BASE-PROMOTED SYNTHESIS OF NEW DIAZEPINE DERIVATIVES VIA ALKYNE CYCLIZATION

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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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M.Sc., Department of Chemistry

Supervisor: Prof. Dr. Metin Balcı

June 2016, 102 pages

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, Dılgeş
Yüksek Lisans, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Balcı

Eylül 2015, 102 sayfa

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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To my beloved husband and my unborn son…

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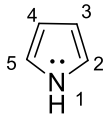
CHAPTER 1

INTRODUCTION

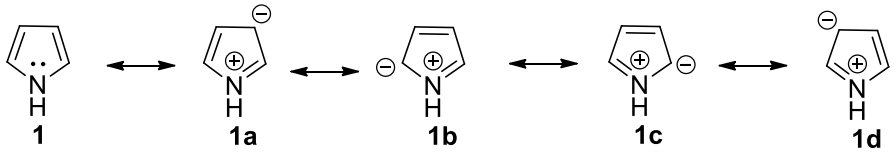
1.1 Pyrrole

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.[1]



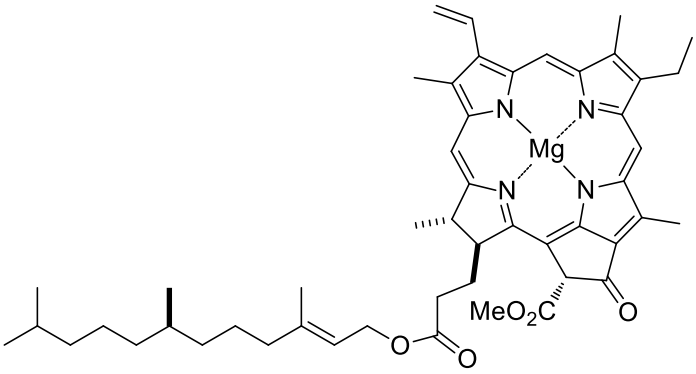
Pyrrole

Resonance structures of pyrrole are shown below (Scheme 1).[1]



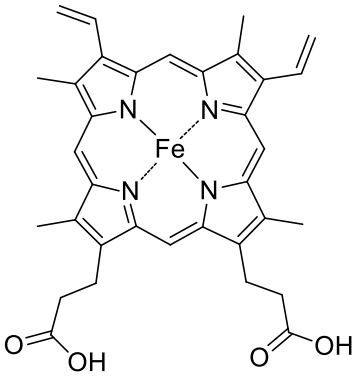
Scheme 1. Resonance structure of pyrrole

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



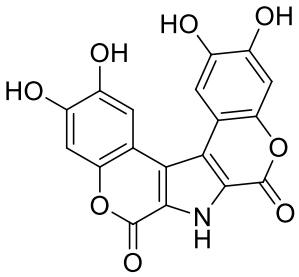
Chloropyll a

2



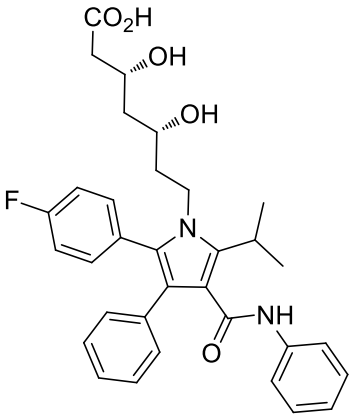
Heme

3



Ningalin A

4



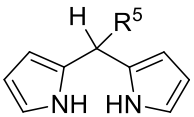
Atorvastatin

5

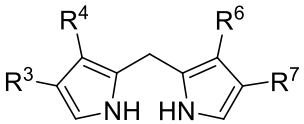
Atrovastatin (Lipitor) (**5**) is one of the example of pyrrole derived drugs and used to decrease cholesterol.[9]

1.2 Dipyrromethanes

Dipyrromethane is a heterocyclic compound in which two pyrroles are connected from the α-positions to a single sp^3 hybridized carbon atom. Dipyrromethane is called as β-substituted dipyrromethane if the beta position(s) of pyrroles are substituted. Whereas, when the beta position(s) of pyrrole is lack of any substituent, dipyrromethane is called as meso-substituted dipyrromethane (Scheme 2).[10]



meso-substituted dipyrromethane



β-substituted dipyrromethane

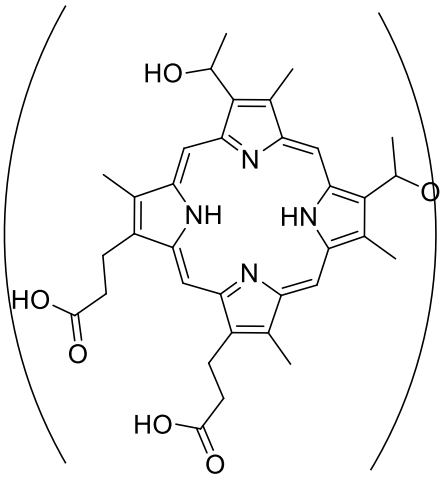
Scheme 2. Naming of dipyrromethanes

1.2.1. Importance of meso-substituted dipyrromethane derivatives

Dipyrromethanes substituted at C-5 position are significant initiator for the synthesis of meso-substituted porphyrins,[11] corroles and porphyrins.[12]

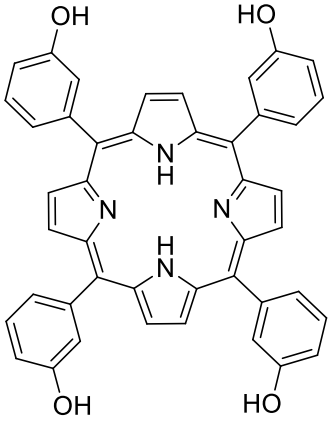
Meso-porphyrin derivatives have implementation in phototherapeutics,[13] biological processes,[14] optoelectronics,[15] catalysis,[16] and material chemistry.[17]

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



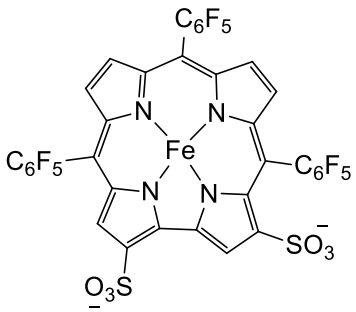
Photofrin

6



Foscan

7



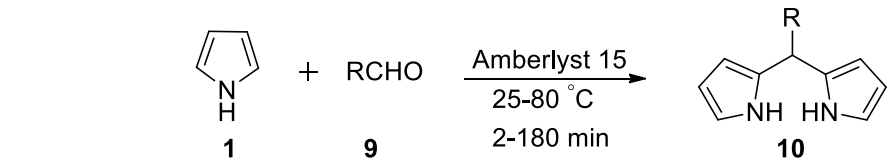
8

Scheme 3. Some dipyrromethane derivatives

1.2.2 Synthesis of dipyrromethanes

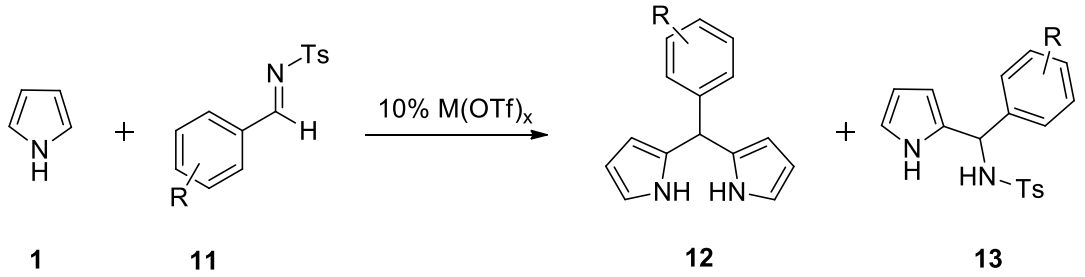
Lately, many procedure have been reported for the synthesis of dipyrromethanes.[20] Most of the procedure include the condensation of an aldehyde and pyrrole in the presence of several acids like BF_3•etherate, trifluoroacetic acid (TFA), propionic acid and *p*-toluenesulfonic acid. The purification of the dipyrromethanes is complicated because of oligomeric compounds which forms in the reaction media.[21]

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). [22]



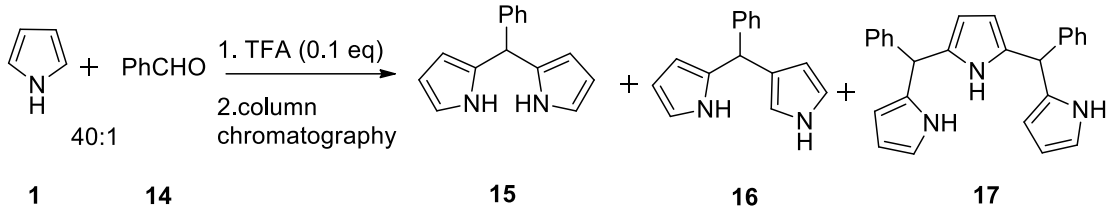
Scheme 4. Synthesis of dipyrromethanes starting from pyrrole and aldehydes

Temelli and Unaleroğlu developed a new synthetic method for the synthesis of dipyrromethanes substituted at C-5 position from the reaction of pyrrole and N-tosyl imine **11** in the presence of metal triflates (Scheme 5).[21]



Scheme 5. Synthesis of dipyrromethane by using metal triflate

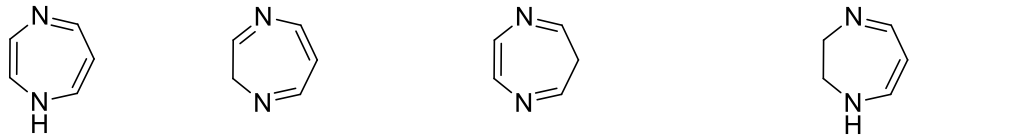
Littler and co-workers developed a condensation reaction of an aldehyde with neat excess pyrrole catalyzed by TFA, followed by bulb-to-bulb distillation to remove oligomeric material and recrystallization to remove the N-confused dipyrromethane (Scheme 6).[23]



Scheme 6. Synthesis of dipyrromethane by using TFA

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.

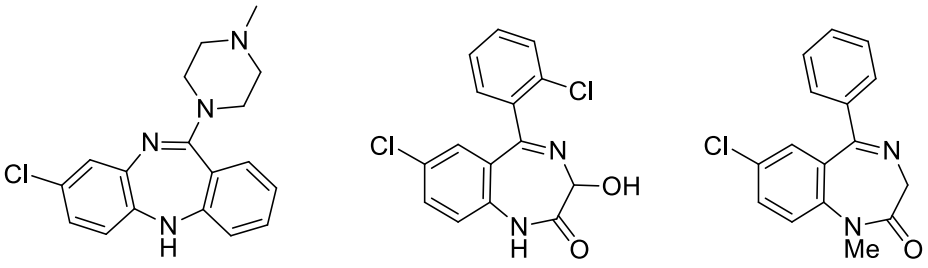


1*H*-1,4-Diazepine **18** | 2*H*-1,4-Diazepine **19** | 6*H*-1,4-Diazepine **20** | 1*H*-2,3-Dihydro-1,4-Diazepine **21**

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.[25] Lorazepam (**23**) is used to treat irritable bowel syndrome, epilepsy, insomnia and to control tention caused by alcohol withdrawal. The compund causes slowing activity in the brain and allow for relaxation.[26] Diazepam (**24**) is used to treat anxiety, acute alcohol withdrawal and seizures. It also used to relieve muscle spasm (Scheme 7).[27]



Clozapine **22** | Lorazepam **23** | Diazepam **24**

Scheme 7. Some diazepine drugs

1.4. Base supported alkyne cylization 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.

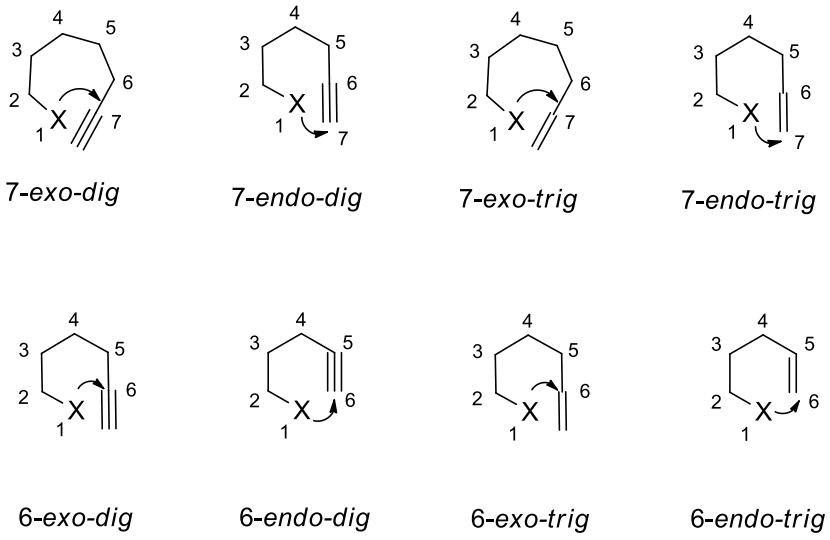
Particularly, forming a nitrogen functionality-alkyne bond via metal-free intramolecular cyclization is a precious synthetic strategy.

It should be mentioned that a compact set of standarts, known as 'the Baldwin rules', has been proven to be a useful tool for assessment the feasibility of ring closure reactions.[28] Baldwin identified the cyclization processes in terms of three factors:

(1) the ring size being formed (a numerical prefix);

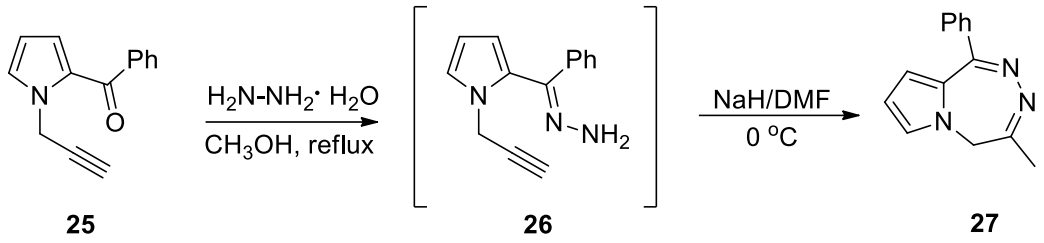
(2) the geometry of carbon atom undergoing the ring-forming reaction (sp = diagonal, sp^2 = trigonal, and sp^3 = tetrahedral);

(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).[29] (Scheme 8)



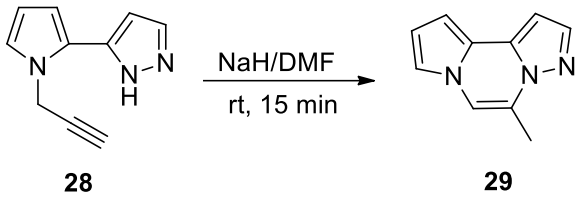
Scheme 8. Patterns of ring closure for 6- and 7-membered rings

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



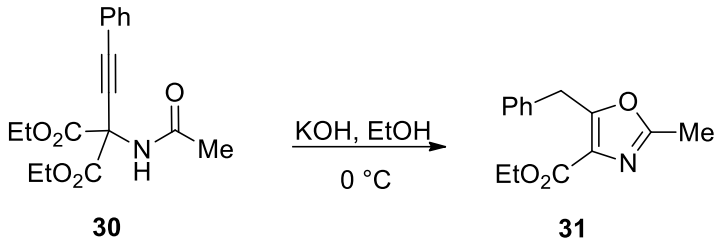
Scheme 9. Metal-free 7-*exo*-dig cyclization reaction of product **25**

Basceken and Balci[31] 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**.[32] (Scheme 11).

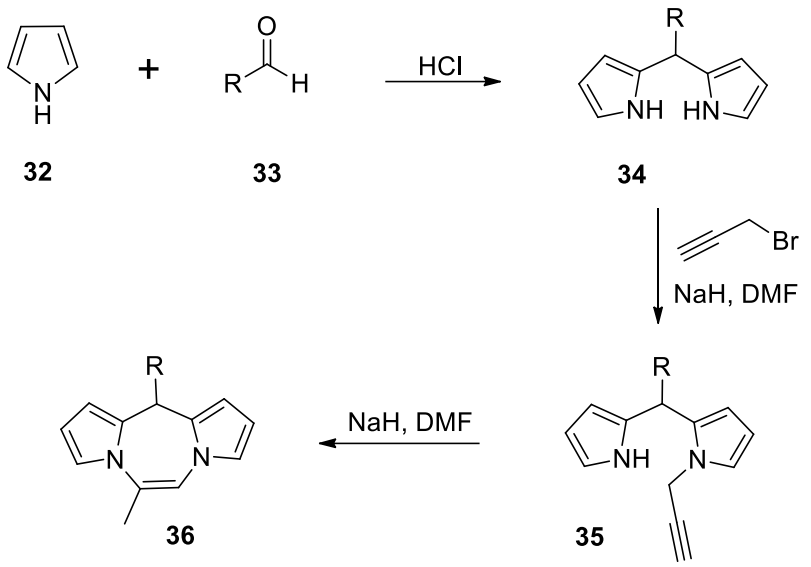


Scheme 11. Cycloisomerization of propargylamides **30**

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).



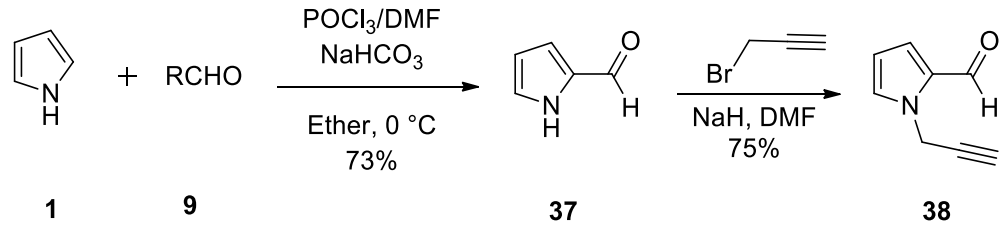
Scheme 12. Synthesis of diazepines **36**

CHAPTER 2

RESULTS AND DISCUSSION

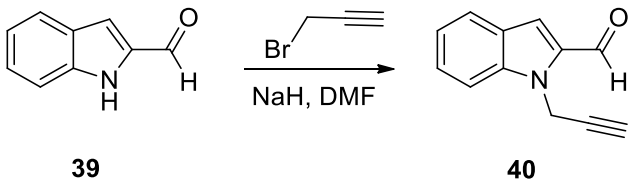
2.1. Synthesis of compounds 38 and 40

Firstly, Vilsmeier Haack reaction[33] was used to get pyrrole carbaldehyde **37**. Pyrrole (**1**) was reacted with $POCl_3$ and DMF in dry ether at 0 °C. In order to get basic medium, the solution of $NaHCO_3$ 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). [34, 35]



Scheme 13. Synthesis of compound **38**

Structure **40** was synthesized in 97% yield from the reaction of ındolecarbaldehyde **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**)**.[36]

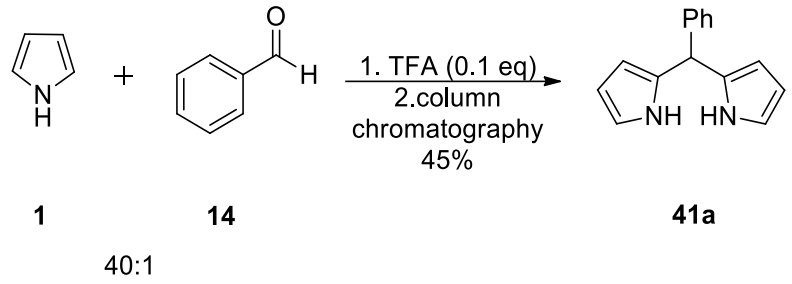


Scheme 14. Synthesis of structure **40**

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

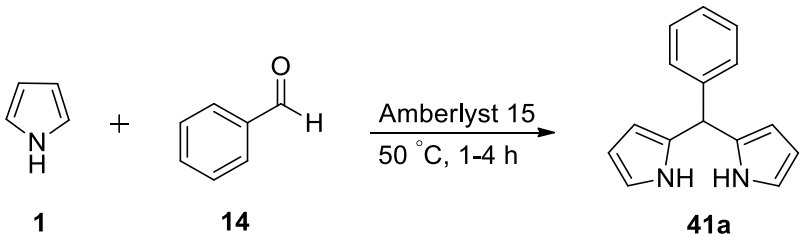
For the synthesis of 2-[phenyl(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41a**), several methods were applied and the most appropriate one was modified and used for the synthesis of other derivatives **41b-i**.

According to the first procedure[24], 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

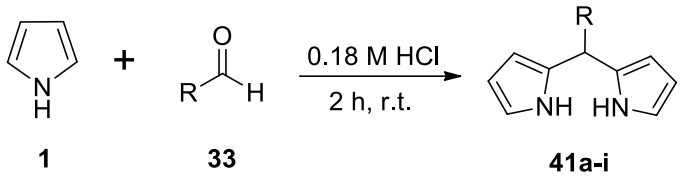
As reported by second procedure, mixing Amberlyst 15 ion exchange resin with pyrrole and benzaldehyde resulted in the formation of 2-[phenyl(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (**41a**) in the absence of solvent in 30% yield after 1 hour and in 35% yield after 4 hours (Scheme 14).[22] Due to low efficiency,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



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

The most appropriate procedure[21] was applied for the synthesis of all starting compounds (**41a-i**) in high yields. The procedure published by Temelli and Unaleroglu[21] 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).



1 **33** **41a-i**

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 = $-CH_3$, 62%
g R = -H, 69%
h R = -*o*-NO_2, 79%
i R = -*p*-NO_2, 81%

Scheme 17. Synthesis of dipyrromethanes by using HCl

The characterization of compounds **41a-i** was done by using ^{1}H-NMR and ^{13}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).

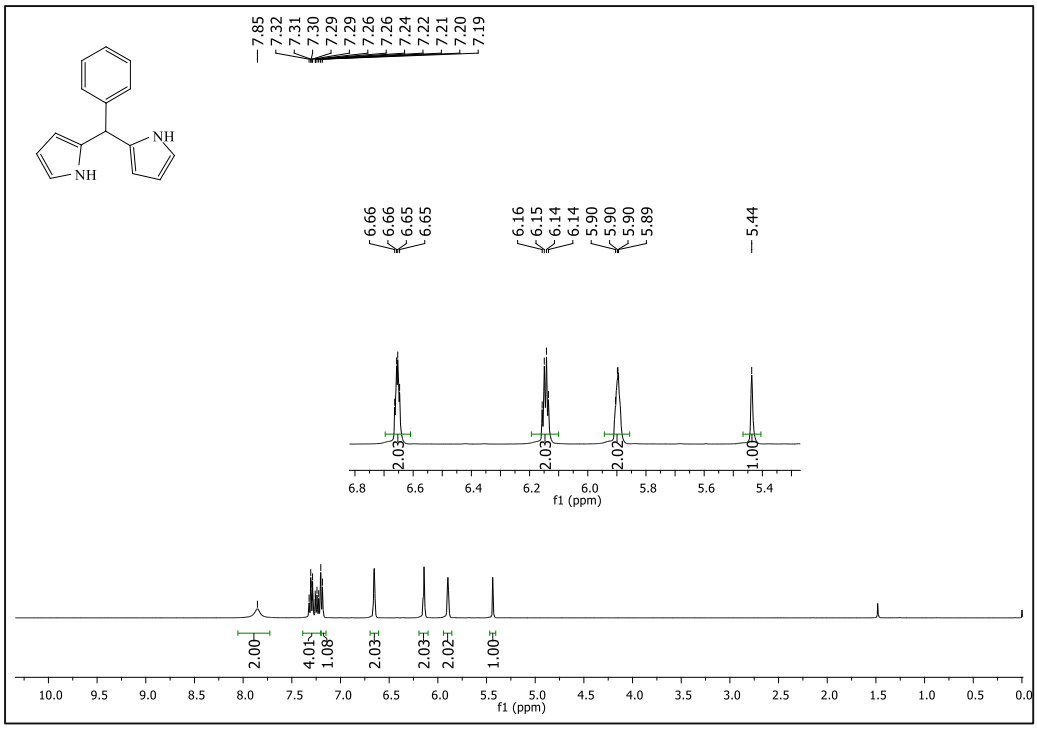
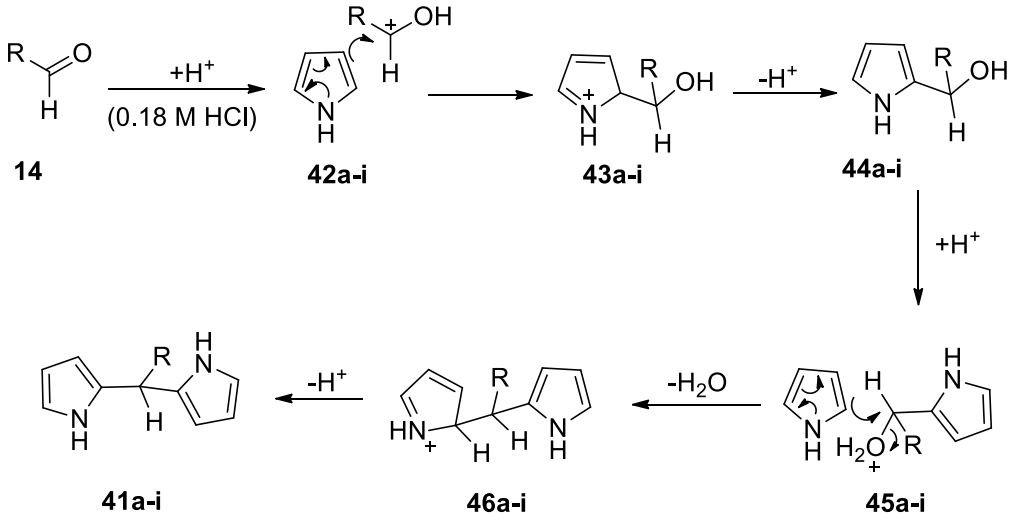


Figure 1: ^{1}H-NMR Spectrum of compound **41a** in $CDCl_3$

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

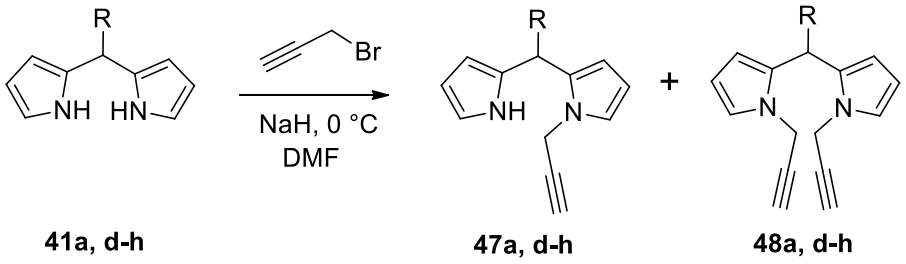
Formation of the products **41a-i** can be visualized through the mechanism proposed in Scheme 18. Thus, initial reaction of pyrrole with carbonyl substrate, activated through protonation by HCl, leads to the adduct **44a-i** obtained from initially formed **43a-i**. Similar nucleophilic attack of the 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

2.4. Propargylation reaction of starting materials 41a, d-h

Propargylation reaction of starting materials was required for the synthesis of **47a** and **47d-h** which are key compounds for the final cyclization reactions (Scheme 19). According to the literature procedure,[34] in the first try, **41a** was reacted first with NaH in the presence of DMF and then a solution of propargyl bromide in dry DMF was added dropwise to the reaction media at 0 °C to obtain **47a** and **48a**. Because of the fact that, the yield of **47a** (16%) was very low compared to the yield of **48a** (45%), an alternative procedure was applied to increase the yields of desired mono-propargylated compounds **47a, d-h**. According to the new procedure, after addition of propargyl bromide in dry DMF to the reaction mixture, NaH was added piecewise to the reaction media. As a result, yields of **47a** was increased enormously.

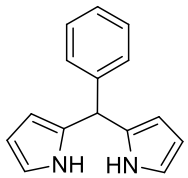
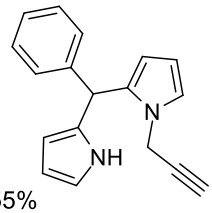
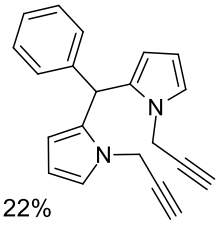
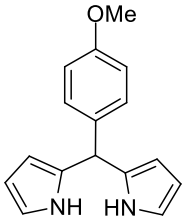
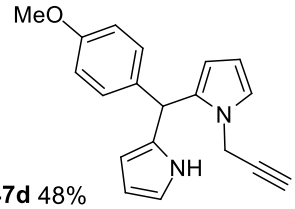
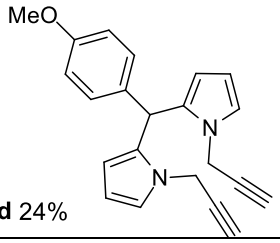
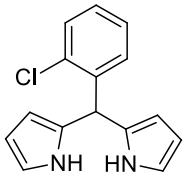
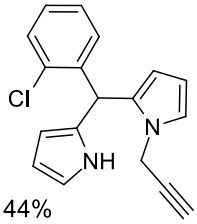
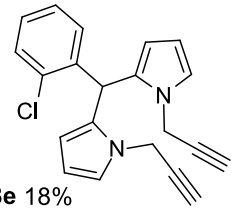
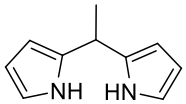
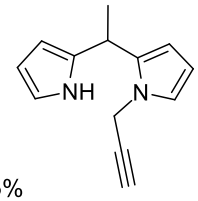
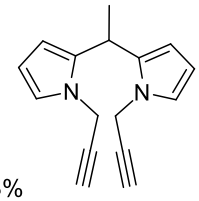
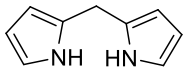
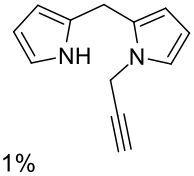
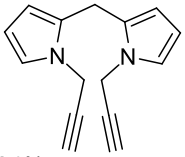
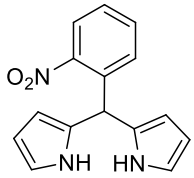
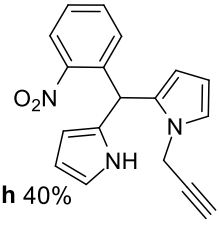
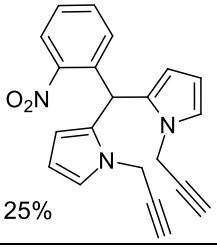


41a, d-h **47a, d-h** **48a, d-h**

a R = -Ph
d R = -*p*-MeOPh
e R = -*o*-ClPh
f R = $-CH_3$
g R = -H
h R = -*o*-NO_2

Scheme 19. Propargylation reaction of dipyrromethane derivatives

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

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

Characterization of compound **47a** and **48a** was achieved by using ^{1}H-NMR and ^{13}C-NMR spectra. In the ^{1}H-NMR spectrum of compound **47a** the NH proton of pyrrole unit resonates at 7.91 ppm as a broad singlet and the terminal alkyne proton resonates at 2.36 ppm as triplet. This terminal alkyne proton can couple with CH_2 proton with a coupling constant of J = 2.5 Hz. Also, CH_2 protons appear as a doublet of doublets (J = 1.6 Hz and J = 2.5 Hz) at 4.39 ppm as shown in (Figure 2).

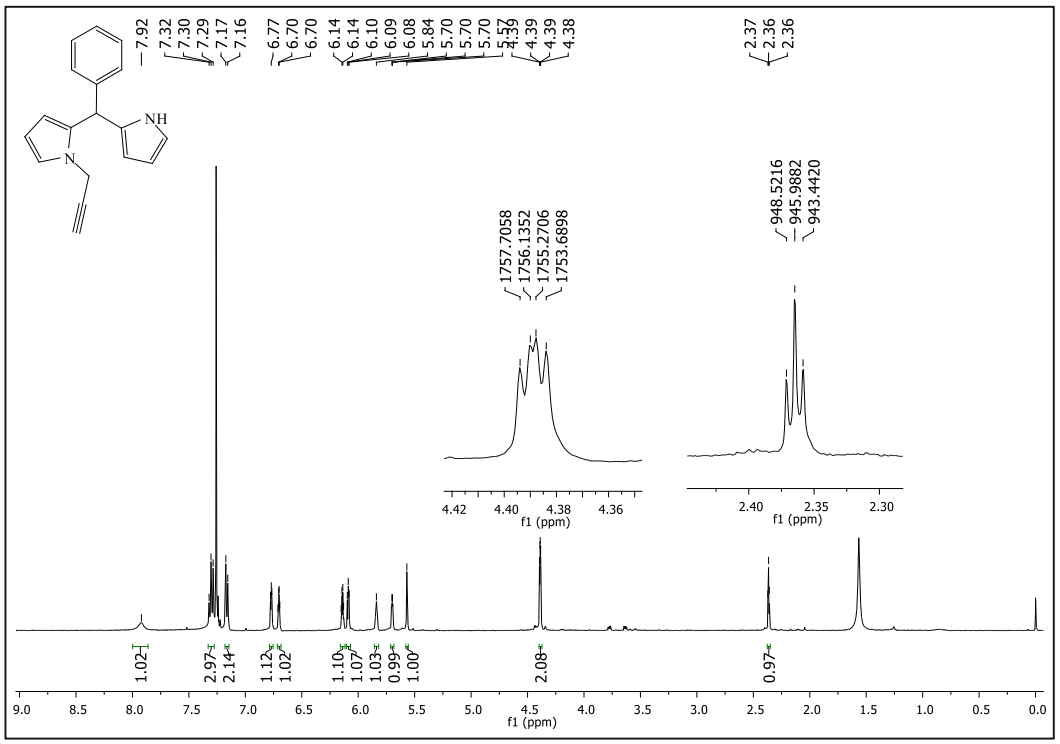


Figure 2: ^{1}H-NMR Spectrum of compound **47a** in $CDCl_3$

As one can see from the Figure 3, in the NMR spectrum of **48a** there are no proton resonance arising from the NH-protons clearly indicating the attachment of two propargyl groups to the nitrogen atoms. Furthermore, the observed symmetry in the ^{1}H- as well as in the ^{13}C-NMR spectra also supports the symmetrical structure. The methylene protons are diastereotopic and they give rise to an AB-system with further splitting with the alkyne proton (^{4}J = 2.5 Hz). A-part of AB-system resonates at 4.36 – 4.35 ppm, whereas the B-part of AB-system appear at 4.32 – 4.27 ppm. The main coupling of the AB-system arising from the coupling of diastereotopic protons was measured as J = 14.0 Hz which is in the expected range. The high field signal at 2.33

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

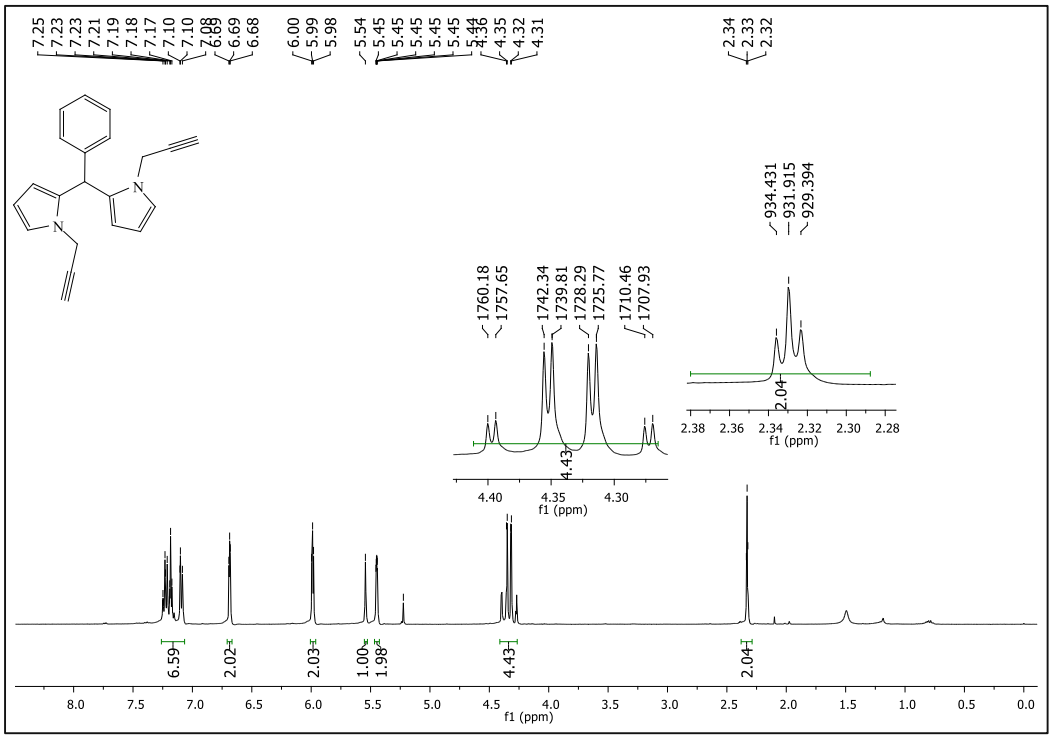
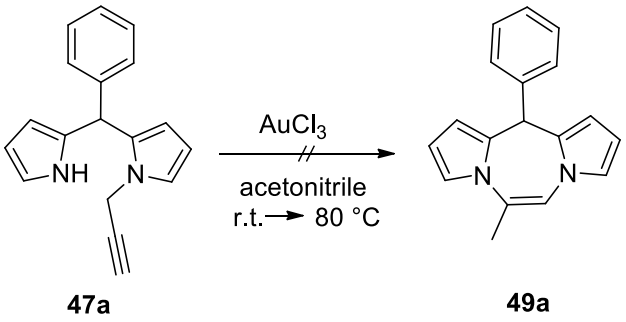


Figure 3: ^{1}H-NMR Spectrum of compound **48a** in $CDCl_3$

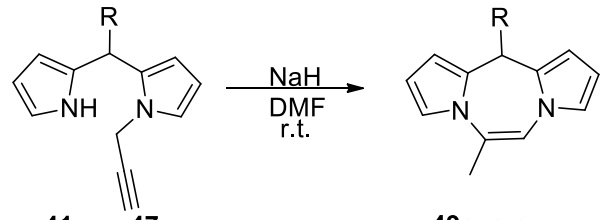
2.5. Cyclization reaction of mono-propargylated compound 47a

Reaction of mono-propargylated compounds **47a** with $AuCl_3$ 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 $AuCl_3$

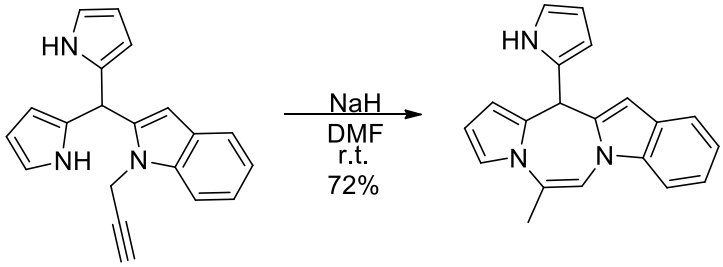
On the other hand, the intramolecular cyclization reactions of compounds **47a, d-g** and **41b-c** with NaH in DMF at room temperature afforded diazepine derivatives **49a-g** in high yields (Scheme 21).



