DESIGN AND SYNTHESIS OF BENZENE-FUSED HETEROCYCLES: AMINOPYRIDAZINONES, CHROMENOPYRIDINONES AND BENZOPYRAZOLOXAZEPINES

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY

SELBİ KESKİN

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY
IN
CHEMISTRY

AUGUST 2015

Approval of the thesis:

DESIGN AND SYNTHESIS OF BENZENE-FUSED HETEROCYCLES: AMINOPYRIDAZINONES, CHROMENOPYRIDINONES AND BENZOPYRAZOLOXAZEPINES

submitted by **SELBİ KESKİN** in partial fulfillment of the requirements for the degree of **Doctor of Philosophy in Chemistry Department, Middle East Technical University** by,

Prof. Dr. Gülbin Dural Ünver

Dean, Graduate School of **Natural and Applied Sciences**

Prof. Dr. Cihangir Tanyeli

Head of Department, **Chemistry**

Prof. Dr. Metin Balcı

Supervisor, **Chemistry Dept., METU**

Examining Committee Members:

Prof. Dr. Canan Ünaleroğlu

Chemistry Dept., Hacettepe University

Prof. Dr. Metin Balcı

Chemistry Dept., METU

Prof. Dr. Cihangir Tanyeli

Chemistry Dept., METU

Prof. Dr. Özdemir Doğan

Chemistry Dept., METU

Prof. Dr. Adnan Bulut

Chemistry Dept.,Kırıkkale University

Date: 12.08.2015

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.

Name, Last name: Selbi Keskin

Signature :

ABSTRACT

DESIGN AND SYNTHESIS OF BENZENE-FUSED HETEROCYCLES: AMINOPYRIDAZINONES, CHROMENOPYRIDINONES AND BENZOPYRAZOLOXAZEPINES

Keskin, Selbi
PhD, Department of Chemistry
Supervisor: Prof. Dr. Metin Balcı
August 2015, 299 pages

The interest in the synthesis of heterocyclic compounds has increased day by day due to their biological activities. This study focuses on the synthesis of different benzene-fused heterocycles. In the first part, we synthesized novel class of compounds, 4-aminophthalazin-1(2*H*)-ones starting from methyl 2-(2-methoxy-2-oxoethyl)-benzoate. Methylene group in this starting material was oxidized to the corresponding ketoester. Reaction of ketoesters with hydrazine derivatives provided the hydrazone derivatives. An intramolecular cyclization in the presence of thionyl chloride formed fused pyridazinone skeleton. Hydrolysis of the remaining ester groups and transformation of the acid functionalities to the acyl azides followed by Curtius rearrangement gave the isocyanates. Reaction of the isocyanates with methanol and water produced urethane and aminopyridazinone derivatives, respectively.

In the second part of this thesis, a concise and regioselective approach to the synthesis of chromenopyridine and chromenopyridinone derivatives was developed. The synthetic strategy relies on the *O*-propargylation of aromatic hydroxyaldehydes followed by the reaction with propargylamine. The intramolecular cycloaddition reaction between the alkyne and azadiene, which was formed as an intermediate, furnished the desired skeleton. Benzopyrazoloxazepine and benzopyrazoloxazocine skeletons were also formed via alkyne cyclization in the presence of gold catalyst.

Keywords: pyridazinone, phthalazinone, chromenopyridine, benzopyrazoloxazepine, benzopyrazoloxazocine.

ÖZ

BENZEN HALKASINA KONDENSE OLMUŞ HETEROHALKALI BİLEŞİKLERİN SENTEZLERİ İÇİN YENİ YÖNTEMLERİN GELİŞTİRİLMESİ: AMİNOFTALAZİNONLAR, KROMENOPİRİDİNONLAR VE BENZOPİRAZOLOKZAZEPİNLER

Keskin, Selbi
Doktora, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Balcı
Ağustos 2015, 299 sayfa

Heterohalkalı bileşiklerin sentezlerine olan ilgi, bu bileşiklerin biyolojik olarak aktif maddeler olmalarından dolayı günden güne artmaktadır. Bu çalışmada, benzen halkasına kondenze olmuş çeşitli heterohalkalı bileşiklerin sentezleri gerçekleştirildi. Çalışmanın ilk kısmında, metil 2-(2-metoksi-2-oksoetil) benzoat' tan başlayarak çeşitli aminoftalazinon bileşikleri sentezlendi. Anahtar bileşik olan ketoester, başlangıç maddesindeki metilen grubunun yükseltgenmesiyle elde edildi. İlgili ketoesterin farklı hidrazin türevleriyle tepkimesiyle oluşan hidrazonların tiyonil klorür varlığında molekül içi halkalaşma tepkimesiyle piridazinon iskeleti oluşturuldu. Elde edilen iskeletteki ester gruplarının hidroliziyle oluşan asit fonksiyonel grupları açil azitlerine dönüştürüldü. Bu açil azitlerin Curtius düzenlenmesi sonucu oluşan izosiyanatların metanol ile tepkimesi ilgili üretan türevlerini verirken, asidik ortamda su ile tepkimesi ise ilgili aminoftalazinon türevlerini oluşturdu.

Çalışmanın ikinci kısmında, kromenopiridinon türevlerinin sentezleri için yeni bir yöntem geliştirildi. Bu sentetik yol, ilk olarak aromatik hidroksialdehitlerin *O*-propargillenmesi ve bu bileşiklerin propargil amin ile reaksiyonunu içermektedir. Alkin ve azadien arasındaki moleküliçi siklokatılma reaksiyonu sonucunda ilgili hetero halkalı iskelet elde edildi. Ayrıca, benzopirazolokzazepin ve benzopirazolokzazosin iskeletleri de altın tuzları katalizörlüğünde moleküliçi alkin halkalaşmasıyla elde edildi.

Anahtar Kelimeler: piridazinon, ftalazinon, kromenopiridinon, benzopirazolokzazepin, benzopirazolokzazosin.

ACKNOWLEDGEMENT

I would like to express my deep thanks to my supervisor Prof. Dr. Metin Balcı for his guidance, endless support, valuable advices, and encouragements. It was a great chance for me to be a student of Prof. Balcı.

I wish to thank Dr. Gani KOZA for his sincere assistance and advices through this research.

I am particularly grateful for working with SYNTHOR group, Serdal Kaya, Yasemin Altun, Merve Gökçen Bekarlar, Melek Sermin Özer, Dilem Doğan, Zeynep Ekmekçi, Benan Kılbaş, Nalan Çokol, Özlem Sarı, Işıl Yenice, Sultan Aslan, Merve Sinem Özer, Çağatay Dengiz, Yasemin Dinçoflaz, Furgan Aslanoğlu, Emrah Karahan, Başak Öztürk, Selin Ceyhan, Fatih Şeybek, Dilgeş Baskın, Emre Hoplamaz, Kübra Kılıç, Meltem Tan, Nurettin Mengeş, Sinan Başçeken, Yasin Çetinkaya, Raşit Çalışkan, Kıvılcım Şendil. Without their warm friendship, great support and assistance, this research process would have been difficult.

I would like to thank all of the members of Chemistry Department.

I would like to thank TÜBİTAK (Scientific and Technological Research Council of Turkey, Project no: TBAG 112T360 and TBAG 110R001) and ÖYP for their financial support.

Finally, my special appreciation and great gratitude is devoted to my family for their endless love, and encouragement in every moment of my life. Specially, to my sister Semra Keskin and my cousins Duygu Özdemir, Gökçe Batur for their patience, moral support.

To my beloved sister, Semra…

TABLE OF CONTENTS

CHAPTERS

LIST OF FIGURES

FIGURES

LIST OF ABBREVIATIONS

DIAD: Diisopropyl azodicarboxylate

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DIPA: Diisopropylamine

NBS: N-Bromosuccinimide

AIBN: Azobisisobutyronitrile

APOs: Aminophthalazinones

DCC: *N*,*N′*-Dicyclohexylcarbodiimide

AHAS: Acetohydroxyacid synthase

RCM: Ring Closure Metathesis

EOMO: Ethoxy methyl ether

TBAF: Tetra-*n*-butylammonium fluoride

DCE: 1,2-dichloroethane

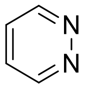
CHAPTER 1

THE SYTHESIS OF AMINOPYRIDAZINONE DERIVATIVES

1.1 INTRODUCTION

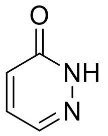
1.1.1 Pyridazines and Pyridazinones

Pyridazine **1** and pyridazinone **2** are six-membered heterocycles which have two adjacent nitrogen atoms. The compounds having these skeleton are found in a lot of natural compounds and have a wide range of pharmaceutical activity.



pyridazine

1

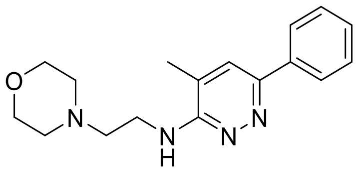


pyridazinone

2

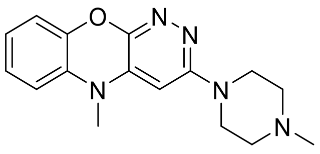
It is known that pyridazines have antimicrobial,[1] anti-hypertensive[2] and anticancer activities.[3] Pyridazinone derivatives are also well known for the treatment of cardiovascular and heart diseases.[4,5] In addition, pyridazinones are used for the treatment of some diseases, such as platelet aggregation inhibitors,[6] inhibitor of cyclooxygenase-2 (COX-2),[7] inhibitors of adenosine 3′,5′-cyclic phosphate phosphodiesterase III (CAMP PDE III),[8] p38 MAP kinase inhibitors,[9] and in compounds with antihypertensive, antithrombotic, antiinflammatory and antiulcer activities.[10,11]

Some commercially available drugs have pyridazine **1** skeleton in their structures. For example, Brantur **3** is a drug which is used for the treatment of depression.[12] Azaphen (pipofezine) **4** is the other drug that has anti-deppresant activity.[13]



brantur

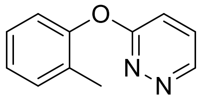
3



pipofezine

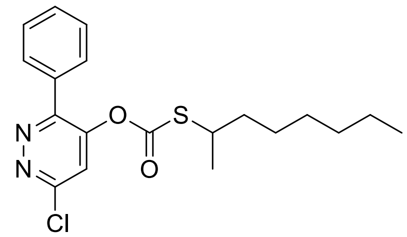
4

Pyridazinones have also importance in terms of agriculture. They are widely used as herbicides to kill pests and unwanted plants. Credazine **5** containing the ether linkage between pyridazine and substituted benzene, pyridate **6** having thiocarbonate composition and pyridafol **7** consisting alcohol unit are the examples of herbicides.[14]



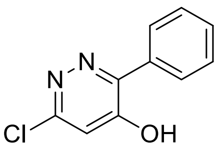
credazine

5



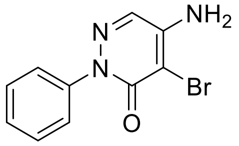
pyridate

6



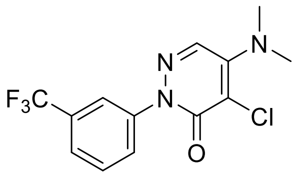
pyridafol

7



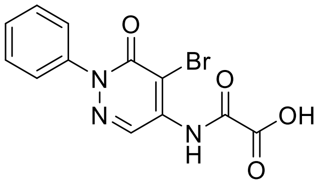
brompyrazon

8



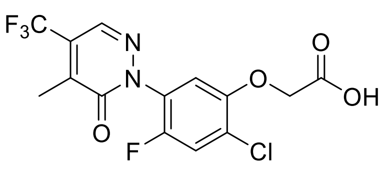
metflurazon

9



oxapyrazon

10



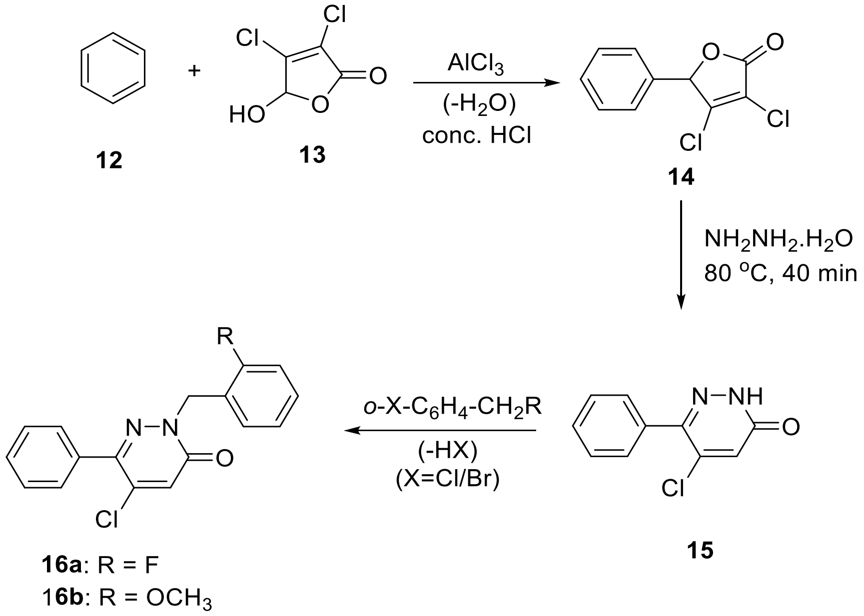
flufenpyr

11

Brompyrazon **8**[15] and metflurazon **9**[16] contain amine functional group in their skeleton and also they have halides such as bromine and florine. Several pyridazinone herbicides contain carboxylic acid as well as halogen group, such as oxapyrazon **10** and flufenpyr **11**[17].

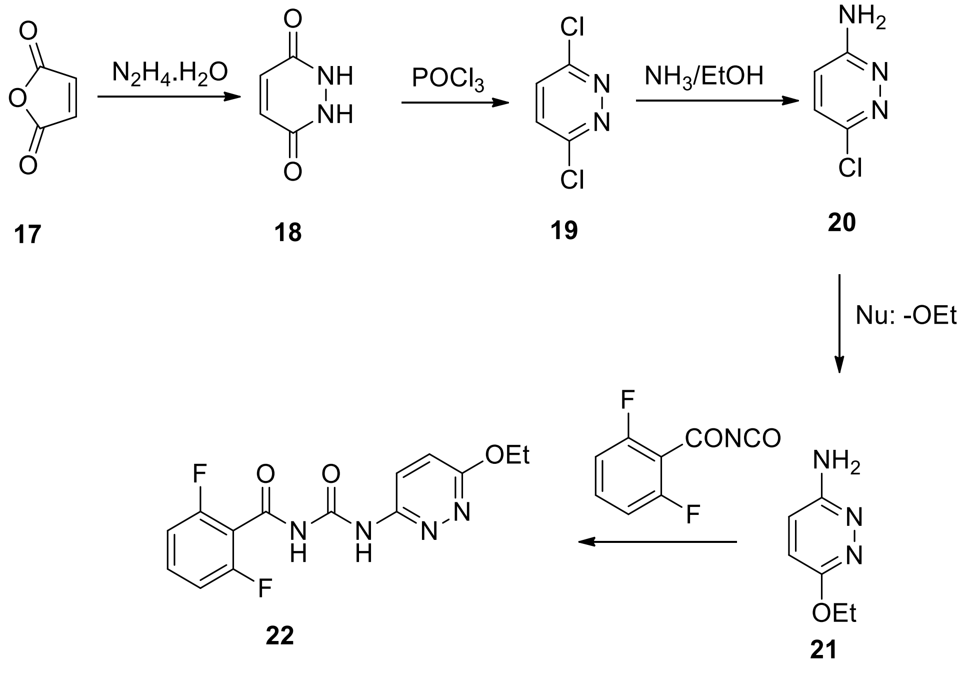
1.1.1.1 The Synthesis of Pyridazines and Pyridazinones

Song *et al.*[18] used a mild and effective method for the preparation of pyridazinone derivatives (Scheme 1). They used benzene **12** and mucochloric acid **13** as the starting materials to synthesize compounds **16** via **14** and **15**. The synthesized compounds were subjected to fungicidal activities *in vitro* against *G. zeae*, *F. Oxysporum* and *C. Mandshurica.* They found that compounds **16a** displayed good antifungal activities.



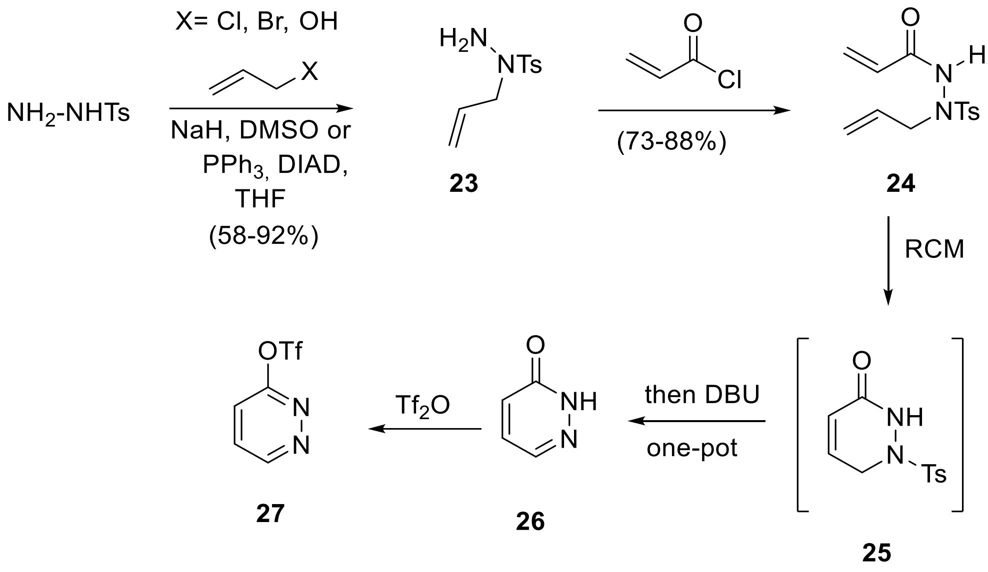
Scheme 1

A series of novel benzoylpyridazyl ureas were designed and synthesized starting from maleic anhydride **17** and hydrazine monohydrate by Wang and coworkers (Scheme 2).[19] They observed that these compounds exhibited larvicidal activities against oriental armyworm and in particular, compound **22** displayed comparable activity to the commercial insecticide Hexaflumuron.



Scheme 2

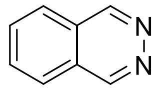
Ring closing metathesis (RCM) can be used to construct aromatic heterocycles. In 2009, Donohoe *et al.*[20] synthesized pyridazinone derivatives by using RCM for the first time (Scheme 3). According to this synthetic pathway, firstly, commercially available H_2NNHTs was allylated at the more acidic nitrogen by either selective deprotonation and reaction with an allylic halide or by a Mitsunobu reaction. Then, the resulting hydrazines **23** was acylated on the free NH_2 group by reaction with acryloyl chloride to give corresponding product **24**. Finally, these compounds were subjected to RCM using standard conditions. The RCM reaction and subsequent DBU elimination was performed in one-pot reaction and in high yields. Activation of the heterocycles **26** with Tf_2O resulted in the formation of pyridazine derivative **27** (Scheme 3).



Scheme 3

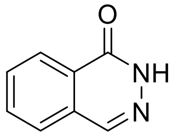
1.1.2 Benzopyridazines and Benzopyridazinones

Benzopyridazines **28** and benzopyridazinones **29**, also known as phthalazines and phthalazinones, are heterocyclic compounds that contain benzene fused pyridazine and pyridazinone skeletons.



benzopyridazine

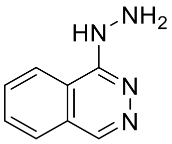
28



benzopyridazinone

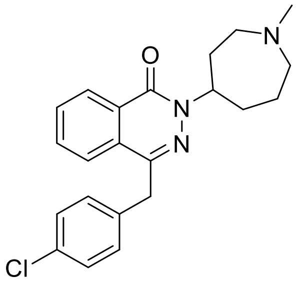
29

Phthalazinone derivatives are found in skeleton of some commercially available drugs like pyridazinones. For instance, hydralazine **30** contains phthalazinone skeleton. It is used to treat hypertension for pregnant.[21] Azelastine **31** having benzopyridazinone skeleton is a potent, second-generation histamine antagonist.[22] Vatalanib **32** belongs to a class of drugs which block the formation of new blood vessels. Joensuu *et al.* determined that vatalanib is active in patients who have imatinib-resistant GIST or imatinib and sunitinib-resistant GIST.[23]



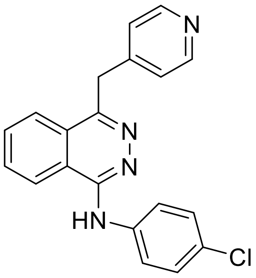
hydralazine

30



Azelastine

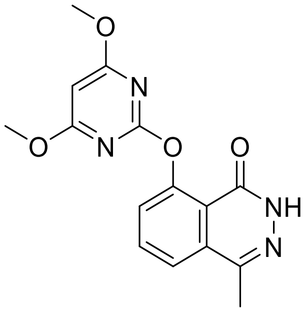
31



Vatalanip

32

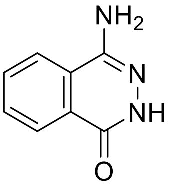
Phthalazinone derivatives are also found as an inhibitor. For example, methylphthalazin-1-one **33** is the inhibitor of acetohydroxyacid synthase (AHAS). This enzyme accelerates the biosynthesis of branched-chain amino acids including leucine and valine.[24]



methylphthalazin-1-one

33

4-Aminophthalazin-1(2*H*)-ones (APOs) **34** have shown potential as anticancer agents[25] and in the treatment of autoimmune and inflammatory diseases.[26] Recently, 2-phenyl APOs have been reported as a decorable core skeleton for the design of potent and selective human A_3 adenosine receptor antagonists.[27]

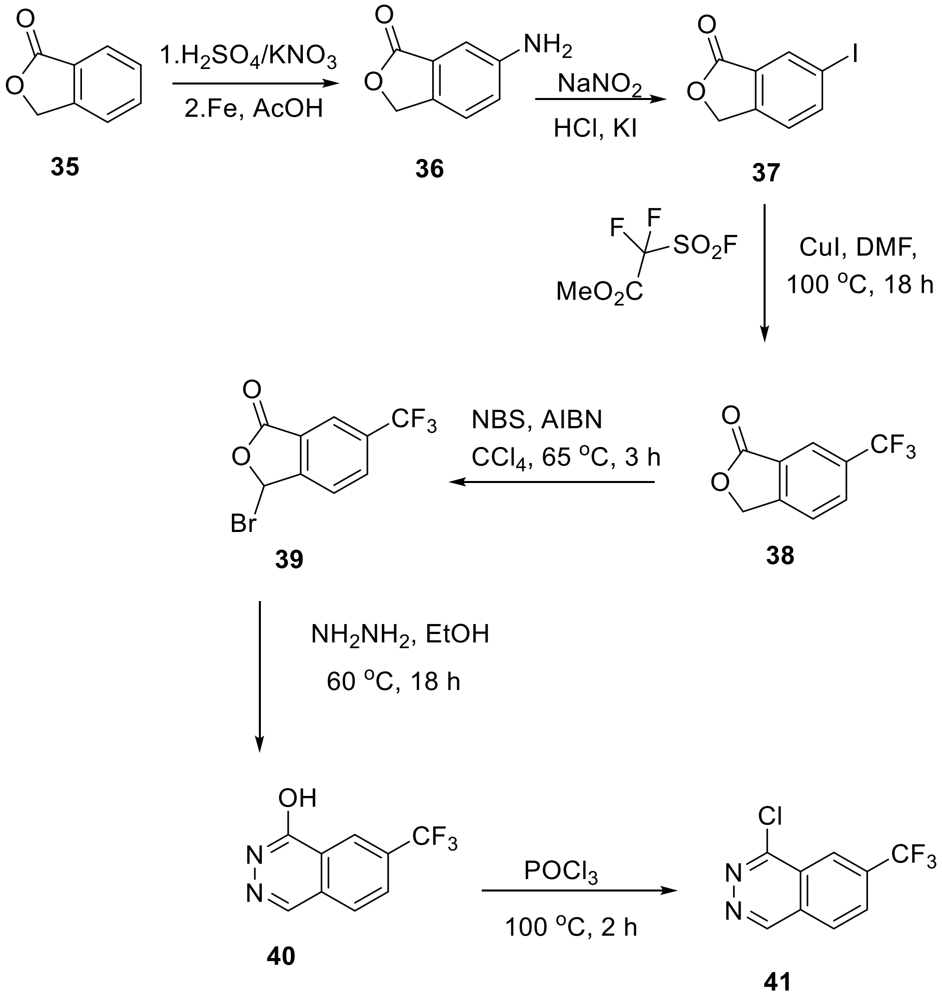


4-Aminophthalazin-1(2H)-one

34

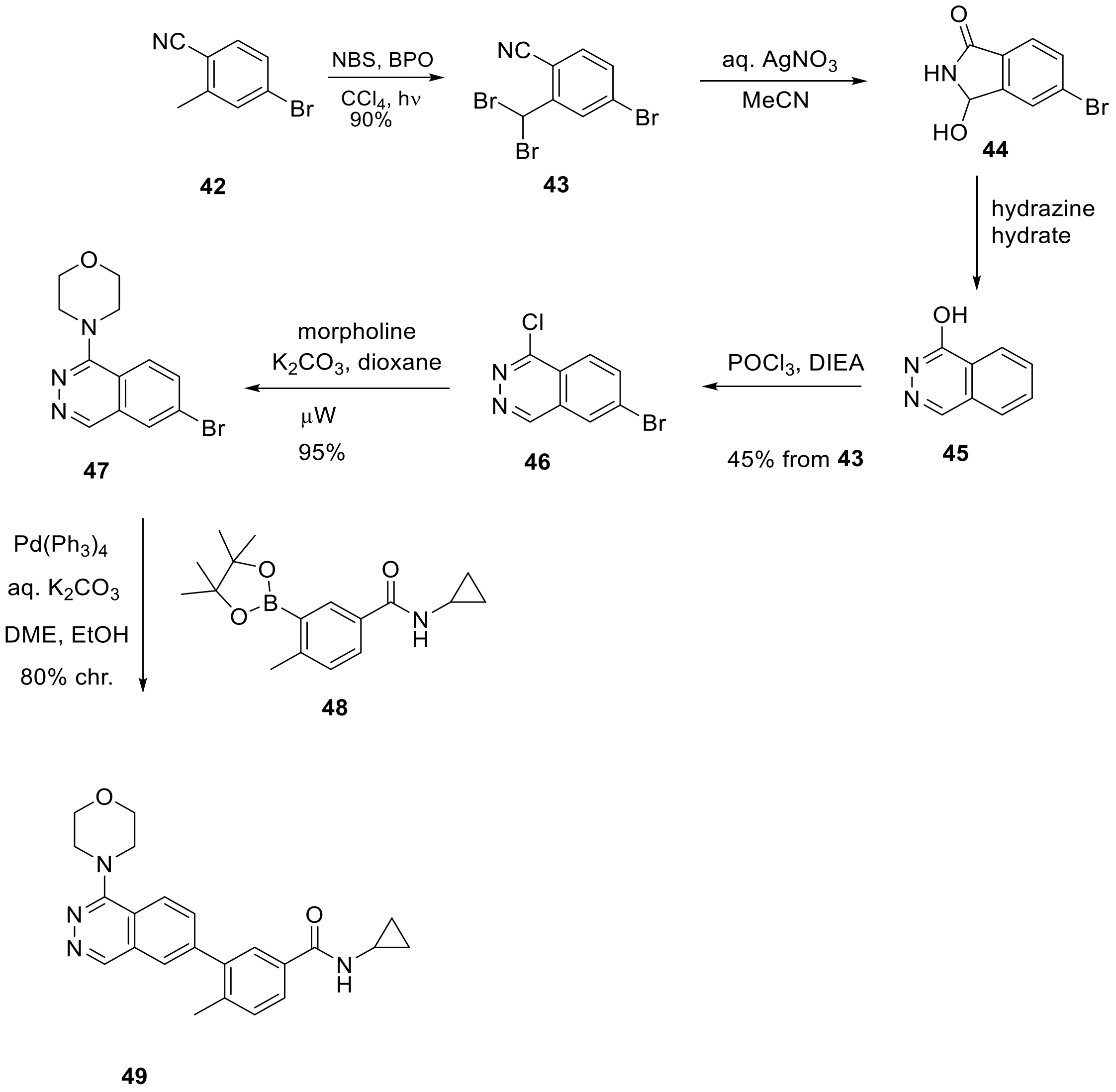
1.1.2.1 The Synthesis of Benzopyridazines and Benzopyridazinones

Phthalazine **41** was synthesized according to Scheme 4.[28] Lactone **35** was nitrated and then reduced to give the aniline derivative **36**. Diazotization of compound **36** in the presence of KI resulted in the formation of the iodobenzofuran **37**. Trifluoromethylation of **37** gave compound **38** by using copper as a catalyst. Compound **38** was brominated and heated in the presence of hydrazine to give the phthalazine **40**, which was converted to chloride **41** (Scheme 4).



Scheme 4

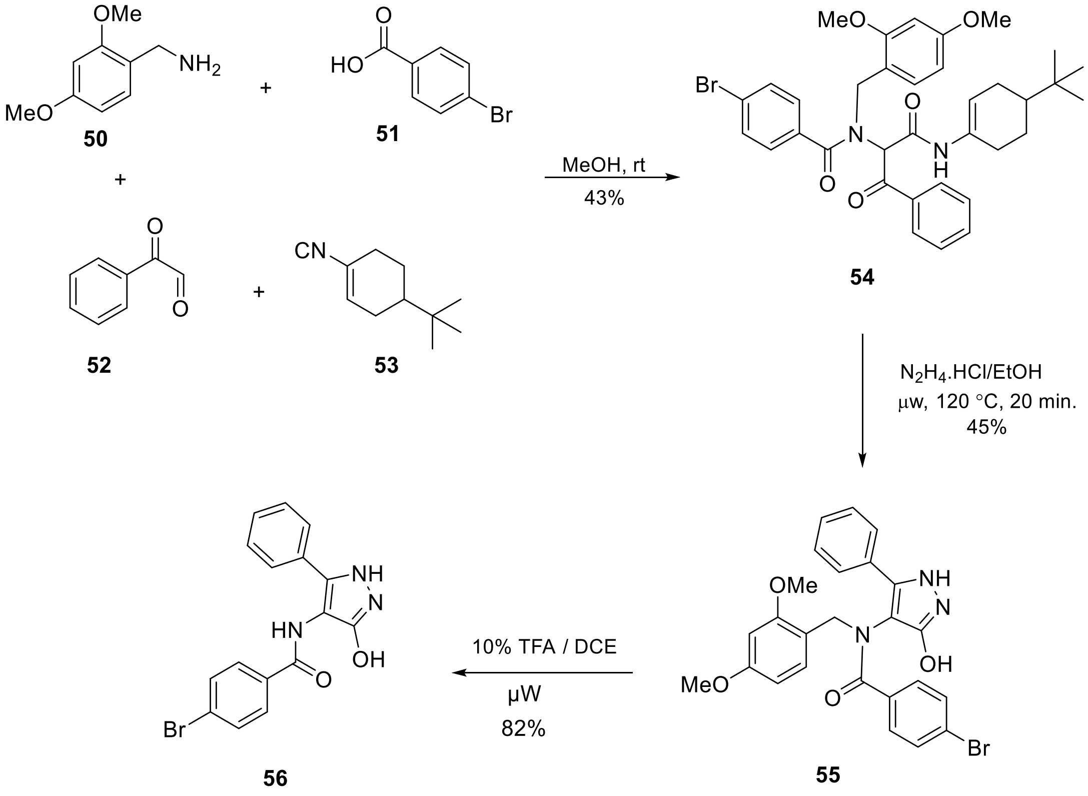
Herberich *et al.*[29] described a concise and efficient synthesis of p38 MAP kinase inhibitor **49** having phthalazine scaffold. For this purpose, 4-bromo-2-methyl-benzonitrile (**42**) was choosen as a starting material. In the first step, radicalic bromination of compound **42** was carried out. Then, the hydrative cyclization of 2-(di-bromomethyl)benzonitrile (**43**) to hydroxyisoindolinone **44** was achieved. To construct phthalazine skeleton, hydroxyisoindolinone **44** was reacted with hydrazine hydrate in the next step. To obtain 6-bromo-1-(4-morpholinyl)phthalazine (**47**), firstly chlorination reaction with $POCl_3$ was carried out and then nucleophilic displacement of the chloride with an appropriate amine followed by Suzuki coupling with boronic ester **48** provided corresponding aminophthalazine **49** (Scheme 5).



Scheme 5

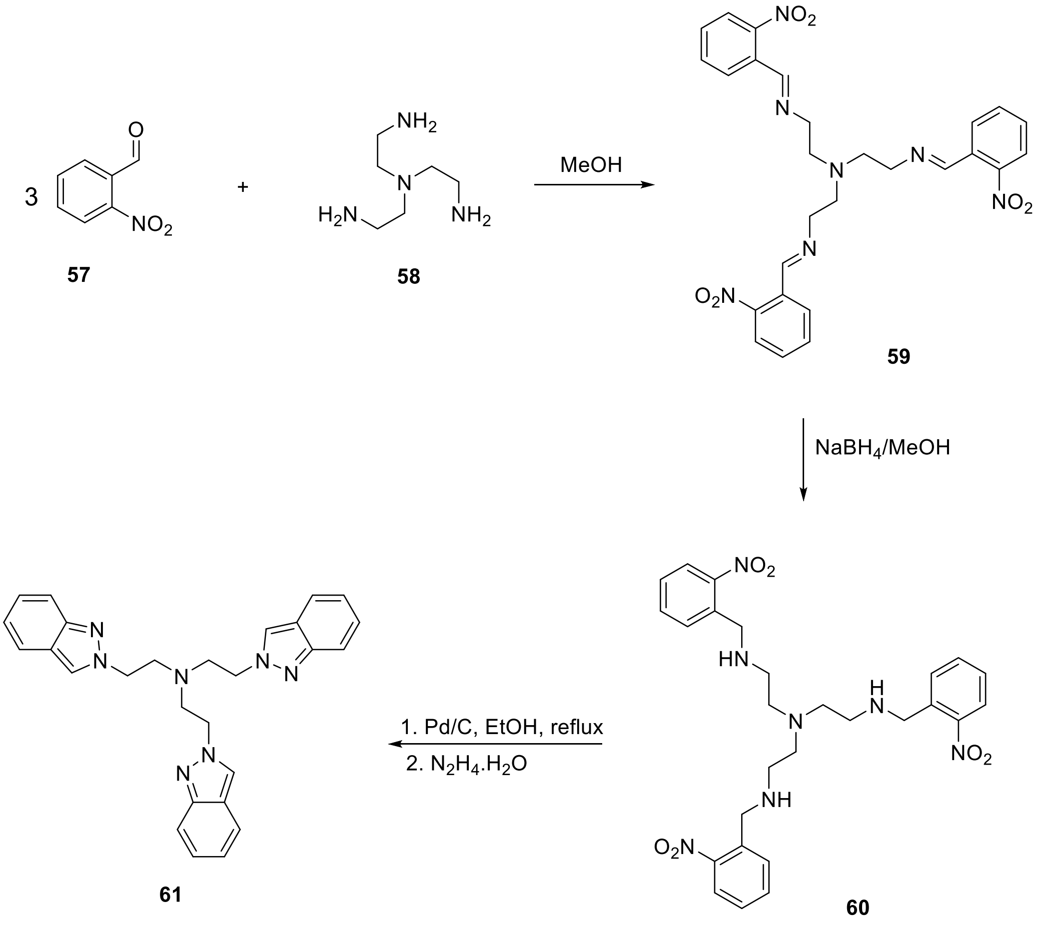
1.1.3 Cyclization with Hydrazine

Hydrazine is an inorganic compound and it is higly toxic and dangerous if it is not stored in solvent. Therefore it is mainly used as hydrazine monohydrate. It has basic property (pKa = 8.1). Hydrazines are very useful compounds for organic synthesis. For example, it is used for reduction, hydrazone formation, and deprotection of phthalimides. In addition to these, hydrazine derivatives are usually used for the construction of some heterocyclic compounds, such as pyrazole, indazole, and triazoles. For instance, Hulma *et al.*[30] synthesized a series of 3-hydroxypyrazoles via a tandem Ugi/debenzylation/hydrazine-mediated cyclization sequence. Ugi product **54** was initially prepared in a one-pot reaction starting from 2,4-dimethoxybenzenylamine (**50**), 4-bromobenzoic acid (**51**), phenylglyoxal (**52**), and 4-tert-butyl-cyclohexen-1-yl isocyanide (**53**). Subsequent treatment of **54** with hydrazine mono-hydrochloride in ethanol, accelerated by using microwave irradiation, resulted in the formation of 3-hydroxypyrazole **55** in 45% isolated yield. To remove 2,4-dimethoxybenzyl group from **55**, it was treated with 10% TFA/DCE solution at 80 °C for 10 min. under microwave irradiation and corresponding 3-hydroxypyrazole **56** was formed (Scheme 6).



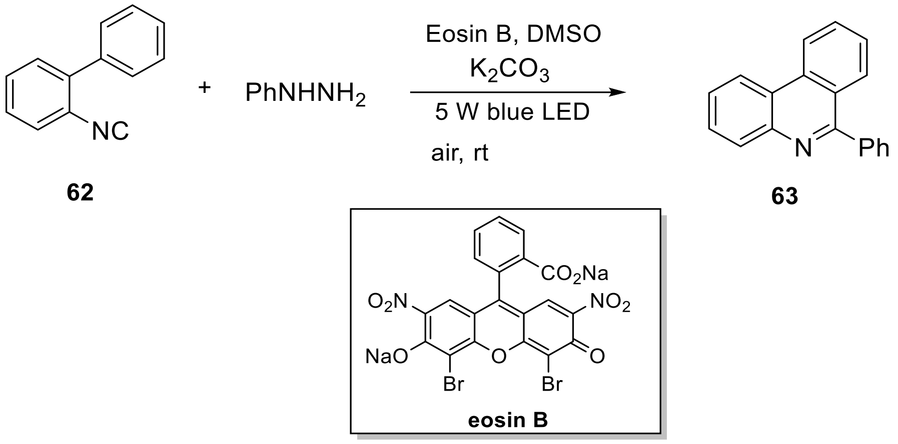
Scheme 6

Flores-Alamo *et al.*[31] obtained tris[2-(2*H*-indazol-2-yl)ethyl]amine (**61**) in three steps. In the first step, tris[N-2-(nitrobenzylideneamino)ethyl]amine (**59**) was formed by condensation between 2-nitrobenzaldehyde (**57**) and tris(2-aminoethyl)amine (**58**) according to literature procedure.[32] Then, selective reduction of imine bonds with $NaBH_4$ in methanol gave the corresponding amine **60**. To the amine solution in ethanol, Pd/C was added and the resulting mixture was refluxed for 4 h. After addition of hydrazine monohydrate, corresponding product **61** was formed (Scheme 7).



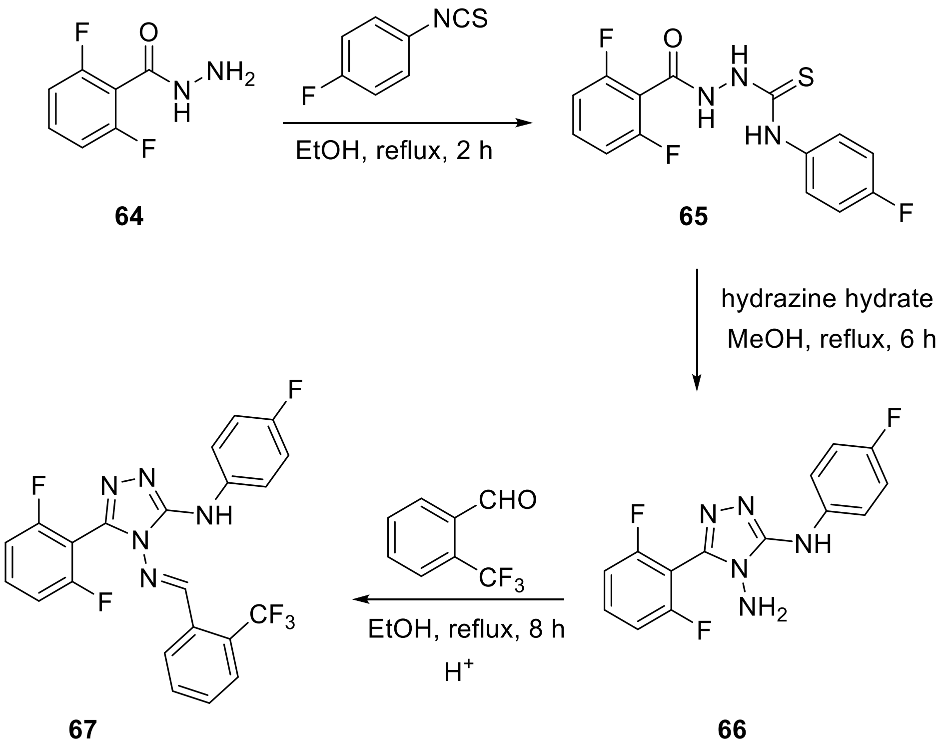
Scheme 7

Zhou *et al.*[33] used hydrazine derivatives for cyclization reactions. Through the radical cyclization of 2-isocyanobiphenyls with hydrazine derivatives under environmentally friendly conditions, they constructed phenanthridine framework, such as **63**, a common structural unit present in a wide variety of naturally occurring alkaloids (Scheme 8).



Scheme 8

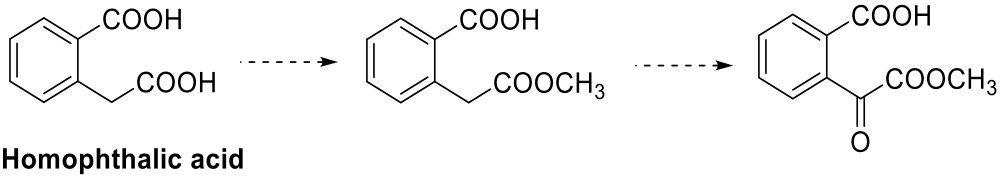
Mohana *et al.*[34] firstly synthesized 5-(2,6-difluorophenyl)-N^3-(4-fluorophenyl)-4*H*-1,2,4-triazole-3,4-diamine (**66**) starting from 2,6-diflurobenzohydrazide (**64**) and 4-fluorophenylisothiocyanate and then compound **66** was reacted with fluoro substituted benzaldehydes to yield Schiff bases **67** and its different derivatives. Antiproliferative activity was evaluated for the new synthesized compounds (Scheme 9).



Scheme 9

1.1.4 Aim of the Study

The aim of this thesis was the development of new synthetic methodologies for the synthesis of phthalazinone **71** and aminophthalazinone **74** derivatives starting from the ketomonoester **70**. Firstly, the half ester **69** should be synthesized starting from the homophthalic acid **68**. Ketomonoester, key compound of this study, will be obtained by the oxidation reaction (Scheme 10).

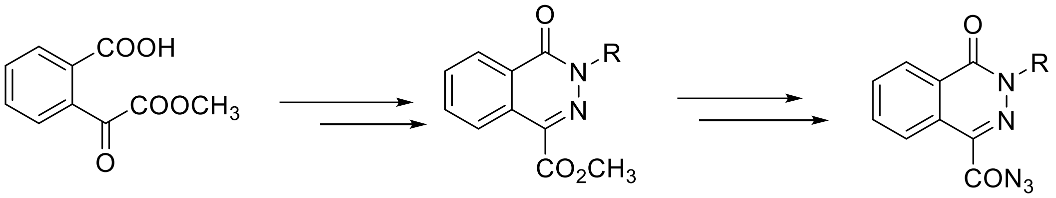


Homophthalic acid

68 **69** **70**

Scheme 10

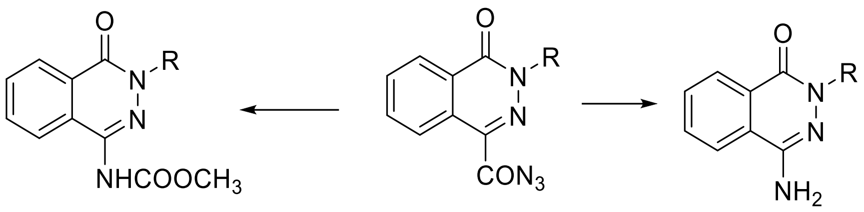
After getting key compound **70**, we planned to apply ring closure reaction by using hydrazine derivatives to form corresponding phthalazinone skeleton **71**. After that we focused on the synthesis of aminophthalazinone **74** since the compounds having –NH or –NH_2 groups generally increases the biological activity of compounds. For this purpose, ester functionality in **71** should be firstly converted to acyl azide **72** (Scheme 11).



70 **71** **72**

Scheme 11

Later, acyl azide **72** can be converted to urethane and also amine functionalities and corresponding products, **73** and **74**, may be obtained (Scheme 12).



73 **72** **74**

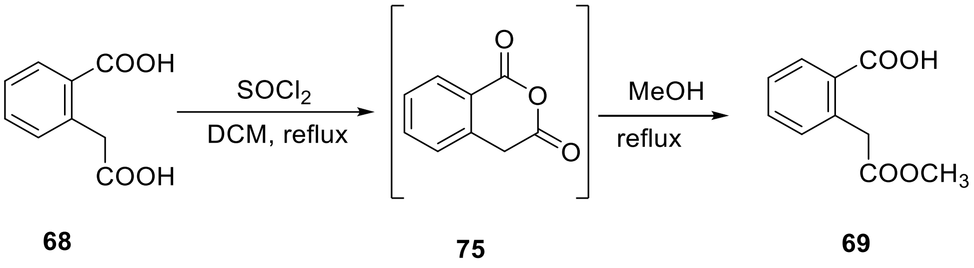
Scheme 12

1.2 RESULTS AND DISCUSSION

1.2.1 Synthesis of Phthalazinone Derivatives

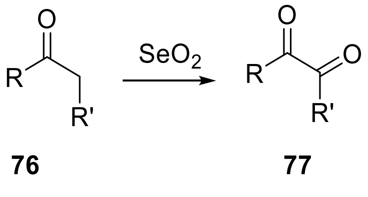
1.2.1.1 Synthesis of Ketoester

To synthesize phthalazinone derivatives, commercially available homophthalic acid **68** was first reacted with thionyl chloride to give an anhydride **75** which was then treated with methanol to produce half ester **69** according to literature procedure[35] (Scheme 13).



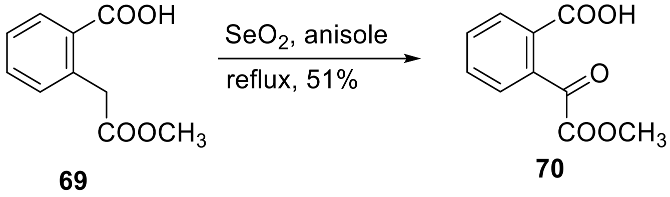
Scheme 13

A methylene group next to a carbonyl group can be oxidized to an α-diketone by using SeO_2 that is known as Riley oxidation (Scheme 14).[36]



Scheme 14

For this conversion, the methylene group between the benzene ring and the carbonyl group in **69** was successfully oxidized to corresponding ketoester **70**. Firstly, the reaction was tried in dioxane as a solvent. Unfourtunately, the oxidation reaction failed. Therefore, we decided to increase reaction temperature by using different solvents. When the reaction was carried out in xylene at reflux temperature, xylene was also oxidized and the desired oxidation compound **70** could not be purified successfully. So we decided to use anisole that has higher boiling point (154 °C). Finally, treatment of half ester **69** with SeO_2 in anisole afforded the ketoester **70** in 51% yield (Scheme 15).

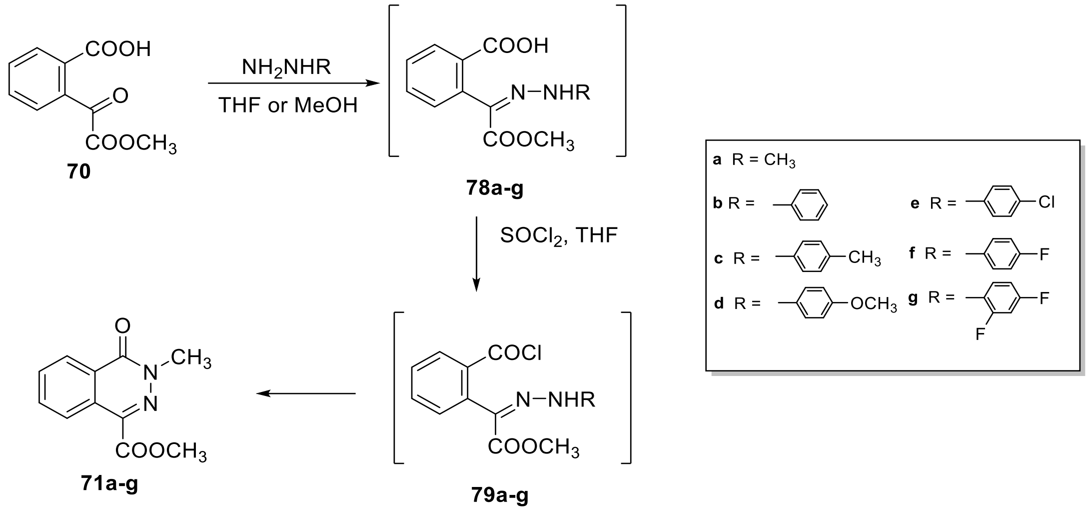


Scheme 15

1.2.1.2 Cyclization with Hydrazine Derivatives

Intramolecular cyclization reactions were achieved by reacting starting compound **70** with hydrazine derivatives. In this step, THF or methanol was used as a solvent depending on the hydrazine used. We used seven different hydrazine derivatives. While THF was used for the reaction with methyl hydrazine as a solvent, methanol was used for the other derivatives due to solubility problem. The formed hydrazones **78a-g** were not isolated and used for further reactions. The solvent was evaporated and the acid functionalities in **78a-g** were converted to acyl chlorides **79a-g** by using thionyl chloride. The in situ generated acyl chlorides, **79a-g** underwent intramolecular cyclization reaction by attacking of amine nitrogen atom to the carbonyl group to form the desired cyclization products **71a-g (**Scheme 16).

Formation of the these bicyclic compounds **71a-g** was verified by ^{1}H and ^{13}C NMR analysis. Compound **71f** has one flourine atom attached to the benzene ring. In the ^{1}H NMR spectrum, the singlet at 4.55 ppm belongs to the ester functionality. Also, there is an AA′BB′X system in the NMR spectrum. A part of AA′BB′X system resonates as multiplet at 7.71-7.66 ppm while B part of AA’BB’X system resonates also as multiplet at 7.25-7.19 ppm (Figure 1). The symmetrical distribution of signals are lost due to the coupling with fluorine atom.



Scheme 16

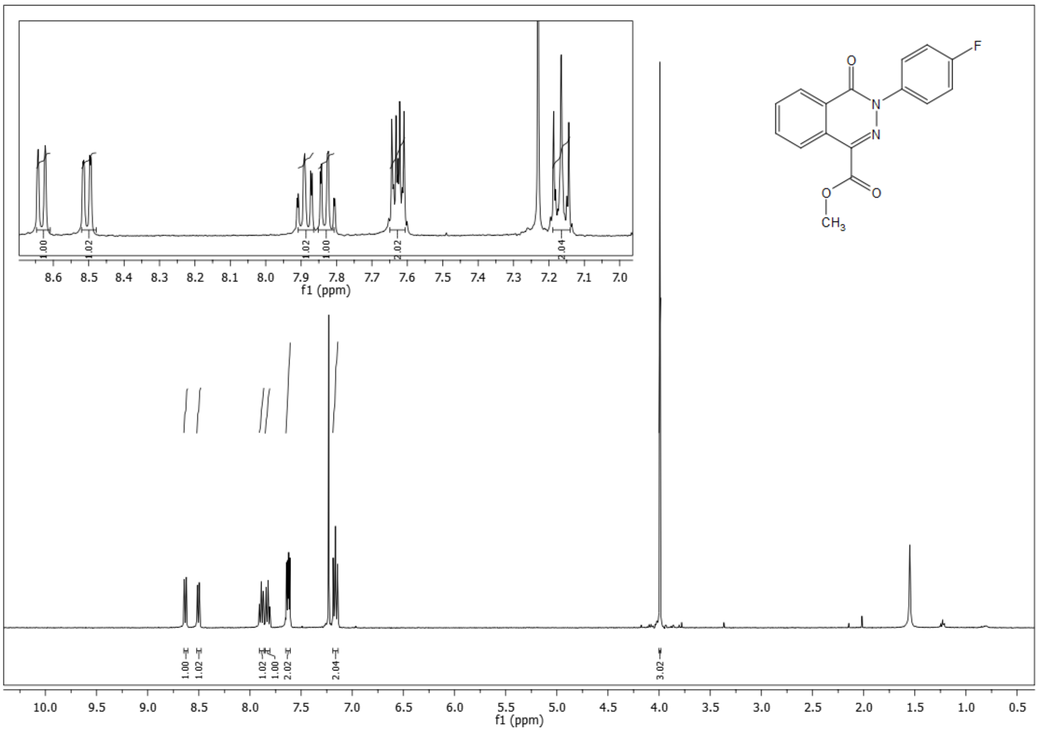


Figure 1: ^{1}H NMR Spectrum of Compound **71f**

In the case of ^{13}C-NMR spectrum of **71f**, ^{19}F coupled with ^{13}C atoms on the benzene ring and split the ^{13}C signals into doublet according to equation $m=2I+1$ since the spin quantum number (I) of ^{19}F is ½. The coupling constant of ^{13}C-^{19}F over one bond ($^{1}J_{C\text{-}F}$) is largest one which is 248.1 Hz. As the distance between ^{13}C and ^{19}F increases, the coupling constant decreases. The coupling constant of ^{13}C-^{19}F over two bonds ($^{2}J_{C\text{-}F}$) is 22.8 Hz. The other coupling constants, ($^{3}J_{C\text{-}F}$) and ($^{4}J_{C\text{-}F}$), are 7.3 Hz and 3.1 Hz, respectively (Figure 2).

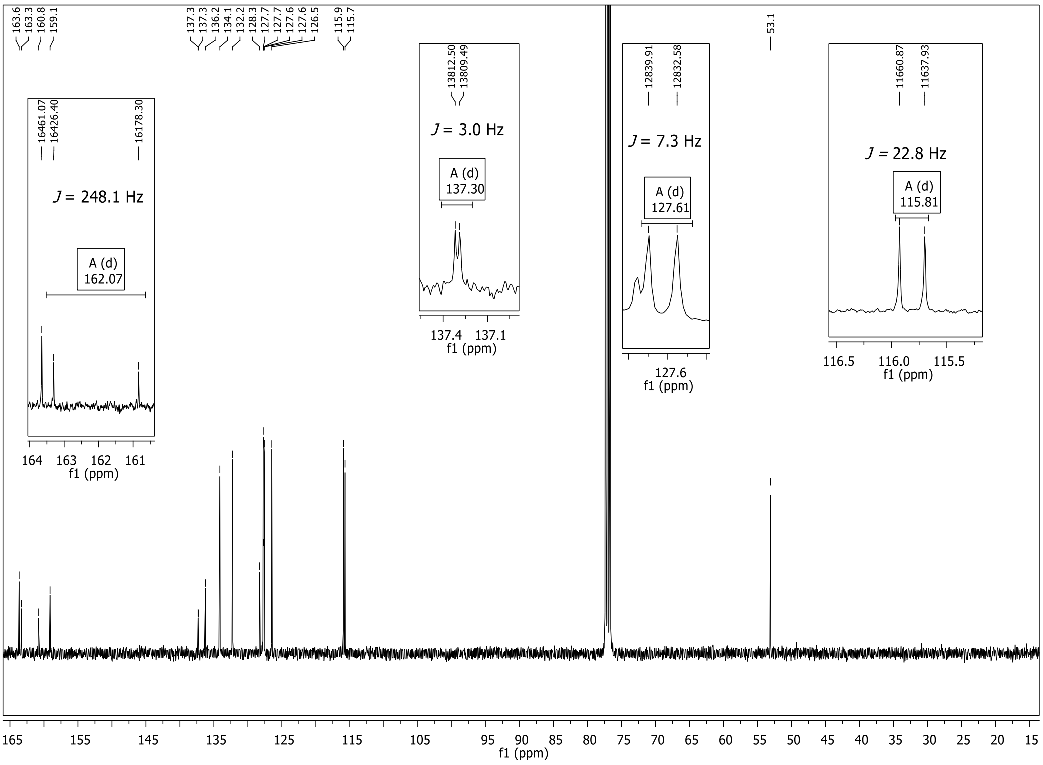
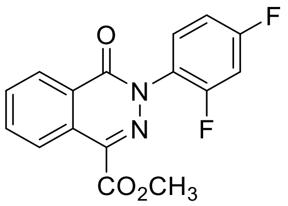


Figure 2: ^{13}C NMR Spectrum of Compound **71f**

On the other hand, the compound **71g** has two fluorine atoms attached to the phenyl ring and therefore, all the carbons of phenyl group split into doublet of doublets (Figure 3). The carbons directly attached to fluorine atoms have the largest coupling constants (^{1}J) about 251.6 and 255.7 Hz and also they show further couplings of 11.1 and 12.6 Hz, respectively due to fluorine atom in the *meta*-position (^{3}J). Furthermore, coupling constant of the quaternary carbon attached to the nitrogen is 22.7 Hz due to fluorine atom in *ortho*-position. Same carbon also has *para* coupling which is 3.7 Hz. The carbon that resonates at 105.1 ppm has two *ortho*-coupling, (^{2}J = 26.4 and 23.5 Hz).



71g

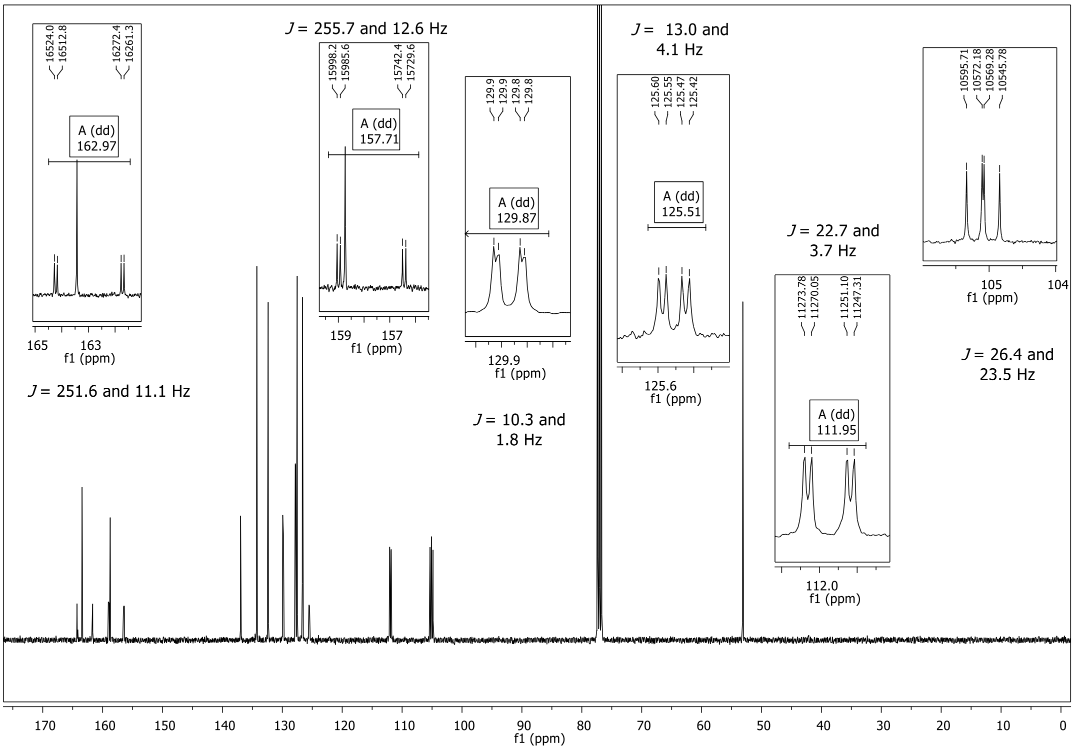
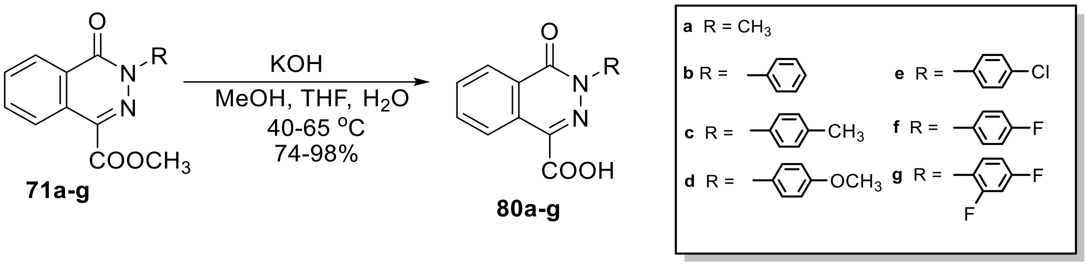


Figure 3: ^{13}C NMR Spectrum of Compound 71g

1.2.1.3 Hydrolysis of Ester Functional Groups in 71a-g

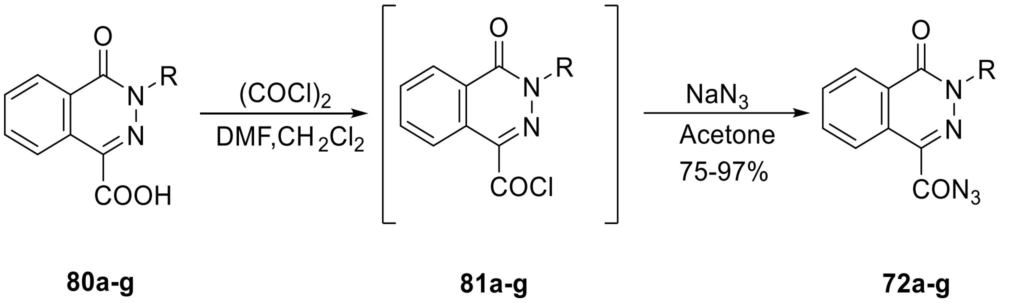
Phthalazinone skeletons having ester functional groups **71a-g** were hydrolyzed under basic conditions in THF-methanol mixture. After the completion of the reaction, the solvent was evoparated and the residue was dissolved in water. The water phase was acidified with aq. HCl, the acids **80a-g** were extracted with ethyl acetate (Scheme 17). The acids **80a-g** formed were analyzed by ^{1}H and ^{13}C NMR spectra. Dissapearance of peaks belonging to ester protons around 4 ppm in ^{1}H NMR and 53 ppm in ^{13}C NMR spectra was the proof of hydrolysis.



Scheme 17

1.2.1.4 Synthesis of Acyl Azides 72a-g

Acyl azides **72a-g** were synthesized starting from corresponding acid **80a-g**. Firstly, these acid functionalities were converted to the corresponding acyl chlorides **81a-g** to activate acid functionality by using oxalyl chloride and catalytic amount of DMF. Later, solvent was evaporated to give the acyl chlorides **81a-g**.



Scheme 18

The acyl chlorides were not isolated and reacted with NaN_3 in acetone/water to form corresponding acyl azides **72a-g** (Scheme 18). The formation of acyl azides was established by IR analysis. The peak around 2100 cm^{-1} is typical for azides and support the formation of desired conversion. In figure 4, IR Spectrum of compound **72c** is shown and the peak at 2120 cm^{-1} is the indicator of the formation of the corresponding acyl azide.

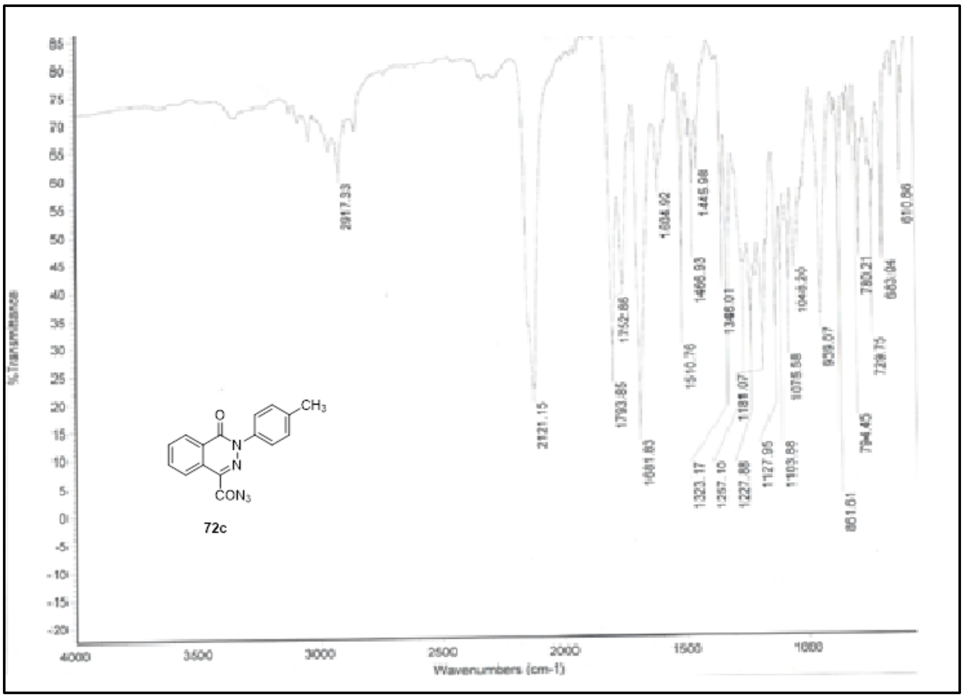
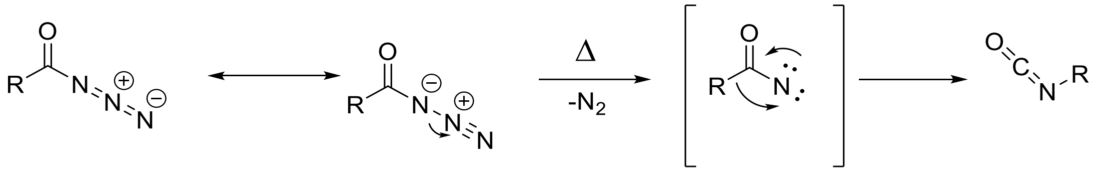


Figure 4: IR Spectrum of Compound 72c

1.2.1.5 Synthesis of Isocyanates 86a-g via Curtius Rearrangement

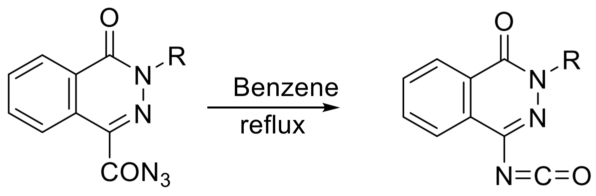
An acyl azide **82** forms corresponding isocyanate **853** by heating. During this process, nitrogen gas is released to form acyl nitrene **84** that is an electron deficient intermediate and it rearranges to isocyanate **85** (Scheme 19). This reaction is called Curtius rearrangement.[37]



82 **83** **84** **85**

Scheme 19

To apply Curtius rearrangement, the acyl azide derivatives **72a-g** were dissolved in benzene, an aprotic solvent, and heated. Formed isocyanates **86a-g** were not isolated. They were directly used for the next step (Scheme 20).

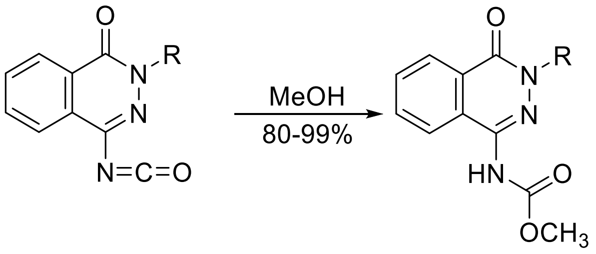


72a-g **86a-g**

Scheme 20

1.2.1.6 Synthesis of Urethanes 73a-g

Isocyanates are quite reactive. The carbon atom of isocyanate is so electrophilic that they can be trapped by various nucleophiles. The reaction of **86a-g** with methanol resulted in the formation of corresponding urethane derivatives **73a-g** (Scheme 21).



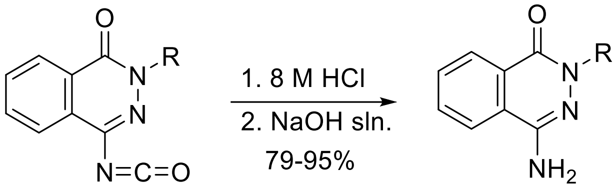
86a-g **73a-g**

Scheme 21

The characterization studies of urethane derivatives **73a-g** were done by using NMR and IR spectra. Methyl protons resonates at around 3.8 ppm as singlets in H-NMR spectrum while NH protons resonates as broad singlet at about 6.8 ppm. These are significant signals for characterization of urethanes. In addition to these, we used IR spectra to be sure about consumption of isocyanate. In the IR spectra, dissapperance of signal at around 2250 cm^{-1} showed that all isocyanates were reacted.

1.2.1.7 Synthesis of Aminophthalazinone Derivatives 74a-g

Hydrolysis of isocyanate in acidic medium resulted in the formation of corresponding amine functionality. Aminophthalazinone derivatives **86a-g** were formed by addition of 8 M HCl solution to the isocyanate in benzene (Scheme 22).



86a-g **74a-g**

Scheme 22

To prevent the intermolecular reaction between the formed amines and unreacted isocyanates, we run this reaction under acidic condition.

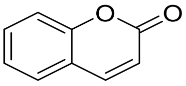
CHAPTER 2

THE SYNTHESIS OF CHROMENOPYRIDINONES AND BENZOPYRAZOLOXAZEPINES

2.1 INTRODUCTION

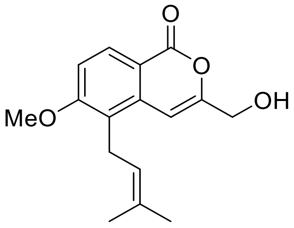
2.1.1 Isocoumarins

Isocoumarines **87** are the heterocyclic compounds having a lactone ring fused to benzene ring. They are found in many natural products which show wide range of biological activities, such as antiallergic and antimicrobial,[38,39] immunomodulatory,[40] cytotoxic,[41] antiinflammatory,[42] antiangiogenic,[43] and antimalaria.[43] They can be isolated from plants, molds, bacteria, and lichens.[44]

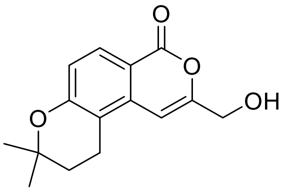


87

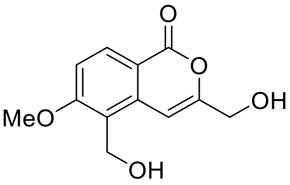
Three different isocoumarin derivatives **88-90** were isolated from *Nicotiana tabacum* which is a herbaceous plant in the Solanaceae that originated in the tropical Americas and cultivated worldwide as the primary commercial source of tobacco.[45] Yang *et al*.[46] prepared 70% aq. acetone extract from the roots and stems of *Nicotiana tabacum* and this extract was partitioned between EtOAc and H_2O. The EtOAc layer was subjected to column chromatography on silica gel, RP-18 and preparative HPLC to afford compounds **88-90**, three new isocoumarin derivatives which named tabaisocoumarins **A**–**C**.



88

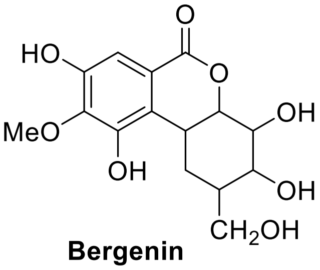


89



90

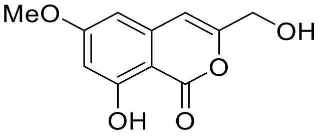
Bergenin **91** is a colourless crystalline polyphenol which was isolated from medicinal plants like *Bergenial crassifolia*, *Sacoglottis gabonensis*, *Corylopsis spicata*, *Caesalpinia digyna* etc. Bergenin exhibits antihepatotoxic,[47] anti-HIV,[48] antiarhythmic,[49] antioxidant,[50] anti-inflammatory,[51] and immunomodulatory[52] properties.



Bergenin

91

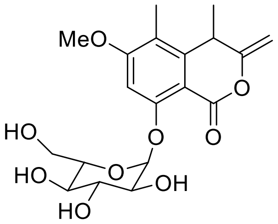
Cytogenin **92** is a natural isocoumarin. It also has different biological activities. For example, cytogenin shows antitumor activity against a syngeneic murine transplantable tumor.[53] In addition to this activity, there are different properties of cytogenin like antiogenic,[54] antidiabetic[55] activities.



Cytogenin

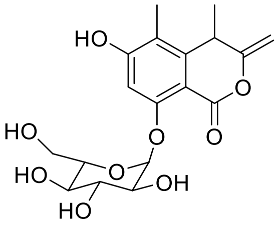
92

Kittakopp and coworkers isolated halorosellins A **93** and B **94** which are structurally unique isocoumarin glucosides from the EtOAc extract of a broth of the marine fungus *Halorosellinia oceanica* in 2002.[56]



Halorosellins A

93

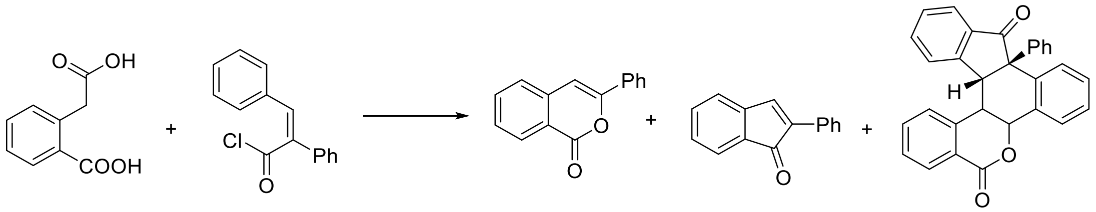


Halorosellins A

94

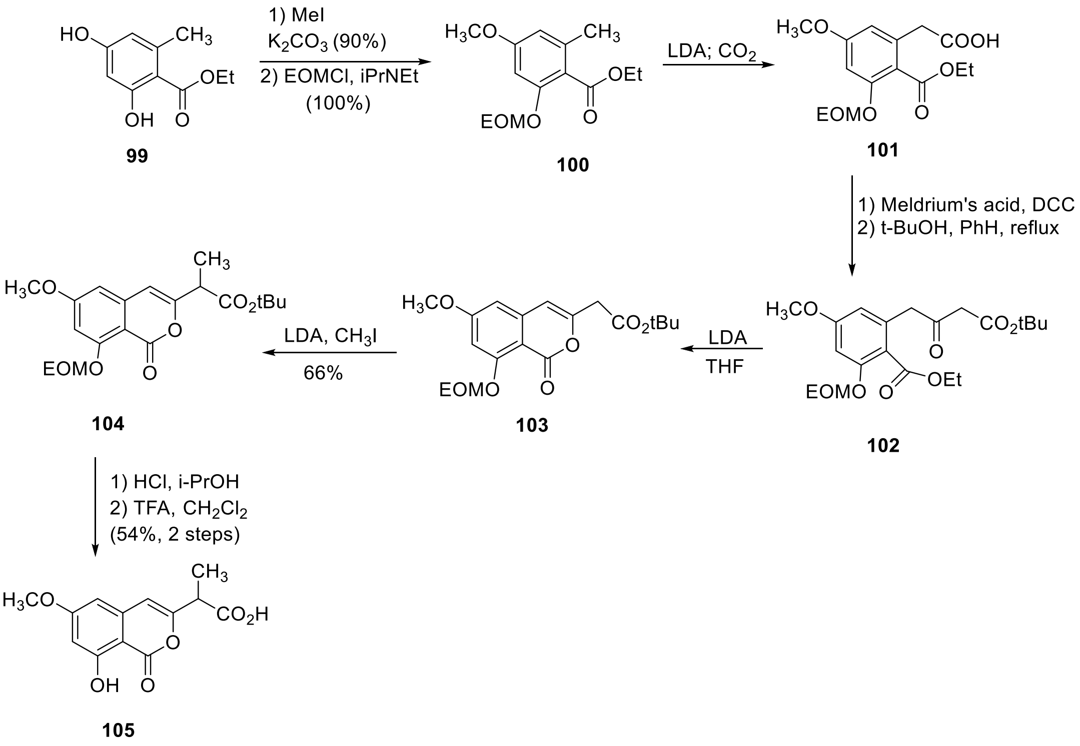
2.1.1.1 The Synthesis of Coumarins

A novel fused isocoumarin skeleton has been synthesized through selective domino multicyclizations by starting from homophthalic acid **68** and 2,3-diphenylacryloyl chloride **(95)** at 200 °C with a catalyst under the solvent free reaction conditions. Hexacyclic fused isocoumarin framework with two stereogenic centers were assembled in a convenient one-pot synthesis in good yield (Scheme 23).[57]



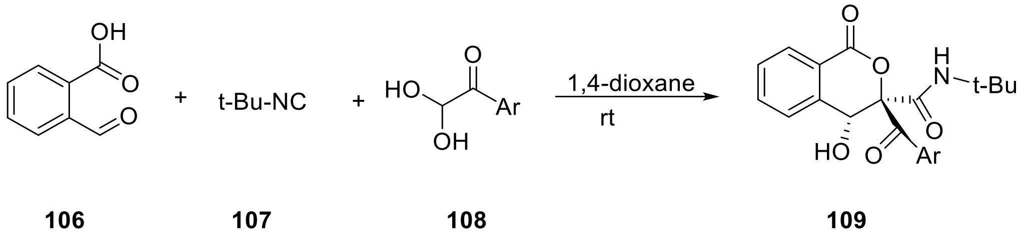
Scheme 23

A synthetic pathway has been developed for the formation of the isocoumarin cytogenin **92** and NM-3 **105** by the Taylor *et al.*[54] Regioselective methylation was done to give the 4-methoxy derivative followed by protection of the phenolic hydroxyl group. The reaction between the compound **100** and LDA resulted in the benzylic anion quenched with CO_2 to obtain homophthalic acids **101**. In the presence of DCC, coupling with Meldrum's acid and then heating with *tert*-butyl alcohol in benzene at reflux temperature gave **102** including the ketoester. Lactonization was achieved by usage of LDA, through an intermediate dianion, which provided the isocoumarin **103**. The compound **104** was formed by the ester enolate alkylation with methyl iodide in the presence of LDA. The product was subjected to sequential *tert*-butyl ester cleavage with HCl/isopropyl alcohol and ethoxymethyl ether removal by the treatment of TFA and finally, NM-3 **105** was obtained (Scheme 24).

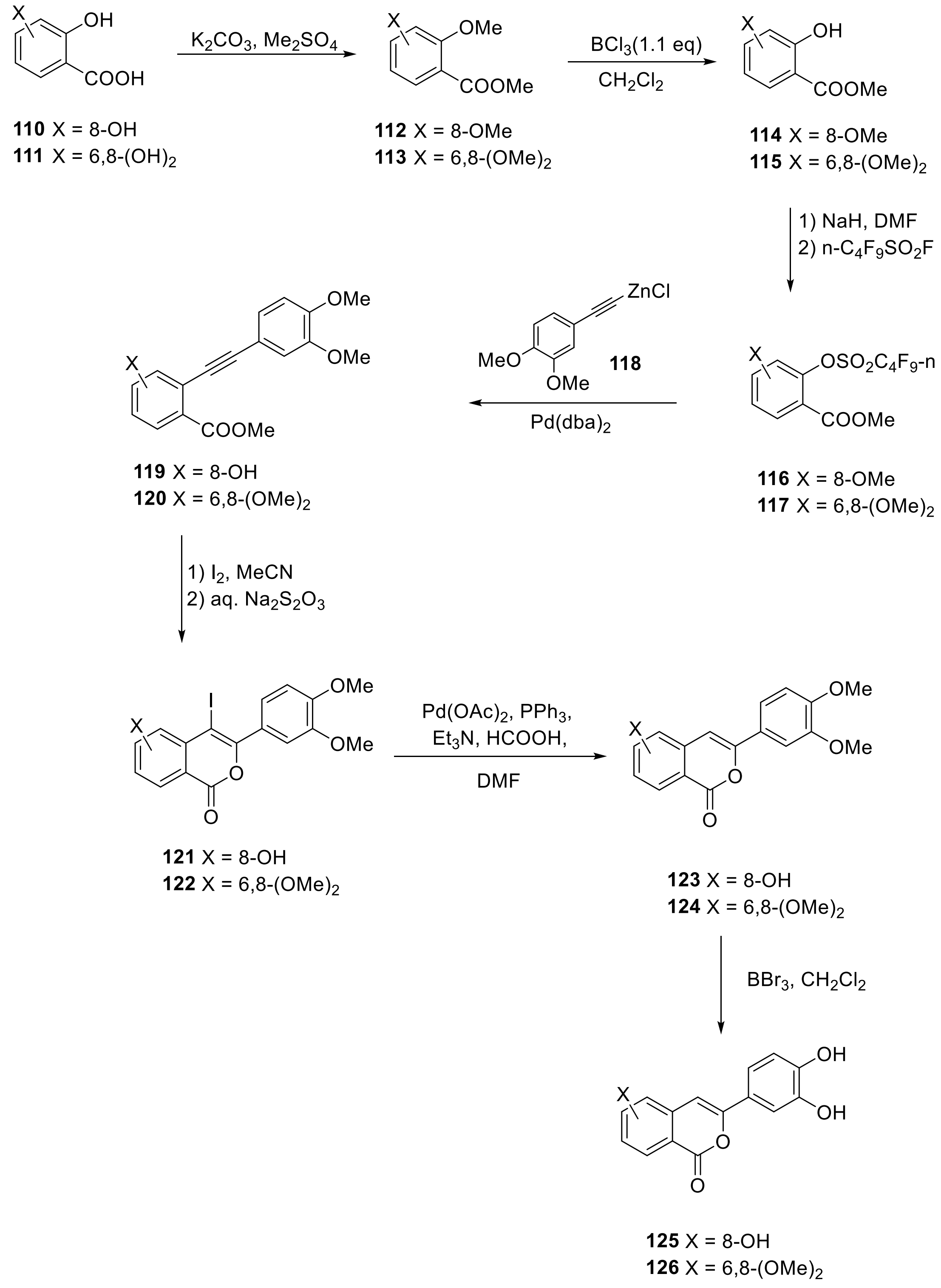


Scheme 24

In 2015, Li and coworkers demonstrated the sequential combination of the Passerini three-component reaction with aldol condensation starting from low-cost and readily accessible 2-formylbenzoic acid **106** and isocyanide **107** with arylglyoxals **108** (Scheme 25).[58]



Scheme 25

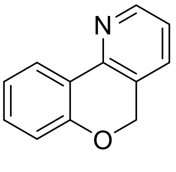


Scheme 26

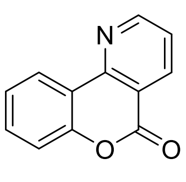
Thunberginol A **125** and B **126** are important antimicrobial, antiallergic and anticancer isocoumarines isolated from Hydrangea Dulcis Foluim.[59] Rossi *et al.* designed a synthetic pathway for the synthesis of these two natural isocoumarines by iodolactonization of methyl-2-(arylethynyl)benzoic acids, **110** and **111**.[60] They firstly converted the hydroxyl groups to methoxy groups to obtain **112** and **113**. After that, *o*-hydroxy esters **114** and **115** were obtained by the usage of 1.1 equivalent of BCl_3. Formed esters **114** and **115** were reacted with NaH in DMF followed by treatment with perfluoro-1-butanesulfonyl fluoride to provide **116** and **117** in high yield. Then, these nonaflates **116** and **117** were reacted with excess of 3,4-dimethylethynyl zinc chloride **118** in the presence of Pd_2(dibenzylideneacetone)$_3$ and 1,1′-bis(diphenylphosphino)ferrocene to obtain the compounds **119** and **120**. Reaction between these esters and iodine in acetonitrile followed by the treatment with aqueous sodiumbisulfite resulted in the formation of 4-aryl-3-iodoisocoumarin **121** and **122**. In the following step, iodine was replaced with hydrogen and then *O*-demethylation was achieved with BBr_3 giving the isocoumarines thunberginol A **125** and B **126**. Both of these compounds were found to be significantly active in the NCI 3-cell line (Scheme 26).

2.1.2 Chromenopyridine and Chromenopyridinone

Chromenopyridine **127** and chromenopyridinone **128** are heterocyclic compounds with a 2*H*-chromene ring and a 2*H*-chromen-2-one ring fused to a pyridine ring are well-known for their pharmacological properties, such as antimicrobial,[61,62] antiinflammotory,[61] antibacterial,[63,64] antifungal,[64] and anticancer[65] activities.

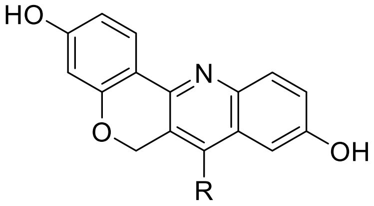


127



128

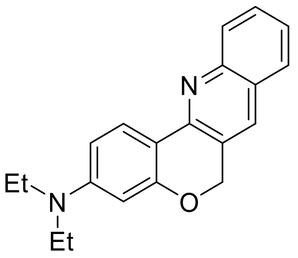
In addition to these activities, Vu and coworkers identified the 6*H*-chromeno[4,3-*b*]quinolines **129** as a new series of estrogen receptor β-selective ligand,[66] which was developed by rigidifying the 2-phenylquinoline framework.



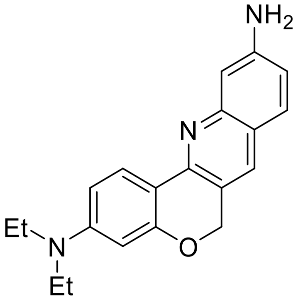
6*H*-Chromeno[4,3-*b*]quinoline
129

Cheng *et al.* reported a novel series of small chromene-based TNF-α inhibitors.[67] Tumor Necrosis Factor α, TNF-α, is a pro-inflammatory cytokine secreted by a variety of cells, including monocytes and macrophages, in response to many inflammatory stimuli or external cellular stress. Macromolecular TNF-α inhibitors have been shown to be useful for the treatment of autoimmune and inflammatory diseases. They were approved for reducing the sign and symptom of moderate to severe rheumatoid arthritis, psoriatic arthritis, and Crohn's disease.[68,69]

Furthermore, chromeno[4,3-b]quinoline and chromene derivatives were found to have other activities, such as fluorescent pH sensors. Lin *et al.*[70] successfully synthesized two chromenoquinoline derivatives **130**, **131** and studied their photophysical properties. They observed that compounds **130** and **131** with electron donating group have pKa values of 4.38 and 6.27, respectively. The favorable features of the sensor **131** include large emission ratios, high selectivity, and good reversibility. Significantly, the sensor **131** can be employed as a ratiometric fluorescent pH sensor for monitoring pH variations from neutral to acidic conditions in living cells.

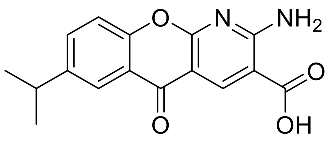


130



131

Amlexanox **132** is an example of an approved drug containing a chromeno[2,3-b]pyridine framework, which is a commonly prescribed anti-allergic,[71] and antiinflammatory properties.[72] It has been used for treatment of asthma and aphthous ulcers.[73] Together with its activity on nonsense mutation containing genes, the relative safety of amlexanox and its current use as an oral treatment of asthma.

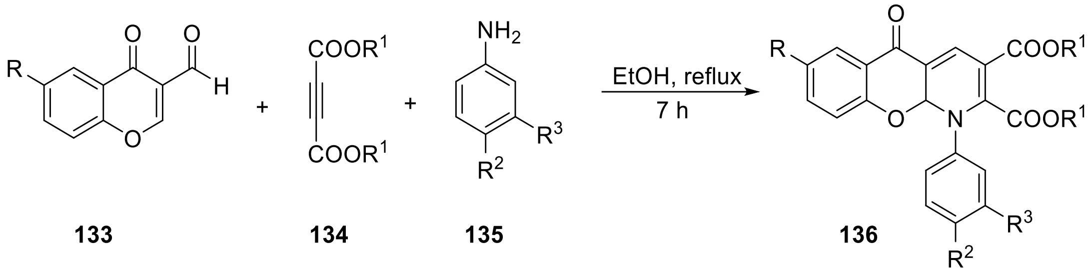


Amblexanox

132

2.1.2.1 The Synthesis of Chromenopyridine and Chromenopyridinone

An efficient and straightforward method for the synthesis of chromeno[2,3-b]pyridines **136** via the catalyst-free, three-component condensation of 3-formylchromones **133**, dialkyl acetylenedicarboxylate (**134**), and amines **135** was reported by Bazgir and co-workers.[74] They obtained different derivatives in good yields (70-86%) (Scheme 27).

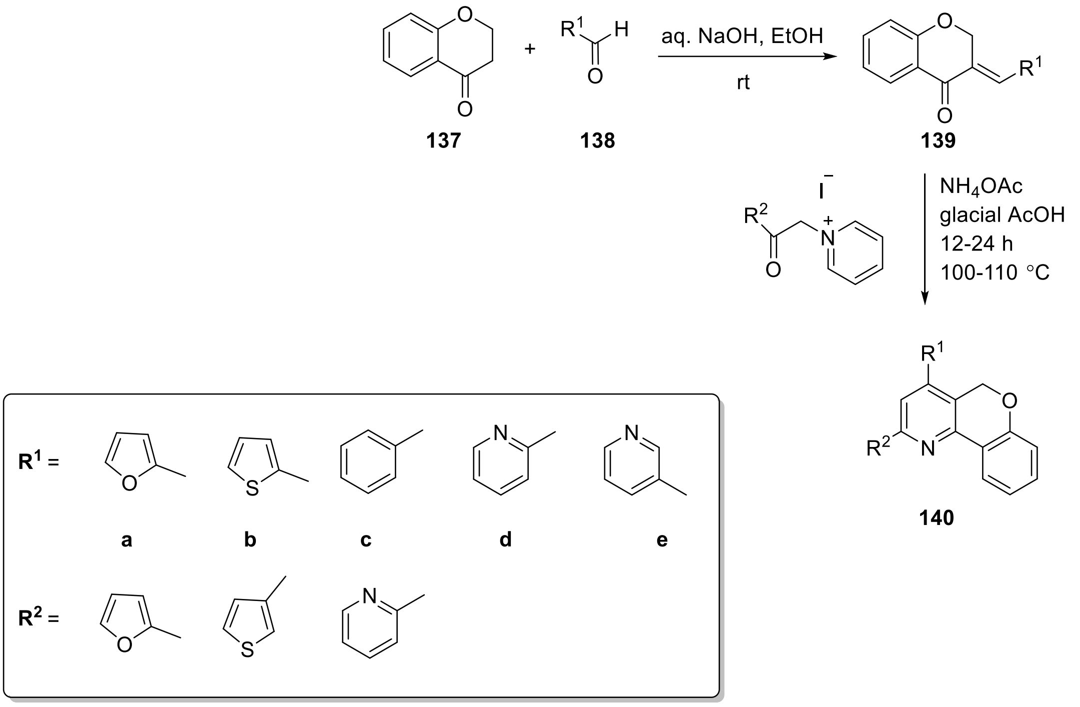


133 **134** **135** **136**

R = H, Cl or Me
R^1 = Me, Et or *t*-Bu
R^2 = H, OMe, Cl or Me
R^3 = H or Me

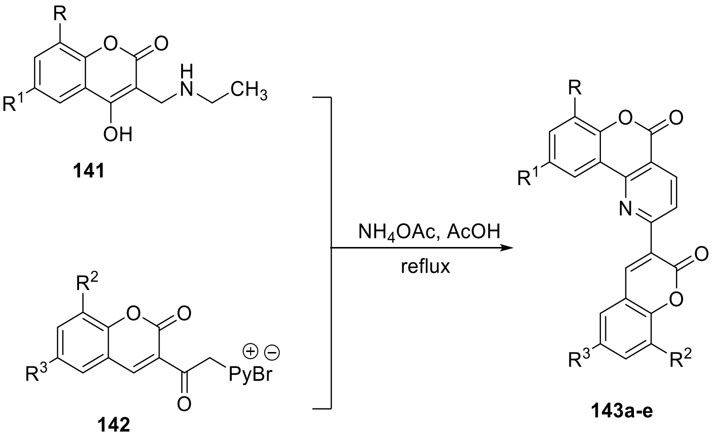
Scheme 27

Lee and co-workers synthesized a lot of chromenopyridine derivatives **139** and evaluated for topo I and II inhibitory activities along with cytotoxicity against several human cancer cell lines. Some of these derivatives displayed significant topo I inhibitory activity, and some of them exhibited moderate topo II inhibitory activity. Compounds having furanyl, phenyl and pyridinyl substituents **140a**, **140c**, **140e** exhibited strong cytotoxicity (Scheme 28).[75]



Scheme 28

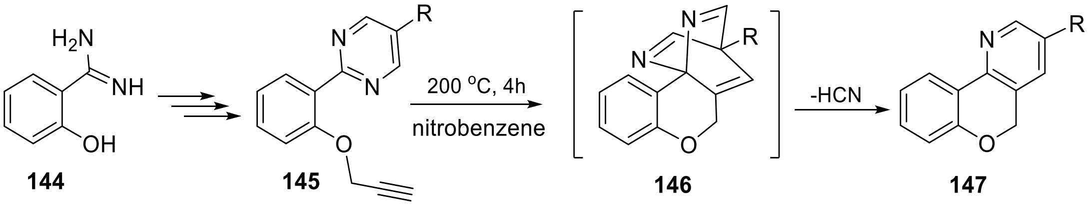
In 2013, Patel and coworkers developed a highly efficient and practical route for the synthesis of 2-(2-oxo-2*H*-chromen-3-yl)-5H-chromeno[4,3-*b*]pyridin-5-ones (**143**). They studied their antimicrobial activities and found that compounds **143a-e** were the most efficient members of the series (Scheme 29).[76]



	R	**R^1**	**R^2**	**R^3**
143a	H	CH$_3$	H	H
143b	H	CH$_3$	H	Benzyl
143c	CH$_3$	H	H	Benzyl
143d	H	Cl	H	Benzyl
143e	H	Cl	OCH$_3$	H

Scheme 29

Plas and coworkers have constructed chromenopyridinone skeleton **147** by using [4 + 2] cycloaddition reaction.[77] The intramolecular [4 + 2] Diels−Alder cycloaddition reactions play a very important role in the design of heterocyclic scaffolds. It requires efficient linking of the two reacting moieties. According to their methodology, the compound **145**, synthesized from *o*-hydroxybenzamidine **144** in a few steps, undergo an intramolecular Diels−Alder reaction and a subsequent retro-Diels−Alder reaction to yield the chromenopyridines **147** (Scheme 30).

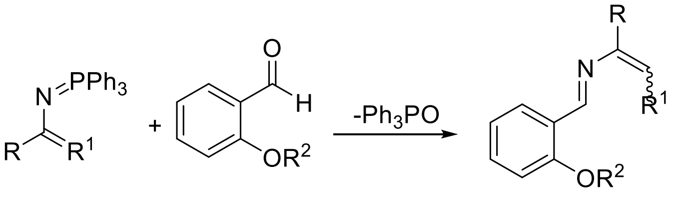


144 **145** **146** **147**

R = H, Cl, Ph

Scheme 30

Palacios et al.[78] reported the synthesis of a variety of tricyclic and tetracyclic condensed chromenopyridines using an aza-Wittig reaction of *N*-vinylic phosphazenes with functionalized aldehydes. In their methodology, they firstly investigated the readily available 2-allyloxybenzaldehyde (**149a**) and 2-propargyloxybenzaldehyde (**149b**) for aza-Wittig reaction as a model system. These aldehydes were reacted with *N*-vinylic phosphazenes **148a-f** in refluxing chloroform to form electronically neutral azadienes **150a** and **150b** (Scheme 31).



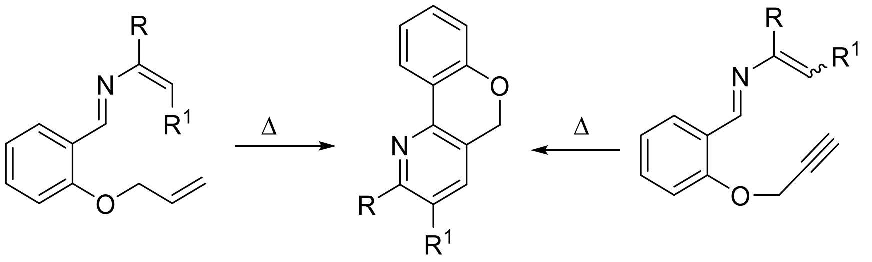
148a-f **149a-b**

150a R^2 = allyl
150b R^2 = propargyl

148a : R = 2-furyl, R^1 = Ph (E)
148b : R = 2-thienyl, R^1 = Ph (E)
148c : R = Ph, R^1 = Ph (E)
148d : R = 3-pyridinyl, R^1 = Ph (E)
148e : R = H, R^1 = Ph (E, Z)
148f : R = H, R^1 = CH_3 (E, Z)

Scheme 31

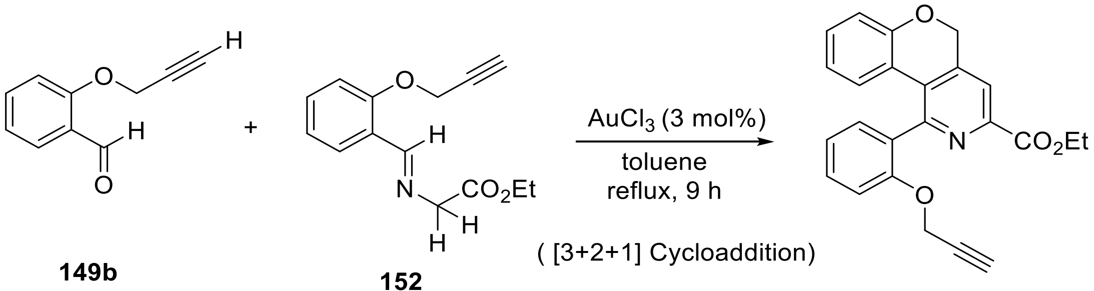
After formation of diene and dienophile system, heating compounds **150a** and **150b** at reflux temperature of xylene afforded polyheterocyclic compounds **151** through simultaneous formation of two rings (Scheme 32).



150a **151** **150b**

Scheme 32

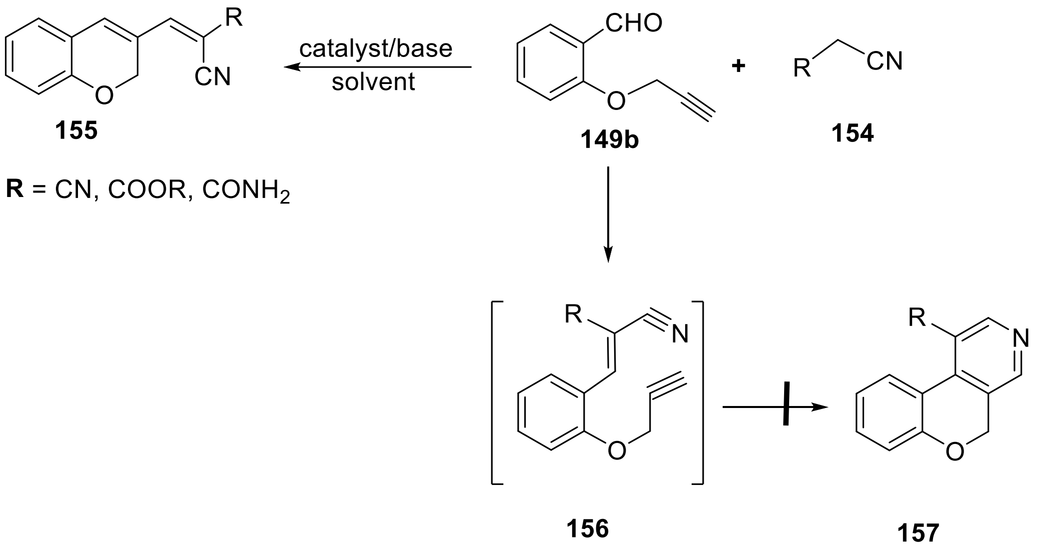
More recently, a new [3 + 2 + 1] cycloaddition strategy was demonstrated using an aldehyde **149b**, an aldimine of a glycine ester **152**, and a terminal triple bond with $AuCl_3$ catalyst to generate novel fused-tricyclic heterocycles such as 5*H*-chromeno[4,3-*c*]pyridine **153** (Scheme 33).[79]



149b **152** **153**

Scheme 33

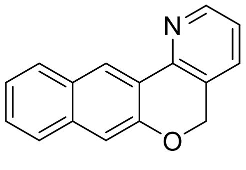
Recently, Singh et al.[80] attempted to prepare 5*H*-chromeno[3,4-*c*]pyridine derivatives **157** by adopting an established strategy related to the domino Knoevenagel/Diels−Alder reaction, involving *O*-propargyl salicylaldehyde **149b** and malononitrile or ethyl cyanoacetate or cyanoacetamide (**154**) (Scheme 34). Unfortunately, instead of formation of the expected product **157**, the product **155** was formed.



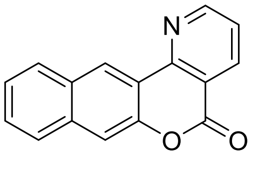
Scheme 34

2.1.3 Benzochromenopyridine and Benzochromenopyridinone

Benzochromenopyridines **158** and benzochromenopyridinones **159** contain benzene fused chromenopyridines and chromenopyridinones. Since molecular scaffold of these compounds contain both coumarin and pyridine unit, they have some medicinal properties such as antiallergic,[81] and antimicrobial[82] activities.



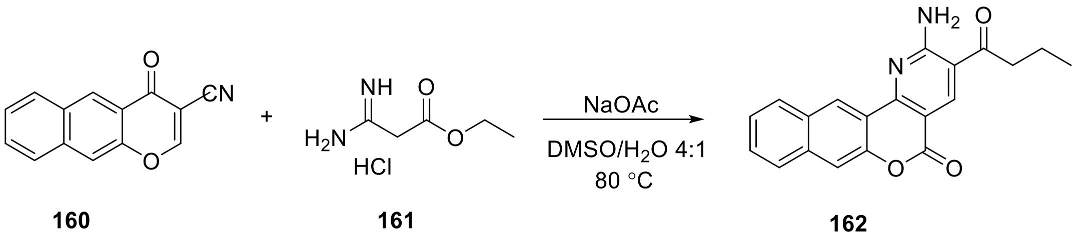
158



159

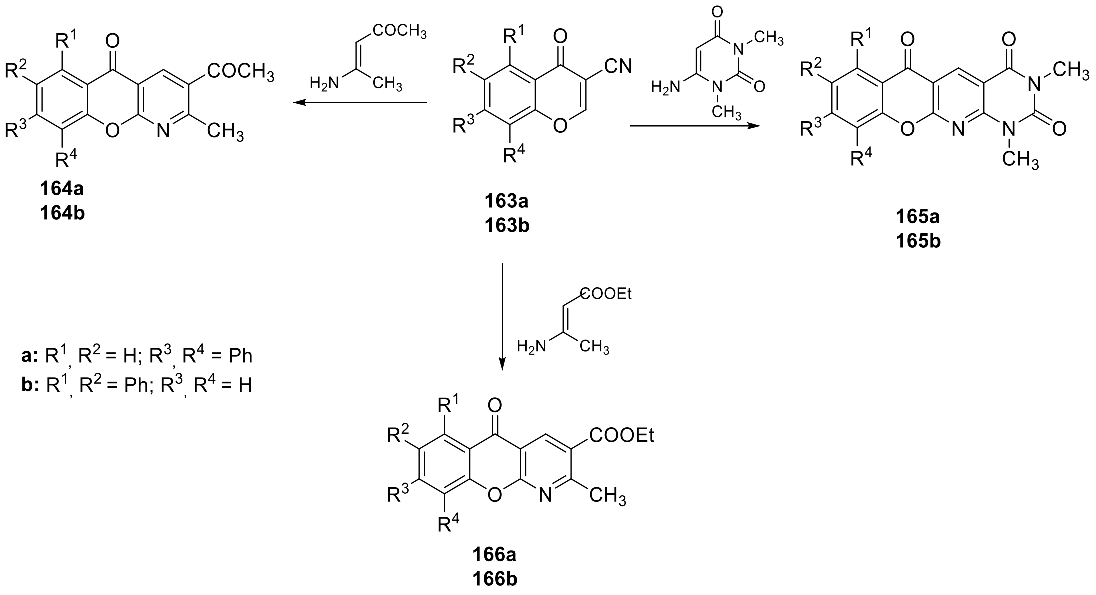
2.1.3.1 The Synthesis of Chromenopyridine and Chromenopyridinone

The work for systematic synthesis of pyridine-fused coumarins is quite rare although the skeleton is so important for organic and medicinal chemistry. For example, Yang *et al.*[83] synthesized pyridine-fused coumarins, including benzochromenopyridines **162**, via a cascade reaction from chromone derivatives **160** in an environmentally friendly aqueous medium. This cascade reaction involves a chemoselective Michael addition–heterocyclization-intramolecular cyclization sequence (Scheme 35).



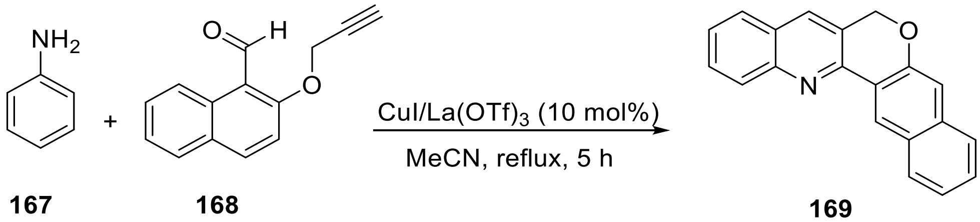
Scheme 35

In 2006, Sallam and coworkers synthesized a number of new benzo[*h*]- and benzo[*f*]chromeno[2,3-*b*] pyridine-5-ones derivatives **164-166** starting from benzo[*h*]- and benzo[*f*]-chromone-carbonitriles **163a** and **163b** (Scheme 36).[84]



Scheme 36

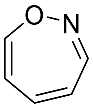
Benzochromenoquinolines include benzochromenopyridine skeletons and only a few reports are available in the literature for the synthesis of 6*H*-chromeno[4,3-*b*]quinolines. Nagarajan *et al.*[85] reported the synthesis of 6*H*-chromeno[4,3-*b*]quinolines. In their synthetic methodology, the mixture of copper(I) iodide and lanthanum triflate were used as an efficient catalyst. Especially, 8*H*-benzo[5,6]chromeno[4,3-*b*]quinoline (**169**) was synthesized starting from aniline (**167**) and *O*-propargylated naphthlaldehyde **168** (Scheme 37).



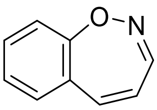
Scheme 37

2.1.4 Benzoxazepines

Oxazepine **170** is seven-membered unsaturated heterocycle containing five carbon atoms, one nitrogen and one oxygen atom (these atom can be adjacent or not), and three double bonds. Benzoxazepine **171** is a bicyclic heterocyclic compound that composed of a benzene ring fused to an oxazepine ring.



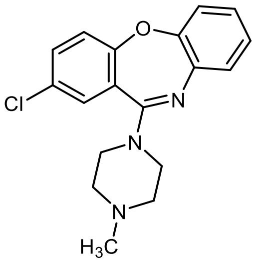
170



171

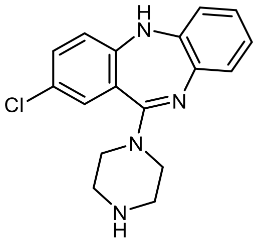
The compounds having oxazepine skeleton shows some pharmacological properties, such as antipsychotic drugs,[86] anticancer,[87] and anti-tumor activities[88].

Loxazepine **172** is a typical neuroleptic that shows great structural and functional homology to a typical antipsyshotic clozapine **173** which belongs to class of dibenzodiazepines.[89] It is used primarily in the treatment of schizophrenia. Loxazepine may be metabolized by N-methylation to amoxapine **174** which tetracyclic antidepressant of the dibenzoxapine family.



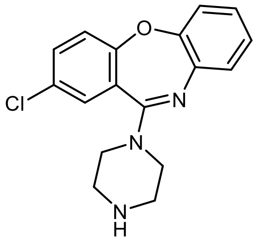
Loxapine

172



Clozapine

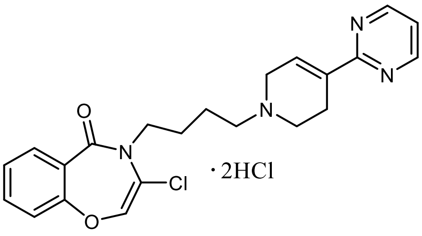
173



Amoxapine

174

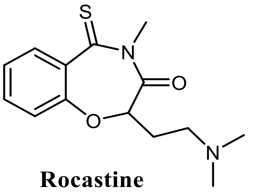
Piclozotan (SUN-N4057)[90] **175** is a selective 5-HT$_{1A}$ receptor agonist which possess 1,4-benzoxazepine scaffold and neuroprotective effects in animal studies.



piclozotan

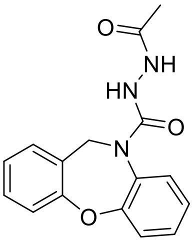
175

Rocastine (AHR-11325) **176** which also contains benzoxazepine skeleton, has a rapid-acting, potent, nonsedating antihistamine activity.[91]



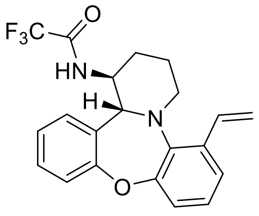
Rocastine

176

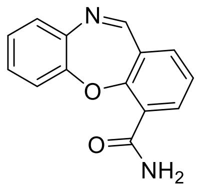


SC-19220

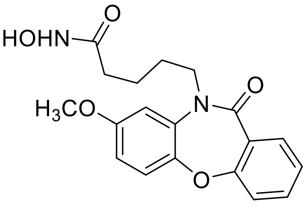
177



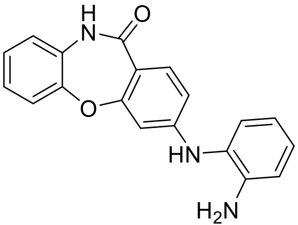
178



179



180

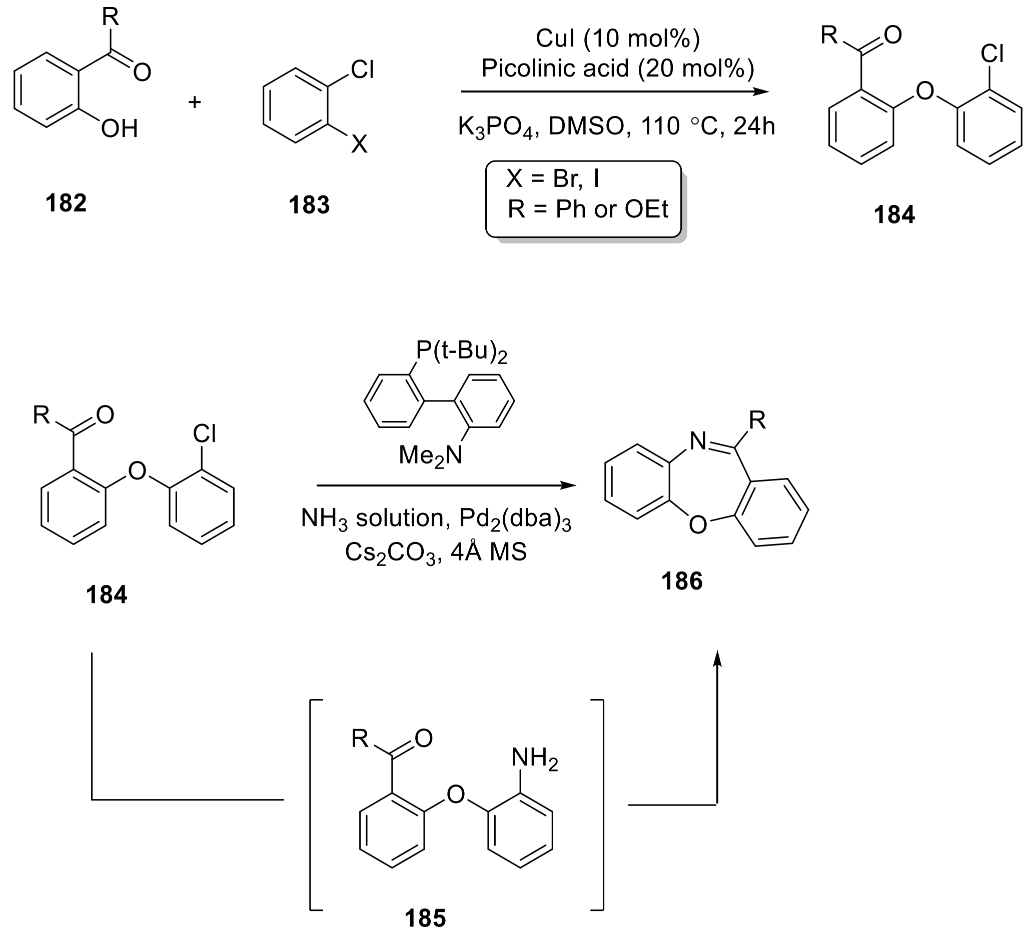


181

In addition to these, SC-19220[92] **177** is used as prostaglandin receptors antagonists and also the utility of dibenzo[*b*,*f*][1,4]oxazepines has recently extended to the design of potent progesterone receptor antagonists **178**,[93] TRPA1 ion channel modulators **179**,[94] and histone deacetylase inhibitors **180**,[95] p38 MAP kinase inhibitors **181**.[96]

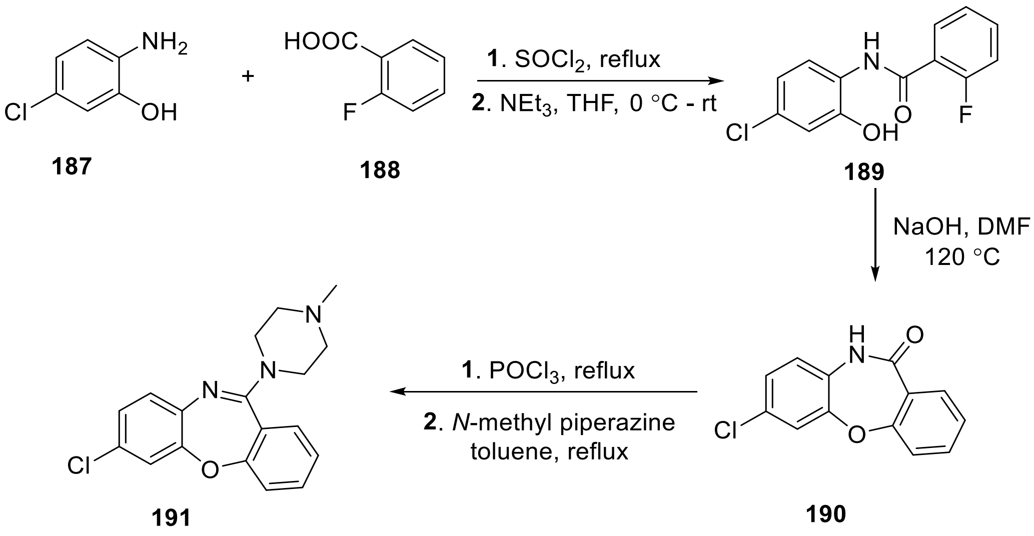
2.1.4.1 The Synthesis of Benzoxazepines

Buchwald and coworkers[97] designed a practical and general method for the Pd-catalyzed synthesis of dibenzodiazepines and dibenzoxazepines that are important class of heteroaromatic compounds. Their synthetic strategy includes firstly the formation of the precursor **184** starting from phenol **182** with aryl chloride **183** in the presence of picolinic acid, CuI, and K_3PO_4 in DMSO. After that, in the presence of catalytic amount of palladium, the precursor **184** generated intermediate **185** via cross-coupling with ammonia and then the corresponding dibenzoxazepine **186** was obtained (Scheme 38).



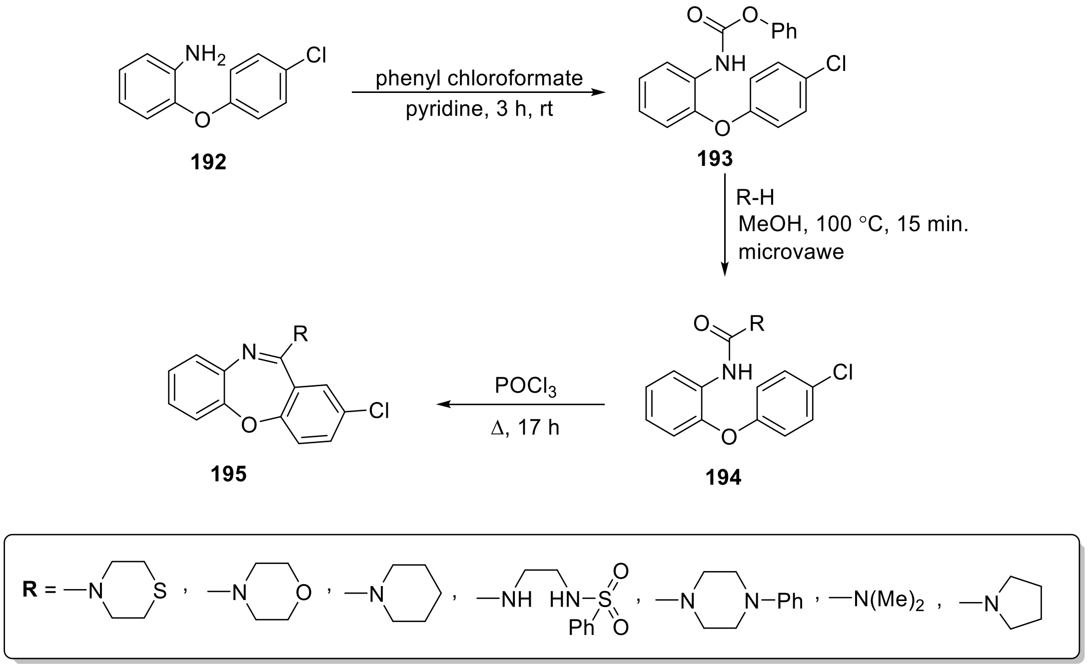
Scheme 38

In 2006, (*E*)-7-chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b*,*f*][1,4]oxazepine (**191**) was synthesized by Leurs and coworkers.[98] They obtained also benzodiazepine derivatives. They evaluated biological activities of the formed products. According to their results, dibenzoxazepine derivative **191** is a potent H4R agonist. In their methodology, firstly, substituted floro acid **188** was converted to the corresponding acyl chloride by using $SOCl_2$, which was then added to a solution of chlorinated *o*-aminophenol **187** and triethylamine in THF to form the respective amide intermediate **189**. Ring closure of the amide was done by using NaOH in DMF. $POCl_3$ was used to convert the benzoxazepines **191** to iminochlorides which could then reacted with N-methyl piperazine (Scheme 39).



Scheme 39

Dibenzo[*b*,*f*][1,4]oxazepine derivatives possess diverse pharmacological activities. Zaware *et al.*[99] reported a new method for synthesis of dibenzo[*b*,*f*][1,4]oxazepine derivatives **195** in 2014. Seven of them were designed as analogs of the antipsychotic drug loxapine **172** and antidepressant amoxapine **174**.

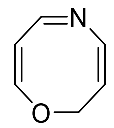


Scheme 40

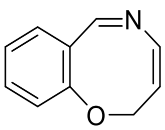
The key transformations include generation of a carbamate intermediate **193** using phenyl chloroformate. A microwave-induced transformation of this intermediate to various urea derivatives **194** was performed, and as a result of the subsequent phosphorous oxychloride induced cyclocondensation, final products **195** was obtained (Scheme 40).

2.1.5 Benzoxazocines

Oxazocine **196** is eight-membered heterocycle containing six carbon atoms, one nitrogen and one oxygen atom. Benzoxazocine **197** is also a bicyclic heterocyclic compound that composed of a benzene ring fused to an oxazocine ring.



oxazocine
196

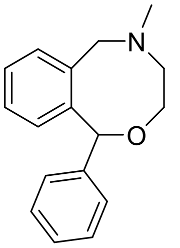


benzoxazocine
197

Dibenzoxazocine framework constitutes an important structural motif present in biologically active molecules. For example, their inhibitory activity against hepatitis

C,[100] as well as CNS and antithrombotic activity,[101] atropisomeric property and the NK1 antagonist activity[102] are recognized.

Nefopam hydrochloride is a potent analgesic compound commercialized in most of Western Europe for over 20 years. Nefopam **198** possesses a profile distinct from that of opioids or anti-inflammatory drugs. Fernandez-Sanchez and coworkers[103] reported that the analgesic nefopam hydrochloride can reduce calcium influx and effectively prevent intracellular formation of cyclic guanosine monophosphate (cGMP) and neuronal death following the activation of voltage-sensitive calcium channels in cultured cerebellar neurons. Their results are consistent with a presynaptic action of nefopam that may be of interest in reducing the excessive release of endogenous glutamate involved in neurological and neuropsychiatric disorders.[103]

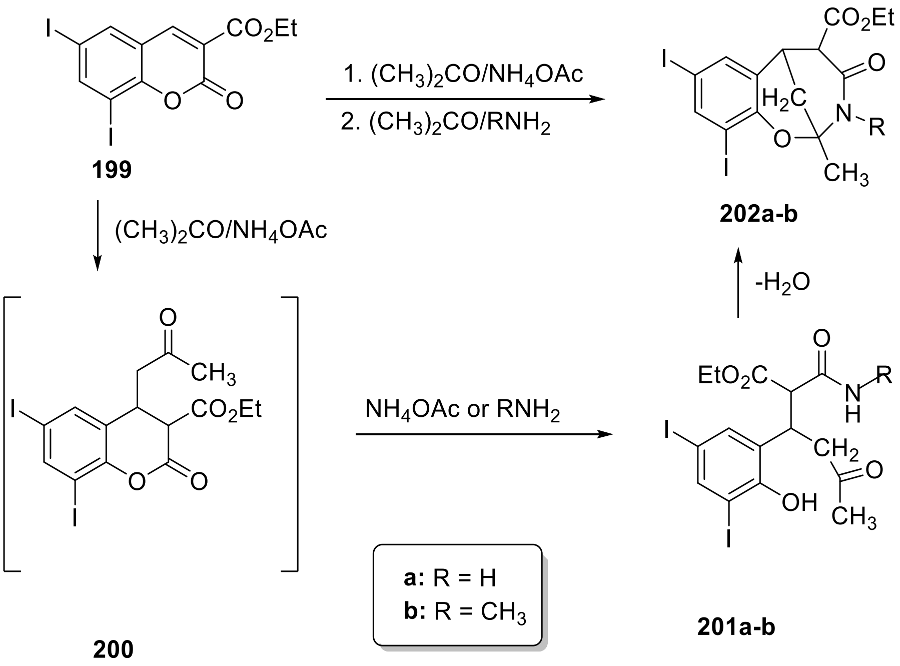


Nefopam

198

2.1.5.1 The Synthesis of Benzoxazocine

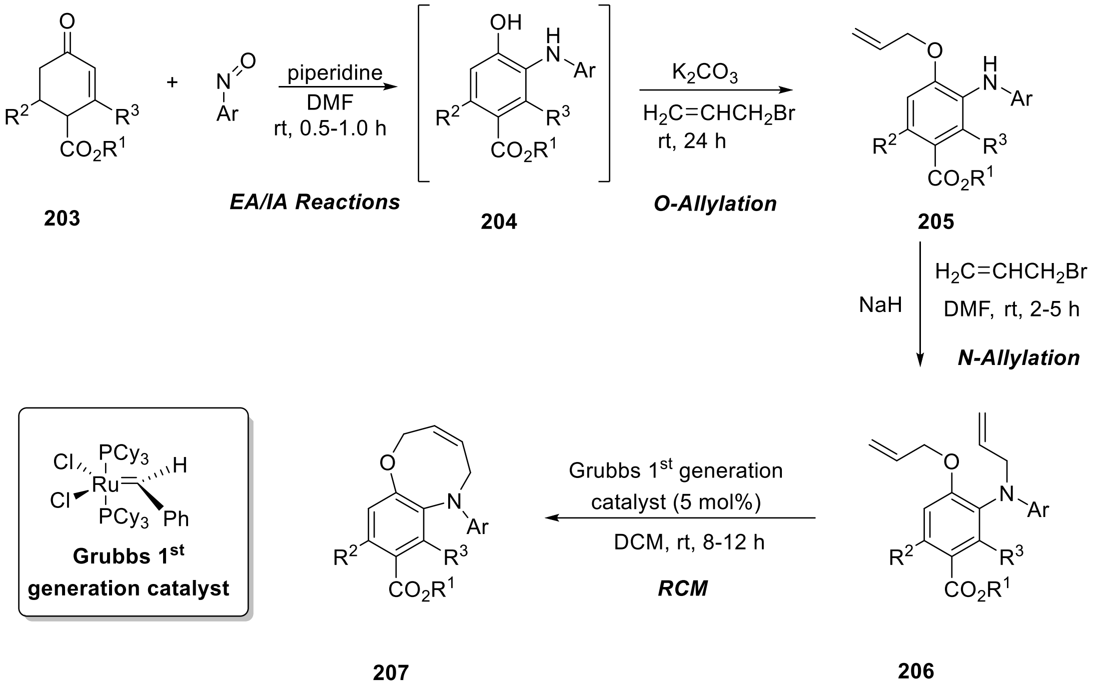
The benzoxazocine derivatives have received considerable attention due to their pharmacological properties. In 2011, Wahab *et al.* [104] synthesized diiodocoumarin and benzoxazocine derivatives and evaluated their biological activities. According to their methodology, reaction of **199** with acetone in the presence of NH_4OAc or methylamine at room temperature for 7 days gave 1,3-oxazocine-5-carboxylate derivatives **202a** and **202b**. The formation of **202** indicates that the activated methylene compounds attack at the olefinic bond in **199** under Michael reaction conditions to yield a cyclic product, which followed hydrolysis by NH_3 or $MeNH_2$ and cyclization through the elimination of H_2O (Scheme 41).[104]



Scheme 41

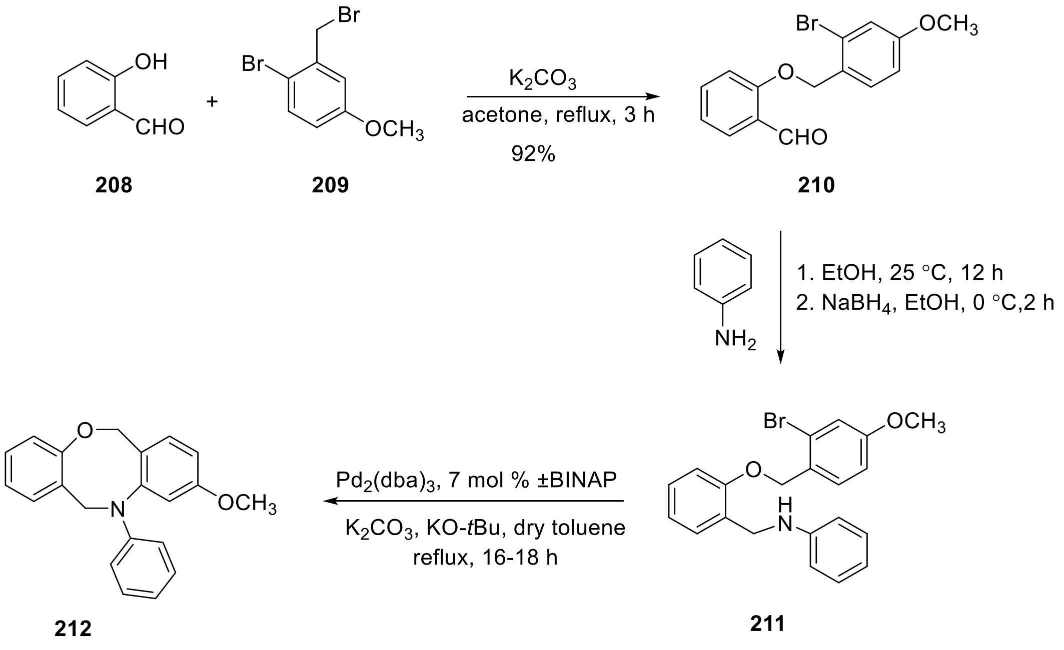
They found that these oxazocines **202** have an antimicrobial activity greater than that of the standard antibiotic ampicillin or the standard antifungal claforan.

The diversity-oriented synthesis of oxygen and nitrogen containing heterocycles represents an important task because of the widespread occurrence of such structural motifs and their use in drug delivery. For example, substituted benzoxazocines and pharmaceutically acceptable salts may be useful as analgesic agents and for the treatment of emesis, depression, posttraumatic stress disorders, attention deficit disorders, obsessive compulsive disorders, sexual dysfunction and centrally acting skeletal muscle relaxants.[105,106] In 2009, Ramachary *et al.*[107] reported for the first time the organocatalytic approach to the high yielding synthesis of functionalized benzoxazocines **207** from a three-step sequence using amine/potassium carbonate/sodium hydride/ruthenium catalysis through cascade enamine amination/iso-aromatization/*O*-allylation, *N*-allylation, and diene or enyne metathesis as key steps starting from commercially available Hagemann's esters **203**, nitrosobenzenes, allyl bromide, secondary amine and Grubbs 1st generated ruthenium catalyst (Scheme 42).



Scheme 42

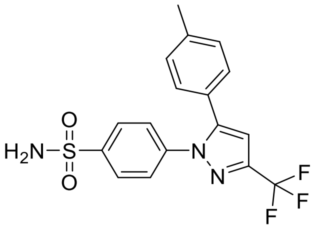
A short and high yield route to synthesize dibenz[*b*, *f*][1, 5]oxazocines **212** has been developed using Pd catalyzed intramolecular cycloamination reaction by Chattopadhyay *et al.*[108] Receptor binding assay using $[^{125}I]$-dynorphin demonstrated that one of the derivative showed selective κ-opioidergic property. In terms of their optimized synthetic route, the starting material **210** was prepared by benzylation of commercially available salicylaldehyde **208** with substituted 2-bromobenzyl bromide **209** in the presence of anhydrous potassium carbonate. Imine formation with aniline and subsequent $NaBH_4$ reduction in ethanol afforded the desired amines in good yield. Among the various catalysts used in the synthesis of dibenzoxazocines, Pd_2(di-benzylideneacetone)$_3$ gave the best result for the cyzlization step. Use of a proper base was also important to obtain good yield. They determined that the combined effect of KO-*t*Bu and K_2CO_3 produced significant increase in the yield. For the investigation of solvent effect, they used different solvents (THF, EtOH, toluene, 1,4-dioxane) and suggested that toluene was the best solvent of choice. Application of the reagents $Pd_2(dba)_3$, ±BINAP, and KO*t*-Bu + K_2CO_3 in toluene gave the desired product in 77% yield (Scheme 43).



Scheme 43

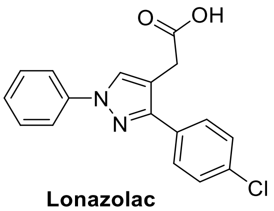
2.1.6 Pyrazoles

Pyrazoles are the heterocyclic organic compounds that contain a 5-membered ring having three carbon atoms and two adjacent nitrogen atoms. There are lots of examples which include pyrazole units as core structures in the pharmaceutical industry. Some molecules containing pyrazole skeleton show antiproliferative,[109] antitumor[110] and antibacterial[111] properties. The pyrazole ring is present as the core in a variety of leading drugs such as Celecoxib **213**, Lonazolac **214**, Rimonabant **215**.



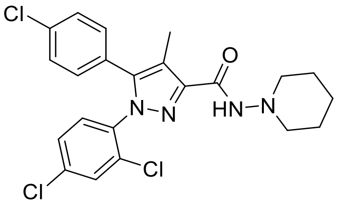
Celecoxib

213



Lonazolac

214



Rimonabant

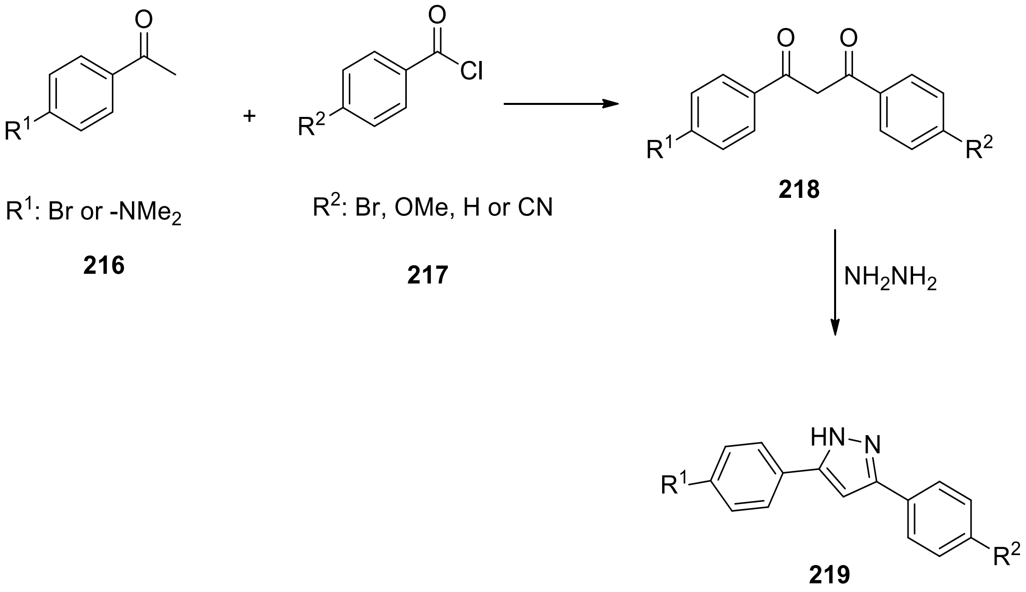
215

2.1.6.1 The Synthesis of Pyrazoles

Importance of the pyrazole based molecules because of their biological activities attracted high attention of scientists. The wide range of methods were developed for construction of substituted pyrazoles.[112] Generally, pyrazoles are synthesized by

- the reaction of 1,3-diketones with hydrazines,
- 1,3-dipolar cycloaddition of diazo compounds to alkynes and
- the reaction of α,β-unsaturated aldehydes and ketones with hydrazines.

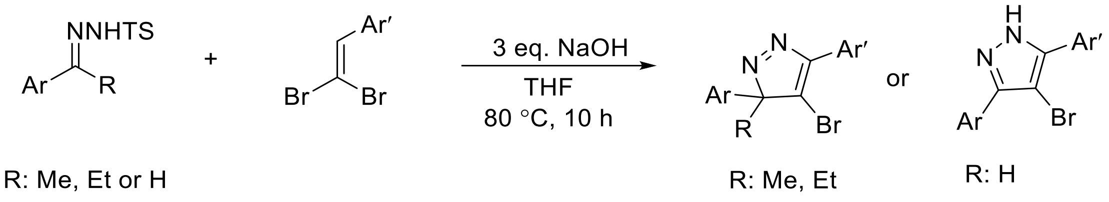
Example of the reaction of 1,3-diketones **218** with hydrazines was published by Heller and coworkers in 2006.[113] They firstly synthesized 1,3-diketones **218** as intermediates from ketones **216** and benzoyl chlorides **217** in the presence of LiHMDS. These diketones **218** were treated in situ with hydrazines to form pyrazoles **219** in good yields. Their methodology was extremely fast, general, and chemoselective (Scheme 44).



Scheme 44

One-pot synthesis of 3,5-diaryl-4-bromopyrazoles via 1,3-dipolar cycloaddition of diazo compounds and alkynyl bromides has been developed by Wei *et al.*[114] The diazo compounds and alkynyl bromides were generated in situ from tosylhydrazones and *gem*-dibromoalkenes, respectively. When they used ketone-derived hydrazones, 3,5-diaryl-4-bromo-3*H*-pyrazoles **222** were obtained and the isomerization products

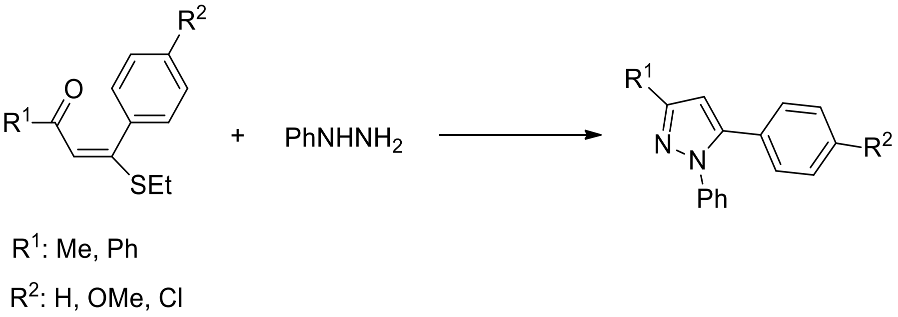
3,5-diaryl-4-bromo-1*H*-pyrazoles **223** were formed when they used aldehyde-derived hydrazones. The reaction exhibited high regioselectivity and good functional group tolerance (Scheme 45).



220 **221** **222** **223**

Scheme 45

Multisubstituted pyrazoles **226** were efficiently obtained by cyclocondensation of β-thioalkyl-α,β-unsaturated ketones (**224**) with hydrazines **225** in the presence of *t*-BuOK or HOAc in refluxing *t*-BuOH by Jin *et al.*[115] An one-pot synthetic protocol through tandem Liebeskind–Srogl cross-coupling/cyclocondensation using α-oxoketene dithioacetals as the starting materials was also realized for the same purpose. This methodology has exhibited exclusive regioselectivity for the target products **226**, generating no pyrazole tautomers (Scheme 46).



224 **225** **226**

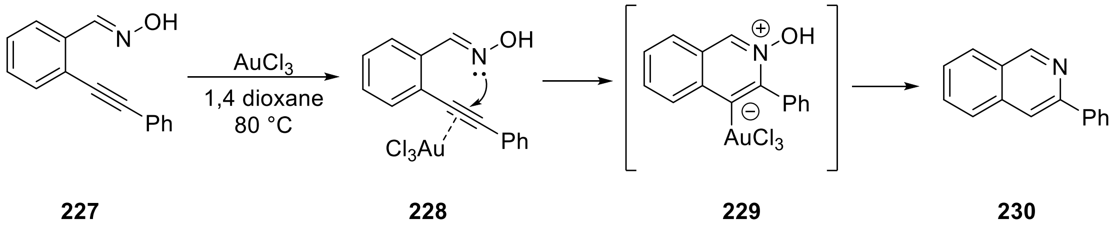
Scheme 46

2.1.7 Gold Catalyzed Alkyne Cyclization

Gold is a heavy metal in a group known as the transition metals. Among the relatively few gold compounds of practical importance are gold chloride, AuCl; gold trichloride, $AuCl_3$; and chlorauric acid, $HAuCl_4$. AuCl is in the +1 oxidation state and in the latter two, the +3 state. In recent years, there has been a revolution in the chemistry of gold.

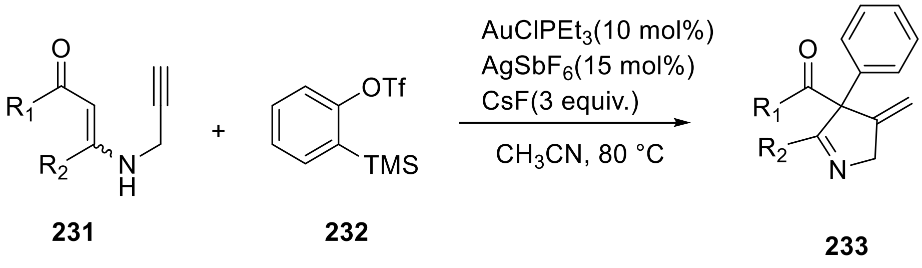
Nowadays, there is an amazingly generous chemistry of catalysis based on gold nanoparticles and complexes. Since the prediction was made that gold would be the best catalyst for the hydrochlorination of acetylene, there has been a spectacular growth in gold-based reactions of acetylenes.[116]

A number of synthetic methods for nitrogen containing heterocycles have been developed. Especially, transition metal catalyzed synthesis of heterocyclic compounds has been studied in last decade. For example, Reddy and coworkers reported that $AuCl_3$ catalyzed intramolecular cyclization reaction of *O*-alkynyloximes **227** in 1,4-dioxane at 80 °C to produce isoquinoline **230** derivative with excellent yield (Scheme 47).[117]



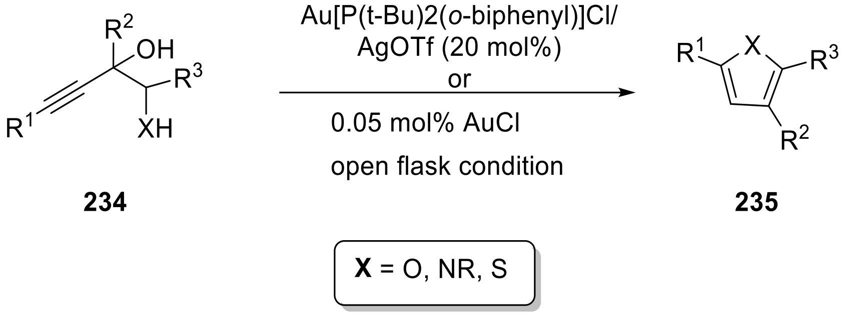
Scheme 47

Karunakar *et al.*[118] have developed a straightforward one pot synthesis of 3-methylene-1-pyrrolines **233** with quaternary stereocenter and exocyclic double bonds from the reaction between N-propargylic β-enaminones **231** and arynes **232** under different reaction conditions where they also used various catalysts. Highest yield for **233** was obtained while utilizing the combination of $AuClPEt_3$ (10 mol%) and $AgSbF_6$ (15 mol%) in CH_3CN at 80 °C (Scheme 48).



Scheme 48

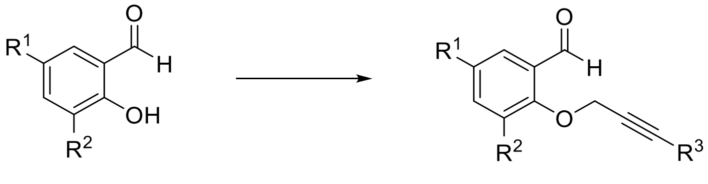
In 2009, Aponick and coworkers have developed an extremely mild and efficient method for the preparation of furans, pyrroles, and thiophenes **235** by gold-catalyzed dehydrative cyclizations.[119] The reactions were carried out by starting from very simple and readily available heteroatom-substituted propargylic alcohols **234**. The reactions are fast, high-yielding, and easy to apply, giving essentially pure aromatic heterocycles in minutes under open-flask conditions with catalyst loadings as low as 0.05 mol % (Scheme 49).[119]



Scheme 49

2.1.8 Aim of the Study

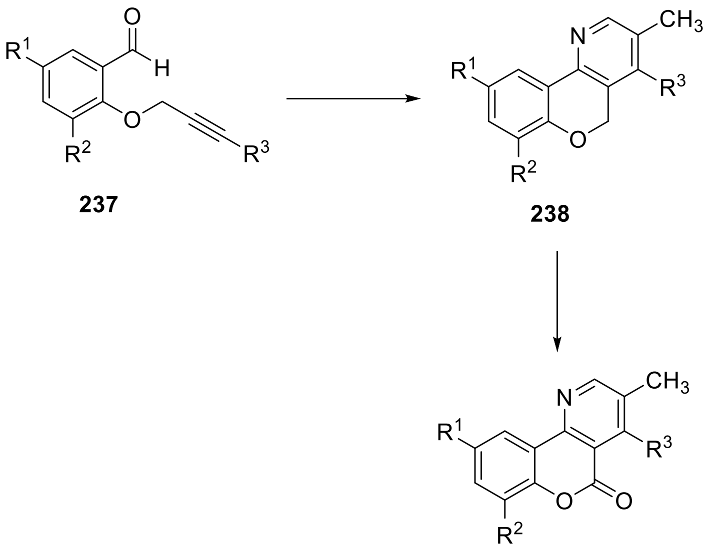
The aim of this part was the development of new synthetic methodologies for the synthesis of (benzo)chromenopyridinone, benzopyrazoloxazepine, and benzopyrazoloxazocine derivatives. We were interested in construction of these type of skeletons because their important pharmacological properties as well as for their fused structures. The construction of fused heterocycles are also important for the organic and pharmaceutical chemistry. Firstly, we focused on synthesis of chromenopyridinone derivatives **239**. For this purpose, we planned to start from substituted salicylaldehydes **236**. Firstly, *O*-propargylated salicylaldehydes **237** should be synthesized starting from the substituted salicylaldehydes **236** as the key compounds. Additionally, Sonogashira cross-coupling reaction can be used to get conjugated system with alkyne functionality (Scheme 50).



236 **237**

Scheme 50

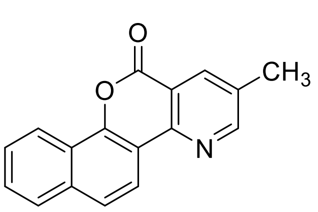
After getting the key compounds, we planned to incorporate second propargyl group into the molecule using propargylamine and then apply intramolecular cyclization reaction. At the end of these reactions, we expect to synthesize tricyclic chromenopyridine derivatives **238** via [4+2] intramolecular heterocyclization. Furthermore, we were interested in the synthesis of chromenopyridinones **239**. To obtain these compounds, chromenopyridine **238** may be submitted to oxidation reaction (Scheme 51).



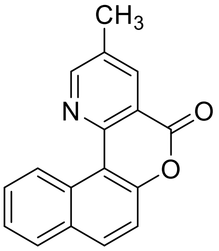
237 **238** **239**

Scheme 51

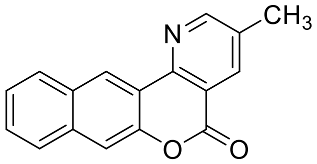
To explore the scope of the reaction, isomeric hydroxynapthaldehydes can also be evaluated. Same methodology will be applied to these system to form tetracyclic benzochromenopyridinone derivatives **240-242** (Scheme 53).



240



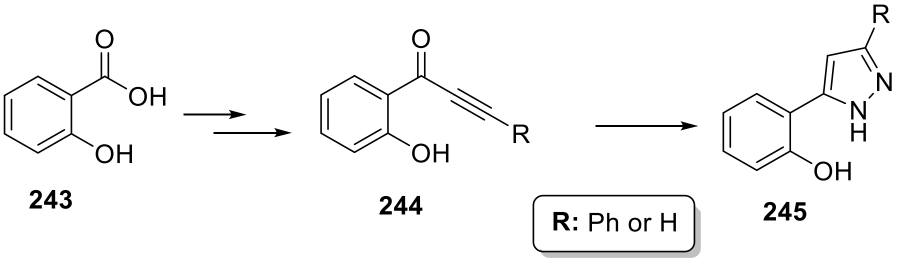
241



242

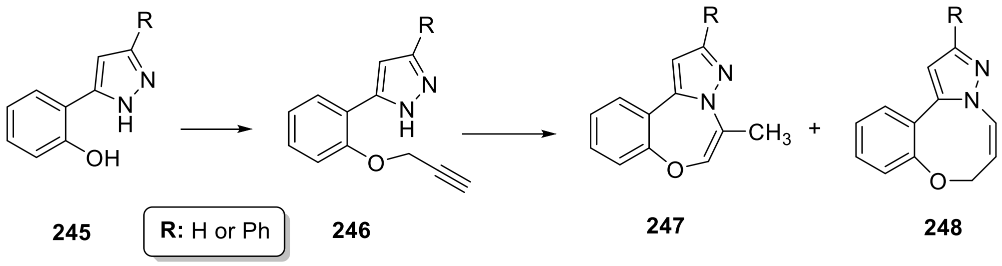
Scheme 52

In the second part of this thesis, we were interested in design of benzopyrazoloxazepines which contain fused benzene, oxazepine and pyrazole ring. In the literature, there are a lot of examples showing important activities of benzoxazepine and pyrazole ring. Therefore, we planned to combine these two skeletons. We thought that this combination might increase the biological activities of compounds. For this purpose, we firstly planned to construct pyrazole skeleton that connected to benzene ring starting from salicylic acid **243** (Scheme 53).



Scheme 53

After that, the compounds having pyrazole unit should be reacted with propargyl bromide in the presence of a base to give *O*-propargylated compounds **246**. The compounds having propargyl and NH group as a nucleophilic center will be treated with gold salts or base to achieve an intramolecular cyclization reaction. At the end of this reacton we expect the formation of tricycles **247** and **248** with interesting structures (Scheme 54).



