SYNTHESIS OF CYCLOHEPTADIENE ANNELATED DIHYDROFURANE DERIVATIVES AND DESIGN OF PYRROLO-PYRROLO-PYRAZINES AND α-ALKYLIDYN-γ-BUTYROLACTONES VIA ALKYNE CYCLIZATION

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

BY

FURGAN ASLANOĞLU

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

MARCH 2018

Approval of the thesis:

SYNTHESIS OF CYCLOHEPTADIENE ANNELATED DIHYDROFURANE DERIVATIVES AND DESIGN OF PYRROLO-PYRROLO-PYRAZINES AND α-ALKYLIDYN-γ-BUTYROLACTONES VIA ALKYNE CYCLIZATION

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

Prof. Dr. Halil Kalıpçılar _____

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. Cihangir Tanyeli _____

Chemistry Dept., METU

Prof. Dr. Metin Balcı _____

Chemistry Dept., METU

Prof. Dr. Canan Ünaleroğlu _____

Chemistry Dept., Hacettepe University

Prof. Dr. Özdemir Doğan _____

Chemistry Dept., METU

Prof. Dr. Adnan Bulut _____

Chemistry Dept.,Kırıkkale University

Date: 20.03.2018

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: Furgan Aslanoğlu

Signature :

ABSTRACT

SYNTHESIS OF CYCLOHEPTADIENE ANNELATED DIHYDROFURANE DERIVATIVES AND DESIGN OF PYRROLO-PYRROLO-PYRAZINES AND α-ALKYLIDYN-γ-BUTYROLACTONES VIA ALKYNE CYCLIZATION

Aslanoğlu, Furgan

PhD, Department of Chemistry

Supervisor: Prof. Dr. Metin Balcı

March 2018, 206 pages

Owing to fascinating regiochemistry and controversial reaction mechanism, the oxidative free radical cyclization reaction of unsaturated bicyclic endoperoxides is an interesting area. In the first part of the thesis, we reacted various 1,3-dicarbonyl compounds with cycloheptatriene in the presence of $Ce(NH_4)_2(NO_3)_6$ to obtain dihydrocyclohepta[*b*]furan derivatives. Then, the formed 1,3-cycloheptadiene unit of dihydrocyclohepta[*b*]furan derivatives was reacted with singlet oxygen to give the corresponding bicyclic endoperoxides. Bicyclic endoperoxides which include acetyl group were reacted with CoTPP, $AuCl_3$ and NEt_3. Dihydrocyclohepta[*b*]furan derivatives were oxidized with SeO_2 to tropone derivatives, biologically interesting molecule.

In the second part of the thesis, a new synthetic method for the synthesis of pyrrolo-pyrrolo-pyrazine derivatives was developed. Firstly, pyrrole was reacted with 2-pyrrolidinone to generate 2,2'-(1'-pyrrolinyl)pyrrole, which was reacted with propargyl bromide derivatives to afford propargylated compounds which were further derivatized via Sonogashira cross coupling reaction. Pd/C-supported cyclization reactionof propargylated compounds and their derivative with Pd/C, afforded pyrrolo-pyrrolo-pyrazine derivatives.

In the last part of the thesis, we examined the reaction of bicyclic endoperoxides with gold salt for the first time. Firstly, we synthesized bicyclic endoperoxide, 2,3-dioxabicyclo[2.2.2]oct-5-ene by the reaction of cyclohexa-1,3-diene with singlet

oxygen. Reaction of unsaturated bicyclic endoperoxide with alkynes in the presence of Au(L)/AgOTf resulted in the formation of α-alkylidine-γ-butyrolacton derivatives.

Keywords: dihydrocyclohepta[*b*]furans, bicyclic endoperoxides, tropone, pyrrolo-pyrrolo-pyrazines, α-alkylidine-γ-butyrolactons.

ÖZ

SİKLOHEPTADİENE KONDENZE DİHİDROFURAN TÜREVLERİNİN SENTEZİ VE PİROLO-PİROLO-PİRAZİNLERİN VE α-ALKİLİDİN-γ-BUTİROLAKTONLARIN ALKİN SİKLİZASYONU İLE TASARIMI

Aslanoğlu, Furgan
Doktora, Kimya Bölümü
Tez Yöneticisi: Prof. Dr. Metin Balcı
Mart 2018, 206 sayfa

Oksidatif radikal halkalaşma reaksiyonu ve doymamış bisiklik endoperoksitlerin etkileyici yerseçimli reaksiyonları ve tartışmalı mekanizmaları nedeniyle ilgi çekici bir alandır. Tezin birinci kısmında, 1,3-dikarbonil bileşiklerini sikloheptatrien ile $Ce(NH_4)_2(NO_3)_6$ varlığında reaksiyona sokarak dihydrocyclohepta[*b*]furan türevleri elde edildi. Sonrasında, oluşan 1,3-sikloheptadien birimini singlet oksijen ile reaksiyona sokup ilgili bisiklik endoperoksitler oluşturuldu. Asetil grubu içeren bisiklik endoperoksit CoTPP, $AuCl_3$ ve NEt_3 ile reaksiyona sokuldu. Dihydrocyclohepta[*b*]furan türevlerini SeO_2 ile biyolojik olarak ilginç moleküller olan troponlara yükseltgendi.

Tezin ikinci kısmında, pirol-pirol-pirazin türevlerinin sentezinde yeni bir sentetik metod geliştirdik. Başlangıçta, pirol ile 2-pirolidinon 2,2'-(1'-pirolinil) pirol bileşiğini olusturmak için reaksiyona sokuldu. Sonrasında, 2,2'-(1'-pirolinill) pirol ile bromo proponil bileşikleri propargilenmiş bileşikleri elde etmek için reaksiyona sokuldu. Propargillenmiş bileşik Sonogashira çapraz eşleşme reaksiyonu ile türevlendirildi. Propargilenmiş bileşikler ve bunların türevlerinin Pd/C ile reaksiyonu olan Pd/C destekli halkalaşma reaksiyonu ile pirol-pirol-pirazin türevlerini elde edildi.

Tezin son kısmında, bisiklik endoperoksitlerin altın tuzları ile reaksiyonlarını ilk olarak biz araştık. İlk olarak, bisiklik endoperoksit, 2,3-diokzabisiklo[2.2.2]okt-5-en bileşiğini siklohekza-1,3-dien singlet oksijen ile reaksiyona sokarak sentezledik.

Doymamış bisiklik endoperoksitlerin Au(L)/AgOTf varlığında alkinlerle reaksiyonu α-alkilidin-γ-buturolakton türevlerinin oluşumuna neden oldu.

Anahtar Kelimeler: dihidrosiklohepta[*b*]furan, bisiklik endoperoksid, tropon, pirol-pirol-pirazine, α-alkilidine-γ-butorolakton.

This work is dedicated to
My soul mate, lovely wife Zeynep,
My childiren Sena and Seza
And also to my parents
Veysel and Mukaddes

ANCNOWLEDGMENT

I would like to express my sincerest gratitude to Professor Metin Balci, for giving me this opportunity to join his research group, for his continuous guidance, patience and support. And also, I would thank to Dr. Balci for his understanding, kindness and sympathy with me in many of the hard times.

I am particularly grateful for working with SYNTHOR group, Arif Baran, Gani Koza, Raşit Çalışkan, Yasin Çetinkaya, Sinan Başçeken, Zeynep Ekmekçi, Nurettin Mengeş, Serdal Kaya, Selbi Keskin, Dilem Doğan, Kıvılcım Şendil, Tolga Yaman, Nalan Çokol, Özlem Sarı, Işıl Yenice, Sultan Aslan, Emrah Karahan, Emre Hoplamaz, Fatih Şeybek, Erol Can Vatansever, Merve Sinem Özer, Yasemin Dinçoflaz, Başak Öztürk, Selin Ceyhan, Dilgeş Baskın, Tolga Kaptı, Kübra Kılıç, Merve Ergun. Without their warm friendship, great support and assistance, this research process would have been difficult.

I would like to thank to NMR specialist Betül Eymür for the NMR experiments.

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).

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 lovely wife Zeynep and my parents Veysel, Mukaddes.

TABLE OF CONTENTS

LIST OF FIGURES

FIGURES

LIST OF ABBREVIATIONS

AIBN: Azobisisobutyronitrile

CAN: Cerrium Ammonium Nitrate

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

DIPA: Diisopropylamine

L: Chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I)

LDA: Lithium diisopropylamide

NBS: N-Bromosuccinimide

TBAF: Tetra-*n*-butylammonium fluoride

TBDMS: *tert*-Butyldimethylsilyl

THF: Tetrahydrofurane

THP: Tetrahydropyran

TPP: Tetraphenlyporphyne

***t*-Boc:** *tert*-Butyloxycarbonyl

PMB: p-methoxybenzyl

CHAPTER 1

SYNTHESIS OF CYCLOHEPTADIENE ANNELATED DIHYDROFURANE DERIVATIVES AND STUDIES OF SYNTHETIC POTENTIAL OF THE FORMED COMPOUNDS

1.1 INTRODUCTION

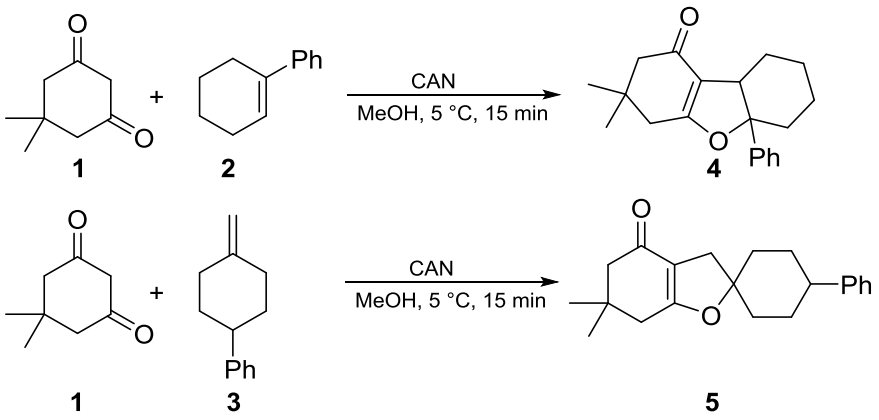
1.1.1. Oxidative Free Radical Cyclization

Free radical cyclization reaction has emerged as an important reaction for the construction of carbon-carbon and carbon-heteroatom bonds in recent years.[1] Especially, metal salts such as Mn(III), Ce(IV), V(V), Co(III), and Cu(II) have been used for radical cyclization reactions. In this group, $Mn(OAc)_3$ has been used most widely.[2] But, there are two limitation for $Mn(OAc)_3$; poor solubility in organic solvents and the formation of byproducts especially by intermolecular reactions. This limitation and the other reagents drawbacks show that Ce (IV) reagents are more proper as one-electron oxidant.

Cerrium ammonium nitrate (CAN) is an oxidant discovered by Smith group.[3] CAN exist in pure form and includes cerium atom in the center surrounded by six nitrate groups around. CAN is valuable chemical reactive because it has a low toxicity, ease of handling, experimental simplicity and solubility in a number organic solvent. Furthermore, CAN as an electron oxidant like $Mn(OAc)_3$ has a large electron potential (+1.61 V). CAN undergoes different oxidative transformation reactions.

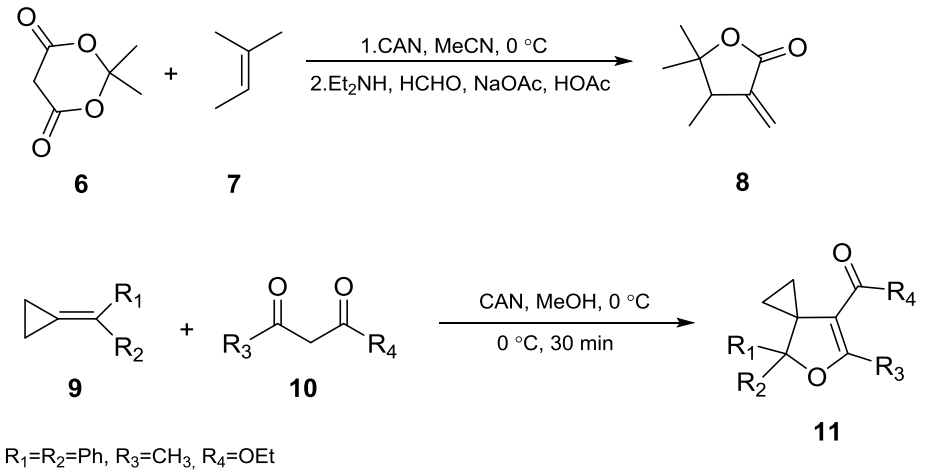
Carbon-carbon bond forming reaction in presence of CAN is an important reaction in organic chemistry and they are divided into two classes; intermolecular and intramolecular reactions. Intermolecular carbon-carbon forming reaction in the presence of CAN is widely used by researchers.

Intermolecular reactions of olefins **2** and **3** with dimedon (**1**) mediated by CAN mainly result in the formation of dihydrofuran and spirodihydrofuran derivatives **4** and **5** as shown in Scheme 1.[4]



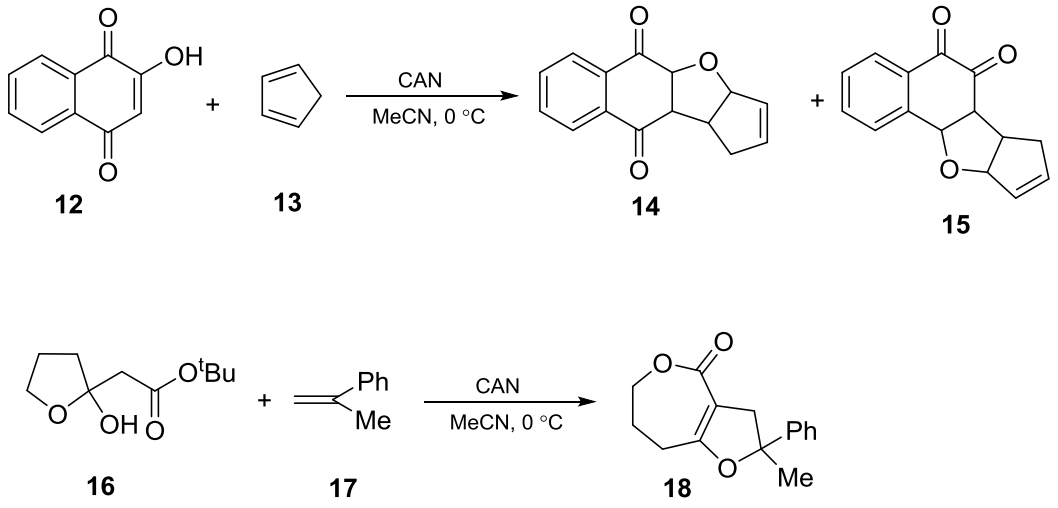
Scheme 1

Addition of acyclic alkene **7** to Meldrum's acid (**6**) mediated by CAN gave α-methylene lactone **8.**[5] Spirocyclopropyl dihydrofurane derivative **11** was synthesized via the similar procedure (Scheme 2).[6]



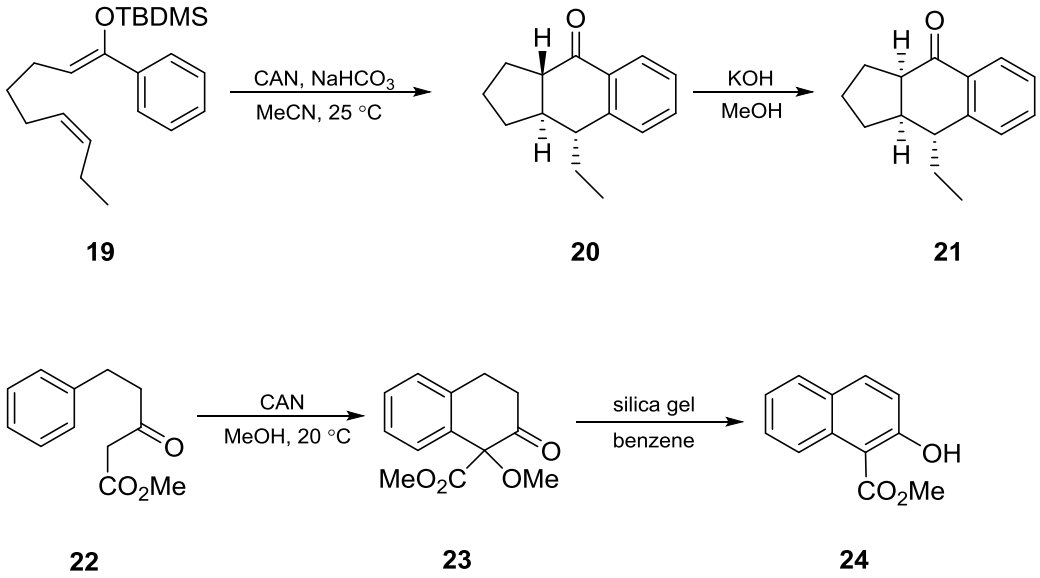
Scheme 2

A procedure for the synthesis of furo-*p*-quinones **14** as well as *o*-quinone **15** was developed by the reaction of 2-hydroxynaphthalene-1,4-dione (**12**) and with cyclopentadiene (**13**) in the presence of CAN.[7] Furthermore, CAN mediated reaction of *t*-butyl 2-(2-hydroxytetrahydrofuran-2-yl)acetate(**16**) with alkene **17** gave tetrahydrofuro[3,2,-*c*]oxepin-4(6*H*)-one (**18**) (Scheme 3).[8]



Scheme 3

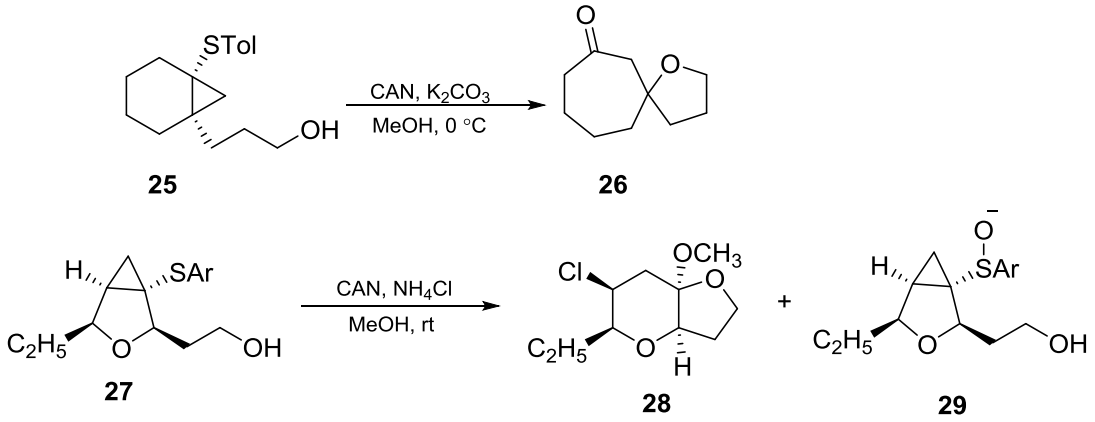
Ce(IV) mediated intramolecular carbon-carbon bond forming reaction was reported for the first time by Hansel *et al.*[9] According to the procedure described by Snider *et al.*[10] unsaturated silyl enolether **19** underwent oxidative cyclization reaction in the presence of CAN affording tricyclic ketone **21**. Citterio *et al.*[11] reported the oxidative cyclization of 5-aryl-3-oxo-pentanoic acid ester (**22**) by CAN leading to 2-hydroxy-1-naphthoic acid ester (**24**) (Scheme 4).



Scheme 4

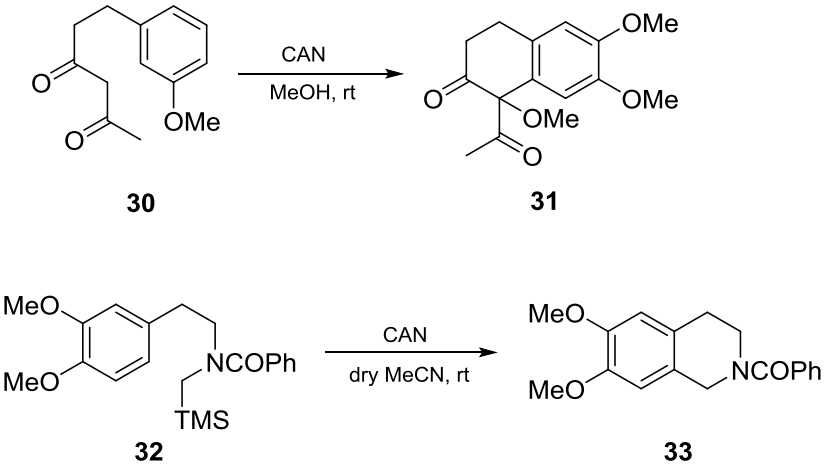
Takemoto *et al.*[12,13] presented that oxaspiro undeconone **26** and *cis*-fused chlorinated bicyclic ether **28** were obtained in good yields by the reaction of bicyclo[4.1.0]heptyl

sulfide having an hydroxyl group in the side chain **25** and cyclopropyl sulfides of the type **27** with CAN, respectively (Scheme 5).



