

BASE-PROMOTED SYNTHESIS OF NEW DIAZEPINE DERIVATIVES VIA  
ALKYNE CYCLIZATION

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**I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.**

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## ABSTRACT

### BASE-PROMOTED SYNTHESIS OF NEW DIAZEPINE DERIVATIVES VIA ALKYNE CYCLIZATION

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A new methodology was developed for the synthesis of dipyrromethane and diazepine derivatives. In the first section of this thesis, synthesis of various dipyrromethanes from aromatic aldehydes was carried out. Dipyrromethanes were used as starting materials for the next step. In the second part of the study, introduction of a propargyl group to nitrogen atom to one of pyrrole units of dipyrromethane gave the expected mono-propargylated compounds which were the key compounds for further cyclization reactions. Base-supported cyclization resulted in the formation of the target compounds, new diazepine derivatives, via metal-free 7-*exo*-dig cyclization.

**Keywords:** Pyrrole, dipyrromethane, diazepine, alkyne cyclization

## ÖZ

### DİAZEPİN TÜREVLERİNİN BAZ DESTEKLİ ALKİN SİKLİZASYONU İLE SENTEZİ

Baskın, Dilgeş  
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Diazepin ve dipirrometan türevlerinin sentezi için yeni bir sentetik metot geliştirildi. Tezin ilk kısmında, çeşitli dipirrometanların sentezi bazı aromatik aldehitlerden çıkarak gerçekleştirildi. Dipirrometanlar bundan sonraki basamak için başlangıç molekülleri olarak kullanıldı. Tezin ikinci kısmında, dipirrometan molekülünde bulunan pirol halkalarına ait olan iki azot atomundan birine propargil grubu kontrollü bir şekilde bağlandı. Tek bir propargil grubu içeren bu bileşikler bazik ortamda siklizasyona tabi tutuldu ve arzu edilen hedef bileşikler, diazepin türevleri, metal katalizör kullanmadan 7-*exo-dig* halkalaşma reaksiyonu ile sentezlendi.

**Anahtar Kelimeler:** Pirol, dipirrometan, diazepin, alkin siklizasyonu

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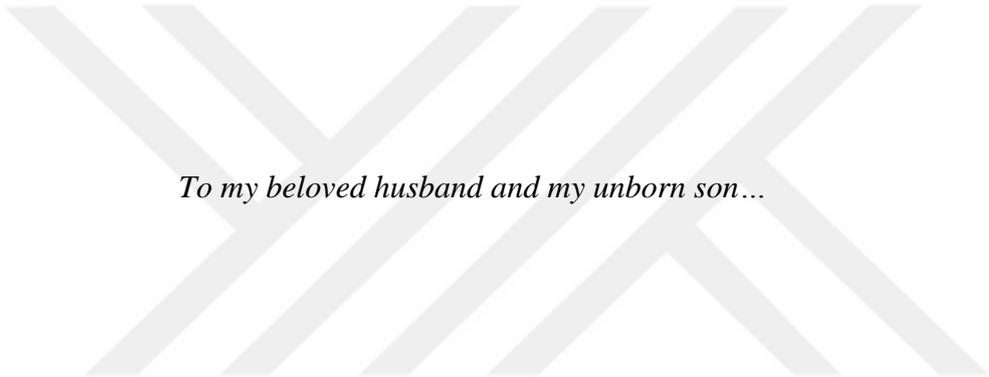
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*To my beloved husband and my unborn son...*

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### TABLE

**Table 1** Yields of mono- and di-propargylated products **47a, d-h, 48a, d**.....12



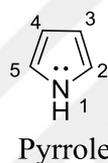


## CHAPTER 1

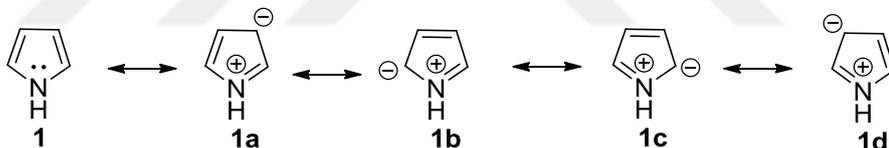
### INTRODUCTION

#### 1.1 Pyrrole

Pyrrole (**1**) is a five-membered heterocyclic compound having four  $sp^2$  hybridized carbon atoms and also one  $sp^2$  hybridized nitrogen atom. The lone pair electrons of nitrogen are delocalized over the ring and contribute to the aromaticity.<sup>1</sup>

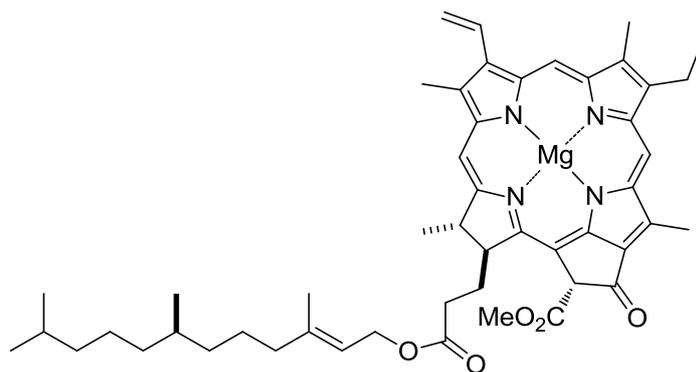


Resonance structures of pyrrole are shown below (Scheme 1).<sup>1</sup>



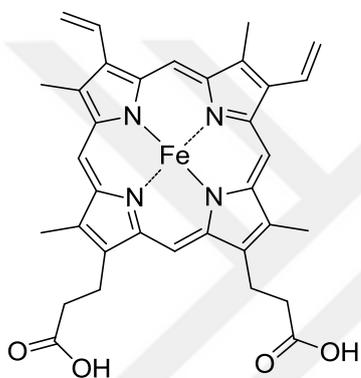
**Scheme 1.** Resonance structure of pyrrole

Pyrroles are one of the most significant molecules among heterocyclic compounds due to their current biological and pharmacological properties.<sup>2</sup> Many pyrrole derivatives show attractive biological properties for instance antibacterial,<sup>3</sup> antiinflammatory,<sup>4</sup> antioxidant,<sup>5</sup> antifungal,<sup>6</sup> and immune suppressant activities.<sup>7</sup> Pyrrole is a quite functionalized subunit of chlorophyll a (**2**), heme (**3**), ningalin A (**4**) and pyrrole alkaloids isolated from marine resource.<sup>8</sup>



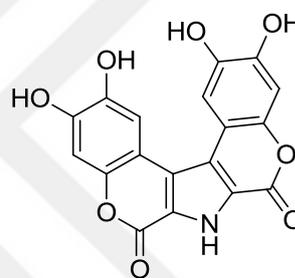
Chlorophyll a

2



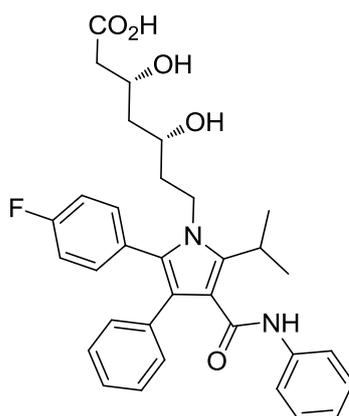
Heme

3



Ningalin A

4



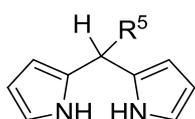
Atorvastatin

5

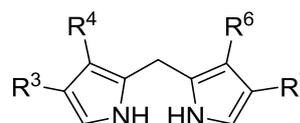
Atorvastatin (Lipitor) (5) is one of the example of pyrrole derived drugs and used to decrease cholesterol.<sup>9</sup>

## 1.2 Dipyrrromethanes

Dipyrrromethane is a heterocyclic compound in which two pyrroles are connected from the  $\alpha$ -positions to a single  $sp^3$  hybridized carbon atom. Dipyrrromethane is called as  $\beta$ -substituted dipyrrromethane if the beta position(s) of pyrroles are substituted. Whereas, when the beta position(s) of pyrrole is lack of any substituent, dipyrrromethane is called as meso-substituted dipyrrromethane (Scheme 2).<sup>10</sup>



meso-substituted dipyrrromethane



$\beta$ -substituted dipyrrromethane

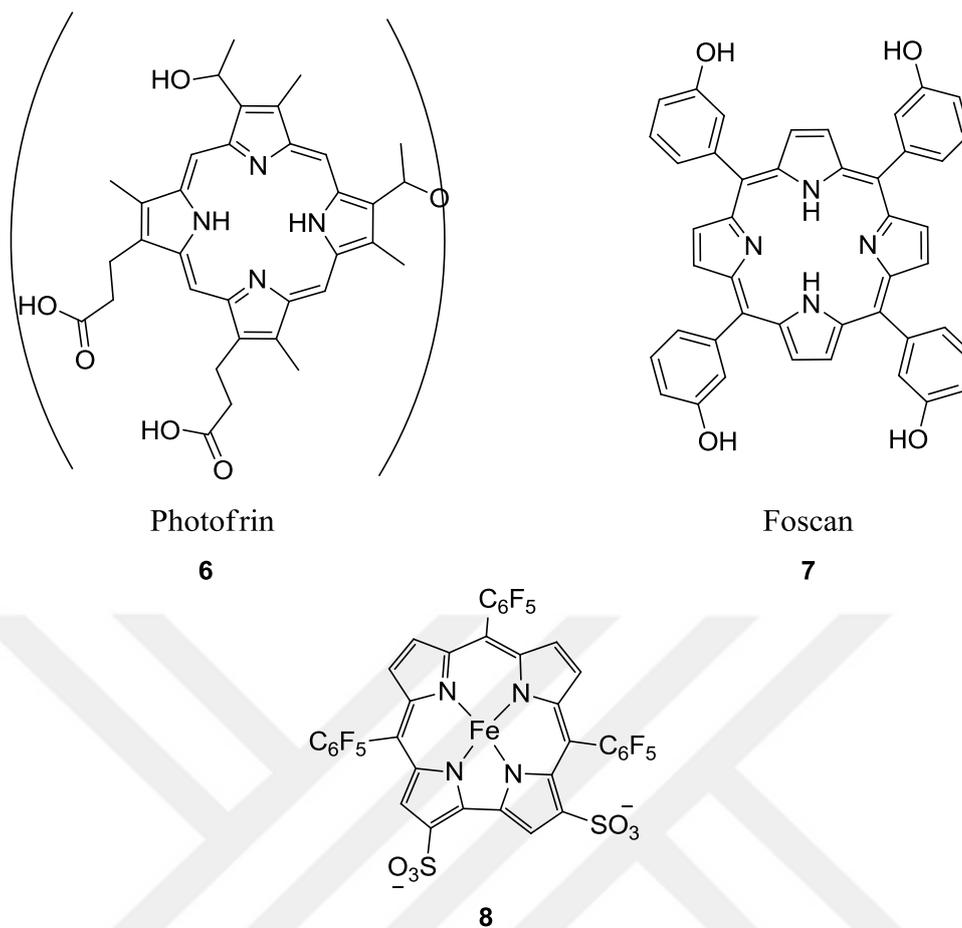
**Scheme 2.** Naming of dipyrrromethanes

### 1.2.1. Importance of meso-substituted dipyrrromethane derivatives

Dipyrrromethanes substituted at C-5 position are significant initiator for the synthesis of meso-substituted porphyrins,<sup>11</sup> corroles and porphyrins.<sup>12</sup>

Meso-porphyrin derivatives have implementation in phototherapeutics,<sup>13</sup> biological processes,<sup>14</sup> optoelectronics,<sup>15</sup> catalysis,<sup>16</sup> and material chemistry.<sup>17</sup>

Two compounds have been approved for PDT (photo dynamic therapy) cancer treatment: porfimer (photofrin) (**6**) and foscan (**7**).<sup>18</sup> Iron(III) complex of an amphipolar corrole (**8**) has been revealed to be a very potent catalytic antioxidant (Scheme 3).<sup>19</sup>



**Scheme 3.** Some dipyrromethane derivatives

### 1.2.2 Synthesis of dipyrromethanes

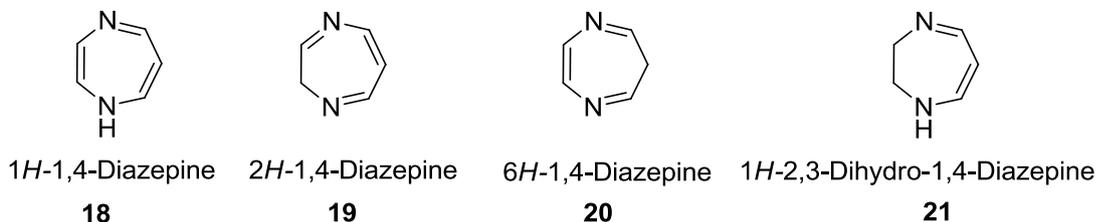
Lately, many procedure have been reported for the synthesis of dipyrromethanes.<sup>20</sup> Most of the procedure include the condensation of an aldehyde and pyrrole in the presence of several acids like  $\text{BF}_3 \cdot \text{etherate}$ , trifluoroacetic acid (TFA), propionic acid and *p*-toluenesulfonic acid. The purification of the dipyrromethanes is complicated because of oligomeric compounds which forms in the reaction media.<sup>21</sup>

Singh and co-workers reported solvent-free condensation of electron rich heterocycles with a variety of aldehydes using Amberlyst 15 catalyst. The condensations of pyrrole (**1**) with aldehydes (**9**) are catalyzed with Amberlyst 15 to afford corresponding dipyrromethane derivatives (**10**) (Scheme 4).<sup>22</sup>



### 1.3. 1,4-Diazepines

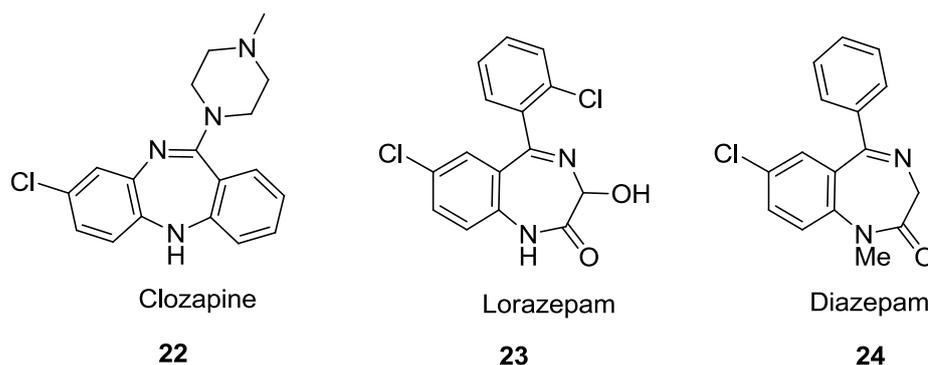
Diazepine is a nitrogen containing, seven-membered heterocyclic structure. The ring numbering and nomenclature for some 1,4-diazepines are given below.



#### 1.3.1 Importance of 1,4-diazepines derivatives

Diazepine derivatives demonstrate a range of clinically important properties. Especially, benzodiazepines are used to treat anxiety disorders. They act on the central nervous system to produce a calming effect.

Clozapine (**22**) is an effective drug in decreasing psychopathology, improving some aspects of cognition, improving quality of life, decreasing hospitalisation, and decreasing suicide attempts and completions.<sup>25</sup> Lorazepam (**23**) is used to treat irritable bowel syndrome, epilepsy, insomnia and to control tension caused by alcohol withdrawal. The compound causes slowing activity in the brain and allow for relaxation.<sup>26</sup> Diazepam (**24**) is used to treat anxiety, acute alcohol withdrawal and seizures. It also used to relieve muscle spasm (Scheme 7).<sup>27</sup>



**Scheme 7.** Some diazepine drugs

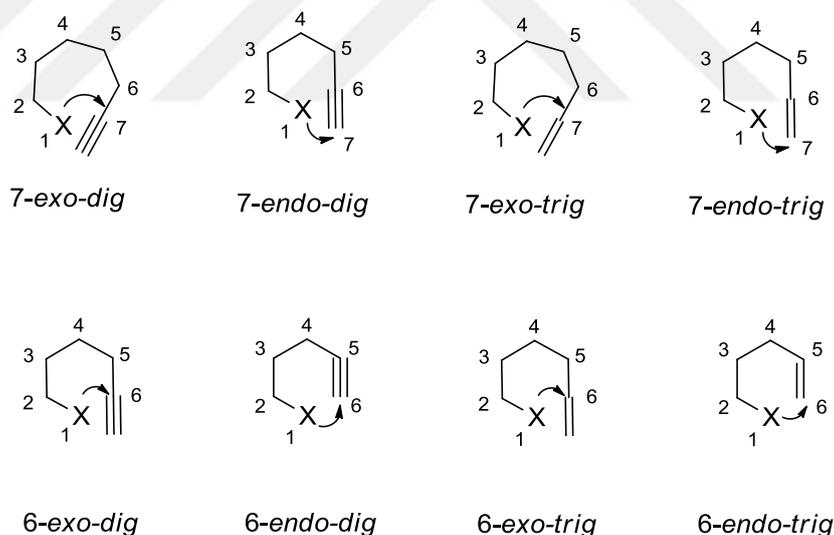
## 1.4. Base supported alkyne cyclization reactions

The ability to perform the key carbon-heteroatom bond formation step which transforms an acyclic precursor into the desired cyclic is a critical process to construct heterocycles.

Particularly, forming a nitrogen functionality-alkyne bond via metal-free intramolecular cyclization is a precious synthetic strategy.

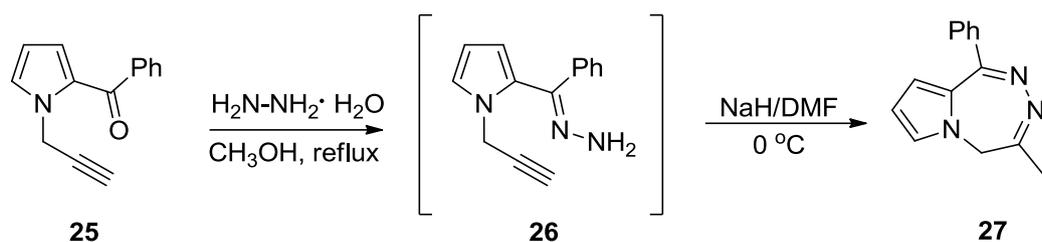
It should be mentioned that a compact set of standards, known as ‘the Baldwin rules’, has been proven to be a useful tool for assessment the feasibility of ring closure reactions.<sup>28</sup> Baldwin identified the cyclization processes in terms of three factors:

- (1) the ring size being formed (a numerical prefix);
- (2) the geometry of carbon atom undergoing the ring-forming reaction ( $sp$  = diagonal,  $sp^2$  = trigonal, and  $sp^3$  = tetrahedral);
- (3) the pattern of the breaking bond (exo, the breaking bond is outside of the formed ring, and endo, the breaking bond is inside of the new ring).<sup>29</sup> (Scheme 8)



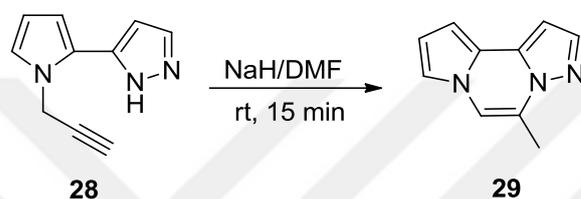
**Scheme 8.** Patterns of ring closure for 6- and 7-membered rings

There are too many examples of metal-free alkyne cyclization reactions in literature. Balci and coworkers<sup>30</sup> reported the formation of trizapine skeletons **27** via *7-exo-dig* cyclization (Scheme 9).



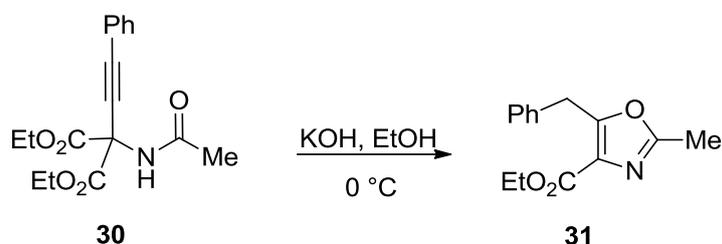
**Scheme 9.** Metal-free 7-*exo*-dig cyclization reaction of product **25**

Basceken and Balci<sup>31</sup> reported the formation of 6-*exo*-dig cyclization product **29** starting from compound **28** by using NaH in DMF (Scheme 10).



**Scheme 10.** 6-*exo*-dig cyclization reaction of compound **29**

Nagao et al. showed KOH-mediated cycloisomerization of propargylamides **30** into 4-carboxylated oxazoles **31**.<sup>32</sup> (Scheme 11).

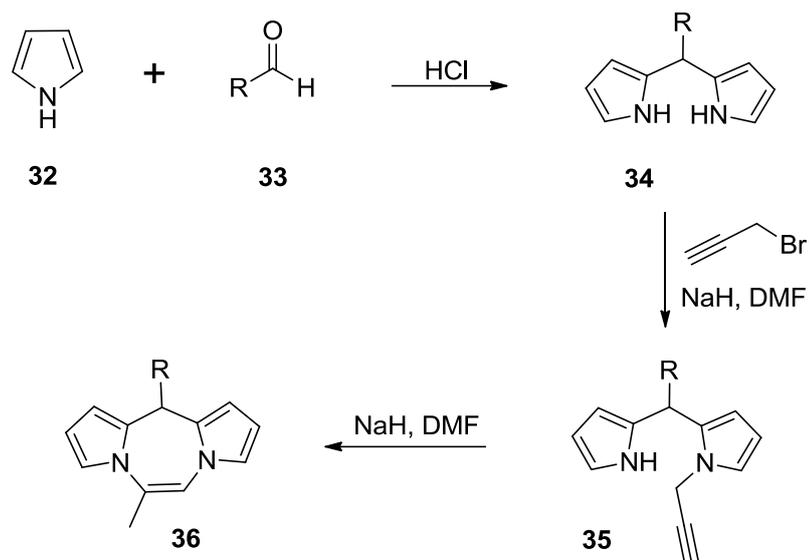


**Scheme 11.** Cycloisomerization of propargylamides **30**

### 1.5. Aim of the study

This study focused on the synthesis of pyrrole-fused 1,4-diazepine derivatives **36** starting from dipyrromethane derivatives **34** by using base-supported reaction.

Our aim was first to improve the methodology for the synthesis of dipyrromethane derivatives (**34**) and then control the propargylation step to get mono-propargylated products **35**. Finally, we target to obtain 1,4 diazepine derivatives from mono-propargylated products via NaH as a base (Scheme 12).



**Scheme 12.** Synthesis of diazepines **36**

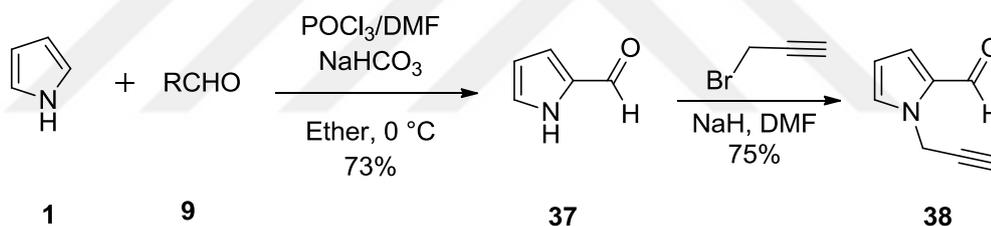


## CHAPTER 2

### RESULTS AND DISCUSSION

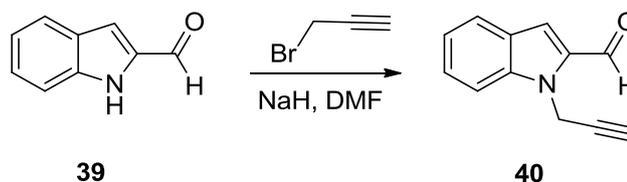
#### 2.1. Synthesis of compounds **38** and **40**

Firstly, Vilsmeier Haack reaction<sup>33</sup> was used to get pyrrole carbaldehyde **37**. Pyrrole (**1**) was reacted with POCl<sub>3</sub> and DMF in dry ether at 0 °C. In order to get basic medium, the solution of NaHCO<sub>3</sub> was used and compound **37** was gained. Afterwards, pyrrole-2-carbaldehyde (**37**) in dry DMF was firstly reacted with NaH at 0 °C and then, solution of propargyl bromide in dry DMF was added to the reaction media to obtain compound **38** (Scheme 13).<sup>34, 35</sup>



**Scheme 13.** Synthesis of compound **38**

Structure **40** was synthesized in 97% yield from the reaction of indolecarbaldehyde **39**, propargyl bromide and NaH at room temperature. After deprotonation of NH-proton with base, anionic nitrogen is formed. Then, anionic nitrogen attack propargyl bromide to generate structure **40** (Scheme 14).<sup>36</sup>

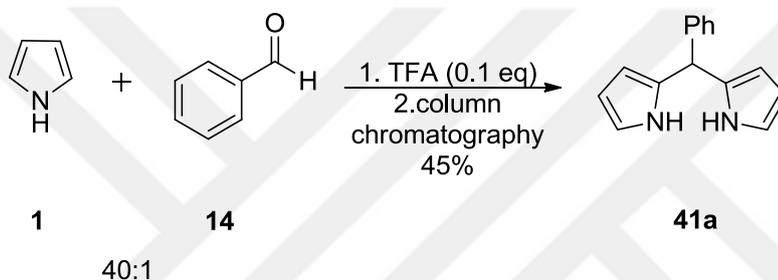


**Scheme 14.** Synthesis of structure **40**

## 2.2. Synthesis of 2-[phenyl(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41a**) and other starting compounds (**41b-i**)

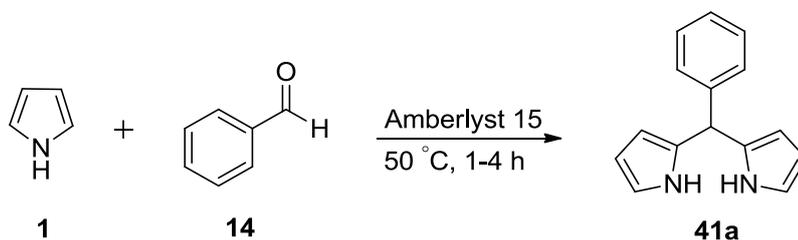
For the synthesis of 2-[phenyl(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41a**), several methods were applied and the most appropriate one was modified and used for the synthesis of other derivatives **41b-i**.

According to the first procedure<sup>24</sup>, excess pyrrole (**1**) and benzaldehyde (**14**) (40:1) were reacted at room temperature in the presence of TFA (0.1 equiv) as a catalyst for 15 minutes to obtain 2-[phenyl(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41a**). Because of the fact that excess pyrrole usage was waste of resources and led to the formation of oligomers, the method was not preferred (Scheme 15).



**Scheme 15.** Synthesis of 5-phenyldipyrromethane **41a** by using THF

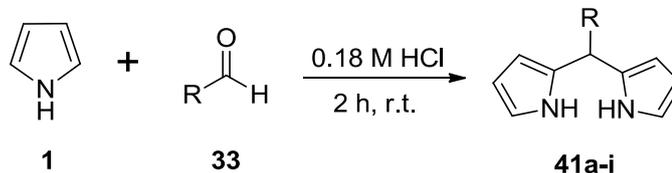
As reported by second procedure, mixing Amberlyst 15 ion exchange resin with pyrrole and benzaldehyde resulted in the formation of 2-[phenyl(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41a**) in the absence of solvent in 30% yield after 1 hour and in 35% yield after 4 hours (Scheme 14).<sup>22</sup> Due to low efficiency, this method was also not preferred (Scheme 16).



**Scheme 16.** Synthesis of **41a** by using Amberlyst 15

The most appropriate procedure<sup>21</sup> was applied for the synthesis of all starting compounds (**41a-i**) in high yields. The procedure published by Temelli and Unaleroglu<sup>21</sup> where metal triflates were replaced by 0.18 M HCl, was used as an acid

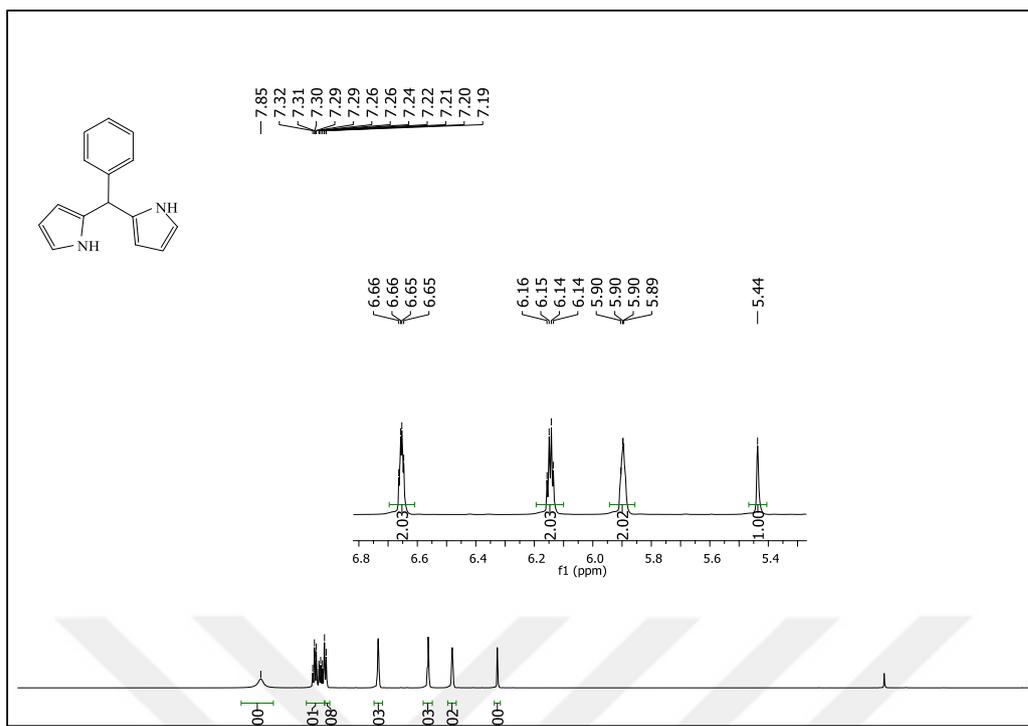
to catalyzed reaction of pyrrole and benzaldehyde at the room temperature to get 2-[phenyl(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41a**). Then, for testing scope of further reactions, additional derivatives **41b-i** were synthesized (Scheme 17).



- a** R = -Ph, 74%
- b** R = -1-(prop-2-yn-1-yl)-1*H*-indole, 59%
- c** R = -1-(prop-2-yn-1-yl)-1*H*-pyrrole, 72%
- d** R = -*p*-MeOPh, 70%
- e** R = -*o*-ClPh, 89%
- f** R = -CH<sub>3</sub>, 62%
- g** R = -H, 69%
- h** R = -*o*-NO<sub>2</sub>, 79%
- i** R = -*p*-NO<sub>2</sub>, 81%

**Scheme 17.** Synthesis of dipyrromethanes by using HCl

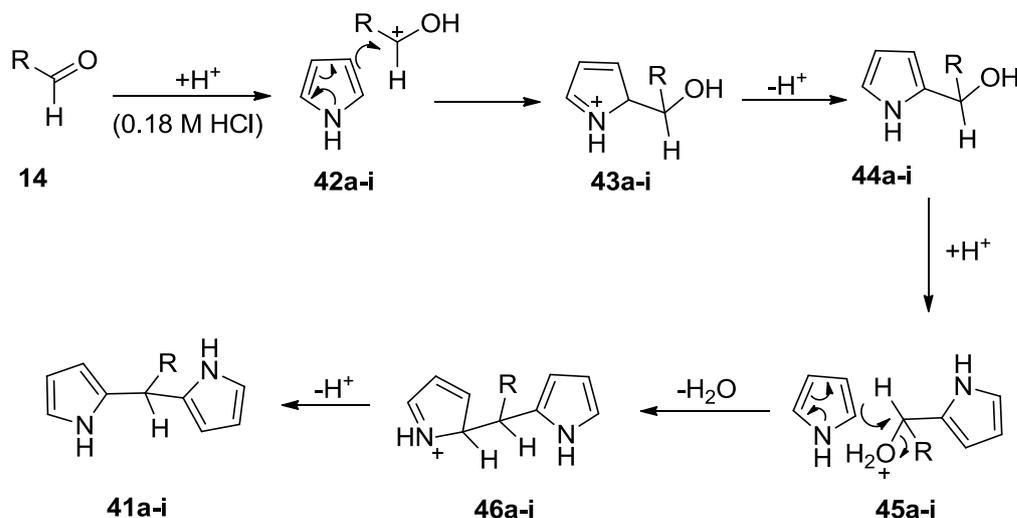
The characterization of compounds **41a-i** was done by using <sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra. The NH protons of structure **41a** resonate at 7.88 ppm as broad singlet and the multiplet signals of protons belong phenyl group appear between 7.22-7.35 ppm as multiplet. In addition, the protons attached to C-4 position of pyrroles resonate at 6.14 ppm and the signal was split into doublet of doublets with coupling constants of *J* = 5.9 Hz and *J* = 2.8 Hz arising from the coupling with protons attached to the C-3 and C-5 carbon atoms of pyrrole (Figure 1).



**Figure 1:**  $^1\text{H-NMR}$  Spectrum of compound **41a** in  $\text{CDCl}_3$

### 2.3. Proposed mechanism for the formation of starting materials (**41a-i**)

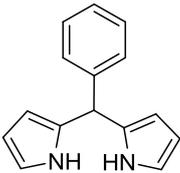
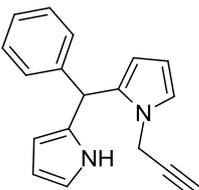
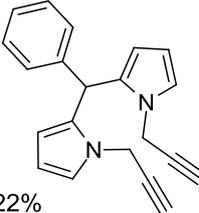
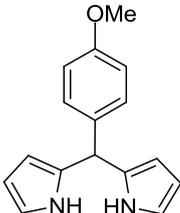
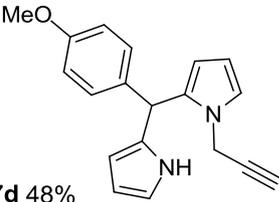
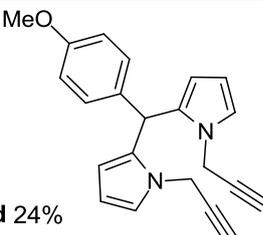
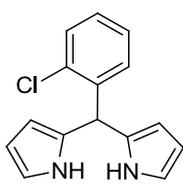
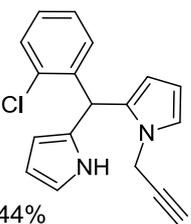
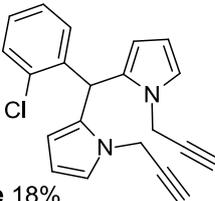
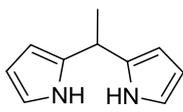
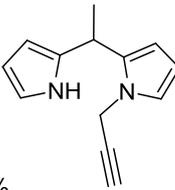
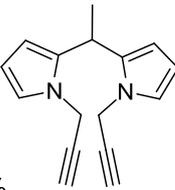
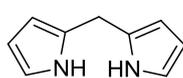
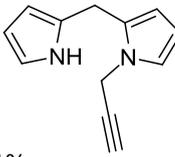
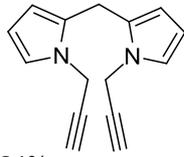
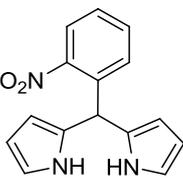
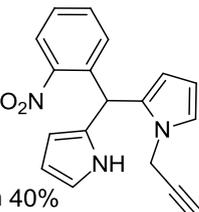
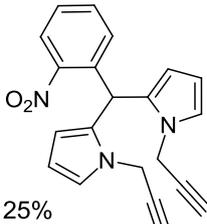
Formation of the products **41a-i** can be visualized through the mechanism proposed in Scheme 18. Thus, initial reaction of pyrrole with carbonyl substrate, activated through protonation by HCl, leads to the adduct **44a-i** obtained from initially formed **43a-i**. Similar nucleophilic attack of the C-2 position of pyrrole to the intermediate **45a-i** results in the formation of adduct **46a-i** which furnish products **41a-i** after deprotonation.



**Scheme 18.** Proposed mechanism for the formation of dipyrromethanes

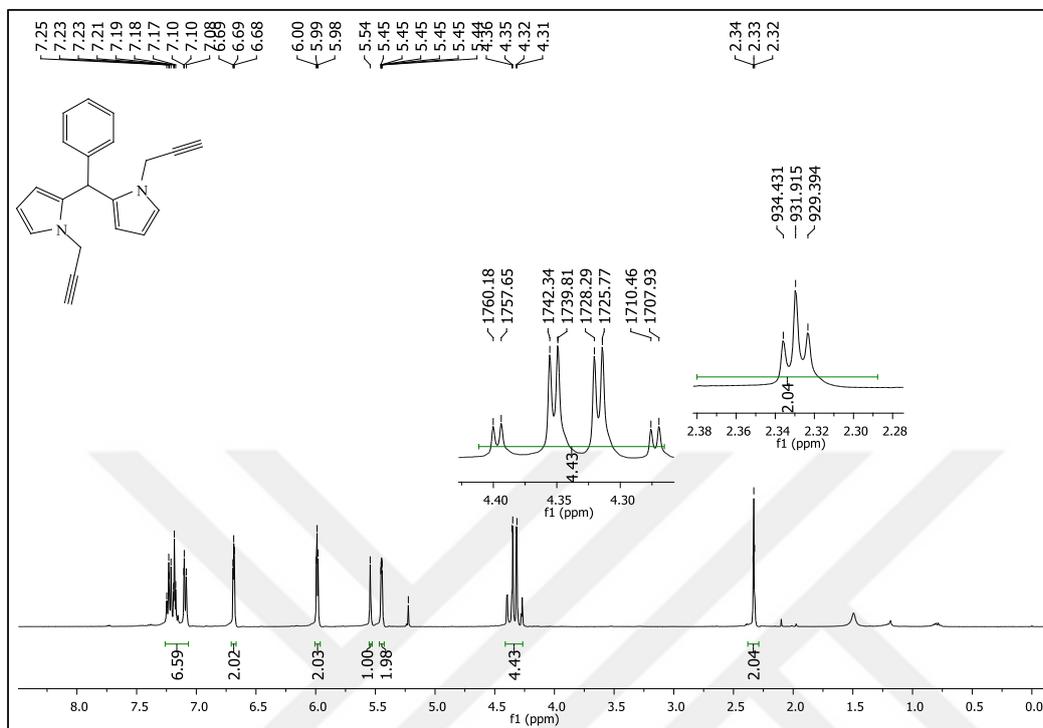


**Table 1** Yields of mono- and di-propargylated products **47a, d-h** and **48a, d-h**

Starting Compounds	Mono- Propargylated Products	Di- Propargylated Products
 <p><b>41a</b></p>	 <p><b>47a</b> 55%</p>	 <p><b>48a</b> 22%</p>
 <p><b>41d</b></p>	 <p><b>47d</b> 48%</p>	 <p><b>48d</b> 24%</p>
 <p><b>41e</b></p>	 <p><b>47e</b> 44%</p>	 <p><b>48e</b> 18%</p>
 <p><b>41f</b></p>	 <p><b>47f</b> 45%</p>	 <p><b>48f</b> 33%</p>
 <p><b>41g</b></p>	 <p><b>47g</b> 51%</p>	 <p><b>48g</b> 24%</p>
 <p><b>41h</b></p>	 <p><b>47h</b> 40%</p>	 <p><b>48h</b> 25%</p>



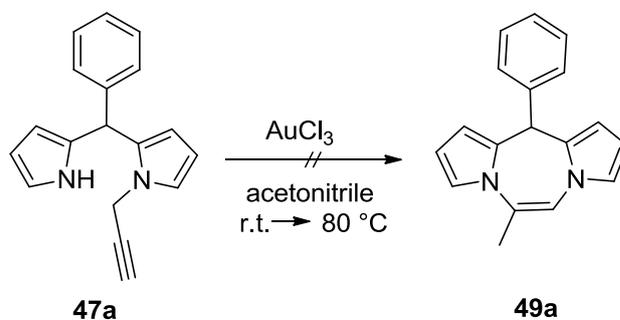
ppm belongs to terminal alkyne protons and split into triplet with a coupling constants of  $J=2.5$  Hz.



**Figure 3:**  $^1\text{H-NMR}$  Spectrum of compound **48a** in  $\text{CDCl}_3$

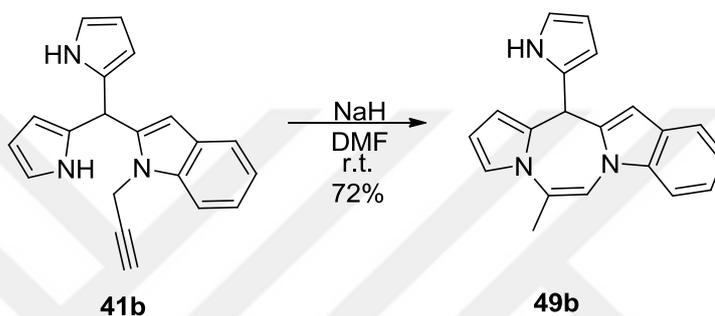
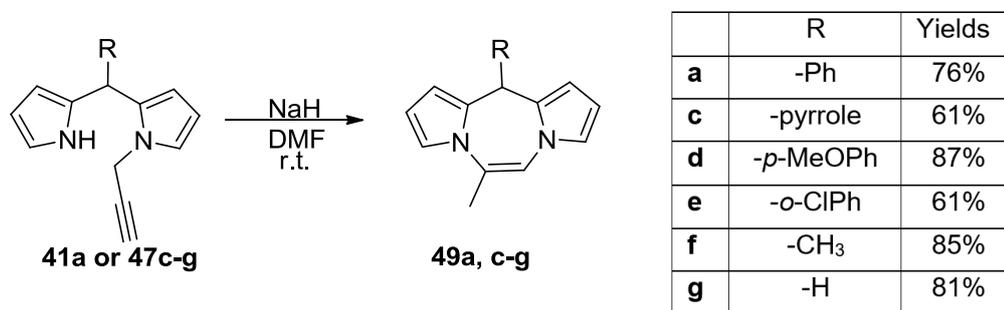
## 2.5. Cyclization reaction of mono-propargylated compound **47a**

Reaction of mono-propargylated compounds **47a** with  $\text{AuCl}_3$  in the presence of acetonitrile was the first attempt to obtain diazepine derivative **49a**. This reaction was carried out at room temperature as well as at reflux temperature. Unfortunately, the desired diazepine derivative **49a** could not be obtained under these conditions. The starting material **47a** was recovered, (Scheme 20).