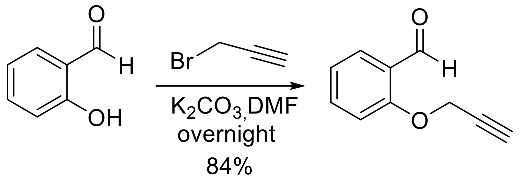
Scheme 54

2.2 RESULTS AND DISCUSSION

2.2.1 Synthesis of Chromenopyridinone Derivatives

2.2.1.1 The Synthesis of *O*-propargylated Aldehydes

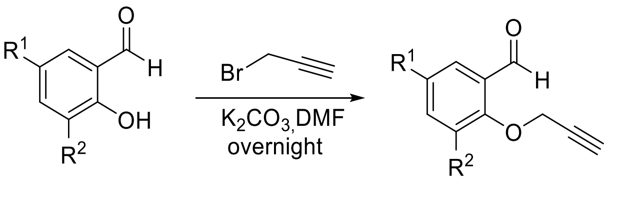
For the construction of the chromenopyridine skeleton, firstly we synthesized 2-(prop-2-yn-1-yloxy)benzaldehyde (**149b**) starting from salicylaldehyde **208**. Treatment of salicylaldehyde **208** with propargyl bromide in the presence of potassium carbonate afforded the compound **149b** in 84% yield (Scheme 55).



208 **149b**

Scheme 55

For the derivatization, we used substituted salicylaldehydes. Same methodology was appllied to the aldehydes, **249** and **250**, having substituent at *meta*-position referred to aldehyde functionality. Corresponding *O*-proporgylated products **251** and **252** were obtained in yields of 97% and 92%, respectively (Scheme 56).



249: R^1= Br, R^2 = H
250: R^1= H, R^2 = OCH_3

251: R^1= Br, R^2 = H
252: R^1= H, R^2 = OCH_3

Scheme 56

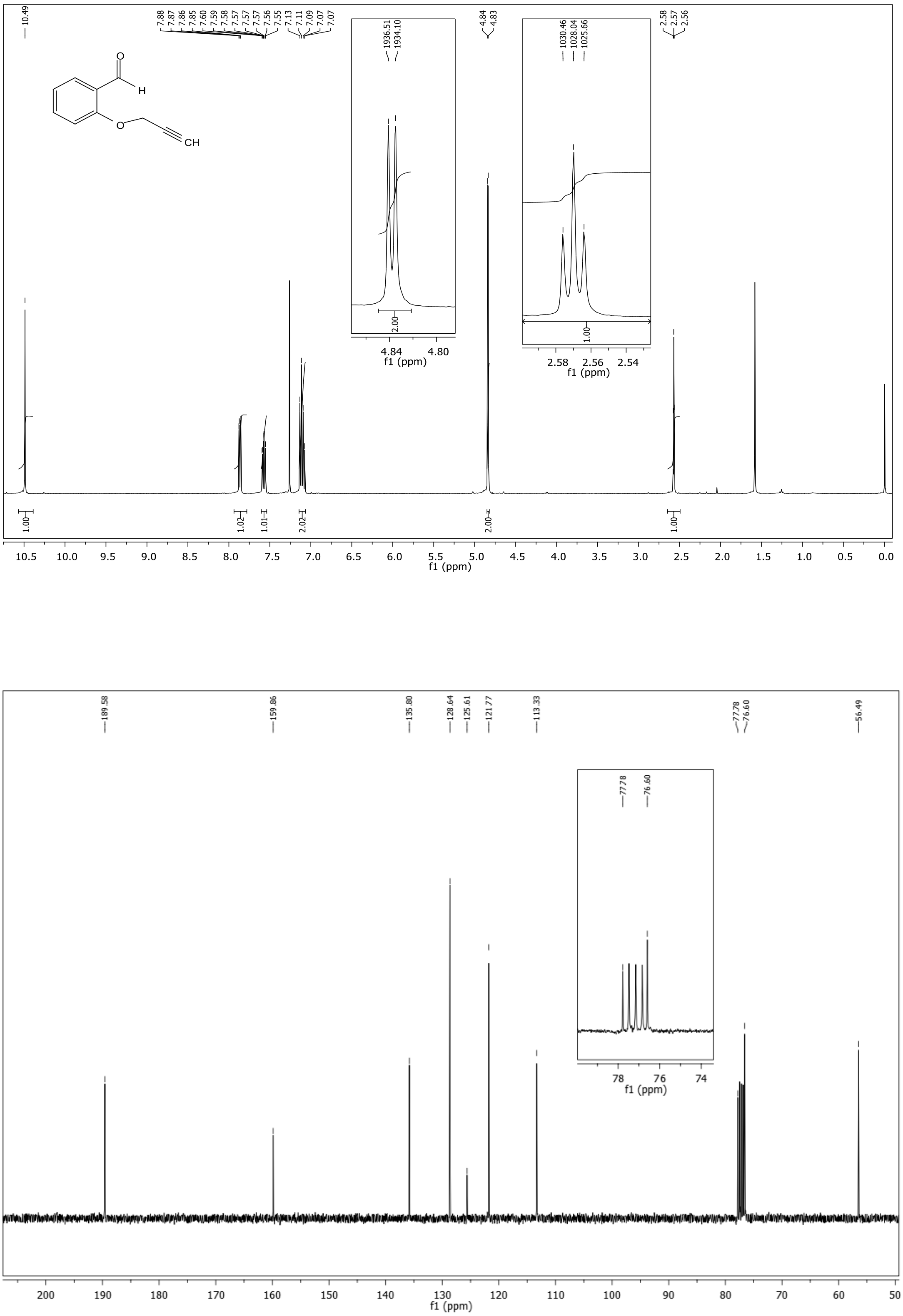
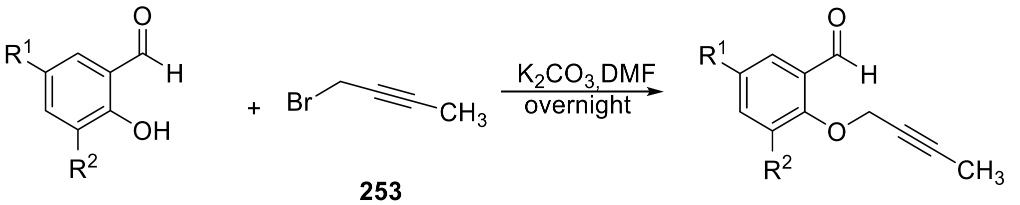


Figure 5: ^{1}H and ^{13}C NMR Spectra of Compound 149b

Formation of these propargylated compounds was verified by ^{1}H and ^{13}C NMR spectral analysis. In the ^{1}H NMR spectrum of compound **149b**, there is long range coupling (^4J) between methylene and alkyne protons. Therefore, the CH_2 protons of propargyl group resonates as doublets at 4.84 ppm while acetylenic proton resonates as triplets at 2.57 ppm. The chemical shift of acetylenic protons is found at high field because acetylene protons are located along the molecular axis, they are strongly shielded. The corresponding coupling constant (^4J) is 2.4 Hz. Acetylenic carbons resonate at 76.6 and 77.8 ppm in the ^{13}C NMR spectrum. The NMR spectra of the other derivatives were also in agreement with the proposed structures. The ^1H and ^{13}C NMR spectra of compound **149b** are shown in Figure 5.

After succesfull synthesis of these derivatives we decided to introduce some substituents at the terminal alkyne carbon atom to test the reactivity of disubstituted alkynes since they are usually less reactive than terminal alkynes. For the synthesis of desired aldehydes, 1-bromobut-2-yne (**253**) was used as a reagent instead of propargyl bromide. The reaction between salicylaldehyde derivatives **208**, **249**, and **250**, and 1-bromo-2-butyne (**253**) in the presence of potassium carbonate resulted in the formation of substituted alkynes **254-256** in high yields (Scheme 57).



253

208: R^1= H, R^2 = H
249: R^1= Br, R^2 = H
250: R^1= H, R^2 = OCH_3

254: R^1= H, R^2 = H (99%)
255: R^1= Br, R^2 = H (99%)
256: R^1= H, R^2 = OCH_3 (93%)

Scheme 57

The characterization of these compounds was done by using ^1H and ^{13}C NMR spectra. In the ^1H NMR spectrum of **254**, methyl group resonates as triplet at 1.87 ppm while CH_2 protons resonates as quartet at 4.79 ppm. The long-range coupling constant (^5J) between the relevant protons was measured as 2.3 Hz. The methyl carbon atom resonates at 3.49 ppm, which is a quite high field for a terminal methyl carbon atom. This high-field resonance can be explained by the presence of methyl carbon atom in shielding zone of acetylene group. The ^1H and ^{13}C NMR spectra of compound **254** are given in Figure 6.

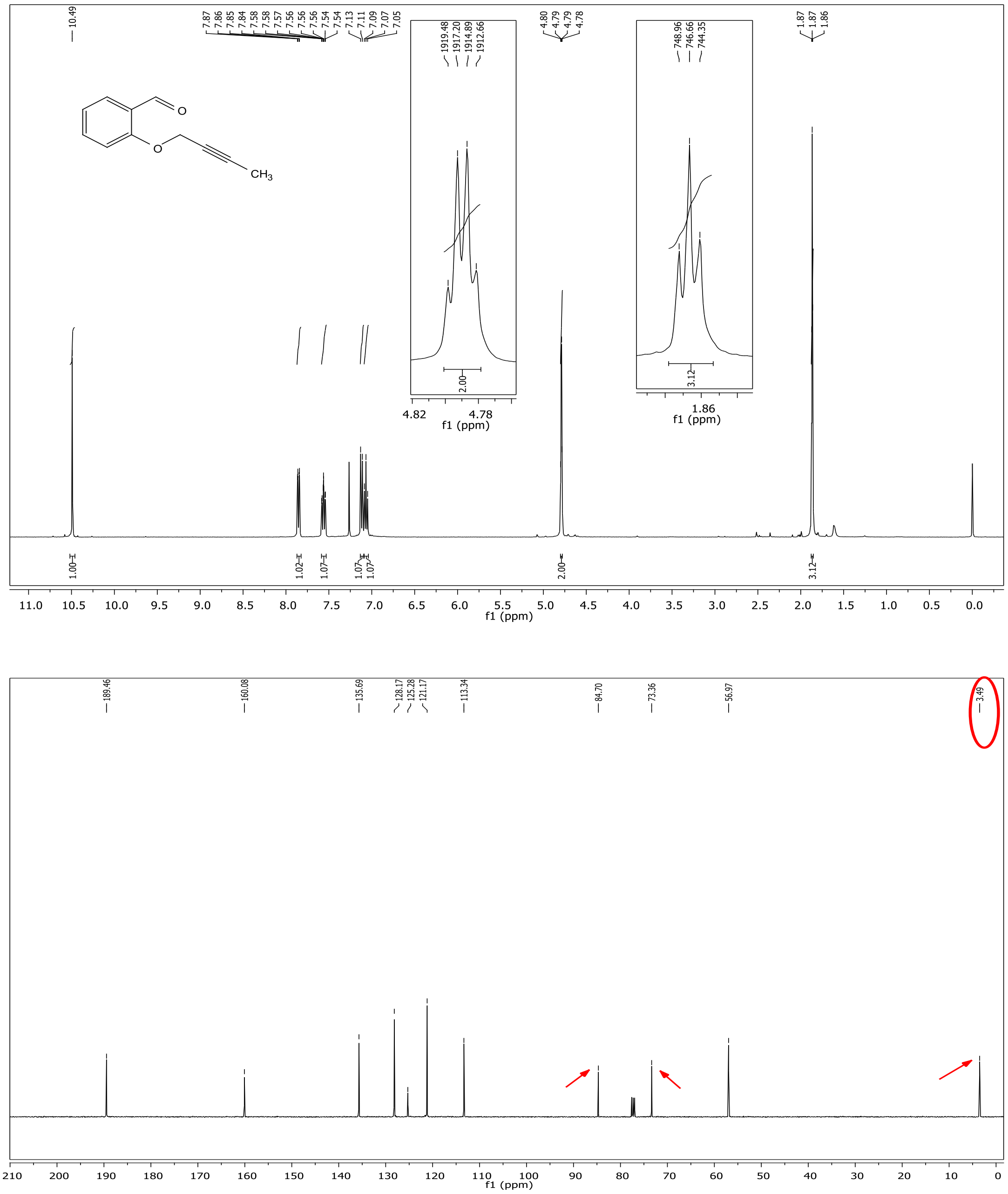
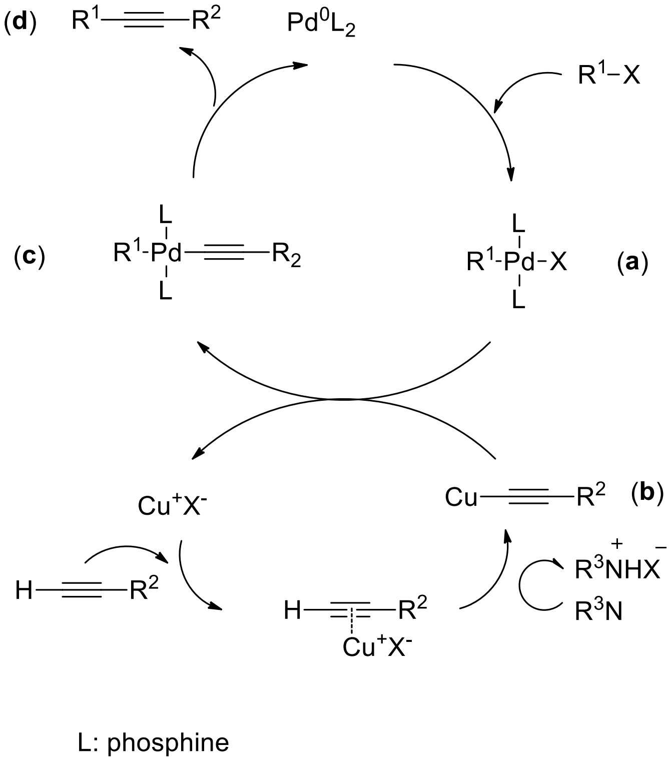


Figure 6: ^{1}H and ^{13}C NMR Spectra of Compound 254

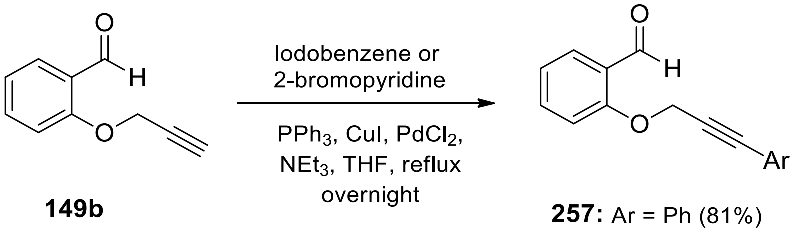
2.2.1.2 Synthesis of Conjugated Alkyne Functionalities

To test the effect of substituents conjugated with alkyne functionality, we synthesized the compounds **261** and **262**. The Sonogashira cross-coupling reaction[120–122] was used for the synthesis of the desired starting materials. For the Sonogashira coupling reaction, we used a palladium catalyst and a copper(I) cocatalyst in the presence of a base, in which terminal alkynes and aryl halides undergo coupling reaction. The proposed mechanism for the coupling reaction is shown in the Scheme 58. Palladium dichloride is reduced by phosphine, amines and ethers to PdL_2. Oxidative addition of R^1-X (aryl, hetaryl, vinyl) took place to generate the activated palladium species **a**. On the other hand, Cu catalytic cycle provided copper acetylide **b**, which then participates in the transmetalation step to form **c**. Finally reductive elimination provided coupling product **d** and regeneration of palladium catalyst (Scheme 58).[123]



Scheme 58

We applied Sonogashira coupling to 2-(prop-2-yn-1-yloxy)benzaldehyde (**149b**) to generate the coupling products **257** and **258** (Scheme 59).



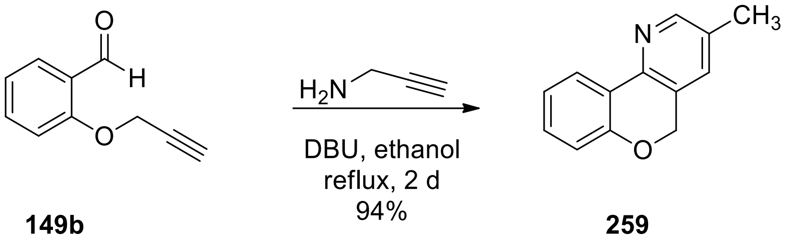
149b

257: Ar = Ph (81%)
258: Ar = pyridinyl (96%)

Scheme 59

2.2.1.3 Construction of Chromenopyridine Skeleton via Alkyne Cyclization

After succesfull synthesis of the starting compound, *O*-propargylated salicylaldehyde **149b**, we planned to incorporate the second propargyl group into the molecule and then apply intramolecular cyclization reaction between two propargyl groups to obtain chromenopyridine scaffold. For introduction of the second propargyl group, the compound **149b** was reacted with the propargylamine in the presence of DBU. This reaction resulted in the formation of tricyclic product **259** instead of the formation of the expected imine **260** (Scheme 60).



Scheme 60

The structure of **259** was determined by 1D and 2D (DEPT, COSY, HSQC, and HMBC) NMR spectral data. In the ^{1}H NMR spectrum, the methylene protons of the chromene ring resonate at 5.19 ppm as singlet and the methyl protons connected to pyridine ring also resonate at 2.36 ppm as singlet. Beside the benzene protons, there are additional two peaks in the aromatic region belonging to pyridine protons. Moreover, HMBC spectrum has important correlations for characterization of the structure. In the HMBC spectrum, we focused on the correlations of the carbon atom C-4. As expected, there are correlations between the carbon atom C-4 and the protons H-6, H-11, H-8, and CH_2. These correlations support the suggested structure (Figure 7).

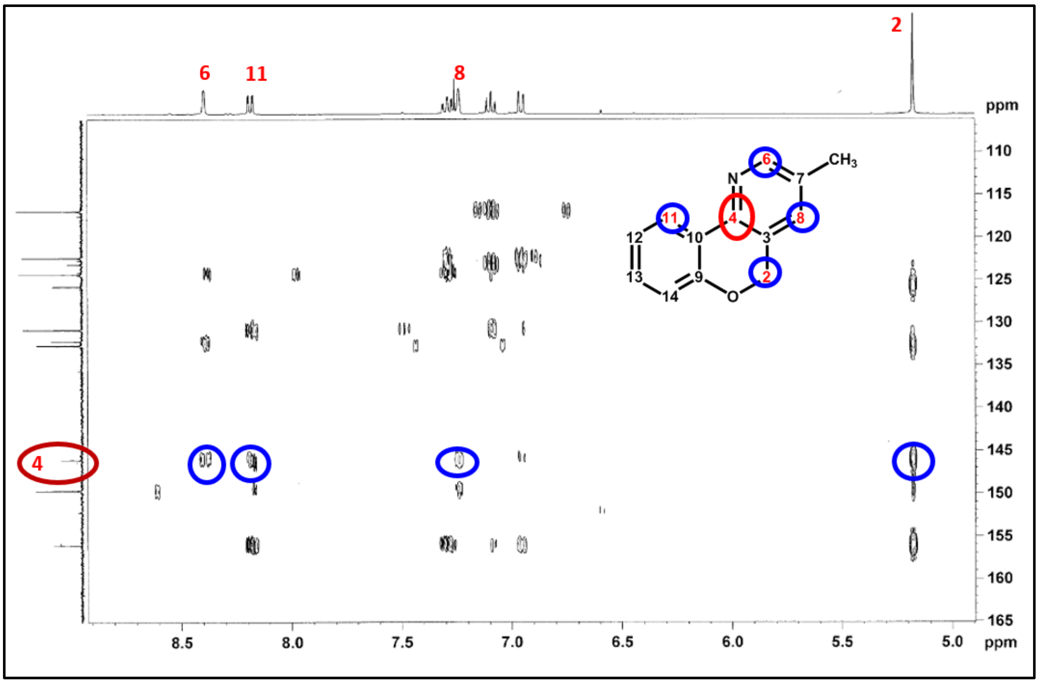
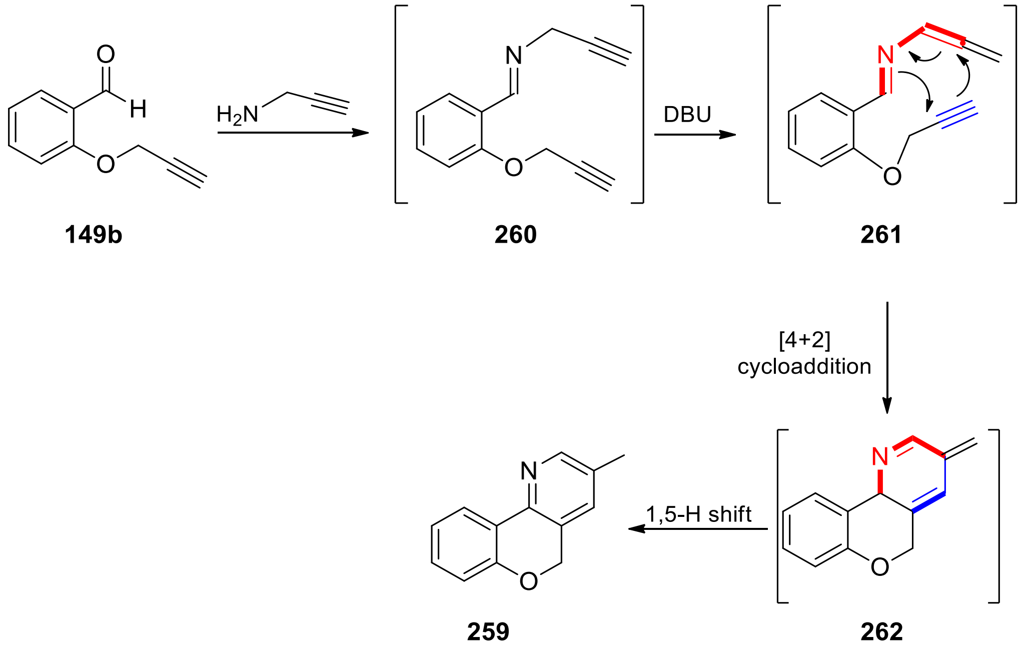


Figure 7: HMBC Spectrum of Compound 259

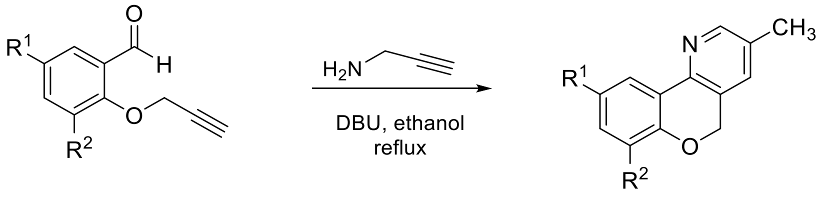
A tentative mechanism for the formation of **259** is outlined in Scheme 61. It is proposed that the first step is formation of the condensation product, imine **260**. With this step, two alkyne functionalities were now incorporated into the starting molecule. The terminal alkyne connected to the imine group can undergo base-catalyzed isomerization to form an allene structure **261**, which is conjugated with the imine double bond. Recently, we demonstrated that alkynes having similar structures can easily undergo isomerization into the corresponding allenes upon treatment with bases.[124,125] Then, the intramolecular [4+2] heterocycloaddition reaction between the alkyne and the diene system (formed with the imine and allene double bond) afforded, after a 1,5-H shift, the tricyclic product **259**.



Scheme 61

2.2.1.4 Synthesis of Chromenopyridine Derivatives

Formed *O*-propargylated salicylaldehydes, **251** and **252**, with substituents at the meta-position (referred to the aldehyde functionality), were also reacted with propargylamine in the presence of base to give the corresponding heterocyclization products, **263** and **264**, in good yields (Scheme 62). We were able to show that these compounds **251** and **252** were also suitable substrates for the synthesis of chromenopyridine derivatives.

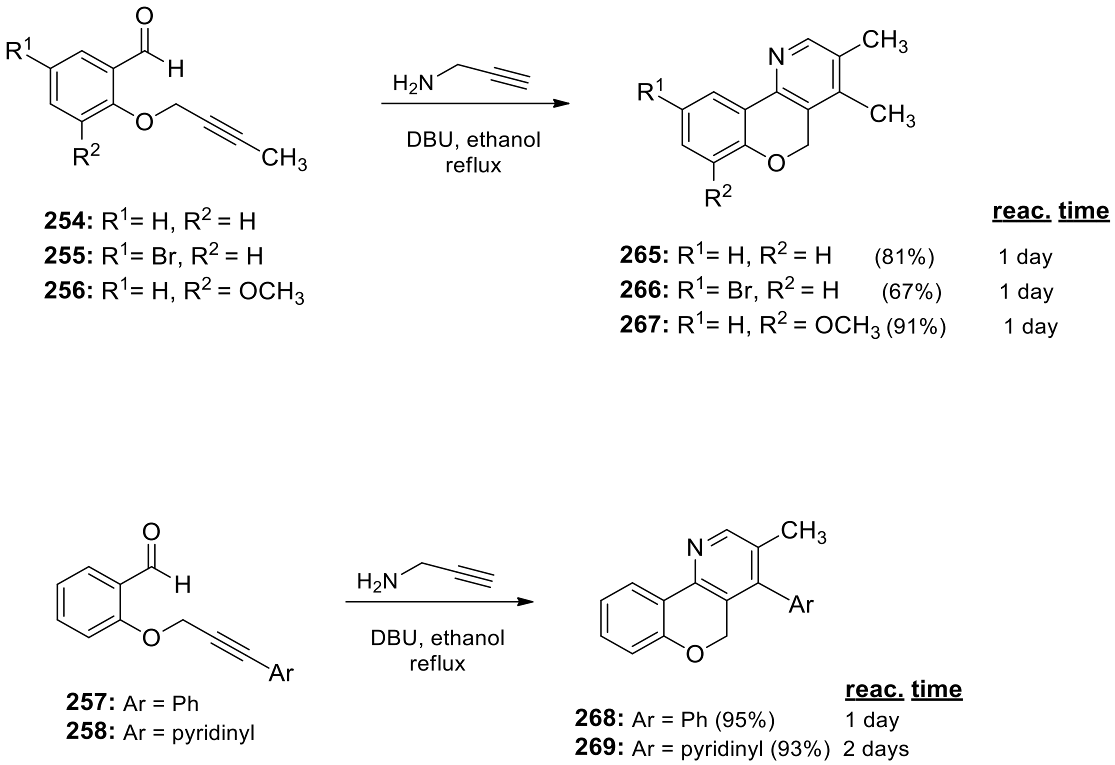


251: R^1= Br, R^2 = H
252: R^1= H, R^2 = OCH$_3$

		reac. time
263: R^1= Br, R^2 = H	(91%)	1 day
264: R^1= H, R^2 = OCH$_3$	(94%)	1 day

Scheme 62

Same methodology was applied to the compounds, **254-256**, having methyl substituted alkyne functionality and the compounds **257** and **258** that containing conjugated systems with triple bonds. All of these compounds were treated with propargylamine in the presence of DBU at reflux temperature of ethanol and the reactions resulted in the formation of corresponding chromenopyridine derivatives, **265-269** in good yields. Reaction times and yields are shown below (Scheme 63).



254: R^1= H, R^2 = H
255: R^1= Br, R^2 = H
256: R^1= H, R^2 = OCH_3

		reac. time
265: R^1= H, R^2 = H	(81%)	1 day
266: R^1= Br, R^2 = H	(67%)	1 day
267: R^1= H, R^2 = OCH_3	(91%)	1 day

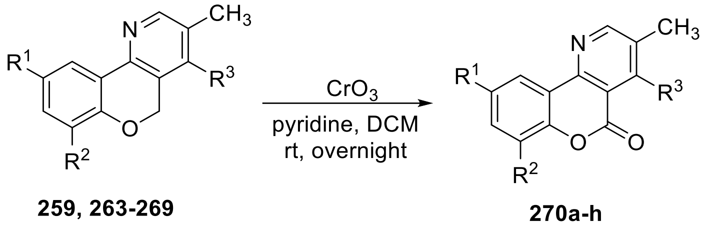
257: Ar = Ph
258: Ar = pyridinyl

	reac. time
268: Ar = Ph (95%)	1 day
269: Ar = pyridinyl (93%)	2 days

Scheme 63

2.2.2 Synthesis of Chromenopyridinone Derivatives

The second objective of this part was the synthesis of chromenopyridinone derivatives **270a-h**. For this purpose, chromenopyridine derivatives **259** and **263-269** were submitted to oxidation reaction using different oxidizing agents. Firstly, selenium dioxide was used as oxidant, however, we were not able to get any oxidation product. Manganase dioxide worked, the conversion was too low although the reaction time was prolonged. Finally, we tried chrominium trioxide and observed that it oxidized methylene group in chromenopyridinone skeleton most effectively. After optimization of the reaction condition, we applied this condition to all chromenopyridine derivatives and obtained chromenopyridinone derivatives **270a-h** in high yields (Scheme 64).

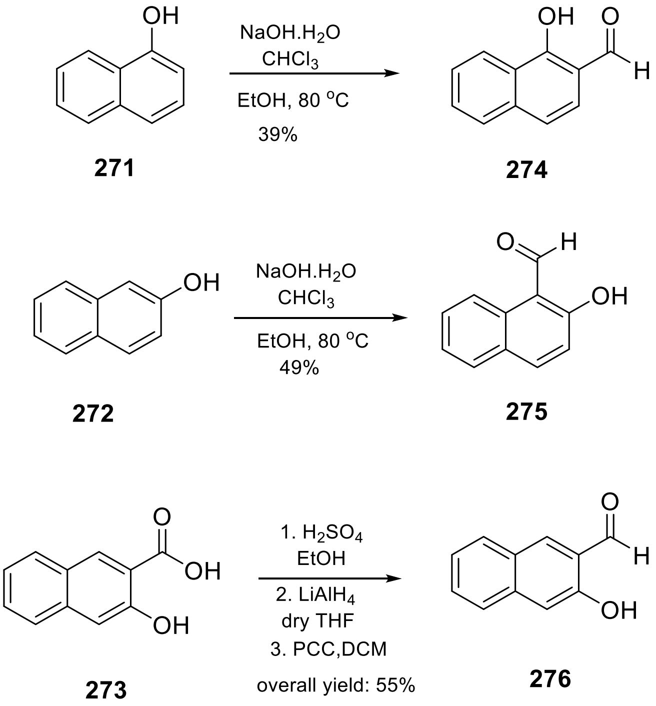


	R^1	R^2	R^3	yield (%)
270a	H	H	H	99
270b	Br	H	H	96
270c	H	OCH_3	H	94
270d	H	H	CH_3	90
270e	Br	H	CH_3	91
270f	H	OCH_3	CH_3	99
270g	H	H	Ph	90
270h	H	H	pyridinyl	98

Scheme 64

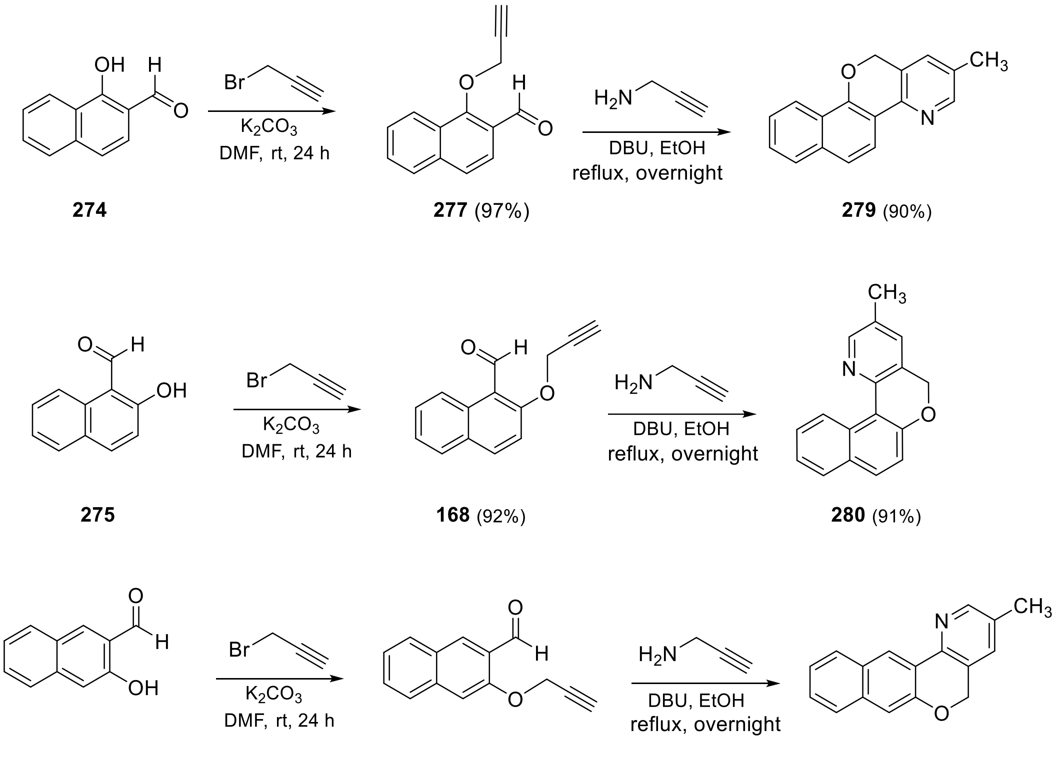
1.2.3 Synthesis of Benzochromenopyridinone Derivatives

To explore the scope of this reaction, three isomeric hydroxynapthaldehydes **271-273** were also evaluated. These aldehydes were prepared according to literature procedures.[126–128] To synthesize two of them, hydroxy-naphthalanes, **271** and **272**, were choosen as starting materials. Last one was obtained by the reduction of acid functionality of the hydroxynaphtanoic acid **273** to aldehyde functionality (Scheme 65).



Scheme 65

Later, the *O*-propargylated naphthaldehydes **277-279** were prepared from the corresponding hydroxynaphthaldehydes **274-276** by using propargyl bromide and potassium carbonate with good to excellent yields as described below (Scheme 66). Using the optimized conditions, naphthaldehydes **168** and **277-278** were treated with propargylamine and DBU under the reflux temperature of ethanol. The isomeric benzochromenopyridine derivatives **279-281** were formed in high yields (Scheme 66).



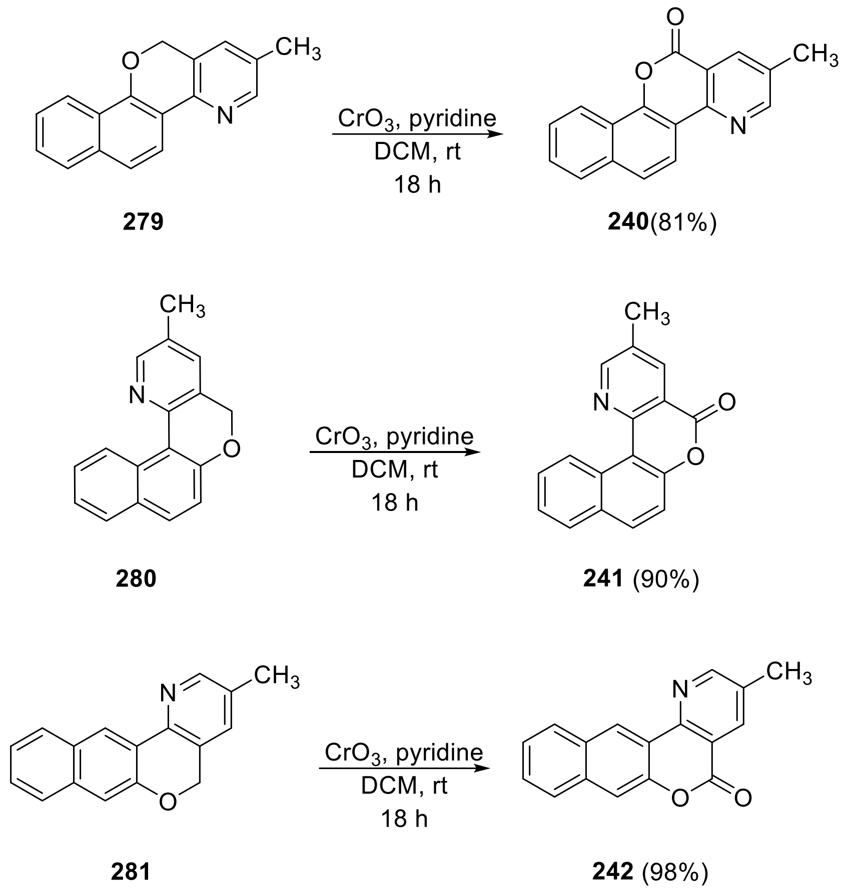
274 **277** (97%) **279** (90%)

275 **168** (92%) **280** (91%)

276 **278** (98%) **281** (94%)

Scheme 66

Oxidation of those compounds **279-281** with CrO_3 in methylene dichloride resulted in the formation of the corresponding benzochromenopyridinone derivatives **240-242** (Scheme 67). The characterization of all compounds was done by using ^{1}H and ^{13}C NMR spectra.

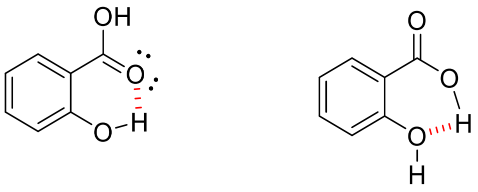


Scheme 67

2.2.4 Synthesis Benzopyrazoloxazepine and Benzopyrazoloxazocine Derivatives

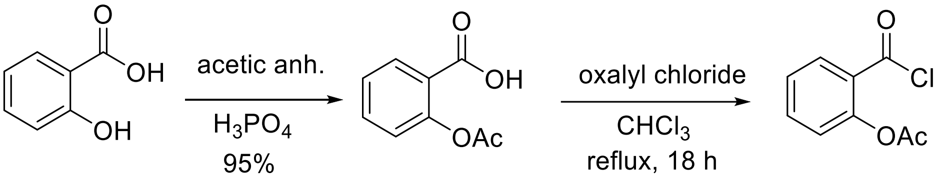
2.2.4.1 Synthesis of Phenyl Substituted Pyrazolyl Phenol 286

To obtain fused tricyclic compound, benzopyrazoloxazepine and benzopyrazoloxazocine, we firstly planned to construct pyrazole skeleton that connected to benzene ring starting from salicylic acid **243**. For this purpose, salicylic acid was converted to the acetyl salicylic acid **282**. Then the formed product was treated with oxalyl chloride in the presence of catalytic amount of DMF to form acyl chloride **283** that was directly used for the next step, Sonogashira coupling reaction. First we reacted salicylic acid **243** with oxalyl chloride to obtain corresponding acyl chloride. But the reaction did not take place. We thought that the intramolecular hydrogen bonding (possible hydrogen bondings are shown below) prevents the occurence of this reaction (Scheme 68).



Scheme 68

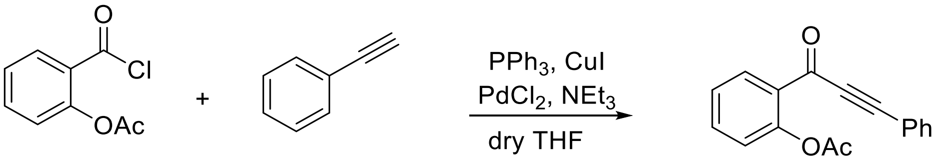
Due to this reason, we decided to protect phenolic OH group by acetylation reaction and then to convert acid functionality into acyl chloride. This methodology worked and we optimized the reaction condition (Scheme 69).



243 **282** **283**

Scheme 69

Acyl chloride was not isolated, it was used directly for Sonogashira coupling reaction. The reaction between acyl chloride **283** and phenylacetylene **284** in the presence of PPh_3, CuI, $PdCl_2$ and triethylamine resulted in the formation of corresponding ynone **285** (Scheme 70).

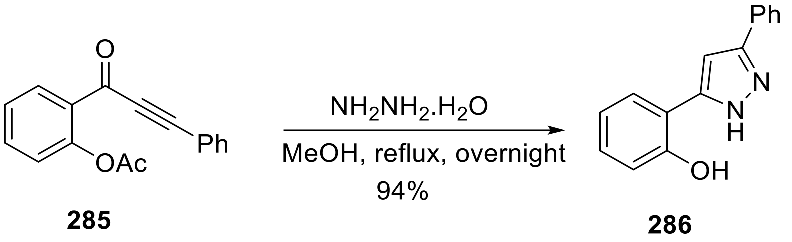


283 **284** **285**

Scheme 70

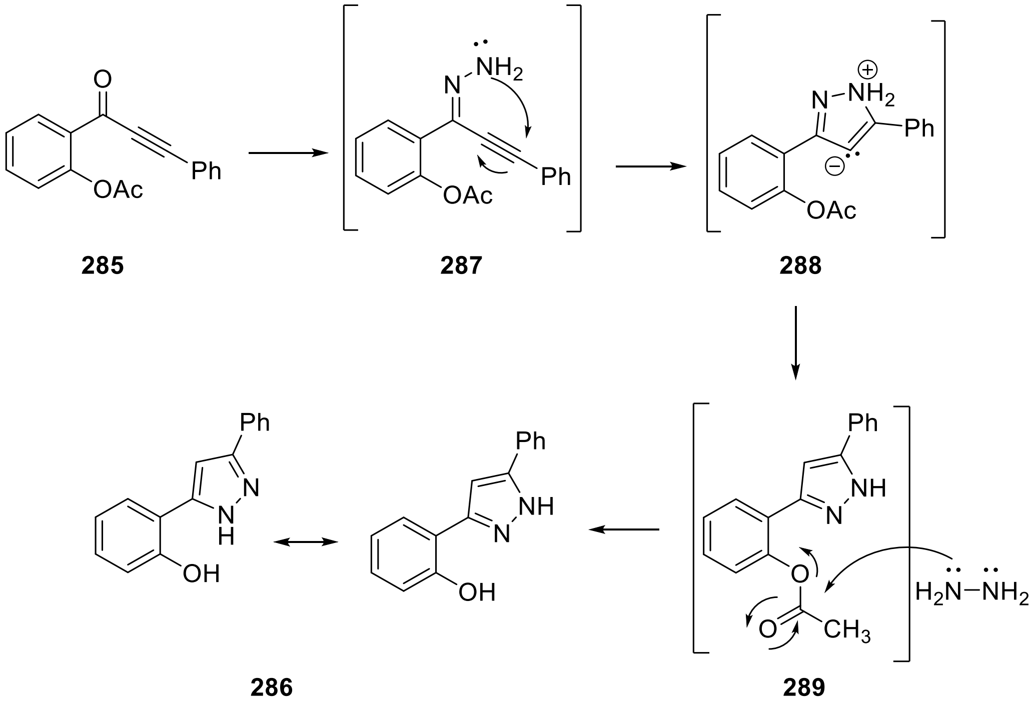
The formation of the product **285** was verified by ^{1}H and ^{13}C NMR analysis. In the ^{13}C NMR spectrum, the peaks at 88.8 and 92.8 ppm belonging to acetylene group shows the incorporation of acetylene unit into the molecule.

To construct pyrazole skeleton **286**, the compound **285** was treated with hydrazine monohydrate in methanol at reflux temperature. While forming pyrazole core, removal of acetate group was occured at the same time because of excess amount of hydrazine (Scheme 71).



Scheme 71

The ^{1}H NMR spectrum of compound **286** was completely in agreement with the proposed structure. The singlet at 6.92 ppm belongs to the proton of the pyrazole ring. Also, dissapparence of singlet belonging to acetyl protons at 2.36 ppm showed the removal of acetate group.

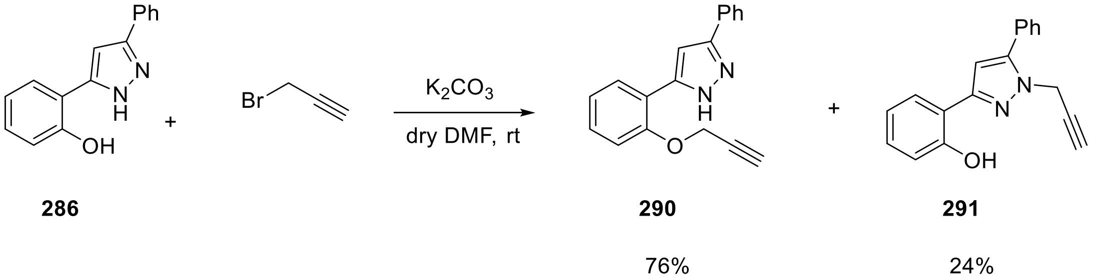


Scheme 72

Proposed mechanism for the formation of pyrazolyl phenol **286** is shown above (Scheme 72). Corresponding hydrazone **287** is firstly formed. Then, the nonbonding electrons of –NH_2 group attacks β-carbon atom of triple bond to form the intermediate **264**. On the other hand, due to usage of the excess amount of hydrazine, it attacks also the carbonyl carbon of acetate group and causes the removal of acetate group to form the corresponding product **286**. The formed pyrazole ring has two tautomers as shown above.

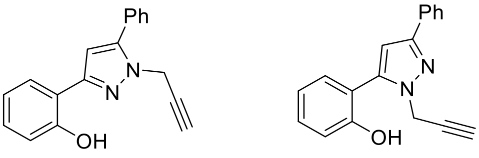
2.2.4.2 Synthesis and Characterization of Precursors of Gold Catalyzed Cyclization Reaction

After construction of pyrazole ring, we planned to connect propargyl group to oxygen atom. For this purpose, propargyl bromide was used in the presence of potassium carbonate in DMF. This reaction was monitored on TLC. After completion of the reaction, two products, **290** and **291**, were isolated (Scheme 73) in 76% and 24% yields, respectively.



Scheme 73

For the characterization studies of these products, we benefitted from 1D and 2D NMR spectra. The major product **290** of this reaction was easily characterized by using the ^{13}C NMR spectrum. The signal of CH_2 carbon connected to the oxygen atom resonates at 56.7 ppm, while the CH_2 carbon connected to the nitrogen atom of the minor product **291** resonates at 39.9 ppm. As expected the inductive effects of oxygen and nitrogen atoms are responsible for this large chemical shift difference of about 17 ppm. On the other hand, two isomeric structures can be proposed for the minor product due to the resonance forms of pyrazole ring. Their structures are shown below (Scheme 74).



291

292

Scheme 74

With the help of 1D and 2D NMR spectra we were not able to distinguish between these possible structures. Firstly, we recorded the HMBC spectrum of the minor product. The methylene protons correlates with one of the quaternary carbons. This quaternary carbon atom may be the carbon atom A or B. However, this information was not enough to distinguish betwen those isomers.

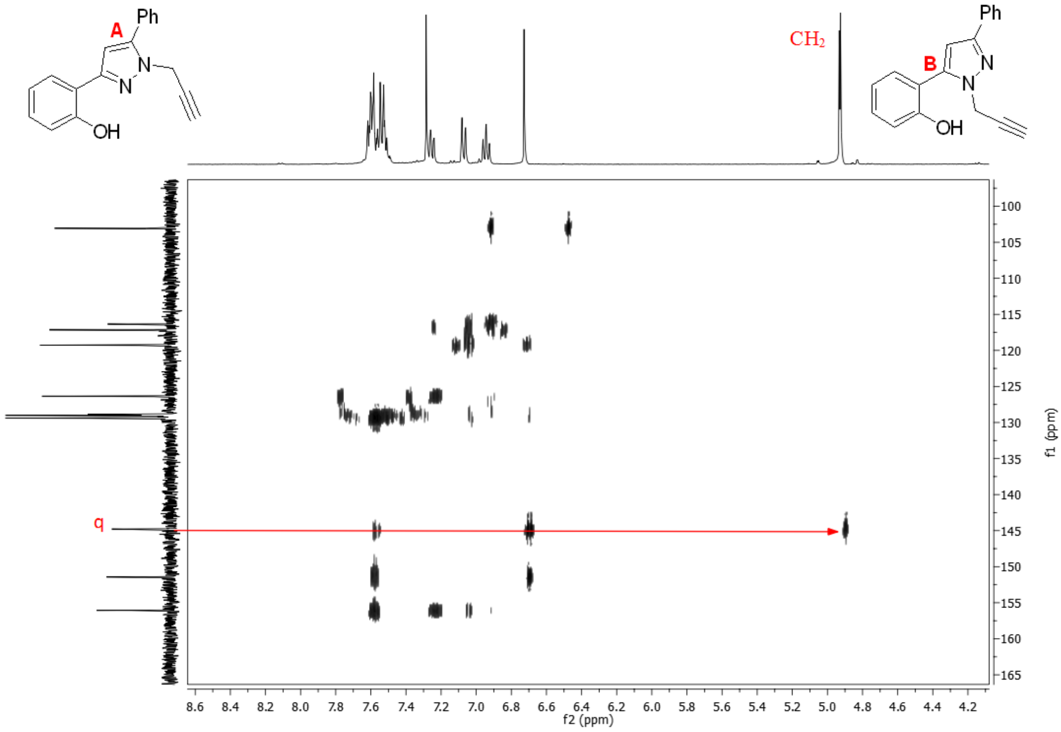
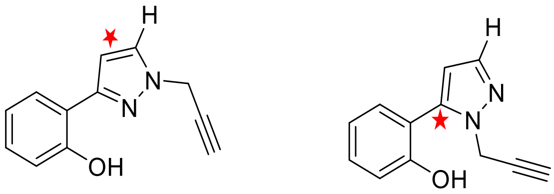


Figure 8: HMBC Spectrum of Minor Product

To make a clear-cut differentiation between these isomers we decided to synthesize an unsubstituted pyrazole skeleton. In the case of a structure **293** the methylene protons should correlate with -CH=CH carbon atoms. In the case of a structure such as **294** CH_2 protons should correlate with the quaternary carbon of pyrazole ring (Scheme 75).



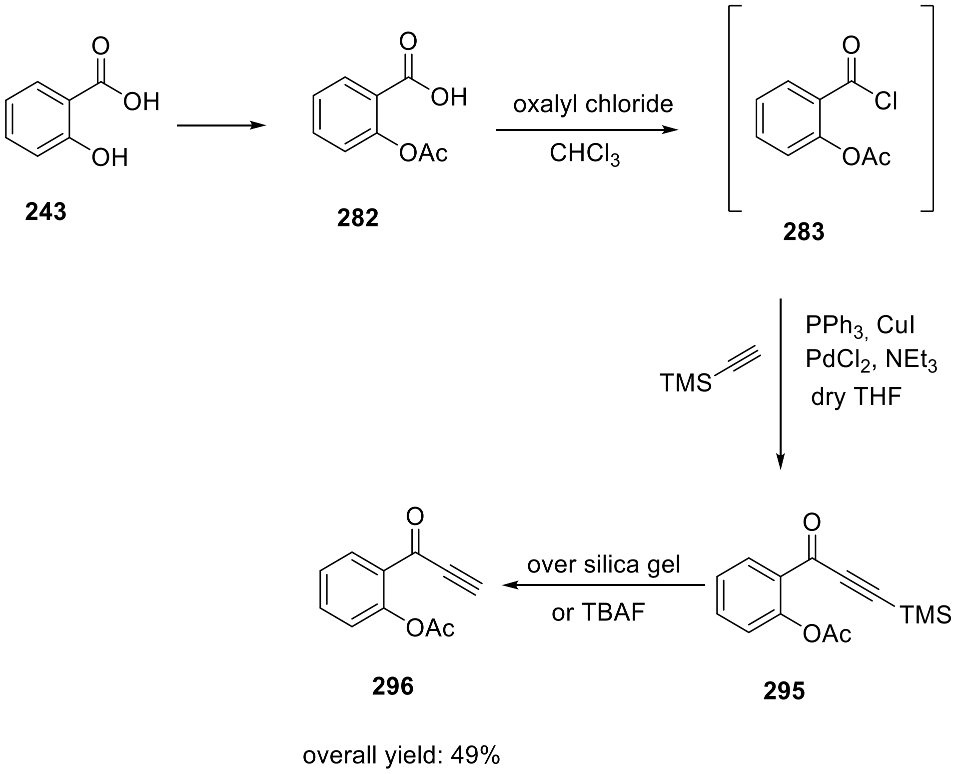
293

294

Scheme 75

2.2.4.2.1 Construction of Unsubstituted Pyrazole Skeleton and Incorporation of Propargyl Group

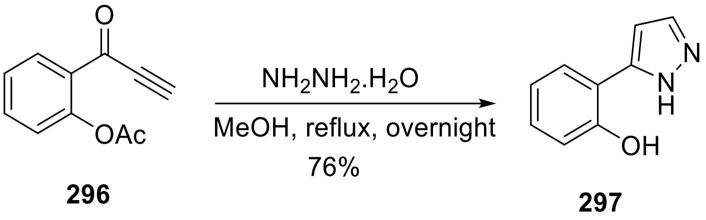
For the construction of unsubstituted pyrazole skeleton, we again started from the salicylic acid **243**. Firstly, it was converted to acetylsalicylic acid **282**. Acetyl salicylic acid **282** was treated with oxalyl chloride in the presence of DMF and corresponding acyl chloride **283** was reacted with trimethylsilylacetylene in the Sonogashira coupling condition. After the completion of the reaction, crude product was subjected to silica gel to purify the product. Two products were isolated after the column chromatography. During column chromatography, trimetyhlsilyl group was hydrolyzed because of the acidity of silica gel. Actually, the hydrolysis product **296** was the desired product. The unhydrolized reaction product **295** was treated with tetrabutylammonium flouride (TBAF) and was converted into **296**. (Scheme 76).



Scheme 76

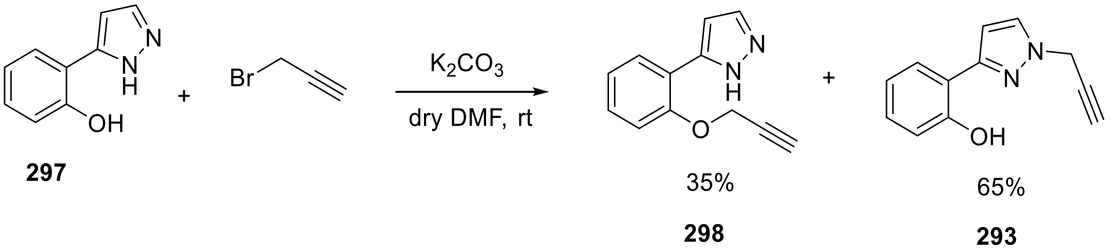
The characterization studies of compound **295** and **296** were done with the help of 1D NMR spectra. In the ^{1}H NMR spectrum of compound **295,** there was specific signal belonging to CH_3 groups of trimethylsilyl group at 0.25 ppm appearing as singlet. These methyl carbon atoms resonate at -0.6 ppm in the ^{13}C NMR spectrum. After hydrolysis of compound **295**, the singlet in the ^1H NMR spectrum disappeared and new signal belonging to acetylene proton appeared at 3.42 ppm in the ^1H NMR spectrum of the hydrolysis product **296**.

The reaction between compound **296** and hydrazine monohydrate resulted in the formation of our desired product **297** (Scheme 77).



Scheme 77

After construction of unsubstituted pyrazole skeleton **297**, the compound was reacted with propargyl bromide in the presence of K_2CO_3 and two products, **298** and **293** were isolated (Scheme 78).



Scheme 78

These products, **298** and **293**, were analyzed by using 1D and 2D NMR spectra. Firstly, we determined the skeleton of propargylated compound **293** and then the exact position of propargyl group. For this reason, the HMBC spectrum of the product was recorded (Figure 9).

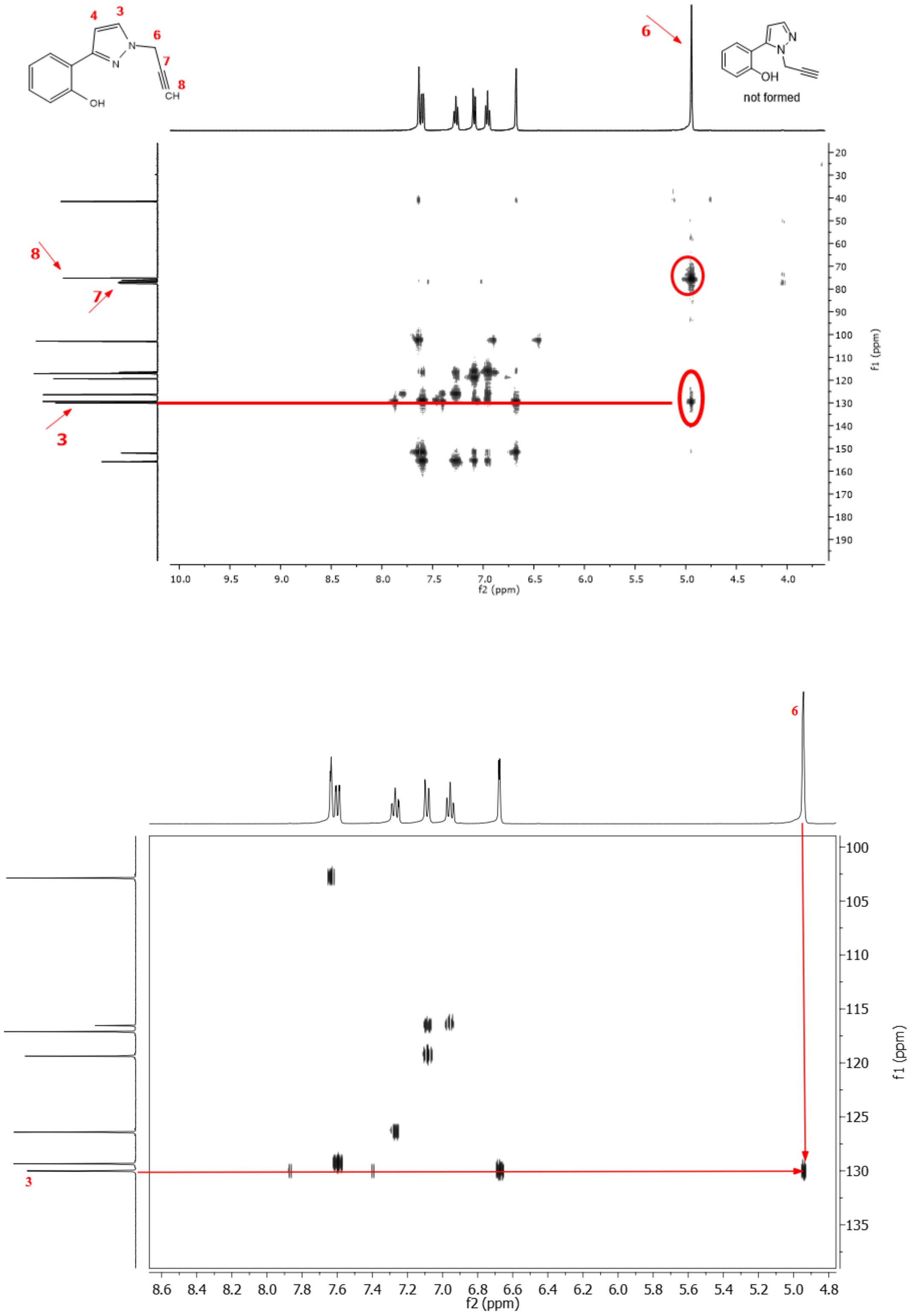


Figure 9: HMBC Spectrum of Compound 293

The ^{1}H NMR spectrum of **293** shows a doublet at 4.98 ppm arising from CH_2 protons. These protons correlate with acetylene carbons (C7 and C8) and one of the sp^{2} hybridized carbon atom. From the HSQC spectrum (Figure 10) we were able te reveal that this sp^{2} hybridized carbon atom belongs to the pyrazole ring. With these results in the hand, we assigned the structure **293** to the minor product. In the case of a structure such as **294** a correlation between the CH_2 protons and a quaternary carbon atom of pyrazole ring should be observed.

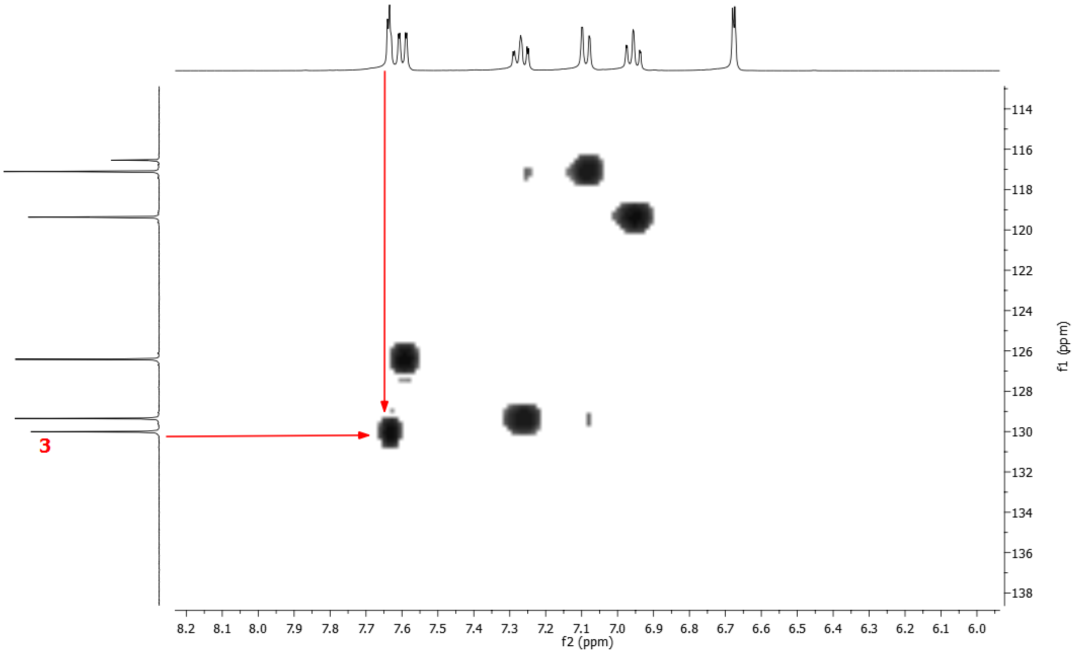
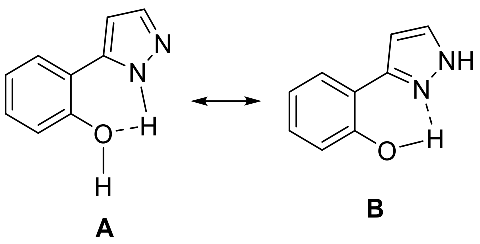


Figure 10: HSQC Spectrum of Compound 293

Next, we should address the question why the propargyl group was regiospecifically bonded to one of the nitrogen atoms? We assume that the hydrogen bonding is responsible for this case. In the form A of compound **297** (Scheme 80), there is hydrogen bonding between NH proton and electronegative oxygen. On the other hand, in the form B of compound **297**, there is also hydrogen bonding between OH proton and electronegative nitrogen atom. However, since the OH proton more acidic than the NH proton, the tendency of OH proton to make hydrogen bonding will be greater than the NH proton. Therefore, we assume that the structure B is dominating structure where NH proton is susceptible to proton abstraction to bond the propargyl group (Scheme 79).

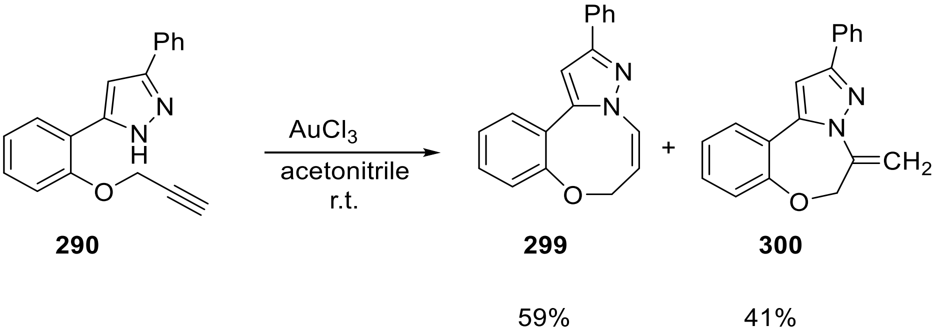


297

Scheme 79

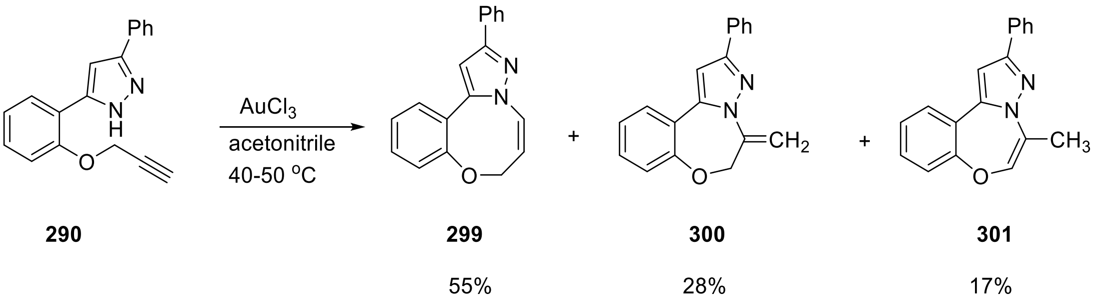
2.2.4.3 Intramolecular Cyclization Reactions of *O*-propargylated Compounds via Gold Catalysis

After obtaining *O*-propargylated compound **290**, we applied an intramolecular cyclization reaction by using gold catalysis. Firstly, we chosed gold (III) chloride as a catalyst. This reaction was carried out in acetonitrile at room temperature and monitored on TLC. After the completion of the reaction, we isolated two products, **299** and **300**. One of the product **299** had oxazocine ring while the other one **300** had oxazepine unit (Scheme 80).



Scheme 80

Furthermore, we checked the effect of the temperature on the distribution of the products. For this purpose, the reaction temperature was raised up to 45 °C. Three products; **299**, **300**, and **301** were formed at this temperature. These products were separated by silica gel column chromatogaphy and preparative TLC (Scheme 81).



Scheme 81

The structures of these products, **299**, **300**, and **301** were determined by using 1D and 2D NMR spectra. There are three specific signals in the ^{1}H NMR spectrum of compound **299**. The CH_2 protons resonate at 4.87 ppm as doublet of doublets with coupling constants of J = 3.6 and 1.9 Hz. The larger coupling is due to the vicinal coupling, whereas the smaller coupling is arising from the allylic coupling ^4J with the olefinic proton. H_b proton resonance at 5.42 ppm appears as doublet of triplets (J = 9.9 and 3.6 Hz) while H_a proton resonates at 7.06 ppm as doublet of triplets (J = 9.9 and 1.9 Hz) as expected (Figure 11).

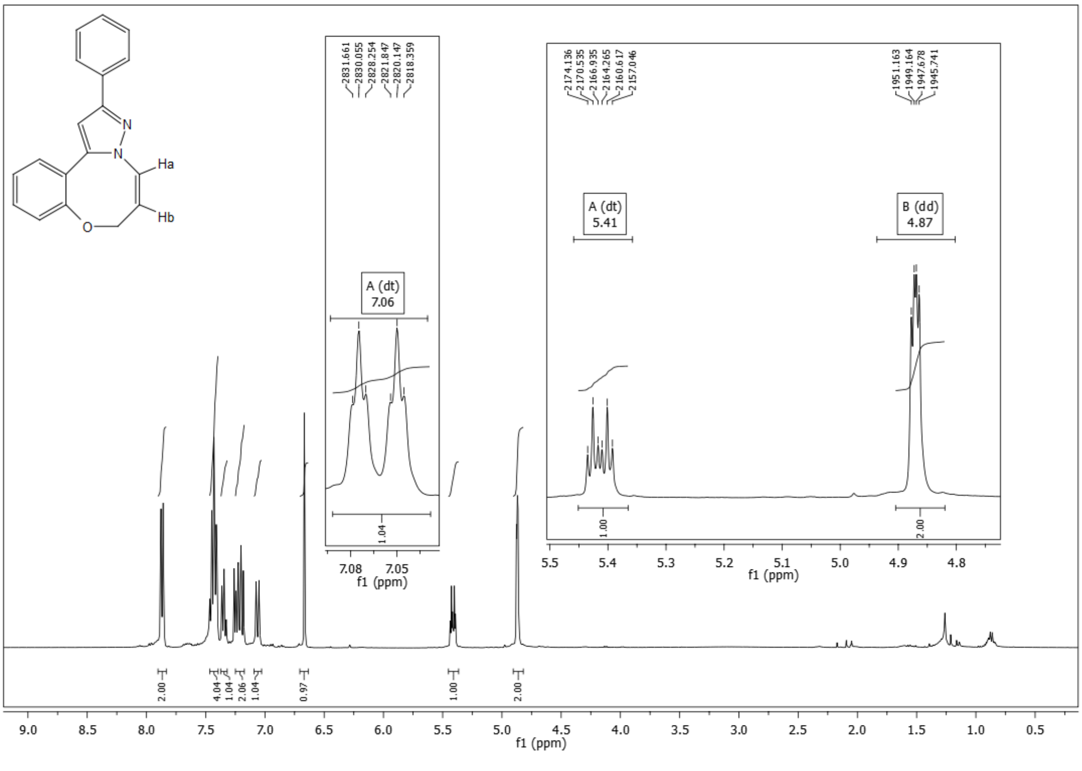


Figure 11: ^{1}H NMR Spectrum of Compound 299

For the characterization of the minor product **301**, 1D NMR spectra were used. The presence of a methyl signal at 2.24 ppm with a coupling constant of *J* = 1.4 Hz as well as a broad quartet resonance (H_a) at 6.30 ppm coupled with the methyl protons (*J* = 1.4 Hz) supported the formation of the proposed structure **301** (Figure 12). The pyrazol proton appears at 6.86 ppm as singlet.

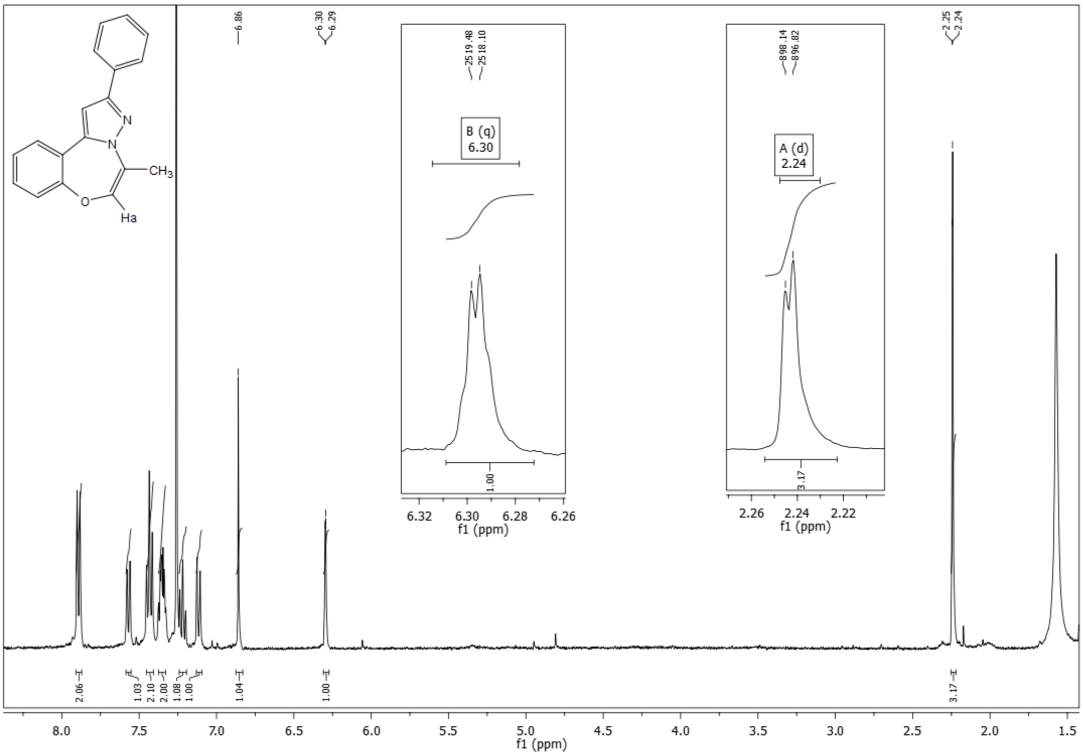


Figure 12: ^{1}H NMR Spectrum of Compound 301

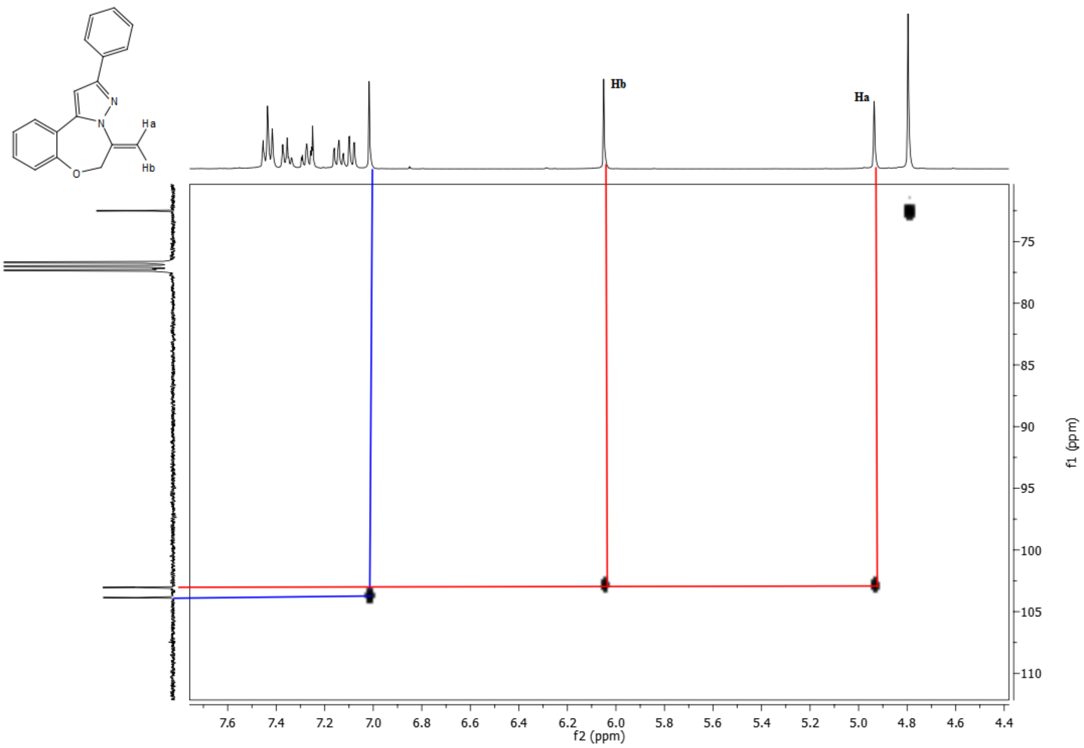


Figure 13: HSQC Spectrum of Compound 300

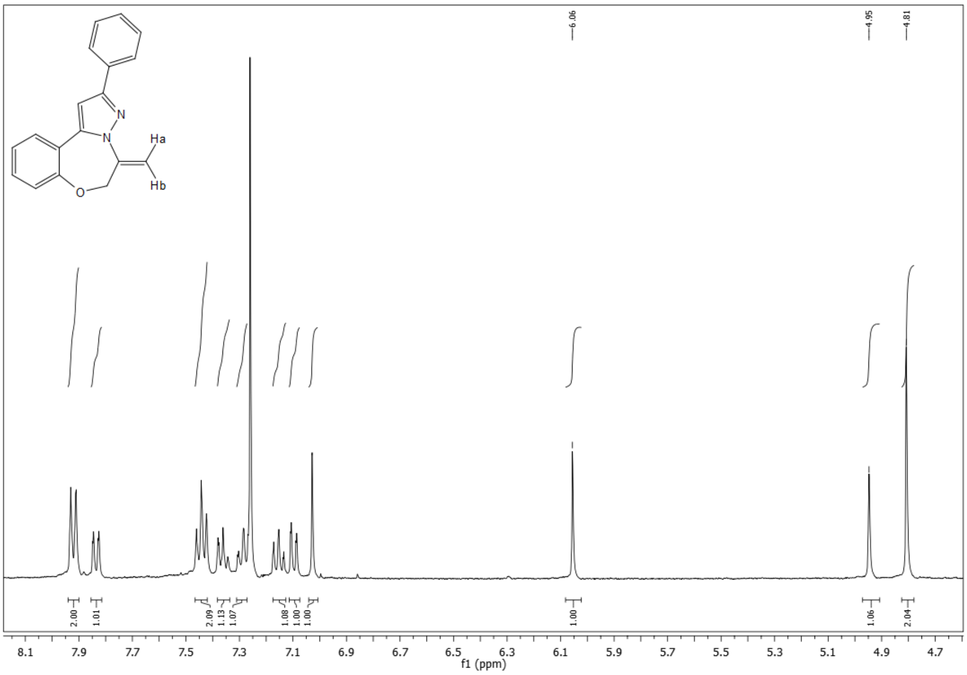
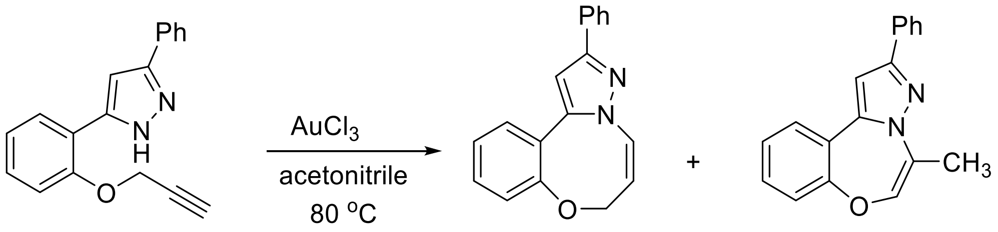


Figure 14: ^{1}H NMR Spectrum of Compound 300

The structure of the compound with the exocyclic methylene group **300** was verified by ^1H and ^{13}C NMR analysis. The methylene protons resonates separately at 4.95 ppm (H_a) and 6.06 ppm (H_b). Analyzing of HSQC spectrum (Figure 13) of compound **300** confirmed that the signals belonging to H_a and H_b correlates with the same carbon signal. The chemical shift difference is due to the presence of the H_b-proton in the deshielding zone of the pyrazole ring. Also, CH_2 protons in the ring resonates as singlet at 6.81 ppm while the pyrazole proton appears at 7.03 ppm as singlet (Figure 14).

After correct assignments of the structures, the reaction conditions were changed in order to see whether the formation of one or two products can be controlled or not. We showed that increasing of the reaction temperature from 25 °C to 40-50 °C resulted in the formation of **301** at the cost of **300**, whereas the amount of the major product **299** did not change remarkably (Scheme 81 and Scheme 82). It is likely that the compound **301** is formed by the isomerization of **300**. Therefore, the reaction temperature was increased. The exocyclic compound **300** was not observed. Two products **299** and **301** were formed in 50% yields (Scheme 82).



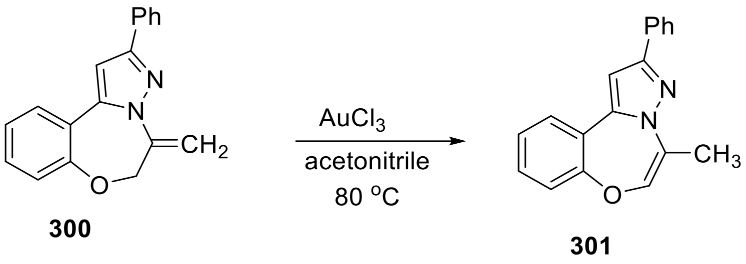
290

299
50%

301
50%

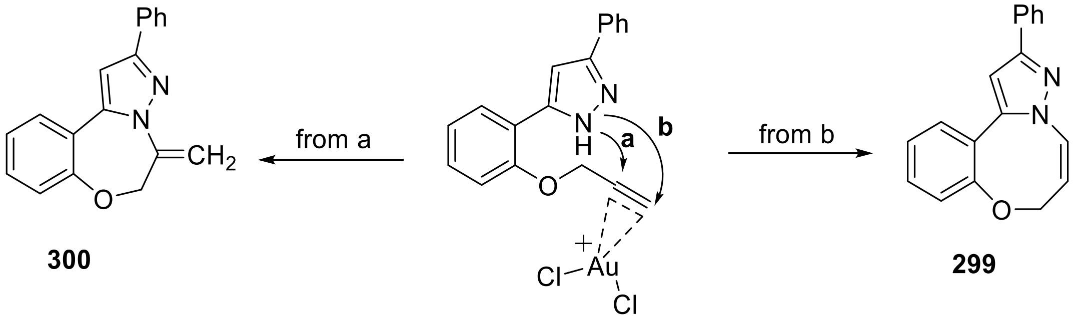
Scheme 82

To show that the compound **301** is a secondary product and formed by isomerization, **300** was separately submitted to gold-catalyzed reaction under the same reaction conditions. It was shown that the reactant **300** was converted to the compound **301**, quantitatively (Scheme 83).



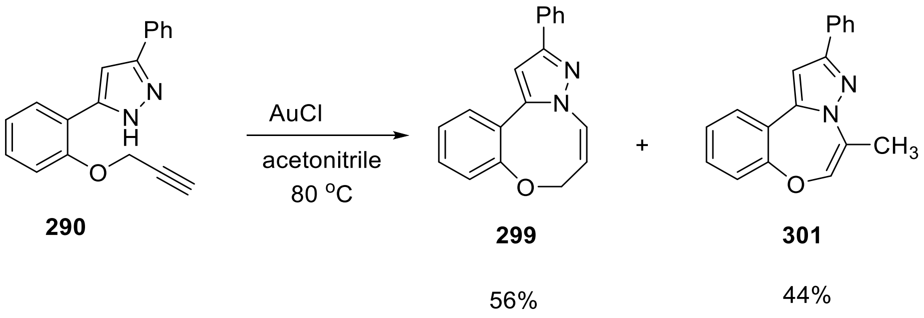
Scheme 83

Mechanistically, this cyclization reaction was started with coordination of gold (III) chloride with triple bond. After the coordination of gold, there were two possible centers for the attacking of nucleophilic nitrogen of pyrazole skeleton as shown below (Scheme 84). When the nitrogen atom attacks the internal carbon atom of acetylene (patway a), compound **300** can be formed. If the reaction progresses through the pathway b, compound **299** can be formed. At high temperatures, isomerization took place and the compound **300** was converted to the compound **301**.



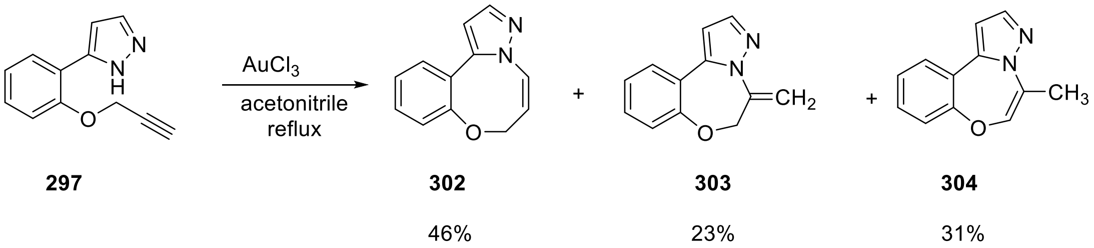
Scheme 84

Furthermore we were interested in the AuCl-catalyzed reaction of **290** to determine the effect of gold (I) on the distribution of the products as well as on ratio. For this reason, **290** was reacted with AuCl in acetonitrile at reflux temperature. Similarly, two products, **299** and **301**, were isolated from this reaction (Scheme 85).



Scheme 85

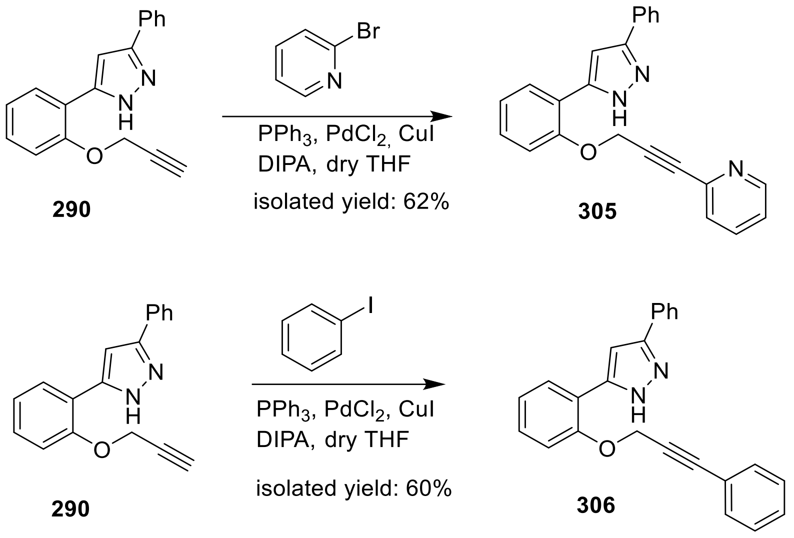
The compound **297** having unsubstituted pyrazole skeleton was also treated with $AuCl_3$. This reaction was carried out in acetonitrile at reflux temperature and monitored on TLC. After consuming of the starting material (18 h), we terminated the reaction. Three products, **302**, **303**, and **304**, were isolated from the reaction (Scheme 86).



Scheme 86

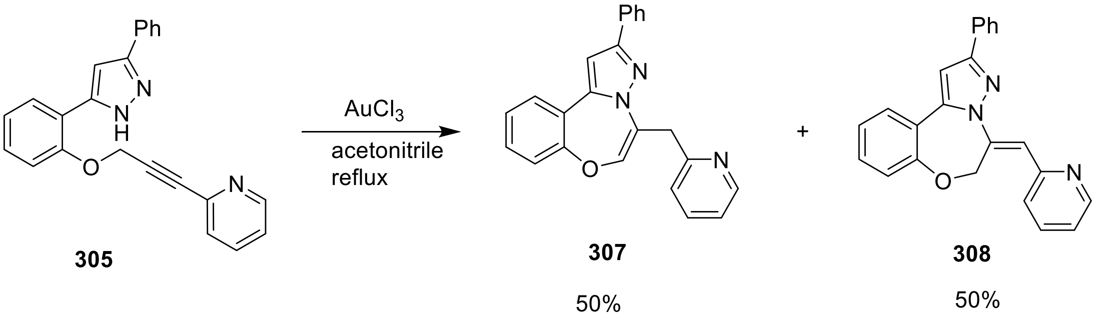
2.2.4.4 Synthesis and Cyclization Reactions of Conjugated Alkynes

For derivatization of these important tri- and tetracyclic compounds, the starting material **290** was submitted to Sonogashira coupling reaction. The compound **290** was reacted with iodobenzene or bromopyridine in the presence of PPh_3, CuI, $PdCl_2$ and DIPA in dry tetrahydrofuran under nitrogen atmosphere. These reaction were monitored on TLC. After the completion of the reactions, the corresponding coupling products **305** and **306** were isolated after column chromatography (Scheme 87).



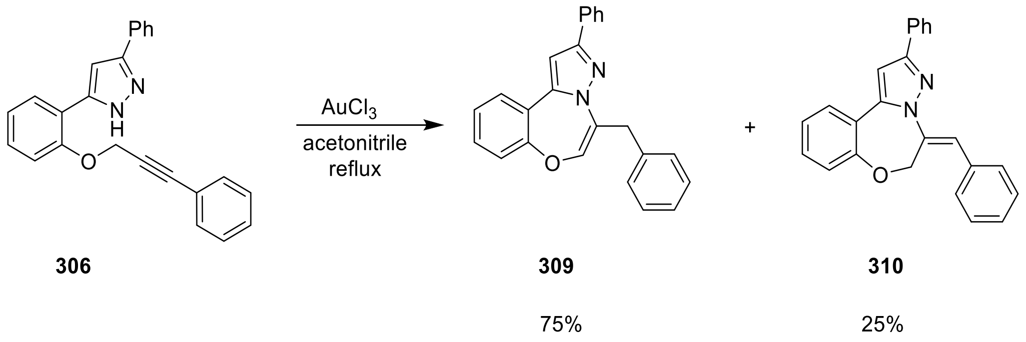
Scheme 87

To test the effect of substituents conjugated with alkyne functionality, the compound **305** was firstly treated with $AuCl_3$ in acetonitrile at reflux temperature. Two products were formed. Careful analysis of the structures indicated the formation of products, benzopyrazolooxazepines. Unfortunately, the expected product with 8-membered ring system was not formed (Scheme 88).



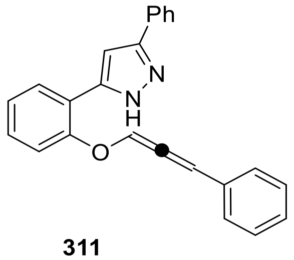
Scheme 88

Same methodology was applied to the compound **306**. Similarly, this reaction also resulted in the formation of 7-membered ring systems **309** and **310** (Scheme 89).



Scheme 89

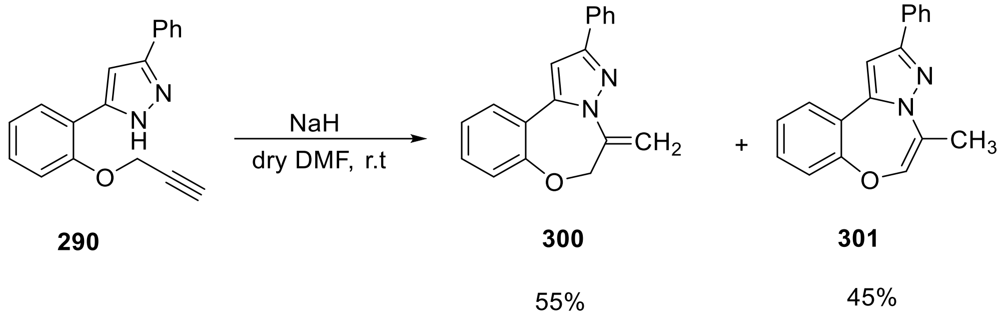
We assume that Au(III) first activates the triple bond. Actually, the positive charge should be closer to the benzene ring attached to the alkyne functionality, which would support the formation of a oxazocine unit. Since oxazocine derivative is not formed, we assume that alkyne first undergoes an isomerization reaction to form the corresponding allene **311**, which may be responsible for cyclization reaction. To support this proposal we decided to synthesize the allene on an independent way and to study the cyclization reaction.



311

2.2.5 Intamolecular Cyclization Reaction of *O*-propargylated Compound Under Basic Condition

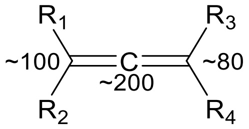
After examining the intramolecular cyclization reactions via gold salts, we decided to use a base for the cyclization. We choosed NaH as a base. The reaction of compound **290** was carried out in dry DMF at rt for 18 h. Two products; **300** and **301** were formed, which were identical with those compounds formed by gold-catalyzed cyclization reaction of **290** (Scheme 90).



Scheme 90

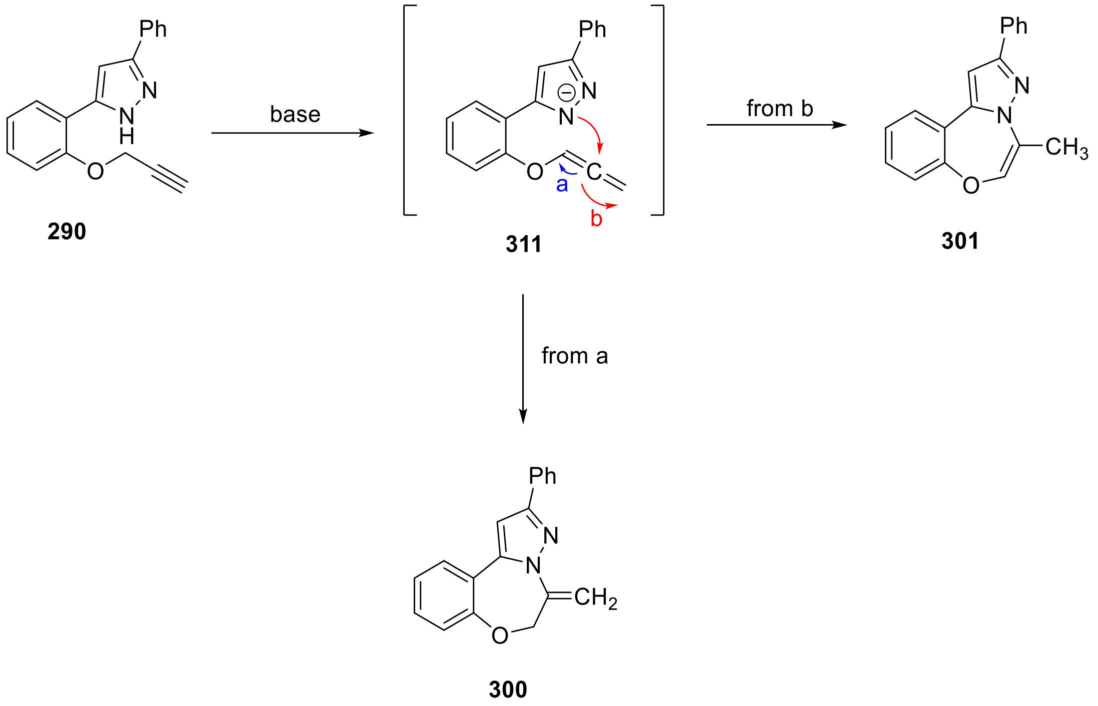
We realized that the eight-membered ring system was not formed under basic condition. In the light of the these results, we can propose that this reaction progresses via allene intermediate. The central carbon atom of allene unit has a positive character, which can be nicely seen from the the ^{13}C NMR shift data of an allene system. The central carbon atom of allene resonates at about 200 ppm while the terminal carbons resonate at about 90 ppm (Scheme 91). It means that the middle carbon is the most electropositive carbon of an allene unit and can easily be attacked by nucleophiles.

^{13}C Chemical Shifts in ppm



Scheme 91

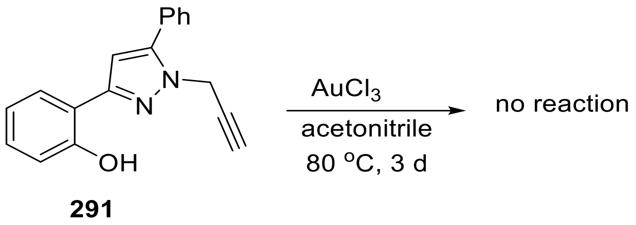
We propose that the starting material **290** of the reaction first underwent an isomerization reaction under the basic condition to form the corresponding allene **311** as the intermediate. After the formation of allene, nitrogen anion formed after proton abstraction, exclusively attacks the central carbon atom of allene due to the electropositive character. Two different carbanions may be formed depending which double bond is opened. The formed product can arise from two different intermediates. It is also possible that first **300** is formed exclusively. The product **301** may be a secondary product formed by the isomerization of **300** under the basic conditions. (Scheme 92).



Scheme 92

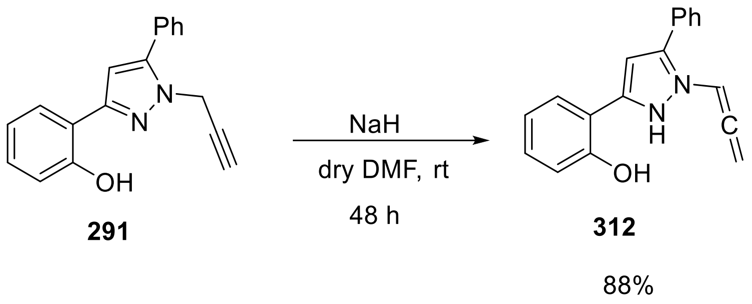
2.2.6 Intamolecular Cyclization Reactions of *N*-propargylated Compound

Previously, we discussed the formation of *N*-propargylated compound **291** (Scheme 79). To test whether this compound can undergo a cyclization reaction or not, **291** was submited to a gold-catalyzed as well as to base-catalyzed cyclization reactions under the similar conditions as discussed before. After three days, there was no change in the case of gold-catalyzed reaction. (Scheme 93).



Scheme 93

The base-catalyzed reaction gave the corresponding allene **312** as expected. However, there was no cyclization product derived from **312** (Scheme 94).



Scheme 94

The formation of allene was established by NMR spectral data. The ^{13}C NMR spectrum showed resonance signal at 203.7 ppm indicating the formation of the allenic structure (Figure 15).

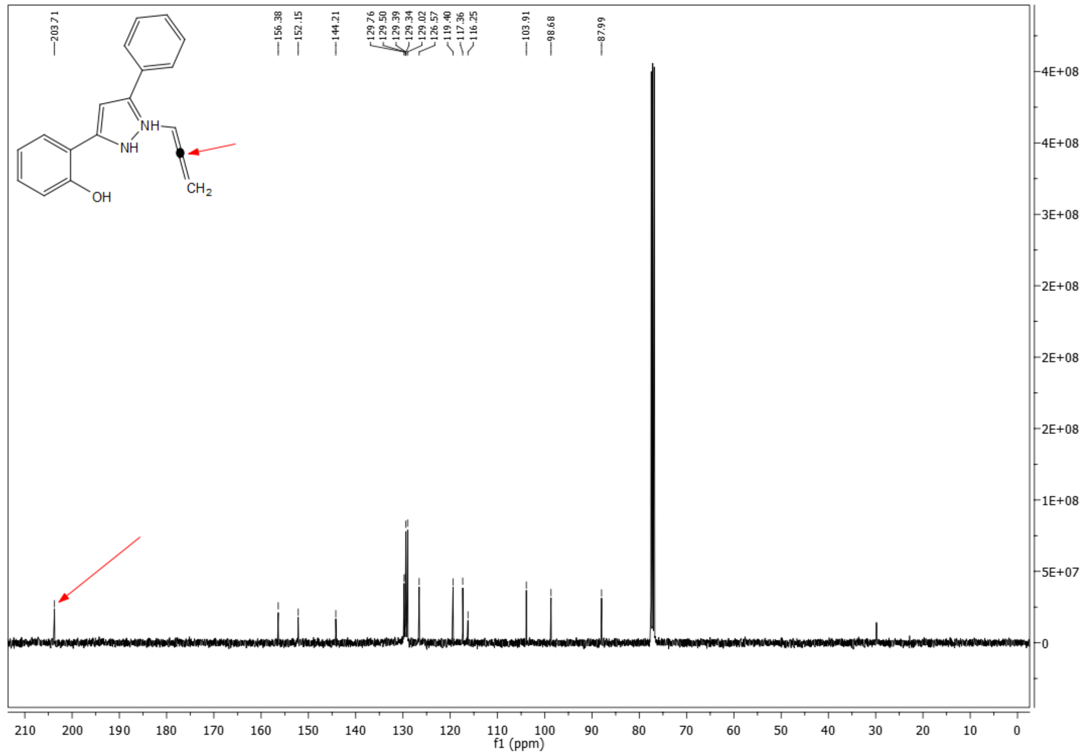


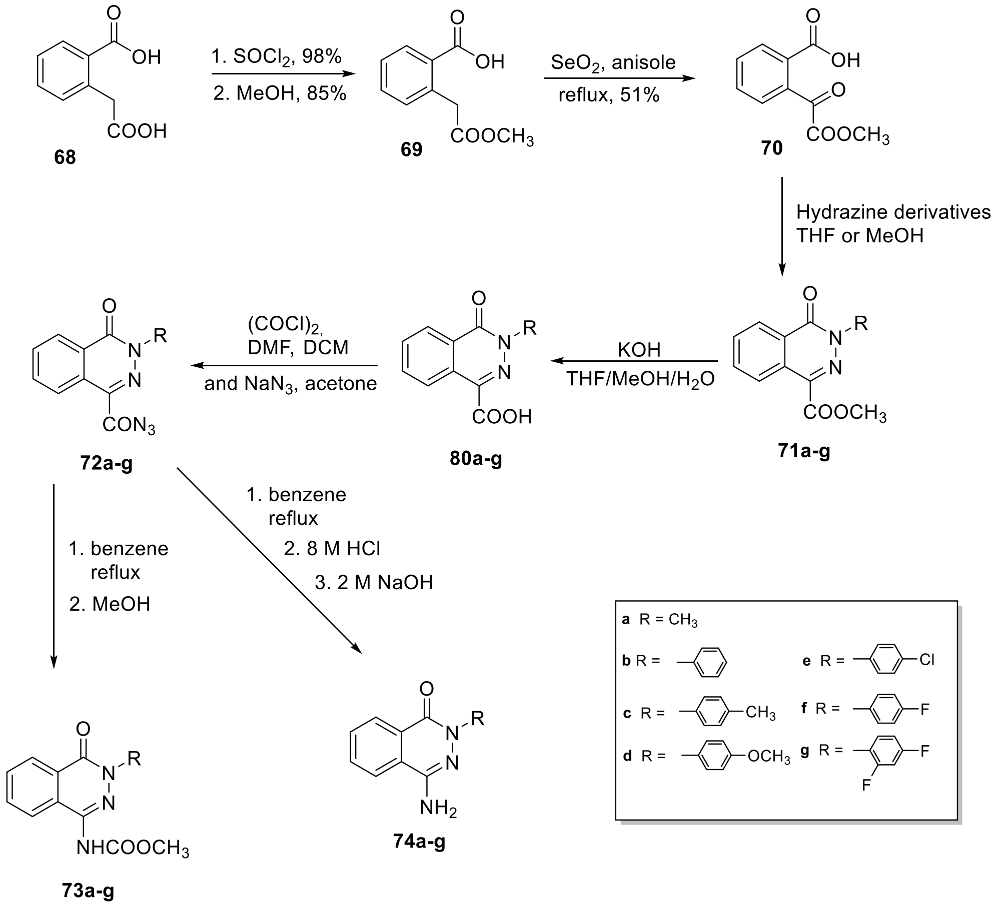
Figure 15: ^{13}C NMR Spectrum of Compound 312

The cyclization reaction of compound **291** was tried at higher temperatures in DMF. Unfortunately, no cyclization product was observed.

CHAPTER 3

CONCLUSION

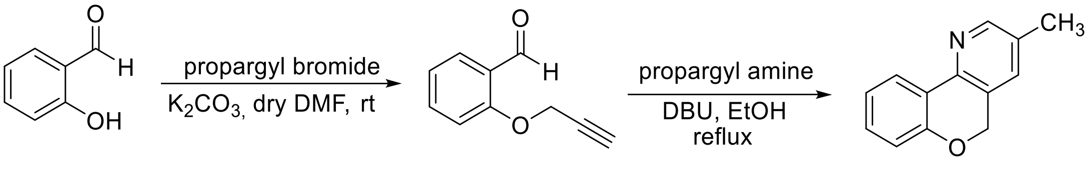
Heterocyclic compounds are important compounds as pharmacologically and biologically. In our project, we have firstly developed a new synthetic methodology for the synthesis of phthalazinone and aminophthalazinone derivatives which might have important biological activities.



Scheme 95

We synthesized aminophthalazinone derivatives **74a-g** (Scheme 95). For this synthesis, we started from the homophthalic acid (**68**). Firstly, esterification was carried out to obtain compound **69** regioselectively. After that, methylene group in **69** was oxidized to ketone **70** with SeO_2. Intramolecular cyclization was achieved by using seven different hydrazine derivatives. Hydrolysis of ester functionalities in **71a-g** resulted in the formation of corresponding acids **80a-g.** Formed acid derivatives were converted to acyl azides **72a-g**. The acyl azides **72a-g** were heated at reflux temperature of methanol to give the corresponding urethanes **73a-g**. On the other hand, aminophthalazinone derivatives **74a-g** were synthesized by treatment of isocyanates with 8 M HCl. This part of the work was published in 2013.[129]

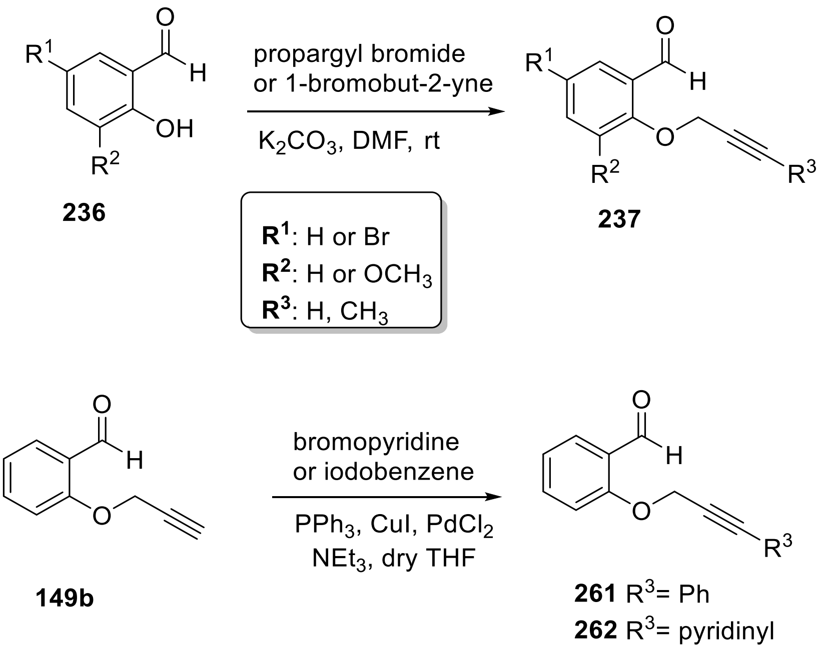
In the second part of thesis, we described a concise synthetic methodology for (benzo)chromenopyridine and (benzo)chromenopyridinone derivatives which might have important biological activities. This methodology has a two step process starting from the commercial starting material, salicylaldehyde **208** (Scheme 96).



208 **149b** **257**

Scheme 96

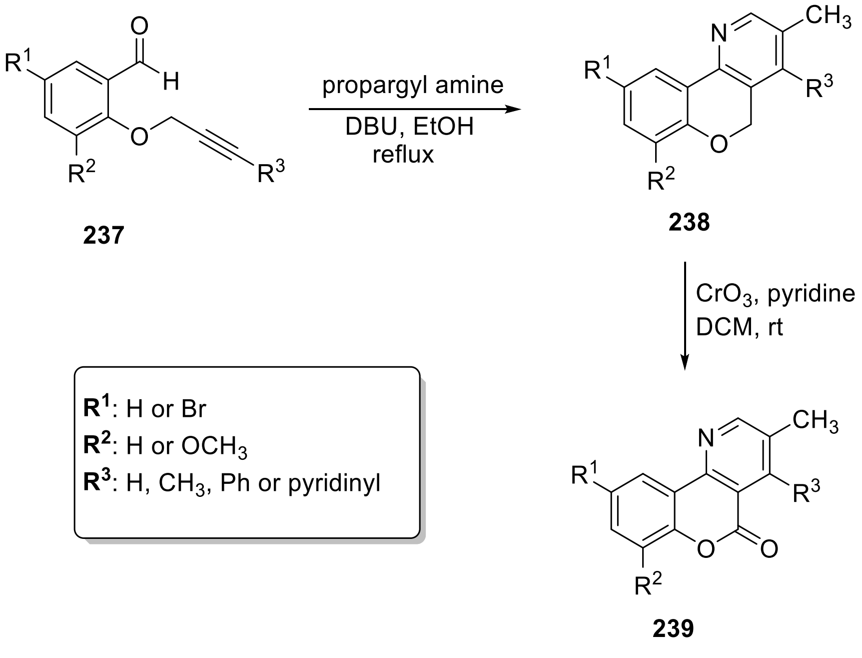
This methodology was successfully extended to the synthesis of polycyclic systems. The key features of this method includes (i) the synthesis of *O*-propargylated benz- and naphthaldehydes; (ii) the introduction of substituents into the alkyne functionality by Sonogashira cross-coupling to obtain precursors of the cyclization reactions (Scheme 97).



Scheme 97

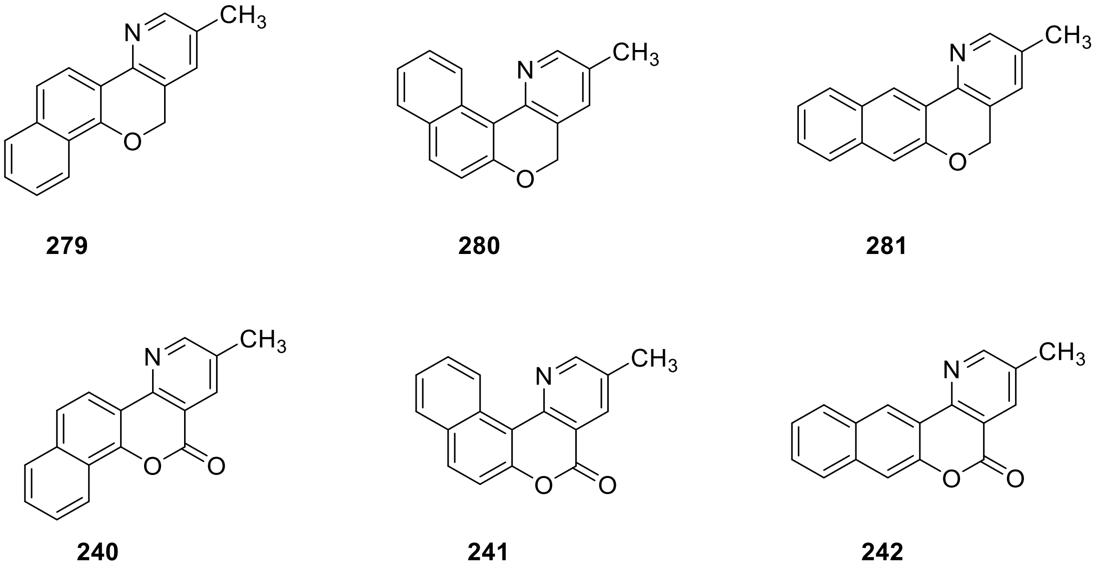
(iii) Alkyne cyclization via heterocycloaddition to form the chromenopyridine scaffold; and (iv) CrO_3 oxidation reaction.

This synthetic strategy also represented a reasonable methodology, that will allow us to introduce various substituents into all positions of the target compounds (Scheme 98).



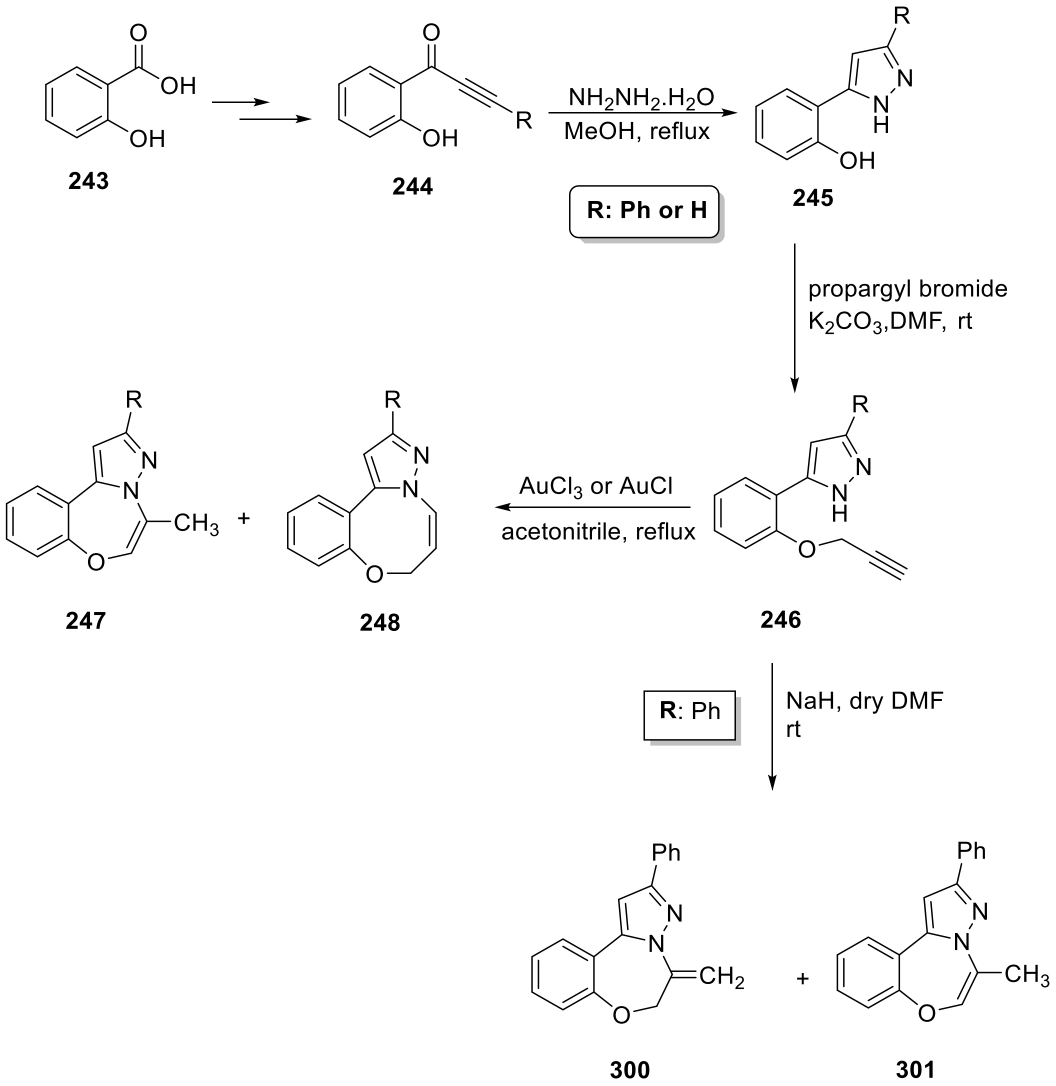
Scheme 98

The structures of synthesized benzochromenopyridine and benzochromenopyridinone derivatives are shown below (Scheme 99). This part of the work was published in 2015.[130]



Scheme 99

In the last part of study, we constructed benzene fused oxazepine and oxazocine units which are important heterocyles for the synthetic organic chemist. Also, the obtained compounds contain pyrazole unit. The newly synthesized compounds contain oxazepine, oxacine units as well as pyrazole units. Therefore, these compounds might have important acitivities. Firstly we constructed pyrazole skeleton that connected to benzene ring starting from the salicylic acid. The obtained compound **245** also have *o*-hydroxy group. Propargyl group was attached to the oxygen atom in the presence of a base. Later, we succeeded in intramolecular cyclization by using gold catalys or a base via alkyne cyclization (Scheme 100).


OH
OH
O
243
244
R
NH2NH2.H2O
MeOH, reflux
R: Ph or H
245
propargyl bromide
K2CO3,DMF, rt
246
AuCl3 or AuCl
acetonitrile, reflux
247
248
CH3
+
R: Ph
NaH, dry DMF
rt
Ph
CH2
300
301

Scheme 100

CHAPTER 4

EXPERIMENTAL

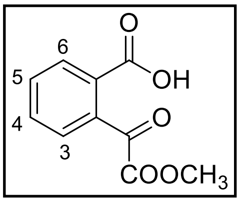
4.1 General

Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in DMSO-d_6 and $CDCl_3$ with TMS as internal reference. Chemical shifts (δ) were expressed in units parts per million (ppm). Spin multiplicities were specified as singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t) and multiplet (m) and coupling constants (J) were reported in Hertz (Hz). Infrared spectra were recorded on a Bruker Platinum ATR FT-IR spectrometer and Thermo Scientific Nicolet IS10 ATR FT-IR spectrometer. Band positions were reported in reciprocal centimeter (cm^{-1}). Mass spectra were recorded by Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) LC/MS on Agilent 1200/6530.

Column chromatographic separations were performed by using Merck Silica Gel 60 plates with a particle size of 0.063–0.200 mm. Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Merck.

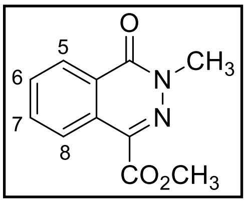
Compounds were named by using ChemDraw Ultra 12.0. Solvents were purified as reported in the literature.[131]

4.2 2-[Methoxy(oxo)acetyl]benzoic acid (70)



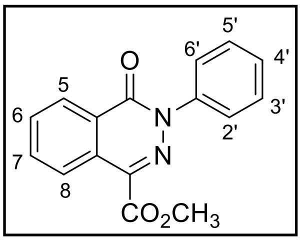
The monoester **69** (4.0 g, 20.61 mmol) was dissolved in anisole (40 mL) and SeO_2 (3.43 g, 30.93 mmol) was added. The mixture was heated at reflux temperature for 6 h. The reaction mixture was cooled, filtered, and washed with ethyl acetate (100 mL). The filtrate was evaporated. The crude product was purified by column chromatography (silica gel) eluting with hexane/EtOAc (5:1, 2:1) to give oxidized monoester **70** as a white solid (2.2 g, 51%), mp 72-73 °C (lit. mp 74-85 °C).[132] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (dt, J = 7.6, J = 0.8 Hz, H_3), 7.77 (dt, J = 7.5, J = 1.1 Hz, H_4), 7.68 (dt, J = 7.5, J = 1.0 Hz, H_6), 7.58 (dt, J = 7.6, J = 0.8 Hz, H_5), 3.82 (s, 3H, $-OCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.3, 167.9, 167.8, 144.8, 134.9, 131.5, 127.0, 125.8, 122.9, 54.3. **IR** (KBr, cm^{-1}) 3507, 3431, 3046, 2853, 1770, 1735, 1465, 1289, 1230, 1149, 1112. **Elemental Analysis** [found: C, 57.83; H, 3.99. $C_{10}H_8O_5$ requires C, 57.70; H, 3.87%].

4.3 Methyl 3-methyl-4-oxo-3,4-dihydrophthalazine-1-carboxylate (71a)



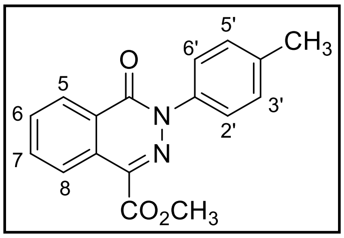
Methyl hydrazine (0.35 mL, 6.7 mmol) was added to a stirred solution of the monoester **70** (1.4 g, 6.7 mmol) in dry THF (25 mL) and stirred at 50 °C for 3 h. The mixture was cooled to rt, thionyl chloride (1 mL, 13.5 mmol) was added dropwise and then stirred at 50 °C for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with dichloromethane/ethyl acetate/hexane (1:1:1) to give a white solid **71a** (1.0 g, 68%), mp 125-126 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57 (ddd, J = 8.2, 1.2, 0.6 Hz, H_5), 8.40 (ddd, J = 8.0, 1.4, 0.4 Hz, H_6), 7.79 (ddd, J = 8.4, 7.3, 1.5 Hz, H_8), 7.73 (ddd, J = 8.0, 7.7, 1.3, H_7), 3.96 (s, 3H, $-OCH_3$), 3.87 (s, 3H, $-NCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.7, 159.7, 135.1, 133.6, 131.8, 128.1, 127.5, 126.9, 126.3, 53.0, 40.1. **IR** (KBr, cm^{-1}) 3046, 2952, 1720, 1675, 1443, 1321, 1288, 1213, 1159. **Elemental Analysis**: [found: C, 60.19; H, 4.78; N, 12.31. $C_{11}H_{10}N_2O_3$ requires C, 60.55; H, 4.62; N, 12.31%].

4.4 Methyl 4-oxo-3-phenyl-3,4-dihydrophthalazine-1- carboxylate (71b)



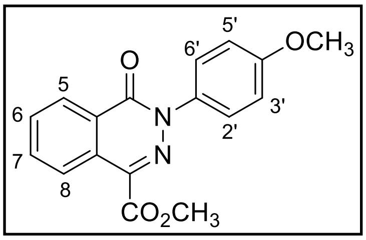
Phenyl hydrazinium chloride (1.1 equiv) was added to a stirred solution of the monoester **70** (1.0 g, 4.8 mmol) in dry methanol (50 mL). This mixture was stirred at 70 °C for 4 h. The solvent was evaporated and the residue was dissolved in dry benzene (70 mL). Thionyl chloride (4 equiv) was added dropwise and then the mixture was stirred for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:4) to give a white solid **71b** (1.1 g, 74%), mp 111-112 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (ddd, J = 8.2, 1.1, 0.4 Hz, H_5), 8.56 (ddd, J = 8.0, 1.1, 0.4 Hz, H_8), 7.93 (ddd, J = 8.2, 7.4, 0.5 Hz, H_6), 7.86 (ddd, J = 8.5, 7.3, 1.2 Hz, H_7), 7.72-7.68 (m, $H_{2'}$ and $H_{6'}$), 7.56-7.51 (m, $H_{3'}$ and $H_{5'}$), 7.44 (tt, J = 7.4, 1.2 Hz, $H_{4'}$), 4.04 (s, 3H, $-OCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.8, 159.1, 141.4, 136.1, 134.0, 132.1, 128.9, 128.4, 128.3, 127.7, 127.6, 126.4, 125.8, 53.0. **IR** (KBr, cm^{-1}) 3040, 2954, 1719, 1666, 1595, 1427, 1321, 1234, 1175, 1143, 1027. **Elemental Analysis** [found: C, 68.45; H, 4.40; N, 9.95. $C_{16}H_{12}N_2O_3$ requires C, 68.56; H, 4.32; N, 9.99%].

4.5 Methyl 3-(4-methylphenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylate (71c)



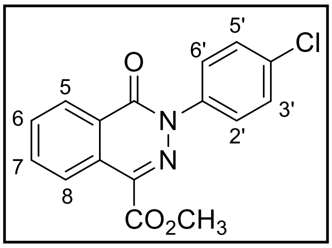
p-Tolylhydrazinium chloride (1.1 equiv) was added to a stirred solution of the monoester **70** (1.0 g, 4.8 mmol) in dry methanol (50 mL). This mixture was stirred at 50 °C for 4 h. The solvent was evaporated and the residue was dissolved in dry benzene (70 mL). Thionyl chloride (4 equiv) was added dropwise and then the mixture was stirred for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:4) to give a white solid **71c** (2.1 g, 74%), mp 152-153 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (br dd, J = 7.9, 0.8 Hz, H_5), 8.47 (dd, J = 7.9, 1.0 Hz, H_8), 7.83 (ddd, J = 8.3, 7.3, 1.5 Hz, H_6), 7.76 (ddd, J = 8.4, 7.4, 1.2 Hz, H_7), 7.48-7.45 (m, $H_{2'}$ and $H_{6'}$), 7.25-7.22 (m, $H_{3'}$ and $H_{5'}$), 3.94 (s, 3H, $-OCH_3$), 2.35 (s, 3H, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.8, 159.1, 138.9, 138.3, 135.9, 133.9, 132.0, 129.5, 128.4, 127.7, 127.5, 126.3, 125.6, 53.0, 21.1. **IR** (KBr, cm^{-1}) 3050, 1720, 1679, 1647, 1515, 1329, 1238, 1142. **Elemental Analysis** [found: C, 69.04; H, 4.71; N, 9.40. $C_{17}H_{14}N_2O_3$ requires C, 69.38; H, 4.79; N, 9.52%].

4.6 Methyl 3-(4-methoxyphenyl)-4-oxo-3,4-dihydro-phthalazine-1-carboxylate (71d)



p-Methoxyphenylhydrazinium chloride (1.1 equiv) were added to a stirred solution of the monoester **70** (1.0 g, 4.8 mmol) in dry methanol (50 mL). This mixture was stirred at 50 °C for 2.5 h. The solvent was evaporated and the residue was dissolved in dry benzene (70 mL). Thionyl chloride (4 equiv) was added dropwise and then the mixture was stirred for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:9) to give a white solid **71d** (0.83 g, 56%), mp 181-182 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.59 (br d, J = 8.7 Hz, H_5), 8.47 (dd, J = 8.0, 1.2 Hz, H_8), 7.83 (ddd, J = 8.7, 7.3, 1.4 Hz, H_6), 7.77 (ddd, J = 8.3, 7.7, 1.2 Hz, H_7), 7.53-7.48 (m, A-part of AA´BB´ system, $H_{2'}$ and $H_{6'}$), 6.97-6.93 (m, B-part of AA´BB´ system, $H_{3'}$ and $H_{5'}$), 3.94 (s, 3H, $-OCH_3$), 3.80 (s, 3H, $-OCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.8, 159.3, 159.2, 135.8, 134.4, 133.9, 132.0, 128.3, 127.7, 127.5, 127.1, 126.3, 114.1, 55.6, 53.0. **IR** (KBr, cm^{-1}) 3000, 2953, 1722, 1671, 1513, 1435, 1253, 1144, 1046. **Elemental Analysis** [found: C, 65.45; H, 4.84; N, 8.95. $C_{17}H_{14}N_2O_4$ requires C, 65.80; H, 4.55; N, 9.03%].

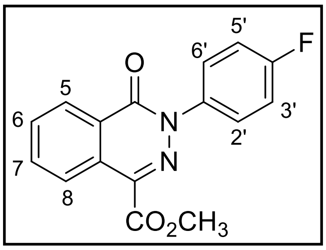
4.7 Methyl 3-(4-chlorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylate (71e)



p-Chlorophenylhydrazinium chloride (1.1 equiv) was added to a stirred solution of the monoester **70** (1.0 g, 4.8 mmol) in dry methanol (50 mL). This mixture was stirred at 65 °C for 4 h. The solvent was evaporated and the residue was dissolved in dry benzene (70 mL). Thionyl chloride (4 equiv) was added dropwise and then the mixture was stirred for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:4) to give a white solid **71e** (0.65 g, 80%), mp

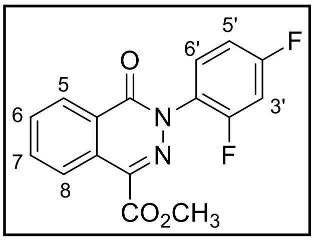
179-181 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (br d, J = 8.1 Hz, H_5), 8.55 (dd, J = 7.9, 0.8 Hz, H_8), 7.94 (ddd, J = 8.2, 7.7, 1.4 Hz, H_6), 7.87 (ddd, J = 8.5, 7.6, 1.2 Hz, H_7), 7.69-7.66 (m, A-part of AA´BB´ system, $H_{2'}$ and $H_{5'}$), 7.52-7.48 (m, B-part of AA´BB´ system, $H_{3'}$ and $H_{6'}$), 4.04 (s, 3H, $-OCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.6, 159.0, 139.8, 136.4, 134.2, 134.0, 132.3, 129.0, 128.2, 127.6, 127.1 (2C), 126.5, 53.1. **IR** (KBr, cm^{-1}) 3085, 2952, 1723, 1683, 1489, 1481, 1435, 1323, 1235, 1171, 1143, 1091, 1064, 1046. **Elemental Analysis** [found: C, 60.79; H, 3.41; N, 8.83. $C_{16}H_{11}ClN_2O_3$ requires C, 61.06; H, 3.53; N, 8.90%].

4.8 Methyl 3-(4-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylate (71f)



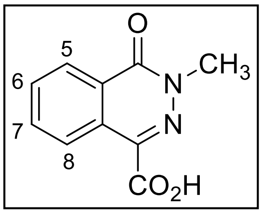
p-Florophenylhydrazinium chloride (1.1 equiv) were added to a stirred solution of the monoester **70** (1.0 g, 4.8 mmol) in dry methanol (50 mL). This mixture was stirred at 65 °C for 4 h. The solvent was evaporated and the residue was dissolved in dry benzene (70 mL). Thionyl chloride (4 equiv) was added dropwise and then the mixture was stirred for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:3) to give a white solid **71f** (1.05 g, 73%), mp 125-127 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (br d, J = 8.0 Hz, H_5), 8.56 (dd, J = 7.9, 0.9 Hz, H_8), 7.93 (ddd, J = 8.6, 7.4, 1.4 Hz, H_6), 7.88 (ddd, J = 8.3, 7.4, 1.2 Hz, H_7), 7.71-7.66 (m, A-part of AA´BB´X system, $H_{2'}$ and $H_{5'}$), 7.25-7.19 (m, B-part of AA´BB´X system, $H_{3'}$ and $H_{6'}$), 4.05 (s, 3H, $-OCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.6, 162.1 (d, J = 248.1 Hz), 159.1, 137.3 (d, J = 3.0 Hz), 136.2, 134.1, 132.2, 128.3, 127.8, 127.7, 127.6 (d, J = 7.3 Hz), 126.5, 115.8 (d, J = 22.8), 53.1. **IR** (KBr, cm^{-1}) 3089, 2953, 1723, 1683, 1505, 1483, 1349, 1233, 1143, 1046. **Elemental Analysis** [found: C, 64.04; H, 3.70; N, 9.22. $C_{16}H_{11}FN_2O_3$ requires C, 64.43; H, 3.72; N, 9.39%].

4.9 Methyl 3-(2,4-difluorophenyl)-4-oxo-3,4-dihydro-phthalazine-1-carboxylate (71g)



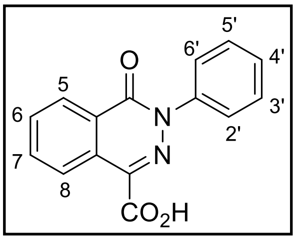
2,4-Diflorophenylhydrazinium chloride (1.1 equiv) was added to a stirred solution of the monoester **70** (1.0 g, 4.8 mmol) in dry methanol (50 mL). This mixture was stirred at 65 °C for 4 h. The solvent was evaporated and the residue was dissolved in dry benzene (70 mL). Thionyl chloride (4 equiv) was added dropwise and then the mixture was stirred for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:3) to give a white solid **71f** (0.5 g, 61%), mp 120-121 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.67 (br d, J = 8.1 Hz, $H_{6'}$), 8.54 (dd, J = 7.7, 1.2 Hz, H_5), 7.95 (dt, J = 8.3, 1.4 Hz, H_8), 7.88 (br dt, J = 7.8, 0.8 Hz, H_6), 7.56-7.50 (m, H_7), 7.09-7.01 (m, $H_{3'}$ and $H_{5'}$), 4.04 (s, 3H, $-OCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.4,163.0 (dd, J = 251.6, 11.1 Hz), 158.7, 157.7 (dd, J = 255.7, 12.6 Hz), 137.0, 134.3, 132.4, 129.9 (dd, J = 10.3, 1.8 Hz), 127.8, 127.8, 127.5, 126.6, 125.5 (dd, J = 13.0, 4.1 Hz), 111.9 (dd, J = 22.7, 3.7 Hz), 105.1 (dd, J = 26.4, 23.5 Hz), 53.1. **IR** (KBr, cm^{-1}) 3021, 2970, 1742, 1679, 1605, 1533, 1434, 1352, 1330, 1274, 1230, 1170, 1143, 1073. **Elemental Analysis** [found: C, 60.59; H, 3.32; N, 8.76. $C_{16}H_{10}F_2N_2O_3$ requires C, 60.76; H, 3.19; N, 8.86%].

4.10 3-Methyl-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (80a)



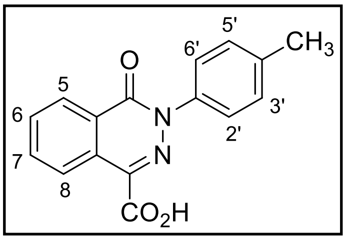
The ester **71a** (1.0 g, 4.59 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 40 °C for 1.5 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The acid derivative **80a** was obtained as a white solid. (0.8 g, 85%), mp 246-247 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.53 (br d, J = 8.1 Hz, H_5), 8.27 (br d, J = 7.8 Hz, H_8), 7.94 (br t, J = 7.7 Hz, H_6), 7.86 (br t, J = 7.5 Hz, H_7), 3.77 (s, 3H, -CH_3). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.4, 158.6, 135.4, 133.6, 131.9, 127.4, 126.8, 126.2, 126.0, 40.1. **IR** (KBr, cm^{-1}) 3017, 2875, 1716, 1624, 1575, 1489, 1415, 1346, 1311, 1209, 1186, 1063. **Elemental Analysis** [found: C, 58.49; H, 4.07; N, 13.43. $C_{10}H_8N_2O_3$ requires C, 58.82; H, 3.95; N, 13.72%].

4.11 4-Oxo-3-phenyl-3,4-dihydrophthalazine-1-carboxylic acid (80b)



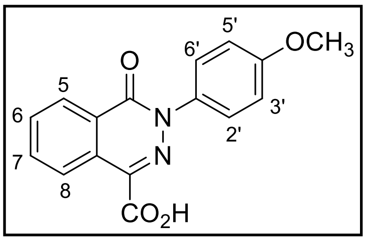
The ester **71b** (1.0 g, 3.57 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 40 °C for 1.5 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The acid derivative **80b** was obtained as a white solid. (0.80 g, 85%), mp 217-218 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.13 (br d, J = 8.2 Hz, H_5), 8.48 (dd, J = 7.8, 0.8 Hz, H_8), 7.90 (dt, J = 7.6, 1.4 Hz, H_6), 7.83 (dt, J = 8.1, 1.1 Hz, H_7), 7.56-7.54 (m, $H_{2'}$ and $H_{6'}$), 7.51-7.47 (m, $H_{3'}$ and $H_{5'}$), 7.42 (tt, J = 7.2, 1.1 Hz, $H_{4'}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.6, 159.2, 140.1, 134.6, 133.1, 132.9, 129.2, 128.9, 128.4, 127.7, 127.6, 127.3, 125.7. **IR** (KBr, cm^{-1}) 2859, 1735, 1708, 1686, 1596, 1576, 1432, 1317, 1281, 1157, 1125; **HRMS-ESI** $[M + Na]^+$ calcd for $C_{15}H_{10}N_2NaO_3$ 267.0764, found: 267.0731.

4.12 3-(4-Methylphenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (80c)



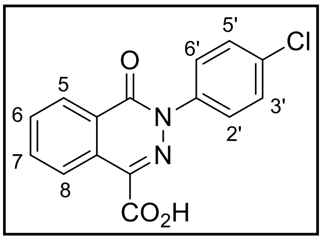
The ester **71c** (1.0 g, 3.4 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 40 °C for 1.5 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The acid derivative **80c** was obtained as a white solid. (1.05 g, 90%), mp 204-205 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.11 (dd, J = 8.3, 0.6 Hz, H_5), 8.47 (dd, J = 7.9, 0.9 Hz, H_8), 7.89 (ddd, J = 8.4, 7.2, 1.2 Hz, H_6), 7.82 (ddd, J = 8.3, 7.2, 1.4 Hz, H_7), 7.43-7.40 (m, A-part of AA´BB´ system, $H_{2'}$ and $H_{6'}$), 7.28-7.26 (m, B-part of AA´BB´ system, $H_{3'}$ and $H_{5'}$), 2.38 (s, 3H, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.0, 159.3, 139.0, 138.1, 134.6, 133.1, 132.8, 129.7, 128.3, 127.7, 127.4, 127.3, 125.5, 21.2. **IR** (KBr, cm^{-1}) 3003, 2970, 1738, 1705, 1682, 1510, 1433, 1320, 1250, 1183, 1171; **HRMS-MALDI** [M - H]$^-$ calcd for $C_{16}H_{11}N_2O_3$ 279.0769; found: 279.0779.

4.13 3-(4-Methoxyphenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (80d)



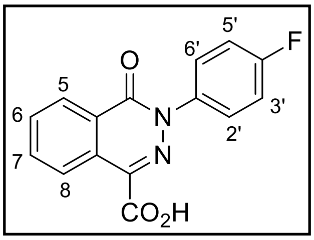
The ester **71d** (1.0 g, 3.22 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 45 °C for 16 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was evaporated. The acid derivative **80d** was obtained as a white solid. (1.01 g, 87%), mp 219-220 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.57 (br d, J = 8.0 Hz, H_5), 8.37 (br dd, J = 7.8, 0.7 Hz, H_8), 8.02 (ddd, J = 8.4, 7.4, 1.3 Hz, H_6), 7.94 (dt, J = 8.0, 1.0 Hz, H_7), 7.56-7.52 (m, A-part of AA´BB´ system, $H_{2'}$ and $H_{6'}$), 7.10-7.06 (m, B-part of AA´BB´ system, $H_{3'}$ and $H_{5'}$), 3.83 (s, 3H, $-OCH_3$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.5, 158.7, 158.4, 136.7, 134.3, 134.0, 132.2, 127.8, 127.5, 127.2, 126.7, 126.4, 113.8, 55.4. **IR** (KBr, cm^{-1}) 2989, 2839, 2560, 1701, 1609, 1511, 1436, 1313, 1248, 1160. **Elemental Analysis** [found: C, 64.52; H, 4.00; N, 9.28. $C_{16}H_{12}N_2O_4$ requires C, 64.86; H, 4.08; N, 9.46%].

4.14 3-(4-Chlorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (80e)



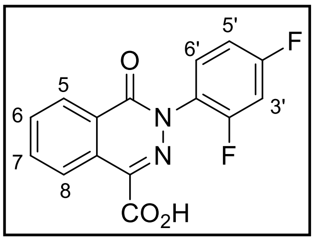
The ester **71e** (1.0 g, 3.17 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 60 °C for 4 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The acid derivative **80e** was obtained as a white solid. (1.0 g, 74%), mp 208-209 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.58 (br d J = 7.7 Hz, H_5), 8.39 (dd, J = 8.8, 0.9 Hz, H_8), 8.04 (dt, J = 7.3, 1.5 Hz, H_6), 7.96 (dt, J = 8.0, 1.2 Hz, H_7), 7.72-7.69 (m, A-part of AA′BB′ system, $H_{2'}$ and $H_{6'}$), 7.74-7.61 (m, B part of AA′BB′ system, $H_{3'}$ and $H_{5'}$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 164.3, 158.3, 140.1, 137.1, 134.2, 132.4, 132.3, 128.6, 127.9, 127.7, 127.2, 126.7, 126.5. **IR** (KBr, cm^{-1}) 3003, 2970, 1738, 1683, 1484, 1431, 1372, 1319, 1230, 1154. **HRMS-MALDI** $[M + H]^+$ calcd for $C_{15}H_{10}ClN_2O_3$ 301.0380, found: 301.0371.

4.15 3-(4-Fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (80f)



The ester **71f** (1.0 g, 3.35 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 60 °C for 2 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated. The acid derivative **80f** was obtained as a white solid. (0.96 g, 77%), mp 215-217 °C. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.58 (br d, J = 8.2 Hz, H_5), 8.38 (dd, J = 7.9, 0.8 Hz, H_8), 8.04 (dt, J = 7.4, 1.4 Hz, H_6), 7.96 (dt, J = 8.2, 1.1 Hz, H_7), 7.71-7.68 (m, A-part of AA′BB′X system, $H_{2'}$ and $H_{6'}$), 7.41-7.37 (m, B-part of AA′BB′X system, $H_{3'}$ and $H_{5'}$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ 173.1, 168.6, 167.1 (d, J = 245.6 Hz), 143.1 (d, J = 3.0 Hz), 140.5, 139.2, 138.0, 128.4 (d, J = 8.8 Hz), 127.8, 127.2, 126.7, 126.4, 115.5 (d, *J* = 22.8 Hz). **IR** (KBr, cm^{-1}) 2980, 2643, 1736, 1672, 1629, 1602, 1507, 1481, 1404, 1346, 1294, 1234, 1216, 1174, 1151, 1130, 1015. **HRMS-MALDI** [M + H]$^+$ calcd for $C_{15}H_{10}FN_2O_3$ 285.0675, found: 285.0666.

4.16 3-(2,4-Difluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (80g)



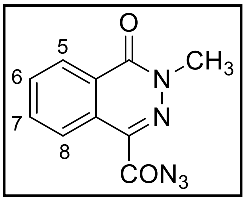
The ester **71g** (1.0 g, 3.16 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 60 °C for 2 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried over $MgSO_4$ and the solvent was evaporated.The acid derivative **80g** were obtained as a white solid. (0.93 g, 98%), mp 225-226 °C. **^{1}H NMR** (400 MHz, DMSO-d$_6$) δ 8.57 (dd, *J* = 8.2, 0.4 Hz, H_5), 8.37 (dd, *J* = 7.9, 0.8 Hz, H_8), 8.07 (dt, *J* = 7.9, 1.4 Hz, H_6), 7.98 (dt, *J* = 8.0, 1.2 Hz, $H_{6'}$), 7.76 (dt, *J* = 8.8, 6.1 Hz, $H_{5'}$), 7.57 (ddd, *J* = 10.4, 9.2, 2.8 Hz, H_7), 7.35-7.30 (m, $H_{3'}$). **^{13}C NMR** (100 MHz, DMSO-d$_6$) δ 163.3, 161.3 (dd, *J* = 248.7, 11.5 Hz), 157.2, 156.2 (dd, *J* = 252.7, 13.2 Hz). 137.0, 133.7, 131.9, 130.1 (d, *J* = 10.2 Hz), 126.5, 126.4, 125.9, 125.8, 124.8 (dd, *J* = 13.0, 4.1 Hz), 111.4 (dd, *J* = 22.6, 3.4 Hz), 104.0 (dd, *J* = 27.1, 24 Hz). **IR** (KBr, cm^{-1}) 3079, 1730, 1658, 1615, 1604, 1511, 1352, 1274, 1229, 1177, 1159, 1148. **Elemental Analysis**: [found: C, 59.28; H, 2.74; N, 8.92. $C_{15}H_8F_2N_2O_3$ requires C, 59.61; H, 2.67; N, 9.27%].

4.17 General Procedure for the Synthesis of Acyl Azide Derivatives (72a-g)

Oxalyl chloride (2 equiv) was added to a stirred suspension of acids **80a-g** (1.0 g) in dichloromethane at rt and then DMF (3 drops) were added. After 10 min, all acid dissolved and the solution was stirred at rt for 90 min. The solvent and excess oxalyl chloride were evaporated. The residue was dissolved in acetone (15 mL) and cooled in an ice bath. A solution of NaN_3 (2 equiv) in water (1 mL) was added dropwise and stirred in an ice-cooled bath for 90 min. The mixture was extracted with ethyl acetate (200 mL) and water (100 mL). The combined water layers were extracted with EtOAc

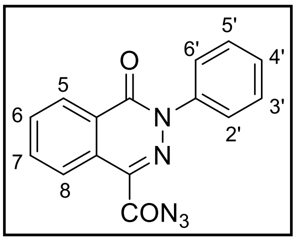
(3 × 75 mL), dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography eluting with ethyl acetate/dichloromethane/hexane (2:2:1) to give acyl azide derivatives **72a-g** as white solids.

4.17.1 3-Methyl-4-oxo-3,4-dihydrophthalazine-1-carbonyl azide (72a).



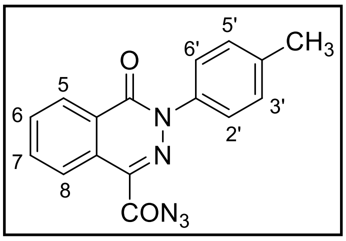
(0.90 g, 81%), mp 110-111 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.75 (br d, *J* = 7.9 Hz, H_5), 8.39 (dd, *J* = 7.9, 1.1 Hz, H_8), 7.82 (ddd, *J* = 8.6, 7.3, 1.5 Hz, H_7), 7.75 (ddd, *J* = 8.2, 8.1, 1.2 Hz, H_6), 3.88 (s, 3H, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 169.3, 159.0, 133.3, 131.8, 131.3, 127.1, 126.5, 126.2, 125.4, 39.5. **IR** (KBr, cm^{-1}) 3123, 2162, 1673, 1603, 1447, 1346, 1322, 1289, 1201, 1044.

4.17.2 4-Oxo-3-phenyl-3,4-dihydrophthalazine-1-carbonyl azide (72b)



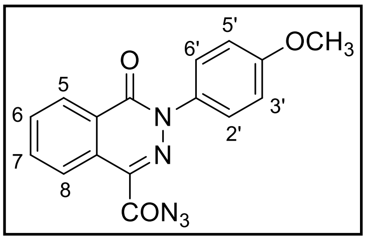
(0.82 g, 75%), mp 87-88 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.78 (br d, *J* = 8.2 Hz, H_5), 8.47 (dd, *J* = 7.9, 0.9 Hz, H_8), 7.87 (dt, *J* = 7.3, 1.4 Hz, H_6), 7.79 (dt, *J* = 8.0, 1.2 Hz, H_7), 7.62-7.58 (m, $H_{2'}$ and $H_{6'}$), 7.48-7.43 (m, $H_{3'}$ and $H_{5'}$), 7.37 (tt, *J* = 7.6, 1.2 Hz, $H_{4'}$). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 169.3, 159.0, 133.3, 131.8, 131.3, 127.1, 126.5, 126.2, 125.4, 39.6. **IR** (KBr, cm^{-1}) 3038, 2924, 2140, 1681, 1595, 1488, 1344, 1318, 1227, 1185, 1126, 1075.

4.17.3 3-(4-Methylphenyl)-4-oxo-3,4-dihydrophthalazine-1-carbonyl azide (72c)



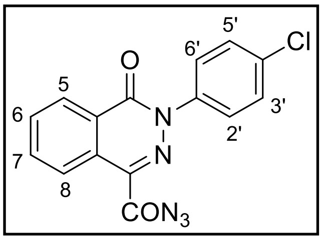
(1.05 g, 97%), mp 111-112°C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.77 (br d, *J* = 8.3 Hz, H_5), 8.45 (br d, *J* = 7.9 Hz, H_8), 7.87-7.83 (m, H_6), 7.80-7.75 (m, H_7), 7.47-7.44 (m, A-part of AA´BB´ system, $H_{2'}$ and $H_{6'}$), 7.26-7.24 (m, B-part of AA´BB´ system, $H_{3'}$ and $H_{5'}$), 2.35 (s, 3H, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 170.3,159.2,138.7, 138.6, 134.6, 134.3, 132.2, 129.6, 128.1, 127.7, 127.5, 126.2, 125.4, 21.2. **IR** (KBr, cm^{-1}) 3110, 2917, 2121, 1793, 1752, 1681, 1604, 1510, 1346, 1181, 1127.

4.17.4 3-(4-Methoxyphenyl)-4-oxo-3,4-dihydrophthalazine-1-carbonyl azide (72d)



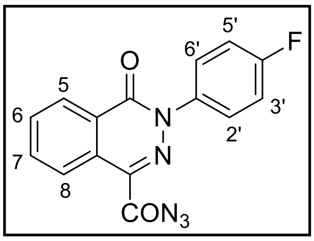
(1.01 g, 94%), mp 110-111 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.78 (dd, *J* = 8.3, 0.5 Hz, H_5), 8.46 (dd, *J* = 7.9, 0.9 Hz, H_8), 7.86 (dt, *J* = 7.3, 1.4 Hz, H_6), 7.78 (dt, *J* = 8.0, 1.2 Hz, H_7), 7.52-7.48 (m, A-part of AA′BB′ system, $H_{2'}$ and $H_{6'}$), 6.98-6.94 (m, B-part of AA′BB′ system, $H_{3'}$ and $H_{5'}$), 3.80 (s, 3H, $-OCH_3$). **IR** (KBr, cm^{-1}) 3078, 2954, 2146, 1724, 1694, 1676, 1509, 1323, 1252, 1173, 1031.

4.17.5 3-(4-Chlorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carbonyl azide (72e)



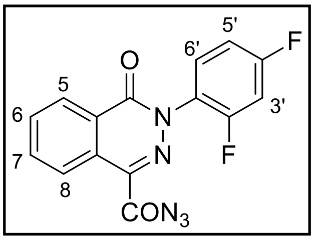
(1.0 g, 92%), mp 123-124 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.77 (dd, *J* = 8.3, 0.53 Hz, H_5), 8.46 (dd, *J* = 7.9, 0.9 Hz, H_8), 7.87 (dt, *J* = 7.3, 1.4 Hz, H_6), 7.79 (dt, *J* = 8.0, 1.2 Hz, H_7), 7.60-7.56 (m, A-part of AA′BB′ system, $H_{2'}$ and $H_{6'}$), 7.44-7.40 (m, B part of AA′BB′ system, $H_{3'}$ and $H_{5'}$). **IR** (KBr, cm^{-1}) 3093, 2969, 2146, 1735, 1691, 1608, 1449, 1439, 1347, 1319, 1276, 1201, 1129, 1069.

4.17.6 3-(4-Fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carbonyl azide (72f)



(0.96 g, 89%), mp 117-118 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.78 (dd, *J* = 8.2, 0.4 Hz, H_5), 8.46 (ddd, *J* = 8.0, 0.7, 0.6 Hz, H_8), 7.90-7.85 (m, H_6), 7.82-7.78 (m, H_7), 7.62-7.56 (m, A-part of AA′BB′X system, $H_{2'}$ and $H_{6'}$), 7.17-7.11 (m, B-part of AA′BB′X system, $H_{3'}$ and $H_{5'}$). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 170.2, 162.2 (d, *J* = 248.7 Hz), 159.1, 137.1 (d, *J* = 3.0 Hz), 135.0, 134.5, 132.4, 128.3, 128.0, 127.6 (d, *J* = 15.3 Hz), 127.4, 126.3, 115.9 (d, *J* = 22.9 Hz). **IR** (KBr, cm^{-1}) 3131, 2940, 2148, 1698, 1683, 1603, 1507, 1350, 1325, 1237, 1182, 1128, 1076.