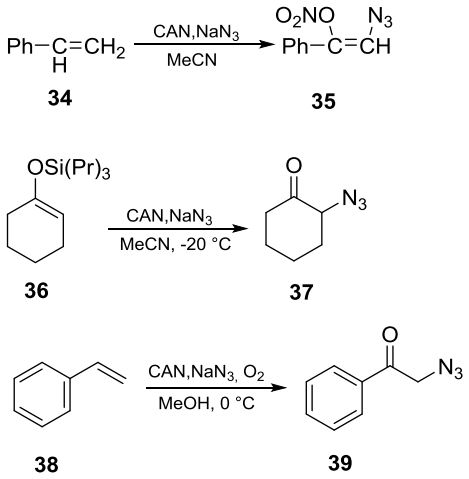
Scheme 5

Jamie *et al.*[14] reported CAN mediated intermolecular cyclization to benzene ring. δ-Aryl-β-dicarbonyl **30** can undergo 6-*endo* cyclization mediated by CAN affording β-tetralone **31**. Kim *et al.*[15] reported that 6-*endo* cyclization reaction of phenethylamide **32** provided dihyroisoquinoline **33** (Scheme 6).



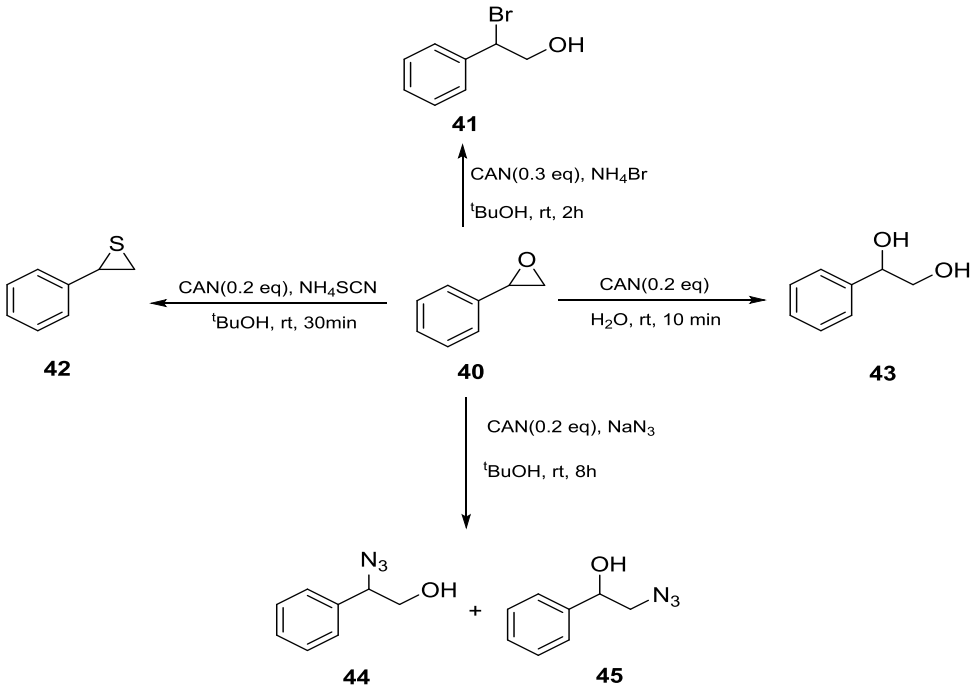
Scheme 6

In 1971, Trahanovsky *et al.*[16] discovered for the first time, azidonitration reaction in presence of CAN. According to this method, oxidation of olefin **34** in the presence of NaN_3 and CAN provided α-azido-β-nitro alkanes **35**. Magnus *et al.*[17] reported that the reaction of triisopropyl silyl enol ether **36** with CAN and sodium azide gave α-azido keton **37**. A procedure for the synthesis α-azido ketone **39** starting from styrene (**38**) and sodium azide was also developed in the presence of CAN (Scheme 7).[18]



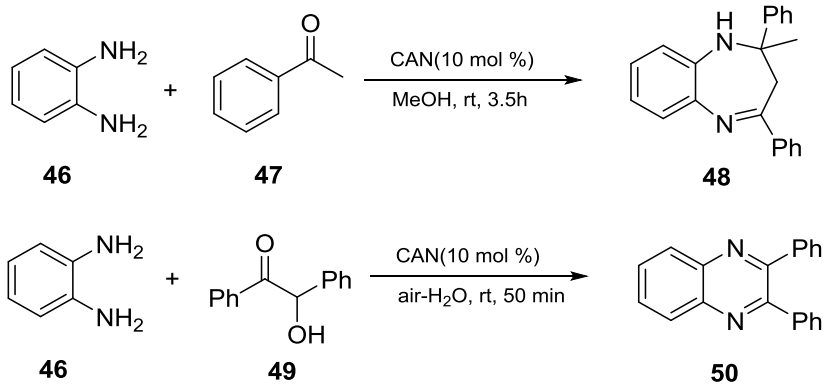
Scheme 7

CAN is also used as a catalytic oxidant in reactions such as regioselective ring opening and transformation of epoxides into dicarbonyl compounds.[19] Salehi *et al.*[20] reported the conversion of epoxides to the corresponding β-halohydrines **41** mediated by catalytic amount of CAN (Scheme 8). Iranpoor and coworkers synthesized 1,2-azidoalcohols **44** and **45** by the reaction of **40** with NaN_3 in presence of catalytic amount of CAN.[21] CAN and ammonium thiocyanate were used to convert epoxide **40** to thiiranes **42** (Scheme 8).[22]



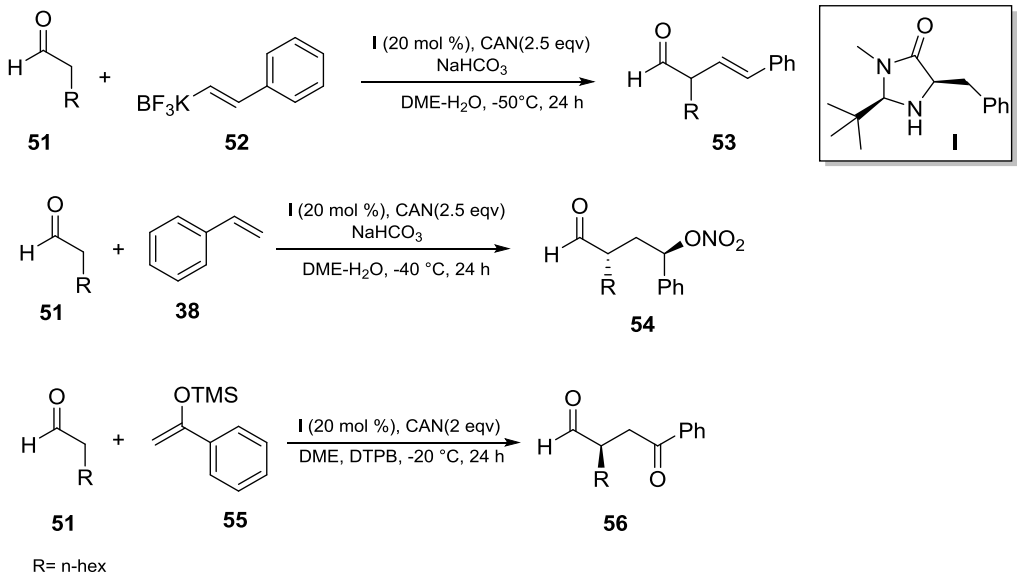
Scheme 8

CAN is an effective catalyst for using condensation reactions to synthesize diazepine and quinoaxiline derivatives. For example, o-phenyldiamine (**46**) was reacted with ketone **47** in presence of catalytic amount of CAN to give 1,5-benzodiazepine derivative **48**.[23] The reaction of α-hydroxyketone **49** and benzene-1,2-diamine**46** leading to the synthesis of quinoaxiline derivative **50** was also catalyzed by CAN (Scheme 9).[24]



Scheme 9

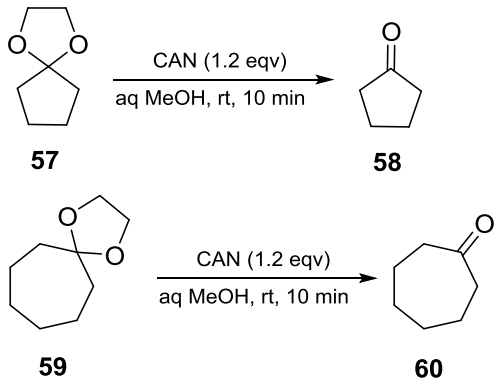
CAN was also used in organocatalyzed reactions as a single electron oxidant composing transient radical species from enamine. Vinylation of aldehyde,[25] carbo-oxidation of styrene[26] and enantioselective α-enolation[27] are example for this strategy. As a result of these reaction, compound **53**, **54** and **56** were obtained, respectively. These reactions are shownin (Scheme 10).



Scheme 10

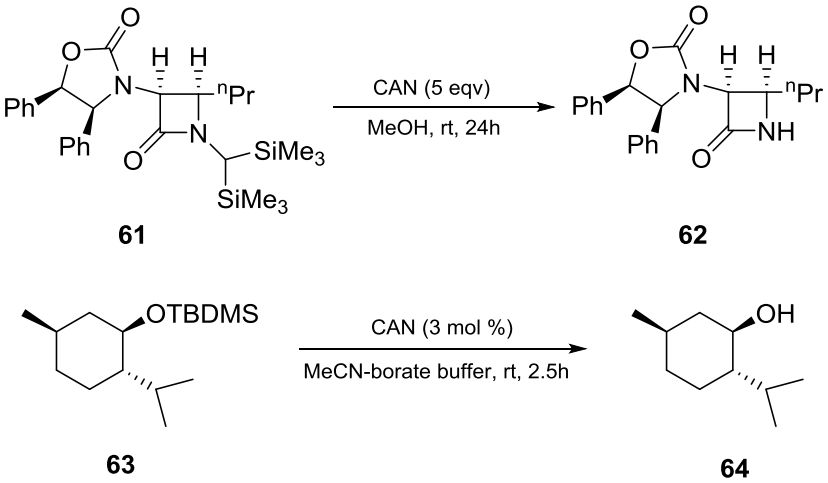
CAN has also been used by several protection and deprotection reactions such as deprotection of acetals, TBDMS, THP, *t*-Boc, Benzyl, PMB and PMPE groups and protection of benzyl and *t*-Boc group.

CAN plays an important role in deprotecting acetal groups. Nair *et al.*[28] reported that 1.2 eqiv. CAN removed acetal groups in **57** and **59** in aqueous methanol (Scheme 11).



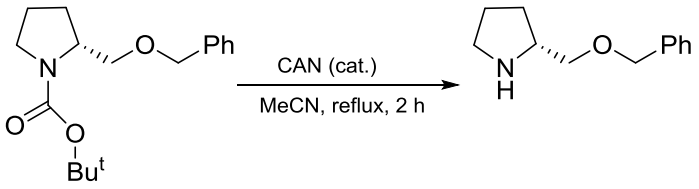
Scheme 11

Singh *et al.*[29] employed CAN in methanol for the deprotection of TBDMS ethers **61**. Otherwise, C-Si bond was broken with CAN in methanol to obtain β-lactam derivatives **62** (Scheme 12).[30]



Scheme 12

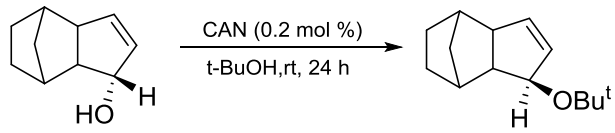
Hakemelahi *et al.*[31] reported an efficient procedure for removal of *t*-Boc-group using catalytic amount of CAN in acetonitrile (Scheme 13).



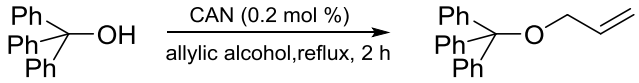
65 **66**

Scheme 13

Examples of protection method; allylic alcohol **67** and tertiary benzylic alcohol **69** were converted to the corresponding allyl ethers by using a catalytic amount of CAN (Scheme 14).[32]



67 **68**



69 **70**

Scheme 14

1.1.2 Photogenerated Singlet Oxygen

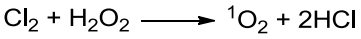
Photogenerated singlet oxygen ($^1O_2$) has been discussed in synthetic organic chemistry since 1924.[33] It is a very short lived species in a exited state, but it easily oxidizes carbon-oxygen and heteroatom-oxygen bonds. Bicyclic endoperoxides synthesized by cycloaddition of singlet oxygen to diene systems are important compounds for the chemical and biological transformations. Especially, biochemists and biologists pay particular attention to singlet oxygen because of biochemical role of the photogenarated singlet oxygen such as free radical aging mechanism, cancer inducing mechanism etc.[34, 35]

1.1.2.1 Generation of Singlet Oxygen

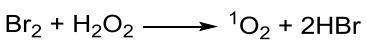
A. Chemical Methods

There are a plenty of laboratory methods to obtain singlet oxygen. These are;

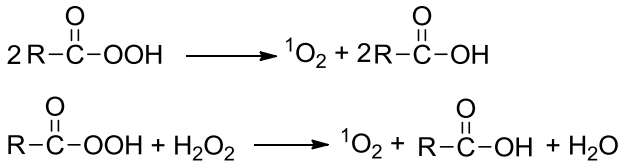
a. Reaction of chlorine with hydrogen peroxide to generate singlet oxygen[36, 37, 38]



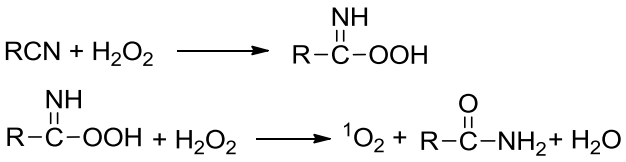
b. Reaction of bromine with hydrogen peroxide to generate singlet oxygen[36]



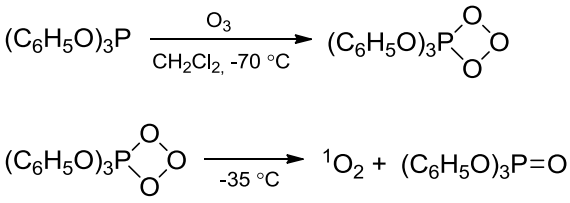
c. Reaction of peracids with hydrogen peroxide[36]



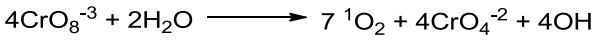
d. Reaction of nitriles with hydrogen peroxide to generate singlet oxygen[36]



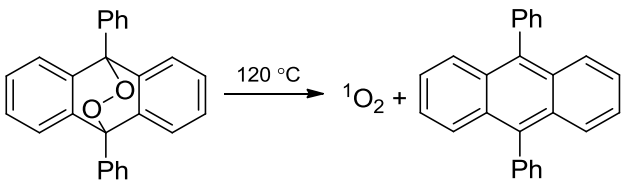
e. Decomposition of triphenyl phosphite ozonide at -35 °C to generate singlet oxygen[36]



f. Decomposition of potassium peroxychromate with water to generate singlet oxygen[36]

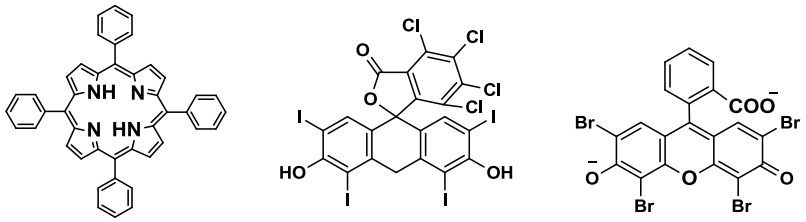


g. Decomposition of 9,10-diphenylantracene at high temperatures[36]



B. Photosensitizing Methods

Researchers used different photosensitizers to synthesize singlet oxygen on a laboratory scale.[36] Popular photosensitizers are dyes such as; *meso-tetraphenylporphin, rose bengal, eosin Y, methylene blue, toluidine blue* etc.



TPP: *meso*-tetraphenylporphyrin Rose Bengal Erosin Y

Firstly, singlet oxygen mechanism was examined by Kautsky. This mechanism includes the excitation of a sensitizer with visible light to form corresponding excited single state. After intersystem crossing, the excited triplet state of the sensitizer undergoes an energy transfer with triplet oxygen to generate singlet oxygen and the ground state sensitizer.[36]

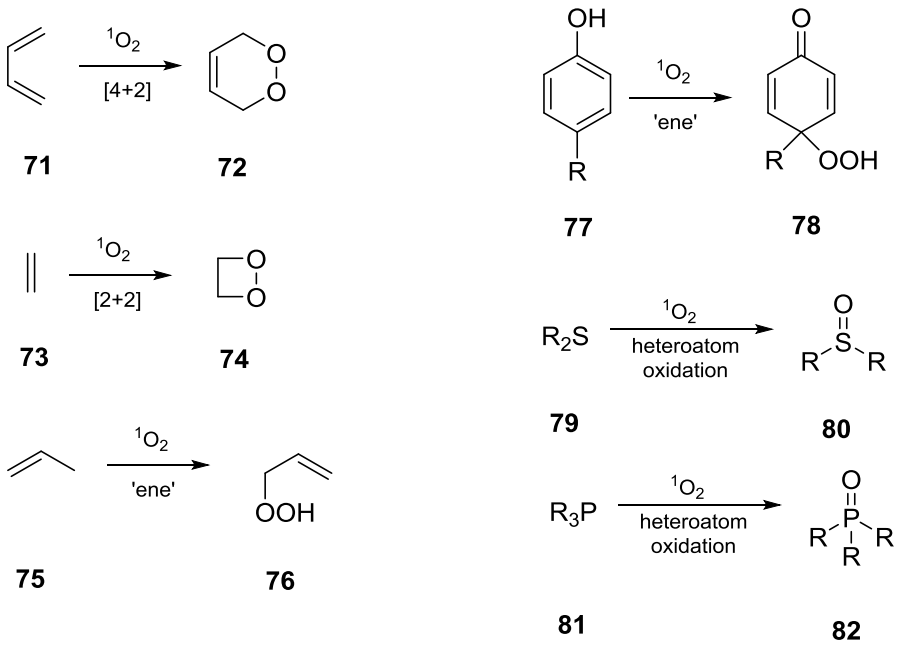
$$^1\text{Sensitizer} \xrightarrow{h\nu} {}^1\text{Sensitizer}^*$$

$$^1\text{Sensitizer}^* \xrightarrow{\text{ISC}} {}^3\text{Sensitizer}^*$$

$$^3\text{Sensitizer}^* \xrightarrow{^3O_2} {}^1\text{Sensitizer} + {}^1O_2$$

1.1.2.2 Reactions of Singlet Oxygen

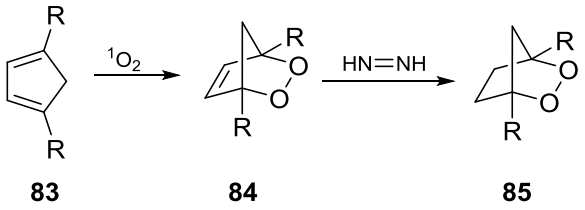
There are three types of singlet oxygen reactions which are cycloadditon reaction, ene reaction and heteroatom oxidation reaction. Cycloaddition of singlet oxygen is divided into two classes; 1,3 dien compounds **71** undergo[4+2] cycloaddition reaction to form cyclic peroxides called as endoperoxides such as **72** and ethylene compounds **73** undergo [2+2] cycloaddition reaction to form dioxetan **74**.[39] Alkenes **75** and phenols **77**, including allylic hydrogen are reacted with singlet oxygen (called ene reaction) to form hydroperoxides **76** and **78**.[40] Singlet oxygen oxidizes sulfides **79** and phosphines **81** to generate sulfoxides **80** and phosphine oxides **82,** respectively. These reactions are called heteroatom oxidation reaction (Scheme 15).[41]



Scheme 15

1.1.2.3 Chemical Transformation of Bicyclic Endoperoxides

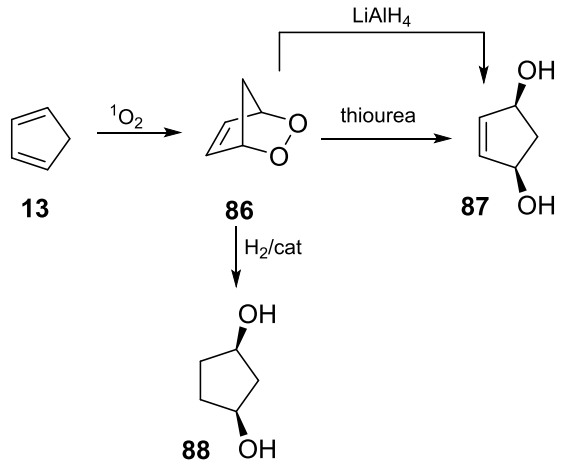
Diimide reduction is an important reaction for a bicyclic endoperoxide because diimide reduces only the C=C double bond not the peroxide linkage. When catalytic hydrogen is used instead of diimide, double bonds as well as peroxide bond are reduced. Diimide is generated by the reaction of potassium azodicarboxylate and acetic acid. Solomon *et al*. used diimide reduction to synthesize prostaglandin substructure **85** (Scheme 16).[42]



Scheme 16

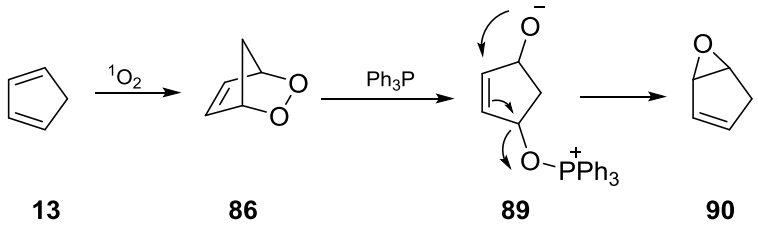
There are three types of reduction reactions of bicyclic endoperoxides. These are $LiAlH_4$, thiourea and catalytic reduction reactions. $LiAlH_4$ and thiourea are used to generate 2-ene-1,4-diols **87**. One the other hand, catalytic reduction is applied to obtain 1,4-diols **88**. Thiourea reduction has some advantages compared to catalytic reduction and lithium aluminum hydride reduction. This advantage is that thiourea

reduces only oxygen-oxygen bond and thus preserves other functional groups. For example, reaction of endoperoxide **86** synhesized by addition of singlet oxygen to cyclopentadiene, was reduced by thiourea, to 2-ene-1,4-diols **87**.[43] On the other hand, catalytic hydrogenation reaction of endoperoxide **86** generates, 1,4-diols **88** (Scheme 17).