41a or 47c-g

49a, c-g

	R	Yields
a	-Ph	76%
c	-pyrrole	61%
d	-*p*-MeOPh	87%
e	-*o*-ClPh	61%
f	-CH_3	85%
g	-H	81%

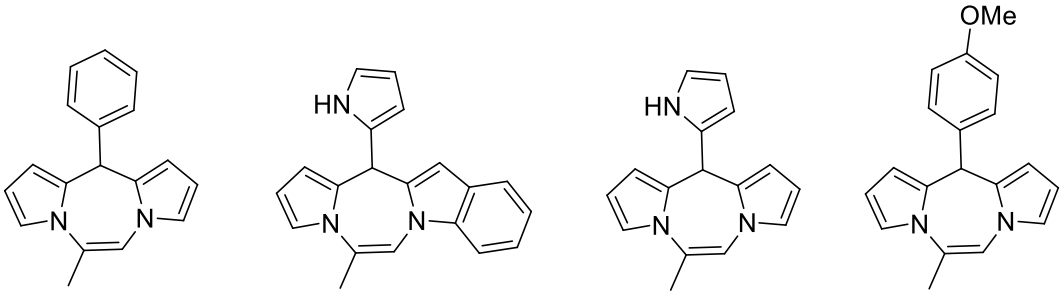


41b

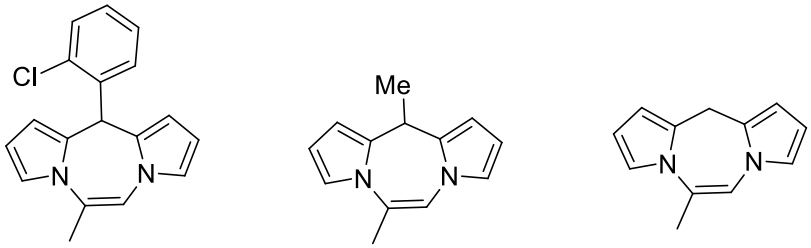
49b

Scheme 21. Cyclization reaction by using NaH

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



49a 49b 49c 49d

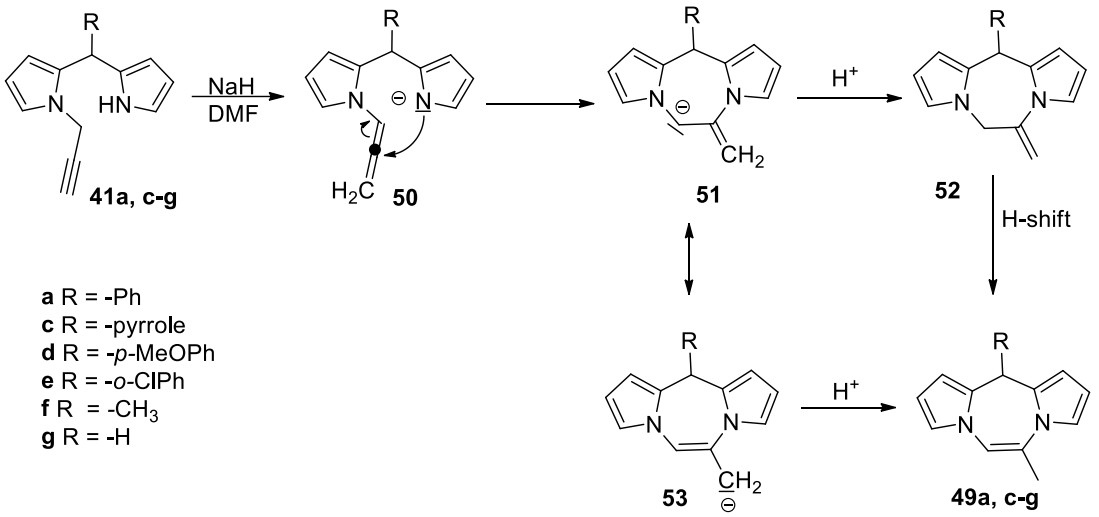


49e 49f 49g

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 ^{1}H-NMR spectrum of compound **41c**, CH_2 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_2 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 ^{13}C-NMR spectrum. (Figure 5).

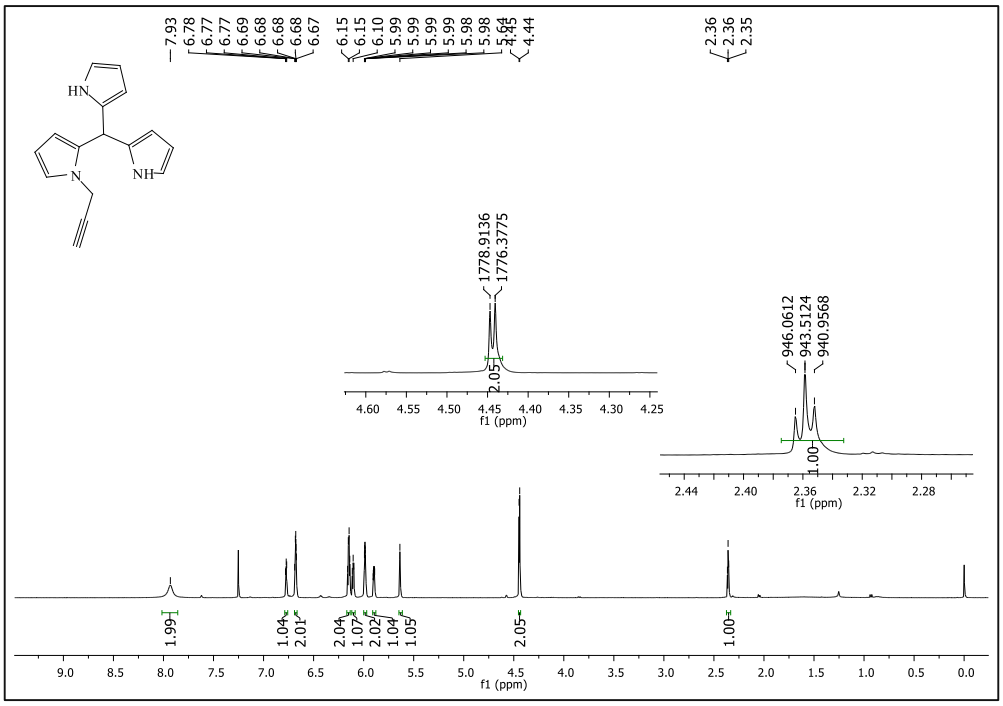


Figure 4: ^{1}H-NMR Spectrum of compound **41c** in $CDCl_3$

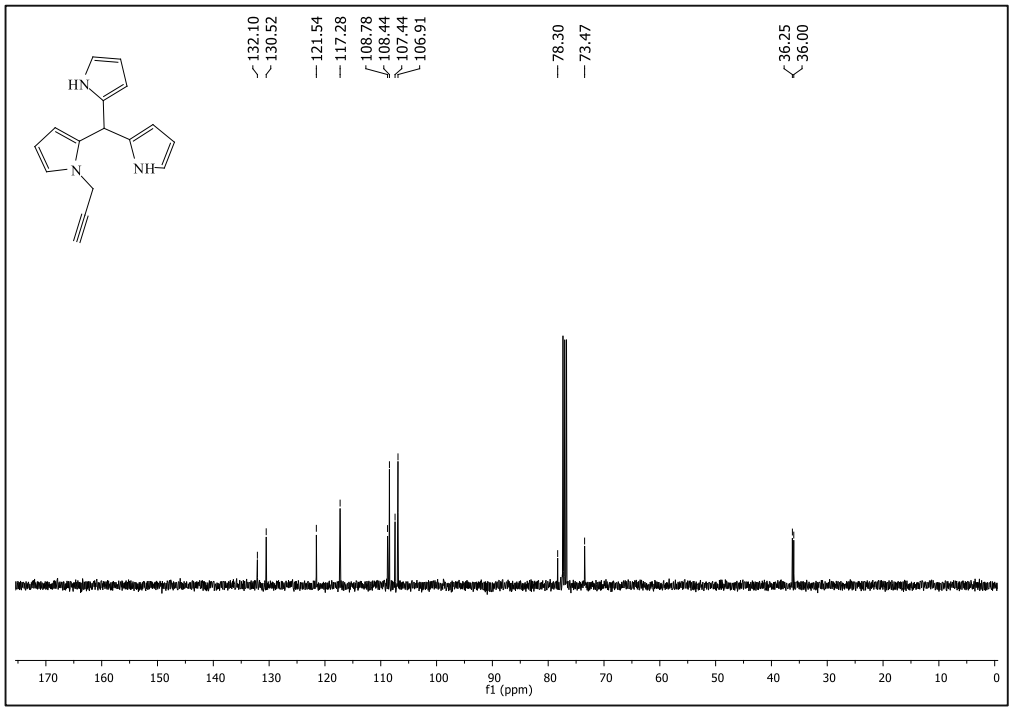


Figure 5: ^{13}C-NMR Spectrum of compound **41c** in $CDCl_3$

The 1D and 2D NMR (HSQC, COSY, HMBC) spectra were used for characterization of cyclization product **49c**. When the ^{1}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_3 protons in the ^{1}H-NMR spectrum of **49c** clearly indicated the cyclization reaction (Figure 6). Moreover, the ^{13}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_3 protons observed in the HMBC spectrum.

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

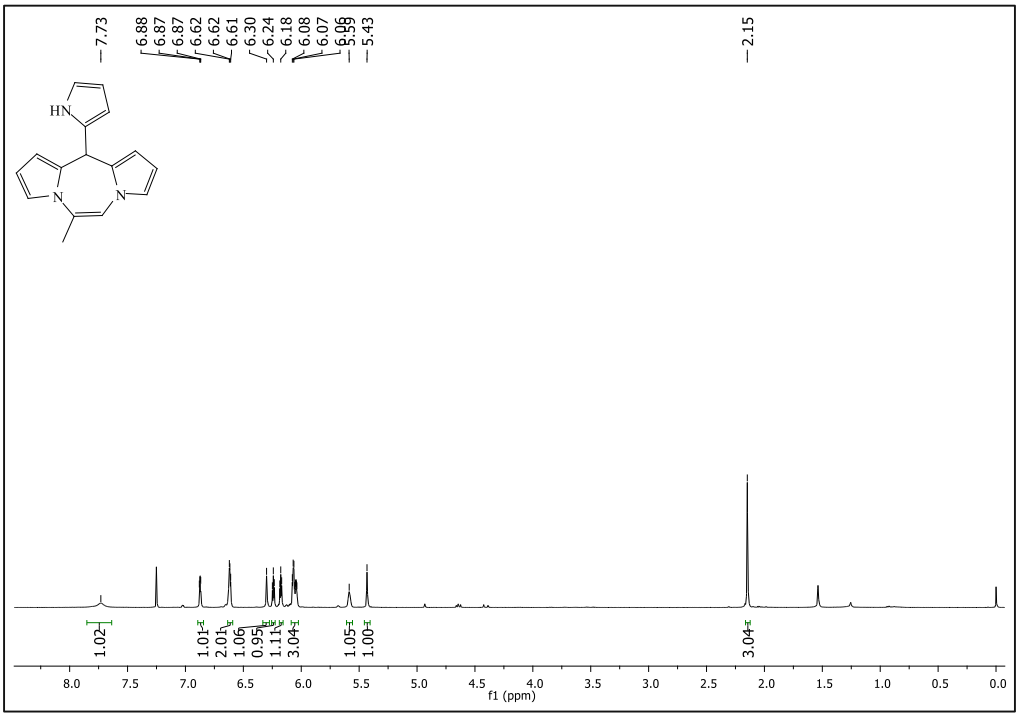


Figure 6: ^{1}H-NMR Spectrum of compound **49c** in $CDCl_3$

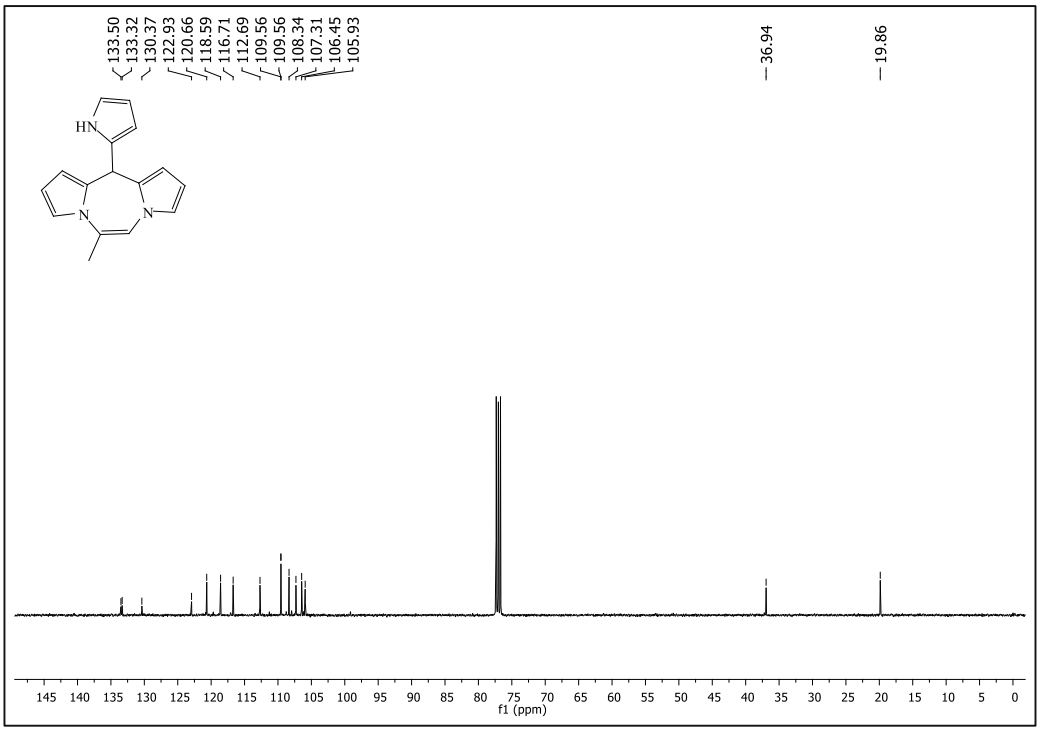


Figure 7: ^{13}C-NMR Spectrum of compound **49c** in $CDCl_3$

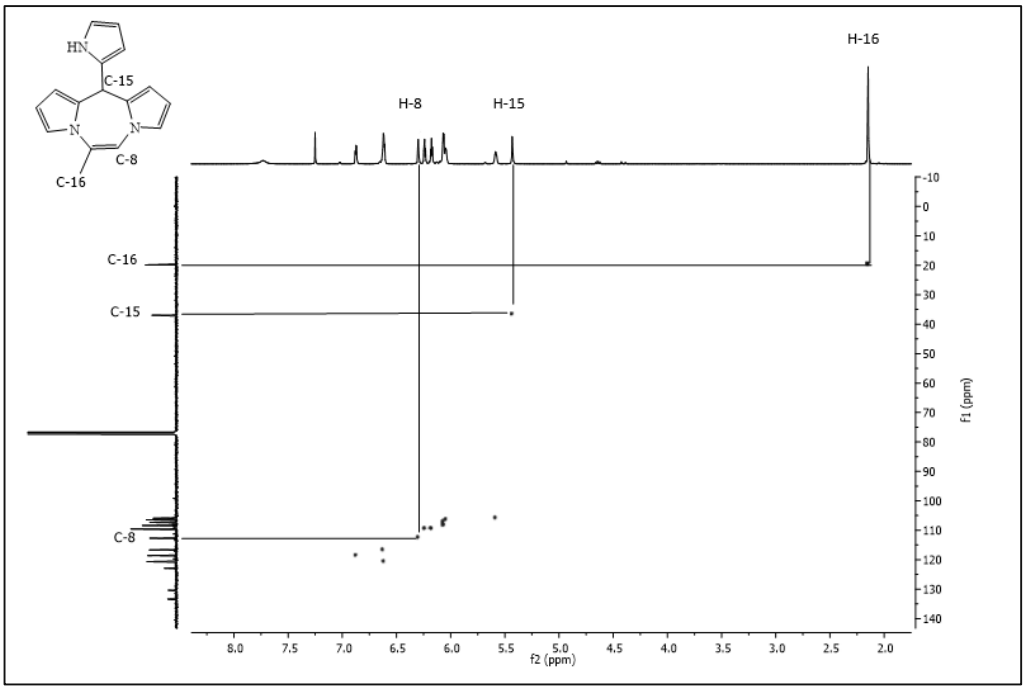


Figure 8: HSQC Spectrum of compound **49c** in $CDCl_3$

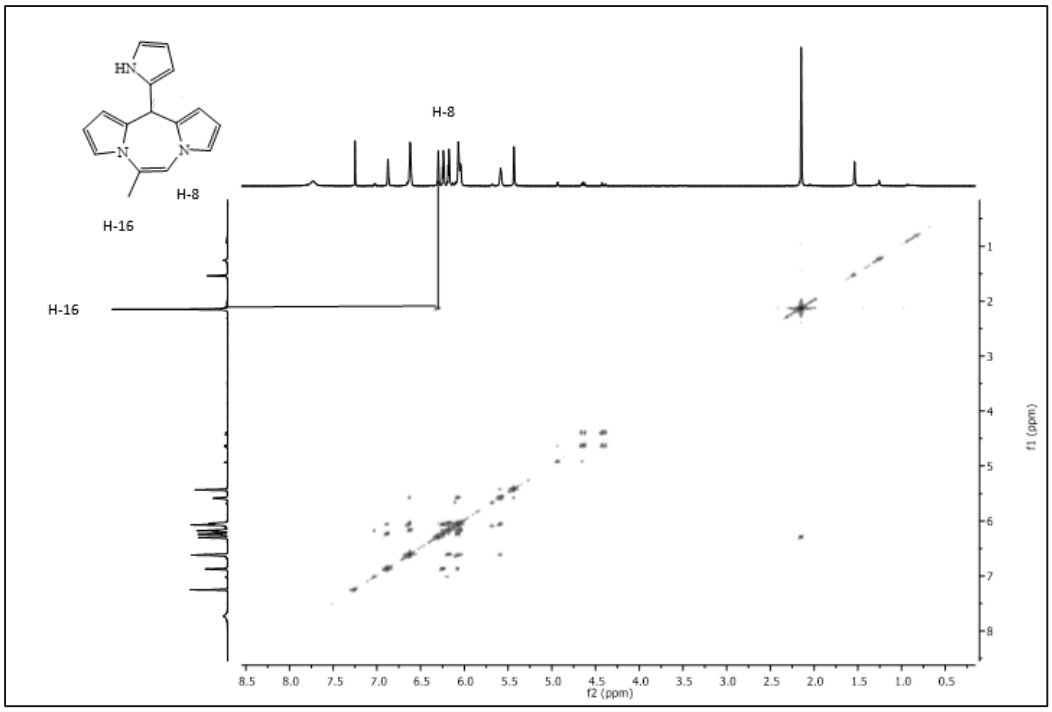


Figure 9: COSY Spectrum of compound **49c** in $CDCl_3$

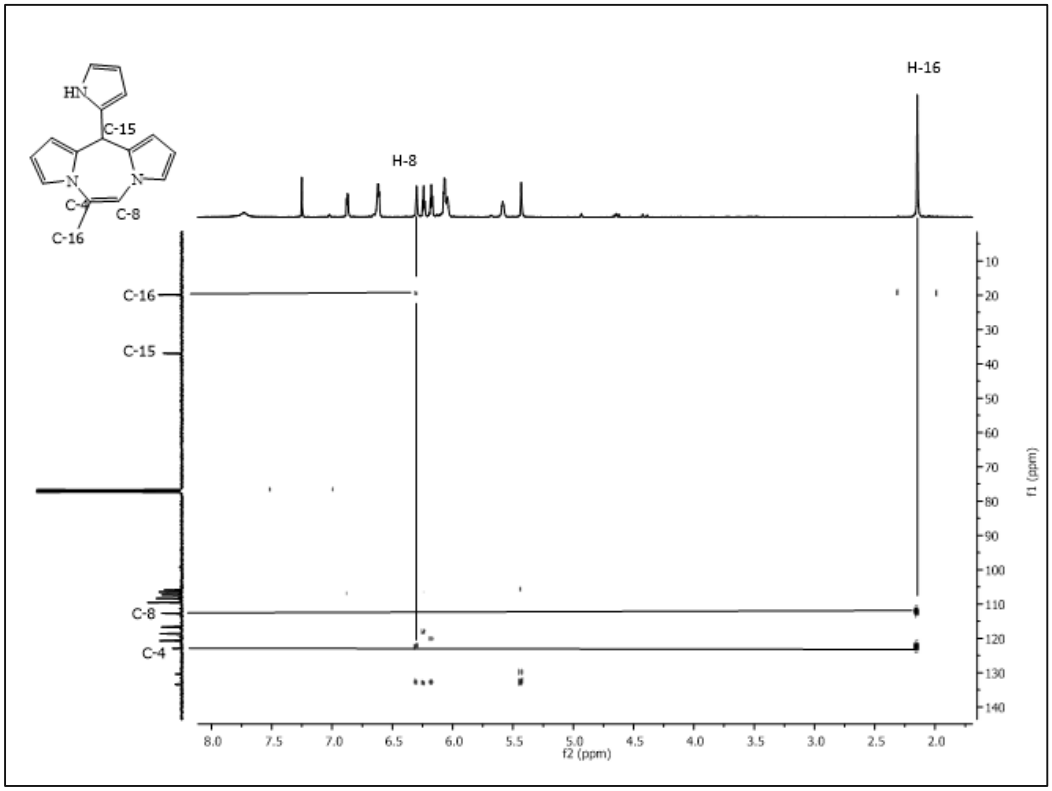
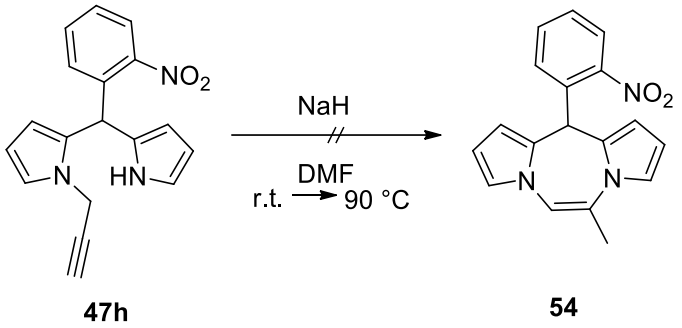


Figure 10: HMBC Spectrum of compound **49c** in $CDCl_3$

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).



47h **54**

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

Intramolecular hydrogen-bonding can be attribute 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.[40] 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 atom of nitro group and hydrogen 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.

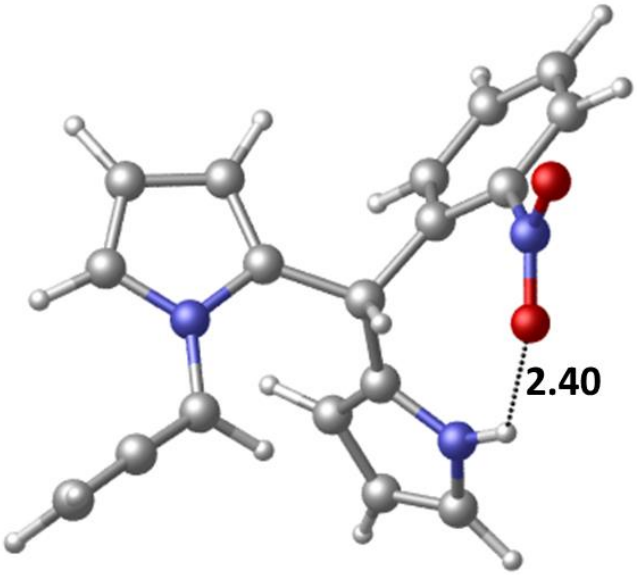
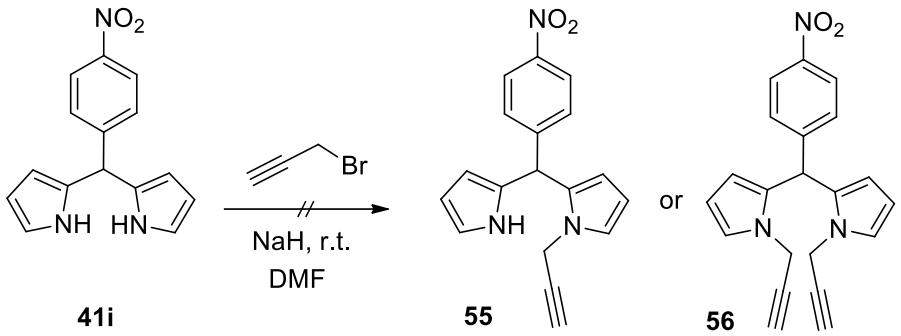


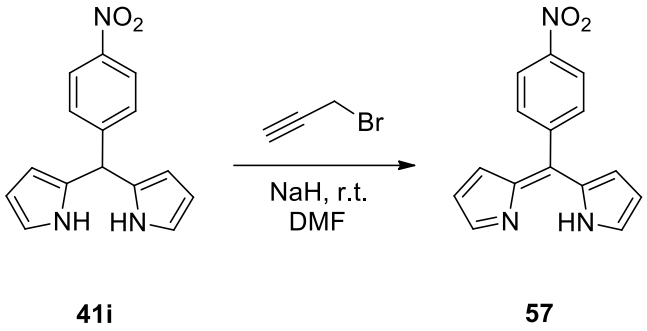
Figure 11. H bonding of compound **50a**

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)(1H-pyrrol- 2-yl)methyl]- 1H-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**[39] was produced under these reaction conditions (Scheme 25) and (Scheme 26).

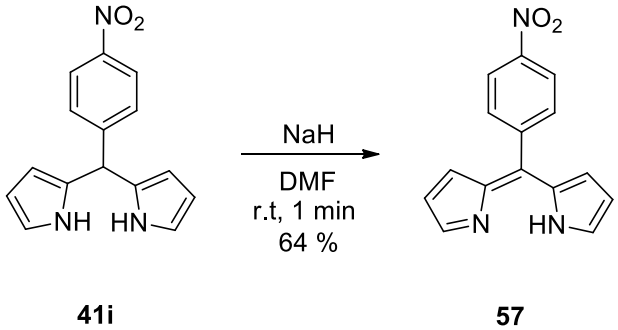


Scheme 25. Attempt to synthesize compound **55**



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

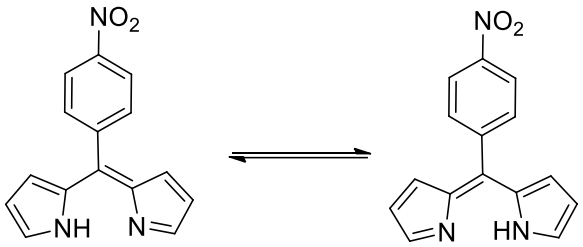
When compound **41i** was reacted only with NaH in DMF, in the absence of propargyl bromide, **57** was again formed even in 1-2 minutes (Scheme 27). Thus, propargyl bromide does not effect the reaction. The spectral data (^{1}H-NMR, ^{13}C-NMR, HRMS) of compound **57** is full-compatible with the literature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



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

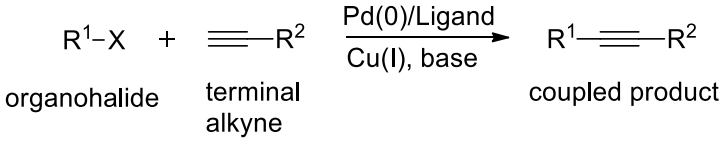
benzene and pyrrole rings. This anion can undergo an oxidation reaction in the presence of air to form the oxidation product **57**. Probably, a similar oxidation in the case of **41h** due to the formation of strong hydrogen bonding is hindered (Figure 11). Because of the very fast tautomery in **57**,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



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

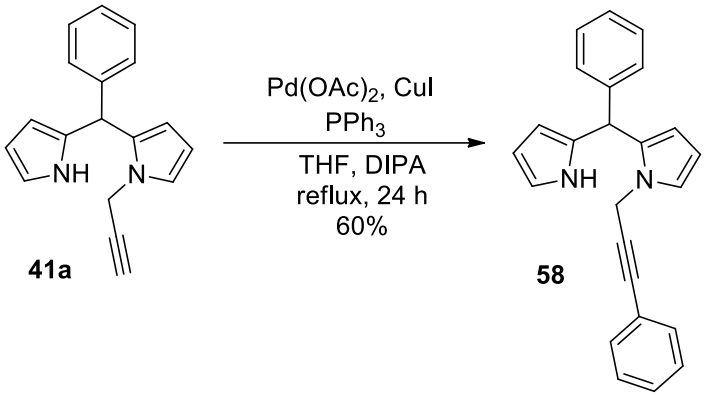
2.9. Synthesis of 2-(phenyl(1H-pyrrol-2-yl)methyl)-1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole (58) with Sonagashira coupling reaction

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



Scheme 29. Sonogashira coupling reaction

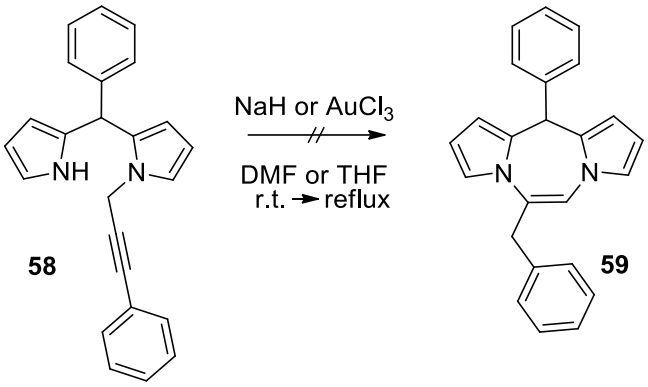
In order to test the scope of the cyclization reaction, additional derivative 2-(phenyl(1H-pyrrol-2-yl)methyl)-1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole (**58**) was synthesized by using Sonagashira coupling reaction procedure[38]. desired coupling product **58** was obtain from the reaction of compound **41c** with phenyl acetylene, $Pd(OAc)_2$, CuI and PPh_3 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)

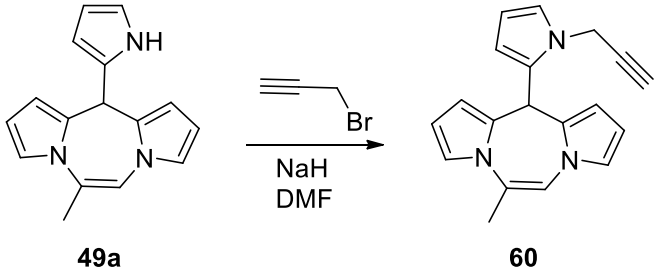
Coupling product **58** was reacted with NaH or $AuCl_3$ in the presence of DMF or THF at room temperature as well as at reflux temperature. However, desired cyclization product **59** did not form under these reaction conditions (Scheme 31).



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

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

The product **49c** was reacted with of NaH in the presence of propargyl bromide in DMF. An S_N2 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**.

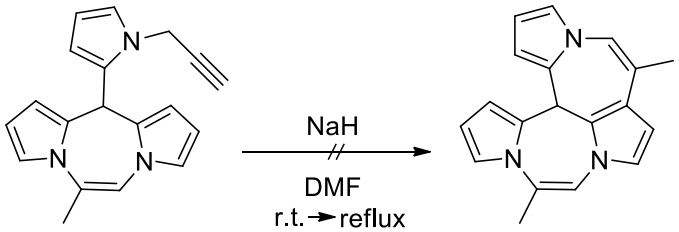


49a **60**

Scheme 32. Propargylation of **49a**

2.12. An attempt for further cyclization reaction of 5-methyl-11-(1-(prop-2-yn-1-yl)-1*H*-pyrrol-2-yl)-11*H*-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).



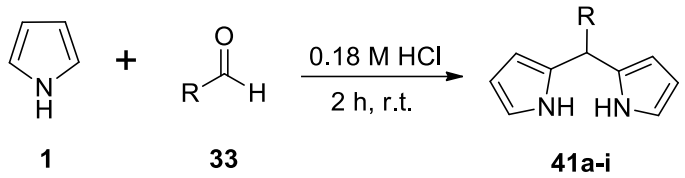
60 **61**

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 startes 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).

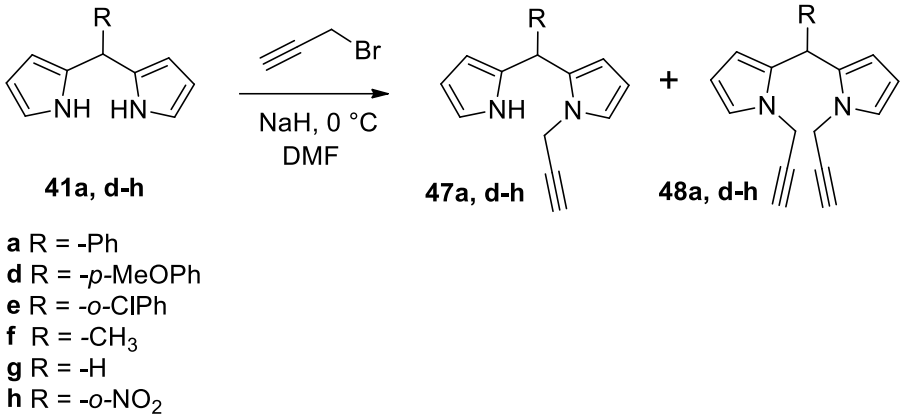


1 **33** **41a-i**

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 = $-CH_3$, 62%
g R = -H, 69%
h R = -*o*-NO_2, 79%
i R = -*p*-NO_2, 81%

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

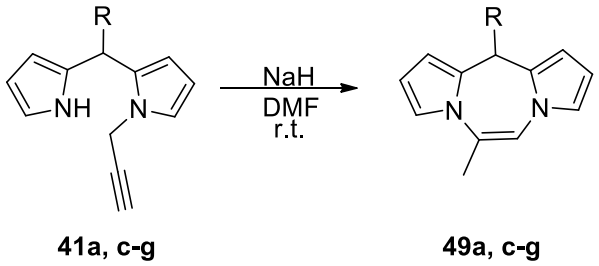
Introducing propargyl group to nitrogen atom of pyrrole(s) gave the expected mono- and di-propargylated compounds **47a, d-h and 48a, d-h**. The trouble for this step was that the yields of mono-propargylated compounds, which were much less than the yields of the di-propargylated compounds. So, this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



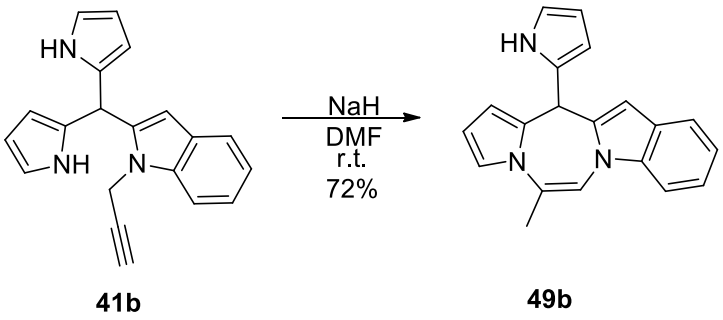
a R = -Ph
d R = -*p*-MeOPh
e R = -*o*-ClPh
f R = $-CH_3$
g R = -H
h R = -*o*-NO_2

Scheme 35. Synthesis of propargylated compounds

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

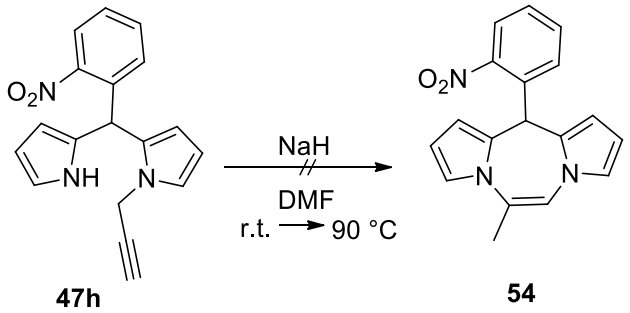


	R	Yields
a	-Ph	76%
c	-pyrrole	61%
d	-*p*-MeOPh	87%
e	-*o*-ClPh	61%
f	$-CH_3$	85%
g	-H	81%



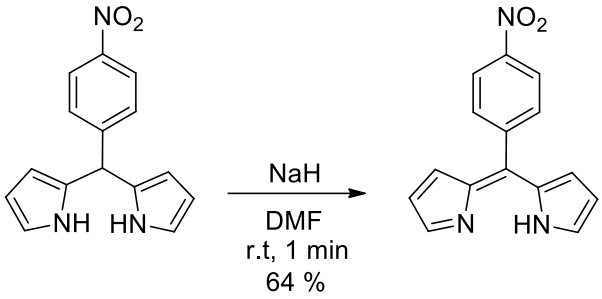
Scheme 36. Synthesis of cyclized derivatives.