4.17.7 3-(2,4-Difluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carbonyl azide (72g)

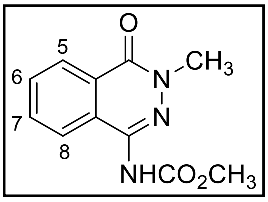


(0.93 g, 86%), mp 104-105 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.75 (br d, J = 8.4 Hz, H_5), 8.44 (dd, J = 7.9, 0.9 Hz, H_8), 7.87 (dt, J = 7.8, 1.4 Hz, H_6), 7.80 (dt, J = 8.1, 1.1 Hz, H_7), 7.45-7.40 (m, $H_{6'}$), 7.00-6.92 (m, $H_{3'}$ and $H_{5'}$). **IR** (KBr, cm^{-1}) 3092, 2969, 2146, 1692, 1607, 1507, 1481, 1346, 1319, 1276, 1201, 1179, 1129, 1109, 1069.

4.18 General Procedure for the Synthesis of Urethane Derivatives 73a-g

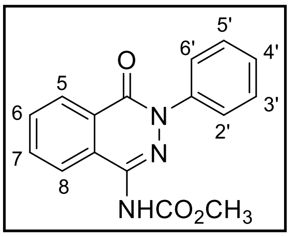
The acyl azide derivatives **72a-g** (0.25 g) were dissolved in dry benzene (40 mL) and heated at reflux for 90 min. To this solution, dry MeOH (2 mL) was added and stirred at same temperature for 2-16 h. The reaction was monitored on TLC. The solvent and excess methanol were evaporated. The crude product was purified by column chromatography (silica gel) with suitable eluent to give urethane derivatives **73a-g** as white solids.

4.18.1 Methyl (3-methyl-4-oxo-3,4-dihydrophthalazin-1-yl)carbamate (73a)



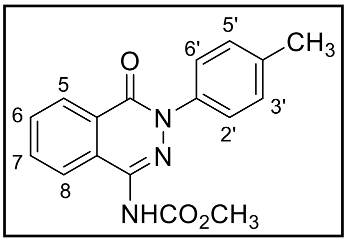
(0.24 g, 96%), mp 173-174 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.38-8.35 (m, H_8), 7.73-7.71 (m, H_5, H_6 and H_7), 6.81 (b s, 1H, -NH), 3.73 (s, 3H, $-OCH_3$), 3.73 (s, 3H, $-NCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 155.4, 137.2, 132.9, 132.0, 128.6, 127.6, 127.1, 124.7, 53.1, 39.3. **IR** (KBr, cm^{-1}) 3218, 2950, 1734, 1626, 1578, 1556, 1489, 1452, 1353, 1230, 1060. [found: C, 56.45; H, 4.83; N, 17.94. $C_{11}H_{11}N_3O_3$ requires C, 56.65; H, 4.75; N, 18.02%].

4.18.2 Methyl (4-oxo-3-phenyl-3,4-dihydrophthalazin-1-yl)carbamate (73b)



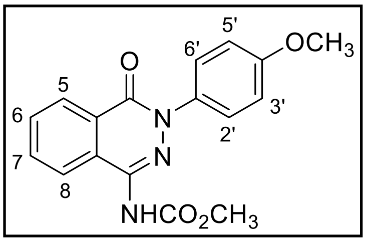
(0.21 g, 85%), mp 175-176 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.57-8.54 (m, H_5), 7.90-7.86 (m, H_6, H_7 and H_8), 7.70-7.67 (m, $H_{2'}$ and $H_{6'}$), 7.54-7.50 (m, $H_{3'}$ and $H_{5'}$), 7.41 (tt, J = 7.4, 7.4 Hz, $H_{4'}$), 6.77 (br s, 1H, -NH), 3.85 (s, 3H, $-OCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.9, 155.5, 147.1, 141.4, 138.2, 133.3, 132.2, 129.3, 128.8, 127.8, 127.3, 125.6, 125.0, 53.1. **IR** (KBr, cm^{-1}) 3276, 3010, 2969, 2955, 1737, 1706, 1668, 1595, 1556, 1484, 1455, 1313, 1254, 1055. **Elemental Analysis** [found: C, 65.00; H, 4.27; N, 13.87. $C_{16}H_{13}N_3O_3$ requires C, 65.08; H, 4.44; N, 14.23%].

4.18.3 Methyl [3-(4-methylphenyl)-4-oxo-3,4-dihydrophthalazin-1-yl]carbamate (73c)



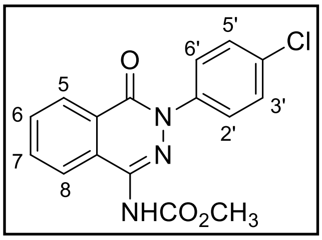
(0.21 g, 80%), mp 195-196 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (m, H_5), 7.77-7.70 (m, H_6, H_7 and H_8), 7.44-7.40 (m, A-part of AA′BB′ system, $H_{2'}$ and $H_{6'}$), 7.17 (m, B-part of AA′BB′ system, $H_{3'}$ and $H_{5'}$), 7.00 (br s, 1H, -NH), 3.72 (s, 3H, $-OCH_3$), 2.30 (s, 3H, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.9, 155.6, 138.9, 138.1, 137.8, 133.2, 132.1, 129.4, 129.3, 127.7, 127.3, 125.4, 125.0, 53.1, 21.1. **IR** (KBr, cm^{-1}) 3206, 3112, 2915, 1709, 1668, 1591, 1512, 1469, 1447, 1354, 1332, 1313, 1180, 1064. **Elemental Analysis** [found: C, 65.98; H, 4.83; N, 13.23. $C_{17}H_{15}N_3O_3$ requires C, 66.01; H, 4.89; N, 13.58%].

4.18.4 Methyl (3-(4-methoxyphenyl)-4-oxo-3,4-dihydrophthalazin-1-yl)carbamate (73d)



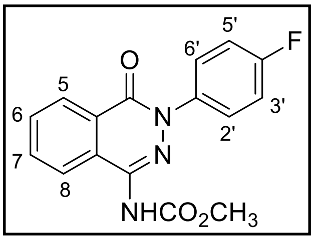
(0.21 g, 83%), mp 153-154 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46-8.44 (m, H_5), 7.80-7.74 (m, H_6, H_7 and H_8), 7.50-7.46 (m, A-part of AA′BB′ system, $H_{2'}$ and $H_{6'}$), 6.95-6.91 (m, B-part of AA′BB′ system, $H_{3'}$ and $H_{5'}$), 6.67 (br s, 1H, -NH), 3.79 (s, 3H, $-OCH_3$), 3.75 (s, 3H, $-OCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.8, 158.7, 155.3, 137.8, 134.2, 133.0, 131.9, 129.0, 127.5, 127.1, 126.6, 124.7, 113.7, 55.3, 52.9. **IR** (KBr, cm^{-1}) 3264, 3070, 2951, 1731, 1667, 1599, 1505, 1466, 1452, 1305, 1239, 1178, 1131, 1009. **Elemental Analysis**: [found: C, 62.97; H, 4.70; N, 12.88. $C_{17}H_{15}N_3O_4$ requires C, 62.76; H, 4.65; N, 12.92%].

4.18.5 Methyl (3-(4-chlorophenyl)-4-oxo-3,4-dihydrophthalazin-1-yl)carbamate (73e)



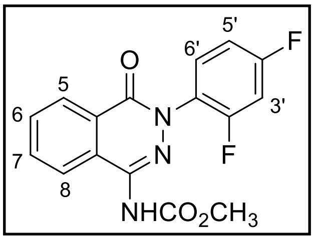
(0.23 g, 92%), mp 178-179 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45-8.43 (m, H_5), 7.82-7.74 (m, H_6, H_7 and H_8), 7.60-7.56 (m, A-part of AA′BB′ system, $H_{2'}$ and $H_{6'}$), 7.38-7.35 (m, B-part of AA′BB′ system, $H_{3'}$ and $H_{5'}$), 6.83 (s, 1H, -NH), 3.75 (s, 3H, -OCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.8, 155.4, 139.9, 138.4, 133.5, 133.3, 132.4, 129.2, 128.8, 127.9, 127.2, 126.7, 124.9, 53.2. **IR** (KBr, cm^{-1}) 3221, 3053, 2969, 1705, 1668, 1597, 1524, 1485, 1327, 1249, 1173, 1132, 1069, 1041, 1021, 1009. **HRMS-MALDI** $[M + H]^+$ calcd for $C_{16}H_{13}ClN_3O_3$ 330.0645, found : 330.0688.

4.18.6 Methyl (3-(4-fluorophenyl)-4-oxo-3,4-dihydrophthalazin-1-yl)carbamate (73f)



(0.25 g, 99%), mp 190-192 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44-8.42 (m, H_5), 7.79-7.74 (m, H_6, H_7 and H_8), 7.58-7.54 (m, A-part of AA′BB′X system, $H_{2'}$ and $H_{6'}$), 7.10-7.05 (m, B-part of AA′BB′X system, $H_{3'}$ and H'_5), 6.90 (s, 1H, -NH), 3.74 (s, 3H, -OCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.7 (d, J = 246.1 Hz), 158.9, 155.4, 138.2, 137.4 (d, J = 3.0 Hz), 133.4, 132.4, 129.2, 127.8, 127.4 (d, J = 8.7 Hz), 127.3, 125.0, 115.6 (d, J = 22.7 Hz), 53.2. **IR** (KBr, cm^{-1}) 3221, 3072, 2923, 1705, 1665, 1587, 1556, 1504, 1454, 1324, 1256, 1213, 1140, 1058. **Elemental Analysis**: [found: C, 61.08; H, 4.11; N, 13.09. $C_{16}H_{12}FN_3O_3$ requires C, 61.34; H, 3.86; N, 13.41%].

4.18.7 Methyl (3-(2,4-difluorophenyl)-4-oxo-3,4-dihydro-phthalazin-1-yl)carbamate (73g).

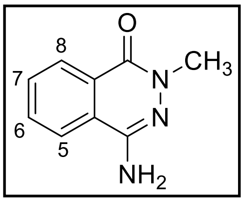


(0.24 g, 97%), mp 202-203 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.45-8.42 (m, H_5), 7.85-7.76 (m, H_6, H_7 and H_8), 7.45-7.40 (m, $H_{6'}$), 6.97-6.90 (m, $H_{3'}$ and $H_{5'}$), 6.65 (s, 1H, -NH), 3.75 (s, 3H, -OCH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.7 (dd, J = 249.7, 11.0 Hz), 158.7, 156.6 (dd, J = 254.1, 12.6 Hz), 155.3, 138.8, 133.6, 132.5, 129.8 (dd, J = 10.1, 1.5 Hz), 128.7, 127.8, 127.5, 125.5 (dd, J = 12.8, 4.1 Hz), 125.3, 111.8 (dd, J = 22.5, 3.6 Hz), 105.0 (dd, J = 26.3, 23.6 Hz), 53.2. **IR** (KBr, cm^{-1}) 3198, 3062, 2970, 2948, 1730, 1650, 1606, 1589, 1509, 1486, 1238, 1216, 1148, 1056. **Elemental Analysis**: [found: C, 58.30; H, 3.44; N, 12.27. $C_{16}H_{11}F_2N_3O_3$ requires C, 58.01; H, 3.35; N, 12.68%].

4.19 General Procedure for the Synthesis of Aminophthalazinone Derivatives (74a-g)

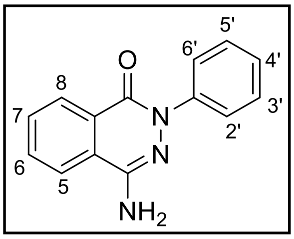
The acyl azide derivatives **72a-g** (0.3 g, 0.92-1.3 mmol) were dissolved in dry benzene (30 mL) and heated at reflux for 90 min. The solution was cooled to 40 °C and HCl (10 mL, 8 M) was added. The mixture was stirred at rt for 15 min.- 4 h and then the pH value was adjusted to pH 10 by the addition of 10% NaOH solution. The mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography eluting with ethyl acetate/dichloromethane (1:2) to give amine derivatives **74a-g** as white solids.

4.19.1. 4-Amino-2-methylphthalazin-1(2*H*)-one (74a)



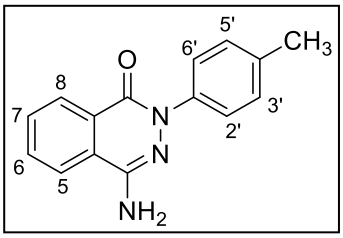
(0.18 g, 79%), mp 151-153°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44-8.39 (m, H_5), 7.75-7.71 (m, H_7 and H_8), 7.62-7.58 (m, H_6), 3.65 (s, 3H, $-OCH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.3, 144.6, 132.5, 131.7, 128.8, 127.7, 124.4, 122.3, 38.5. **IR** (KBr, cm^{-1}) 3392, 3329, 3203, 1624, 1560, 1497, 1436, 1365, 1133, 1104. **HRMS-ESI** $[M + Na]^+$ calcd for $C_9H_9N_3NaO$ 198.0638, found: 198.0624.

4.19.2. 4-Amino-2-phenylphthalazin-1(2*H*)-one (74b)



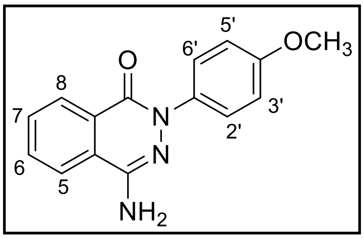
(0.19 g, 80%), mp 176-178 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50-8.48 (m, H_5), 7.80-7.73 (m, H_7 and H_8), 7.67-7.63 (m, 6, 7.62-7.59 (m, $H_{2'}$ and $H_{6'}$), 7.43-7.38 (m, $H_{3'}$ and $H_{5'}$), 7.27 (tt, *J* = 7.4, 1.1 Hz, $H_{4'}$), 4.13 (br s, 2H, $-NH_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.8, 144.8, 141.7, 132.7, 131.6, 129.1, 128.4, 127.9, 127.1, 125.5, 124.2, 122.2. **IR** (KBr, cm^{-1}) 3421, 3319, 3212, 3064, 1609, 1592, 1578, 1552, 1494, 1455, 1342, 1311. **HRMS-MALDI** $[M + H]^+$ calcd for $C_{14}H_{12}N_3O$ 238.0980, found: 238.0996.

4.19.3. 4-Amino-2-(4-methylphenyl)phthalazin-1(2*H*)-one (74c)



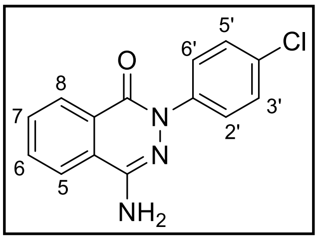
(0.22 g, 95%), mp 208-209 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.50-8.48 (m, H_5), 7.80-7.72 (m, H_7 and H_8), 7.64-7.62 (m, H_6), 7.48-7.45 (m, A-part of AA´BB´ system, $H_{2'}$ and $H_{6'}$), 7.23-7.20 (m, B-part of AA´BB´ system, $H_{3'}$ and $H_{5'}$), 4.33 (br s, 2H, -NH_2), 2.32 (s, 3H, -CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 158.1, 144.9, 139.6, 137.2, 132.9, 131.7, 129.4, 129.3, 128.2, 125.5, 124.5, 122.5, 21.1. **IR** (KBr, cm^{-1}) 3295, 3195, 3016, 2970, 1738, 1623, 1574, 1553, 1514, 1354, 1229, 1216, 1205. **Elemental Analysis** [found: C, 71.53; H, 5.09; N, 16.54. $C_{15}H_{13}N_3O$ requires C, 71.70; H, 5.21; N, 16.72%].

4.19.4. 4-Amino-2-(4-methoxyphenyl)phthalazin-1(2*H*)-one (74d)



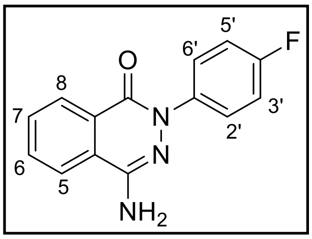
(0.23 g, 94%), mp 274-275 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.50 (dd, *J* = 8.0, 0.8 Hz, H_5), 7.79-7.73 (m, H_7 and H_8), 7.57-7.54 (m, H_6), 7.55-7.51 (m, A-part of AA´BB´ system, $H_{2'}$ and $H_{6'}$), 6.90-6.86 (m, B part of AA´BB´ system, $H_{3'}$ and $H_{5'}$), 3.76 (s, 3H, -OCH_3). **^{13}C NMR** (100 MHz, DMSO-d_6) *δ* 159.0, 158.1, 153.8, 138.9, 134.6, 133.3, 132.4, 129.4, 128.1, 126.8, 123.5, 114.1, 55.5. **IR** (KBr, cm^{-1}) 3247, 3144, 2839, 1683, 1666, 1650, 1630, 1561, 1508, 1469, 1447, 1323, 1308, 1249, 1170, 1028. **HRMS-MALDI** $[M + H]^+$ calcd for $C_{15}H_{14}N_3O_2$ 268.1086, found: 268.1112.

4.19.5. 4-Amino-2-(4-chlorophenyl)phthalazin-1(2*H*)-one (74e)



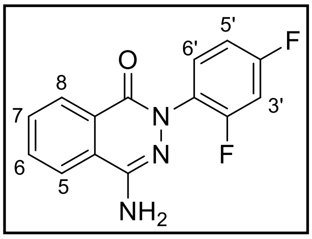
(0.24 g, 98%), mp 214-215 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.48-8.46 (m, H_5), 7.80-7.72 (m, H_7 and H_8), 7.64-7.61 (m, H_6), 7.62-7.58 (m, A-part of AA´BB´ system, $H_{2'}$ and $H_{6'}$), 7.36-7.32 (m, B-part of AA´BB´ system, $H_{3'}$ and $H_{5'}$), 4.40 (br s, 2H, -NH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 158.1, 145.1, 140.5, 133.2, 132.6, 132.0, 129.3, 128.7, 128.3, 126.8, 124.5, 22.4. **IR** (KBr, cm^{-1}) 3453, 3344, 3220, 3035, 1738, 1617, 1589, 1577, 1551, 1490, 1430, 1347, 1088, 683. **HRMS-MALDI** $[M + H]^+$ calcd for $C_{14}H_{11}ClN_3O$ 272.0591, found: 272.0586.

4.19.6. 4-Amino-2-(4-fluorophenyl)phthalazin-1(2*H*)-one (74f)



(0.22 g, 92%), mp 224-225 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.49-8.47 (m, H_5), 7.81-7.74 (m, H_7 and H_8), 7.65-7.62 (m, H_6), 7.61-7.58 (m, A-part of AA´BB´X system, $H_{2'}$ and $H_{6'}$), 7.10-7.06 (m, B-part of AA´BB´X system, $H_{3'}$ and $H_{5'}$), 4.36 (br s, 2H, $-NH_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 161.4 (d, *J* = 246.8 Hz), 158.1, 145.0, 138.0 (d, *J* = 3.1 Hz), 133.1, 131.9, 129.3, 128.3, 127.4 (d, *J* = 8.6 Hz), 124.5, 122.4, 115.4 (d, *J* = 22.8 Hz). **IR** (KBr, cm^{-1}) 3479, 3358, 3227, 3071, 1617, 1578, 1552, 1431, 1352, 1211, 1153; **HRMS-MALDI** $[M + H]^+$ calcd for $C_{14}H_{11}FN_3O$ 256.0886, found : 256.0888.,

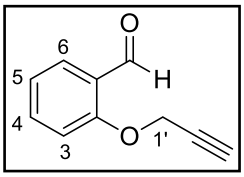
4.19.7. 4-Amino-2-(2,4-difluorophenyl)phthalazin-1(2*H*)-one (74g)



(0.23 g, 94%), mp 187-188 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) *δ* 8.48-8.46 (m, H_5), 7.83-7.75 (m, H_7 and H_8), 7.65-7.63 (m, H_6), 7.44 - 7.39 (m, $H_{6'}$), 6.97-6.87 (m, $H_{3'}$ and $H_{5'}$), 4.34 (br s, 2H, $-NH_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 161.4 (dd, *J* = 245.7, 11.1 Hz), 157.1, 156.7 (dd, *J* = 253.8, 12.6 Hz), 144.4, 132.3, 131.0, 128.9 (dd, *J* = 10.2, 2.1 Hz), 127.7, 127.2, 125.2 (dd, *J* = 12.9, 4.2 Hz), 123.8, 121.7, 110.7 (dd, *J* = 22.5, 3.7 Hz), 103.9 (dd, *J* = 26.3, 23.7 Hz). **IR** (KBr, cm^{-1}) 3469, 3343, 3220, 3071, 1738, 1621, 1579, 1553, 1507, 1453, 1429, 1357, 1269, 1253, 1141, 1099, 964. **HRMS-MALDI** $[M + H]^+$ calcd for $C_{14}H_{10}F_2N_3O$ 274.0792, found: 274.0790.

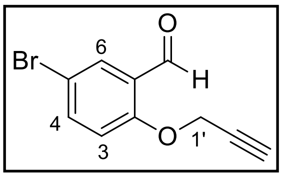
4.20 General Procedure for the Synthesis of Substituted 2-(Prop-2-yn-1-yloxy)benzaldehyde: Aromatic hydroxyaldehyde (10 mmol) was dissolved in 5 mL of DMF and anhydrous K_2CO_3 (12.0 mmol) was added to this solution at rt. After stirring for 20 min., propargyl bromide (11.0 mmol) was added and the resulting mixture was stirred overnight at rt. After the completion of the reaction, ethyl acetate (30 mL) was added, the organic phase was washed with water (3 × 50 mL) and then dried over $MgSO_4$. Removal of solvent gave the product.

4.20.1 2-(Prop-2-yn-1-yloxy)benzaldehyde (149b)



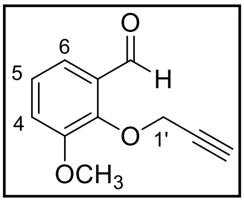
Salicylaldehyde (**208**) (1.0 g, 8.19 mmol) was reacted with anhydrous K_2CO_3 (1.7 g, 12.3 mmol) and propargyl bromide (1.05 mL, 9.82 mmol) as described above to give the product **149b** as colorless cubic crystals from chloroform (1.1 g, 84%), mp 68-69 °C (Lit. mp, 69-70 °C[133]). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.49 (s, -COH), 7.87 (dd, J = 7.7, 1.8 Hz, H_6), 7.57 (ddd, J = 8.6, 7.3, 1.8 Hz, H_4), 7.15 – 7.05 (m, H_3 and H_5), 4.84 (d, J = 2.4 Hz, $H_{1'}$), 2.57 (t, J = 2.4 Hz, C≡CH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.6, 159.9, 135.8, 128.6, 125.6, 121.8, 113.3, 77.8, 76.6, 56.5. **IR** (KBr, cm^{-1}) 3270, 2887, 2117, 1678, 1594, 1456, 1286, 1221, 1191, 1006, 757, 676, 654, 609. **HRMS-TOF** $[M - H]^-$ Calcd for $C_{10}H_7O_2$ 159.04515, found : 159.04432.

4.20.2 5-Bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (251)



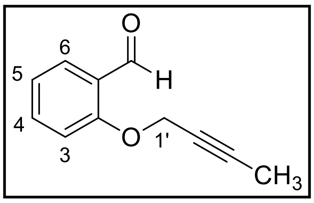
5-Bromo-salicylaldehyde (**249**) (2.0 g, 9.95 mmol), K_2CO_3 (2.1 g, 14.9 mmol) and propargyl bromide (1.3 mL g, 11.9 mmol) were reacted as described above to give the product **251** as white needles crystals from chloroform/hexane (2.3 g, 97%), mp 94-95 °C (Lit. mp, 94-96 °C[133]). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.40 (s, -COH), 7.96 (d, J = 2.6 Hz, H_6), 7.65 (dd, J = 8.9, 2.6 Hz, H_4), 7.04 (d, J = 8.9 Hz, H_3), 4.83 (d, J = 2.4 Hz, $H_{1'}$), 2.58 (t, J = 2.4 Hz, C≡CH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.2, 158.7, 138.2, 131.3, 126.9, 115.5, 114.7, 77.3, 77.1, 56.8. **IR** (KBr, cm^{-1}) 3099, 3080, 2870, 2762, 2120, 1680, 1589, 1472, 1454, 1395, 1291, 1275, 1216, 1183, 1124, 1011, 927, 906, 877, 815, 784, 684, 620, 588. **HRMS-TOF**; $[M - H]^-$ Calcd for $C_{10}H_6BrO_2$ 236.95567, found: 236.95485.

4.20.3 3-Metoxy-2-(prop-2-ynyloxy)benzaldehyde (252)



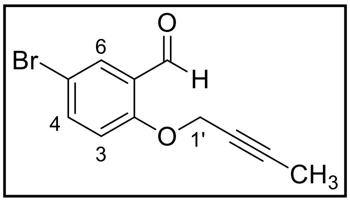
3-Methoxy-salicylaldehyde (**250**) (2.0 g, 13.1 mmol), K_2CO_3 (2.7 g, 19.7 mmol), and propargyl bromide (1.7 mL, 15.8 mmol) were reacted as described above to yield the product **252** as colorless cubic crystal from chloroform/hexane (2.3 g, 92%), mp 49-50 °C (Lit. (49-50 °C[134]). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.50 (s, -COH), 7.46 (dd, J = 7.2, 2.1 Hz, H_6), 7.22 – 7.13 (m, H_5 and H_4), 4.89 (d, J = 2.4 Hz, $H_{1'}$), 3.91 (s, $-OCH_3$), 2.48 (t, J = 2.4 Hz, C≡CH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.64, 152.95, 149.58, 131.25, 125.00, 118.97, 117.86, 77.29, 77.11, 60.94, 56.14. **IR** (KBr, cm^{-1}) 3266, 2950, 2890, 2838, 2118, 1681, 1583, 1476, 1437, 1383, 1317, 1266, 1250, 1202, 1178, 1066, 982, 913, 782, 749, 666, 650, 602. **HRMS-TOF** [M-H]$^-$ Calcd for $C_{11}H_9O_3$ 189.05572, found: 189.05505.

4.20.4 2-(But-2-ynyloxy)benzaldehyde (254)



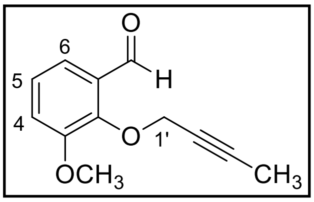
Salicylaldehyde **(208)** (0.5 g, 4.1 mmol), 1-bromobut-2-yne **253** (0.66 mL, 6.14 mmol), and K_2CO_3 (0.68 g, 4.9 mmol) in 5 mL of DMF were reacted as described above to give the product **254** as colorless oil (0.71 g, 99%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.49 (s, -COH), 7.85 (dd, J = 7.7, 1.8 Hz, H_6), 7.56 (ddd, J = 8.5, 7.4, 1.8 Hz, H_4), 7.11 (br d, J = 8.4 Hz, H_3), 7.06 (br t, J = 7.5 Hz, H_5), 4.78 (q, J = 2.3 Hz, $H_{1'}$), 1.86 (t, J = 2.3 Hz, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.5, 160.1, 135.7, 128.2, 125.3, 121.2, 113.3, 84.7, 73.4, 57.0, 3.5. **IR** (KBr, cm^{-1}) 2917, 2864, 2231, 1686, 1597, 1480, 1458, 1397, 1369, 1286, 1261, 1217, 1190, 1162, 1102, 1042, 995, 831, 755, 645, 595. **HRMS-TOF** [M+Na]$^+$ Calcd for $C_{11}H_9NaO_2$ 197.05785, found: 197.05761**.**

4.20.5 5-Bromo-2-(but-2-ynyloxy)benzaldehyde (255)



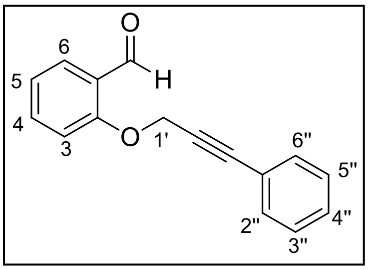
5-Bromo-salicylaldehyde (**249**) (2.0 g, 9.95 mmol), 1-bromobut-2-yne **253** (1.05 mL, 11.9 mmol), and K_2CO_3 (2.1 g, 14.9 mmol) in 10 mL of DMF were reacted as described above to give the product **255** as white tiny needle from EtOAc (2.5 g, 99%), mp 79-80 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.39 (s, -COH), 7.94 (d, J = 2.6 Hz, H_6), 7.63 (dd, J = 8.9, 2.6 Hz, H_4), 7.03 (d, J = 8.9 Hz, H_3), 4.77 (q, J = 2.3 Hz, $H_{1'}$), 1.86 (t, J = 2.3 Hz, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.4, 159.1, 138.2, 131.1, 126.9, 115.7, 114.3, 85.5, 73.0, 57.5, 3.8. **IR** (KBr, cm^{-1}) 2861, 2246, 1680, 1588, 1474, 1382, 1270, 1235, 1184, 1125, 989, 880, 810, 643. **HRMS-TOF** [M + Na]$^+$ Calcd for $C_{11}H_9BrNaO_2$ 274.96781, found: 274.97018.

4.20.6 3-Methoxy-2-(but-2-ynyloxy)benzaldehyde (256)



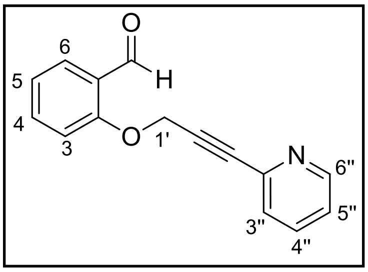
3-Methoxy-salicylaldehyde (**250**) (2.0 g, 13.1 mmol), propargyl bromide (1.4 mL, 15.8 mmol), and K_2CO_3 (2.7 g, 19.7 mmol) in 10 mL of DMF were reacted as described above to give the product **256** as white tiny needle from EtOAc/petroleum ether (2.5 g, 93%), mp 51-52 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.47 (s, -COH), 7.46 (dd, J = 7.3, 2.1 Hz, H_6), 7.19 (dd, A-part of AB system, J = 8.1, 0.7 Hz, H_5), 7.15 (dd, B-part of AB system, J = 8.1, 2.1 Hz, H_4), 4.80 (q, J = 2.3 Hz, $H_{1'}$), 3.90 (s, $-OCH_3$), 1.76 (t, J = 2.4 Hz, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.8, 153.2, 149.9, 131.6, 124.9, 118.8, 117.8, 85.7, 74.1, 62.0, 56.1, 3.56. **IR** (KBr, cm^{-1}) 2843, 1682, 1583, 1479, 1442, 1248, 1064, 961, 775, 7461. **HRMS-TOF** $[M+Na]^+$ Calcd for $C_{12}H_{12}NaO_3$ 227.06787, found: 227.06991.

4.20.7 2-[(3-Phenylprop-2-ynyl)oxy]benzaldehyde (257)



To a solution of 2-(prop-2-ynyloxy)benzaldehyde (**149b**) (0.8 g, 5 mmol) in dry THF (8 mL), iodobenzene (0.6 mL, 5.5 mmol), PPh_3 (52 mg, 0.2 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), dry triethylamine (1.5 mL, 7.5 mmol) and CuI (28 mg, 0.15 mmol) were added. The resulting mixture was refluxed overnight. After the completion of the reaction, the solvent was evaporated and the reaction mixture was extracted with ethyl acetate (75 mL) and water (3 × 50 mL). The combined organic layer was washed with brine (50 mL) and dried over $MgSO_4$. After removing of solvent under vacuum, the crude product was purified by column chromatography eluting with ethyl acetate/hexane (1:8) to give **257** as white needle-like crystals from chloroform/hexane (crude yield: 0.96 g, 81%, pure isolated yield: 0.65 g, 55%), mp 79-80 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.53 (s, -COH), 7.88 (dd, J = 7.7, 1.8 Hz, H_6), 7.59 (ddd, J = 8.5, 7.4, 1.8 Hz, H_4), 7.45 – 7.40 (m, $H_{2''}$ and $H_{6''}$), 7.36 – 7.28 (m, H_5, $H_{5''}$ and $H_{3''}$), 7.21 (br d, J = 8.4 Hz, H_3), 7.09 (br t, J = 7.5 Hz, $H_{4'}$), 5.06 (s, $-CH_2$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.8, 160.2, 135.8, 131.9 (2 C), 129.1, 128.7, 128.5 (2 C), 125.8, 122.0, 121.7, 113.6, 88.2, 83.1, 57.5. **IR** (KBr, cm^{-1}) 2888, 1679, 1596, 1479, 1459, 1400, 1284, 1222, 1005, 958, 757, 687. **HRMS-TOF** [M +Na]+ Calcd for $C_{16}H_{12}NaO_2$ 259.07295, found: 259.07528.

4.20.8 2-[(3-Pyridin-2-ylprop-2-ynyl)oxy]benzaldehyde (258)

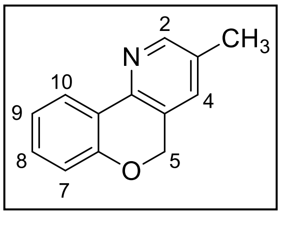


2-(Prop-2-ynyloxy)-benzal-dehyde (**149b**) (0.8 g, 5 mmol), 2-bromopyridine (1.4 mL, 6 mmol), PPh_3 (52 mg, 0.2 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), dry triethylamine (1.5 mL, 7.5 mmol) and CuI (28 mg, 0.15 mmol) in THF (7 mL) were reacted as described above. The residue was purified by column chromatography eluting with ethyl acetate/hexane (1:4 to 1:1) to give the product **258** as white needle-like crystals from chloroform/hexane (1.14 g; NMR yield: 96%, 0.81 g; isolated yield: 69%), mp 103-104 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.53 (s, -COH), 8.58 (ddd, J = 4.9, 1.8, 0.9 Hz, $H_{6''}$), 7.87 (dd, J = 7.7, 1.8 Hz, H_6), 7.66 (dt, J = 1.8, 7.8 Hz, H_3), 7.59 (ddd, J = 8.6, 7.3, 1.8 Hz, $H_{4''}$), 7.43 (dt, J = 1.0, 7.4 Hz, $H_{5''}$), 7.29 – 7.24 (m, H_4), 7.21 (br d, J = 8.4 Hz, $H_{3''}$), 7.12-7.07 (br t, J = 7.4, H_5), 5.09 (s, $-CH_2$). **^{13}C NMR** (100 MHz, CDCl3) δ 189.6, 160.0, 150.2, 142.3, 136.4, 135.9, 128.7, 127.5, 125.6, 123.6, 121.8, 113.4, 87.2, 82.9, 57.0. **IR** (KBr, cm^{-1}) 2858, 1682, 1600, 1464, 1379, 1239, 995, 985, 844, 761. **HRMS-TOF** $[M - H]^-$ Calcd for $C_{15}H_{10}NaNO_2$ 260.0682, found: 260.07134.

4.21 General Procedure for Cyclization of Substituted Aldehydes with Propargyl Amine.

Substituted benzaldehyde (5 mmol) was dissolved in 15 mL of ethanol. To this solution, DBU (0.8 mL, 5 mmol) and propargylamine (0.66 mL, 10.44 mmol) was added at room temperature and the resulting mixture was refluxed for 2 days. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the residual product was dissolved in ethyl acetate (50 mL). The organic solution was washed with water (3 × 50 mL) and brine (50 mL). The combined organic extracts were dried over $MgSO_4$. Removal of the solvent gave the crude product which was crystallized from suitable solvents to give the product.

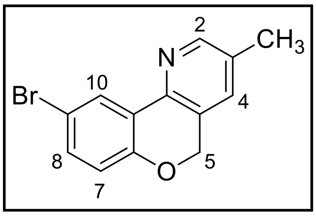
4.21.1 3-Methyl-5*H*-chromeno[4,3-b]pyridine (259)



2-(Prop-2-ynyloxy)benzaldehyde (**149b**) (0.5 g, 3.12 mmol), DBU (0.47 mL, 3.12 mmol), and propargylamine (0.4 mL, 6.27 mmol) were reacted as described above. The crude product was crystallized from $CHCl_3$/petroleum ether to give **259** as white crystals (580 mg, 94%), mp 174-176 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (br d, J

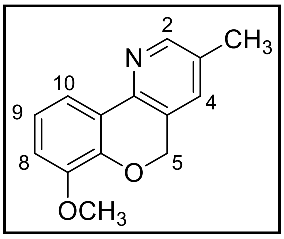
= 1.2 Hz, H_2), 8.19 (dd, *J* = 7.7, 1.5 Hz, H_{10}), 7.29 (ddd, *J* = 8.1, 7.5, 1.7 Hz, H_8), 7.25 (s, H_4), 7.10 (dt, *J* = 1.1, 7.6 Hz, H_9), 6.96 (dd, *J* = 8.1, 1.0 Hz, H_7), 5.19 (s, H_5), 2.36 (s, -CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.2, 149.8, 146.2, 132.8, 132.4, 131.0, 125.9, 124.5, 123.3, 122.5, 117.1, 68.0, 18.5. **IR** (KBr, cm-1) 2920, 1719, 1605, 1455, 1254, 1174, 1151, 936, 751. **HRMS-TOF** $[M + H]^+$ Calcd for $C_{13}H_{12}NO$ 198.09134, found: 198.09148.

4.21.2 9-Bromo-3-methyl-5*H*-chromeno[4,3-*b*]pyridine (263)



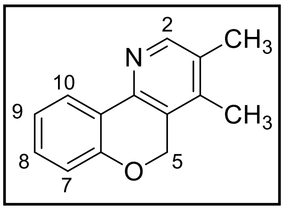
5-Bromo-2-(prop-2-ynyloxy)benzal-dehyde (**251**) (0.4 g, 1.67 mmol), DBU (0.25 mL, 1.67 mmol) and propargylamine (0.22 mL, 3.34 mmol) in 10 mL of ethanol were reacted as described above (reflux overnight) to give **263** as white cubic crystals from EtOH/petroleum ether (420 mg, 91%), mp 91-93 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40 (br s, H_2), 8.30 (d, *J* = 2.5 Hz, H_{10}), 7.36 (dd, *J* = 8.6, 2.5 Hz, H_8), 7.25 (br s, H_4), 6.83 (d, *J* = 8.6 Hz, H_7), 5.18 (s, H_5), 2.37 (s, -CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.1, 150.0, 144.9, 133.4, 133.1, 132.8, 127.1, 125.7, 125.0, 118.8, 115.0, 68.0, 18.5. **IR** (KBr, cm-1) 2917, 1685, 1586, 1456, 1259, 1216, 1026, 875, 809, 750. **HRMS-TOF** $[M + H]^+$ Calcd for $C_{13}H_{11}BrNO$ 276.00185, found: 275.99979.

4.21.3 7-Methoxy-3-methyl-5*H*-chromeno[4,3-*b*]pyridine (264)



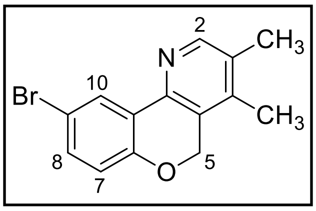
3-Methoxy-2-(prop-2-ynyloxy)-benzaldehyde (**252**) (0.4 g, 2.1 mmol), DBU (0.31 mL, 2.1 mmol) and propargylamine (0.27 mL, 4.2 mmol) in 10 mL of ethanol were reacted as described above (reflux overnight) to give the product **264** as white needles from EtOH (0.45 g, 94%), mp 105-106 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (s, H_2), 8.10 (dd, *J* = 8.0, 1.1 Hz, H_{10}), 7.64 (s, H_4), 7.10 (t, *J* = 8.1 Hz, H_9), 7.00 (dd, *J* = 8.2, 1.2 Hz, H_8), 5.28 (s, H_5), 3.88 (s, -CH_3), 2.43 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 148.8, 146.0, 143.7, 143.1, 138.4, 134.6, 128.2, 123.1, 118.5, 117.5, 115.6, 67.3, 56.3, 18.4. **IR** (KBr, cm^{-1}) 2943, 2842, 1689, 1581, 1482, 1441, 1270, 1255, 1184, 1103, 1075, 952, 867, 797, 761, 738, 658. **HRMS-TOF**; $[M + H]^+$ Calcd for $C_{14}H_{14}NO_2$ 228.10191, found: 228.10159.

4.21.4 3,4-Dimethyl-5*H*-chromeno[4,3-*b*]pyridine (265)



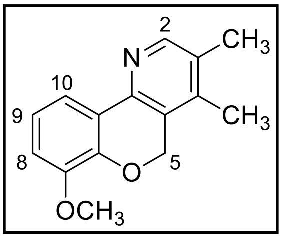
2-(But-2-ynyloxy)benzaldehyde (**254**) (0.4 g, 2.3 mmol), DBU (0.35 mL, 2.3 mmol), and propargylamine (0.3 mL, 4.6 mmol) in 10 mL of ethanol were reacted as described above to give the product **265** as white needles from chloroform/petroleum ether (0,39 g, 81%), mp 153-154 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (s, H_2), 8.17 (dd, *J* = 7.7, 1.7 Hz, H_{10}), 7.29 (dd, *J* = 7.8, 1.5 Hz, H_7), 7.08 (dt, *J* = 1.0, 7.6 Hz, H_8), 6.94 (dd, *J* = 8.1, 0.9 Hz, H_9), 5.29 (s, H_5), 2.29 (s, $-CH_3$), 2.19 (s, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.8, 149.5, 146.2, 140.7, 131.5, 130.7, 124.8, 124.7, 123.6, 122.4, 116.7, 65.7, 17.1, 14.1. **IR** (KBr, cm^{-1}) 2993, 1595, 1497, 1458, 1385, 1218, 1036, 1012, 857, 750. **HRMS-TOF**; $[M + H]^+$ Calcd for $C_{14}H_{14}NO$ 212.10699, found: 212.10710.

4.21.5 9-Bromo-3,4-dimethyl-5*H*-chromeno[4,3-*b*]pyridine (266)



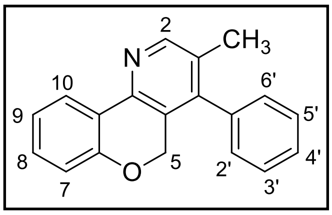
5-Bromo-2-(but-2-ynyloxy)benz-aldehyde (**255**) (0.5 g, 1.98 mmol), DBU (0.3 mL, 1.98 mmol) and propargylamine (0.5 mL, 7.9 mmol) in 10 mL of ethanol were reacted as described above to give the product **266** as a white powder from chloroform/petroleum ether (0,38 g, 67%), mp 143-144 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (br s, H_{10}), 8.33 (s, H_2), 7.36 (dd, *J* = 8.6, 2.5 Hz, H_8), 6.82 (d, *J* = 8.6 Hz, H_7), 5.29 (s, H_5), 2.30 (s, $-CH_3$), 2.20 (s, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.5, 149.4, 144.7, 140.9, 133.1, 132.0, 127.2, 125.1, 124.5, 118.4, 114.8, 65.6, 16.9, 13.9. **IR** (KBr, cm^{-1}) 2917, 1595, 1455, 1381, 1315, 1219, 1012, 812. **HRMS-MALDI** $[M + H]^+$ Calcd for $C_{14}H_{13}BrNO$ 290.01750, found: 290.01743.

4.21.6 7-Methoxy-3,4-dimethyl-5*H*-chromeno[4,3-*b*]pyridine (267)



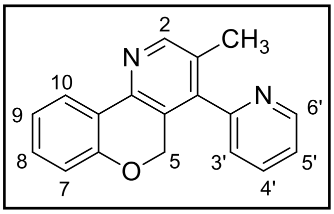
3-Methoxy-2-(but-2-ynyloxy)-benzaldehyde (**256**) (0.5 g, 2.4 mmol), DBU (0.36 mL, 2.4 mmol), and propargylamine (0.3 mL, 4.9 mmol) in 10 mL of ethanol were reacted as described above to give the product **267** as white needle-like crystals from EtOAc (540 mg, 91%), mp 147-148 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (s, H_2), 7.79 (dd, *J* = 8.0, 1.4 Hz, H_{10}), 7.03 (t, *J* = 8.0 Hz, H_9), 6.91 (dd, *J* = 8.0, 1.4 Hz, H_8), 5.35 (s, H_5), 3.91 (s, $-OCH_3$), 2.28 (s, $-CH_3$), 2.18 (s, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 149.5, 148.5, 146.2, 145.0, 140.7, 131.6, 124.7, 124.4, 121.9, 116.7, 112.9, 66.0, 56.3, 17.1, 14.1. **IR** (KBr, cm^{-1}) 2916, 1595, 1561, 1441, 1390, 1218, 1176, 1059, 878, 743. **HRMS-TOF** [M + H]$^+$ Calcd for $C_{15}H_{16}NO_2$ 242.11756, found: 242.11759.

4.21.7 3-Methyl-4-phenyl-5*H*-chromeno[4,3-*b*]pyridine (268)



2-[(3-phenylprop-2-ynyl)oxy]benz-aldehyde (**257**) (170 g, 0.7 mmol), DBU (0.1 mL, 0.7 mmol),and propargylamine (0.14 mL, 2.15 mmol) were reacted as described above (reflux overnight) to give the product **268** as white cubic crystals from chloroform/hexane (186 mg, 95%), mp 140-141 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.50 (s, H_2), 8.25 (dd, *J* = 7.7, 1.5 Hz, H_{10}), 7.52 – 7.40 (m, $H_{2'}$ and $H_{6'}$), 7.33 – 7.26 (m, $H_{3'}$ and $H_{5'}$), 7.18 – 7.14 (m, H_9 and $H_{4'}$), 7.11 (dt, *J* = 1.1, 7.7 Hz, H_8), 6.92 (dd, *J* = 8.1, 0.9 Hz, H_7), 4.93 (s, H_5), 2.11 (s, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.0, 150.0, 146.7, 146.2, 136.1, 131.0, 130.6, 129.0 (2C), 128.4, 128.2 (2 C), 124.7, 124.1, 123.6, 122.5, 116.9, 66.3, 17.3. **IR** (KBr, cm^{-1}) 2922, 1605, 1511, 1456, 1245, 1176, 1030, 832. **HRMS-TOF** [M+ H]$^+$ Calcd for $C_{19}H_{16}NO$ 274.12264, found: 274.12436.

4.21.8 3-Methyl-4-pyridin-2-yl-5*H*-chromeno[4,3-*b*]pyridine (269)



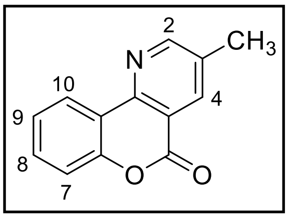
2-[(3-pyridin-2-ylprop-2-ynyl)-oxy]benzaldehyde (**258**) (0.5 g, 2.1 mmol), DBU (0.3 mL, 2.1 mmol) and propargylamine (0.5 mL, 8.4 mmol) in 10 mL of ethanol were reacted as described above to give the product **269** as a light brown powder from EtOH/petroleum ether (540 mg, 93%), mp 115-116 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (ddd, *J* = 4.9, 1.7, 1.0 Hz, $H_{6'}$), 8.52 (br s, H_2), 8.23 (dd, *J* = 7.8, 1.6 Hz, H_{10}), 7.85 (dt, *J* = 1.8, 7.7 Hz, H_8), 7.37 (ddd, *J* = 7.7, 4.9, 1.1 Hz, $H_{5'}$), 7.34 – 7.27 (m, $H_{3'}$ and $H_{5'}$), 7.11 (dt, *J* = 1.1, 7.6 Hz, H_9), 6.92 (dd, *J* = 8.1, 1.0 Hz, H_7), 4.97 (s, H_5), 2.17 (s, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.1, 155.2, 150.4, 150.2, 147.0, 144.4, 136.8, 131.0, 130.0, 124.70, 124.2, 124.1, 123.5, 123.1, 122.4, 116.9, 66.2, 17.1. **IR** (KBr, cm^{-1}) 2933, 2848, 1732, 1589, 1494, 1459, 1434, 1385, 1303, 1275, 1248, 1212, 1039, 1009, 955, 837, 786, 756, 719, 662, 598. **HRMS-TOF** [M + H]$^+$ Calcd for $C_{18}H_{15}BrN_2O$ 275.11789, found : 275.11910.

4.22 General Procedure for the Oxidation of Chromenopyridine Derivatives

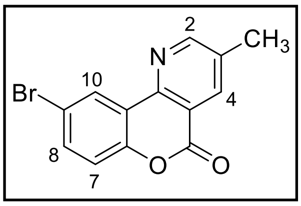
To a suspension of CrO_3 (10 mmol) in 15 mL of dichloromethane was added pyridine (15 mmol) at room temperature. The mixture was stirred at room temperature for 20 min and cooled to 0 ºC. Then, a solution of chromenopyridine derivative in 4 mL of dichloromethane was added and the mixture was stirred at rt overnight. After the completion of the reaction, the mixture was filtered over silica by using dichloromethane as mobile phase. Solvent was evaporated under the vacuum and the oxidation product was obtained.

4.22.1 3-Methyl-5*H*-chromeno[4,3-*b*]pyridin-5-one (270a)



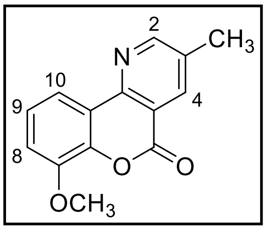
CrO_3 (710 mg, 7.10 mmol), pyridine (0.86 mL, 10.7 mmol), and chromenopyridine derivative **259** (70 mg, 0.355 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product **270a** as a white needle-like crystals from EtOAc (74 mg, 99%), mp 182-183 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.86 (br s, H_2), 8.56 (br d, J = 7.8 Hz, H_{10}), 8.43 (br s, H_4), 7.56 (dt, J = 1.3, 7.8, Hz, H_8), 7.40 (br t, J = 8.6 Hz, H_7 and H_9), 2.52 (s, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.4, 156.7, 152.3, 149.5, 137.7, 134.0, 131.7, 124.9, 124.4, 119.4, 117.2, 116.9, 18.5. **IR** (KBr, cm-1) 2923, 1737, 1608, 1563, 1452, 1254, 1113, 938, 756. **HRMS-TOF**; $[M + Na]^+$ Calcd for $C_{13}H_9NaNO_2$ 234.05255, found: 234.05422.

4.22.2 9-Bromo-3-methyl-5*H*-chromeno[4,3-*b*]pyridin-5-one (270b)



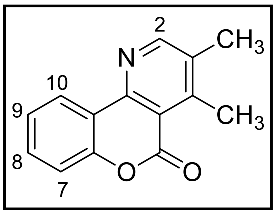
CrO_3 (815 mg, 8.15 mmol), pyridine (0.65 mL, 8.15 mmol), and chromenopyridine derivative **263** (75 mg, 0.272 mmol) in 10 mL of dichloromethane were reacted as described above to give the product **270b** as white tiny needle from EtOAc (75 mg, 96%), mp 207-208 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.86 (d, J = 2.3 Hz, H_2), 8.70 (d, J = 2.3 Hz, H_4), 8.42 (dd, J = 2,4 0.8 Hz, H_{10}), 7.64 (dd, J = 8.7, 2.4 Hz, H_8), 7.27 (d, J = 8.7 Hz, H_7), 2.54 (s, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.9, 156.9, 151.2, 148.4, 137.9, 134.9, 134.6, 127.3, 121.2, 119.0, 118.1, 117.2, 18.7. **IR** (KBr, cm^{-1}) 2923, 1727, 1603, 1496, 1451, 1252, 1109, 1059, 789, 770. **HRMS-TOF** $[M - H]^-$ Calcd for $C_{13}H_9BrNO_2$ 287.96656, found: 287.96444.

4.22.3 7-Methoxy-3-methyl-5*H*-chromeno[4,3-*b*]pyridin-5-one (270c)



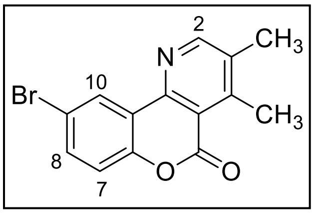
CrO$_3$ (100 mg, 0.44 mmol), pyridine (0.7 mL, 8.8 mmol), and chromenopyridine derivative **264** (0.88 g, 8.8 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product **270c** as tiny needles from EtOAc (100 mg, 94%), mp 222-223 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.86 (d, J = 1.9 Hz, H$_2$), 8.44 (dd, J = 2.2, 0.7 Hz, H$_4$), 8.14 (dd, J = 8.1, 1.4 Hz, H$_{10}$), 7.33 (t, J = 8.1 Hz, H$_9$), 7.12 (dd, J = 8.1, 1.3 Hz, H$_8$), 4.00 (s, -OCH$_3$), 2.52 (s, -CH$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ 161.0, 156.8, 149.7, 147.7, 142.2, 137.8, 134.2, 124.7, 120.4, 117.1, 115.8, 113.7, 56.4, 18.6. **IR** (KBr, cm^{-1}) 2923, 1725, 1564, 1482, 1452, 1186, 1073, 938, 765. **HRMS-TOF** [M + Na]$^+$ Calcd for C$_{14}$H$_{11}$NaNO$_3$ 264.06311, found: 264.06525.

4.22.4 3,4-Dimethyl-5*H*-chromeno[4,3-*b*]pyridin-5-one (270d)



CrO$_3$ (284 mg, 2.84 mmol), pyridine (0.228 mL, 2.84 mmol), and the chromenopyridine derivative **265** (20 mg, 0.095 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product **270d** as a white powder (19.0 mg, 90%), mp 181-182 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.71 (br s, H$_2$), 8.56 (dd, J = 7.9, 1.5 Hz, H$_{10}$), 7.53 (ddd, J = 8.2, 7.4, 1.7 Hz, H$_8$), 7.39 – 7.31 (m, H$_7$ and H$_9$), 2.84 (s, -CH$_3$), 2.44 (s, -CH$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ 161.1, 155.5, 152.3, 151.7, 151.4, 133.6, 131.69, 125.1, 124.6, 119.9, 116.7, 116.2, 17.9, 17.8. **IR** (KBr, cm^{-1}) 2921, 1726, 1598, 1452, 1257, 1129, 1016, 761. **HRMS-TOF**; [M - H]$^-$ Calcd for C$_{14}$H$_{10}$NO$_2$ 224.07170, found: 224.06787.

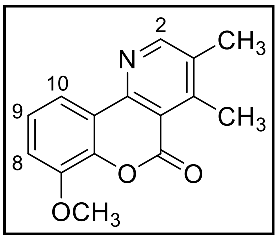
4.22.5 9-Bromo-3,4-dimethyl-5*H*-chromeno[4,3-*b*]pyridin-5-one (270e)



CrO$_3$ (207 mg, 2.07 mmol), pyridine (0.166 mL, 2.07 mmol) and chromenopyridine derivative **266** (20 mg, 0.069 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product **270e** as white needles from EtOAc (19 mg, 91%), mp 210-211 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.72 (br s, H$_2$), 8.71 (d, J = 2.2 Hz, H$_{10}$), 7.61 (dd, J = 8.6, 2.2 Hz, H$_8$), 7.22 (d, J = 8.7 Hz, H$_7$), 2.84 (s, -CH$_3$), 2.45 (s, -CH$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ 160.4, 155.5, 151.8, 151.1, 150.0, 134.4, 134.3, 127.8, 121.6, 118.4, 117.7, 116.2, 17.8, 17.8. **IR**

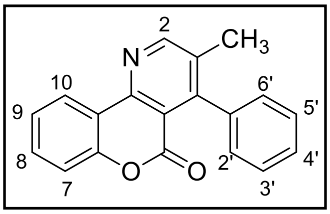
(KBr, cm^{-1}); 2919, 1734, 1553, 1454, 1379, 1251, 1094, 1012, 828, 803. **HRMS-TOF** M + H]$^+$ Calcd for $C_{14}H_{11}BrNO_2$ 303.99677, found: 303.99939.

4.22.6 7-Methoxy-3,4-dimethyl-5*H*-chromeno[4,3-*b*]pyridin-5-one (270f)



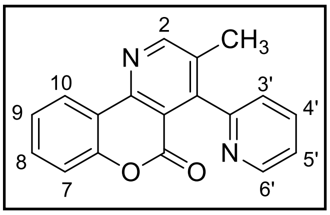
CrO$_3$ (498 mg, 4.98 mmol), pyridine (0.4 mL, 4.98 mmol), and chromenopyridine derivative **267** (60 mg, 0.249 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product **270f** as colorless cubic crystals from EtOH (63 mg, 99%), mp 213-214 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.71 (br s, H$_2$), 8.13 (d, J = 8.0 Hz, H$_{10}$), 7.30 (t, J = 8.0 Hz, H$_9$), 7.09 (d, J = 8.0 Hz, H$_8$), 3.99 (s, -OCH$_3$), 2.84 (s, -CH$_3$), 2.44 (s, -CH$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ 160.3, 155.4, 151.6, 151.3, 147.2, 142.0, 133.6, 124.2, 120.7, 116.2, 116.1, 113.3, 56.4, 17.8, 17.7. **IR** (KBr, cm^{-1}) 2918, 1734, 1558, 1485, 1436, 1278, 1129, 1062, 898, 785. **HRMS-TOF**; [M + Na]$^+$ Calcd for $C_{15}H_{13}NaNO_3$ 278. 07876, found: 278.08066.

4.22.7 3-Methyl-4-phenyl-5*H*-chromeno[4,3-*b*]pyridin-5-one (270g)



CrO$_3$ (384 mg, 3.85 mmol), pyridine (0.31 mL, 3.85 mmol), and chromenopyridine derivative **268** (35 mg, 0.128 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product **270g** was as white needles from EtOAc/petroleum ether (33 mg, 90%), mp 134-135 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.89 (br s, H$_2$), 8.63 (dd, J = 7.9, 1.6 Hz, H$_{10}$), 7.56–7.43 (m, H$_{4'}$, H$_{6'}$, H$_{2'}$ and H$_8$), 7.41–7.35 (m, H$_9$), 7.32 (dd, J = 8.2, 0.9 Hz, H$_7$), 7.17 – 7.13 (m, H$_{3'}$ and H$_{5'}$), 2.14 (s, -CH$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ 159.5, 156.2, 153.2, 152.6, 151.0, 138.2, 133.5, 131.8, 128.6 (2 C), 127.8, 126.9 (2 C), 125.0, 124.6, 119.7, 116.8, 115.2, 17.7. **IR** (KBr, cm^{-1}) 2922, 1737, 1612, 1450, 1252, 1155, 1111, 939, 758, 746. **HRMS-TOF** [M + Na]$^+$ Calcd for $C_{19}H_{13}NaNO_2$ 310.08385, found: 310.08615.

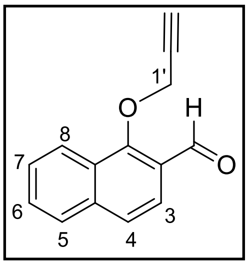
4.22.8 3-Methyl-4-pyridin-2-yl-5*H*-chromeno[4,3-*b*]pyridin-5-one (270h)



CrO$_3$ (546 mg, 5.46 mmol), pyridine (0.44 mL, 5.46 mmol) and chromenopyridine derivative **269** (50 mg, 0.182 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product **270h** as white tiny needles from EtOAc (49 mg, 98%), mp 199-200 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.94 (br s, H_2), 8.75 (d, J = 3.9 Hz, $H_{6'}$), 8.62 (dd, J = 8.0, 1.2 Hz, H_{10}), 7.86 (br t, J = 7.4 Hz, H_8), 7.55 (dt, J = 1.2, 7.8 Hz, H_9), 7.40 (br t, J = 7.1 Hz, $H_{4'}$ and $H_{5'}$), 7.34 – 7.28 (m, H_7 and $H_{6'}$), 2.17 (s, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.6, 156.7, 156.6, 152.3, 150.7, 150.5, 149.6, 136.5, 133.0, 131.7, 124.8, 124.6, 122.7, 122.7, 119.4, 116.7, 114.8, 16.9. **IR** (KBr, cm^{-1}) 2915, 1739, 1611, 1454, 1256, 1119, 941, 761. **HRMS-TOF** $[M + Na]^+$ Calcd for $C_{18}H_{12}NaN_2O_2$ 311.07910, found: 311.08191.

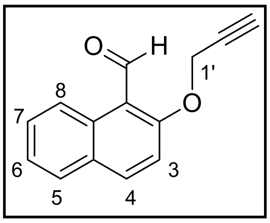
4.23 Synthesis of Naphthaldehydes

4.23.1 1-(Prop-2-ynyloxy)-2-naphthaldehyde (277)



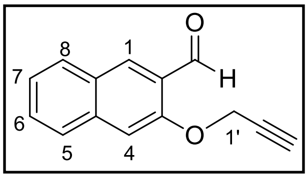
1-Hydroxy-2-naphthaldehyde (**274**) (160 mg, 0.93 mmol), anhydrous K_2CO_3 (0.19 g, 1.14 mmol), and propargyl bromide (0.12 mL, 1.12 mmol) in 7 mL of DMF were reacted as described above the give the product **277** pale yellow solid (190 mg, 97%), mp 77-78 ºC (Lit. mp 78-81 °C[134]). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.65 (d, J = 0.6 Hz, -COH), 8.23 (dd, J = 8.1, 0.6 Hz, H_8), 7.91 (d, J = 8.6 Hz, H_3 and H_4), 7.71 (d, J = 8.6 Hz, H_5), 7.68-7.58 (m, H_6 and H7), 4.95 (d, J = 2.4 Hz, $H_{1'}$), 2.61 (t, J = 2.4 Hz, -C≡CH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.1, 159.3, 138.1, 129.4, 128.6, 127.7, 127.1, 126.5, 125.5, 123.2, 122.6, 78.4, 77.8, 64.2. **HRMS-TOF** $[M + Na]^+$ Calcd for $C_{14}H_{10}NaO_2$ 233.0573, found: 233.05974.

4.23.2 2-(Prop-2-ynyloxy)-1-naphthaldehyde (168)



2-Hydroxy-1-naphthaldehyde (**275**) (2.0 g, 11.63 mmol), anhydrous K_2CO_3 (2.4 g, 17.44 mmol) and propargyl bromide (1.5 mL, 13.95 mmol) in 10 mL of DMF were reacted as described above to give the product **168** as colorless crystals (2.2 g, 92%), mp 113-115 ºC (Lit. mp 113-115 °C[135]). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.91 (s, -COH), 9.28 (d, J = 8.7 Hz, H_8), 8.08 (d, J = 9.1 Hz, H_4), 7.80 (d, J = 8.2 Hz, H_5), 7.64 (ddd, J = 8.5, 6.9, 1.4 Hz, H_7), 7.45 (ddd, J = 8.0, 6.9, 1.1 Hz, H_6), 7.40 (d, J = 9.1 Hz, H_3), 4.96 (d, J = 2.4 Hz, $H_{1'}$), 2.58 (t, J = 2.4 Hz, -C≡CH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.0, 162.0, 137.4, 131.5, 130.0, 129.2, 128.3, 125.3, 125.2, 118.1, 114.1, 77.8, 76.9, 57.5. **HRMS-TOF** $[M + Na]^+$ Calcd for $C_{14}H_{10}NaO_2$ 233.0573 found: 233.05935.

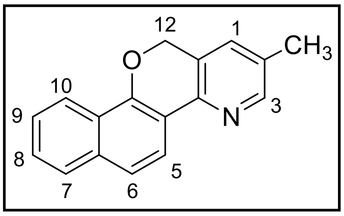
4.23.3 3-(Prop-2-ynyloxy)-2-naphthaldehyde (278)



3-Hydroxy-2-naphthaldehyde (**276**) (46 mg, 0.267 mmol), anhydrous K_2CO_3 (55 mg, 0.4 mmol), and propargyl bromide (35 µL, 0.32 mmol) in 5 mL of DMF were reacted as described above to give the product **278** as white powder (55 mg, 98%), mp 107- 109 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.59 (s, -COH), 8.41 (s, H_1), 7.91 (d, J = 8.3 Hz, H_5), 7.78 (d, J = 8.5 Hz, H_8), 7.57 (ddd, J = 8.2, 6.9, 1.2 Hz, H_7), 7.42 (ddd, J = 8.2, 6.9, 1.1 Hz, H_6), 7.34 (s, H_4), 4.94 (d, J = 2.4 Hz, $H_{1'}$), 2.60 (t, J = 2.4 Hz, -C≡CH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 190.0, 155.6, 137.3, 131.1, 130.1, 129.4, 128.3, 127.0, 126.0, 125.2, 108.3, 77.9, 76.6, 56.5. **HRMS-TOF** $[M + H]^+$ Calcd for $C_{14}H_{11}O_2$ 211.07536, found: 211.0757.

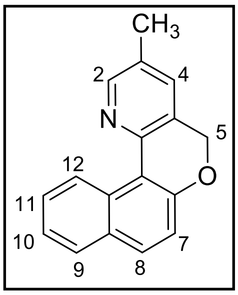
4.24 Synthesis of Benzochromenopyridines

4.24.1 2-Methyl-12*H*-benzo[7,8]chromeno[4,3-*b*]pyridine (279)



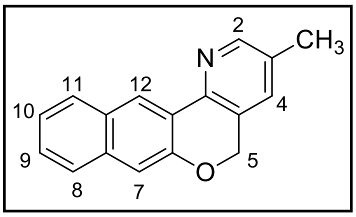
1-(Prop-2-ynyloxy)-2-naphth-aldehyde (**277**) (190 mg, 0.90 mmol), DBU (0.14 mL, 0.90 mmol), and propargylamine (0.18 mL, 2.83 mmol) in 15 mL of ethanol were reacted as described above (reflux overnight) to give the product **279** as yellowish tiny needle crystals from EtOAc (200 mg, 90%), mp 148-149 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (br s, H_3), 8.28 (d, J = 8.6 Hz, H_{10}), 8.25 – 8.22 (m, H_5), 7.84 – 7.79 (m, H_7), 7.56 (d, J = 8.6 Hz, H_6), 7.53 – 7.45 (m, H_9 and H_8), 7.27 (br s, H_1), 5.38 (s, H_{12}), 2.36 (s, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.3, 149.9, 146.9, 135.4, 132.6, 132.0, 127.9, 127.2, 125.8, 125.2, 125.1, 122.4, 121.8, 121.5, 117.8, 68.6, 18.5. **IR** (KBr, cm^{-1}) 2964, 1581, 1453, 1403, 1344, 1256, 1242, 1101, 1002, 954, 818, 778, 749. **HRMS-TOF** $[M + H]^+$ Calcd for $C_{17}H_{14}NO$ 248.10699, found: 248.1086.

4.24.2 3-Methyl-5*H*-benzo[5,6]chromeno[4,3-*b*]pyridine (280)



2-(Prop-2-ynyloxy)-1-naphthalde-hyde (**168**) (150 g, 0.71 mmol), DBU (0.10 mL, 0.71 mmol), and propargylamine (93 μL, 1.42 mmol) in 10 mL of ethanol were reacted as described above (reflux overnight) to give the product **280** as yellowish needles from EtOH (160 mg, 91%), mp 108-109 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.62 (d, *J* = 8.4 Hz, H_{12}), 8.55 (d, *J* = 1.5 Hz, H_2), 7.83 – 7.77 (m, H_8 and H_9), 7.61 (ddd, *J* = 8.5, 6.8, 1.4 Hz, H_{11}), 7.43 (ddd, *J* = 8.0, 6.9, 1.1 Hz, H_{10}), 7.33 (d, *J* = 1.4 Hz, H_4), 7.20 (d, *J* = 8.9 Hz, H_7), 5.11 (s, H_5), 2.39 (s, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156,0, 149.1, 148.1, 132.7, 131.8, 131.2, 130.9, 130.6, 128.4, 127.5, 127.0, 126.8, 124.3, 118.1, 116.5, 68.4, 18.3. **IR** (KBr, cm^{-1}) 2964, 1597, 1512, 1456, 1383, 1244, 1211, 972, 819, 738. **HRMS-TOF** $[M + H]^+$ Calcd for $C_{17}H_{14}NO$ 248.10699, found: 248.10883.

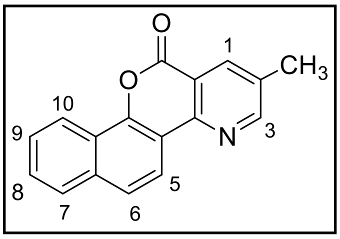
4.24.3 3-Methyl-5*H*-benzo[6,7]chromeno[4,3-*b*]pyridine (281)



3-(Prop-2-ynyloxy)-2-naphth-aldehyde (**278**) (50 mg, 0.238 mmol), DBU (35 μL, 0.238 mmol), and propargylamine (46 μL, 0.71 mmol) in 10 mL of ethanol were reacted as described above (reflux overnight) to give the product **281** as colorless needles from $CHCl_3$/hexane (55 mg, 94%), mp 128-129 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.7 (s, H_{12}), 8.48 (br s, H_2), 7.9 (d, *J* = 8.2 Hz, H_{11}), 7.71 (d, *J* = 8.2 Hz, H_8), 7.43 (ddd, *J* = 8.2, 6.9, 1.2, Hz, H_{10}), 7.38-7.34 (m, H_9), 7.35 (s, H_7), 7.3 (br s, H_4), 5.23 (s, H_5), 2.40 (s, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 153.7, 150.2, 146.1, 135.3, 132.9, 132.7, 130.1, 128.9, 127.2, 127.1, 126.8, 124.5, 124.2, 112.3, 106.4, 68.0, 18.6. **IR** (KBr, cm^{-1}) 2920, 1630, 1443, 1241, 1163, 1030, 947, 884, 869, 743. **HRMS-TOF** $[M + H]^+$ Calcd for $C_{17}H_{14}NO$ 248.10699, found: 248.10771.

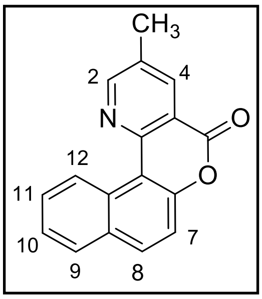
4.25 Synthesis of Benzochromenopyridinones

4.25.1 2-Methyl-12*H*-benzo[7,8]chromeno[4,3-*b*]pyridin-12-one (240)



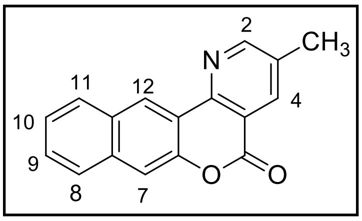
CrO_3 (0.80 mg, 8.5 mmol), pyridine (0.68 mL, 8.5 mmol), and benzochromenopyridine **279** (70 mg, 0.283 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product **240** as white needles from EtOAc (74 mg, 81%), mp 260-261 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.91 (d, J = 2.3 Hz, H_3), 8.61 – 8.57 (m, H_{10}), 8.58 (d, J = 8.6 Hz, H_5), 8.49 (dd, J = 2.3 Hz, H_1), 7.95 – 7.90 (m, H_7), 7.83 (d, J = 8.6 Hz, H_6), 7.69 – 7.62 (m, H_9 and H_8), 2.55 (s, -CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.6, 157.0, 150.2, 148.9, 137.8, 135.3, 133.8, 128.4, 128.0, 127.2, 124.8, 123.6, 122.4, 120.4, 117.0, 114.9, 18.6. **IR** (KBr, cm^{-1}) 2918, 1731, 1603, 1492, 1448, 1348, 1295, 1147, 1111, 1061, 943, 776. **HRMS-TOF** $[M - H]^-$ Calcd for $C_{17}H_9NO_2$ 260.06716, found: 260.0717.

4.25.2 3-Methyl-5*H*-benzo[5,6]chromeno[4,3-*b*]pyridin-5-one (241)



CrO_3 (1.62 g, 16.2 mmol), pyridine (1.3 mL, 16.2 mmol), and **280** (200 mg, 0.81 mmol) in 15 mL of dichloromethane were reacted as described above to give the oxidation product **241** as a white tiny needle-like crystals from chloroform (190 mg, 90%), mp 244-245 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.58 (d, J = 8.4 Hz, H_{12}), 9.03 (dd, J = 2.4, 0.5 Hz, H2), 8.54 (dd, J = 2.4, 0.8 Hz, H4), 8.01 (d, J = 8.9 Hz, H_8), 7.92 (dd, J = 8.0, 1.2 Hz, H_9), 7.75 (ddd, J = 8.6, 6.9, 1.5 Hz, H_{11}), 7.59 (ddd, J = 8.0, 6.9, 1.1 Hz, H_{10}), 7.52 (d, J = 8.9 Hz, H_7), 2.56 (s, -CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.7, 155.7, 152.6, 152.1, 138.0, 133.4, 132.9, 131.6, 130.7, 128.8, 128.5, 128.0, 125.9, 117.6, 117.5, 112.1, 18.5. **IR** (KBr, cm^{-1}) 2920, 1725, 1554, 1474, 1269, 1218, 1156, 1014, 815, 752. **HRMS-TOF** $[M + Na]^+$ Calcd for $C_{17}H_{11}NaNO_2$ 284.0692, found: 284.0707.

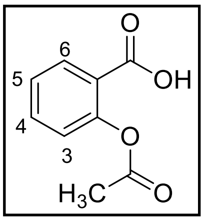
4.25.3 3-Methyl-5*H*-benzo[6,7]chromeno[4,3-*b*]pyridin-5-one (242)



CrO_3 (340 mg, 3.4 mmol), pyridine (0.27 mL, 3.4 mmol), and benzochromenopyridine **281** in 10 mL of dichloromethane were reacted as described above to give the oxidation product **242** as colorless cubic crystals from chloroform (43 mg, 98%), mp 287-288 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.10 (br s, H_{12}), 8.89 (bd, J = 2.2 Hz, H_2), 8.45 (bd, J = 2.2 Hz, H_4), 8.04 (bd, J = 8.2 Hz, H_{11}), 7.90 (br d, J = 8.3 Hz, H_8), 7.79 (br s, H_7) 7.58 (ddd, J = 8.2, 6.9, 1.3 Hz, H_{10}), 7.52 (ddd, J = 8.1, 6.9, 1.2 Hz, H_9), 2.54 (s, -CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.5, 156.8, 149.7, 149.5, 138.1, 135.0, 134.3, 130.7, 129.1, 128.2, 127.6, 126.0, 124.9, 119.3, 117.4, 113.4, 18.6. **IR** (KBr, cm^{-1}) 2920, 1724, 1601, 1486, 1292, 1258, 1179, 1130, 1074, 888, 793, 752. **HRMS-TOF**; $[M + H]^+$ Calcd for $C_{17}H_{12}NO_2$ 262.0868, found: 262.08324.

4.26 Synthesis of Benzopyrazolooxazepine and Benzopyrazolooxazocine Derivatives

4.26.1 2-(Acetyloxy)benzoic acid (282)

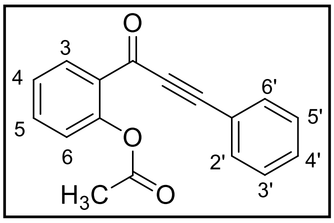


To salicylic acid **243** (4.0 g, 29 mmol) in an erlenmayer flask, acetic anhydride (10 mL, 100 mmol) and 10 drops 85% phosphoric acid are added. The mixture is stirred well. It was heated in water bath for 10 min. and removed from bath. 4 mL of water was added to the mixture while it was still hot cautiously in one portion. Then, 100 mL of water was added and after a while, crystals began to form. The mixture was cooled in an ice bath to complete the crystallization. The product **282** was collected by filtration, washed with cold water and dried. The product was obtained as white cubic crystal (4.9 g, 95%). Mp = 136-137 °C. (lit. Mp =136 °C)[136] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.0, 1.6 Hz, H_6), 7.62 (dt, J = 1.7, 7.8 Hz, H_4), 7.36 (dt, J = 1.0, 7.7 Hz, H_5), 7.14 (dd, J = 8.0, 0.9 Hz, H_3), 2.35 (s, -CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.3, 169.9, 151.4, 135.0, 132.7, 126.3, 124.2, 122.4, 21.1.

4.26.2 General Procedure for Synthesis of Phenyl Acetate Derivatives

Acetylsalicylic acid **282** (1 g, 5.55 mmol) was dissolved in chloroform (15 mL) and to this solution, oxalyl chloride (0. 95 mL, 11.1 mmol) was added dropwise. After adding 8-10 drops dry DMF, this mixture was refluxed overnight. Then, it was cooled to rt and the solvent and excess oxalyl chloride was removed under vacumm. To the empty flask, $PdCl_2$ (1% mol), PPh_3 (4% mol), CuI (3% mol) and NEt_3 (1 mL) were taken. They were stirred at around 50 °C for 5 min under nitrogen atmosphere. Formed acyl chloride **283** was dissolved in 10 mL dry THF and acetylene derivative was added to this solution in seperate flask. The mixture was added to stirred solution at 40 °C. The reaction mixture was refluxed under nitrogen atmosphere. After the completion of the reaction, the solvent was removed under vacuum and the residue was dissolved in EtOAc (100 mL). This solution was washed with water (3 × 75 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed. The residue was purified by column chromatography.

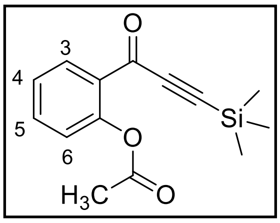
4.26.2.1 2-(3-phenylprop-2-ynoyl)phenyl acetate (285)



Acyl chloride **283** formed as describe above was reacted with phenyl acetylene (1.22 mL, 11.1 mmol), $PdCl_2$ (11 mg, 0.062 mmol), PPh_3 (66 mg, 0.25 mmol), CuI (36 mg, 0.189 mmol) and NEt_3 (1 mL) in THF (10 mL) according to general procedure. The reaction mixture was refluxed for 6 h. The residue was purified by column chromatography eluting with ethyl acetate/hexane (1:10 to 1:3) to give the product **285** as yellow viscous liquid (1 g, isolated yield = 68%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 (dd, J = 7.8, 1.6 Hz, H_6), 7.67 – 7.59 (m, H_5, $H_{2'}$ and $H_{6'}$), 7.51 – 7.45 (m, H_4), 7.44 – 7.38 (m, $H_{3'}$, $H_{4'}$ and $H_{5'}$), 7.15 (dd, J = 8.0, 0.9 Hz, H_3), 2.36 (s, $-CH_3$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.1, 169.7, 150.2, 134.8, 133.2, 133.1, 131.0, 129.6, 128.8, 126.3, 124.2, 120.1, 92.8, 87.8, 21.2.

4.26.2.2 2-(3-(trimethylsilyl)propioloyl)phenyl acetate (295)

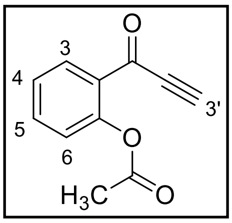
Acyl chloride **283** formed as described above was reacted with trimethylsilyl acetylene (0,95 mL, 6.66 mmol), $PdCl_2$ (11 mg, 0.062 mmol), PPh_3 (66 mg, 0.25 mmol), CuI (36 mg, 0.189 mmol) and NEt_3 (1 mL) in THF (10 mL) according to general procedure. The reaction mixture was refluxed for 2 h. The residue was purified by column chromatography by eluting ethyl acetate/hexane (1:50 to 1:8) to give the product **269** as yellow oil (130 mg). The reaction product was hydrolyzed after treatment of silica gel and new product **295** was also collected from the column (410 mg).



^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 (dd, J = 7.9, 1.6 Hz, H$_6$), 7.34 (dt, J = 1.6, 7.7 Hz, H$_4$), 7.18 (dt, J = 1.0, 7.7 Hz, H$_5$), 7.07 (dd, J = 7.9, 1.0 Hz, H$_3$), 2.33 (s, -CH$_3$), 0.25 (s, -Si(CH$_3$)$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ 175.8, 169.6, 150.3, 135.0, 133.8, 129.0, 126.3, 124.2, 101.5, 100.3, 21.2, -0.6.

4.26.2.3 2-Propioloylphenyl Acetate (296)

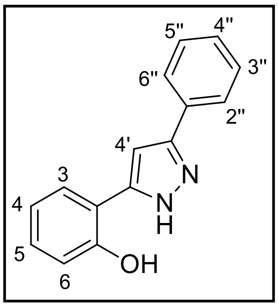
Unhydrolyzed product **295** of the previous reaction (130 mg, 0.5 mmol) was dissolved in dry THF (5 mL). To this solution, TBAF (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added and the mixture was stirred for 20 min. in an ice bath. After the completion of the reaction, the reaction mixture was diluted with dietylether (40 mL) and was washed with brine (3 × 50 mL). The organic phase was dried over MgSO$_4$ and the solvent was removed under reduced pressure. The product **296** was obtained as yellow oil (95 mg).



(0.51 g, isolated overall yield from compound **296** = 49%).**^{1}H NMR** (400 MHz, CDCl$_3$) δ 8.25 (dd, J = 7.8, 1.6 Hz, H$_6$), 7.64 (dt, J = 1.6, 7.8 Hz, H$_4$), 7.41 (dt, J = 0.6, 7.8 Hz, H$_5$), 7.13 (br d, J = 8.2 Hz, H$_3$), 3.42 (s, H$_{3'}$), 2.37 (s, -CH$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$) 175.3, 169.6, 150.4, 135.4, 133.8, 128.7, 126.4, 124.3, 81.0, 80.4, 21.2. **IR** (KBr, cm^{-1}) 2981, 2094, 1747, 1652, 1602, 1377, 1234, 1184, 1002, 851, 753, 510. **HRMS-TOF**; [M + Na]$^+$ Calcd for $C_{11}H_8NO_3$ 211.03657, found: 211.0371.

4.26.3 Synthesis of Pyrazoyl Phenols 286 and 297

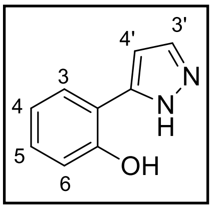
4.26.3.1 2-(3-phenyl-1*H*-pyrazol-5-yl)phenol (286)



Phenyl acetate derivative **285** (650 mg, 2.46 mmol) was dissolved in methanol (20 mL). Hydrazine monohydrate (8 eq.) was added to this solution and the reaction mixture was refluxed overnight. After the completion of the reaction, excess methanol was removed under reduced pressure and the residue was dissolved in EtOAc (40 mL). The organic phase was washed with water (3 × 50 mL) and brine (50 mL). The organic phase was dried over

$MgSO_4$ and then the solvent was evaporated. The obtained product **286** was crystallized from $CHCl_3$/petroleum ether as yellow cubic crytals (550 mg, 94%). mp =139-140 °C. (Lit. mp: 144 °C[137]) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.72 (br s, -OH), 7.66 – 7.60 (m, H_3, $H_{2''}$ and $H_{6''}$), 7.52 – 7.47 (m, $H_{3''}$ and $H_{5''}$), 7.46 – 7.41 (m, H_5), 7.27 – 7.22 (m, H_4), 7.05 (dd, J = 8.2, 0.9 Hz, H_3), 6.95 (dt, J = 1.0, 7.6 Hz, H_6), 6.92 (s, $H_{4'}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.8, 152.8, 144.1, 129.4, 129.2, 129.1, 128.8, 126.6, 125.7, 119.5, 117.1, 116.6, 99.5.

4.26.3.2 2-(1*H*-pyrazol-5-yl)phenol (297)



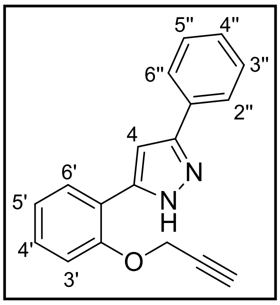
Phenyl acetate derivative **296** (380 mg, 2 mmol) was dissolved in methanol (20 mL). Hydrazine monohydrate (8 eq.) was added to this solution and the reaction mixture was refluxed overnight. After the completion of the reaction, excess methanol was removed under reduced pressure and the residue was dissolved in EtOAc (40 mL). The organic phase was washed with water (3 × 50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$ and then the solvent was evaporated. The formed product **297** was crystallized from $CHCl_3$/hexane as a white needle crystals (290 mg, 76%). Mp = 92-93 °C (lit. mp = 91-93 °C[138]). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (d, J = 2.5 Hz, $H_{3'}$), 7.60 (dd, J = 7.8, 1.6 Hz, H_3), 7.24 – 7.19 (m, H_5), 7.05 (br d, J = 8.2 Hz, H_6), 6.93 (dt, J = 1.1, 7.6 Hz, H_4), 6.73 (d, J = 2.5 Hz, $H_{4'}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.8, 151.7, 129.5 (2C), 126.8, 119.6, 117.1, 116.7, 102.1.

4.26.4 Synthesis of Propargylated Compounds

4.26.4.1 Synthesis of 3-phenyl-5-[2-(prop-2-ynyloxy)phenyl]-1*H*-pyrazole (290) and 2-(5-phenyl-1-prop-2-ynyl-1*H*-pyrazol-3-yl)phenol (291).

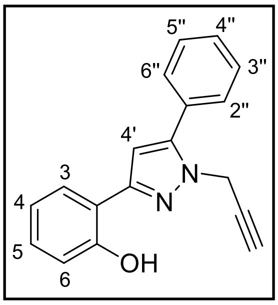
The compound **286** (290 mg, 1.23 mmol) was dissolved in dry DMF (10 mL). To this solution, K_2CO_3 (630 mg, 1.23 mmol) was added directly and the mixture was stirred for 30 min. at room temperature. After that, propargyl bromide (0.45 mL, 1.23 mmol) was added and the reaction mixture was stirred for 18 h at rt. The reaction was monitored on TLC. After the completion of the reaction, the mixture was diluted with EtOAc (50 mL) and the solution was washed with water (4 × 75 mL) and brine (2 × 50 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with hexane/EtOAc (4:1) to give corresponding products **290** (190 mg, 74%) as yellow oil and **291** (60 mg, 26%) as white solid. white tiny needle crystallized from $CHCl_3$/petroleum ether.

3-phenyl-5-[2-(prop-2-ynyloxy)phenyl]-1*H*-pyrazole (290)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.5 Hz, 2H, arom.), 7.76 (br d, J = 7.7 Hz, $H_{6'}$), 7.43 (t, J = 7.6 Hz, 2H, arom.), 7.36 – 7.30 (m, 2H, arom.), 7.11 (br t, J = 7.7 Hz, 2H, arom.), 6.97 (s, H_4), 4.85 (d, J = 2.3 Hz, $-CH_2$), 2.61 (t, J = 2.3 Hz, $-C\equiv CH$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.1, 151.2, 142.0, 133.3, 129.4, 128.8, 128.4, 128.0, 125.8, 122.5, 118.5, 113.3, 100.6, 77.8, 76.8, 56.7. **IR** (KBr, cm^{-1}) 3283, 2923, 1725, 1501, 1480, 1469, 1216, 1050, 1020, 968, 750, 692. **HRMS-TOF**; $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O$ 275.11789, found: 275.11936.

2-(5-phenyl-1-prop-2-ynyl-1*H*-pyrazol-3-yl)phenol (291)

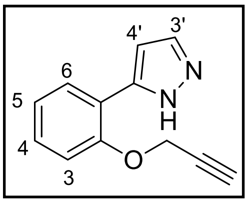


White tiny needles crystallized from $CHCl_3$/petroleum ether. mp =122-123 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 – 7.41 (m, 6H, arom.), 7.26 – 7.21 (m, 1H, arom.), 7.05 (dd, J = 8.2, 1.1 Hz, H_5), 6.92 (dt, J = 1.1, 7.6 Hz, H_4), 6.70 (s, $H_{4'}$), 4.90 (d, J = 2.5 Hz, $-CH_2$), 2.45 (t, J = 2.5 Hz, $-C\equiv CH$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.2, 151.6, 144.9, 129.6, 129.5, 129.2, 129.0 (2 C), 126.5, 119.4, 117.3, 116.5, 103.2, 77.7, 74.1, 39.9. **IR** (KBr, cm^{-1}) 2922, 1650, 1578, 1465, 1454, 1367, 1201, 1080, 1004, 956, 890, 744, 756, 690, 680. **HRMS-TOF**; $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O$ 275.11789, found: 275.11927.

4.26.4.2 Synthesis of 5-[2-(prop-2-ynyloxy)phenyl]-1*H*-pyrazole (298) and 2-(1-prop-2-ynyl-1*H*-pyrazol-3-yl)phenol (293)

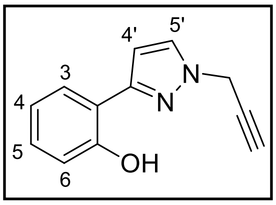
The compound **297** (290 mg, 1.8 mmol) was dissolved in dry DMF (10 mL). To this solution, K_2CO_3 (630 mg, 1.23 mmol) was added directly and the mixture was stirred for 30 min. at room temperature. After that, propargyl bromide (0.45 mL, 1.23 mmol) was added and the reaction mixture was stirred for 18 h at rt. The reaction was monitored on TLC. After the completion of the reaction, the mixture was diluted with EtOAc (50 mL) and the solution was washed with water (4 × 75 mL) and brine (2 × 50 mL). The organic phase was dried over $MgSO_4$ and the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with hexane/EtOAC (8 : 1) to give corresponding products **298** (125 mg, 35%) as yellow oil and **293** (230 mg, 65%) as white solid.

5-[2-(prop-2-ynyloxy)phenyl]-1*H*-pyrazole (298)



White needles crystal from $CHCl_3$/petroleum ether. mp = 88-89 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.31 (s, -NH), 7.73 (dd, *J* = 7.5, 6.3 Hz, H_6), 7.65 (d, *J* = 5.1 Hz, $H_{5'}$), 7.40 – 7.20 (m, H_4), 7.20 – 7.00 (m, H_3 and H_5), 6.70 (d, *J* = 5.1 Hz, $H_{4'}$), 4.97 – 4.72 (m, CH_2), 2.69 – 2.36 (m, -C≡CH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.0, 141.0, 138.6, 129.1, 128.4, 122.4, 119.0, 113.2, 103.5, 77.9, 76.6, 56.6. **IR** (KBr, cm^{-1}) 2918, 1649, 1578, 1454, 1368, 1219, 1201, 1079, 1012, 1004, 756, 744, 690, 680. **HRMS-TOF**; $[M + H]^+$ Calcd for $C_{12}H_{11}N_2O$ 199.08659, found: 199.0859

2-(1-prop-2-ynyl-1*H*-pyrazol-3-yl)phenol (293)

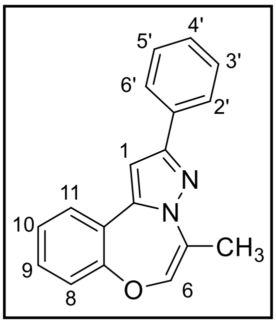


^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, -OH), 7.67 (d, *J* = 2.5 Hz, $H_{5'}$), 7.56 (dd, *J* = 7.8, 1.6 Hz, H_3), 7.22 (ddd, *J* = 8.7, 7.3, 1.6 Hz, H_5), 7.02 (dd, *J* = 8.2, 1.1 Hz, H_6), 6.91 (dt, *J* = 1.2, 7.6 Hz, H_4), 6.68 (d, *J* = 2.5 Hz, $H_{4'}$), 4.98 (d, *J* = 2.6 Hz, -CH_2), 2.55 (t, *J* = 2.6 Hz, -C≡CH). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 155.8, 152.0, 130.0, 129.3, 126.4, 119.4, 117.1, 116.5, 102.9, 76.2, 75.2, 41.6. **IR** (KBr, cm^{-1}) 1622, 1585, 1506, 1417, 1294, 1248, 1208, 1056, 940, 751, 697, 667. **HRMS-TOF** $[M + H]^+$ Calcd for $C_{12}H_{11}N_2O$ 199.08659, found: 199.08661

4.26.5 Formation of cyclization products 299, 300 and 301

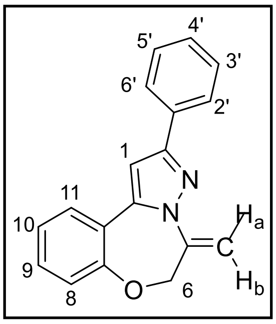
3-phenyl-5-[2-(prop-2-ynyloxy)phenyl]-1*H*-pyrazole (**290**) (150 mg, 0.75 mmol) was dissolved in acetonitrile and catalytic amount of gold (III) chloride (7 mg, $2.3x10^{-2}$ mmol) was added to this solution. Then, this mixture was stirred at 45 °C for 18 h. The reaction was monitored on TLC. After the consuming of the starting material, acetonitrile was evoparated and the crude product was purified by column chromatography and preperative TLC eluting with hexane/EtOAC (20 : 1 then 10: 1) to give corresponding products **300** (26 mg, 17%), **299** (82 mg, 55%) and **301** (42 mg, 28%).

4.26.5.1 5-methyl-2-phenylpyrazolo[1,5-*d*][1,4]benzoxazepine (301)



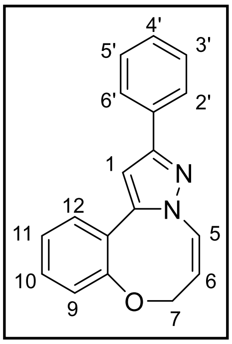
Yellow oil. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.89 (d, J = 7.3 Hz, 2H, arom.), 7.57 (dd, J = 7.7, 1.6 Hz, 1H, arom.), 7.44 (t, J = 7.5 Hz, 2H, arom.), 7.38 – 7.32 (m, 2H, arom.), 7.22 (dt, J = 1.1, 7.5 Hz, 1H, arom.), 7.12 (dd, J = 8.0, 1.0 Hz, 1H, arom.), 6.86 (s, H$_1$), 6.30 (q, J = 1.4 Hz, H$_6$), 2.24 (d, J = 1.4 Hz, CH$_3$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ 157.8, 151.6, 143.0, 133.0, 133.0, 130.6, 128.9, 128.7, 128.5, 128.2, 125.9, 125.2, 122.8, 120.9, 102.8, 15.3. **IR** (KBr, cm^{-1}) 3061, 1685, 1468, 1376, 1191, 797, 756. **HRMS-TOF**; [M + H]$^+$ Calcd for $C_{18}H_{15}N_2O$ 275.11789, found: 275.11993.

4.26.5.2 5-methylene-2-phenyl-5,6-dihydropyrazolo[1,5-*d*][1,4]benzoxazepine (300)



mp =109-110 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.95 – 7.90 (m, 2H, arom.), 7.84 (dd, J = 8.0, 1.5 Hz, H$_{11}$), 7.47 – 7.41 (m, 2H, arom.), 7.37 (ddd, J = 7.3, 3.7, 1.2 Hz, H$_8$), 7.31 – 7.25 (m, 1H, arom.), 7.18 – 7.13 (m, 1H, arom.), 7.10 (dd, J = 8.1, 1.2 Hz, H$_{10}$), 7.03 (s, H$_1$), 6.06 (s, H$_b$), 4.95 (s, H$_a$), 4.81 (s, -CH$_2$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ 157.5, 152.4, 141.7, 141.6, 132.8, 130.0, 129.0, 128.8, 128.5, 126.1, 123.8, 120.9, 119.7, 104.0, 103.2, 72.7. **IR** (KBr, cm^{-1}) 2987, 1652, 1578, 1452, 1378, 1214, 1017, 884, 770, 699. **HRMS-TOF**; [M + H]$^+$ Calcd for $C_{18}H_{15}N_2O$ 275.11789, found: 275.11999.

4.26.5.3 2-phenyl-7*H*-pyrazolo[1,5-*e*][1,5]benzoxazocine (299)

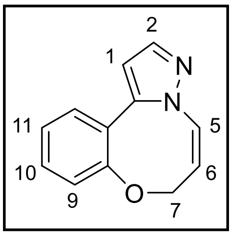


colorless cubic crystal from $CHCl_3$-petroleum ether. mp: 118-119 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 – 7.83 (m, 2H, arom.), 7.47 – 7.39 (m, 4H, arom.), 7.37 – 7.30 (m, 1H, arom.), 7.25 – 7.17 (m, 2H, arom.), 7.06 (dt, J = 9.9, 1.9 Hz, H_5), 6.66 (s, H_1), 5.42 (dt, J = 9.9, 3.6 Hz, H_6), 4.87 (dd, J = 3.6, 1.9 Hz, -CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.3, 153.0, 143.2, 132.9, 131.3, 131.2, 128.9, 128.8, 128.3, 125.9, 124.6, 124.2, 122.1, 118.9, 104.6, 72.4. **IR** (KBr, cm^{-1}) 2997, 1652, 1579, 1452, 1375, 1212, 1017, 770, 697. **HRMS-TOF**; $[M + H]^+$ Calcd for $C_{18}H_{15}N_2O$ 275.11789, found: 275.11989.

4.26.6. Formation of Cyclization Products 245b, 246b and 270b

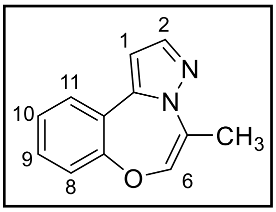
5-[2-(prop-2-ynyloxy)phenyl]-1*H*-pyrazole (**297**) (100 mg, 0.5 mmol) was dissolved in acetonitrile (10 mL) and catalytic amount of gold (III) chloride (5 mg, 1.6x10^{-2} mmol) was added to this solution. Then, this mixture was refluxed for 18 h. The reaction was monitored on TLC. After the consuming of the starting material, acetonitrile was evoparated and the crude product was purified by column chromatography and preperative TLC eluting with hexane/EtOAC (20 : 1) to give corresponding products **304** (31 mg, 31%), **302** (46 mg, 46%) and **303 (**23 mg, 23%).

4.26.6.1 7*H*-pyrazolo[1,5-*e*][1,5]benzoxazocine (302)



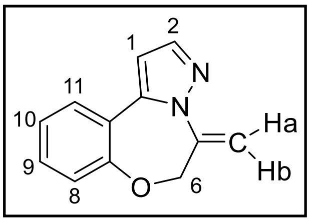
colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (s, H_2), 7.42 (dt, J = 1.7, 7.9 Hz, H_{12}), 7.34 (dd, J = 7.7, 1.6 Hz, H_9), 7.22 – 7.15 (m, H_{10} and H_{11}), 7.01 (br dt, J = 9.9 , 1.8 Hz, H_5), 6.36 (s, H_1), 5.38 (dt, J = 9.9, 3.5 Hz, H_6), 4.84 (dd, J = 3.5, 1.8 Hz, H_7). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.3, 141.9, 141.2, 131.2, 131.2, 128.7, 124.6, 124.3, 122.1, 118.9, 107.3, 72.4. **IR** (KBr, cm^{-1}) 2918, 1649, 1578, 1454, 1421, 1219, 1201, 1079, 1012, 756, 744, 733, 690, 680. **HRMS-TOF**; $[M + H]^+$ Calcd for $C_{12}H_{11}N_2O$ 199.08659, found: 199.08664

4.26.6.2 5-methylpyrazolo[1,5-*d*][1,4]benzoxazepine (304)



White tiny needles from $CHCl_3$-petroleum ether. mp: 55-56 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (d, J = 1.9 Hz, H_2), 7.50 (dd, J = 7.7, 1.7 Hz, H_{11}), 7.36 – 7.31 (m, H_9), 7.19 (dt, J = 1.2, 7.5 Hz, H_{10}), 7.10 (dd, J = 8.1, 1.1 Hz, H_8), 6.55 (d, J = 1.9 Hz, H_1), 6.28 (q, J = 1.4 Hz, H_6), 2.19 (d, J = 1.4 Hz, -CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.9, 141.7, 140.1, 133.2, 130.7, 129.0, 128.3, 125.3, 122.8, 120.9, 105.6, 15.3. **IR** (KBr, cm^{-1}) 2967, 1745, 1686, 1470, 1407, 1228, 1201, 1107, 924, 765, 674. **HRMS-TOF**; [M + H]$^+$ Calcd for $C_{12}H_{11}N_2O$ 199.08659, found: 199.08642

4.26.6.3 5-methylene-5,6-dihydropyrazolo[1,5-*d*][1,4]benzoxazepine (303)

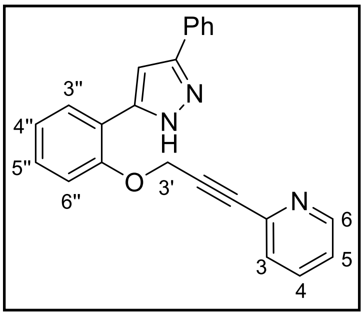


White tiny needles from $CHCl_3$/petrleum eher. mp = 56-57 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 8.0, 1.5 Hz, H_{11}), 7.67 (d, J = 1.8 Hz, H_2), 7.29 – 7.23 (m, H_9), 7.14 – 7.06 (m, H_8 and H_{10}), 6.71 (d, J = 1.8 Hz, H_1), 5.93 (s, H_b), 4.93 (s, H_a), 4.77 (s, H_6). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.2, 141.5, 140.9, 129.9, 128.8, 123.6, 120.7, 119.6, 119.4, 106.6, 103.2, 72.4. **IR** (KBr, cm^{-1}) 2923, 1648, 1580, 1532, 1468, 1408, 1382, 1208, 1102, 1002, 923, 878, 786, 764, 522. **HRMS-TOF**; [M + H]$^+$ Calcd for $C_{12}H_{11}N_2O$ 199.08659, found: 199.08667.

4.26.7 General Procedure of Sonogashira Coupling Reactions for Derivatization

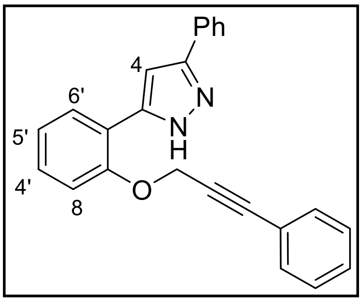
To a solution of 3-phenyl-5-[2-(prop-2-ynyloxy)phenyl]-1H-pyrazole (**290**) (0.25 g, 0.9 mmol) in dry THF (10 mL), iodobenzene (0.1 mL, 0.9 mmol) or bromopyridine (0.1 mL, 0.9 mmol), PPh_3 (10 mg, 0.2 mmol), $Pd(Cl)_2$ (2 mg, 0.05 mmol), dry diisopropylamine (0.2 mL, 1.4 mmol) and CuI (5 mg, 0.15 mmol) were added. The resulting mixture was refluxed for 4 h. After the completion of the reaction, the reaction mixture was cooled to rt and filtered over celite. The residue was washed with etyl acetate. The organic solvents in filtrate were removed under the vacuum, the crude product was purified by column chromatography eluting with ethyl acetate/hexane (1:20) to give corresponding products **305** and **306**.

2-{3-[2-(3-phenyl-1*H*-pyrazol-5-yl)phenoxy]prop-1-ynyl}pyridine (305)



yellow oil. . **^{1}H NMR** (400 MHz, CDCl$_3$) 8.51 (d, *J* = 4.8 Hz, 1H), 7.83 – 7.77 (m, 2H, arom.), 7.69 (dd, *J* = 7.7, 1.5 Hz, 1H, arom.), 7.60 – 7.52 (m, 1H, arom.), 7.39 – 7.31 (m, 3H arom.), 7.30 – 7.21 (m, 2H, arom.), 7.20 – 7.16 (m, 1H, aom.), 7.12 (d, *J* = 8.4 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.90 (s, 1H), 5.03 (d, *J* = 1.4 Hz, 2H, H$_{3'}$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ 158.0, 154.9, 152.24, 149.3, 142.5, 139.5, 136.6, 132.8, 130.2, 128.9, 128.8, 128.6, 126.2, 126.0, 123.7, 121.7, 120.9, 120.1, 117.5, 104.5, 68.7. **IR** (KBr, cm^{-1}) 2955, 1640, 1578, 1454, 1363, 1220, 1201, 1079, 1004, 955, 755, 744, 690, 680.

3-phenyl-5-{2-[(3-phenylprop-2-ynyl)oxy]phenyl}-1*H*-pyrazole (306)

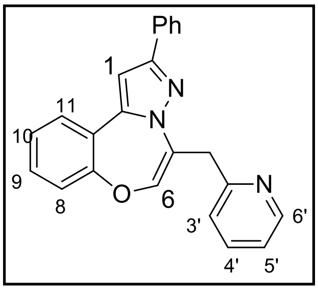


isolated yield: (0.21 g, 60%), white needle crystal from CHCl$_3$. mp 137-138 °C. **^{1}H NMR** (400 MHz, CDCl$_3$) δ 7.89 – 7.84 (m, 2H, arom.), 7.77 (dd, *J* = 7.7, 1.5 Hz, H$_{6'}$), 7.48 – 7.39 (m, 4H, arom.), 7.38 – 7.30 (m, 5H, arom.), 7.23 (d, *J* = 8.2 Hz, 1H), 7.13 (dt, *J* = 0.9, 7.5 Hz, H$_{5'}$), 6.97 (s, H4), 5.12 (s, -CH$_2$). **^{13}C NMR** (100 MHz, CDCl$_3$) δ 154.3, 150.8, 142.0, 133.1, 131.9 (2 C), 129.4, 128.9 (2 C), 128.8, 128.4 (2 C), 128.3, 128, 125.8 (2 C), 122.2, 122.0, 118.5, 113.5, 100.6, 88.2, 83.2, 57.4. **IR** (KBr, cm^{-1}) 3224, 1567, 1491, 1216, 1020, 968, 810, 748,689. **HRMS-TOF**; $[M + H]^+$ Calcd for $C_{24}H_{18}N_2O$ 351.14919, found: 351.14949

4.26.8 Synthesis of Pyridine Substituted Benzopyrazoloxazepine Derivatives

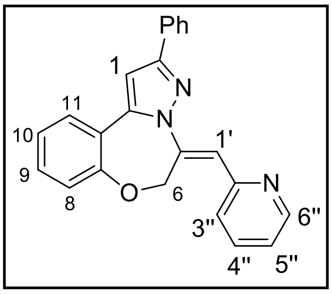
The starting compound (**305**) (100 mg, 0.28 mmol) was dissolved in acetonitrile (10 mL) and catalytic amount of gold (III) chloride (3 mg, 0.9x10^{-2} mmol) was added to this solution. Then, this mixture was refluxed for 18 h. The reaction was monitored on TLC. After the consuming of the starting material, acetonitrile was evoparated and the crude product was purified by column chromatography and preperative TLC eluting with hexane/EtOAC (20 : 1) to give corresponding products **307** (50 mg, crude yield: 50%), **308** (50 mg, crude yield: 50%)

2-phenyl-5-(pyridin-2-ylmethyl)pyrazolo[1,5-*d*][1,4]benzoxazepine (307)



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (br s, 1H), 7.91 – 7.77 (m, 2H, arom.), 7.56 – 7.49 (m, 2H), 7.42 (br t, *J* = 7.4 Hz, 2H, arom.), 7.36 – 7.30 (m, 2H, arom.), 7.27 (br d, *J* = 2.3 Hz, 1H, arom.), 7.19 (dt, *J* = 0.9, 7.5 Hz, 1H, arom.), 7.10 (dd, *J* = 7.9, 0.7 Hz, 2H, arom.), 6.81 (s, 1H), 6.45 (s,H_1), 4.24 (s, -CH_2).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.7, 157.5, 151.5, 148.4, 143.2, 137.5, 135.5, 132.7, 130.8, 129.8, 128.9, 128.8, 128.3, 125.8, 125.3, 124.0, 122.3, 122.1, 121.2, 103.0, 37.3 **HRMS-TOF**; [M + H]$^+$ Calcd for $C_{23}H_{18}N_3O$ 352.14444, found: 352.14505.

(5*E*)-2-phenyl-5-(pyridin-2-ylmethylene)-5,6-dihydropyrazolo[1,5-*d*][1,4]benzoxazepine (308)



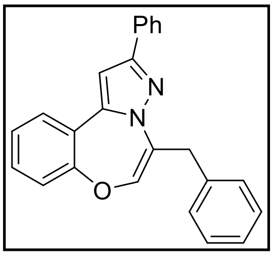
White needles crystal from $CHCl_3$-petroleum ether. mp: 129-130 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 3.7 Hz, 1H, arom.), 7.97 (d, *J* = 7.2 Hz, 2H, arom.), 7.83 (d, *J* = 7.8 Hz, 1H, arom.), 7.69 (dt, *J* = 7.7, 1.7 Hz, 1H, arom.), 7.66 (s, 1H), 7.47 (t, *J* = 7.5 Hz, 2H, arom.), 7.43 – 7.37 (m, 2H, arom.), 7.30 (dd, *J* = 7.9, 1.0 Hz, 1H, arom.), 7.16 (dd, *J* = 9.3, 5.7 Hz, 3H), 7.07 (s, H_1), 5.77 (s, -CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.0, 154.9, 152.2, 149.3, 142.5, 139.5, 136.6, 132.8, 130.2, 128.9, 128.8 (2 C), 128.6, 126.2 (2 C), 126.03 123.7, 121.7, 120.9, 120.08, 117.6, 104.5, 68.7. **IR** (KBr, cm^{-1}) 2920, 1650, 1465, 1454, 1367, 1201, 1080, 1004, 890, 756, 743, 680. **HRMS-TOF**; [M + H]$^+$ Calcd for $C_{23}H_{18}N_3O$ 352.14444, found: 352.14492.

4.26.9 The Synthesis of Benzene Substituted Benzopyrazoloxazepine Derivatives

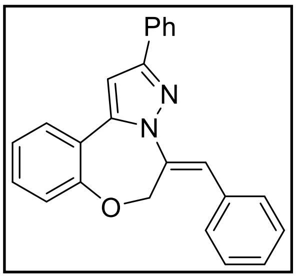
The starting compound (**308**) (180 mg, 0.51 mmol) was dissolved in acetonitrile (15 mL) and catalytic amount of gold (III) chloride (5 mg, 1.5x10^{-2} mmol) was added to this solution. Then, this mixture was refluxed for 48 h. The reaction was monitored on TLC. After the consuming of the starting material, acetonitrile was evoparated and the crude product was purified by column chromatography and preperative TLC eluting with hexane/EtOAC (10 : 1) to give corresponding products **309** (135 mg, crude yield: 75%), **310** (45 mg, crude yield: 25%)

5-benzyl-2-phenylpyrazolo[1,5-*d*][1,4]benzoxazepine (309)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.79 (m, 2H, arom.), 7.46 – 7.22 (m, 10 H, arom.), 6.99 (d, J = 7.6 Hz, 2H, arom.), 6.72 (s, 1H, arom.), 6.32 (quasi t, 1H, arom.), 4.87 – 4.78 (m, 1H, A part of AB system), 4.70 – 4.61 (1H, B part of AB system). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.5, 154.2, 146.6, 146.3, 134.9, 133.7, 132.8, 130.9, 129.7, 128.6, 128.5, 128.2, 127.1, 125.9, 121.3, 120.4, 117.4, 117.2, 105.0, 77.4, 77.0, 76.7, 65.0 .**IR** (KBr, cm^{-1}) 1654, 1584, 1465, 1448, 1363, 1201, 1079, 1010, 765, 750, 690, 640.

(5*E*)-5-benzylidene-2-phenyl-5,6-dihydropyrazolo[1,5-*d*][1,4]benzoxazepine (310)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.77 (m, 1H), 7.69 – 7.61 (m, 1H), 7.41 – 7.25 (m, 10H), 7.12 (t, J = 7.4 Hz, 2H), 7.06 (s, 1H), 6.56 (s, 1H), 4.90 (s, 2H). **IR** (KBr, cm^{-1}) 1464, 1442, 1208, 1010, 908, 752, 731, 691, 516.

REFERENCES

(1) Caprosu, M. D.; Roxana M. B; Ionel I M. *Heterocycles* **2005**, *65*, 1871–1879.

(2) Kurup, A.; Garg, R.; Carini, D. J.; Hansch, C. *Chem. Rev.* **2001**, *101*, 2727–2750.

(3) Carotti, A.; Catto, M.; Leonetti, F.; Campagna, F.; Soto-Otero, R.; Méndez-Álvarez, E.; Thull, U.; Testa, B.; Altomare, C. *J. Med. Chem.* **2007**, *50*, 5364–5371.

(4) Nomoto, Y.; Takai, H.; Ohno, T.; Nagashima, K.; Yao, K.; Yamada, K.; Kubo, K.; Ichimura, M.; Mihara, A.; Kase, H. *J. Med. Chem.* **1996**, *39*, 297–303.

(5) Estevez, I.; Ravina, E.; Sotela, E. *J. Heterocycl. Chem.* **1998**, *35*, 1421–1428.

(6) Thyes, M.; Lehmann, H. D.; Gries, J.; Konig, H.; Kretzschmar, R.; Kunze, J.; Lebkucher, R.; Lenke, D. *J. Med. Chem.* **1983**, *26*, 800–807.

(7) Abouzida, K.; Bekhit, S. A. *Bioorg. Med. Chem.* **2008**, *16*, 5547–5556.

(8) Moos, W. H.; Humblet, C. C.; Sircar, I.; Rithner, C.; Weishaar, R. E.; Bristol, J. A.; McPhailt, A. T. *J. Med. Chem.* **1987**, *30*, 1963–1972.

(9) Colletti, S. L.; Frie, J. L.; Dixone, E. C.; Singh, S. B.; Choi, B. K.; Scapin, G.; Fitzgerald, C. E.; Kumar, S.; Nichols, E. A.; O'Keefe, S. J.; O'Neill, E. A.; Porter, G.; Samuel, K.; Schmatz, D. M.; Schwartz, C. D.; Shoop, W. L.; Thompson, C. M.; Thompson, J. E.; Wang, R.; Woods, A.; Zaller, D. M.; Doherty, J. B. *J. Med. Chem.* **2003**, *46*, 349–352.

(10) Curran, W. V; Ross, A. *J. Med. Chem.* **1974**, *17*, 273–281.

(11) Sircar, I.; Steffen, R. .; Bobowski, G.; Burke, S. E.; Newton, R. S.; Weishaar, R. E.; Bristol, J. A.; Evans, D. B. *J. Med. Chem.* **1989**, *32*, 342–350.

(12) Montgomery, S. A.; Baldwin, D. S.; Priest, R. G.; Steinert, J.; Patel, A.; Herrington, R. N.; Livingston, H. M. *Pharmacopsychiatry* **1991**, *24*, 168–174.

(13) Aleeva, G. N.; Molodavkin, G. M.; Voronina, T. A. *Bull. Exp. Biol. Med.* **2009**, *148*, 54–56.

(14) Kellogg, R. L.; Nehring, R.; Grube, A.; Goss, D. W.; Plotkin, S. "Environmental Indicators of Pesticide Leaching and Run off from Farm Fields" United States Department of Agriculture Natural Resources Conservation Service.

(15) Pilgram, K. H.; Pollard, G. E. *J. Heterocycl. Chem.* **1977**, *14*, 1039–1043.

(16) Tantawy, M. M.; Braumann, T.; Horst Grimme, L. *Pestic. Biochem. Physiol.* **1984**, *22*, 224–231.

(17) Nagahori, H.; Matsunaga, H.; Tomigahara, Y.; Isobe, N.; Kaneko, H. *J. Agric. Food Chem.* **2009**, *57*, 4872–4877.

(18) Wu, J.; Song, B.; Chen, H.; Bhadury, P.; Hu, D. *Molecules* **2009**, *14*, 3676–3687.

(19) Ranfeng, S.; Zhang, Y.; Fuchun, B.; Wang, Q. *J. Agric. Food Chem.* **2009**, *57*, 6356–6361.

(20) Donohoe, T. J.; Fishlock, L. P.; Basutto, J. A.; Bower, J. F.; Procopiou, P. A.; Thompson, A. L. *Chem. Commun.* **2009**, *104*, 3008–3010.

(21) Vigil-De Gracia, P.; Lasso, M.; Ruiz, E.; Vega-Malek, J. C.; de Mena, F. T.; Lopez, J. C. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2006**, *128*, 157–162.

(22) DeRuiter, J. *Princ. Drug Action* **2001**, *2*, 1–20.

(23) Joensuu, H.; De Braud, F.; Grignagni, G.; De Pas, T.; Spitalieri, G.; Coco, P.; Spreafico, C.; Boselli, S.; Toffalorio, F.; Bono, P.; Jalava, T.; Kappeler, C.; Aglietta, M.; Laurent, D.; Casali, P. G. *Br. J. Cancer* **2011**, *104*, 1686–1690.

(24) Li, Y. X.; Luo, Y. P.; Xi, Z.; Niu, C.; He, Y. Z.; Yang, G. F. *J. Agric. Food Chem.* **2006**, *54*, 9135–9139.

(25) Tao, M.; Raddatz, R.; Aimone, L. D.; Hudkins, R. L. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6126–6130.

(26) Yamaguchi, M.; Maruyama, N.; Koga, T.; Kameli, K.; Akima, M.; Kuroki, T.; Hamana, M.; Oki, N. *Chem. Pharm. Bull.* **1995**, *43*, 236–240.

(27) Poli, D.; Catarzi, D.; Colotta, V.; Varano, F.; Filacchioni, G.; Daniele, S.; Trincavelli, L.; Martini, C.; Paoletta, S.; Moro, S. *J. Med. Chem.* **2011**, *54*, 2102–2113.

(28) Subasinghe, N. L.; Lanter, J.; Markotan, T.; Opas, E.; McKenney, S.; Crysler, C.; Hou, C.; O'Neill, J.; Johnson, D.; Sui, Z. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 1063–1069.

(29) Herberich, B.; Cao, G. Q.; Chakrabarti, P. P.; Falsey, J. R.; Pettus, L.; Rzasa, R. M.; Reed, A. B.; Reichelt, A.; Sham, K.; Thaman, M.; Wurz, R. P.; Xu, S.; Zhang, D.; Hsieh, F.; Lee, M. R.; Syed, R.; Li, V.; Grosfeld, D.; Plant, M. H.; Henkle, B.; Sherman, L.; Middleton, S.; Lu, M. W.; Tasker, A. S. *J. Med. Chem.* **2008**, *51*, 6271–6279.

(30) Shaw, A. Y.; Mclaren, J. A.; Nichol, G. S.; Hulme, C. *Tetrahedron Lett.* **2012**, *53*, 2592–2594.

(31) Ovalle, S.; Rodriguez, N. P.; Bernes, S.; Flores-Alamo, M. *Acta Crystallogr.* **2012**, *68*, 1879–1880.

(32) McKee, V.; Morgan, G. G.; Nelson, J. *Acta Crystallogr.* **2006**, *62*, 3747–3749.

(33) Xiao, T.; Li, L.; Lin, G.; Wang, Q.; Zhang, P.; Mao, Z.; Zhou, L. *Green Chem.* **2014**, *16*, 2418–2421.

(34) Prasanna Kumar, B. N.; Mohana, K. N.; Mallesha, L. *J. Fluor. Chem.* **2013**, *156*, 15–20.

(35) Özcan, S.; Balci, M. *Tetrahedron* **2008**, *64*, 5531–5540.

(36) Riley, H. L.; Morley, J. F.; Friend, N. A. C. *J. Chem. Soc.* **1932**, 1875–1883.

(37) Curtius, T. *J. Prak. Chem.* **1894**, *50*, 275–294.

(38) Matsuda, H.; Shimoda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **1999**, *7*, 1445–1450.

(39) Yoshikawa, M.; Harada, E.; Naitoh, Y.; Inoue, K.; Matsuda, H.; Shimoda, H.; Yamahara, J.; Murakami, N. *Chem. Pharm. Bull.* **1994**, *42*, 2225–2230.

(40) Matsuda, H.; Shimoda, H.; Yamahara, J.; Yoshikawa, M. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 215–220.

(41) Whyte, A. C.; Gloer, J. B.; Scott, J. A.; Malloch, D. *J. Nat. Prod.* **1996**, *59*, 765–769.

(42) Furuta, T.; Fukuyama, Y.; Asakawa, Y. *Phytochemistry* **1986**, *25*, 517–520.

(43) Lee, J. H.; Park, Y. J.; Kim, H. S.; Hong, Y. S.; Kim, K. W.; Lee, J. J. *J. Antibiot.* **2001**, *54*, 463–466.

(44) Barry, R. D. *Chem. Rev.* **1964**, *64*, 229–260.

(45) Shang, S.; Xu, W.; Li, L.; Tang, J.; Zhao, W.; Lei, P. *Phytochem. Lett.* **2015**, *11*, 53–56.

(46) Shang, S.-Z.; Xu, W.-X.; Li, L.; Tang, J.-G.; Zhao, W.; Lei, P.; Miao, M.-M.; Sun, H.-D.; Pu, J.-X.; Chen, Y.-K.; Yang, G.-Y. *Phytochem. Lett.* **2015**, *11*, 53–56.

(47) Kim, H. S.; Lim, H. K.; Chung, M. W.; Kim, Y. C. *J. Ethnopharmacol.* **2000**, *69*, 79–83.

(48) Piacente, S.; Pizza, C.; De Tommasi, N.; Mahmood, N. *J. Nat. Prod.* **1996**, *59*, 565–569.

(49) Pu, H.-L.; Huang, X.; Zhao, J.-H.; Hong, A. *Planta Med.* **2002**, *68*, 372–374.

(50) Srinivasan, R.; Chandrasekar, M. J. N.; Nanjan, M. J.; Suresh, B. *J. Ethnopharmacol.* **2007**, *113*, 284–291.

(51) Gao, X. J.; Guo, M. Y.; Zhang, Z. C.; Wang, T. C.; Cao, Y. G.; Zhang, N. S. *Inflammation* **2015**, *38*, 1442–1450.

(52) Nazir, N.; Koul, S.; Qurishi, M. A.; Taneja, S. C.; Ahmad, S. F.; Bani, S.; Qazi, G. N. *J. Ethnopharmacol.* **2007**, *112*, 401–405.

(53) Kumagai, H.; Masuda, T.; Ishizuka, M.; Takeuchi, T. *J. Antibiot. (Tokyo).* **1995**, *48*, 175–178.

(54) Yuan, H.; Junker, B.; Helquist, P.; Taylor, R. *Curr. Org. Synth.* **2004**, *1*, 1–9.

(55) Kumagai, H.; Wakazono, K.; Agata, N.; Isshiki, K.; Ishizuka, M.; Ikeda, D. *J. Antibiot. (Tokyo).* **2005**, *58*, 202–205.

(56) Chinworrungsee, M.; Kittakoop, P.; Isaka, M.; Chanphen, R.; Tanticharoen, M.; Thebtaranonth, Y. *J. Chem. Soc. Perkin Trans. 1* **2002**, 2473–2476.

(57) Babar, T. M.; Naseer, M. M.; Rauf, M. K.; Pervez, H.; Ebihara, M.; Rama, N. H. *Chinese Chem. Lett.* **2014**, *25*, 1282–1286.

(58) Ma, G.-H.; Jiang, B.; Tu, X.-J.; Ning, Y.; Tu, S.-J.; Li, G. *Org. Lett.* **2014**, *16*, 4505–4507.

(59) Yoshikawa, M.; Shimada, H.; Yagi, N.; Murakami, N.; Shimoda, H.; Yamahara, J.; Matsuda, H. *Chem. Pharm. Bull.* **1996**, *44*, 1890–1898.

(60) Rossi, R.; Carpita, A.; Bellina, F.; Stabile, P.; Mannina, L. *Tetrahedron* **2003**, *59*, 2067–2081.

(61) Khan, I. A.; Kulkarni, M. V.; Gopal, M.; Shahabuddin, M. S.; Sun, C. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3584–3587.

(62) El-Essawy, F. A.; El-Etrawy, A. S. *J. Heterocycl. Chem.* **2014**, *51*, 191–195.

(63) Frolova, L. V.; Malik, I.; Uglinskii, P. Y.; Rogelj, S.; Kornienko, A.; Magedov, I. V. *Tetrahedron Lett.* **2011**, *52*, 6643–6645.

(64) Ramalingam, P.; Ganapaty, S.; Rao, C. B.; Ravi, T. K. *Indian J. Heterocycl. Chem.* **2006**, *15*, 359–362.

(65) Al-Said, M. S.; Ghorab, M. M.; Nissan, Y. M. *Chem. Cent. J.* **2012**, *6*, 64.

(66) Vu, A. T.; Campbell, A. N.; Harris, H. a.; Unwalla, R. J.; Manas, E. S.; Mewshaw, R. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4053–4056.

(67) Cheng, J. F.; Ishikawa, A.; Ono, Y.; Arrhenius, T.; Nadzan, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3647–3650.

(68) Van Assche, G.; Rutgeerts, P. *Expert Opin. Investig. Drugs* **2000**, *9*, 103–111.

(69) Moreland, L. W. *Expert Opin. Investig. Drugs* **1999**, *8*, 1443–1451.

(70) Huang, W.; Lin, W.; Guan, X. *Tetrahedron Lett.* **2014**, *55*, 116–119.

(71) Saijo, T.; Kuriki, H.; Ashida, Y.; Makino, H.; Maki, Y. *Int. Arch. Allergy Immunol.* **1985**, *78*, 43–50.

(72) Saijo, T.; Kuriki, H.; Ashida, Y.; Makino, H.; Maki, Y. *Int. Arch. Allergy Immunol.* **1985**, *77*, 315–321.

(73) Meng, W.; Dong, Y.; Liu, J.; Wang, Z.; Zhong, X.; Chen, R.; Zhou, H.; Lin, M.; Jiang, L.; Gao, F.; Xu, T.; Chen, Q.; Zeng, X. *Trials* **2009**, *10*, 30.

(74) Dolatkhah, Z.; Nasiri-aghdam, M.; Bazgir, A. *Tetrahedron Lett.* **2013**, *54*, 1960–1962.

(75) Thapa, U.; Thapa, P.; Karki, R.; Yun, M.; Choi, J. H.; Jahng, Y.; Lee, E.; Jeon, K. H.; Na, Y.; Ha, E. M.; Cho, W. J.; Kwon, Y.; Lee, E. S. *Eur. J. Med. Chem.* **2011**, *46*, 3201–3209.

(76) Patel, A. A.; Lad, H. B.; Pandya, K. R.; Patel, C. V.; Brahmbhatt, D. I. *Med. Chem. Res.* **2013**, *22*, 4745–4754.

(77) Stolle, W. A. W.; Frissen, A. E.; Marcelis, A. T. M.; Van Der Plas, H. C. *J. Org. Chem.* **1992**, *57*, 3000–3007.

(78) Palacios, F.; Alonso, C.; Amezua, P.; Rubiales, G. *J. Org. Chem.* **2002**, *67*, 1941–1946.

(79) Gayen, K. S.; Maiti, D. K. *RSC Adv.* **2014**, *4*, 10204–10207.

(80) Kumari, K.; Raghuvanshi, D. S.; Singh, K. N. *Tetrahedron* **2013**, *69*, 82–88.

(81) Nohara, A.; Ishiguro, T.; Ukawa, K.; Sugihara, H.; Maki, Y.; Sanno, Y. *J. Med. Chem.* **1985**, *28*, 559–568.

(82) Narodiya, V. P.; Vadodaria, M. S.; Vagadiya, G. V; Gadara, S. A.; Ladwa, K. D. *Int. J. Eng. Tech. Res.* **2014**, *2*, 1–8.

(83) Xiang, H.; Chen, J.; Miao, Z.; Yang, C. *RSC Adv.* **2014**, *4*, 16132–16135.

(84) Abdel-Rahman, A.-R. H.; Girges, M. M.; El-Ahl, A.-A. S.; Sallam, L. M. *Heteroat. Chem.* **2006**, *17*, 2–7.

(85) Ramesh, S.; Gaddam, V.; Nagarajan, R. *Synlett* **2010**, *5*, 757–760.

(86) Ruff, R. *J. Head Trauma Rehab.* **1976**, *24*, 418–419.

(87) Díaz-Gavilán, M.; Gómez-Vidal, J. A.; Rodríguez-Serrano, F.; Marchal, J. A.; Caba, O.; Aránega, A.; Gallo, M. A.; Espinosa, A.; Campos, J. M. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1457–1460.

(88) Samanta, K.; Chakravarti, B.; Mishra, J. K.; Dwivedi, S. K. D.; Nayak, L. V.; Choudhry, P.; Bid, H. K.; Konwar, R.; Chattopadhyay, N.; Panda, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 283–287.

(89) Singh, a. N.; Barlas, C.; Singh, S.; Franks, P.; Mishra, R. K. *J. Psychiatr Neurosci* **1996**, *21*, 29–35.

(90) Kamei, K.; Maeda, N.; Nomura, K.; Shibata, M.; Katsuragi-Ogino, R.; Koyama, M.; Nakajima, M.; Inoue, T.; Ohno, T.; Tatsuoka, T. *Bioorg. Med. Chem.* **2006**, *14*, 1978–1992.

(91) Nolan, J. C.; Stephens, D. J.; Proakis, A. G.; Leonard, C. A.; Johnson, D. N.; Kilpatrick, B. F.; Foxwell, M. H.; Yanni, J. M. *Agents Actions* **1989**, *28*, 53–61.

(92) Hallinan, E. A.; Stapelfeld, A.; Savage, M. A.; Reichman, M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 509–514.

(93) Dols, P. P. M. A.; Folmer, B. J. B.; Hamersma, H.; Kuil, C. W.; Lucas, H.; Ollero, L.; Rewinkel, J. B. M.; Hermkens, P. H. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1461–1467.

(94) Gijsen, H. J. M.; Berthelot, D.; Zaja, M.; Brône, B.; Geuens, I.; Mercken, M. *J. Med. Chem.* **2010**, *53*, 7011–7020.

(95) Binaschi, M.; Boldetti, A.; Gianni, M.; Maggi, C. a; Gensini, M.; Bigioni, M.; Parlani, M.; Giolitti, A.; Fratelli, M.; Valli, C.; Terao, M.; Garattini, E. *ACS Med. Chem. Lett.* **2010**, *1*, 411–415.

(96) Dorn, A.; Schattel, V.; Laufer, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 3074–3077.

(97) Tsvelikhovsky, D.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 14228–14231.

(98) Smits, R. a.; Lim, H. D.; Stegink, B.; Bakker, R. a.; De Esch, I. J. P.; Leurs, R. *J. Med. Chem.* **2006**, *49*, 4512–4516.

(99) Zaware, N.; Ohlmeyer, M. *Heterocycl. Commun.* **2014**, *20*, 189–191.

(100) Ouyang, X.; Kiselyov, A. S. *Tetrahedron Lett.* **1999**, *40*, 5827–5830.

(101) Mishra, J. K.; Samanta, K.; Jain, M.; Dikshit, M.; Panda, G. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 244–247.

(102) Seto, S.; Tanioka, A.; Ikeda, M.; Izawa, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1485–1488.

(103) Novelli, a.; Díaz-Trelles, R.; Groppetti, a.; Fernández-Sánchez, M. T. *Amino Acids* **2005**, *28*, 183–191.

(104) Mohamed, H. M.; El-Wahab, A. H. F. A.; El-Agrody, A. M.; Bedair, A. H.; Eid, F. A.; Khafagy, M. M.; Abd-El-rehem, K. A. *Beilstein J. Org. Chem.* **2011**, *7*, 1688–1696.

(105) Ohnmacht, C. J.; Albert, J. S.; Bernstein, P. R.; Rumsey, W. L.; Masek, B. B.; Dembofsky, B. T.; Koether, G. M.; Andisik, D. W.; Aharony, D. *Bioorg. Med. Chem.* **2004**, *12*, 2653–2669.

(106) Stillings, M. R.; Freeman, S.; Myers, P. L.; Readhead, M. J.; Welbourn, A. P.; Rance, M. J.; Atkinson, D. C. *J. Med. Chem.* **1985**, *5*, 225–233.

(107) Ramachary, D. B.; Narayana, V. V; Prasad, M. S.; Ramakumar, K. *Org. Biomol. Chem.* **2009**, *7*, 3372–3378.

(108) Mitra, S.; Banerjee, T. S.; Hota, S. K.; Bhattacharya, D.; Das, S.; Chattopadhyay, P. *Eur. J. Med. Chem.* **2011**, *46*, 1713–1720.

(109) Kamal, A.; Shaik, A. B.; Jain, N.; Kishor, C.; Nagabhushana, A.; Supriya, B.; Bharath Kumar, G.; Chourasiya, S. S.; Suresh, Y.; Mishra, R. K.; Addlagatta, A. *Eur. J. Med. Chem.* **2015**, *92*, 501–513.

(110) Zhang, H.; Zhu, P.; Liu, J.; Lin, Y.; Yao, H.; Jiang, J.; Ye, W.; Wu, X.; Xu, J. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 728–732.

(111) Yu, L.-G.; Ni, T.-F.; Gao, W.; He, Y.; Wang, Y.-Y.; Cui, H.-W.; Yang, C.-G.; Qiu, W.-W. *Eur. J. Med. Chem.* **2015**, *90*, 10–20.

(112) Kumar, K. A.; Jayaroopa, P. *Int. J. Pharm. Tech. Res.* **2013**, *5*, 1473–1486.

(113) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675–2678.

(114) Sha, Q.; Wei, Y. *Synthesis (Stuttg).* **2013**, *45*, 413–420.

(115) Jin, W.; Yu, H.; Yu, Z. *Tetrahedron Lett.* **2011**, *52*, 5884–5887.

(116) Stephen A; Hashmi K.; Dean Toste F. *Modern Gold Catalyzed Synthesis*; 2012.

(117) Subbarao, K. P. V.; Raveendra Reddy, G.; Muralikrishna, A.; Reddy, K. V. *J. Heterocycl. Chem.* **2014**, *51*, 1045–1050.

(118) Goutham, K.; Mangina, N. S. V. M. R.; Suresh, S.; Raghavaiah, P.; Karunakar, G. V. *Org. Biomol. Chem.* **2014**, *12*, 2869–2873.

(119) Aponick, A.; Li, C. Y.; Malinge, J.; Marques, E. F. *Org. Lett.* **2009**, *11*, 4624–4627.

(120) Doucet, H.; Hierso, J. C. *Angew. Chem. - Int. Ed.* **2007**, *46*, 834–871.

(121) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467–4470.

(122) Caporale, A.; Tartaggia, S.; Castellin, A.; De Lucchi, O. *Beilstein J. Org. Chem.* **2014**, *10*, 384–393.

(123) Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874–922.

(124) Menges, N.; Sari, O.; Abdullayev, Y.; Erdem, S. S.; Balci, M. *J. Org. Chem.* **2013**, *78*, 5184–5195.

(125) Çetinkaya, Y.; Balci, M. *Tetrahedron Lett.* **2014**, *55*, 6698–6702.

(126) Gawinecki, R.; Kuczek, A.; Kolehmainen, E.; Osmialowski, B.; Krygowski, T. M.; Kauppinen, R. *J. Org. Chem.* **2007**, *72*, 5598–5607.

(127) Synder, H. R.; Swaminathan, S.; Sims, H. J. *J. Am. Chem. Soc.* **1952**, *74*, 5110–5113.

(128) Wu, K.-C.; Lin, Y.-S.; Yeh, Y.-S.; Chen, C.-Y.; Ahmed, M. O.; Chou, P.-T.; Hon, Y.-S. *Tetrahedron* **2004**, *60*, 11861–11868.

(129) Koza, G.; Keskin, S.; Özer, M. S.; Cengiz, B.; Şahin, E.; Balci, M. *Tetrahedron* **2013**, *69*, 395–409.

(130) Keskin, S.; Balci, M. *Org. Lett.* **2015**, *17*, 964–967.

(131) Furniss B S; Hannaford A C; Smith G S W; Tatchell A R. *Textbook of Practical Organic Chemistry 5th ed*; 1994.

(132) Schank, K.; Beck, H.; Pistorius, S. *Helv. Chim. Acta* **2004**, *87*, 2025–2049.

(133) Khoshkholgh, M. J.; Balalaie, S.; Bijanzadeh, H. R.; Grossc, J. H. *Arkivoc* **2009**, *9*, 114–121.

(134) Sze, E. M. L.; Rao, W.; Koh, M. J.; Chan, P. W. H. *Chem. Eur. J.* **2011**, *17*, 1437–1441.

(135) Vedachalam, S.; Wong, Q.-L.; Maji, B.; Zeng, J.; Ma, J.; Liu, X.-W. *Adv. Synth. Catal.* **2011**, *353*, 219–225.

(136) Kiran, T. S.; Nandibewoor, S. T. *J. Chem. Res.* **2006**, *2006*, 431–436.

(137) Baker, W.; Harborne, J. B.; Ollis, W. D. *J. Chem. Soc.* **1952**, 1303–1309.

(138) Ibrahim, M. A. *J. Braz. Chem. Soc.* **2013**, *24*, 1754–1763.