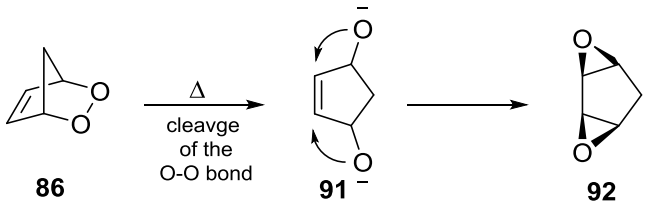
Scheme 17

Endoperoxide **86** was reacted with triphenylphosphine to give unsaturated epoxide **90**. Mechanism of triphenylphosphine deoxygenation; trivalent phosphorus atom provides the reductive extrusion of one oxygen atom then ensure the unsaturated epoxide **90** (Scheme 18).[39]



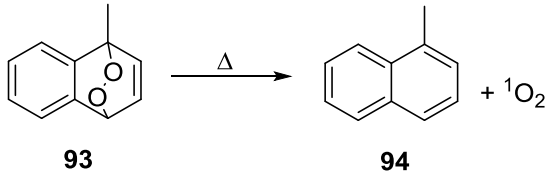
Scheme 18

There are two types of decomposition reactions in the thermochemical reaction of endoperoxide **86**; loss of molecular oxygen or cleavage of the O-O bond (Scheme 19). [44, 45]



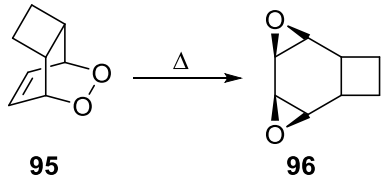
Scheme 19

Example for loss of molecular oxygen; Wasserman and Larsen studied decompositon of alkyl-substituted naphthalene 1,4-endoperoxides **94** to obtain the starting material and singlet oxygen (Scheme 20).[46] Thermal fragmentation of bicyclic endoperoxides is an important reaction for singlet oxygen generation.



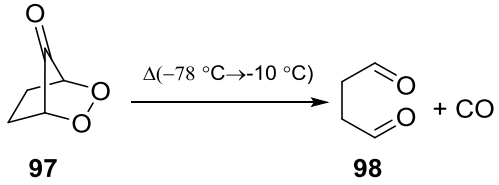
Scheme 20

Example for cleavage of the O-O bond; thermal isomerization of bicyclo[4.2.0]octa-2,4-diene endoperoxide **95** in CCl_4 at 110 °C provides bicyclo[4.2.0]octa-2,4-diene diepoxide (**96**) (Scheme 21).[47]



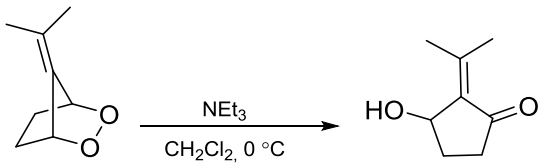
Scheme 21

Adam and Erden reported that warming of (1*R*,4*S*)-2,3-dioxabicyclo[2.2.1]heptan-7-one (**97)** up to -10 °C gave succinaldehyde (**98**) and carbonmonoxide (Scheme 22).[48]



Scheme 22

Base catalyzed decomposition of bicyclic endoperoxides is a rearrangement reaction and used to obtain cyclic hydroxy ketones. First base abstracts a hydrogen atom from the bridgehead carbon atom then the rearrangement occurs. For example, 2,3-dioxabicyclo[2.2.1]heptane derivative (**99**) was reacted with NEt_3 and it was converted to cyclic hydroxy ketone **100** (Scheme 23).[48]

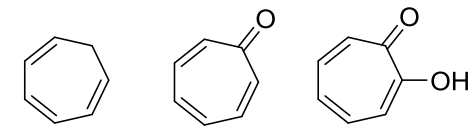


99 **100**

Scheme 23

1.1.3 Troponoids

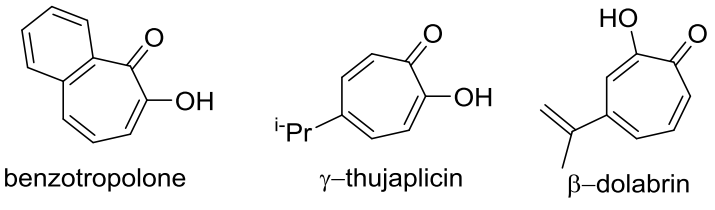
Troponoids are natural compounds having seven membered aromatic rings, tropone and tropolone. Tropone is not present in the nature, but many natural compounds have tropone in their structures. Troponoids having these skeleton have a wide range of pharmacological activities. Trust *et al.*[49] studied that tropolidine and tropone posses bactericidal and bacteriostatic activities, but don't have sporicidal activity against gram positive and gram negative species (Scheme 24).



tropilidine tropone tropolone

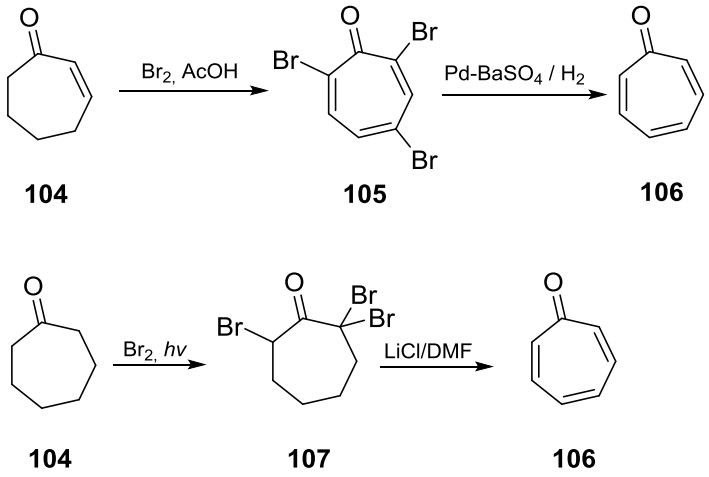
Scheme 24

Further studies showed that tropolone for instance benzotropolone and thujaplicins exhibit strong antimicrobial and antifungal activity.[50] According to Inamori groups, tropolones such as β-dolabrin, γ-thuiaplicin showed strong antimicrobial activity (Scheme 25).[51]



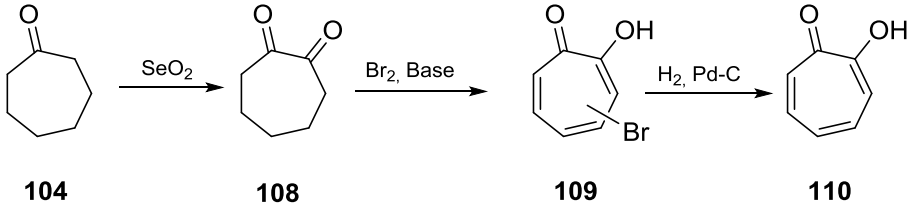
Scheme 25

To synthesize tropone (**106**), firstly cycloheptanone (**104**) was reacted with bromine under acidic condition to give **105**, then the adduct was reduced with catalytic hydrogen to give **106**.[52] According to the Collington's method, α-position of cycloheptanone (**104**) was firstly brominated with bromine. Then the product **107** was reacted with lithium chloride to obtain tropone (**106**) (Scheme 26).[53]



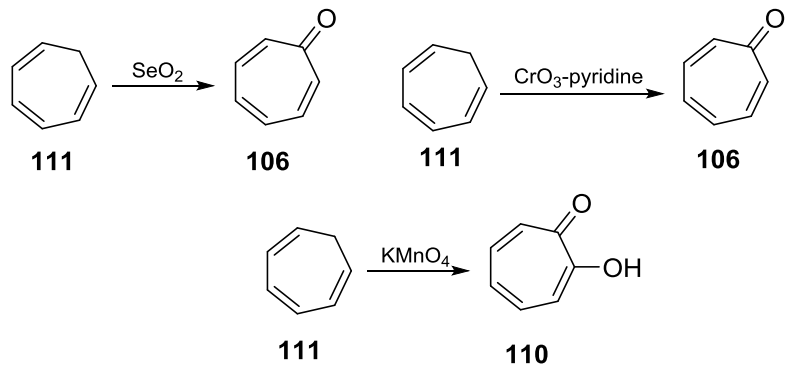
Scheme 26

For a general synthesis for tropolone (**110**), cycloheptanone (**104**) was first oxidixed with SeO_2 to α-diketone **108**. Bromination of **108** followed by debromination and catalytic reduction resulted in the formation of tropolone (**110**) (Scheme 27).[54,55]



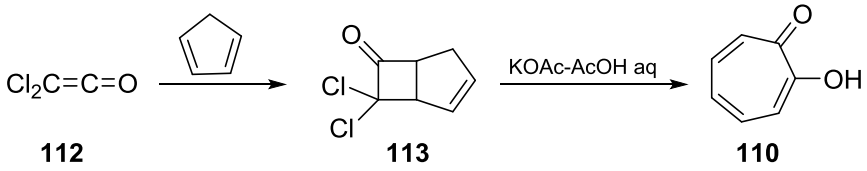
Scheme 27

Oxidation reaction is used to synthesize tropone (**106**) and tropolone (**110**) most widely. Nozoe[56] and Radlick[57] oxidized cycloheptatriene (**111**) to tropone (**106**) with SeO_2 or CrO_3 in pyridine. On the other hand, for the synthesis of tropolone (**110**) Doering *et. al.*[58] used $KMnO_4$ as oxidation reagent (Scheme 28).



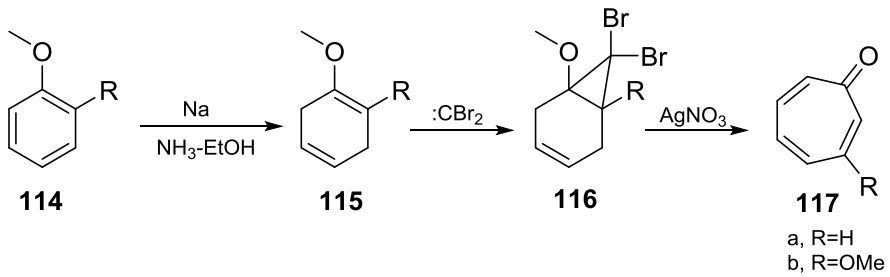
Scheme 28

Cycloaddition reaction is also a method to synthesize tropone or tropolones. Stevens *et. al.*[59] reported that cycloaddition of dichloroketene (**112**) to cyclopentadiene afforded cyclobutanone derivative **113**. Then the adduct **113** underwent a ring enlargement reaction to form tropolone (**110**) (Scheme 29).



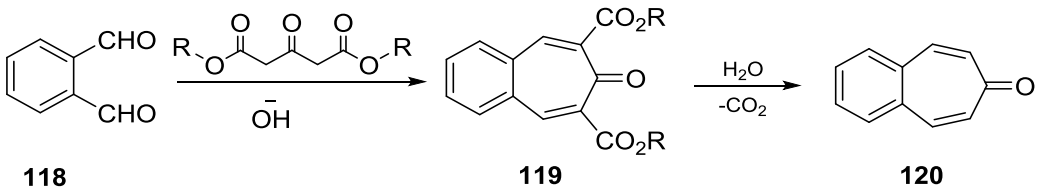
Scheme 29

Birch, *et al.*[60] reduced anisole derivatives **114** to 1-methoxycyclohexa-1,4-diene **115** by the Birch reduction. Addition of dibromocarbene to 1,4-dienes **115** followed by the reaction with aqueous $AgNO_3$ afforded corresponding tropone derivatives **117** (Scheme 30).



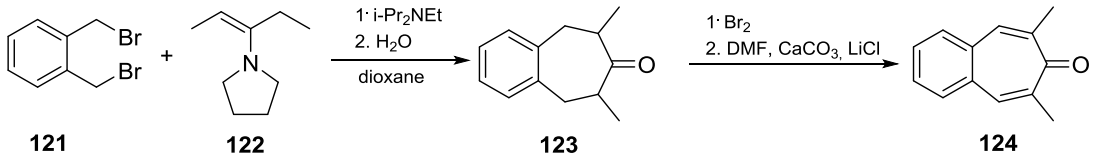
Scheme 30

Weitz, *et al.*[61] synthesized benzotropone **120** by a condensation reaction. According to this synthetic pathway, firstly, commercially available phthalaldehyde (**118**) was reacted with 1,3-acetonedicarboxylates. Condensation product **119** was hydrolyzed to afford benzotropone **120** (Scheme 31).



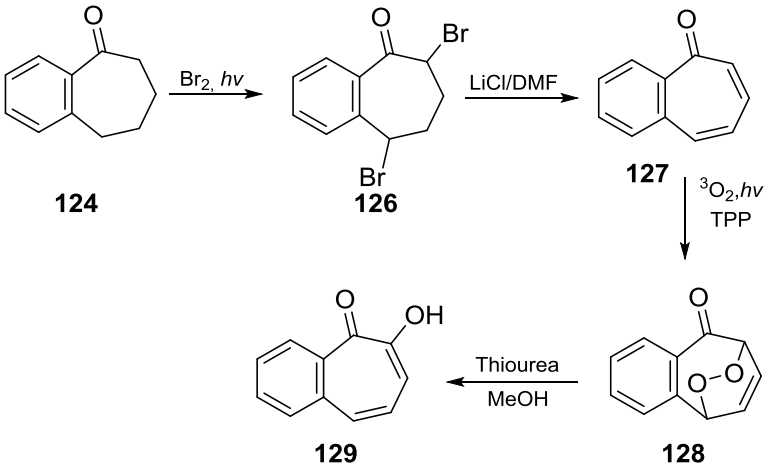
Scheme 31

An alternate pathway to synthesize benzotropone **124** was the reaction of α,α'-dibromo-o-xylene (**121**) with 1-[(1*Z*)-1-ethylprop-1-enyl]pyrrolidine (**122**) to afford desired compound **123**. Bromination of **123** followed by dehydrobromination gave benzotropone derivative **124** (Scheme 32).[62]



Scheme 32

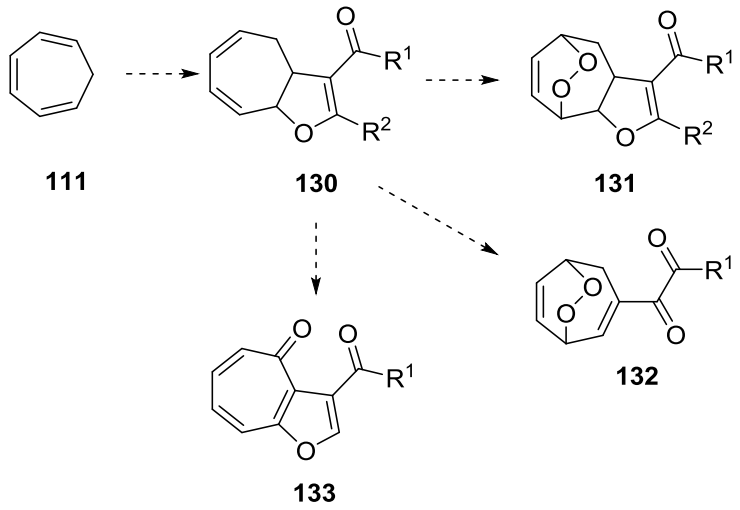
Balci *et al.*[63] synthesized benzotropolone (**129**) using an unusual endoperoxide rearrangement. Firstly, benzotropone (**127**) was synthesized by the Collington's method. Then, benzotropone (**127**) was reacted with singlet oxygen to form benzotropone endoperoxide **128**. Thiourea reduction of **134** followed by water elimination gave benzotropolone (**129**) (Scheme 33).



Scheme 33

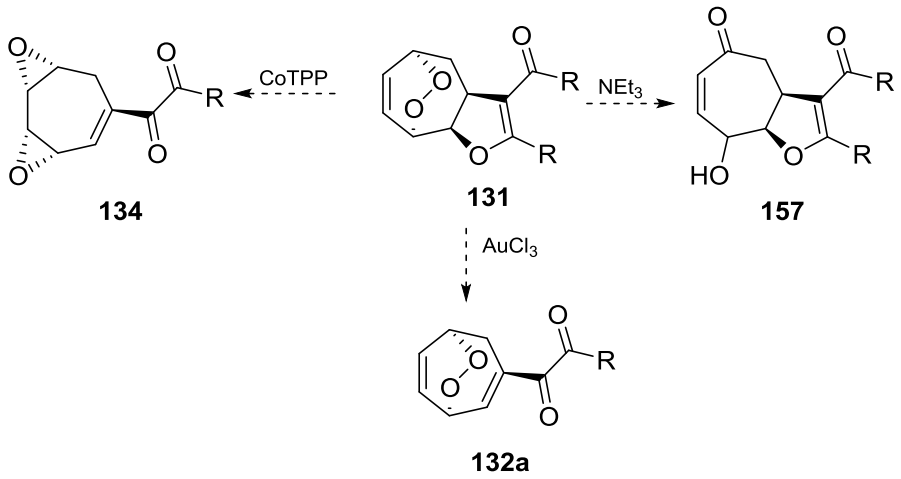
1.1.4 Aim of the Study

The aim of this part was the synthesis of cycloheptadiene-fused dihydrofurane derivatives and searching further reactions of dihyrofuranes **130**. We were interested in the construction of these type of skeletons due to their important mechanistic properties and as well as pharmacological properties. In this project, cycloheptatriene (**111**) will be reacted with 1,3-dicarbonyl compounds in the presence of cerium ammonium nitrate to generate dihydrofurane-fused cycloheptadiene **130**. The diene system in **130** will be submitted to photoxygenation reaction to obtain endoperoxides **131** and **132**. Furthermore, compound **130** will be converted to furan-fused tropone derivatives **133** (Scheme 34).



Scheme 34

In addition, we are also interested in the transformation reactions of endoperoxide **131**. Firstly, we will examine reaction of endoperoxide **131** with CoTPP to form **134**. After that, gold-catalyzed oxidative ring-opening reaction of endoperoxide **131** will be studied to generate **132a**. The reaction of endoperoxide **131** with triethyl amine is also planned to form **157**

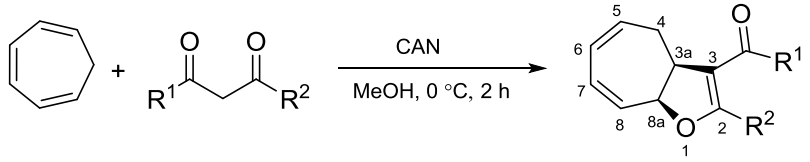


Scheme 35

1.2 RESULTS AND DISCUSSION

1.2.1 Synthesis of Dihydrocyclohepta[*b*]furan (130)

Commercially available cycloheptatriene (**111**) was treated with 1,3-diketones **137** in the presence of CAN to obtain dihydrocyclohepta[*b*]furan derivatives 1**30**. The reaction proceded cleanly, no side products were formed during this addition reaction (Scheme 36).



111 **137 a-d** **130 a-d**

a: R^1= CH_3, R^2= CH_3
b: R^1=OCH_3, R^2=CH_3
c: R^1= OC_2H_5, R^2=CH_3
d: R^1= OCH_3, R^2= $CH_2(CO)OCH_3$

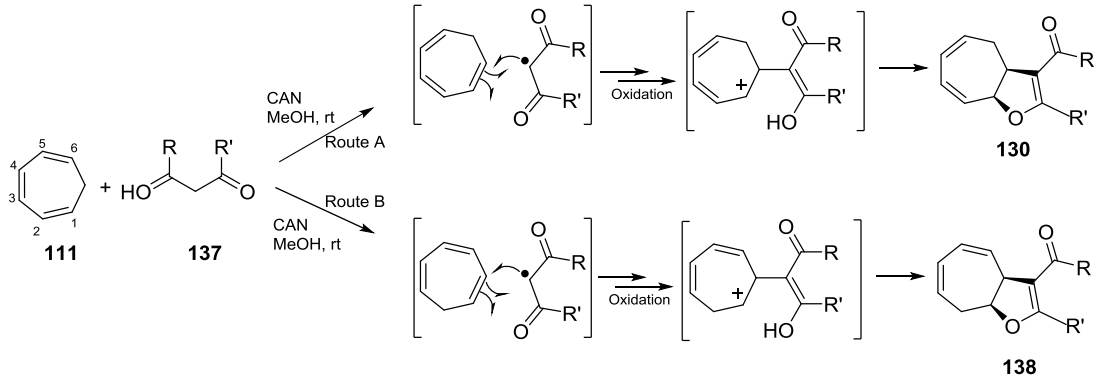
a: 95%
b: 86%
c: 74%
d: 68%

Scheme 36

The characterization of compound **130a** was performed by using ^{1}H and ^{13}C NMR spectra (Fig 3 and Fig 4 - p. 109-110). In the ^{1}H NMR spectrum of compound **130a**, the methine proton H-8a resonates as a broad doublet at 5.01 ppm with a coupling costant of J = 8.7 Hz. The value of of coupling costant is in agreement with the *cis*-configuration of the annulated five-membered ring. Furthermore, this peak is a characteristic peak for this kind of compounds. Inspection of the Dreiding models shows that the dihedral angle between the protons H-8 and H-8a is approximately 80-90°. Due to the lack of a coupling between those protons, the doublet splitting arises from the coupling with the neighboring proton H-3a. Olefinic protons for these compounds resonate between 6.21-5.97 ppm. The other methine proton H-3a resonates as a broad triplet at 3.27 ppm due to the coupling with the proton H-8a and one of the methylene protons H-4. The fact that this proton couples only with one of the methylene protons H-4 can be ascribed to the dihedral angels formed between the relevant protons. The other signals in the ^{1}H NMR spectrum are in agreement with the proposed structure.

