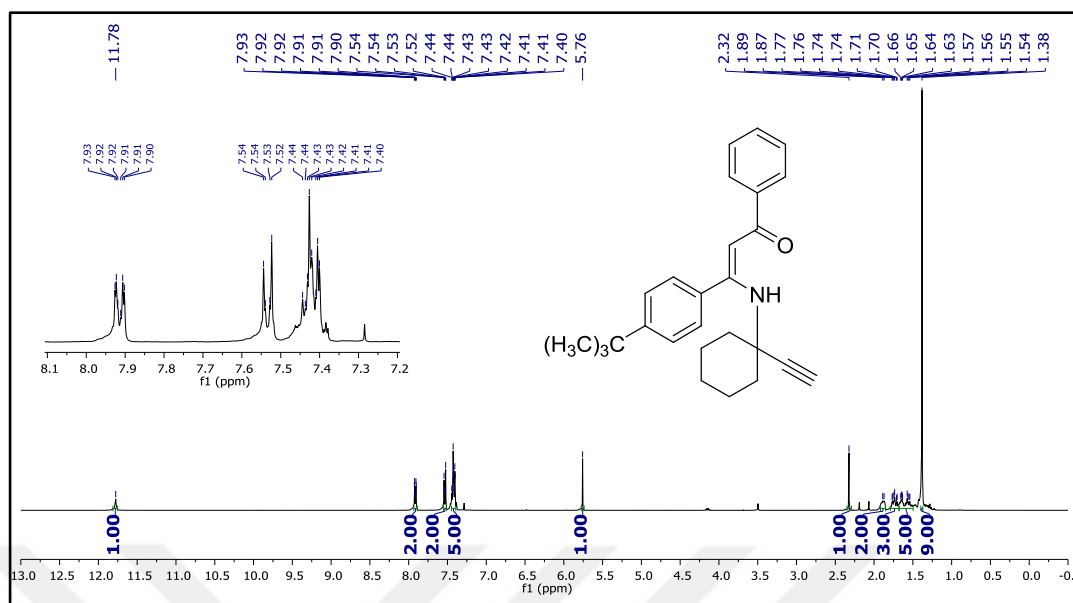


Figure 65. ¹H NMR spectrum of compound 31j.

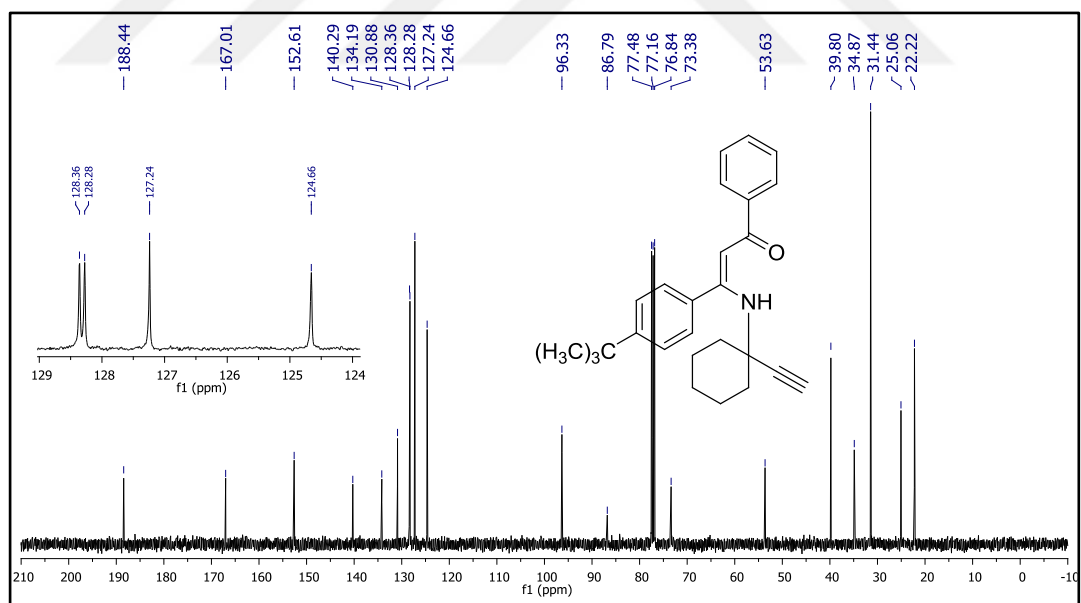


Figure 66. ¹³C NMR spectrum of compound 31j.

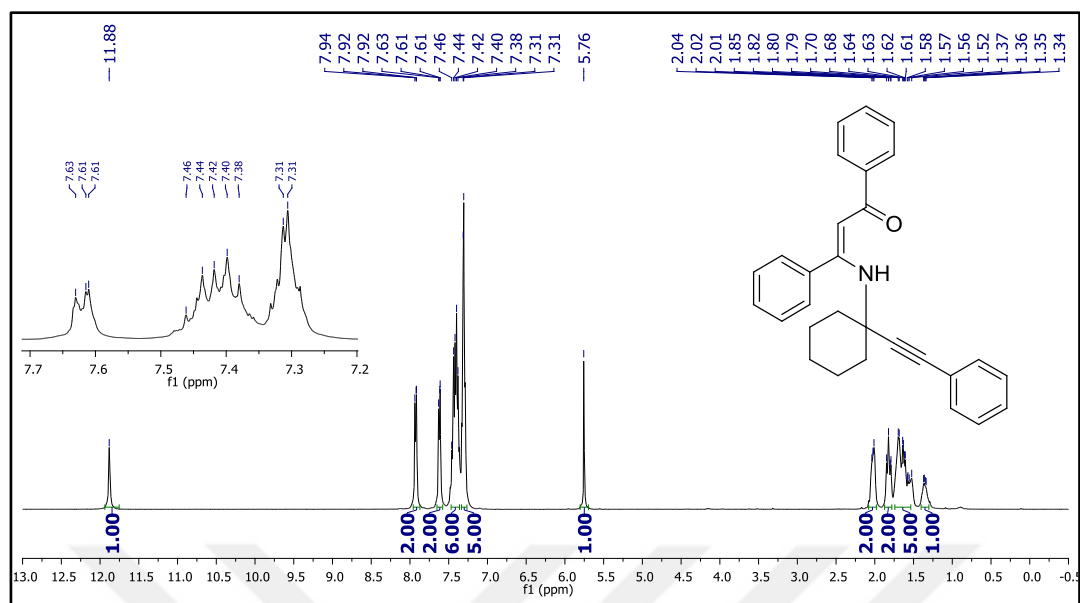


Figure 67. ¹H NMR spectrum of compound 33a.

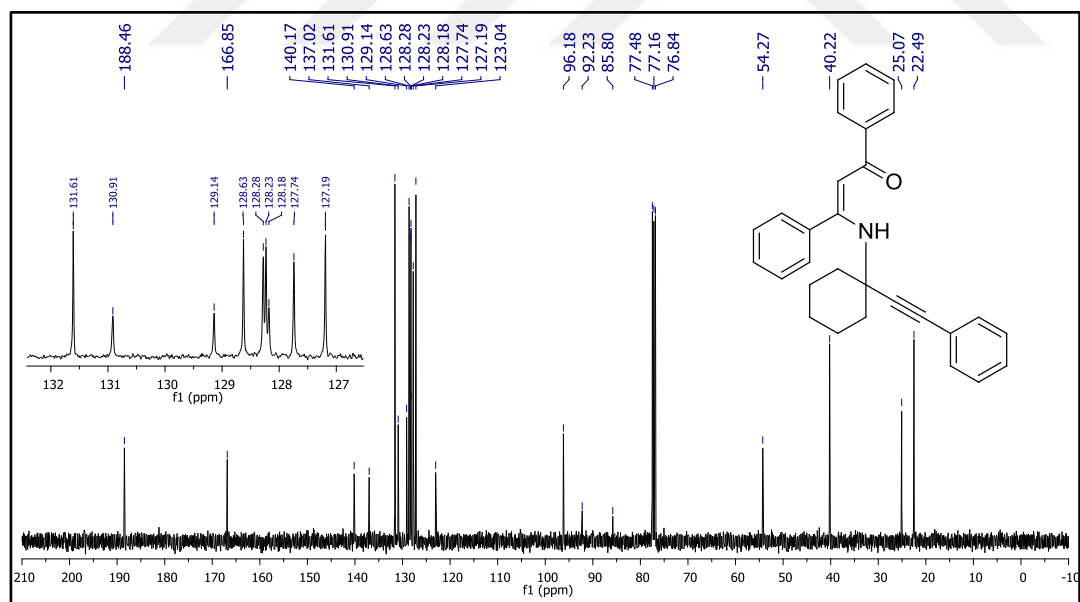


Figure 68. ¹³C NMR spectrum of compound 33a.

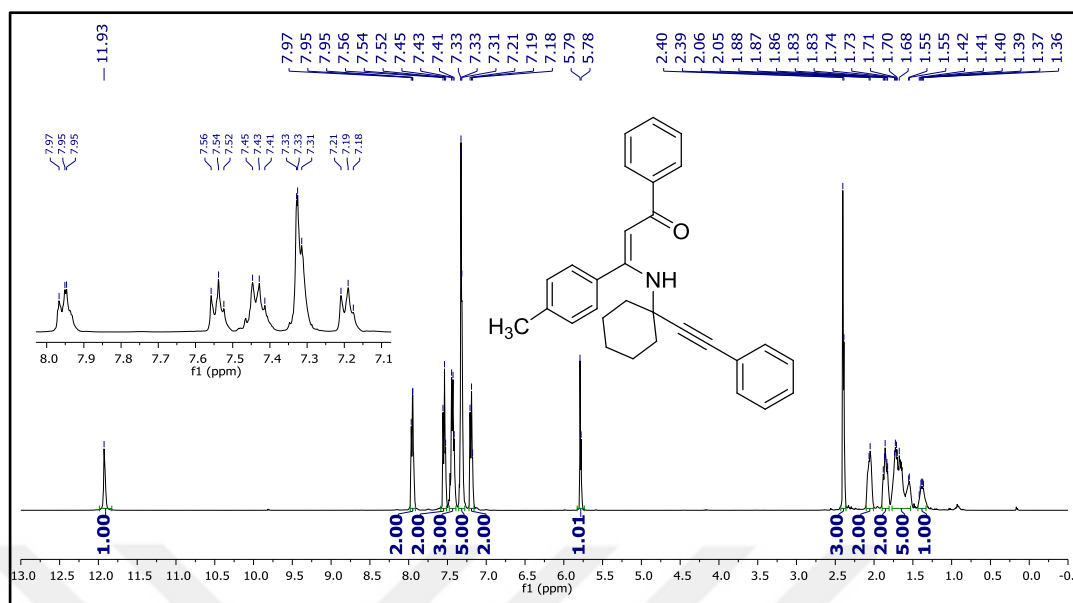


Figure 69. ¹H NMR spectrum of compound 33b.

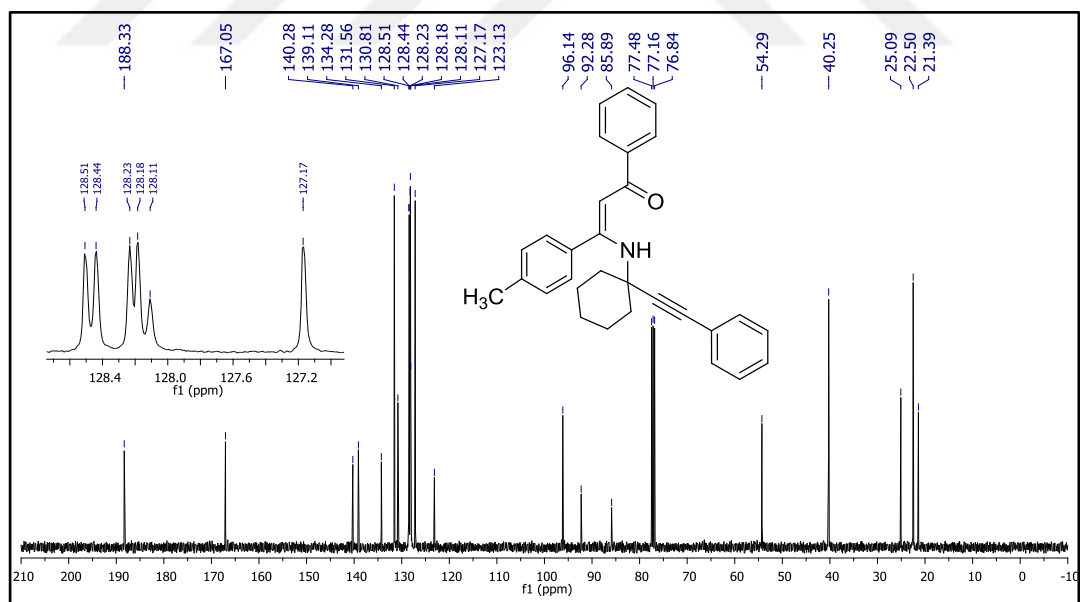


Figure 70. ¹³C NMR spectrum of compound 33b.

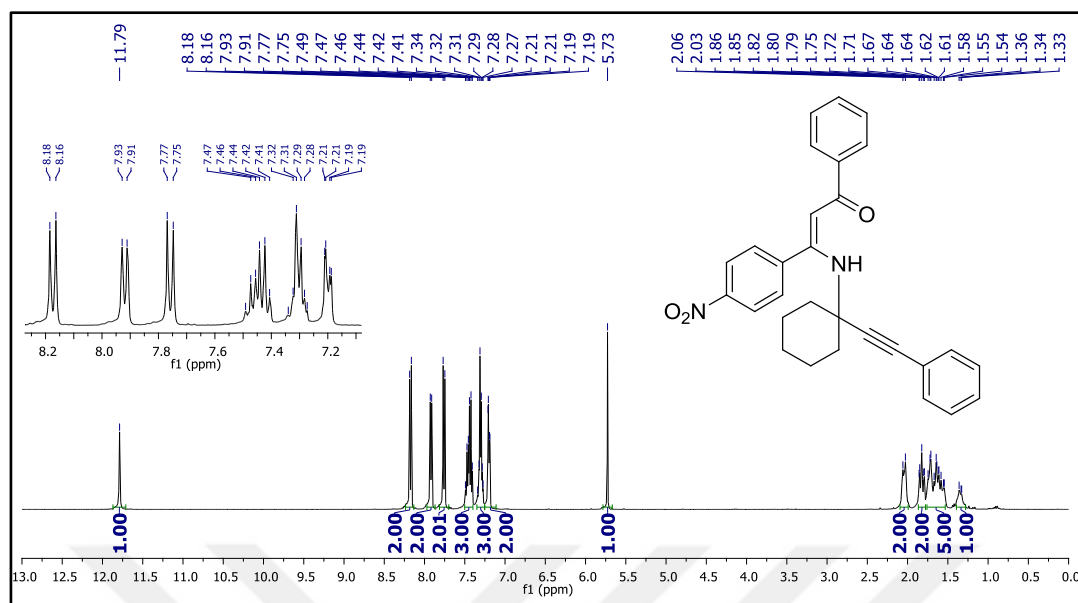


Figure 71. ^1H NMR spectrum of compound **33c**.

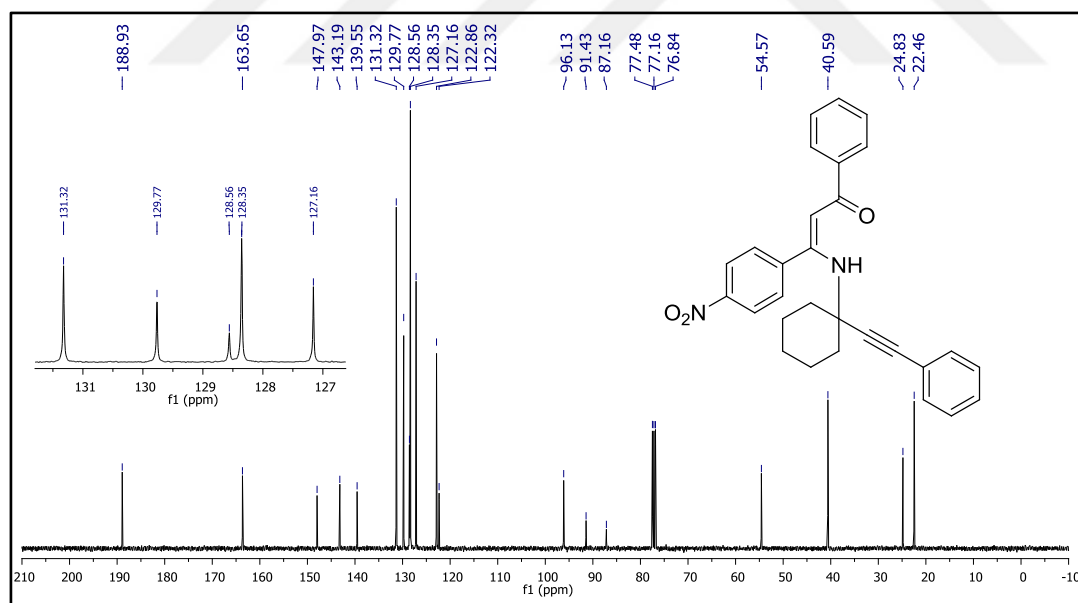


Figure 72. ^{13}C NMR spectrum of compound **33c**.

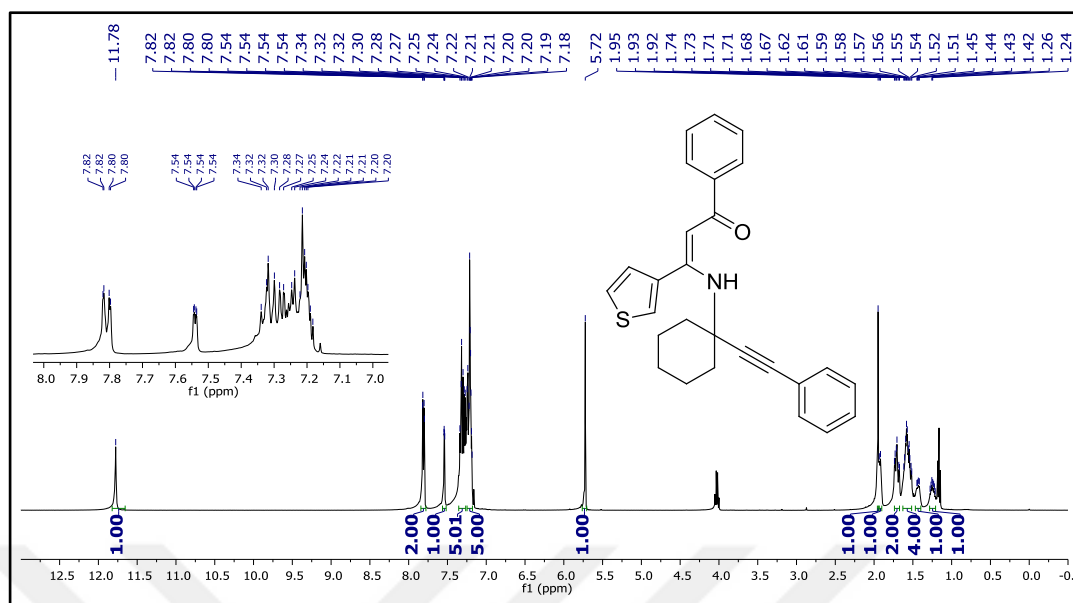


Figure 73. ¹H NMR spectrum of compound 33d.

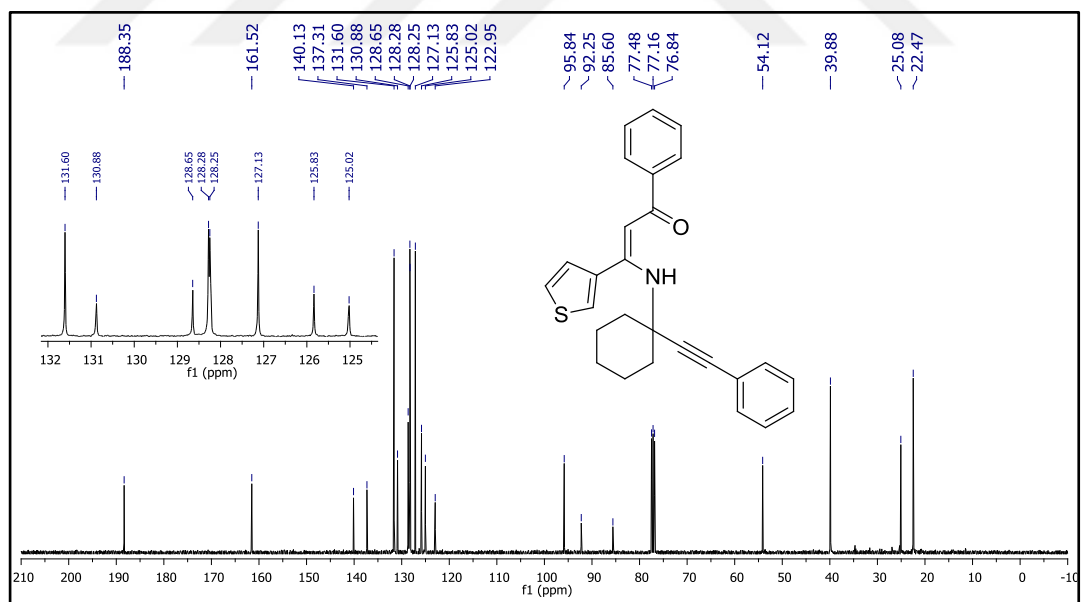


Figure 74. ¹³C NMR spectrum of compound 33d.

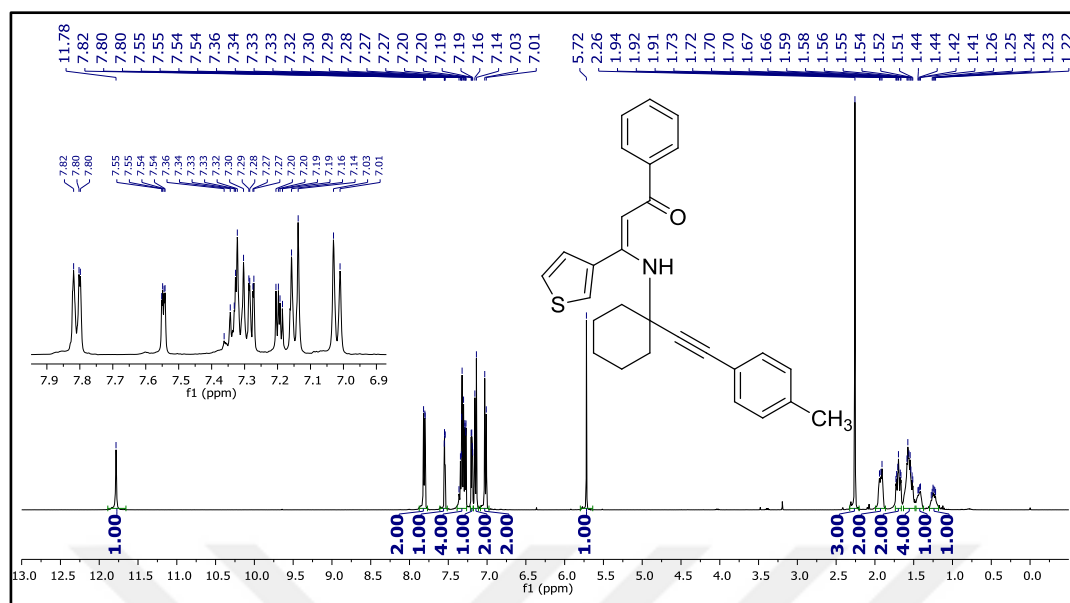


Figure 75. ¹H NMR spectrum of compound 33e.

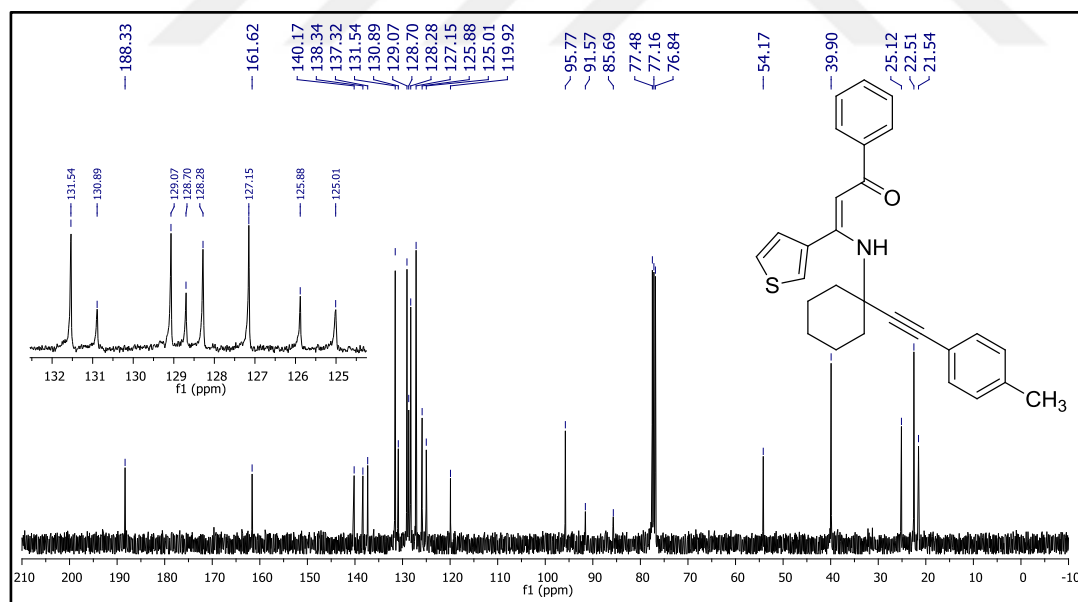


Figure 76. ¹³C NMR spectrum of compound 33e.

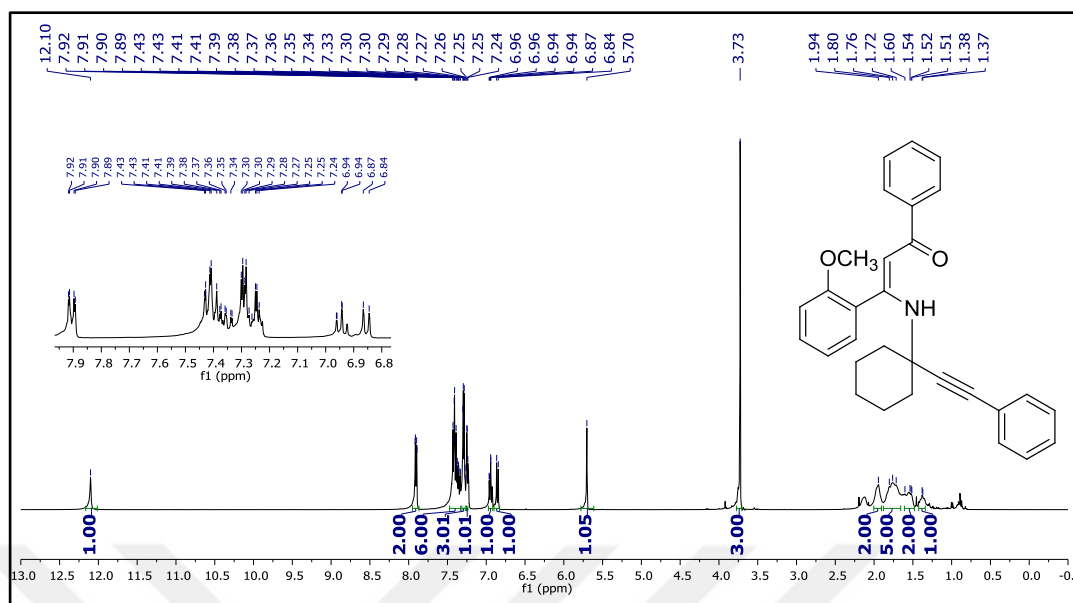


Figure 77. ¹H NMR spectrum of compound 33f.

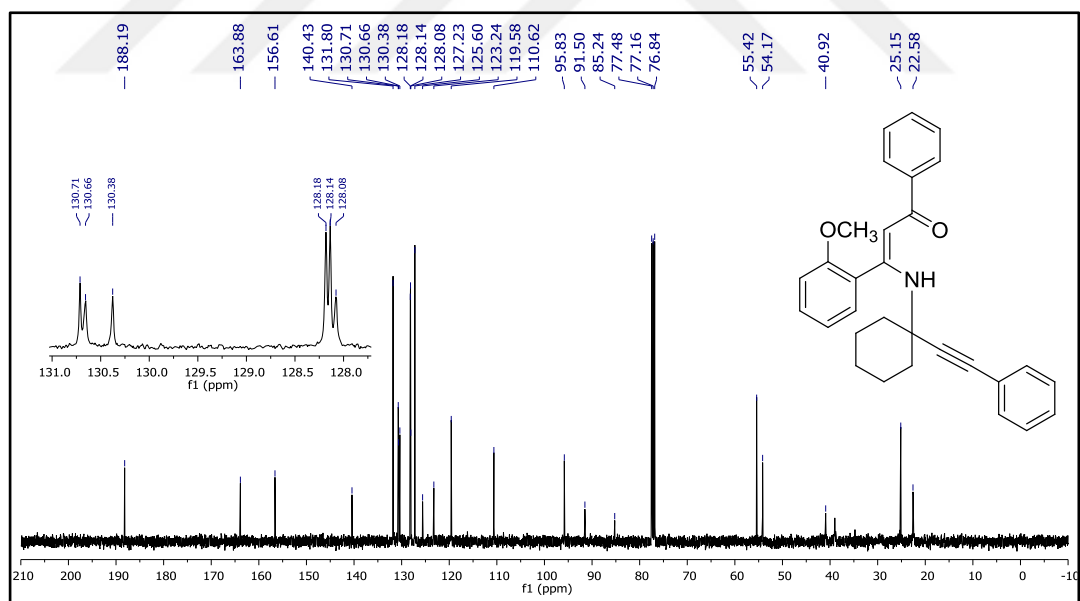


Figure 78. ¹³C NMR spectrum of compound 33f.

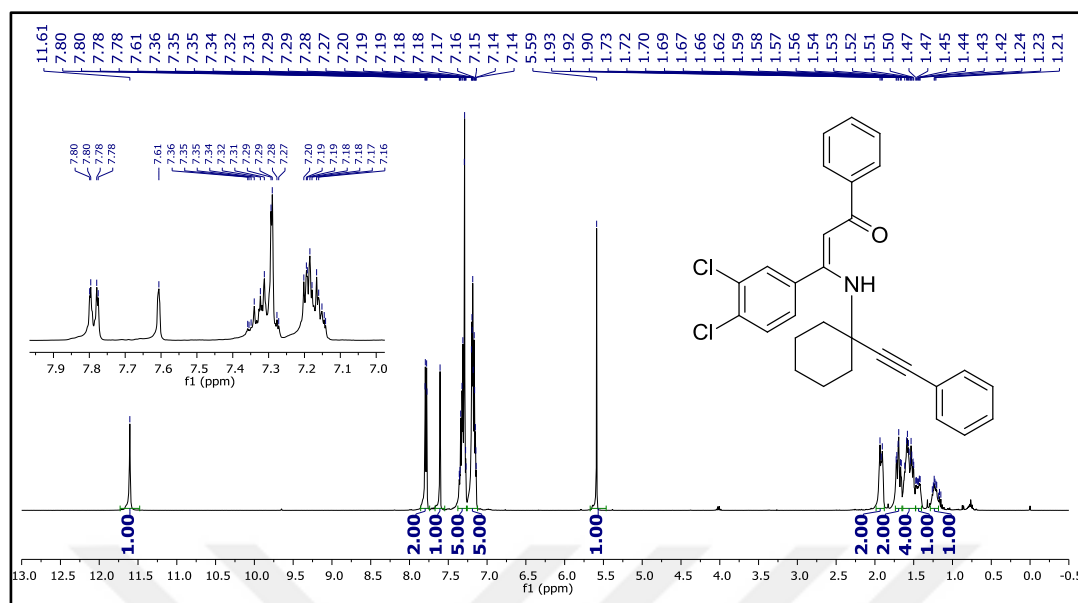


Figure 79. ¹H NMR spectrum of compound 33g.

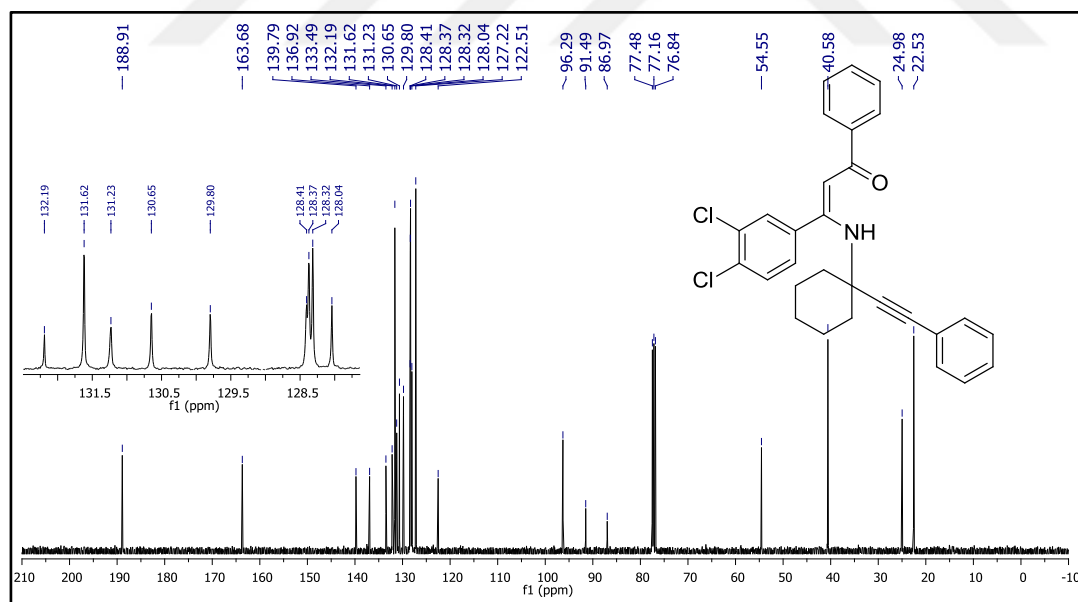


Figure 80. ¹³C NMR spectrum of compound 33g.

