AN APPROACH TO THE SYNTHESIS OF NOVEL PYRROLE FUSED HETEROCYCLES

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UĞUR BAŞAK ÖZTÜRK

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AN APPROACH TO THE SYNTHESIS OF NOVEL PYRROLE FUSED HETEROCYCLES

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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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Signature :

ABSTRACT

AN APPROACH TO THE SYNYHESIS OF NOVEL PYRROLE FUSED HETEROCYCLES

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February 2016, 82 pages

Pyrrole and pyrrole derivatives are prominent building blocks in organic synthesis due to their biological activities and natural occurrence. For the formation of pyrrole derivatives, electrophilic cyclizations are considered efficient and significant processes. In this thesis, novel *N*-alkynyl-2-phenyl-substituted pyrrole derivatives were synthesized and electrophilic cyclization reactions of these compounds were investigated. Catalyst such as $AuCl_3$, $AuBr_3$, I_2, ICl, $FeCl_3$, $InCl_3$ and $Cu(OTf)_2$ were used for the ring closure studies.

Keywords: Pyrrole synthesis, electrophilic cyclization reactions

ÖZ

PİROL İSKELETİ İÇEREN YENİ HETEROSİKLİK BİLEŞİKLERİN SENTEZİNE BİR YAKLAŞIM

Öztürk, Uğur Başak
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Tez Yöneticisi: Prof. Dr. Metin Balcı

Şubat 2016, 82 sayfa

Pirol ve pirol türevleri doğada sıkça bulunmaları ve gösterdikleri biyolojik aktiviteler nedeni ile organik sentezin önemli yapı bloklarıdır. Yapısında pirol içeren heterosiklik bileşiklerin elektrofilik halkalaşma reaksiyonları ile sentezi literatürde yer alan önemli ve etkili proseslerdendir. Bu çalışmada, *N*-alkinil-2-fenil-sübstütiye pirol türevleri sentezlendi ve bu bileşiklerin elektrofilik halkalaşma reaksiyonları araştırıldı. Halka kapama reaksiyon denemeleri için $AuCl_3$, $AuBr_3$, I_2, ICl, $FeCl_3$, $InCl_3$, ve $Cu(OTf)_2$ katalizörleri kullanıldı.

Anahtar kelimeler: Pirol sentezi, elektrofilik halkalaşma reaksiyonları

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To my dear family…

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CHAPTER 1

INTRODUCTION

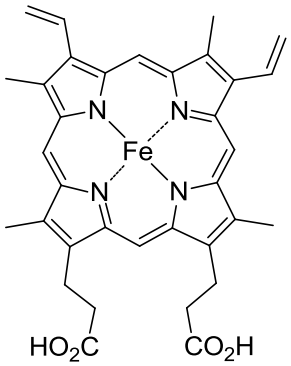
1.1. Heterocycles Containing Nitrogen Atom

Heterocyclic compounds are among one of the largest classical branch of the organic chemistry and possess immense biological and industrial importance.[1] Of the heterocyclic compounds, nitrogen-containing heterocycles have a significant place in biological and pharmaceutical applications. Hence, the development of synthetic methodologies for the synthesis of N-containing heterocycles has attracted considerable attention in the last few decades.[2] Especially, pyrrole and pyrrole containing heterocycles are important synthetic targets because of their potential biological activities and occurrence in various natural products.

1.2. Pyrrole and Pyrrole Containing Heterocycles

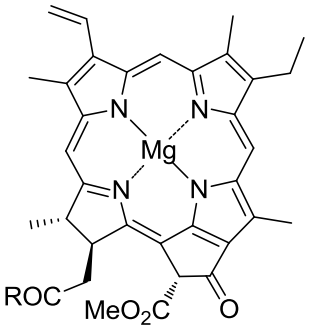
1

Pyrrole **(1)** is an important and fundamental heterocycle which presents widely in natural products, drugs, catalysts and advanced materials. Haem **(2)**, a fundemental blood respiratory pigment, and chlorophyll **(3)**, an essential photosynthesis pigment, consist of pyrrole as a subunit. A pyrrole derivative atorvastatin **(4)** is a bioactive ingredient of a widely used drug for cholesterol treatment. In addition, because of their conducting properties, polypyrroles are used in batteries and solar cells.[3]



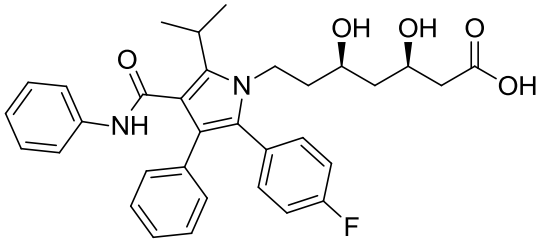
2

Haem



3

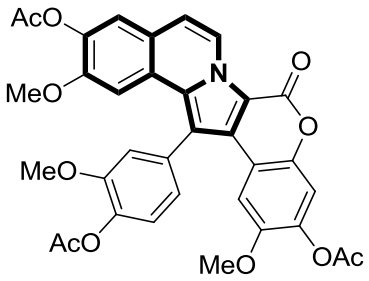
Chlorophyll a



4

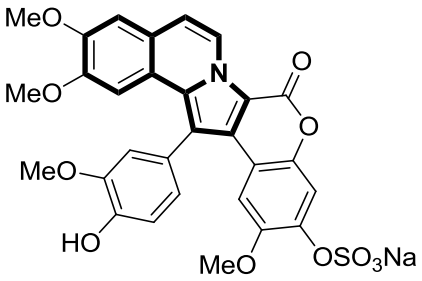
Atorvastatin

Pyrrole motif also presents in lamellarins such as **5** and **6** which are natural alkaloids obtained from marine organisms. Lamellarins are known to possess diverse range of biological activities such as cytotoxicity, cell division inhibition, HIV-1 integrase inhibition and antibiotic activity.[4]



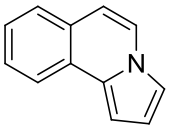
5

Lamellarin D triacetate



6

Lamellarin a-20-sulfate



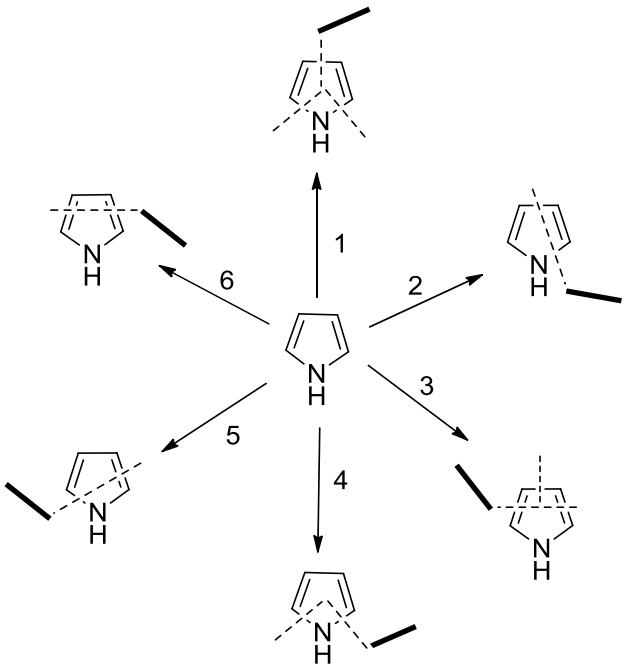
7

pyrrolo[2,1-*a*]isoquinoline

A pyrrole fused heterocycle, pyrroloisoquinoline **7**, is the core structure of lamellarin alkaloids.[5] Thus, synthesis of pyrroloisoquinoline frameworks has provoked a great deal of interest because of their afore-mentioned potential biological activities.

1.3. Synthesis of Pyrrole and Pyrrole Containing Heterocycles

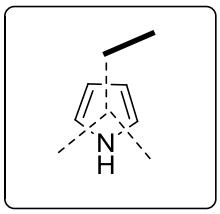
There are numerous protocols and methods for the synthesis of pyrrole and pyrrole containing heterocyles. Construction of a pyrrole ring can be categorized according to the number and type of bonds being formed. Some selected disconnection approaches for the ring closure formation of pyrroles and pyrrole derivatives are shown in Scheme 1.



Scheme 1. Selected disconnection approaches for constructing a pyrrole ring

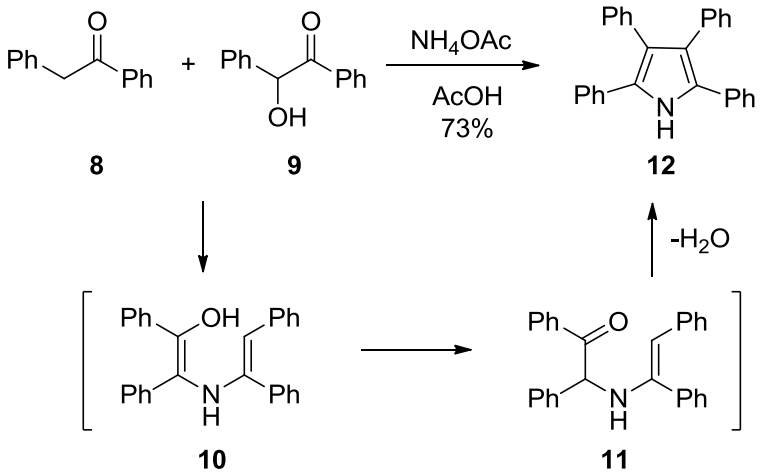
These disconnection approaches include many classical methods such as Knorr, Paal−Knorr, and Hantzsch syntheses and 1,3-dipolar cycloaddition reactions. In general, these methods involve polar cyclization reactions in which pyrrole molecule is formed by intermolecular ring closure of nucleophilic and electrophilic counterparts. Nucleophiles such as amines, enols, enolates or enamines attack to an electrophilic center of carbonyl groups, imine groups, or double bond of α,β-unsaturated carbonyl compounds forming a pyrrole ring. Another widely used reaction for constructing pyrrole rings is concerted cycloaddition reactions such as 1-3 dipolar cycloadditions in which reaction between a 1,3-dipole and a dipolarophile forms a five-membered ring.[6]

1.3.1. Disconnection 1: Formation of Two N-C Bonds and One C-C Bond



1.3.1.1.Condensation reaction of Benzyl Ketone, Benzoins and Ammonia

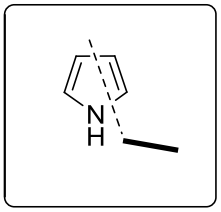
Synthesis of aryl substituted pyrrole derivatives can be achieved by the condensation reaction between benzyl aryl ketone **8**, benzoin **9** and ammonia in acetic acid.[7]



Scheme 2. Synthesis of aryl substituted pyrroles

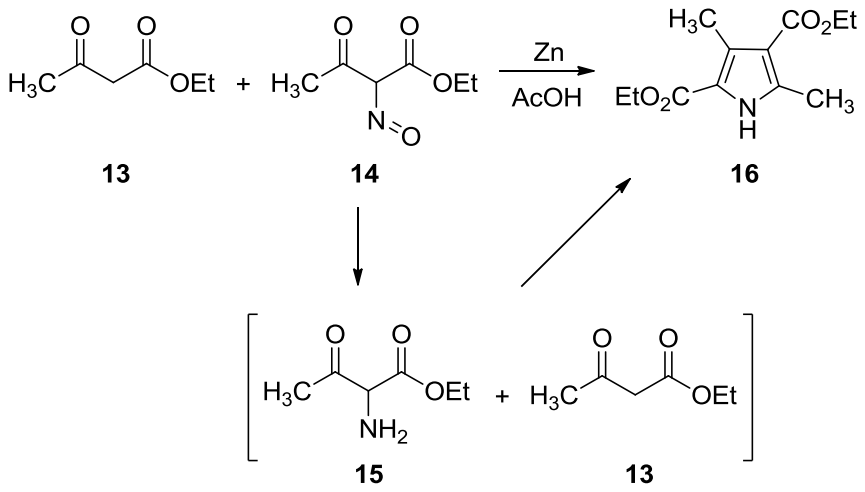
Formation of the enamine intermediates **10** and **11** is followed by the cyclization reaction. Loss of a water molecule yields pyrrole derivative **12** (Scheme 2).

1.3.2. Disconnection 2: Formation of One N-C Bonds and One C-C Bond



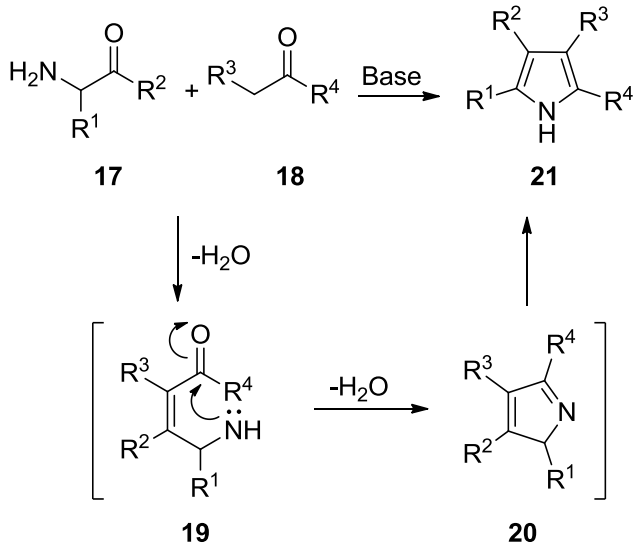
1.3.2.1.Knorr Pyrrole Synthesis

This pyrrole synthesis was reported by Knorr in 1884.[8] In general, synthesis of substituted pyrrole derivatives by condensation reaction between carbonyl compounds having α-methylene group with α-amino ketones is known as Knorr Pyrrole Synthesis.



Scheme 3. Knorr pyrrole reaction

In the original Knorr reaction, *α*-amino ketone **15** is formed in situ by the reduction of oxime moiety **14** in the presence of zinc and acetic acid. Subsequent condensation with **13** followed by cyclization and loss of a water molecule affords **16** (Scheme 3).



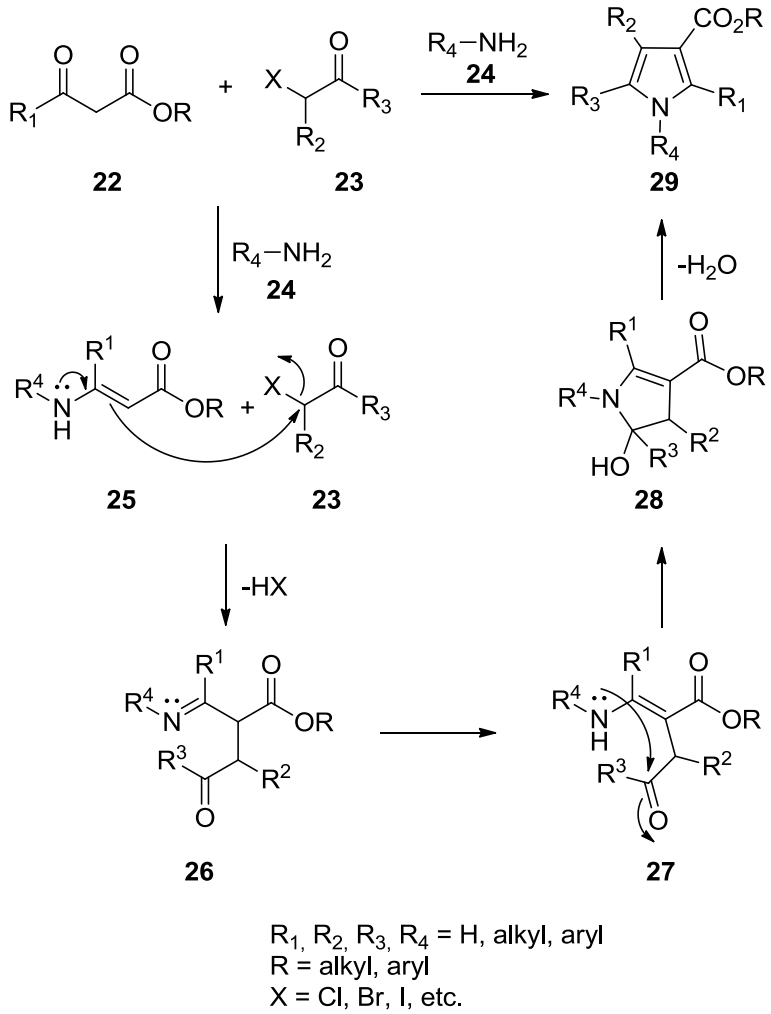
Scheme 4. General reaction mechanism for Knorr pyrrole synthesis

General mechanism for the Knorr pyrrole synthesis is shown in Scheme 4. After one of the methylene protons of compound **18** is removed in the presence of a base, the resulting anion attacks the carbonyl carbon atom of *α*-amino ketone **17** forming

intermediate **19**. Subsequent cyclization and loss of an water molecule affords pyrrole derivative **21**.

1.3.2.2.Hantzsch Pyrrole Synthesis

Condensation of α-halo-ketones **23** and β-ketoesters **22** in the presence of ammonia or primary amines **24** is known as Hantzsch pyrrole synthesis (Scheme 5). Synthesis of 2,5-dialkyl or 2,4,5-trialkylpyrrole derivatives **29** can be achived by this method.[9]

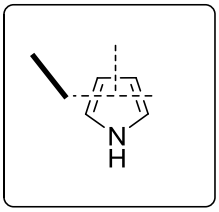


Scheme 5. General reaction mechanism for Hantzsch pyrrole synthesis

Enamine intermediate **25** is formed by the nucleophilic attack of the nitrogen atom of the amine **24** to the carbonyl carbon of **22**. Intermediate **25** reacts with **23** yielding

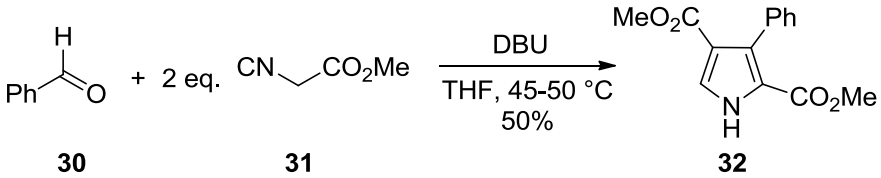
the condensation intermediate **26**. Subsequent cyclization reaction and loss of a water molecule gives **29** as shown in Scheme 5.

1.3.3. Disconnection 3: Formation of Three C-C bonds



1.3.3.1. Reactions of Alkyl Isocyanoacetates with Aldehydes

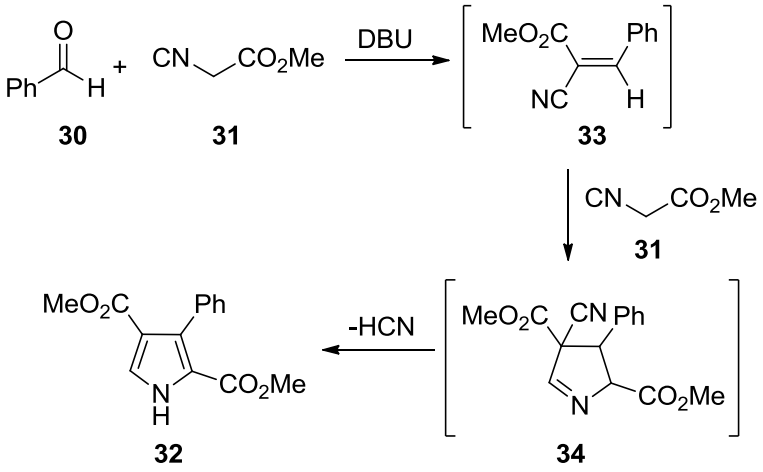
Pyrrole 2,4-dicarboxylic esters **32** are synthesized from two equivalents of an alkyl isocyanoacetate **31** and one equivalent of an aldehyde **30** (Scheme 6) .[10]



30 **31** **32**

Scheme 6. Pyrrole synthesis via reaction of methyl isocyanoacetate **(31)** with benzaldehyde **(30)**

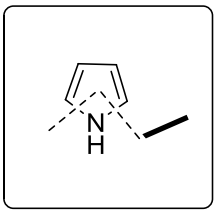
Both C-N-C component and C_1 component were provided by isocyanide.[11]



Scheme 7. Proposed reaction mechanism for the reaction between methyl isocyanoacetate **(31)** and benzaldehyde **(30)**

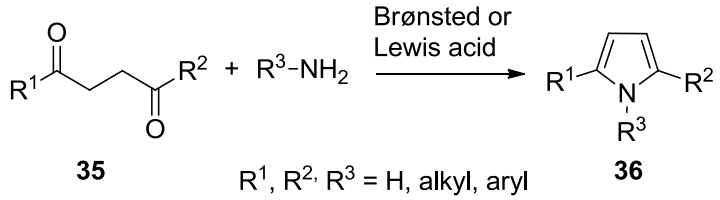
It is presumed that reaction mechanism involves an aldol reaction between benzaldehyde **(30)** and isocyanoacetate **31** forming intermediate **33** and proceeds with the Michael addition of second equivalent of isocyanoacetate **31** yielding the cyclization intermediate **34**. Elimination of hydrogen cyanide affords pyrrole derivative **32**.

1.3.4. Disconnection 4: Formation of Two N-C bonds



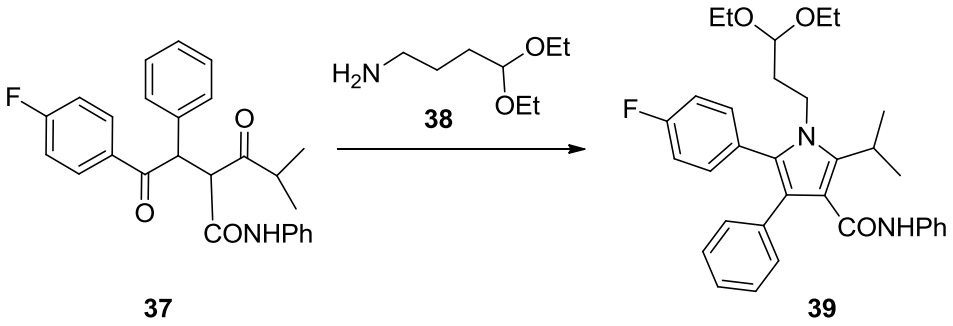
1.3.4.1.Paal-Knorr Pyrrole Synthesis

Synthesis of pyrrole derivatives via condensation reaction between 1,4-dicarbonyl compounds **35** and primary amines in the presence of either a Brønsted acid or Lewis acid catalyst yields pyrrole compounds **36**. This type of reactions is called Paal- Knorr pyrrole synthesis (Scheme 8).[12]



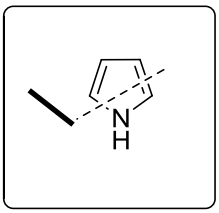
Scheme 8. Paal-Knorr pyrrole synthesis

Atorvastatin **4** which is the bioactive component of Lipitor, a widely used drug, contains a pyrrole subunit and atorvastatin derivatives **39** can be synthesized by Paal-Knorr pyrrole synthesis (Scheme 9).



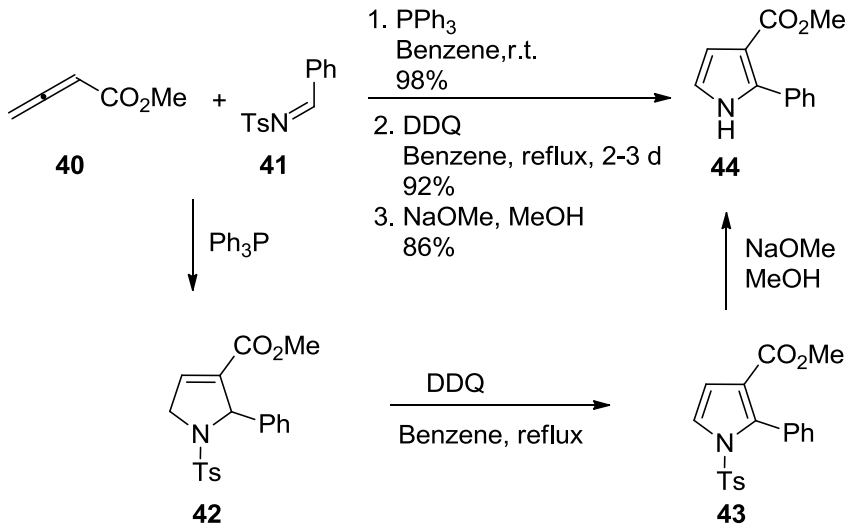
Scheme 9. Synthesis of atorvastatin derivative **39** by Paal-Knorr pyrrole synthesis

1.3.5. Disconnection 5: Formation of One N-C Bonds and One C=C Bond



1.3.5.1.Reactions of Allenes and Tosyl Imines

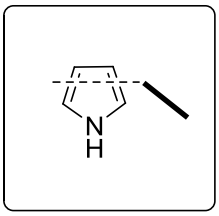
Pyrrole derivatives can be obtained by [3 + 2] cycloaddition reaction between *N*-tosylimines **41** and allenyl ester **40**, catalyzed by triphenylphosphine (Scheme 10).[13]



Scheme 10. Synthesis of pyrrole ring from the reaction between *N*-tosylimines **41** and allenyl ester **40**

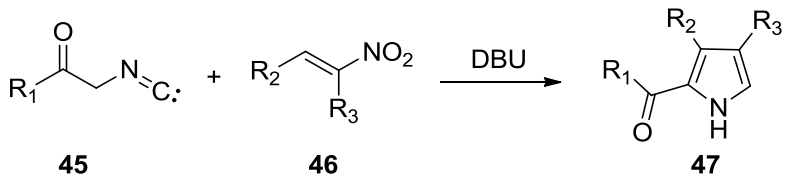
Dihydropyrrole obtained from the reaction between **40** and **41** was oxidized to corresponding pyrrole **43** and elimination of the tosyl group gave compound **44**.

1.3.6. Disconnection 6: Formation of Two C-C bonds



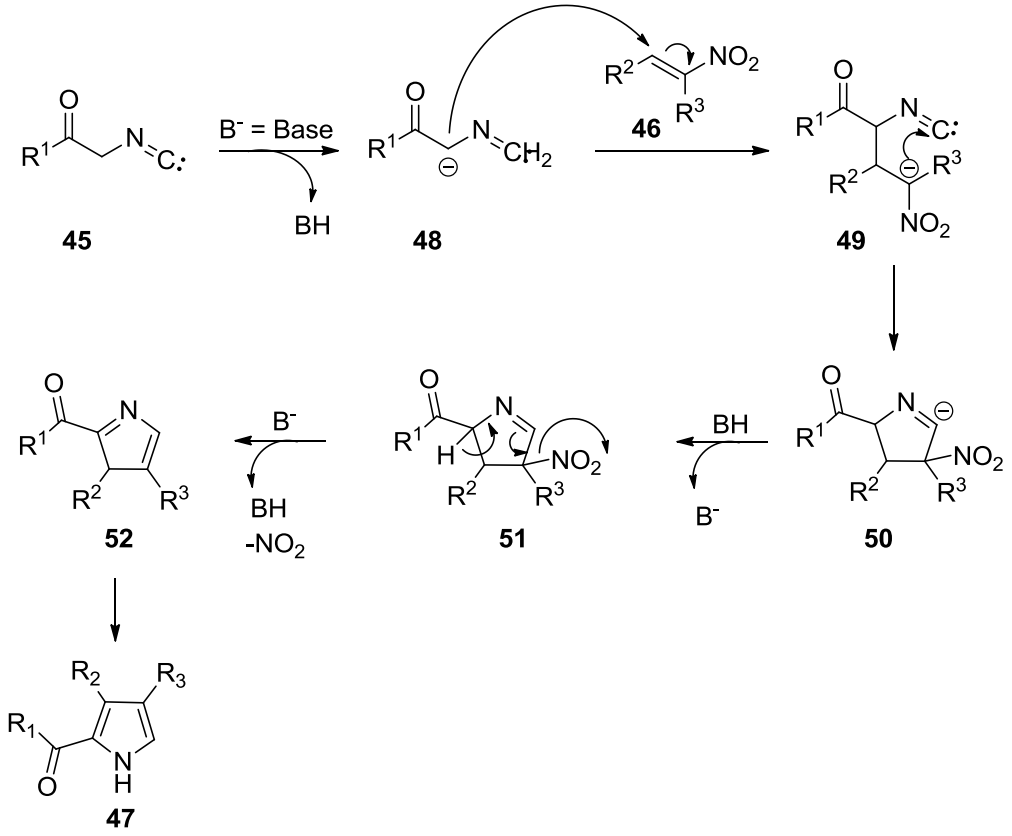
1.3.6.1.Barton-Zard Pyrrole Synthesis

Barton-Zard pyrrole synthesis is the basic condensation between alkyl isocyanoacetate **45** and α,β-unsaturated nitroalkenes **46** yielding 2-substituted pyrroles **47**.[14]



Scheme 11. Barton-Zard pyrrole synthesis

General mechanism for the Barton-Zard pyrrole synthesis is given in Scheme 11.