APPENDIX A

SPECTRAL DATA

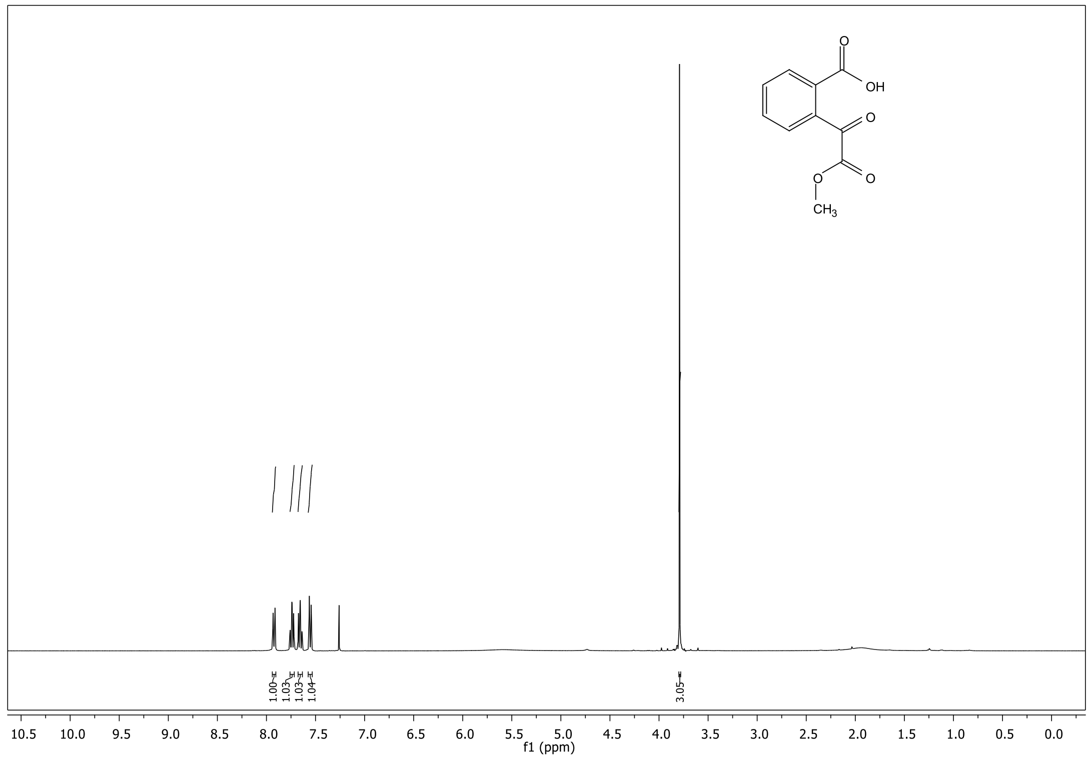


Figure 16: ^{1}H NMR Spectrum of Compound 70

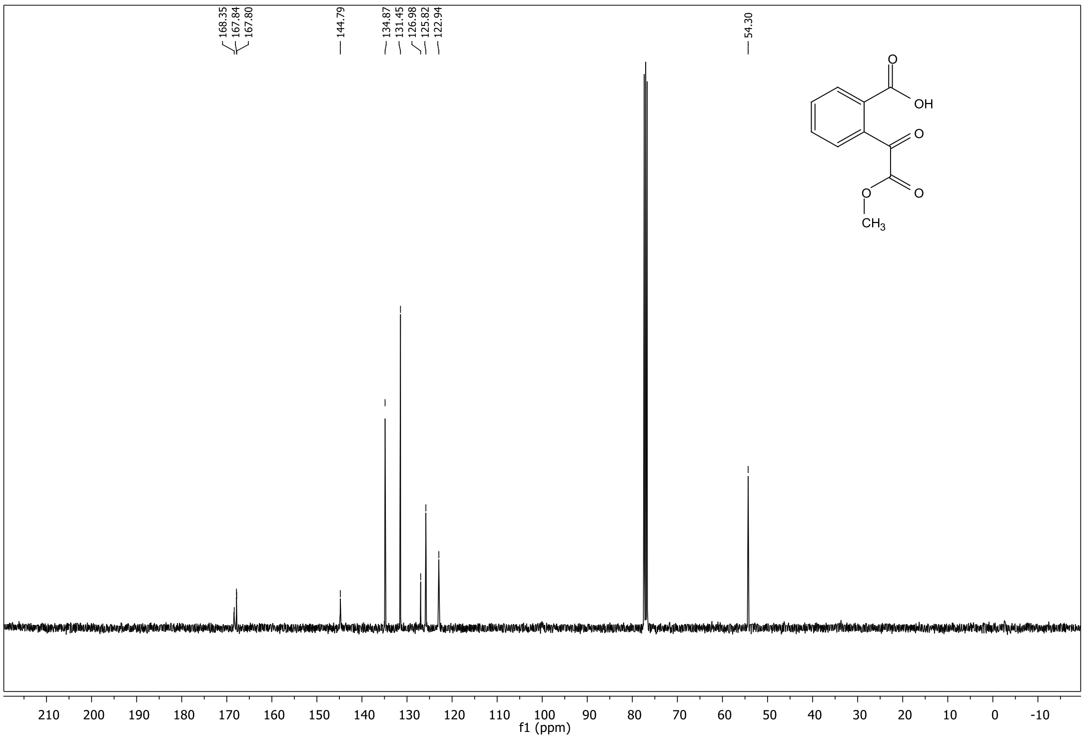


Figure 17: ^{13}C NMR Spectrum of Compound 70

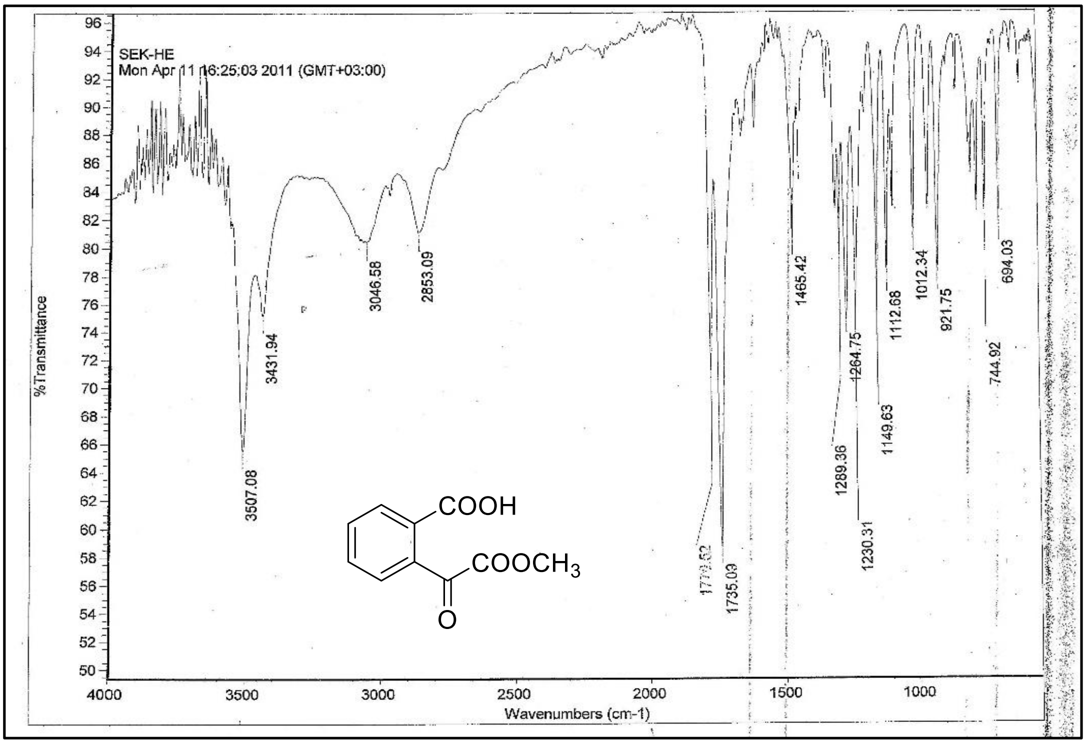


Figure 18: IR Spectrum of Compound 70

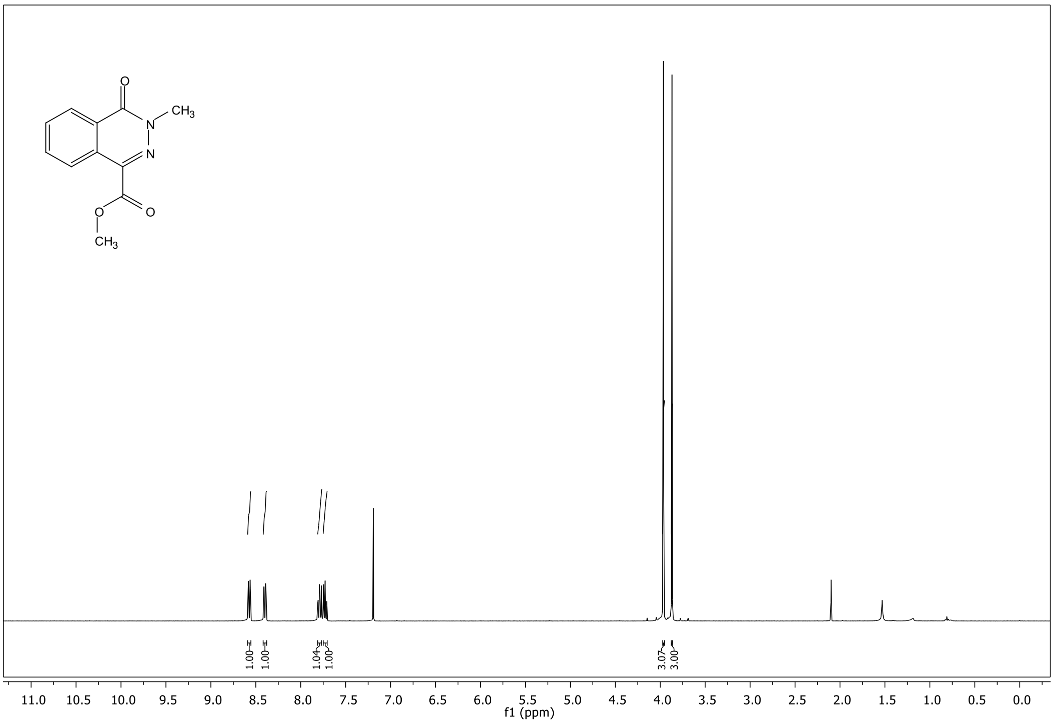


Figure 19: ^{1}H NMR Spectrum of Compound 71a

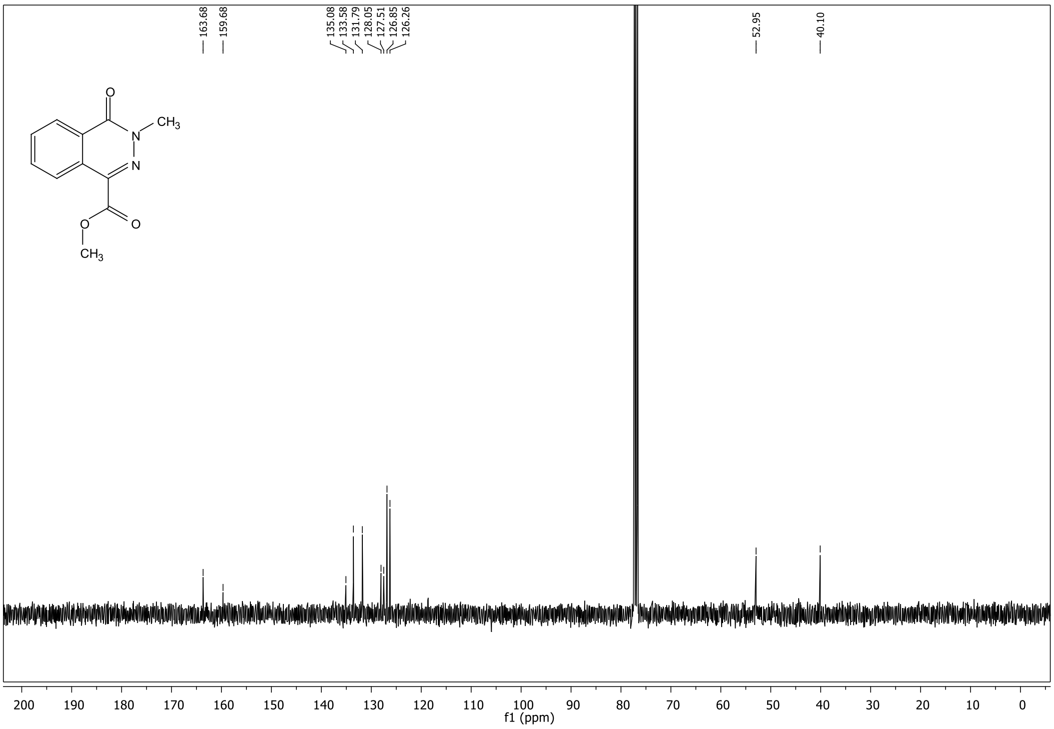


Figure 20: ^{13}C NMR Spectrum of Compound 71a

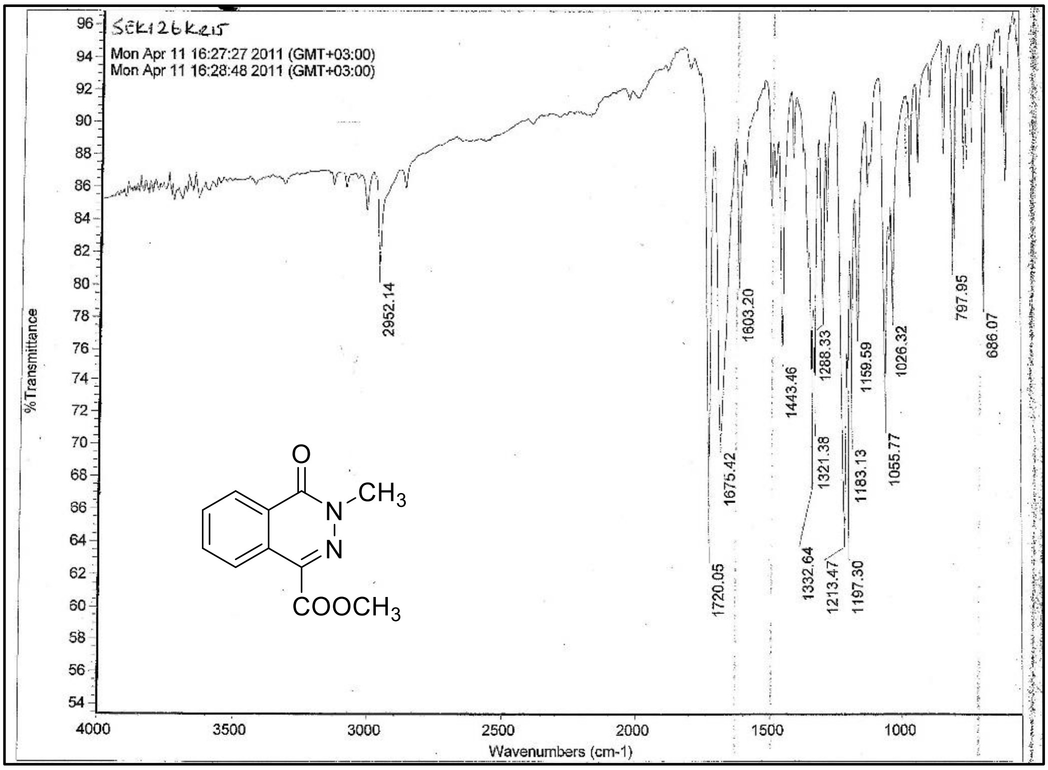


Figure 21: IR Spectrum of Compound 71a

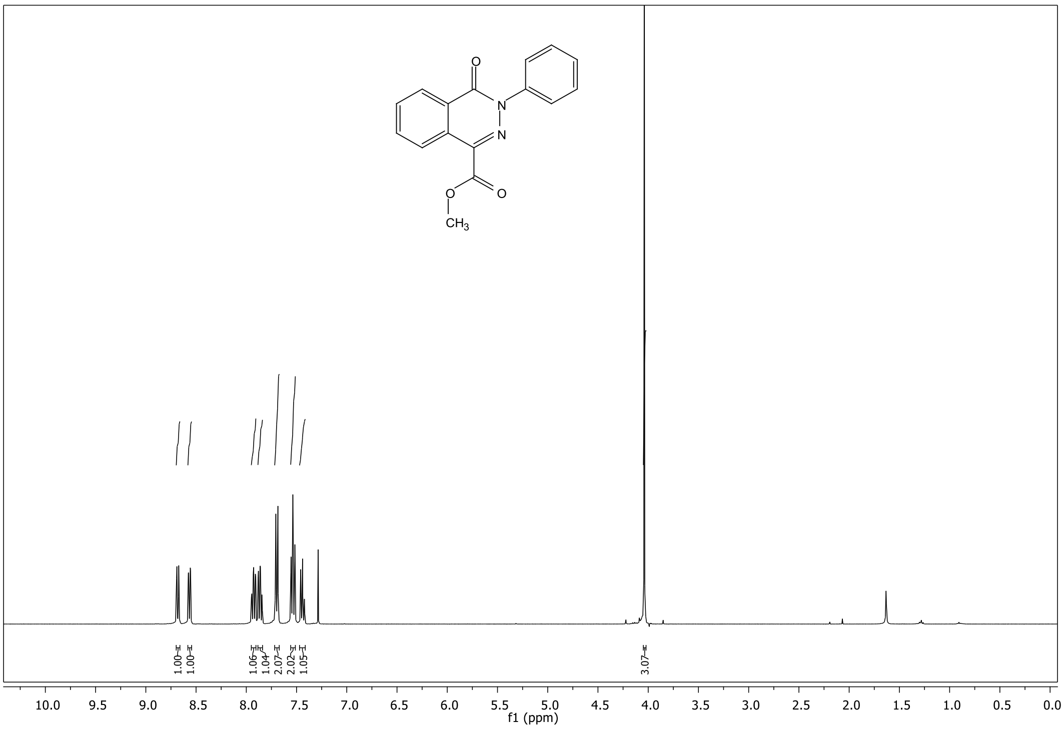


Figure 22: ^{1}H NMR Spectrum of Compound 71b

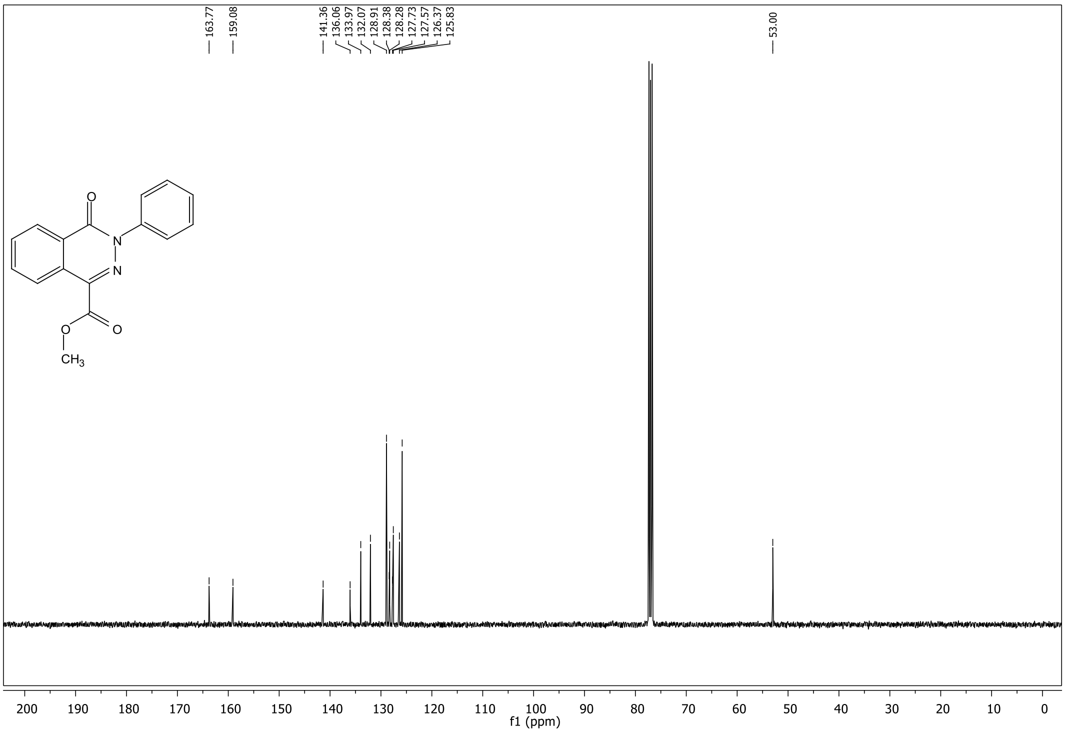


Figure 23: ^{13}C NMR Spectrum of Compound 71b

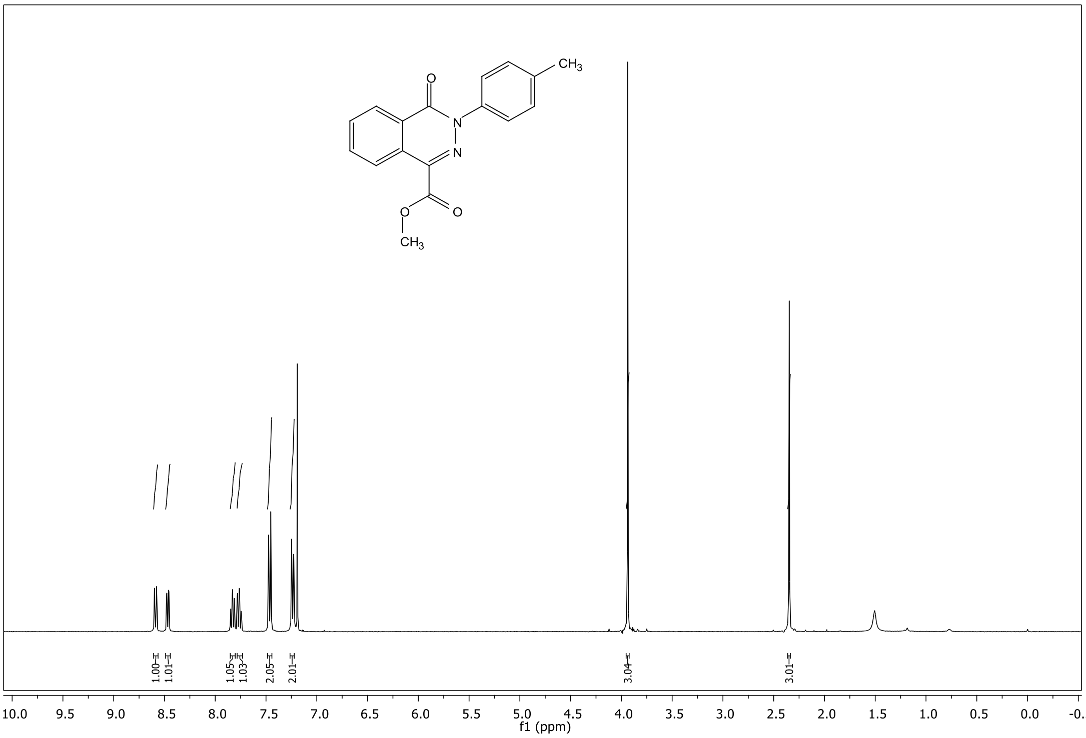


Figure 24: ^{1}H NMR Spectrum of Compound 71c

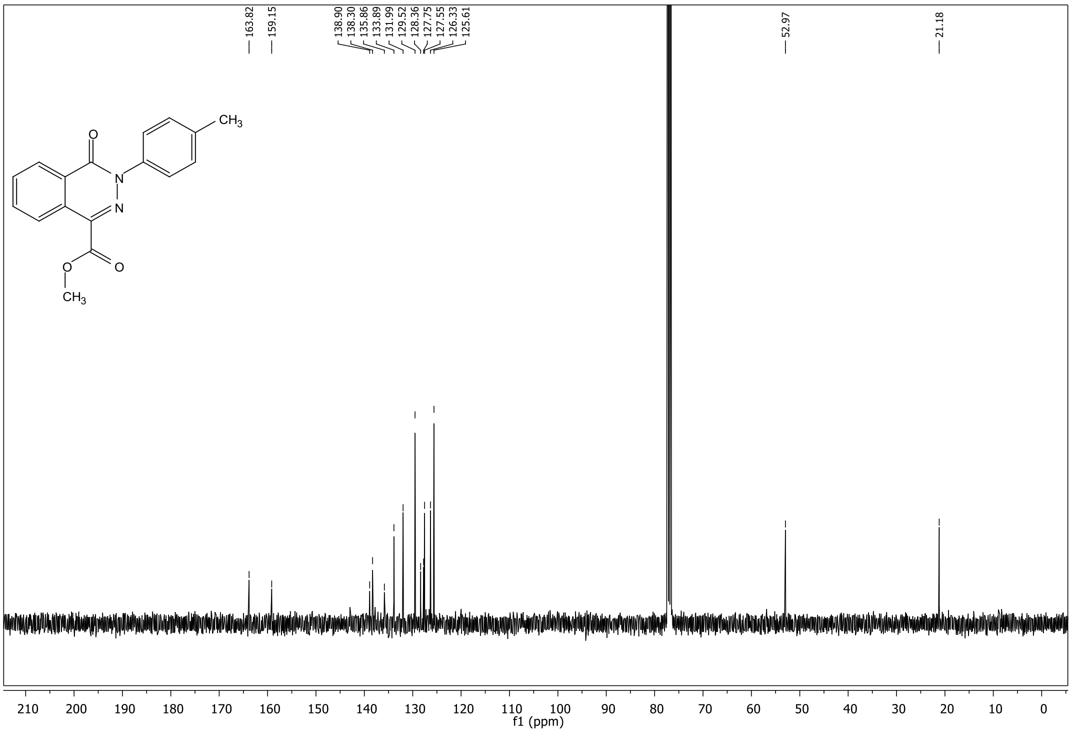


Figure 25: ^{13}C NMR Spectrum of Compound 71c

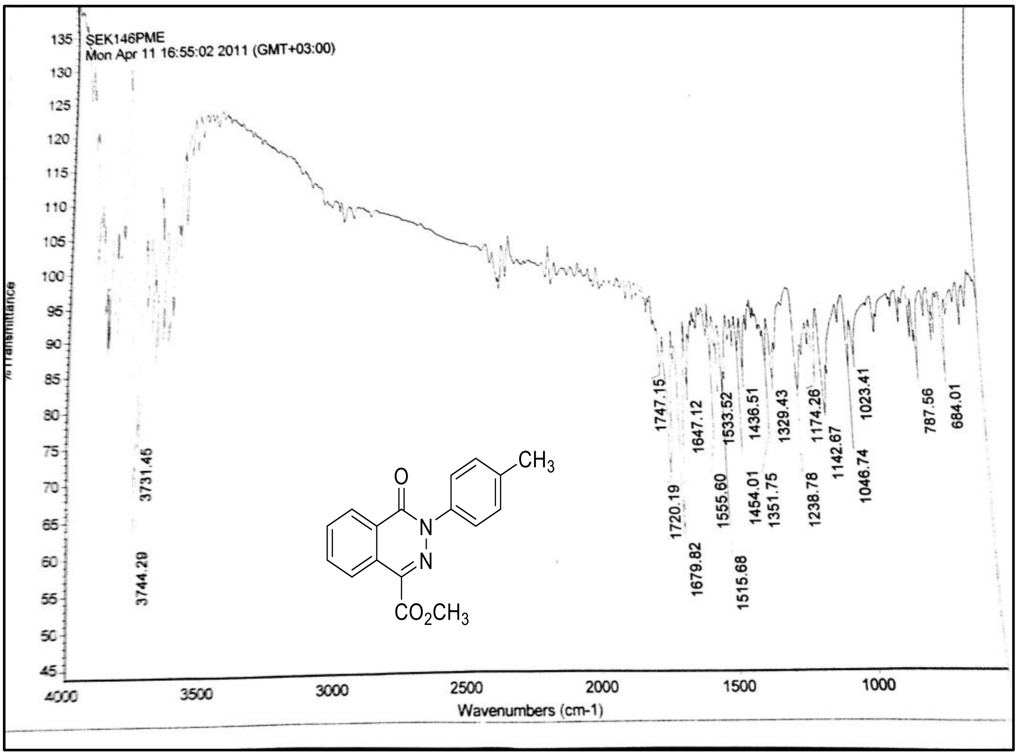


Figure 26: IR Spectrum of Compound 71c

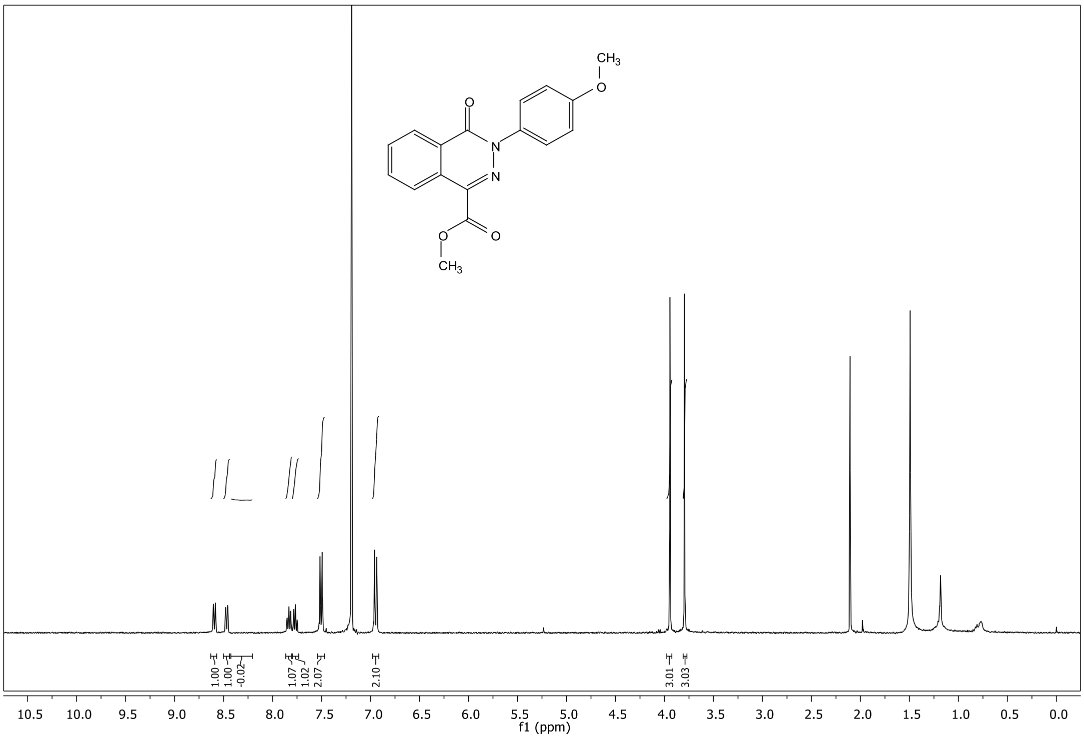


Figure 27: ^{1}H NMR Spectrum of Compound 71d

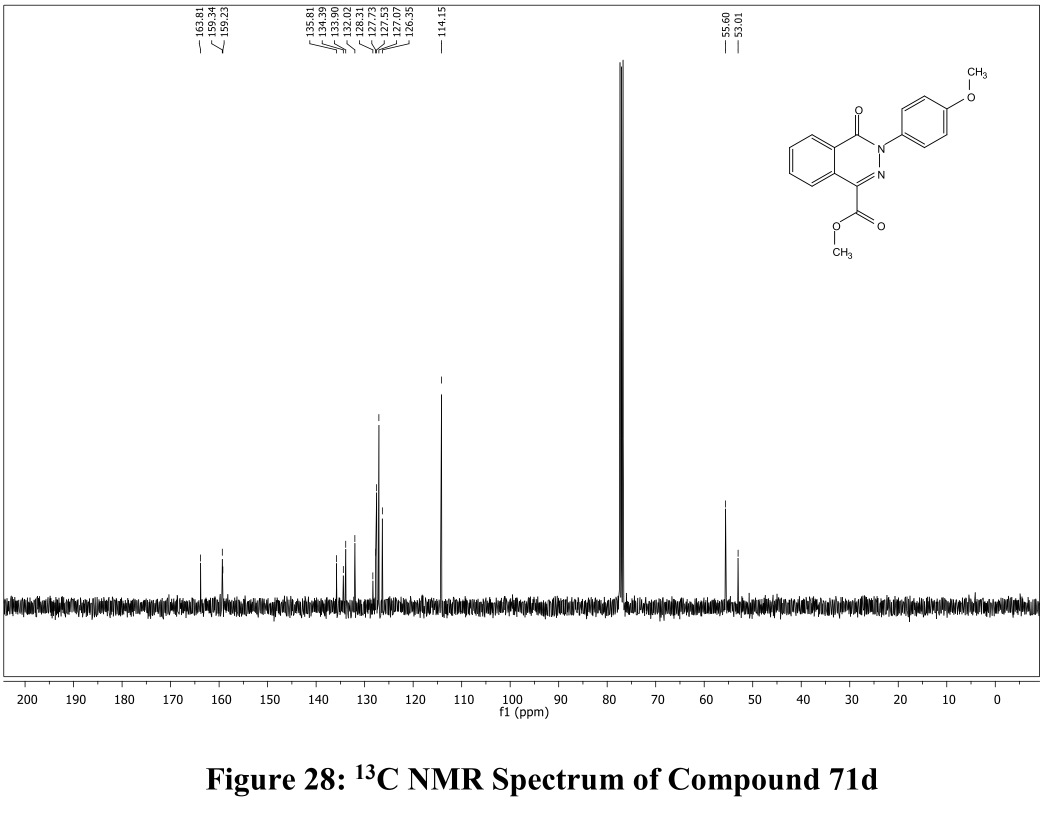


Figure 28: ^{13}C NMR Spectrum of Compound 71d

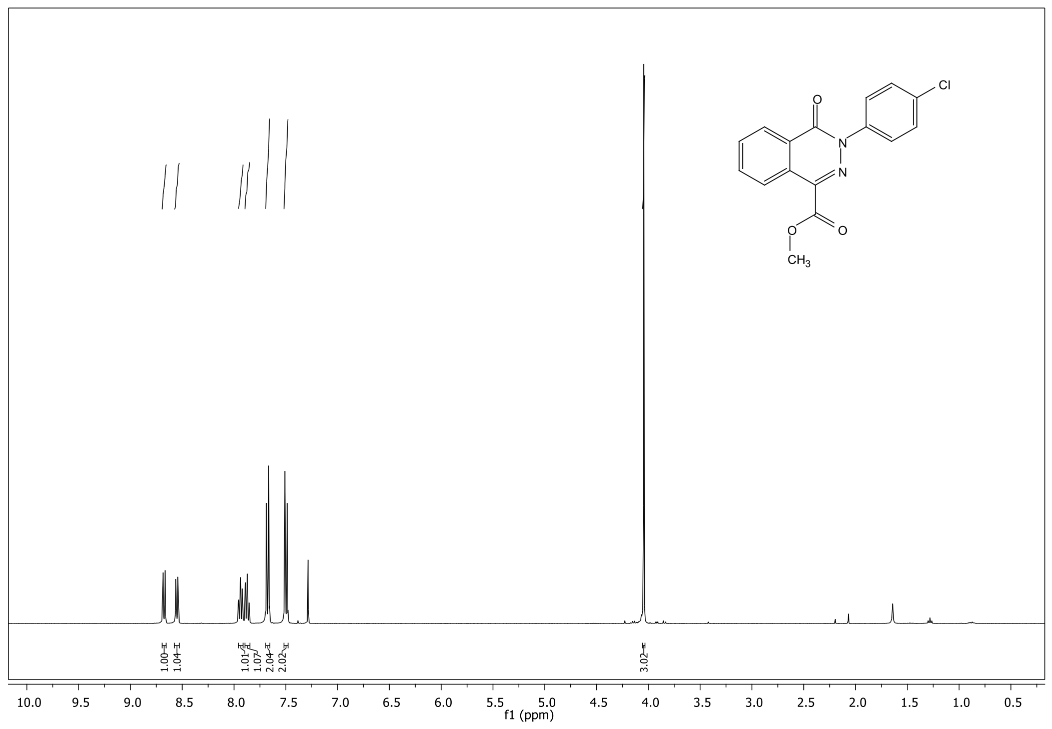


Figure 29: ^{1}H NMR Spectrum of Compound 71e

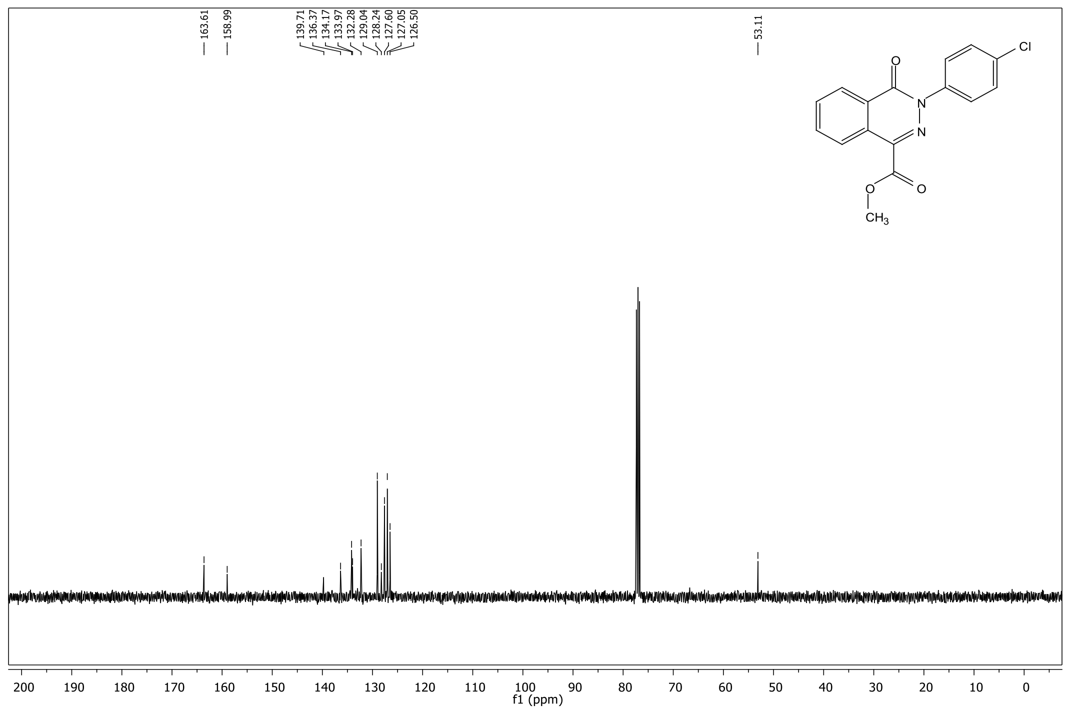


Figure 30: ^{13}C NMR Spectrum of Compound 71e

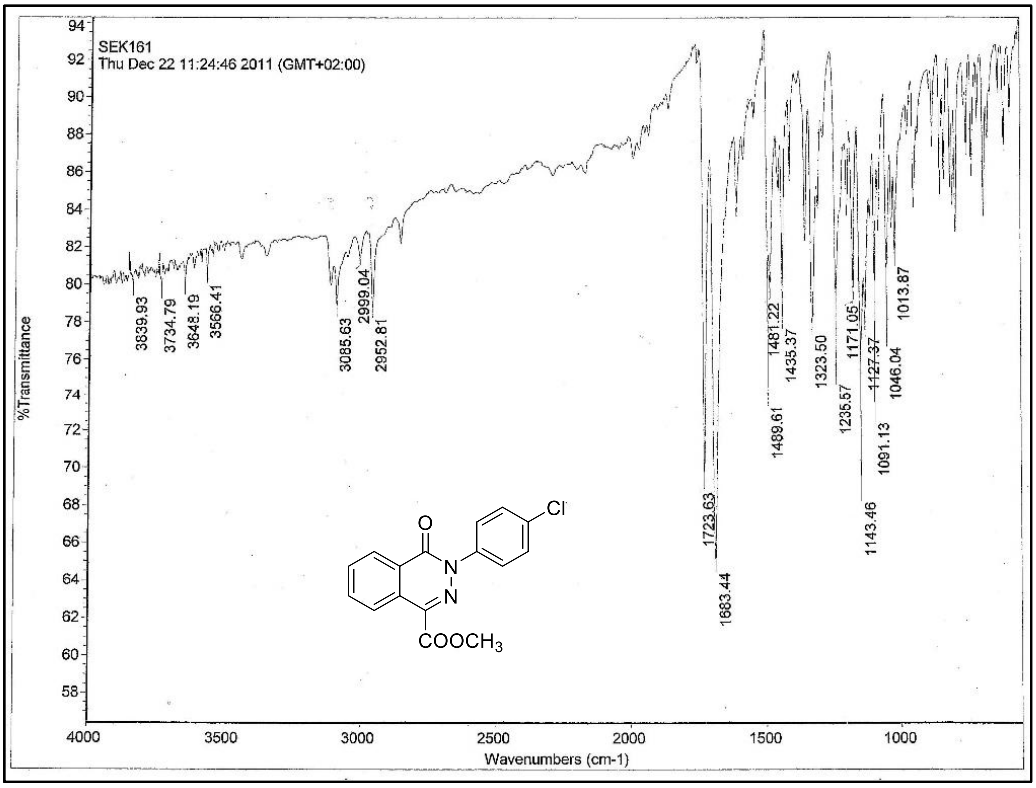


Figure 31: IR Spectrum of Compound 71e

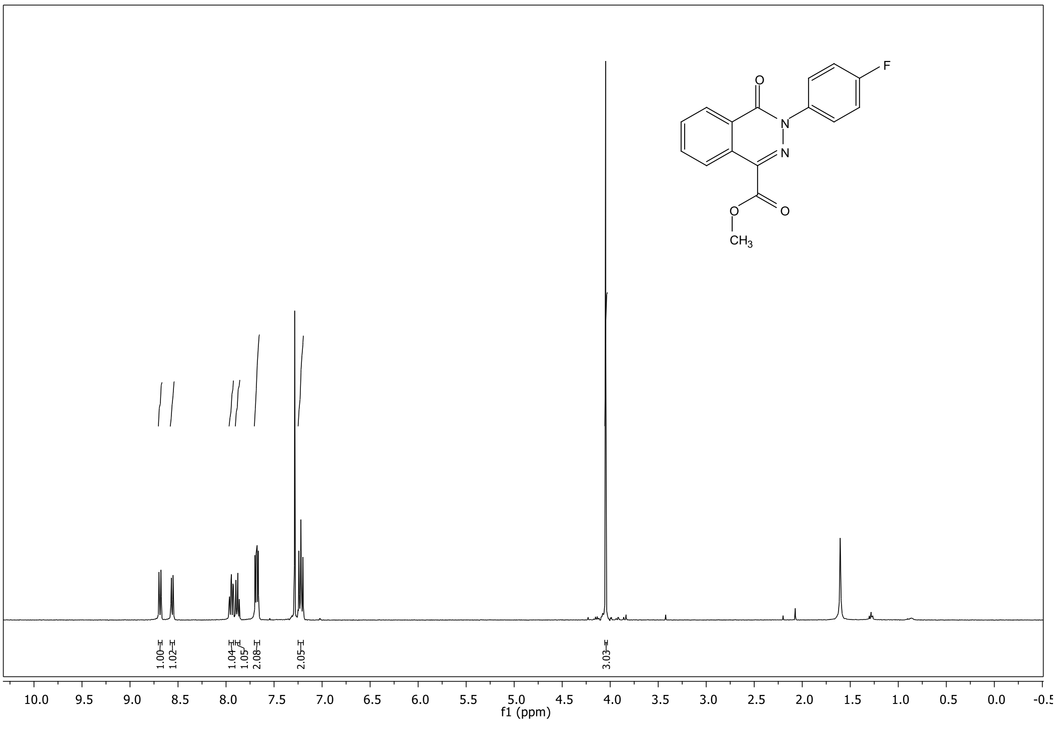


Figure 32: ^{1}H NMR Spectrum of Compound 71f

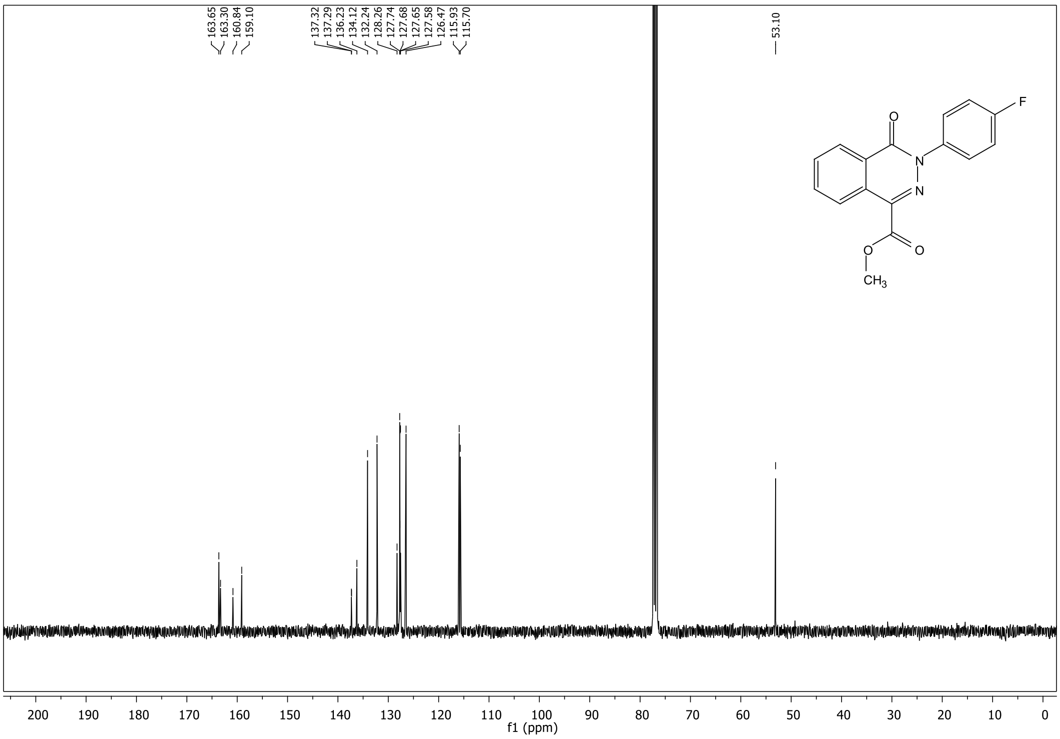


Figure 33: ^{13}C NMR Spectrum of Compound 71f

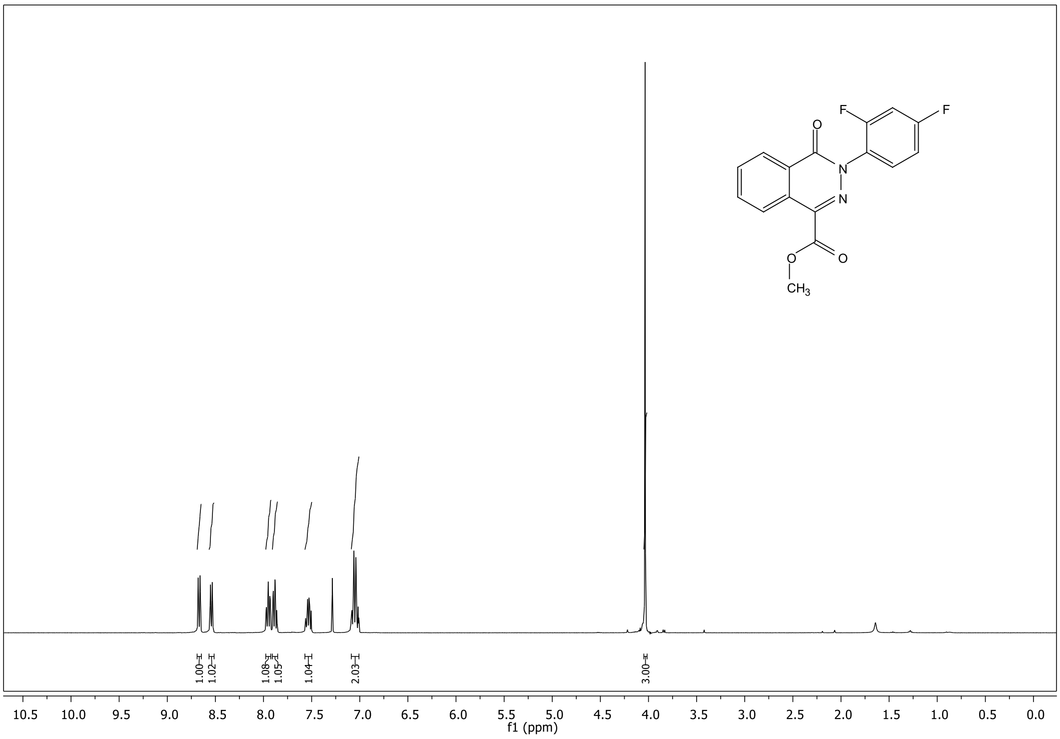


Figure 34: ^{1}H NMR Spectrum of Compound 71g

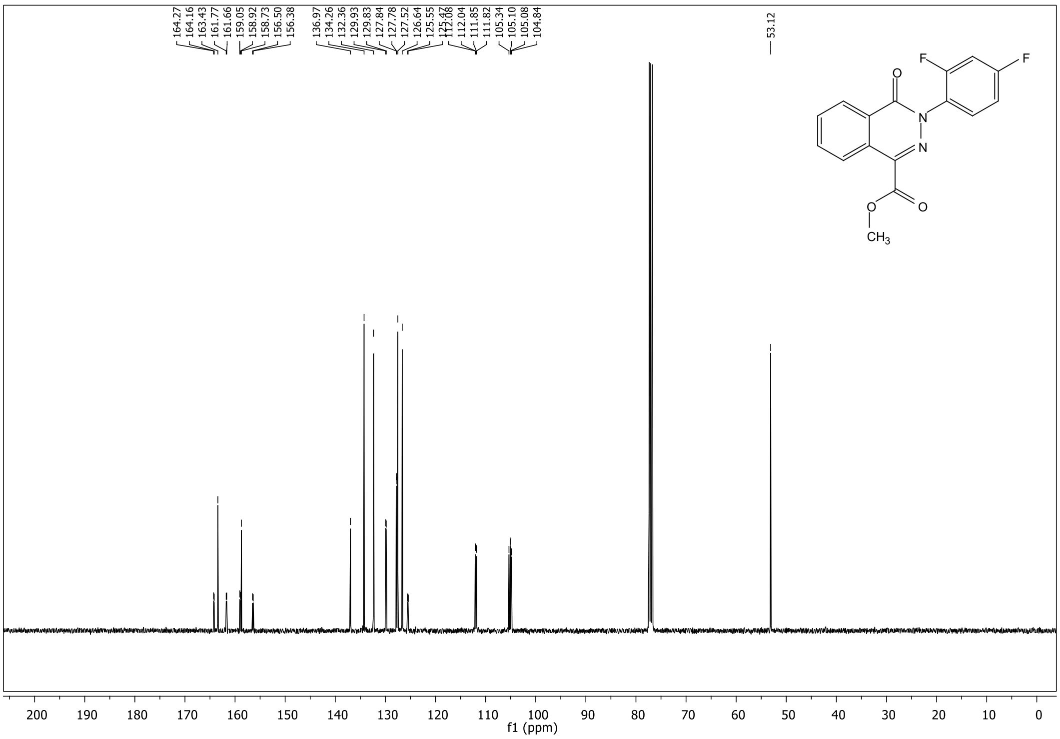


Figure 35: ^{13}C NMR Spectrum of Compound 71g

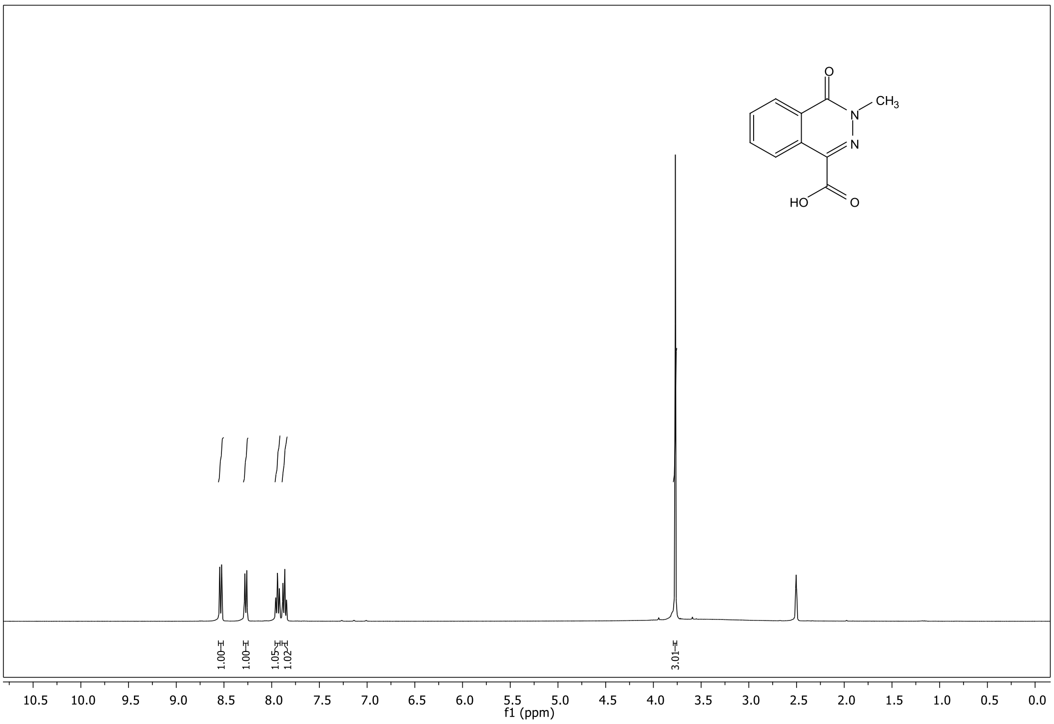


Figure 36: ^{1}H NMR Spectrum of Compound 80a

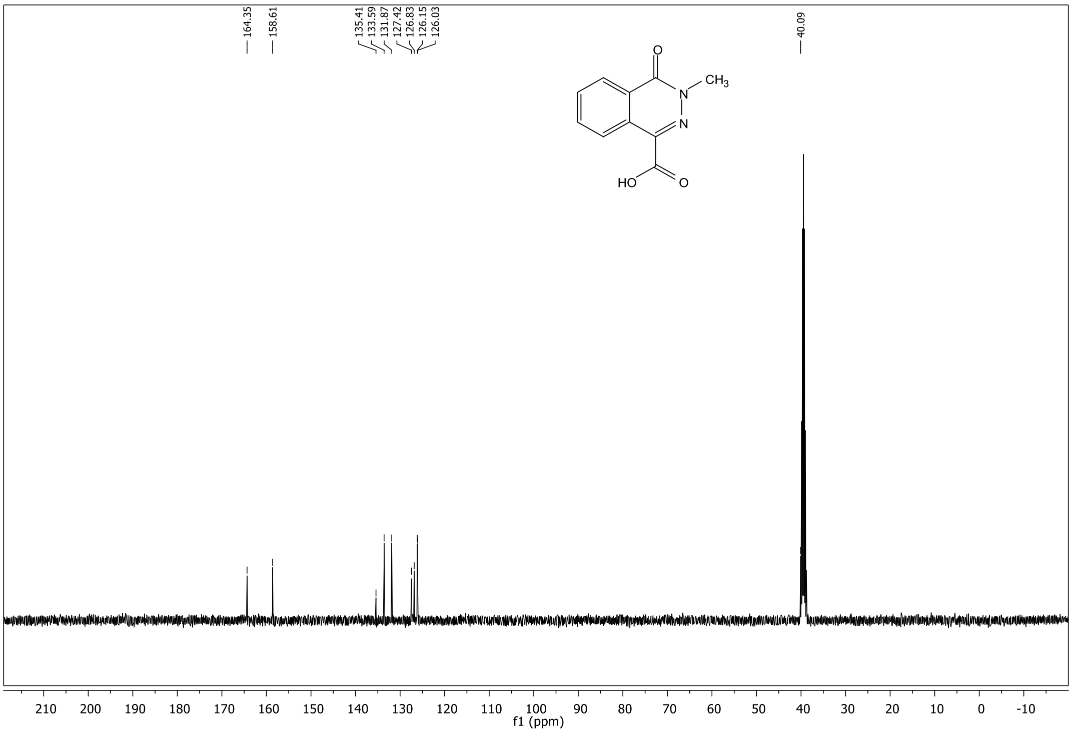


Figure 37: ^{13}C NMR Spectrum of Compound 80a

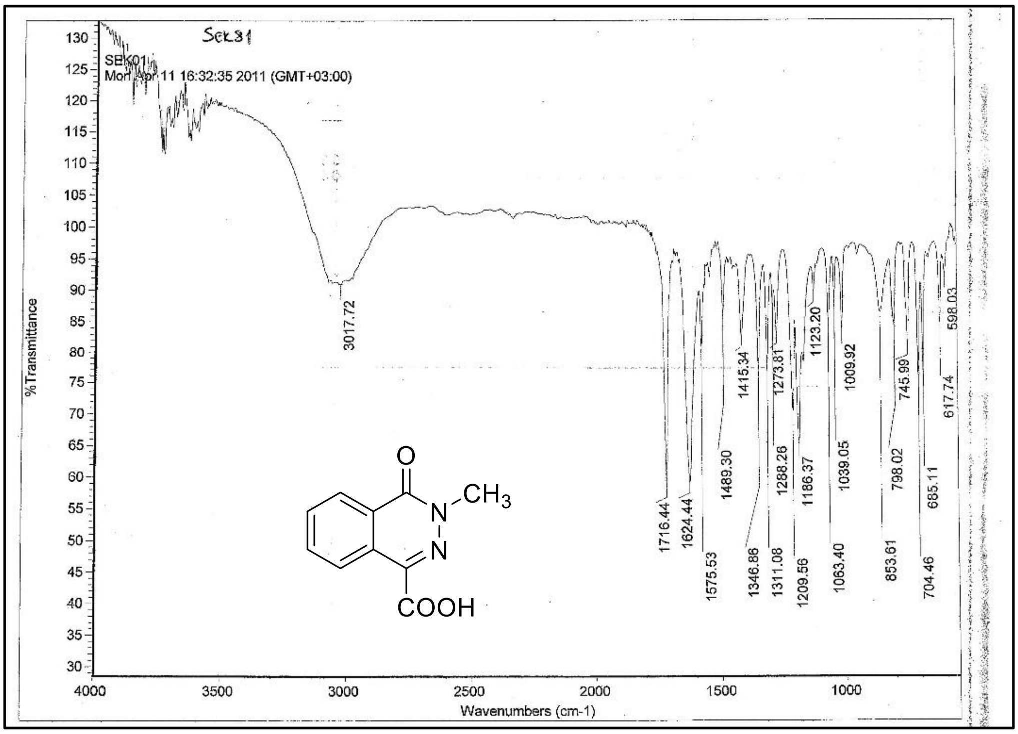


Figure 38: IR Spectrum of Compound 80a

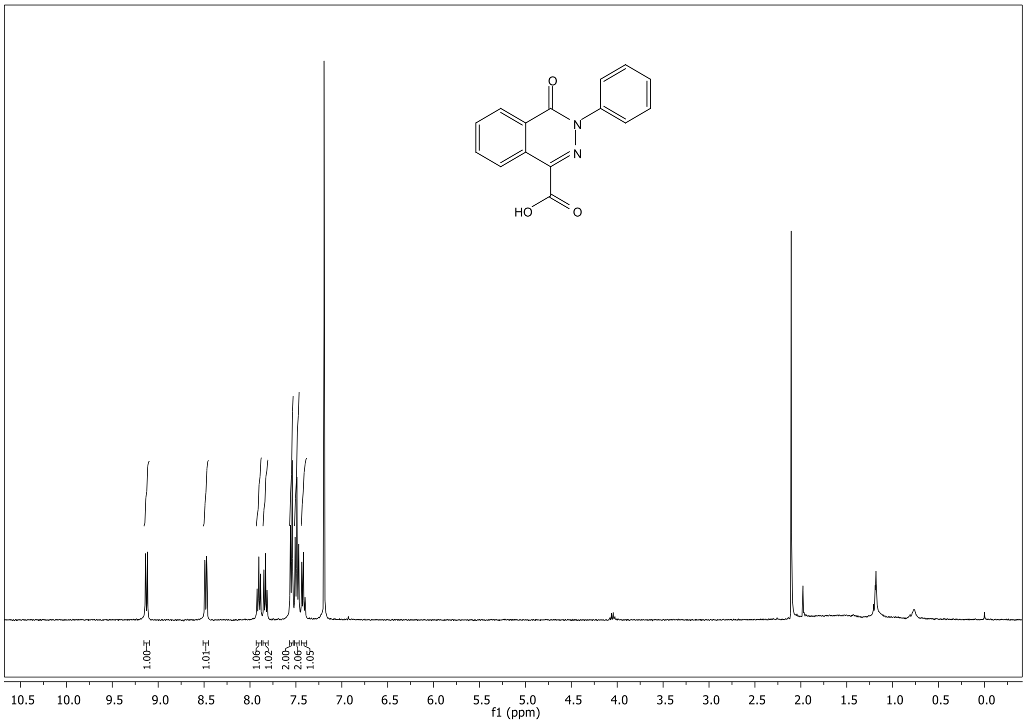


Figure 39: ^{1}H NMR Spectrum of Compound 80b

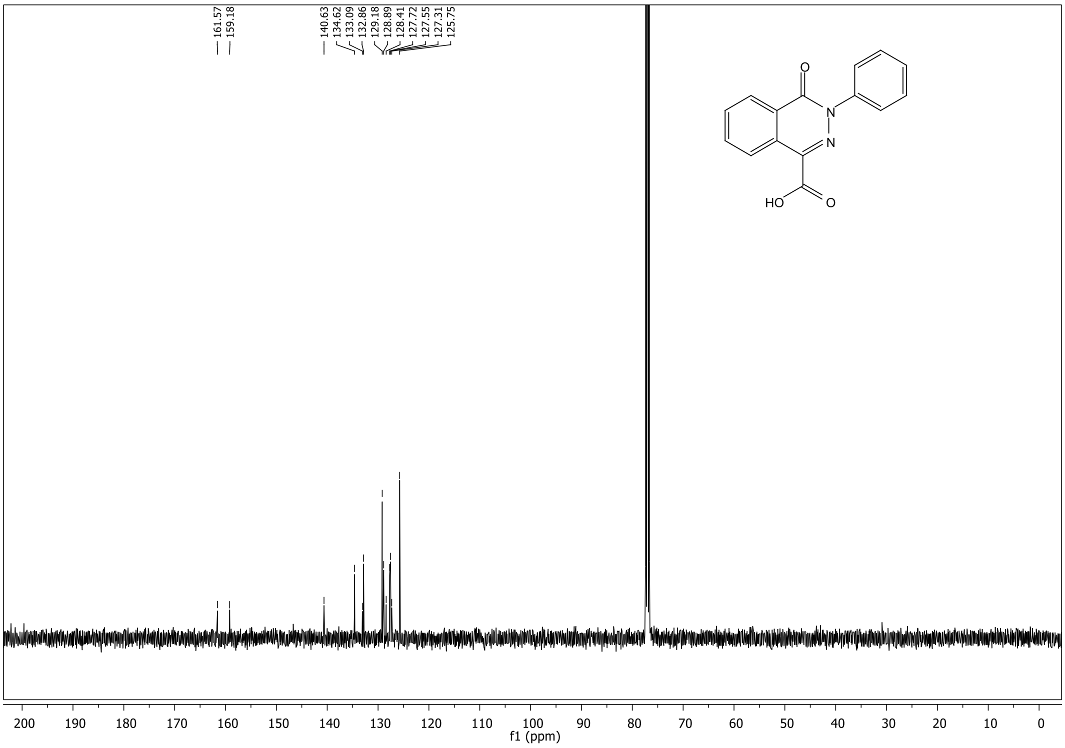


Figure 40: ^{13}C NMR Spectrum of Compound 80b

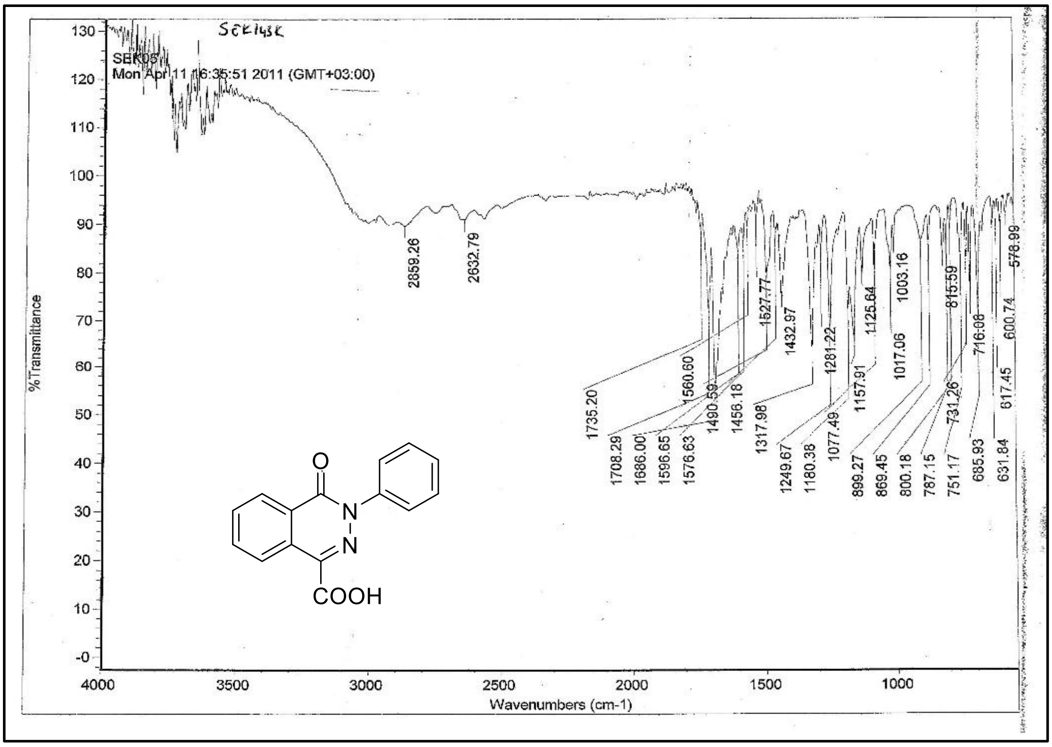


Figure 41: IR Spectrum of Compound 80b

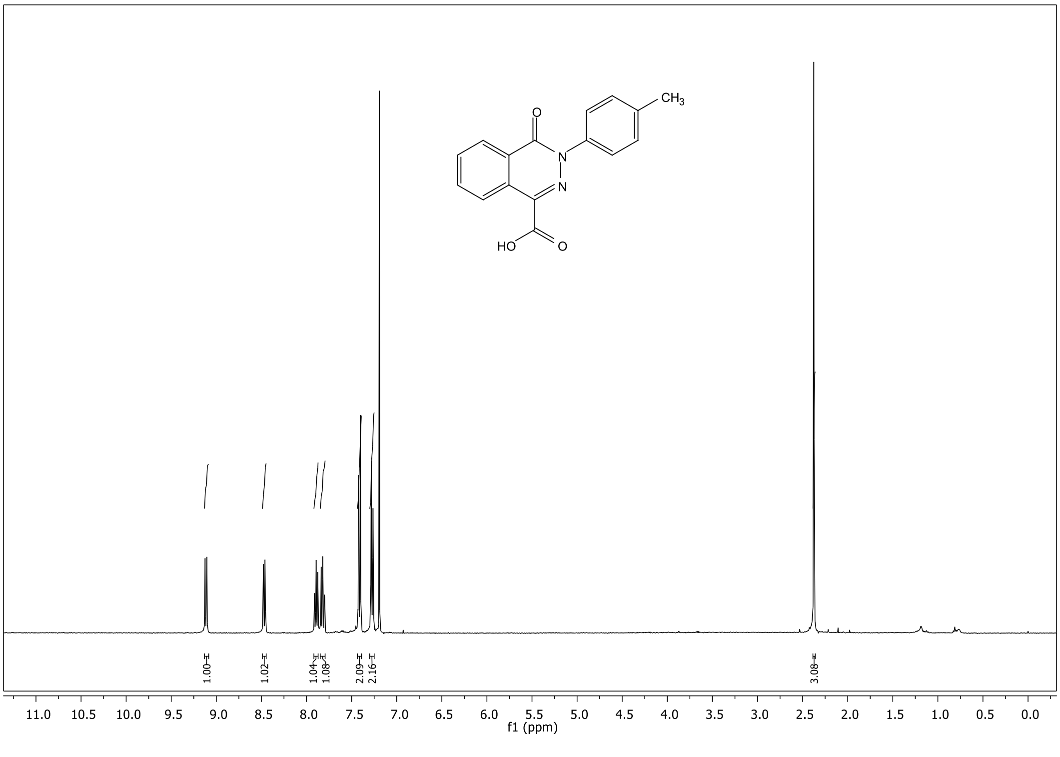


Figure 42: ^{1}H NMR Spectrum of Compound 80c

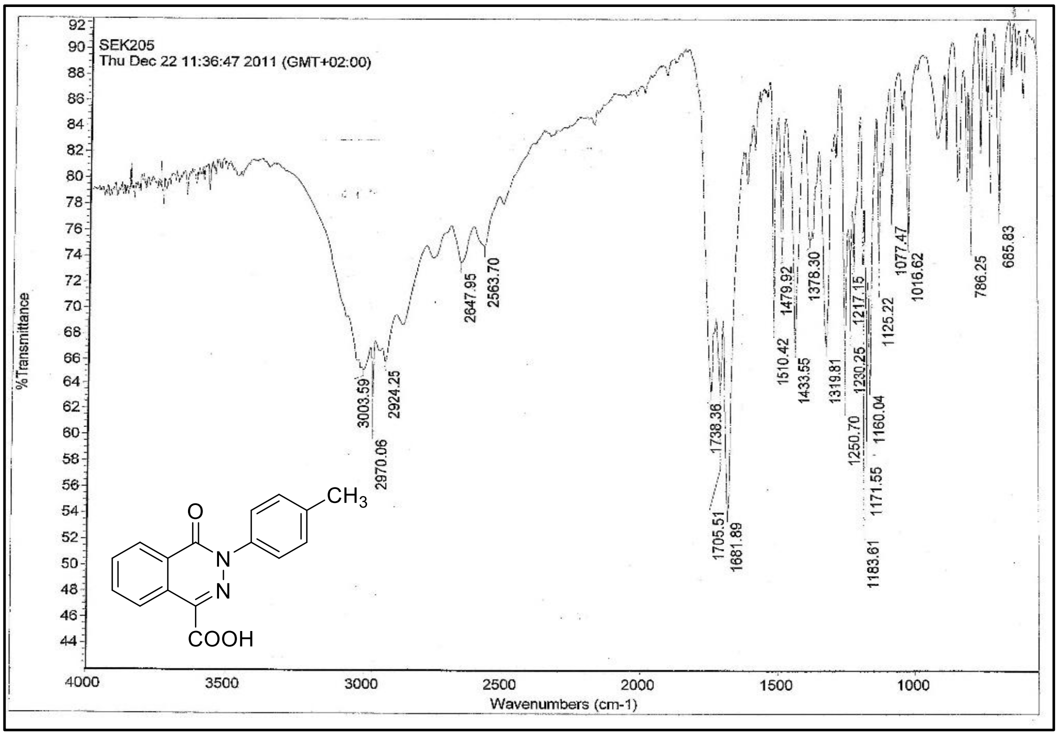


Figure 43: IR Spectrum of Compound 80c

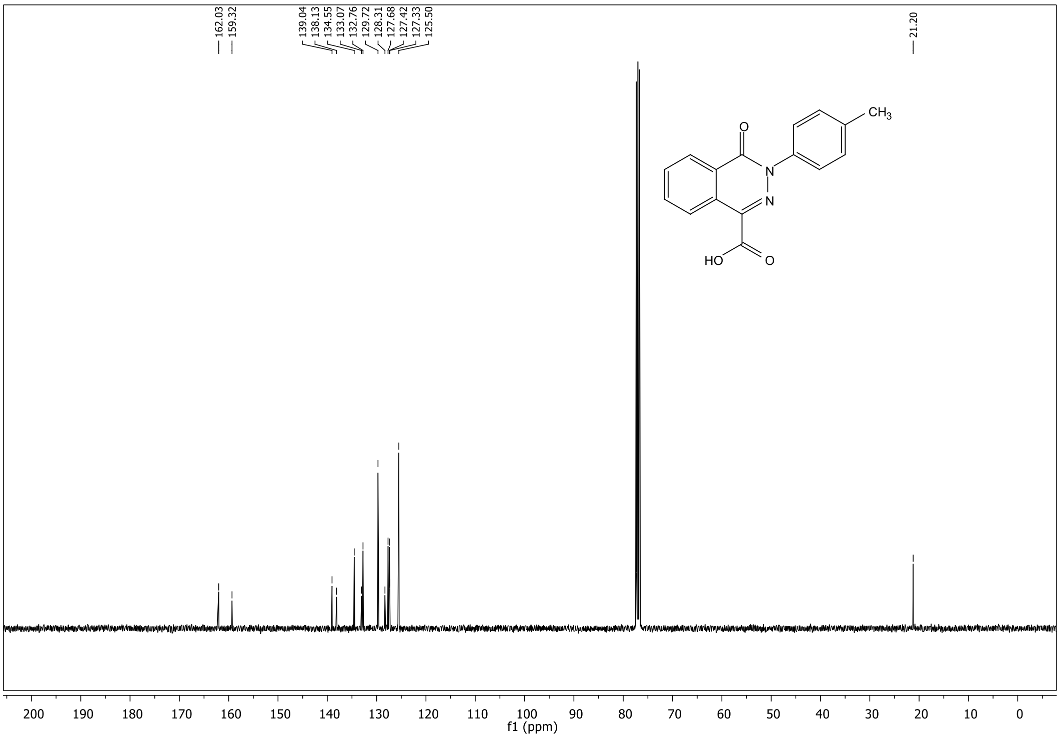


Figure 44: ^{13}C NMR Spectrum of Compound 80c

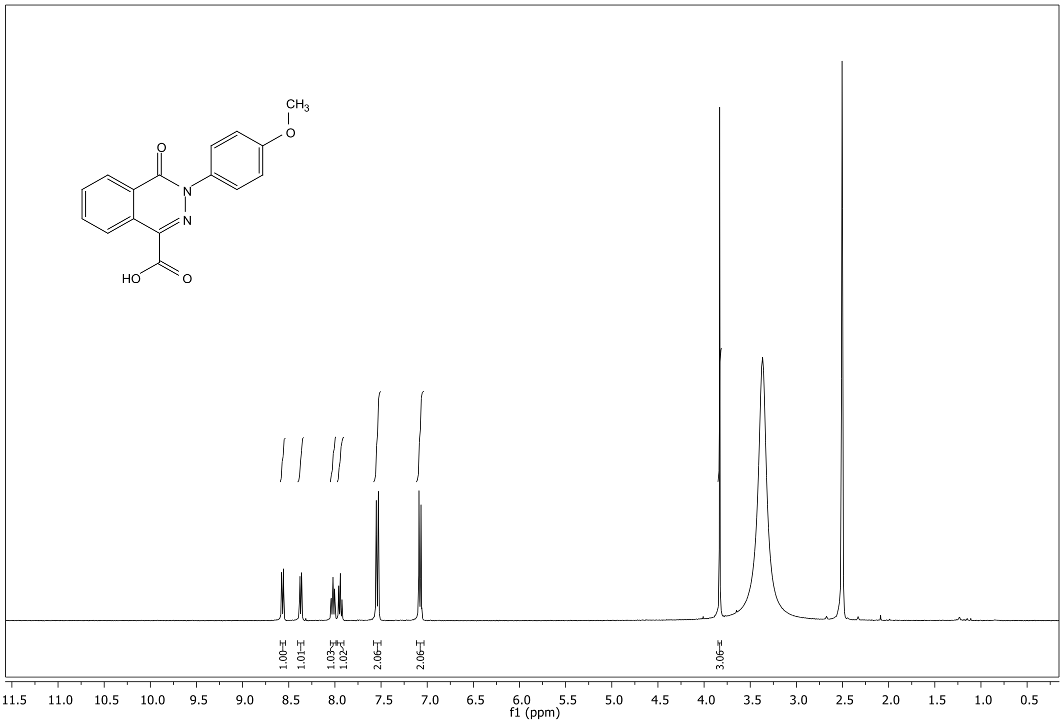


Figure 45: ^{1}H NMR Spectrum of Compound 80d

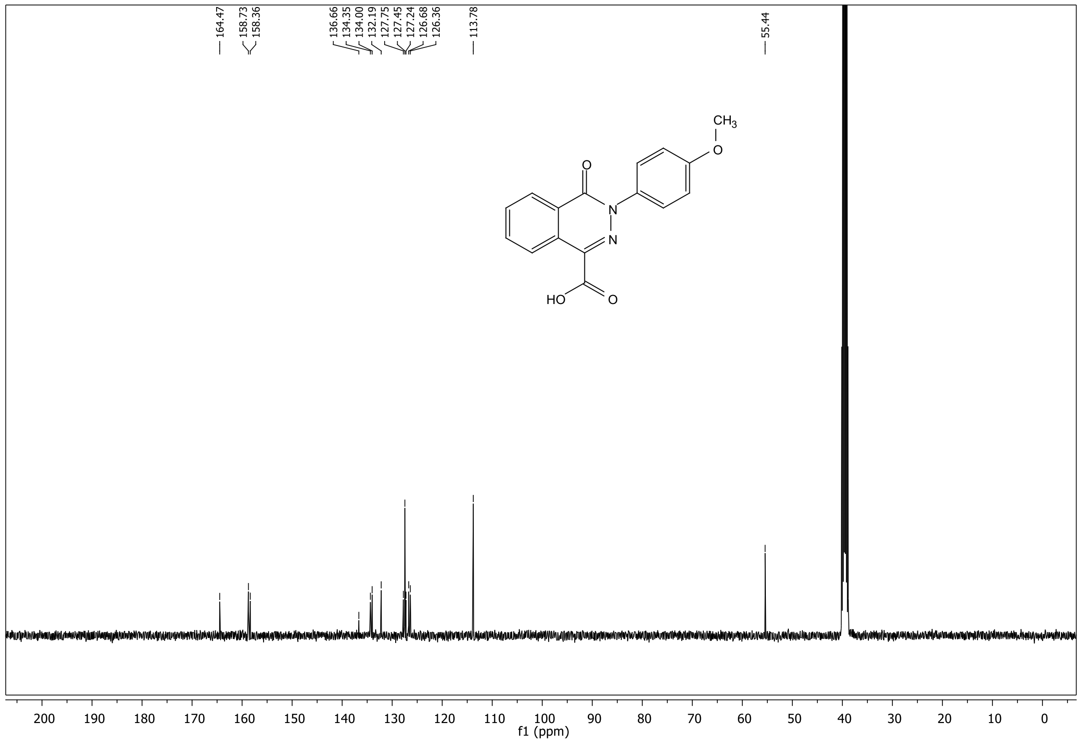


Figure 46: ^{13}C NMR Spectrum of Compound 80d

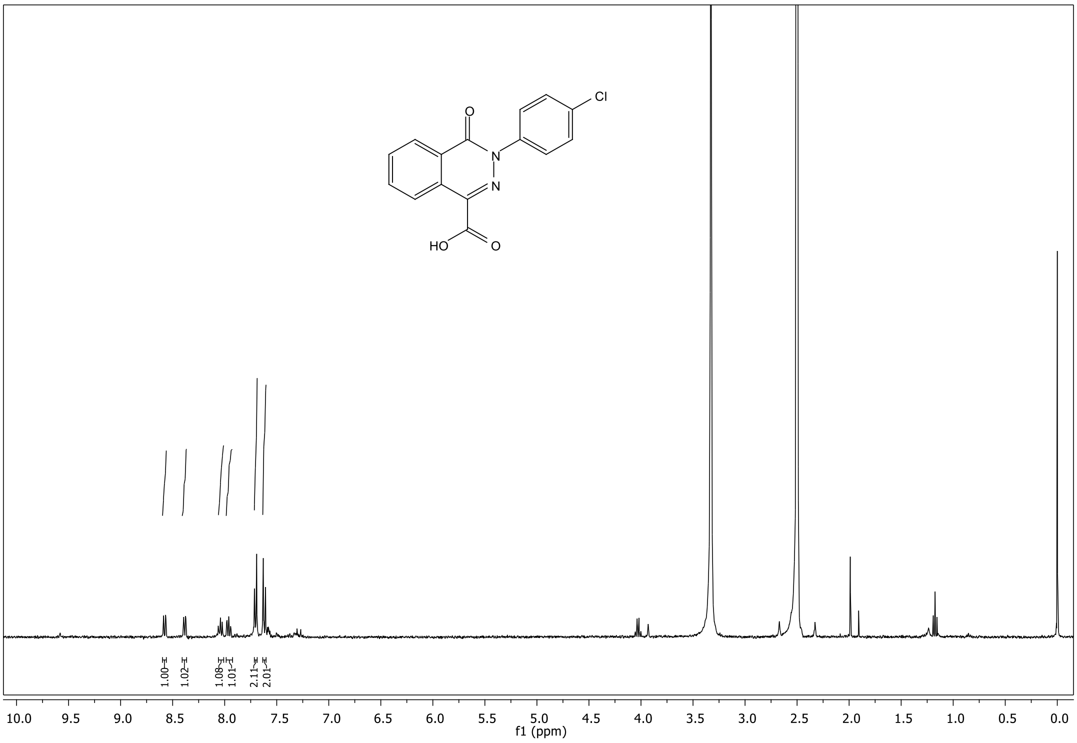


Figure 47: ^{1}H NMR Spectrum of Compound 80e

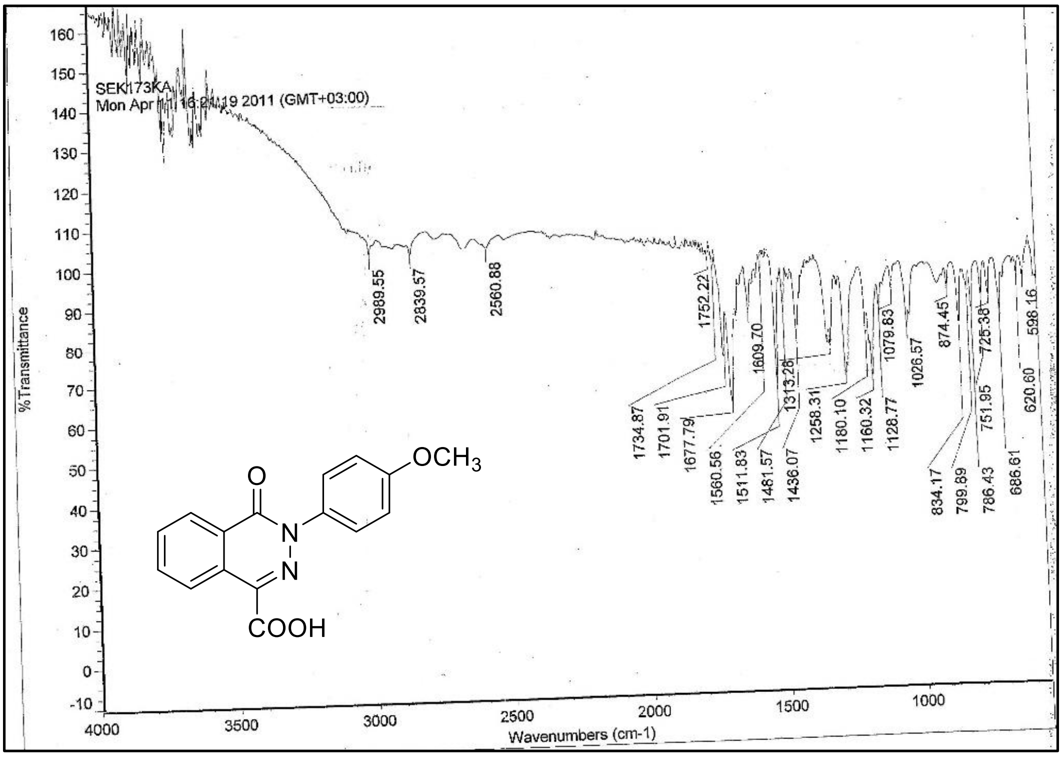


Figure 48: IR Spectrum of Compound 80e

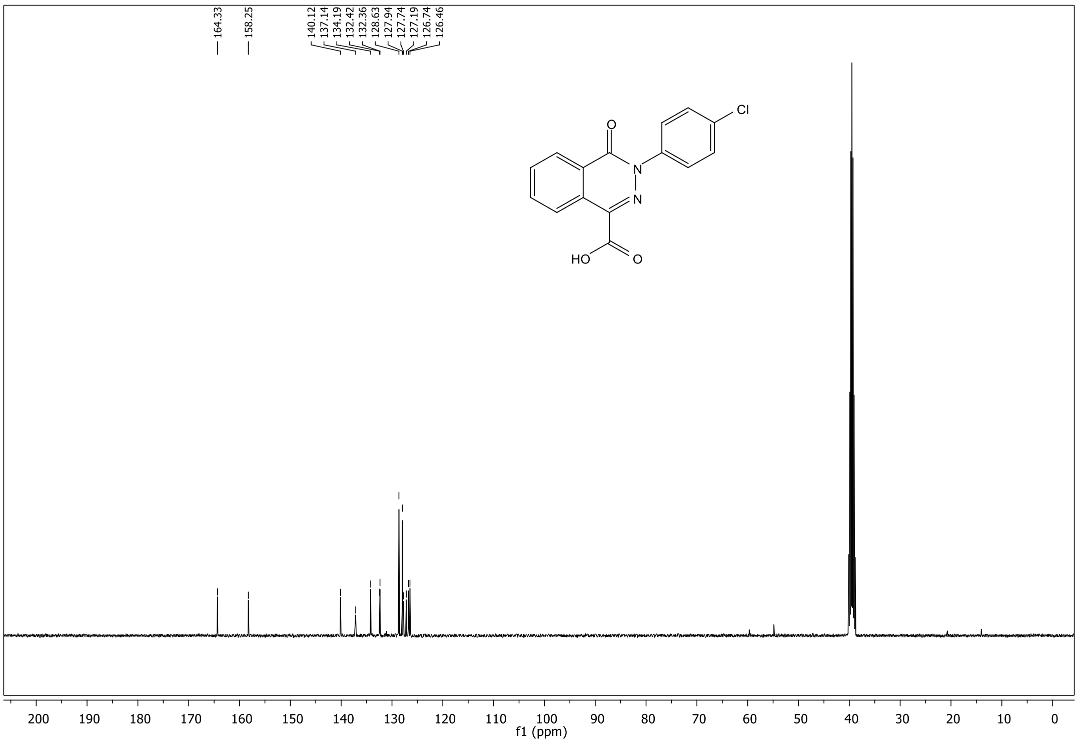


Figure 49: ^{13}C NMR Spectrum of Compound 80e

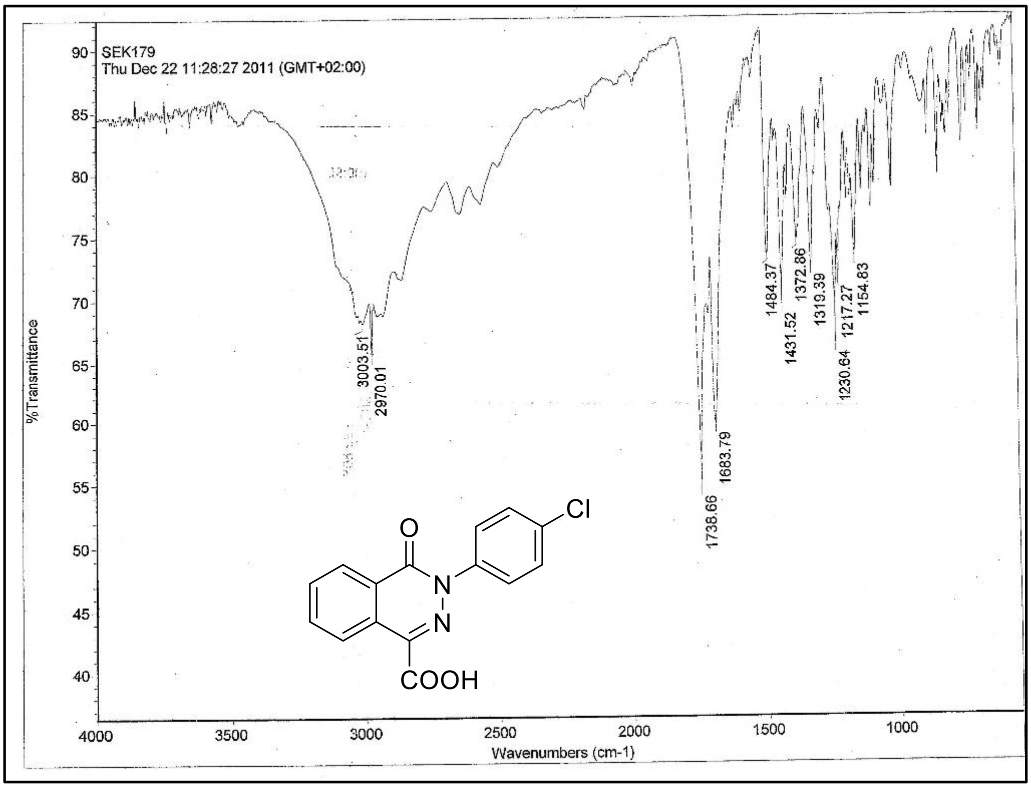


Figure 50: IR Spectrum of Compound 80e

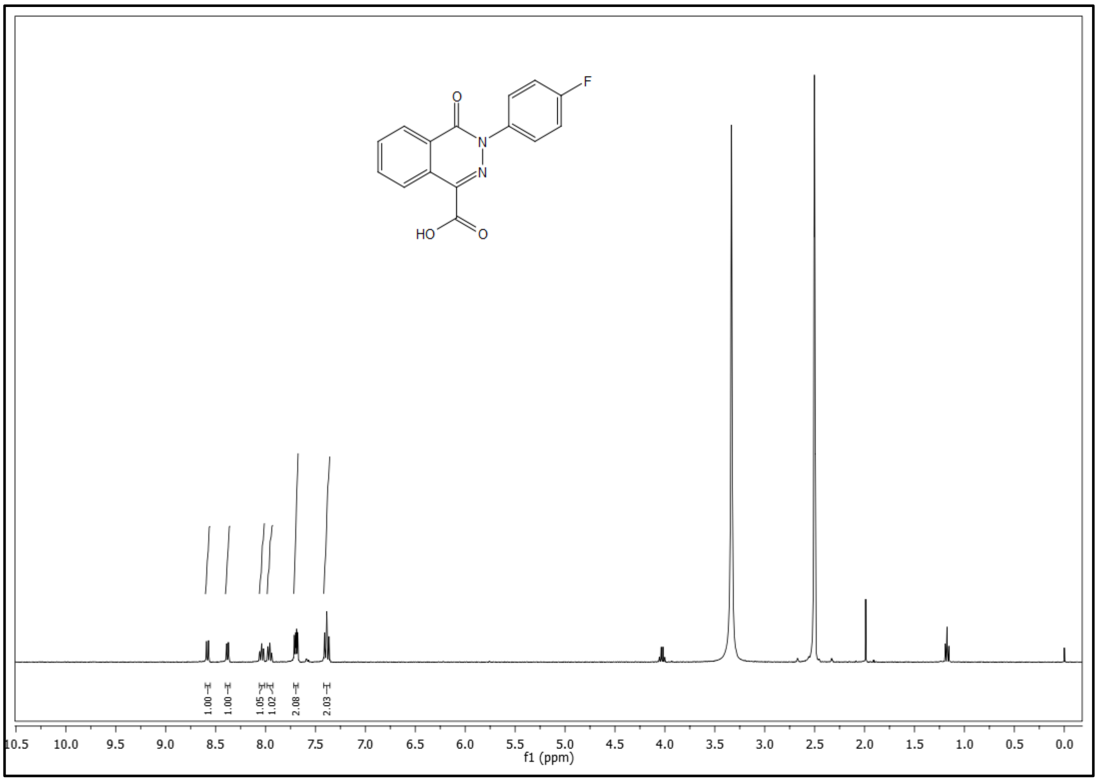


Figure 51: ^{1}H NMR Spectrum of Compound 80f

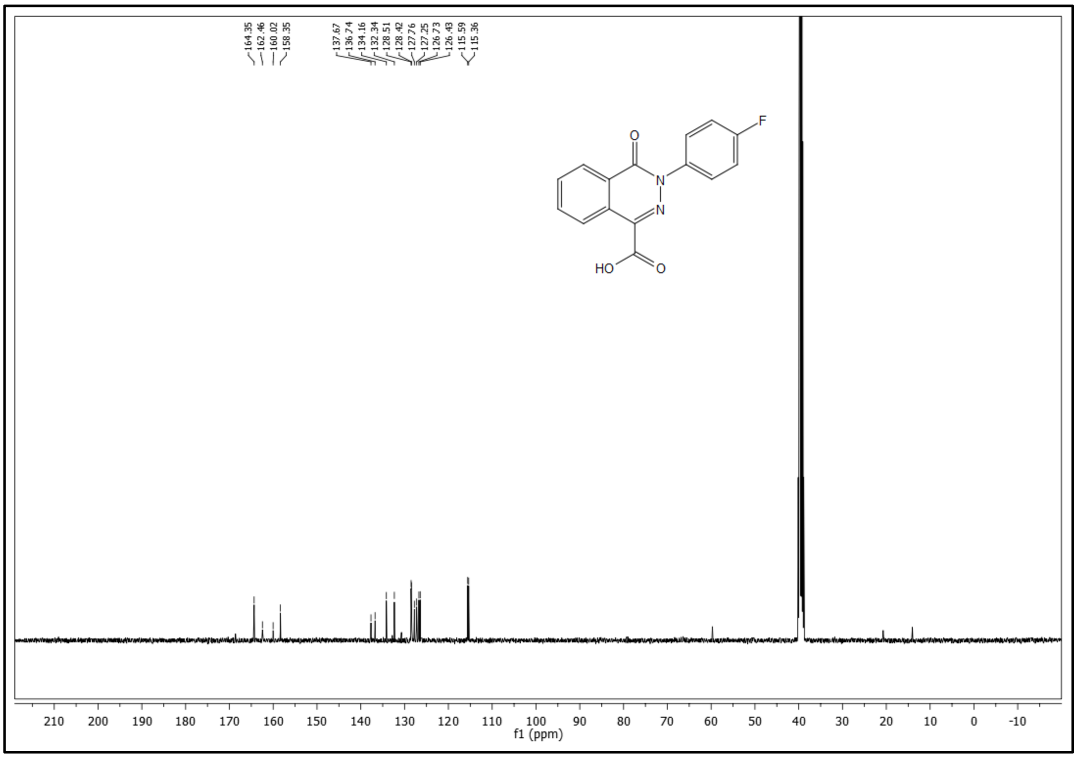


Figure 52: ^{13}C NMR Spectrum of Compound 80f

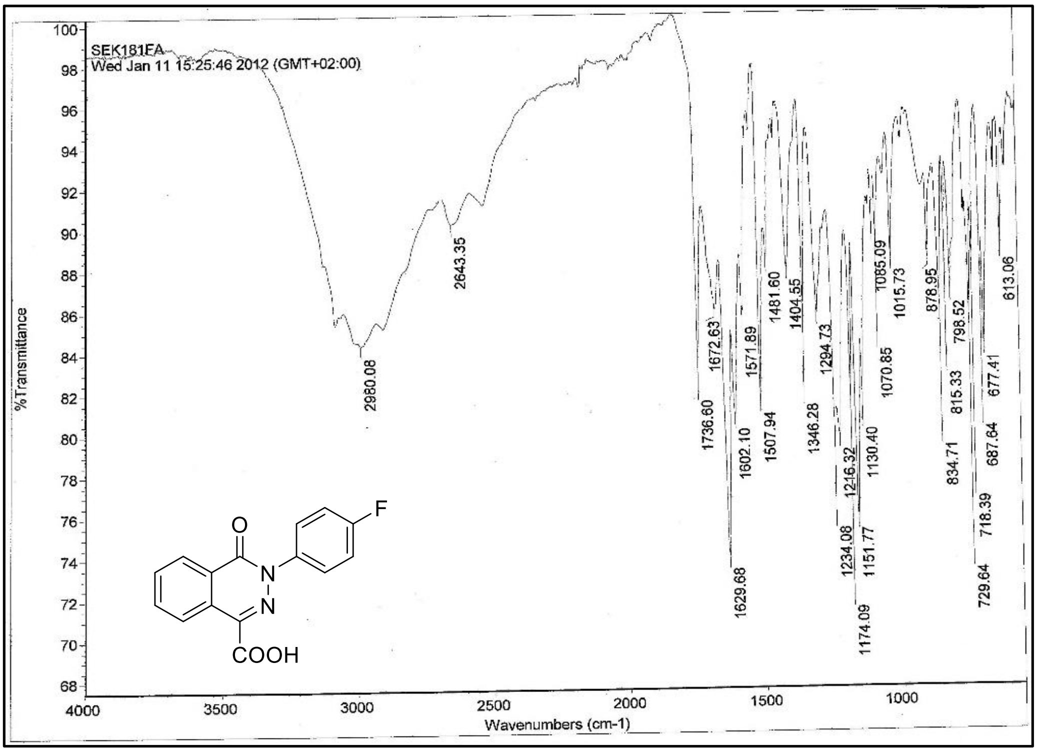


Figure 53: IR Spectrum of Compound 80f

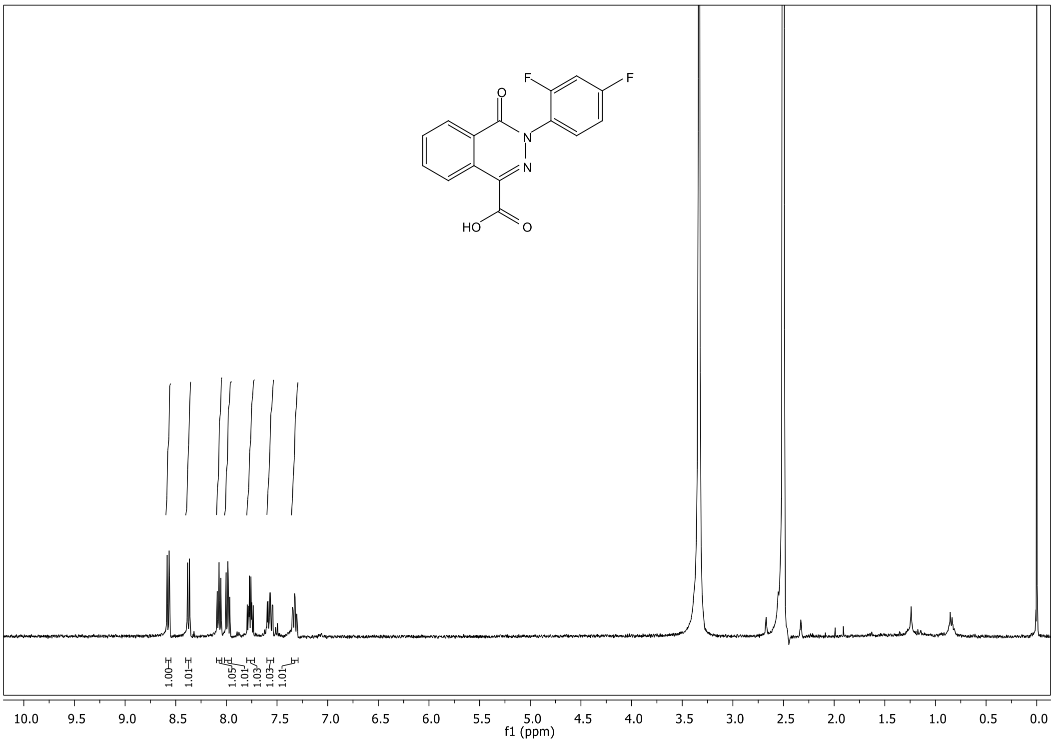


Figure 54: ^{1}H NMR Spectrum of Compound 80g

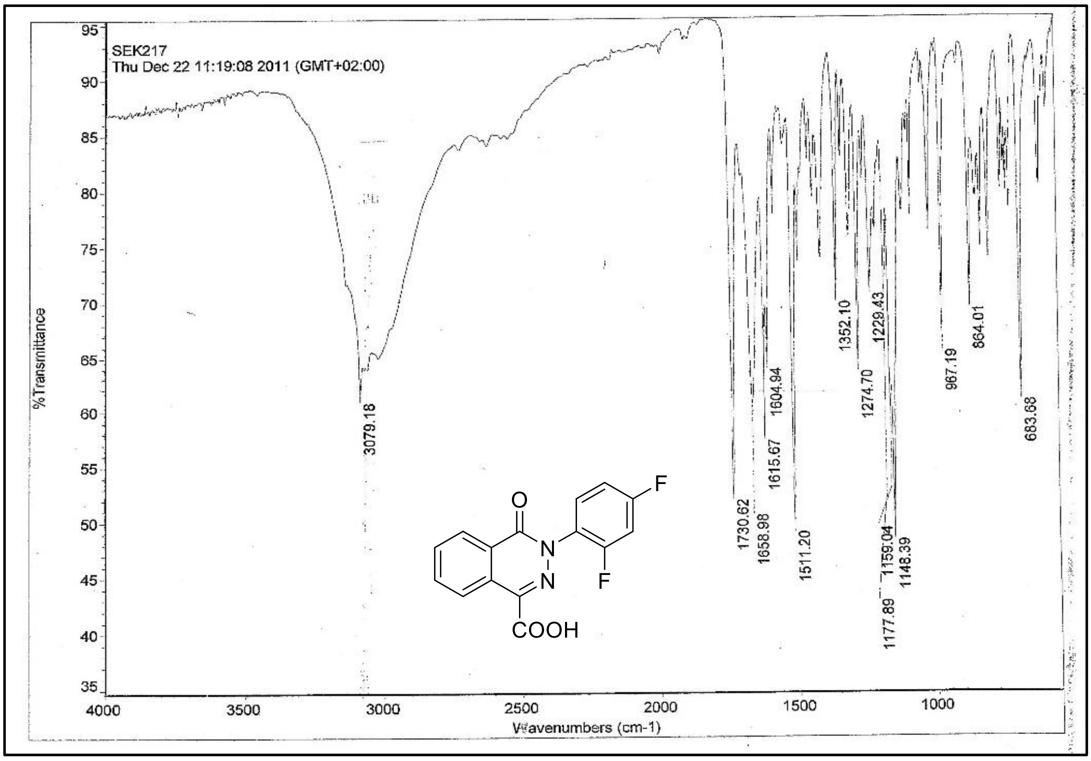


Figure 55: IR Spectrum of Compound 80g

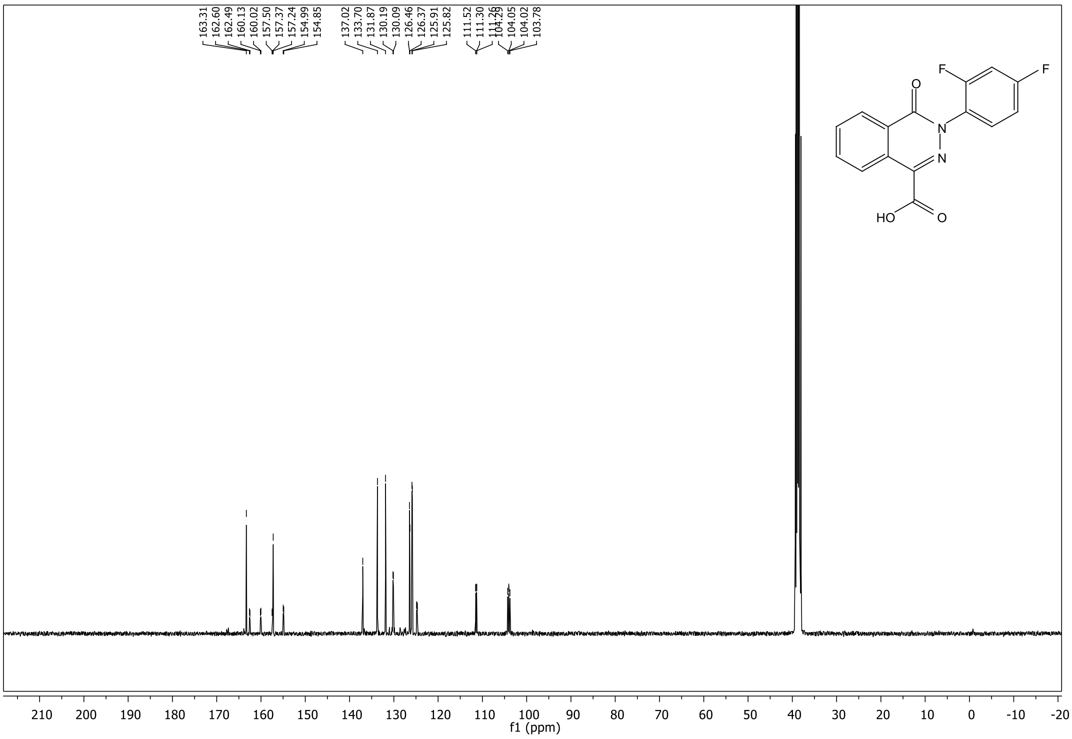


Figure 56: ^{13}C NMR Spectrum of Compound 80g

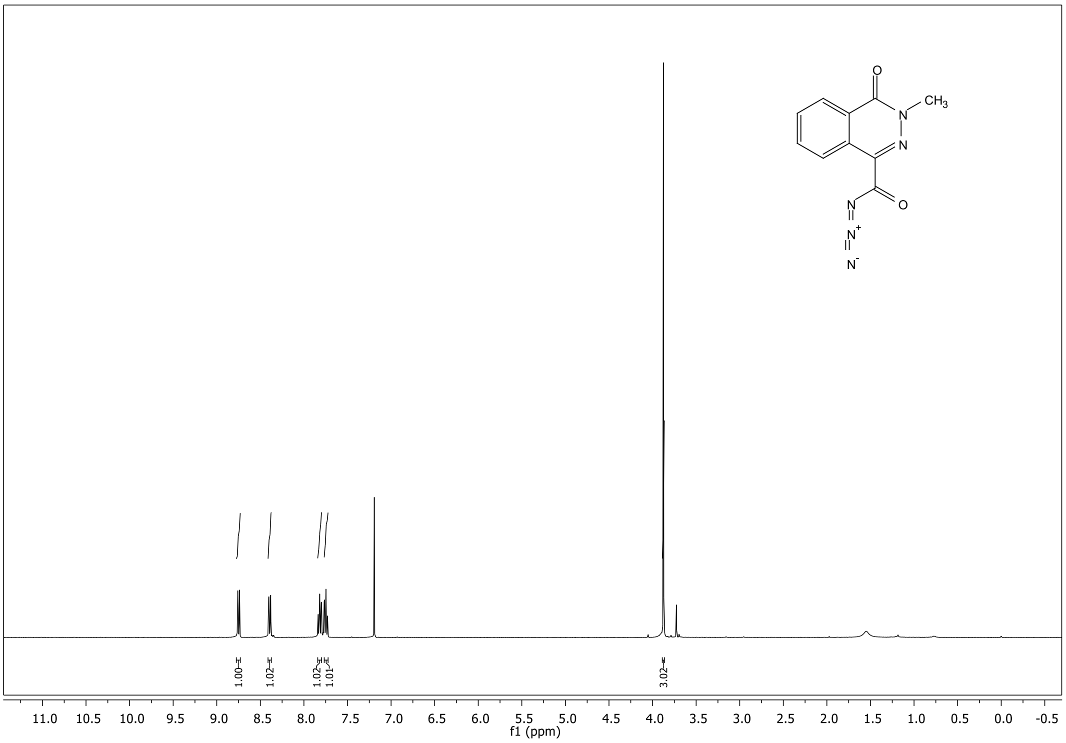


Figure 57: ^{1}H NMR Spectrum of Compound 72a

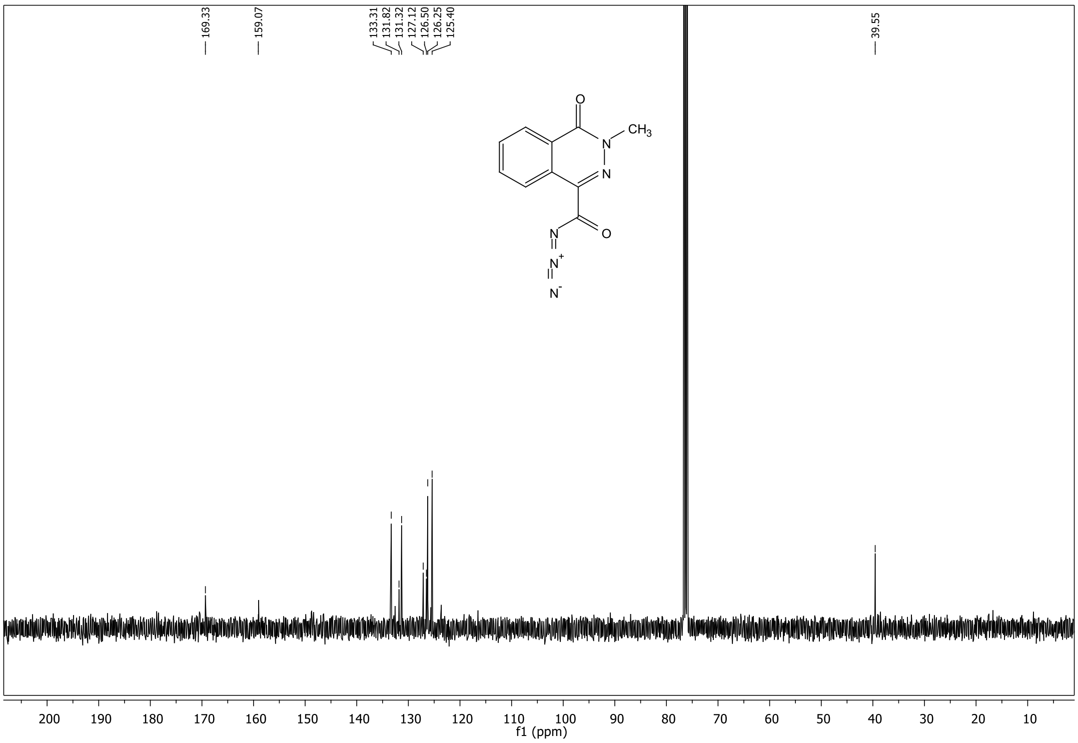


Figure 58: ^{13}C NMR Spectrum of Compound 72a

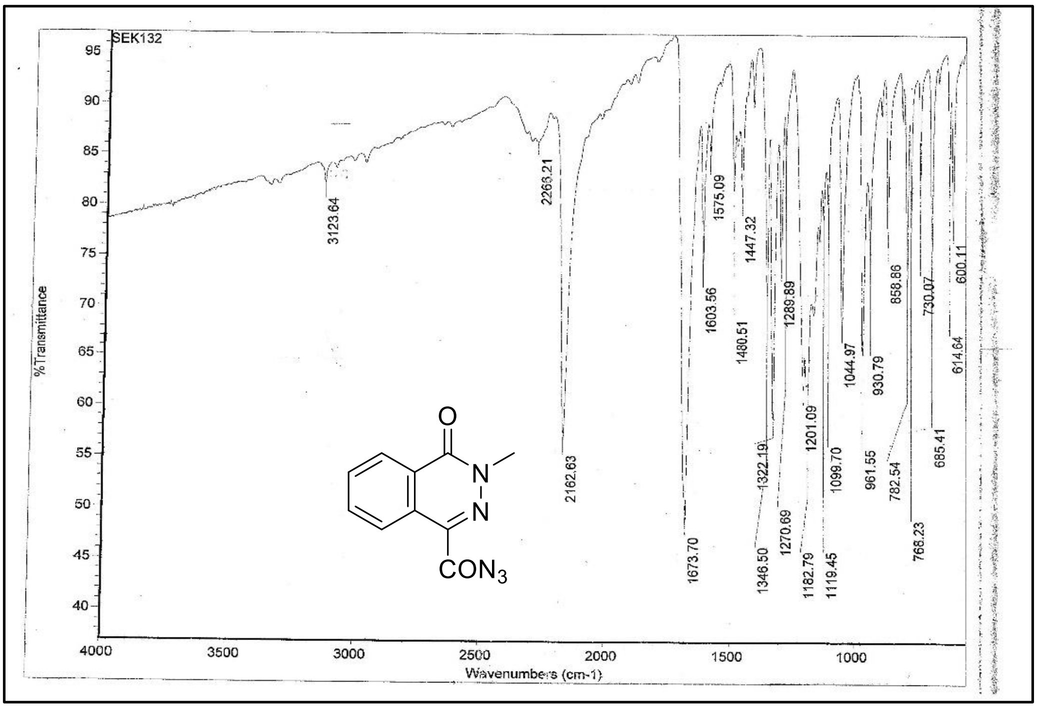


Figure 59: IR Spectrum of Compound 72a

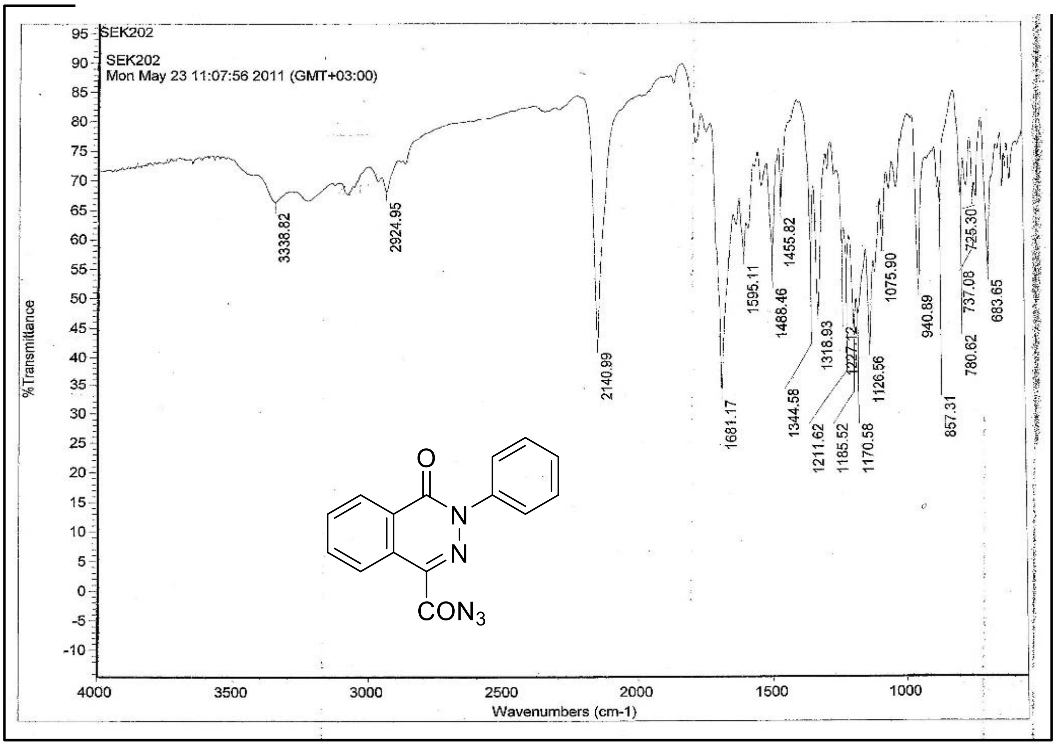


Figure 60: IR Spectrum of Compound 72b

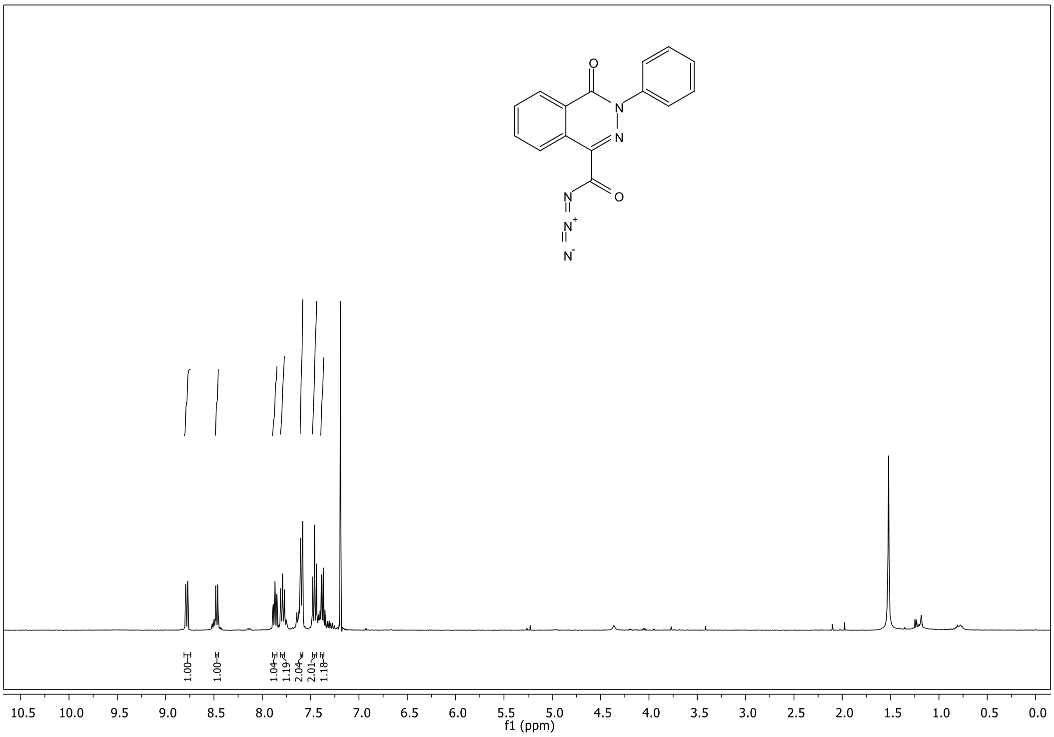


Figure 61: ^{1}H NMR Spectrum of Compound 72b

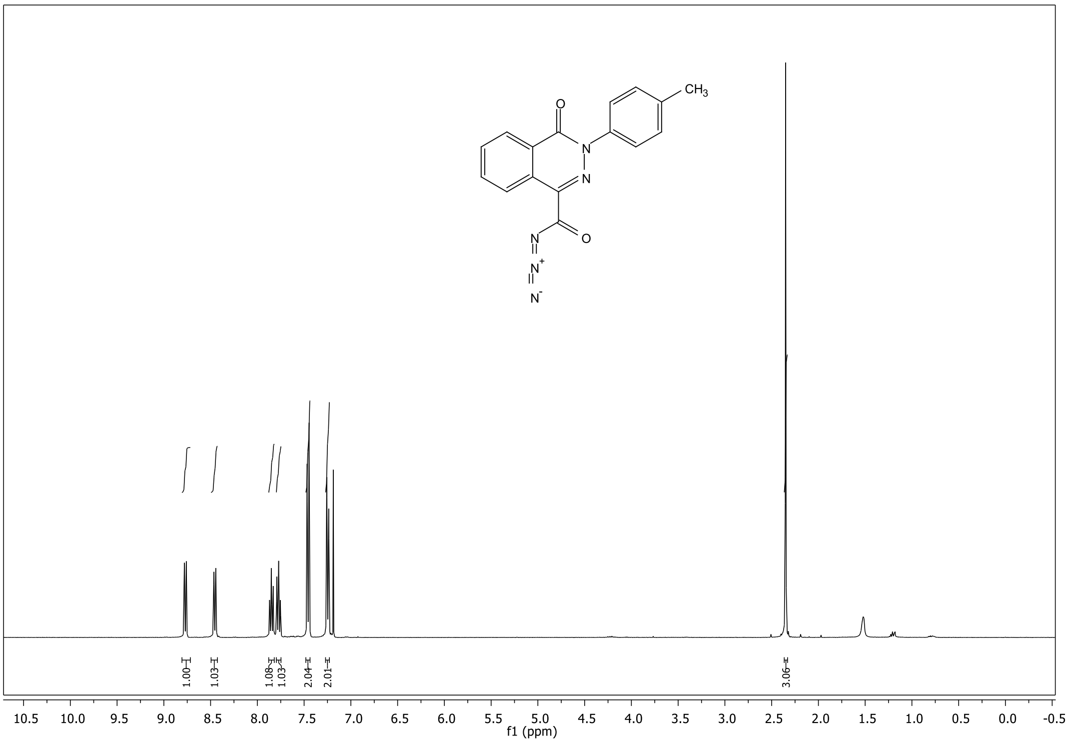


Figure 62: ^{1}H NMR Spectrum of Compound 72c

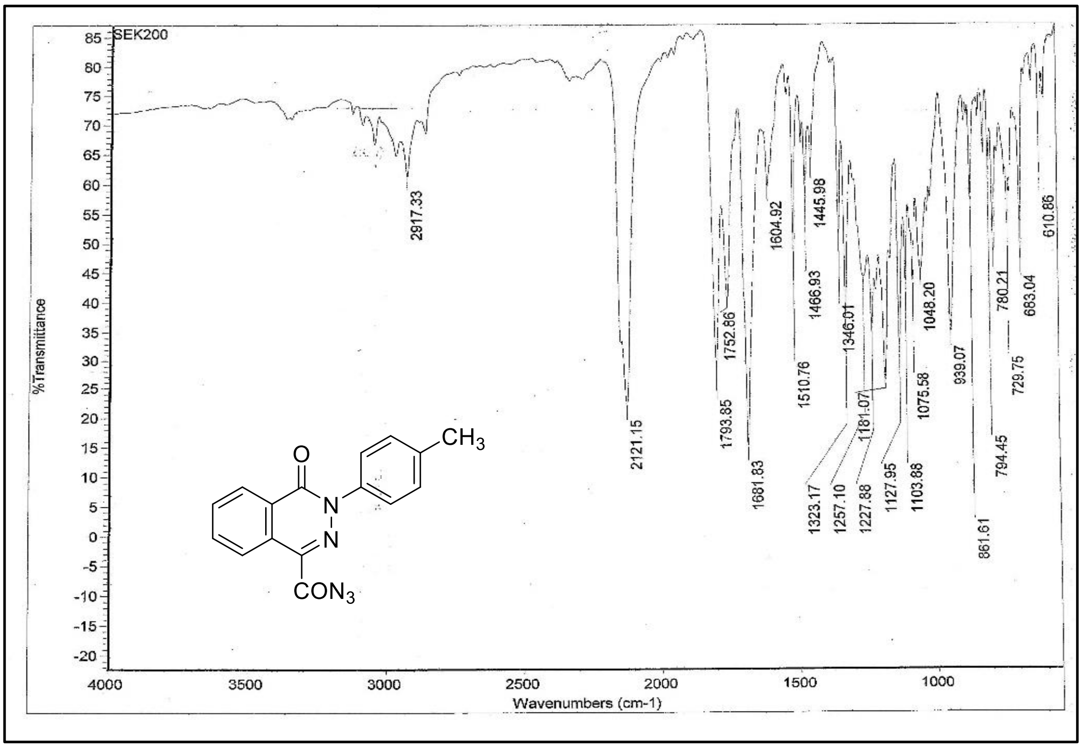


Figure 63: IR Spectrum of Compound 72c

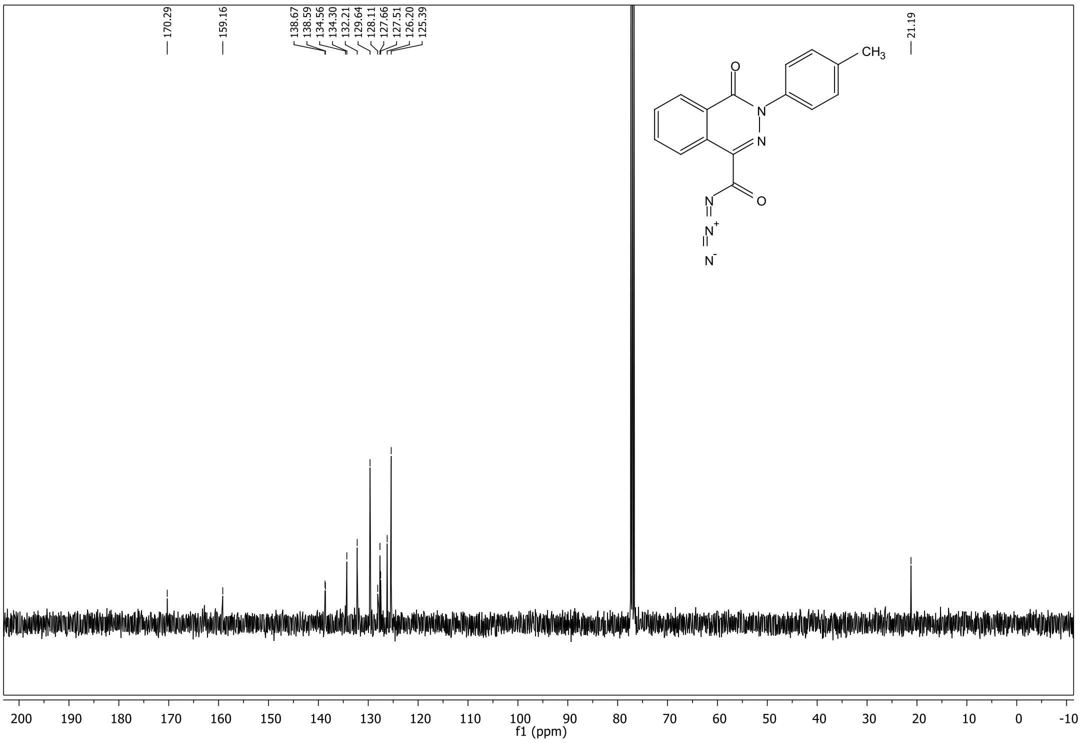


Figure 64: ^{13}C NMR Spectrum of Compound 72c

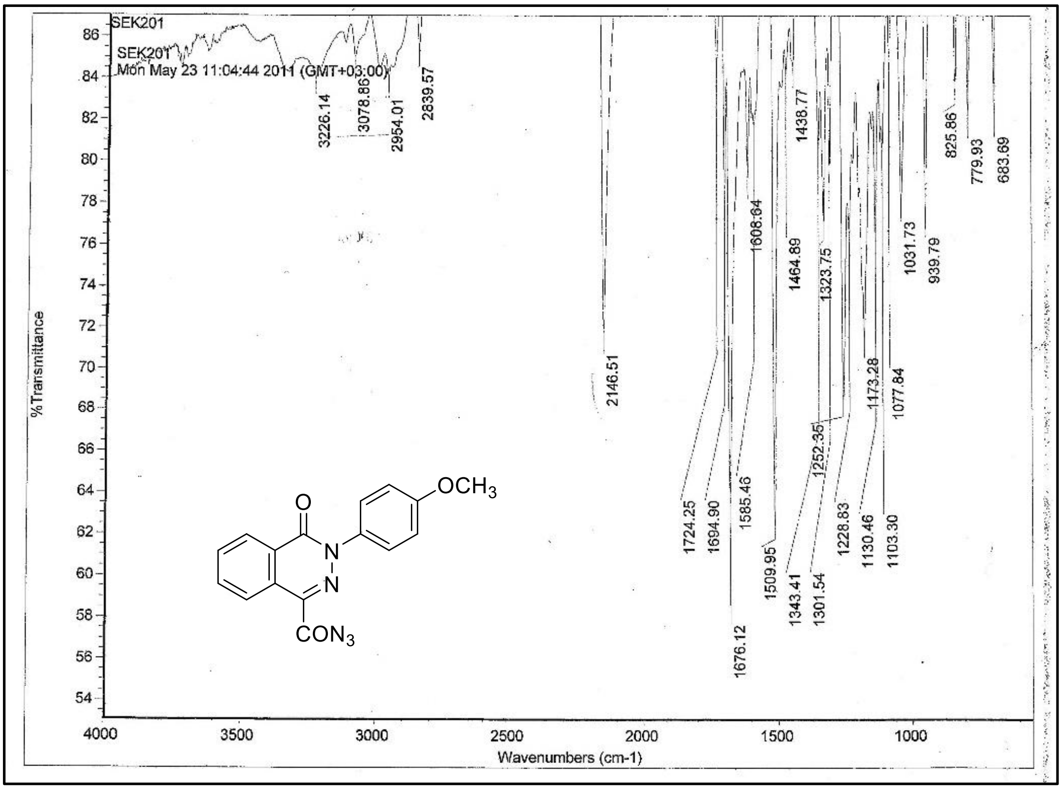


Figure 65: IR Spectrum of Compound 72d

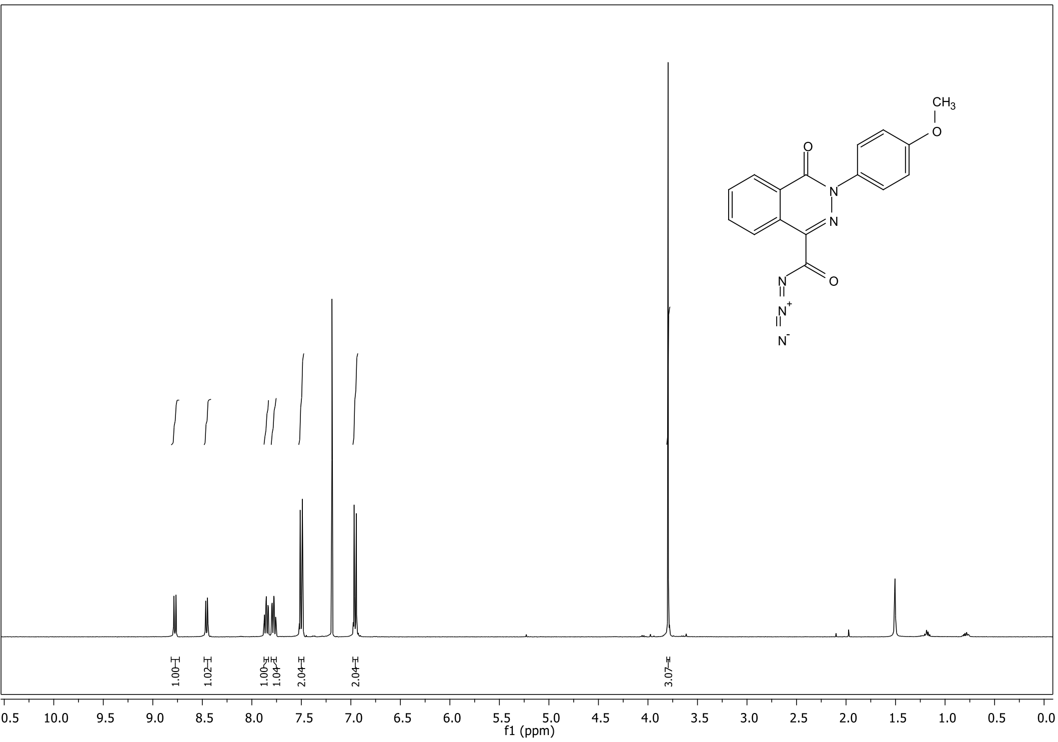


Figure 66: ^{1}H NMR Spectrum of Compound 72d

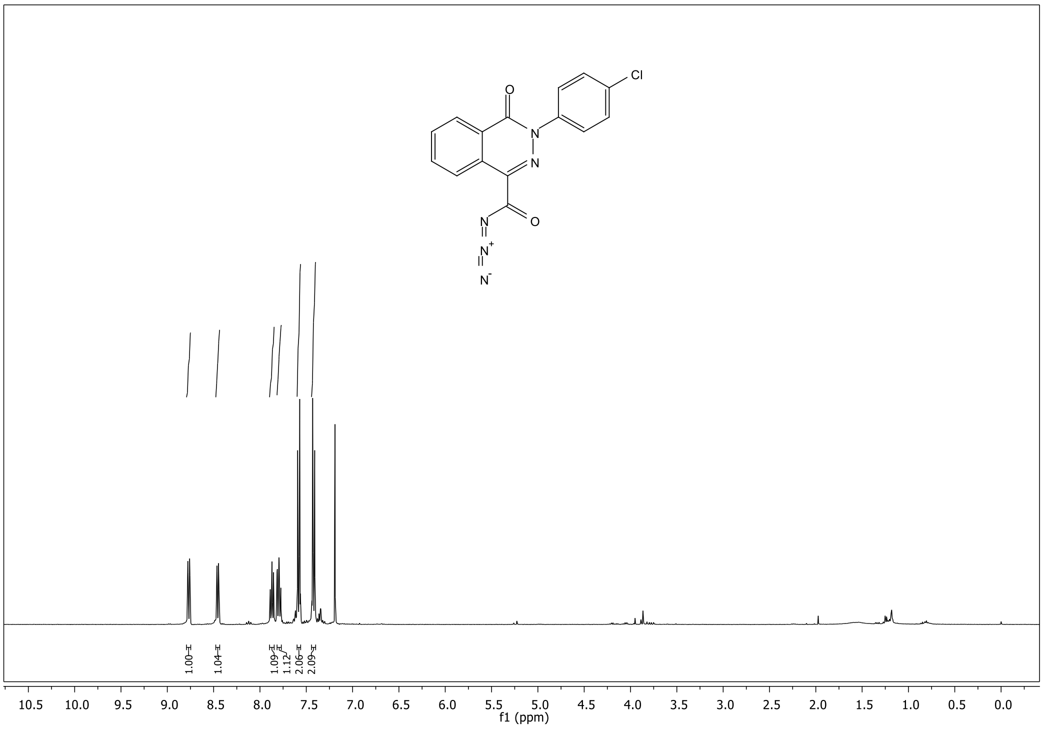


Figure 67: ^{1}H NMR Spectrum of Compound 72e

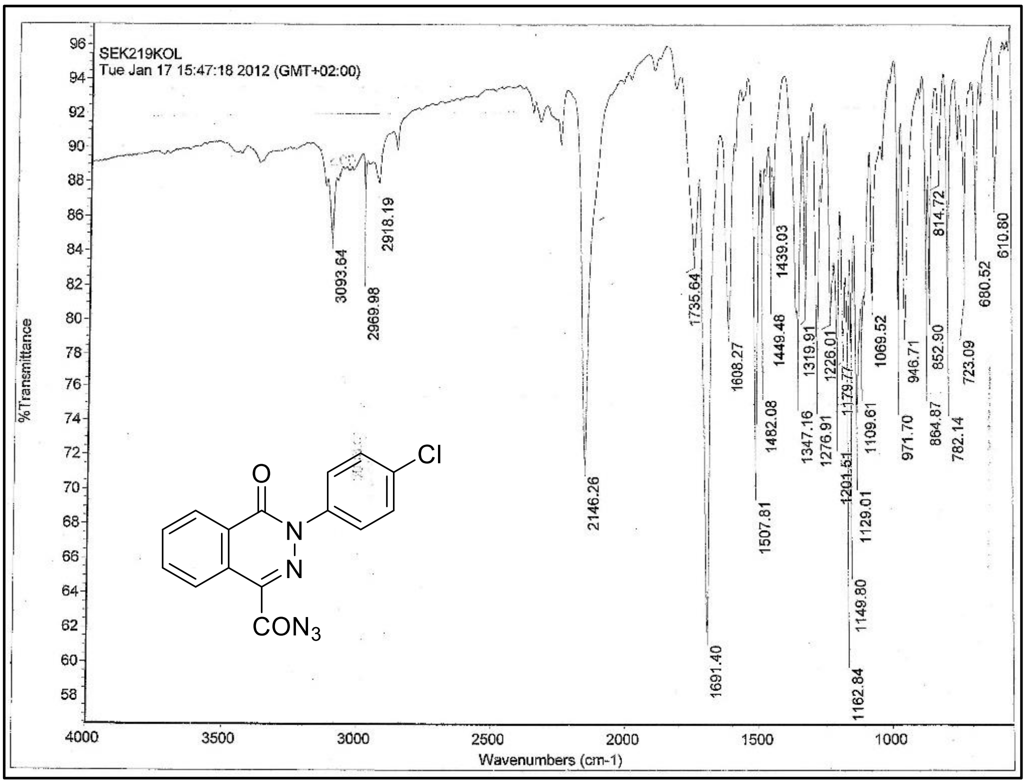


Figure 68: IR Spectrum of Compound 72e

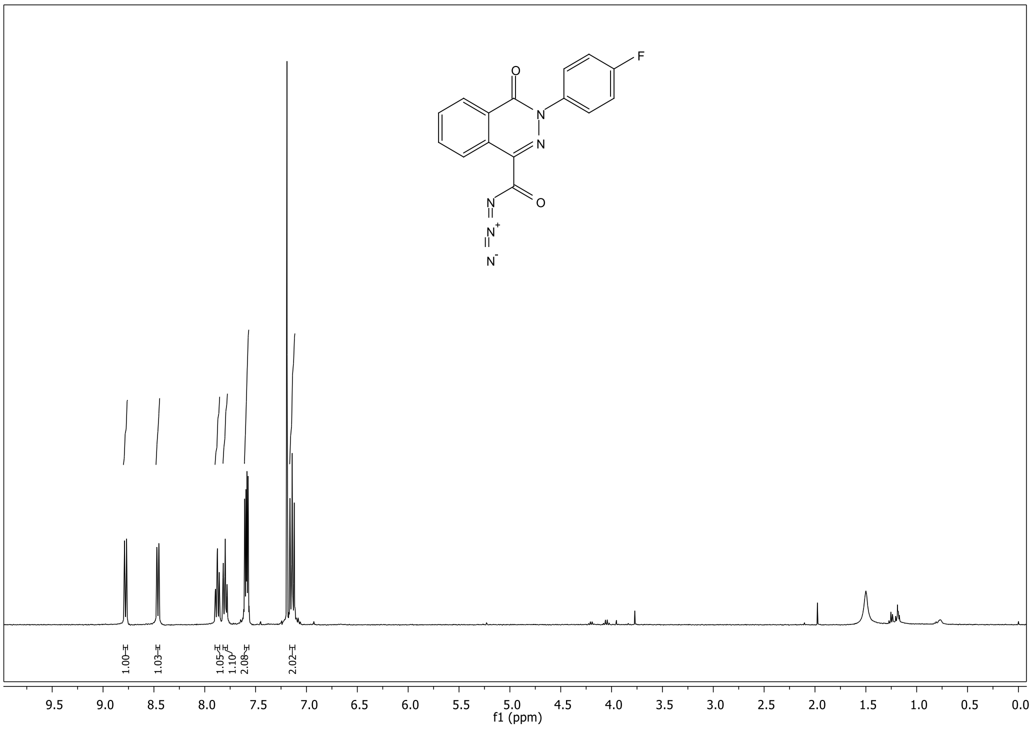


Figure 69: ^{1}H NMR Spectrum of Compound 72f

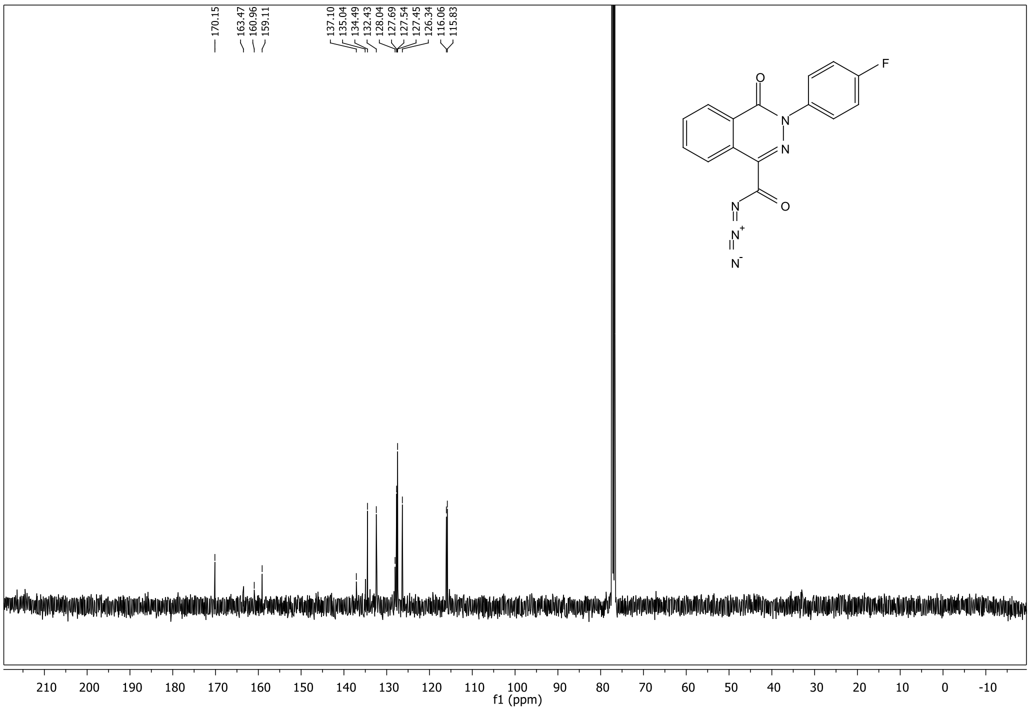


Figure 70: ^{13}C NMR Spectrum of Compound 72f

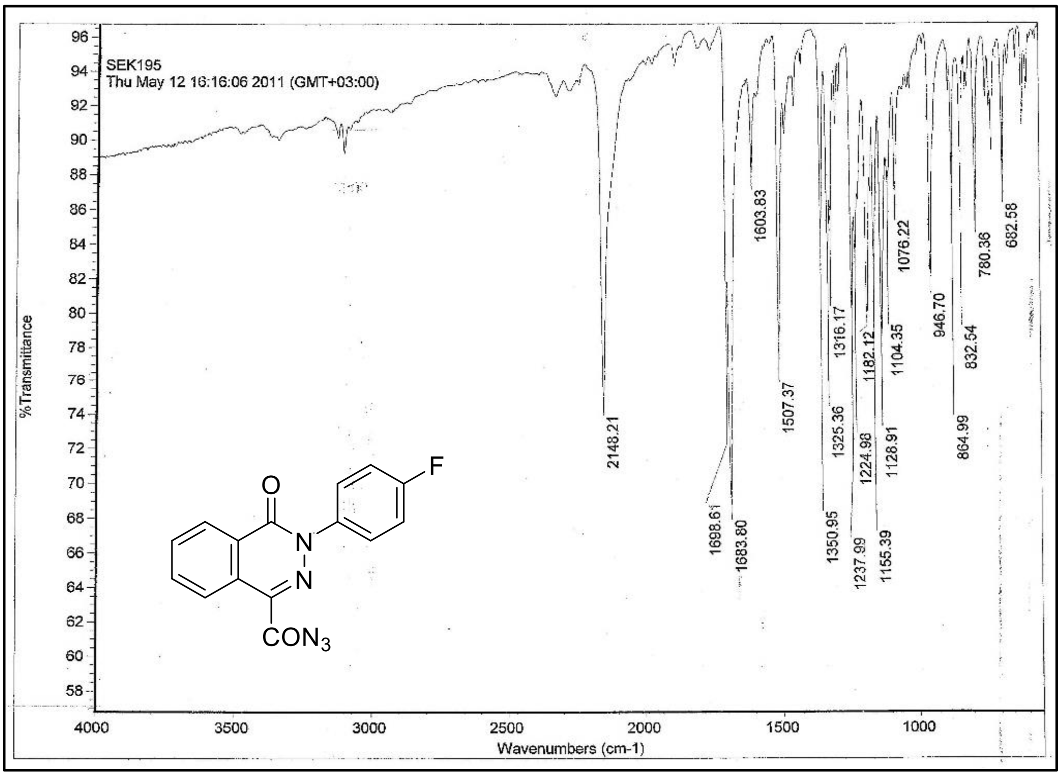


Figure 71: IR Spectrum of Compound 72f

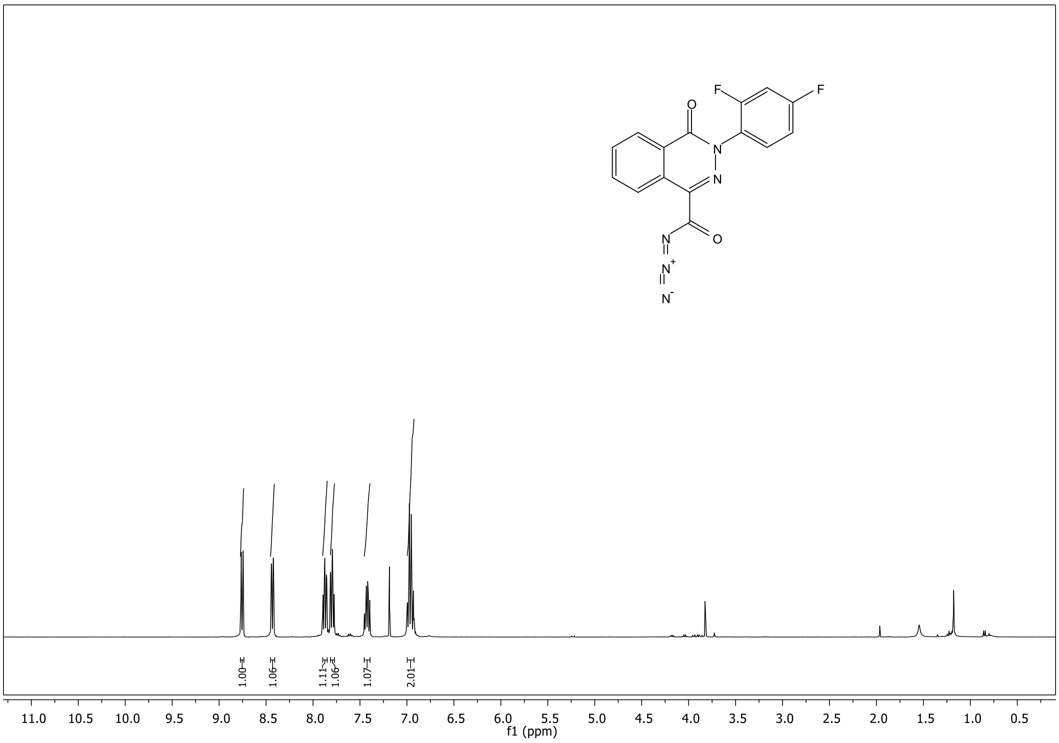


Figure 72: ^{1}H NMR Spectrum of Compound 72g

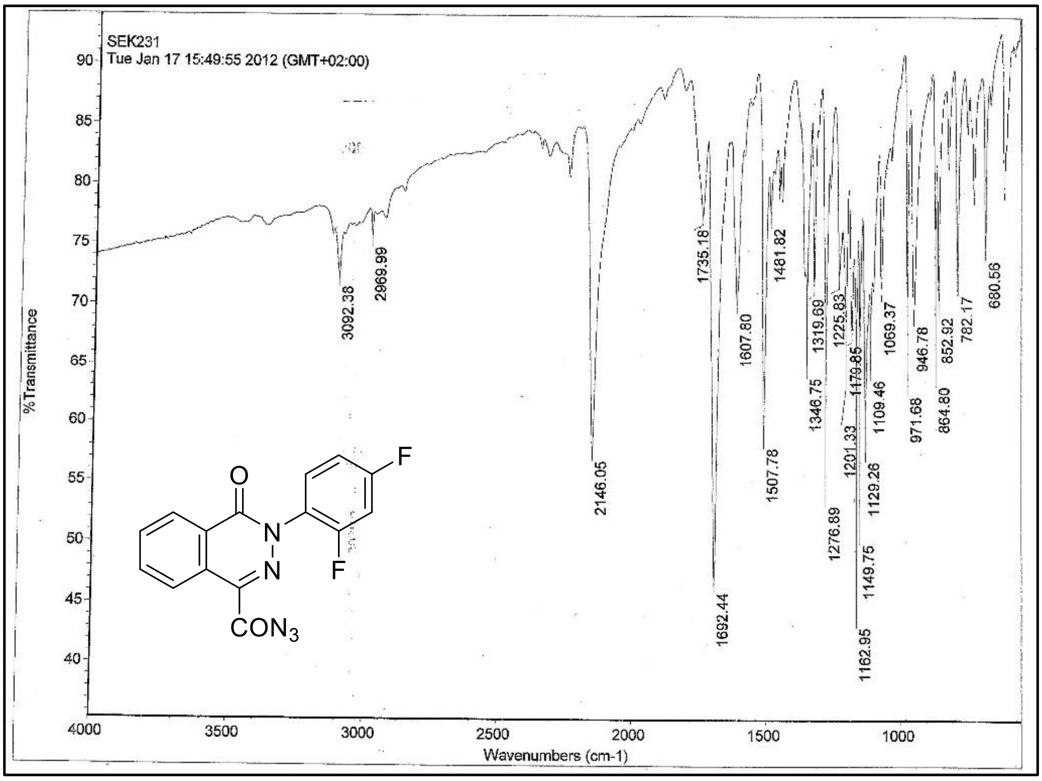


Figure 73: IR Spectrum of Compound 72g

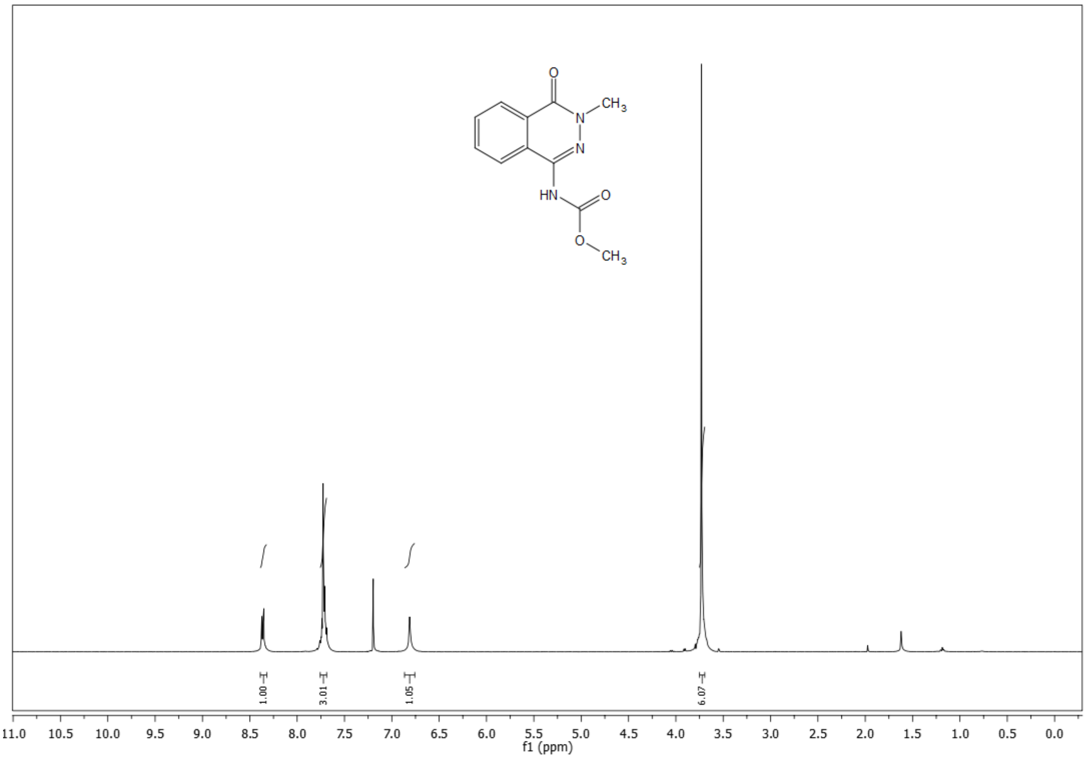


Figure 74: ^{1}H NMR Spectrum of Compound 73a

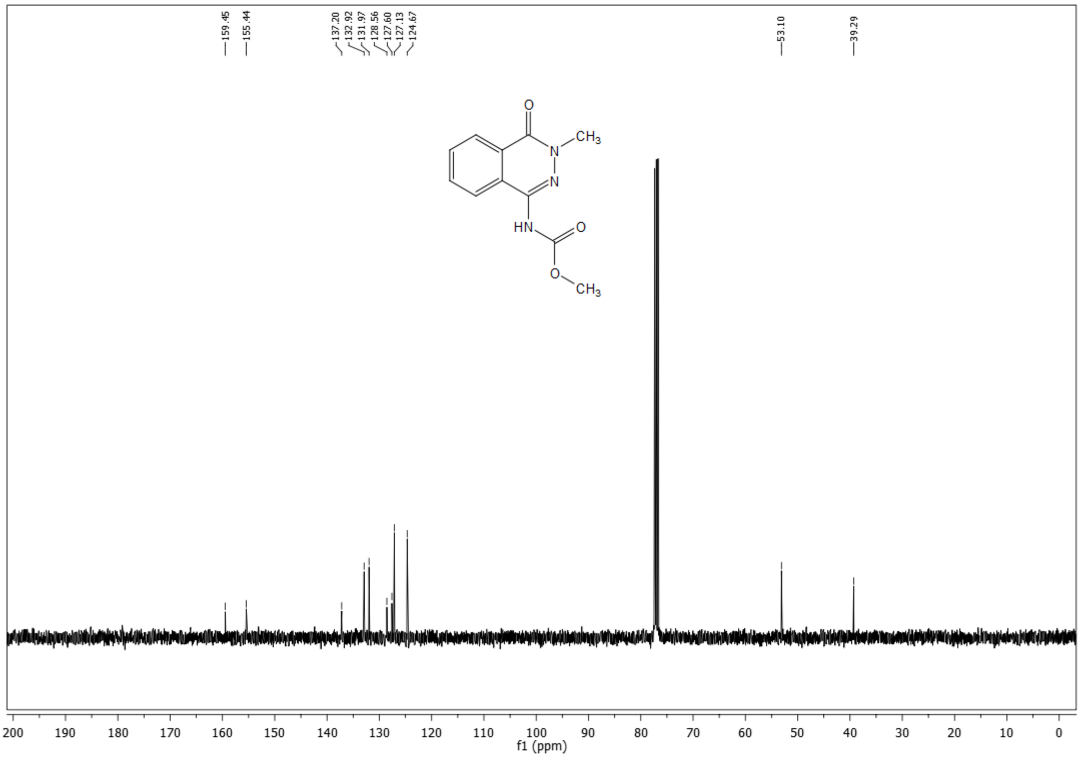


Figure 75: ^{13}C NMR Spectrum of Compound 73a

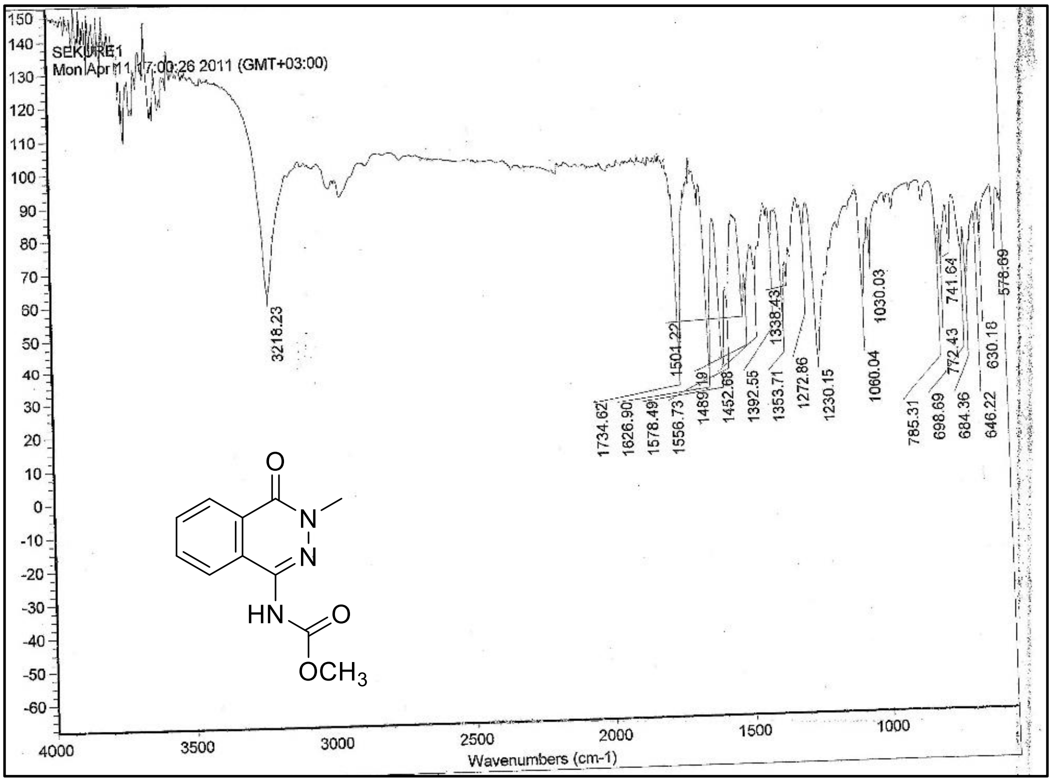


Figure 76: IR Spectrum of Compound 73b

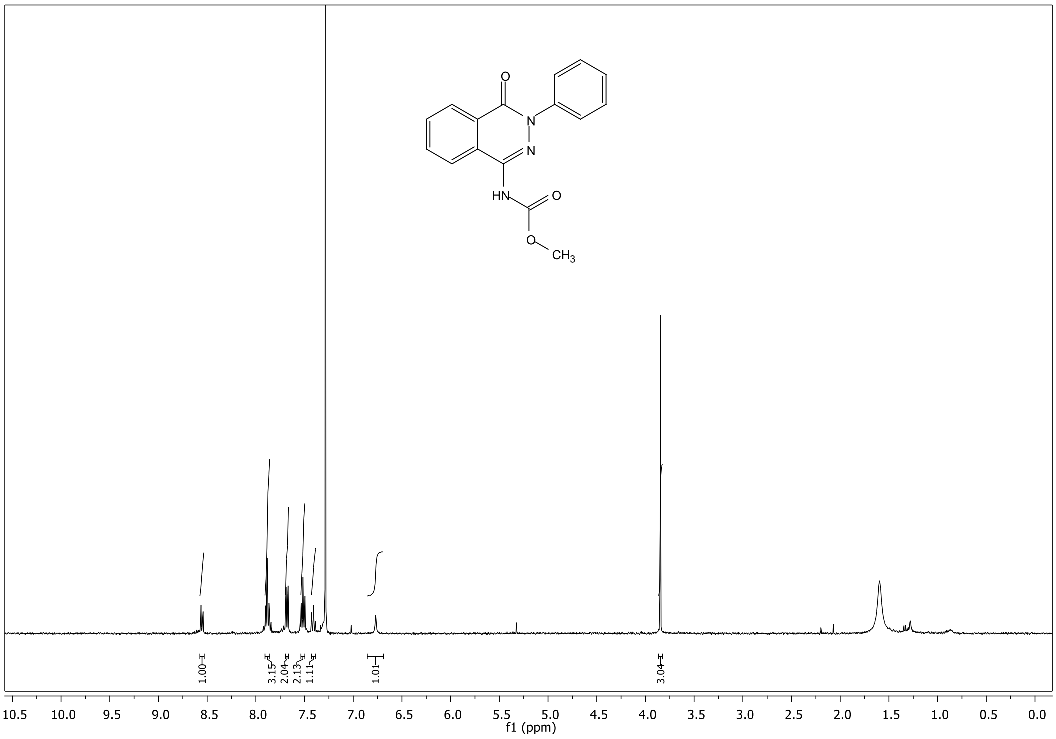


Figure 77: ^{1}H NMR Spectrum of Compound 73b

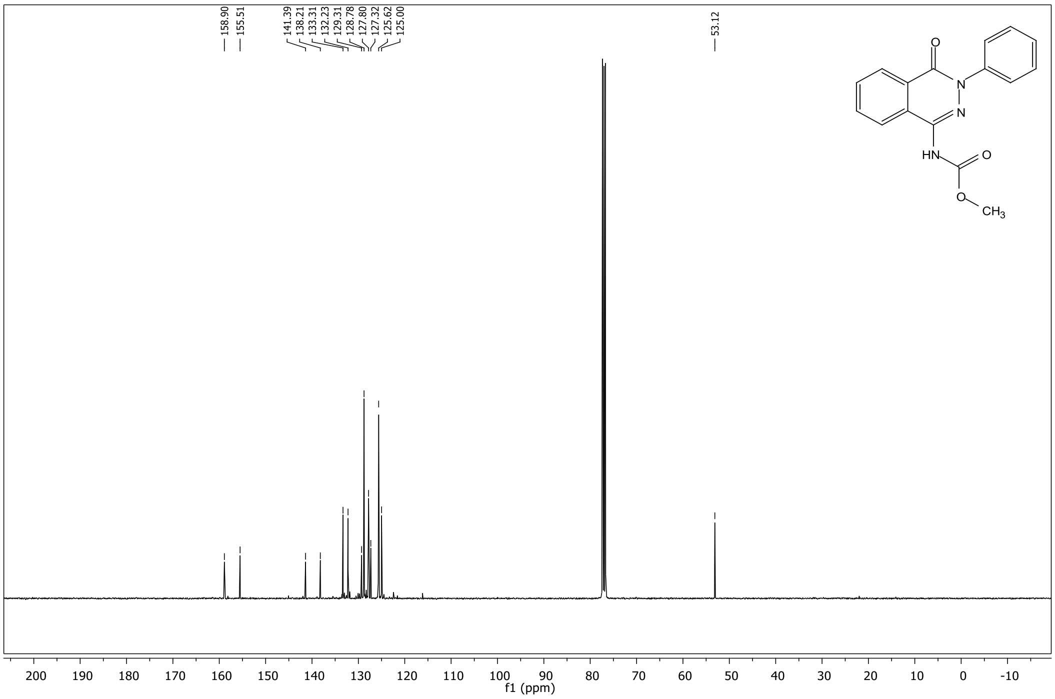


Figure 78: ^{13}C NMR Spectrum of Compound 73b

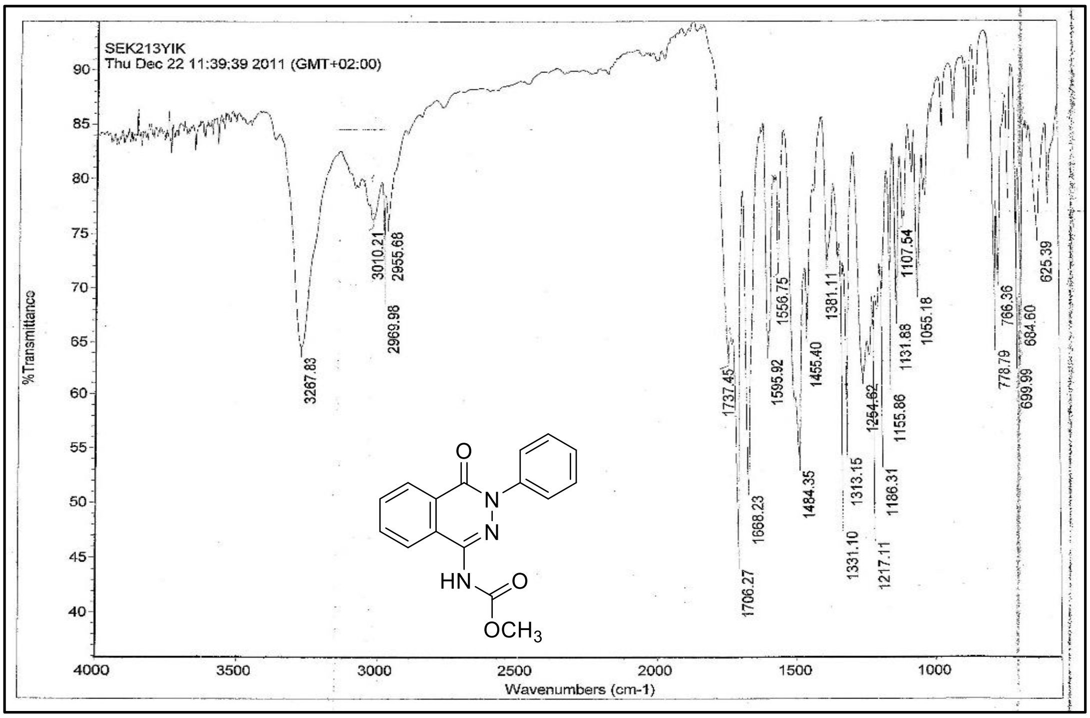


Figure 79: IR Spectrum of Compound 73b

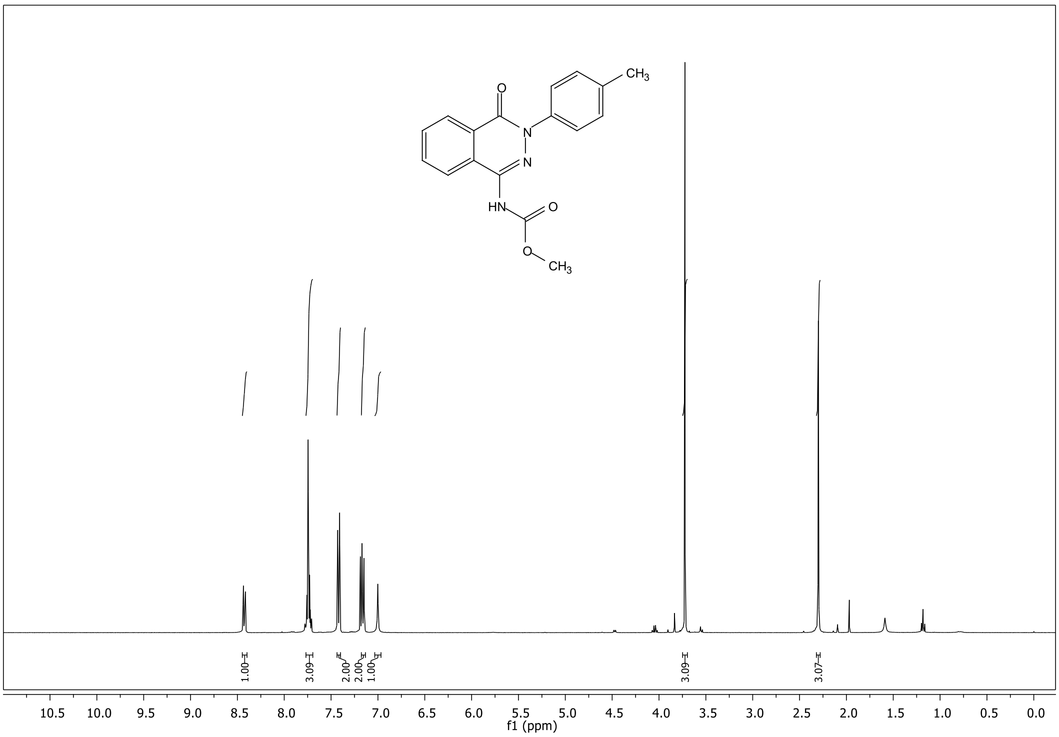


Figure 80: ^{1}H NMR Spectrum of Compound 73c

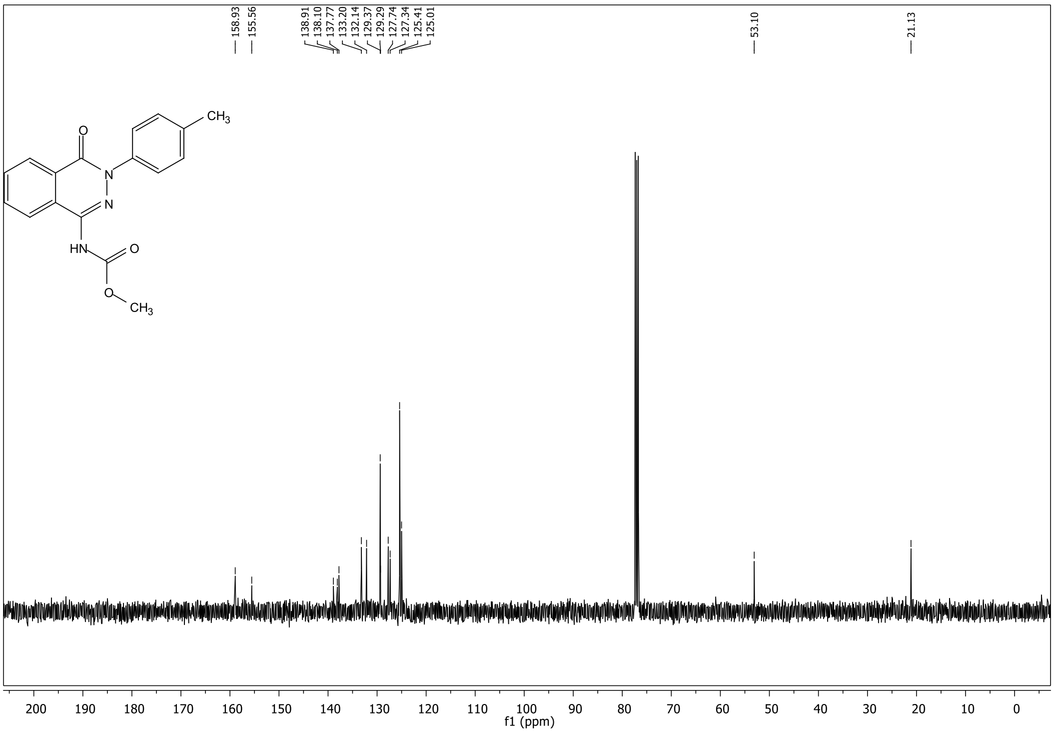


Figure 81: ^{13}C NMR Spectrum of Compound 73c

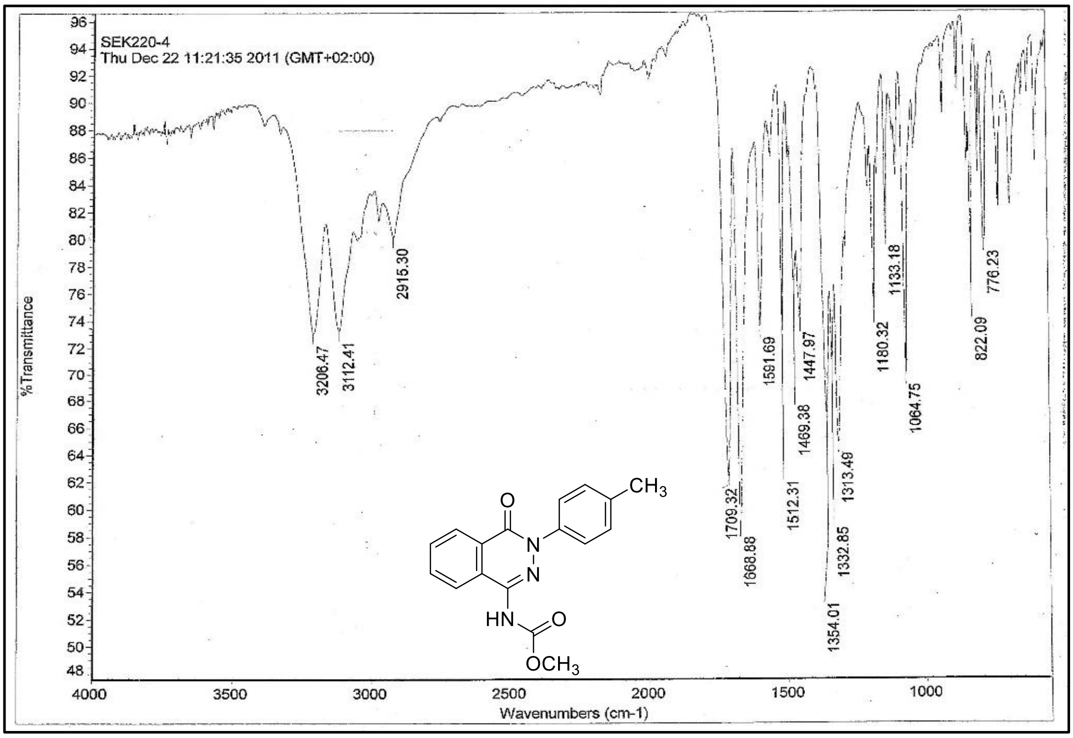