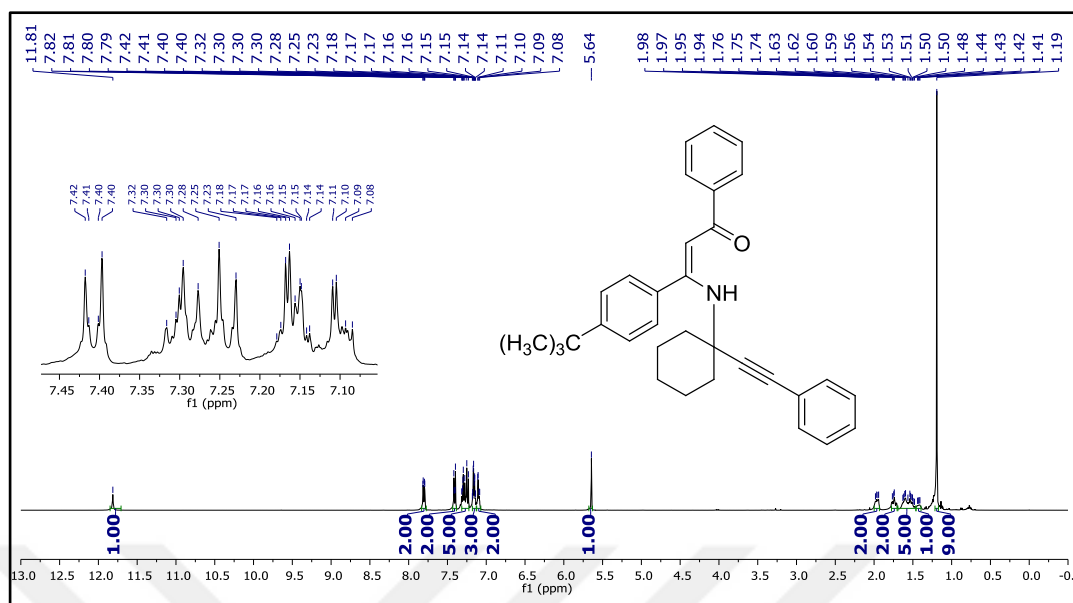


Figure 81. ^1H NMR spectrum of compound 33h.

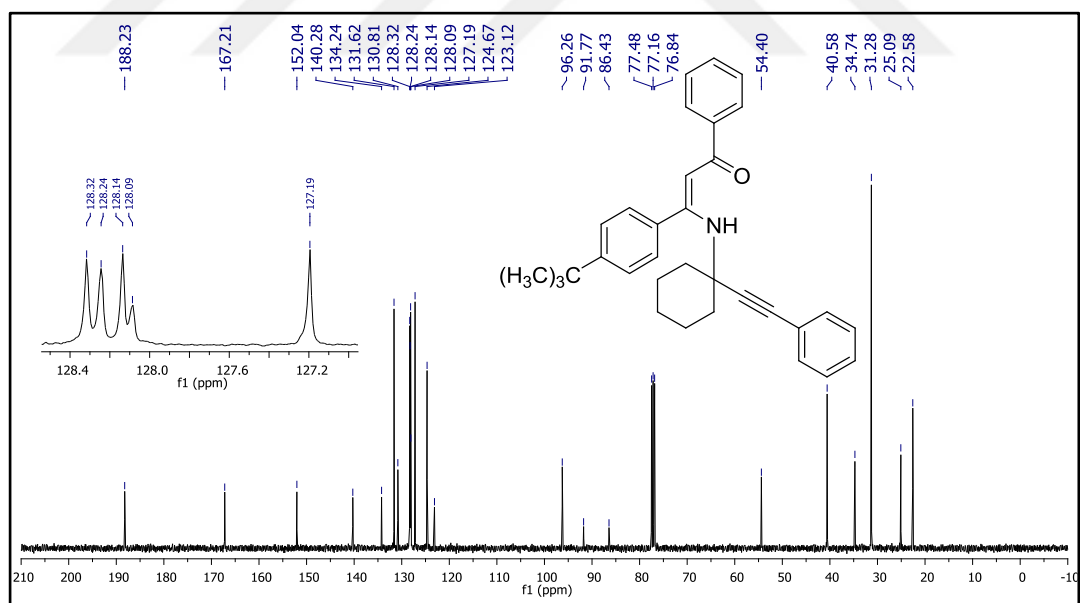


Figure 82. ^{13}C NMR spectrum of compound 33h.

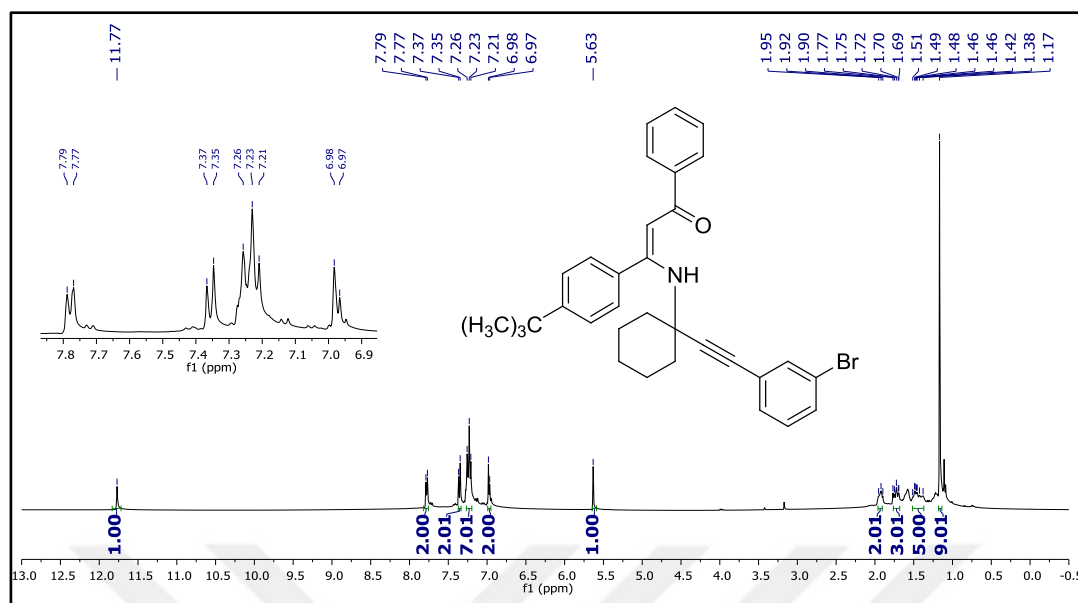


Figure 83. ¹H NMR spectrum of compound 33i.

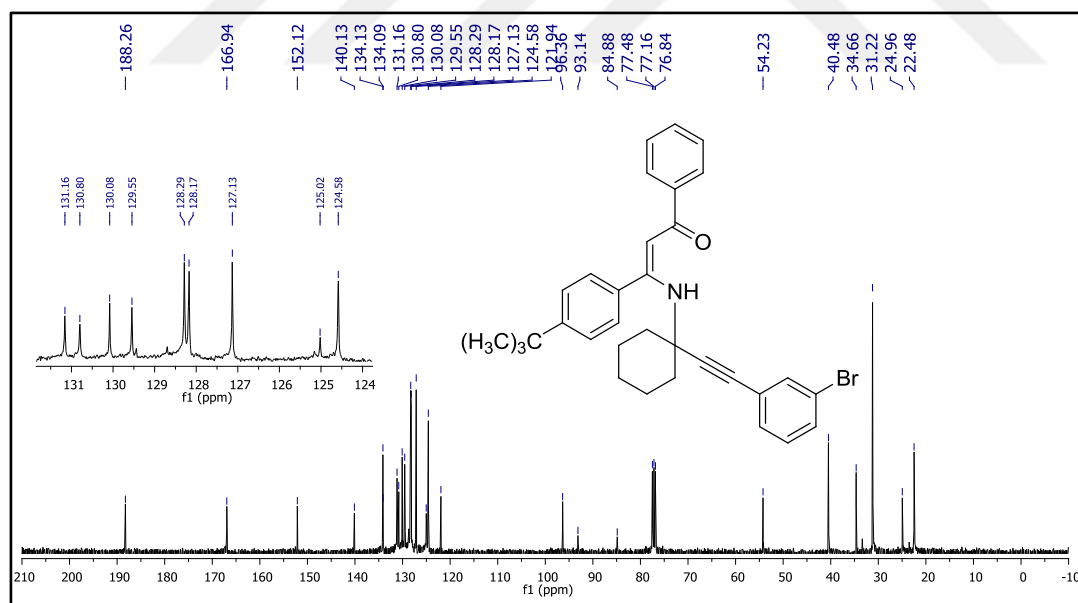


Figure 84. ¹³C NMR spectrum of compound 33i.

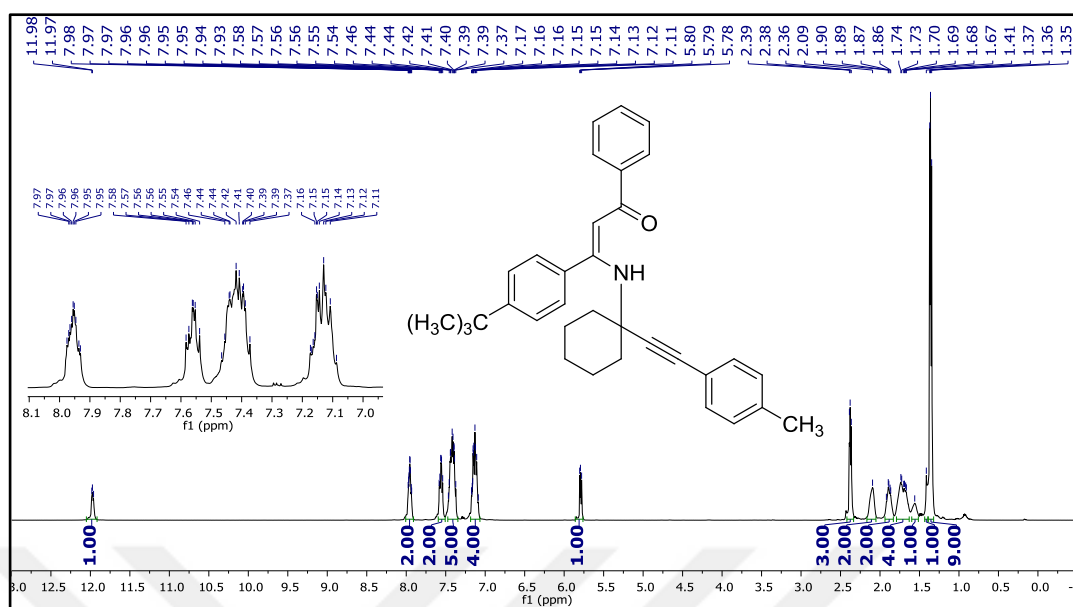


Figure 85. ¹H NMR spectrum of compound 33j.

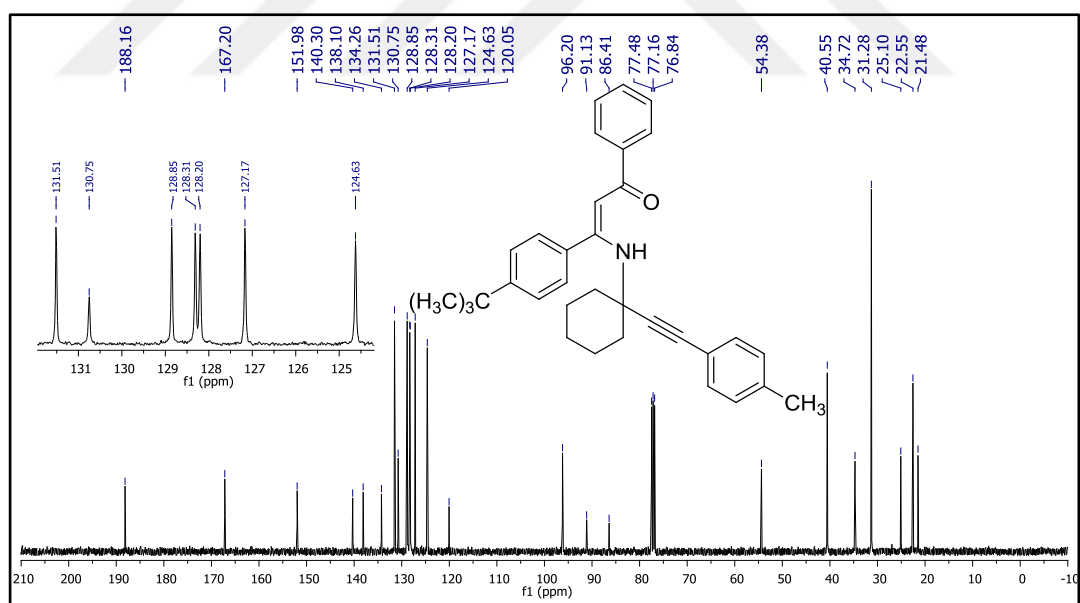


Figure 86. ¹³C NMR spectrum of compound 33j.

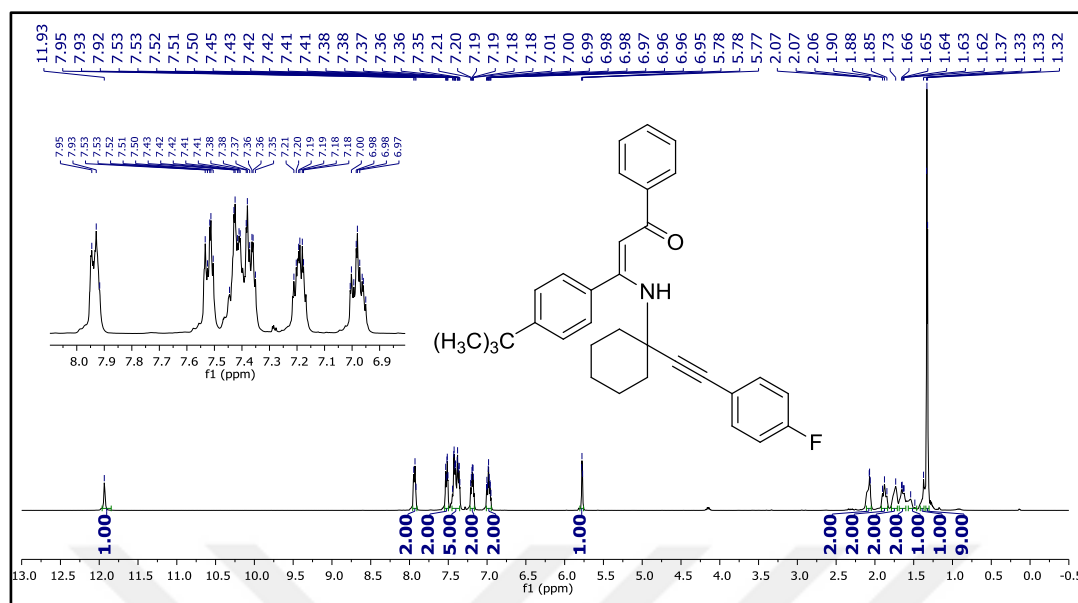


Figure 87. ¹H NMR spectrum of compound 33k.

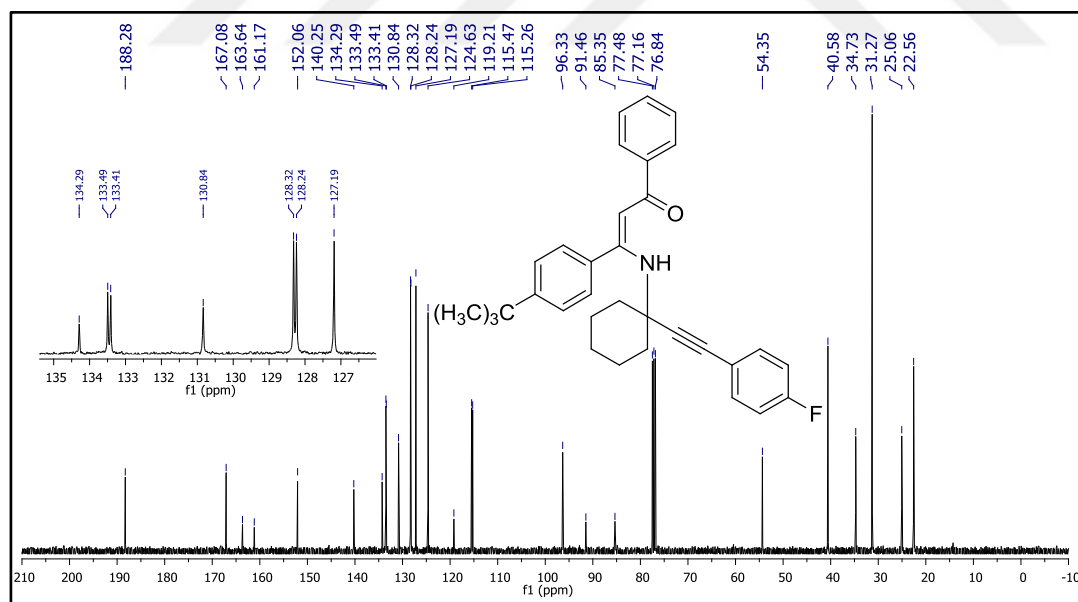


Figure 88. ¹³C NMR spectrum of compound 33k.

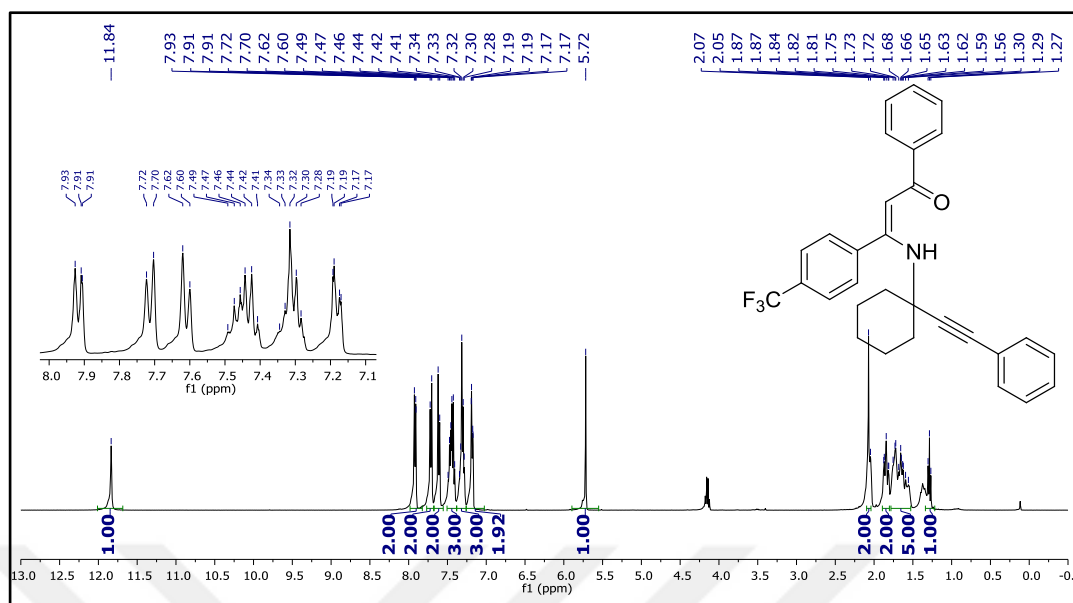


Figure 89. ^1H NMR spectrum of compound **33l**.

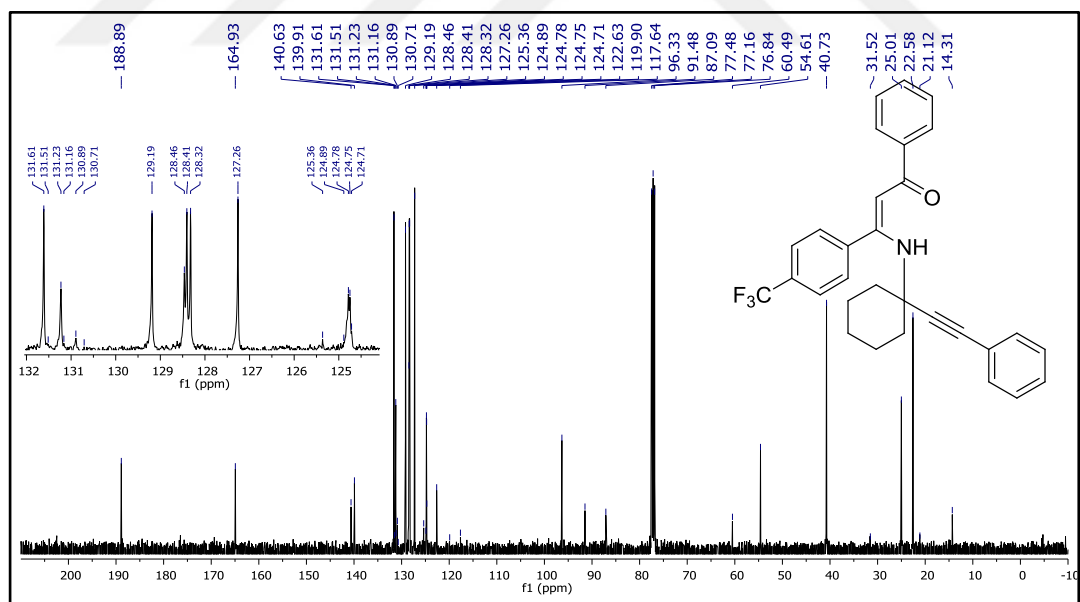
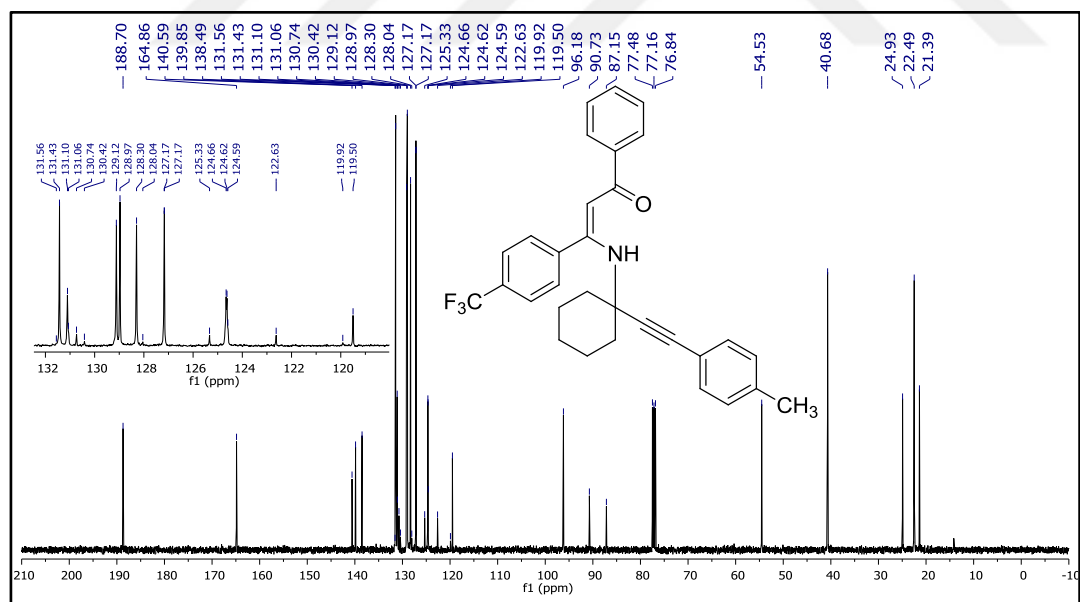
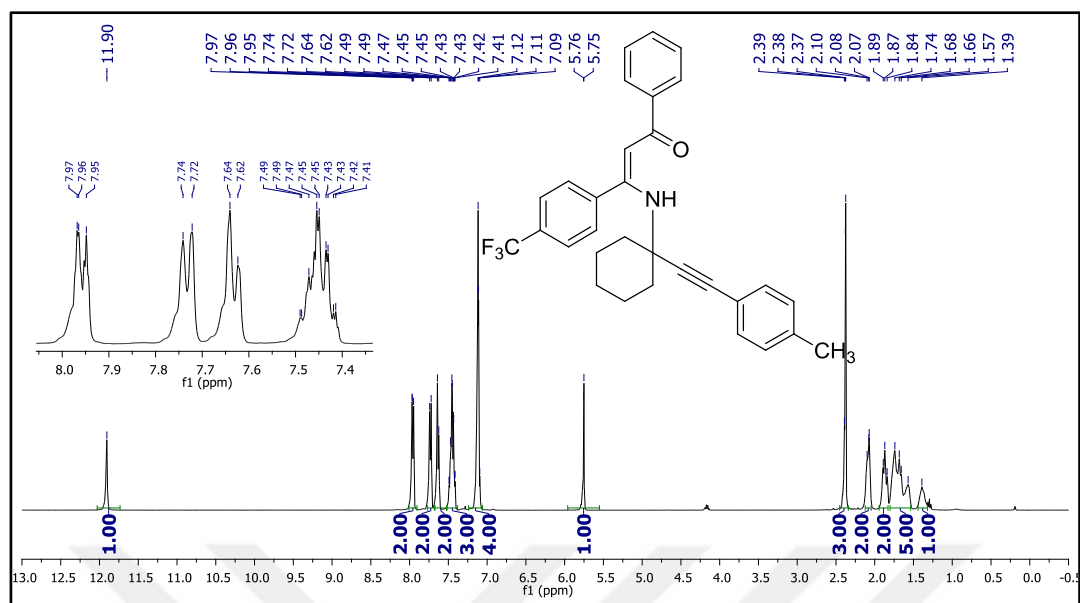


Figure 90. ^{13}C NMR spectrum of compound **33l**.



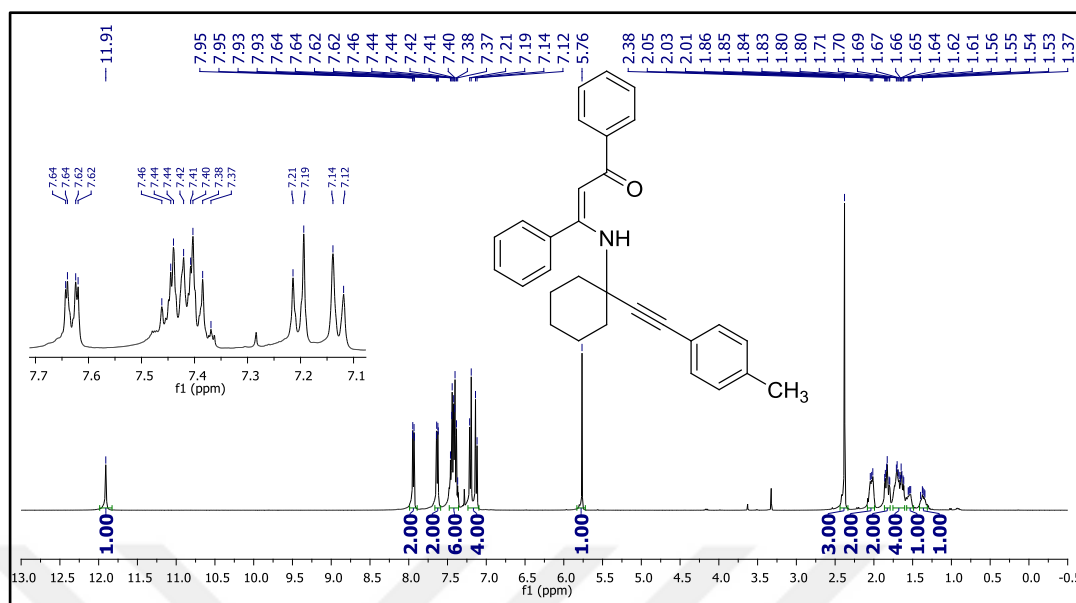


Figure 93. ¹H NMR spectrum of compound 33n.

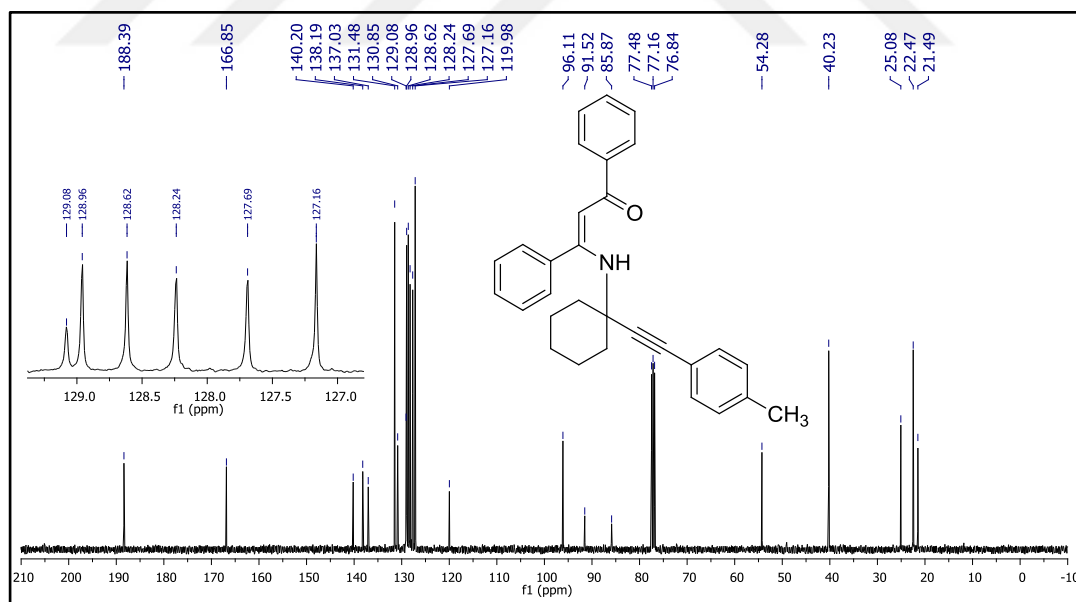


Figure 94. ¹³C NMR spectrum of compound 33n.

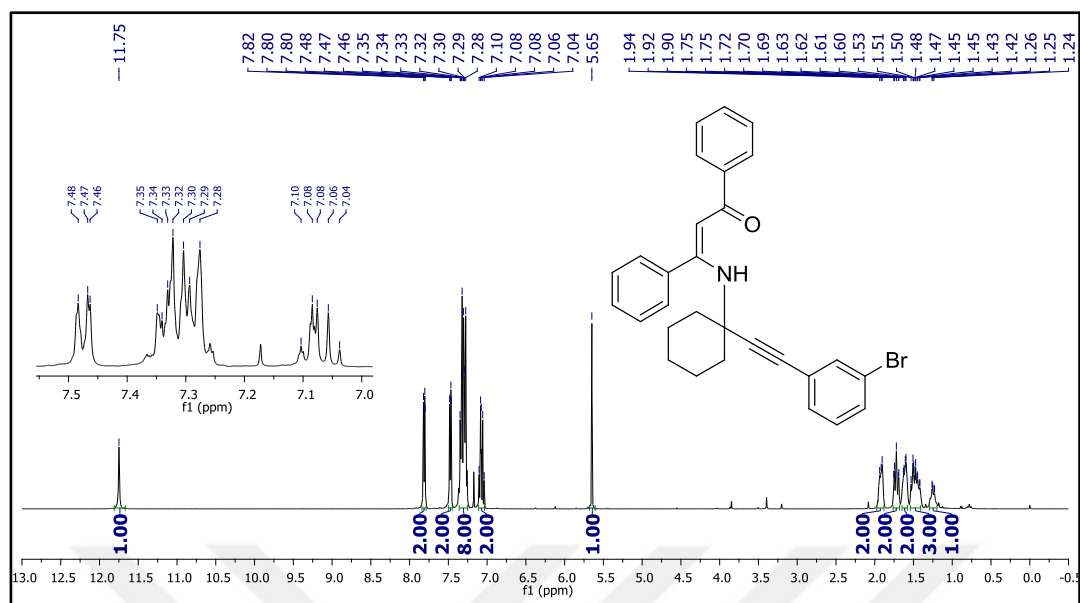


Figure 95. ¹H NMR spectrum of compound 33o.

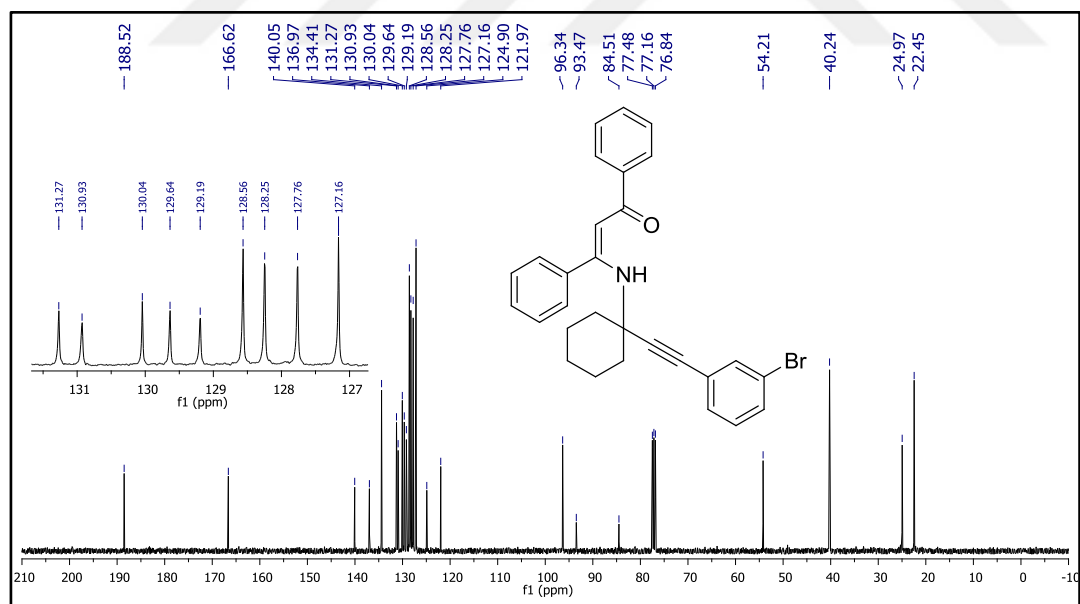


Figure 96. ¹³C NMR spectrum of compound 33o.