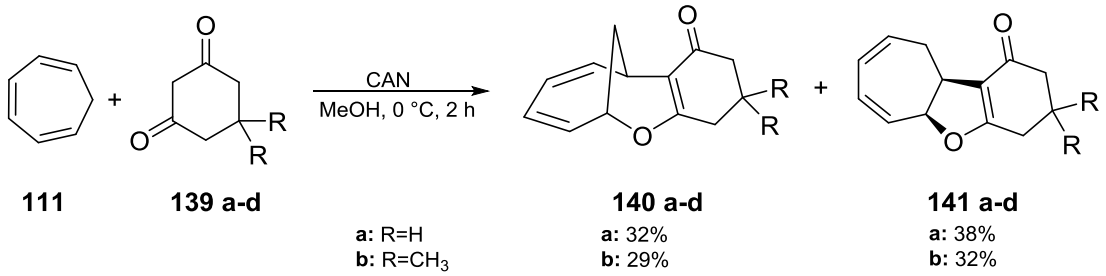
The signal at 193.6 ppm in the ^{13}C NMR spectrum of **130a** belongs to the carbonyl carbon. The olefinic carbon resonances appear at 167.1, 134.6, 129.8, 127.2, 126.9, and 118.2 ppm. There are five aliphatic carbons and they resonate at 84.6, 51.8, 30.0, 29.1 and 15.3 ppm. The NMR spectra of the other derivatives **130b-d** were also in agreement with the proposed structures (p. 109-116).

The addition of dicarbonyl compounds is a regiospecific reaction. The radical generated from dicarbonyl compounds **137** can attack two different double bonds (C1-C2 or C3-C4) in cycloheptatriene. The final structure of the compounds **130** shows that the radical exclusively attacks the terminal double bond (C1-C2) in cycloheptatriene. Even in this case there are two different routes for the attacks so that two different products can be formed. The dicarbonyl radical can attack the carbon atom C-1 as well as C-2. In the case of Route A (Scheme 35) the generated carbocation formed after oxidation will be in conjugation with the diene system and will be stabilized. However, in the case of an attach on C-2 carbon atom, the formed carbocation cannot be stabilized. Therefore, the route A will be preferred. Careful examination of the reaction products did not reveal the formation of any trace of compound having the structure **138** (Scheme 37).



Scheme 37

In the light of this result, we decided to react cycloheptatriene with 3-cyclohexanedione (**139a**) and dimedone (**139b**), with more enolizable characters than acetyl acetone and derivatives to check the generality of this reaction (Scheme 38).



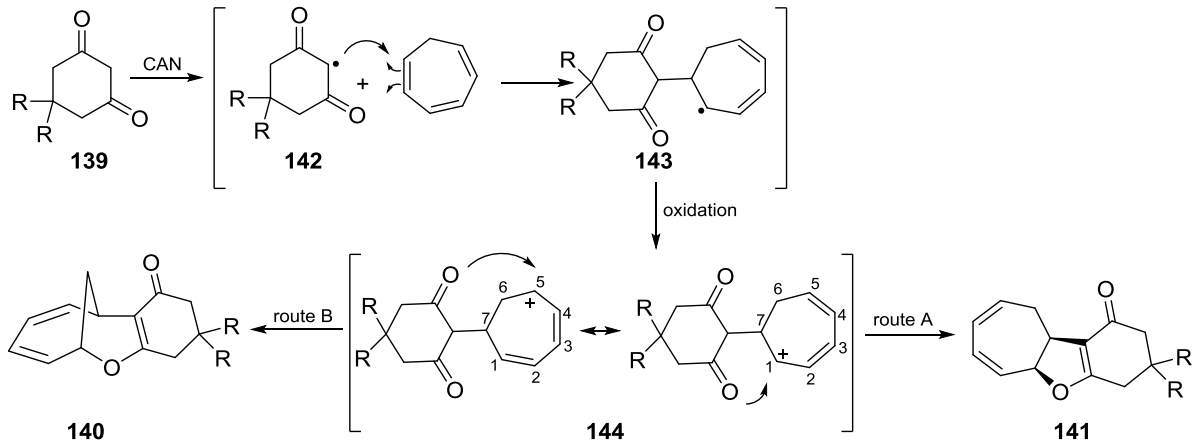
Scheme 38

The ^{1}H NMR spectrum (Fig 19 - p. 118) of **140a** exhibits four olefinic proton signals in the range of 6.5 to 5.6 ppm. The observed coupling constants between the olefinic protons are in the usual range. Additionally, alkoxy methine proton resonates as doublet of doublets of triplets at the 4.90 ppm due to double bond in the α-position and the oxygen atom. Other methine proton for compound **140a** resonates as a broad triplet at 3.39 ppm with a coupling constant of J = 6.3 Hz. The other signals of ^{1}H NMR spectrum were coherent with the proposed structure.

For the compound **140a**, in the ^{13}C NMR spectrum (Fig 20 - p. 118) there are three characteristic groups which are carbonyl group resonating at 197.5 ppm, tertiary carbon atoms appearing at 169.9 and 114.5 ppm and olefinic carbon resonances at 139.1, 129.6, 128.8 and 123.2 ppm. The remaining carbon resonances appear in the aliphatic area at 72.4, 36.7, 28.4, 28.3, 27.4, 20.6 ppm.

The NMR spectra of compounds **141a** and **141b** looked similar to the NMR spectrum of compounds **130 a-d**.

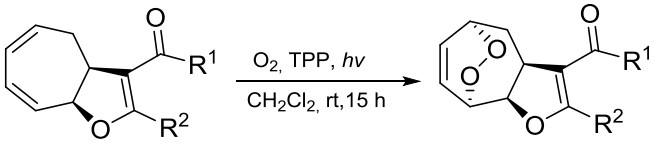
We propose the following mechanism for the formation of these products. CAN firstly abstract acidic proton in a cyclo-1,3-carbonyl compound **139** to form carboxyl methyl radical **142** which adds to double bond of cycloheptatriene (**111**) to afford new radical **143** on the cycloheptariene. Oxidation of **143** by CAN results in the formation of **144** that can undergo two different ring closure reaction to form **140** and **141**(Scheme 39).



Scheme 39

1.2.2 Photooxygenation of the Dihydrocyclohepta[*b*] (130)

Tetraphenylporphyrin sensitized photooxgenation of dihydrocyclohepta[*b*]furan derivatives **130 a-d** in methylene chloride at room temperature for 15 h produced endoperoxides **131 a-d** which are stable at room temperature for many days (Scheme 40).



130 a-c **a:** R^1= CH_3, R^2=CH_3
b: R^1=OCH_3, R^2= CH_3
c: R^1=OC_2H_5, R^2= CH_3
d: R^1= OCH_3, R^2= $CH_2(CO)OCH_3$

131 a-c **a:** 79% **b:** 76% **c:** 69% **d:** 66%

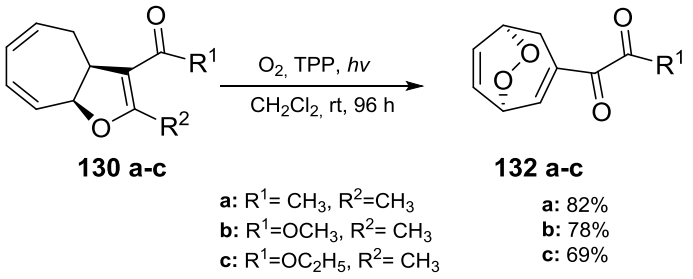
Scheme 40

Comparison of the NMR spectra of the products **131a** with those of the starting material shows that one double bond is missing and two new bridgehead protons are formed instead. In the ^{1}H NMR spectrum (Fig 35 - p. 126) of **131a** olefinic protons resonate as an AB-system. A-part of this systems appears at 6.57 ppm as doublet of doublets (J = 9.10 and 7.1 Hz) whereas the B-part resonate at 6.47 ppm as doublet of doublets (J = 9.10 and 6.8 Hz). Bridgehead protons of **131a** resonate at 5.11 and 4.64 ppm. The other signals of ^{1}H NMR spectrum were in agreement with the proposed structure.

In the ^{13}C NMR spectrum (Fig 36 - p. 126), the carbonyl carbon resonates at 192.6 ppm. Olefinic carbons appear at 168.4, 134.1, 124.3, 118.8 ppm. The other carbon

signals were coherent with the structure. The NMR spectra of the other derivatives were also in agreement with the proposed structures.

When, dihydrocyclohepta[*b*]furan derivatives **130** were submitted to the photooxygenation reaction under the same reaction conditions; in methylene chloride at room temperature. However the reaction time was increased up to 96 h to give endoperoxide **132** (Scheme 41).

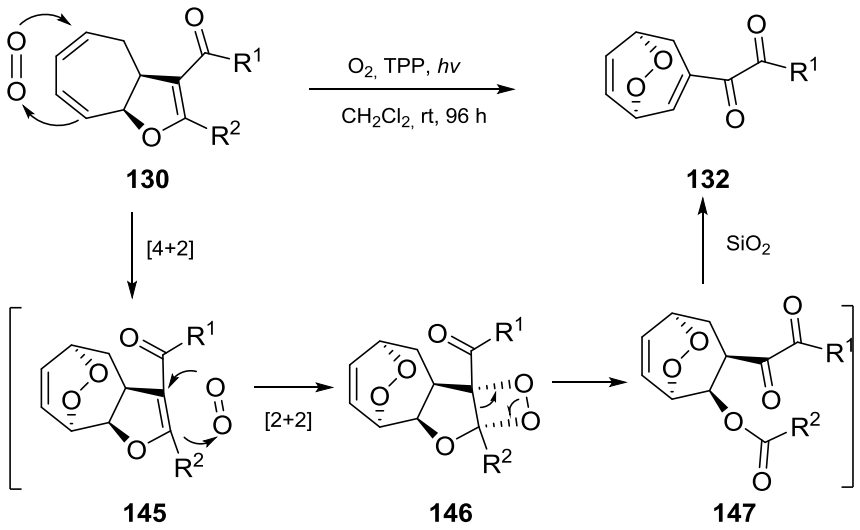


Scheme 41

Endoperoxide **132a** was characterized on the basis of the ^{1}H and ^{13}C NMR spectra, which were in agreement with the proposed structure. There are three olefinic protons in ^{1}H NMR spectrum (Fig 51 - p. 134) of **132a**. Neighbouring olefinic protons resonate as an AB system. The A-part resonates at 6.73 as broad doublet of triplets (J = 8.0 and 0.9 Hz). The B-part appears at 6.51 as doublet of triplets (J = 8.7 and 1.0 Hz). The other olefinic proton resonates at 7.32 as doublet of triplets (J = 6.8 and 1.7 Hz). Methylenic protons of **132a** also resonate as an AB system. A-part resonates at 3.13 ppm as doublet of doublets of triplets with coupling constants of J = 19.4, 4.5 and 2.0 Hz and B-part resonates at 2.70 ppm as doublet of triplets with coupling constant J= 19.4 and 1.3 Hz. Bridgehead protons resonate as multiplet at 5.02-4.94 ppm.

The ^{13}C NMR spectrum (Fig 52 - p. 134) of **132a** shows ten different signals. The resonance signals at 200.1 and 193.3 ppm belong to two carbonyl groups. Four of the resonances appear in the range of sp^2 hybridized carbon atoms, at 146.5, 136.6, 131.8 and 128.5 ppm. Bridgehead carbons signal appear at 75.0 and 72.3 ppm. Aliphatic carbons resonate at 33.2 and 26.6 ppm. The NMR spectra of the other derivatives were also in agreement with the proposed structures.

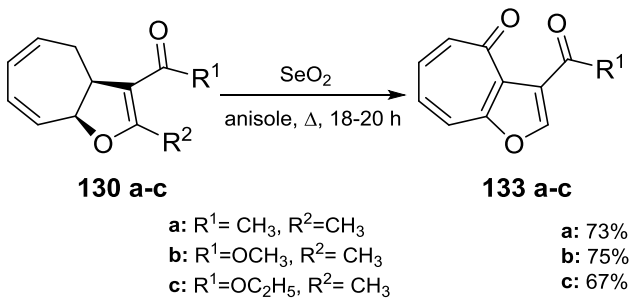
For this reaction, we proposed the following reaction mechanism. Singlet oxygen first undergoes a [4+2] cycloaddition reaction with the diene unit of cycloheptadiene. We assume, that singlet oxygen undergoes a [2+2] cycloaddition reaction with the double bond present in the five-membered ring during the increased reaction time to form a dioxetane **146**. Thermal decomposition of dioxetane unit in **146** gives ester intermediate **147** which undergoes an elimination reaction upon treatment with silica gel to form the final produt **132**. (Scheme 42).



Scheme 42

1.2.3 SeO_2 Oxidation Reaction for Dihydrocyclohepta[*b*]furans (133)

Because of the biological importance of tropones and structural suitability of synthesized compounds, we decided to synthesize tropone derivatives. Dihydro cyclohepta[*b*]furan derivatives **130** were submitted to oxidation reaction with SeO_2. This method includes forceful reaction conditions such as high temperatures. Reaction of **130** with SeO_2 in anisole at 154 °C for 18-20 h provided the corresponding tropone derivatives **133** in acceptable yields (Scheme 43).



Scheme 43

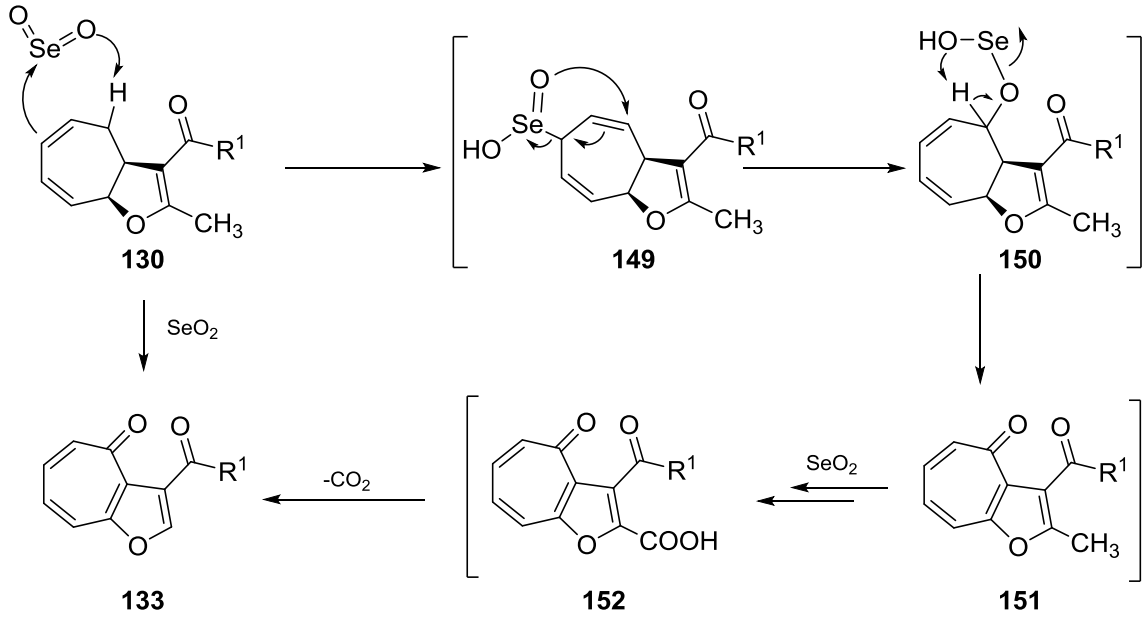
Comparison of the ^{1}H NMR spectra (Fig 55 - p. 136) of **130a** with those of (Fig 62 - p. 139) **133a** clearly shows that the resonances of methylene, methine protons in seven-membered ring and the methyl protons attached to the double bond are disappeared. Appearing of olefinic proton resonances in the ^{1}H NMR spectrum of **133a**, clearly indicates the formation of tropone unit. One of the five olefinic protons resonates at 9.14 ppm as doublet with a coupling constant of J = 11.2 Hz. The proton resonance at 7.64 ppm appears as doublet of doublets (J = 11.2 and 8.9 Hz). The double bond proton in the five-membered ring resonates as singlet at 7.52 ppm. The other protons appear at 7.54-7.49 ppm as multiplet and 7.36 ppm as doublet of doublets of doublets (J = 11.5, 8.5 and 4.0 Hz). Methyl proton resonance appears at 2.58 ppm as singlet.

In the ^{13}C NMR spectrum (Fig 56 - p. 136), carbonyl carbons resonate at 195.1 and 167.6. The signal of eight olefinic carbons appear in a range of 159.2 to 103.6. Methyl protons group resonate at 30.1 ppm. The NMR spectra of the other derivatives were also in agreement with the proposed structures.

For the formation of this interesting product **133**, we propose the following reaction mechanism. In the first step SeO_2 undergoes an ene reaction. The allylic seleninic acid **149** formed as an intermediate undergoes a [2,3]-sigmatropic rearrangement to form **150** that may decompose to an allylic alcohol or an allylic carbonyl compounds as shown below. In the case of formation of an allylic alcohol, oxidation may continue to give an α,β-unsaturated carbonyl product.

The methyl group attached to the double bond may also be oxidized to the corresponding carboxylic acid. The decarboxylation at high temperature results in

removal of the methyl group. These two oxidation reactions can take place one after one or at the same time (Scheme 44).

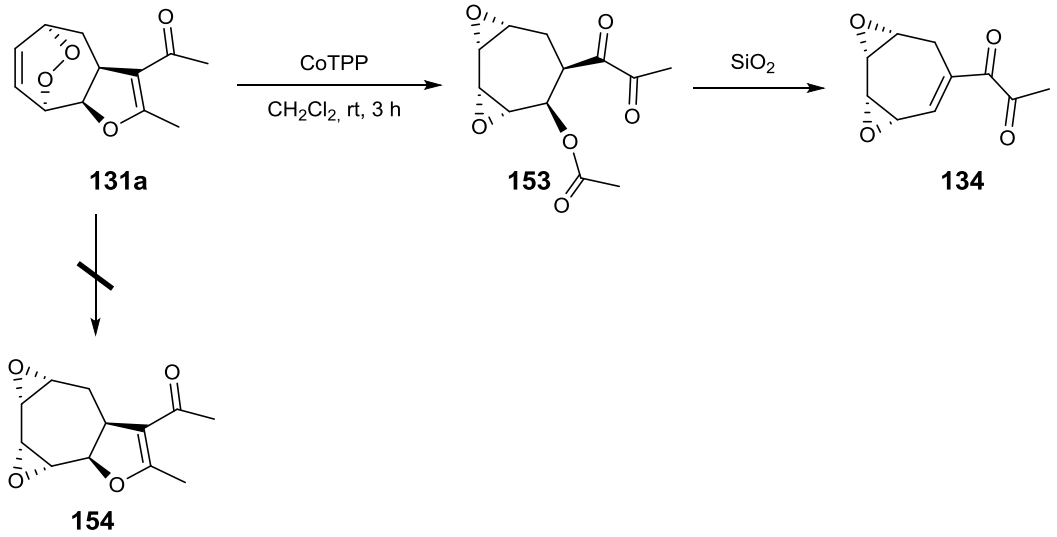


Scheme 44

1.2.4 Reaction of Endoperoxide (130a) with Co-TPP (153 and 134)

To examine the behavior of synthesized endoperoxide **130a** against CoTPP, endoperoxide **130a** was treated with CoTPP in CH_2Cl_2 at room temperature. Surprisingly, the compound **134** was formed instead of the expected product **154** (Scheme 45).

Careful inspection of the NMR spectra indicated the formation of the epoxide-rings beside the opening the dihydrofurane ring and formation of two new carbonyl groups in compound **134**. For this oxidative transformation reaction, the addition of oxygen molecule to the double bond in the five-membered ring is necessary. The mechanism of formation of this product is not clear and will be searched in the future. For purification of **153**, silica gel column chromatography was used. We noticed that the ester functionality in **153** was eliminated during purification to give **134** where newly formed double bond is conjugated with the carbonyl group (Scheme 45).



Scheme 45

Comparison of the ^{1}H NMR spectrum of **131a** with those of **153** (Fig 77 - p. 147) showed disappearance of the olefinic proton and bridgehead proton resonances. The epoxide proton resonances were formed instead. Four epoxide protons resonate at 3.50 ppm as a broad triplet (J = 3.1 Hz), 3.40 ppm as doublet of doublets (J = 3.9 and 2.0 Hz) and other two epoxide protons epoxide signals appear at 3.20-3.11 ppm as multiplet. There are two methine protons in the structure. The methine proton next to the oxygen atom resonates at 5.46 as doublet of doublets with coupling constants of J = 4.7 and 2.2 Hz. The other methine proton resonates at 3.78-3.73 ppm as multiplet. In addition to methylene proton resonances at 2.19 ppm as triplet (J = 6.7 Hz), two methyl groups resonate at 2.30, 1.99 as singlets.

^{13}C NMR spectrum (Fig 78 - p. 147) of **153** includes twelve different signals. Three of them are arising from the carbonyl groups which appear at 197.5, 196.0 and 170.3 ppm. Methine carbons of **153** resonate at 69.5 and 43.3. Epoxide carbons resonate at 58.1, 53.8, 51.6 and 50.4 ppm. Additionally, methylene carbon resonates at 23.5 and two methyl groups appear at 24.0 and 20.8 ppm.