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).



47h 54

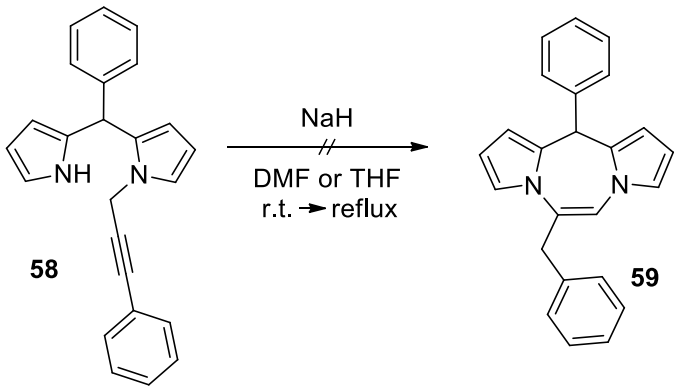
Scheme 37. Reaction of **47h** with NaH



41i 57

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

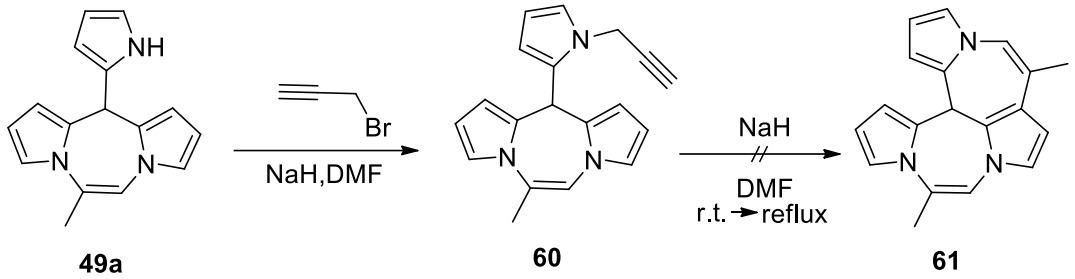
Further, attempts with compounds having a benzene ring attached to the terminal carbon atom of alkyne functionality, was failed to give any cyclization product (Scheme 39).



58 59

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).



49a **60** **61**

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

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

CHAPTER 4

EXPERIMENTAL SECTION

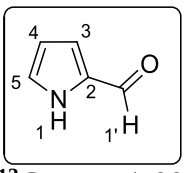
4.1 General Methods

All reagents were acquired from commercial provider and additional purification was not done. ^{1}H NMR spectra were recorded on an instrument 400 MHz and chemical shifts are shown in ppm. $CDCl_3$ and CD_3COCD_3 were used as internal standarts. In addition, ^{13}C-NMR spectra were recorded on an instrument 100 MHz and $CDCl_3$ and CD_3COCD_3 were used as internal standarts. Also, ^{13}C-NMR spectra were reported in ppm. IR were recorded in the range 4000-600 cm^{-1} via ATR diamond. Melting point instrument was used to measure melting points.ee

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 (λ = 254 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)[33]

To a stirred solution of $POCl_3$ (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 °C. The composition was mixed at room temperature for 14h. Afterwards, the satiated solution of $NaHCO_3$ was added to media until a basic medium was beholded. Then, the composition was extracted with EtOAc (3 × 30 mL). DMF in extracts were removed with brine (3 × 15 mL) and the mixture dried over $MgSO_4$, 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. 44-45 °C.

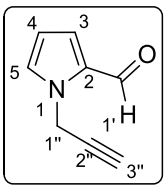


^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.47 (br s, 1H, -NH), 9.51 (d, J = 1.0, 1H, -H-1'), 7.18 (br s, 1H, H-3), 7.01 (ddd, $J_{4,3}$ = 3.8 Hz, $J_{5,4}$ = 2.3 Hz, 1H, H-4), 6.35 (ddd, $J_{4,3}$ = 3.8 Hz, $J_{4,5}$ = 2.4 Hz, 1H, H-4)

^{13}CNMR (100 MHz, CDCl3) δ 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)[35]

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 × 25 mL). DMF in media was removed with brine (6 × 15 mL), dried over $MgSO_4$, 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%).[35]

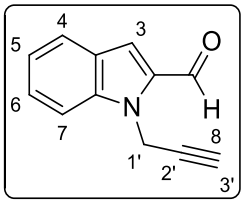


^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (bd, J = 1.2 Hz, 1H, H-1'), 7.20−7.19 (m, 1H, H-5), 6.90 (dd, $J_{3,4}$ = 4.0 and $J_{3,5}$ = 1.6 Hz, 1H, H-3), 6.22 (dd, $J_{4,5}$ = 2.4, $J_{4,3}$ = 4.0 Hz, 1H, H-4), 5.14 (d, J = 2.6 Hz, 2H, H-1"), 2.39 (t, J = 2.6 Hz, 1H, H-3").

^{13}C NMR (100 MHz, CDCl3) δ 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)[36]

Solid NaH was added (0.17 g, 7.1 mmol) piecewise at 0 ºC to a stirred solution of 1*H*-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 × 50 mL) was used to extract product. The final composition were dried over $MgSO_4$ and filtered. After vaporisation, the product (**40**) was obtained. Brown solid (0.91 g, 82%) from CH_2Cl_2, m.p. 101-103 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 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').

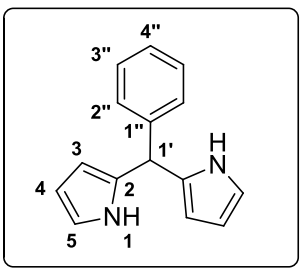
^{13}C NMR (100 MHz, $CDCl_3$) δ 182.6, 140.1, 134.5, 127.4, 126.6, 123.5, 121.5, 118.7, 110.8, 78.2, 72.5, 33.9.

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 × 50 mL) and dried over $MgSO_4$ 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)[21]

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 ºC from EtOAc/hexane.

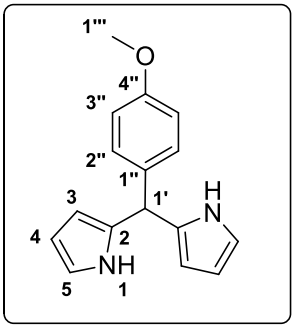


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88 (bs, 2H, H-1), 7.22-7.35 (m, 5H, arom), 6.63-6.59 (m, 2H, H-5), 6.15 – 6.13 (m,2H, H-4), 5.92 (bs, 2H, H-3), 5.49 (s, 1H, H-1').

^{13}C NMR (100 MHz, $CDCl_3$) δ 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)(1*H*-pyrrol-2-yl)methyl]-1*H*-pyrrole (41d)[21]

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 ºC.

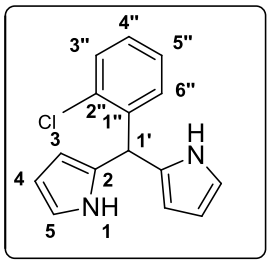


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.82 (bs, 2H, H-1'), 7.14 (d, $J_{2",3"}$ = 8.6, 2H, H-2"), 6.85 (d, $J_{2",3"}$ = 8.6, 2H, H-3"), 6.65-6.67 (m, 2H, H-5), 6.15 – 6.13 (m, 2H, H-4), 5.90-5.92 (m, 2H, H-3), 5.42 (s, 1H, H-1'), 3.82 (s, 3H, H-1'").

^{13}C NMR (100 MHz $CDCl_3$): δ 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)(1*H*-pyrrol-2-yl)methyl]-1*H*-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 ºC.



^{1}H NMR (400 MHz, $CDCl_3$) δ 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),

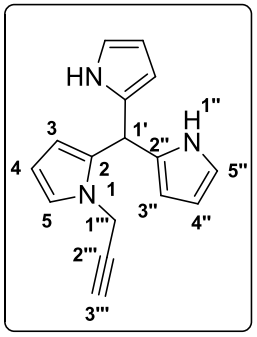
^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0, 133.7, 131.2, 129.7, 129.6, 128.2, 127.1, 117.3, 108.5, 107.4, 40.6.

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

HRMS calcd for $C_{15}H_{13}ClN_2$ $[M+H]^+$: 257.0840, found: 257.0842

4.9. Synthesis of 2-[di(1*H*-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1*H*-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 ºC.



^{1}H NMR (400 MHz, $CDCl_3$) δ 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'").

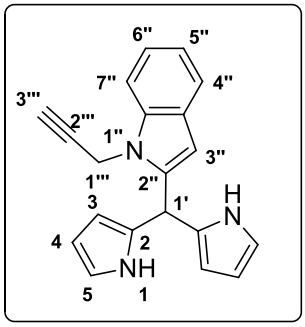
^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1, 130.5, 121.5, 117.2, 108.7, 108.4, 107.4, 106.9, 78.3, 73.4, 36.2, 36.0.

IR (ATR, 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 $C_{16}H_{15}N_3$ $[M+H]^+$: 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)-1H-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}H NMR (400 MHz, $CDCl_3$) δ 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''').

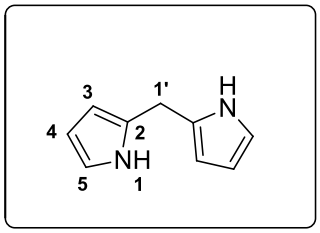
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7, 137.1, 129.7, 127.6, 122.0, 120.6, 120.2, 117.6, 109.2, 108.6, 107.3, 102.5, 78.3, 72.4, 36.5, 32.5.

IR (ATR, 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 $C_{20}H_{17}N_3$ $[M+H]^+$: 299.1542 found: 299.1553

4.11. Synthesis of 2-(1*H*-pyrrol-2-ylmethyl)-1*H*-pyrrole (41g)[21]

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 ºC. (0.50 g, 69 %).

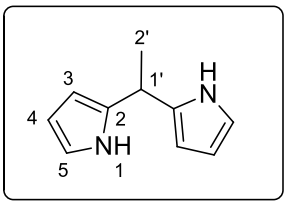


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (bs, 2H, H-1), 6.56 – 6.54 (m, 2H, H-5), 6.14 – 6.12 (m, 2H, H-4), 6.08 – 5.95 (m, 2H, H-3), 3.89 (s, 2H, H-1').

^{13}C NMR (100 MHz, $CDCl_3$) δ 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)[21]

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%).

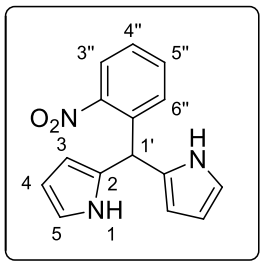


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (bs, 2H, H-1), 6.67 – 6.42 (m, 2H, H-5), 6.08 – 6.06 (m, 2H, H-4), 5.98 (bs, 2H, H-3), 4.06 (q, $J_{2',1'}$ = 7.2 Hz, 1H, H-1'), 1.50 (d, $J_{2',1'}$ = 7.2 Hz, 3H, H-2').

^{13}C NMR ($CDCl_3$): δ 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)[22]

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_2Cl_2 (1.05 g, 79%), m.p. 145-147 ºC.

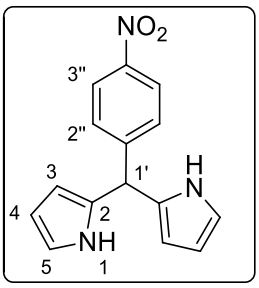


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (bs, 2H, H-1), 7.90 (dd, $J_{4",3"}$ = 8.1 and $J_{3",5"}$ = 1.2 Hz, 1H, H-3"), 7.54 (td, $J_{4",3"-5"}$ = 7.7 and $J_{4",6"}$ = 1.2 Hz, 1H, H-4") 7.46 – 7.35 (m, 1H-5"), 7.30 (dd, $J_{6",5"}$ = 8.1 and $J_{6",4"}$ = 1.5 Hz, 1H, H-6"), 6.75 – 6.71 (m, 1H, H-5), 6.22 (s, 1H, H-1'), 6.18 (m, 1H, H-4), 5.89 – 5.84 (m, 1H, H-3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 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)[21]

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 ºC. (1.08 g, 81%).

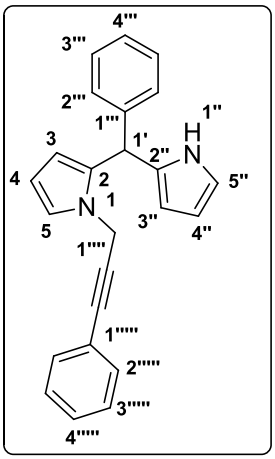


^{1}H NMR (400 MHz, Acetone-d_6) δ 9.84 (bs, 1H, H-1), 8.28 – 8.08 (m, 2H, H-3"), 7.54 – 7.43 (m, 2H, H-2"), 6.77 – 6.74 (m, 2H. H-5), 6.04 (m, 2H, H-4), 5.82 – 5.78 (m, 1H, H-3), 5.67 (s, 1H, H-1').

^{13}C NMR (100 MHz, Acetone-d_6) δ 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_3 (40 mg, 0.15 mmol), and $PdCl_2$ (20 mg 0.10 mmol) was mixed under the nitrogen atmosphere for 2 min. After that, 2-[phenyl(1***H***-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1***H***-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}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (101 MHz, $CDCl_3$) δ 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, cm^{-1}) 3375, 2919, 1682, 1597, 1489, 1442, 1386, 1342, 1284, 1233, 1115, 1071, 1027, 968, 915, 883, 845, 755, 689, 602.

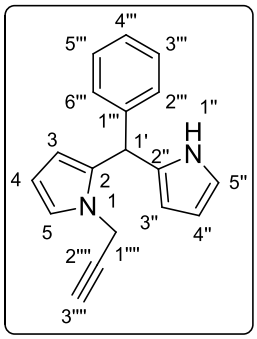
HRMS calcd for $C_{24}H_{20}N_2$ $[M+H]^+$: 337.1699 found: 337.1720

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 $MgSO_4$. 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.

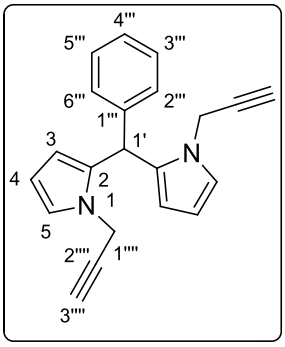


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (bs, 1H, H-1''), 7.39 – 7.10 (m, 5H-arom), 6.79 – 6.72 (m, 1H, H-5), 6.68 (dd, $J_{4,3}$ = 4.1 and $J_{4,5}$ = 2.5 Hz, 1H, H-4), 6.14 – 6.12 (m, 1H, H-4''), 6.10 – 6.06 (m, 1H, H-5''), 5.83 – 5.82 (m, 1H, H-3), 5.70 – 5.68 (m, 1H, H-3''), 5.56 (s, 1H, H-1'), 4.39 – 4.36 (m, 2H, H-1''''), 2.35 (t, $J_{1'''',3''''}$ = 2.5 Hz, 1H, H-3'''').

^{13}C NMR (101 MHz, $CDCl_3$) 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^{-1}) 1662, 1510, 1416, 1381, 1342, 1287, 1272, 1252, 1118, 1094, 1043, 1002, 935, 909, 845, 808, 773, 714, 638, 593, 575.

HRMS calcd for $C_{18}H_{16}N_2$ $[M+H]^+$: 259.1151 found: 259.1158



^{1}H NMR (400 MHz, $CDCl_3$) 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, $J_{geminal}$ = 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'''').

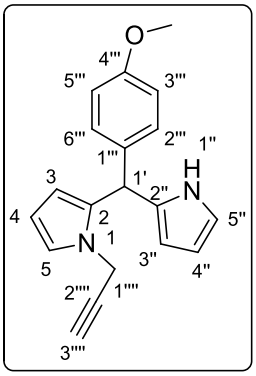
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.6, 132.9, 128.7, 128.5, 126.9, 121.1, 109.9, 107.3, 78.7, 73.3, 41.2, 36.3.

IR (ATR, cm^{-1}) 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 $C_{21}H_{18}N_2$ $[M+H]^+$: 299.1542 found: 299.1553

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

To a stirred solution of 2-[(4-methoxyphenyl)(1***H***-pyrrol-2-yl)methyl]-1***H***-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.

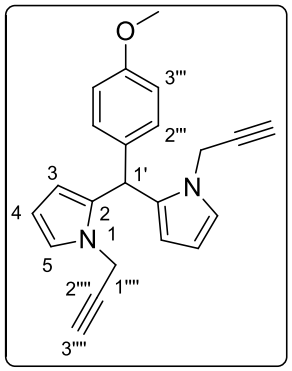


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (bs, 1H, H-1''), 7.13 – 6.81 (m, 4H-arom), 6.78 – 6.74 (m, 1H, H-5), 6.69 (dd, $J_{4,3}$ = 4.1 and $J_{4,5}$ = 2.6 Hz, 1H, H-4), 6.14 – 6.12 (m, 1H, H-4''), 6.08 (t, J = 3.2 Hz, 1H, H-5''), 5.82 (m, 1H, H-3''), 5.71 – 5.69 (m, 1H, H-3), 5.51 (s, 1H, H-1'), 4.38 (d, $J_{1'''',3''''}$ = 2.5 Hz, 3H, H-1''''), 3.79 (s, 3H-OMe), 2.36 (t, $J_{1'''',3''''}$ = 2.5 Hz, 1H, H-3'''').

^{13}C NMR (101 MHz, $CDCl_3$) 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^{-1}) 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 $C_{19}H_{18}N_2O$ $[M+H]^+$: 291.1491 found: 291.1507.



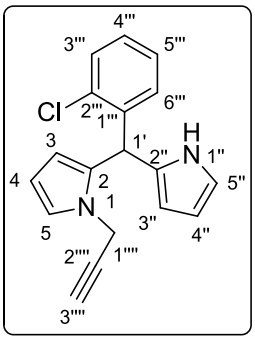
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 – 7.04 (m, 2H, H-3'''), 6.86 – 6.82 (m, 2H, H-2'''), 6.76 – 6.74 (m, 2H, H-5), 6.06 – 6.04 (m, 2H, H-4), 5.55 (s, 1H, H-1'), 5.52 – 5.49 (m, 1H, H-3), 4.40 (dd, , $J_{geminal}$ = 11.1 Hz and $J_{1'''',3''''}$ = 2.5 Hz, 4H, H-1''''), 3.79 (s, 3H-OMe), 2.39 (t, $J_{1'''',3''''}$ = 2.5 Hz, 2H, H-3''''). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 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^{-1}) 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 $C_{22}H_{20}N_2O$ $[M+H]^+$: 329.1648 found: 329.1684.

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

To a stirred solution of 2-[(2-chlorophenyl)(1***H***-pyrrol-2-yl)methyl]-1***H***-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%).

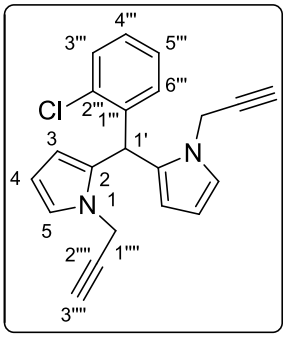


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (bs, 1H, H-1''), 7.40 – 7.35 (m, 1H, H-3'''), 7.22 – 7.15 (m, 2H, arom), 7.01 – 6.96 (m, 1H, arom), 6.81 – 6.77 (m, 1H, H-5), 6.70 (dd, $J_{4,3}$ = 4.2 and $J_{4,5}$ = 2.6 Hz, 1H, H-4), 6.15 – 6.13 (m, 1H, H-4''), 6.11 – 6.07 (m, 1H, H-5''), 5.93 (s, 1H, H-1'), 5.81 – 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'''').

^{13}C NMR (101 MHz, $CDCl_3$) δ 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^{-1}) 3376, 3291, 1723, 1571, 1468, 1434, 1285, 1235, 1115, 1072, 1046, 1029, 936, 884, 847, 751, 712, 663, 609.

HRMS calcd for $C_{18}H_{15}ClN_2$ $[M+H]^+$: 295.0996 found: 295.0979.



^{1}H NMR (400 MHz, $CDCl_3$) δ 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, , $J_{geminal}$ = 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'''').

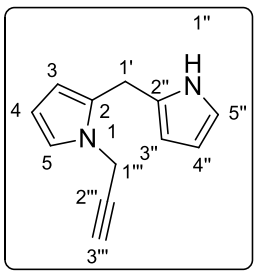
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 133.9, 131.6, 130.4, 129.5, 128.2, 126.9, 121.2, 110.0, 107.4, 78.2, 73.4, 37.0, 36.3.

IR (ATR, cm^{-1}) 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 $C_{21}H_{17}ClN_2$ $[M+H]^+$: 333.1153 found: 333.1168

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

To a stirred solution of 2-(1*H*-pyrrol-2-ylmethyl)-1*H*-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%).

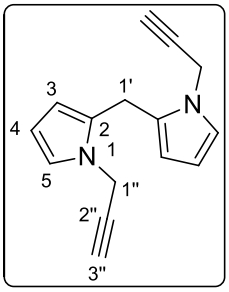


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (bs, 1H, H-1''), 6.72-6.70 (m, 2H, H-5, H-5''), 6.61 (dd, $J_{4,3}$ = 4.0 and $J_{4,5}$ = 2.5 Hz, 1H, H-4), 6.16 – 6.15 (m, 1H, H-4''), 6.02 – 5.98 (m, 2H, H-3''), 4.42 (d, $J_{1''',3'''}$ = 2.5 Hz, 2H, H-1'''), 3.99 (s, 2H, H-1'), 2.33 (t, $J_{1''',3'''}$ = 2.5 Hz, 1H, H-3''').

^{13}C NMR (101 MHz, $CDCl_3$) δ 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^{-1}) 3377, 3282, 1698, 1567, 1482, 1420, 1342, 1311, 1286, 1240, 1205, 1180, 1115, 1088, 1071, 1025, 935, 883, 775, 707, 640.

HRMS calcd for $C_{12}H_{12}N_2$ $[M+H]^+$: 185.1073 found: 185.1079.



^{1}H NMR (400 MHz, $CDCl_3$) δ 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").

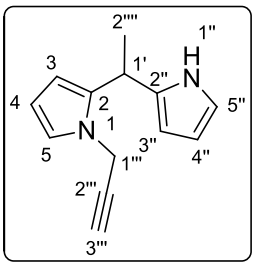
^{13}C NMR (101 MHz, $CDCl_3$) δ 128.9, 120.9, 108.6, 107.5, 78.4, 73.2, 36.3, 24.3.

IR (ATR, cm^{-1}) 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 $C_{12}H_{12}N_2$ $[M+H]^+$: 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%).

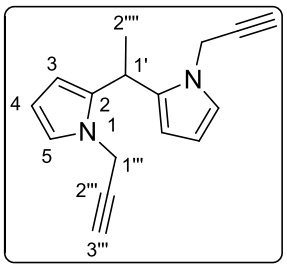


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (bs, 1H, H-1"), 6.78 – 6.70 (m, 1H, H-5), 6.59 (dd, $J_{4,3}$ = 4.1 and $J_{4,5}$ = 2.5 Hz, 1H, H-4), 6.14 – 6.12 (m, 1H, H-4"), 6.12 – 6.10 (m, 1H, H-5"), 6.10 – 6.08 (m, 1H, H-3), 6.02 – 6.00 (m, 1H, H-3"), 4.40 (dd, $J_{geminal}$ = 6.7, $J_{1'",3'"}$ = 2.5 Hz, 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"").

^{13}C NMR (101 MHz, $CDCl_3$) δ 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^{-1}) 3383, 3284, 2971, 2930, 1682, 1561, 1481, 1372, 1343, 1283, 1242, 1116, 1071, 1027, 936, 882, 789, 763, 710, 641, 561.

HRMS calcd for $C_{13}H_{14}N_2$ $[M+H]^+$: 199.1229 found: 199.1238.



^{1}H NMR (400 MHz, $CDCl_3$) δ 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'''').

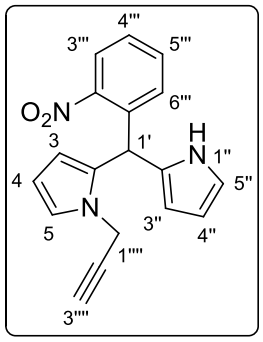
^{13}C NMR (101 MHz, $CDCl_3$) δ 134.6, 120.9, 107.4, 107.0, 78.7, 73.13, 36.0, 29.5, 20.8.

IR (ATR, cm^{-1}) 3286, 2927, 2851, 1712, 1479, 1420, 1373, 1340, 1283, 1234, 1202, 1128, 1077, 1011, 934, 789, 759, 706, 637, 572.

HRMS calcd for $C_{16}H_{16}N_2$ $[M+H]^+$: 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)(1***H***-pyrrol-2-yl)methyl]-1***H***-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 $CHCl_3$, m.p. 143-144 ºC from EtOAc/ hexzane.

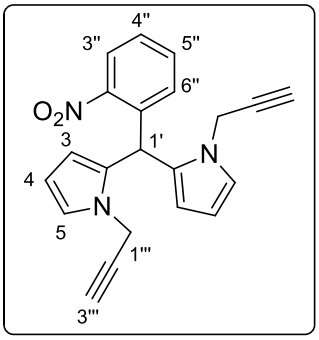


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (bs, 1H, H-1"), 7.93 (dd, $J_{4''', 3'''}$ = 8.1 and $J_{3''', 5'''}$ = 1.2 Hz, 1H, H-3'''), 7.51 (td, $J_{4''', 3'''\text{-}5'''}$ = 7.6 and $J_{4''', 6'''}$ = 1.2 Hz, 1H, H-4''') 7.43 – 7.38 (m, 1H-5'''), 7.13 (dd, $J_{6''', 5'''}$ = 7.8 and $J_{6''', 4'''}$ = 1.0 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'''').

^{13}C NMR (101 MHz, $CDCl_3$) δ 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^{-1}) 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 $C_{18}H_{15}N_3O_2$ $[M+H]^+$: 306.1237 found: 306.1237



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, $J_{4'', 3''}$ = 8.1 and $J_{3'', 5''}$ = 1.2 Hz, 1H, H-3''), 7.51 (td, $J_{4'', 3''\text{-}5''}$ = 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_{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''').

^{13}C NMR (101 MHz, $CDCl_3$) δ 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^{-1}) 3300, 3281, 1519, 1477, 1355, 1301, 1288, 1253, 1131, 1071, 1017, 937, 864, 836, 819, 742, 719, 687, 638, 606, 572.

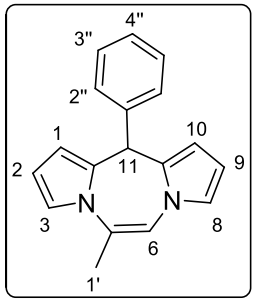
HRMS calcd for $C_{21}H_{17}N_3O_2$ $[M+H]^+$: 344.1393 found: 344.1418

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

To a stirred solution of N-propargyl dipyrromethane 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 $MgSO_4$. 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-11*H*-dipyrrolo[1,2-*d*:2',1'-*g*][1,4]diazepine (49a)

A stirred solution of 2-[phenyl(1***H***-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1***H***-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}H NMR (400 MHz, $CDCl_3$) δ 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').

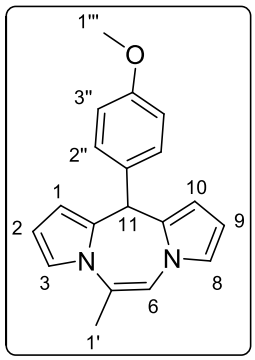
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 134.6, 134.5, 128.0, 127.3, 126.3, 123.2, 120.2, 118.2, 113.0, 109.5, 109.5, 107.7, 107.0, 42.1, 19.6.

IR (ATR, 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 $C_{16}H_{16}N_2$ $[M+H]^+$: 261.1386 found: 261.1398.

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

A stirred solution of 2-[(4-methoxyphenyl)(1*H*-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1*H*-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}H NMR (400 MHz, $CDCl_3$) δ 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').

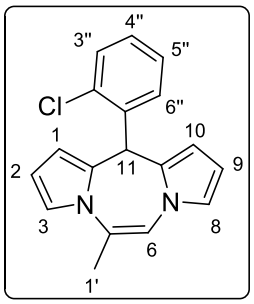
^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2, 135.0, 134.9, 132.5, 128.5, 123.8, 120.2, 118.2, 113.4, 113.0, 109.6, 109.5, 107.6, 106.9, 55.2, 41.5, 19.7.

IR (ATR, 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 $C_{19}H_{18}N_2O$ $[M+H]^+$: 291.1491 found: 291.1508.

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

A stirred solution of 2-[(2-chlorophenyl)(1*H*-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1*H*-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%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 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').

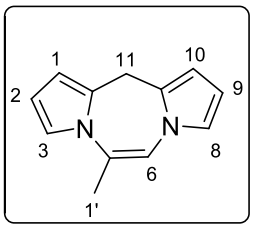
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.5, 134.7, 134.4, 133.8, 131.3, 129.9, 128.4, 126.3, 123.4, 120.3, 118.3, 113.2, 109.4, 109.4, 107.5, 106.9, 39.1, 20.1.

IR (ATR, cm^{-1}) 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 $C_{18}H_{15}ClN_2$ $[M+H]^+$: 295.0996 found: 295.1000.

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

A stirred solution of 1-prop-2-ynyl-2-(1*H*-pyrrol-2-ylmethyl)-1*H*-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.



^{1}H NMR (400 MHz, $CDCl_3$) δ 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').

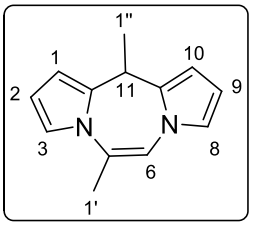
^{13}C NMR (101 MHz, $CDCl_3$) δ 132.8, 132.6, 123.2, 119.4, 117.5, 112.7, 109.7 (2C), 105.3, 104.4, 26.0, 19.9.

IR (ATR, cm^{-1}) 2916, 2849, 1715, 1507, 1480, 1417, 1378, 1331, 1235, 1180, 1114, 1024, 885, 826, 747, 695, 610, 546.

HRMS calcd for $C_{12}H_{12}N_2$ $[M+H]^+$: 185.1084 found:185.1073.

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

A stirred solution of 1-prop-2-ynyl-2-[1-(1*H*-pyrrol-2-yl)ethyl]-1*H*-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%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 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").

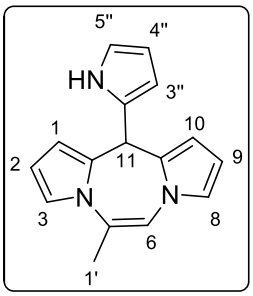
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.0, 137.8, 123.7, 119.2, 117.3, 113.0, 109.4 (2C), 103.2, 102.5, 30.1, 19.8, 15.0.

IR (ATR, cm^{-1}) 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 $C_{13}H_{14}N_2$ $[M+H]^+$: 198.1157 found: 199.1236.

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

A stirred solution of 2-[di(1*H*-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1*H*-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.



^{1}H NMR (400 MHz, $CDCl_3$) δ 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').

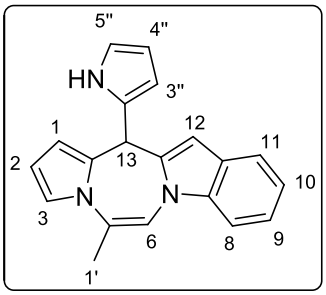
^{13}C NMR (101 MHz, $CDCl_3$) δ 133.5, 133.3, 130.3, 122.9, 120.6, 118.5, 116.7, 112.6, 109.5, 109.5, 108.3, 107.3, 106.4, 105.9, 36.9, 19.8.

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

HRMS calcd for $C_{16}H_{15}N_3$ $[M+H]^+$: 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%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H, H-1''), 7.57 (d, $J_{8,9}$ = 7.6 Hz, 1H, H-8), 7.32 (d, $J_{11,10}$ = 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').

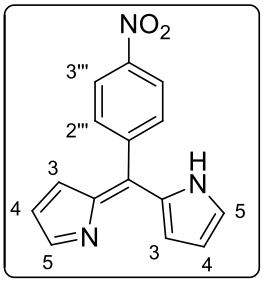
^{13}C NMR (101 MHz, $CDCl_3$) δ 136.2, 128.4, 128.3, 123.8, 122.0, 121.9, 120.8, 120.6, 118.8, 116.9, 110.1, 109.7, 109.4, 109.3, 108.5, 107.8, 106.3, 100.3, 37.6, 19.9.

IR (ATR, cm^{-1}) 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 $C_{20}H_{17}N_3$ $[M+H]^+$: 300.1495 found: 300.1507

4.31. Synthesis of (Z)-2-((4-nitrophenyl)(2H-pyrrol-2-ylidene)methyl)-1H-pyrrole (57)[39]

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 hyride 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 $MgSO_4$, 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)(2H-pyrrol-2-ylidene)methyl)-1H-pyrrole (**57**) (0.32 g, 64%) as yellow sticky solid.

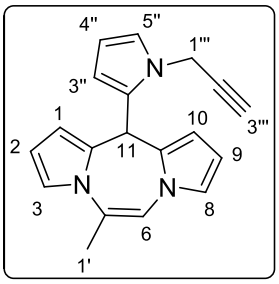


^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 – 8.21 (m, 2H, H-3'''), 7.63 – 7.62 (m, 2H, H-2'''), 7.63 – 7.59 (m, 2H, H-5), 6.41 (dd, J = 4.2 Hz and J = 1.0 Hz, 2H, H-3), 6.36 (dd, J = 4.2 Hz and J = 1.5 Hz, 2H, H-4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 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-(1*H*-pyrrol-2-yl)-11*H*-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 $MgSO_4$. 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}H NMR (400 MHz, $CDCl_3$) δ 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, $J_{geminal}$ = 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}C NMR (101 MHz, $CDCl_3$) δ 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, 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 $C_{20}H_{17}N_3$ $[M+H]^+$: 288.1495 found: 288.1514.

