DEVELOPMENT OF NEW METHODOLOGIES FOR SYNTHESES OF 1,3-BIS-PYRAZOLE, 1,3-BIS-BENZO[*b*][1,4]DIAZEPINE AND HEXAHYDROIMIDAZO[1,2-*a*]PYRIDINE DERIVATIVES

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ABSTRACT

DEVELOPMENT OF NEW METHODOLOGIES FOR SYNTHESES OF 1,3-BIS-PYRAZOLE, 1,3-BIS-BENZO[*b*][1,4]DIAZEPINE AND HEXAHYDROIMIDAZO[1,2-*a*]PYRIDINE DERIVATIVES

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Pyrazoles are the nitrogen-containing five membered heterocycles. They possess a primary position in the design and synthesis of novel biologically active agents. In particular, bis-pyrazoles receive a gaining interest in therapeutic chemistry. Benzodiazepines are another class of heterocyclic compounds in the field of drugs and pharmaceuticals. Notably, 1,4-benzodiazepines are benefical as analgesics, muscle relaxants, sedatives and anticancer drugs. In addition, imidazo[1,2-*a*]pyridines are important fused heterocycles due to their presence in large number of bioactive compounds. In particular, hexahydroimidazo[1,2-*a*]pyridine derivatives have gained considerable attention in pharmaceutical chemistry and materials science. In this thesis, new methodologies for synthesis of 1,3-bis-pyrazoles, 1,3-bis-benzo[*b*][1,4]diazepines and hexahydroimidazo[1,2-*a*]pyridines from bis-α,β-alkynic ketones were developed. In the first part of the thesis study, a variety of bis-α,β-alkynic ketones as the starting materials have been synthesized by the reaction of 1,6-heptadiynes with aryloyl chlorides via Sonogashira cross coupling reaction. Then, their addition and cyclocondensation reactions were investigated, which

provided the formation 1,3-bis-pyrazoles in the presence of benzylhydrazine dihydrochloride and 2-hydrazinopyridine. In the second part of this study, the reaction conditions were improved for the synthesis of 1,4-diazepine compounds. The conjugate addition and cyclocondensation reactions of bis-α,β-alkynic ketones with *o*-phenylenediamine yielded various 1,3-bis-benzo[*b*][1,4]diazepine derivatives. In the last part, an efficient one-pot method has been developed for the synthesis of hexahydroimidazo[1,2-*a*]pyridines from bis-α,β-alkynic ketones. When reacted with ethylenediamine, bis-α,β-alkynic ketones provided the formation of new 5-alkylidene-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine derivatives in moderate to good yields.

Keywords: Heterocyclic compounds, bis-α,β-alkynic ketones, 1,3-bis-pyrazoles, 1,3-bis-benzo[*b*][1,4]diazepines, hexahydroimidazo[1,2-*a*]pyridines.

ÖZ

1,3-BİS-PİRAZOL, 1,3-BİS-BENZO[*b*]|[1,4]DİAZEPİN VE HEKZAHİDROİMİDAZO[1,2-*a*]PİRİDİN TÜREVLERİNİN SENTEZİ İÇİN YENİ YÖNTEMLERİN GELİŞTİRİLMESİ

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Pirazoller, azot içeren beş üyeli heterosiklik bileşiklerdir. Yeni biyoaktif ajanların tasarımında ve sentezinde birincil bir konuma sahiptirler. Özellikle, bis-pirazoller terapötik kimyada giderek daha fazla ilgi görmektedir. Benzodiazepinler, ilaç ve farmasötikler alanında bir başka heterosiklik bileşik sınıfıdır. Bilhassa, 1,4-benzodiazepinler analjezik, kas gevşetici, yatıştırıcı ve antikanser ilaçları olarak faydalıdır. Ayrıca, imidazo[1,2-*a*]piridinler çok sayıda biyoaktif bileşikte bulunmaları nedeniyle önemli kaynaşmış heterosiklik yapılardır. Özellikle, hekzahidroimidazo[1,2-*a*]piridinler farmasötik kimya ve malzeme biliminde çok ilgi görmüştür. Bu tez çalışmasında, bis-α,β-alkinik ketonlardan 1,3-bis-pirazol, 1,3-bis-benzo[*b*][1,4]diazepin ve hekzahidroimidazo[1,2-*a*]piridinlerin sentezi için yeni metodolojiler geliştirildi. Tez çalışmasının ilk bölümünde, 1,6-heptadiyenlerin ariloil klorürlerle Sonogashira tepkimeleri ile reaksiyonundan başlangıç malzemesi olarak çeşitli bis-α,β-alkinik ketonlar sentezlendi. Daha sonra, bunların

benzilhidrazin dihidroklorür ve 2-hidrazinopiridin varlığında 1,3-bis-pirazollerin oluşumunu sağlayan katılma ve siklohalkalaşma reaksiyonları incelendi. Çalışmanın ikinci bölümünde, 1,4-diazepin bileşiklerinin sentezi için reaksiyon koşulları optimize edildi ve bu koşullarda bis-α,β-alkinik ketonların *o*-fenilendiamin ile konjuge ekleme ve siklohalkalaşma reaksiyonları çeşitli 1,3-bis-benzo[*b*][1,4]diazepin türevlerini oluşturdu. Son bölümde ise, bis-α,β-alkinik ketonlardan hekzahidroimidazo[1,2-*a*]piridinlerin sentezlenmesi için etkili bir tek balon yöntemi geliştirilmiştir. Etilendiamin ile reaksiyona girdiğinde, bis-α,β-alkinik ketonlar orta ile iyi verimlerde yeni 5-alkiliden-2,3,5,6,7,8-hekzahidroimidazo[1,2-*a*]piridin türevlerinin oluşumunu sağlamıştır.

Anahtar Kelimeler: Heterosiklik bileşikler, bis-α,β-alkinik ketonlar, 1,3-bis-pirazoller, 1,3-bis-benzo[*b*][1,4]diazepinler ve hekzahidroimidazo[1,2-*a*]piridinler.

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CHAPTER 1

INTRODUCTION

Organic chemistry is the chemistry of compounds formed by carbon and other elements, which are present in living beings, natural products, and everything containing carbon.[1] Living beings consist of many organic compounds. For example, many organic molecules such as the nucleic acids, creating DNA and RNA, amino acids that forms proteins, and carbohydrates promote life. Organic compounds in nature include essential oils and alkaloids. These could be extracted from plants by distilling or crushing with acids. In addition, natural organic products can be employed to cure diseases. Therefore, the main role of organic molecules in the pharmaceutical industry is inevitable. That is, they take place in every aspect of our lives.[1,2]

In particular, heterocyclic compounds are known as the cyclic organic compounds that include at least one heteroatom, commonly nitrogen, oxygen and sulphur in their ring skeletons. There are heterocyclic rings comprising other hetero atoms as well. They play a vital role in many branches of science, such as medicinal chemistry, biochemistry and materials science.[3] For instance, heterocyclic rings are found in biologically active compounds and many natural products as DNA, RNA, haemoglobin and vitamins. Moreover, heterocycles are present as a key constituent in synthetic pharmaceuticals, agrochemicals and veterinary products. For example, a large number of natural and synthetic drugs like atropine, procaine, diazepam and captopril includes heterocyclic units in their structures (Figure 1).[4]

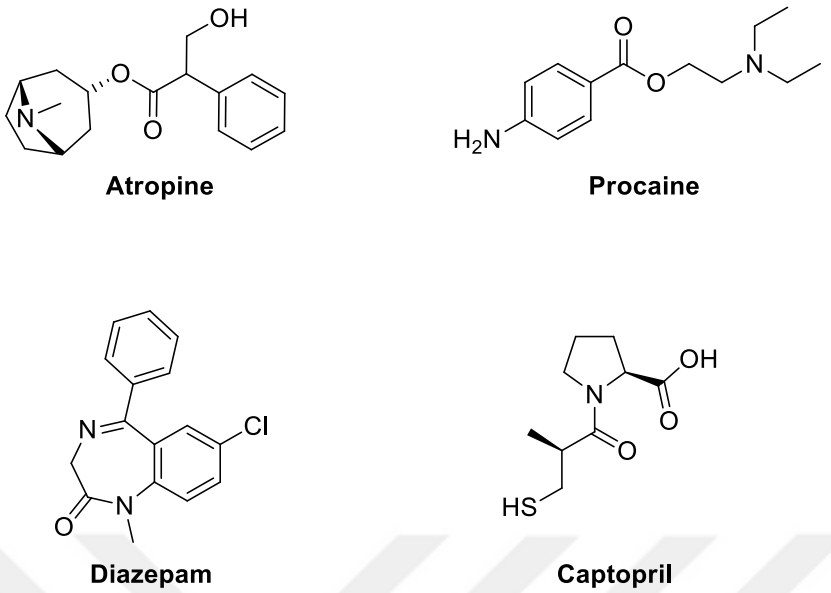


Figure 1. Natural and synthetic drugs containing heterocyclic units.

In addition to this, heterocylic structures have a wide range of uses in materials science as developers, copolymers and dye-stuff.[5] Therefore, the development of novel and efficient approaches for the synthesis of heterocyclic structures is of great importance.[6] In particular, five, six and seven-membered heterocyclic compounds, like pyrazoles, benzodiazepines and imidazo[1,2-a]pyridines, have attracted considerable attention due to their importance in the pharmaceutical chemistry and organic synthesis.[7]

1.1 Pyrazoles

Nitrogen-containing heterocycles are the main structures of many biologically active compounds and have a wide range of applications in chemistry, biology and other sciences. Among them, pyrazoles are one of the most important examples of aromatic heterocyclic compounds, including two nitrogen atoms at 1 and 2 positions in their five-membered structures (Figure 2).[8]

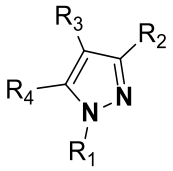
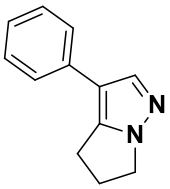


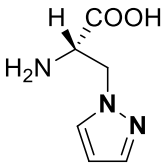
Figure 2. General structure of pyrazoles.

Structural changes at different positions of pyrazole molecules allow them to acquire new properties. Therefore, the pyrazole nucleus in diversified structures provides a variety of applications in distinct areas like technology, medicine and agriculture.[9] They are present in natural products such as alkaloids and amino acids (Figure 3) and include a broad spectrum of biological activities like antiviral, anticancer, anti-inflammatory, antibacterial, analgesic, antifungal and cardiovascular properties. Moreover, these compounds allow the formation of scaffolds necessary to produce durable and qualified drugs. For example, a number of pyrazole derivatives have been used as anti-Alzheimer agents in the development of new anti-Alzheimer drugs.[10] Additionally, studies on the use of natural pyrazoles as effective chemotherapeutics are ongoing.[11]

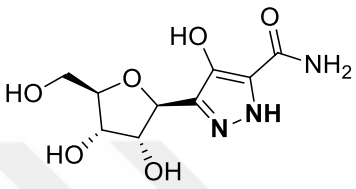
Apart from this, various substituted pyrazoles are employed as chelating and extracting reagents for many metal ions. Moreover, they are starting materials for the formation of condensed heterocyclic systems and form a template for combinatorial chemistry.[11]



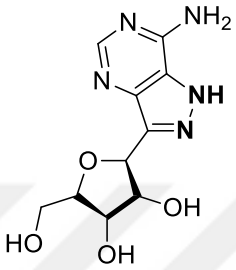
Withasomnine



L-Amino-*ß* (pyrazolyl-*N*)-propanoic acid



Pyrazofurin



Formycin

Figure 3. Natural products including pyrazole cores.

1.1.1 Bis-pyrazoles

Among many pyrazole derivatives, bis-pyrazole compounds enable the development of diverse bioactive molecules as antioxidant, anti-inflammatory, antitubercular, antiviral, and antimicrobial agents, as shown in Figure 4. They attract a great interest due to their diverse biological activities.[12,13]

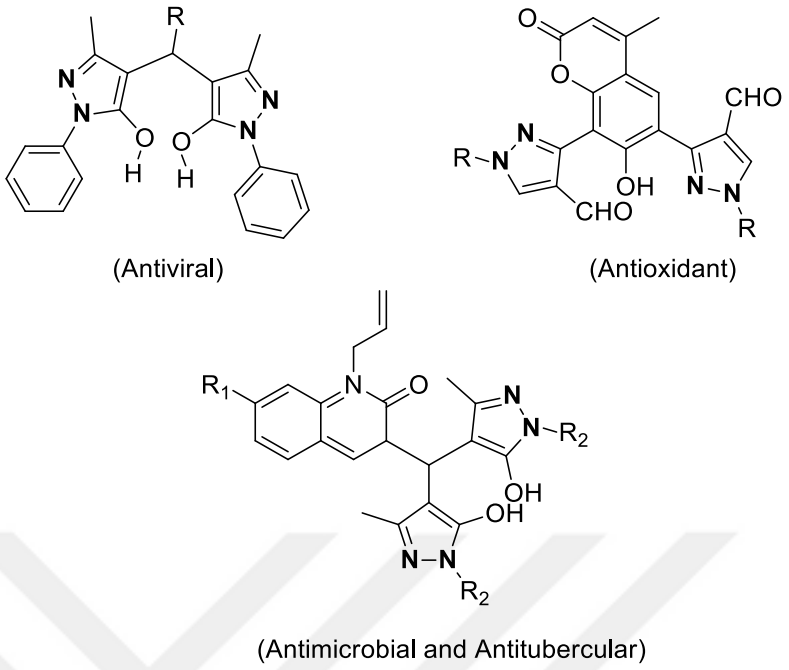


Figure 4. Structures of some bioactive bis-pyrazole derivatives.

1.1.2 Importance of Bis-pyrazoles

Bis-pyrazoles have a vital role in medicinal chemistry as anticancer agents. Recent studies demonstrated that the enhancement of the number of pyrazole rings in the molecules enables to promote bioactivity. In this context, the development of new bis-pyrazole derivatives can enhance the anticancer activity of these molecules since compounds consisting of pyrazole rings demonstrate good growth inhibitory activities against MIAPaCa-2, MCF-7 and HeLa human cancer cells.[14]

Apart from that, they are significant building blocks for the formation of coordination complexes with beneficial applications in many fields such as catalysis, biology and agricultural biotechnology. These coordination complexes that consist of pyrazole nucleus could allow the construction of novel compounds to explore different functionalities and to investigate their chemical and electronic behaviours.

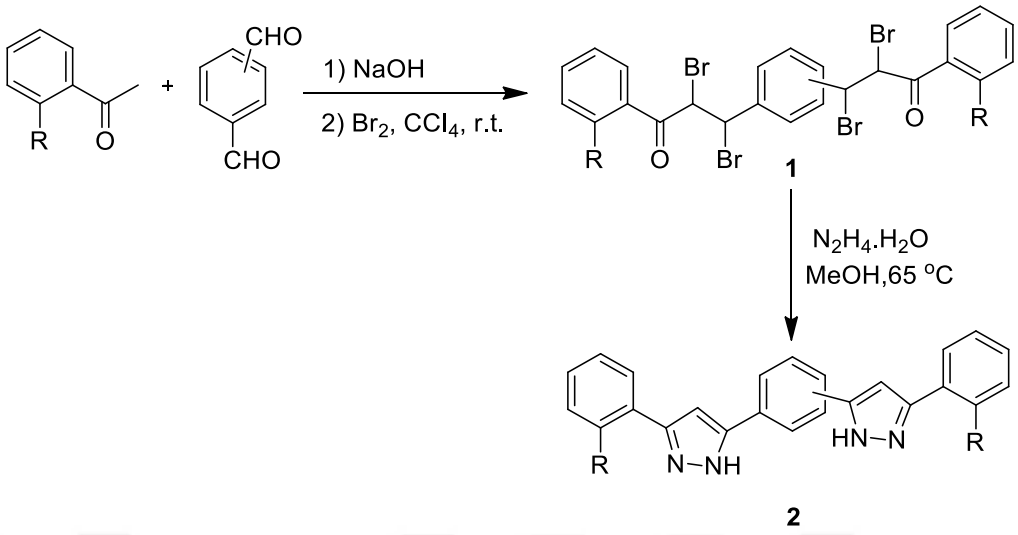
For instance, pyrazole based coordination complexes formed with cobalt, copper and iron have been proven to indicate exceptional electronic properties, catalytic selectivity and antioxidant activities as shown by recent literature studies. In addition, pyrazolate complexes containing cadmium, nickel and mercury have been demostrated to be effective antimicrobial agents against Gram-positive and Gram-negative bacteria.[15]

Inspired by these properties of bis-pyrazoles, many researchers have been directed towards the synthesis of these molecules. Therefore, there is intense interest in finding new derivatives of these molecules.[15]

1.1.3 Synthesis of Bis-pyrazoles

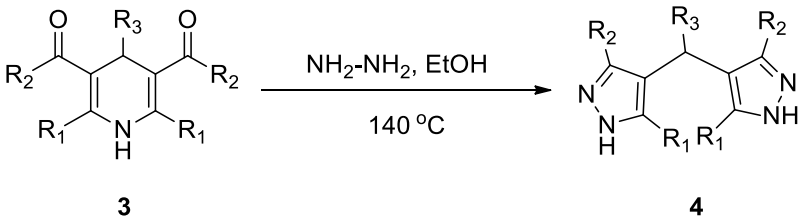
Pyrazoles and their derivatives exhibit significant biological and pharmaceutical activities as well as they are benefical intermediates for a variety of industrial products. Therefore, many methods have been developed for the synthesis of compounds formed with pyrazole cores.[16] In general, the cycloaddition and condensation reactions of carbonyl systems allow the synthesis of bis-pyrazole compounds.[9] Some of them are shown below.

In 2003, Diana and co-workers developed a method for the synthesis of bis-pyrazole derivatives **2** by the reaction of bis-chalcone tetrabromo derivatives **1** with hydrazine hydrate in good yields as shown in Scheme 1.[17]



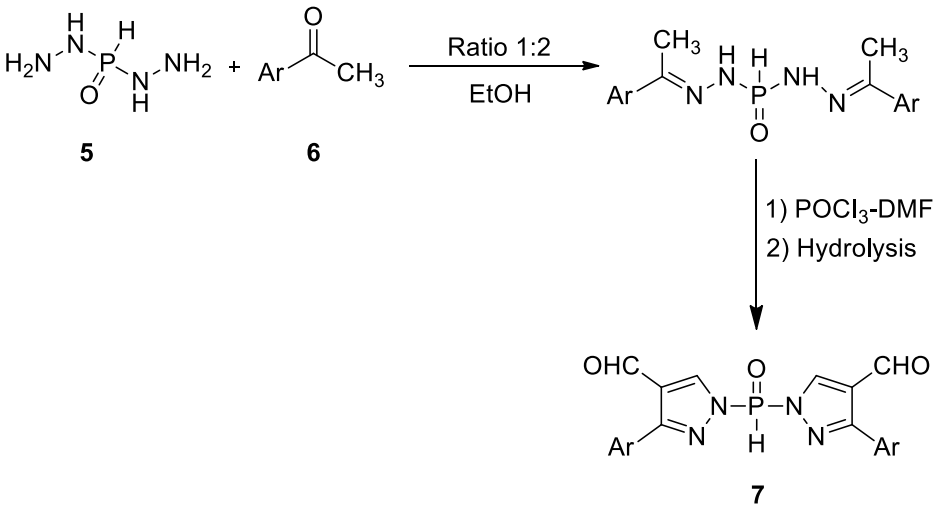
Scheme 1. Synthesis of bis-pyrazole compounds from bis-chalcones.

One year later, Bisenieks research group prepared bis-pyrazolyl methanes **4** with the reaction between 3,5-carbonyl substituted 1,4-dihydropyridines **3** and hydrazine hydrates with EtOH in sealed tube (Scheme 2). This reaction provided the formation of new bis-pyrazole compounds in high yields.[18]



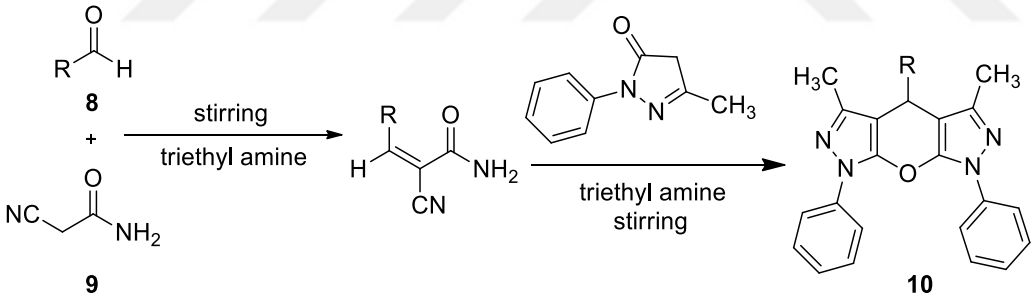
Scheme 2. Synthesis of bis-pyrazolyl methane derivatives.

Salah *et al.* obtained bis-pyrazole derivatives **7** with a hydro-phosphoryl substituent by the reaction of phosphonic dihydrazides **5** with methyl ketone derivatives **6**, followed by the Vilsmeier-Haack reaction, as demonstrated in Scheme 3.[19]



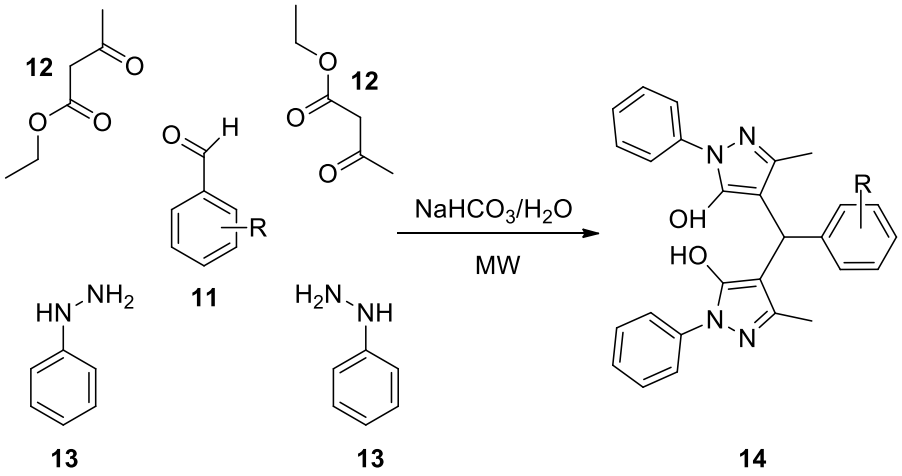
Scheme 3. Synthesis of bis-pyrazoles with a hydro-phosphoryl substituent.

In 2015, the synthesis of novel oxino bis-pyrazoles **10** was carried out by the reaction of aldehydes **8** and cyanoacetamide **9** with using triethylamine, as given in Scheme 4, by Ghafoor and co-workers. [20]



Scheme 4. Synthetic pathway of bis-pyrazole compounds with alkyl and aryl aldehydes.

Recently, Robert and Maddila described a novel approach for the synthesis of bis-pyrazole derivatives **14** with the reaction of various benzaldehyde **11**, ethyl-3-oxobutanoate **12** and phenylhydrazine **13** in the presence of microwave irradiation and sodium bicarbonate catalyst (Scheme 5).[21]



Scheme 5. Synthesis of bis-pyrazole derivatives under microwave irradiation.

1.2 Benzodiazepines

Another class of remarkable heterocyclic compounds is the benzodiazepines (BZDs). They are bicyclic molecules composed from benzene and fused seven membered ring including two nitrogen atoms. The relative positions of nitrogen atoms determine the chemical properties of these compounds.[22] They have different species such as 1,2-BZDs, 1,3-BZDs, 1,4-BZDs, 1,5-BZDs, 2,3-BZDs, and 2,4-BZDs, as illustrated in Figure 5.[23]

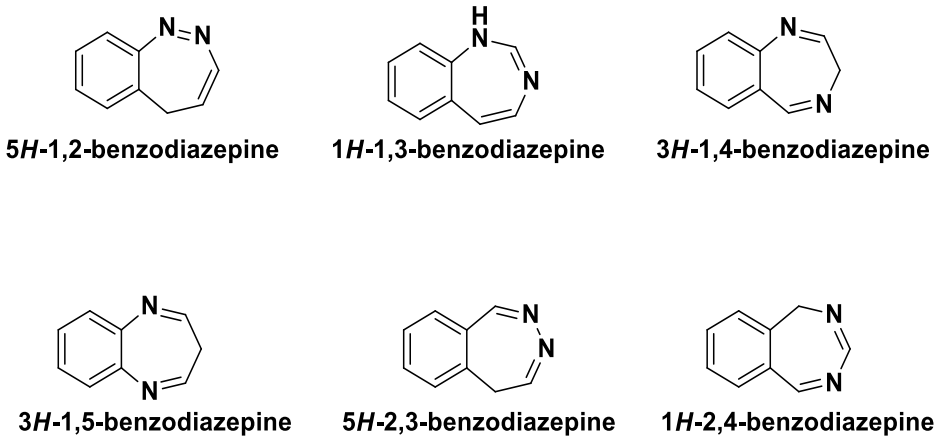


Figure 5. Structures of BDZs.

The existence of benzodiazepine moiety in compounds provides a broad range of pharmacological and biological activities. Therefore, they are generally employed as anticonvulsants, anti-anxiety drugs, analgesics, sedatives, antidepressants and anti-inflammatory agents.[24] Moreover, since benzodiazepines are privileged molecules used in treatment of cancer, viral infection, and cardiovascular disorders, they take more attention in medicinal chemistry. Besides this they are also employed in crop control as pesticides, antifeedants for insect control, herbicides and fungicides.[25]

There are many synthetic methods for benzodiazepines, but the most common is the condensation reaction of carbonyl compounds with *o*-phenylenediamines (OPDs) using several catalysts or catalyst-free systems. Recently, new methods for their synthesis continue to be developed, taking into account properties such as reaction efficiency, purity and environmental friendliness.[23]

1.2.1 1,4-Benzodiazepines

In particular, the most abundant type of benzodiazepines are 1,4-benzodiazepines. These compounds, found in many natural alkaloids, have been noticed in 1960s and they were initially marketed as tranquilizers under the trade name Librium.[26] The synthesis of them has recently become a focus of interest due to its versatile use in the medicinal chemistry.[27]

1.2.2 Importance of 1,4-Benzodiazepines

1,4-benzodiazepines have several applications in the organic synthesis, medicinal and industrial fields. These compounds demonstrate varied biological and pharmacological activities.[23] For example, they are known as muscle relaxants, blood pressure reducers and central nervous system depressants. Beside this, they are employed as anti-microbials, anxiolytics, anticonvulsants and antipsychotics.[28] Due to these properties, there are many available drugs consisting of 1,4-

benzodiazepine rings, such as diazepam, halazepam, prazepam and alprazolam (Figure 6).[29]

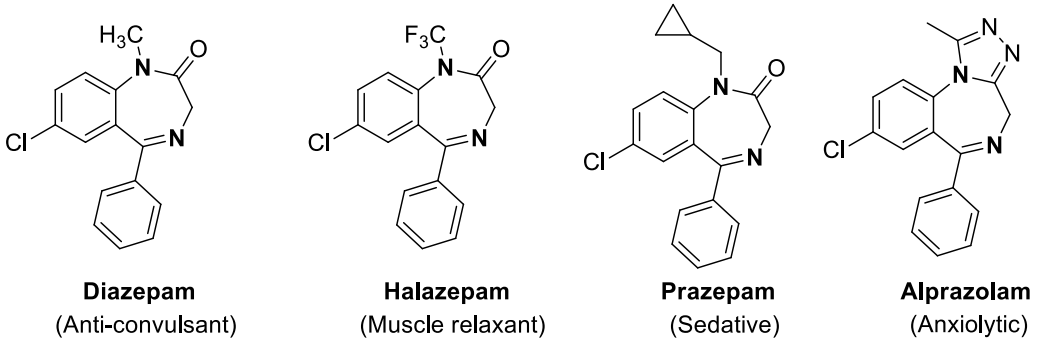


Figure 6. Some available drugs containing the 1,4-benzodiazepine ring.

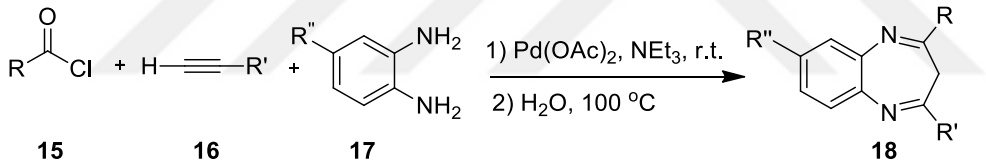
What makes 1,4-benzodiazepine cores so important in medicine and pharmacy is their connection to the central nervous system. Drugs containing them are active both inside and outside the central nervous system. These drugs become active according to specific binding sites within $GABA_AR$, which is the central nervous system benzodiazepine receptor.[30,31] Different side groups found in 1,4-benzodiazepines affect the molecule's binding to $GABA_AR$, allowing its pharmacological properties to be fine-tuned.[31]

Apart from the above mentioned, 1,4-benzodiazepine derivatives have other applications. For instance, they are used as essential intermediates for the production of several fused ring systems like oxazino or furano benzodiazepines and they also operate as dyes for acrylic fibers in photography. Due to these unique properties of 1,4-benzodiazepines, the studies on their synthesis are ongoing and thus, an increase in the number of compounds with 1,4-benzodiazepine scaffolds in the coming years is expected.[32]

1.2.3 Synthesis of 1,4-Benzodiazepines

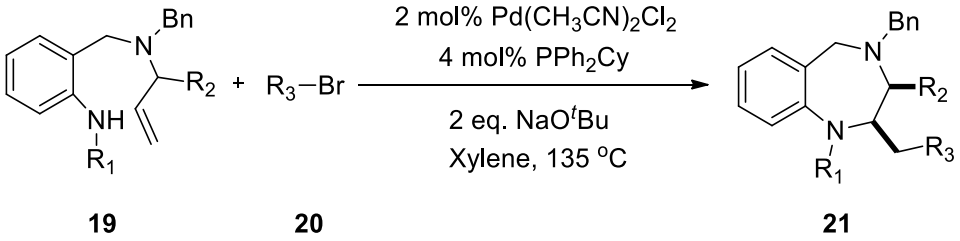
Due to the diversity of application areas of 1,4-benzodiazepines, many synthesis methods for them have been shown in the literature. In general, the condensation reactions of *o*-phenylenediamines (OPDs) provides the construction of 1,4-benzodiazepines in the presence of α,β-unsaturated ketones.[32] Some of them are demonstrated below.

In 2007, Srinivasan research group described a novel one-pot three-component method to synthesize 2,4-disubstituted 1,4-benzodiazepines **18** from the reaction of acid chloride **15**, terminal alkyne **16** and *o*-phenylenediamine **17** in the presence of water solvent. After obtaining unsaturated ketone, its Michael addition and cyclocondensation reaction with *o*-phenylenediamine **17** *in situ* gave the expected product, as depicted in Scheme 6.[33]



Scheme 6. Synthesis of 2,4-disubstituted 1,4-benzodiazepines via one-pot three-component method.

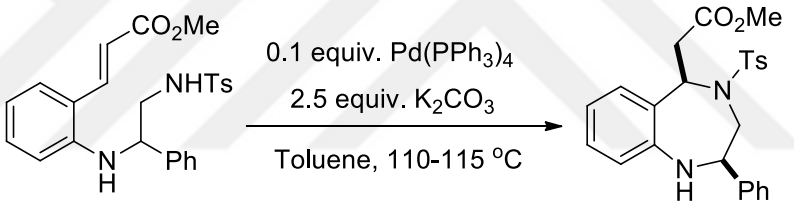
After that, saturated 1,4-benzodiazepines **21** were produced from *N*-allyl-2-aminobenzylamines **19** and several aryl bromides **20** with Pd-catalyzed alkene carboamination reactions by Wolfe research group as given in Scheme 7.[34]



19 **20** **21**

Scheme 7. Synthesis of saturated 1,4-benzodiazepines via carboamination reaction.

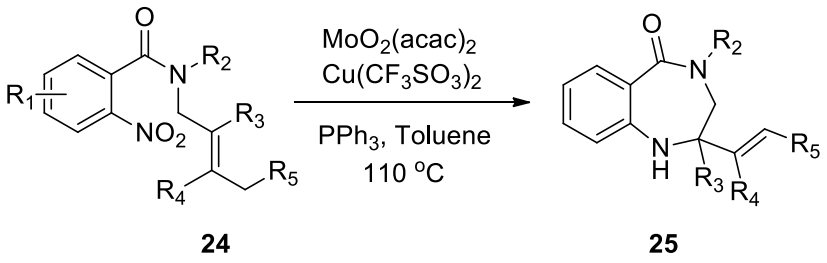
Then, Ghorai and co-workers developed a route for the synthesis of 2,3,4,5-tetrahydrobenzodiazepine **23** via a palladium-catalyzed aza-Michael reaction from the starting material **22**. The reaction, conducted in the presence of K_2CO_3, provided the formation of a singe diastereomer of resulting product (Scheme 8).[35]



22 **23**

Scheme 8. Synthesis of tetrahydrobenzodiazepine through aza-Michael addition.

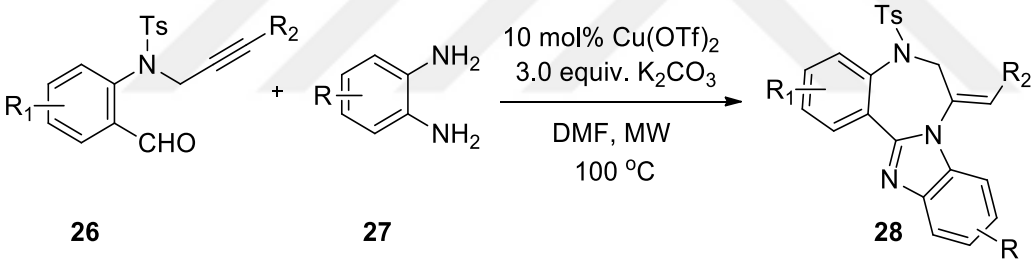
Later, He research group synthesized of 1,4-benzodiazepines-5-one derivatives **25** by the reaction of *o*-nitrobenzoic *N*-allylamides **24** in the presence of copper and molybdenum catalysts in high yields as demonstrated in Scheme 9.[36]



24 25

Scheme 9. Synthesis of 1,4-benzodiazepines-5-ones through a copper-catalyzed rearrangement.

In 2022, Sridharan *et al.* reported a new approach for the synthesis of imidazo substituted 1,4-benzodiazepines **28** through the reaction of *N*-propargylated-2-aminobenzaldehyde **26** and *o*-phenylenediamine **27** in the presence of a copper-catalyst under microwave irradiation as illustrated in Scheme 10.[37]



26 27 28

Scheme 10. Synthesis of imidazo substituted 1,4-benzodiazepines under the microwave irradiation.

1.3 Imidazo[1,2-*a*]pyridines

Imidazo[1,2-*a*]pyridines, as one of the other important heterocyclic skeletons, are one of the most abundant nitrogen-based structures. These compounds consist of 5,6-fused bicyclic structures containing a pyridine ring and a nitrogen atom-substituted five-membered ring, as shown in Figure 7.[38]

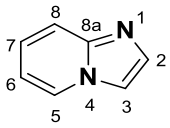


Figure 7. General structure of imidazo[1,2-*a*]pyridines.

They are precious scaffolds in organic synthesis and they have received considerable attention because of their diversified applications in pharmaceutical chemistry, natural products and materials science.[39,40] Due to the presence of the pyridine ring in the imidazole structure, which increases biological activity, they have been proven to possess a broad range of biological activities, exhibiting antiviral, antibacterial, anticancer, antifungal, anti-inflammatory, antiulcer, anticonvulsant and analgesic effects. Therefore, they play an important role in many applications in the field of pharmaceuticals.[40,41] For example, many commercially avaiable drugs (Figure 8), including Zolpidem, Zolimidine, Saripidem, Olprinone, are derived from imidazo[1,2-*a*]pyridine core entities.[41] In addition, they are also useful molecules as the enzyme inhibitors, the receptor ligands and anti-infectious agents.[42] Their effectiveness has been demonstrated in studies on $GABA_A$ receptor agonists, 5-lipoxygenase inhibitors, cyclic dependent kinase inhibitors, and histamine H2 receptor antagonists.[40]

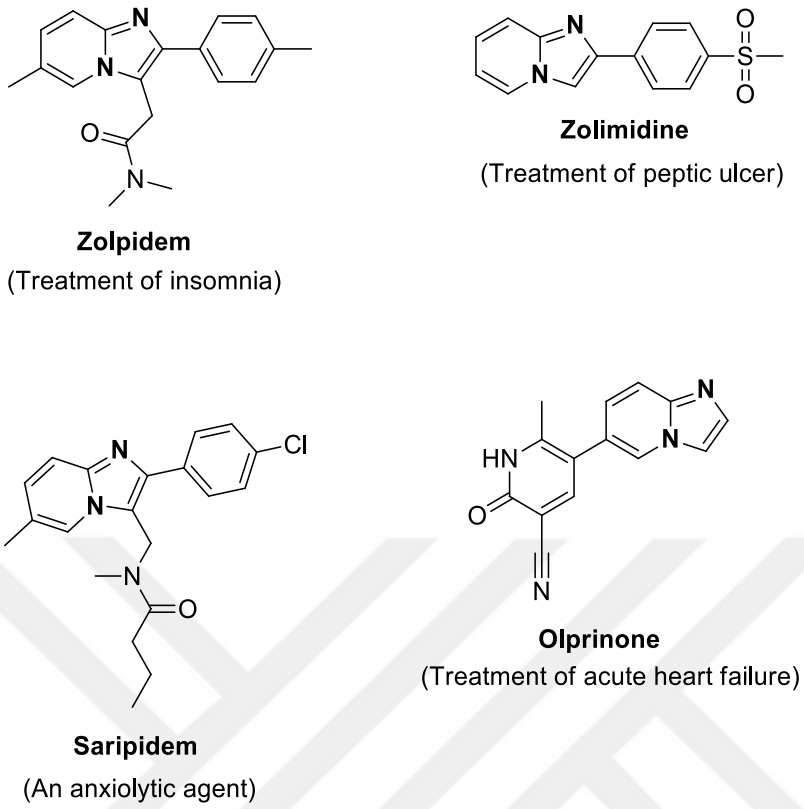


Figure 8. Imidazo[1,2-*a*]pyridine-based drugs.

1.3.1 Hexahydroimidazo[1,2-*a*]pyridines

Among imidazo[1,2-*a*]pyridines, saturated and partially saturated imidazo[1,2-*a*]pyridines, particularly hexahydroimidazo[1,2-*a*]pyridines (HImPs) have gained attention owing to their pharmacological activities like antiviral, antimalarial and antiulcer.[43] These compounds are classified as three groups such as HImP-1 (1,2,3,5,6,7-HImP), HImP-2 (1,2,3,7,8,8a-HImP) and HImP-3 (2,3,5,6,7,8-HImP), as demonstrated in Figure 9.

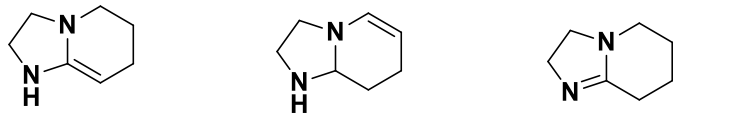


Figure 9. Structures of HImP derivatives.

1.3.2 Importance of Hexahydroimidazo[1,2-*a*]pyridines

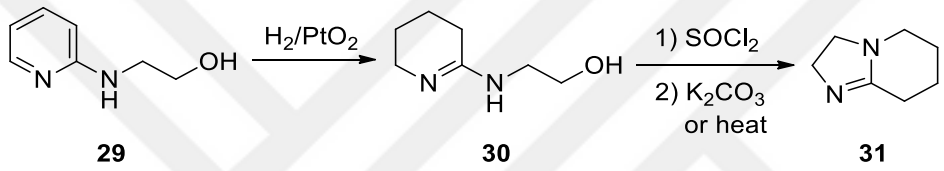
Hexahydroimidazo[1,2-*a*]pyridine compounds have pharmacological and biological potential. However, their all biological potential, especially their mechanism of action and dynamics in living cells, are not fully known.[44] For this reason, the properties of hexahydroimidazo[1,2-*a*]pyridine derivatives are not sufficiently mentioned in medicinal chemistry.[45] Despite the unknowns in the fields of pharmacology and medicine, studies on their insecticidal activities have been conducted in agricultural chemistry and they have been proven to be potential insecticidal molecules.[46] Additionally, studies have been conducted on the photodegradation of hexahydroimidazo[1,2-*a*]pyridine compounds and their photodegradation pathways were recommended based on the structures of photoproducts.[47] Therefore, more different structures related to hexahydroimidazo[1,2-*a*]pyridines need to be synthesized.[44] In particular, HImPs-3 (2,3,5,6,7,8-HImPs) are very rare, and to the best of our knowledge, there are only a few studies in this regard.

1.3.3 Synthesis of 2,3,5,6,7,8-Hexahydroimidazo[1,2-*a*]pyridines

There is a major lack of information on the synthesis of 2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridines.[44] Therefore, new methods for their synthesis

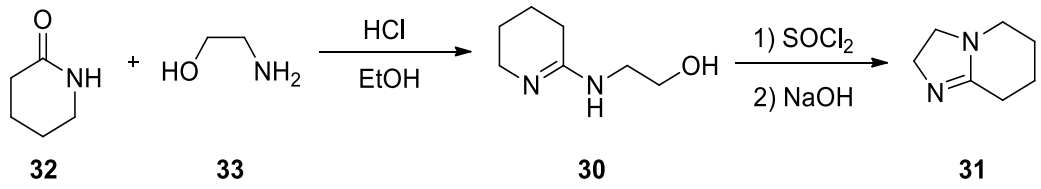
need to be developed. Only four studies regarding their synthesis were reported in literature, as summarized below.

The first study was conducted in 1970 by Mikhlina, Vorob'eva and Yakhontov. They have reported the hydrogenation reaction of 2-(pyridin-2-ylamino)ethanol (**29**) in the presence of catalyst, which gave rise to the formation of intermediate **30**. Then, the successive chlorination and cyclization reactions of **30** allowed to form 2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine compound **31**, as shown in Scheme 11.[48]



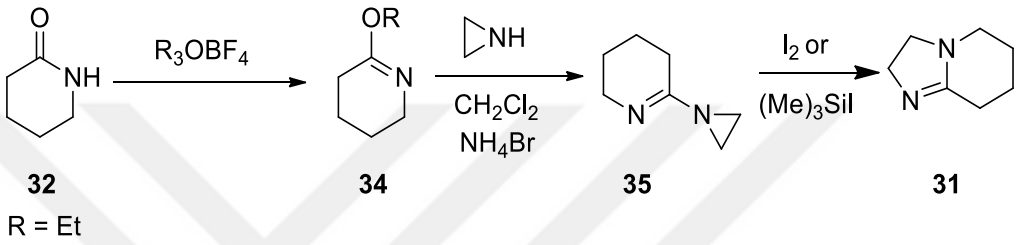
Scheme 11. Synthesis of 2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine.

After that, Rokach and Andersan described a method for the synthesis of 2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine **31**, in which the reaction between piperidin-2-one (**32**) and 2-aminoethanol (**33**) produced intermediate **30**, which upon chlorination and cyclization afforded target compound (Scheme 12).[49]



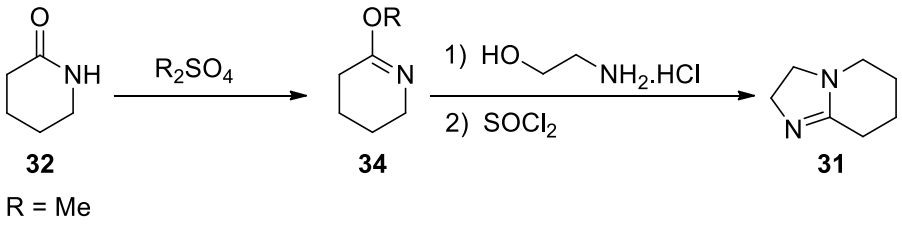
Scheme 12. Synthesis of 2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine from piperidin-2-one.

In 1981, Yamamoto and co-workers synthesized 2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine **31** with the rearrangement of 6-aziridin-1-yl-2,3,4,5-tetrahydropyridine (**35**) in the presence of molecular iodine or trimethylsilyl iodide. Therefore, 6-aziridin-1-yl-2,3,4,5-tetrahydropyridine (**35**) was prepared from the reaction of lactam **32** with triethyloxonium tetrafluoroborate, followed by the reaction of resulting product **34** with aziridine, as depicted in Scheme 13.[50]



Scheme 13. Synthesis of 2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine from cyclic amides.

Apart from this, Birman research group have reported the synthesis of 2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine (**31**) by the reaction of *o*-methylvalerolactim **34** by using aminoethanol hydrochloride and thionyl chloride after the conversion of lactam **32** to *o*-methylvalerolactim **34**, as demonstrated in Scheme 14.[51]

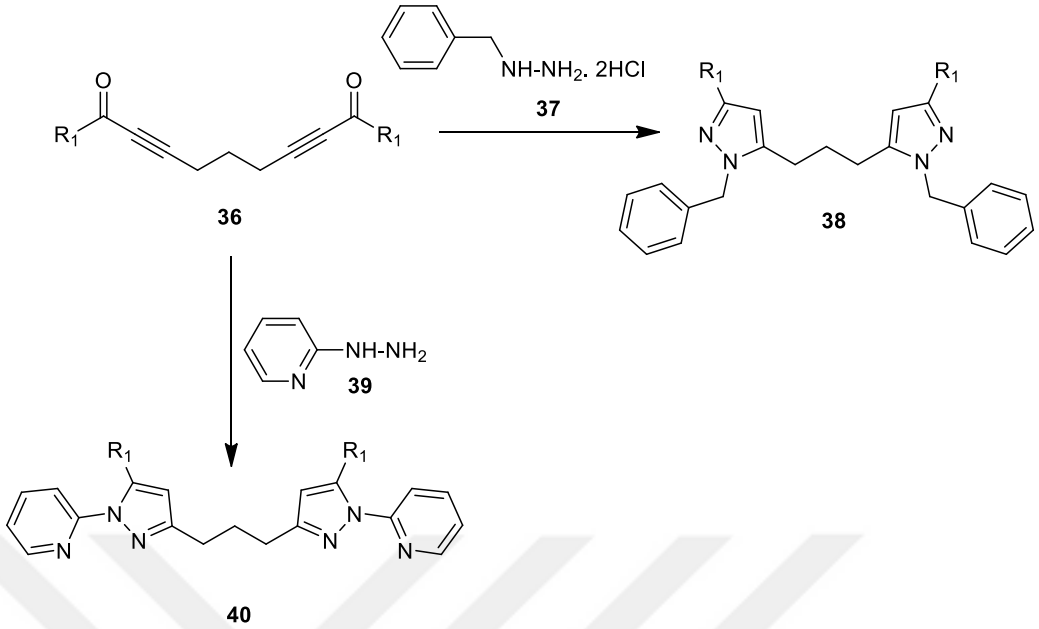


Scheme 14. Synthesis of 2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine from *o*-methylvalerolactim.

1.4 Aim of the Thesis

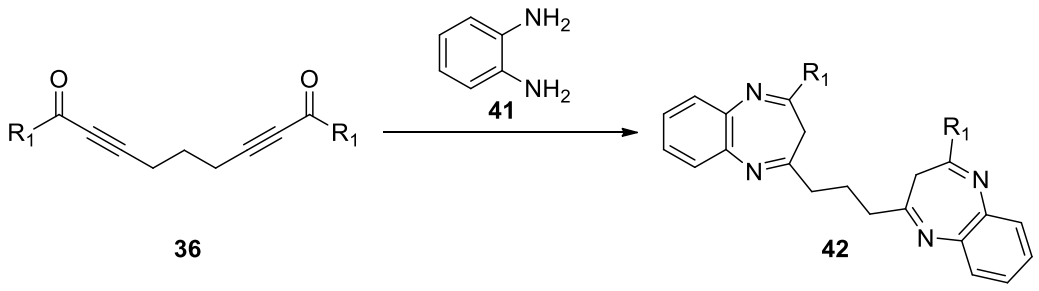
As mentioned before, bis-pyrazoles, 1,4-benzodiazepines and hexahydroimidazo[1,2-*a*]pyridines are heterocyclic structures of interest in organic chemistry due to their prominent applications in many fields. At this point, bis-α,β-alkynic ketones are suitable starting materials for the synthesis of new compounds. Their cycloaddition and cyclization reactions allow the formation of novel molecules. Moreover, their tandem cyclization enables the synthesis of unprecedented compounds. The aim of this study is to develop new methodologies in order to synthesize 1,3-bis-pyrazole, 1,3-bis-benzo[*b*][1,4]diazepine and hexahydroimidazo[1,2-*a*]pyridine derivatives from bis-α,β-alkynic ketones.

In our research group, studies on the synthesis of pyrazole compounds from α,β-unsaturated aldehydes and ketones were previously carried out and a variety of pyrazole compounds were synthesized.[52,53,54] Inspired by these studies, it has been concentrated on the synthesis of bis-pyrazole compounds. In this respect, bis-α,β-alkynic ketones have become desirable building blocks for the production of bis-pyrazole derivatives. Therefore, in the first part of study, 1,4-conjugate addition and cyclization reaction of bis-α,β-alkynic ketones **36** have been explored by employing hydrazine derivatives **37** and **39**, which gave different 1,3-bis-pyrazole derivatives **38** and **40** (Scheme 15).



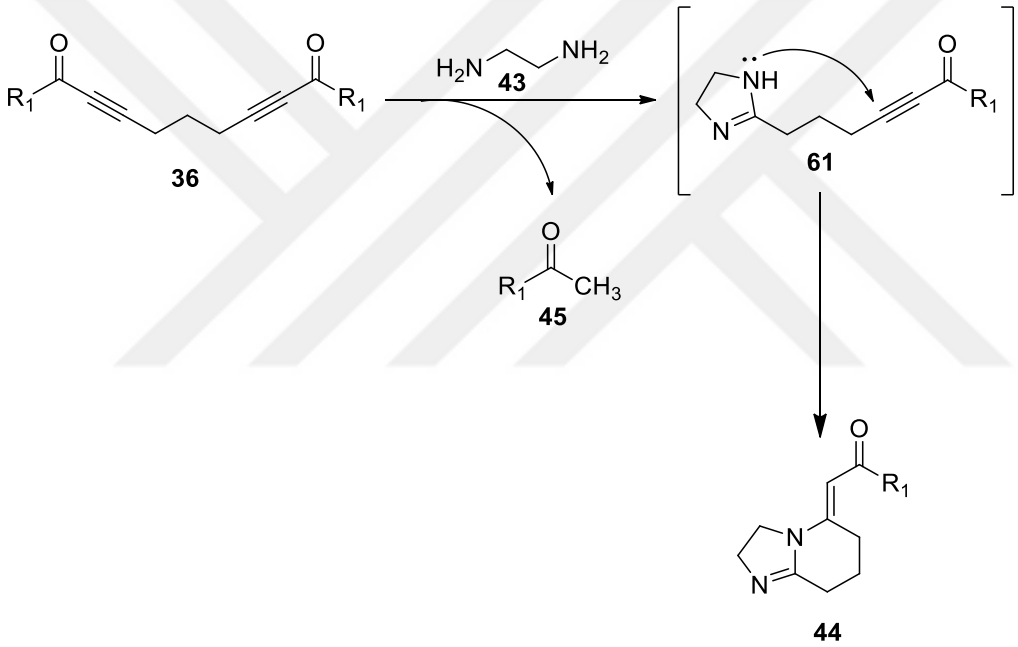
Scheme 15. Synthesis of 1,3-bis-pyrazole derivatives.

In the second part of study, the focus was on the reaction of bis-α,β-alkynic ketones **36** with *o*-phenylenediamine **41**. Therefore, bis-α,β-alkynic ketones **36** were exposed to *o*-phenylenediamine **41** and thus, an efficient methodology has been developed for the synthesis of 1,3-bis-benzo[*b*][1,4]diazepine compounds **42** (Scheme 16).



Scheme 16. Synthesis of 1,3-bis-benzo[*b*][1,4]diazepine compounds.

In the last part, the scope of reactions of bis-α,β-alkynic ketones **36** as the starting materials were expanded. For this reason, the reaction of bis-α,β-alkynic ketones **36** has been performed in the presence of ethylenediamine **43**. This formed an intermediate obtained from the reaction of one carbonyl group with addition product by expelling acetophenone **45**. The formation of this intermediate **61** gave us an advantage because it initiated another reaction and thus, a new and novel method for the synthesis of 5-alkylidene-substituted-hexahydroimidazo[1,2-*a*]pyridine **44** and acetophenone **45** derivatives was discovered (Scheme 17).



Scheme 17. Synthesis of 5-alkylidene-substituted-hexahydroimidazo[1,2-*a*]pyridines.

In brief, the scope, limitations and mechanisms for the synthesis of 1,3-bis-pyrazoles **38** and **40**, 1,3-bis-benzo[*b*][1,4]diazepines **42** and 5-alkylidene-substituted-hexahydroimidazo[1,2-*a*]pyridines **44** will be discussed in detail.

CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of Starting Materials

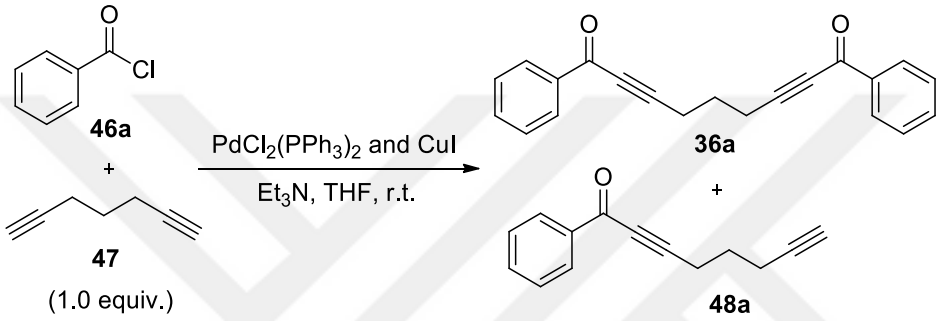
2.1.1 Synthesis of 1,9-Diarylnona-2,7-diyne-1,9-diones 36

In the first part of our study, symmetrical 1,9-diarylnona-2,7-diyne-1,9-diones (**36**), as starting materials, were synthesized by the reaction of aryloyl chloride **46** and 1,6-heptadiyne (**47**) by using Pd and Cu catalysts via Sonogashira cross coupling reaction (Table 1).[55] In this reaction, NEt_3 and THF were employed as the base and solvent, respectively. Reaction was performed at room temperature under argon atmosphere. This reaction afforded the expected bis-α,β-alkynic ketone **36**, along with a byproduct **48**. The formation of mono-coupled product **48** was unavoidable and we could not suppress the formation of this compound, which decreased the yield of the desired product **36**. Therefore, optimization reactions were performed to increase the yield of desired symmetrical 1,9-diarylnona-2,7-diyne-1,9-diones (**36**) (Table 1).

For optimization reactions, we first tried some reactions by changing the amount of benzoyl chloride (**46a**) in the presence of 2 mol% Pd and Cu (Table 1, entries 1-3). In these reactions, target product **36a** was obtained in 47% yield when 2.0 equiv. of **46a** was used (Table 1, entry 2). Then, the reaction of 2.4 equiv. of benzoyl chloride (**46a**) with 1,6-heptadiyne (**47**) was carried out by increasing the amount of Pd and Cu from 2 mol% to 4 mol%, and this reaction formed the target product **36a** in 41% yield (Table 1, entry 4). Apart from this, the same reaction was performed by adding equal amount of Pd and Cu twice, after observing that the benzoyl chloride (**46a**) was not consumed according to TLC analysis (Table 1, entries 5 and 6). While

increasing the amount of Pd provided the formation of the target product **36a** with 33% yield, increasing the amount of Cu did not allow the formation of the target product **36a** because it was observed that benzoyl chloride was not consumed at the end of these reactions.

Table 1. Optimization studies for synthesis of symmetrical 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**).[a]



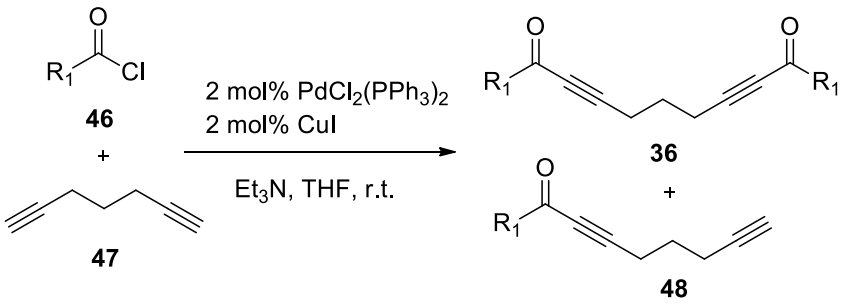
Entry	Equiv. of 46a	Equiv. of $PdCl_2(PPh_3)_2$	Equiv. of CuI	Yield(%) of 36a	Yield(%) of 48a
1	1.0	0.02	0.02	24	17
2	**2.0**	**0.02**	**0.02**	**47**	**29**
3	2.4	0.02	0.02	33	21
4	2.4	0.04	0.04	41	37
5	2.4	0.04 + 0.04	0.04	33	Mixture with **46a**
6	2.4	0.04	0.04 + 0.04	-	Mixture with **46a**

[a]Yields of the isolated products. [b]Reactions were performed on a scale of 1.63 mmol of 1,6-heptadiyne (**47**), 3.26 mmol of benzoyl chloride (**46a**), 0.033 mmol of $PdCl_2(PPh_3)_2$ and 0.033 mmol of CuI in 12 mL THF at room temperature for 5 h.

As a result of optimization reactions, we realized that it is not possible to achieve bis-α,β-alkynic ketone **36a** alone. Therefore, we decided to synthesize the starting bis-α,β-alkynic ketone derivatives **36** by the reaction of 1.0 equiv. of 1,6-heptadiyne (**47**) and 2.0 equiv. of benzoyl chloride (**46a**) in the presence of 2 mol% Pd and Cu catalysts because this condition afforded the highest yield 47% of **36a** (Table 1, entry 2). Moreover, the formation of mono-coupled alkynic ketones **48** gave us an advantage because we used these compounds as the starting materials for the synthesis of unsymmetrical bis-α,β-alkynic ketone derivatives.

By using optimized conditions, 20 symmetrical 1,9-diarylnona-2,7-diyne-1,9-dione derivatives (**36**), including electron-withdrawing and electron-donating groups were synthesized in 23-64% yields, along with byproducts **48** in 6-48% yields, as demonstrated in Table 2. When we evaluate the yields of them, the highest yield (64%) was obtained for *p*-chloro- and *p*-bromo-substituted bis-α,β-alkynic ketone derivatives **36b** and **36i**. On the other hand, *p*-cyano-containing derivative **36p** gave the lowest yield (23%) (Table 2).

Table 2. Synthesis of symmetrical 1,9-diarylnona-2,7-diyne-1,9-dione derivatives (**36**).[a,b]



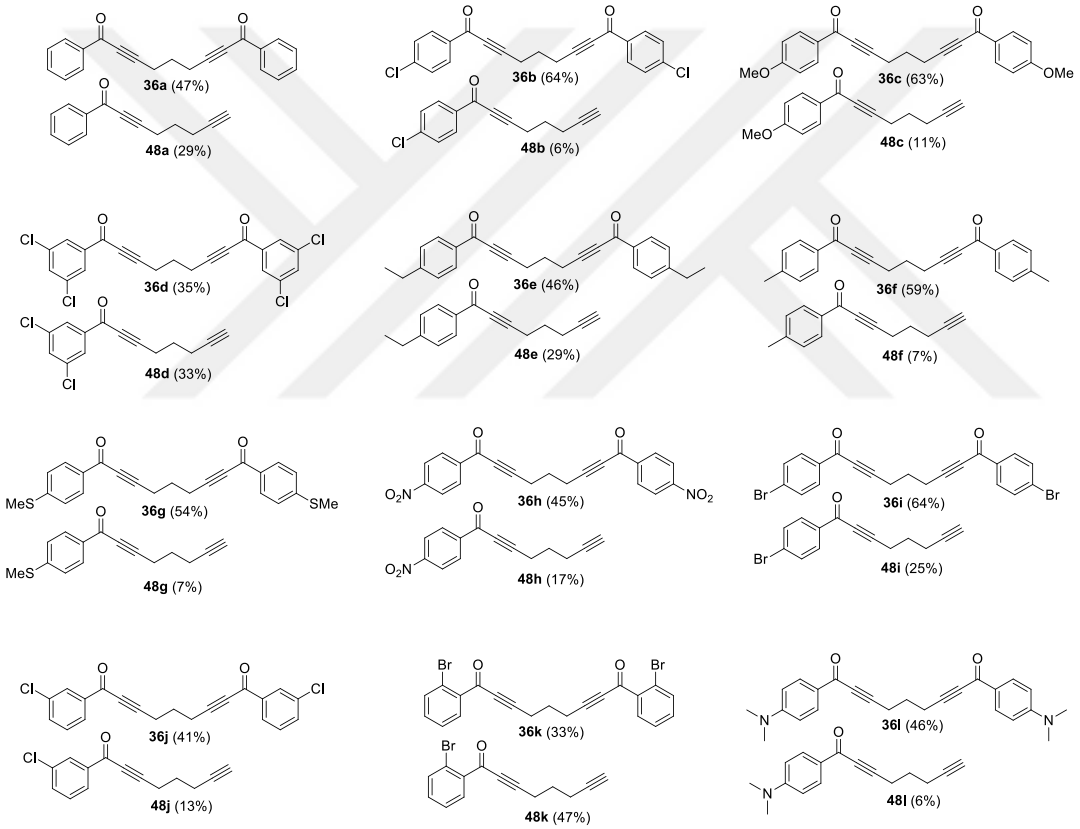
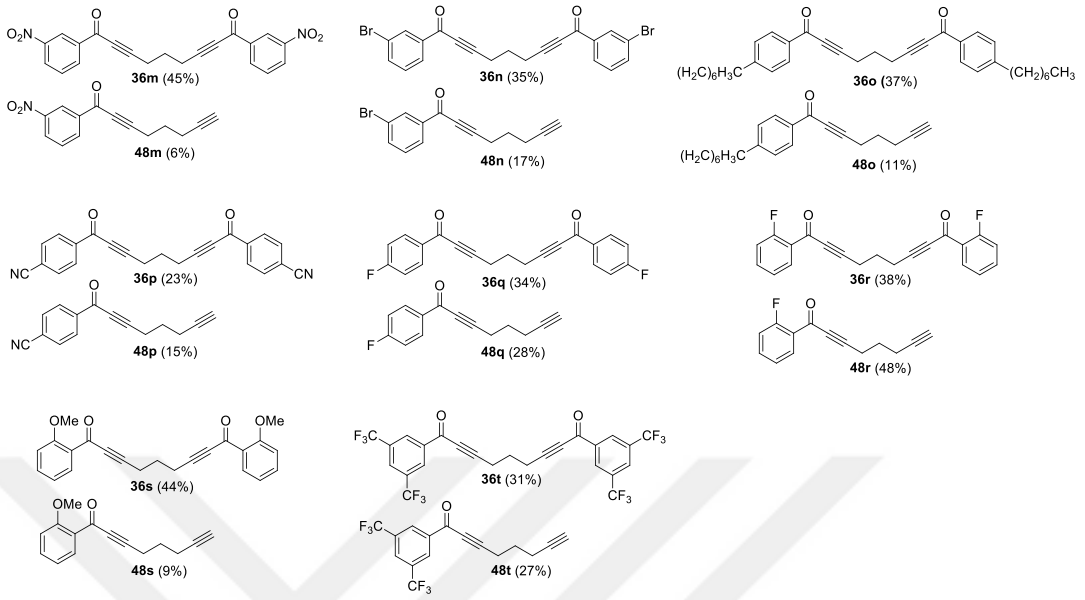


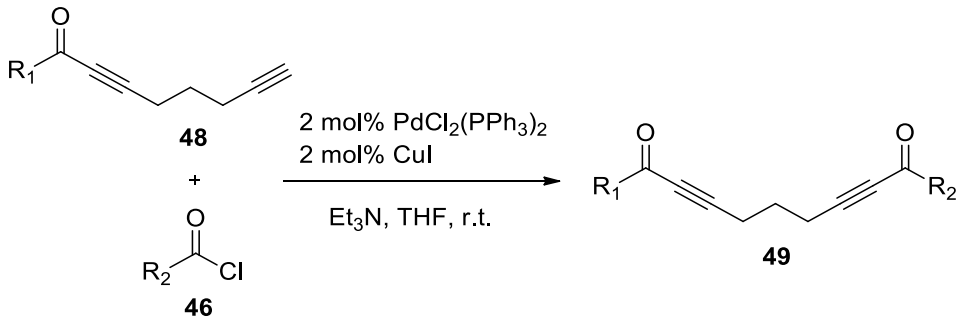
Table 2. Continued.

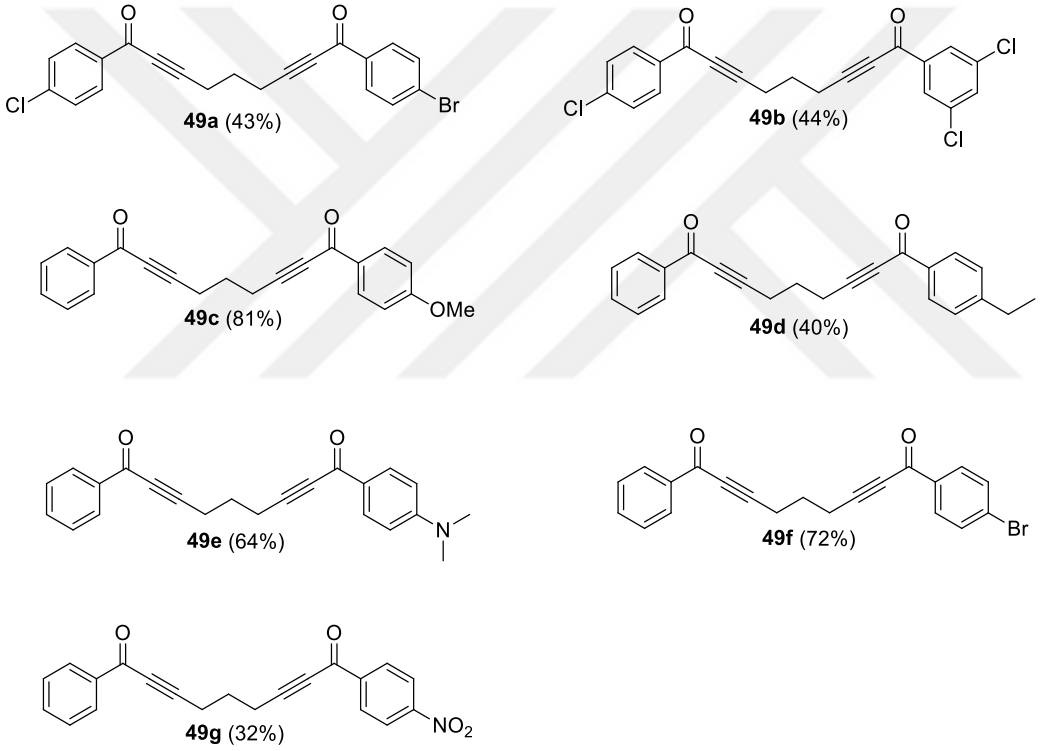


[a]Yields of isolated products. [b]Reactions were generaly performed on a scale of 1.63 mmol of 1,6-heptadiyne (**47**) and 3.26 mmol of aryloyl chlorides **46** in 12 mL THF at room temperature. For workup and purification, see Experimental Section.

Furthermore, 7 unsymmetrical 1,9-diarylnona-2,7-diyne-1,9-dione derivatives **49** were synthesized, as shown in Table 3. In this reaction, 1.0 equiv. of isolated mono-coupled alkynic ketone **48** as a starting material was reacted with 1.2 equiv. of aryloyl chloride **46**, which allowed the formation of unsymmetrical bis-α,β-alkynic ketone derivatives **49**. These compounds containing electron-withdrawing and electron-donating groups were obtained in moderate to good yields.

Table 3. Synthesized unsymmetrical 1,9-diarylnona-2,7-diyne-1,9-dione derivatives (**49**).[a,b]





[a]Yields of the isolated products. [b]Reactions were performed on a scale of approximately 0.5 mmol of 1-arylocta-2,7-diyne-1-one derivative **48** and 0.6 mmol of aryloyl chloride **46** in 8 mL THF at room temperature. For workup and purification, see Experimental Section.

The structure of 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**) was identified according to ^{1}H and ^{13}C NMR spectra, which were given in Figures 10 and 11.

As shown, in the ^{1}H NMR spectrum (Figure 10), ten aromatic hydrogens for two phenyl groups peaks resonate between 7.40-8.20 ppm. The peaks of two different methylene hydrogens are seen at 2.03 and 2.70 ppm as pentet and triplet, respectively.

In the ^{13}C NMR spectrum (Figure 11), carbonyl carbon resonates at 177.8 ppm while aromatic four carbons for phenyl groups appear between 127.0-137.0 ppm. Moreover, the peaks of two alkynic carbons appear at 94.3 and 80.3 ppm whereas two CH_2 carbons resonate at 25.9 and 18.3 ppm.

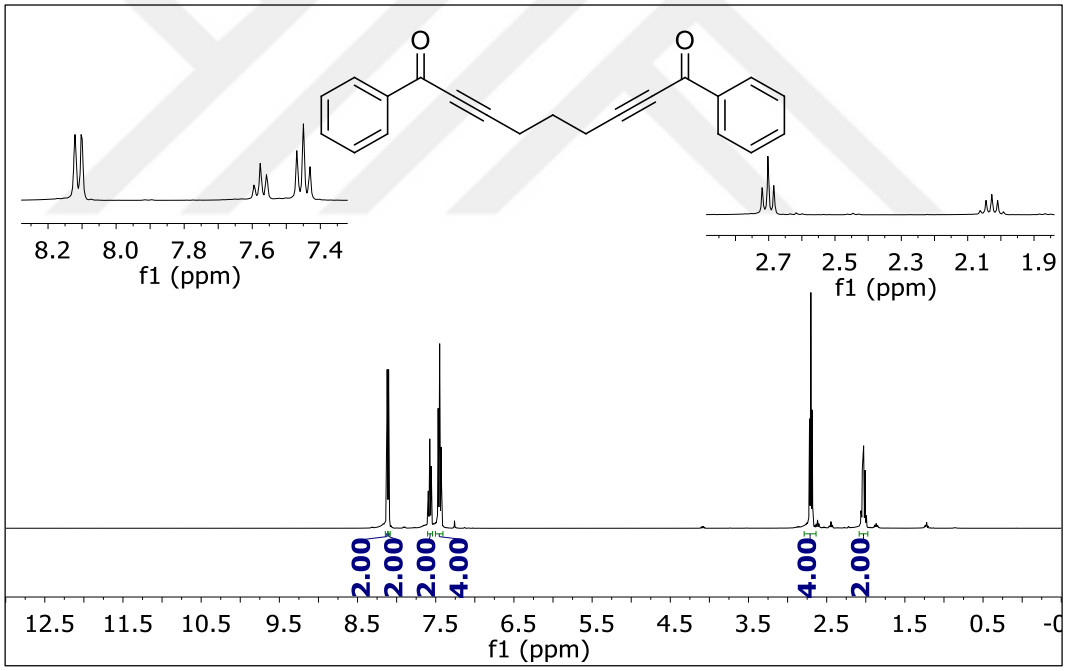


Figure 10. ^{1}H NMR spectrum of 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**).

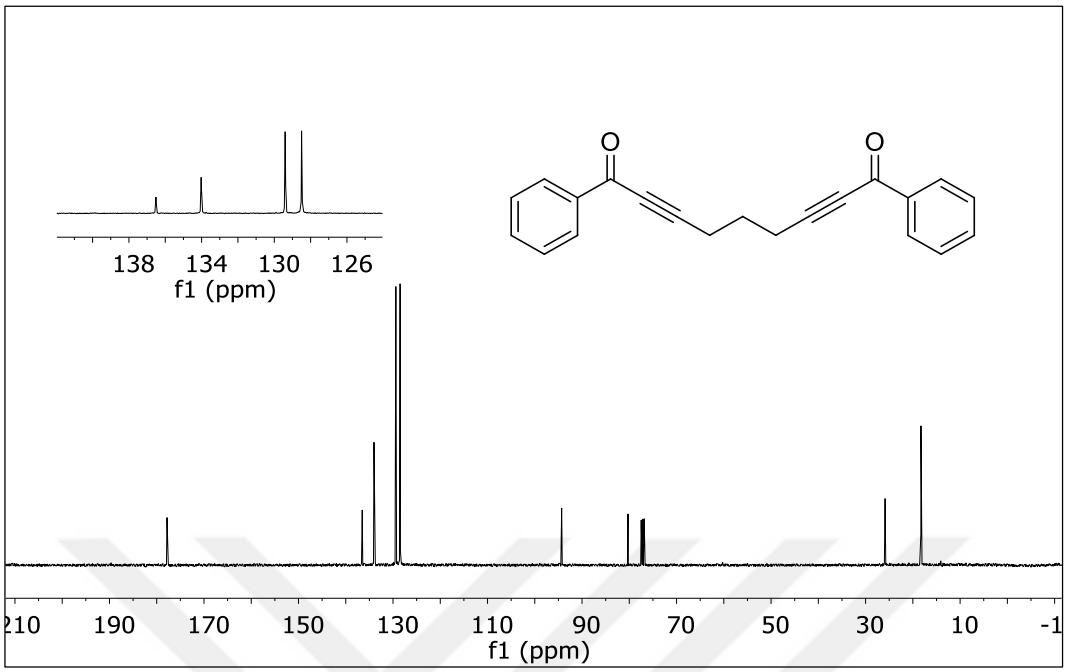


Figure 11. ^{13}C NMR spectrum of 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**).

2.2 Synthesis of Target Compounds

2.2.1 Synthesis of 1,3-Bis-Pyrazole Derivatives 38 and 40

The first part of thesis study was about the synthesis of 1,3-bis-pyrazole compounds **38** and **40**. After the synthesis of starting materials **36** and **49**, their reactions were investigated by employing hydrazine derivatives to test the formation of 1,3-bis-pyrazoles **38** and **40**.

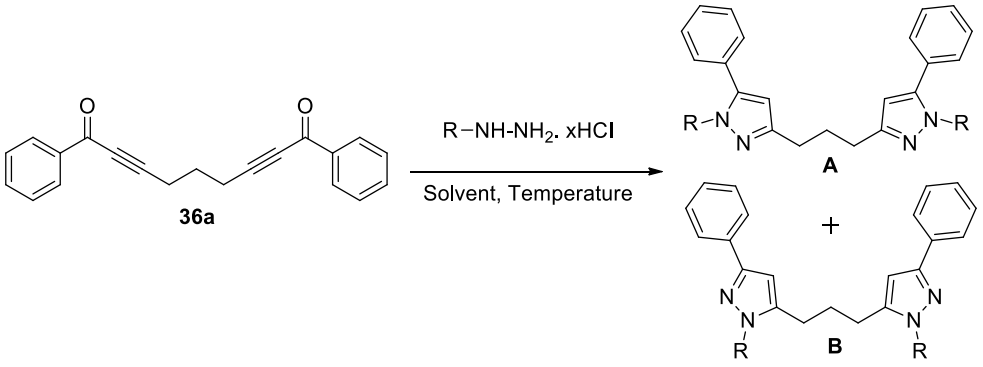
For optimization studies, a reaction condition was used, in which 1.0 equiv. of starting material **36a** was reacted with 2.0 equiv. of hydrazine or hydrazine salts by using different solvents. According to literature studies, the synthesis of new pyrazole compounds was generally conducted in the neat conditions (without solvent) or in some solvents like methanol and dioxane. Moreover, acidic medium

promotes the formation of pyrazole derivatives.[52,53,56,57] In the first phase of the study, 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**) was reacted with phenyl hydrazine in MeOH, CH_3COOH and dioxane at reflux condition (Table 4, entries 1-3). As a result of these reactions, a mixture of 1,3-bis-pyrazole compounds **A** and **B** was obtained in 42-67% yields, respectively. Unfortunately, we were not able to isolate these products separately in column chromatography due to very small polarity difference between them. After this, we tried the reaction of phenyl hydrazine with starting material **36a** in the neat condition at 80 ^oC (Table 4, entry 4), but contrary to our expectations, no product formation was observed in this reaction. As a result, we could not obtain 1,3-bis-pyrazole isomers seperately in their pure forms. After investigating the studies on pyrazole synthesis, we saw that the formation of pure product can be related to the substitution pattern of hydrazine derivative.[54,58] Therefore, we performed the reaction with a different hydrazine derivative. So bis- α,β-alkynic ketone **36a** was refluxed with benzylhydrazine dihydrochloride in MeOH, CH_3COOH and dioxane (Table 4, entries 5-7). The reaction in MeOH and CH_3COOH gave a mixture of 1,3-bis-pyrazole compounds **A** and **B** in low yields (Table 4, entries 5 and 6) whereas reaction with dioxane formed 1,3-bis-pyrazole compound **B** as a single product in 54% yield (Table 4, entry 7). In addition, reaction was tried employing 2-hydrazinopyridine derivative as well in MeOH, CH_3COOH and dioxane under reflux condition (Table 4, entries 8-10). While the reaction with MeOH yielded a mixture of 1,3-bis-pyrazole compounds **A** and **B** (Table 4, entry 8), it was not observed any product formation in refluxing CH_3COOH (Table 4, entry 9). However, the reaction of 2-hydrazinopyridine in dioxane formed 1,3-bis-pyrazole compound **A** as a single product in 36% yield (Table 4, entry 10). Moreover, another reactions were carried out in the presence of 2-nitrophenylhydrazine in dioxane and CH_3COOH at reflux condition (Table 4, entries 11 and 12). However, these reactions did not afford any product. Subsequently, the same condition was applied with employing 2-hydrazinobenzothiazole **(**Table 4, entries 13 and 14). Here, the reaction in dioxane gave a mixture of 1,3-bis-pyrazole compounds **A** and **B** in 48% yield. Finally, we

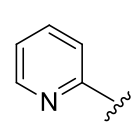
performed the reaction with 2-hydroxyethylhydrazine in the neat condition at 80 ^{o}C (Table 4, entry 15), but it did not turn out as we expected and this reaction did not afford any product formation.

As a result of optimization studies, the yield and course of the reactions for different hydrazine derivatives were compared. The reactions of benzylhydrazine dihydrochloride and 2-hydrazinopyridine formed single isomer of 1,3-bis-pyrazole product at **B** and **A** in dioxane at reflux condition with 54 and 36% yields, respectively. Therefore, it was decided to make derivatization studies by employing both benzylhydrazine dihydrochloride (**37**) and 2-hydrazinopyridine (**39**) in dioxane at reflux condition (Table 4, entries 7 and 10), which afforded various 1,3-bis-pyrazole derivatives **38** and **40** in Tables 5 and 6, respectively.

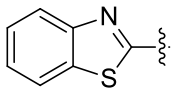
Table 4. Optimization studies for the synthesis of 1,3-bis-pyrazole compounds **A** and **B**.[a,b]



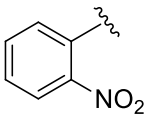
Entry	R	x	Solvent	Temp. (°C)	Time (h)	Yield (%)[a]
1	C_6H_5	-	MeOH	65	11.5	67 (**A**+**B**)
2	C_6H_5	-	CH_3COOH	118	4.0	63 (**A**+**B**)
3	C_6H_5	-	Dioxane	101	6.0	42 (**A**+**B**)
4	C_6H_5	-	neat	80	5.0	-
5	C_6H_5-CH_2	2	MeOH	65	7.0	15 (**A**+**B**)
6	C_6H_5-CH_2	2	CH_3COOH	118	6.0	34 (**A**+**B**)
7	**C_6H_5-CH_2**	**2**	**Dioxane**	**101**	**6.5**	**54** (**B**)
8	C_5H_4N	-	MeOH	65	7.0	16 (**A**+**B**)
9	C_5H_4N	-	CH_3COOH	118	4.0	-
10	**C_5H_4N**	**-**	**Dioxane**	**101**	**4.5**	**36** (**A**)
11	*o*-NO_2-C_6H_4	-	Dioxane	101	9.0	-
12	*o*-NO_2-C_6H_4	-	CH_3COOH	118	6.0	-
13	C_7H_4NS	-	Dioxane	101	9.0	48 (**A**+**B**)
14	C_7H_4NS	-	CH_3COOH	118	6.0	-
15	HO-CH_2-CH_2	-	neat	80	5.0	-



R= C_5H_4N



R= C_7H_4NS

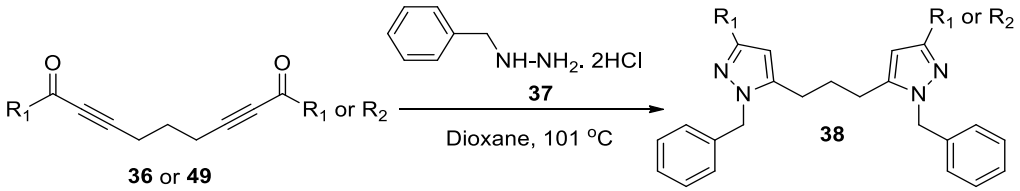


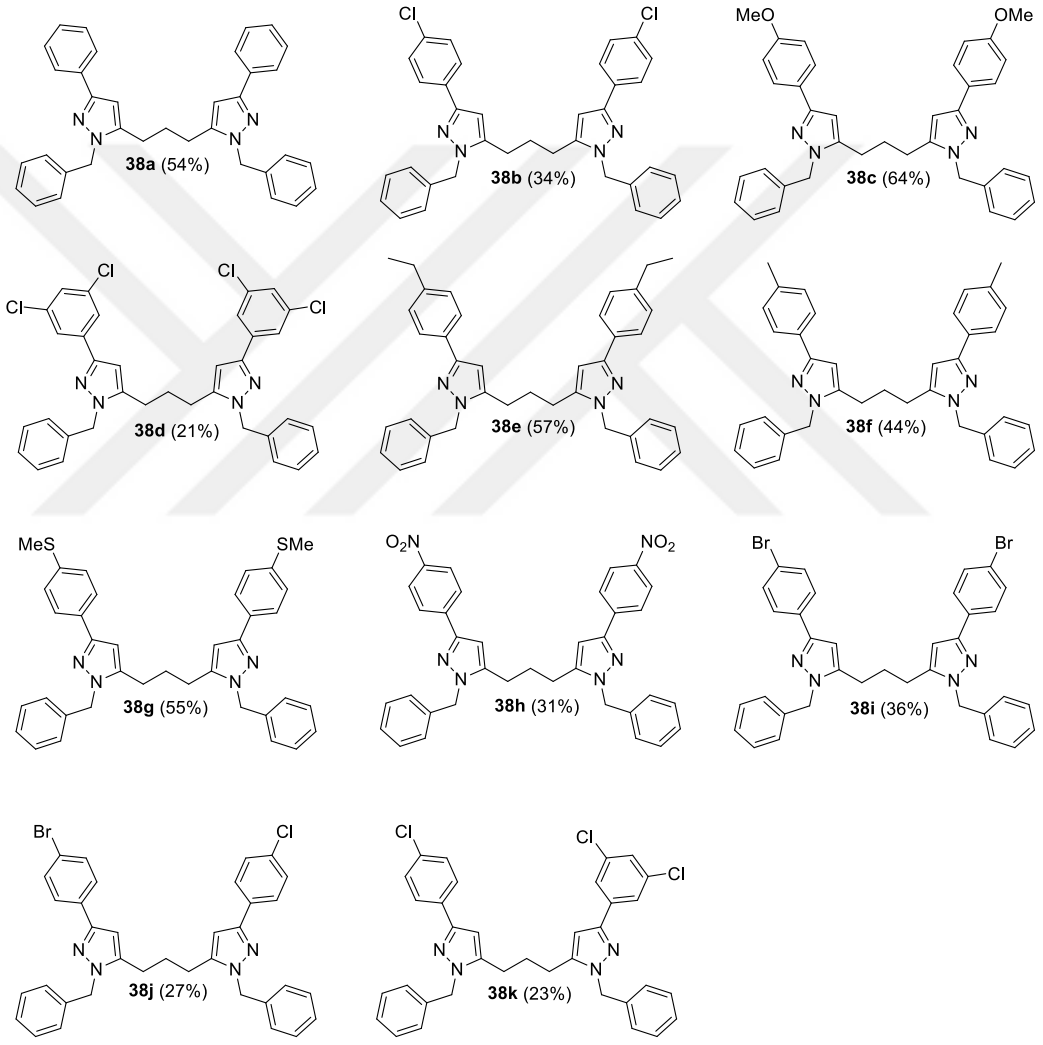
R= *o*-NO_2-C_6H_4

[a]Yields of the isolated products. [b]The reactions were performed on a scale of 0.3 mmol of 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**) and 0.6 mmol of hydrazine derivatives in 4 mL solvent.

According to these conditions, we synthesized 20 different derivatives of 1,3-bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propane (**38**) and 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (**40**), with electron-donating and electron-withdrawing substituents (Table 5 and 6). When we handle the yields of pyrazole derivatives synthesized from benzylhydrazine dihydrochloride (**37**), *p*-methoxy-substituted 1,3-bis-pyrazole derivative **38c** gave the highest yield (64%) whereas the lowest yield (21%) was obtained from 3,5-dichloro-substituted 1,3-bis-pyrazole derivative **38d**, as shown in Table 5. However, when the yields of derivatives synthesized from 2-hydrazinopyridine (**39**) were evaluated, *p*-methylthio-substituted 1,3-bis-pyrazole derivative **40g** resulted in the lowest yield (13%). Halogen containing unsymmetrical 1,3-bis-pyrazole derivative **40h** was produced with the highest yield (61%), as illustrated in Table 6. In addition, an interesting result was observed in the reaction of 2-hydrazinopyridine **39**. Here, we obtained different products from the reactions of *p*-methoxy and *p*-methylthio-substituted starting materials **36c** and **36g**, which provided the formation of unsymmetrical 1,3-bis-pyrazole compounds **40c** and **40g**, including different pyrazole moieties. (Table 6).

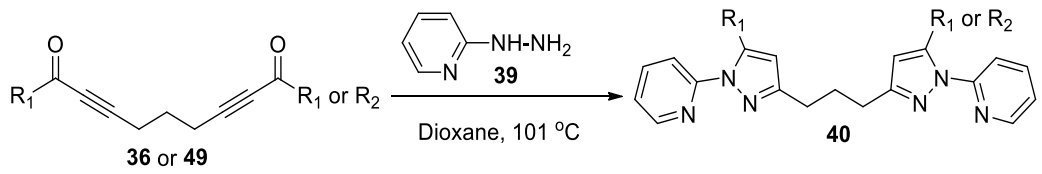
Table 5. Synthesis of 1,3-bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propane derivatives (**38**) from benzylhydrazine dihydrochloride (**37**).[a,b]

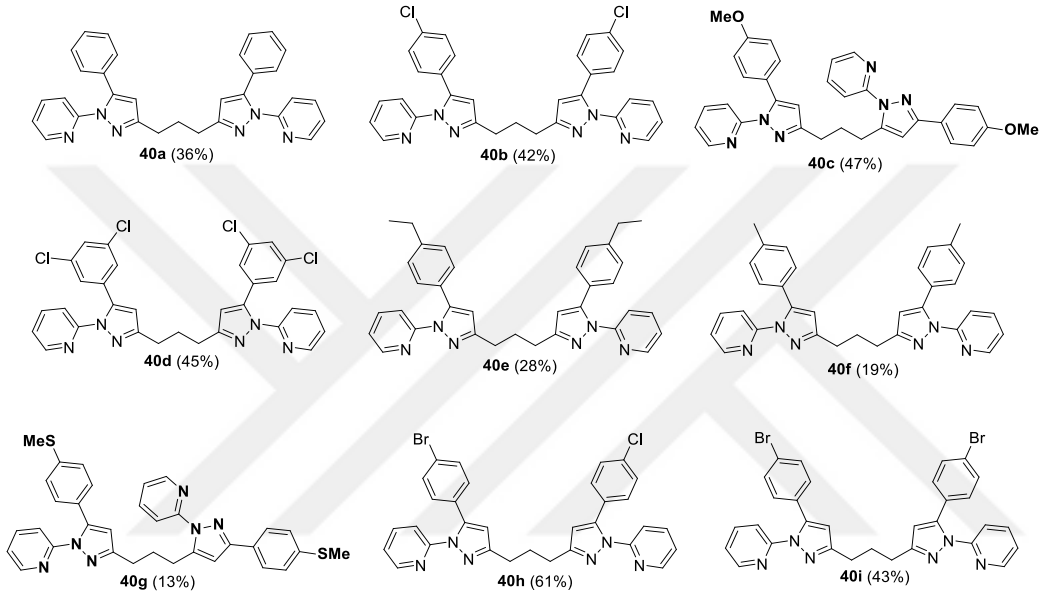




[a]Yields of the isolated products. [b]The reactions were performed on a scale of approximately 0.3 mmol of starting materials **36** and **49** and 0.6 mmol of benzylhydrazine dihydrochloride (**37**) in 4 mL of dioxane at reflux. For workup and purification, see Experimental Section.

Table 6. Synthesis of 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane derivatives (**40**) from 2-hydrazinopyridine (**39**).[a,b,c]





[a]Yields of the isolated products. [b]The reactions were performed on a scale of approximately 0.3 mmol of starting materials **36** and **49** and 0.6 mmol of 2-hydrazinopyridine (**39**) in 4 mL of dioxane at reflux. For workup and purification, see Experimental Section. [c]Unsymmetrical product formation for **40c** and **40g** was observed.

The structures of 1,3-bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propane (**38a**) and 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (**40a**) were identified by **t**he spectra of ^{1}H and ^{13}C NMR, given in Figures 12-15.

For 1,3-bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propane (**38a**), twenty aromatic hydrogens of four phenyl groups resonate between 7.0-8.0 ppm as seen in ^{1}H NMR spectrum (Figure 12). In addition, nitrogen-bonded methylene hydrogens appear at 5.29 ppm as a singlet while the hydrogens in pyrazole core appear as a singlet peak at 6.36 ppm. Except this, the peaks of two different methylene hydrogens between pyrazole units come at 1.86 and 2.52 ppm as pentet and triplet, respectively (Figure 12).

In the ^{13}C NMR spectrum of 1,3-bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propane (**38a**) (Figure 13), the resonation of CH carbon in the pyrazole core is seen at 102.2 ppm, while nitrogen-bonded methylene carbon peak comes at 53.1 ppm. Eight aromatic carbons for two different phenyl groups resonate between 124.0-130.0 ppm. One nitrogen-bonded carbon peak (C=N) in pyrazole moiety appears at 150.4 ppm whereas the other nitrogen bonded carbon (C-N) peak comes at 143.5 ppm. Finally, two CH_2 carbons between pyrazole units resonate at 27.0 and 24.9 ppm (Figure 13).

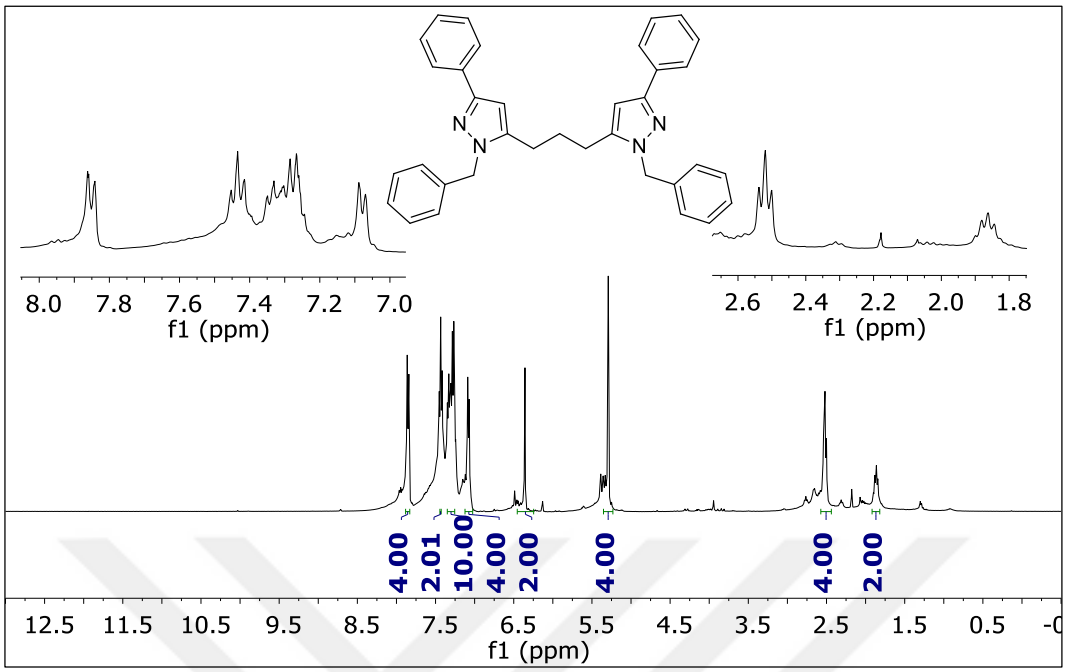


Figure 12. ^{1}H NMR spectrum of 1,3-bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propane (**38a**).

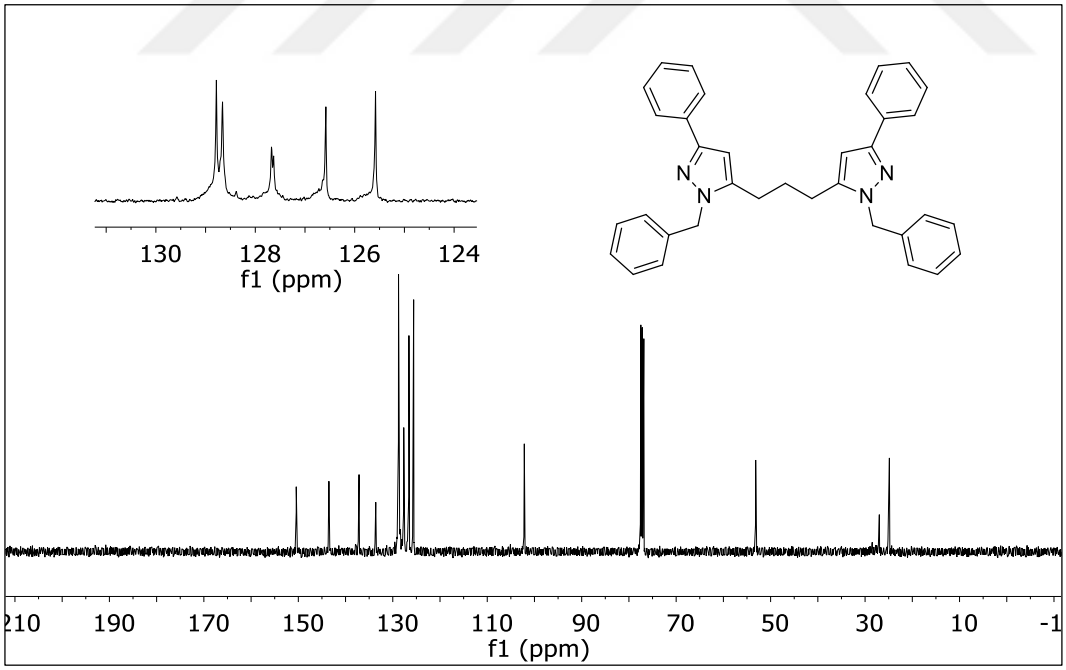


Figure 13. ^{13}C NMR spectrum of 1,3-bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propane (**38a**).

Identification of 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (**40a**) was achieved by analysis of ^{1}H and ^{13}C NMR spectra supplied in Figures 14 and 15.

In the ^{1}H NMR spectrum of 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (**40a**) (Figure 14), the characteristic α-CH protons of pyridine unit appear at 8.5 ppm. The remaining sixteen hydrogens in the aromatic groups resonate between 7.0-8.0 ppm. Hydrogens in the pyrazole core give a singlet peak at 6.41 ppm. Apart from this, the resonation of two different methylene hydrogens between pyrazole units is seen at 2.23 and 2.91 ppm as pentet and triplet, respectively, (Figure 14).

In the ^{13}C NMR spectrum of 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (**40a**) (Figure 15), the resonation of CH carbon in the pyrazole core appears at 108.2 ppm. The peaks of nine aromatic carbons are seen between 117.0-149.0 ppm. In the pyrazole core, one nitrogen-bonded carbon peak (C=N) appears at 152.4 ppm while the other nitrogen-bonded carbon (C-N) peak comes at 144.2 ppm. However, nitrogen-bonded α' carbon (C=N) of the pyridine core gives a peak at 154.6 ppm. Finally, two CH_2 carbon peaks resonate at 29.3 and 28.2 ppm (Figure 15).

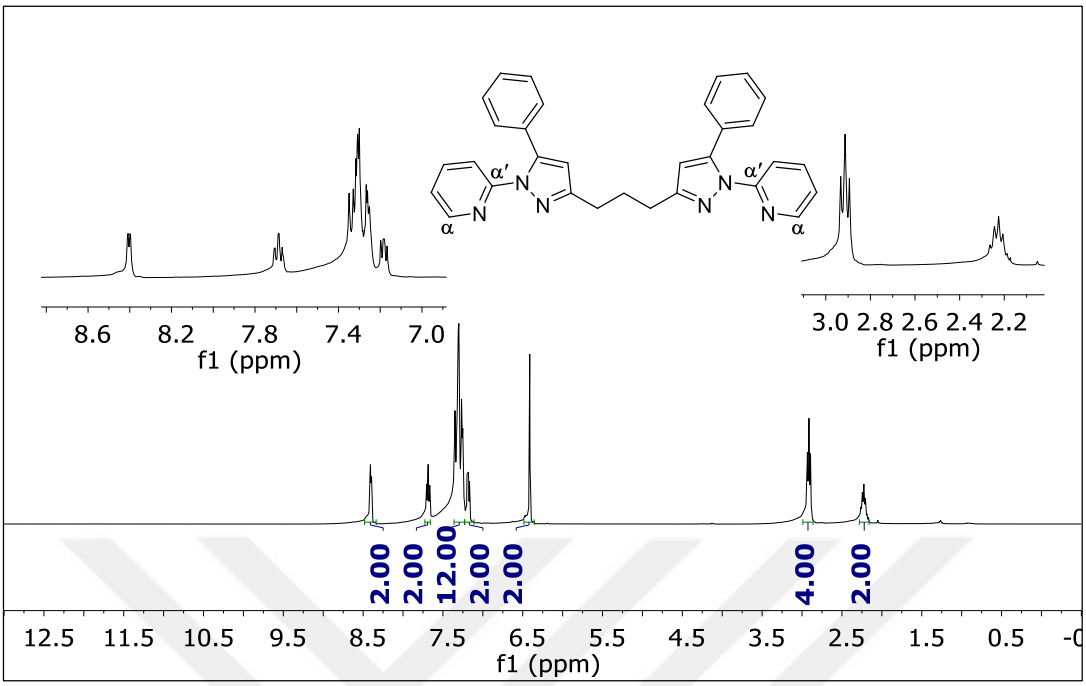


Figure 14. [1]H NMR spectrum of 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (**40a**).

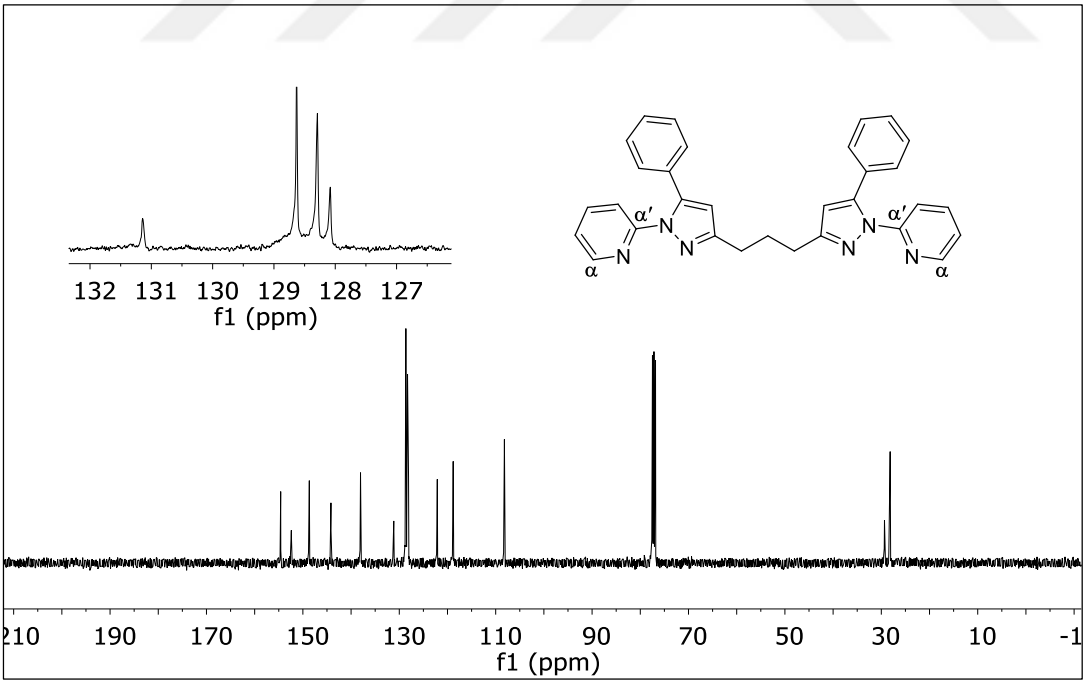


Figure 15. [13]C NMR spectrum of 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (**40a**).

Moreover, the structures of 1,3-bis-pyrazole compounds **38a** and **40a** were identified by the NOESY experiments. In the NOESY spectrum of 1,3-bis-pyrazole compound **38a**, an NOE interaction was observed between the methylenic hydrogens, as depicted in Figure 16. Cross peaks in circles indicated the above-mentioned NOE interactions.

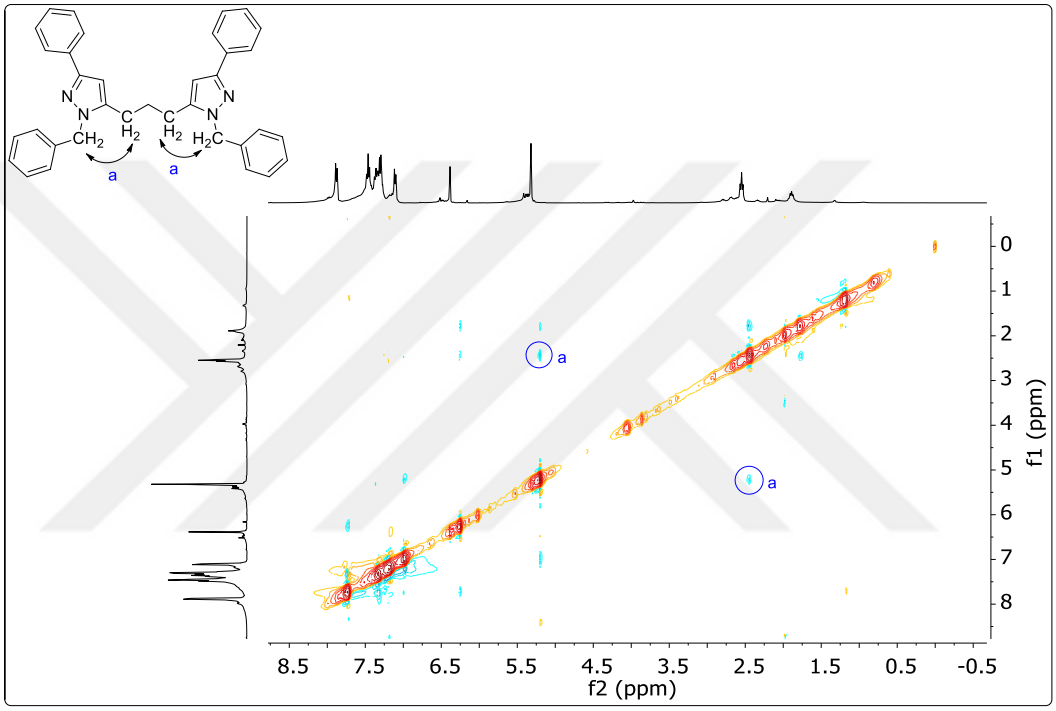


Figure 16. NOESY spectrum of 1,3-bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propane (**38a**).

On the other hand, there was not seen any NOE interaction between the methylenic hydrogens and aromatic hydrogens of pyridine ring in 1,3-bis-pyrazole compound **40a**, indicating the assigned structure, as demonstrated in Figure 17.