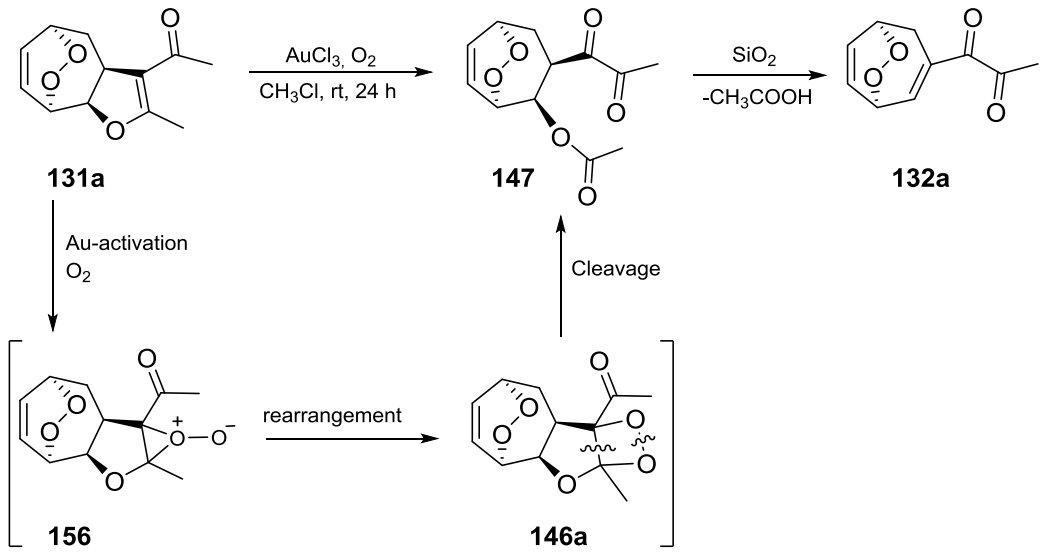
The presence of four epoxide protons and methylenic protons in the ^{1}H NMR spectrum (Fig 86 - p. 151) of **134** showed that this part of the molecule was not changed during column chromatography. However, the presence of an olefinic proton resonance at 6.86 ppm as doublet of doublets (J = 4.2 and 1.8 Hz) indicated the elimination of the ester group.

^{13}C NMR spectrum (Fig 87 - p. 152) of **134** was much more informative. The signal of one of the carbonyl groups was disappeared and the remaining carbon resonances appear at 200.5 ppm and 191.8 ppm. The formation of C=C double bond carbons at 141.5 and 136.5 ppm further confirmed the elimination of the ester group. Four epoxide carbon resonances were found at 52.8, 52.8, 49.7, and 48.1 ppm. Additionally methyl carbon and methylene carbon resonances were observed at 26.8 ppm 22.4 ppm, respectively.

1.2.5 $AuCl_3$-Catalyzed Reaction of Endoperoxide (130a)

To examine the reaction of endoperoxides with gold salt, we treated compound **131a** with gold trichloride at the room temperature under the oxygen atmosphere. We expected that endoperoxide unit in **131a** would undergo some kind of reaction with $Au(Cl)_3$. However, we noticed that the endoperoxide unit was intact. On the other hand, five-membered ring underwent an oxidative ring-opening reaction to give **147** (Scheme 46).

For this transformation, we suggest the following reaction mechanism. We assume that the double bond in the five-membered ring is activated with Au^{3+} ions upon complexation so that the oxygen can atact this bond and form perepoxide **156** which has tedency to rearange to corresponding dioxetane **146a**. Cleavage of the dioxetane **146a** will provide dicarbonyl compound **147**. Elimination of CH_3COOH group on silica gel may funish **132a**.



Scheme 46

The characterization studies of compound **147** were done with the help of ^{1}H and ^{13}C NMR spectra. In the ^{13}C NMR spectrum (Fig 96 - p. 156) two new carbonyl carbons were formed that resonate at 196.7 and 170.7 ppm the other carbonyl carbon resonates at 197.1 ppm. At the same time two olefinic carbon resonances of dihydrofuran ring disappeared. The other signals of ^{13}C NMR spectrum were in accordance with the proposed structure.

In the ^{1}H NMR spectrum (Fig 95 - p. 156) of **147**, two bridgehead protons resonate at 4.95 ppm as triplet of triplets (J = 6.4 and 1.0 Hz) and at 4.81 ppm as doublet of triplets (J = 6.7 and 1.2 Hz) . Olefinic proton resonates as multiplet between 6.56 to 6.45 ppm.

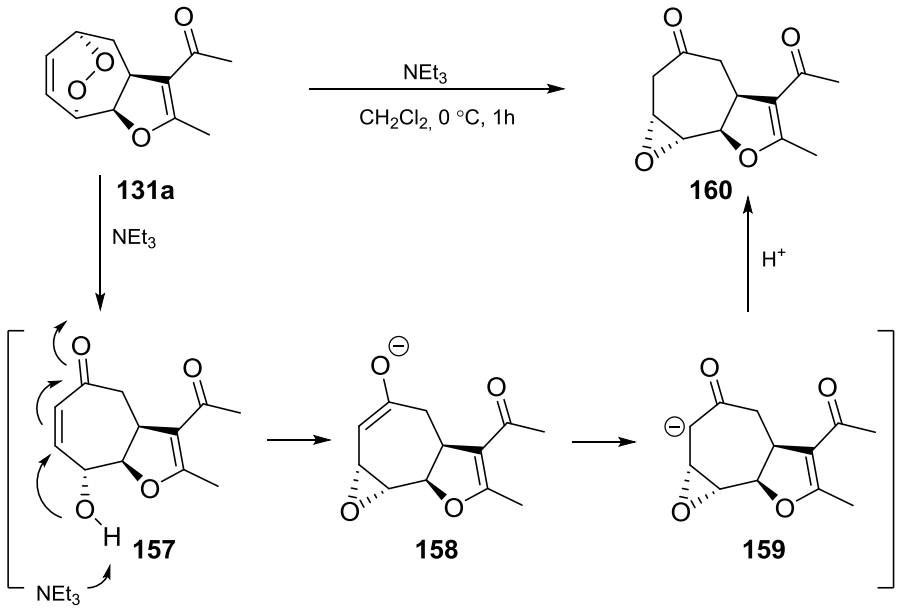
NMR spectra of **132a** were discussed above.

1.2.6 Reaction of endoperoxide (130a) with NEt_3

It is well established that the unsaturated bicyclic endoperoxides reacts with bases to give the rearranged α,β-unsaturated enones. For further functionalization, endoperoxide **131a** was treated with triethyl amine in dichloromethane at 0 °C. Contrary to our expectation, compound **160** was formed instead of **157** (Scheme 47).

We propose the following mechanism for the formation of compound **160**. We assume that the expected product enone **157** is formed in the first step. Then,

triethylamine abstracts the proton from the hydroxyl group generating an alkoxy anion that attacks the β-carbon atom of enone forming an epoxide ring. The formed carbanion can easily be protonated to generate final compound **160** (Scheme 45).



Scheme 47

When we compare ^{1}H NMR (Fig 35 - p. 126) spectrum of the starting compound **131a** with the ^{1}H NMR spectrum (Fig 104 - p. 160) of product **160**, we observe that bridgehead protons and olefinic protons signals are disappeared and epoxide protons signals are formed instead. Epoxide protons appear as a doublet of doublets of doublets at 4.79 ppm (J = 8.1, 5.8, 2.3 Hz) and doublet of doublets at 4.55 ppm (J = 7.9, 5.8 Hz). Methine protons signal shows a broad doublet at 5.38 (J = 2.1 Hz) and multiplet in the range of 2.76 to 2.71 ppm. The other protons were coherent with the structure.

In the ^{13}C NMR spectrum (Fig 105 - p. 161), there are two carbonyl carbon signals resonating at 201.9 and 197.3 ppm and two olefinic carbon signals at 169.3 and 104.2 ppm. Epoxide carbon signals appear at 76.7 and 70.9 ppm.

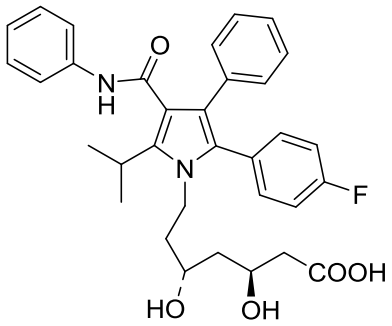
CHAPTER 2

DESIGN OF PYRROLO-PYRROLO-PYRAZINES VIA Pd/C-CATALYZED CYCLIZATION OF *N*-PROPARGYL PYRROLINYL-PYRROLE DERIVATIVES

2.1 INTRODUCTION

2.1.1 Pyrrole

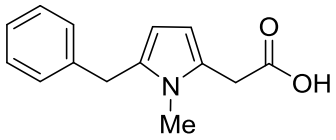
Pyrrole, from Greek meaning red, is an attractive azaheterocyclic compound. Pyrrole and its derivatives show interesting biological and pharmacological properties such as antitumor,[64] antibacterial,[65] antioxidative,[66] anti-inflammatory,[67] antifungal activities.[68] These properties show that pyrrole is an important pharmaceutical compound. For instance, antrovastatin, marketed name is Lipitor®,[69] (**1**) posseses a cholesterol-lowering properties.



Lipitor®

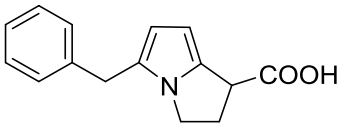
1

Pyrrole ring was used to synthesize non-steroidal anti-inflammatory drugs, which are called tolmetin (Rumatol®) (**2**) and ketorac (Ketorac®) (**3**).[70]



Rulmatol®

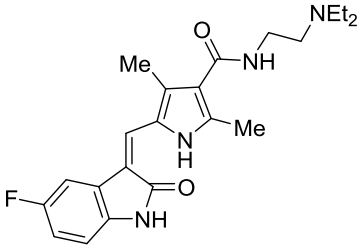
2



Ketorolac®

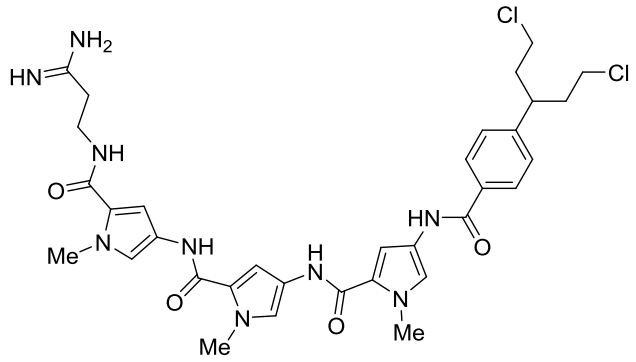
3

Recently, anticancer drugs having pyrrole ring have been used by treatment of cancer diseases. Sunitinib (**4**) is an important example, this marketing drug, is used for treatment of renal cancer.[71] The other example of synthetic anticancer drug including pyrrole ring is a tallimustine (**5**).[72]



Sunitib

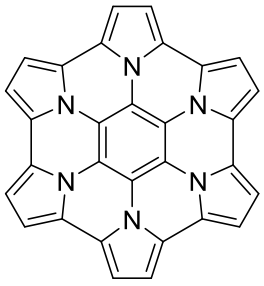
4



Tallimustine

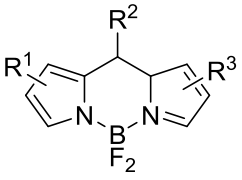
5

Optoelectronic materials having pyrrole ring, such as OLED (Organic Light-Emitting Diodes), PLED (Polimeric Light-Emitting Diodes), polypyrrole-latex materials, polypyrrole, hexa(*N*-pyrrolyl)benzene (**6**) are important for the material science. In addition to, BODIPY (4,4-difluoro-4-boradipyrrin system) (**7**) is an important pyrrole derivative used by many scientist because it posseses strong absorption properties in the UV and emit very intense fluorescence.[73]



A pyrrole based semiconductor

6



BODIPY dyes

7

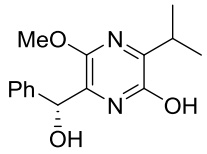
2.1.2 Pyrazines

Pyrazine (**8**) is a heterocyclic compound having two nitrogen atoms with a six membered aromatic ring. Compounds including the pyrazine skeleton represent important role in materials science[74] and drug chemistry.[75] In other words, they show a greate range of biological activities, such as antihypersensetive,[76] antiarrhythmic,[77] psychotropic,[78] antihypoxic.[79]

pyrazine

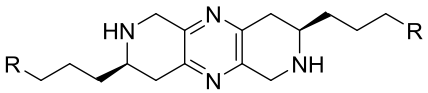
8

Pyrazine is found in many natural products but larger part of natural pyrazines are found in amino acids such as, terezine A[80] (**9**), barrenazine A and B[81] (**10**), actinopolymorphol C[82] (**11**), 2,5-diisopropylpyrazine[83] (**12**), botryllazine A (**13**) and botryllazine B[84] (**14**).



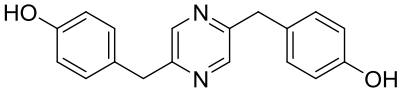
(-)-terezine A

9



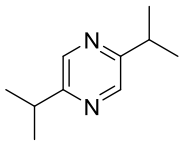
barrenazine A, R= $(CH_2)_3Me$
barrenazine B, R= $(CH_2)_2CH=CH_2$

10



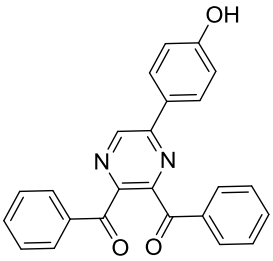
actinopolymorphol C

11



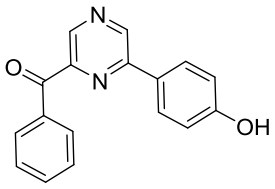
2,5-diisopropylpyrazine

12



botryllazine A

13



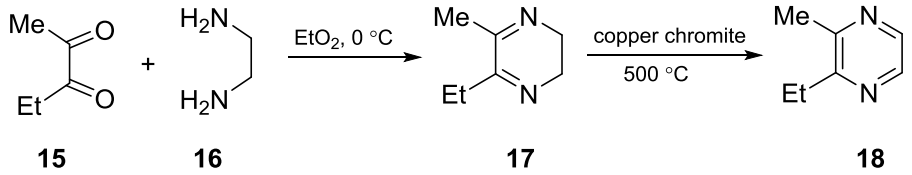
botryllazine B

14

2.1.2.1 The Synthesis of Pyrazines

Cyclocondensation reaction is an important and most common way to synthesize pyrazine ring. Masuda *et al.*[85] synthesized 2,3-dihydropyrazine **17** by cyclocondensation reaction of 1,2-dicarbonyl compound **15** with 1,2-diaminoethane

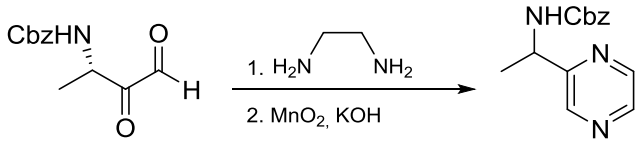
(**16**). Oxidation of 2,3-dihydropyrazine **17** with copper chromite gave pyrazine **18** (Scheme 1).



15 **16** **17** **18**

Scheme 1

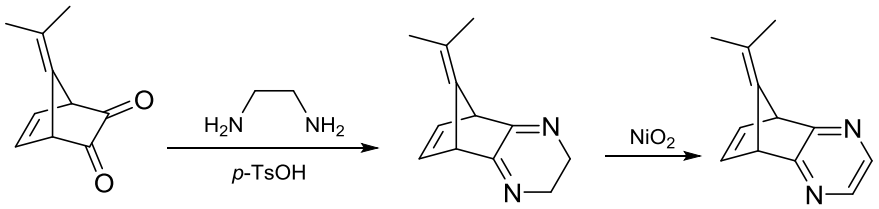
Darkins *et al.*[86] reported that *N*-protected 1,2-dicarbonyl compound **19** was condensed with 1,2- diaminoethane to generate dihydropyrazine which is oxidized to pyrazine **20** by MnO_2 in the presence of KOH (Scheme 2).



19 **20**

Scheme 2

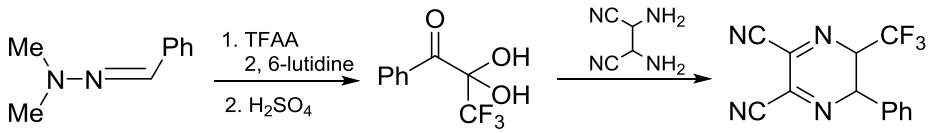
1,4-Diazine scafold **23** was generated by the reaction of bicyclo[2.2.1]hept-5-ene-2,3-dione (**21**) with 1,2-diaminoethan followed by oxidation in the presence of NiO_2 (Scheme 3).[87]



21 **22** **23**

Scheme 3

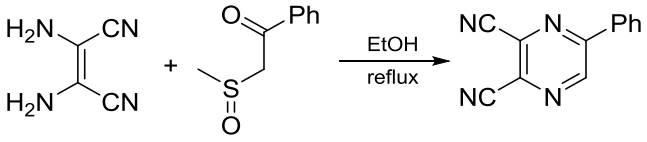
According to a new synthetic methodology developed by Kamitori,[88] dialkylhydrazone **24** was first reacted with TFAA (trifluoroacetic acid) followed by hydrolysis with H_2SO_4 to generate α-diketohydrate **25** which was condensed with diamines to obtain pyrazine derivative **26** (Scheme 4).



24 **25** **26**

Scheme 4

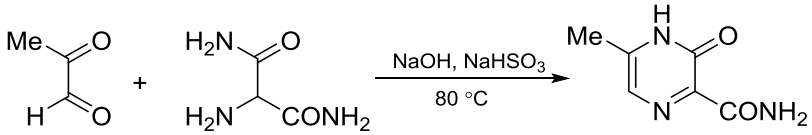
Kano and coworkers demonstrated the direct synthesis of pyrazine by the reaction of diaminomalononitrile **27** with β-keto sulfoxide **28** to form 2,3-dicyanopyrazine **29** (Scheme 5).[89]



27 **28** **29**

Scheme 5

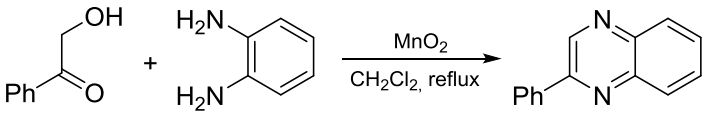
Bradbury *et al.*[90] synthesized new pyrazinone derivatives **32** starting from 1,2-dicarbonyl compound **30** and α-amino malonamides **31** in the presence of $NaOH/NaHSO_3$ (Scheme 6).



30 **31** **32**

Scheme 6

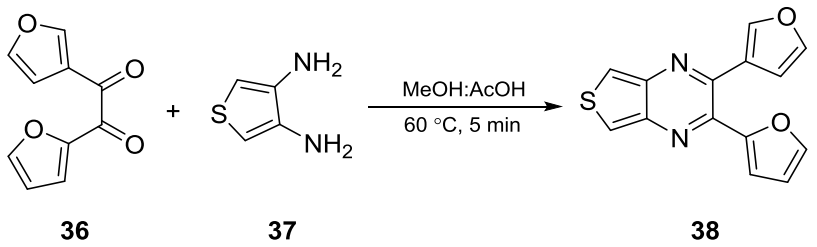
In 2003, Taylor and coworkers developed a highly efficient and novel route for the synthesis of quinoxaline derivative **35** by a tandem oxidation procedure, where α-hydroxyketone **33** was reacted with 1,2-diamines **34** in presence of MnO_2 (Scheme 7).[91]



33 **34** **35**

Scheme 7

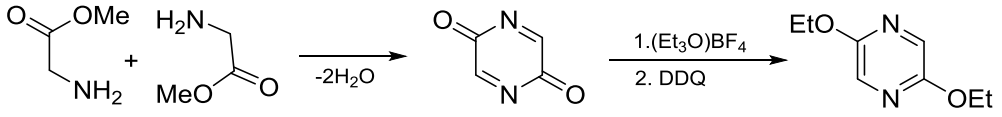
Lindsley *et al.*[92] designed a practical and general method under the microwave irradiation conditions to synthesize functionalized pyrazine **38** that are important class of heteroaromatic compounds (Scheme 8).



36 **37** **38**

Scheme 8

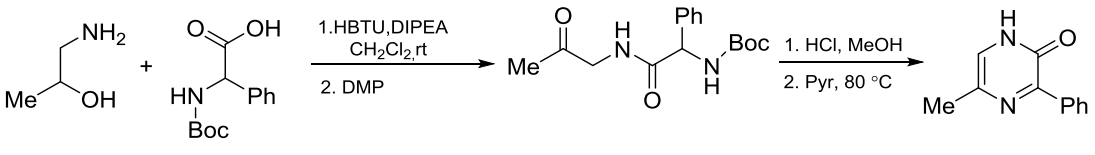
An alternate way to synthesize pyrazine ring is the cyclodimerization of α-amino carbonyl compounds. Firstly, α-amino ester **39** undergoes a self-condensation reaction to form 2,5-dihydropyrazine **40**. Treatment of **40** with trialkloxonium salt followed by oxidation with DDQ resulted in the formation of 3,6-dialkoxypyradazine **41** (Scheme 9).[93]



39 **39** **40** **41**

Scheme 9

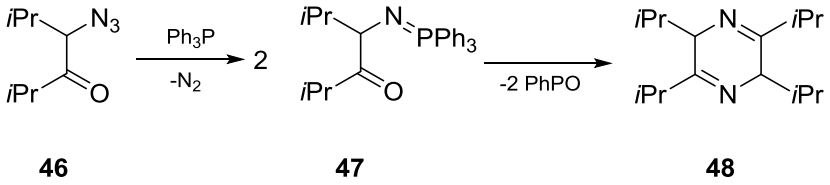
Meier *et al.*[94] reported a new procedure to synthesize trisubstituted 1*H*-pyrazine-2-ones. Boc-protected amino acid **43** was treated with α-aminoalcohol **42** or with α-amino ketone followed by oxidation with DMP (Dess–Martin periodinane) to obtain coupling adduct **44**. Reaction of **44** with HCl in pyridine at 80 °C afforded 1*H*-pyrazin-2-one **45** in good yield (Scheme 10).