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APPENDIX A

SPECTRAL DATA

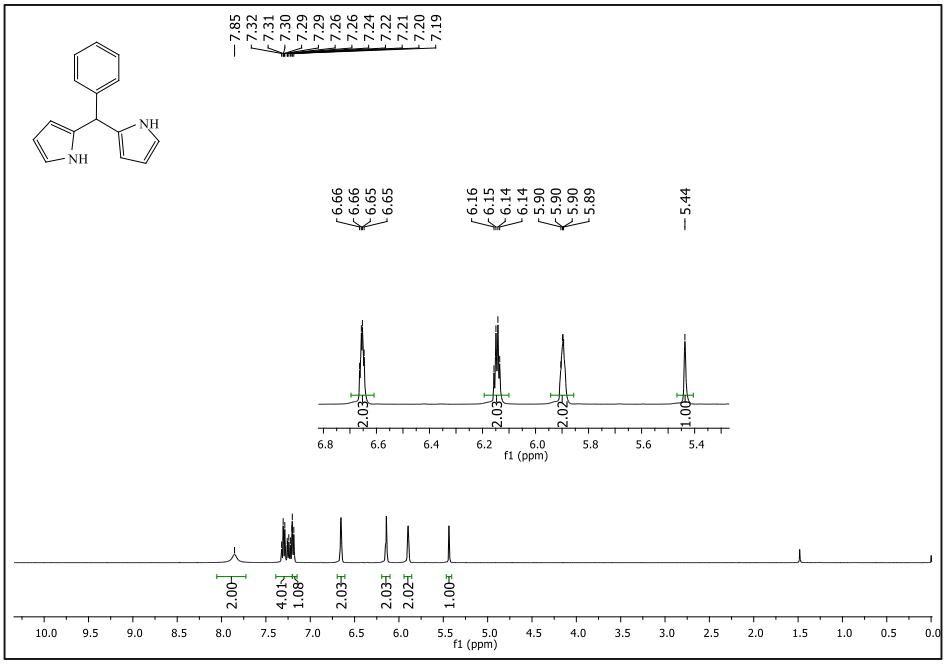

Figure 12 ^{1}H-NMR Spectrum of Compound **41a** in $CDCl_3$

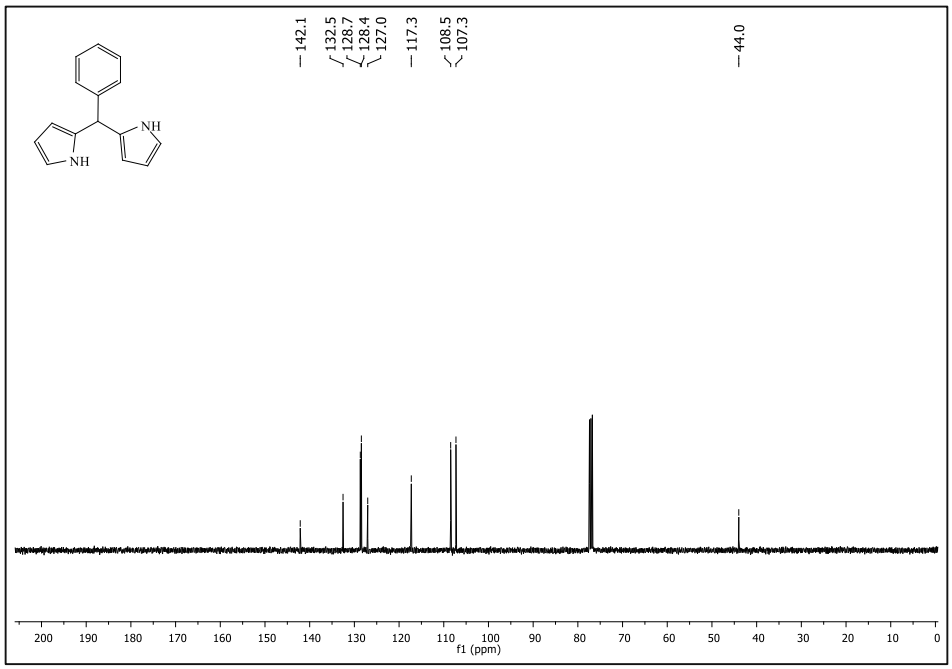

Figure 13 ^{13}C-NMR Spectrum of Compound **41a** in $CDCl_3$

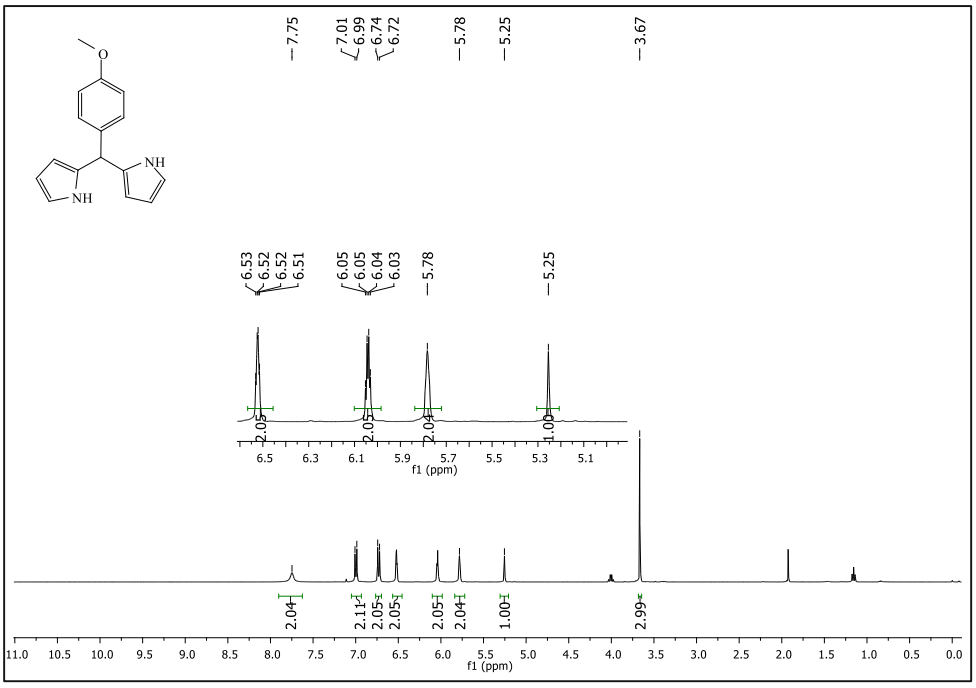

Figure 14 ^{1}H-NMR Spectrum of Compound **41d** in $CDCl_3$

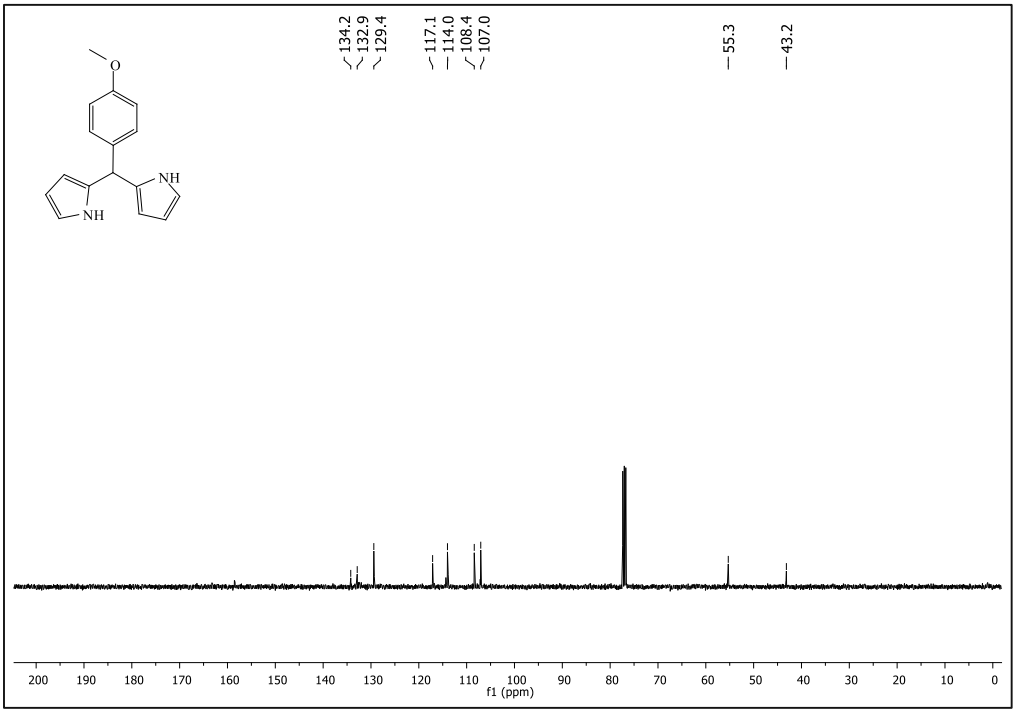

Figure 15 ^{13}C-NMR Spectrum of Compound **41d** in $CDCl_3$

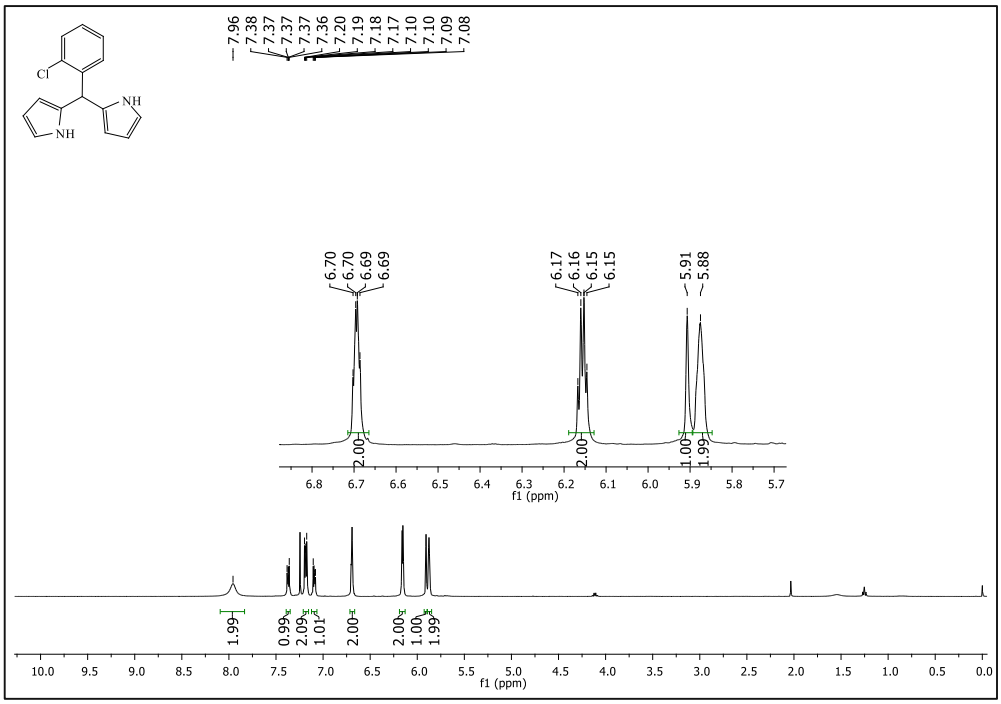

Figure 16 ^{1}H-NMR Spectrum of Compound **41e** in $CDCl_3$

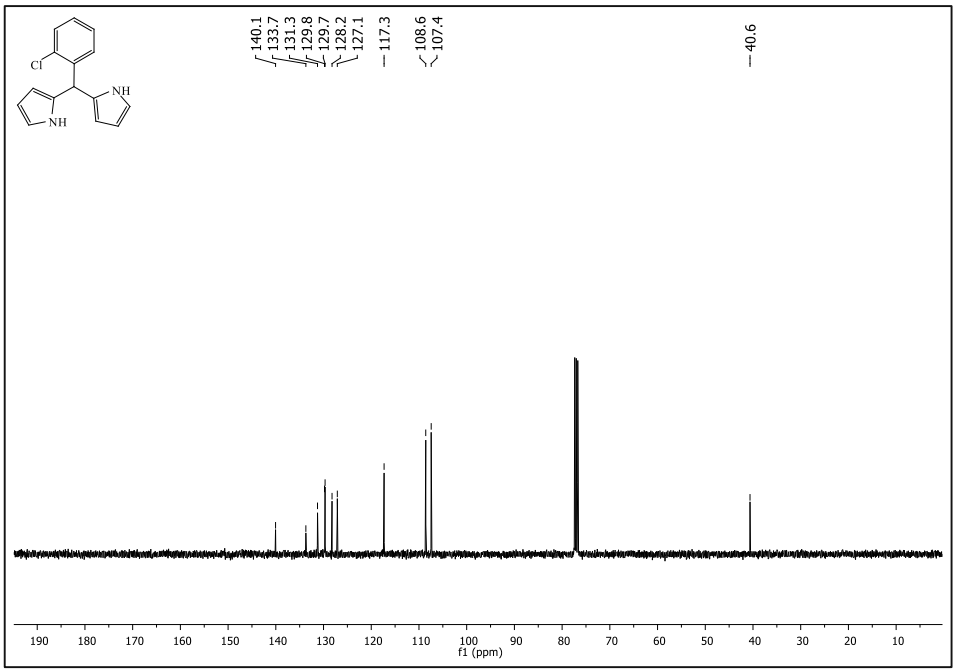

Figure 17 ^{13}C-NMR Spectrum of Compound **41e** in $CDCl_3$

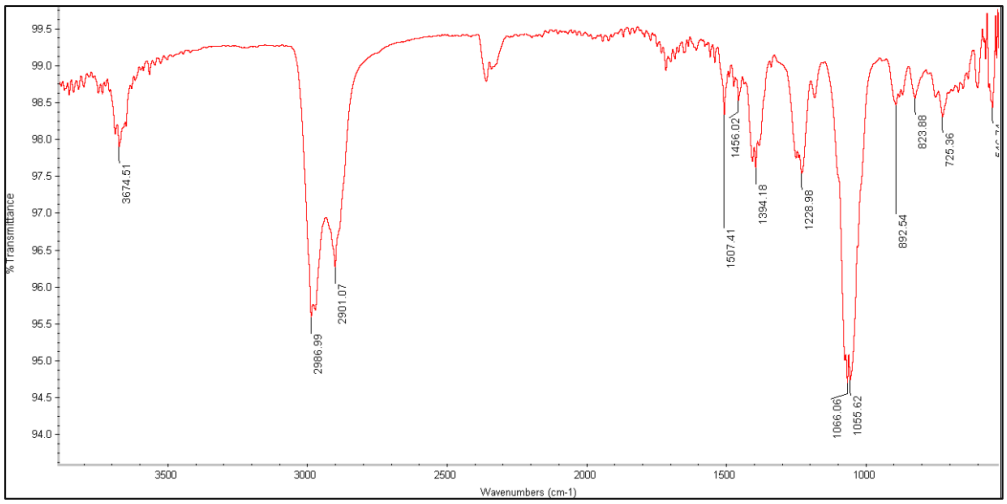

Figure 18 IR Spectrum of Compound **41e**

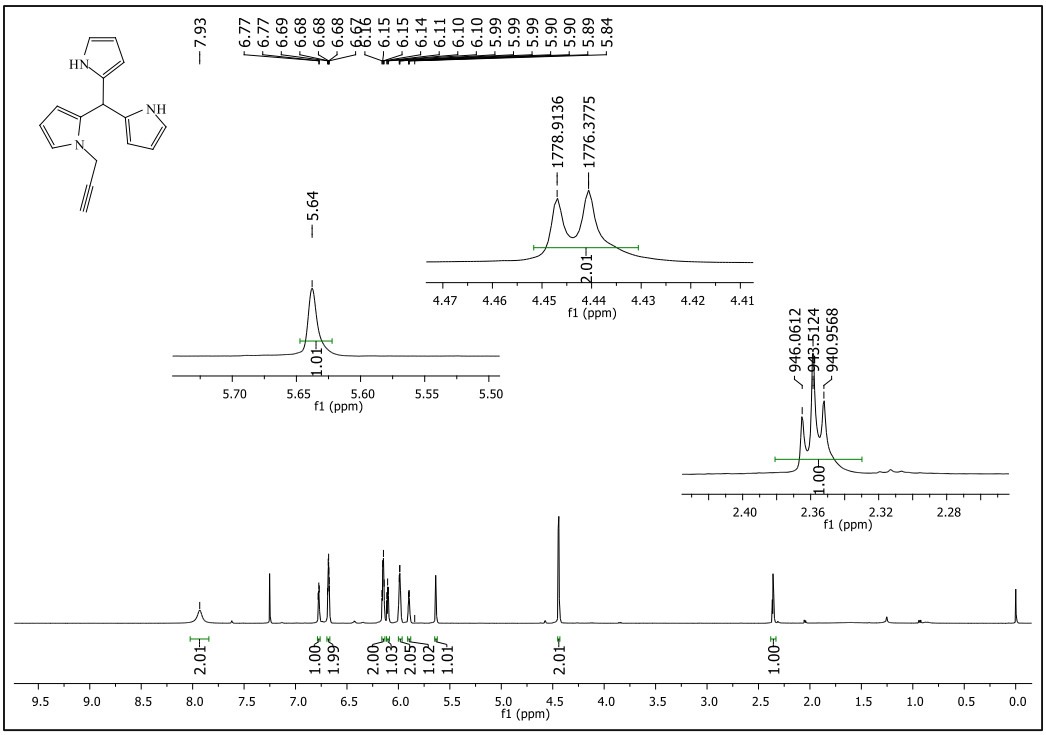

Figure 19 ^{1}H-NMR Spectrum of Compound **41c** in $CDCl_3$

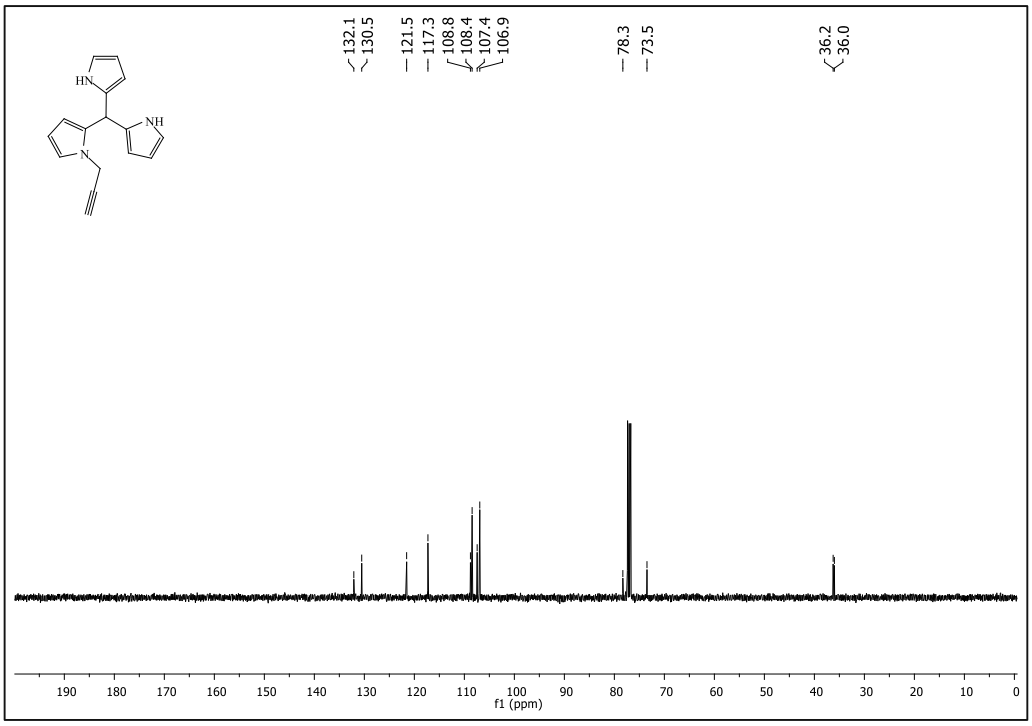

Figure 20 ^{13}C-NMR Spectrum of Compound **41c** in $CDCl_3$

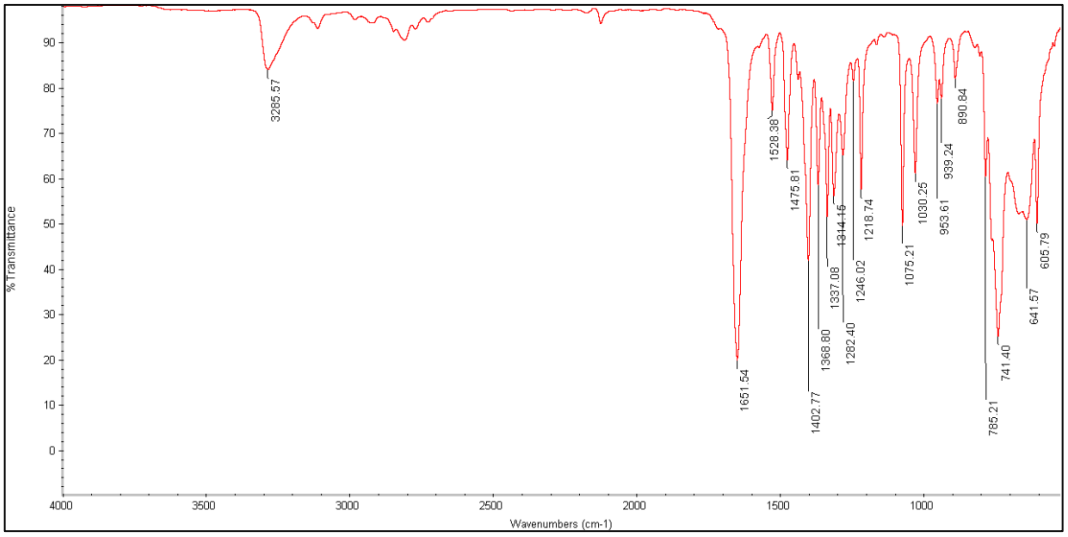

Figure 21 IR Spectrum of Compound **41c**

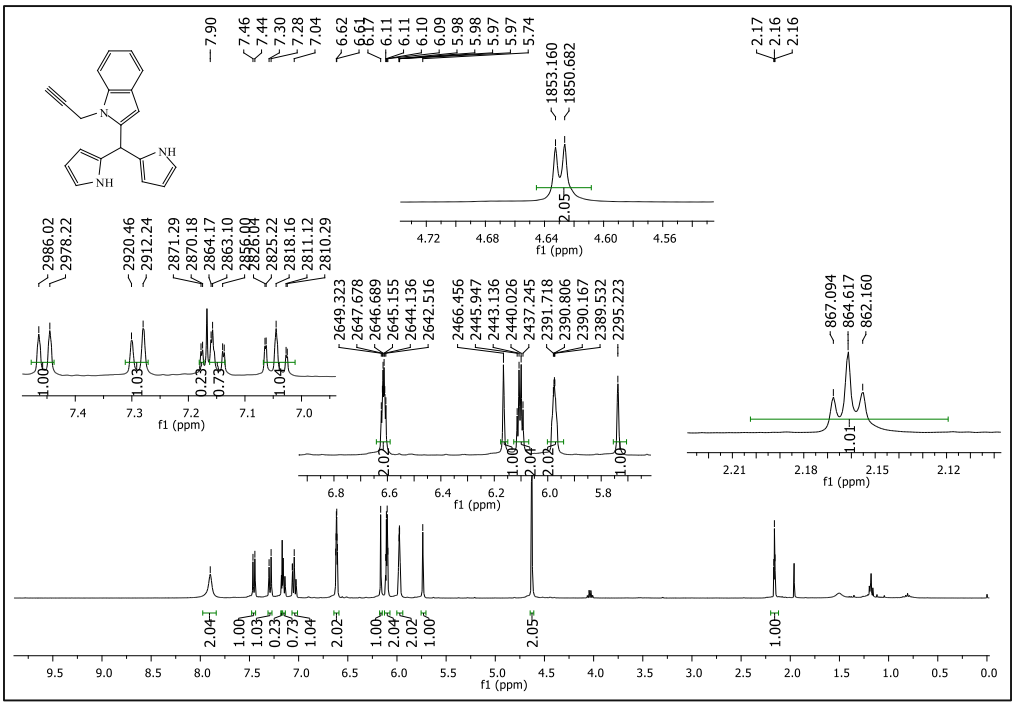

Figure 22 ^{1}H-NMR Spectrum of Compound **41b** in $CDCl_3$

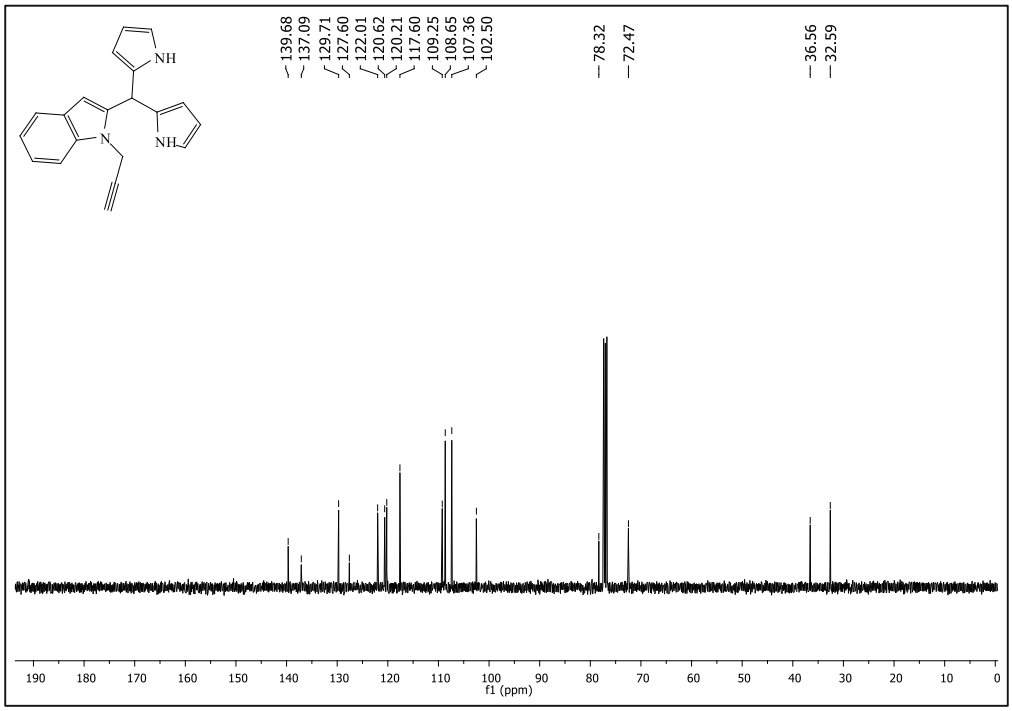

Figure 23 ^{13}C-NMR Spectrum of Compound **41b** in $CDCl_3$

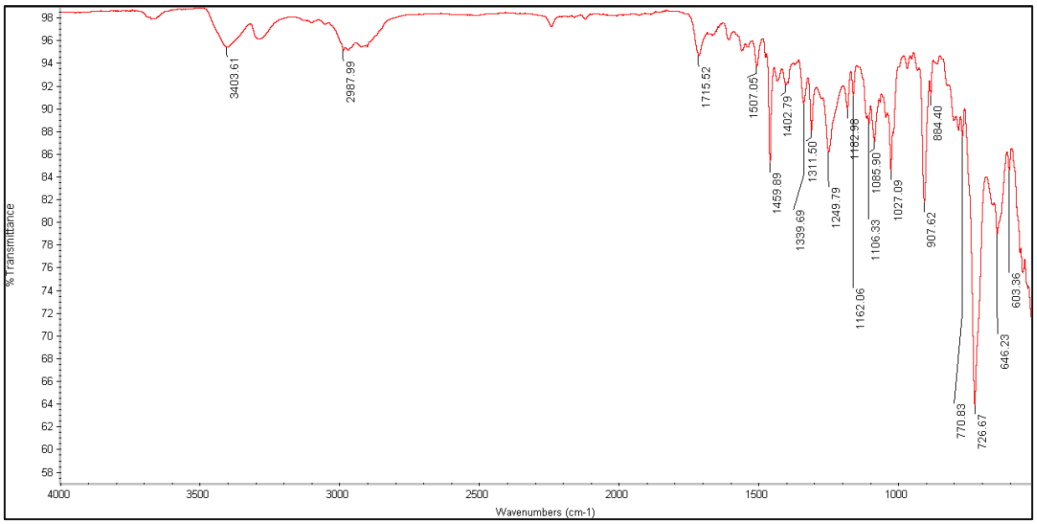

Figure 24 IR Spectrum of Compound **41b**

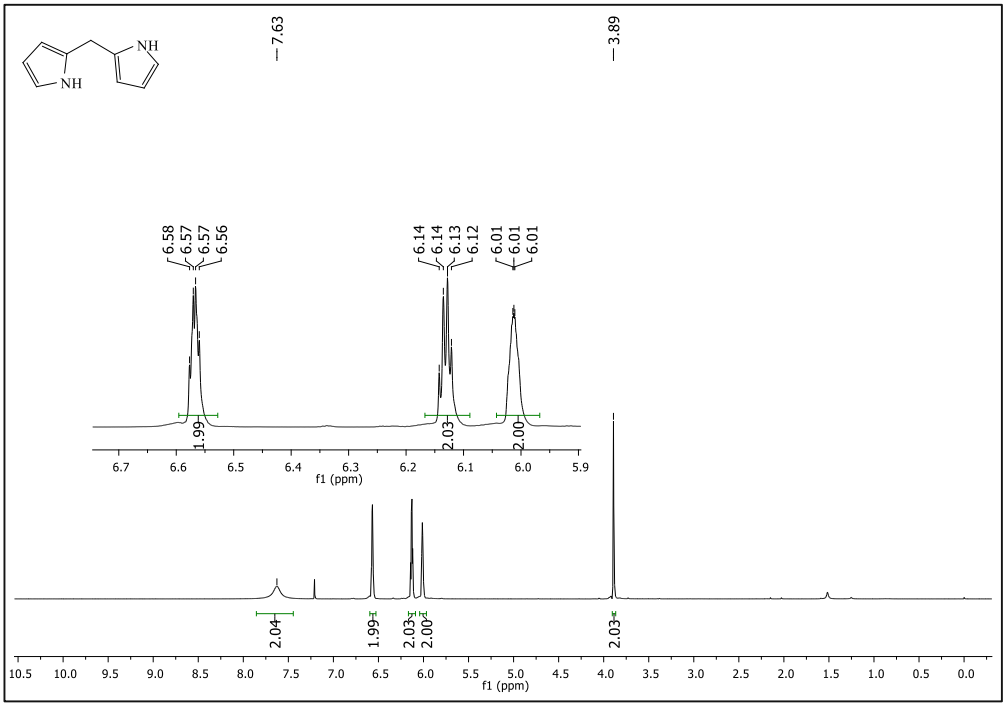

Figure 25 ^{1}H-NMR Spectrum of Compound **41g** in $CDCl_3$

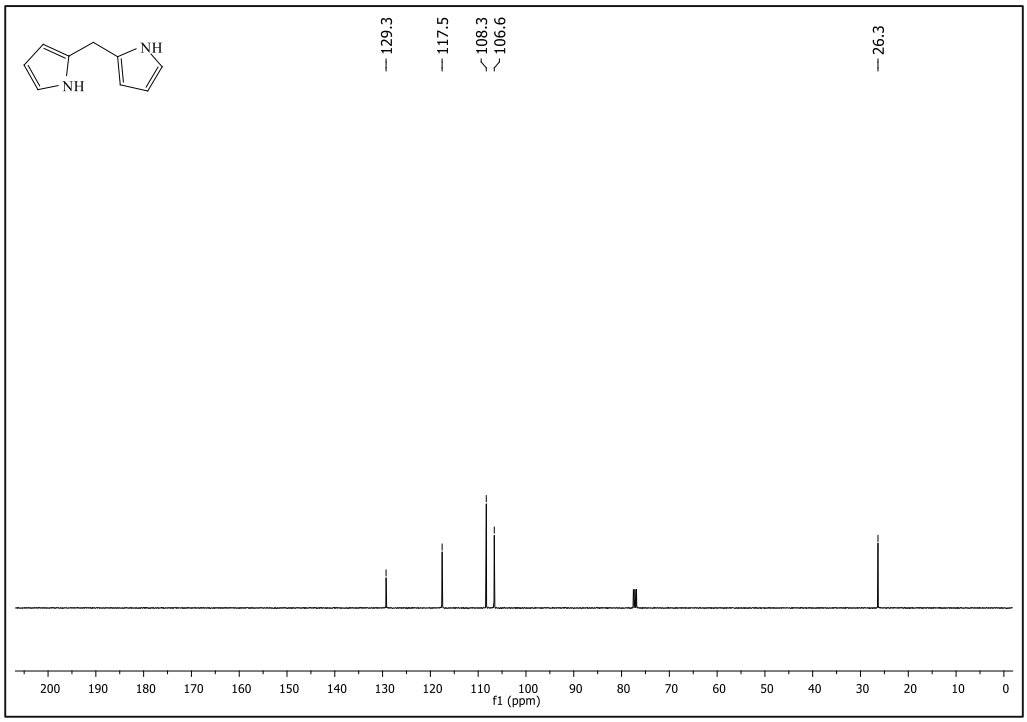

Figure 26 ^{13}C-NMR Spectrum of Compound **41g** in $CDCl_3$

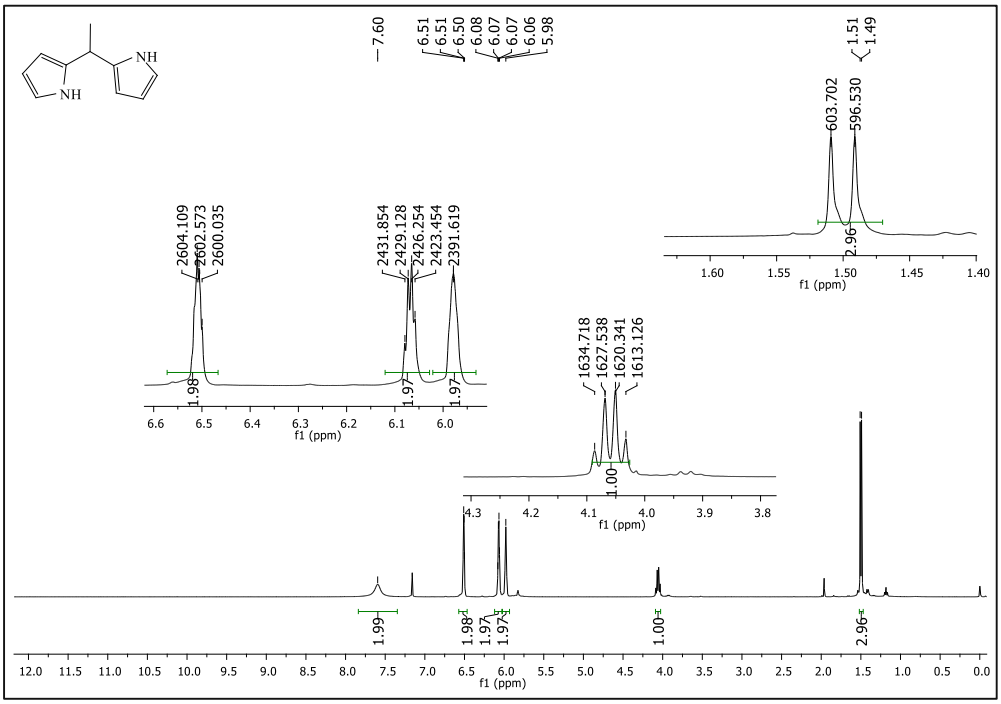

Figure 27 ^{1}H-NMR Spectrum of Compound **41f** in $CDCl_3$