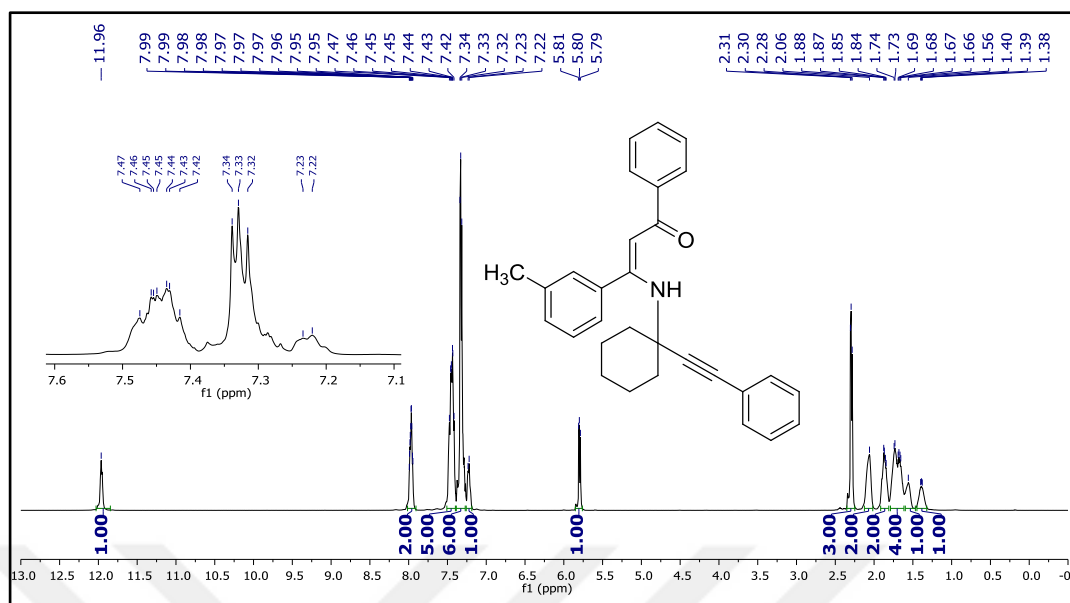


Figure 97. ¹H NMR spectrum of compound 33p.

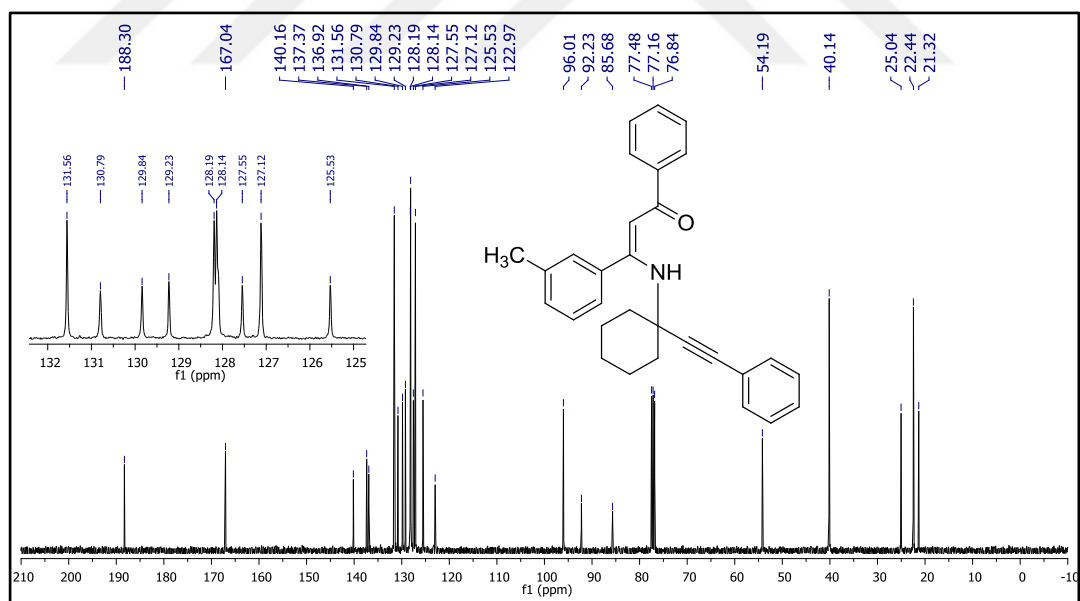
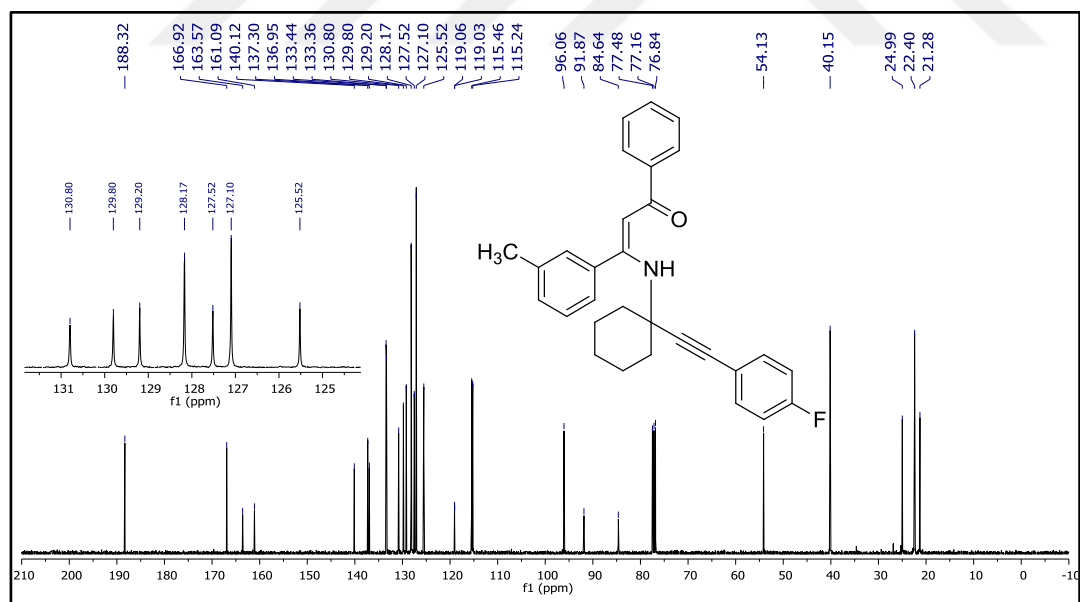
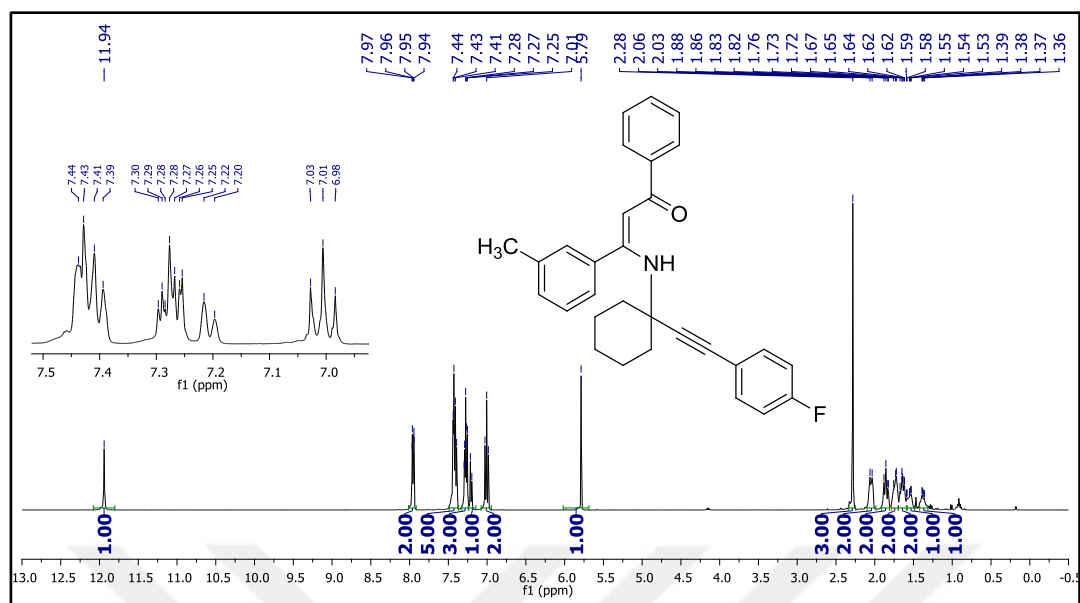


Figure 98. ¹³C NMR spectrum of compound 33p.



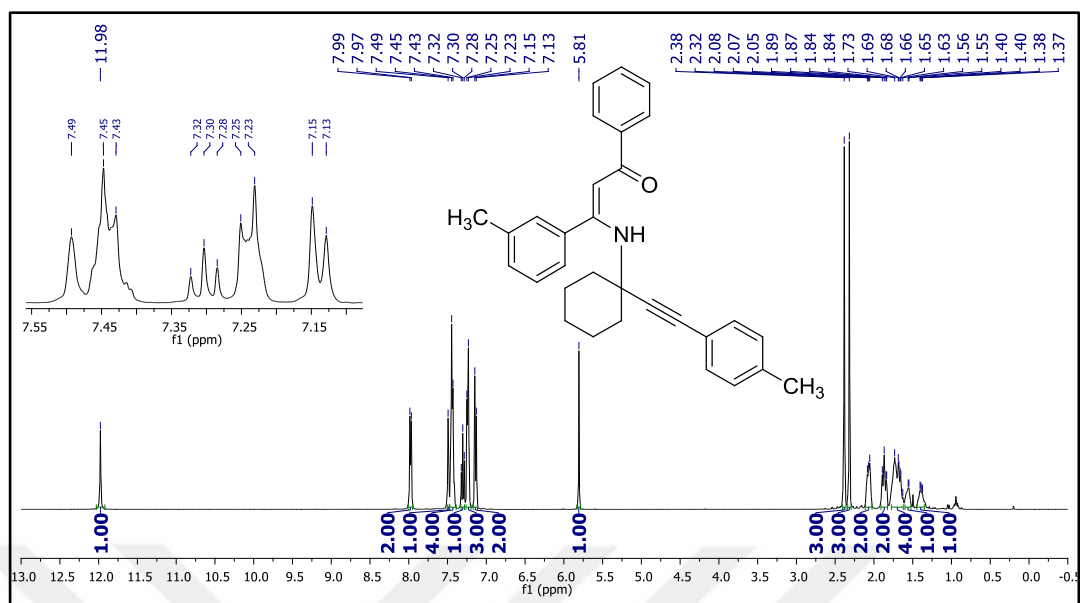


Figure 101. ^1H NMR spectrum of compound 33r.

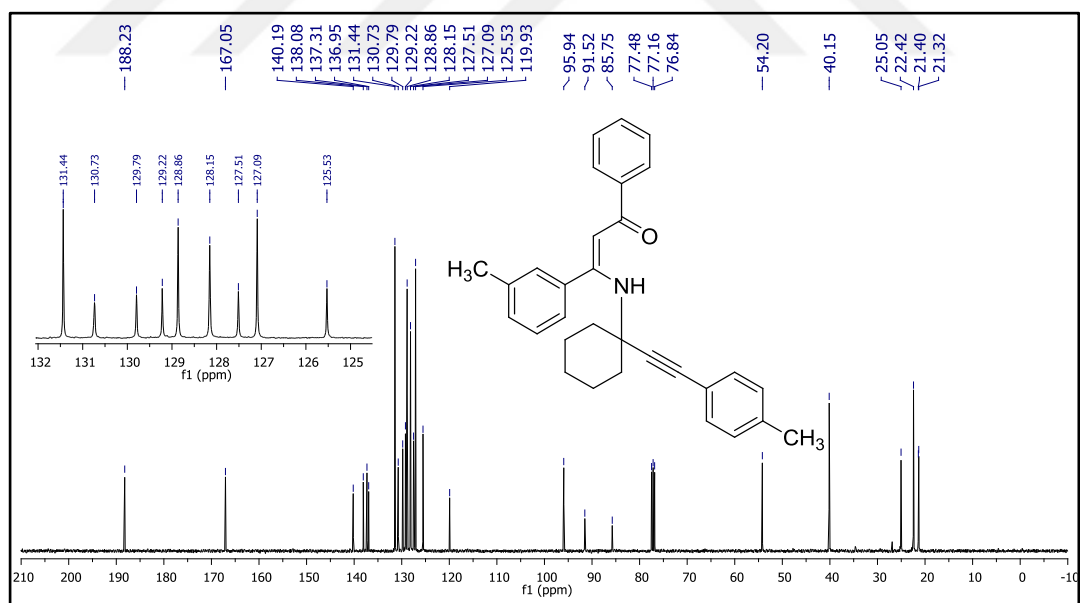


Figure 102. ^{13}C NMR spectrum of compound 33r.

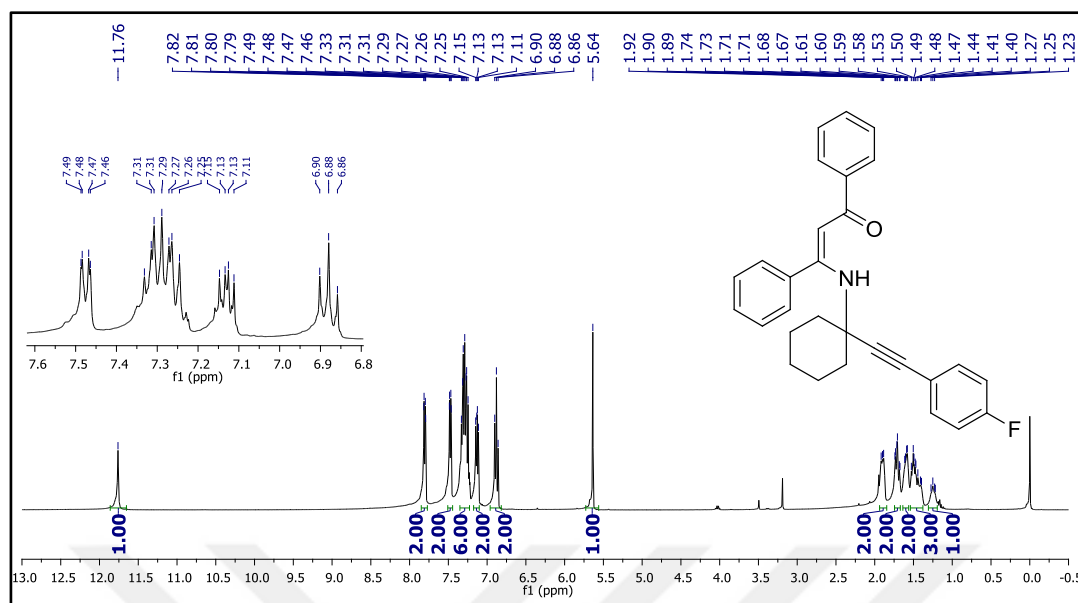


Figure 103. ¹H NMR spectrum of compound 33s.

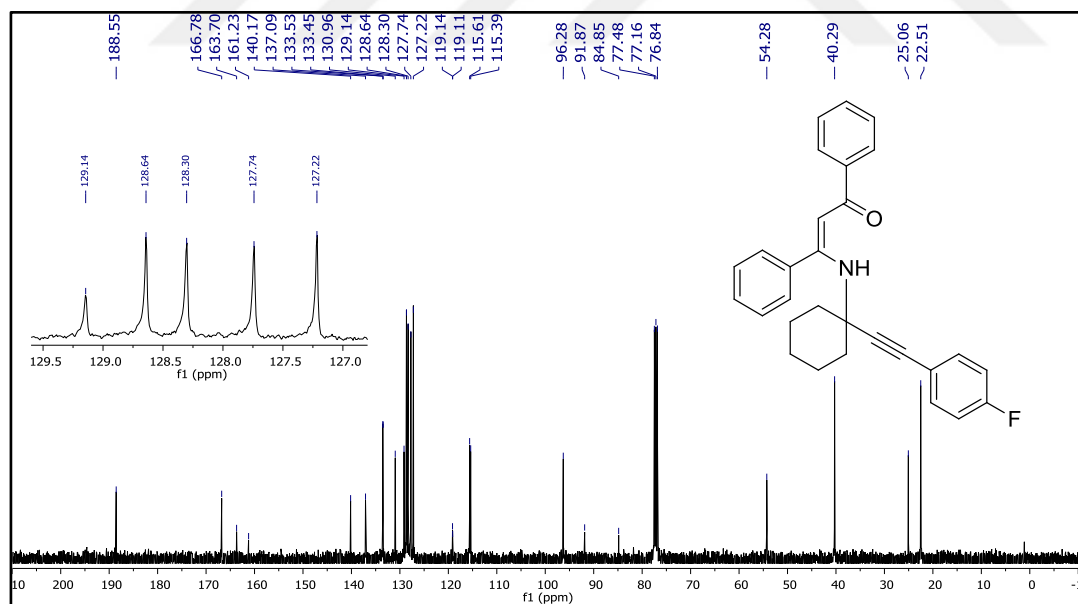


Figure 104. ¹³C NMR spectrum of compound 33s.

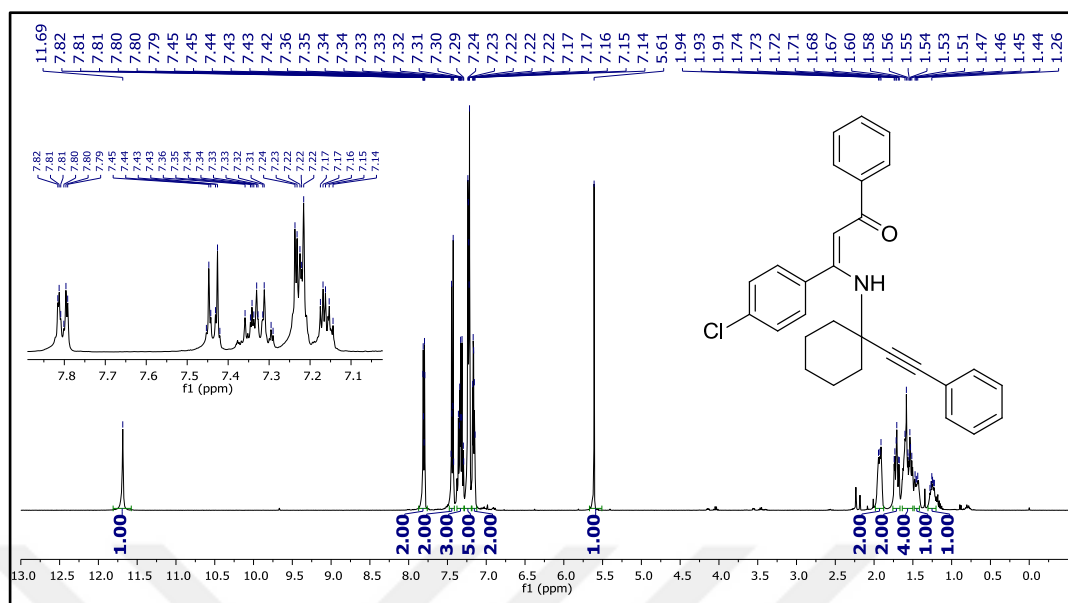


Figure 105. ^1H NMR spectrum of compound **33t**.

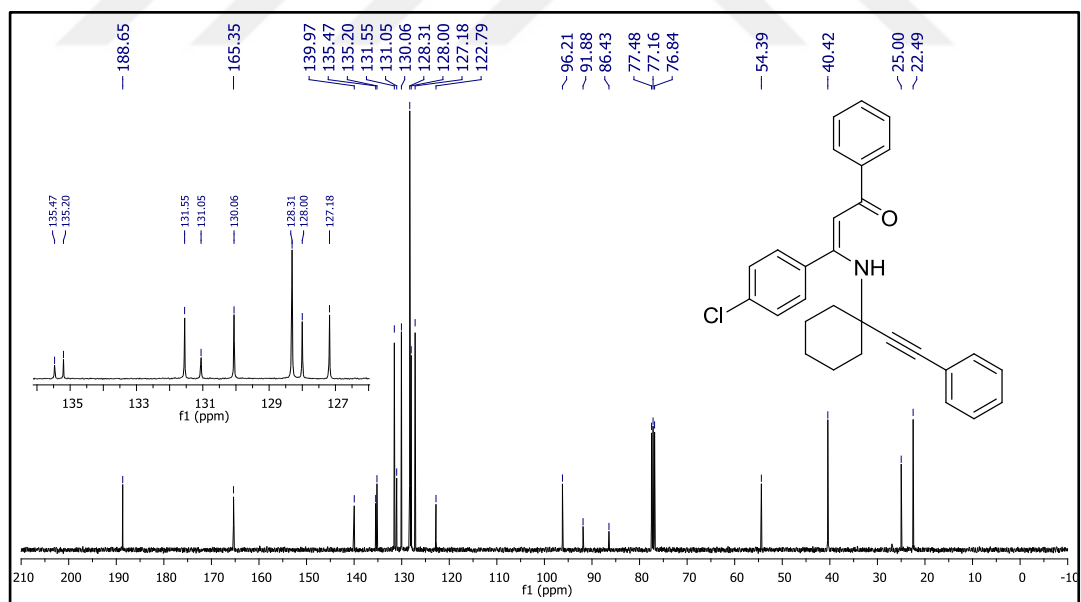


Figure 106. ^{13}C NMR spectrum of compound **33t**.

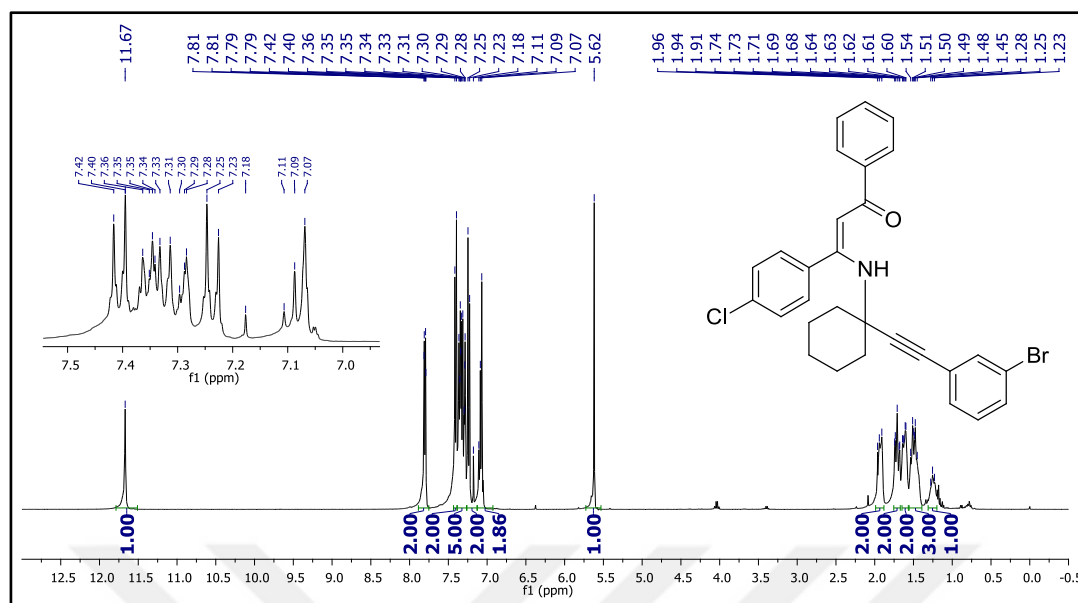


Figure 107. ^1H NMR spectrum of compound **33u**.

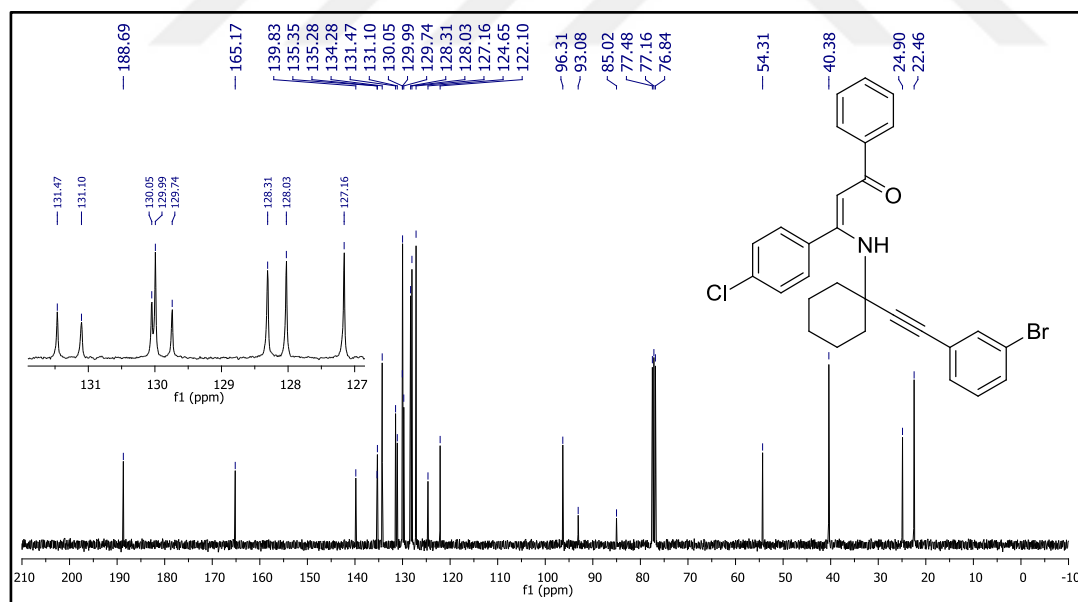


Figure 108. ^{13}C NMR spectrum of compound **33u**.

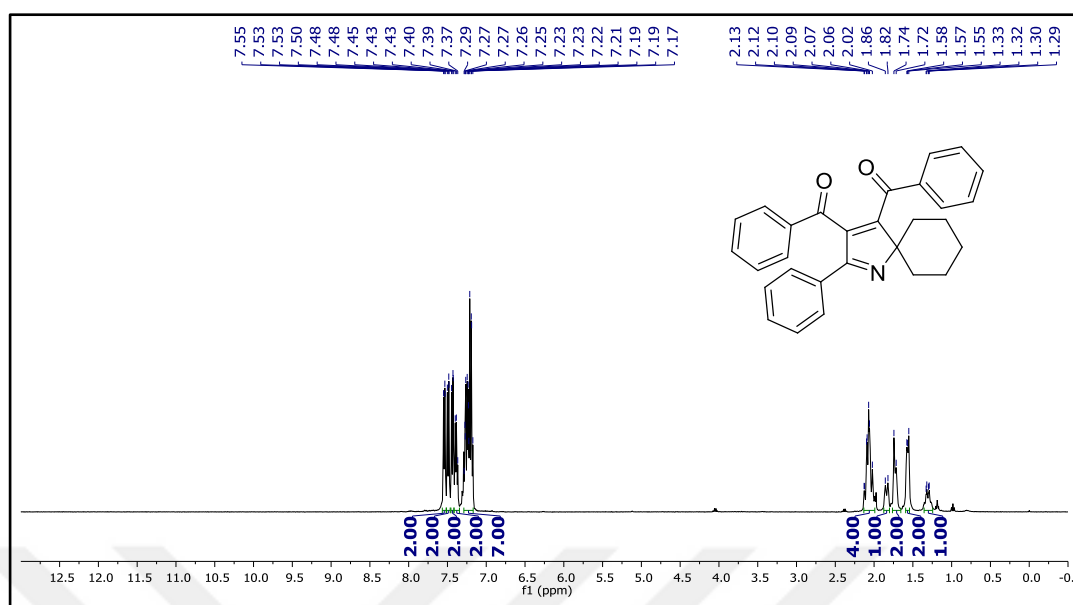


Figure 109. ¹H NMR spectrum of compound 34a.

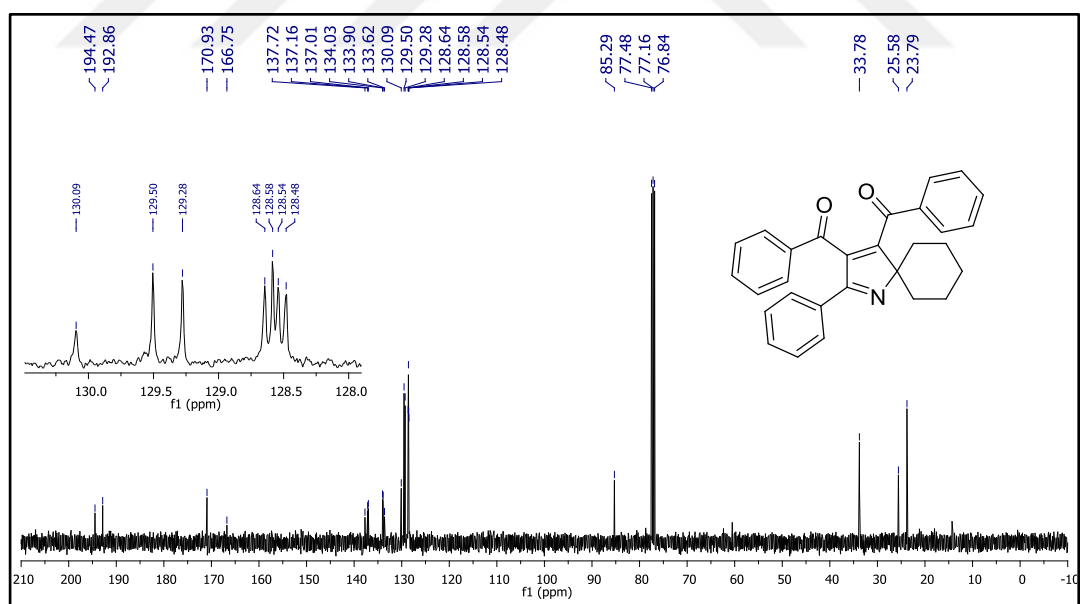


Figure 110. ¹³C NMR spectrum of compound 34a.

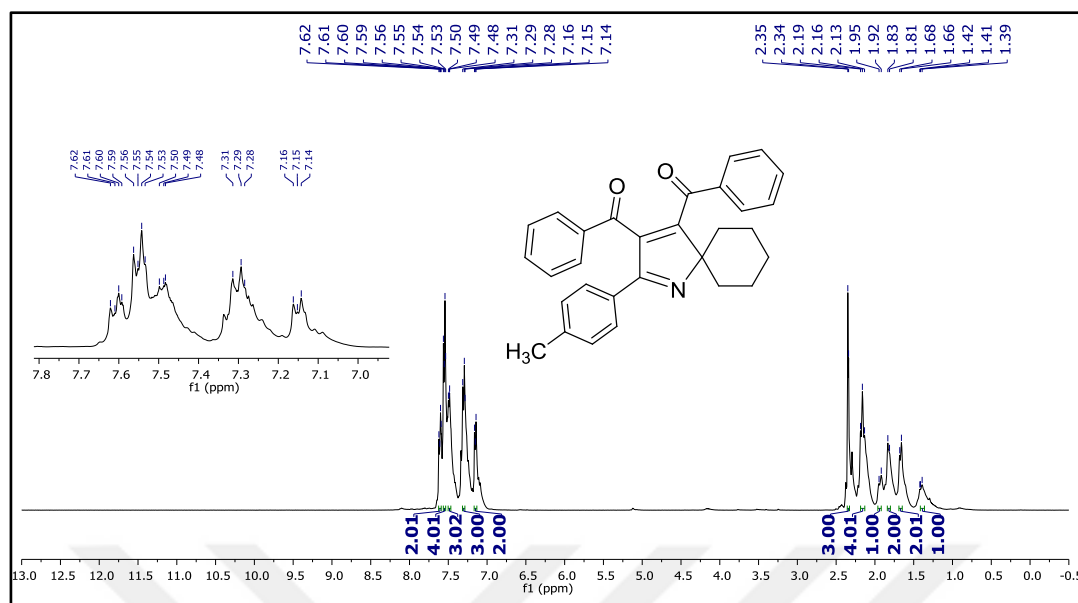


Figure 111. ¹H NMR spectrum of compound **34b**.

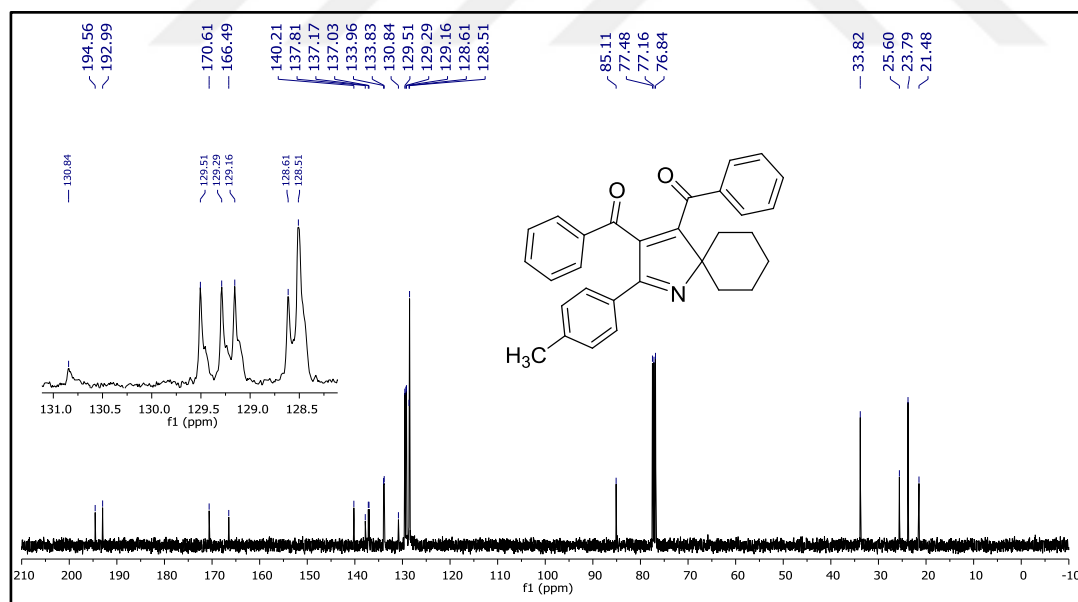


Figure 112. ¹³C NMR spectrum of compound **34b**.