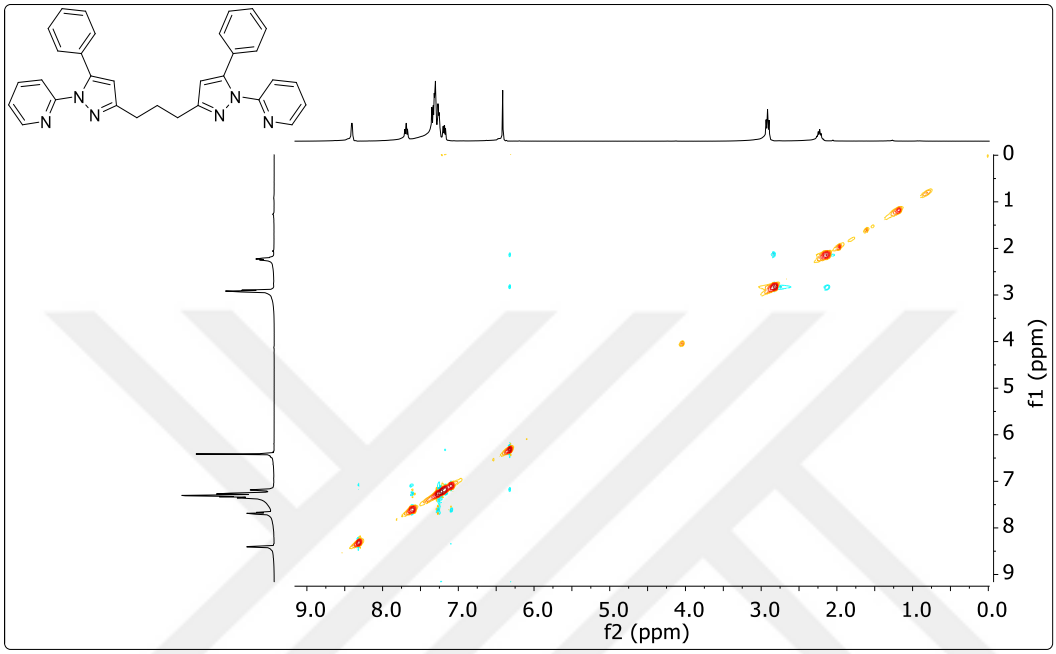


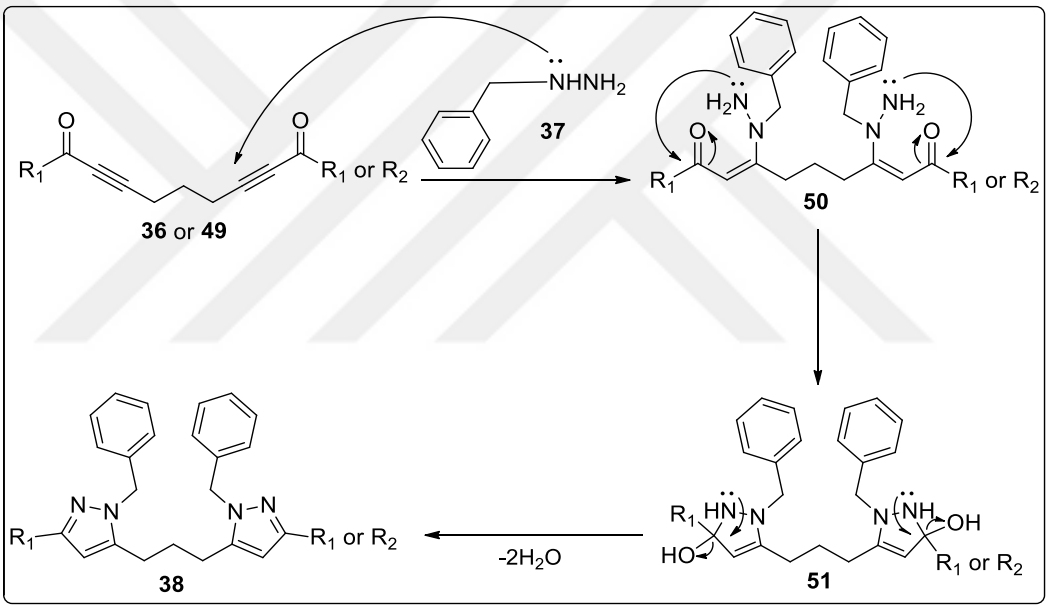
Figure 17. NOESY spectrum of 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (**40a**).

Proposed mechanism for the synthesis of 1,3-bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propane derivatives (**38**) is represented in Scheme 18. In order to reach the target product **38**, intermediate **50** first forms by the 1,4-conjugate addition of secondary amine of benzylhydrazine dihydrochloride (**37**) to starting materials **36** or **49**. Then, cyclocondensation reaction occurs to produce intermediate **51** which, upon water elimination, affords 1,3-bis-pyrazole derivatives **38** (Scheme 18).

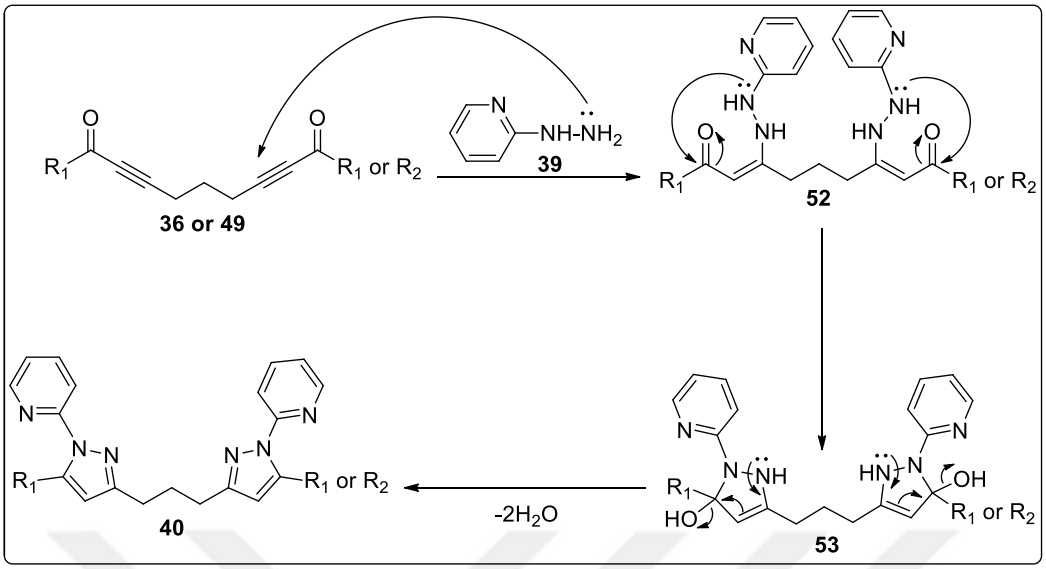
For the formation of 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (**40a**), the proposed mechanism is given in Scheme 19. 1,4-Conjugate addition of primary amine of 2-hydrazinopyridine (**39**) to starting materials **36** or **49** forms

intermediate **52**. Then, cyclocondensation gives intermediate **53**. Finally, water elimination provides 1,3-bis-pyrazole derivatives **40**, as illustrated in Scheme 19.

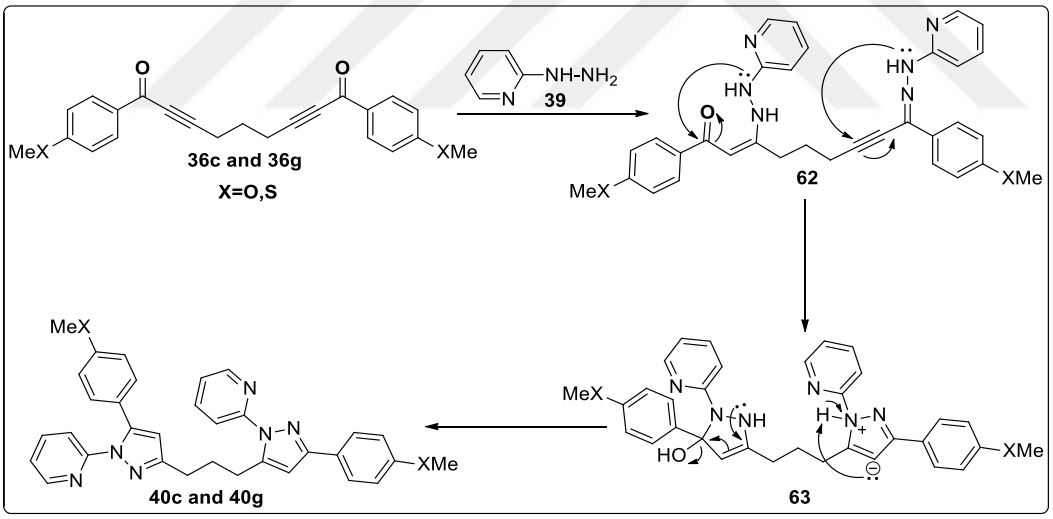
Proposed mechanism for the synthesis of unsymmetrical 1,3-bis-pyrazole compounds **40c** and **40g** is depicted in Scheme 20. 1,4-Conjugate addition of primary and secondary amines of 2-hydrazinopyridine (**39**) to bis-α,β-alkynic ketone moieties of starting materials **36c** and **36g** yields intermediate **62**. Then, cyclocondensation of **62** generates intermediate **63**. Finally, elimination of water from **63** affords unsymmetrical 1,3-bis-pyrazoles **40c** and **40g** (Scheme 20).



Scheme 18. Proposed mechanism for the synthesis of 1,3-bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propanes (**38**).



Scheme 19. Proposed mechanism for the synthesis of 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propanes (**40**).



Scheme 20. Proposed mechanism for the synthesis of 1,3-bis-pyrazoles **40c** and **40g**.

2.2.2 Synthesis of 1,3-Bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane Derivatives 42

In this part of thesis study, it was focused on what other reactions could be performed with bis-α,β-alkynic ketones **36**. A literature review revealed that benzo[*b*][1,4]diazepines could be achieved from the addition and cyclization reactions of *o*-phenylenediamine (**41**) with various starting materials like 1,3-diketones, α,β-conjugated alkenones or α,β-conjugated alkynones.[59,60] This condition enabled to be tried the reactions of bis-α,β-alkynic ketones **36** with *o*-phenylenediamine (**41**) since it was thought that they could generate new molecules.

For this purpose, the reactions of 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**) were explored in the presence of *o*-phenylenediamine (**41**). This reaction provided a new molecule, 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (**42a**) (Table 7).

In the optimization reactions, we have employed a reaction condition, in which 1.0 equiv. of starting compound **36a** was reacted with 2.0 equiv. of *o*-phenylenediamine (**41**) in the presence of various solvents, additive or base. First of all, solvent effect was investigated by changing reaction solvents on the formation of target product **42a**. Therefore, the starting material **36a** was refluxed with *o*-phenylenediamine (**41**) in MeOH. This afforded the expected product **42a** in 30% yield (Table 7, entry 1). When the reaction was carried out in EtOH at reflux condition, the yield of the product **42a** was increased from 30 to 33% (Table 7, entry 2). Subsequently, the reaction was repeated in CH_3COOH at reflux condition, but this reaction did not provide any of the desired product **42a** (Table 7, entry 3). Thus, it became clear that acidic medium have a negative effect on the formation of the product. Afterwards, the reaction was performed in dioxane at reflux condition, which increased the yield of product **42a** to 45%, (Table 7, entry 4). Then, the effect of the amount of solvent was examined in order to obtain the higher yields of the product. Accordingly, the reaction was repeated in dioxane with increasing the amount of the solvent. In this case, the yield of product **42a** was increased to 52% (Table 7, entry 5). At the same

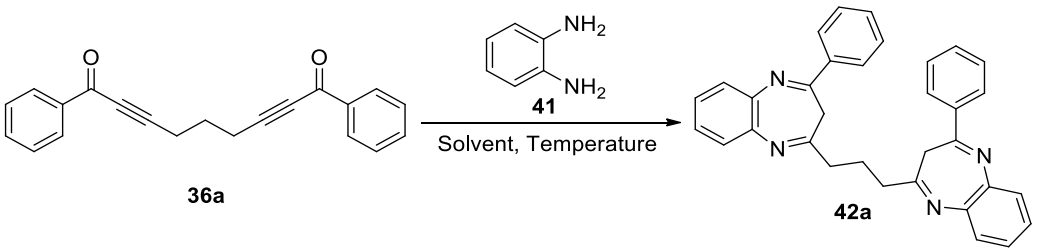
time, reaction time was decreased from 8.0 h to 6.5 h. Then, the reaction was performed in 4.0 mL dioxane (Table 7, entry 6), which provided an increase in the yield of the product **42a** (60%) while it decreased the reaction time to 4.0 h.

In addition, we investigated the effect of some additives and bases in the course of the reaction to achieve better efficiencies. Therefore, the reaction in dioxane was carried out in the presence of KO^tBu base (Table 7, entry 7). However, this reaction did not result in the formation of product **42a**. Apart from this, the reaction was performed in the presence of $ZnCl_2$ in $CHCl_3$ at reflux condition, (Table 7, entry 8). However, no reaction was observed in this case too. Finally, the reaction in dioxane at reflux condition was also tested by *o*-phenylenediamine dihydrochloride salt instead of *o*-phenylenediamine (**41**) (Table 7, entry 9). Unfortunately no product formation was observed in this case, as well.

As a result of these optimization reactions, we decided to make derivatization studies of starting compounds **36** and **49** with *o*-phenylenediamine (**41**) in 4.0 mL dioxane at reflux condition according to entry 6 at Table 7 because this condition enabled the formation of the expected 1,3-bis(4-phenyl-3H-benzo[*b*][1,4]diazepin-2-yl)propane (**42a**) with the highest yield (60%).

Then, we synthesized 15 different 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane derivatives (**42**). They include various electron-withdrawing and electron-donating substituents, as demonstrated in Table 8. When looking at the yields of synthesized compounds **42**, 60% as the highest yield was obtained from the synthesis of phenyl-substituted 1,3-bis-benzo[*b*][1,4]diazepine derivative **42a**. However, trifluoromethylphenyl-substituted 1,3-bis-benzo[*b*][1,4]diazepine derivative **42n** yielded the lowest efficiency (19%) (Table 8).

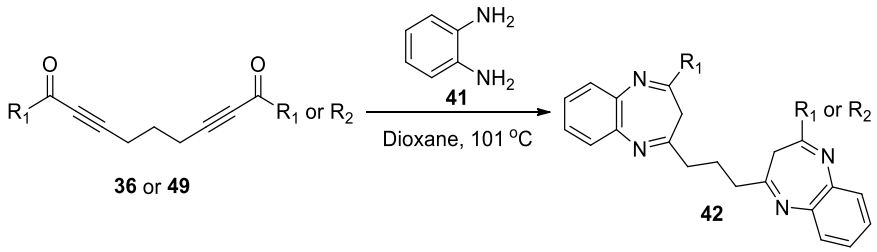
Table 7. Optimization studies for the synthesis of 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propanes (**42a**).[a,b]



Entry	Additive	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	-	MeOH	65	5.0	30
2	-	EtOH	78	7.0	33
3	-	CH_3COOH	118	7.0	-
4	-	Dioxane (2 mL)	101	8.0	45
5	-	Dioxane (3 mL)	101	6.5	52
6	**-**	**Dioxane (4 mL)**	**101**	**4.0**	**60**
7	KO^tBu (2.0 eqv.)	Dioxane	101	4.0	-
8	$ZnCl_2$ (2.0 eqv.)	$CHCl_3$	61	6.0	-
9	*o*-phenylenediamine dihydrochloride	Dioxane	101	4.0	-

[a]Yields of the isolated products. [b]The reactions were performed on a scale of 0.3 mmol of 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**) and 0.6 mmol of *o*-phenylenediamine dihydrochloride salt or *o*-phenylenediamine (**41**) in 4 mL solvent.

Table 8. Synthesis of 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane derivatives (**42**).[a,b]



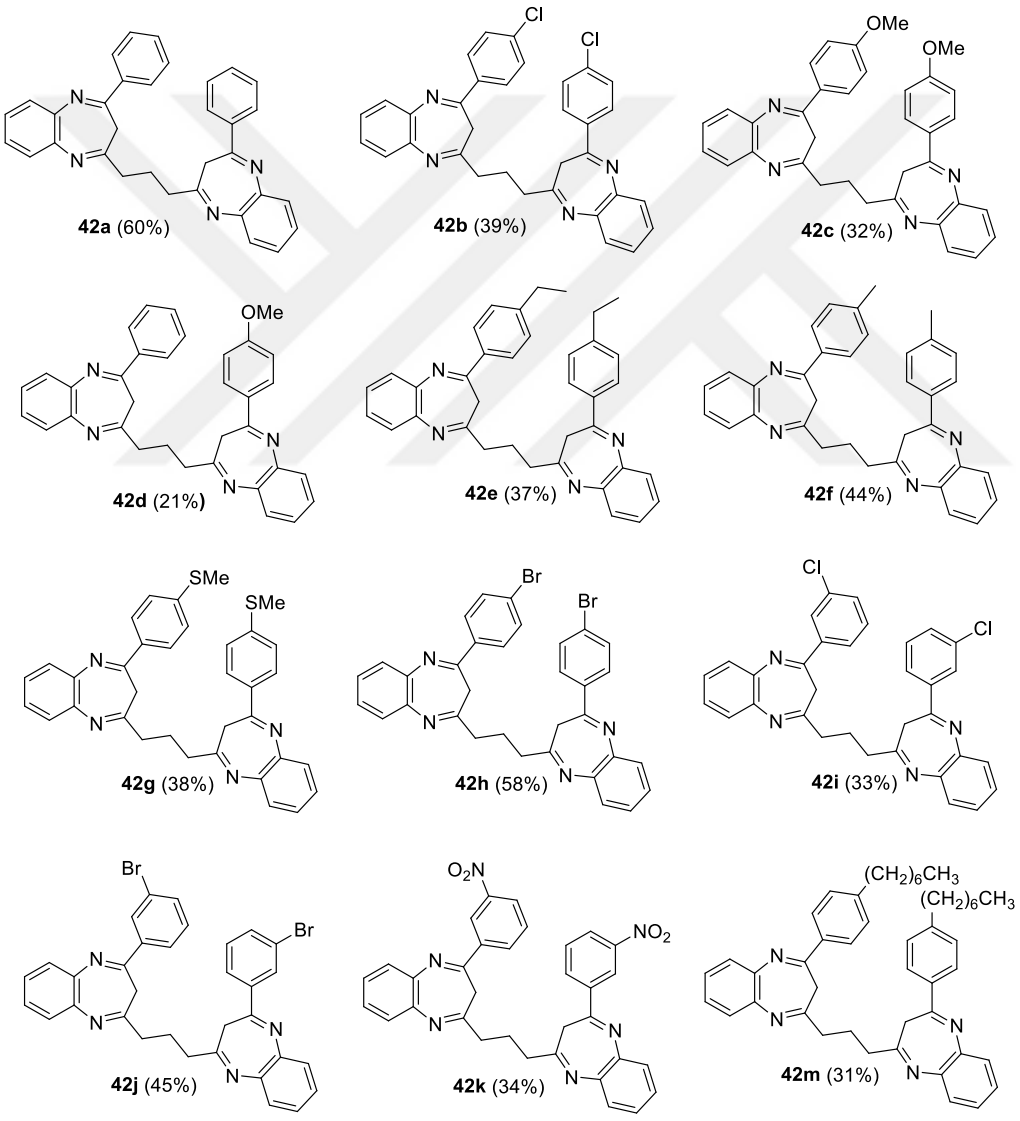
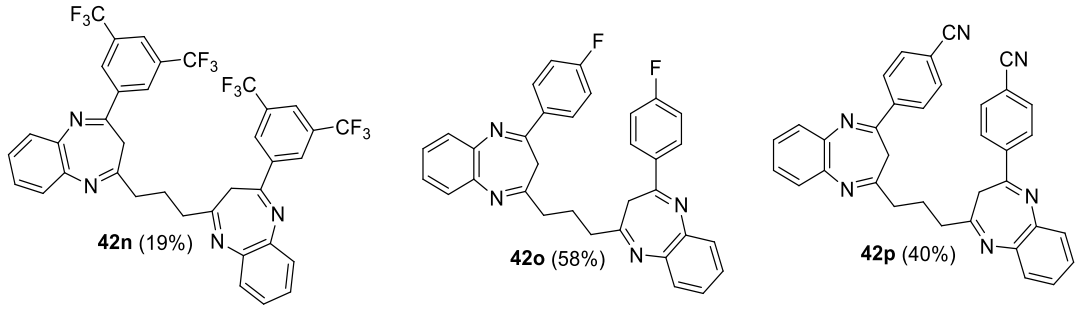


Table 8. Continued.



[a]Yields of the isolated products. [b]The reactions were performed on a scale of approximately 0.3 mmol of starting materials **36** and **49** and 0.6 mmol of *o*-phenylenediamine **41** in 4 mL of dioxane at reflux. For workup and purification, see Experimental Section.

The synthesized 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane derivatives (**42**) were characterized through ^{1}H and ^{13}C NMR spectroscopy (Figures 18 and 19).

In the ^{1}H NMR spectrum of 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (**42a**) (Figure 18), eighteen aromatic hydrogens of phenyl groups appeared between 7.0-8.5 ppm. In addition, two different methylene hydrogens resonated at 2.13 and 2.60 ppm as pentet and triplet, respectively. However, no signal could not be observed for CH_2 group due to ring inversion, presumably by coalescence consistent with the findings of earlier researchers working on the similar structures.[59,61,62]

In the ^{13}C NMR spectrum of 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (**42a**) (Figure 19), the peaks of nitrogen-bonded carbons (C=N) come at 160.5 ppm while the other nitrogen-bonded carbons (C=N) are seen at 153.7 ppm. Moreover, ten aromatic carbons of different phenyl groups resonate between 125.0-141.0 ppm. Finally, three CH_2 carbon give peaks at 39.1, 37.9 and 22.5 ppm, respectively (Figure 19).

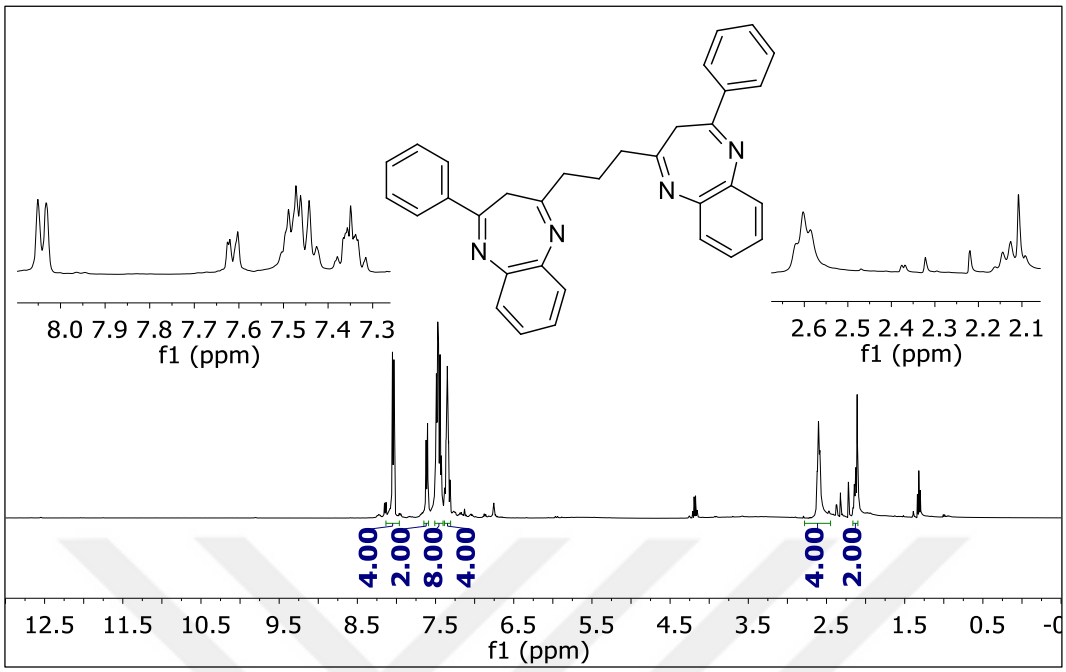


Figure 18. ^{1}H NMR spectrum of 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (**42a**).

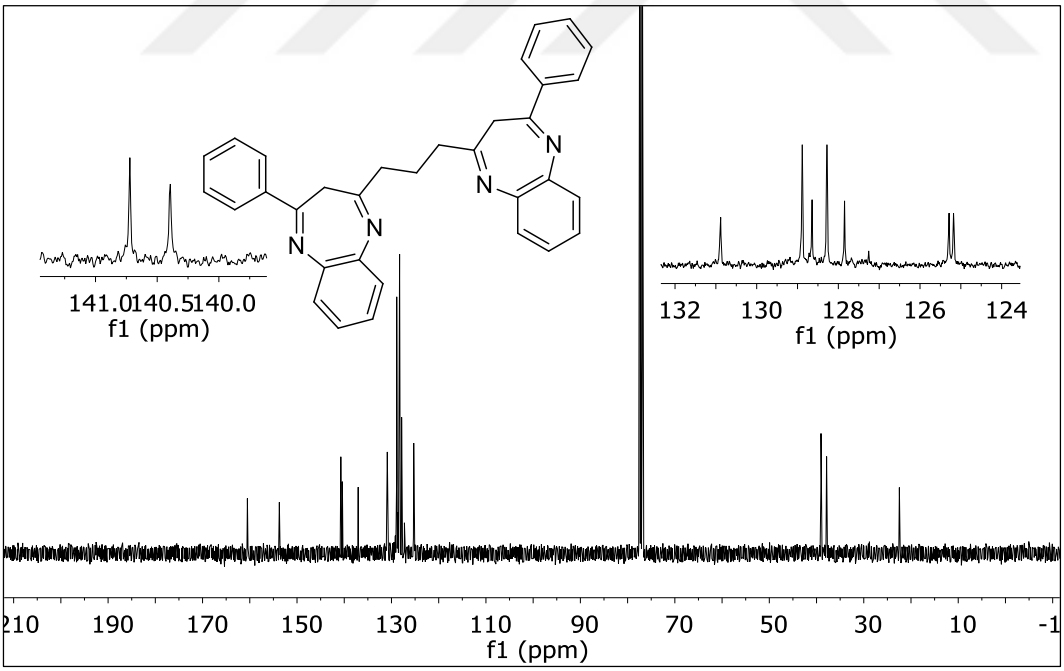
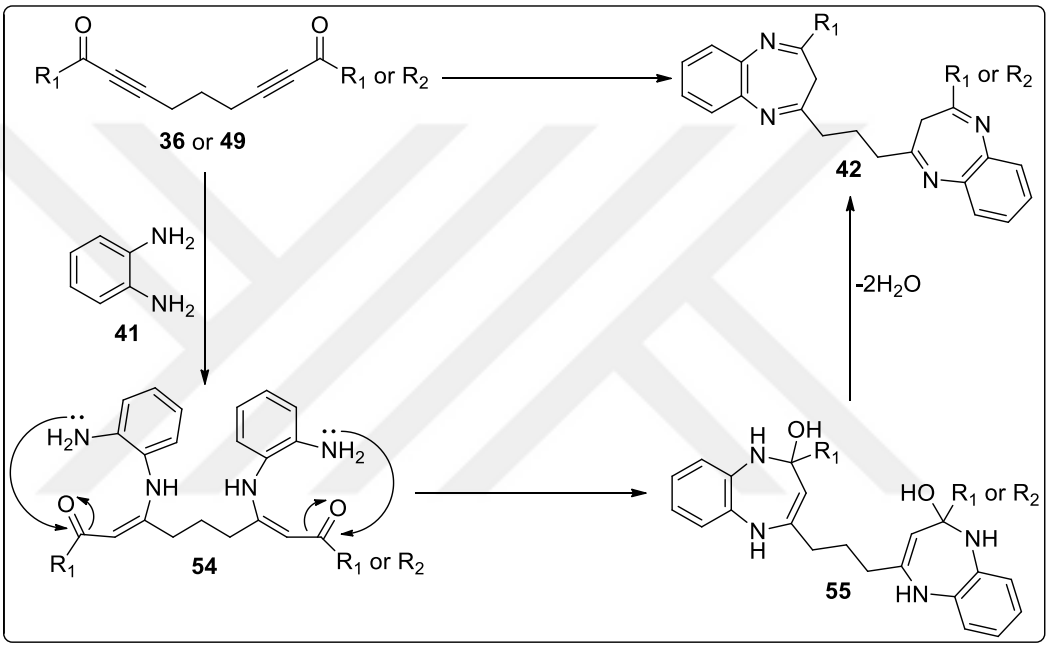


Figure 19. ^{13}C NMR spectrum of 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (**42a**).

Proposed mechanism for the synthesis of 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane derivatives (**42**) is represented in Scheme 21. Initially, 1,4-conjugate addition of one amino group of *o*- phenylenediamine (**41**) to starting material **36** or **49** generates addition product **54**. Then, cyclocondensation of the other amino group of **41** with carbonyl group yields intermediate **55**. Finally, water elimination, followed by isomerization, affords the target product **42** (Scheme 21).

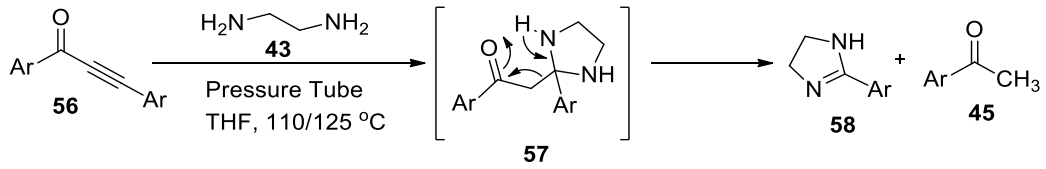


Scheme 21. Proposed mechanism for the synthesis of 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane derivatives (**42**).

2.2.3 One-Pot Synthesis of 5-Alkylidene-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine Derivatives 44

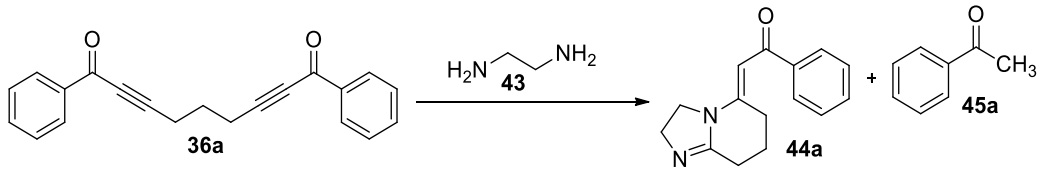
In the last part of thesis study, we expanded the scope of reactions of the starting material **36** and we tried reaction with ethylenediamine (**43**). In fact, we were inspired by a study of Vasilevsky and Alabugin research groups in which alkynic ketone **56** reacts with ethylenediamine (**43**), leading to the formation of intermediate

57 (Scheme 22).[63] Then, a retro-Mannich fragmentation takes place, which produces dihydroimidazole **58**, along with aryl methyl ketone **45**. Importantly, in this reaction, alkynic bond of ketone **56** breaks down and this enables the formation of dihydroimidazole **58** and methyl ketone **45**, as shown in Scheme 22.[63]



Scheme 22. Study of the Vasilevsky and Alabugin research groups.

When we tried same reaction with our starting material bis-α,β-alkynic ketone **36a**, we discovered a new and unprecedent method for the synthesis of 5-alkylidene-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine **44a** along with acetophenone (**45a**) (Scheme 23). This reaction revealed that the formation of acetophenone (**45a**) is an indication of the formation of hexahydroimidazo[1,2-*a*]pyridine **44a**, as it will be discussed in the mechanism. Then, we investigated the full details of this one-pot method for the synthesis of hexahydroimidazo[1,2-*a*]pyridines **44** from the reaction of ethylenediamine (**43**) with bis-α,β-alkynic ketones **36**.



Scheme 23. Synthesis of 5-alkylidene-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine **44a**.

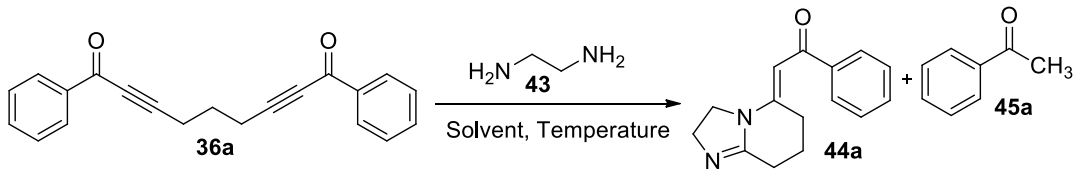
In order to optimize the reaction conditions, we examined the reactions of 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**) with ethylenediamine (**43**) under several

conditions, as shown in Table 9. Firstly, we performed the reactions of starting compound **36a** by varying the amount of ethylenediamine (**43**) in dioxane at reflux condition. These reactions afforded hexahydroimidazo[1,2-*a*]pyridine **44a** in 41-54% yields (Table 9, entries 1-3). The reaction with 2.0 equiv. of ethylenediamine (**43**) gave the highest yield (54%) (Table 9, entry 2). The reaction at room temperature did not produce the expected product **44a** (Table 9, entry 4). In addition, same reaction was carried out in pressure tubes with different amounts of solvents (Table 9, entries 5 and 6) since we anticipated that the use of pressure tube could increase the yield of **44a** in the concentrated condition. However, these reactions did not improve the yield of hexahydroimidazo[1,2-*a*]pyridine **44a**. So far, it was observed that the reactions conducted with 1.0 and 2.0 equiv. of ethylenediamine (**43**) gave the highest yields of the product **44a** (51 and 54%, respectively). Therefore, the same reactions were performed with different solvents. Subsequently, the starting compound **36a** was refluxed in toluene by employing 1.0 and 2.0 equiv. of ethylenediamine (**43**) (Table 9, entries 7 and 8). These reactions yielded the desired product **44a** in 48 and 53% yields, respectively. After obtaining the highest yield from the reaction in the presence of 2.0 equiv. of ethylenediamine (**43**), we continued the optimization reactions with 2.0 equiv. of ethylenediamine (**43**) by using other solvents at different polarity. Next, the reaction of starting compound **36a** was refluxed with ethylenediamine (**43**) in *p*-xylene, which formed hexahydroimidazo[1,2-*a*]pyridine **44a** in 45% yield (Table 9, entry 9). When the reaction time was increased for this reaction, yield decreased to 35%, probably owing to decomposition (Table 9, entry 10). Then, same reaction was carried out in MeCN and $CHCl_3$ under reflux conditions. These furnished desired product **44a** in low yields (31 and 37%, respectively), (Table 9, entries 11 and 12). Moreover, we conducted the reaction of 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**) with ethylenediamine (**43**) in alcohols such as MeOH, EtOH, *n*-propanol, isopropanol and *n*-BuOH under reflux conditions (Table 9, entries 13-17). While reaction in MeOH formed the expected product **44a** in 44% yield, other reactions gave this product in lower yields (15-39%). Even it was also observed that no product was obtained from

the reaction with *n*-BuOH. After these reactions, we further expanded the solvent scope of the reaction and thus, starting material **36a** was refluxed in water, DMF and DMSO, but reactions in water and DMSO did not yield the target product **44a** (Table 9, entries 18 and 20). Reaction in DMF did not also show a significant increase in the yield of product **44a** and afforded the product **44a** in 35% (Table 9, entry 19).

As a result of optimization studies, we decided to carry out the derivatization studies by using 1.0 equiv. of 1,9-diarylnona-2,7-diyne-1,9-diones **36** and 2.0 equiv. of ethylenediamine (**43**) in dioxane at reflux condition since this condition gave the highest yield of the product **44a** in 54% yield (Table 9, entry 2).

Table 9. Optimization studies for the synthesis of 5-alkylidene-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridines **44a**.[a,b]



Entry	Equiv. of 43[c]	Solvent	Temp. (°C)	Time (h)	Yield (%) of 44a	Yield (%) of 45a[d]
1	1.0	Dioxane	101	5	51	n.d.
2	**2.0**	**Dioxane**	**101**	**4**	**54**	**41**
3	3.0	Dioxane	101	7	41	n.d.
4	2.0	Dioxane	RT	20	–	–
5[e]	2.0	Dioxane	101	5	37	12
6[f]	2.0	Dioxane	101	5	40	n.d.
7	1.0	Toluene	110	3	48	n.d.
8	2.0	Toluene	110	3	53	20
9	2.0	*p*-Xylene	138	2	45	29
10	2.0	*p*-Xylene	138	6	35	n.d.
11	2.0	MeCN	82	6	31	n.d.
12	2.0	$CHCl_3$	62	6	37	13
13	2.0	MeOH	65	6	44	11
14	2.0	EtOH	78	2	39	46

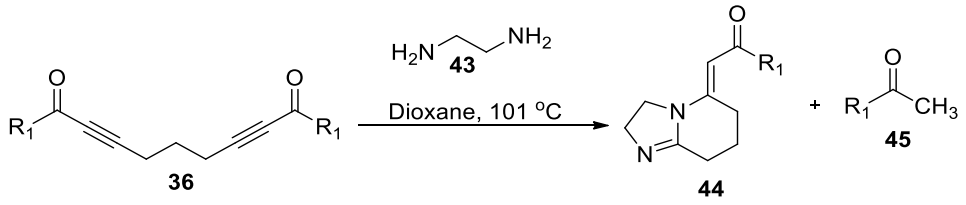
15	2.0	*n*-Propanol	97	7	15	n.d.
16	2.0	Isopropanol	82.5	8	16	n.d.
17	2.0	*n*-BuOH	117	4	–	–
18	2.0	Water	100	7	–	–
19[g]	2.0	DMF	120	6	35	43
20	2.0	DMSO	120	4.5	–	–

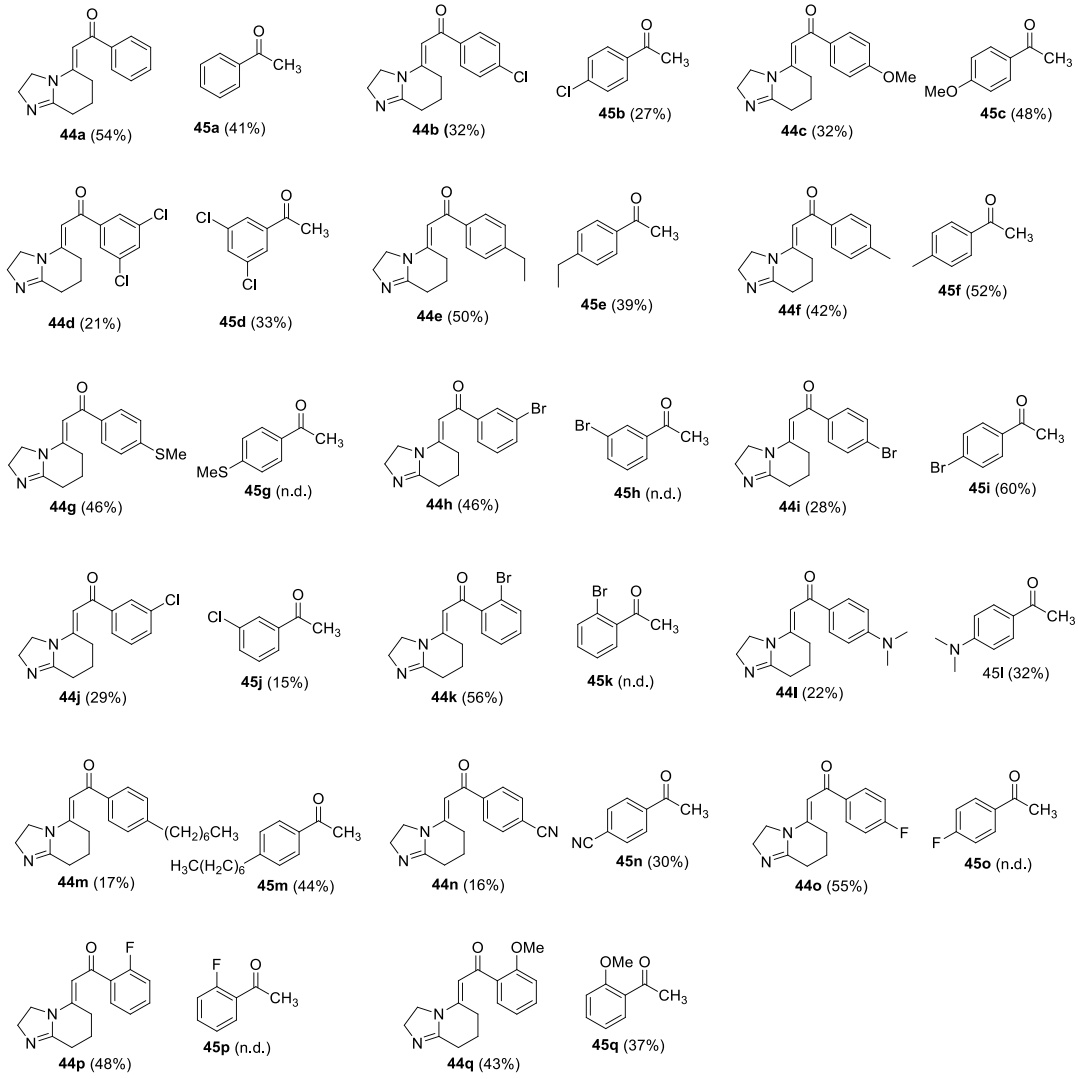
[a]Isolated yields. [b] The reactions were performed on a scale of 0.25 mmol of 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**) in 5 mL of solvent. [c]Equivalency of **43** is given according to that of **36a**. [d]*n.d.* = Yield not determined. [e]This reaction was performed by using a pressure tube in 2.5 mL of solvent. [f]This reaction was conducted by using a pressure tube. [g]This reaction was carried out in the presence of 2 mL of solvent.

By employing the optimized reaction conditions, we undertook a derivatization study (Table 10). All reactions proceeded well and yielded the expected products **44**. Overall, we synthesized 17 derivatives of 5-alkylidene-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridines **44** including electron-donating and electron-withdrawing substituents, and their yield changed from 15 to 56%. Due to its impact in pharmaceutical chemistry[64], many halogenated derivatives have been synthesized. Among the synthesized derivatives, the highest yield (56%) was obtained for the synthesis of product **44k** while the lowest yield (16%) was obtained for the synthesis of product **44n**. On the other hand, *p*-ethyl, *p*-methyl and *p*-methylthio-substituted-hexahydroimidazo[1,2-*a*]pyridine derivatives **44e-44g** were synthesized in 42-50% yields. Additionally, various aryl methyl ketone derivatives **45** were isolated along with the expected products **44** (Table 10) because the formation of intermediate **61** occurs concomitantly with the formation of methyl ketone derivatives **45** as it will be discussed in the mechanism.

This reaction was performed in a relatively larger scale as well. From this reaction, hexahydroimidazo[1,2-*a*]pyridine **44a** and acetophenone (**45a**) were isolated with the yields of 43 and 33%, respectively.

Table 10. Synthesis of 5-alkylidene-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine derivatives **44.**[a,b,c]



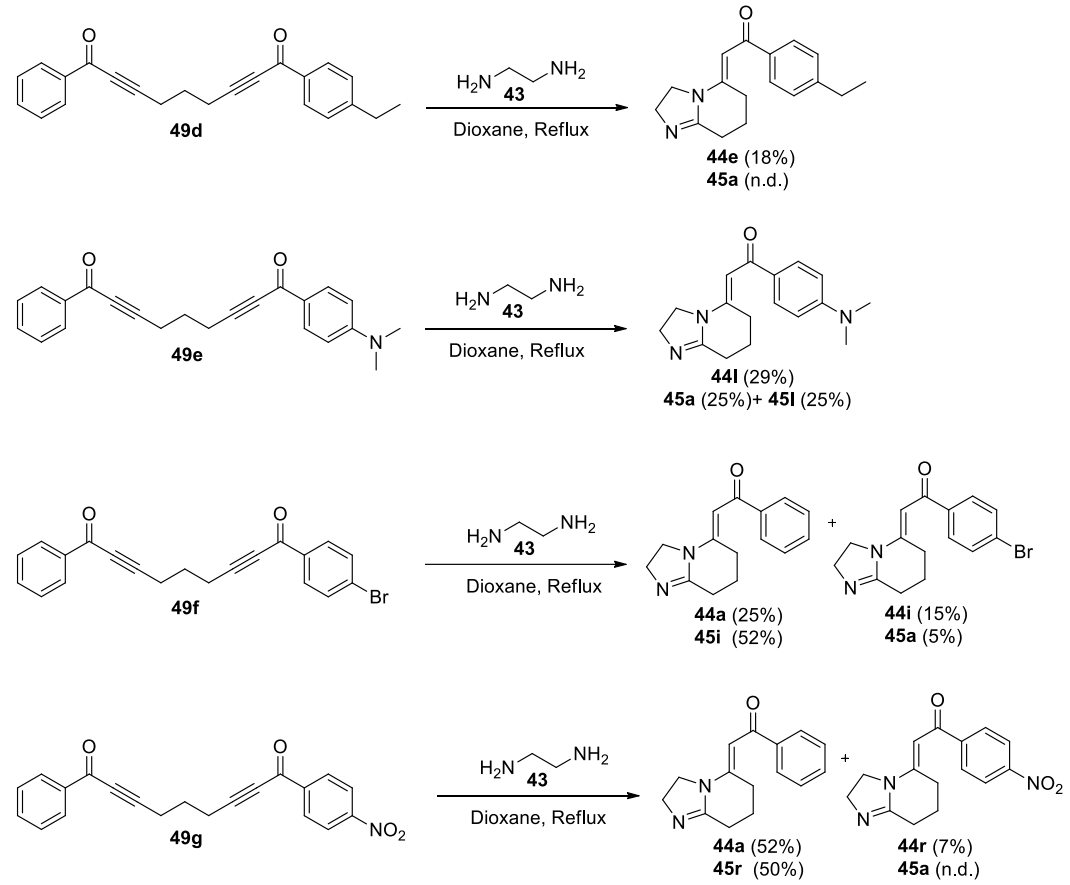


[a]Isolated yields. [b]*n.d.* = Yield not determined. [c]The reactions were performed on a scale of 0.25 mmol of bis-*α,β*-alkynic ketones **36** and 0.50 mmol of ethylenediamine **43** in 5 mL of dioxane at reflux. For workup and purification, see Experimental Section.

In this study, all aspects of the reaction were tried to be covered. Therefore, the reactions of ethylenediamine (**43**) with unsymmetrical bis-α,β-alkynic ketones **49** were also investigated. For this purpose, firstly, reactions were performed with unsymmetrical starting materials **49d** and **49e** including *p*-ethyl and *p*-dimethylamino substituents as the weak and strong electron-donating groups, respectively. Here, reactions proceeded from the less electrophilic carbonic side, yielding the hexahydroimidazo[1,2-*a*]pyridine derivatives **44e** and **44l** in 18 and 29% yields, respectively. Apart from this, a mixture of acetophenone derivatives **45a** and **45l** was also isolated from the reaction of unsymmetrical bis-α,β-alkynic ketone **49e**. In fact, the formation of **45l** in this reaction was an indicatican of the occurance of **44a** but it was unable to get this compound from the column chromatography, possibly due to low yield or it could escape from isolation (Table 11). However, the reaction of unsymmetrical bis-α,β-alkynic ketone **49f** with ethylenediamine (**43**) formed a mixture of hexahydroimidazo[1,2-*a*]pyridine derivatives **44a** and **44i** along with a mixture of acetophenone derivatives **45a** and **45i**. Similarly, the reaction of unsymmetrical bis-α,β-alkynic ketone **49g** with ethylenediamine (**43**) produced a mixture of hexahydroimidazo[1,2-*a*]pyridine derivatives **44a** and **44r**. From this reaction, only one acetophenone derivative **45r** could be isolated (Table 11). Unfortunately, the other expected acetophenone derivative **45a** could not be isolated from this reaction.

According to these reactions, unsymmetrical bis-α,β-alkynic ketones **49** affect the electrophilicity of the carbonyl and alkynyl groups because of including two various α,β-alkynic ketone functionalities, which influences the reaction pathway. Ethylenediamine (**43**) reacts with the more reactive (electrophilic) alkynyl ketone moiety containing electron-withdrawing group, which forms hexahydroimidazo[1,2-*a*]pyridine **44**, including electron-donating group and aryl methyl ketone **45**, including electron-withdrawing group as the major products. On the other hand, as less favored route, hexahydroimidazo[1,2-*a*]pyridine **44**, containing electron-withdrawing group and aryl methyl ketone **45**, containing electron-donating group can be generated as the minor products.

Table 11. Synthesis of 5-alkylidene-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine derivatives **44** from unsymmetrical bis-α,β-alkynic ketones **49**.[a,b,c]



[a]Isolated yields. [b]*n.d.* = Yield not determined. [c]Reactions were carried out on a scale of 0.25 mmol of unsymmetrical starting materials **49** and 0.50 mmol of ethylenediamine **43** in 5 mL dioxane solvent at reflux condition. For workup and purification, see Experimental Section.

All the synthesized 5-alkylidene-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine derivatives **44** were characterized by the spectra of ^{1}H and ^{13}C NMR, as summarized below.

In the ^{1}H NMR spectrum of 1-phenyl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (**44a**) (Figure 20), while exo vinylic hydrogen (=CH) resonates at 5.84 as a singlet, the peaks of the nitrogen-bonded methylene hydrogens (CH_2) come at 3.94 and 3.70 ppm as triplets while those of the other methylene hydrogens (CH_2) appear at 3.33, 2.62 and 1.83 ppm as triplets or a pentet. Finally, five aromatic hydrogens of phenyl group resonate between 7.0-8.0 ppm (Figure 20).

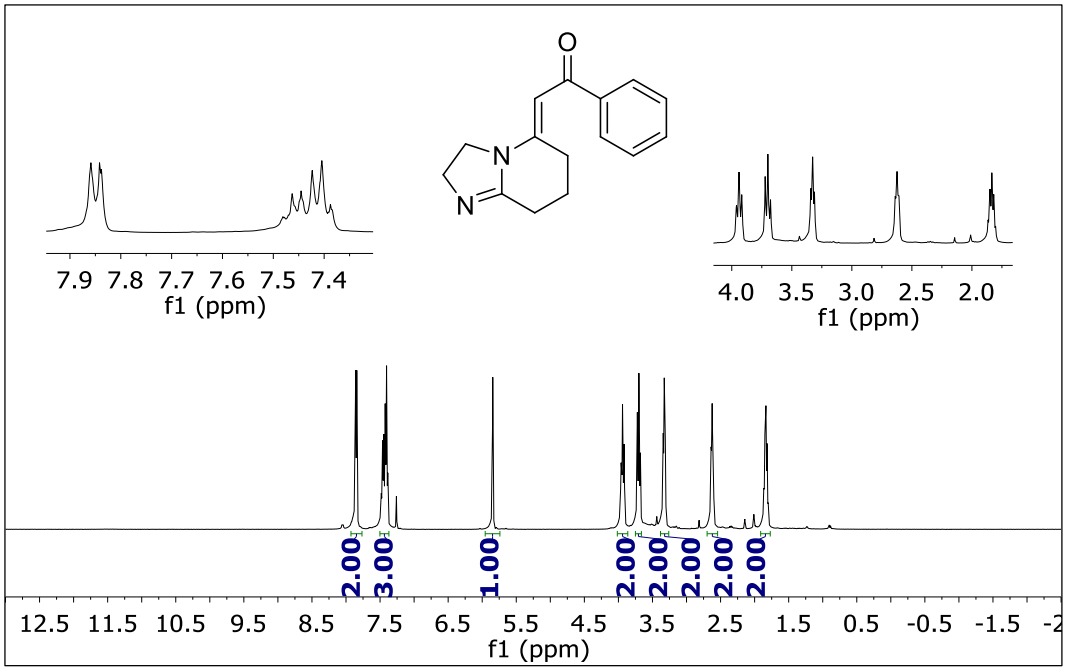


Figure 20. ^{1}H NMR spectrum of 1-phenyl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (**44a**).

In the ^{13}C NMR spectrum of 1-phenyl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (**44a**) (Figure 21), carbonyl carbon (C=O) gives a peak at 190.2 ppm while the peak of nitrogen-bonded carbon (C=N) comes at 158.3 ppm. Four aromatic carbons of phenyl group resonate between 126.0-142.0 ppm. Apart

from this, one of the exo double bond carbons (═C) resonate at 155.6 ppm while the other carbon (═CH) resonates at 96.7 ppm. Finally, methylene carbons (CH_2) show peaks between 53.0-18.0 ppm.

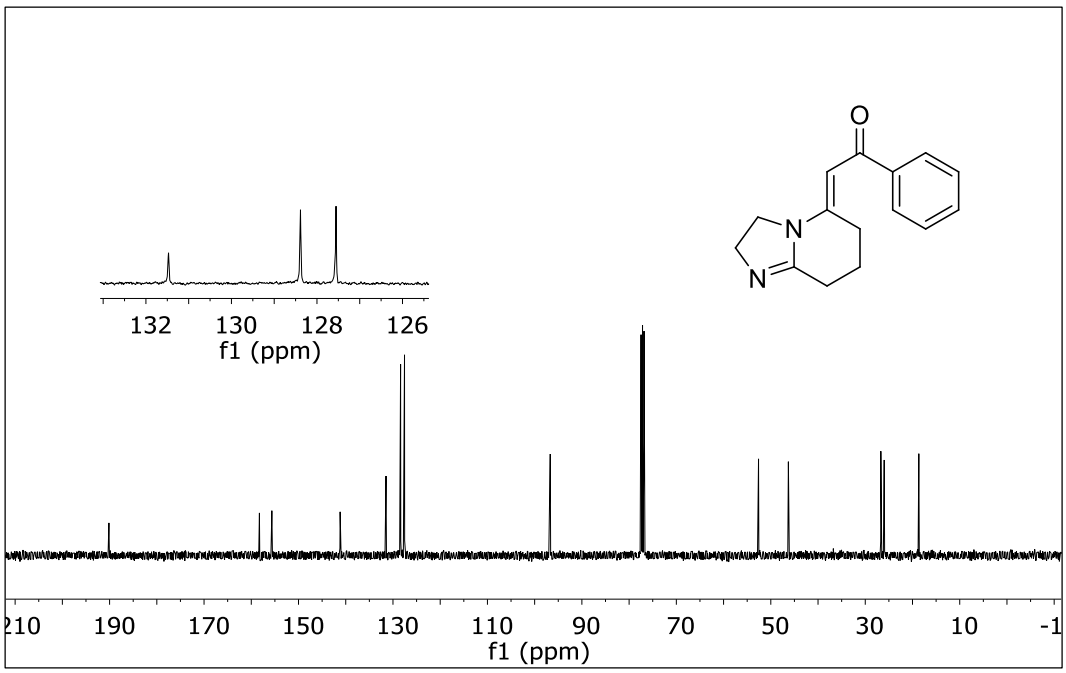


Figure 21. ^{13}C NMR spectrum of 1-phenyl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (**44a**).

We also examined the geometry of exo double bond, by obtaining NOESY spectrum of compound **44a** (Figure 22). We found that this double bond has *E* stereochemistry as a result of the NOE interaction observed between exo vinylic hydrogen (CH) and nitrogen-bonded methylene hydrogens, as shown in Figure 22.

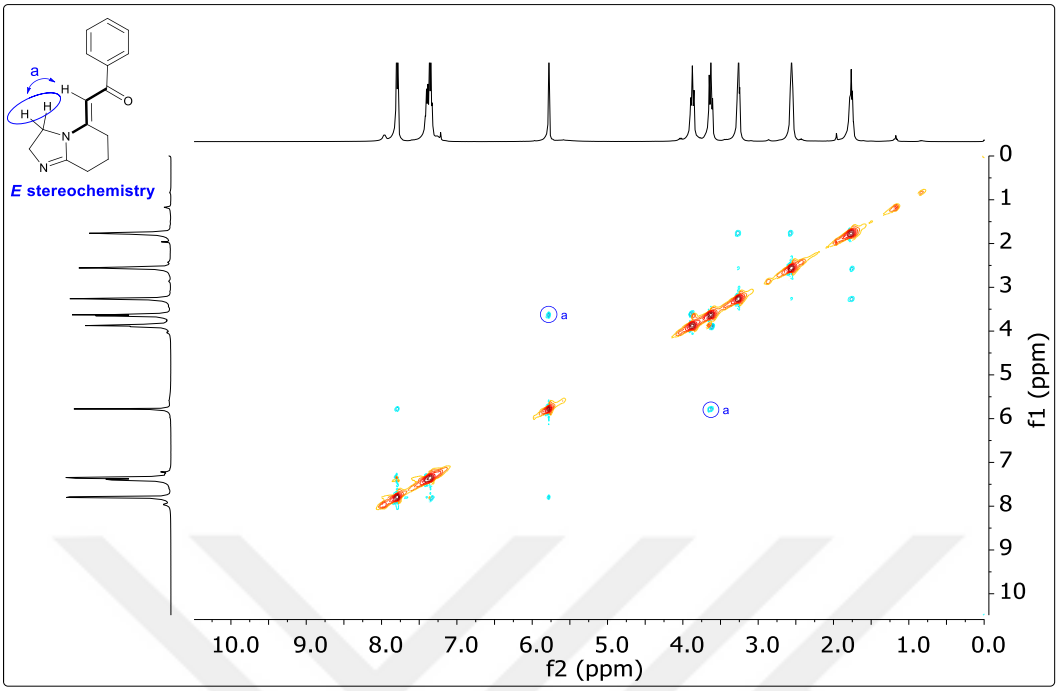
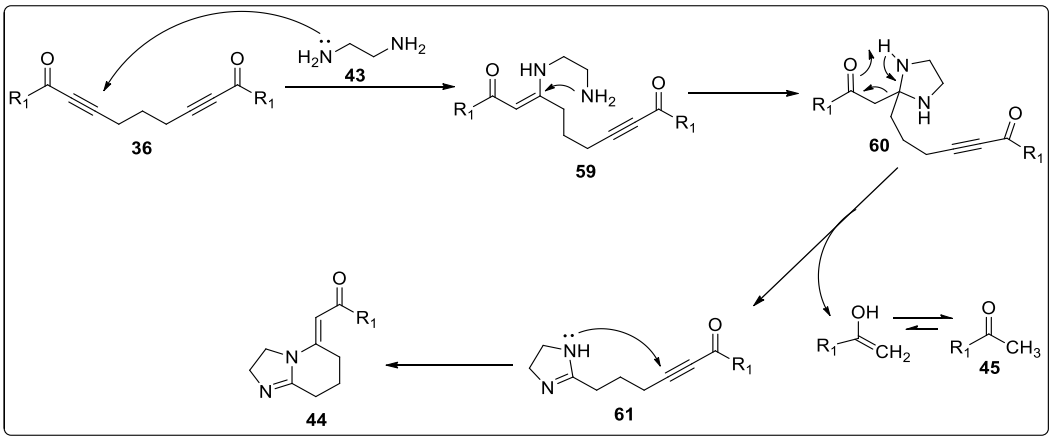


Figure 22. NOESY spectrum of 1-phenyl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (**44a**).

The proposed mechanism for the formation of 5-alkylidene-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine derivatives **44** is depicted in Scheme 24. First, intermolecular conjugate (Michael) addition of ethylenediamine (**43**) to bis-α,β-alkynic ketone **36** happens and the resulting intermediate **59** experiences second intramolecular conjugate (Michael) addition to form five-membered intermediate **60**. Then, this intermediate undergoes a retro-Mannich fragmentation to yield dihydroimidazolyl-substituted α,β-alkynic ketone **61**, along with the corresponding enol, which converts into methyl ketone **45** after tautomerization, which is an indication of the formation of product **44** and the formation of intermediate **61** and aryl methyl ketone **45** is consistent with the findings of earlier researchers.[63] Finally, another intramolecular conjugate (Michael) addition in **61** takes place to afford the target compound **44** (Scheme 24).

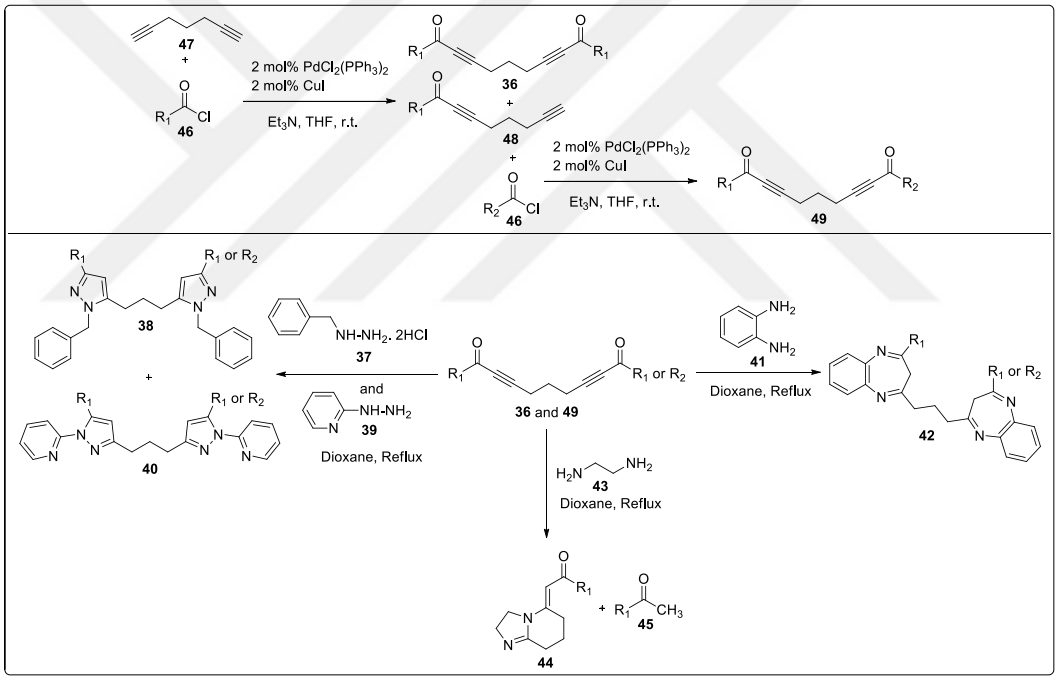


Scheme 24. Proposed mechanism for the synthesis of 5-alkylidene-2,3,5,6,7,8-hexahydroimidazo[1,2-*a*]pyridine derivatives **44**.

CHAPTER 3

CONCLUSION

In summary, many novel and potentially bioactive 1,3-bis-pyrazoles **38** and **40**, 1,3-bis-benzo[*b*][1,4]diazepines **42** and hexahydroimidazo[1,2-*a*]pyridines **44** have been synthesized from symmetrical and/or unsymmetrical bis-α,β-alkynic ketones **36**, as illustrated in Scheme 25.



Scheme 25. General routes for the synthesis of target compounds.

The best conditions were determined by performing the optimization studies for the synthesis of these new compounds. For this purpose, firstly, the starting materials **36** were synthesized, as shown in Scheme 25. 20 different symmetrical 1,9-diarylnona-2,7-diyne-1,9-diones **36** were synthesized by the Sonogashira cross-coupling

reaction of 1,6-heptadiyne (**47**) and aryloyl chlorides **46** in the presence of Pd and Cu catalysts with 23-64% yields. In addition, 7 unsymmetrical 1,9-diarylnona-2,7-diyne-1,9-dione derivatives **49** were prepared by the Sonogashira cross-coupling reaction of 1-arylocta-2,7-diyn-1-ones **48** with aryloyl chlorides **46** in 32-81% yields.

After synthesis of starting materials **36** and **49**, the most suitable reaction conditions were explored to obtain desired products. Therefore, optimization reactions were conducted to synthesize 1,3-bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propanes (**38**) and 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propanes (**40**). As a result of these optimization studies, the best yields (54% and 36%) were obtained from the reaction of 1.0 equiv. of starting material (**36** or **49**) with 2.0 equiv. of benzylhydrazine dihydrochloride (**37**) or 2-hydrazinopyridine (**39**) in dioxane at reflux condition. According to this condition, 20 different derivatives of 1,3-bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propane (**38**) and 1,3-bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (**40**) were synthesized, bearing electron-donating and electron-withdrawing substituents.

Moreover, 1,9-diarylnona-2,7-diyne-1,9-dione **36** were subjected to some reactions to yield 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane derivatives (**42**). Therefore, reaction conditions were optimized in the presence of starting compound **36** with *o*-phenylenediamine (**41**). The best reaction condition afforded the desired product **42** with 60% yield in dioxane at reflux condition. According to this condition, 15 different 1,3-bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane derivatives (**42**) were synthesized in moderate to good yields (19-60%).

Finally, the reactions of bis-α,β-alkynic ketones **36** with ethylenediamine (**43**) were investigated. This one-pot reaction afforded a new and novel method for the synthesis of 1-aryl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone derivatives **44** and aryl methyl ketone derivatives **45**. After many optimization reactions, the highest yield (54%) was obtained from the reaction of 1.0

equiv. of starting material **36** with 2.0 equiv. of ethylenediamine (**43**) in dioxane at reflux condition. 17 derivatives of hexahydroimidazo[1,2-*a*]pyridines **44** with various substituents were synthesized in 16-56% yieds. The reactions of unsymmetrical bis-α,β-alkynic ketones **49** with ethylenediamine (**43**) were also investigated. It was found that unsymmetrical starting materials **49** influence the reaction pathway by affecting the electrophilicity of the carbonyl and alkynyl groups due to the addition of two different α,β-alkynyl ketone functionalities to the aryl groups.

CHAPTER 4

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts were given in parts per million (ppm) relative to $CDCl_3$ (7.26 and 77.16 ppm in ^{1}H and ^{13}C NMR, respectively). Coupling constants (*J*) were given in hertz (Hz), and spin multiplicities were shown by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet) and m (multiplet). Infrared (IR) spectra were obtained using attenuated total reflection (ATR). Band positions were recorded in reciprocal centimeters (cm^{-1}). Mass spectra (MS) and high-resolution MS (HRMS) were obtained using electrospray ionization (ESI) with micro-Tof; *m/z* values are reported (for each measurement, the mass scale was recalibrated with sodium formate clusters, and samples were dissolved and measured in MeOH or CH_3CN). Flash chromatography was performed using thick-walled glass columns and "flash-grade" silica gel (230−400 mesh). TLC was accomplished by using commercially prepared 0.25 mm silica gel plates and visualization was effected with a short-wavelength UV lamp (254 nm). The relative proportions of solvents in chromatography refer to the volume/volume ratio. All commercially available reagents were used directly without purification unless otherwise stated. All solvents used in reactions and chromatography were distilled and/or dried properly for purity. The inert atmosphere was created using slight positive pressure (ca. 0.1 psi) of argon. All glassware was dried in an oven prior to use.

4.1 General Procedure 1. Synthesis of 1,9-Diarylnona-2,7-diyne-1,9-dione Derivatives 36

To a stirred solution of the proper aryloyl chloride **46** (3.26 mmol) in THF (12 mL) under argon was added $PdCl_2(PPh_3)_2$ (0.033 mmol) and Et_3N (1.96 mmol), and the resulting mixture was stirred for 10 min at room temperature and CuI (0.033 mmol) was added. After stirring the reaction mixture for another 10 min, 1,6-heptadiyne (**47**) (1.63 mmol) was added slowly, and the stirring at room temperature continued until the end of the reaction (The progress of the reaction was monitored by routine TLC analysis for the disappearance of 1,6-heptadiyne (**47**) using 9:1 hexane/ethyl acetate as the eluent). After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (50 mL) and a saturated aqueous solution of NH_4Cl solution (50 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford the corresponding symmetrical 1,9-diarylnona-2,7-diyne-1,9-dione **36** and 1-arylocta-2,7-diyn-1-one **48**.

4.1.1 Synthesis of 1,9-Diphenylnona-2,7-diyne-1,9-dione (36a)

General Procedure **1** was followed by using benzoyl chloride (458.4 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 92.6 mg (29%) of the indicated product **48a** as dark brownish orange oil (R_f = 0.62 in 4:1 hexane/ethyl acetate). Second fraction gave 227.7 mg (47%) of the indicated product **36a** as an orange solid (R_f = 0.37 in 4:1 hexane/ethyl acetate; mp 55.5–58.2°C).

36a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 2H), 8.10 (d, *J* = 1.2 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 2H), 7.45 (t, *J* = 7.7 Hz, 4H), 2.70 (t, *J* = 7.0 Hz, 4H), 2.03 (p, *J* = 7.0 Hz,

2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (CO), 136.5 (C), 134.0 (CH), 129.4 (CH), 128.5 (CH), 94.3 (C), 80.3 (C), 25.9 (CH_2), 18.3 (CH_2); IR (neat): 3055, 2233, 2195, 1635, 1577, 1445, 1311, 1261, 1171, 1015, 921, 893, 793, 691, 615, 502, 425 cm^{-1}; MS (ESI, m/z): 301.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{17}O_2$: 301.1223 $[M+H]^+$, found: 301.1227.

48a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17–8.10 (m, 2H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.50–7.43 (m, 2H), 2.65 (t, *J* = 7.1 Hz, 2H), 2.39 (td, *J* = 6.8, 2.3 Hz, 2H), 2.02 (t, *J* = 2.3 Hz, 1H), 1.89 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (CO), 136.7 (C), 134.0 (CH), 129.6 (CH), 128.6 (CH), 95.3 (C), 82.7 (C), 80.0 (C), 69.6 (CH), 26.6 (CH_2), 18.1 (CH_2), 17.7 (CH_2); IR (neat): 2922, 2853, 2236, 2198, 1686, 1642, 1604, 1570, 1457, 1414, 1309, 1264, 1176, 1114, 1018, 920, 851, 754, 694, 635, 549 cm^{-1}; MS (ESI, m/z): 197.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{13}O$: 197.0961 $[M+H]^+$, found: 197.0960.

4.1.2 Synthesis of 1,9-Bis(4-chlorophenyl)nona-2,7-diyne-1,9-dione (36b)

General Procedure **1** was followed by using 4-chlorobenzoyl chloride (570.5 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 21 mg (6%) of the indicated product **48b** as brownish orange oil (R_f = 0.83 in 4:1 hexane/ethyl acetate). Second fraction gave 382.7 mg (64%) of the indicated product **36b** as a brown solid (R_f = 0.37 in 4:1 hexane/ethyl acetate; mp 135.0–137.0 ºC).

36b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 4H), 7.41 (d, *J* = 8.5 Hz, 4H), 2.70 (t, *J* = 7.0 Hz, 4H), 2.03 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (CO), 140.7 (C-Cl), 135.0 (C), 130.9 (CH), 129.0 (CH), 94.8 (C), 80.2 (C), 25.9 (CH_2), 18.5 (CH_2); IR (neat): 2234, 2195, 1786, 1639, 1587, 1483, 1398, 1260, 1223, 1171, 1088, 1008, 924, 897, 843, 743, 674, 629, 523, 471 cm^{-1}; MS (ESI, m/z): 369.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{15}Cl_2O_2$: 369.0444 $[M+H]^+$, found: 369.0454.

48b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 2.64 (t, *J* = 6.8 Hz, 2H), 2.37 (td, *J* = 6.9, 2.2 Hz, 2H), 2.02 (t, *J* = 2.7 Hz, 1H), 1.88 (p, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (CO), 140.6 (C-Cl) 135.2 (C), 130.9 (CH), 129.0 (CH), 95.9 (C), 82.7 (C), 79.8 (C), 69.8 (C), 26.6 (CH_2), 18.2 (CH_2), 17.8 (CH_2); IR (neat): 3300, 2939, 2235, 2198, 1736, 1644, 1586, 1485, 1399, 1260, 1170, 1089, 1011, 844, 745, 674, 632, 524, 474 cm^{-1}; MS (ESI, m/z): 231.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{12}ClO$: 231.0571 $[M+H]^+$, found: 231.0574.

4.1.3 Synthesis of 1,9-Bis(4-methoxyphenyl)nona-2,7-diyne-1,9-dione (36c)

General Procedure **1** was followed by using 4-methoxybenzoyl chloride (556.1 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 42 mg (11%) of the indicated product **48c** as brownish orange oil (R_f = 0.41 in 4:1 hexane/ethyl acetate). Second fraction gave 369.3 mg (63%) of the indicated product **36c** as brownish orange oil (*R*f = 0.13 in 4:1 hexane/ethyl acetate).

36c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.9 Hz, 4H), 6.92 (d, *J* = 8.8 Hz, 4H), 3.86 (s, 6H), 2.69 (t, *J* = 7.0 Hz, 4H), 2.02 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (CO), 164.5 (C-OMe), 132.0 (CH), 130.1 (C), 113.9 (CH), 93.6 (C), 80.5 (C), 55.7 (OMe), 26.1 (CH_2), 18.5 (CH_2); IR (neat): 2915, 2849, 2237, 2197, 1735, 1594, 1571, 1507, 1458, 1420, 1252, 1164, 1110, 1021, 898, 842, 755, 685, 596, 507 cm^{-1}; MS (ESI, m/z): 361.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{21}O_4$: 361.1434 $[M+H]^+$, found: 361.1439.

48c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 3.82 (s, 3H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.34 (td, *J* = 6.9, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.84 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7 (CO), 164.3 (C-OMe), 131.9 (CH), 130.1 (C), 113.8 (CH), 94.3 (C), 82.8 (C), 80.0 (C), 69.6 (C), 55.5 (OMe), 26.6 (CH_2), 18.1 (CH_2), 17.7 (CH_2); IR (neat): 2933, 2838,

2234, 2196, 1716, 1631, 1591, 1570, 1456, 1420, 1317, 1250, 1162, 1109, 1022, 915, 842, 756, 685, 595, 540, 507, 418 cm^{-1}; MS (ESI, m/z): 227.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{15}O_2$: 227.1067 $[M+H]^+$, found: 227.1069.

4.1.4 Synthesis of 1,9-Bis(3,5-dichlorophenyl)nona-2,7-diyne-1,9-dione (36d)

General Procedure **1** was followed by using 3,5-dichlorobenzoyl chloride (683 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 144 mg (33%) of the indicated product **48d** as dark orange oil (R_f = 0.88 in 4:1 hexane/ethyl acetate). Second fraction gave 251.9 mg (35%) of the indicated product **36d** as a light brown solid (R_f = 0.57 in 4:1 hexane/ethyl acetate; mp 90.1–92.6 ^oC).

36d: ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 1.7 Hz, 4H), 7.53 (s, 2H), 2.74 (t, *J* = 7.0 Hz, 4H), 2.06 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0 (CO), 139.0 (C), 135.7 (C-Cl), 133.7 (CH), 127.8 (CH), 95.9 (C), 79.8 (C), 25.8 (CH_2), 18.6 (CH_2); IR (neat): 3742, 3067, 2208, 1646, 1563, 1426, 1398, 1248, 1138, 1100, 987, 953, 877, 802, 774, 738, 656, 631, 474 cm^{-1}; MS (ESI, m/z): 436.96 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{13}Cl_4O_2$: 436.9664 $[M+H]^+$, found: 436.9659.

48d: ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.9 Hz, 2H), 7.55 (s, 1H), 2.67 (t, *J* = 7.1 Hz, 2H), 2.39 (td, *J* = 6.8, 2.7 Hz, 2H), 2.03 (t, *J* = 2.6 Hz, 1H), 1.89 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2 (CO), 139.2 (C) 135.7 (2C-Cl), 133.6 (CH), 127.8 (2CH), 97.2 (C), 82.6 (C), 79.5 (C), 69.9 (CH), 26.5 (CH_2), 18.3 (CH_2), 17.8 (CH_2). (Note that two C and CH peaks overlap with each other); IR (neat): 3305, 3067, 2945, 2211, 1793, 1732, 1683, 1652, 1565, 1541, 1521, 1507, 1488, 1473, 1456, 1428, 1251, 1203, 1105, 1039, 992, 865, 802, 743, 658, 630 cm^{-1}; MS (ESI, m/z): 265.01 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{11}Cl_2O$: 265.0182 $[M+H]^+$, found: 265.0179.

4.1.5 Synthesis of 1,9-Bis(4-ethylphenyl)nona-2,7-diyne-1,9-dione (36e)

General Procedure **1** was followed by using 4-ethylbenzoyl chloride (549.7 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 106.7 mg (29%) of the indicated product **48e** as orange oil (R_f = 0.68 in 4:1 hexane/ethyl acetate). Second fraction gave 265.9 mg (46%) of the indicated product **36e** as brownish orange oil (R_f = 0.4 in 4:1 hexane/ethyl acetate).

36e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 4H), 7.20 (d, *J* = 8.1 Hz, 4H), 2.62 (q, *J* = 7.5 Hz, 8H), 1.96 (p, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (CO), 151.4 (C-CH_2CH_3), 134.7 (C), 129.9 (CH), 128.2 (CH), 93.8 (C), 80.5 (C), 29.1 (CH_2), 26.1 (CH_2), 18.5 (CH_2), 15.2 (CH_3); IR (neat): 2965, 2933, 2872, 2235, 2196, 1637, 1602, 1568, 1414, 1308, 1262, 1175, 1112, 1050, 976, 919, 898, 876, 848, 753, 690, 629, 594, 518, 419 cm^{-1}; MS (ESI, m/z): 357.18 $[M+H]^+$; HRMS (ESI) calcd. for $C_{25}H_{25}O_2$: 357.1849 $[M+H]^+$, found: 357.1844.

48e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 8.3, 2.2 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 2.75–2.58 (m, 4H), 2.39 (ddt, *J* = 6.6, 4.9, 2.4 Hz, 2H), 2.03 (d, *J* = 2.6 Hz, 1H), 1.88 (ddd, *J* = 13.6, 6.9, 2.2 Hz, 2H), 1.30–1.20 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (CO), 151.2 (C), 134.7 (C), 129.8 (CH), 128.1 (CH), 94.6 (C), 82.7 (C), 80.1 (C), 69.6 (CH), 29.0 (CH_2), 26.6 (CH_2), 18.1 (CH_2), 17.7 (CH_2), 15.2 (CH_3); IR (neat): 3298, 2965, 2934, 2235, 2197, 1717, 1686, 1638, 1603, 1569, 1541, 1507, 1456, 1415, 1309, 1264, 1176, 1110, 1051, 1017, 993, 905, 877, 849, 781, 753, 691, 631, 595, 518 cm^{-1}; MS (ESI, m/z): 225.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{17}O$: 225.1274 $[M+H]^+$, found: 225.1279.

4.1.6 Synthesis of 1,9-Di-*p*-tolylnona-2,7-diyne-1,9-dione (36f)

General Procedure **1** was followed by using 4-methylbenzoyl chloride (504 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 24 mg (7%) of the indicated product **48f** as brownish orange oil (R_f = 0.64 in 4:1 hexane/ethyl acetate). Second fraction gave 314.9 mg (59%) of the indicated product **32f** as an orange solid (R_f = 0.37 in 4:1 hexane/ethyl acetate; mp 77.9–81.2 ºC).

36f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 9.6 Hz, 4H), 7.26 (d, *J* = 7.4 Hz, 4H), 2.71 (t, *J* = 7.0 Hz, 4H), 2.41 (s, 6H), 2.04 (p, *J* = 6.8, 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7 (CO), 145.2 (C-Me), 134.4 (C), 129.6 (CH), 129.3 (CH), 93.8 (C), 80.4 (C), 26.0 (CH_2), 21.8 (CH_3), 18.4 (CH_2); IR (neat): 3742, 2919, 2242, 2202, 1744, 1631, 1603, 1571, 1404, 1267, 1168, 1111, 1013, 925, 894, 831, 793, 738, 677, 591, 521, 469, 418 cm^{-1}; MS (ESI, m/z): 329.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{21}O_2$: 329.1536 $[M+H]^+$, found: 329.1538.

48f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 2.67 (t, *J* = 7.0 Hz, 2H), 2.46 (s, 5H), 2.05 (t, *J* = 2.4 Hz, 1H), 1.91 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (CO), 162.6 (C), 145.6 (C), 130.6 (CH), 129.6 (CH), 94.7 (C), 82.8 (C), 80.1 (C), 69.6 (CH), 26.7 (CH_2), 21.9 (CH_3), 18.2 (CH_2), 17.7 (CH_2); IR (neat): 3290, 2935, 2235, 2195, 1781, 1717, 1637, 1603, 1571, 1540, 1507, 1455, 1430, 1309, 1266, 1221, 1174, 1110, 1038, 1003, 919, 834, 794, 741, 682, 634, 594, 517, 472, 445, 435, 425, 417 cm^{-1}; MS (ESI, m/z): 211.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{15}O$: 211.1117 $[M+H]^+$, found: 211.1077.

4.1.7 Synthesis of 1,9-Bis(4-(methylthio)phenyl)nona-2,7-diyne-1,9-dione (36g)

General Procedure **1** was followed by using 4-(methylthio)benzoyl chloride (407 mg, 2.18 mmol), $PdCl_2(PPh_3)_2$ (15.4 mg, 0.022 mmol), Et_3N (133.5 mg, 1.31 mmol), CuI (4.2 mg, 0.022 mmol) and 1,6-heptadiyne (**47**) (100 mg, 1.09 mmol) were employed

and this reaction formed two fractions. First fraction afforded 18.5 mg (7%) of the indicated product **48g** as dark brownish orange oil (R_f = 0.85 in 4:1 hexane/ethyl acetate). Second fraction gave 230 mg (54%) of the indicated product **36g** as light orange oil (R_f = 0.17 in 4:1 hexane/ethyl acetate).

36g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.5 Hz, 4H), 7.20 (d, *J* = 10.7 Hz, 4H), 2.68 (t, *J* = 7.0 Hz, 4H), 2.46 (s, 6H), 2.00 (p, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (CO), 147.5 (C-SMe), 133.0 (C), 129.7 (CH), 124.5 (CH), 93.9 (C), 80.2 (C), 25.9 (CH_2), 18.3 (CH_2), 14.5 (CH_3); IR (neat): 2920, 2238, 2193, 1629, 1583, 1552, 1399, 1310, 1263, 1178, 1086, 969, 918, 898, 874, 834, 743, 679, 519, 476 cm^{-1}; MS (ESI, m/z): 393.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{21}O_2S_2$: 393.0978 $[M+H]^+$, found: 393.0978.

48g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 3.8 Hz, 2H), 7.87 (d, *J* = 8.4 Hz, 2H), 2.76 (dt, *J* = 13.7, 7.1 Hz, 3H), 2.65 (q, *J* = 7.5, 7.0 Hz, 2H), 2.55 (s, 3H), 2.09 (p, *J* = 7.09 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (CO), 130.0 (C-SMe), 129.2 (C), 125.1 (CH), 124.9 (CH), 94.3 (C), 94.0 (C), 80.6 (C), 80.5 (CH), 25.2 (CH_2), 18.5 (CH_2), 18.1 (CH_2), 14.8 (CH_3); IR (neat): 3289, 2922, 2238, 2194, 1771, 1715, 1684, 1635, 1586, 1556, 1507, 1488, 1433, 1400, 1362, 1311, 1265, 1219, 1177, 1111, 1088, 1034, 995, 905, 871, 835, 759, 745, 681, 645, 518, 476, 417 cm^{-1}; MS (ESI, m/z): 243.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{15}OS$: 243.0838 $[M+H]^+$, found: 243.0831.

4.1.8 Synthesis of 1,9-Bis(4-nitrophenyl)nona-2,7-diyne-1,9-dione (36h)

General Procedure **1** was followed by using 4-nitrobenzoyl chloride (605 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 67.2 mg (17%) of the indicated product **48h** as brownish orange oil (R_f = 0.71 in 4:1 hexane/ethyl acetate). Second fraction gave 287.1 mg (45%) of the indicated product **36h** as a dark brown solid (R_f = 0.28 in 1:1 methanol/ethyl acetate; mp 144.1–148.9 °C).

36h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (q, *J* = 8.9 Hz, 8H), 2.78 (t, *J* = 7.0 Hz, 4H), 2.10 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 175.9 (CO), 151.0 (C-NO_2), 140.8 (C), 130.6 (CH), 124.0 (CH), 96.5 (C), 80.3 (C) 25.8 (CH_2), 18.6 (CH_2); IR (neat): 3743, 3079, 2970, 2309, 1736, 1693, 1650, 1601, 1519, 1427, 1343, 1282, 1230, 1103, 932, 872, 849, 800, 711, 513, 504, 442, 419 cm^{-1}; MS (ESI, m/z): 391.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{15}N_2O_6$: 391.0925 $[M+H]^+$, found: 391.0914.

48h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, *J* = 7.0, 3.0 Hz, 4H), 2.66 (t, *J* = 3.6 Hz, 2H), 2.38–2.35 (m, 2H), 2.02 (t, *J* = 2.8 Hz, 1H), 1.86 (p, *J* = 3.5 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9 (CO), 150.8 (C-NO_2), 140.9 (C), 130.4 (CH), 123.8 (CH), 97.8 (C), 82.5 (C), 79.7 (C), 69.8 (CH), 26.4 (CH_2), 18.2 (CH_2), 17.7 (CH_2); IR (neat): 3290, 2937, 2236, 2198, 1732, 1650, 1601, 1523, 1429, 1342, 1319, 1257, 1103, 1011, 921, 868, 849, 773, 709, 638, 506 cm^{-1}; MS (ESI, m/z): 240.06 $[M+H]^-$; HRMS (ESI) calcd. for $C_{14}H_{10}NO_3$: 240.0661 $[M+H]^+$, found: 240.0663.

4.1.9 Synthesis of 1,9-Bis(4-bromophenyl)nona-2,7-diyne-1,9-dione (36i)

General Procedure **1** was followed by using 4-bromobenzoyl chloride (715.5 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 112 mg (25%) of the indicated product **48i** as a yellow solid (R_f = 0.78 in 4:1 hexane/ethyl acetate; mp 106–108.2 °C). Second fraction gave 480.4 mg (64%) of the indicated product **36i** as a brown solid (R_f = 0.31 in 4:1 hexane/ethyl acetate; mp 111.3–115.1 °C).

36i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.6 Hz, 4H), 7.62 (d, *J* = 8.5 Hz, 4H), 2.72 (t, *J* = 7.0 Hz, 4H), 2.05 (p, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.8 (CO), 135.5 (C), 132.0 (CH), 130.9 (CH), 129.6 (C-Br), 94.9 (C), 80.2 (C), 25.9 (CH_2), 18.5 (CH_2); IR (neat): 3744, 2942, 2231, 2193, 1786, 1730, 1640, 1567, 1394, 1262, 1230, 1065, 1007, 974, 874, 839, 740, 672, 628, 535, 466, 420 cm^{-1}; MS

(ESI, m/z): 456.94 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{15}Br_2O_2$: 456.9433 $[M+H]^+$, found: 456.9428.

48i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 2.63 (t, *J* = 7.1 Hz, 2H), 2.36 (td, *J* = 6.9, 2.6 Hz, 2H), 2.01 (t, *J* = 2.6 Hz, 1H), 1.87 (p, *J* = 7.0 Hz, 2H); IR (neat): 3301, 2954, 2235, 2196, 1674, 1646, 1584, 1541, 1521, 1507, 1480, 1456, 1429, 1396, 1363, 1262, 1229, 1200, 1172, 1111, 1067, 1009, 919, 871, 841, 756, 741, 717, 703, 675, 642, 626, 538, 466, 437, 418 cm^{-1}; MS (ESI, m/z): 275.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{12}BrO$: 275.007 $[M+H]^+$, found: 275.0060.

4.1.10 Synthesis of 1,9-Bis(3-chlorophenyl)nona-2,7-diyne-1,9-dione (36j)

General Procedure **1** was followed by using 3-chlorobenzoyl chloride (570.5 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 47.3 mg (13%) of the indicated product **48j** as a brown solid (R_f = 0.63 in 4:1 hexane/ethyl acetate; mp 91-93.7 °C). Second fraction gave 243.6 mg (41%) of the indicated product **36j** as a brown solid (R_f = 0.52 in 4:1 hexane/ethyl acetate; mp 92.1–93.6 °C).

36j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09–8.07 (m, 2H), 8.01 (d, *J* = 6.5 Hz, 2H), 7.57 (d, *J* = 7.1 Hz, 2H), 7.44 (d, *J* = 7.8 Hz, 2H), 2.74 (t, *J* = 7.0 Hz, 4H), 2.07 (p, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6(CO), 138.3(C), 135.0(C-Cl), 134.2(CH), 130.1(CH), 129.6(CH), 127.8(CH), 95.2(C), 80.2(C), 26.0(CH_2), 18.6(CH_2); IR (neat): 3742, 2970, 2165, 1737, 1688, 1640, 1568, 1421, 1298, 1247, 1230, 1138, 1072, 913, 896, 849, 802, 747, 719, 652, 546, 493, 418 cm^{-1}. MS (ESI, m/z): 369.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{15}Cl_2O_2$: 369.0444 $[M+H]^+$, found: 369.0441.

48j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.40–7.27 (m, 3H), 2.52 (dq, *J* = 13.8, 7.1 Hz, 2H), 2.26 (td, *J* = 6.6, 2.4 Hz, 2H), 1.94 (dt, *J* = 8.3, 2.5 Hz, 1H), 1.76 (dt, *J* = 13.5, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2 (CO), 138.1 (C),

134.5 (CH), 133.7 (CH), 130.2 (CH), 128.5 (CH), 127.5 (C-Br), 96.2 (C), 82.5 (C), 79.5 (C), 69.7 (CH), 26.4 (CH_2), 18.0 (CH_2), 17.6 (CH_2); IR (neat): 3297, 3073, 2969, 2204, 1789, 1731, 1697, 1646, 1594, 1572, 1541, 1521, 1507, 1472, 1419, 1373, 1288, 1252, 1196, 1143, 1061, 996, 895, 847, 798, 730, 718, 685, 665, 651, 611, 543, 492, 467, 417 cm^{-1}; MS (ESI, m/z): 231.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{12}ClO$: 231.0571 $[M+H]^+$, found: 231.0552.

4.1.11 Synthesis of 1,9-Bis(2-bromophenyl)nona-2,7-diyne-1,9-dione (36k)

General Procedure **1** was followed by using 2-bromobenzoyl chloride (715.5 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 209.9 mg (47%) of the indicated product **48k** as orange oil (R_f = 0.57 in 4:1 hexane/ethyl acetate). Second fraction gave 248.1 mg (33%) of the indicated product **36k** as brownish orange oil (R_f = 0.42 in 4:1 hexane/ethyl acetate).

36k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 7.7, 1.8 Hz, 2H), 7.64 (dd, *J* = 7.9, 1.1 Hz, 2H), 7.43–7.31 (m, 4H), 2.66 (t, *J* = 7.0 Hz, 4H), 1.97 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5 (CO), 137.4 (C) 135.0 (CH), 133.4 (CH), 132.9 (CH), 127.4 (CH), 121.1 (C-Br), 95.6 (C), 81.5 (C), 25.7 (CH_2), 18.6 (CH_2); IR (neat): 3063, 2939, 2199, 1647, 1583, 1461, 1427, 1286, 1237, 1135, 1028, 974, 917, 875, 779, 735, 682, 648, 620, 555, 474, 448 cm^{-1}; MS (ESI, m/z): 456.94 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{15}Br_2O_2$: 456.9433 $[M+H]^+$, found: 456.9423.

48k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.62 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.35 (ddd, *J* = 19.5, 7.6, 1.5 Hz, 2H), 2.59 (t, *J* = 7.1 Hz, 2H), 2.33 (td, *J* = 6.9, 2.7 Hz, 2H), 1.99 (t, *J* = 2.7 Hz, 1H), 1.82 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4 (CO), 137.1 (C), 134.9 (CH), 133.3 (CH), 132.9 (CH), 127.3 (CH), 121.0 (C-Br), 96.5 (C), 82.7 (C), 81.0 (C), 69.7 (CH), 26.4 (CH_2), 18.2 (CH_2), 17.7 (CH_2); IR (neat): 3295, 2939, 2202, 1717, 1649, 1585, 1559, 1541, 1497, 1458, 1429, 1373, 1289, 1238, 1136, 1046, 1028, 991, 917, 905, 877, 779, 736, 636,

446 cm^{-1}; MS (ESI, m/z): 275.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{12}BrO$: 275.007 $[M+H]^+$, found: 275.0068.

4.1.12 Synthesis of 1,9-Bis(4-(dimethylamino)phenyl)nona-2,7-diyne-1,9-dione (36l)

General Procedure **1** was followed by using 4-(dimethylamino)benzoyl chloride (598.6 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 24.5 mg (6%) of the indicated product **48l** as a brownish orange solid (R_f = 0.35 in 4:1 hexane/ethyl acetate; mp 80.1-82.6 ºC). Second fraction gave 286.8 mg (46%) of the indicated product **36l** as a brown solid (R_f = 0.38 in 1:1 methanol/ethyl acetate; mp 98.1–103.8 ºC).

36l: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 9.1 Hz, 4H), 6.60 (d, *J* = 9.1 Hz, 4H), 3.02 (s, 12H), 2.65 (t, *J* = 7.0 Hz, 4H), 1.98 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1 (CO), 154.1 (C-N$(Me)_2$), 132.0 (CH), 125.3 (C), 110.6 (CH), 92.3 (C) 80.7 (C), 40.0 (NMe_2), 26.4 (CH_2), 18.4 (CH_2); IR (neat): 3742, 2813, 2231, 2193, 1743, 1583, 1527, 1436, 1371, 1282, 1229, 1180, 1156, 1009, 970, 941, 821, 754, 686, 584, 503, 457, 418 cm^{-1}; MS (ESI, m/z): 387.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{25}H_{27}N_2O_2$: 387.2067 $[M+H]^+$, found: 387.2060.

48l: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 3.05 (s, 6H), 2.60 (t, *J* = 7.0 Hz, 2H), 2.37 (td, *J* = 6.9, 2.6 Hz, 2H), 1.99 (t, *J* = 2.5 Hz, 1H), 1.86 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3 (CO), 154.1 (C), 132.0 (CH), 125.5 (C) 110.6 (CH), 92.9 (C), 83.0 (C), 80.4 (C), 69.4 (CH), 40.1 (NMe_2), 26.9 (CH_2), 18.2 (CH_2), 17.8 (CH_2); IR (neat): 3231, 2906, 2236, 2156, 1748, 1716, 1652, 1616, 1579, 1541, 1488, 1456, 1443, 1375, 1339, 1318, 1287, 1232, 1183, 1110, 1066, 1018, 942, 899, 823, 756, 689, 586, 540, 502, 469, 418 cm^{-1}; MS (ESI, m/z): 240.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{18}NO$: 240.1383 $[M+H]^+$, found: 240.1379.

4.1.13 Synthesis of 1,9-Bis(3-nitrophenyl)nona-2,7-diyne-1,9-dione (36m)

General Procedure **1** was followed by using 3-nitrobenzoyl chloride (605 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 24.6 mg (6%) of the indicated product **48m** as a dark brownish orange oil (R_f = 0.48 in 4:1 hexane/ethyl acetate). Second fraction gave 285 mg (45%) of the indicated product **36m** as a brown solid (R_f = 0.19 in 4:1 hexane/ethyl acetate; mp 114.4–117.2 ^oC).

36m: ^1H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 2H), 8.48–8.43 (m, 4H), 7.72 (t, *J* = 7.9 Hz, 2H), 2.82 (t, *J* = 6.9 Hz, 4H), 2.13 (p, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5 (CO), 148.5 (C-NO_2), 138.0 (C), 134.7 (CH), 130.1 (CH), 128.4 (CH), 124.7 (CH), 96.4 (C), 80.0 (C), 25.9 (CH_2), 18.7 (CH_2); IR (neat): 3088, 2873, 2211, 2195, 1703, 1641, 1613, 1530, 1346, 1253, 1127, 1071, 927, 821, 707, 661, 526, 419 cm^{-1}; MS (ESI, m/z): 391.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{15}N_2O_6$: 391.0925 $[M+H]^+$, found: 391.0928.

48m: ^1H NMR (400 MHz, $CDCl_3$) δ 9.06–8.73 (m, 1H), 8.49–8.36 (m, 2H), 7.69 (t, *J* = 8.0 Hz, 1H), 2.70 (t, *J* = 7.1 Hz, 2H), 2.40 (td, *J* = 6.8, 2.6 Hz, 2H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.91 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5 (CO), 148.4 (C-NO_2), 138.0 (C), 134.7 (CH), 130.0 (CH), 128.2 (CH), 124.5 (CH), 97.7 (C), 82.5 (C), 79.4 (C), 69.9 (CH), 26.5 (CH_2), 18.2 (CH_2), 17.8 (CH_2); IR (neat): 3291, 2943, 2203, 1735, 1683, 1646, 1612, 1577, 1530, 1474, 1456, 1436, 1347, 1321, 1291, 1249, 1131, 1077, 993, 921, 863, 818, 710, 655, 527, 418 cm^{-1}; MS (ESI, m/z): 242.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{12}NO_3$: 242.0812 $[M+H]^+$, found: 242.0791.

4.1.14 Synthesis of 1,9-Bis(3-bromophenyl)nona-2,7-diyne-1,9-dione (36n)

General Procedure **1** was followed by using 3-bromobenzoyl chloride (715,5 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI

(6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 74.8 mg (17%) of the indicated product **48n** as dark orange oil (R_f = 0.71 in 4:1 hexane/ethyl acetate). Second fraction gave 263.9 mg (35%) of the indicated product **36n** as a brown solid (R_f = 0.48 in 4:1 hexane/ethyl acetate; mp 99.7–101.3 ºC).

36n: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 1.7 Hz, 2H), 7.95 (d, *J* = 8.9 Hz, 2H), 7.62 (d, *J* = 5.0 Hz, 2H), 7.27 (t, *J* = 7.8 Hz, 2H), 2.66 (t, *J* = 7.0 Hz, 4H), 1.98 (dq, *J* = 12.8, 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3 (CO), 138.3 (C), 136.9 (CH), 132.3 (CH), 130.2 (CH), 128.1 (CH), 122.9 (C-Br), 95.2 (C), 80.1 (C), 25.9 (CH_2), 18.5 (CH_2); IR (neat): 3062, 2940, 2235, 2199, 1788, 1725, 1638, 1563, 1459, 1419, 1242, 1197, 1064, 1017, 994, 914, 897, 799, 726, 661, 615, 481, 431 cm^{-1}; MS (ESI, m/z): 456.94 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{15}Br_2O_2$: 456.9433 $[M+H]^+$, found: 456.9440.

48n: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23–8.18 (m, 1H), 8.04–8.00 (m, 1H), 7.71–7.67 (m, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 2.72 (t, *J* = 7.0 Hz, 2H), 2.04 (dt, *J* = 19.5, 7.2 Hz, 3H), 1.83 (p, *J* = 3.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6 (CO), 138.6 (C), 136.9 (CH), 132.5 (CH), 130.3 (CH), 128.2 (CH), 123.0 (C-Br), 96.5 (C), 96.3 (C), 79.94 (C), 79.91 (CH), 29.8 (CH_2), 18.6 (CH_2), 18.4 (CH_2); IR (neat): 3308, 2955, 2204, 1735, 1653, 1586, 1568, 1540, 1521, 1471, 1464, 1431, 1363, 1289, 1231, 1216, 1028, 739, 648, 507 cm^{-1}; MS (ESI, m/z): 275.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{12}BrO$: 275.0066 $[M+H]^+$, found: 275.0061.

4.1.15 Synthesis of 1,9-Bis(4-heptylphenyl)nona-2,7-diyne-1,9-dione (36o)

General Procedure **1** was followed by using 4-heptylbenzoyl chloride (778.3 mg, 3.26 mmol), $PdCl_2(PPh_3)_2$ (23.2 mg, 0.033 mmol), Et_3N (199.7 mg, 1.96 mmol), CuI (6.3 mg, 0.033 mmol) and 1,6-heptadiyne (**47**) (150 mg, 1.63 mmol) were employed and this reaction formed two fractions. First fraction afforded 53.7 mg (11%) of the indicated product **48o** as dark orange oil (R_f = 0.82 in 4:1 hexane/ethyl acetate).

Second fraction gave 303.2 mg (37%) of the indicated product **36o** as dark orange oil (R_f = 0.76 in 4:1 hexane/ethyl acetate).

36o: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.2 Hz, 4H), 7.29 (d, *J* = 8.2 Hz, 4H), 2.74–2.67 (m, 6H), 2.06 (p, *J* = 7.0 Hz, 2H), 1.71–1.56 (m, 6H), 1.30 (dd, *J* = 12.0, 5.8 Hz, 16H), 0.89 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8 (CO), 150.2 (C), 134.6 (C), 129.8 (CH), 128.7 (CH), 93.8 (C), 80.5 (C), 36.2 (CH_2), 31.8 (CH_2), 31.1 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.1 (CH_2), 22.7 (CH_2), 18.5 (CH_2), 14.2 (CH_3); IR (neat): 2923, 2853, 2236, 2196, 1733, 1716, 1684, 1643, 1603, 1570, 1540, 1507, 1457, 1415, 1375, 1309, 1264, 1175, 1113, 1017, 975, 851, 802, 753, 722, 693, 634, 525, 470, 434 cm^{-1}; MS (ESI, m/z): 497.34 $[M+H]^+$; HRMS (ESI) calcd. for $C_{35}H_{45}O_2$: 497.3414 $[M+H]^+$, found: 497.3415.

48o: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 10.4 Hz, 2H), 2.63 (q, *J* = 7.2 Hz, 4H), 2.37 (td, *J* = 6.9, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.87 (p, *J* = 7.0 Hz, 2H), 1.60 (s, 2H), 1.36–1.11 (m, 8H), 0.84 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0 (CO), 150.2 (C), 134.8 (C), 129.9 (CH), 128.8 (CH), 94.7 (C), 82.9 (C), 80.3 (C), 69.6 (CH), 36.3 (CH_2), 31.9 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.8 (CH_2), 22.8 (CH_2), 18.3 (CH_2), 17.9 (CH_2), 14.2 (CH_3); IR (neat): 2925, 2854, 2235, 2202, 1772, 1717, 1684, 1642, 1603, 1569, 1521, 1507, 1457, 1414, 1309, 1265, 1174, 1111, 1038, 995, 876, 850, 753, 693, 628, 526 cm^{-1}; MS (ESI, m/z): 295.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{27}O$: 295.2056 $[M+H]^+$, found: 295.2058.

4.1.16 Synthesis of 4,4'-(nona-2,7-diynedioyl)dibenzonitrile (36p)

General Procedure **1** was followed by using 4-cyanobenzoyl chloride (943.8 mg, 5.70 mmol), $PdCl_2(PPh_3)_2$ (40 mg, 0.057 mmol), Et_3N (348.5 mg, 3.42 mmol), CuI (11 mg, 0.057 mmol) and 1,6-heptadiyne (**47**) (263 mg, 2.85 mmol) were employed and this reaction formed two fractions. First fraction afforded 95.4 mg (15%) of the indicated product **48p** as a yellowish brown solid (R_f = 0.58 in 4:1 hexane/ethyl acetate; mp 59.3-59.9 ºC). Second fraction gave 225.5 mg (23%) of the indicated

product **36p** as a brownish orange solid (R_f = 0.13 in 4:1 hexane/ethyl acetate; mp > 149.5 ºC decomp.).

36p: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.3 Hz, 2H), 2.75 (t, *J* = 7.0 Hz, 4H), 2.08 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1 (CO), 139.3 (C), 132.5 (CH), 129.8 (CH), 117.8 (C≡N), 117.2 (C-CN), 96.1 (C), 80.1 (C), 25.8 (CH_2), 18.5 (CH_2); IR (neat): 3210, 2969, 2929, 2228, 2192, 1735, 1670, 1646, 1602, 1558, 1541, 1521, 1507, 1489, 1472, 1456, 1418, 1397, 1308, 1290, 1259, 1217, 1172, 1109, 1011, 975, 918, 862, 777, 753, 678, 545 cm^{-1}; MS (ESI, m/z): 351.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{15}N_2O_2$: 351.1128 $[M+H]^+$, found: 351.1137.

48p: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H), 2.67 (t, *J* = 7.1 Hz, 2H), 2.37 (td, *J* = 6.8, 2.6 Hz, 2H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.89 (p, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3 (CO), 139.5 (C), 132.5 (CH), 129.8 (CH), 117.9 (C≡N), 117.1 (C-CN), 97.5 (C), 82.5 (C), 79.6 (C), 69.9 (CH), 26.5 (CH_2), 18.2 (CH_2), 17.7 (CH_2); IR (neat): 3240, 3087, 2958, 2229, 2197, 1735, 1683, 1644, 1603, 1558, 1541, 1520, 1507, 1472, 1447, 1399, 1364, 1311, 1293, 1265, 1175, 1111, 1017, 951, 897, 863, 846, 772, 756, 686, 535 cm^{-1}; MS (ESI, m/z): 222.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{12}NO$: 222.0913 $[M+H]^+$, found: 222.0909.

4.1.17 Synthesis of 1,9-Bis(4-fluorophenyl)nona-2,7-diyne-1,9-dione (36q)

General Procedure **1** was followed by using 4-fluorobenzoyl chloride (942 mg, 5.94 mmol), $PdCl_2(PPh_3)_2$ (41 mg, 0.059 mmol), Et_3N (363 mg, 3.56 mmol), CuI (11 mg, 0.059 mmol) and 1,6-heptadiyne (**47**) (274 mg, 2.97 mmol) were employed and this reaction formed two fractions. First fraction afforded 175 mg (28%) of the indicated product **48q** as dark brownish orange oil (R_f = 0.69 in 4:1 hexane/ethyl acetate). Second fraction gave 343.8 mg (34%) of the indicated product **36q** as a brownish orange solid (R_f = 0.61 in 4:1 hexane/ethyl acetate; mp 103.4-104.5 ºC).

36q: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (ddd, *J* = 7.3, 5.4, 2.6 Hz, 4H), 7.14–7.06 (m, 4H), 2.69 (t, *J* = 7.0 Hz, 4H), 2.02 (p, *J* = 6.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3 (CO), 166.4 (d, ^{1}J = 256.6 Hz, CF), 133.2 (d, ^{4}J = 2.2 Hz, C), 132.2 (d, ^{3}J = 9.6 Hz, CH), 115.8 (d, ^{2}J = 22.1 Hz, CH), 94.6 (C), 80.2 (C), 25.9 (CH_2), 18.4 (CH_2); IR (neat): 2969, 2239, 2199, 1736, 1683, 1635, 1591, 1558, 1541, 1489, 1456, 1409, 1364, 1263, 1217, 1145, 1103, 1011, 924, 897, 845, 813, 768, 751, 676, 654, 610, 589, 547, 518, 498, 424 cm^{-1}; MS (ESI, m/z): 337.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{15}F_2O_2$: 337.1035 $[M+H]^+$, found: 337.1041.

48q: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dt, *J* = 7.3, 2.0 Hz, 2H), 7.17 (dt, *J* = 23.0, 8.6 Hz, 2H), 2.65 (t, *J* = 7.1 Hz, 2H), 2.39 (td, *J* = 6.9, 2.6 Hz, 2H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.89 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (CO), 166.4 (d, ^{1}J = 256.4 Hz, CF), 133.3 (d, ^{4}J = 9.6 Hz, C), 132.2 (d, ^{3}J = 9.6 Hz, CH), 116.3 (d, ^{2}J = 22.4 Hz, CH), 95.5 (C), 82.7 (C), 79.8 (C), 69.6 (CH), 26.6 (CH_2), 18.1 (CH_2), 17.7 (CH_2); IR (neat): 3304, 2969, 2942, 2236, 2197, 1718, 1683, 1646, 1593, 1558, 1540, 1473, 1456, 1410, 1364, 1264, 1227, 1150, 1108, 1090, 1032, 1004, 918, 879, 846, 753, 676, 632, 592, 571, 497 cm^{-1}; MS (ESI, m/z): 215.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{12}FO$: 215.0867 $[M+H]^+$, found: 215.0853.

4.1.18 Synthesis of 1,9-Bis(2-fluorophenyl)nona-2,7-diyne-1,9-dione (36r)

General Procedure **1** was followed by using 2-fluorobenzoyl chloride (942 mg, 5.94 mmol), $PdCl_2(PPh_3)_2$ (41 mg, 0.059 mmol), Et_3N (363 mg, 3.56 mmol), CuI (11 mg, 0.059 mmol) and 1,6-heptadiyne (**47**) (274 mg, 2.97 mmol) were employed and this reaction formed two fractions. First fraction afforded 305.5 mg (48%) of the indicated product **48r** as dark brown oil (R_f = 0.64 in 4:1 hexane/ethyl acetate). Second fraction gave 376.9 mg (38%) of the indicated product **36r** as a brown solid (R_f = 0.36 in 4:1 hexane/ethyl acetate; mp 45.3-46.7 °C).