Figure 82: IR Spectrum of Compound 73c

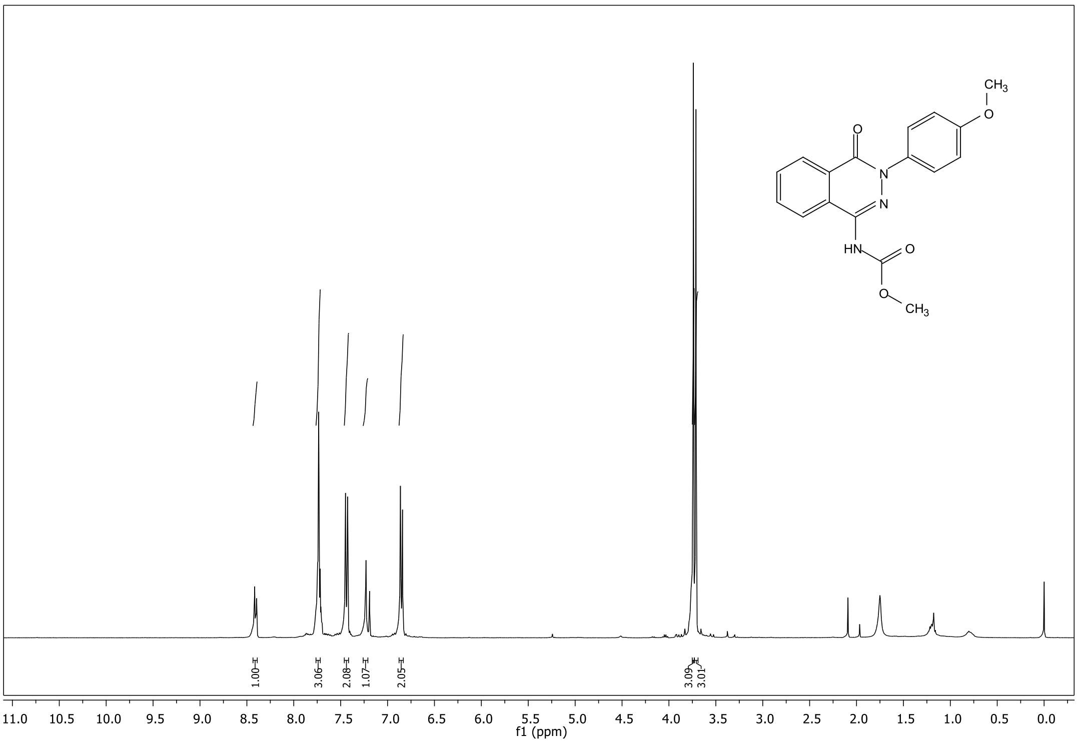


Figure 83: ^{1}H NMR Spectrum of Compound 73d

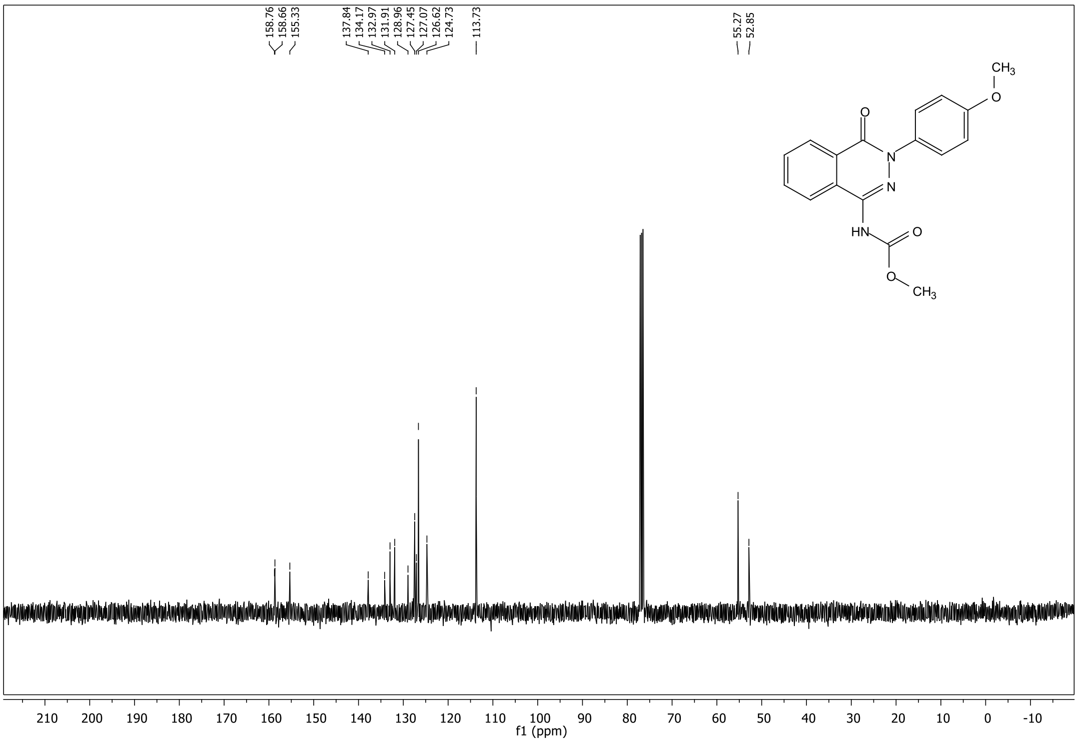


Figure 84: ^{13}C NMR Spectrum of Compound 73d

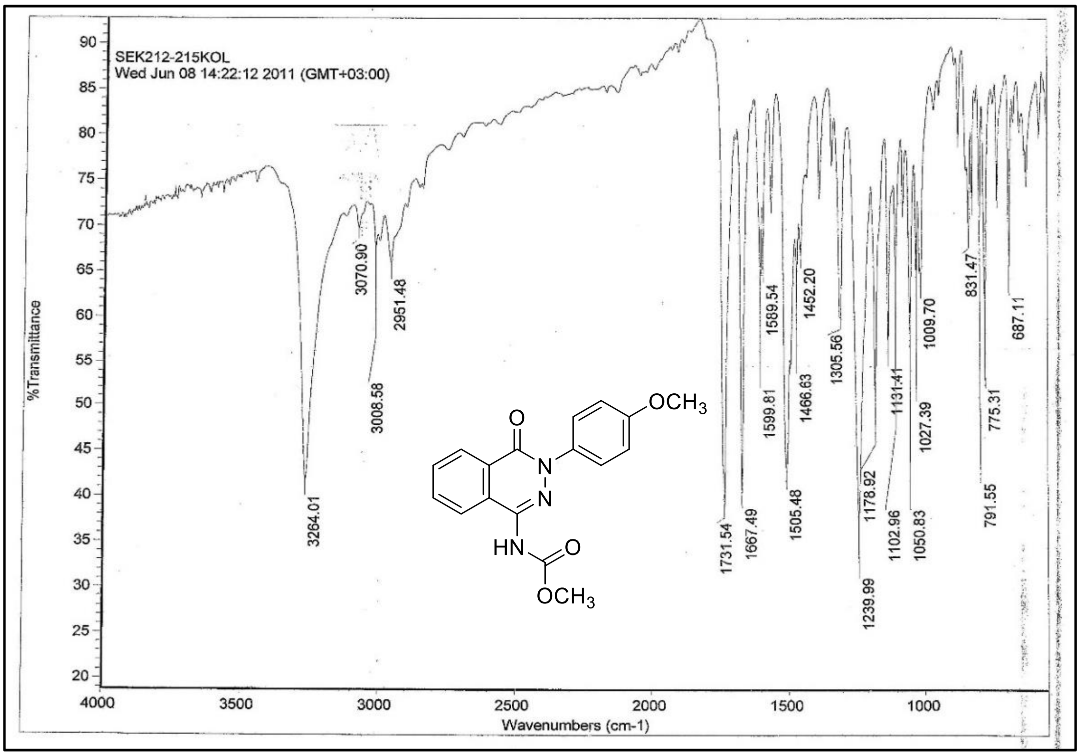


Figure 85: IR Spectrum of Compound 73d

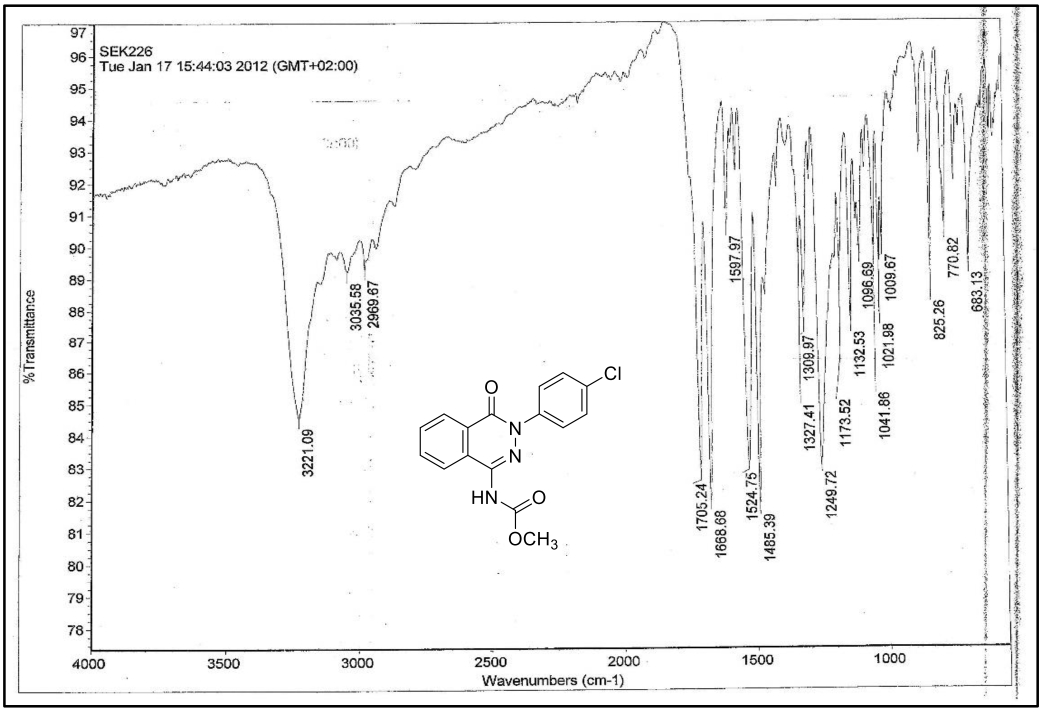


Figure 86: IR Spectrum of Compound 73e

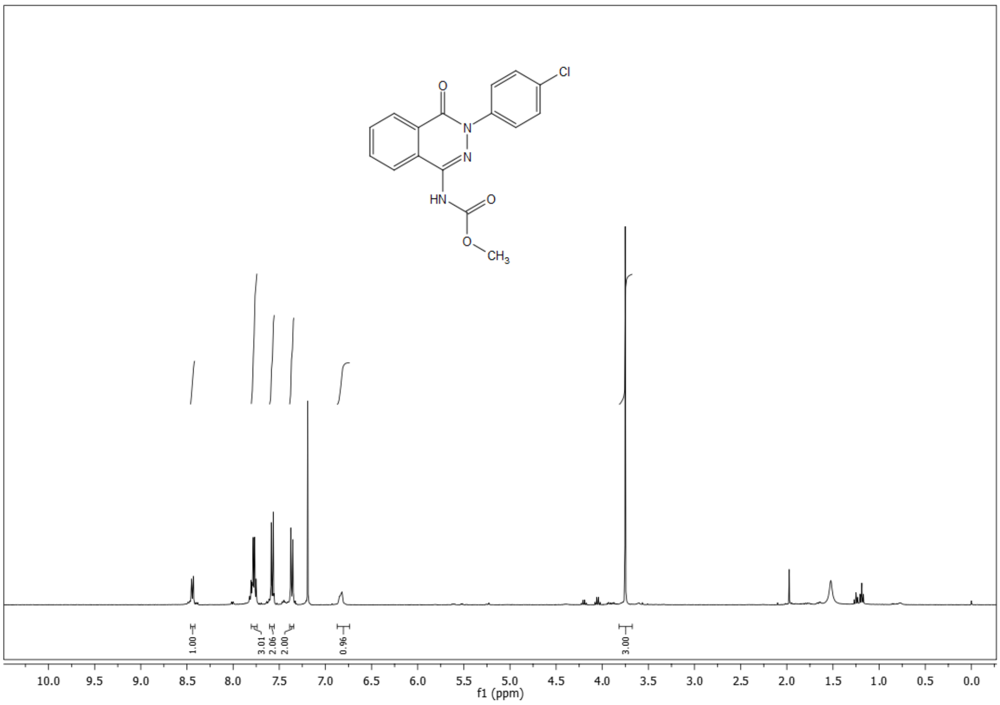


Figure 87: ^{1}H NMR Spectrum of Compound 73e

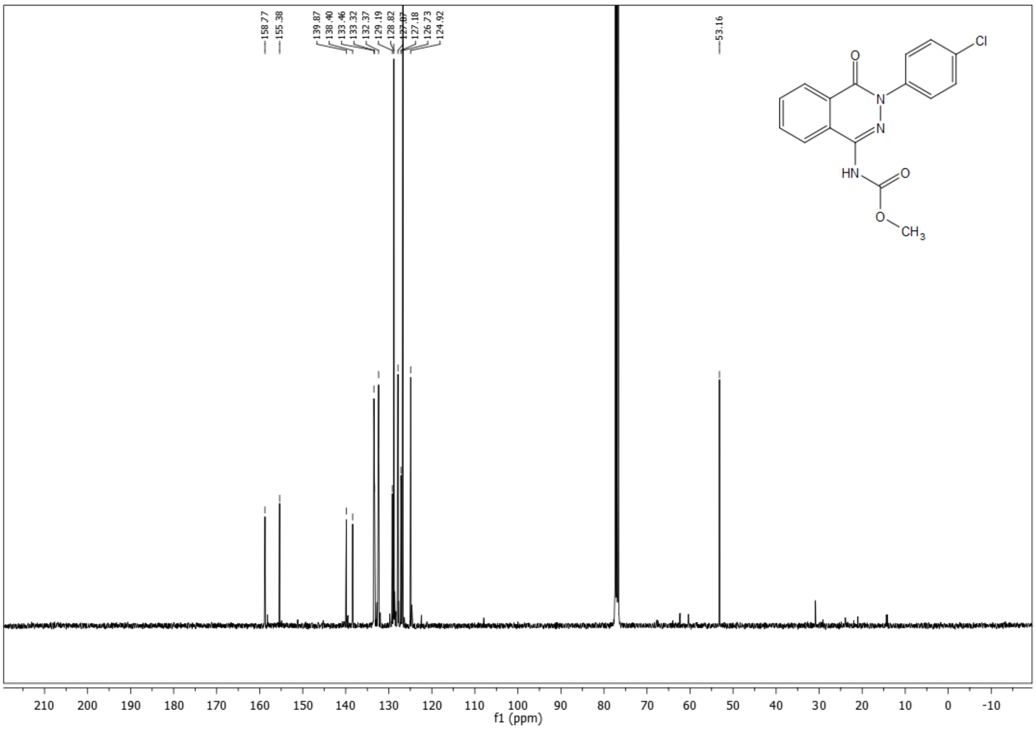


Figure 88: ^{13}C NMR Spectrum of Compound 73e

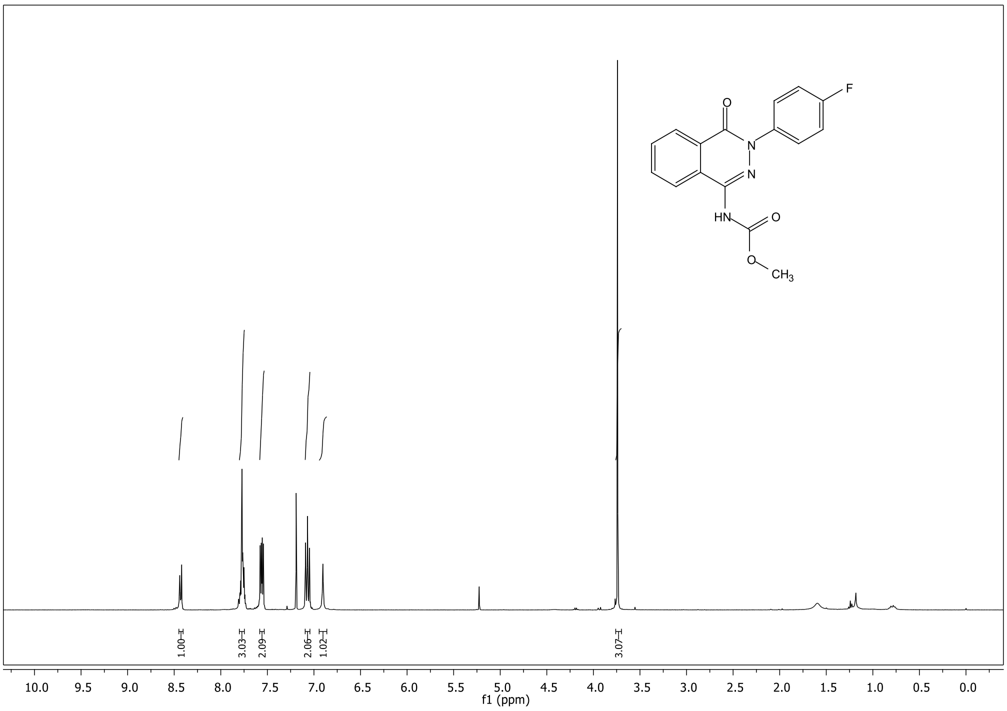


Figure 89: ^{1}H NMR Spectrum of Compound 73f

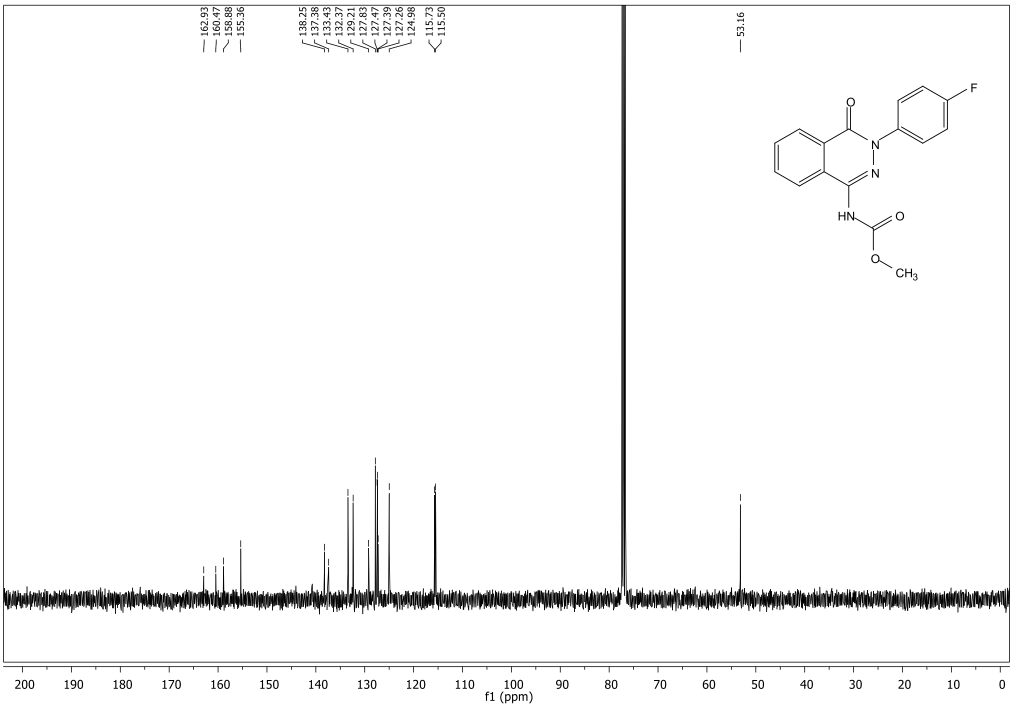


Figure 90: ^{13}C NMR Spectrum of Compound 73f

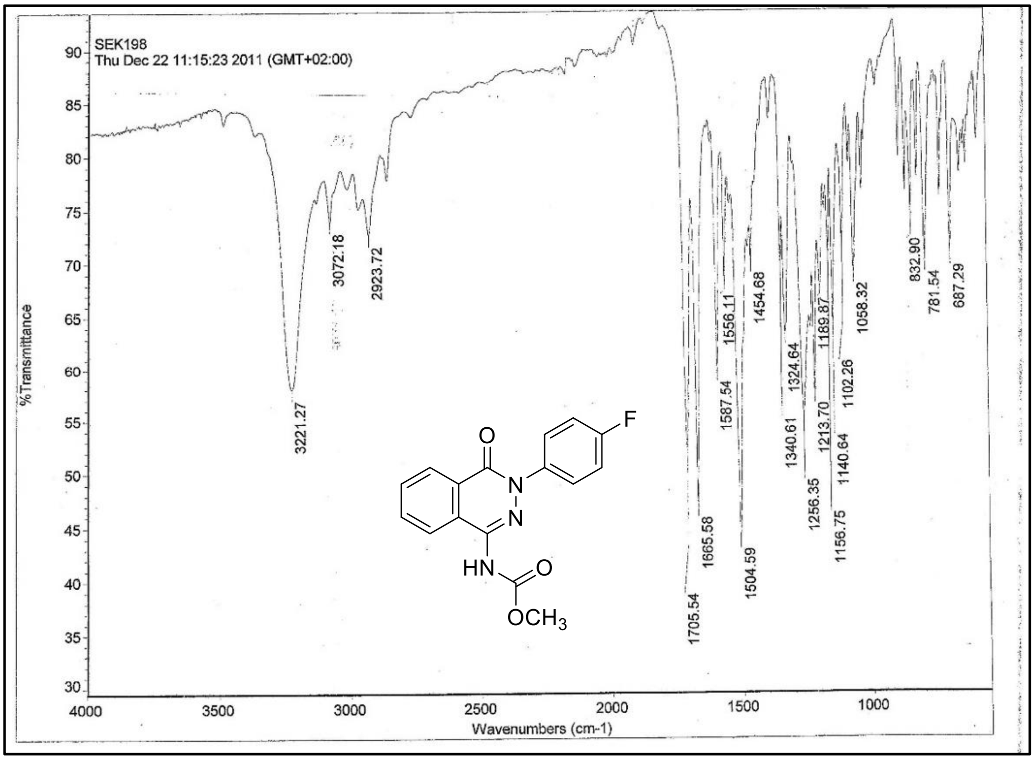


Figure 91: IR Spectrum of Compound 73f

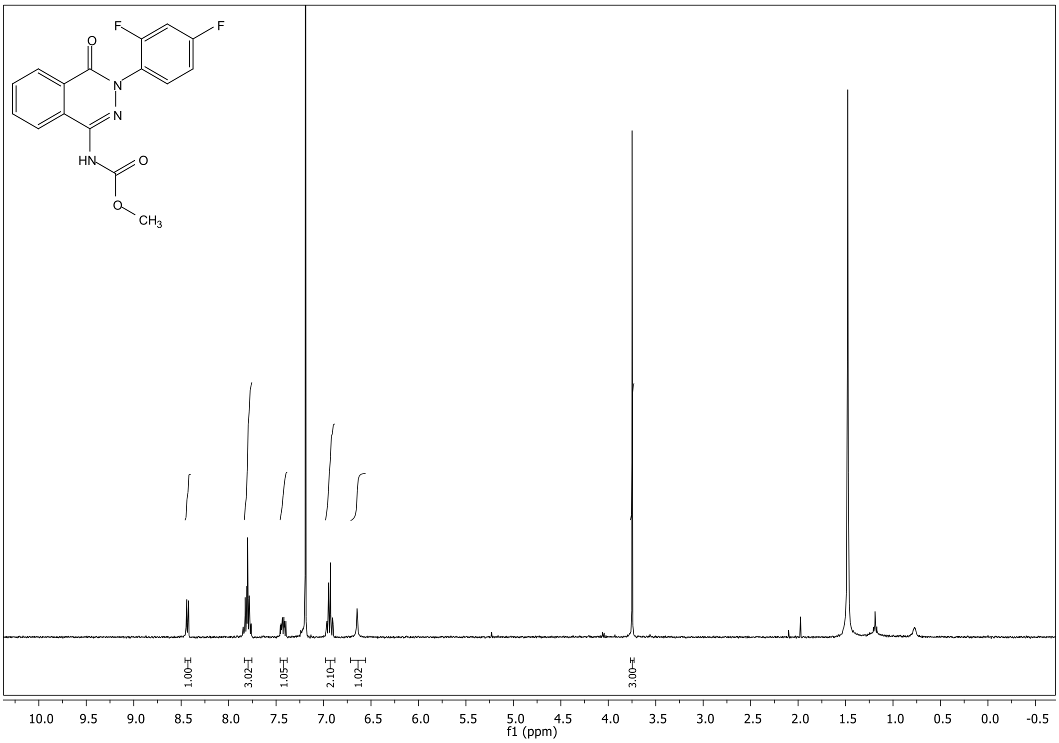


Figure 92: ^{1}H NMR Spectrum of Compound 73g

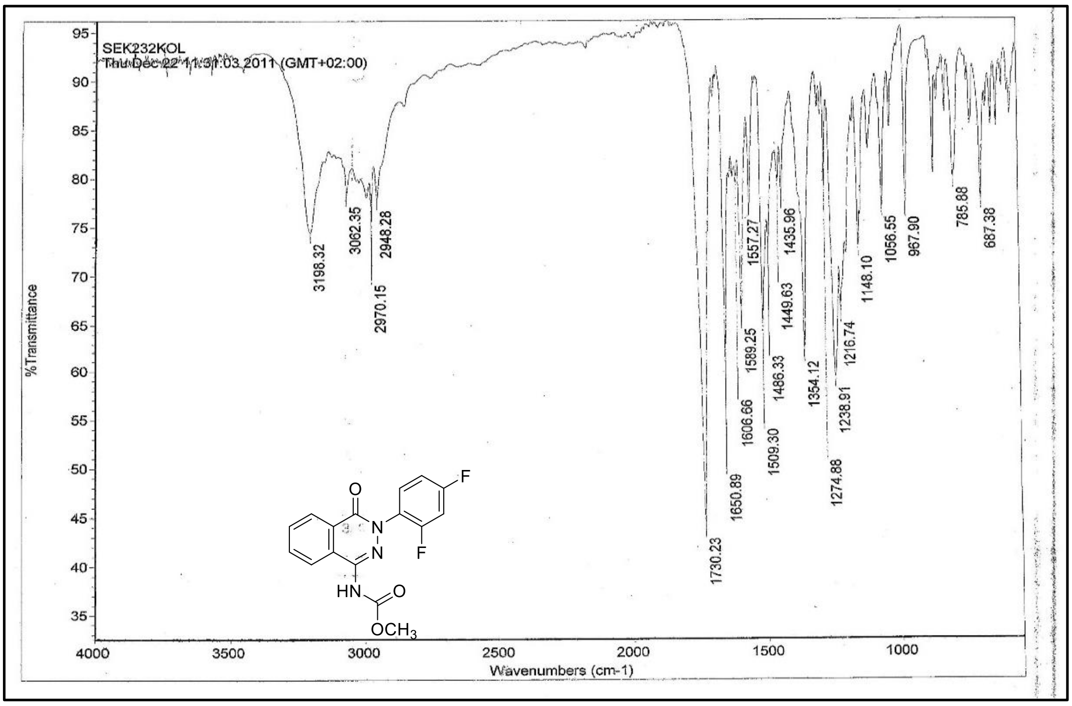


Figure 93: IR Spectrum of Compound 73g

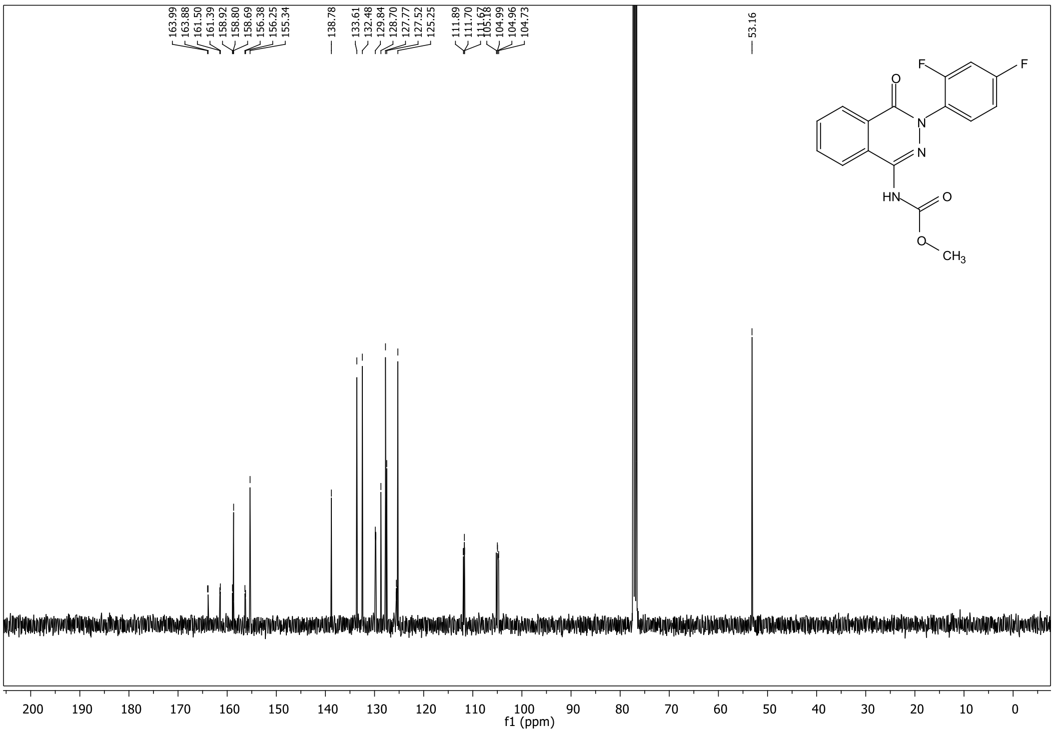


Figure 94: ^{13}C NMR Spectrum of Compound 73g

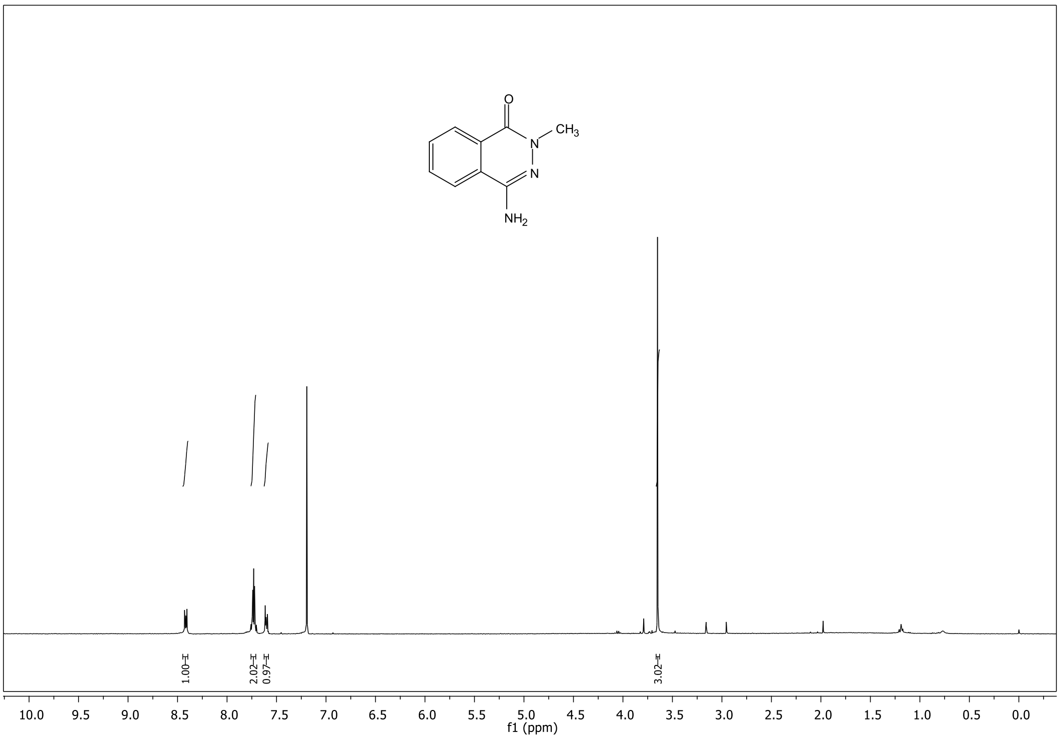


Figure 95: ^{1}H NMR Spectrum of Compound 74a

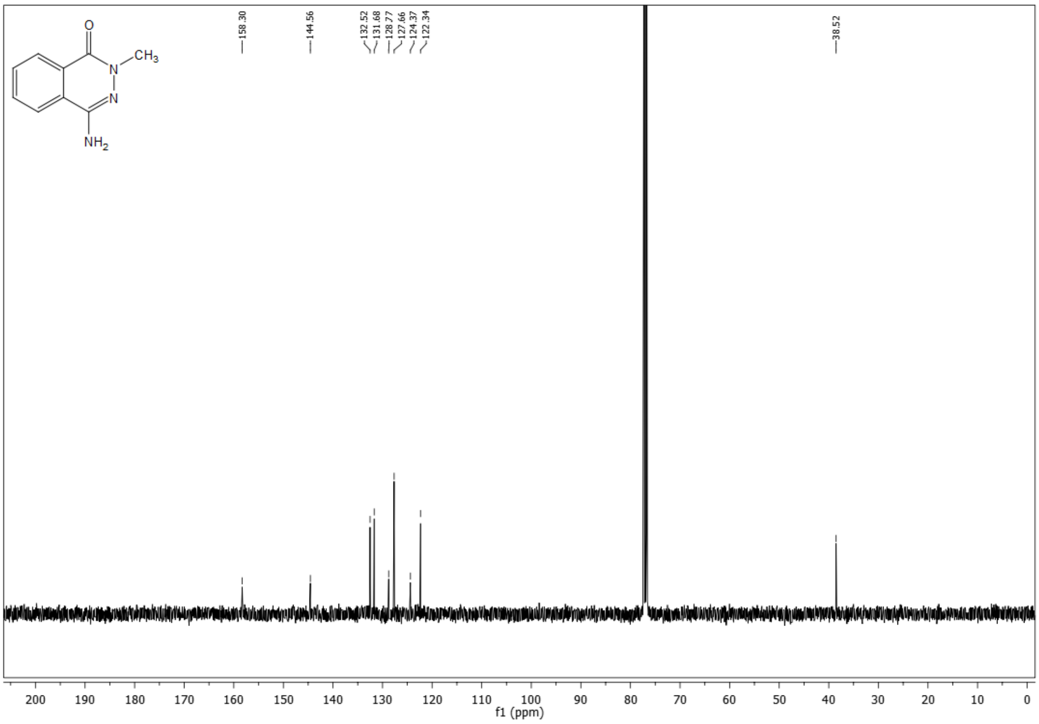


Figure 96: ^{13}C NMR Spectrum of Compound 74a

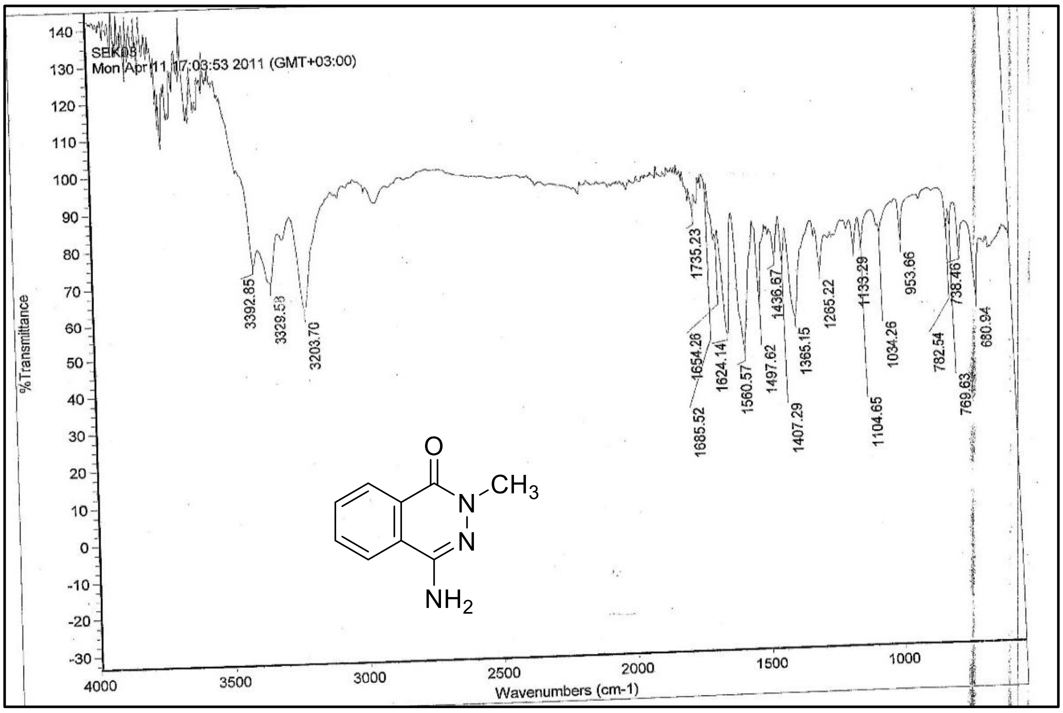


Figure 97: IR Spectrum of Compound 74a

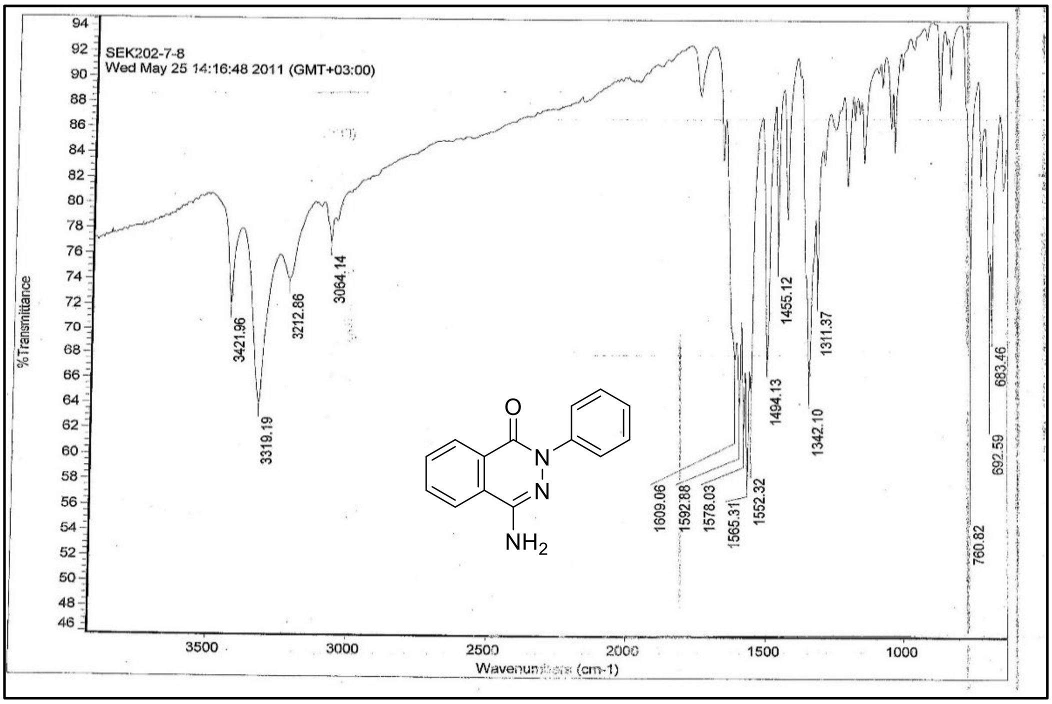


Figure 98: IR Spectrum of Compund 74b

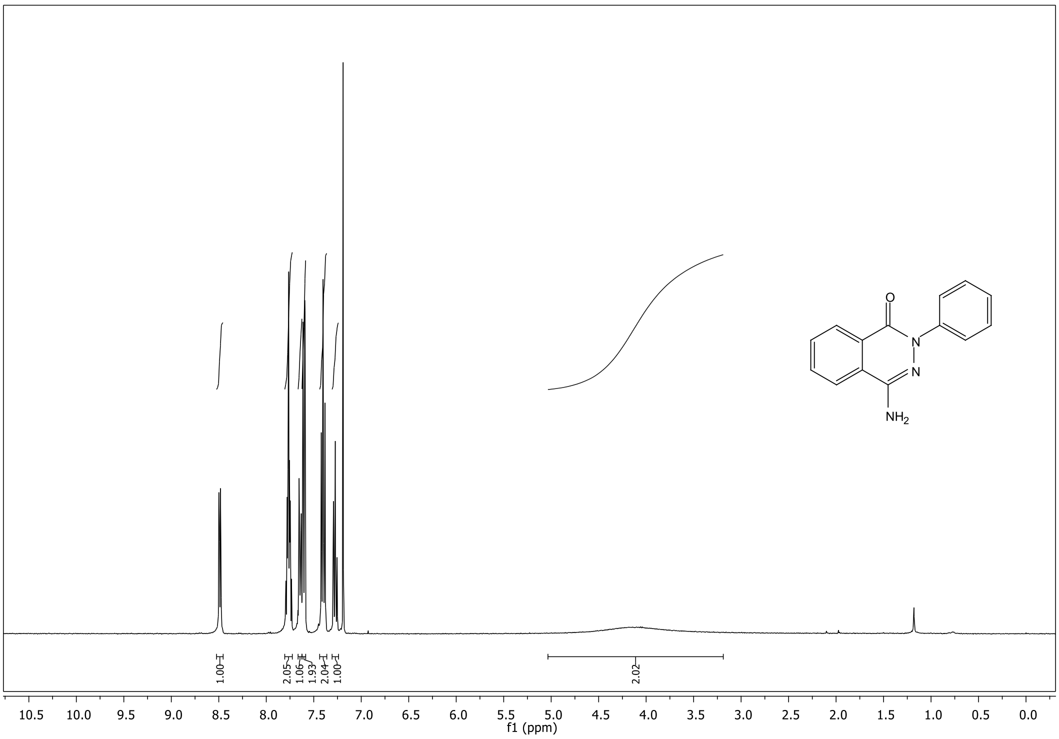


Figure 99: ^{1}H NMR Spectrum of Compund 74b

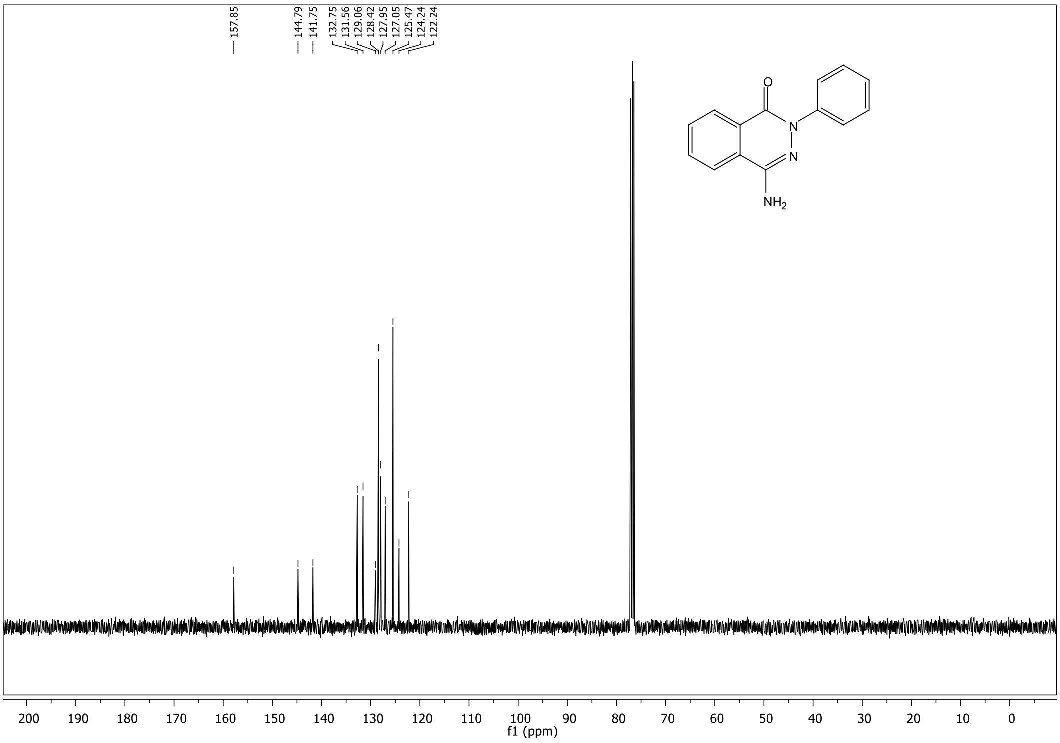


Figure 100: ^{13}C NMR Spectrum of Compound 74b

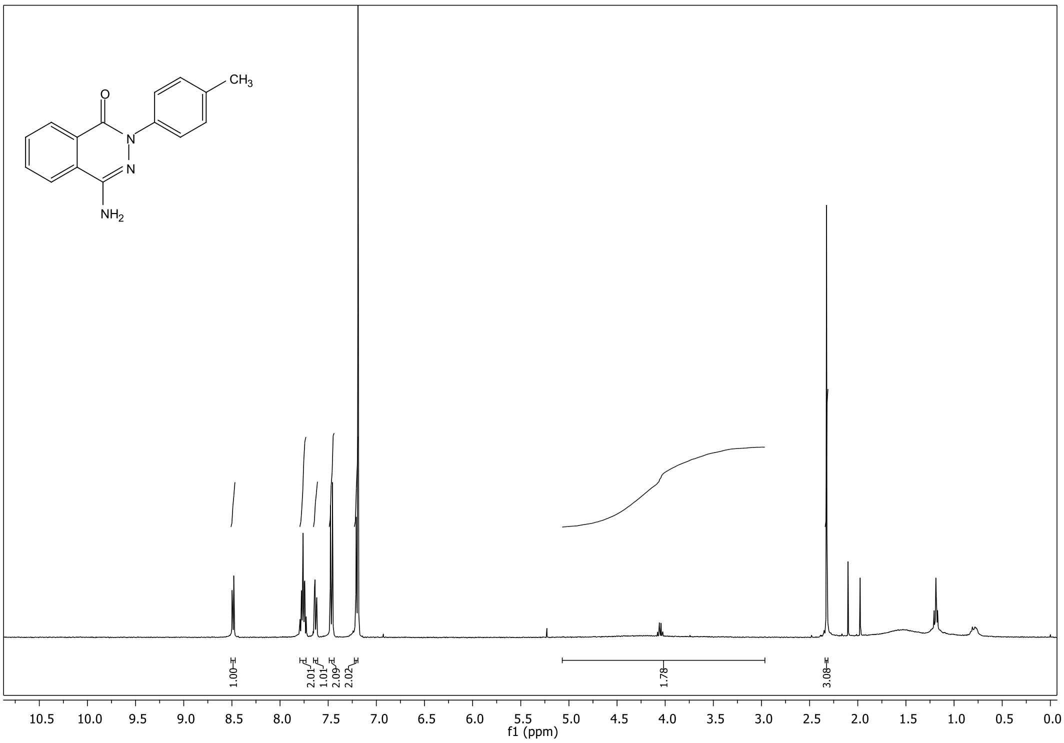


Figure 101: ^{1}H NMR Spectrum of Compound 74c

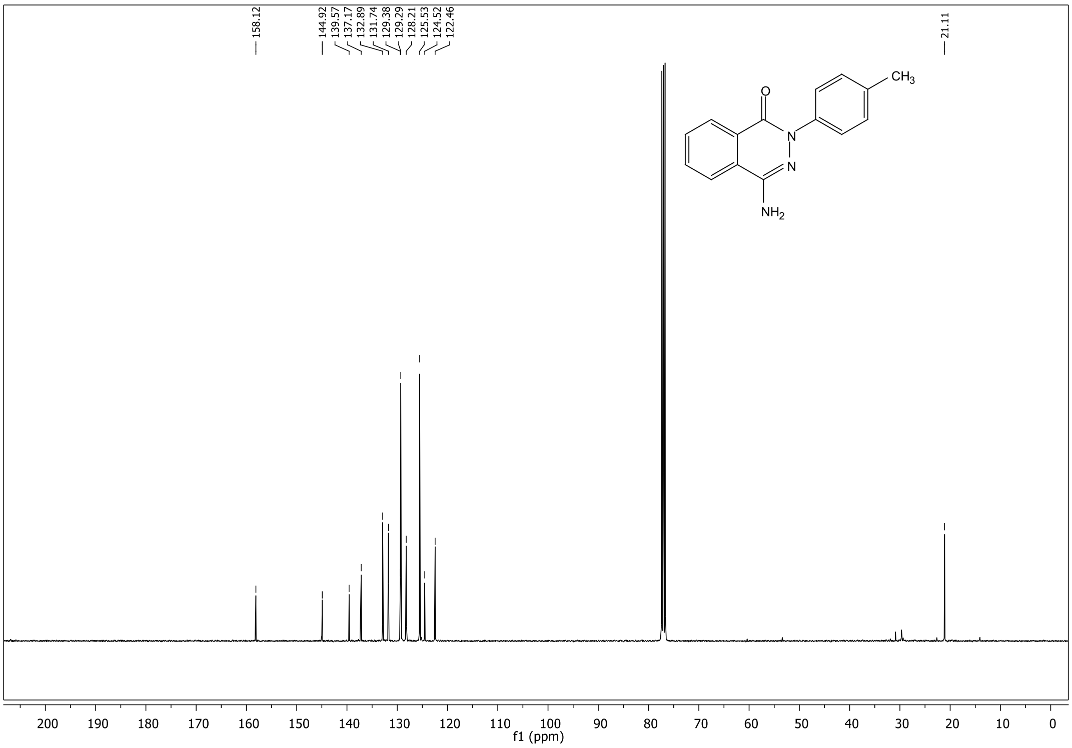


Figure 102: ^{13}C NMR Spectrum of Compound 74c

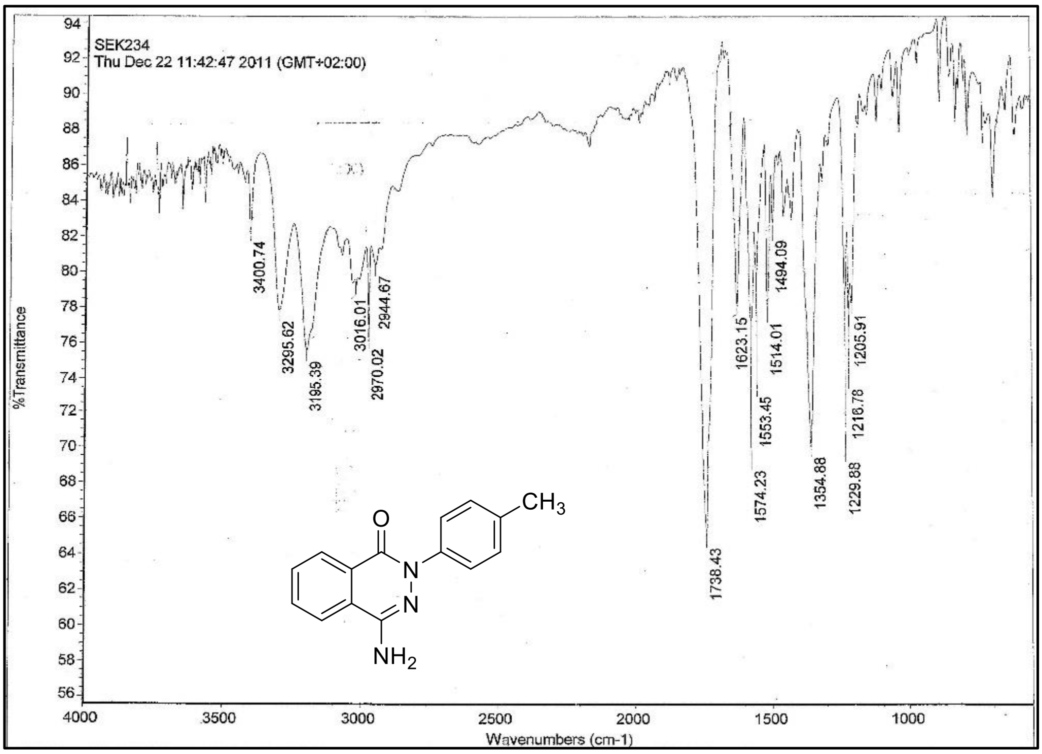


Figure 103: IR Spectrum of Compound 74c

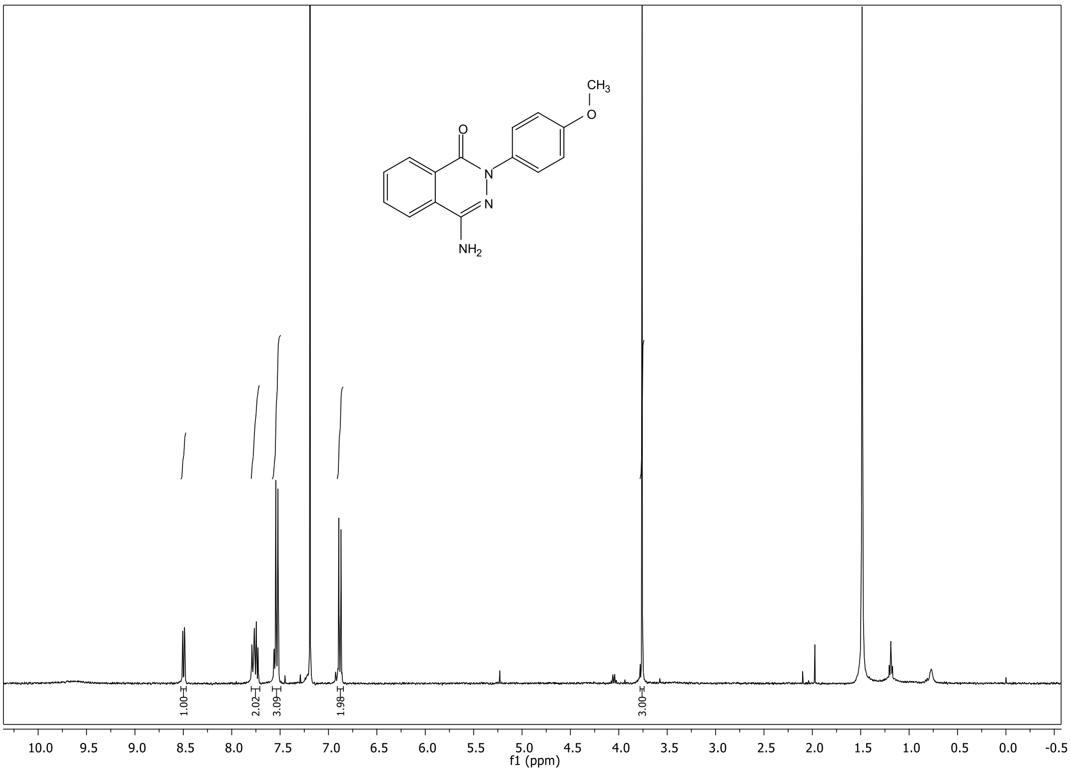


Figure 104: ^{1}H NMR Spectrum of Compound 74d

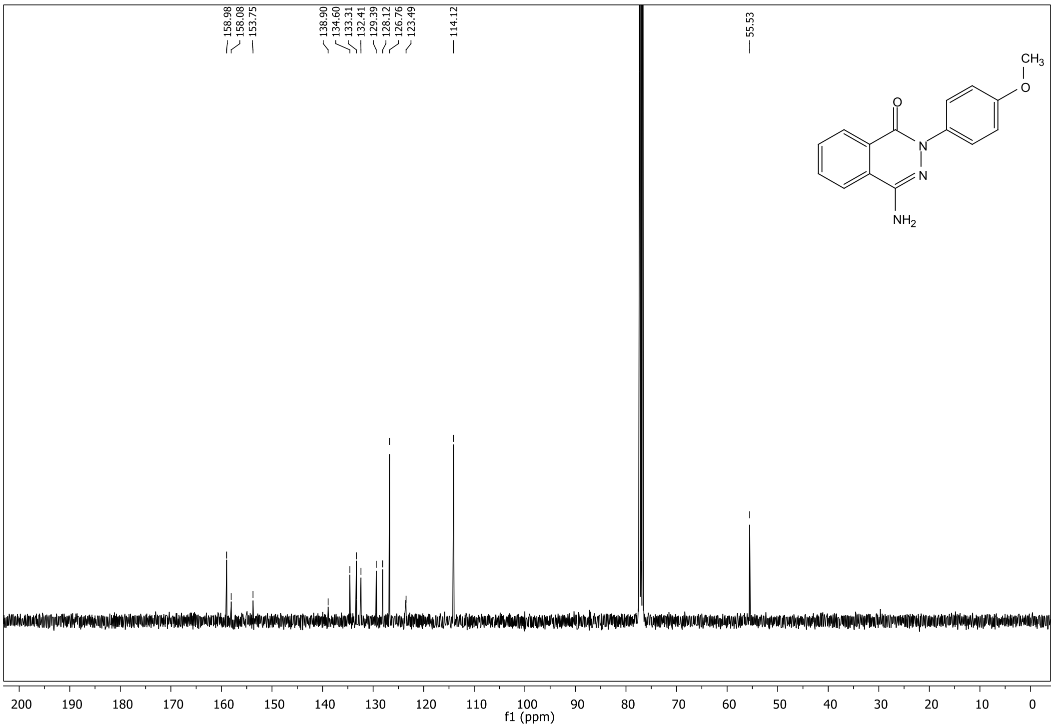


Figure 105: ^{13}C NMR Spectrum of Compound 74d

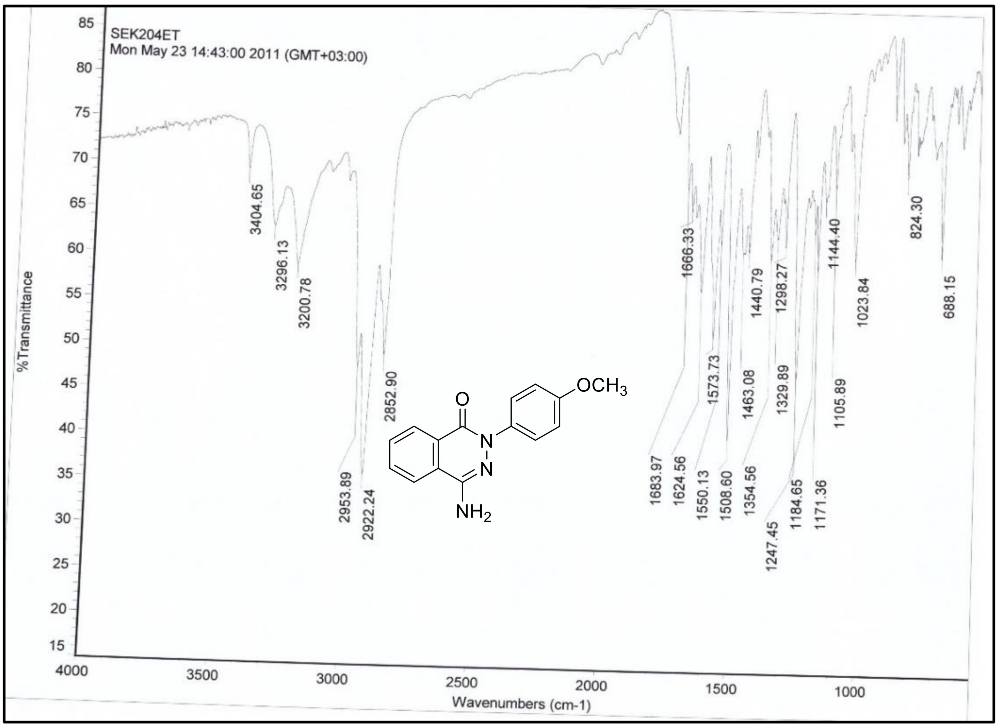


Figure 106: IR Spectrum of Compound 74d

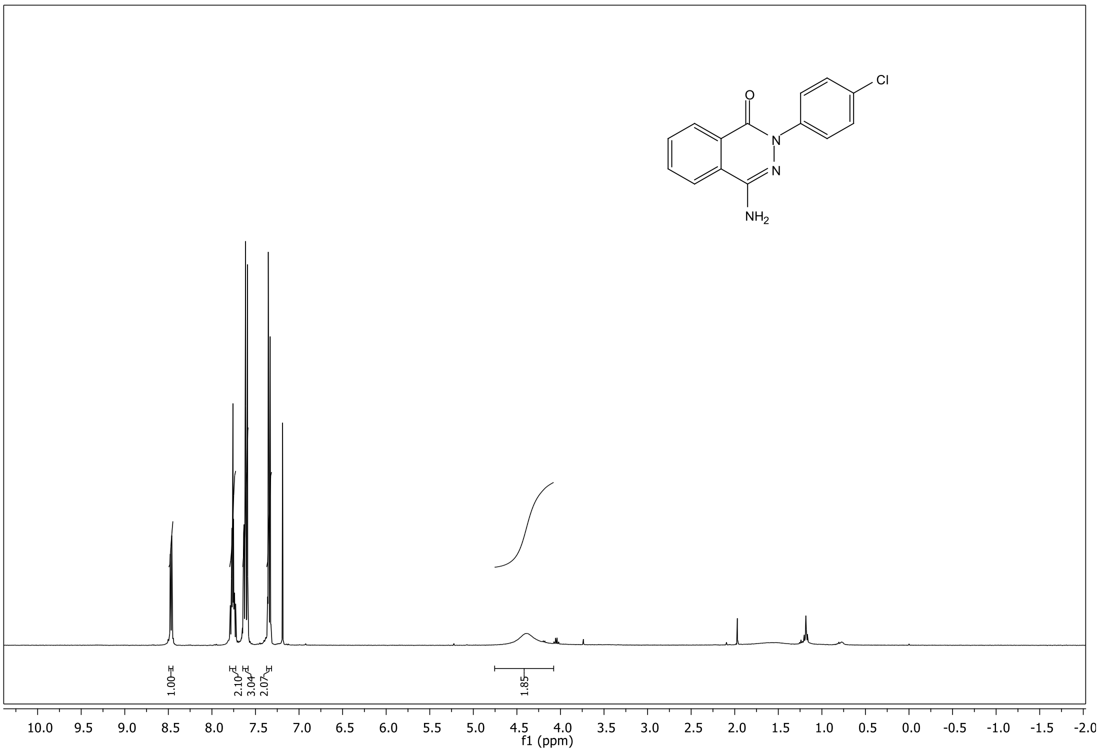


Figure 107: ^{1}H NMR Spectrum of Compound 74e

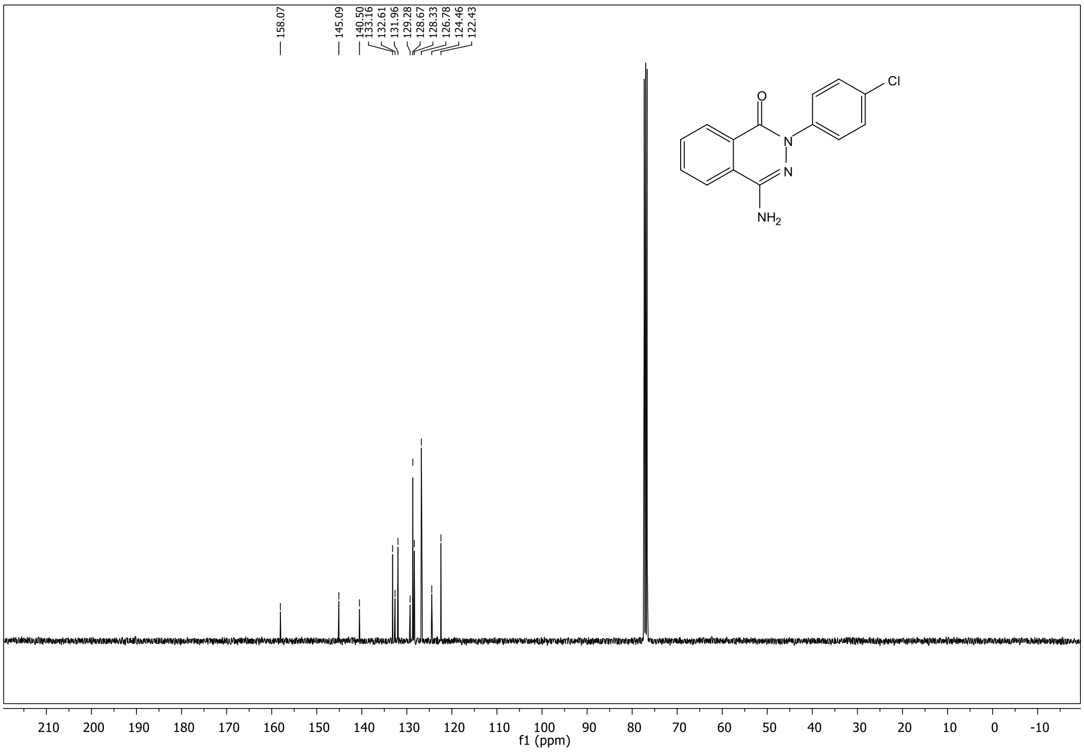


Figure 108: ^{13}C NMR Spectrum of Compound 74e

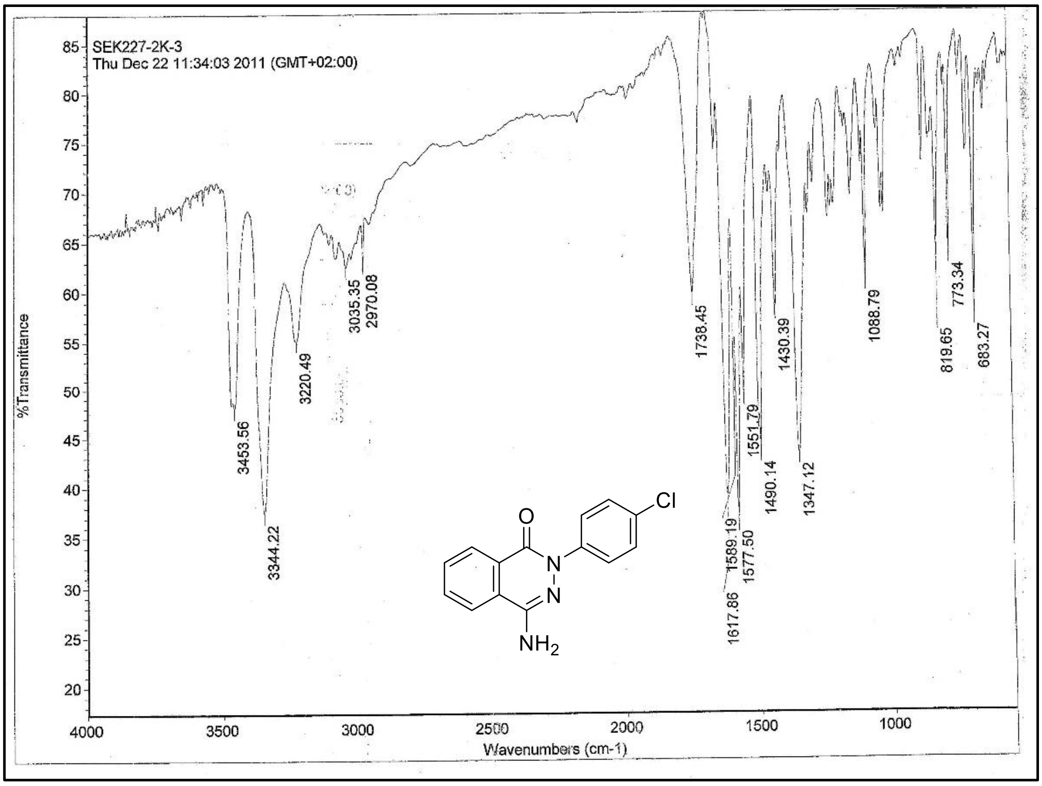


Figure 109: IR Spectrum of Compound 74e

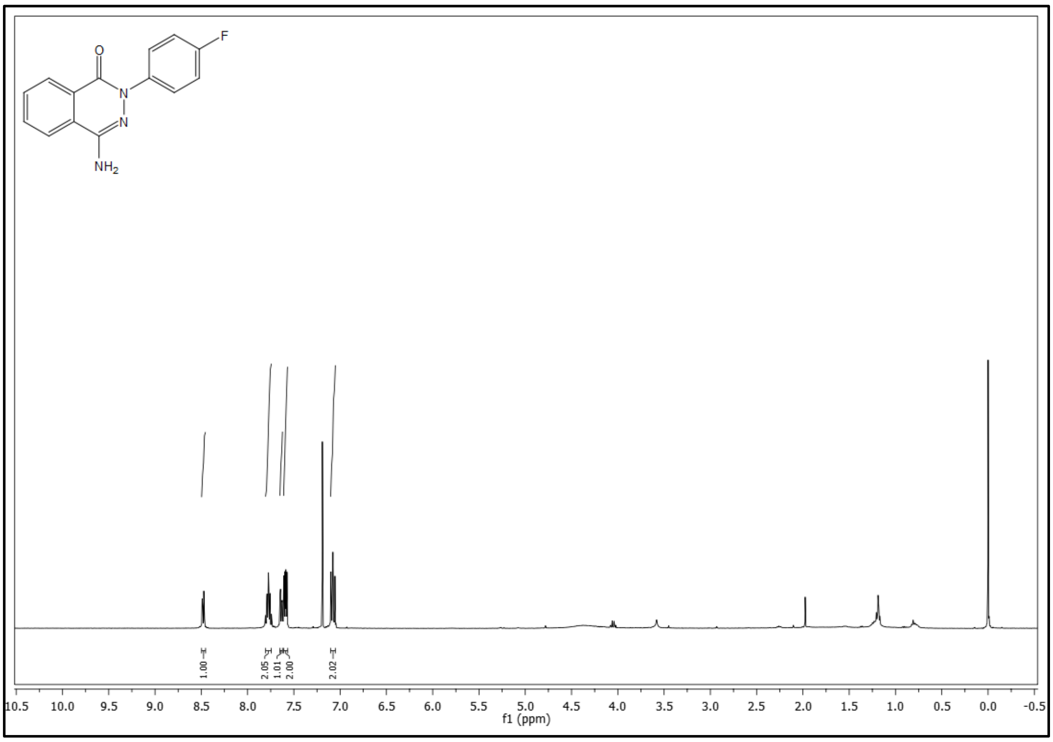


Figure 110: ^{1}H NMR Spectrum of Compound 74f

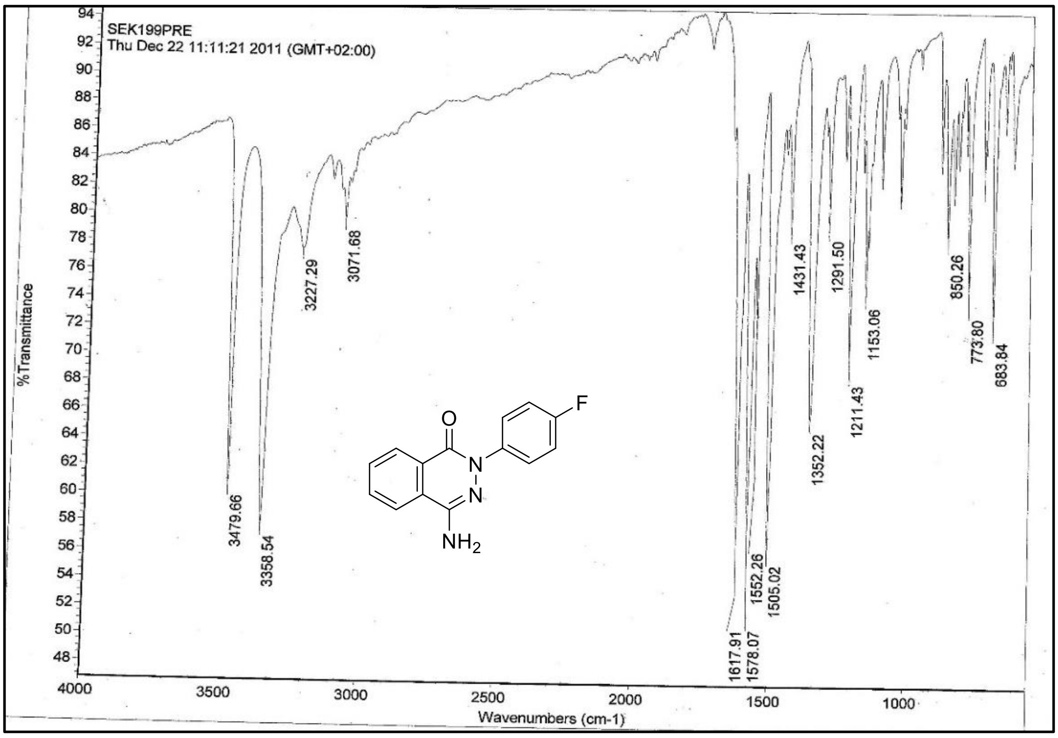


Figure 111: IR Spectrum of Compound 74f

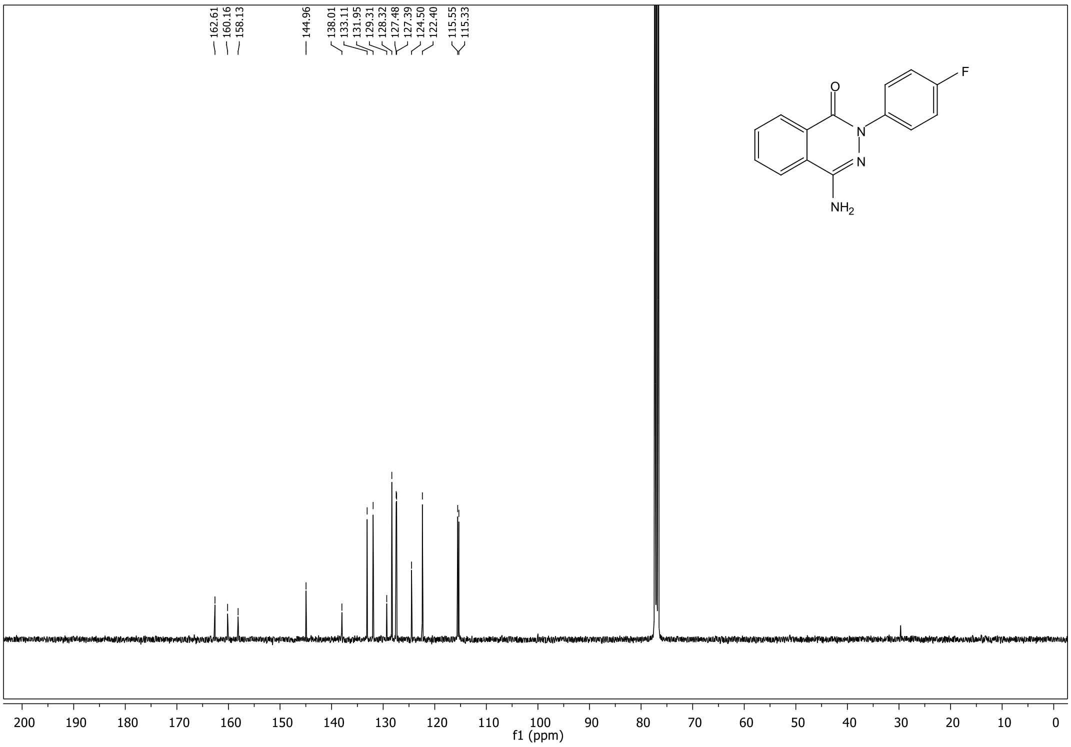


Figure 112: ^{13}C NMR Spectrum of Compound 74f

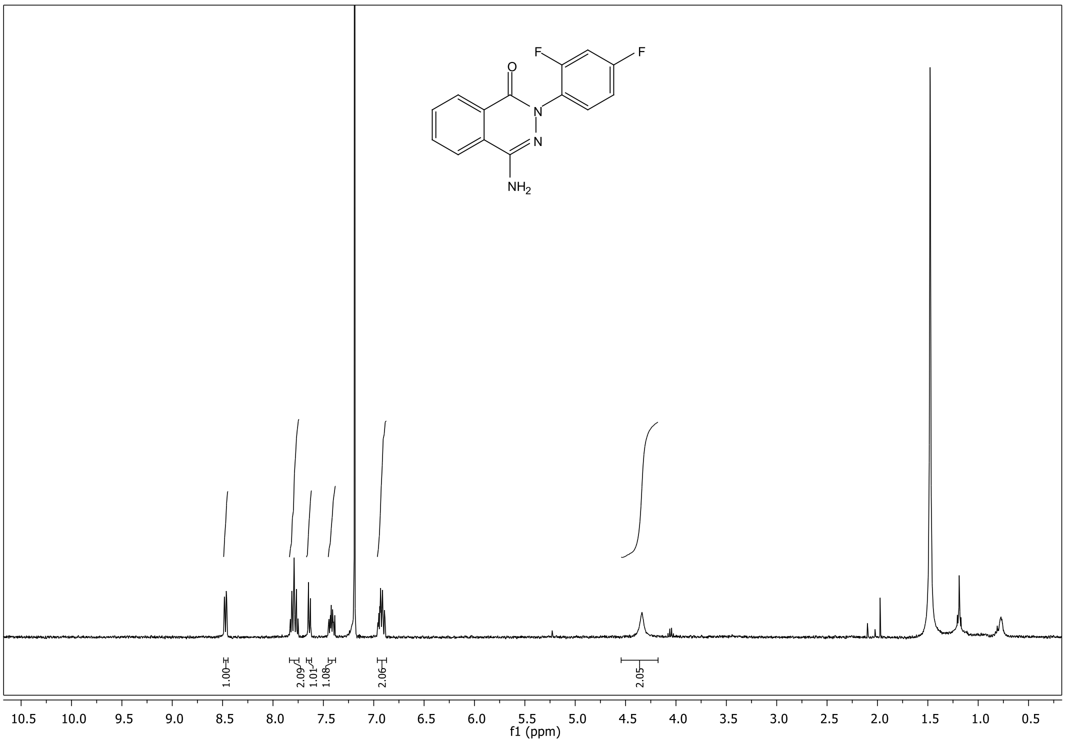


Figure 113: ^{1}H NMR Spectrum of Compound 74g

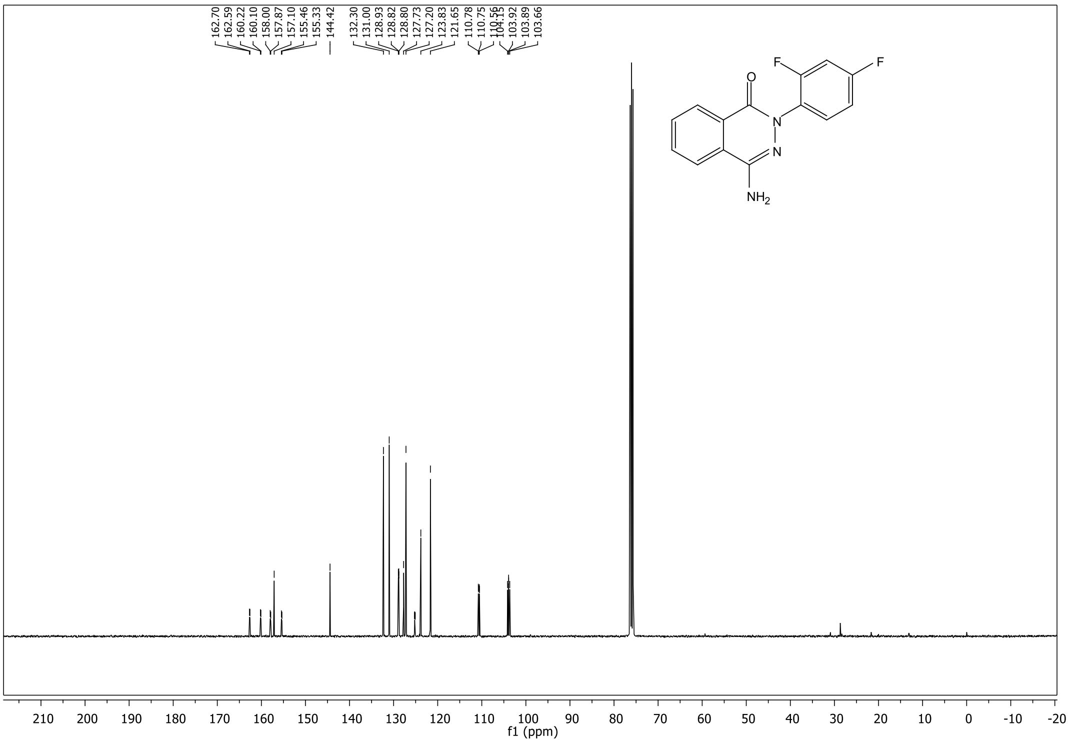


Figure 114: ^{13}C NMR Spectrum of Compound 74g

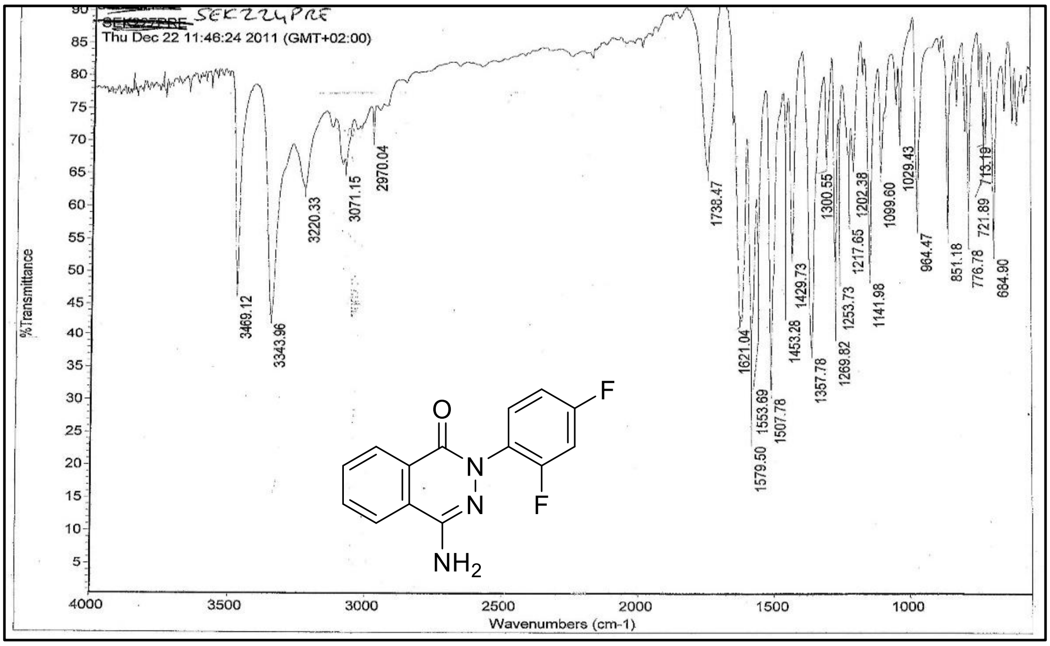


Figure 115: IR Spectrum of Compound 74g

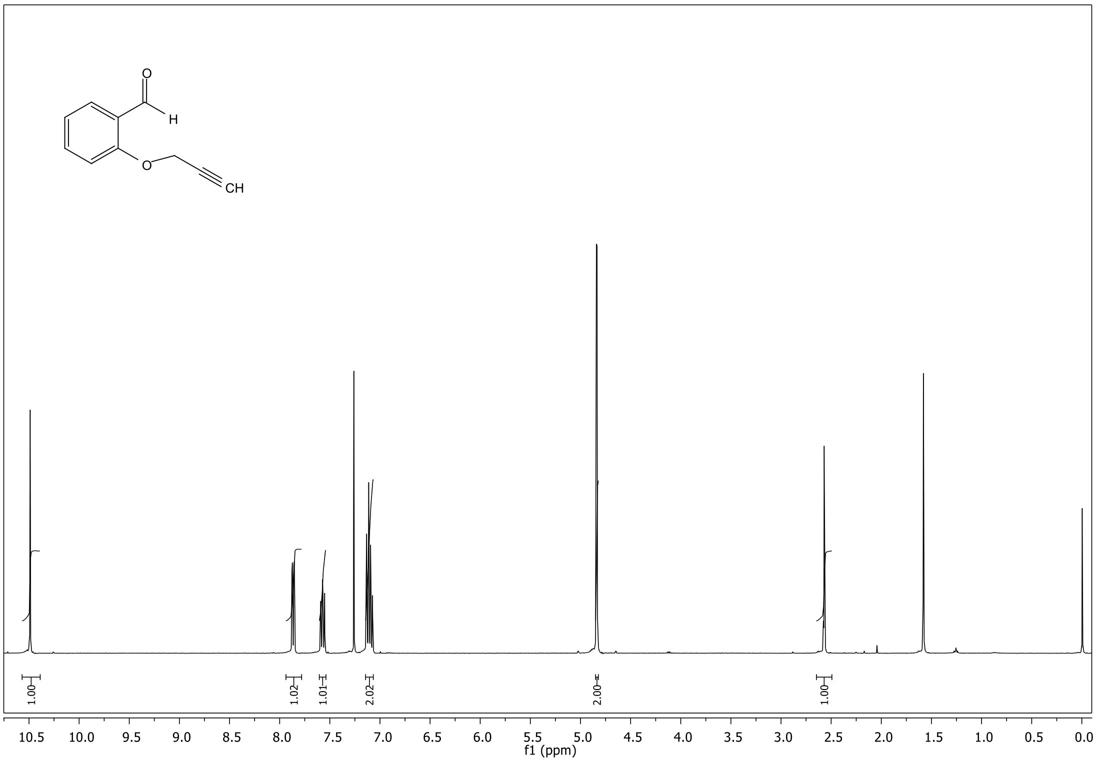


Figure 116: ^{1}H NMR Spectrum of Compound 149b

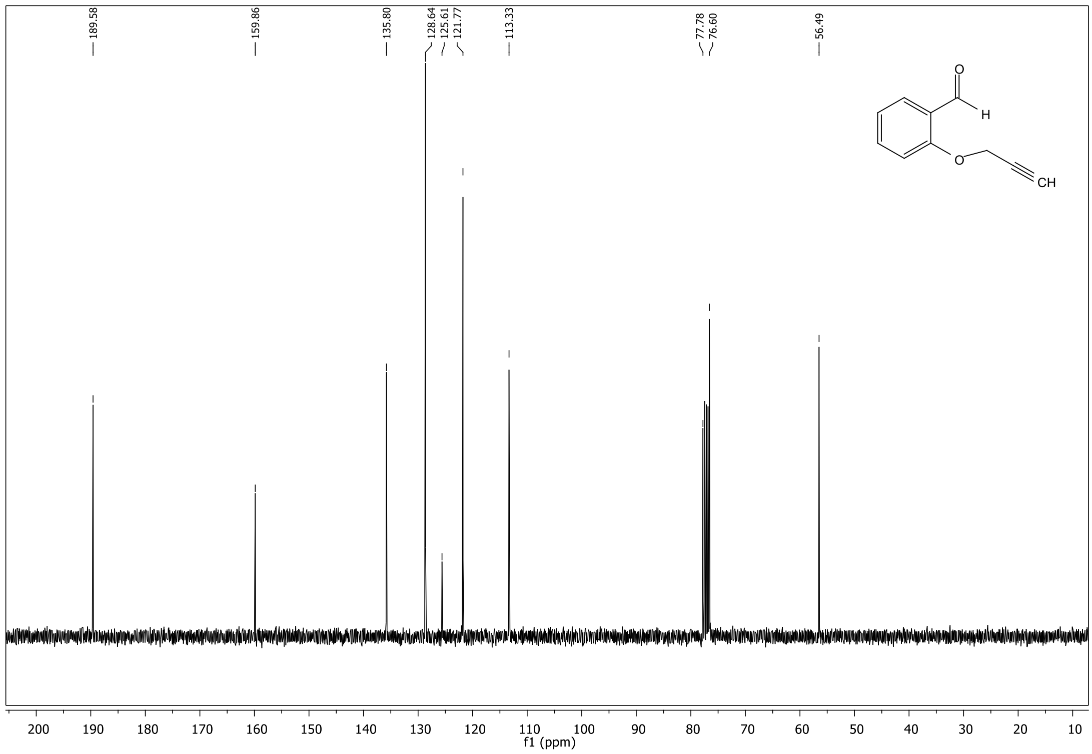


Figure 117: ^{13}C NMR Spectrum of Compound 149b

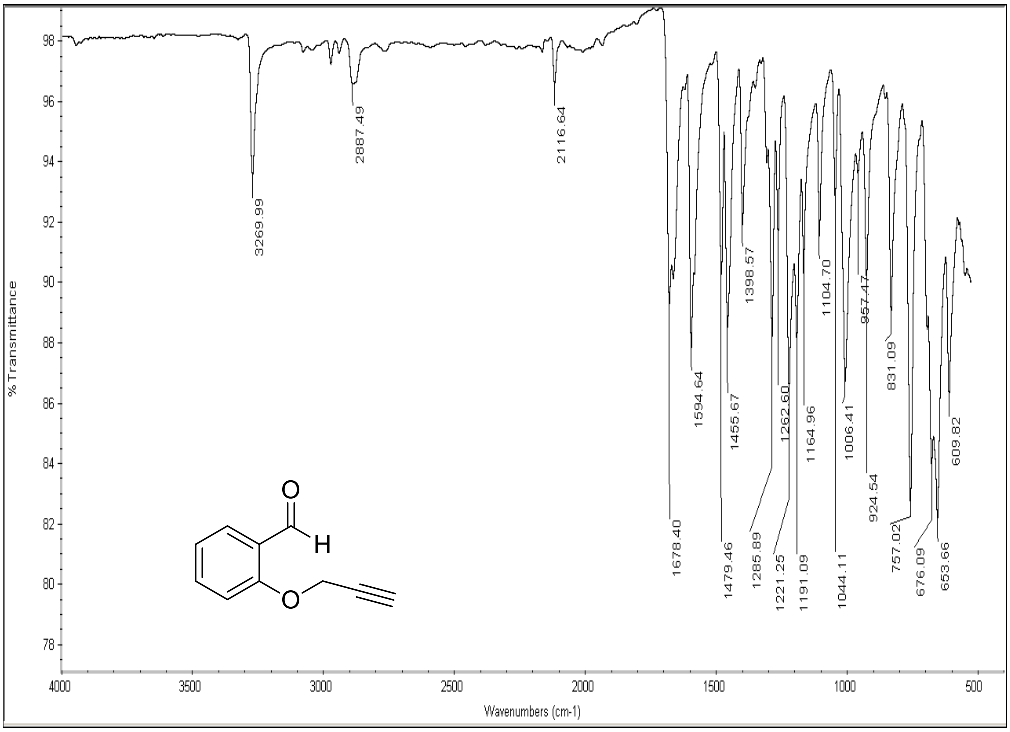


Figure 118: IR Spectrum of Compound 149b

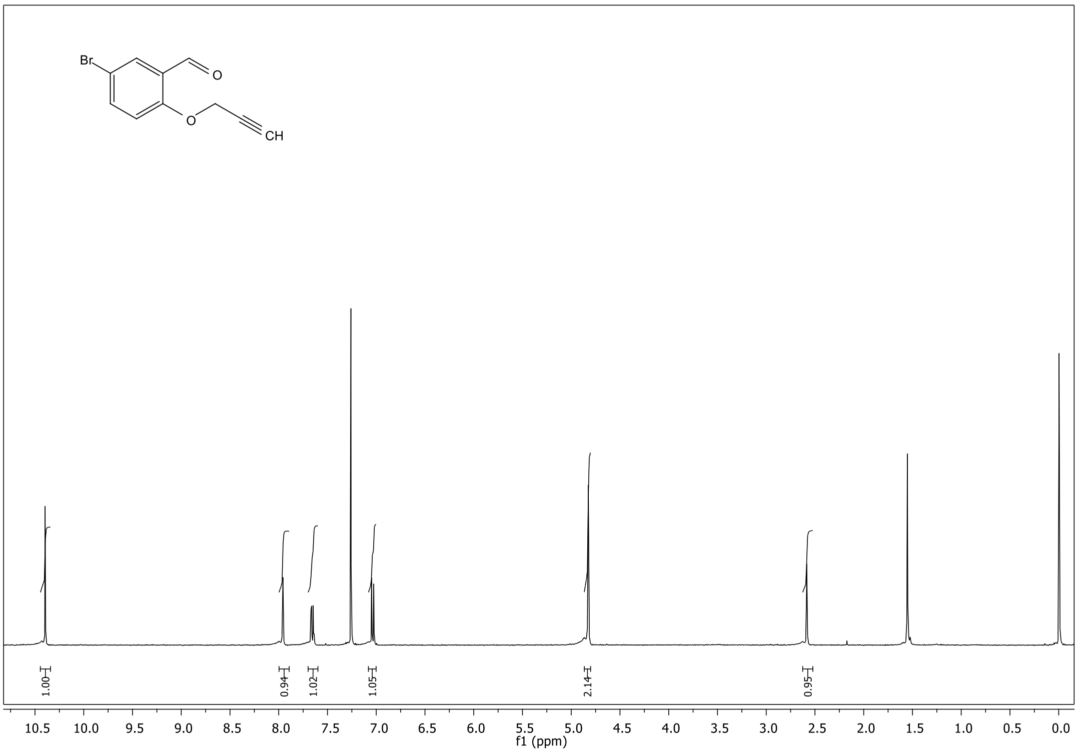


Figure 119: ^{1}H NMR Spectrum of Compound 251

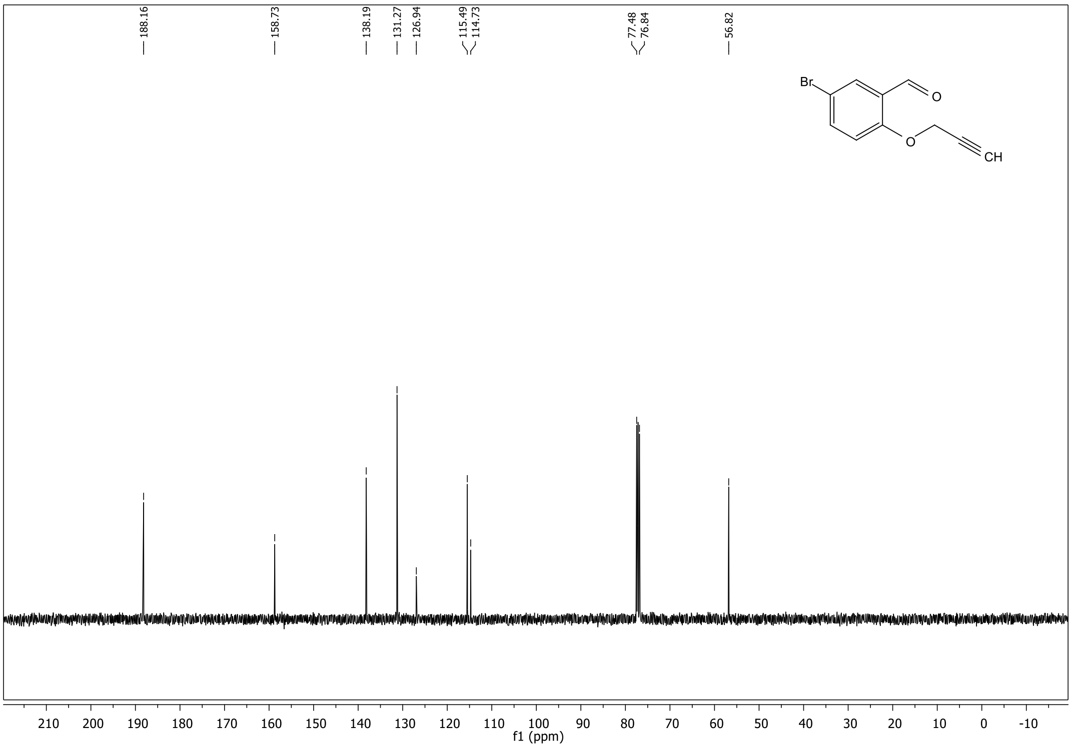


Figure 120: ^{13}C NMR Spectrum of Compound 251

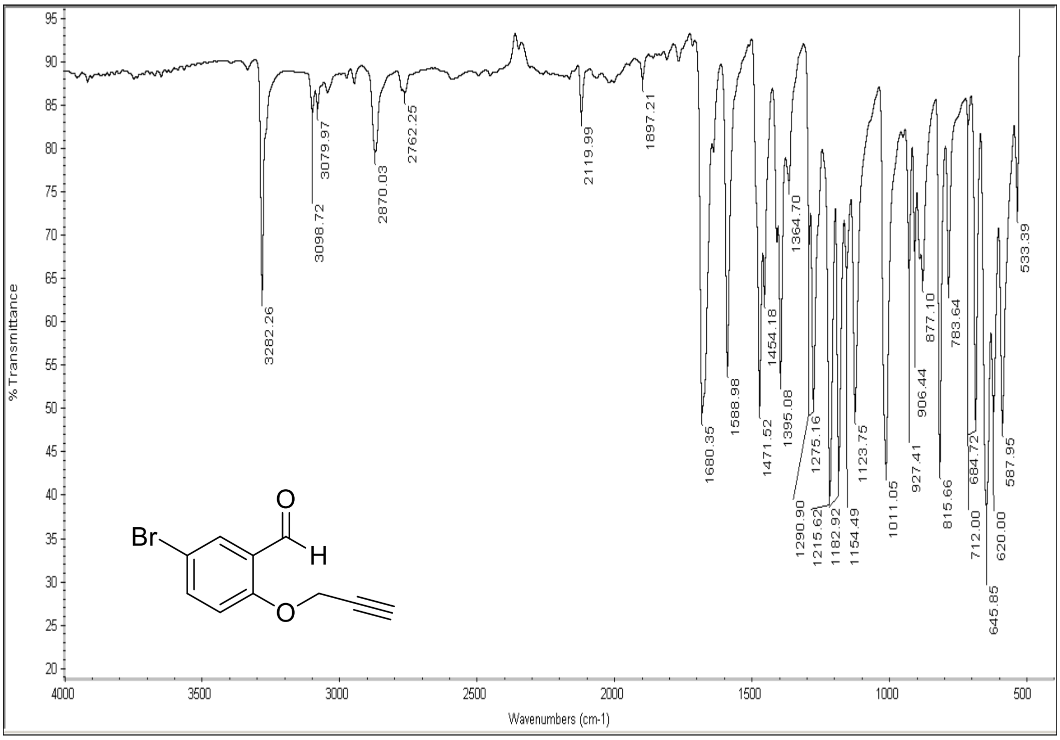


Figure 121: IR Spectrum of Compound 251

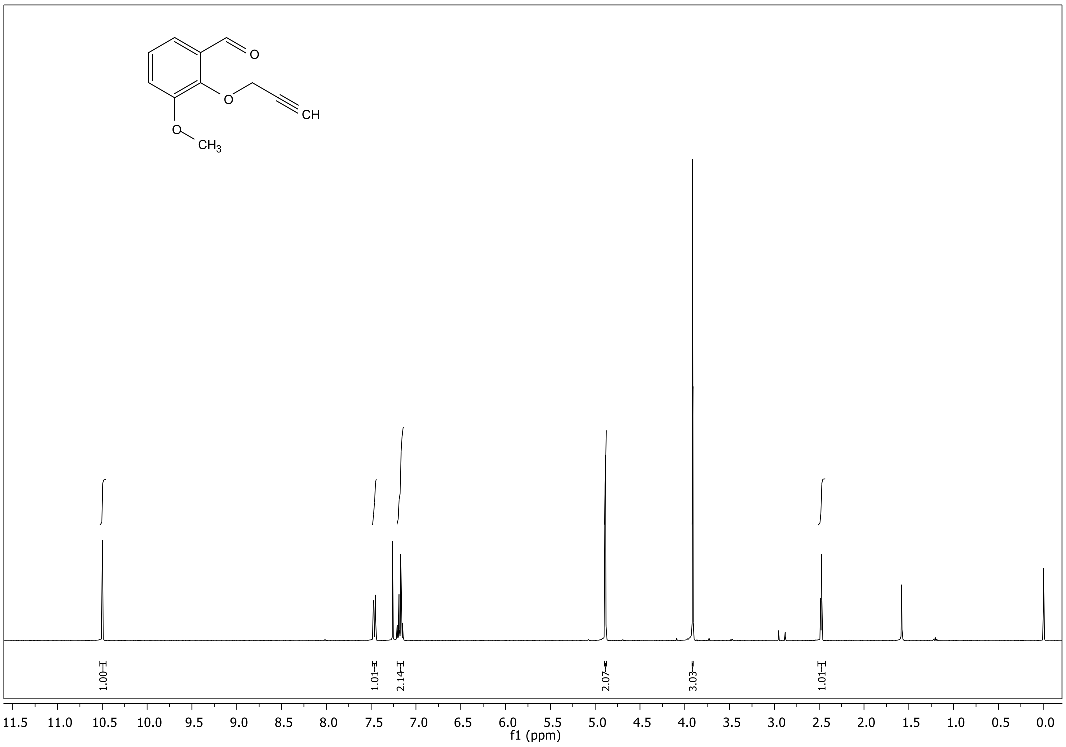


Figure 122: ^{1}H NMR Spectrum of Compound 252

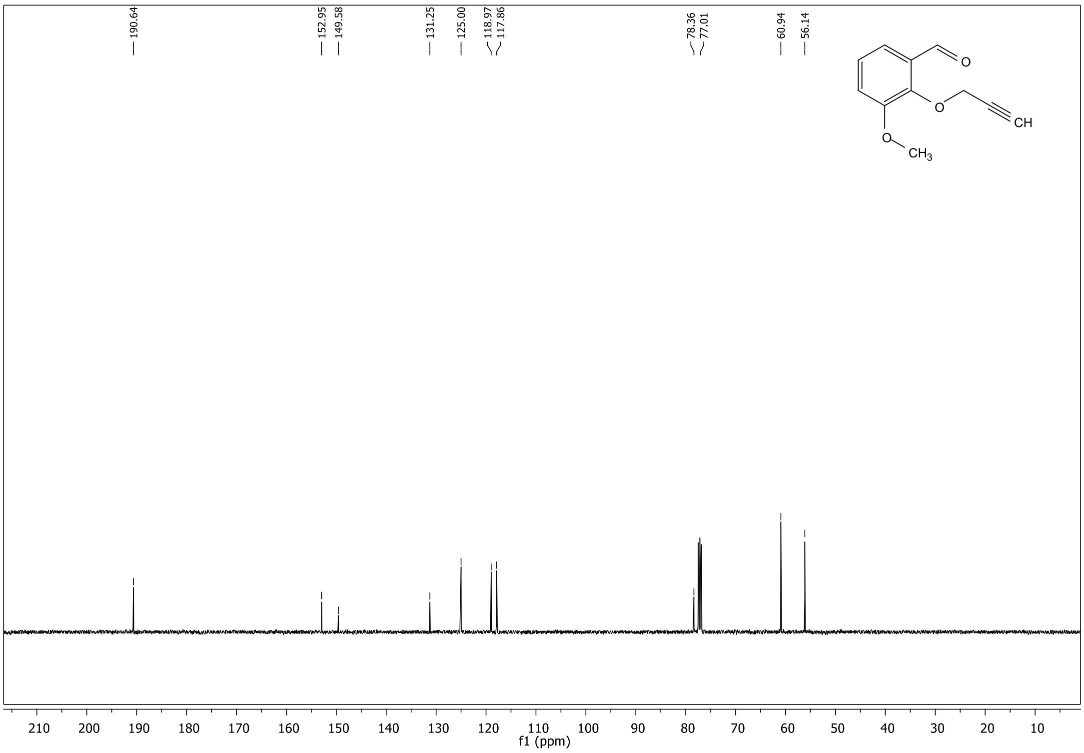


Figure 123: ^{13}C NMR Spectrum of Compound 252

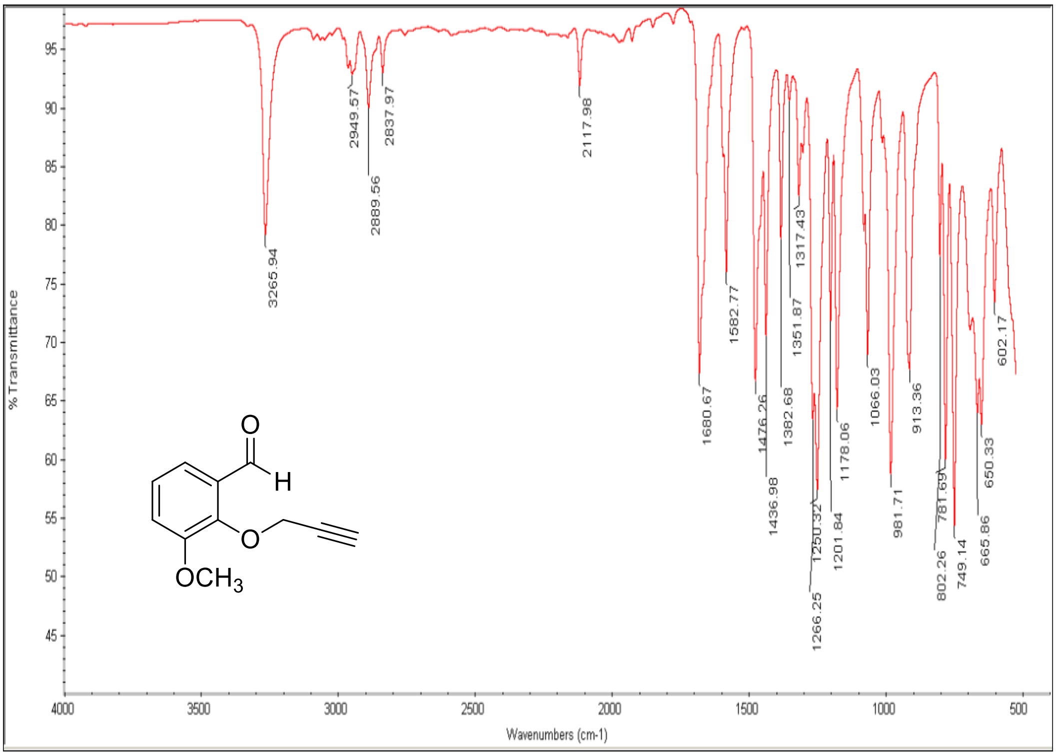


Figure 124: IR Spectrum of Compound 252

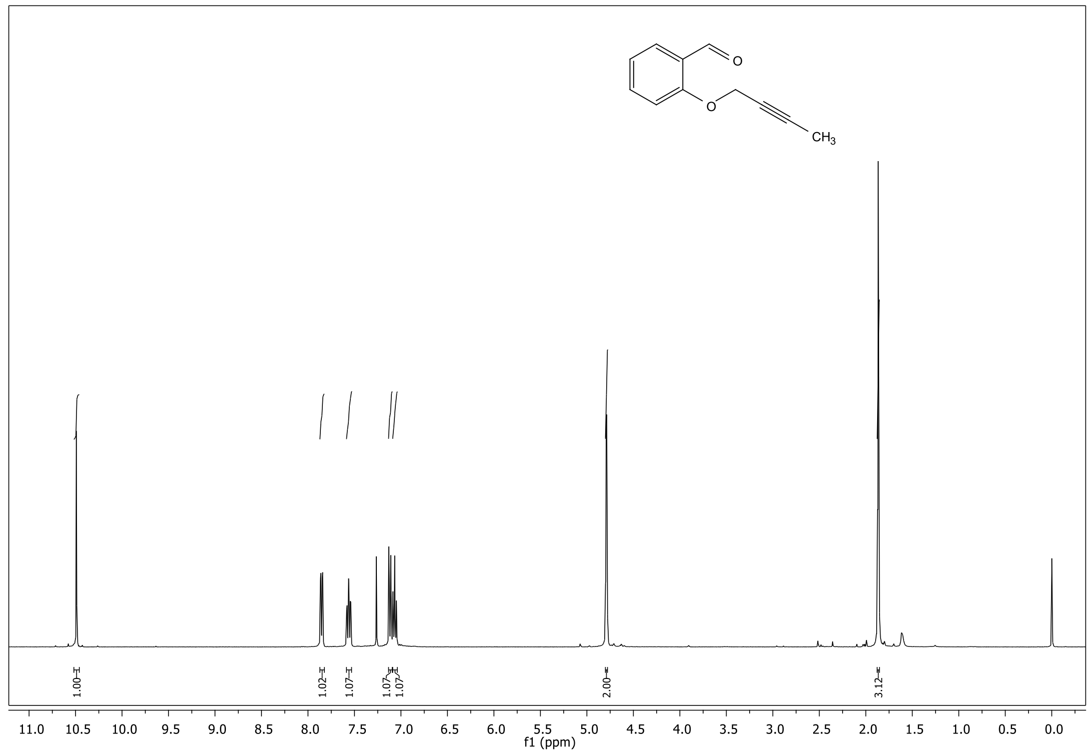


Figure 125: ^{1}H NMR Spectrum of Compound 254

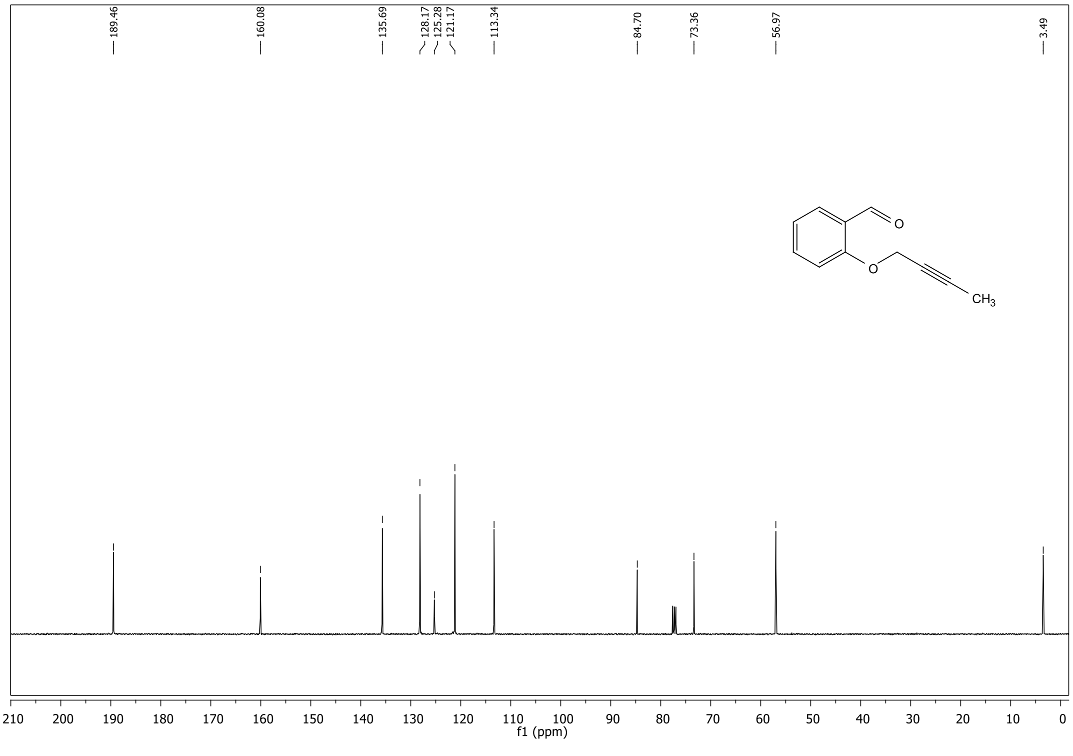


Figure 126: ^{13}C NMR Spectrum of Compound 254

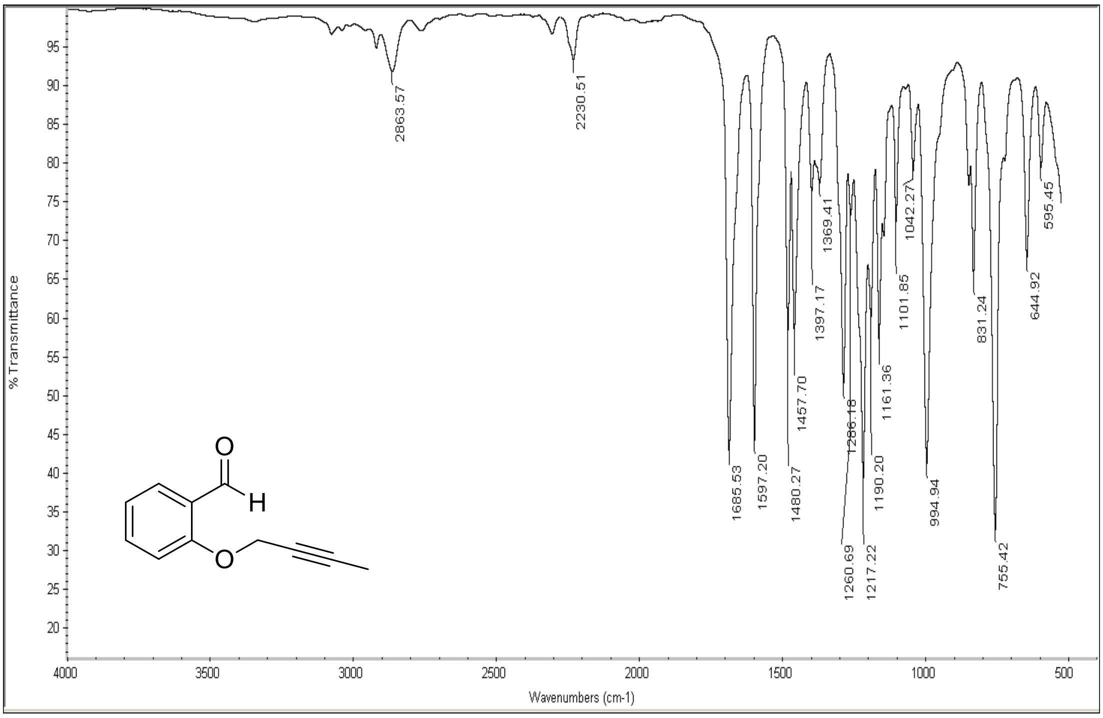


Figure 127: IR Spectrum of Compound 254

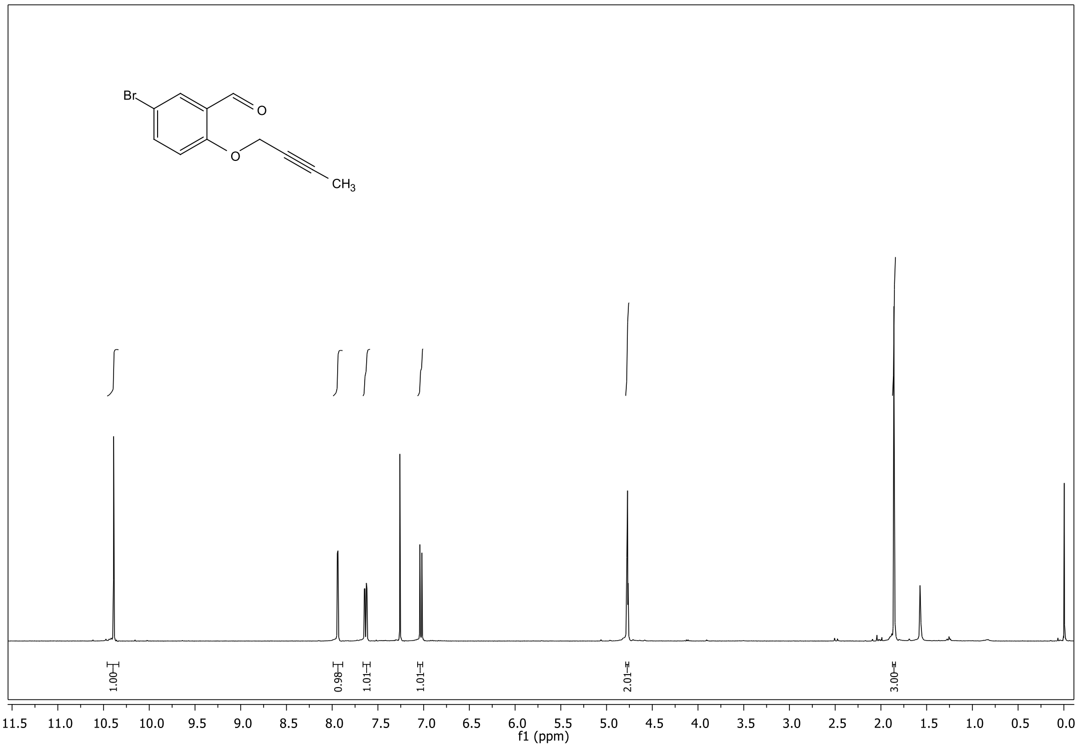


Figure 128: ^{1}H NMR Spectrum of Compound 255

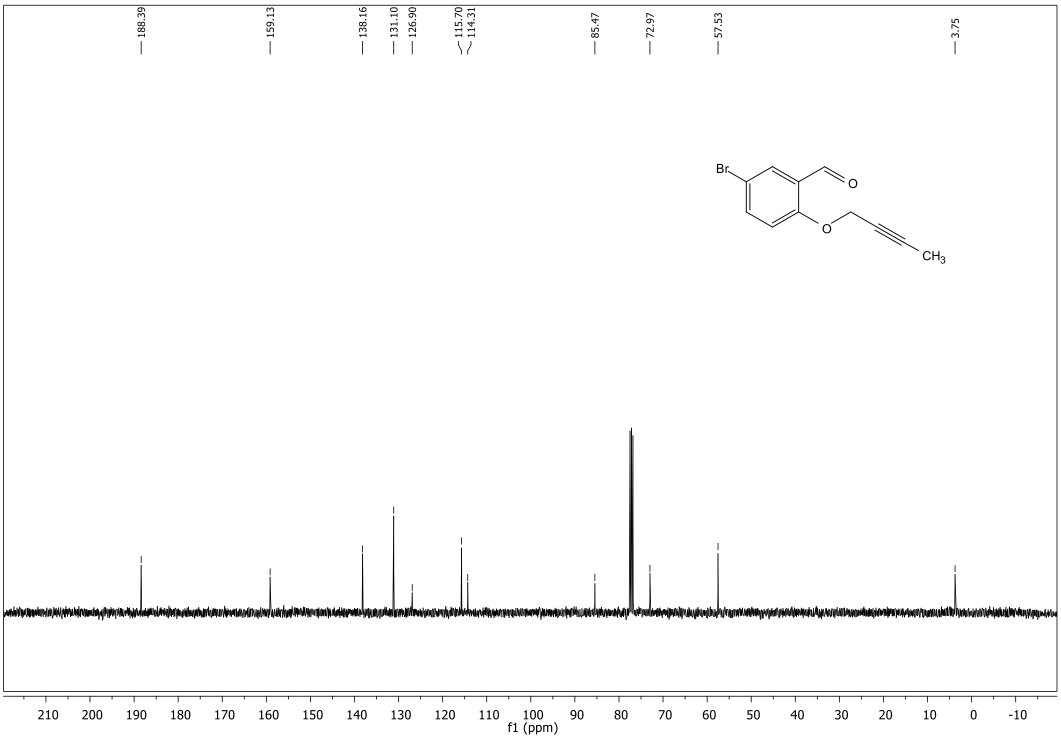


Figure 129: ^{13}C NMR Spectrum of Compound 255

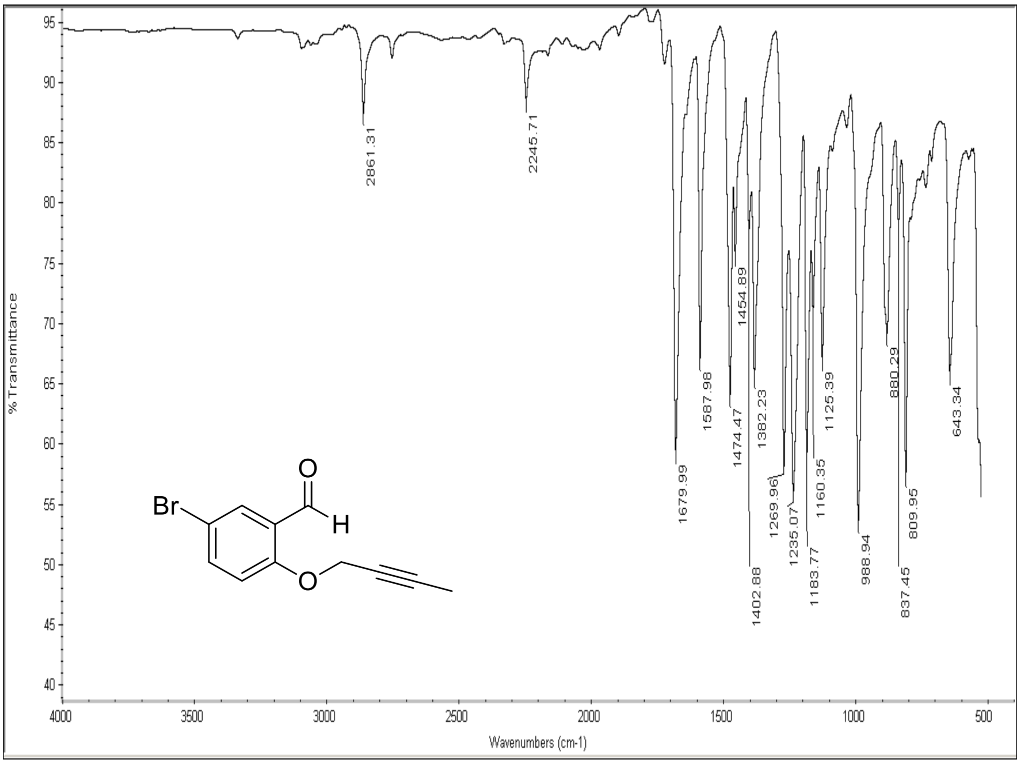


Figure 130 : IR Spectrum of Compound 255

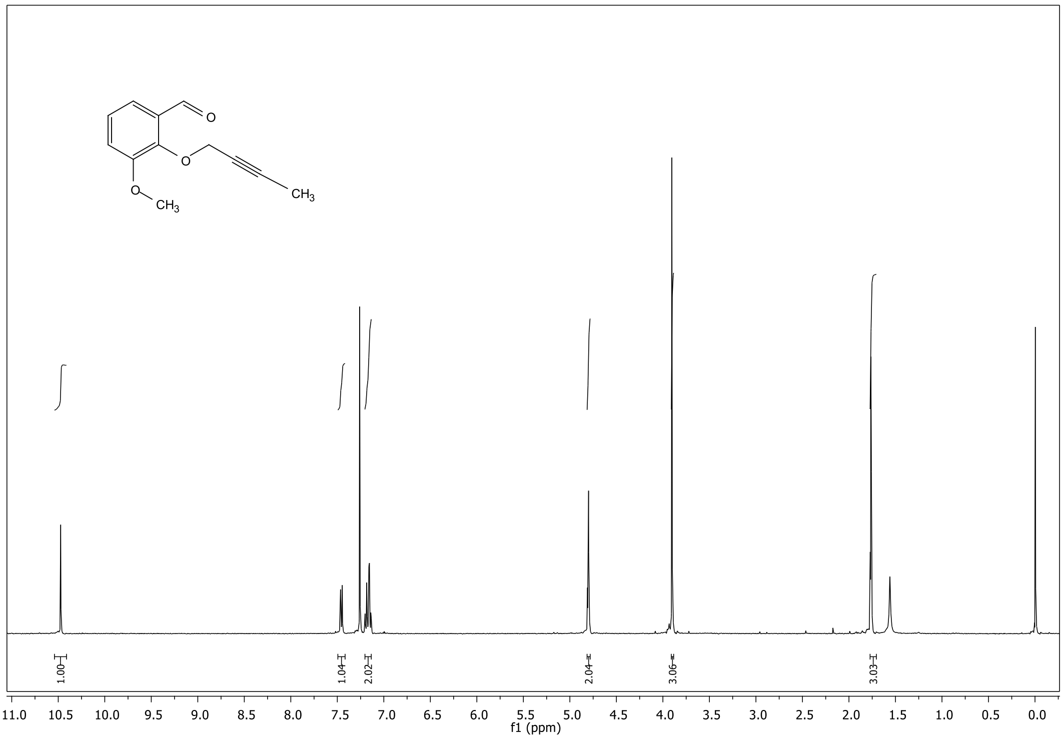


Figure 131: ^{1}H NMR Spectrum of Compound 256

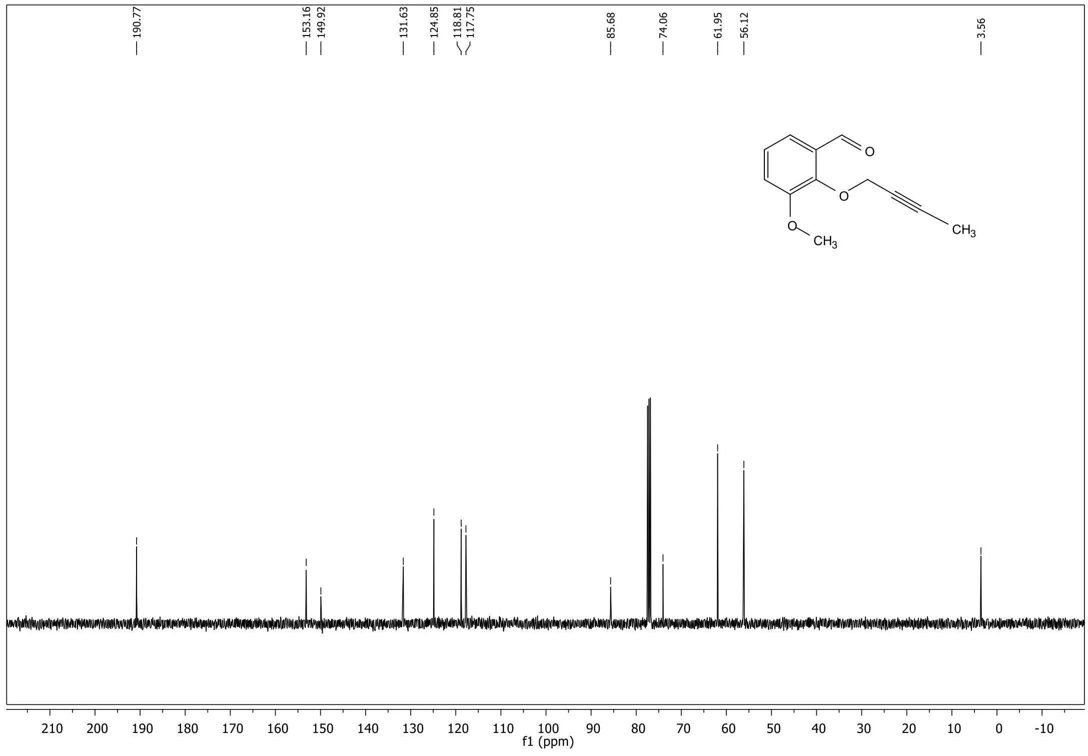


Figure 132: ^{13}C NMR Spectrum of Compound 256

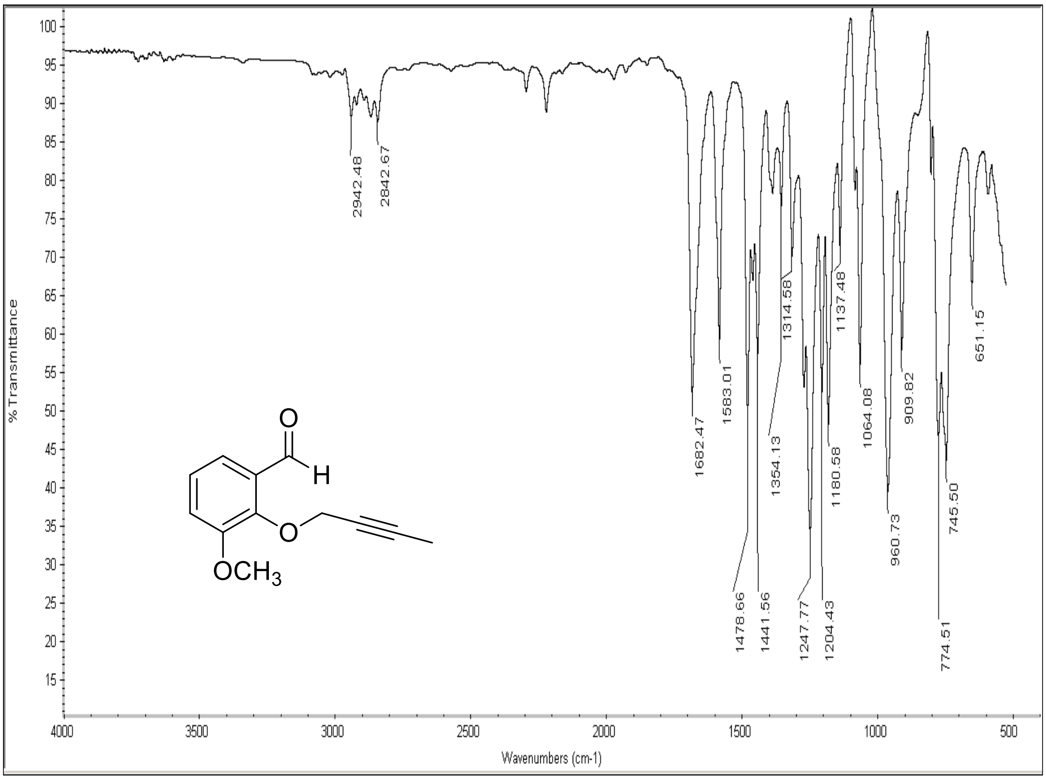


Figure 133: IR Spectrum of Compound 256

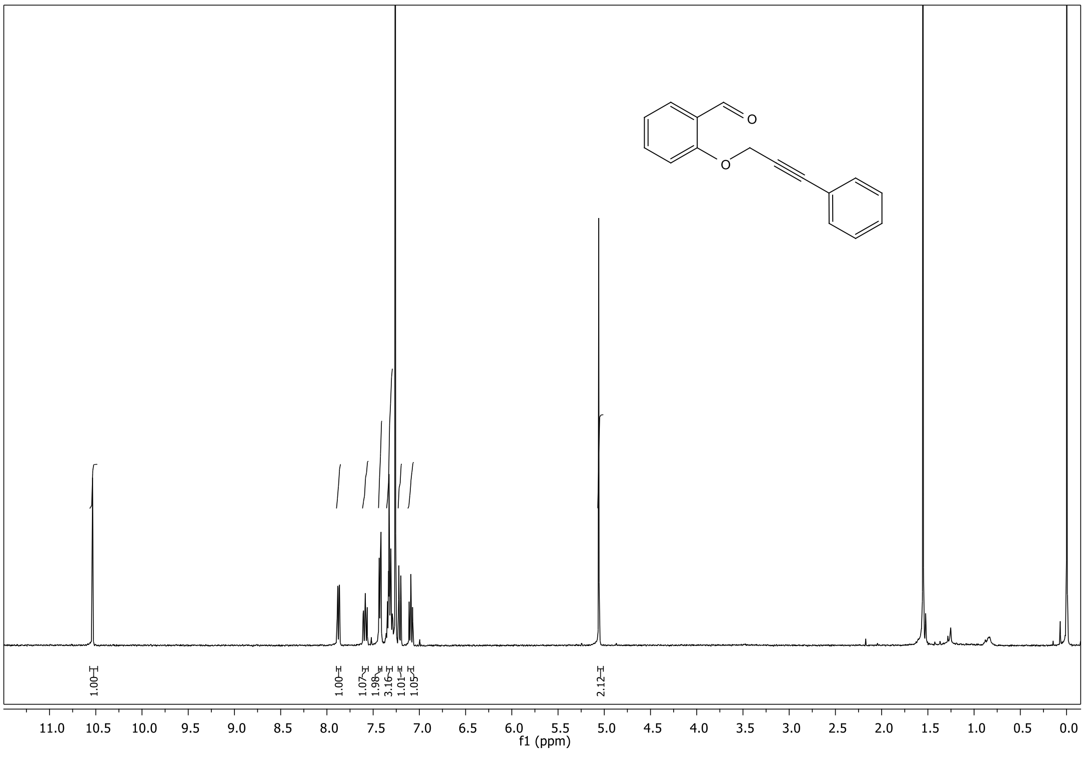


Figure 134: ^{1}H NMR Spectrum of Compound 257

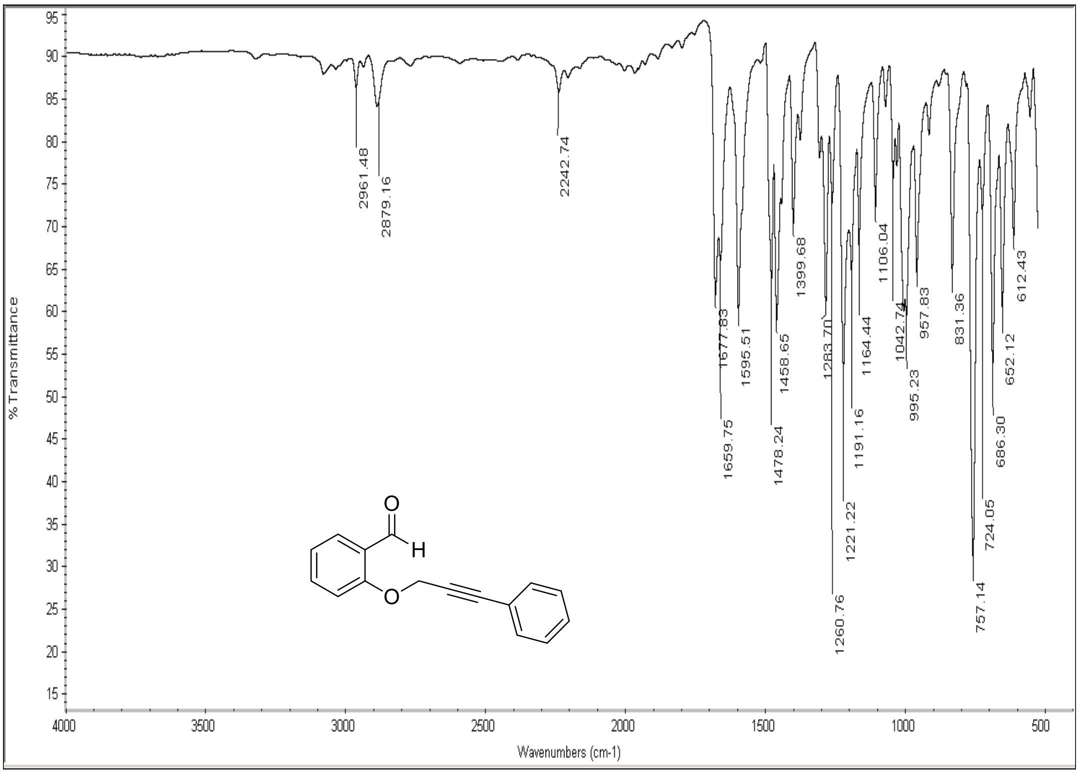


Figure 135: ^{13}C NMR Spectrum of Compound 257

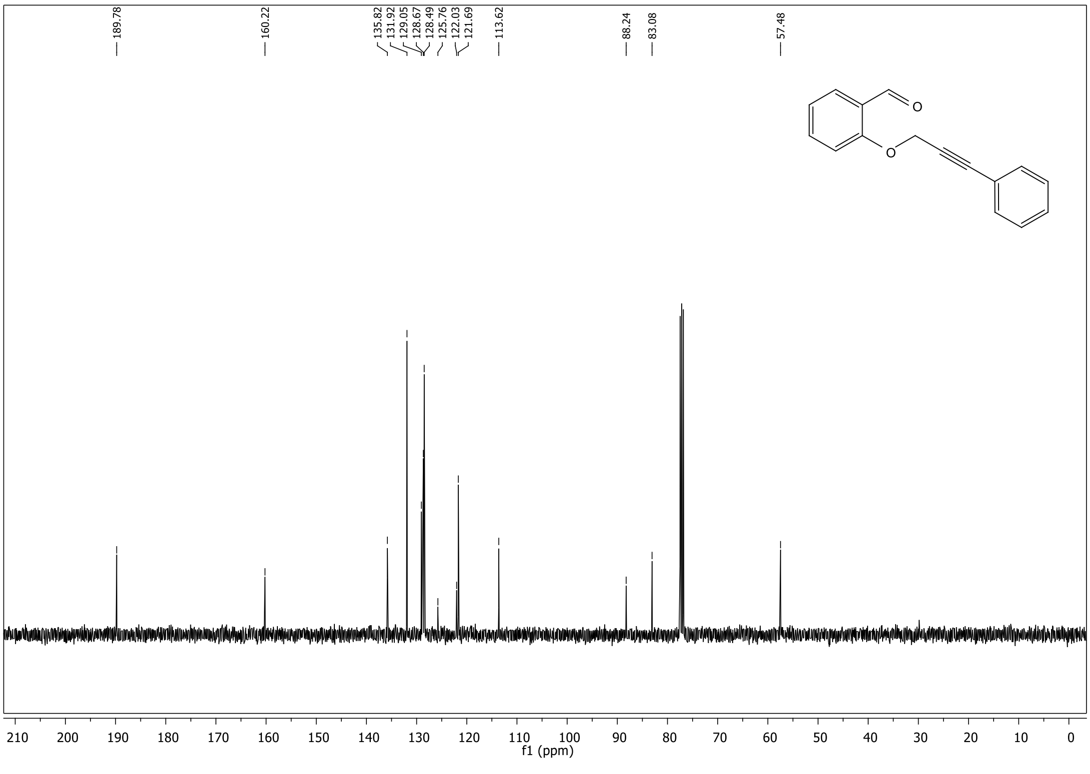


Figure 136: IR Spectrum of Compound 257

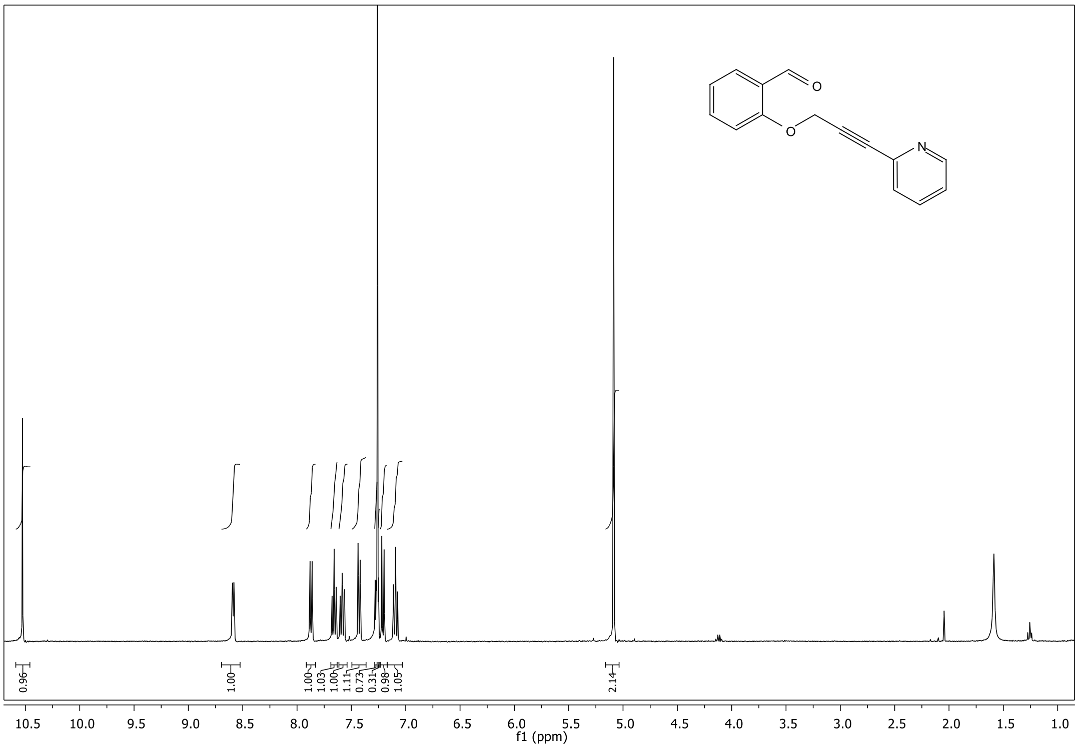


Figure 137: ^{1}H NMR Spectrum of Compound 258

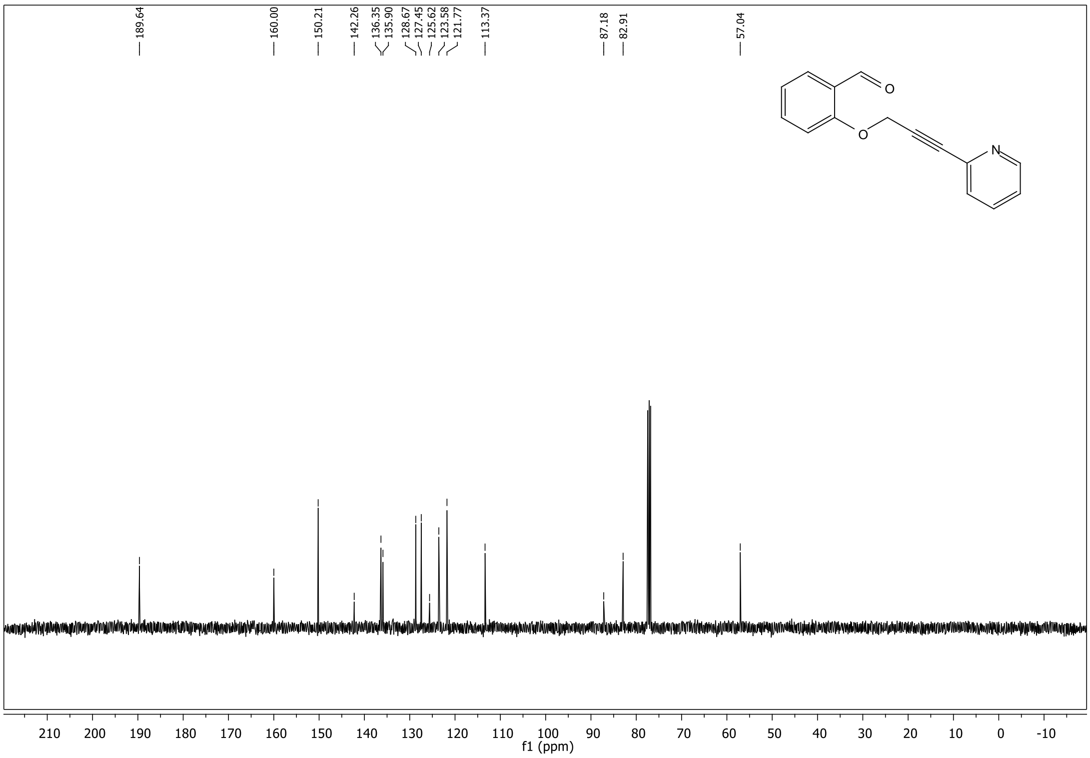


Figure 138: ^{13}C NMR Spectrum of Compound 258

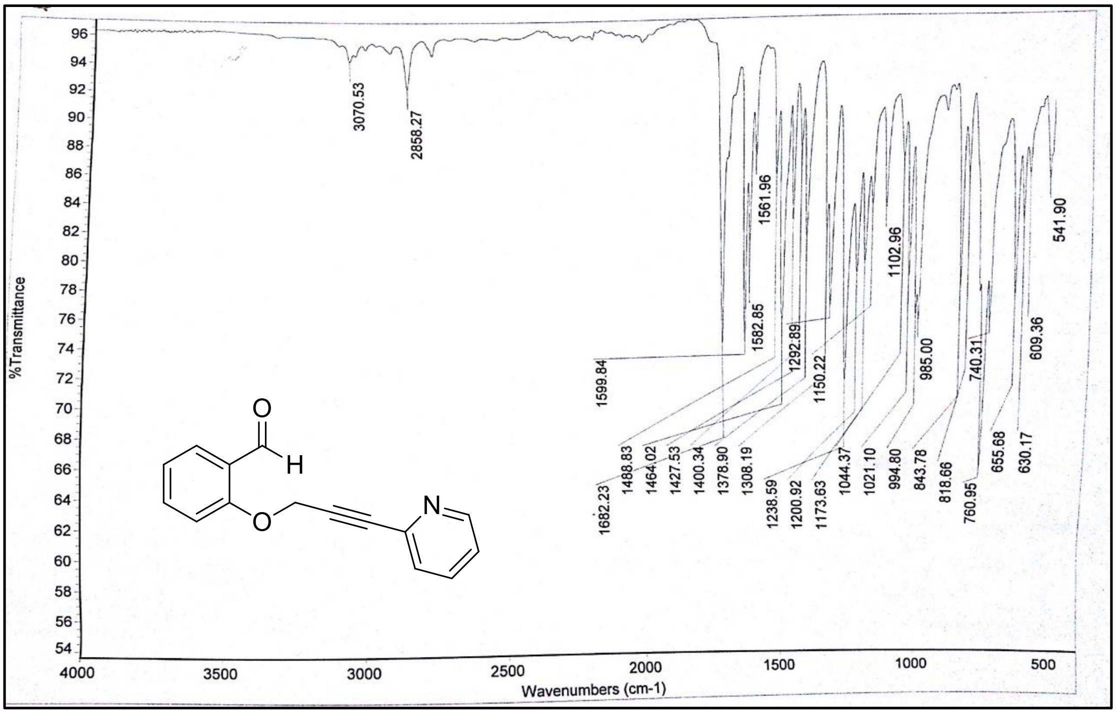


Figure 139: IR Spectrum of Compound 258

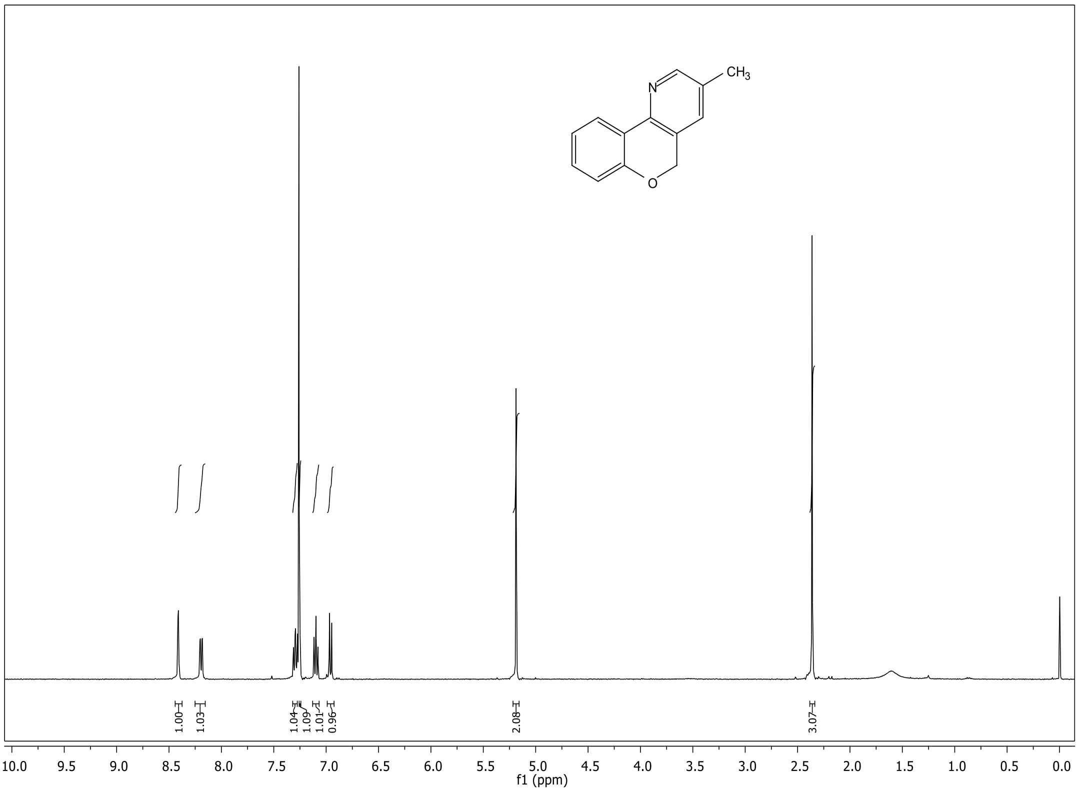


Figure 140: ^{1}H NMR Spectrum of Compound 259

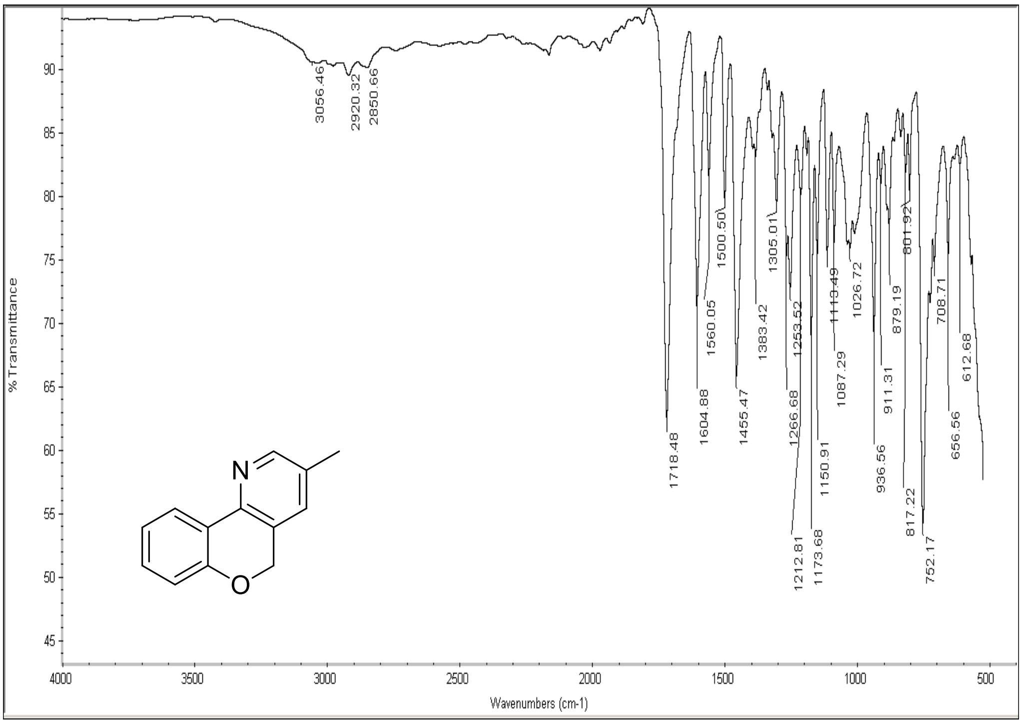


Figure 141: IR Spectrum of Compound 259

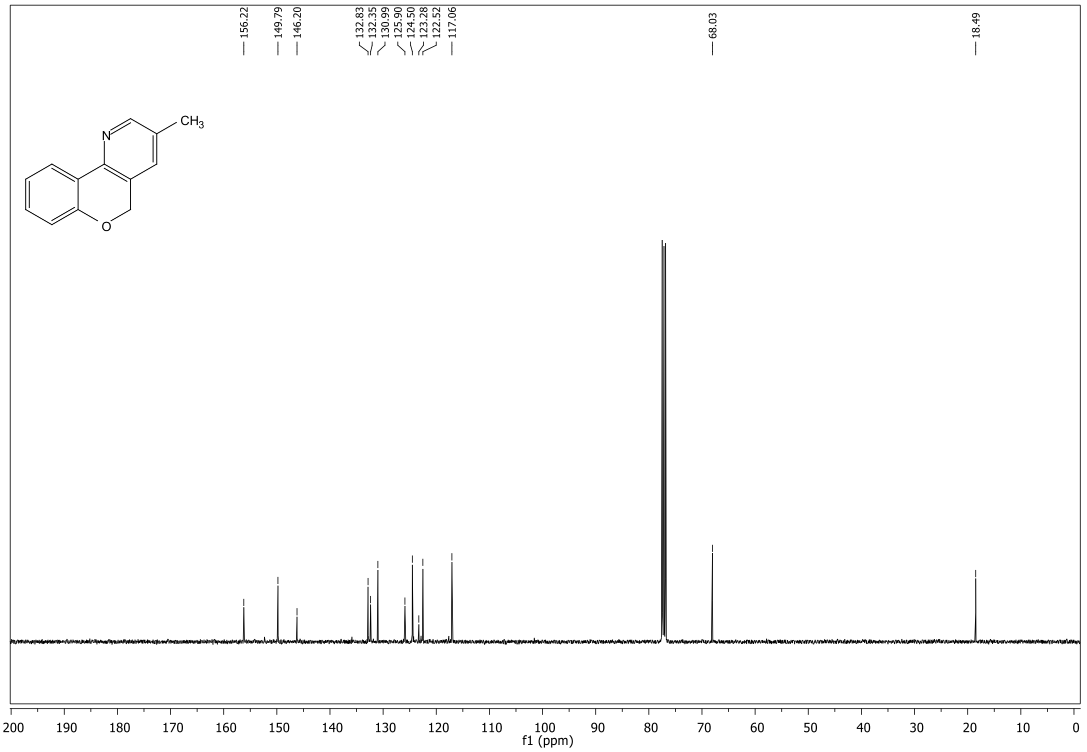


Figure 142: ^{13}C NMR Spectrum of Compound 259

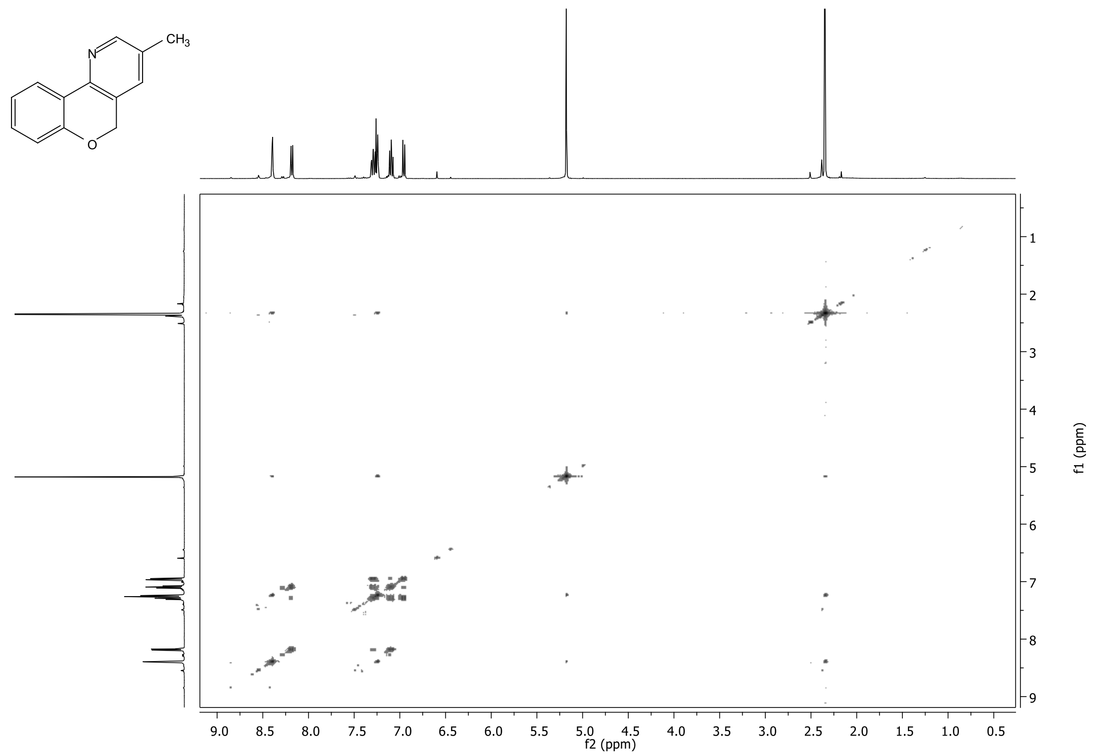


Figure 143: COSY Spectrum of Compound 259

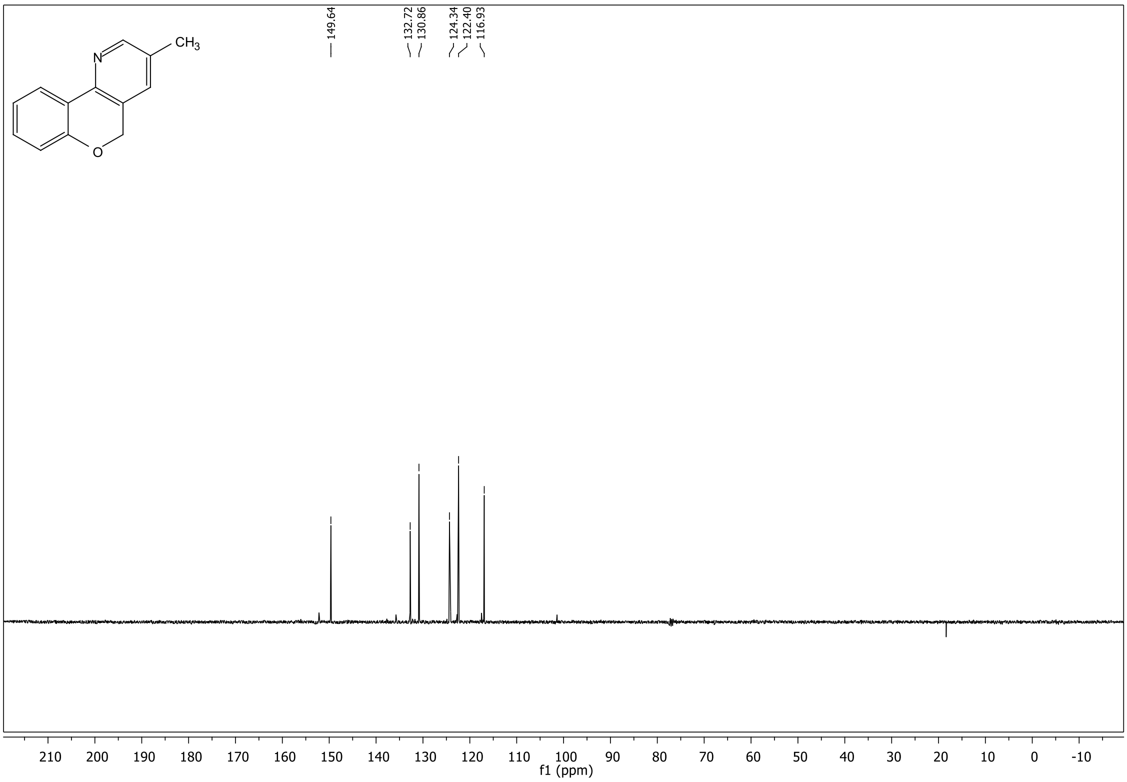


Figure 144: DEPT 90 Spectrum of Compound 259

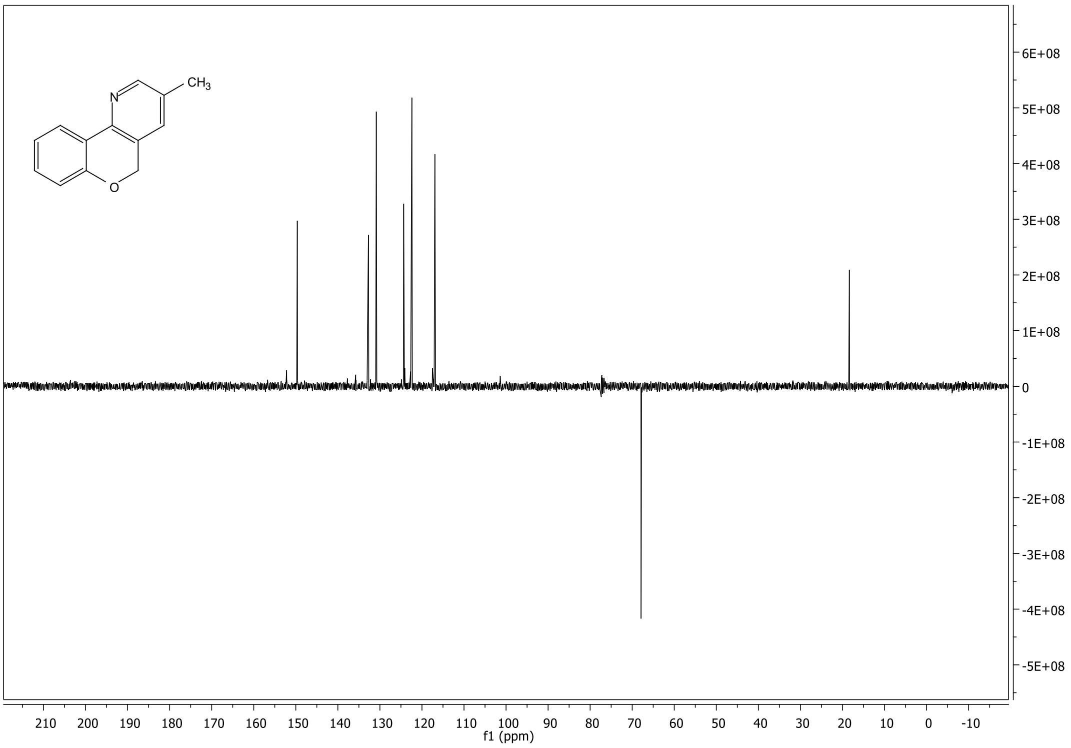


Figure 145: DEPT 135 Spectrum of Compound 259

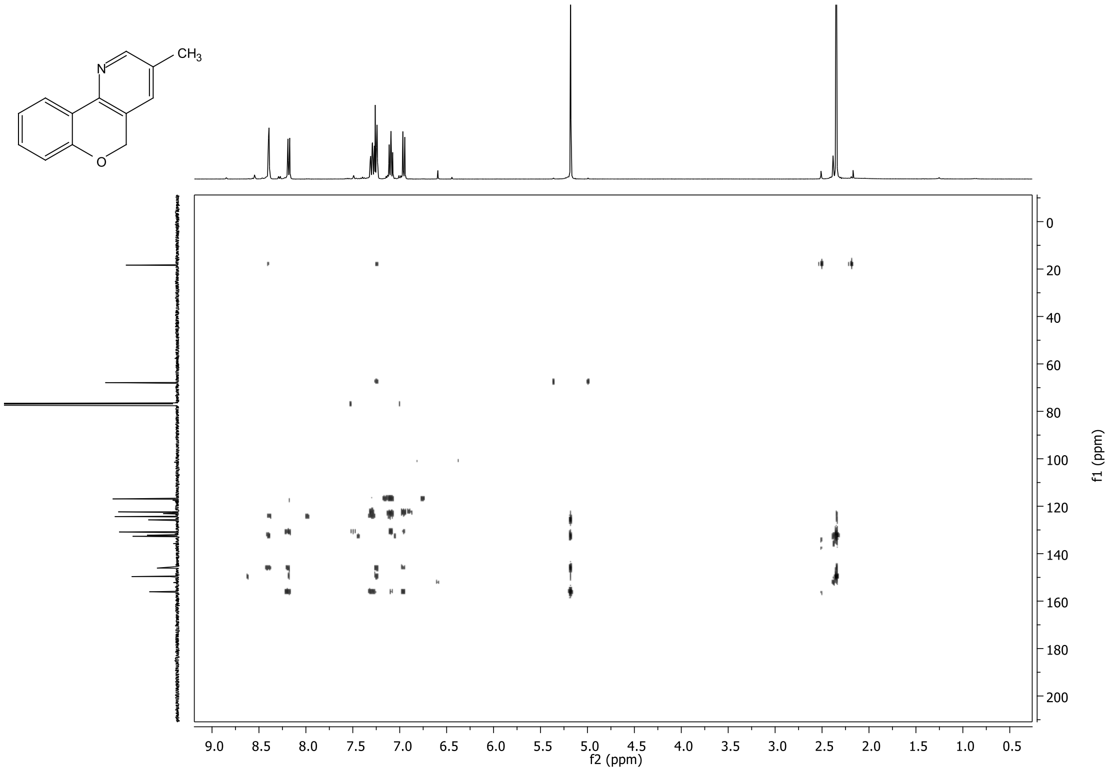


Figure 146: HMBC Spectrum of Compound 259

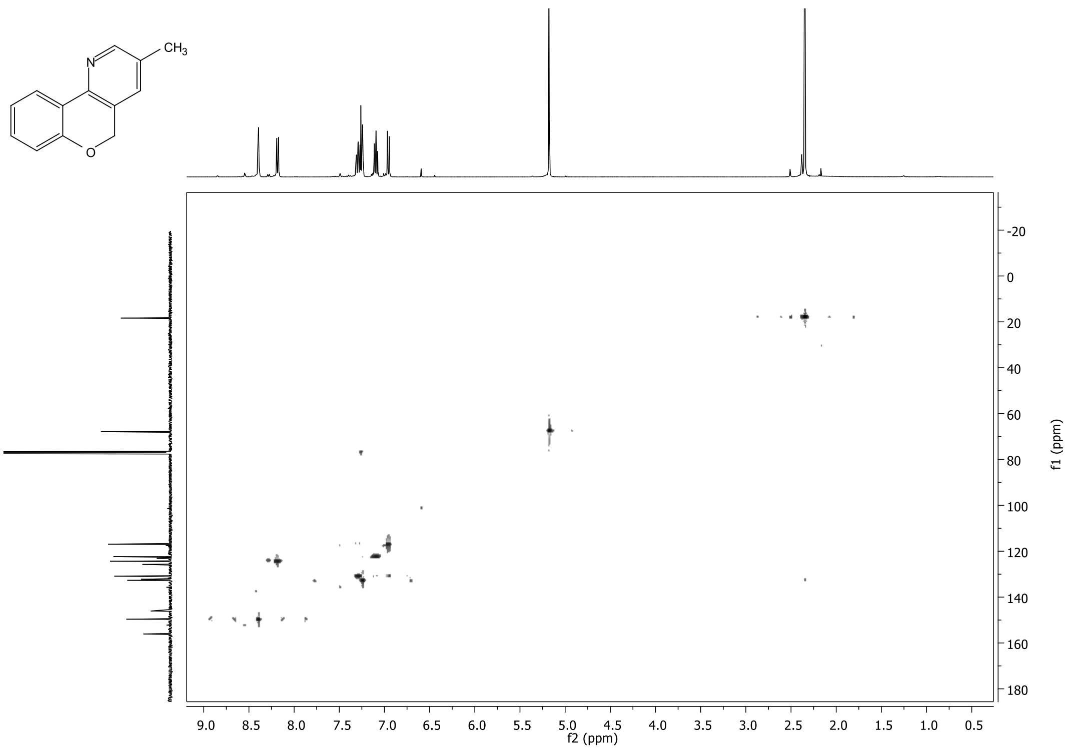


Figure 147: HSQC Spectrum of Compound 259

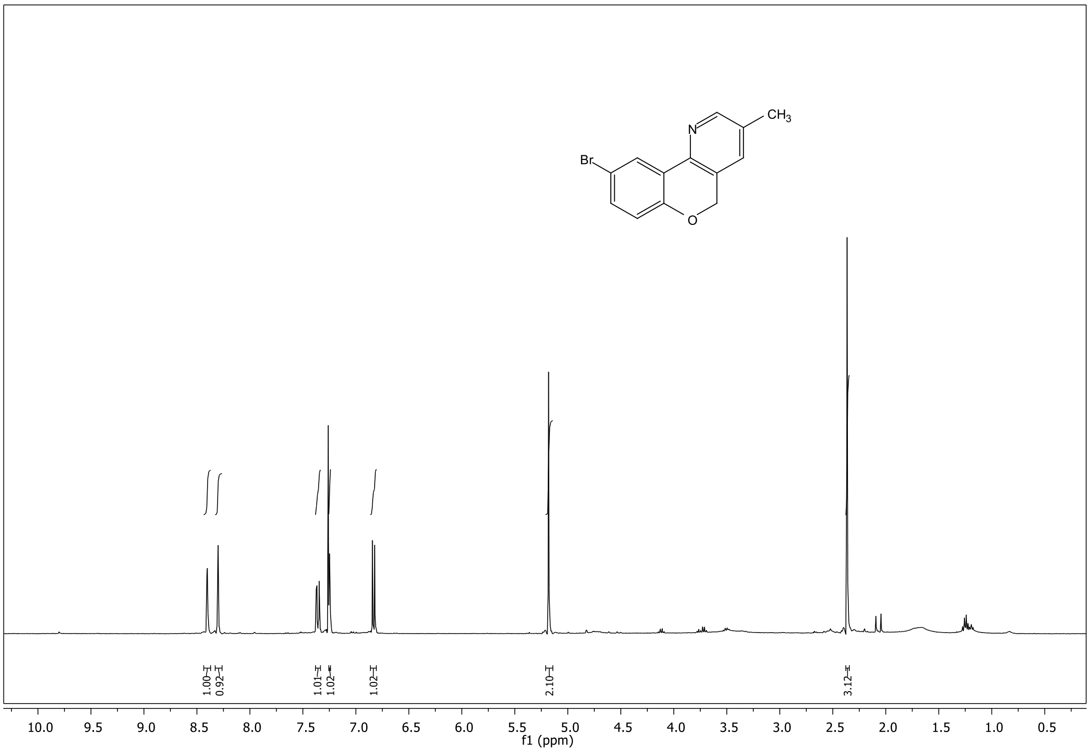


Figure 148: ^{1}H NMR Spectrum of Compound 263

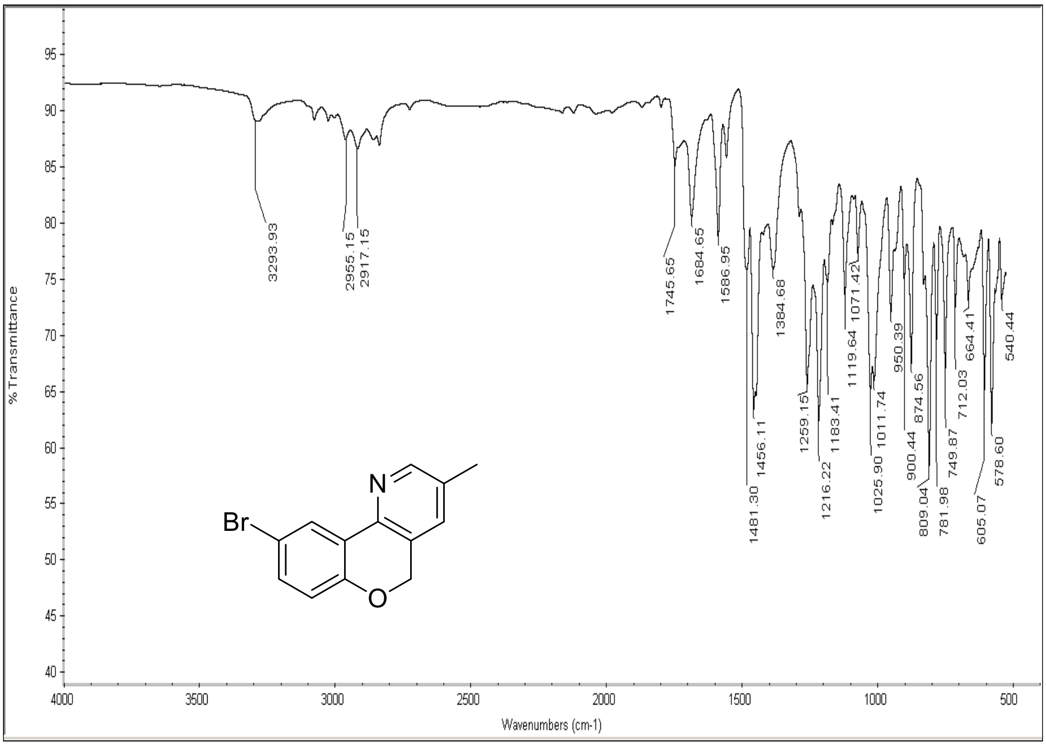