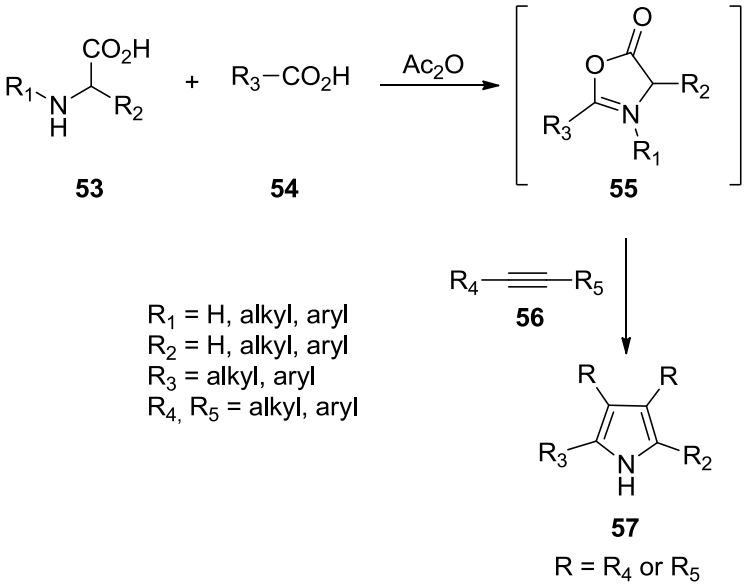


Scheme 12. General mechanism for the Barton-Zard pyrrole synthesis

Proton abstraction from the α-position of **45** leads to the condensation reaction with **46** followed by the cyclization reaction yielding compound **50**. Elimination of the nitro group and subsequent aromatization affords **47**.

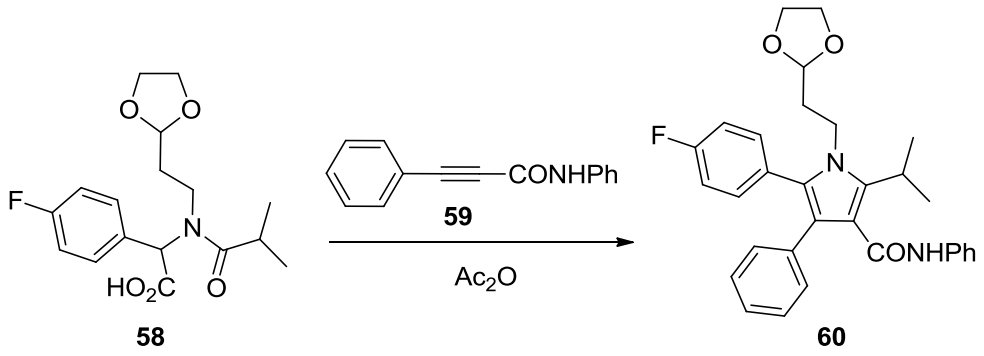
1.3.6.2.1,3-Dipolar Cycloaddition Reaction

In Huisgen pyrrole synthesis, pyrrole derivatives **57** are synthesized by 1,3-dipolar cycloaddition of the mesoionic-2-oxazilium-5-olates **55** to the corresponding acetylenic or olefinic dipolarophiles **56**, followed by carbon dioxide evolution and successive aromatization or tautomerization. (Scheme 13)



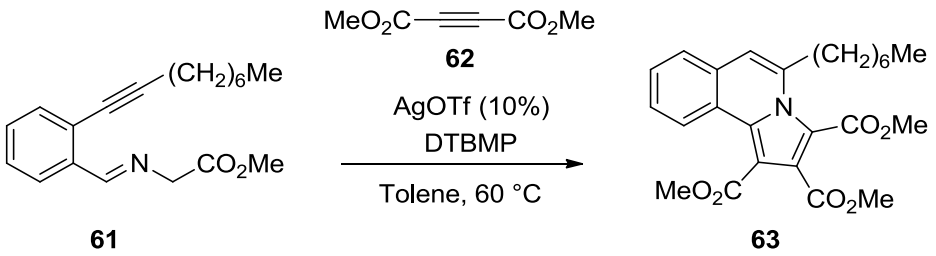
Scheme 13. Huisgen pyrrole synthesis

Huisgen pyrrole synthesis is another method for the synthesis of atorvastatin **60** and its derivatives (Scheme 14).



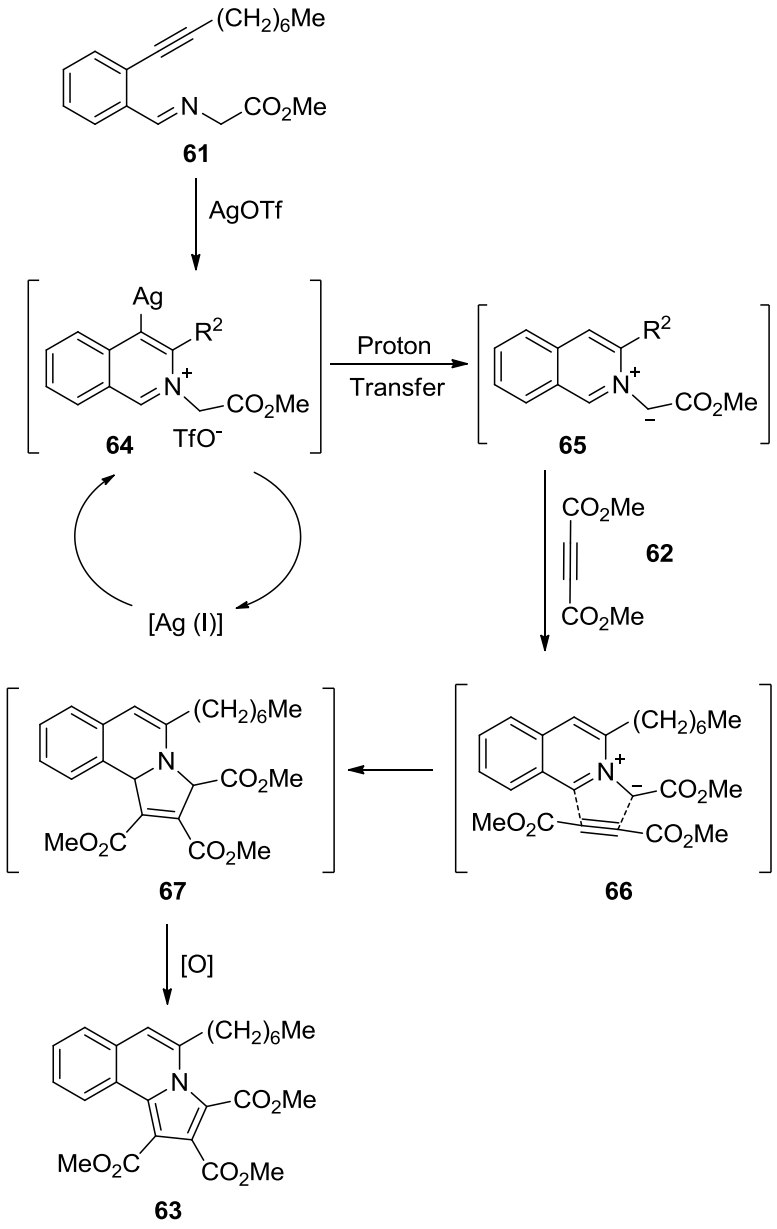
Scheme 14. Synthesis of atorvastatin derivative **60** by Huisgen pyrrole synthesis

1,3-Dipolar cycloaddition reactions have also been used for the synthesis of pyrrolo-isoquinolines which are the core structures of lamellarin alkaloids. In 2007, Porco and Su[5] developed a methodology for the synthesis of pyrroloisoquinoline derivatives using metal catalysts (Scheme 15).



Scheme 15. Synthesis of pyrroloisoquinoline **63** from alkynyl imine **61** and dimethyl acetylenedicarboxylate **62**

In this approach, cycloisomerization of alkynyl imine **61** with an alkynophlilic metal catalyst yields azomethine ylide **65** which affords formation of pyrrolo isoquinoline derivative **63** via dipolar cycloaddition when treated with dipolarophile **62**.

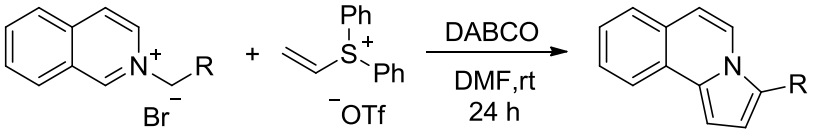


Scheme 16. Reaction mechanism for the synthesis of pyrroloisoquinoline derivative **63**

Treatment of alkynyl imine **61** with AgOTf in toluene yields cycloisomerization forming isoquinolinium **64** species. Azomethine ylide **65** is afforded by subsequent proton transfer and regeneration of the Ag (I). Dipolar cycloaddition reaction between **65** and dimethyl acetylenedicarboxylate **62** gives dihydopyrrole **67**.

Successive isomerization and thermal oxidation of **67** yields pyrroloisoquinoline **63** (Scheme 16).

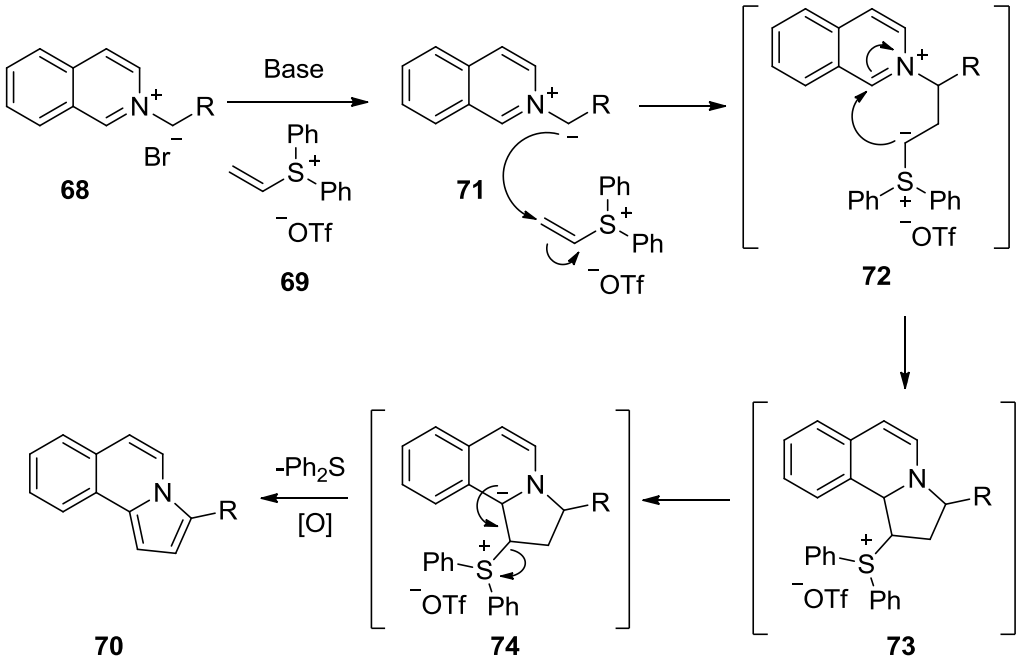
In 2013, Xiao and coworkers described the direct synthesis of pyrrolo[2,1-a]isoquinolines **(5)** via 1,3-dipolar cycloaddition reaction between isoquinolinium *N*-ylides **71** with vinyl sulfonium salts **69** in the presence of a base (Scheme 17).[15]



68 **69** **70**

Scheme 17. Synthesis of pyrroloisoquinoline **70** from isoquinolinium salt **68** and vinyl sulfonium salt **69**

Under basic conditions stabilized isoquinolinium salt **68** turns into isoquinolinium ylide **71** and reacts with vinyl sulfonium salt **69** forming intermediate **72** and **73**. 2,3-Unsubstituted 1-acylpyrrolo[2,1-a]isoquinoline **70** is afforded by the subsequent elimination of Ph_2S and dehydroaromatization. (Scheme 18).

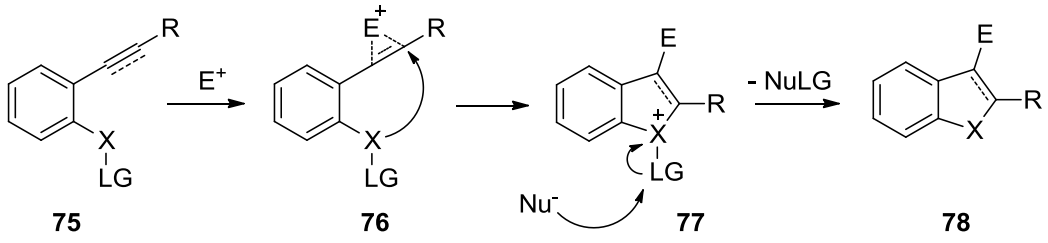


Scheme 18. . Reaction mechanism for the synthesis of pyrroloisoquinoline **70**

1,3-Dipolar cycloaddition reaction is one of the most frequently used methods for constructing pyrroloisoquinoline frameworks. Biological importance of pyrroloisoquinoline core structures has already been pointed out.

1.4. Electrophilic Cyclizations

Electrophilic cyclizations have become one of the most prominent and efficient methods for the synthesis of highly functionalized heterocyles such as pyrrole, furan, thiophene and indole.[16]



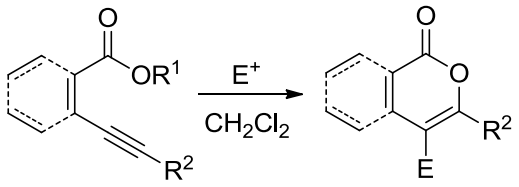
Scheme 19. General mechanism for the electrophilic cyclizations

General mechanism for the electrophilic cyclizations can be shown as in Scheme 19. Electrophile coordinates to the π bond of alkenes, alkynes, allenes or other carbon-carbon multiple bonds and activates the π bond toward a nucleophlic attack. Then, intermediate **77** is generated by the intramolecular nucleophilic attack of the carbon or heteroatom. Removal of the leaving group by a nucleophile present in the reaction medium yields heterocycle **78**.[16]

1.4.1. Electrophilic Cyclizations of Alkynes

1.4.1.1. Electrophilic Cyclizations of Alkynes via Nucleophilic Attack of a Heteroatom

Construction of substituted isocumarines and α-pyrones **80** starting from corresponding o-(1-alkynyl)benzoates and (Z)-2-alken-4-ynoates **79** was developed by Larock and co-workers.[17] This highly efficient synthesis affords wide variety of isocumarines and α-pyrones **80** in good yields by electrophilic cyclization of alkynyl esters **79** using ICl, I_2, PhSeCl and *p*-$O_2NC_6H_4SCl$ as the electrophile source (Scheme 20).

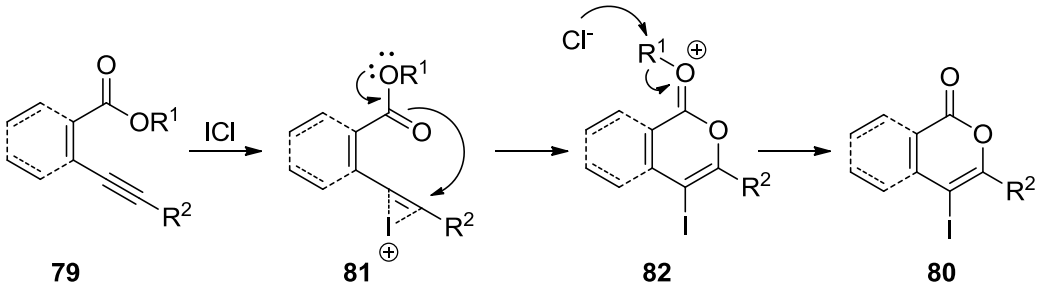


79 **80** (51-100%)

E^+ = ICl, I_2, PhSeCl, *p*-$O_2NC_6H_4SCl$, HI
R^1 = Me, Et, *t*-Bu
R^2 = H, *n*-C_4H_9, *n*-C_6H_{13}, $(CH_2)_3OH$, Si(*i*-Pr)$_3$, Ph

Scheme 20. Synthesis of substituted isocumarines and α-pyrones **80**

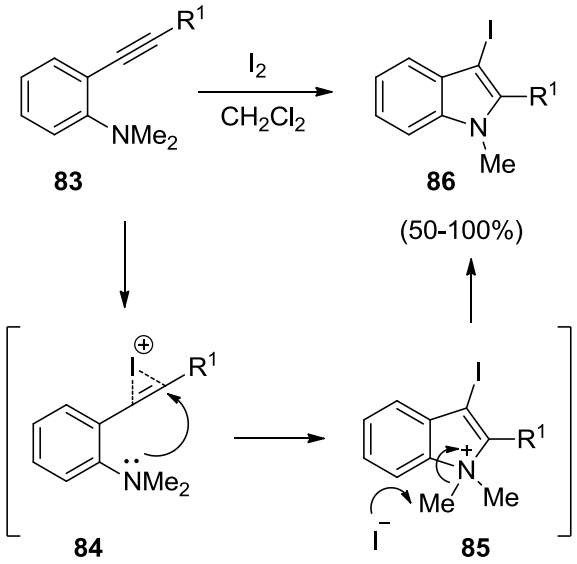
Authors observed that the reaction rate or the product yield was not affected by the R^1 group. Hence, they proposed that nucleophilic attack of the oxygen atom of the carbonyl group affords the cyclization product.



Scheme 21. Reaction mechanism for the synthesis of substituted isocumarines and α-pyrones **80**

Carbon-carbon triple bond is activated by the electrophile I^+ and ring closure occurs by the nucleophilic attack of the oxygen atom of the carbonyl group followed by the removal of R^1 group (Scheme 21). In addition iodide functionality present in the product provides synthesis of highly substituted heterocycles via coupling reactions such as Sonogashira, Heck and Suzuki reactions.

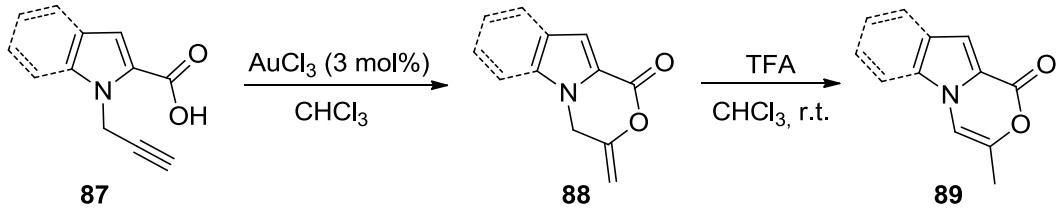
In a subsequent study, Larock's group reported the synthesis of 3-iodoindoles **86** by electrophilic cyclization of *N*,*N*-dialkynly-*o*-(-1-alkynyl)anilines (**83**) using I_2 in CH_2Cl_2.[18]



Scheme 22. Synthesis of 3-iodoindole **86**

Similarly, the nucleophilic attack of the nitrogen atom to the iodonium salt **84**, which is derived from the coordination of iodine to the alkyne moiety, yields intermediate **85**. Removal of one of the methylene group by iodide ion present in the reaction medium affords 3-iodoindole **86** (Scheme 22).

Very recently, Balcı and his group reported a study about the formation of pyrrolo- and indolo-oxazin-1-one **89** derivatives by gold catalyzed cyclization (Scheme 23).[19]



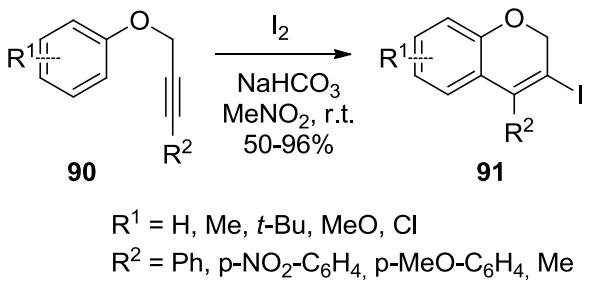
87 88 89

Scheme 23. Synthesis of pyrrolo- and indolo-oxazin-1-one **89** derivatives

Triple bond of the propargyl group is activated by the coordination of the Au(III) catalyst. Nucleophilic attack of the oxygen atom of the carboxylic group affords compound **88** in excellent yield. Double bond isomarization yielding **89** was observed when **88** treated with TFA in $CHCl_3$.

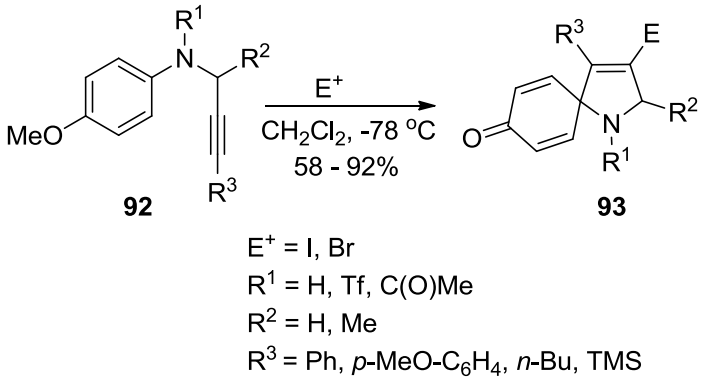
1.4.1.2.Electrophilic Cyclizations of Alkynes via Nucleophilic Attack of a Carbon Atom

Electrophilic cyclization of alkynes by a carbon nucleophile is a noteworthy approach for the synthesis of wide range of heterocyles. In 2007, Larock and coworkers reported the synthesis of 2*H*-benzopyrans **91** by iodocyclization of propargyl substituted aryl esters **90** in good yields (Scheme 24).[20]



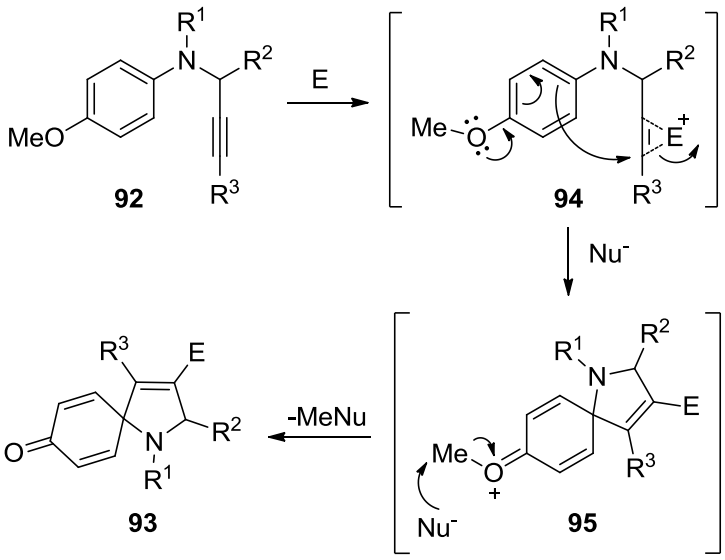
Scheme 24. Synthesis of 2*H*-benzopyrans derivatives **91** by iodocyclization

In a closely related study, electrophilic cyclization of arylalkynes **92** to spirotrienones **93** by using I_2, Br_2 and ICl was described by Larock and Zhang (Scheme 25).[21]



Scheme 25. Synthesis of spirotrienones derivatives **93**

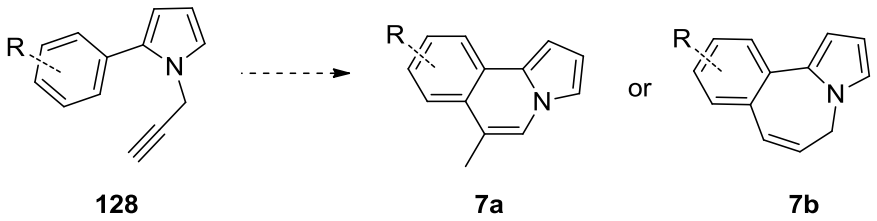
After the activation of the alkyne moeity by electrophile, nucleophilic attack from the ipso position of the aromatic ring forms intermediate **95**. Removal of the methyl group by a nucleophile presents in the reaction medium affords the compound **93** (Scheme 26).



Scheme 26. Reaction mechanism for the synthesis of spirotrienone **93** derivatives

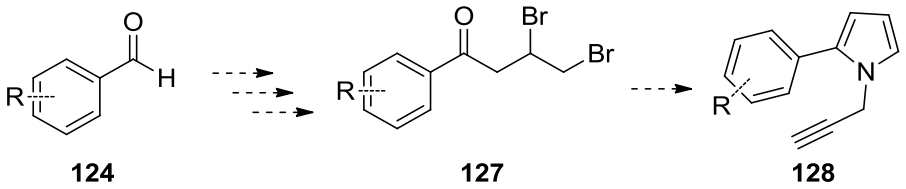
1.5.Aim of the Study

The objective of this thesis was to design and develop intramolecular alkyne cyclization reactions of propargyl substituted pyrrole derivatives by using various catalysts to design new heterocycles with new skeletons.



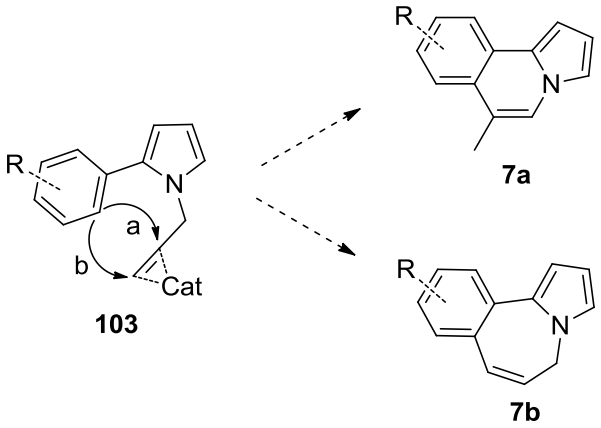
Scheme 27. Expected cyclization products

First part of the study was focused on the construction of *N*-alkynyl 2-phenyl substituted pyrrole structures. In this direction starting from benzaldehyde derivatives dibromo ketone derivatives should be synthesized. Pyrrolization should be achieved when dibromo ketone is treated with a primary amine.



Scheme 28. Designed synthesis route

Then, it was aimed to the ring closure of synthesized pyrrole derivatives by electrophilic cyclization reactions. It was expected that after the activation of the triple bond of the propargyl group by an electrophilic catalyst, nucleophilic attack of the benzene double bond from path a would yield a pyrrolo-isoquinoline derivative. In case of a nucleophilic attack which occurs from path b, a seven-membered cyclization product was expected.



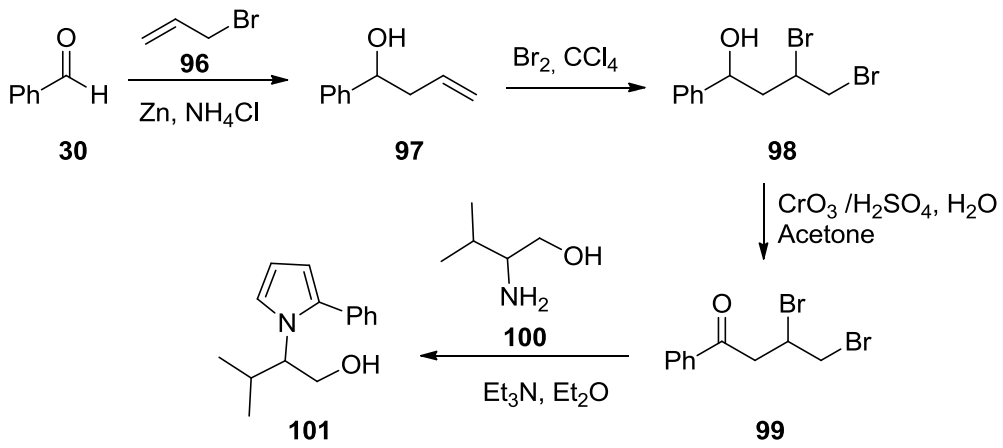
Scheme 29. Expected electrophilic cyclization reactions

CHAPTER 2

RESULTS AND DISCUSSION

2.1.Synthesis of Key Compounds

Construction of pyrrole rings from halogeno enones, which contain halide and carbonyl functionality, with primary amines was chosen as a convenient method for the synthesis of the key compouds; *N*-alkynl-2-substituted pyrrole derivatives. In 2001, Demir and his co-workers[22] reported a synthetic method for the formation of 2-phenyl substituted pyrrole rings from the reaction between dibromo compound **99** and valinol **100** starting from benzaldehyde **(30)** (Scheme 30).