36r: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (td, *J* = 7.7, 1.8 Hz, 2H), 7.61–7.55 (m, 2H), 7.29–7.24 (m, 2H), 7.16 (dd, *J* = 10.9, 8.7 Hz, 2H), 2.72 (t, *J* = 6.9 Hz, 4H), 2.03 (p, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (CO), 162.2 (d, ^{1}J = 261.7

Hz, CF), 135.7 (d, ^{3}J = 8.9 Hz, CH), 132.1 (CH), 125.6 (d, ^{2}J = 7.6 Hz, C), 124.3 (d, ^{4}J = 3.9 Hz, CH), 117.2 (d, ^{2}J = 21.8 Hz, CH), 94.6 (C), 82.0 (C), 25.8 (CH_2), 18.5 (CH_2); IR (neat): 2969, 2228, 1736, 1717, 1647, 1637, 1606, 1558, 1541, 1507, 1478, 1455, 1419, 1364, 1291, 1217, 1155, 1088, 1032, 1016, 978, 959, 922, 900, 807, 779, 749, 676, 650, 614, 570, 545, 518 cm^{-1}; MS (ESI, m/z): 337.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{15}F_2O_2$: 337.1035 $[M+H]^+$, found: 337.1047.

48r: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00–7.94 (m, 1H), 7.58–7.54 (m, 1H), 7.13 (dd, *J* = 13.8, 8.0 Hz, 2H), 2.55 (t, *J* = 7.0 Hz, 2H), 2.29 (td, *J* = 6.9, 2.6 Hz, 2H), 1.93 (t, *J* = 2.6 Hz, 1H), 1.78 (p, *J* = 6.9 Hz, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4 (d, ^{3}J = 1.3 Hz, CO), 163.0 (d, ^{1}J = 49.2 Hz, CF), 137.1 (d, ^{3}J = 9.5 Hz, CH), 135.5 (d, ^{5}J = 9.3 Hz, CH), 125.5 (d, ^{2}J = 7.8 Hz, C), 124.6 (d, ^{4}J = 3.9 Hz, CH), 117.3 (d, ^{2}J = 21.3 Hz, CH), 95.4 (d, ^{4}J = 2.6 Hz, C), 82.8 (C), 81.5 (C), 69.6 (CH), 26.5 (CH_2), 18.2 (CH_2), 17.6 (CH_2); IR (neat): 3304, 2969, 2207, 1868, 1783, 1735, 1683, 1652, 1635, 1606, 1576, 1558, 1540, 1520, 1507, 1481, 1454, 1364, 1291, 1272, 1231, 1195, 1156, 1116, 1022, 995, 881, 792, 752, 734, 643, 540, 515 cm^{-1}; MS (ESI, m/z): 215.08 $[M+H]^+$; HRMS (ESI) calcd. for $C_{14}H_{12}FO$: 215.0867 $[M+H]^+$, found: 215.0846.

4.1.19 Synthesis of 1,9-Bis(2-methoxyphenyl)nona-2,7-diyne-1,9-dione (36s)

General Procedure **1** was followed by using 2-methoxybenzoyl chloride (945 mg, 5.54 mmol), $PdCl_2(PPh_3)_2$ (39 mg, 0.055 mmol), Et_3N (363 mg, 3.56 mmol), CuI (11 mg, 0.055 mmol) and 1,6-heptadiyne (**47**) (255 mg, 2.77 mmol) were employed and this reaction formed two fractions. First fraction afforded 58.8 mg (9%) of the indicated product **48s** as yellow oil (R_f = 0.57 in 4:1 hexane/ethyl acetate). Second fraction gave 437.6 mg (44%) of the indicated product **36s** as orange oil (R_f = 0.34 in 4:1 hexane/ethyl acetate).

36s: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.8 Hz, 2H), 7.50 (t, *J* = 7.9 Hz, 2H), 7.01–6.92 (m, 4H), 3.78 (s, 6H), 2.53 (t, *J* = 7.1 Hz, 4H), 2.01 (p, *J* = 8.4 Hz, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0 (CO), 158.4 (C-OMe), 130.9 (CH), 130.8 (C) 126.0

(CH), 121.0 (CH), 111.6 (CH), 83.4 (C), 69.4 (C), 55.8 (OMe), 25.9 (CH_2), 17.2 (CH_2); IR (neat): 2968, 2934, 2354, 2322, 1736, 1654, 1597, 1541, 1507, 1484, 1457, 1435, 1362, 1282, 1241, 1215, 1162, 1115, 1019, 867, 753, 630, 538 cm^{-1}; MS (ESI, m/z): 361.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{21}O_4$: 361.1434 $[M+H]^+$, found: 361.1446.

48s: ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.08 (t, *J* = 7.5 Hz, 1H), 2.30 (td, *J* = 7.2, 2.4 Hz, 2H), 1.98 (t, *J* = 2.1 Hz, 2H), 1.91 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9 (CO), 158.3 (C-OMe), 133.8 (CH), 130.8 (C), 128.5 (CH), 120.9 (CH), 111.7 (CH), 83.8 (2C), 80.0 (C), 68.9 (CH), 55.8 (OMe), 35.7 (CH_2), 26.9 (CH_2), 17.9 (CH_2). (Note that two C peaks overlap on each other); IR (neat): 2941, 2354, 1735, 1654, 1597, 1558, 1540, 1520, 1507, 1485, 1457, 1434, 1363, 1282, 1241, 1215, 1180, 1162, 1116, 1077, 1020, 862, 753, 632, 527 cm^{-1}; MS (ESI, m/z): 227.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{15}O_2$: 227.1067 $[M+H]^+$, found: 227.1052.

4.1.20 Synthesis of 1,9-Bis(3,5-bis(trifluoromethyl)phenyl)nona-2,7-diyne-1,9-dione (36t)

General Procedure **1** was followed by using 3,5-bis(trifluoromethyl)benzoyl chloride (1449 mg, 5.24 mmol), $PdCl_2(PPh_3)_2$ (37 mg, 0.052 mmol), Et_3N (320 mg, 3.14 mmol), CuI (10 mg, 0.052 mmol) and 1,6-heptadiyne (**47**) (255 mg, 2.62 mmol) were employed and this reaction formed two fractions. First fraction afforded 238.2 mg (27%) of the indicated product **48t** as orange oil (R_f = 0.78 in 4:1 hexane/ethyl acetate). Second fraction gave 462 mg (31%) of the indicated product **36t** as an orange solid (R_f = 0.64 in 4:1 hexane/ethyl acetate; mp 115.9-117.8 °C).

36t: ^1H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 12.0 Hz, 2H), 8.12 (d, *J* = 13.8 Hz, 1H), 2.81 (t, *J* = 7.0 Hz, 4H), 2.13 (p, *J* = 6.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8 (CO), 138.1 (C), 132.5 (q, ^2J = 14.5 Hz, C), 129.5 (q, ^3J = 10.2 Hz, CH), 127.2 (q, ^3J = 10.9 Hz, CH), 125.8 (q, ^1J = 295.8 Hz, CF_3), 97.0 (C), 79.8 (C), 25.8

(CH_2), 18.6 (CH_2); IR (neat): 2945, 2243, 1736, 1715, 1655, 1616, 1557, 1540, 1497, 1472, 1456, 1435, 1365, 1274, 1230, 1171, 1126, 938, 887, 845, 774, 747, 699, 681, 634, 547 cm^{-1}; MS (ESI, m/z): 573.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{25}H_{13}F_{12}O_2$: 573.0718 $[M+H]^+$, found: 573.0720.

48t: ^1H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 2H), 8.08 (s, 1H), 2.73 (t, *J* = 7.1 Hz, 2H), 2.41 (td, *J* = 6.8, 2.6 Hz, 2H), 2.02 (t, *J* = 2.6 Hz, 1H), 1.92 (p, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9 (CO), 138.3 (C), 132.5 (q, ^2J = 34.1 Hz, C-CF_3), 129.5 (CH), 127.1 (q, ^2J = 3.6 Hz, CH), 122.8 (q, ^1J = 254.7 Hz, CF_3), 98.5 (C), 82.4 (C), 79.3 (C), 69.9 (CH), 26.4 (CH_2), 18.3 (CH_2), 17.7 (CH_2); IR (neat): 3311, 2969, 2943, 2243, 1735, 1656, 1615, 1557, 1540, 1507, 1456, 1364, 1276, 1230, 1175, 1130, 911, 845, 793, 747, 698, 680, 633, 517 cm^{-1}; MS (ESI, m/z): 333.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{11}F_6O$: 333.0709 $[M+H]^+$, found: 333.0721.

4.2 General Procedure 2. Synthesis of Unsymmetrical 1,9-Diarylnona-2,7-diyne-1,9-dione Derivatives 49

To a stirred solution of the proper aryloyl chloride **46** (0.6 mmol) in THF (8 mL) under argon was added $PdCl_2(PPh_3)_2$ (0.01 mmol) and Et_3N (0.6 mmol), and the resulting mixture was stirred for 10 min at room temperature and CuI (0.01 mmol) was added. After stirring the reaction mixture for another 10 min, 1-arylocta-2,7-diyne-1-one **48** (approximately 0.5 mmol) was added slowly, and the stirring at room temperature continued until the end of the reaction (The progress of the reaction was monitored by routine TLC analysis for the disappearance of 1-arylocta-2,7-diyne-1-one **48** using 9:1 hexane/ethyl acetate as the eluent). After the reaction was over, the solvent was removed on a rotary evaporator, and ethyl acetate (50 mL) and a saturated aqueous solution of NH_4Cl solution (50 mL) were added. After the layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography

on silica gel using 9:1 hexane/ethyl acetate as the eluent to afford the corresponding unsymmetrical 1,9-diarylnona-2,7-diyne-1,9-dione **49**.

4.2.1 Synthesis of 1-(4-Bromophenyl)-9-(4-chlorophenyl)nona-2,7-diyne-1,9-dione (49a)

General Procedure **2** was followed by using 4-bromobenzoyl chloride (163 mg, 0.74 mmol), $PdCl_2(PPh_3)_2$ (9.2 mg, 0.013 mmol), Et_3N (75.4 mg, 0.74 mmol), CuI (2.5 mg, 0.013 mmol) and 1-(4-chlorophenyl)octa-2,7-diyn-1-one (143.1 mg, 0.62 mmol) were employed to afford 110.7 mg (43%) of the indicated product **49a** as a brown solid (R_f = 0.37 in 4:1 hexane/ethyl acetate; mp 120.1–122.1 ºC).

49a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.7 Hz, 2H), 7.96 (d, *J* = 6.6 Hz, 2H), 7.60 (d, *J* = 8.7 Hz, 2H), 7.43 (d, *J* = 8.7 Hz, 2H), 2.71 (t, *J* = 7.0 Hz, 4H), 2.04 (p, *J* = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9 (CO), 176.7 (CO), 140.8 (C-Cl), 135.5 (C), 135.1 (C), 132.0 (CH), 131.0 (CH), 130.9 (CH), 129.7 (C-Br), 129.0 (CH), 94.8 (C), 80.3 (C), 26.0 (CH_2), 18.5 (CH_2). (Note that two CH_2 and C peaks overlap on each other); IR (neat): 2927, 2233, 2194, 1785, 1637, 1583, 1480, 1396, 1259, 1165, 1088, 1066, 1008, 895, 840, 741, 672, 628, 521, 468 cm^{-1}; MS (ESI, m/z): 412.99 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{15}BrClO_2$: 412.9939 $[M+H]^+$, found: 412.9931.

4.2.2 Synthesis of 1-(4-Chlorophenyl)-9-(3,5-dichlorophenyl)nona-2,7-diyne-1,9-dione (49b)

General Procedure **2** was followed by using 3,5-dichlorobenzoyl chloride (131 mg, 0.63 mmol), $PdCl_2(PPh_3)_2$ (7.7 mg, 0.011 mmol), Et_3N (64.2 mg, 0.63 mmol), CuI (2.1 mg, 0.011 mmol) and 1-(4-chlorophenyl)octa-2,7-diyn-1-one (122.3 mg, 0.53 mmol) were employed to afford 94.5 mg (44%) of the indicated product **49b** as brownish orange oil (R_f = 0.46 in 4:1 hexane/ethyl acetate).

49b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.6 Hz, 2H), 7.87 (d, *J* = 2.0 Hz, 2H), 7.49 (t, *J* = 1.9 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 2.67 (q, *J* = 7.2 Hz, 4H), 1.99 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7 (CO), 175.1 (CO), 140.9 (C), 139.1 (C-Cl), 135.8 (C-Cl), 133.8 (CH), 133.7 (C), 131.0 (CH), 129.1 (CH), 127.8 (CH), 96.1 (C), 94.6 (C), 80.3 (C), 79.9 (C), 25.9 (CH_2), 18.6 (CH_2), 18.6 (CH_2); IR (neat): 3076, 2923, 2852, 2236, 2207, 1646, 1586, 1564, 1420, 1397, 1253, 1170, 1089, 1012, 843, 800, 744, 674, 660, 523, 474 cm^{-1}; MS (ESI, m/z): 403.00 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{14}Cl_3O_2$: 403.0054 $[M+H]^+$, found: 403.0051.

4.2.3 Synthesis of 1-(4-Methoxyphenyl)-9-phenylnona-2,7-diyne-1,9-dione (49c)

General Procedure **2** was followed by using benzoyl chloride (81.5 mg, 0.58 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), Et_3N (59.1 mg, 0.58 mmol), CuI (2 mg, 0.01 mmol) and 1-(4-methoxyphenyl)octa-2,7-diyn-1-one (110.9 mg, 0.49 mmol) were employed to afford 130.8 mg (81%) of the indicated product **49c** as dark brownish orange oil (R_f = 0.35 in 4:1 hexane/ethyl acetate).

49c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15–8.07 (m, 4H), 7.61–7.57 (m, 1H), 7.48–7.44 (m, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 2.70 (q, *J* = 7.0 Hz, 4H), 2.03 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1 (CO), 176.7 (CO) 164.5 (C-OMe), 136.7 (C), 134.2 (CH), 132.0 (CH), 130.2 (C), 129.6 (CH), 128.7 (CH), 113.9 (CH), 94.5 (C), 93.5 (C), 80.5 (C), 80.4 (C), 55.7 (OMe), 26.1 (CH_2), 18.5 (CH_2), (Note that two CH_2 peaks overlap on each other); IR (neat): 3059, 2950, 2917,

2838, 2236, 2198, 1722, 1637, 1594, 1572, 1507, 1449, 1419, 1313, 1254, 1165, 1022, 893, 843, 795, 756, 700, 598, 528, 493 cm^{-1}; MS (ESI, m/z): 331.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{19}O_3$: 331.1329 $[M+H]^+$, found: 331.1329.

4.2.4 Synthesis of 1-(4-Ethylphenyl)-9-phenylnona-2,7-diyne-1,9-dione (49d)

General Procedure **2** was followed by using benzoyl chloride (87.2 mg, 0.62 mmol), $PdCl_2(PPh_3)_2$ (7 mg, 0.01 mmol), Et_3N (63.2 mg, 0.62 mmol), CuI (1,9 mg, 0.01 mmol) and 1-(4-ethylphenyl)octa-2,7-diyn-1-one (116.6 mg, 0.52 mmol) were employed to afford 67.9 mg (40%) of the indicated product **49d** as brownish orange oil (R_f = 0.47 in 4:1 hexane/ethyl acetate).

49d: ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.4 Hz, 2H), 7.97 (d, *J* = 8.1 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 2.64 (td, *J* = 8.0, 7.5, 3.7 Hz, 6H), 1.97 (p, *J* = 7.0 Hz, 2H), 1.17 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0 (CO), 177.8 (CO), 151.4 (C-CH_2CH_3), 136.7 (C), 134.7 (C), 134.2 (CH), 129.9 (CH), 129.6 (CH), 128.7 (CH), 128.2 (CH), 94.4 (C), 93.8 (C), 80.6 (C), 80.5 (C), 29.1 (CH_2), 26.1 (CH_2), 18.5 (CH_2), 15.2 (CH_2). (Note that two CH_2 peaks overlap on each other); IR (neat): 2965, 2932, 2235, 2197, 1687, 1639, 1602, 1449, 1415, 1311, 1262, 1175, 1109, 975, 920, 849, 700, 595, 518,418 cm^{-1}; MS (ESI, m/z): 329.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{21}O_2$: 329.1536 $[M+H]^+$, found: 329.1529.

4.2.5 Synthesis of 1-(4-(Dimethylamino)phenyl)-9-phenylnona-2,7-diyne-1,9-dione (49e)

General Procedure **2** was followed by using 4-(dimethylamino)benzoyl chloride (156.1 mg, 0.85 mmol), $PdCl_2(PPh_3)_2$ (9.8 mg, 0.014 mmol), Et_3N (86.6 mg, 0.85 mmol), CuI (2.7 mg, 0.014 mmol) and 1-phenylocta-2,7-diyn-1-one (139.3 mg, 0.71 mmol) were employed to afford 155 mg (64%) of the indicated product **49e** as a dark brown solid (R_f = 0.19 in 4:1 hexane/ethyl acetate; mp 52.1-54.8 ^oC).

49e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14–8.10 (m, 3H), 8.01 (d, *J* = 9.0 Hz, 1H), 7.46 (dt, *J* = 7.5, 4.1 Hz, 3H), 6.63 (d, *J* = 9.0 Hz, 2H), 3.06 (s, 6H), 2.70 (dt, *J* = 13.6, 7.0 Hz, 4H), 2.02 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2 (CO), 176.2 (CO), 154.2 (C-N$(Me)_2$), 133.8 (C), 130.2 (CH), 129.6 (CH), 128.7 (CH), 128.5 (CH), 110.7 (CH), 94.8 (C), 92.2 (C), 80.9 (C), 80.4 (C), 26.3 (CH_2), 18.53 (CH_2), 18.50 (CH_2); IR (neat): 3069, 2821, 2235, 2196, 1682, 1643, 1618, 1580, 1541, 1451, 1417, 1374, 1321, 1285, 1264, 1182, 1126, 1070, 1025, 999, 921, 878, 824, 805, 756, 701, 666, 589, 550, 506, 417 cm^{-1}; MS (ESI, m/z): 344.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{23}H_{22}NO_2$: 344.1645 $[M+H]^+$, found: 344.1654.

4.2.6 Synthesis of 1-(4-Bromophenyl)-9-phenylnona-2,7-diyne-1,9-dione (49f)

General Procedure **2** was followed by using 4-bromobenzoyl chloride (261 mg, 1.19 mmol), $PdCl_2(PPh_3)_2$ (14 mg, 0.02 mmol), Et_3N (121.3 mg, 1.19 mmol), CuI (4 mg, 0.02 mmol) and 1-phenylocta-2,7-diyn-1-one (194 mg, 0.99 mmol) were employed to afford 269.3 mg (72%) of the indicated product **49f** as dark brownish orange oil (R_f = 0.36 in 4:1 hexane/ethyl acetate).

49f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.12 (m, 3H), 8.01–7.97 (m, 2H), 7.63–7.61 (m, 2H), 7.53–7.48 (m, 2H), 2.73 (td, *J* = 7.0, 3.1 Hz, 4H), 2.06 (p, *J* = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0 (CO), 177.4 (CO), 134.9 (CH), 134.2 (CH), 133.4 (C), 132.9 (C), 129.6 (CH), 128.6 (CH), 127.4 (CH), 121.0 (C-Br), 95.6 (C), 94.3 (C), 81.4 (C), 80.4 (C), 25.8 (CH_2), 18.5 (CH_2), 18.4 (CH_2). (Note that two CH_2 peaks overlap on each other); IR (neat): 3059, 2936, 2200, 1638, 1579, 1464, 1448, 1429, 1311, 1263, 1240, 1173, 1118, 1026, 974, 872, 811, 739, 700, 639, 555, 448, 425 cm^{-1}; MS (ESI, m/z): 379.03 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{16}BrO_2$: 379.0328 $[M+H]^+$, found: 379.0333.

4.2.7 Synthesis of 1-(4-Nitrophenyl)-9-phenylnona-2,7-diyne-1,9-dione (49g)

General Procedure **2** was followed by using 4-nitrobenzoyl chloride (124.3 mg, 0.67 mmol), $PdCl_2(PPh_3)_2$ (8 mg, 0.011 mmol), Et_3N (68.3 mg, 0.67 mmol), CuI (2.1 mg, 0.011 mmol) and 1-phenylocta-2,7-diyn-1-one (109.2 mg, 0.56 mmol) were employed to afford 62.6 mg (32%) of the indicated product **49g** as orange oil (R_f = 0.29 in 4:1 hexane/ethyl acetate).

49g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 6.1 Hz, 2H), 8.12 (d, *J* = 7.9 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 2H), 7.50–7.46 (m, 3H), 2.76 (dt, *J* = 16.0, 7.0 Hz, 4H), 2.08 (dt, *J* = 14.3, 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0 (CO), 176.0 (CO), 150.9 (C-NO_2), 134.3 (C), 133.9 (C), 130.6 (CH), 130.3 (CH), 129.7 (CH), 128.7 (CH), 128.6 (CH), 123.9 (CH), 96.9 (C), 94.0 (C), 80.7 (C), 80.2 (C), 25.9 (CH_2) 18.59 (CH_2), 18.55 (CH_2); IR (neat): 2961, 2630, 2365, 1716, 1698, 1683, 1647, 1557, 1533, 1507, 1456, 1418, 1387, 1259, 1086, 1016, 862, 796, 690, 659, 507, 417 cm^{-1}; MS (ESI, m/z): 346.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{21}H_{16}NO_4$: 346.1074 $[M+H]^+$, found: 346.1076.

4.3 General Procedure 3. Synthesis of 1,3-Bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propane derivatives and 1,3-Bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane Derivatives 38 and 40

To a stirred solution of the proper 1,9-diarylnona-2,7-diyne-1,9-dione **36** or **49** (approximately 0.3 mmol) in dioxane (4.0 mL) under argon was added benzylhydrazine dihydrochloride (**37**) or 2-hydrazinopyridine (**39**) (0.6 mmol) and the resulting mixture was refluxed until the end of the reaction. The progress of the reaction was monitored by routine TLC analysis for the disappearance of 1,9-diarylnona-2,7-diyne-1,9-dione **36** or **49** using 4:1 hexane/ethyl acetate as the eluent. After the reaction was over, the solvent was removed on a rotary evaporator, and chloroform (30 mL) and water (30 mL) were added. After the layers were separated, the aqueous layer was extracted with chloroform (2 x 30 mL). The

combined organic layers were dried over $MgSO_4$ and evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using 4:1 hexane/ethyl acetate as the eluent to afford the corresponding 1,3-bis-pyrazole compounds **38** and **40**.

4.3.1 Synthesis of 1,3-Bis(1-benzyl-3-phenyl-1*H*-pyrazol-5-yl)propane (38a)

General Procedure **3** was followed by using 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**) (123.8 mg, 0.41 mmol) and benzylhydrazine dihydrochloride (**37)** (159.9 mg, 0.82 mmol) were employed to afford 113 mg (54%) of the indicated product **38a** as a yellow solid (R_f = 0.80 in 1:1 hexane/ethyl acetate); mp 129–132.8 ^oC.

38a: ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3 Hz, 4H), 7.43 (t, *J* = 6.9 Hz, 2H), 7.35–7.25 (m, 10H), 7.08 (d, *J* = 7.7 Hz, 4H), 6.36 (s, 2H), 5.29 (s, 4H), 2.52 (t, *J* = 7.5 Hz, 4H), 1.86 (p, *J* = 7.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4 (C=N), 143.5 (C-N), 137.1 (C), 133.6 (C), 128.8 (CH), 128.7 (CH), 127.7 (CH), 127.6 (CH), 126.6 (CH), 125.6 (CH), 102.2 (CH), 53.1 (CH_2), 27.0 (CH_2), 24.9 (CH_2); IR (neat): 3059, 3028, 2919, 2850, 1734, 1602, 1546, 1494, 1451, 1363, 1316, 1240, 1081, 1025, 957, 758, 731, 690, 578, 505, 454 cm^{-1}; MS (ESI, m/z): 509.27 $[M+H]^+$; HRMS (ESI) calcd. for $C_{35}H_{33}N_4$: 509.2700 $[M+H]^+$, found: 509.2713.

4.3.2 Synthesis of 1,3-Bis(1-benzyl-3-(4-chlorophenyl)-1*H*-pyrazol-5-yl)propane (38b)

General Procedure **3** was followed by using 1,9-bis(4-chlorophenyl)nona-2,7-diyne-1,9-dione (**36b**) (66.7 mg, 0.18 mmol) and benzylhydrazine dihydrochloride (**37**) (70.3 mg, 0.36 mmol) were employed to afford 35 mg (34%) of the indicated product **38b** as a yellowish orange solid (R_f = 0.85 in 1:1 hexane/ethyl acetate); mp 124.8–127.1 ^oC.

38b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.5 Hz, 4H), 7.27 (d, *J* = 8.5 Hz, 4H), 7.20-7.13 (m, 6H), 6.95 (d, *J* = 6.4 Hz, 4H), 6.19 (s, 2H), 5.17 (s, 4H), 2.41 (t, *J* = 7.5 Hz, 4H), 1.75 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5 (C=N), 143.8 (C-N), 137.0 (C-Cl), 133.4 (C), 132.1 (C), 128.90 (CH), 128.86 (CH), 127.8 (CH), 126.9 (CH), 126.7 (CH), 102.2 (CH), 53.3 (CH_2), 27.0 (CH_2), 24.9 (CH_2); IR (neat): 3028, 2947, 2162, 1681, 1591, 1504, 1454, 1428, 1356, 1318, 1089, 1013, 956, 834, 772, 761, 720, 695, 576, 550, 509, 472 cm^{-1}; MS (ESI, m/z): 577.19 $[M+H]^+$; HRMS (ESI) calcd. for $C_{35}H_{31}Cl_2N_4$: 577.1920 $[M+H]^+$, found: 577.1906.

4.3.3 Synthesis of 1,3-Bis(1-benzyl-3-(4-methoxyphenyl)-1*H*-pyrazol-5-yl)propane (38c)

General Procedure **3** was followed by using 1,9-bis(4-methoxyphenyl)nona-2,7-diyne-1,9-dione (**36c**) (122.6 mg, 0.34 mmol) and benzylhydrazine dihydrochloride (**37**) (132.6 mg, 0.68 mmol) were employed to afford 123.6 mg (64%) of the indicated product **38c** as brownish orange oil (R_f = 0.56 in 1:1 hexane/ethyl acetate).

38c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 4H), 7.15 (td, *J* = 13.3, 5.5 Hz, 6H), 6.96 (d, *J* = 7.2 Hz, 4H), 6.85 (d, *J* = 8.5 Hz, 4H), 6.16 (s, 2H), 5.16 (s, 4H), 3.74 (s, 6H), 2.40 (t, *J* = 7.5 Hz, 4H), 1.74 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C-OMe), 150.2 (C=N), 143.5 (C-N), 137.2 (C), 130.7 (C), 128.7 (CH), 127.6 (CH), 126.8 (CH), 126.5 (CH), 114.0 (CH), 101.6 (CH), 55.3 (OMe), 53.0 (CH_2), 27.0 (CH_2), 24.8 (CH_2); IR (neat): 3002, 2928, 2835, 2161, 1677, 1657, 1598, 1520, 1434, 1245, 1171, 1029, 956, 833, 780, 721, 695, 633, 599, 528, 456 cm^{-1}; MS (ESI, m/z): 569.29 $[M+H]^+$; HRMS (ESI) calcd. for $C_{37}H_{37}N_4O_2$: 569.2911 $[M+H]^+$, found: 569.2918.

4.3.4 Synthesis of 1,3-Bis(1-benzyl-3-(3,5-dichlorophenyl)-1*H*-pyrazol-5-yl)propane (38d)

General Procedure **3** was followed by using 1,9-bis(3,5-dichlorophenyl)nona-2,7-diyne-1,9-dione (**36d**) (100 mg, 0.23 mmol) and benzylhydrazine dihydrochloride (**37**) (89.7 mg, 0.46 mmol) were employed to afford 31 mg (21%) of the indicated product **38d** as an orange solid (R_f = 0.83 in 1:1 hexane/ethyl acetate); mp 81.7–89.0 ^oC.

38d: ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.5 Hz, 4H), 7.23-7.17 (m, 8H), 6.96 (d, *J* = 6.6 Hz, 4H), 6.17 (s, 2H), 5.18 (s, 4H), 2.43 (t, *J* = 7.4 Hz, 4H), 1.75 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1 (C=N), 143.9 (C-N), 136.7 (C), 136.6 (C), 135.3 (C-Cl), 129.0 (CH), 128.0 (CH), 127.4 (CH), 126.7 (CH), 124.0 (CH), 102.6 (CH), 53.5 (CH_2), 26.9 (CH_2), 24.9 (CH_2); IR (neat): 3734, 2932, 2310, 2150, 1714, 1592, 1564, 1433, 1417, 1392, 1342, 1316, 1213, 1124, 983, 850, 798, 723, 695, 671, 457, 419 cm^{-1}; MS (ESI, m/z): 645.11 $[M+H]^+$; HRMS (ESI) calcd. for $C_{35}H_{29}Cl_4N_4$: 645.1141 $[M+H]^+$, found: 645.1133.

4.3.5 Synthesis of 1,3-Bis(1-benzyl-3-(4-ethylphenyl)-1*H*-pyrazol-5-yl)propane (38e)

General Procedure **3** was followed by using 1,9-bis(4-ethylphenyl)nona-2,7-diyne-1,9-dione (**36e**) (118.5 mg, 0.33 mmol) and benzylhydrazine dihydrochloride (**37**) (128.7 mg, 0.66 mmol) were employed to afford 107 mg (57%) of the indicated product **38e** as an orange solid (R_f = 0.73 in 1:1 hexane/ethyl acetate); mp 90.2–91.1 ^oC.

38e: ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 4H), 7.16 (dt, *J* = 8.8, 4.8 Hz, 10H), 6.97 (d, *J* = 6.4 Hz, 4H), 6.22 (s, 2H), 5.20 (s, 4H), 2.60 (q, *J* = 7.6 Hz, 4H), 2.42 (t, *J* = 7.5 Hz, 4H), 1.76 (p, *J* = 7.5 Hz, 2H), 1.17 (d, *J* = 7.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6 (C=N), 143.8 (C-CH_2CH_3), 143.5 (C-N), 137.3 (C), 131.1 (C), 128.8 (CH), 128.2 (CH), 127.7 (CH), 126.6 (CH), 125.6 (CH), 102.1

(CH), 53.2 (CH_2), 28.8 (CH_2), 27.1 (CH_2), 24.9 (CH_2), 15.8 (CH_3); IR (neat): 3747, 3741, 2964, 2929, 2373, 2321, 2036, 1715, 1521, 1454, 1360, 1313, 1212, 958, 841, 782, 726, 694, 547, 517, 455, 418 cm^{-1}; MS (ESI, m/z): 565.33 $[M+H]^+$; HRMS (ESI) calcd. for $C_{39}H_{41}N_4$: 565.3326 $[M+H]^+$, found: 565.3336.

4.3.6 Synthesis of 1,3-Bis(1-benzyl-3-(p-tolyl)-1*H*-pyrazol-5-yl)propane (38f)

General Procedure **3** was followed by using 1,9-di-*p*-tolylnona-2,7-diyne-1,9-dione (**36f**) (110.5 mg, 0.34 mmol) and benzylhydrazine dihydrochloride (**37**) (132.6 mg, 0.68 mmol) were employed to afford 80 mg (44%) of the indicated product **38f** as yellow oil (R_f = 0.89 in 1:1 hexane/ethyl acetate).

38f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 4H), 7.31–7.24 (m, 10H), 7.09 (d, *J* = 6.6 Hz, 4H), 6.34 (s, 2H), 5.30 (s, 4H), 2.53 (t, *J* = 7.6 Hz, 4H), 2.42 (s, 6H), 1.88 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5 (C=N), 143.5 (C-N), 137.4 (C), 137.3 (C), 130.8 (C-CH_3), 129.4 (CH), 128.8 (CH), 127.7 (CH), 126.6 (CH), 125.5 (CH), 102.0 (CH), 53.2 (CH_2), 27.0 (CH_2), 24.9 (CH_2), 21.4 (CH_3); IR (neat): 3058, 3026, 2920, 2161, 1734, 1681, 1604, 1549, 1521, 1494, 1452, 1437, 1354, 1314, 1180, 1111, 1075, 1028, 957, 822, 783, 725, 694, 575, 510, 455, 419 cm^{-1}; MS (ESI, m/z): 537.30 $[M+H]^+$; HRMS (ESI) calcd. for $C_{37}H_{37}N_4$: 537.3013 $[M+H]^+$, found: 537.3027.

4.3.7 Synthesis of 1,3-Bis(1-benzyl-3-(4-(methylthio)phenyl)-1*H*-pyrazol-5-yl)propane (38g)

General Procedure **3** was followed by using 1,9-bis(4-(methylthio)phenyl)nona-2,7-diyne-1,9-dione (**36g**) (150 mg, 0.38 mmol) and benzylhydrazine dihydrochloride (**37**) (148.3 mg, 0.76 mmol) were employed to afford 125 mg (55%) of the indicated product **38g** as an orange solid (R_f = 0.79 in 1:1 hexane/ethyl acetate); mp 99.1–103.9 °C.

38g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.4 Hz, 4H), 7.19–7.13 (m, 10H), 6.94 (d, *J* = 6.7 Hz, 4H), 6.18 (s, 2H), 5.15 (s, 4H), 2.39 (s, 10H), 1.72 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9 (C=N), 143.6 (C-N), 137.6 (C-SMe), 137.1 (C), 130.5 (C), 128.8 (CH), 127.7 (CH), 126.7 (CH), 126.6 (CH), 126.0 (CH), 101.9 (CH), 53.1 (CH_2), 27.0 (CH_2), 24.8 (CH_2), 15.9 (CH_3); IR (neat): 3027, 2919, 1731, 1587, 1543, 1506, 1453, 1430, 1355, 1315, 1194, 1093, 955, 824, 782, 715, 693, 577, 512, 456, 419 cm^{-1}; MS (ESI, m/z): 601.24 $[M+H]^+$; HRMS (ESI) calcd. for $C_{37}H_{37}N_4S_2$: 601.2454 $[M+H]^+$, found: 601.2461.

4.3.8 Synthesis of 1,3-Bis(1-benzyl-3-(4-nitrophenyl)-1*H*-pyrazol-5-yl)propane (38h)

General Procedure **3** was followed by using 1,9-bis(4-nitrophenyl)nona-2,7-diyne-1,9-dione (**36h**) (130 mg, 0.33 mmol) and benzylhydrazine dihydrochloride (**37**) (128.7 mg, 0.66 mmol) were employed to afford 60.2 mg (30,5%) of the indicated product **38h** as brown oil (R_f = 0.75 in 1:1 hexane/ethyl acetate).

38h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.9 Hz, 4H), 7.89 (d, *J* = 8.8 Hz, 4H), 7.23–7.20 (m, 6H), 7.02 (d, *J* = 6.3 Hz, 4H), 6.36 (s, 2H), 5.25 (s, 4H), 2.50 (t, *J* = 7.5 Hz, 4H), 1.83 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3 (C=N), 147.1 (C-NO_2), 144.2 (C-N), 140.0 (C), 136.6 (C), 129.0 (CH), 128.0 (CH), 126.7 (CH), 126.0 (CH), 124.2 (CH), 103.2 (CH), 53.6 (CH_2), 27.0 (CH_2), 25.0 (CH_2); IR (neat): 3747, 3734, 2925, 2909, 1731, 1598, 1511, 1453, 1338, 1232, 1106, 957, 852, 754, 695, 456, 420, 406 cm^{-1}; MS (ESI, m/z): 599.24 $[M+H]^+$; HRMS (ESI) calcd. for $C_{35}H_{31}N_6O_4$: 599.2401 $[M+H]^+$, found: 599.2411.

4.3.9 Synthesis of 1,3-Bis(1-benzyl-3-(4-bromophenyl)-1*H*-pyrazol-5-yl)propane (38i)

General Procedure **3** was followed by using 1,9-bis(4-bromophenyl)nona-2,7-diyne-1,9-dione (**36i**) (150 mg, 0.33 mmol) and benzylhydrazine dihydrochloride (**37**)

(128.7 mg, 0.66 mmol) were employed to afford 78.7 mg (36%) of the indicated product **38i** as a brown solid (R_f = 0.85 in 1:1 hexane/ethyl acetate); mp 88.3–92 ºC. **38i:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.4 Hz, 4H), 7.44 (d, *J* = 8.4 Hz, 4H), 7.23-7.14 (m, 10H), 6.96 (d, *J* = 6.6 Hz, 4H), 6.20 (s, 2H), 5.18 (s, 4H), 2.42 (t, *J* = 7.5 Hz, 4H), 1.76 (p, *J* = 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4 (C=N), 143.8 (C-N), 136.9 (C), 132.5 (C), 131.8 (CH), 128.9 (CH), 127.8 (CH), 127.2 (CH), 126.6 (CH), 121.5 (C-Br), 102.2 (CH), 53.3 (CH_2), 27.0 (CH_2), 24.9 (CH_2); IR (neat): 3748, 3647, 3610, 2186, 2036, 1997, 1734, 1493, 1454, 1213, 1067, 1007, 954, 836, 784, 712, 692, 504, 418 cm^{-1}; MS (ESI, m/z): 665.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{35}H_{31}Br_2N_4$: 665.0910 $[M+H]^+$, found: 665.0902.

4.3.10 Synthesis of 1-Benzyl-5-(3-(1-benzyl-3-(4-bromophenyl)-1*H*-pyrazol-5-yl)propyl)-3-(4-chlorophenyl)-1*H*-pyrazole (38j)

General Procedure **3** was followed by using 1-(4-bromophenyl)-9-(4-chlorophenyl)nona-2,7-diyne-1,9-dione (**49a**) (100 mg, 0.24 mmol) and benzylhydrazine dihydrochloride (**37**) (93.6 mg, 0.48 mmol) were employed to afford 39.5 mg (26,5%) of the indicated product **38j** as a yellow solid (R_f = 0.89 in 1:1 hexane/ethyl acetate); mp 145.2–148.3 ºC.

38j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.22–7.15 (m, 6H), 6.96 (d, *J* = 6.5 Hz, 4H), 6.20 (s, 2H), 5.17 (s, 4H), 2.42 (t, *J* = 7.5 Hz, 4H), 1.76 (p, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5 (2C=N), 143.8 (C-N), 143.7 (C-N), 137.03 (C), 137.01 (C-Cl), 133.4 (C), 132.7 (C), 132.2 (C), 131.8 (2CH), 128.9 (4CH), 128.9 (2CH), 127.9 (2CH), 127.2 (2CH), 126.9 (4CH), 126.7 (2CH), 121.5 (C-Br), 102.2 (2CH), 53.6 (CH_2), 27.1 (CH_2), 24.9 (CH_2); IR (neat): 3745, 2230, 2178, 2162, 2120, 2039, 1974, 1731, 1496, 1454, 1432, 1349, 1205, 1086, 1068, 1008, 954, 820, 784, 723, 690, 614, 528, 482, 419 cm^{-1}; MS (ESI, m/z): 621.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{35}H_{31}BrClN_4$: 621.14151 $[M+H]^+$, found: 621.14197.

4.3.11 Synthesis of 1-Benzyl-5-(3-(1-benzyl-3-(3,5-dichlorophenyl)-1*H*-pyrazol-5-yl)propyl)-3-(4-chlorophenyl)-1*H*-pyrazole (38k)

General Procedure **3** was followed by using 1-(4-chlorophenyl)-9-(3,5-dichlorophenyl)nona-2,7-diyne-1,9-dione (**49b**) (85 mg, 0.21 mmol) and benzylhydrazine dihydrochloride (**37**) (81.9 mg, 0.42 mmol) were employed to afford 29.6 mg (23%) of the indicated product **38k** as orange oil (R_f = 0.76 in 1:1 hexane/ethyl acetate).

38k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 1.8 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 7.22–7.16 (m, 7H), 6.99–6.95 (m, 3H), 6.21 (s, 1H), 6.17 (s, 1H), 5.20 (s, 2H), 5.17 (s, 2H), 2.43 (t, *J* = 7.3 Hz, 4H), 1.76 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0 (2C=N), 144.0 (2C-N), 136.8 (C-Cl), 136.7 (2C), 136.6 (C), 135.3 (2C-CI), 133.7 (C), 128.99 (4CH), 128.95 (2CH), 128.0 (2CH), 127.4 (CH), 127.0 (2CH), 126.72 (2CH), 126.71 (2CH), 124.0 (2CH), 102.6 (CH), 102.3 (CH), 53.5 (CH_2), 53.3 (CH_2), 29.8 (CH_2), 26.9 (CH_2), 24.9 (CH_2); IR (neat): 3062, 3029, 2928, 2850, 1731, 1592, 1564, 1496, 1453, 1433, 1315, 1239, 1089, 1012, 956, 834, 795, 721, 694, 671, 577, 504, 454, 422, 406 cm^{-1}; MS (ESI, m/z): 611.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{35}H_{30}Cl_3N_4$: 611.1531 $[M+H]^+$, found: 611.1537.

4.3.12 Synthesis of 1,3-Bis(5-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (40a)

General Procedure **3** was followed by using 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**) (116 mg, 0.38 mmol) and 2-hydrazinopyridine (**39**) (82.9 mg, 0.76 mmol) were employed to afford 66.6 mg (36%) of the indicated product **40a** as a light yellow solid (R_f = 0.11 in 1:1 hexane/ethyl acetate); mp 89.3–90.6 °C.

40a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48–8.34 (m, 2H), 7.69 (td, *J* = 8.1, 1.9 Hz, 2H), 7.36-7.23 (m, 12H), 7.23–7.11 (m, 2H), 6.41 (s, 2H), 2.91 (t, *J* = 7.7 Hz, 4H), 2.23 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6 (C=N), 152.4 (C=N), 148.7

(CH), 144.2 (C-N), 138.0 (CH), 131.1 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 122.1 (CH), 118.8 (CH), 108.2 (CH), 29.3 (CH_2), 28.2 (CH_2); IR (neat): 3058, 2951, 2930, 2370, 1737, 1586, 1548, 1495, 1470, 1424, 1371, 1192, 1144, 991, 972, 782, 765, 739, 694, 616, 581, 528, 438, 418 cm^{-1}; MS (ESI, m/z): 483.23 $[M+H]^+$; HRMS (ESI) calcd. for $C_{31}H_{27}N_6$: 483.2292 $[M+H]^+$, found: 483.2305.

4.3.13 Synthesis of 1,3-Bis(5-(4-chlorophenyl)-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (40b)

General Procedure **3** was followed by using 1,9-bis(4-chlorophenyl)nona-2,7-diyne-1,9-dione (**36b**) (104 mg, 0.28 mmol) and 2-hydrazinopyridine (**39**) (61 mg, 0.56 mmol) were employed to afford 65.6 mg (42%) of the indicated product **40b** as a light brown solid (R_f = 0.23 in 1:1 hexane/ethyl acetate); mp 141–144.1 ^oC.
40b: ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 4.6 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.73 (t, *J* = 7.3 Hz, 2H), 7.44 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.3 Hz, 4H), 7.17 (d, *J* = 8.5 Hz, 4H), 6.37 (s, 2H), 2.87 (t, *J* = 7.7 Hz, 4H), 2.18 (p, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7 (C=N), 152.4 (C=N), 148.6 (CH), 143.1 (C-N), 138.4 (CH), 134.1 (C-Cl), 130.0 (CH), 128.9 (C), 128.6 (CH), 122.3 (CH), 118.6 (CH), 108.5 (CH), 29.3 (CH_2), 28.1 (CH_2); IR (neat): 3219, 2927, 1658, 1589, 1471, 1453, 1432, 1399, 1368, 1299, 1272, 1192, 1089, 1011, 994, 974, 896, 845, 789, 761, 739, 714, 661, 619, 582, 527, 490, 464, 450 cm^{-1}; MS (ESI, m/z): 551.15 $[M+H]^+$; HRMS (ESI) calcd. for $C_{31}H_{25}Cl_2N_6$: 551.1512 $[M+H]^+$, found: 551.1518.

4.3.14 Synthesis of 2-(5-(4-Methoxyphenyl)-3-(3-(3-(4-methoxyphenyl)-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl)propyl)-1*H*-pyrazol-1-yl)pyridine (40c)

General Procedure **3** was followed by using 1,9-bis(4-methoxyphenyl)nona-2,7-diyne-1,9-dione (**36c**) (60.4 mg, 0.17 mmol) and 2-hydrazinopyridine (**39**) (37 mg, 0.34 mmol) were employed to afford 43.5 mg (47%) of the indicated product **40c** as yellow oil (R_f = 0.23 in 1:1 hexane/ethyl acetate)

40c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 4.8, 1.1 Hz, 2H), 8.03 (d, *J* = 8.9 Hz, 2H), 7.61 (td, *J* = 8.0, 1.9 Hz, 2H), 7.27–7.15 (m, 2H), 7.15–7.01 (m, 4H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.24 (s, 2H), 3.79 (s, 3H), 3.73 (s, 3H), 2.84 (t, *J* = 7.5 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.05 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4 (2C-OMe), 159.7 (2C=N), 153.4 (2C=N), 148.8 (2C-N), 144.4 (2CH), 138.2 (2CH), 132.1 (2CH), 130.4 (2C), 130.0 (2CH), 122.3 (2CH), 119.1 (2CH), 113.91 (2CH), 113.87 (2CH), 107.7 (2CH), 55.7 (CH_3), 55.4 (CH_3), 27.7 (CH_2), 27.6 (CH_2), 19.1 (CH_2). (Note that five C peaks overlap with other C peaks and nine CH peaks overlap with other CH peaks); IR (neat): 3005, 2932, 2837, 2234, 2197, 1633, 1591, 1507, 1470, 1426, 1369, 1250, 1165, 1110, 1027, 971, 915, 834, 785, 740, 687, 597, 577, 512, 409 cm^{-1}; MS (ESI, m/z): 543.25 $[M+H]^+$; HRMS (ESI) calcd. for $C_{33}H_{31}N_6O_2$: 543.2503 $[M+H]^+$, found: 543.2502.

4.3.15 Synthesis of 1,3-Bis(5-(3,5-dichlorophenyl)-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (40d)

General Procedure **3** was followed by using 1,9-bis(3,5-dichlorophenyl)nona-2,7-diyne-1,9-dione (**36d**) (71 mg, 0.16 mmol) and 2-hydrazinopyridine (**39**) (35 mg, 0.32 mmol) were employed to afford 44.8 mg (45%) of the indicated product **40d** as an orange solid (R_f = 0.57 in 1:1 hexane/ethyl acetate); mp 89.5–93.3 ºC.

40d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 4.8, 1.0 Hz, 2H), 7.80 (td, *J* = 7.8, 1.8 Hz, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.29 (t, *J* = 1.8 Hz, 2H), 7.23–7.19 (m, 2H), 7.14 (d, *J* = 1.8 Hz, 4H), 6.39 (s, 2H), 2.86 (t, *J* = 7.6 Hz, 4H), 2.17 (p, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6 (C=N), 152.1 (C=N), 148.3 (CH), 141.6 (C-N), 138.7 (CH), 134.7 (C-Cl), 134.4 (C), 128.1 (CH), 127.2 (CH), 122.5 (CH), 118.1 (CH), 109.4 (CH), 29.1 (CH_2), 28.0 (CH_2); IR (neat): 2921, 2367, 1738, 1591, 1564, 1475, 1439, 1412, 1366, 1241, 1010, 858, 797, 771, 738, 685, 620, 599, 577, 506, 434 cm^{-1}; MS (ESI, m/z): 619.07 $[M+H]^+$; HRMS (ESI) calcd. for $C_{31}H_{23}Cl_4N_6$: 619.0733 $[M+H]^+$, found: 619.0734.

4.3.16 Synthesis of 1,3-Bis(5-(4-ethylphenyl)-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (40e)

General Procedure **3** was followed by using 1,9-bis(4-ethylphenyl)nona-2,7-diyne-1,9-dione (**36e**) (74 mg, 0.21 mmol) and 2-hydrazinopyridine (**39**) (46 mg, 0.42 mmol) were employed to afford 32 mg (28%) of the indicated product **40e** as brownish orange oil (R_f = 0.13 in 1:1 hexane/ethyl acetate).

40e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51–8.31 (m, 2H), 7.68 (td, *J* = 7.9, 1.9 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.21–7.06 (m, 10H), 6.36 (s, 2H), 2.88 (t, *J* = 7.7 Hz, 4H), 2.64 (q, *J* = 7.6 Hz, 4H), 2.19 (p, *J* = 7.7 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7 (C=N), 152.6 (C=N), 148.8 (CH), 144.39 (C-CH_2CH_3), 144.35 (C), 138.1 (CH), 128.7 (CH), 128.5 (C), 127.9 (CH), 122.1 (CH), 119.0 (CH), 108.0 (CH), 29.4 (CH_2), 28.7 (CH_2), 28.3 (CH_2), 15.4 (CH_3); IR (neat): 3751, 2968, 2930, 2220, 2185, 2161, 1977, 1578, 1508, 1472, 1427, 1367, 992, 970, 834, 787, 682, 580, 520, 498, 416 cm^{-1}; MS (ESI, m/z): 539.29 $[M+H]^+$; HRMS (ESI) calcd. for $C_{35}H_{35}N_6$: 539.2918 $[M+H]^+$, found: 539.2929.

4.3.17 Synthesis of 1,3-Bis(1-(pyridin-2-yl)-5-(*p*-tolyl)-1*H*-pyrazol-3-yl)propane (40f)

General Procedure **3** was followed by using 1,9-di-*p*-tolylnona-2,7-diyne-1,9-dione (**36f**) (110 mg, 0.33 mmol) and 2-hydrazinopyridine (**39**) (72 mg, 0.66 mmol) were employed to afford 31.3 mg (19%) of the indicated product **40f** as dark brownish orange oil (R_f = 0.05 in 1:1 hexane/ethyl acetate).

40f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64–8.22 (m, 2H), 7.67 (td, *J* = 8.0, 1.8 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.21–7.14 (m, 3H), 7.15–7.06 (m, 7H), 6.36 (s, 2H), 3.03–2.72 (t, *J* = 7.7 Hz, 4H), 2.34 (s, 6H), 2.19 (p, *J* = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7 (C=N), 152.6 (C=N), 148.8 (CH), 144.3 (C-N), 138.0 (CH and C-Me), 130.1 (C), 129.1 (CH), 128.6 (CH), 122.1 (CH), 119.0 (CH), 108.0 (CH), 29.4 (CH_2), 28.2 (CH_2), 21.4 (CH_3). (Note that CH and C-Me peaks overlap on each

other); IR (neat): 3013, 2929, 2859, 1706, 1585, 1509, 1471, 1428, 1368, 1267, 1241, 1173, 1146, 1041, 992, 971, 783, 739, 576, 511, 418 cm^{-1}; MS (ESI, m/z): 511.26 $[M+H]^+$; HRMS (ESI) calcd. for $C_{33}H_{31}N_6$: 511.2605 $[M+H]^+$, found: 511.2619.

4.3.18 Synthesis of 2-(5-(4-(Methylthio)phenyl)-3-(3-(3-(4-(methylthio)phenyl)-1-(pyridin-2-yl)-1*H*-pyrazol-5-yl)propyl)-1*H*-pyrazol-1-yl)pyridine (40g)

General Procedure **3** was followed by using 1,9-bis(4-(methylthio)phenyl)nona-2,7-diyne-1,9-dione (**36g**) (101.1 mg, 0.26 mmol) and 2-hydrazinopyridine (**39**) (57 mg, 0.52 mmol) were employed to afford 19.6 mg (13%) of the indicated product **40g** as dark brownish orange oil (R_f = 0.40 in 1:1 hexane/ethyl acetate).
40g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 5.8 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 7.74 (td, *J* = 7.8, 1.8 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 2.3 Hz, 2H), 7.26–7.19 (m, 3H), 7.18–7.15 (m, 4H), 6.38 (s, 2H), 2.94 (t, *J* = 7.4 Hz, 2H), 2.65 (t, *J* = 7.1 Hz, 2H), 2.54 (s, 3H), 2.50 (s, 3H), 2.15 (p, *J* = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5 (2C=N), 152.5 (2C=N) 148.8 (2CH), 144.0 (2C-N), 139.1 (2C), 138.3 (2CH), 130.1 (2CH), 129.0 (2CH), 127.5 (2C), 125.9 (2CH), 124.8 (2CH), 122.4 (2CH), 119.0 (2CH), 108.0 (2CH), 27.7 (CH_2), 27.6 (CH_2), 19.0 (CH_2), 15.5 (CH_3), 14.8 (CH_3). (Note that five C peaks overlap with other C peaks and nine CH peaks overlap with other CH peaks); IR (neat): 2918, 2852, 2237, 2200, 1735, 1630, 1583, 1494, 1469, 1425, 1398, 1366, 1264, 1178, 1146, 1087, 968, 782, 743, 680, 619, 579, 516, 485, 410 cm^{-1}; MS (ESI, m/z): 575.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{33}H_{31}N_6S_2$: 575.2046 $[M+H]^+$, found: 575.2056.

4.3.19 Synthesis of 2-(3-(3-(5-(4-Bromophenyl)-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propyl)-5-(4-chlorophenyl)-1*H*-pyrazol-1-yl)pyridine (40h)

General Procedure **3** was followed by using 1-(4-bromophenyl)-9-(4-chlorophenyl)nona-2,7-diyne-1,9-dione (**49a**) (91 mg, 0.22 mmol) and 2-hydrazinopyridine (**39**) (48 mg, 0.44 mmol) were employed to afford 79.8 mg (61%)

of the indicated product **40h** as a light yellow solid (R_f = 0.21 in 1:1 hexane/ethyl acetate); mp 145.5–147.0 ºC.

40h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 4.7 Hz, 2H), 7.63 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 4H), 7.17 (dd, *J* = 7.8, 4.0 Hz, 2H), 7.08 (t, *J* = 8.9 Hz, 4H), 7.01 (d, *J* = 8.3 Hz, 2H), 6.28 (s, 2H), 2.77 (t, *J* = 7.6 Hz, 4H), 2.09 (p, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2 (C=N), 154.63 (C=N), 154.60 (C=N), 152.3 (C=N), 148.5 (2CH), 143.1 (2C-N), 138.4 (2CH), 134.1 (C-Cl), 131.4 (2CH), 131.3 (C), 130.2 (2CH), 129.9 (2CH), 129.7 (C), 128.6 (C-Br), 128.5 (2CH), 122.3 (2CH), 118.6 (2CH), 108.5 (2CH), 29.2 ($2CH_2$), 28.1 (CH_2); IR (neat): 3052, 2930, 2855, 1726, 1660, 1589, 1543, 1471, 1425, 1398, 1368, 1278, 1192, 1153, 1089, 1067, 1045, 1008, 994, 973, 843, 788, 759, 739, 709, 660, 618, 582, 525, 448 cm^{-1}; MS (ESI, m/z): 595.10 $[M+H]^+$; HRMS (ESI) calcd. for $C_{31}H_{25}BrClN_6$: 595.1007 $[M+H]^+$, found: 595.1010.

4.3.20 Synthesis of 1,3-Bis(5-(4-bromophenyl)-1-(pyridin-2-yl)-1*H*-pyrazol-3-yl)propane (40i)

General Procedure **3** was followed by using 1,9-bis(4-bromophenyl)nona-2,7-diyne-1,9-dione (**36i**) (96.2 mg, 0.21 mmol) and 2-hydrazinopyridine (**39**) (46 mg, 0.42 mmol) were employed to afford 58.2 mg (43%) of the indicated product **40i** as orange oil (R_f = 0.15 in 1:1 hexane/ethyl acetate).

40i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 4.9, 1.1 Hz, 2H), 7.76–7.71 (m, 2H), 7.55 (t, *J* = 8.7 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 4H), 7.22–7.15 (m, 2H), 7.11 (d, *J* = 8.5 Hz, 4H), 6.37 (s, 2H), 2.87 (t, *J* = 7.7 Hz, 4H), 2.18 (p, *J* = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7 (C=N), 152.4 (C=N), 148.6 (CH), 143.2 (C-N), 138.4 (CH), 132.1 (C), 131.5 (CH), 130.3 (CH), 129.1 (C-Br), 122.3 (CH), 118.6 (CH), 108.6 (CH), 29.3 (CH_2), 28.2 (CH_2); IR (neat): 3061, 2929, 1730, 1659, 1586, 1491, 1470, 1427, 1395, 1367, 1241, 1069, 1009, 993, 970, 828, 789, 739, 707, 600, 579, 505 cm^{-1}; MS (ESI, m/z): 639.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{31}H_{25}Br_2N_6$: 639.0502 $[M+H]^+$, found: 639.0505.

4.4 General Procedure 4. Synthesis of 1,3-Bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane Derivatives 42

To a stirred solution of the proper 1,9-diarylnona-2,7-diyne-1,9-dione **36** or **49** (approximately 0.3 mmol) in dioxane (4.0 mL) under argon was added *o*-phenylenediamine (**41**) (0.6 mmol) and the resulting mixture was refluxed until the end of the reaction. The progress of the reaction was monitored by routine TLC analysis for the disappearance of 1,9-diarylnona-2,7-diyne-1,9-dione **36** or **49** using 1:1 hexane/ethyl acetate as the eluent. When the reaction finished, solvent is evaporated on a rotary evaporator to give the crude product, which was purified by flash chromatography on silica gel using hexane/ethyl acetate (1:1) as the eluent to afford the corresponding 1,3-bis(4-aryl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propanes (**42**).

4.4.1 Synthesis of 1,3-Bis(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42a)

General Procedure **4** was followed by using 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**) (99.4 mg, 0.33 mmol) and *o*-phenylenediamine (**41**) (71.4 mg, 0.66 mmol) were employed to afford 95 mg (60%) of the indicated product **42a** as reddish brown oil (R_f = 0.5 in 1:1 hexane/ethyl acetate).

42a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.4 Hz, 4H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.51–7.40 (m, 8H), 7.35 (ddd, *J* = 6.4, 3.5, 2.1 Hz, 4H), 2.60 (t, *J* = 6.6 Hz, 4H), 2.13 (p, *J* = 6.9 Hz, 2H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5 (C=N), 153.7 (C=N), 140.7 (C), 140.4 (C), 137.0 (C), 130.9 (CH), 128.9 (CH), 128.7 (CH), 128.3 (CH), 127.9 (CH), 125.3 (CH), 125.2 (CH), 39.1 (CH_2), 37.9 (CH_2), 22.5 (CH_2); IR (neat): 3054, 2931, 1731, 1626, 1602, 1568, 1445, 1316, 1253, 1207, 1112, 1009, 756, 690, 664, 617, 511, 493 cm^{-1}; MS (ESI, m/z): 481.23 $[M+H]^+$; HRMS (ESI) calcd. for $C_{33}H_{29}N_4$: 481.2387 $[M+H]^+$, found: 481.2389.

4.4.2 Synthesis of 1,3-Bis(4-(4-chlorophenyl)-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42b)

General Procedure **4** was followed by using 1,9-bis(4-chlorophenyl)nona-2,7-diyne-1,9-dione (**36b**) (93.4 mg, 0.25 mmol) and *o*-phenylenediamine (**41**) (54.1 mg, 0.50 mmol) were employed to afford 53 mg (39%) of the indicated product **42b** as dark brown oil (R_f = 0.48 in 1:1 hexane/ethyl acetate); mp 65.8–68.0 °C.

42b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.5 Hz, 4H), 7.52 (dd, *J* = 5.7, 3.7 Hz, 2H), 7.37 (dd, *J* = 7.0, 2.5 Hz, 2H), 7.35–7.27 (m, 8H), 2.51 (t, *J* = 6.6 Hz, 4H), 2.04 (br s, 2H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (C=N), 152.3 (C=N), 140.5 (C-Cl), 140.3 (C), 137.2 (C), 135.4 (C), 129.6 (CH), 129.1 (CH), 128.7 (CH), 127.9 (CH), 125.6 (CH), 125.3 (CH), 38.9 (CH_2), 37.8 (CH_2), 22.3 (CH_2); IR (neat): 2919, 2849, 1727, 1628, 1587, 1562, 1460, 1428, 1312, 1259, 1206, 1089, 1008, 835, 755, 615, 480 cm^{-1}; MS (ESI, m/z): 549.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{33}H_{27}Cl_2N_4$: 549.1607 $[M+H]^+$, found: 549.1604.

4.4.3 Synthesis of 1,3-Bis(4-(4-methoxyphenyl)-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42c)

General Procedure **4** was followed by using 1,9-bis(4-methoxyphenyl)nona-2,7-diyne-1,9-dione (**36c**) (75 mg, 0.21 mmol) and *o*-phenylenediamine (**41**) (45 mg, 0.42 mmol) were employed to afford 36.3 mg (32%) of the indicated product **42c** as reddish brown oil (R_f = 0.15 in 1:1 hexane/ethyl acetate).

42c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01–7.68 (m, 4H), 7.47 (dd, *J* = 7.5, 1.9 Hz, 2H), 7.40–7.29 (m, 2H), 7.26–7.17 (m, 4H), 6.90–6.72 (m, 4H), 3.75 (s, 6H), 2.47 (br s, 4H), 2.07–1.95 (m, 2H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (C-OMe), 160.7 (C=N), 153.2 (C=N), 141.0 (C), 140.4 (C), 132.3 (C), 130.1 (CH), 128.6 (CH), 127.9 (CH), 125.2 (CH), 124.9 (CH), 114.2 (CH), 55.5 (OMe), 38.9 (CH_2), 37.8

(CH_2), 22.4 (CH_2); IR (neat): 2931, 2836, 1733, 1601, 1562, 1509, 1457, 1433, 1371, 1316, 1249, 1171, 1109, 1027, 834, 761, 542, 505, 419 cm^{-1}; MS (ESI, m/z): 541.26 $[M+H]^+$; HRMS (ESI) calcd. for $C_{35}H_{33}N_4O_2$: 541.2598 $[M+H]^+$, found: 541.2611.

4.4.4 Synthesis of 2-(4-Methoxyphenyl)-4-(3-(4-phenyl-3*H*-benzo[*b*][1,4]diazepin-2-yl)propyl)-3*H*-benzo[*b*][1,4]diazepine (42d)

General Procedure **4** was followed by 2using 1-(4-methoxyphenyl)-9-phenylnona-2,7-diyne-1,9-dione (**49c**) (120 mg, 0.36 mmol) and *o*-phenylenediamine (**41**) (78 mg, 0.72 mmol) were employed to afford 39.4 mg (21%) of the indicated product **42d** as a brown solid (R_f = 0.33 in 1:1 hexane/ethyl acetate); mp 66.8–70.2 ºC.

42d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.9, 1.2 Hz,, 2H), 7.96 (d, *J* = 8.8 Hz, 2H), 7.68 (t, *J* = 3.1 Hz, 1H), 7.59–7.54 (m, 2H), 7.43 (dd, *J* = 7.3, 3.6 Hz, 4H), 7.34–7.29 (m, 4H), 6.88 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 3H), 2.55 (t, *J* = 5.2 Hz, 4H), 2.09 (p, *J* = 6.1 Hz, 2H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9 (C-OMe), 160.6 (C=N), 160.5 (C=N), 153.8 (C=N), 153.1 (C=N), 141.0 (C), 140.8 (C), 140.5 (C), 140.4 (C), 137.1 (C), 130.9 (CH), 130.1 (CH), 129.8 (C), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 127.91 (CH), 127.86 (CH), 125.3 (CH), 125.2 (CH), 125.1 (CH), 124.9 (CH), 114.2 (CH), 55.5 (OMe), 39.1 (CH_2), 39.0 (CH_2), 38.0 (CH_2), 37.7 (CH_2), 22.5 (CH_2); IR (neat): 2929, 2836, 1733, 1601, 1563, 1509, 1443, 1316, 1251, 1206, 1172, 1110, 1027, 836, 756, 690, 616, 517, 407 cm^{-1}; MS (ESI, m/z): 511.25 $[M+H]^+$; HRMS (ESI) calcd. for $C_{34}H_{31}N_4O$: 511.2492 $[M+H]^+$, found: 511.2507.

4.4.5 Synthesis of 1,3-Bis(4-(4-ethylphenyl)-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42e)

General Procedure **4** was followed by using 1,9-bis(4-ethylphenyl)nona-2,7-diyne-1,9-dione (**36e**) (96.3 mg, 0.27 mmol) and *o*-phenylenediamine (**41**) (58 mg,

0.54 mmol) were employed to afford 53.7 mg (37%) of the indicated product **42e** as brownish orange oil (R_f = 0.45 in 1:1 hexane/ethyl acetate).

42e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 4H), 7.45 (d, *J* = 7.0 Hz, 2H), 7.33 (dd, *J* = 7.2, 1.5 Hz, 2H), 7.19 (d, *J* = 5.4 Hz, 4H), 7.13 (d, *J* = 8.0 Hz, 4H), 2.57 (q, *J* = 7.5 Hz, 4H), 2.46 (br s, 4H), 2.04–1.93 (m, 2H), 1.14 (t, *J* = 7.6 Hz, 6H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6 (C=N), 153.7 (C=N), 147.6 (C-CH_2CH_3), 140.9 (C), 140.5 (C), 134.6 (C), 128.7 (CH), 128.43 (CH), 128.40 (CH), 127.9 (CH), 125.12 (CH), 125.07 (CH), 39.0 (CH_2), 37.8 (CH_2), 28.8 (CH_2), 22.5 (CH_2), 15.3 (CH_3); IR (neat): 2963, 2930, 2870, 1736, 1602, 1561, 1518, 1456, 1435, 1374, 1312, 1260, 1209, 1169, 1041, 1010, 845, 760, 729, 632, 616, 542, 510, 418 cm^{-1}; MS (ESI, m/z): 537.30 $[M+H]^+$; HRMS (ESI) calcd. for $C_{37}H_{37}N_4$: 537.3013 $[M+H]^+$, found: 537.3022.

4.4.6 Synthesis of 1,3-Bis(4-(*p*-tolyl)-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42f)

General Procedure **4** was followed by using 1,9-di-*p*-tolylnona-2,7-diyne-1,9-dione (**36f**) (97 mg, 0.29 mmol) and *o*-phenylenediamine (**41**) (63 mg, 0.58 mmol) were employed to afford 65 mg (44%) of the indicated product **42f** as dark brown oil (R_f = 0.48 in 1:1 hexane/ethyl acetate).

42f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.8 Hz, 4H), 7.54 (d, *J* = 7.0 Hz, 2H), 7.41 (d, *J* = 6.9 Hz, 2H), 7.33–7.26 (m, 4H), 7.20 (d, *J* = 7.8 Hz, 4H), 2.37 (br s, 4H), 2.07 (br s, 2H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6 (C=N), 153.7 (C=N), 141.3 (C-Me), 140.9 (C), 140.4 (C), 134.3 (C), 129.6 (CH), 128.6 (CH), 128.3 (CH), 127.8 (CH), 125.1 (CH), 125.0 (CH), 39.0 (CH_2), 37.8 (CH_2), 22.4 (CH_2), 21.5 (CH_3); IR (neat): 2921, 2858, 1733, 1627, 1603, 1563, 1517, 1441, 1316, 1261, 1205, 1181, 1112, 1034, 1013, 944, 818, 761, 543, 513 cm^{-1}; MS (ESI, m/z): 509.26 $[M+H]^+$; HRMS (ESI) calcd. for $C_{35}H_{33}N_4$: 509.2700 $[M+H]^+$, found: 509.2694.

4.4.7 Synthesis of 1,3-Bis(4-(4-(methylthio)phenyl)-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42g)

General Procedure **4** was followed by using 1,9-bis(4-(methylthio)phenyl)nona-2,7-diyne-1,9-dione (**36g**) (82 mg, 0.21 mmol) and *o*-phenylenediamine (**41**) (45 mg, 0.42 mmol) were employed to afford 46 mg (38%) of the indicated product **42g** as brownish orange oil (R_f = 0.25 in 1:1 hexane/ethyl acetate).

42g: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 4H), 7.47 (dt, *J* = 7.0, 1.8 Hz, 2H), 7.35 (dd, *J* = 7.3, 2.1 Hz, 2H), 7.23 (dt, *J* = 6.4, 2.6 Hz, 4H), 7.12 (d, *J* = 8.5 Hz, 4H), 2.41 (s, 3H), 2.37 (br s, 4H), 2.00 (br s, 2H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5 (C=N), 153.0 (C=N), 142.9 (C-SMe), 140.8 (C), 140.4 (C), 133.3 (C), 128.6 (CH), 127.8 (CH), 125.7 (CH), 125.18 (CH), 125.17 (CH), 38.9 (CH_2), 37.6 (CH_2), 22.3 (CH_2), 15.1 (CH_3). (Note that two CH peaks overlap on each other); IR (neat): 2958, 2918, 2852, 1729, 1625, 1584, 1544, 1490, 1429, 1398, 1312, 1259, 1185, 1089, 1033, 1007, 953, 802, 743, 616, 517 cm^{-1}; MS (ESI, m/z): 573.21 $[M+H]^+$; HRMS (ESI) calcd. for $C_{35}H_{33}N_4S_2$: 573.2141 $[M+H]^+$, found: 573.2147.

4.4.8 Synthesis of 1,3-Bis(4-(4-bromophenyl)-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42h)

General Procedure **4** was followed by using 1,9-bis(4-bromophenyl)nona-2,7-diyne-1,9-dione (**36i**) (101 mg, 0.22 mmol) and *o*-phenylenediamine (**41**) (47.6 mg, 0.44 mmol) were employed to afford 81 mg (58%) of the indicated product **42h** as a pale brown solid (R_f = 0.37 in 1:1 hexane/ethyl acetate); mp 121.7–122.4 °C.

42h: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.6 Hz, 4H), 7.56–7.53 (m, 4H), 7.37–7.33 (m, 4H), 7.31 (d, *J* = 5.3 Hz, 4H), 2.56 (t, *J* = 6.1 Hz, 4H), 2.11–2.06 (m, 2H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (C=N), 152.4 (C=N), 140.5 (C), 140.3 (C), 135.9 (C), 132.1 (CH), 129.8 (CH), 128.7 (CH), 127.9 (CH), 125.8 (C-Br), 125.6

(CH), 125.4 (CH), 39.0 (CH_2), 37.7 (CH_2), 22.3 (CH_2); IR (neat): 2921, 2845, 1710, 1625, 1582, 1426, 1312, 1206, 1111, 1070, 1005, 829, 744, 614, 502, 440, 407 cm^{-1}; MS (ESI, m/z): 637.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{33}H_{27}Br_2N_4$: 637.0597 $[M+H]^+$, found: 637.0581.

4.4.9 Synthesis of 1,3-Bis(4-(3-chlorophenyl)-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42i)

General Procedure **4** was followed by using 1,9-bis(3-chlorophenyl)nona-2,7-diyne-1,9-dione (**36j**) (95 mg, 0.26 mmol) and *o*-phenylenediamine (**41**) (56 mg, 0.52 mmol) were employed to afford 47.7 mg (33%) of the indicated product **42i** as pale brown oil (R_f = 0.37 in 1:1 hexane/ethyl acetate).

42i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 2H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.61 (dd, *J* = 5.9, 3.1 Hz, 2H), 7.55–7.50 (m, 2H), 7.41–7.37 (m, 2H), 7.32–7.27 (m, 6H), 2.55 (t, *J* = 6.9 Hz, 4H), 2.06 (p, *J* = 5.2 Hz, 2H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (C=N), 152.1 (C=N), 140.4 (C), 138.9 (C), 135.2 (C), 130.9 (CH), 130.1 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 126.2 (CH), 125.7 (CH), 125.4 (CH), 123.6 (C-Cl), 39.0 (CH_2), 37.9 (CH_2), 22.3 (CH_2); IR (neat): 3058, 2919, 1733, 1628, 1601, 1562, 1433, 1371, 1311, 1259, 1206, 1113, 1077, 1033, 878, 760, 705, 683, 445, 420 cm^{-1}; MS (ESI, m/z): 549.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{33}H_{27}Cl_2N_4$: 549.1607 $[M+H]^+$, found: 549.1617.

4.4.10 Synthesis of 1,3-Bis(4-(3-bromophenyl)-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42j)

General Procedure **4** was followed by using 1,9-bis(3-bromophenyl)nona-2,7-diyne-1,9-dione (**36k**) (129 mg, 0.28 mmol) and *o*-phenylenediamine (**41**) (60.5 mg, 0.56 mmol) were employed to afford 81 mg (45%) of the indicated product **42j** as a dark yellow solid (R_f = 0.43 in 1:1 hexane/ethyl acetate); mp 65.3–68.8 °C.

42j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.07 (s, 1H), 7.87 (d, *J* = 7.9 Hz, 2H), 7.56 (dd, *J* = 11.6, 7.9 Hz, 4H), 7.33 (dt, *J* = 7.3, 4.3 Hz, 5H), 7.27 (dd, *J* = 13.4, 5.4 Hz, 3H), 2.57 (t, *J* = 6.6 Hz, 4H), 2.08 (p, *J* = 10.2, 8.6 Hz, 2H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1 (C=N), 152.0 (C=N), 140.4 (C), 140.3 (C), 139.0 (C), 133.8 (CH), 131.4 (CH), 130.4 (CH), 128.7 (CH), 127.9 (CH), 126.7 (CH), 125.7 (CH), 125.4 (C-Br), 123.3 (CH), 39.0 (CH_2), 37.9 (CH_2), 22.3 (CH_2); IR (neat): 3058, 2920, 1733, 1624, 1592, 1559, 1509, 1454, 1383, 1309, 1258, 1206, 1112, 1069, 1033, 995, 895, 747, 681, 461, 435 cm^{-1}; MS (ESI, m/z): 637.06 $[M+H]^+$; HRMS (ESI) calcd. for $C_{33}H_{27}Br_2N_4$: 637.0600 $[M+H]^+$, found: 637.0610.

4.4.11 Synthesis of 1,3-Bis(4-(3-nitrophenyl)-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42k)

General Procedure **4** was followed by using 1,9-bis(3-nitrophenyl)nona-2,7-diyne-1,9-dione (**36m**) (85 mg, 0.22 mmol) and *o*-phenylenediamine (**41**) (47.6 mg, 0.44 mmol) were employed to afford 42 mg (34%) of the indicated product **42k** as brown oil (R_f = 0.16 in 1:1 hexane/ethyl acetate).

42k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 2H), 8.25 (d, *J* = 8.3 Hz, 4H), 7.49 (t, *J* = 7.2 Hz, 4H), 7.35–7.28 (m, 6H), 2.59 (t, *J* = 6.2 Hz, 4H), 2.12–2.02 (m, 2H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5 (C=N), 150.6 (C=N), 148.6 (C-NO_2), 140.3 (C), 139.9 (C), 138.5 (C), 133.7 (CH), 129.9 (CH), 128.8 (CH), 127.8 (CH), 126.1 (CH), 125.5 (CH), 125.2 (CH), 122.9 (CH), 38.7 (CH_2), 37.8 (CH_2), 21.9 (CH_2); IR (neat): 2920, 1733, 1603, 1526, 1433, 1345, 1261, 1109, 1036, 896, 805, 737, 694, 677, 490 cm^{-1}; MS (ESI, m/z): 571.20 $[M+H]^+$; HRMS (ESI) calcd. for $C_{33}H_{27}N_6O_4$: 571.2088 $[M+H]^+$, found: 571.2087.

4.4.12 Synthesis of 1,3-Bis(4-(4-heptylphenyl)-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42m)

General Procedure **4** was followed by using 1,9-bis(4-heptylphenyl)nona-2,7-diyne-1,9-dione (**36o**) (83 mg, 0.17 mmol) and *o*-phenylenediamine (**41**) (36.7 mg, 0.34 mmol) were employed to afford 35.2 mg (31%) of the indicated product **42m** as orange oil (R_f = 0.91 in 1:1 hexane/ethyl acetate).

42m: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 4H), 7.46 (dd, *J* = 7.6, 1.9 Hz, 2H), 7.33 (dd, *J* = 7.5, 2.0 Hz, 2H), 7.20 (ddd, *J* = 7.2, 5.0, 2.3 Hz, 4H), 7.11 (d, *J* = 8.2 Hz, 4H), 2.56–2.49 (m, 4H), 2.00 (t, *J* = 7.3 Hz, 2H), 1.54–1.46 (m, 4H), 1.26–1.17 (m, 16H), 0.81 (t, *J* = 6.9 Hz, 6H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7 (C=N), 153.7 (C=N), 146.4 (C), 140.9 (C), 140.5 (C), 134.6 (C), 129.0 (CH), 128.7 (CH), 128.3 (CH), 127.9 (CH), 125.11 (CH), 125.07 (CH), 39.1 (CH_2), 37.8 (CH_2), 35.9 (CH_2), 31.9 (CH_2), 31.3 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 23.9 (CH_2), 22.8 (CH_2), 14.2 (CH_3); IR (neat): 2923, 2853, 1717, 1603, 1559, 1541, 1507, 1457, 1412, 1375, 1311, 1259, 1206, 1183, 1113, 1071, 1032, 1010, 846, 759 cm^{-1}; MS (ESI, m/z): 677.45 $[M+H]^+$; HRMS (ESI) calcd. for $C_{47}H_{57}N_4$: 677.4578 $[M+H]^+$, found: 677.4562.

4.4.13 Synthesis of 1,3-Bis(4-(3,5-bis(trifluoromethyl)phenyl)-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42n)

General Procedure **4** was followed by using 1,9-bis(3,5-bis(trifluoromethyl)phenyl)nona-2,7-diyne-1,9-dione (**36t**) (70 mg, 0.12 mmol) and *o*-phenylenediamine (**41**) (26 mg, 0.24 mmol) were employed to afford 17.3 mg (19%) of the indicated product **42n** as brownish orange oil (R_f = 0.17 in 9:1 hexane/ethyl acetate).

42n: ^{1}H NMR (400 MHz, $CDCI_3$) δ 8.51 (s, 2H), 8.44 (s, 2H), 7.92 (s, 2H), 7.54–7.48 (m, 2H), 7.35–7.29 (m, 6H), 2.63 (t, *J* = 7.1 Hz, 4H), 2.10 (p, *J* = 7.6 Hz, 2H)

(no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (C=N), 149.8 (C=N), 139.8 (C), 139.0 (C), 133.3 (C), 132.6 (q, ^2J = 25 Hz, C), 128.9 (CH), 127.9 (CH), 126.4 (CH), 125.56 (CH), 124.1 (q, ^3J = 3.6 Hz, CH), 123.5 (q, ^3J = 3.7 Hz, CH), 123.1 (q, ^1J = 250.5 Hz, CF_3), 38.9 (CH_2), 37.7 (CH_2), 22.0 (CH_2); IR (neat): 3062, 2930, 1736, 1633, 1416, 1384, 1350, 1274, 1172, 1123, 1007, 982, 898, 844, 764, 745, 697, 680 cm^{-1}.

4.4.14 Synthesis of 1,3-Bis(4-(4-fluorophenyl)-3*H*-benzo[*b*][1,4]diazepin-2-yl)propane (42o)

General Procedure **4** was followed by using 1,9-bis(4-fluorophenyl)nona-2,7-diyne-1,9-dione (**36q**) (111 mg, 0.33 mmol) and *o*-phenylenediamine (**41**) (71.4 mg, 0.66 mmol) were employed to afford 99 mg (58%) of the indicated product **42o** as brownish orange oil (R_f = 0.73 in 1:1 hexane/ethyl acetate).

42o: ^1H NMR (400 MHz, $CDCI_3$) δ 7.99 (dd, *J* = 8.8, 5.4 Hz, 4H), 7.57–7.51 (m, 2H), 7.44–7.38 (m, 2H), 7.36–7.21 (m, 4H), 7.06 (t, *J* = 8.6 Hz, 4H), 2.54 (t, *J* = 6.8 Hz, 4H), 2.08 (p, *J* = 7.1 Hz, 2H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7 (C=N), 161.6 (d, ^1J = 305.9 Hz, CF), 152.3 (C=N), 140.5 (C), 140.3 (C), 133.2 (d, ^4J = 2.5 Hz, C), 130.4 (d, ^3J = 8.7 Hz, CH), 128.6 (CH), 127.8 (CH), 125.3 (CH), 125.2 (CH), 115.9 (d, ^2J = 21.8 Hz, CH), 38.9 (CH_2), 37.8 (CH_2), 22.2 (CH_2); IR (neat): 3054, 2931, 1732, 1628, 1599, 1573, 1506, 1459, 1436, 1407, 1371, 1312, 1229, 1156, 1112, 1097, 1044, 1010, 946, 910, 837, 761, 730, 631, 614, 541, 516 cm^{-1}.

4.4.15 Synthesis of 4,4'-(4,4'-(Propane-1,3-diyl)bis(3*H*-benzo[*b*][1,4]diazepine-4,2-diyl))dibenzonitrile (42p)

General Procedure **4** was followed by using 4,4'-(nona-2,7-diynedioyl)dibenzonitrile (**36p**) (83.6 mg, 0.24 mmol) and *o*-phenylenediamine (**41**) (51.9 mg, 0.48 mmol)

were employed to afford 51 mg (40%) of the indicated product **42p** as brownish orange oil (R_f = 0.31 in 1:1 hexane/ethyl acetate).

42p: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 4H), 7.58 (d, *J* = 8.3 Hz, 4H), 7.55–7.46 (m, 2H), 7.49–7.23 (m, 6H), 2.55 (t, *J* = 6.8 Hz, 4H), 2.04 (p, *J* = 7.0 Hz, 2H) (no CH_2 signal in the ring observed at room temperature due to ring inversion); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6 (C=N), 151.2 (C=N), 140.3 (C), 140.0 (C), 132.5 (CH), 128.9 (C), 128.5 (CH), 127.8 (CH), 126.2 (CH), 125.6 (CH), 120.3 (CH), 116.8 (C≡N), 114.0 (C-CN), 38.6 (CH_2), 37.7 (CH_2), 21.9 (CH_2); IR (neat): 3055, 2922, 2226, 1729, 1623, 1604, 1501, 1458, 1405, 1372, 1314, 1247, 1206, 1111, 1033, 1011, 851, 744, 618, 664, 553, 500, 449 cm^{-1}.

4.5 General Procedure 5. Synthesis of (*E*)-1-Phenyl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone Derivatives 44 From Symmetrical Bis-α,β-alkynic Ketones 36

To a stirred solution of the proper 1,9-diarylnona-2,7-diyne-1,9-dione **36** (0.25 mmol) in dioxane (5.0 mL) under argon was added ethylenediamine (**43**) (0.50 mmol), and the resulting mixture was refluxed until the end of the reaction (The progress of the reaction was monitored by routine TLC analysis for the disappearance of bis-α,β-alkynic ketone **36** using 4:1 hexane/ethyl acetate as the eluent). After the reaction was over, the solvent was removed on a rotary evaporator, and the resulting crude product was purified by flash chromatography on silica gel using 4:1 hexane/ethyl acetate, followed by 1:1 methanol/ethyl acetate, as the eluent to afford the corresponding 1-aryl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanones **44** and aryl methyl ketones **45**.

4.5.1 Synthesis of (*E*)-1-Phenyl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44a)

General Procedure **5** was followed by using 1,9-diphenylnona-2,7-diyne-1,9-dione (**36a**) (86.9 mg, 0.29 mmol) and ethylenediamine (**43**) (34.8 mg, 0.58 mmol) were employed and this reaction formed two fractions. First fraction afforded 14.2 mg (41%) of the indicated product **45a** as brownish orange oil (R_f = 0.72 in 4:1 hexane/ethyl acetate). Second fraction gave 37.3 mg (54%) of the indicated product **44a** as an orange solid (R_f = 0.53 in 1:1 methanol/ethyl acetate; mp 125.9-129.7 ^oC). **44a:** ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 6.9 Hz, 2H), 7.43 (dq, *J* = 14.4, 7.1 Hz, 3H), 5.84 (s, 1H), 3.94 (t, *J* = 8.7 Hz, 2H), 3.70 (t, *J* = 8.9 Hz, 2H), 3.33 (t, *J* = 6.0 Hz, 2H), 2.62 (t, *J* = 6.2 Hz, 2H), 1.83 (p, *J* = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.2 (CO), 158.3 (C=N), 155.6 (C), 141.2 (C), 131.5 (CH), 128.4 (CH), 127.6 (CH), 96.7 (CH), 52.6 (CH_2), 46.3 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 18.7 (CH_2); IR (neat): 2939, 2871, 1649, 1624, 1540, 1399, 1358, 1295, 1262, 1215, 1180, 1041, 988, 875, 766, 706, 671, 572, 496, 415 cm^{-1}; MS (ESI, m/z): 241.13 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{17}N_2O$: 241.1335 $[M+H]^+$, found: 241.1336.
45a: ^1H NMR (400 MHz, $CDCI_3$) δ 7.97–7.95 (m, 2H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.46 (d, *J* = 7.4 Hz, 2H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCI_3$) δ 198.3 (CO), 137.2 (C), 133.2 (CH), 128.7 (CH), 128.4 (CH), 26.8 (CH_3). The spectral data are in agreement with those reported previously for this compound.[65-70]

This reaction was also performed on a larger scale as summarized below: 1,9-Diphenylnona-2,7-diyne-1,9-dione (**36a**) (721.2 mg, 2.40 mmol) and ethylenediamine (**43**) (288.5 mg, 4.80 mmol) were employed in 10 ml dioxane. Two fractions were isolated. First fraction afforded 94.3 mg (33%) of the indicated product **45a** as brownish orange oil (R_f = 0.72 in 4:1 hexane/ethyl acetate). Second fraction gave 248.3 mg (43%) of the indicated product **44a** as an orange solid (R_f = 0.53 in 1:1 methanol/ethyl acetate).

4.5.2 Synthesis of (*E*)-1-(4-Chlorophenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44b)

General Procedure **5** was followed by using 1,9-bis(4-chlorophenyl)nona-2,7-diyne-1,9-dione (**36b**) (103 mg, 0.28 mmol) and ethylenediamine (**43**) (33.6 mg, 0.56 mmol) were employed and this reaction formed two fractions. First fraction afforded 11.5 mg (27%) of the indicated product **45b** as brownish orange oil (R_f = 0.64 in 4:1 hexane/ethyl acetate). Second fraction gave 24.3 mg (32%) of the indicated product **44b** as an orange solid (R_f = 0.81 in 1:1 methanol/ethyl acetate; mp 150.3-153.5 ^oC).

44b: ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 5.83 (s, 1H), 4.01 (t, *J* = 8.7 Hz, 2H), 3.77 (t, *J* = 8.9 Hz, 2H), 3.33 (t, *J* = 5.8 Hz, 2H), 2.72 (t, *J* = 5.5 Hz, 2H), 1.87 (t, *J* = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8 (CO), 155.9 (C=N), 139.3 (C), 137.9 (C-Cl), 131.5 (C), 129.1 (CH), 128.7 (CH), 97.0 (CH), 46.4 (CH_2), 29.8 (CH_2), 26.7 (CH_2), 25.7 (CH_2), 18.5 (CH_2); IR (neat): 3069, 2948, 2542, 1680, 1588, 1539, 1400, 1279, 1215, 1174, 1089, 1043, 1013, 927, 849, 761, 683, 524, 471, 437, 409 cm^{-1}; MS (ESI, m/z): 275.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{16}ClN_2O$: 275.0946 $[M+H]^+$, found: 275.0943.

45b: ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 2.59 (s, 3H). The spectral data are in agreement with those reported previously for this compound.[65-68]

4.5.3 Synthesis of (*E*)-1-(4-Methoxyphenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44c)

General Procedure **5** was followed by using 1,9-bis(4-methoxyphenyl)nona-2,7-diyne-1,9-dione (**36c**) (121 mg, 0.34 mmol) and ethylenediamine (**43**) (40.8 mg, 0.68 mmol) were employed and this reaction formed two fractions. First fraction afforded 24.5 mg (48%) of the indicated product **45c** as dark orange oil (R_f = 0.48 in

4:1 hexane/ethyl acetate). Second fraction gave 29 mg (32%) of the indicated product **44c** as a brown solid (R_f = 0.17 in 1:1 methanol/ethyl acetate; mp 116.3-118.6 ºC).
44c: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.86 (s, 1H), 3.96 (t, *J* = 9.0 Hz, 2H), 3.84 (s, 3H), 3.73 (t, *J* = 8.5 Hz, 2H), 3.32 (t, *J* = 6.1 Hz, 2H), 2.65 (t, *J* = 6.2 Hz, 2H), 1.84 (p, *J* = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.0 (CO), 162.5 (C-OMe), 158.7 (C=N), 154.8 (C), 133.8 (C), 129.7 (CH), 113.6 (CH), 96.8 (CH), 55.5 (O-Me), 52.3 (CH_2), 46.3 (CH_2), 26.6 (CH_2), 26.0 (CH_2), 18.7 (CH_2); IR (neat): 2950, 2874, 2831, 1648, 1542, 1506, 1397, 1359, 1298, 1255, 1219, 1169, 1024, 987, 879, 844, 778, 689, 667, 631, 602, 575, 510, 462, 419 cm^{-1}; MS (ESI, m/z): 271.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{19}N_2O_2$: 271.1441 $[M+H]^+$, found: 271.1441.
45c: ^{1}H NMR (400 MHz, $CDCI_3$) δ 7.92 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCI_3$) δ 196.7 (CO), 163.5 (C), 130.6 (CH), 130.3 (C), 113.6 (CH), 55.4 (OMe), 26.3 (CH_3). The spectral data are in agreement with those reported previously for this compound.[65-70]

4.5.4 Synthesis of (*E*)-1-(3,5-Dichlorophenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44d)

General Procedure **5** was followed by using 1,9-bis(3,5-dichlorophenyl)nona-2,7-diyne-1,9-dione (**36d**) (88.5 mg, 0.202 mmol) and ethylenediamine (**43**) (24.3 mg, 0.404 mmol) were employed and this reaction formed two fractions. First fraction afforded 12.6 mg (33%) of the indicated product **45d** as brownish orange oil (R_f = 0.64 in 4:1 hexane/ethyl acetate). Second fraction gave 12.8 mg (21%) of the indicated product **44d** as orange oil (R_f = 0.63 in 1:1 methanol/ethyl acetate).
44d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 1.6 Hz, 2H), 7.48 (s, 1H), 5.82 (s, 1H), 4.06 (t, *J* = 8.8 Hz, 2H), 3.88 (t, *J* = 9.0 Hz, 2H), 3.33 (t, *J* = 6.1 Hz, 2H), 2.81 (t, *J* = 6.0 Hz, 2H), 1.90 (p, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.9 (CO), 156.7 (C=N), 143.7 (C), 135.4 (C and C-Cl), 131.3 (CH), 126.2 (2CH), 96.7 (CH), 51.9 (CH_2), 46.5 (CH_2), 26.8 (CH_2), 25.7 (CH_2), 18.4 (CH_2). (Note that two C

and CH peaks overlap on each other); IR (neat): 3070, 2918, 2875, 1732, 1651, 1524, 1470, 1395, 1357, 1303, 1260, 1205, 1180, 1122, 1046, 991, 859, 790, 729, 658, 577, 518, 427 cm^{-1}; MS (ESI, m/z): 309.05 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{15}Cl_2N_2O$: 309.0556 $[M+H]^+$, found: 309.0557.

45d: ^1H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 1.9 Hz, 2H), 7.57 (t, *J* = 1.9 Hz, 1H), 2.61 (s, 3H). The spectral data are in agreement with those reported previously for this compound.[70]

4.5.5 Synthesis of (*E*)-1-(4-Ethylphenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44e)

General Procedure **5** was followed by using 1,9-bis(4-ethylphenyl)nona-2,7-diyne-1,9-dione (**36e**) (107 mg, 0.30 mmol) and ethylenediamine (**43**) (36.1 mg, 0.60 mmol) were employed and this reaction formed two fractions. First fraction afforded 17.2 mg (39%) of the indicated product **45e** as dark orange oil (R_f = 0.68 in 4:1 hexane/ethyl acetate). Second fraction gave 40.1 mg (50%) of the indicated product **44e** as a light yellow solid (R_f = 0.53 in 1:1 methanol/ethyl acetate; mp 131.7-134.4 ^oC).

44e: ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.88 (s, 1H), 3.97 (t, *J* = 8.8 Hz, 2H), 3.73 (t, *J* = 8.3 Hz, 2H), 3.36 (t, *J* = 6.0 Hz, 2H), 2.74 – 2.62 (m, 4H), 1.86 (p, *J* = 6.3 Hz, 2H), 1.26 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0 (CO), 158.3 (C=N), 155.3 (C), 148.3 (C-CH_2CH_3), 138.8 (C), 127.9 (CH), 127.8 (CH), 96.7 (CH), 52.7 (CH_2), 46.3 (CH_2), 28.9 (CH_2), 26.7 (CH_2), 26.1 (CH_2), 18.7 (CH_2), 15.5 (CH_3); IR (neat): 2939, 2874, 1738, 1654, 1603, 1536, 1474, 1431, 1396, 1356, 1295, 1260, 1220, 1181, 1105, 1042, 987, 877, 833, 769, 694, 669, 635, 581, 564, 527, 468, 418 cm^{-1}; MS (ESI, m/z): 269.16 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{21}N_2O$: 269.1648 $[M+H]^+$, found: 269.1646.

45e: ^1H NMR (400 MHz, $CDCI_3$) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 2.71 (q, *J* = 7.6 Hz, 2H), 2.58 (s, 3H), 1.25 (d, *J* = 7.6 Hz, 3H);); ^{13}C NMR (100 MHz, $CDCI_3$) δ 198.0 (CO), 150.2 (C), 135.1 (C), 128.7 (CH), 128.2 (CH),

29.1 (CH_2), 26.7 (CH_3), 15.3 (CH_3). The spectral data are in agreement with those reported previously for this compound.[66,69]

4.5.6 Synthesis of (*E*)-2-(2,3,7,8-Tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)-1-(p-tolyl)ethanone (44f)

General Procedure **5** was followed by using 1,9-di-*p*-tolylnona-2,7-diyne-1,9-dione (**36f**) (70.8 mg, 0.22 mmol) and ethylenediamine (**43**) (26.4 mg, 0.44 mmol) were employed and this reaction formed two fractions. First fraction afforded 15.3 mg (52%) of the indicated product **45f** as dark orange oil (R_f = 0.67 in 4:1 hexane/ethyl acetate). Second fraction gave 23.7 mg (42%) of the indicated product **44f** as a light orange solid (R_f = 0.22 in 1:1 methanol/ethyl acetate; mp 197.1-199.6 ^oC).

44f: ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.7 Hz, 2H), 5.85 (s, 1H), 3.95 (t, *J* = 8.9 Hz, 2H), 3.71 (t, *J* = 8.8 Hz, 2H), 3.34 (t, *J* = 6.0 Hz, 2H), 2.63 (t, *J* = 5.7 Hz, 2H), 2.39 (s, 3H), 1.84 (p, *J* = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9 (CO), 158.3 (C=N), 155.4 (C), 142.0 (C-CH_3), 138.6 (C), 129.1 (CH), 127.7 (CH), 96.6 (CH), 52.7 (CH_2), 46.3 (CH_2), 26.7 (CH_2), 26.1 (CH_2), 21.6 (CH_3), 18.8(CH_2); IR (neat): 2948, 2876, 2369, 1651, 1603, 1536, 1428, 1356, 1295, 1260, 1227, 1181, 1043, 986, 877, 776, 668, 634, 571, 499, 471, 418 cm^{-1}; MS (ESI, m/z): 255.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{19}N_2O$: 255.1492 $[M+H]^+$, found: 255.1486.

45f: ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 2.51 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1 (CO), 144.0 (C), 134.8 (C), 129.4 (CH), 128.6 (CH), 26.7 (CH_3), 21.8 (CH_3). The spectral data are in agreement with those reported previously for this compound.[65-70]

4.5.7 Synthesis of (*E*)-1-(4-(Methylthio)phenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44g)

General Procedure **5** was followed by using 1,9-bis(4-(methylthio)phenyl)nona-2,7-diyne-1,9-dione (**36g**) (137.3 mg, 0.35 mmol) and ethylenediamine (**43**) (42.1 mg, 0.70 mmol) were employed to afford 45.8 mg (46%) of the indicated product **44g** as an orange solid (R_f = 0.17 in 1:1 methanol/ethyl acetate; mp 173.0-175.3 ^oC). Other fraction containing **45g** was not isolated.

44g: ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 2H), 5.81 (s, 1H), 3.94 (t, *J* = 8.9 Hz, 2H), 3.70 (t, *J* = 8.9 Hz, 2H), 3.32 (t, *J* = 6.1 Hz, 2H), 2.62 (t, *J* = 6.3 Hz, 2H), 2.49 (s, 3H), 1.83 (p, *J* = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.1 (CO), 158.3 (C=N), 155.5 (C), 143.5 (C-Sme), 137.5 (C), 128.1 (CH), 125.2 (CH), 96.3 (CH), 52.6 (CH_2), 46.3 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 18.7 (CH_2), 15.1 (CH_3); IR (neat): 2915, 2870, 1733, 1657, 1619, 1589, 1529, 1465, 1392, 1356, 1305, 1259, 1216, 1180, 1087, 1041, 983, 878, 842, 828, 782, 674, 575, 462 cm^{-1}; MS (ESI, m/z): 287.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{19}N_2OS$: 287.1213 $[M+H]^+$, found: 287.1211.

4.5.8 Synthesis of (*E*)-1-(3-Bromophenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44h)

General Procedure **5** was followed by using 1,9-bis(3-bromophenyl)nona-2,7-diyne-1,9-dione (**36n**) (73.6 mg, 0.16 mmol) and ethylenediamine (**43**) (19.2 mg, 0.32 mmol) were employed to afford 23.7 mg (46%) of the indicated product **44h** as dark orange oil (R_f = 0.54 in 1:1 methanol/ethyl acetate). Other fraction containing **45h** was not isolated.

44h: ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 5.77 (s, 1H), 3.98 (t, *J* = 8.9 Hz, 2H), 3.74 (t, *J* = 7.5 Hz, 2H), 3.33 (t, *J* = 6.1 Hz, 2H), 2.66 (t, *J* = 6.0 Hz, 2H), 1.86 (p, *J* = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5 (CO), 158.3 (C=N), 156.6 (C), 143.2

(C), 134.3 (CH), 130.7 (CH), 130.1 (CH), 126.2 (CH), 122.7 (C-Br), 96.3 (CH), 52.6 (CH_2), 46.4 (CH_2), 26.8 (CH_2), 25.9 (CH_2), 18.6 (CH_2); IR (neat): 2929, 2875, 1648, 1630, 1526, 1469, 1396, 1357, 1303, 1263, 1206, 1180, 1041, 990, 882, 781, 718, 672, 578, 517, 439 cm^{-1}; MS (ESI, m/z): 319.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{16}BrN_2O$: 319.0441 $[M+H]^+$, found: 319.0439.

4.5.9 Synthesis of (*E*)-1-(4-Bromophenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44i)

General Procedure **5** was followed by using 1,9-bis(4-bromophenyl)nona-2,7-diyne-1,9-dione (**36i**) (102.7 mg, 0.22 mmol) and ethylenediamine (**43**) (26.4 mg, 0.44 mmol) were employed and this reaction formed two fractions. First fraction afforded 26.3 mg (60%) of the indicated product **45i** as dark orange oil (R_f = 0.64 in 4:1 hexane/ethyl acetate). Second fraction gave 20.2 mg (28%) of the indicated product **44i** as an orange solid (R_f = 0.56 in 1:1 methanol/ethyl acetate; mp 172.8-174.4 ^oC).

44i: ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.1 Hz, 2H), 7.55 (d, *J* = 7.1 Hz, 2H), 5.82 (s, 1H), 3.99 (t, *J* = 8.6 Hz, 2H), 3.76 (t, *J* = 9.1 Hz, 2H), 3.33 (t, *J* = 6.0 Hz, 2H), 2.69 (t, *J* = 5.6 Hz, 2H), 1.87 (p, *J* = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (CO), 158.9 (C=N), 155.9 (C), 139.8 (C), 131.7 (CH), 129.3 (CH), 126.4 (C-Br), 96.8 (CH), 52.1 (CH_2), 46.4 (CH_2), 26.7 (CH_2), 25.9 (CH_2), 18.5 (CH_2); IR (neat): 2937, 2874, 1744, 1661, 1616, 1582, 1535, 1400, 1355, 1259, 1214, 1180, 1069, 1044, 989, 862, 772, 676, 624, 571, 473, 458, 420 cm^{-1}; MS (ESI, m/z): 319.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{16}BrN_2O$: 319.0441 $[M+H]^+$, found: 319.0439.

45i: ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.2 Hz, 2H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.1 (CO), 131.9 (C), 129.9 (CH), 129.8 (CH), 128.9 (C-Br), 26.6 (CH_3). The spectral data are in agreement with those reported previously for this compound.[65-70]

4.5.10 Synthesis of (*E*)-1-(3-Chlorophenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44j)

General Procedure **5** was followed by using 1,9-bis(3-chlorophenyl)nona-2,7-diyne-1,9-dione (**36j**) (97.6 mg, 0.26 mmol) and ethylenediamine (**43**) (31.3 mg, 0.52 mmol) were employed and this reaction formed two fractions. First fraction afforded 6 mg (15%) of the indicated product **45j** as brownish orange oil (R_f = 0.64 in 4:1 hexane/ethyl acetate). Second fraction gave 20.6 mg (29%) of the indicated product **44j** as a brownish orange solid (R_f = 0.22 in 1:1 methanol/ethyl acetate; mp 92.1-93.5 ºC).

44j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 9.9 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 5.79 (s, 1H), 3.99 (t, *J* = 8.7 Hz, 2H), 3.75 (t, *J* = 7.2 Hz, 2H), 3.34 (t, *J* = 6.2 Hz, 2H), 2.67 (t, *J* = 6.2 Hz, 2H), 1.87 (p, *J* = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6 (CO), 158.5 (C=N), 156.5 (C), 142.9 (C), 134.6 (C-Cl), 131.4 (CH), 129.8 (CH), 127.8 (CH), 125.7 (CH), 96.4 (CH), 52.5 (CH_2), 46.4 (CH_2), 26.8 (CH_2), 25.9 (CH_2), 18.6 (CH_2); IR (neat): 3063, 2922, 2851, 1632, 1529, 1424, 1396, 1361, 1302, 1263, 1208, 1182, 1040, 991, 887, 787, 756, 730, 646, 582, 495, 414 cm^{-1}; MS (ESI, m/z): 275.09 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{16}ClN_2O$: 275.0946 $[M+H]^+$, found: 275.0941.

45j: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 2.60 (s, 3H). The spectral data are in agreement with those reported previously for this compound.[68-70]

4.5.11 Synthesis of (*E*)-1-(2-Bromophenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44k)

General Procedure **5** was followed by using 1,9-bis(2-bromophenyl)nona-2,7-diyne-1,9-dione (**36k**) (61 mg, 0.13 mmol) and ethylenediamine (**43**) (15.6 mg, 0.26 mmol) were employed to afford 23.4 mg (56%) of the indicated product **44k** as

orange oil (R_f = 0.26 in 1:1 methanol/ethyl acetate). Other fraction containing **45k** was not isolated.

44k: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.9 Hz, 1H), 7.25 (ddd, *J* = 29.4, 15.0, 7.0 Hz, 3H), 5.43 (s, 1H), 3.88 (t, *J* = 8.6, 2H), 3.63 – 3.56 (m, 2H), 3.29 (t, *J* = 6.2, 2H), 2.58 (t, *J* = 6.2 Hz, 2H), 1.83 (t, *J* = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.1 (CO), 157.9 (C=N), 155.7 (C), 144.9 (C), 133.4 (CH), 130.5 (CH), 128.8 (CH), 127.5 (CH), 119.0 (C-Br), 100.1 (CH), 52.8 (CH_2), 46.3 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 18.6 (CH_2); IR (neat): 2954, 2929, 2871, 1650, 1616, 1584, 1528, 1474, 1401, 1333, 1302, 1261, 1210, 1182, 1113, 1093, 1034, 986, 882, 748, 677, 583, 529, 444 cm^{-1}; MS (ESI, m/z): 319.04 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{16}BrN_2O$: 319.0441 $[M+H]^+$, found: 319.0438.

4.5.12 Synthesis of (*E*)-1-(4-(Dimethylamino)phenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44l)

General Procedure **5** was followed by using 1,9-bis(4-(dimethylamino)phenyl)nona-2,7-diyne-1,9-dione (**36l**) (100.5 mg, 0.26 mmol) and ethylenediamine (**43**) (31.3 mg, 0.52 mmol) were employed and this reaction formed two fractions. First fraction afforded 13.6 mg (32%) of the indicated product **45l** as a yellow solid (R_f = 0.38 in 4:1 hexane/ethyl acetate; mp 92.6–94.3 ºC). Second fraction gave 16.1 mg (22%) of the indicated product **44l** as a yellow solid (R_f = 0.17 in 1:1 methanol/ethyl acetate; mp 153.3-155.4 ºC).

44l: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.9 Hz, 2H), 6.66 (d, *J* = 8.9 Hz, 2H), 5.89 (s, 1H), 3.94 (t, *J* = 8.8 Hz, 2H), 3.72 (t, *J* = 10.45 Hz, 2H), 3.33 (t, *J* = 6.0 Hz, 2H), 3.04 (s, 6H), 2.63 (t, *J* = 6.2 Hz, 2H), 1.83 (p, *J* = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9 (CO), 159.1 (C=N), 153.6 (C-N(Me)$_2$), 152.8 (C), 129.7 (CH), 128.7 (C), 110.9 (CH), 97.1 (CH), 52.2 (CH_2), 46.3 (CH_2), 40.2 (N-CH_3), 26.6 (CH_2), 26.0 (CH_2), 18.8 (CH_2); IR (neat): 2946, 2830, 1736, 1646, 1584, 1559, 1524, 1475, 1399, 1372, 1269, 1245, 1166, 1041, 997, 942, 881, 843, 788, 750, 578, 540, 493,

458, 417 cm^{-1}; MS (ESI, m/z): 284.17 $[M+H]^+$; HRMS (ESI) calcd. for $C_{17}H_{22}N_3O$: 284.1757 $[M+H]^+$, found: 284.1755.

45l: ^1H NMR (400 MHz, $CDCI_3$) δ 7.87 (d, *J* = 9.1 Hz, 2H), 6.65 (d, *J* = 9.0 Hz, 2H), 3.05 (s, 6H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCI_3$) δ 196.5 (CO), 153.5 (C), 130.7 (CH), 125.5 (C), 110.8 (CH), 40.2 (NMe_2), 26.1 (CH_3). The spectral data are in agreement with those reported previously for this compound.[68]

4.5.13 Synthesis of (*E*)-1-(4-Heptylphenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44m)

General Procedure **5** was followed by using 1,9-bis(4-heptylphenyl)nona-2,7-diyne-1,9-dione (**36o**) (101.8 mg, 0.20 mmol) and ethylenediamine (**43**) (24 mg, 0.40 mmol) were employed and this reaction formed two fractions. First fraction afforded 19.3 mg (44%) of the indicated product **45m** as orange oil (R_f = 0.74 in 4:1 hexane/ethyl acetate). Second fraction gave to 11.2 mg (17%) of the indicated product **44m** as a light yellow solid (R_f = 0.65 in 1:1 methanol/ethyl acetate; mp 141.4-144.2 ºC).