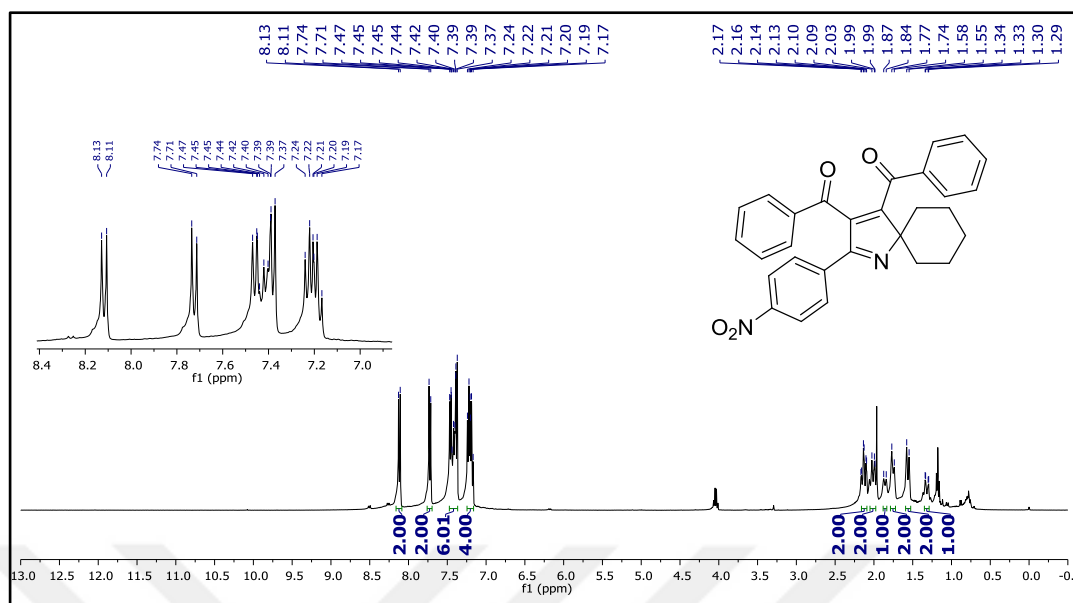


Figure 113. ¹H NMR spectrum of compound 34c.

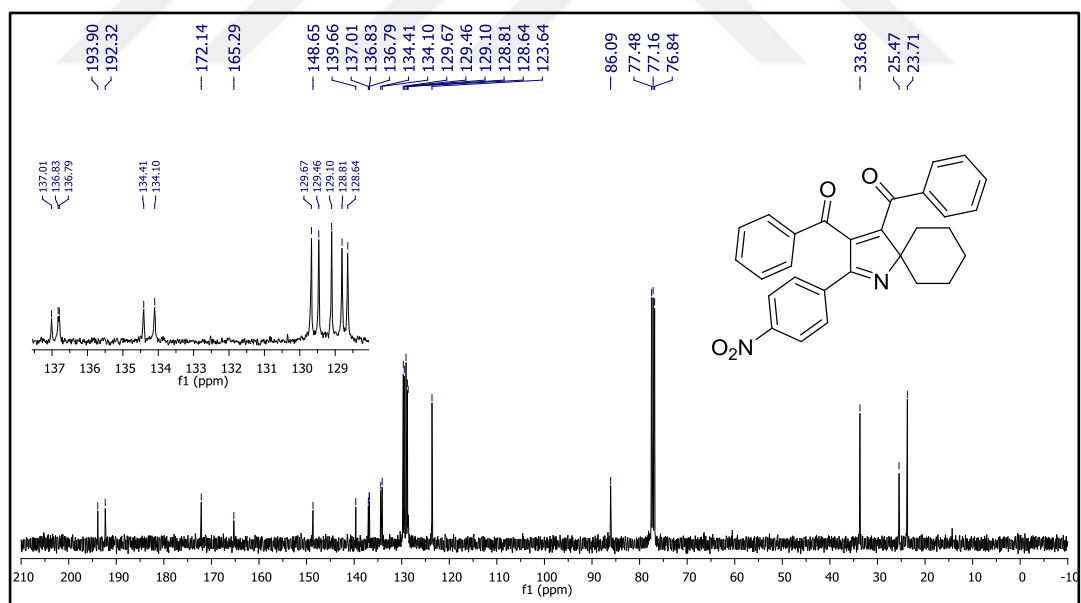


Figure 114. ¹³C NMR spectrum of compound 34c.

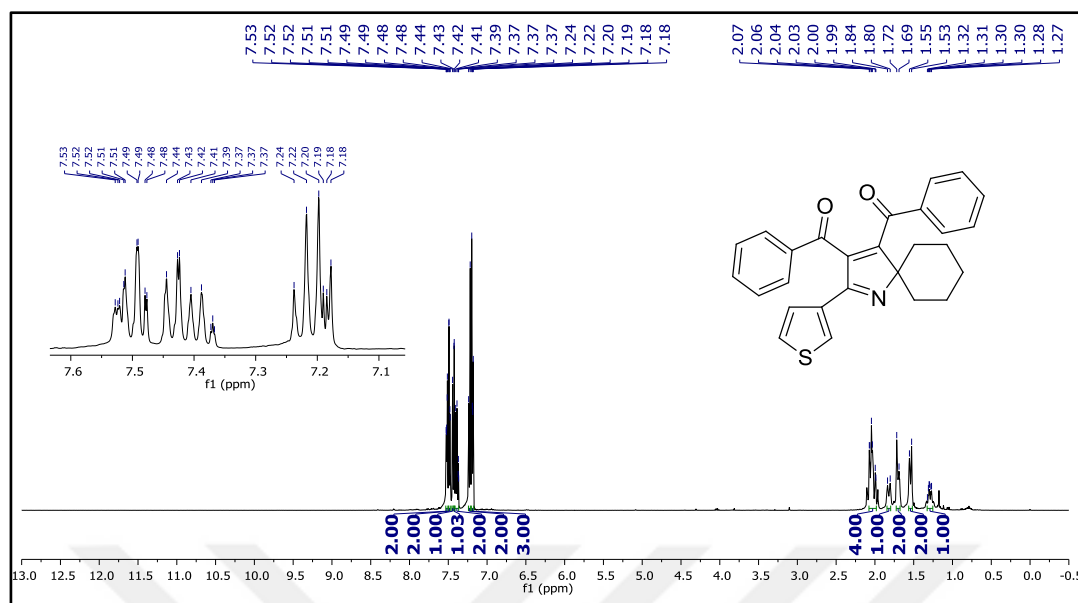


Figure 115. ¹H NMR spectrum of compound **34d**.

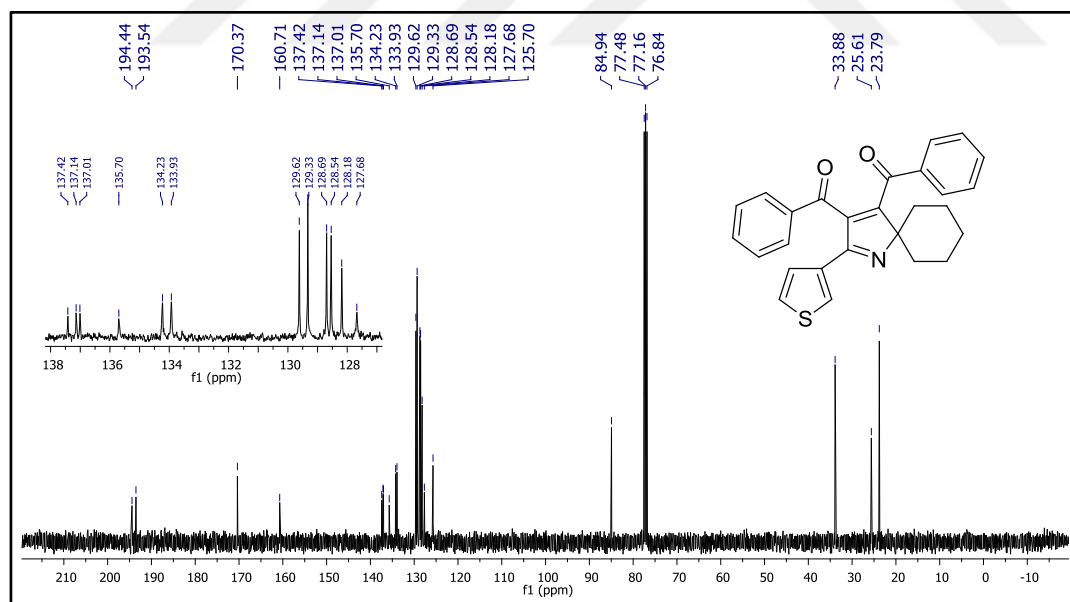


Figure 116. ¹³C NMR spectrum of compound **34d**.

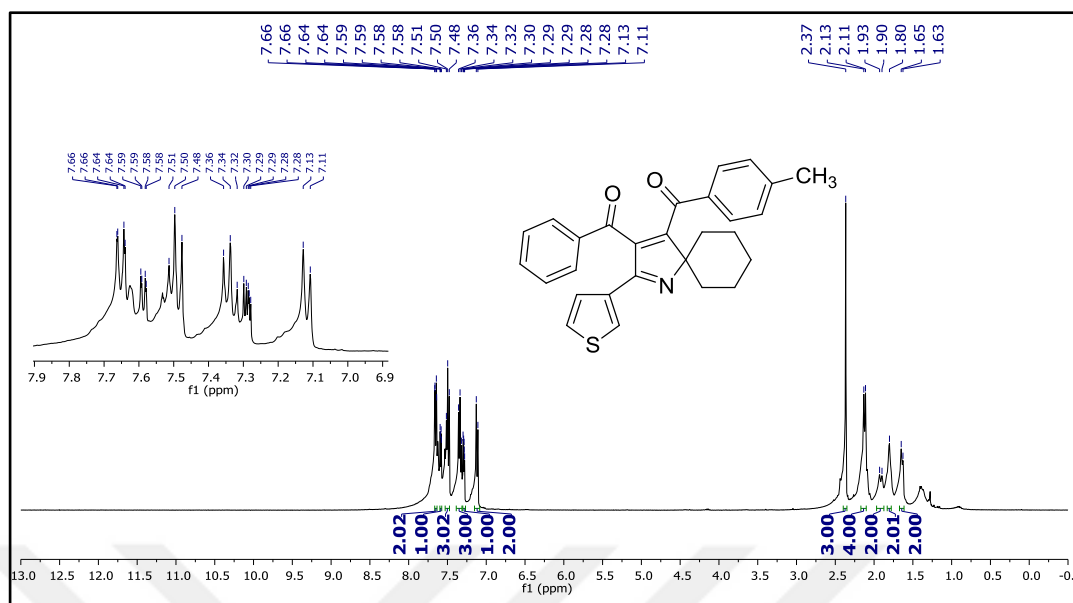


Figure 117. ¹H NMR spectrum of compound 34e.

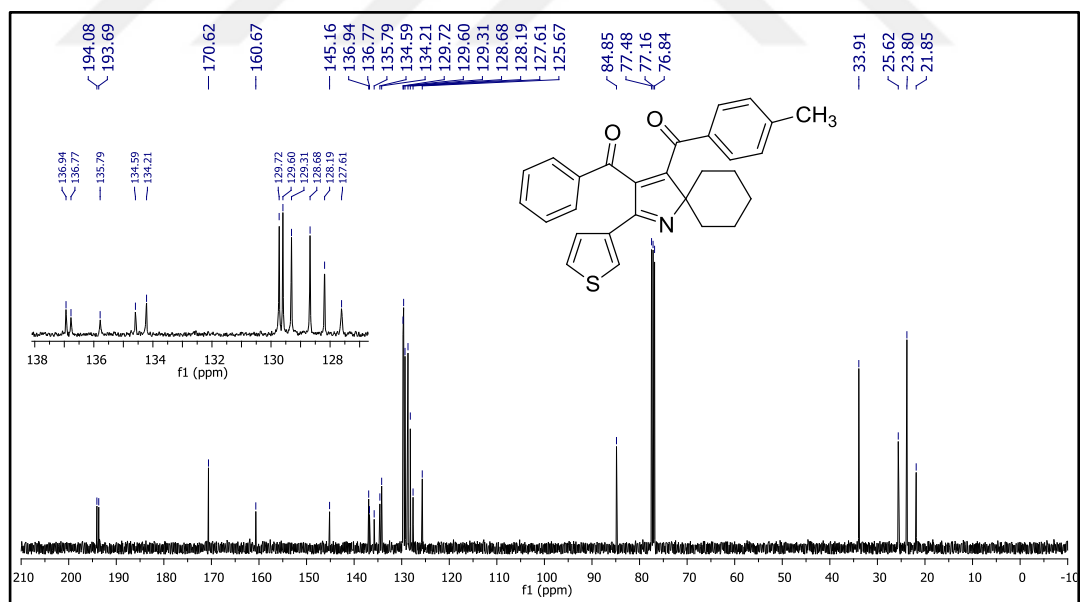


Figure 118. ¹³C NMR spectrum of compound 34e.

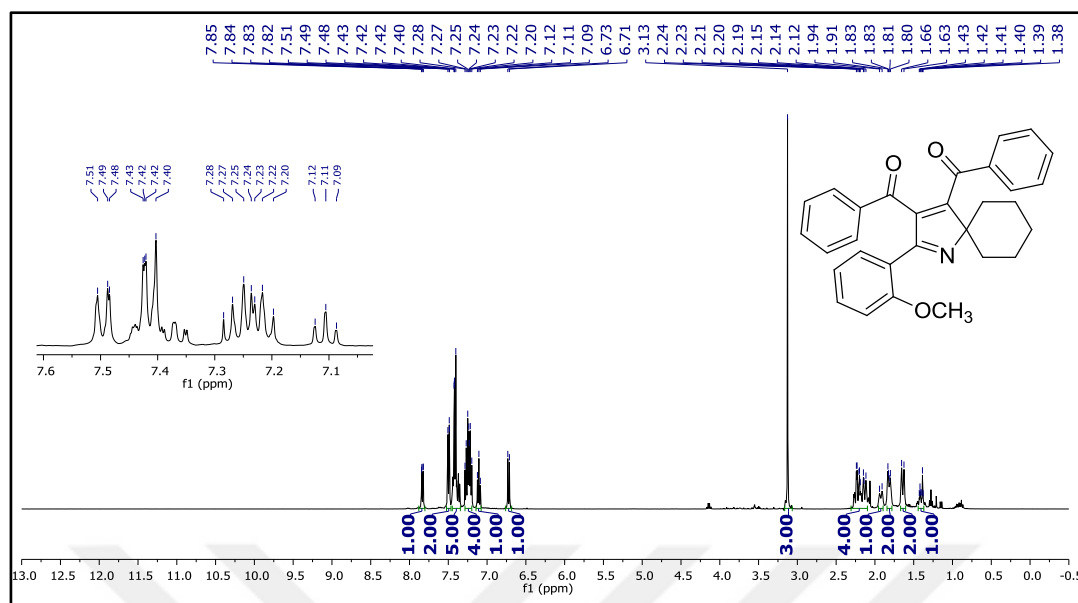


Figure 119. ¹H NMR spectrum of compound **34f**.

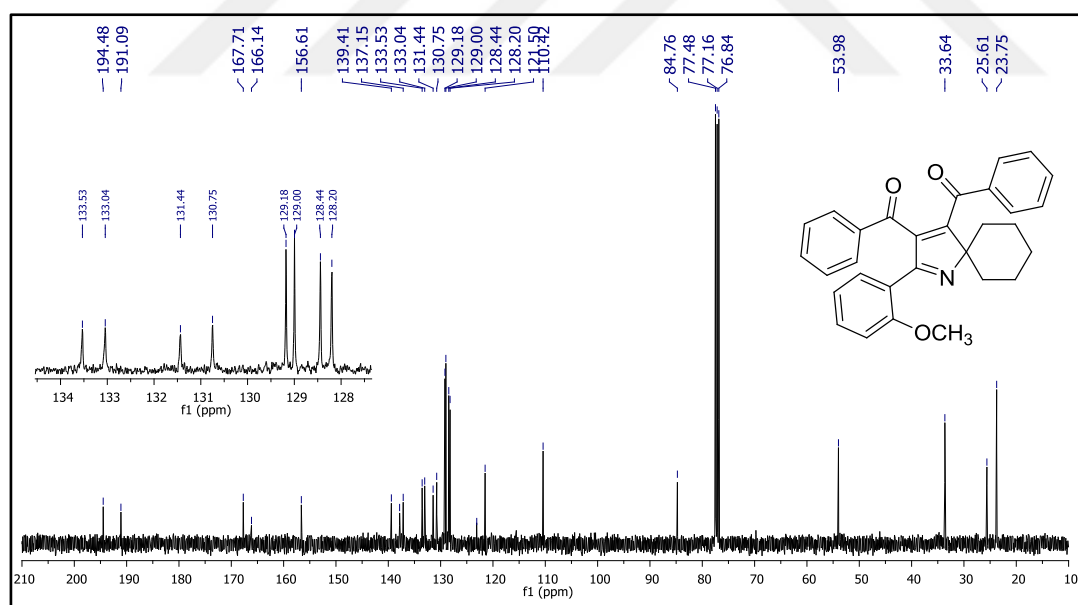


Figure 120. ¹³C NMR spectrum of compound **34f**.

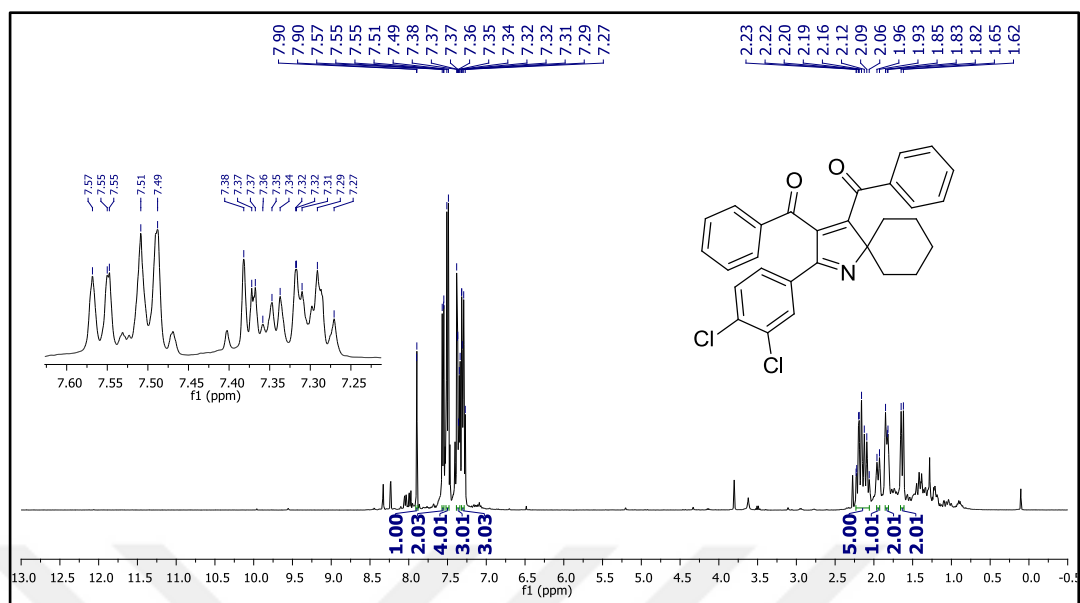


Figure 121. ^1H NMR spectrum of compound **34g**.

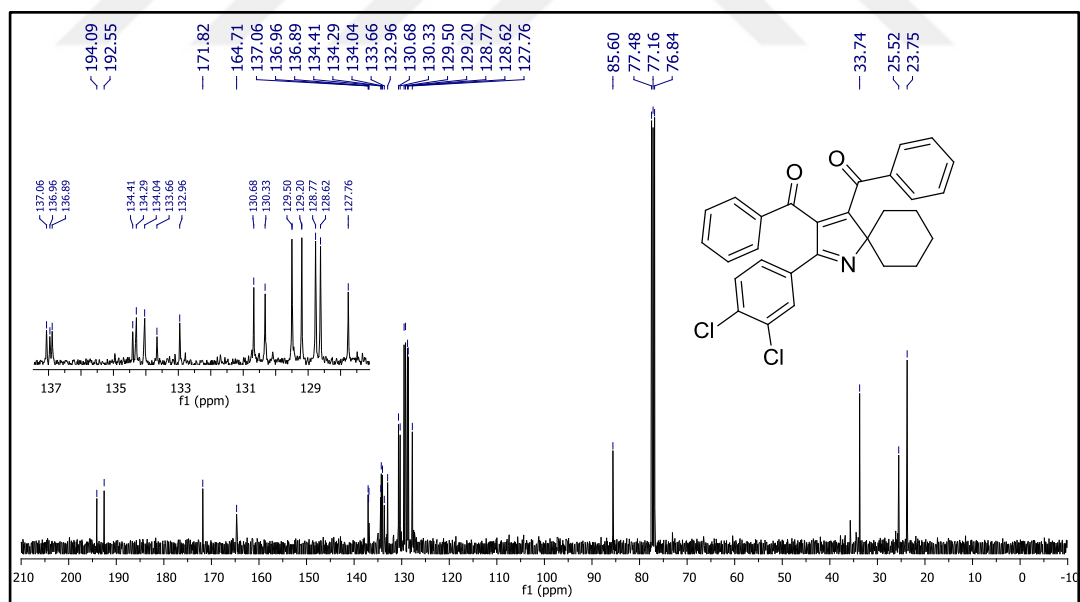


Figure 122. ^{13}C NMR spectrum of compound **34g**.

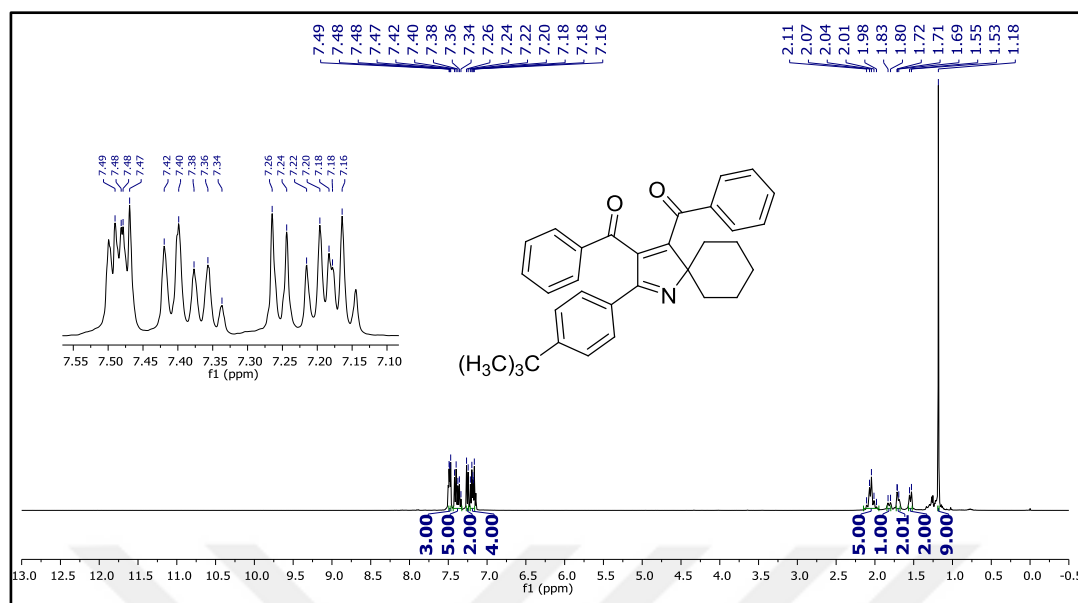


Figure 123. ¹H NMR spectrum of compound **34h**.

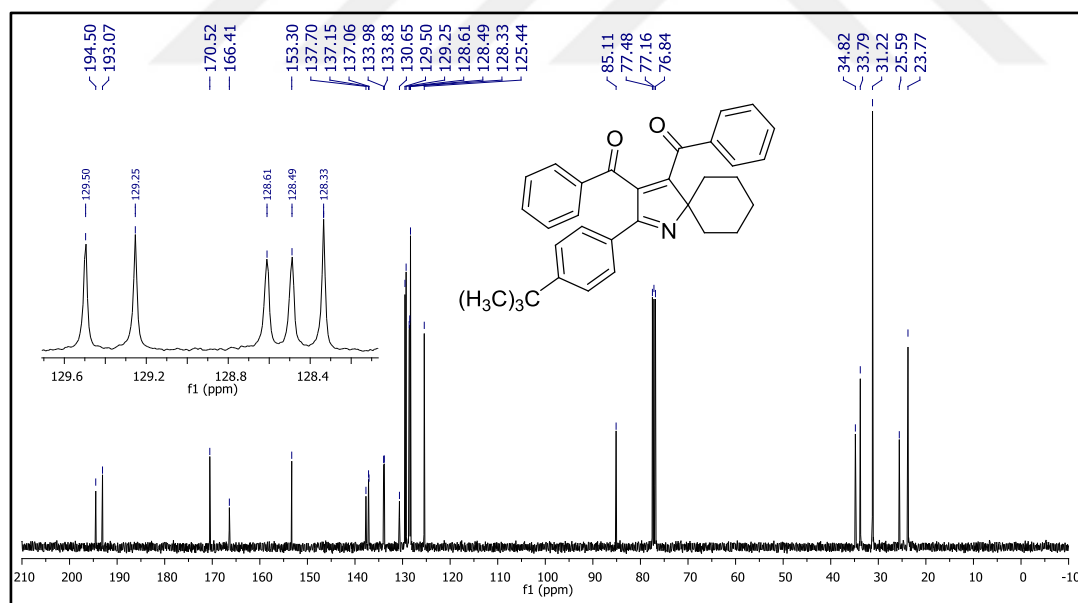


Figure 124. ¹³C NMR spectrum of compound **34h**.

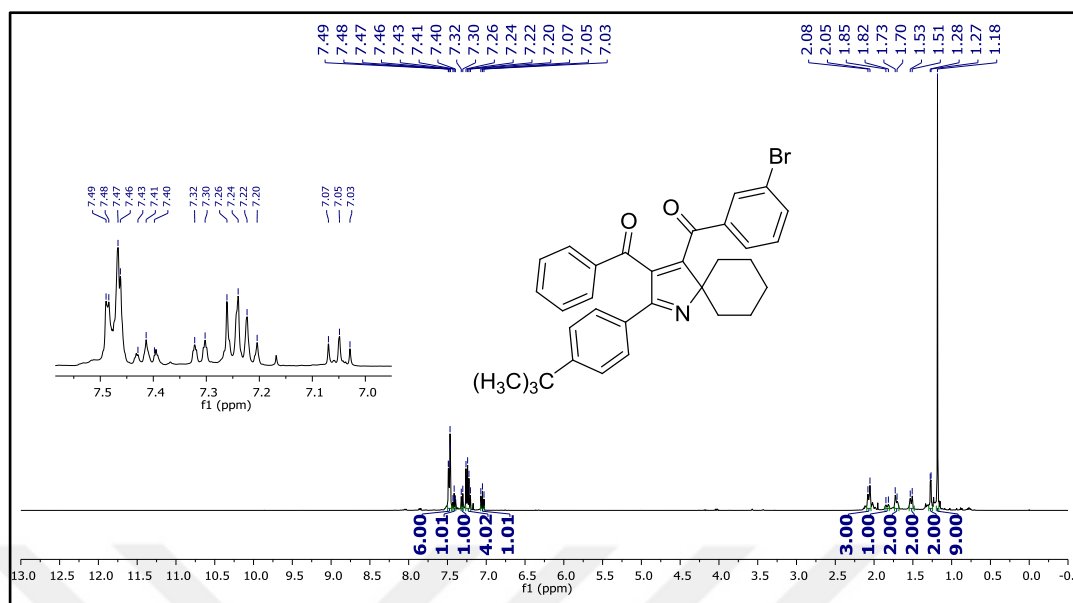


Figure 125. ¹H NMR spectrum of compound **34i**.

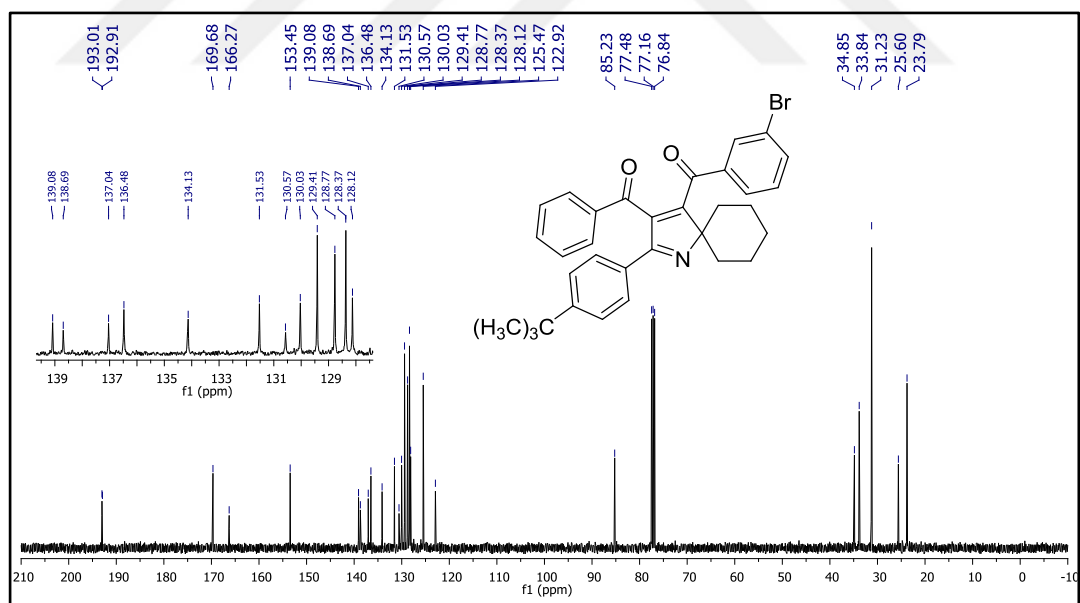


Figure 126. ¹³C NMR spectrum of compound **34i**.

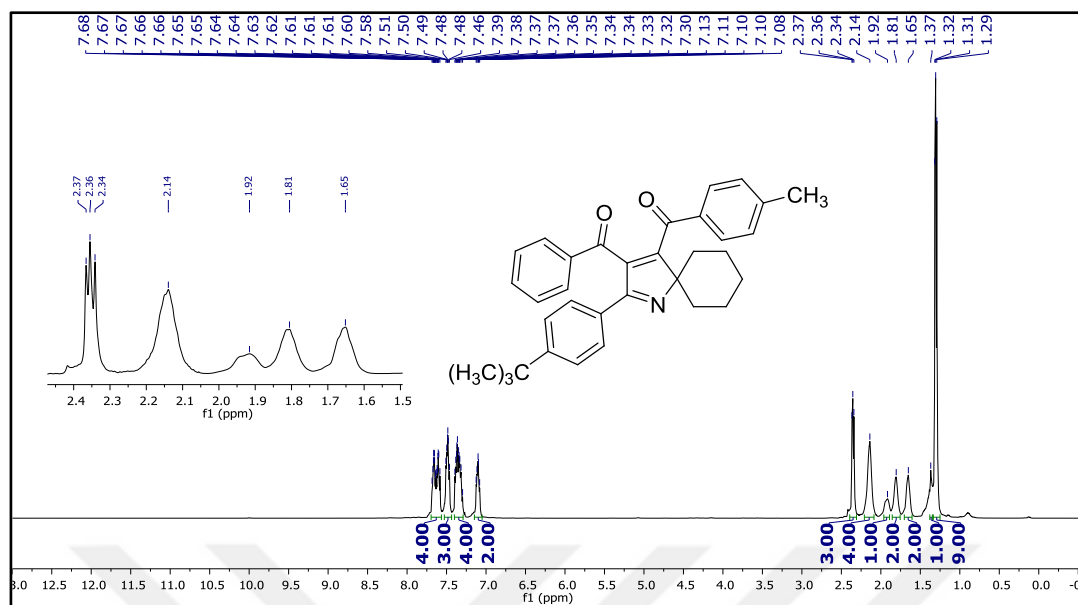


Figure 127. ¹H NMR spectrum of compound 34j.

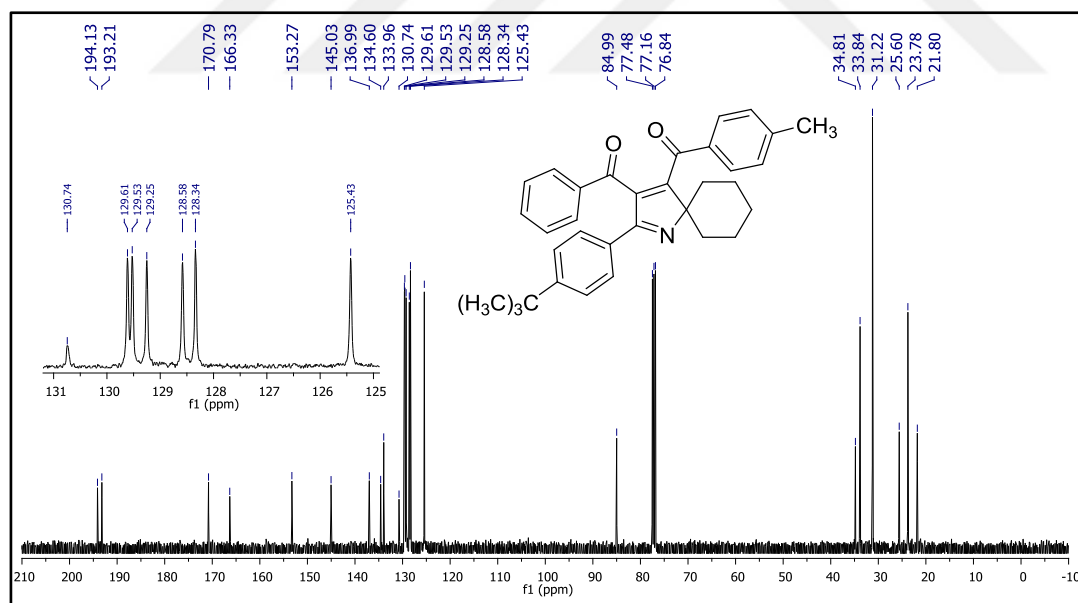


Figure 128. ¹³C NMR spectrum of compound 34j.