Figure 149: IR Spectrum of Compound 263

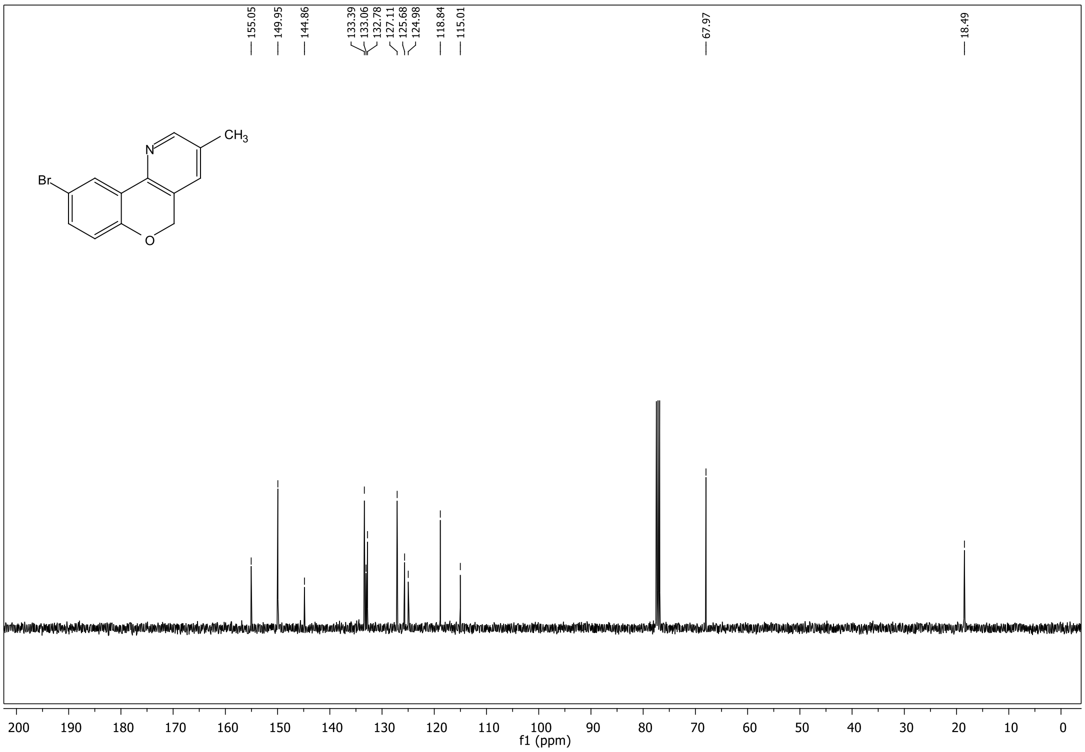


Figure 150: ^{13}C NMR Spectrum of Compound 263

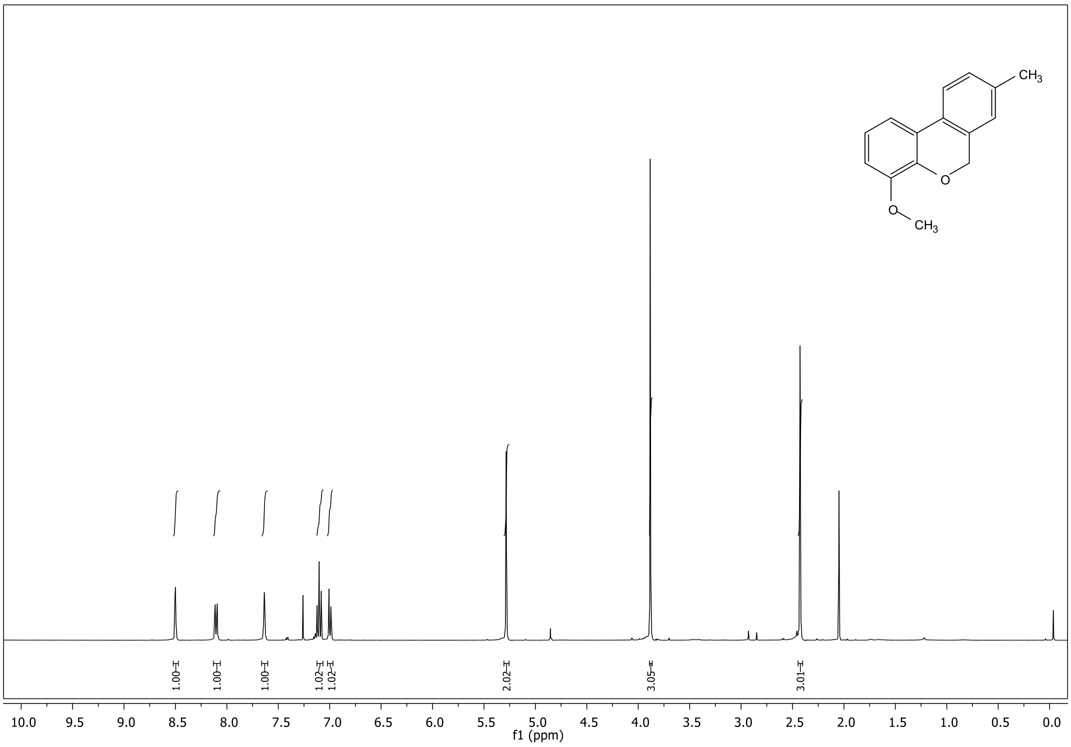


Figure 151: ^{1}H NMR Spectrum of Compound 264

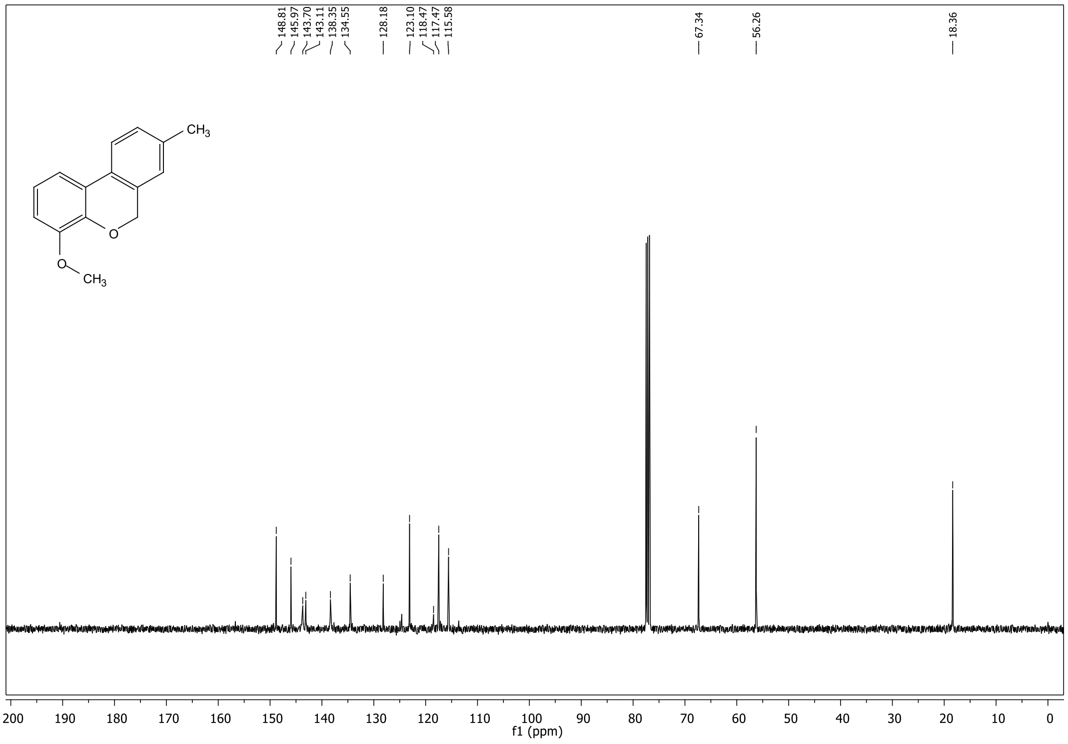


Figure 152: ^{13}C NMR Spectrum of Compound 264

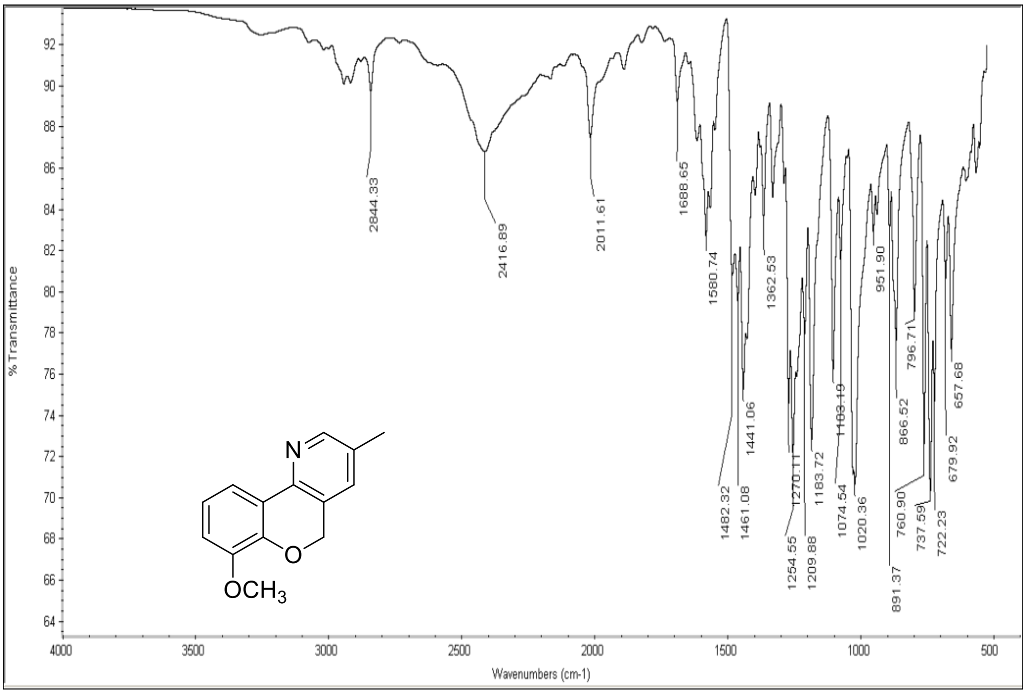


Figure 153: IR Spectrum of Compound 264

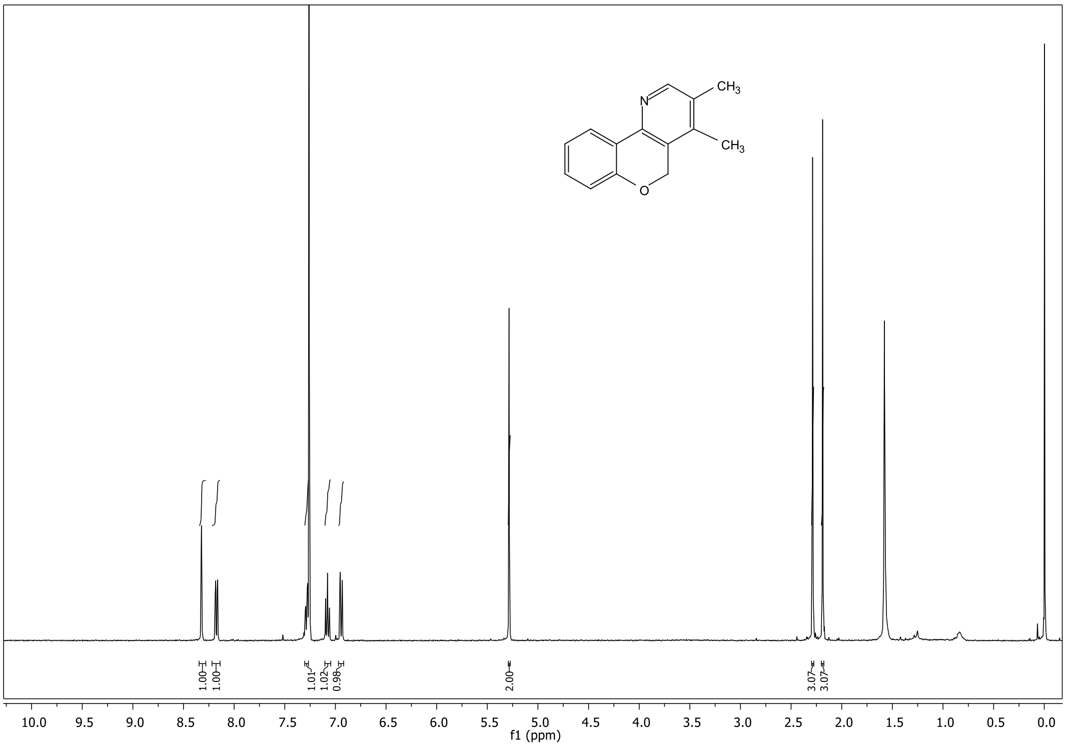


Figure 154: ^{1}H NMR Spectrum of Compound 265

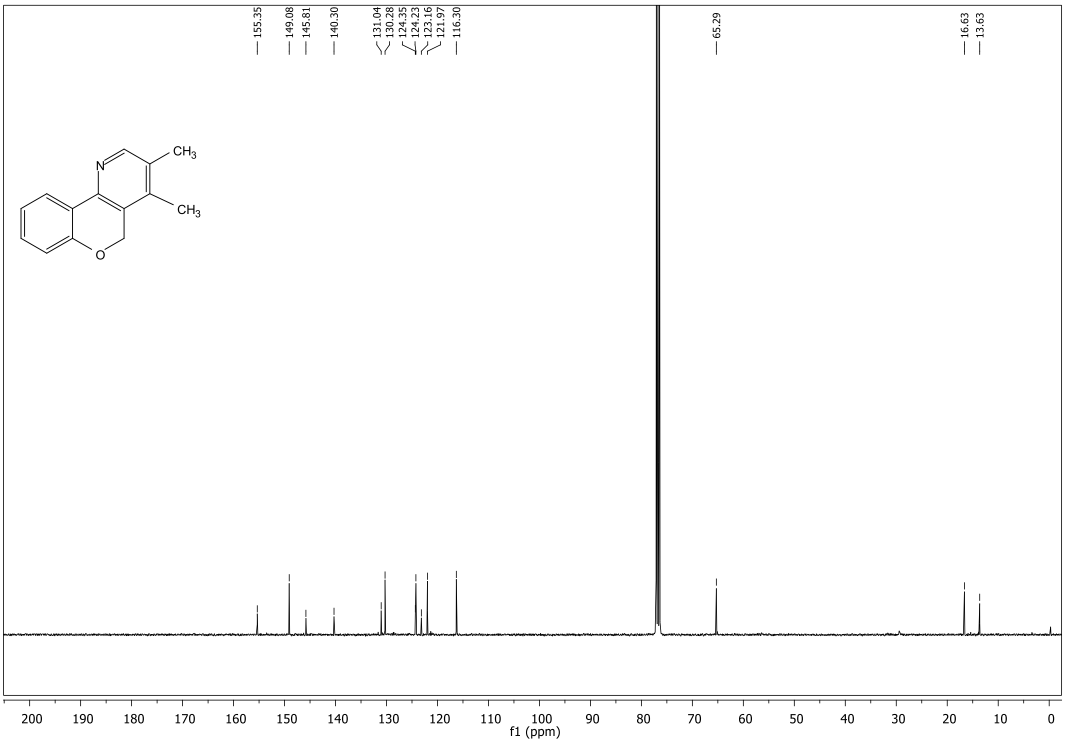


Figure 155: ^{13}C NMR Spectrum of Compound 265

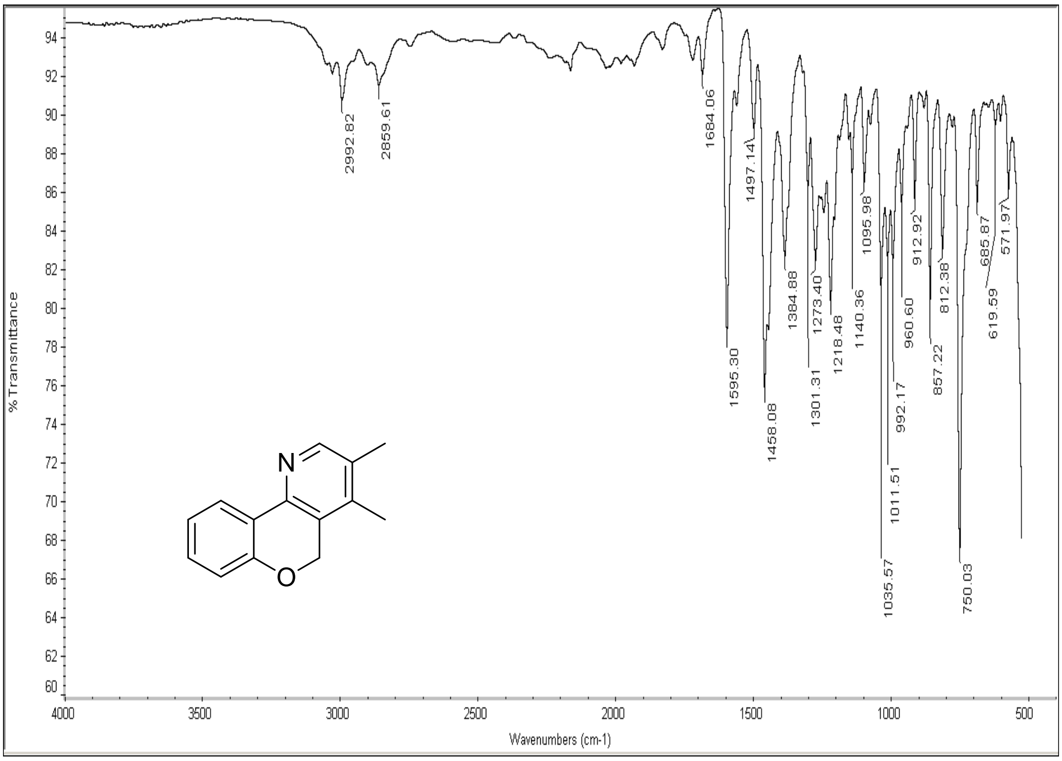


Figure 156: IR Spectrum of Compound 265

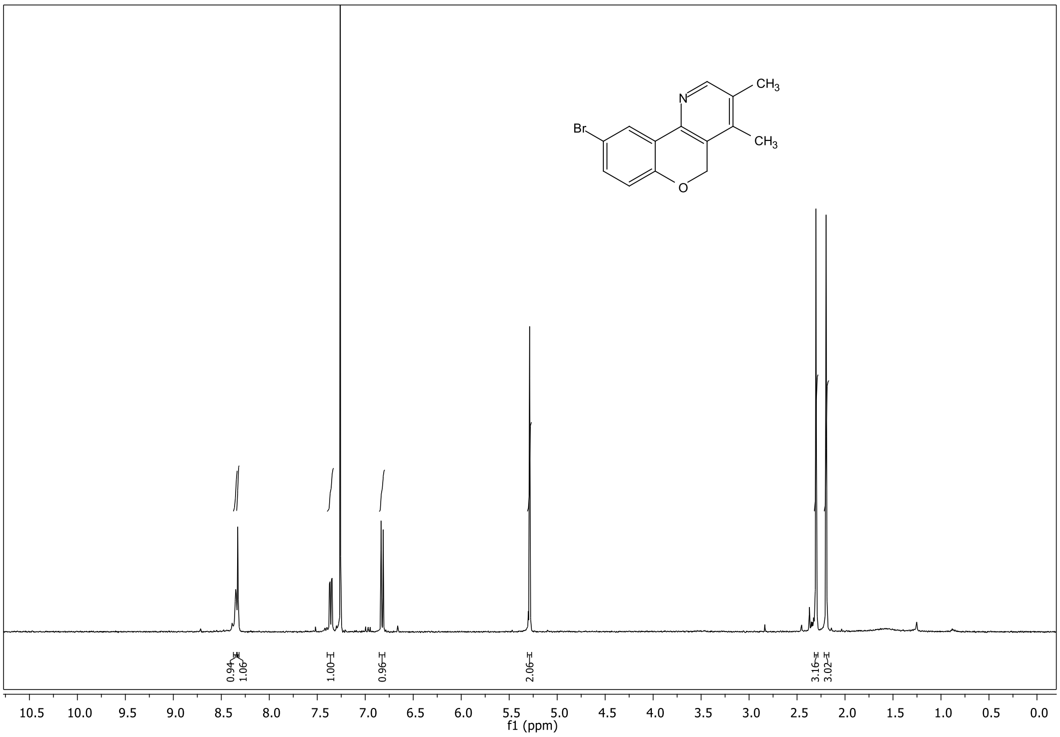


Figure 157: ^{1}H NMR Spectrum of Compound 266

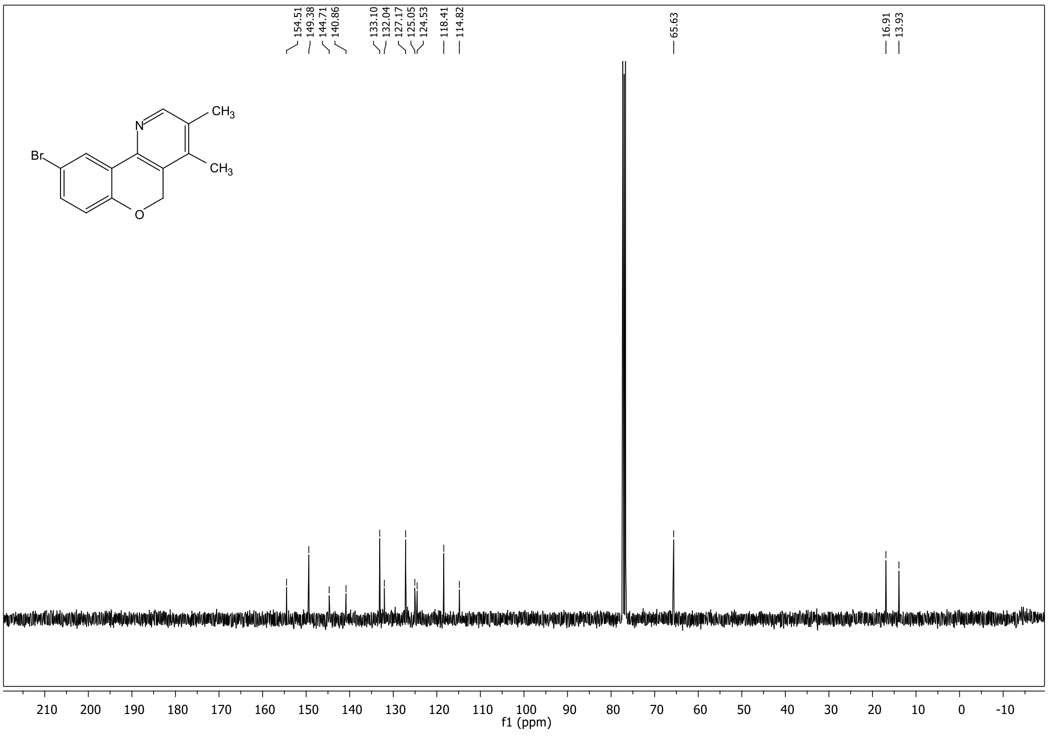


Figure 158: ^{13}C NMR Spectrum of Compound 266

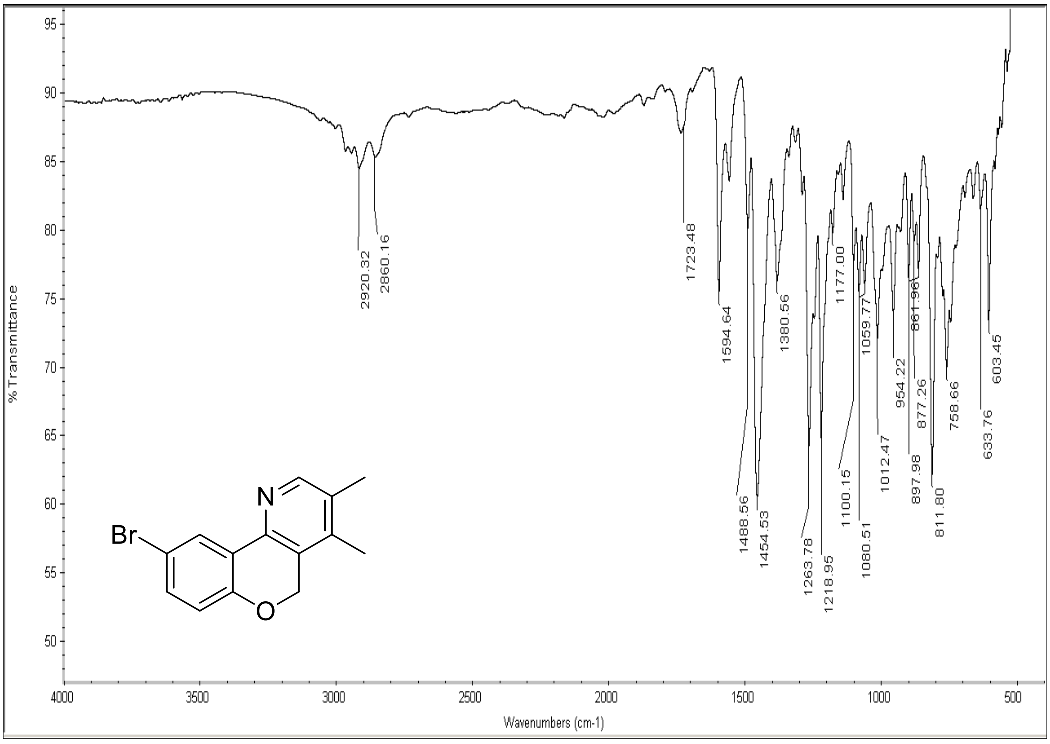


Figure 159: IR Spectrum of Compound 266

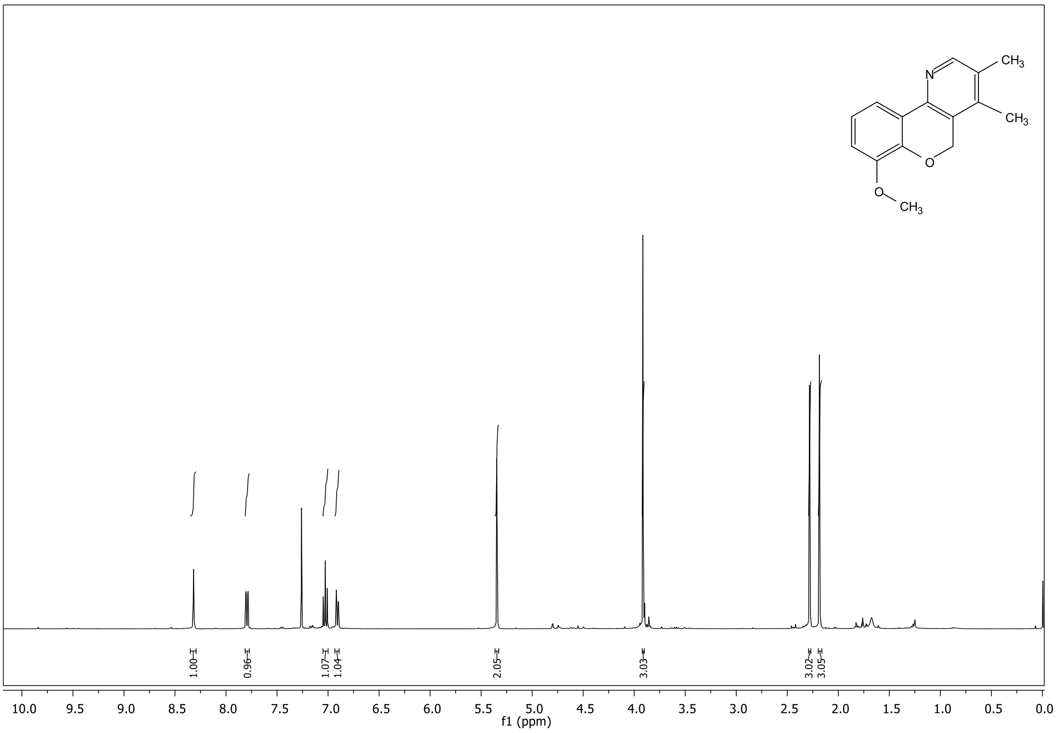


Figure 160: ^{1}H NMR Spectrum of Compound 267

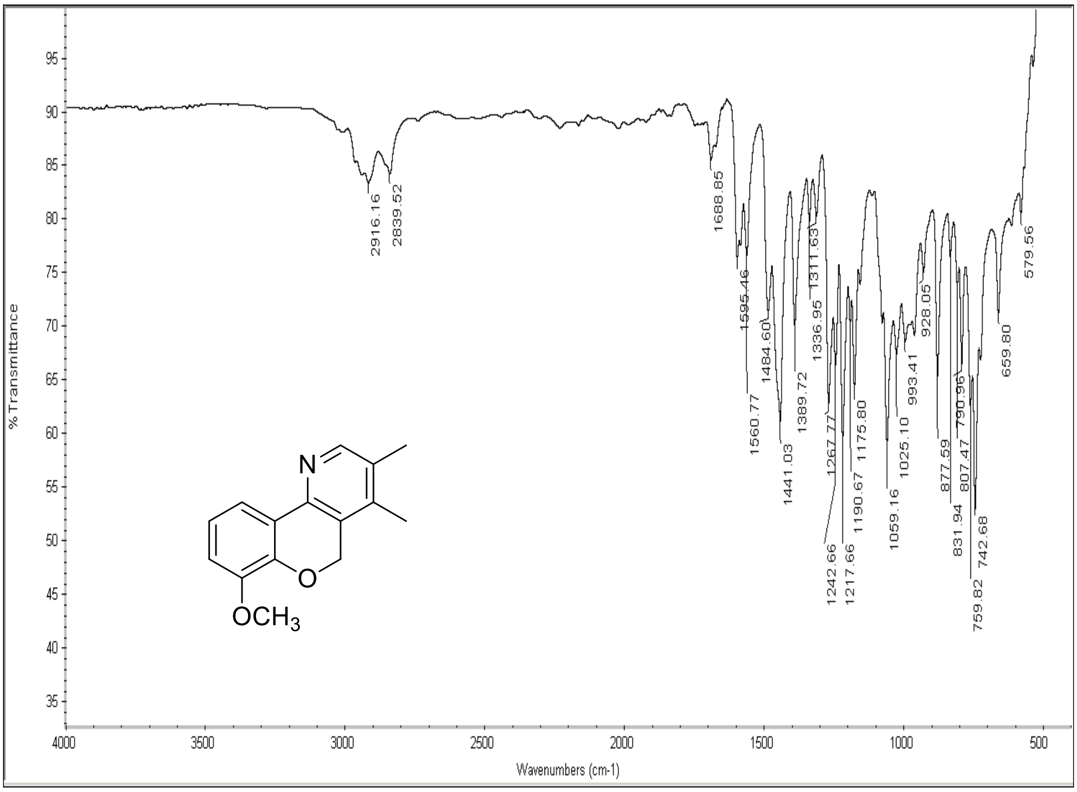


Figure 161: IR Spectrum of Compound 267

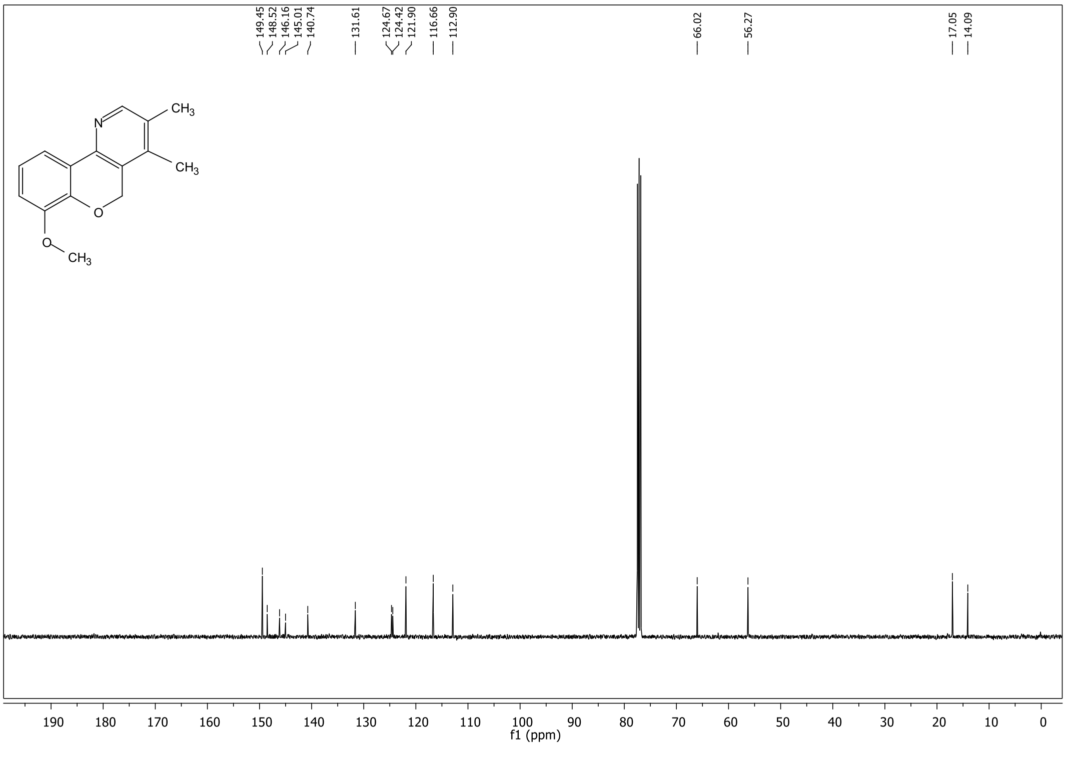


Figure 162: ^{13}C NMR Spectrum of Compound 267

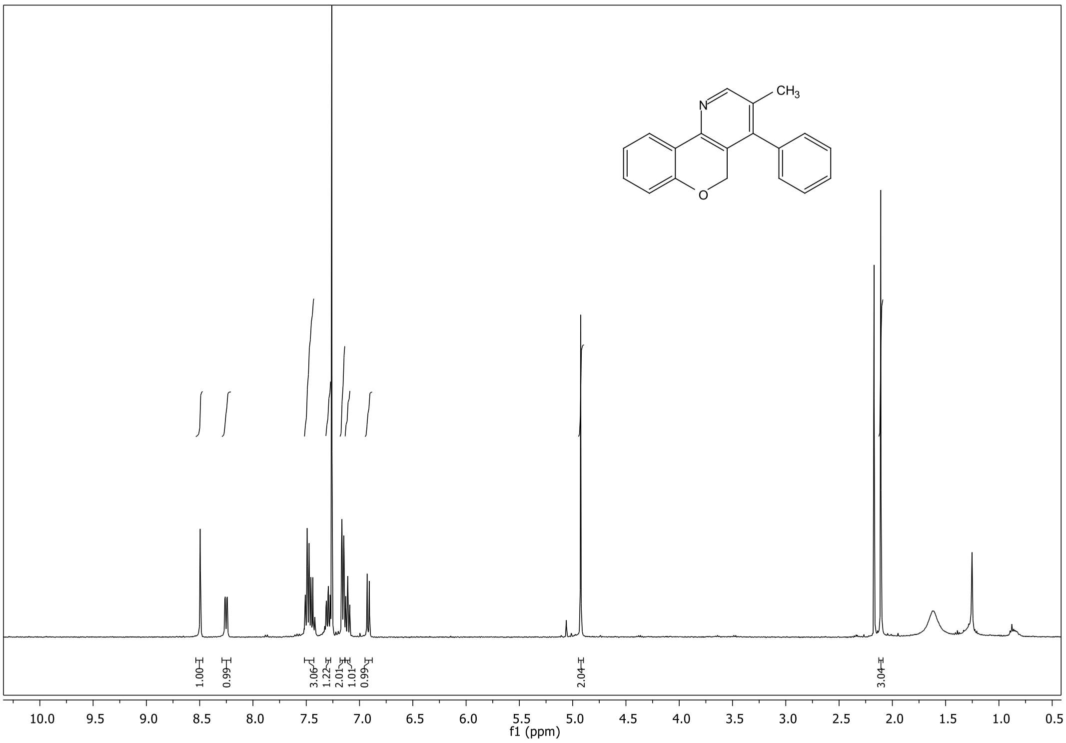


Figure 163: ^{1}H NMR Spectrum of Compound 268

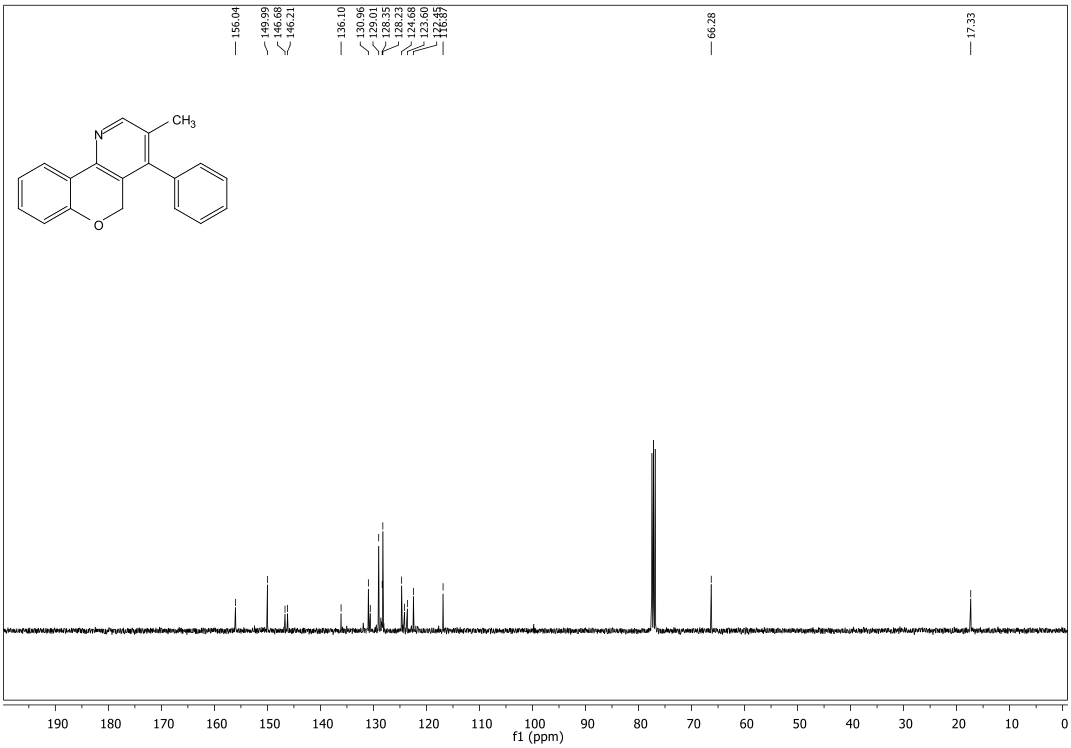


Figure 164: ^{13}C NMR Spectrum of Compound 268

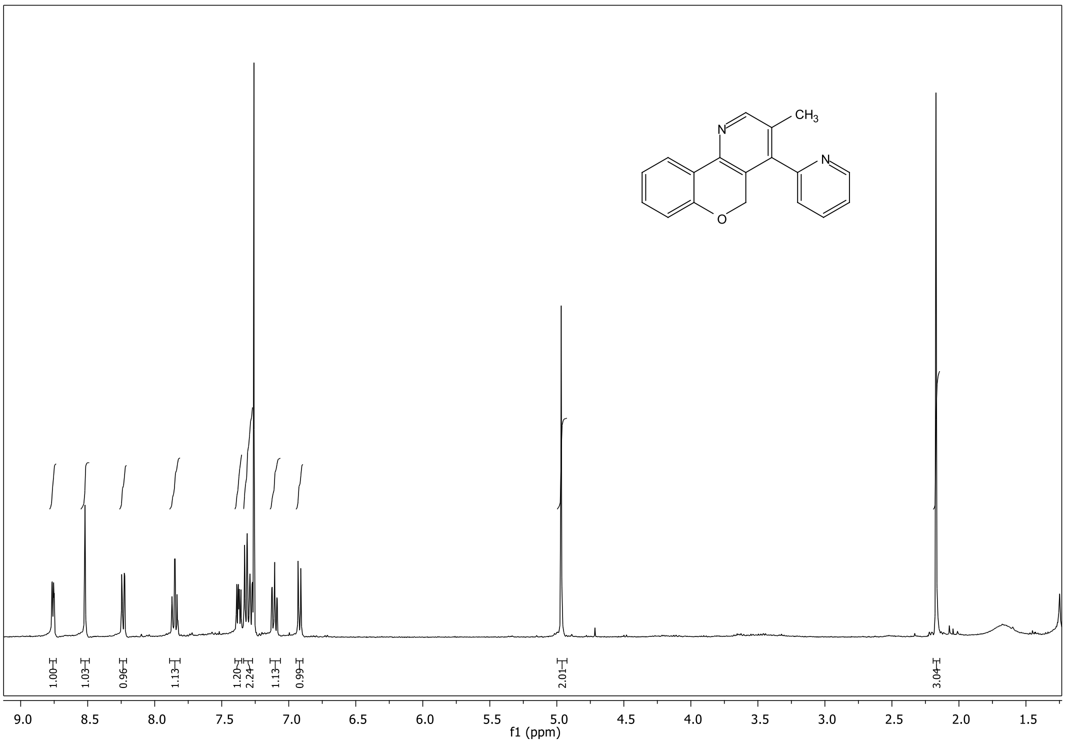


Figure 165: ^{1}H NMR Spectrum of Compound 269

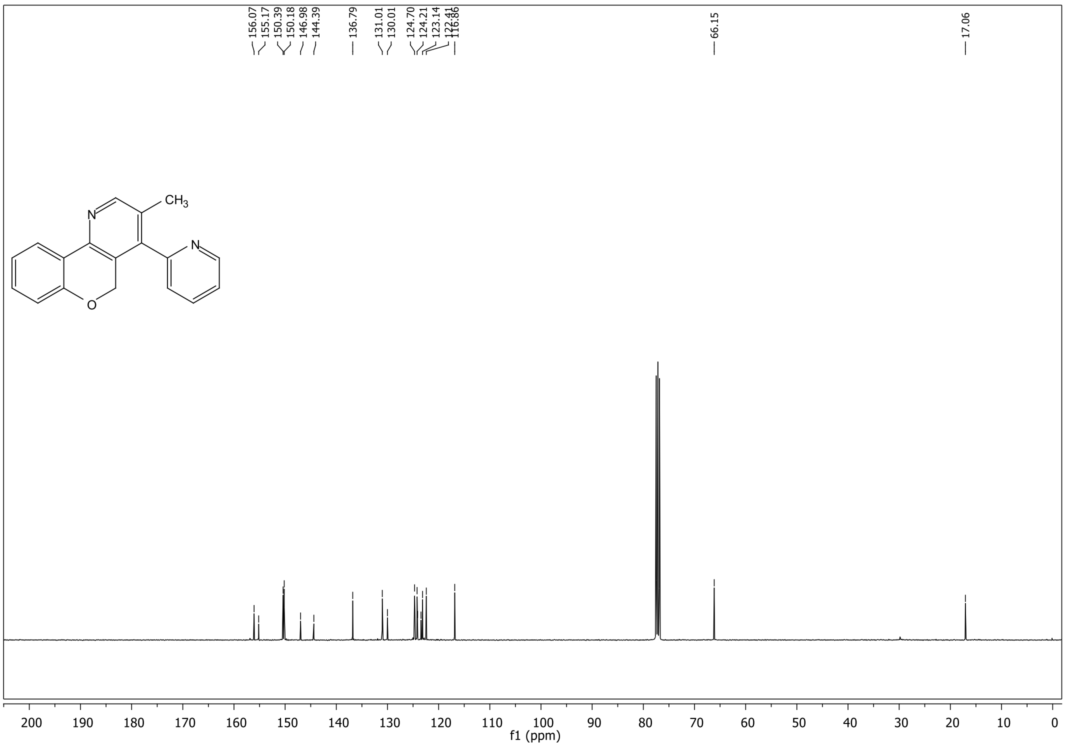


Figure 166: ^{13}C NMR Spectrum of Compound 269

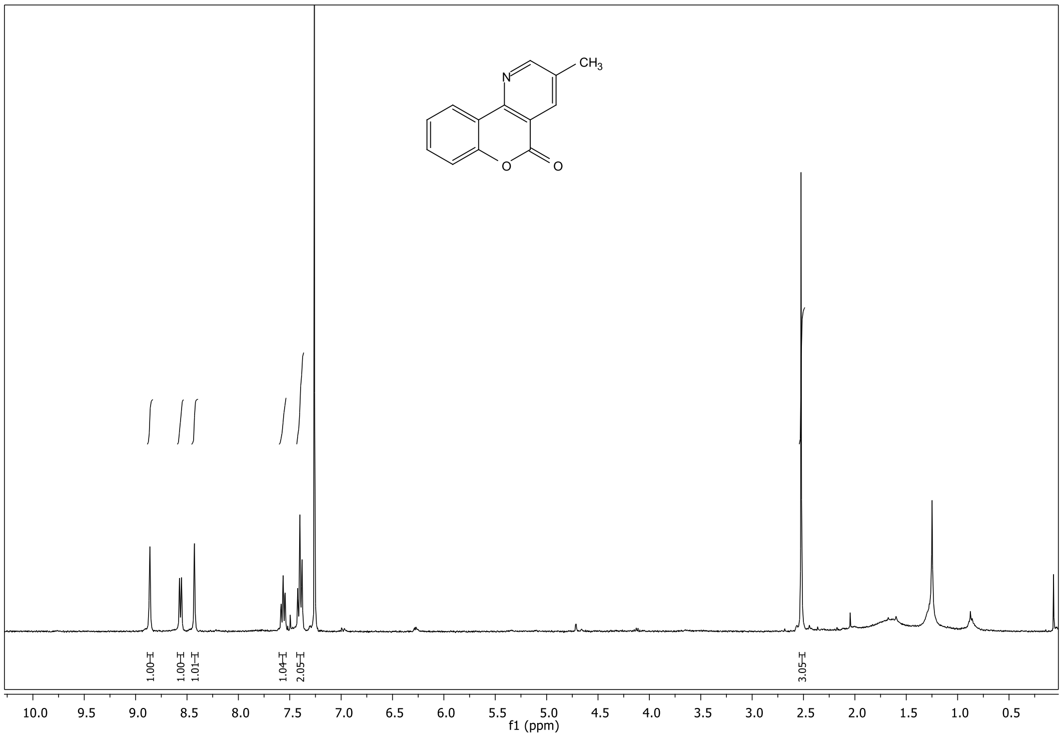


Figure 167: ^{1}H NMR Spectrum of Compound 270a

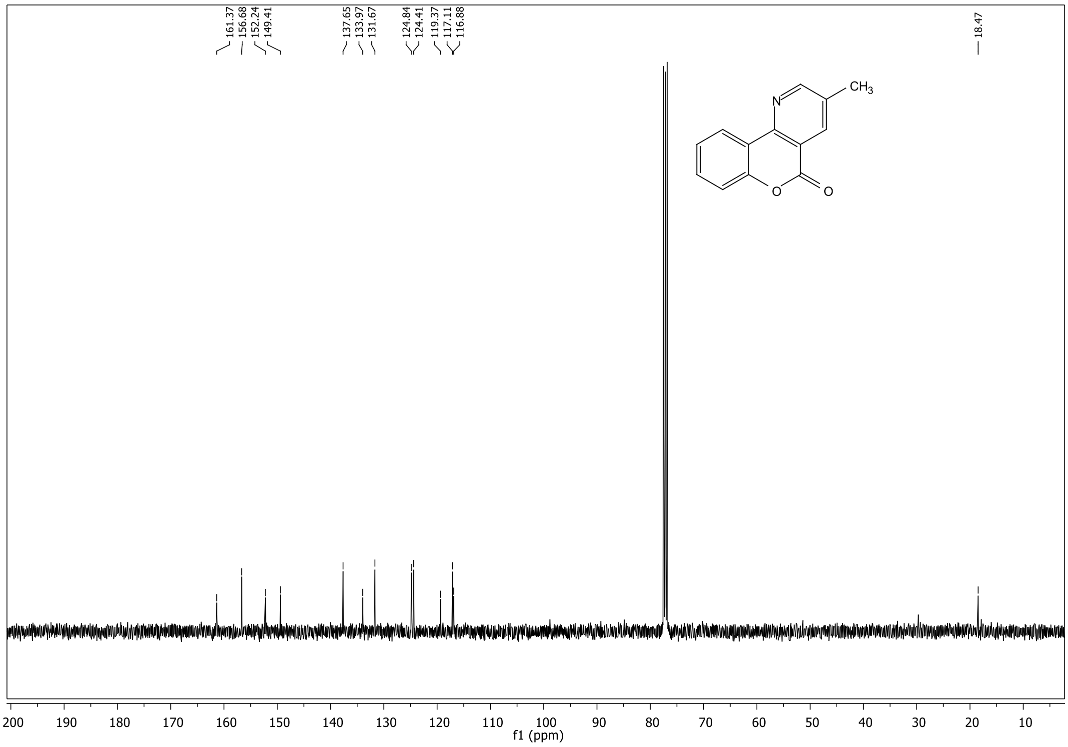


Figure 168: ^{13}C NMR Spectrum of Compound 270a

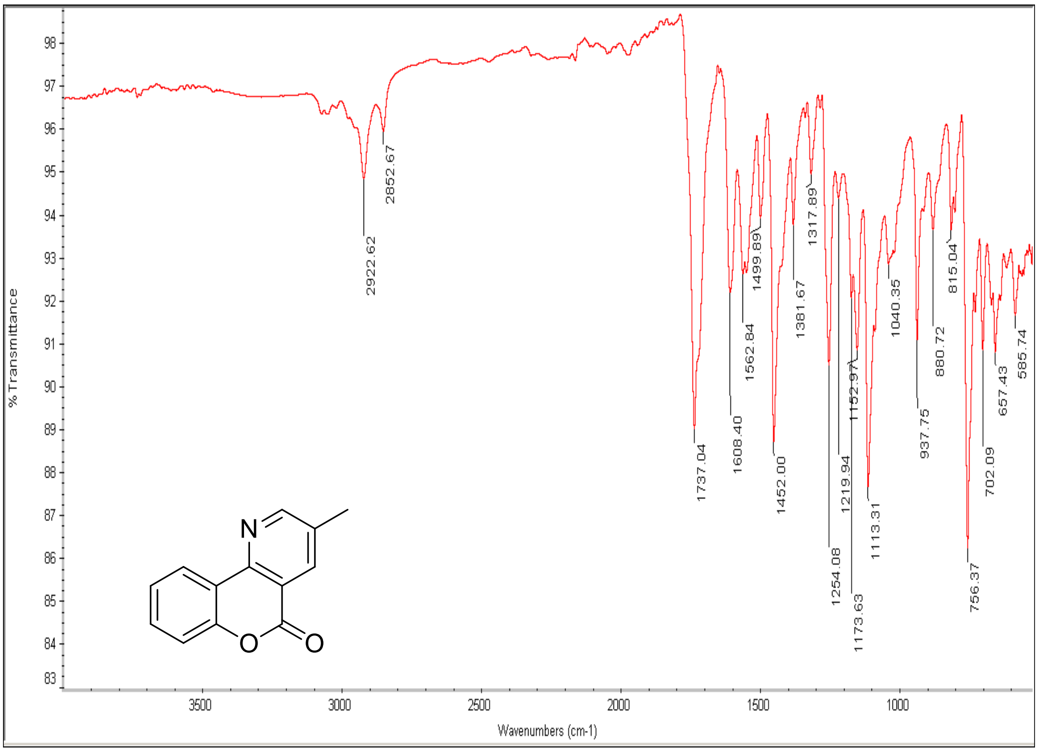


Figure 169: IR Spectrum of Compound 270a

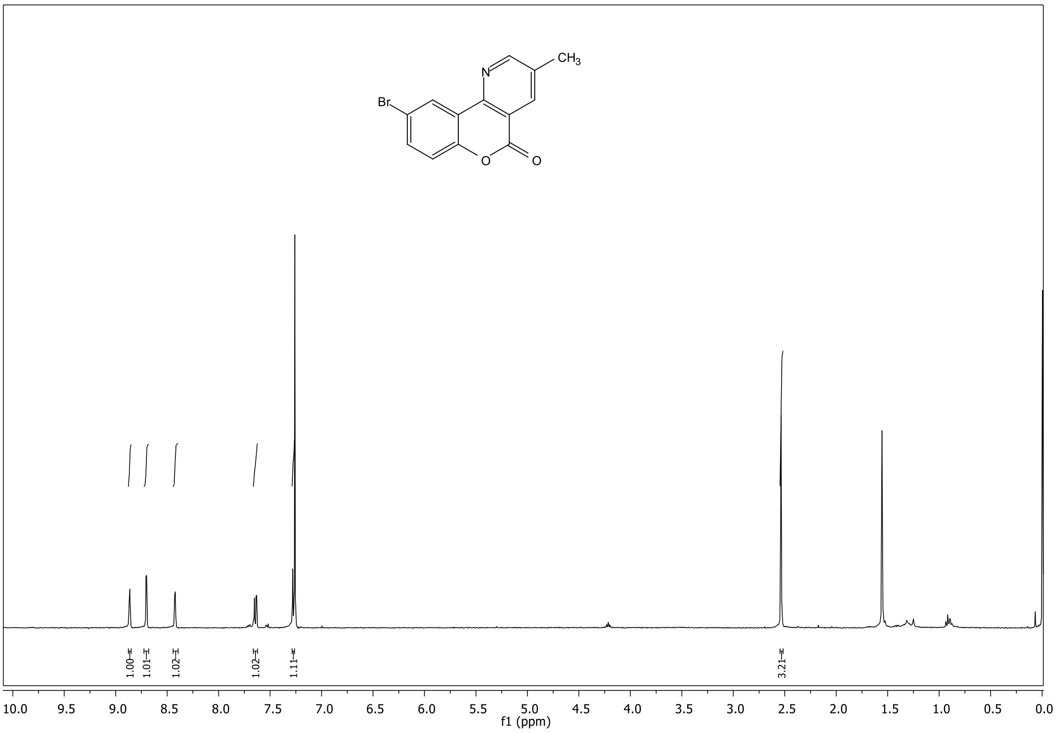


Figure 170: ^{1}H NMR Spectrum of Compound 270b

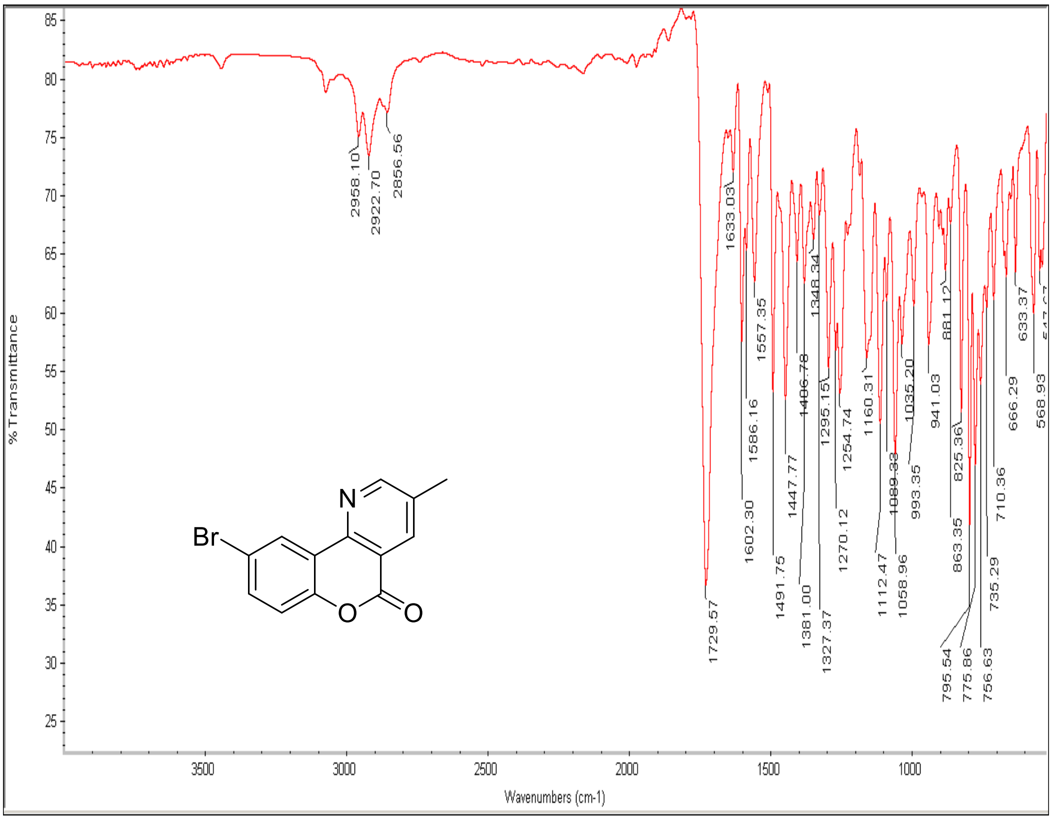


Figure 171: IR Spectrum of Compound 270b

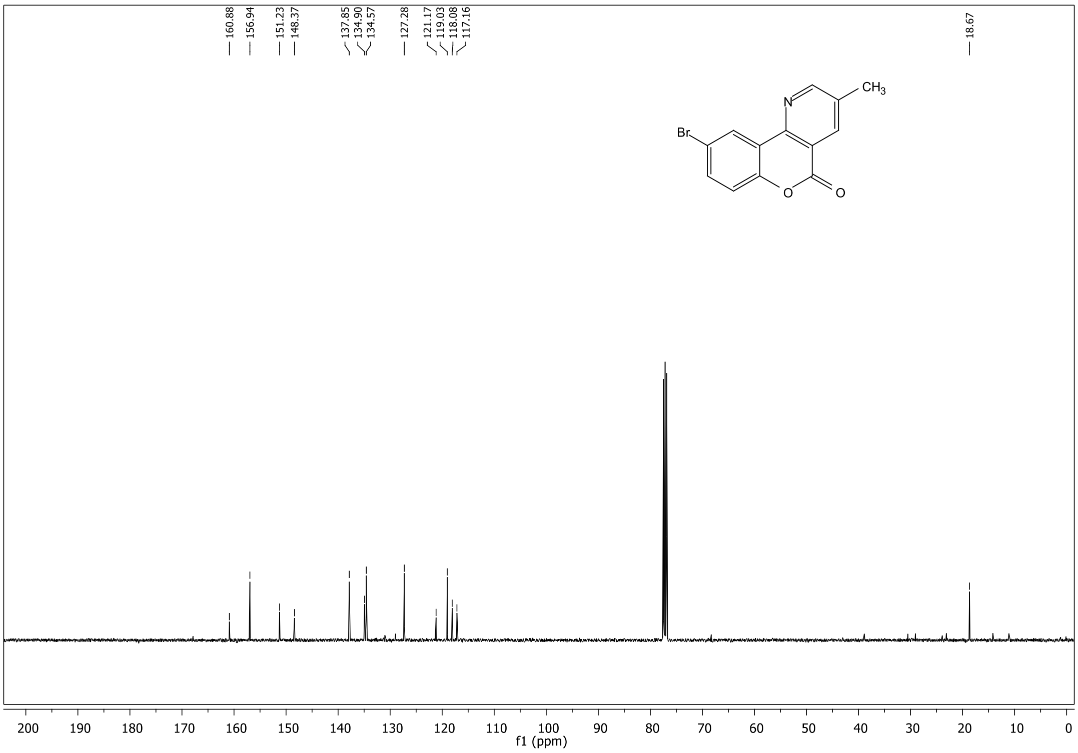


Figure 172: ^{13}C NMR Spectrum of Compound 270b

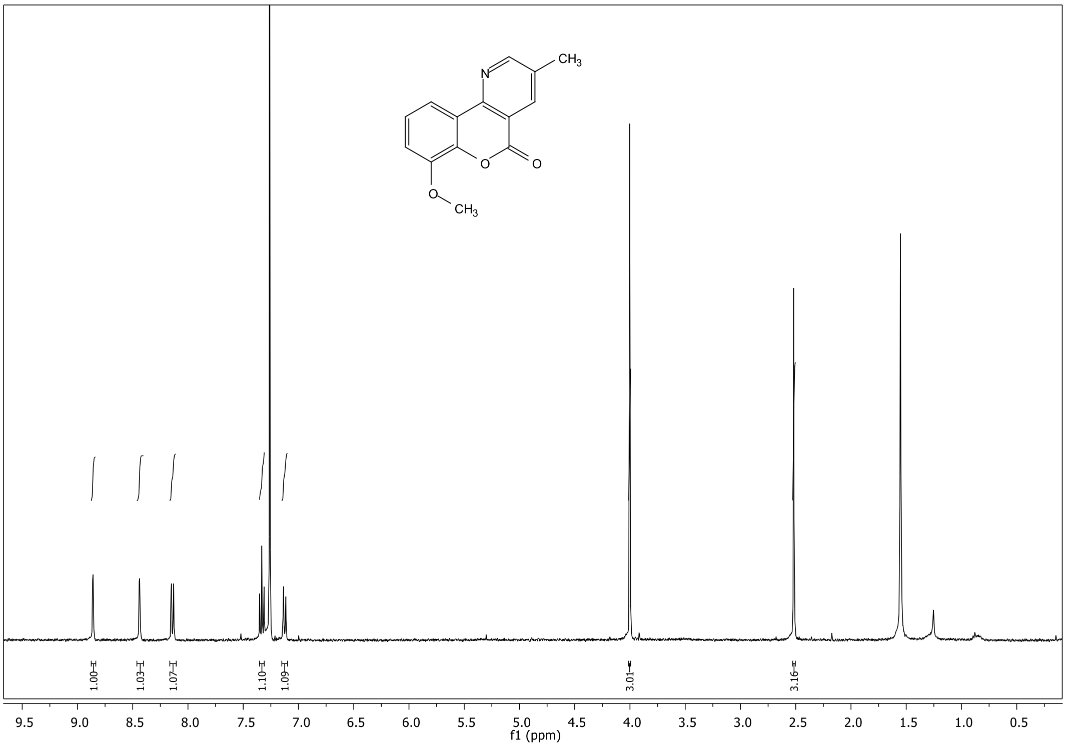


Figure 173: ^{1}H NMR Spectrum of Compound 270c

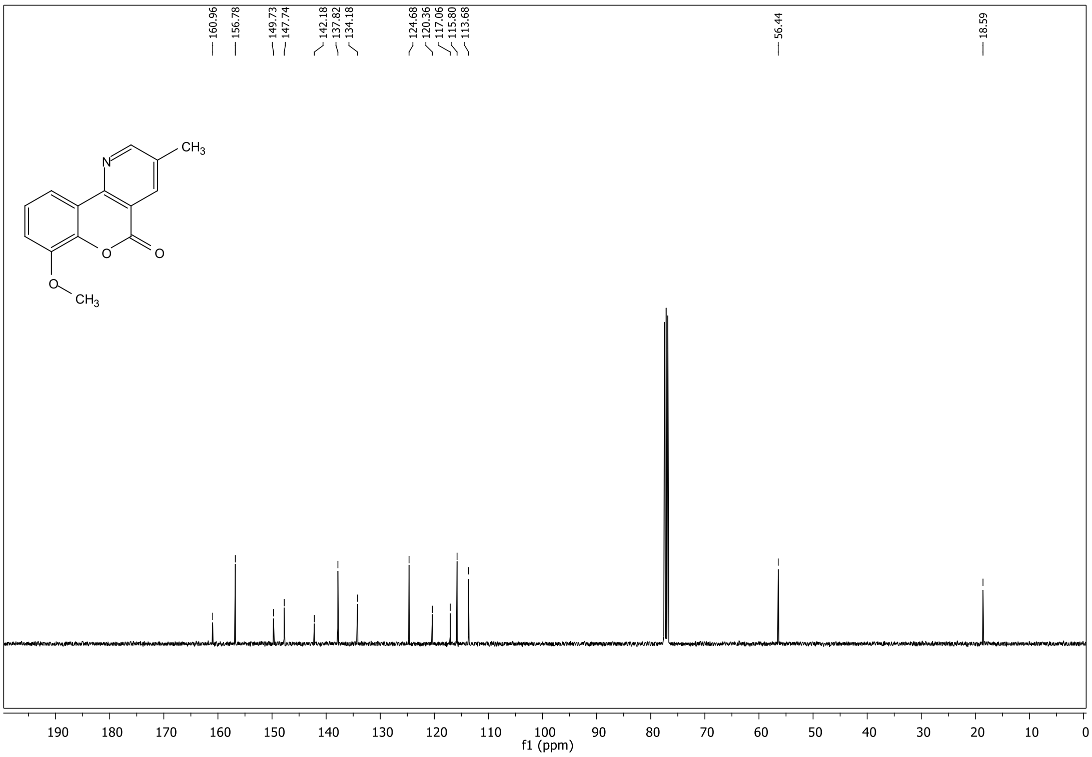


Figure 174: ^{13}C NMR Spectrum of Compound 270c

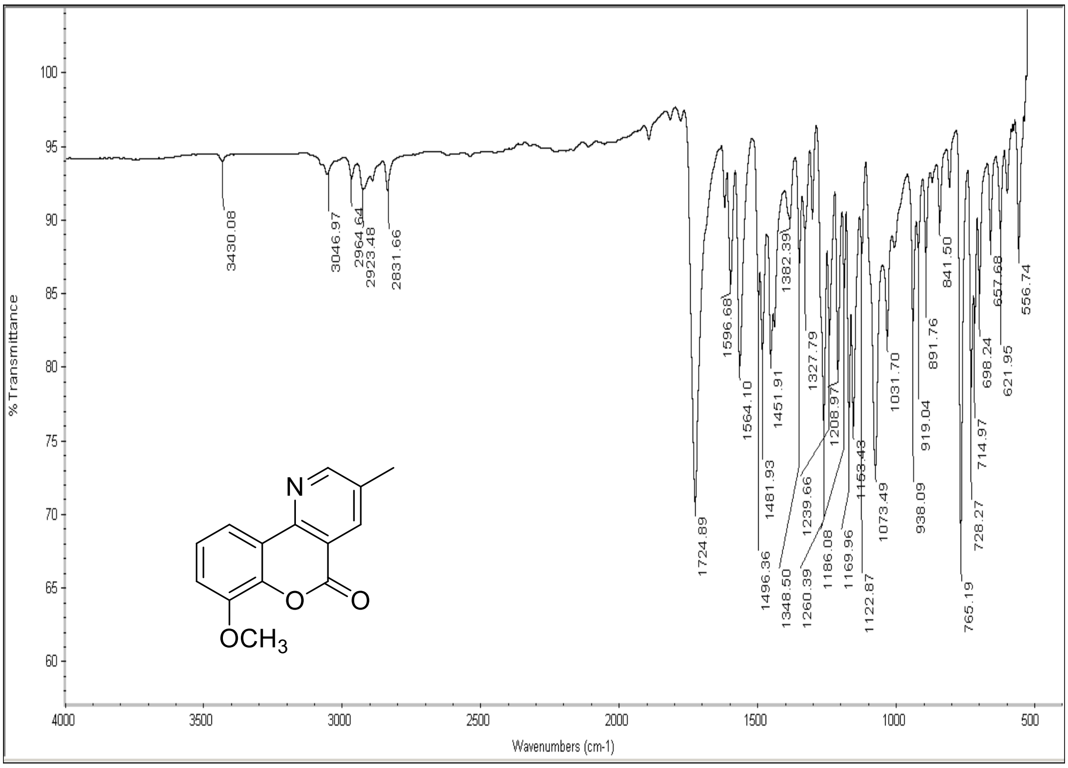


Figure 175: IR Spectrum of Compound 270c

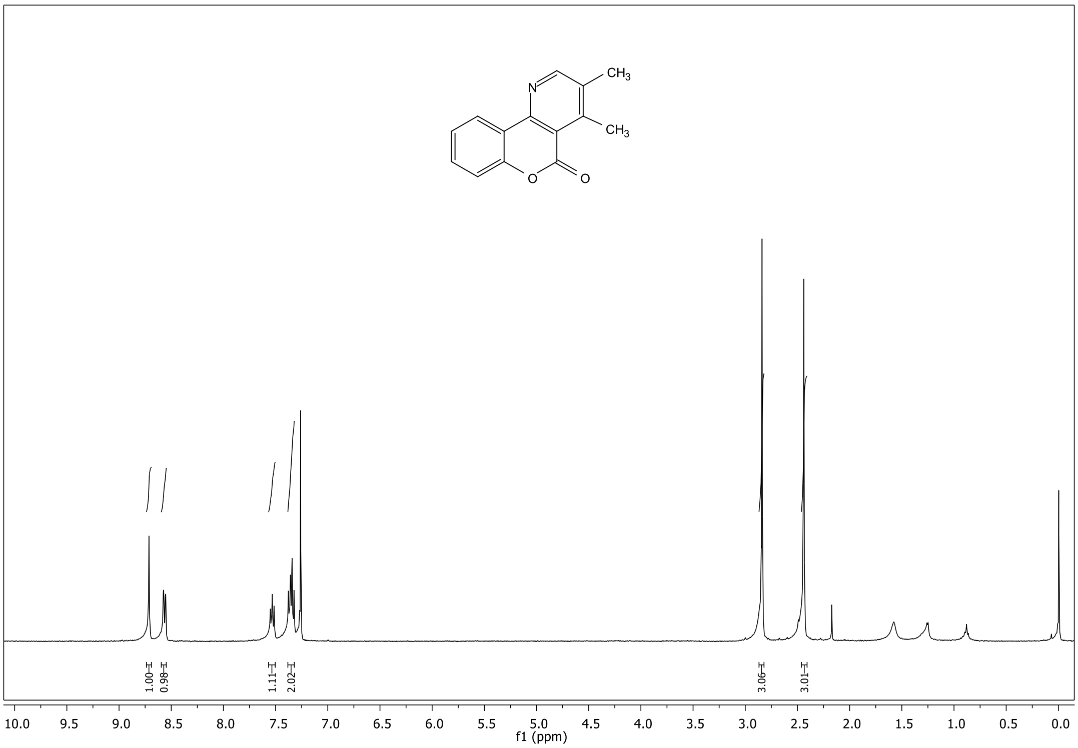


Figure 176: ^{1}H NMR Spectrum of Compound 270d

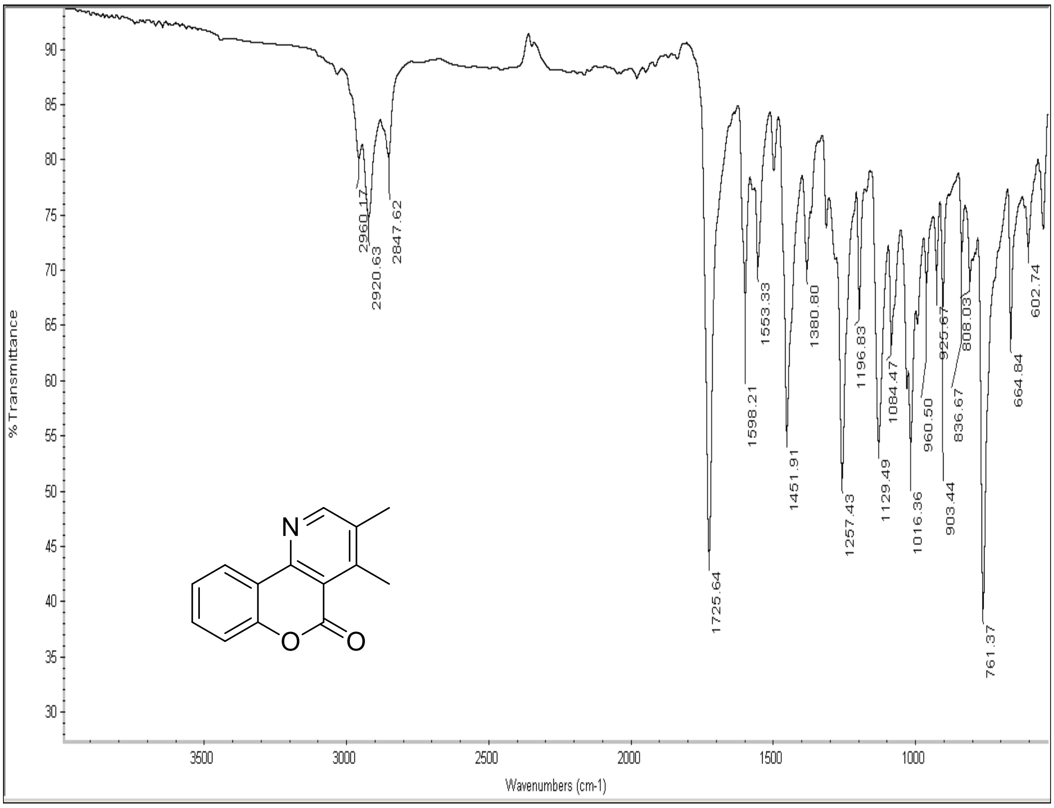


Figure 177: IR Spectrum of Compound 270d

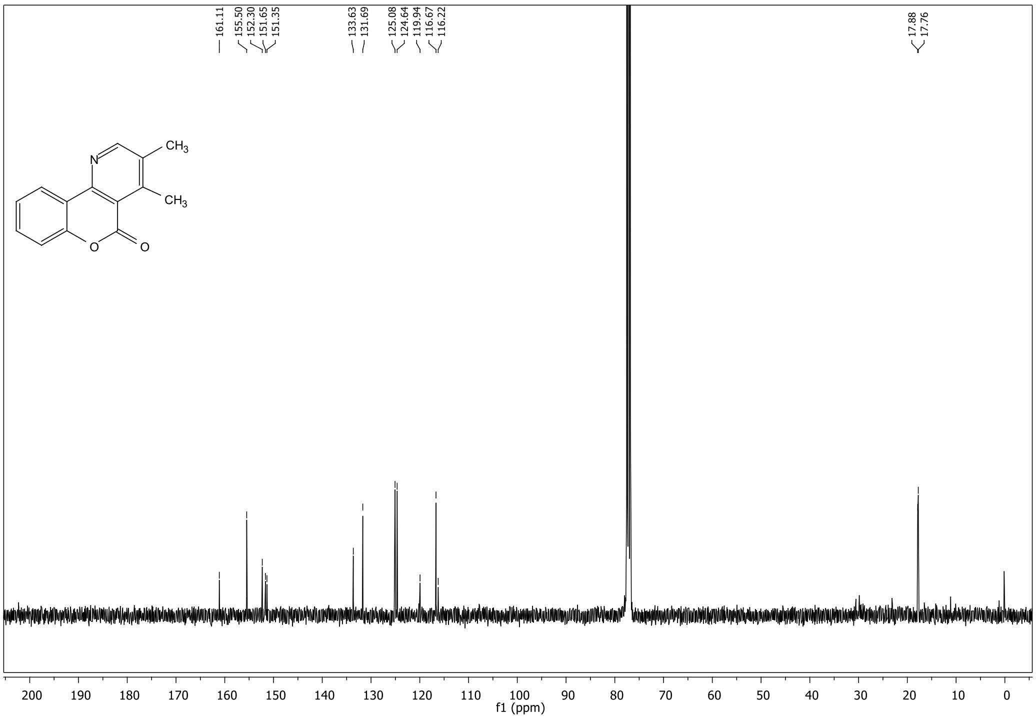


Figure 178: ^{13}C NMR Spectrum of Compound 270d

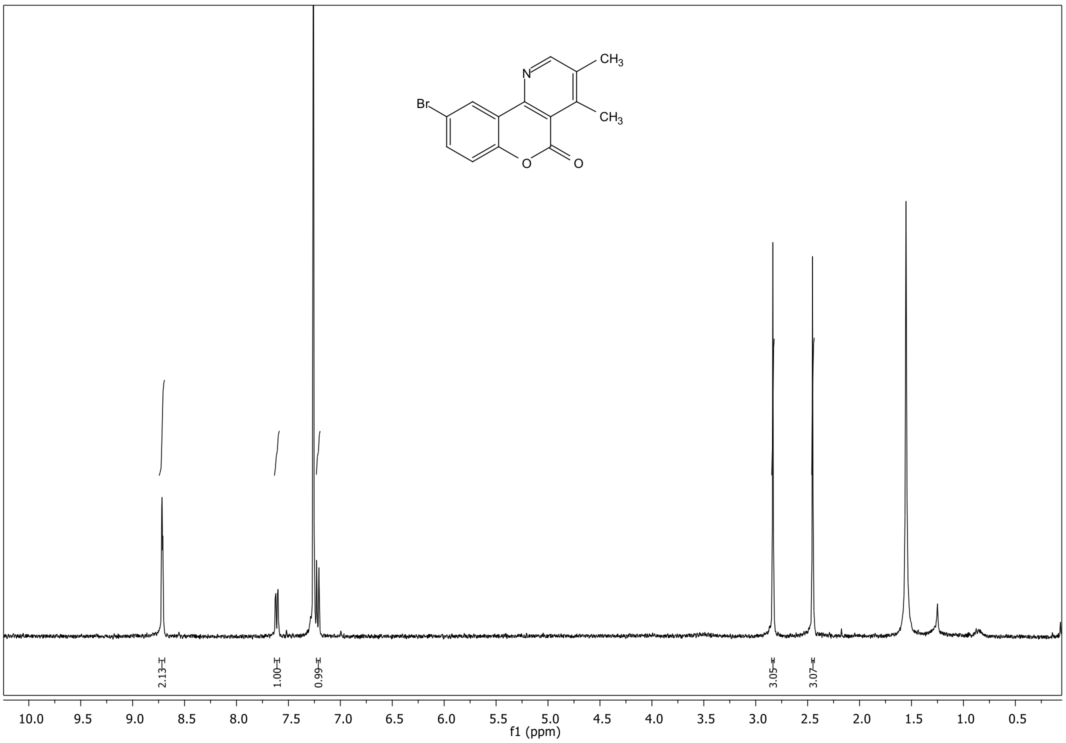


Figure 179: ^{1}H NMR Spectrum of Compound 270e

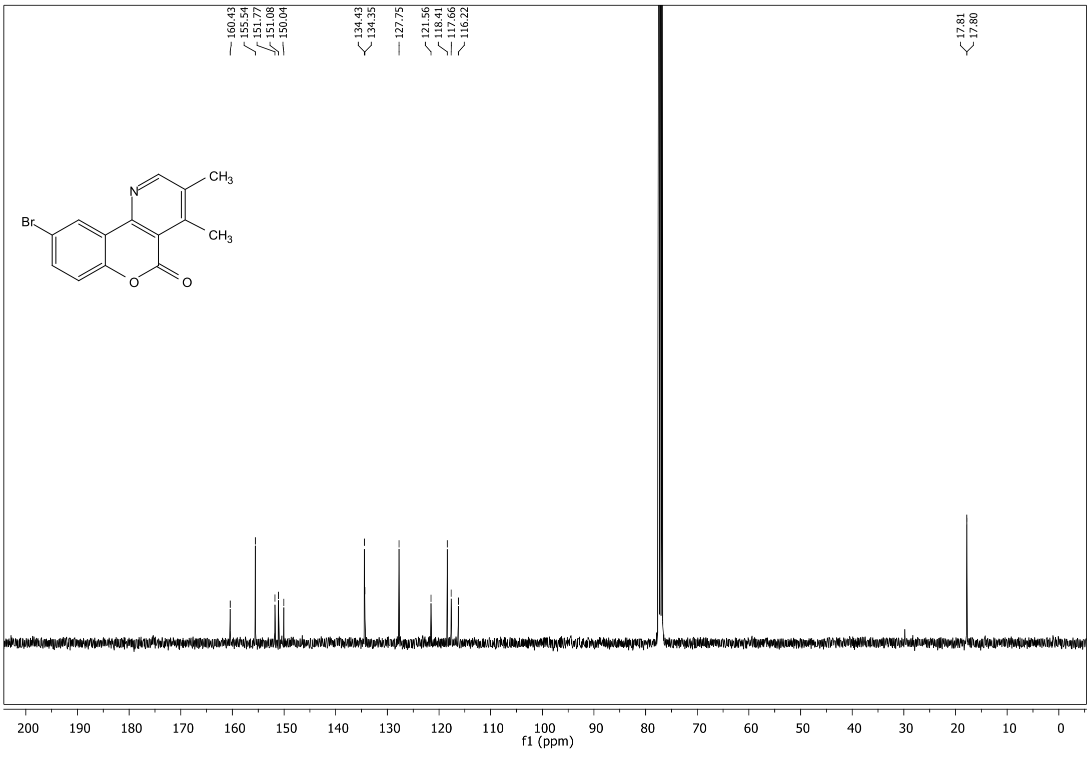


Figure 180: ^{13}C NMR Spectrum of Compound 270e

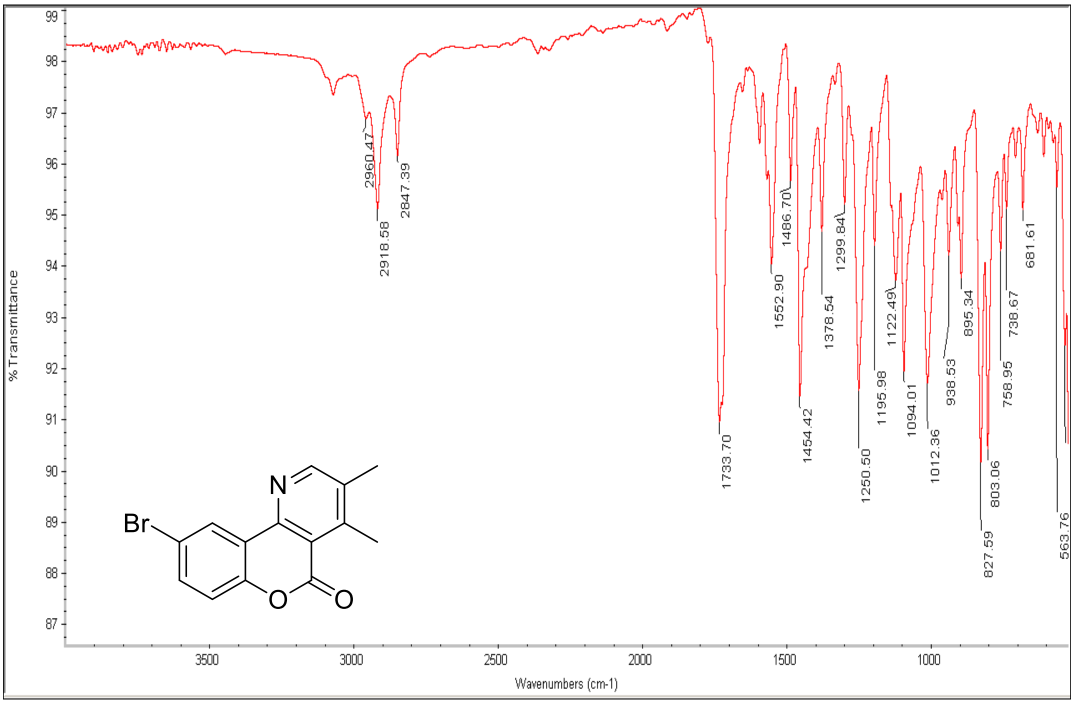


Figure 181: IR Spectrum of Compound 270e

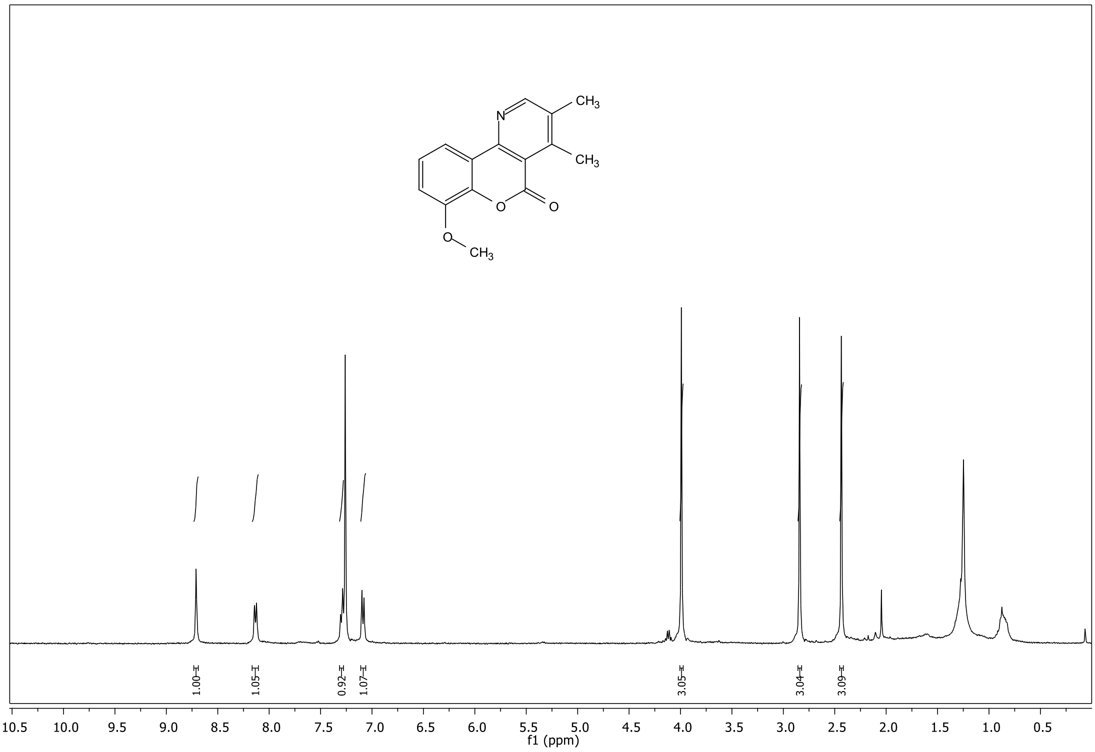


Figure 182: ^{1}H NMR Spectrum of Compound 270f

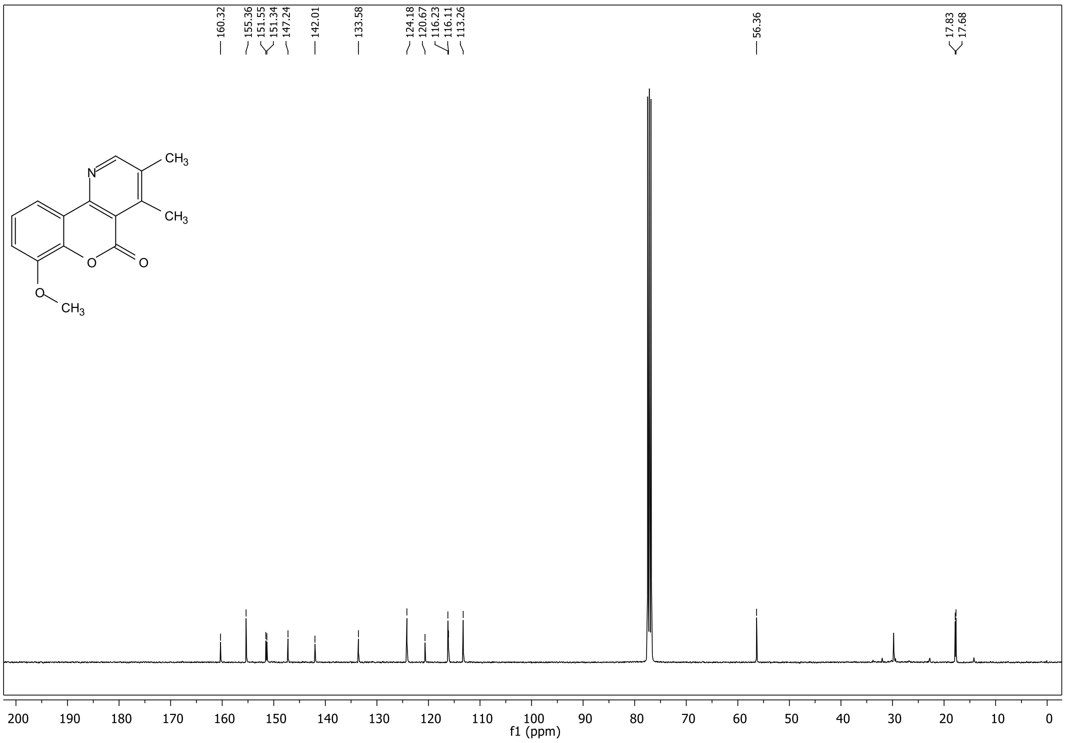


Figure 183: ^{13}C NMR Spectrum of Compound 270f

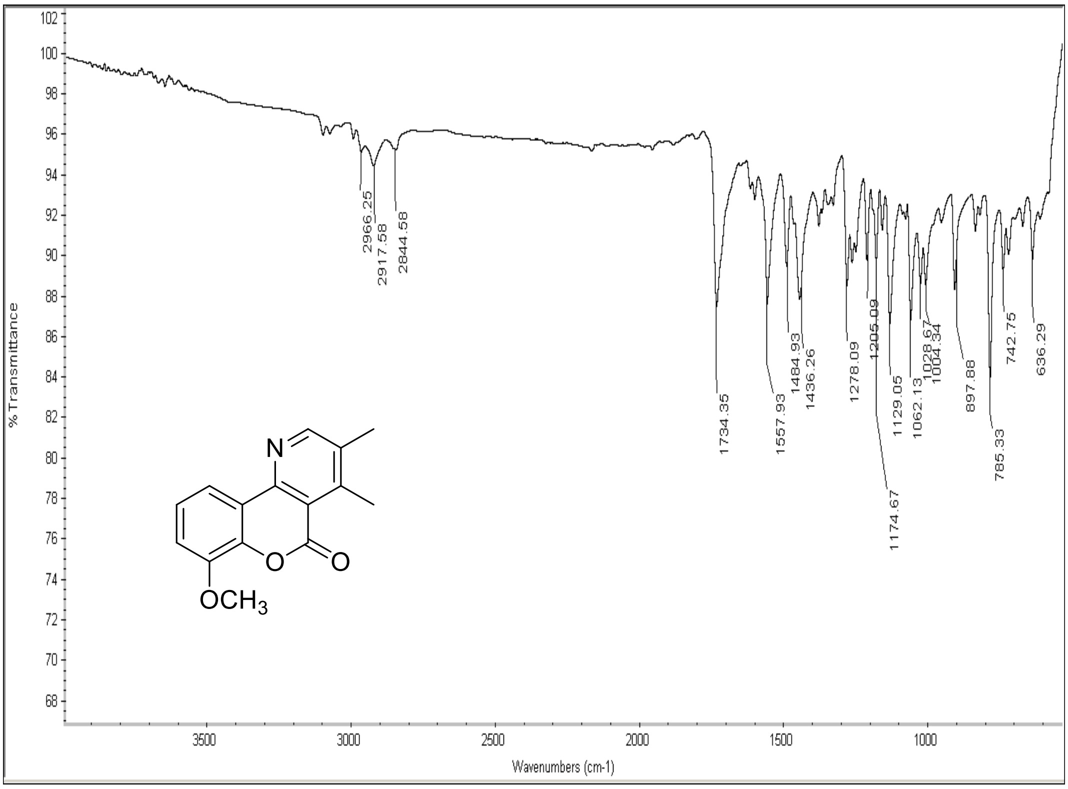


Figure 184: IR Spectrum of Compound 270f

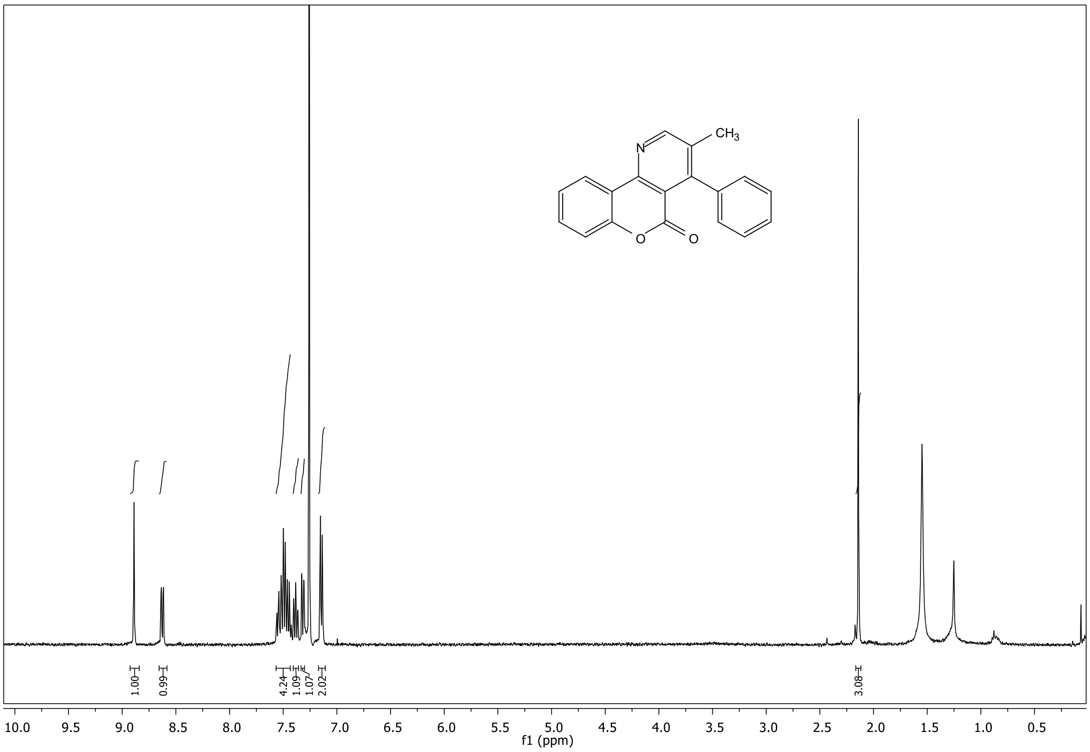


Figure 185: ^{1}H NMR Spectrum of Compound 270g

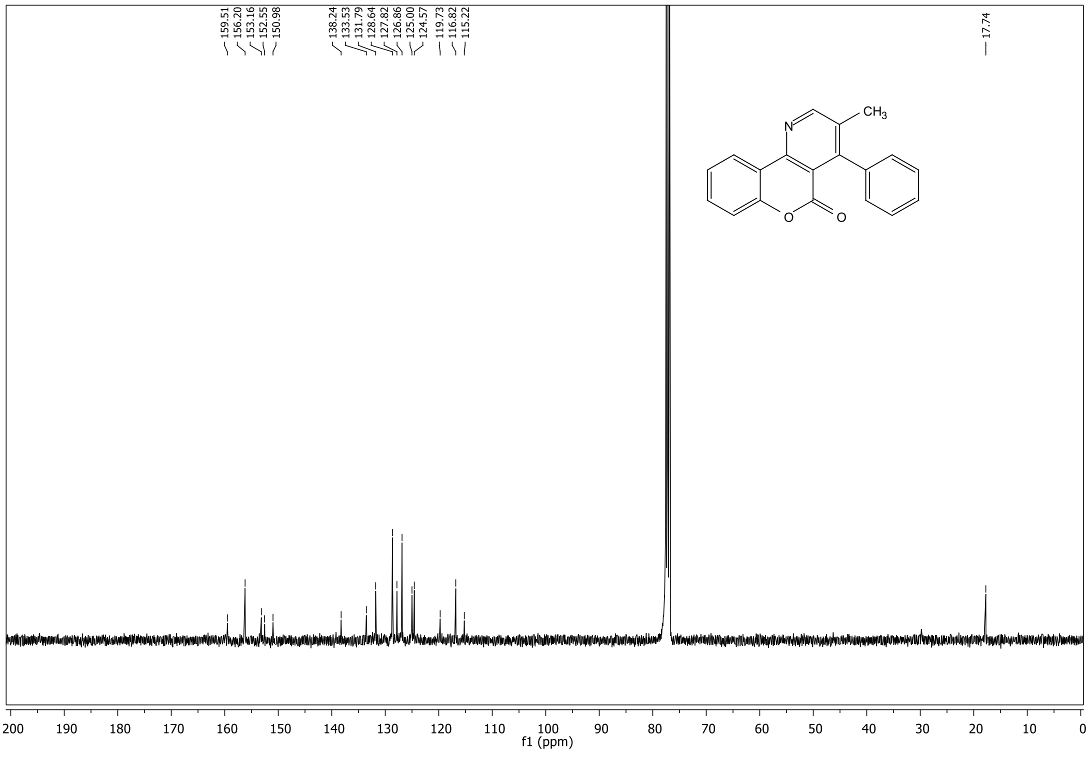


Figure 186: ^{13}C NMR Spectrum of Compound 270g

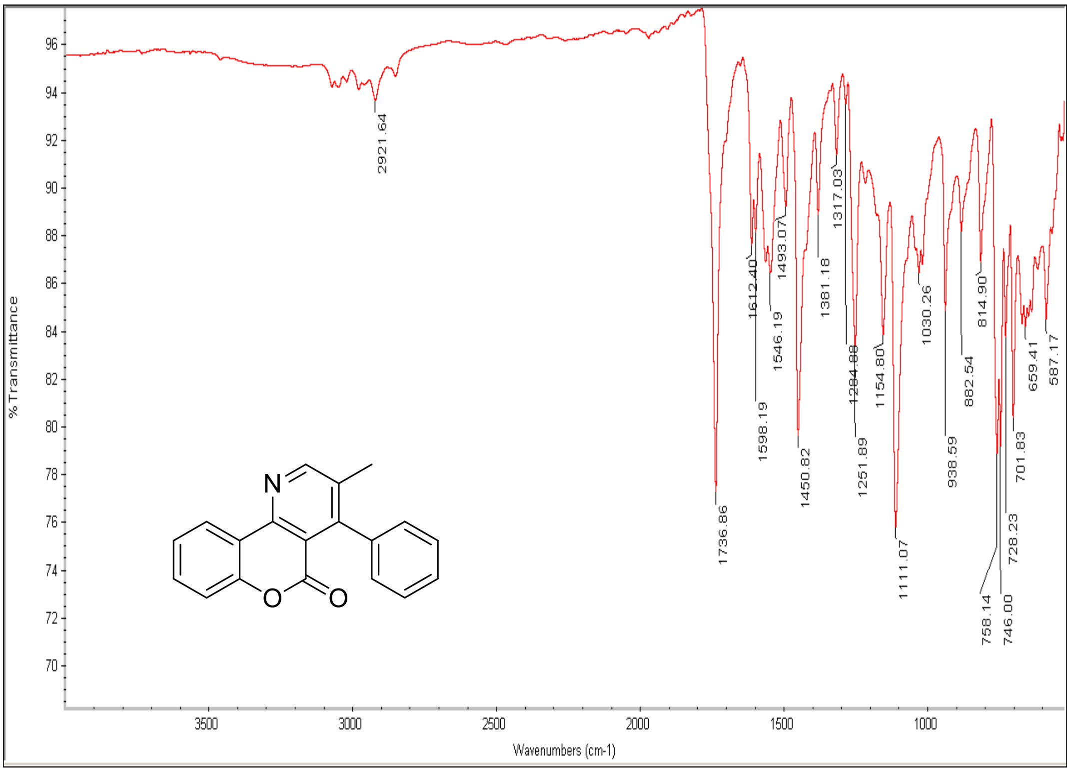


Figure 187: IR Spectrum of Compound 270h

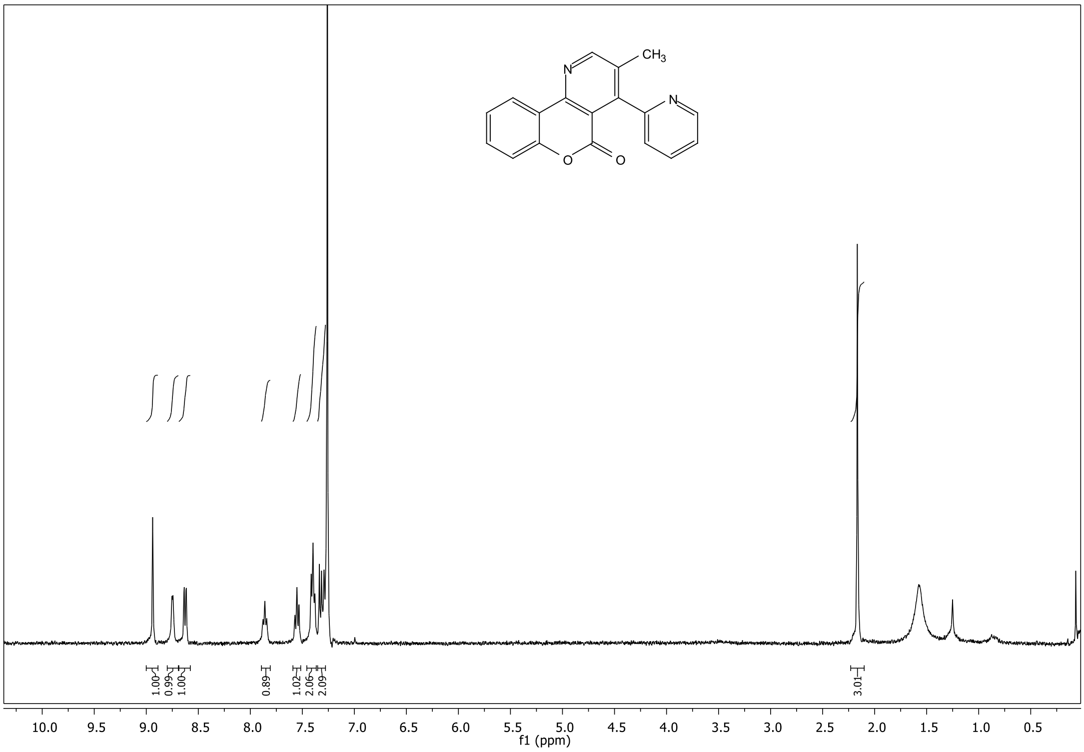


Figure 188: ^{1}H NMR Spectrum of Compound 270h

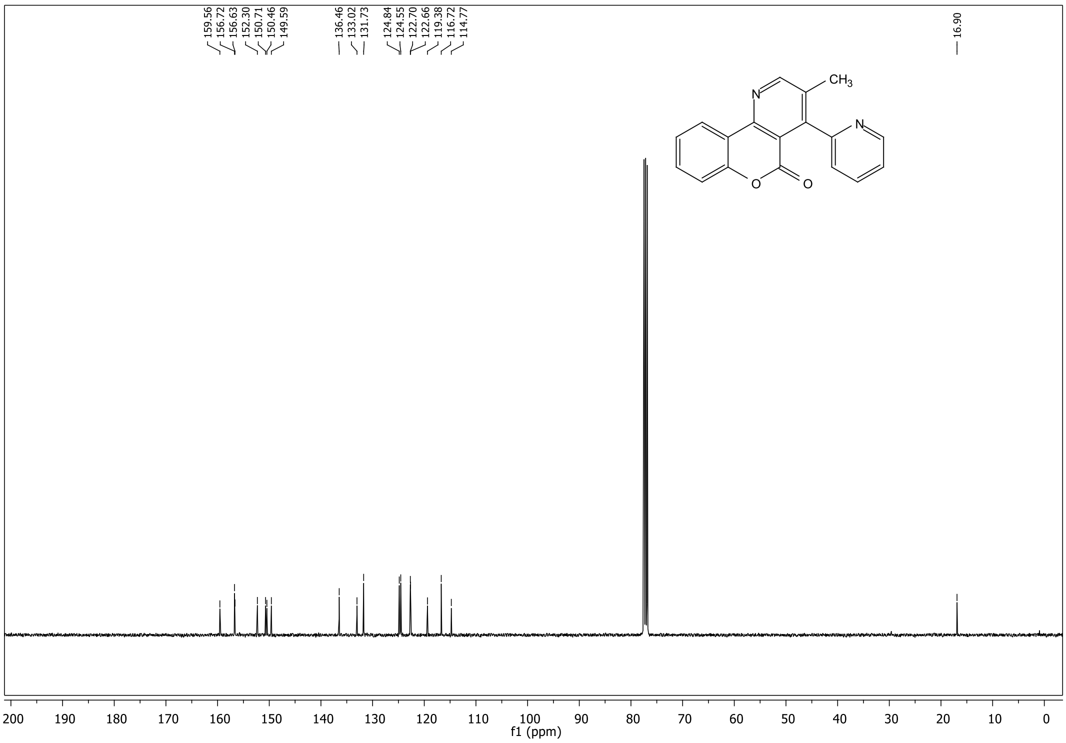


Figure 189: ^{13}C NMR Spectrum of Compound 270h

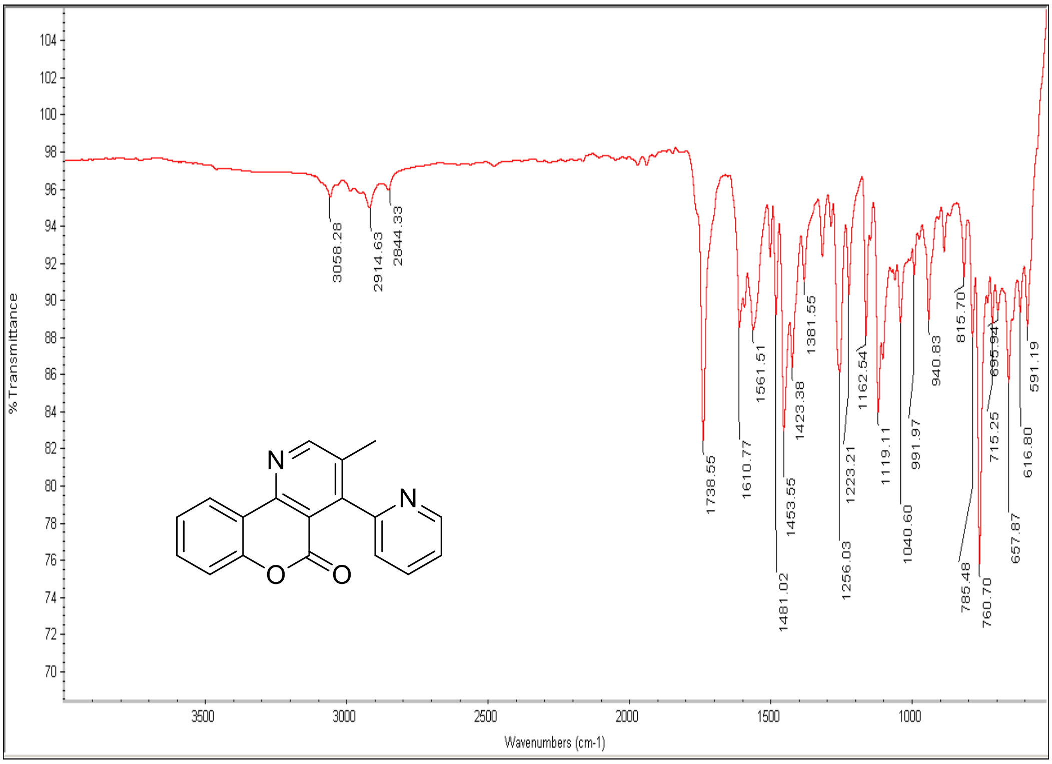


Figure 190: IR Spectrum of Compound 270h

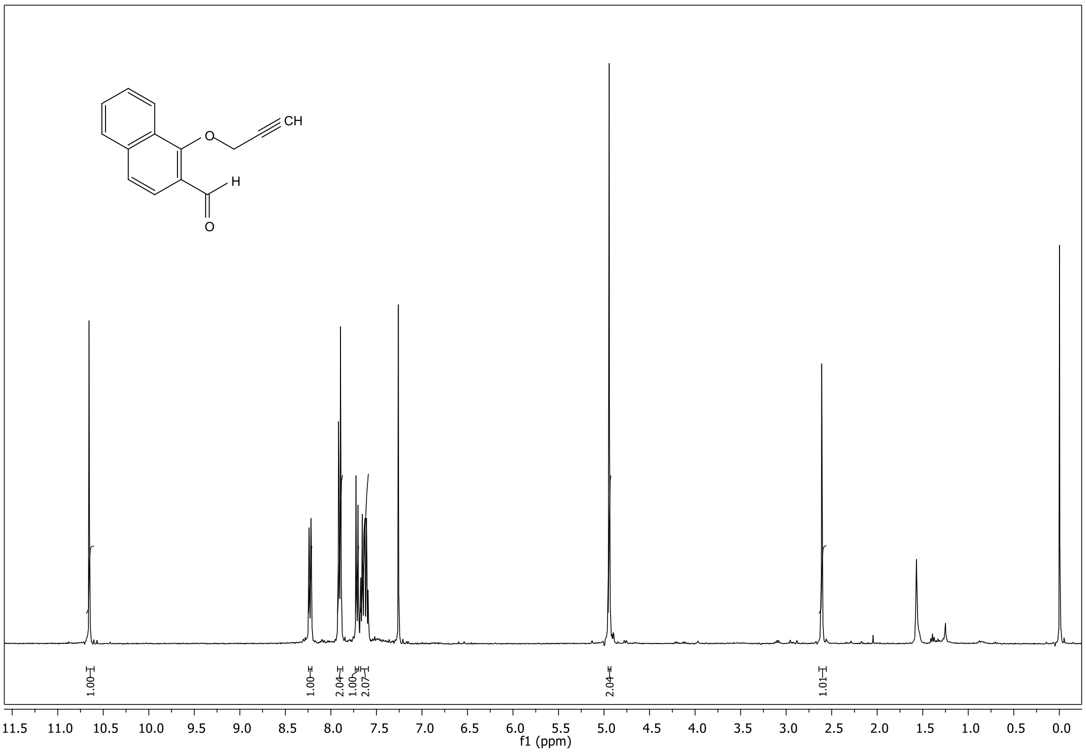


Figure 191: ^{1}H NMR Spectrum of Compound 277

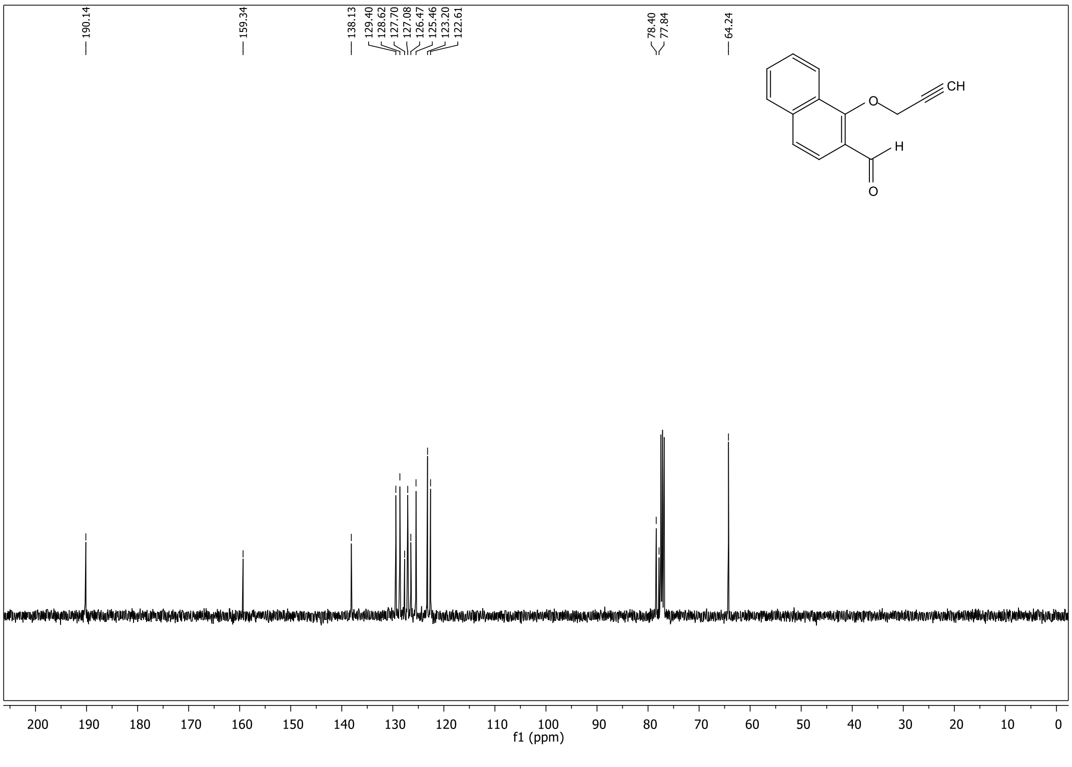


Figure 192: ^{13}C NMR Spectrum of Compound 277

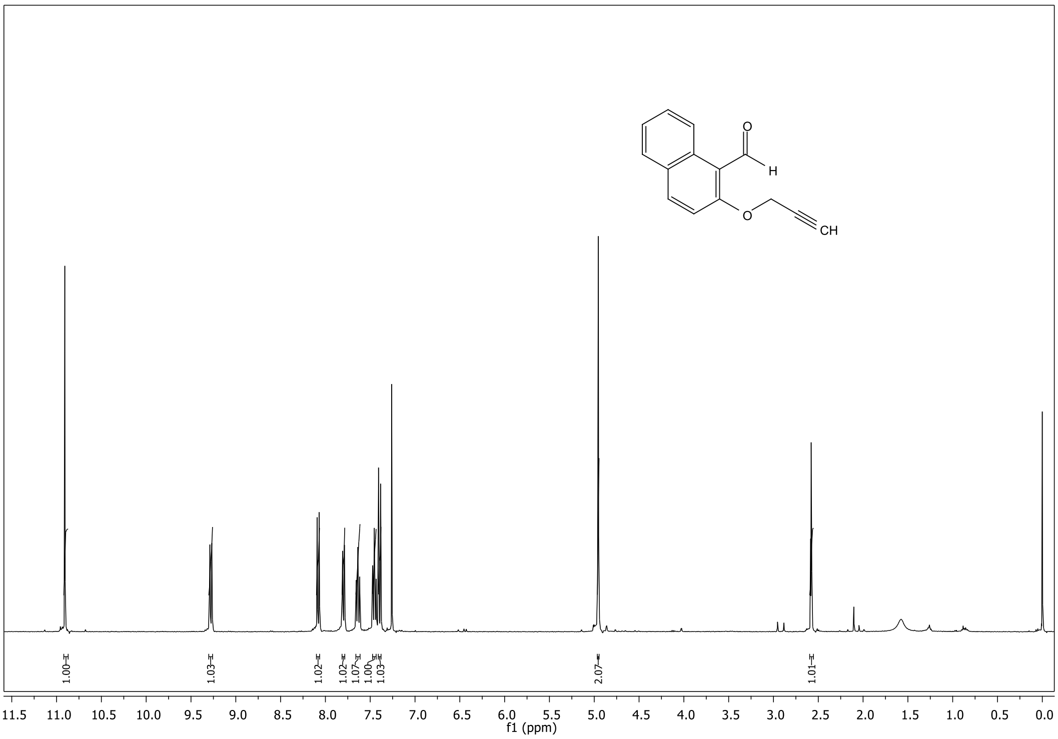


Figure 193: ^{1}H NMR Spectrum of Compound 168

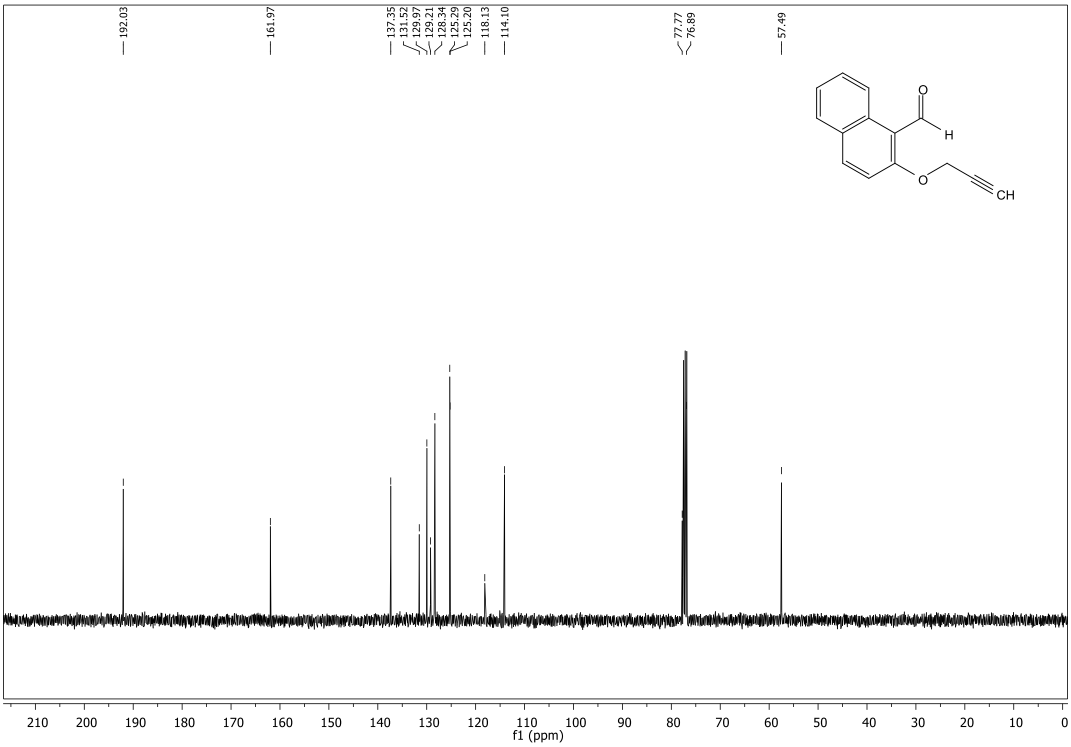


Figure 194: ^{13}C NMR Spectrum of Compound 168

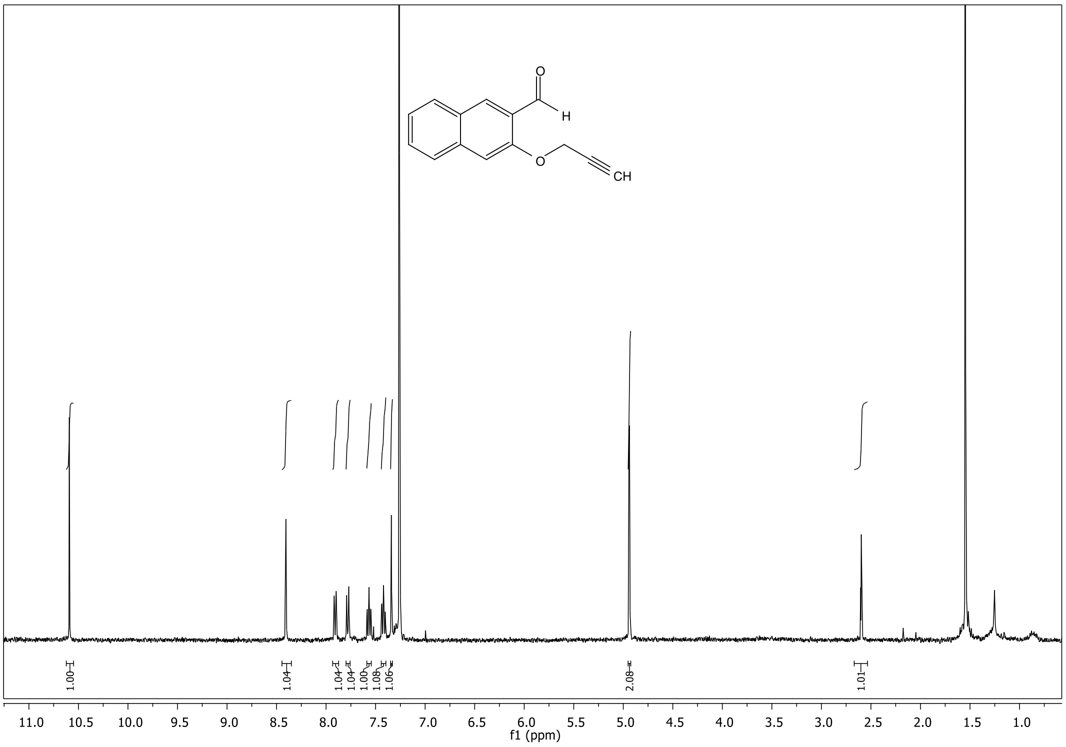


Figure 195: ^{1}H NMR Spectrum of Compound 278

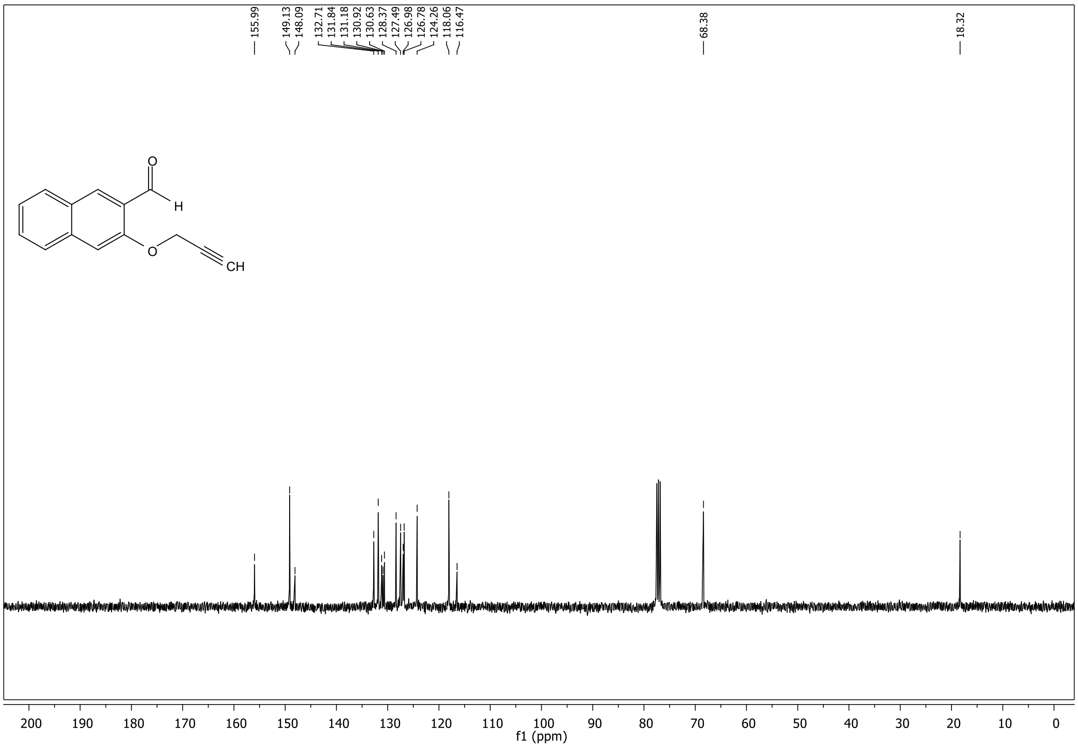


Figure 196: ^{13}C NMR Spectrum of Compound 278

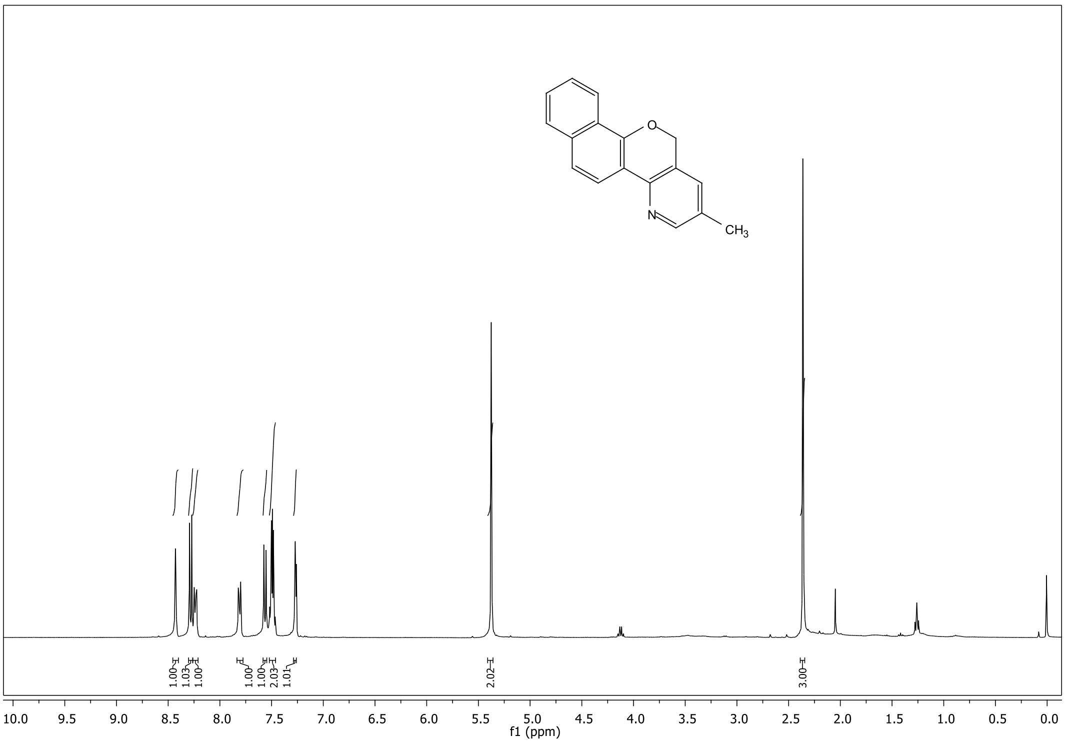


Figure 197: ^{1}H NMR Spectrum of Compound 279

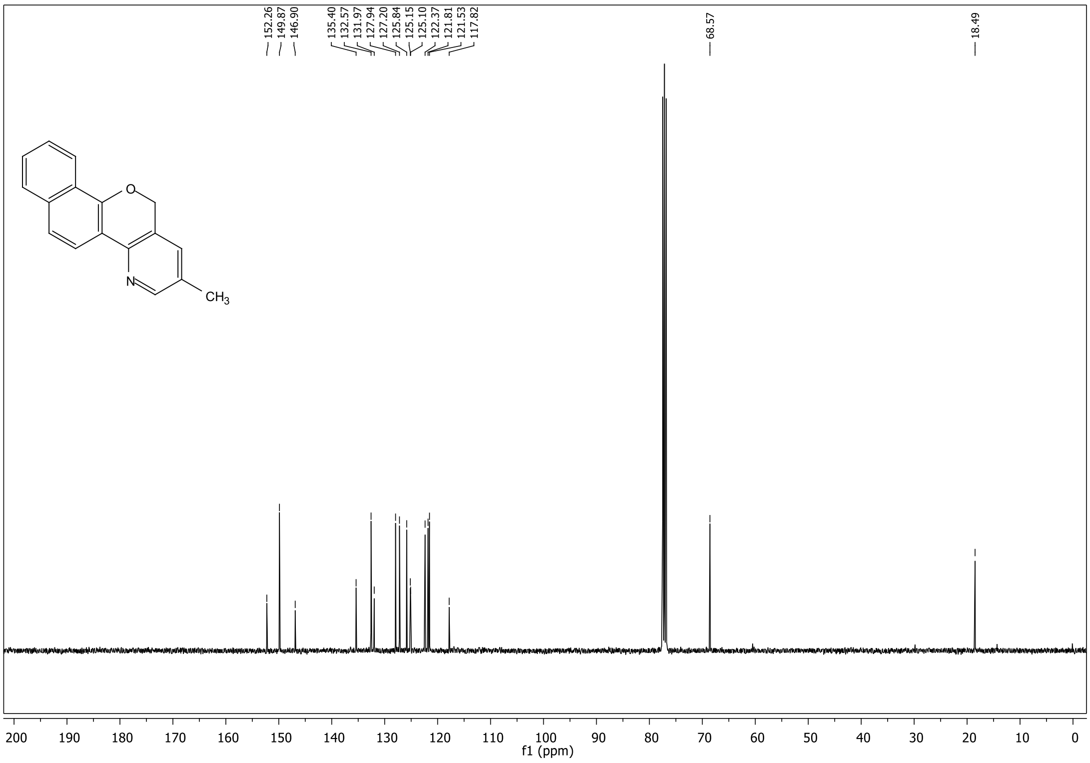


Figure 198: ^{13}C NMR Spectrum of Compound 279

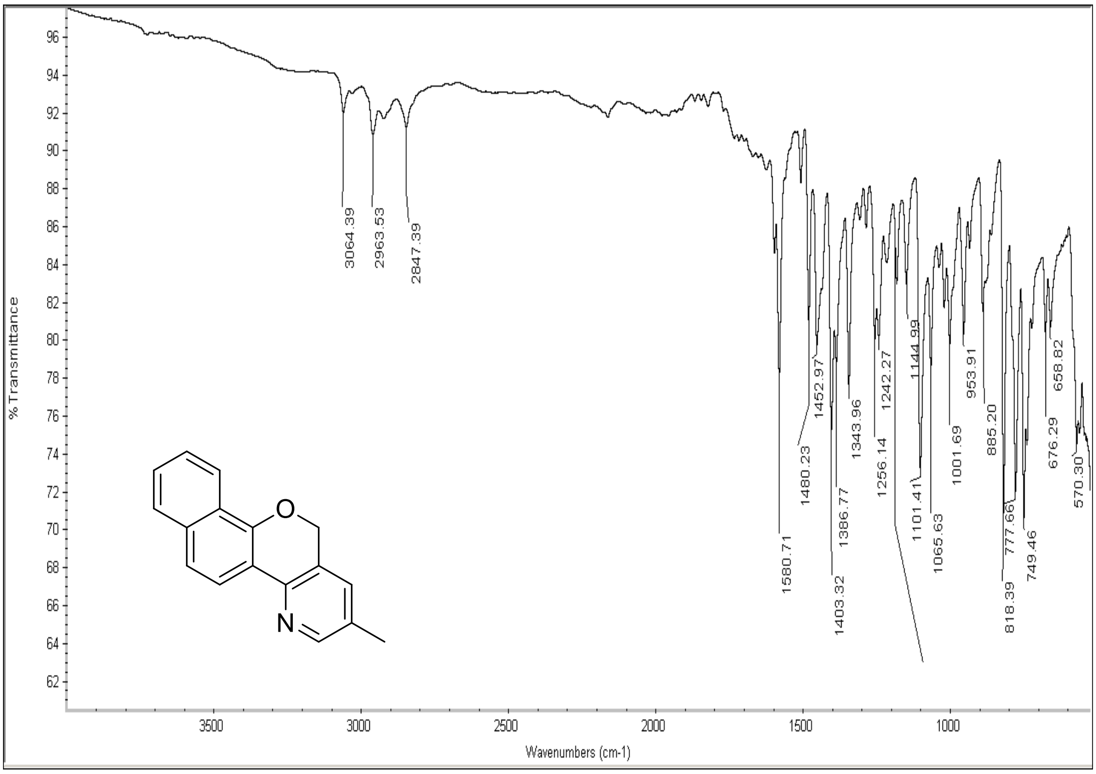


Figure 199: IR Spectrum of Compound 279

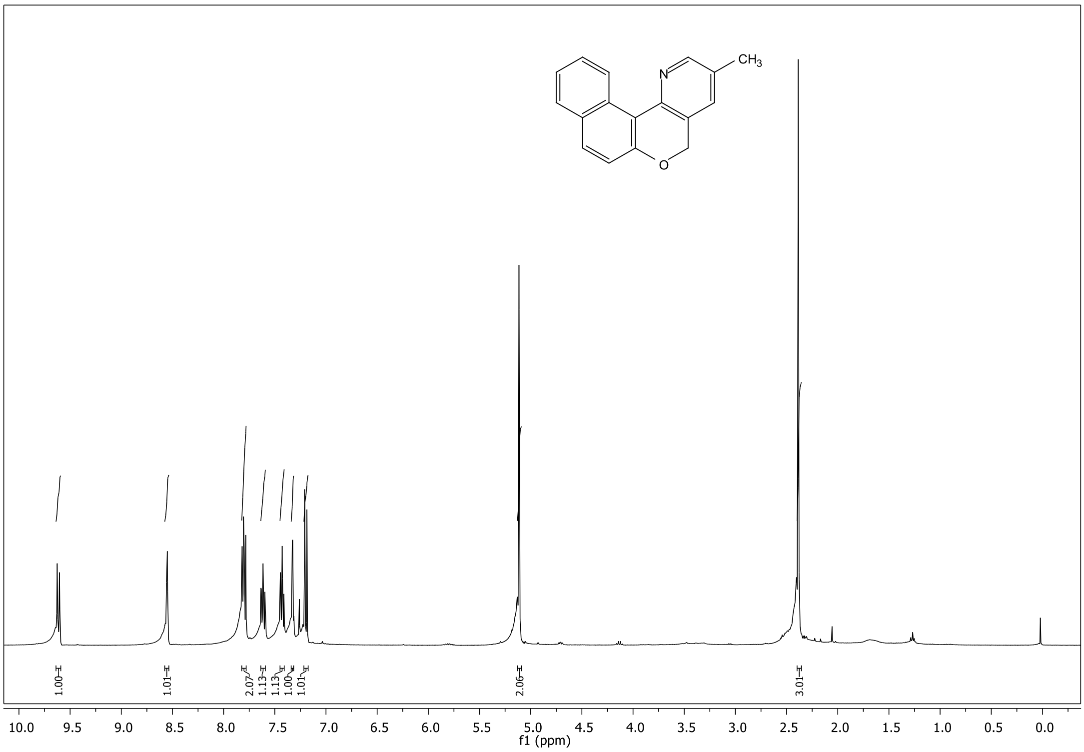


Figure 200: ^{1}H NMR Spectrum of Compound 280

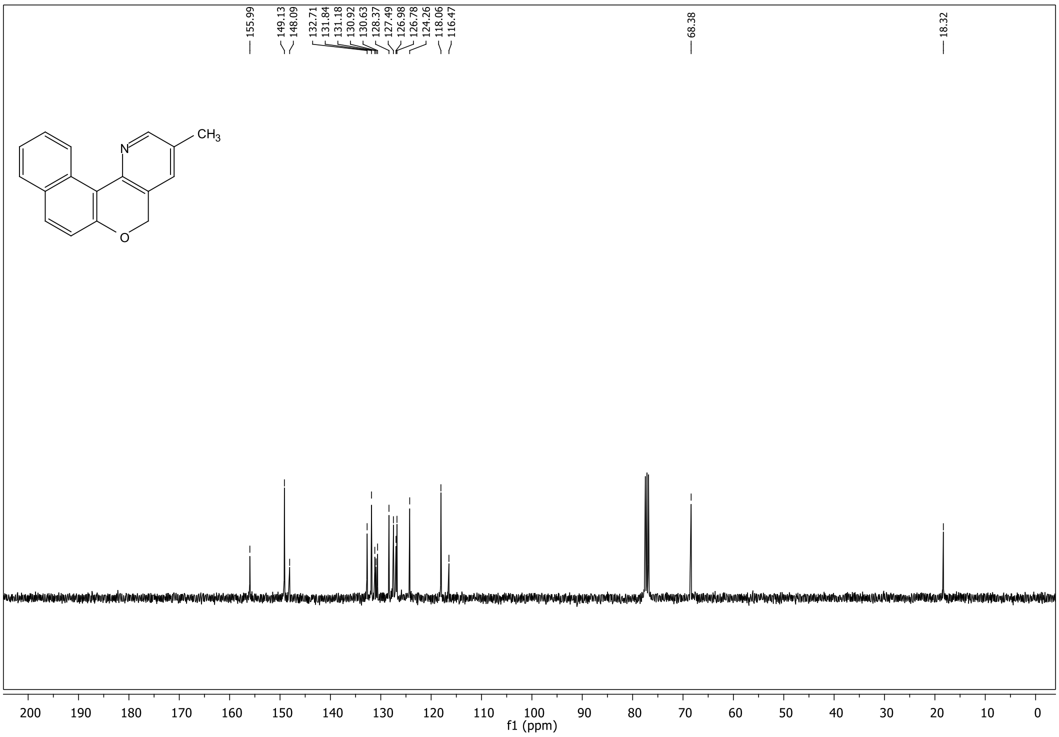


Figure 201: ^{13}C NMR Spectrum of Compound 280

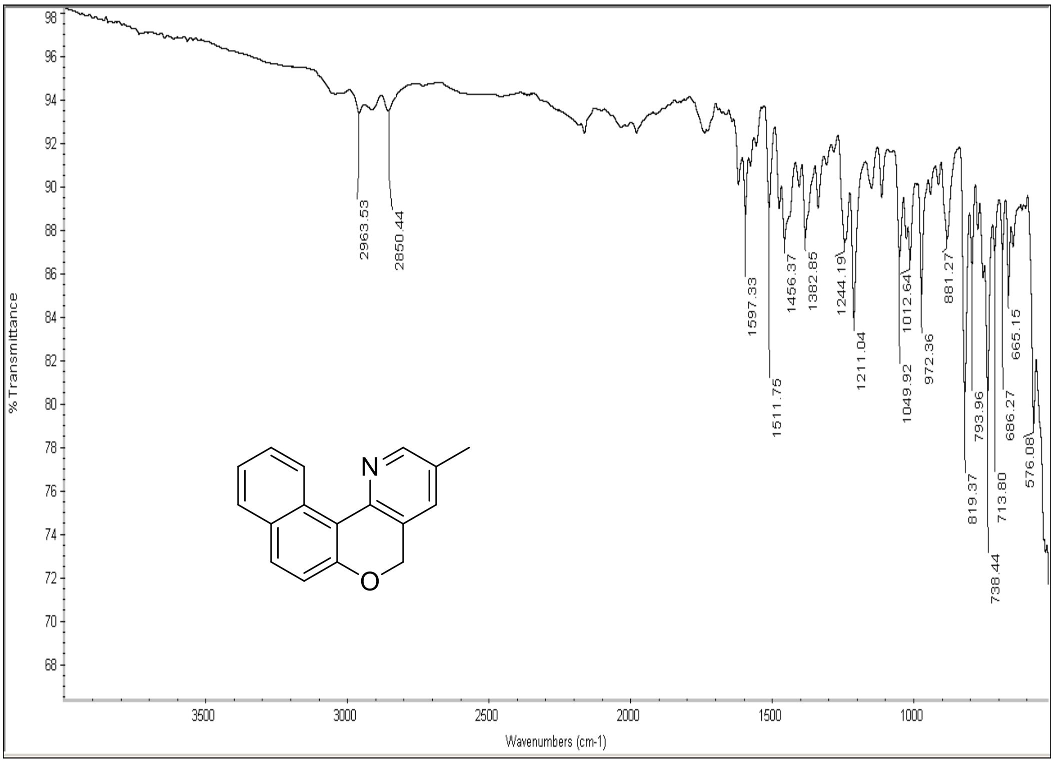


Figure 202: IR Spectrum of Compound 280

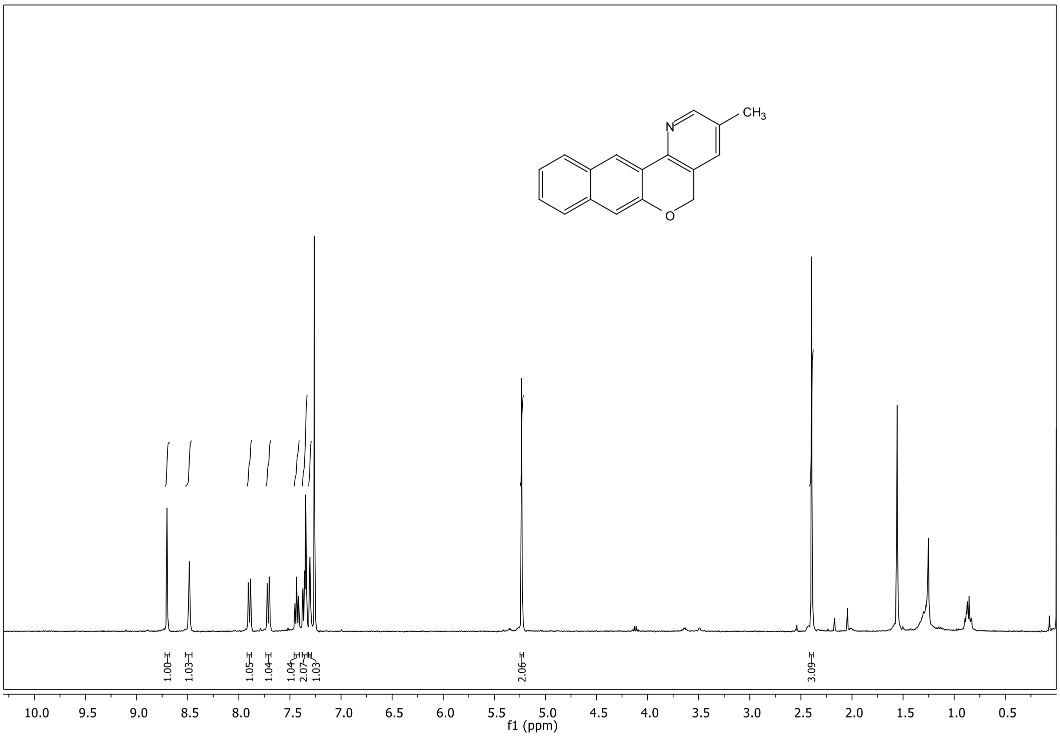


Figure 203: ^{1}H NMR Spectrum of Compound 281

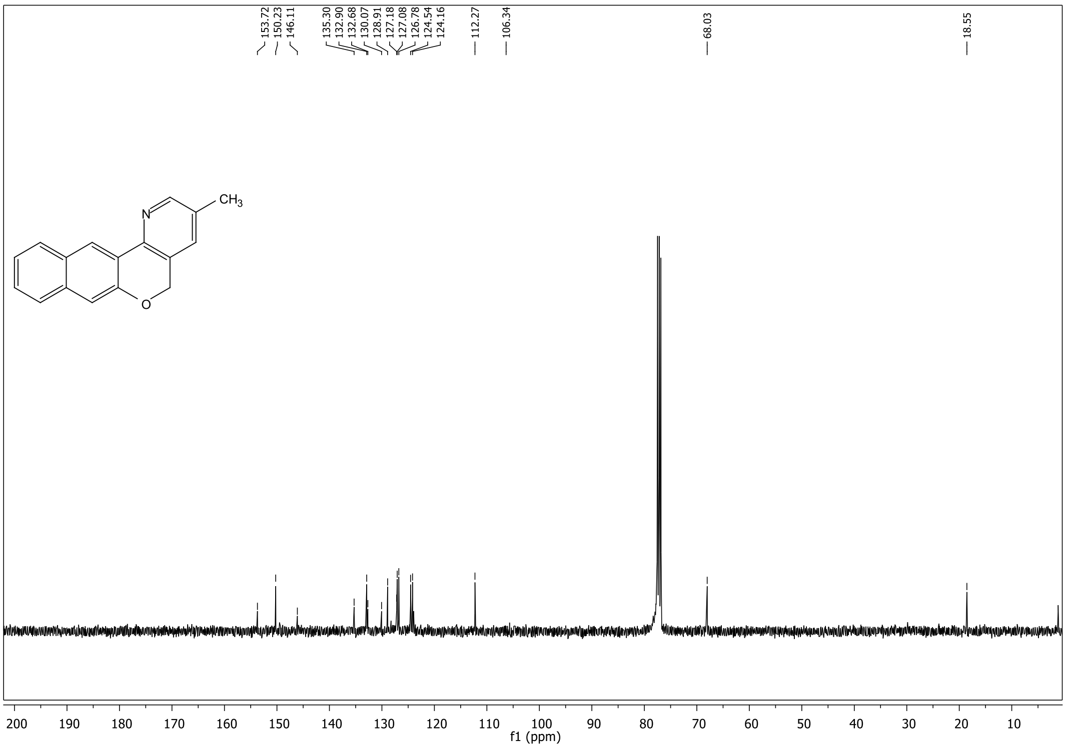


Figure 204: ^{13}C NMR Spectrum of Compound 281

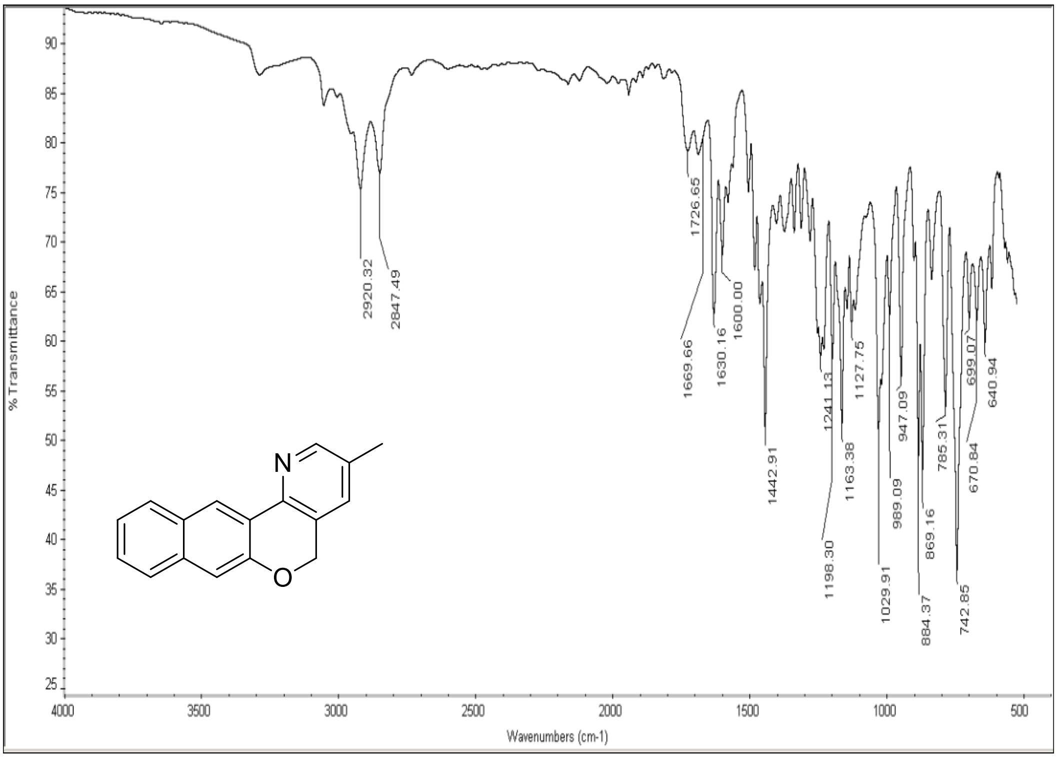


Figure 205: IR Spectrum of Compound 281

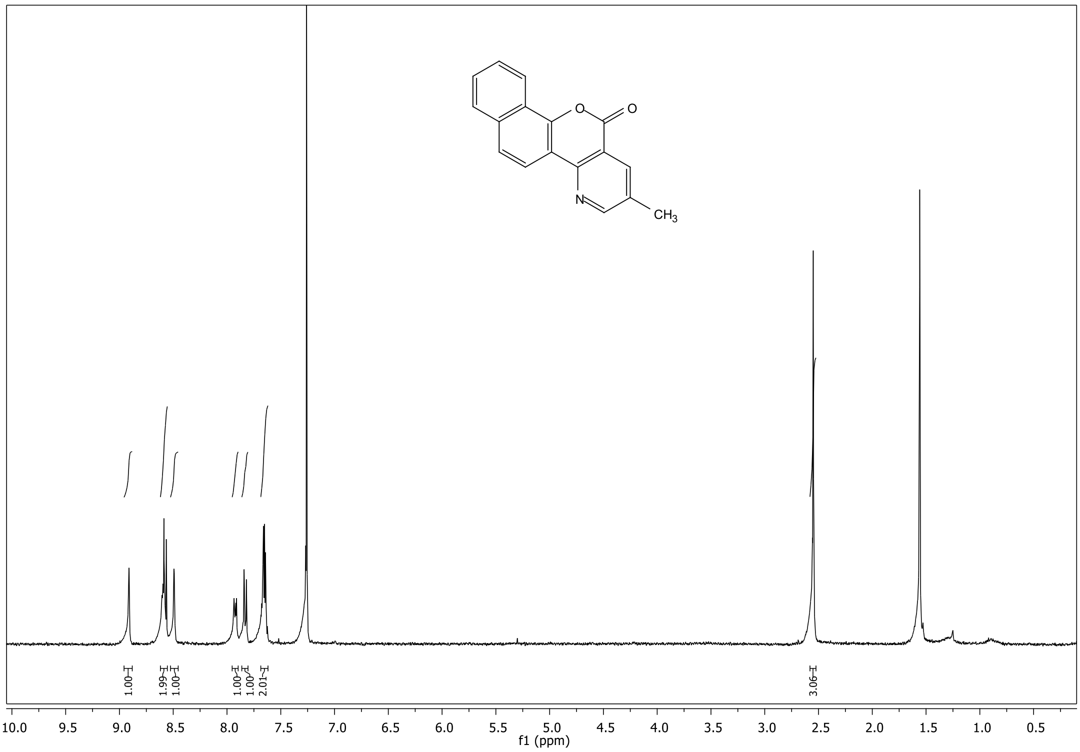


Figure 206: ^{1}H NMR Spectrum of Compound 240

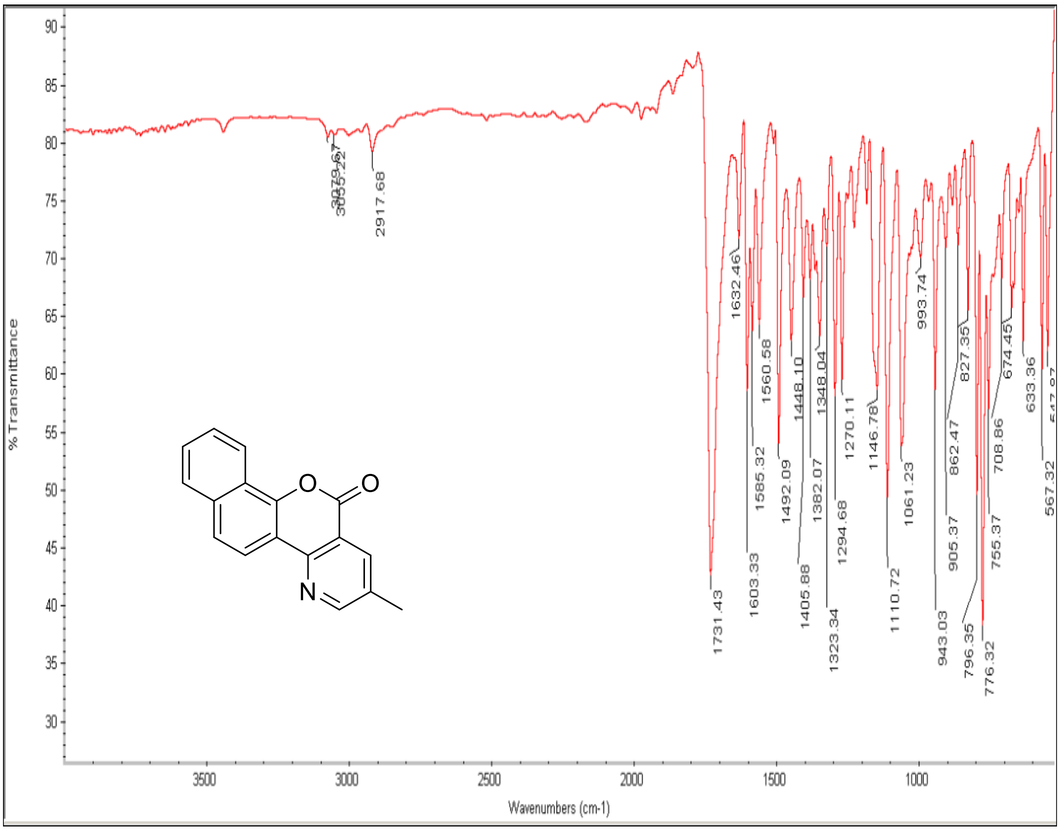


Figure 207: IR Spectrum of Compound 240

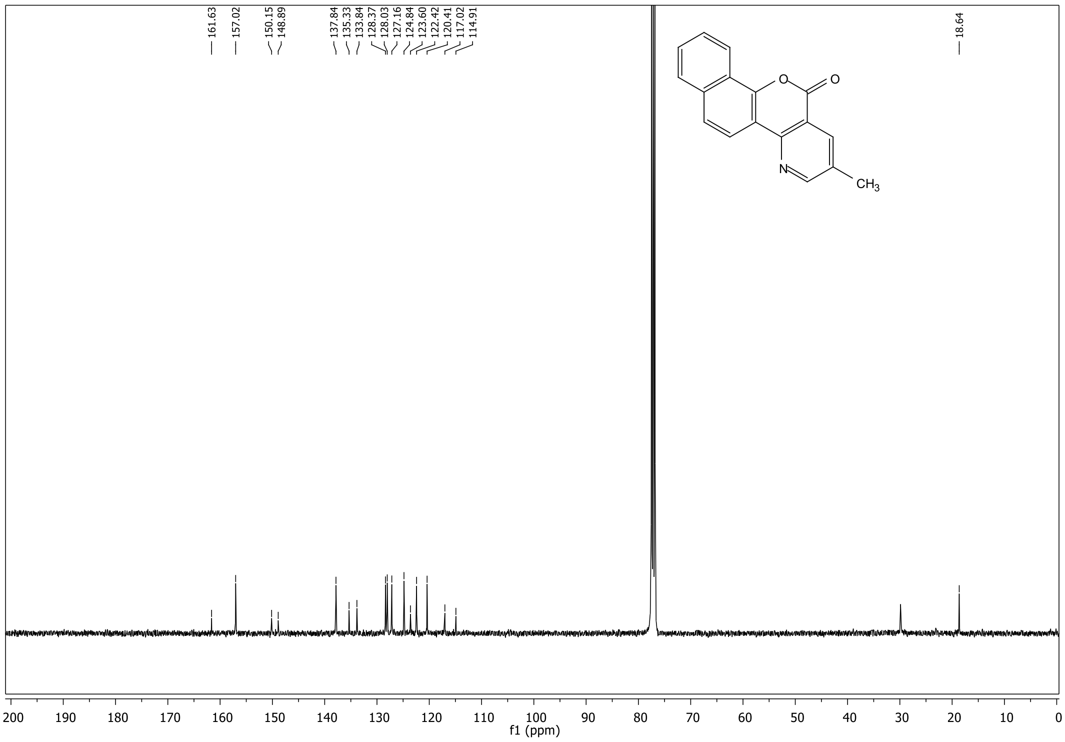


Figure 208 : ^{13}C NMR Spectrum of Compound 240

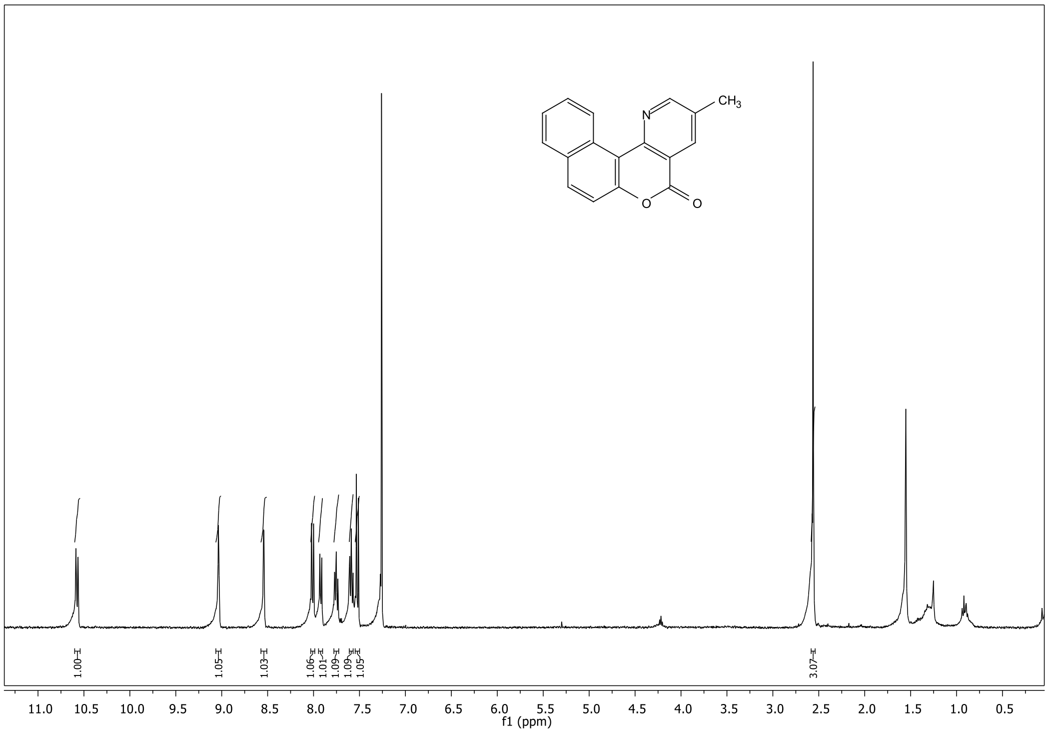


Figure 209: ^{1}H NMR Spectrum of Compound 241

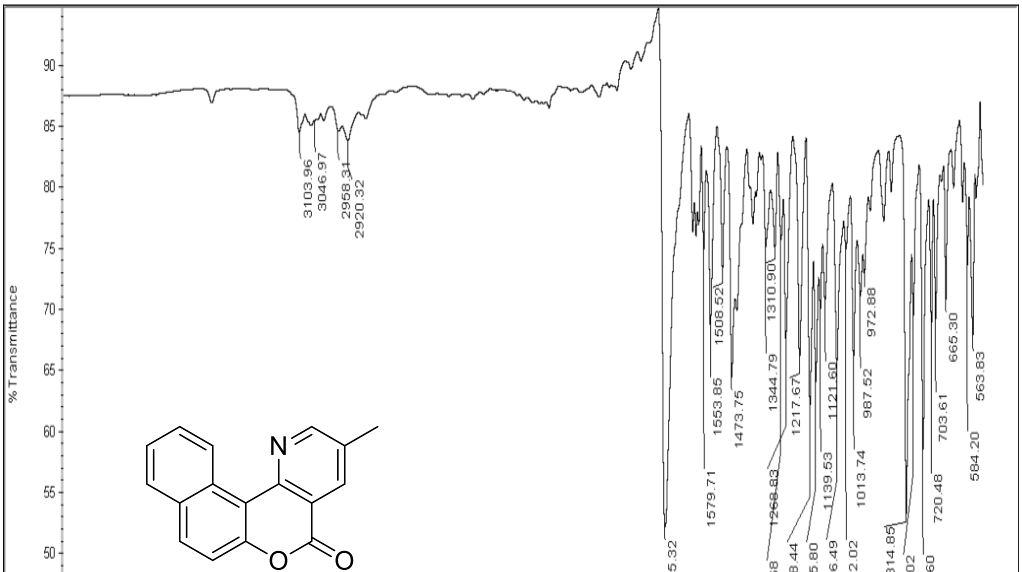


Figure 210 : IR Spectrum of Compound 241

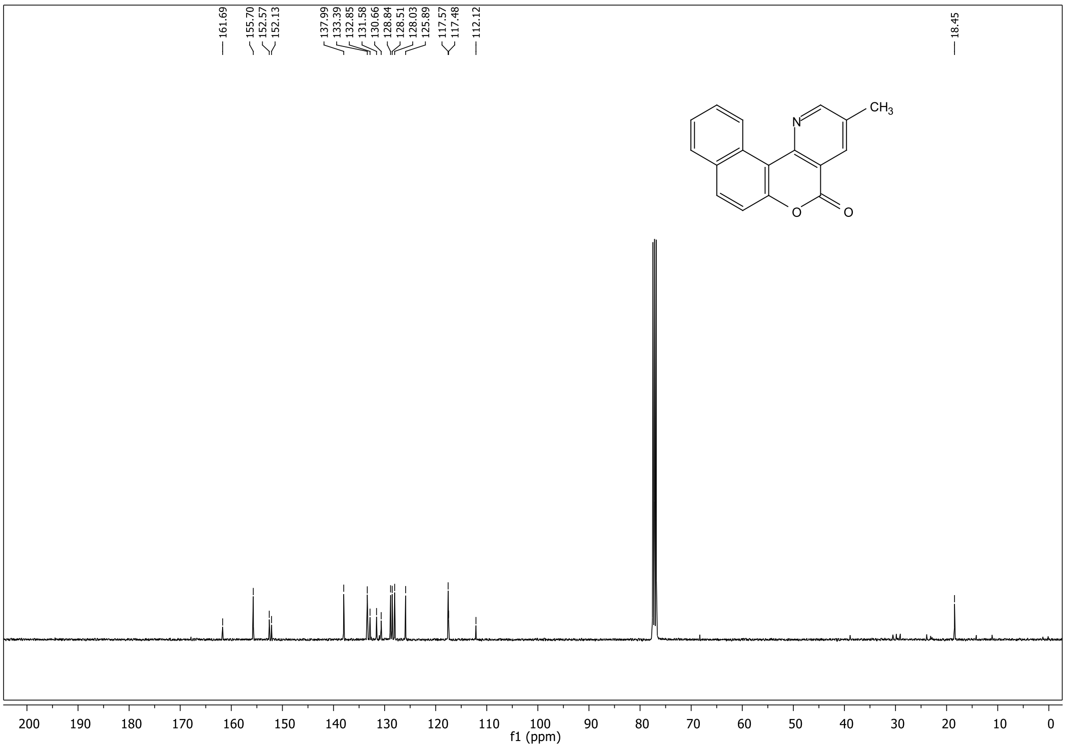


Figure 211: ^{13}C NMR Spectrum of Compound 241

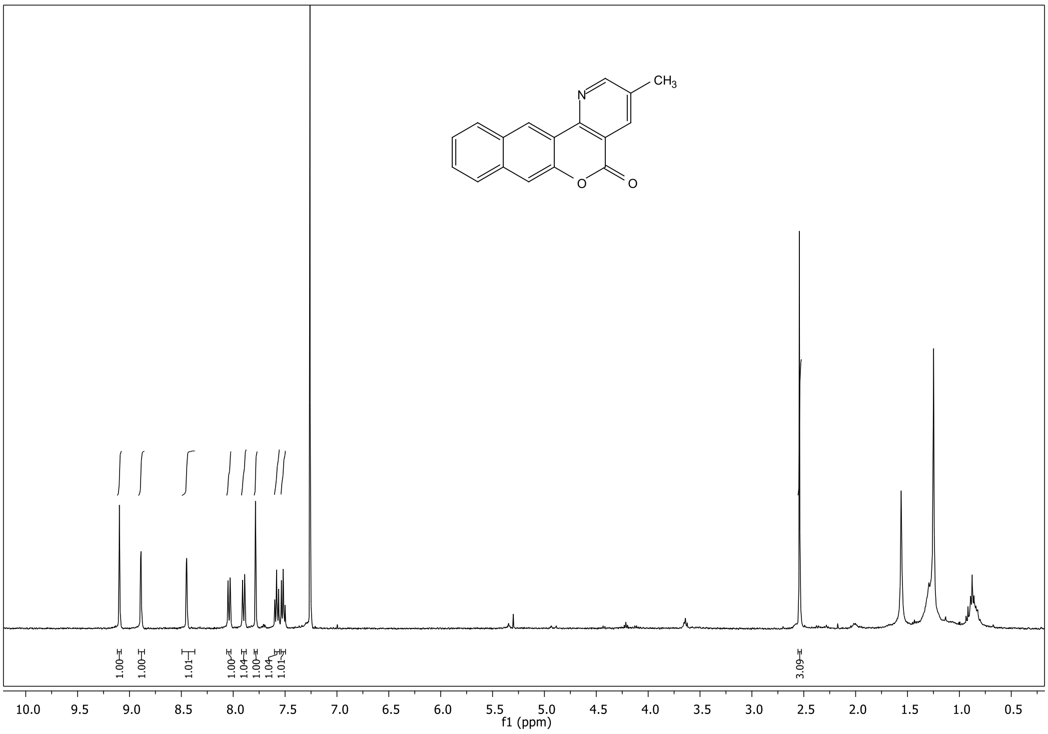


Figure 212: ^{1}H NMR Spectrum of Compound 242

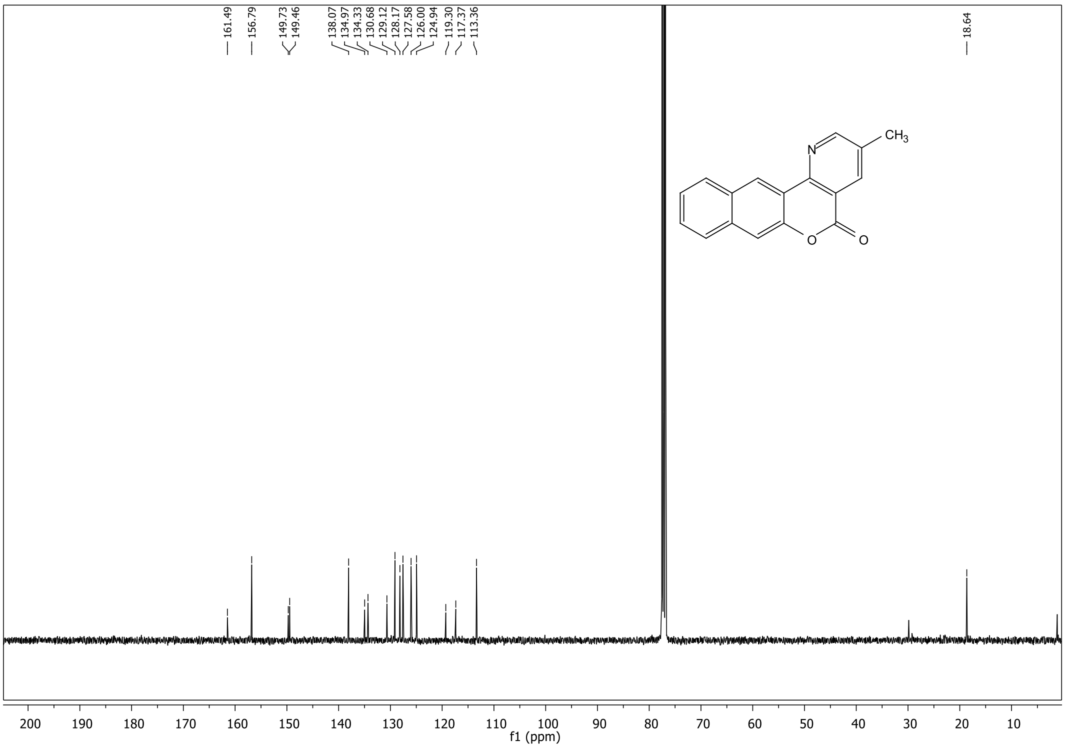


Figure 213: ^{13}C NMR Spectrum of Compound 242

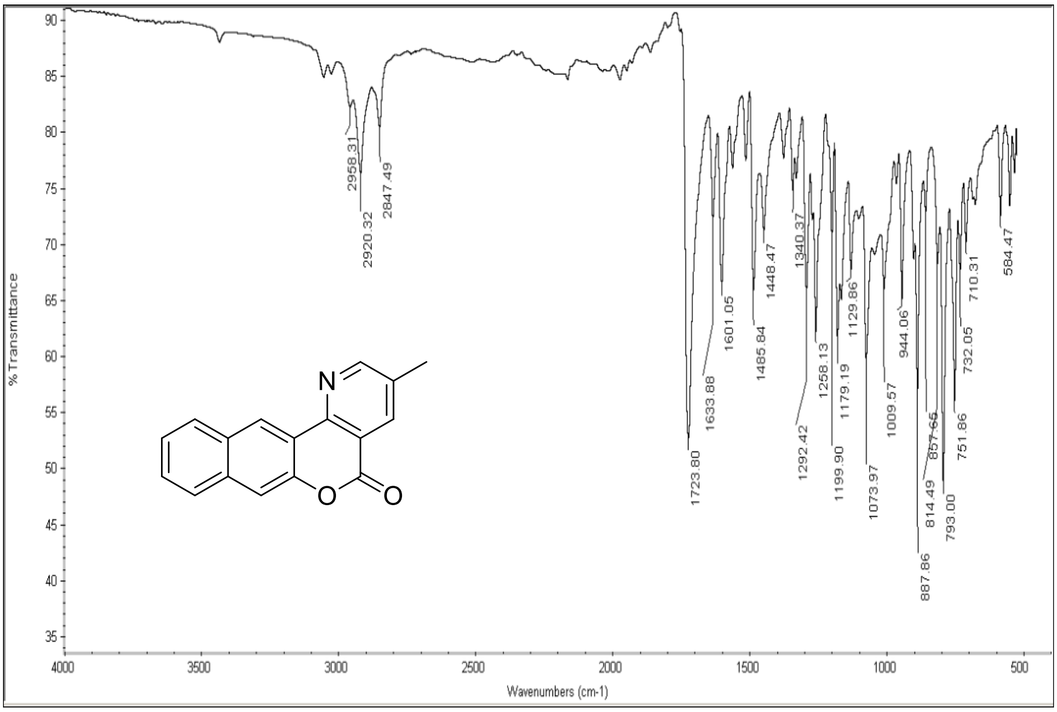


Figure 214: IR Spectrum of Compound 242