42 **43** **44** **45**

Scheme 10

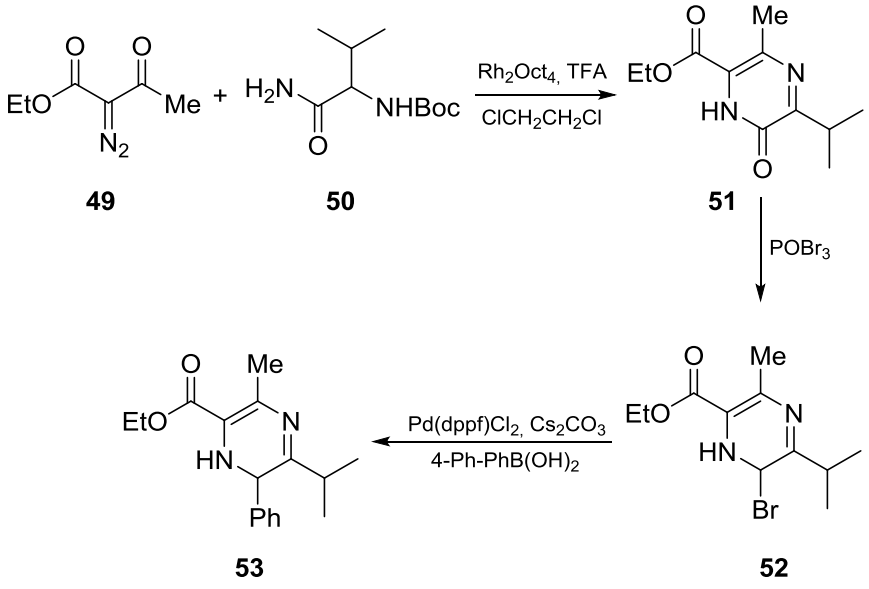
Schulz and coworkers designed a practical and alternative method for the synthesis of pyrazine derivatives via aza-Witting cyclization reaction. Their synthetic strategy includes firstly the formation of α-phosphazinyl ketone **47** starting from α-azidoketone **46** and triphenylphosphine. After that, aza-Witting cyclization reaction of α-phosphazinyl ketone **47** formed dihydropyrazine derivative **48** (Scheme 11).[95]



46 **47** **48**

Scheme 11

Janda *et al.*[96] presented that pyrazine-6-one **51** was obtained in good yields by the reaction of α-diazo-β-ketoester **49** with Boc-protected α-aminoamide **50** mediated by rhodium octanoate catalyst. Pyrazine-6-one **51** was treated with $POBr_3$ to afford 6-bromopyrazine **52**, which was reacted with biphenyl boronic acid under the Suzuki coupling conditions to obtain 6-arylpyrazine **53** (Scheme 12).

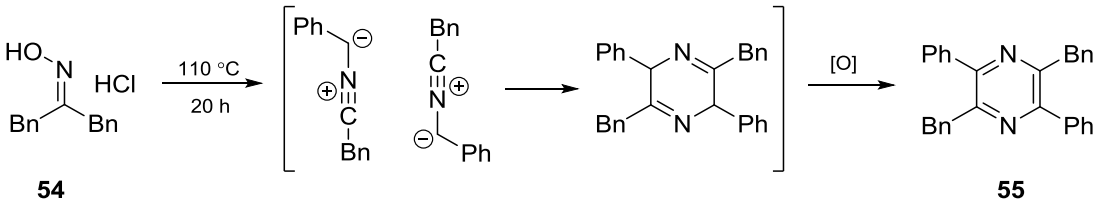


49 **50** **51** **52** **53**

Scheme 12

An interesting and straightforward method for the synthesis of tetrasubstituted pyrazine is the thermal Beckmann rearrangement. Firstly, thermally deprotonated oxime hydrocloride **54** affords the nitrile ylide that undergoes dimerization to give

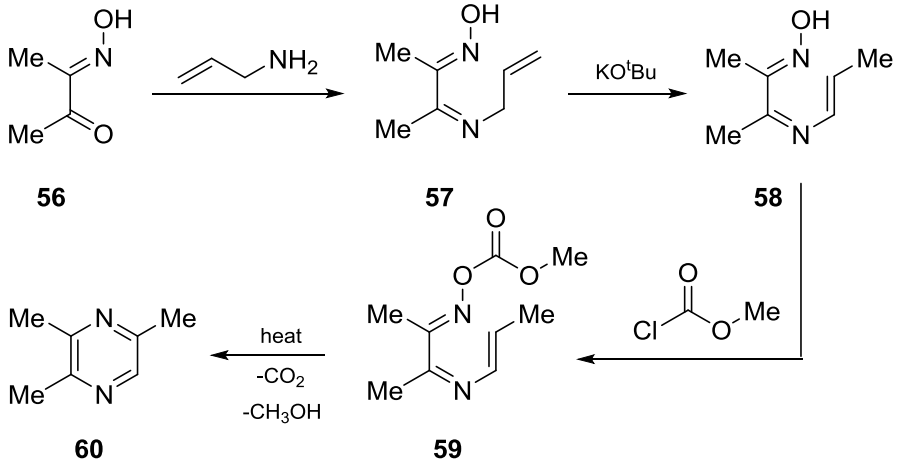
the dihydropyrazine derivative intermediate. Air oxidation of this intermediate furnishes tetrasubstituted pyrazine **55** (Scheme 13).[97]



54 **55**

Scheme 13

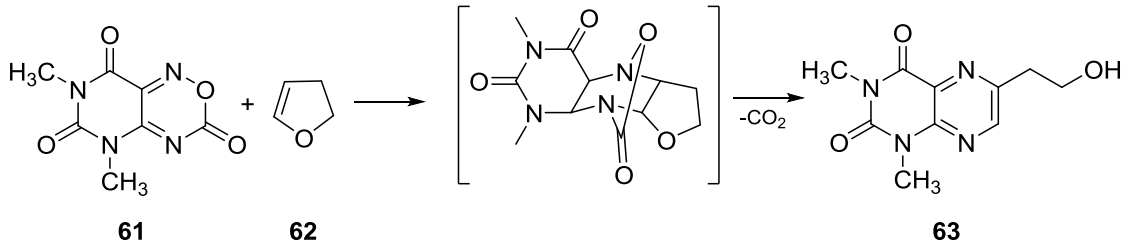
Büchi *et al.*[98] showed that α-hydroxyimino ketone **56** reacts with allylamine to give imine derivative **57**. Base-catalyzed isomerization of **57** with K^{t}OBu followed by O-acylation and finally electrocyclization reaction provides pyrazine derivative **60** (Scheme 14)



56 **57** **58** **59** **60**

Scheme 14

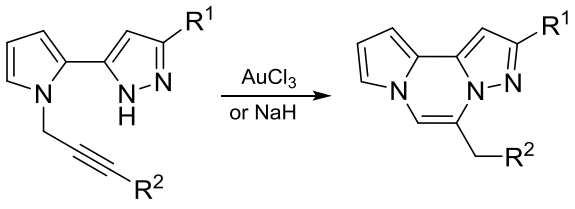
The another and interesting way to synthesize pyrazine ring is a [4+2] cycloaddition reaction. Sato *et al.*[99] benefited this way to synthesize lumuzines (**63**) starting from **61** and **62** which is an important biological active compound (Scheme 15).



61 **62** **63**

Scheme 15

Recently, Balci *et al.* reported a new synthetic methodology for the construction of novel pyrazine derivatives using alkyne cyclization reactions.[100] They synthesized a number of pyrazolo-pyrrolo-pyrazine derivatives **65** by the cyclization of *N*-propargyl pyrroles derivatives **64** either by $AuCl_3$-catalyzed or NaH supported reactions (Scheme 16).

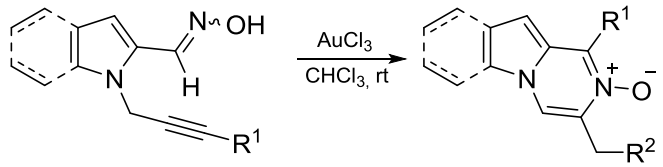


64 a-c **65 a-c**

a: R^1=H, R^2=H
b: R^1=Ph, R^2=H
c: R^1=*n*-Bu, R^2=H

Scheme 16

Furthermore, Balci *et al.* developed a synthetic methodology for pyrazine oxides **67**. Oxime derivatives of *N*-propargy pyrroles and *N*-propargy indols **66** were reacted with $AuCl_3$ to obtain pyrazole or indol fused pyrazine oxides **67** (Scheme 17).[101]



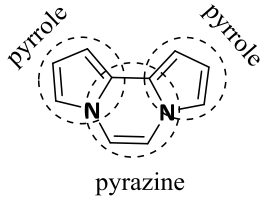
66 a-c **67 a-c**

a: R^1=H, R^2=Me
b: R^1=Me, R^2=Me
c: R^1=H, R^2=Me (Indole)

Scheme 17

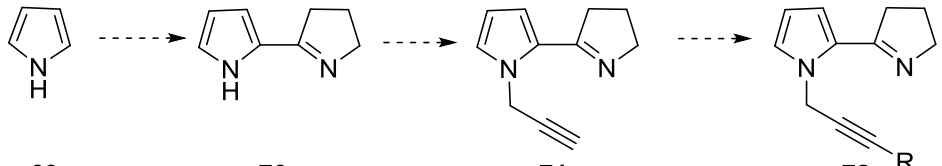
2.1.3 Aim of the Study

The aim of this part was development of a new synthetic methodology for the synthesis of pyrrolo-pyrrolo-pyrazine derivatives via cyclization of *N*-propargyl 2,2'-(1'-pyrrolinyl) pyrroles.



68

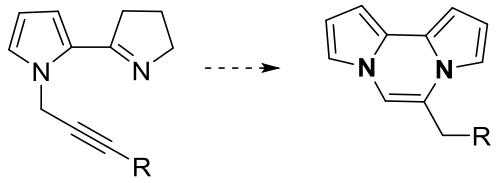
Firstly, 2,2'-(1'-pyrrolinyl)-pyrrole (**70**) should be synthesized starting from pyrrole (**69**). *N*-propargyl 2,2'-(1'-pyrrolinyl) pyrrole (**71**) which is key compound of this study, will be obtained by the reaction of 2,2'-(1'-pyrrolinyl)-pyrrole (**70**) with propargyl bromide. The Sonogashira cross-coupling reaction of *N*-propargyl 2,2'-(1'-pyrrolinyl) pyrrole (**71**) with various aromatic bromides will result in the formation of further substituted derivatives **72** (Scheme 18).



69 **70** **71** **72**

Scheme 18

After getting compound **72**, we planned aromatization of **72** followed by ring-cyclization reaction to obtain the target compound pyrrolo-pyrrolo-pyrazine derivatives **73** (Scheme 19).



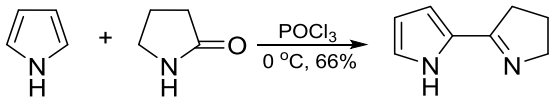
72 **73**

Scheme 19

2.2 RESULTS AND DISCUSSION

2.2.1 Synthesis of 2,2'-(1'-pyrrolinyl)pyrrole (70)

Firstly, we synthesized starting compound, 2,2'-(1'-pyrrolinyl)pyrrole (**70**). To synthesize this compound, pyrrole (**69**) was treated with 2-pyrrolidinone (**74**) in the presence of phosphoryl chloride. Reaction must be done carefully because polymerization take place very quickly (Scheme 20).



69 **74** **70**

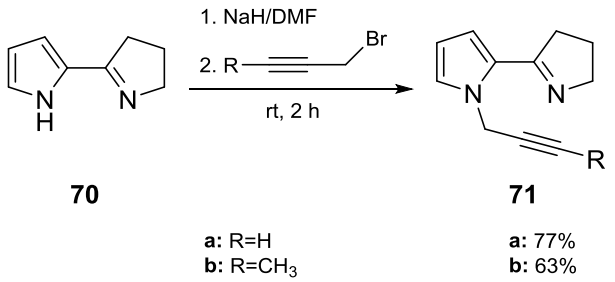
Scheme 20

There are three pyrrole hydrogens and six methylene hydrogens in the structure of **70.** In the ^{1}H NMR spectrum (Fig 111 - p. 164) of **70**, pyrrole protons resonate at 6.93 ppm as doublet of doublets (J = 2.4 and 1.1 Hz), at 6.54 ppm as doublet of doublets (J = 3.5 and 1.1 Hz), and at 6.21 ppm as doublet of doublets (J = 3.5 and 2.4 Hz). In addition, methylene protons resonate at 4.02 ppm as a broad triplet (J = 7.0 Hz), at 2.90 ppm as a triplet of triplets (J = 8.2 and 1.4 Hz) and at 2.00 ppm as a quintet (J = 8.2 Hz).

In the ^{13}C-NMR spectrum (Fig 112 - p. 164) of **70,** we observe five olefinic carbons signals resonating at 166.5, 127.8, 122.2, 113.2 and 109.1 ppm. Other remaining signals are arising from the methylene carbons appearing at 60.5, 35.0 and 22.7 ppm.

2.2.2 Synthesis of 1-Prop-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (71)

To synthesize target molecules, we had to attach propargyl group on the pyrrole nitrogen atom in **70**. In order to synthesize compound **71**, 2,2'-(1'-pyrrolinyl)pyrrole (**70**) was reacted with propargyl bromide derivatives in the presence of sodium hydride in dry DMF to give the expected propargylated compounds **71** (Scheme 21).



Scheme 21

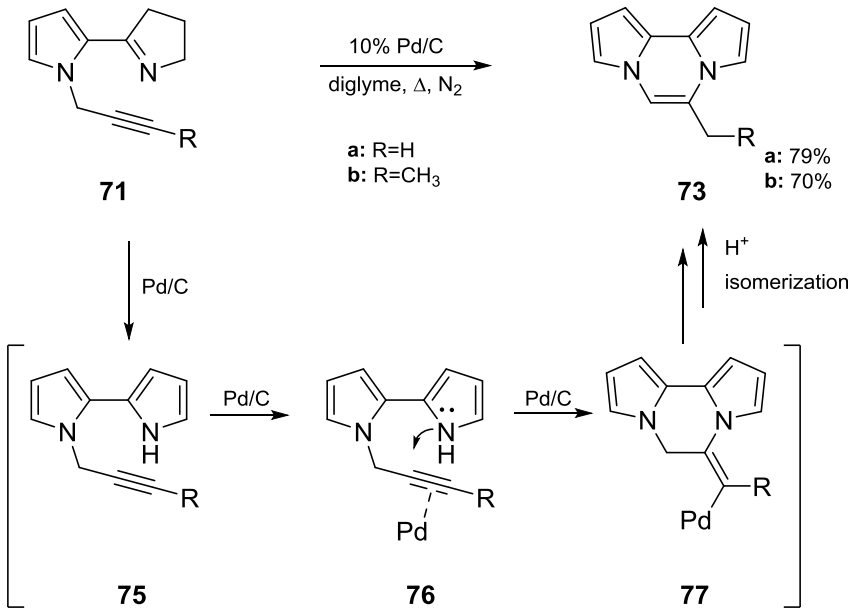
The characterization of compounds **71a** and **71b** was done on the basis of ^{1}H NMR (Fig 113-117 - p. 165-167) and ^{13}C NMR (Fig 114 118 - p. 165-167) spectra. When we compare the structures of **70** and **71a**, compound **71a** has an additional methylene group and alkyne group. In the ^{1}H NMR spectrum of **71a**, this methylene protons resonate at 5.41 ppm as doublet (J = 2.5 Hz) due to long range coupling with the alkyne proton. Acetylenic proton appears at 2.37 ppm as triplet (J = 2.5 Hz).
The ^{13}C NMR spectrum shows eleven distinct signals. Acetylenic carbons resonate at 79.3 and 73.1 ppm whereas the olefinic carbons appear at 165.9, 127.3, 125.8, 115.4 and 108.3 ppm. In addition aliphatic carbons resonate at 61.8, 38.3, 36.6, and 21.8.

The NMR spectra of compound **71b** is also in agreement with the proposed structure.

2.2.3 Intramolecular Pd/C-catalyzed Cyclization Reaction of *N*-propargyl Pyrrole-Pyrrolinyl Derivative (71a)

For the synthesis of target molecule **73**, first the dihydropyrrole unit should be aromatized followed by cyclization. For aromatization we decided to use Pd/C as catalyst. When compound **71** was reacted with Pd/C in diglyme, surprisingly, the cyclization product **73** was formed. This result was very important because two step reactions were completed in one pot (Scheme 22).

We propose the following mechanism for the formation of compound **73**. Pd/C firstly dehydrogenates the methylene protons of pyrrolinyl unit to afford compound **75**. The π coordination of alkynyl group with Pd produces the alkyne π complex. After that, nitrogen atom of pyrrole attacks the activated alkyne π complex to occur 6-*exo*-dig cyclization product **77** followed by isomerization to release the compound **73** (Scheme 22).



Scheme 22

Comparison of the ^{1}H NMR spectra(Fig 113-137 - p. 165-177) of **71a** and **73a** show that the resonances of acetylenic proton and methylene protons are disappeared in the NMR spectrum of **73a** (Fig 137- p. 177) and a methyl and olefinic proton resonances appeared. Furthermore, methylene protons of pyrrolinyl group also disappeared and pyrrole protons are observed instead. In the ^{1}H NMR spectrum of compound **73a**, formed olefinic proton of the pyrazine ring resonates at 6.89 ppm as a broad singlet. On the other hand, methyl protons appear as a doublet at 2.35 ppm (J =1.2 Hz). Additionally, six pyrrole protons resonate at 6.98, 6.92, 6.56, and 6.42 ppm.

In the ^{13}C NMR spectrum (Fig 138- p. 177), methyl protons appear at 15.62 ppm. On the other hand, olefinic carbons signals appear at 124.8, 123.9, 118.9, 113.7, 111.9, 111.3, 110.8, 109.1, 99.8, 98.6.

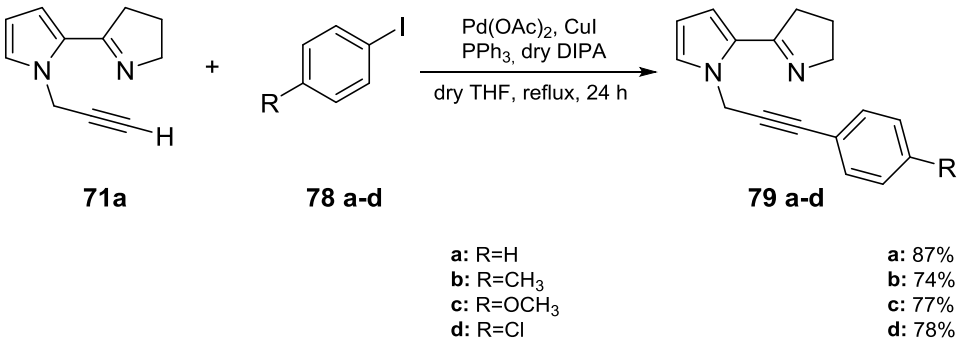
The NMR spectra of compound **73b** is similar to the NMR spectra of compound **73a**.

2.2.4 Derivatization of Compound 71a with Sonagashira coupling reaction (79)

To test the scope of this cyclization and to show the generality of this reaction, we decided to synthesize compound **79** having aromatic groups attached to the terminal carbon atom of acetylene unit. The most suitable methodology for derivatization of compound **71a** was a Sonagashira coupling reaction. There are many variation of Sonogashira cross-coupling reaction in the literature.[100, 101] We preferred copper-

cocatalyzed Sonogashira coupling reaction which uses Pd catalyst and CuI cocatalyst in dry DMF in the presence of a base.

We applied Sonogashira cross coupling reaction to 1-prop-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**71a**) to form **79** by using iodobenzene derivatives **78** (Scheme 23).



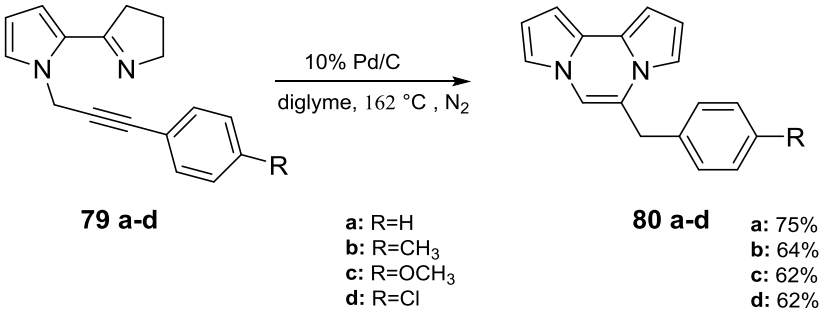
Scheme 23

Comparison of the ^{1}H NMR spectra (Fig 113 - p. 165) of (**71a**) with those of compounds **79** clearly showed that acetylenic proton resonance at 2.37 ppm was missing and benzene protons were formed instead. In the ^{1}H NMR spectrum (Fig 121 - p. 169) of **79a** benzene protons resonate between 7.38 and 7.20 ppm as multiplet. Pyrrole protons resonate at 7.11 ppm as doublet of doublets (J = 2.9 and 1.6 Hz), 6.46 ppm as doublet of doublets (J = 3.6 and 1.6 Hz), and 6.12 ppm as doublet of doublets (J = 3.6 and 2.9 Hz). Methylene protons (next to the alkyne) resonate at 5.55 ppm as singlet. The other signals were consistent with the proposed structure.