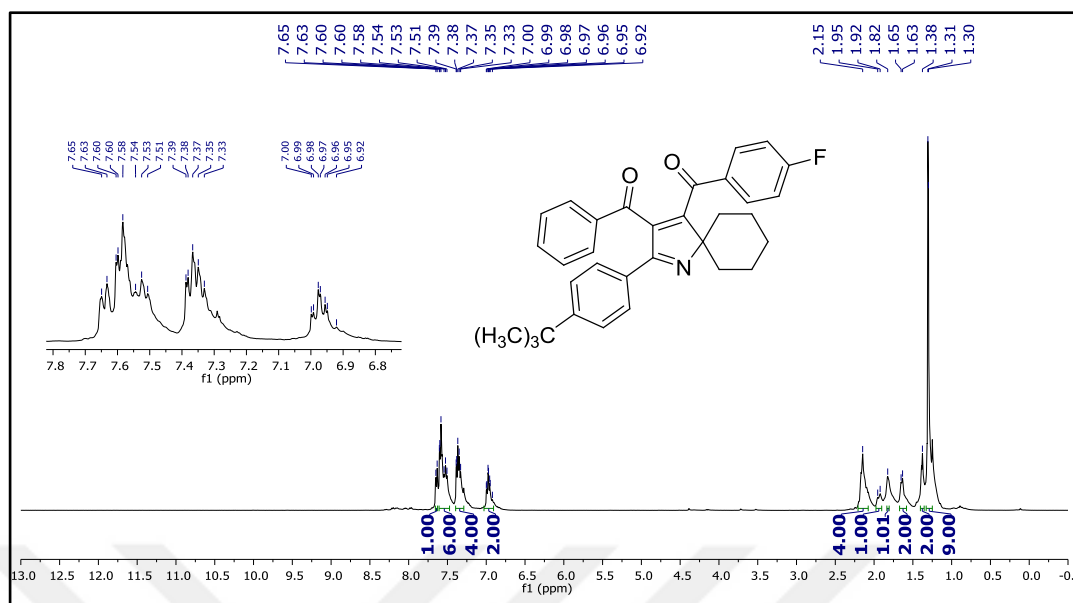


Figure 129. ¹H NMR spectrum of compound 34k.

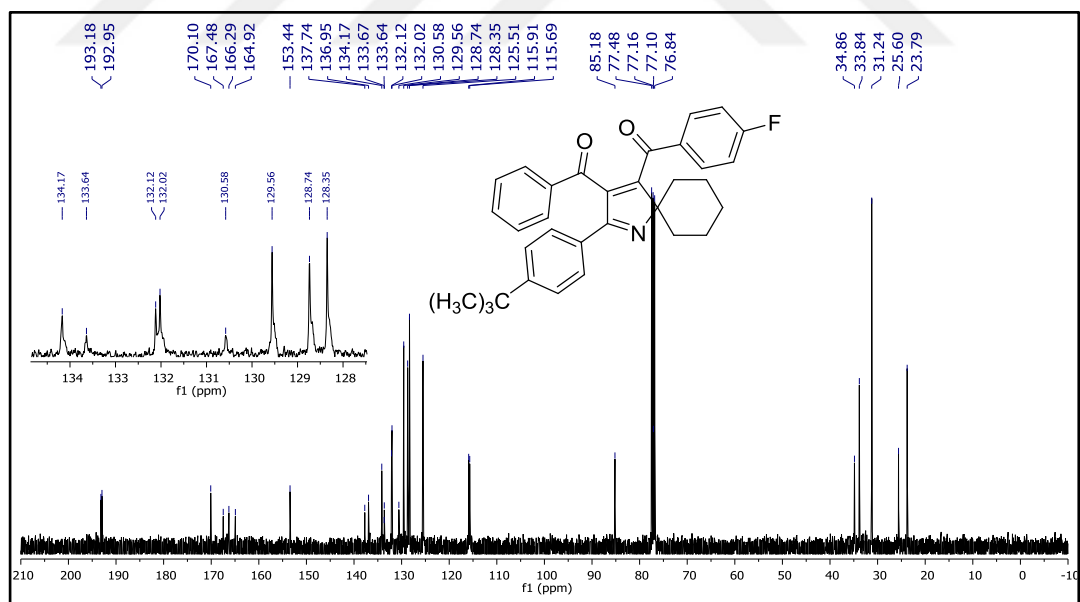


Figure 130. ¹³C NMR spectrum of compound 34k.

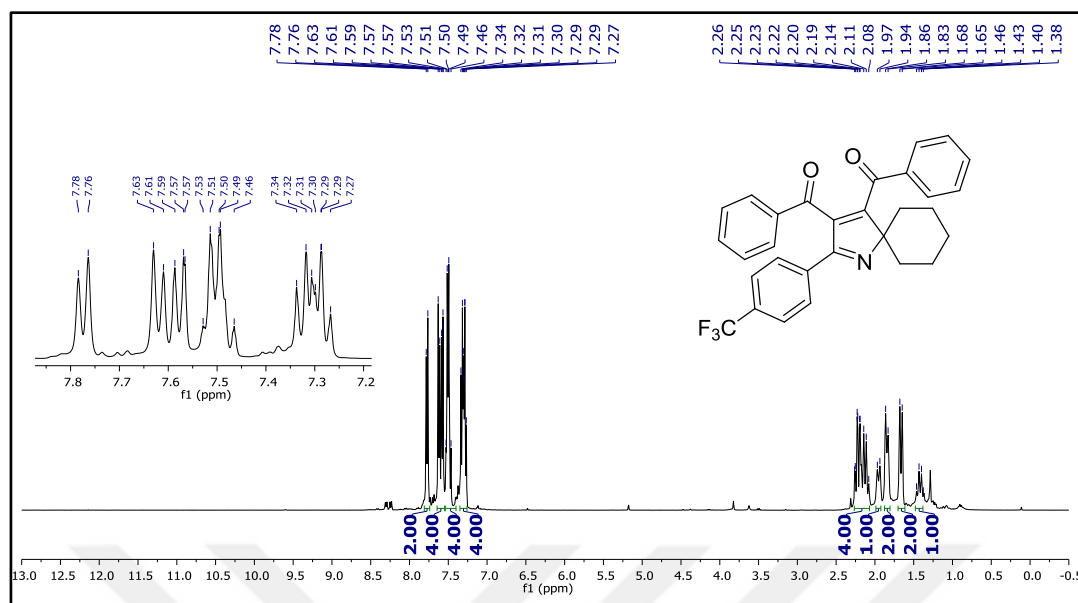


Figure 131. ^1H NMR spectrum of compound 34l.

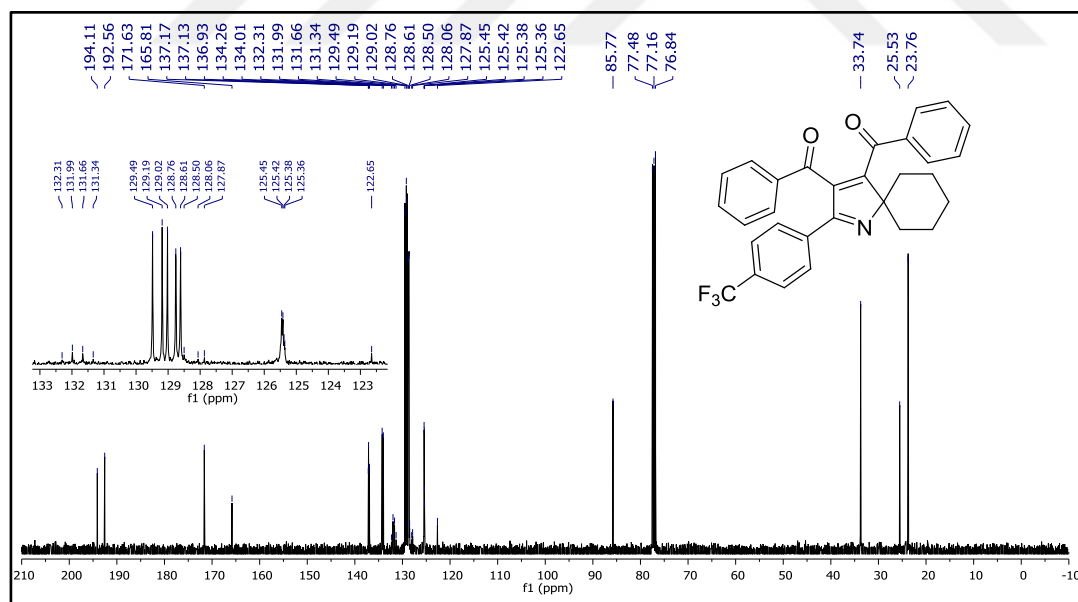


Figure 132. ^{13}C NMR spectrum of compound 34l.

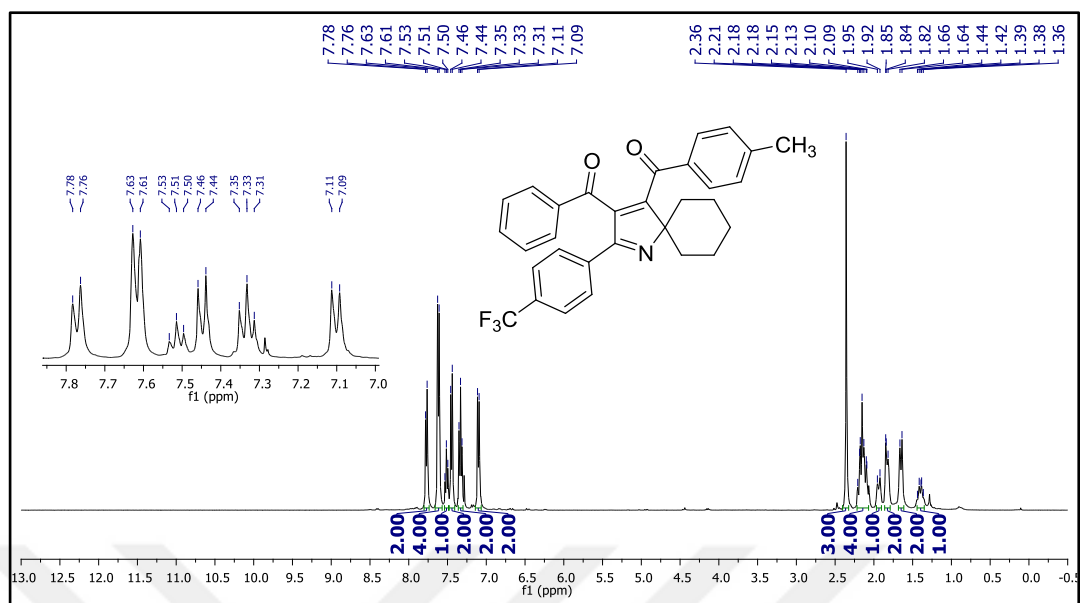


Figure 133. ¹H NMR spectrum of compound 34m.

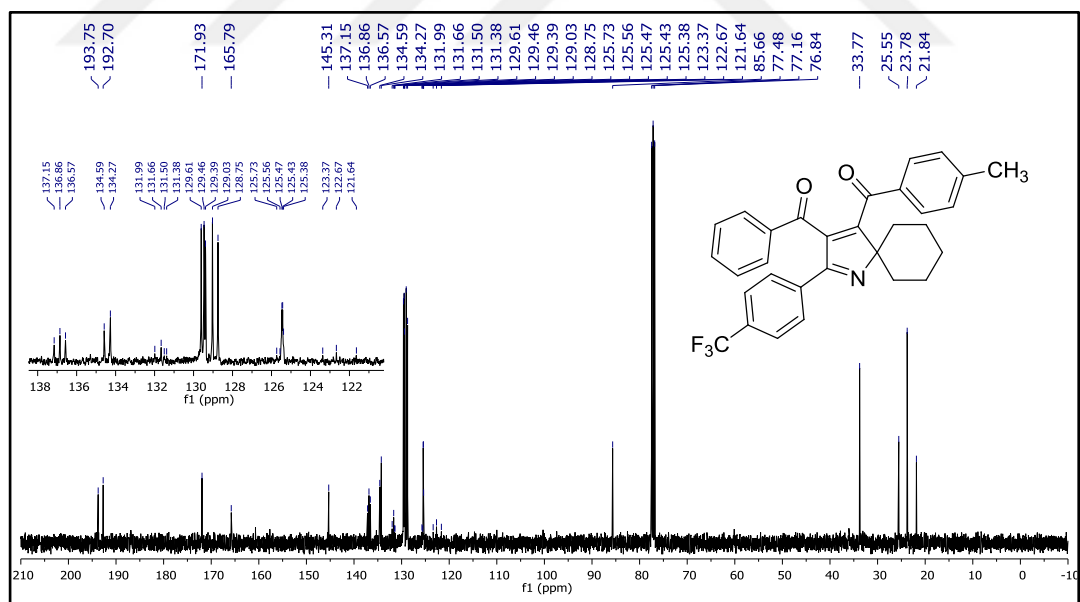


Figure 134. ¹³C NMR spectrum of compound 34m.

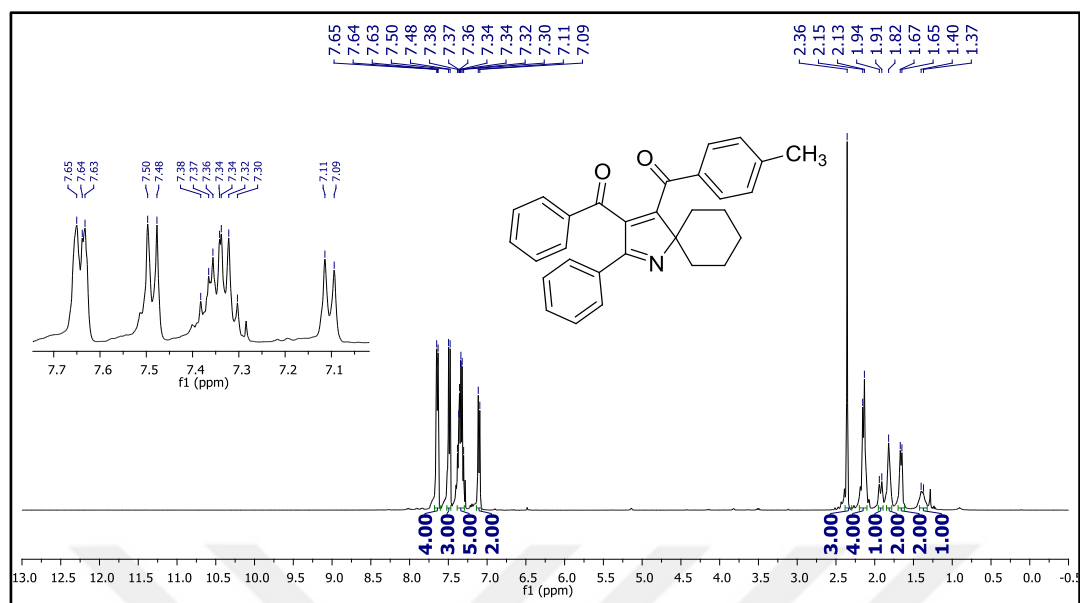


Figure 135. ¹H NMR spectrum of compound **34n**.

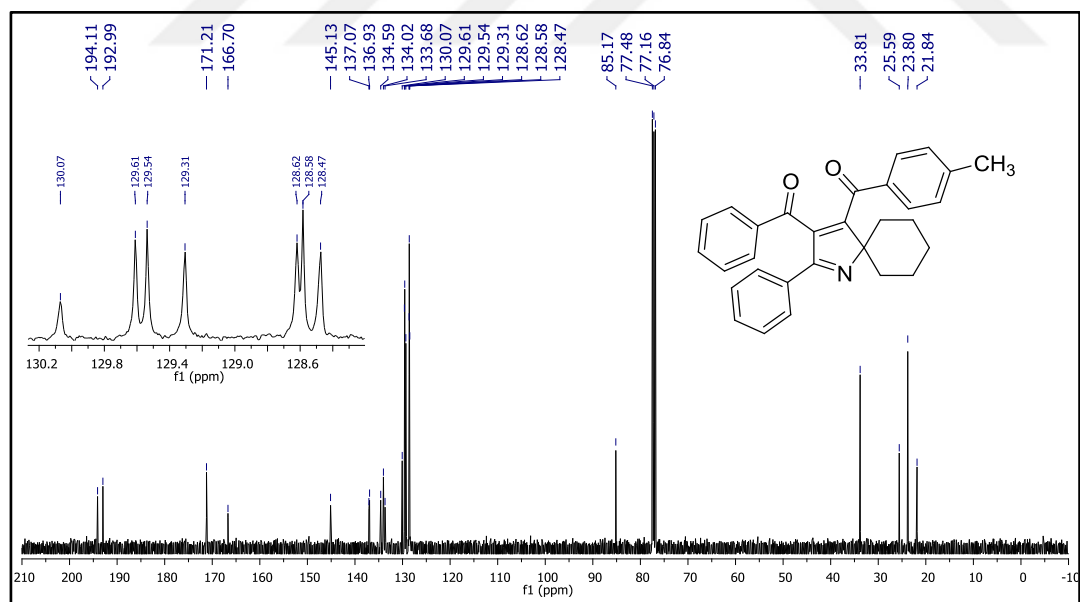


Figure 136. ¹³C NMR spectrum of compound **34n**.

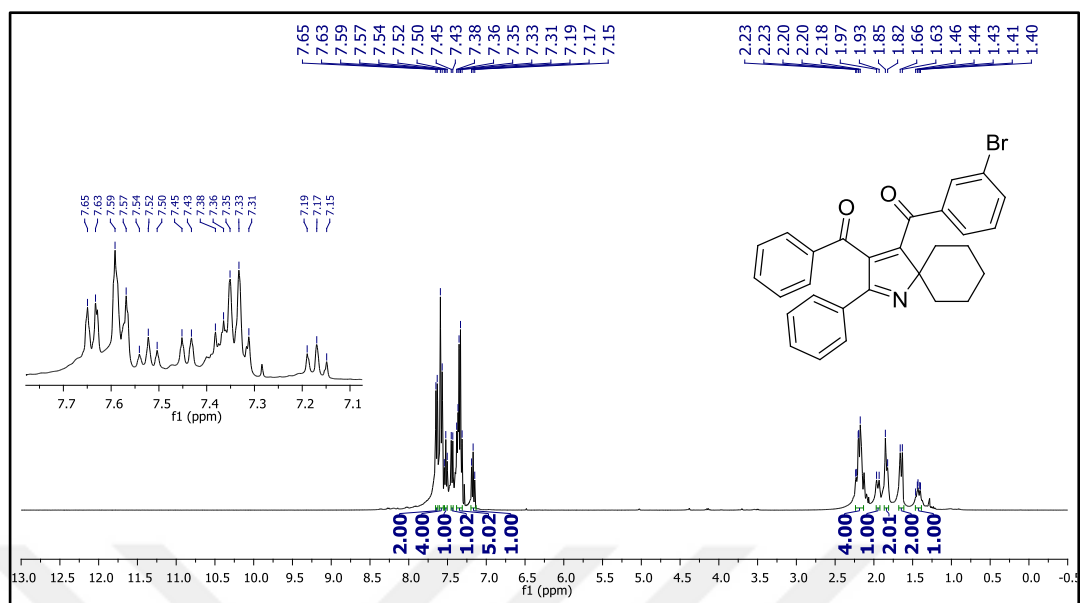


Figure 137. ¹H NMR spectrum of compound **34o**.

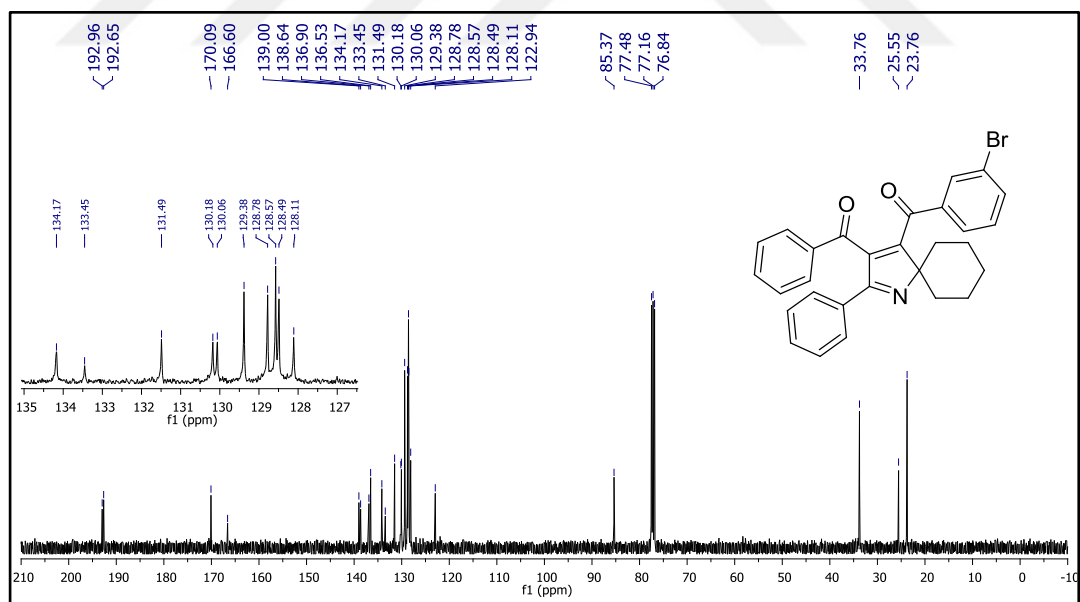


Figure 138. ¹³C NMR spectrum of compound **34o**.

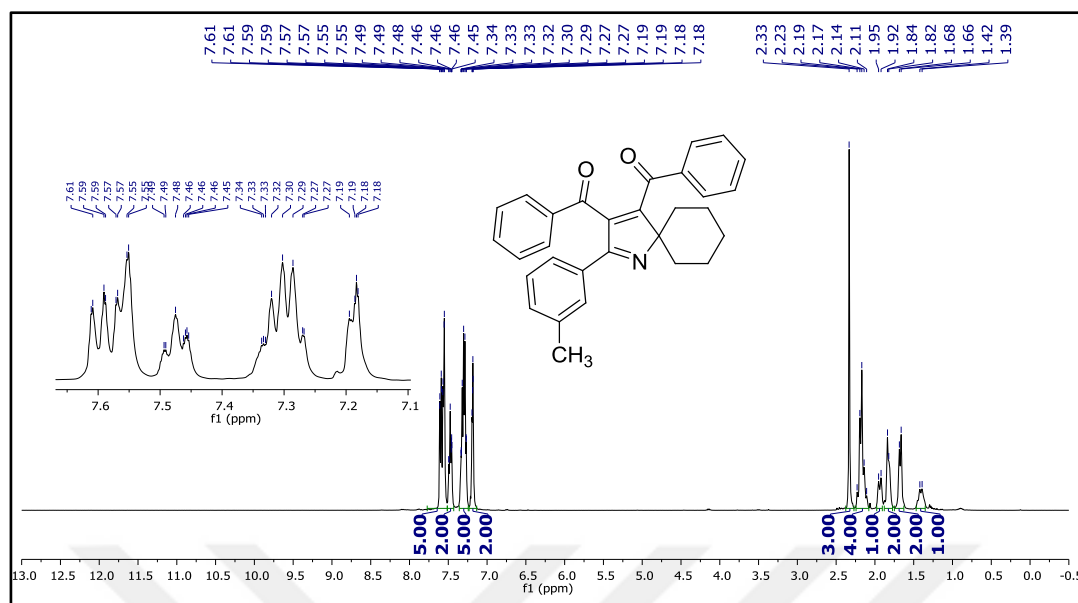


Figure 139. ¹H NMR spectrum of compound **34p**.

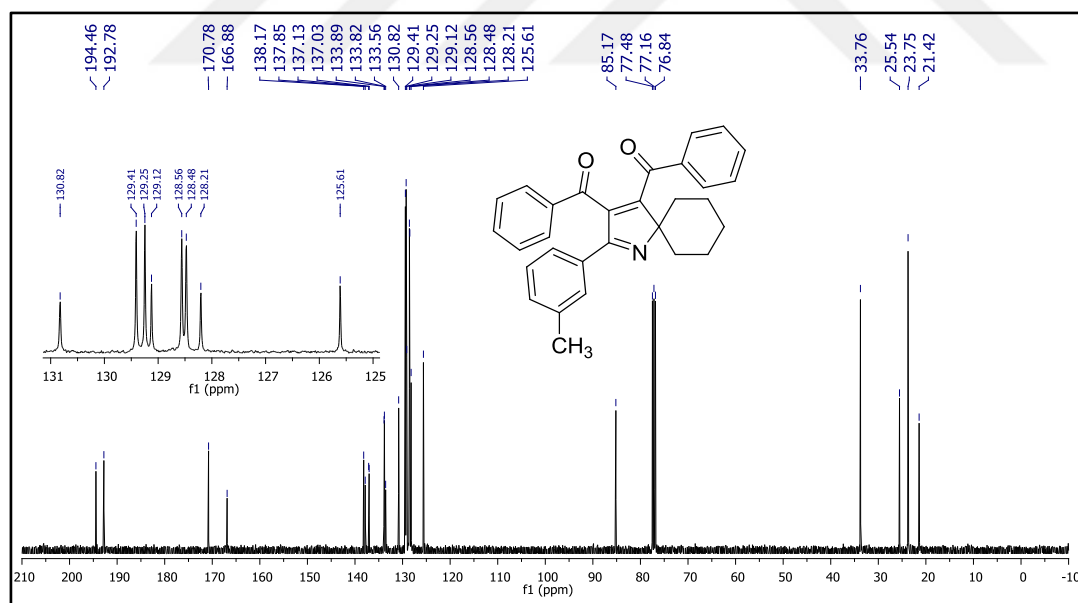


Figure 140. ¹³C NMR spectrum of compound **34p**.

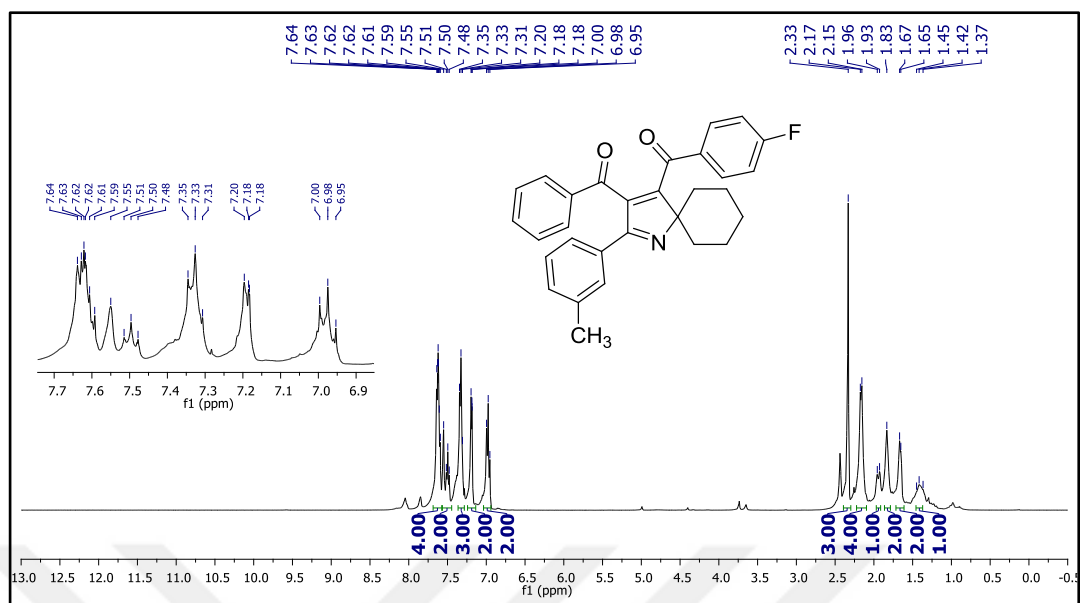


Figure 141. ¹H NMR spectrum of compound 34q.

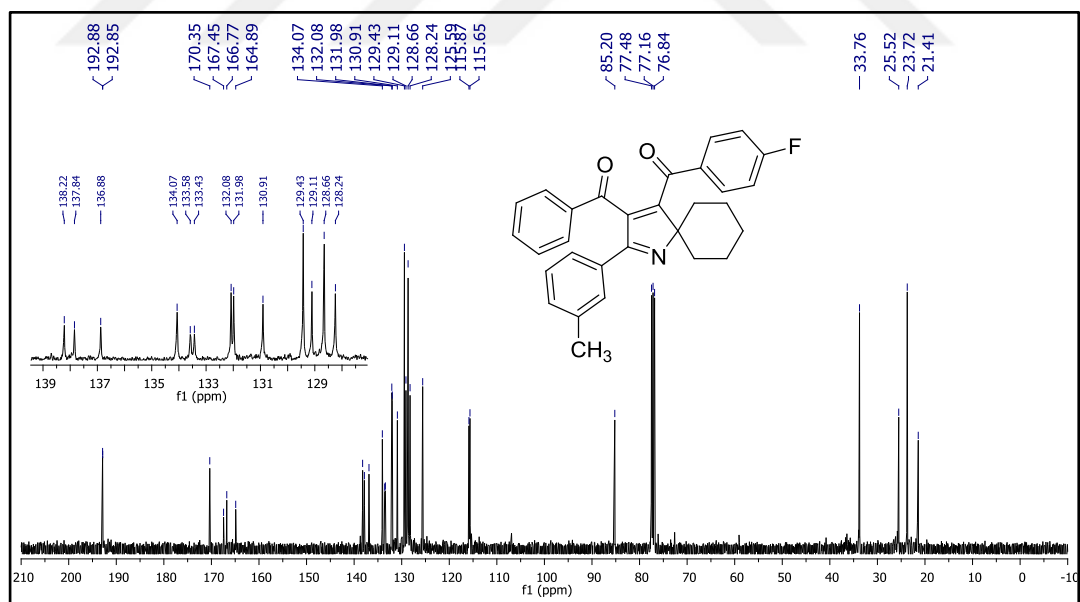


Figure 142. ¹³C NMR spectrum of compound 34q.

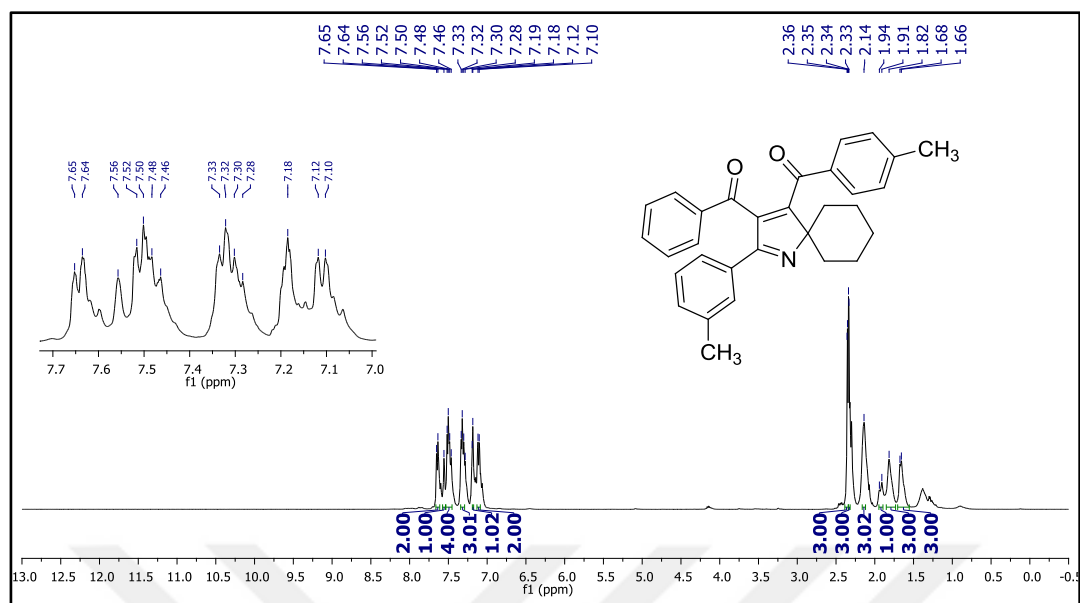


Figure 143. ¹H NMR spectrum of compound **34r**.

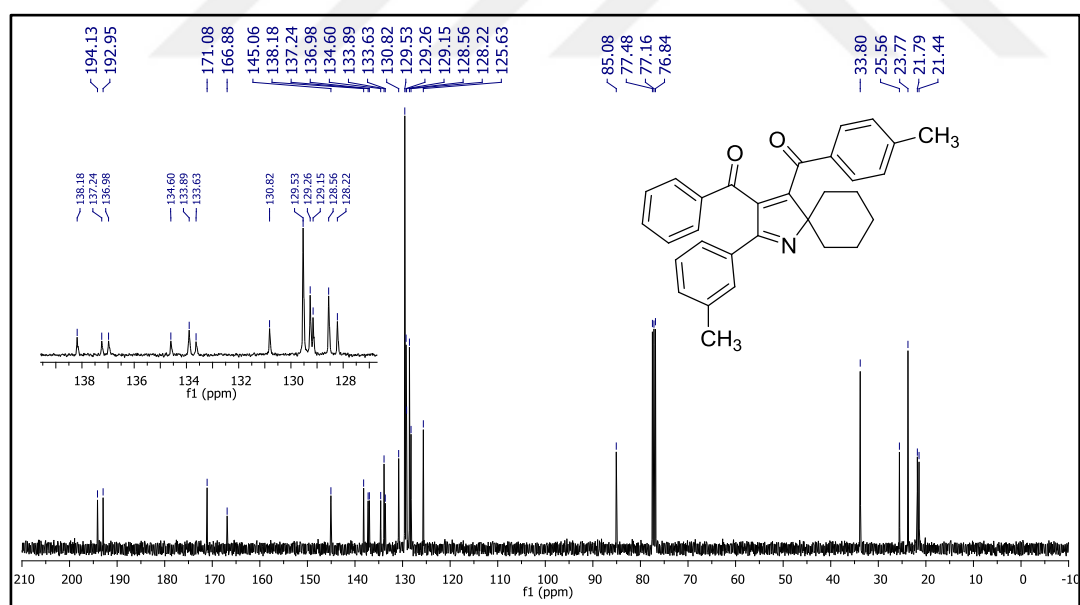


Figure 144. ¹³C NMR spectrum of compound **34r**.