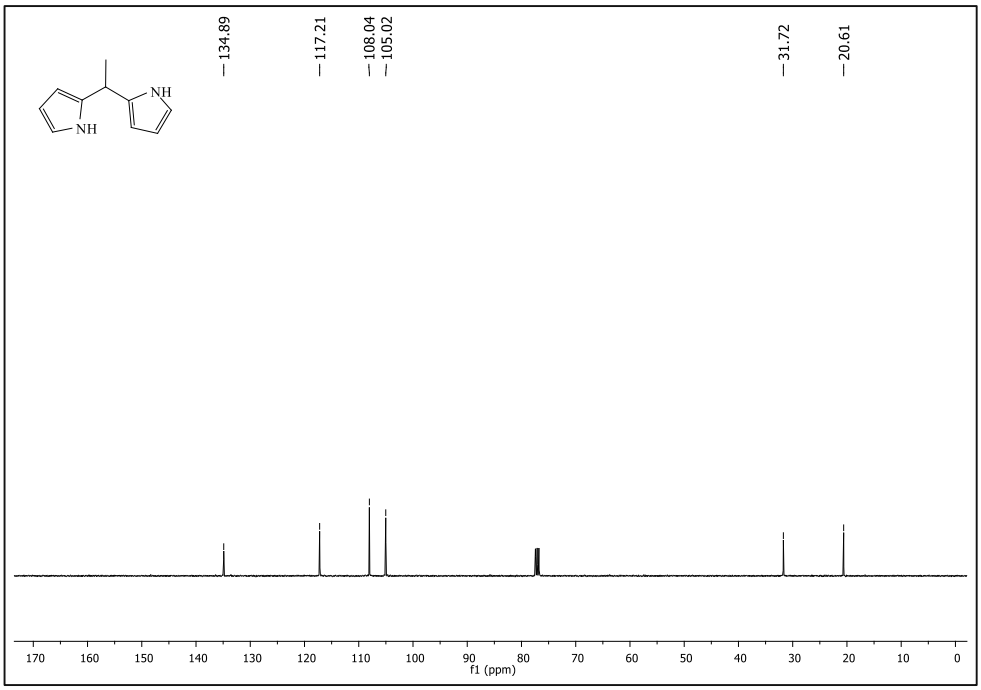

Figure 28 ^{13}C-NMR Spectrum of Compound **41f** in $CDCl_3$

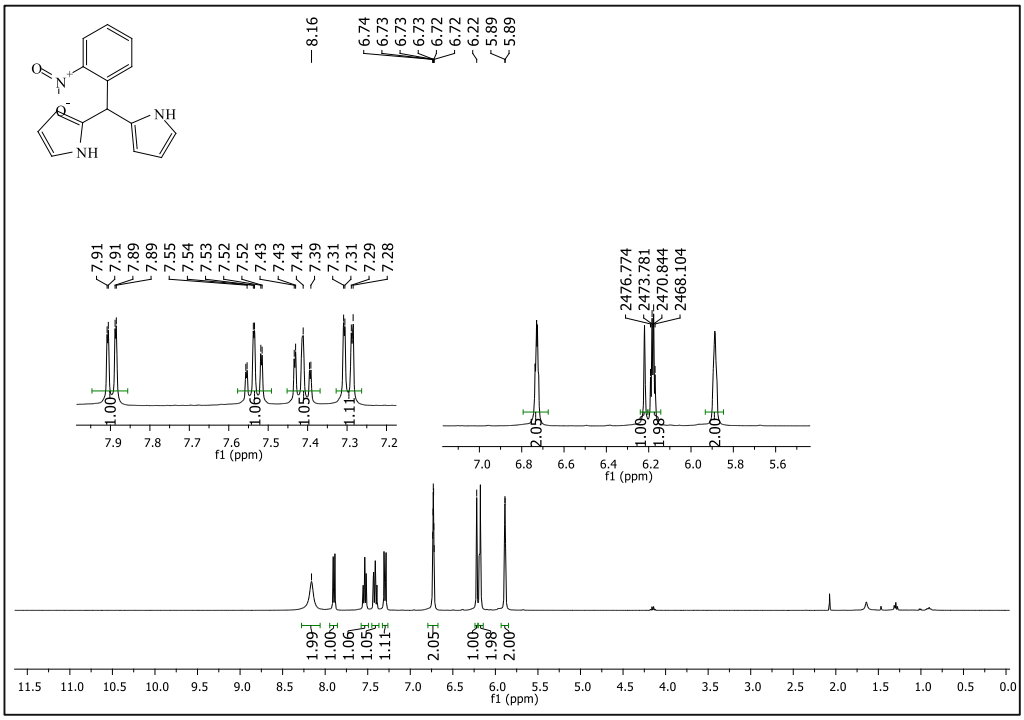

Figure 29 ^{1}H-NMR Spectrum of Compound **41h** in $CDCl_3$

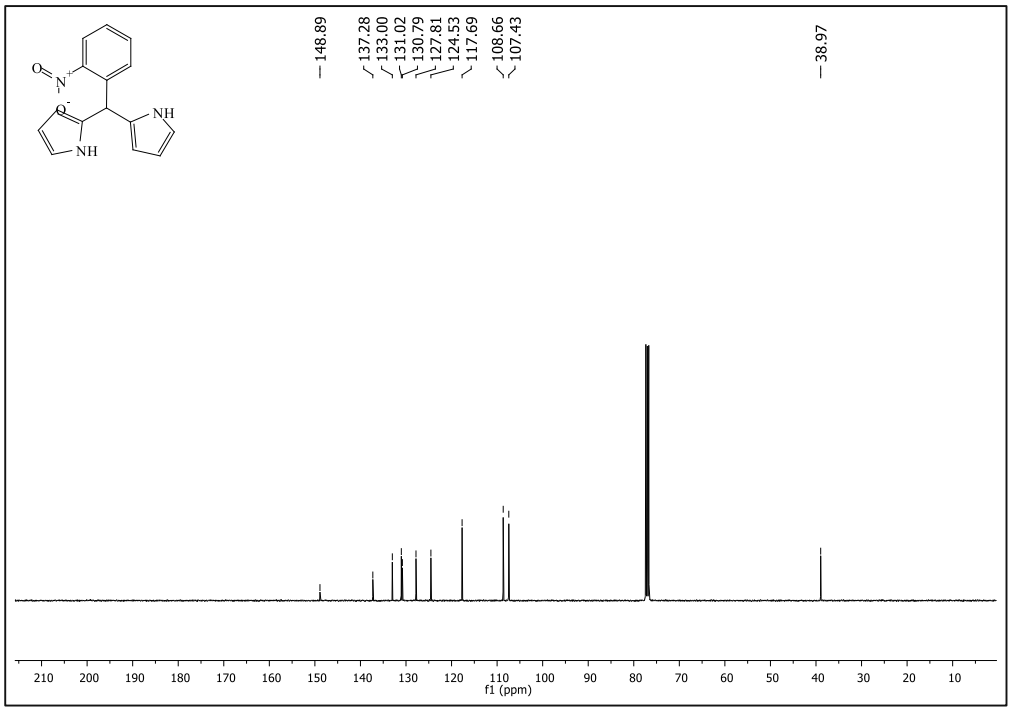

Figure 30 ^{13}C-NMR Spectrum of Compound **45h** in $CDCl_3$

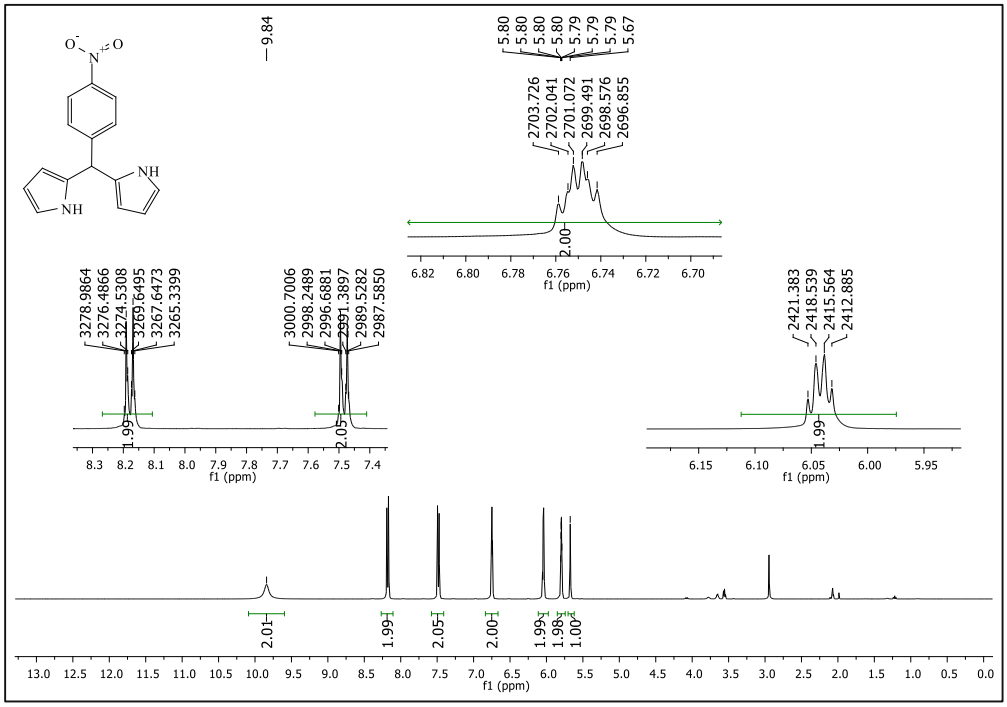

Figure 31 ^{1}H-NMR Spectrum of Compound **41i** in CD_3COCD_3

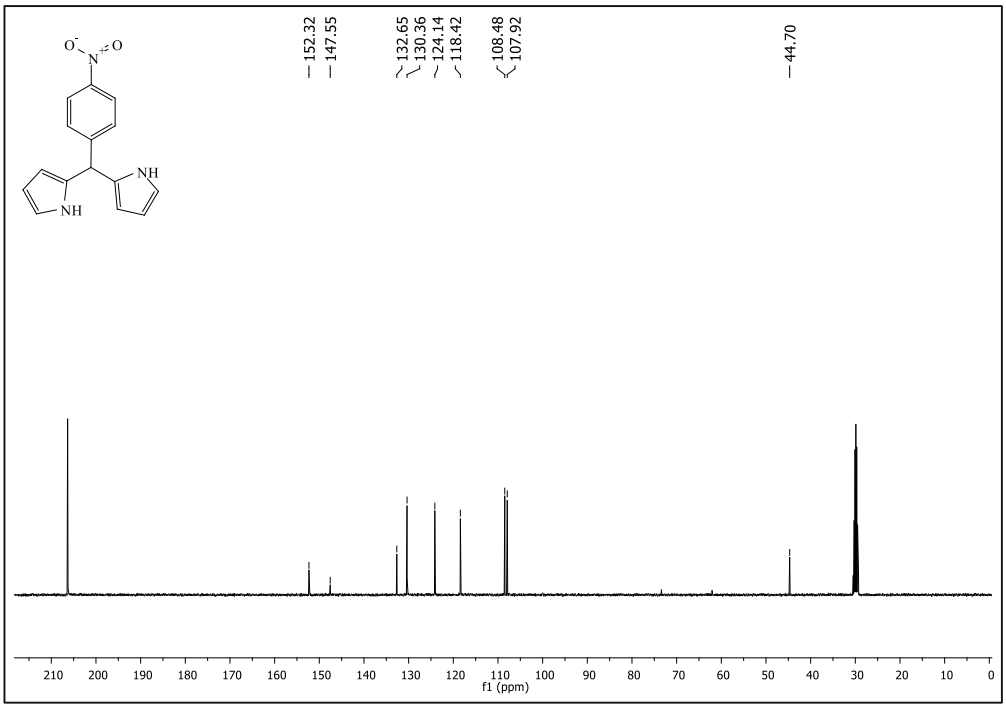

Figure 32 ^{13}C-NMR Spectrum of Compound **41i** in CD_3COCD_3

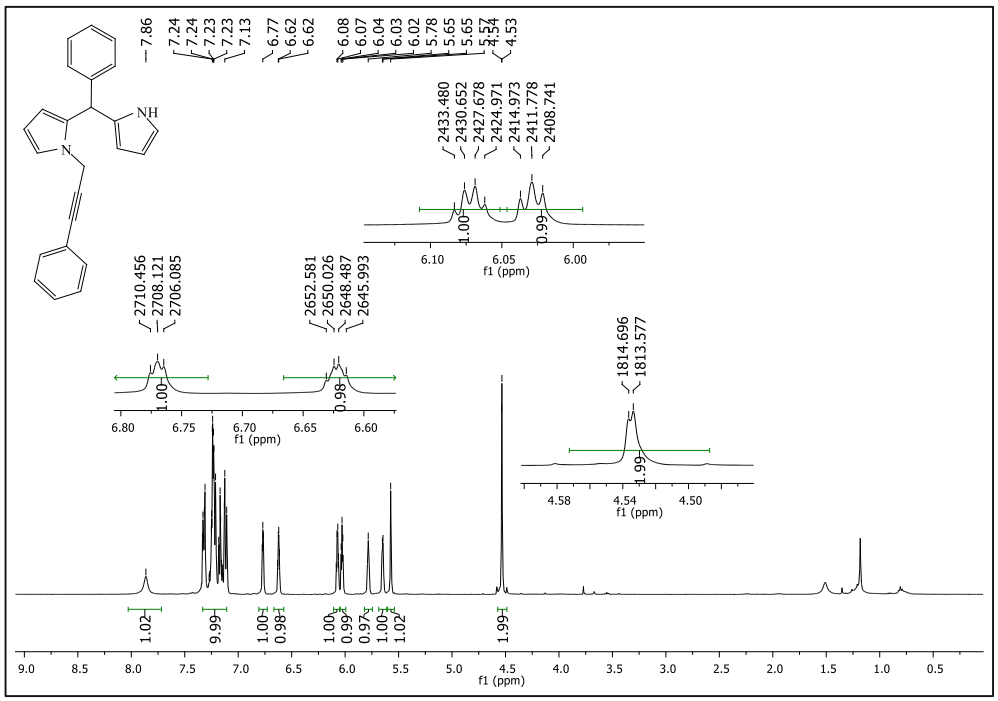

Figure 33 ^{1}H-NMR Spectrum of Compound **58** in $CDCl_3$

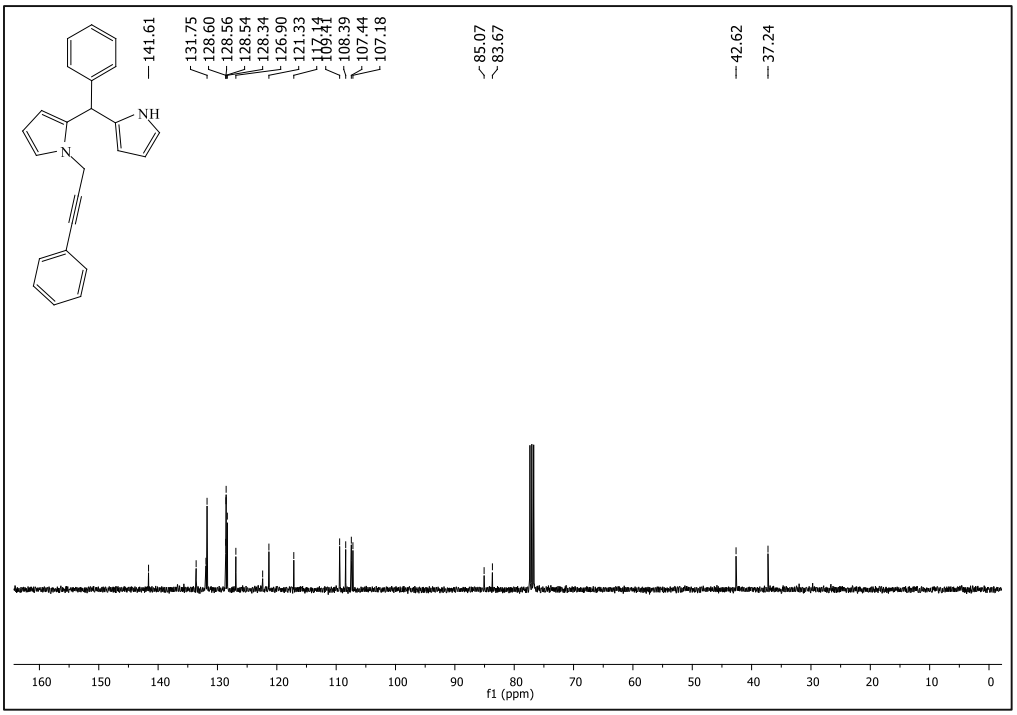

Figure 34 ^{13}C-NMR Spectrum of Compound **58** in $CDCl_3$

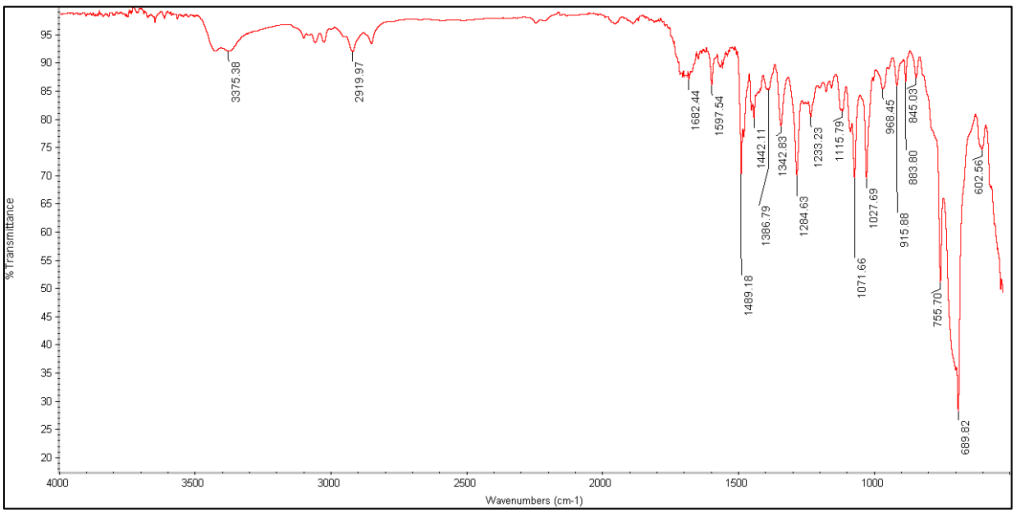

Figure 35 IR Spectrum of Compound **58**

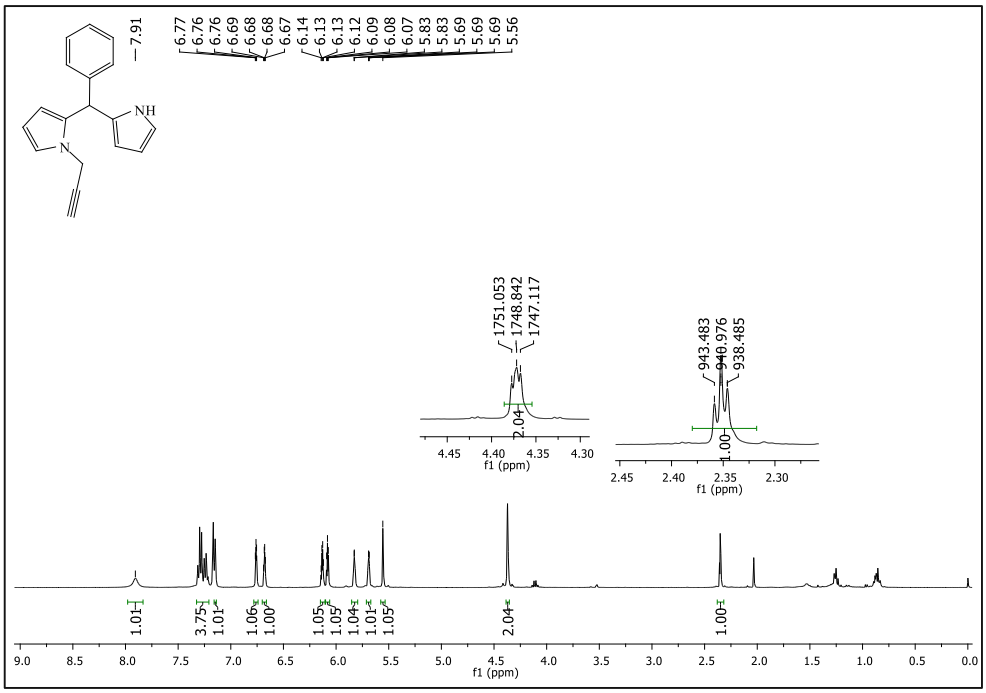

Figure 36 ^{1}H-NMR Spectrum of Compound **47a** in $CDCl_3$

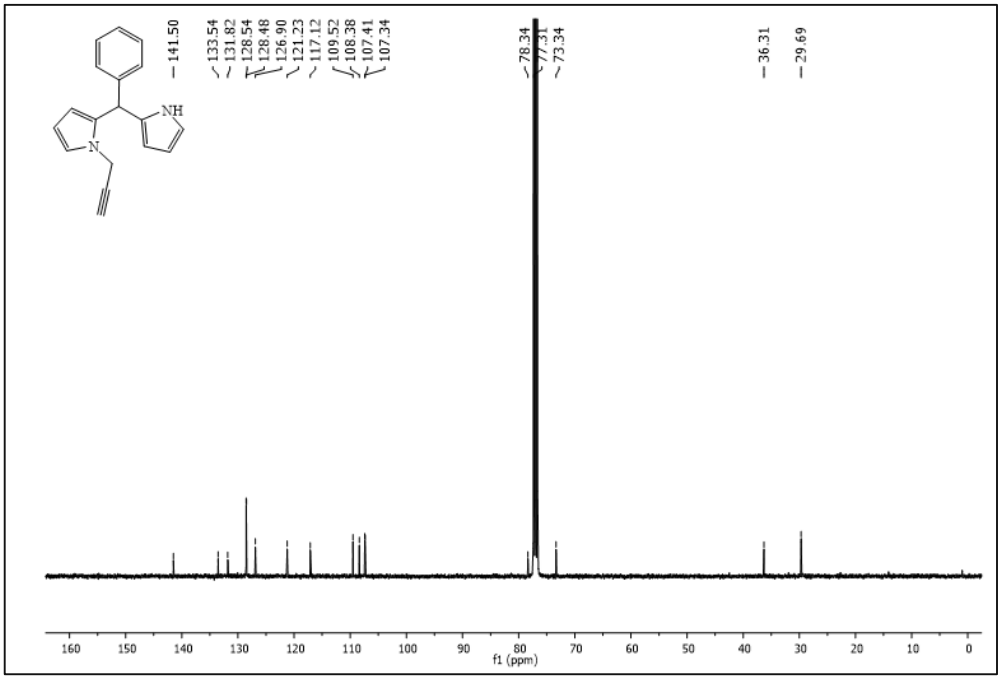

Figure 37 ^{13}C-NMR Spectrum of Compound **47a** in $CDCl_3$

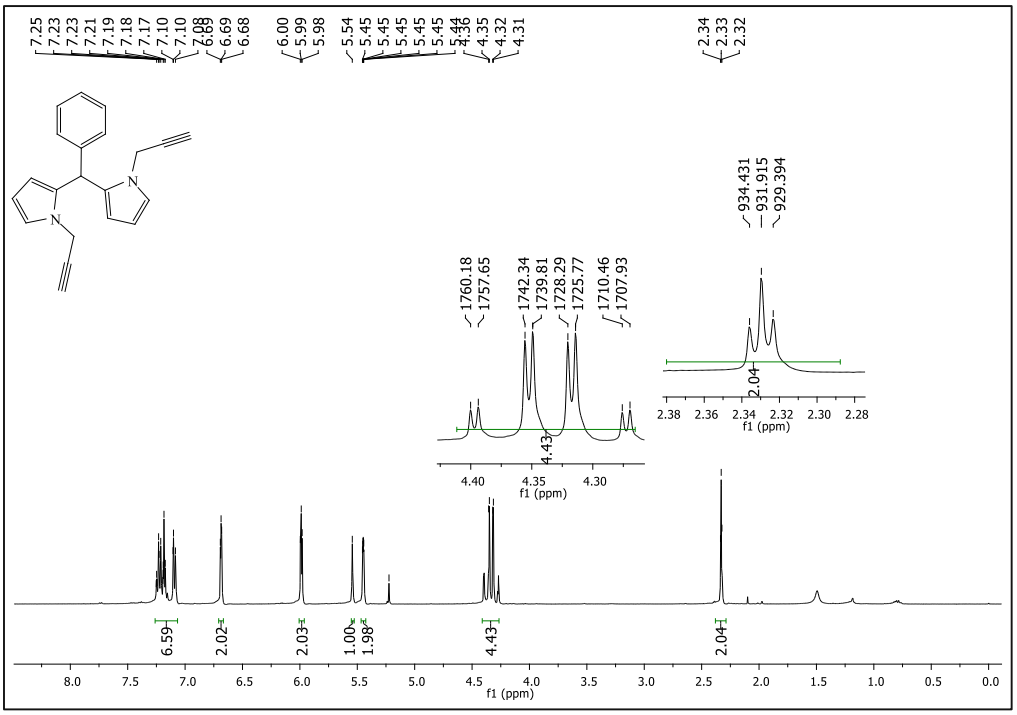

Figure 38 ^{1}H-NMR Spectrum of Compound **48a** in $CDCl_3$

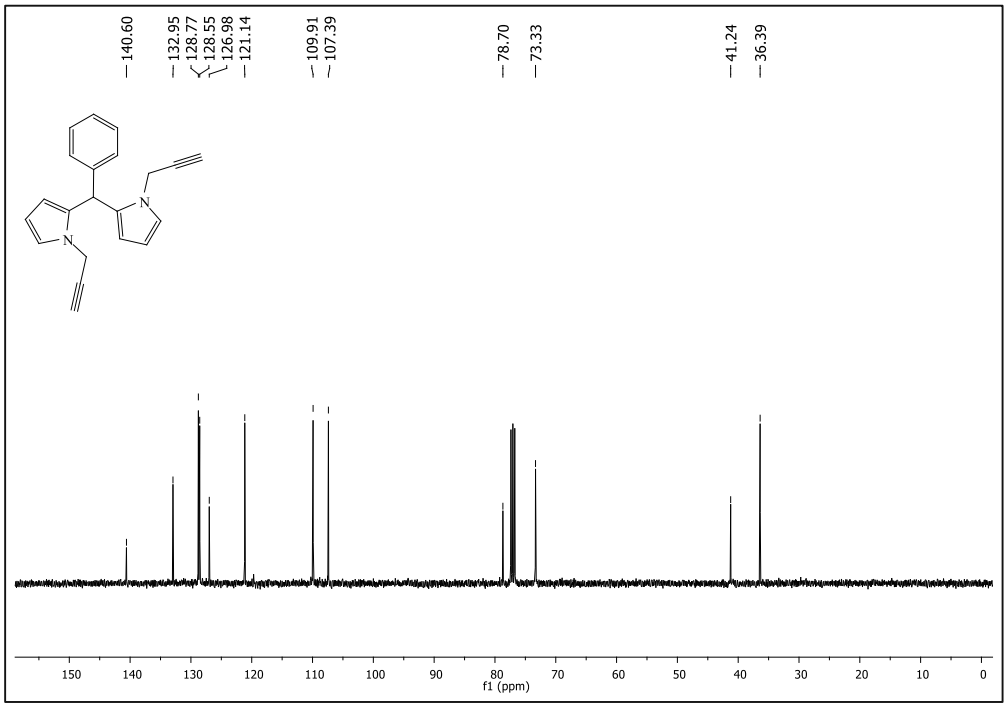

Figure 39 ^{13}C-NMR Spectrum of Compound **48a** in $CDCl_3$

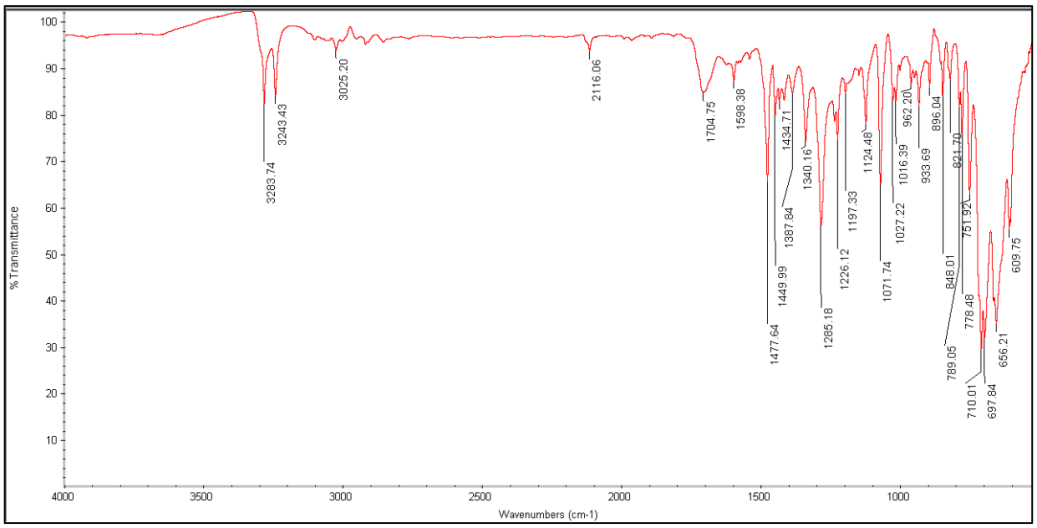

Figure 40 IR Spectrum of Compound **48a**

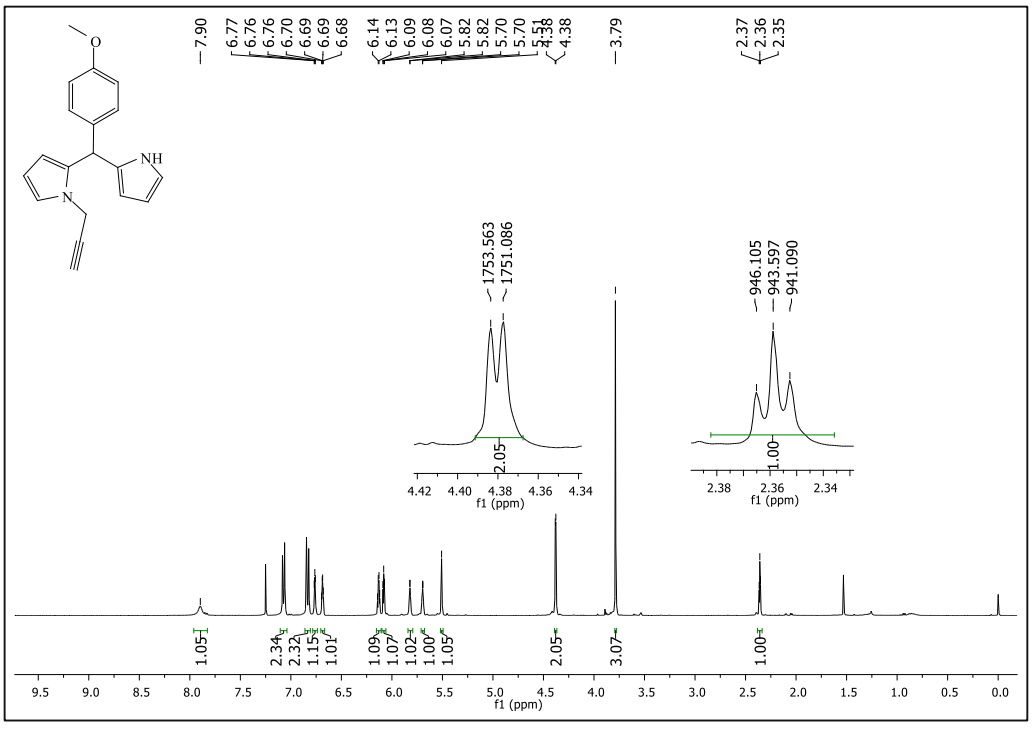

Figure 41 ^{1}H-NMR Spectrum of Compound **47d** in $CDCl_3$

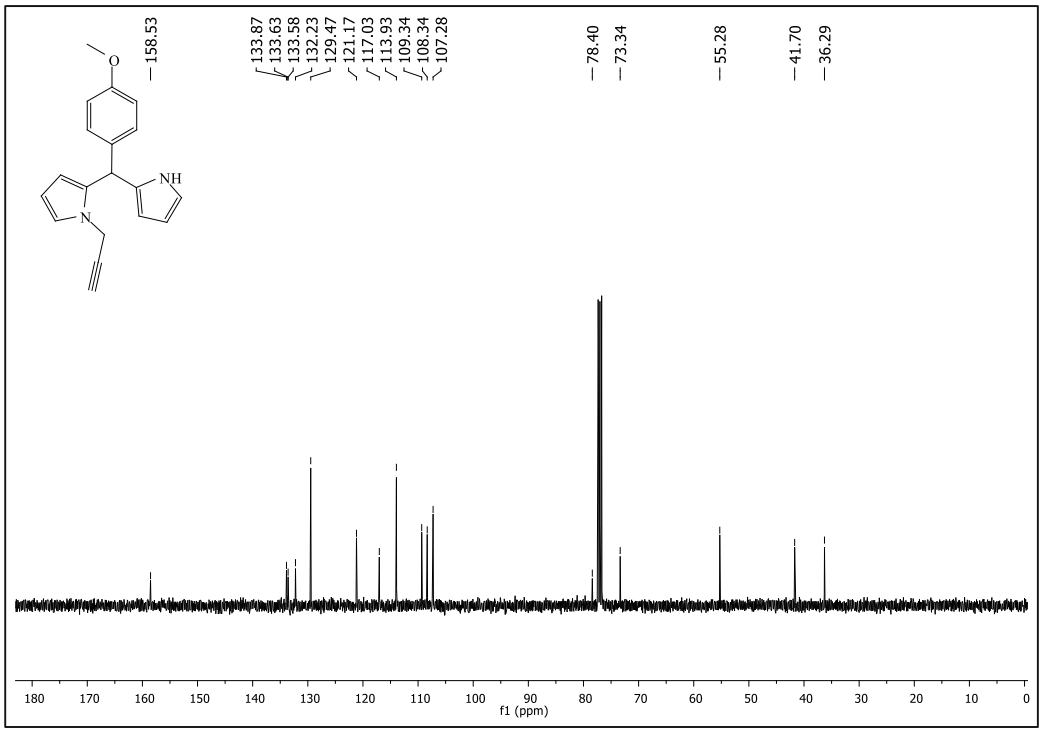

Figure 42 ^{13}C-NMR Spectrum of Compound **47d** in $CDCl_3$

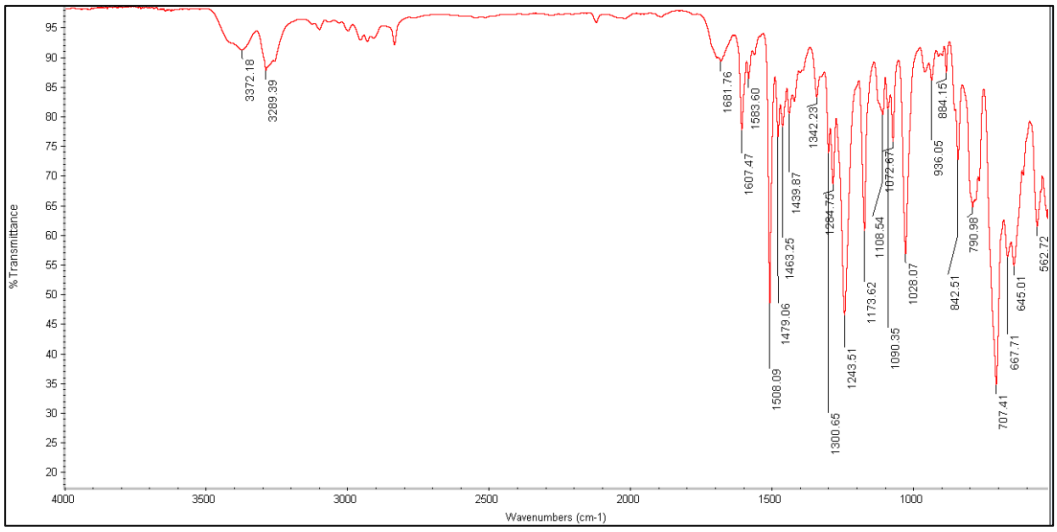

Figure 43 IR Spectrum of Compound **47d**

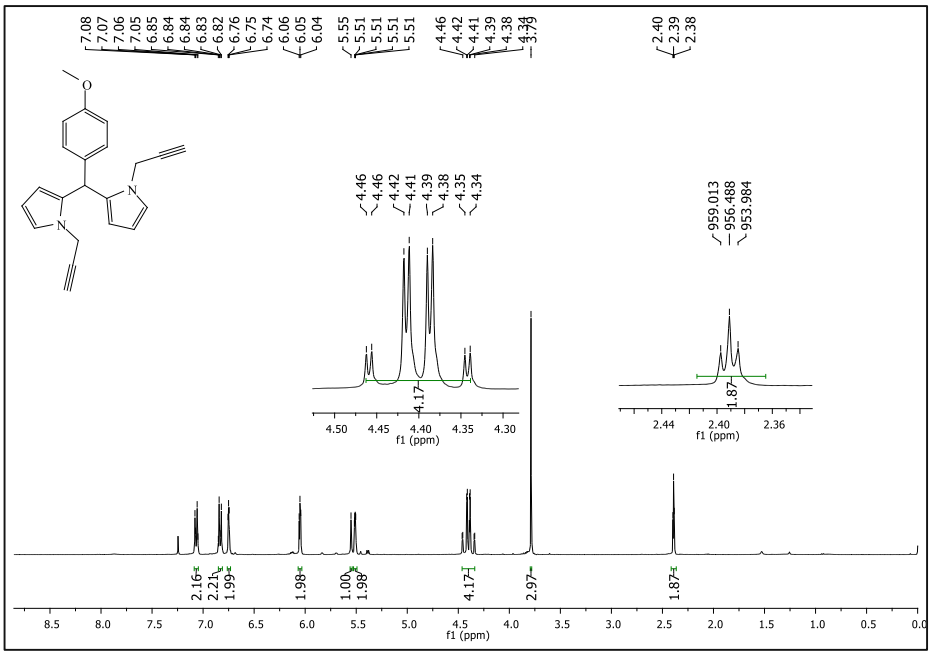

Figure 44 ^{1}H-NMR Spectrum of **48d** in $CDCl_3$