The ^{13}C NMR spectrum (Fig 122 - p. 169) of **79a** show acetylenic carbon resonances at 85.0 and 84.6 ppm. Aliphatic carbons resonate at 61.8, 39.2, 36.6, and 21.9. The other carbon signals are in agreement with the proposed structure.

The NMR spectra of compounds **79b-79d** are also in agreement with the proposed structures.

Compounds **79** synthesized via Sonogashira cross coupling reaction were submitted to the cyclization reaction with Pd/C in diglyme under the nitrogen atmosphere to give cyclization products **80** (Scheme 24).



Scheme 24

In the ^{1}H NMR spectrum (Fig 145 - p. 181) of **80a**, the methylene proton resonance appears at 4.05 ppm and olefinic proton resonance at 6.75 ppm clearly indicating that cyclization reaction occurred. Six pyrrole protons resonate at 6.96, 6.91, 6.55 and 6.50 ppm. Benzene protons resonate in a range of 7.37 to7.28 ppm.

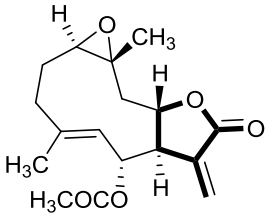
The NMR spectra of compounds **80b**-**80d** are also in agreement with the proposed structure.

CHAPTER 3

THE SYNTHESIS OF α-ALKYLIDYN-γ-BUTYROLACTONES VIA GOLD-CATALYZED CLAISEN REARRANGEMENT

3.1 INTRODUCTION

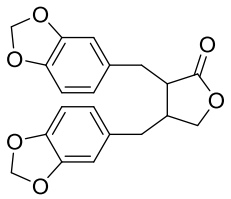
Syntheses of α-alkylidine-γ-butyrolactone derivatives have drawn the attention of researcher in recent years. The first α-alkylidine-γ-butyrolacton, pyrethrosin (**1**), was extracted from *Tanacetum cinerariifolium* by Toms in 1891.[102] α-Alkylidine-γ-butyrolactone is a five-membered cyclic ester. Its derivatives show anticancer, antiviral, antibacterial, antiinflammatory activities.[103-104]



pyrethrosin

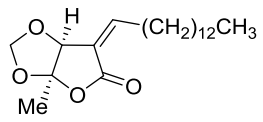
1

For example, Chang and coworkers reported that Taiwainin A (**2**) isolated from *Taiwania cryplomeriides*[105] is an interesting molecule to use in the treatment of human tumor inhibition. Kotolactone A[106] (**3**) extracted from *Cinnamomum ketones*, subamolides D and E[107] (**4**) extracted from *Cinnamomum subavenium*, were found that these molecule have an activity against colon cancer. The other example of natural compound including α-alkylidine-γ-butyrolactone ring is a Hispitolide A (**5**), showing activity against HCV (hepatitis C virus).[108]



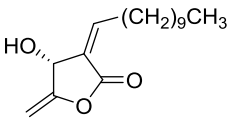
Taiwanin A

2



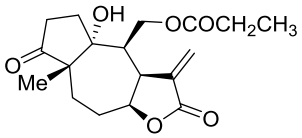
Kotolactone A

3



subamolide D (Z)
subamolide D (E)

4



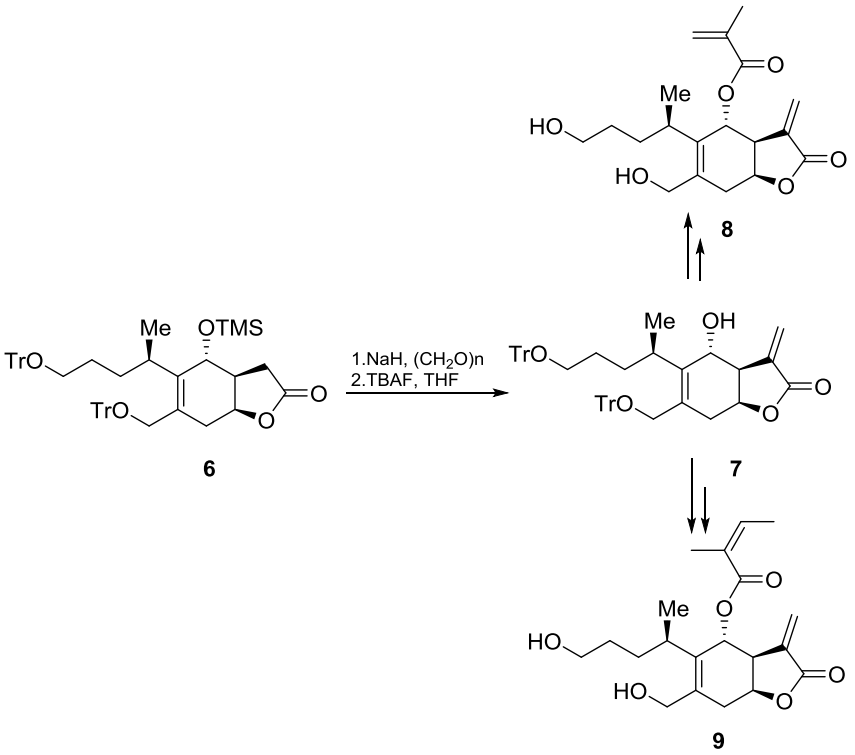
Hispitolide A

5

3.1.1. The Synthesis of α-Alkylidine-γ-Butyrolactones

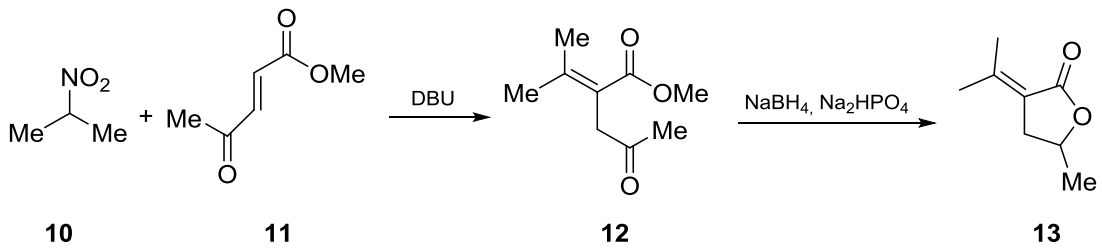
For the synthesis of substituted α-alkylidine-γ-butyrolactone derivatives, there are many strategic ways which are alkylidenation of γ-butyrolactons, lactonization approach, the Dreiding-Schmidt approach, radical cyclization, Diels-Alder and retro-Diels-Alder reaction, Baeyer-Villiger reaction on cyclobutanones, Pd-catalyzed cross-coupling and tandem intramolecular C-H insertion.

Alkylation of γ-butyrolactons is most commonly used method to synthesize α-methylene-γ-butyrolactons. To synthesize (-)-eriolanin (**8**) and (-)-eriolangin (**9**), γ-butyrolacton derivative **6** was reacted with NaH then adduct was treated with paraformaldehyde to give **7** (Scheme 1).[109]



Scheme 1

Lactonization approaches were used to design α-methylene-γ-butyrolactons. In 1999, Ballini *et al.*[110] demonstrated the reaction of nitro alkene **10** with enone **11** to give **12**. Treatment of adduct **12** with $NaBH_4$ mediated by Na_2HPO_4 gave α-alkylidine-γ-butyrolactone **13** (Scheme 2).



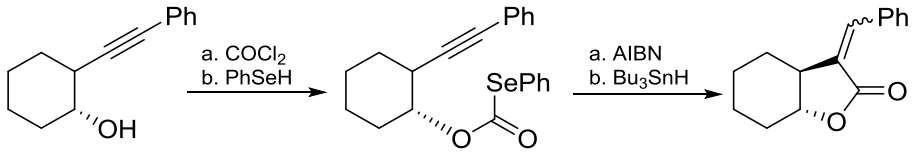
Scheme 2

Dreiding-Schmidt organometalic method, as the name implies that Dreiding and Schmidt groups improved this method for the first time to synthesize α-methylene-γ-butyrolactones. There are various variations of this reaction. In one of these, Chu *et al.*[111] reacted 3-phenylallyl bromine (**15**) with propanal (**14**) in the presence of zinc and diiodoethane to afford 3,4-disubstituted-α-methylene-γ-butyrolacton (**16**) (Scheme 3).

14 **15** **16**

Scheme 3

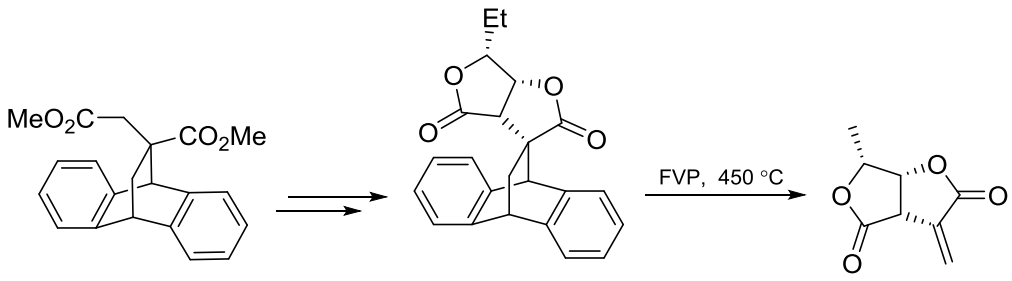
The important pathway to synthesize α-alkylidine-γ-butyrolactons is a radical cyclization method. Bosch *et al.*[112] presented that homopropargyl alcohol **17** firstly reacts with phosgene and then with phenylselenol to furnish seleno carbonate **18**. Treatment of **18** with AIBN initiated cyclization reaction to form α-arylidine-γ-butyrolacton **19** (Scheme 4).



17 **18** **19**

Scheme 4

Thebtaranonth and coworkers synthesized the natural compound xylobovide (**22**) exhibiting antifungal and antibacterial activity, by a retro-Diels-Alder process. Firstly itaconate-antracene derivative **20** was converted into the bislactone **21** then adduct was submitted to FVP (flash vacuum pyrolysis) to afford xylobovide (**22**) (Scheme 5).[113]

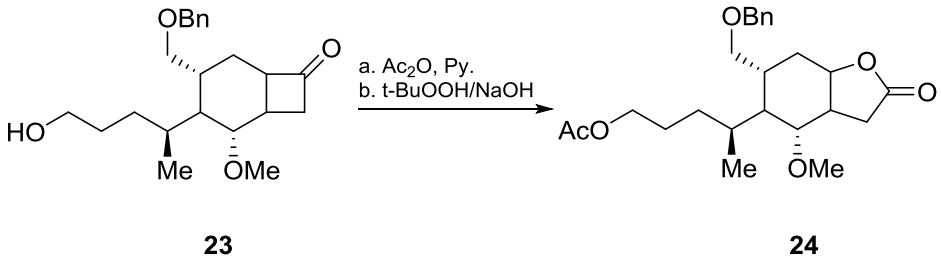


20 **21** **22**

Scheme 5

An efficient and straightforward way to synthesize γ-butyrolacton is a Baeyer-Villiger oxidation on cyclobutanone derivative **23**. Cyclobutanone derivative **23** was

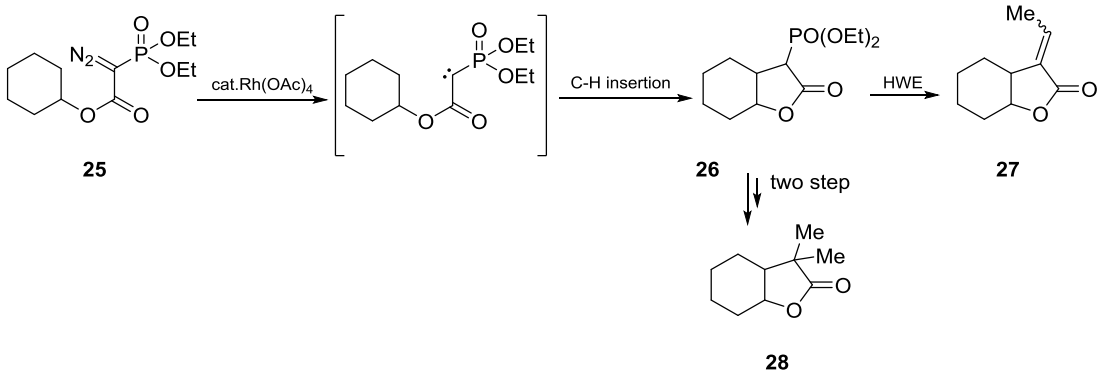
treated with acetic anhydride in pyridine to give the corresponding acetate followed by the reaction with *tert*-butyl hydroperoxide to generate γ-butyrolacton derivative **24** (Scheme 6).[114]



23 **24**

Scheme 6

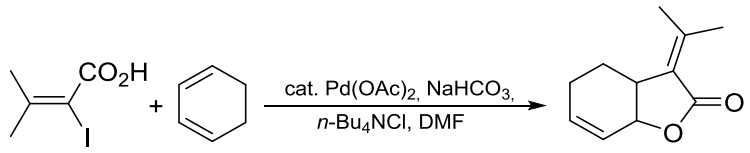
Design of α-alkylidine-γ-butyrolactons by tandem intramolecular C-H insertions has increased dramatically in recent years. For example, Shie and Zhu reported that treatment of cyclohexyl-α-diazo-α-phosphoryl acetate **25** with $Rh_2(OAc)_4$ in DCM gave the γ-butyrolactone derivative **28** which is an insertion/cyclization products (Scheme 7).[115]



25 **26** **27** **28**

Scheme 7

Pd-catalyzed cross-coupling reaction was developed for the formation of the α-alkylidine-γ-butyrolactons **31** by Larock *et al*.[116] For this, α-iodo acrylicacids **29** was reacted with 1,3-cyclohexadiene (**30**) in the presence of $Pd(OAc)_2$ to generate α-alkylidine-γ-butyrolacton **31** (Scheme 78).[116]

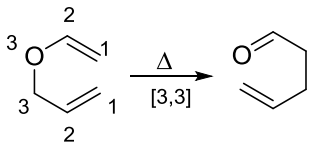


29 **30** **31**

Scheme 8

3.1.2 Claisen Rearrangement

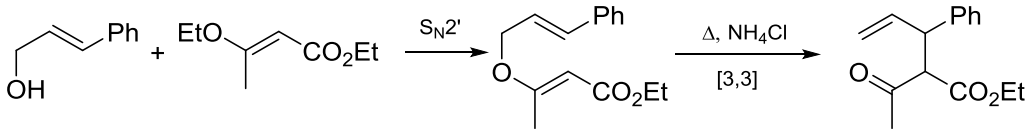
Claisen Rearangement discovered by Claisen in 1912,[117] is a [3,3] sigmatropic rearrangement of allyl vinyl ethers which utilize the synthesis of γ,δ-unsaturated carbonyl compounds (Scheme 9).



32 **33**

Scheme 9

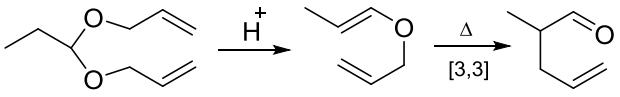
Bergmann *et al.*[118] showed that rearrangement of ethyl cinnamyl oxycrotonate **36** obtained by the reaction of cinamyl alcohol **34** with ethyl-3-ethoxytonate **35**, was mediated by NH_4Cl at higher temperature to give the Claisen rearrangement product **37** (Scheme 10).



34 **35** **36** **37**

Scheme 10

Hurd and coworker utilized a new method for designing of the starting material **39**. Diallyl dimethylketals **38** was treated with acid, a methylvinyl allyl ether **39** was formed. Heating of **39** gave γ,δ-unsaturated carbonyl compound **40** (Scheme 11).[119]

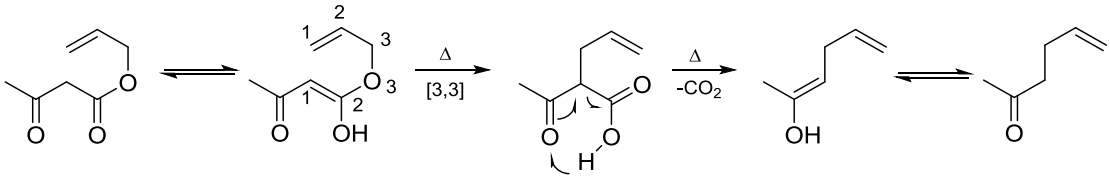


38 **39** **40**

Scheme 11

There are different versions of Claisen rearrangement such as Carroll rearrangement, Eschenmoser rearrangement, Johnson rearrangement, Ireland-Claisen rearrangement, Reformatsky-Claisen rearrangement, thio-Claisen rearrangement, aza-Claisen rearrangement, chelate Claisen Rearangment, diosphenol-Claisen rearrangement, metallo-Claisen rearrangement and retro-Claisen rearrangement.

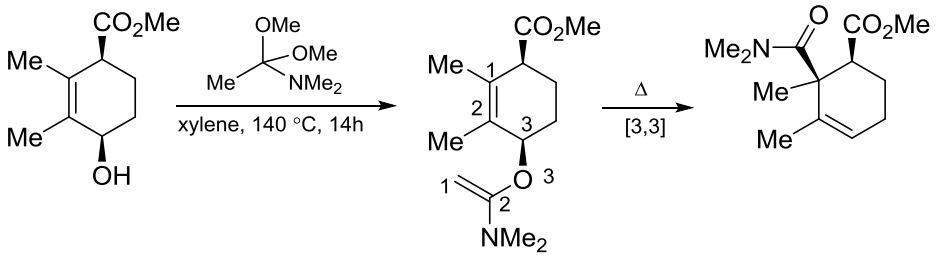
In 1940, M. F. Carroll showed that thermal rearrangement of allyl acetoacetate **41** first formed **43** that underwent decarboxylation to furnish product **45**. Claisen rearrangement followed by a decarboxylation is called as the Carroll rearrangement (Scheme 12).[120]



41 **42** **43** **44** **45**

Scheme 12

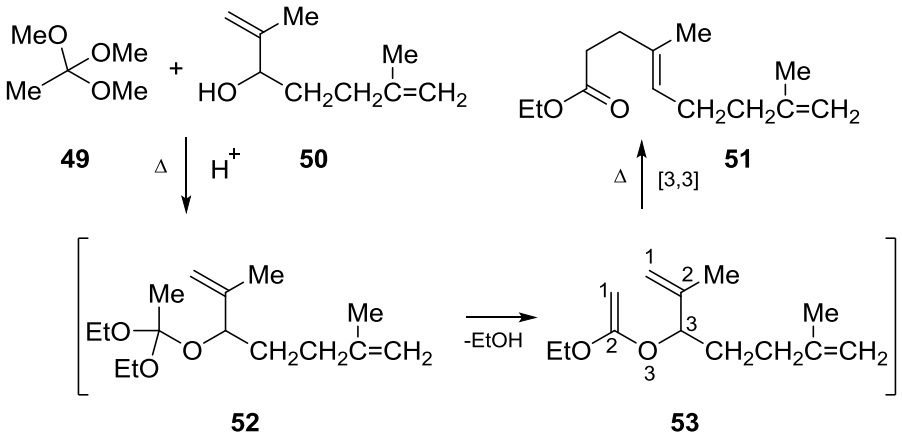
In 1964, Eschenmoser observed that the reaction of hydroxy-dimethylcyclohex-2-ene derivative **46** with 1,1-dimethoxy *N*,*N*-dimethylethan-1-amine gave an unpredictable product **48**. In this reaction, firstly *N*,*O*-ketene acetals **47** was formed, which was called as the Eshenmoser rearrangement, followed by the formation of γ,δ-unsaturated amide **48** (Scheme 13).[121]



46 **47** **48**

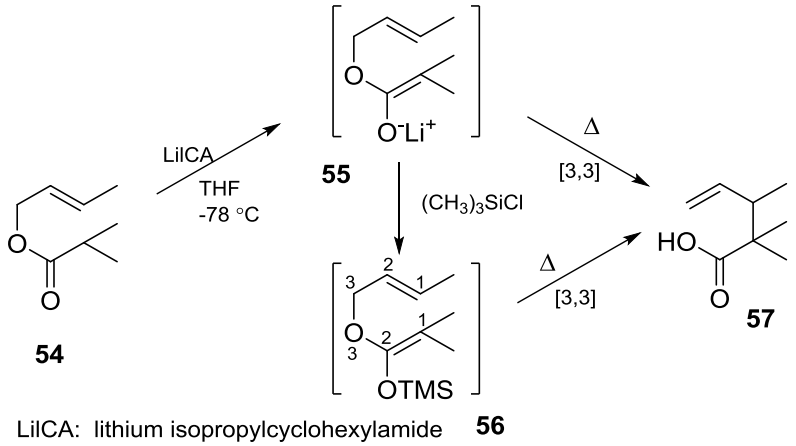
Scheme 13

In 1970, Johnson reported that γ,δ-unsaturated ester **51** was formed as a result of the rearrangement of ketene acetal **53**, prepared by reaction of trimethoxyethane **49** with allyllic alcohol **50** (Scheme 14).[122]



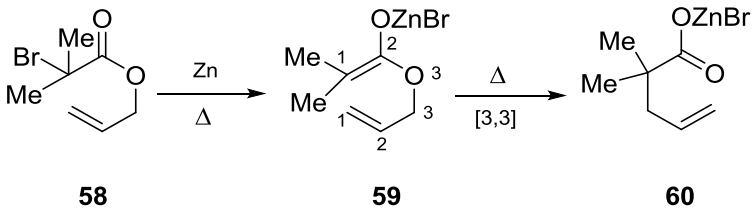
Scheme 14

The Ireland-Claisen rearrangement firstly reported in 1972 afforded the synthesis of γ,δ-unsaturated carboxylic acid **57** starting from ester **54**. The ester **54** was first converted into the corresponding enolate **55** which was trapped with trimethylsilyl chloride to furnish allyl trimethylsilyl keten acetals **56**. Upon heating, compound **56** underwent Claisen rearrangement to give product **57** (Scheme 15).[123]