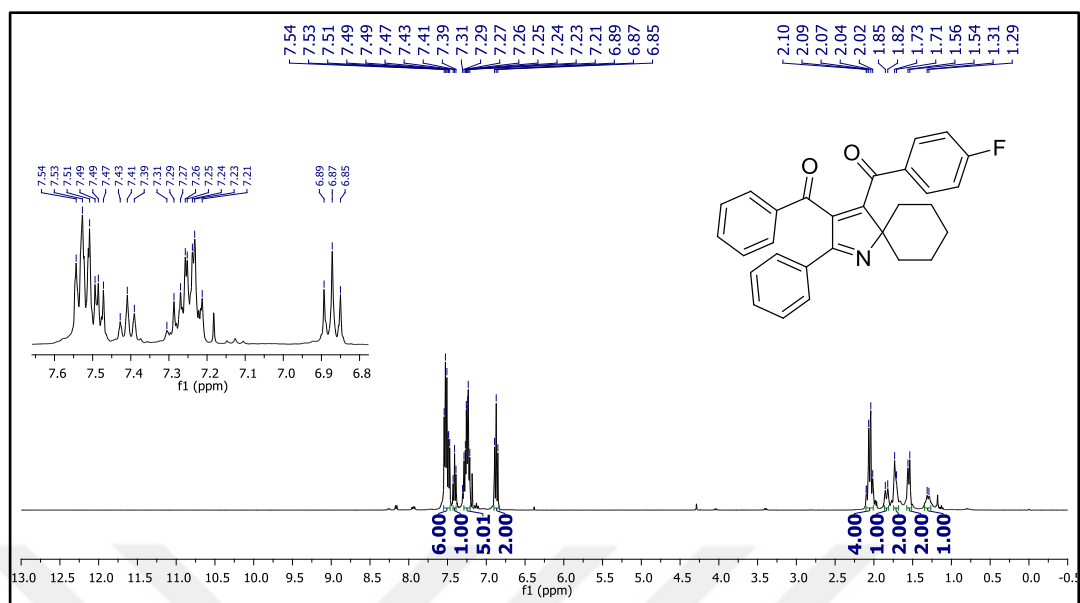


Figure 145. ¹H NMR spectrum of compound 34s.

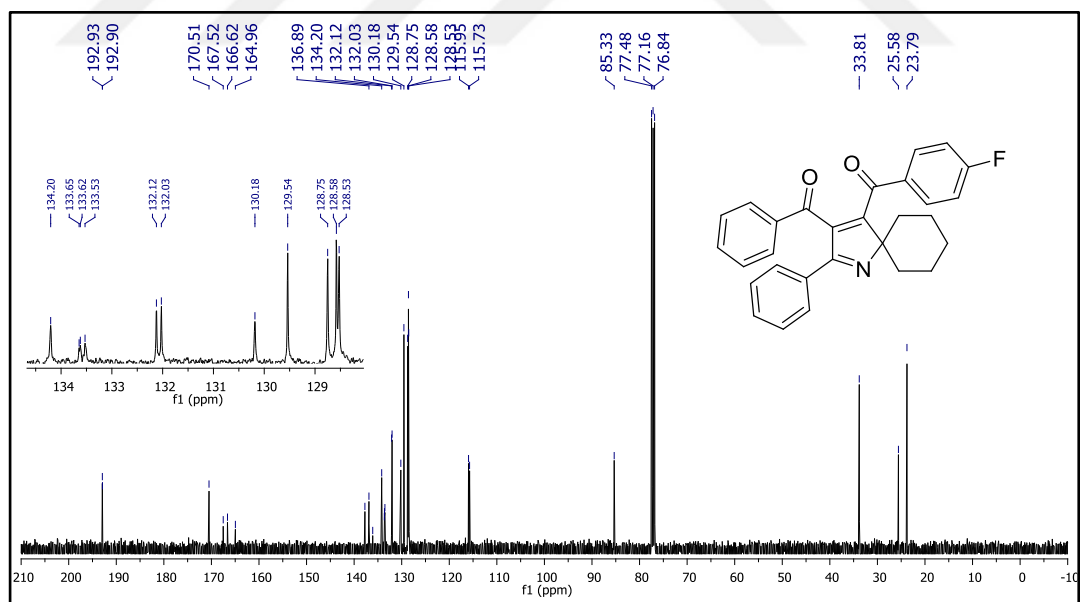


Figure 146. ¹³C NMR spectrum of compound 34s.

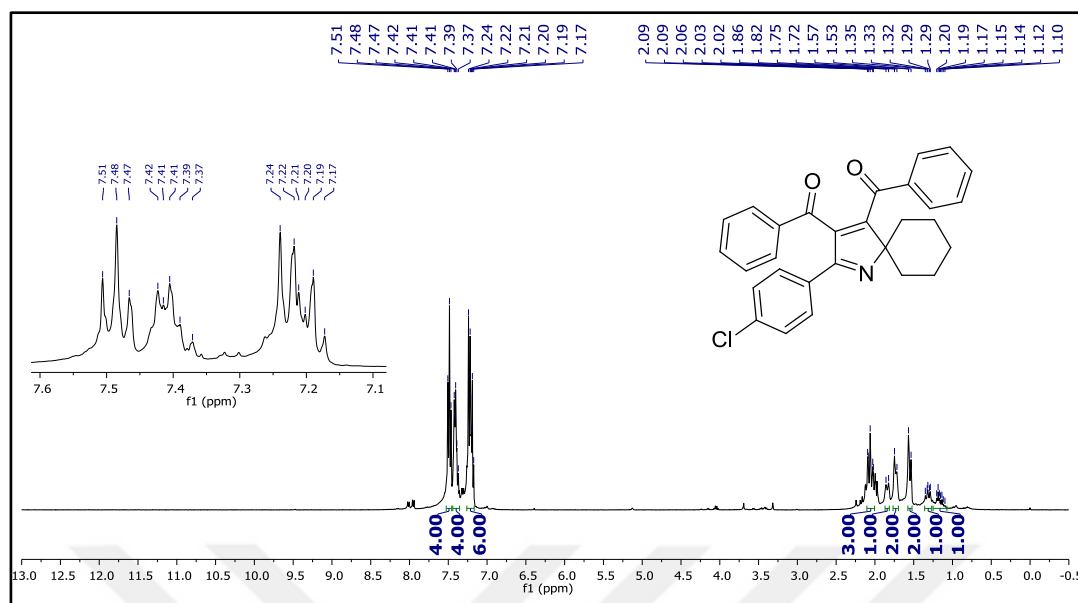


Figure 147. ¹H NMR spectrum of compound **34t**.

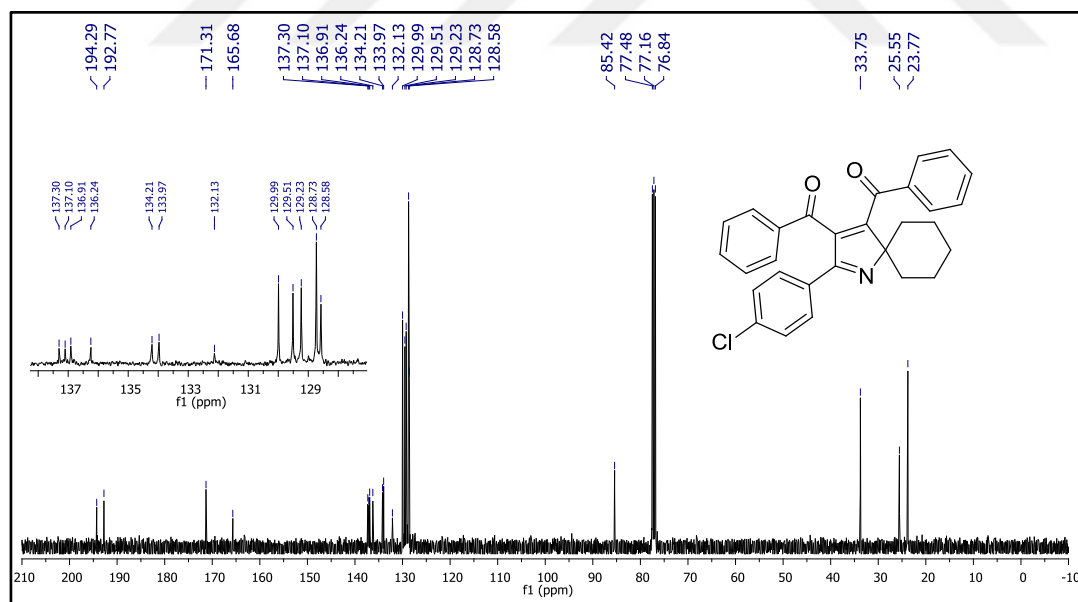


Figure 148. ¹³C NMR spectrum of compound **34t**.

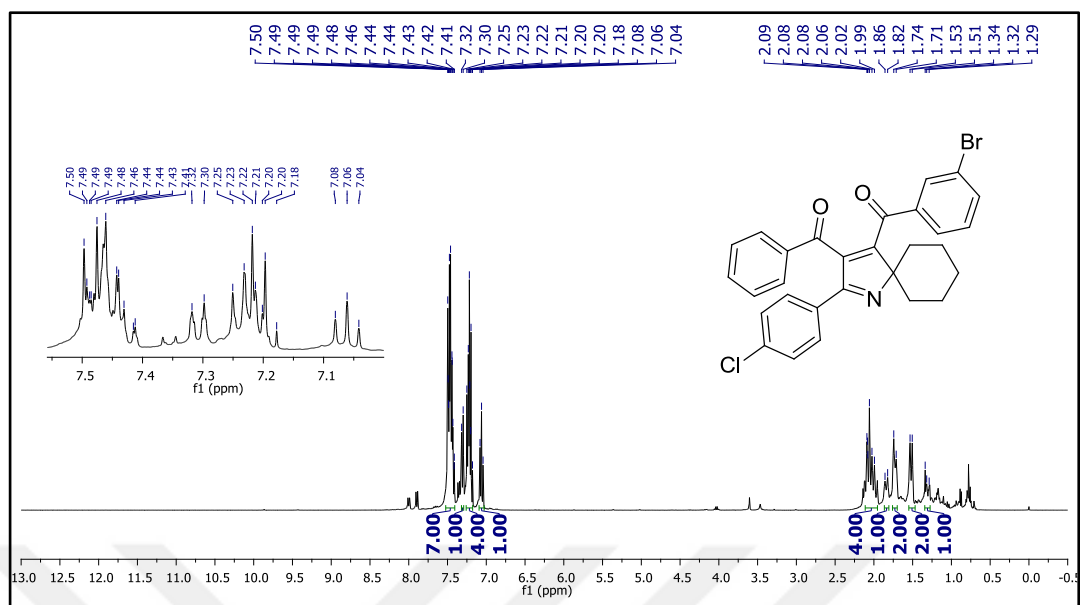


Figure 149. ¹H NMR spectrum of compound 34u.

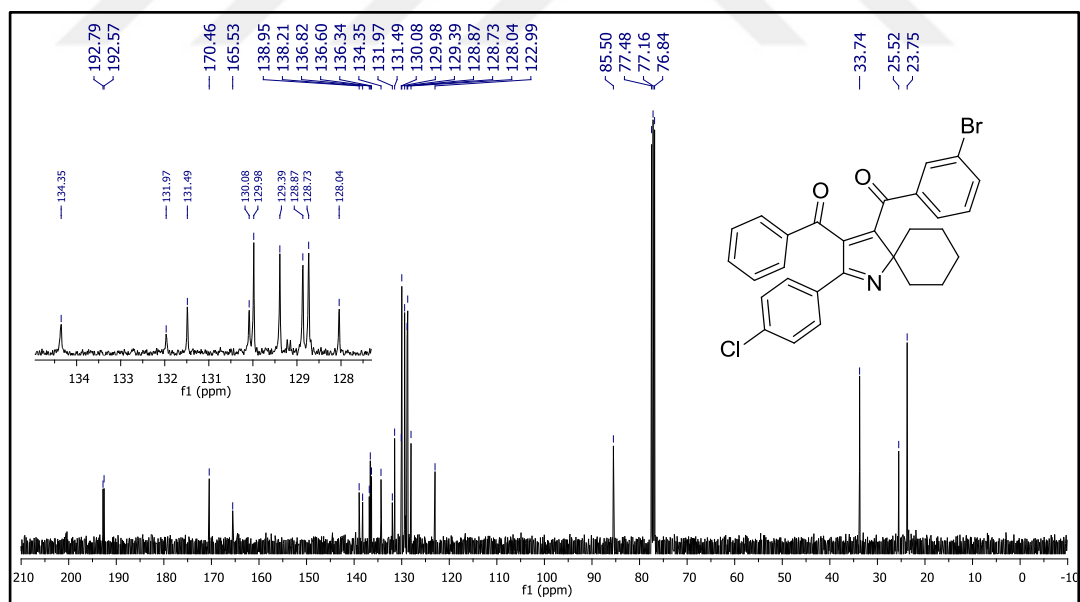


Figure 150. ¹³C NMR spectrum of compound 34u.

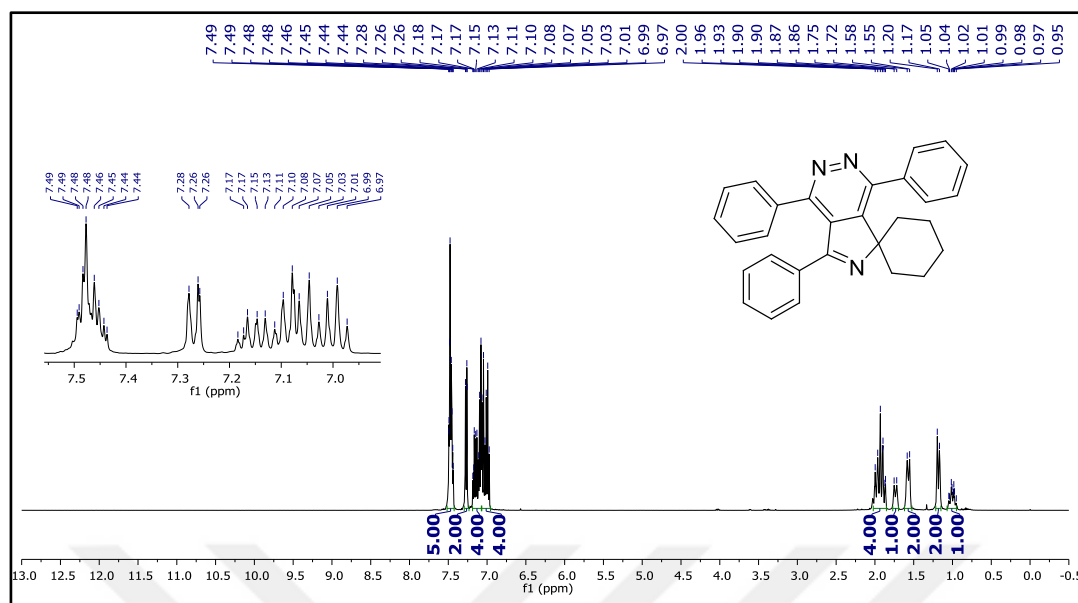


Figure 151. ¹H NMR spectrum of compound 35a.

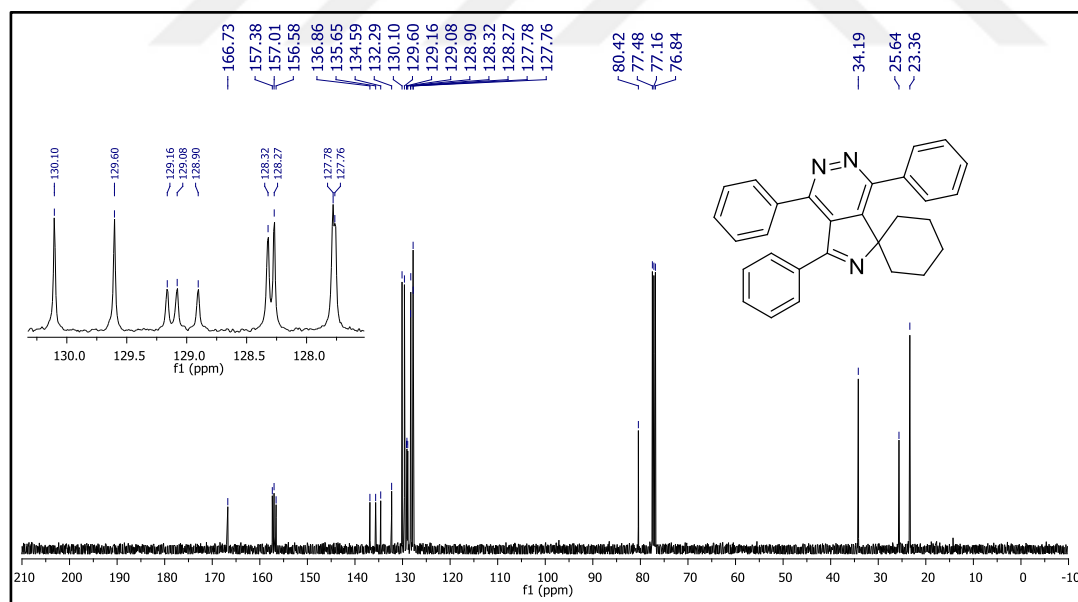


Figure 152. ¹³C NMR spectrum of compound 35a.

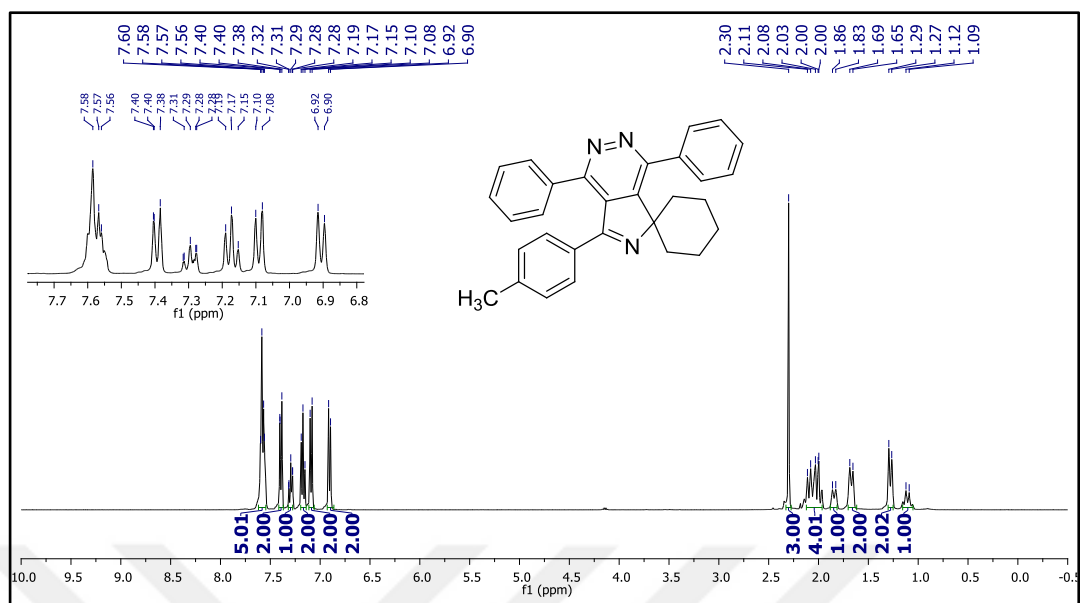


Figure 153. ¹H NMR spectrum of compound 35b.

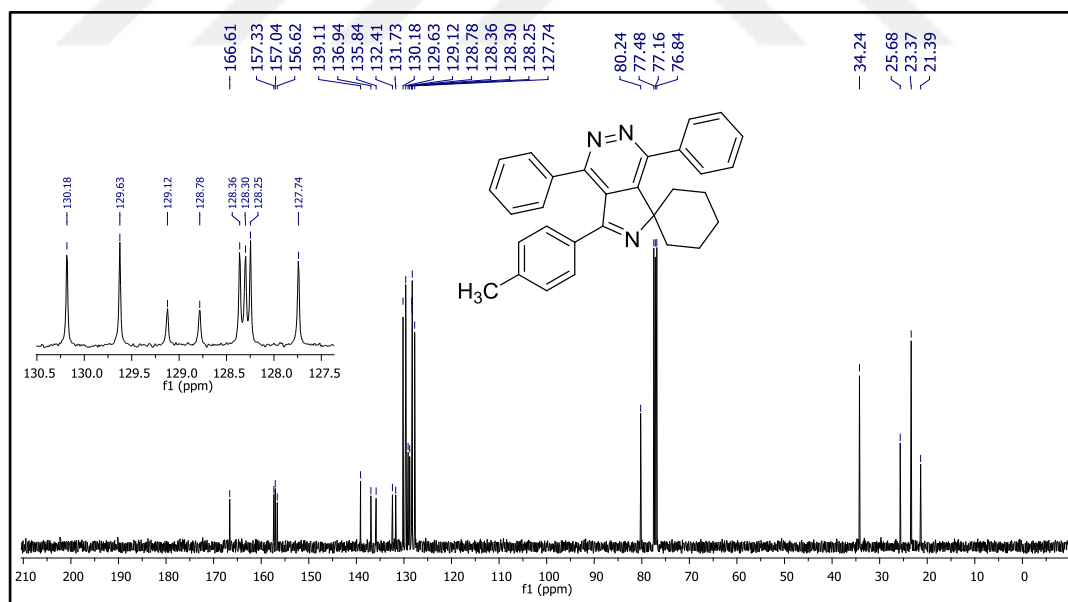


Figure 154. ¹³C NMR spectrum of compound 35b.

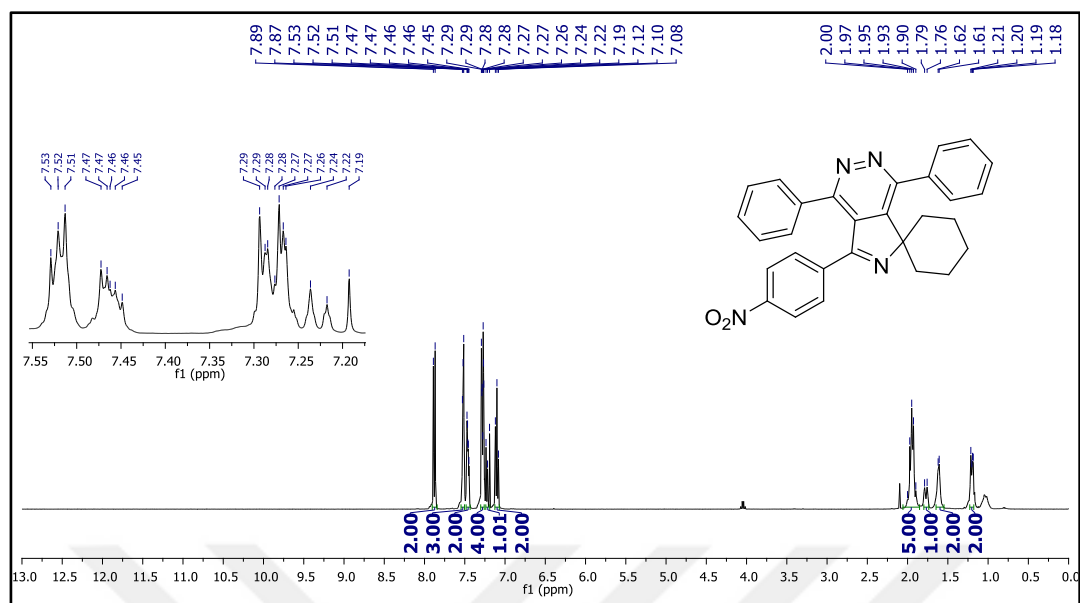


Figure 155. ¹H NMR spectrum of compound 35c.

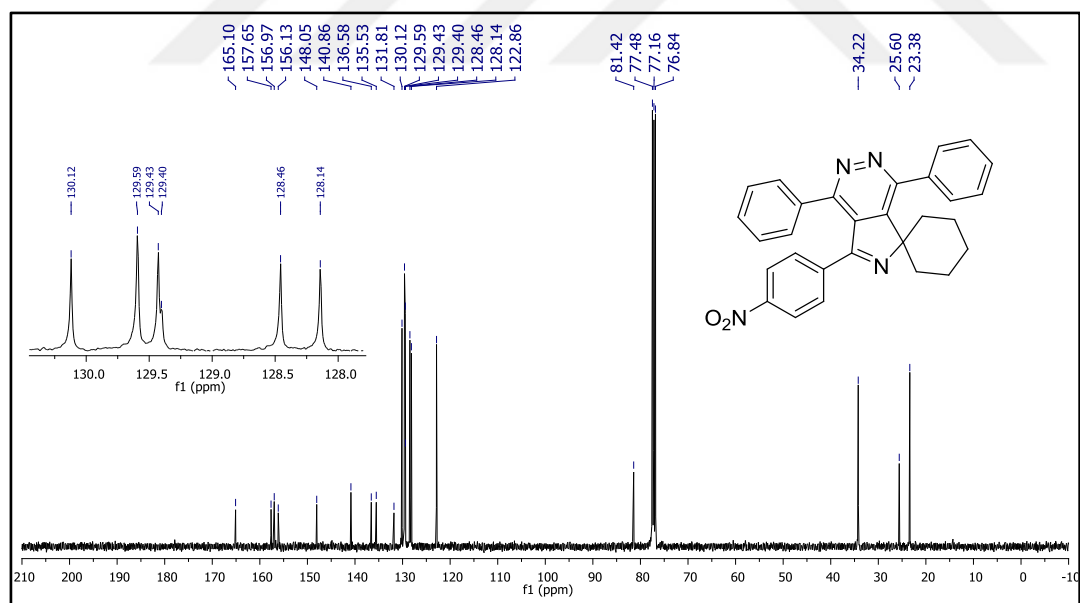


Figure 156. ¹³C NMR spectrum of compound 35c.

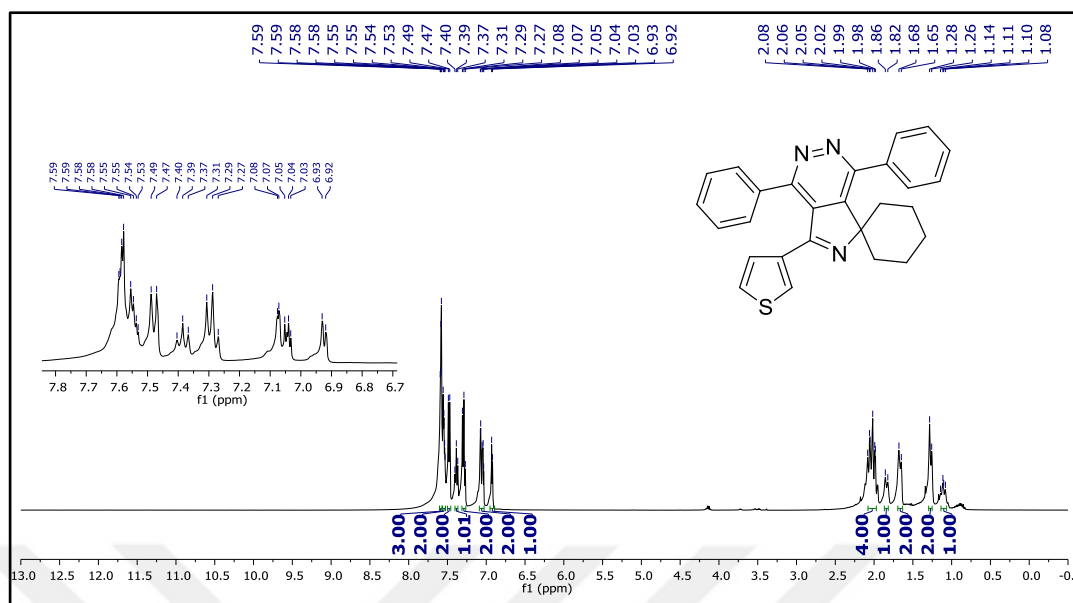


Figure 157. ¹H NMR spectrum of compound 35d.

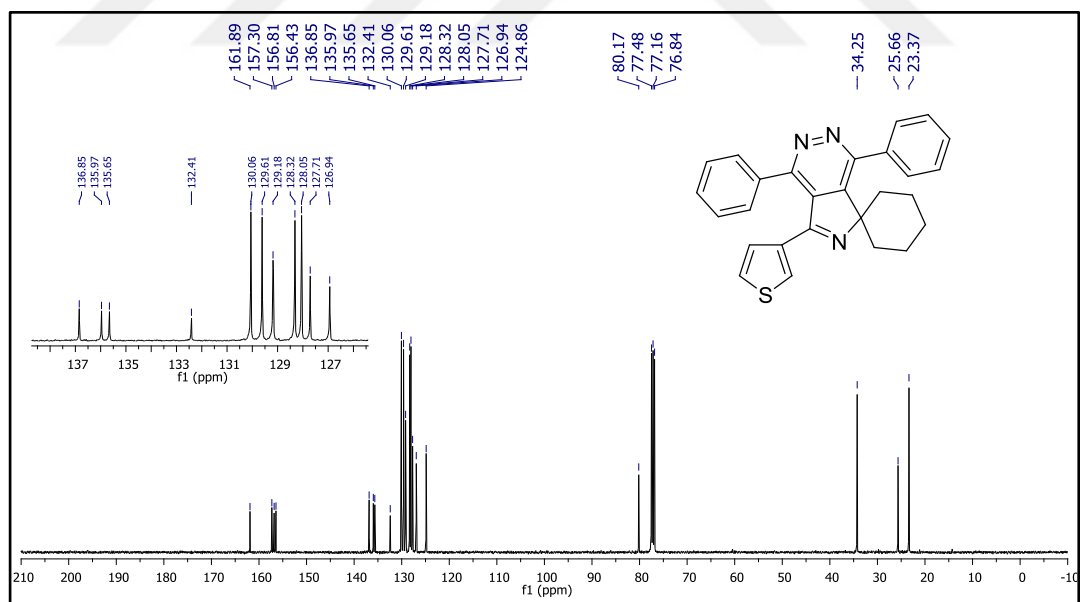


Figure 158. ¹³C NMR spectrum of compound 35d.

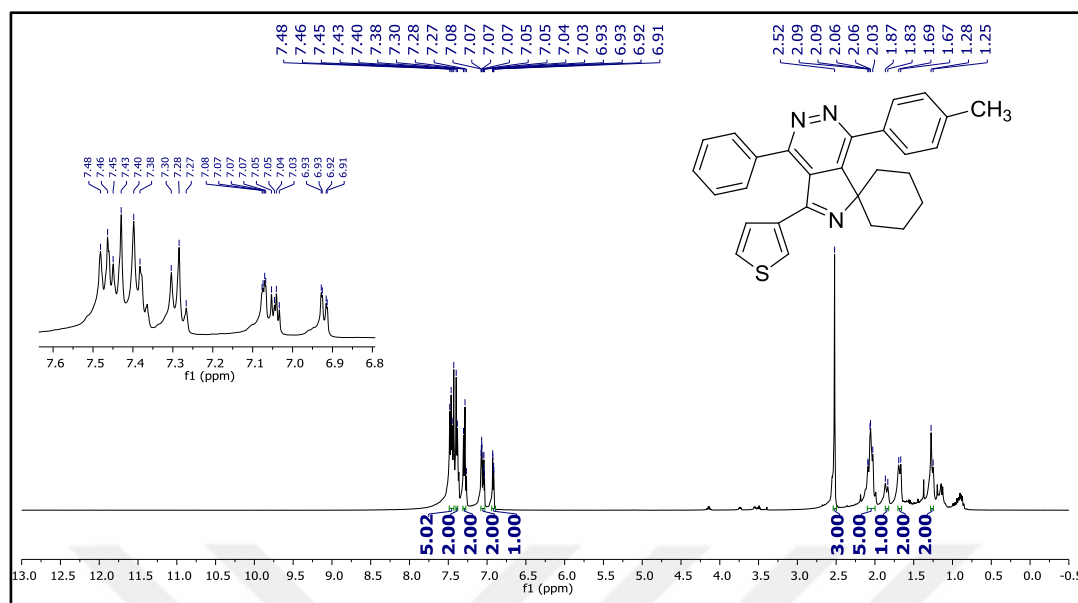


Figure 159. ¹H NMR spectrum of compound 35e.

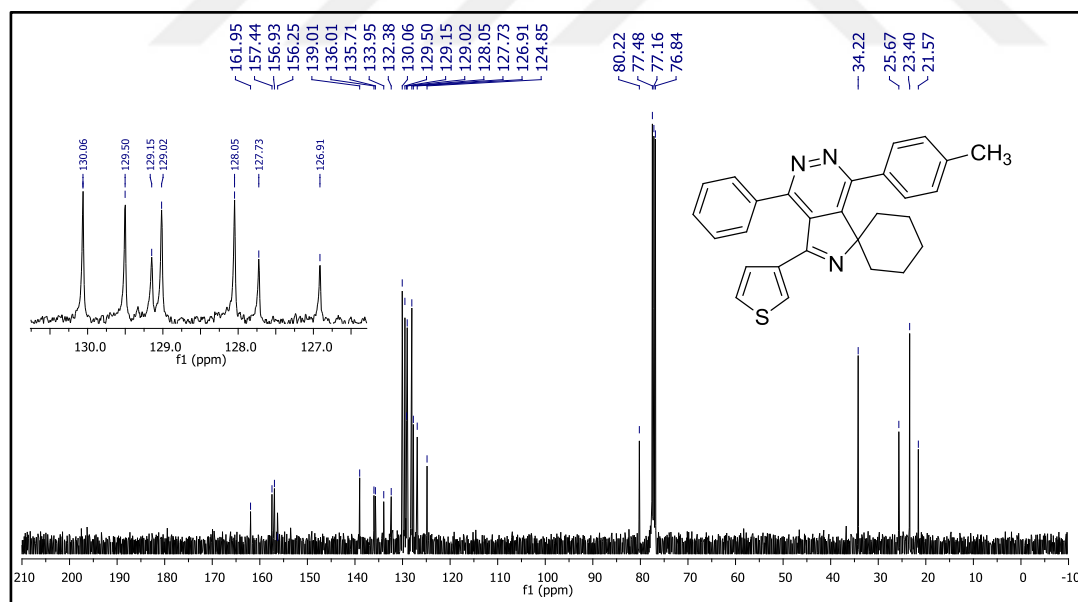


Figure 160. ¹³C NMR spectrum of compound 35e.