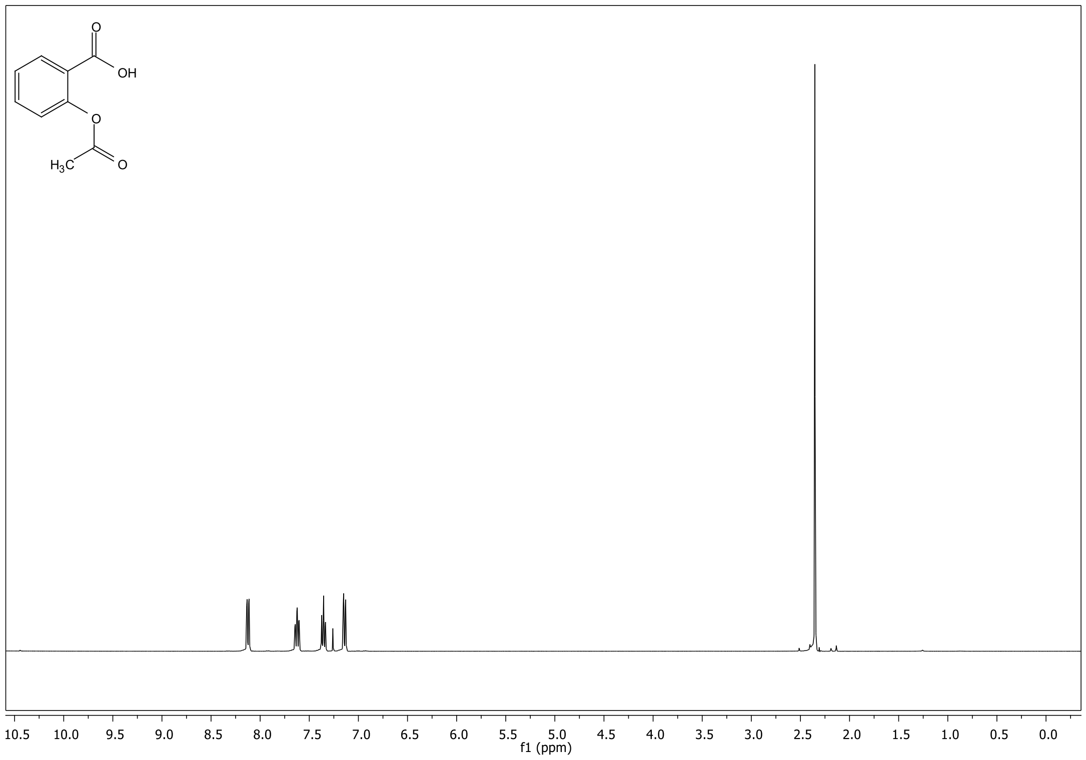


Figure 215: ^{1}H NMR Spectrum of Compound 282

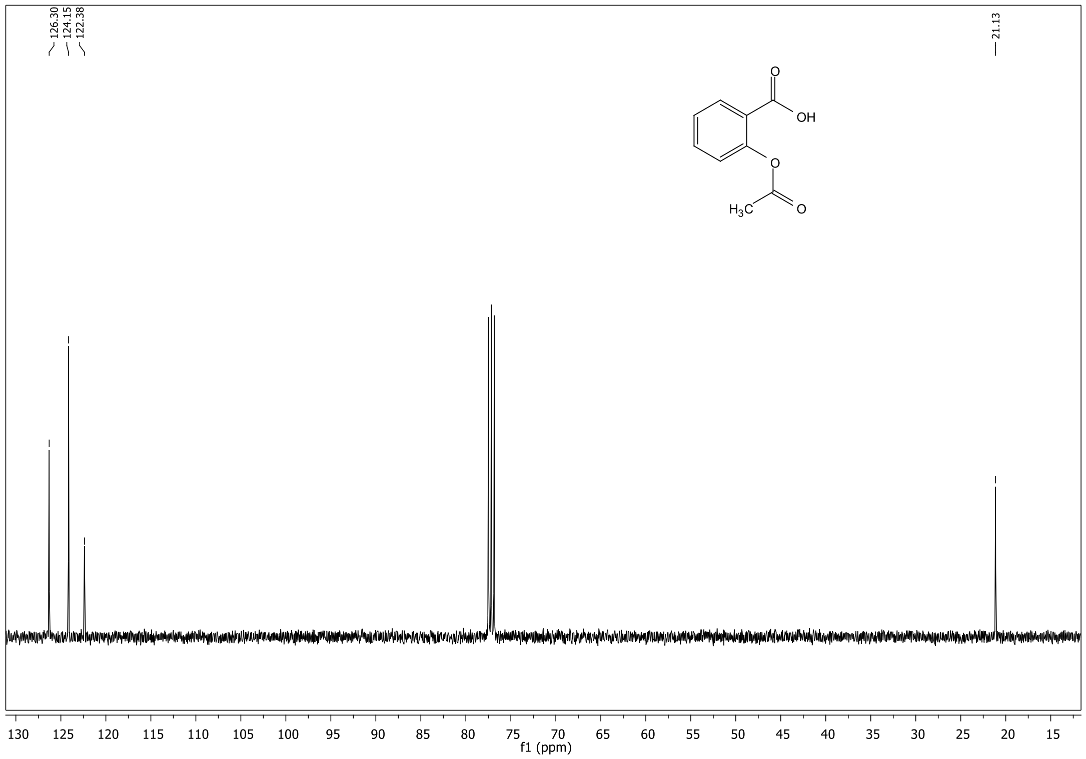


Figure 216: ^{13}C NMR Spectrum of Compound 282

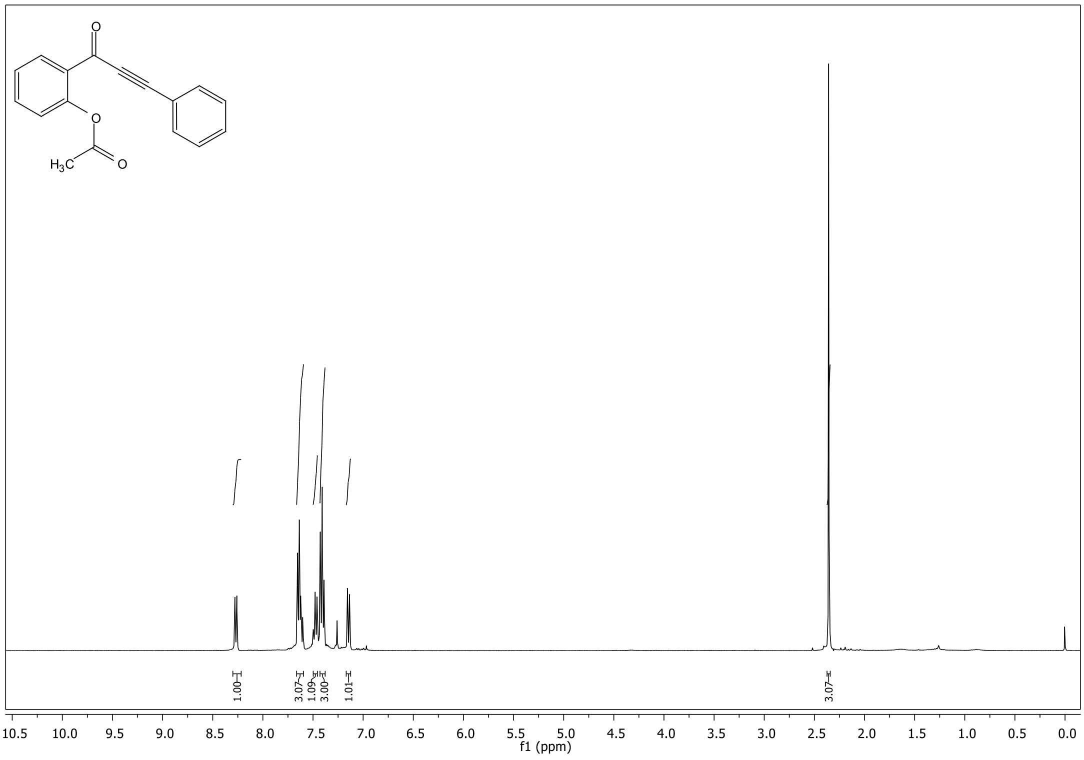


Figure 217: ^{1}H NMR Spectrum of Compound 285

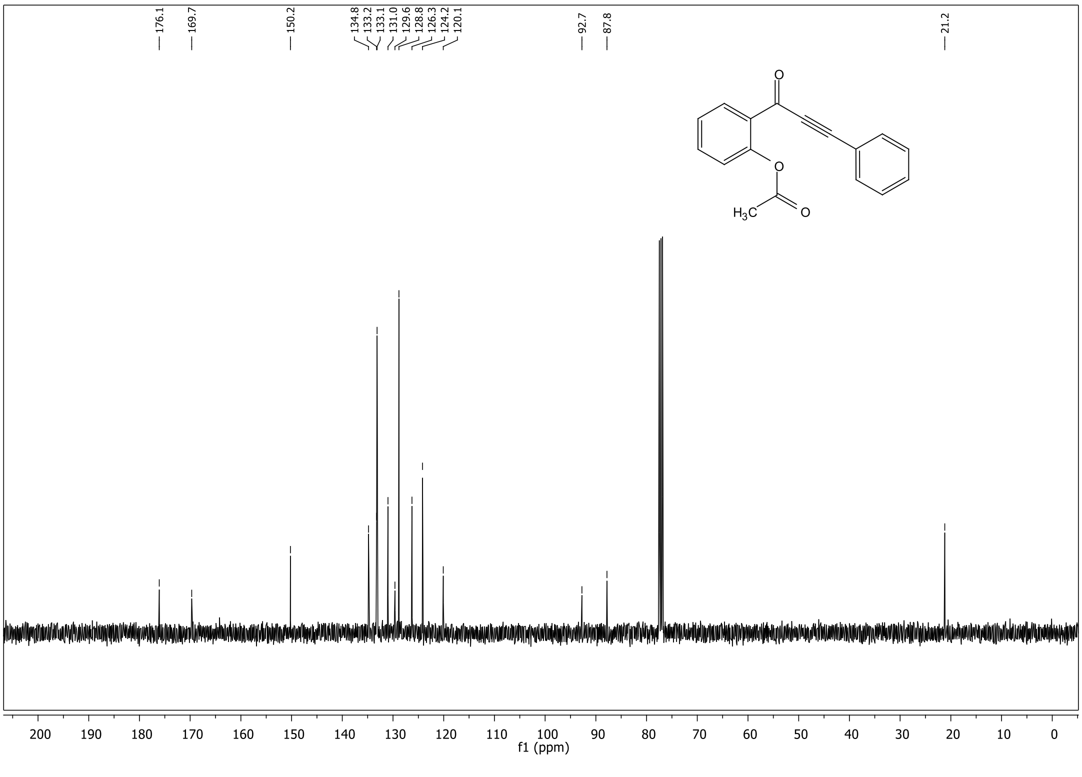


Figure 218: ^{13}C NMR Spectrum of Compound 285

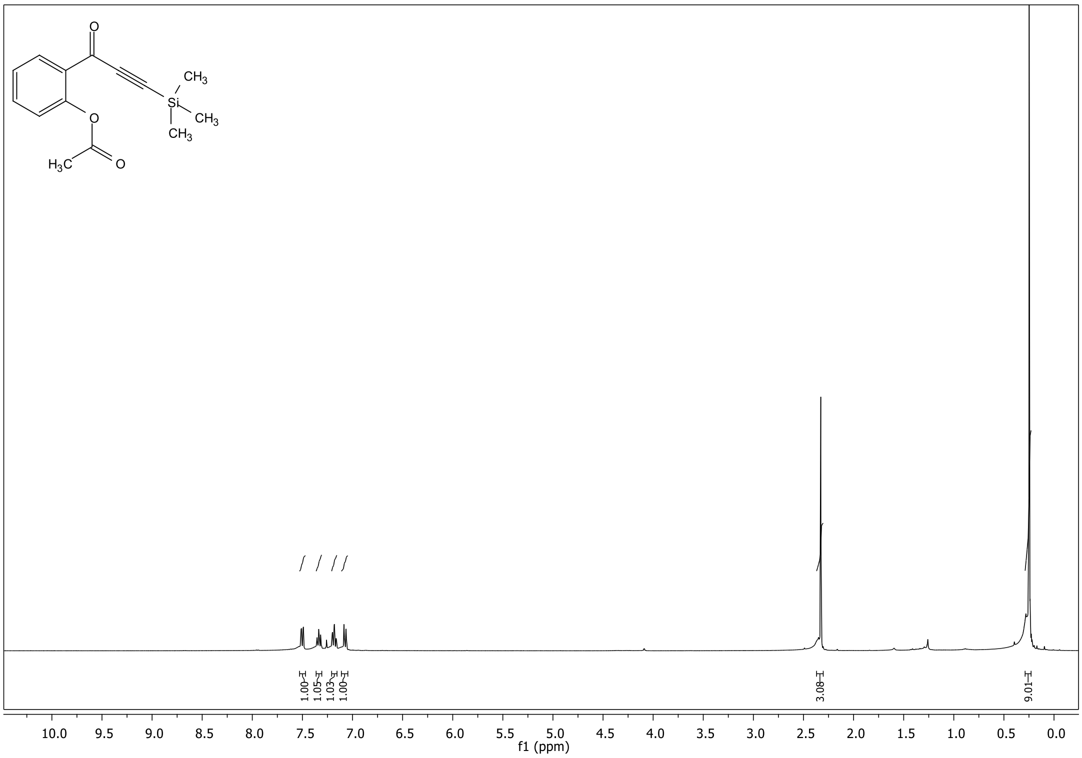


Figure 219: ^{1}H NMR Spectrum of Compound 295

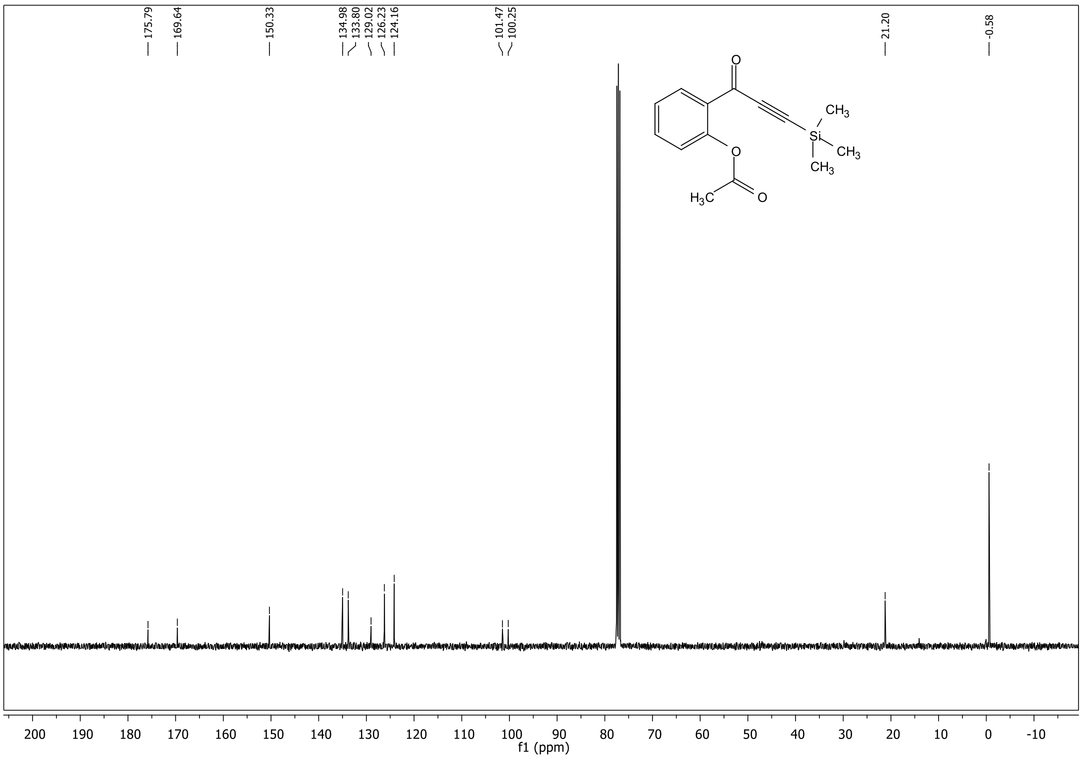


Figure 220: ^{13}C NMR Spectrum of Compound 295

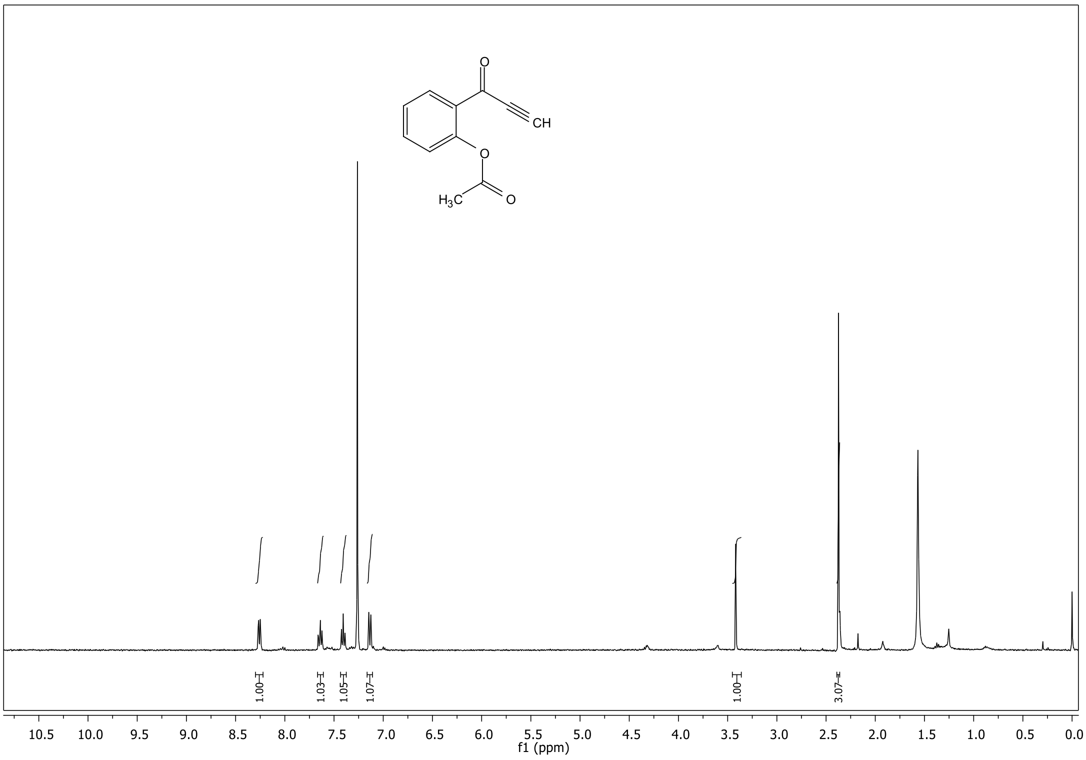


Figure 221: ^{1}H NMR Spectrum of Compound 296

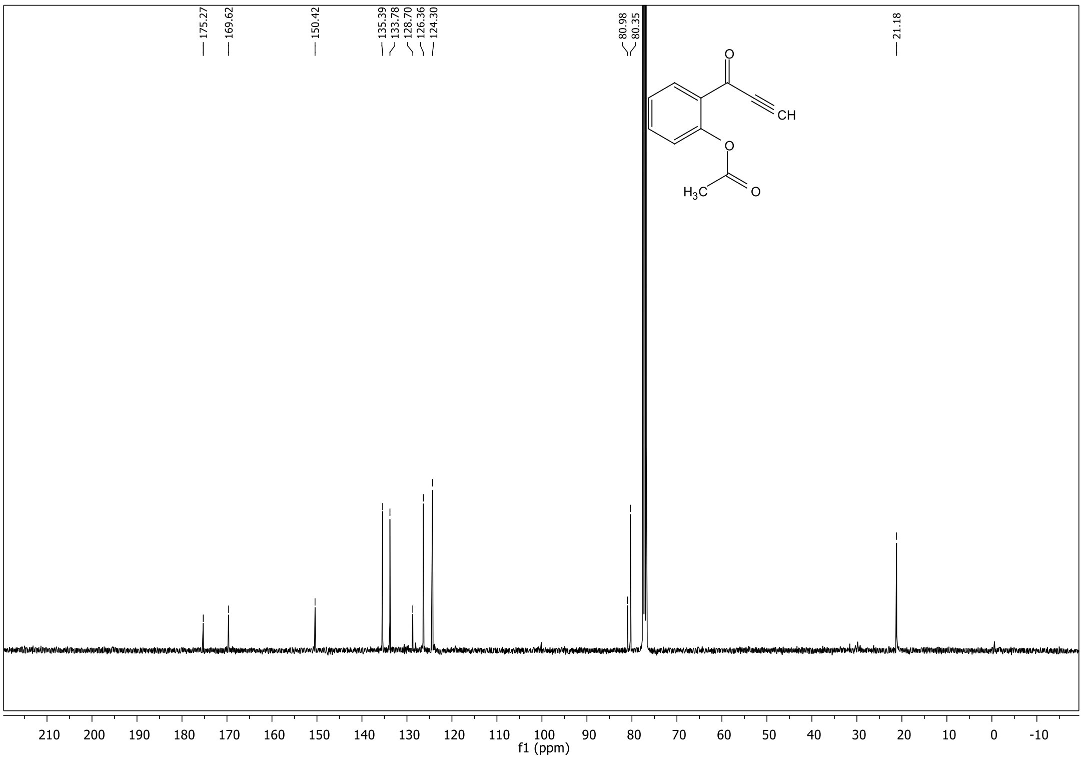


Figure 222: ^{13}C NMR Spectrum of Compound 296

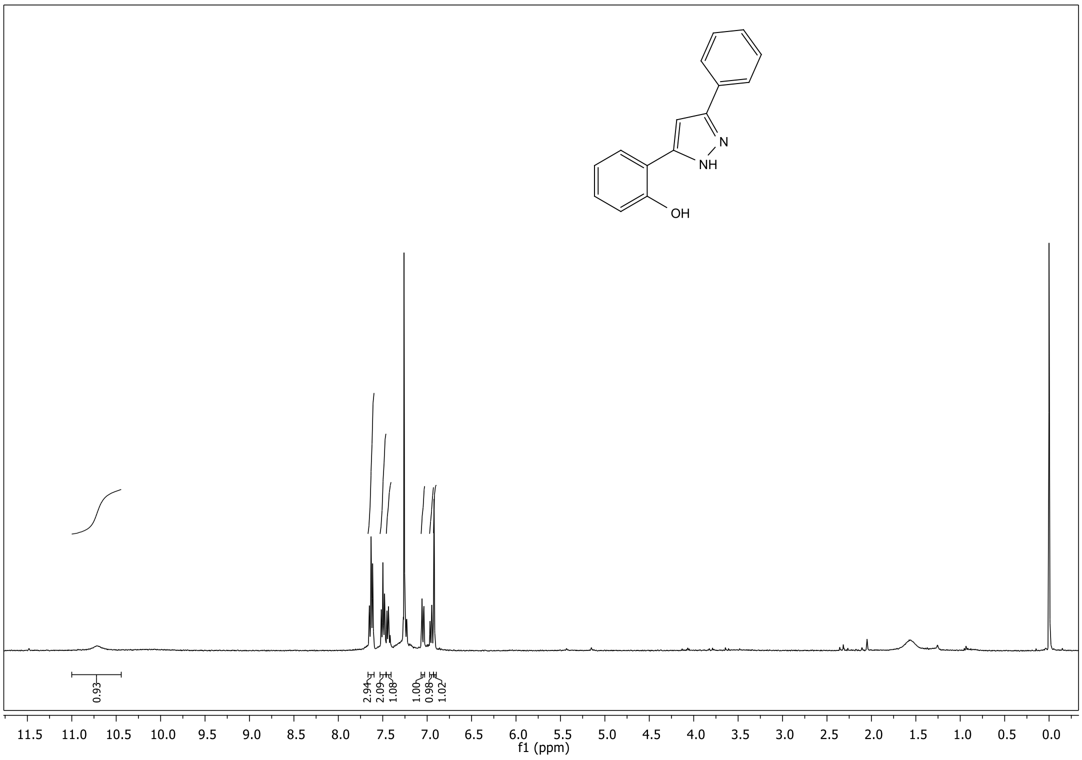


Figure 223: ^{1}H NMR Spectrum of Compound 286

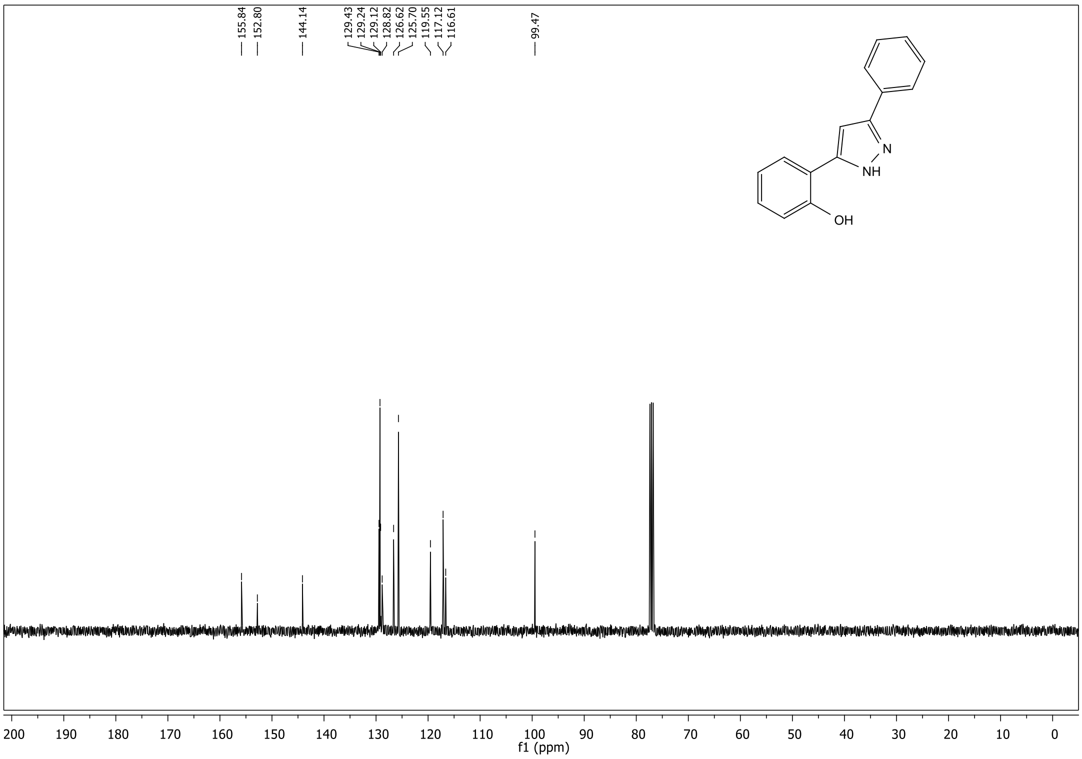


Figure 224: ^{13}C NMR Spectrum of Compound 286

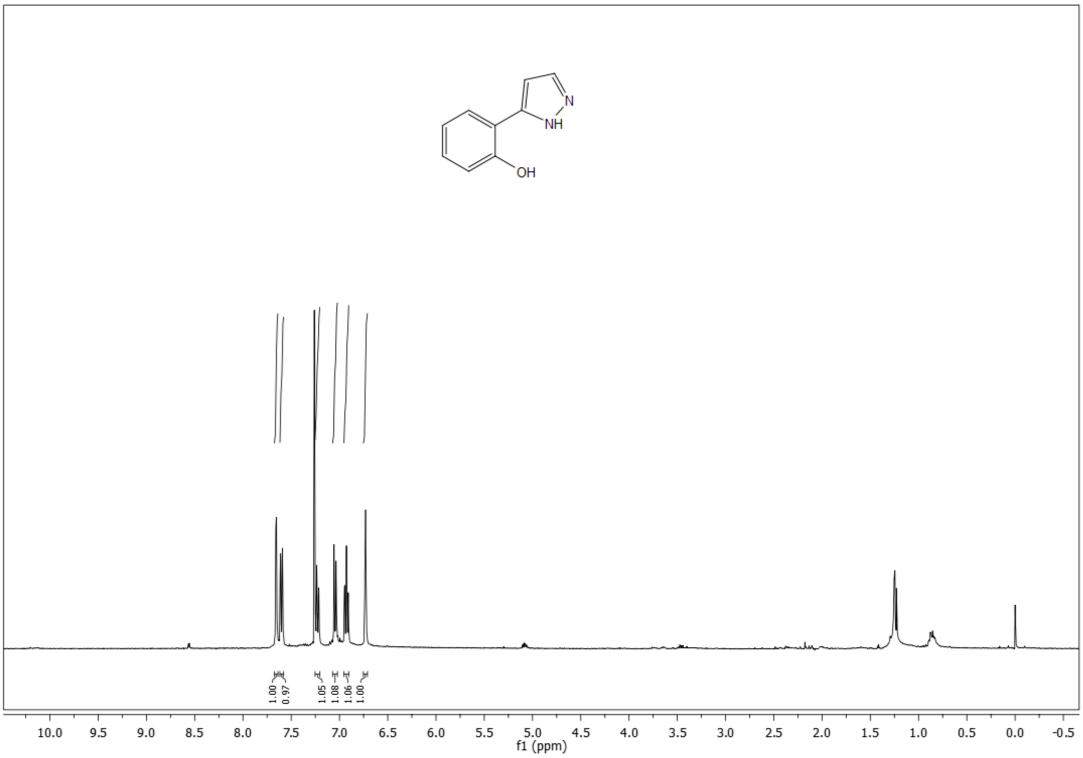


Figure 225: ^{1}H NMR Spectrum of Compound 297

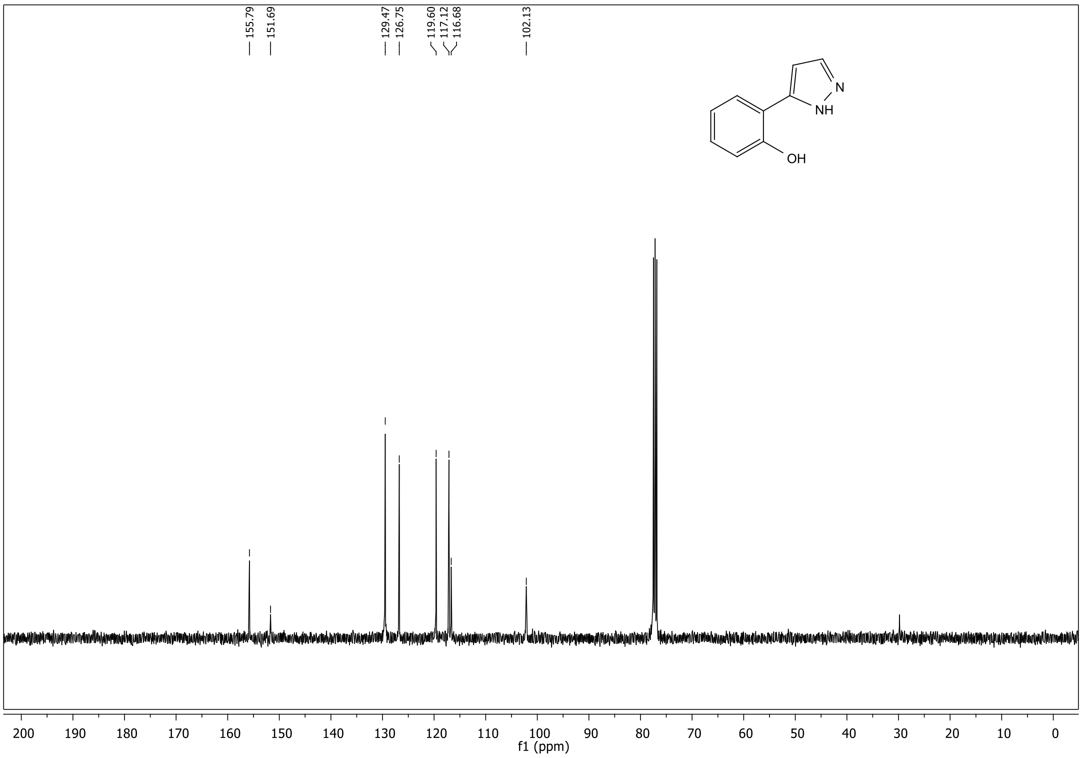


Figure 226: ^{13}C NMR Spectrum of Compound 297

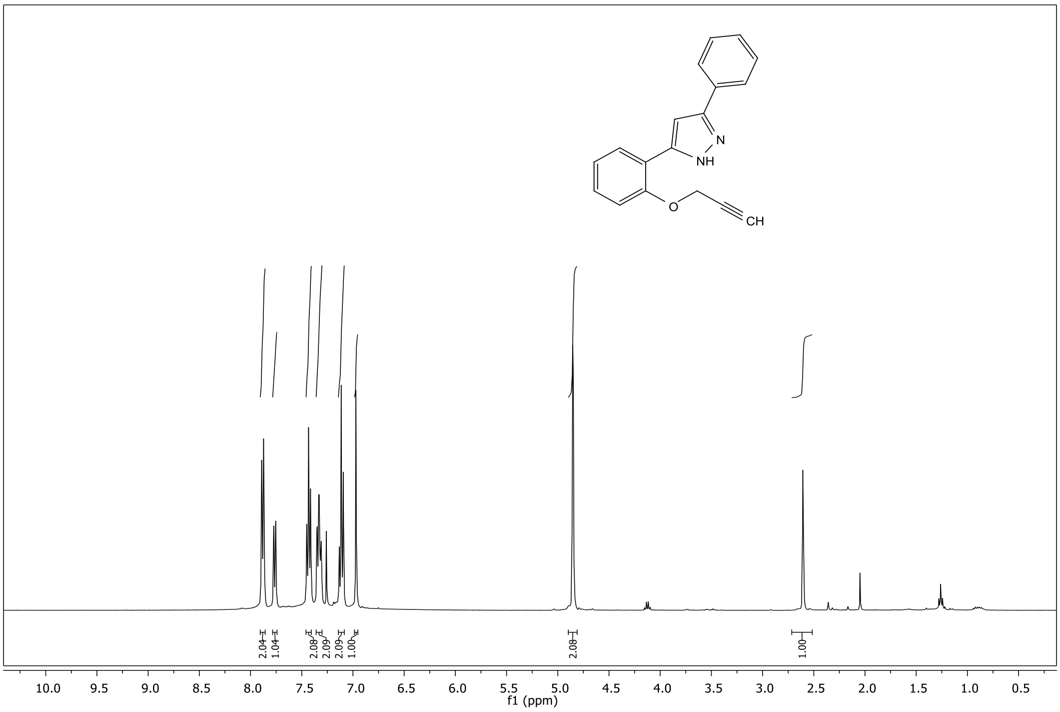


Figure 227: ^{1}H NMR Spectrum of Compound 290

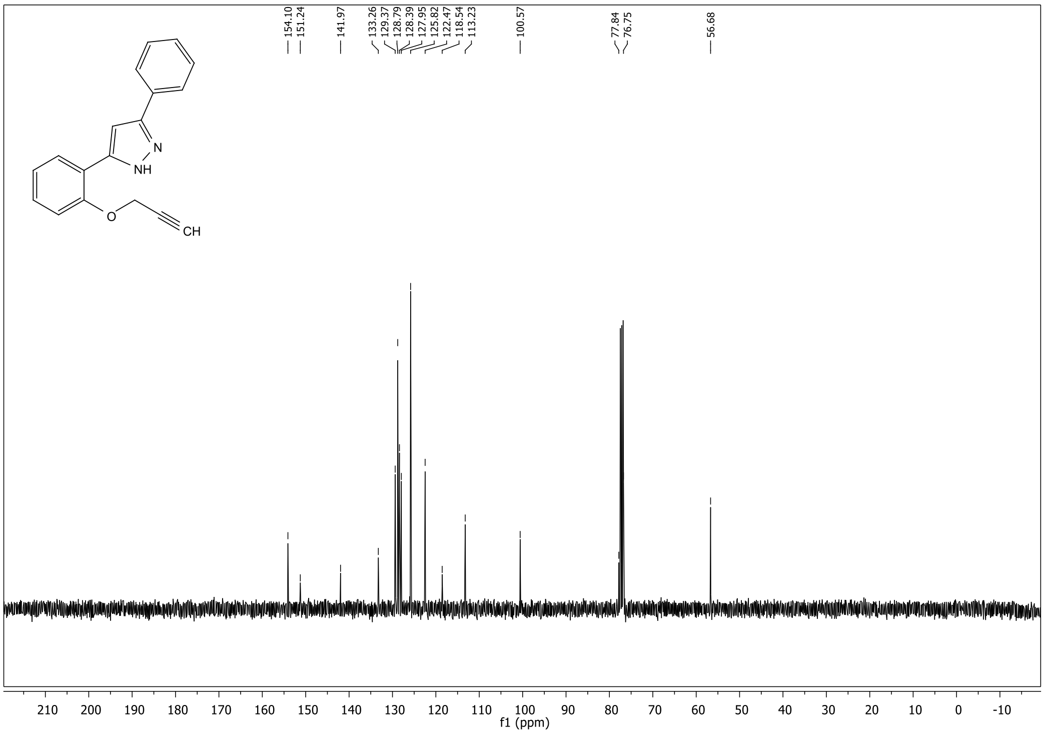


Figure 228: ^{13}C NMR Spectrum of Compound 290

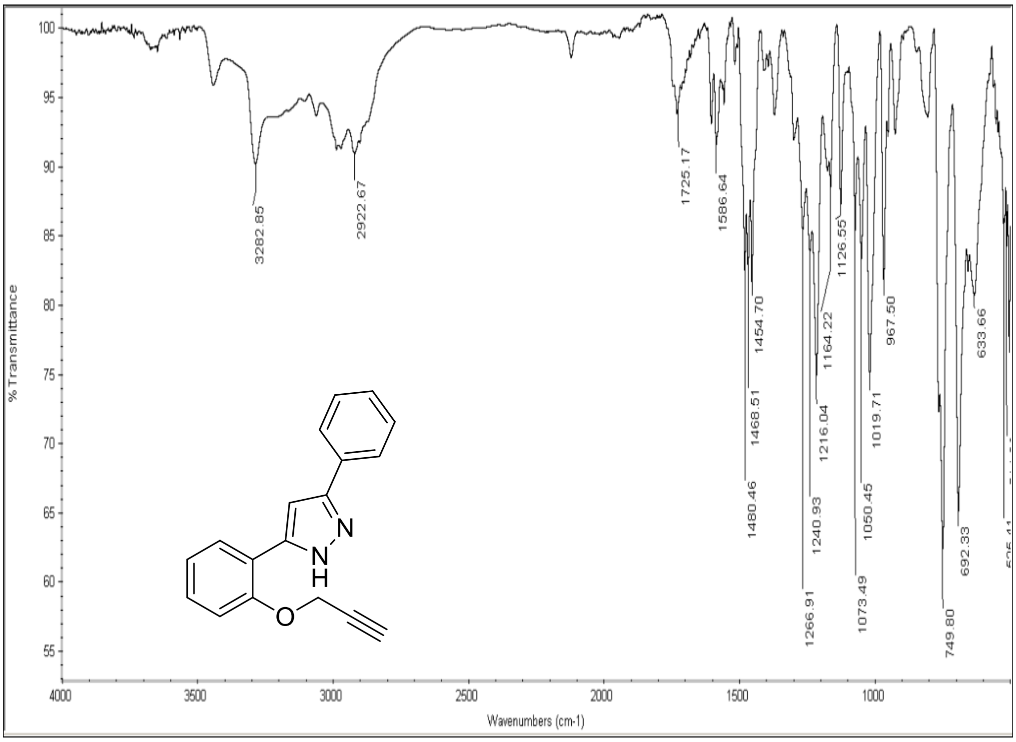


Figure 229: IR Spectrum of Compound 290

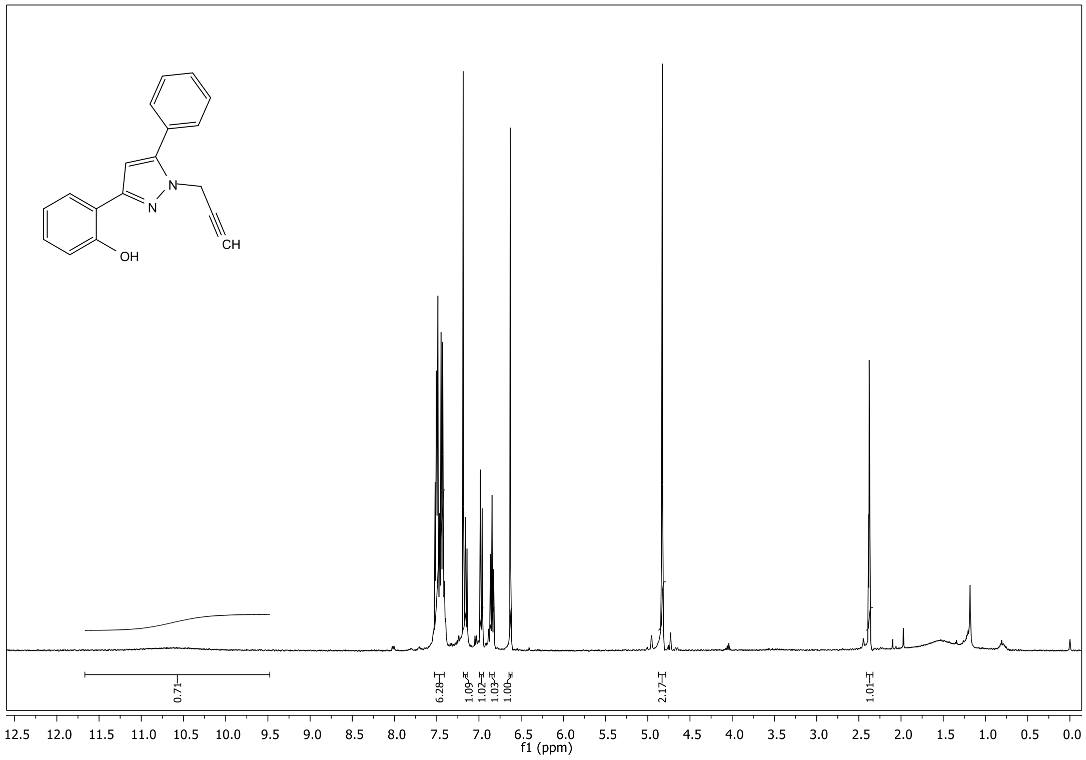


Figure 230: ^{1}H NMR Spectrum of Compound 291

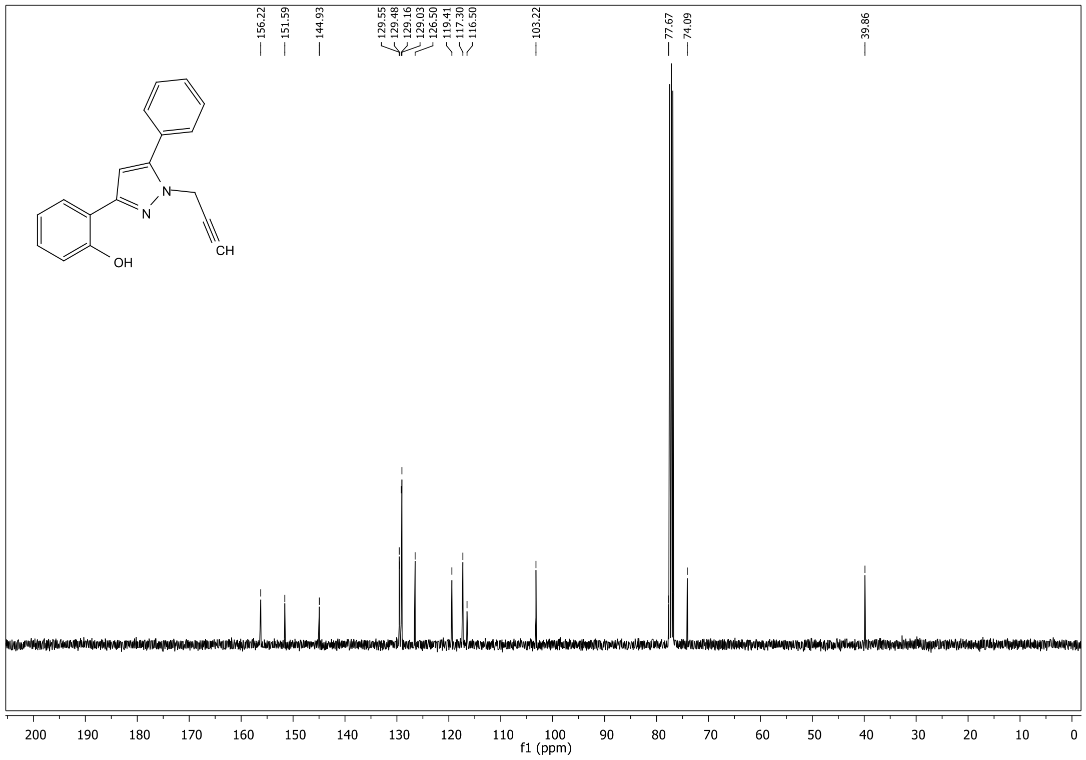


Figure 231: ^{13}C NMR Spectrum of Compound 291

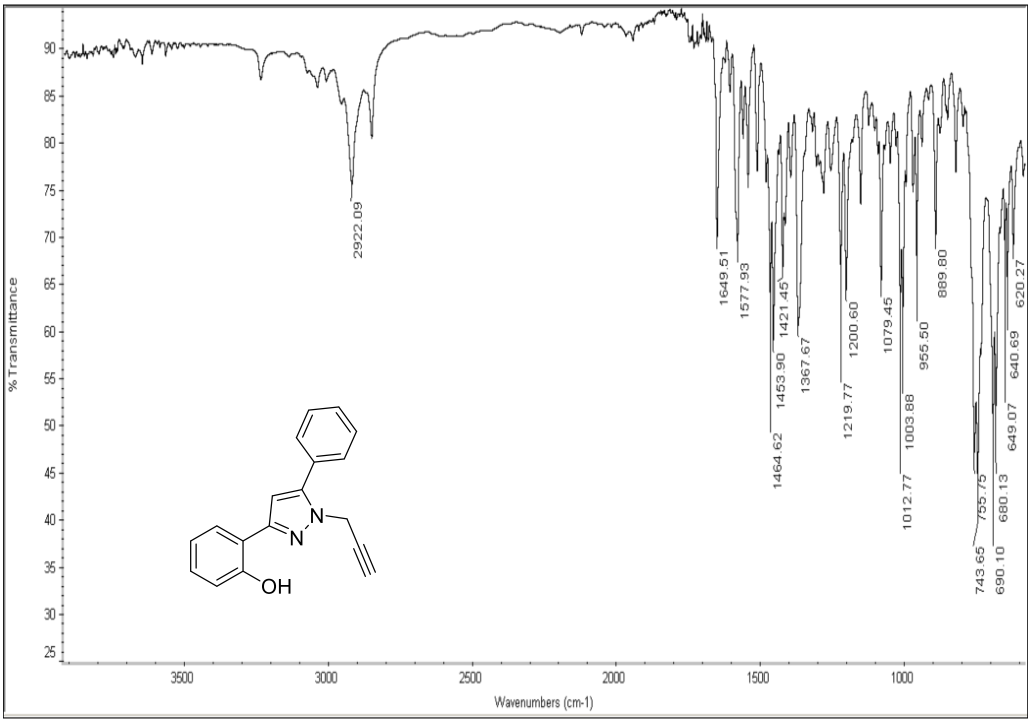


Figure 232: IR Spectrum of Compound 291

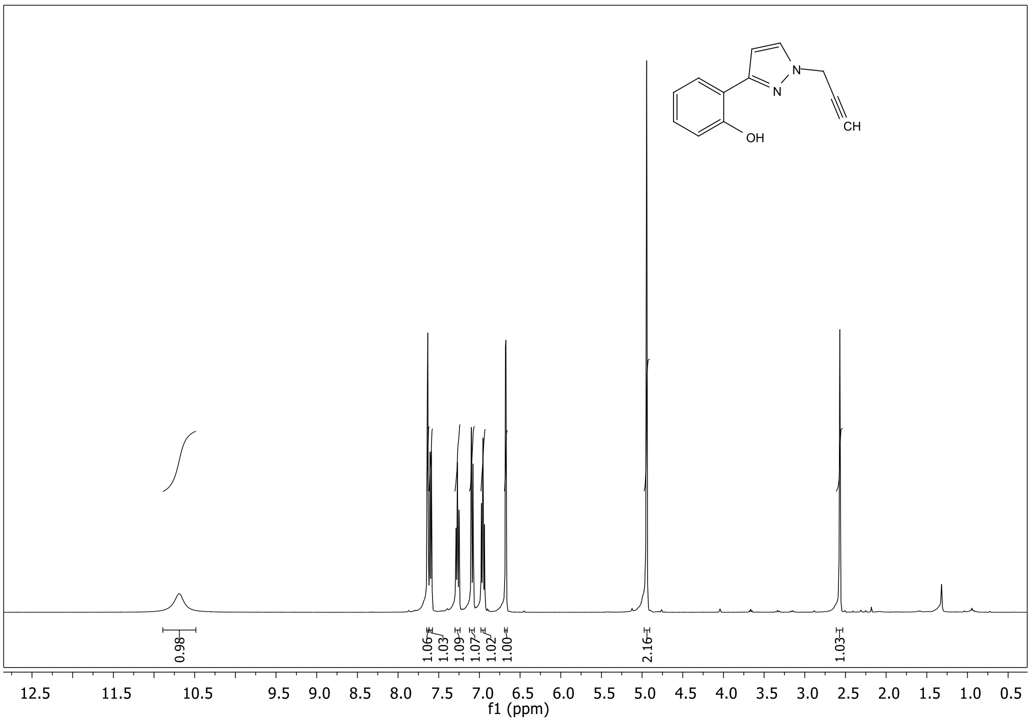


Figure 233: ^{1}H NMR Spectrum of Compound 293

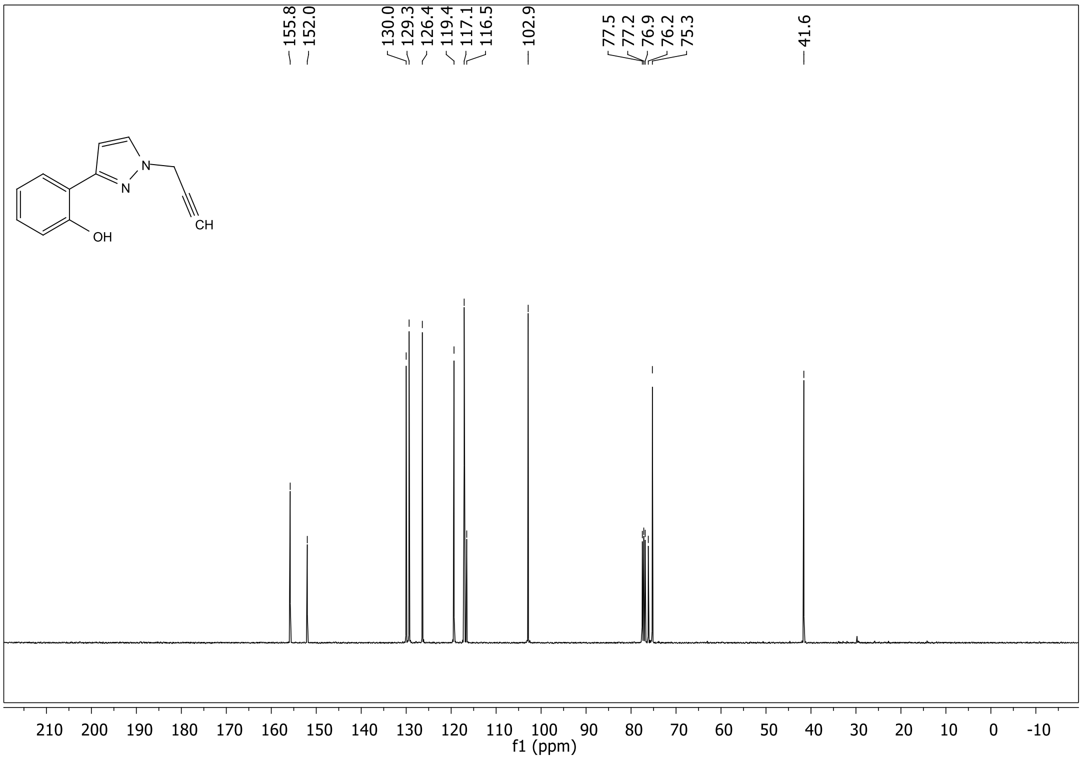


Figure 234: ^{13}C NMR Spectrum of Compound 293

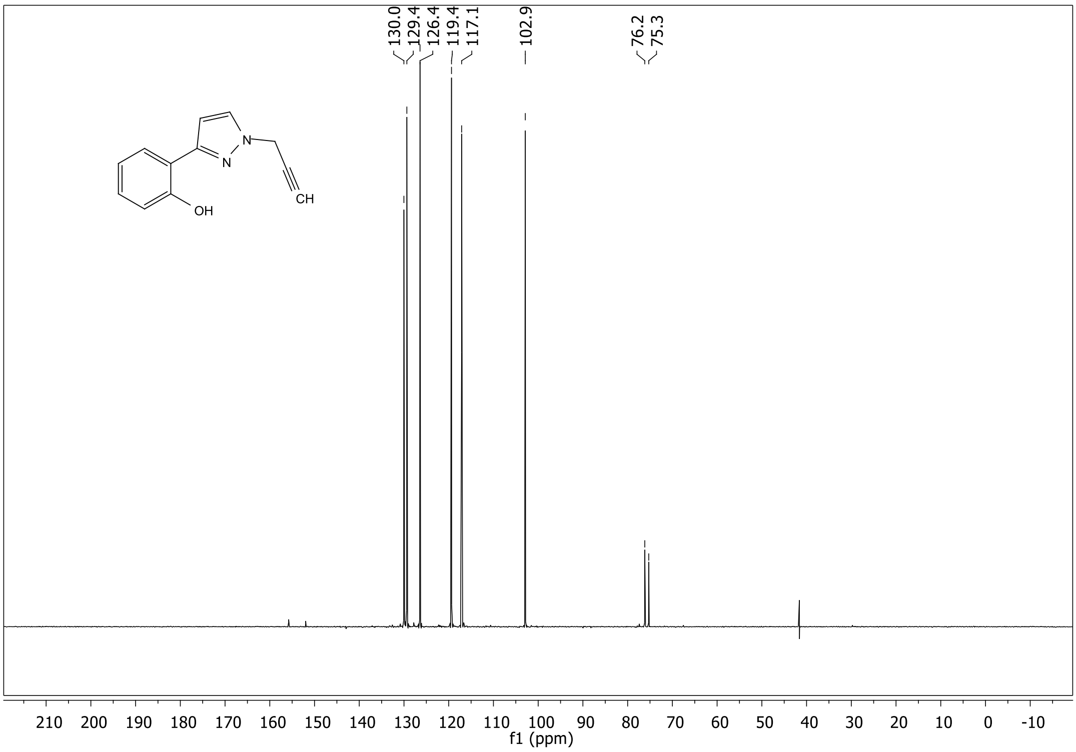


Figure 235: DEPT 90 Spectrum of Compound 293

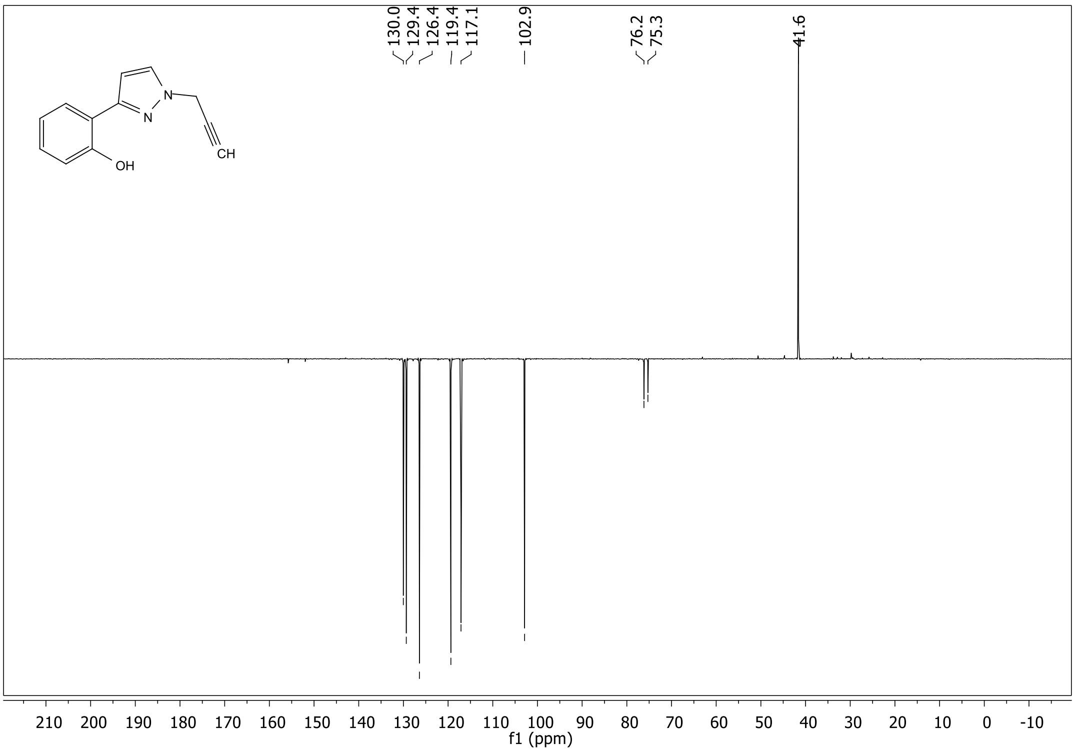


Figure 236: DEPT 135 Spectrum of Compound 293

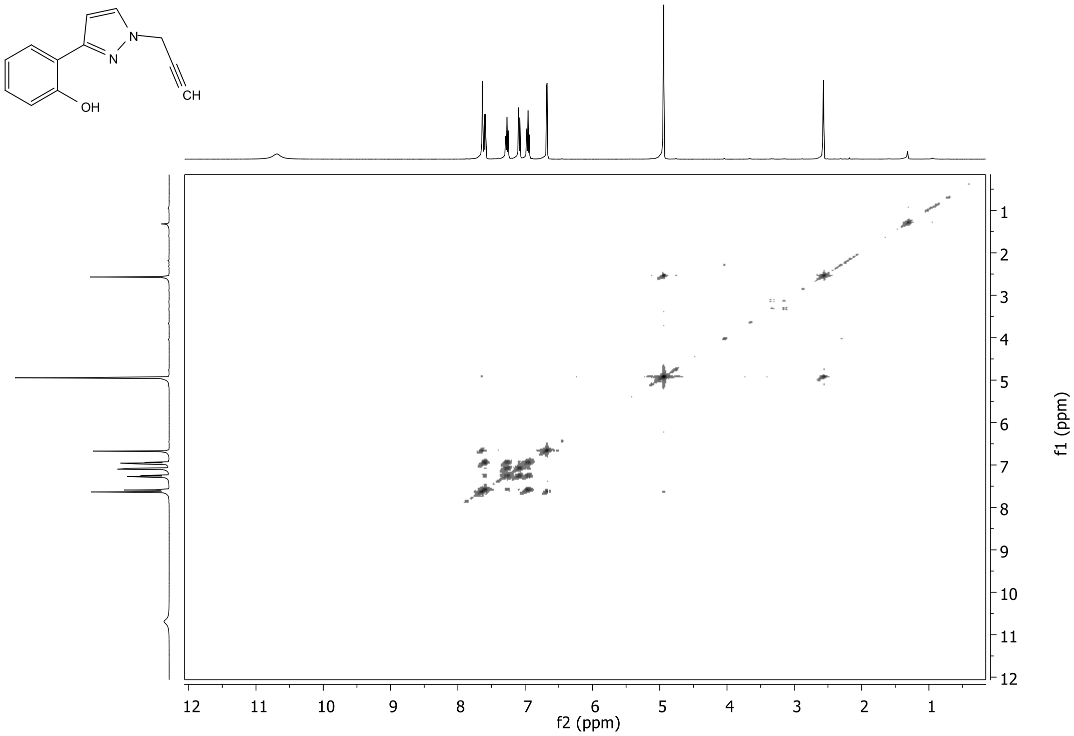


Figure 237: COSY Spectrum of Compound 293

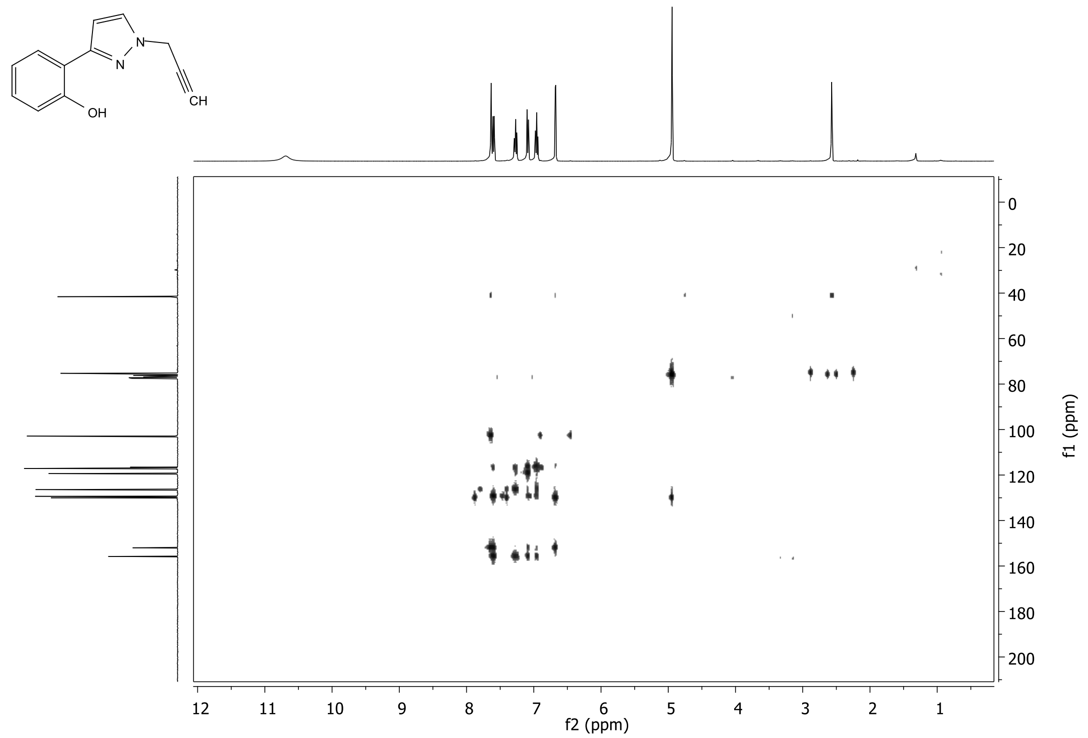


Figure 238: HMBC Spectrum of Compound 293

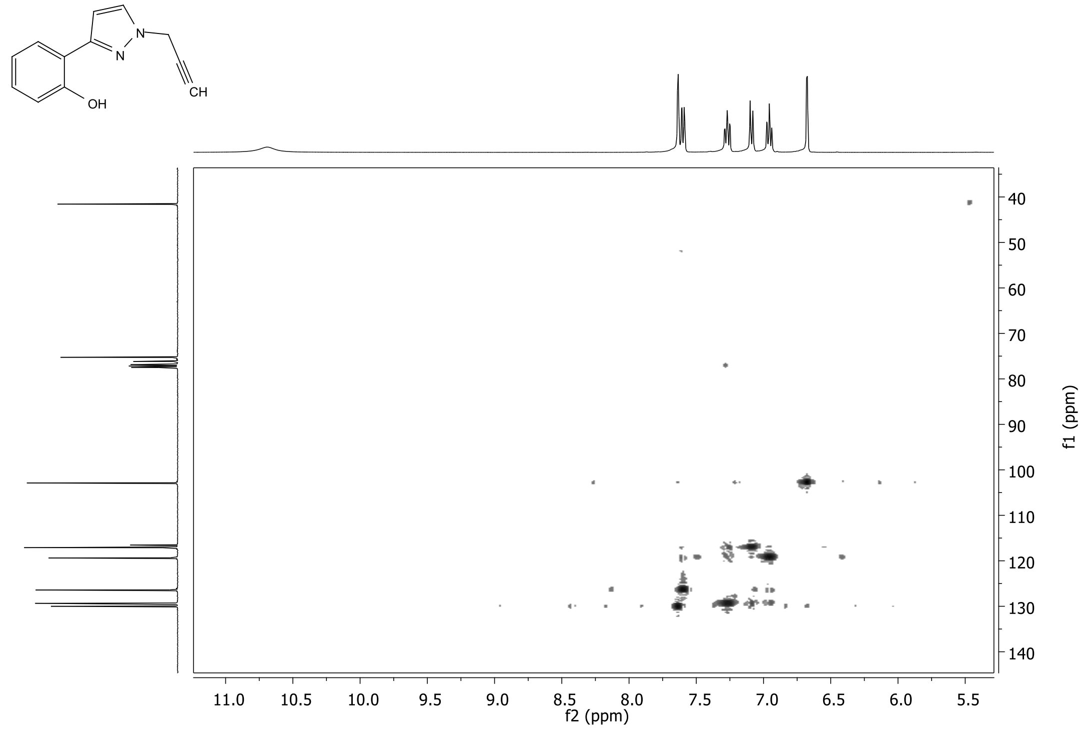


Figure 239: HSQC Spectrum of Compound 293

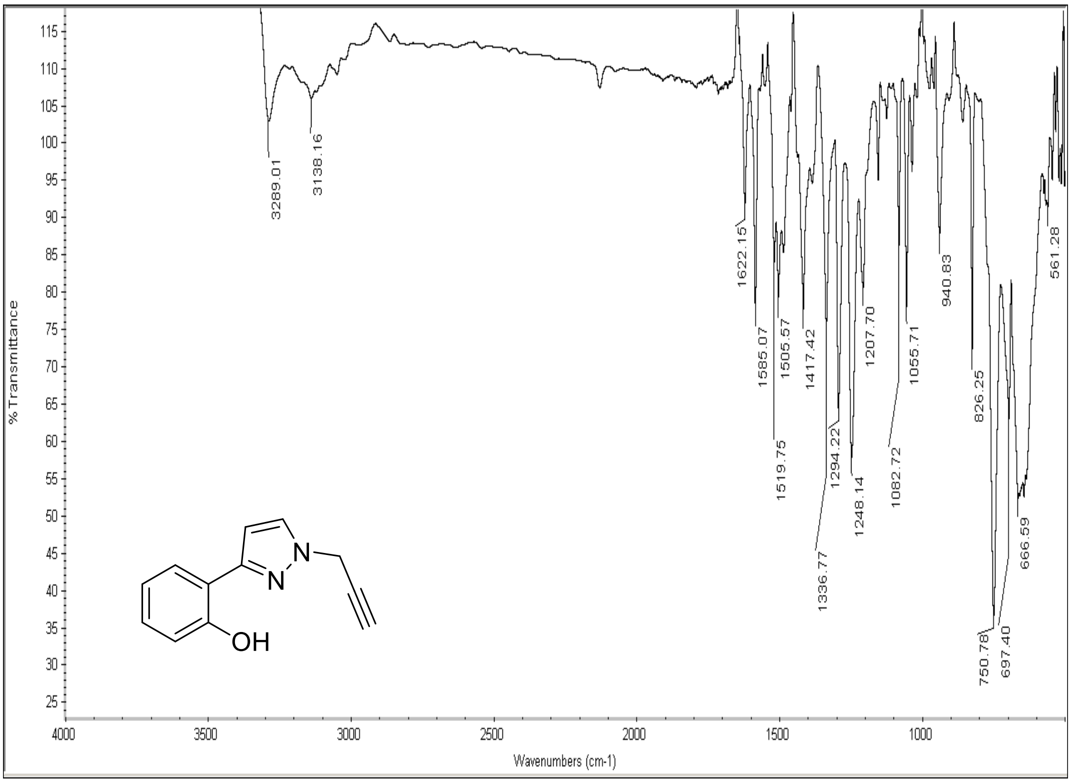


Figure 240: IR Spectrum of Compound 293

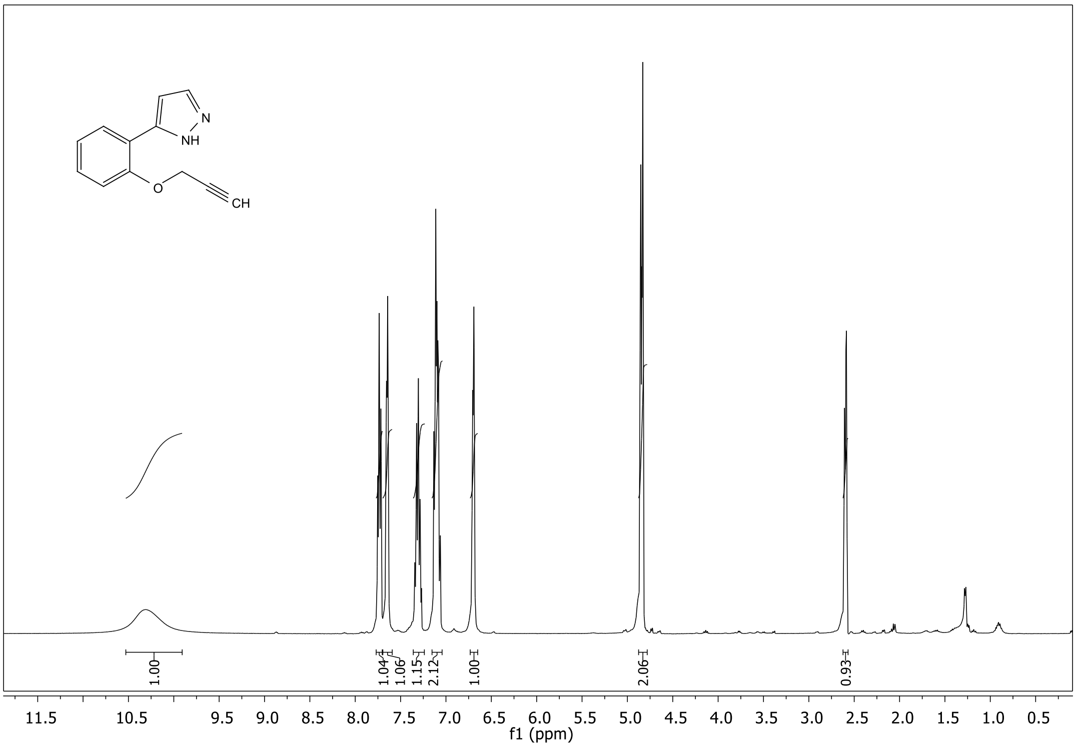


Figure 241: ^{1}H NMR Spectrum of Compound 298

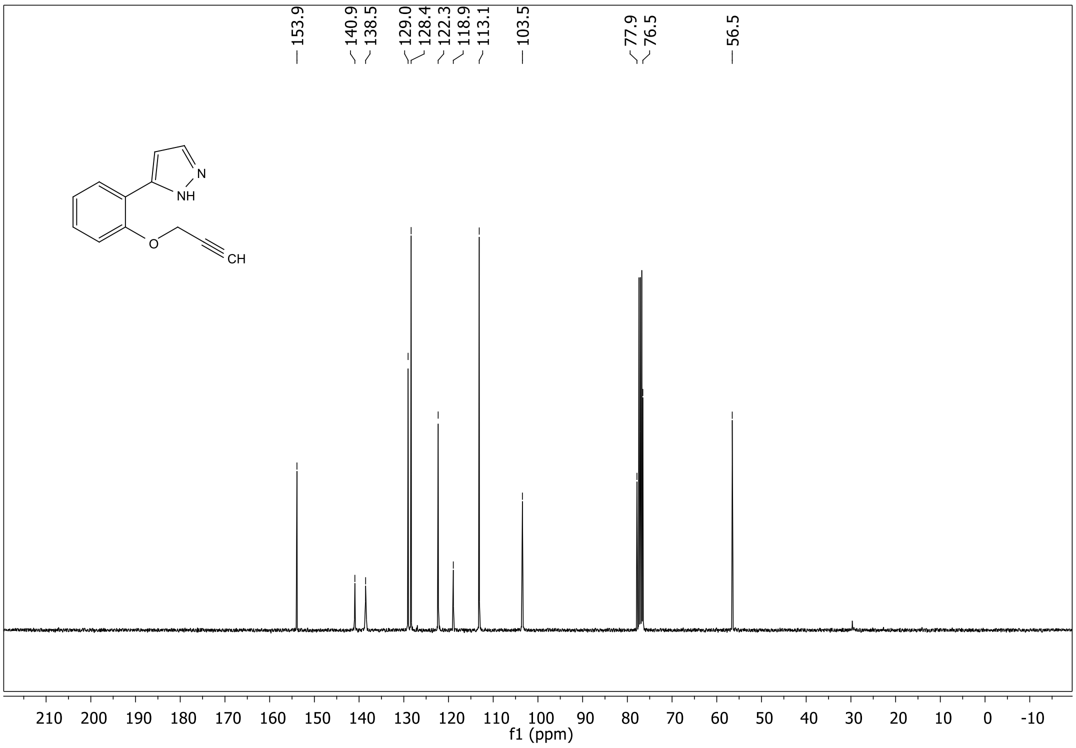


Figure 242: ^{13}C NMR Spectrum of Compound 298

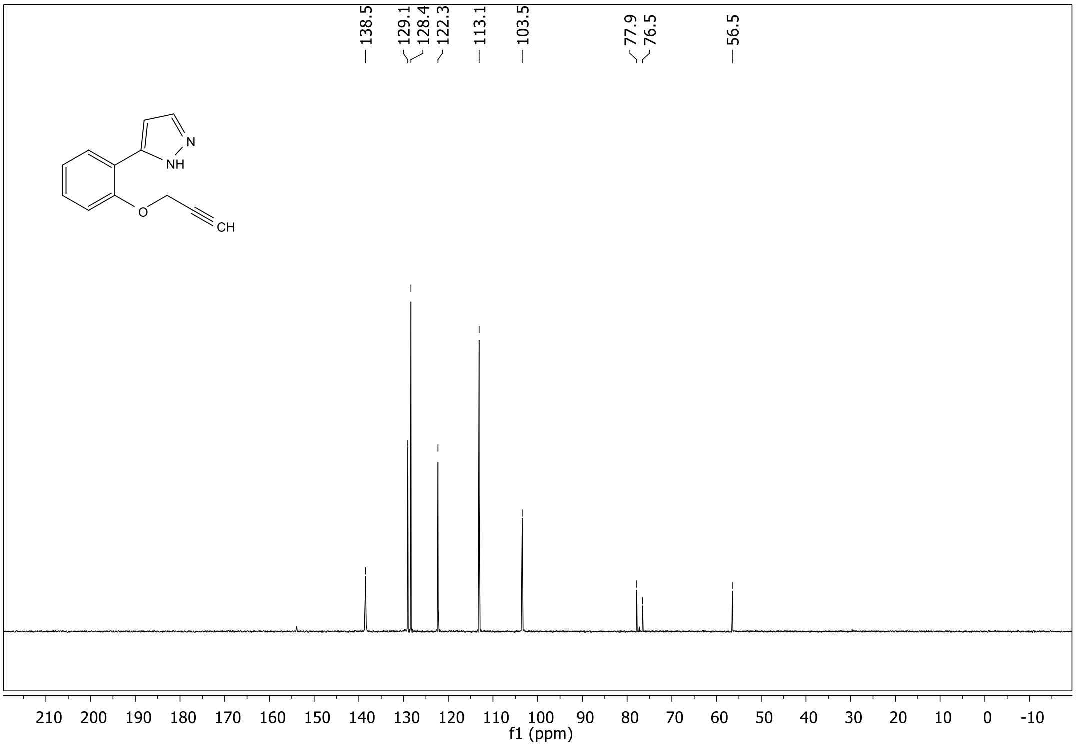


Figure 243: DEPT 90 Spectrum of Compound 298

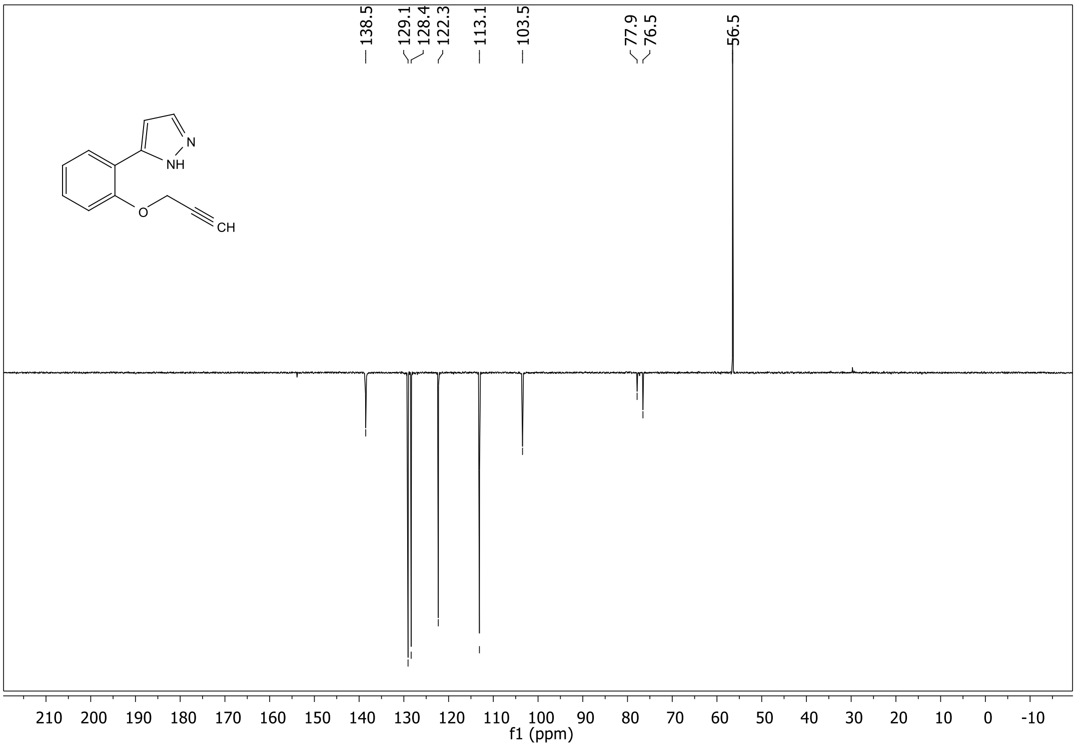


Figure 244: DEPT 135 Spectrum of Compound 298

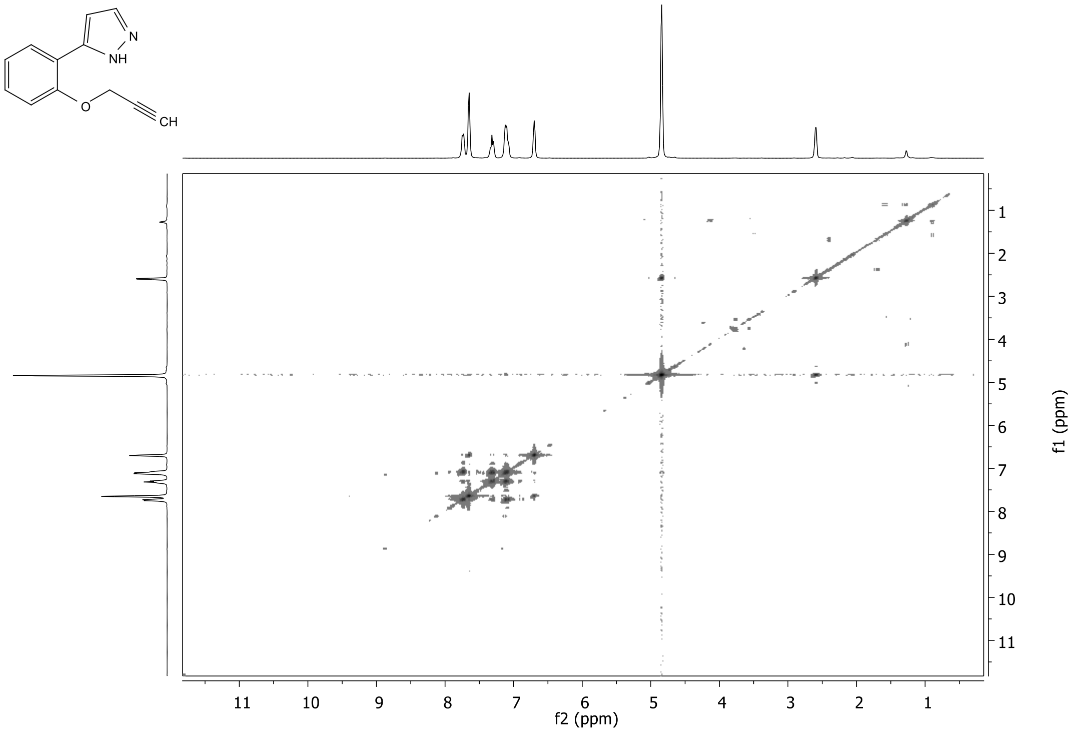


Figure 245: COSY Spectrum of Compound 298

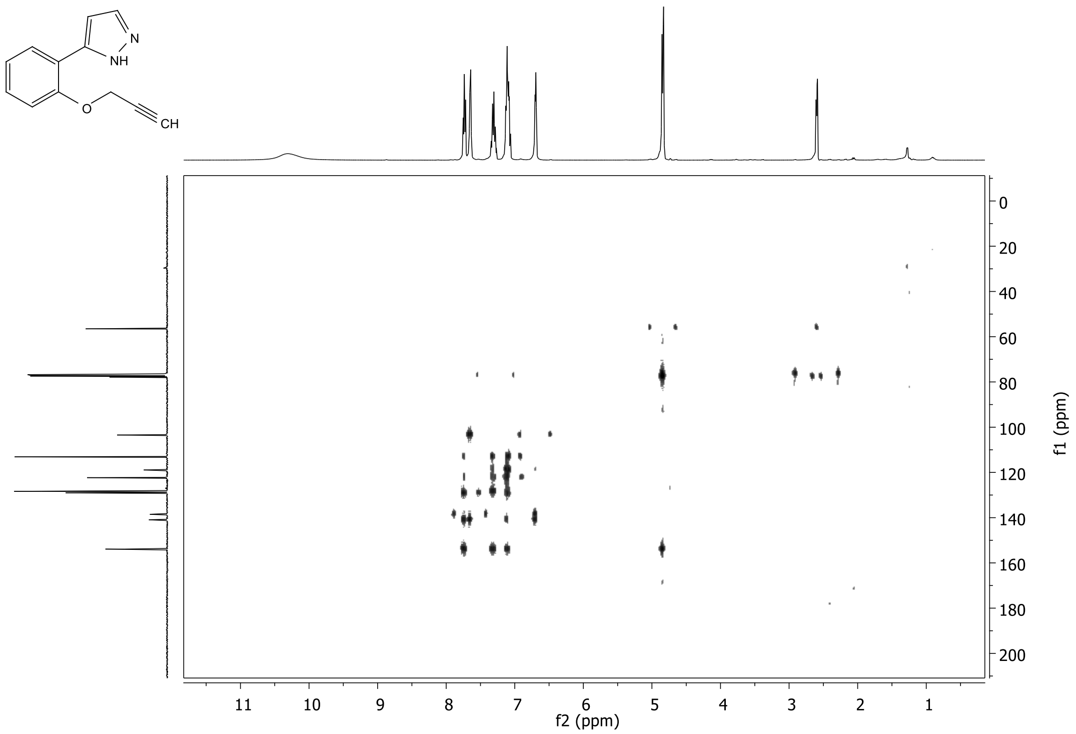


Figure 246: HMBC Spectrum of Compound 298

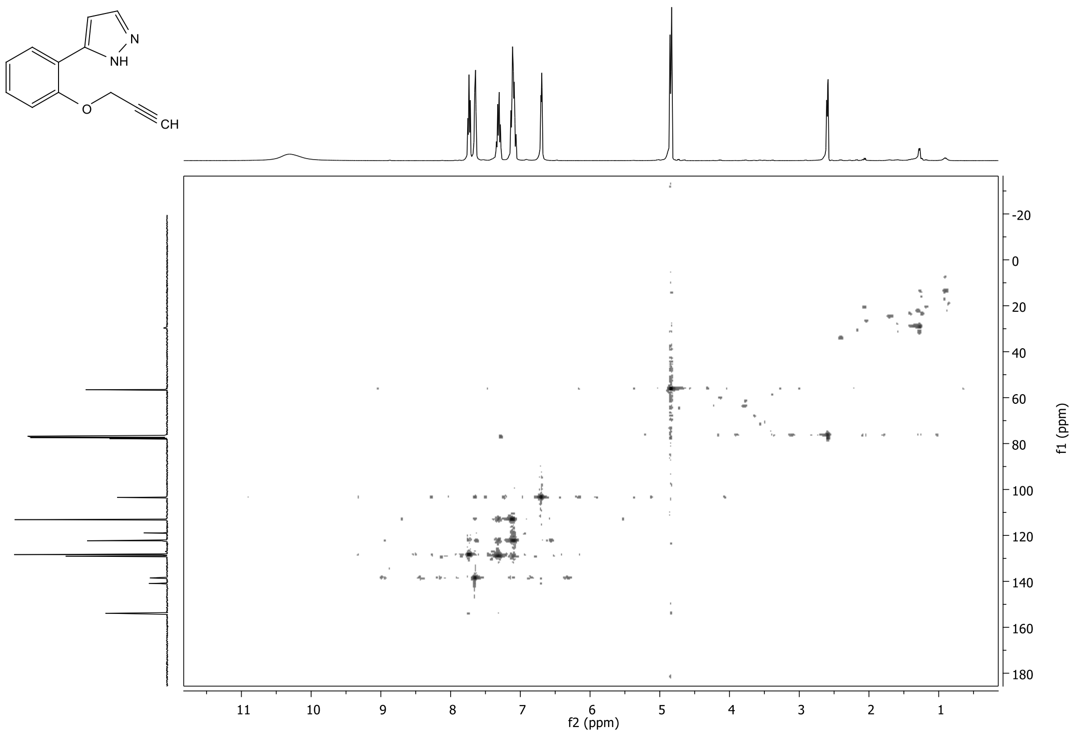


Figure 247: HSQC Spectrum of Compound 298

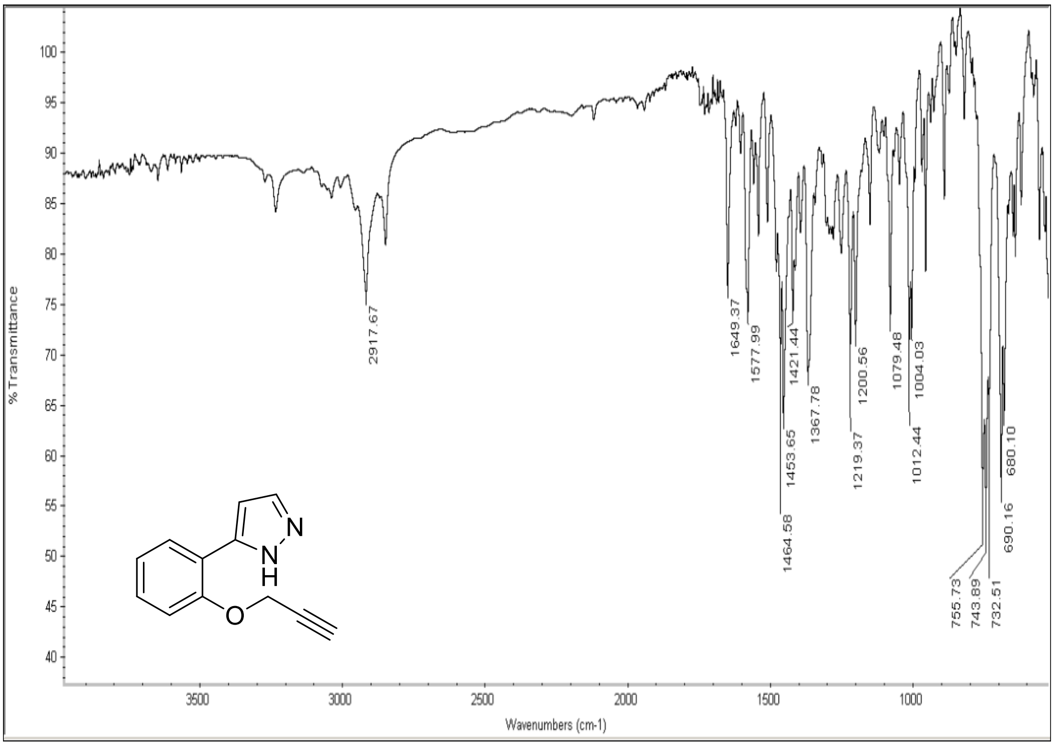


Figure 248: IR Spectrum of Compound 298

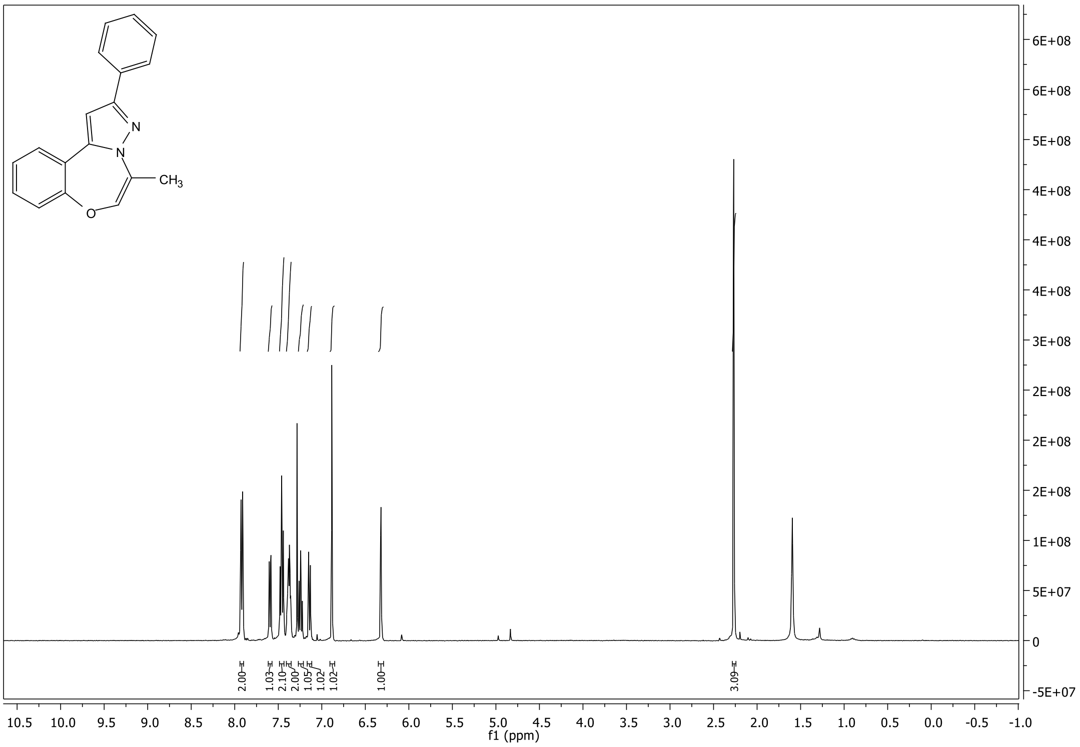


Figure 249: ^{1}H NMR Spectrum of Compound 301

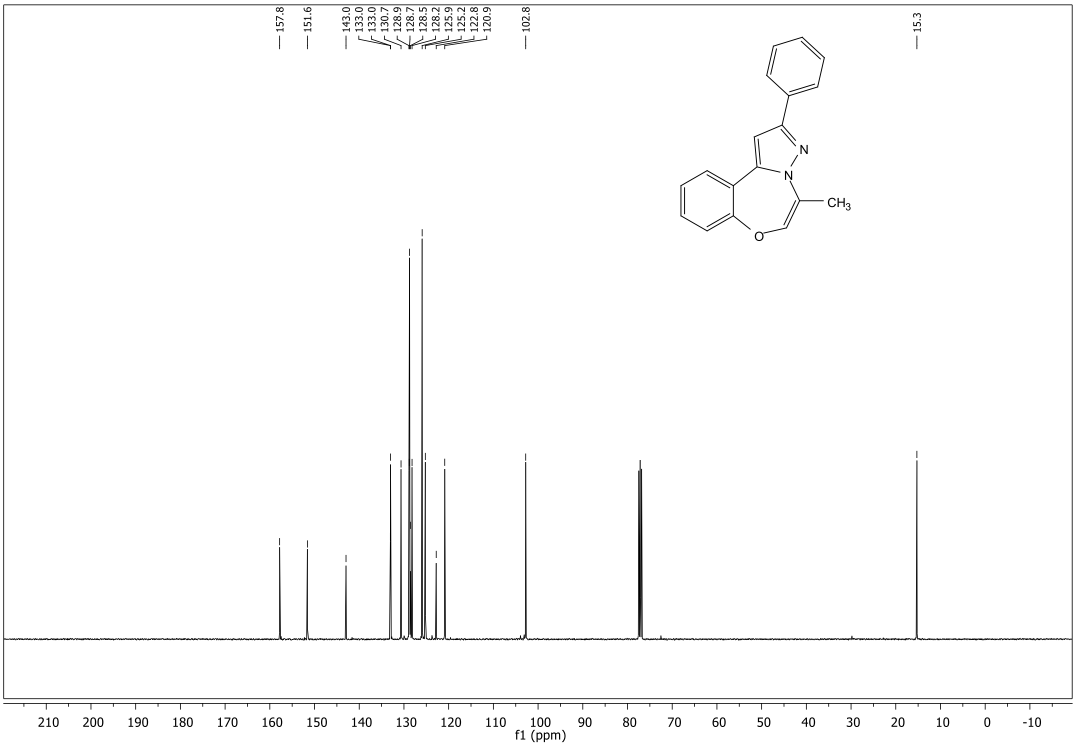


Figure 250: ^{13}C NMR Spectrum of Compound 301

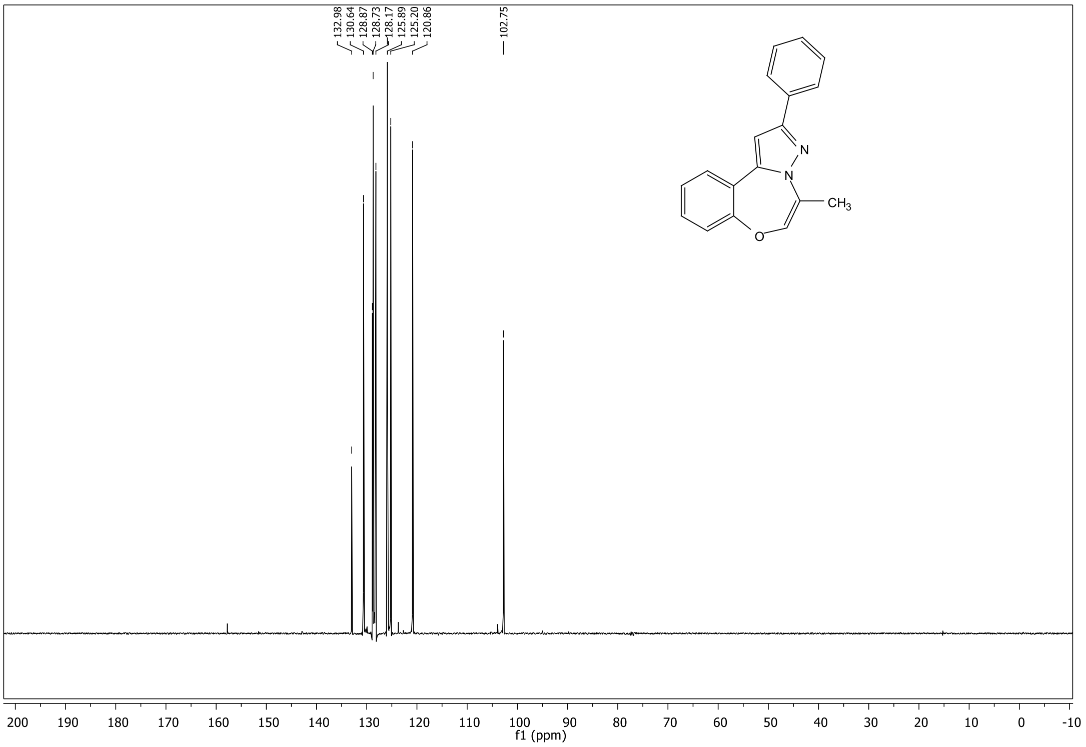


Figure 251: DEPT 90 Spectrum of Compound 301

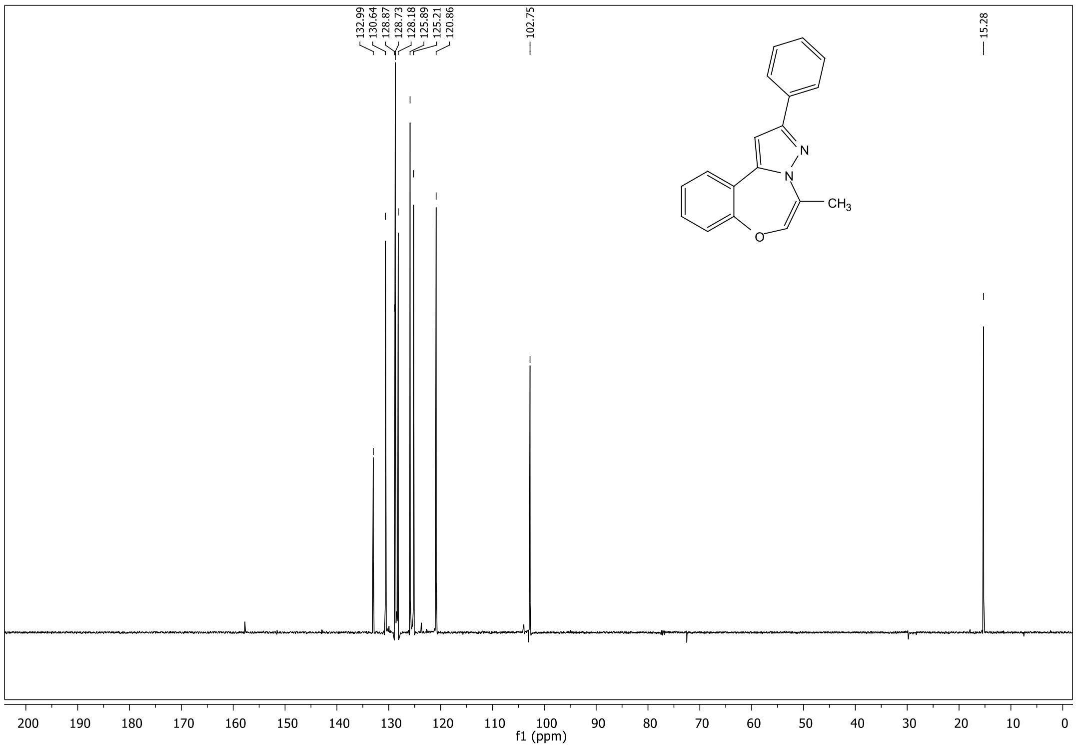


Figure 252: DEPT 135 Spectrum of Compound 301

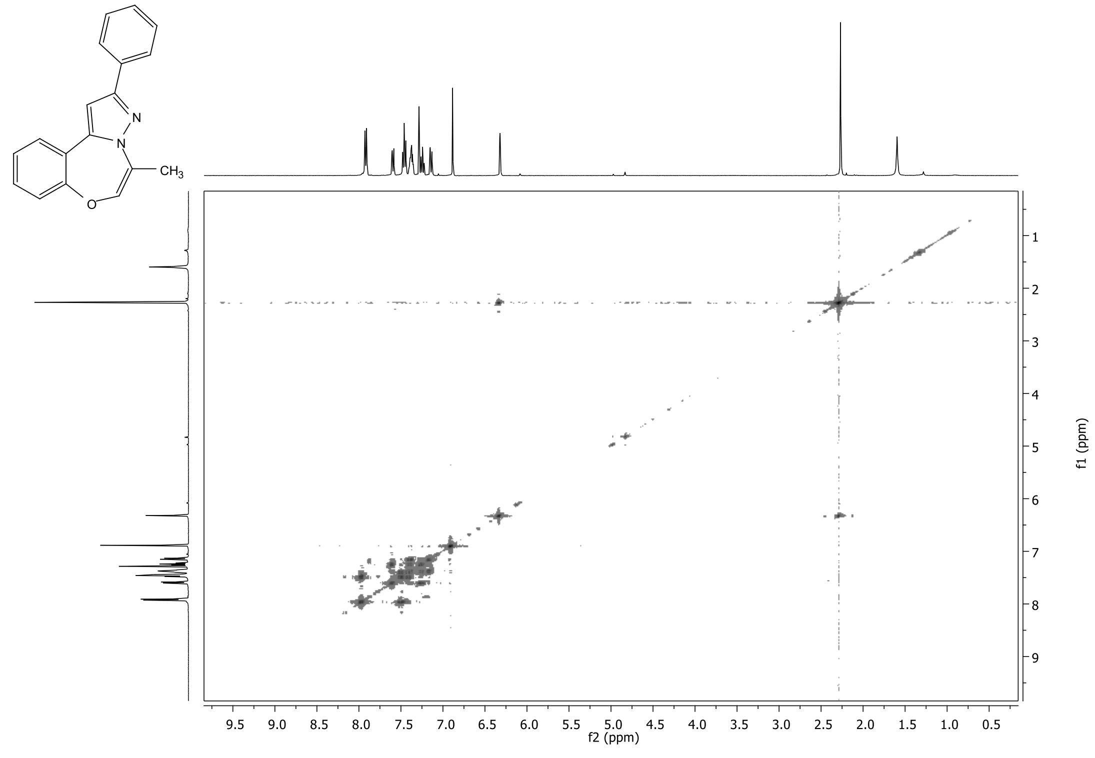


Figure 253: COSY Spectrum of Compound 301

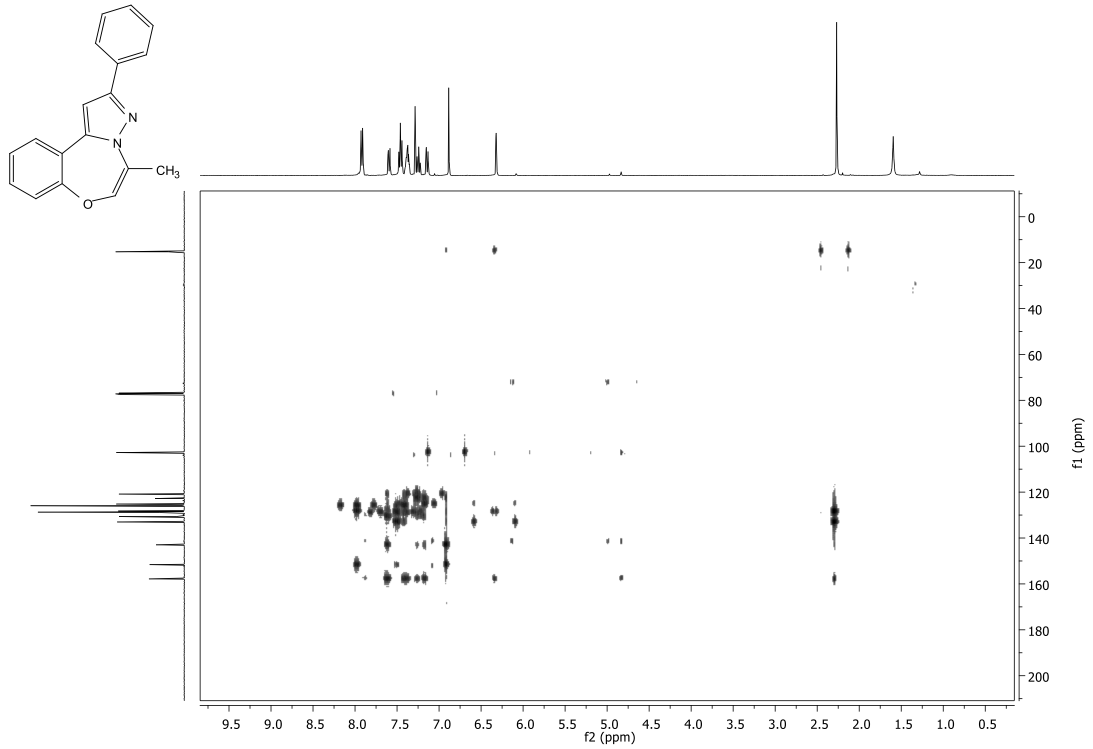


Figure 254: HMBC Spectrum of Compound 301

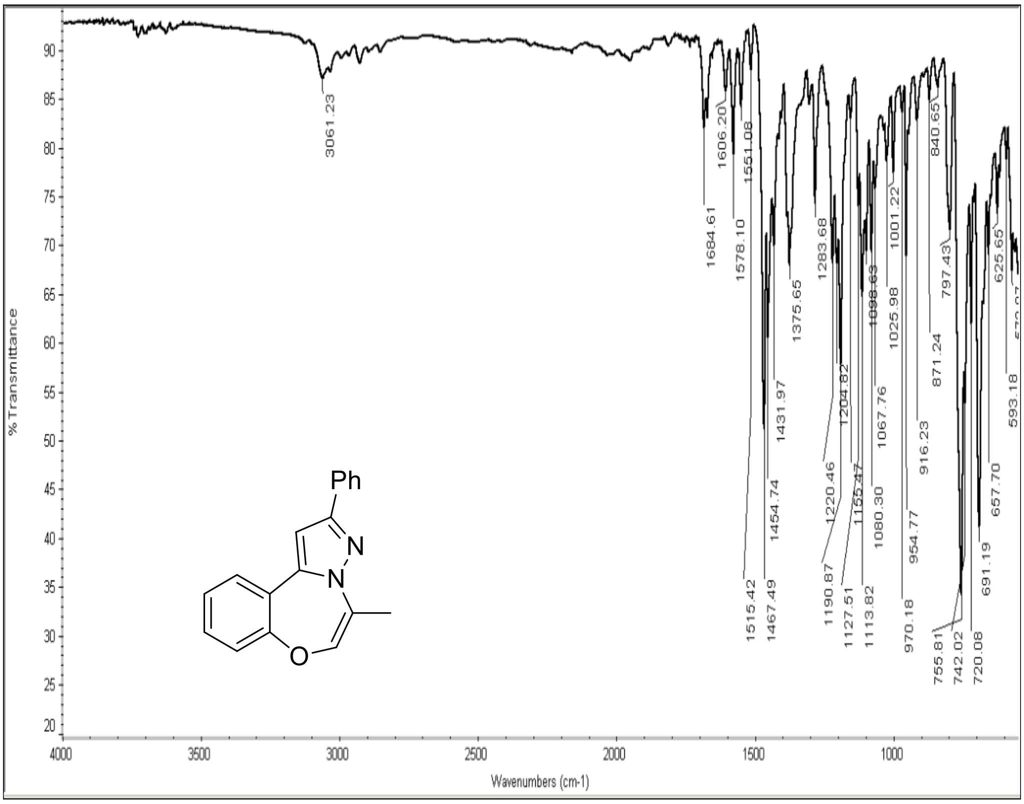


Figure 255: IR Spectrum of Compound 301

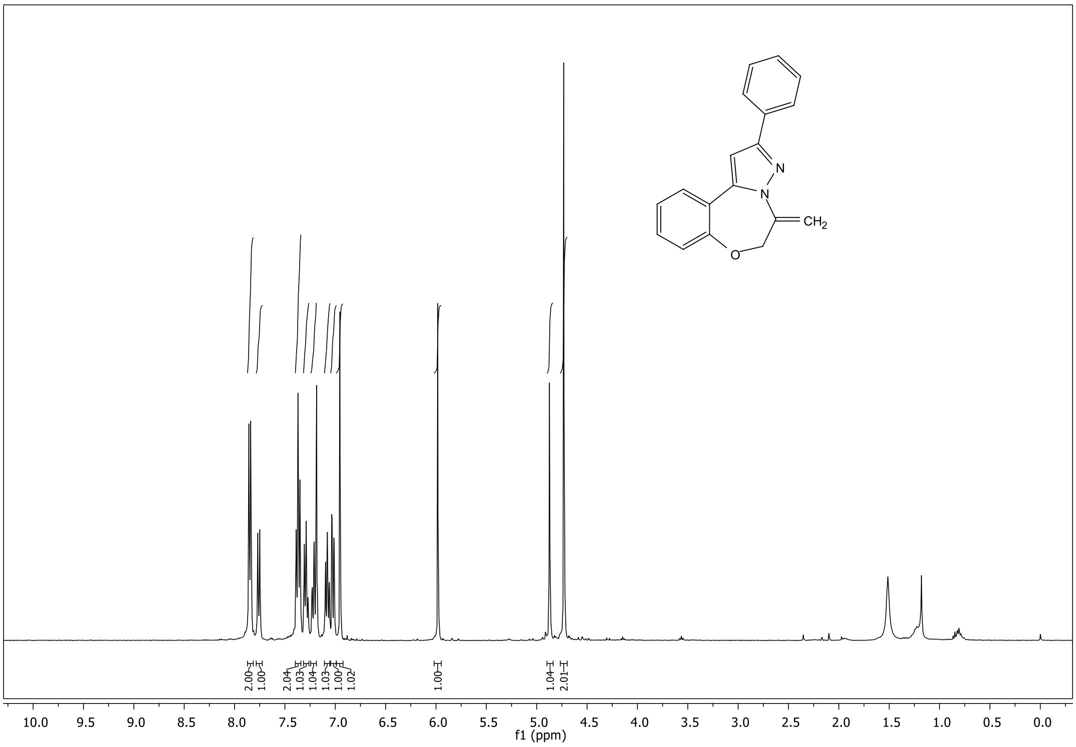


Figure 256: ^{1}H NMR Spectrum of Compound 300

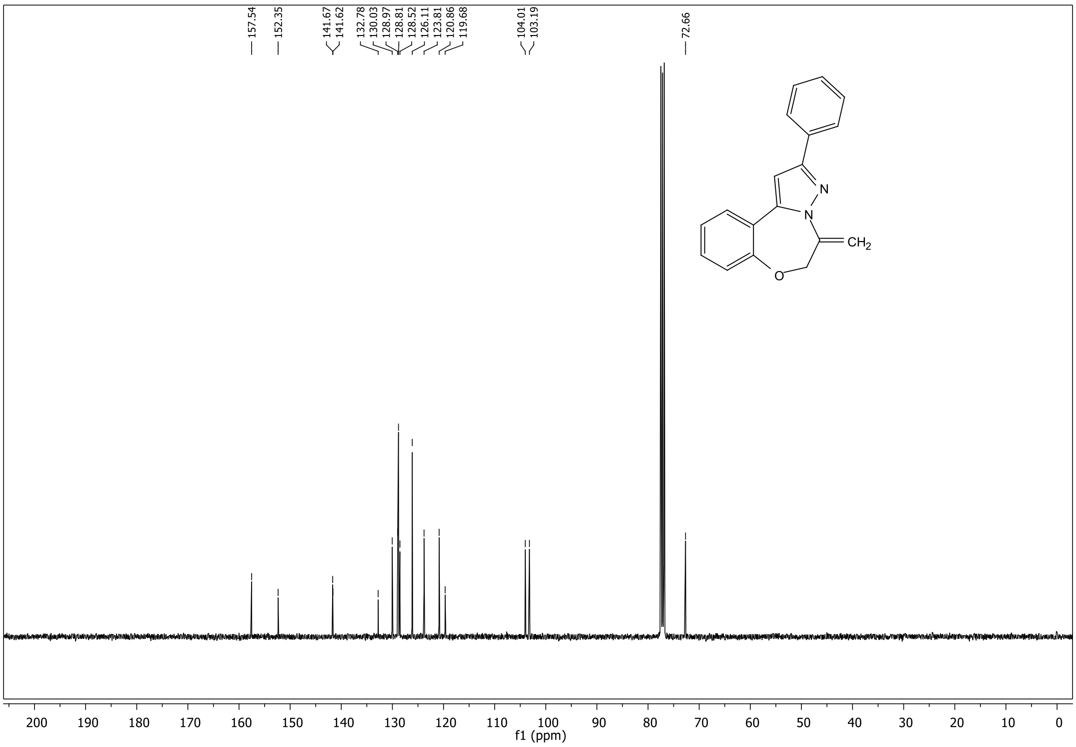


Figure 257: ^{13}C NMR Spectrum of Compound 300

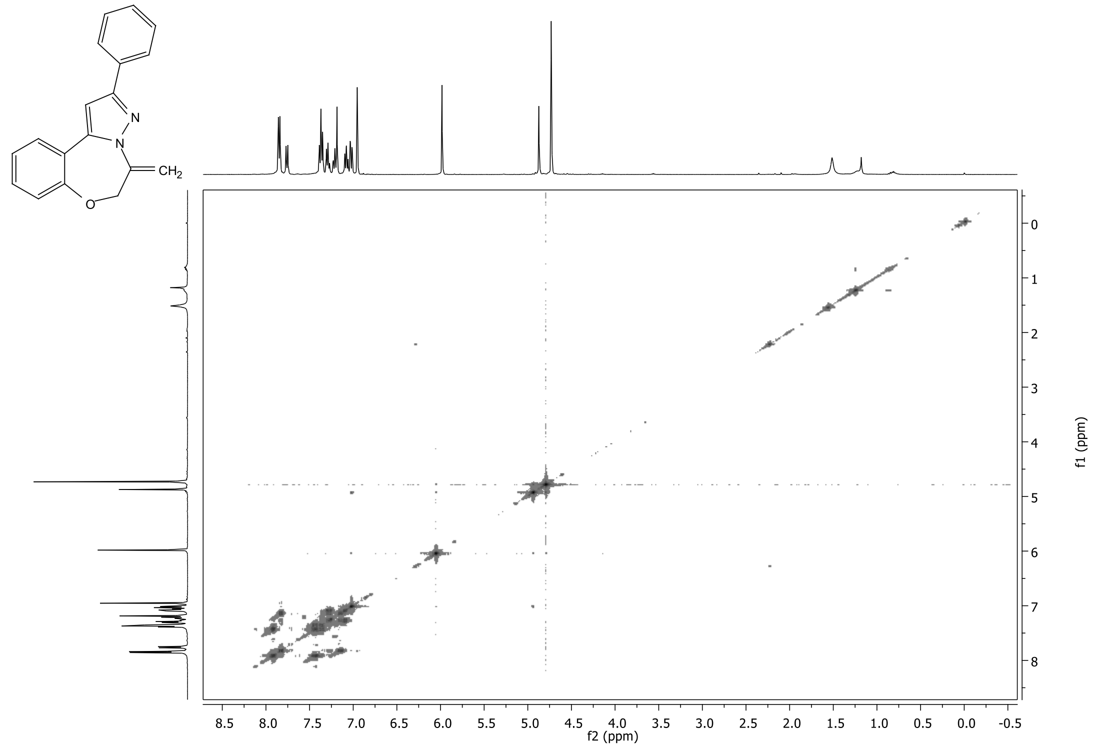


Figure 258: COSY Spectrum of Compound 300

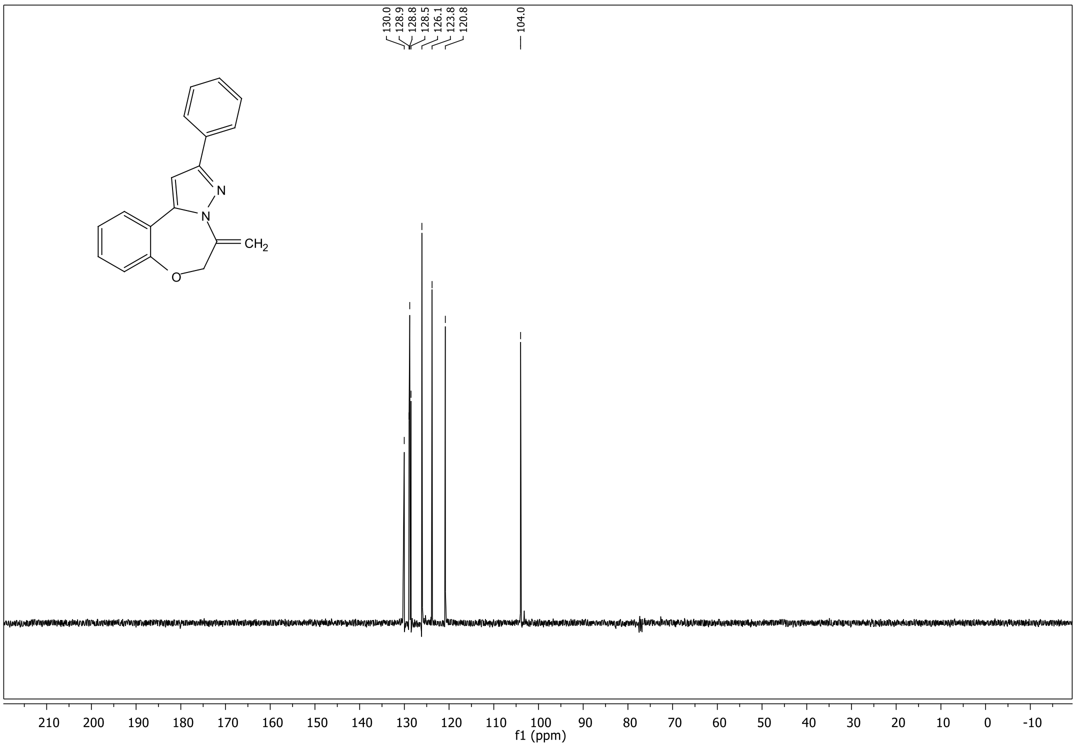


Figure 259: DEPT 90 Spectrum of Compound 300

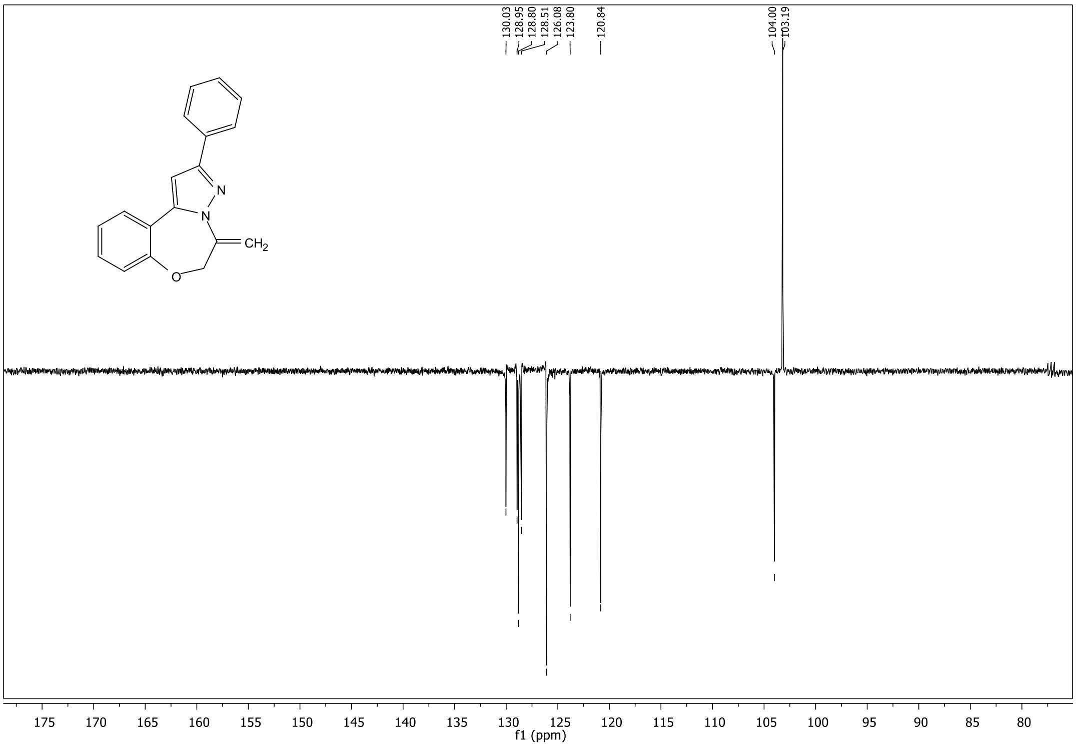


Figure 260: DEPT 135 Spectrum of Compound 300

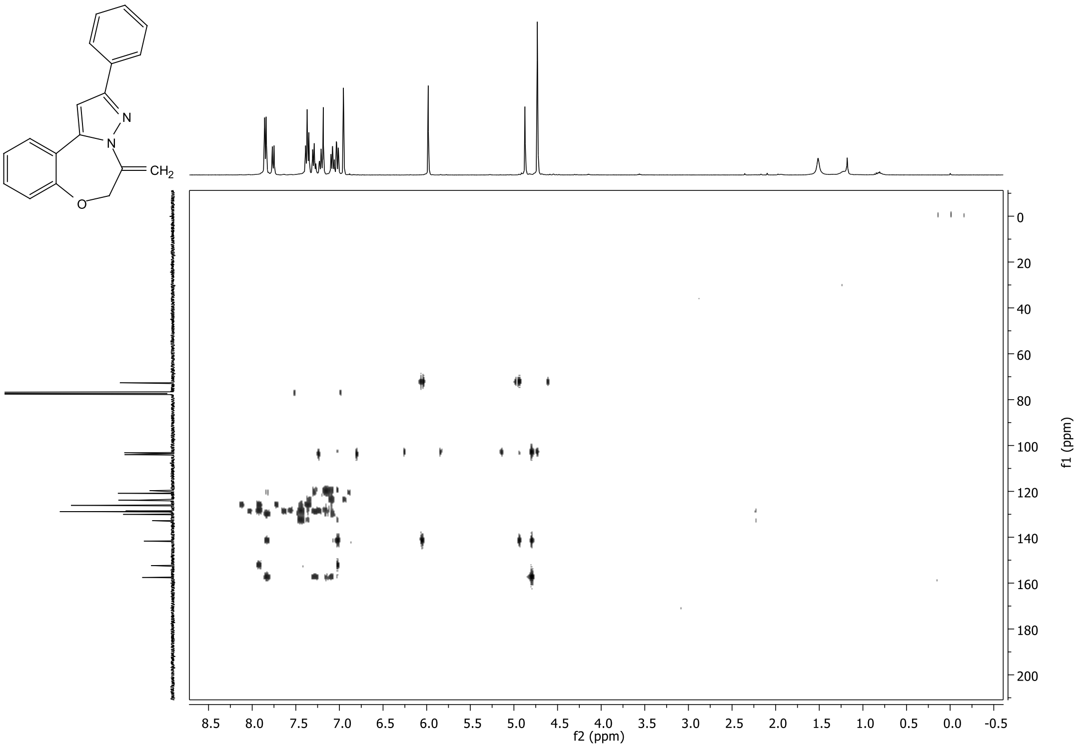


Figure 261: HMBC Spectrum of Compound 300

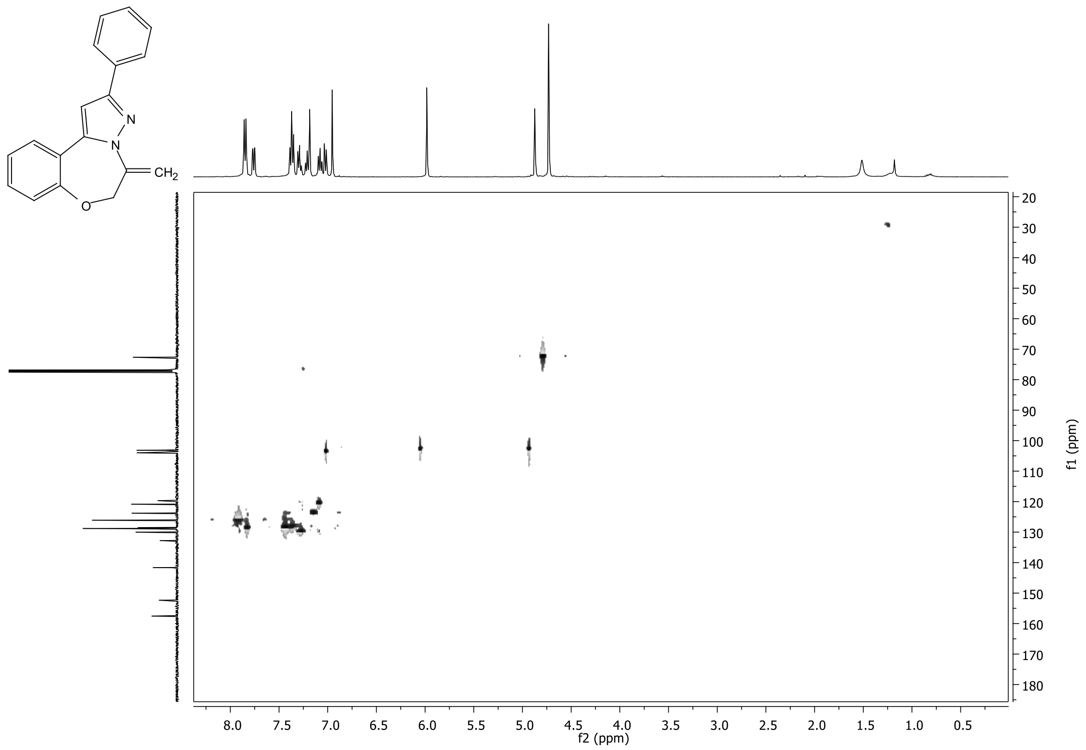


Figure 262: HSQC Spectrum of Compound 300

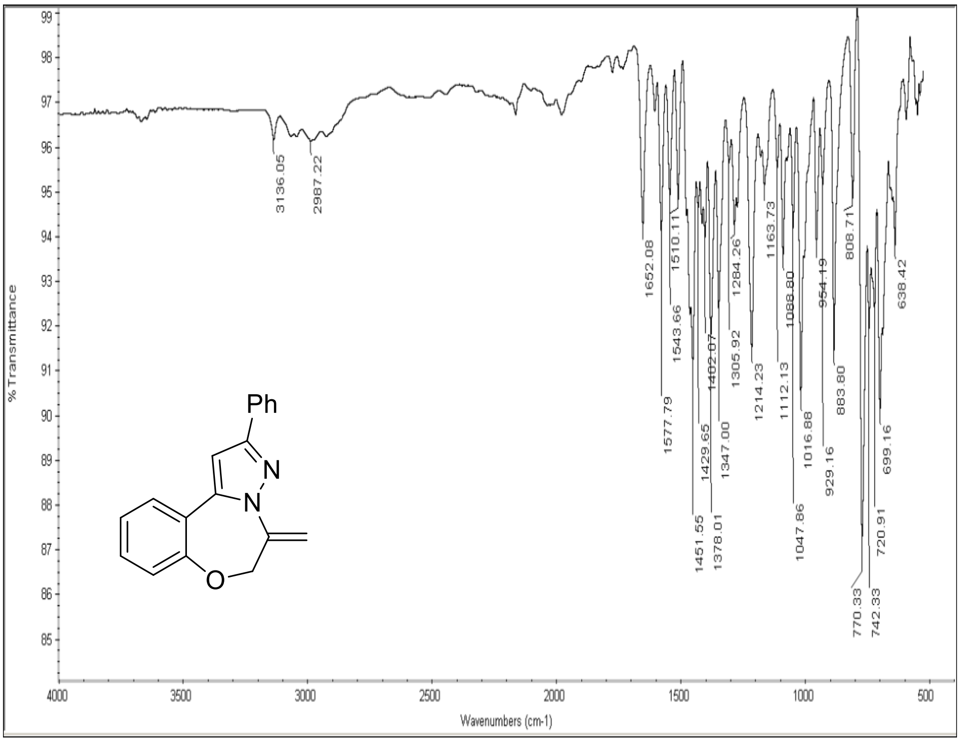


Figure 263: IR Spectrum of Compound 300

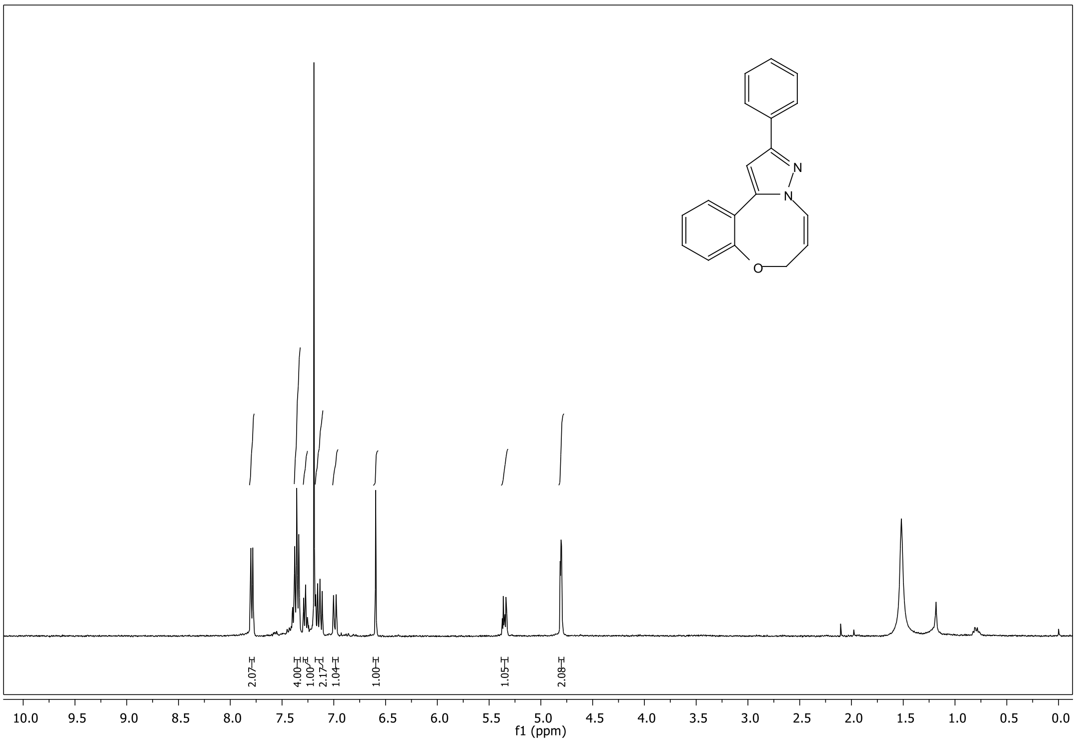


Figure 264: ^{1}H NMR Spectrum of Compound 299

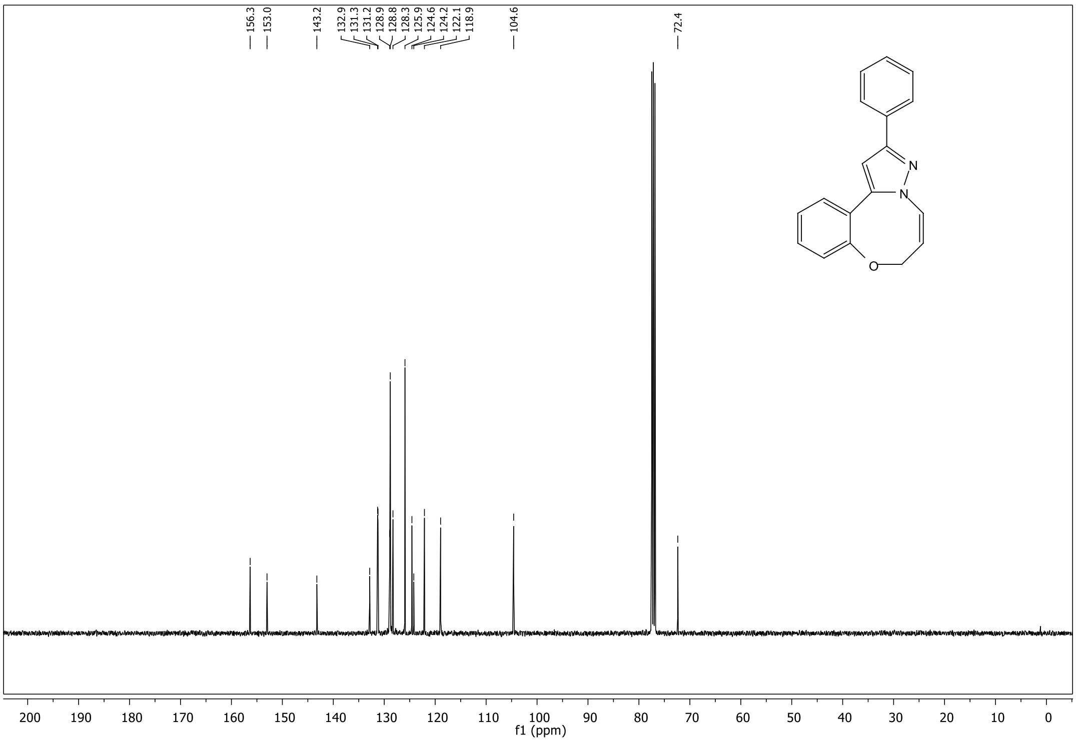


Figure 265: ^{13}C NMR Spectrum of Compound 299

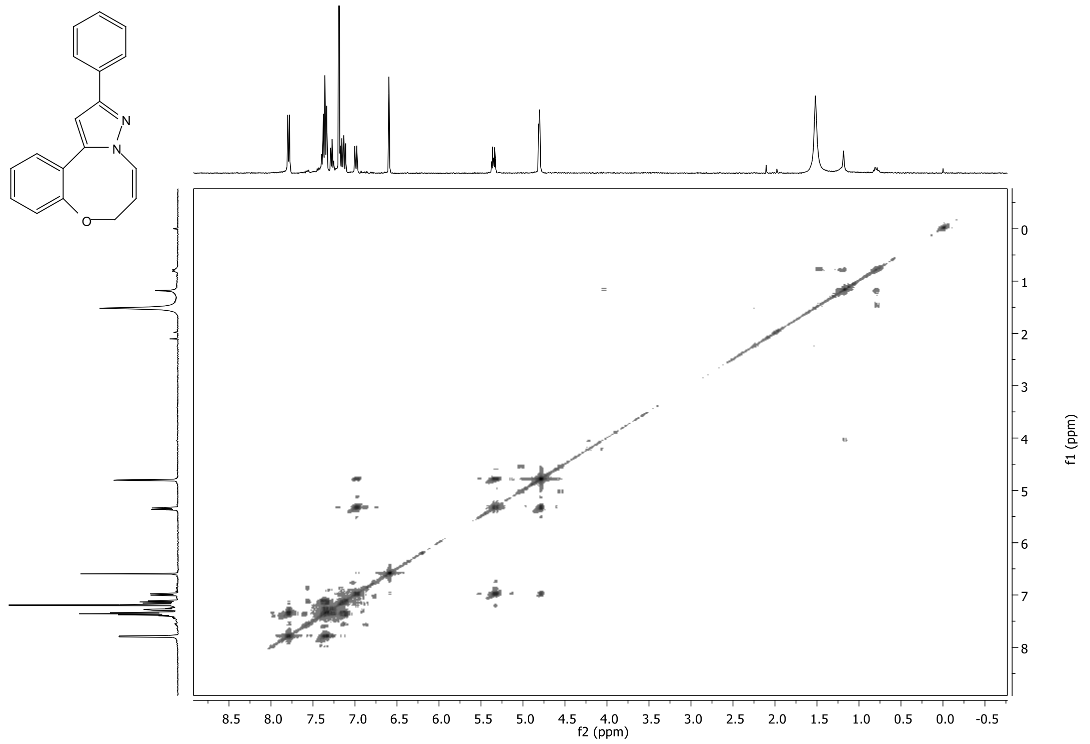


Figure 266: COSY Spectrum of Compound 299

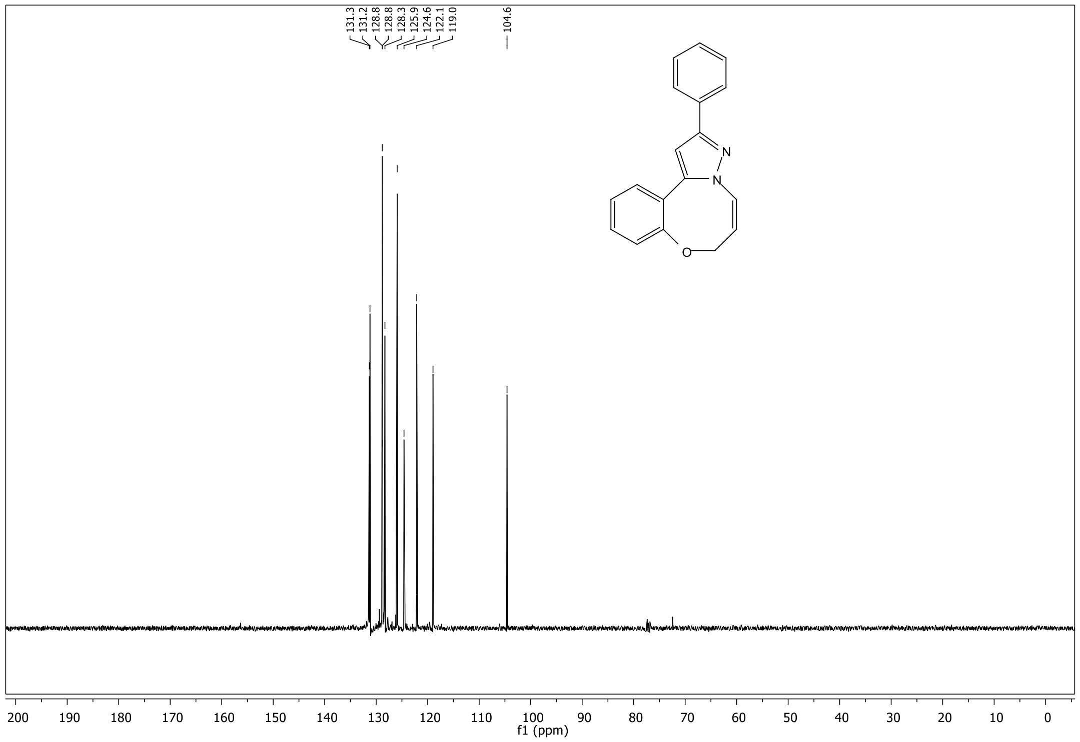


Figure 267: DEPT 90 Spectrum of Compound 299

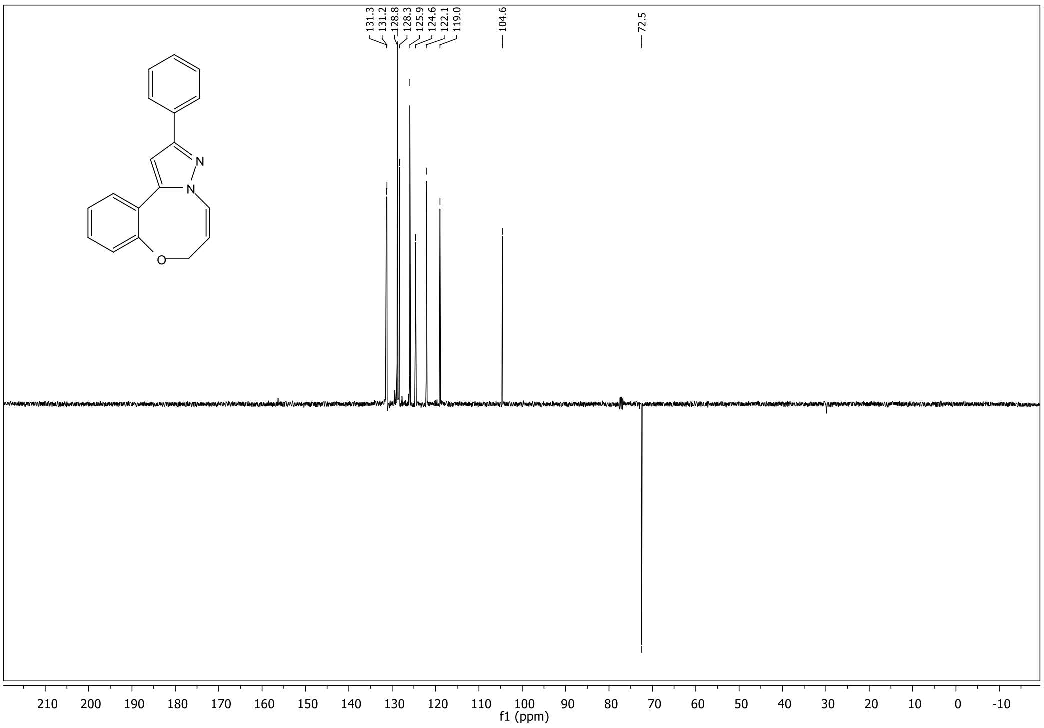


Figure 268: DEPT 135 Spectrum of Compound 299

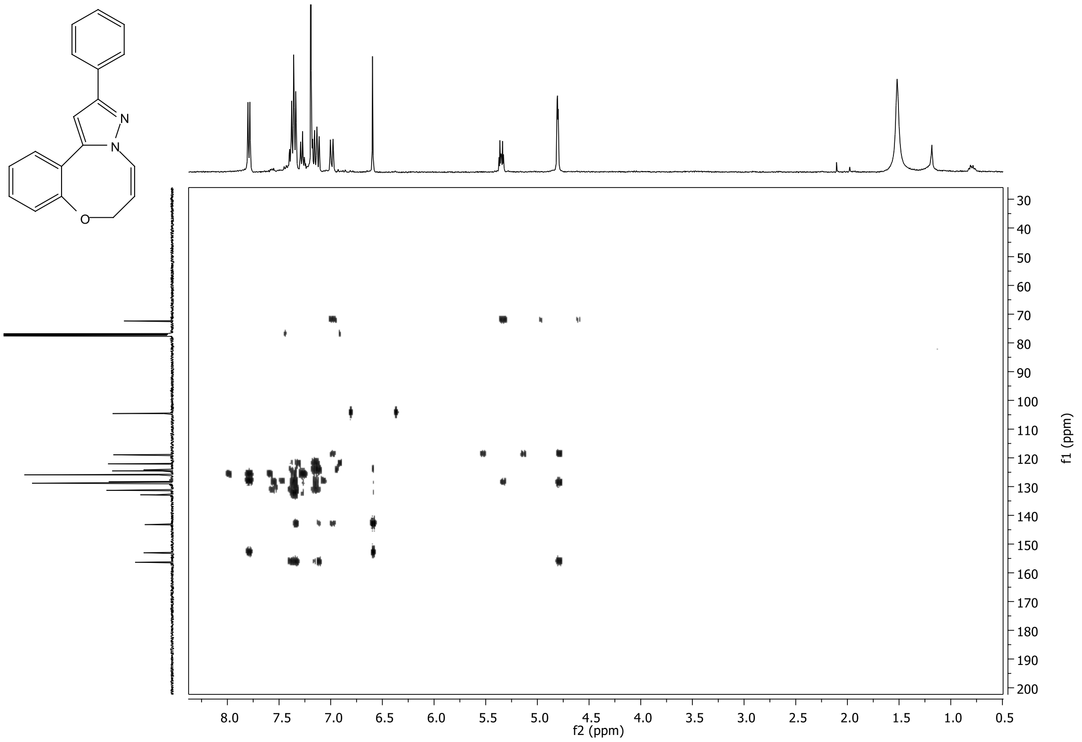


Figure 269: HMBC Spectrum of Compound 299

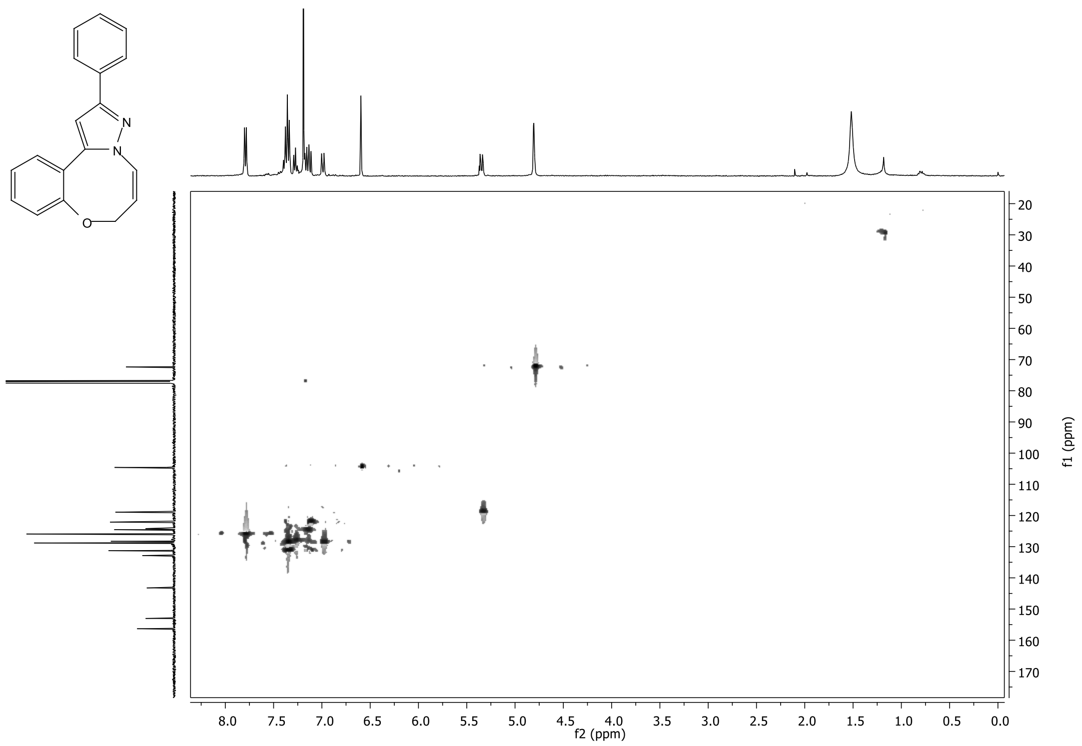


Figure 270: HSQC Spectrum of Compound 299

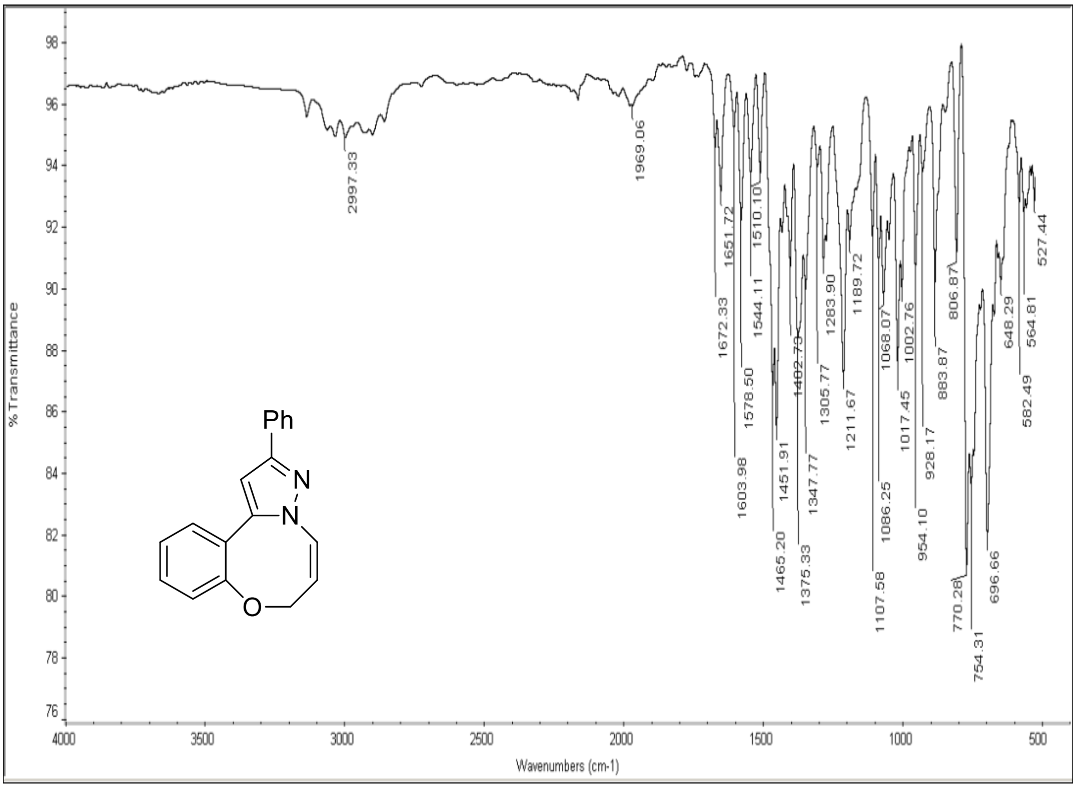


Figure 271: IR Spectrum of Compound 299

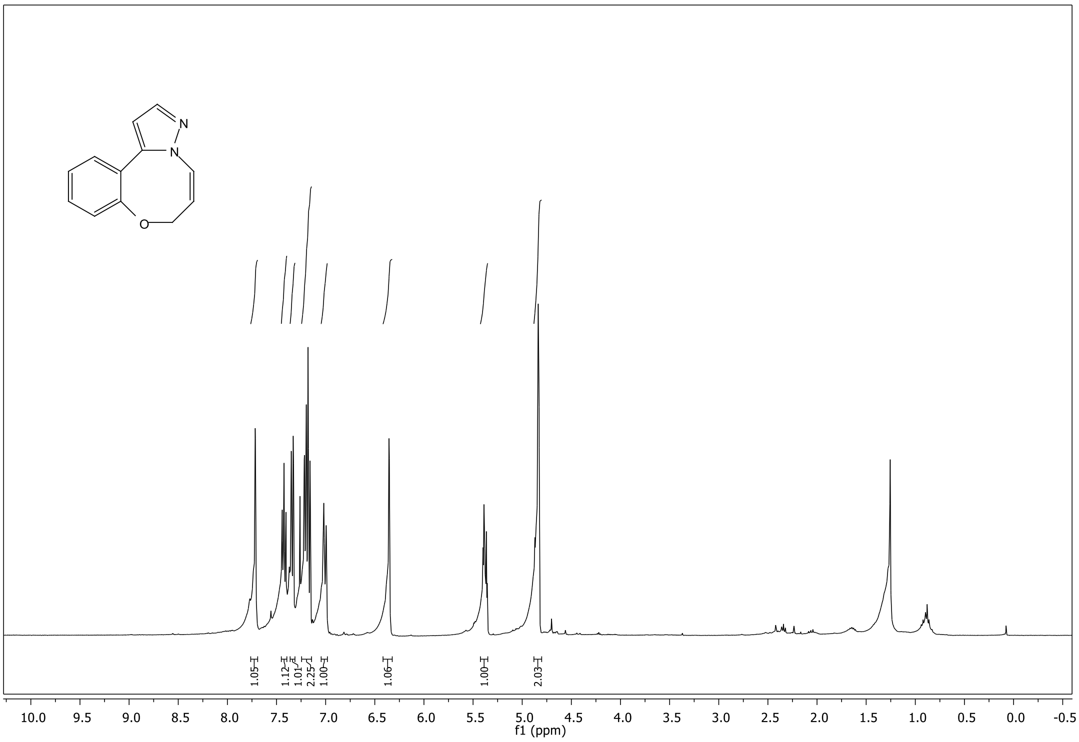


Figure 272: ^{1}H NMR Spectrum of Compound 302

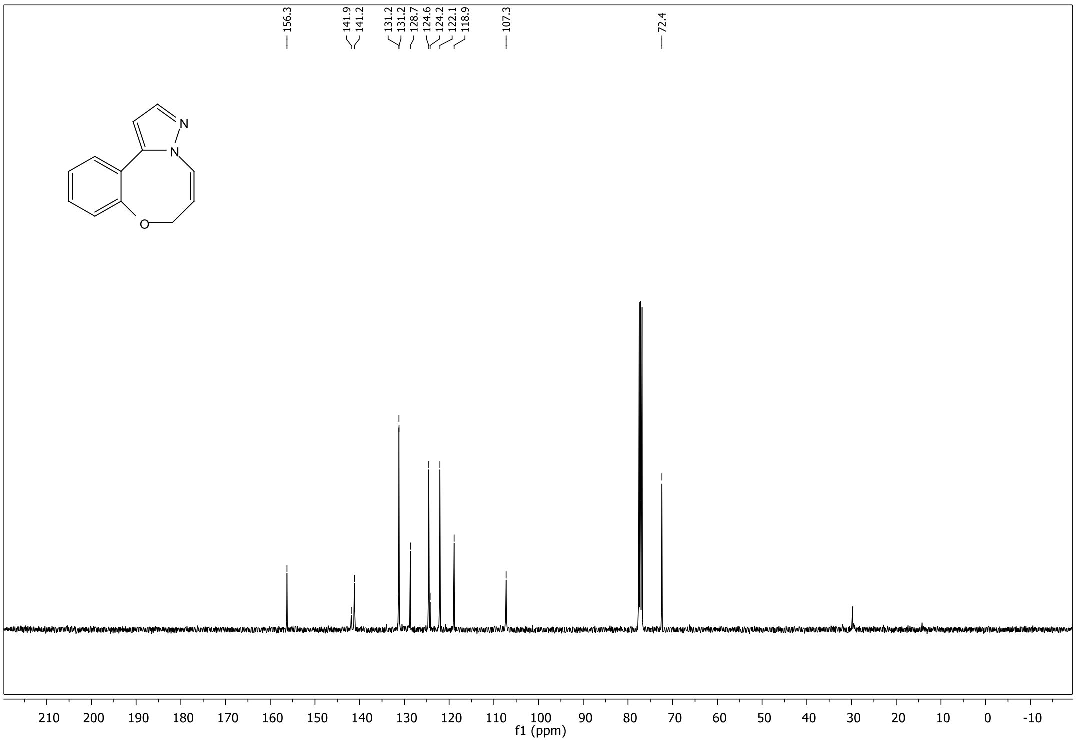


Figure 273: ^{13}C NMR Spectrum of Compound 302

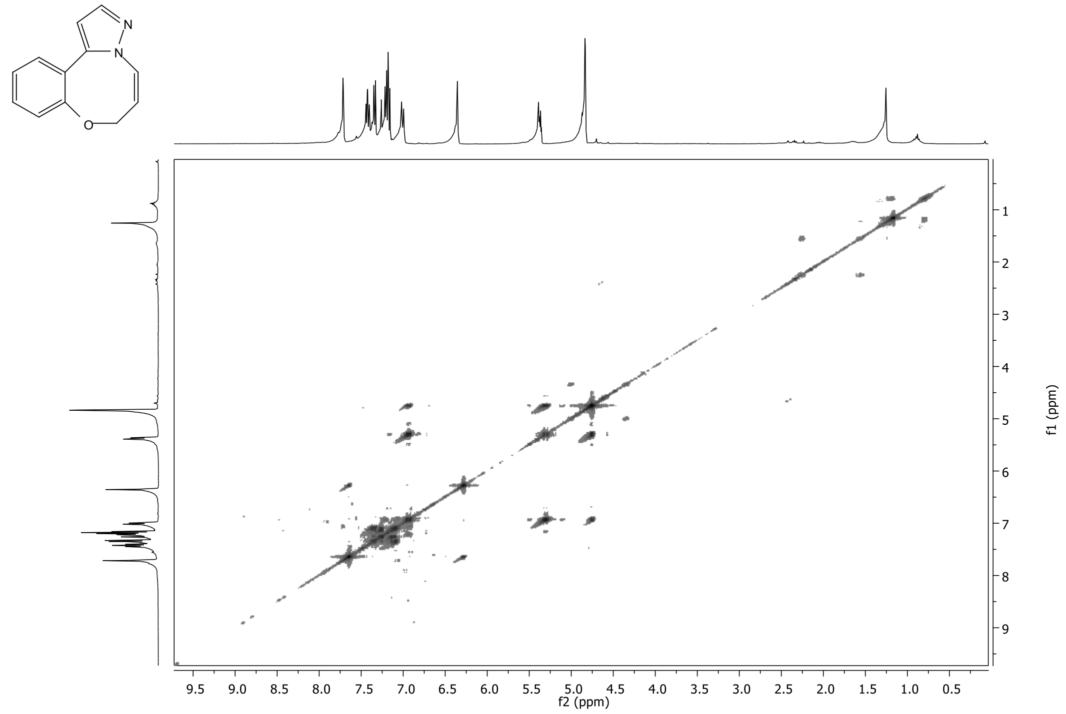


Figure 274: COSY Spectrum of Compound 302

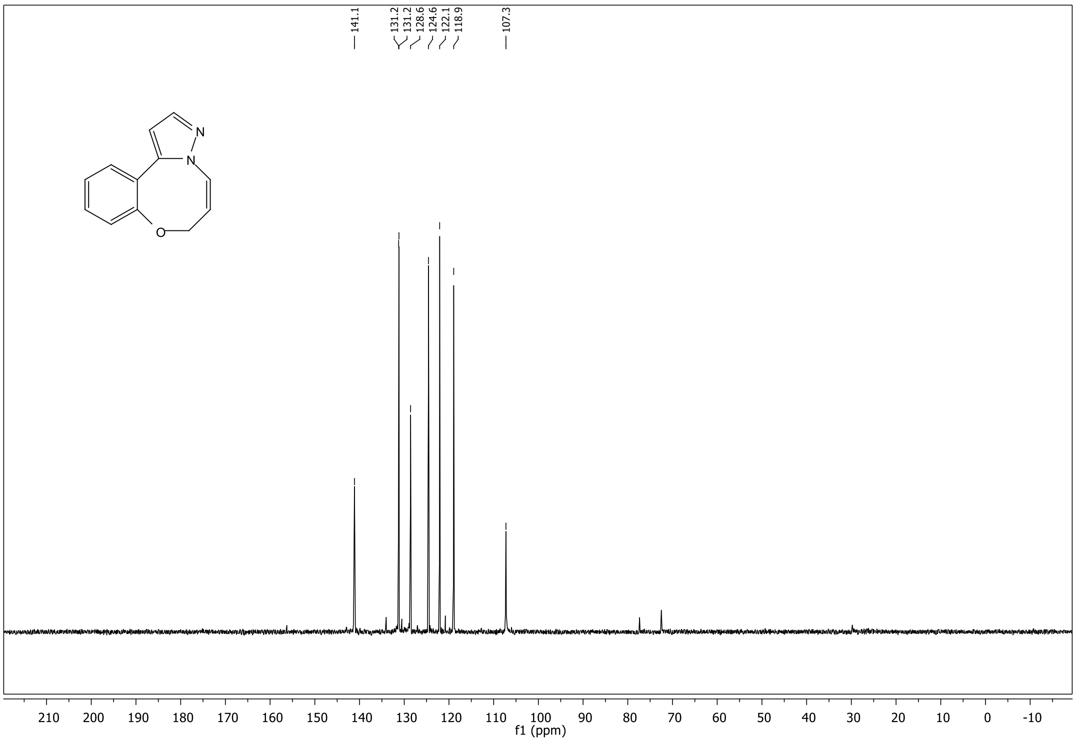


Figure 275: DEPT 90 Spectrum of Compound 302

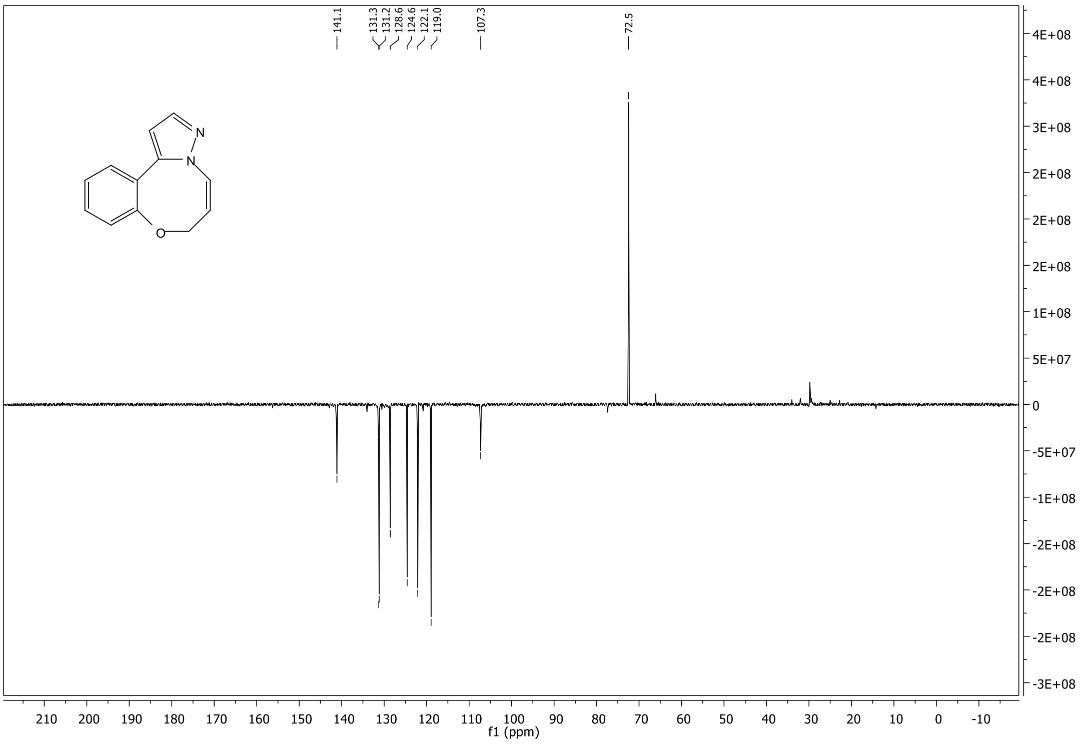


Figure 276: DEPT 135 Spectrum of Compound 302

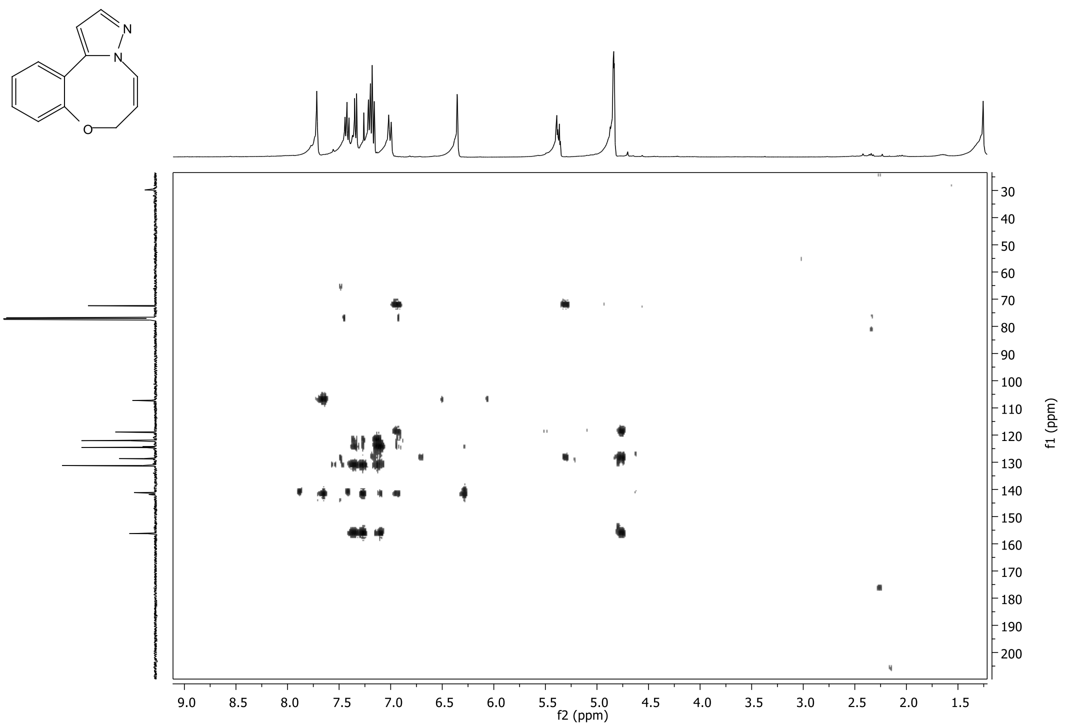


Figure 277: HMBC Spectrum of Compound 302

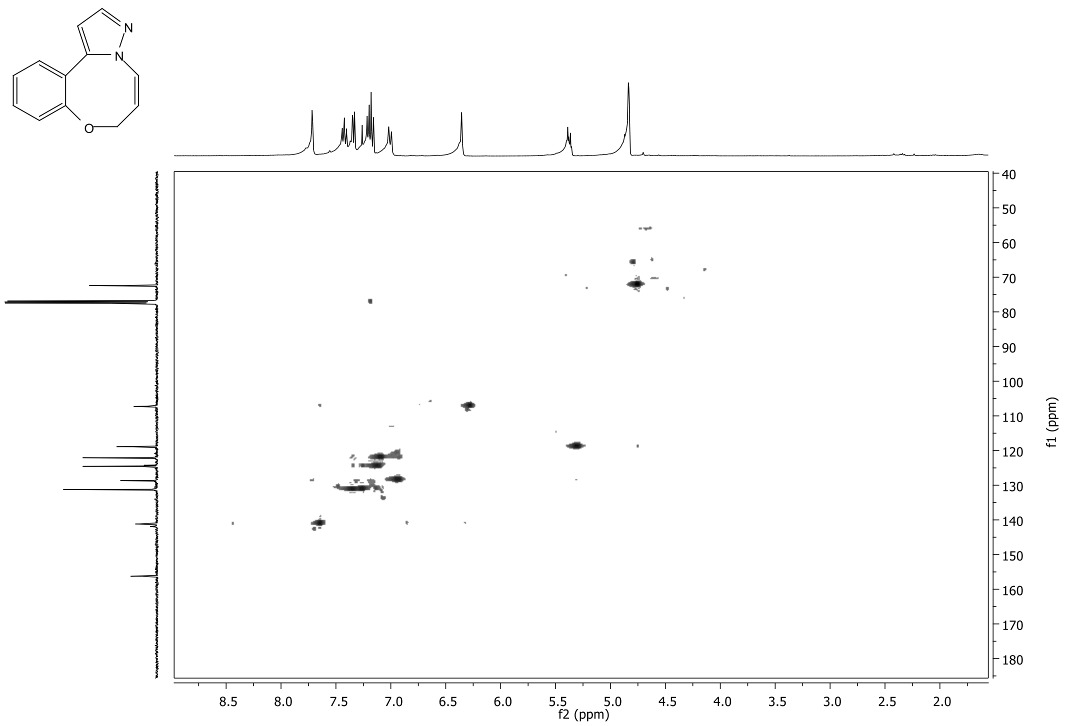


Figure 278: HSQC Spectrum of Compound 302

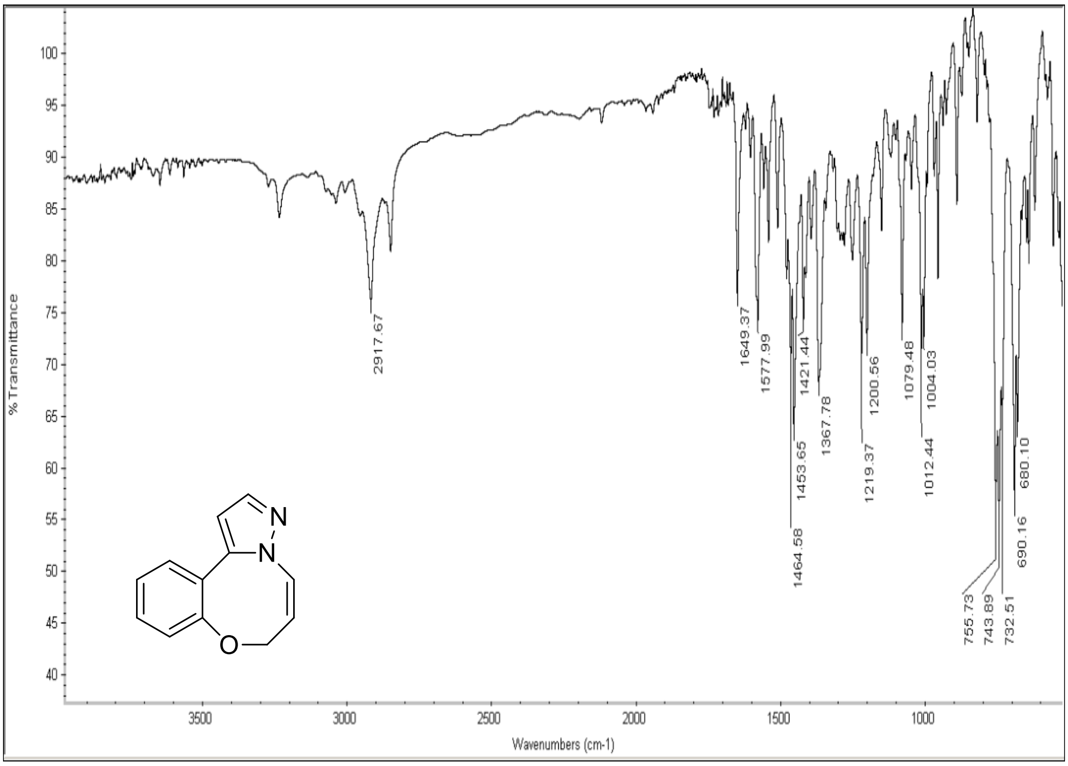


Figure 279: IR Spectrum of Compound 302

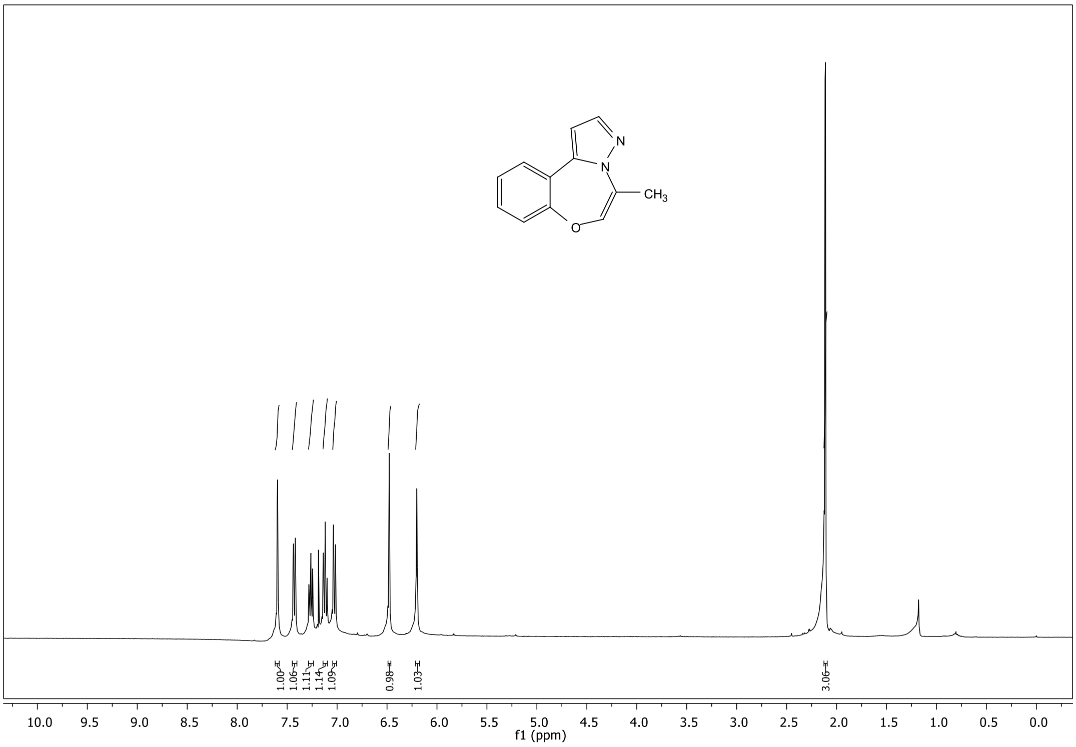


Figure 280: ^{1}H NMR Spectrum of Compound 304

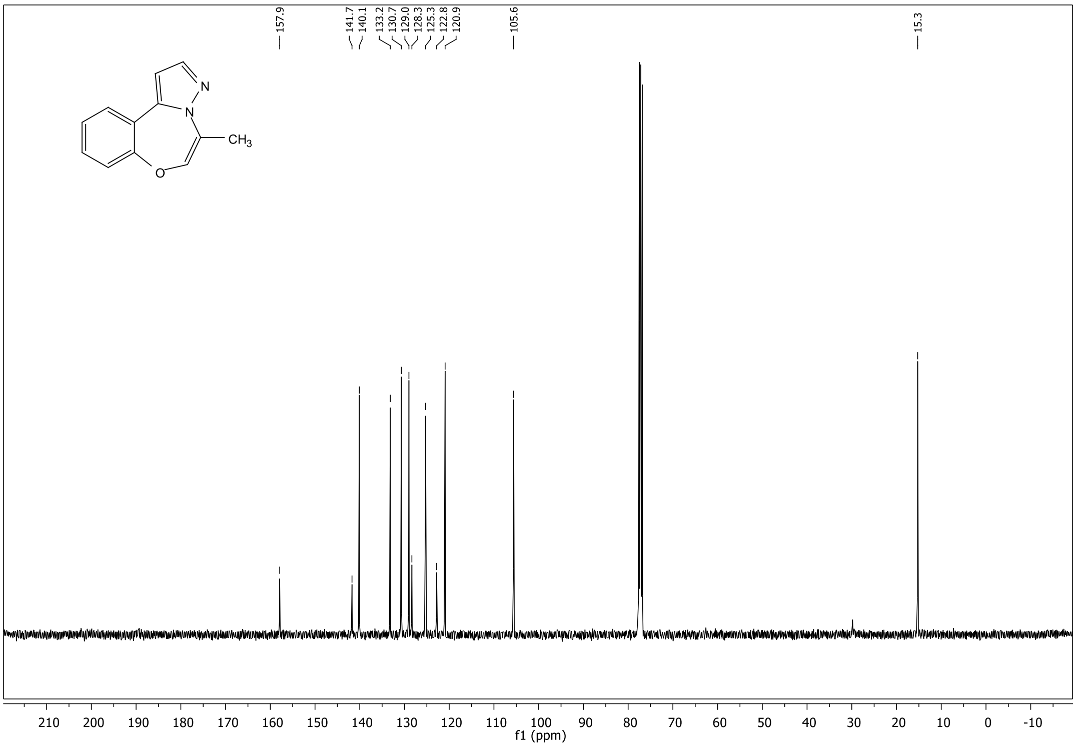