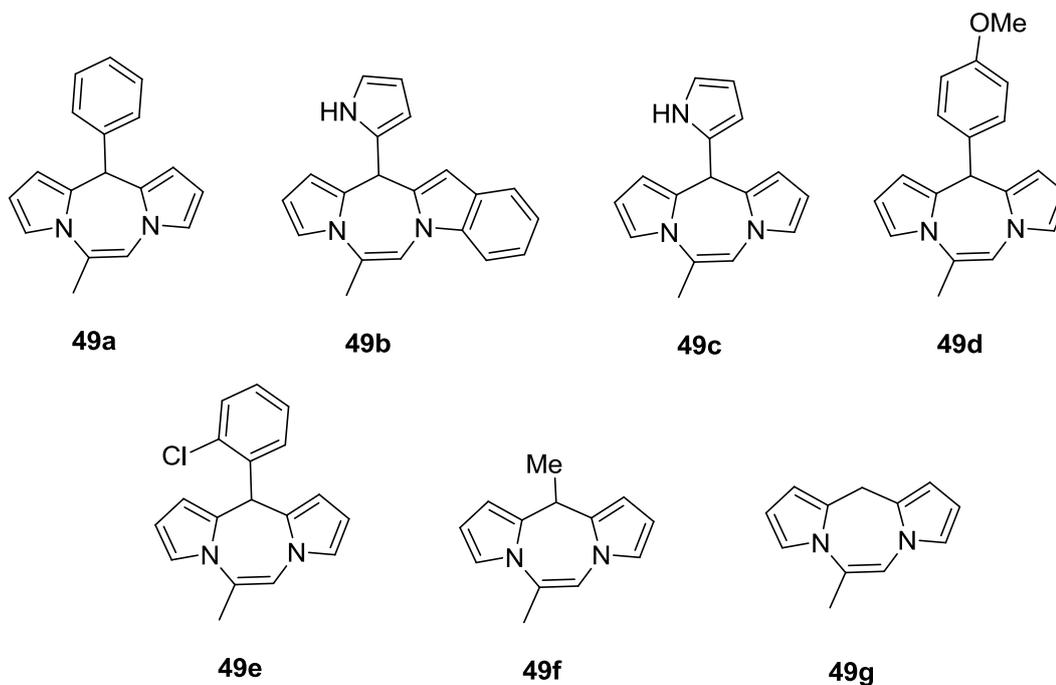
**Scheme 20.** Reaction between compound **47a** with  $\text{AuCl}_3$

On the other hand, the intramolecular cyclization reactions of compounds **47a, d-g** and **41b-c** with NaH in DMF at room temperature afforded diazepine derivatives **49a-g** in high yields (Scheme 21).



**Scheme 21.** Cyclization reaction by using NaH

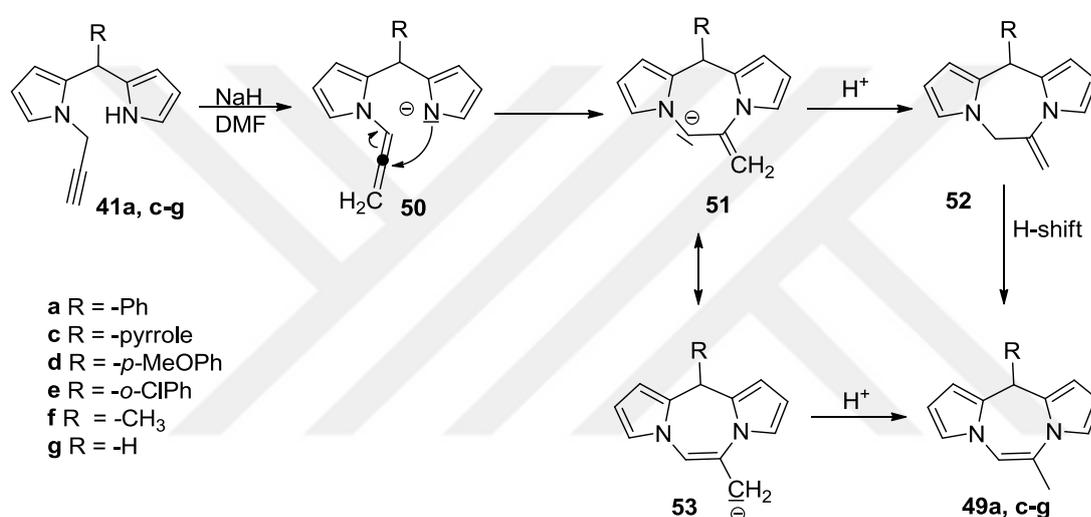
The structures of newly synthesized diazepine derivatives **49a-g** are shown in the Scheme 22.



**Scheme 22.** Diazepine derivatives synthesized from mono-propargylated compounds

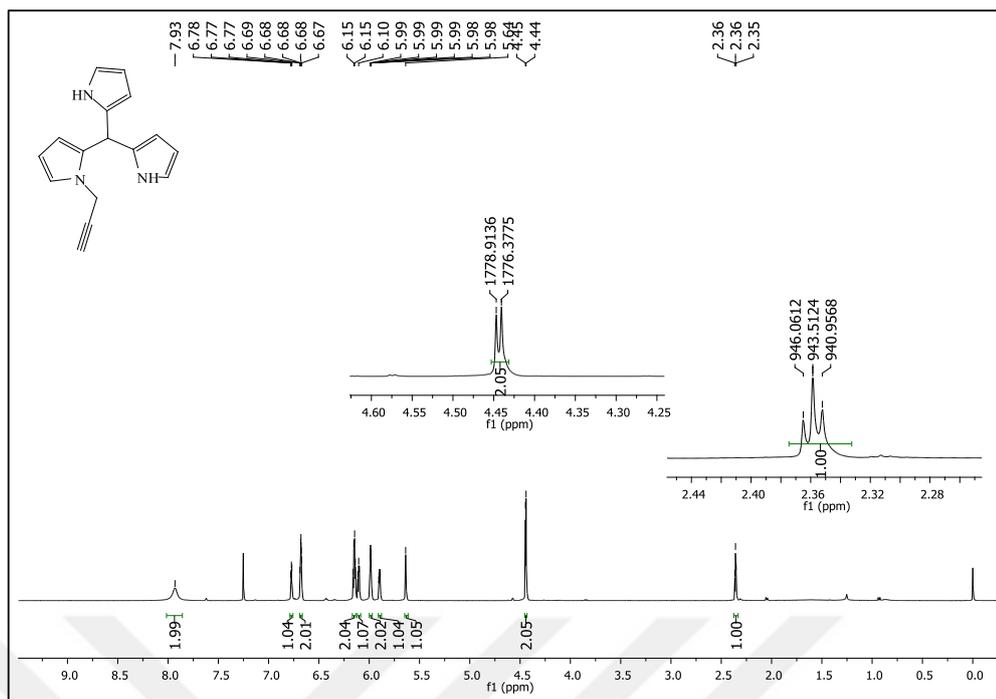
## 2.6. Proposed mechanism for the cyclization reaction

The mechanism of the alkyne cyclization reaction is mentioned in Scheme 21. In the first step, because of the basic reaction, **41a, c-g** can easily give allene formation **50** which have an electropositive carbon center. Thus, the nitrogen atom of pyrrole with increased electron density on its, attacks the central carbon atom of allene unit to give **52** through the intermediate **51**, which can form directly **49a, c-g** or **52**. The exo-cyclic products **52** can easily rearrange to **49a, c-g** under the basic conditions by 1,3-H shifting.(Scheme 23).

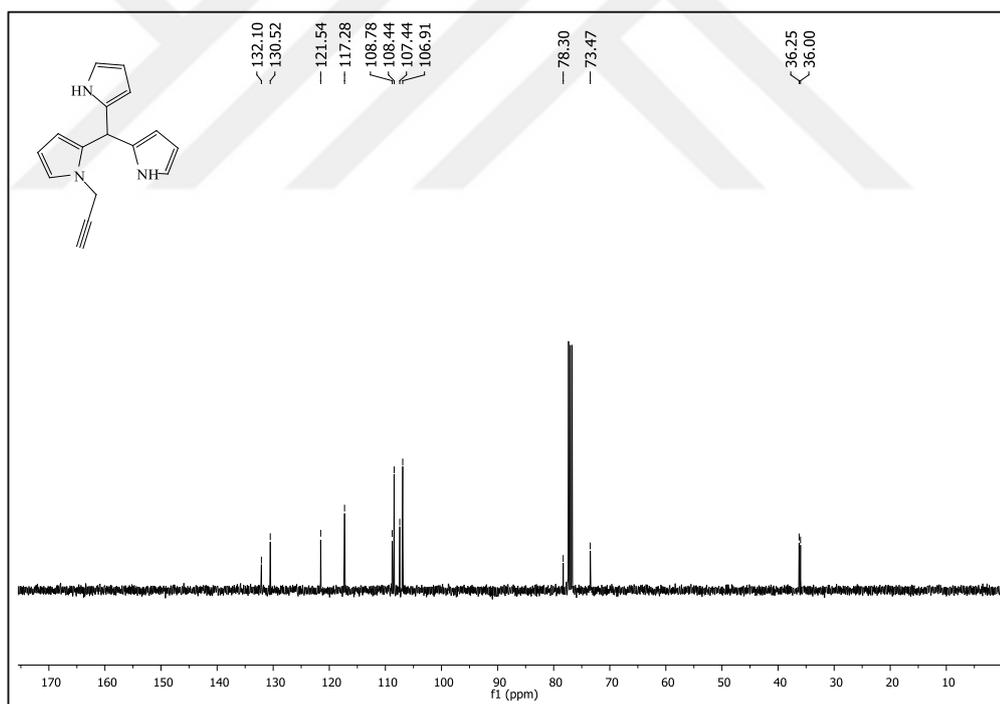


**Scheme 23.** Proposed mechanism for the formation of diazepine derivatives **49a-g**

The structure of **41c** and **49c** were proven by NMR studies as shown below (Figure 4). In the <sup>1</sup>H-NMR spectrum of compound **41c**, CH<sub>2</sub> protons resonate at 4.44 ppm as a doublet with a coupling constant of  $J = 2.5$  Hz and alkyne proton resonate at 2.36 ppm as triplet with a coupling constant of  $J = 2.5$  Hz because of long range coupling with CH<sub>2</sub> protons. In addition, two protons attached to the nitrogen atoms resonate at 7.93 ppm as a broad singlet (Figure 4). On the other hand, structure **41c** is in agreement with 12 distinct signals in the <sup>13</sup>C-NMR spectrum. (Figure 5).



**Figure 4:**  $^1\text{H-NMR}$  Spectrum of compound **41c** in  $\text{CDCl}_3$



**Figure 5:**  $^{13}\text{C-NMR}$  Spectrum of compound **41c** in  $\text{CDCl}_3$

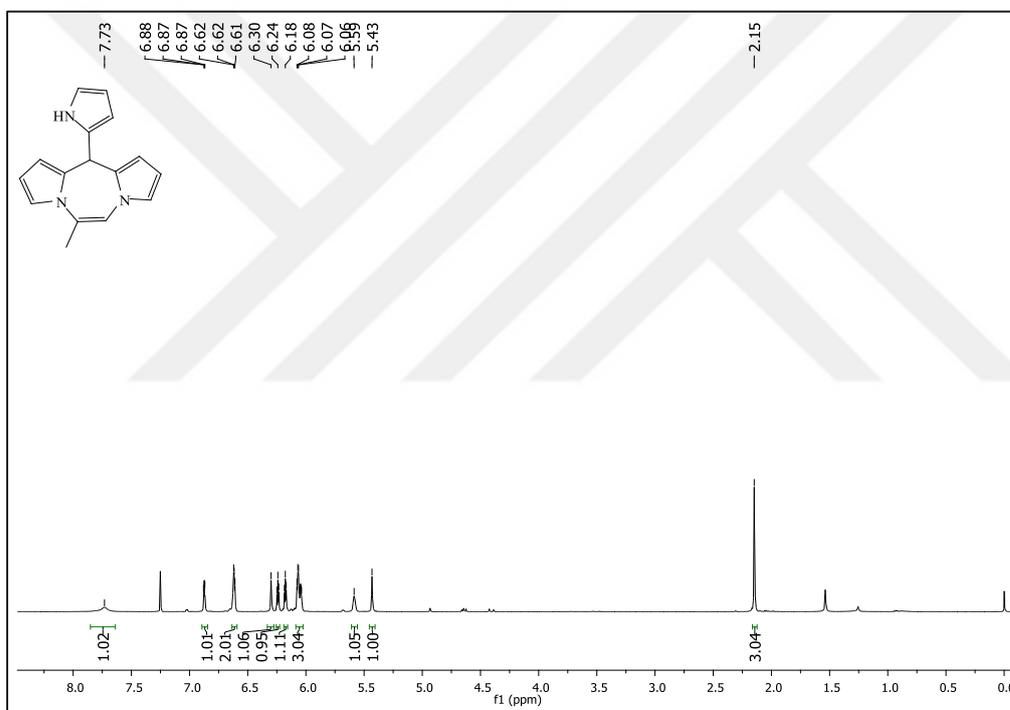
The 1D and 2D NMR (HSQC, COSY, HMBC) spectra were used for characterization of cyclization product **49c**. When the  $^1\text{H-NMR}$  spectra of **49c** and **41c** were compared, disappearance of alkyne protons and one of the nitrogen protons was very informative in view of the proposed structure. Furthermore, appearance of a singlet at 2.15 ppm

arising from the CH<sub>3</sub> protons in the <sup>1</sup>H-NMR spectrum of **49c** clearly indicated the cyclization reaction (Figure 6). Moreover, the <sup>13</sup>C-NMR spectrum with 16 distinct carbon resonance signals also supports the formation of product **49c** (Figure 7).

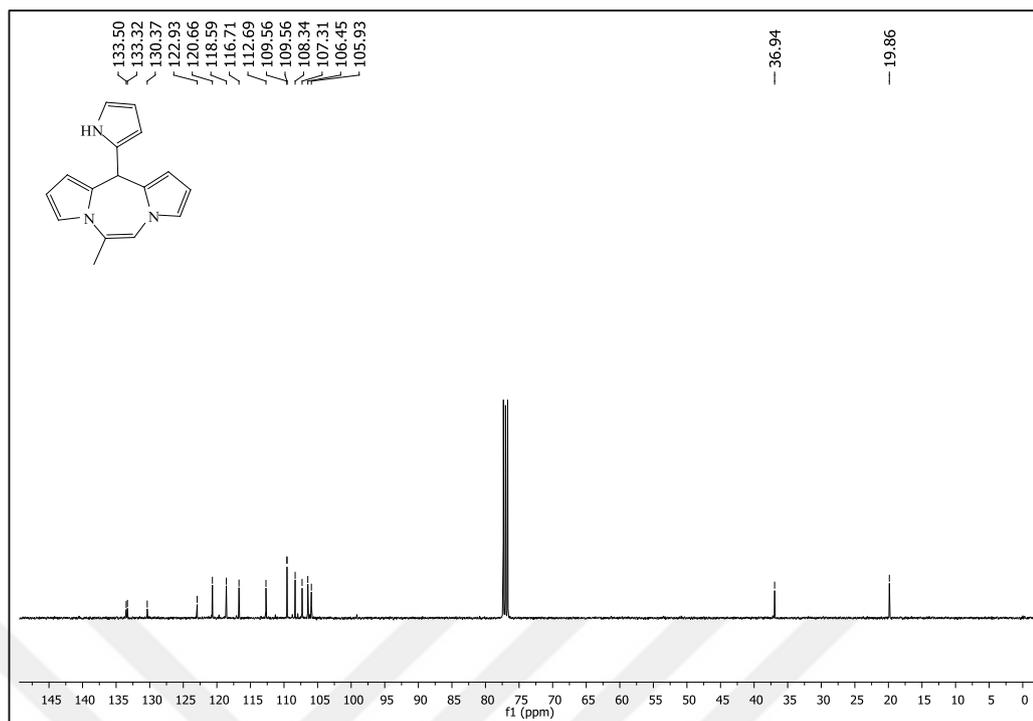
In the HSQC spectrum of compound **49c**, there are some significant heteronuclear correlations supporting the cyclic structure (Figure 8).

In COSY spectrum, we observe a correlation between the methyl protons and the newly formed double bond proton (Figure 9). The location of C-4 carbon atom was determined by the correlations between the C-4 carbon atom and H-8 olefinic proton and CH<sub>3</sub> protons observed in the HMBC spectrum.

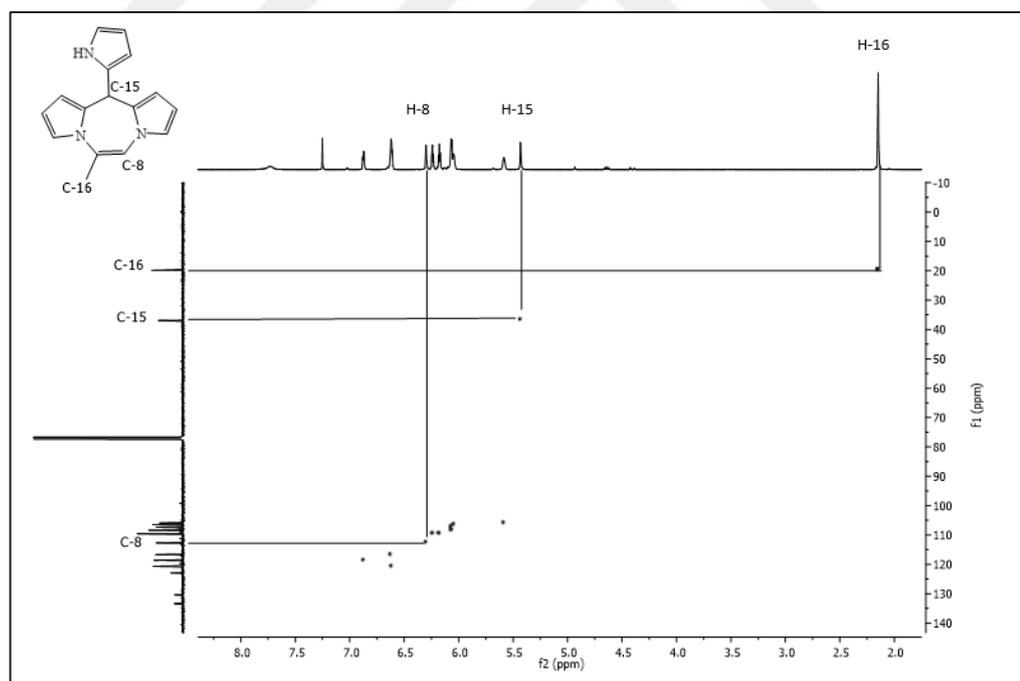
The other correlations were in complete agreement with the proposed structure too.



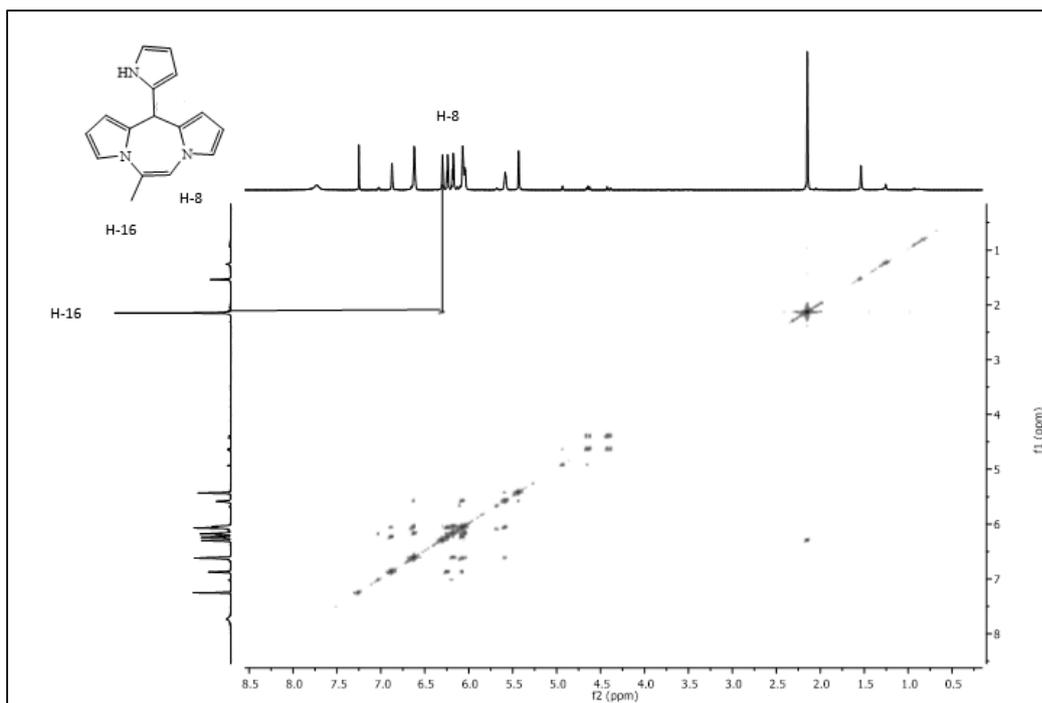
**Figure 6:** <sup>1</sup>H-NMR Spectrum of compound **49c** in CDCl<sub>3</sub>



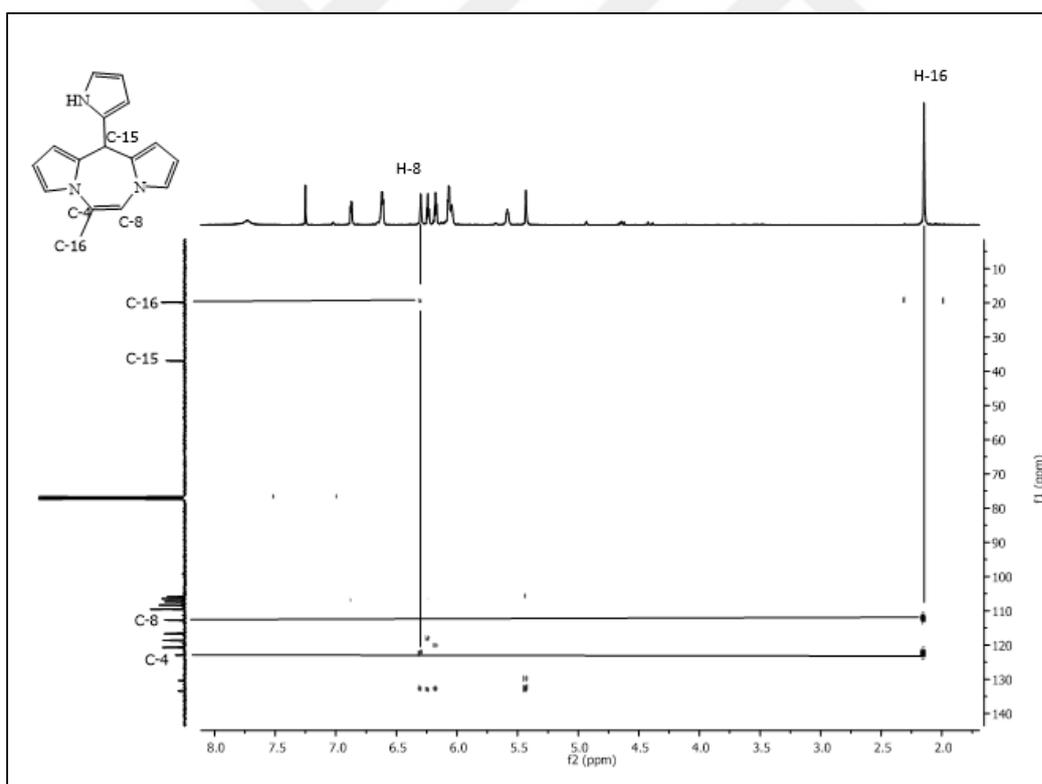
**Figure 7:**  $^{13}\text{C}$ -NMR Spectrum of compound **49c** in  $\text{CDCl}_3$



**Figure 8:** HSQC Spectrum of compound **49c** in  $\text{CDCl}_3$



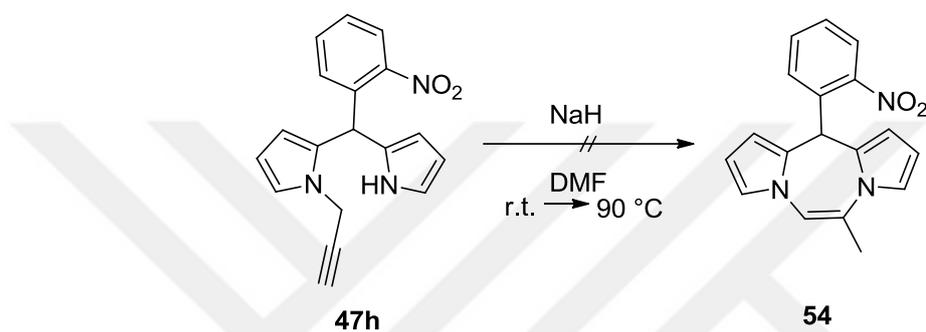
**Figure 9:** COSY Spectrum of compound **49c** in  $\text{CDCl}_3$



**Figure 10:** HMBC Spectrum of compound **49c** in  $\text{CDCl}_3$

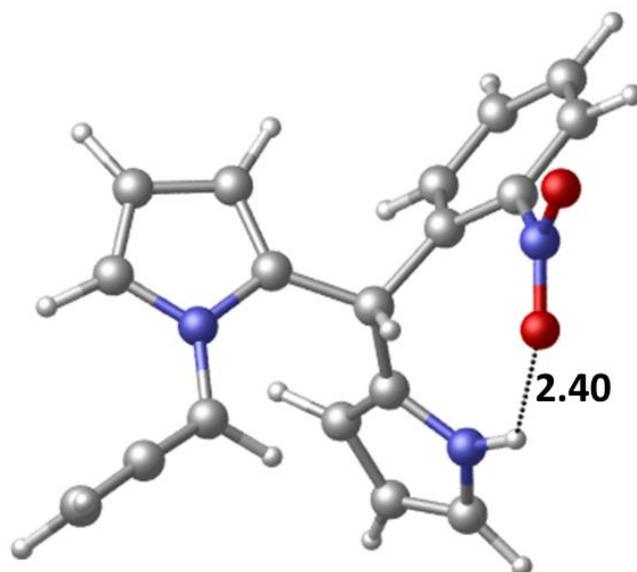
## 2.7. An attempt for the cyclization reaction of 2-[(2-nitrophenyl)(1*H*-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1*H*-pyrrole (**47h**)

2-[(2-Nitrophenyl)(1*H*-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1*H*-pyrrole (**47h**) was another mono-propargylated derivative having a benzene group bearing a nitro-functionality at the *ortho*-position, which was synthesized in order to control the scope of the cyclization reaction. Unfortunately, expected cyclization product **54** was not obtained from the reaction of **47h** with NaH in DMF even at high temperatures (Scheme 24).



**Scheme 24.** Reaction of structure **47h** with NaH

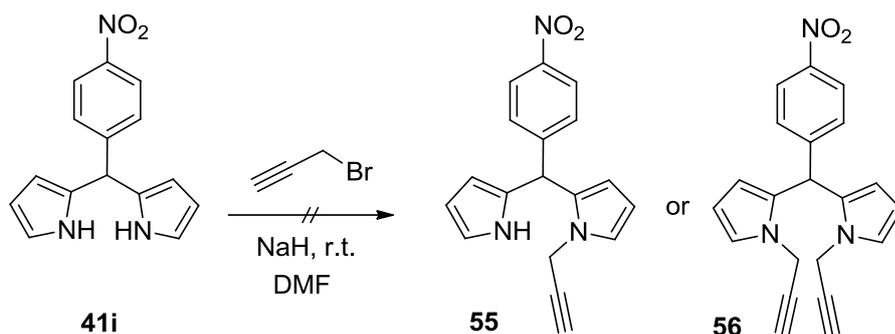
Intramolecular hydrogen-bonding can be attributed to this unexpected situation. Hydrogen-bonding is accepted as “strong, mostly covalent” with donor-acceptor distances of 2.2-2.5 Å; as “moderate, mostly electrostatic” if distance is between 2.5-3.2 Å and as “weak, electrostatic” with distance of 3.2 - 4.0 Å.<sup>40</sup> The geometry of **50a** was optimized by using B3LYP with 6-31+G(d,p) basis set in the gas phase to prove the formation of intramolecular hydrogen-bonding. As one can see from Figure 11, the distance between one of the oxygen atoms of the nitro group and the hydrogen atom attached to the nitrogen atom of pyrrole is 2.40 Å. Thus, the intramolecular hydrogen-bonding of compound **50a** is mostly covalent and this fact blocks the cyclization reaction.



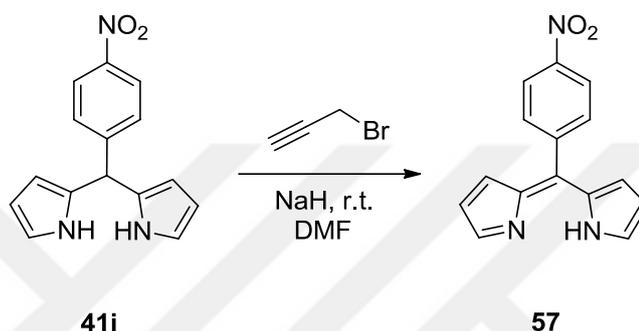
**Figure 11.** H bonding of compound **50a**

### 2.8. An attempt for the propargylation reaction of 2-[(4-nitrophenyl)(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41i**)

After failure of the cyclization reaction of **47h** we decided to change to position of nitro group from the ortho-position to the para-position as in **55** to prove the intramolecular hydrogen-bonding in compound **47h** which prevented the cyclization reaction. In designed structure **56**, a similar hydrogen bonding will not be possible due to the distance between oxygen atom and NH hydrogen of pyrrole. For the synthesis of **55**, dipyrromethane derivative **41i** was submitted to propargylation reaction under the same reaction conditions. For that reason, compound 2-[(4-nitrophenyl)(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41i**) was reacted with NaH and propargyl bromide in the presence of DMF. Unlikely, instead of expected mono-propargylated product **55** or di-propargylated product **56**, compound **57**<sup>39</sup> was produced under these reaction conditions (Scheme 25) and (Scheme 26).

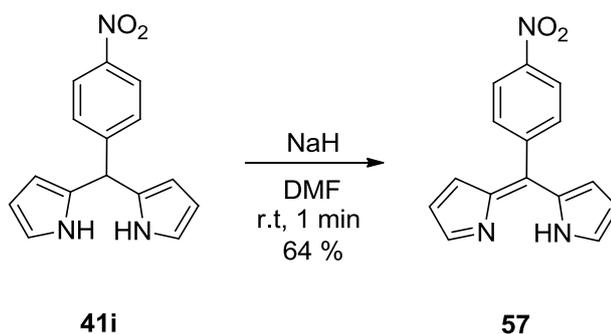


**Scheme 25.** Attempt to synthesize compound **55**



**Scheme 26.** Synthesis of compound **57** in the presence of propargyl bromide and NaH

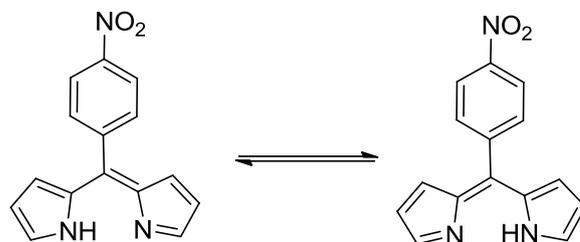
When compound **41i** was reacted only with NaH in DMF, in the absence of propargyl bromide, **57** was again formed even in 1-2 minutes (Scheme 27). Thus, propargyl bromide does not effect the reaction. The spectral data ( $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$ , HRMS) of compound **57** is full-compatible with the literature data<sup>39</sup>.



**Scheme 27.** Synthesis of compound **57** with NaH

Due to the presence of a strong electron-withdrawing group such as nitro group, the acidity of methine proton is enhanced. Therefore, the base can easily abstract this proton forming an anion which can be stabilized due to the delocalization over the

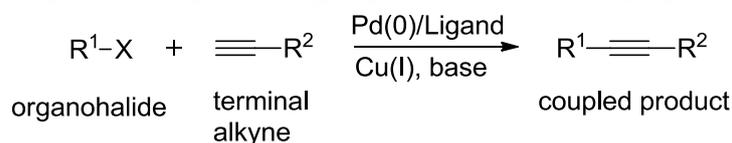
benzene and pyrrole rings. This anion can undergo an oxidation reaction in the presence of air to form the oxidation product **57**. Probably, a similar oxidation in the case of **41h** due to the formation of strong hydrogen bonding is hindered (Figure 11). Because of the very fast tautomerism in **57**, two pyrrole rings are equal. This can be nicely seen in the symmetrical NMR spectra (Scheme 28).



**Scheme 28.** Resonance structures of compound **57**

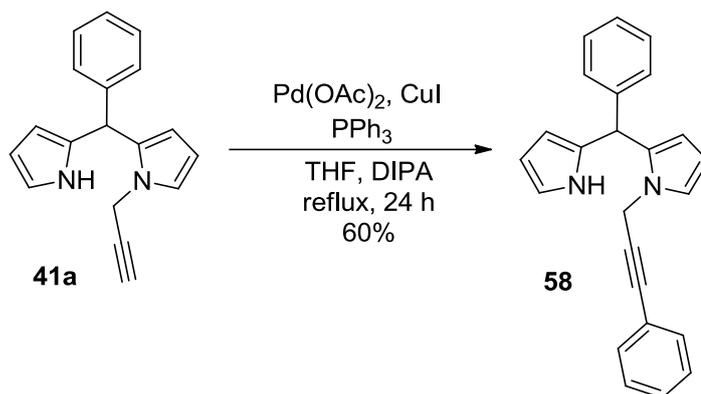
## 2.9. Synthesis of 2-(phenyl(1H-pyrrol-2-yl)methyl)-1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole (**58**) with Sonogashira coupling reaction

Sonogashira cross-coupling reaction is used to form a new C-C bond between aryl or vinyl halide and a terminal alkyne by using copper catalyst, palladium catalyst, bulky ligand and base (Scheme 29).<sup>37</sup>



**Scheme 29.** Sonogashira coupling reaction

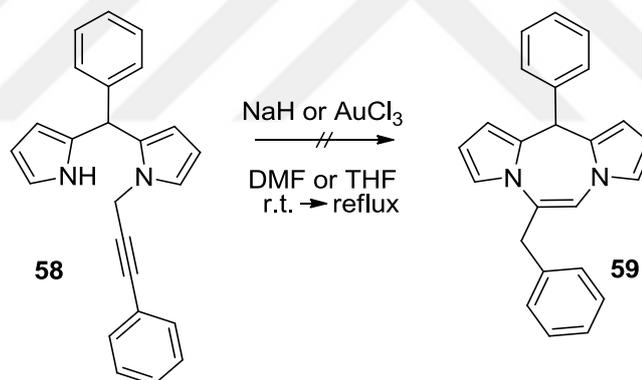
In order to test the scope of the cyclization reaction, additional derivative 2-(phenyl(1H-pyrrol-2-yl)methyl)-1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole (**58**) was synthesized by using Sonogashira coupling reaction procedure<sup>38</sup>. desired coupling product **58** was obtained from the reaction of compound **41c** with phenyl acetylene, Pd(OAc)<sub>2</sub>, CuI and PPh<sub>3</sub> in dry DIPA and dry THF (Scheme 30).



**Scheme 30.** Synthesis of **57** by using Sonogashira coupling reaction

### 2.10. An attempt for the cyclization reaction of 2-(phenyl(1H-pyrrol-2-yl)methyl)-1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole (**58**)

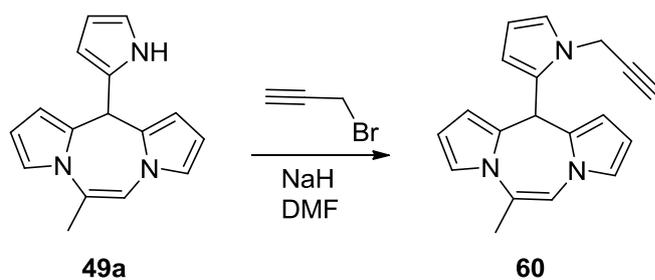
Coupling product **58** was reacted with NaH or AuCl<sub>3</sub> in the presence of DMF or THF at room temperature as well as at reflux temperature. However, desired cyclization product **59** did not form under these reaction conditions (Scheme 31).



**Scheme 31.** Reaction of compound **58** with NaH

### 2.11. Further propargylation of 5-methyl-11-(1H-pyrrol-2-yl)-11H-dipyrrolo[1,2-*d*:2',1'-*g*][1,4]diazepine (**49c**)

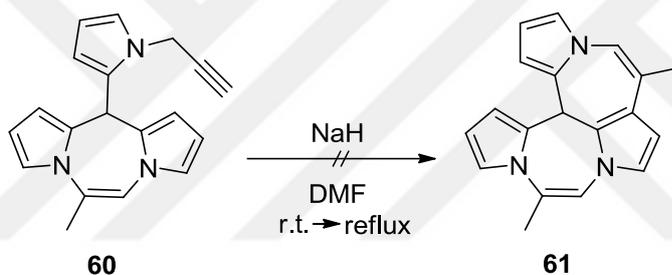
The product **49c** was reacted with NaH in the presence of propargyl bromide in DMF. An S<sub>N</sub>2 reaction occur to give propargylated product **60** in 61% yield (Scheme 32). The compound **60** was suitable for further cyclization reactions. Therefore, the further cyclization reaction could be tried for compound **60**.



**Scheme 32.** Propargylation of **49a**

**2.12. An attempt for further cyclization reaction of 5-methyl-11-(1-(prop-2-yn-1-yl)-1H-pyrrol-2-yl)-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (60)**

The key compound **60** was reacted with NaH with the expectation of the formation of derivative **61**. Unfortunately, no trace of a cyclization product could be observed even at reflux temperature (Scheme 33).

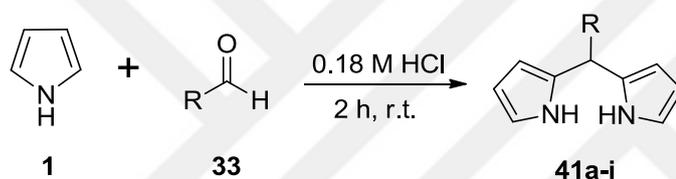


**Scheme 33.** Reaction of **60** with NaH

## CHAPTER 3

### CONCLUSION

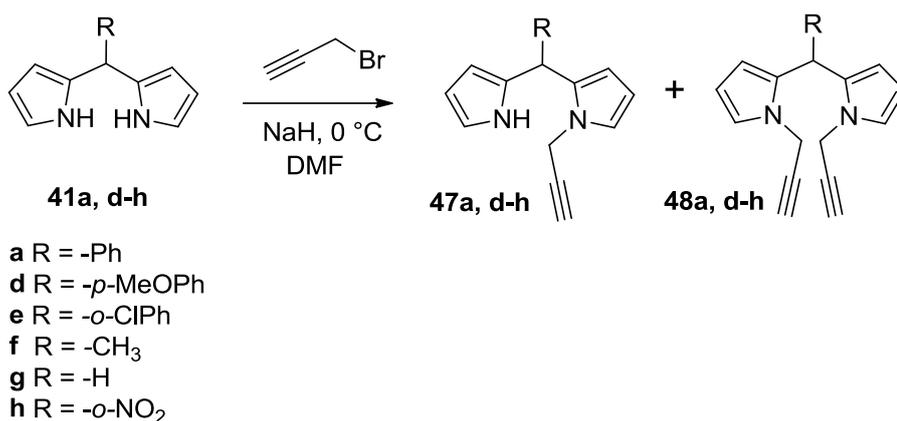
A novel synthetic methodology was improved for the synthesis of new diazepine derivatives which may show potential activities especially for psychological disorders. The method which is described starts with the synthesis of dipyrromethanes. In this step, some procedure were tried and the most favorable one was modified to obtain the starting dipyrromethane derivatives **41a-i** (Scheme 34).



- a** R = -Ph, 74%
- b** R = -1-(prop-2-yn-1-yl)-1*H*-indole, 59%
- c** R = -1-(prop-2-yn-1-yl)-1*H*-pyrrole, 72%
- d** R = -*p*-MeOPh, 70%
- e** R = -*o*-ClPh, 89%
- f** R = -CH<sub>3</sub>, 62%
- g** R = -H, 69%
- h** R = -*o*-NO<sub>2</sub>, 79%
- i** R = -*p*-NO<sub>2</sub>, 81%

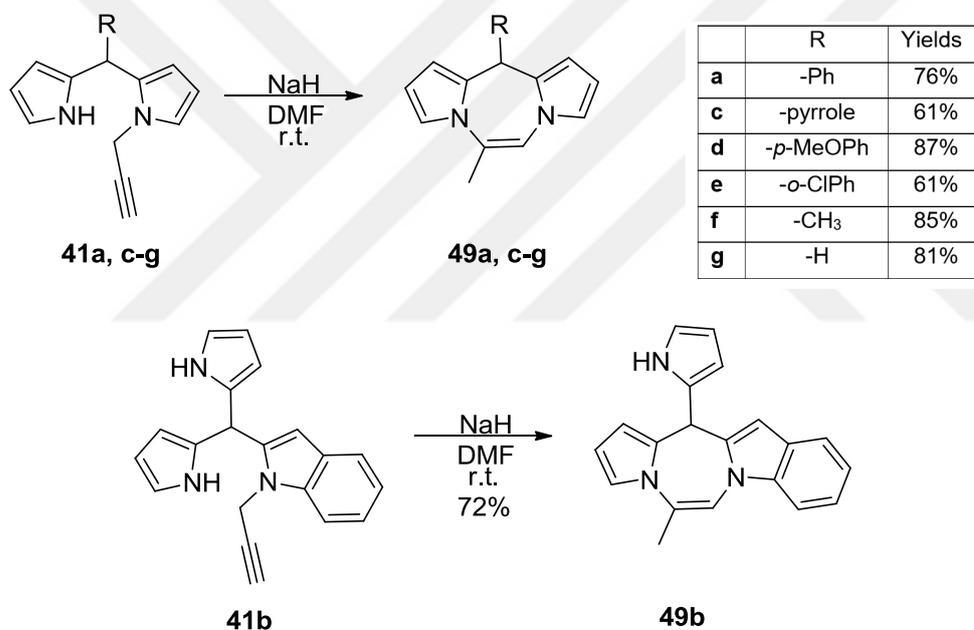
**Scheme 34.** Synthesis of starting compound **41a, d-h**

Introducing propargyl group to nitrogen atom of pyrrole(s) gave the expected mono- and di-propargylated compounds **47a, d-h** and **48a, d-h**. The trouble for this step was that the yields of mono-propargylated compounds, which were much less than the yields of the di-propargylated compounds. So, this problem was solved by modification of the procedure<sup>21</sup> (Scheme 35).