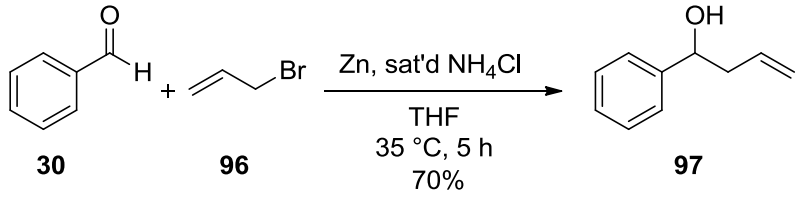


Scheme 30. Synthesis of *N*-alkynl-2-substituted pyrrole derivative **101**

In the light of this study, *N*-alkynl-2-substituted pyrrole derivatives were synthesized starting from benzaldehyde **(30)** and its derivatives. Propargyl amine **(102)** was used as the primary amine in the pyrrolization steps. Our research was focused on the catalyzed intramolecular cyclization reactions of these key compounds.

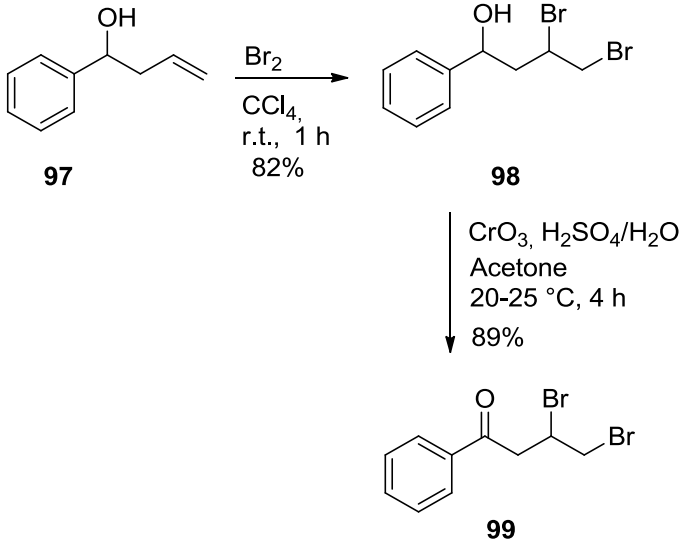
2.1.1. Synthesis of 2-Phenyl-1-prop-2-ynyl-1H-pyrrol (103)

Barbier type carbonyl allylation is a highly important synthetic transformation in the synthesis of homoallylic alcohols.[23] Compound **97** was synthesized via zinc mediated Barbier type allylation between benzaldehyde **(30)** and allyl bromide **96** with 70% yield (Scheme 31).



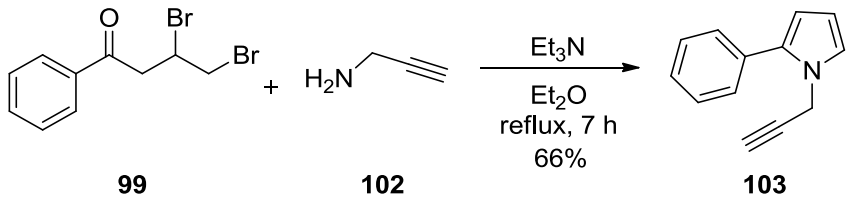
Scheme 31. Synthesis of compound **97** by Barbier type allylation

Bromination of terminal double bond of compound **97** with bromine in CCl_4 yielded compound **98**. Then, the corresponding bromo ketone **99** was synthesized by the oxidation of the hydroxyl group of compound **98** with chromium trioxide in the presence of H_2SO_4 and water in acetone (Scheme 32).



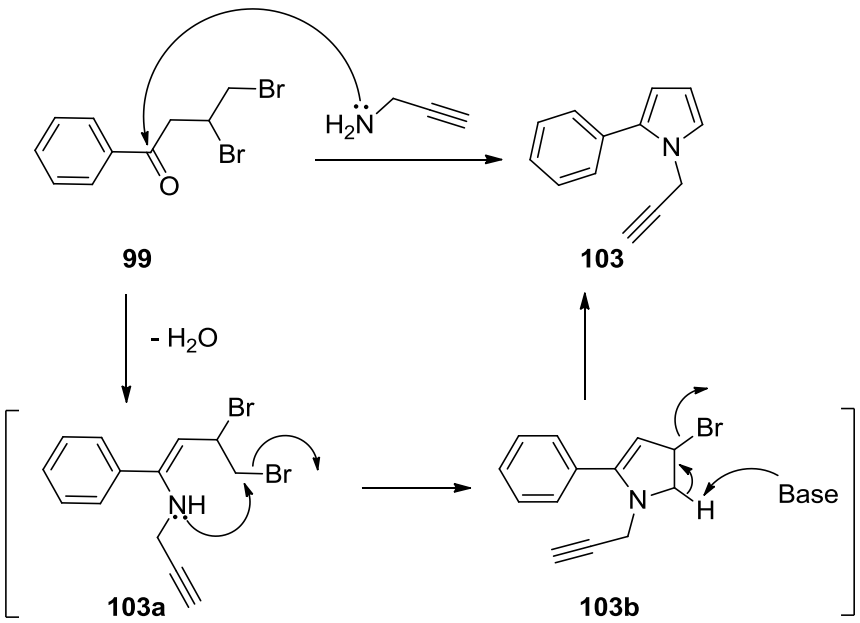
Scheme 32. Synthesis of compounds **98** and **99**

When **99** was treated with propargyl amine **102** and triethyl amine in diethyl ether, compound **103** was synthesized in 66% yield (Scheme 33).



Scheme 33. Synthesis of compound **103**

Probable formation mechanism of compound **103** can be depicted as shown in Scheme 34. Nucleophilic attack of the lone pair electrons of propargyl amine to the carbonyl carbon results in formation of enamine intermediate **103a**. Intramolecular cyclization of **103a** by the nucleophilic attack of nitrogen followed by the elimination of bromine atom, yields intermediate **103b**. Subsequent elimination reaction affords compound **103**.



Scheme 34. Propose mechanism for the synthesis of compound **103**

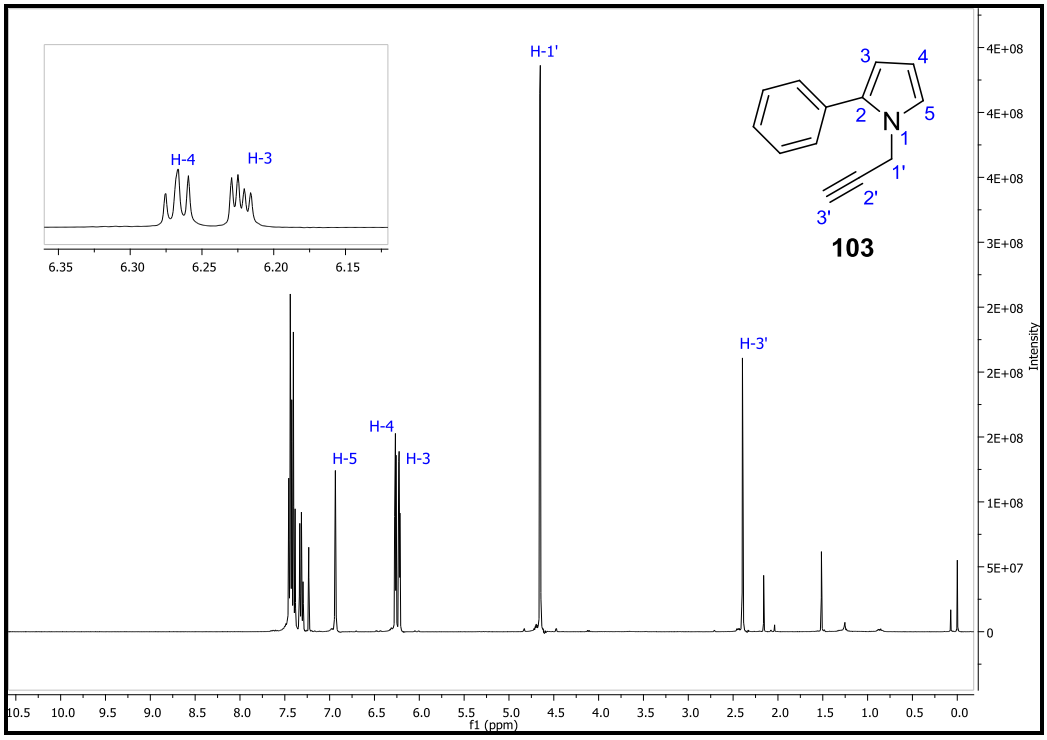
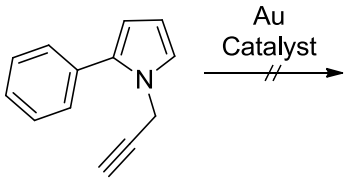


Figure 1. ^{1}H NMR spectrum of compound **103**

From the ^{1}H NMR spectrum of compound **103**, pyrrole protons, terminal alkyne proton and the methylene protons of propargyl group were observed. Terminal proton of the propargyl group was detected as a triplet at 2.40 ppm and methylene protons of the propargyl group were detected as a doublet at 4.65 ppm due to the long range coupling between these protons.

2.1.1.1. Attempted cyclization reactions of 2-phenyl-1-prop-2-ynyl-1*H*-pyrrol (103)

After the synthesis of key compound **103**, various cyclization reactions were carried out with different gold catalysts shown in Table 1. However, there were no reactions in each case (Scheme 35).



103

Scheme 35. Attempted cyclization reactions of **103**

Table 1: Au catalysts and reaction conditions for the cyclization reactions of compound **103**.

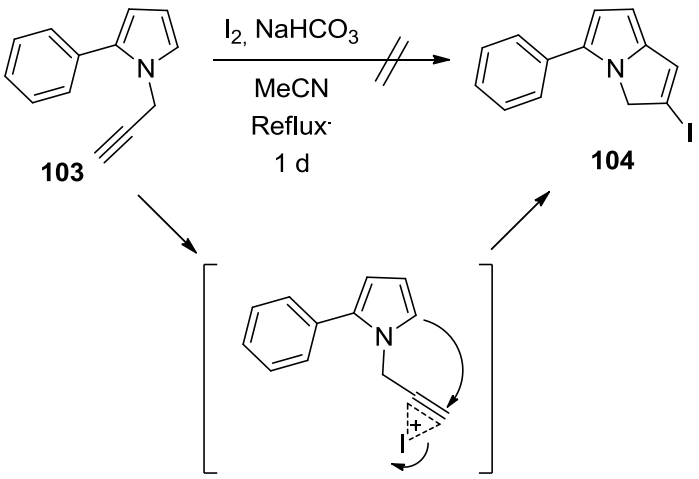
Catalyst	Solvent	Condition	Time (d)
$AuCl_3$	$CHCl_3$	Room temp.	1-3
$AuCl_3$	$CHCl_3$	Reflux temp.	1-3
$AuCl_3$	PhMe	Reflux temp.	1-2
$AuBr_3$	$CHCl_3$	Room temp.	1
$AuBr_3$	$CHCl_3$	Reflux temp.	1
$AuCl_3$ + AgOTf	$CHCl_3$	Room temp.	1
$AuCl_3$ + AgOTf	$CHCl_3$	Reflux temp.	1
$AuBr_3$ + NaH	$CHCl_3$	Reflux temp.	2

Apart from gold catalysts, other catalysts shown in Table 2 were also used. Nevertheless none of the reactions were successful.

Table 2: Various catalysts and reaction conditions for the cyclization reaction experiments of compound **103**.

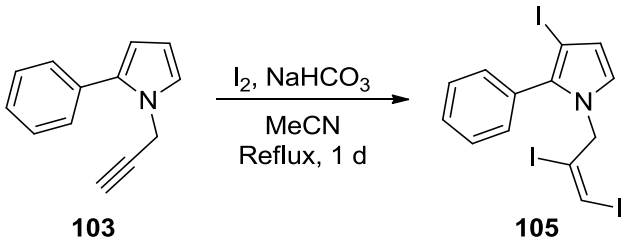
Catalyst	Solvent	Condition	Time (d)
$InCl_3$	PhMe	Room temp.	1
$InCl_3$	PhMe	Reflux temp.	1
$Cu(OTf)_2$	$CHCl_3$	Room temp.	1
$Cu(OTf)_2$	$CHCl_3$	Reflux temp.	1
ICl	CH_2Cl_2	0 °C	1
$TsOH.H_2O$	EtOH	Room temp.	1

In addition, iodine was used for the cyclization reaction. Compound **103** was reacted with iodine in the presence of $NaHCO_3$ in acetonitrile. After the reaction mixture was refluxed for a day, the product was isolated by column chromatography. According to the ^1H NMR spectrum, triplet peak of the terminal alkyne proton of the propargyl group disappeared. Also while the five protons of benzene ring remained only two pyrrole protons were observed. These results made us think that a cyclization product may have formed by the nucleophilic attack of the pyrrole double bond to the terminal carbon of the activated triple bond forming a five-membered cyclization product. The ^{13}C NMR spectrum was also consisted with the proposed structure **104** (Scheme 36).



Scheme 36. Expected cyclization reaction of **103**

However, the exact structure could not be characterized from the NMR spectra. Therefore, X-Ray analysis of the product was recorded and it was found that the structure was not a cyclization product but an iodo-substituted product **105** (Scheme 37).



Scheme 37. Reaction of **103** with iodine

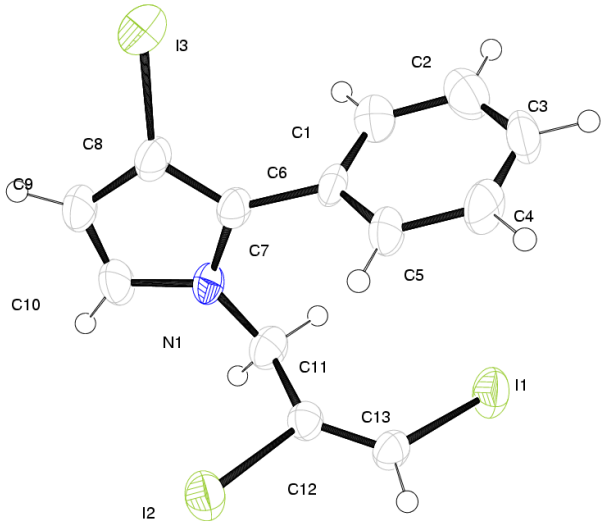
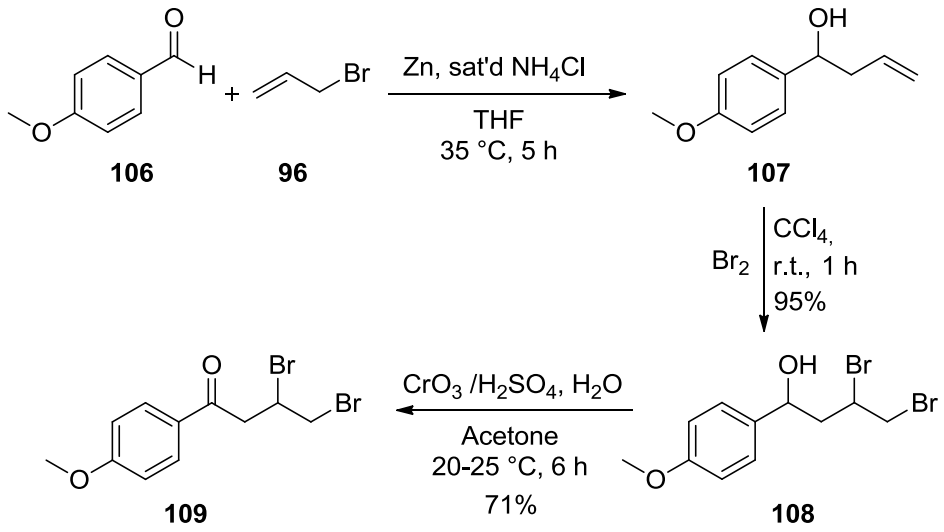


Figure 2. X-Ray analysis of compound **105**

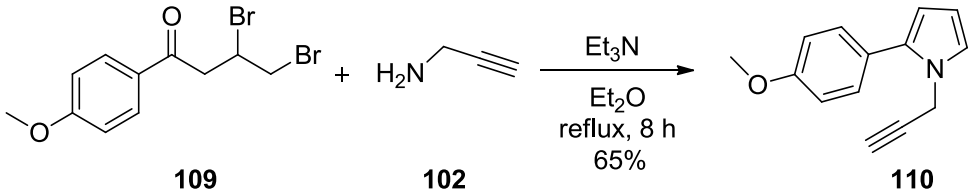
2.1.2. Synthesis of 2-(4-Methoxyphenyl)-1-(prop-2-yn-1-yl)-1H-pyrrole (110) and Attempted Cyclization Reactions

After the failure of the ring closure reactions of compound **103**, it was thought that benzene double bond may not be nucleophilic enough to attack to the triple bond activated by catalysts. Therefore, to increase the electron density of the benzene ring, a methoxyl group was introduced to the para position of the benzene ring. Starting from the p-methoxy benzaldehyde **(106)** compound **107** was synthesized by the Barbier type allylation with allyl bromide **96**. Successive bromination followed by the oxidation of the compound **108** gave compound **109** in 71% yield (Scheme 38).



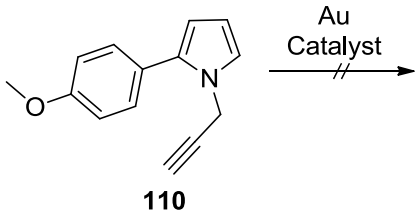
Scheme 38. Synthesis route of compound **109**

When **109** was treated with propargyl amine and triethyl amine in diethyl ether, compound **110** was synthesized in 65% yield. Both ^{13}C and ^{1}H NMR spectra were consistent with the structure **110** (Scheme 39).



Scheme 39. Synthesis of compound **110**

After the synthesis of compound **110**, several cyclization reactions shown in Table 3 were performed, however recorded ^{1}H NMR spectra indicated that there was no reaction in neither of the cases.

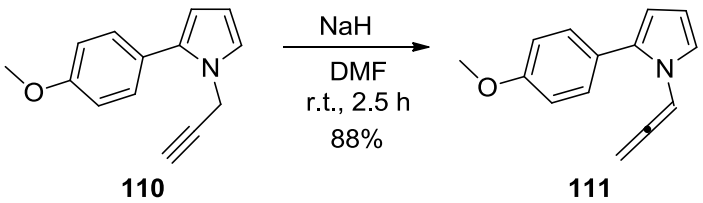


Scheme 40. Attempted cyclization reactions of **110**

Table 3: Au catalysts and reaction conditions for the cyclization reaction experiments of compound **110**.

Catalyst	Solvent	Condition	Time (d)
$AuCl_3$	$CHCl_3$	Reflux temp.	1
$AuCl_3$	$CHCl_3$	Room temp.	1
$AuCl_3$ +NaH	$CHCl_3$	Reflux temp.	1
$AuBr_3$	$CHCl_3$	Room temp.	1
$AuBr_3$	$CHCl_3$	Reflux temp.	1

Unsuccessful attempts of the intramolecular cyclization of compound **110** directed us to try a different approach. The idea was to increase the electropositivity of the carbon on which the nucleophilic attack would occur, since increasing the electron density of the benzene ring alone may have not been enough for the cyclization reaction. When the propargyl group of compound **110** is converted to its allene isomer, reactivity towards to a nucleophilic attack would increase since the sp-hybridized carbon of the allene group is considerably electropositive.



Scheme 41. Synthesis of compound **111**

When compound **110** was reacted with NaH in DMF at room temperature, the corresponding allene isomer **111** was obtained in 88% yield (Scheme 41).

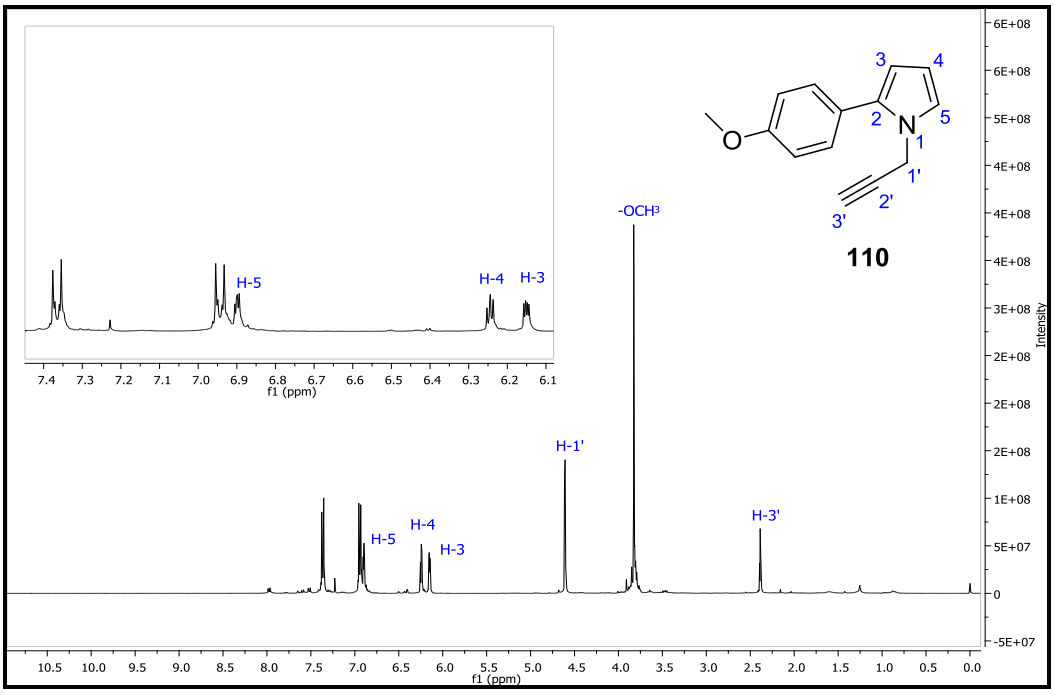


Figure 3. ^{1}H NMR spectrum of compound **110**

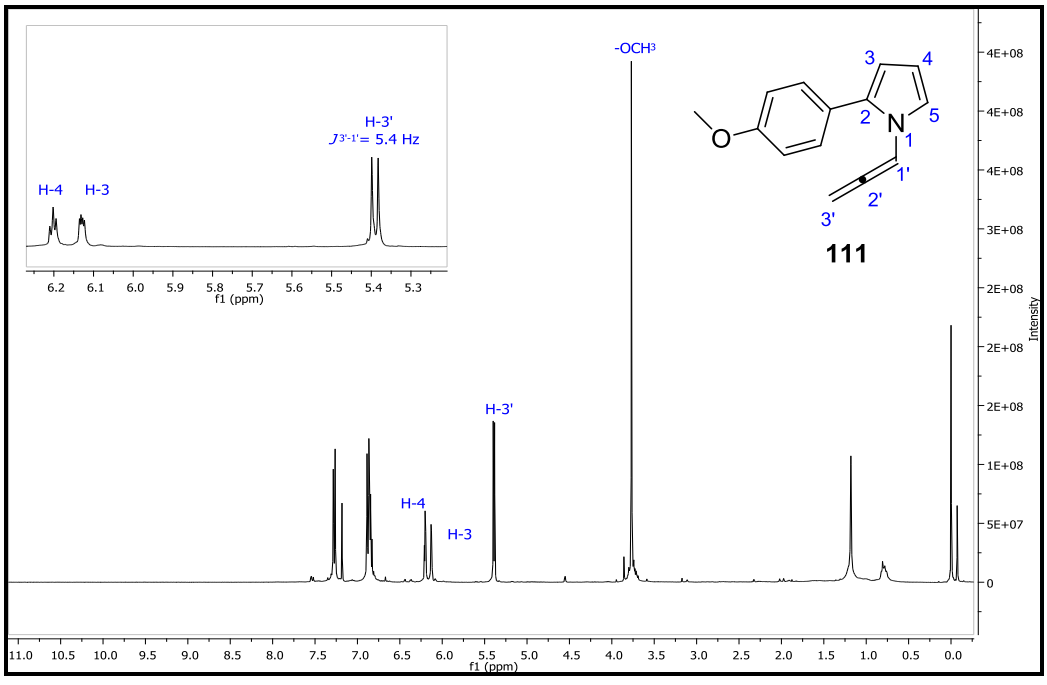
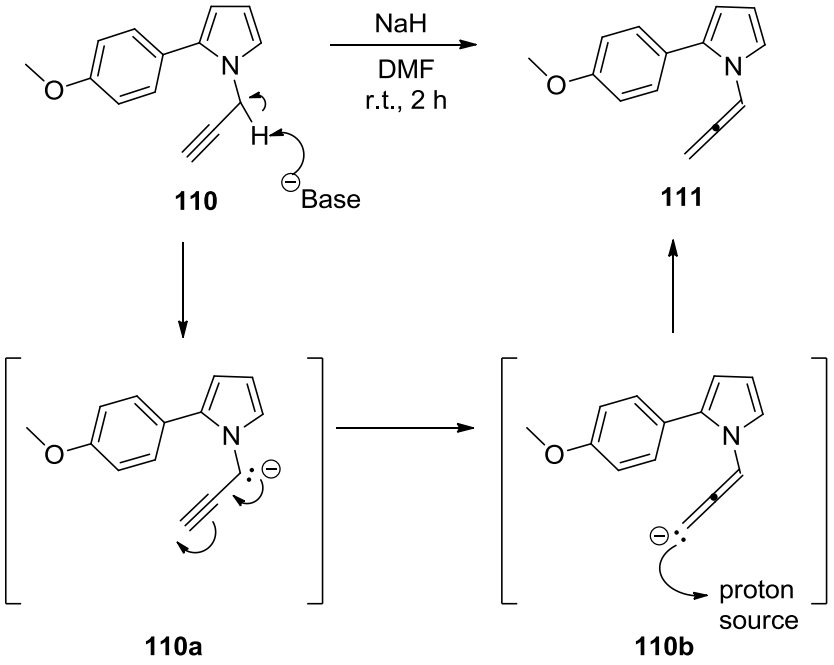


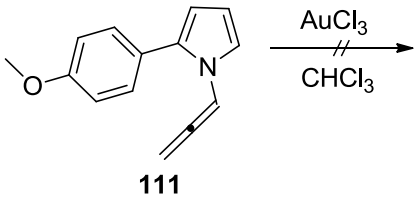
Figure 4. ^{1}H NMR spectrum of compound **111**

The central carbon atom of the allene unit resonates at 203.1 ppm in the ^{13}C NMR spectrum, clearly indicating the formation of the allene isomer **111**. From the ^{1}H NMR spectrum, it was observed that the triplet peak of the terminal proton of the propargyl group disappeared and the allenic $=CH_2$ proton resonance at 5.40 ppm appeared as doublet with a coupling constant of 6.4 Hz. The allenic –CH= proton peak, which is expected to be a triplet with a coupling constant of 5.4 Hz, overlapped with two proton resonances of benzene and a pyrrole protons.



Scheme 42. Proposed propargyl-allene isomerization mechanism of **110** to **111**

Proposed propargyl-allene isomerization mechanism is shown in Scheme **42**. Removal of one of the methylene protons by NaH as base yielded the corresponding carbanion **110a** and then its allene isomer **110b**. This resulting anion **110b** abstracts a proton from the reaction medium forming allene isomer **111**. This proton source could be water or the allene anion **110b** itself could act as a base and abstract one of the methylene protons of the propargyl group of compound **110**. Although the most acidic proton of the compound **110** is the terminal proton of the triple bond, proton abstraction occurs from the methylene protons because the resulting carbanion intermediate **110a** is more stable.



111

Scheme 43. Attempted cyclization reactions of **111**

Table 4: Reaction conditions for the cyclization reaction of allene isomer **111** with $AuCl_3$.