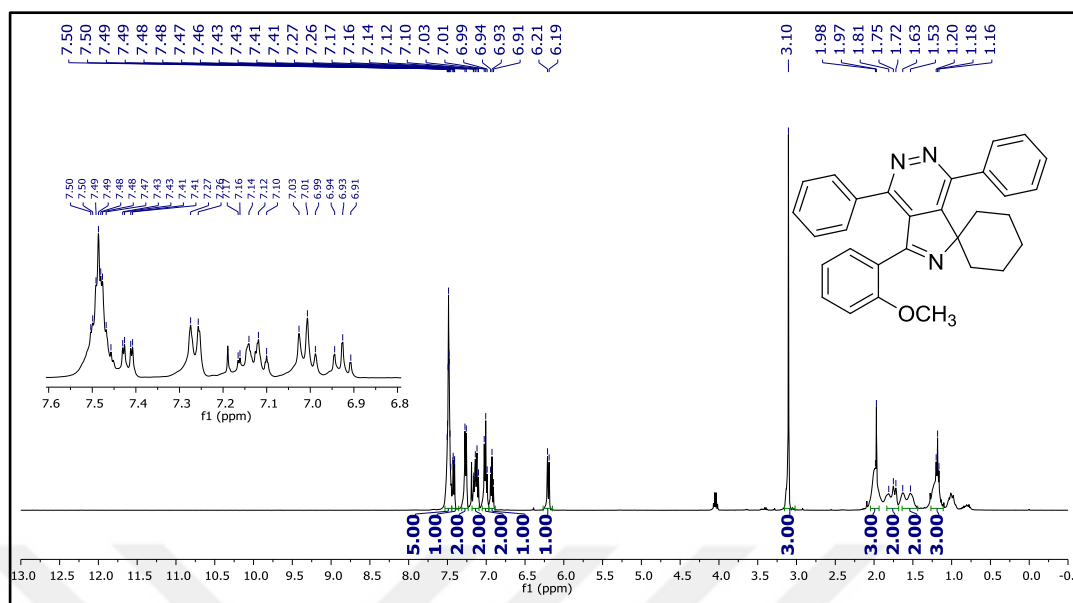


Figure 161. ¹H NMR spectrum of compound 35f.

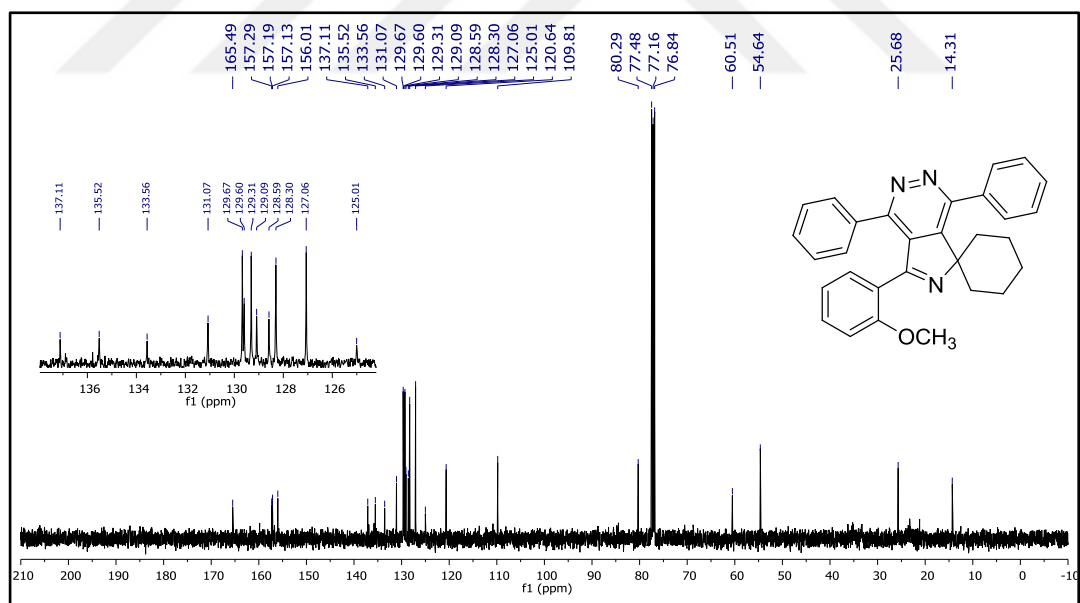


Figure 162. ¹³C NMR spectrum of compound 35f.

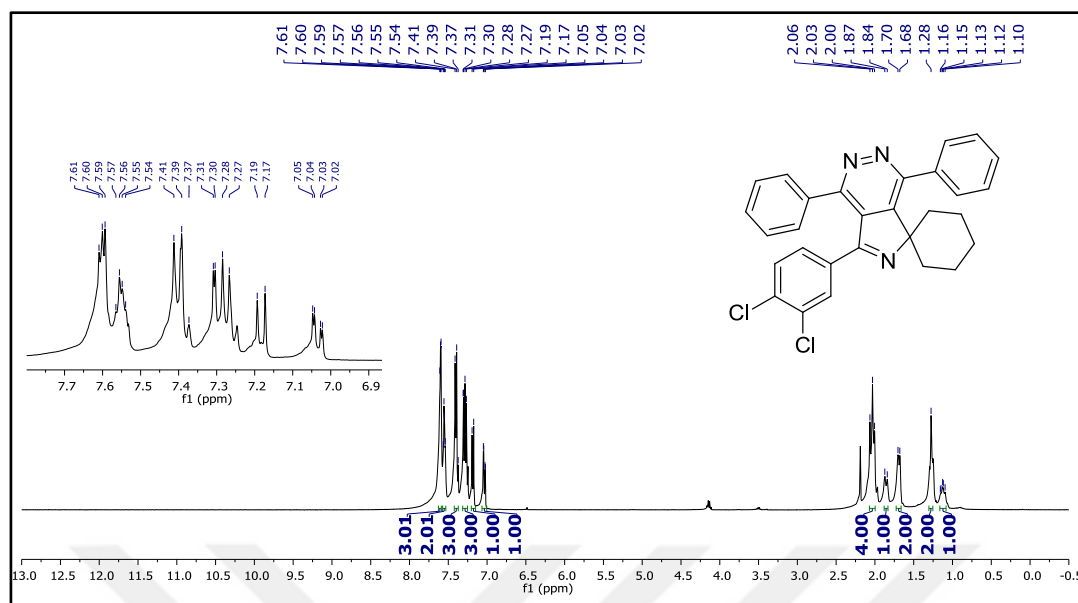


Figure 163. ¹H NMR spectrum of compound **35g**.

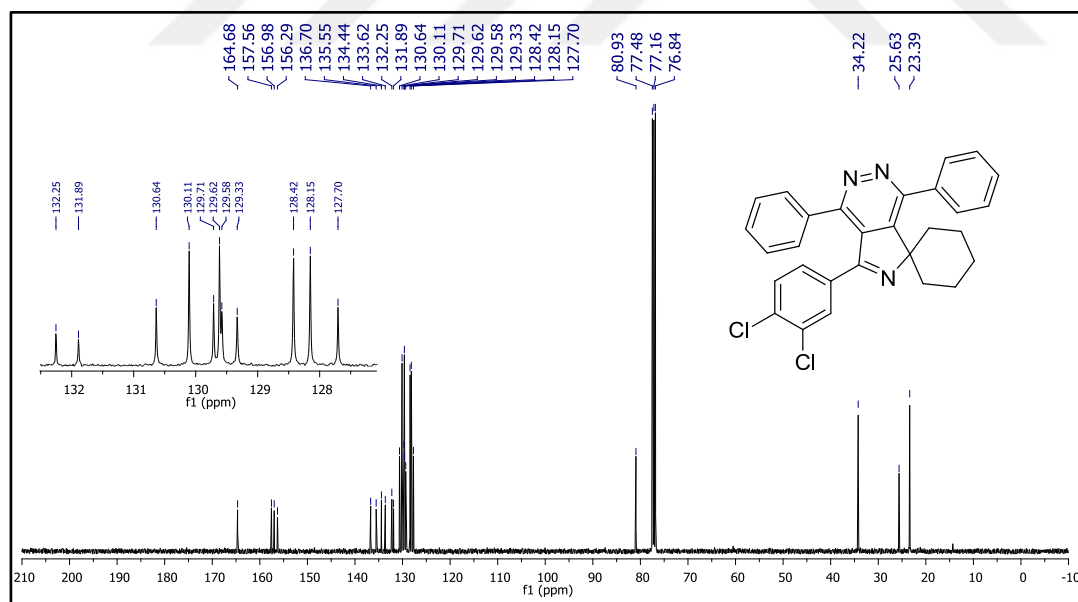


Figure 164. ¹³C NMR spectrum of compound **35g**.

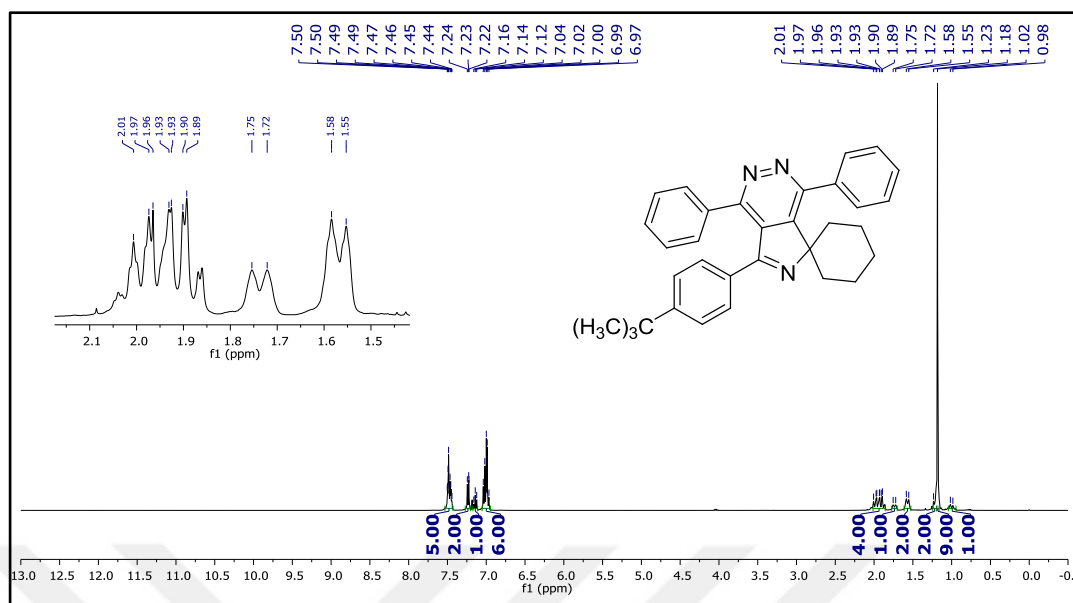


Figure 165. ¹H NMR spectrum of compound 35h.

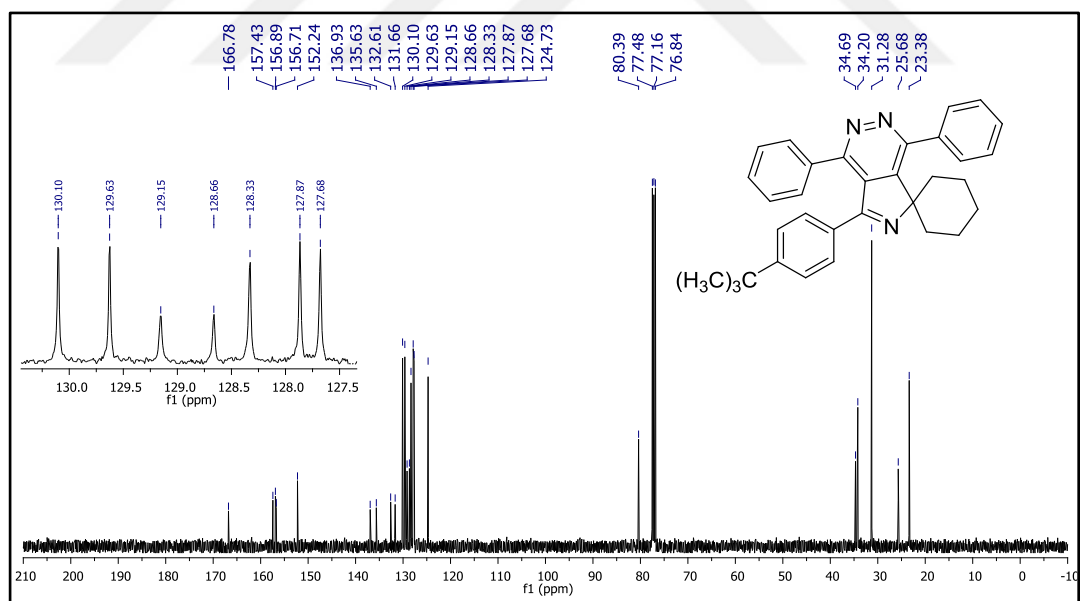


Figure 166. ¹³C NMR spectrum of compound 35h.

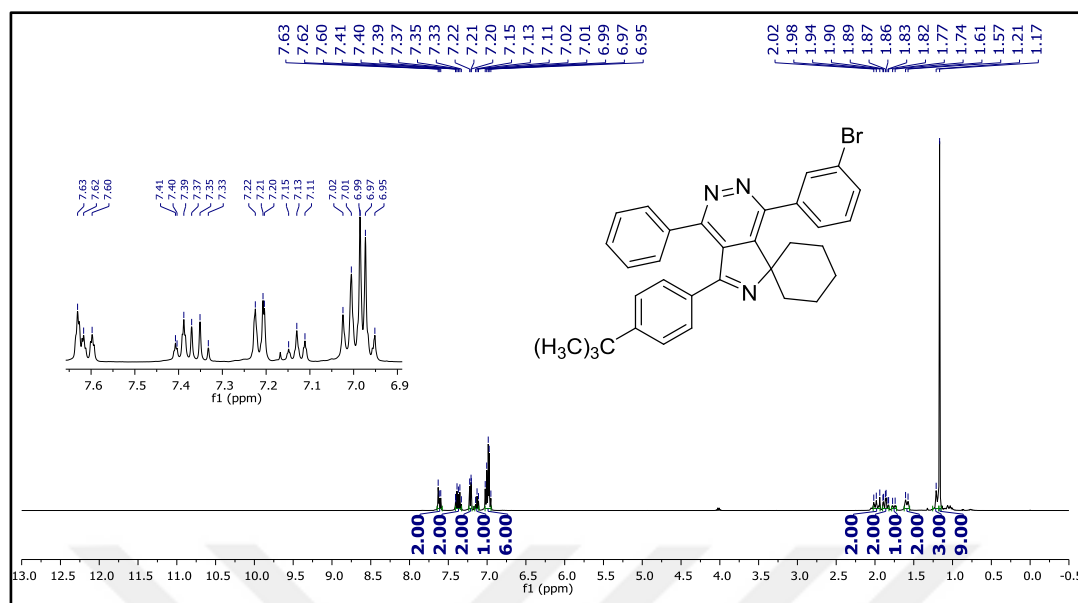


Figure 167. ¹H NMR spectrum of compound **35i**.

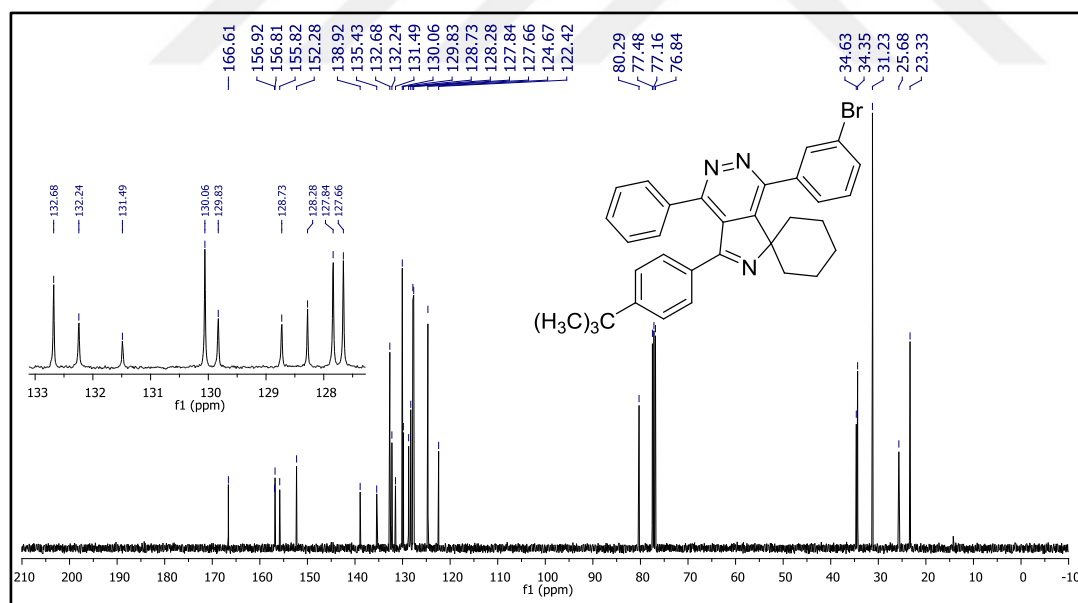


Figure 168. ¹³C NMR spectrum of compound **35i**.

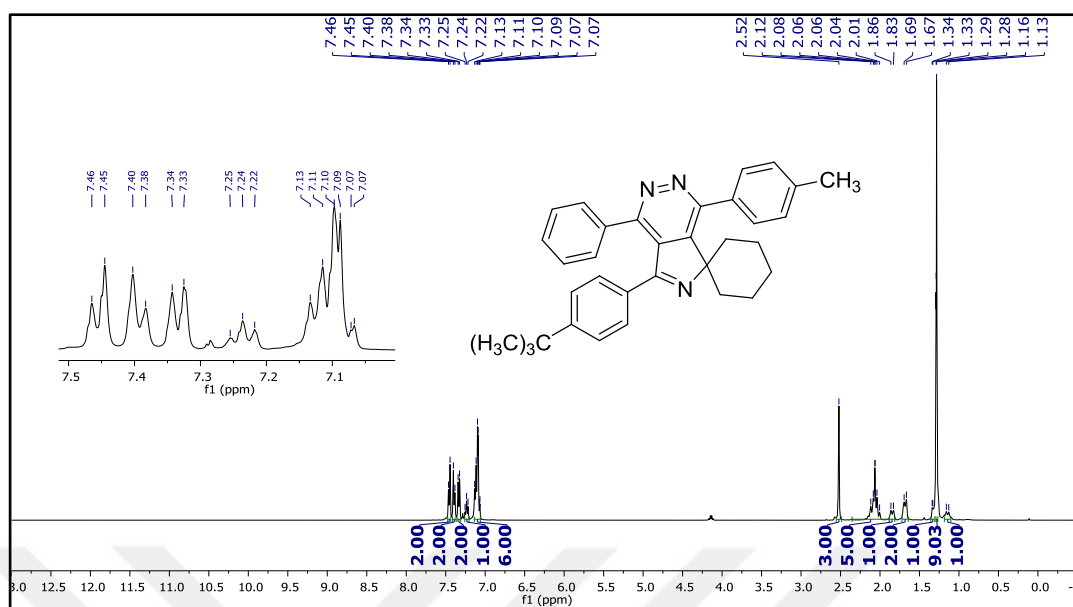


Figure 169. ¹H NMR spectrum of compound 35j.

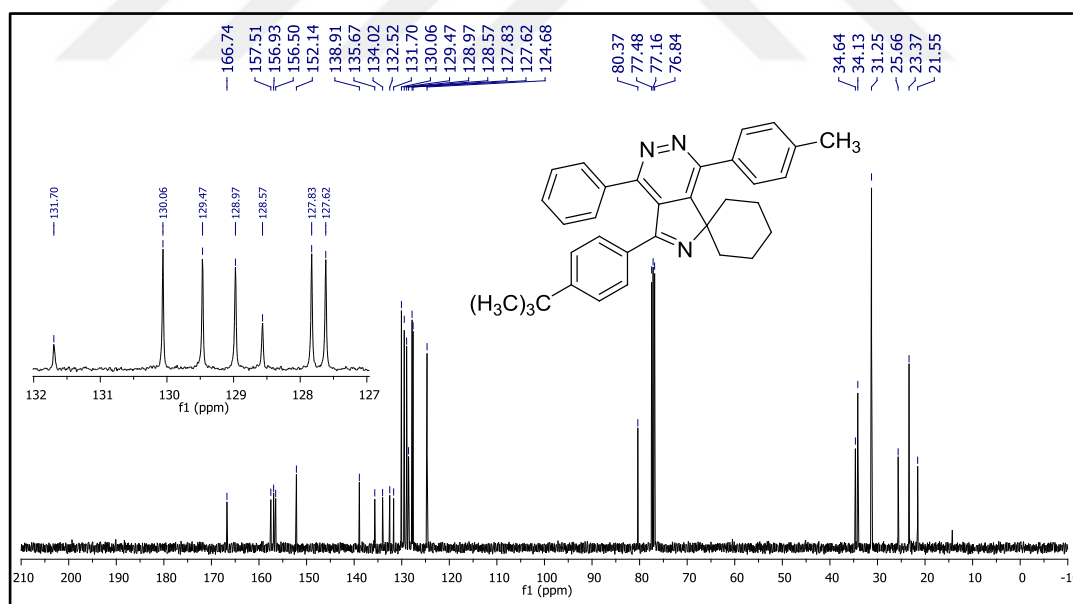


Figure 170. ¹³C NMR spectrum of compound 35j.

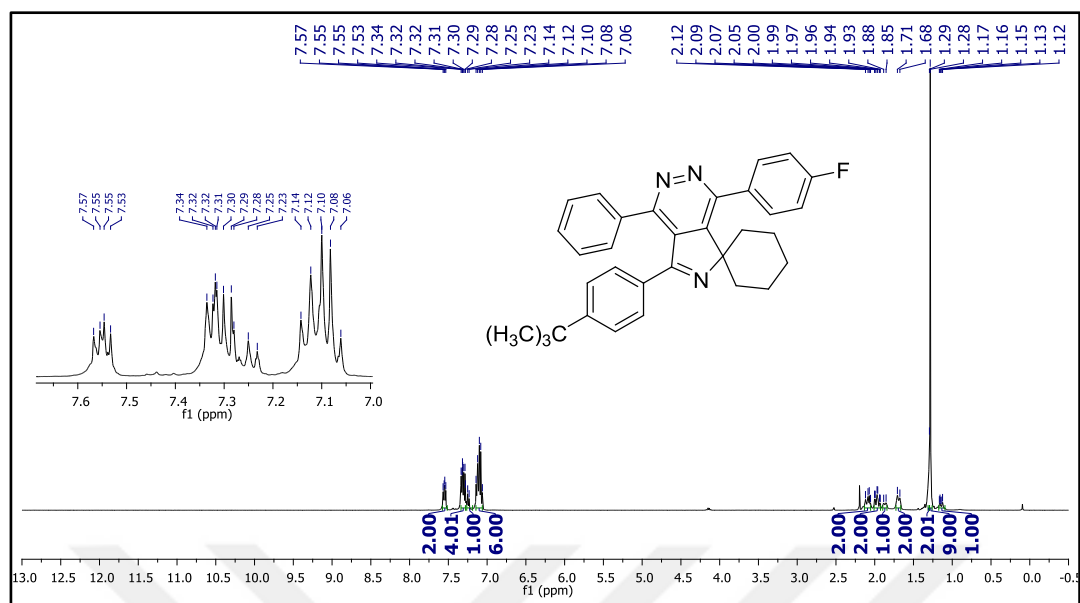


Figure 171. ¹H NMR spectrum of compound 35k.

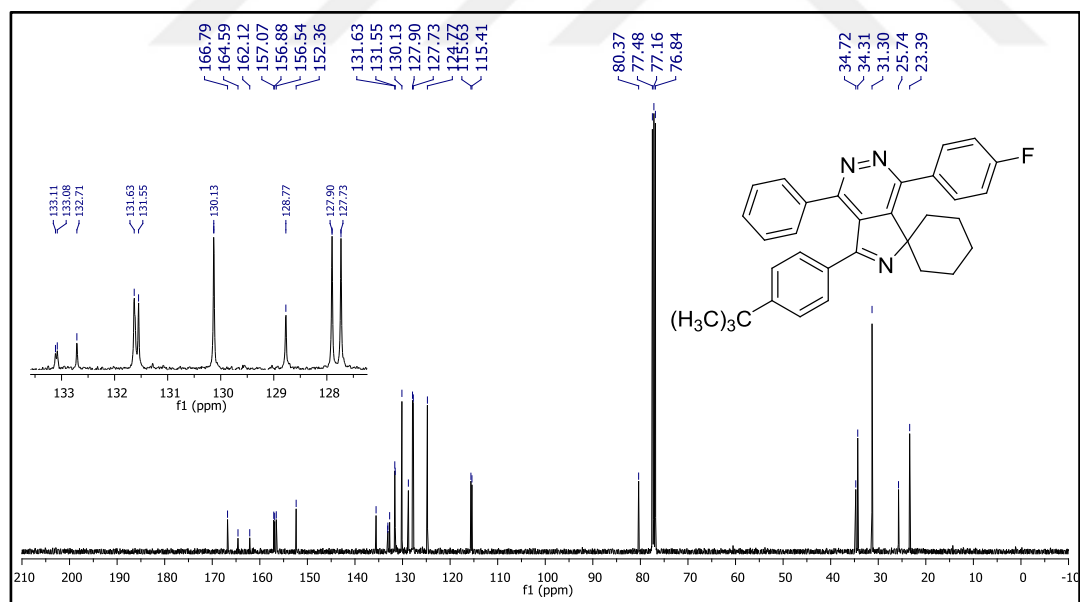


Figure 172. ¹³C NMR spectrum of compound 35k.

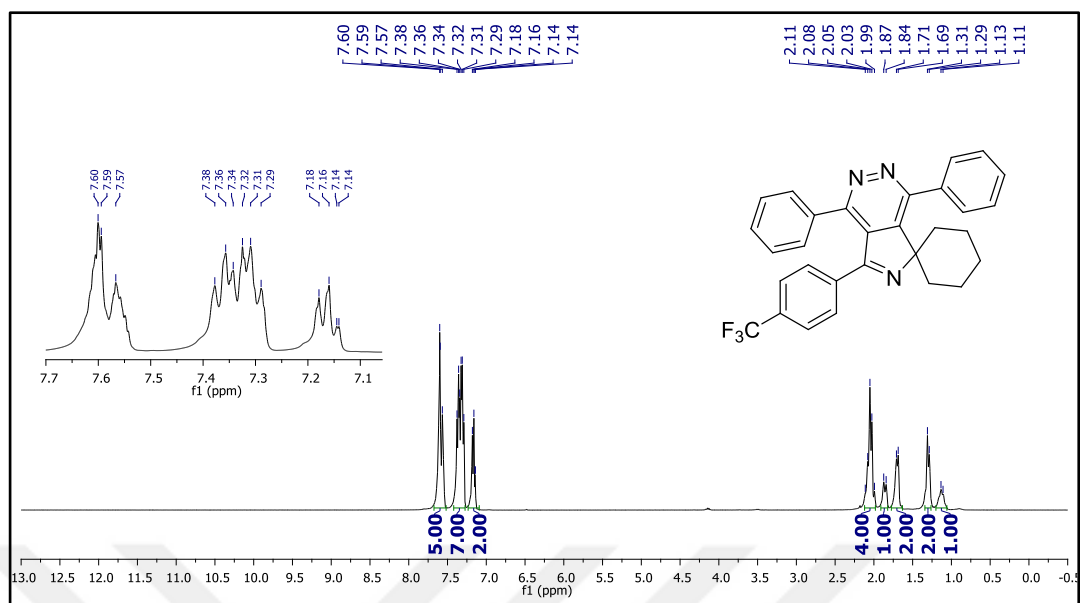


Figure 173. ¹H NMR spectrum of compound 35l.

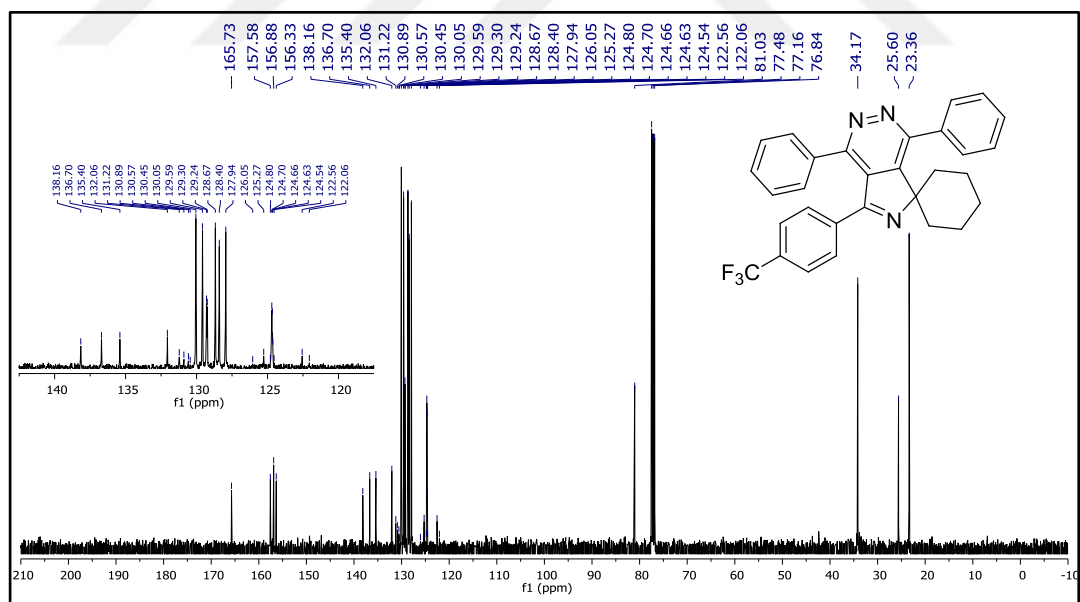


Figure 174. ¹³C NMR spectrum of compound 35l.

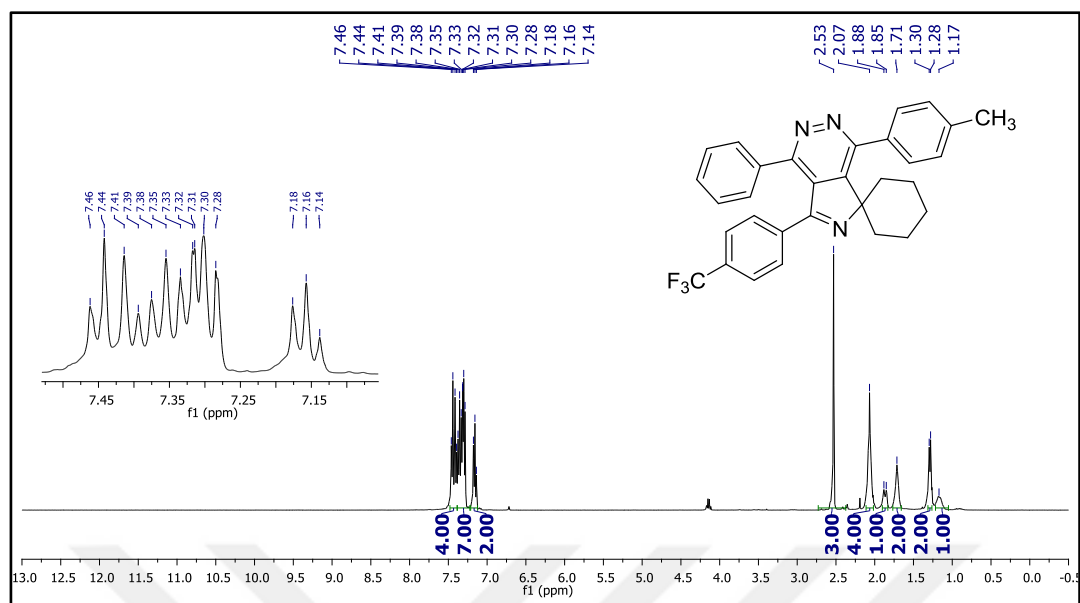


Figure 175. ¹H NMR spectrum of compound 35m.

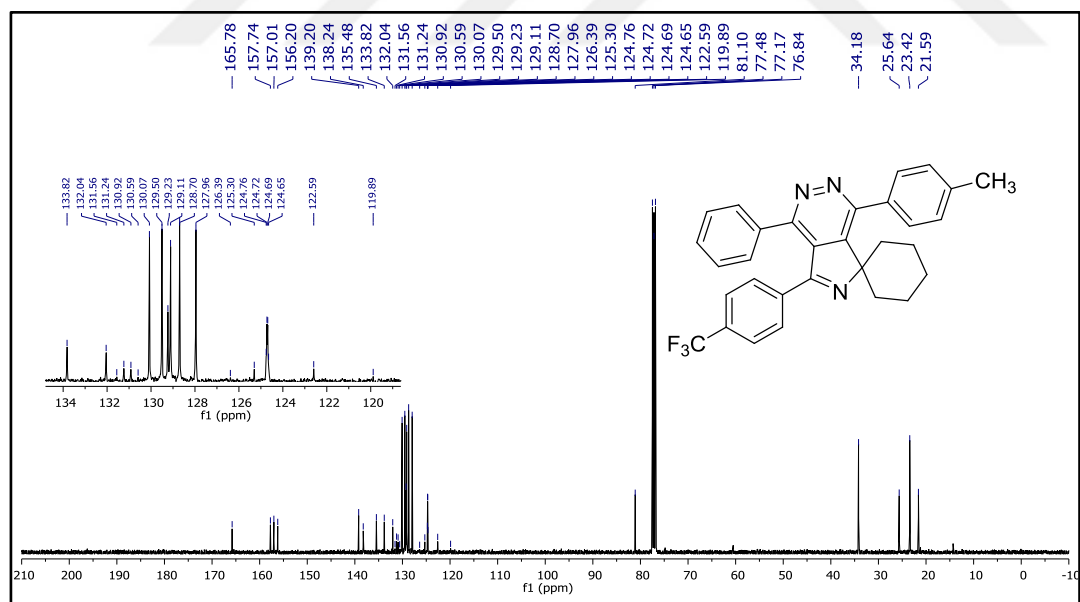


Figure 176. ¹³C NMR spectrum of compound 35m.