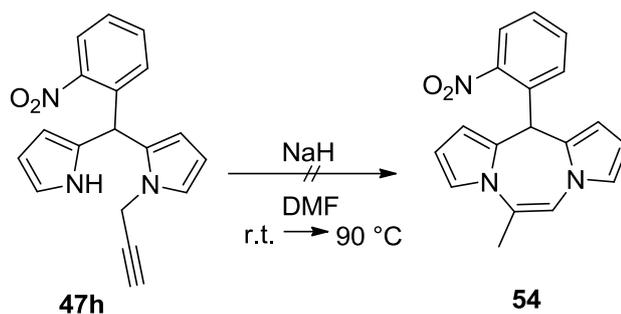
**Scheme 35.** Synthesis of propargylated compounds

Then, with the following simple cyclization reaction, desired diazepine derivatives **49a-g** were obtained (Scheme 36).

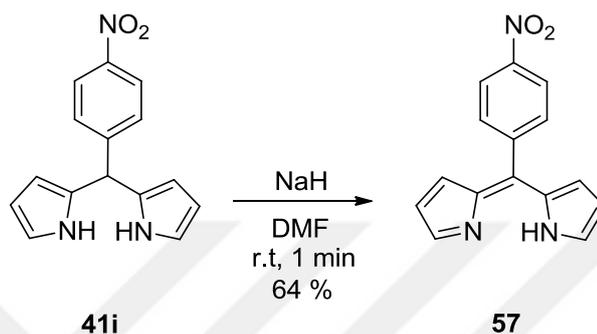


**Scheme 36.** Synthesis of cyclized derivatives.

Moreover, attempt for the cyclization reaction of derivative **47h** was done. The failure of cyclization reaction of **54** was attributed to the formation of intramolecular hydrogen-bonding between oxygen atom nitro group and pyrrole NH-hydrogen atom (Scheme 37). Surprisingly, the reaction of **41i** with NaH gave an oxidation product **57** (Scheme 38).

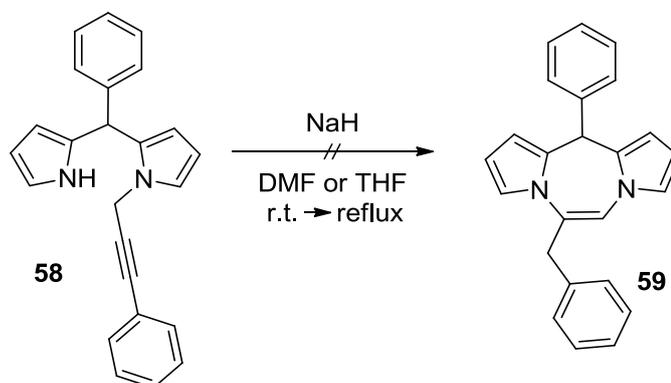


**Scheme 37.** Reaction of **47h** with NaH



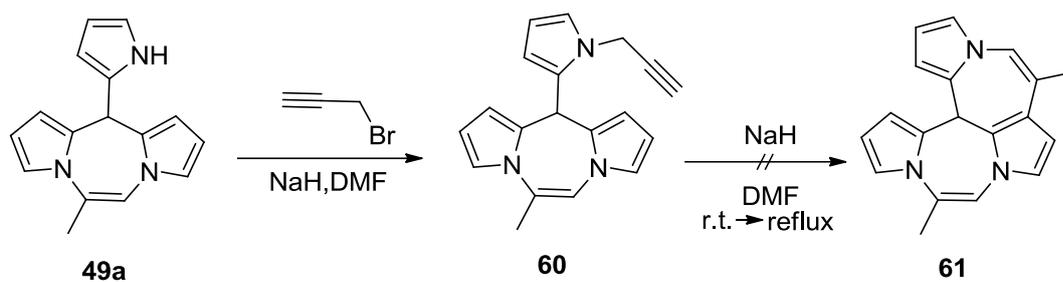
**Scheme 38.** Reaction of **41i** with NaH in the presence of air oxygen

Further, attempts with compounds having a benzene ring attached to the terminal carbon atom of alkyne functionality, was failed to give any cyclization product (Scheme 39).



**Scheme 39.** Synthesis of **59** by using Sonagahira reaction

Finally, we succeeded in the synthesis of **60**, however, further cyclization to generate a new skeleton such as **61** was failed (Scheme 40).



**Scheme 40.** Reactions to get target compound **61**

The characterization of newly synthesized compounds were succeeded by using  $^1\text{H}$ -NMR,  $^{13}\text{C}$ -NMR, IR and HRMS spectra.

## CHAPTER 4

### EXPERIMENTAL SECTION

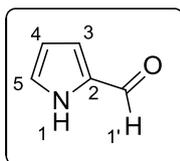
#### 4.1 General Methods

All reagents were acquired from commercial provider and additional purification was not done.  $^1\text{H}$  NMR spectra were recorded on an instrument 400 MHz and chemical shifts are shown in ppm.  $\text{CDCl}_3$  and  $\text{CD}_3\text{COCD}_3$  were used as internal standarts. In addition,  $^{13}\text{C}$ -NMR spectra were recorded on an instrument 100 MHz and  $\text{CDCl}_3$  and  $\text{CD}_3\text{COCD}_3$  were used as internal standarts. Also,  $^{13}\text{C}$ -NMR spectra were reported in ppm. IR were recorded in the range  $4000\text{-}600\text{ cm}^{-1}$  via ATR diamond. Melting point instrument was used to measure melting points.<sup>ee</sup>

Rotary vacuum evaporator was used for vaporisation of solvents at reduced pressure. Column chromatography was carried out on silica gel). TLC was performed on 0.2 mm silica gel aluminum plates. UV light ( $\lambda = 254\text{ nm}$ ) was used to visualize the spots on TLC. LC-MS TOF electrospray ionization technique was used to record HRMS.

#### 4.2. Synthesis of 1H-pyrrole 2-carbaldehyde(37)<sup>33</sup>

To a stirred solution of  $\text{POCl}_3$  (1.4 g, 9.1 mmol) and DMF (0.73 g, 9.7 mmol) was added pyrrole (0.6 g, 9.1 mmol) in dry ether (20 mL) dropwise at  $0\text{ }^\circ\text{C}$ . The composition was mixed at room temperature for 14h. Afterwards, the satiated solution of  $\text{NaHCO}_3$  was added to media until a basic medium was beholded. Then, the composition was extracted with EtOAc ( $3 \times 30\text{ mL}$ ). DMF in extracts were removed with brine ( $3 \times 15\text{ mL}$ ) and the mixture dried over  $\text{MgSO}_4$ , and the solvent was vaporized. The crude composition was chromatographed eluting with hexane/EtOAc (10:1) to give (37) as a needle crystals (0.63 g, 73%), m.p.  $44\text{-}45\text{ }^\circ\text{C}$ .

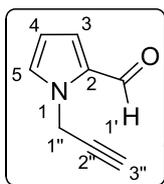


**$^1\text{H-NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  10.47 (br s, 1H, -NH), 9.51 (d,  $J = 1.0$ , 1H, -H-1'), 7.18 (br s, 1H, H-3), 7.01 (ddd,  $J_{4,3} = 3.8$  Hz,  $J_{5,4} = 2.3$  Hz, 1H, H-4), 6.35 (ddd,  $J_{4,3} = 3.8$  Hz,  $J_{4,5} = 2.4$  Hz, 1H, H-4)

**$^{13}\text{C-NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  179.4, 132.8, 126.9, 121.8, 111.3.

#### 4.3. Synthesis of 1-(Prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde (**38**)<sup>35</sup>

To a solution of pyrrole-2-carbaldehyde (0.63 g, 6.7 mmol) (**37**) in DMF (10 mL) was added NaH (0.2 g, 11 mmol) at 0 °C portionwise over 1 h. The composition was mixed at 0 °C for 0.5 h, and to the reaction media was added propargyl bromide (0.11 mL, 8.5 mmol) in DMF (10 mL) dropwise over 0.5 h. The reaction mixture was mixed at room temperature for 16 h, and water addition (50 mL), the mixture was extracted with EtOAc (4  $\times$  25 mL). DMF in media was removed with brine (6  $\times$  15 mL), dried over  $\text{MgSO}_4$ , and solvent in composition was evaporated. The crude product was chromatographed eluting with hexane/EtOAc (7/1) to give (**38**) as a yellow liquid (0.66 g 75%).<sup>35</sup>

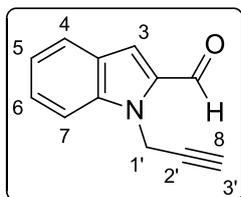


**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.49 (bd,  $J = 1.2$  Hz, 1H, H-1'), 7.20–7.19 (m, 1H, H-5), 6.90 (dd,  $J_{3,4} = 4.0$  and  $J_{3,5} = 1.6$  Hz, 1H, H-3), 6.22 (dd,  $J_{4,5} = 2.4$ ,  $J_{4,3} = 4.0$  Hz, 1H, H-4), 5.14 (d,  $J = 2.6$  Hz, 2H, H-1''), 2.39 (t,  $J = 2.6$  Hz, 1H, H-3'').

**$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  179.5, 131.1, 130.4, 124.9, 110.1, 77.8, 74.4, 38.1.

#### 4.4. Synthesis of 1-prop-2-ynyl-1H-indole-2-carbaldehyde (**40**)<sup>36</sup>

Solid NaH was added (0.17 g, 7.1 mmol) piecewise at 0 °C to a stirred solution of 1H-indole-2-carbaldehyde (**39**) (0.94 g, 5.5 mmol) in dry DMF (10 mL). Then, propargyl bromide (0.85 mL, 7.8 mmol) was added to the stirring solution. After 7 hours, brine was added (50 mL) to remove DMF and ethyl acetate (3  $\times$  50 mL) was used to extract product. The final composition were dried over  $\text{MgSO}_4$  and filtered. After vaporisation, the product (**40**) was obtained. Brown solid (0.91 g, 82%) from  $\text{CH}_2\text{Cl}_2$ , m.p. 101-103 °C.



**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.81 (s, 1H, H-8), 7.68 (dt,  $J_{4,5} = 8.0$ ,  $J_{4,6} = J_{4,3} = 0.9$  Hz, 1H, H-4), 7.47 (dd,  $J_{7,6} = 8.5$ ,  $J_{7,5} = 1.0$  Hz, 1H, H-7), 7.40 (ddd,  $J_{6,7} = 8.5$ ,  $J_{6,5} = 7.0$ ,  $J_{6,4} = 0.9$  Hz, 1H, H-6), 7.22 (d,  $J_{3,4} = 0.9$  Hz, 1H, H-3), 7.15 (ddd,  $J_{5,4} = 8.0$ ,  $J_{5,6} =$

7.0,  $J_{5,7} = 1.0$  Hz, 1H, H-5), 5.39 (d,  $J_{1',3'} = 2.5$  Hz, 2H, H-1'), 2.20 (t,  $J_{3',1'} = 2.5$  Hz, 1H, H-3').

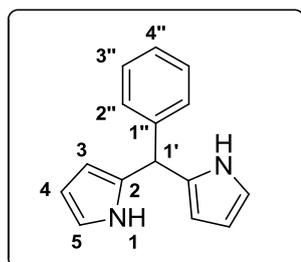
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  182.6, 140.1, 134.5, 127.4, 126.6, 123.5, 121.5, 118.7, 110.8, 78.2, 72.5, 33.9.

#### 4.5. General procedure for synthesis of 5-substituted dipyrromethanes (41a-i)

Corresponding aldehydes (**33a** and **33d-i**) and N-propargyl substituted aldehydes (**38**, **40**) (5 mmol) were dissolved in pyrrole (15 mmol) and then HCl (0.18 M, 0.045 mmol, 250 mL) was added to media and the composition was mixed at room temperature for 3 hours. The reaction was followed with TLC and after completion of the reaction. The composition was extracted with EtOAc ( $3 \times 50$  mL) and dried over  $\text{MgSO}_4$  and after evaporation, the residue was purified with gradient column chromatography eluting with hexane:ethyl acetate (10:1 to 5:1) and the product were crystallized from appropriate solvents.

#### 4.6. Synthesis of 2-[phenyl(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41a)<sup>21</sup>

Benzaldehyde (0.5 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) was reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above. (**41a**) was receipt as a pale yellow crystals (0.82 g, 74%), m.p. 105-106 °C from EtOAc/hexane.

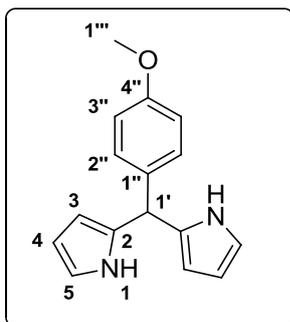


$^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (bs, 2H, H-1), 7.22-7.35 (m, 5H, arom), 6.63-6.59 (m, 2H, H-5), 6.15 – 6.13 (m, 2H, H-4), 5.92 (bs, 2H, H-3), 5.49 (s, 1H, H-1').

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  44.1, 107.5, 108.8, 117.1, 127.0, 128.5, 128.7, 132.4, 142.2.

#### 4.7. Synthesis of 2-[(4-methoxyphenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41d)<sup>21</sup>

HCl (0.18 M, 0.045 mmol, 250 mL) was added to a mixture of 4-methoxybenzaldehyde (0.75 g, 5 mmol) and pyrrole (1.005 g, 15 mmol). Then, procedure was continued as described above. **41d** was obtain as pale yellow powder (0.88 g, 70%), m.p. 102-103 °C.

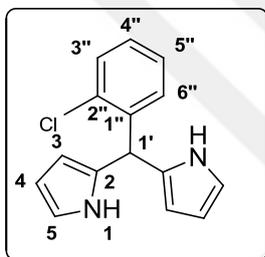


**$^1\text{H-NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.82 (bs, 2H, H-1'), 7.14 (d,  $J_{2'',3''} = 8.6$ , 2H, H-2''), 6.85 (d,  $J_{2'',3''} = 8.6$ , 2H, H-3''), 6.65-6.67 (m, 2H, H-5), 6.15 – 6.13 (m, 2H, H-4), 5.90-5.92 (m, 2H, H-3), 5.42 (s, 1H, H-1'), 3.82 (s, 3H, H-1'').

**$^{13}\text{C NMR}$**  (100 MHz  $\text{CDCl}_3$ ):  $\delta$  43.2, 55.2, 107.3, 108.7, 114.0, 117.0, 129.4, 132.8, 134.3, 158.6.

#### 4.8. Synthesis of 2-[(2-chlorophenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41e)

4-chlorobenzaldehyde ( 0.70 g, 5 mmol ) and pyrrole (1.005 g, 15 mmol) was reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above (41e) was receipt as pale yellow powder (1.14 g, 89%), m.p. 108-109 °C.



**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 (bs, 2H, H-1), 7.41 – 7.31 (m, 1H, H-3''), 7.22 – 7.16 (m, 2H, H-4'', H-5''), 7.12 – 7.07 (m, 1H, H-6''), 6.70 – 6.68 (m, 2H, H-3), 6.16 (m, 2H, H-4), 5.91 (s, 1H, H-1'), 5.88 – 5.85 (m, 2H, H-5),

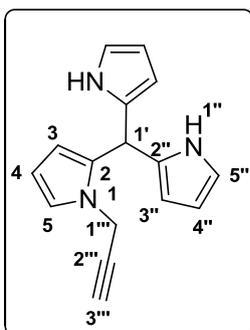
**$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  140.0, 133.7, 131.2, 129.7, 129.6, 128.2, 127.1, 117.3, 108.5, 107.4, 40.6.

**IR (ATR,  $\text{cm}^{-1}$ )** 3674, 2986, 2901, 1507, 1456, 1394, 1228, 1066, 1055, 892, 823, 725.

**HRMS** calcd for  $\text{C}_{15}\text{H}_{13}\text{ClN}_2$  [ $\text{M}+\text{H}$ ] $^+$ : 257.0840, found: 257.0842

#### 4.9. Synthesis of 2-[di(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (41c)

1-(Prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde (38) (0.665 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) was reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above to give compound (41c). Yellow solid (0.89 g, 72%), m.p. 92-93 °C.



**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.93 (bs, 2H, H-1''), 6.77 (dd,  $J = 2.6, 2.0$  Hz, 1H, H-5), 6.69 – 6.66 (m, 2H, H-5''), 6.16 – 6.14 (m, 2H, H-4''), 6.12 – 6.09 (m, 1H, H-4), 6.00 – 5.97 (m, 2H, H-3''), 5.91 – 5.88 (m, 1H, H-3), 5.64 (s, 1H, H-1'), 4.44 (d,  $J_{3''',1'''} = 2.6$  Hz, 2H, H-1'''), 2.36 (t,  $J_{3''',1'''} = 2.6$  Hz, 1H, H-3''').

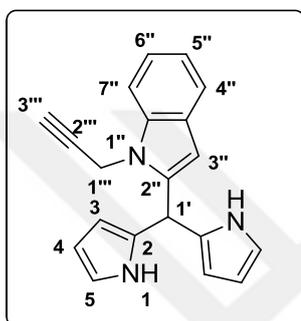
**$^{13}\text{C NMR}$**  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  132.1, 130.5, 121.5, 117.2, 108.7, 108.4, 107.4, 106.9, 78.3, 73.4, 36.2, 36.0.

**IR (ATR,  $\text{cm}^{-1}$ )** 3285, 1651, 1528, 1475, 1402, 1368, 1337, 1314, 1282, 1246, 1218, 1075, 1030, 953, 939, 890, 785, 741, 641, 605.

**HRMS** calcd for  $\text{C}_{16}\text{H}_{15}\text{N}_3$   $[\text{M}+\text{H}]^+$ : 249.1024, found: 249.1043

#### 4.10. Synthesis of 2-[di(1*H*-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1*H*-indole (**41b**)

1-(Prop-2-yn-1-yl)-1*H*-indole-2-carbaldehyde (**40**) (0.916 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) were reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above to give compound (**41b**). Yellow oil (0.88 g, 59%).



**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.90 (bs, 2H, H-1), 7.45 (d,  $J = 7.8$  Hz, 1H, H-7''), 7.29 (d,  $J = 8.2$  Hz, 1H, H-6''), 7.20 – 7.12 (m, 1H, H-5''), 7.08 – 7.01 (m, 1H, H-4''), 6.62 – 6.60 (m, 2H, H-5), 6.17 (s, 1H, H-3''), 6.11 – 6.09 (m, 2H, H-4), 6.01 – 5.95 (m, 2H, H-3), 5.74 (s, 1H, H-1'), 4.63 (d,  $J_{1''',3'''} = 2.5$  Hz, 2H, H-1'''), 2.16 (t,  $J_{1''',3'''} = 2.5$  Hz, 1H, H-3''').

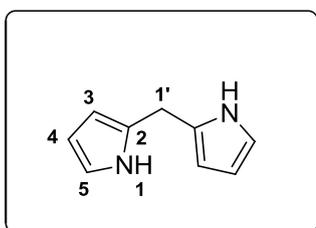
**$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  139.7, 137.1, 129.7, 127.6, 122.0, 120.6, 120.2, 117.6, 109.2, 108.6, 107.3, 102.5, 78.3, 72.4, 36.5, 32.5.

**IR (ATR,  $\text{cm}^{-1}$ )** 3403, 2987, 1715, 1507, 1459, 1402, 1339, 1311, 1249, 1182, 1162, 1106, 1085, 1027, 907, 884, 770, 726, 646, 603.

**HRMS** calcd for  $\text{C}_{20}\text{H}_{17}\text{N}_3$   $[\text{M}+\text{H}]^+$ : 299.1542 found: 299.1553

#### 4.11. Synthesis of 2-(1*H*-pyrrol-2-ylmethyl)-1*H*-pyrrole (**41g**)<sup>21</sup>

Formaldehyde (0.15 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) was reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above to give compound (**41g**). Colorless needles from EtOAc/ hexane, m.p. 75 °C. (0.50 g, 69 %).

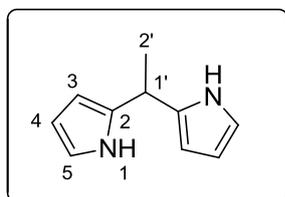


**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.63 (bs, 2H, H-1), 6.56 – 6.54 (m, 2H, H-5), 6.14 – 6.12 (m, 2H, H-4), 6.08 – 5.95 (m, 2H, H-3), 3.89 (s, 2H, H-1').

**$^{13}\text{C}$  NMR** (100 MHz,  $\text{CDCl}_3$ )  $\delta$  129.2, 117.5, 108.3, 106.6, 26.3.

#### 4.12. Synthesis of 2-[1-(1*H*-pyrrol-2-yl)ethyl]-1*H*-pyrrole (**41f**)<sup>21</sup>

Acetaldehyde (0.22 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) were reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above to give compound (**41f**). Colorless sticky solid (0.49 g, 62%).

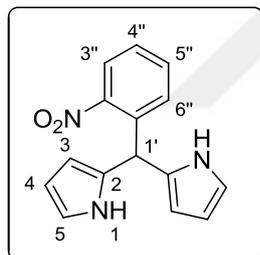


<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.60 (bs, 2H, H-1), 6.67 – 6.42 (m, 2H, H-5), 6.08 – 6.06 (m, 2H, H-4), 5.98 (bs, 2H, H-3), 4.06 (q,  $J_{2',1'} = 7.2$  Hz, 1H, H-1'), 1.50 (d,  $J_{2',1'} = 7.2$  Hz, 3H, H-2').

<sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  20.6, 31.7, 105.0, 108.0, 117.2, 134.8.

#### 4.13. Synthesis of 2-[(2-nitrophenyl)(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41h**)<sup>22</sup>

2-Nitrobenzaldehyde (0.75 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) were reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above to give compound (**41h**). Yellow needle crystals from CH<sub>2</sub>Cl<sub>2</sub> (1.05 g, 79%), m.p. 145-147 °C.

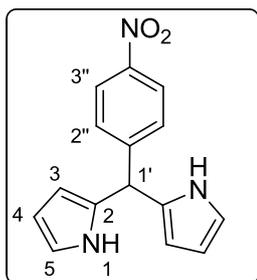


<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.16 (bs, 2H, H-1), 7.90 (dd,  $J_{4'',3''} = 8.1$  and  $J_{3'',5''} = 1.2$  Hz, 1H, H-3''), 7.54 (td,  $J_{4'',3''-5''} = 7.7$  and  $J_{4'',6''} = 1.2$  Hz, 1H, H-4''), 7.46 – 7.35 (m, 1H, H-5''), 7.30 (dd,  $J_{6'',5''} = 8.1$  and  $J_{6'',4''} = 1.5$  Hz, 1H, H-6''), 6.75 – 6.71 (m, 1H, H-5), 6.22 (s, 1H, H-1'), 6.18 (m, 1H, H-4), 5.89 – 5.84 (m, 1H, H-3).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  148.8, 137.2, 133.0, 131.0, 130.7, 127.8, 124.5, 117.6, 108.6, 107.4, 38.9.

#### 4.14. Synthesis of 2-[(4-nitrophenyl)(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41i**)<sup>21</sup>

4-Nitrobenzaldehyde (0.75 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) were reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above to give compound (**41i**) as light yellow needles from hexane/ethyl acetate, m.p. 161 °C. (1.08 g, 81%).

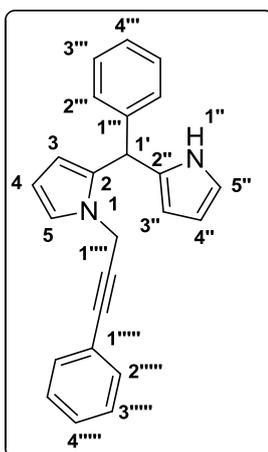


**$^1\text{H}$  NMR** (400 MHz, Acetone- $d_6$ )  $\delta$  9.84 (bs, 1H, H-1), 8.28 – 8.08 (m, 2H, H-3''), 7.54 – 7.43 (m, 2H, H-2''), 6.77 – 6.74 (m, . H-5), 6.04 (m, 2H, H-4), 5.82 – 5.78 (m, 1H, H-3), 5.67 (s, 1H, H-1').

**$^{13}\text{C}$  NMR** (100 MHz, Acetone- $d_6$ )  $\delta$  152.3, 147.5, 132.6, 130.3, 124.1, 118.4, 108.4, 107.9, 44.7.

#### 4.15. Synthesis of 2-(phenyl(1H-pyrrol-2-yl)methyl)-1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole (**58**)

A mixture of CuI (20 mg, 0.10 mmol), PPh<sub>3</sub> (40 mg, 0.15 mmol), and PdCl<sub>2</sub> (20 mg 0.10 mmol) was mixed under the nitrogen atmosphere for 2 min. After that, 2-[phenyl(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (0.2 g, 1.42 mmol), iodobenzene (0.34 g, 1.70 mmol) and DIPA (2 mL) in dry THF (20 mL) was added to the reaction mixture. The reaction was monitored with thin-layer chromatography and was completed after 1.5 h. After evaporation, the crude product was purified by column chromatography (silica gel/hexane-EtOAc 10:1) to give 2-(phenyl(1H-pyrrol-2-yl)methyl)-1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole (**58**) as brown viscous oil (0.303 g, 60%).



**$^1\text{H}$  NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.86 (bs, 1H, H-1''), 7.39 – 7.06 (m, 12H, arom), 6.81 – 6.72 (m, 1H, H-5), 6.62 (dd,  $J_{4,3} = 4.1$  and  $J_{4,5} = 2.5$  Hz, 1H, H-4), 6.08 – 6.06 (m, 1H, H-4''), 6.04 – 6.02 (m, 1H, H-3''), 5.81 – 5.75 (m, 1H, H-3), 5.65 5.57 (s, 1H, H-1'), 4.54 (s, 2H, H-1''').

**$^{13}\text{C}$  NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  141.6, 133.5, 131.9, 131.7, 128.6, 128.5, 128.5, 128.3, 126.9, 122.3, 121.3, 117.14, 109.4, 108.3, 107.4, 107.1, 85.0, 83.6, 42.6, 37.2.

**IR** (ATR,  $\text{cm}^{-1}$ ) 3375, 2919, 1682, 1597, 1489, 1442, 1386,

1342, 1284, 1233, 1115, 1071, 1027, 968, 915, 883, 845, 755, 689, 602.

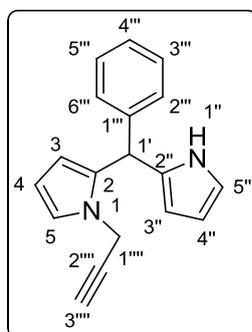
**HRMS** calcd for C<sub>24</sub>H<sub>20</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 337.1699 found: 337.1720

#### 4.16. General procedure for propargylation of dipyrromethanes substituted at C-5 position

To a stirred solution of 5-substituted dipyrromethanes (**40a** and **40d-h**) (3 mmol) in DMF (30 mL) was added propargyl bromide (3.6 mmol) in DMF (5 mL) dropwise at 0 °C over a period of 30 min. The process was followed by portionwise addition of NaH (3.6 mmol) at 0 °C over a period of 30 min. The reaction was monitored with thin-layer chromatography and completed after 12-17 h. After completion of the reaction, the composition was extracted with EtOAc (4 × 40 mL). Then, DMF in media was removed with brine (8 × 50 mL) and mixture dried over MgSO<sub>4</sub>. The eluent was removed under reduced pressure and the residue was purified with gradient column chromatography on silica gel eluted with hexane:ethyl acetate (20:1 to 7:1) and crystallized appropriate solvent.

#### 4.17. Synthesis of 2-[phenyl(1*H*-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1*H*-pyrrole (**47a**) and 2-[phenyl(1-prop-2-ynyl-1*H*-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1*H*-pyrrole (**48a**)

To a stirred solution of 2-[phenyl(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41a**) (0.82 g, 3.9 mmol) in DMF (30 mL) was added propargyl bromide (0.384 mL, 4.6 mmol) in DMF at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.112 g, 4.6 mmol). The reaction was completed after 12 h. and the further procedure was applied as described above. Mono-propargylated product (**47a**) was isolated as light yellow oil (0.49 g, 55%) and di-propargylated product (**48a**) was isolated as light yellow solid (0.20 g, 22%) m.p. 73-74 °C from EtOAc/ hexzane.

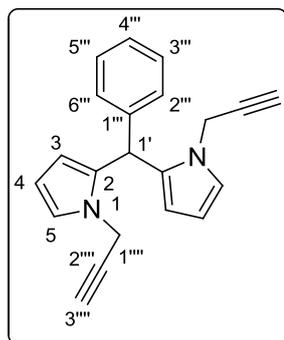


**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.91 (bs, 1H, H-1''), 7.39 – 7.10 (m, 5H-arom), 6.79 – 6.72 (m, 1H, H-5), 6.68 (dd,  $J_{4,3} = 4.1$  and  $J_{4,5} = 2.5$  Hz, 1H, H-4), 6.14 – 6.12 (m, 1H, H-4''), 6.10 – 6.06 (m, 1H, H-5''), 5.83 – 5.82 (m, 1H, H-3), 5.70 – 5.68 (m, 1H, H-3''), 5.56 (s, 1H, H-1'), 4.39 – 4.36 (m, 2H, H-1'''), 2.35 (t,  $J_{1''',3'''} = 2.5$  Hz, 1H, H-3''').

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 141.5, 133.5, 131.8, 128.5, 128.4, 126.9, 121.2, 117.1, 109.5, 108.3, 107.4, 107.3, 78.3, 73.4, 36.3, 29.6

**IR (ATR, cm<sup>-1</sup>)** 1662, 1510, 1416, 1381, 1342, 1287, 1272, 1252, 1118, 1094, 1043, 1002, 935, 909, 845, 808, 773, 714, 638, 593, 575.

**HRMS** calcd for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 259.1151 found: 259.1158



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.28 – 7.06 (m, 5H-arom), 6.71 – 6.66 (m, 2H, H-5), 6.03 – 5.94 (m, 2H, H-4), 5.54 (s, 1H, H-1'), 5.50 – 5.41 (m, 2H, H-3), 4.33 (dd,  $J_{\text{geminal}} = 14.0$  Hz and  $J_{1''',3'''} = 2.5$  Hz, 4H, H-1'''), 2.33 (t,  $J_{1''',3'''} = 2.5$  Hz, 2H, H-3''').

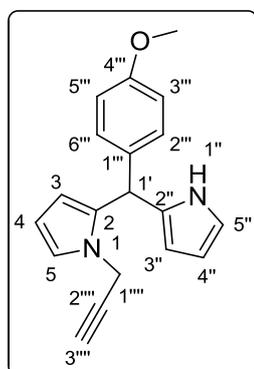
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 140.6, 132.9, 128.7, 128.5, 126.9, 121.1, 109.9, 107.3, 78.7, 73.3, 41.2, 36.3.

**IR (ATR, cm<sup>-1</sup>)** 3283, 3243, 3025, 2116, 1704, 1598, 1477, 1449, 1434, 1340, 1226, 1197, 1124, 1071, 1027, 1016, 962, 933, 896, 821, 789, 778, 751, 710, 697, 656, 609.

**HRMS** calcd for C<sub>21</sub>H<sub>18</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 299.1542 found: 299.1553

#### 4.18. Synthesis of 2-[(4-methoxyphenyl)(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (47d) and 2-[(4-methoxyphenyl)(1-prop-2-ynyl-1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (48d)

To a stirred solution of 2-[(4-methoxyphenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41d) (0.88 g, 3.48 mmol) in DMF (30 mL) was added propargyl bromide (0.36 mL, 4.18 mmol) in DMF at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.10 g, 4.18 mmol). After 10 h. reaction was completed. The further procedure was done as described above. Mono- propargylated product (47d) was isolated as yellow oil (0.15 g, 48%) and di- propargylated product (48d) was isolated as yellow needles (0.12 g, 24%) from EtOAc/ hexane, m.p. 72-73 °C.

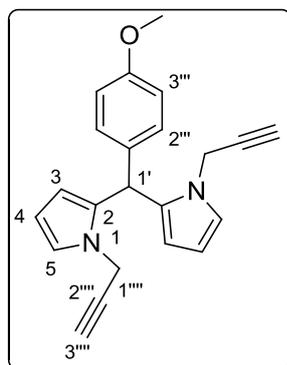


**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.90 (bs, 1H, H-1''), 7.13 – 6.81 (m, 4H-arom), 6.78 – 6.74 (m, 1H, H-5), 6.69 (dd,  $J_{4,3} = 4.1$  and  $J_{4,5} = 2.6$  Hz, 1H, H-4), 6.14 – 6.12 (m, 1H, H-4''), 6.08 (t,  $J = 3.2$  Hz, 1H, H-5''), 5.82 (m, 1H, H-3''), 5.71 – 5.69 (m, 1H, H-3), 5.51 (s, 1H, H-1'), 4.38 (d,  $J_{1''',3'''} = 2.5$  Hz, 3H, H-1'''), 3.79 (s, 3H-OMe), 2.36 (t,  $J_{1''',3'''} = 2.5$  Hz, 1H, H-3''').

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 158.5, 133.8, 133.6, 133.5, 132.2, 129.4, 121.1, 117.0, 113.9, 109.3, 108.3, 107.2, 78.4, 73.3, 55.2, 41.7, 36.2.

**IR (ATR, cm<sup>-1</sup>)** 3372, 3289, 1681, 1607, 1583, 1508, 1479, 1463, 1439, 1342, 1300, 1284, 1243, 1173, 1108, 1090, 1072, 1028, 936, 884, 842, 790, 707, 667, 645, 592.

**HRMS** calcd for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 291.1491 found: 291.1507.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.09 – 7.04 (m, 2H, H-3'''), 6.86 – 6.82 (m, 2H, H-2'''), 6.76 – 6.74 (m, 2H, H-5), 6.06 – 6.04 (m, 2H, H-4), 5.55 (s, 1H, H-1'), 5.52 – 5.49 (m, 1H, H-3), 4.40 (dd,  $J_{\text{geminal}} = 11.1$  Hz and  $J_{1''',3'''} = 2.5$  Hz, 4H, H-1'''), 3.79 (s, 3H-OMe), 2.39 (t,  $J_{1''',3'''} = 2.5$  Hz, 2H, H-3''').

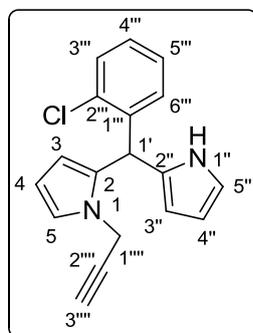
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  158.5, 133.2, 132.6, 129.7, 121.0, 113.9, 109.7, 107.3, 78.7, 73.2, 55.2, 40.4, 36.3.

**IR** (ATR, cm<sup>-1</sup>) 3289, 3256, 1680, 1603, 1577, 1507, 1478, 1454, 1420, 1390, 1341, 1319, 1299, 1281, 1256, 1242, 1196, 1172, 1159, 1127, 1104, 1072, 1028, 956, 936, 898, 856, 826, 732, 721, 707, 687, 668, 644, 610, 571.

**HRMS** calcd for C<sub>22</sub>H<sub>20</sub>N<sub>2</sub>O [M+H]<sup>+</sup>: 329.1648 found: 329.1684.

#### 4.19. Synthesis of 2-[(2-chlorophenyl)(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (47e) and 2-[(2-chlorophenyl)(1-prop-2-ynyl-1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (48e)

To a stirred solution of 2-[(2-chlorophenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (**41e**) (1.14 g, 4.44 mmol) in DMF (30 mL) was added propargyl bromide (0.46 mL 5.3 mmol) in DMF at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.10 g, 5.3 mmol). The reaction was completed after 16 h. and the further procedure was done as described above. Mono- propargylated (**47e**) product was isolated as colorless oil (0.35 g, 44 %) and di- propargylated (**48e**) product was isolated as light yellow needles from EtOAc/ hexane (0.21 g, 18%).

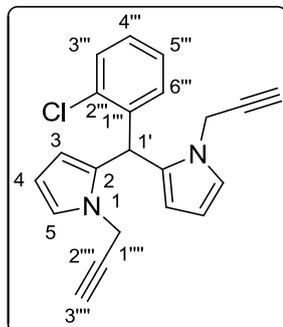


**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.94 (bs, 1H, H-1''), 7.40 – 7.35 (m, 1H, H-3'''), 7.22 – 7.15 (m, 2H, arom), 7.01 – 6.96 (m, 1H, arom), 6.81 – 6.77 (m, 1H, H-5), 6.70 (dd,  $J_{4,3} = 4.2$  and  $J_{4,5} = 2.6$  Hz, 1H, H-4), 6.15 – 6.13 (m, 1H, H-4''), 6.11 – 6.07 (m, 1H, H-5''), 5.93 (s, 1H, H-1'), 5.81 – 5.80 (m, 1H, H-3), 5.68 – 5.61 (m, 1H, H-3'''), 4.41 (d,  $J_{1''',3'''} = 2.5$  Hz, 2H, H-1'''), 2.33 (t,  $J_{1''',3'''} = 2.5$  Hz, 1H, H-3''').

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  139.5, 133.7, 132.3, 130.4, 130.0, 129.5, 128.2, 127.0, 121.2, 117.2, 109.4, 108.8, 107.7, 107.4, 77.9, 73.5, 39.9, 36.2.

**IR (ATR, cm<sup>-1</sup>)** 3376, 3291, 1723, 1571, 1468, 1434, 1285, 1235, 1115, 1072, 1046, 1029, 936, 884, 847, 751, 712, 663, 609.

**HRMS** calcd for C<sub>18</sub>H<sub>15</sub>ClN<sub>2</sub> [M+H]<sup>+</sup>: 295.0996 found: 295.0979.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.41 – 7.37 (m, 1H, H-3'''), 7.23 – 7.16 (m, 2H, arom), 7.00 – 6.95 (m, 1H, arom), 6.79 – 6.77 (m, 2H, H-5), 6.07 – 6.05 (m, 2H, H-4), 6.01 (s, 1H, H-1'), 5.52 – 5.49 (m, 2H, H-3), 4.42 (dd, ,  $J_{\text{geminal}} = 7.9$  Hz and  $J_{1''',3'''} = 2.5$  Hz, 4H, H-1'''), 2.37 (t,  $J_{1''',3'''} = 2.5$  Hz, 2H, H-3''').

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  138.2, 133.9, 131.6, 130.4,

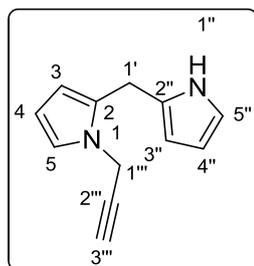
129.5, 128.2, 126.9, 121.2, 110.0, 107.4, 78.2, 73.4, 37.0, 36.3.

**IR (ATR, cm<sup>-1</sup>)** 3295, 1475, 1434, 1339, 1306, 1291, 1254, 1233, 1130, 1071, 1044, 1029, 1016, 936, 846, 819, 787, 777, 734, 706, 666, 628, 607, 574.

**HRMS** calcd for C<sub>21</sub>H<sub>17</sub>ClN<sub>2</sub> [M+H]<sup>+</sup>: 333.1153 found: 333.1168

#### 4.20. Synthesis of 1-prop-2-ynyl-2-(1H-pyrrol-2-ylmethyl)-1H-pyrrole (**47g**) and 1-prop-2-ynyl-2-[(1-prop-2-ynyl-1H-pyrrol-2-yl)methyl]-1H-pyrrole (**48g**)

To a stirred solution of 2-(1H-pyrrol-2-ylmethyl)-1H-pyrrole (0.50 g, 3.42 mmol) (**41g**) in DMF (30 mL) was added propargyl bromide (3.5 mL, 4.1 mmol) in DMF at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.09 g, 4.1 mmol). The reaction was completed after 11 h. and the further procedure was done as described above. Mono- propargylated (**47g**) product was isolated as colorless liquid (0.12 g, 51%) and di- propargylated (**48g**) product was isolated as light yellow oil (0.14 g, 24%).

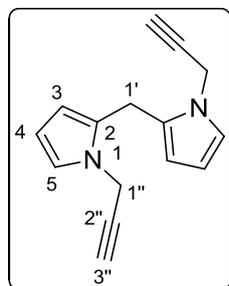


**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.84 (bs, 1H, H-1''), 6.72-6.70 (m, 2H, H-5, H-5''), 6.61 (dd,  $J_{4,3} = 4.0$  and  $J_{4,5} = 2.5$  Hz, 1H, H-4), 6.16 – 6.15 (m, 1H, H-4''), 6.02 – 5.98 (m, 2H, H-3''), 4.42 (d,  $J_{1''',3'''} = 2.5$  Hz, 2H, H-1'''), 3.99 (s, 2H, H-1'), 2.33 (t,  $J_{1''',3'''} = 2.5$  Hz, 1H, H-3''').

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  129.3, 128.5, 121.1, 117.0, 108.6, 108.4, 107.5, 106.0, 78.8, 73.2, 36.1, 25.3.

**IR (ATR, cm<sup>-1</sup>)** 3377, 3282, 1698, 1567, 1482, 1420, 1342, 1311, 1286, 1240, 1205, 1180, 1115, 1088, 1071, 1025, 935, 883, 775, 707, 640.

**HRMS** calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 185.1073 found: 185.1079.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.73 – 6.71 (m, 2H, H-5), 6.08 – 6.06 (m, 2H, H-4), 5.92 – 5.89 (m, 2H, H-3), 4.55 (d,  $J_{1'',3''} = 2.5$  Hz, 2H, H-1''), 4.05 (s, 2H, H-1'), 2.38 (t,  $J_{1'',3''} = 2.5$  Hz, 1H, H-3'').

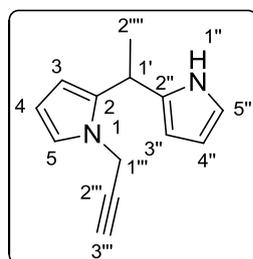
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  128.9, 120.9, 108.6, 107.5, 78.4, 73.2, 36.3, 24.3.

**IR (ATR, cm<sup>-1</sup>)** 3321, 3247, 2917, 2849, 1660, 1480, 1424, 1336, 1290, 1283, 1204, 1182, 1137, 1071, 1016, 930, 882, 800, 707, 693, 655, 629, 614.

**HRMS** calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 223.1229 found: 223.1240.

#### 4.21. Synthesis of 1-prop-2-ynyl-2-[1-(1*H*-pyrrol-2-yl)ethyl]-1*H*-pyrrole (**47f**) and 1-prop-2-ynyl-2-[1-(1-prop-2-ynyl-1*H*-pyrrol-2-yl)ethyl]-1*H*-pyrrole (**48f**)

To a stirred solution of 2-[1-(1*H*-pyrrol-2-yl)ethyl]-1*H*-pyrrole (0.49 g, 3.05 mmol) (**41f**) in DMF (30 mL) was added propargyl bromide (0.31 g, 3.66 mmol) in DMF at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.08 g, 3.6 mmol). After 10 h. reaction was completed. The further procedure was done as described above. Mono- propargylated product (**47f**) was isolated as colorless liquid (0.08 g, 33%) and di- propargylated compound (**48f**) was isolated as colorless liquid (0.26 g, 45%).