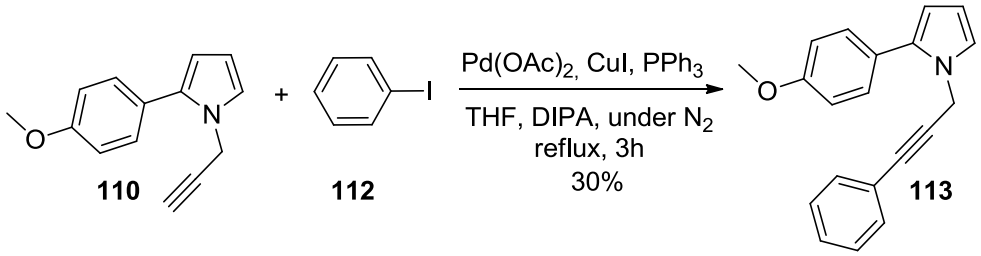
Temperature	Reaction Time
Room temp.	2.5 h
Room temp.	1 d
Reflux temp.	1 d

After the synthesis of allene isomer **111**, reactions with gold (III) chloride shown in Table 4 were performed at room and reflux temperatures. Reaction courses were monitored by TLC and ^{1}H NMR spectrum of the reaction mixtures were recorded at the end of the reactions after solvent was evaporated under the reduced pressure. When the reaction was ended after 2.5 h at room temperature, starting material was not consumed completely. Therefore, the reaction time was prolonged and the consumption of the allene **111** was controlled with TLC. Crude ^{1}H NMR spectra were complicated and difficult to interpret since numerous peaks were observed. Column chromatography was applied to the reaction mixtures; however, no product could be isolated. Therefore, results of these reactions were inconclusive.

2.1.3. Synthesis of 2-(4-Methoxyphenyl)-1-(3-phenylprop-2-ynyl)-1*H*-pyrrole (113) and Attempted Cyclization Reactions

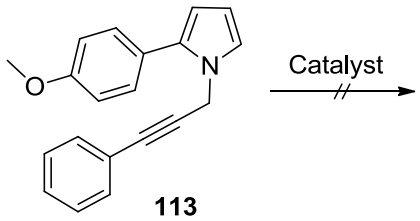
Another approach was to activate the alkyne moiety by introducing a benzene ring so that π-complex can be formed by a catalyst which could subsequently lead to a cyclization reaction. In this direction, Sonogashira coupling[24] was considered as a

conceivable way for the construction of new C-C bonds. To investigate this idea, compound **113** was synthesized by Sonogashira coupling reaction between compound **110** and iodobenzene **(112)** (Scheme 44). Product was isolated by column chromatography in 30% yield. Both ^{1}H and ^{13}C NMR spectral data indicated the formation of the desired product. In the ^{1}H NMR spectrum, triplet peak of the propargyl group disappeared as expected. Methylene protons of the propargyl group resonate at 4.86 ppm as a singlet.



Scheme 44. Synthesis of compound **113**

Several catalyst and different solvents were screened for the cyclization reaction of compound **113**. Unfortunately, all attempts were unsuccessful and none of the reactions gave a cyclization product. Catalysts and solvents used for the reactions are shown in Table 5.



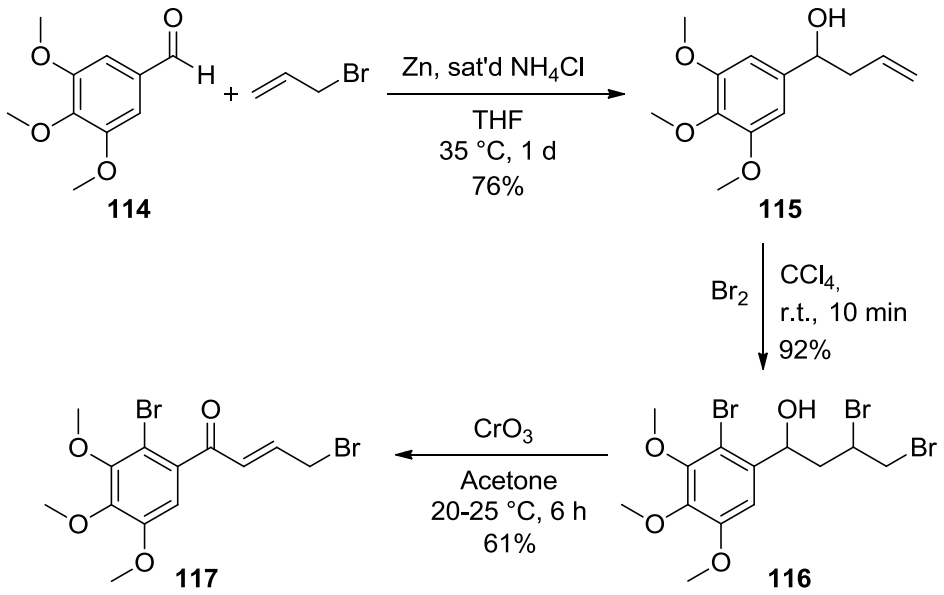
Scheme 45. Attempted cyclization reactions of **113**

Table 5: Reaction conditions and catalyst used for the ring closure experiments of compound **113**.

Catalyst	Solvent	Time (d)	Temperature
$AuCl_3$	$CHCl_3$	1	Room Temp.
$AuCl_3$	$CHCl_3$	1	62 ^oC
$AuCl_3$	Dioxane	1	100 ^oC
I_2 / $NaHCO_3$	MeCN	1	Room Temp.
I_2 / $NaHCO_3$	MeCN	1	82 ^oC
I_2 / $NaHCO_3$	CH_2Cl_2	1	40 ^oC
ICl / Na_2HPO_4	MeCN	1	82 ^oC
$FeCl_3$	MeCN	1	82 ^oC

2.1.4. Synthesis of 2-(2-Bromo-3,4,5-trimethoxyphenyl)-1-prop-2-ynyl-1*H*-pyrrole (118) and Attempted Cyclization Reactions

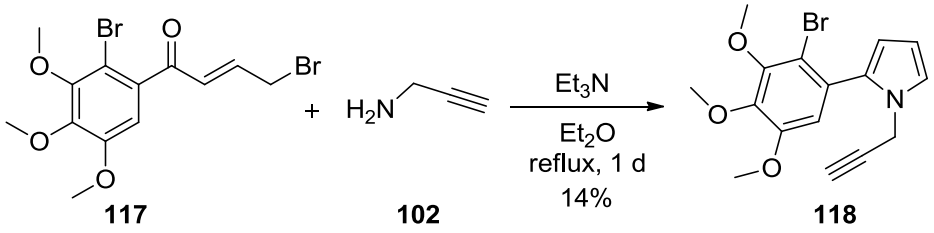
After the failed cyclization reactions of compound **113**, our attention was again focused on the reactivity of the benzene double bonds. Investigation of the attempted cyclization reactions of compound **110** may indicate that para substituted metoxy group was alone not sufficient for the activation of the benzene ring. Increasing the electron density with more electron donating groups could induce the nucleophilic attack of the double bond to the alkyne moiety activated by the catalyst. Consequently, introducing two more methoxyl group to the meta positions of the benzene ring would considerably increase the electron density and activate the ortho positions. Thus, 3,4,5-trimetoxybenzaldehyde **(114)** was chosen as the starting material. Barbier type allylation between **114** and allyl bromide **(96)** gave compound **115** in 76% yield. After the bromination of compound **115** in CCl_4, oxidation of the resulting product **116** yielded bromoketone **117** in 61% yield (Scheme 46).



Scheme 46. Synthesis route of compound **117**

Since the ortho positions of the benzene ring are highly nucleophilic because of the electron donating effect of the metoxyl groups, bromine atom was introduced to the ortho position of compound **115**. In addition, one of the bromine atoms added to the double bond was eliminated forming α-β unsaturated functionality. Structure of compound **117** was characterized by ^{1}H and ^{13}C NMR spectral data.

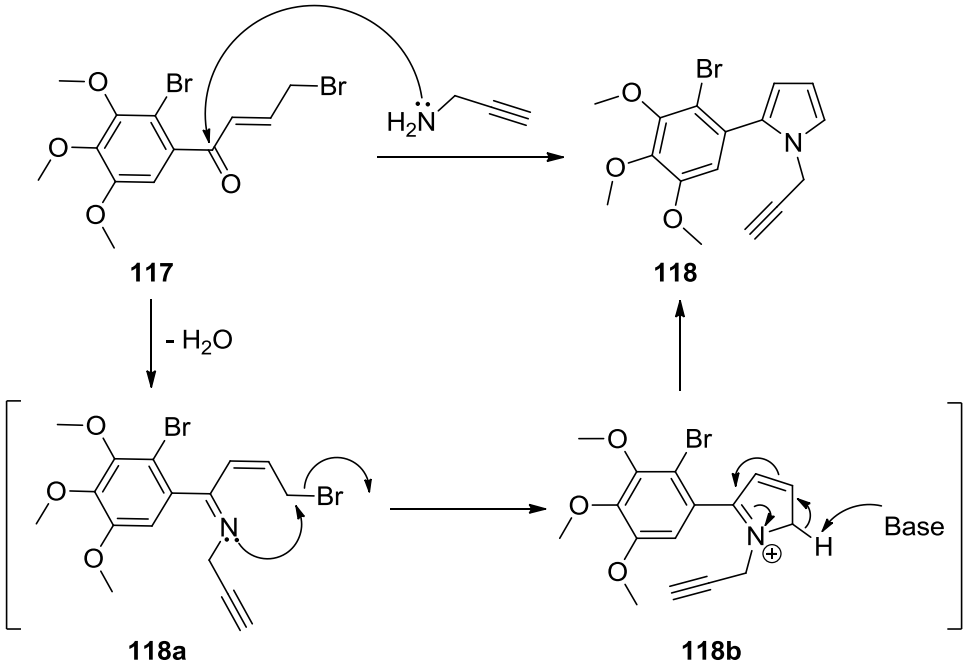
Compound **118** was formed, when compound **117** was refluxed in Et_2O with propargyl amine **(102)** in the presence of Et_3N for 8 hours (Scheme 47).



Scheme 47. Synthesis of compound **118**

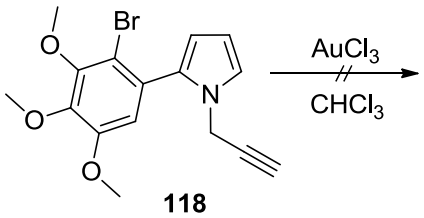
Suggested reaction mechanism for the formation of compound **118** is shown in Scheme 48. Formation of imine intermediate **118a** is afforded by the nucleophilic

attack of the lone pair electrons of propargyl amine to the carbonyl carbon. Intramolecular cyclization of **118a** by the nucleophilic attack of imine nitrogen followed by the elimination of Br atom, yields compound **118.**



Scheme 48. Proposed reaction mechanism for the synthesis of **118**

Structure of compound **118** was consisted with the ^{1}H and ^{13}C NMR spectra and the substitution of Br atom was also supported by GC-MS analysis. Compound **118** was submitted to $AuCl_3$ catalyzed cyclization reaction in $CHCl_3$ at room temperature and reaction course was monitored by TLC.

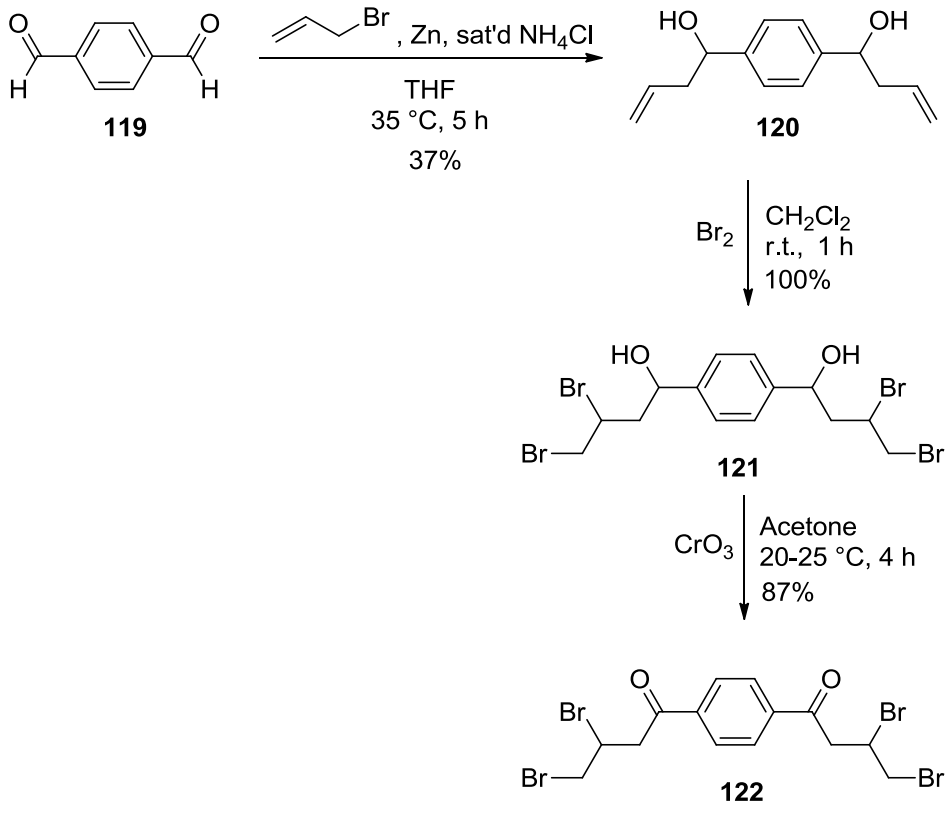


Scheme 49. Attempted cyclization reaction of **118**

Reaction mixture was stirred overnight and the ^{1}H NMR spectrum was recorded after solvent was evaporated under the reduced pressure. Unfortunately, no formation of product was observed. Reaction was repeated at reflux temperature; however, there was again no reaction. Deactivating effect of Br or/and steric effects caused by methoxyl groups may have prevented the ring closure.

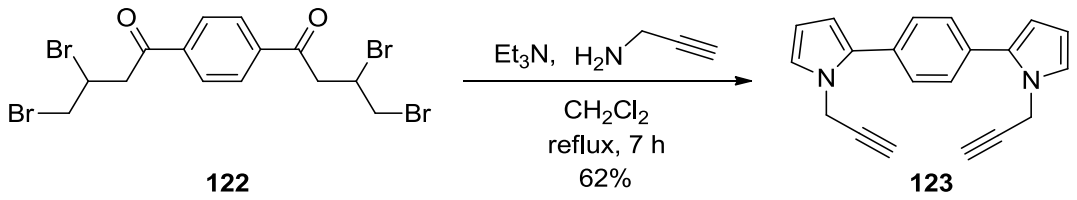
2.1.5. Synthesis of 1,4-Bis(1-(prop-2-yn-1-yl)-1H-pyrrol-2-yl)benzene (123) and Attempted Cyclization Reactions

Compound **123**, another *N*-alkynl-2-substituted pyrrole derivative, was synthesized by afore-mentioned synthetic route. Zinc mediated Barbier type allylation of terephthalaldehyde **(119)** with allyl bromide **(96)** gave compound **23** in 37% yield. Electrophilic bromination of compound **120** and successive oxidation of the resulting compound **121** yielded compound **122** (Scheme 50).



Scheme 50. Synthesis route of compound **122**

Compound **122** was treated with propargyl amine and Et_3N in CH_2Cl_2 at reflux temperature and **123** was obtained in 62% yield (Scheme 51).



122 **123**

Scheme 51. Synthesis of compound **123**

From the ^{1}H NMR spectrum of **123**, benzene protons were observed as singlet at 7.42 ppm since the compound has a symmetrical structure. Pyrrole protons H-5 and H-4 resonate as multiplets. H-3 which is coupled with H-5 and H-4 was observed as doublet of doublets with coupling constants of J_{34} = 3.4 Hz and J_{35} =1.8 Hz. Terminal proton of the propargyl groups H-3' was detected as a triplet at 2.35 ppm and methylene protons of the propargyl groups H-1' appear as a doublet at 4.63 ppm.

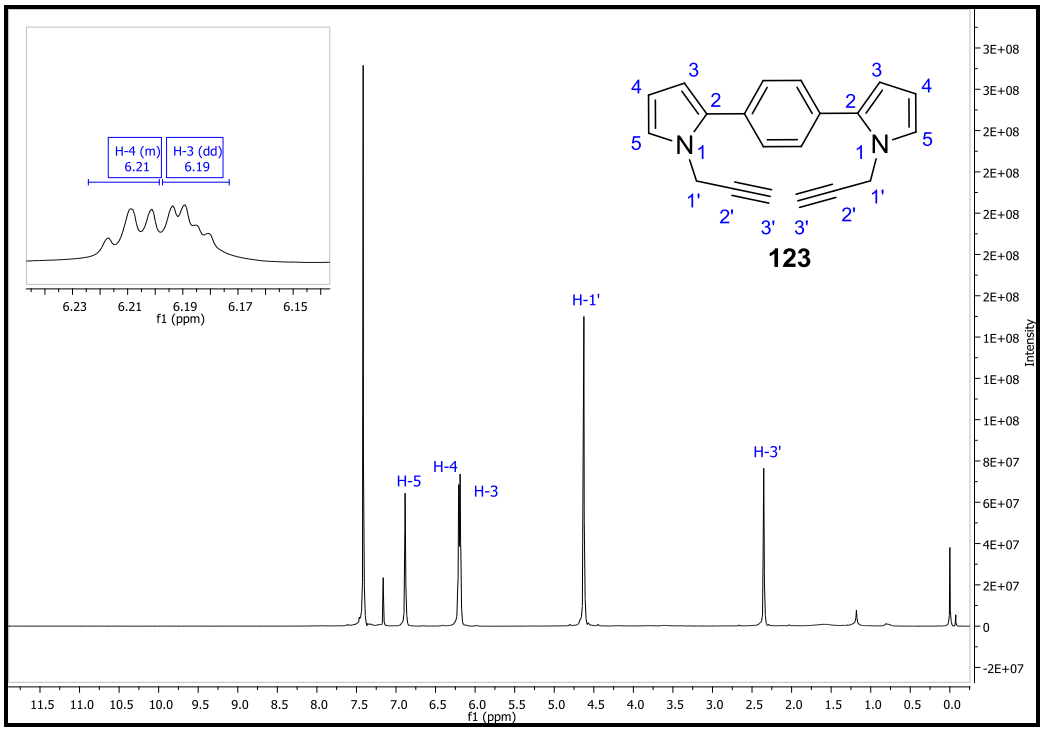
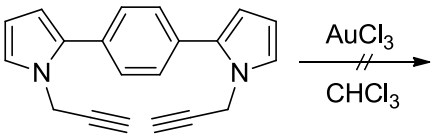


Figure 5. ^{1}H NMR spectrum of compound **123**

After the synthesis of compound **123** ring closure reaction with $AuCl_3$ in $CHCl_3$ was performed. Reaction was carried out in room temperature and stirred overnight. Recorded ^{1}H NMR spectrum showed no formation of a cyclization product. Same reaction was conducted at reflux temperature and controlled by TLC. After the reaction mixture was stirred overnight, reaction was finalized and ^{1}H NMR spectrum was recorded. However, no product formation was observed.



123

Scheme 52. Attempted cyclization reaction of **123**

CHAPTER 3

EXPERIMENTAL

3.1. General

Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument was used for the recording of ^{1}H and ^{13}C Nuclear magnetic resonance spectra. $CDCl_3$ was used as the solvent and TMS was used as the internal reference. Chemical shifts (δ) were reported as parts per million (ppm). Spin multiplicities were reported as singlet (s), doublet (d), doublet of doublet (dd), doublet of doublet of doublet of doublet (dddd), quasi-doublet (quasi-d), triplet (t), broad triplet (bt), doublet of doublet of triplet (ddt), triplet of triplet (tt) and multiplet (m). Coupling constants (J) were reported in Hertz (Hz).

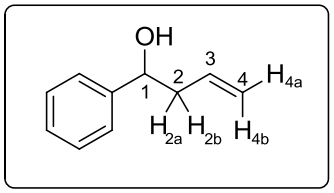
Infrared spectra were recorded with Matson FT-IR spectrometer and Vertex 70 series FT-IR spectrometer. Band positions were reported in reciprocal centimeters (cm-1).

Column chromatograpies were performed by using Fluka Silica Gel 60 plates with a particle size of 0.063-0.20 mm. Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Fluka.

Compounds were named by using ACD Name Generator.

3.2. 1-Phenylbut-3-en-1-ol (97)

5 mL saturated aq. NH_4Cl and 0.25 mL THF was added to a flask charged with Zn (0.74 g, 11.30 mmol). Then, a mixture of allyl bromide (1.37 g, 11.30 mmol) and benzaldehyde (1.00 g, 9.42 mmol) was added dropwise and the resulting reaction mixture was stirred at 35 °C for 5 hours. The mixture was cooled to room temperature and quenched with 5 mL of 7% HCl and 2.5 mL of saturated aqueous NH_4Cl. Reaction mixture was filtered via vacuum filtration. Work-up of the reaction mixture was performed by using ethyl acetate (3 x 20 mL). Extracts were combined together and washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Further purification was performed by column chromatography on silica gel with solvent system of 4:1 Hexane-Ethyl acetate and product was obtained as pale yellow viscous oil (0.98 g, 70%).

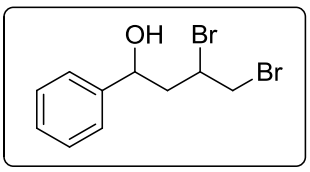


^{1}H NMR (400 MHz, Chloroform-d) δ 7.39 – 7.19 (m, 5H, -CH), 5.77 (ddt, J_{34b} = 17.2 Hz, J_{34a} = 10.2 Hz, J_{32} = 7.1 Hz, 1H, H-3, -CH), 5.17 – 5.05 (m, 2H, H-4, $-CH_2$), 4.67 (dd, J_{12a} = 7.2 Hz, J_{12b} =5.8 Hz, 1H, H-1, -CH), 2.52 – 2.42 (m, 2H, H-2, $-CH_2$), 2.34 (bs, 1H, -OH)

^{13}C NMR (100 MHz, Chloroform-d) δ 144.0, 134.5, 128.4, 127.5, 125.9, 118.3, 73.4, 43.8

3.3. 3,4-Dibromo-1-phenylbutan-1-ol (98)

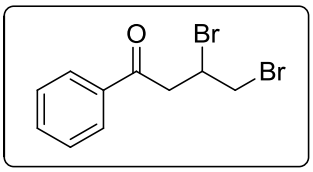
To a solution of 1-phenylbut-3-en-1-ol (7.65 g, 51.62 mmol) and 20 ml CCl_4, Br_2 (8.25 g, 51.62 mmol) in 10 ml CCl_4 was added dropwise at 0 °C. After the addition, the mixture was stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and product was obtained as green viscous oil (12.98 g, 82%).



^{1}H NMR (400 MHz, Chloroform-d) δ: mixture of diastereomers

3.4. 3,4-Dibromo-1-phenylbutan-1-one (99)

CrO_3 (14.33 g, 143.31 mmol) was dissolved in 10 ml water and 6 ml concentrated H_2SO_4. This mixture was added dropwise to 3,4-dibromo-1-phenylbutan-1-ol (12.98 g, 42.14 mmol) in 30 ml acetone. The reaction mixture was stirred at 20-25 °C for 4 hours. Acetone was evaporated and the mixture was extracted with ethyl acetate (3 x 30 ml). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and product was obtained as brown crystals (11.50 g, 89%).

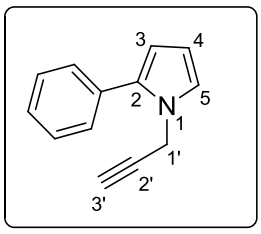


^{1}H NMR (400MHz, $CDCl_3$) δ 7.94 – 7.86 (m, 2H, -CH), 7.59 – 7.50 (m, 1H, -CH), 7.47 – 7.39 (m, 2H, -CH), 4.72 (tt, *J* = 8.6, 4.3 Hz, 1H, -CH), 3.95 (dd, *J* = 10.5, 4.3 Hz, 1H, $-CH_2$), 3.82 – 3.72 (m, 2H, $-2CH_2$), 3.58 (dd, J = 17.8, 8.6 Hz, 1H, $-CH_2$).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 136.9, 131.4, 128.6, 128.5, 49.8, 48.6, 37.3

3.5. 2-Phenyl-1-prop-2-ynyl-1*H*-pyrrole (103)

After bromo ketone (3.00 g, 9.80 mmol) was dissolved in 20 mL diethyl eter, propargyl amine (1.35 g, 24.50 mmol) was added and the mixture refluxed for 2 hours. Then, triethyl amine (2.00 g, 19.60 mmol) was added and the resulting mixture refluxed for another 5 hours. The mixture was cooled to room temperature diluted with water and extracted with ethyl acetate (3x25 mL). The combined extracts washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Further purification was performed by column chromatography on silica gel with 10:1 Hexane- Ethyl acetate solvent system and product was obtained as colorless liquid (1.17 g, 66%).



^{1}H NMR (400 MHz, Chloroform-d) 7.46 – 7.43 (m, 2H, -CH), 7.43 – 7.38 (m, 2H,-CH), 7.34 – 7.29 (m, 1H, -CH), 6.94 (dd, J_{54} = 2.8 Hz, 1.8 Hz, J_{53} = 1.8 Hz, 1H, H-5, -CH), 6.28 – 6.25 (m, 1H, H-4, -CH), 6.22 (dd, J_{34} = 3.6 Hz, J_{35}=1.8

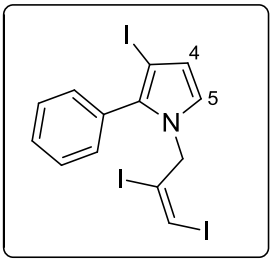
Hz, 1H, H-3, -CH), 4.65 (d, $J_{1'3'}$ = 2.5 Hz, 2H, H-1', -CH_2), 2.40 (t, $J_{3'1'}$ = 2.5 Hz, 1H, H-3', -CH).

^{13}C NMR (100 MHz, Chloroform-d) δ 134.4, 132.8, 128.9, 128.6, 127.2, 122.1, 109.0, 108.9, 79.1, 73.3, 36.7.

IR (ATR) 3284, 1602, 1493, 1469, 1303, 1238, 1076, 933, 761, 697, 535

3.6. (*E*)-1-(2,3-Diiodoallyl)-3-iodo-2-phenyl-1*H*-pyrrole (105)

To a solution of 2-Phenyl-1-prop-2-ynyl-1*H*-pyrrole (0.5 g, 2.76 mmol) in 15 ml acetonitrile, I_2 (2.1 g, 8.28 mmol) and $NaHCO_3$ (0.6 g, 8.28 mmol) was added. The reaction mixture was refluxed for a day. Then, it was cooled to room temperature, quenched with 15 ml of 30% sodium thiosulfate solution and extracted with ethyl acetate (3 x 20 mL). Combined extracts washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Column chromatography was performed on silica gel with 15:1 Hexane - Ethyl acetate solvent system. For further purification, crystallization was performed in hexane and product was obtained as colorless cubic crystals (0.33 g, 21%).



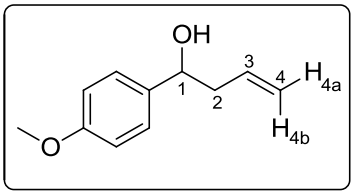
^{1}H NMR (400 MHz, Chloroform-d) δ 7.40 – 7.29 (m, 5H, -CH), 6.97 (s, 1H, -CH), 6.64 (d, J_{45} = 2.9 Hz, 1H, H-4, -CH), 6.34 (d, J_{54} = 2.9 Hz, 1H, H-5, -CH), 4.61 (s, 2H, -CH_2)

^{13}C NMR (100 MHz, Chloroform-d) δ 141.0, 131.4, 129.7, 129.33, 128.5, 128.3, 121.9, 105.8, 61.8, 61.0, 52.7

3.7. 1-(4-methoxyphenyl)but-3-en-1-ol (107)

15 mL saturated aq. NH_4Cl and 2 mL THF was added to a 100 mL two-necked flask charged with Zn (2.88 g, 44.01 mmol). Then, a mixture of allyl bromide (5.33 g, 44.01 mmol) and 4-methoxybenzaldehyde (5.00 g, 36.7 mmol) was added dropwise and the resulting reaction mixture was stirred at 35 °C for 5 hours. The mixture was cooled to room temperature and quenched with 10 mL of 7% HCl and 5 mL of saturated aqueous NH_4Cl. Reaction mixture was filtered via vacuum filtration.