44m: ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.1 Hz, 2H), 7.80 (d, *J* = 8.1 Hz, 2H), 6.14 (s, 1H), 4.19–4.06 (m, 1H), 4.12–3.95 (m, 1H), 3.32 (t, *J* = 6.1 Hz, 1H), 3.01 (t, *J* = 5.9 Hz, 1H), 2.69–2.61 (m, 2H), 1.91 (p, *J* = 6.0 Hz, 1H), 1.65–1.57 (m, 2H), 1.28 (dd, *J* = 12.7, 5.6 Hz, 13H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.6 (CO), 171.0 (C=N), 149.3 (C), 148.5 (C), 137.3 (C), 130.3 (CH), 128.6 (CH), 102.7 (CH), 46.7 (CH_2), 36.2 (CH_2), 36.1 (CH_2), 31.9 (CH_2), 31.32 (CH_2), 31.28 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 25.8 (CH_2), 24.5 (CH_2), 22.8 (CH_2), 17.5 (CH_2), 14.2 (CH_3); IR (neat): 2920, 2852, 1691, 1648, 1634, 1605, 1572, 1521, 1466, 1416, 1394, 1224, 1177, 1119, 1041, 947, 829, 748, 696, 622, 572, 522, 485 cm^{-1}; MS (ESI, m/z): 339.24 $[M+H]^+$; HRMS (ESI) calcd. for $C_{22}H_{31}N_2O$: 339.2431 $[M+H]^+$, found: 339.2422.

45m: ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 3.0 Hz, 2H), 2.63 (d, *J* = 7.9 Hz, 2H), 2.57 (s, 3H), 1.61 (p, *J* = 7.3 Hz, 2H), 1.31–1.24 (m,

8H), 0.86 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.0 (CO), 149.0 (C), 135.0 (C), 128.7 (CH), 128.6 (CH), 36.1 (CH_2), 31.9 (CH_2), 31.3 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.7 (CH_3), 22.8 (CH_2), 14.2 (CH_3). The spectral data are in agreement with those reported previously for this compound.[71]

4.5.14 Synthesis of (*E*)-4-(2-(2,3,7,8-Tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)acetyl)benzonitrile (44n)

General Procedure **5** was followed by using 4,4'-(nona-2,7-diynedioyl)dibenzonitrile (**36p**) (94 mg, 0.27 mmol) and ethylenediamine (**43**) (32.5 mg, 0.54 mmol) were employed and this reaction formed two fractions. First fraction afforded 11.9 mg (30%) of the indicated product **45n** as orange oil (R_f = 0.88 in 1:1 methanol/ethyl acetate). Second fraction gave 11.2 mg (16%) of the indicated product **44n** as orange oil (R_f = 0.65 in 1:1 methanol/ethyl acetate).

44n: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.9 Hz, 2H), 7.72 (d, J = 8.0 Hz, 2H), 5.77 (s, 1H), 3.99 (t, J = 8.6 Hz, 2H), 3.73 (t, J = 8.7 Hz, 2H), 3.35 (t, J = 6.1 Hz, 2H), 2.65 (s, 2H), 1.88 (p, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.9 (CO), 157.3 (C=N), 144.7 (C), 139.8 (C), 132.2 (CH), 127.8 (CH), 118.3 (C≡N), 114.4 (C), 95.7 (CH), 52.7 (CH_2), 46.1 (CH_2), 26.7 (CH_2), 25.7 (CH_2), 18.3 (CH_2); IR (neat): 2969, 2356, 2226, 1737, 1683, 1669, 1652, 1635, 1557, 1540, 1522, 1507, 1497, 1473, 1456, 1435, 1363, 1299, 1260, 1216, 1107, 1043, 988, 841, 781, 677, 539, 471, 457, 418 cm^{-1}; MS (ESI, m/z): 266.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{16}N_3O$: 266.1288 $[M+H]^+$, found: 266.1286.

45n: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7 (CO), 140.1 (C), 132.7 (CH), 128.8 (CH), 118.1 (CN), 116.6 (C-CN), 26.9 (CH_3). The spectral data are in agreement with those reported previously for this compound.[70]

4.5.15 Synthesis of (*E*)-1-(4-Fluorophenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44o)

General Procedure **5** was followed by using 1,9-bis(4-fluorophenyl)nona-2,7-diyne-1,9-dione (**36q**) (92 mg, 0.27 mmol) and ethylenediamine (**43**) (32.5 mg, 0.54 mmol) were employed to afford 38.4 mg (55%) of the indicated product **44o** as a yellow solid (R_f = 0.69 in 1:1 methanol/ethyl acetate; mp 155.2-156.6 ºC). Other fraction containing **45o** was not isolated.

44o: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.85 (m, 2H), 7.08 (t, *J* = 8.6 Hz, 2H), 5.79 (s, 1H), 3.96 (t, *J* = 8.8 Hz, 2H), 3.70 (t, *J* = 4.3 Hz, 2H), 3.32 (t, *J* = 6.1 Hz, 2H), 2.63 (t, *J* = 6.4 Hz, 2H), 1.84 (p, *J* = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6 (CO), 164.8 (d, ^1J = 251.8 Hz, CF), 158.2 (C=N), 156.0 (C), 137.4 (d, ^4J = 3.0 Hz, C), 130.0 (d, ^3J = 9.0 Hz, CH), 115.3 (d, ^4J = 21.6 Hz, CH), 96.2 (CH), 52.7 (CH_2), 46.3 (CH_2), 26.8 (CH_2), 26.0 (CH_2), 18.7 (CH_2); IR (neat): 2954, 2356, 2323, 1737, 1683, 1653, 1635, 1617, 1585, 1541, 1505, 1474, 1457, 1435, 1356, 1304, 1260, 1216, 1182, 1161, 1104, 1045, 988, 879, 856, 777, 669, 630, 602, 574, 508 cm^{-1}; MS (ESI, m/z): 259.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{16}FN_2O$: 259.1241 $[M+H]^+$, found: 259.1246.

4.5.16 Synthesis of (*E*)-1-(2-Fluorophenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44p)

General Procedure **5** was followed by using 1,9-bis(2-fluorophenyl)nona-2,7-diyne-1,9-dione (**36r**) (102 mg, 0.30 mmol) and ethylenediamine (**43**) (36.1 mg, 0.60 mmol) were employed to afford 37.2 mg (48%) of the indicated product **44p** as a brownish orange solid (R_f = 0.76 in 1:1 methanol/ethyl acetate; mp 130.9-132.1 ºC). Other fraction containing **45p** was not isolated.

44p: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75–7.68 (m, 1H), 7.42–7.36 (m, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.06 (dd, *J* = 10.8, 8.4 Hz, 1H), 5.76 (s, 1H), 3.92 (t, *J* = 8.8 Hz, 2H), 3.66 (t, *J* = 8.9 Hz, 2H), 3.32 (t, *J* = 6.1 Hz, 2H), 2.62 (t, *J* = 6.3 Hz, 2H), 1.85

(p, J = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6 (d, ^3J = 2.8 Hz, CO), 160.3 (d, ^1J = 250.3 Hz, CF), 157.9 (C=N), 155.7 (C), 132.4 (d, ^3J = 8.7 Hz, CH), 130.6 (d, ^3J = 2.8 Hz, CH), 130.0 (d, ^2J = 13.7 Hz, C), 124.3 (d, ^4J = 3.3 Hz, CH), 116.2 (d, ^2J = 23.8 Hz, CH), 100.6 (d, ^4J = 7.3 Hz, CH), 52.7 (CH_2), 46.2 (CH_2), 26.9 (CH_2), 25.9 (CH_2), 18.5 (CH_2); IR (neat): 2969, 2945, 2365, 1737, 1651, 1574, 1540, 1521, 1497, 1473, 1456, 1419, 1397, 1362, 1301, 1264, 1229, 1216, 1180, 1100, 1033, 989, 876, 777, 751, 685, 670, 624, 577, 518 cm^{-1}; MS (ESI, m/z): 259.12 $[M+H]^+$; HRMS (ESI) calcd. for $C_{15}H_{16}FN_2O$: 259.1241 $[M+H]^+$, found: 259.1246.

4.5.17 Synthesis of (*E*)-1-(2-Methoxyphenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44q)

General Procedure **5** was followed by using 1,9-bis(2-methoxyphenyl)nona-2,7-diyne-1,9-dione (**36s**) (66.4 mg, 0.18 mmol) and ethylenediamine (**43**) (21.6 mg, 0.36 mmol) were employed and this reaction formed two fractions. First fraction afforded 10 mg (37%) of the indicated product **45q** as orange oil (R_f = 0.57 in 4:1 hexane/ethyl acetate). Second fraction gave 20.8 mg (43%) of the indicated product **44q** as orange oil (R_f = 0.65 in 1:1 methanol/ethyl acetate).

44q: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 7.6, 1.7 Hz, 1H), 7.38 (td, J = 8.3, 7.8, 1.7 Hz, 1H), 7.00-6.92 (m, 2H), 5.85 (s, 1H), 3.94 (t, J = 9.1 Hz, 2H), 3.86 (s, 3H), 3.68 (t, J = 9.2 Hz, 2H), 3.33 (t, J = 6.1 Hz, 2H), 2.66 (t, J = 6.3 Hz, 2H), 1.85 (p, J = 6.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.2 (CO), 159.4 (C-OMe), 157.2 (C=N), 153.6 (C), 131.8 (CH), 130.0 (CH), 120.8 (CH), 120.7 (C), 111.7 (CH), 102.7 (CH), 55.8 (OMe), 51.8 (CH_2), 46.4 (CH_2), 26.7 (CH_2), 25.8 (CH_2), 18.5 (CH_2); IR (neat): 2942, 2877, 2495, 1649, 1593, 1524, 1480, 1434, 1396, 1357, 1278, 1239, 1181, 1114, 1038, 1018, 988, 879, 754, 674, 635, 581, 540, 508 cm^{-1}; MS (ESI, m/z): 271.14 $[M+H]^+$; HRMS (ESI) calcd. for $C_{16}H_{19}N_2O_2$: 271.1441 $[M+H]^+$, found: 271.1449.

45q: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.49–7.44 (m, 1H), 7.02–6.94 (m, 2H), 3.91 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1 (CO), 167.9 (C-OMe), 132.6 (CH), 131.0 (CH), 130.5 (C), 129.0 (CH), 124.1 (CH), 55.6 (OMe), 30.5 (CH_3). The spectral data are in agreement with those reported previously for this compound.[65,67,70]

4.6 General Procedure 6. Synthesis of (*E*)-1-Phenyl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone Derivatives 44 From Unsymmetrical Bis-α,β-alkynic Ketones 49

To a stirred solution of the proper unsymmetrical 1,9-diarylnona-2,7-diyne-1,9-dione **49** (0.25 mmol) in dioxane (5.0 mL) under argon was added ethylenediamine (**43**) (0.50 mmol), and the resulting mixture was refluxed until the end of the reaction (The progress of the reaction was monitored by routine TLC analysis for the disappearance of unsymmetrical bis-α,β-alkynic ketone **49** using 4:1 hexane/ethyl acetate as the eluent). After the reaction was over, the solvent was removed on a rotary evaporator, and the resulting crude product was purified by flash chromatography on silica gel using 4:1 hexane/ethyl acetate, followed by 1:1 methanol/ethyl acetate, as the eluent to afford 1-aryl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanones **44** and aryl methyl ketones **45**.

4.6.1 Synthesis of (*E*)-1-(4-Ethylphenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44e) from 49d

General Procedure **6** was followed by using 1-(4-ethylphenyl)-9-phenylnona-2,7-diyne-1,9-dione (**49d**) (55.8 mg, 0.17 mmol) and ethylenediamine (**43**) (20 mg, 0.34 mmol) were employed and this reaction formed 8 mg (18%) of the indicated product **44e** as light yellow solid (R_f = 0.53 in 1:1 methanol/ethyl acetate; mp 131.7-134.4 ^{o}C). Other fraction containing **45a** was not isolated.

4.6.2 Synthesis of (*E*)-1-(4-(Dimethylamino)phenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44l) from 49e

General Procedure **6** was followed by using 1-(4-(dimethylamino)phenyl)-9-phenylnona-2,7-diyne-1,9-dione (**49e**) (85.2 mg, 0.25 mmol) and ethylenediamine (**43**) (30.1 mg, 0.50 mmol) were employed and this reaction formed two fractions. First fraction afforded 17.8 mg of a mixture of the indicated products **45a** (7.6 mg, 25%) and **45l** (10.3 mg, 25%) in a 1.0:1.0 molar ratio, respectively, determined from the ^{1}H NMR integral data. Second fraction gave 20.3 mg (29%) of the indicated product **44l** as a yellow solid (R_f = 0.17 in 1:1 methanol/ethyl acetate; mp 153.3-155.4 ^{o}C).

45a + 45l: ^{1}H NMR (400 MHz, $CDCI_3$) δ 7.98–7.95 (m, 2H), 7.86 (d, *J* = 5.2 Hz, 2H), 7.58–7.54 (m, 1H), 7.49–7.46 (m, 2H), 6.66 (d, *J* = 5.1 Hz, 2H), 3.05 (s, 6H), 2.61 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCI_3$) δ 198.3 (CO), 196.6 (CO), 153.5 (C), 137.2 (C), 133.2 (CH), 130.7 (CH), 128.7 (CH), 128.4 (CH), 125.5 (C), 110.7 (CH), 40.2 (NMe_2), 26.7 (CH_3), 26.1 (CH_3). The spectral data are in agreement with those reported previously for these compounds.[65,68]

4.6.3 Synthesis of (*E*)-1-Phenyl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44a) and (*E*)-1-(4-Bromophenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44i) from 49f

General Procedure **6** was followed by using 1-(4-bromophenyl)-9-phenylnona-2,7-diyne-1,9-dione (**49f**) (233.6 mg, 0.62 mmol) and ethylenediamine (**43**) (74.5 mg, 1.24 mmol) were employed and this reaction formed two fractions. First fraction afforded 67.2 mg of a mixture of the indicated products **45a** (3.8 mg, 5%) and **45i** (63.4 mg, 52%) in a 1.0:10.0 molar ratio, respectively, determined from the ^{1}H NMR integral data. Second fraction gave 65.9 mg of a mixture of the indicated products **44a** (37.2 mg, 25%) and **44i** (28.7 mg, 15%) in a 1.72:1.0 molar ratio, respectively, determined from the ^{1}H NMR integral data.

45a + 45i: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 0.21H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 4.1 Hz, 0.25H), 7.49–7.42 (m, 0.48H), 2.61 (s, 0.3H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4 (CO), 197.2 (CO), 137.8 (C), 135.9 (C), 133.3 (CH), 132.0 (CH), 130.0 (CH), 128.5 (CH), 127.2 (C-Br), 26.8 (CH_3), 26.7 (CH_3). (Note that two CH peaks overlap on each other). The spectral data are in agreement with those reported previously for this compound.[65-70]

4.6.4 Synthesis of (*E*)-1-Phenyl-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44a) and (*E*)-1-(4-Nitrophenyl)-2-(2,3,7,8-tetrahydroimidazo[1,2-*a*]pyridin-5(6*H*)-ylidene)ethanone (44r) from 49g

General Procedure **6** was followed by using 1-(4-nitrophenyl)-9-phenylnona-2,7-diyne-1,9-dione (**49g**) (60.8 mg, 0.176 mmol) and ethylenediamine (**43**) (21 mg, 0.35 mmol) were employed and this reaction formed two fractions. First fraction afforded 14.4 mg (50%) of the indicated products **45r** as brownish orange oil (R_f = 0.31 in 4:1 hexane/ethyl acetate). Second fraction gave 25.8 mg of a mixture of the indicated products **44a** (22.1 mg, 52%) and **44r** (3.7 mg, 7%) in a 7.0:1.0 molar ratio, respectively, determined from the ^{1}H NMR integral data. Other fraction containing **45a** was not isolated.

45r: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.8 Hz, 2H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5 (CO), 150.5 (C), 141.5 (C), 129.5 (CH), 124.0 (CH), 27.2 (CH3). The spectral data are in agreement with those reported previously for this compound.[67,69,70]

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APPENDIX A

NMR SPECTRA

Bruker Spectrospin Avance DPX400 Ultrashield spectromer was used in getting ^{1}H, ^{13}C, NOESY (nuclear overhauser effect spectroscopy), DEPT-90, DEPT-135, COSY, HSQC and HMBC NMR spectra.

NMR spectra for all compounds are demonstrated below.

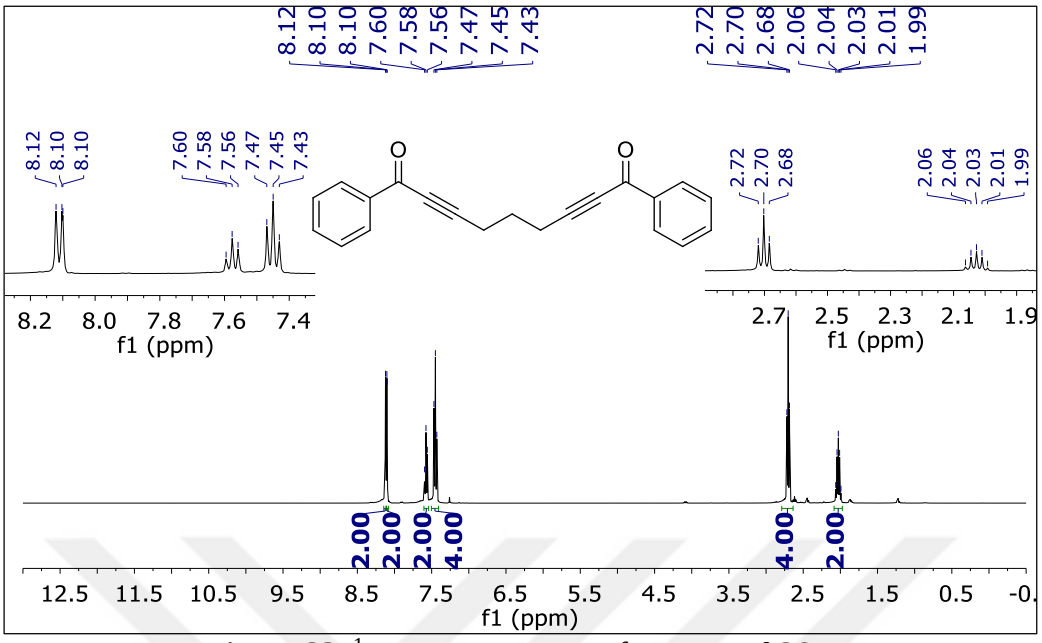


Figure 23. ^{1}H NMR spectrum of compound **36a**.

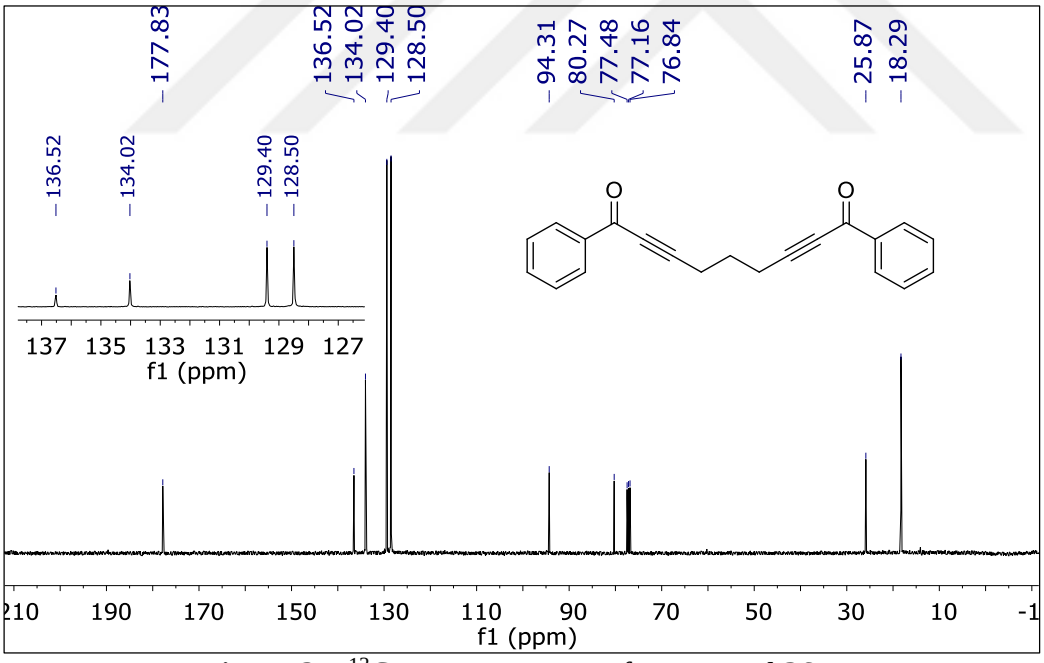


Figure 24. ^{13}C NMR spectrum of compound **36a**.

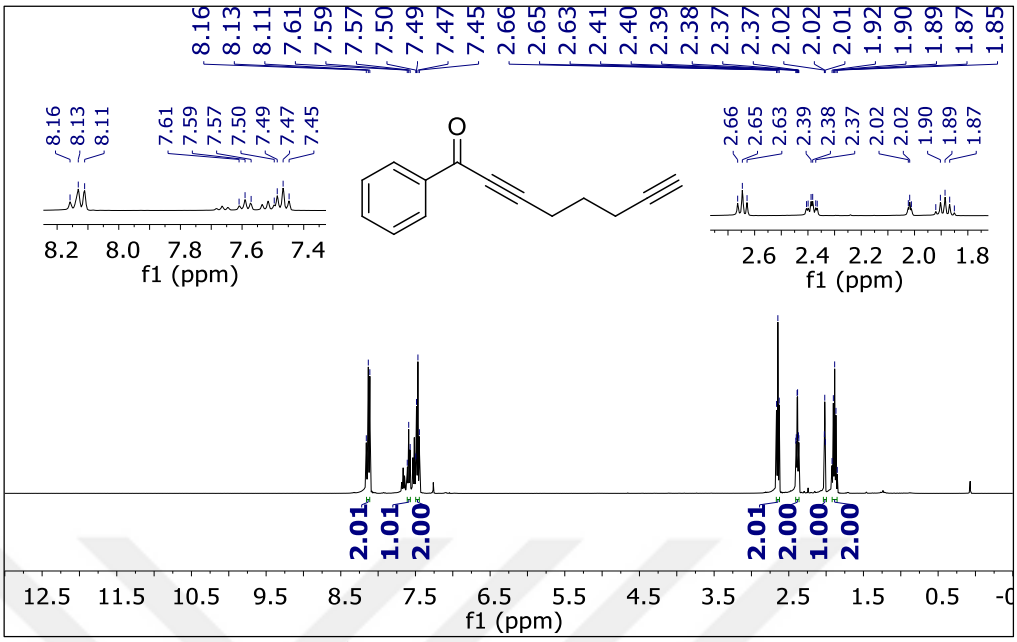


Figure 25. ^{1}H NMR spectrum of compound **48a**.

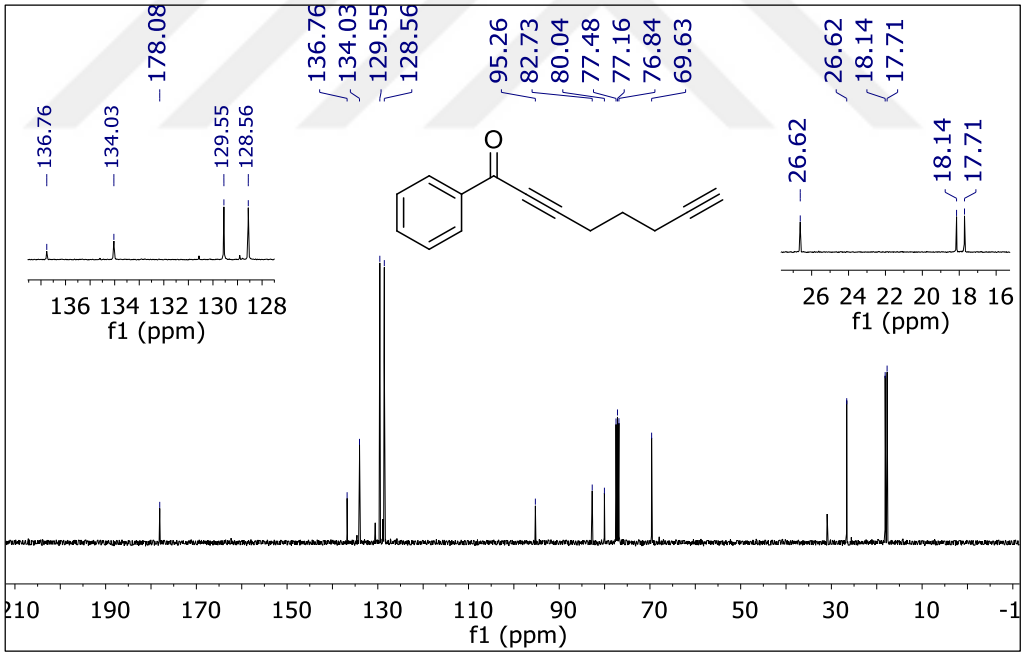


Figure 26. ^{13}C NMR spectrum of compound **48a**.

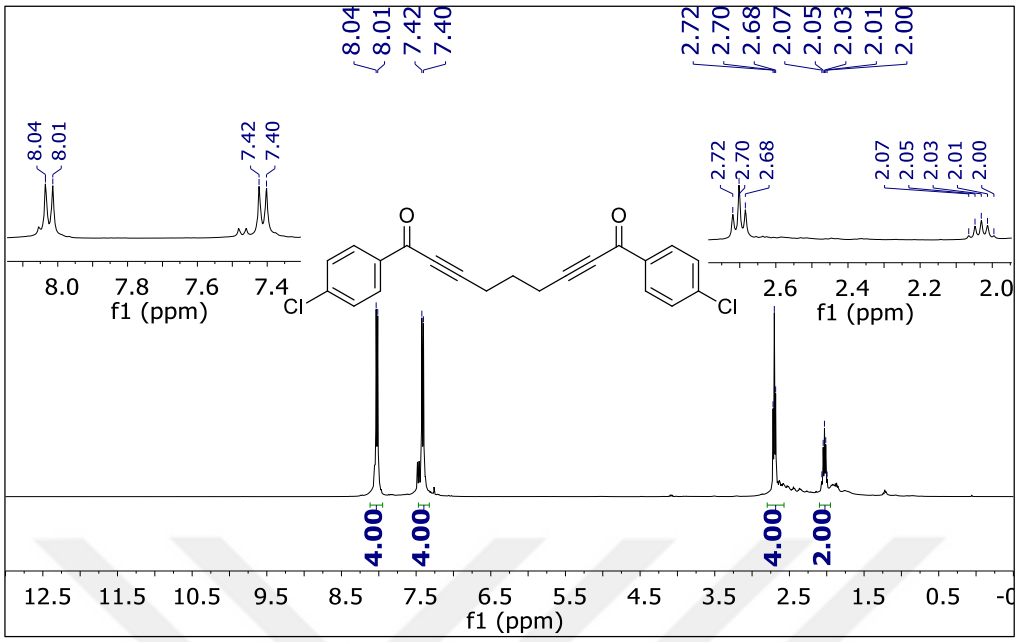


Figure 27. ^{1}H NMR spectrum of compound **36b**.

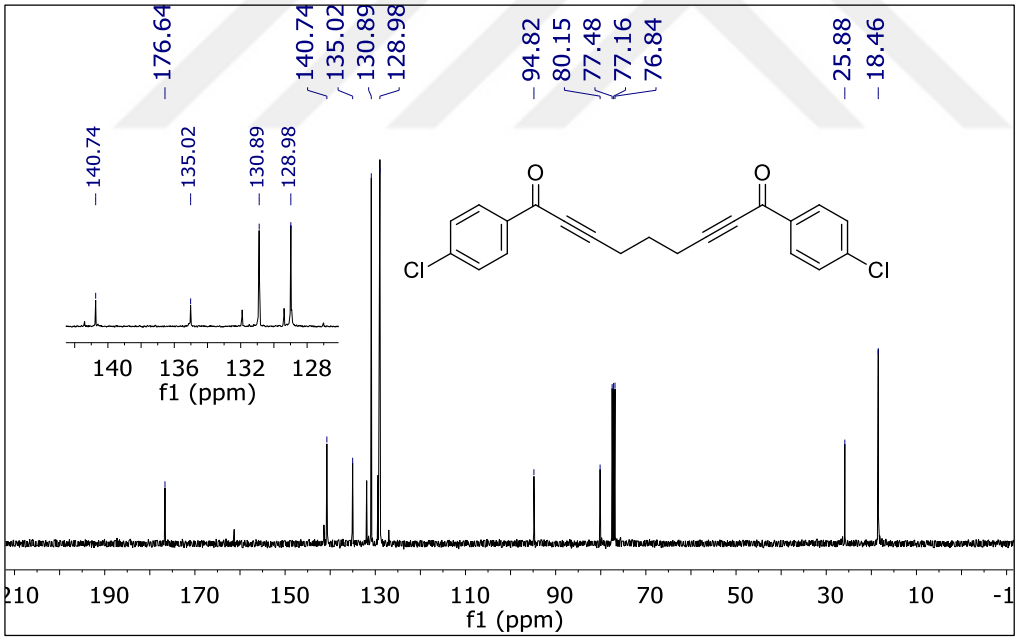


Figure 28. ^{13}C NMR spectrum of compound **36b**.

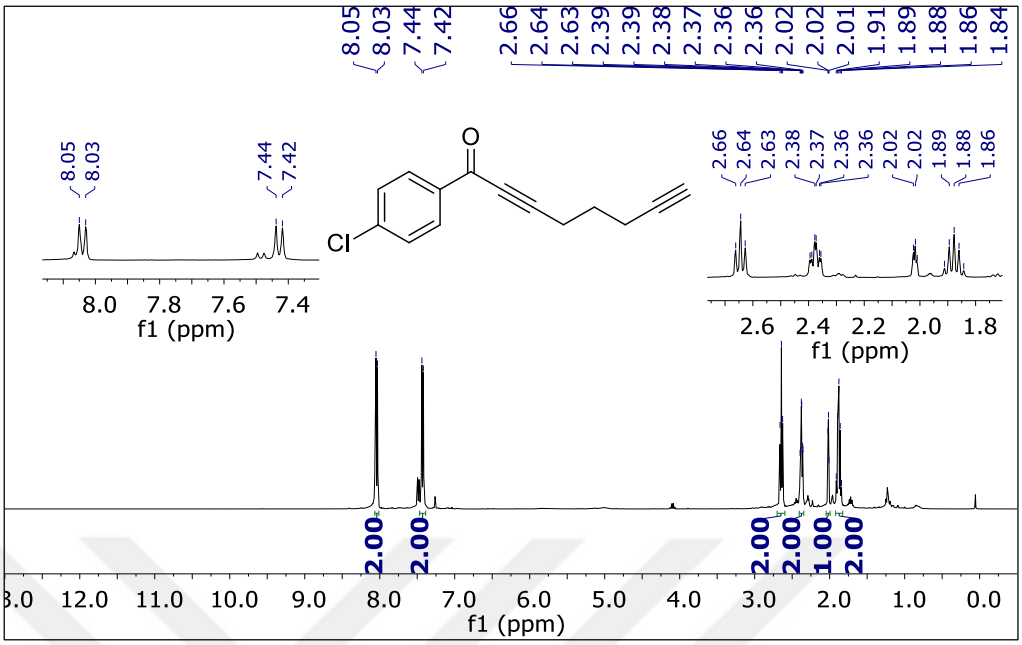


Figure 29. ^{1}H NMR spectrum of compound **48b**.

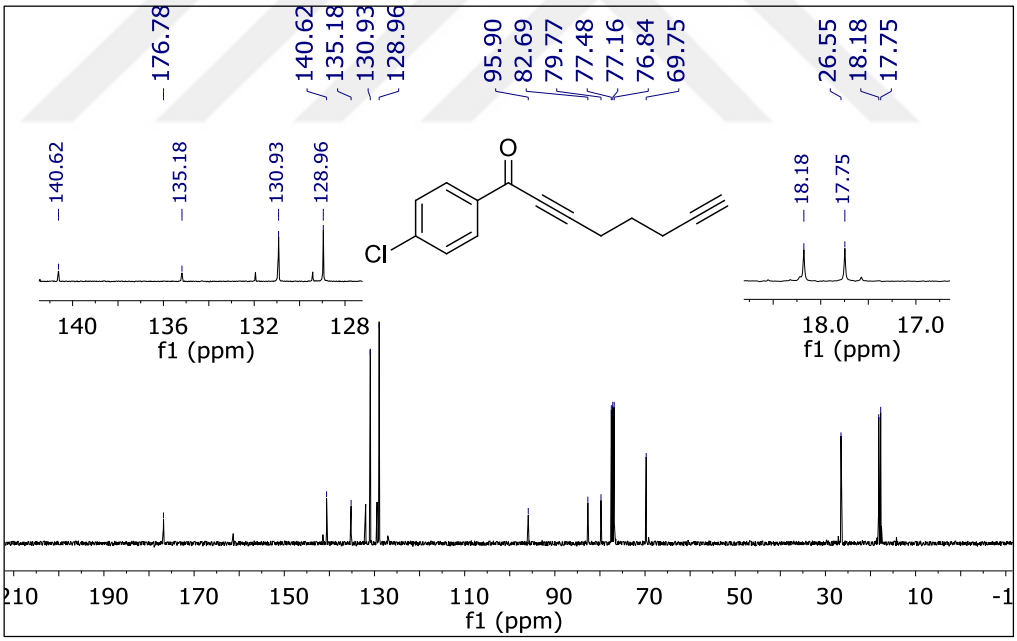


Figure 30. ^{13}C NMR spectrum of compound **48b**.

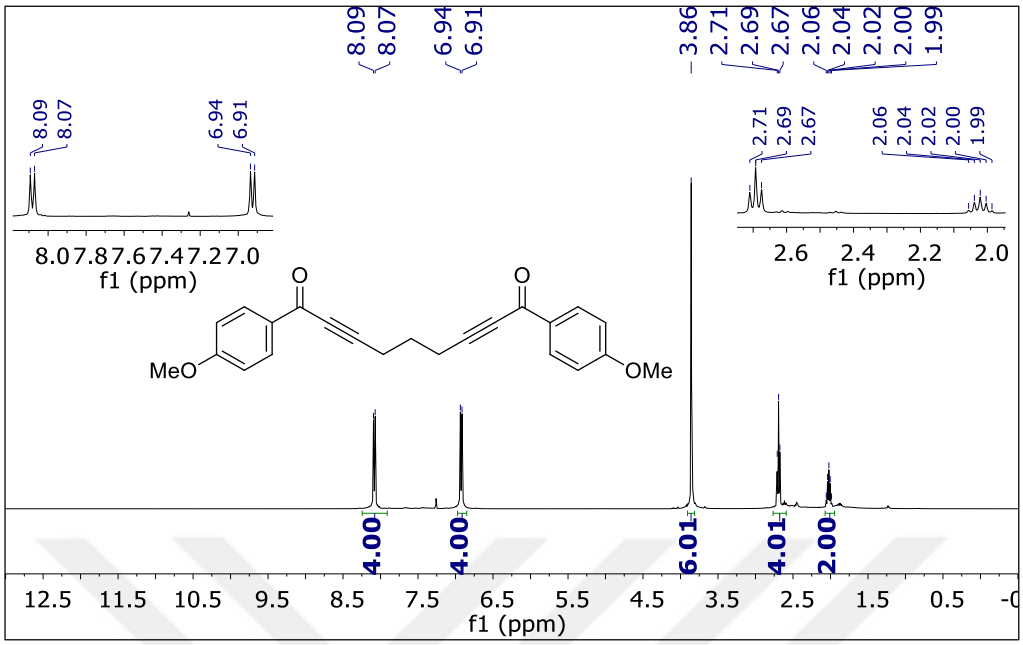


Figure 31. ^{1}H NMR spectrum of compound **36c**.

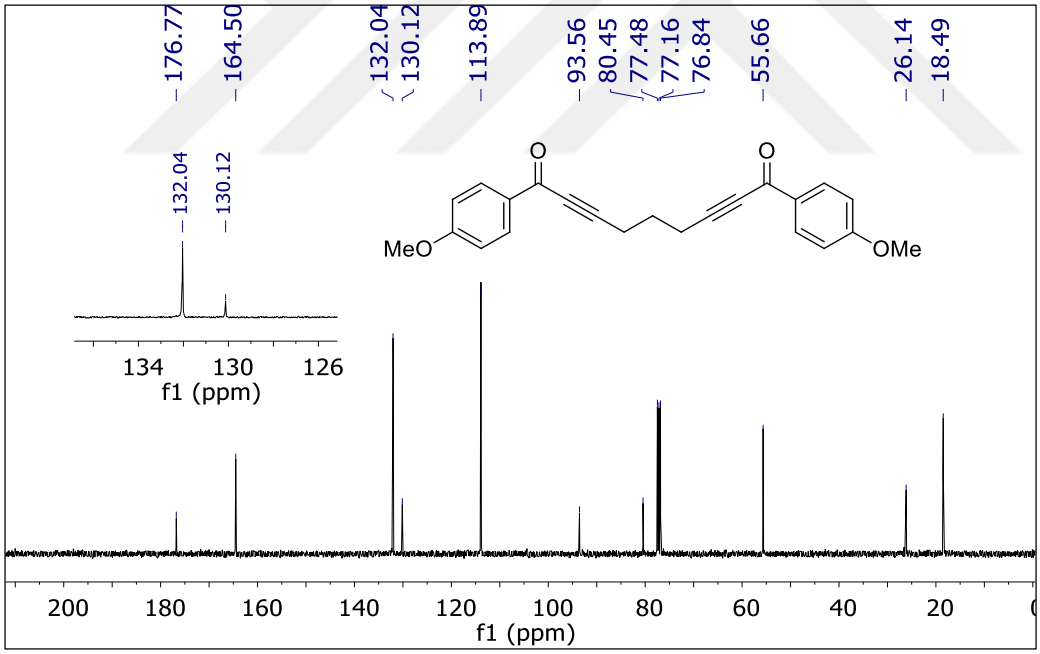


Figure 32. ^{13}C NMR spectrum of compound **36c**.

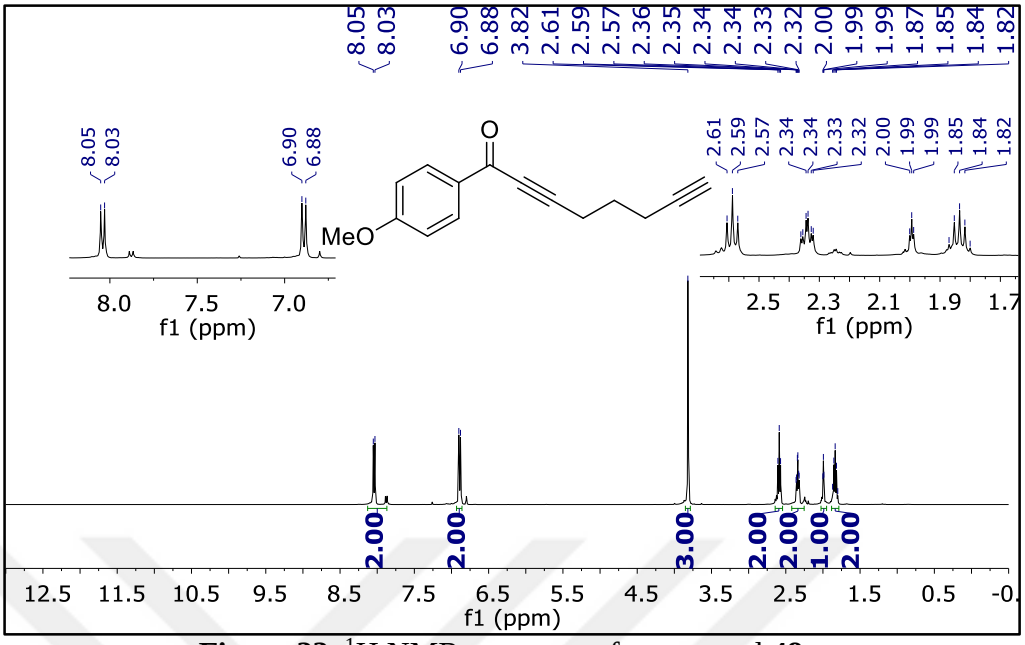


Figure 33. ^{1}H NMR spectrum of compound **48c**.

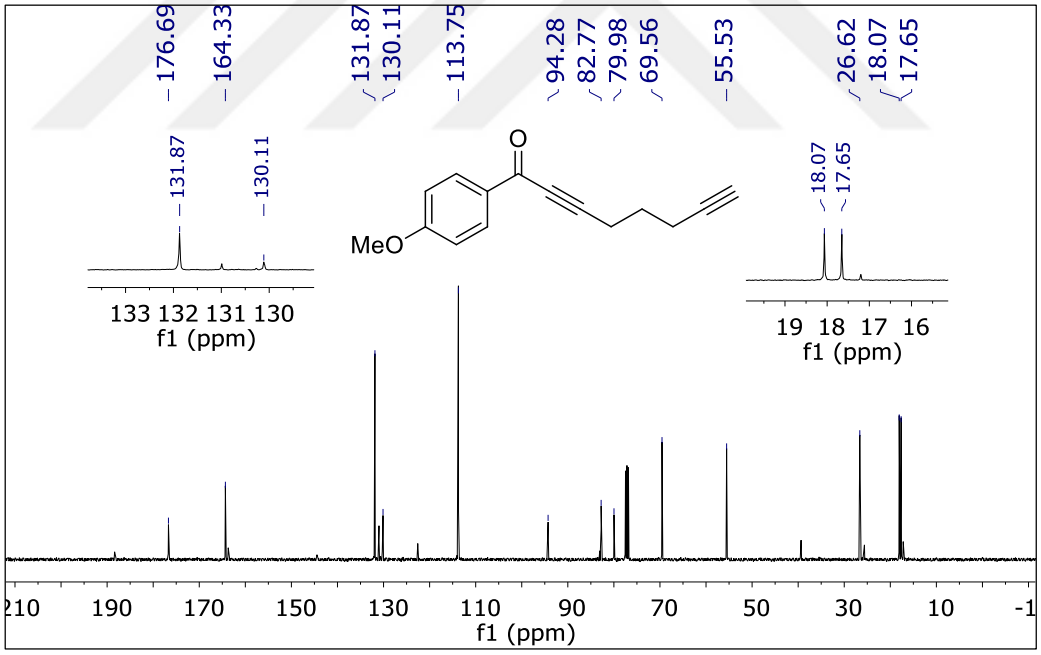


Figure 34. ^{13}C NMR spectrum of compound **48c**.

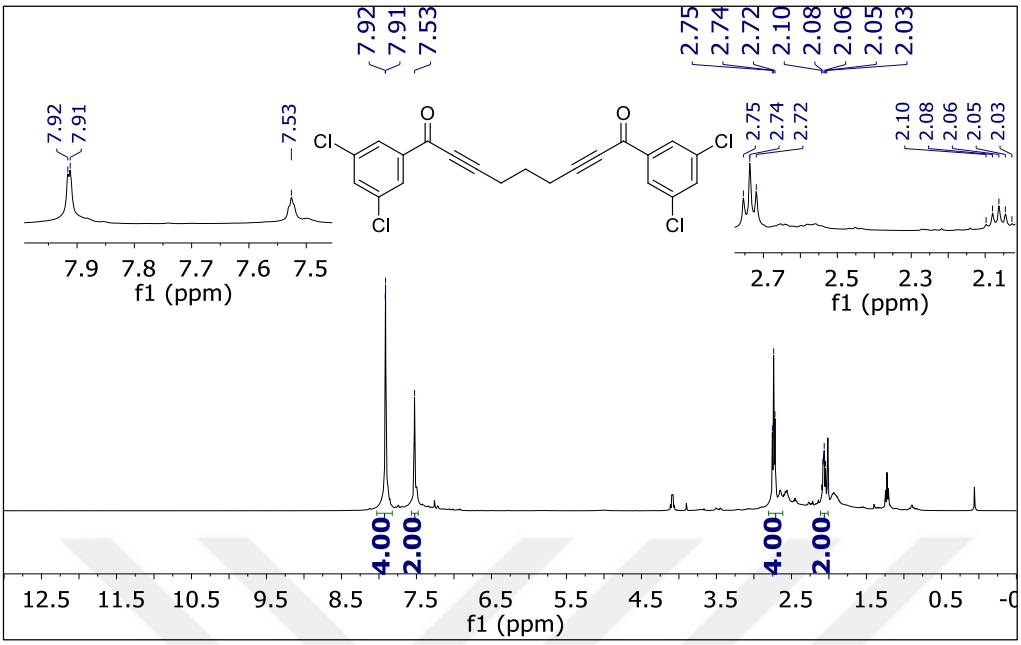


Figure 35. ^{1}H NMR spectrum of compound **36d**.

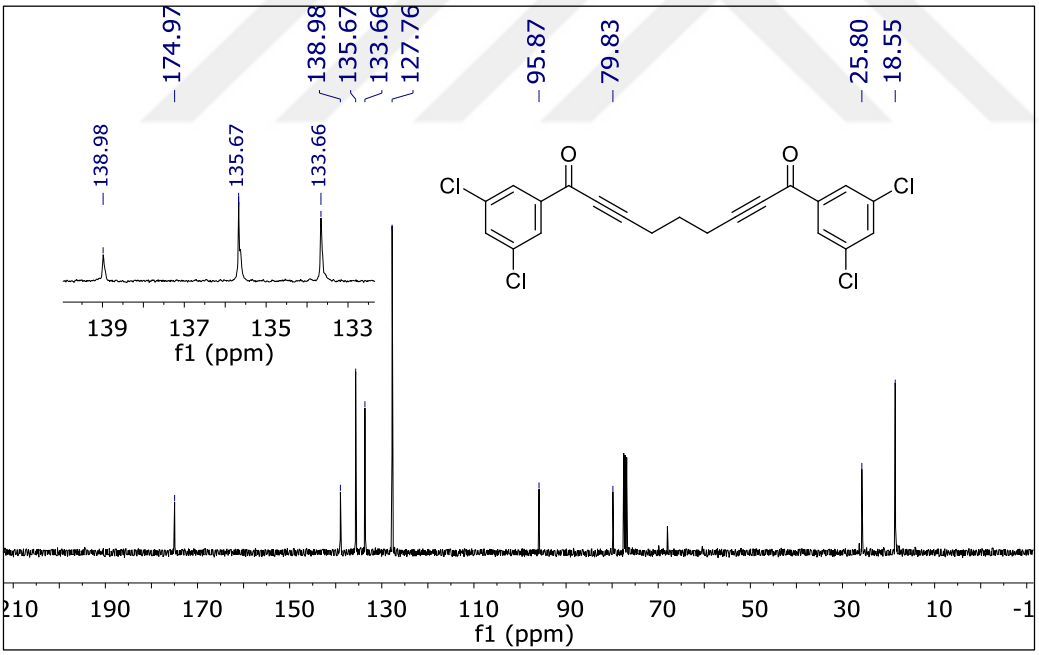


Figure 36. ^{13}C NMR spectrum of compound **36d**.

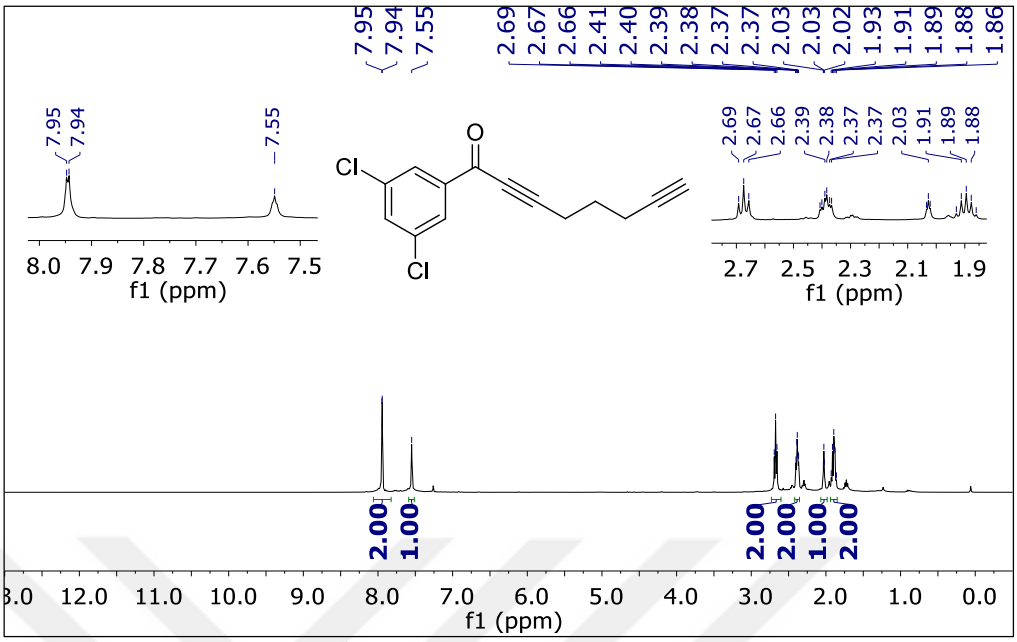


Figure 37. ^{1}H NMR spectrum of compound **48d**.

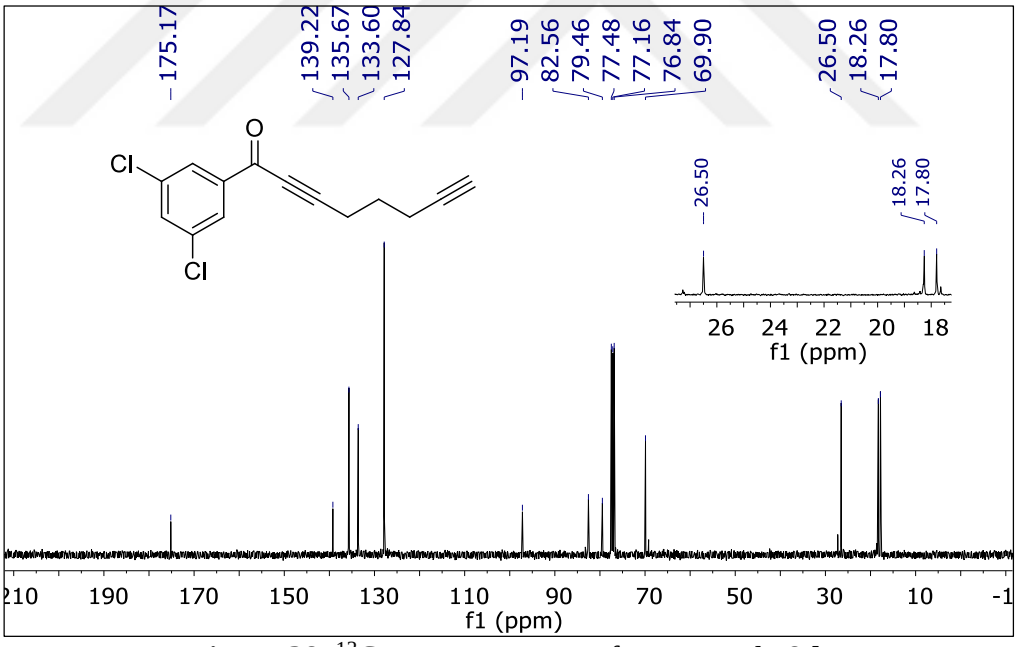


Figure 38. ^{13}C NMR spectrum of compound **48d**.

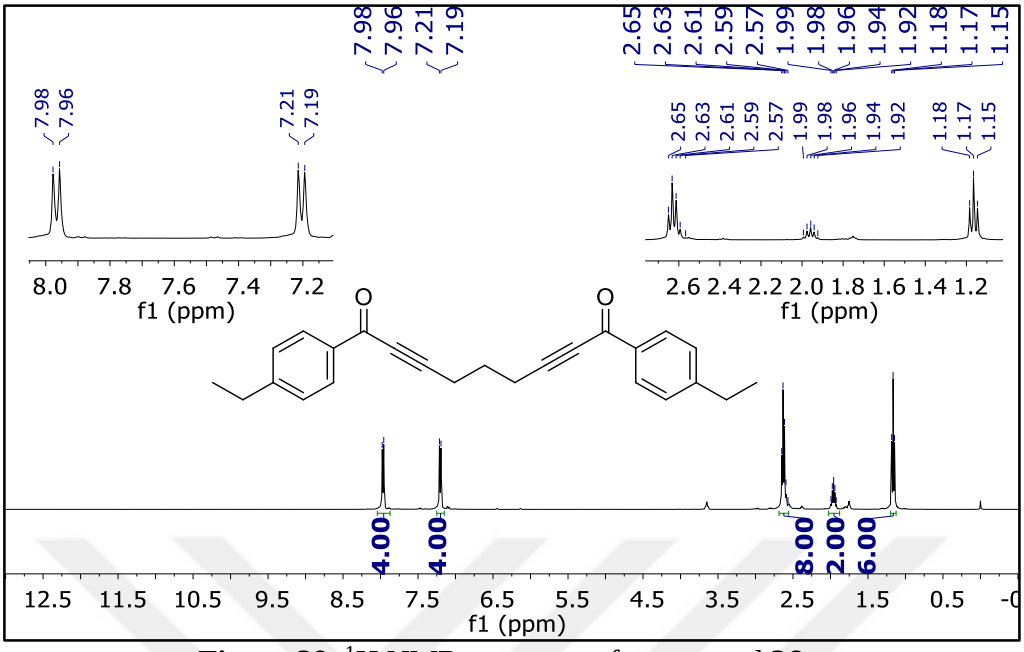


Figure 39. ^{1}H NMR spectrum of compound **36e**.

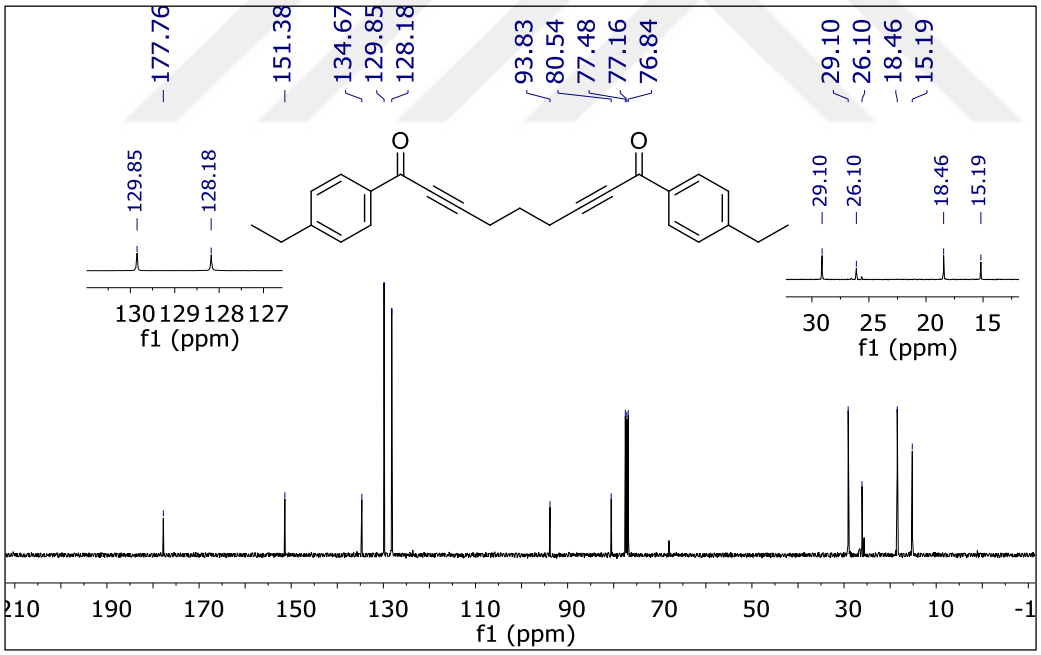


Figure 40. ^{13}C NMR spectrum of compound **36e**.

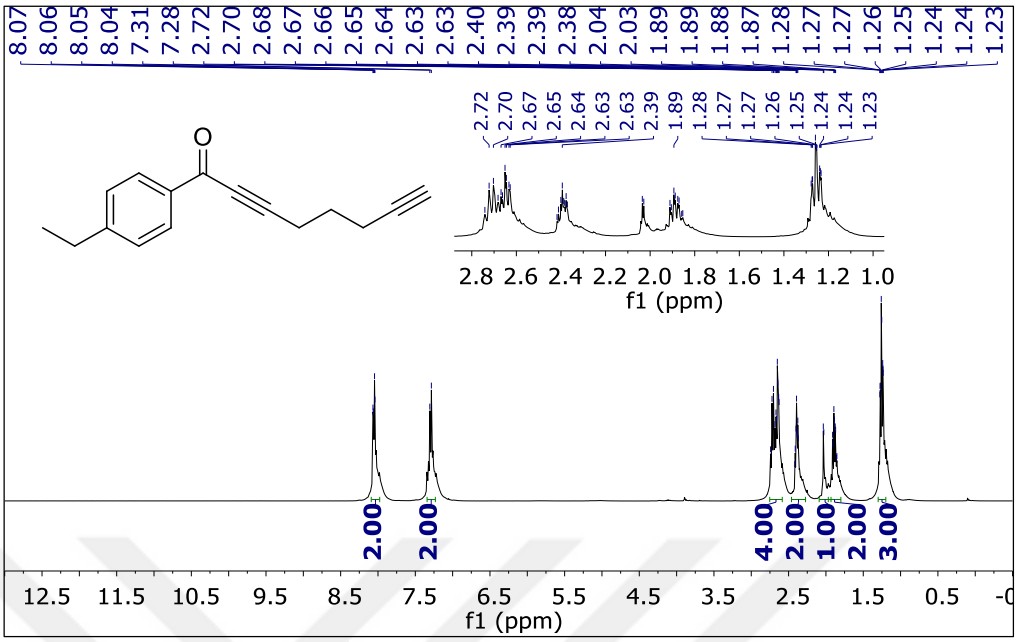


Figure 41. ^{1}H NMR spectrum of compound **48e**.

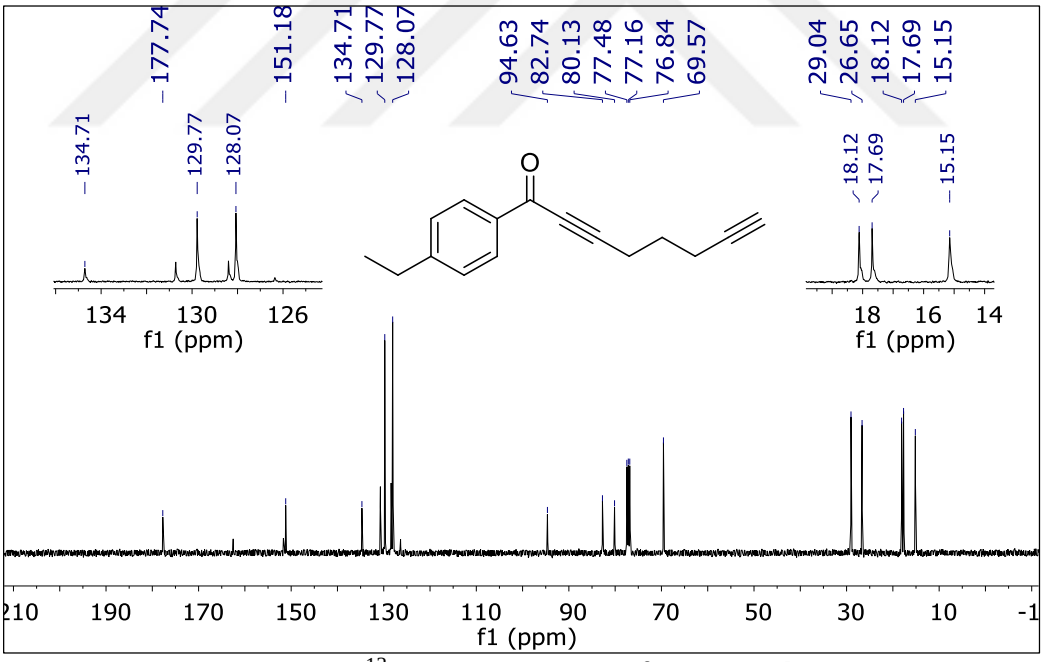


Figure 42. ^{13}C NMR spectrum of compound **48e**.

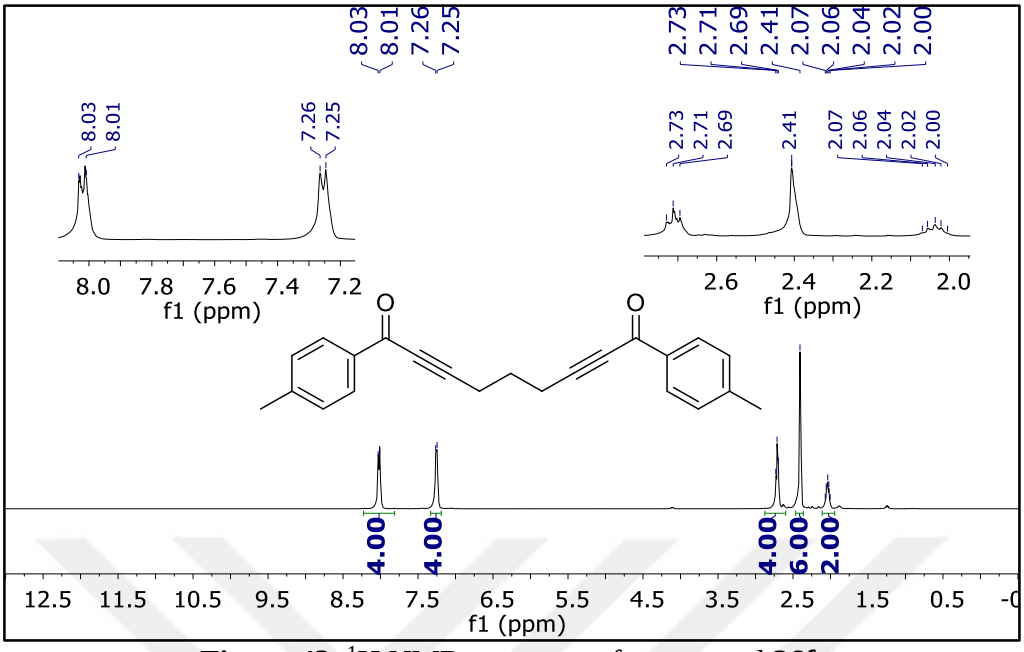


Figure 43. ^{1}H NMR spectrum of compound **36f**.

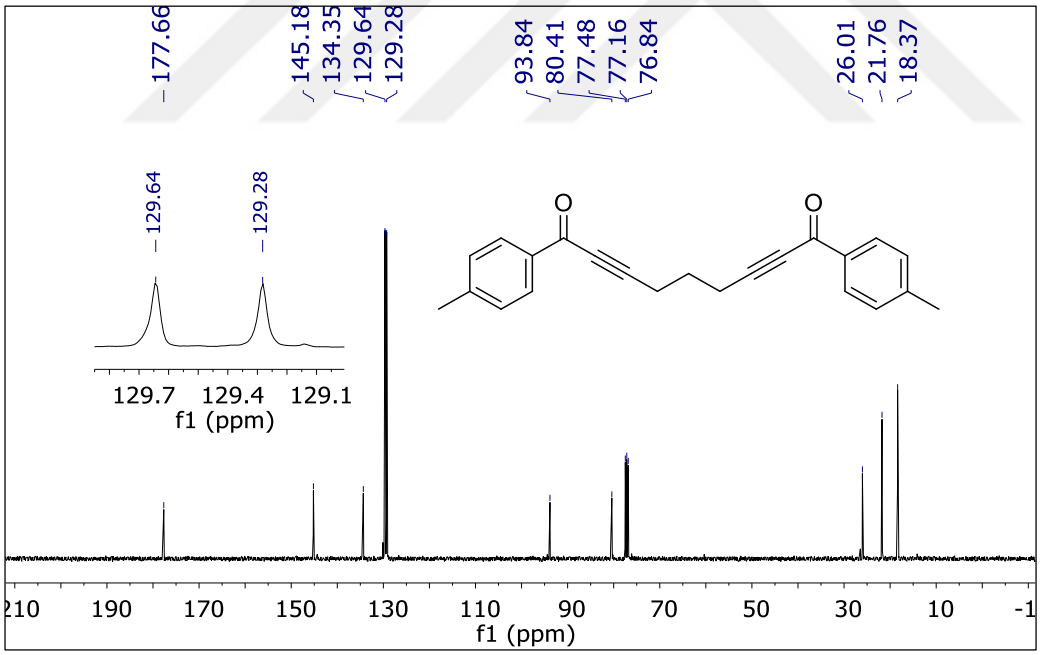


Figure 44. ^{13}C NMR spectrum of compound **36f**.

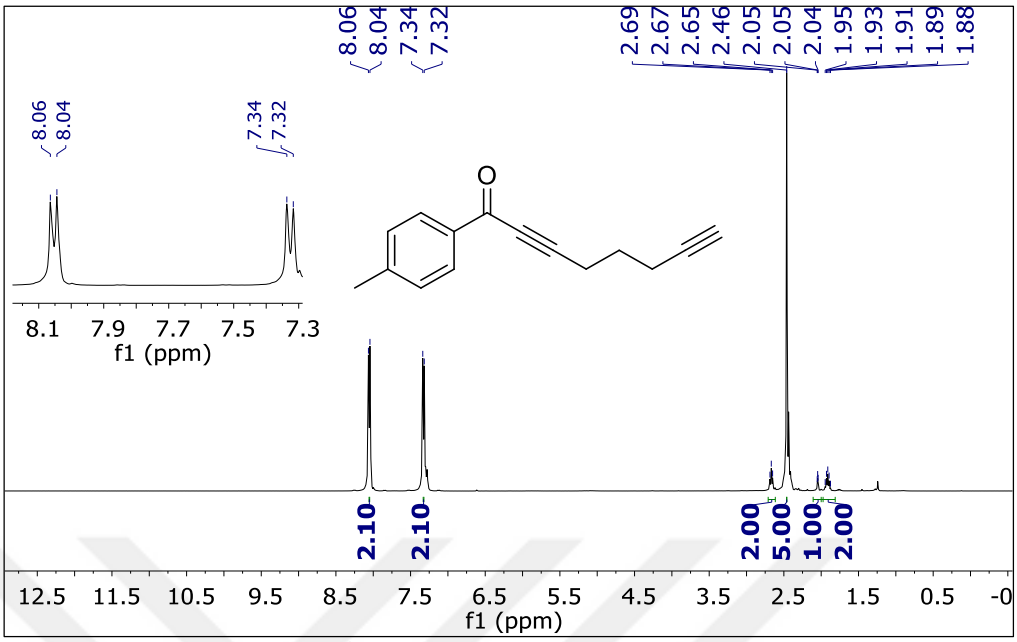


Figure 45. ^{1}H NMR spectrum of compound **48f**.

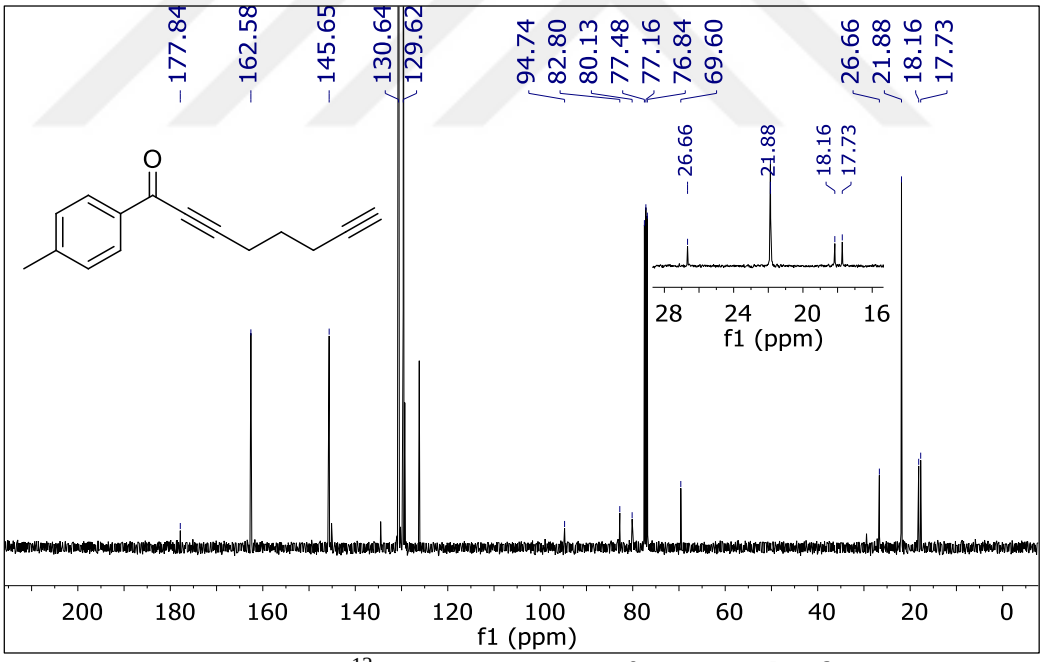


Figure 46. ^{13}C NMR spectrum of compound **48f**.

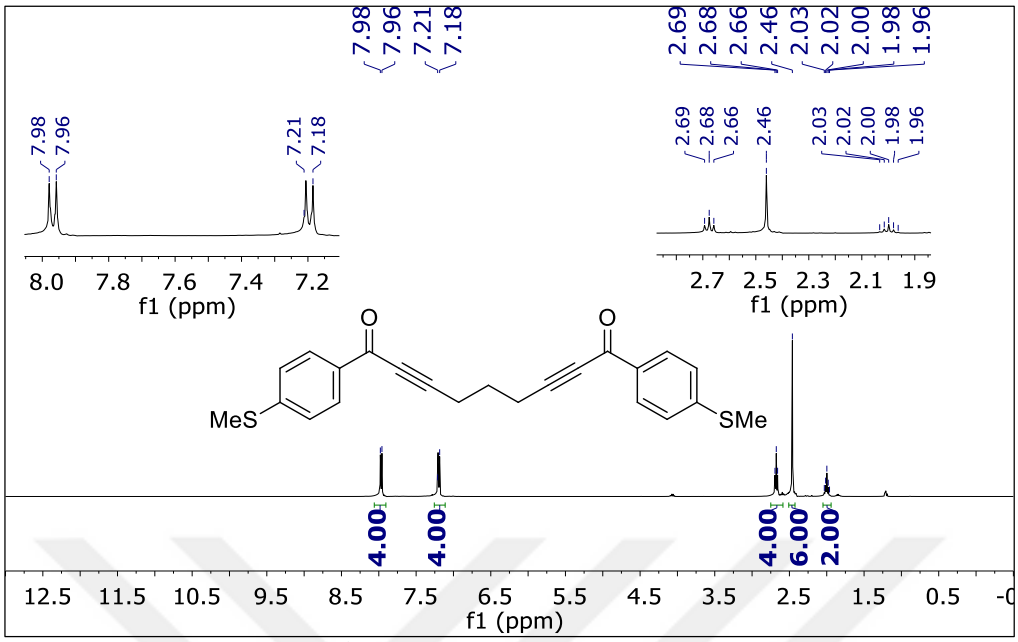


Figure 47. ^{1}H NMR spectrum of compound **36g**.

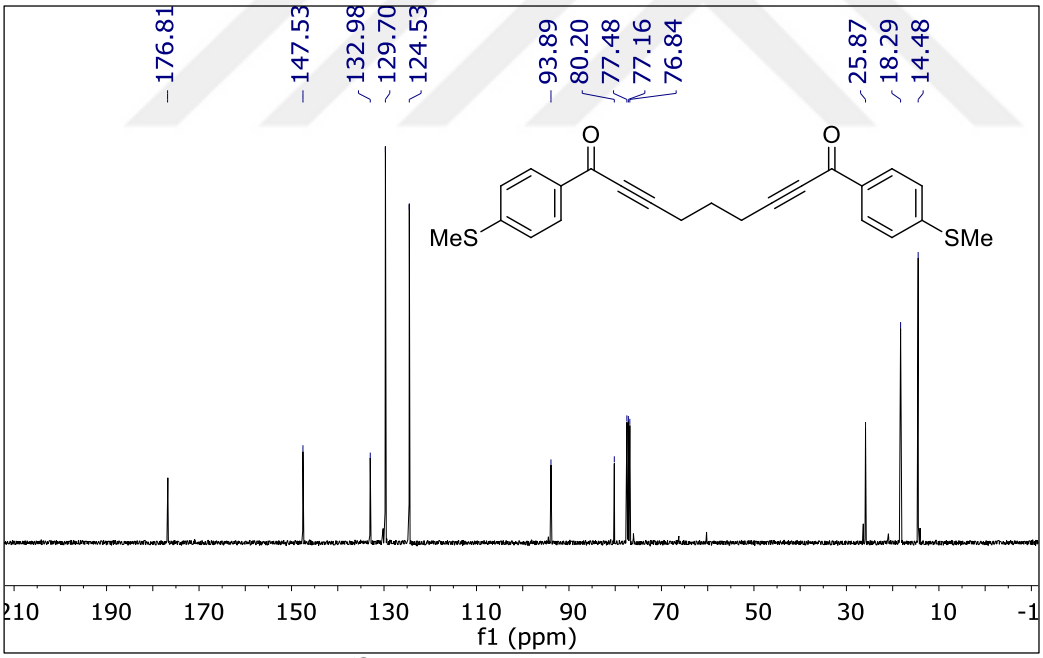


Figure 48. ^{13}C NMR spectrum of compound **36g**.

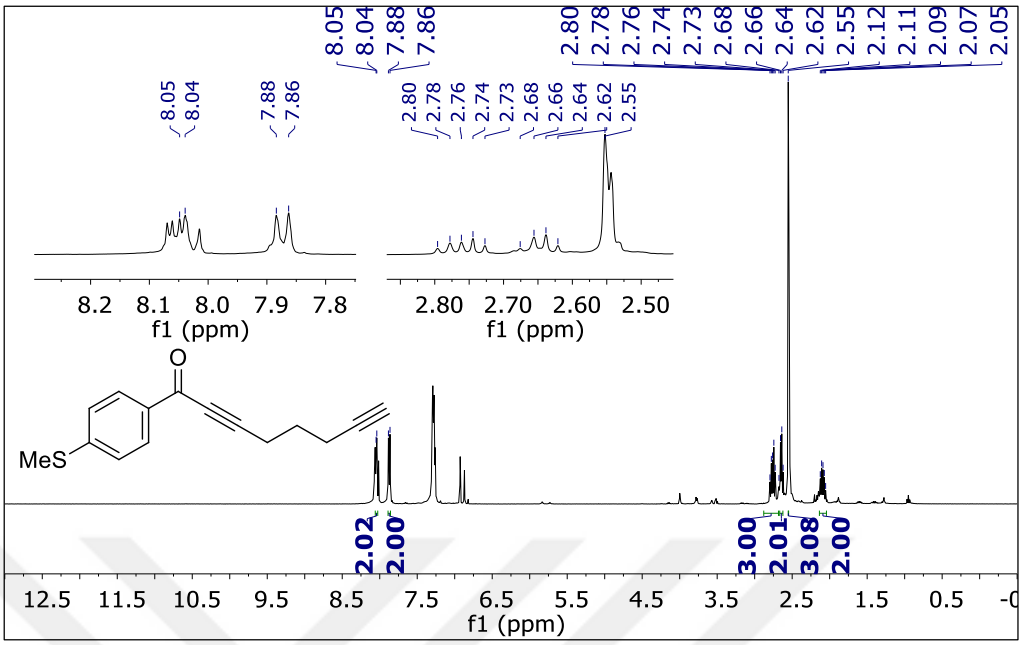


Figure 49. ^{1}H NMR spectrum of compound **48g**.

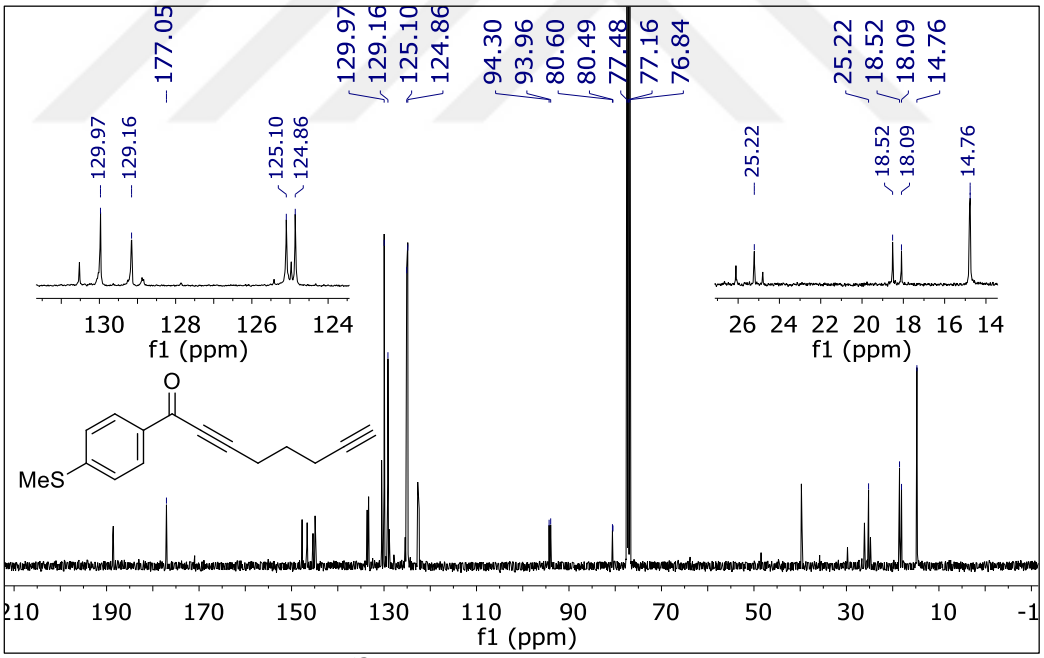


Figure 50. ^{13}C NMR spectrum of compound **48g**.

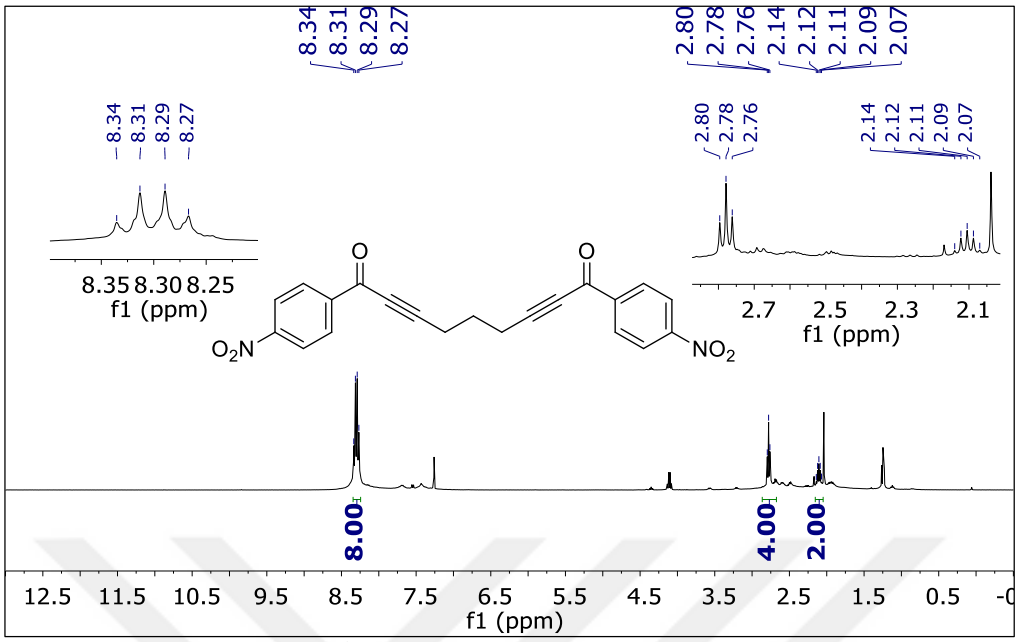


Figure 51. ^{1}H NMR spectrum of compound **36h**.

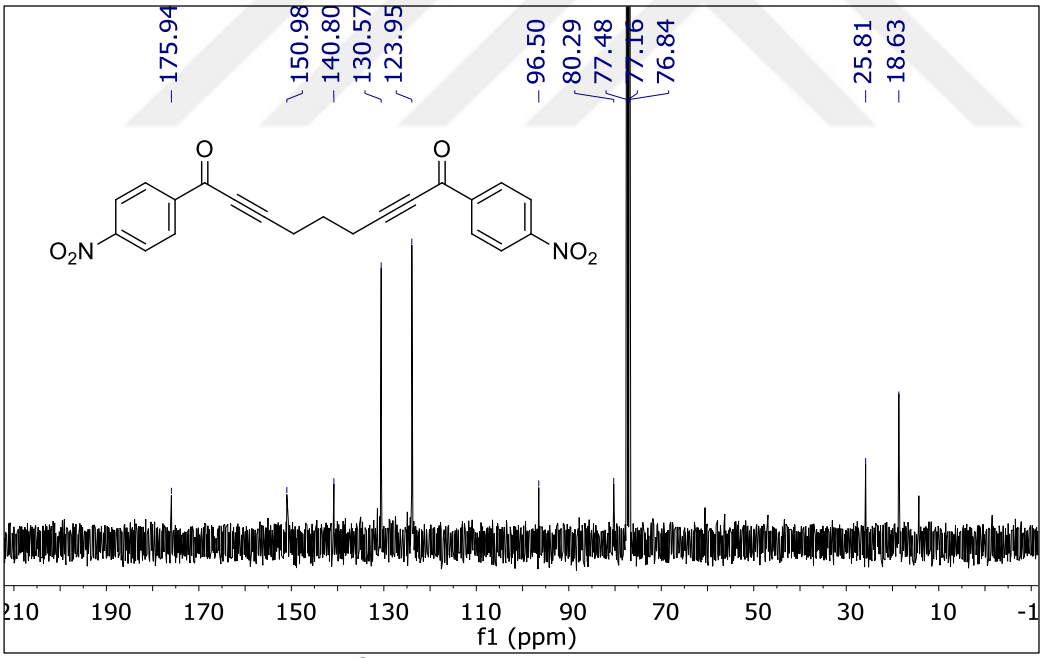


Figure 52. ^{13}C NMR spectrum of compound **36h**.

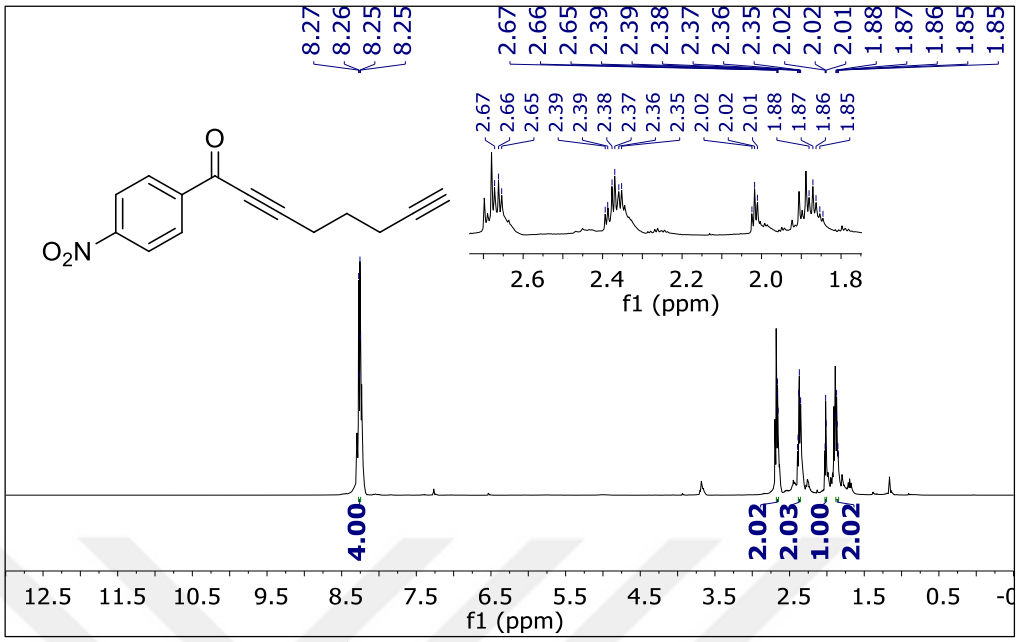


Figure 53. ^{1}H NMR spectrum of compound **48h**.

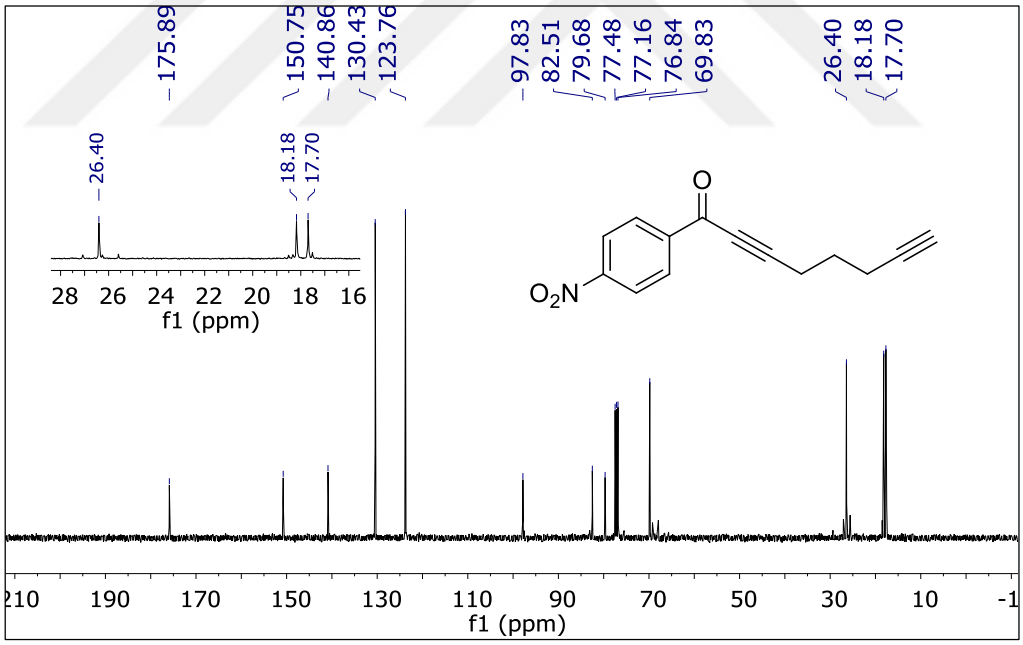


Figure 54. ^{13}C NMR spectrum of compound **48h**.

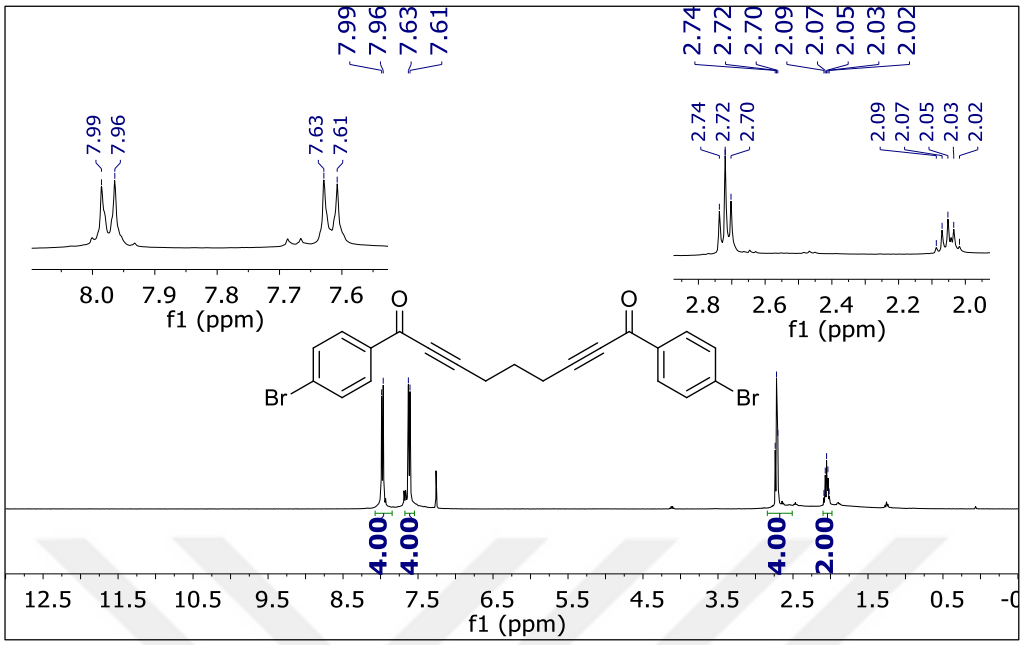


Figure 55. ^{1}H NMR spectrum of compound **36i**.

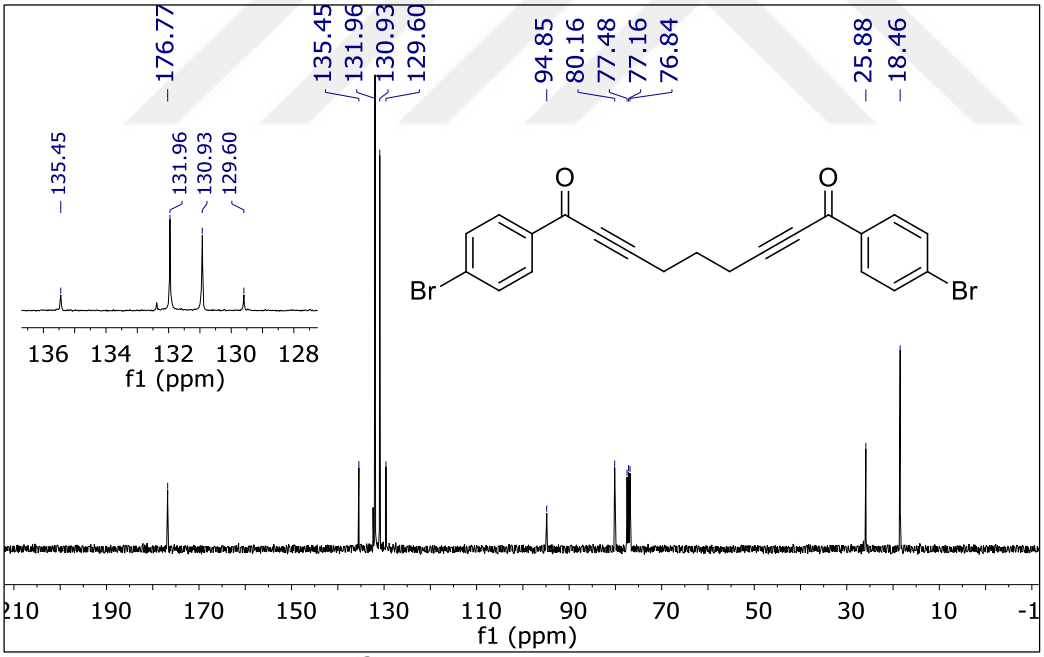


Figure 56. ^{13}C NMR spectrum of compound **36i**.

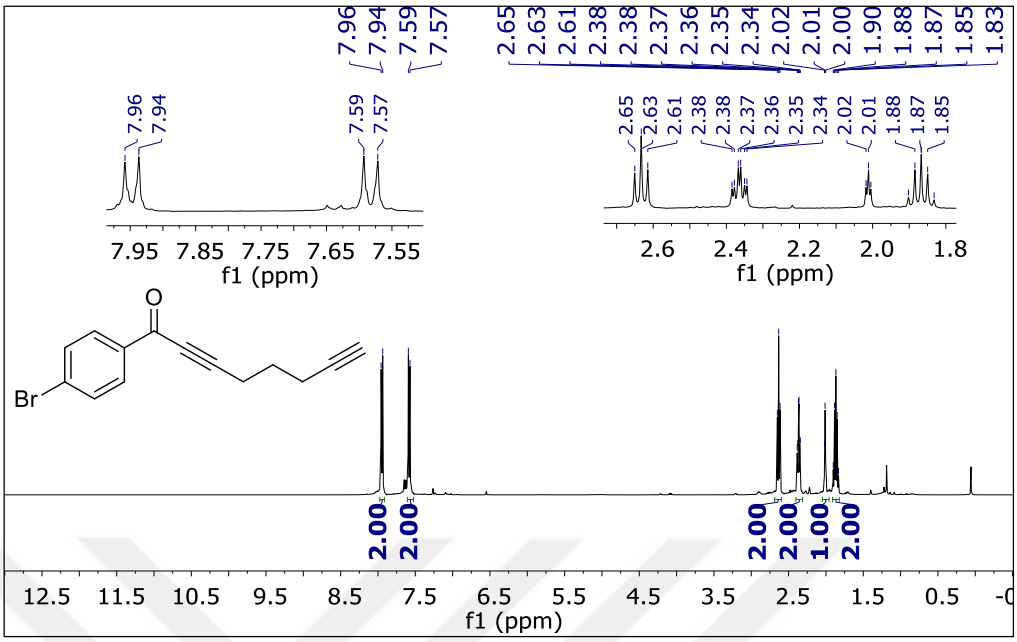


Figure 57. ^{1}H NMR spectrum of compound **48i**.

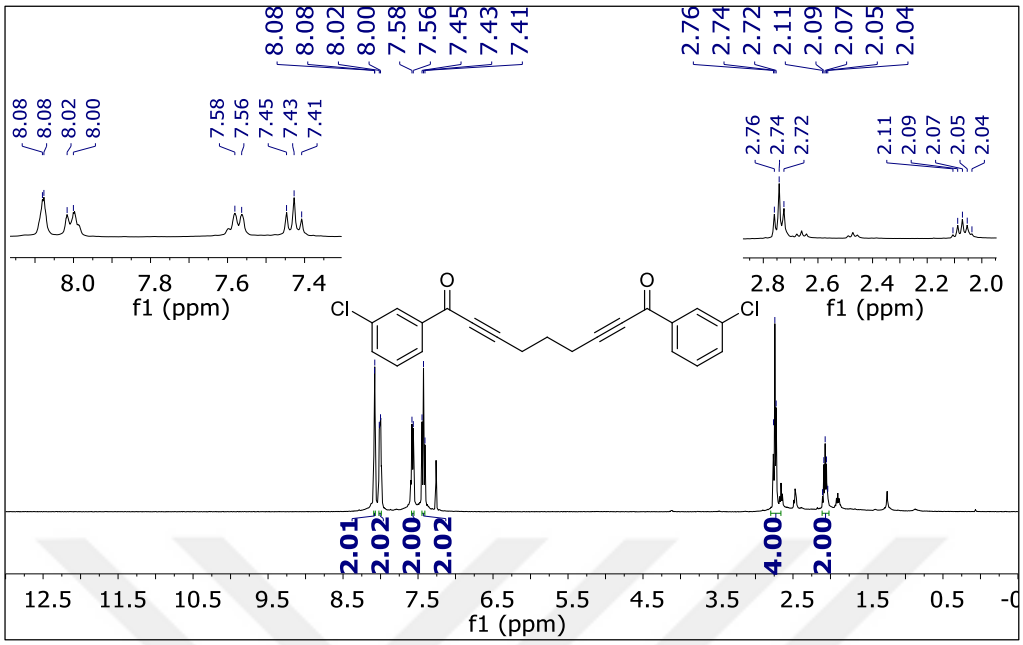


Figure 58. ^{1}H NMR spectrum of compound **36j**.

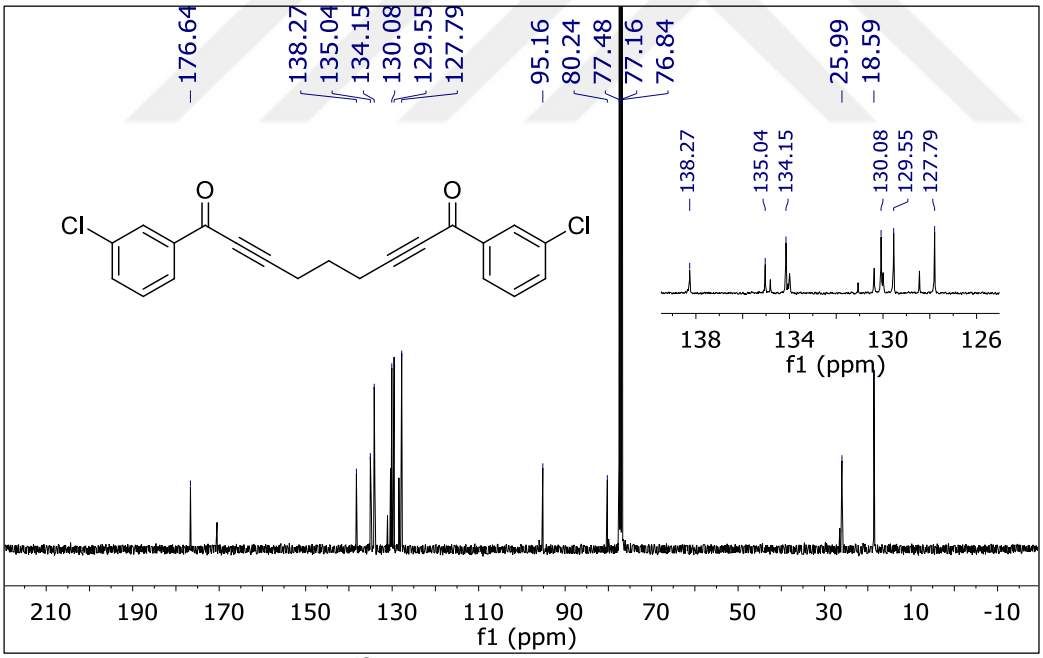


Figure 59. ^{13}C NMR spectrum of compound **36j**.

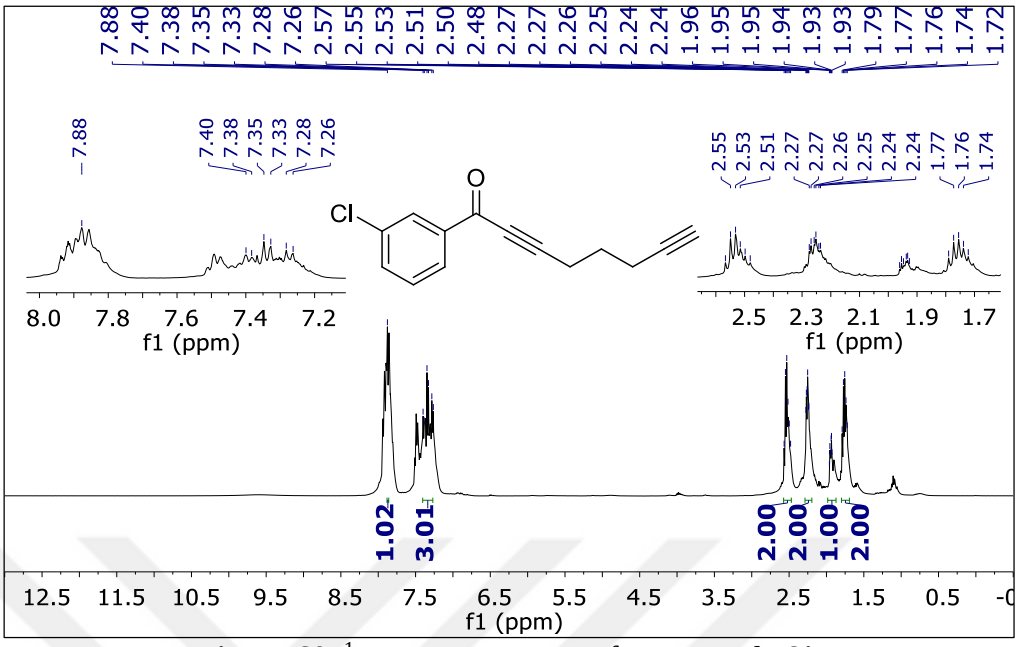


Figure 60. ^{1}H NMR spectrum of compound **48j**.

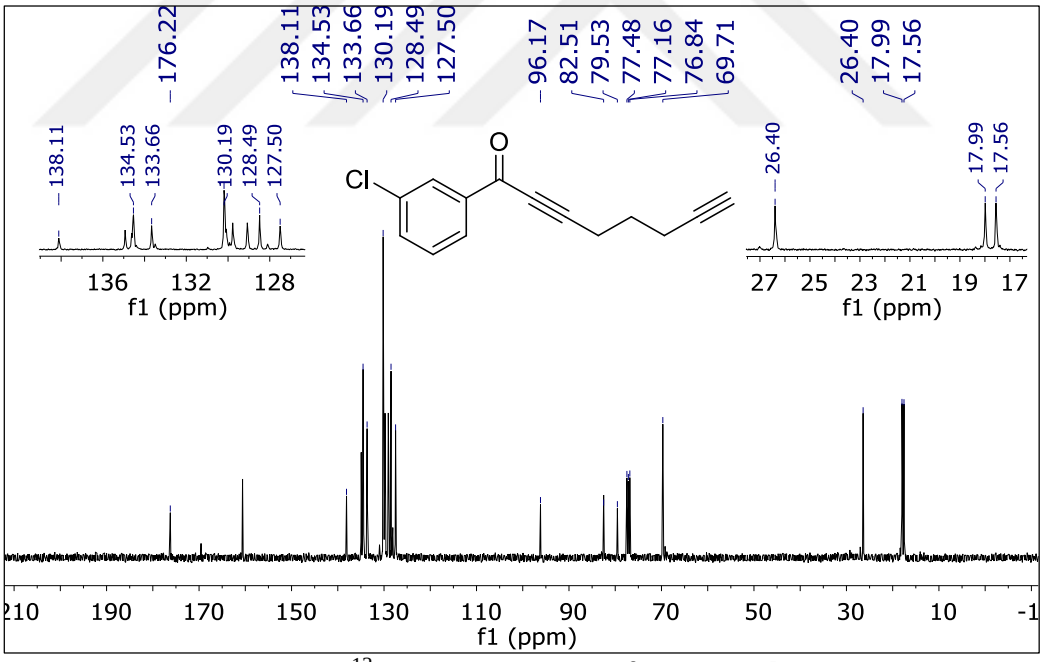


Figure 61. ^{13}C NMR spectrum of compound **48j**.

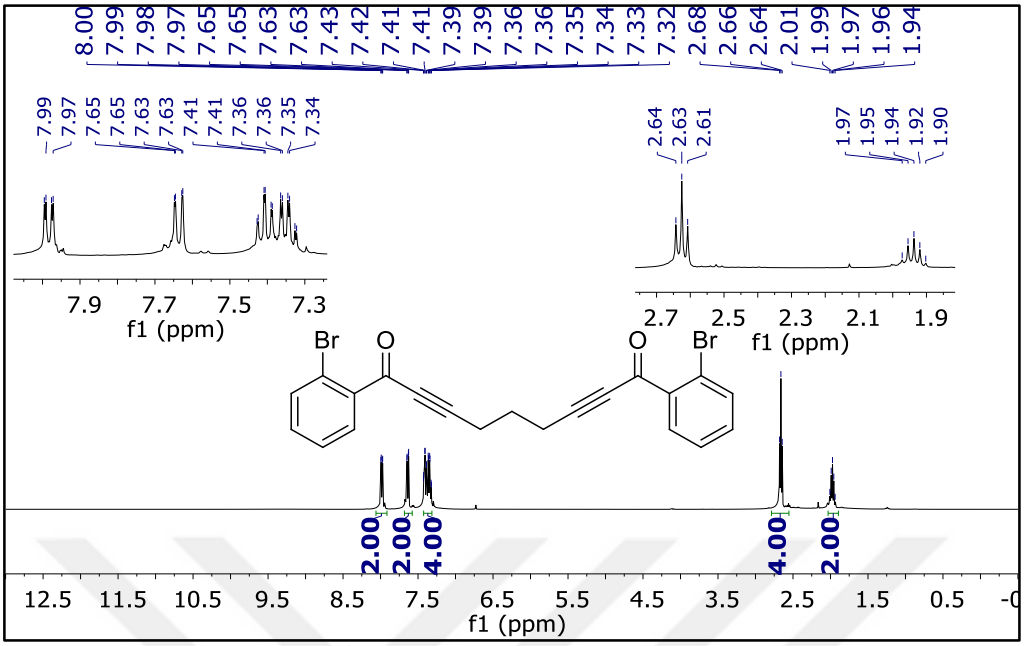


Figure 62. ^{1}H NMR spectrum of compound **36k**.

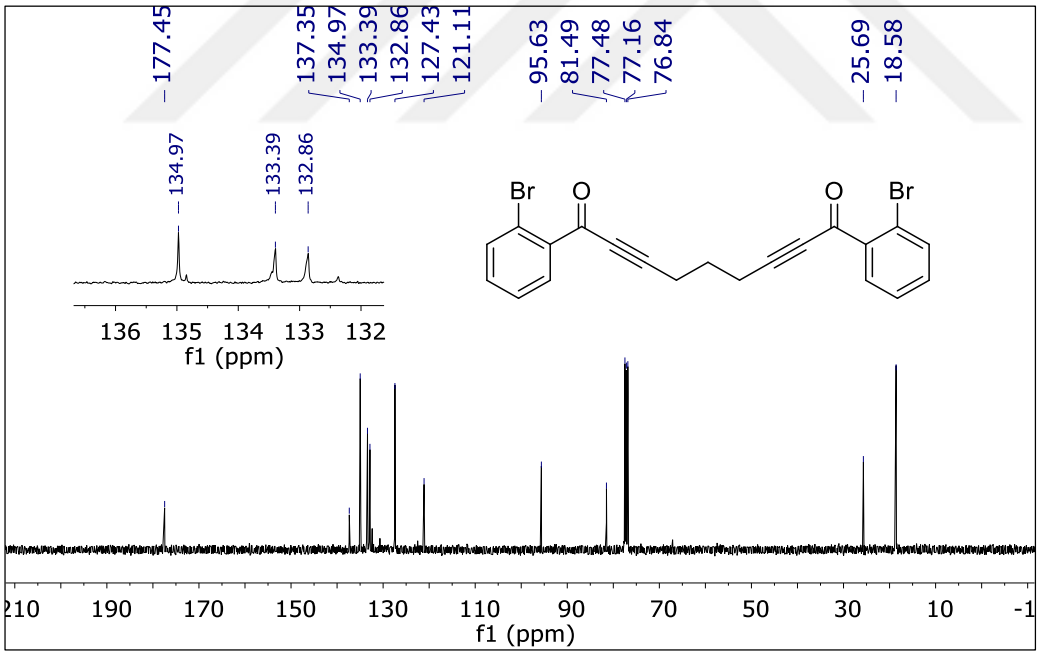


Figure 63. ^{13}C NMR spectrum of compound **36k**.