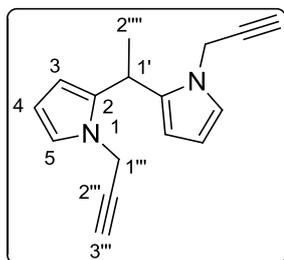


**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.72 (bs, 1H, H-1''), 6.78 – 6.70 (m, 1H, H-5), 6.59 (dd,  $J_{4,3} = 4.1$  and  $J_{4,5} = 2.5$  Hz, 1H, H-4), 6.14 – 6.12 (m, 1H, H-4''), 6.12 – 6.10 (m, 1H, H-5''), 6.10 – 6.08 (m, 1H, H-3), 6.02 – 6.00 (m, 1H, H-3''), 4.40 (dd,  $J_{\text{geminal}} = 6.7$ ,  $J_{1''',3'''} = 2.5$  Hz, 2H, H-1'''), 4.27 (q,  $J_{1',2'''} = 7.1$  Hz, 1H, H-1'), 2.32 (t,  $J_{1''',3'''} = 2.5$  Hz, 1H, H-3'''), 1.61 (d,  $J_{1',2'''} = 7.1$  Hz, 3H, H-2''').

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  134.5, 134.5, 121.1, 116.6, 108.2, 107.3, 106.5, 104.7, 78.4, 73.1, 35.9, 30.5, 21.3.

**IR (ATR, cm<sup>-1</sup>)** 3383, 3284, 2971, 2930, 1682, 1561, 1481, 1372, 1343, 1283, 1242, 1116, 1071, 1027, 936, 882, 789, 763, 710, 641, 561.

**HRMS** calcd for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 199.1229 found: 199.1238.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.66 – 6.63 (m, 2H, H-5), 6.04 – 6.01 (m, 2H, H-4), 5.83 – 5.81 (m, 2H, H-3), 4.39 (d,  $J_{1'',3''} = 2.5$  Hz, 2H, H-1''), 4.24 (q,  $J_{1',2''} = 6.9$  Hz, 1H, H-1'), 2.29 (t,  $J_{1'',3''} = 2.5$  Hz, 1H, H-3''), 1.55 (d,  $J_{1',2''} = 6.9$  Hz, 3H, H-2'').

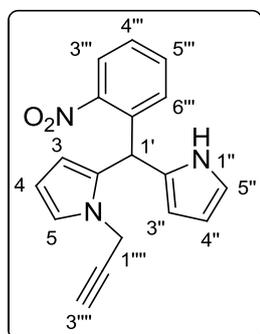
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  134.6, 120.9, 107.4, 107.0, 78.7, 73.13, 36.0, 29.5, 20.8.

**IR (ATR, cm<sup>-1</sup>)** 3286, 2927, 2851, 1712, 1479, 1420, 1373, 1340, 1283, 1234, 1202, 1128, 1077, 1011, 934, 789, 759, 706, 637, 572.

**HRMS** calcd for C<sub>16</sub>H<sub>16</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 237.1386 found: 237.1395.

#### 4.22. Synthesis of 2-[(2-nitrophenyl)(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole(47h) and 2-[(2-nitrophenyl)(1-prop-2-ynyl-1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (48h)

To a stirred solution of 2-[(2-nitrophenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (**41h**) (1.05 g, 3.9 mmol) in DMF (20 mL) was added propargyl bromide (0.384 mL, 4.6 mmol) in DMF (5 mL) at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.112 g, 4.6 mmol). The reaction was completed after 12 h. and the further procedure was done as described above. Mono- propargylated (**47h**) product was isolated as yellow sticky solid (0.24 g, 44 %) and di- propargylated product (**48h**) was isolated as colorless cubic crystals (0.10 g, 12%) from CHCl<sub>3</sub>, m.p. 143-144 °C from EtOAc/ hexzane.

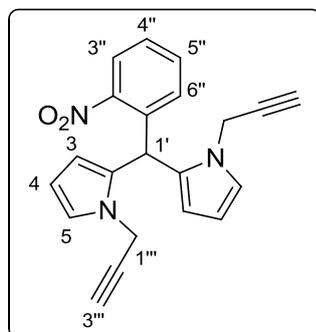


**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.98 (bs, 1H, H-1''), 7.93 (dd,  $J_{4'',3''} = 8.1$  and  $J_{3'',5''} = 1.2$  Hz, 1H, H-3''), 7.51 (td,  $J_{4'',3''-5''} = 7.6$  and  $J_{4'',6''} = 1.2$  Hz, 1H, H-4''), 7.43 – 7.38 (m, 1H-5''), 7.13 (dd,  $J_{6'',5''} = 7.8$  and  $J_{6'',4''} = 1.0$  Hz, 1H, H-6''), 6.87 – 6.77 (m, 1H, H-5), 6.73 – 6.71 (m, 1H, H-4), 6.38 (s, 1H, H-5''), 6.17 – 6.15 (m, 1H, H-4''), 6.09 – 6.03 (m, 1H, H-3), 5.85 (s, 1H, H-1'), 5.61 – 5.58 (m, 1H, H-3''), 4.49 (d,  $J_{1'',3''} = 2.6$  Hz, 2H, H-1''), 2.33 (t,  $J_{1'',3''} = 2.6$  Hz, 1H, H-3'').

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  148.6, 136.8, 133.0, 131.5, 130.9, 129.7, 127.8, 124.8, 121.6, 117.6, 109.3, 108.8, 107.9, 107.4, 77.2, 73.7, 37.5, 36.2.

**IR (ATR, cm<sup>-1</sup>)** 3286, 2914, 2849, 1669, 1605, 1520, 1472, 1423, 1397, 1342, 1285, 1183, 1117, 1073, 1028, 937, 883, 834, 784, 713, 657, 604.

**HRMS** calcd for C<sub>18</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 306.1237 found: 306.1237



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.96 (dd,  $J_{4'',3''} = 8.1$  and  $J_{3'',5''} = 1.2$  Hz, 1H, H-3''), 7.51 (td,  $J_{4'',3''-5''} = 7.6$  and  $J_{4'',6''} = 1.2$  Hz, 1H, H-4''), 7.47 – 7.37 (m, 1H-5''), 7.15 (dd,  $J_{6'',5''} = 7.6$  and  $J_{6'',4''} = 1.2$  Hz, 1H, H-6''), 6.81 – 6.75 (m, 2H, H-5.), 6.50 (s, 1H), 6.08 – 6.02 (m, 2H, H-4.), 5.50 – 5.48 (m, 2H, H-3.), 4.36 (dd,  $J_{\text{geminal}} = 13.9$  Hz and  $J_{1''',3'''} = 2.5$  Hz, 4H, H-1'''), 2.36 (t,  $J_{1''',3'''} = 2.5$  Hz, 2H, H-3''').

**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  148.8, 135.5, 133.0, 131.3, 131.0, 128.0, 124.9, 121.5, 110.3, 107.5, 77.8, 73.7, 36.3, 36.0.

**IR (ATR, cm<sup>-1</sup>)** 3300, 3281, 1519, 1477, 1355, 1301, 1288, 1253, 1131, 1071, 1017, 937, 864, 836, 819, 742, 719, 687, 638, 606, 572.

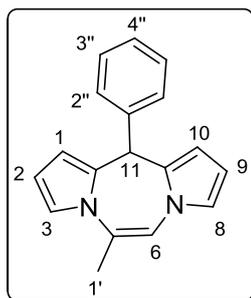
**HRMS** calcd for C<sub>21</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>: 344.1393 found: 344.1418

#### 4.23. General procedure for NaH-supported cyclization reactions of N-propargyl dipyrrromethane derivatives

To a stirred solution of N-propargyl dipyrrromethane derivatives (**47a-g**) (1 mmol) in DMF (10 mL) was added solid NaH (1.2 mmol) portionwise at room temperature and the reaction composition was mixed for 1 h. After completion of the reaction, the composition was extracted with EtOAc (3 × 50 mL). Afterwards, DMF in media was removed with brine (3 × 25 mL) and the mixture was dried over MgSO<sub>4</sub>. Evaporation of solvent gave the residue which was purified with gradient column chromatography eluted with hexane:ethyl acetate (10:1 to 4:1) and crystallized appropriate solvent.

#### 4.24. Synthesis of 5-methyl-11-phenyl-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (**49a**)

A stirred solution of 2-[phenyl(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (**47a**) (0.49 g, 1.88 mmol) in DMF (20 mL) was reacted with NaH (0.05 g, 2.25 mmol) as described above to give cyclization product (**49a**). White tiny needles (0.37 g, 76%) from EtOAc/ hexane, (m.p. 106-107 °C).



**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.24 – 7.15 (m, 4H, arom), 6.90 (bs, 1H, arom), 6.89 – 6.86 (m, 1H, H-3), 6.64 – 6.60 (m, 1H, H-8), 6.29 – 6.25 (m, 1H, H-2), 6.23 (s, 1H, H-6), 6.23 – 6.18 (m, 1H, H-9), 6.10 – 6.07 (m, 1H, H-1), 6.06 – 6.05 (m, 1H, H-10), 5.40 (s, 1H, H-11), 2.08 (s, 3H, H-1').

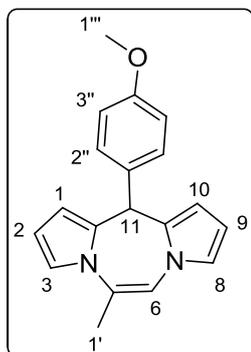
**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  140.4, 134.6, 134.5, 128.0, 127.3, 126.3, 123.2, 120.2, 118.2, 113.0, 109.5, 109.5, 107.7, 107.0, 42.1, 19.6.

**IR (ATR,  $\text{cm}^{-1}$ )** 3095, 1689, 1599, 1480, 1445, 1424, 1377, 1348, 1333, 1300, 1290, 1279, 1247, 1215, 1198, 1169, 1152, 1116, 1074, 1031, 1023, 889, 849, 828, 811, 776, 726, 713, 704, 694, 611, 591.

**HRMS** calcd for  $\text{C}_{16}\text{H}_{16}\text{N}_2$   $[\text{M}+\text{H}]^+$ : 261.1386 found: 261.1398.

#### 4.25. Synthesis of 11-(4-methoxyphenyl)-5-methyl-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (49d)

A stirred solution of 2-[(4-methoxyphenyl)(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (**47d**) (0.15 g, 0.5 mmol) in DMF (15 mL) was reacted with NaH (0.01 g, 0.6 mmol) as described above to give cyclization product (**49d**). Yellow needles (0.12 g, 87%) from EtOAc/hexane, (m.p. 65-68 °C).



**$^1\text{H NMR}$**  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.86 – 6.84 (m, 1H, H-3), 6.83 – 6.81 (m, 2H, H-3''), 6.75 – 6.73 (m, 2H, H-2''), 6.59 (dd,  $J_{8,9} = 2.8$  and  $J_{8,10} = 1.4$  Hz, 1H, H-8), 6.26 – 6.23 (m, 2H, H-9 and H-6), 6.20 – 6.16 (m, 1H, H-2), 6.05 – 6.02 (m, 1H, H-1), 6.02 – 6.00 (m, 1H, H-10), 5.32 (s, 1H, H-11), 3.73 (s, 3H, H-1'''), 2.07 (s, 3H, H-1').

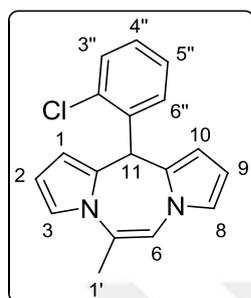
**$^{13}\text{C NMR}$**  (101 MHz,  $\text{CDCl}_3$ )  $\delta$  158.2, 135.0, 134.9, 132.5, 128.5, 123.8, 120.2, 118.2, 113.4, 113.0, 109.6, 109.5, 107.6, 106.9, 55.2, 41.5, 19.7.

**IR (ATR,  $\text{cm}^{-1}$ )** 2922, 1693, 1605, 1507, 1481, 1424, 1379, 1348, 1333, 1281, 1243, 1199, 1175, 1114, 1082, 1028, 889, 829, 789, 766, 700, 635, 609, 585, 562.

**HRMS** calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}$   $[\text{M}+\text{H}]^+$ : 291.1491 found: 291.1508.

#### 4.26. Synthesis of 11-(2-chlorophenyl)-5-methyl-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (49e)

A stirred solution of 2-[(2-chlorophenyl)(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (**47e**) (0.35 g, 1.2 mmol) in DMF (15 mL) was reacted with NaH (0.03 g, 1.44 mmol) as described above to give cyclization product (**49e**). Light orange liquid (0.21 g, 61%).



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.63 (dd,  $J_{3'',4''} = 7.6$  and  $J_{3'',5''} = 1.8$  Hz, 1H, H-3''), 7.41 (dd,  $J_{6'',5''} = 7.7$  and  $J_{6'',4''} = 1.6$  Hz, 1H, H-6''), 7.32 – 7.21 (m, 2H, arom), 6.87 (dd,  $J_{3,2} = 2.9$  and  $J_{3,1} = 1.8$  Hz, 1H, H-3), 6.64 (dd,  $J_{8,9} = 2.9$  and  $J_{8,10} = 1.8$  Hz, 1H, H-8), 6.54 (s, 1H, H-6), 6.17 – 6.15 (m, 1H, H-9), 6.12 – 6.11 (m, 1H, H-2), 5.77 (s, 1H, H-11), 5.74 – 5.68 (m, 2H, H-10 and H-1), 2.33 (s, 3H, H-1').

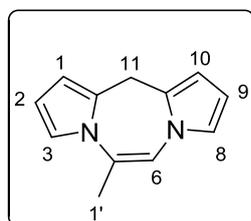
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  136.5, 134.7, 134.4, 133.8, 131.3, 129.9, 128.4, 126.3, 123.4, 120.3, 118.3, 113.2, 109.4, 109.4, 107.5, 106.9, 39.1, 20.1.

**IR (ATR, cm<sup>-1</sup>)** 2924, 1732, 1694, 1570, 1474, 1434, 1418, 1380, 1347, 1316, 1288, 1242, 1160, 1197, 1115, 1084, 1041, 895, 857, 808, 782, 748, 698, 641, 607, 562.

**HRMS** calcd for C<sub>18</sub>H<sub>15</sub>ClN<sub>2</sub> [M+H]<sup>+</sup>: 295.0996 found: 295.1000.

#### 4.27. Synthesis of 5-methyl-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (49g)

A stirred solution of 1-prop-2-ynyl-2-(1H-pyrrol-2-ylmethyl)-1H-pyrrole (**47g**) (0.12 g, 0.65 mmol) in DMF (15 mL) was reacted with NaH (0.01 g, 0.78 mmol) as described above to give cyclization product (**49g**). Light yellow solid (0.09 g, 81%) m.p. 58-60 °C.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.80 (dd,  $J_{3,2} = 3.0$  and  $J_{3,1} = 1.7$  Hz, 1H, H-3), 6.58 (dd,  $J_{8,9} = 2.7$  and  $J_{8,10} = 1.7$  Hz, 1H, H-8), 6.47 (s, 1H, H-6), 6.19 (t,  $J = 3.2$  Hz, 1H, H-9), 6.13 (t,  $J = 3.1$  Hz, 1H, H-2), 5.96 – 5.85 (m, 2H, H-1 and H-10), 3.85 (s, 2H, H-11), 2.29 (s, 3H, H-1').

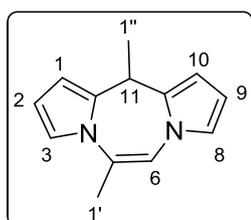
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  132.8, 132.6, 123.2, 119.4, 117.5, 112.7, 109.7 (2C), 105.3, 104.4, 26.0, 19.9.

**IR (ATR, cm<sup>-1</sup>)** 2916, 2849, 1715, 1507, 1480, 1417, 1378, 1331, 1235, 1180, 1114, 1024, 885, 826, 747, 695, 610, 546.

**HRMS** calcd for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 185.1084 found: 185.1073.

#### 4.28. Synthesis of 5,11-dimethyl-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (49f)

A stirred solution of 1-prop-2-ynyl-2-[1-(1H-pyrrol-2-yl)ethyl]-1H-pyrrole (**47f**) (0.08 g, 0.4 mmol) in DMF (15 mL) was reacted with NaH (0.01 g, 0.78 mmol) as described above to give cyclization product (**49f**) as colorless liquid (0.06 g, 85%).



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  6.81 (dd,  $J_{3,2} = 2.7$  and  $J_{3,1} = 1.7$  Hz, 1H, H-3), 6.60 – 6.57 (m, 1H, H-8), 6.52 (s, 1H, H-6), 6.22 – 6.21 (m 1H, H-9), 6.15 – 6.14 (m, 1H, H-2), 5.92 – 5.84 (m, 2H, H-1 and H-10), 3.85 (q,  $J_{11,1''} = 7.0$  Hz, 1H, H-11), 2.29 (d,  $J = 1.0$  Hz, 3H, H-1'), 1.69 (d,  $J_{11,1''} = 7.0$  Hz, 3H, H-1'').

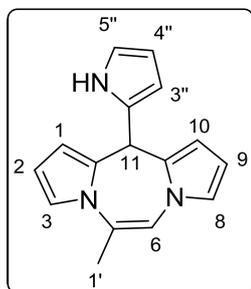
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  138.0, 137.8, 123.7, 119.2, 117.3, 113.0, 109.4 (2C), 103.2, 102.5, 30.1, 19.8, 15.0.

**IR (ATR, cm<sup>-1</sup>)** 3100, 2973, 1686, 1556, 1482, 1454, 1432, 1418, 1379, 1344, 1300, 1261, 1223, 1186, 1170, 1157, 1114, 1087, 1051, 1038, 1022, 971, 884, 791, 730, 691, 622, 591, 579.

**HRMS** calcd for C<sub>13</sub>H<sub>14</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 198.1157 found: 199.1236.

#### 4.29. Synthesis of 5-methyl-11-(1H-pyrrol-2-yl)-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (49c)

A stirred solution of 2-[di(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (**41c**) (0.89 g, 3.6 mmol) in DMF (15 mL) was reacted with NaH (0.1 g, 4.2 mmol) as described above to give cyclization product (**49c**). Brown solid (0.5 g, 65%) m.p. 130-131 °C.



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (s, 1H, H-1''), 6.87 (dd,  $J_{3,2} = 3.1$  and  $J_{3,1} = 1.8$  Hz, 1H, H-3), 6.66 – 6.59 (m, 2H, H-5'' and H-8), 6.30 (s, 1H, H-6), 6.24 (t,  $J = 3.2$  Hz, 1H, H-9), 6.18 (t,  $J = 3.1$  Hz, 1H, H-2), 6.07 – 6.03 (m, 3H, H-10, 4'', 1), 5.59 – 5.55 (m, 1H, H-3''), 5.43 (s, 1H, H-11), 2.15 (s, 3H, H-1').

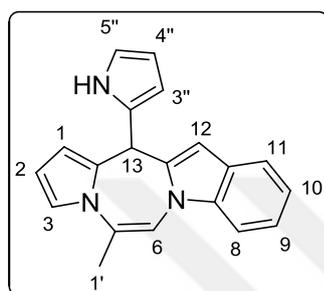
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>)  $\delta$  133.5, 133.3, 130.3, 122.9, 120.6, 118.5, 116.7, 112.6, 109.5, 109.5, 108.3, 107.3, 106.4, 105.9, 36.9, 19.8.

**IR (ATR, cm<sup>-1</sup>)** 3285, 1651, 1528, 1475, 1402, 1368, 1337, 1314, 1282, 1246, 1218, 1075, 1030, 953, 939, 890, 785, 741, 641, 605.

**HRMS** calcd for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 250.1338 found: 250.1350

#### 4.30. Synthesis of 5-methyl-13-(1*H*-pyrrol-2-yl)-13*H*-pyrrolo[1',2':4,5][1,4]diazepino[1,7-*a*]indole (**49b**)

A stirred solution of 2-[di(1*H*-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1*H*-indole (**41b**) (0.91 g, 3 mmol) in DMF (20 mL) was reacted with NaH (0.09 g, 3.6 mmol) as described above to give cyclization product (**49b**). Yellow sticky oil (0.61 g, 72%).



**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>) δ 7.79 (s, 1H, H-1''), 7.57 (d, *J*<sub>8,9</sub> = 7.6 Hz, 1H, H-8), 7.32 (d, *J*<sub>11,10</sub> = 8.1 Hz, 1H, H-11), 7.23 – 7.18 (m, 1H, H-10), 7.17 – 7.12 (m, 1H, H-9), 6.92 – 6.89 (m, 1H, H-3), 6.68 – 6.58 (m, 1H, H-5''), 6.53 (bs, 1H, H-3''), 6.44 (s, 1H, H-6), 6.29 – 6.24 (m, 1H, H-2), 6.14 (s, 1H, H-12), 6.08 (dd, *J* = 5.6, 2.7 Hz, 1H, H-4''), 5.66 (bs, 1H, H-1), 5.58 (s, 1H, H-13), 2.24 (s, 3H, H-1').

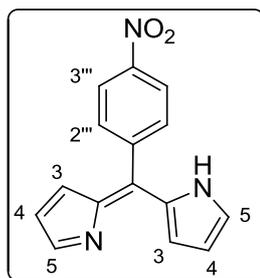
**<sup>13</sup>C NMR** (101 MHz, CDCl<sub>3</sub>) δ 136.2, 128.4, 128.3, 123.8, 122.0, 121.9, 120.8, 120.6, 118.8, 116.9, 110.1, 109.7, 109.4, 109.3, 108.5, 107.8, 106.3, 100.3, 37.6, 19.9.

**IR** (ATR, cm<sup>-1</sup>) 3396, 2917, 1715, 1556, 1480, 1458, 1426, 1373, 1350, 1314, 1243, 1175, 1087, 1024, 937, 884, 767, 746, 735, 707, 666, 604.

**HRMS** calcd for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub> [M+H]<sup>+</sup>: 300.1495 found: 300.1507

#### 4.31. Synthesis of (*Z*)-2-((4-nitrophenyl)(2*H*-pyrrol-2-ylidene)methyl)-1*H*-pyrrole (**57**)<sup>39</sup>

To a stirring solution of 2-[(4-nitrophenyl)(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41i**) (0.5 g, 1.8 mmol) in DMF (10 mL), sodium hydride was added (0.04 g mL, 2 mmol) portionwise and stirred for 2-3 minutes at room temperature. After completion of the reaction which was monitored by using TLC, solvent was removed and water (10 mL) was added. The resulting composition was extracted with ethyl acetate (3 × 20 mL). The organic mixture dried over MgSO<sub>4</sub>, then filtered. After vaporisation of the solvent, the compound **57** was chromatographed on silica gel column eluting with hexane/EtOAc (7:1) to give (*Z*)-2-((4-nitrophenyl)(2*H*-pyrrol-2-ylidene)methyl)-1*H*-pyrrole (**57**) (0.32 g, 64%) as yellow sticky solid.

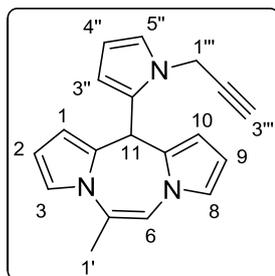


**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.30 – 8.21 (m, 2H, H-3'''), 7.63 – 7.62 (m, 2H, H-2'''), 7.63 – 7.59 (m, 2H, H-5), 6.41 (dd,  $J = 4.2$  Hz and  $J = 1.0$  Hz, 2H, H-3), 6.36 (dd,  $J = 4.2$  Hz and  $J = 1.5$  Hz, 2H, H-4).

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  148.2, 144.6, 143.8, 139.8, 139.7, 131.5, 128.6, 122.9, 118.3.

#### 4.32. Synthesis of 5-methyl-11-(1-(prop-2-yn-1-yl)-1H-pyrrol-2-yl)-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (**60**)

To a stirred solution of 5-methyl-11-(1H-pyrrol-2-yl)-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (**49c**) (0.5 g, 1.7 mmol) in DMF (20 mL) was added propargyl bromide (0.170 mL, 2.04 mmol) in DMF (5 mL) at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.05 g, 2.04 mmol). The reaction was completed after 12 h. and the mixture was extracted with EtOAc (3 × 50 mL). Then the organic extracts were washed with brine (8 × 50 mL) and dried over  $\text{MgSO}_4$ . The eluent was removed under reduced pressure and the residue was purified with gradient column chromatography eluted with hexane:ethyl acetate (20:1 to 7:1). Compound **60** product was isolated as brown sticky solid (0.44 g, 61 %).



**$^1\text{H}$  NMR** (400 MHz,  $\text{CDCl}_3$ )  $\delta$  6.91 (bs, 1H, H-5''), 6.74 (bs, 1H, H-4''), 6.64 (bs, 1H, H-8), 6.44 (bs, 1H, H-3), 6.26 (m, 1H, H-2), 6.20 (m, 1H, H-9), 6.07 (m, 3H, H-1, 10, 3'') 5.69 (s, 1H, H-11), 5.61 (s, 1H, H-11), 4.57 (dd,  $J_{\text{geminal}} = 8.7$  and  $J_{1''',3'''} = 2.3$  Hz, 2H, H-1'''), 2.43 (t,  $J_{1''',3'''} = 2.3$  Hz, 1H, H-3'''), 2.27 (s, 3H, H-1').

**$^{13}\text{C}$  NMR** (101 MHz,  $\text{CDCl}_3$ )  $\delta$  133.8, 133.2, 129.5, 123.3, 121.4, 120.3, 118.3, 113.0, 109.7, 109.6, 109.1, 107.1, 107.1, 106.4, 78.6, 73.5, 37.0, 36.1, 19.9.

**IR (ATR,  $\text{cm}^{-1}$ )** 3264, 1698, 1480, 1424, 1394, 1266, 1250, 1237, 1225, 1184, 1163, 1120, 1087, 1075, 1033, 1019, 938, 909, 886, 852, 793, 771, 714, 701, 647, 617, 609.

**HRMS** calcd for  $\text{C}_{20}\text{H}_{17}\text{N}_3$  [ $\text{M}+\text{H}$ ] $^+$ : 288.1495 found: 288.1514.



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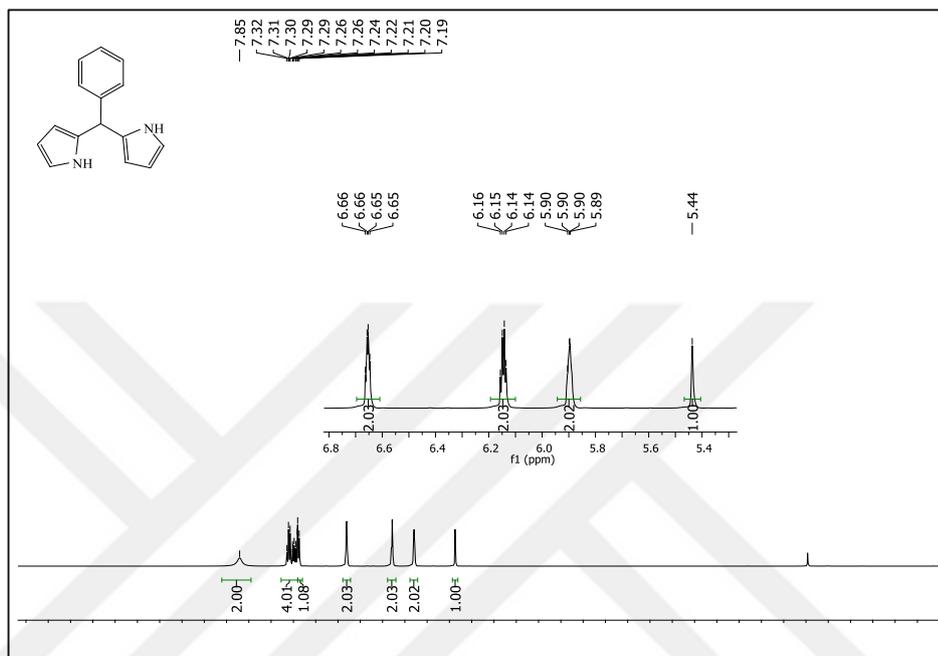
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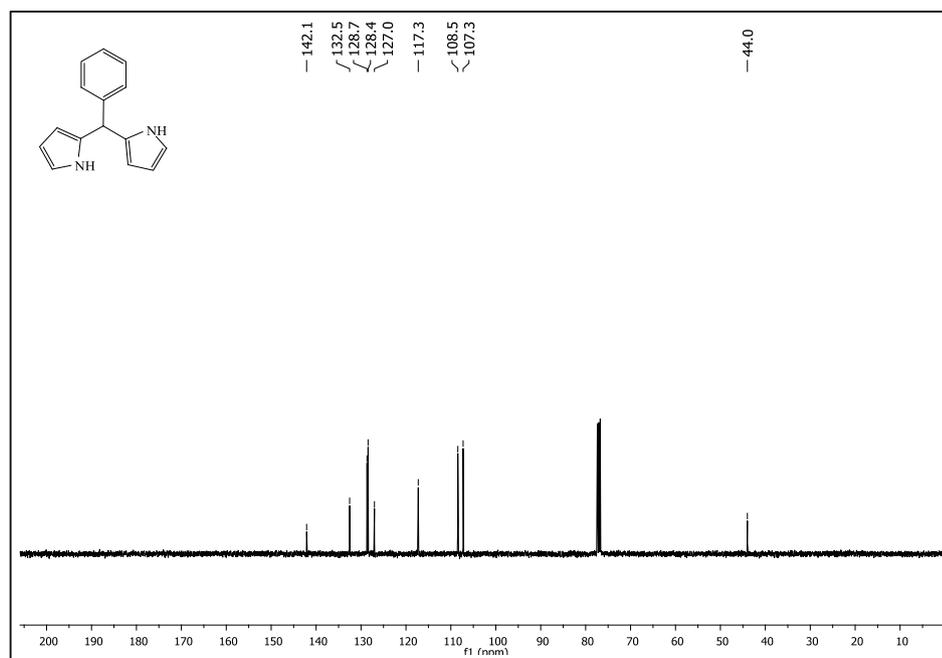
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## APPENDIX A

### SPECTRAL DATA



**Figure 12** <sup>1</sup>H-NMR Spectrum of Compound **41a** in CDCl<sub>3</sub>



**Figure 13** <sup>13</sup>C-NMR Spectrum of Compound **41a** in CDCl<sub>3</sub>

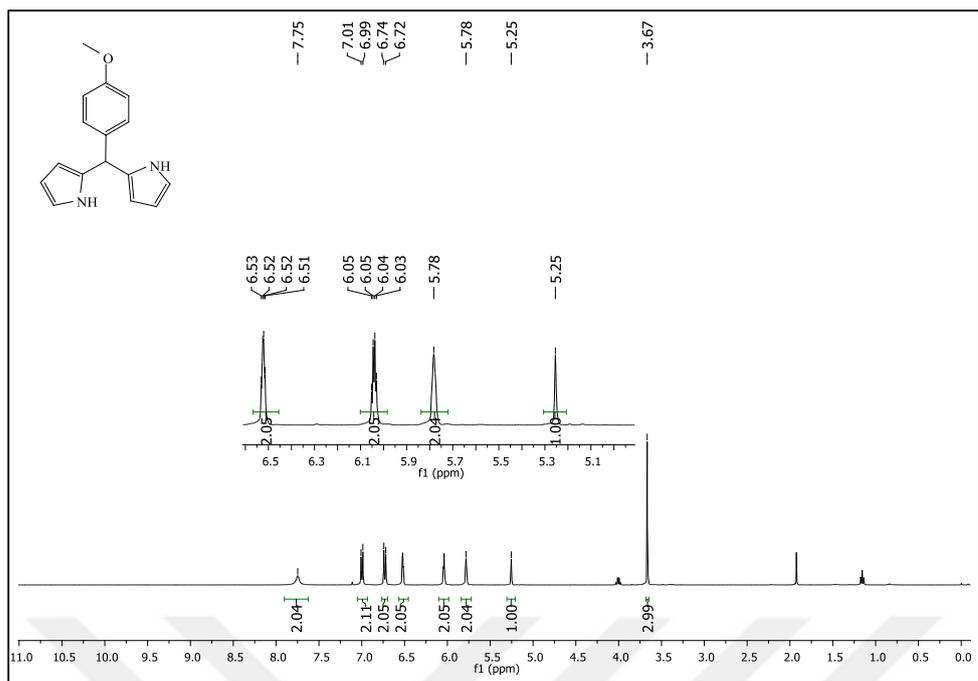


Figure 14  $^1\text{H-NMR}$  Spectrum of Compound 41d in  $\text{CDCl}_3$

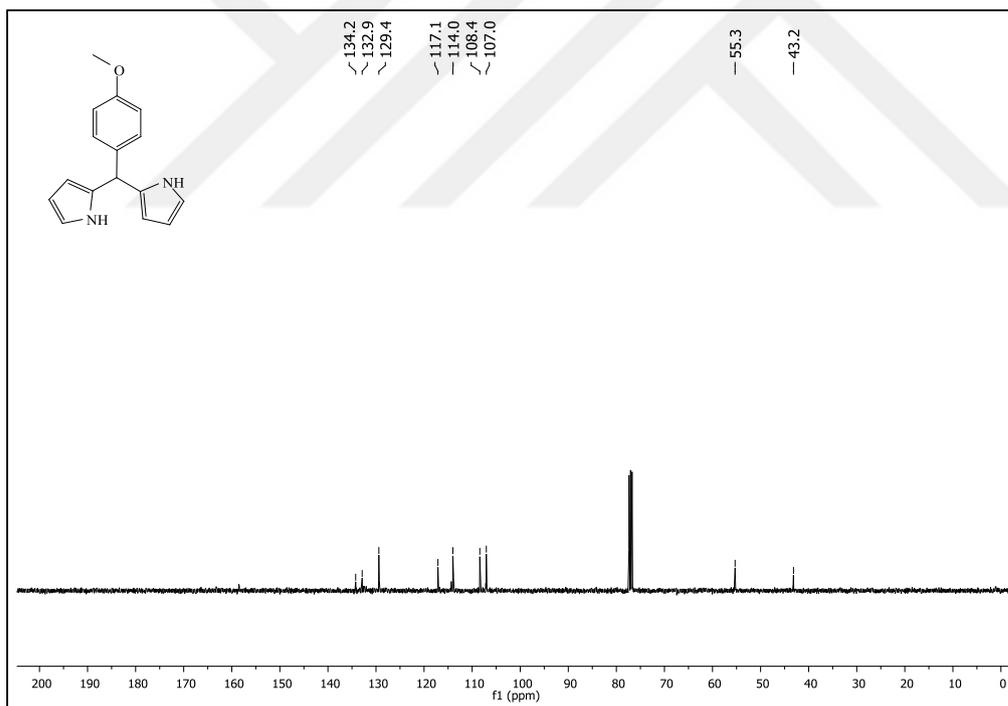
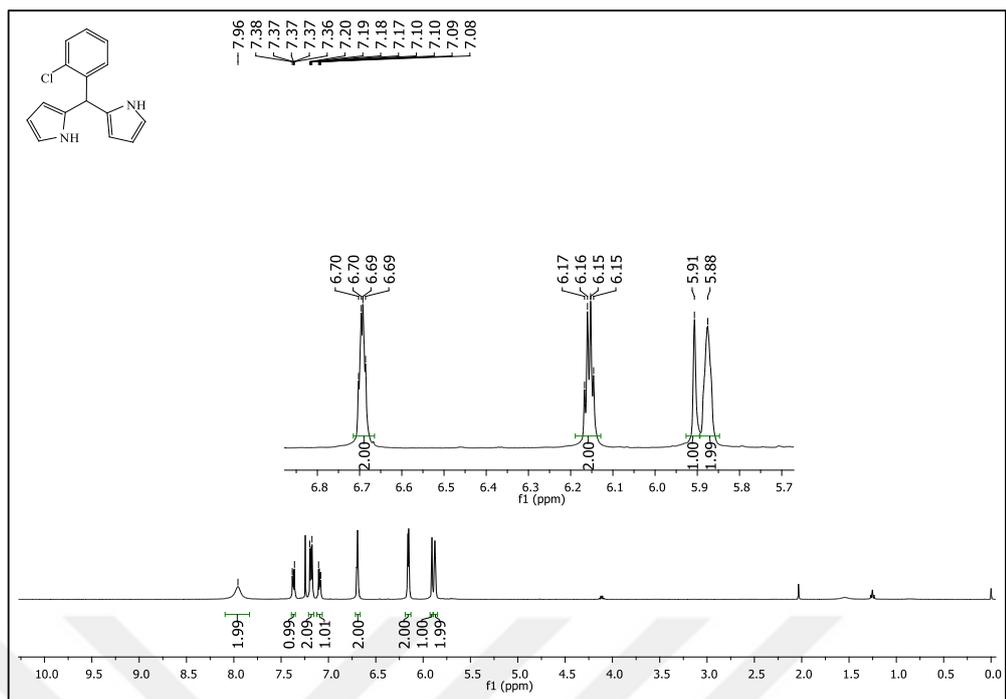
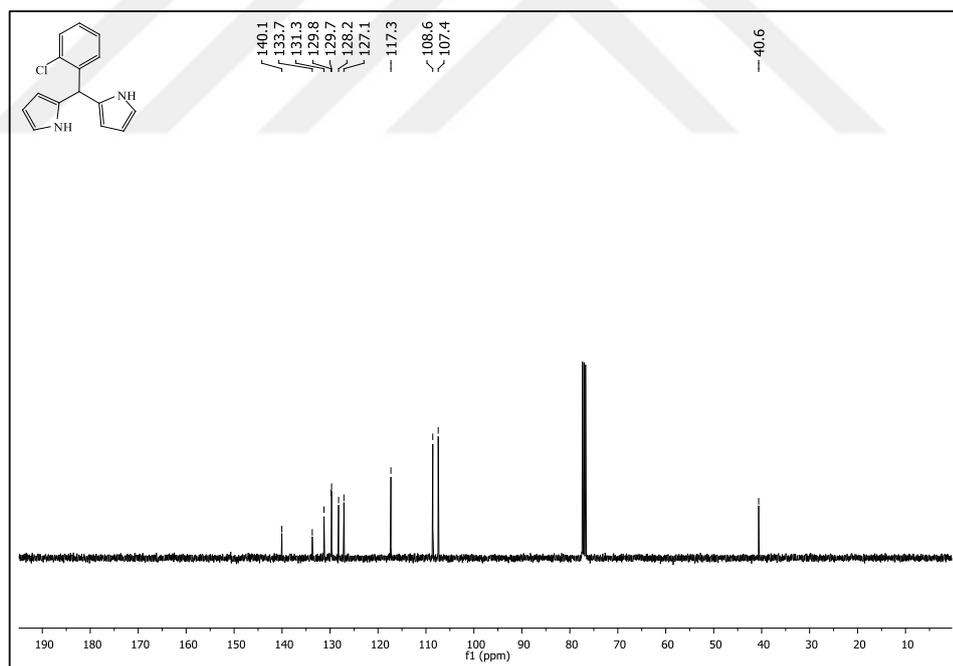