Work-up of the reaction mixture was performed by using ethyl acetate (3 x 20 mL). Extracts were combined together and washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Further purification was performed by column chromatography on silica gel with solvent system of 20:1 Hexane-Ethyl acetate and product was obtained as yellow liquid (6.12 g, 93%).

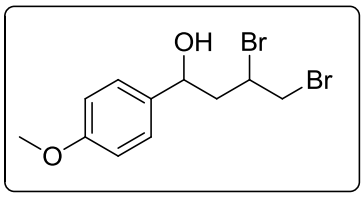


^{1}H NMR (400 MHz, Chloroform-d) δ 7.31 (quasi-d, *J* = 8.7 Hz, 2H, -CH), 6.91 (quasi-d, *J* = 8.4 Hz, 2H, -CH), 5.82 (ddt, J_{34b} = 17.3 Hz, J_{34a} = 10.2 Hz, J_{32} =6.9 Hz, 1H, H-3, -CH), 5.22 – 5.12 (m, 2H, H-4, -CH_2), 4.71 (bt, J_{12} = 6.9 Hz, 1H, H-1, -CH), 3.83 (s, 3H, -CH_3), 2.52 (bt, J_{21} = J_{23} = 6.9 Hz, 2H, H-2, -CH_2), 2.04 (s, 1H, -OH).

^{13}C NMR (100 MHz, Chloroform-d) δ 159.0, 136.1, 134.6, 127.1, 118.2, 113.8, 73.0, 55.3, 43.7.

3.8. 3,4-dibromo-1-(4-methoxyphenyl)butan-1-ol (108)

To a solution of 1-(4-methoxyphenyl)but-3-en-1-ol (1.00g, 5.61 mmol) in 8 mL CCl_4, Br_2 (0.99g, 6.17mmol) in 2 mL CCl_4 was added dropwise at 0 °C. After the addition, the mixture was stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and product was obtained as green viscous oil (1.81 g, 95%).

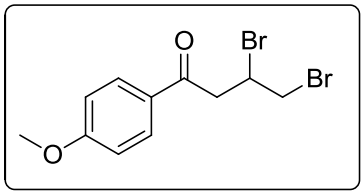


^{1}H NMR (400 MHz, Chloroform-d) δ: mixture of diastereomers

3.9. 3,4-dibromo-1-(4-methoxyphenyl)butan-1-one (109)

CrO_3 (3.85 g, 38.50 mmol) was dissolved in 5 mL water and 3 mL concentrated H_2SO_4. This mixture was added drop wise to 3,4-dibromo-1-(4-methoxyphenyl)butan-1-ol (3.83 g, 11.33 mmol) in 10 mL acetone. The reaction

mixture was stirred at 20-25 °C for 6 hours. Acetone was evaporated and the mixture was extracted with ethyl acetate (3 x 25 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Further purification was achieved by column chromatography on silica gel with hexane. Product was obtained as green viscous oil (2.69 g, 71%).



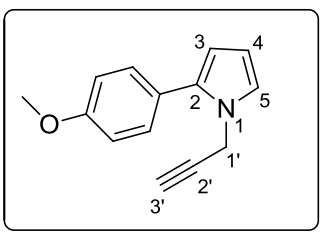
^{1}H NMR (400 MHz, Chloroform-d) δ 7.95 (quasi-d, *J* = 8.9 Hz, 2H, -CH), 6.96 (quasi-d, *J* = 8.9 Hz, 2H, -CH), 4.78 (tt, *J* = 4.3, 8.5 Hz, 1H, -CH), 4.01 (dd, *J* = 10.5, 4.3 Hz, 1H, $-CH_2$), 3.88 (s, 3H, $-CH_3$), 3.82 (dd, *J* = 10.5, 8.9 Hz, 1H, $-CH_2$) 3.79 (dd, *J* = 17.6, 4.3 Hz, 1H, $-CH_2$), 3.59 (dd, *J* = 17.6, 8.3 Hz, 1H, $-CH_2$)

^{13}C NMR (100 MHz, Chloroform-d) δ 194.2, 164.0, 130.5, 129.4, 114.0, 55.6, 45.0, 44.7, 36.7

IR (ATR) 3004, 2960, 2934, 2837, 1672, 1597, 1509, 1457, 1420, 1367, 1307, 1251, 1171, 1025, 832, 548

3.10. 2-(4-Methoxyphenyl)-1-(prop-2-yn-1-yl)-1*H*-pyrrole (110)

After bromo ketone (0.88 g 2.62 mmol) was dissolved in 10 mL diethyl eter, propargyl amine (0.36 g, 6.55 mmol) was added and the mixture refluxed for 2 hours. Then, triethyl amine (0.53 g, 5.24 mmol) was added and the resulting mixture refluxed for another 6 hours. The mixture was cooled to room temperature diluted with water and extracted with ethyl acetate (3 x 25 mL). The combined extracts washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Further purification was performed by column chromatography on silica gel with hexane and product was obtained as orange liquid (0.36 g, 65%).



^{1}H NMR (400 MHz, Chloroform-d) δ 7.37 (quasi-d, *J* = 8.8 Hz, 2H, -CH), 6.94 (quasi-d, *J* = 8.8 Hz, 2H,-CH), 6.90 (dd, J_{54} = 2.8 Hz, J_{53} = 1.8 Hz, 1H, H-5, -CH), 6.26 – 6.23 (m, 1H, H-4, -CH), 6.15 (dd, J_{34} = 3.5 Hz, J_{35}

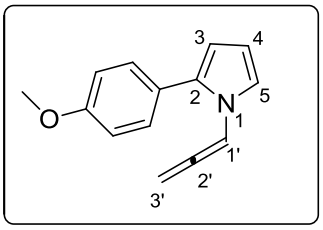
=1.8 Hz, 1H, H-3, -CH), 4.61 (d, $J_{1',3'}$ = 2.6 Hz, 2H, H-1', -CH_2), 3.83 (s, 3H, -CH_3), 2.39 (t, $J_{3',1'}$ = 2.6 Hz, 1H, H-3' -CH).

^{13}C NMR (100 MHz, Chloroform-d) δ 159.0, 134.1, 130.2, 125.3, 121.5, 114.0, 108.7, 108.4, 79.3, 73.2, 55.4, 36.1.

IR (ATR) 3282, 2999, 2933, 2834, 2123, 2041, 1683, 1671, 1610, 1575, 1551, 1506, 1465, 1438, 1344, 1287, 1244, 1175, 1109, 1028, 933, 833, 784, 712

3.11. 2-(4-Methoxyphenyl)-1-(propa-1,2-dien-1-yl)-1*H*-pyrrole (111)

2-(4-Methoxyphenyl)-1-(prop-2-yn-1-yl)-1*H*-pyrrole (0.057 g, 0.27 mmol) was dissolved in 5 ml dry DMF. Then, NaH (0.0065 g, 0.27 mmol) was added and the mixture was stirred for 2.5 h at room temperature. The reaction mixture was added 10 mL ethyl acetate and resulting organic phase was washed with brine (8 x 10 mL) and dried over $MgSO_4$. Solvent was evaporated under reduced pressure. Product was obtained as orange liquid (0.05 g, 88%)



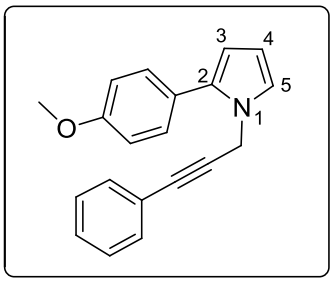
^{1}H NMR (400 MHz, Chloroform-d) δ 7.27 (quasi-d, *J* = 8.7 Hz, 2H, -CH), 6.88 (quasi-d, *J* = 8.9 Hz, 2H, -CH), 6.86 – 6.82 (m, 2H, H-5 and H-1', -CH), 6.20 (t, *J* = 3.2 Hz, 1H, H-4, -CH), 6.13 (dd, J_{34} = 3.4 Hz, J_{35} =1.7 Hz, 1H, H-3, -CH), 5.39 (d, $J_{3',1'}$ = 6.4 Hz, 2H, -CH2), 3.77 (s, 3H, -CH3).

^{13}C NMR (100 MHz, Chloroform-d) δ 203.1, 159.0, 133.7, 130.5, 125.0, 119.7, 113.9, 109.7, 109.1, 98.5, 86.8, 55.3

3.12. 2-(4-Methoxyphenyl)-1-(3-phenylprop-2-ynyl)-1*H*-pyrrole (113)

A 50 mL two necked flask was charged with $Pd(OAc)_2$ (0.005 g, 0.02 mmol), CuI (0.001 g, 0.04 mmol), PPh_3 (0.02 g, 0.08 mmol) under N_2 gas. Then, a solution of 2-(4-methoxyphenyl)-1-(prop-2-yn-1-yl)-1*H*-pyrrole (0.36 g, 1.70 mmol) in 7mL dry THF, iodobenzene (0.35 g, 1.70 mmol) and 3 mL dry DIPA was added successively. The reaction mixture was refluxed for 3 hours. Completion of the

reaction was controlled with TLC. THF was removed under reduced pressure and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Further purification was performed by column chromatography on silica gel with solvent system of 5:1 Hexane-Ethyl acetate and product was obtained as orange liquid (0.15 g, 30%).



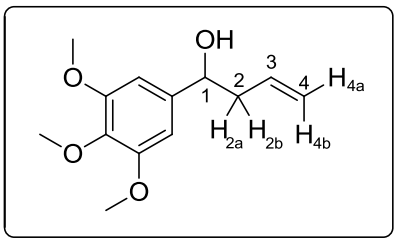
^{1}H NMR (400 MHz, Chloroform-d) δ 7.48 – 7.39 (m, 4H, -CH), 7.37 – 7.28 (m, 3H, -CH), 7.00 (dd, J_{54} = 2.8 Hz, J_{53} =1.8 Hz, 1H, H-5 -CH), 6.99 – 6.95 (m, 2H, -CH), 6.28 (t, J_{43} = 3.4 Hz, 1H, H-4, -CH), 6.20 (dd, J_{34} = 3.4 Hz, J_{35} = 1.8 Hz, 1H, H-3, -CH), 4.86 (s, 2H, -CH_2), 3.85 (s, 3H, -CH_3).

^{13}C NMR (100 MHz, Chloroform-d) δ 158.9, 134.1, 131.8, 130.3, 128.5, 128.3, 125.5, 122.5, 121.7, 114.0 , 108.5, 108.3, 84.8, 84.6, 55.3, 37.5.

IR(ATR) 3054, 2996, 2924, 2852, 1717, 1506, 1289, 1248, 1176, 1073, 1030, 967,834, 757, 692.

3.13. 1-(3,4,5-Trimethoxyphenyl)but-3-en-1-ol (115)

10 mL saturated aq. NH_4Cl was added to a 50 mL two-necked flask charged with Zn (0.40 g 6.11 mmol). Then, 3,4,5-trimethoxybenzaldehyde (1.00 g, 5.01 mmol) was dissolved in 2 mL THF and allyl bromide (0.74 g, 6.11 mmol). This mixture was added to the flask dropwise and the resulting reaction mixture was stirred at 35 °C for one day. The mixture was cooled to room temperature and quenched with 5 mL of 7% HCL and 2.5 mL of saturated aq. NH_4Cl. Reaction mixture was filtered via vacuum filtration. Work-up of the reaction mixture was performed by using ethyl acetate (3 x 20 mL). Extracts were combined together and washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Further purification was performed by column chromatography on silica gel with solvent system of 10:1 Hexane-Ethyl acetate and product was obtained as yellow liquid (0.91 g, 76%).

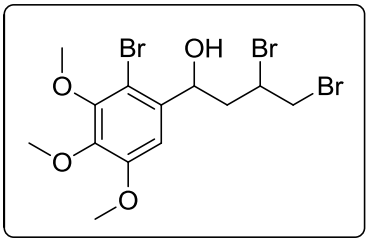


^{1}H NMR (400 MHz, Chloroform-d) δ 6.58 (s, 2H, -CH), 5.82 (dddd, J_{34b} = 17.1 Hz, J_{34a} = 10.2 Hz, J_{32a} = 7.4 Hz, J_{32b} = 6.8 Hz, 1H, H-3, -CH), 5.23 – 5.10 (m, 2H, H-4, –CH_2), 4.66 (dd, J_{12b} = 7.7 Hz, J_{12a} = 5.2 Hz, H-1, 1H), 3.86 (s, 6H, -CH_3), 3.83 (s, 3H, -CH_3), 2.55 – 2.42 (m, 2H, H-2, -CH_2).

^{13}C NMR (100 MHz, Chloroform-d) δ 153.2, 139.7, 137.1, 134.5, 118.4, 102.7, 73.5, 60.8, 56.1, 43.9.

3.14. (2*E*)-4-Bromo-1-(2-bromo-3,4,5-trimethoxyphenyl)but-2-en-1-ol (116)

To a solution of 1-(3,4,5-trimethoxyphenyl)but-3-en-1-ol (0.90 g, 3.78 mmol) in 5 mL CCl_4, Br_2 (0.60 g, 3.78 mmol) in 2 mL CCl_4 was added dropwise at 0 ^{o}C. After the addition, the mixture was stirred at room temperature for 10 minutes. The solvent was evaporated under reduced pressure and product was obtained as yellow viscous oil (1.66 g, 92%).

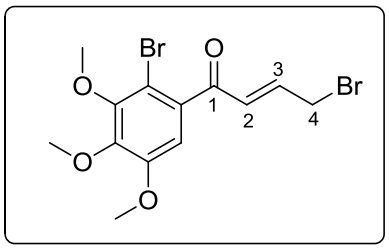


^{1}H NMR (400 MHz, Chloroform-d): diastereomer mixtures

3.15. (2*E*)-4-bromo-1-(2-bromo-3,4,5-trimethoxyphenyl)but-2-en-1-one (117)

CrO_3 (1.18 g, 11.83 mmol) was dissolved in 2.5 mL water and 1.5 mL concentrated H_2SO_4. This mixture was added dropwise to (2E)-4-bromo-1-(2-bromo-3,4,5-trimethoxyphenyl)but-2-en-1-ol (1.66 g, 3.48 mmol) in 10 mL acetone. The reaction mixture was stirred at 20-25 ^{o}C for 6 hours. Acetone was evaporated and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced

pressure. Further purification was achived by column chromatography on silica gel with hexane. Obtained product was white crystals in the form of small needles (1.01 g, 61%).



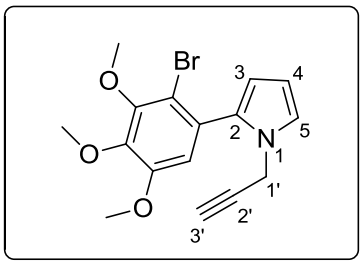
^{1}H NMR (400 MHz, Chloroform-d) δ 6.81 (dt, J_{32} = 15.6 Hz, J_{34} = 7.2 Hz, 1H, H-3, -CH), 6.75 (s, 1H, -CH), 6.68 (dt, J_{23} = 15.6 Hz, J_{24} = 1.1 Hz, 1H, H-2, -CH), 4.09 (dd, J_{43} = 7.2 Hz, J_{42} =1.1 Hz, 2H), 3.93 (s, 3H, -CH_3), 3.91 (s, 3H, -CH_3), 3.87 (s, 3H, -CH_3).

^{13}C NMR (101 MHz, Chloroform-d) δ 193.2, 153.0, 151.1, 145.1, 142.6, 135.8, 131.8, 108.2, 106.7, 61.2, 61.2, 56.3, 29.5.

IR (ATR) 2939, 2834, 1672, 1617, 1580, 1559, 1479, 1427, 1388, 1345, 1281, 1251, 1197, 1164, 1104, 998, 917, 833, 739

3.16. 2-(2-bromo-3,4,5-trimethoxyphenyl)-1-prop-2-ynyl-1*H*-pyrrole (118)

After bromo ketone (1.01 g, 2.13 mmol) was dissolved in 10 mL diethyl eter, propargyl amine (0.35 g, 6.37 mmol) was added and the mixture refluxed for 2 hours. Then, triethyl amine (0.43 g, 4.26 mmol) was added and the resulting mixture refluxed for one day. The mixture was cooled to room temperature diluted with water and extracted with ethyl acetate (3x25mL). The combined extracts washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Further purification was performed by column chromatography on silica gel with hexane and product was obtained as dark red liquid (0.10 g, 14%).



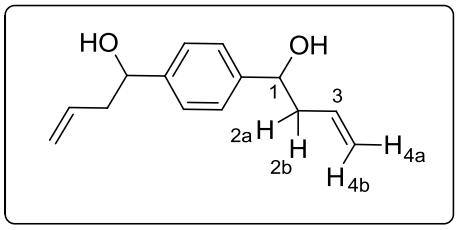
^{1}H NMR (400 MHz, Chloroform-d) δ 6.96 (dd, J_{34} = 2.8 Hz, J_{35} =1.8 Hz, 1H, H-5, -CH), 6.79 (s, 1H, -CH), 6.28 (t, J_{45} = 3.4 Hz, 1H, H-4, -CH), 6.16 (dd, J_{54} = 3.4 Hz, J_{53} = 1.8 Hz, 1H, H-3, -CH), 4.49 (d, $J_{1'3'}$ = 2.7 Hz, 2H, -CH_2), 3.94 (s, 3H, -CH_3), 3.93 (s, 3H, -CH_3), 3.84 (s, 3H, -CH_3), 2.34 (t, $J_{3'1'}$ = 2.7 Hz, 1H).

^{13}C NMR (100 MHz, Chloroform-d) δ 152.4, 151.0, 143.2, 132.2, 129.2, 120.7, 112.1, 111.9, 109.6, 108.3, 78.7, 73.2, 61.2, 61.0, 56.2, 36.7.

IR(ATR) 3288, 3105, 3001, 2937, 2842, 1706, 1561, 1481, 1382, 1336, 1241, 1103, 1004, 928, 750

3.17. 1,4-Benzenedimethanol, α^1,α^4-di-2-propen-1-yl- (120)

15 mL saturated aq. NH_4Cl and 2 mL THF was added to a 100 mL two-necked flask charged with Zn (3.22 g, 49.25 mmol). Then, terephthalaldehyde (3.00 g, 22.40 mmol) was added portion wise to the mixture while allyl bromide (5.96 g, 49.25 mmol) was added drop wise by using a dropping funnel. The resulting reaction mixture was stirred at 35 °C for 8 hours. The mixture was cooled to room temperature and quenched with 10 mL of 7% HCl and 5 mL of saturated aqueous NH_4Cl. Reaction mixture was filtered via vacuum filtration. Work-up of the reaction mixture was performed by using ethyl acetate (3 x 25 mL). Extracts were combined together and washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Further purification was performed by column chromatography on silica gel with solvent system of 3:1 Hexane-Ethyl acetate and product was obtained as white needle crystals (1.81 g, 37%).



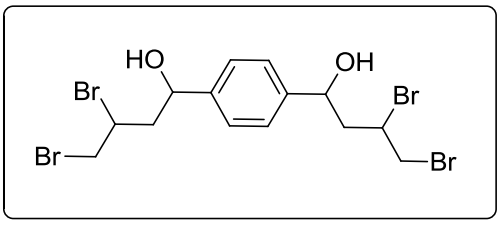
^{1}H NMR (400 MHz, Chloroform-d) δ 7.35 (s, 4H, -CH), 5.82 (ddt, J_{34b} = 17.1 Hz, J_{34a} = 10.2 Hz, J_{32} = 7.3 Hz, 2H, H-3, -CH), 5.24 – 5.11 (m, 4H, H-4, -CH_2), 4.74 (dd, J_{12a} = 7.5 Hz, J_{12b} = 5.4 Hz, 2H, H-1 -CH), 2.60 – 2.43 (m, 4H, -CH_2), 2.18 (s, 1H, -OH).

^{13}C NMR (100 MHz, Chloroform-d) δ 143.2, 134.4, 125.9, 118.4, 73.1, 43.8

3.18. 1,1'-(1,4-phenylene)bis(3,4-dibromobutan-1-ol) (121)

To a solution of 1,4-Benzenedimethanol, α^1,α^4-di-2-propen-1-yl- (1.17 g, 5.36 mmol) in 10 mL CH_2Cl_2, Br_2 (1.71 g, 10.7 mmol) in 4 mL CH_2Cl_2 was added dropwise at 0 °C. After the addition, the mixture was stirred at room temperature for

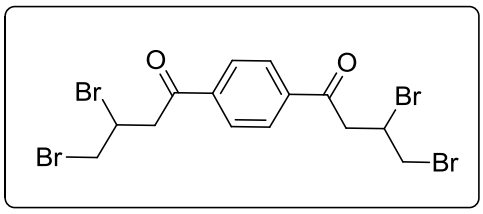
1 hour. The solvent was evaporated under reduced pressure and product was obtained as orange viscous oil (2.9 g, 100%).



^{1}H NMR (400 MHz, Chloroform-d): diastereomer mixtures

3.19. 1,1'-(1,4-phenylene)bis(3,4-dibromobutan-1-one) (122)

CrO_3 (3.57 g, 35.7 mmol) was dissolved in 5 mL water and 3 mL concentrated H_2SO_4. This mixture was added drop wise to 1,1'-(1,4-phenylene)bis(3,4-dibromobutan-1-ol) (2.82 g, 5.25 mmol) in 15 mL acetone. The reaction mixture was stirred at 20-25 °C for 4 hours. Acetone was evaporated and the mixture was extracted with ethyl acetate (3 x 30 mL). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Further purification was achieved by column chromatography on silica gel with hexane. Product was obtained as green viscous oil (2.45 g, 87%).



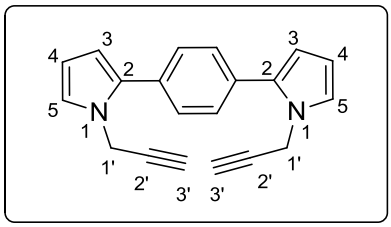
^{1}H NMR (400 MHz, Chloroform-d) δ 8.00 (s, 4H, -CH), 4.70 (tt, *J* = 8.4, 4.0 Hz, 2H, -CH), 3.95 (dd, *J* = 10.5, 4.1 Hz, 2H, -CH), 3.83 (dd, J = 17.9, 4.0 Hz, 2H, -CH), 3.75 (dd, *J* = 10.3, 9.6 Hz, 2H, -CH), 3.60 (dd, *J* = 17.9, 8.6 Hz, 2H, -CH).

^{13}C NMR (100 MHz, Chloroform-d) δ 199.3, 142.9, 129.1, 49.9, 48.5, 37.6

3.20. 1,4-bis(1-(prop-2-yn-1-yl)-1H-pyrrol-2-yl)benzene (123)

After 1,1'-(1,4-phenylene)bis(3,4-dibromobutan-1-one) (1.00 g, 1.87 mmol) was dissolved in 15 ml dichloromethane, propargyl amine (0.52 g, 9.40 mmol) was added and the mixture refluxed for 2 hours. Then, triethyl amine (0.76 g, 7.50 mmol) was added and the resulting mixture refluxed for another 5 hours. The mixture was cooled to room temperature diluted with water and extracted with ethyl

acetate (3 x 30). The combined extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Further purification was performed by column chromatography on silica gel with solvent system of 4:1 Hexane-Ethyl acetate and product was obtained as yellow needle crystals (0.34 g, 62%).



^{1}H NMR (400 MHz, Chloroform-d) δ 7.42 (s, 4H, -CH), 6.91 – 6.86 (m, 2H, H-5, -CH), 6.22 – 6.20 (m, 2H, H-4, -CH), 6.19 (dd, J_{34} = 3.4 Hz, J_{35} =1.8 Hz, 1H, H-3, -CH), 4.63 (d, $J_{1'3'}$ = 2.6 Hz, 4H, H-1', -CH_2), 2.35 (t, $J_{3'1'}$ = 2.6 Hz, 2H, H-3', -CH).

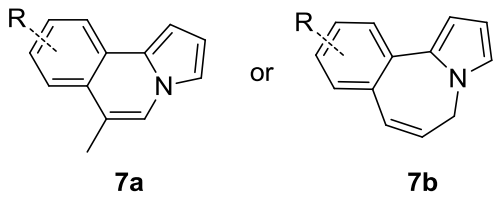
^{13}C NMR (100 MHz, Chloroform-d) δ 134.0, 131.4, 128.8, 122.5, 109.3, 109.1, 79.1, 73.4, 36.8.

IR (ATR) 3278, 2962, 2935, 1700, 1561, 1497, 1497, 1467, 1434, 1422, 1347, 1304, 1261, 1242, 1109, 1058, 1018, 933, 852, 745.

CHAPTER 4

CONCLUSION

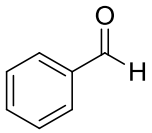
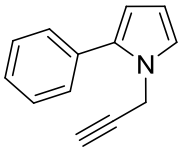
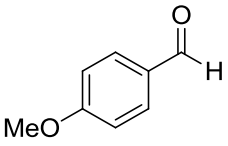
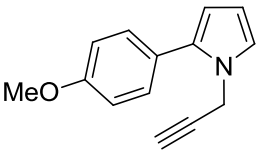
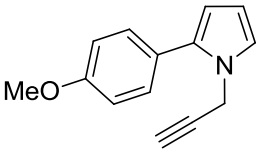
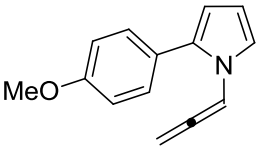
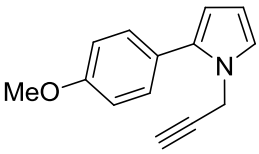
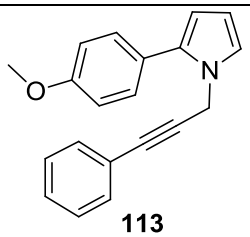
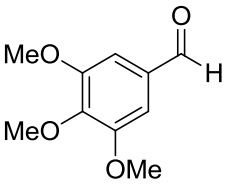
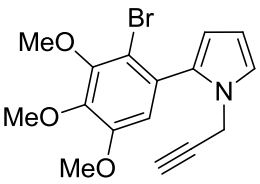
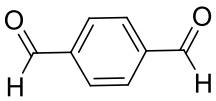
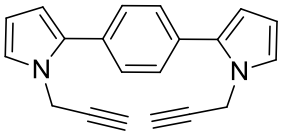
Pyrrole and pyrrole derivatives are not only prevalent in a wide variety of biologically and pharmaceutically significant compounds, but also used as building blocks in organic synthesis.[25] Formation of heterocyclic compounds of pyrrole derivatives by intramolecular electrophilic cyclization are very distinguished processes in the field of synthetic methodology. In this study, we aimed to develop a new methodology for the synthesis of pyrrole fused tricyclic heterocycles.



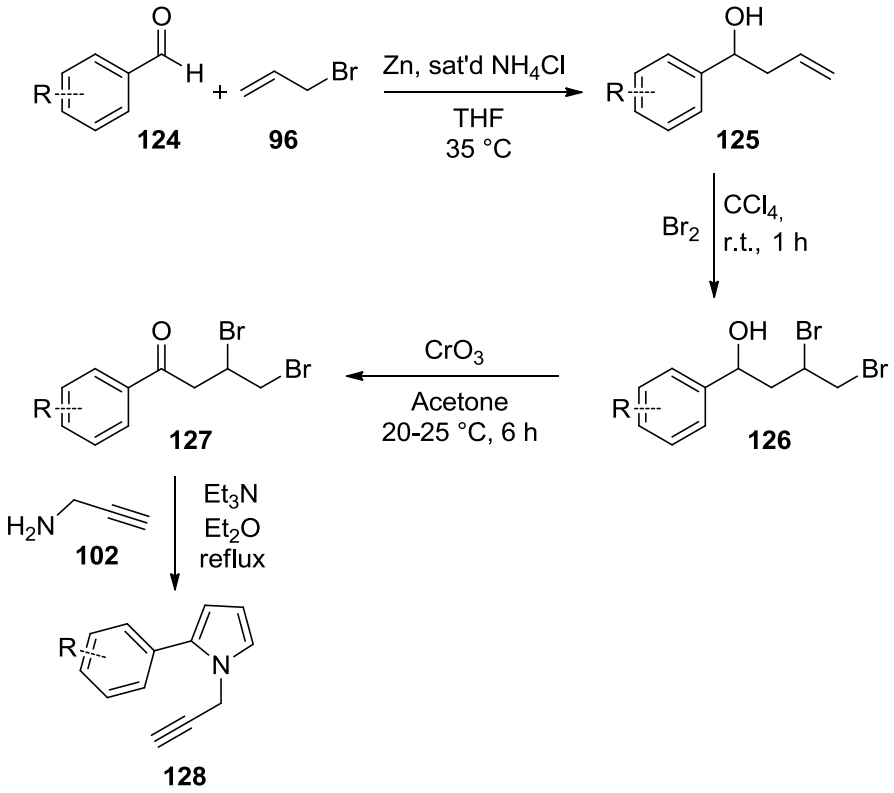
Scheme 53. Targeted molecules

Our strategy was to construct the targeted molecules shown in Scheme 53 by electrophilic cyclization of alkyne tethered pyrrole derivatives. In this manner, *N*-alkynyl 2-phenyl substituted pyrrole derivatives, shown in Table 6, were synthesized starting from benzaldehyde derivatives.