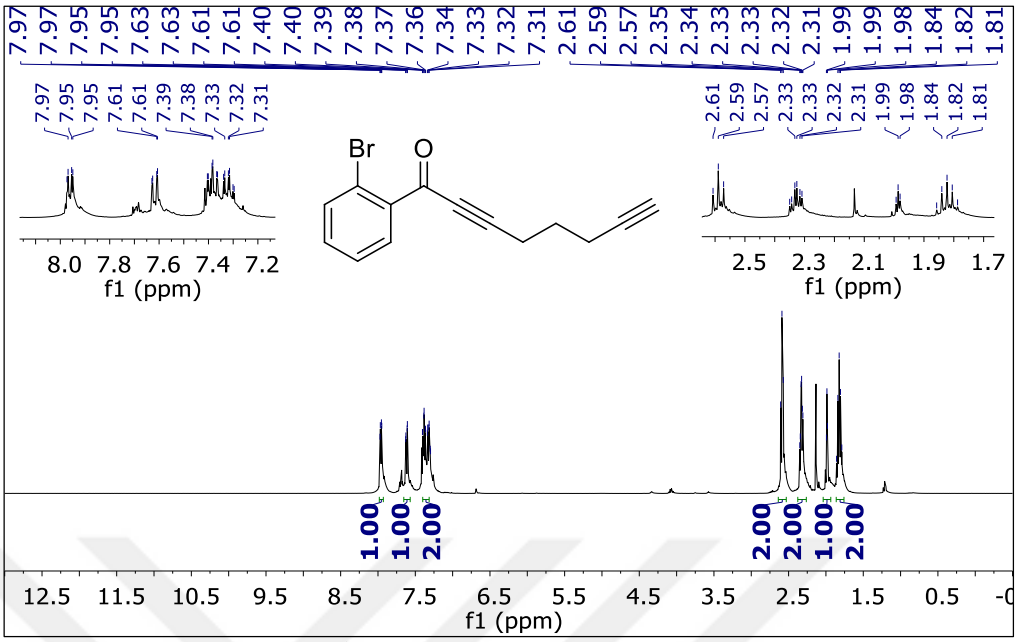


Figure 64. ^{1}H NMR spectrum of compound **48k**.

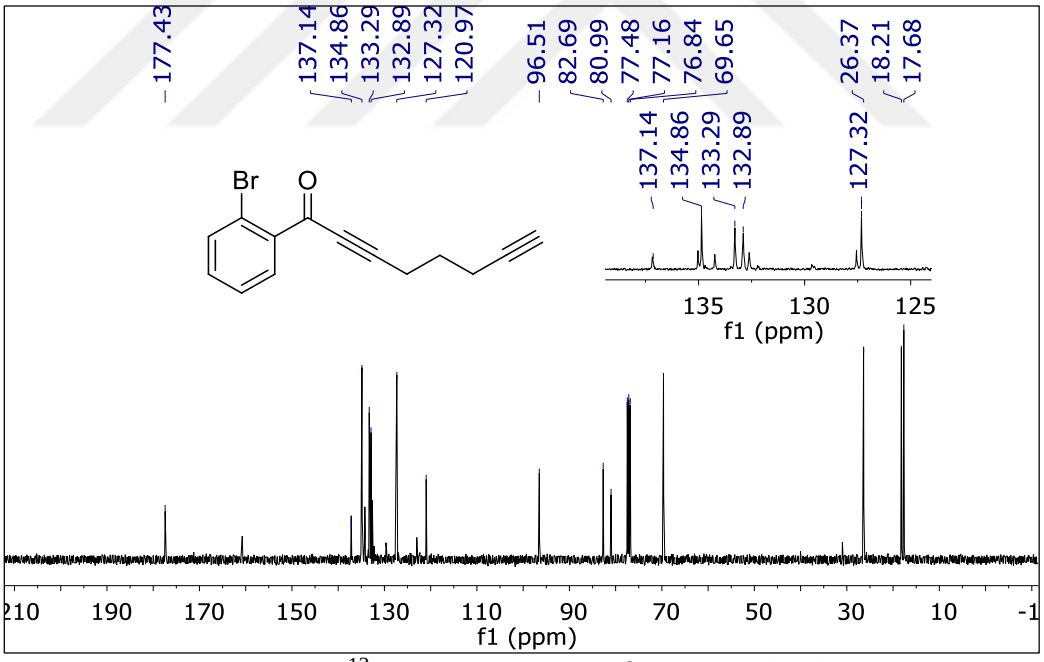


Figure 65. ^{13}C NMR spectrum of compound **48k**.

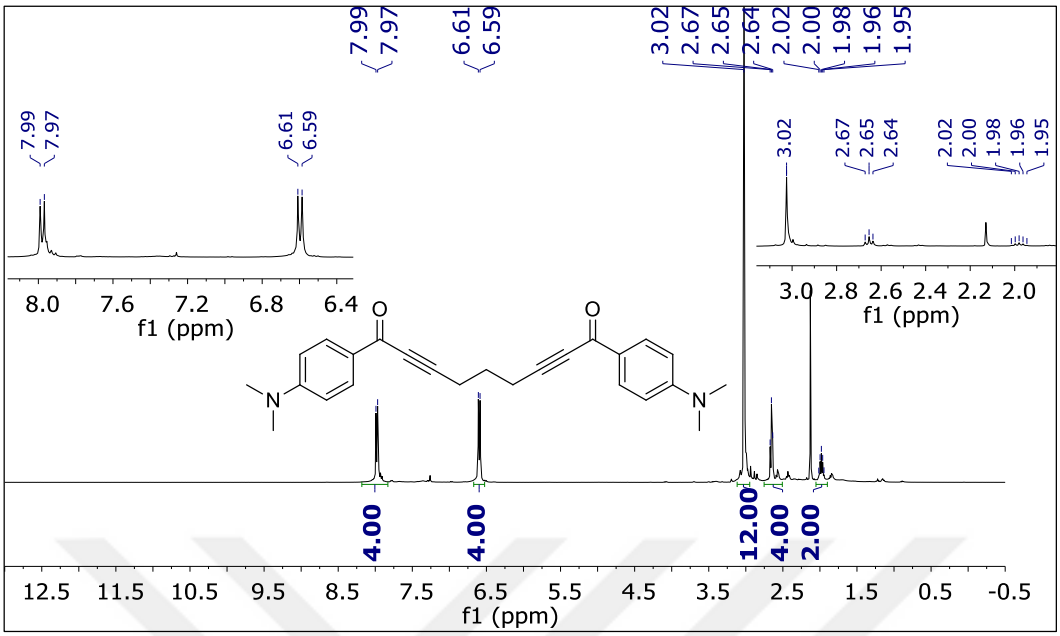


Figure 66. ^{1}H NMR spectrum of compound **36l**.

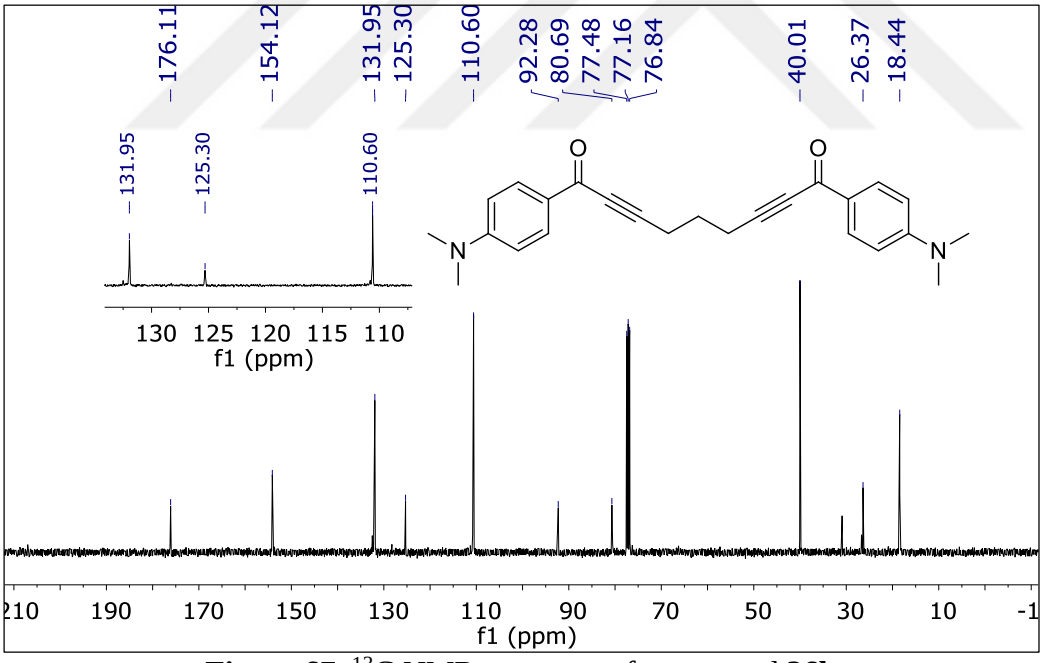


Figure 67. ^{13}C NMR spectrum of compound **36l**.

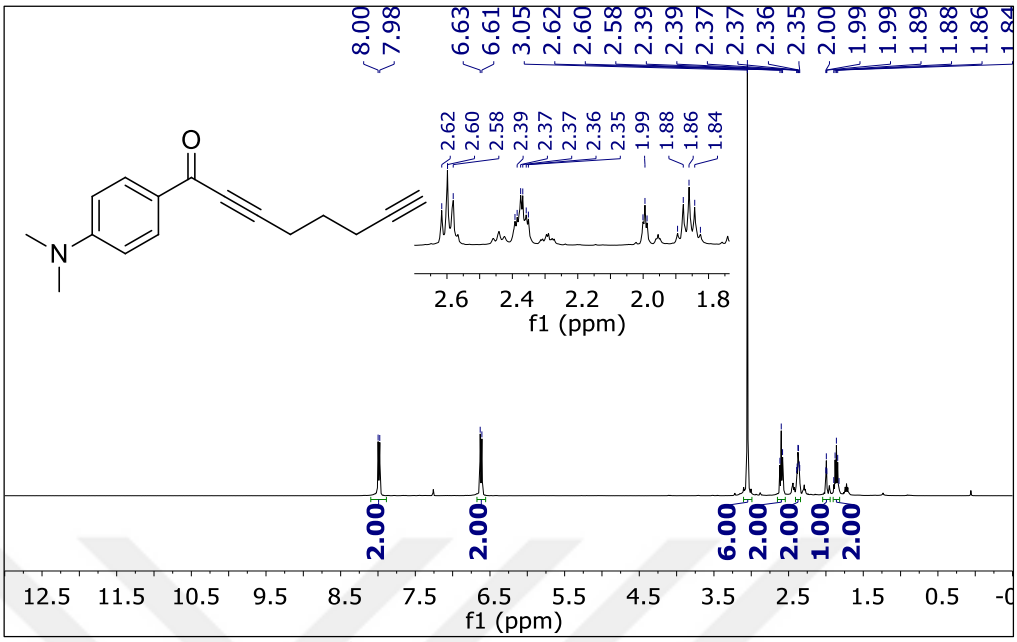


Figure 68. ^{1}H NMR spectrum of compound **48l**.

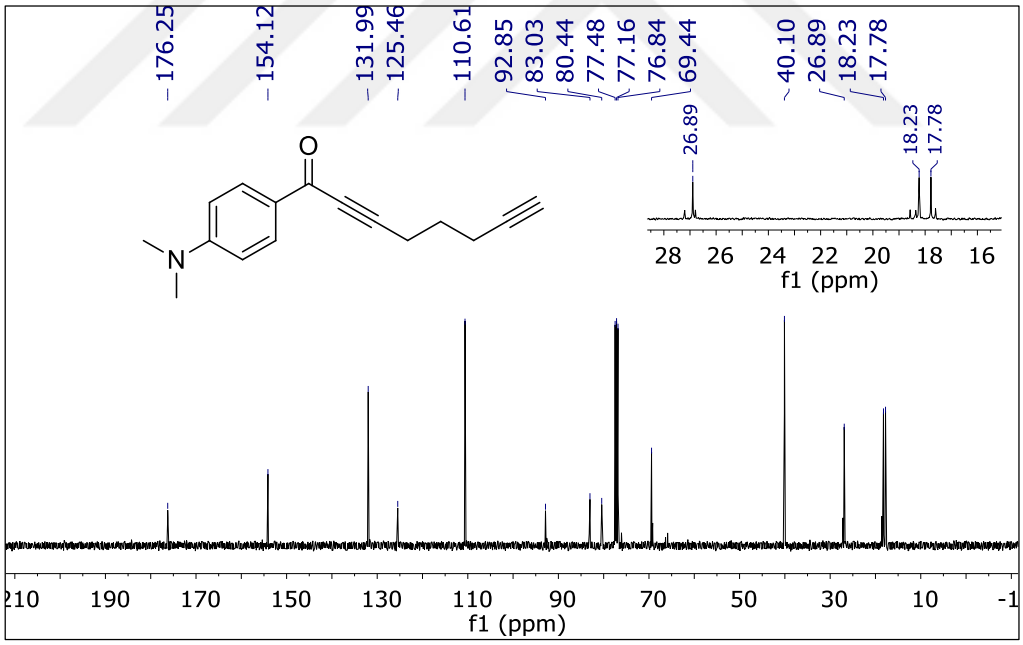


Figure 69. ^{13}C NMR spectrum of compound **48l**.

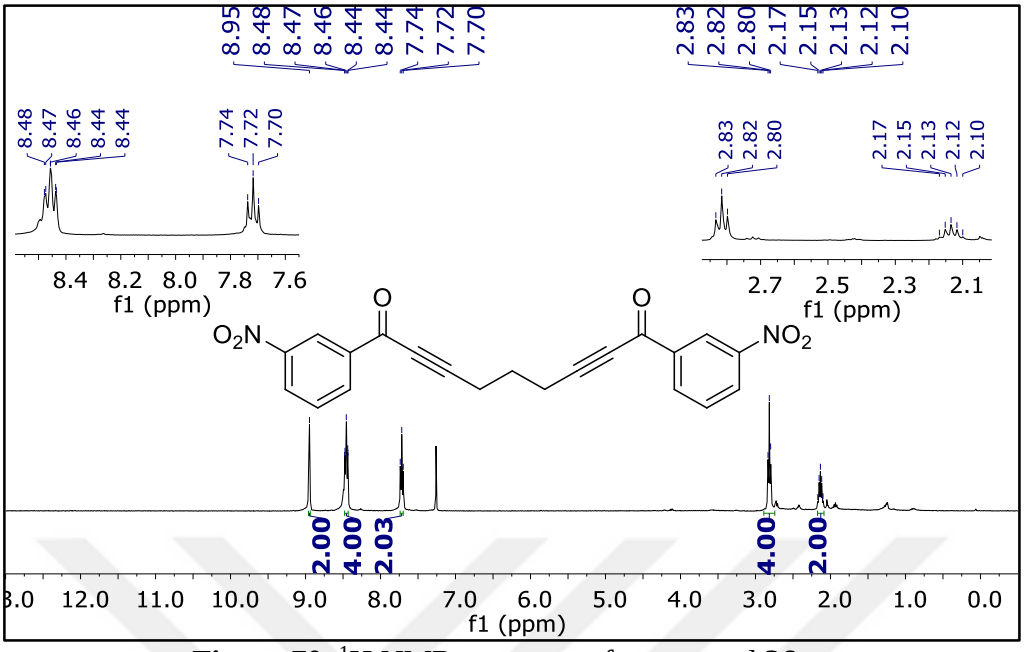


Figure 70. [1]H NMR spectrum of compound **36m**.

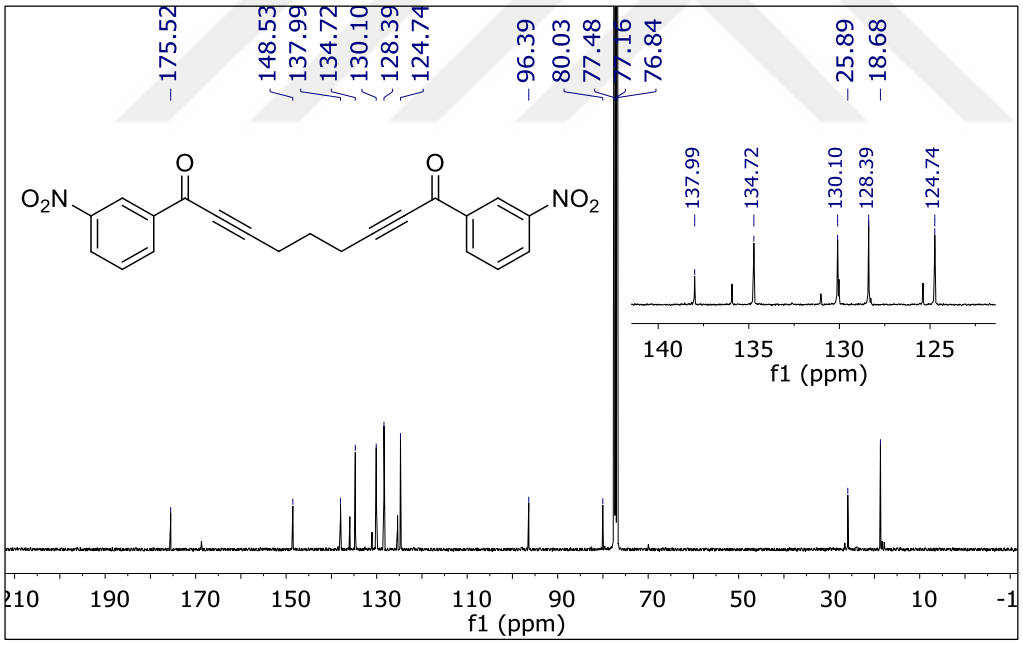


Figure 71. [13]C NMR spectrum of compound **36m**.

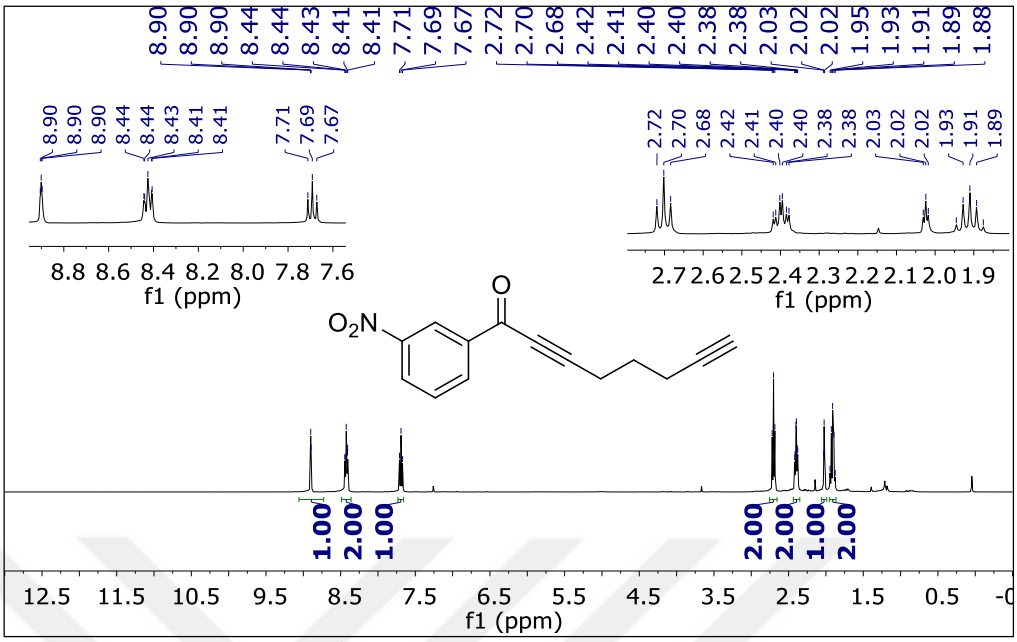


Figure 72. ^{1}H NMR spectrum of compound **48m**.

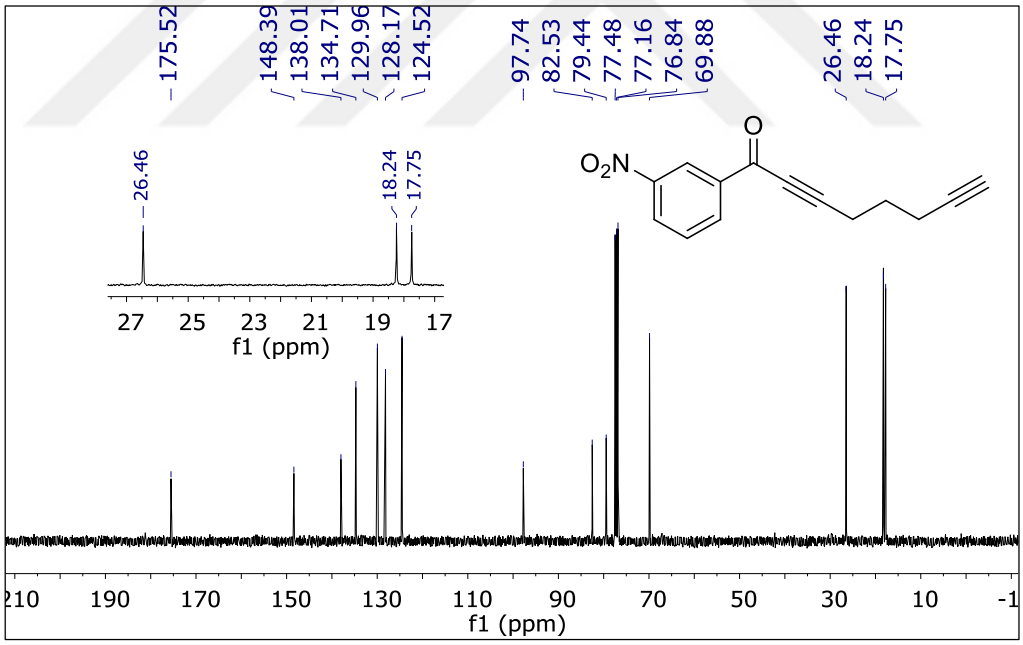


Figure 73. ^{13}C NMR spectrum of compound **48m**.

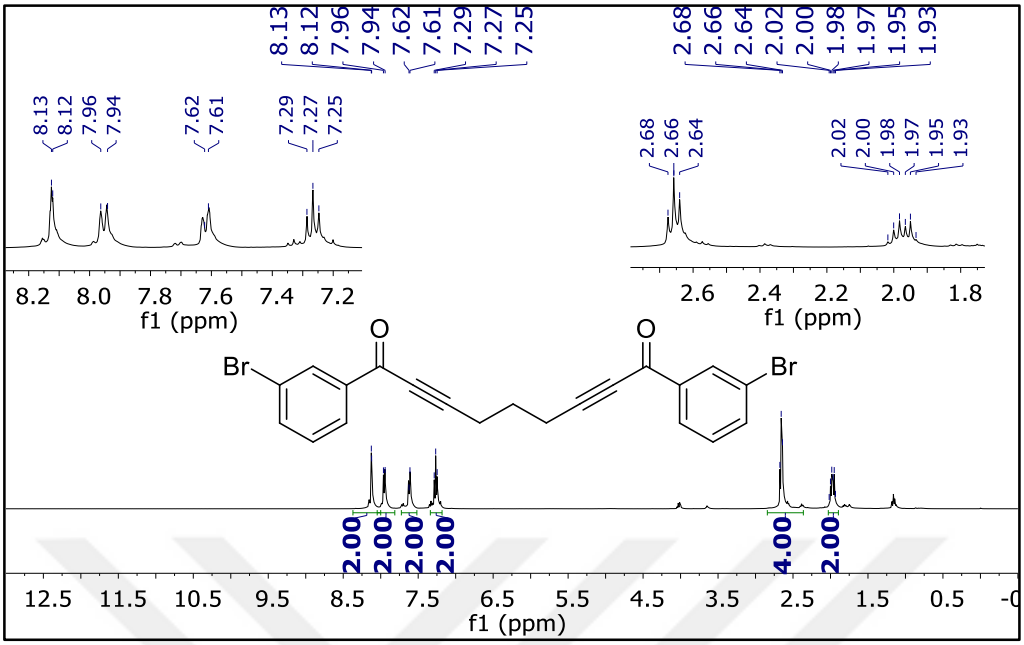


Figure 74. ^{1}H NMR spectrum of compound **36n**.

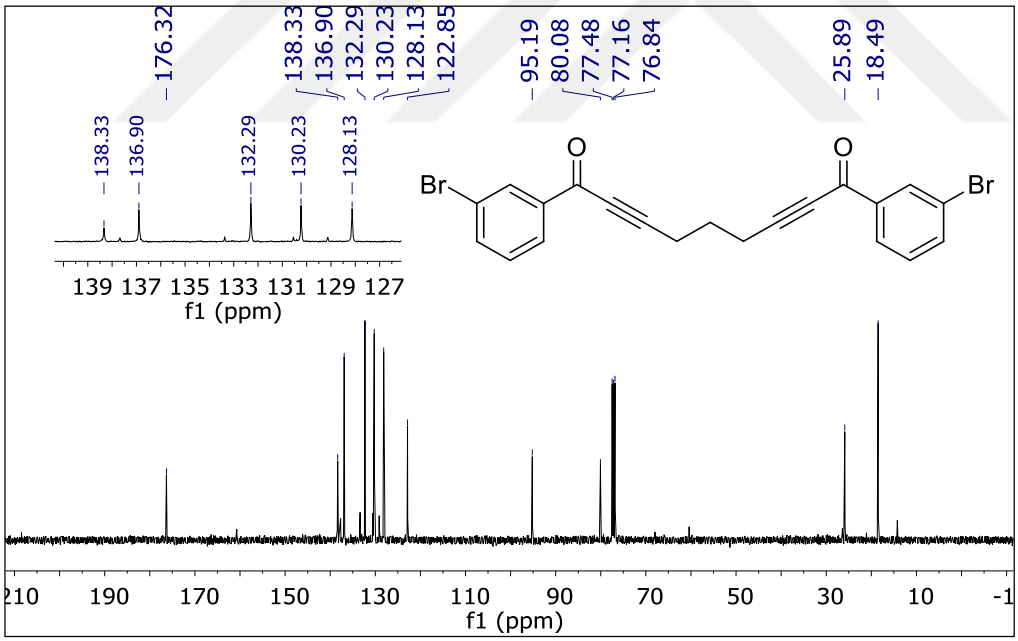


Figure 75. ^{13}C NMR spectrum of compound **36n**.

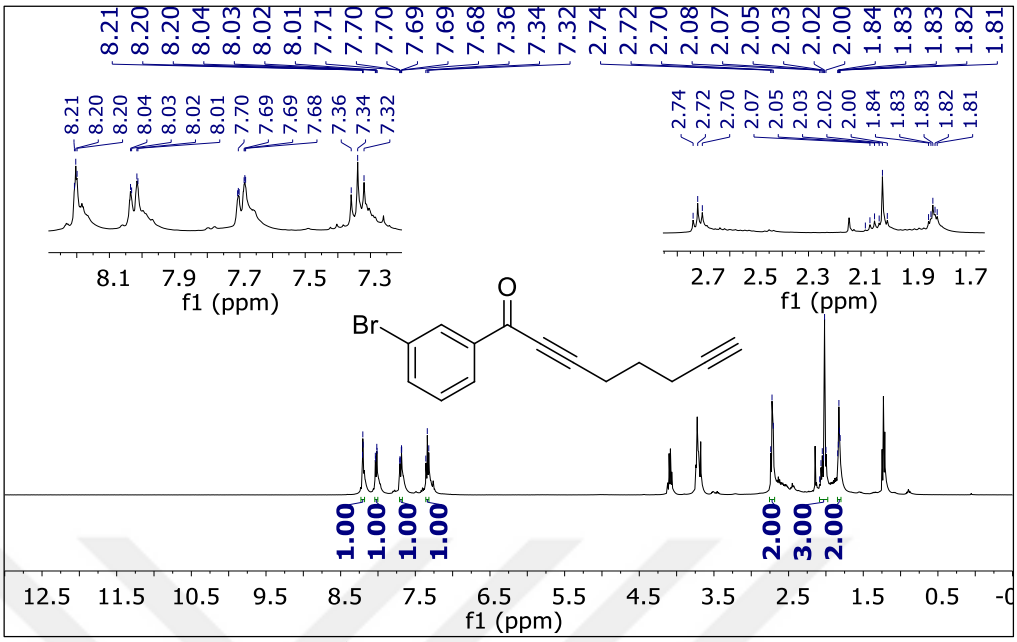


Figure 76. ^{1}H NMR spectrum of compound **48n**.

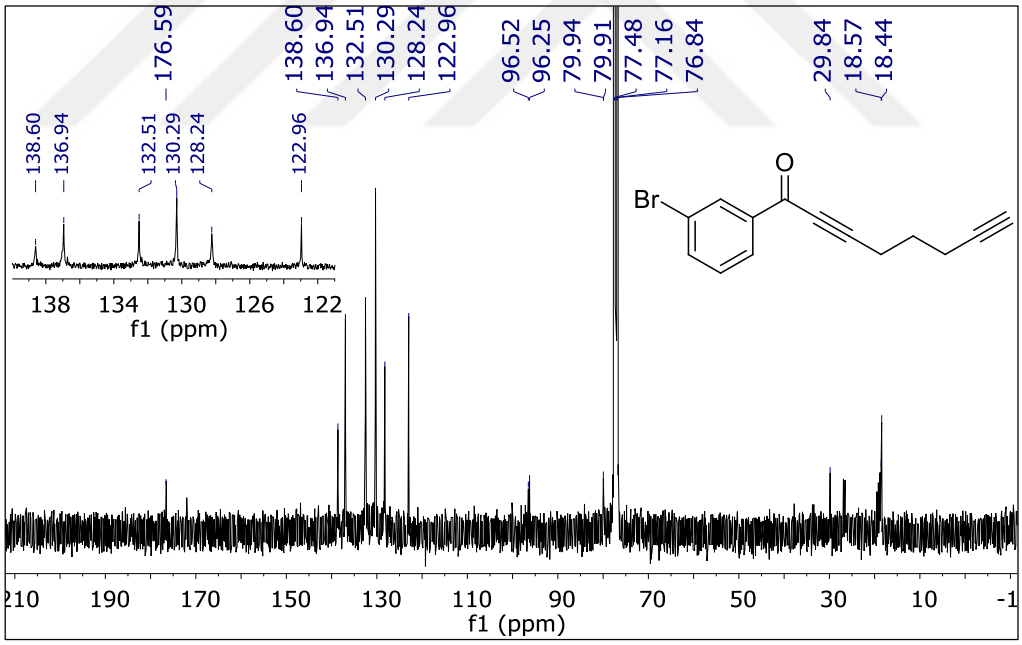


Figure 77. ^{13}C NMR spectrum of compound **48n**.

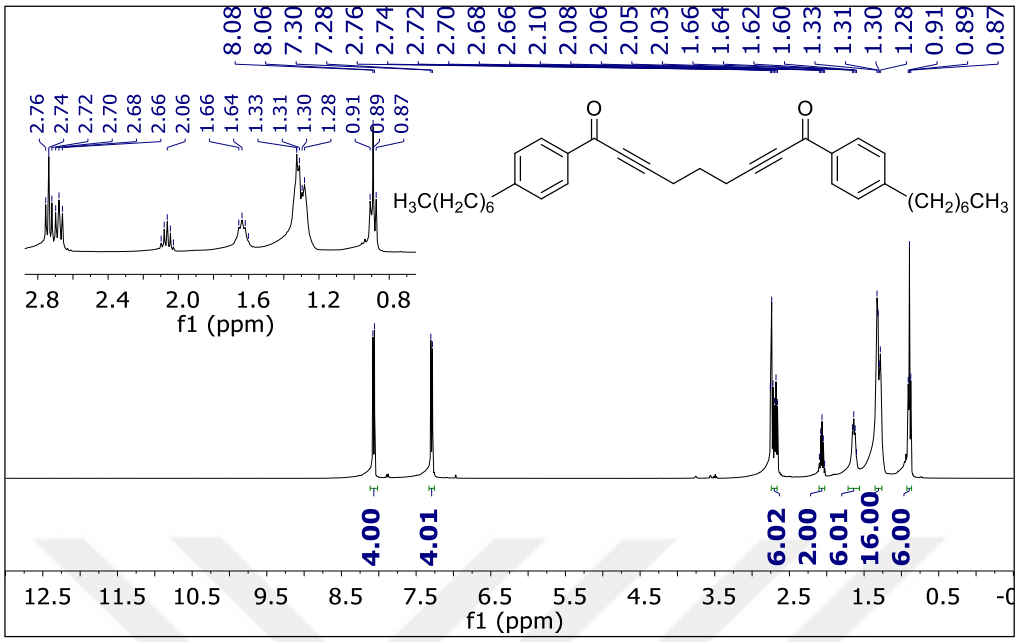


Figure 78. ^{1}H NMR spectrum of compound **36o**.

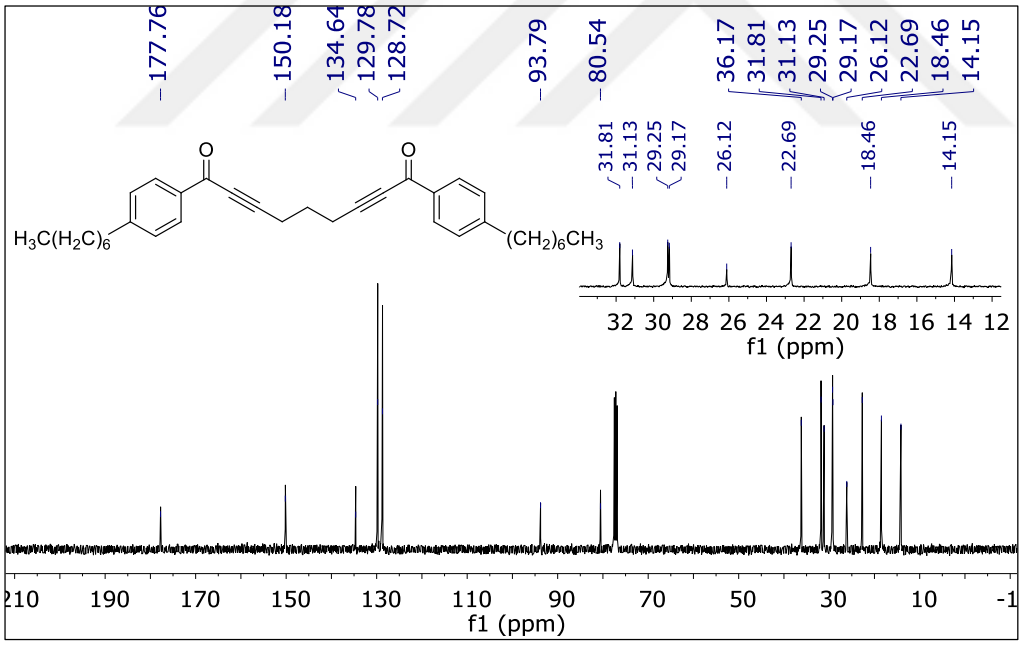


Figure 79. ^{13}C NMR spectrum of compound **36o**.

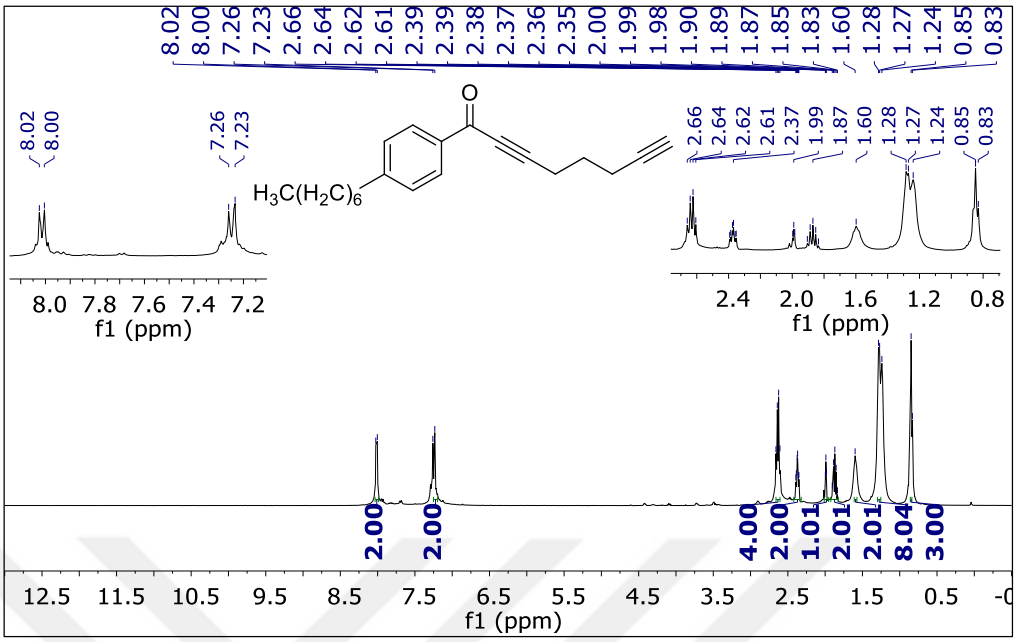


Figure 80. ^{1}H NMR spectrum of compound **48o**.

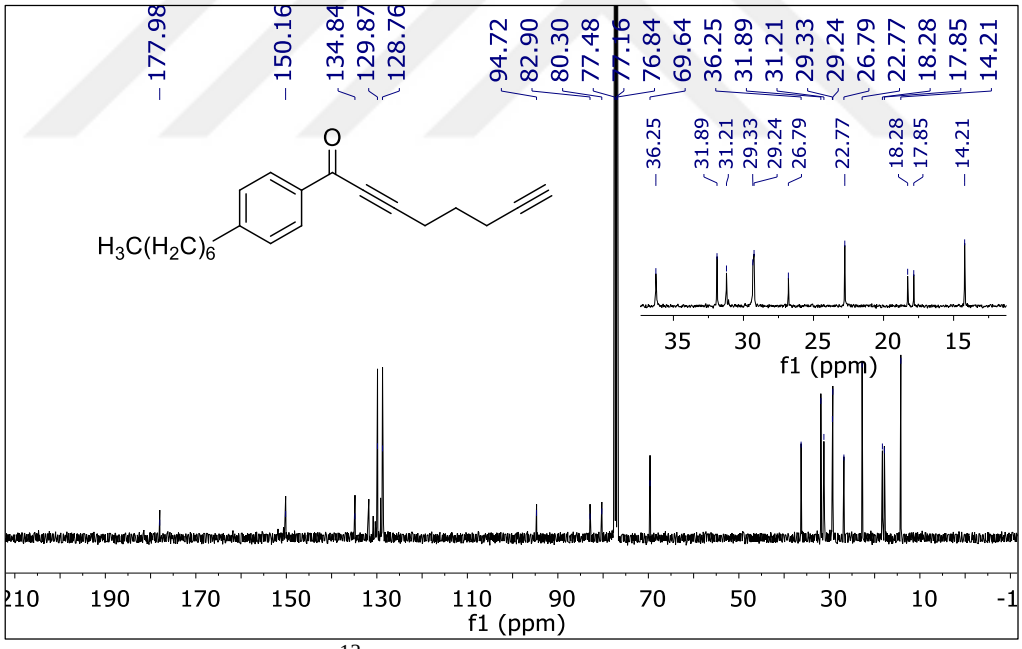


Figure 81. ^{13}C NMR spectrum of compound **48o**.

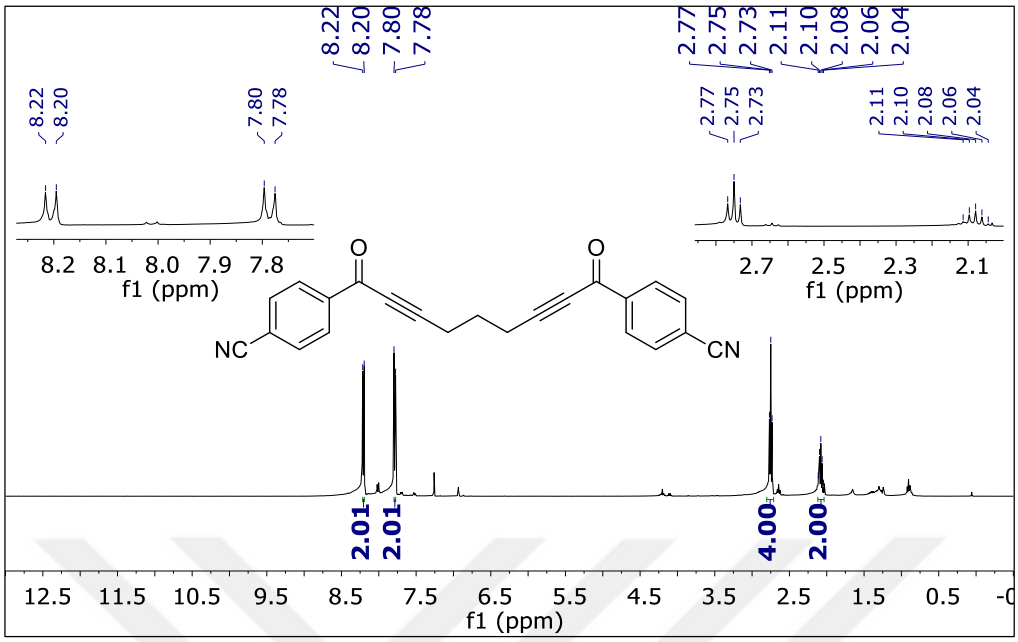


Figure 82. ^{1}H NMR spectrum of compound **36p**.

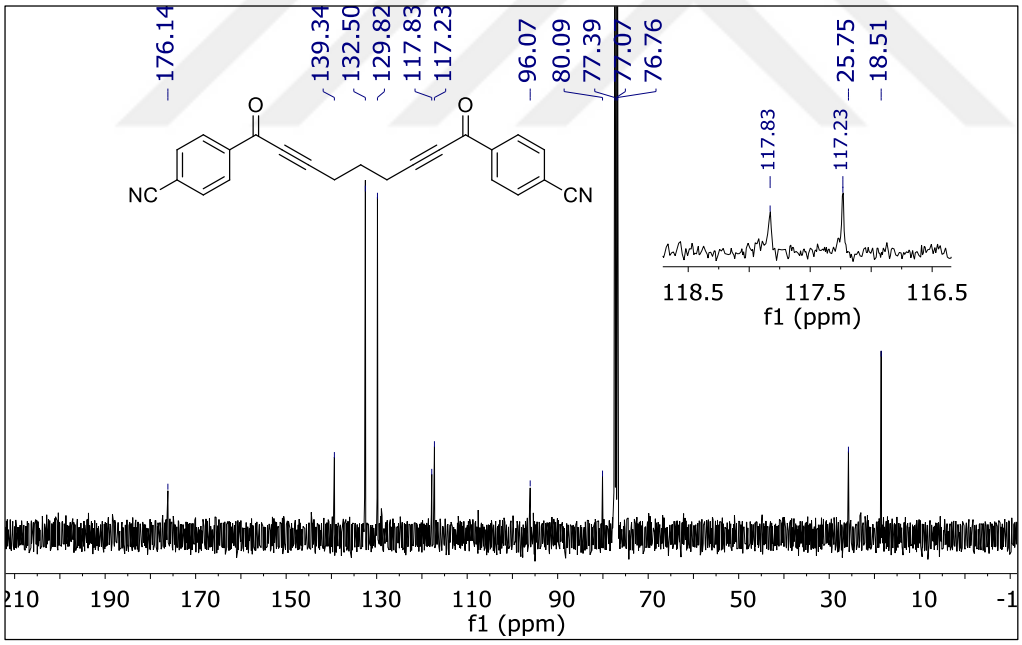


Figure 83. ^{13}C NMR spectrum of compound **36p**.

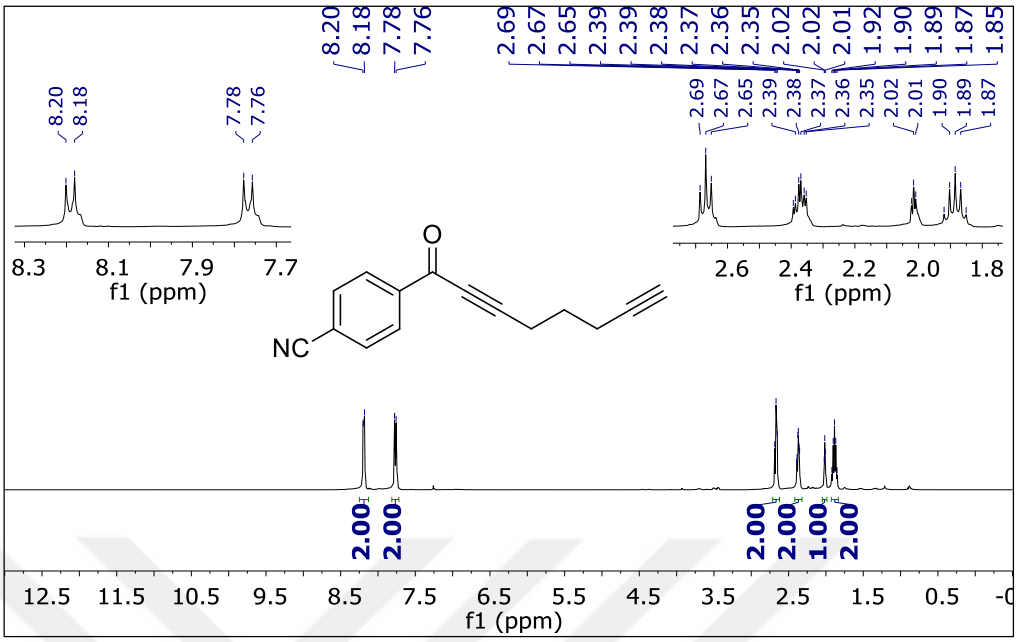


Figure 84. ^{1}H NMR spectrum of compound **48p**.

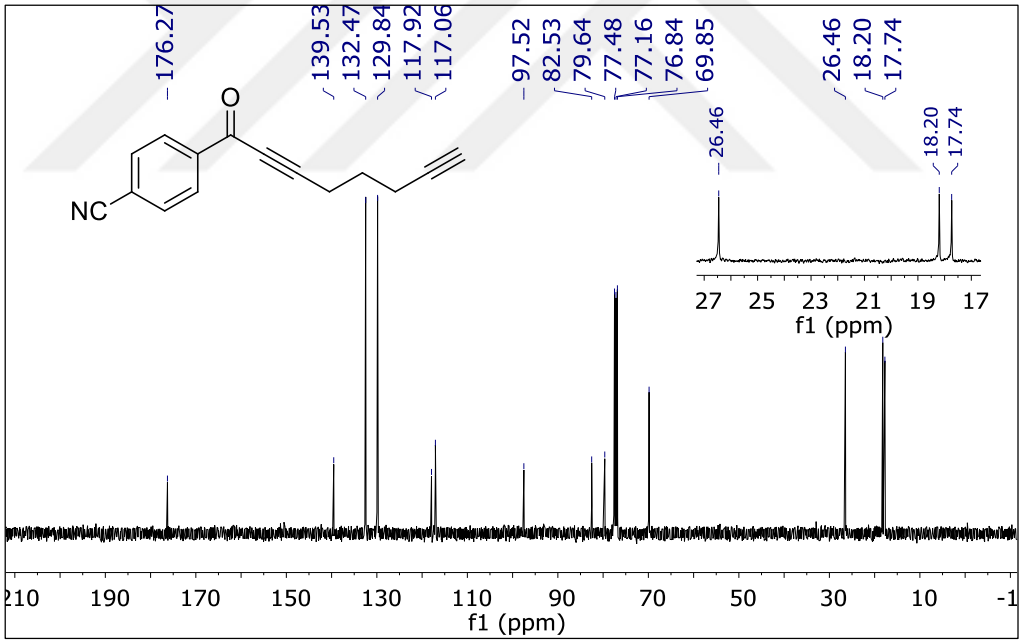


Figure 85. ^{13}C NMR spectrum of compound **48p**.

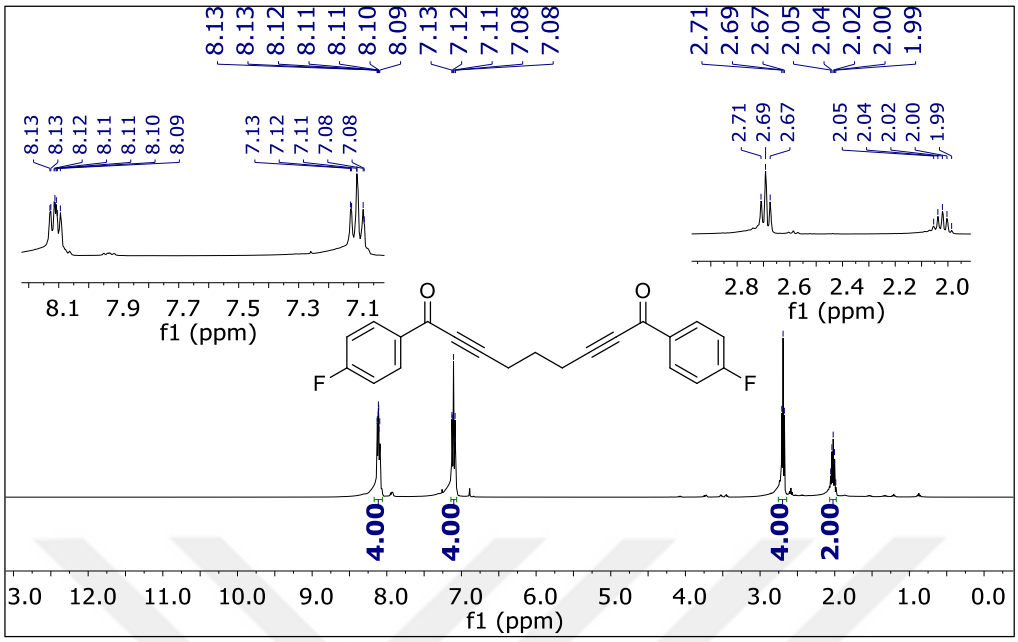


Figure 86. ^{1}H NMR spectrum of compound **36q**.

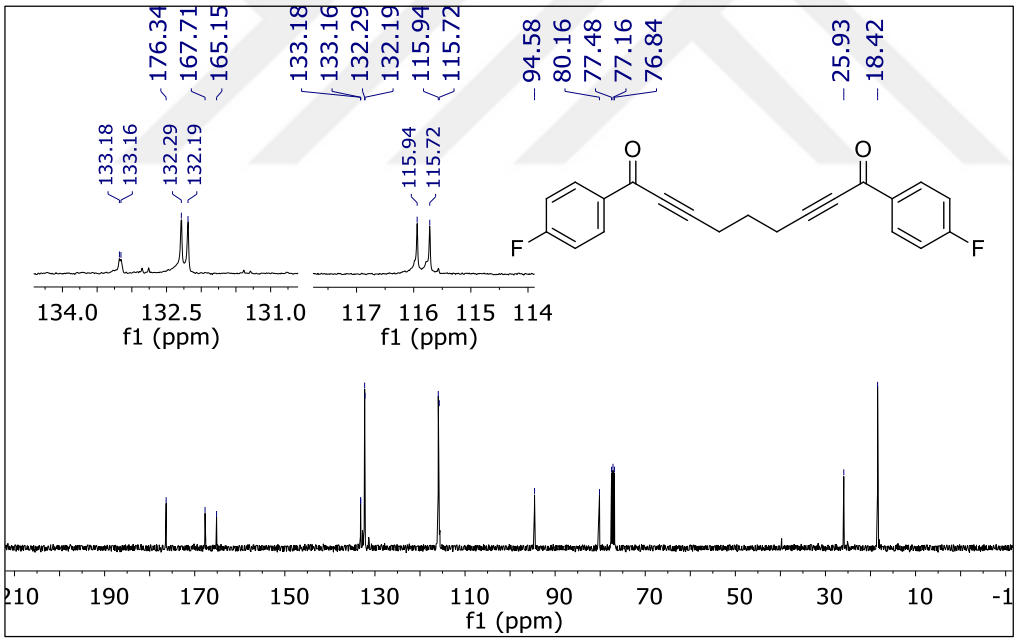


Figure 87. ^{13}C NMR spectrum of compound **36q**.

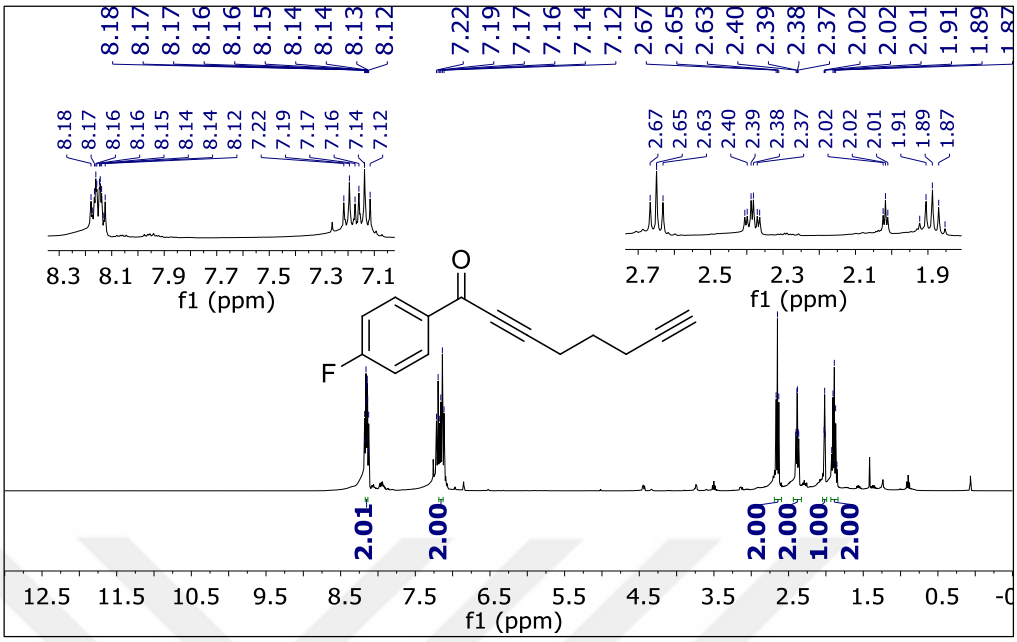


Figure 88. ^{1}H NMR spectrum of compound **48q**.

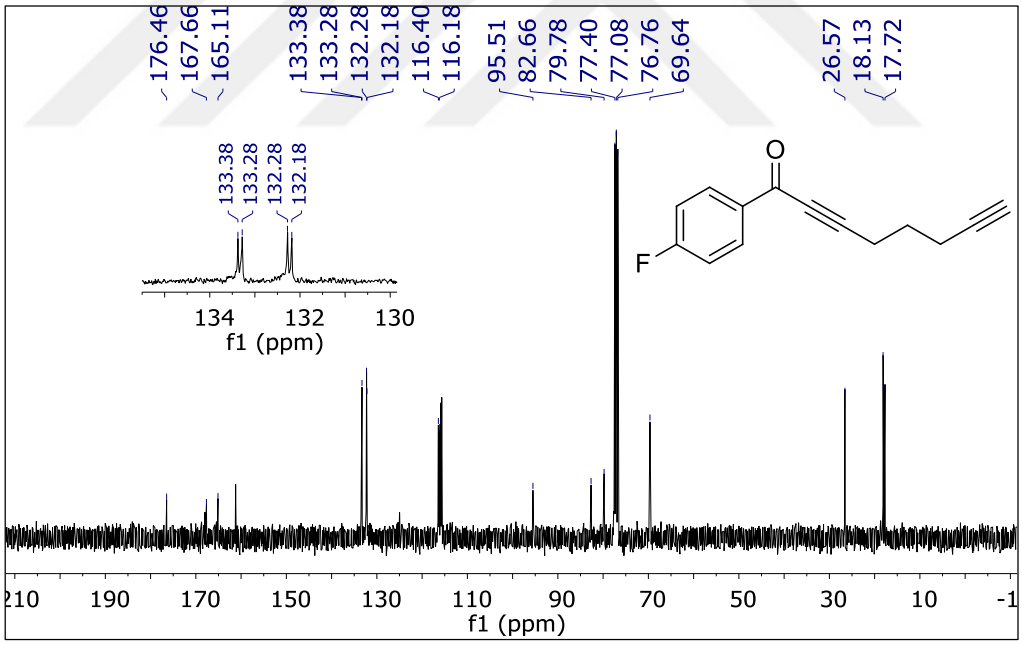


Figure 89. ^{13}C NMR spectrum of compound **48q**.

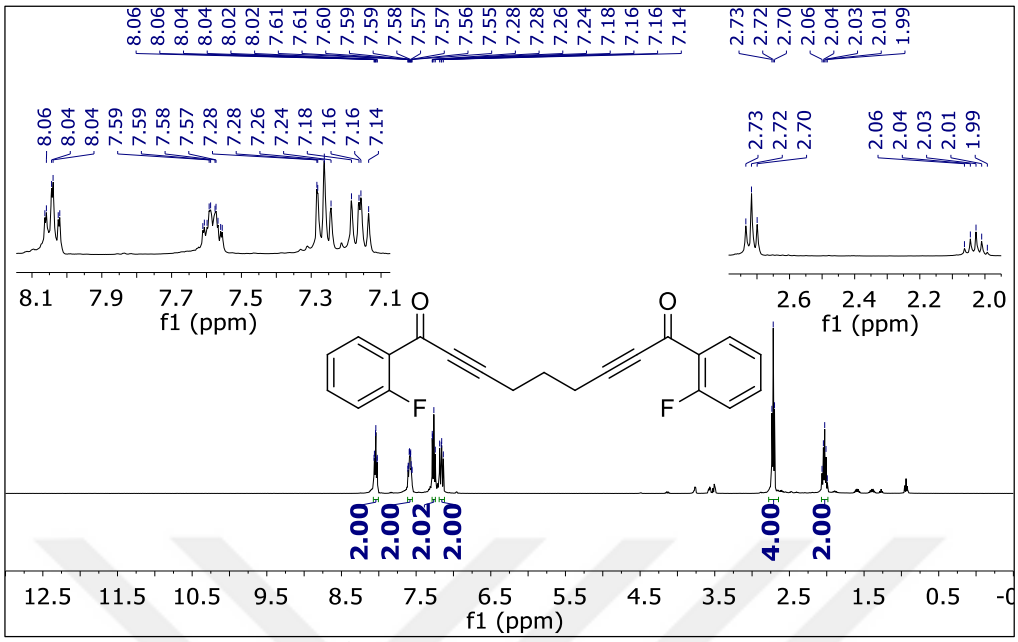


Figure 90. ^{1}H NMR spectrum of compound **36r**.

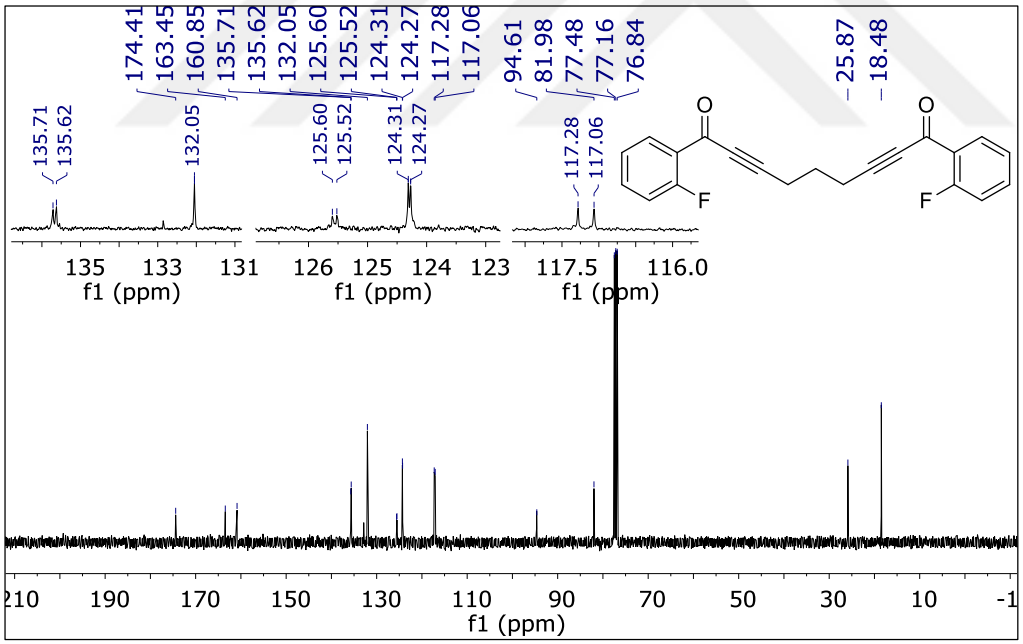


Figure 91. ^{13}C NMR spectrum of compound **36r**.

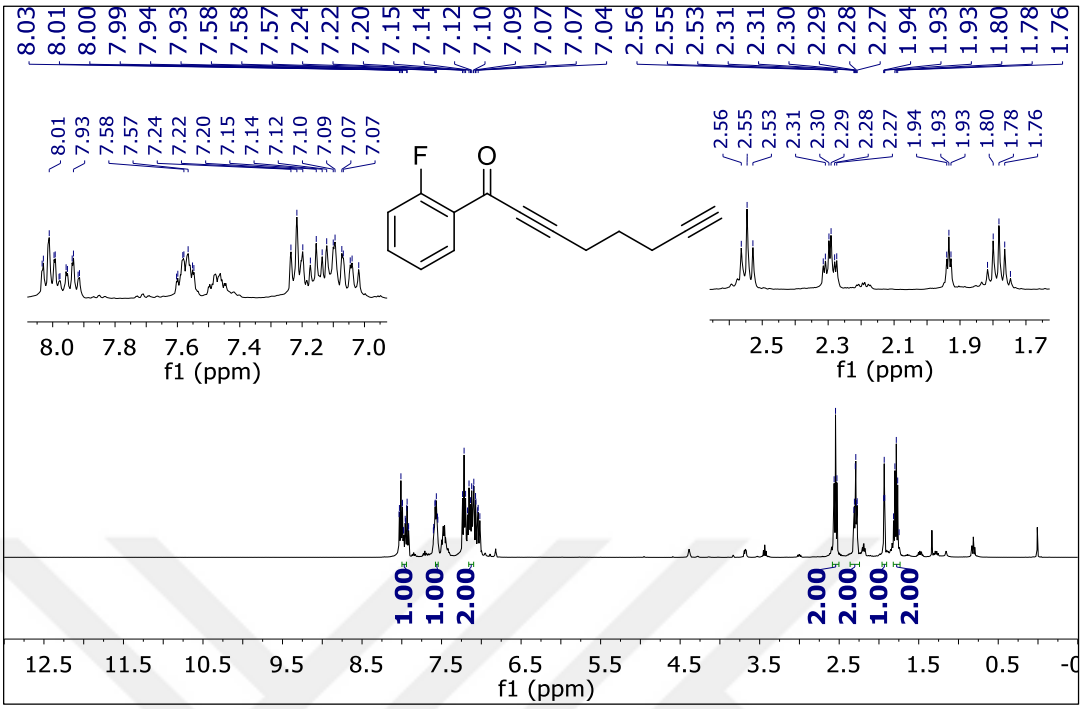


Figure 92. ^{1}H NMR spectrum of compound **48r**.

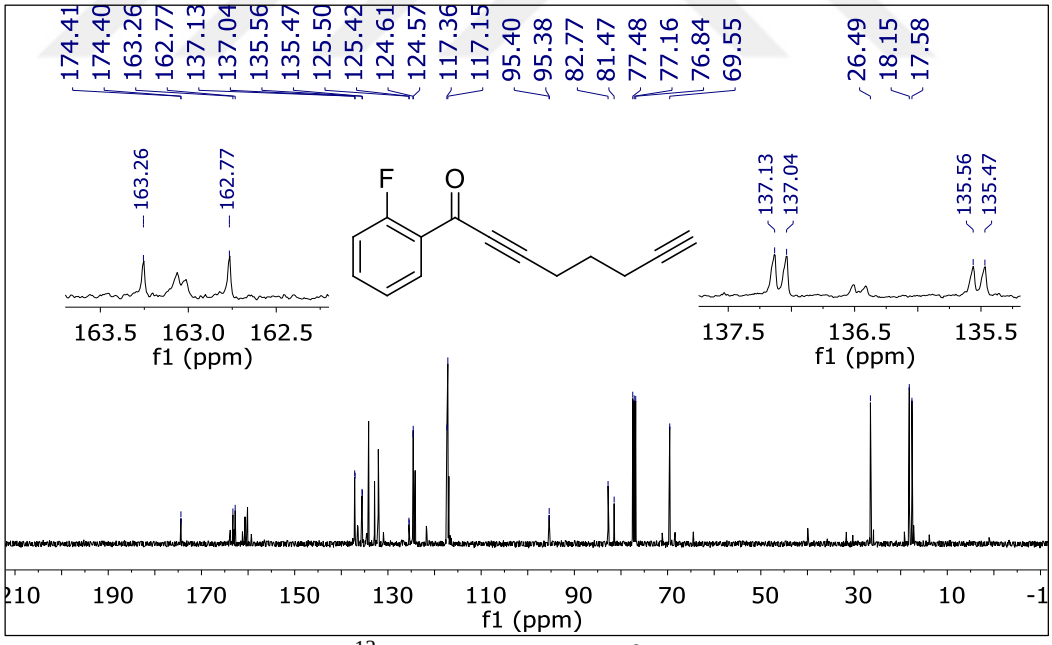


Figure 93. ^{13}C NMR spectrum of compound **48r**.

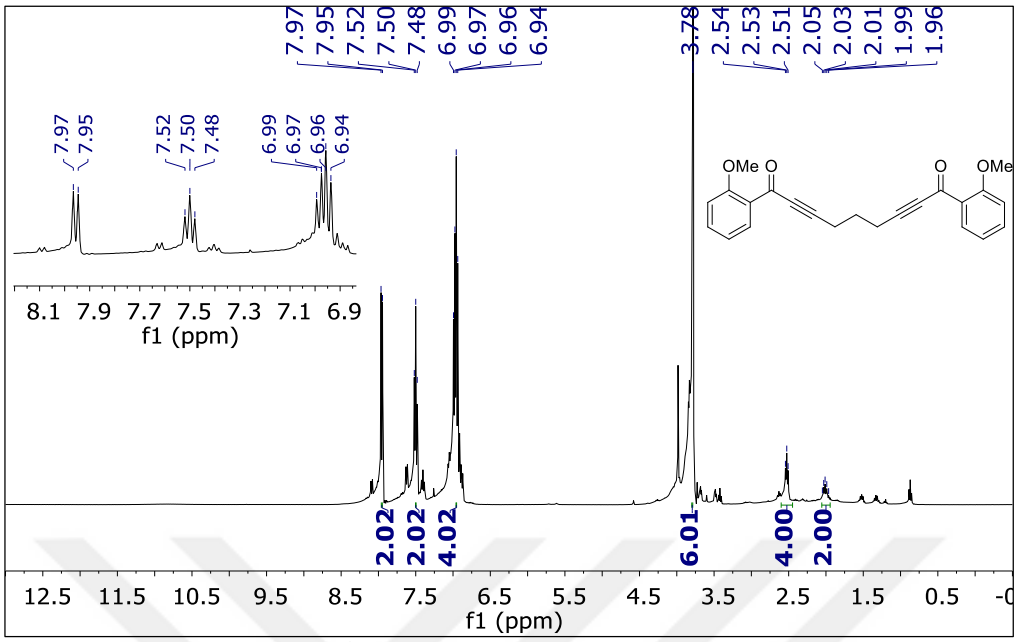


Figure 94. ^{1}H NMR spectrum of compound **36s**.

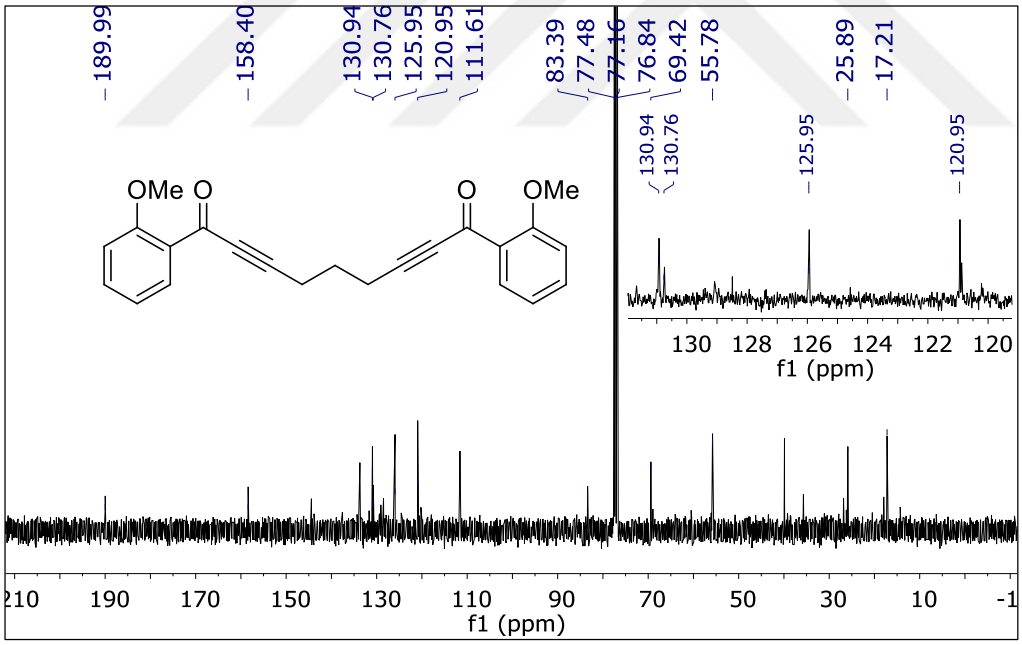


Figure 95. ^{13}C NMR spectrum of compound **36s**.

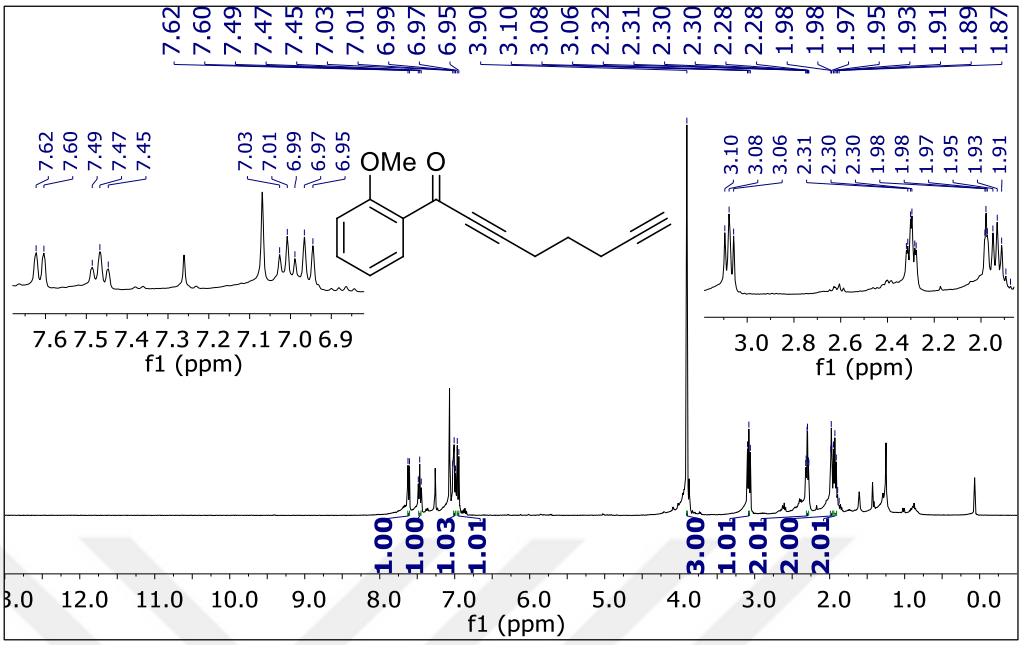


Figure 96. ^{1}H NMR spectrum of compound **48s**.

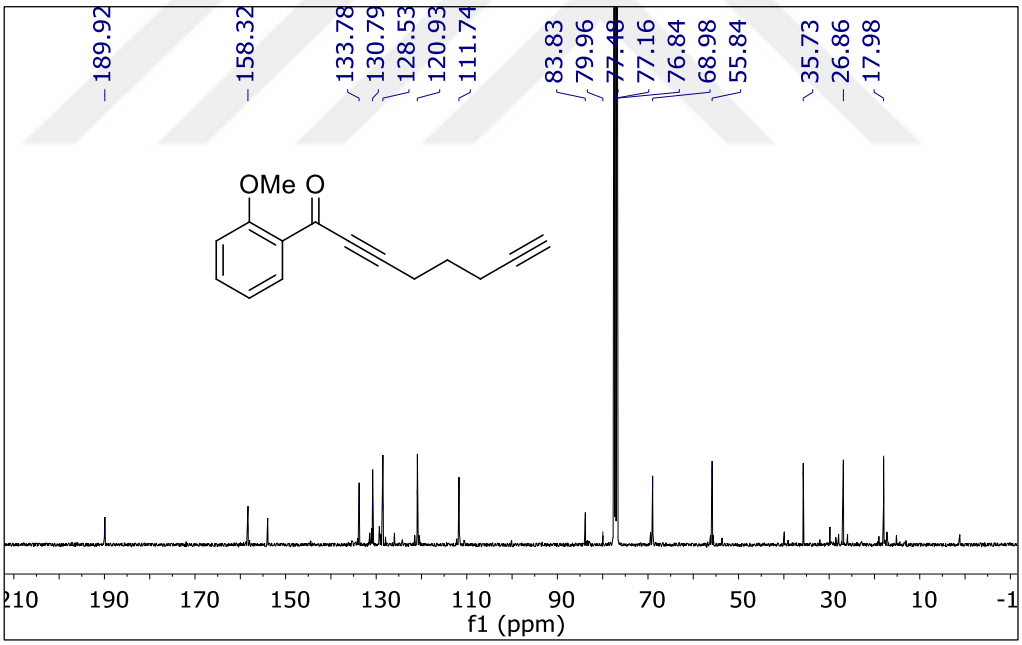


Figure 97. ^{13}C NMR spectrum of compound **48s**.

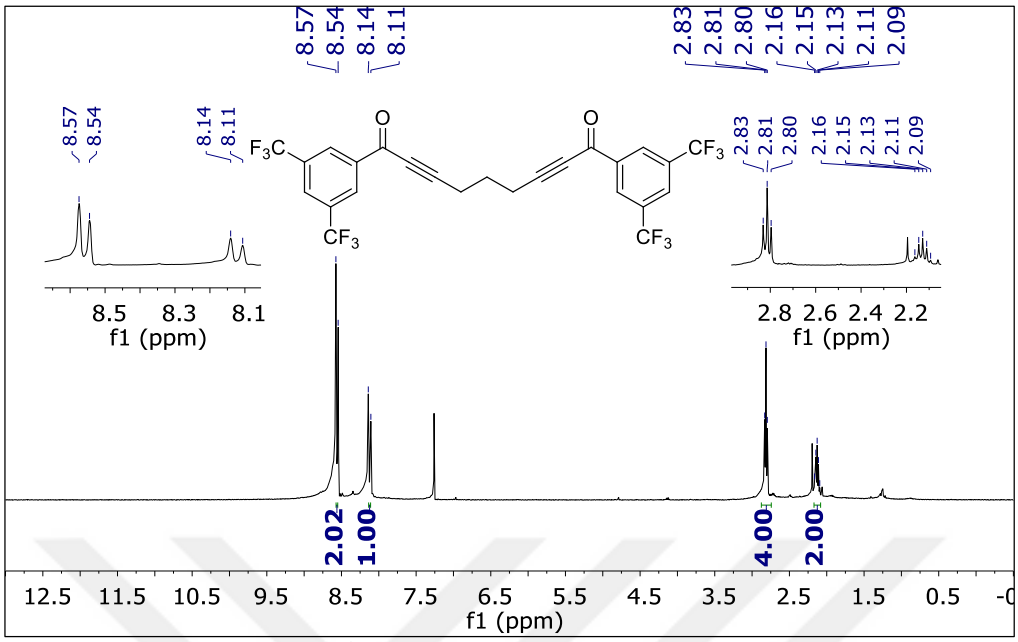


Figure 98. ^{1}H NMR spectrum of compound **36t**.

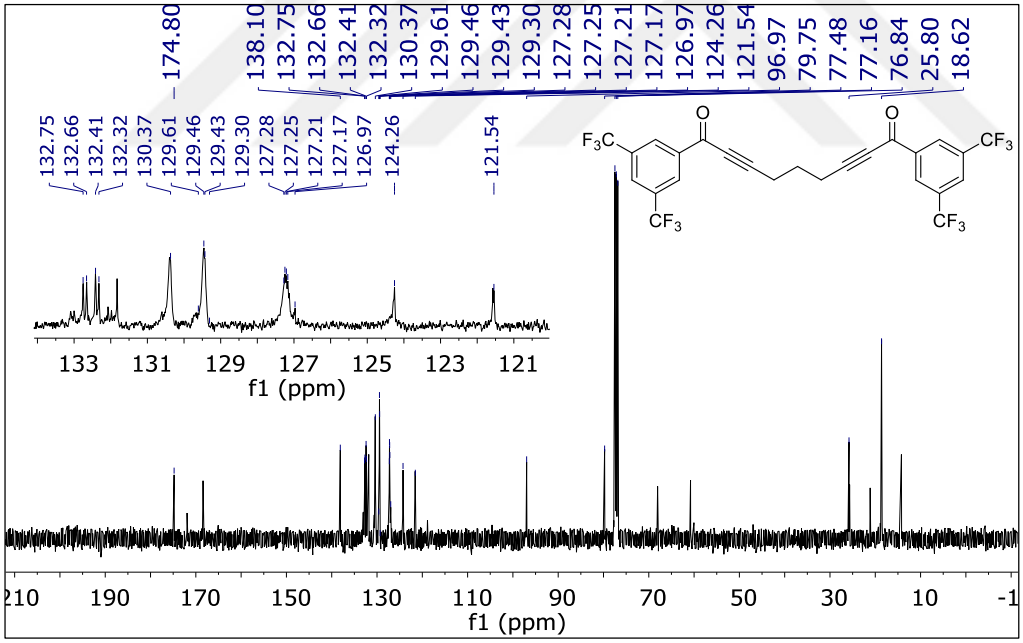


Figure 99. ^{13}C NMR spectrum of compound **36t**.

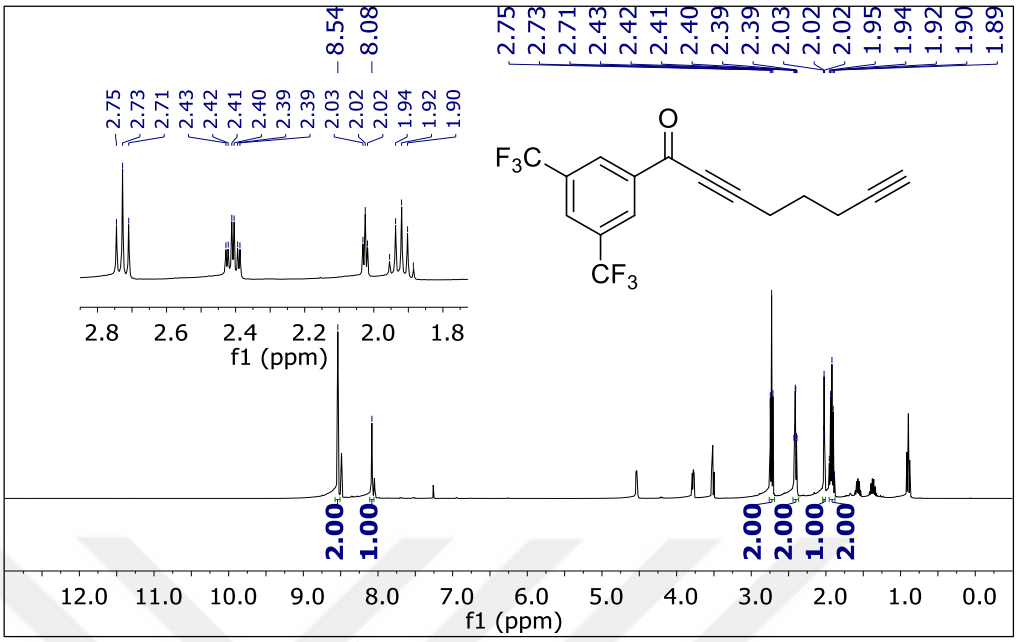


Figure 100. ^{1}H NMR spectrum of compound **48t**.

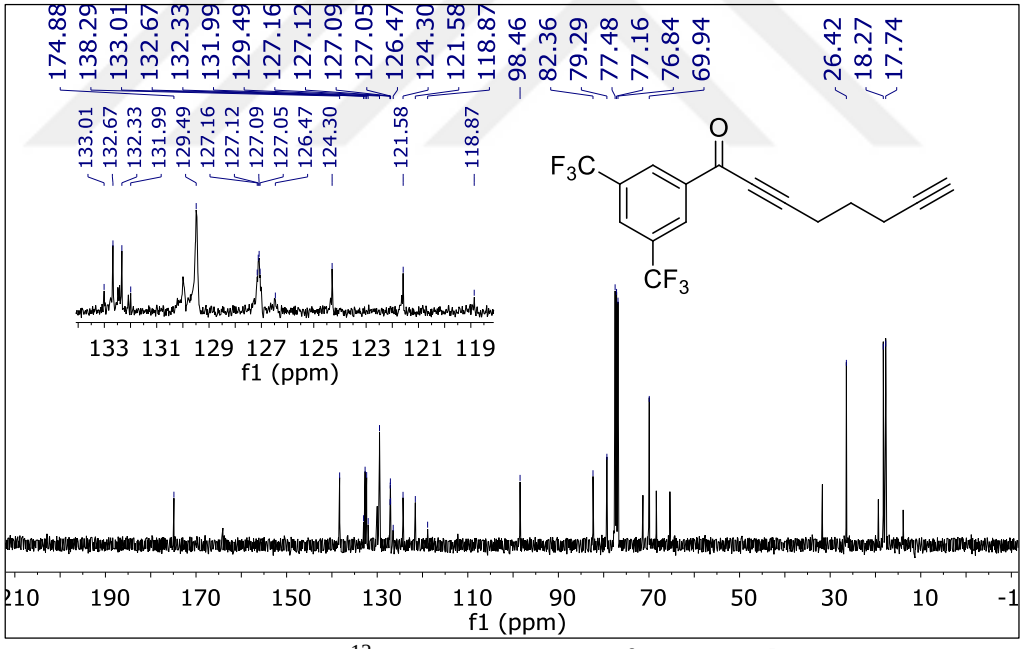


Figure 101. ^{13}C NMR spectrum of compound **48t**.

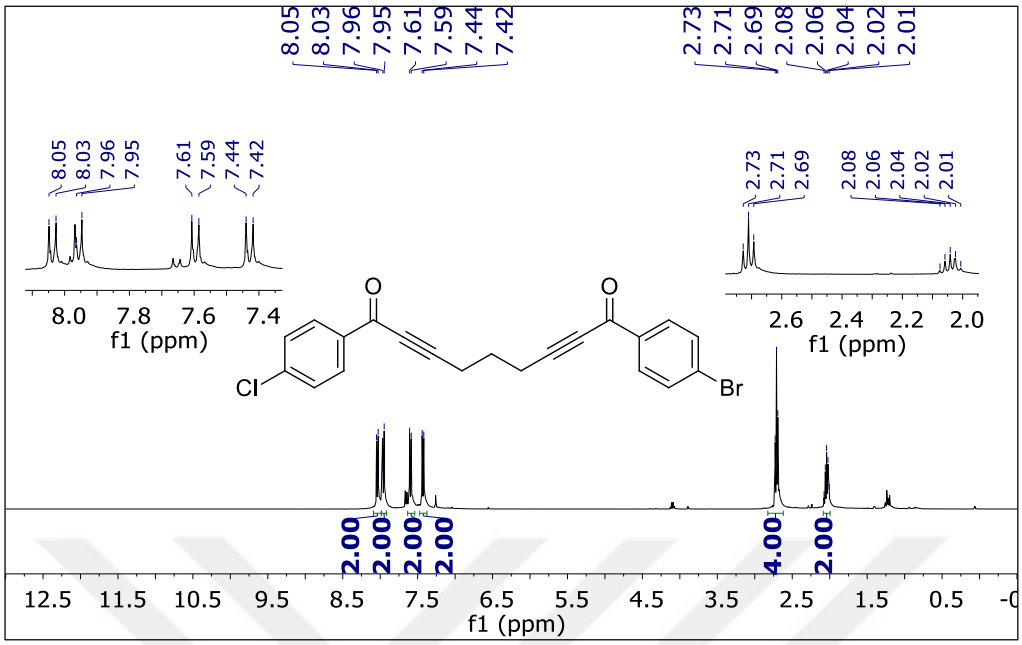


Figure 102. ^{1}H NMR spectrum of compound **49a**.

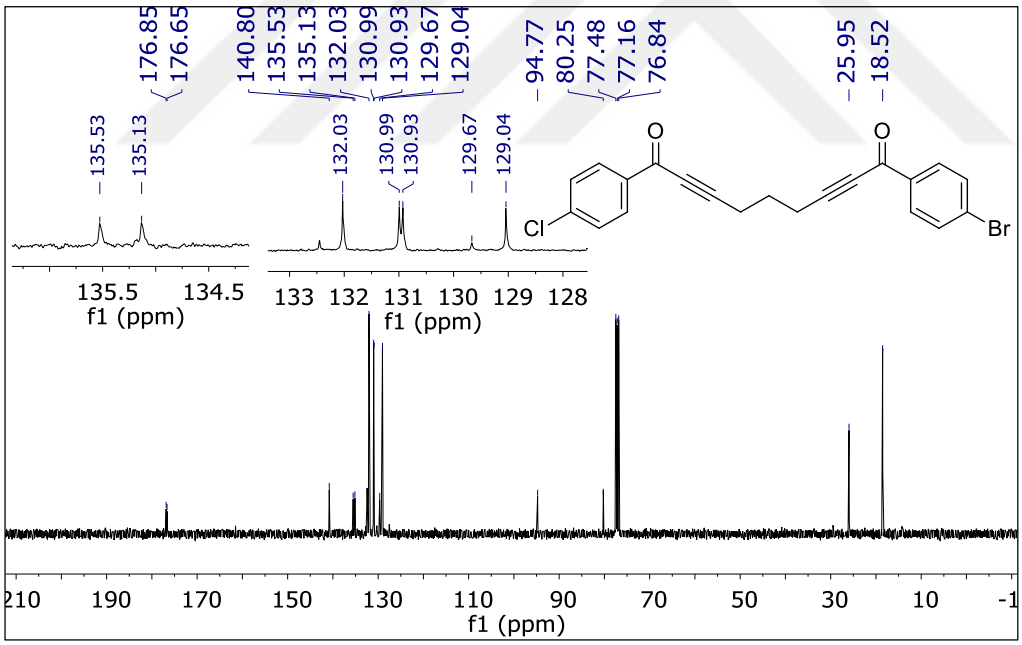


Figure 103. ^{13}C NMR spectrum of compound **49a**.

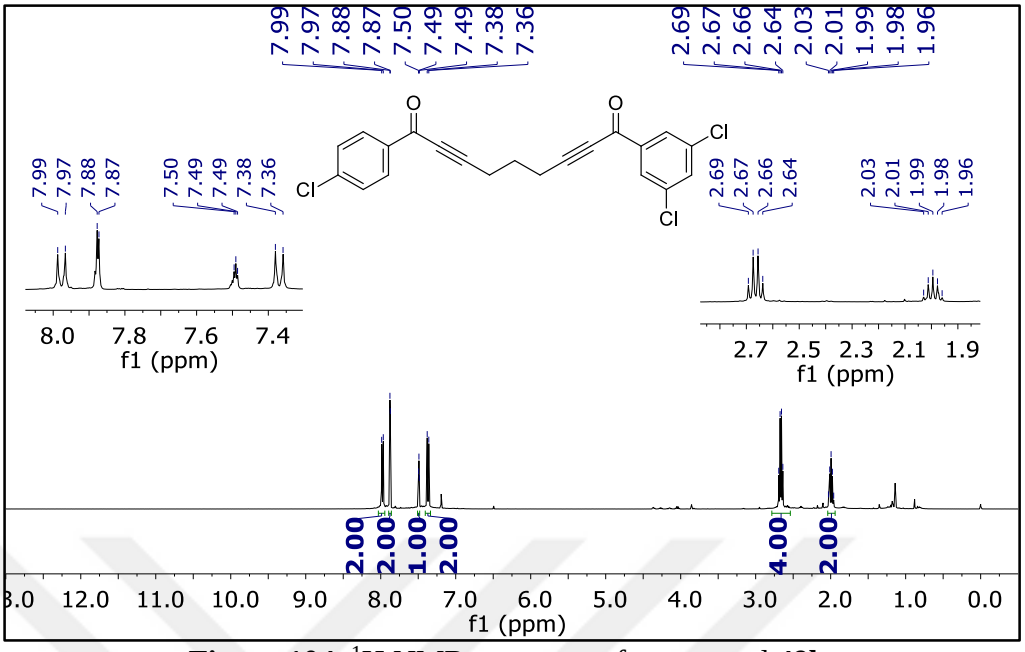


Figure 104. [1]H NMR spectrum of compound **49b**.

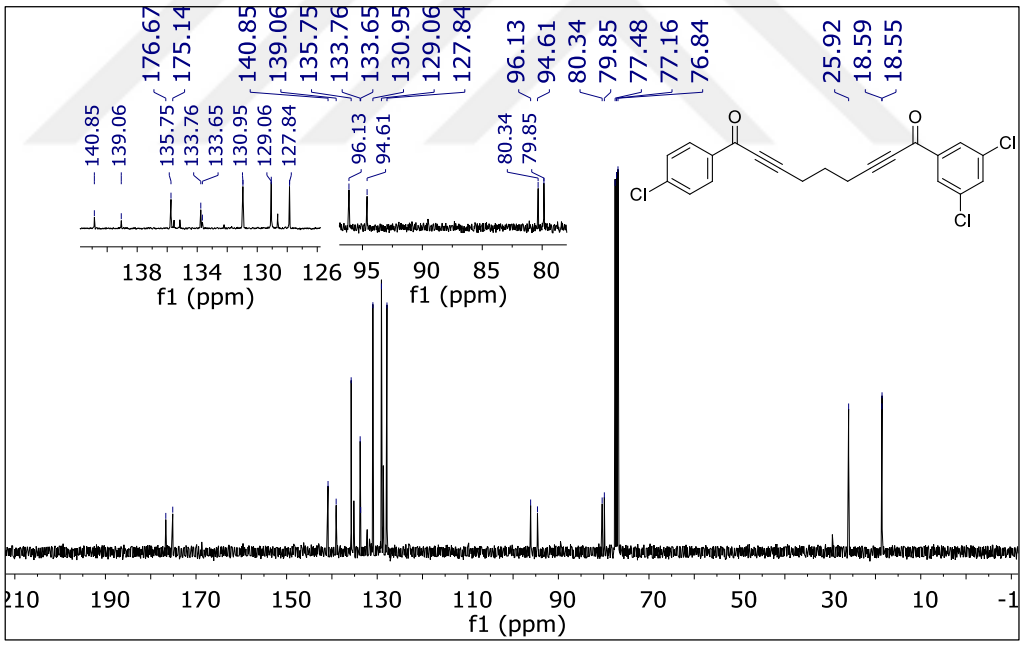


Figure 105. [13]C NMR spectrum of compound **49b**.

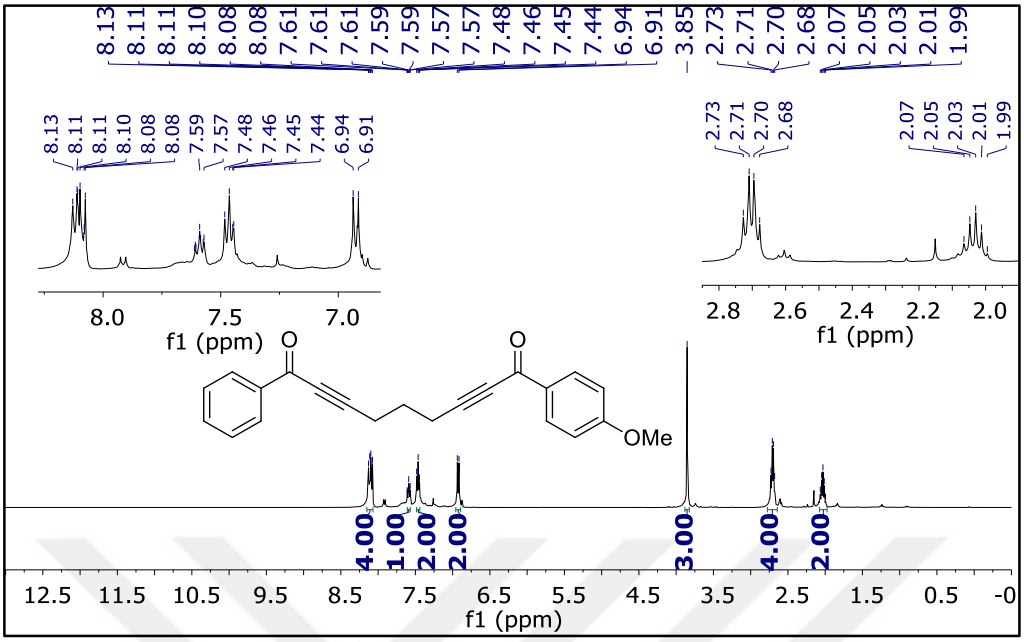


Figure 106. ^{1}H NMR spectrum of compound **49c**.

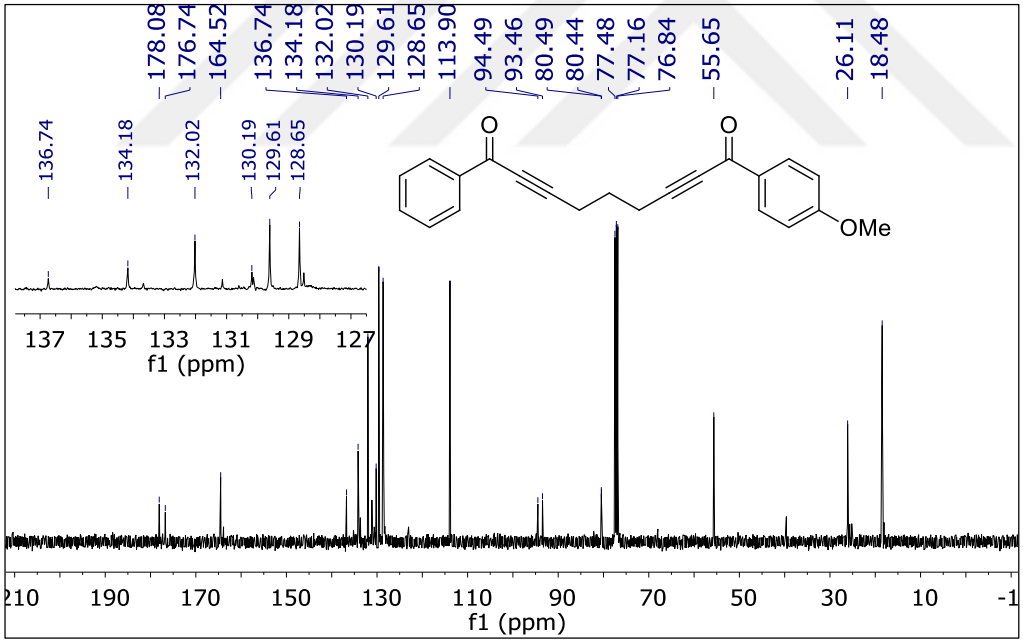


Figure 107. ^{13}C NMR spectrum of compound **49c**.

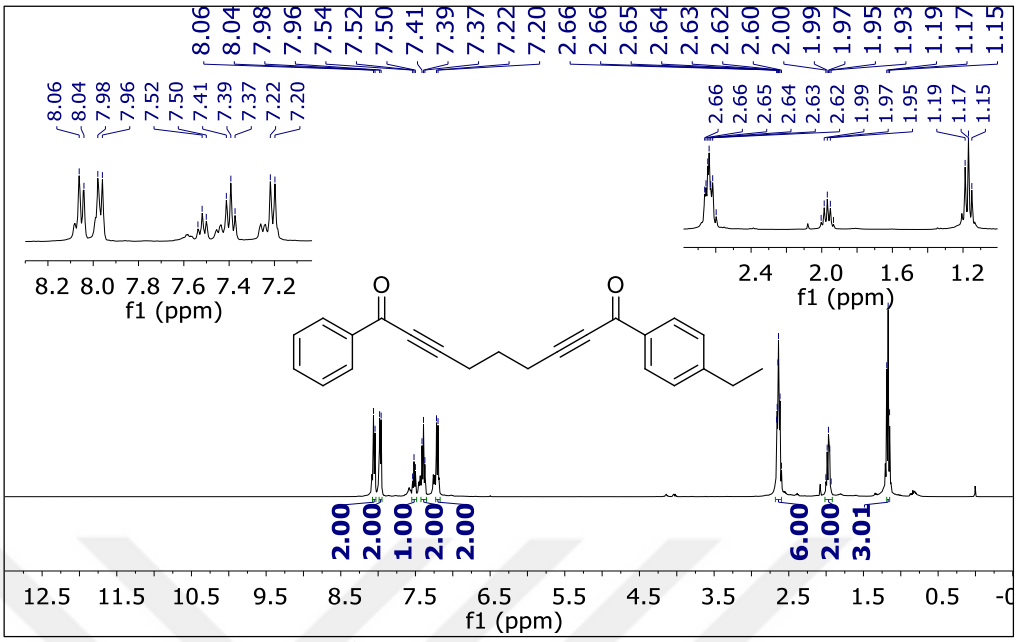


Figure 108. ^{1}H NMR spectrum of compound **49d**.

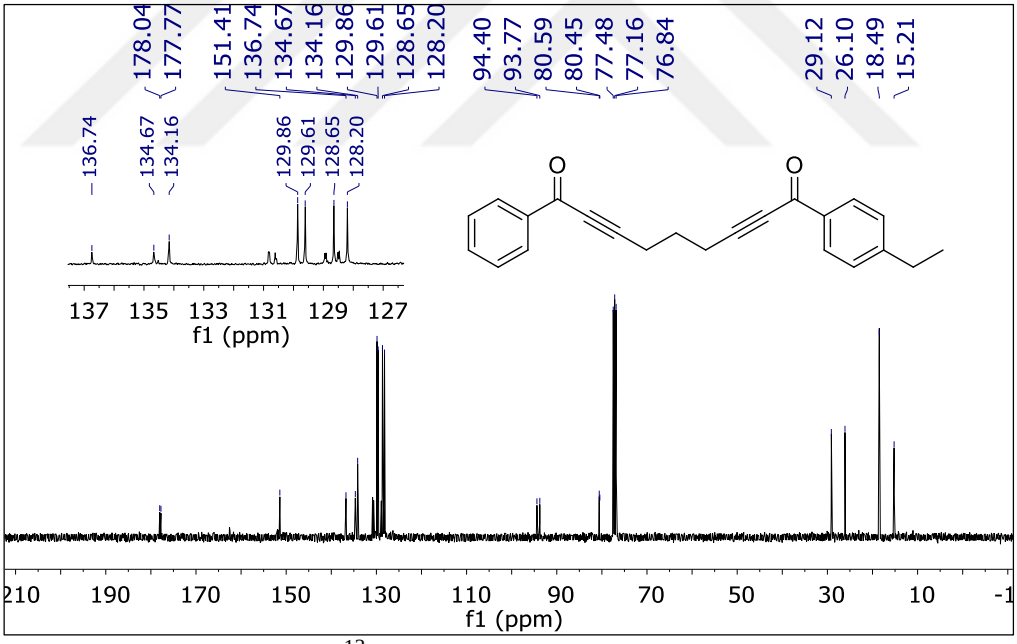


Figure 109. ^{13}C NMR spectrum of compound **49d**.

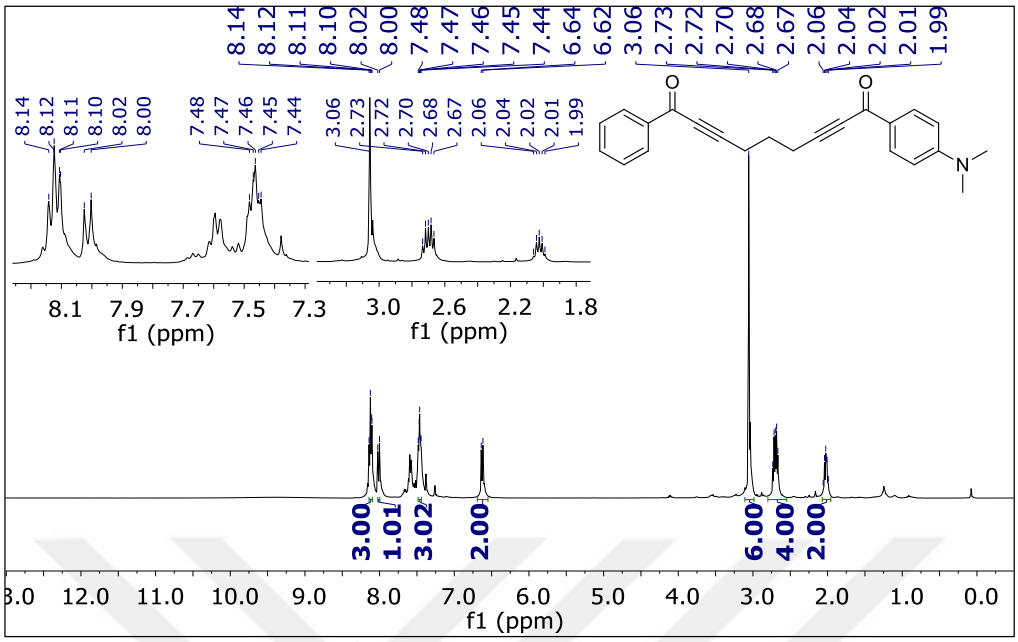


Figure 110. ^{1}H NMR spectrum of compound **49e**.

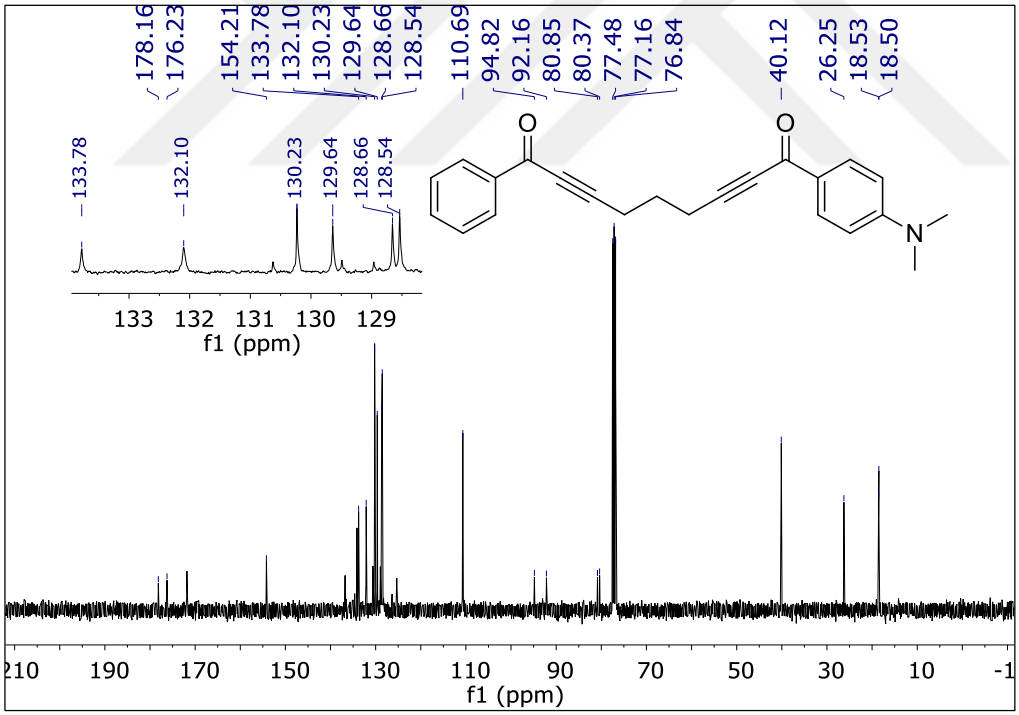


Figure 111. ^{13}C NMR spectrum of compound **49e**.

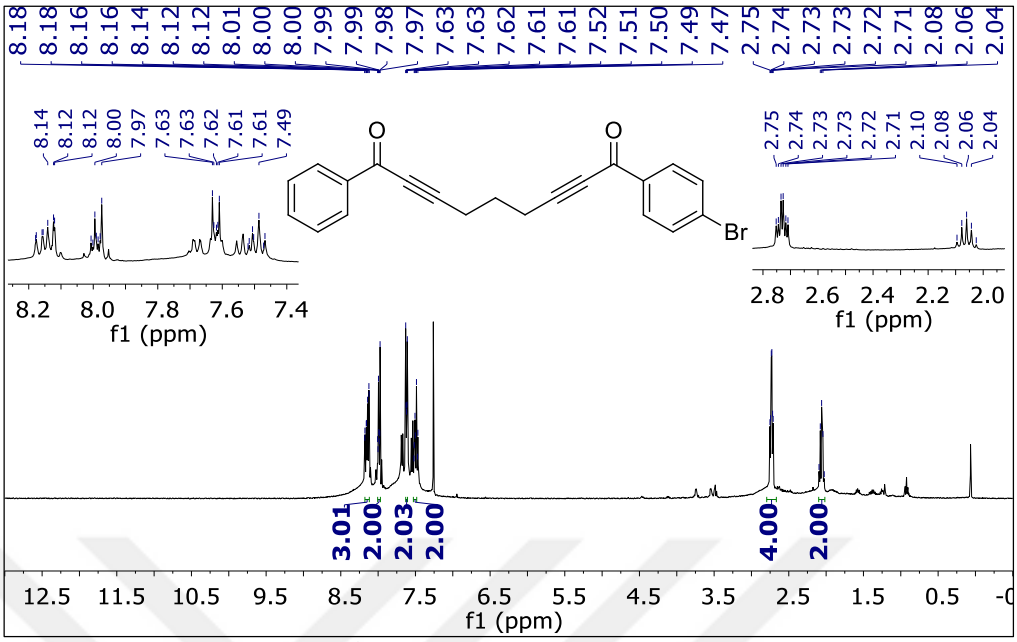


Figure 112. ^{1}H NMR spectrum of compound **49f**.