Figure 15  $^{13}\text{C-NMR}$  Spectrum of Compound 41d in  $\text{CDCl}_3$



**Figure 16**  $^1\text{H-NMR}$  Spectrum of Compound **41e** in  $\text{CDCl}_3$



**Figure 17**  $^{13}\text{C-NMR}$  Spectrum of Compound **41e** in  $\text{CDCl}_3$

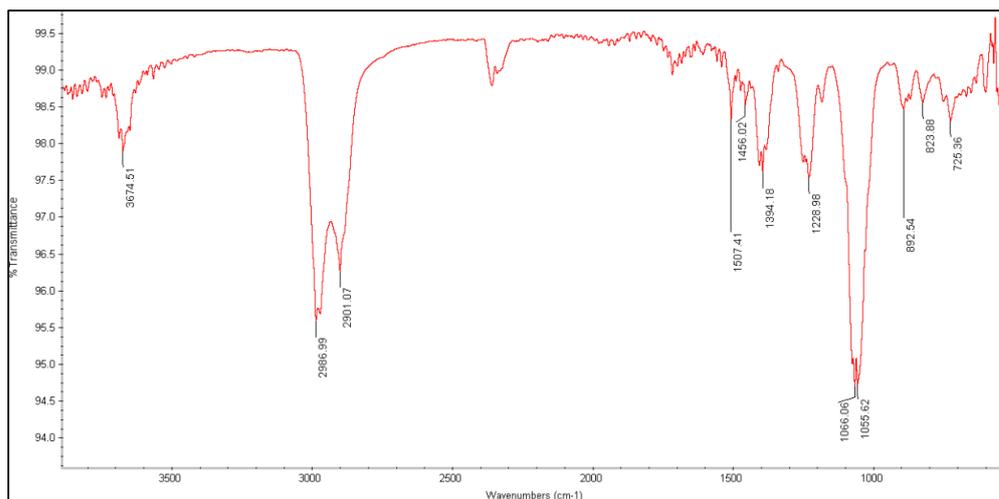


Figure 18 IR Spectrum of Compound 41e

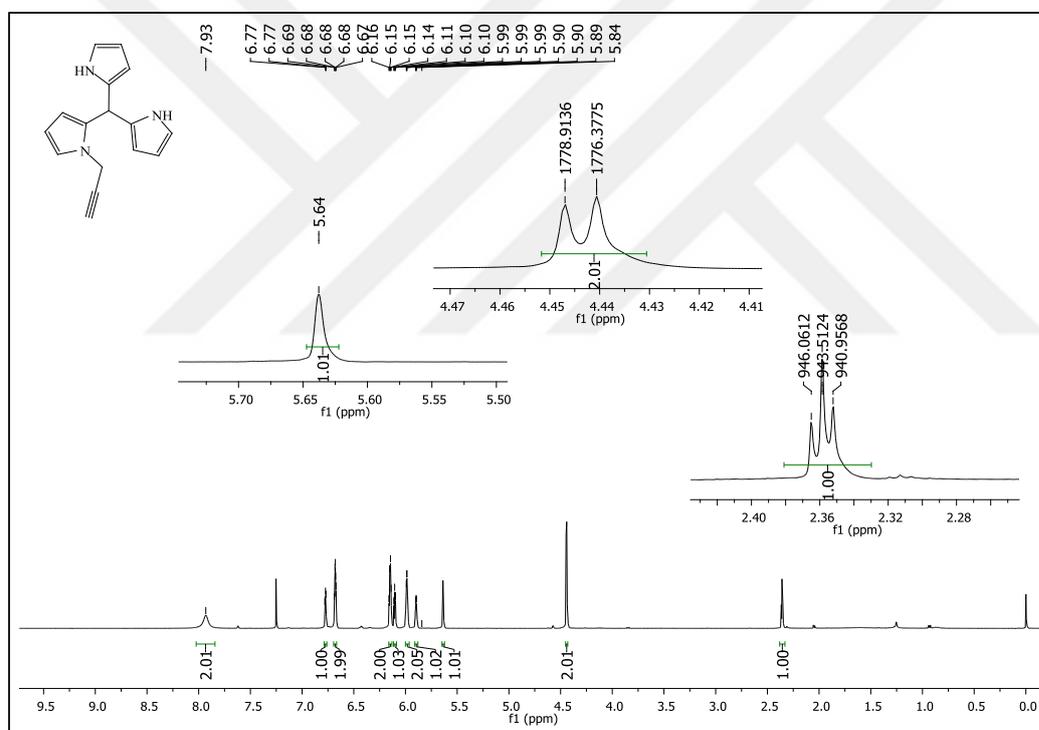
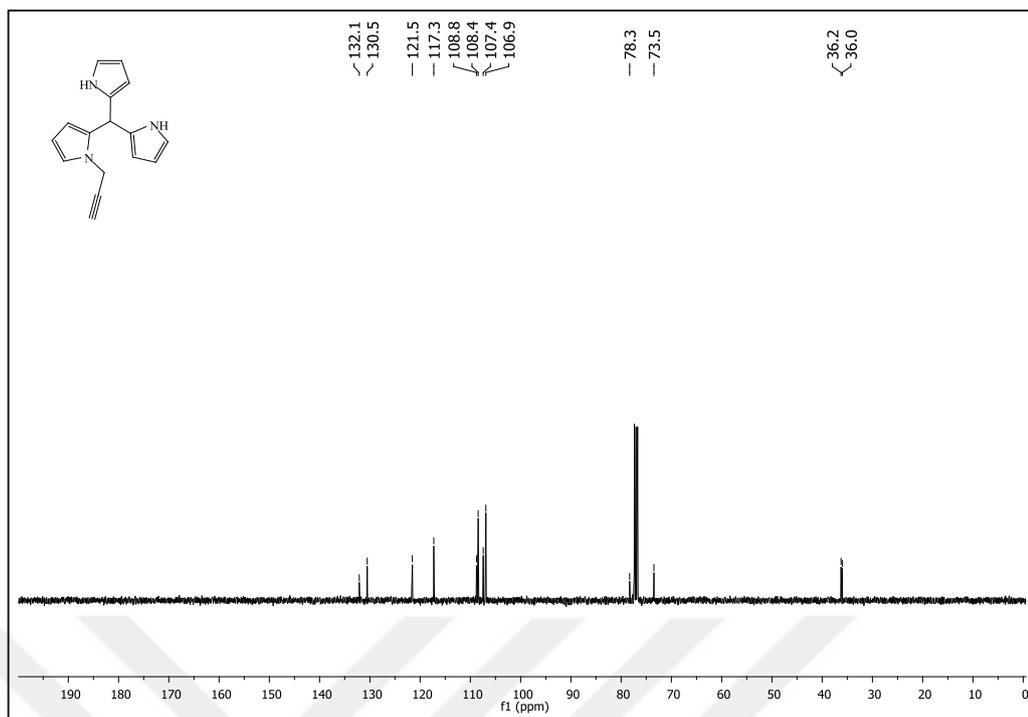
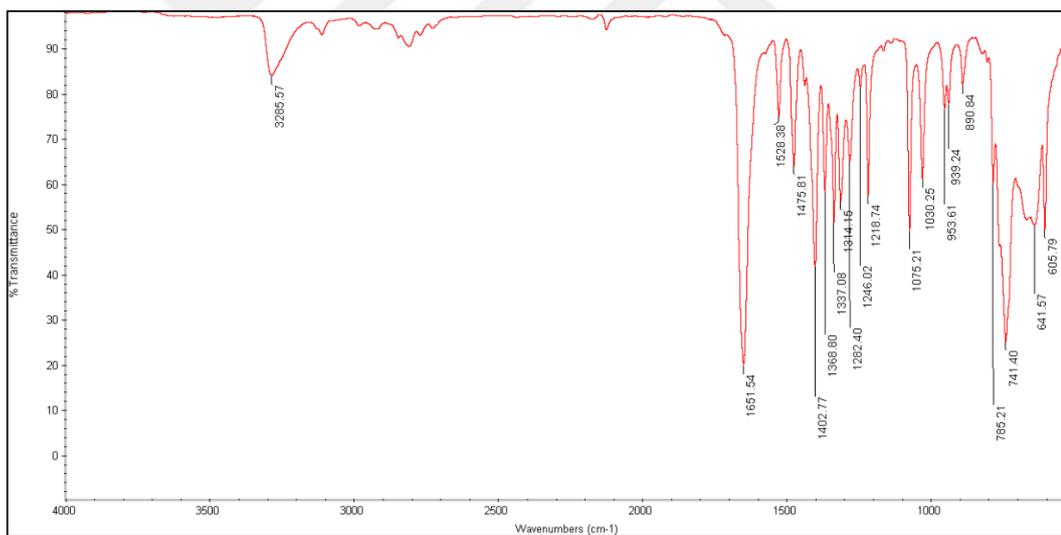


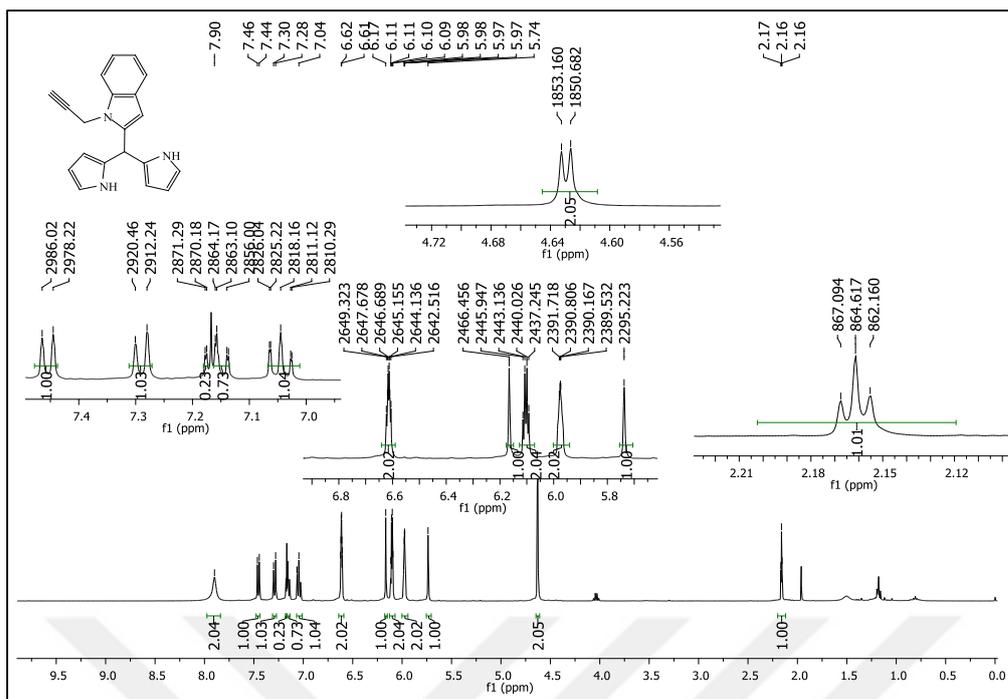
Figure 19 <sup>1</sup>H-NMR Spectrum of Compound 41c in CDCl<sub>3</sub>



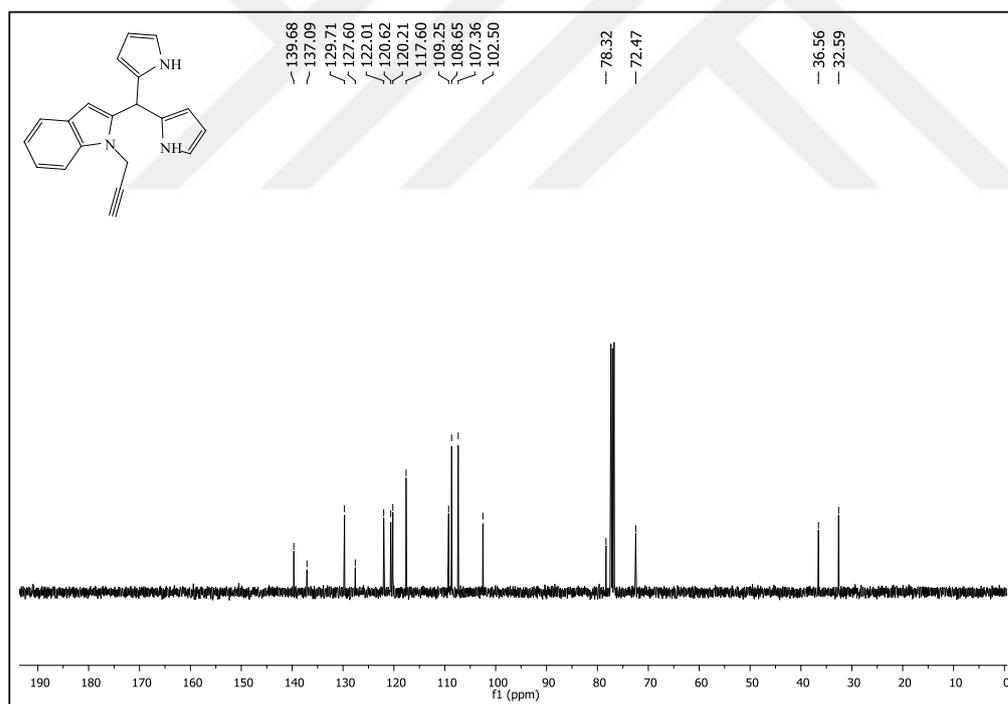
**Figure 20**  $^{13}\text{C-NMR}$  Spectrum of Compound **41c** in  $\text{CDCl}_3$



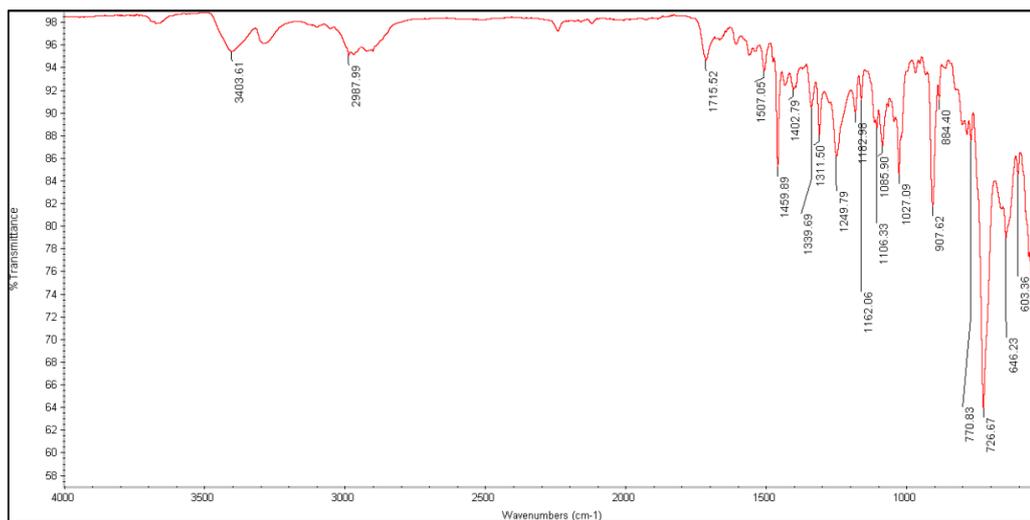
**Figure 21** IR Spectrum of Compound **41c**



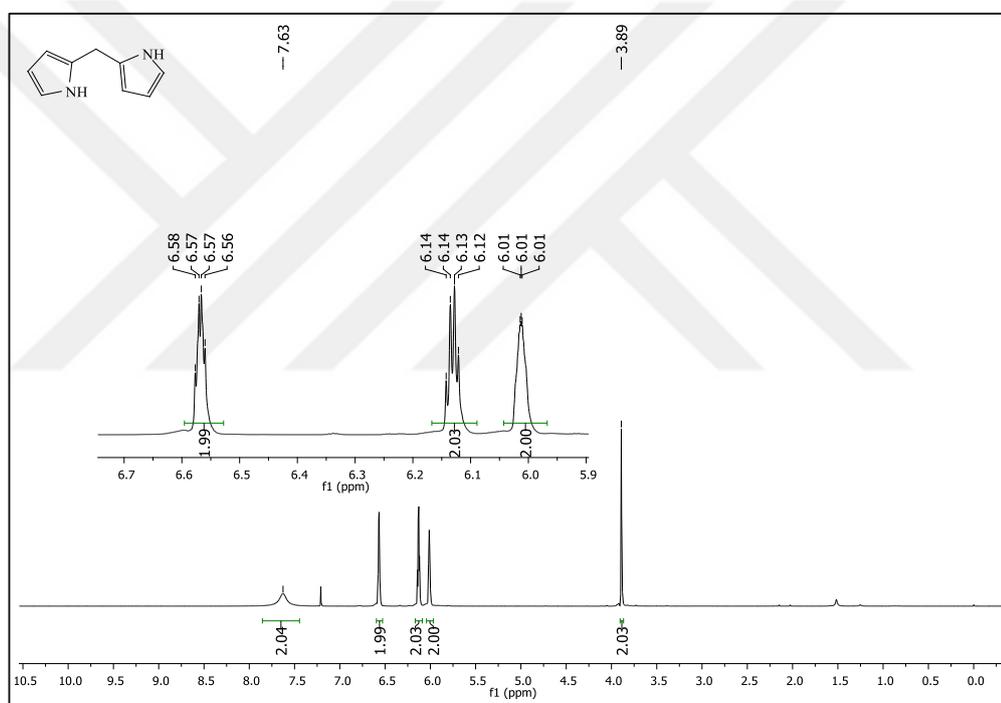
**Figure 22**  $^1\text{H-NMR}$  Spectrum of Compound **41b** in  $\text{CDCl}_3$



**Figure 23**  $^{13}\text{C-NMR}$  Spectrum of Compound **41b** in  $\text{CDCl}_3$



**Figure 24** IR Spectrum of Compound **41b**



**Figure 25**  $^1\text{H-NMR}$  Spectrum of Compound **41g** in  $\text{CDCl}_3$

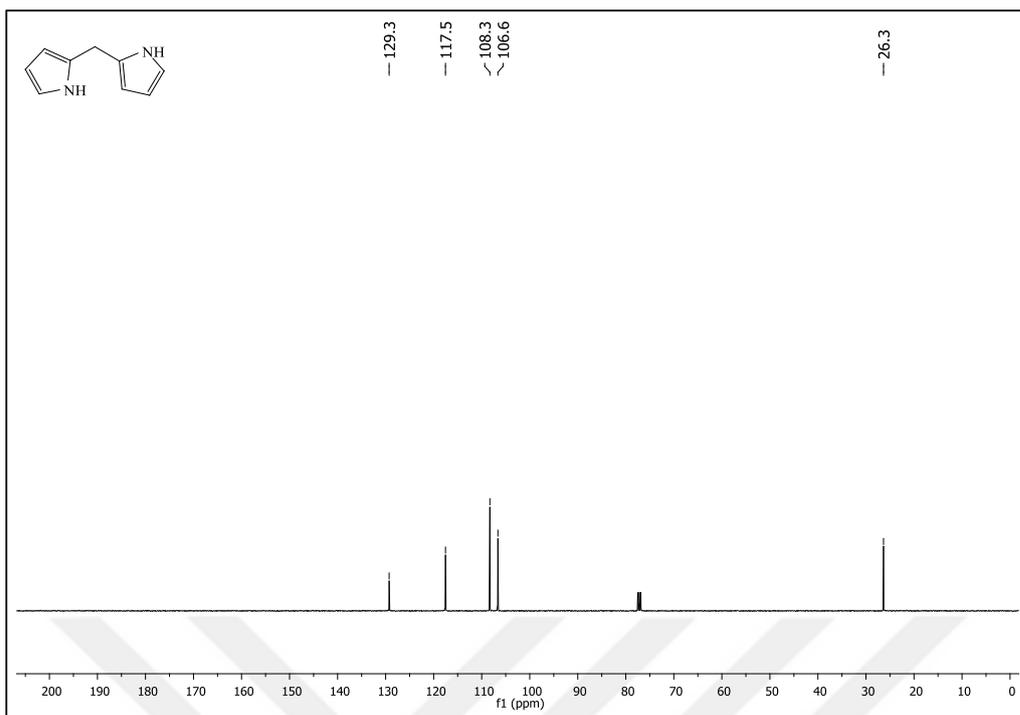


Figure 26  $^{13}\text{C-NMR}$  Spectrum of Compound 41g in  $\text{CDCl}_3$

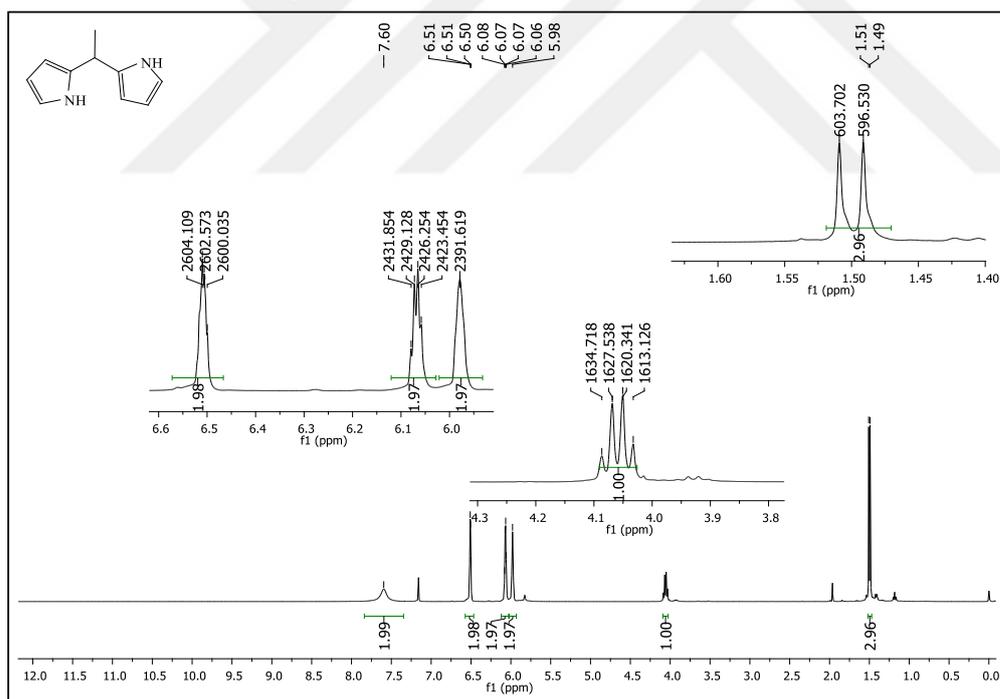
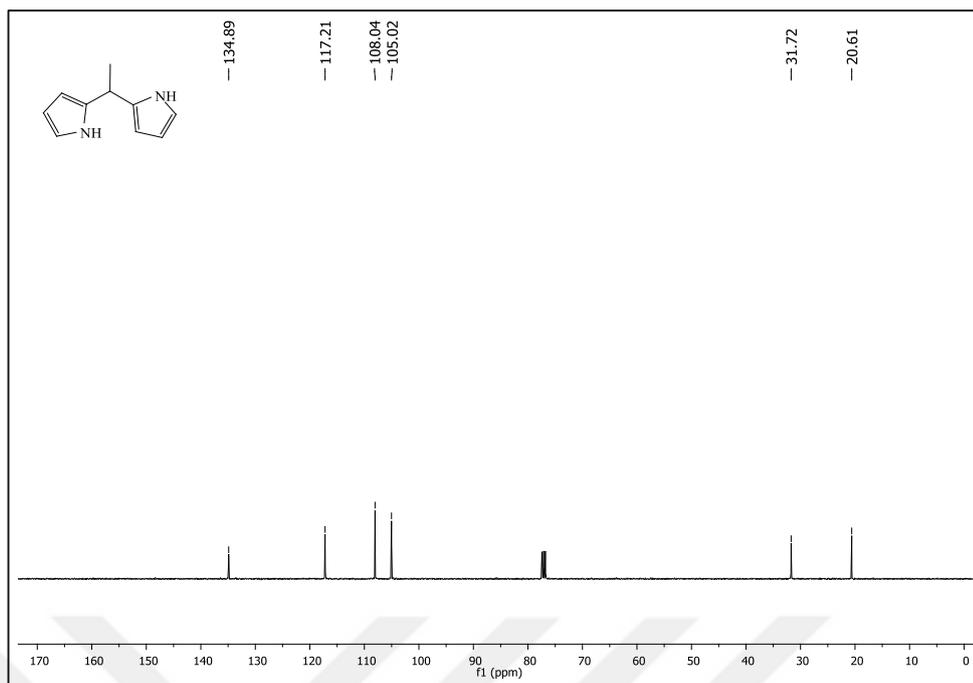
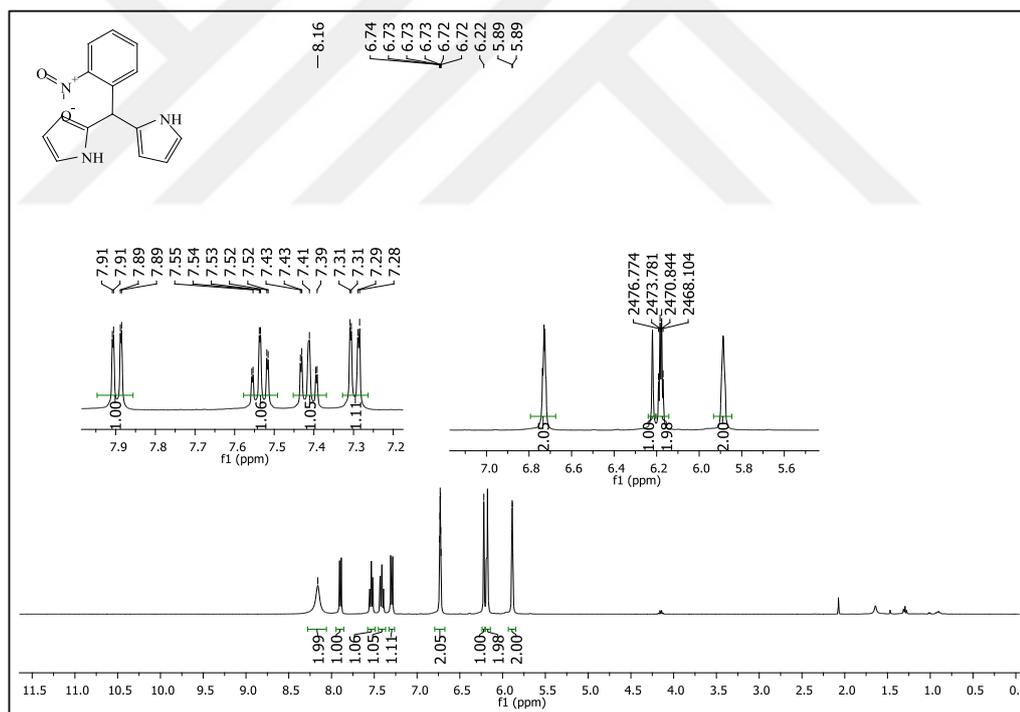


Figure 27  $^1\text{H-NMR}$  Spectrum of Compound 41f in  $\text{CDCl}_3$



**Figure 28**  $^{13}\text{C-NMR}$  Spectrum of Compound **41f** in  $\text{CDCl}_3$



**Figure 29**  $^1\text{H-NMR}$  Spectrum of Compound **41h** in  $\text{CDCl}_3$

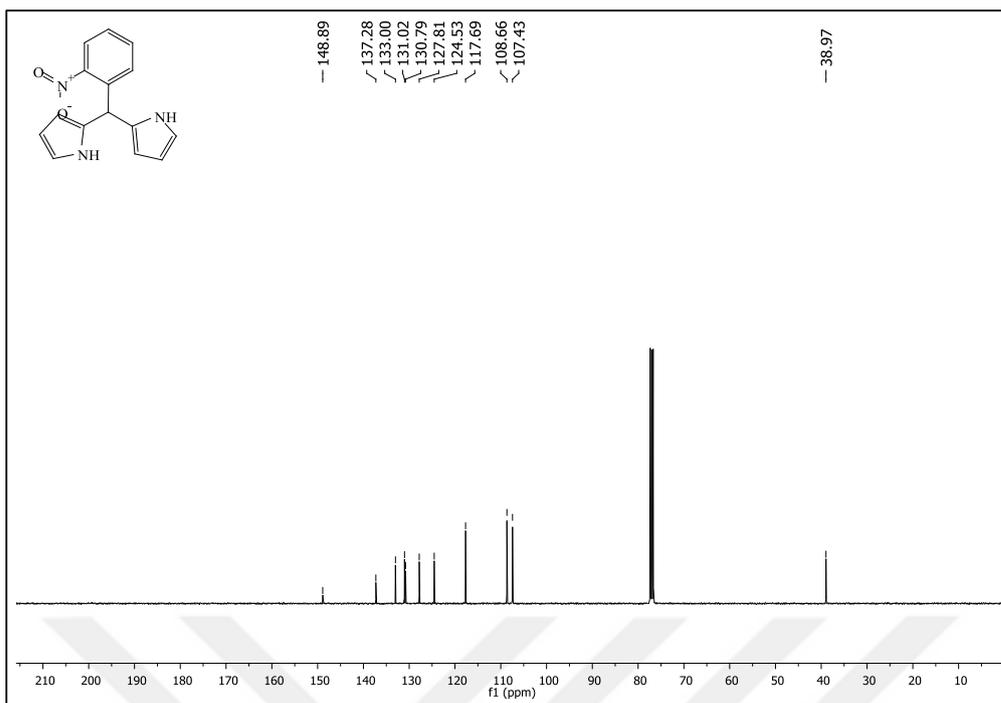


Figure 30  $^{13}\text{C-NMR}$  Spectrum of Compound 45h in  $\text{CDCl}_3$

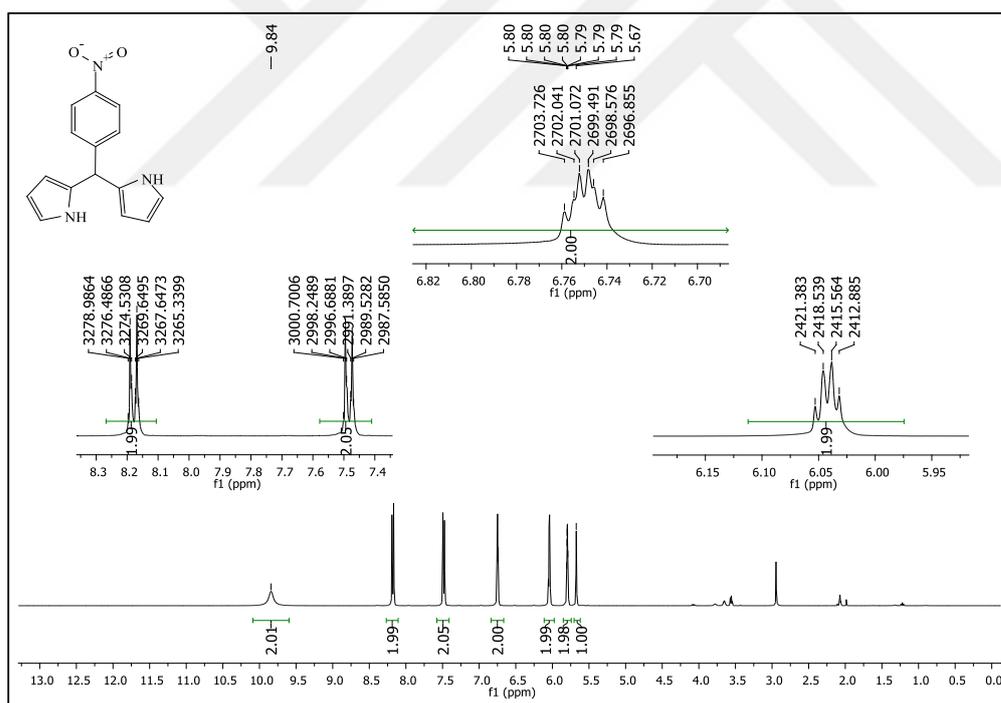


Figure 31  $^1\text{H-NMR}$  Spectrum of Compound 41i in  $\text{CD}_3\text{COCD}_3$

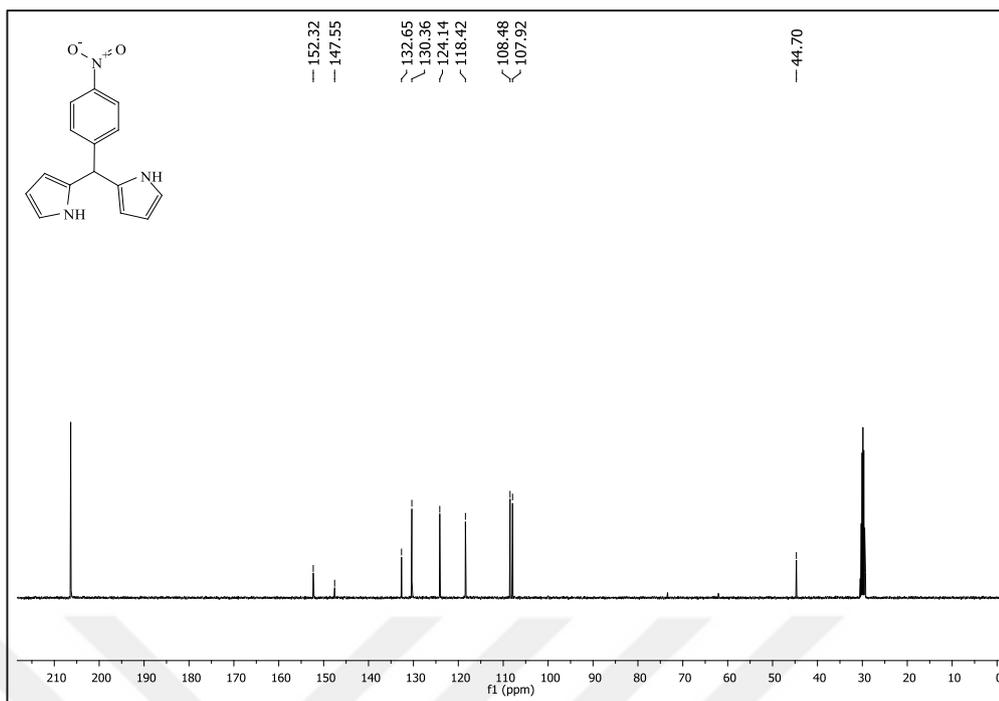


Figure 32  $^{13}\text{C-NMR}$  Spectrum of Compound 41i in  $\text{CD}_3\text{COCD}_3$

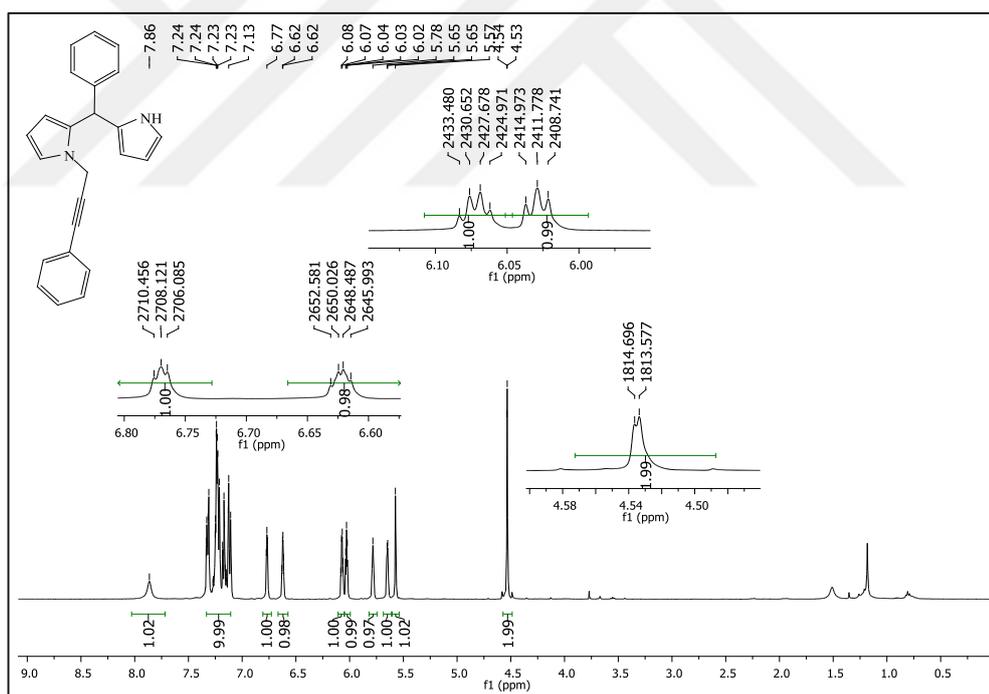
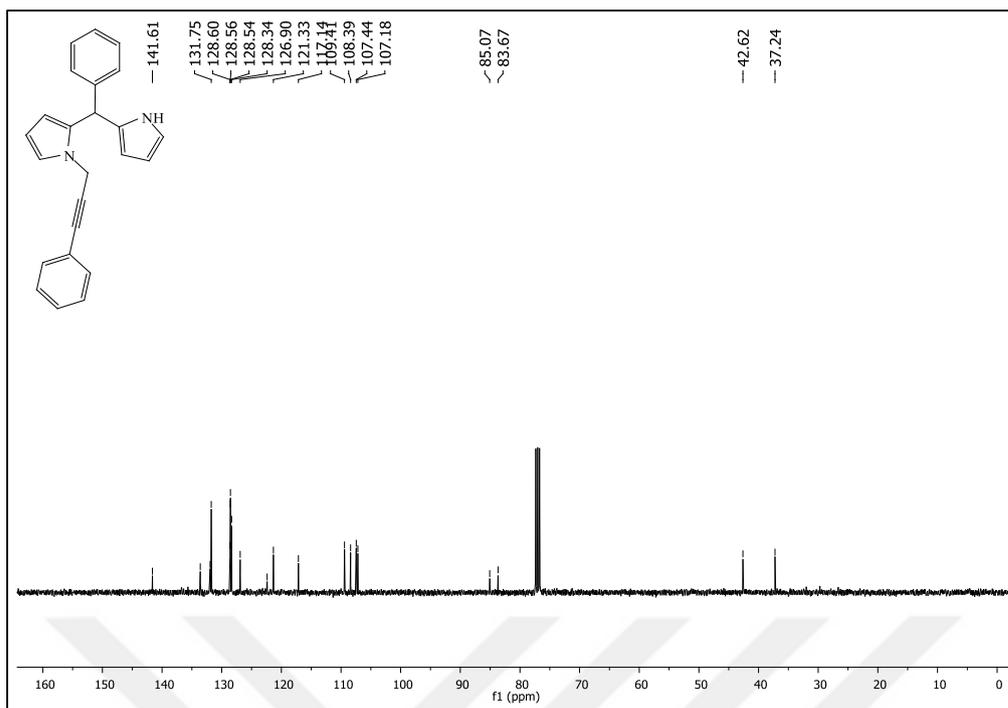
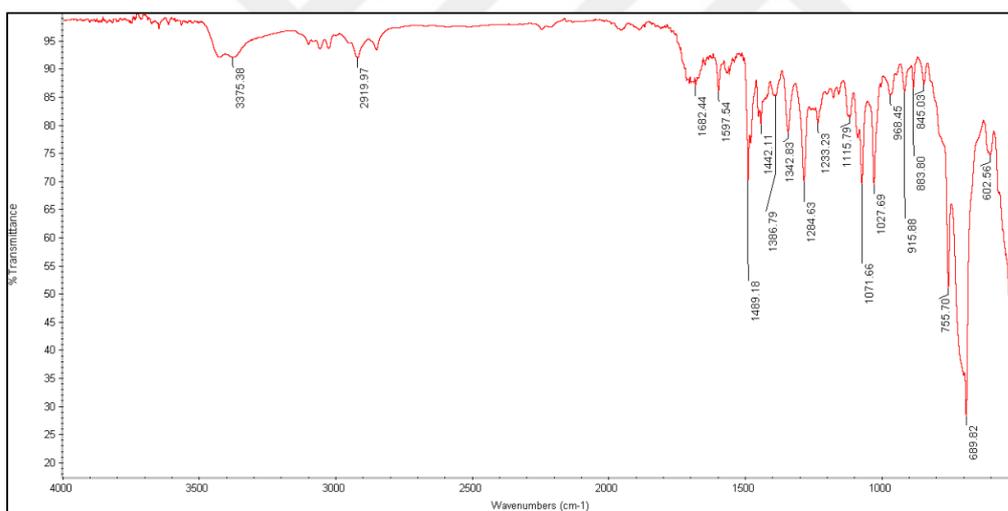


Figure 33  $^1\text{H-NMR}$  Spectrum of Compound 58 in  $\text{CDCl}_3$



**Figure 34** <sup>13</sup>C-NMR Spectrum of Compound **58** in CDCl<sub>3</sub>



**Figure 35** IR Spectrum of Compound **58**

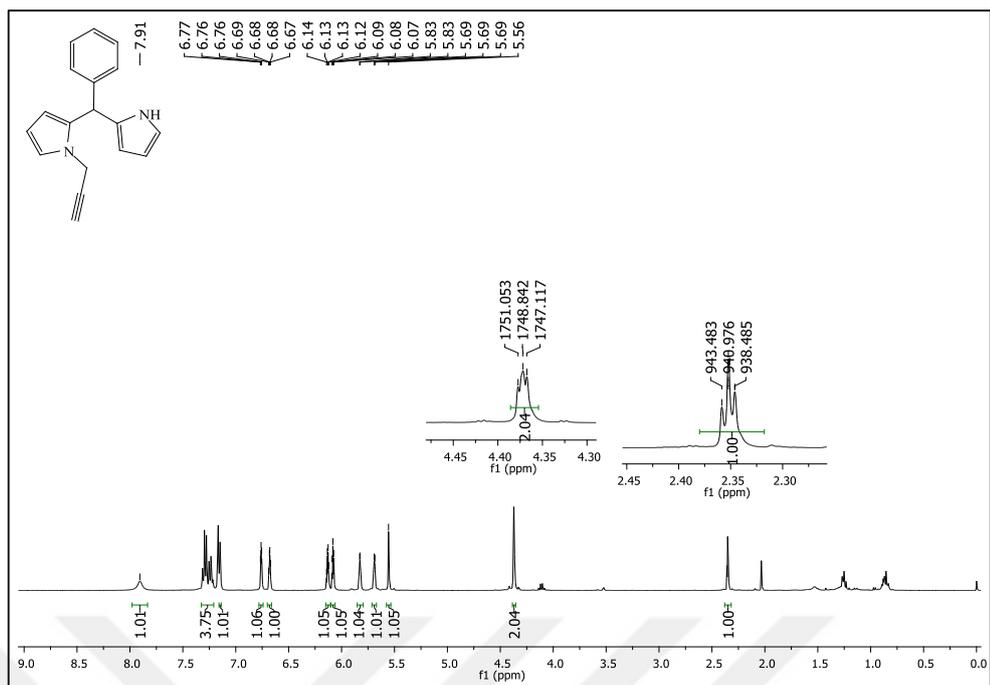


Figure 36 <sup>1</sup>H-NMR Spectrum of Compound 47a in CDCl<sub>3</sub>

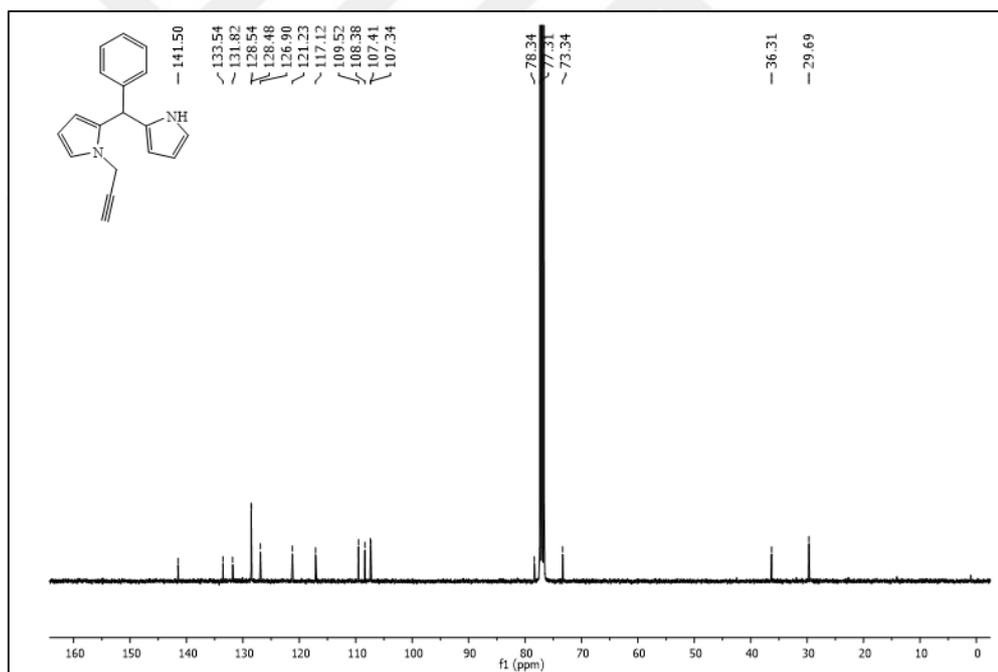
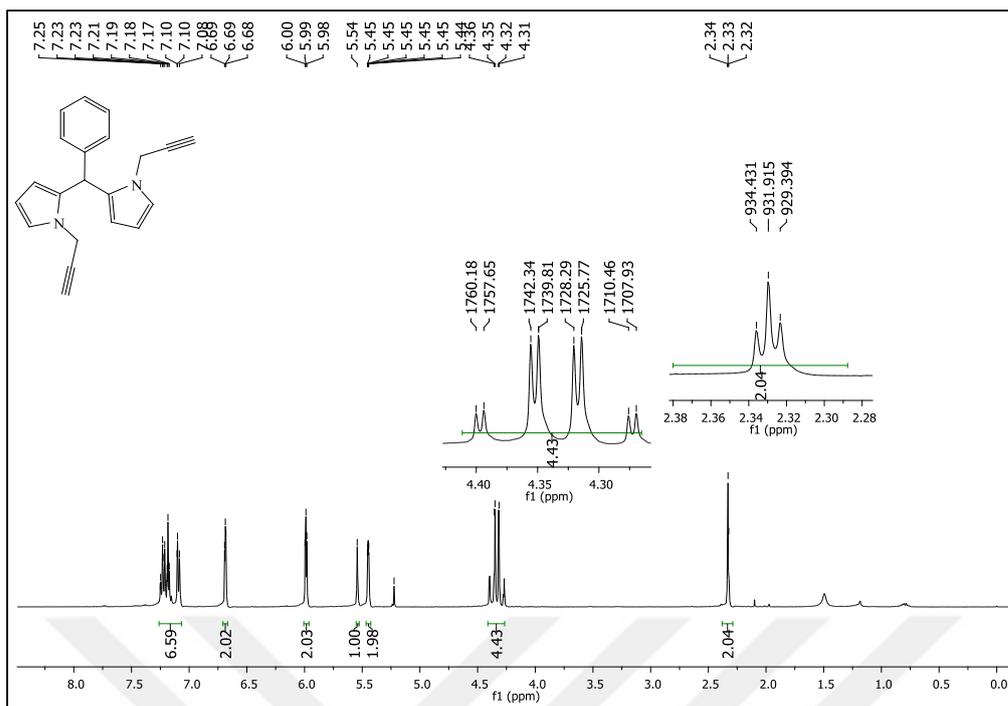
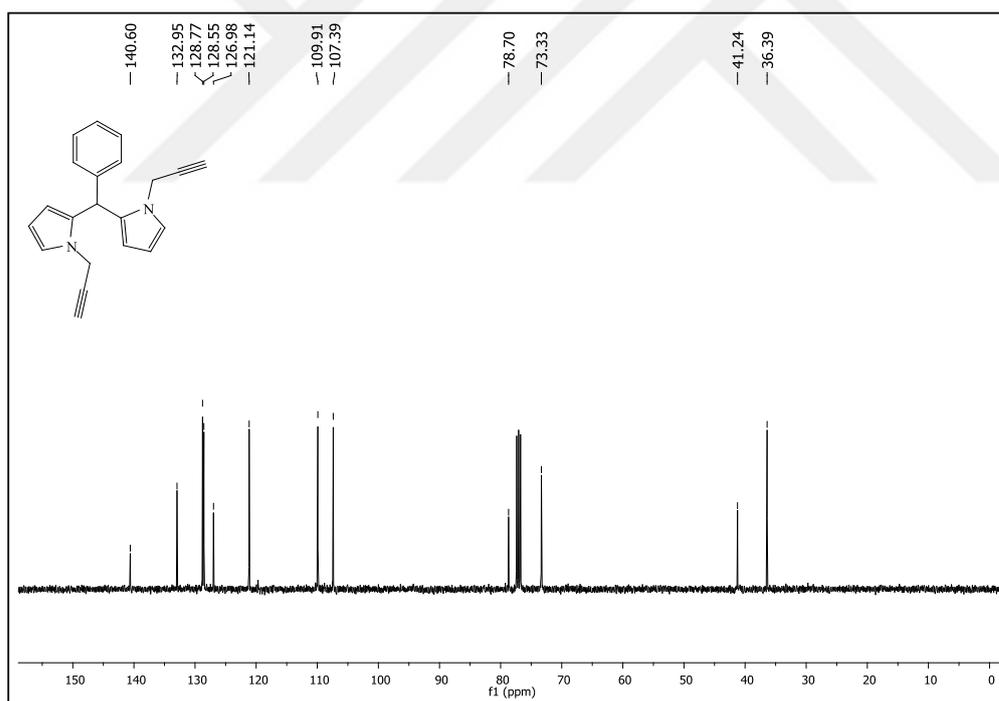