Table 6: Synthesized key compounds and their starting materials

Starting material	Key compounds
 **30**	 **103**
 **106**	 **110**
 **110**	 **111**
 **110**	 **113**
 **114**	 **118**
 **119**	 **123**

General synthesis route for the key compounds is given in Scheme 54. Barbier type allylation was used to construct allylic alcohol derivatives **125**. Dibromo ketone derivatives **127** were synthesized by subsequent bromination and oxidation of **125**. Finally, key compounds **128** were obtained by the pyrrolization of **127** when treated with propargyl amine in the presence of Et_3N.



Scheme 54. General synthesis route for the key compounds

Once the key pyrrole compounds were synthesized, several electrophilic cyclization reactions were carried out. Gold catalyst such as $AuCl_3$ and $AuBr_3$, $InCl_3$, $Cu(OTf)_2$, ICl, $TsOH.H_2O$ and I_2 were used for the ring closure of compound **103**. However**,** no cyclization reaction was observed in neither of the cases. Nevertheless, an iodo-substituted product **105** was obtained when iodine was used. For compound **110**, several reactions with gold catalysts were performed but no cyclization product was obtained. Although compound **111,** allene isomer of **110,** reacted with $AuCl_3$, isolation of any product could not be achieved from the reaction medium. Compound **113** was synthesized by Sonogashira coupling between **110** and

iodobenzene. $AuCl_3$, I_2, ICl, and $FeCl_3$ were reacted with **113** but no cyclization product was observed. Cyclization reactions of compound **118** and **123** with $AuCl_3$ were also unsuccessful.

In this study, synthesis of novel pyrrole derivatives was achieved and electrophilic cyclization reactions of these compounds were studied.