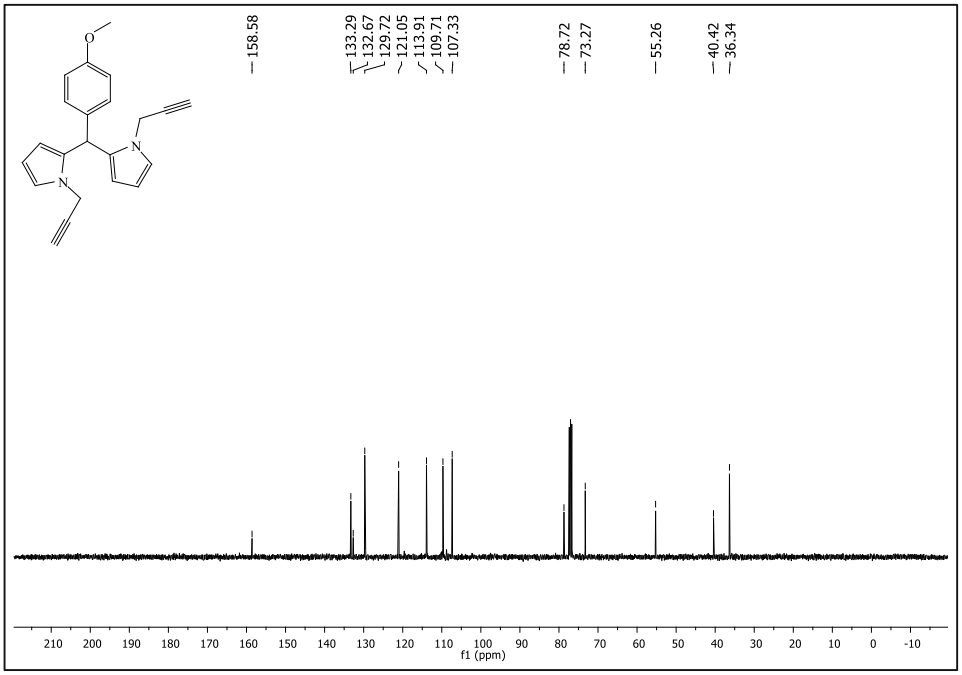

Figure 45 ^{13}C-NMR Spectrum of Compound **48d** in $CDCl_3$

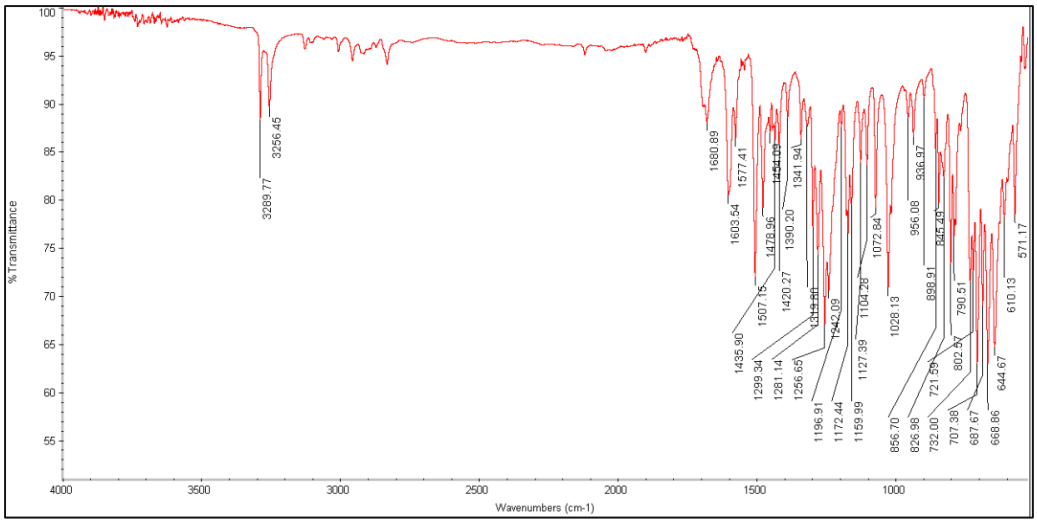

Figure 46 IR Spectrum of Compound **48d**

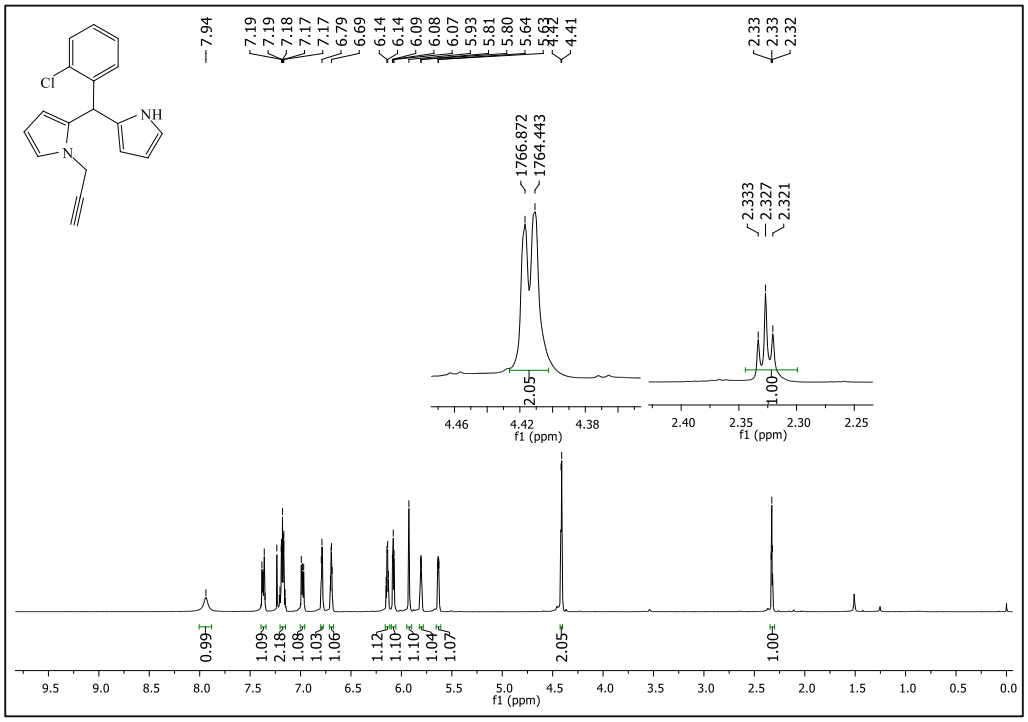

Figure 47 ^{1}H-NMR Spectrum of Compound **47e** in $CDCl_3$

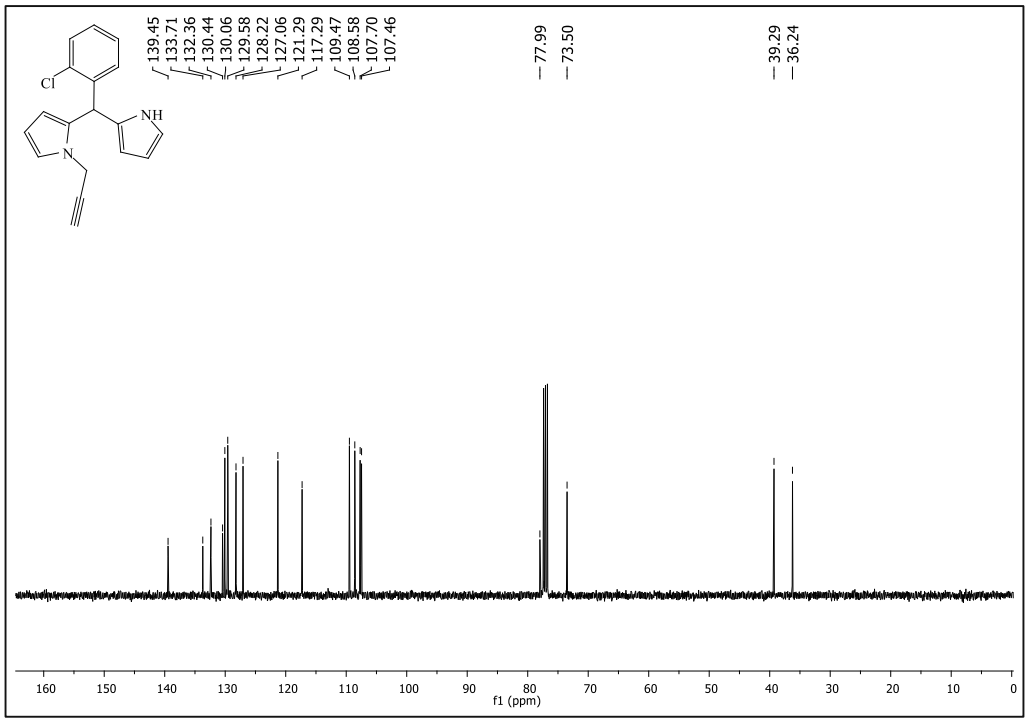

Figure 48 ^{13}C-NMR Spectrum of Compound **47e** in $CDCl_3$

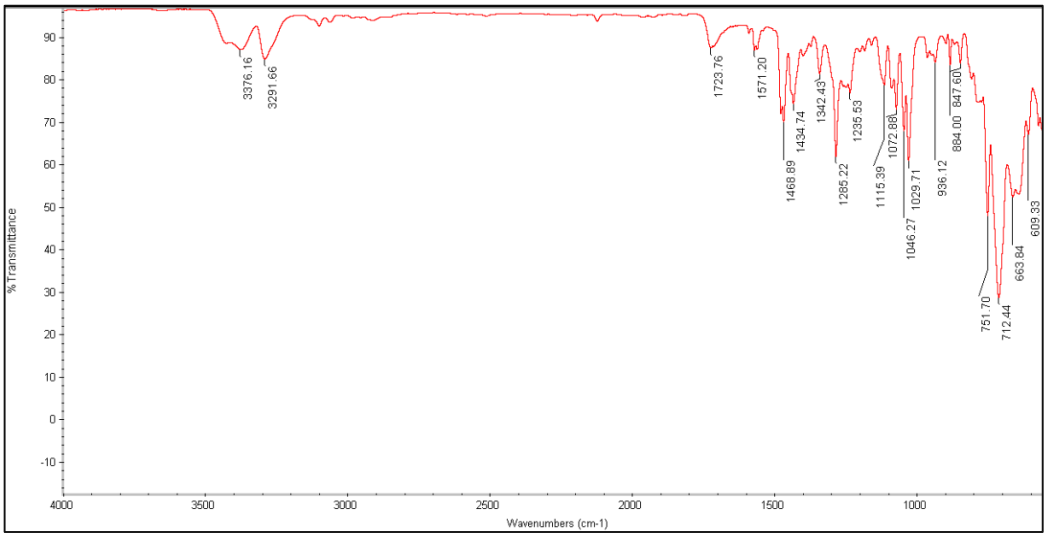

Figure 49 IR Spectrum of Compound **47e**

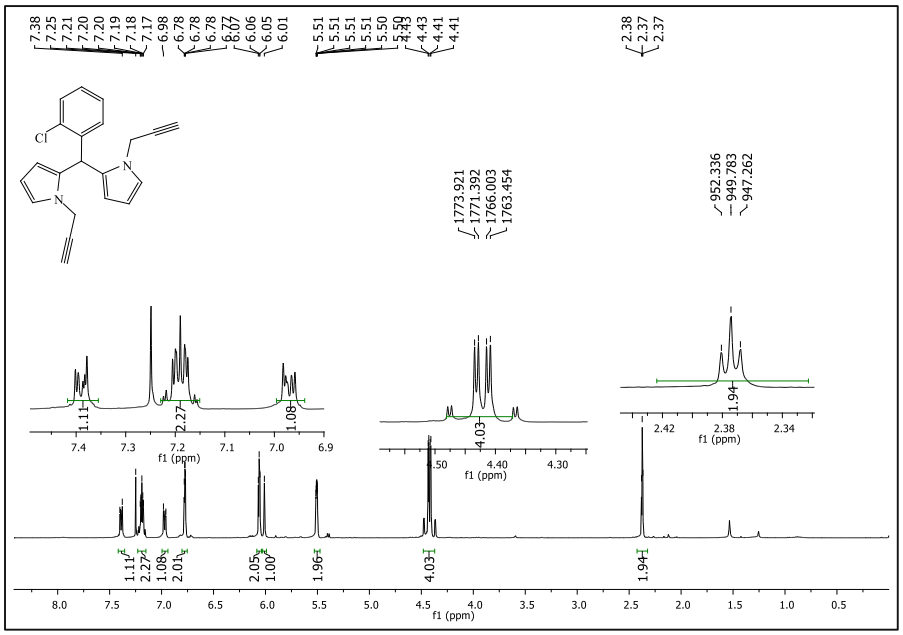

Figure 50 ^{1}H-NMR Spectrum of Compound **48e** in $CDCl_3$

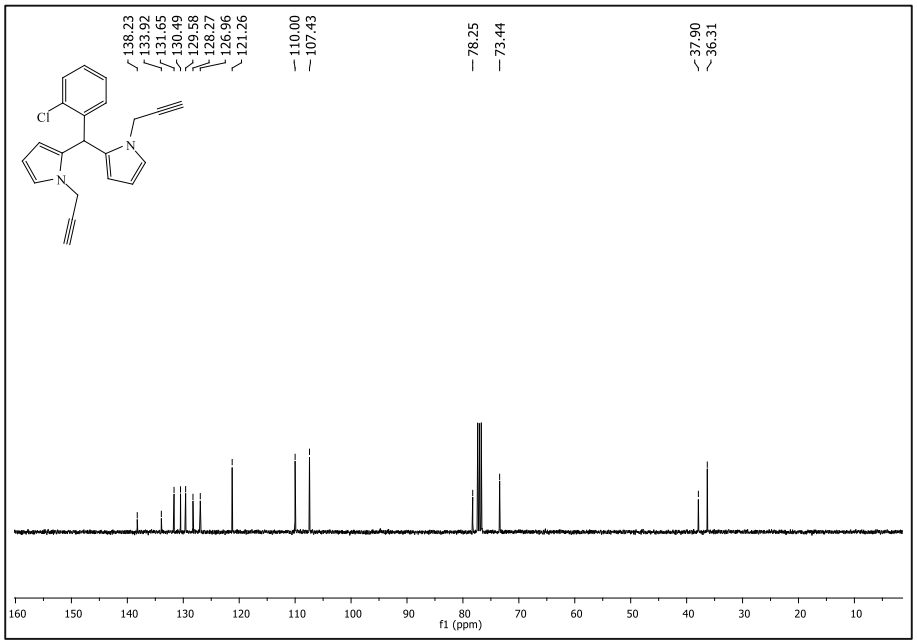

Figure 51 ^{13}C-NMR Spectrum of Compound **48e** in $CDCl_3$

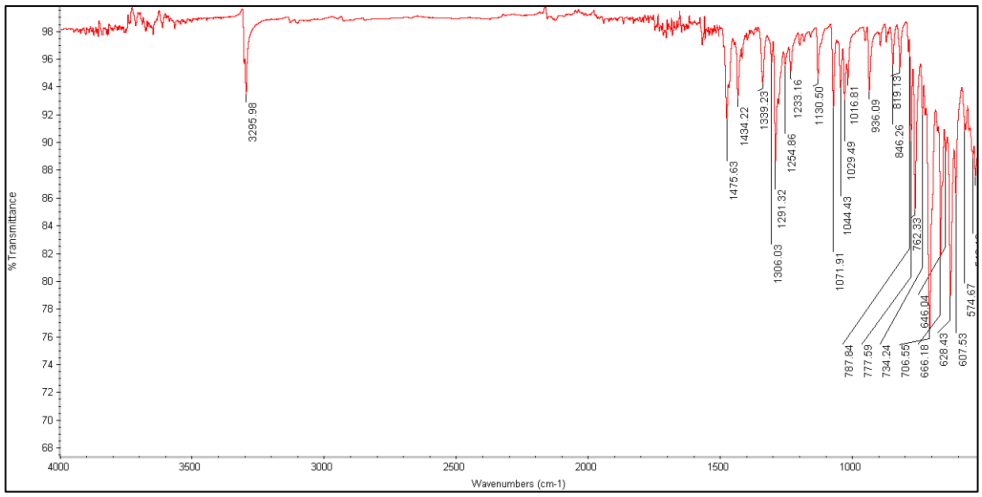

Figure 52 IR Spectrum of Compound **48e**

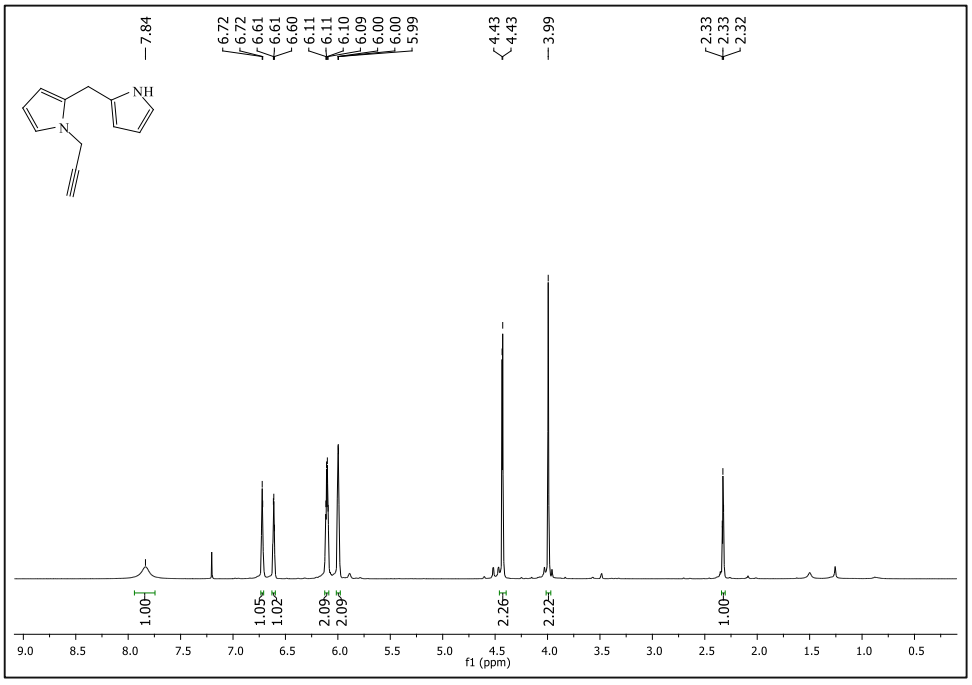

Figure 53 ^{1}H-NMR Spectrum of Compound **47g** in $CDCl_3$

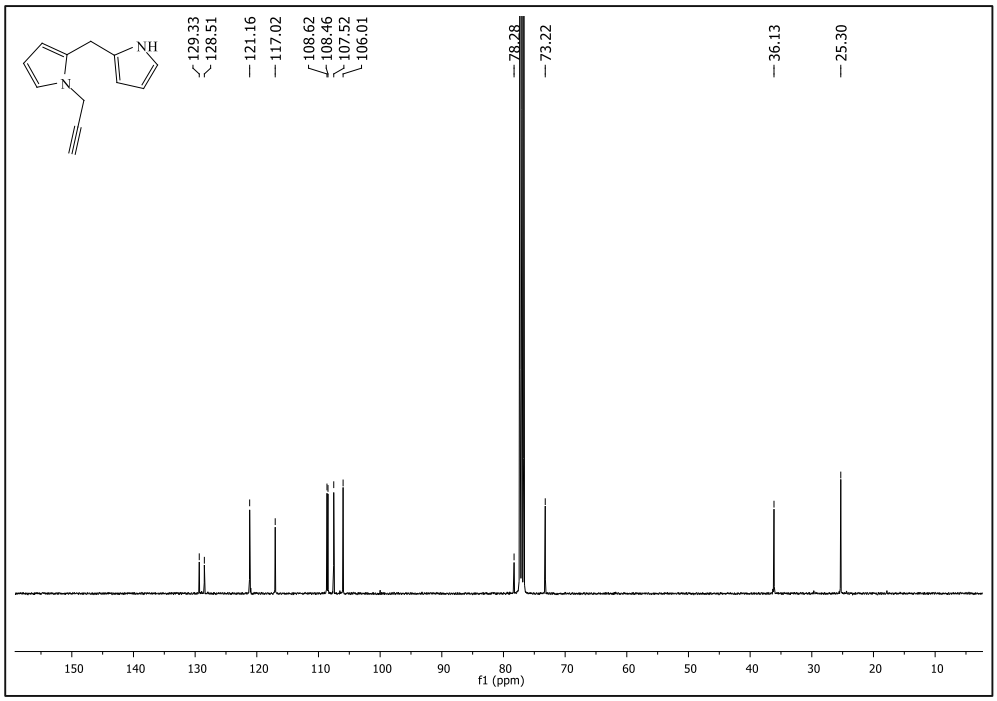

Figure 54 ^{13}C-NMR Spectrum of Compound **47g**

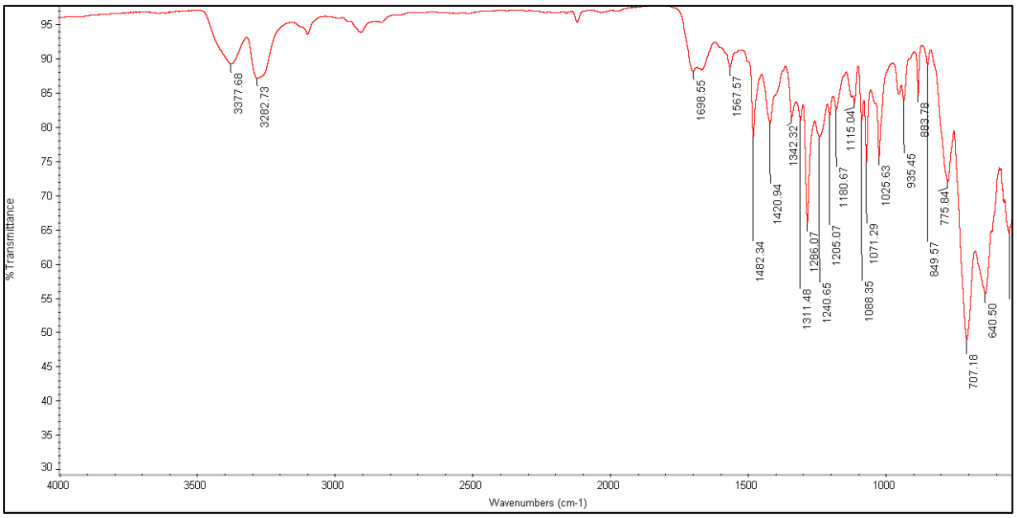

Figure 55 IR Spectrum of Compound **47g**

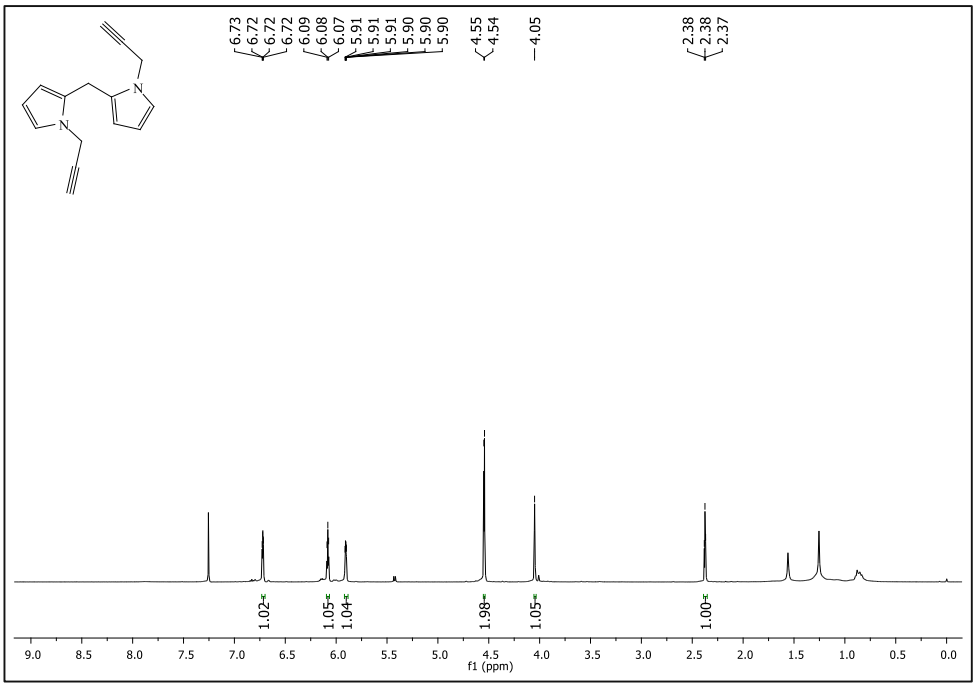

Figure 56 ^{1}H-NMR Spectrum of Compound **48g** in $CDCl_3$

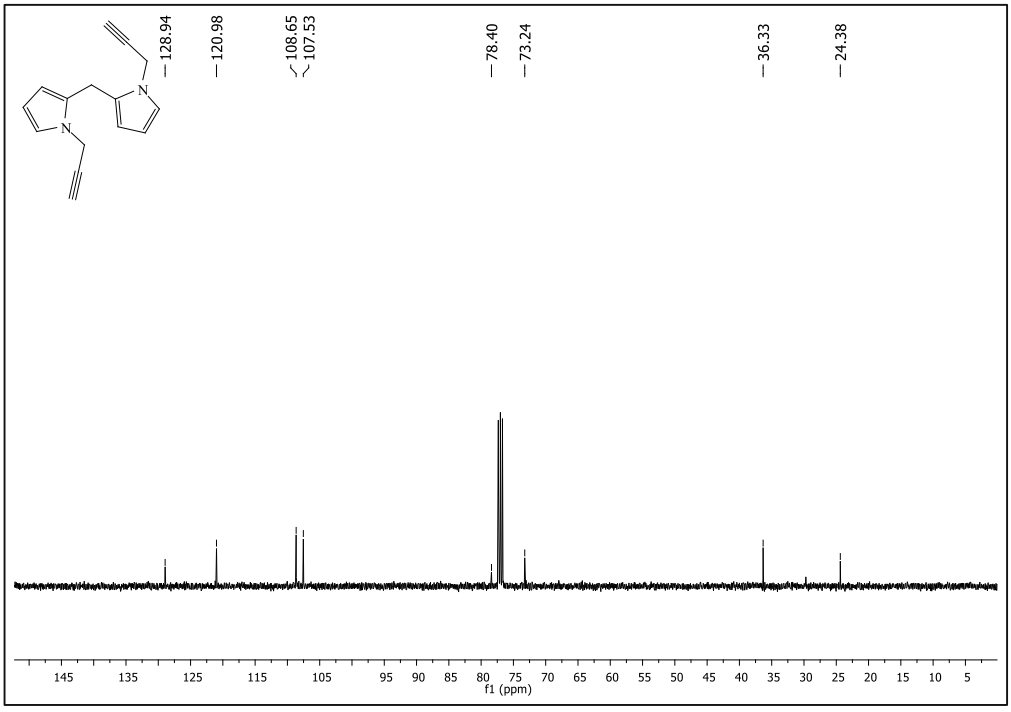

Figure 57 ^{13}C-NMR Spectrum of Compound **48g**

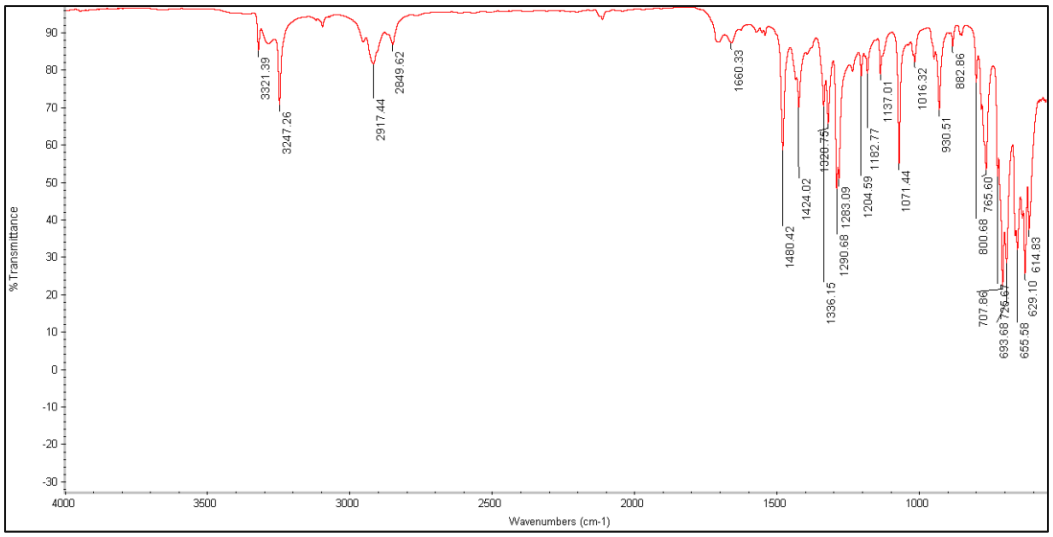

Figure 58 IR Spectrum of Compound **48g**

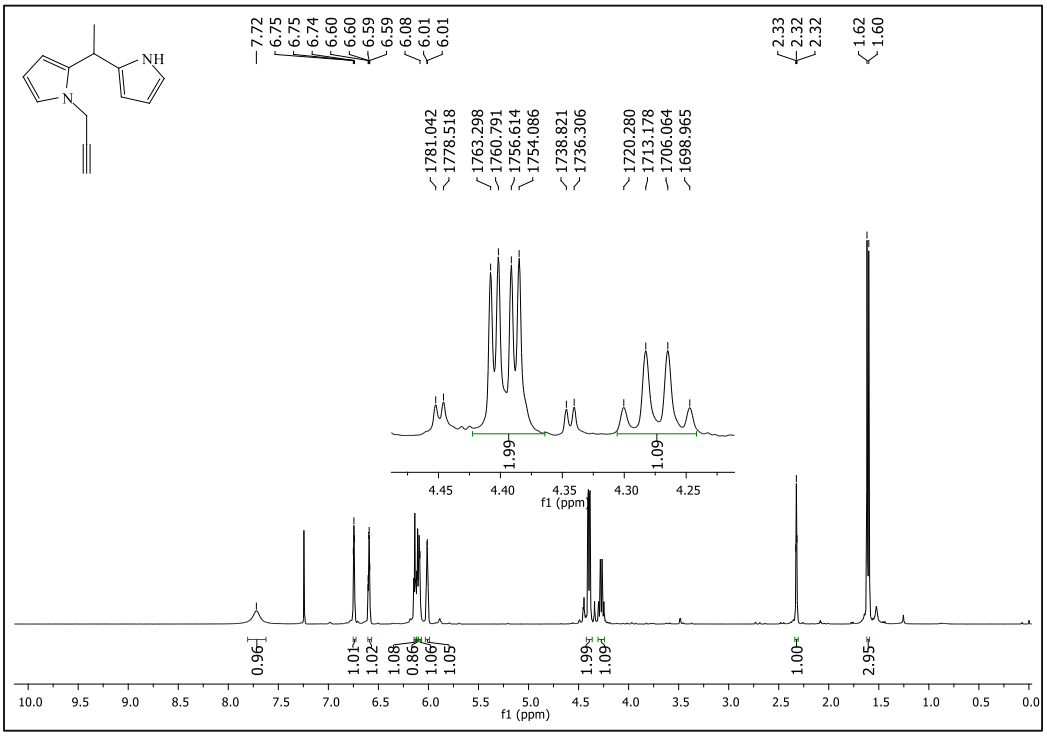

Figure 59 ^{1}H-NMR Spectrum of Compound **47f** in $CDCl_3$

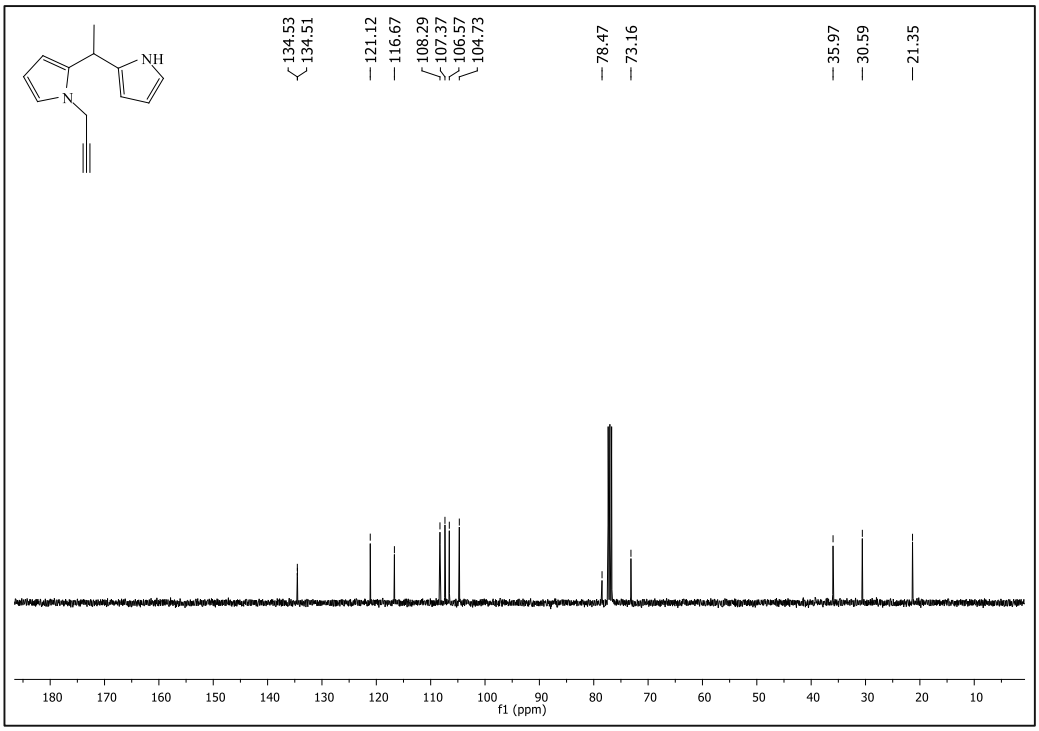

Figure 60 ^{13}C-NMR Spectrum of Compound **47f** in $CDCl_3$

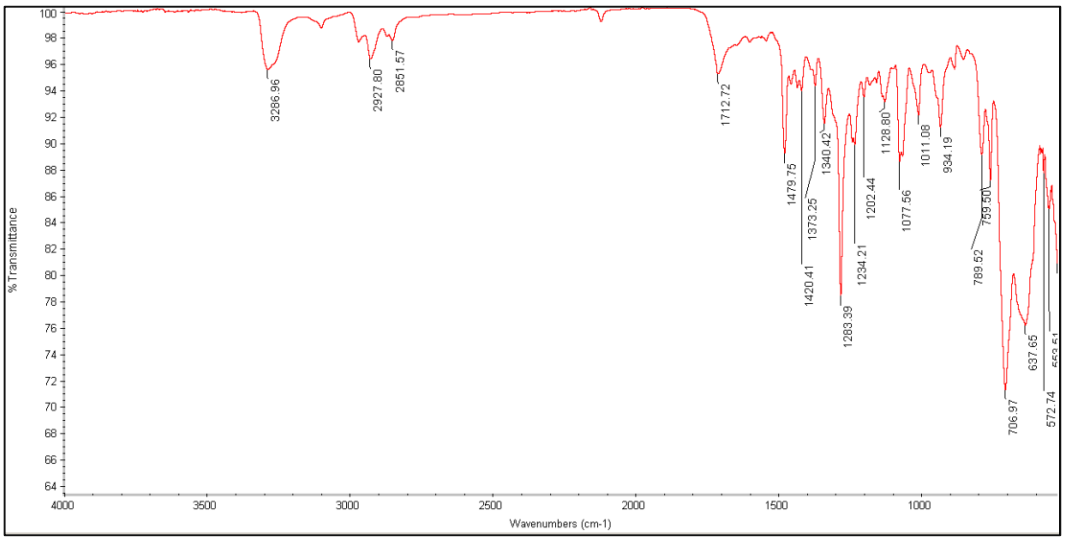

Figure 61 IR Spectrum of Compound **47f**

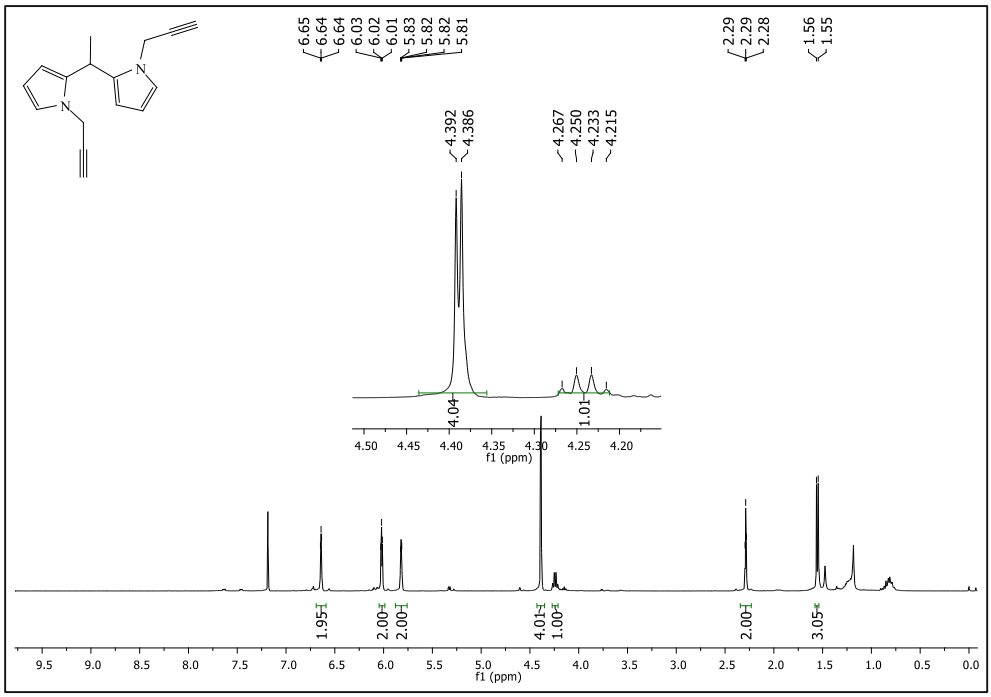

Figure 62 ^{1}H-NMR Spectrum of Compound **48f** in $CDCl_3$