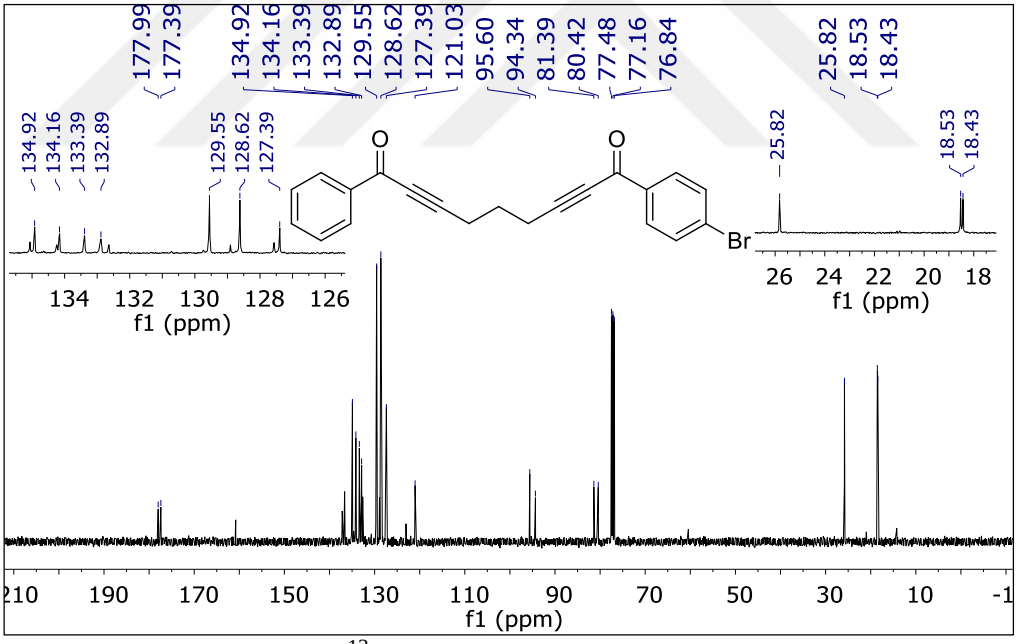


Figure 113. ^{13}C NMR spectrum of compound **49f**.

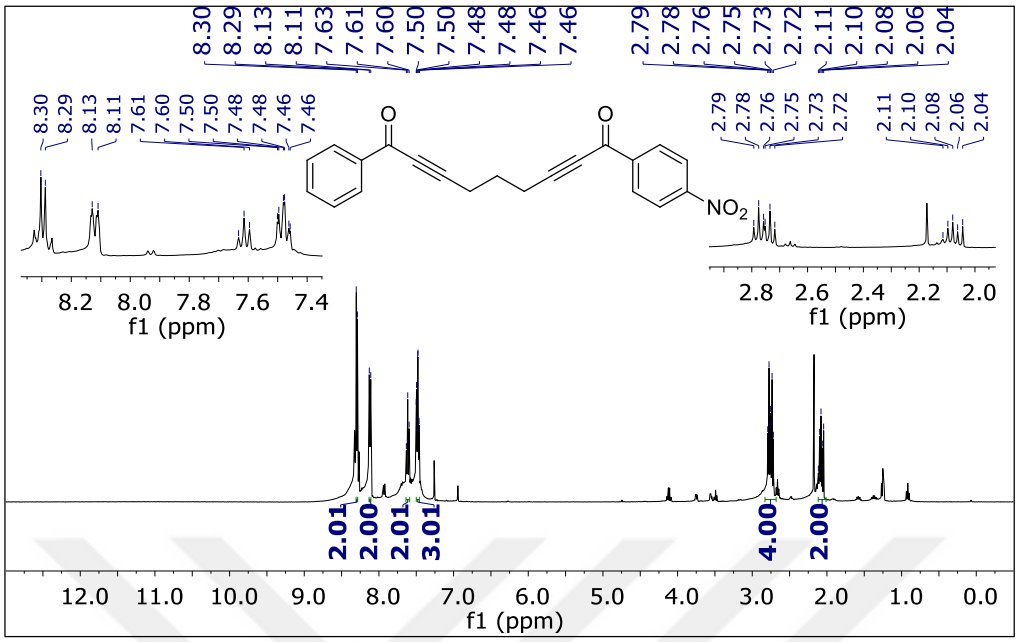


Figure 114. ^{1}H NMR spectrum of compound **49g**.

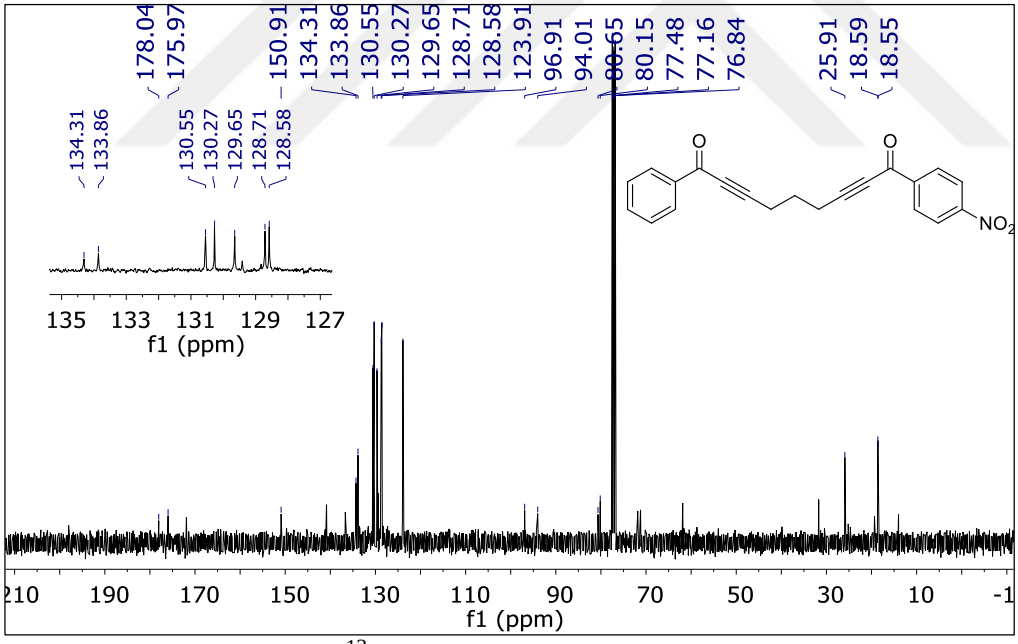


Figure 115. ^{13}C NMR spectrum of compound **49g**.

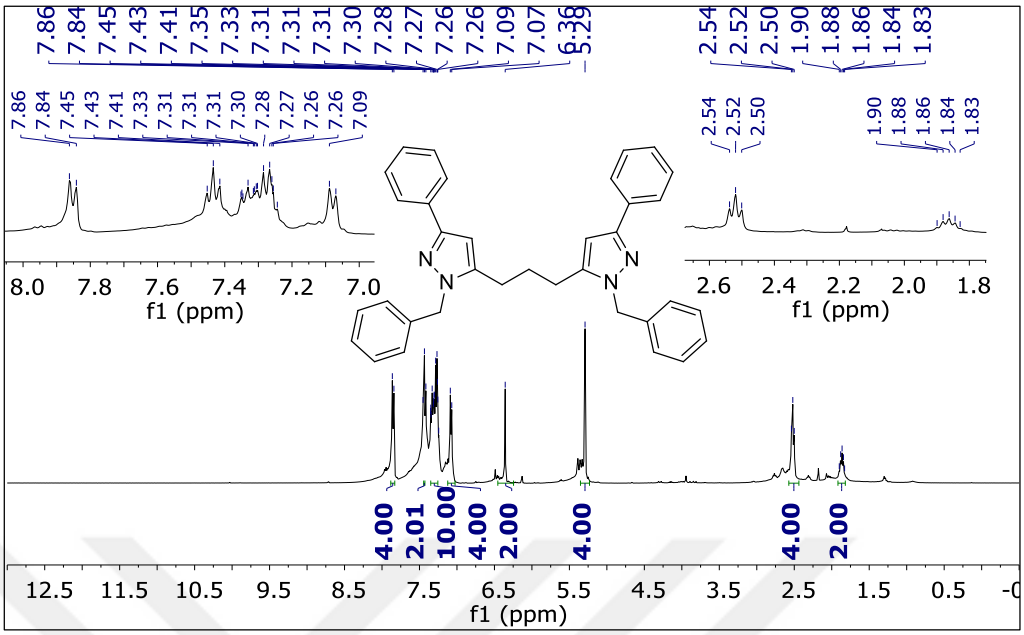


Figure 116. ^{1}H NMR spectrum of compound **38a**.

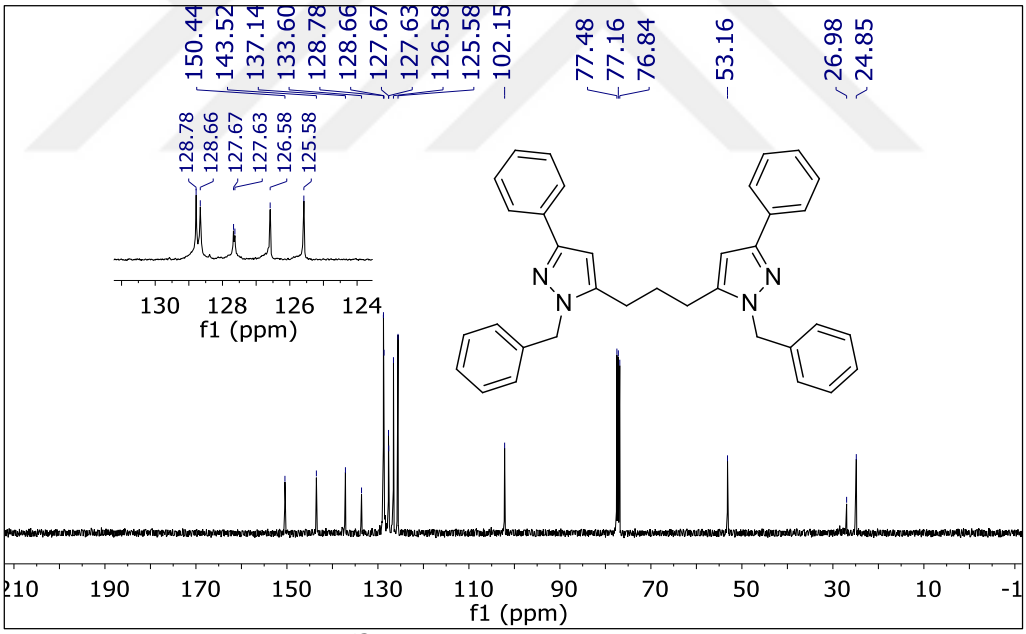


Figure 117. ^{13}C NMR spectrum of compound **38a**.

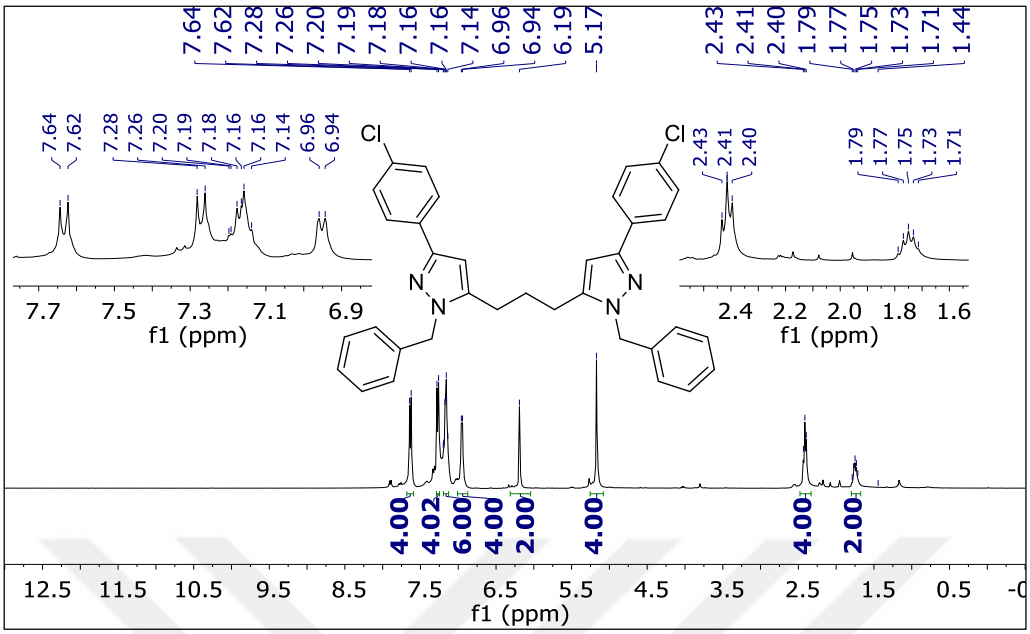


Figure 118. ^{1}H NMR spectrum of compound **38b**.

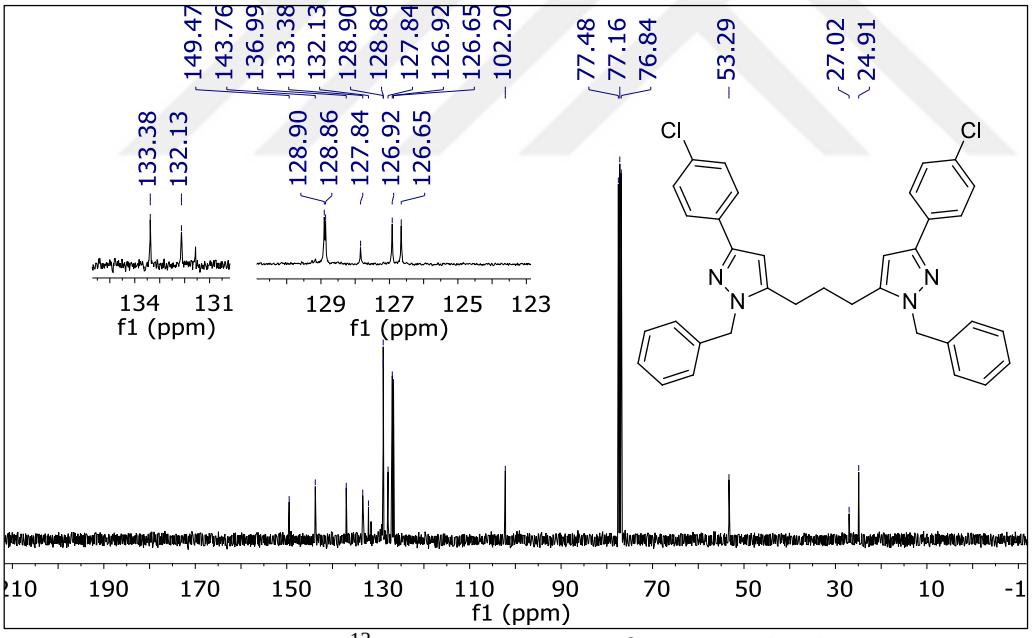


Figure 119. ^{13}C NMR spectrum of compound **38b**.

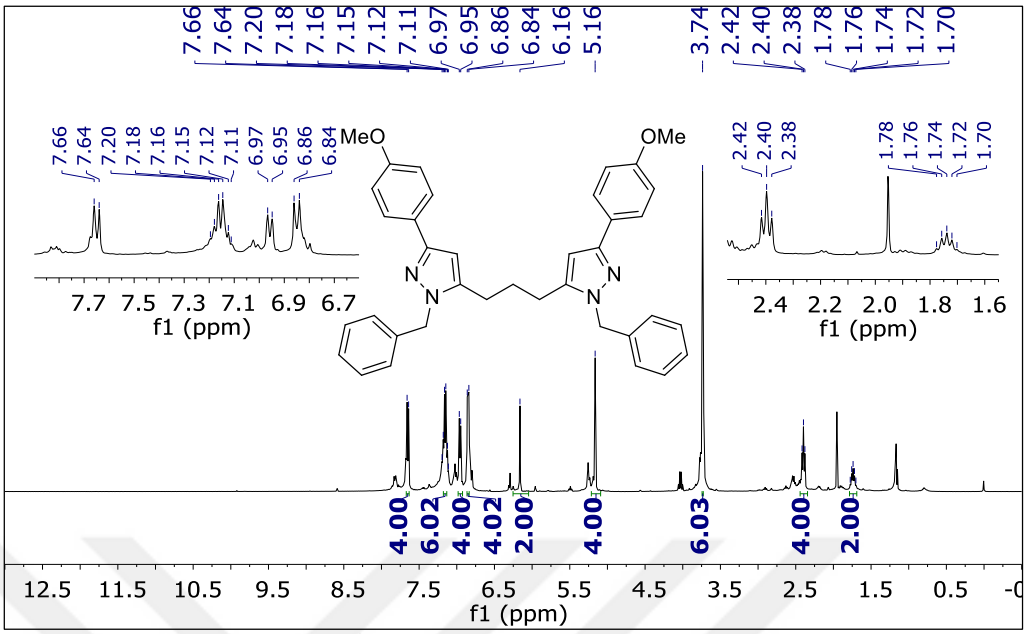


Figure 120. ^{1}H NMR spectrum of compound **38c**.

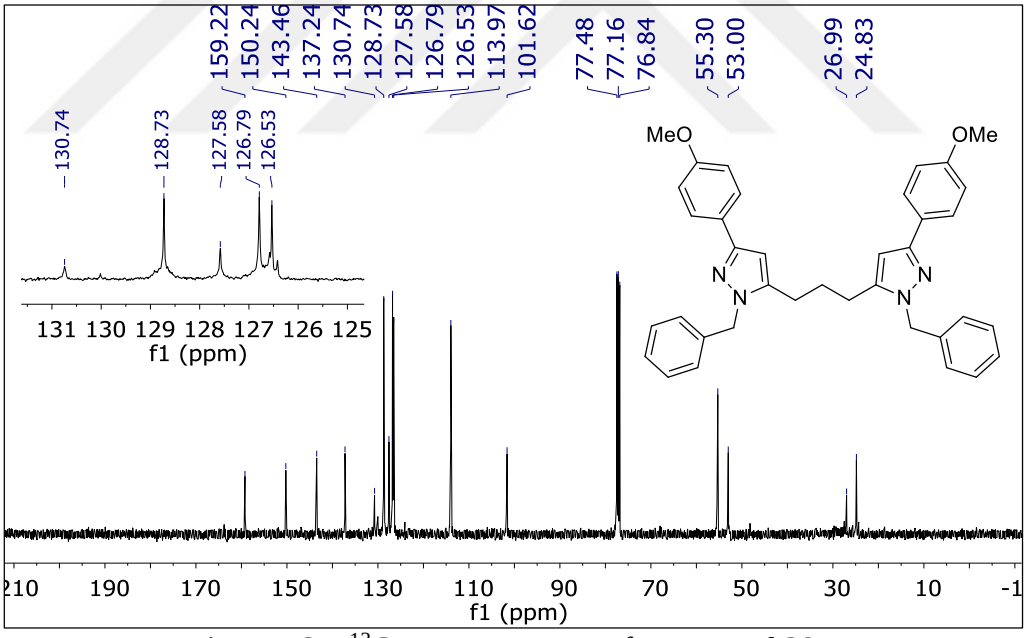


Figure 121. ^{13}C NMR spectrum of compound **38c**.

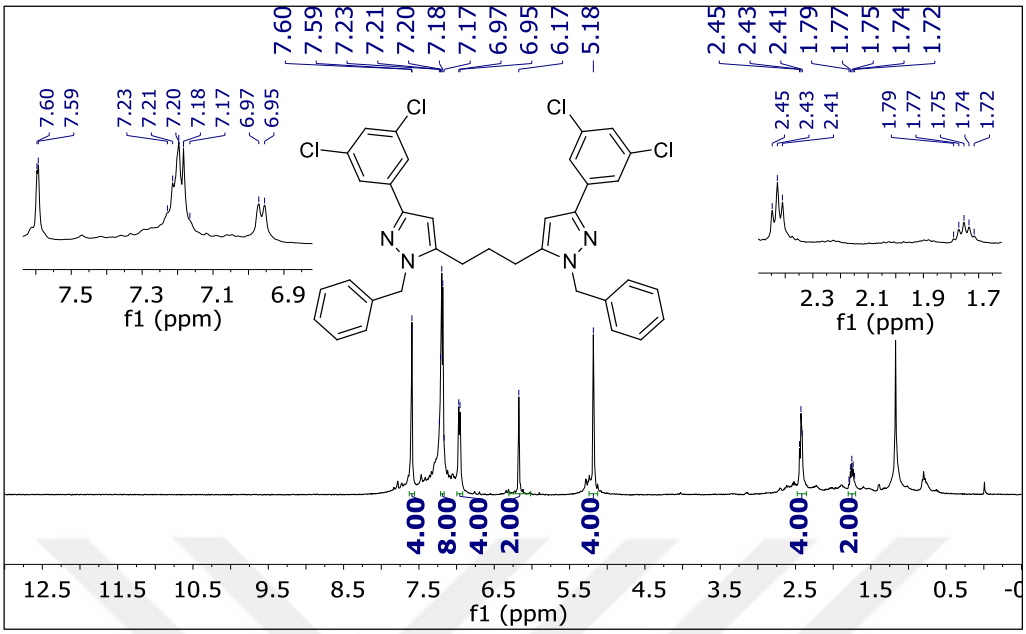


Figure 122. ^{1}H NMR spectrum of compound **38d**.

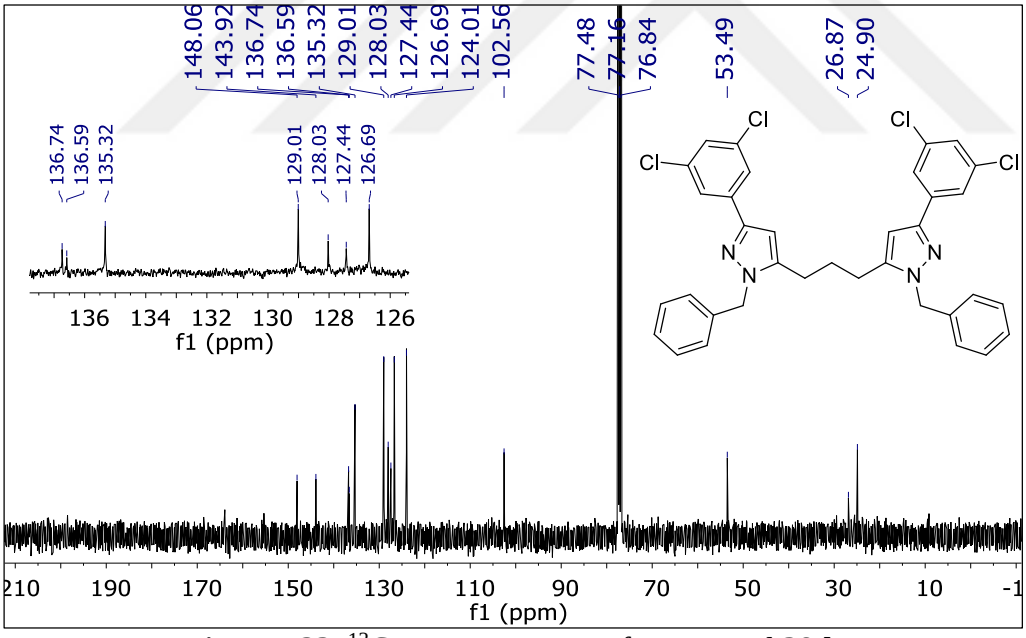


Figure 123. ^{13}C NMR spectrum of compound **38d**.

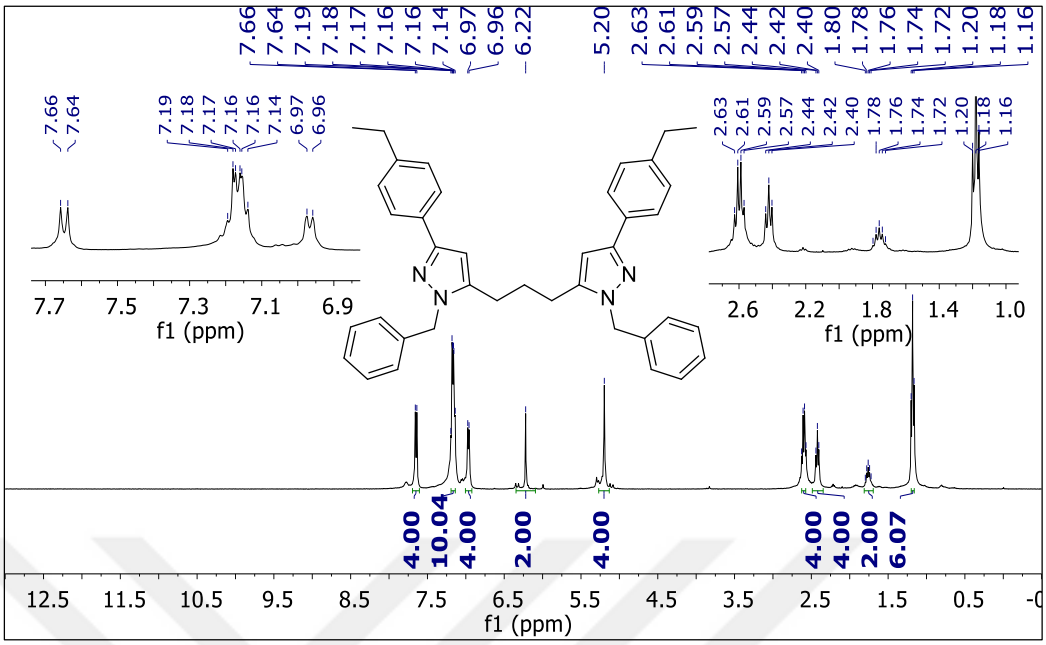


Figure 124. [1]H NMR spectrum of compound **38e**.

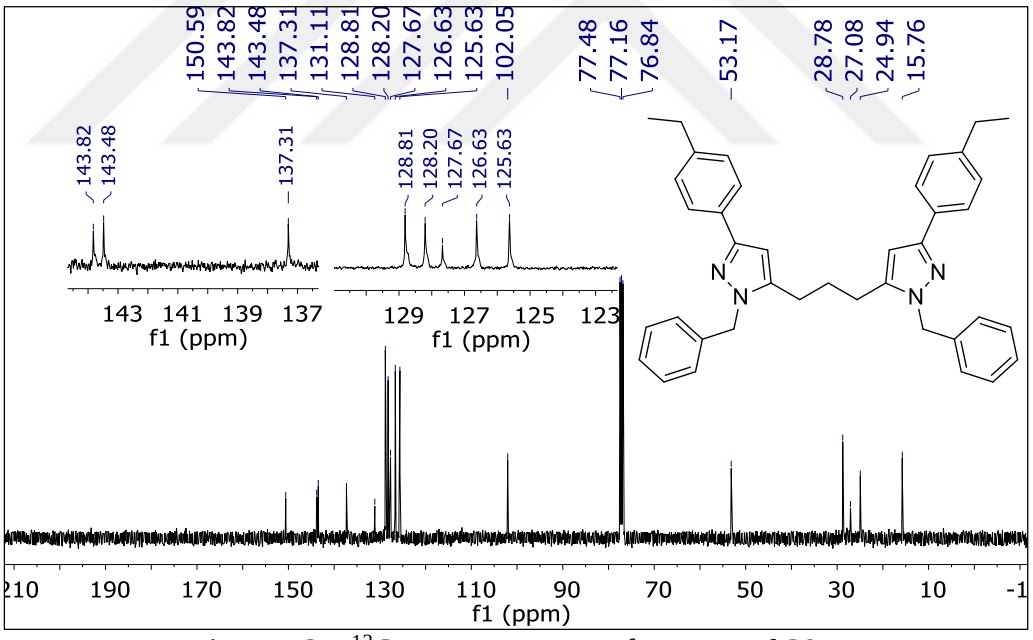


Figure 125. [13]C NMR spectrum of compound **38e**.

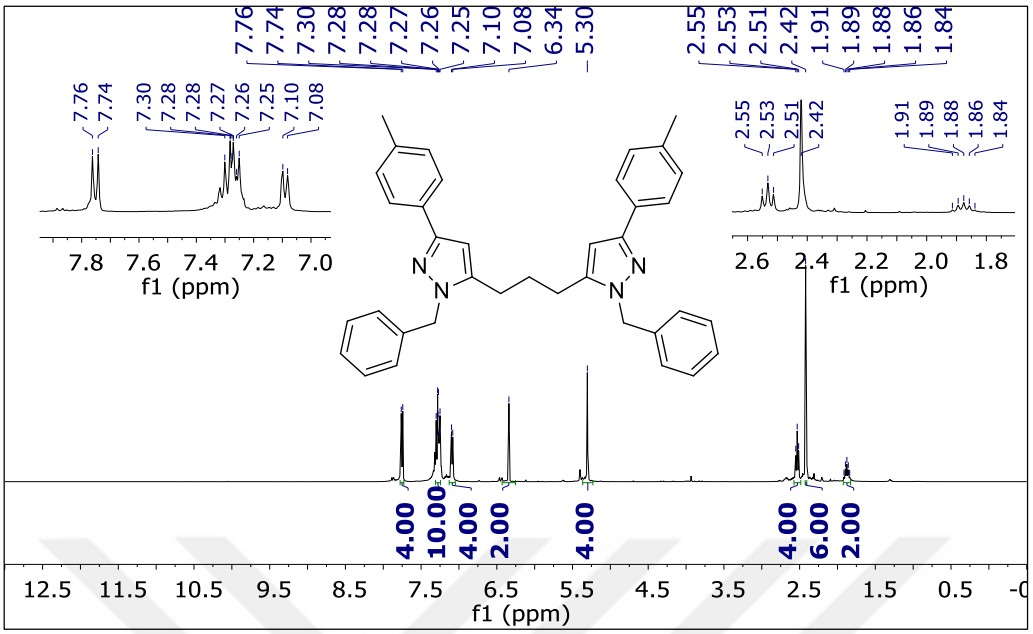


Figure 126. ^{1}H NMR spectrum of compound **38f**.

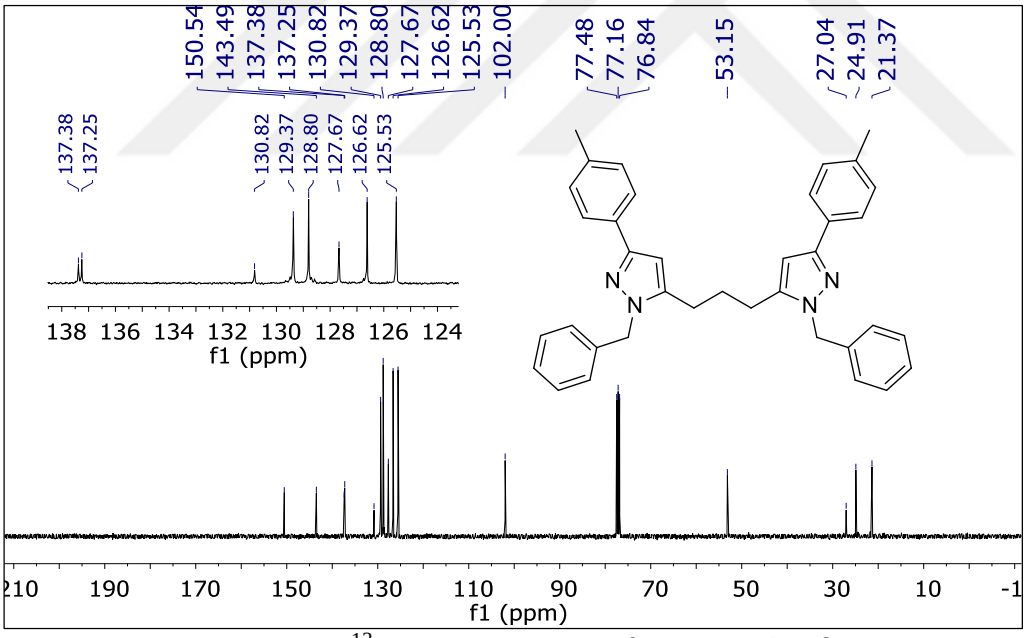


Figure 127. ^{13}C NMR spectrum of compound **38f**.

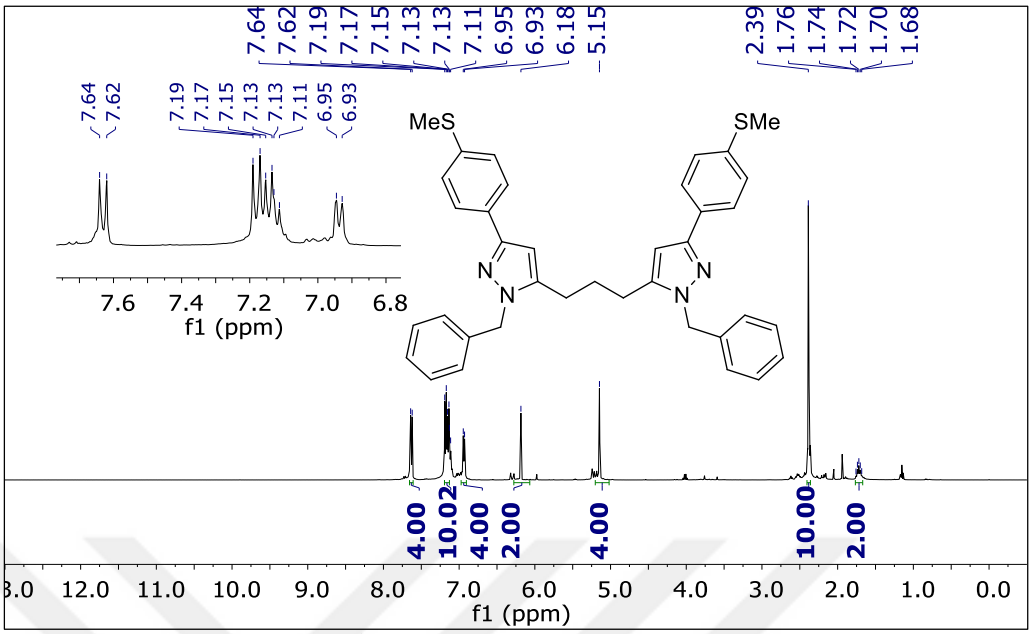


Figure 128. ^{1}H NMR spectrum of compound **38g**.

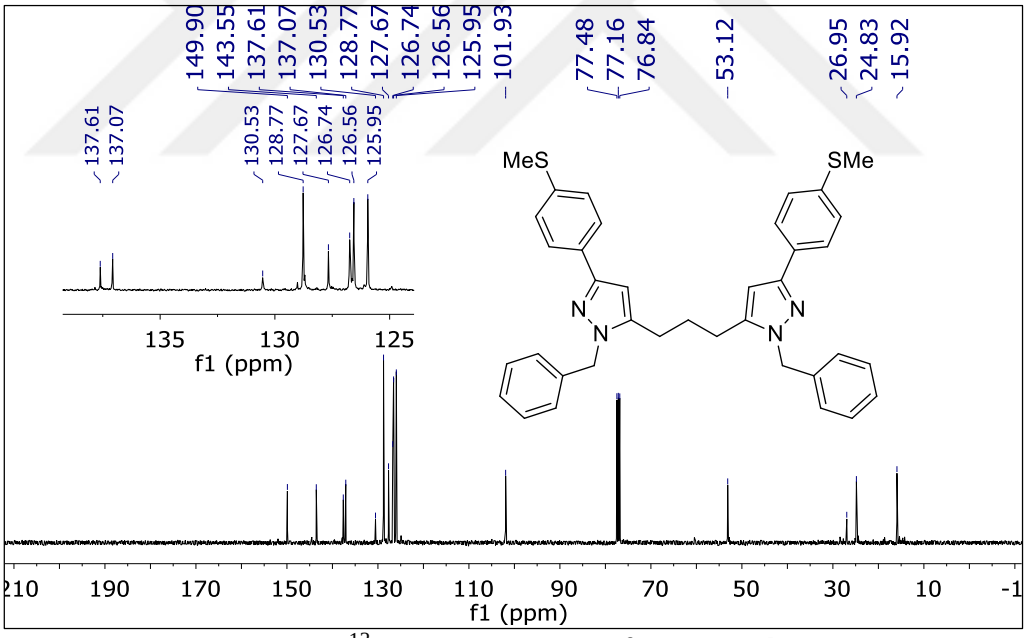


Figure 129. ^{13}C NMR spectrum of compound **38g**.

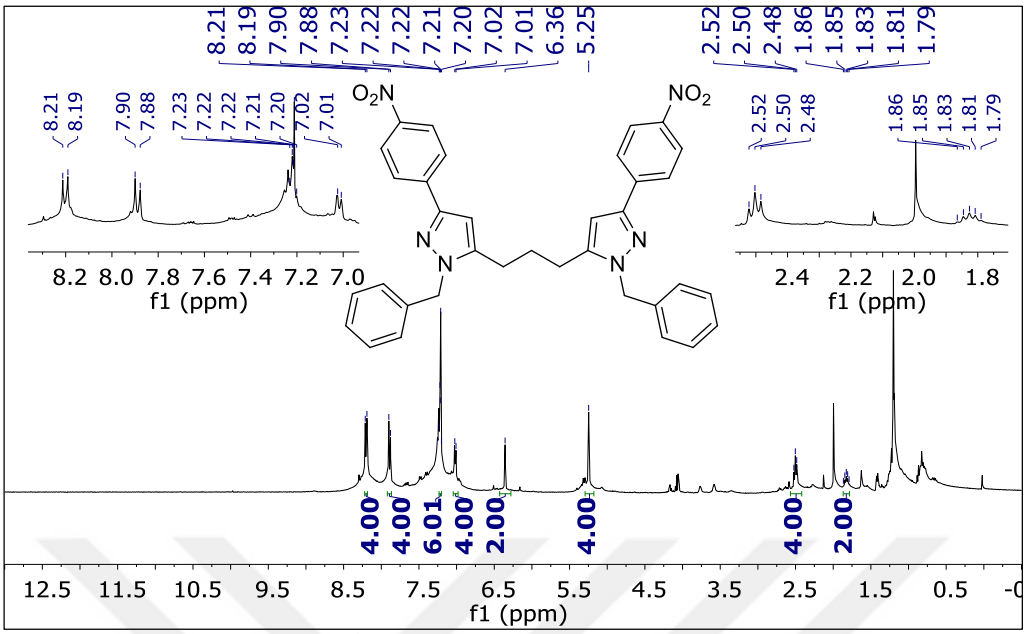


Figure 130. ^{1}H NMR spectrum of compound **38h**.

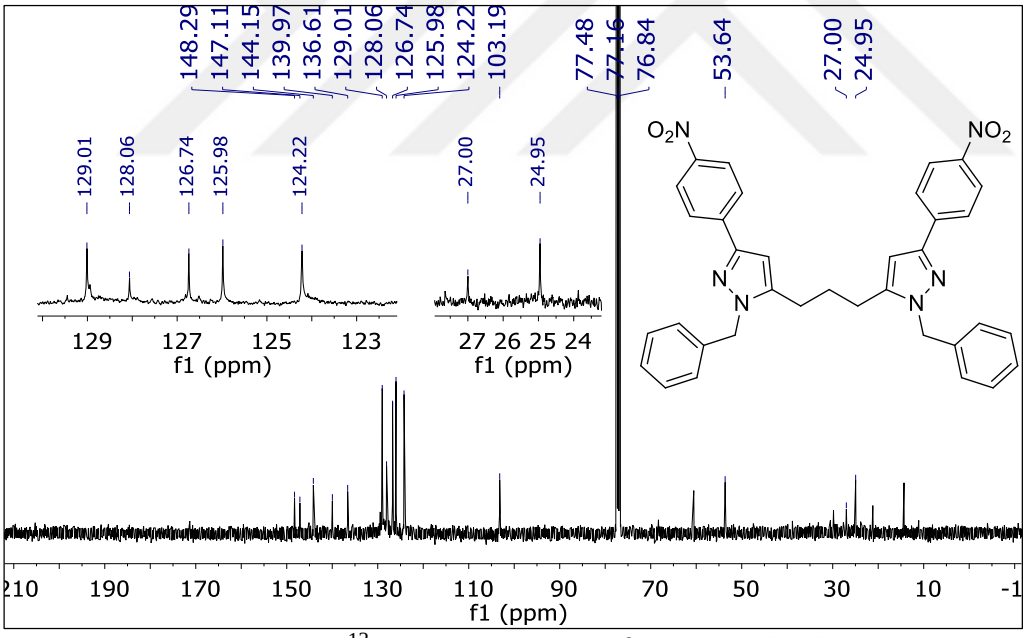


Figure 131. ^{13}C NMR spectrum of compound **38h**.

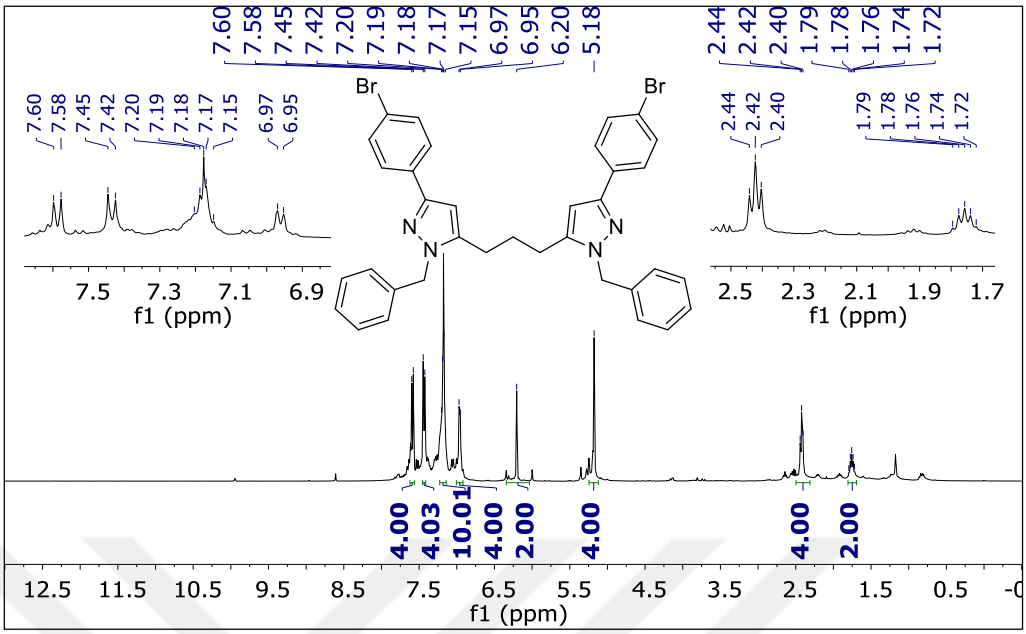


Figure 132. ^{1}H NMR spectrum of compound **38i**.

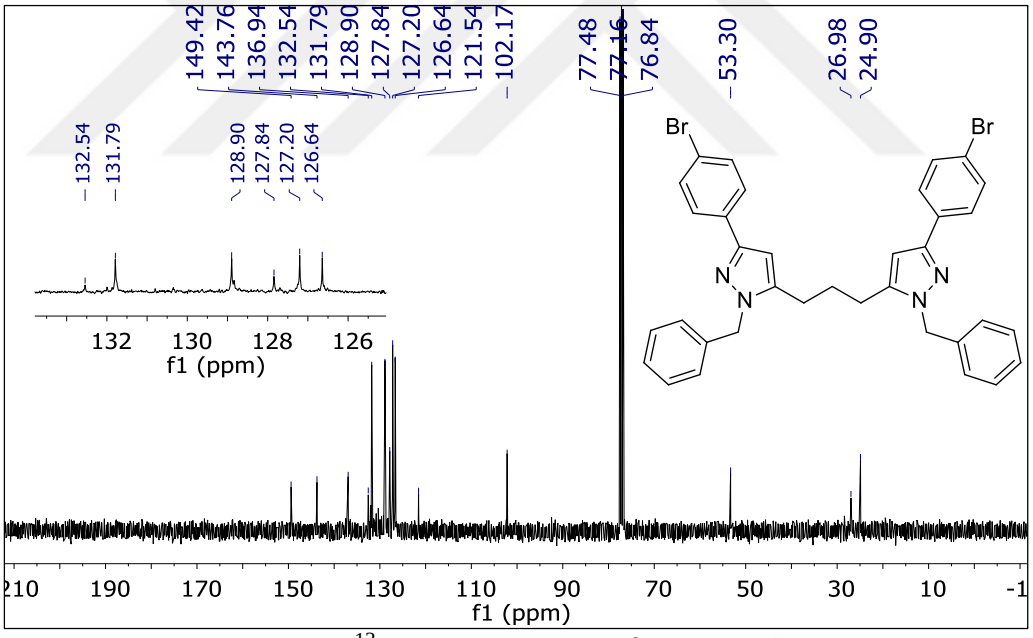


Figure 133. ^{13}C NMR spectrum of compound **38i**.

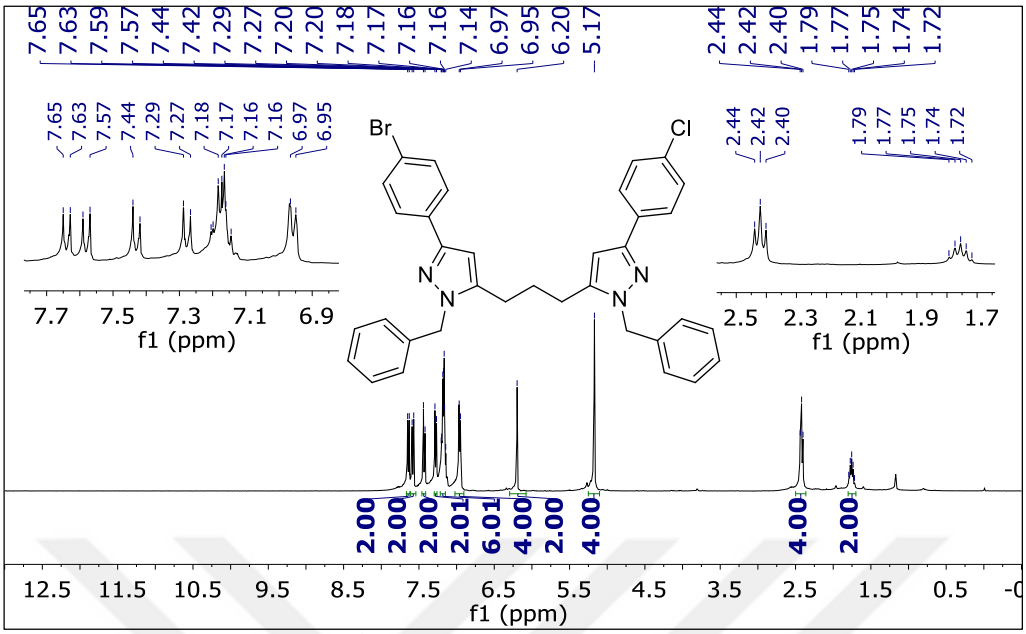


Figure 134. ^{1}H NMR spectrum of compound **38j**.

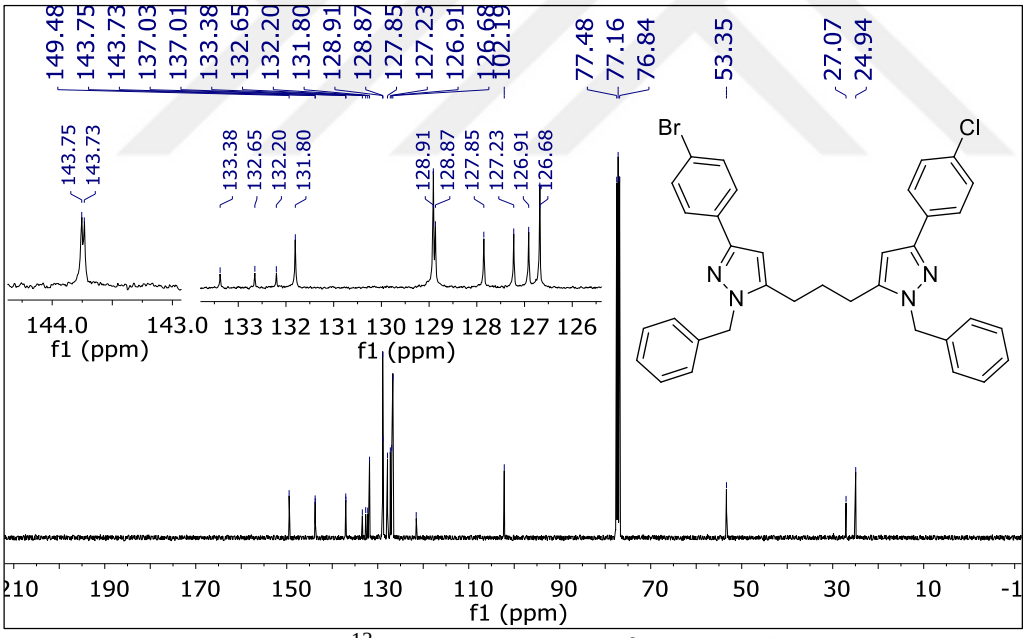


Figure 135. ^{13}C NMR spectrum of compound **38j**.

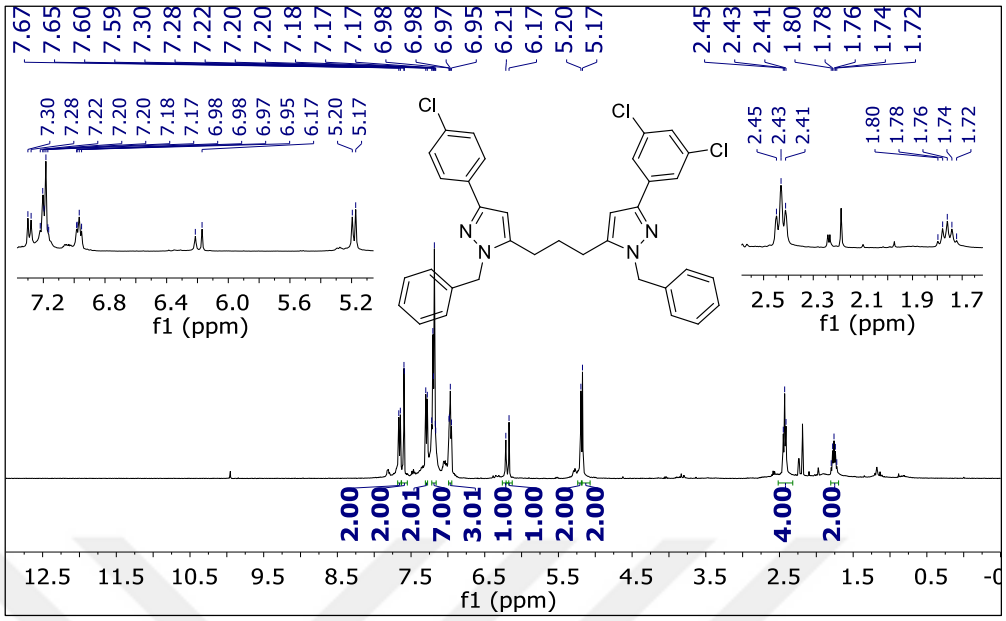


Figure 136. ^{1}H NMR spectrum of compound **38k**.

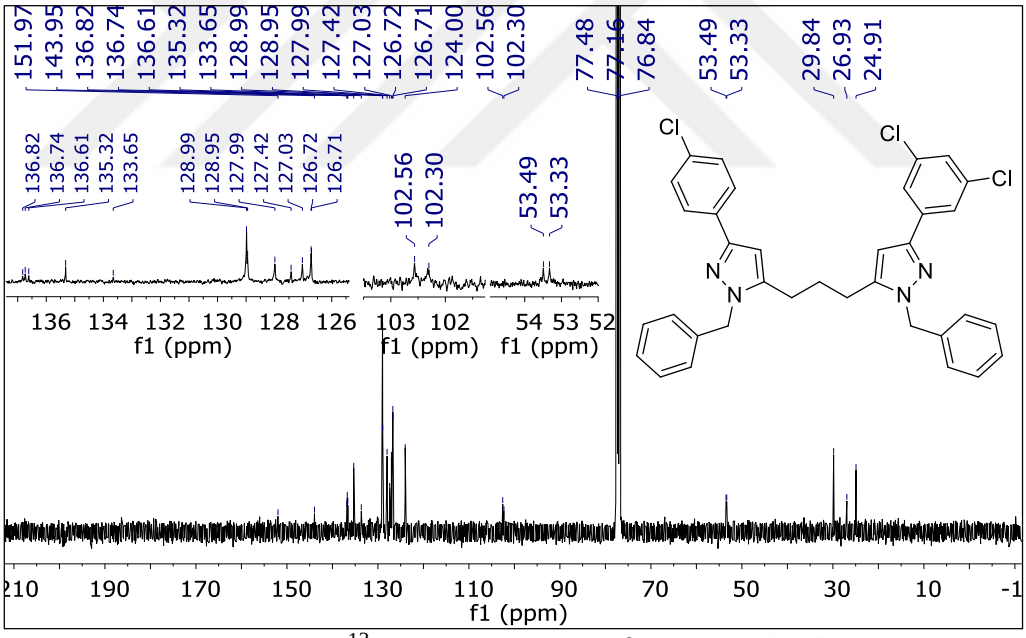


Figure 137. ^{13}C NMR spectrum of compound **38k**.

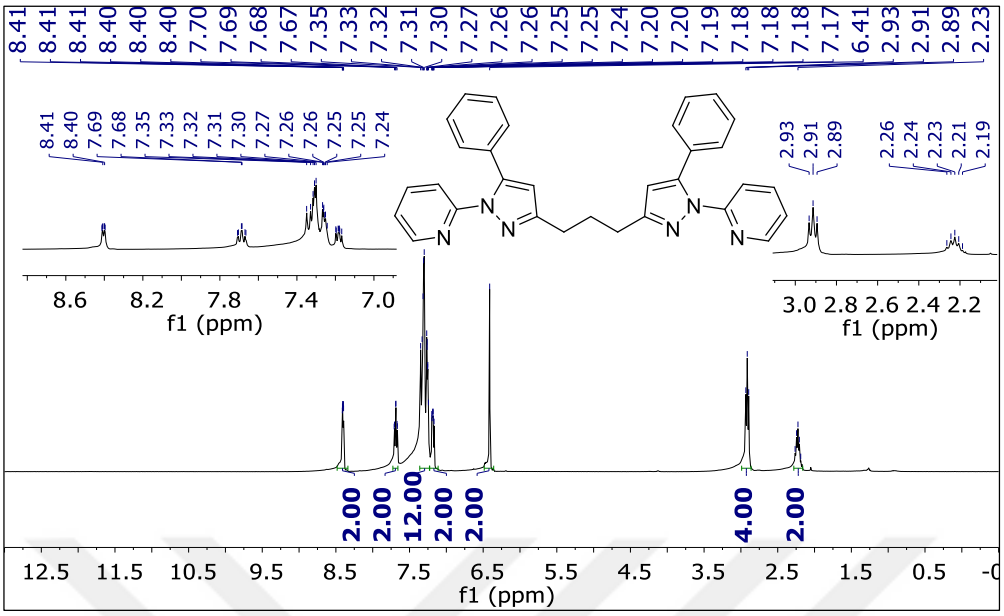


Figure 138. ^{1}H NMR spectrum of compound **40a**.

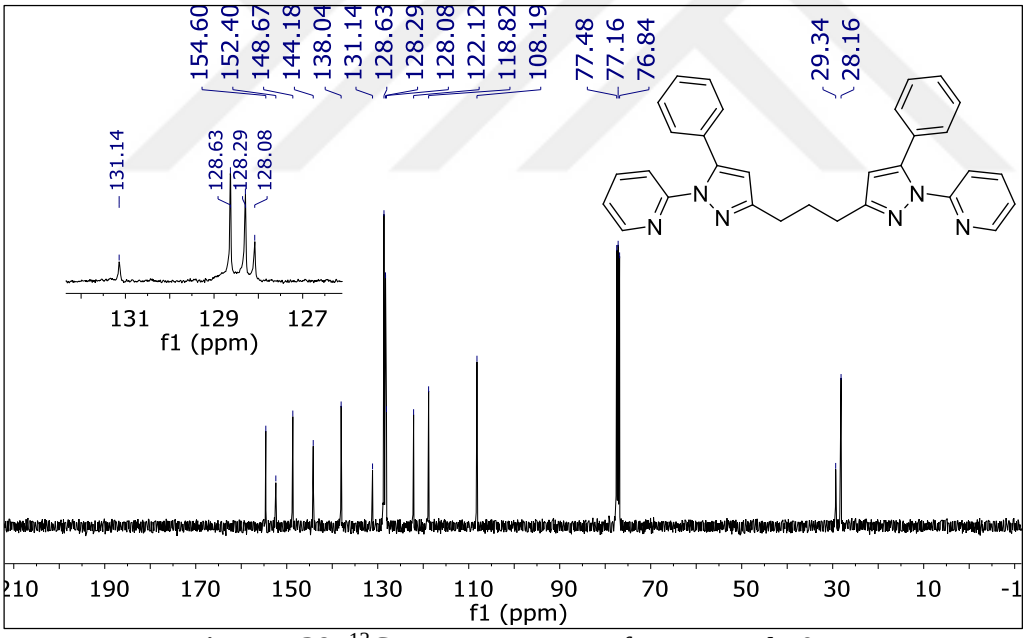


Figure 139. ^{13}C NMR spectrum of compound **40a**.

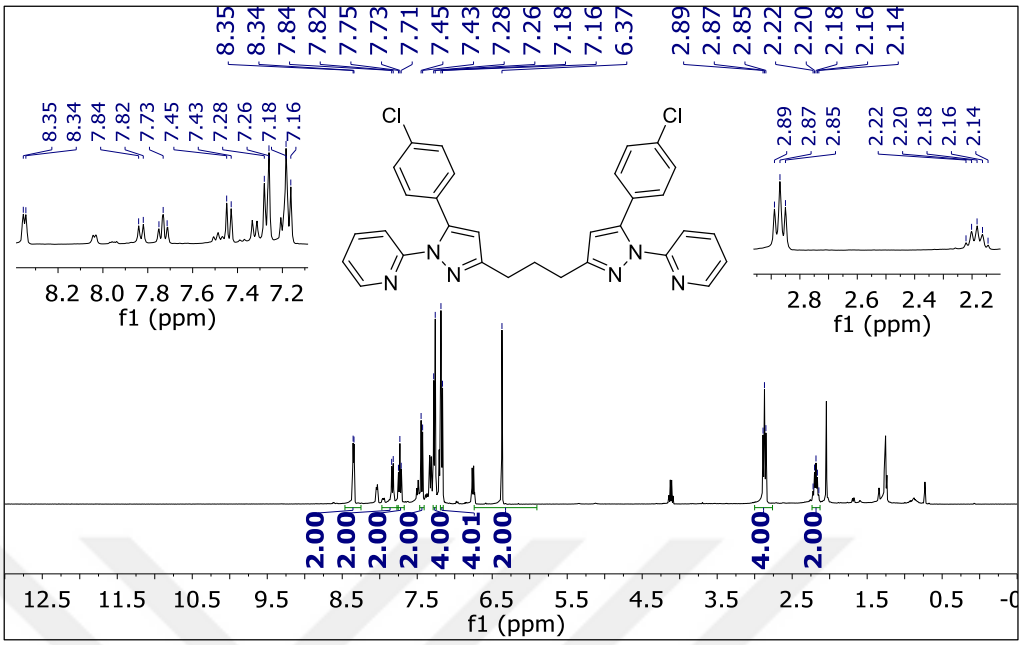


Figure 140. ^{1}H NMR spectrum of compound **40b**.

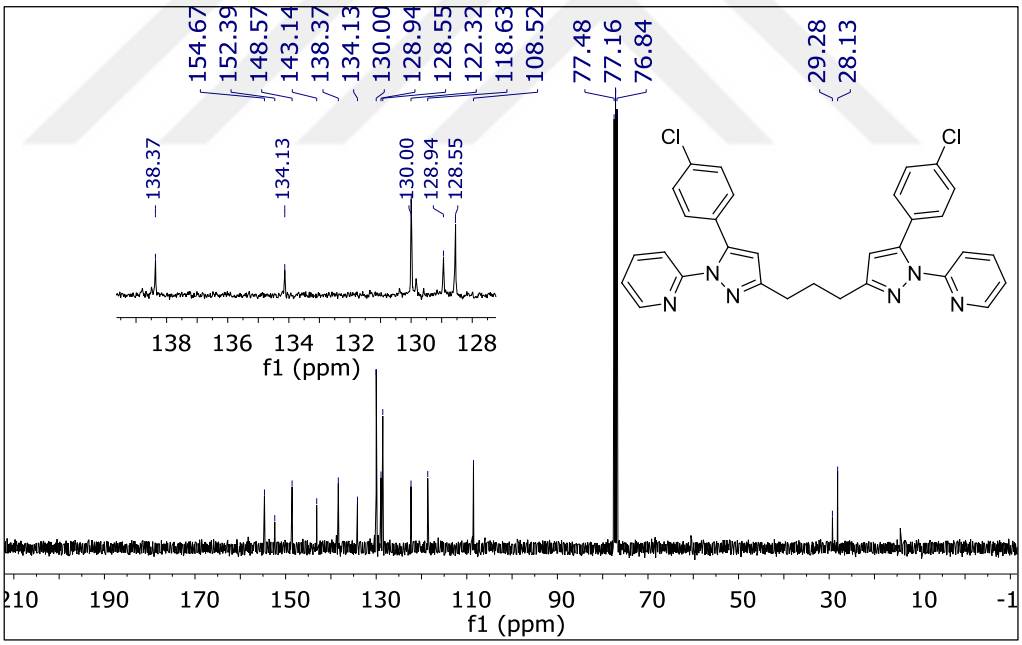


Figure 141. ^{13}C NMR spectrum of compound **40b**.

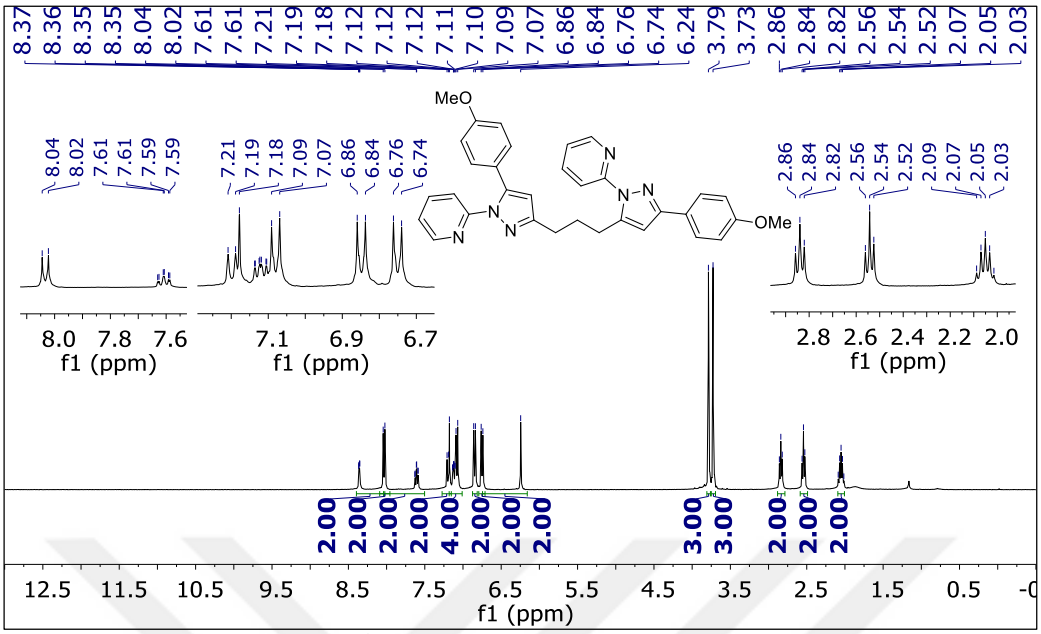


Figure 142. ^{1}H NMR spectrum of compound **40c**.

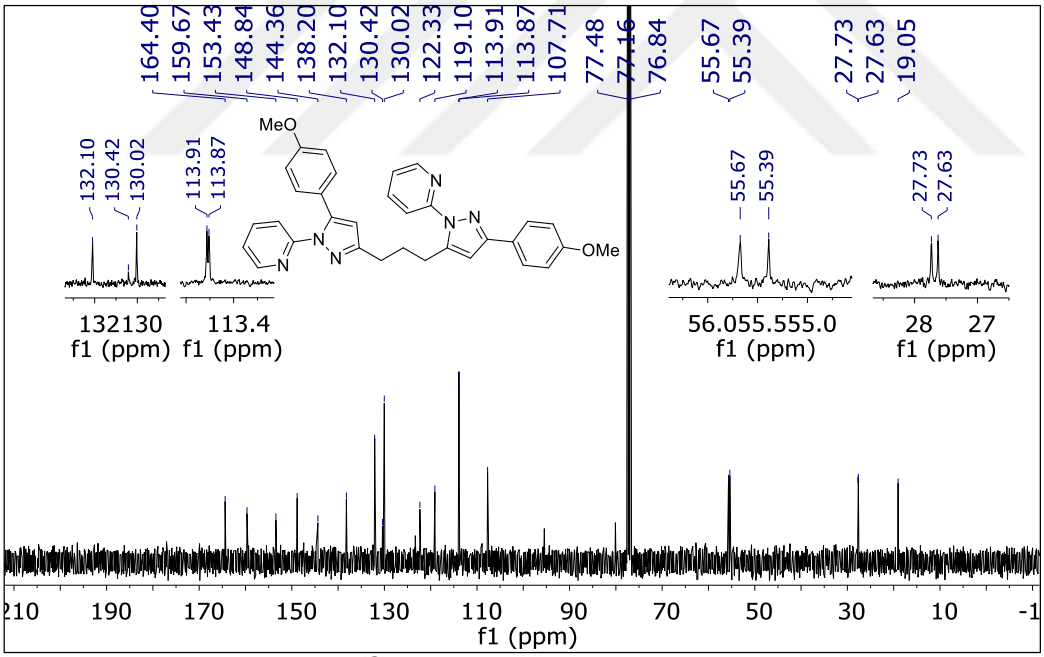


Figure 143. ^{13}C NMR spectrum of compound **40c**.

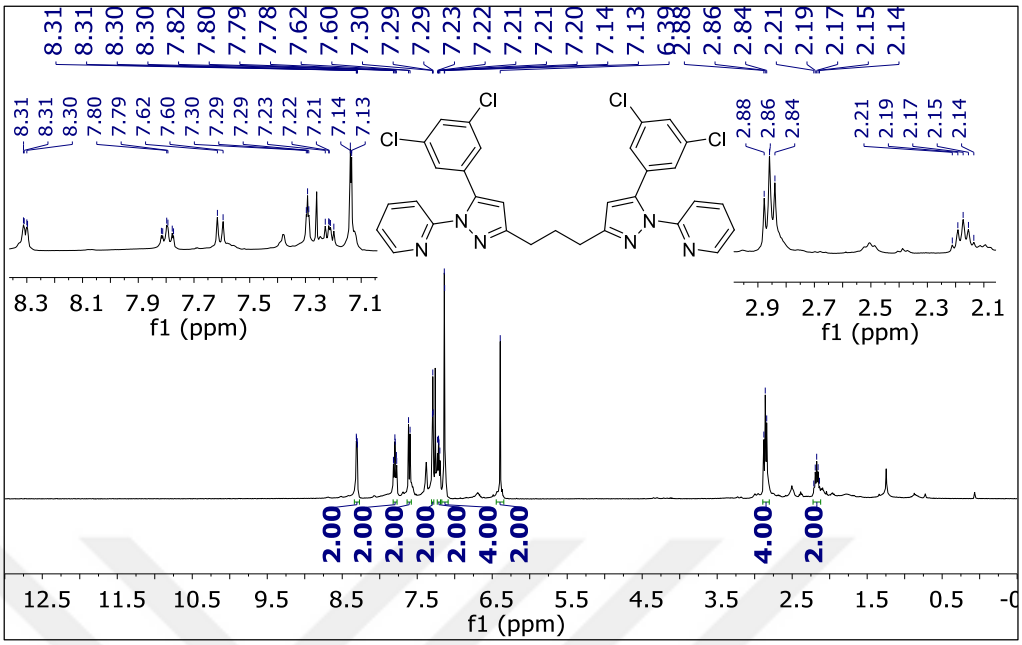


Figure 144. [1]H NMR spectrum of compound **40d**.

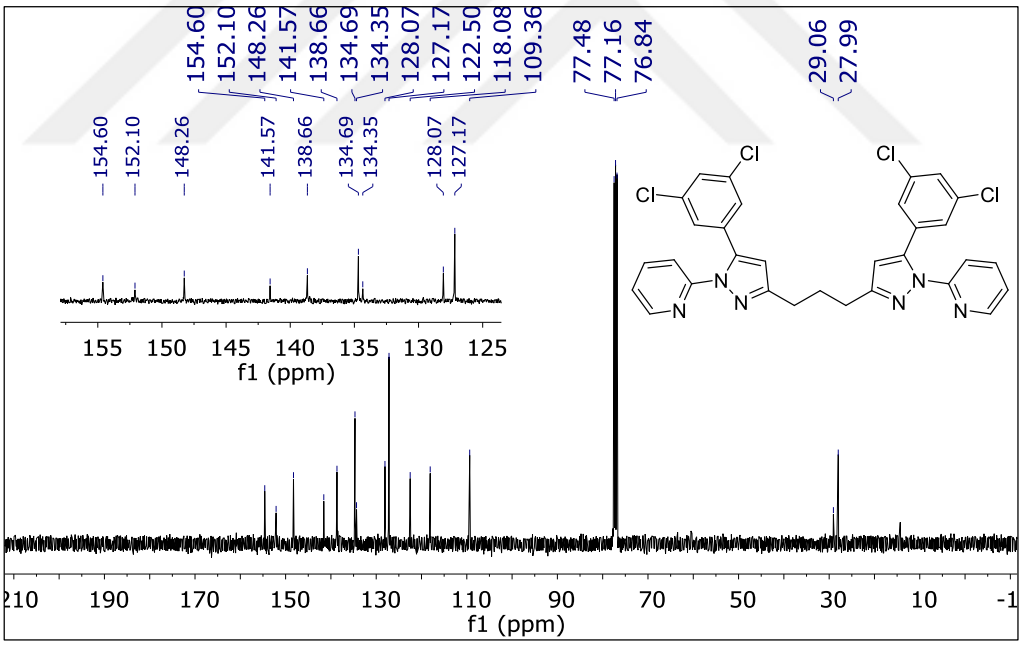


Figure 145. [13]C NMR spectrum of compound **40d**.

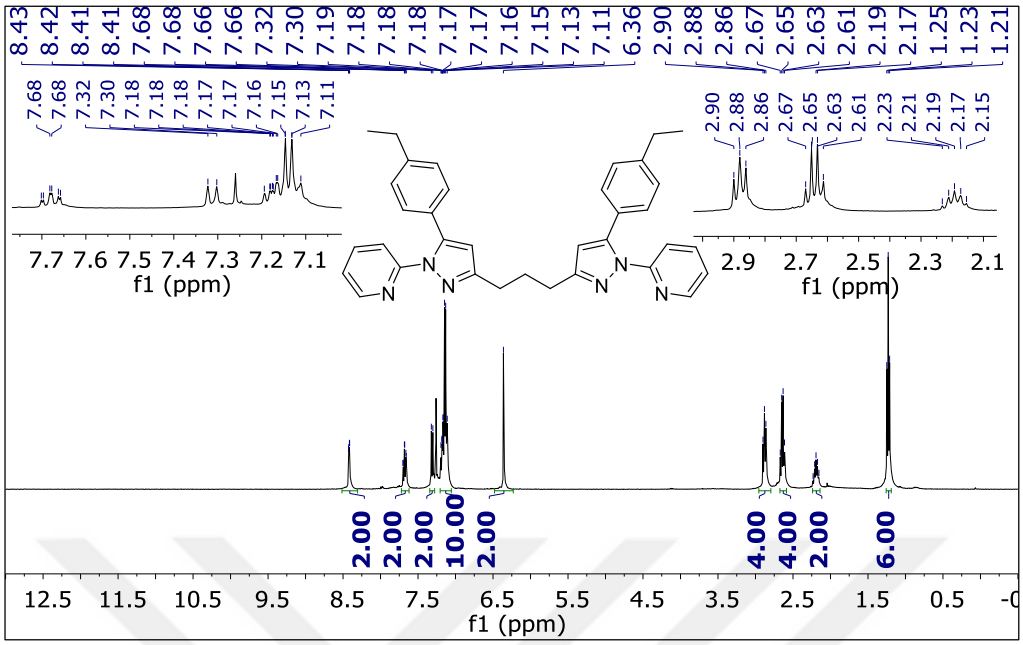


Figure 146. ^{1}H NMR spectrum of compound **40e**.

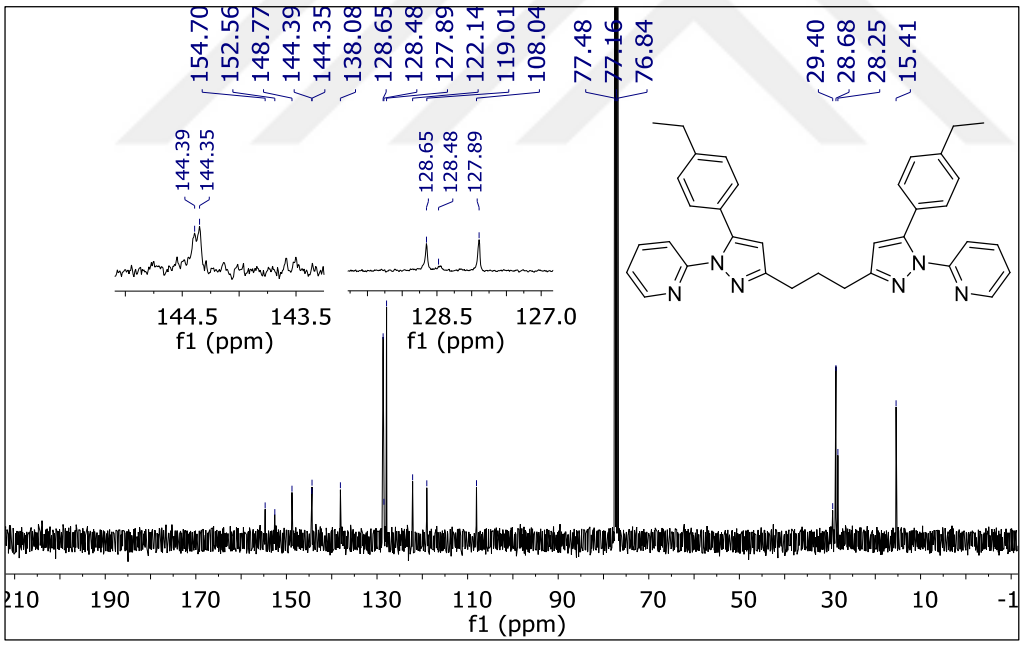


Figure 147. ^{13}C NMR spectrum of compound **40e**.

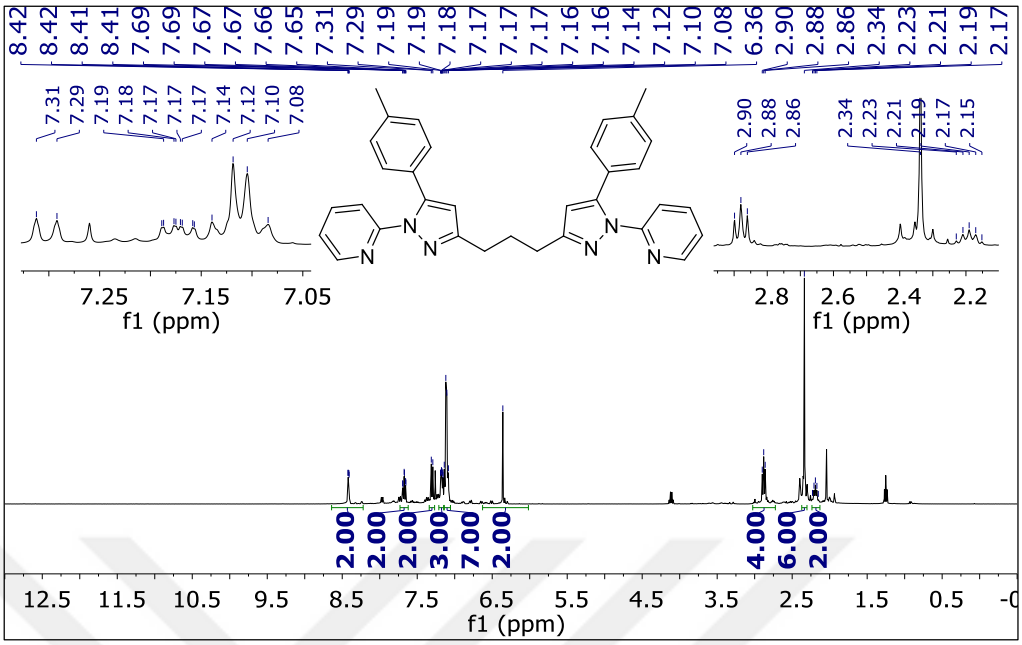


Figure 148. [1]H NMR spectrum of compound **40f**.

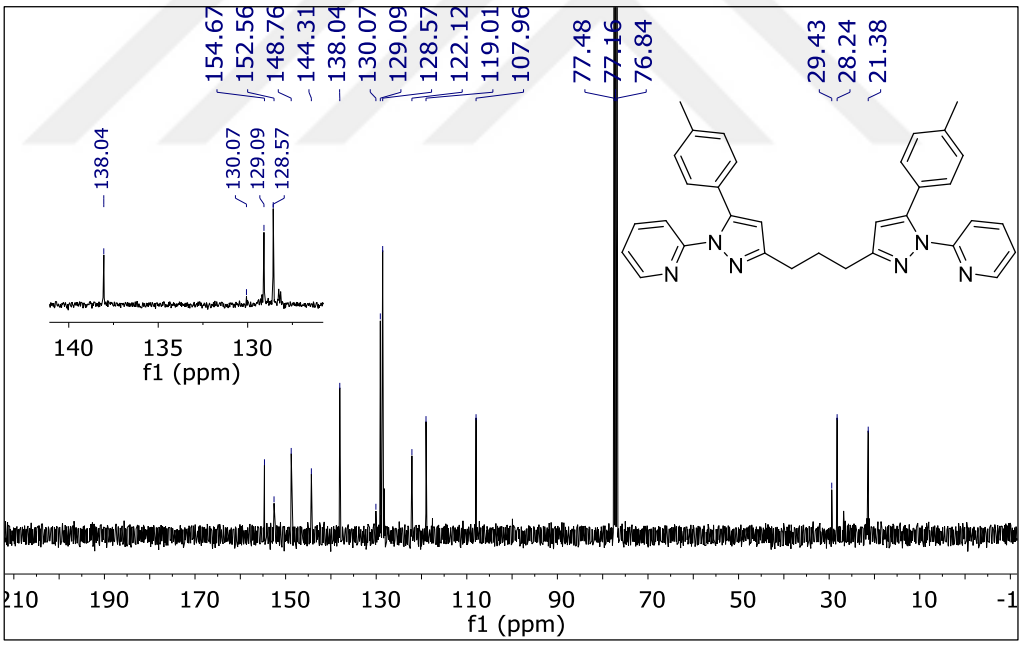


Figure 149. [13]C NMR spectrum of compound **40f**.

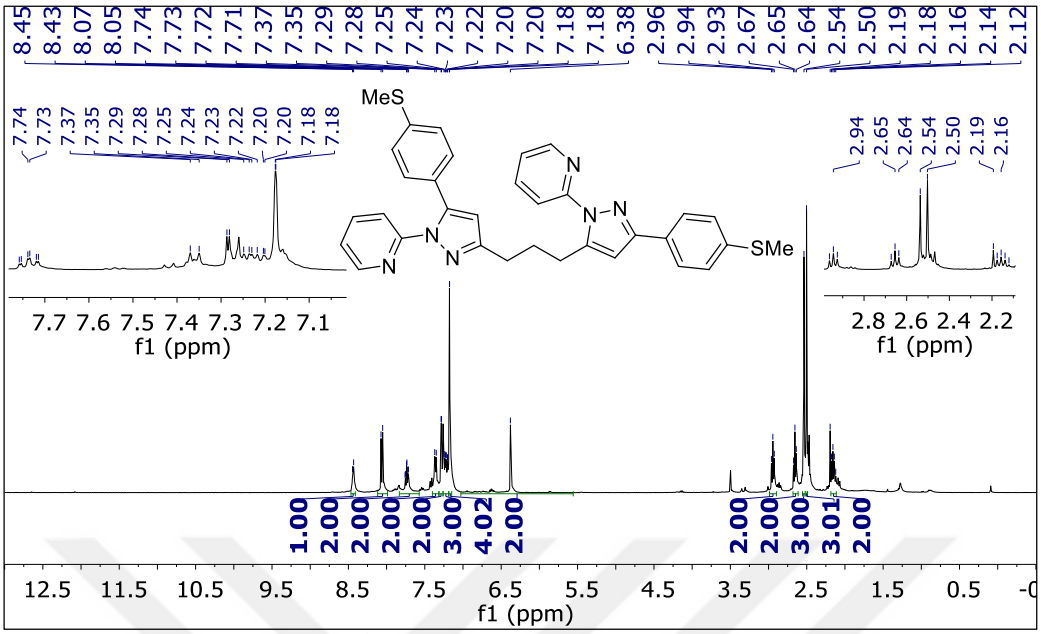


Figure 150. ^{1}H NMR spectrum of compound **40g**.

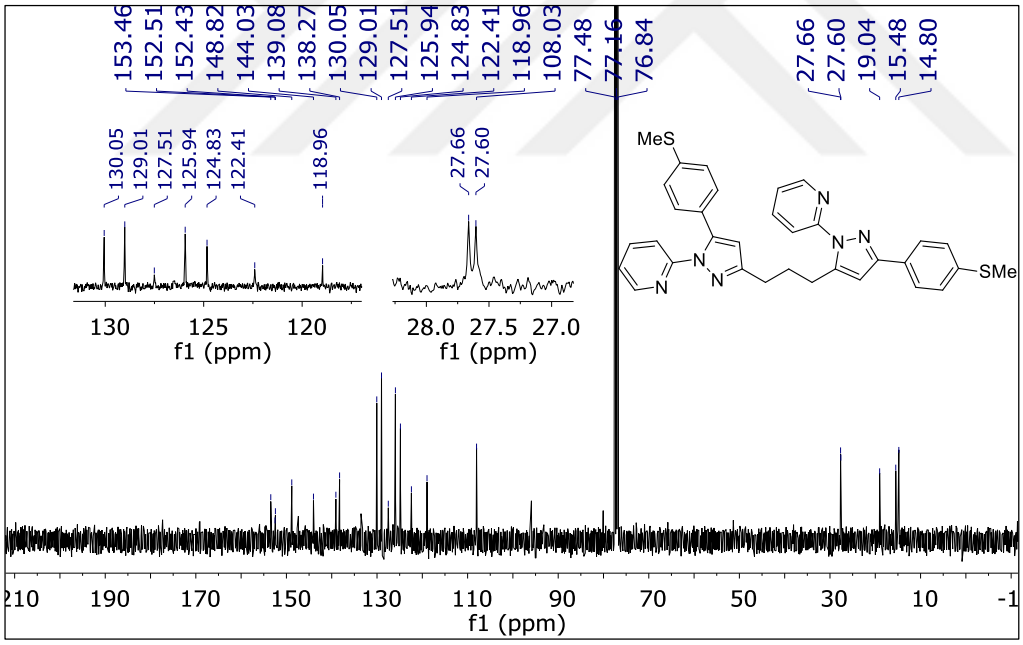


Figure 151. ^{13}C NMR spectrum of compound **40g**.

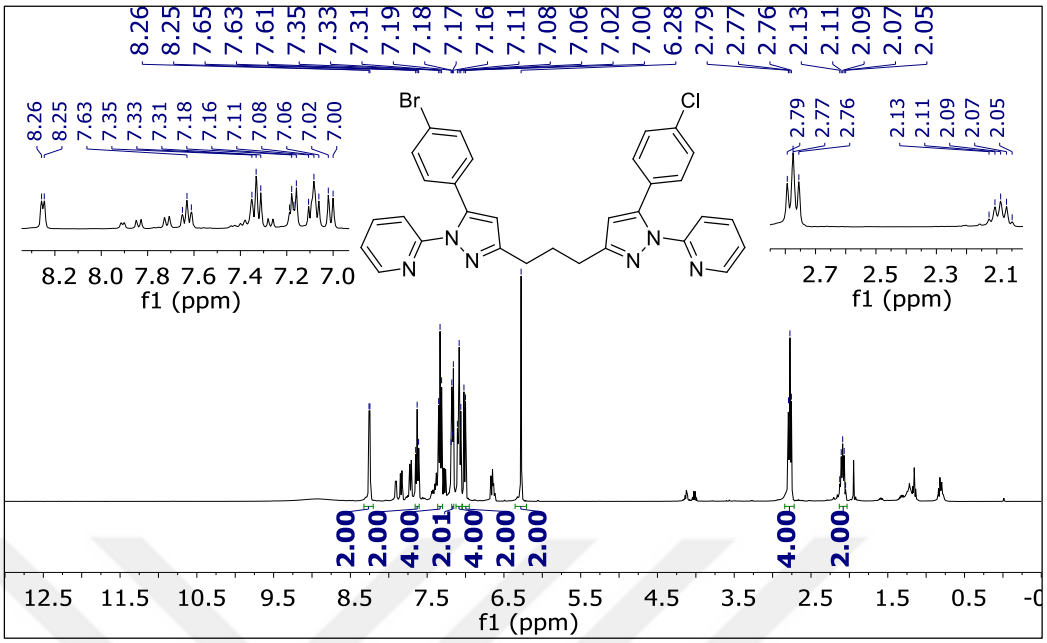


Figure 152. [1]H NMR spectrum of compound **40h**.

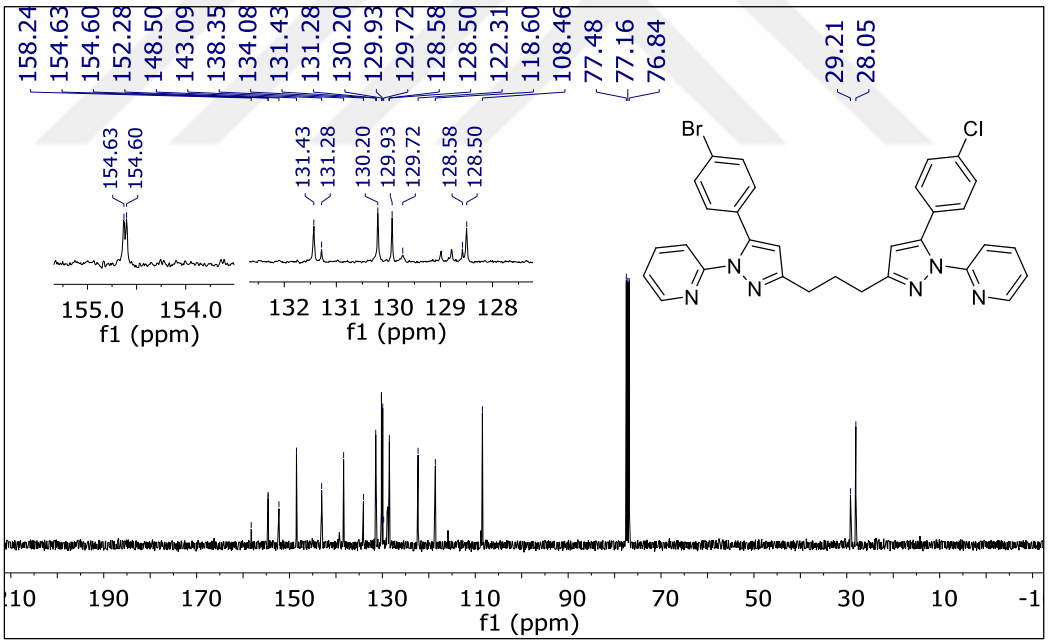


Figure 153. [1]H NMR spectrum of compound **40h**.

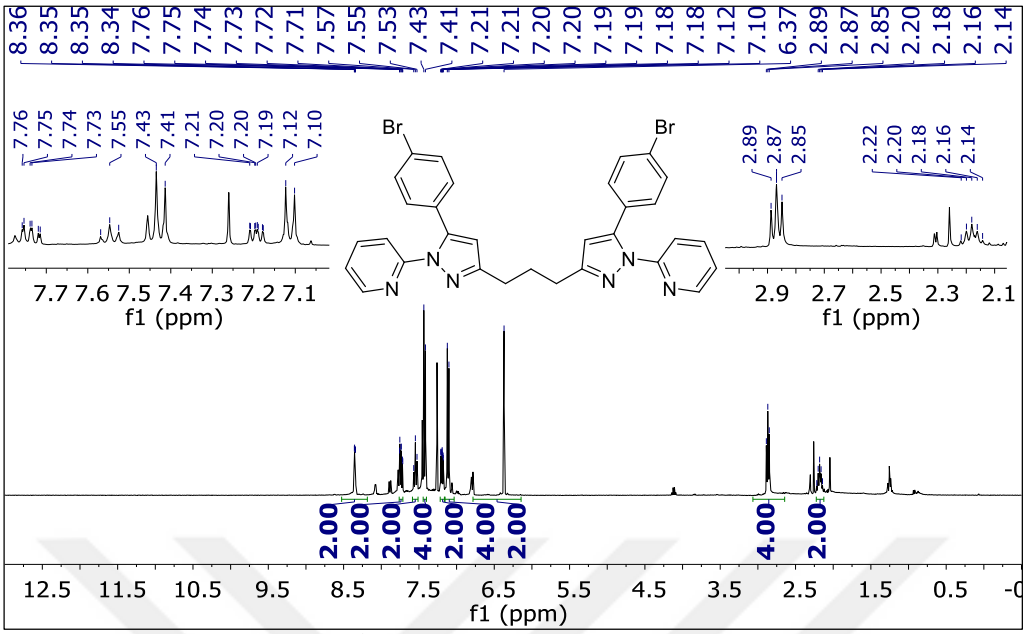


Figure 154. ^{1}H NMR spectrum of compound **40i**.

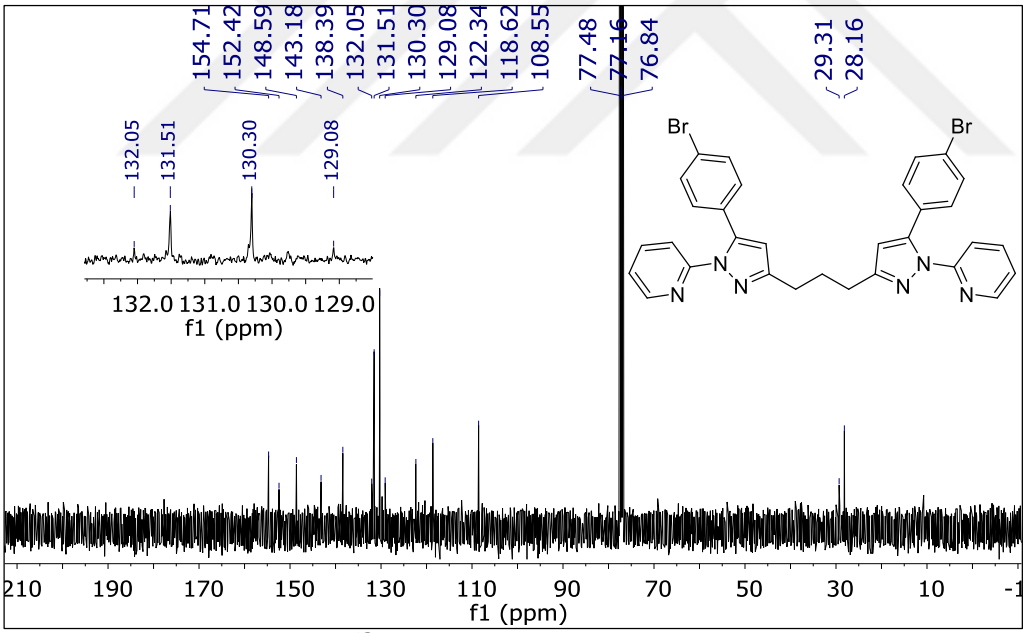


Figure 155. ^{13}C NMR spectrum of compound **40i**.

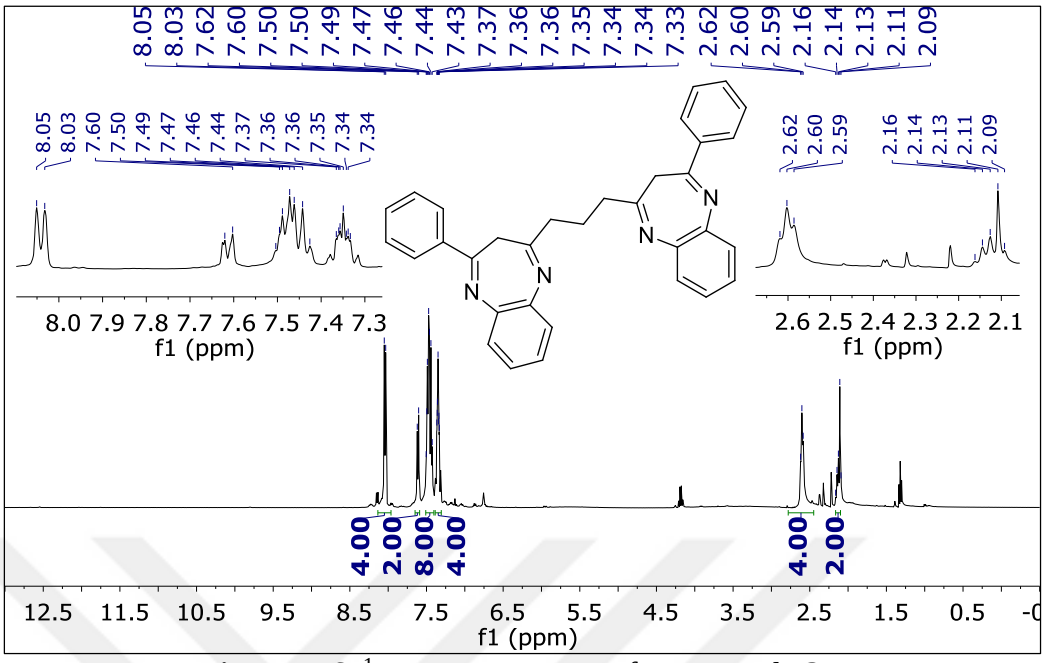


Figure 156. ^{1}H NMR spectrum of compound **42a**.

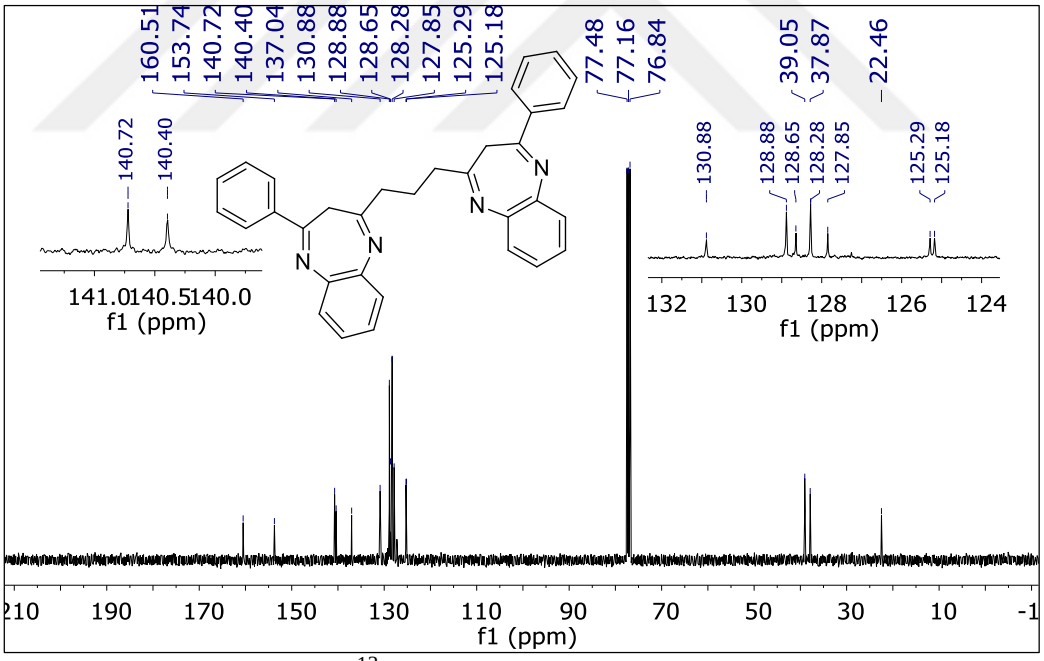


Figure 157. ^{13}C NMR spectrum of compound **42a**.

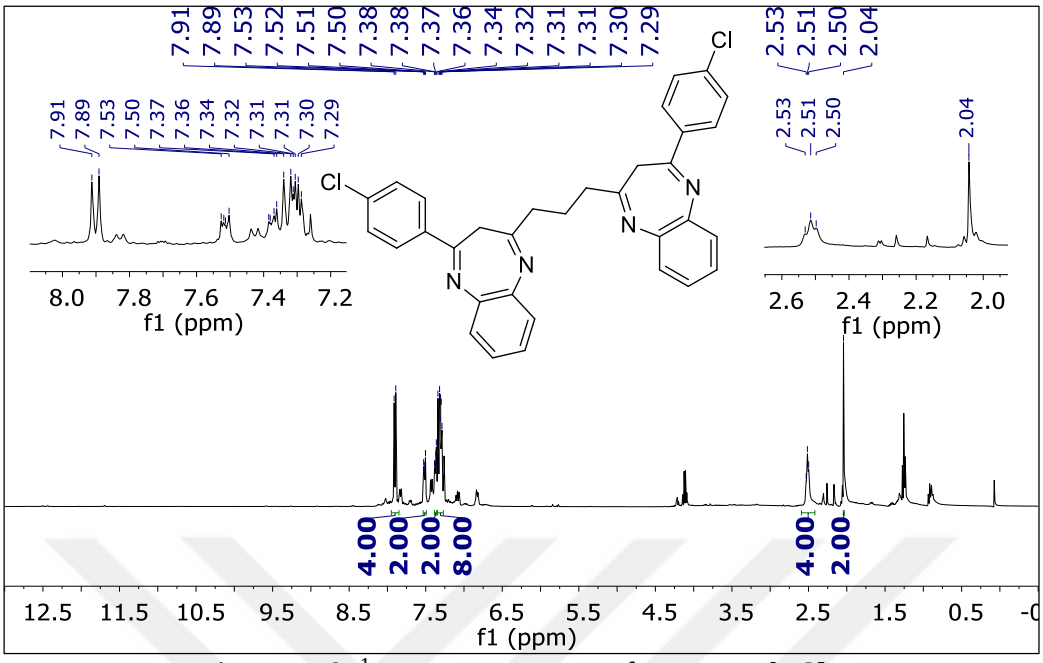


Figure 158. ^{1}H NMR spectrum of compound **42b**.

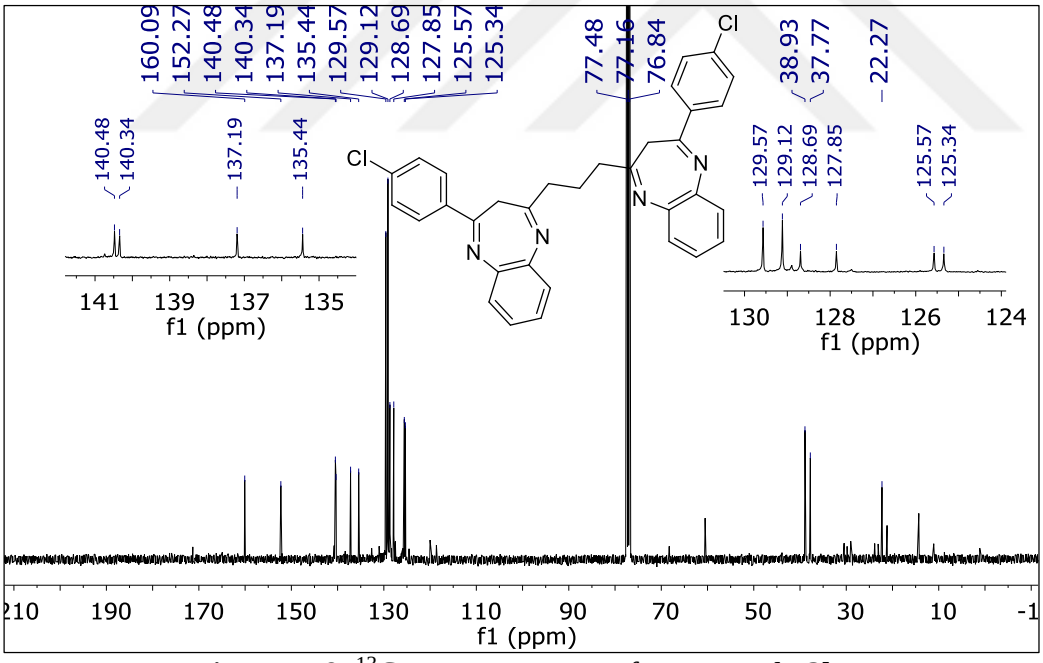


Figure 159. ^{13}C NMR spectrum of compound **42b**.

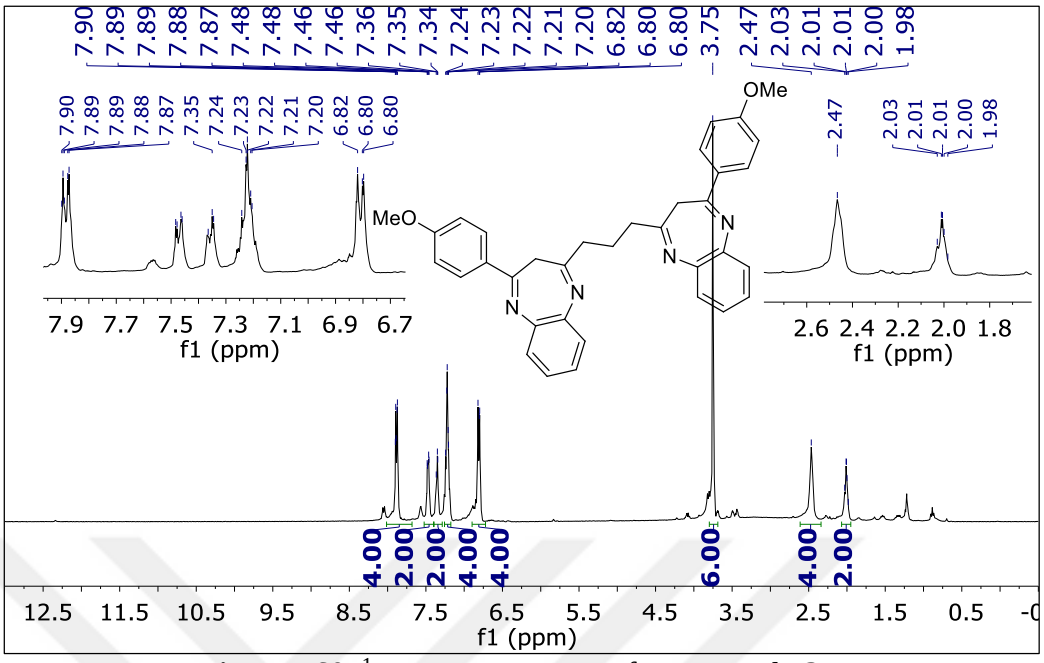


Figure 160. [1]H NMR spectrum of compound **42c**.

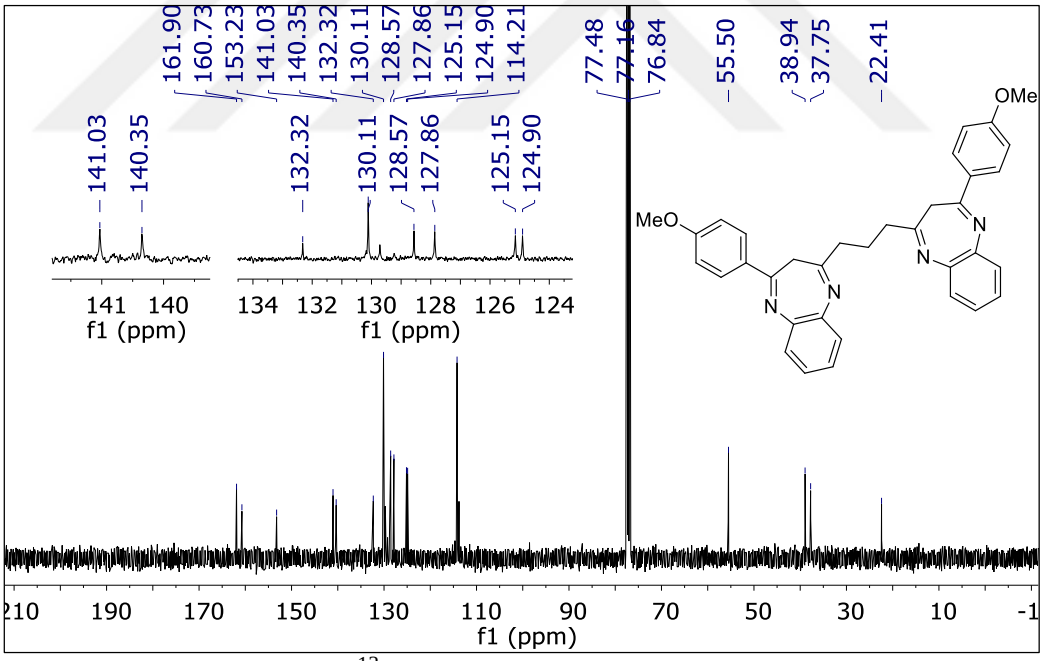


Figure 161. [13]C NMR spectrum of compound **42c**.

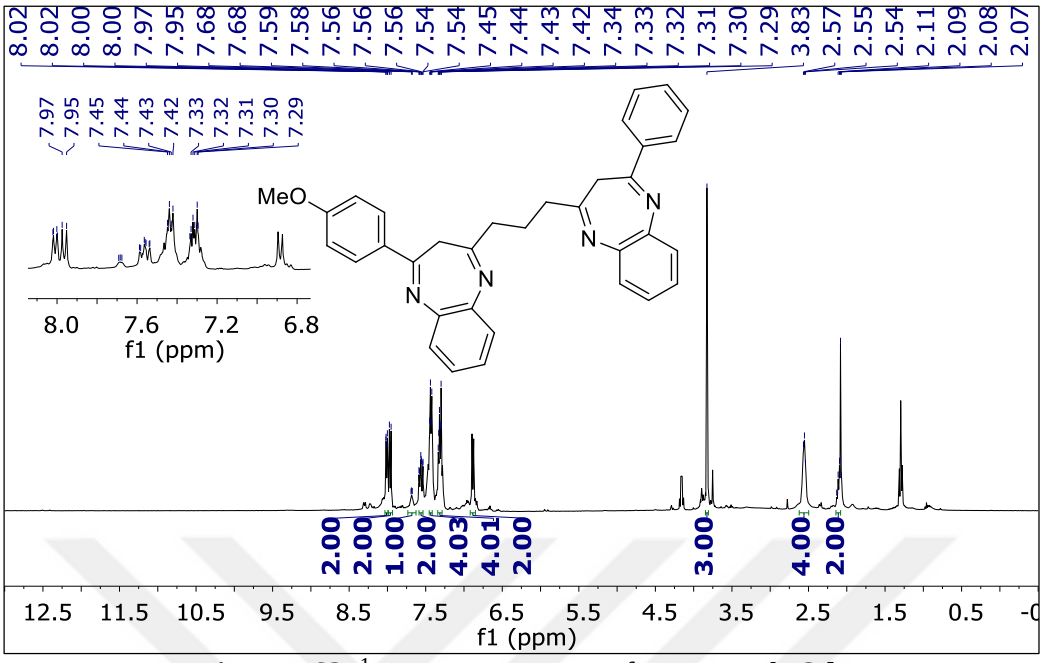


Figure 162. [1]H NMR spectrum of compound **42d**.