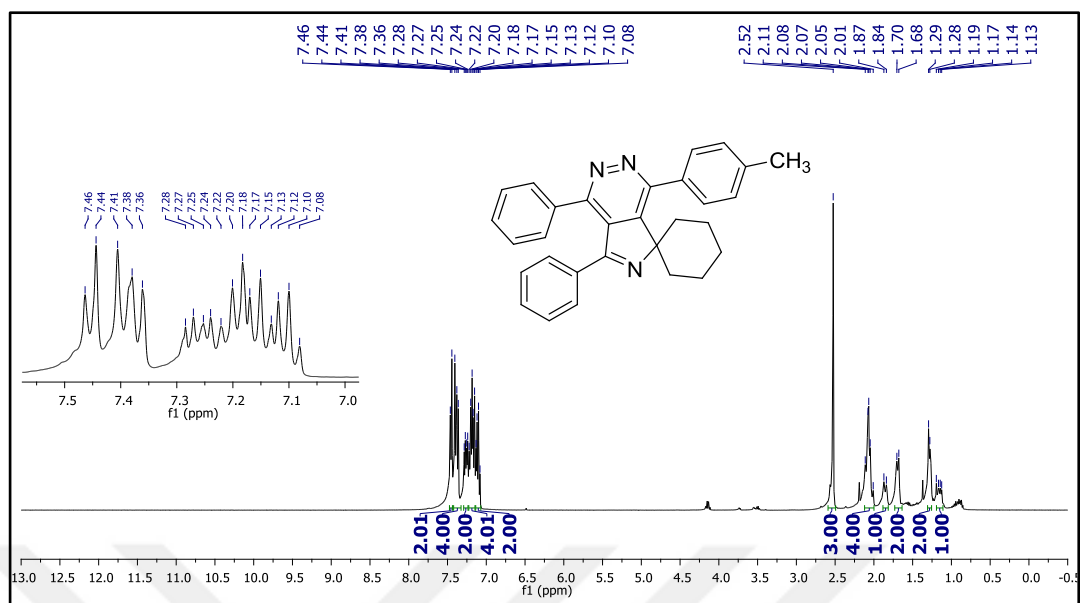


Figure 177. ¹H NMR spectrum of compound 35n.

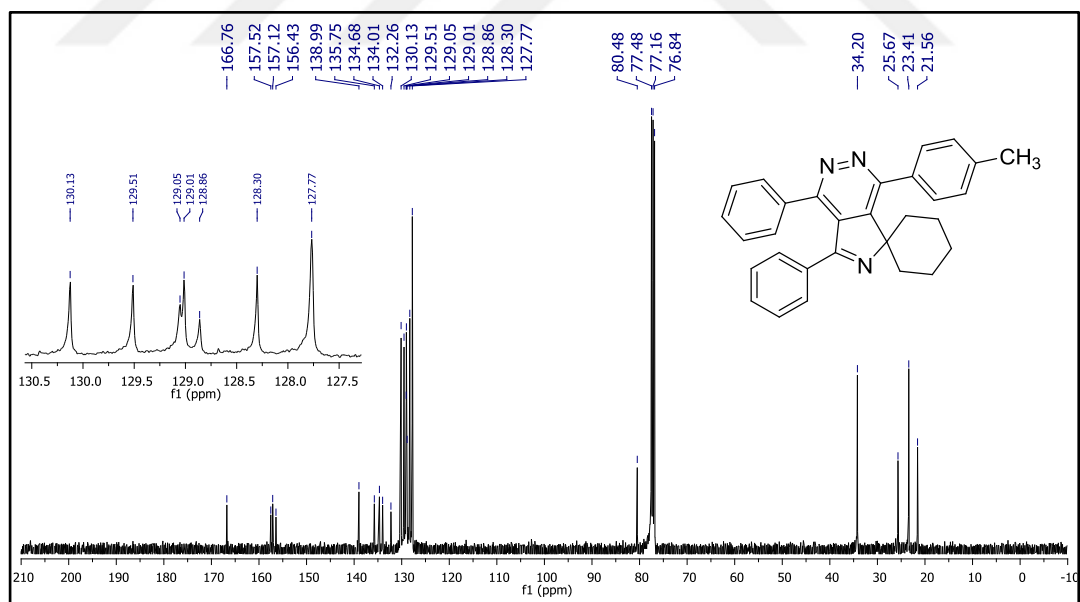


Figure 178. ¹³C NMR spectrum of compound 35n.

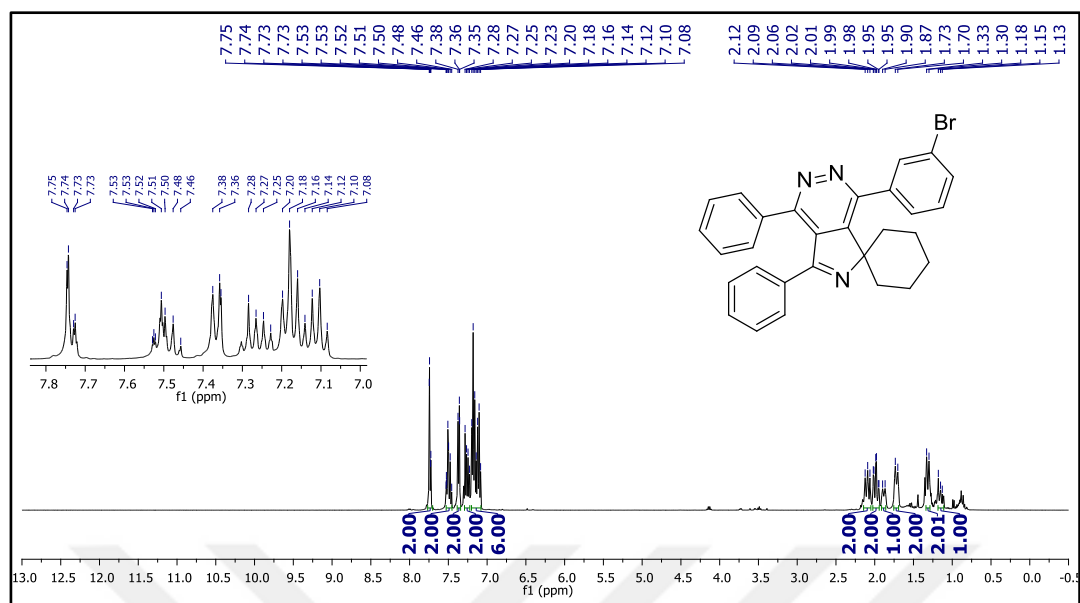


Figure 179. ¹H NMR spectrum of compound **35o**.

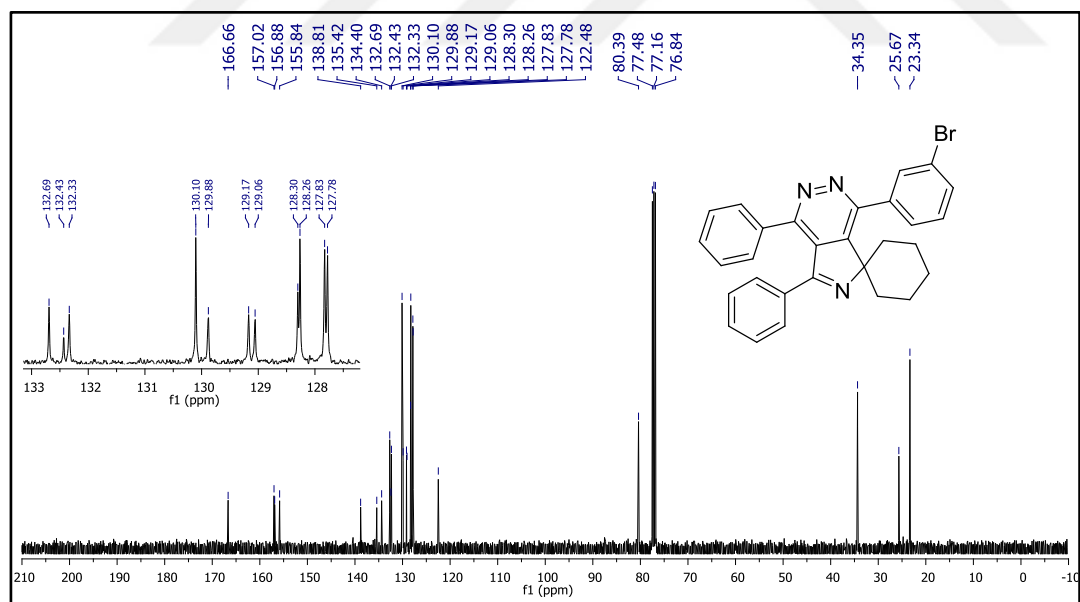


Figure 180. ¹³C NMR spectrum of compound **35o**.

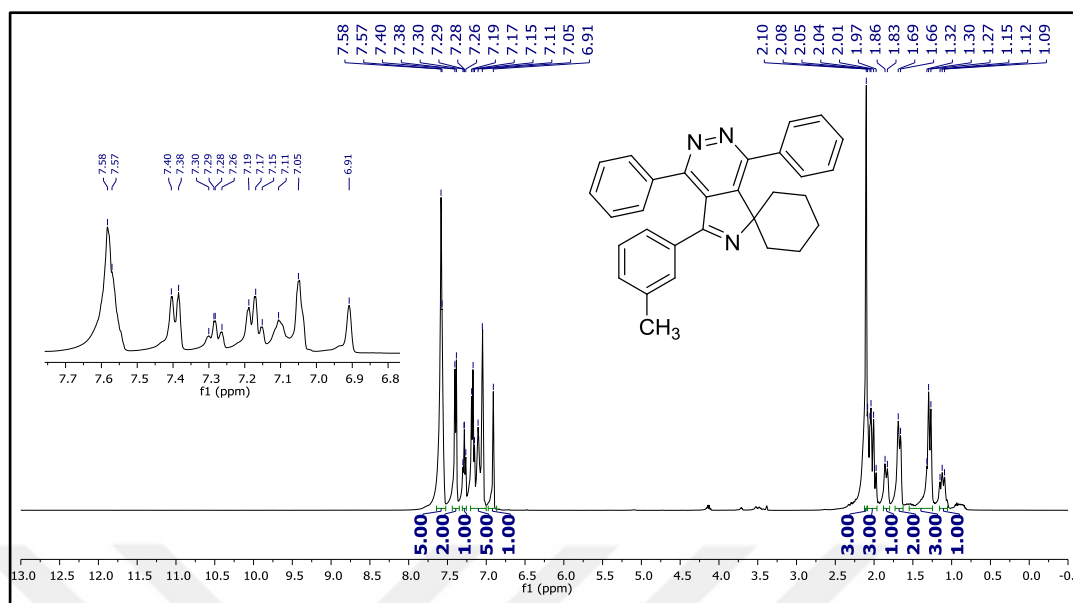


Figure 181. ¹H NMR spectrum of compound 35p.

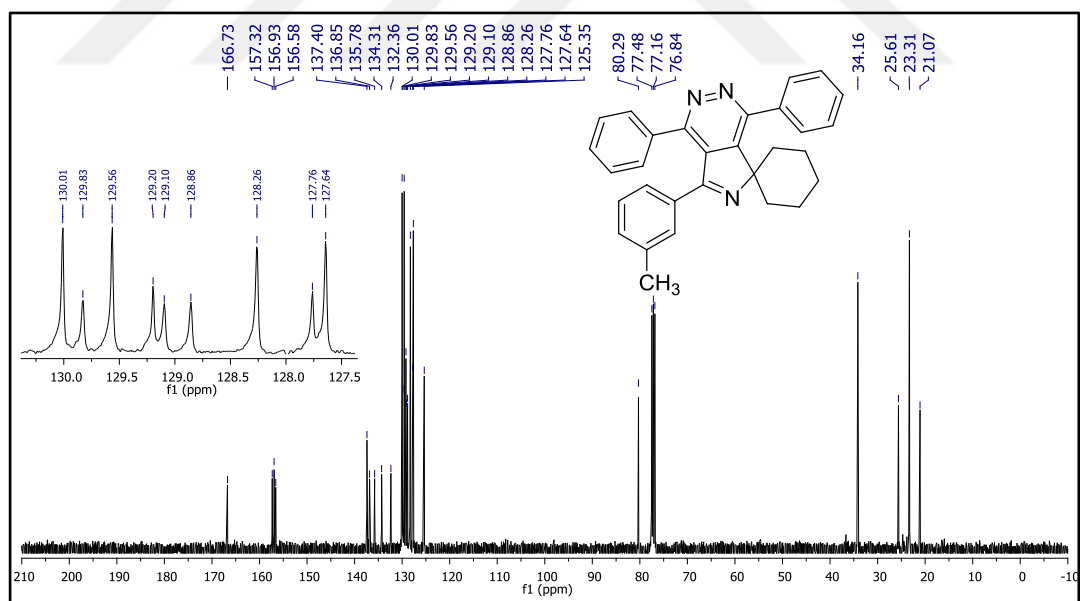


Figure 182. ¹³C NMR spectrum of compound 35p.

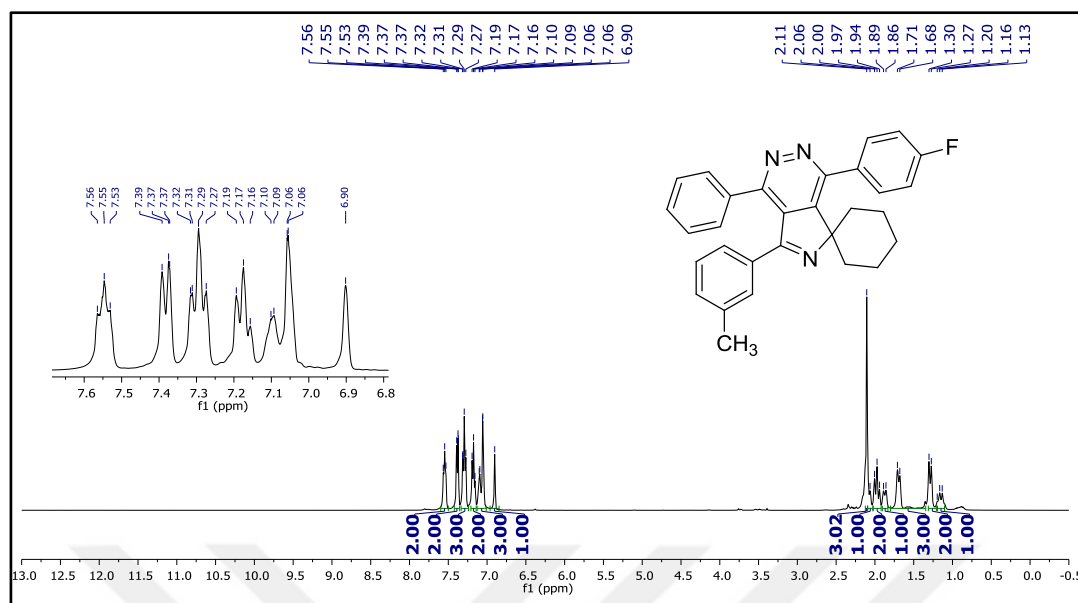


Figure 183. ¹H NMR spectrum of compound **35q**.

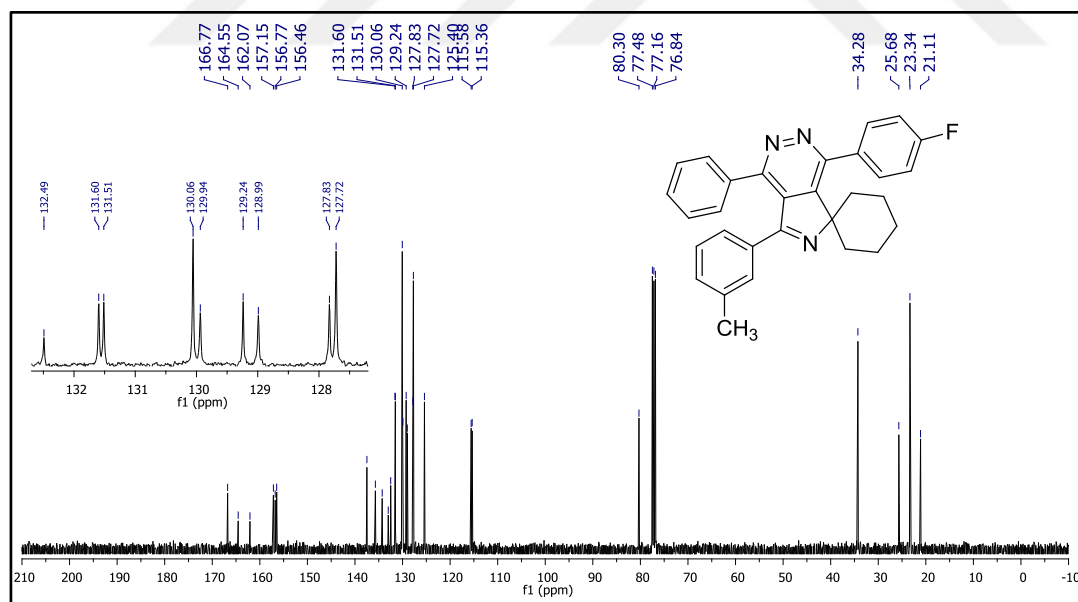


Figure 184. ¹³C NMR spectrum of compound **35q**.

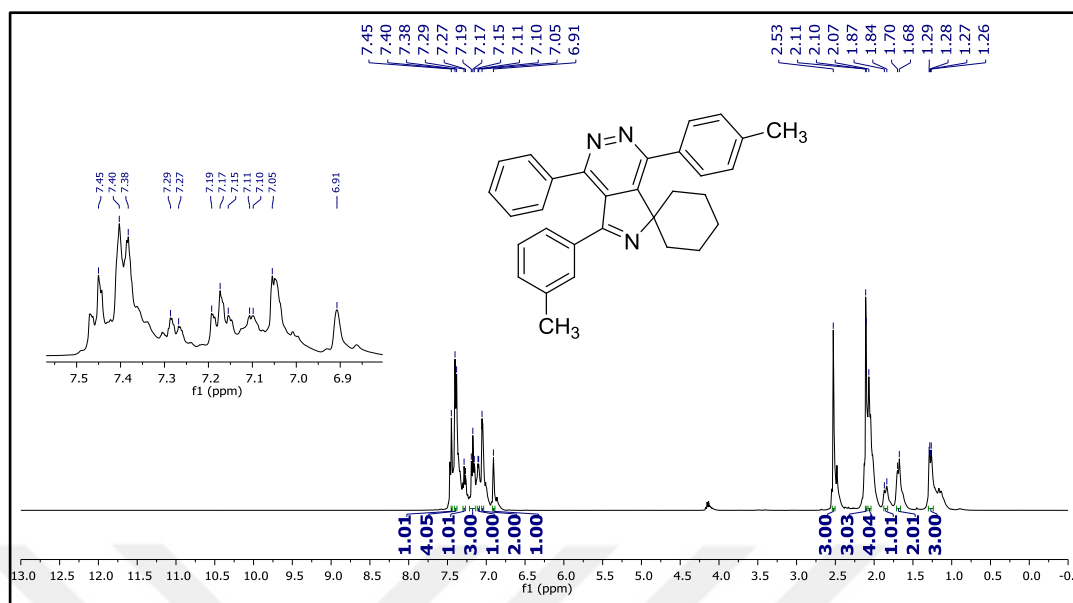


Figure 185. ¹H NMR spectrum of compound 35r.

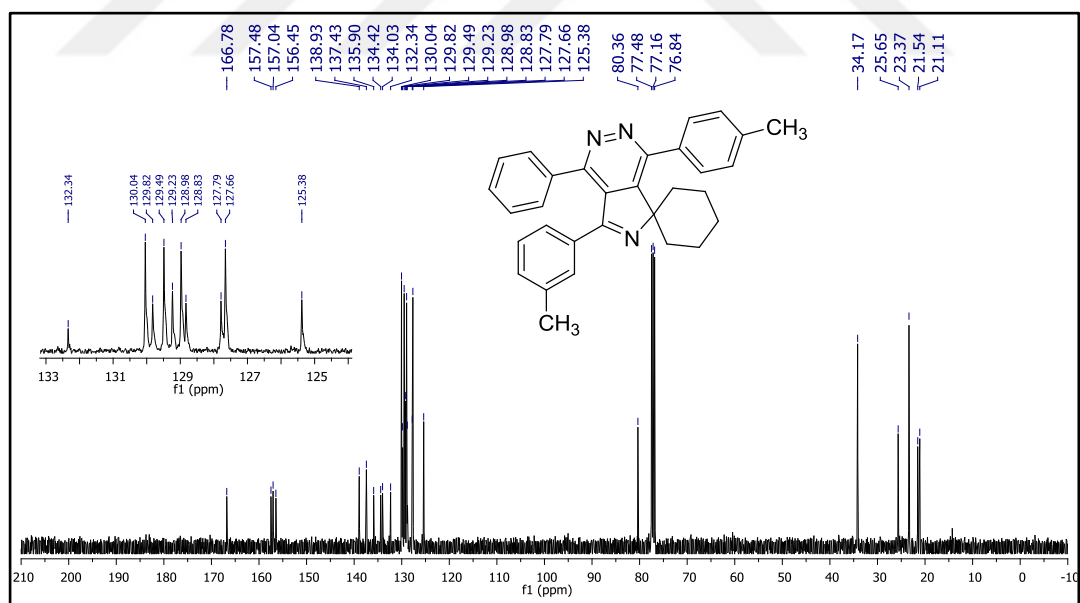


Figure 186. ¹³C NMR spectrum of compound 35r.

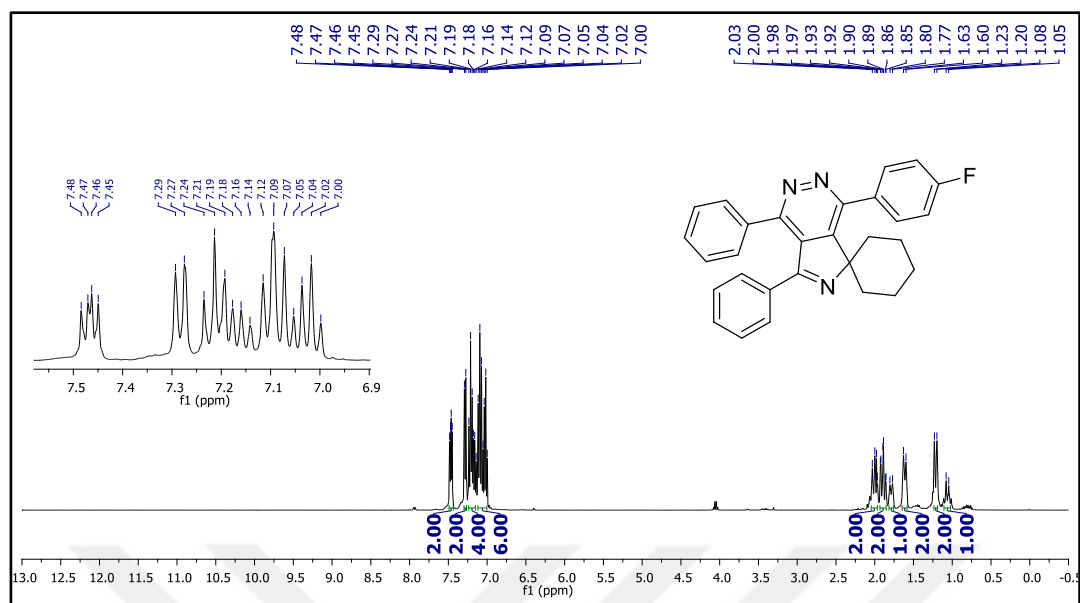


Figure 187. ¹H NMR spectrum of compound 35s.

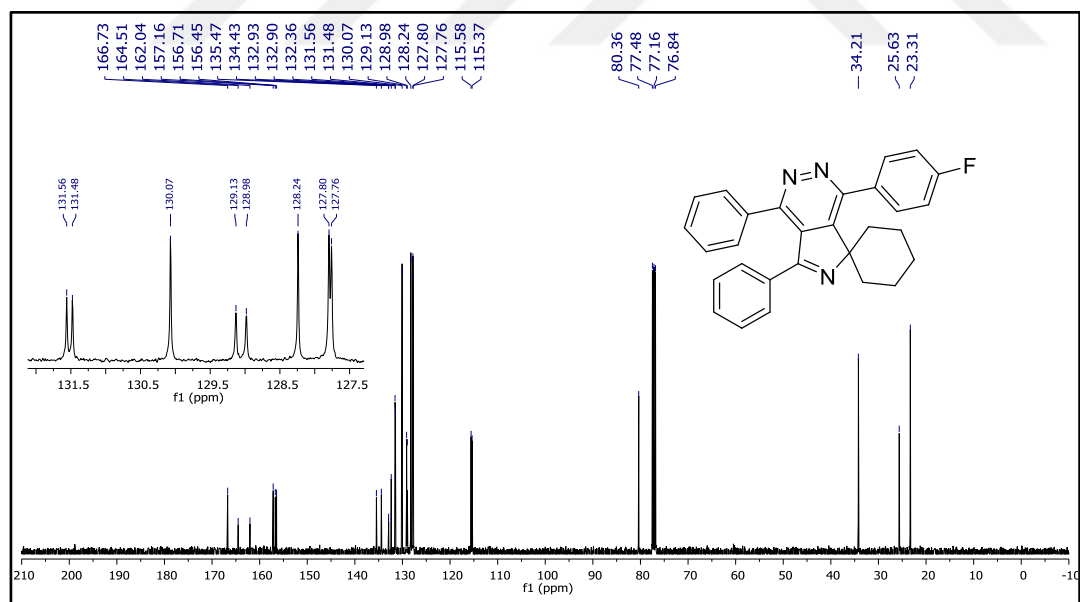


Figure 188. ¹³C NMR spectrum of compound 35s.

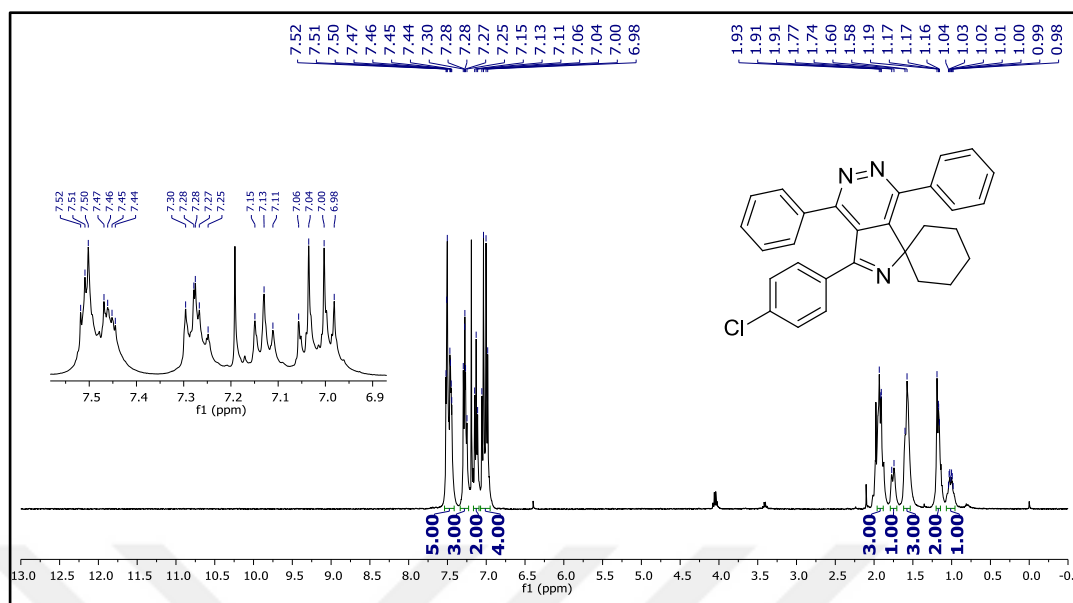


Figure 189. ¹H NMR spectrum of compound 35t.

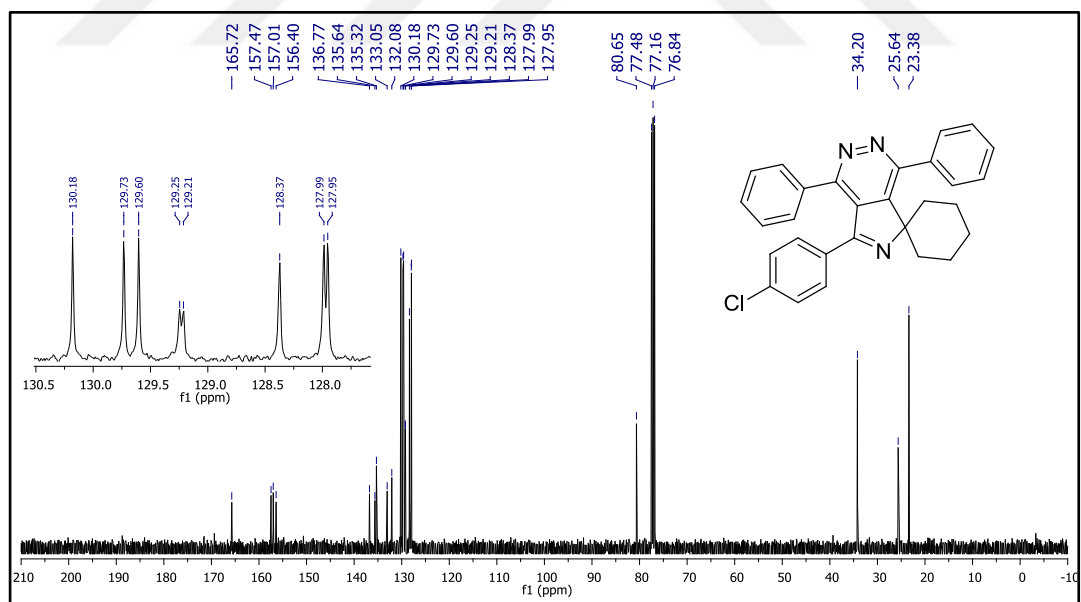


Figure 190. ¹³C NMR spectrum of compound 35t.

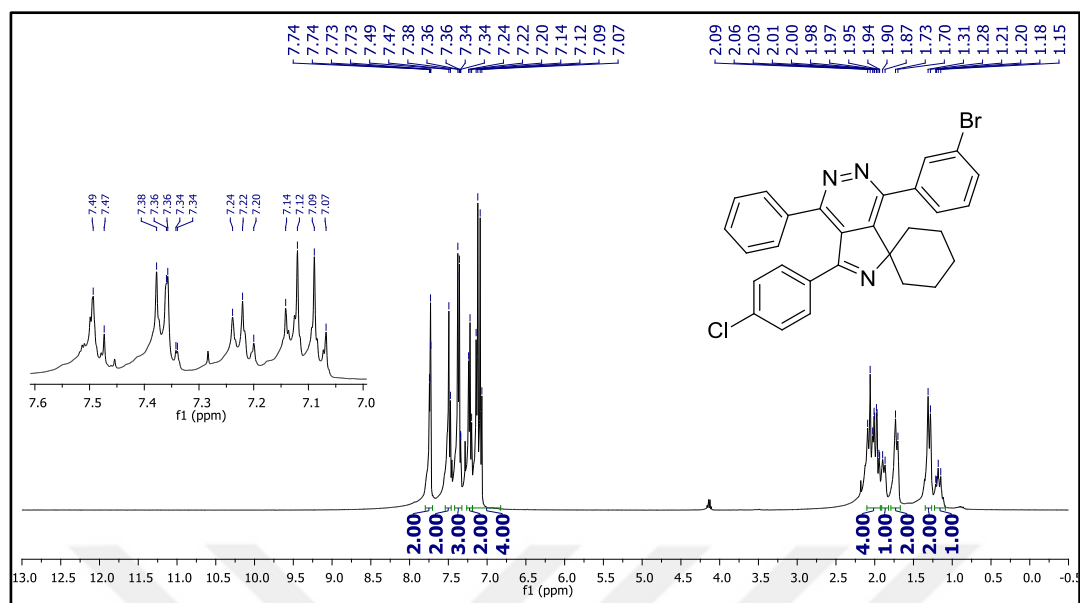


Figure 191. ¹H NMR spectrum of compound 35u.

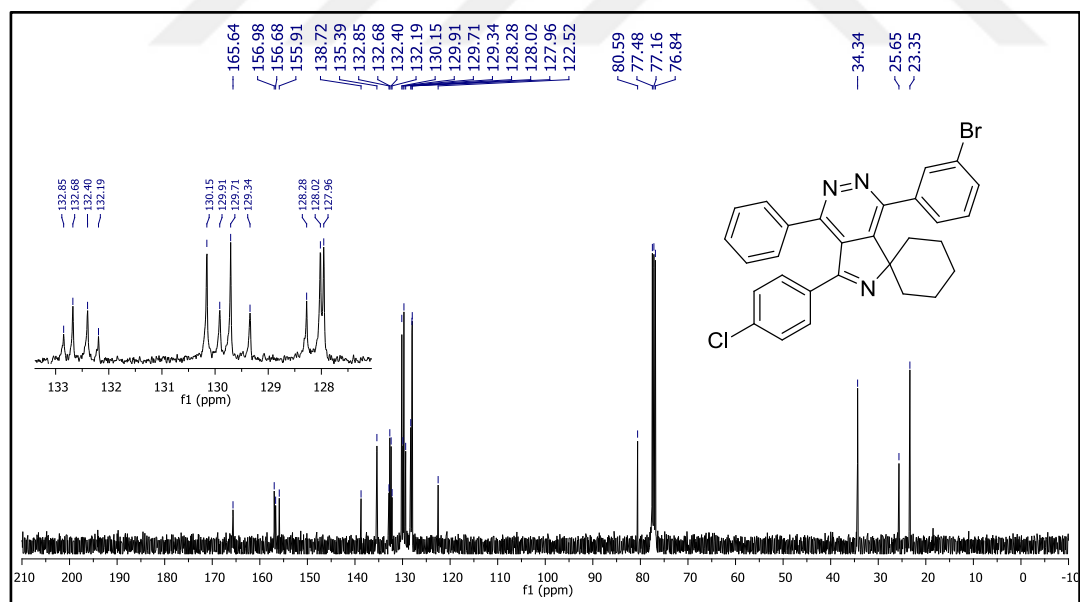


Figure 192. ¹³C NMR spectrum of compound 35u.