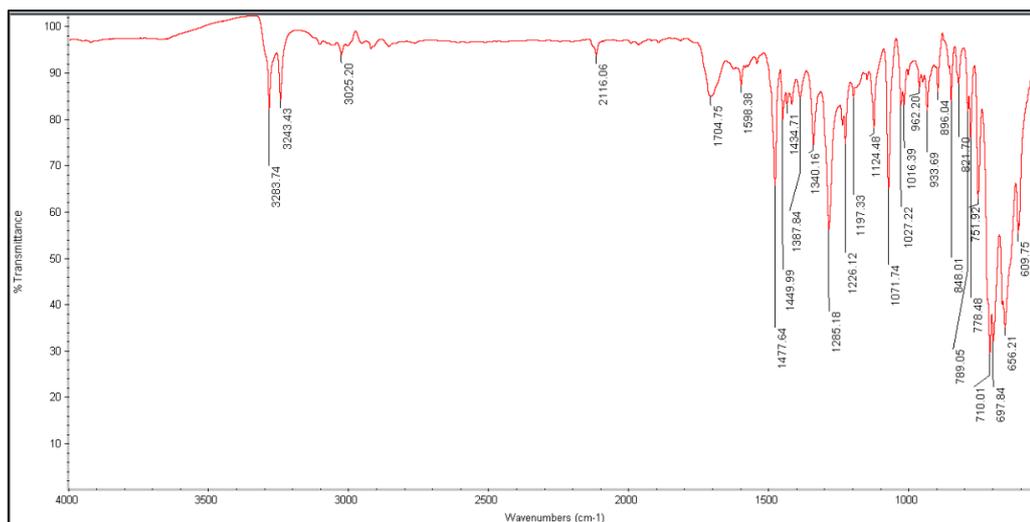
Figure 37 <sup>13</sup>C-NMR Spectrum of Compound 47a in CDCl<sub>3</sub>



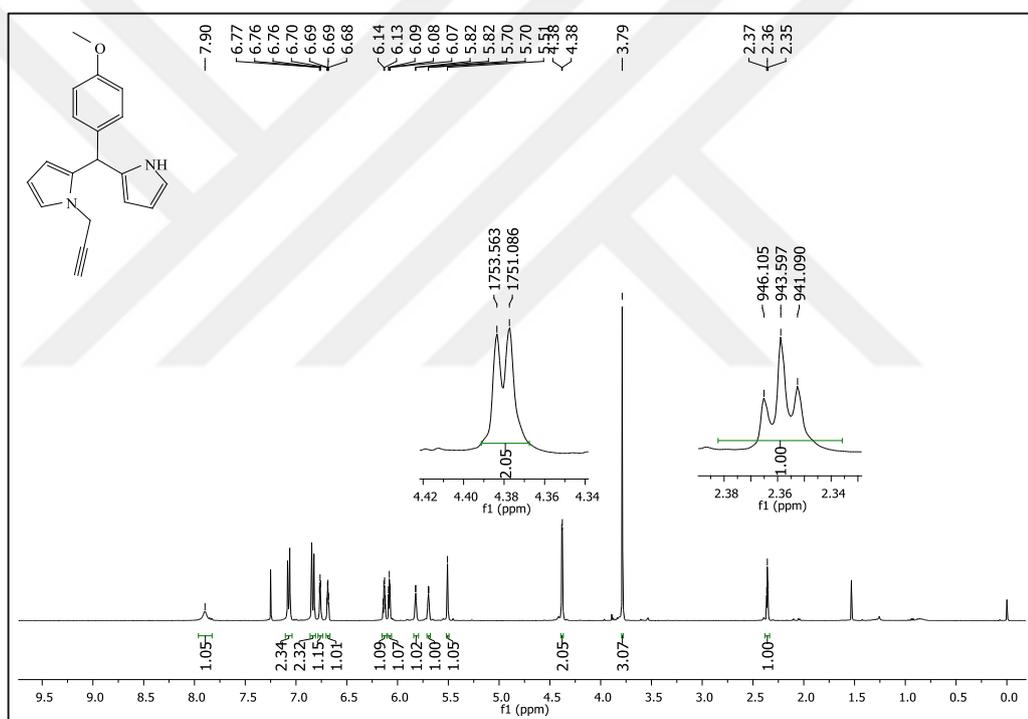
**Figure 38**  $^1\text{H-NMR}$  Spectrum of Compound **48a** in  $\text{CDCl}_3$



**Figure 39**  $^{13}\text{C-NMR}$  Spectrum of Compound **48a** in  $\text{CDCl}_3$



**Figure 40** IR Spectrum of Compound **48a**



**Figure 41** <sup>1</sup>H-NMR Spectrum of Compound **47d** in CDCl<sub>3</sub>

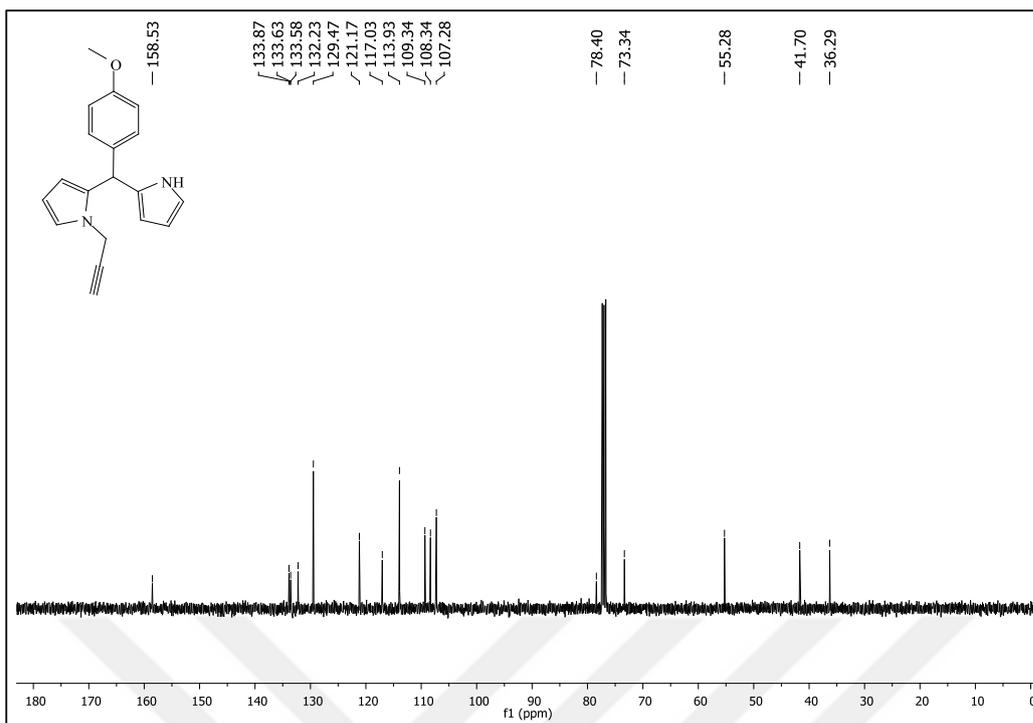


Figure 42  $^{13}\text{C-NMR}$  Spectrum of Compound 47d in  $\text{CDCl}_3$

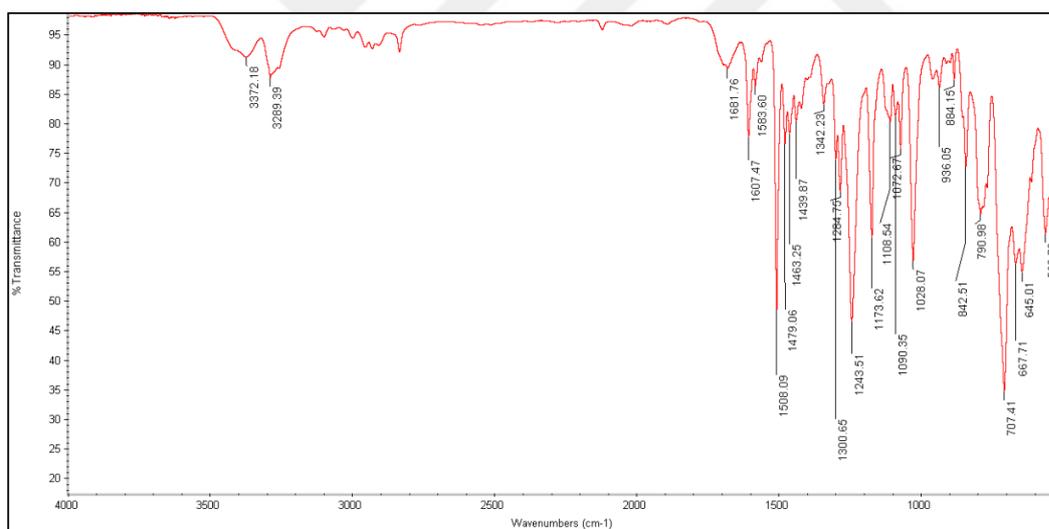


Figure 43 IR Spectrum of Compound 47d

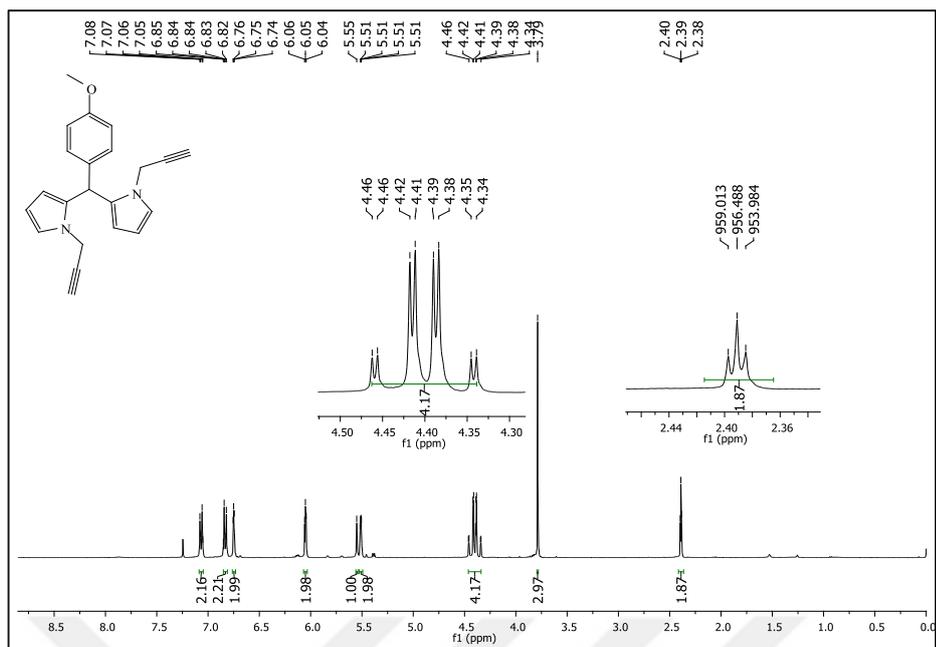


Figure 44 <sup>1</sup>H-NMR Spectrum of **48d** in CDCl<sub>3</sub>

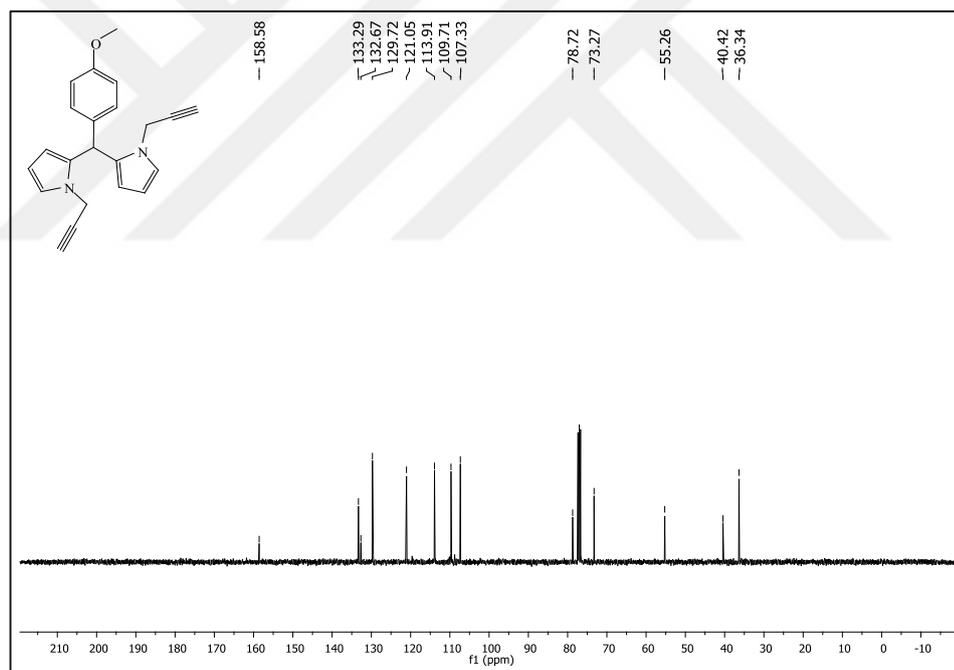


Figure 45 <sup>13</sup>C-NMR Spectrum of Compound **48d** in CDCl<sub>3</sub>

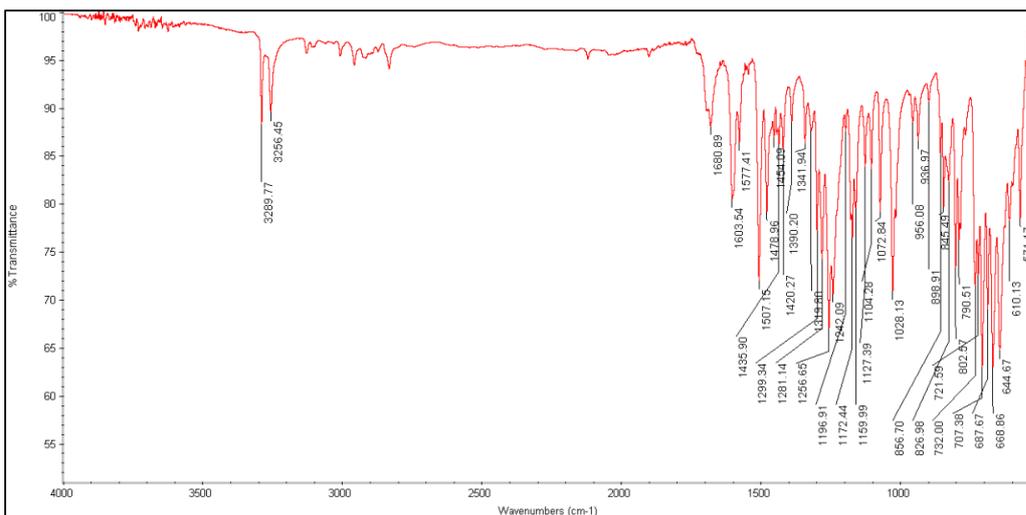


Figure 46 IR Spectrum of Compound 48d

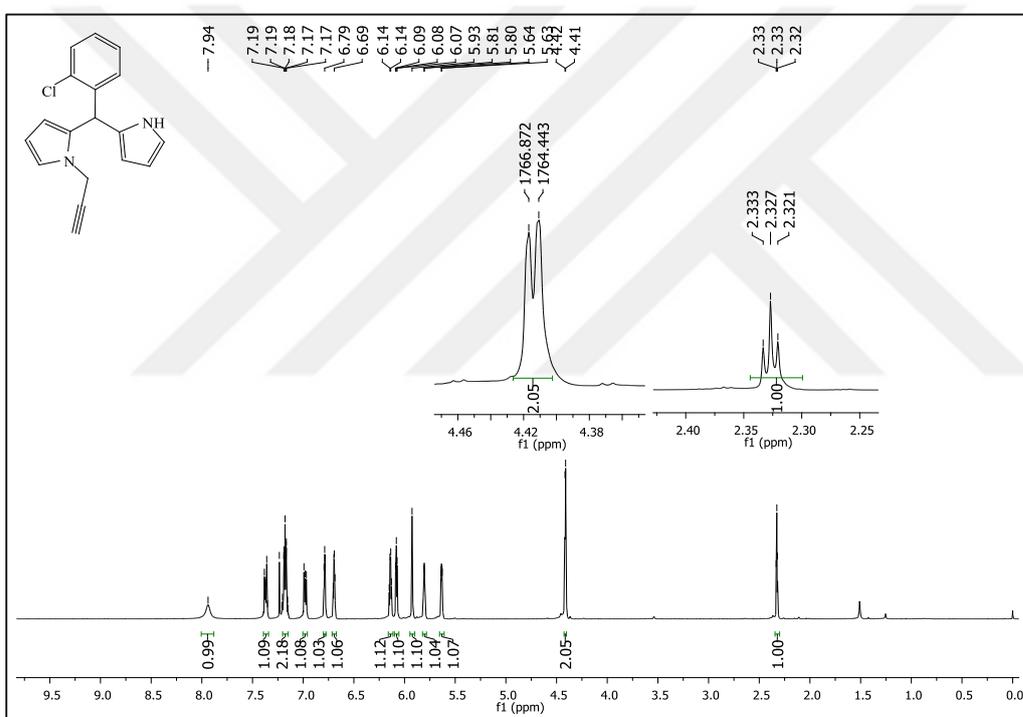


Figure 47 <sup>1</sup>H-NMR Spectrum of Compound 47e in CDCl<sub>3</sub>

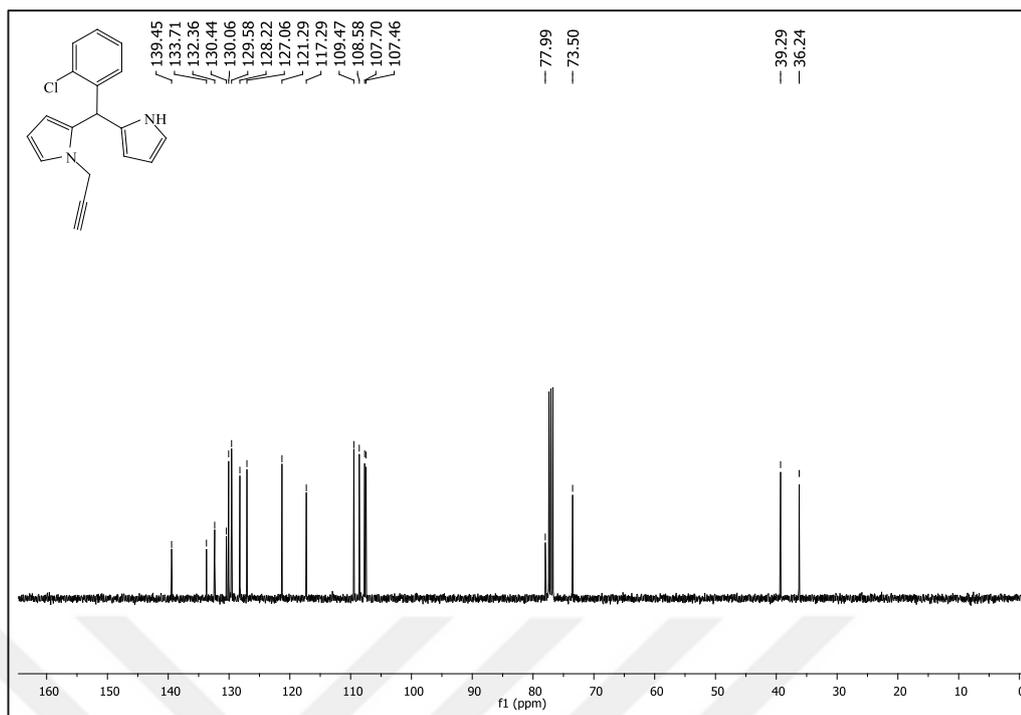


Figure 48  $^{13}\text{C-NMR}$  Spectrum of Compound 47e in  $\text{CDCl}_3$

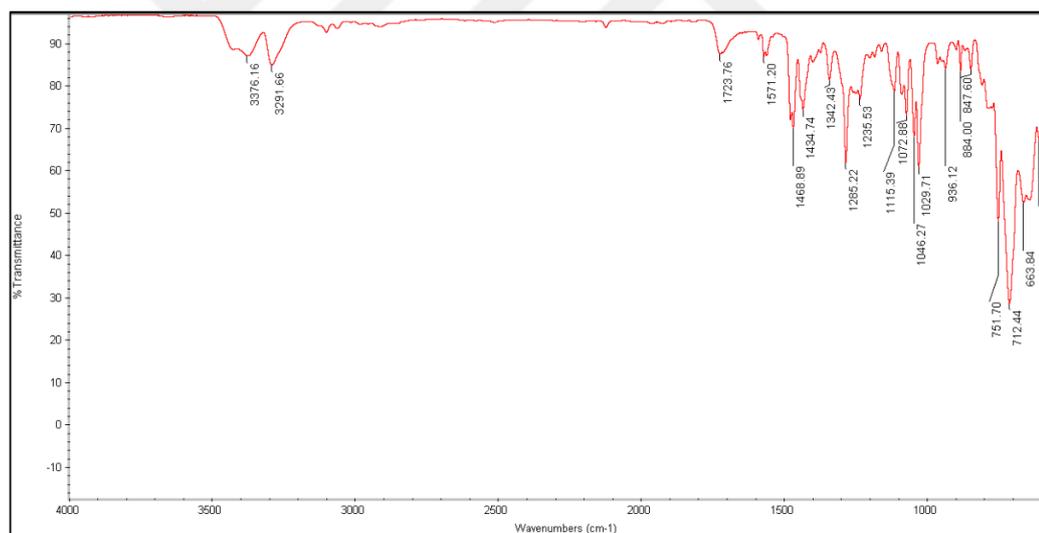
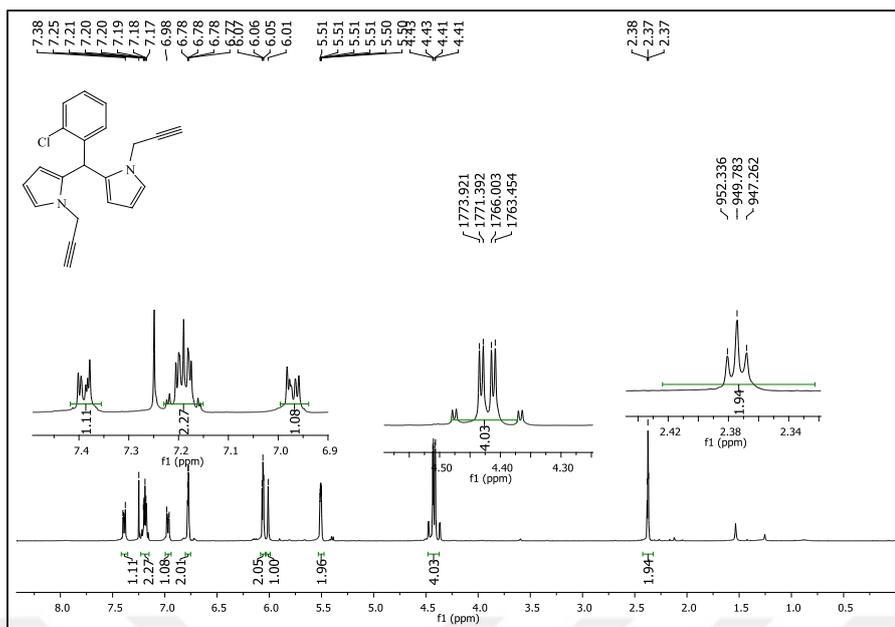
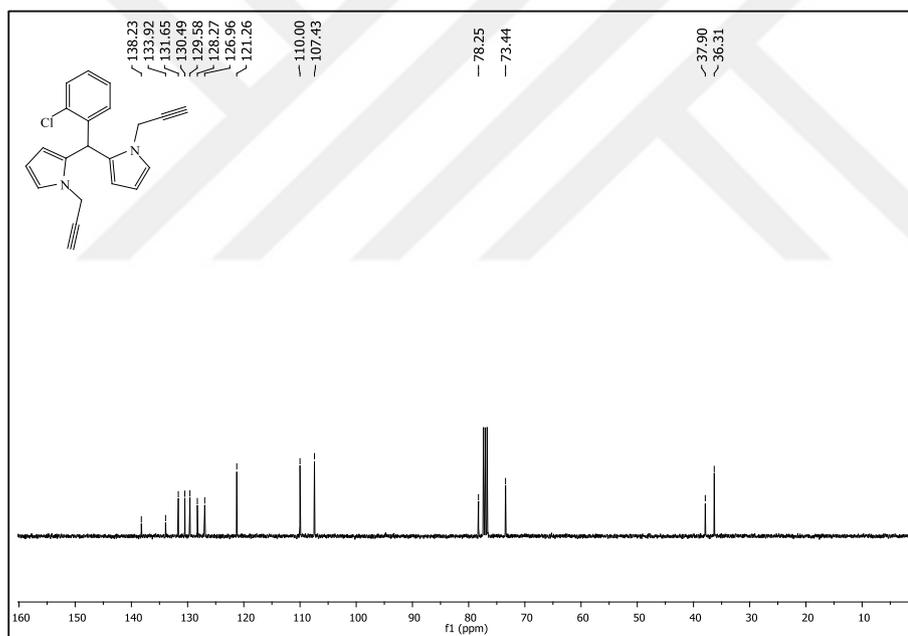


Figure 49 IR Spectrum of Compound 47e



**Figure 50** <sup>1</sup>H-NMR Spectrum of Compound **48e** in CDCl<sub>3</sub>



**Figure 51** <sup>13</sup>C-NMR Spectrum of Compound **48e** in CDCl<sub>3</sub>

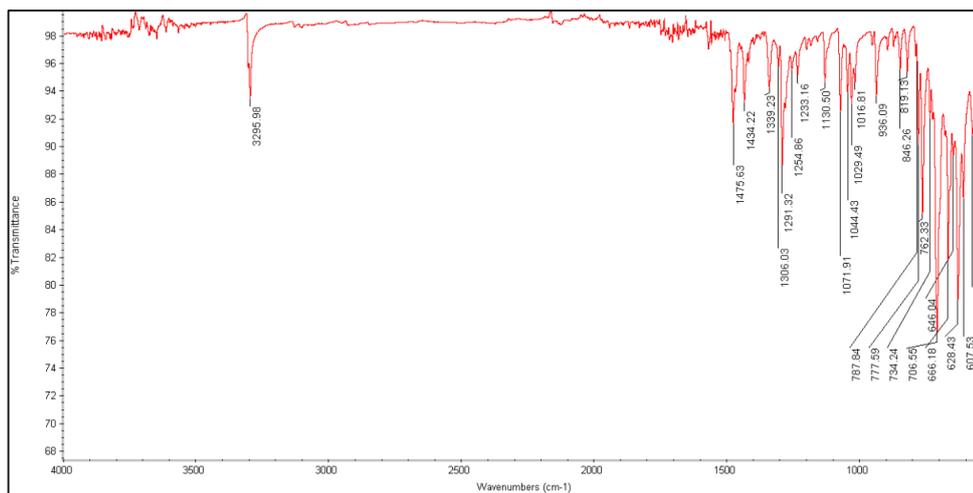


Figure 52 IR Spectrum of Compound 48e

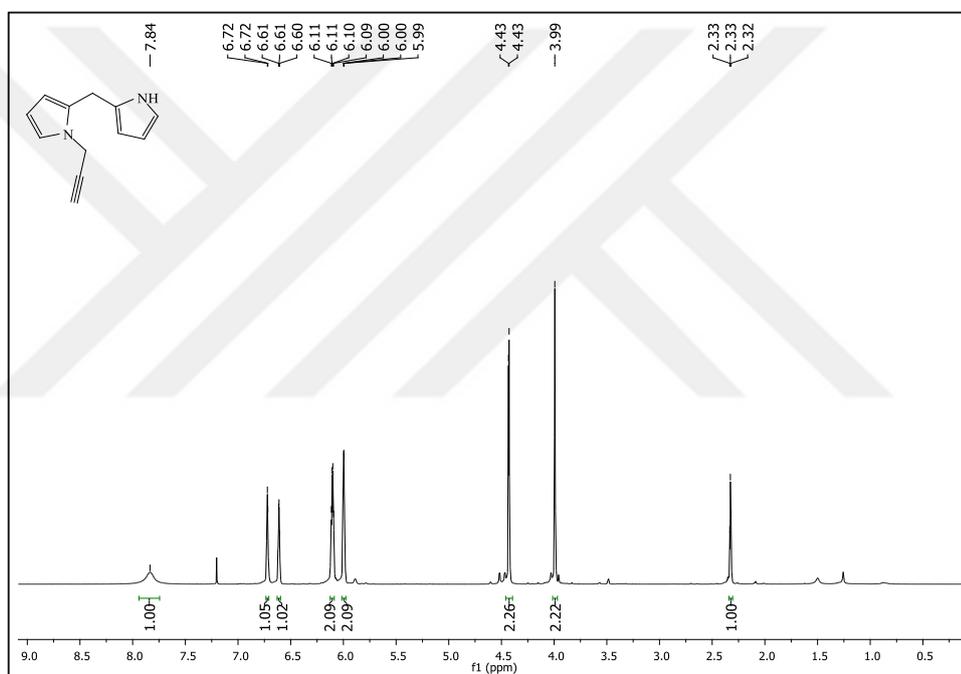
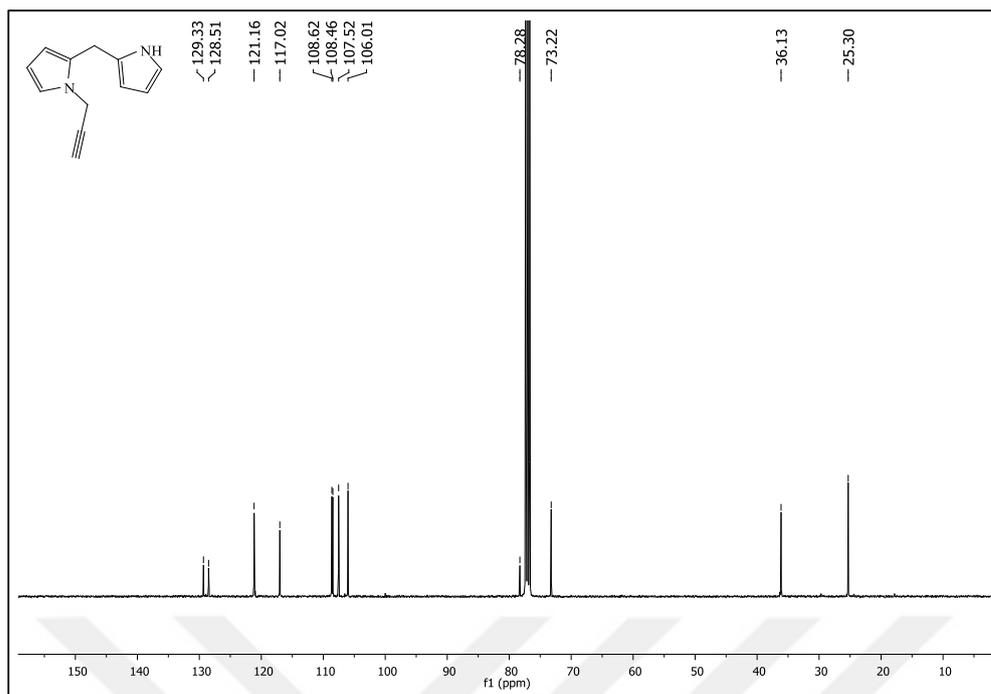
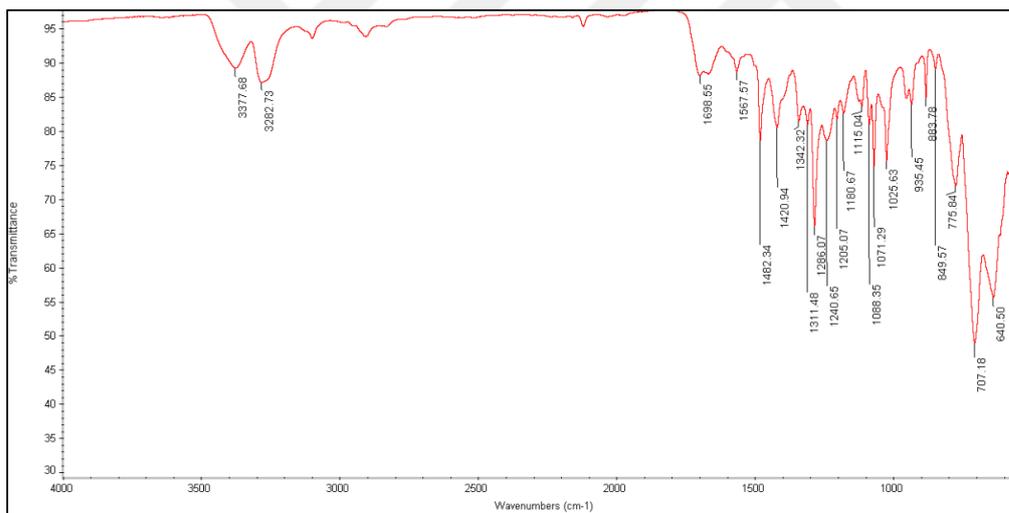


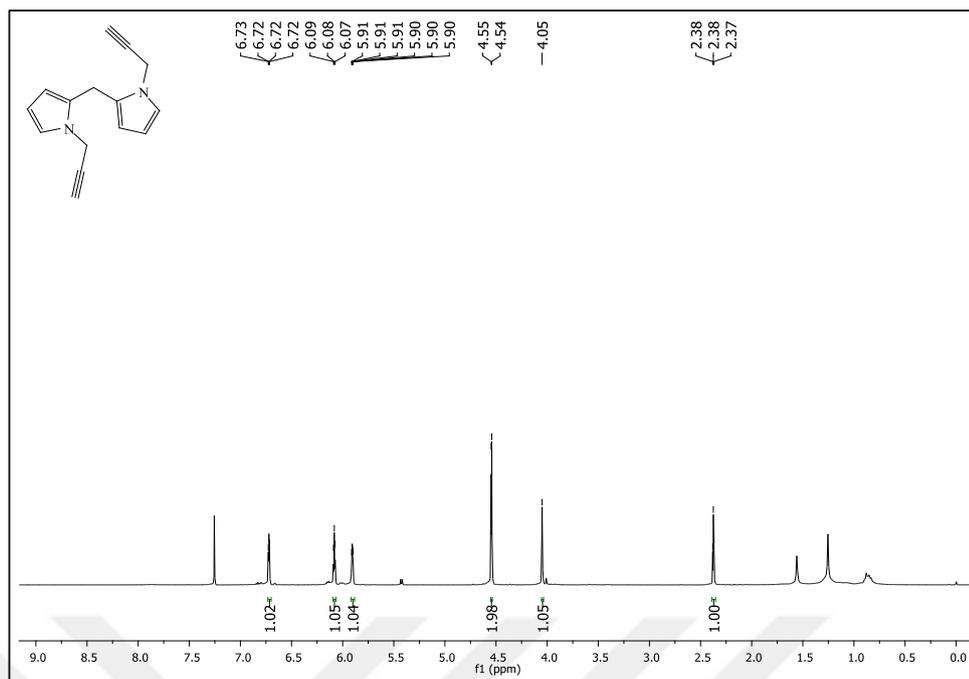
Figure 53 <sup>1</sup>H-NMR Spectrum of Compound 47g in CDCl<sub>3</sub>



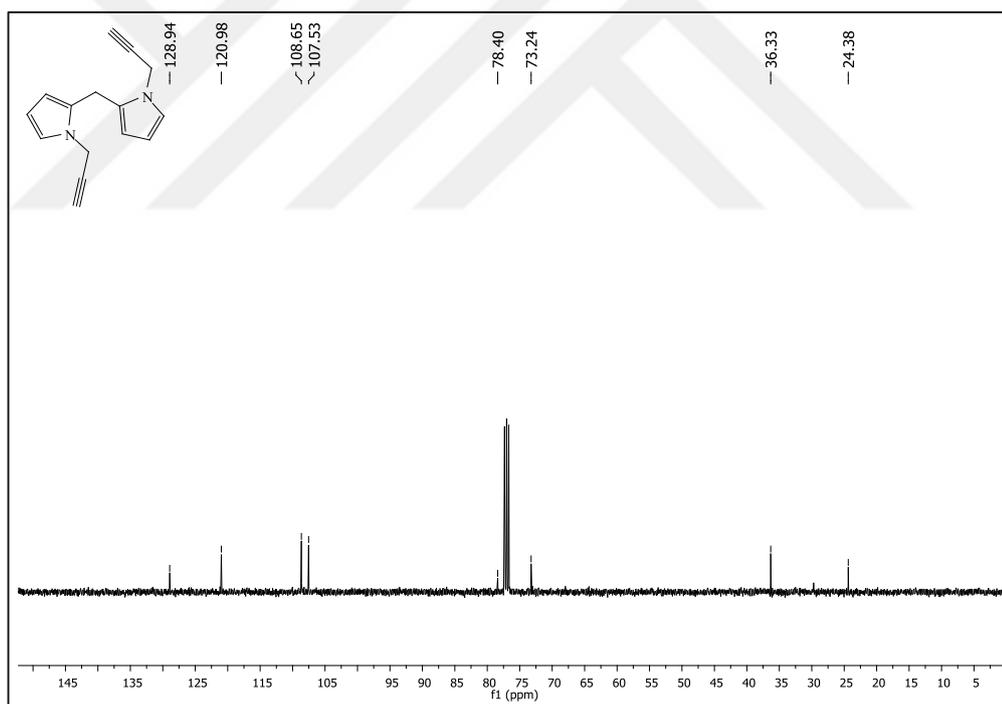
**Figure 54**  $^{13}\text{C}$ -NMR Spectrum of Compound **47g**