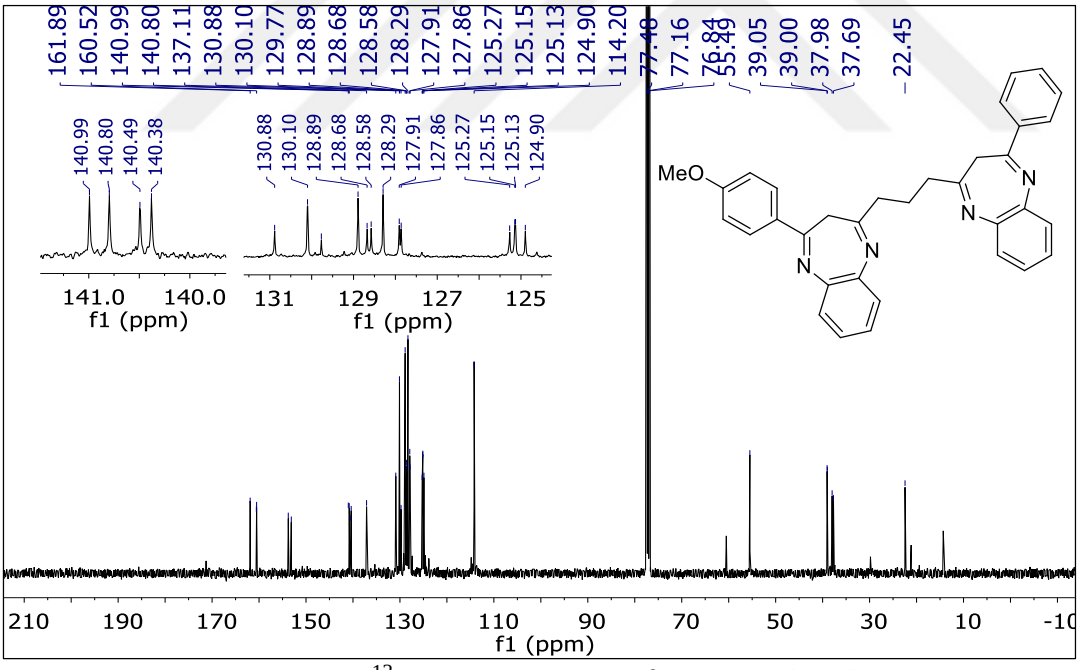


Figure 163. [13]C NMR spectrum of compound **42d**.

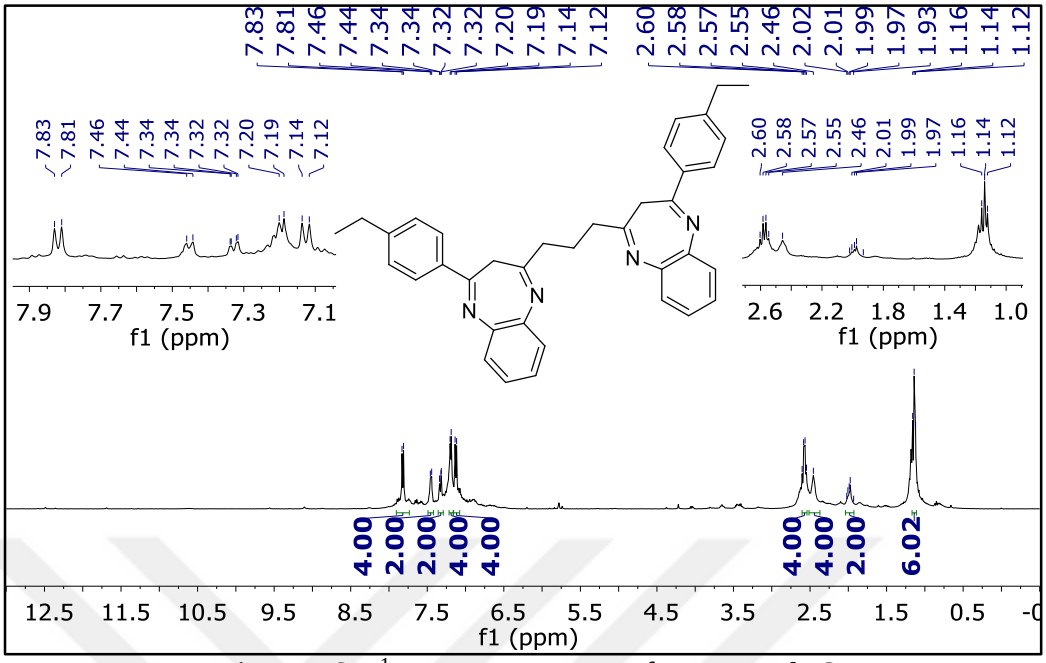


Figure 164. ^{1}H NMR spectrum of compound **42e**.

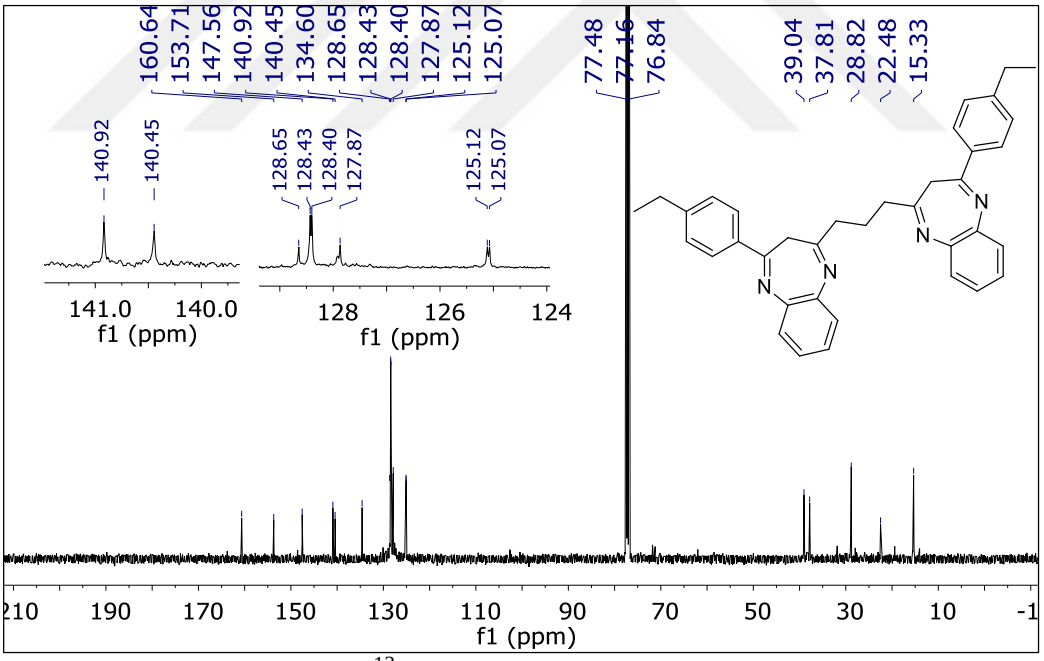


Figure 165. ^{13}C NMR spectrum of compound **42e**.

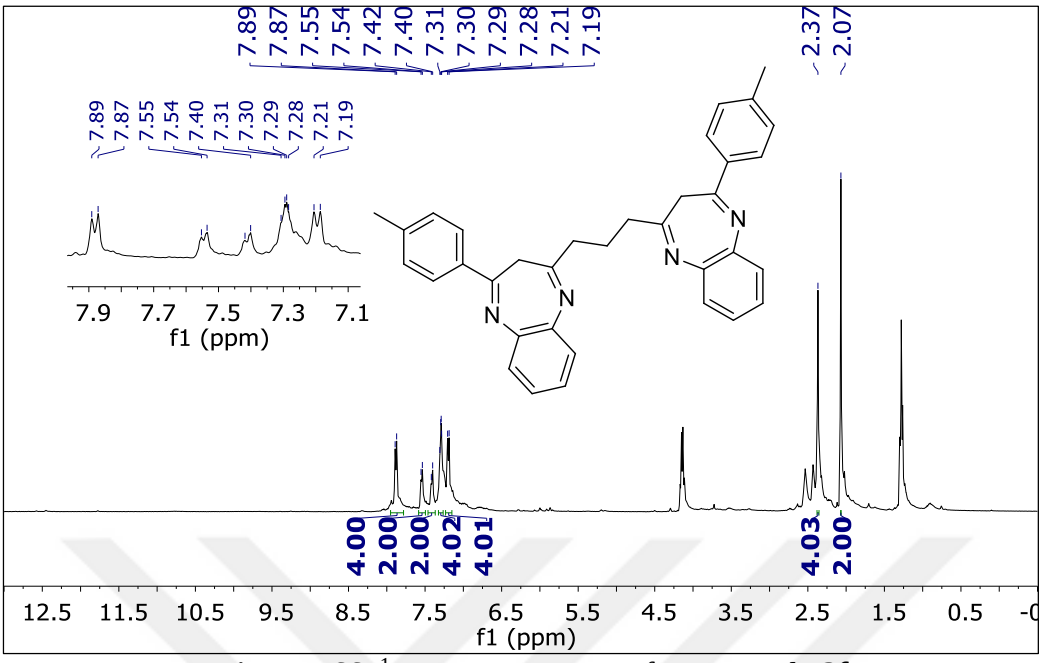


Figure 166. ^{1}H NMR spectrum of compound **42f**.

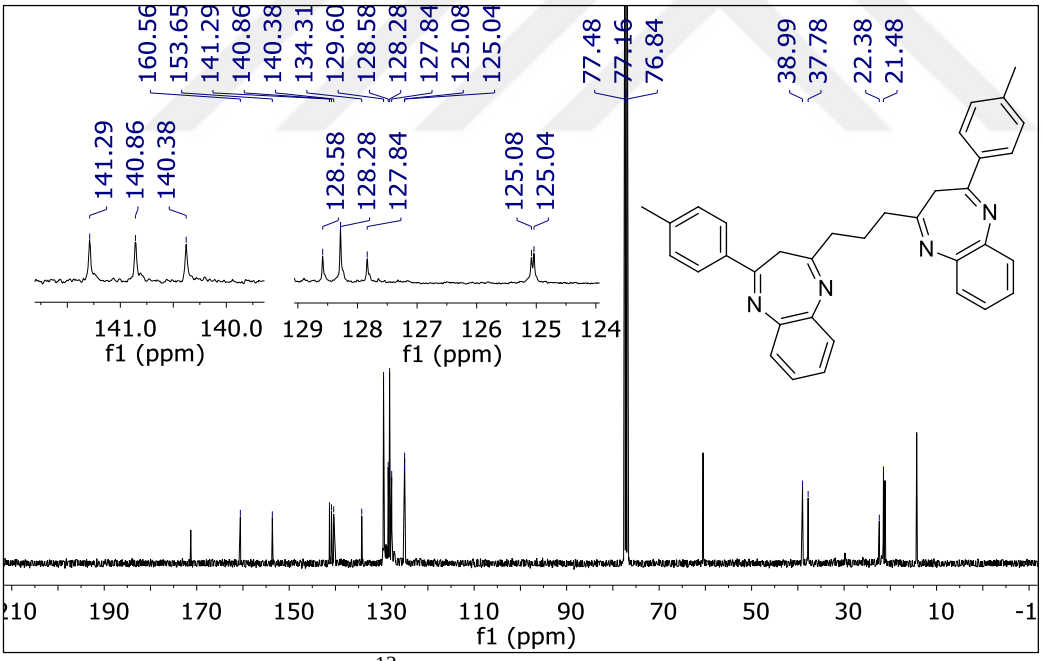


Figure 167. ^{13}C NMR spectrum of compound **42f**.

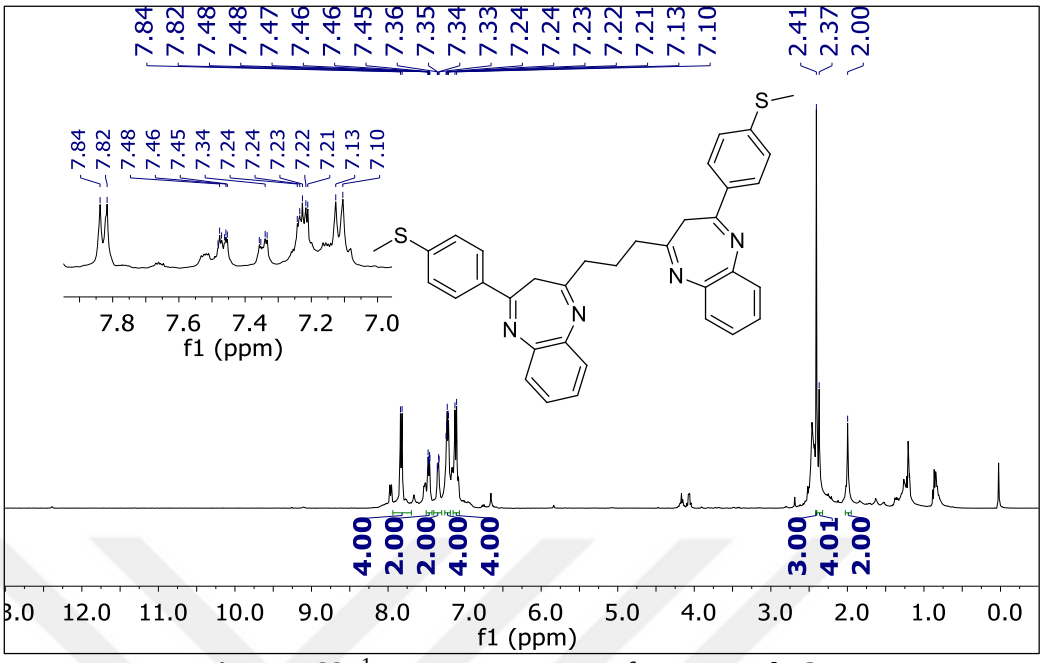


Figure 168. ^{1}H NMR spectrum of compound **42g**.

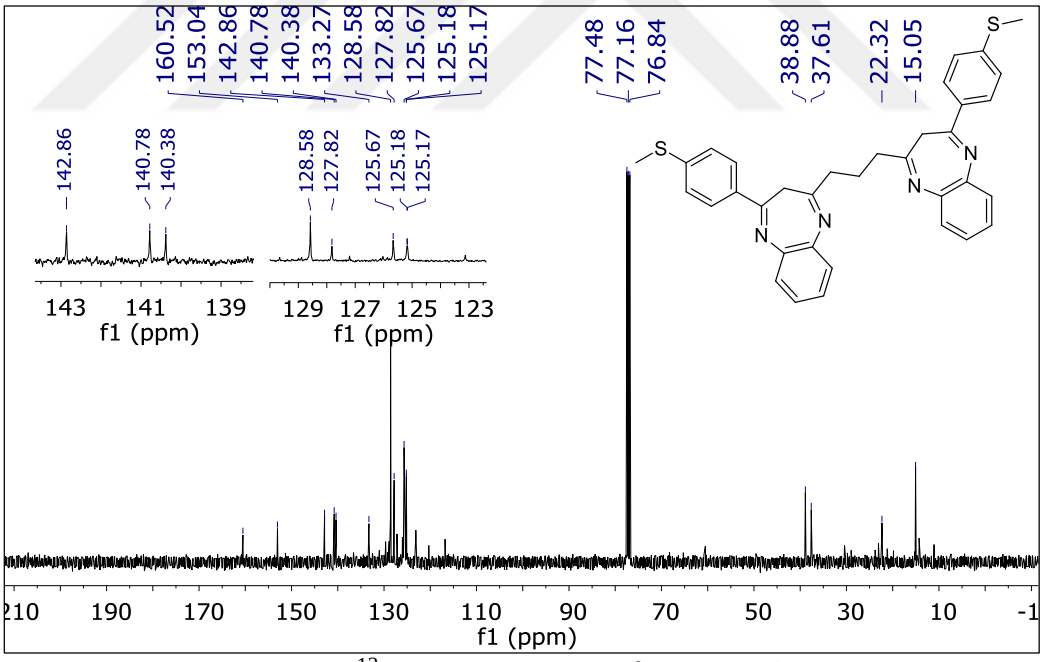


Figure 169. ^{13}C NMR spectrum of compound **42g**.

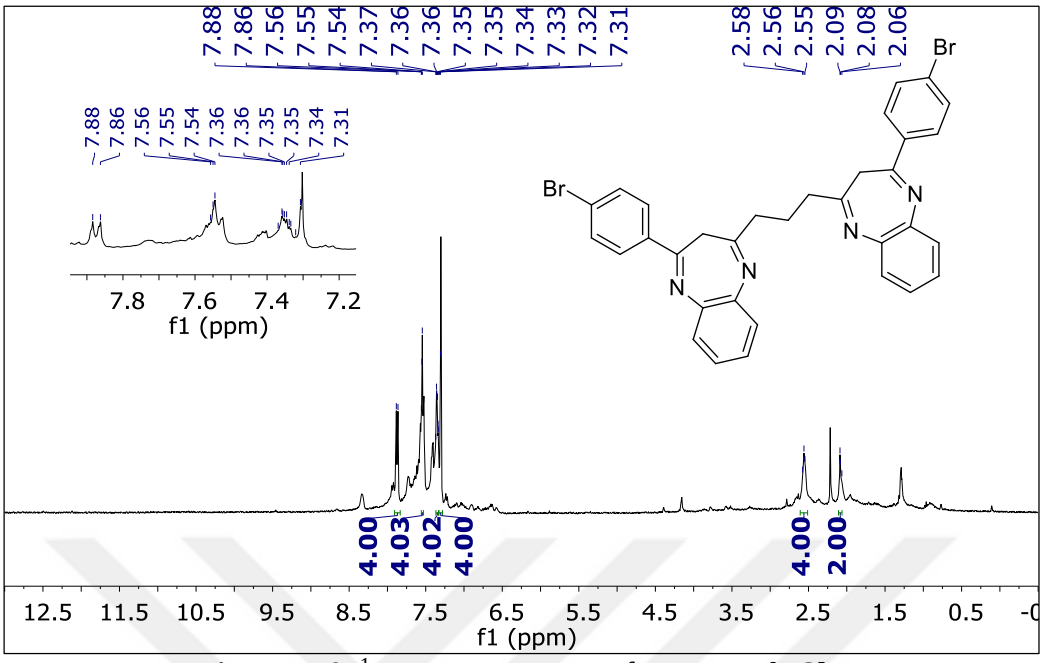


Figure 170. [1]H NMR spectrum of compound **42h**.

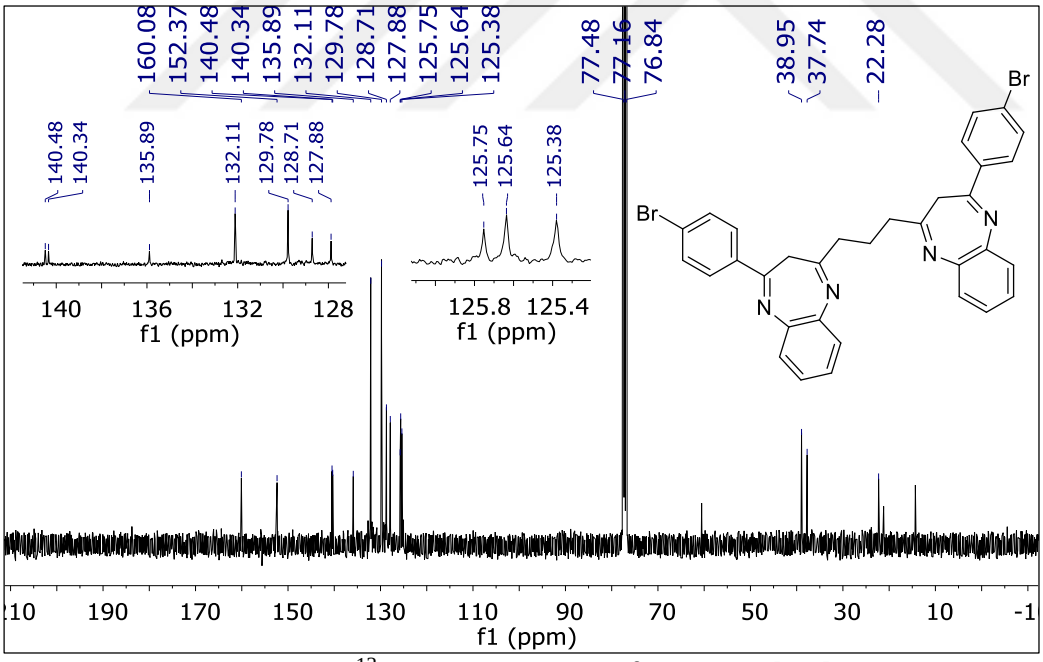


Figure 171. [13]C NMR spectrum of compound **42h**.

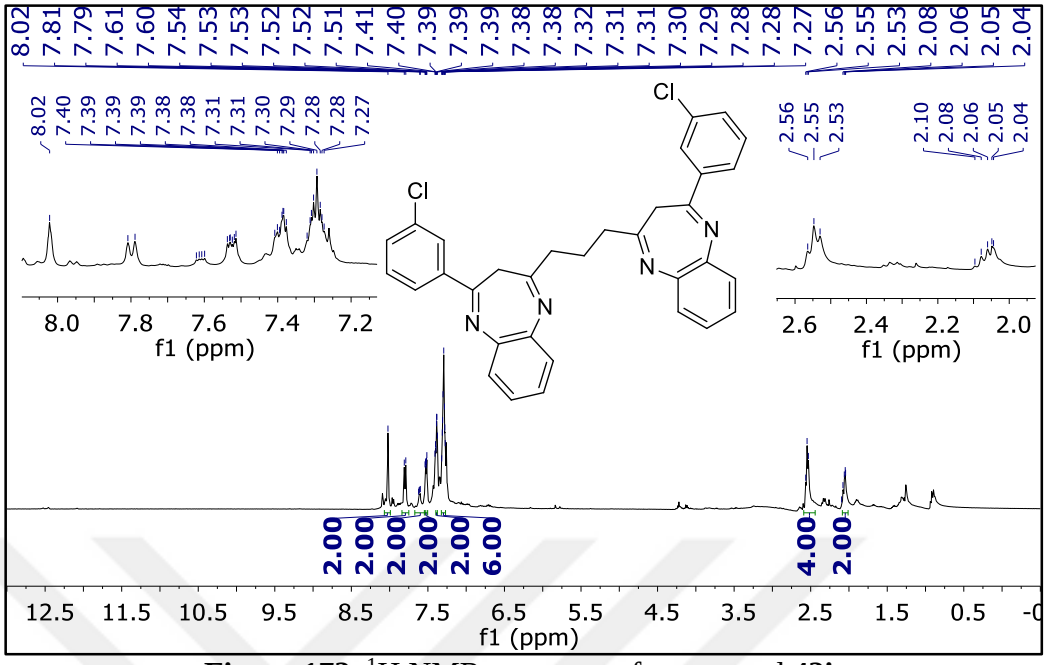


Figure 172. [1]H NMR spectrum of compound **42i**.

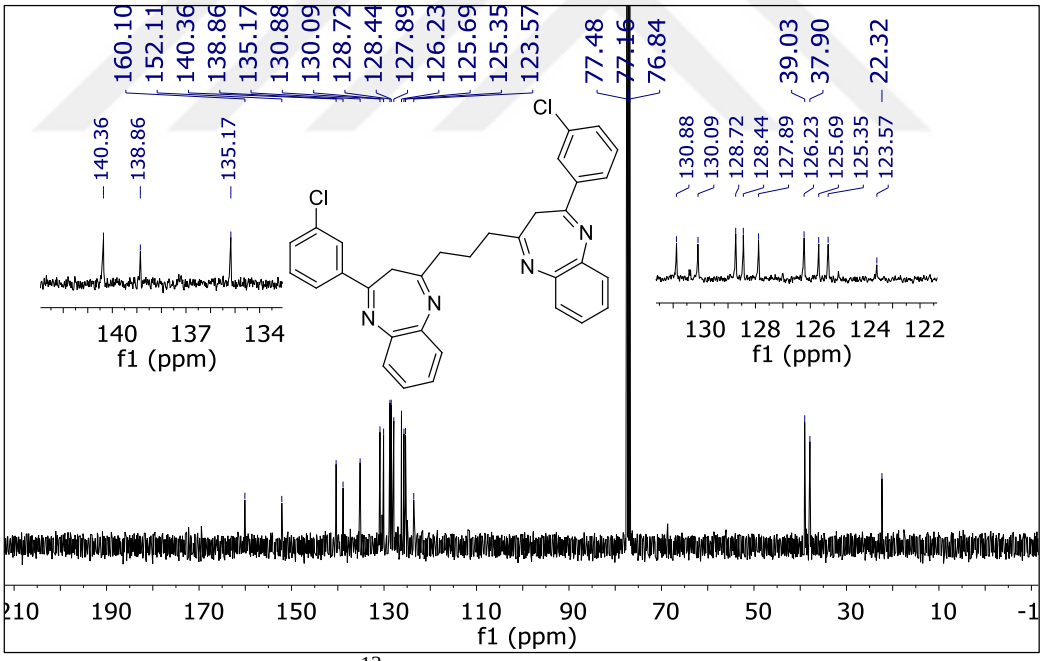


Figure 173. [13]C NMR spectrum of compound **42i**.

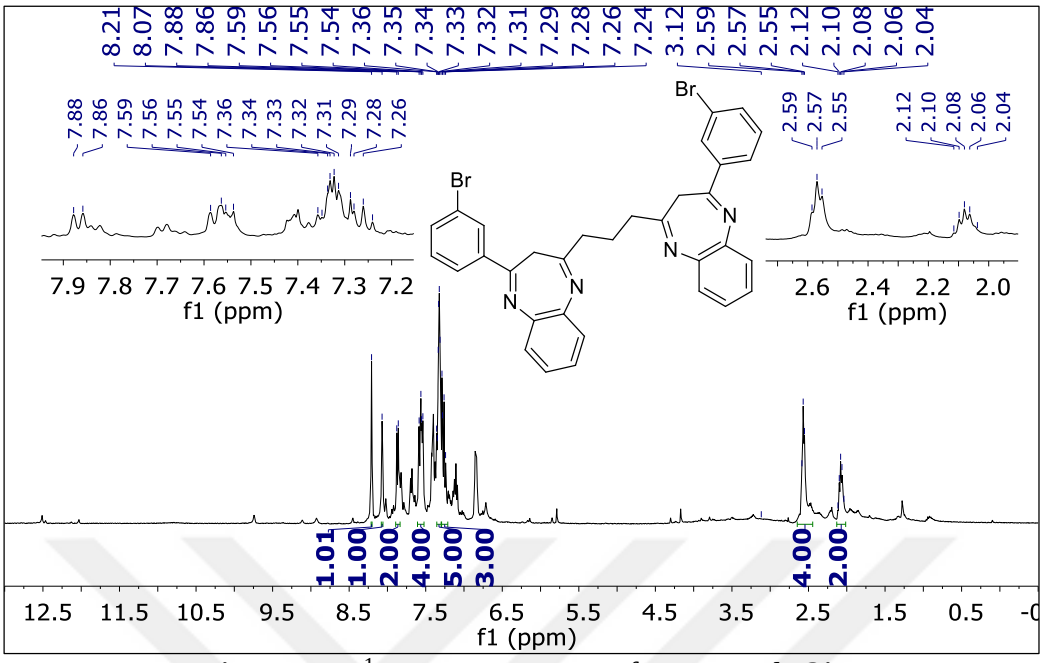


Figure 174. ^{1}H NMR spectrum of compound **42j**.

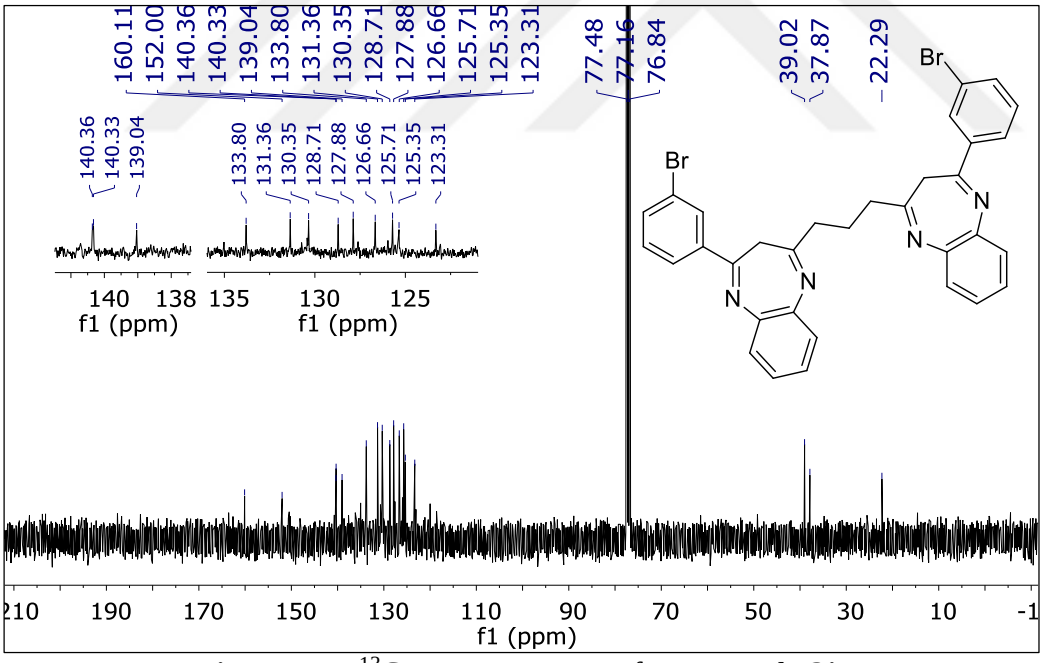


Figure 175. ^{13}C NMR spectrum of compound **42j**.

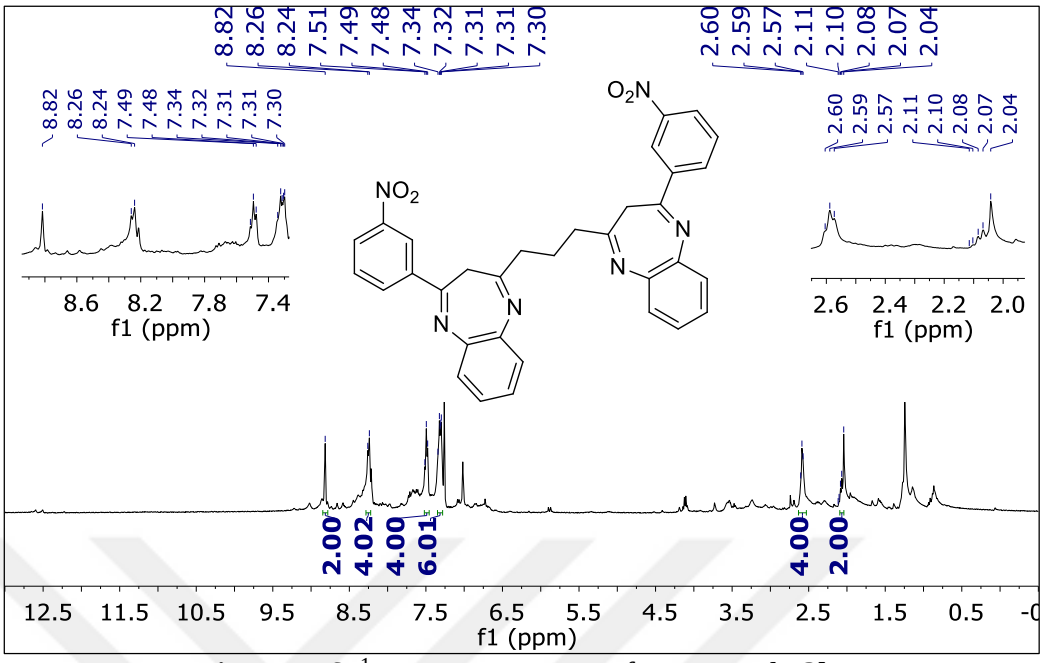


Figure 176. ^{1}H NMR spectrum of compound **42k**.

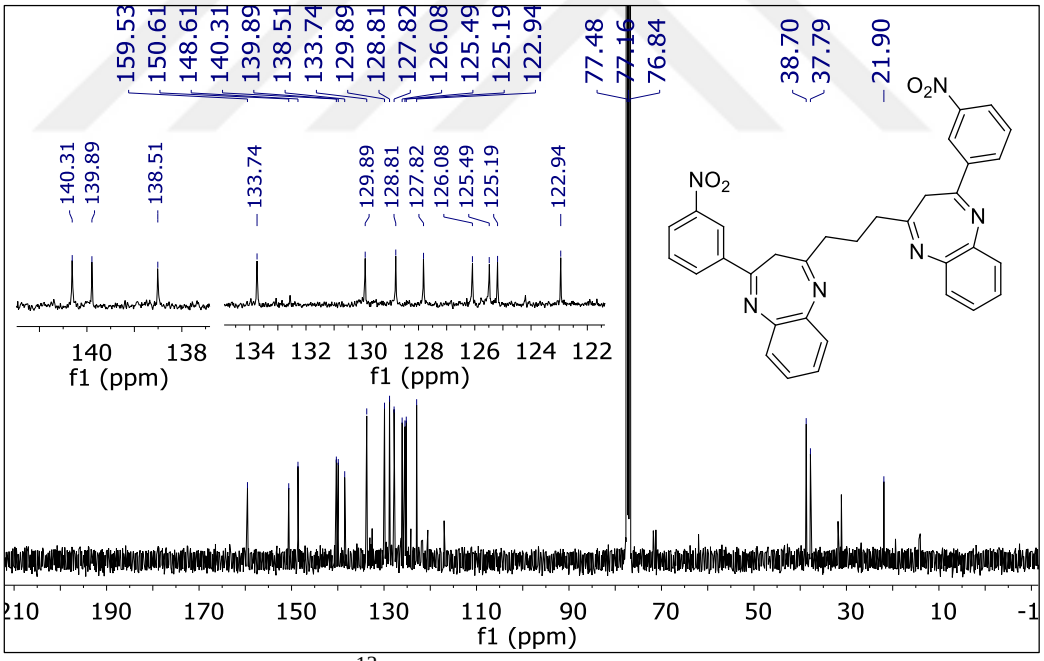


Figure 177. ^{13}C NMR spectrum of compound **42k**.

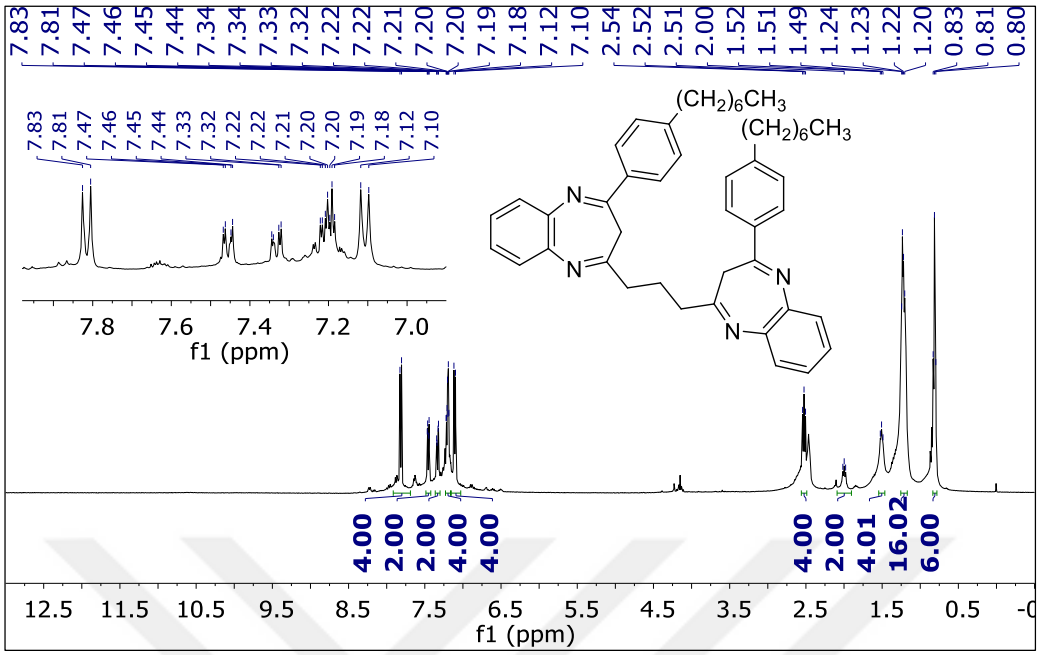


Figure 178. ^{1}H NMR spectrum of compound **42m**.

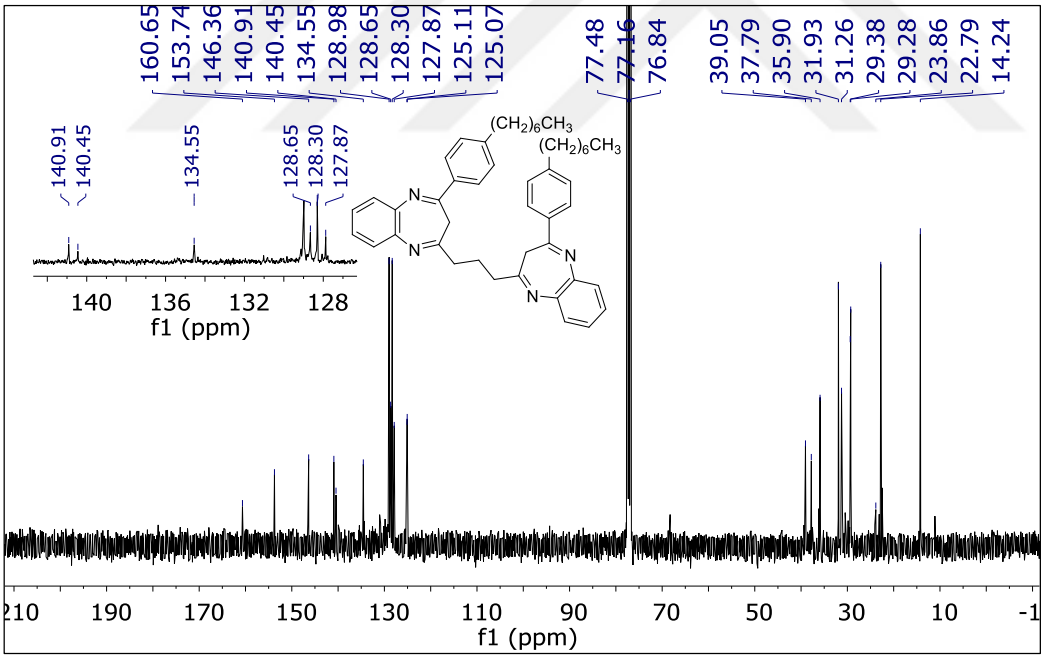


Figure 179. ^{13}C NMR spectrum of compound **42m**.

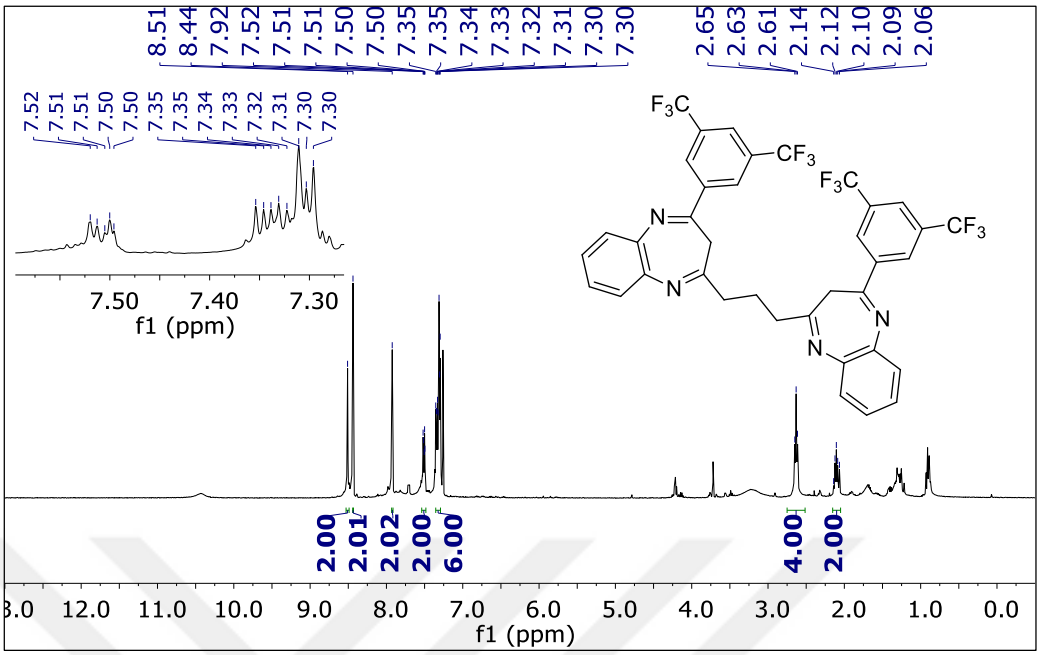


Figure 180. ^{1}H NMR spectrum of compound **42n**.

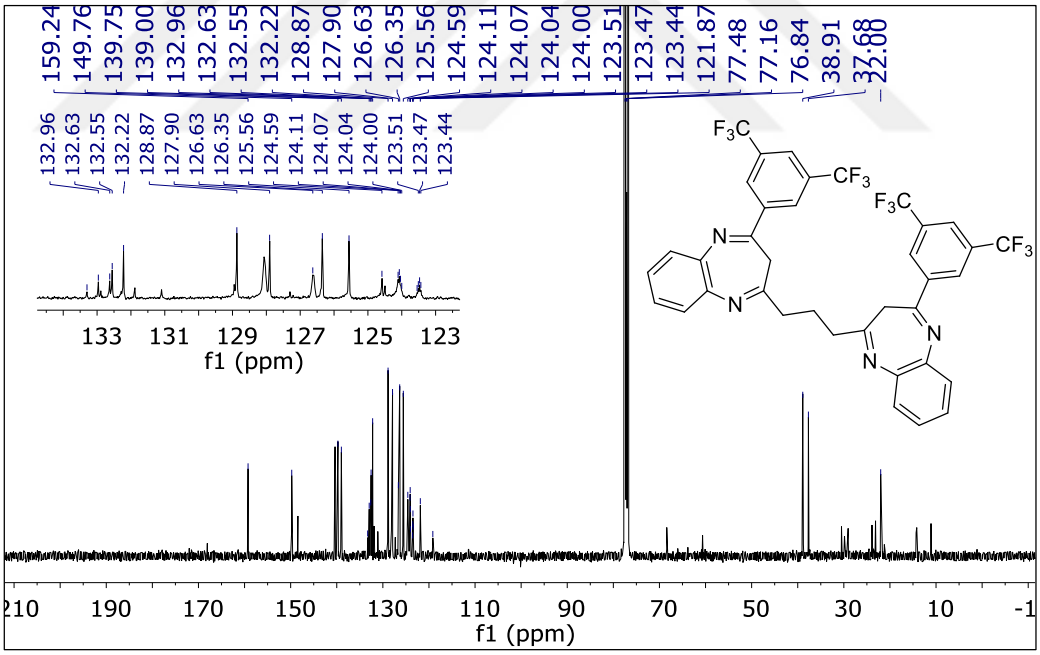


Figure 181. ^{13}C NMR spectrum of compound **42n**.

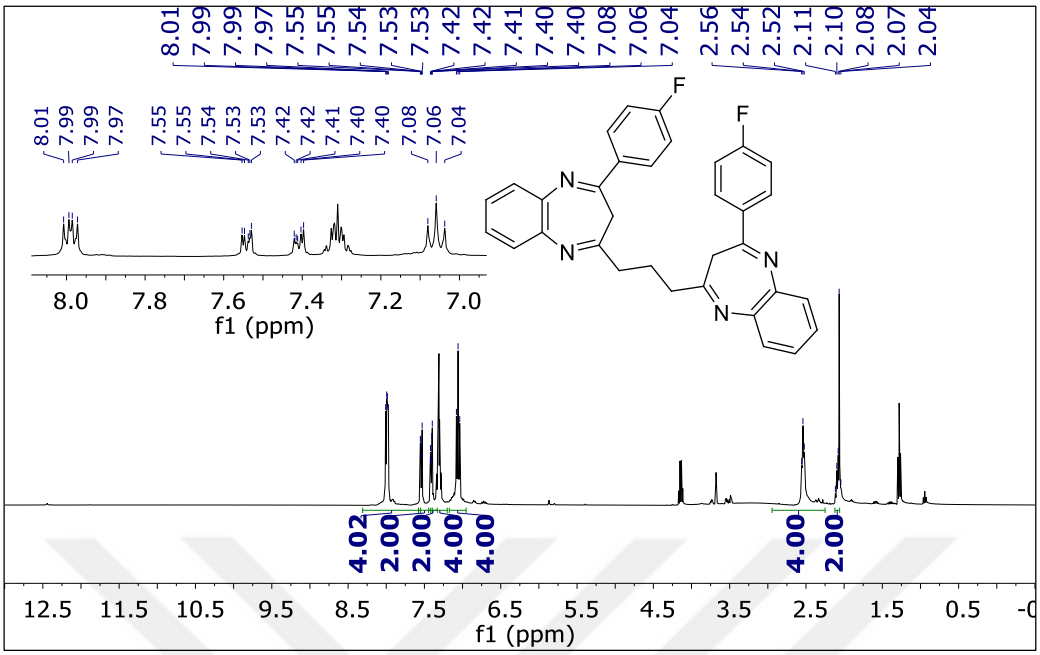


Figure 182. ^{1}H NMR spectrum of compound **42o**.

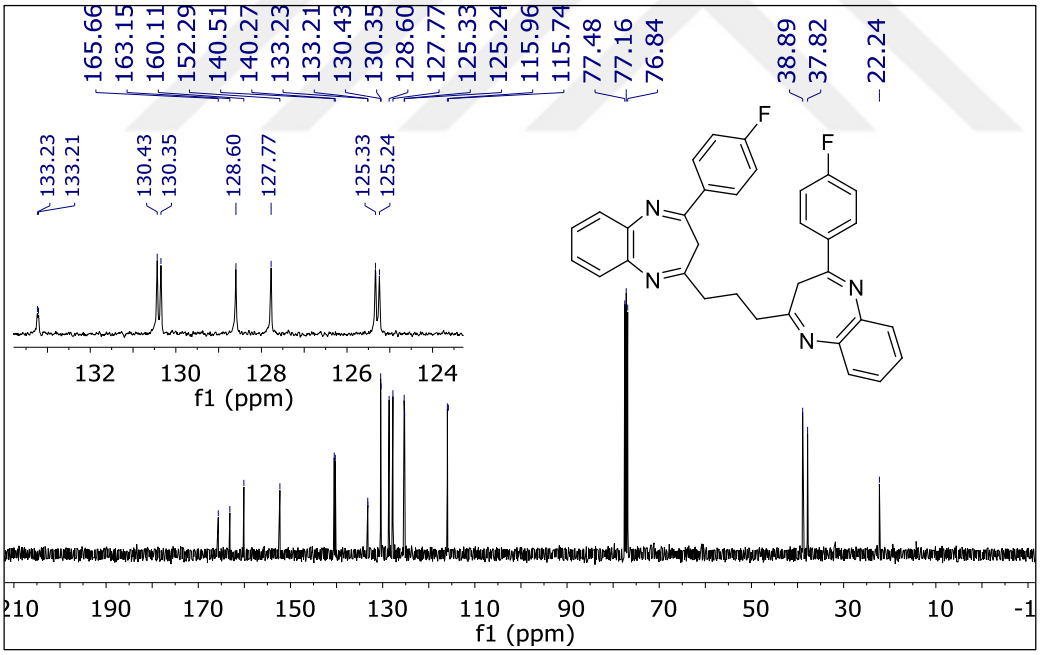


Figure 183. ^{13}C NMR spectrum of compound **42o**.

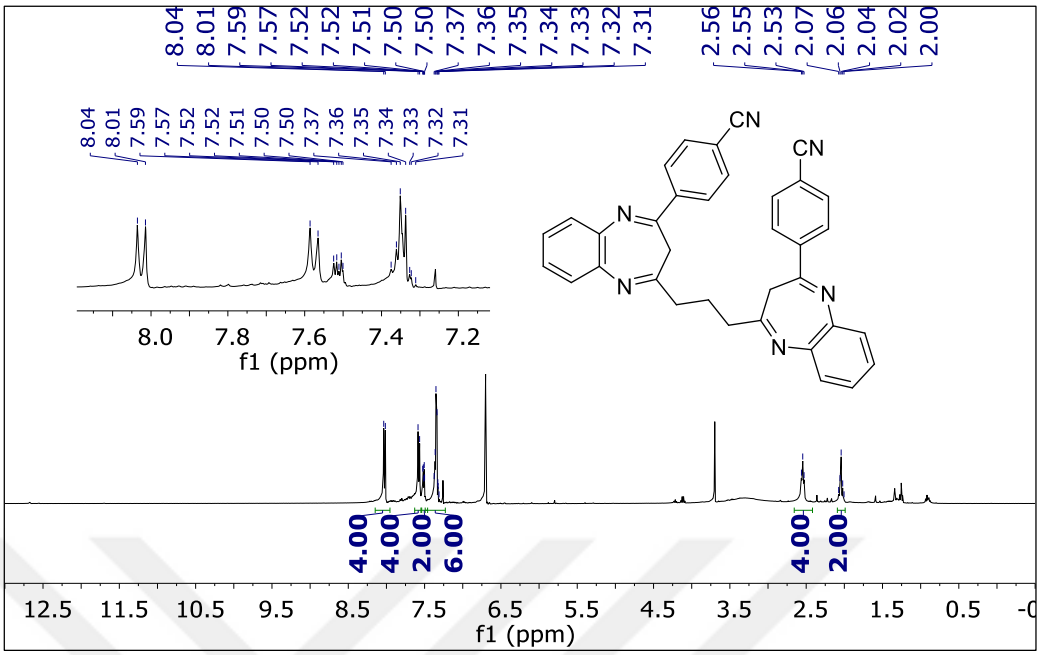


Figure 184. ^{1}H NMR spectrum of compound **42p**.

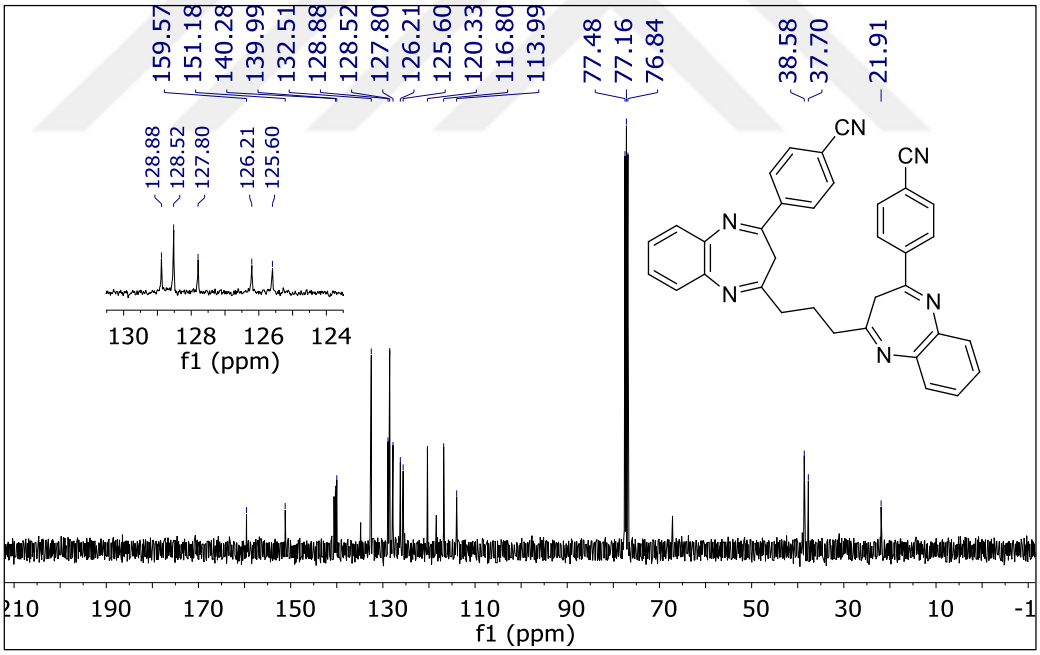


Figure 185. ^{13}C NMR spectrum of compound **42p**.

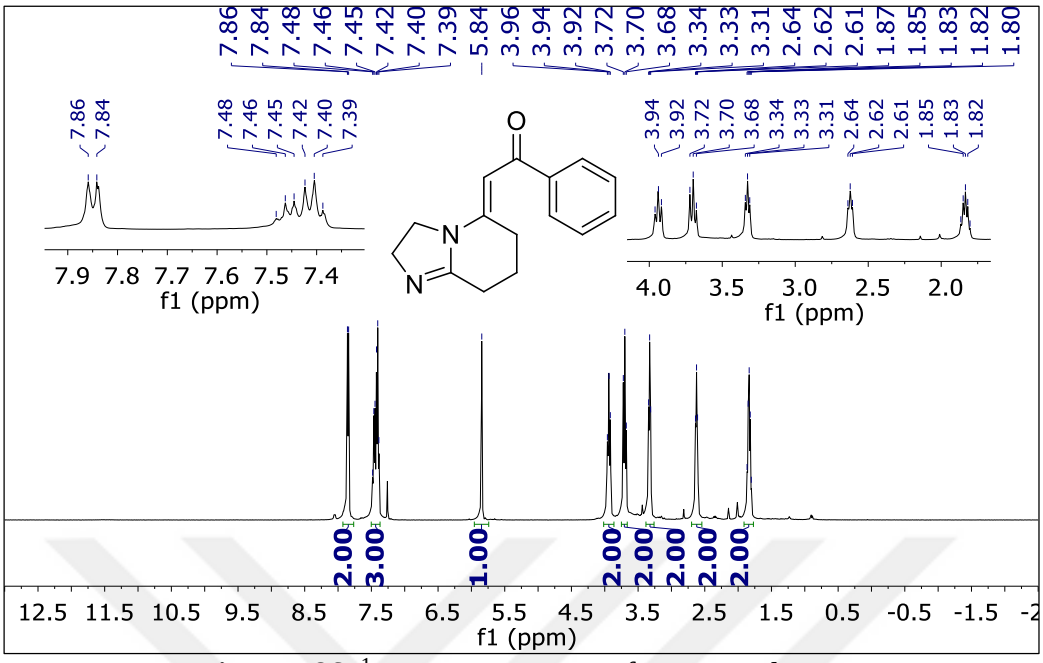


Figure 186. ^{1}H NMR spectrum of compound **44a**.

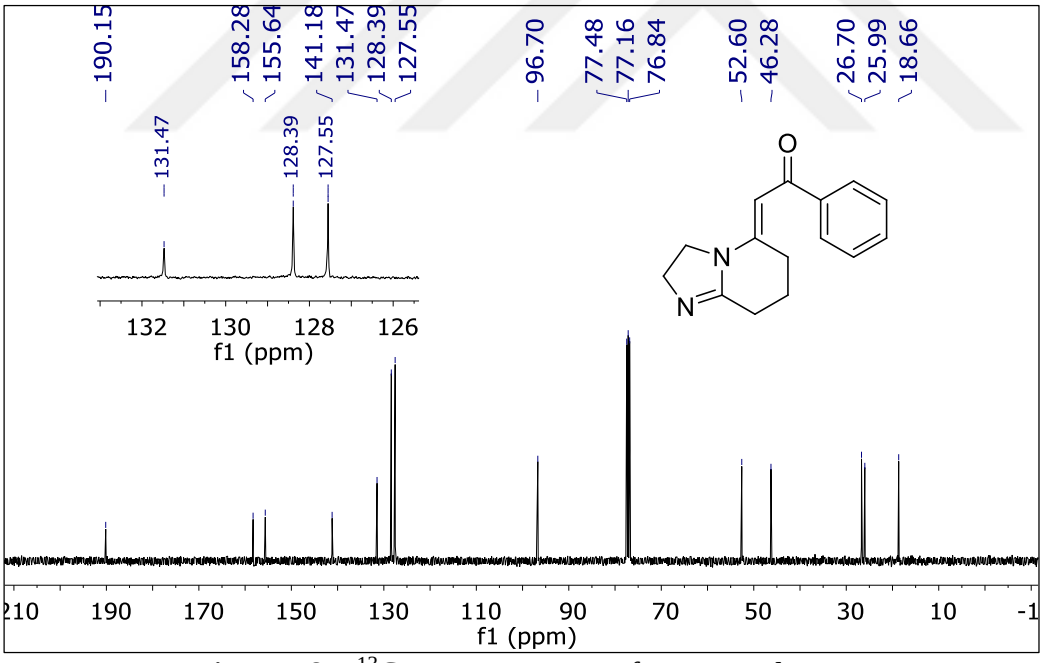


Figure 187. ^{13}C NMR spectrum of compound **44a**.

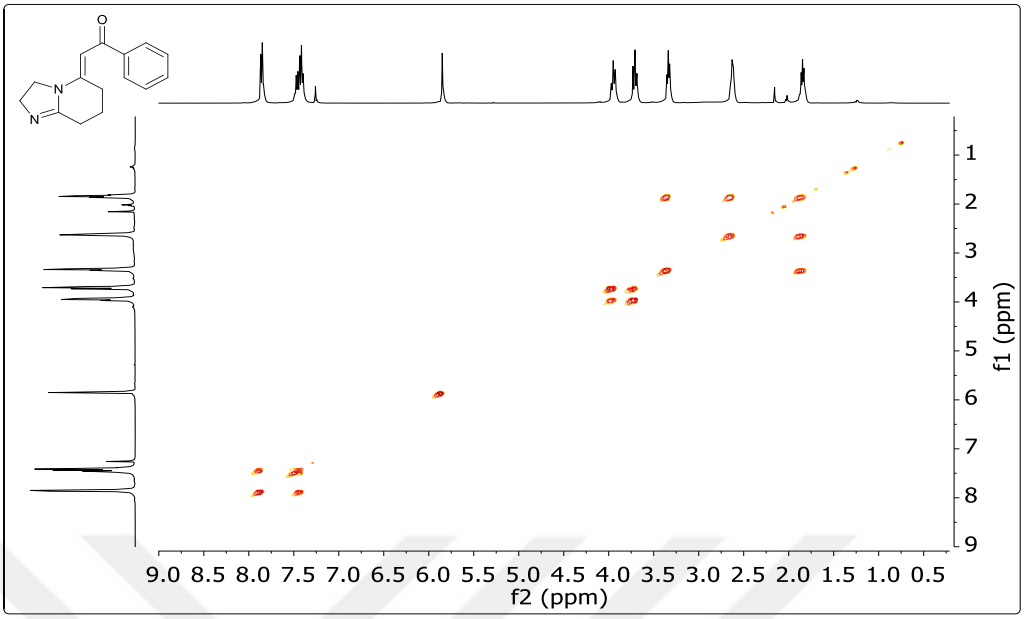


Figure 188. COSY spectrum of compound **44a**.

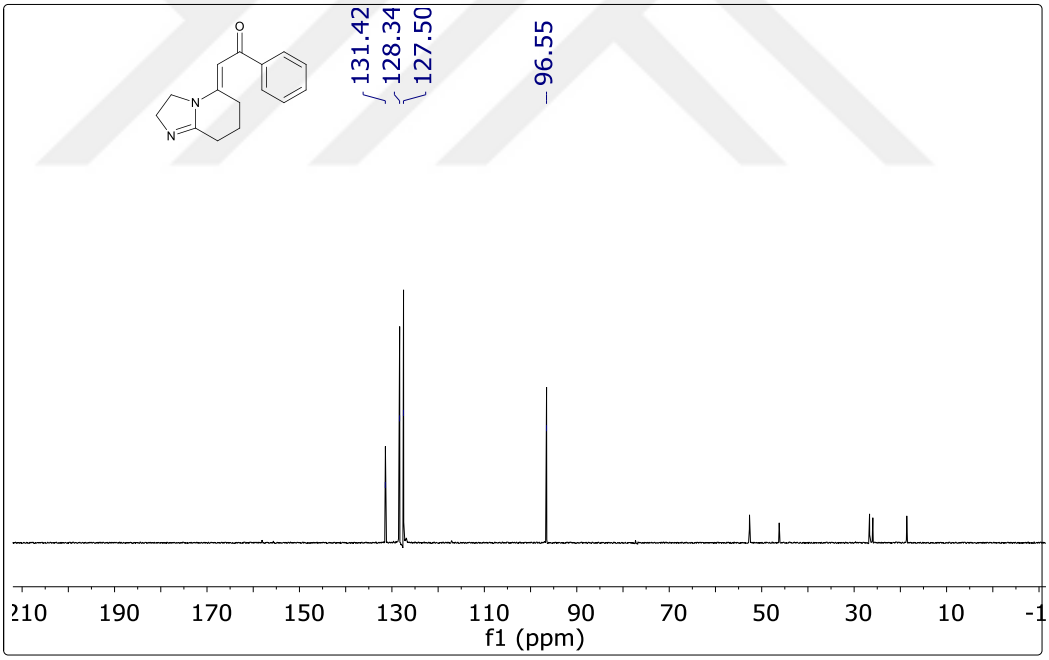


Figure 189. DEPT-90 spectrum of compound **44a**.

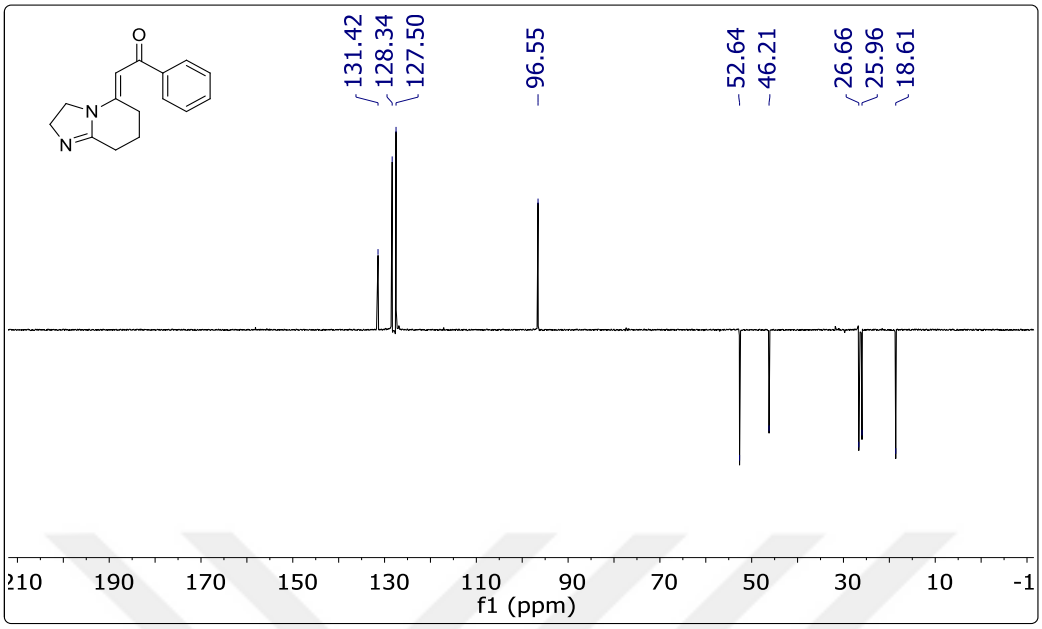


Figure 190. DEPT-135 spectrum of compound **44a**.

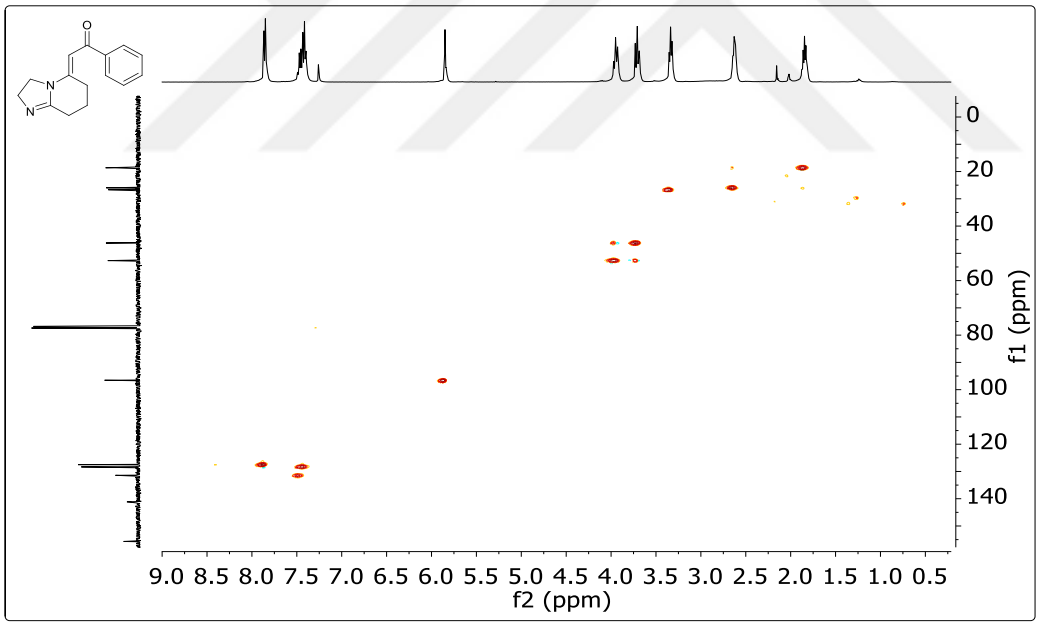


Figure 191. HSQC spectrum of compound **44a**.

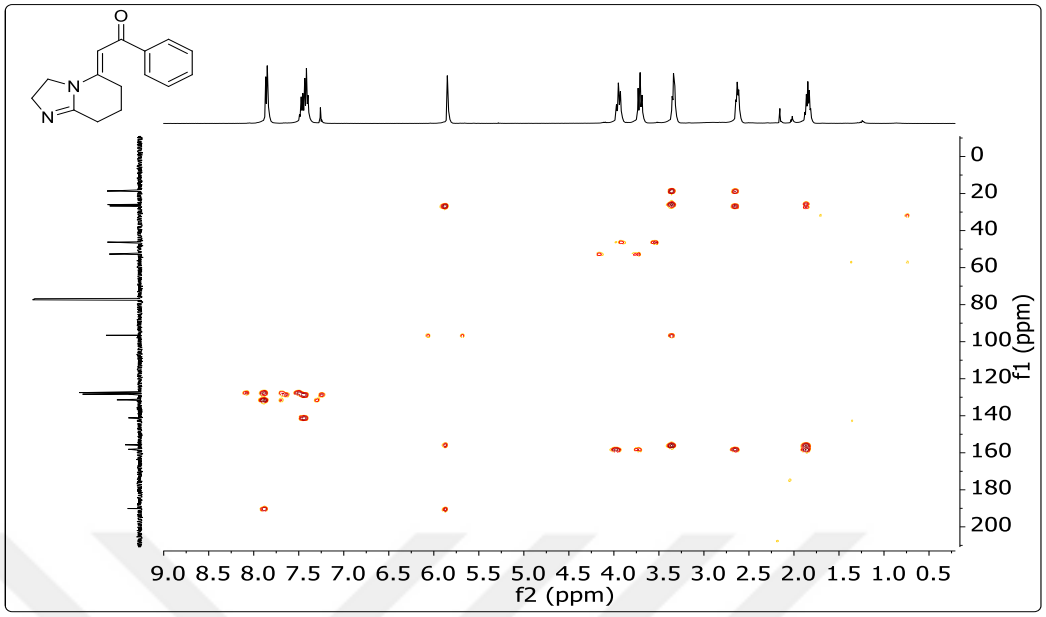


Figure 192. HMBC spectrum of compound **44a**.

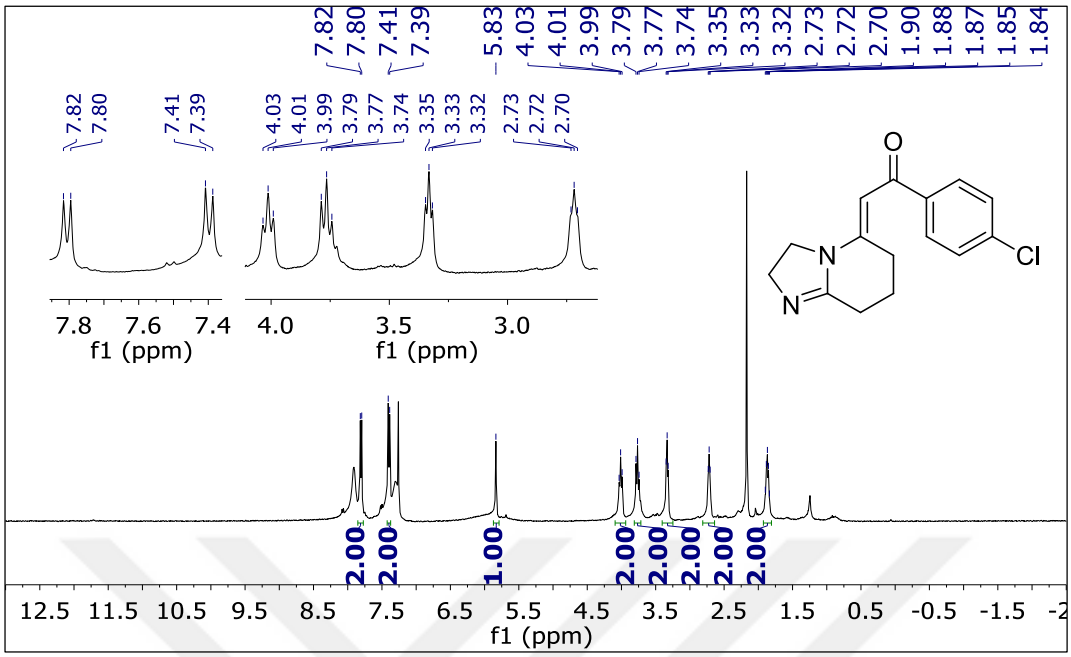


Figure 193. [1]H NMR spectrum of compound **44b**.

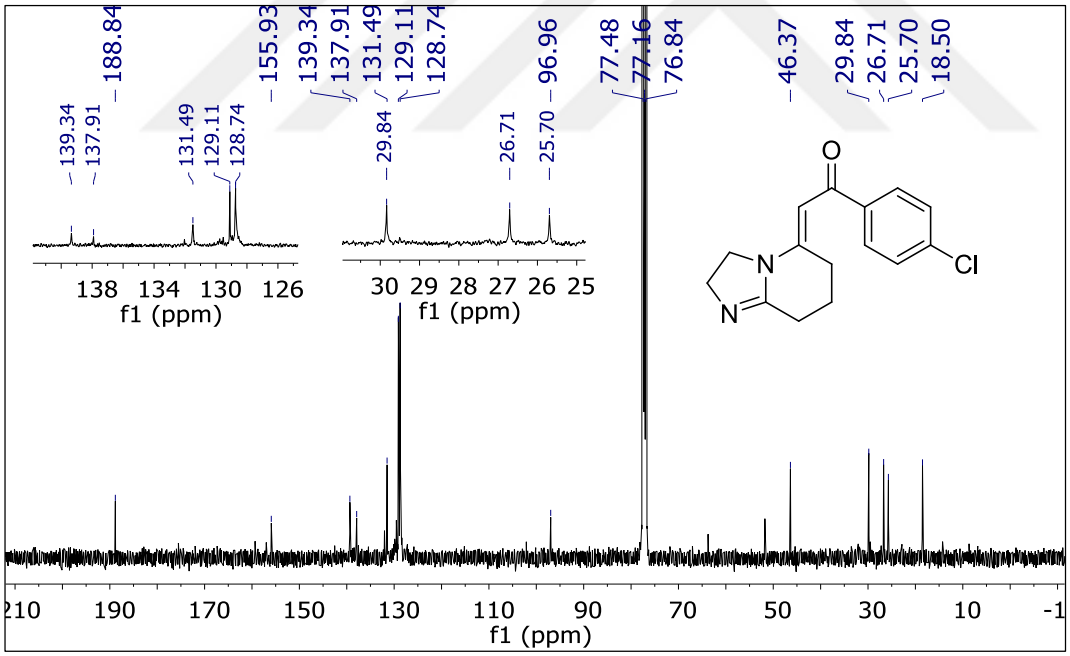


Figure 194. [13]C NMR spectrum of compound **44b**.

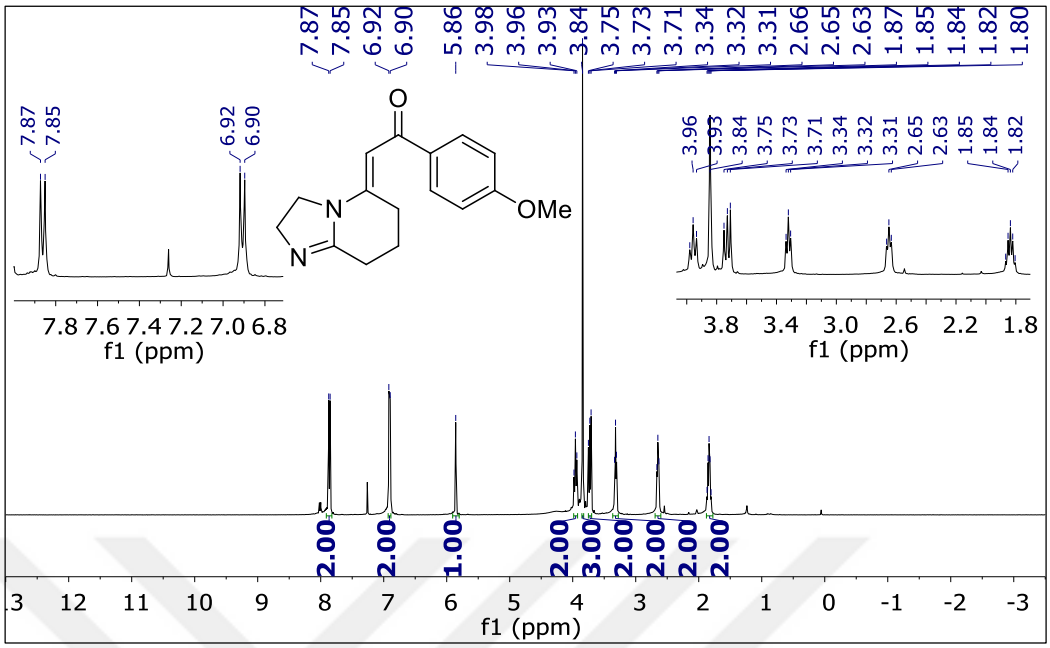


Figure 195. ^{1}H NMR spectrum of compound **44c**.

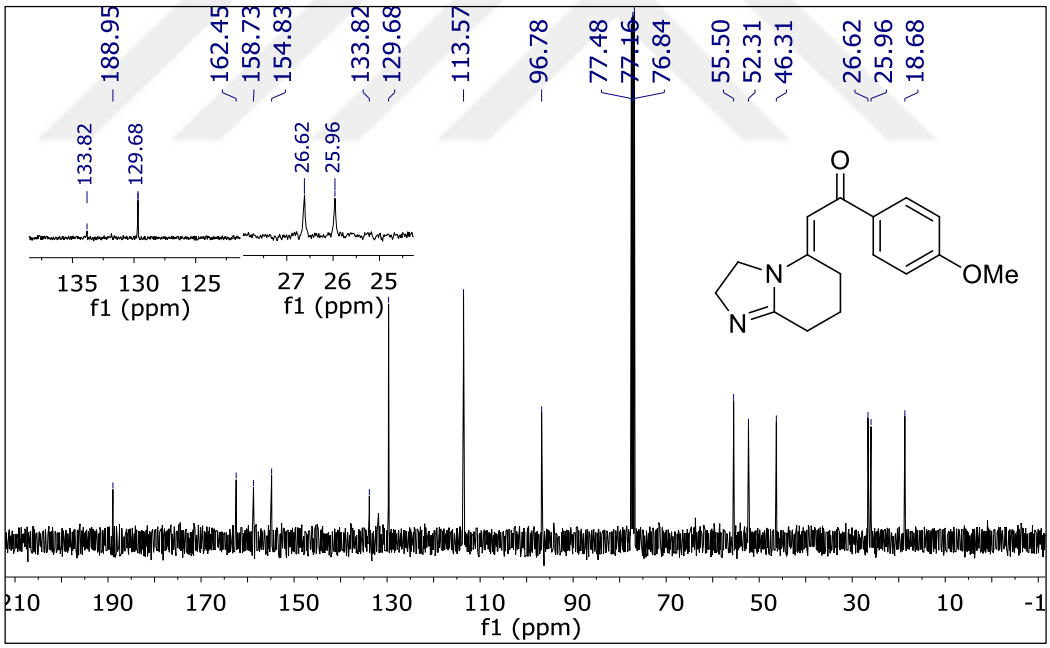


Figure 196. ^{13}C NMR spectrum of compound **44c**.

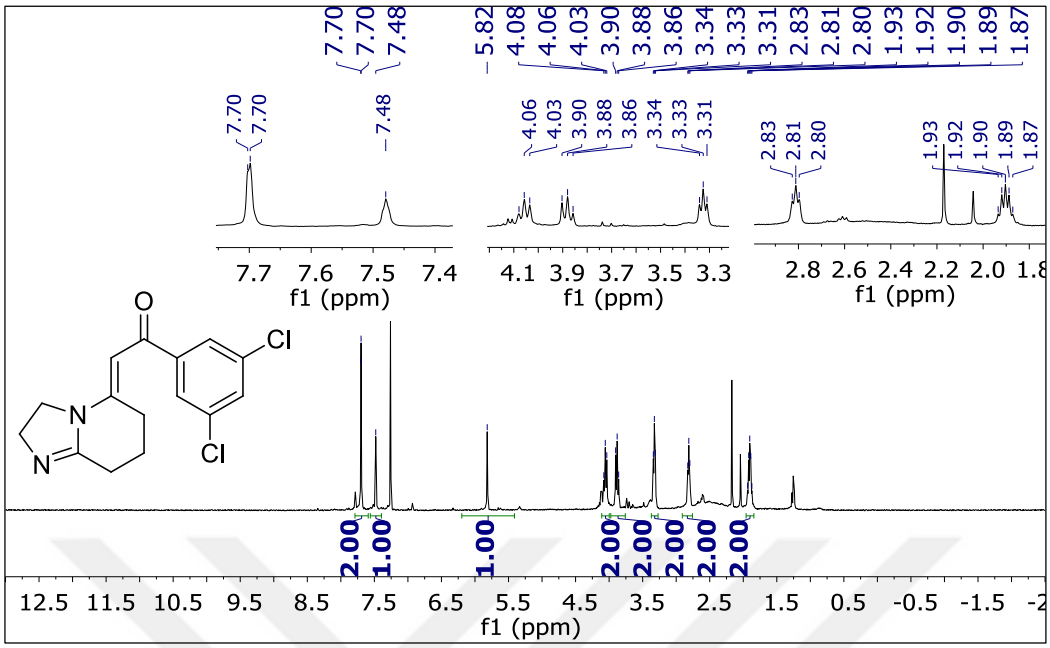


Figure 197. [1]H NMR spectrum of compound **44d**.

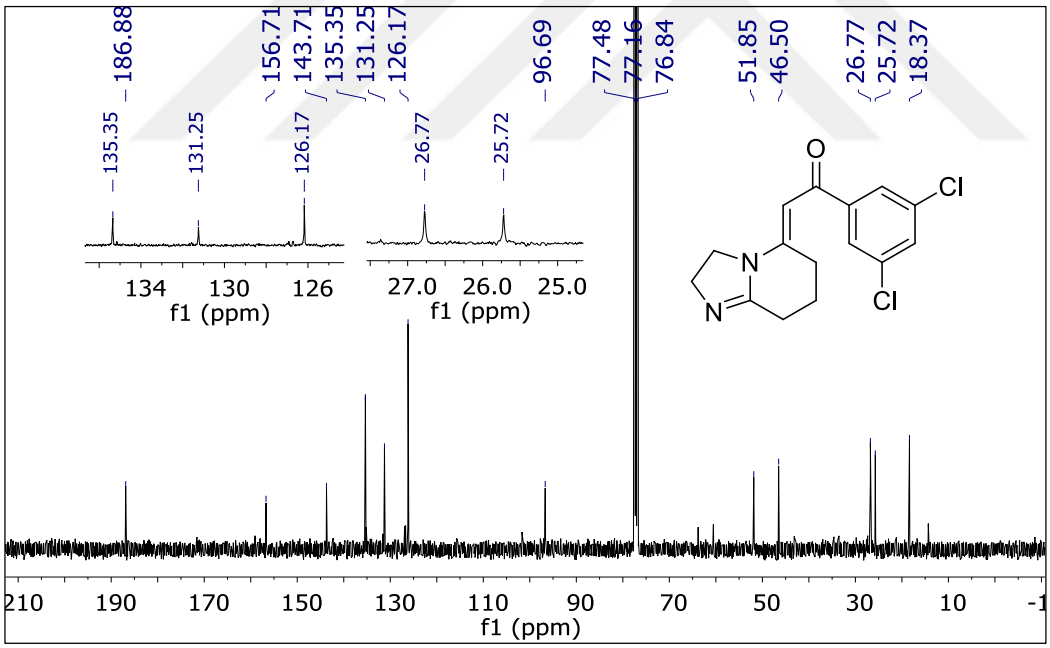


Figure 198. [13]C NMR spectrum of compound **44d**.

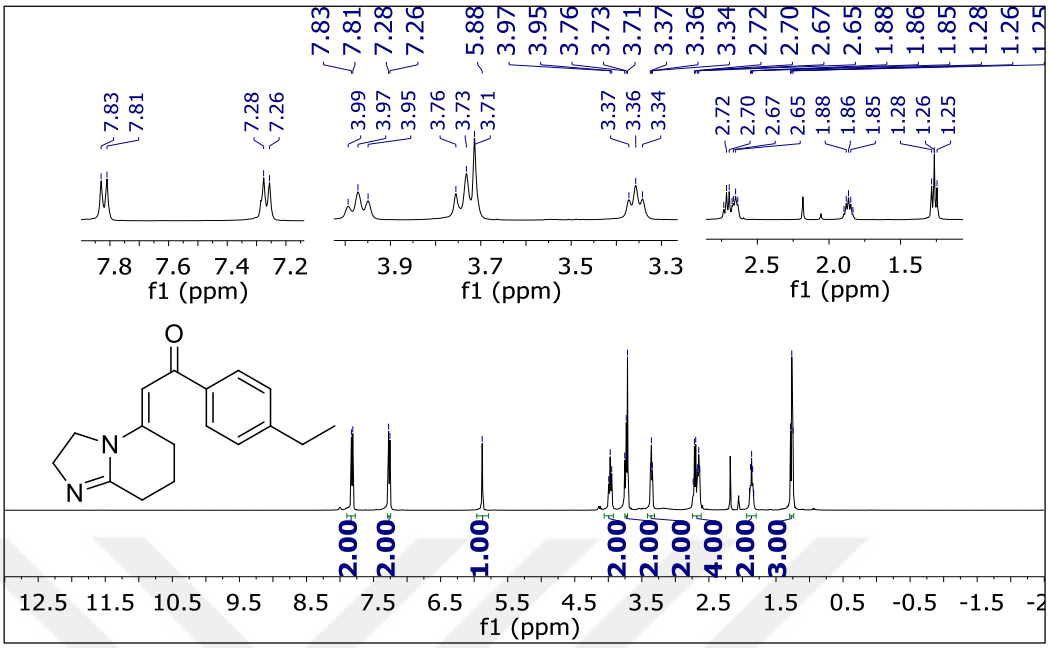


Figure 199. ^{1}H NMR spectrum of compound **44e**.

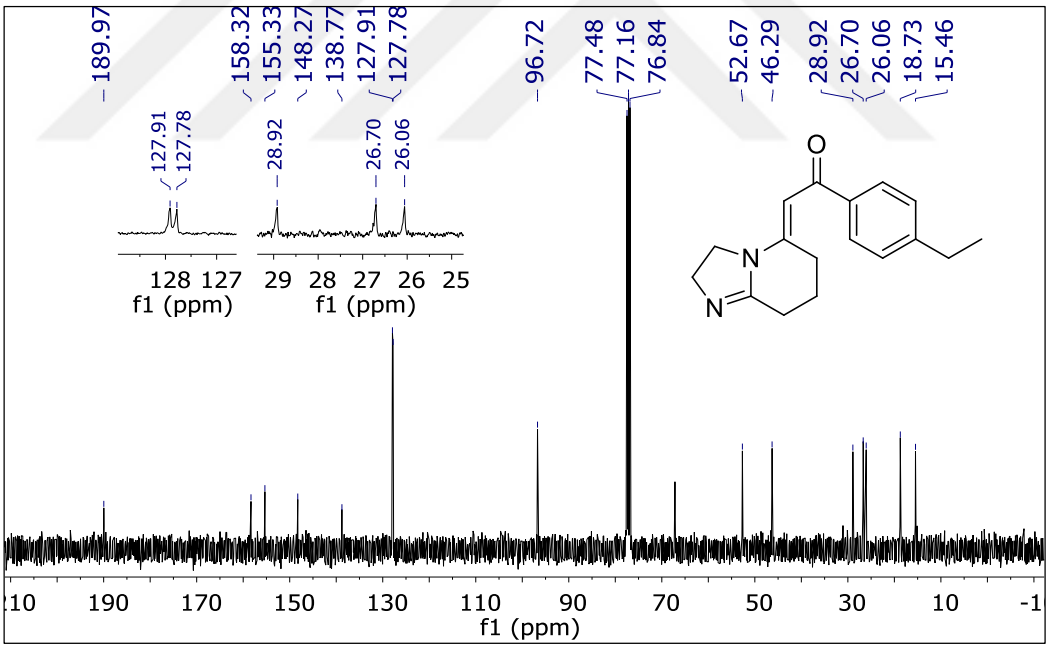


Figure 200. ^{13}C NMR spectrum of compound **44e**.

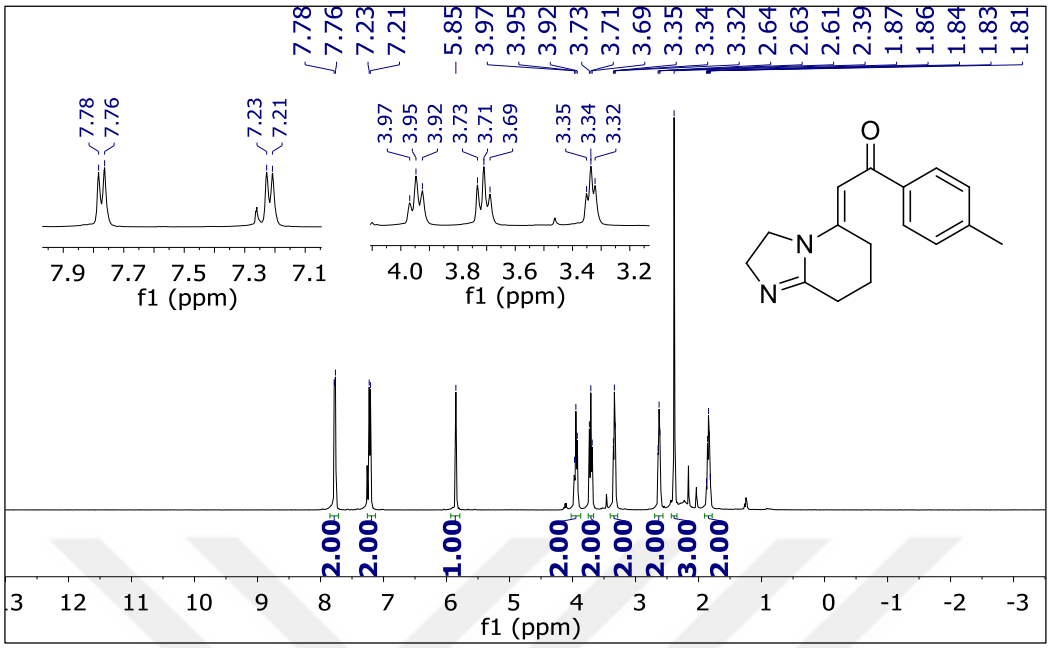


Figure 201. [1]H NMR spectrum of compound **44f**.

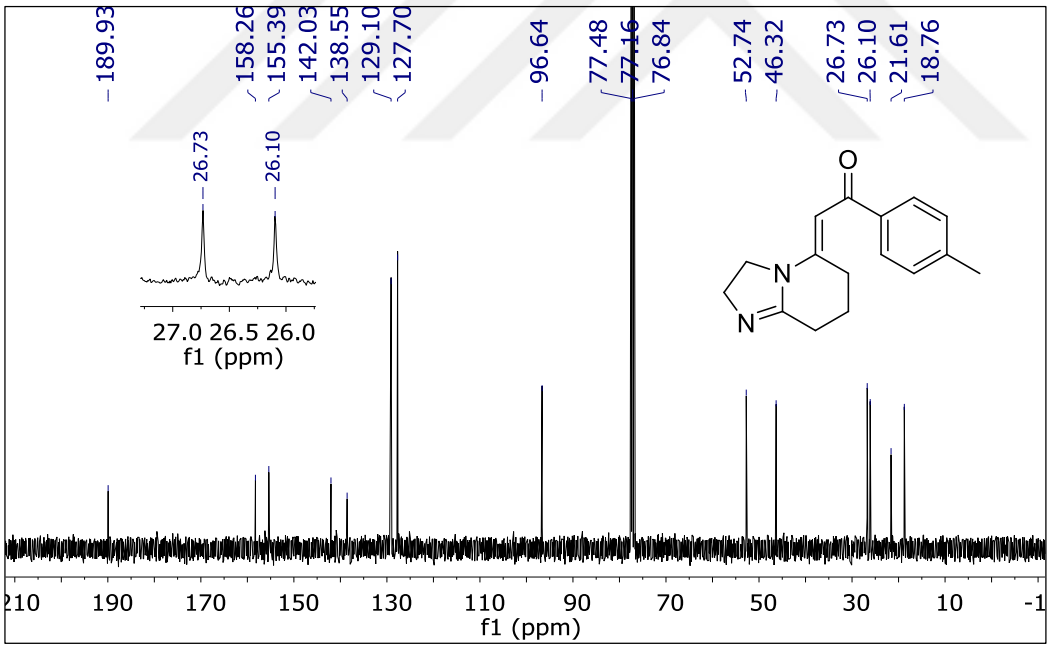


Figure 202. [13]C NMR spectrum of compound **44f**.

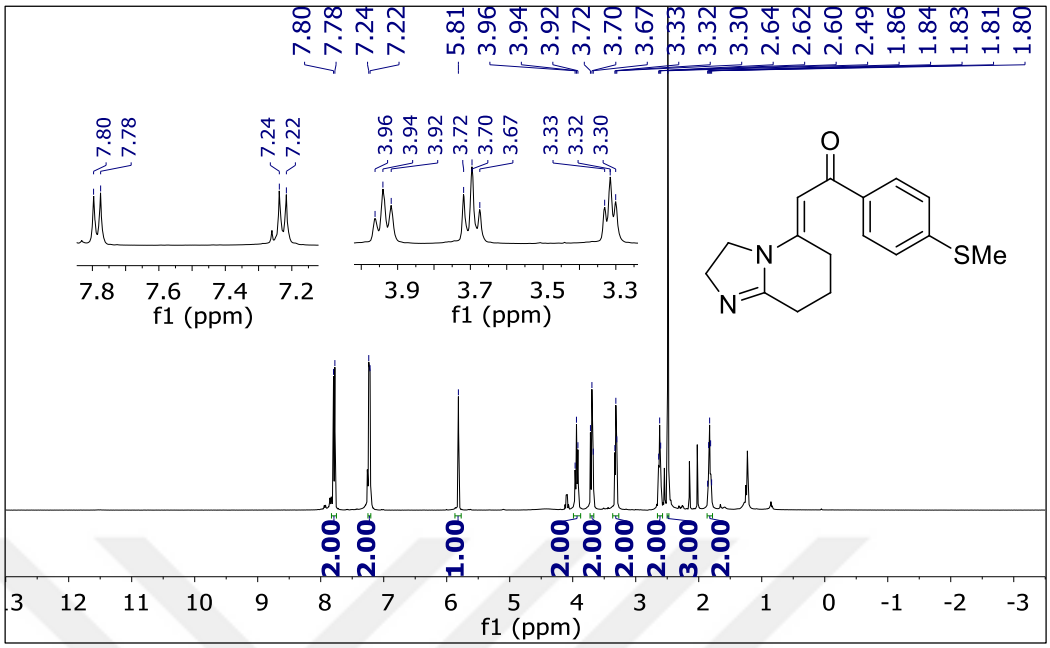


Figure 203. ^{1}H NMR spectrum of compound **44g**.

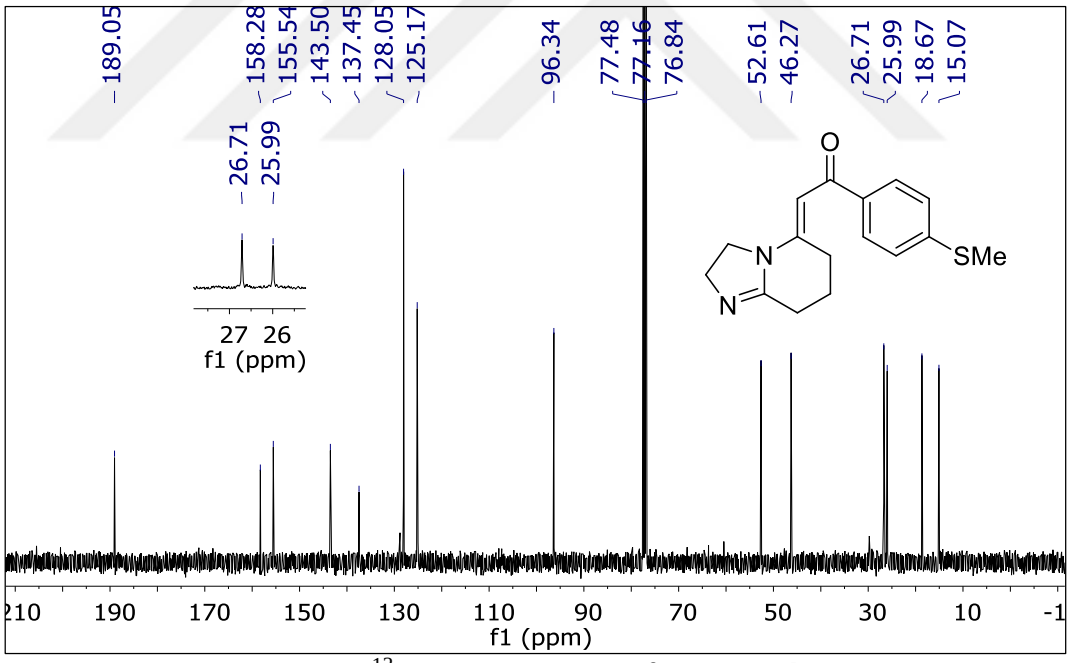


Figure 204. ^{13}C NMR spectrum of compound **44g**.

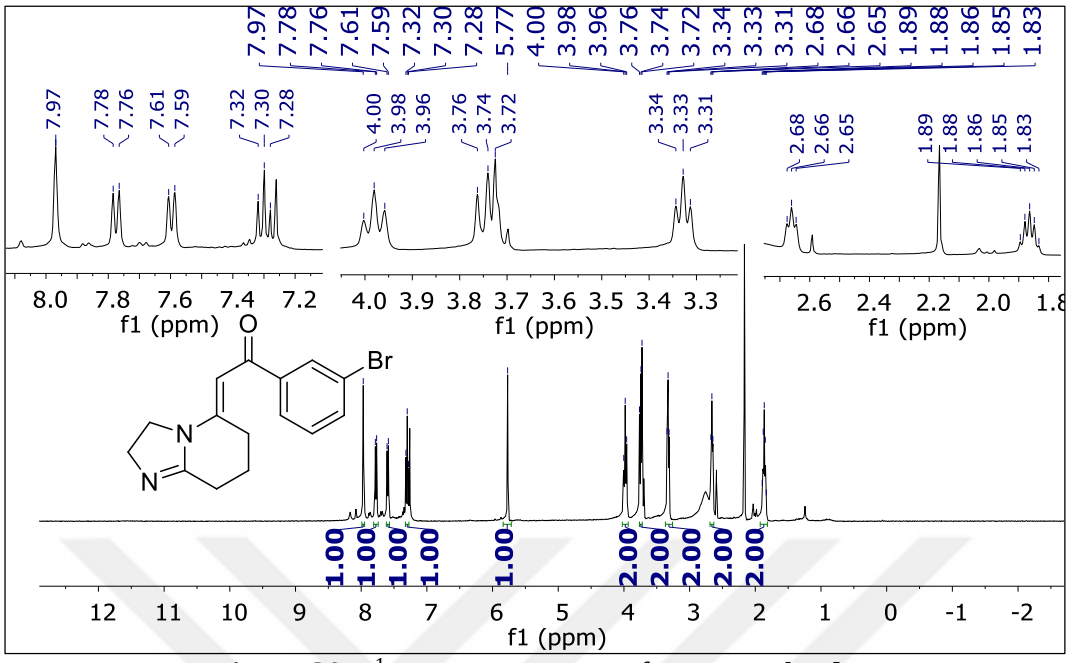


Figure 205. [1]H NMR spectrum of compound **44h**.

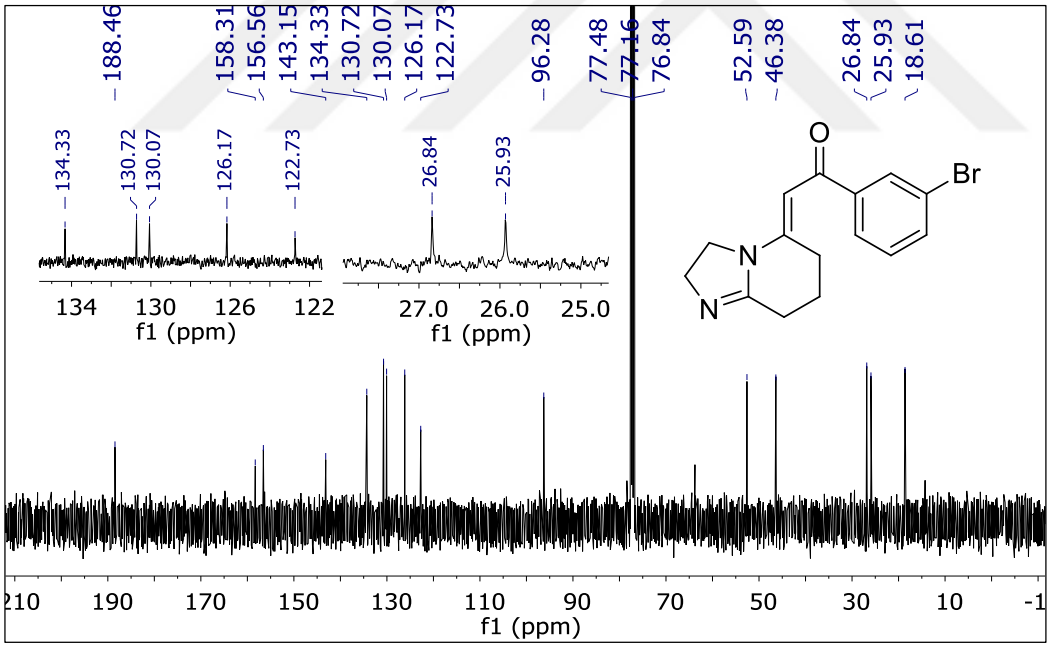


Figure 206. [13]C NMR spectrum of compound **44h**.

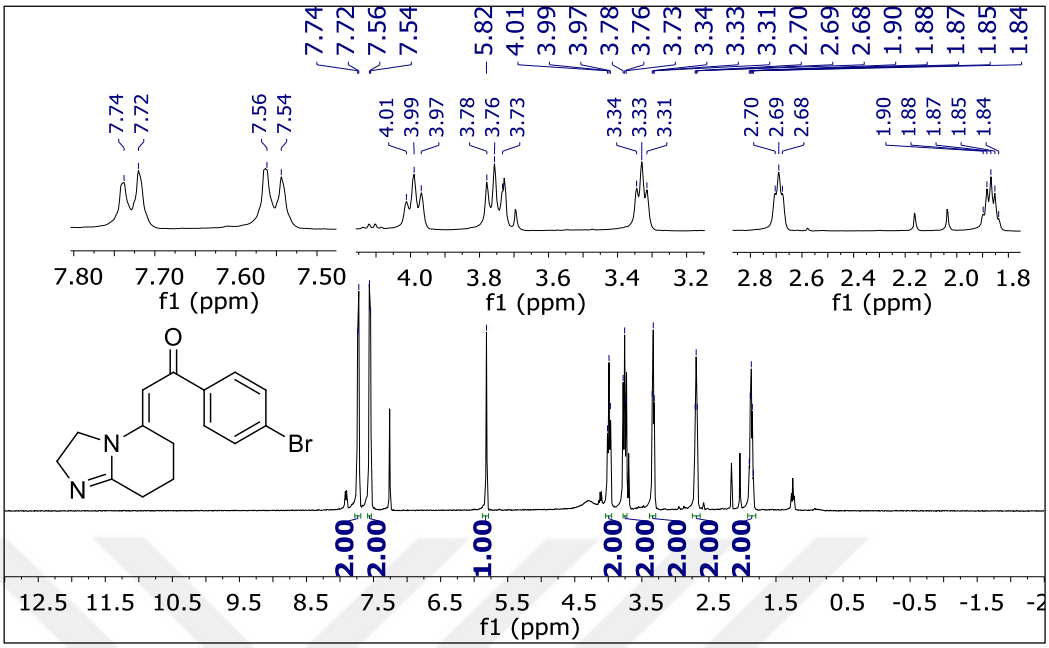


Figure 207. ^{1}H NMR spectrum of compound **44i**.

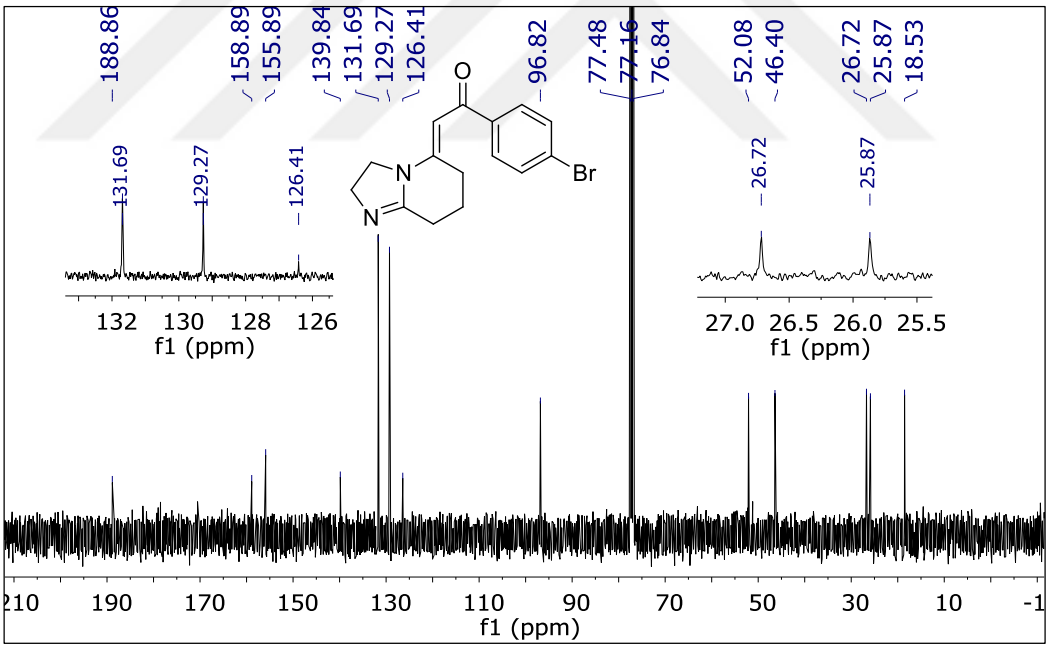


Figure 208. ^{13}C NMR spectrum of compound **44i**.

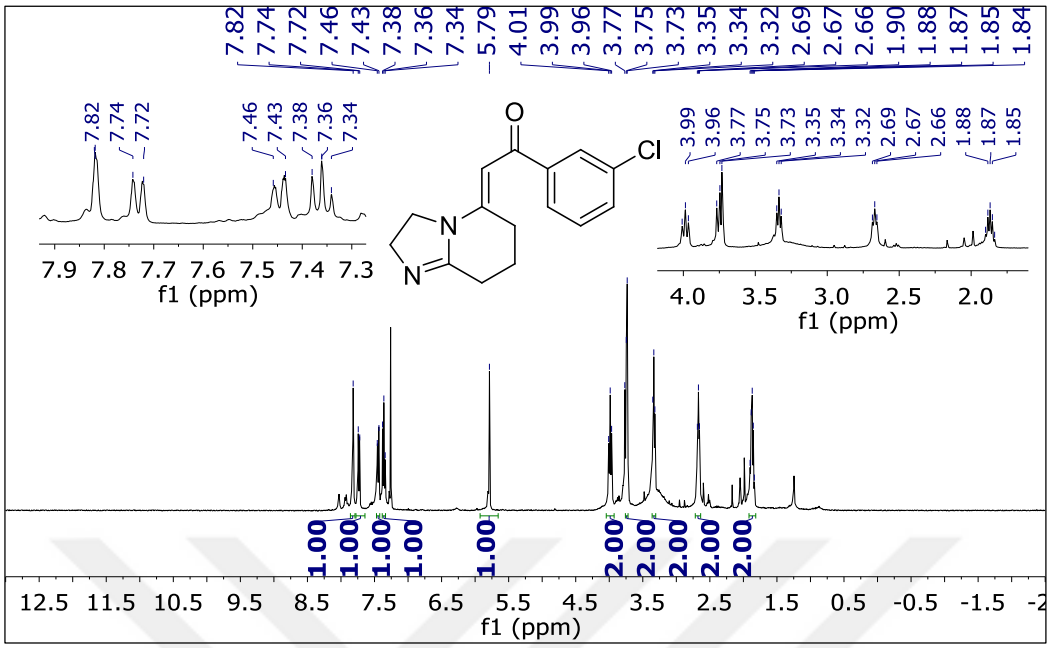


Figure 209. ^{1}H NMR spectrum of compound **44j**.