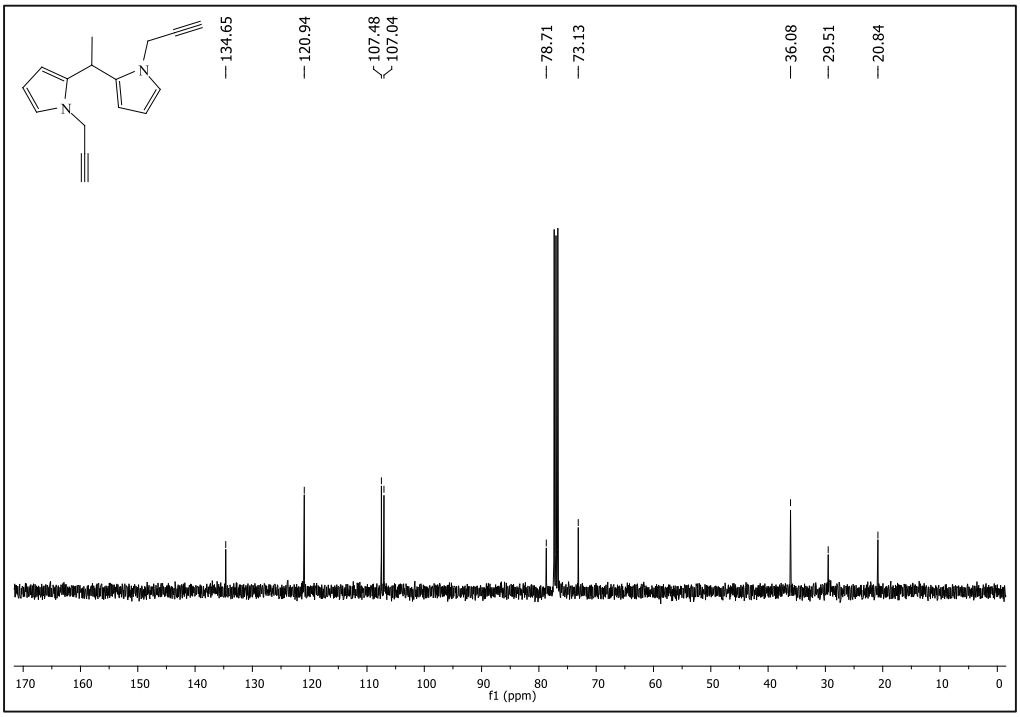

Figure 63 ^{13}C-NMR Spectrum of Compound **48f** in $CDCl_3$

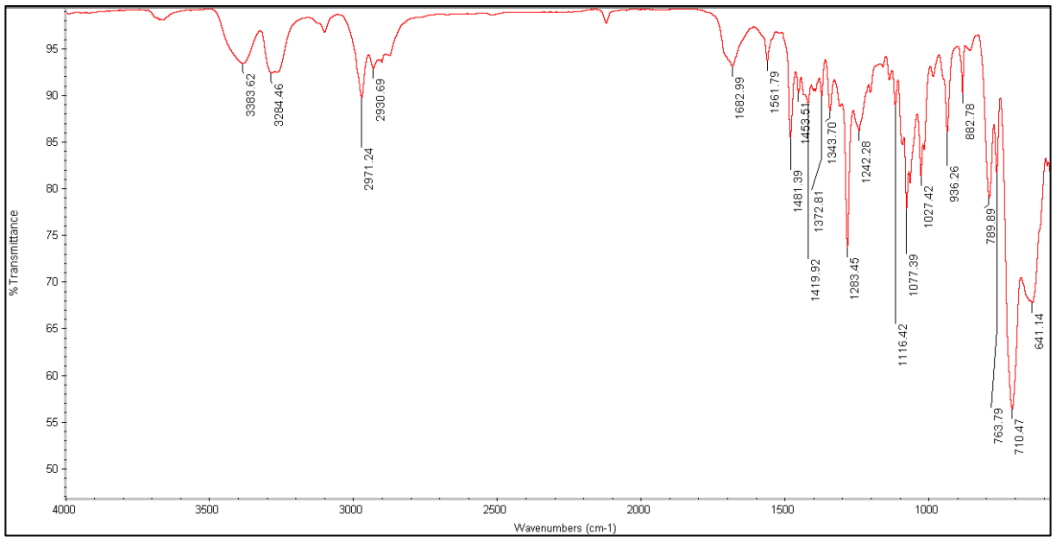

Figure 64 IR Spectrum of Compound **48f**

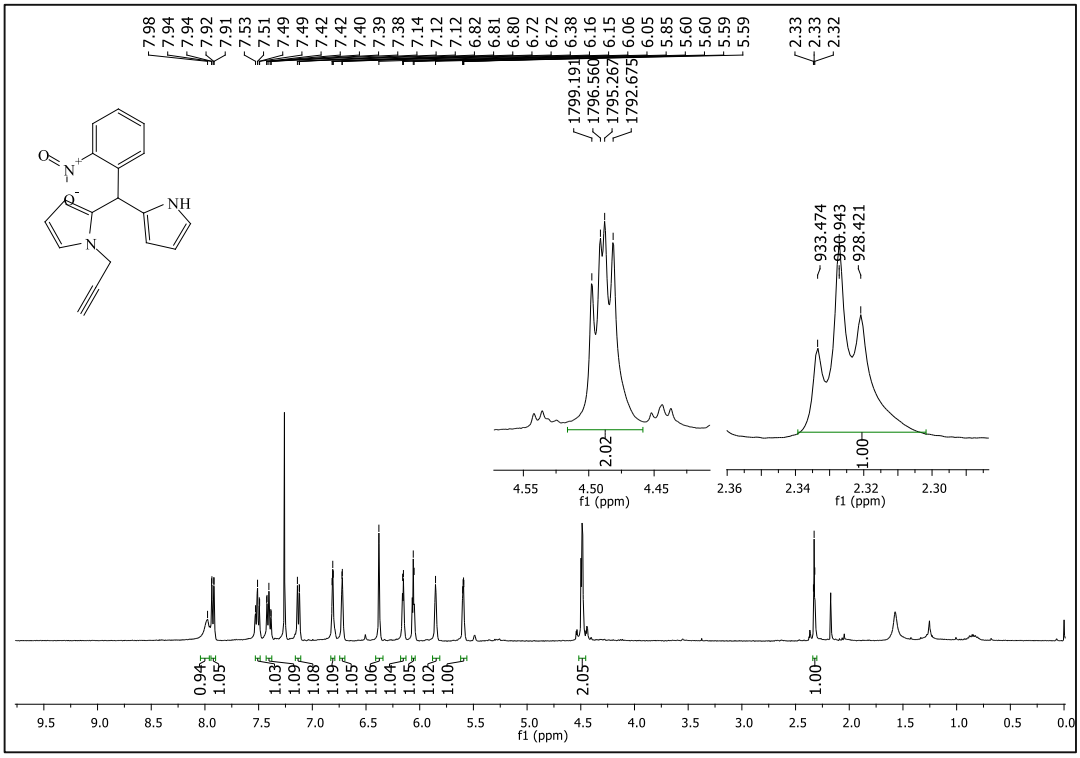

Figure 65 ^{1}H-NMR Spectrum of Compound **47h** in $CDCl_3$

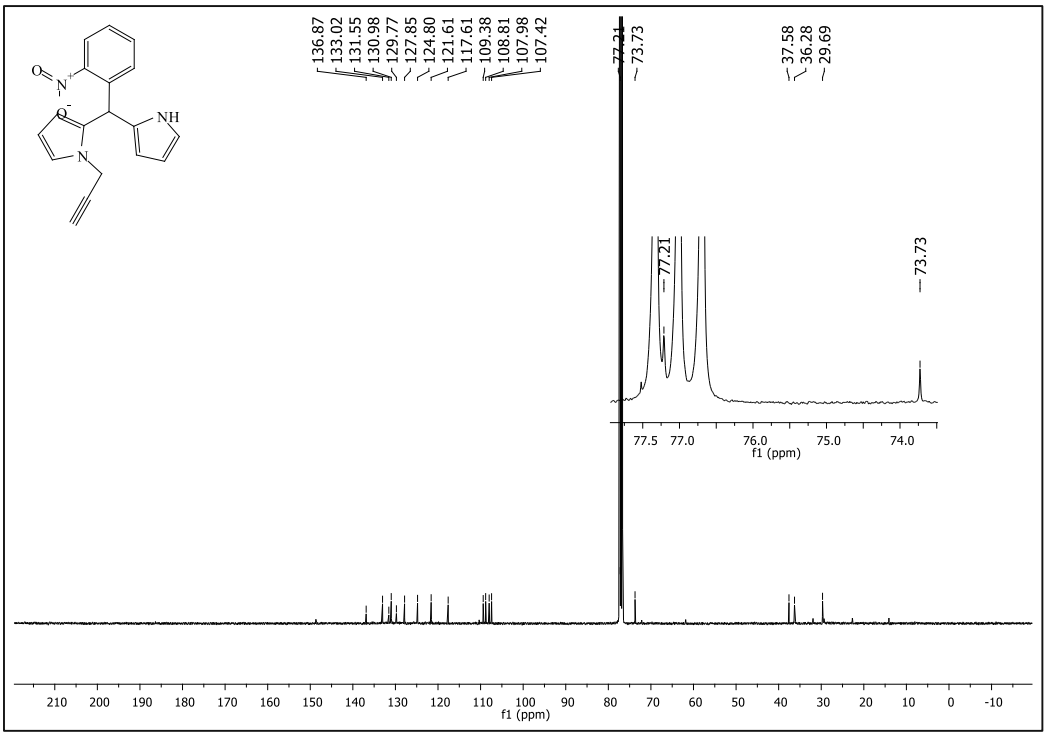

Figure 66 ^{13}C-NMR Spectrum of Compound **47h** in $CDCl_3$

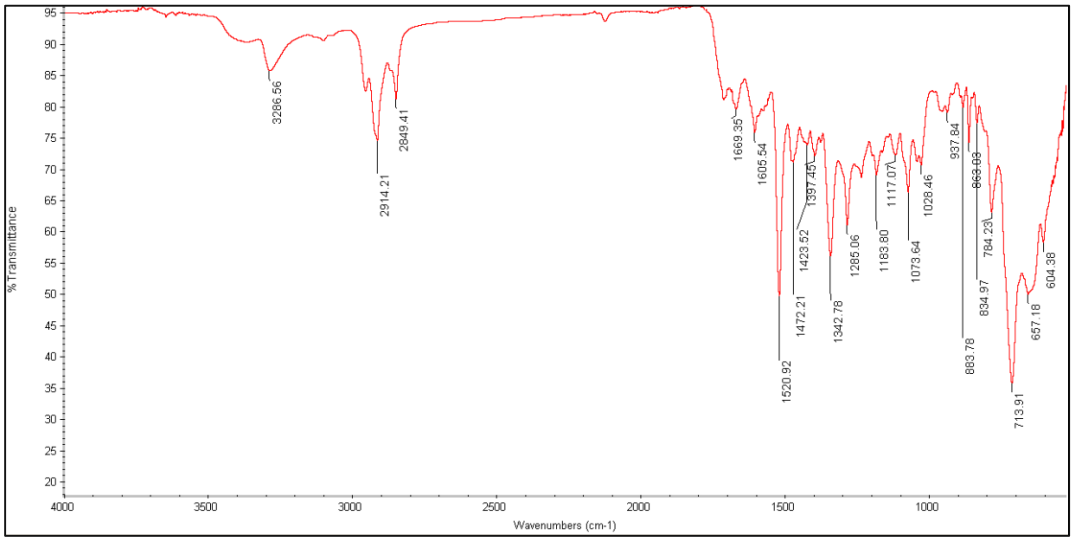

Figure 67 IR Spectrum of Compound **47h**

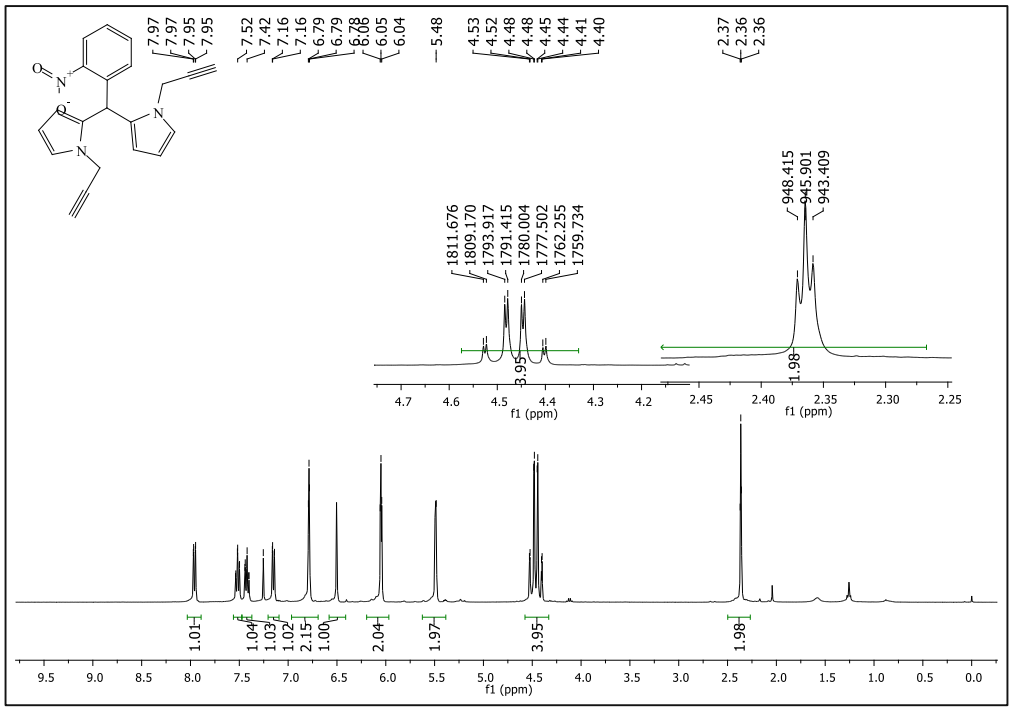

Figure 68 ^{1}H-NMR Spectrum of Compound **48h** in $CDCl_3$

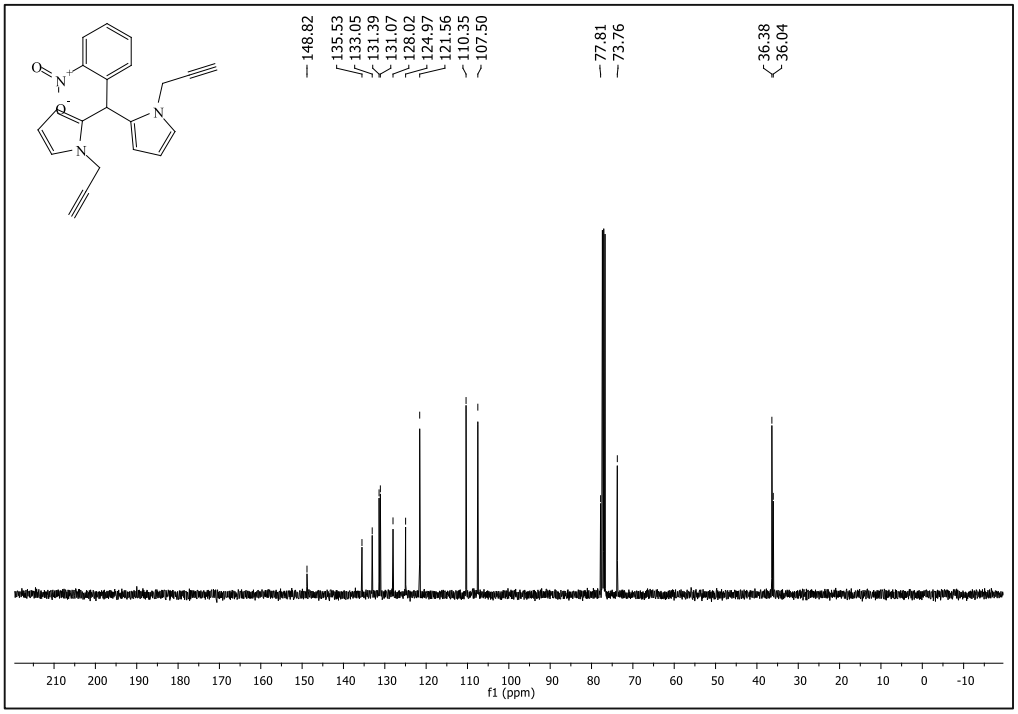

Figure 69 ^{13}C-NMR Spectrum of Compound **48h** in $CDCl_3$

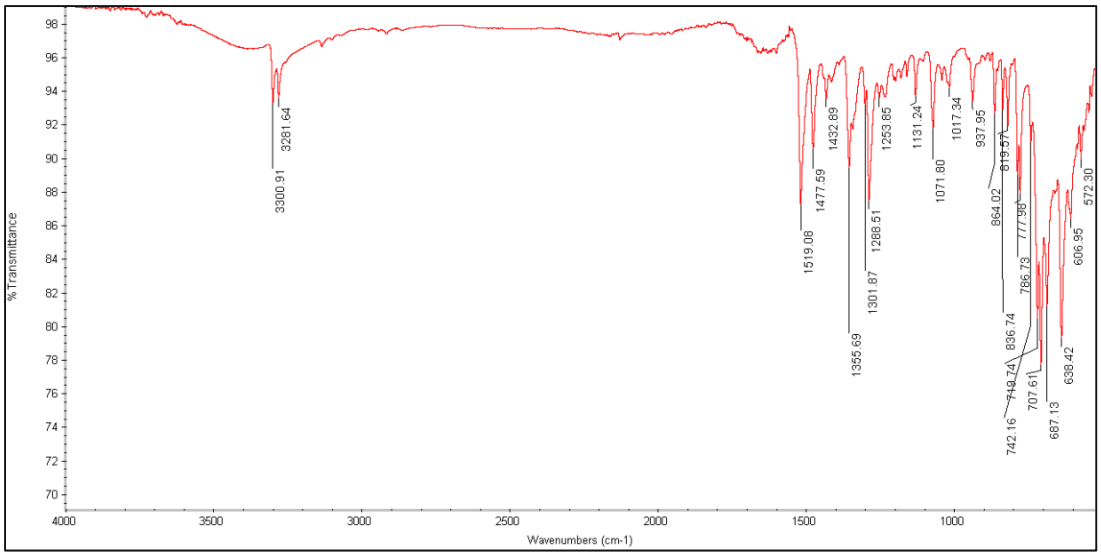

Figure 70 IR Spectrum of Compound **48h**

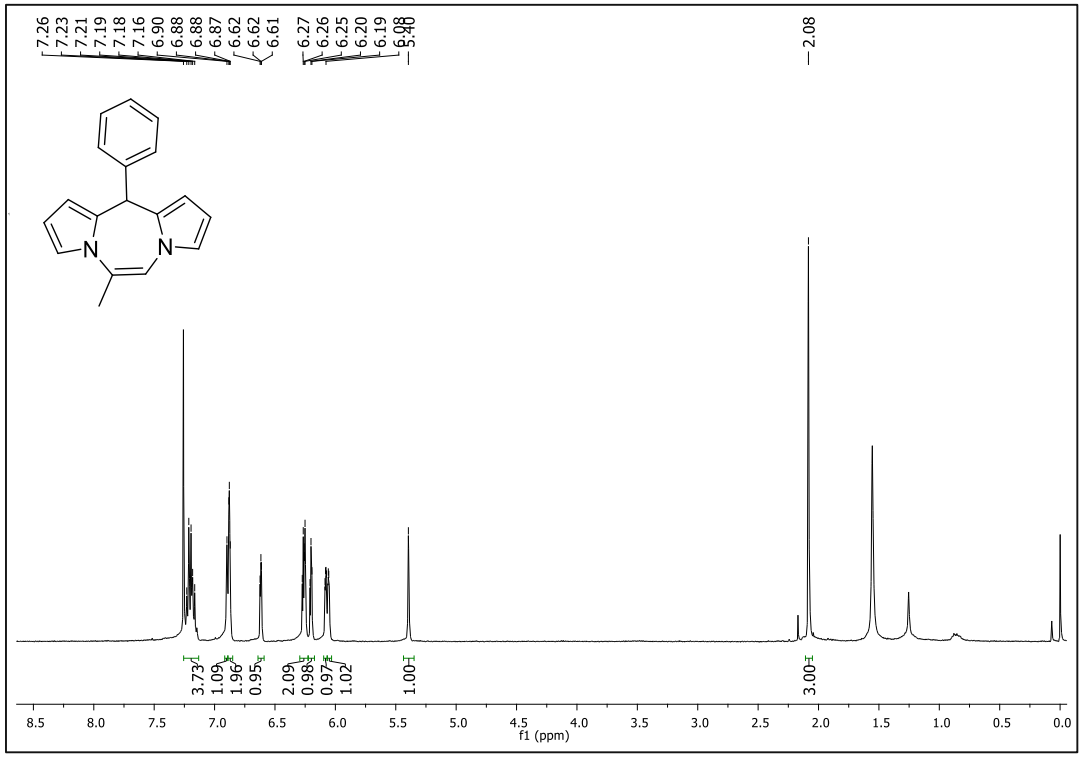

Figure 71 ^{1}H-NMR Spectrum of Compound **49a** in $CDCl_3$

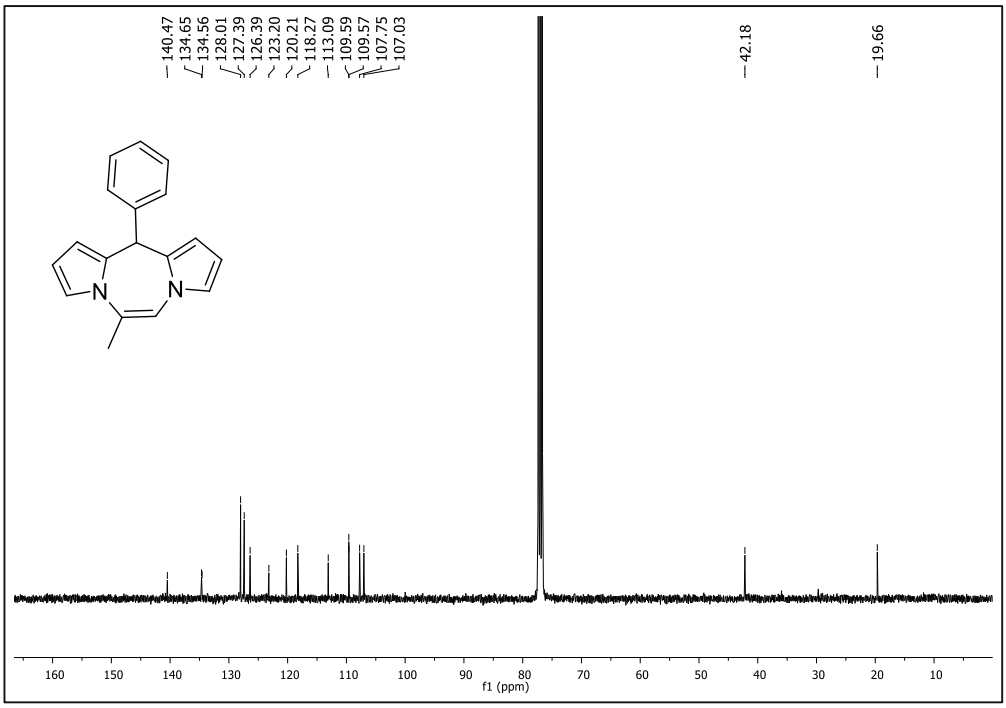

Figure 72 ^{13}C-NMR Spectrum of Compound **49a** in $CDCl_3$

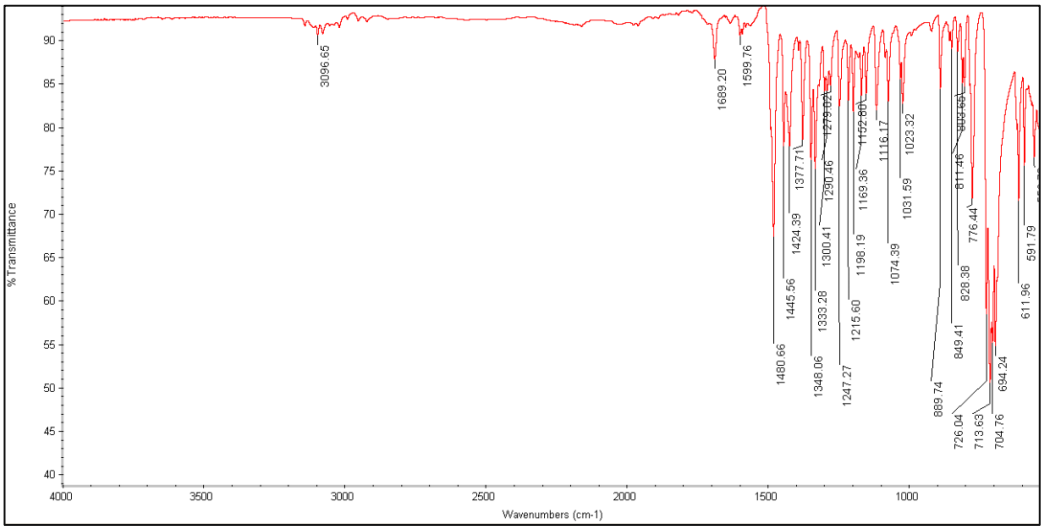

Figure 73 IR Spectrum of Compound **49a**

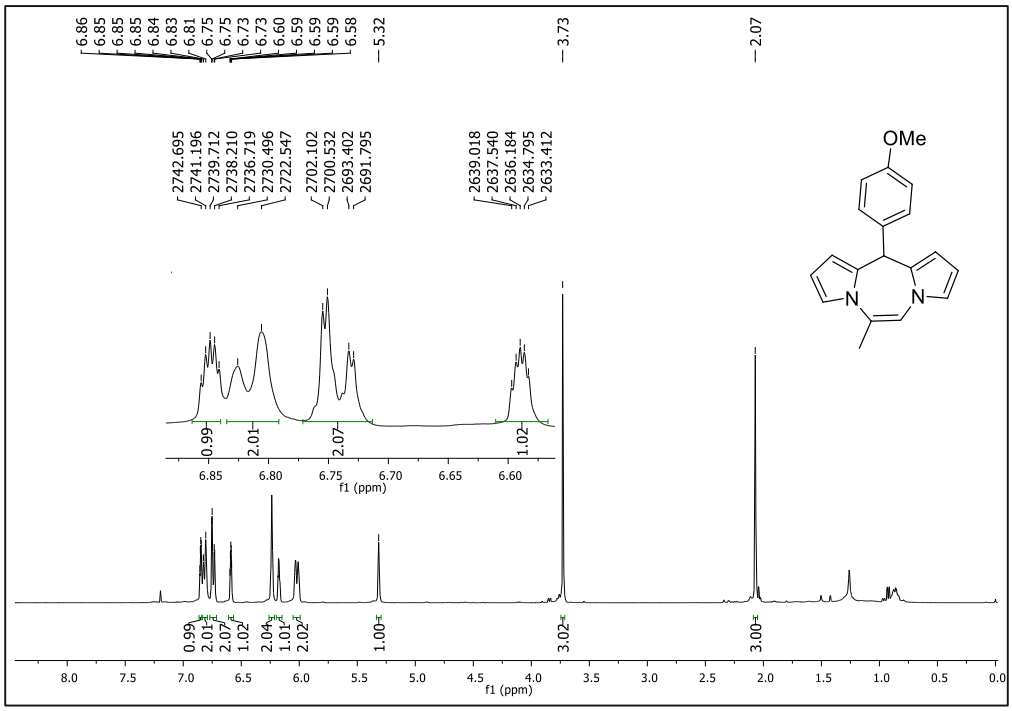

Figure 74 ^{1}H-NMR Spectrum of Compound **49d** in $CDCl_3$

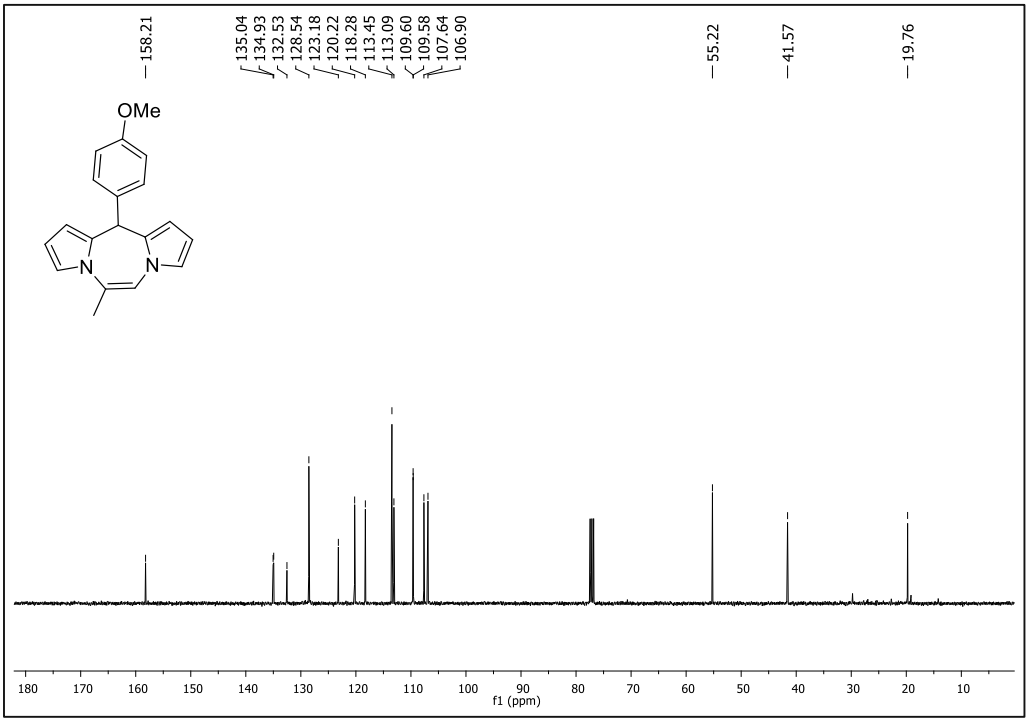

Figure 75 ^{13}C-NMR Spectrum of Compound **49d** in $CDCl_3$

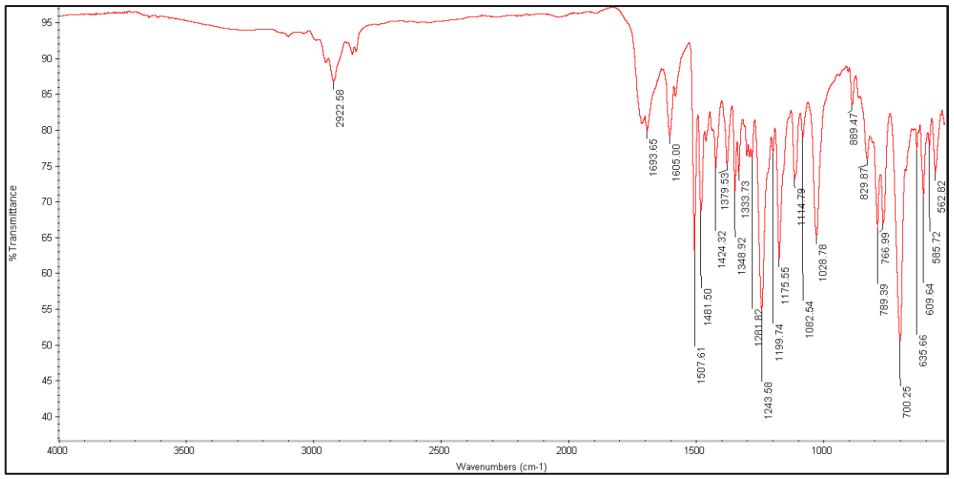

Figure 76 IR Spectrum of Compound **49d**

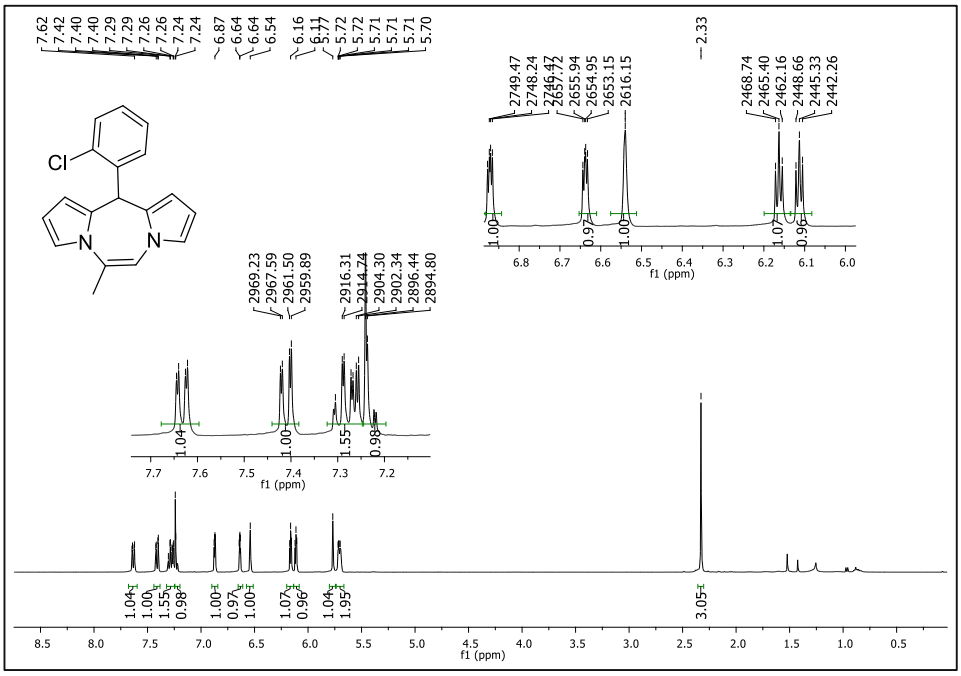

Figure 77 ^{1}H-NMR Spectrum of **49e** in $CDCl_3$

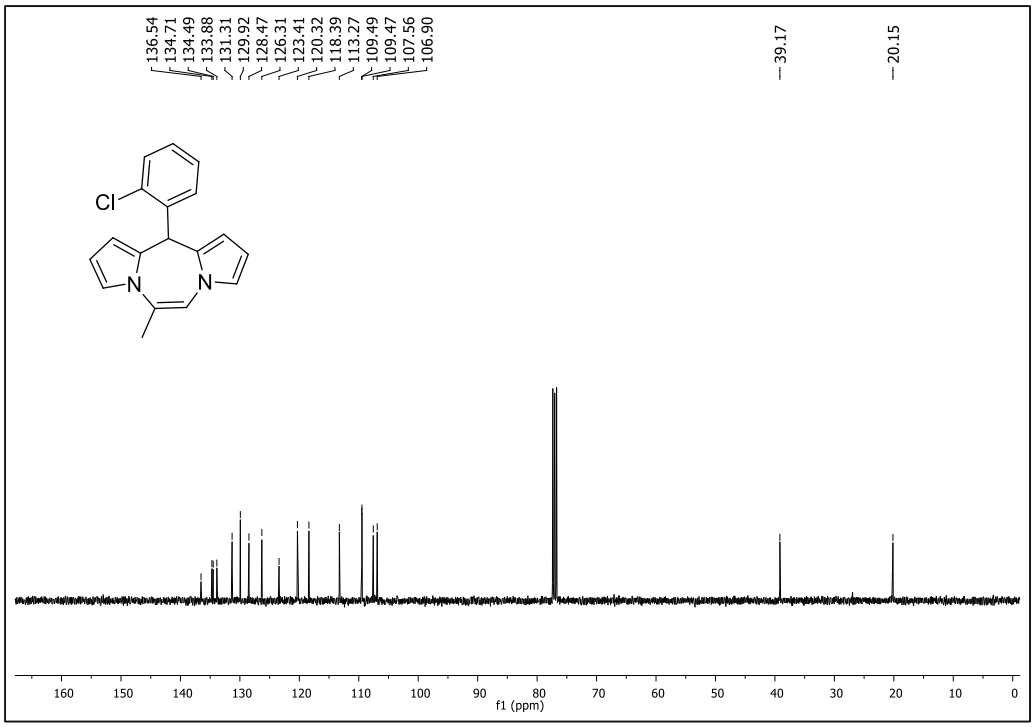

Figure 78 ^{13}C-NMR Spectrum of Compound **49e** in $CDCl_3$

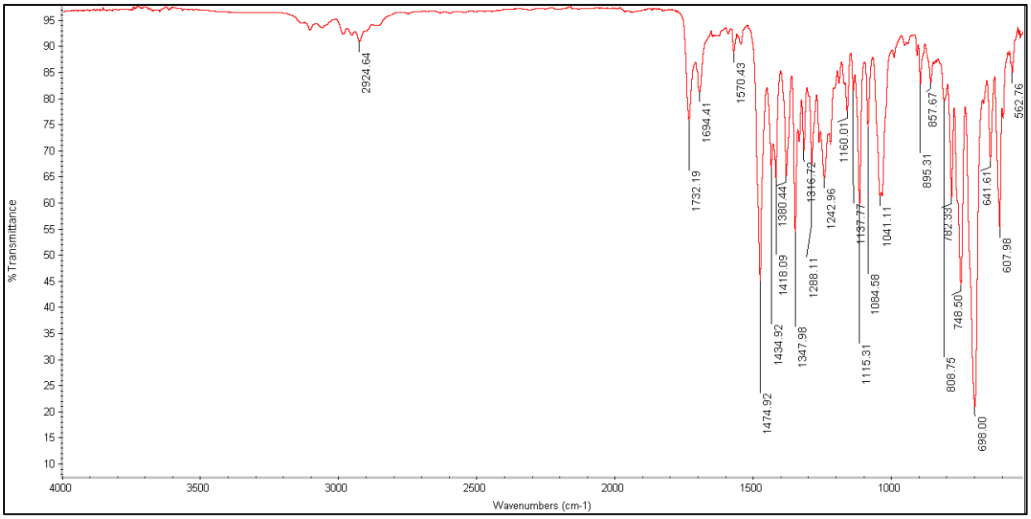

Figure 79 IR Spectrum of Compound **49e**

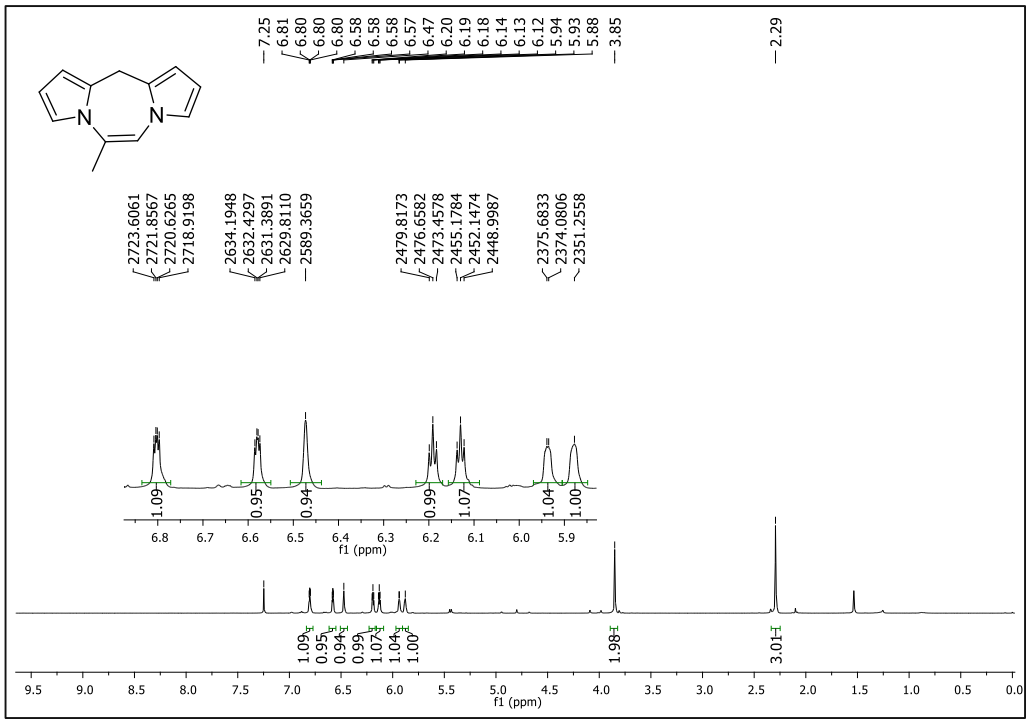