**Figure 55** IR Spectrum of Compound **47g**



**Figure 56**  $^1\text{H-NMR}$  Spectrum of Compound **48g** in  $\text{CDCl}_3$



**Figure 57**  $^{13}\text{C-NMR}$  Spectrum of Compound **48g**

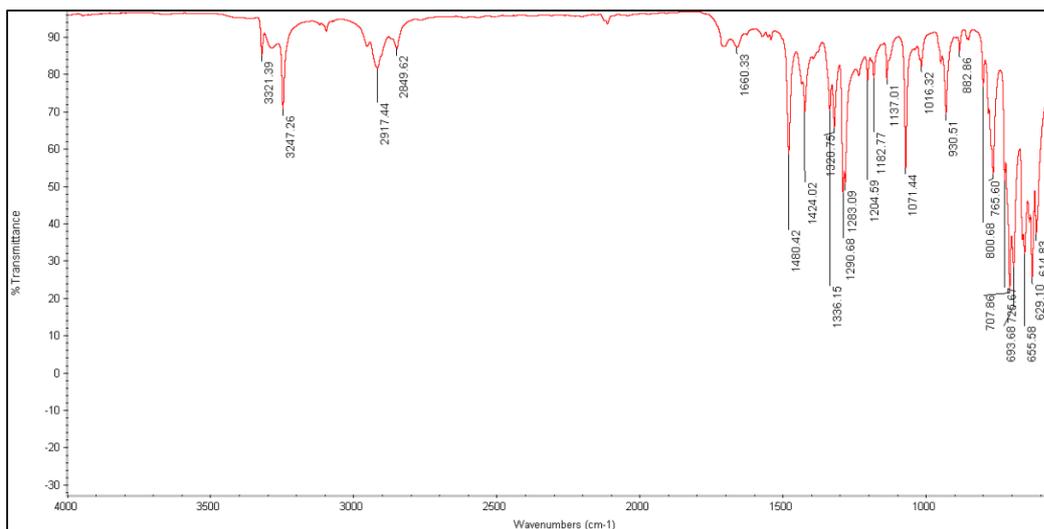


Figure 58 IR Spectrum of Compound 48g

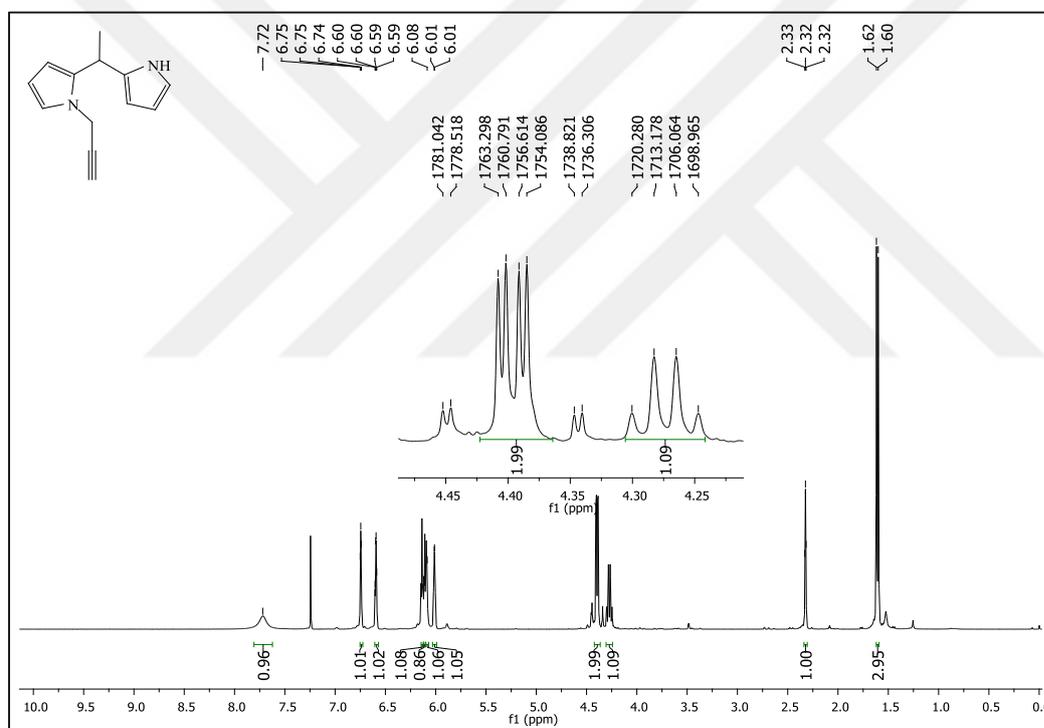
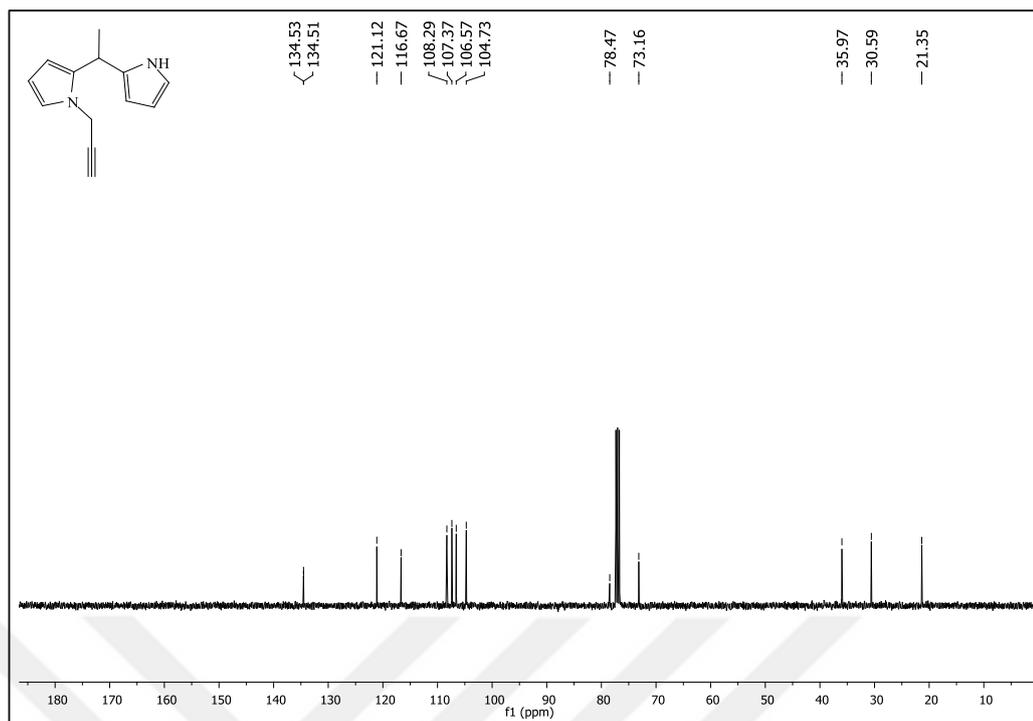
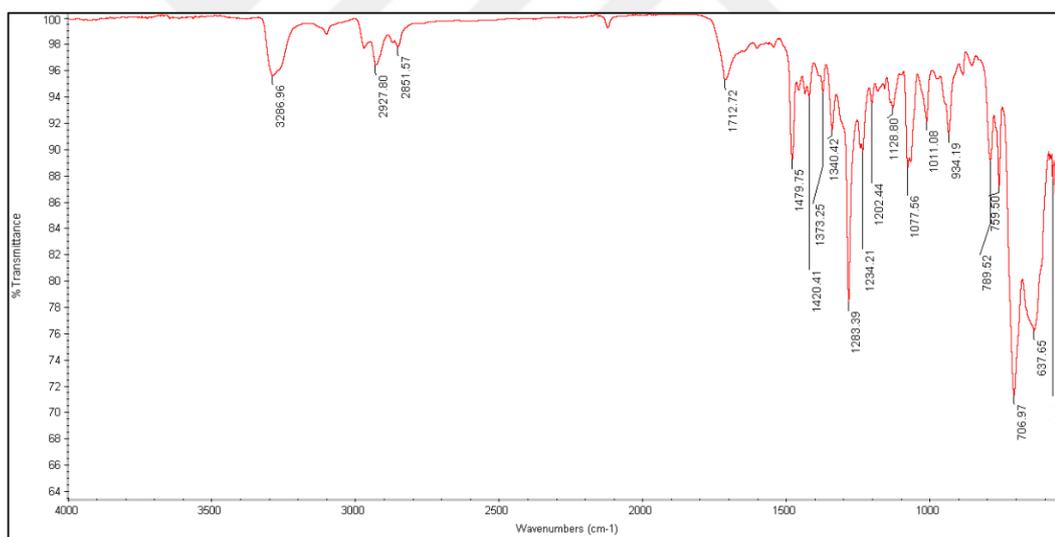


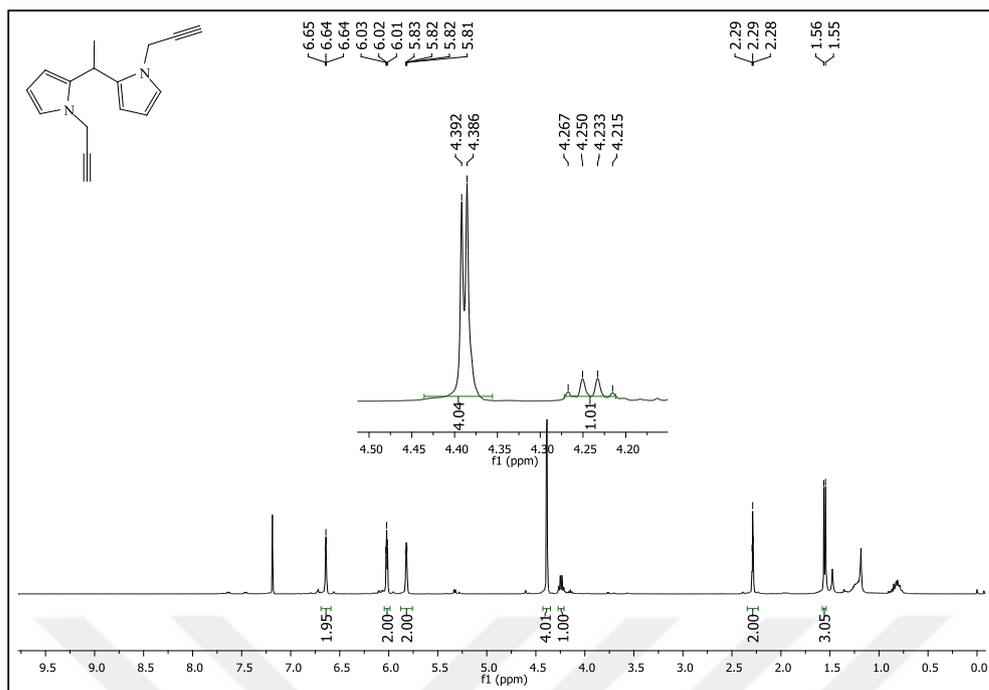
Figure 59 <sup>1</sup>H-NMR Spectrum of Compound 47f in CDCl<sub>3</sub>



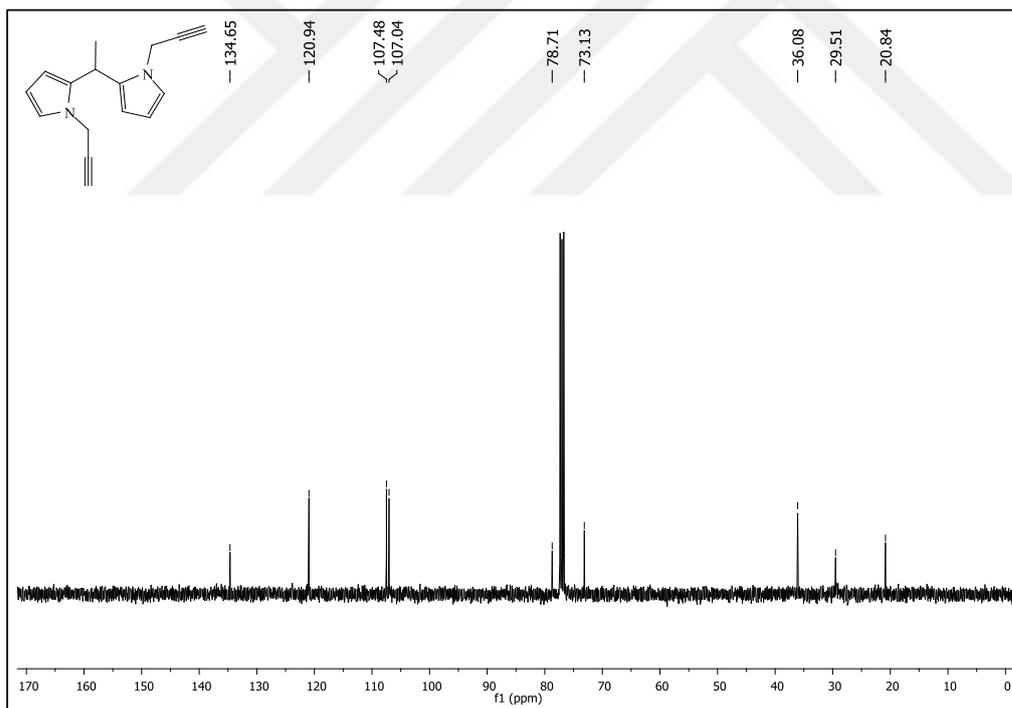
**Figure 60**  $^{13}\text{C-NMR}$  Spectrum of Compound 47f in  $\text{CDCl}_3$



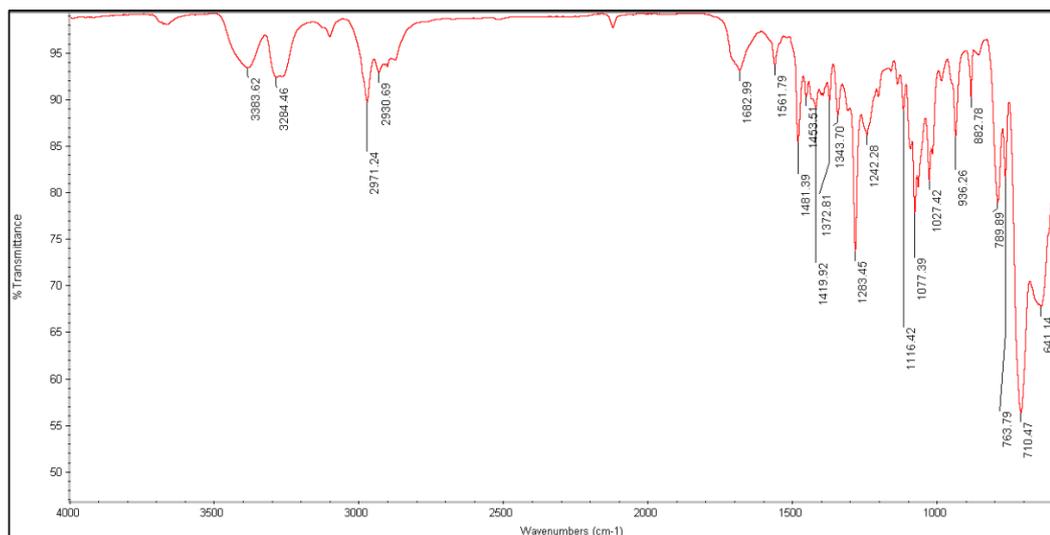
**Figure 61** IR Spectrum of Compound 47f



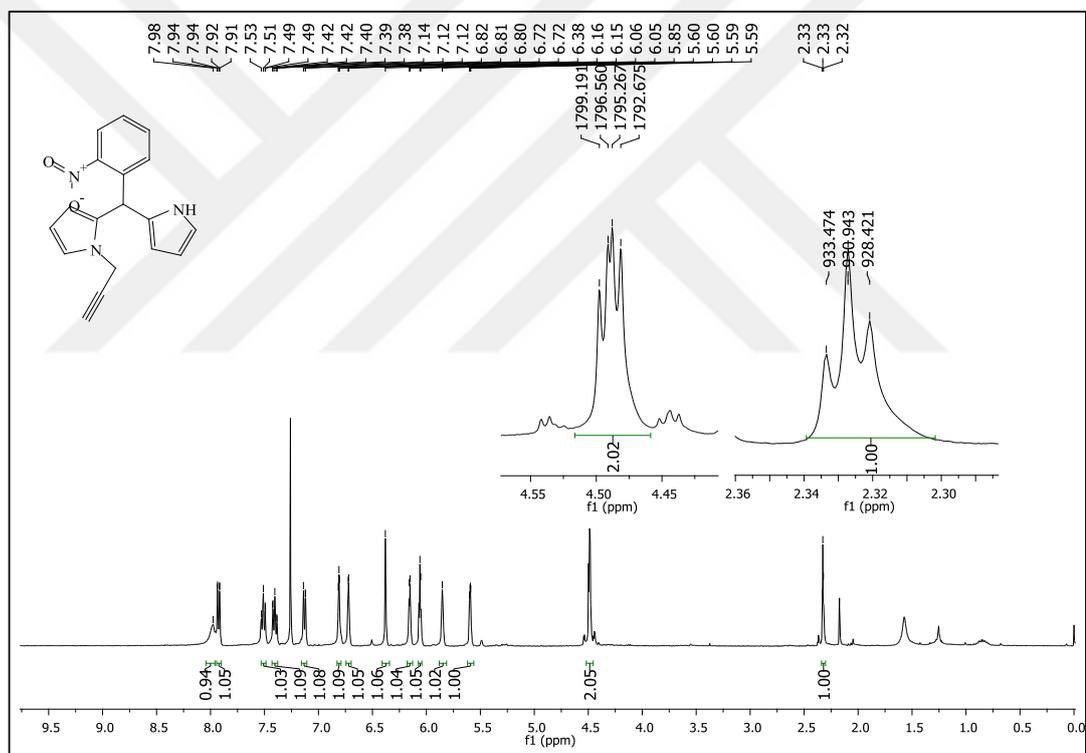
**Figure 62** <sup>1</sup>H-NMR Spectrum of Compound **48f** in CDCl<sub>3</sub>



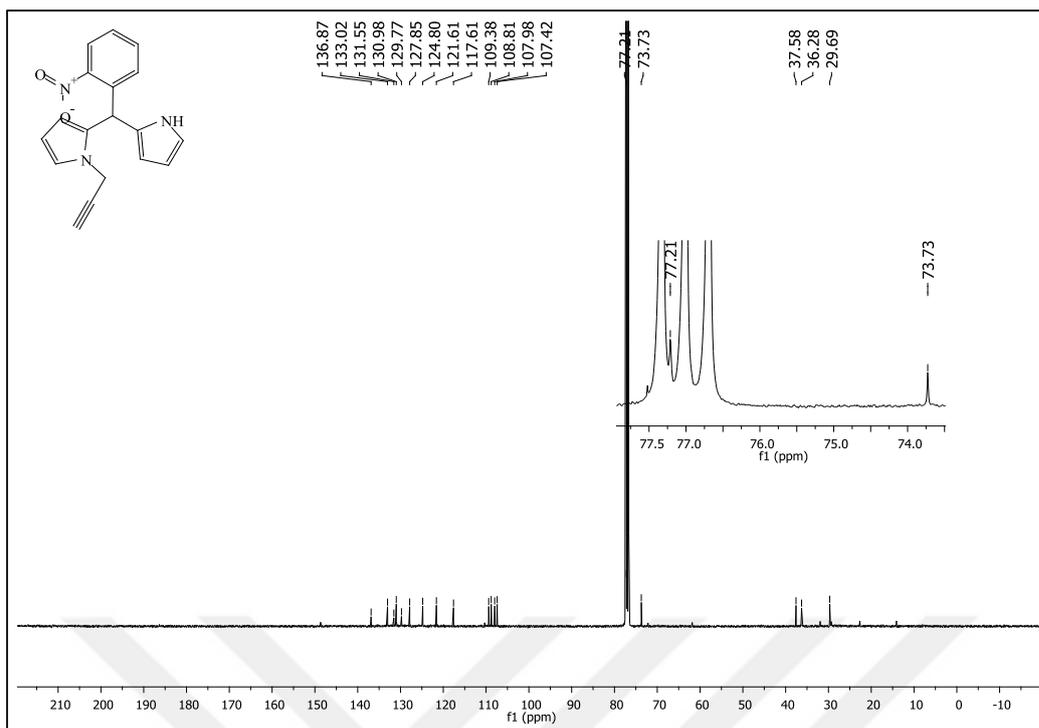
**Figure 63** <sup>13</sup>C-NMR Spectrum of Compound **48f** in CDCl<sub>3</sub>



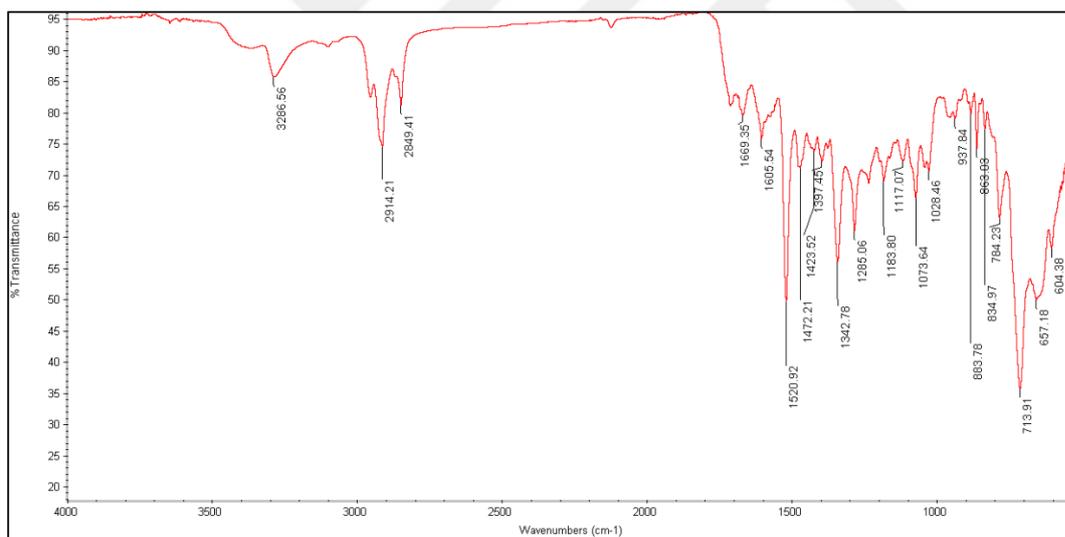
**Figure 64** IR Spectrum of Compound **48f**



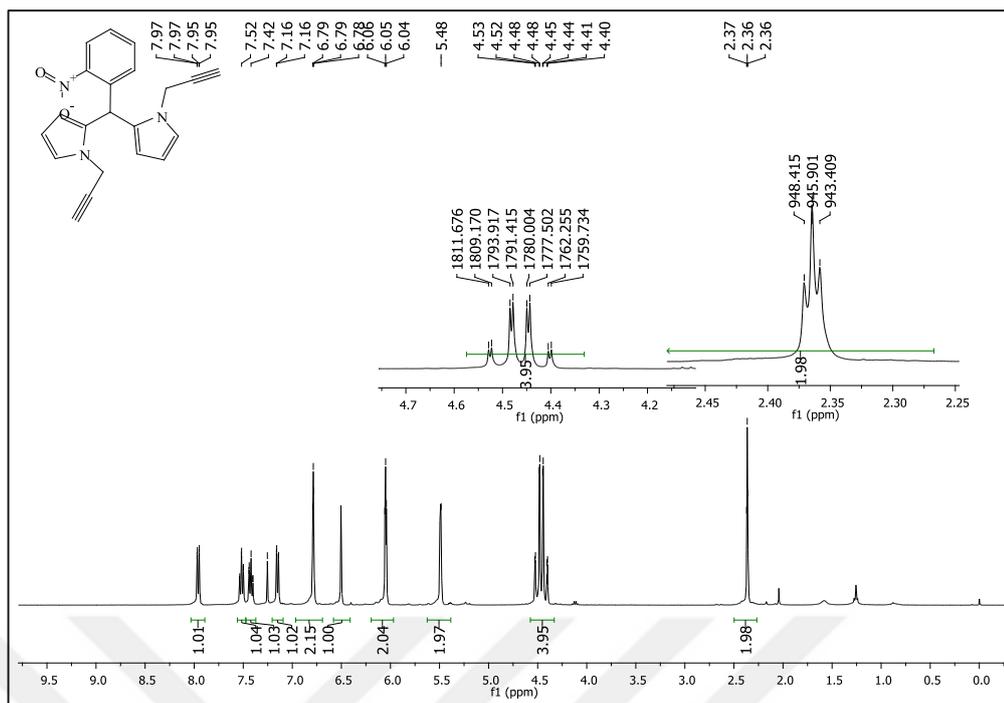
**Figure 65**  $^1\text{H-NMR}$  Spectrum of Compound **47h** in  $\text{CDCl}_3$



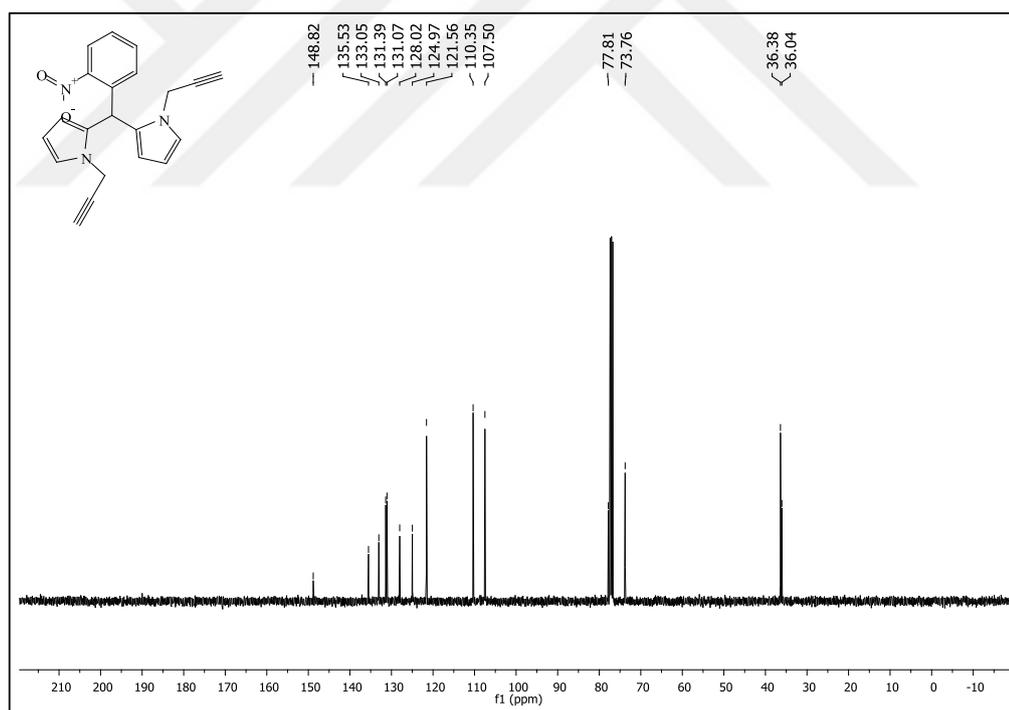
**Figure 66** <sup>13</sup>C-NMR Spectrum of Compound **47h** in CDCl<sub>3</sub>



**Figure 67** IR Spectrum of Compound **47h**



**Figure 68**  $^1\text{H-NMR}$  Spectrum of Compound **48h** in  $\text{CDCl}_3$



**Figure 69**  $^{13}\text{C-NMR}$  Spectrum of Compound **48h** in  $\text{CDCl}_3$

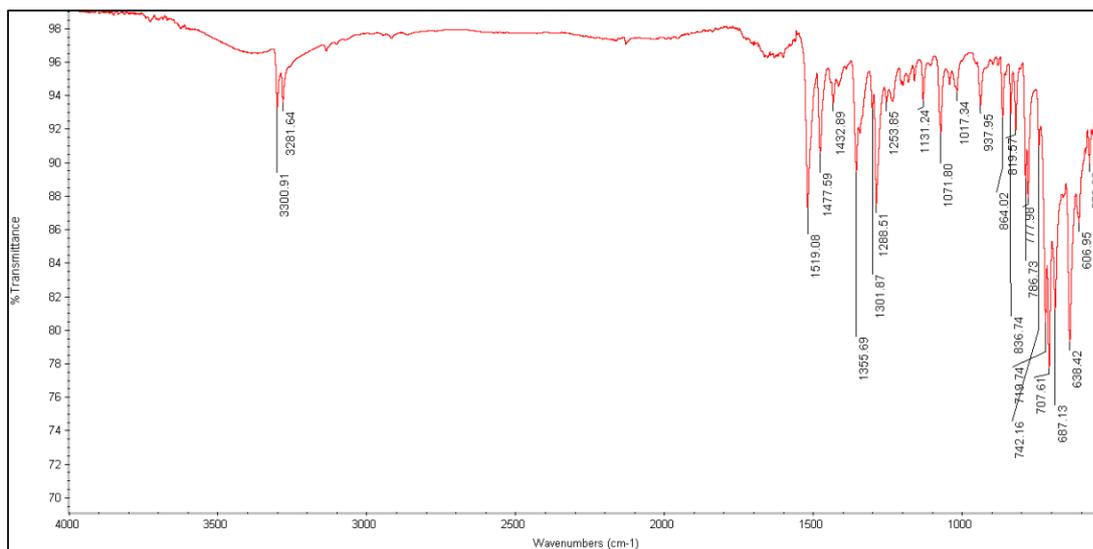


Figure 70 IR Spectrum of Compound 48h

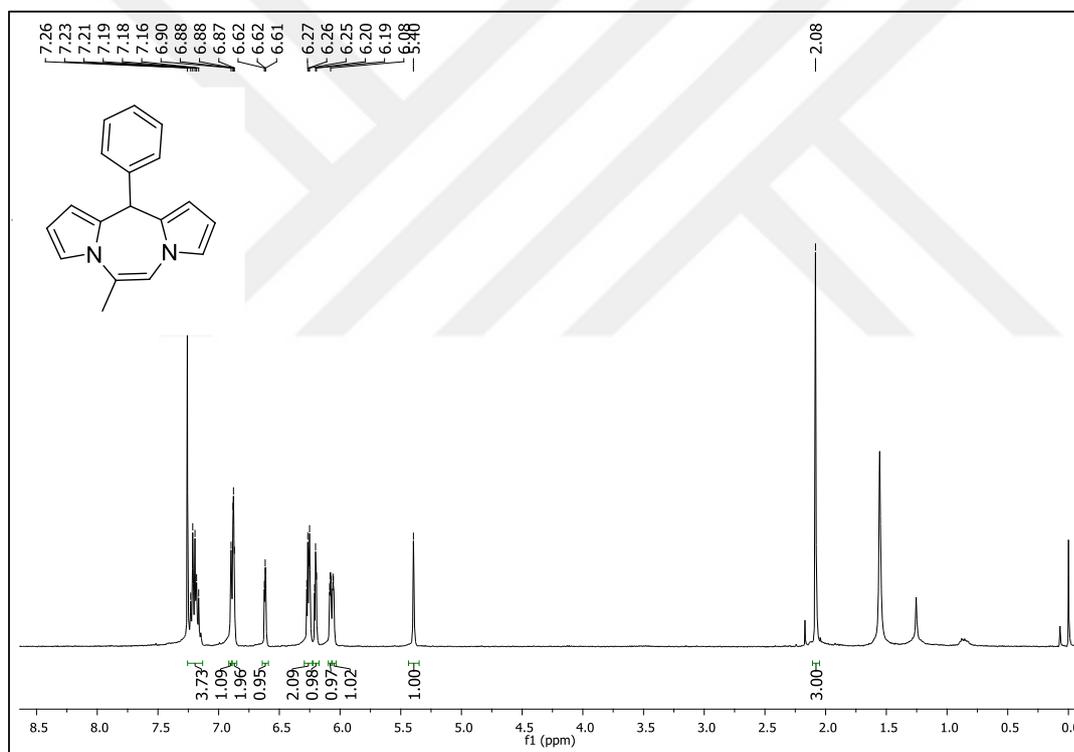


Figure 71 <sup>1</sup>H-NMR Spectrum of Compound 49a in CDCl<sub>3</sub>

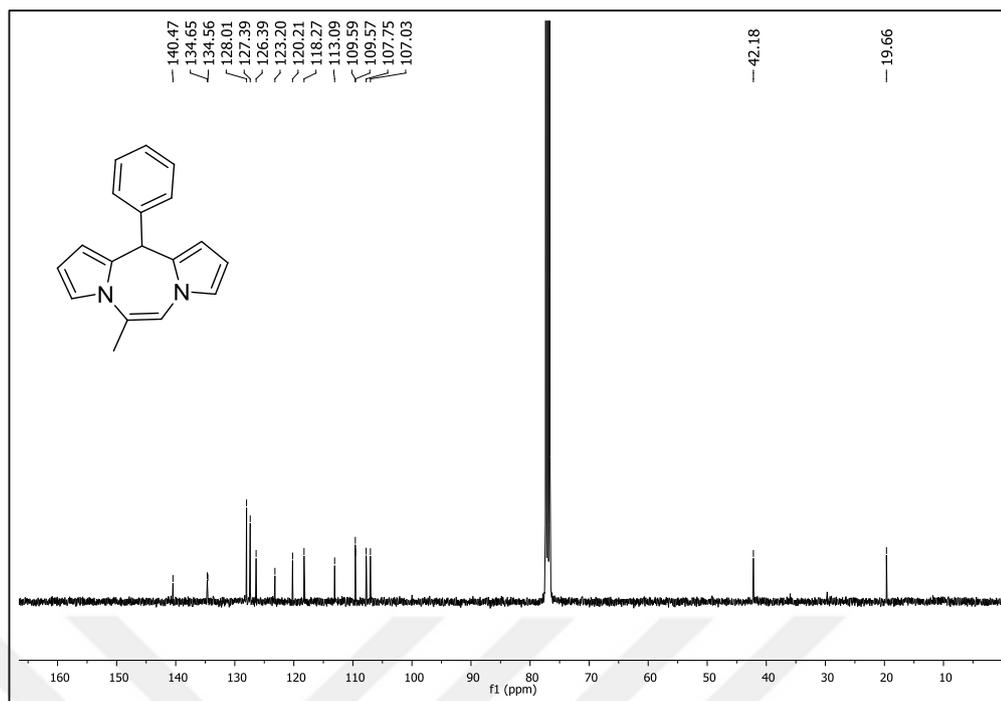


Figure 72 <sup>13</sup>C-NMR Spectrum of Compound 49a in CDCl<sub>3</sub>

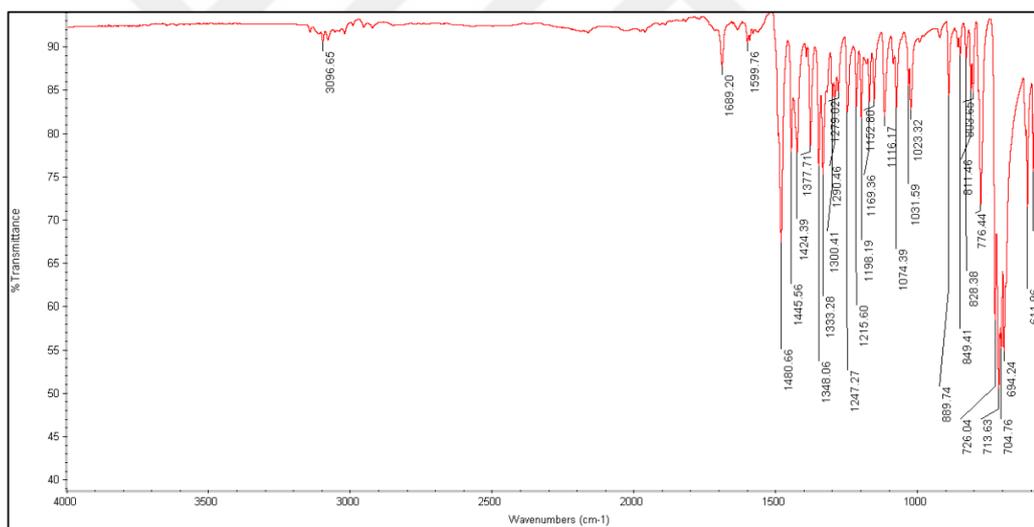
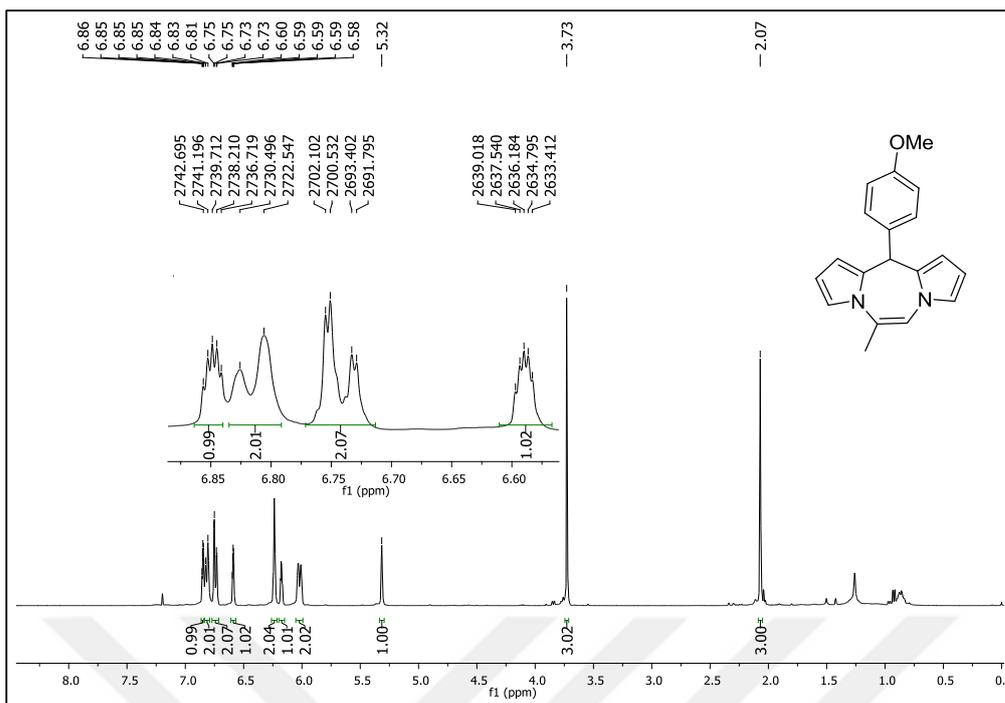
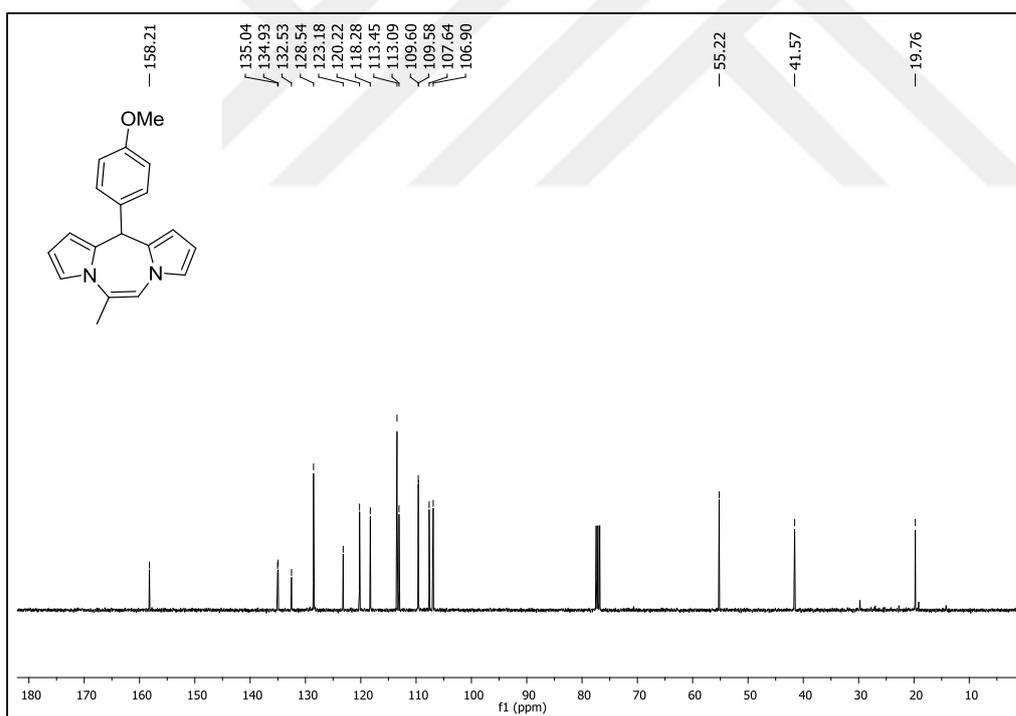