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APPENDIX A

SPECTRAL DATA

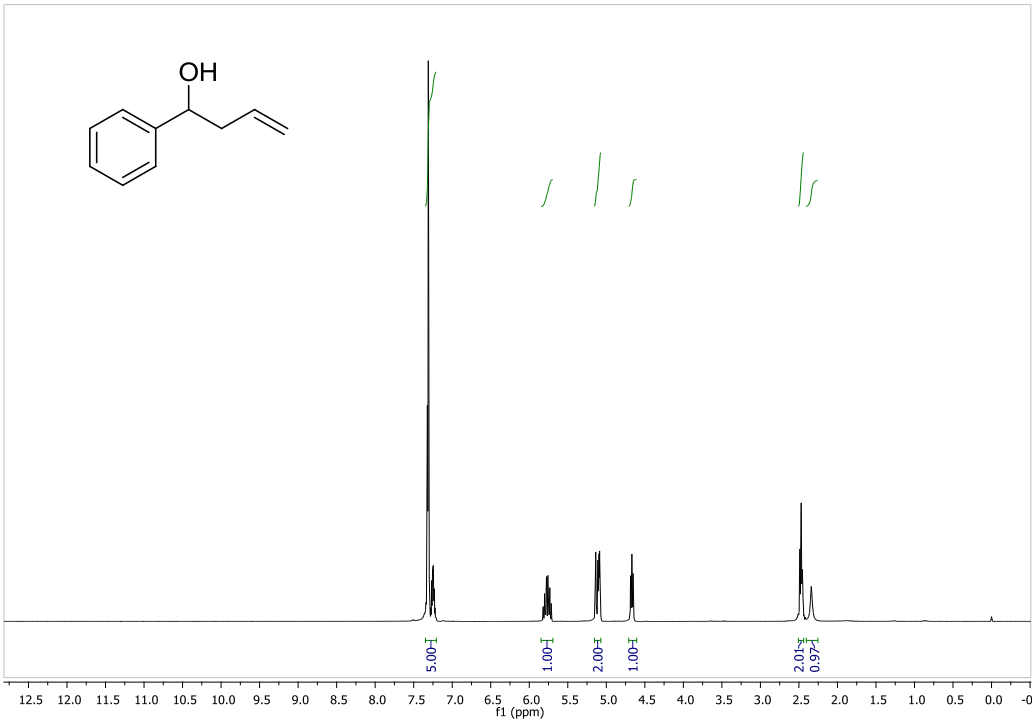

Figure 6. ^{1}H NMR Spectrum of compound **97**

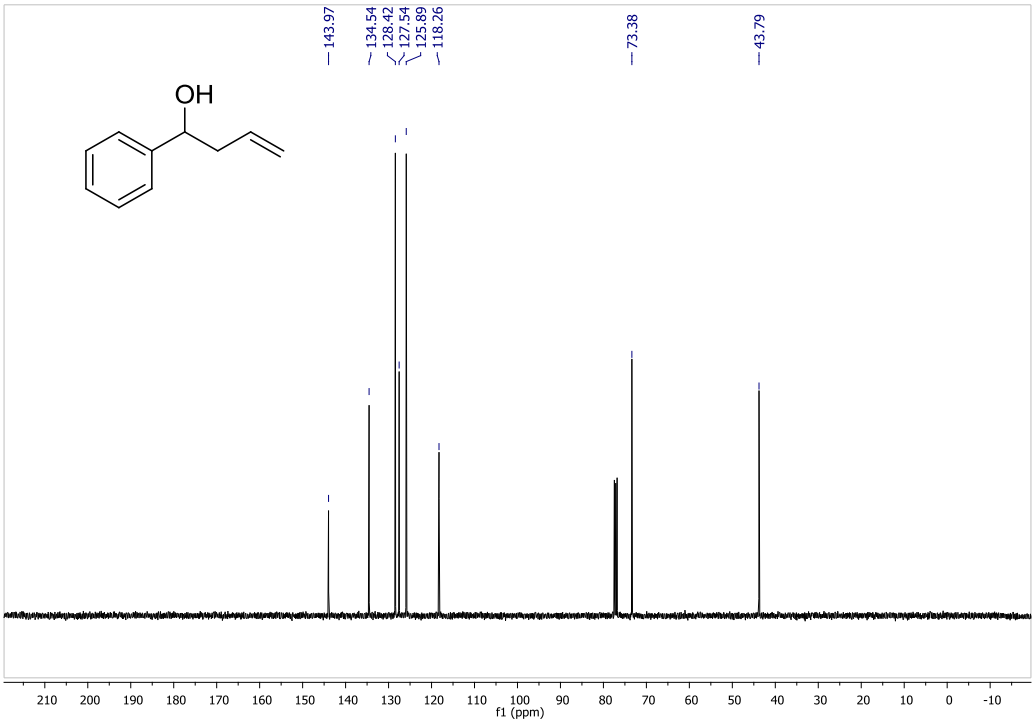

Figure 7. ^{13}C NMR Spectrum of compound **97**

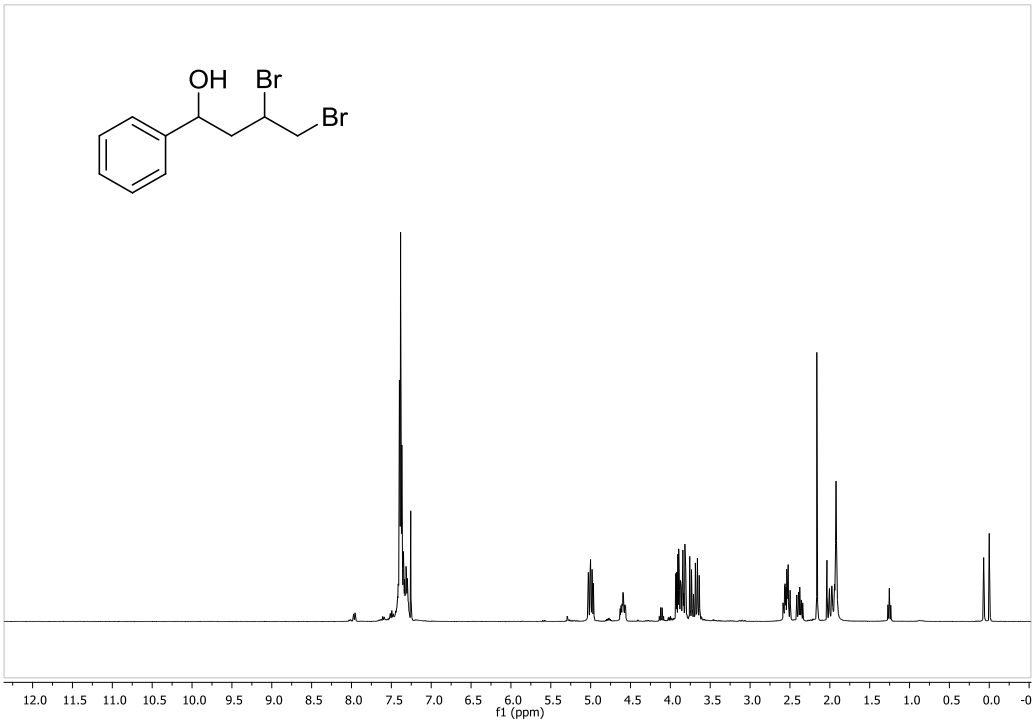

Figure 8. ^{1}H NMR Spectrum of compound **98**

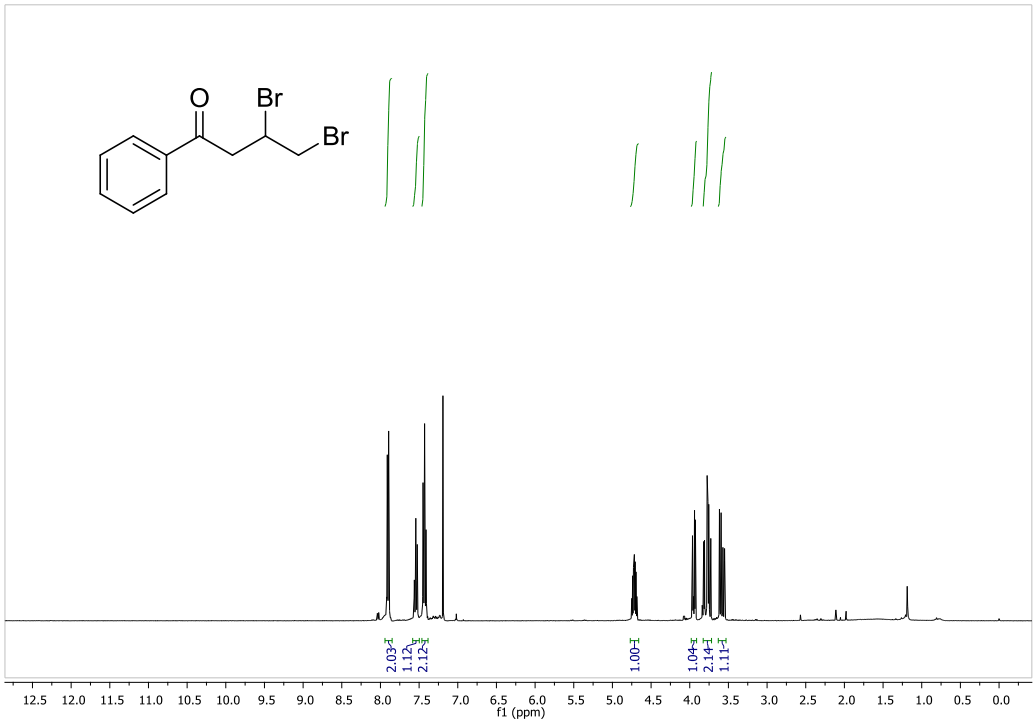

Figure 9. ^{1}H NMR Spectrum of compound **99**

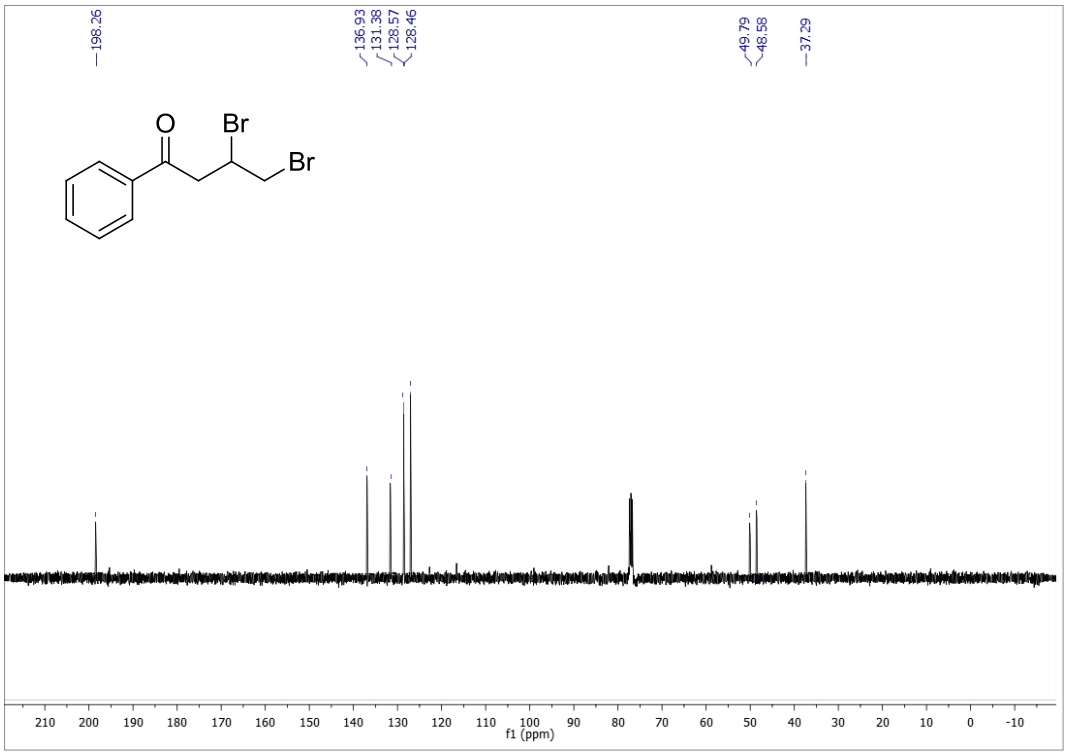

Figure 10. ^{13}C NMR Spectrum of compound **99**

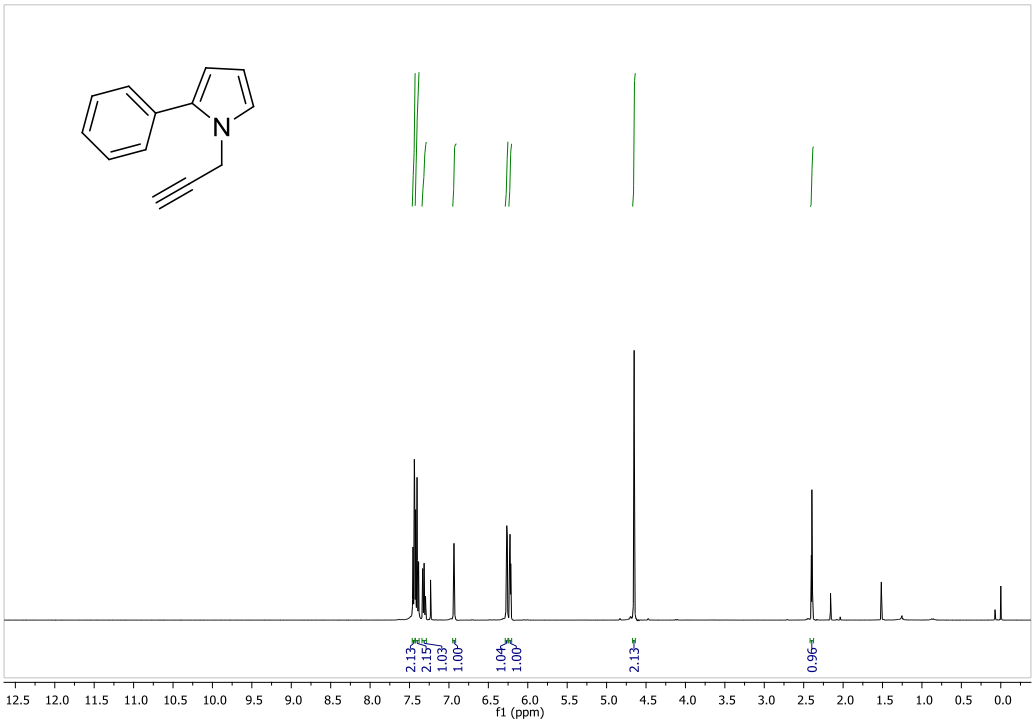

Figure 11. ^{1}H NMR Spectrum of compound **103**

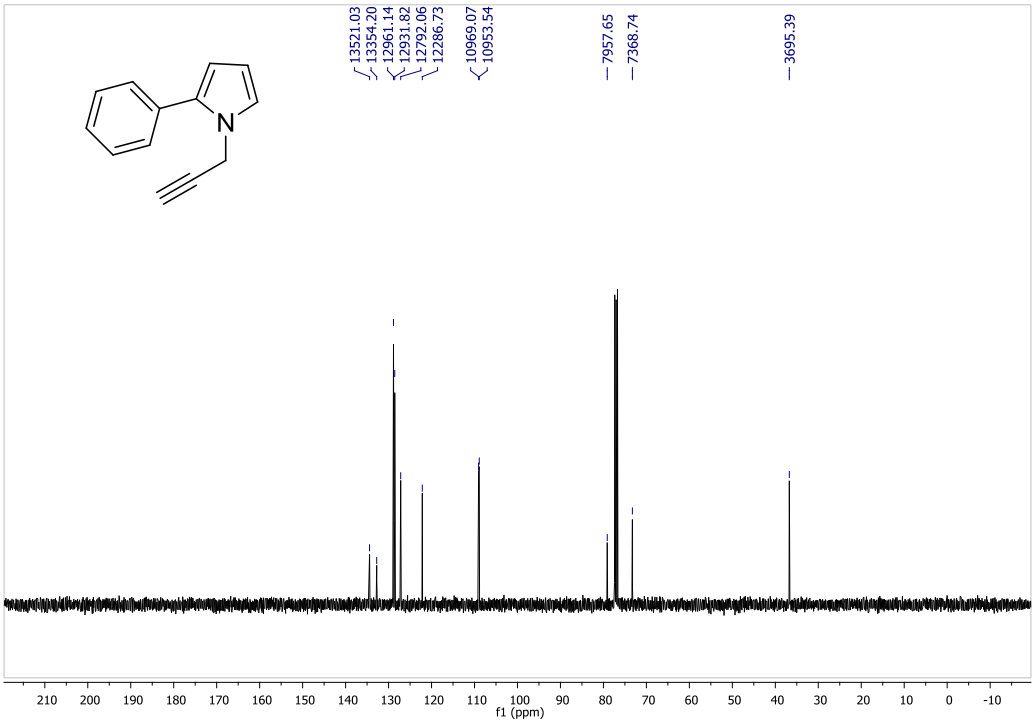

Figure 12. ^{13}C NMR Spectrum of compound **103**

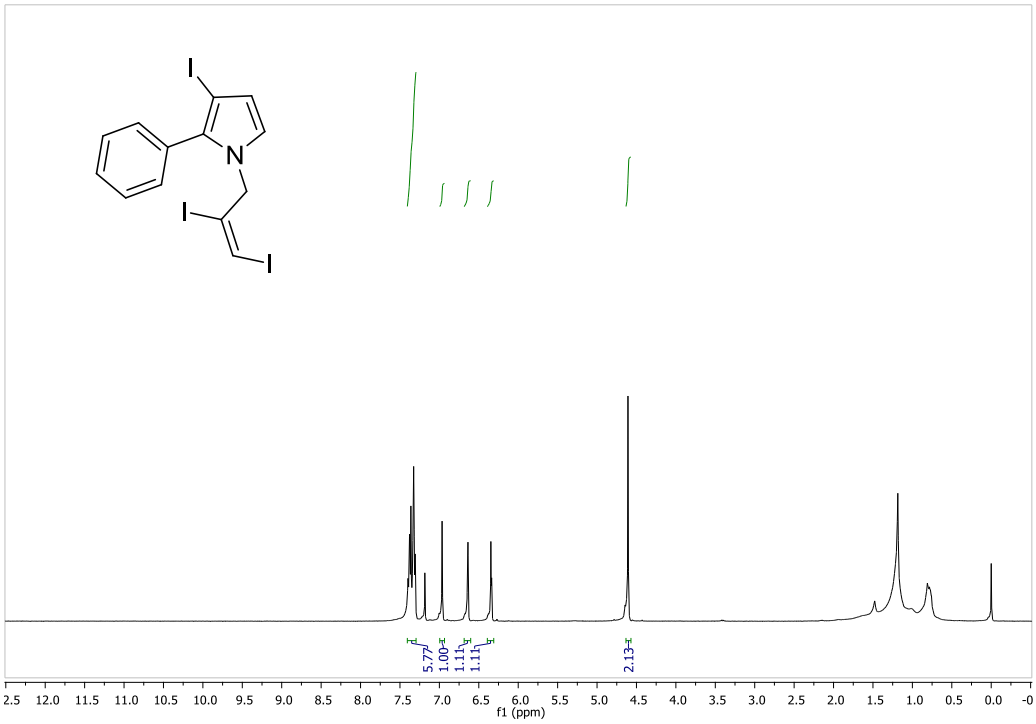

Figure 13. ^{1}H NMR Spectrum of compound **105**

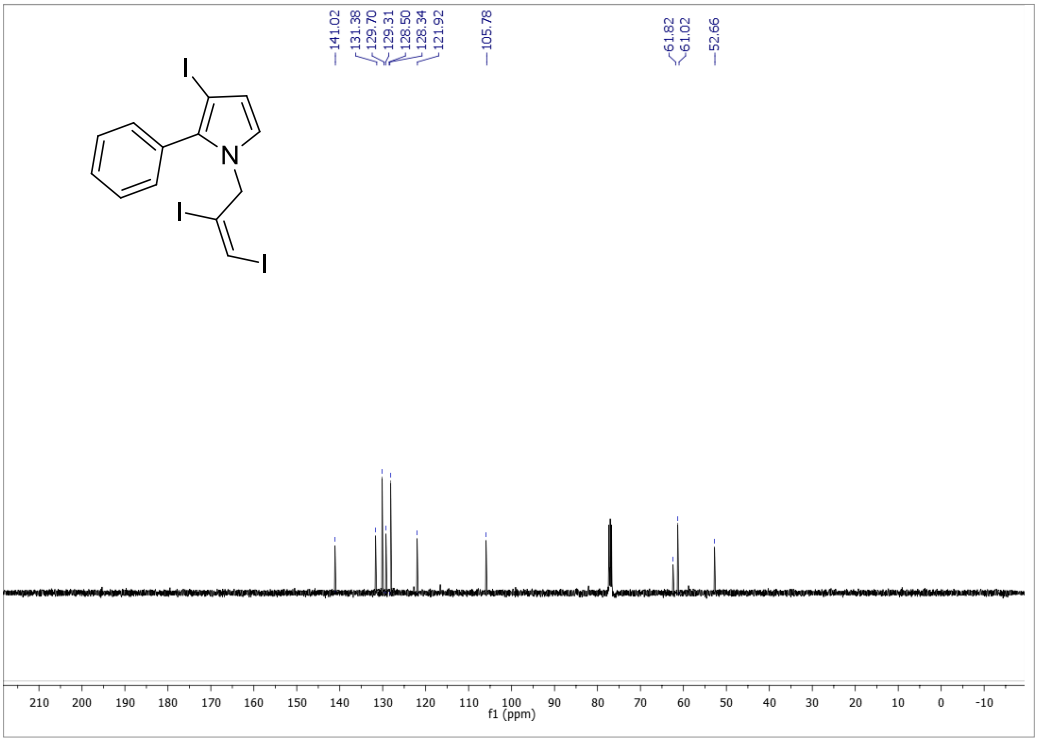

Figure 14. ^{13}C NMR Spectrum of compound **105**

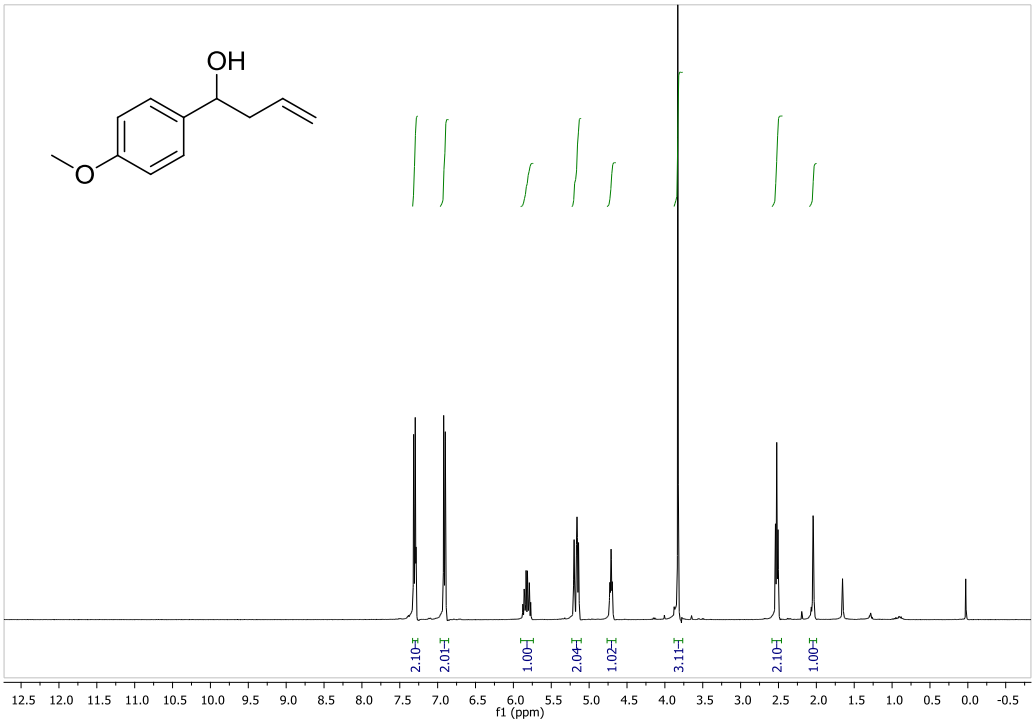

Figure 15. ^{1}H NMR Spectrum of compound **107**

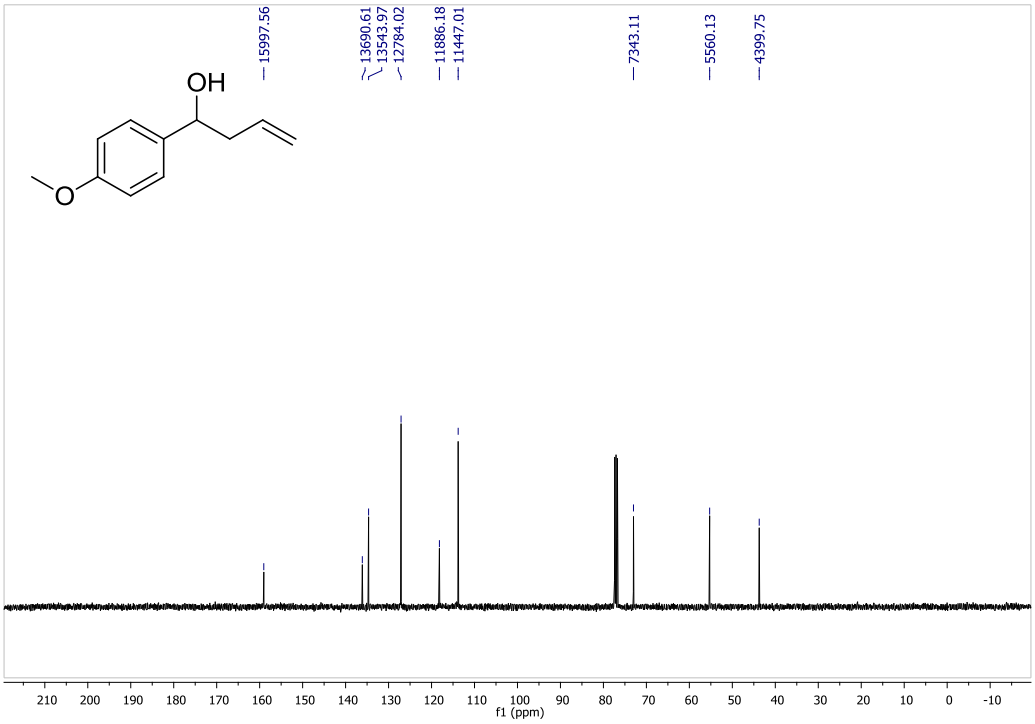

Figure 16. ^{13}C NMR Spectrum of compound **107**

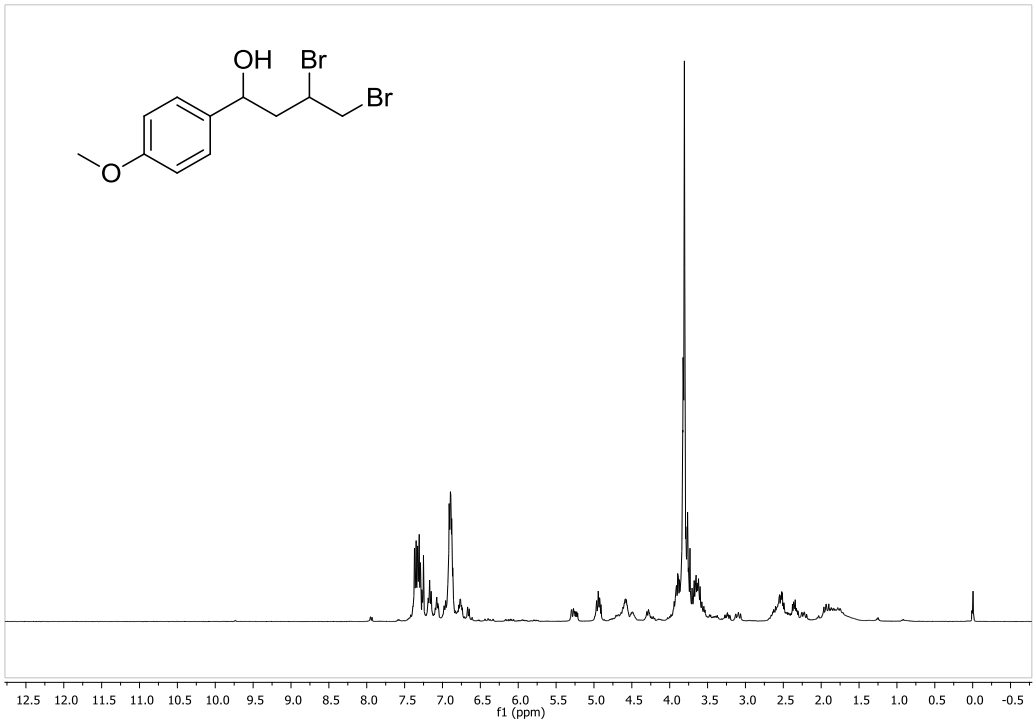

Figure 17. ^{1}H NMR Spectrum of compound **108**

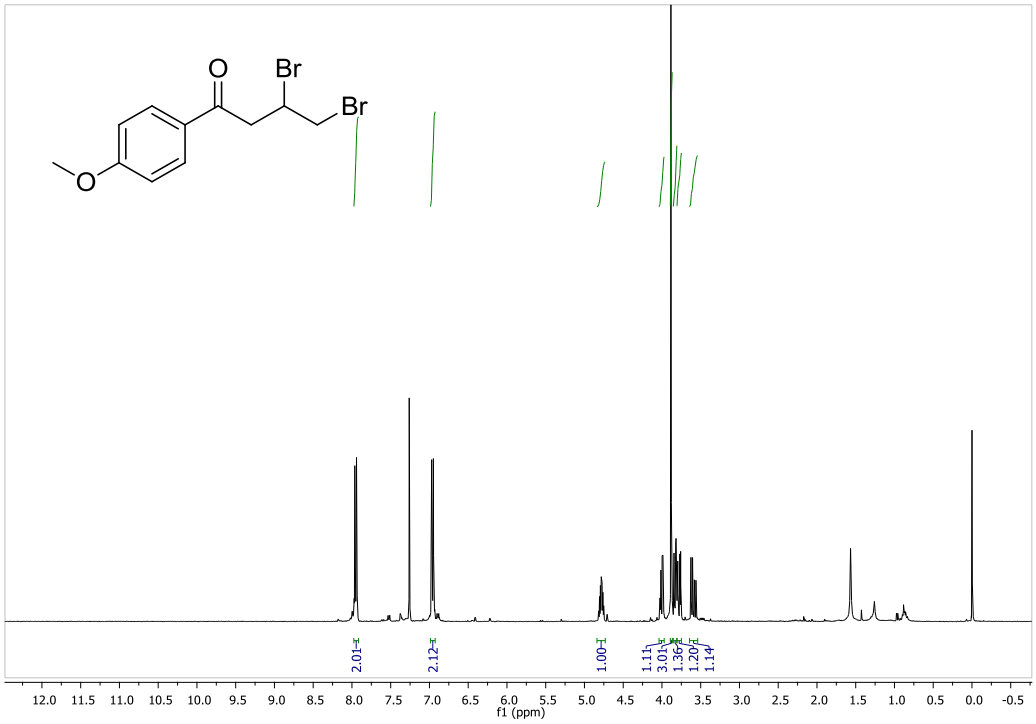

Figure 18. ^{1}H NMR Spectrum of compound **109**

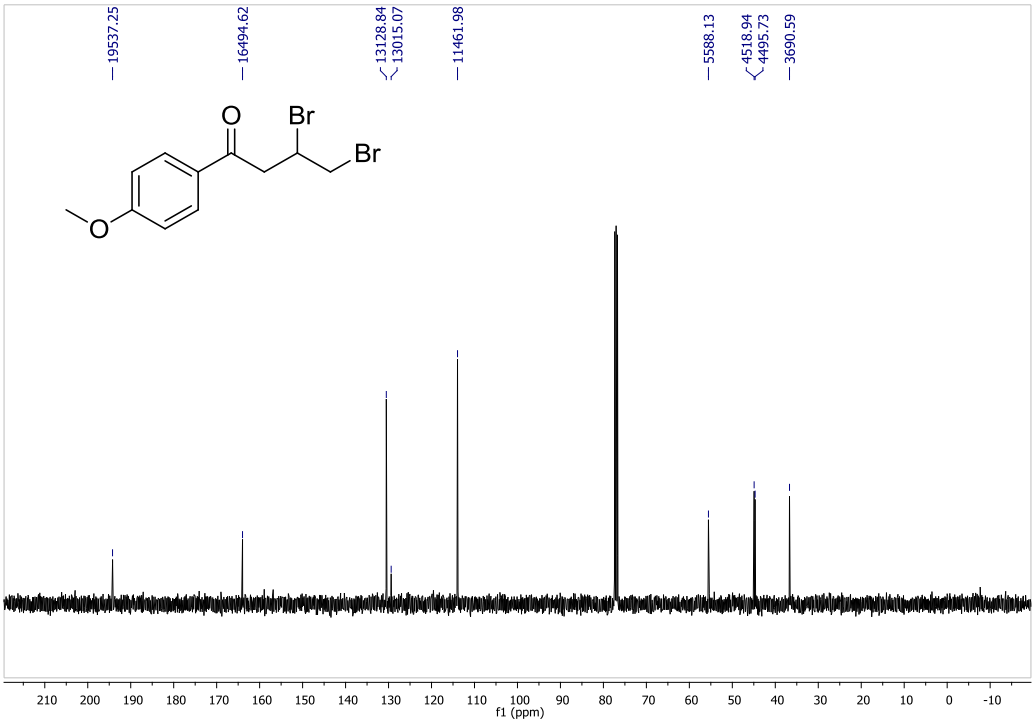

Figure 19. ^{13}C NMR Spectrum of compound **109**

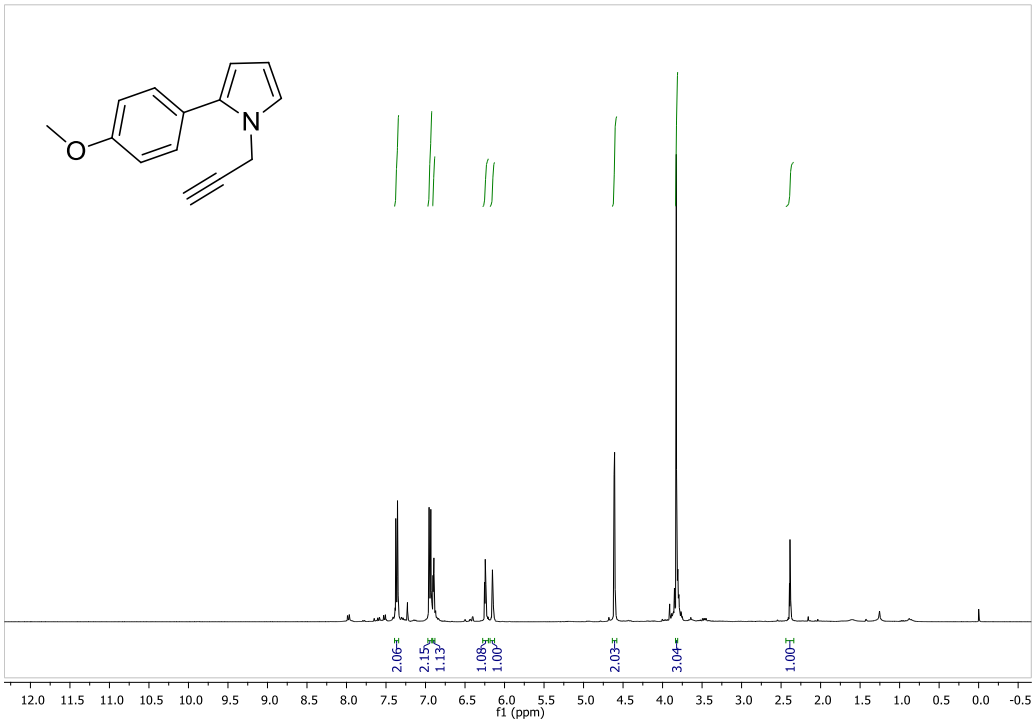

Figure 20. ^{1}H NMR Spectrum of compound **110**

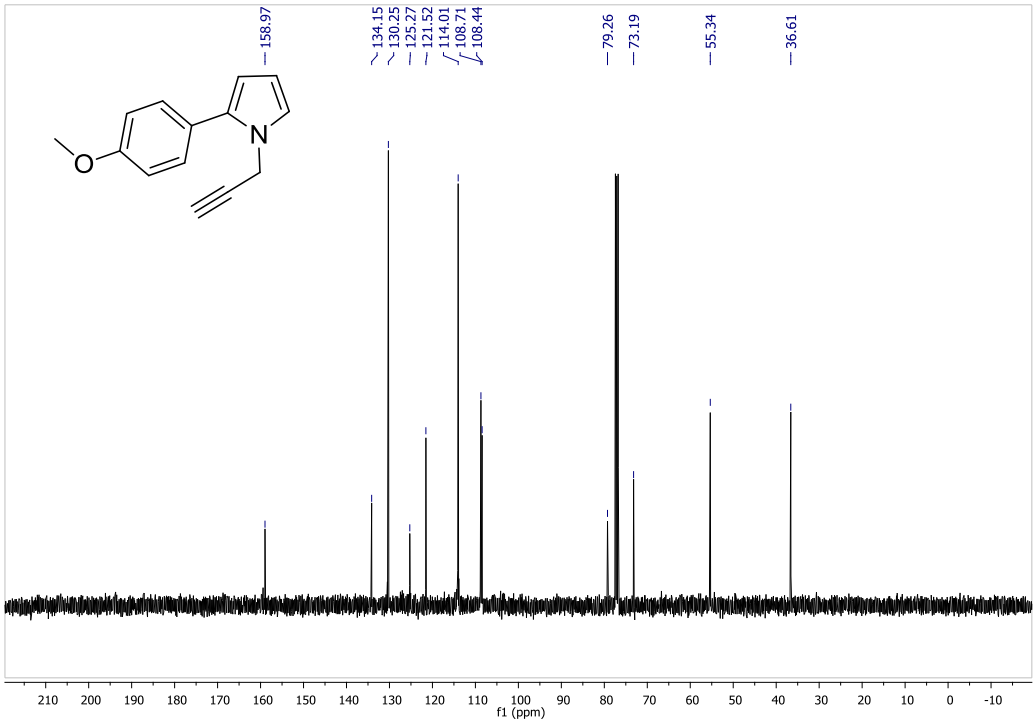

Figure 21. ^{13}C NMR Spectrum of compound **110**

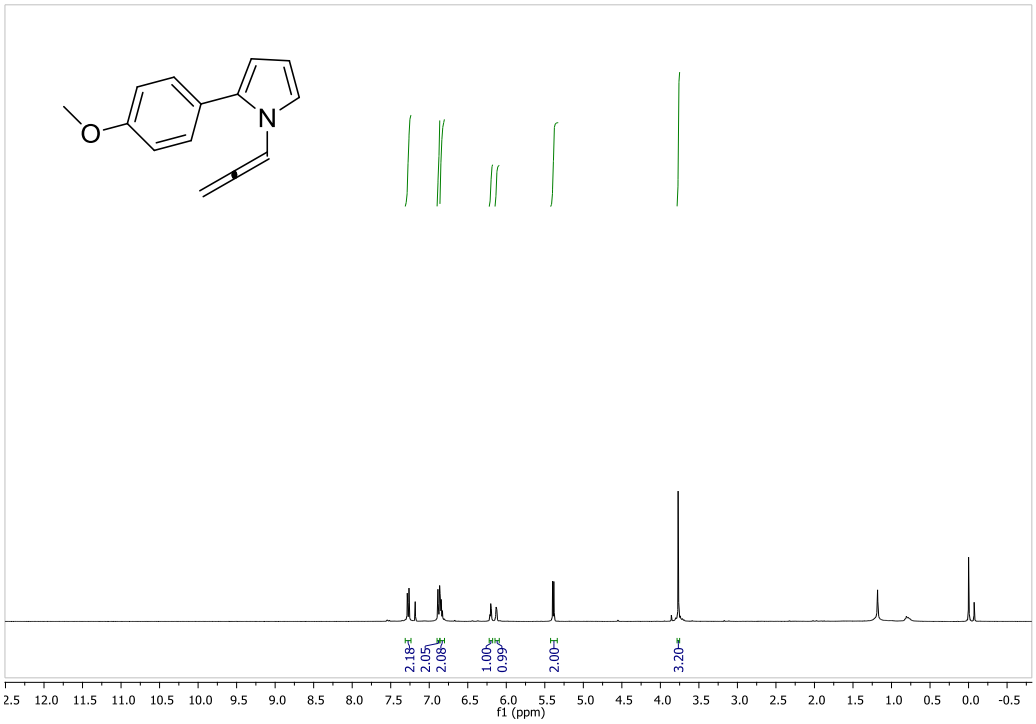