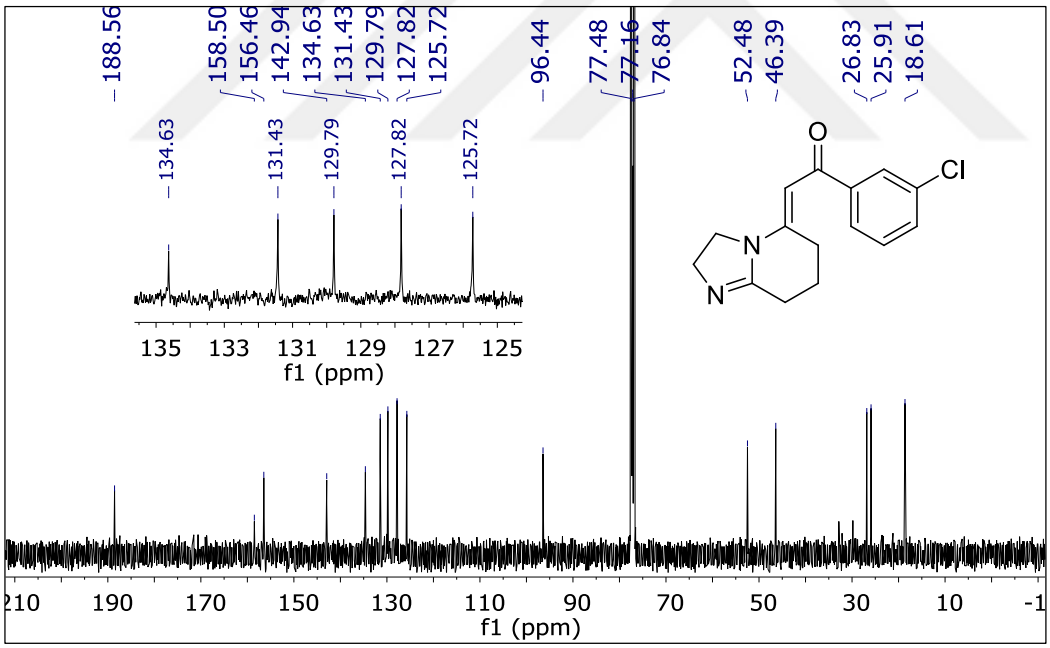


Figure 210. ^{13}C NMR spectrum of compound **44j**.

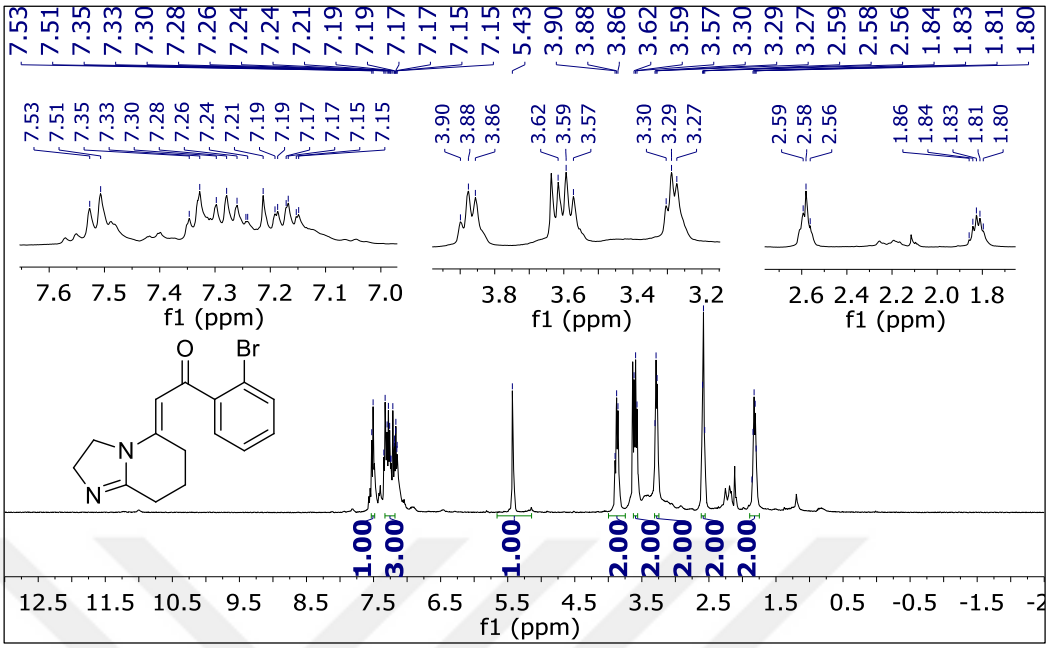


Figure 211. ^{1}H NMR spectrum of compound **44k**.

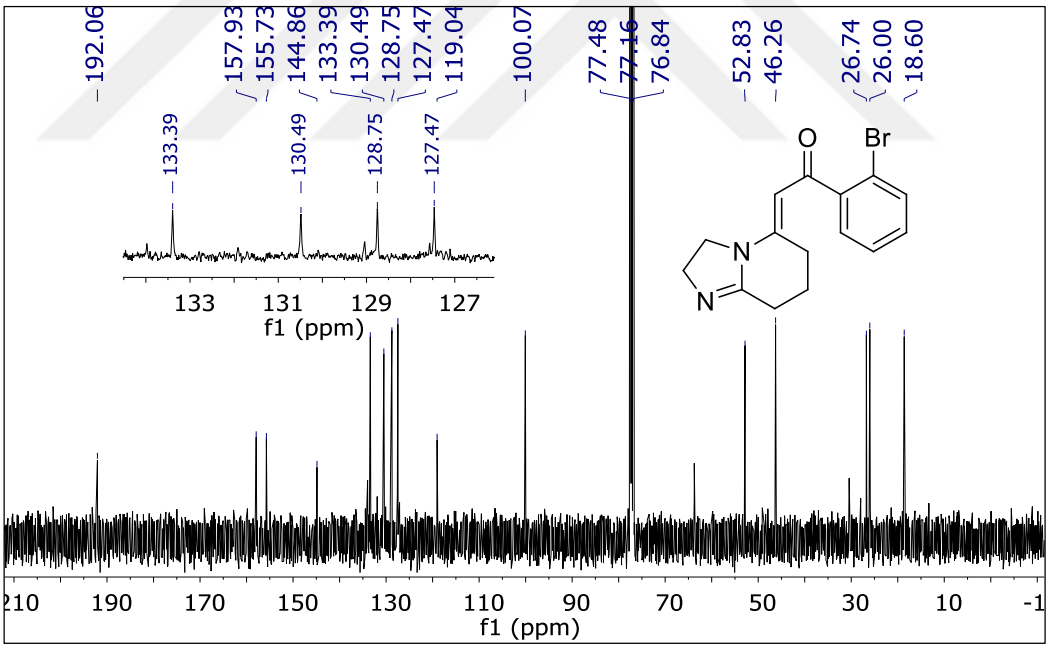


Figure 212. ^{13}C NMR spectrum of compound **44k**.

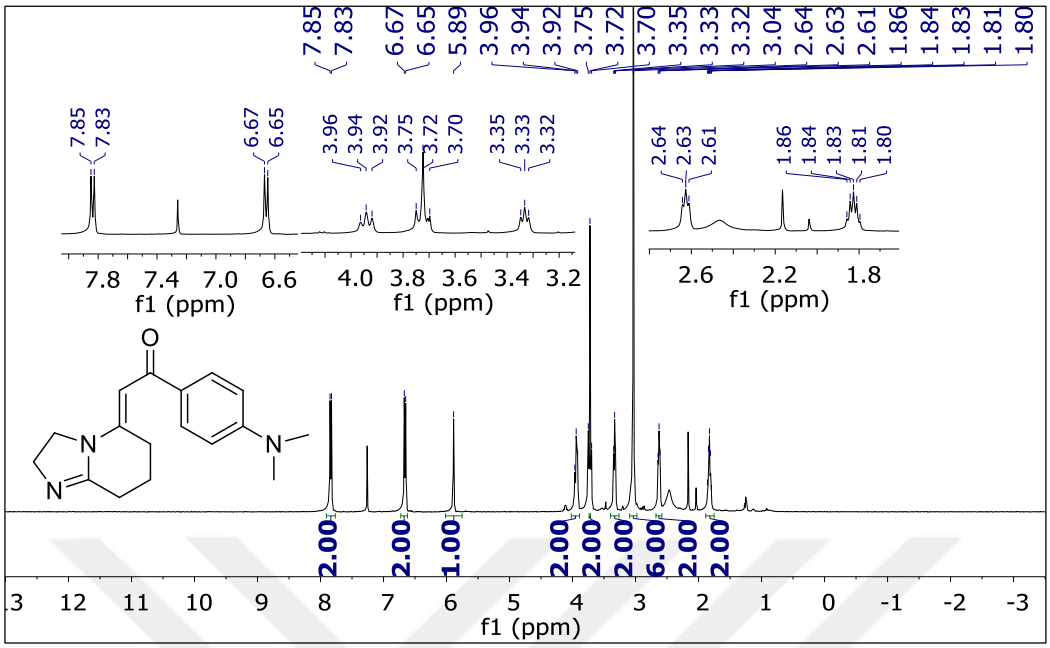


Figure 213. [1]H NMR spectrum of compound **44l**.

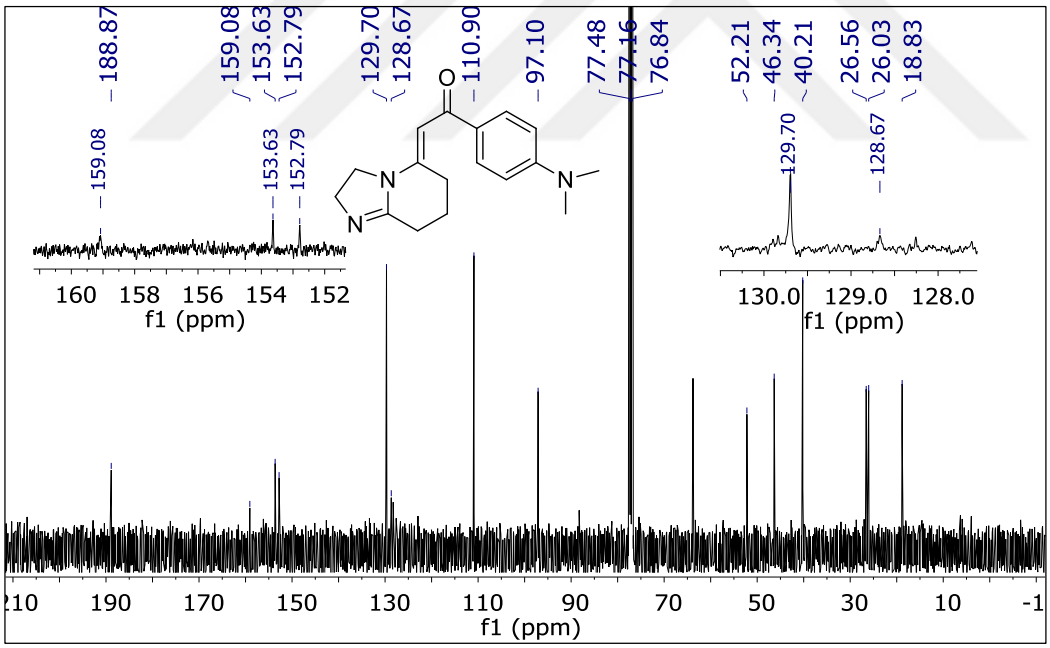


Figure 214. [13]C NMR spectrum of compound **44l**.

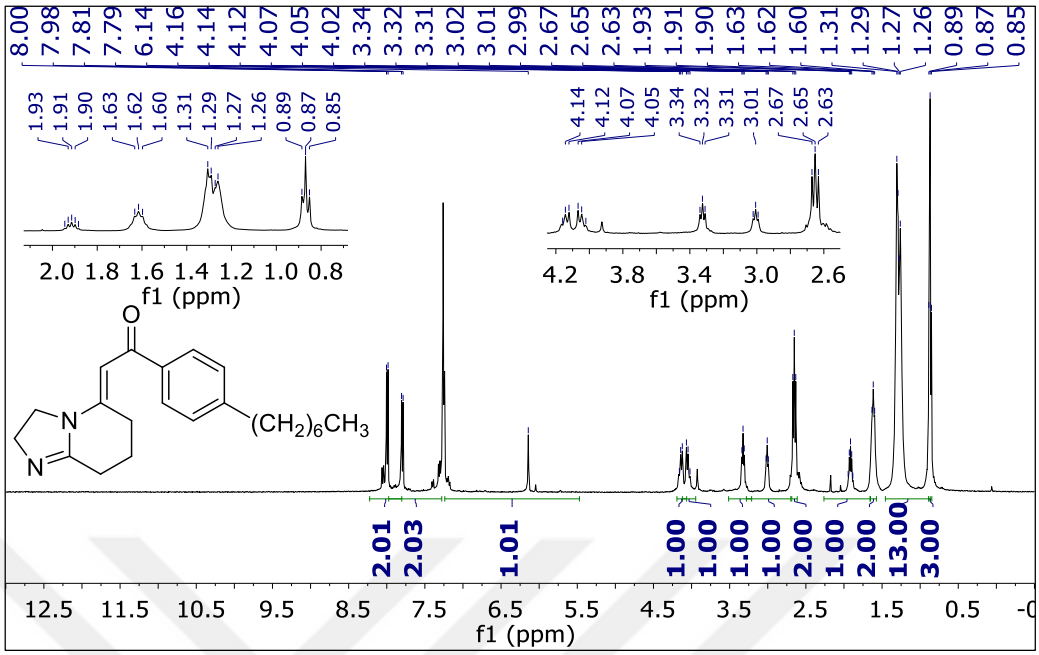


Figure 215. ^{1}H NMR spectrum of compound **44m**.

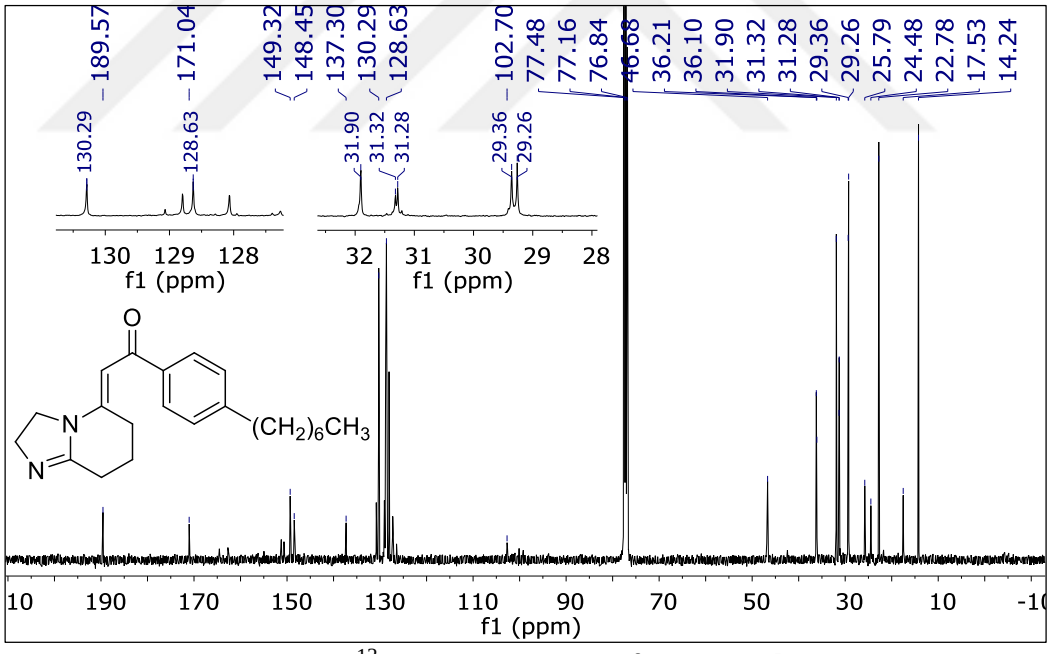


Figure 216. ^{13}C NMR spectrum of compound **44m**.

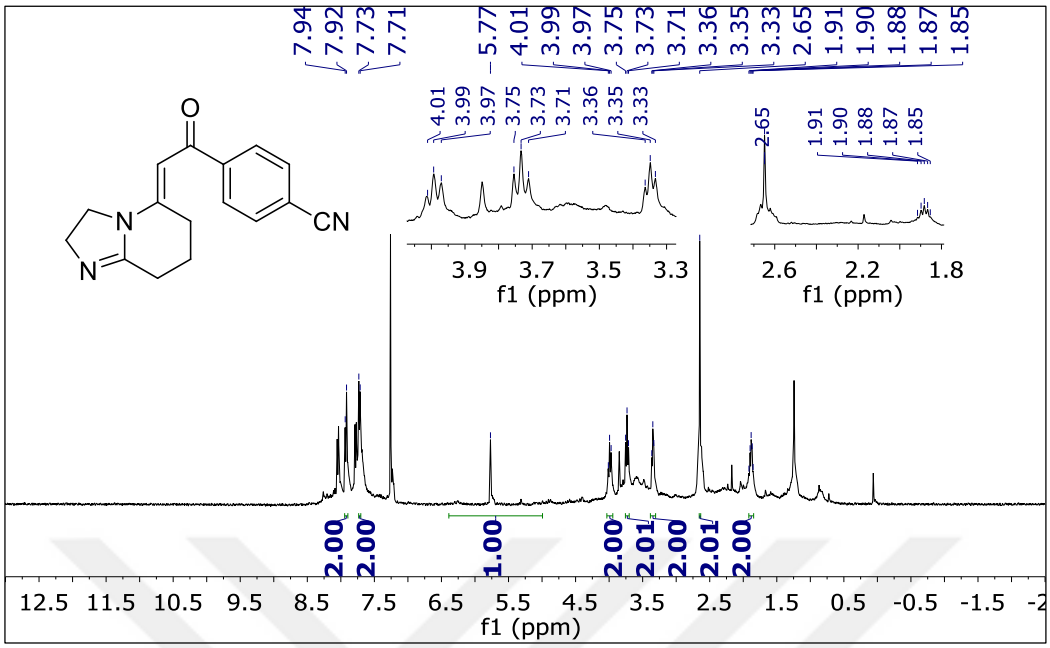


Figure 217. ^{1}H NMR spectrum of compound **44n**.

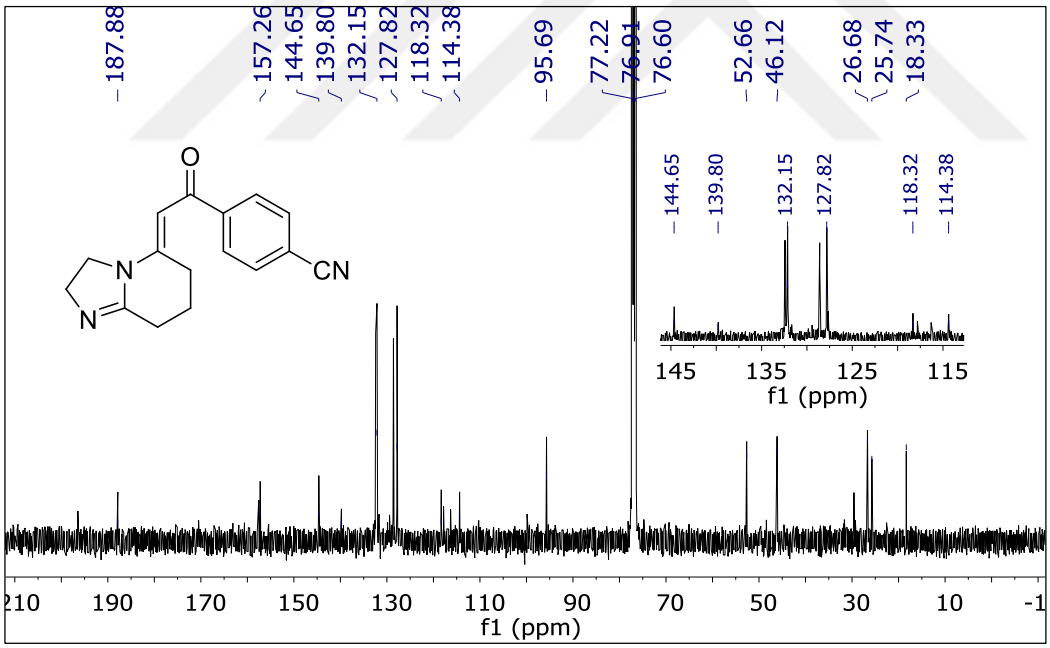


Figure 218. ^{13}C NMR spectrum of compound **44n**.

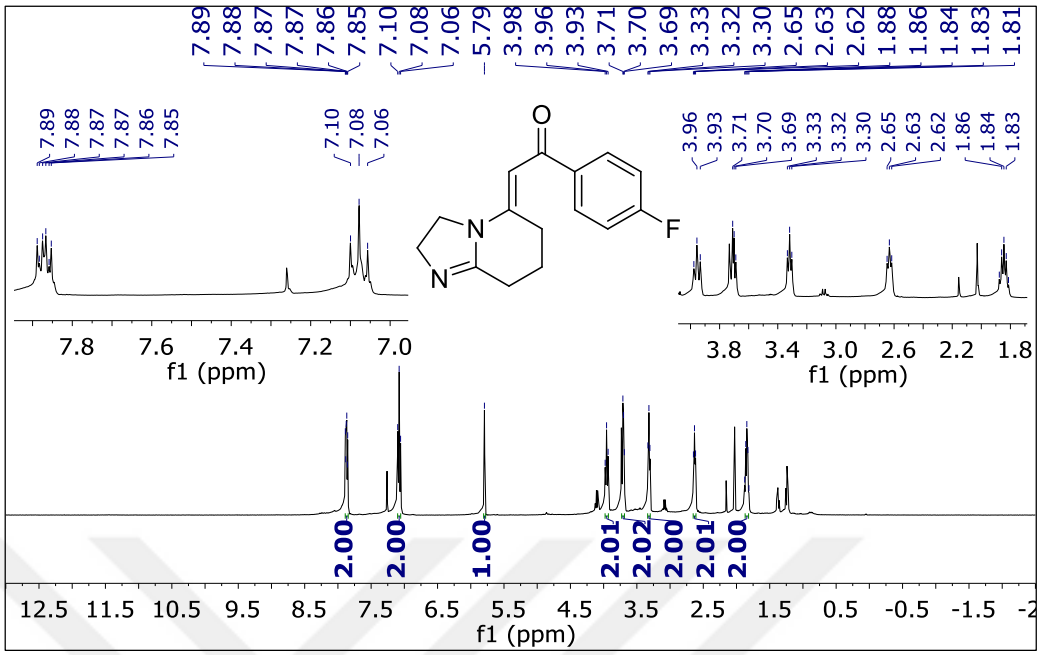


Figure 219. ^{1}H NMR spectrum of compound **44o**.

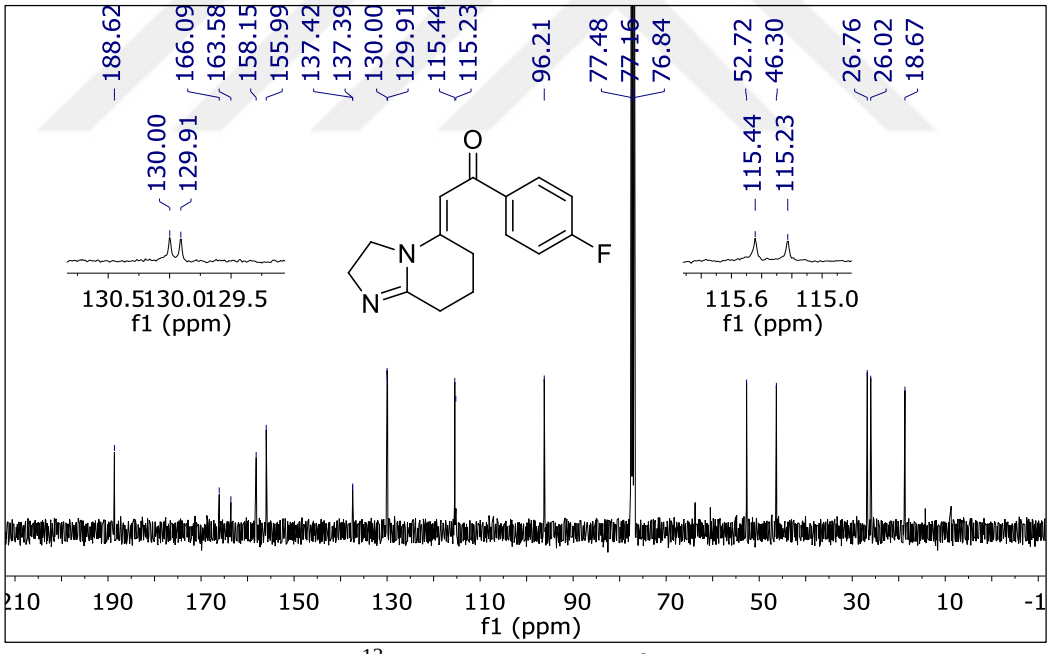


Figure 220. ^{13}C NMR spectrum of compound **44o**.

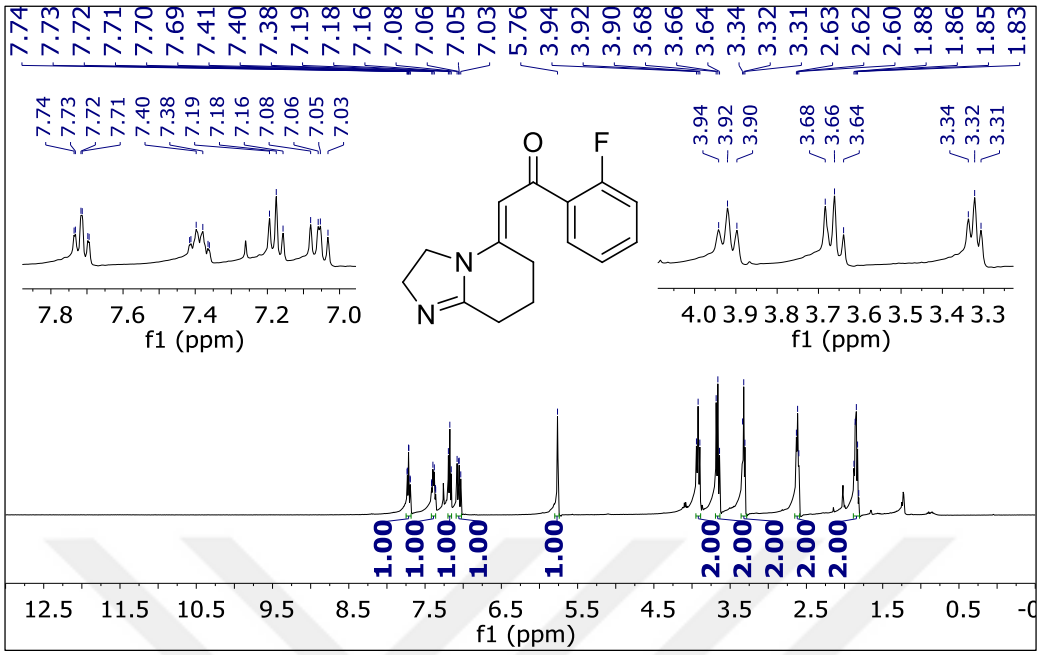


Figure 221. [1]H NMR spectrum of compound **44p**.

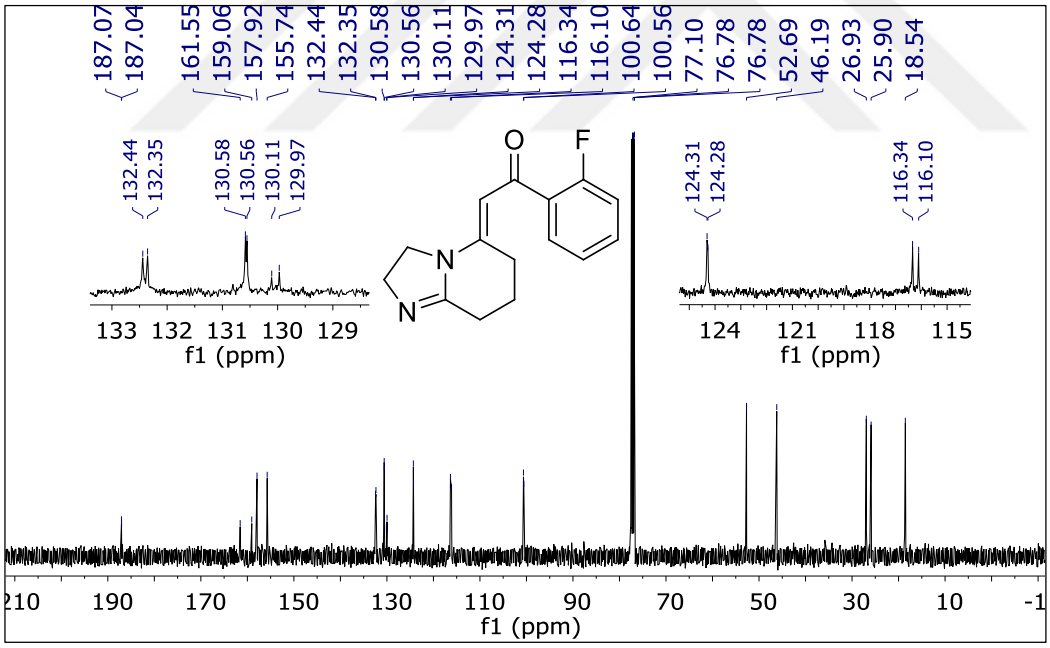


Figure 222. [13]C NMR spectrum of compound **44p**.

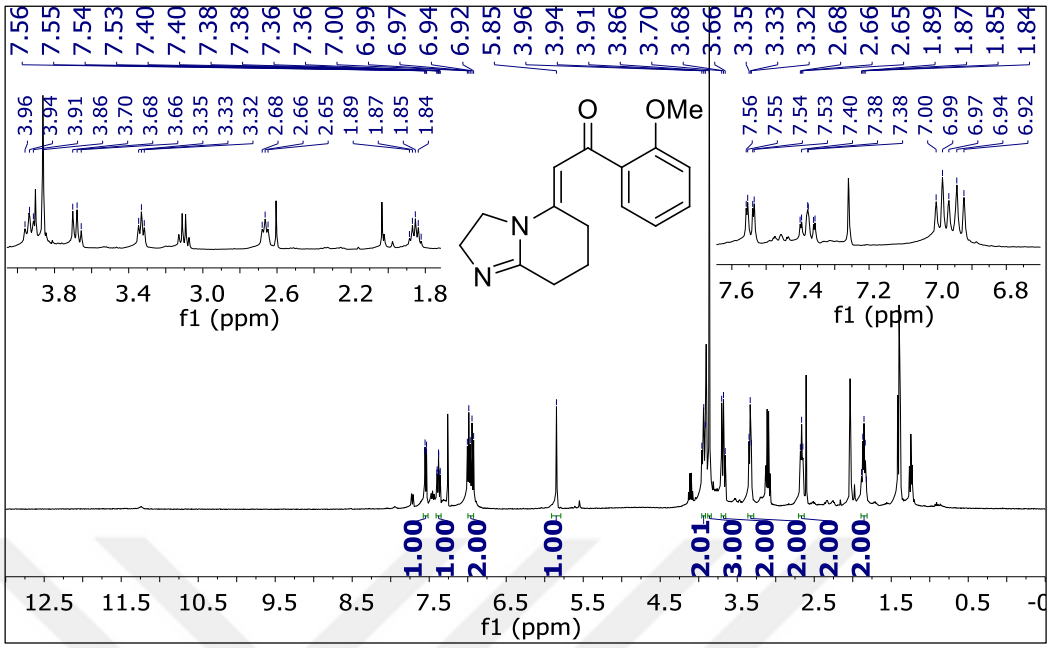


Figure 223. ^{1}H NMR spectrum of compound **44q**.

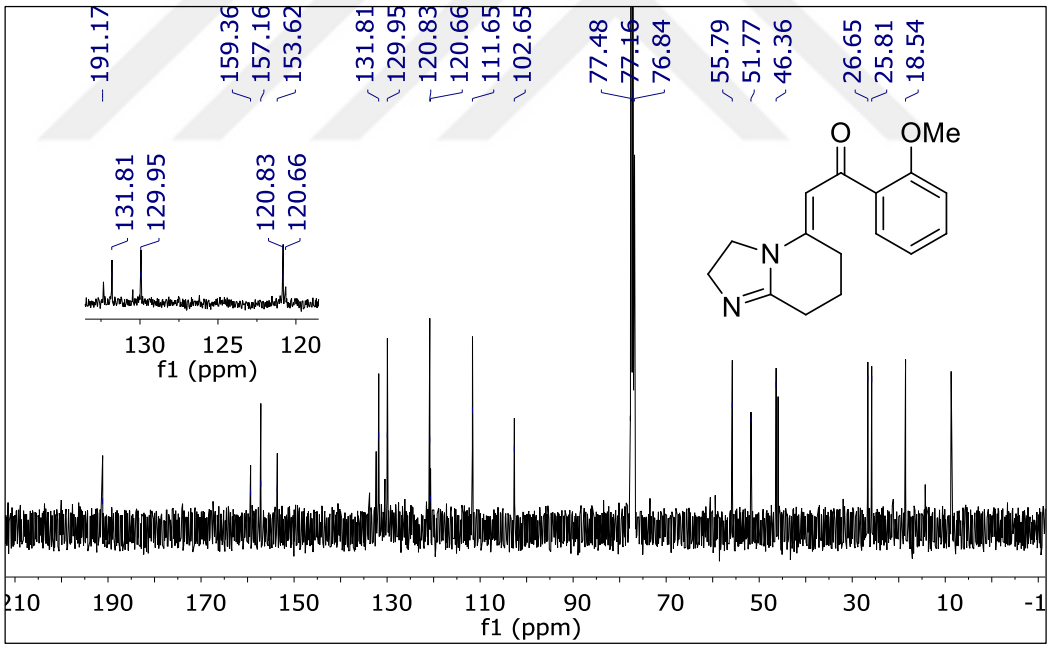


Figure 224. ^{13}C NMR spectrum of compound **44q**.

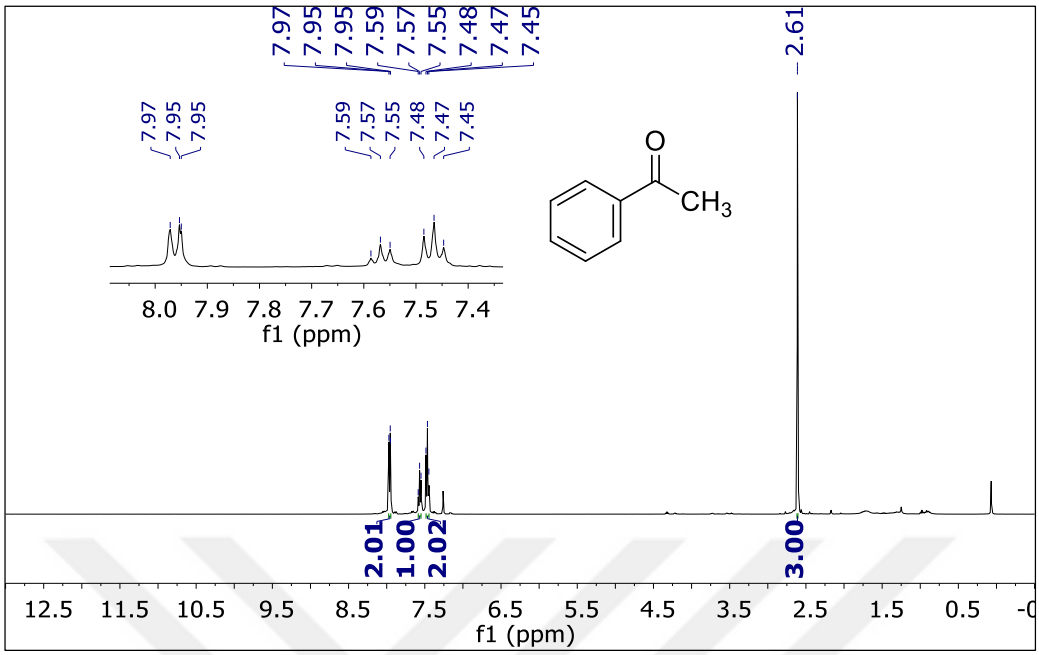


Figure 225. ^{1}H NMR spectrum of compound **45a**.

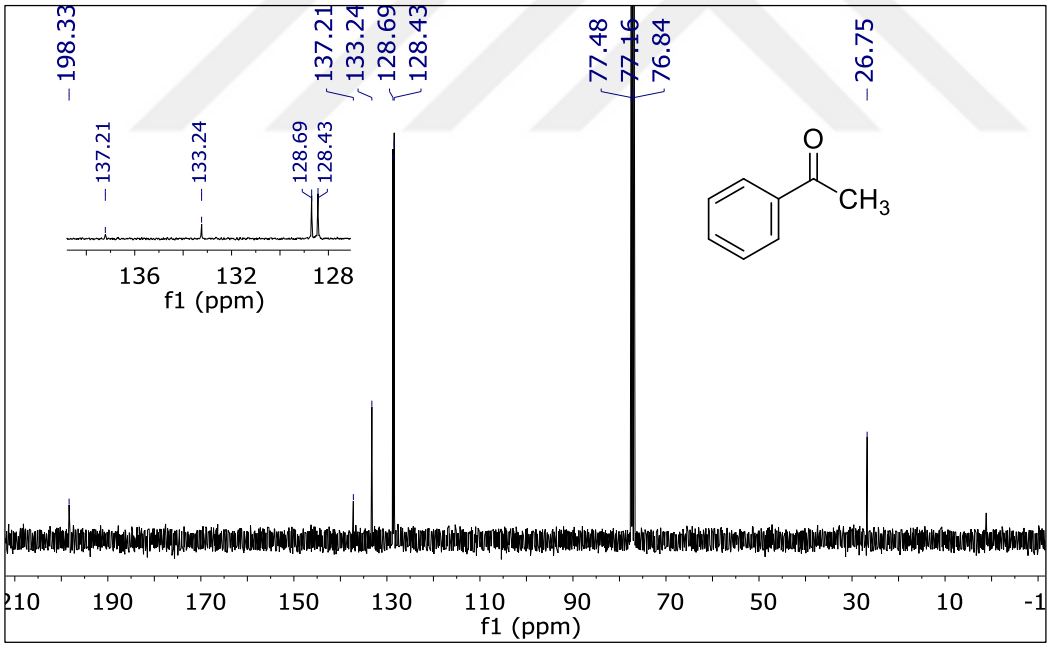


Figure 226. ^{13}C NMR spectrum of compound **45a**.

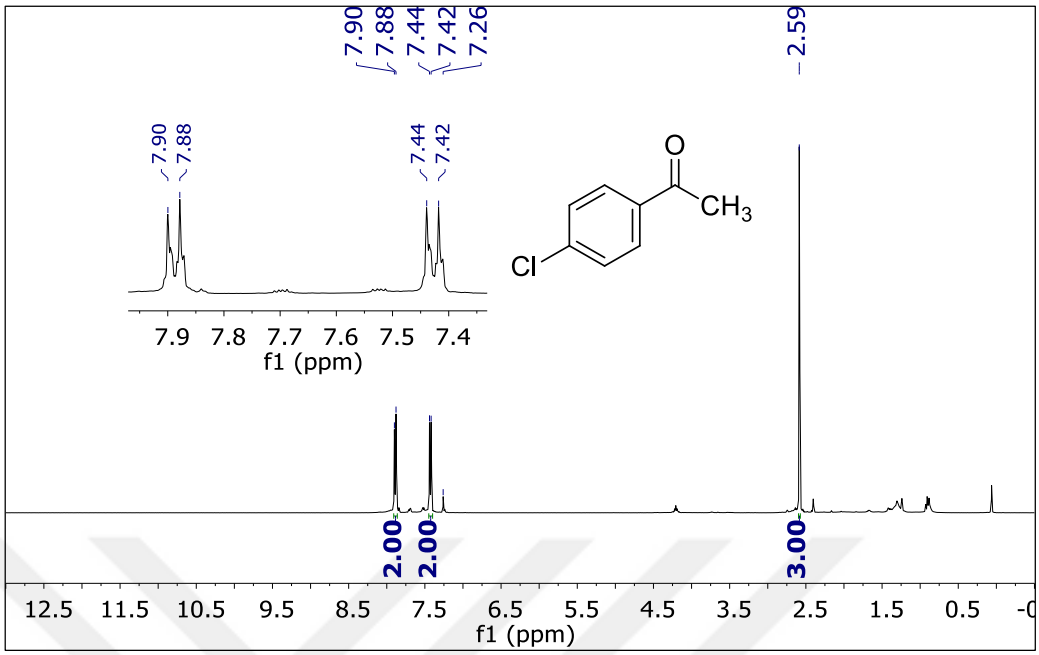


Figure 227. ^{1}H NMR spectrum of compound **45b**.

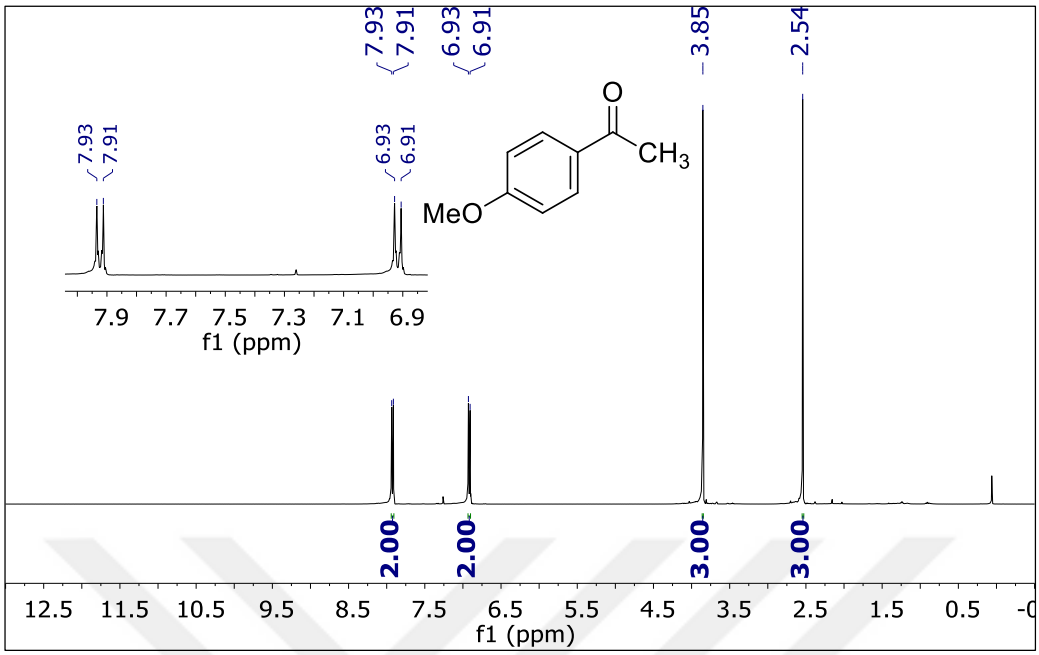


Figure 228. ^{1}H NMR spectrum of compound **45c**.

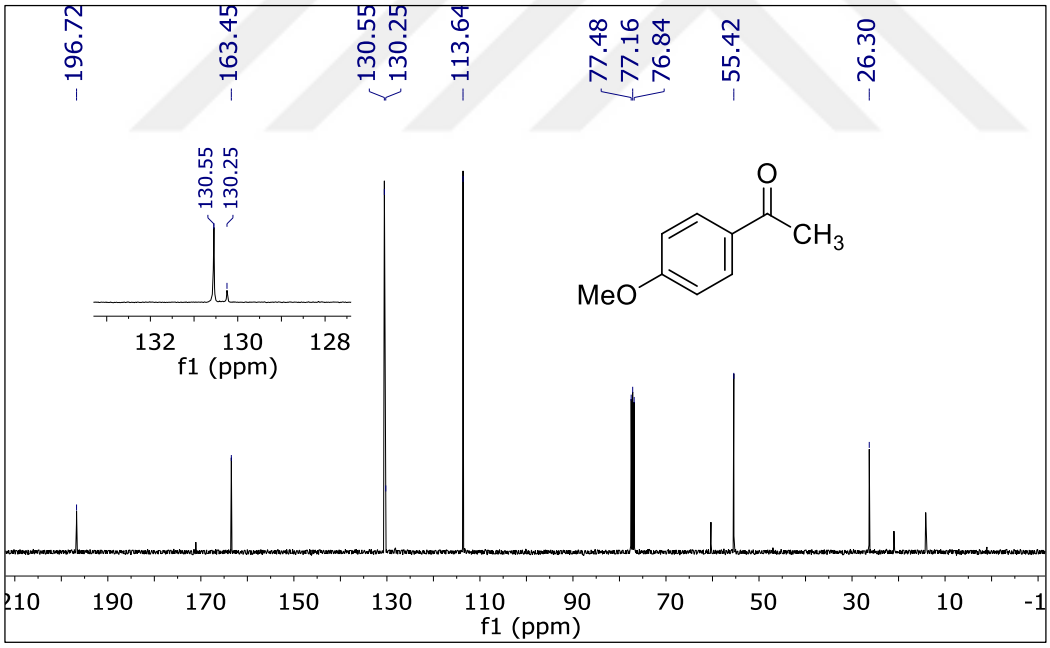


Figure 229. ^{13}C NMR spectrum of compound **45c**.

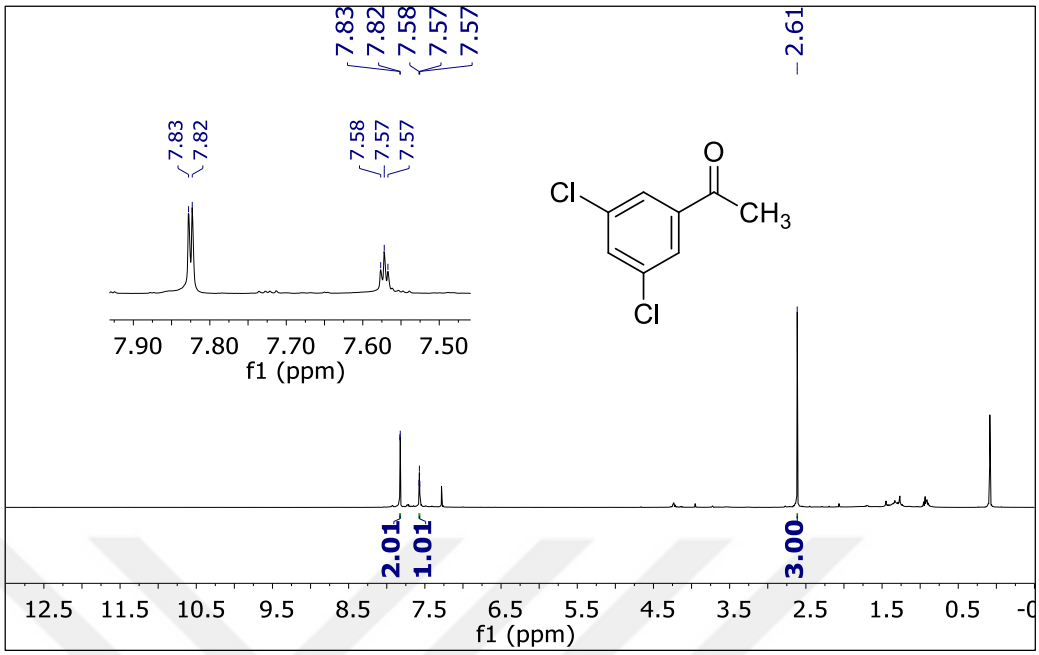


Figure 230. ^{1}H NMR spectrum of compound **45d.**

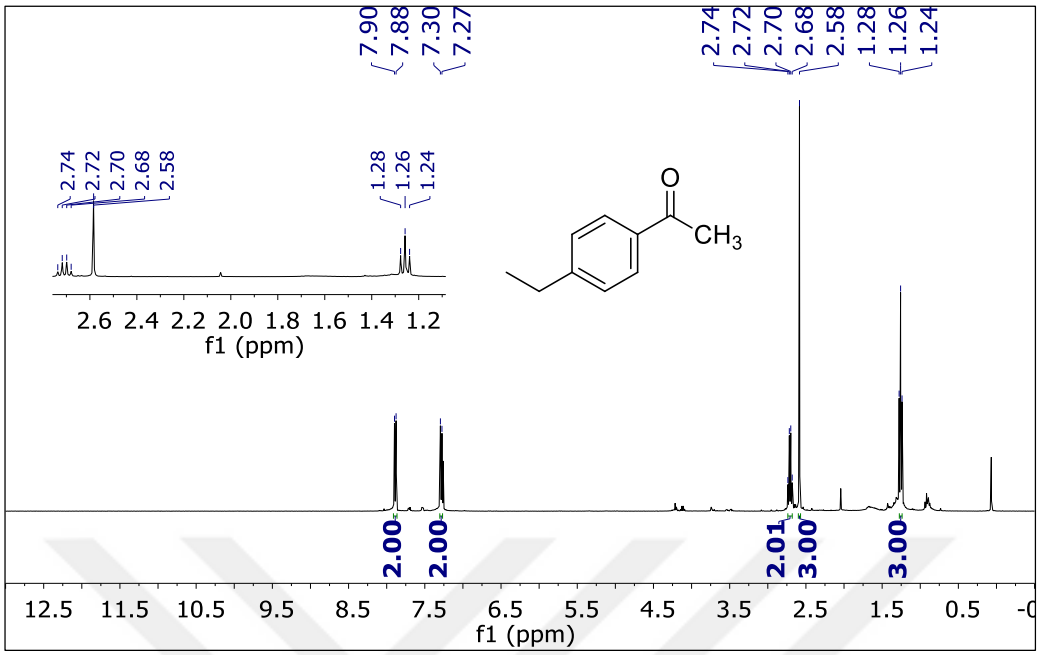


Figure 231. ^{1}H NMR spectrum of compound **45e**.

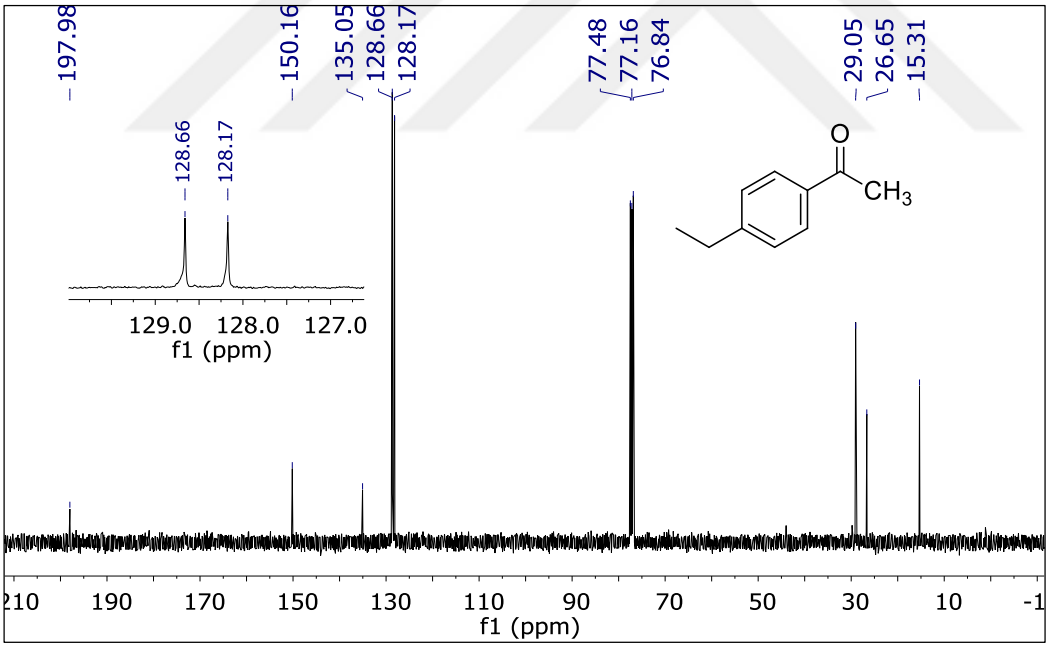


Figure 232. ^{13}C NMR spectrum of compound **45e**.

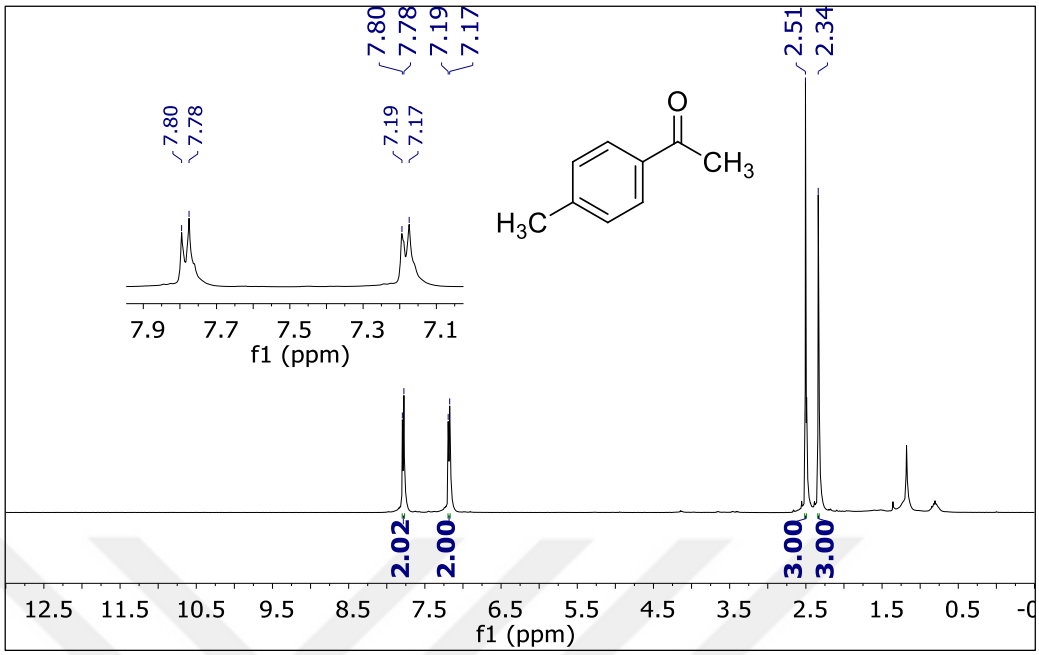


Figure 233. ^{1}H NMR spectrum of compound **45f**.

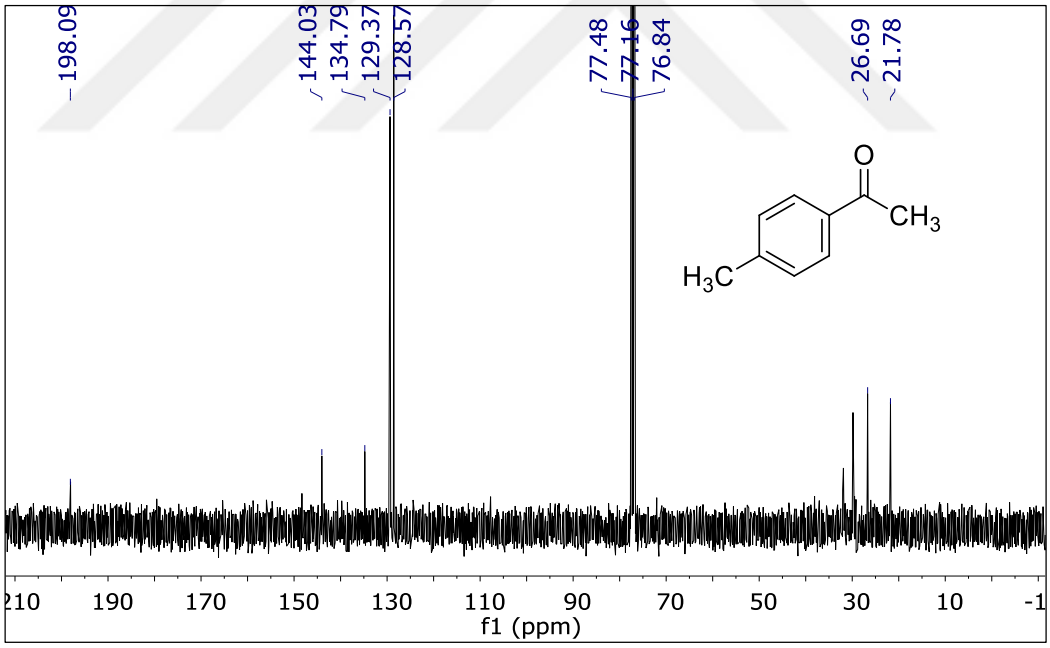


Figure 234. ^{13}C NMR spectrum of compound **45f**.

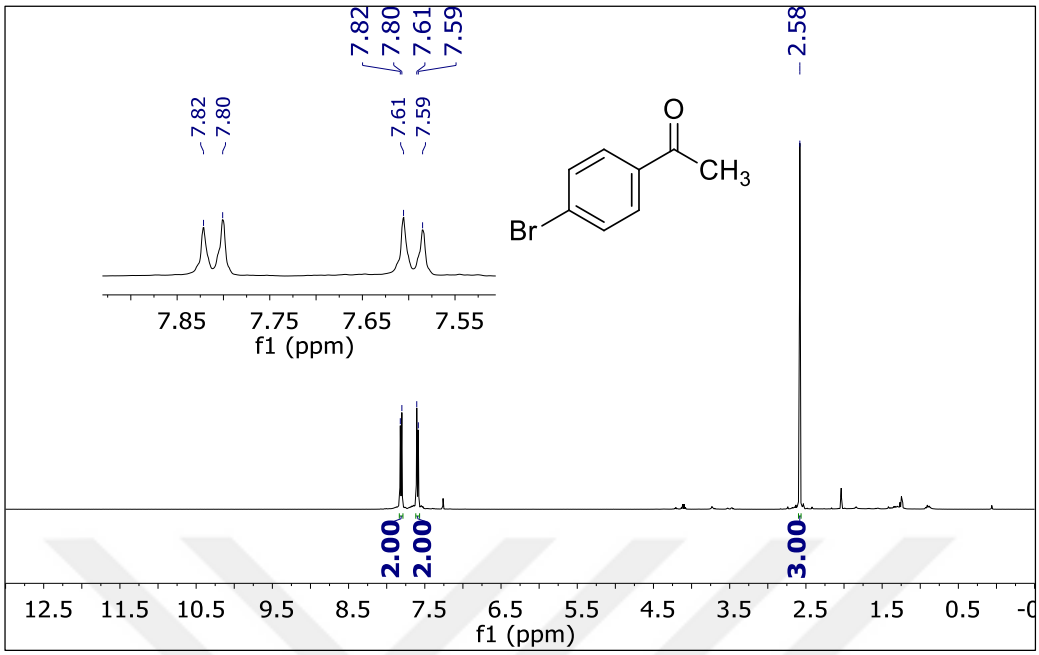


Figure 235. ^{1}H NMR spectrum of compound **45i**.

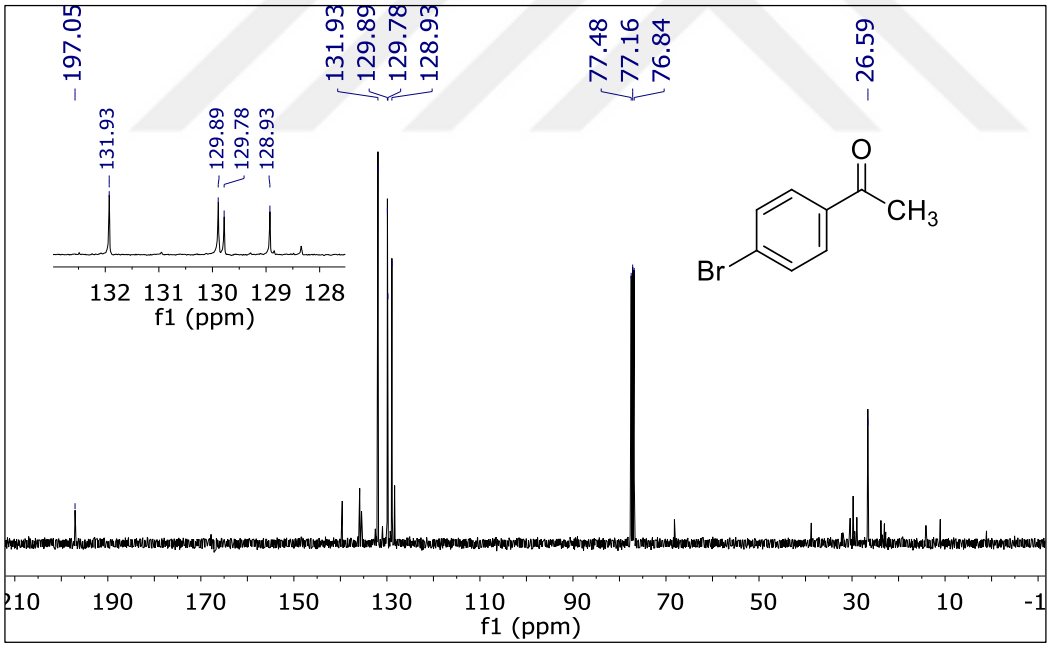


Figure 236. ^{13}C NMR spectrum of compound **45i**.

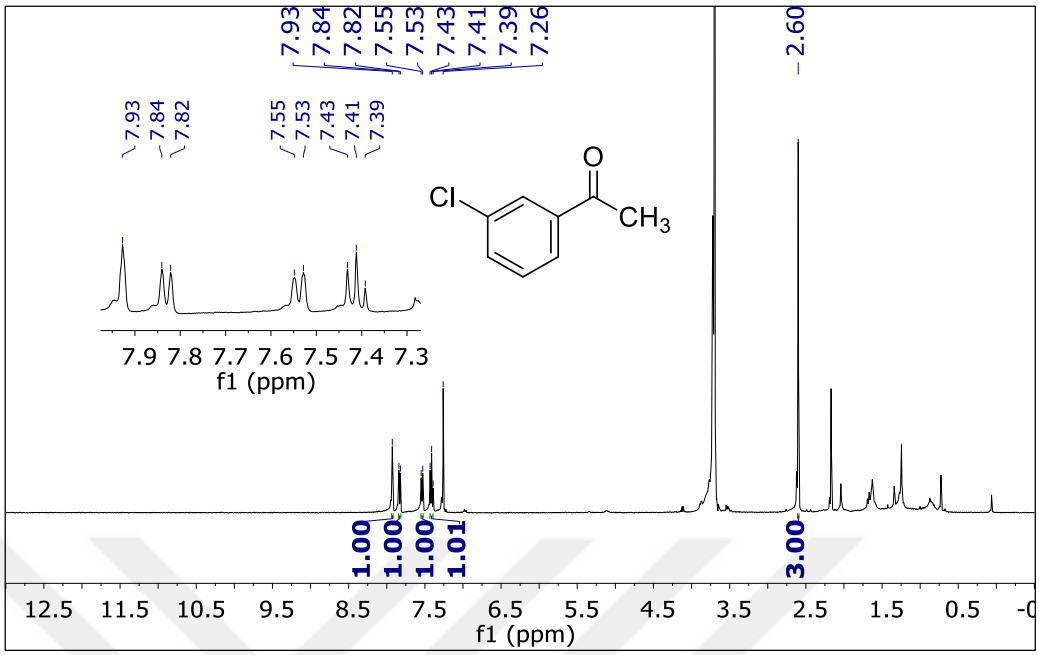


Figure 237. ^{1}H NMR spectrum of compound **45j**.

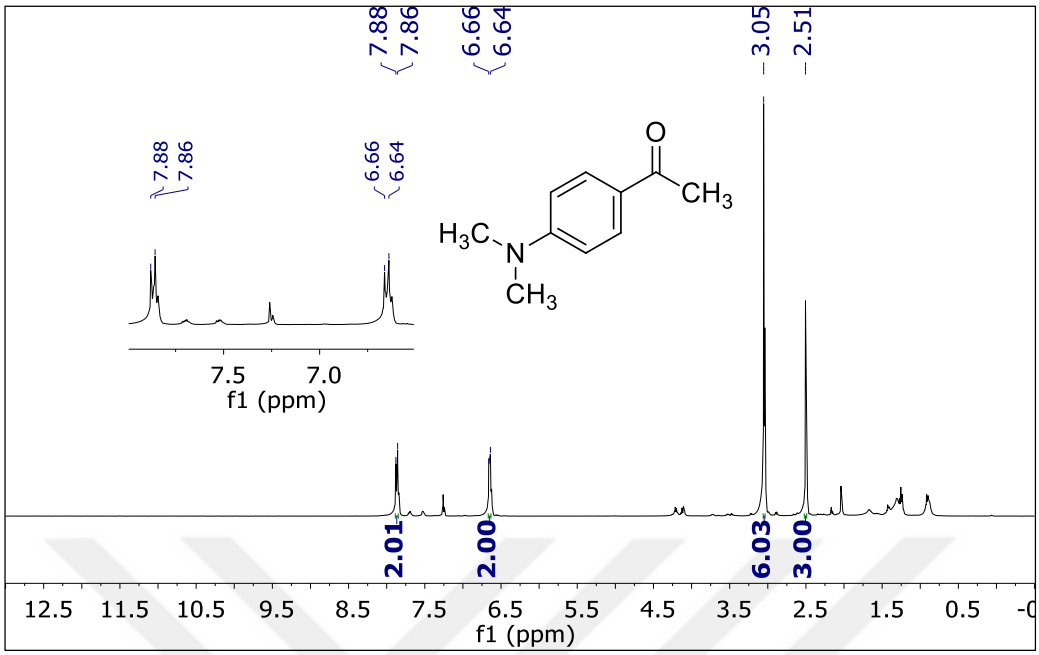


Figure 238. ^{1}H NMR spectrum of compound **45l**.

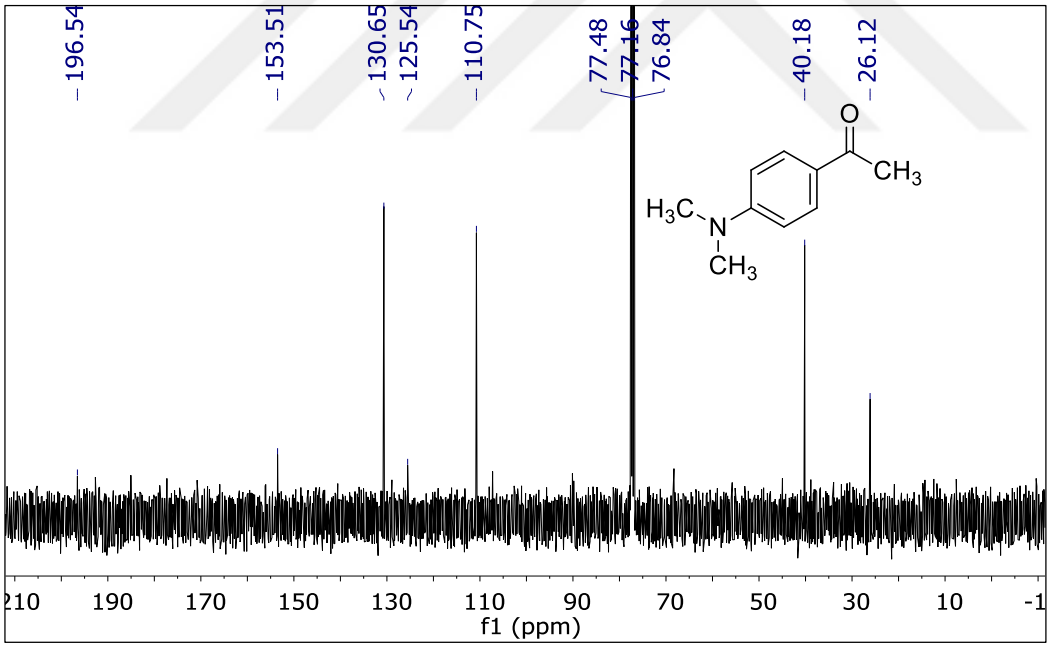


Figure 239. ^{13}C NMR spectrum of compound **45l**.

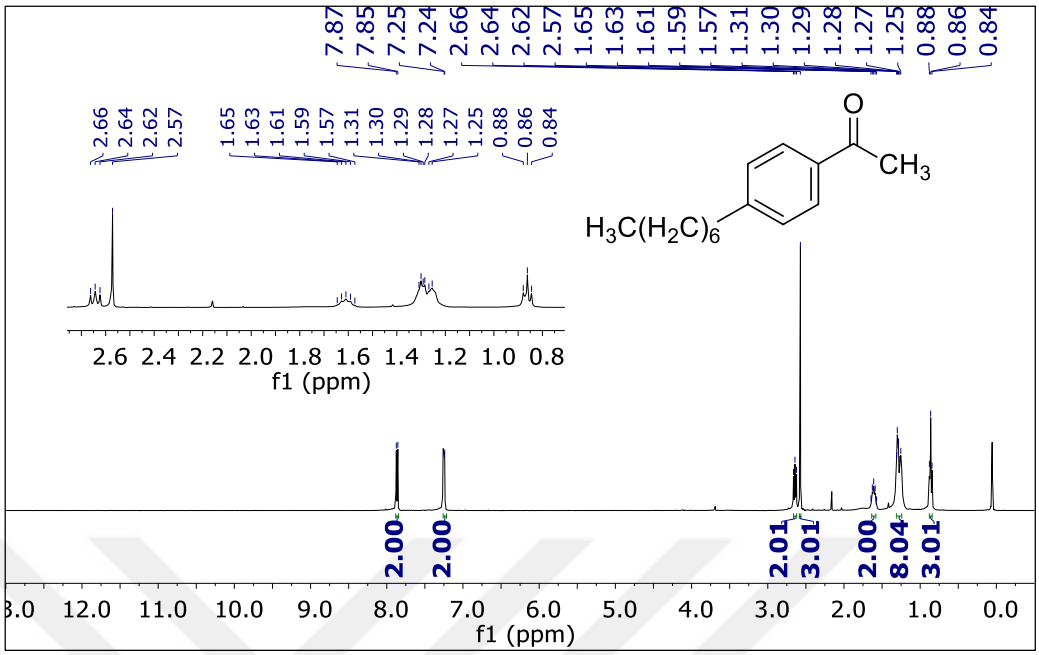


Figure 240. ^{1}H NMR spectrum of compound **45m**.

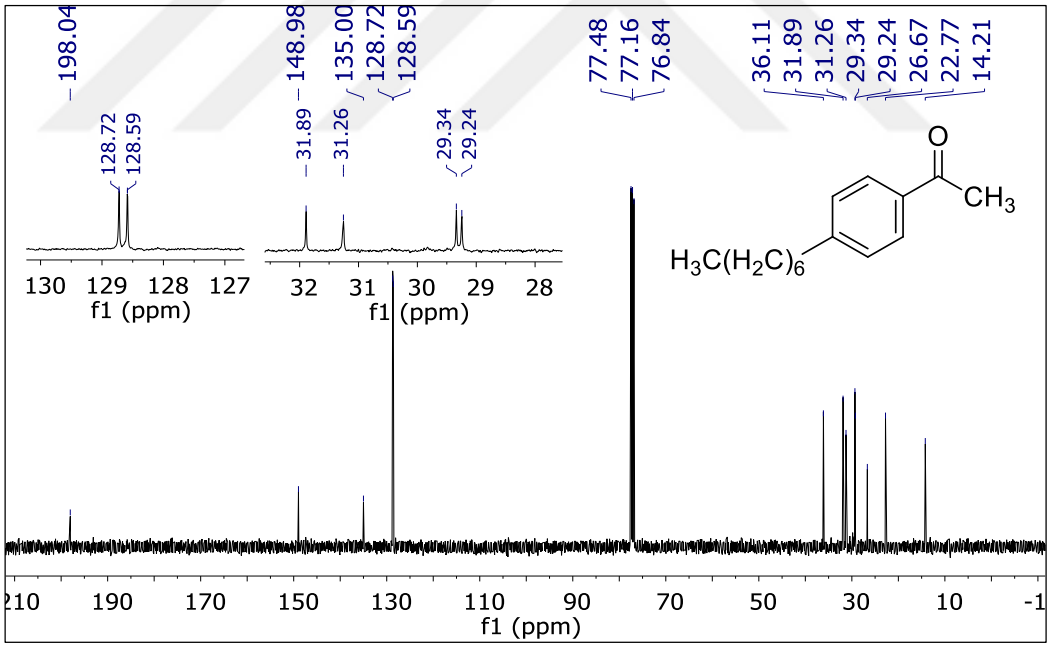


Figure 241. ^{13}C NMR spectrum of compound **45m**.

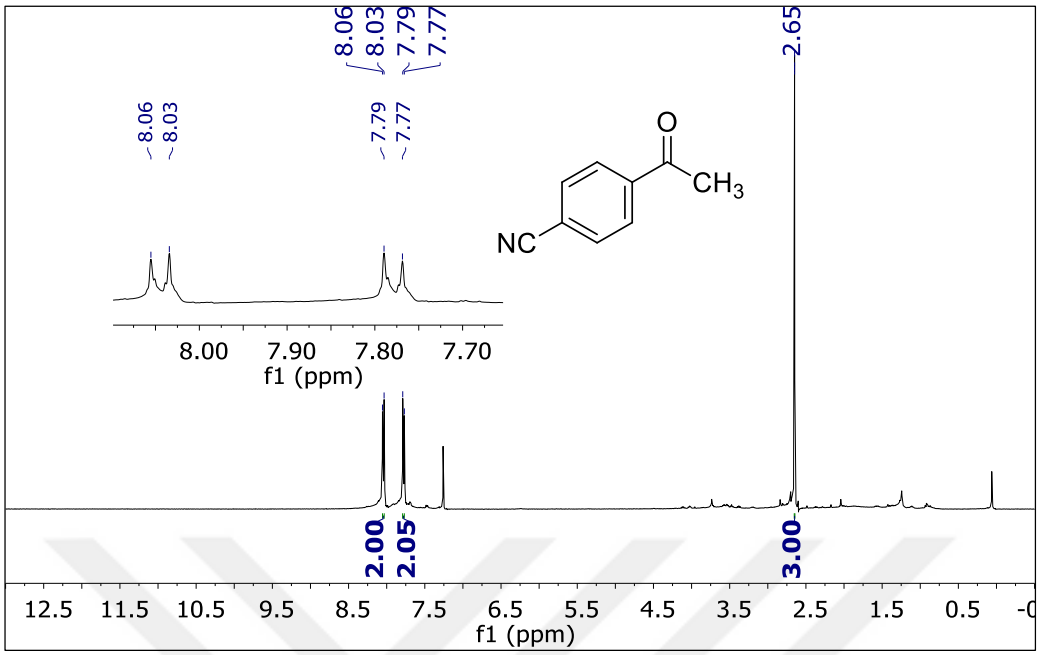


Figure 242. ^{1}H NMR spectrum of compound **45n**.

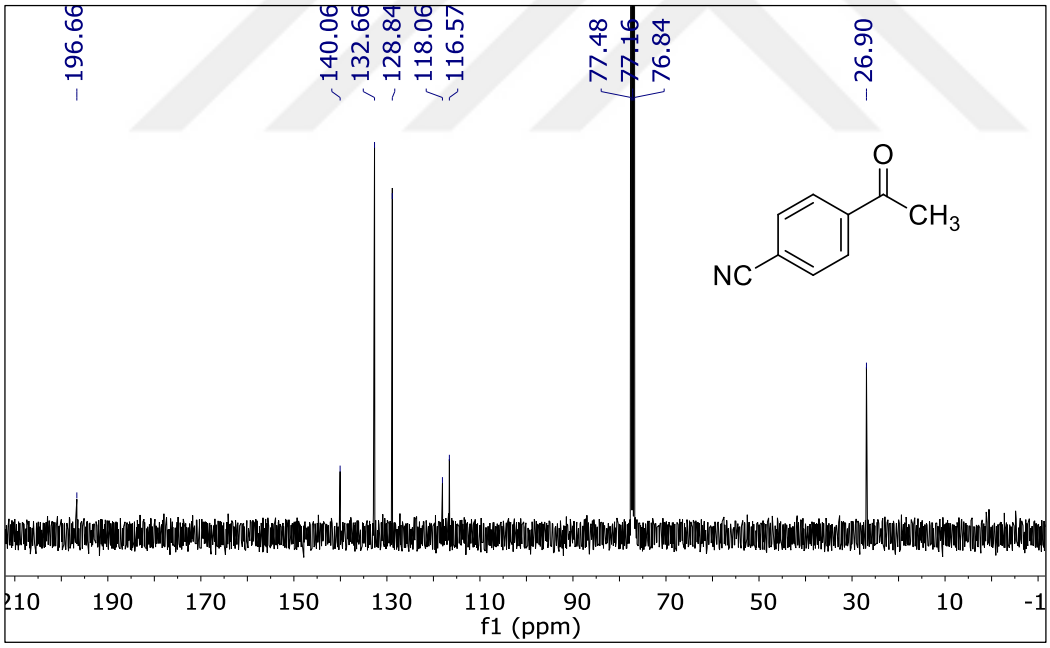


Figure 243. ^{13}C NMR spectrum of compound **45n**.

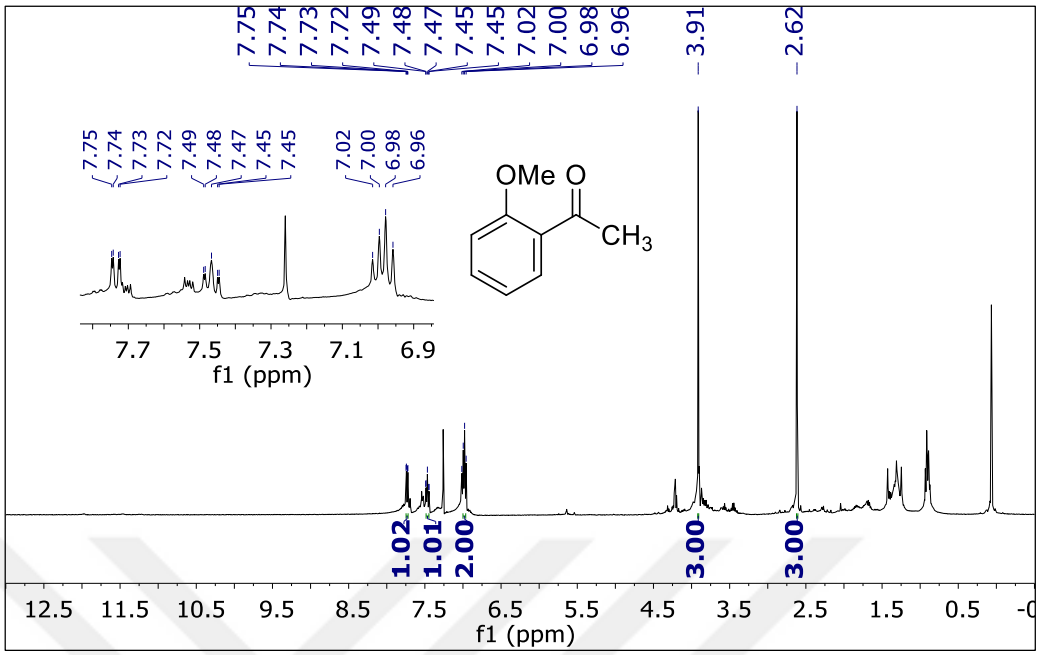


Figure 244. ^{1}H NMR spectrum of compound **45q**.

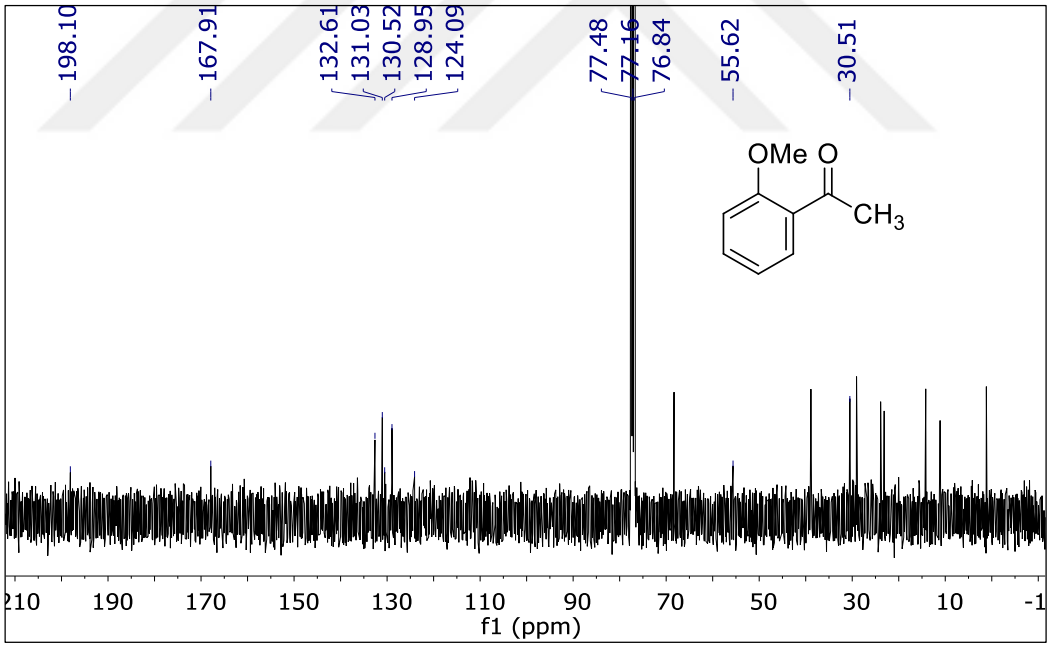


Figure 245. ^{13}C NMR spectrum of compound **45q**.

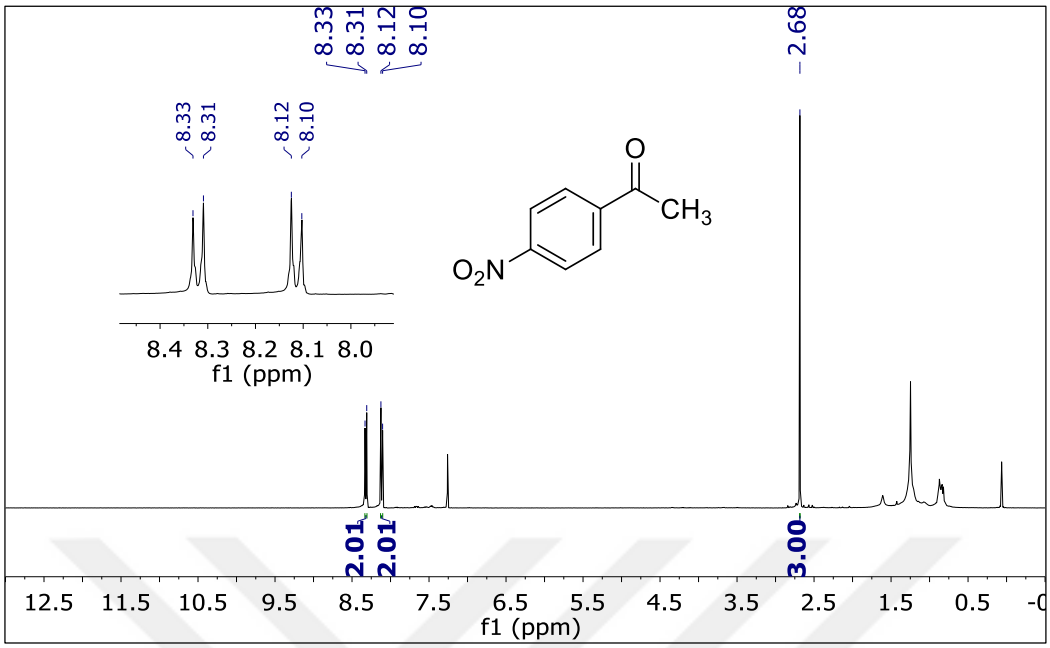


Figure 246. [1]H NMR spectrum of compound **45r**.

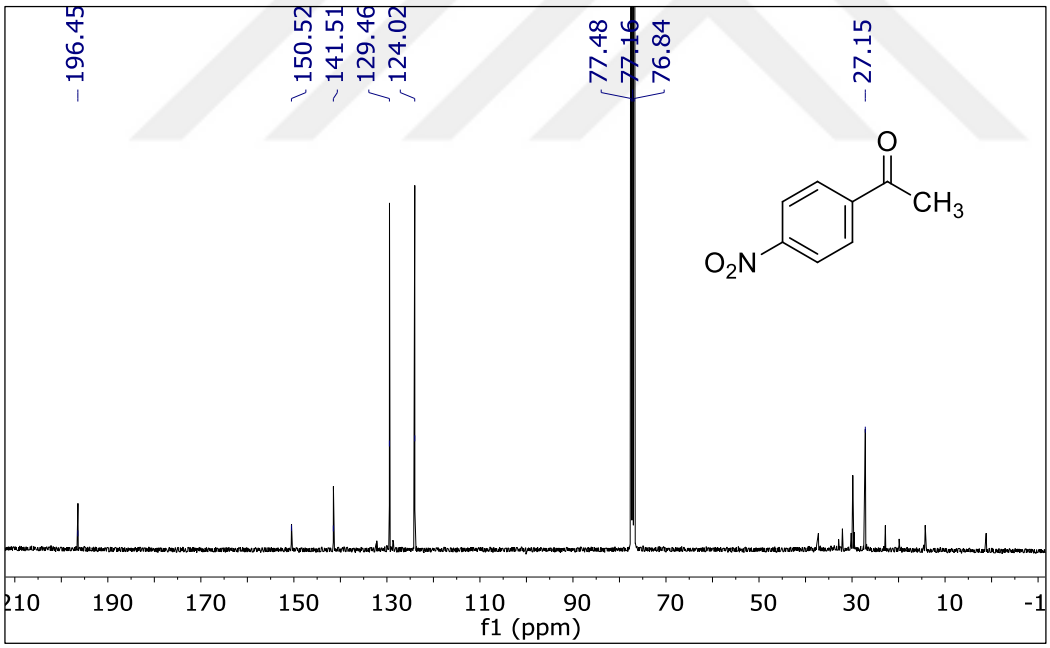


Figure 247. [13]C NMR spectrum of compound **45r**.

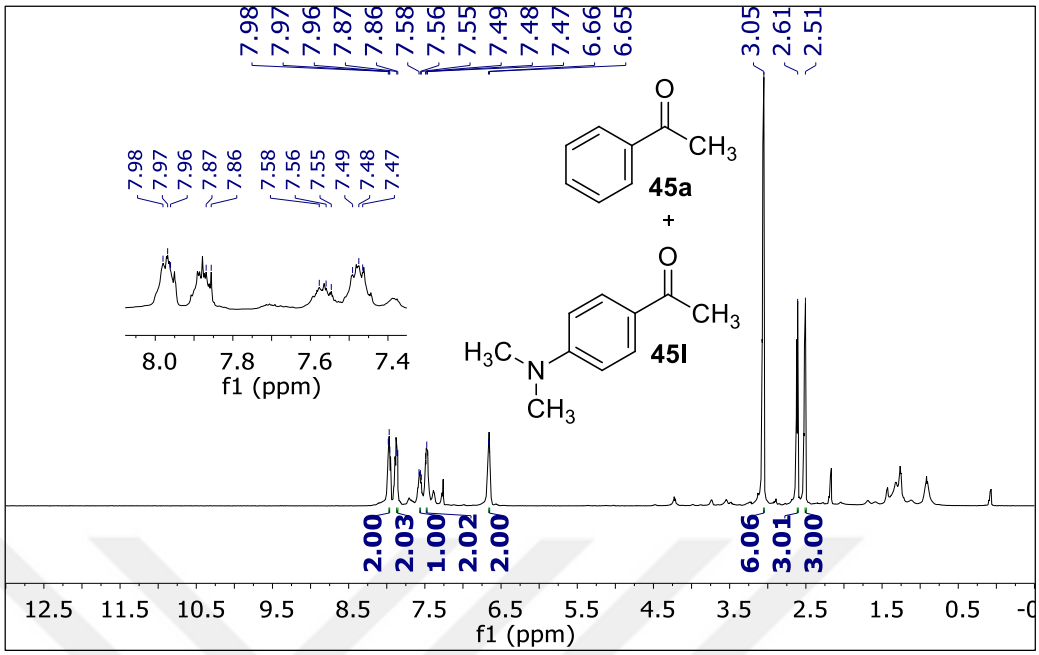


Figure 248. [1]H NMR spectrum of compound **45a + 45l**.

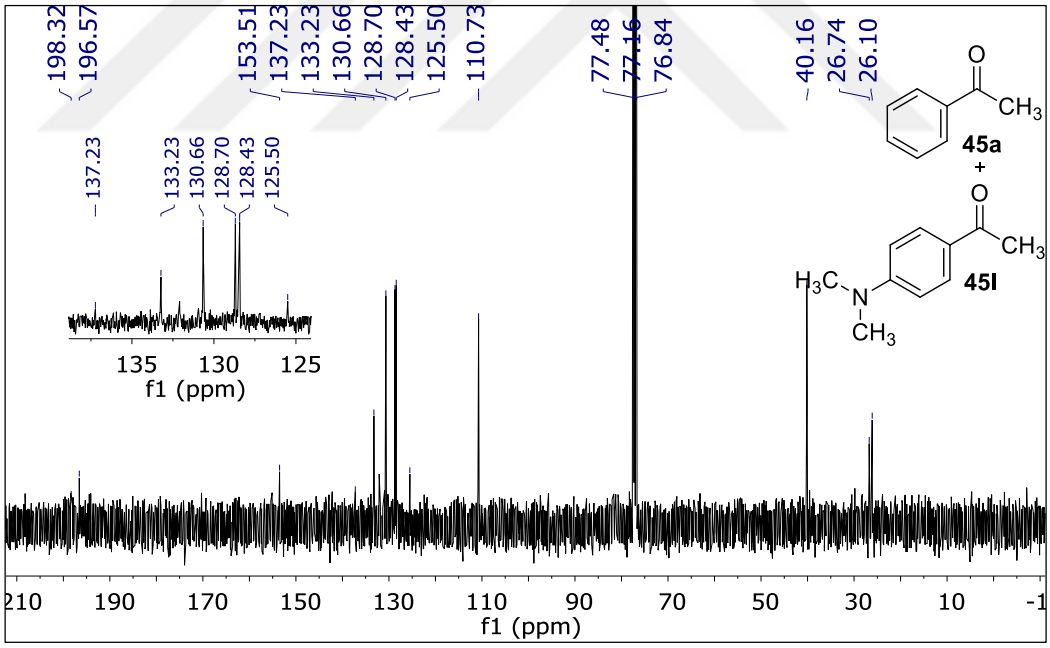


Figure 249. [13]C NMR spectrum of compound **45a + 45l**.

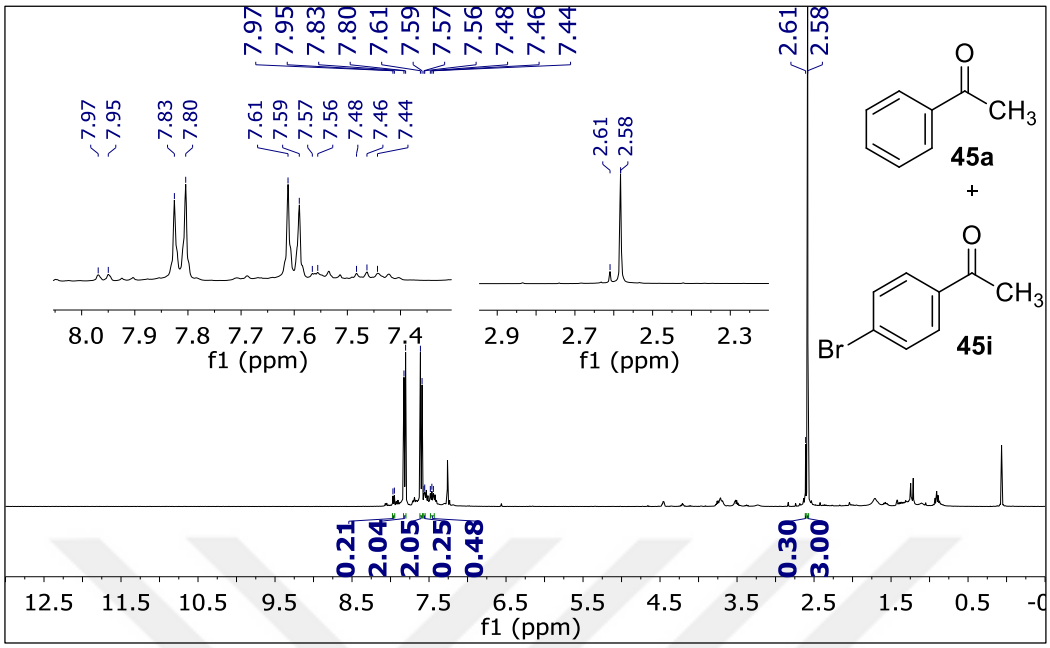


Figure 250. ^{1}H NMR spectrum of compound **45a + 45i**.

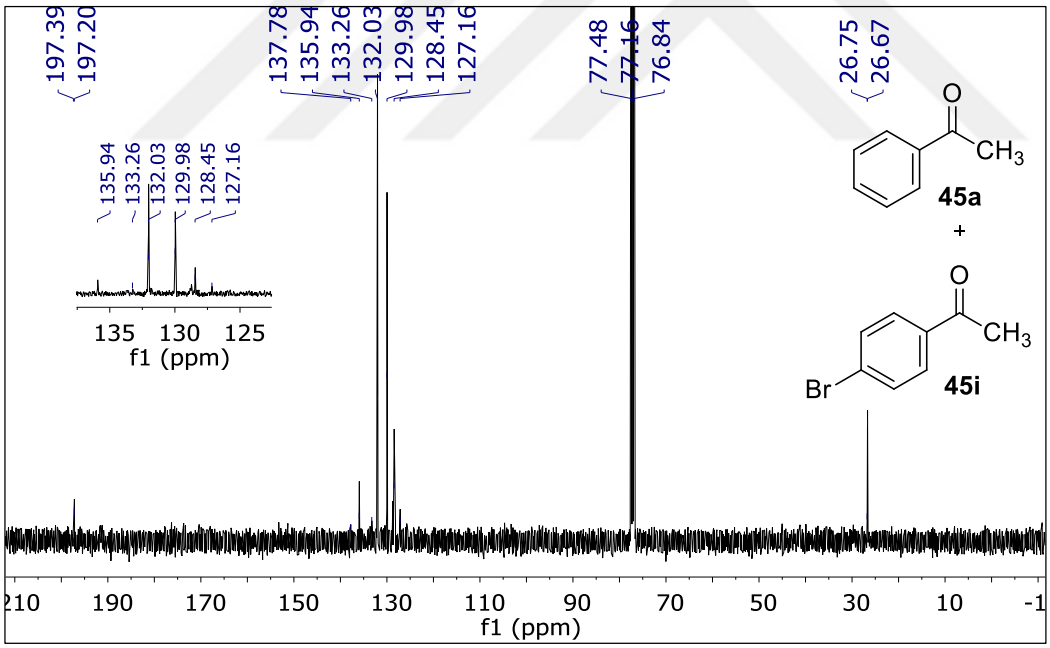


Figure 251. ^{13}C NMR spectrum of compound **45a + 45i**.

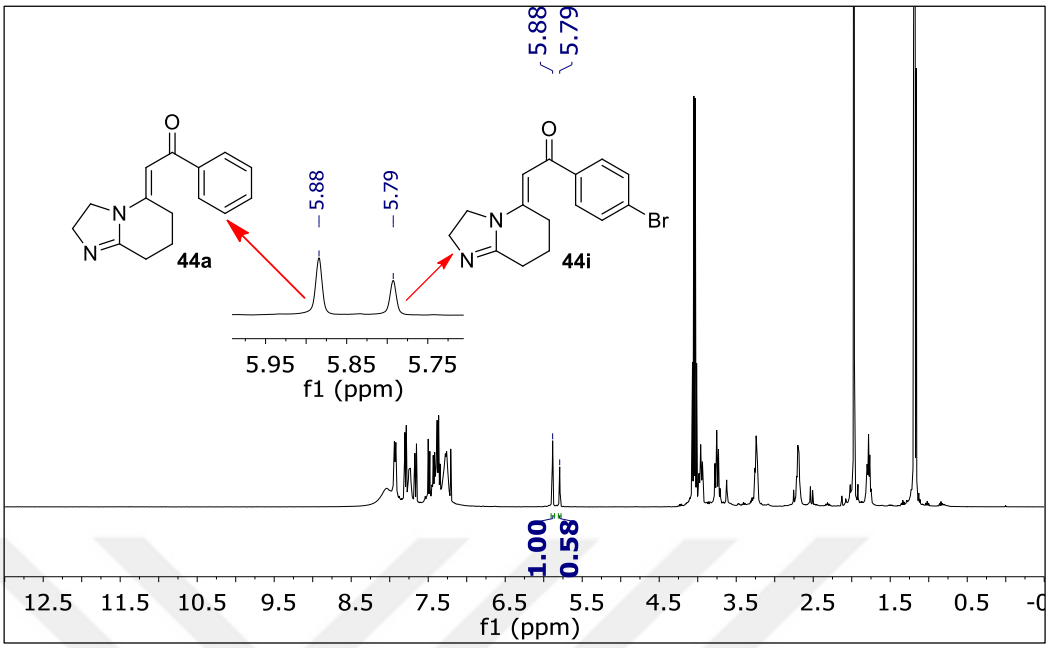


Figure 252. ^{1}H NMR spectrum of compound **44a** + **44i**.

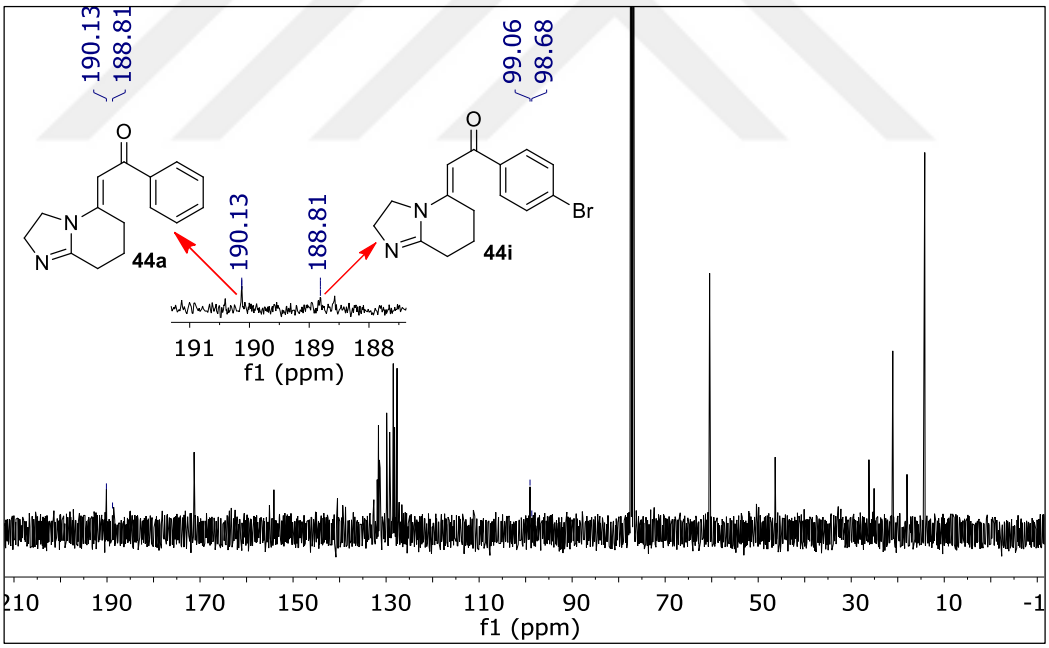


Figure 253. ^{13}C NMR spectrum of compound **44a** + **44i**.

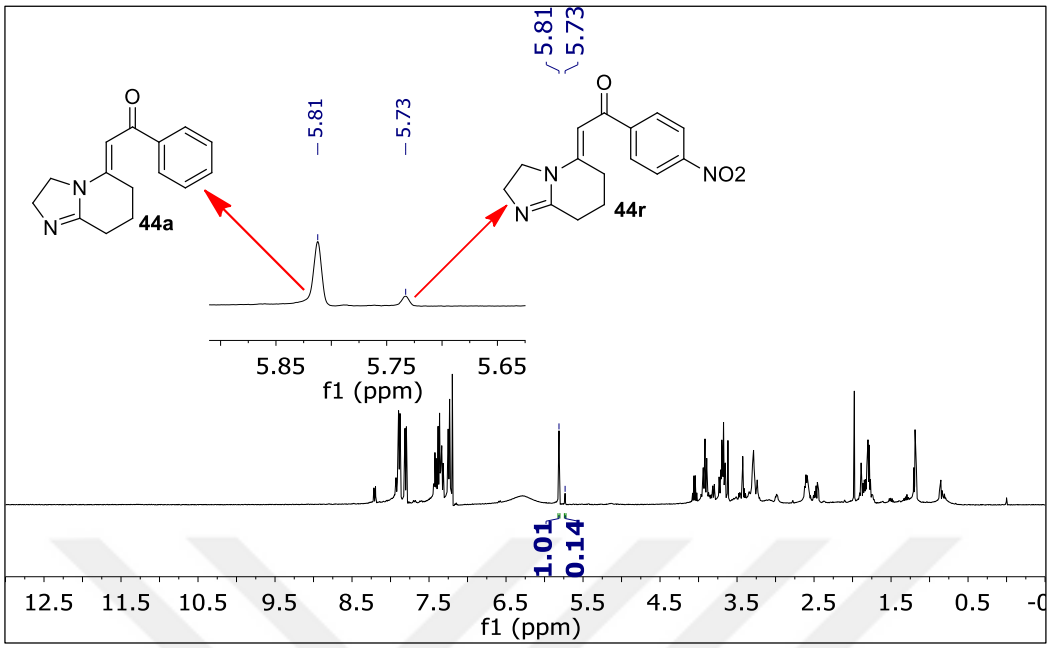


Figure 254. ^{1}H NMR spectrum of compound **44a** + **44r**.

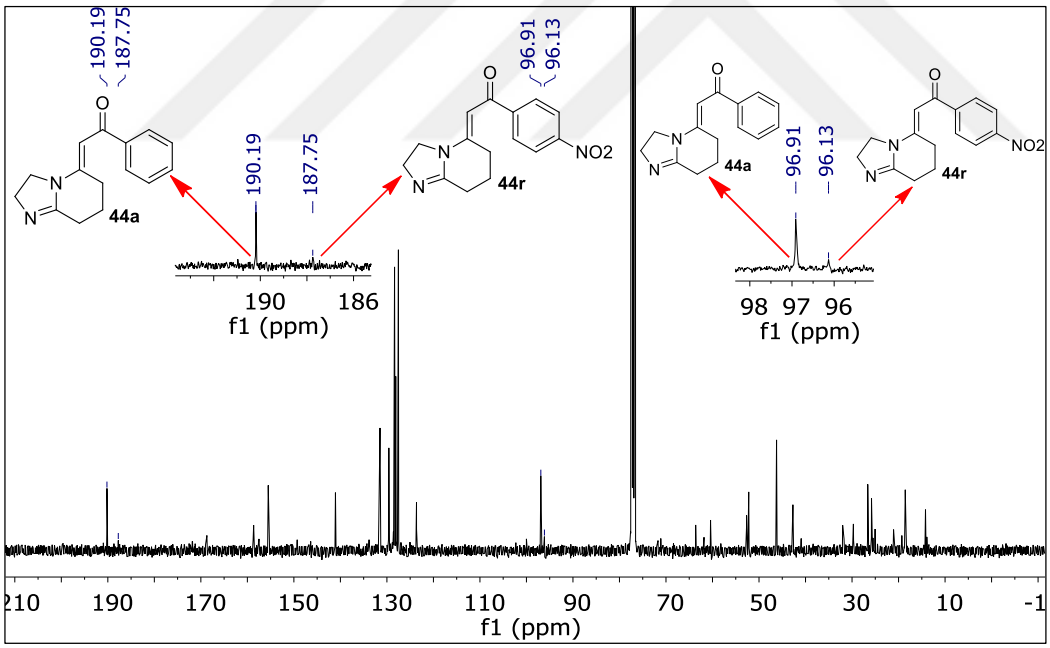


Figure 255. ^{13}C NMR spectrum of compound **44a** + **44r**.

CURRICULUM VITAE

PERSONAL INFORMATION

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EDUCATION

2019-2025:	PhD Middle East Technical University Department of Chemistry GPA: 3.57 / 4.00
2016-2019:	Master's Degree Middle East Technical University Department of Chemistry GPA: 3.21 / 4.00
2010-2016:	Bachelor's Degree Middle East Technical University Department of Chemistry GPA: 3.25 / 4.00
2006-2010:	Yahya Kemal Beyatlı High School GPA: 87.29 / 100

WORK EXPERIENCE

2019 April-Present:	Research and Teaching Asssistant, Middle East Technical University

FOREIGN LANGUAGES

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PUBLICATIONS

1. **KORKMAZ E.**, Zora, M. Synthesis of 3-[(4-Nitrophenyl) thio]-substituted 4-methylene-1-pyrrolines from N-propargylic β-enaminones. *J. Org. Chem.* **2020**, *85*, 4937. (DOI:10.1021/acs.joc.0c00109)

2. Kelgokmen, Y., **KORKMAZ E.**, Zora, M. A facile synthesis of 6-[(4-nitrophenyl) thio]-substituted 2-methylene-2, 3-dihydro-1, 4-oxazepines from N-propargylic β-enaminones. *Synth. Commun.* **2021**, *51*, 541. (DOI:10.1080/00397911.2020.1837171)

3. Atmaca, H., Ilhan, S., **KORKMAZ E.**, Zora, M. Endoplasmic reticulum stress-induced apoptotic effects of novel 1-pyrroline (3, 4-dihydro-2H-pyrrole) derivatives on breast cancer cells. *Chem. Biodivers.* **2022**, *19*, e202200123. (DOI:10.1002/cbdv.202200123)

4. Ilhan, S., Atmaca, H., Yilmaz, E. S., **KORKMAZ E.**, Zora, M. N-Propargylic β-enaminones in breast cancer cells: Cytotoxicity, apoptosis, and cell cycle analyses. *J. Biochem. Mol. Toxicol*. **2023**, *37*, e23299.(DOI:10.1002/jbt.23299)

INTERNATIONAL CONFERENCE PROCEEDINGS

1. **Korkmaz, E.**, & Zora, M. Synthesis of 1,3-Bis-Pyrazole Derivatives *Anatolian Conference on Organic Chemistry* (*ACOC IV)*, Kemer-Antalya, **Mart 2024**. *(Poster presentation and Oral Presentation)*

2. **Korkmaz, E.**, & Zora, M. Synthesis of Selenium-Substituted Pyridine Derivatives *Anatolian Conference on Organic Chemistry* (*ACOC III*), Kemer-Antalya, **Mart 2023.** *(Poster presentation)*