Figure 73 IR Spectrum of Compound 49a



**Figure 74**  $^1\text{H-NMR}$  Spectrum of Compound **49d** in  $\text{CDCl}_3$



**Figure 75**  $^{13}\text{C-NMR}$  Spectrum of Compound **49d** in  $\text{CDCl}_3$

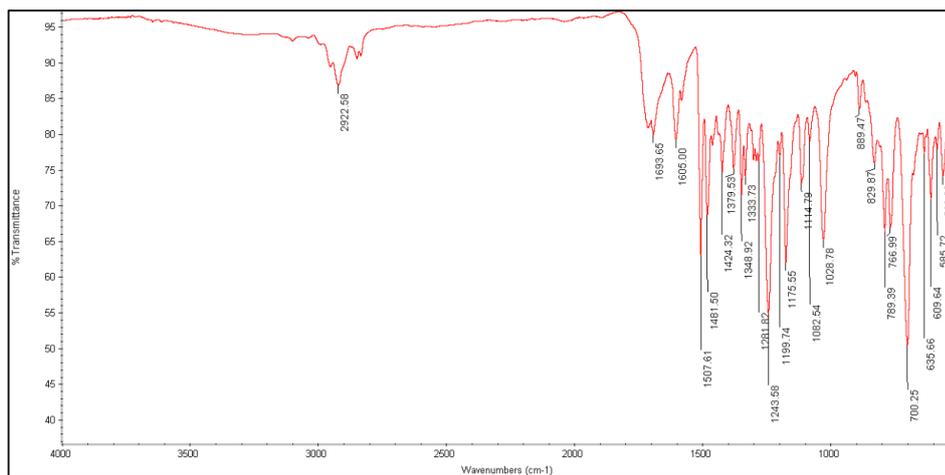


Figure 76 IR Spectrum of Compound 49d

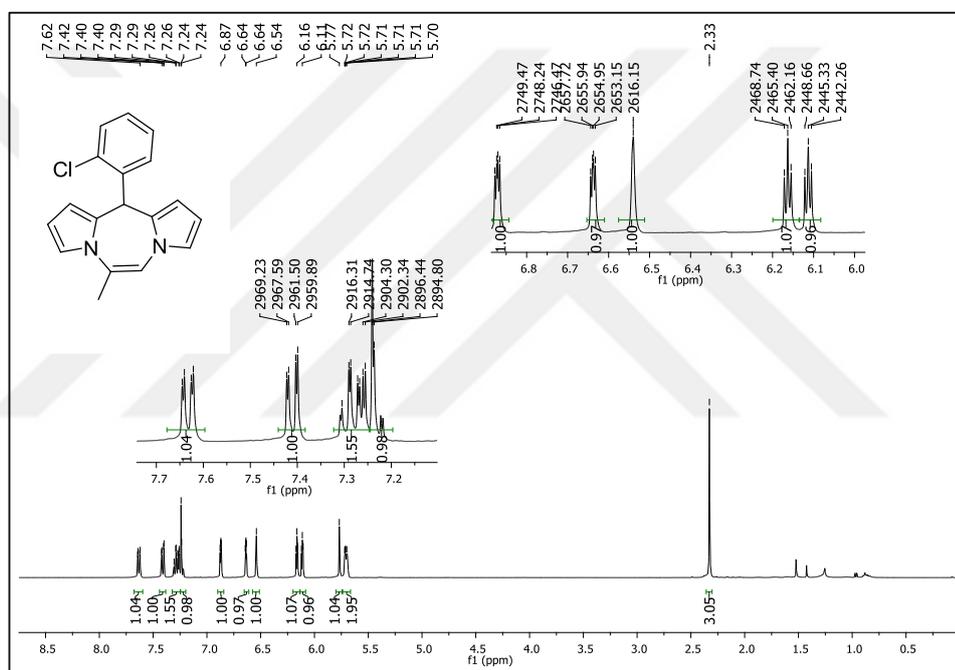


Figure 77 <sup>1</sup>H-NMR Spectrum of 49e in CDCl<sub>3</sub>

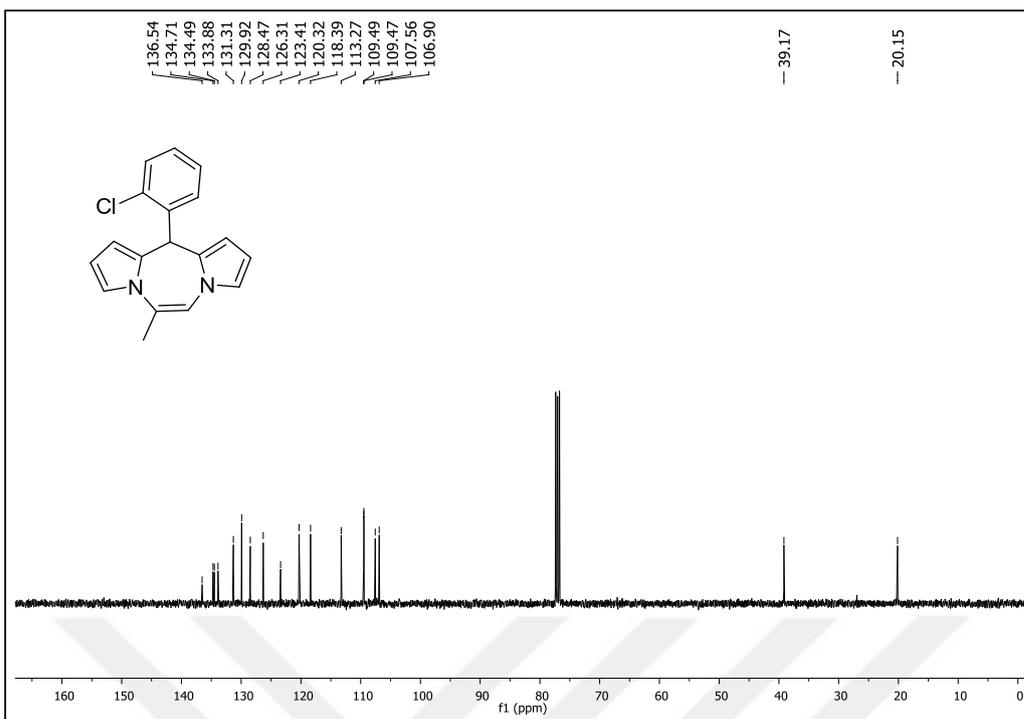


Figure 78 <sup>13</sup>C-NMR Spectrum of Compound 49e in CDCl<sub>3</sub>

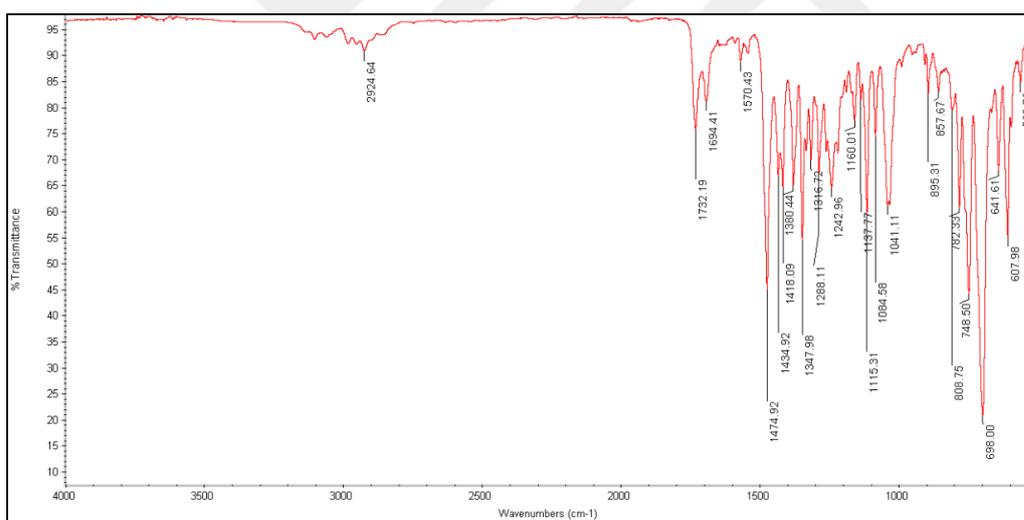


Figure 79 IR Spectrum of Compound 49e

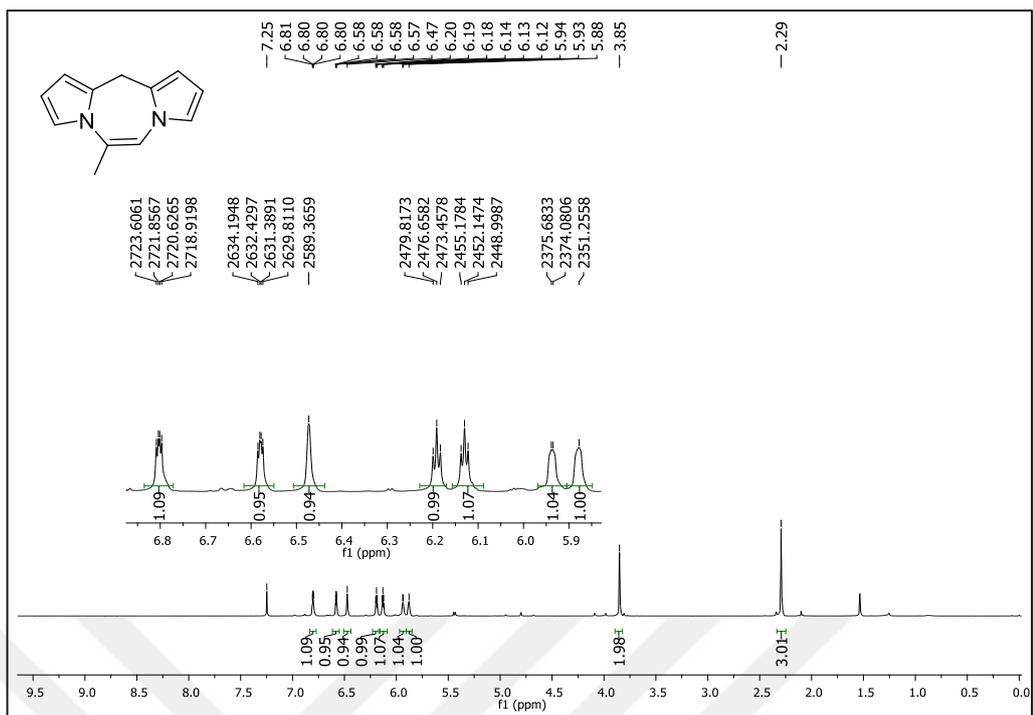


Figure 80 <sup>1</sup>H-NMR Spectrum of Compound 49g in CDCl<sub>3</sub>

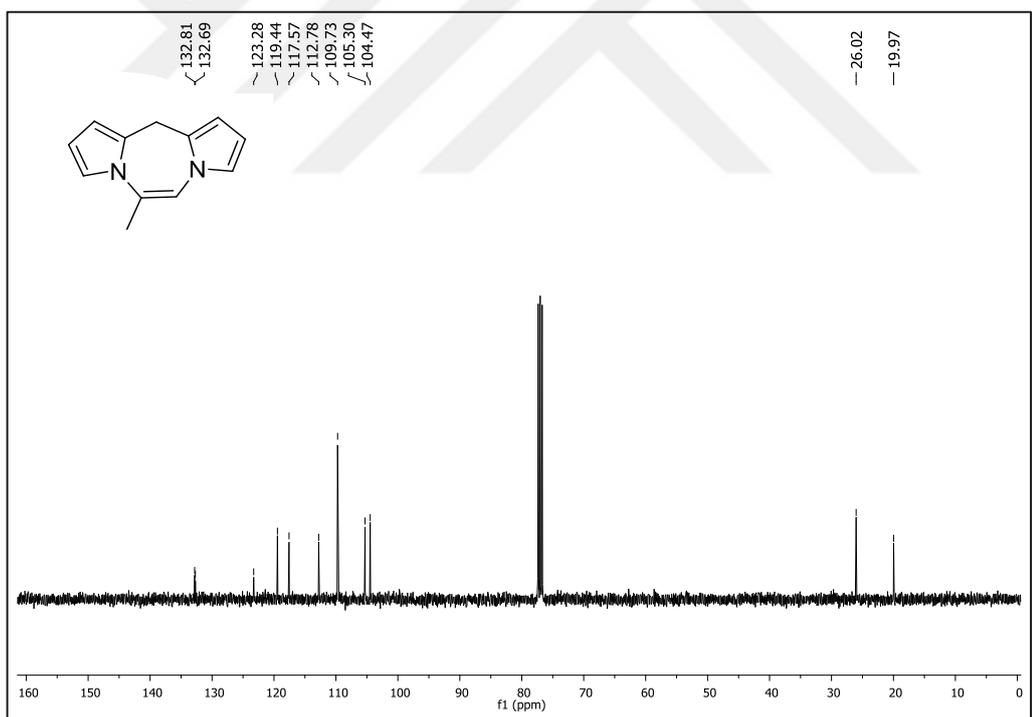


Figure 81 <sup>13</sup>C-NMR Spectrum of Compound 49g in CDCl<sub>3</sub>

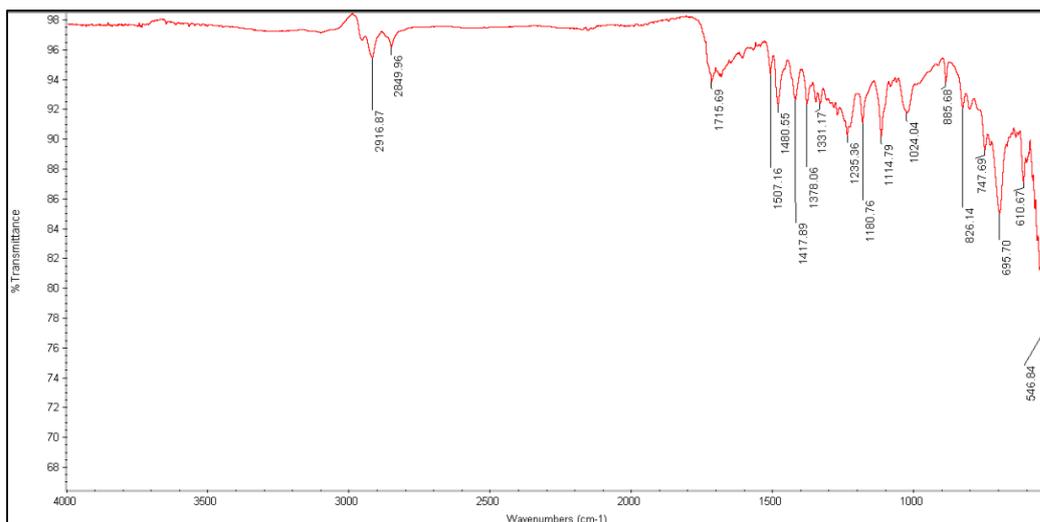


Figure 82 IR Spectrum of Compound 49g

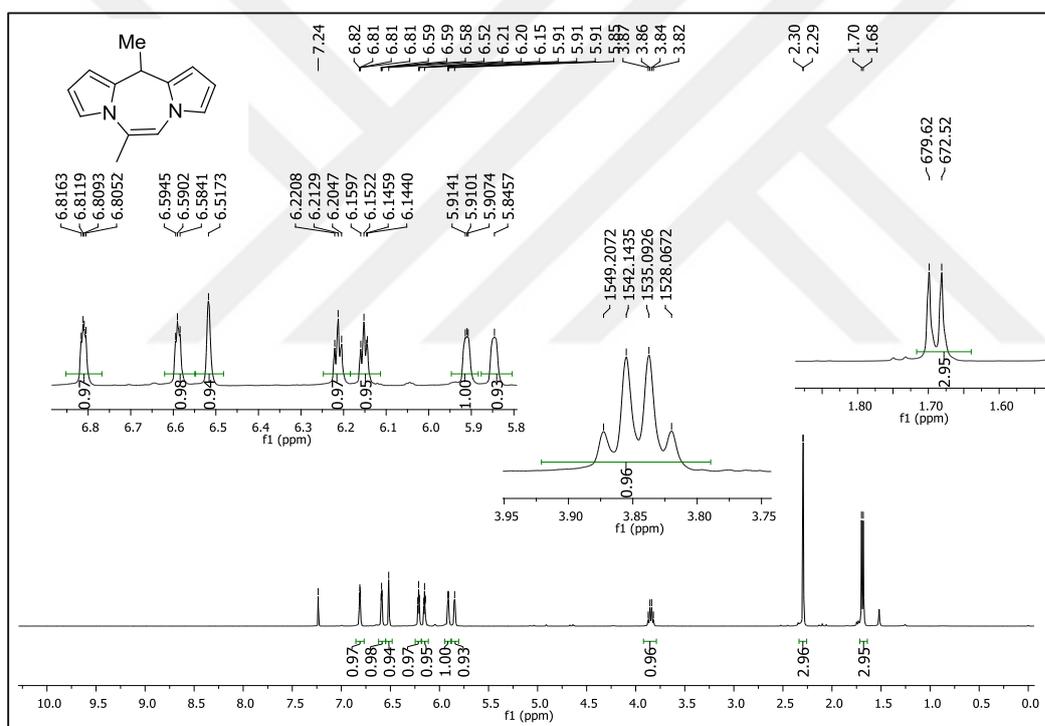
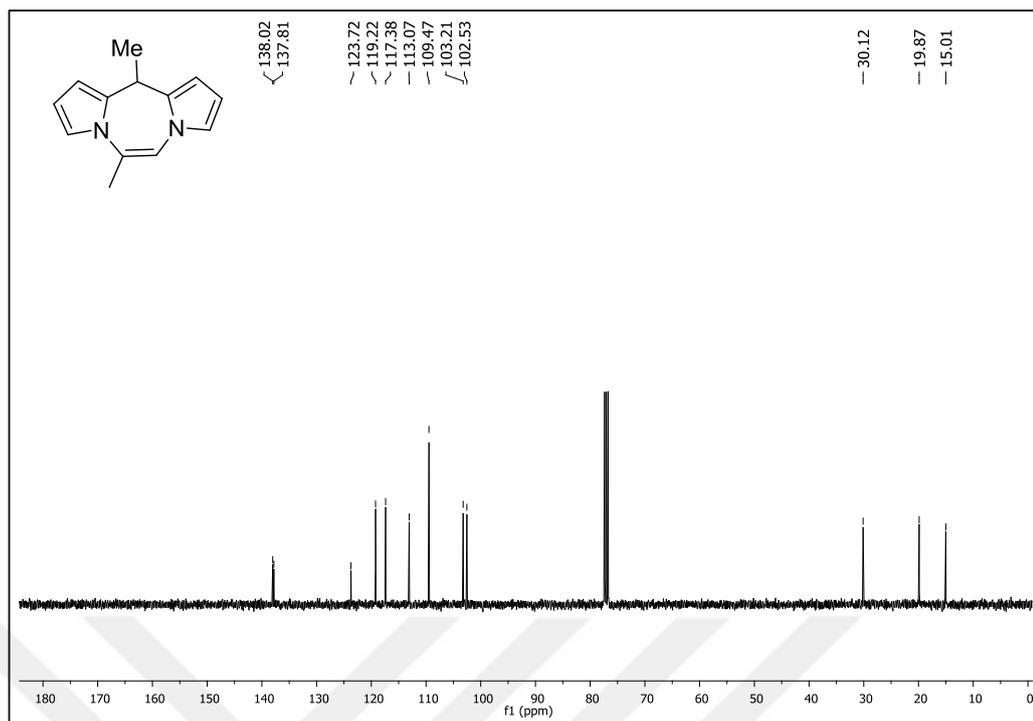
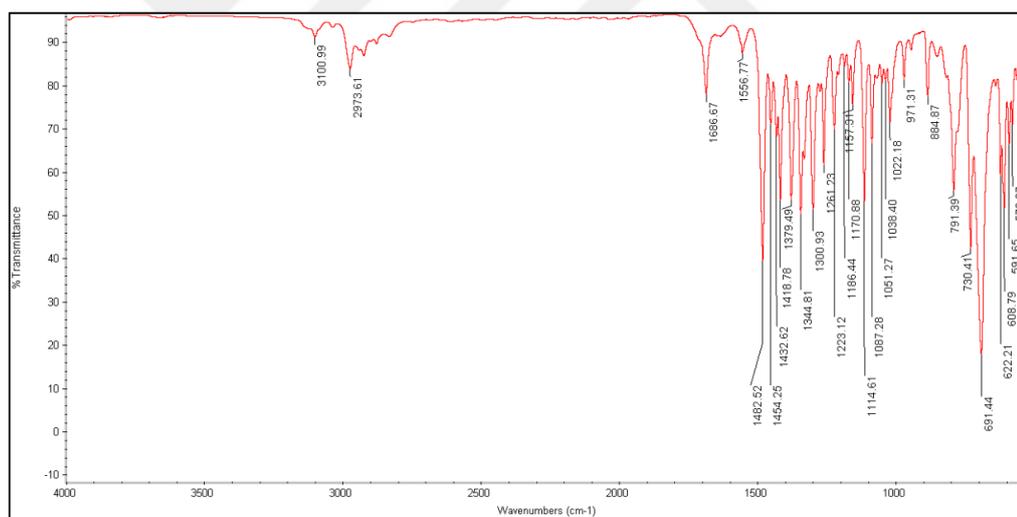


Figure 83 <sup>1</sup>H-NMR Spectrum of 49f in CDCl<sub>3</sub>



**Figure 84**  $^{13}\text{C-NMR}$  Spectrum of Compound **49f** in  $\text{CDCl}_3$



**Figure 85** IR Spectrum of Compound **49f**

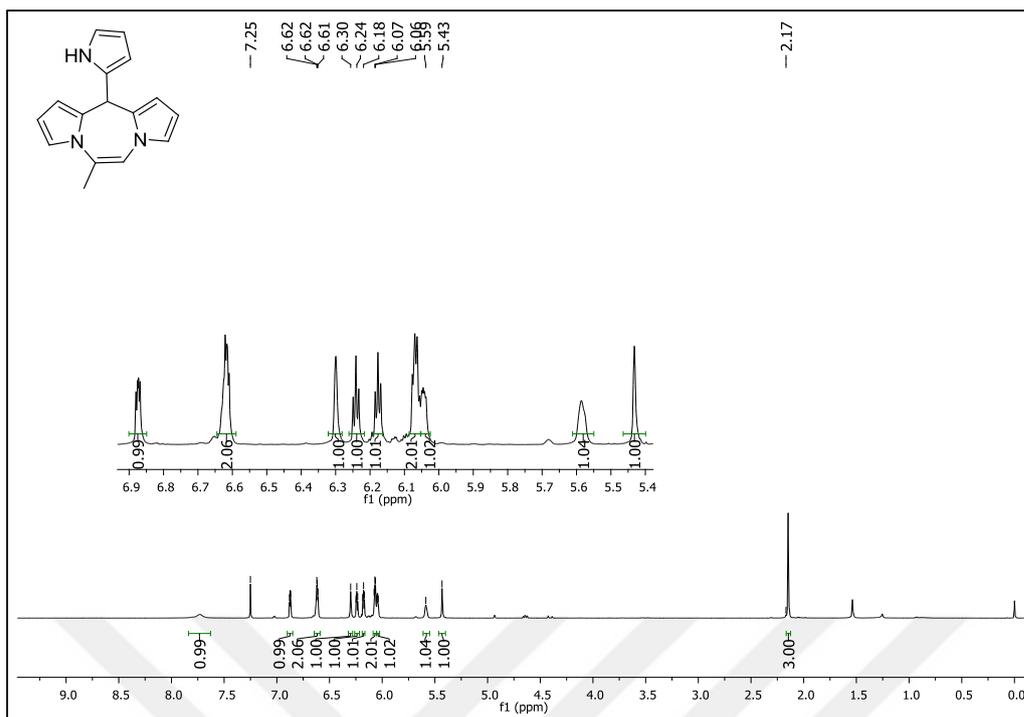


Figure 86 <sup>1</sup>H-NMR Spectrum of 49c in CDCl<sub>3</sub>

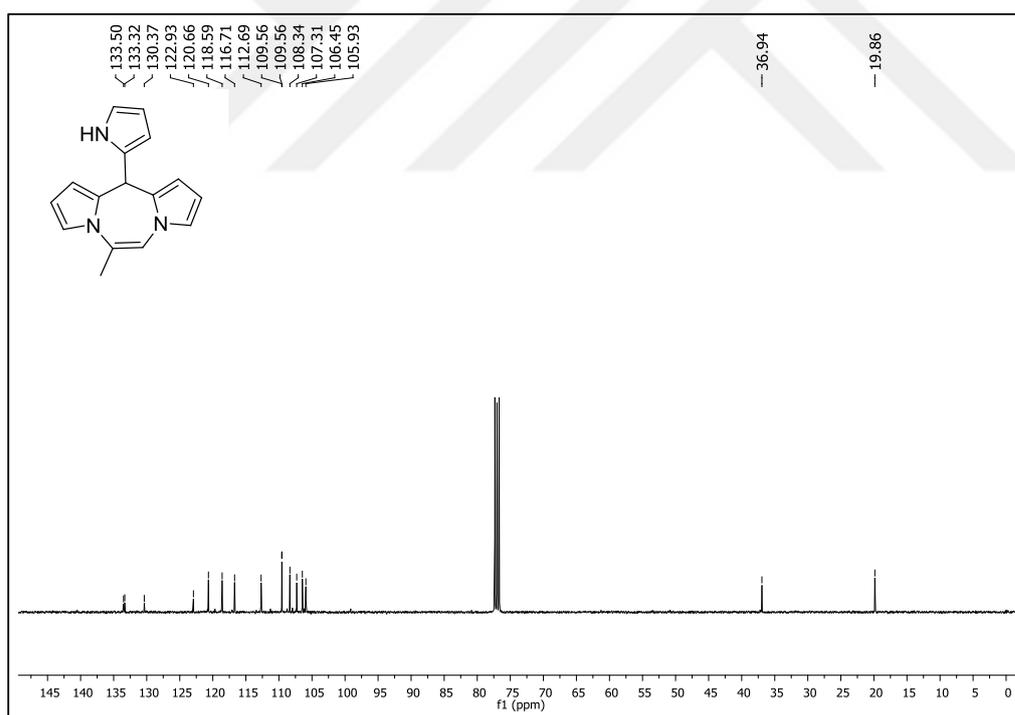
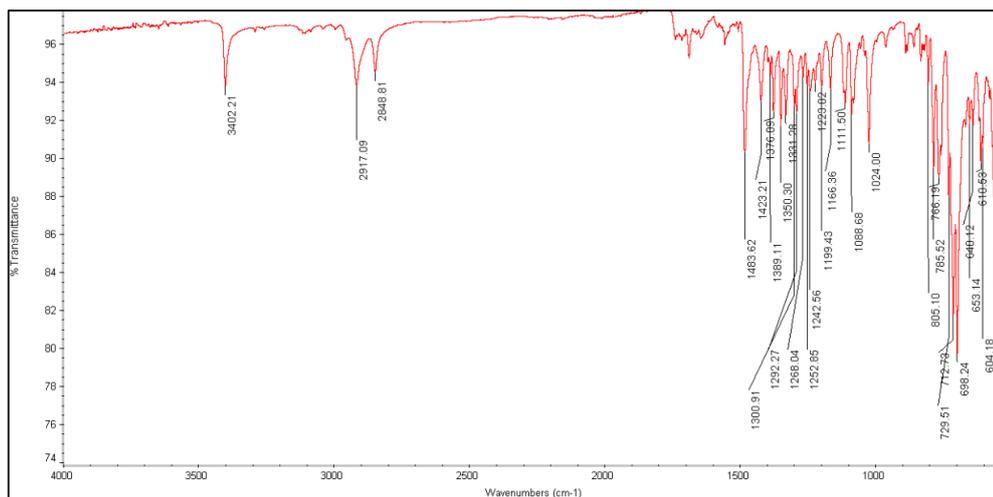
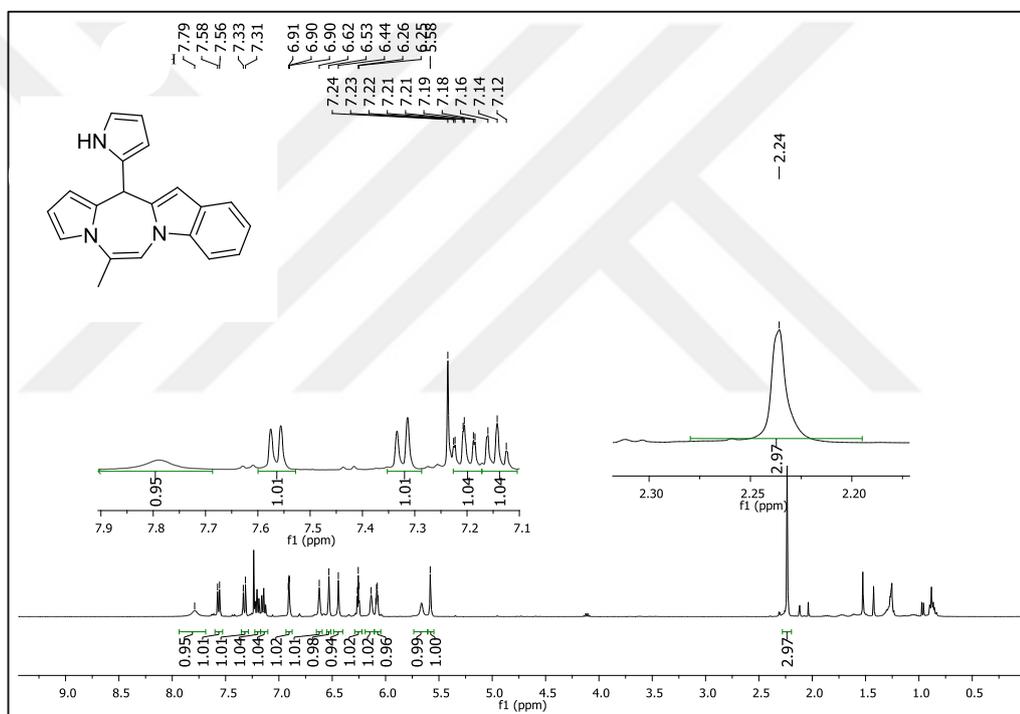


Figure 87 <sup>13</sup>C-NMR Spectrum of Compound 49c in CDCl<sub>3</sub>



**Figure 88** IR Spectrum of Compound **49c**



**Figure 89** <sup>1</sup>H-NMR Spectrum of **49b** in CDCl<sub>3</sub>

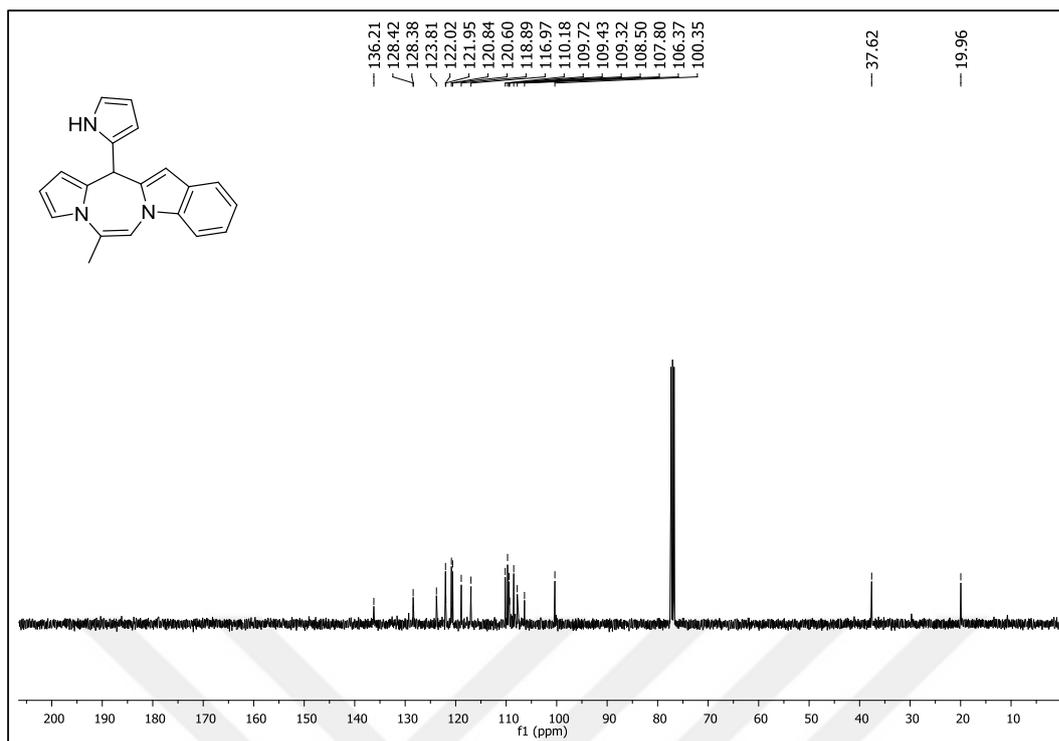


Figure 90 <sup>13</sup>C-NMR Spectrum of Compound 49b in CDCl<sub>3</sub>

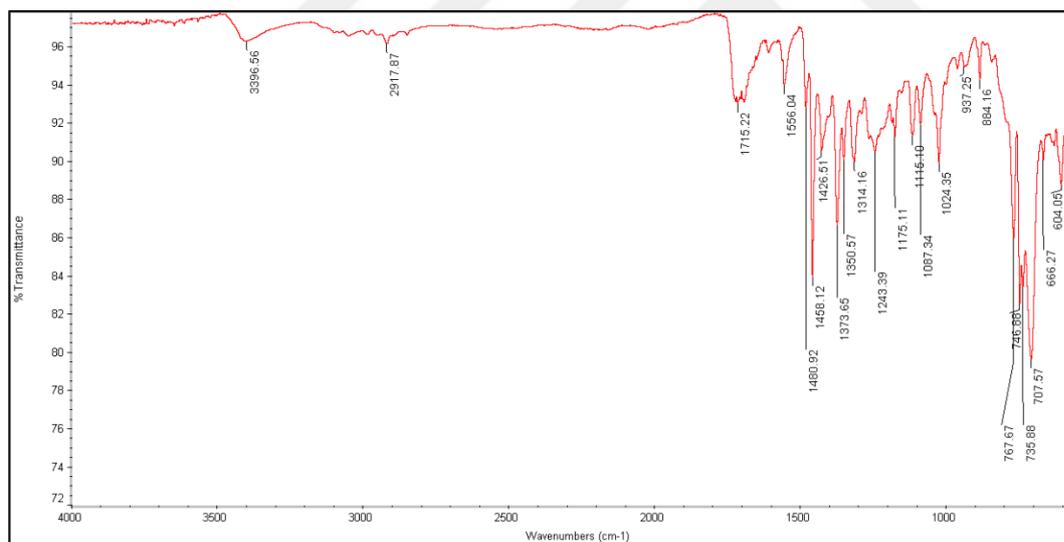


Figure 91 IR Spectrum of Compound 49b

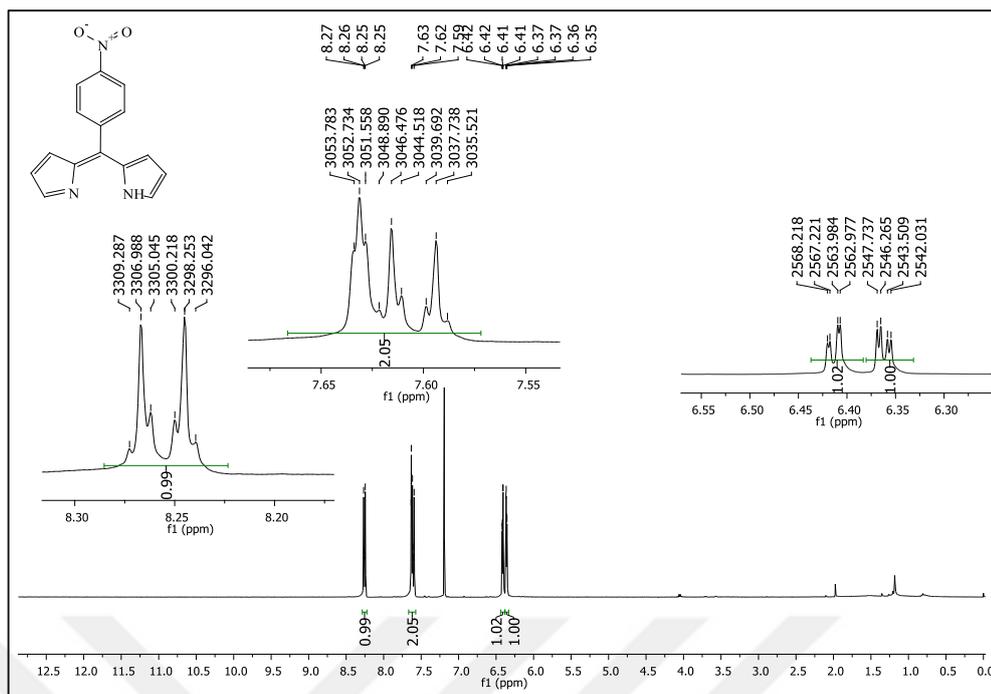


Figure 92 <sup>1</sup>H-NMR Spectrum of 57 in CDCl<sub>3</sub>

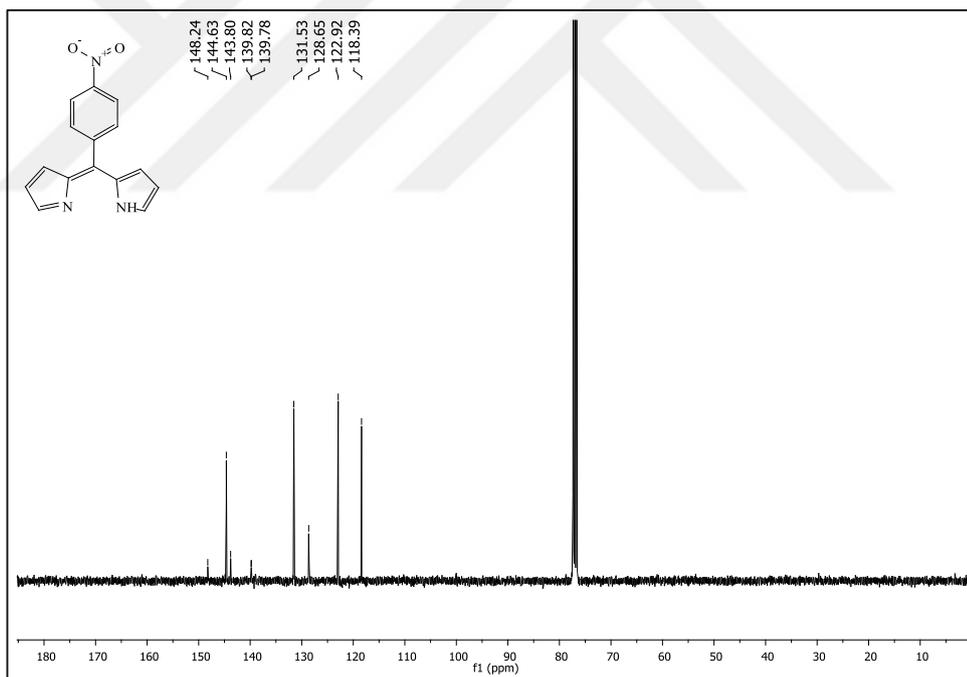
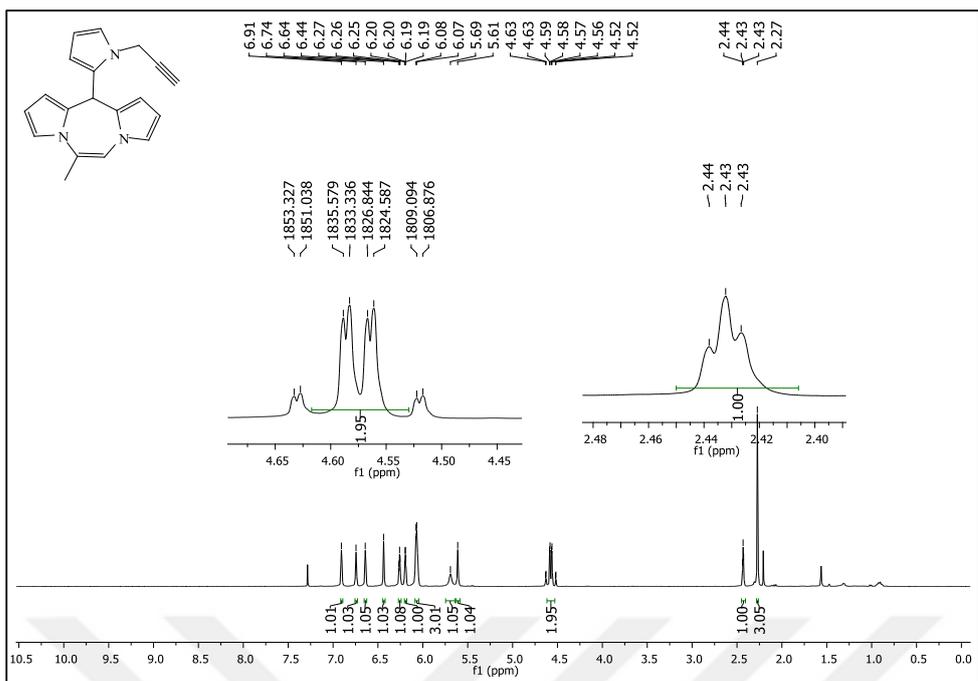
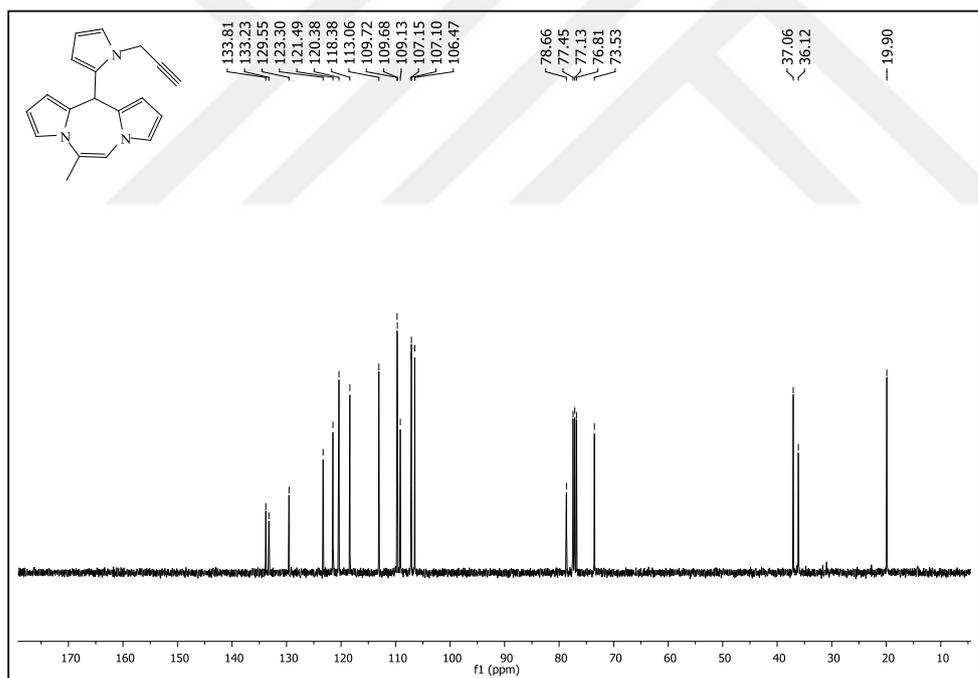


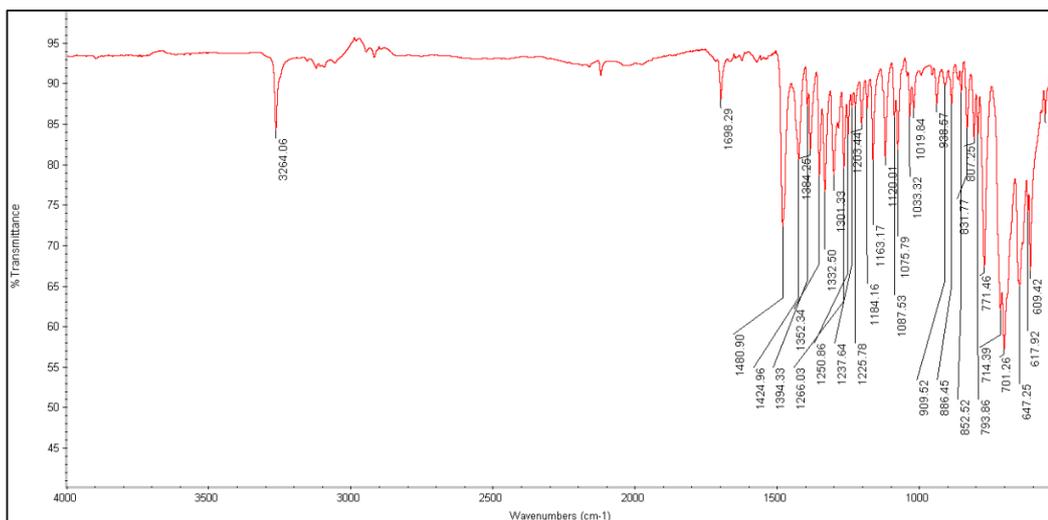
Figure 93 <sup>13</sup>C-NMR Spectrum of Compound 57 in CDCl<sub>3</sub>



**Figure 94** <sup>1</sup>H-NMR Spectrum of **60** in CDCl<sub>3</sub>



**Figure 95** <sup>13</sup>C-NMR Spectrum of Compound **60** in CDCl<sub>3</sub>



**Figure 96** IR Spectrum of Compound **60**

Cartesian Coordinates for the Optimized Structure **50a**

X Y Z

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6	-2.528104	-1.840017	1.083876
6	-1.494474	-2.416150	1.782231
6	-0.286418	-1.790324	1.350058
6	-0.612168	-0.843254	0.401511
7	-1.998510	-0.877657	0.240119
1	-3.593061	-2.012936	1.111052
1	-1.589726	-3.196256	2.524494
1	0.714728	-2.012440	1.689171
6	-2.739511	-0.080282	-0.659568
1	-2.231255	0.818776	-0.993327
6	-3.967374	-0.331008	-1.057152
6	-5.196974	-0.532079	-1.455637
1	-6.049340	-0.148440	-0.895996
1	-5.418803	-1.094266	-2.361732

6	0.271143	0.083744	-0.405493
1	-0.056982	0.013206	-1.454921
6	1.729052	-0.393901	-0.392595
6	2.181564	-1.274274	-1.384850
6	2.625432	0.017027	0.602641
6	3.498580	-1.739962	-1.382984
1	1.494290	-1.604658	-2.160557
6	3.942742	-0.450100	0.609754
1	2.289872	0.709175	1.369487
6	4.384289	-1.329416	-0.382603
1	3.831504	-2.420812	-2.161367
1	4.624584	-0.122803	1.389734
1	5.409505	-1.688287	-0.379036
6	0.126755	1.528715	0.020098
6	-0.441387	2.112196	1.137915
6	0.405307	3.767246	-0.149571
6	-0.266145	3.524964	1.030553
7	0.629890	2.552071	-0.758193
1	1.160709	2.420566	-1.605920
1	-0.930548	1.575507	1.938623
1	-0.600666	4.274229	1.734359
1	0.731678	4.689797	-0.606656