Figure 281: ^{13}C NMR Spectrum of Compound 304

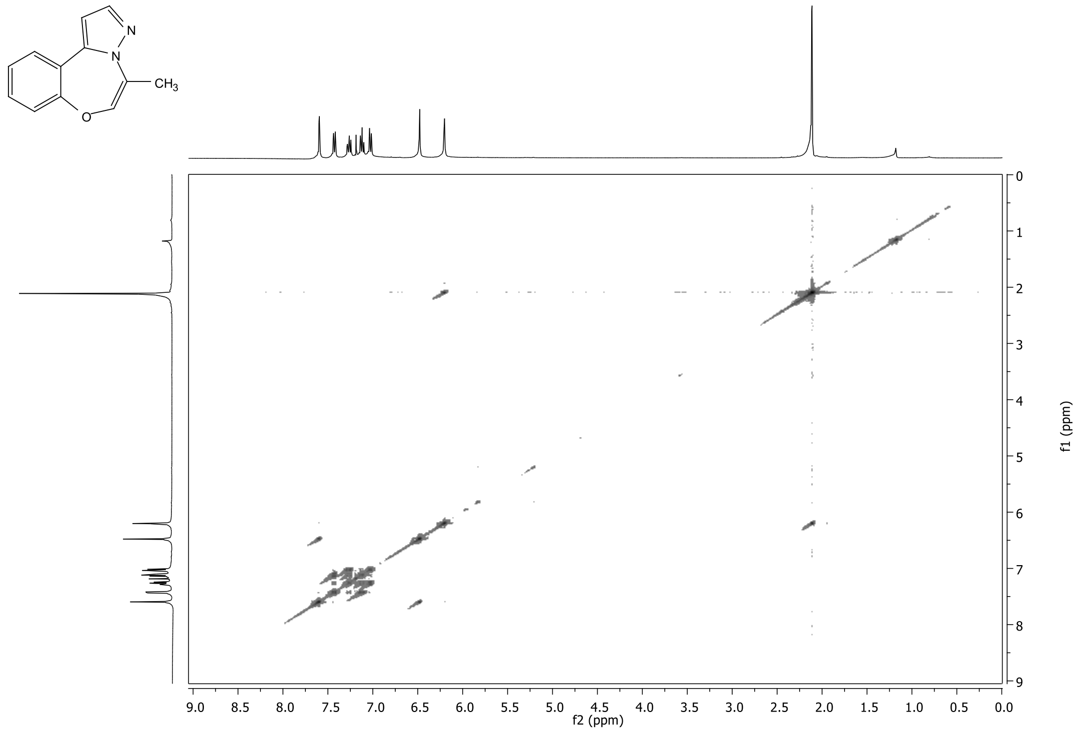


Figure 282: COSY Spectrum of Compound 304

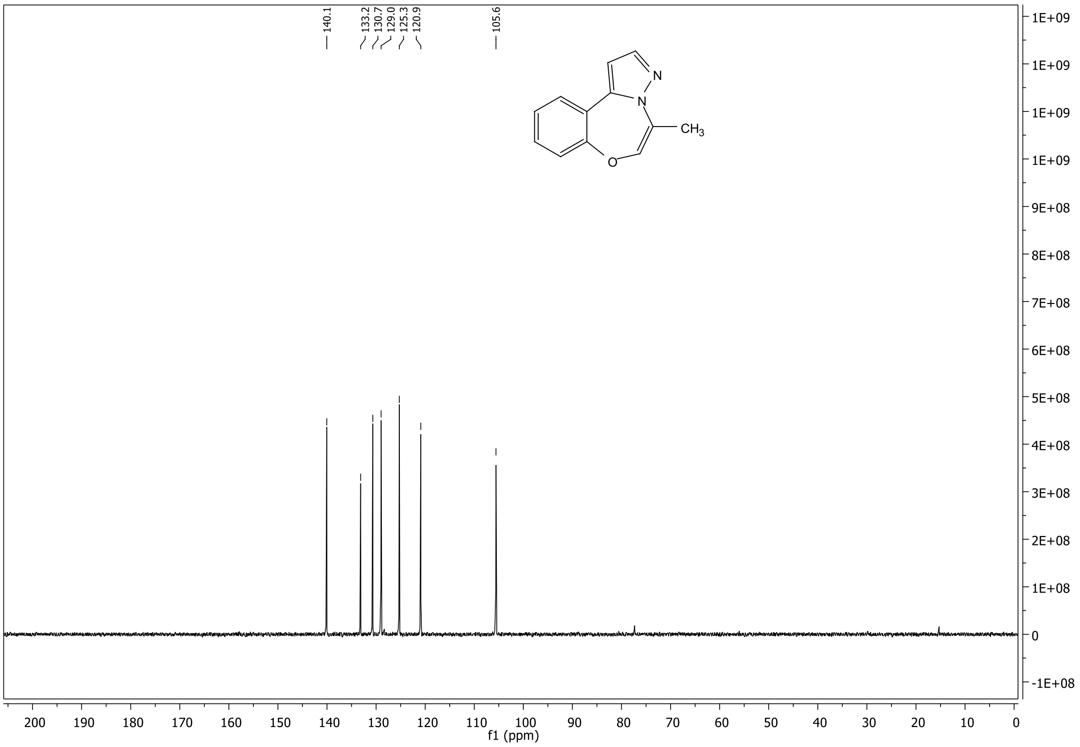


Figure 283: DEPT 90 Spectrum of Compound 304

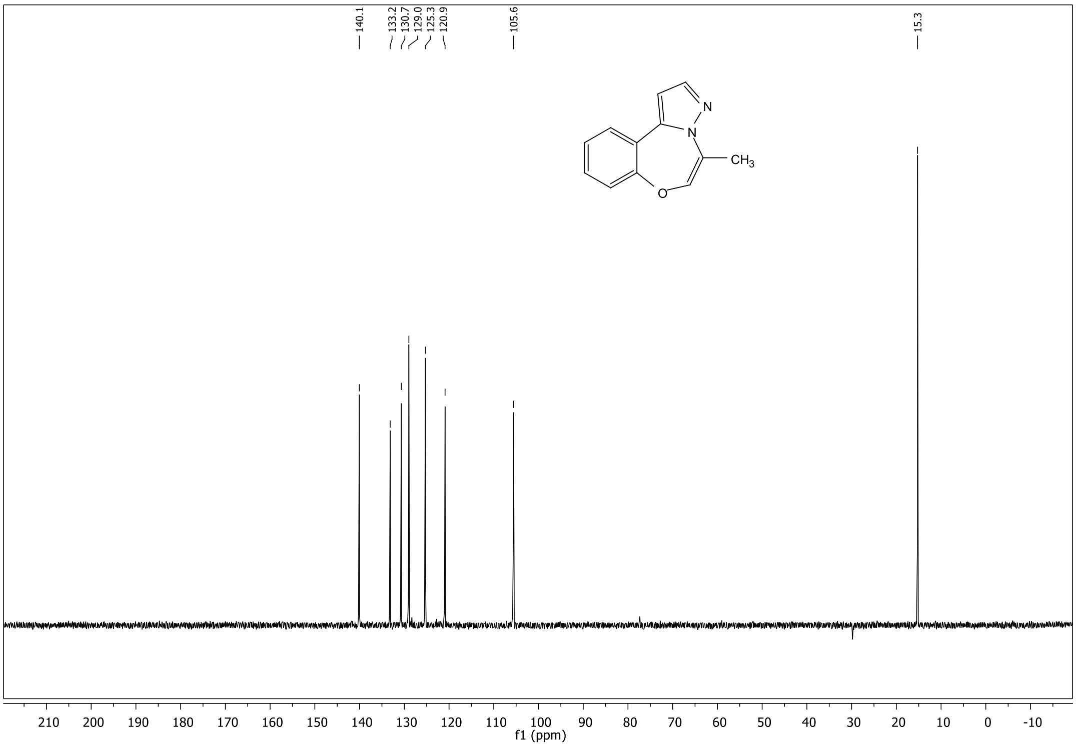


Figure 284: DEPT 135 Spectrum of Compound 304

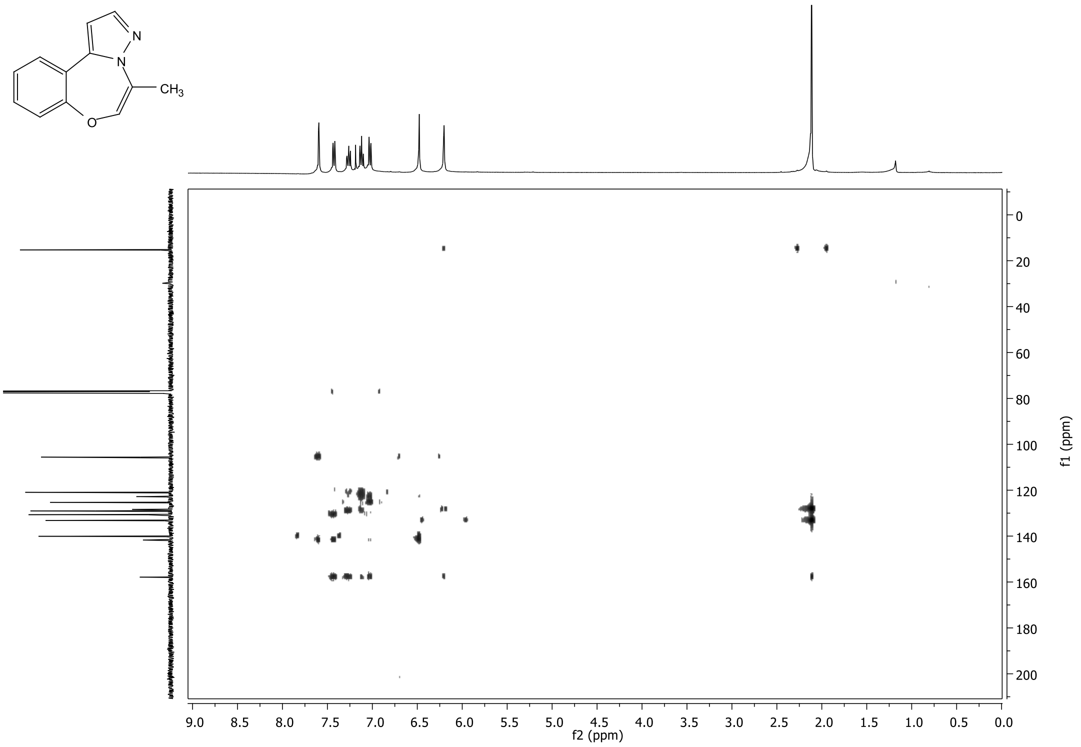


Figure 285: HMBC Spectrum of Compound 304

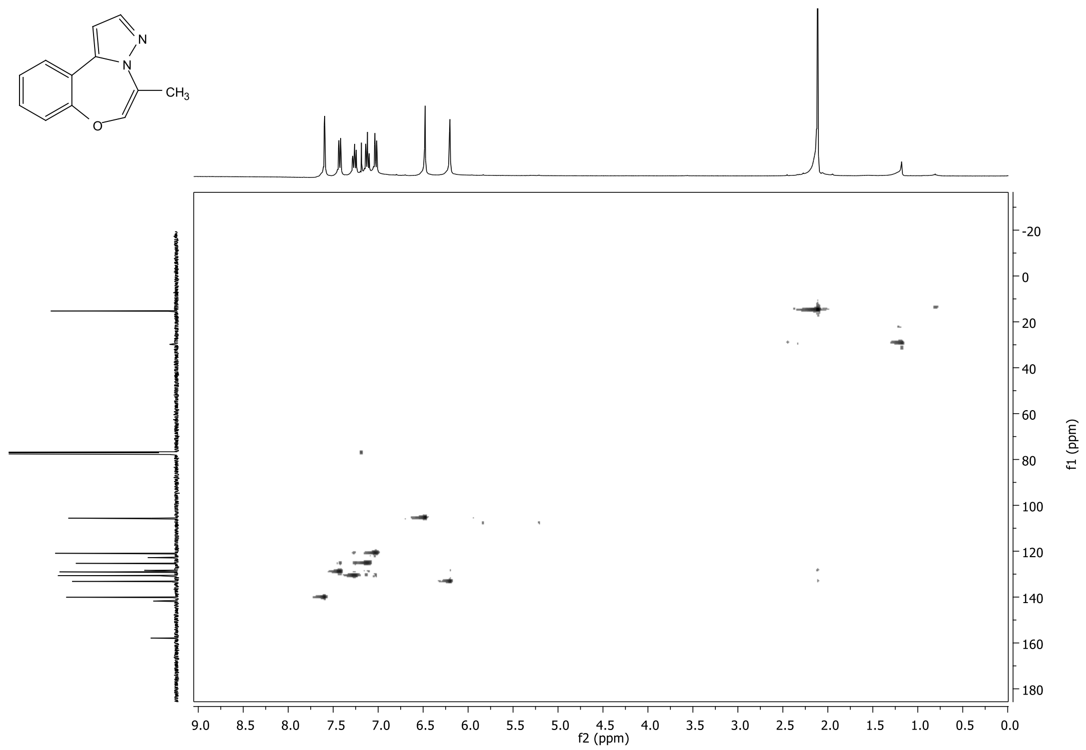


Figure 286: HSQC Spectrum of Compound 304

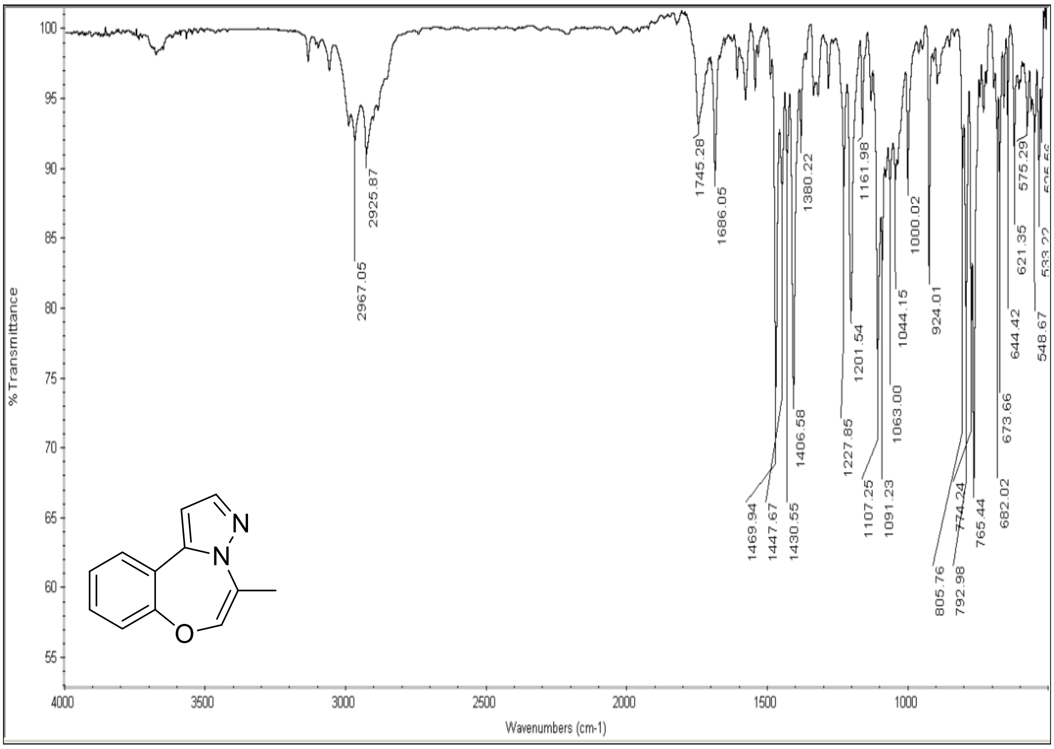


Figure 287: IR Spectrum of Compound 304

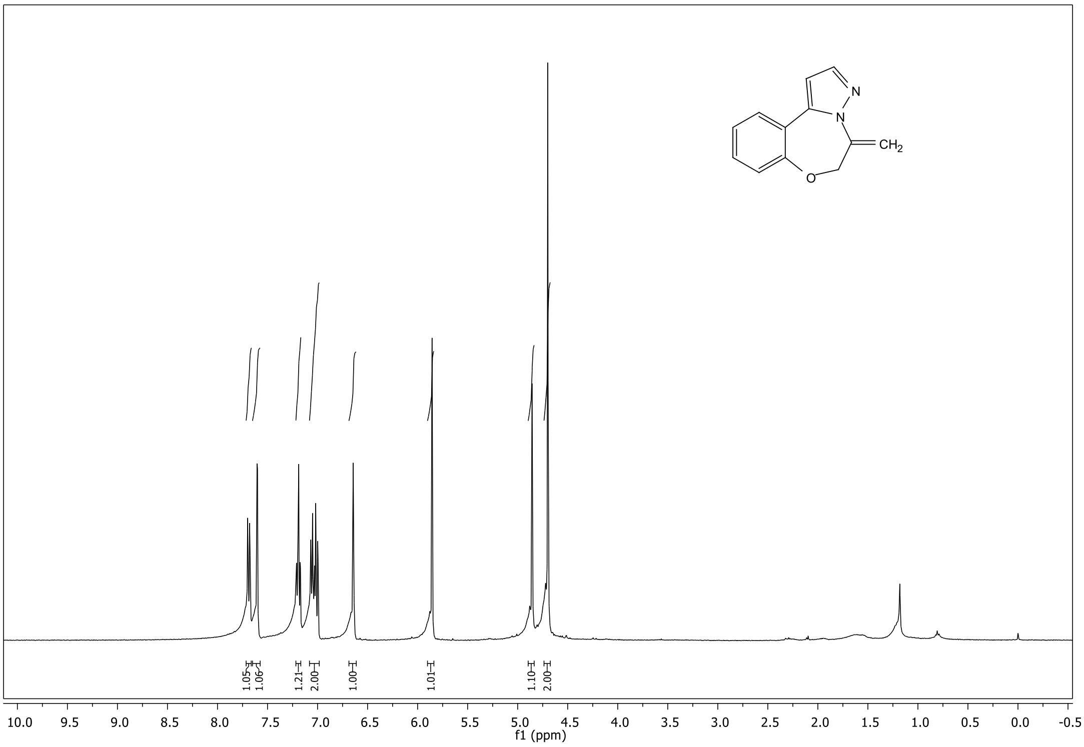


Figure 288: ^{1}H NMR Spectrum of Compound 304

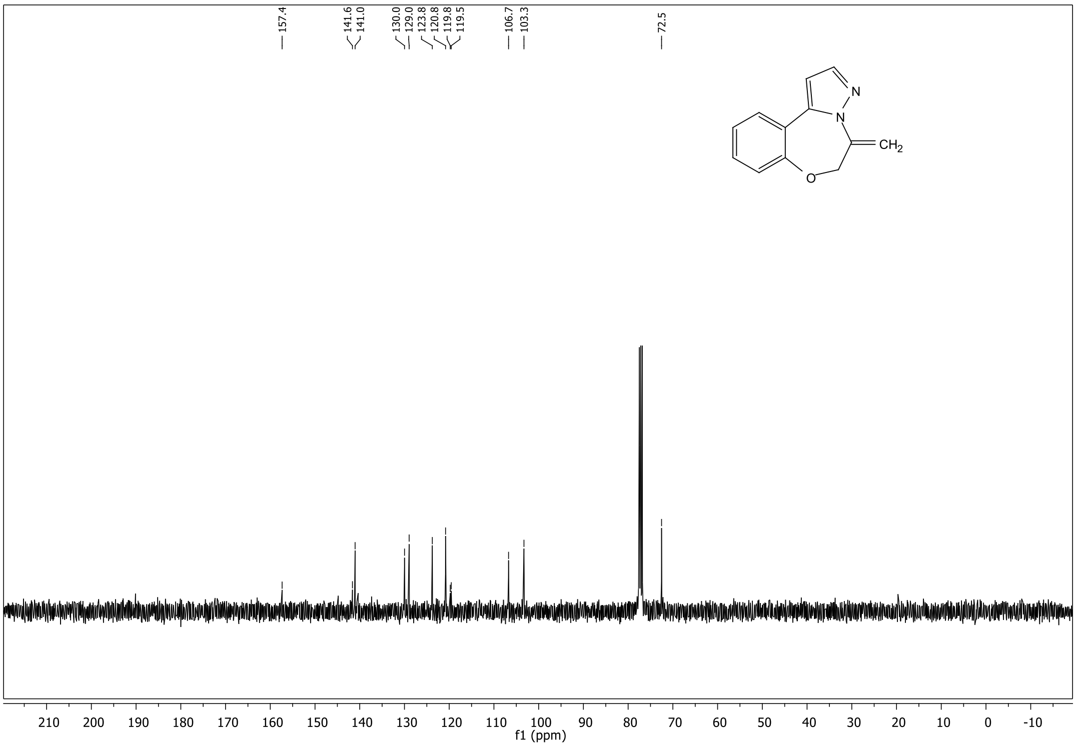


Figure 289: ^{13}C NMR Spectrum of Compound 303

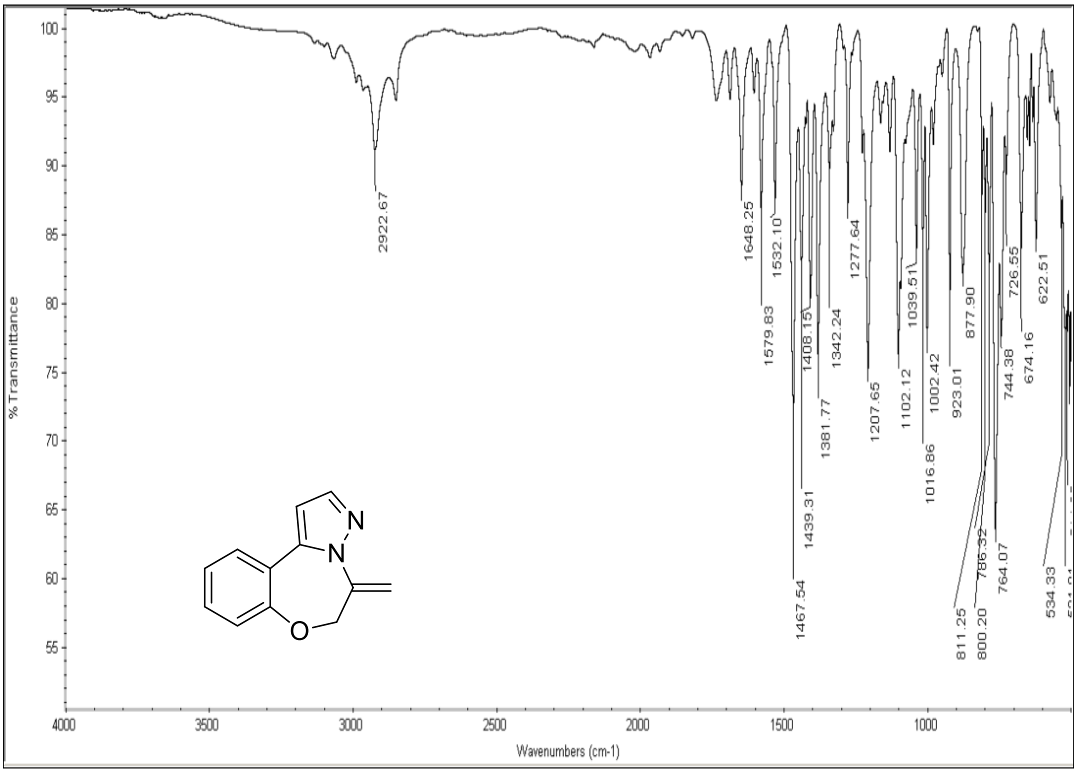


Figure 290: IR Spectrum of Compound 303

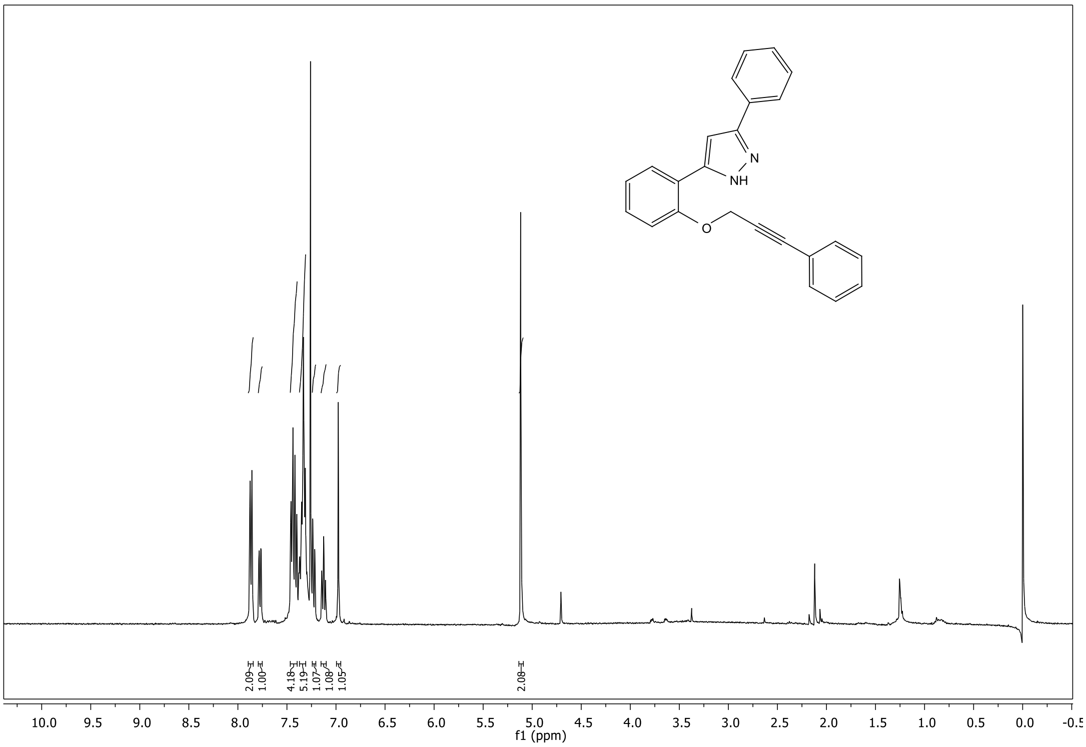


Figure 291: ^{1}H NMR Spectrum of Compound 306

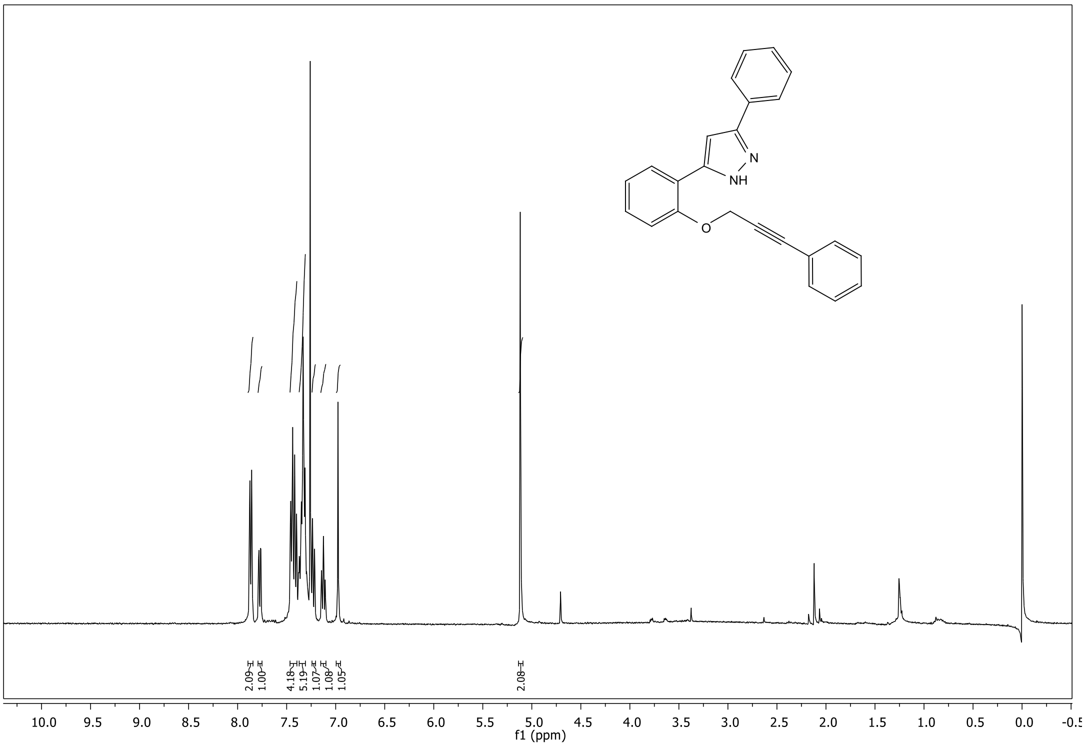


Figure 292: ^{13}C NMR Spectrum of Compound 306

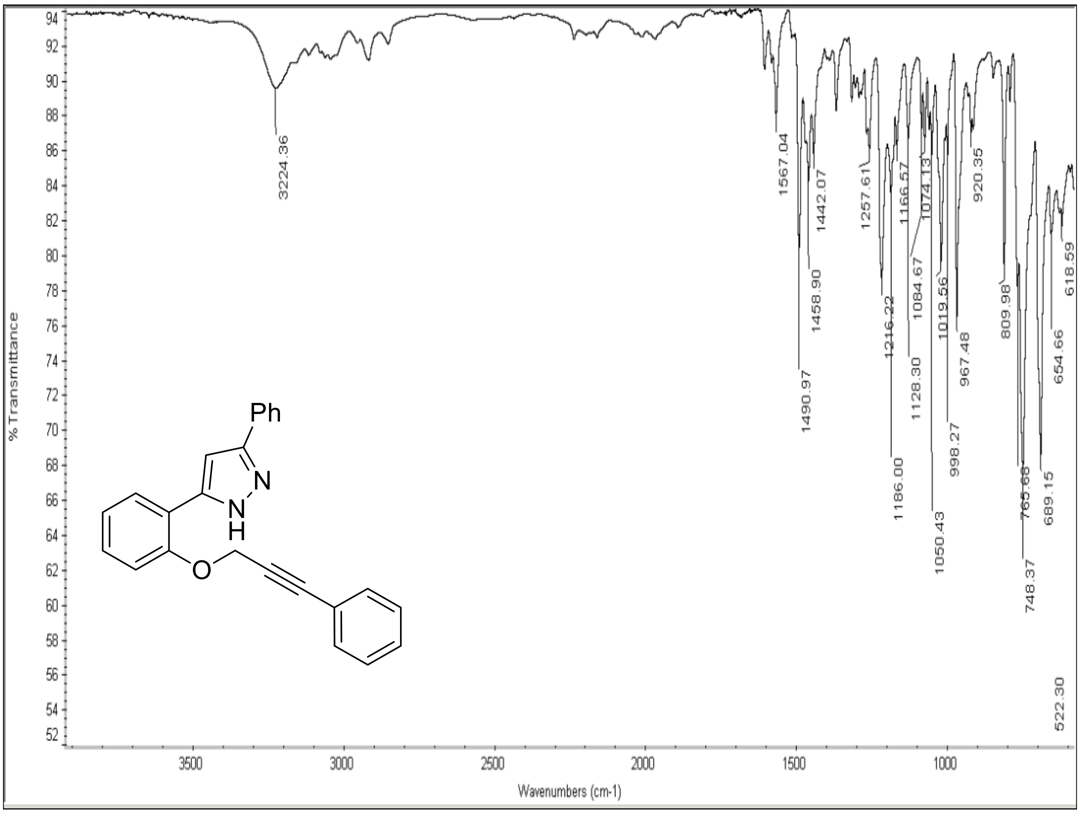


Figure 293: IR Spectrum of Compound 306

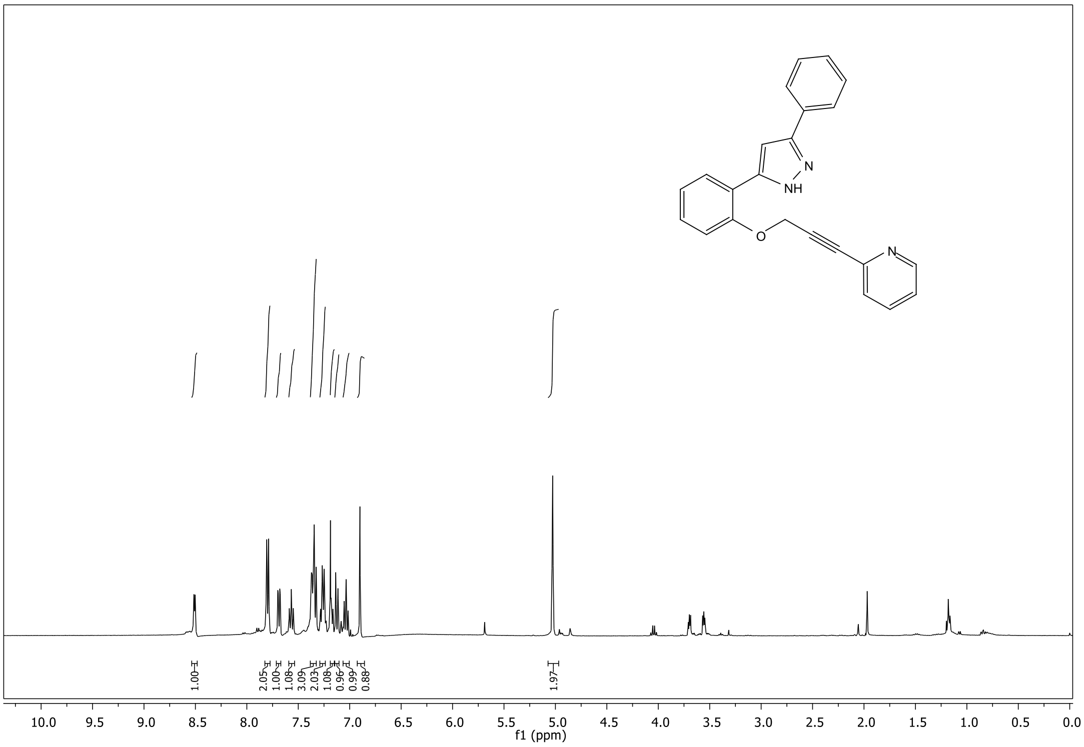


Figure 294: ^{1}H NMR Spectrum of Compound 305

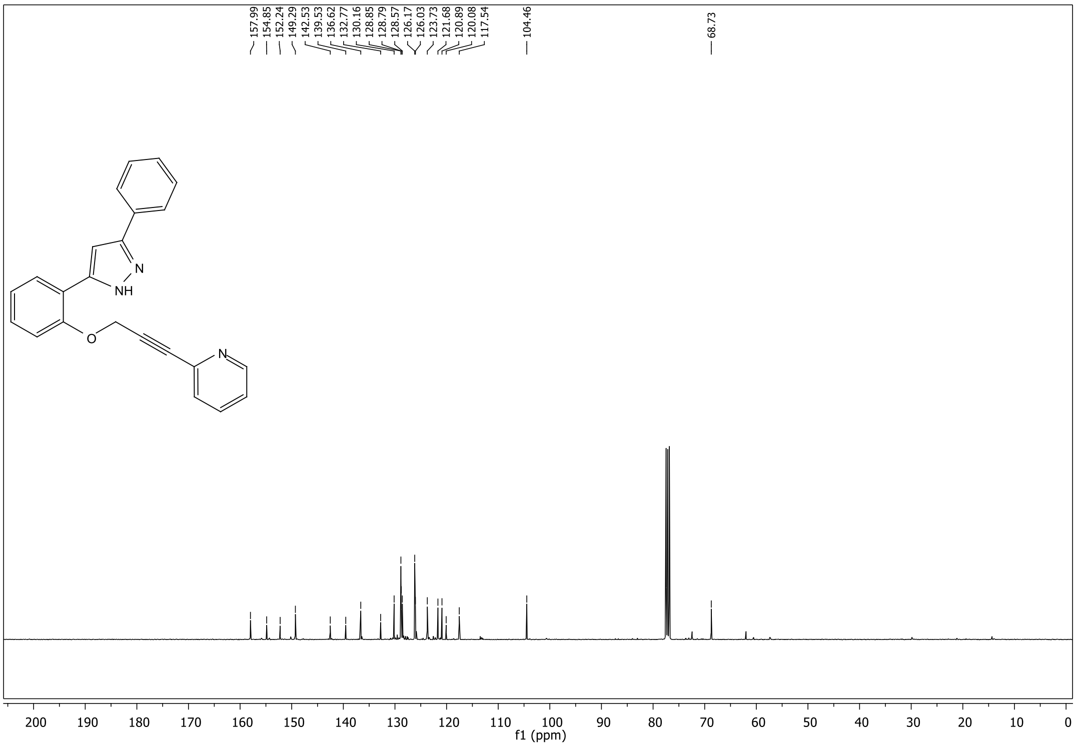


Figure 295: ^{13}C NMR Spectrum of Compound 305

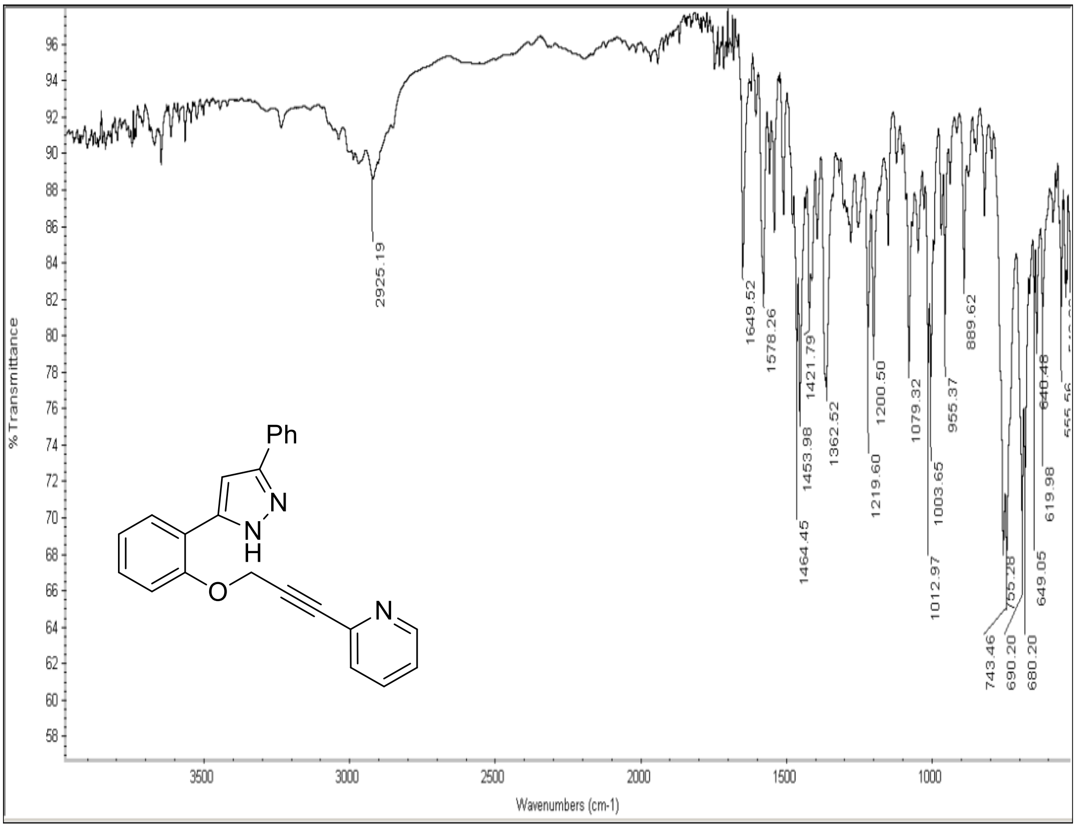


Figure 296: IR Spectrum of Compound 305

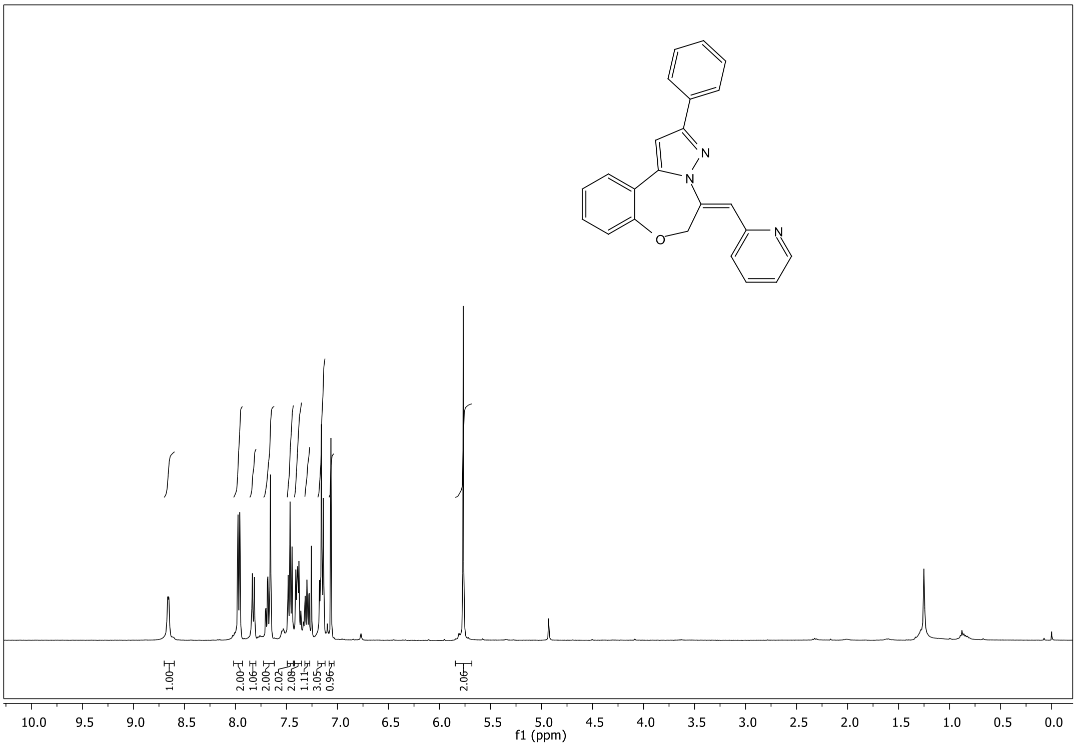


Figure 297: ^{1}H NMR Spectrum of Compound 308

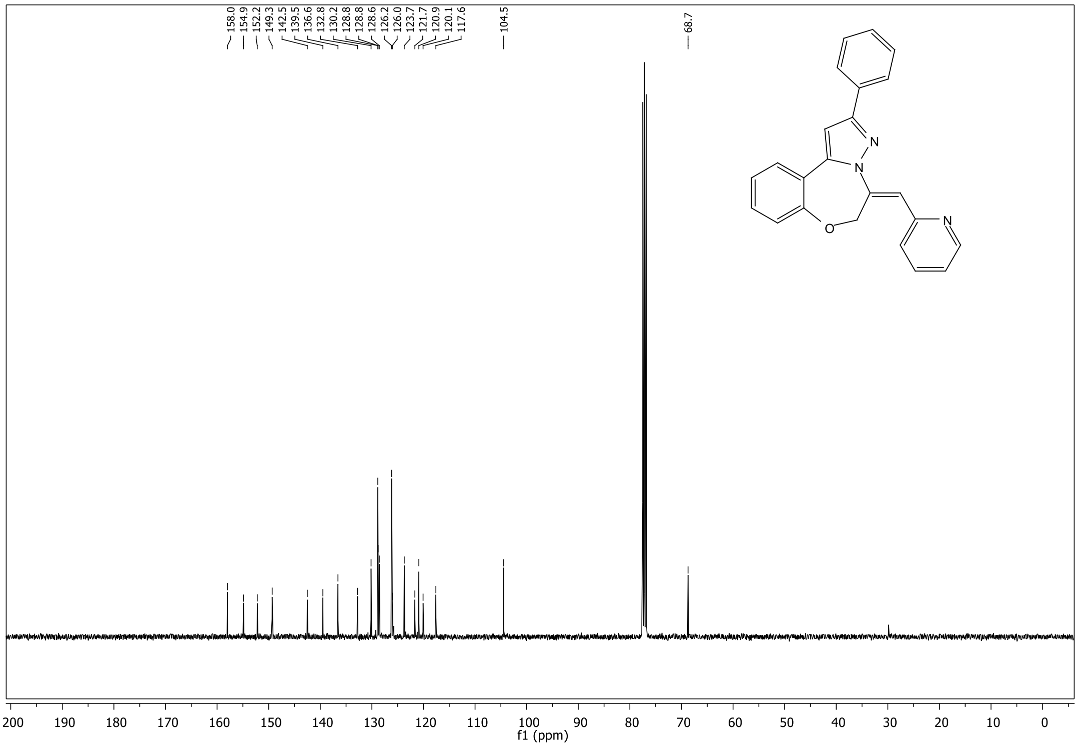


Figure 298: ^{13}C NMR Spectrum of Compound 308

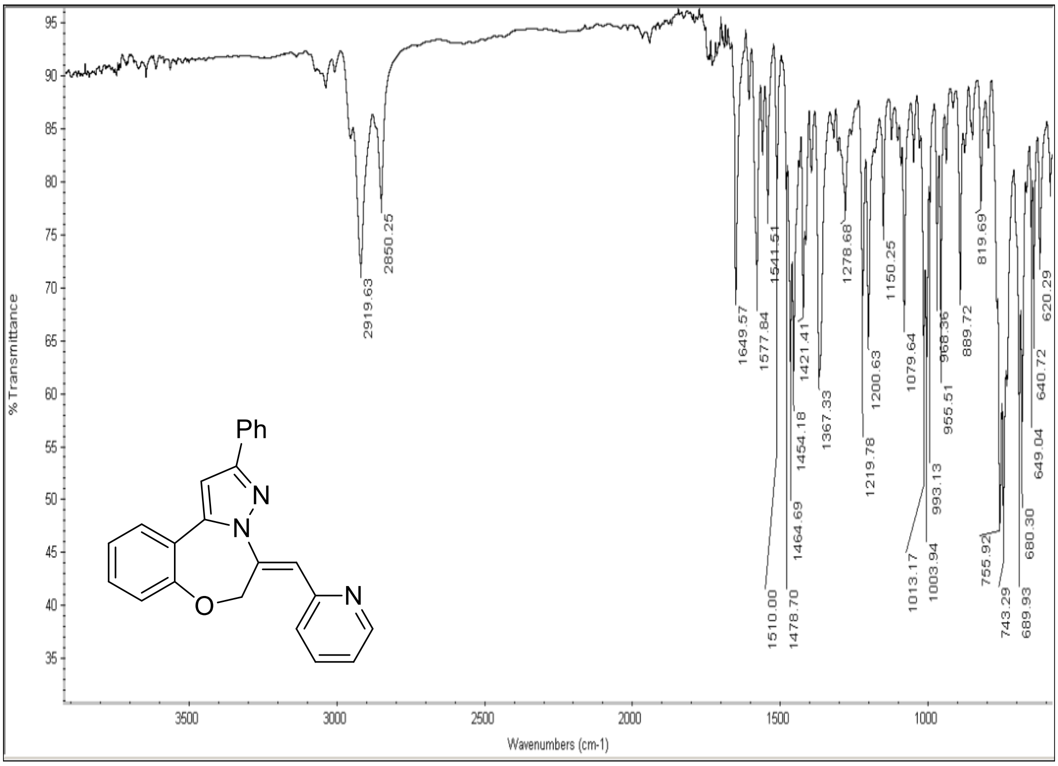


Figure 299: IR Spectrum of Compound 308

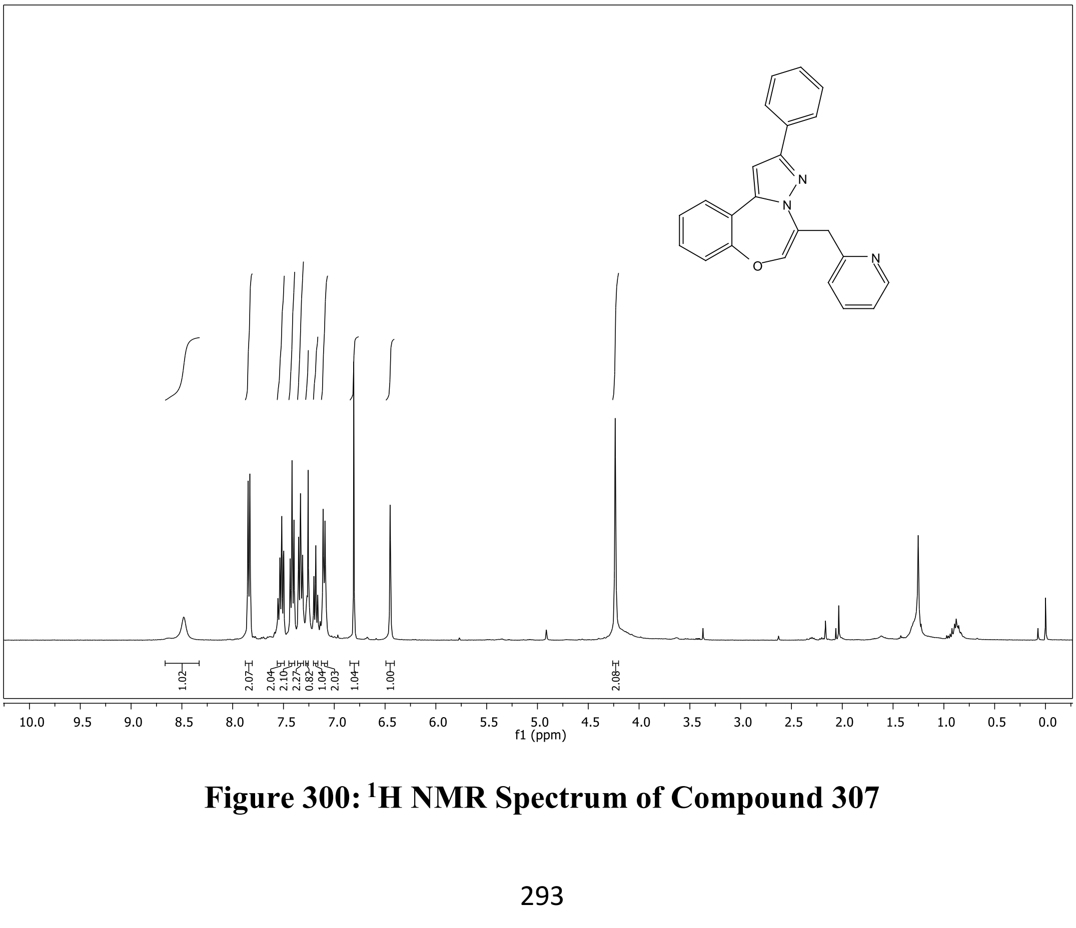


Figure 300: ^{1}H NMR Spectrum of Compound 307

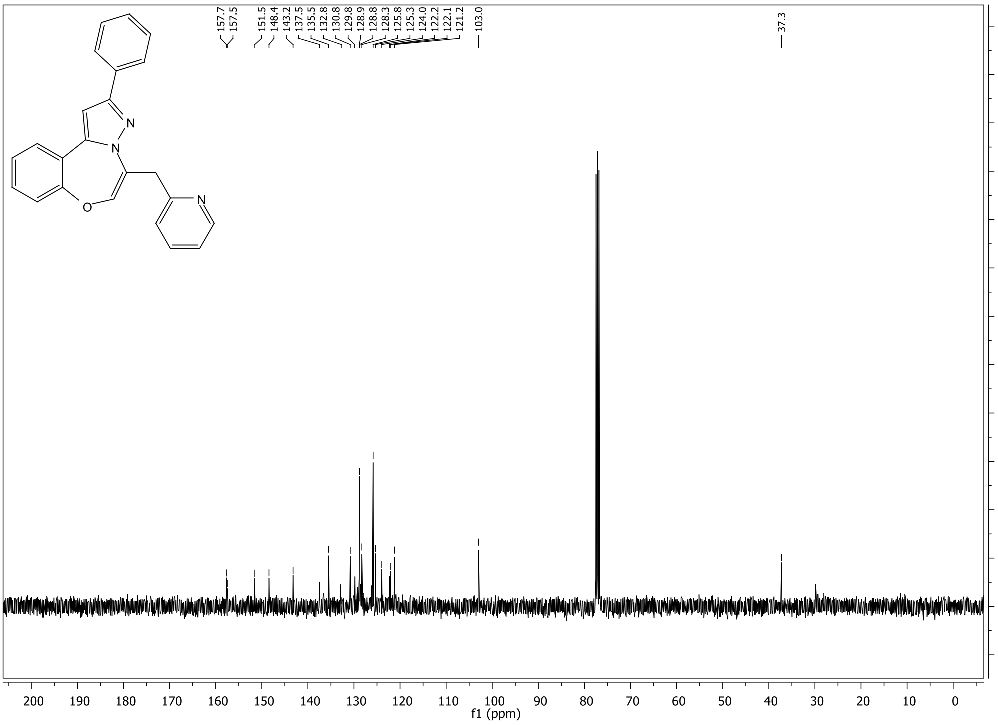


Figure 301: ^{13}C NMR Spectrum of Compound 307

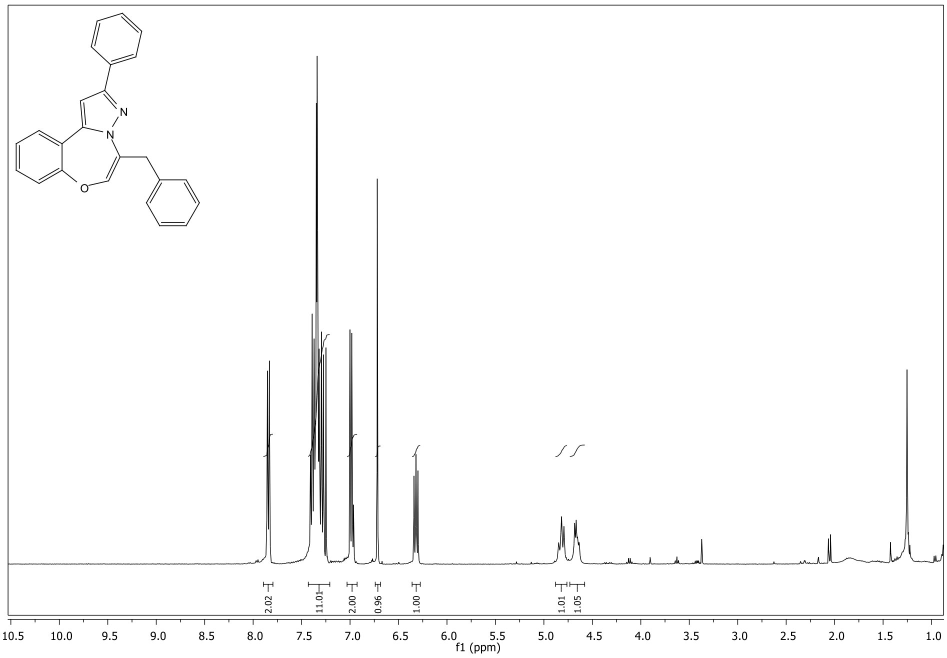


Figure 302: ^{1}H NMR Spectrum of Compound 309

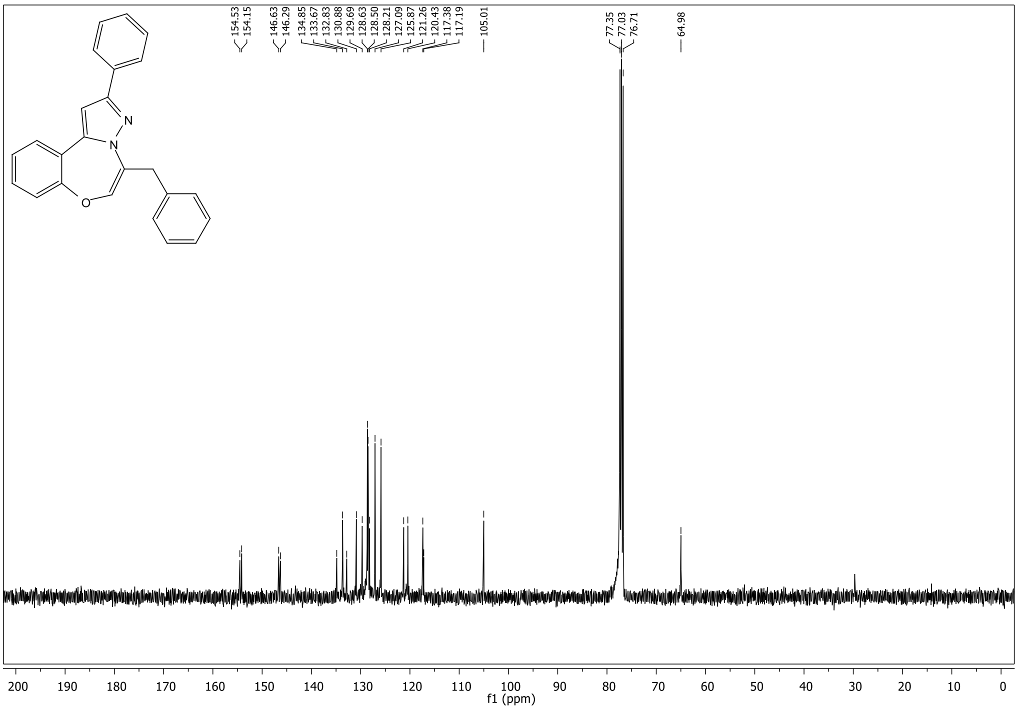


Figure 303: ^{13}C NMR Spectrum of Compound 309

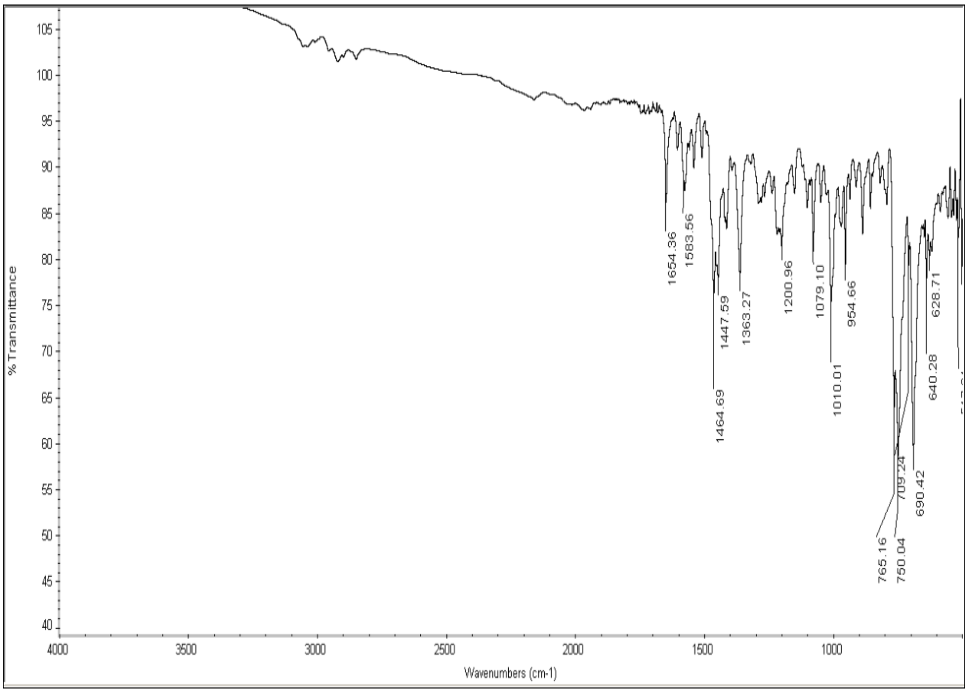


Figure 304: IR Spectrum of Compound 309

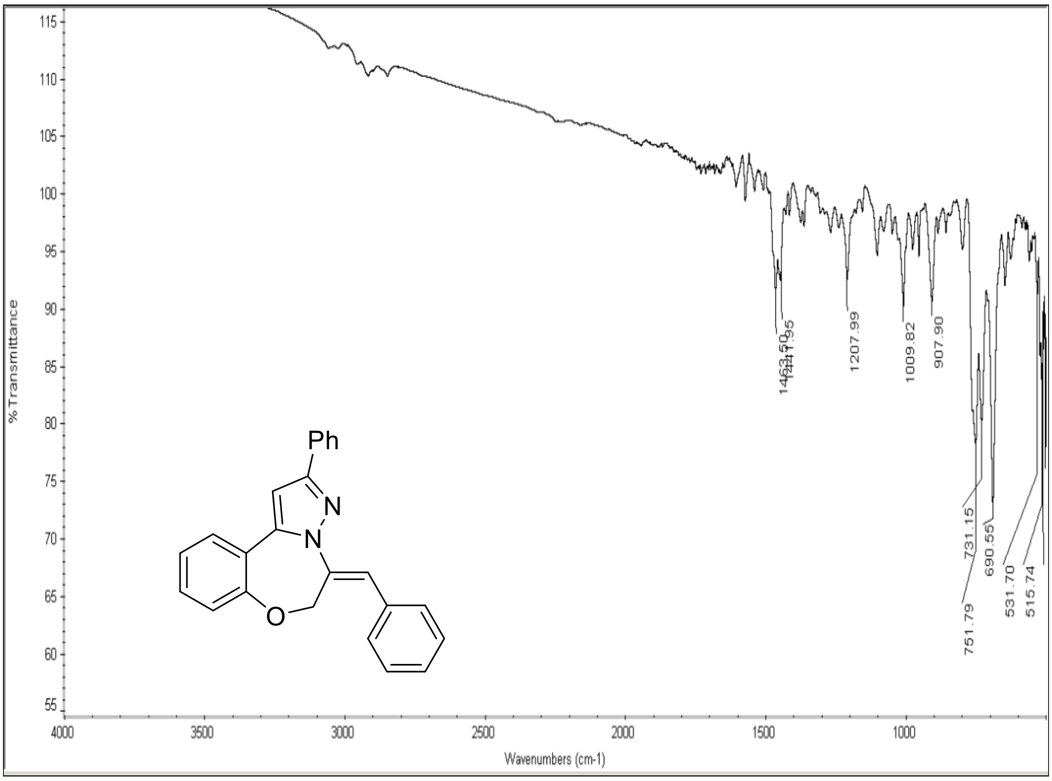


Figure 305: IR Spectrum of Compound 310

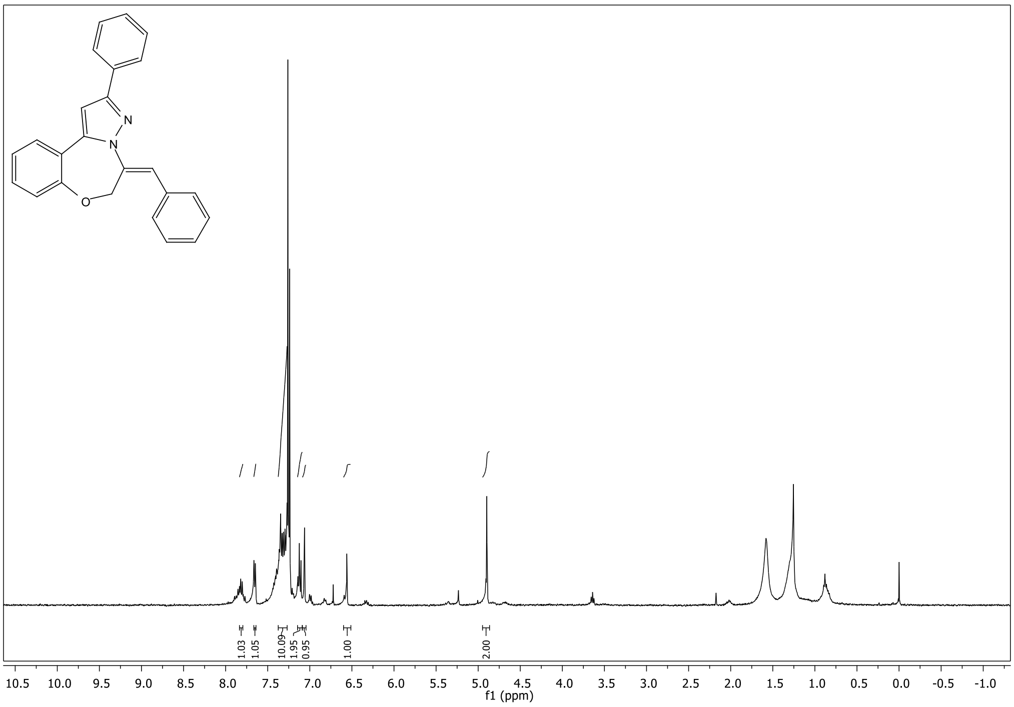


Figure 306: ^{1}H NMR Spectrum of Compound 310

VITA

PERSONAL INFORMATION:

Name Surname: Selbi KESKİN

Date and Place of Birth: 21/10/1983, Adana (TURKEY)

Marital Status: Single

Nationality: Republic of Turkey

E-mail: kselbi@metu.edu.tr

EDUCATIONAL BACKGROUND:

B.S.: Mersin University Department of Chemistry, Mersin

Date of Graduation: June, 2004

High School: Adana Kız Lisesi, Adana

Date of Graduation: June, 2000

WORK EXPERIENCES

Year	Place	Enrollment
2009-present	METU	Research Assistant

PUBLICATION LIST:

International Refereed Journal Papers

1. Koza, G.; **Keskin, S.**; Ozer, M. S.; Cengiz, B.; Sahin, E.; Balci, M., Facile synthesis of novel 7-aminofuro- and 7-amino-thieno[2,3-d]pyridazin-4(5*H*)-one and 4-aminophthalazin- 1(2*H*)-ones. "Tetrahedron", 69, (2013), p.395-409. (DOI: 10.1016/j.tet.2012.10.010)

2. **Keskin, S.**; Balci, M., Intramolecular heterocyclization of *O*-propargylated aromatic hydroxyaldehydes as an expedient route to substituted chromenopyridines under metal-free conditions. "Organic Letters", 17, (2015), p.964-967. (DOI: 10.1021/acs.orglett.5b00067)

PROFESSIONAL MEETINGS AND ACTIVITIES:

Conferences

1. Poster Presentation at "Hesaplamalı Kimya Kongresi", 02-05 June 2015, Kars-Turkey

   Keskin, S.; Basceken, S.; Balci, M., Benzopirazolokzazepin ve benzopirazolokzazosin türevlerinin sentezi ve reaksiyon mekanizması üzerine teorik çalışmalar.
2. Oral Presentation at "Anatolian Conference on Synthetic Organic Chemistry", 16-19 March 2015, Antalya-Turkey

   Keskin, S.; Balci, M., Synthesis of chromenopyridinone and benzopyrazolooxazepine derivatives via alkyne cyclization.
3. Oral Presentation at "13th IBN SINA International Conference on Pure and Applied Heterocyclic Chemistry", 14-17 February 2014, Hurghada, Egypt

   Keskin, S.; Balci, M., Design and Synthesis of Benzene-Fused Heterocycles: Chromenopyridinones and Benzopyrazolooxazepines.
4. Oral Presentation at "2. Ulusal Organik Kimya Kongresi", 24-26 September 2014, Ankara-Turkey

Keskin, S.; Balci, M., Yeni bir yöntemle kromenopiridin, benzokromenopiridin ve kromenopiridinon türevlerinin sentezleri

5. Poster Presentation at “2. Ulusal Organik Kimya Kongresi”, 24-26 September 2014, Ankara-Turkey

   Hoplamaz, E.; **Keskin, S.**; Balci, M., Benzonaftiridin türevlerinin sentezi için yeni yöntemlerin geliştirilmesi
6. Poster Presentation at “2. İlaç Kongresi”, 21-23 March 2014, Antalya-Turkey

   Keskin, S.; Balci, M., Kromenopiridin, benzokromenopiridin ve kromenopiridinon türevlerinin sentezleri için yeni yöntemlerin geliştirilmesi
7. Poster Presentation at “2. İlaç Kongresi”, 21-23 March 2014, Antalya-Turkey

   Hoplamaz, E.; **Keskin, S.**; Balci, M., Benzonaftiridin türevlerinin sentezi için yeni yöntemleri geliştirilmesi
8. Oral Presentation at “1. İlaç Kongresi”, 29-31 March 2013, Antalya-Turkey

   Keskin, S.; Koza, G.; Balci, M., Ftalazinon ve aminoftalazinon türevlerinin sentezi için yeni metotların geliştirilmesi
9. Oral Presentation at “26th National Chemistry Congress with International Participation”, 1-6 October 2012, Fethiye, Muğla-Turkey

   Keskin, S.; Koza, G.; Balci, M., Ftalazinon, aminoftalazinon ve benzodiazepinon türevlerinin sentezi
10. Poster Presentation at “25th National Chemistry Congress with International Participation”, 26 June-02 July 2011, Erzurum- Turkey

    Keskin, S.; Koza, G.; Balci, M., Ftalazinon ve aminoftalazinon türevlerinin yeni bir yöntemle sentezi
11. Poster Presentation at “24th National Chemistry Congress with International Participation”, 29 June-02 July 2010, Zonguldak- Turkey

    Keskin, S.; Koza, G.; Balci, M., Yeni bir yöntemle ftalazinon ve aminoftalazinon türevlerinin sentezi