Figure 22. ^{1}H NMR Spectrum of compound **111**

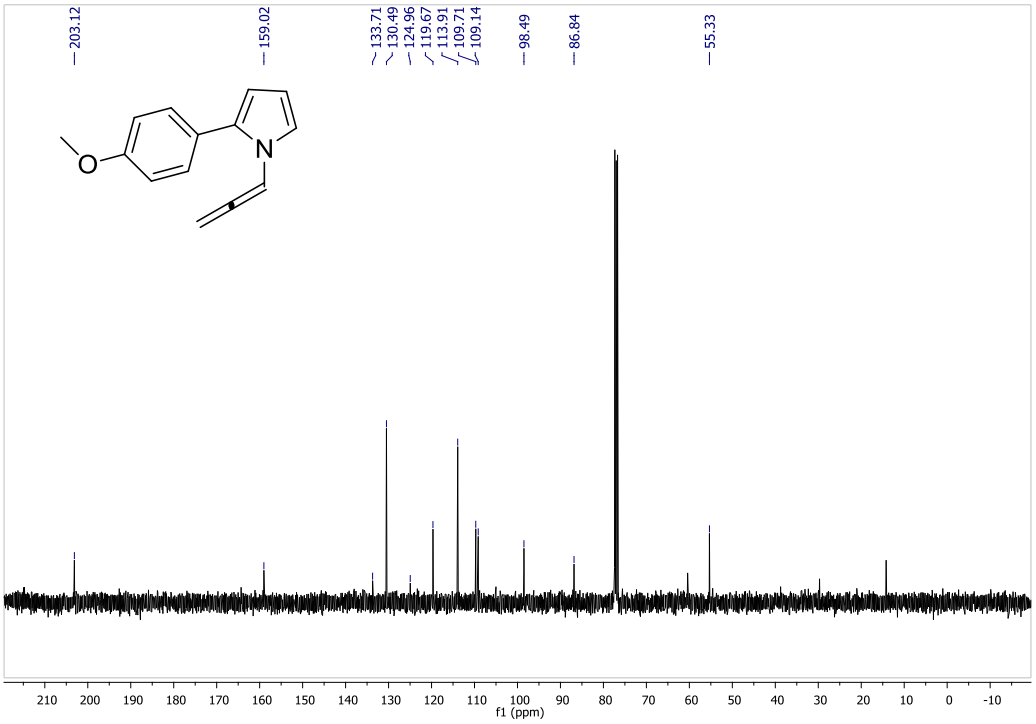

Figure 23. ^{13}C NMR Spectrum of compound **111**

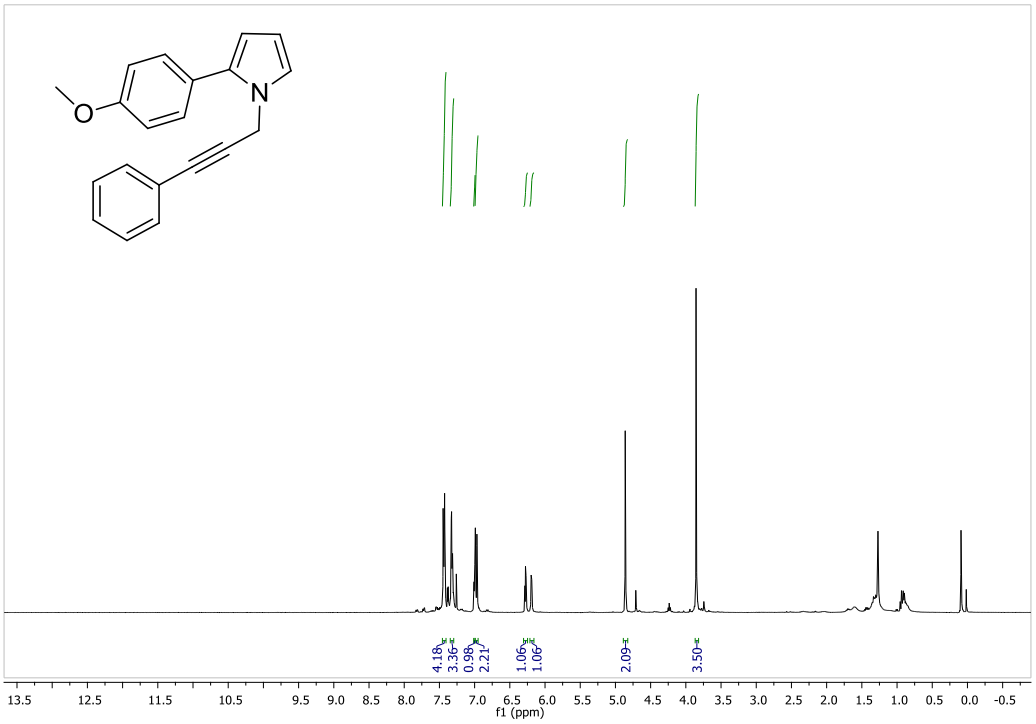

Figure 24. ^{1}H NMR Spectrum of compound **113**

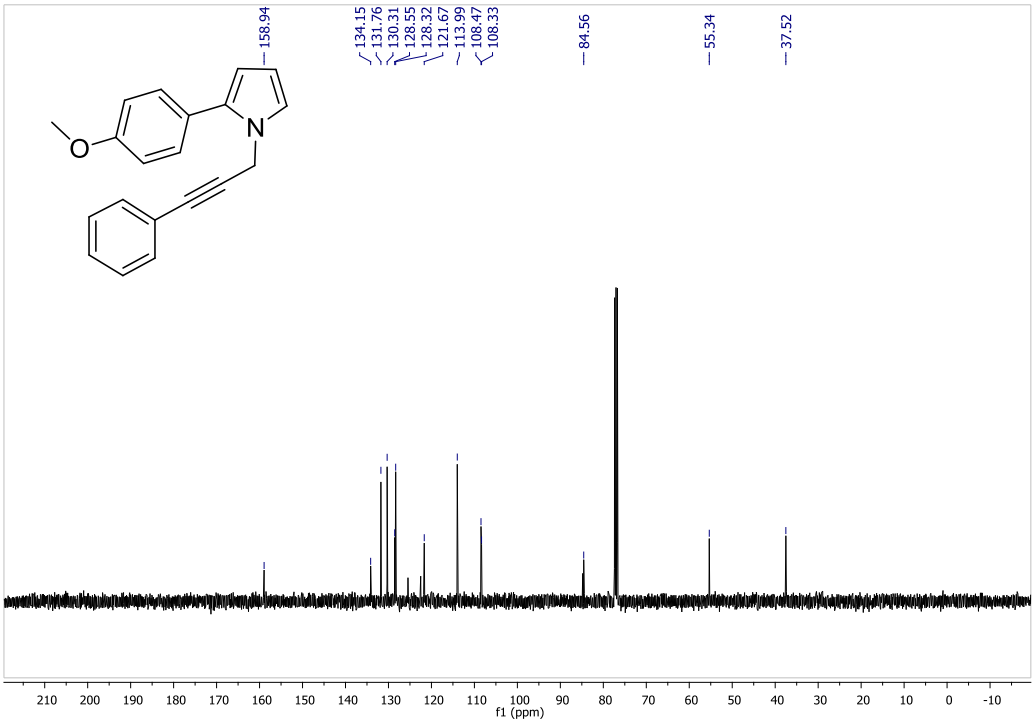

Figure 25. ^{13}C NMR Spectrum of compound **113**

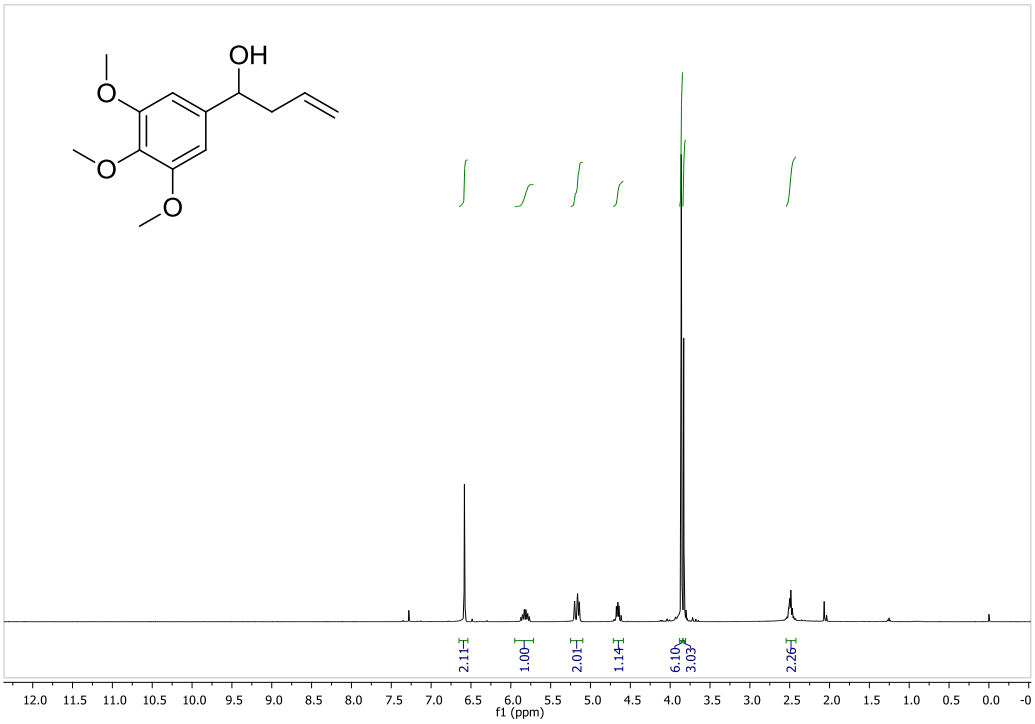

Figure 26. ^{1}H NMR Spectrum of compound **115**

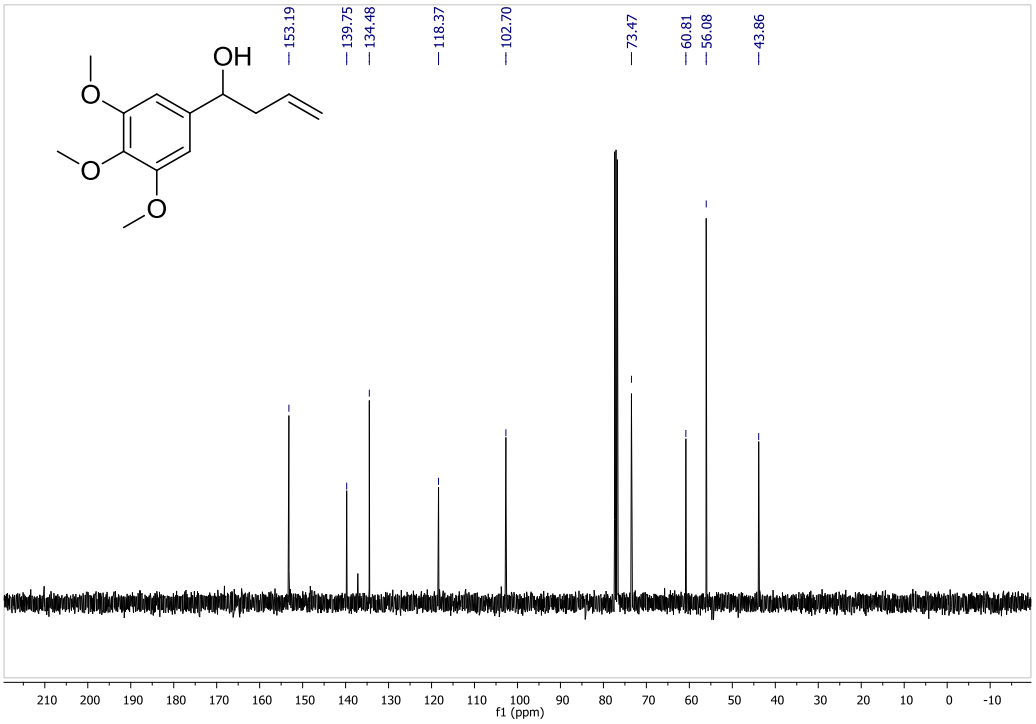

Figure 27. ^{13}C NMR Spectrum of compound **115**

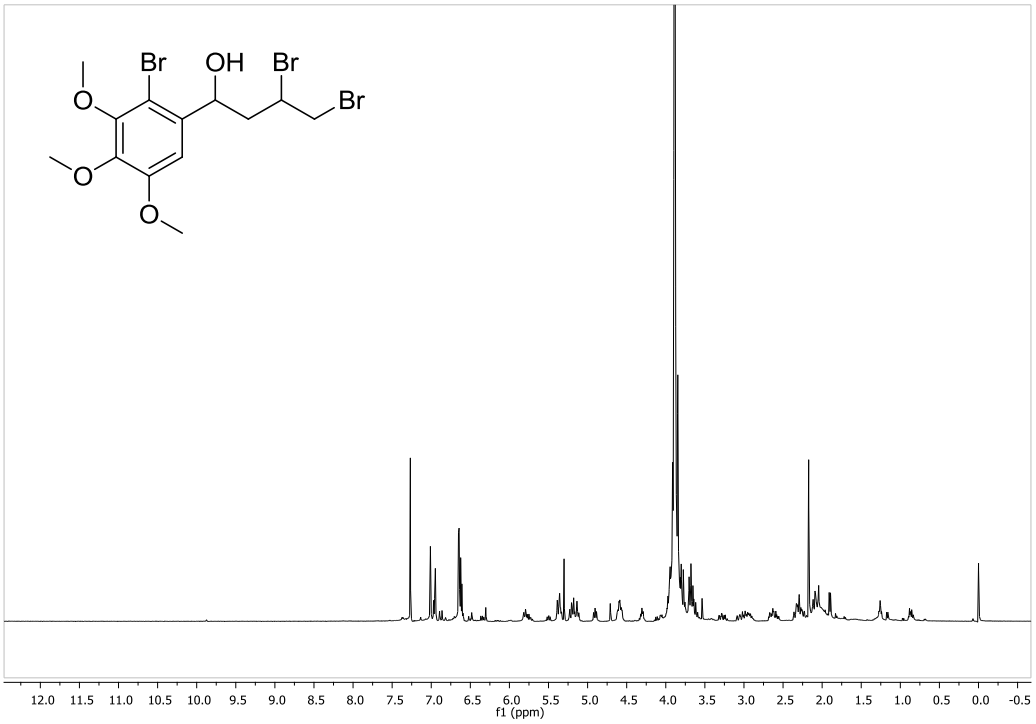

Figure 28. ^{1}H NMR Spectrum of compound **116**

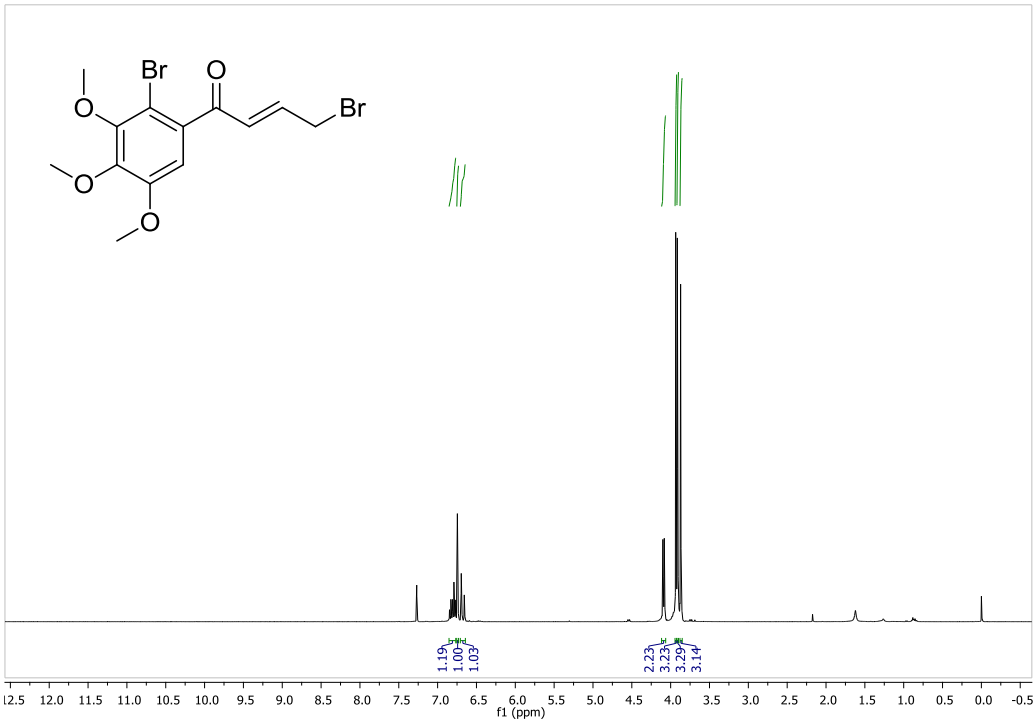

Figure 29. ^{1}H NMR Spectrum of compound **117**

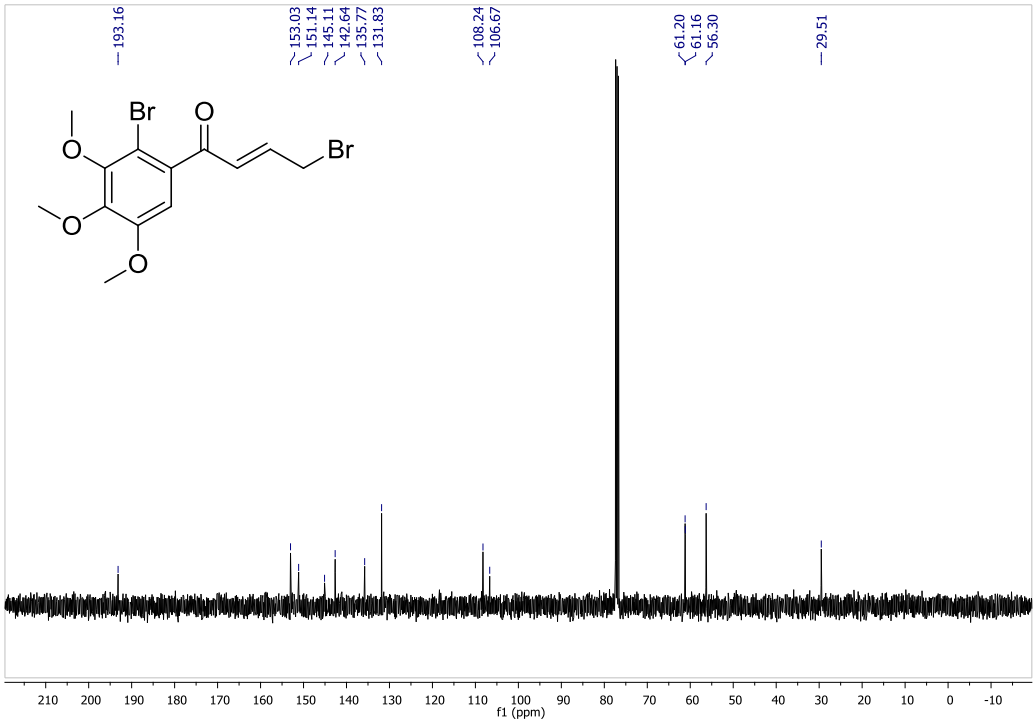

Figure 30. ^{13}C NMR Spectrum of compound **117**

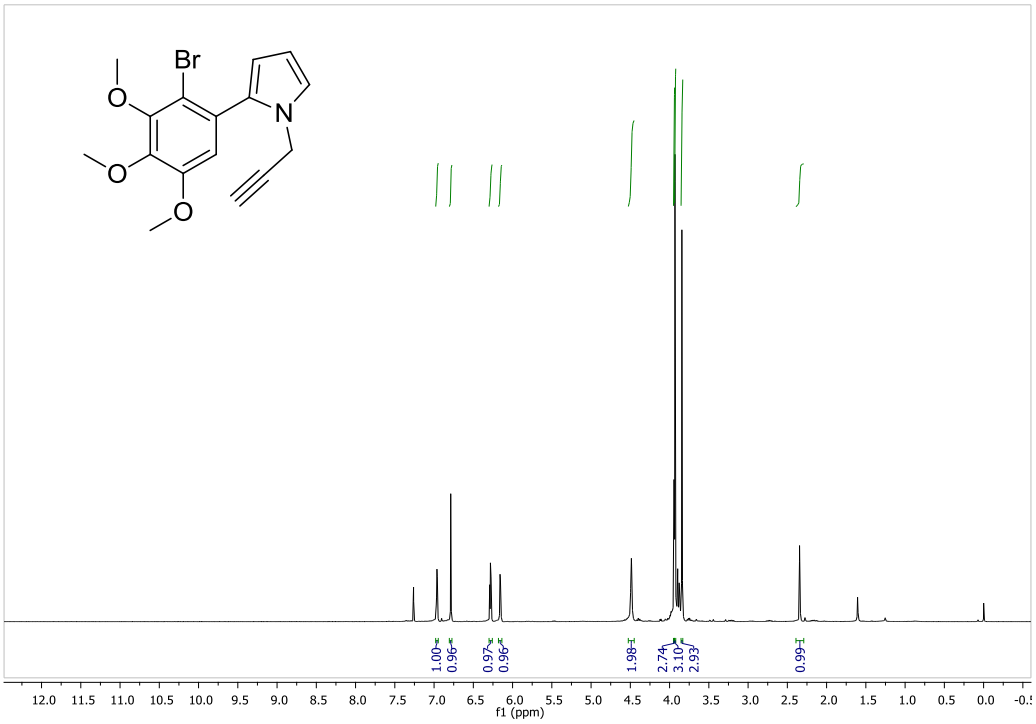

Figure 31. ^{1}H NMR Spectrum of compound **118**

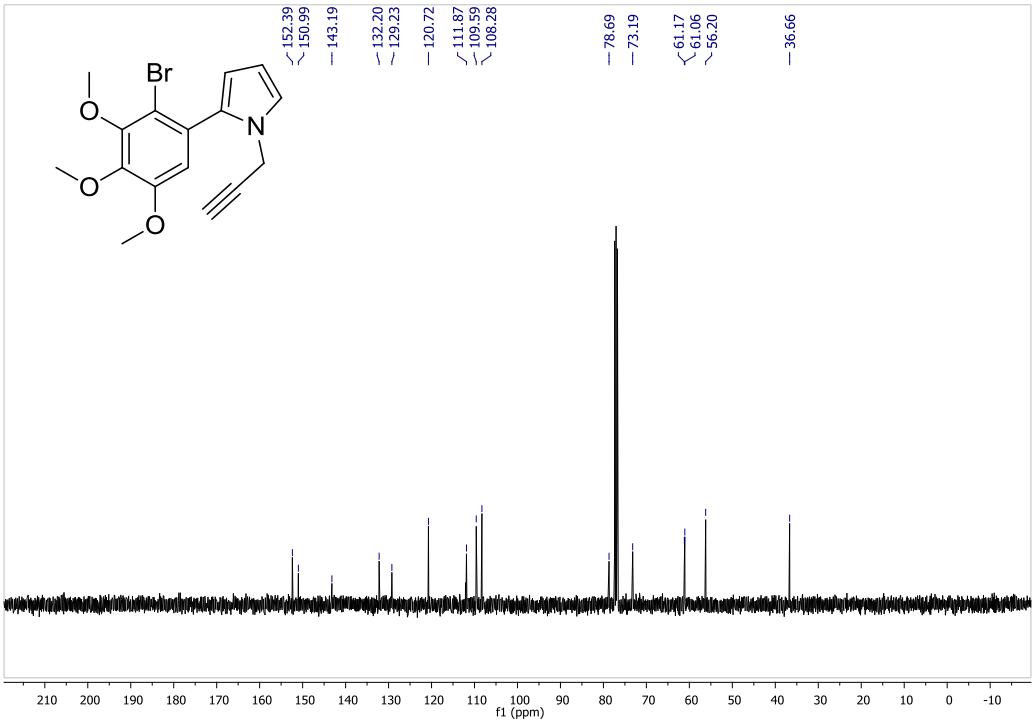

Figure 32. ^{13}C NMR Spectrum of compound **118**

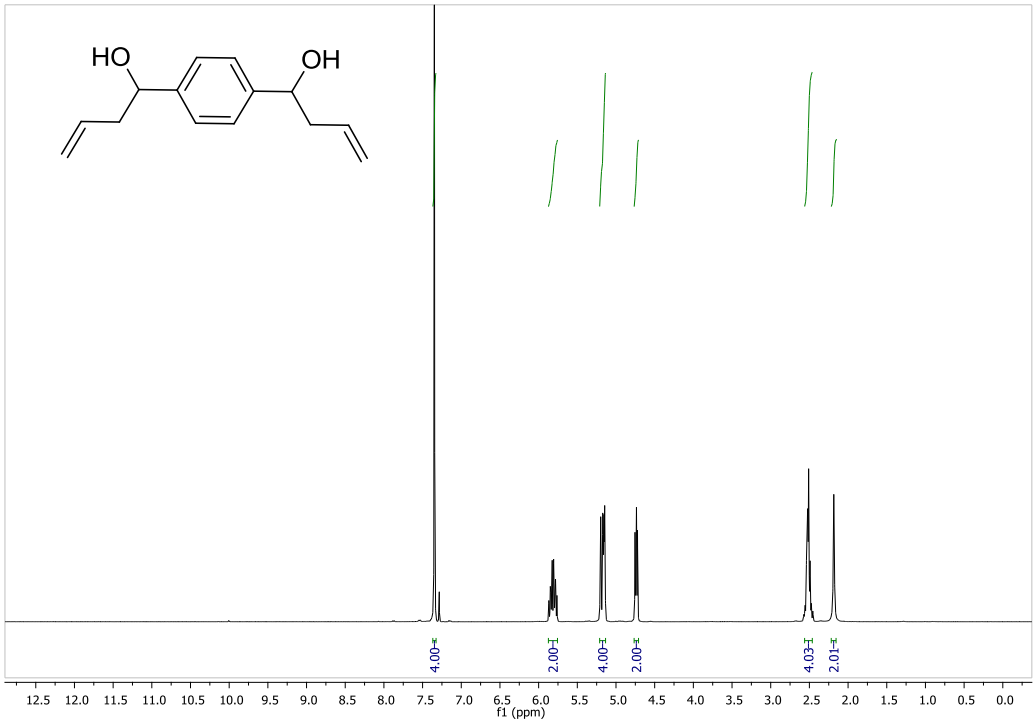

Figure 33. ^{1}H NMR Spectrum of compound **120**

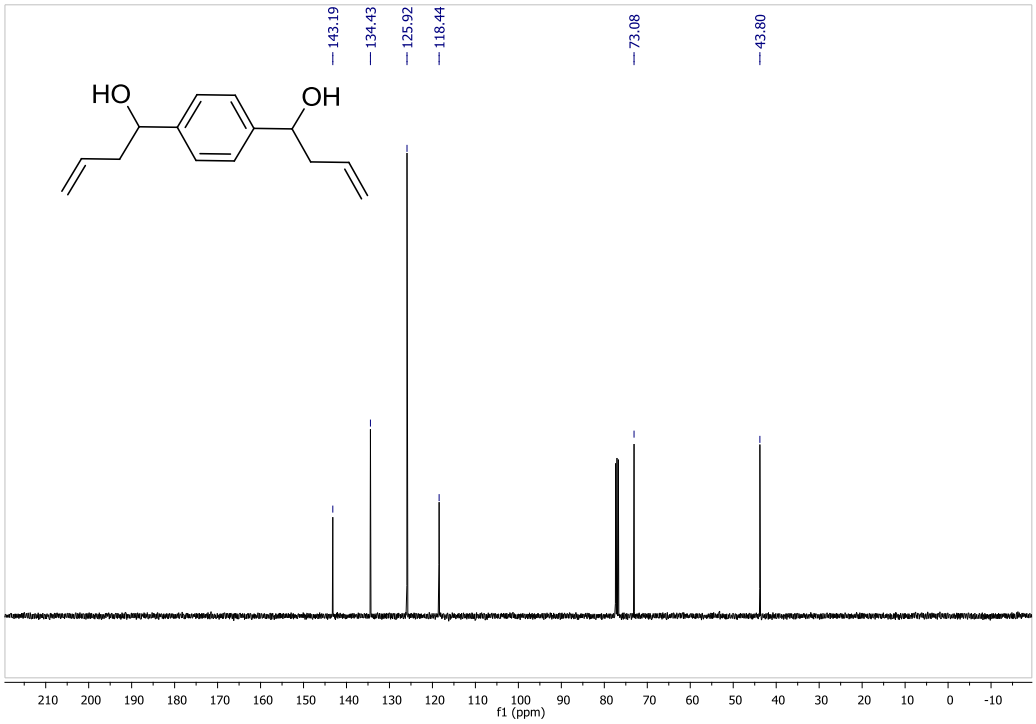

Figure 34. ^{13}C NMR Spectrum of compound **120**

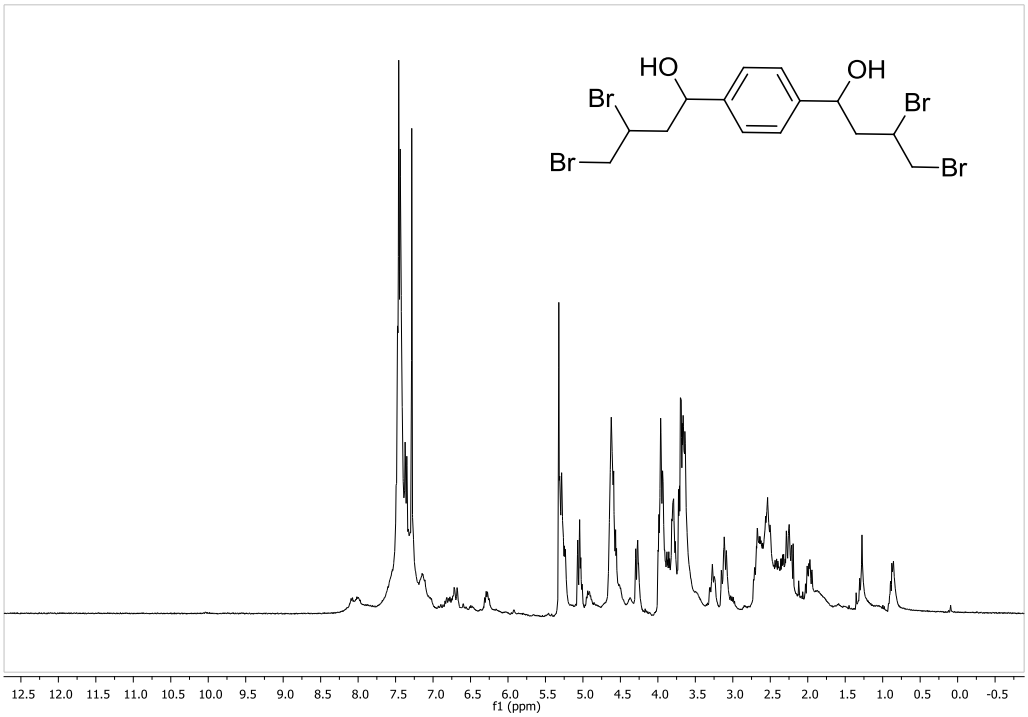

Figure 35. ^{1}H NMR Spectrum of compound **121**

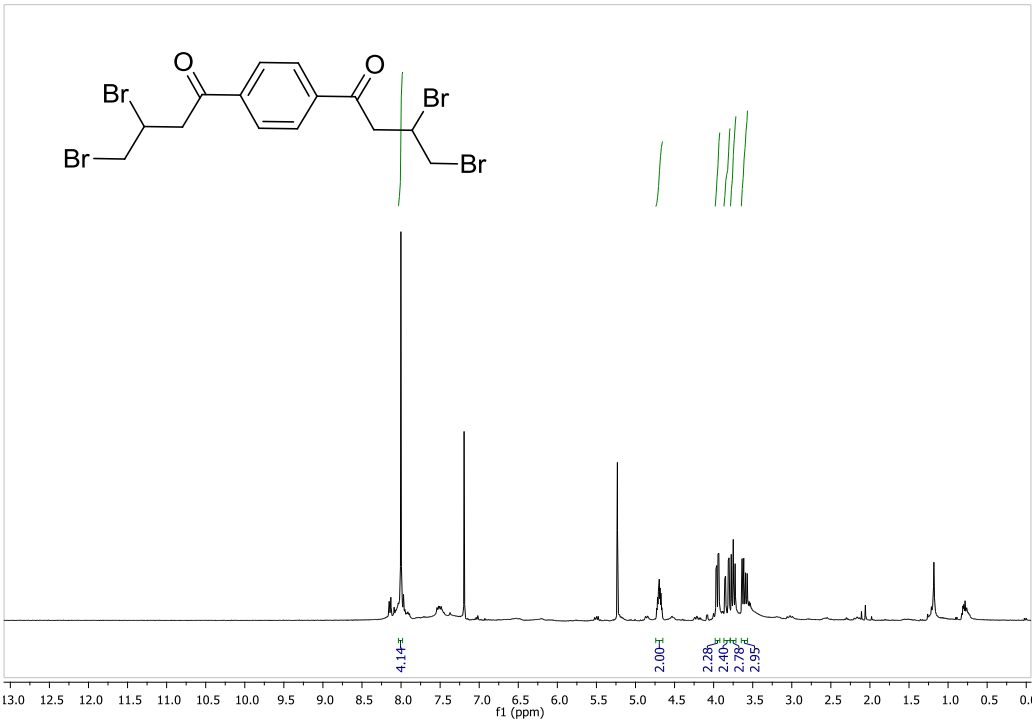

Figure 36. ^{1}H NMR Spectrum of compound **122**

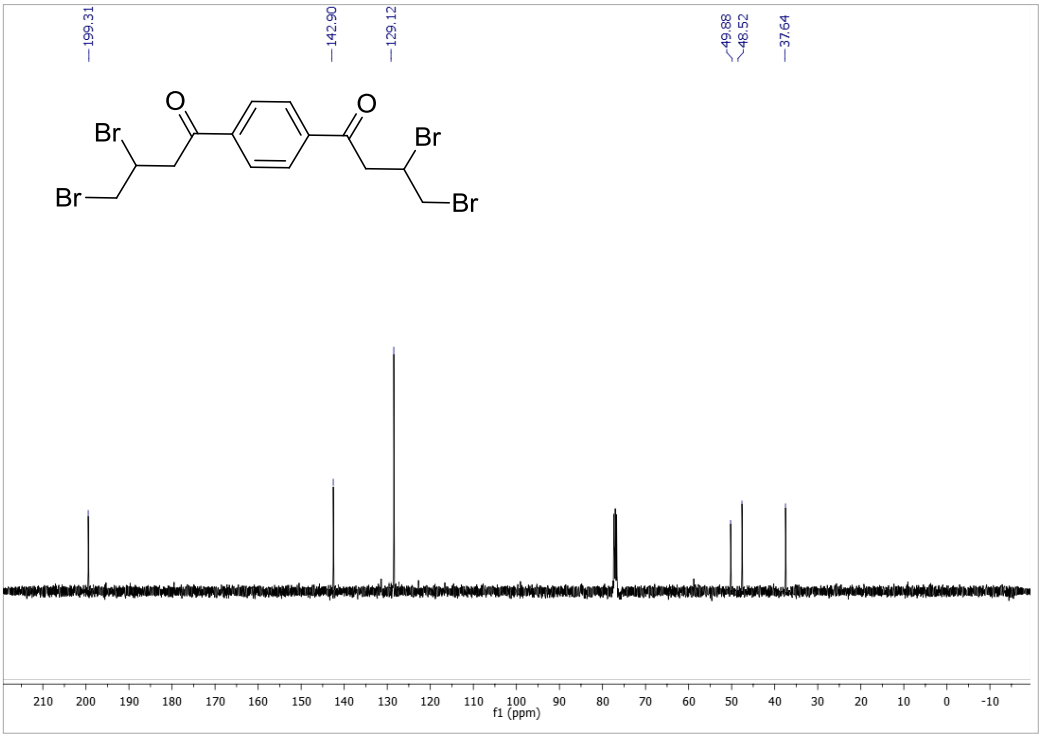

Figure 37. ^{13}C NMR Spectrum of compound **122**

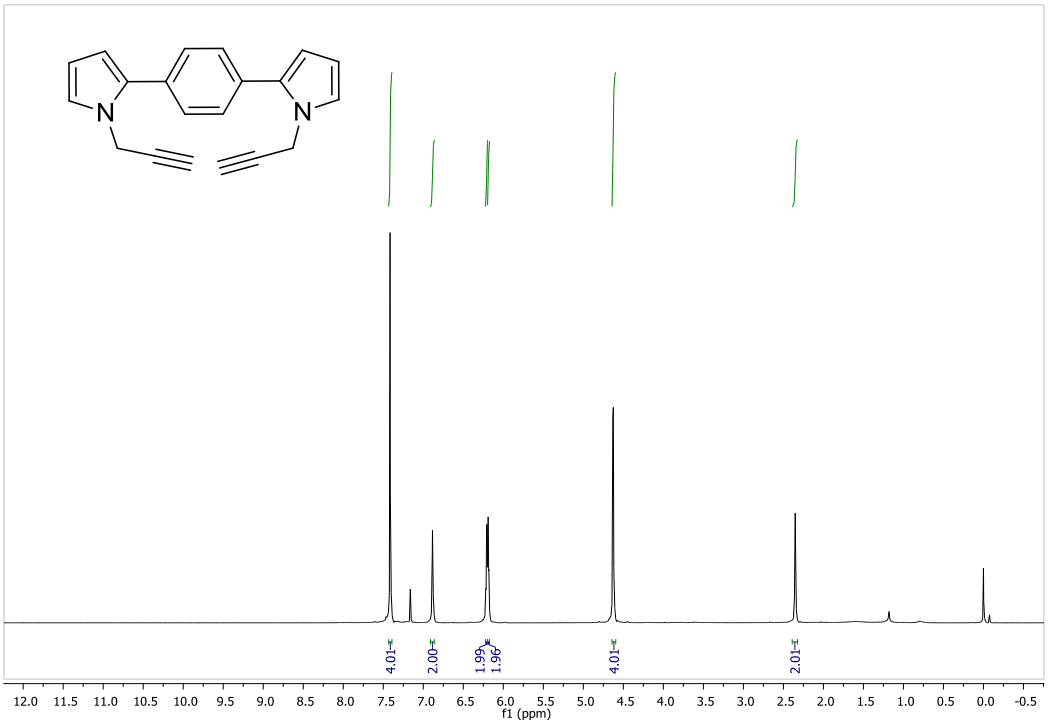

Figure 38. ^{1}H NMR Spectrum of compound **123**

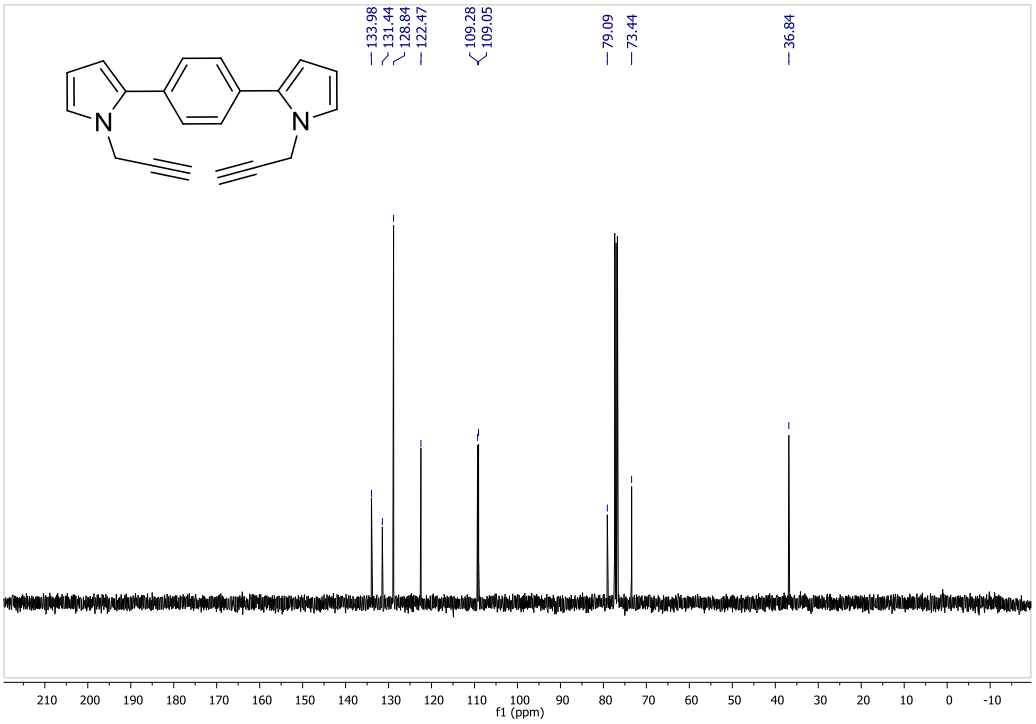

Figure 39. ^{13}C NMR Spectrum of compound **123**