Figure 80 ^{1}H-NMR Spectrum of Compound **49g** in $CDCl_3$

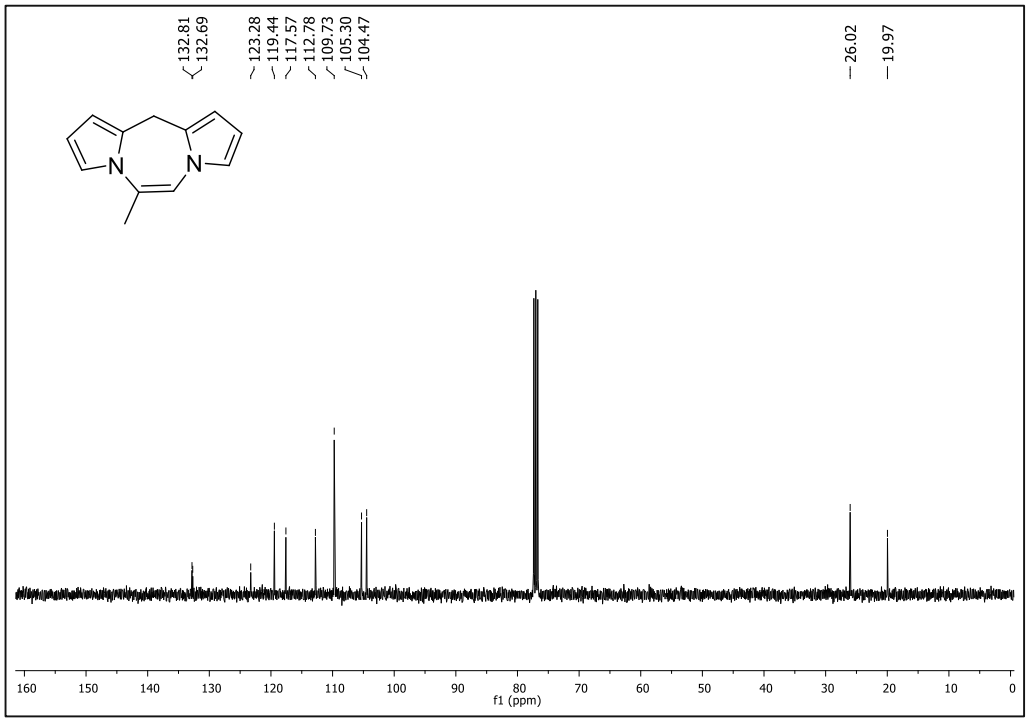

Figure 81 ^{13}C-NMR Spectrum of Compound **49g** in $CDCl_3$

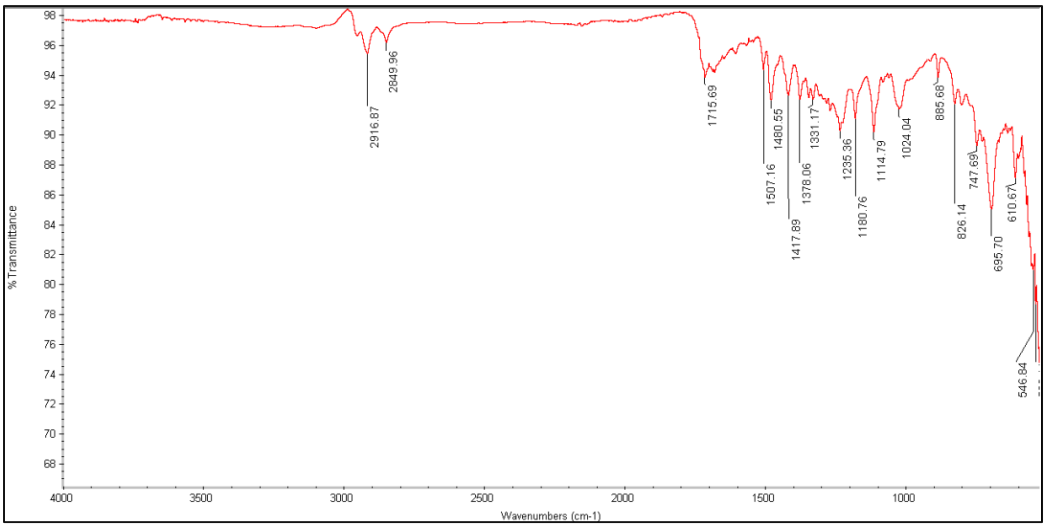

Figure 82 IR Spectrum of Compound **49g**

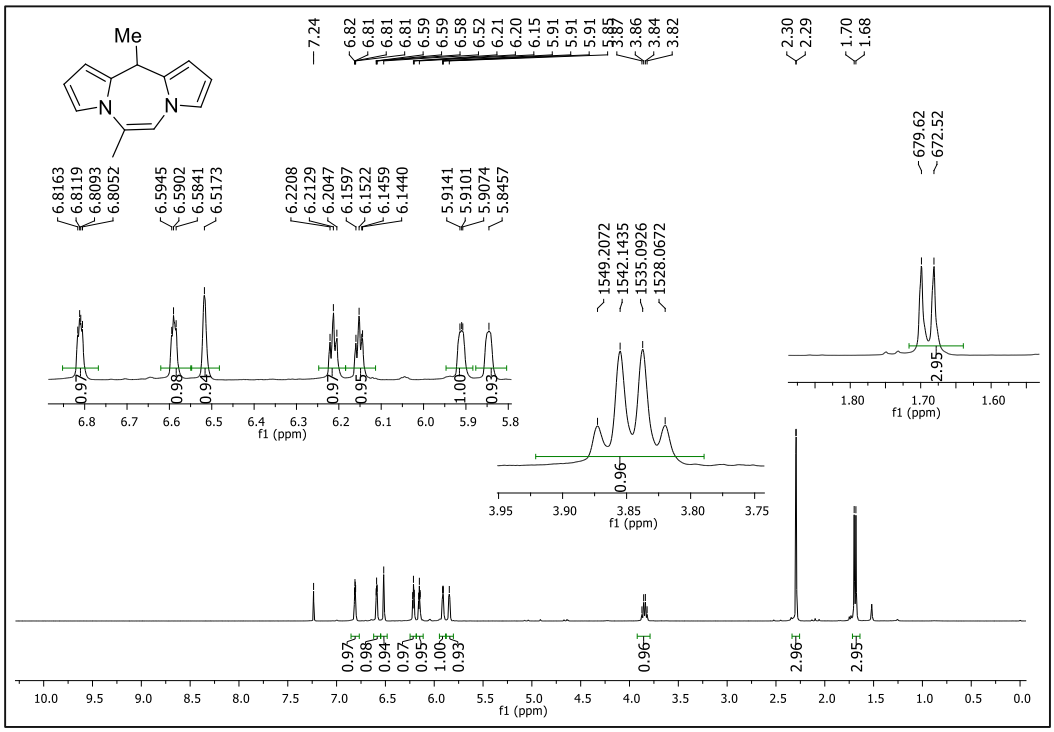

Figure 83 ^{1}H-NMR Spectrum of **49f** in $CDCl_3$

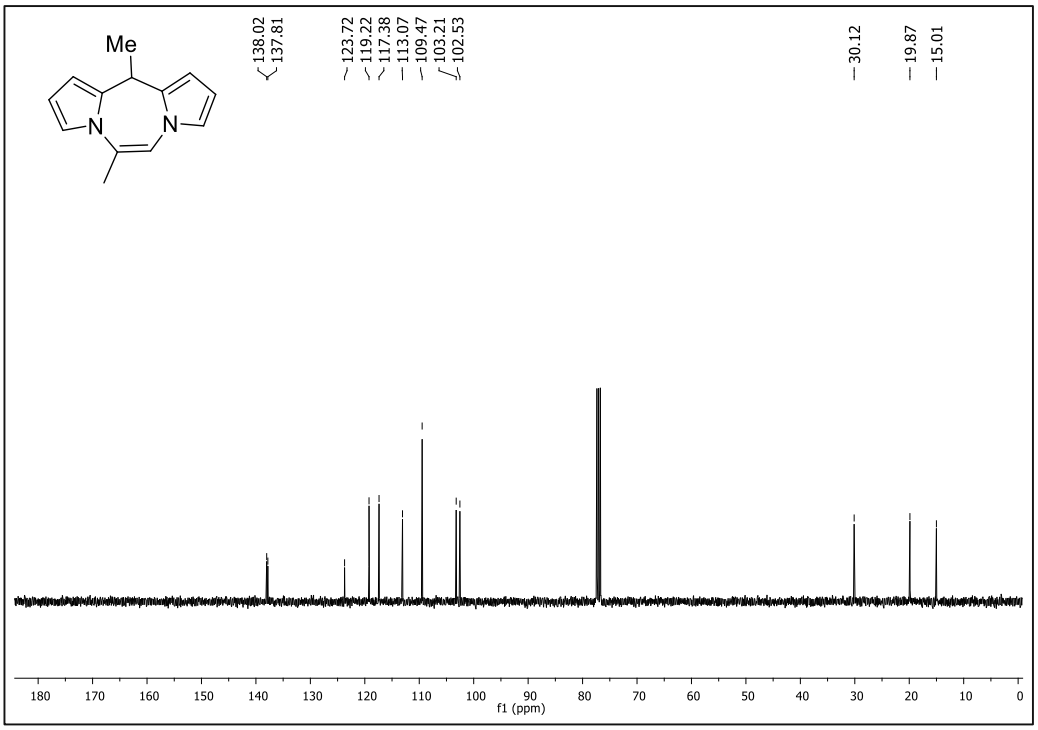

Figure 84 ^{13}C-NMR Spectrum of Compound **49f** in $CDCl_3$

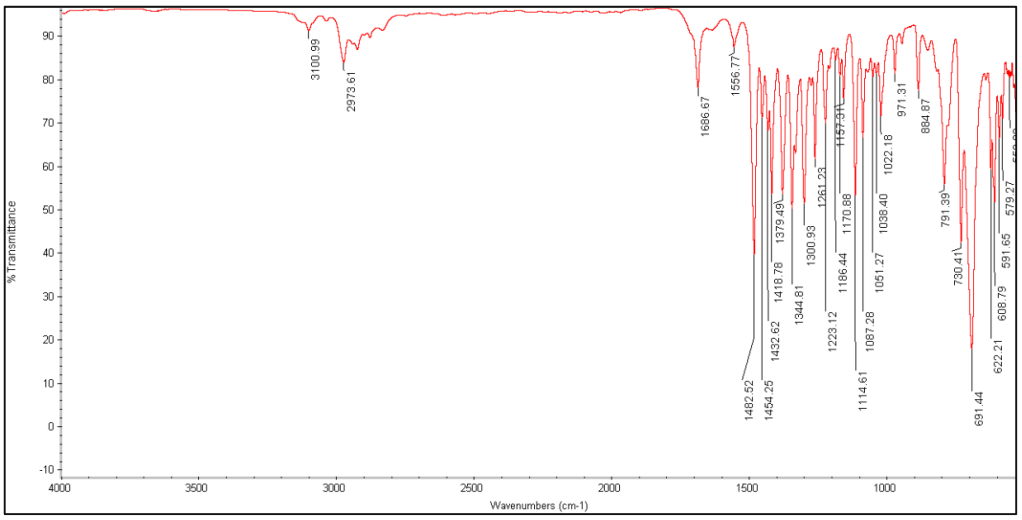

Figure 85 IR Spectrum of Compound **49f**

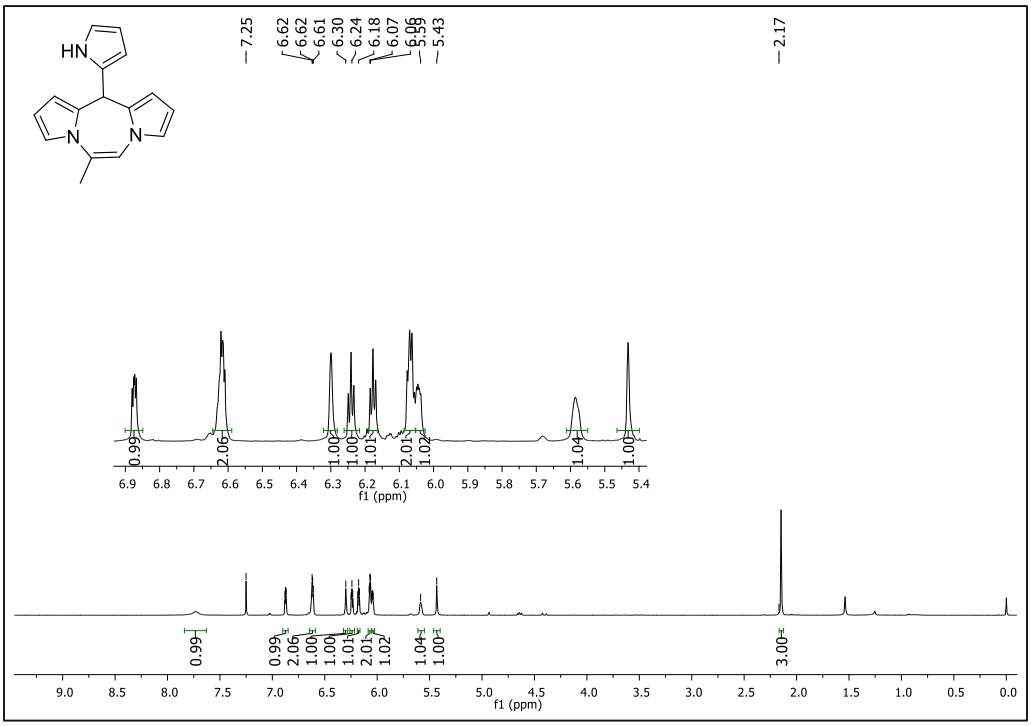

Figure 86 ^{1}H-NMR Spectrum of **49c** in $CDCl_3$

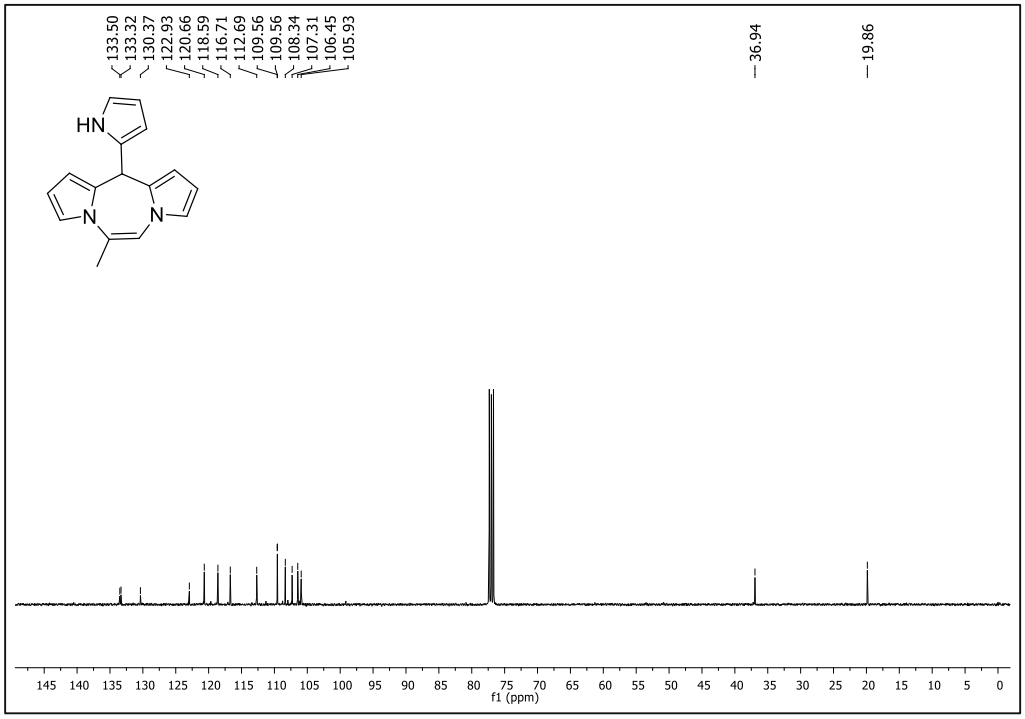

Figure 87 ^{13}C-NMR Spectrum of Compound **49c** in $CDCl_3$

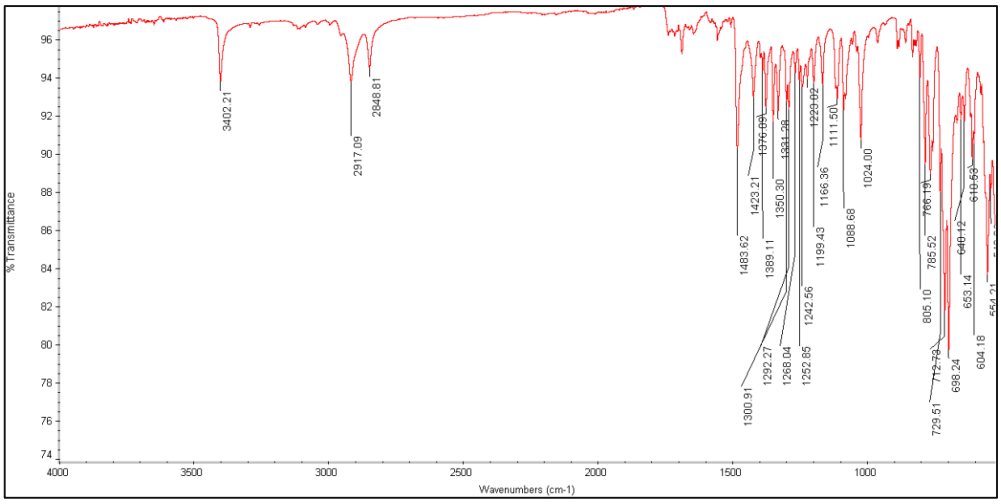

Figure 88 IR Spectrum of Compound **49c**

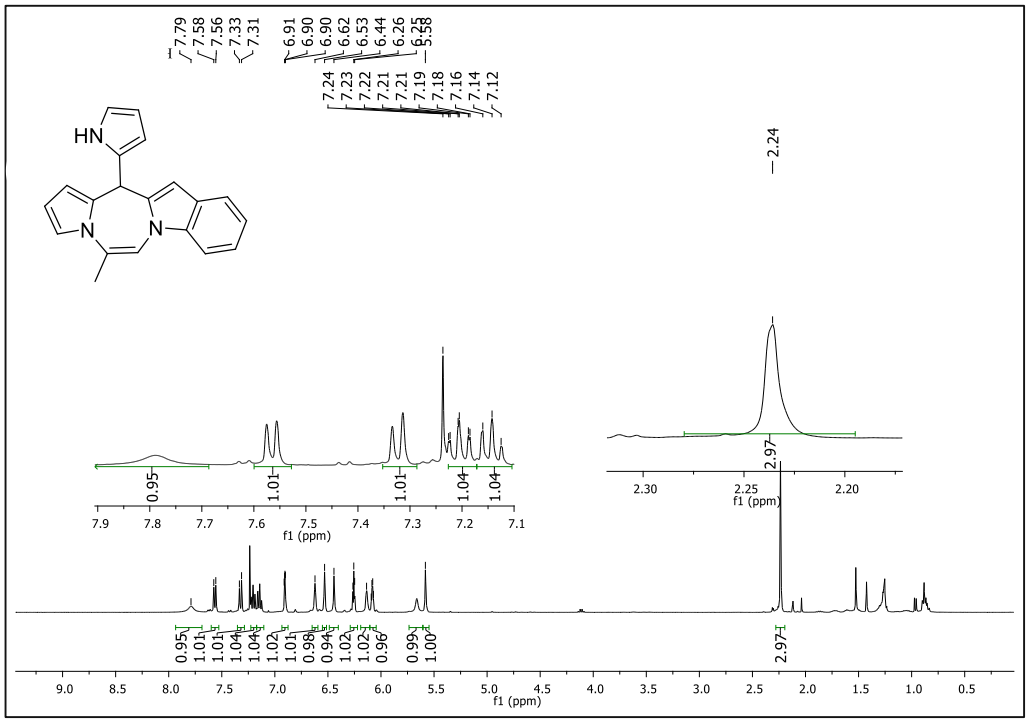

Figure 89 1H-NMR Spectrum of **49b** in $CDCl_3$

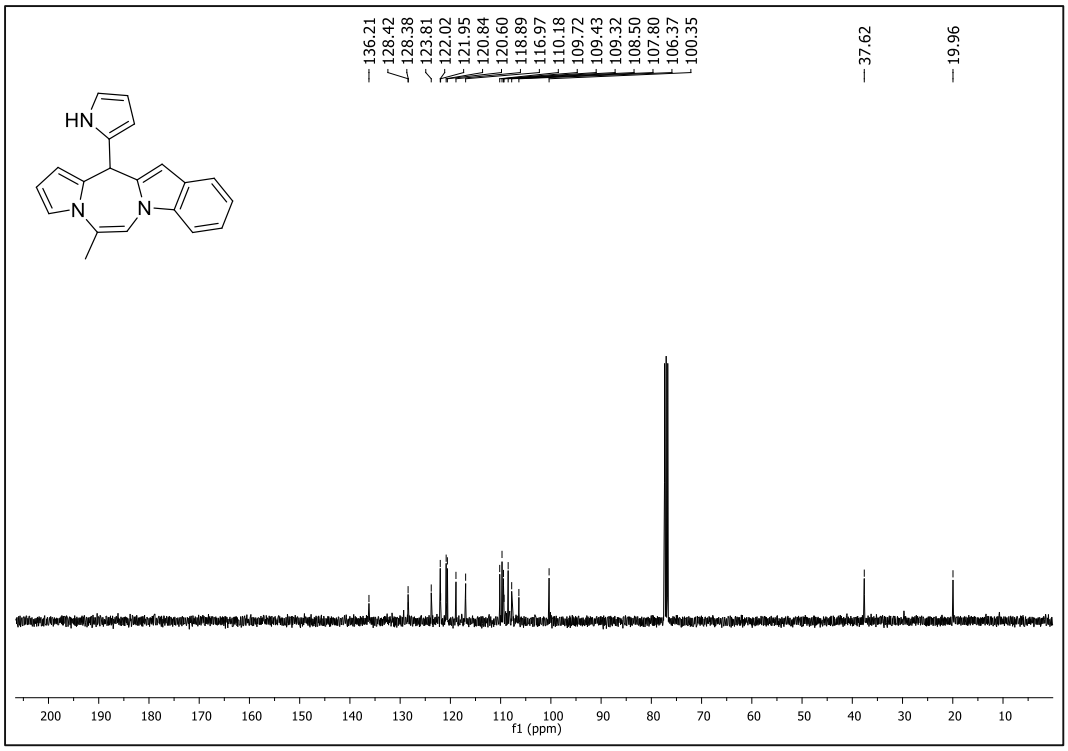

Figure 90 ^{13}C-NMR Spectrum of Compound **49b** in $CDCl_3$

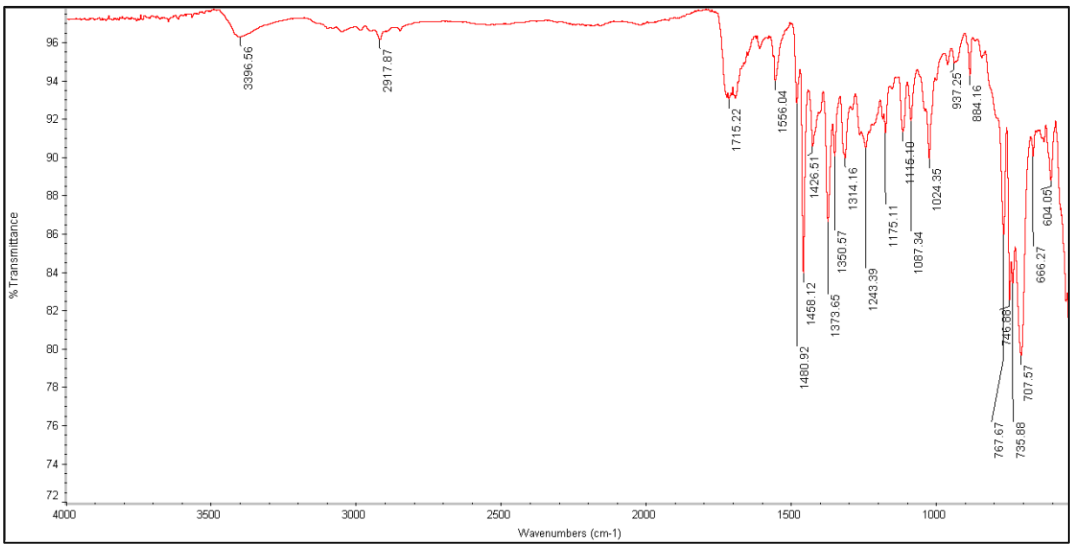

Figure 91 IR Spectrum of Compound **49b**

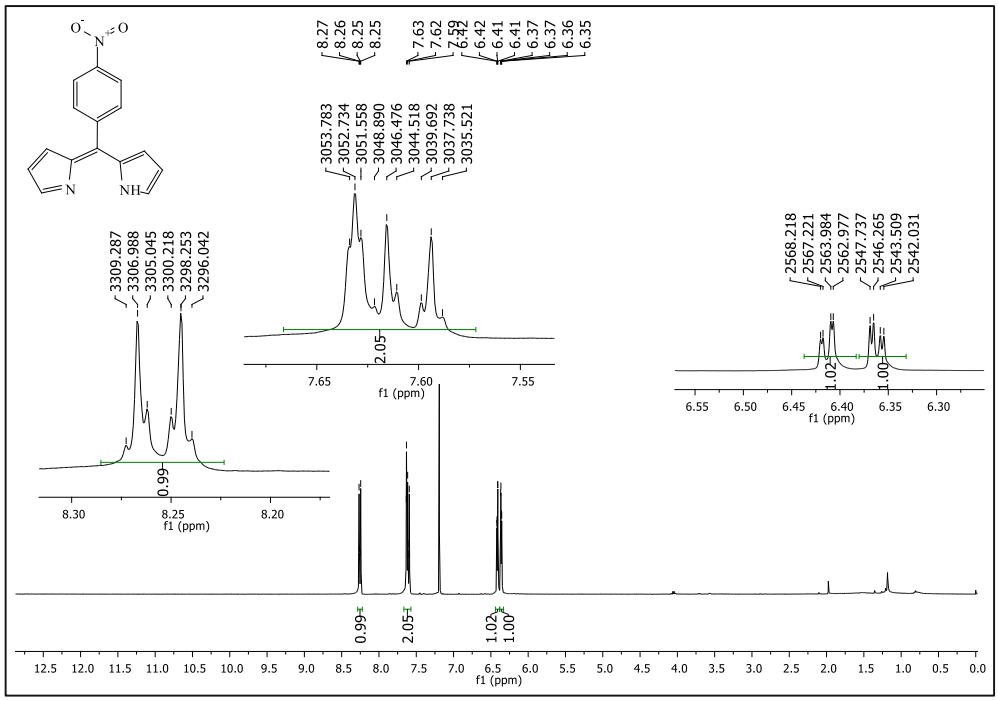

Figure 92 ^{1}H-NMR Spectrum of **57** in $CDCl_3$

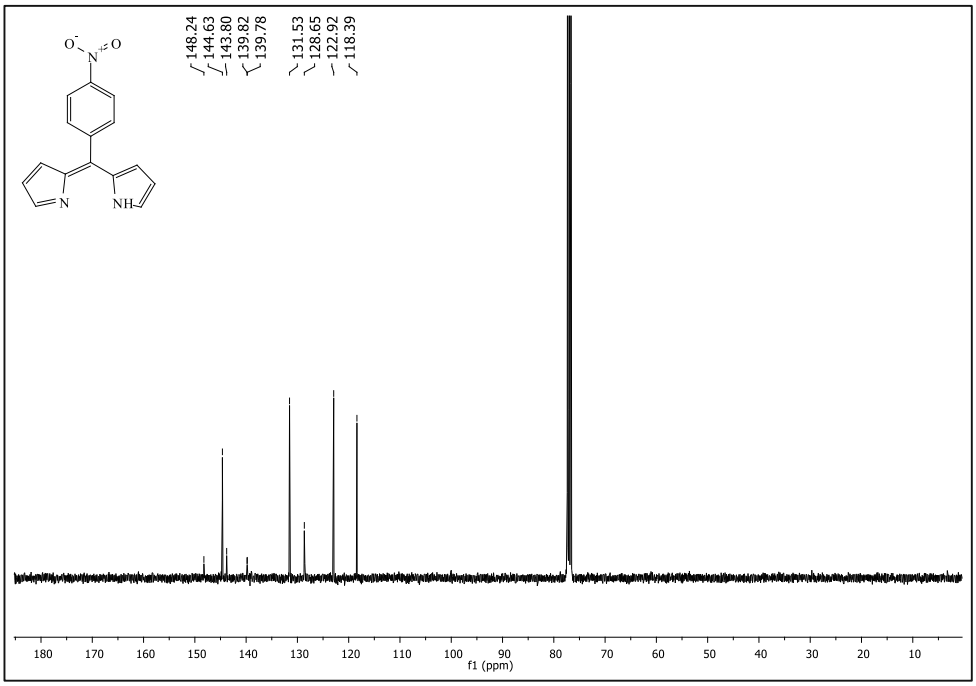

Figure 93 ^{13}C-NMR Spectrum of Compound 57 in $CDCl_3$

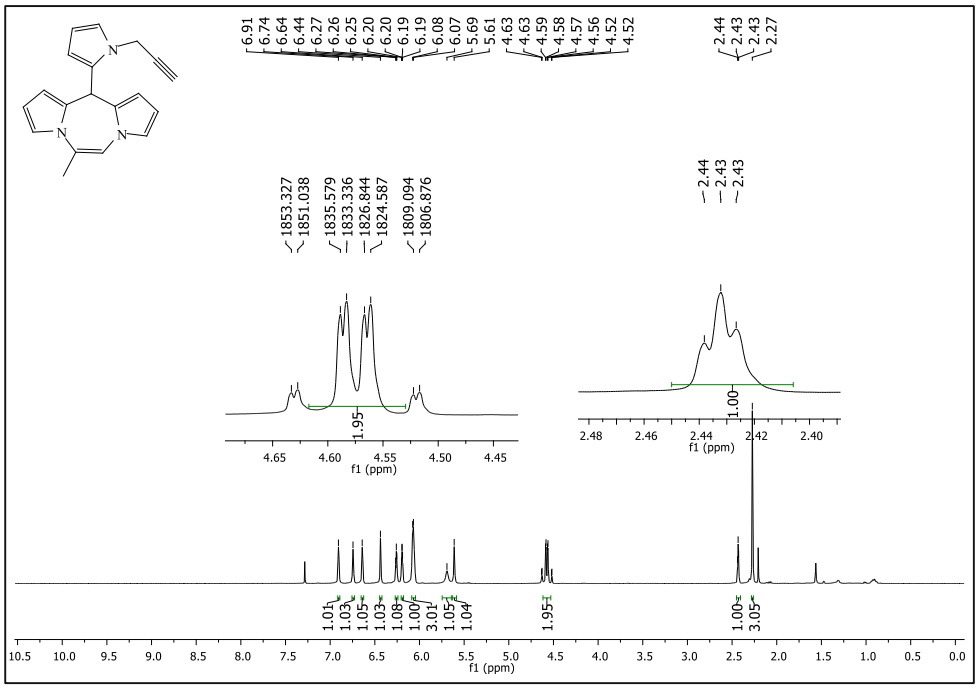

Figure 94 ^{1}H-NMR Spectrum of **60** in $CDCl_3$

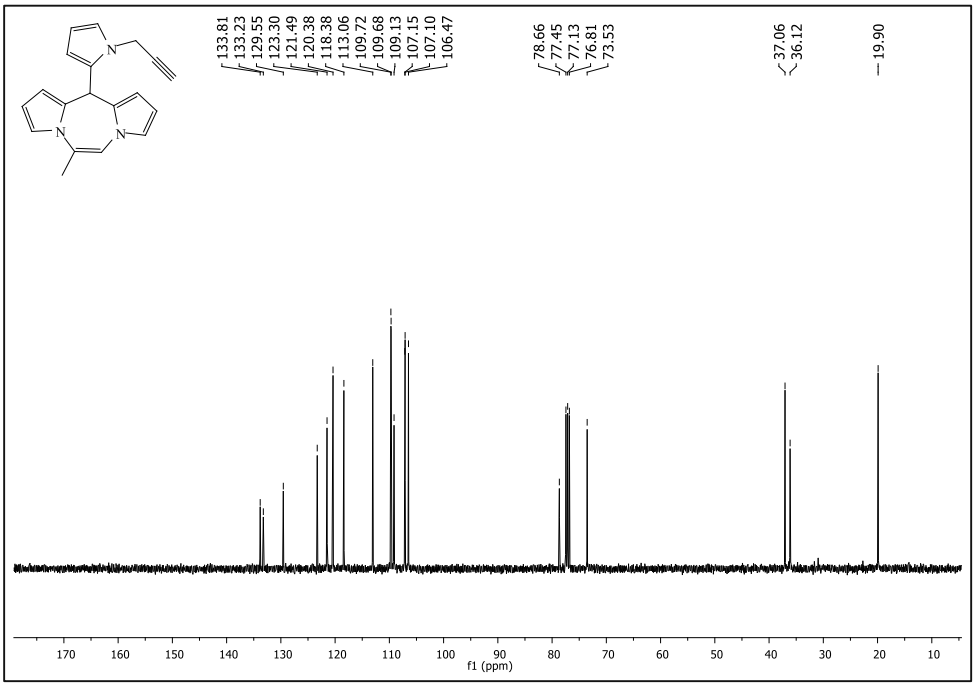

Figure 95 ^{13}C-NMR Spectrum of Compound **60** in $CDCl_3$

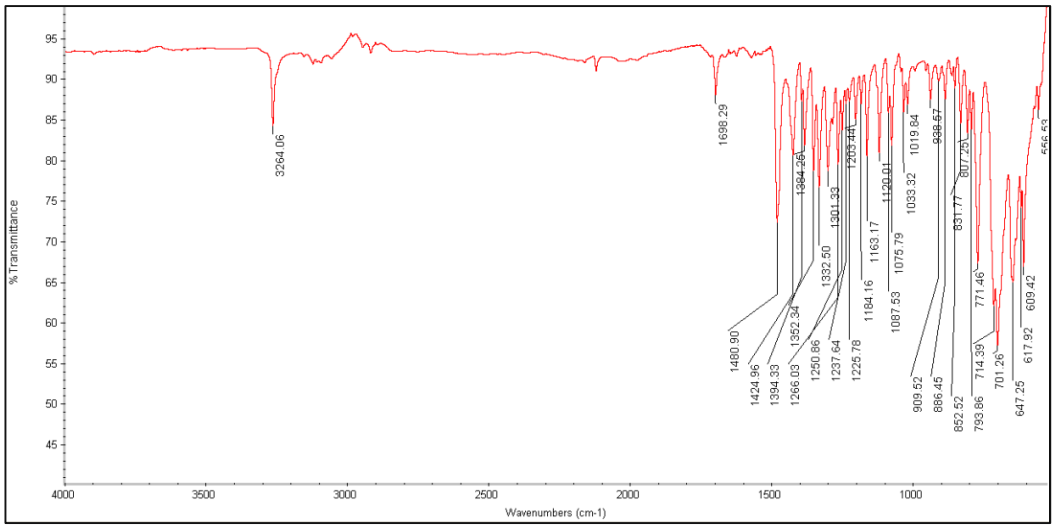

Figure 96 IR Spectrum of Compound **60**

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

	X	Y	Z
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