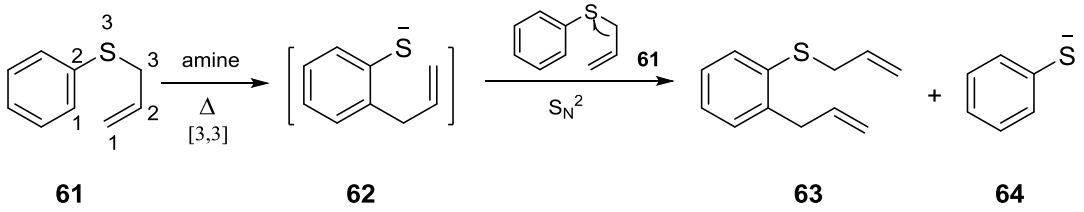
Scheme 15

Reformatsky-Claisen rearrangement is a thermal rearrangement of a zinc enolate **59** generated by the reaction of a α-bromo ester **58** with zinc dust. Heating of **59** furnished γ,δ-unsaturated zinc carboxylate **60** (Scheme 16).[124]



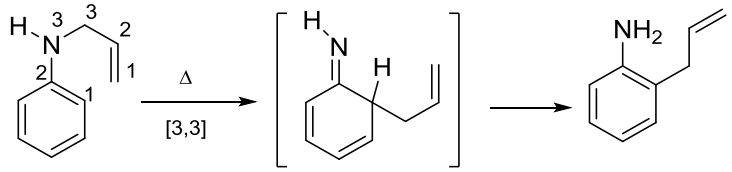
Scheme 16

Kwart and Schwartz reported that thermal rearrangement of allyl phenyl sulfide **61** produced thiol **62** that was not isolated. The intermediate **62** underwent a S_N2 type reaction with starting sulfide **61** under the same reaction conditions to afford diallyl derivative **63**. This methodology is called as thio-Claisen rearrangement (Scheme 17).[125]



Scheme 17

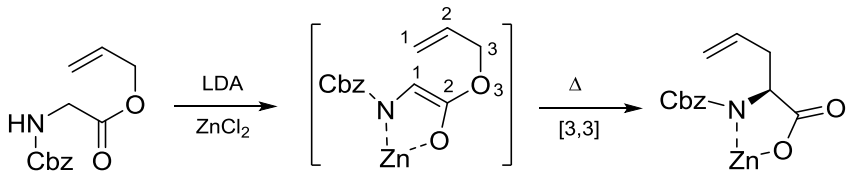
Jolidon and Hansen discovered the aza-Claisen rearrangement that is a thermal rearrangement of allyl arylamines **65.** This rearrangement required harsh conditions (200-350 °C) than the other Claisen rearrangements. (Scheme 18).[126]



65 **66** **67**

Scheme 18

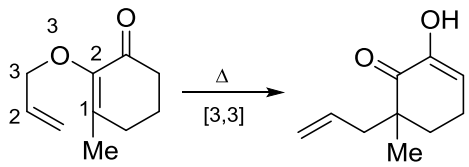
[3,3] sigmatropic rearrangement of a chelate enolate is called as chelate Claisen rearrangement. Reaction of a protected amino acid having an allylic group with $ZnCl_2$ in the presence of LDA results in the formation of the intermediate **69** that undergoes a Claisen rearrangement to form amino acid **70** (Scheme 19).[127]



68 **69** **70**

Scheme 19

In 1980, Ponaras developed an extremely new method, known as Diosphenol-Claisen rearrangement, for the preparation of diosphenol **72** affording the thermal rearrangement of allyl ether **71** at 200 °C (Scheme 20).[128]

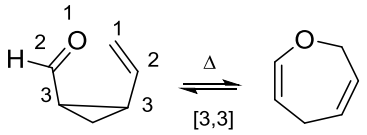


71 **72**

Scheme 20

Retro-Claisen rearrangement is a general process for a number of substrates including neighbour quarternary centers when the α-carbonyl substituent is not an

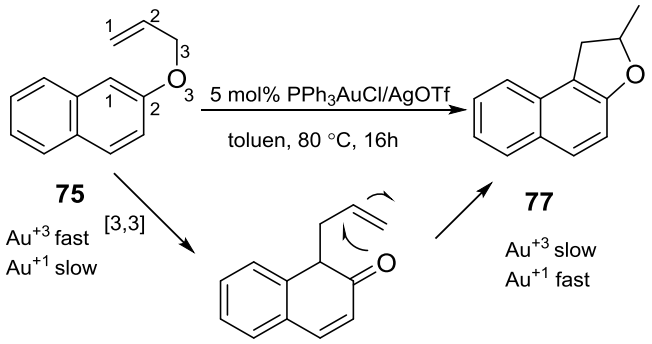
electron-releasing group For example, Rhoads and Cockroft reported the rearrangement of vinylcyclopropane carboxaldehyde **73** leading to formation of 2,5-dihydrooxepin **74** via retro-Claisen reaction (Scheme 21).[129]



73 **74**

Scheme 21

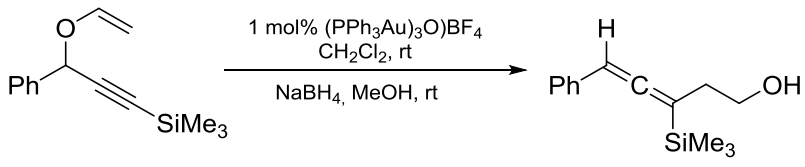
Gold-catalyzed sigmatropic rearrangements, especially Claisen rearrangements, have attracted intense research in past few decades. He and coworkers achieved the synthesis of dihydrobenzofurane derivative **77** by using gold-catalyzed Claisen rearrangements (Scheme 22).[130]



76

Scheme 22

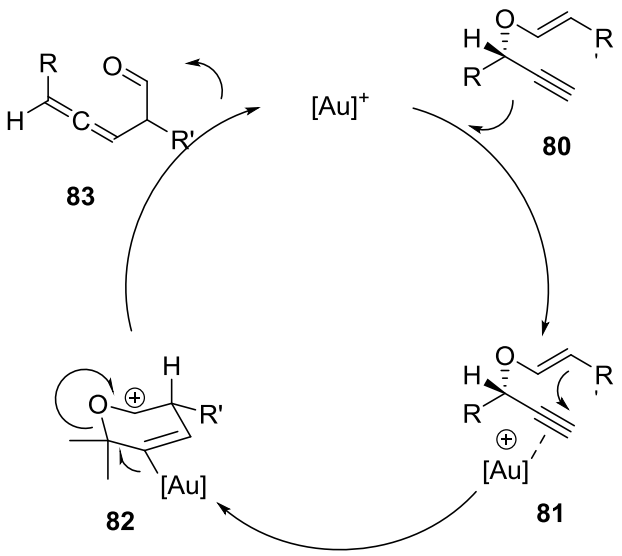
Important synthetic approach for Gold-catalyzed Claisen rearrangements was reported by Toste and coworkers.[131] In the presence of gold(I) and silylactylene **78**, Claisen rearrangements took place to obtain homoallenic alcohol **79** at room temperature (Scheme 23).



78 **79**

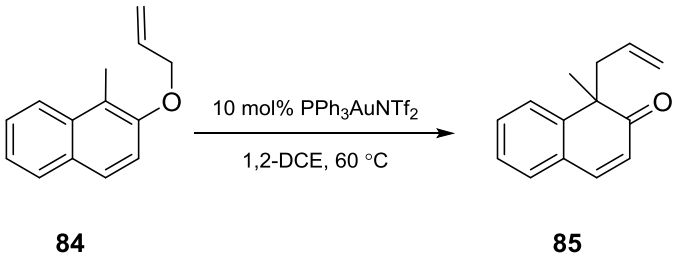
Scheme 23

According to the proposed mechanism for this reaction, firstly gold(I) catalyst coordinates to the alkyne functionality in **80**to generate more electrophilic alkyne which undergoes rearrangement to form cationic dihydropyran intermediate **82**. Removal of gold forms allenic aldehyde **83** (Scheme 23).[131]



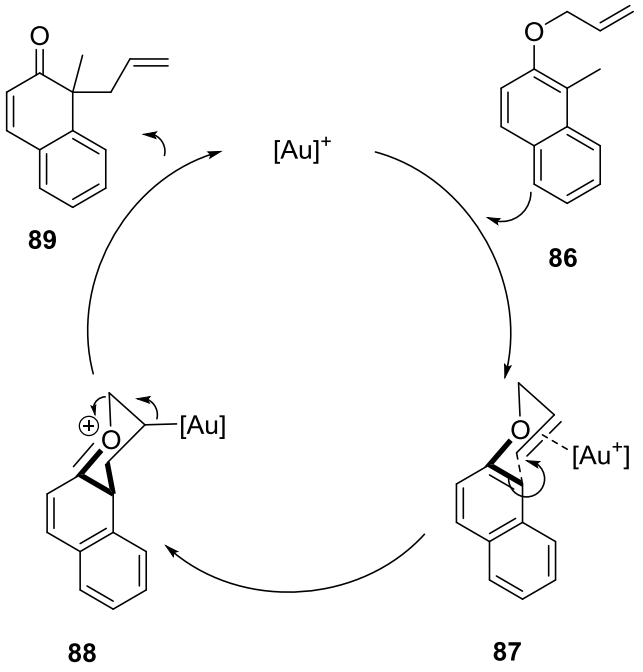
Scheme 24

Gagnè and coworkers reported that allyll aryl ethers **84** was converted to enones **85** in the presence of gold(I) catalyst and under the mild conditions via Claisen rearrangement reaction (Scheme 24).[132]



Scheme 25

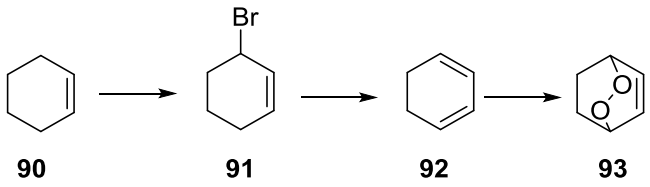
According to the proposed mechanism, firstly gold(I) catalyst coordinates the double bond in **87** forming a cationic chair like transition state **88**. Removal of gold generates enone **89** (Scheme 25).[132]



Scheme 26

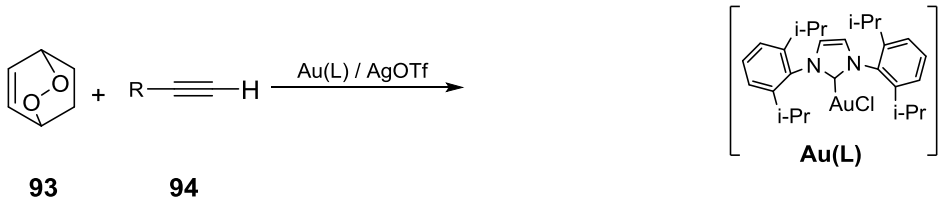
3.1.3 Aim of the Study

This part of this thesis focused on the reaction of bicyclic endoperoxides with gold salt because there is no study on this subject in the literature. Our aim was first to synthesize simple structured endoperoxide derived from cyclohexa-1,3-diene (**90**). So, cyclohexdiene (**92**) will be synthesized as reported in the literature starting from cyclohexene (**90**)by bromination with NBS followed by dehydrobromination to form **91**.. Reaction of cyclohexa-1,3-diene with singlet oxygen will result in the formation of the key compound named 2,3-dioxabicyclo[2.2.2]oct-5-ene (**93**) via [4+2] addition reaction (Scheme 26).[133]



Scheme 27

Synthesized simple structured endoperoxide **93** will be reacted with alkynes in the presence of Au(L)/AgOTf. The structures of the formed compounds will be determined and the formation mechanism of the products will be discussed. (Scheme 27).



93 **94**

Scheme 28

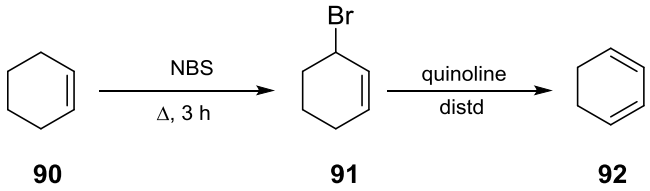
3.2 RESULTS AND DISCUSSION

Since there is no study in the literature involving the reaction of endoperoxides with gold salt, we decided to examine this reaction. At the beginning of our work, we wanted to study simple structured endoperoxide. So, we decided to synthesize firstly cyclohexa-1,3-diene and then the bicyclic endoperoxide derived from cyclohexa-1,3-diene.

3.2.1 Synthesis of Cyclohexa-1,3-diene (92)

To afford cyclohexa-1,3-diene (**92**), cyclohexene (**90**) was firstly treated with N-bromosuccinimide to generate 3-bromocyclohex-1-ene (**91**) which was distilled in the presence of quinoline to form the desired compound **92** (Scheme 28).[133]

The ^{1}H NMR spectrum (Fig 161 - p. 189) of compound **92** include three signals. Olefinic protons resonate at 5.82-5.76 and 5.72-5.65 ppm as multiplet. Methylene protons resonate at 2.05 ppm as quasi triplet**.**

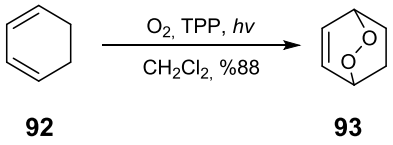


Scheme 29

3.2.2 Photooxygenation of the Cyclohexa-1,3-diene (92)

Tetraphenylporphyrin sensitized photooxygenation of cyclohexa-1,3-diene (**92**) in methylene chloride at room temperature for 18 h produced endoperoxide **93** (Scheme 29).[134]

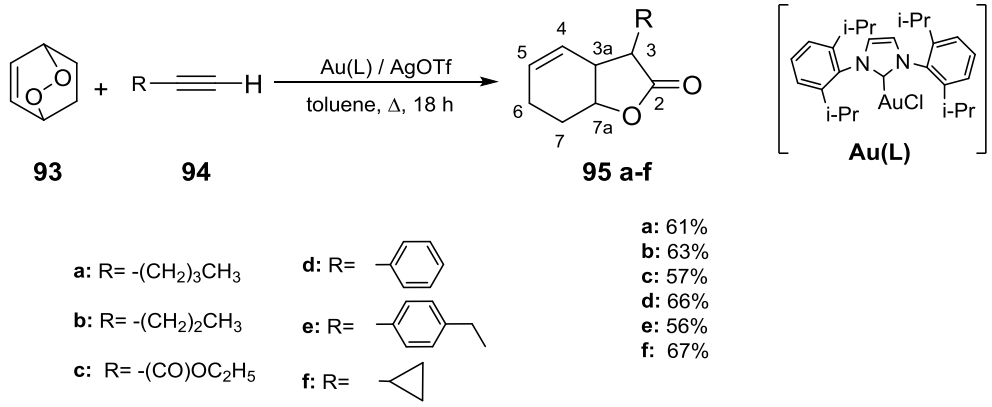
In the ^{1}H NMR spectrum (Fig 163 - p. 190) of **92**, two olefinic protons give multiplet at 6.62-6.57 ppm. Two bridgehead protons resonate at 4.60-4.55 ppm as a broad multiplet. Methylene protons resonate as an AB-systems.



Scheme 30

3.2.3 Reaction of Endoperoxide (93) with Alkyne Derivatives in Presence of Au(L)/AgOTf

After synthesis of key compound **93**, 2,3-dioxabicyclo[2.2.2]oct-5-ene, we treated endoperoxide **93** with alkyne derivatives **94** in the presence of Au(L)/AgOTf then we obtained new products **95** (Scheme 30).



Scheme 31

The structures of **95 a-f** were determined by 1D and 2D (DEPT, COSY, HSQC and HMBC) NMR spectral data. In the ^{1}H NMR spectrum (Fig 165 - p. 191) of **95a**, methine protons H-7a, H-3a and H-3 resonate at 4.64, 2.64-2.61 and 2.26, respectively. Olefinic protons resonate at 5.78 ppm as doublet of doublets of triplets (J = 9.9, 3.9 and 1.8 Hz) and 5.50 ppm as doublet of doublets of doublets (J = 9.9, 3.7 and 1.9 Hz).

In the ^{13}C NMR spectrum (Fig 166 - p. 192) a new carbonyl carbon was formed which resonates at 178.1 ppm. Furthermore, new formed olefinic carbons resonate at 127.3 and 125.0 ppm, respectively. The other signals of ^{13}C NMR spectrum were in accordance with the proposed structure.

HMBC spectrum has important correlations supporting the proposed structure. In the HMBC spectrum, we focused on the correlations of methine proton (H-3) with the carbon atoms. As expected, there are correlations between the H-3 and the carbons C-2, C-4, C-7a, C-3a, and C-8 or C-9. These correlations support the proposed structure (Figure 1).

The NMR spectra of the other derivatives **95b-95f** were also in agreement with the proposed structures.

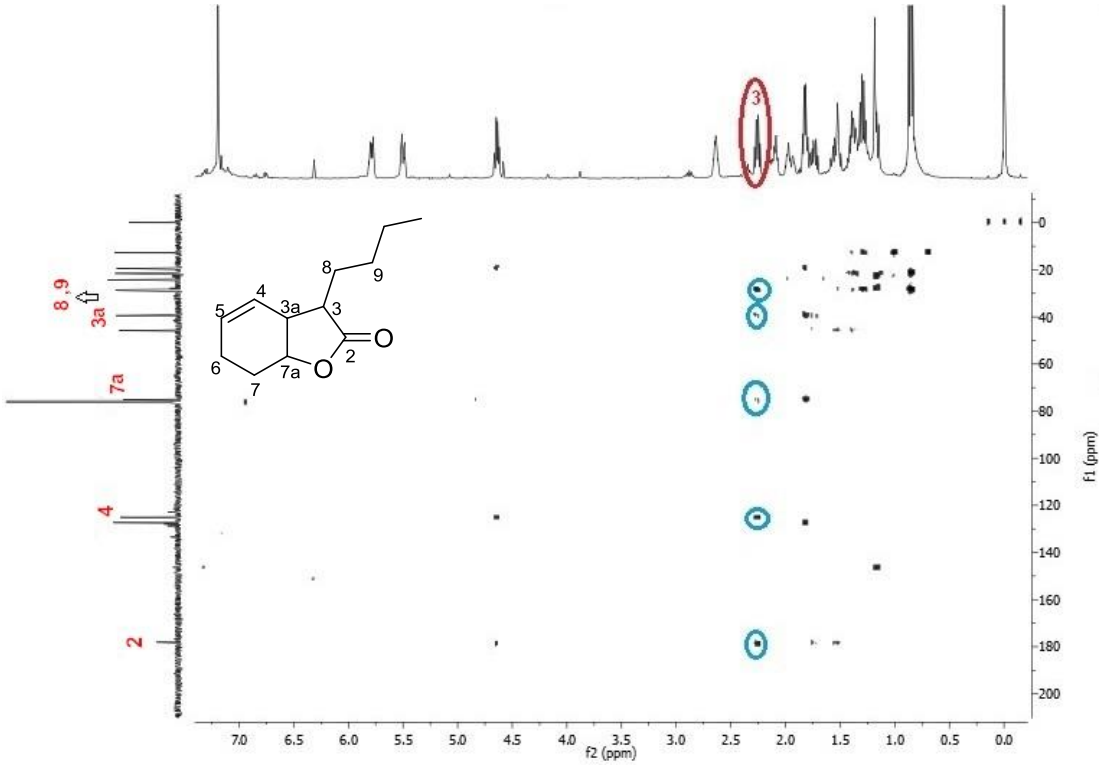
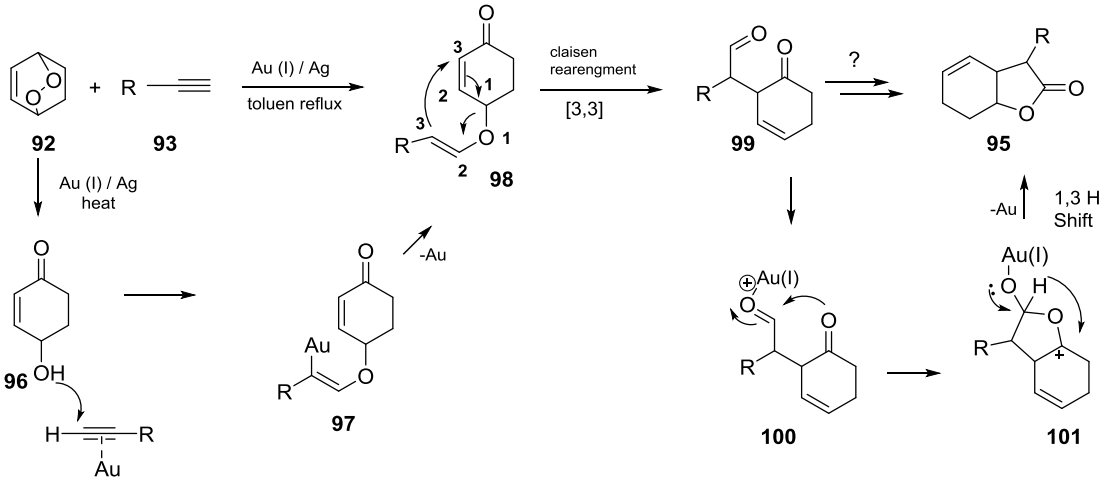


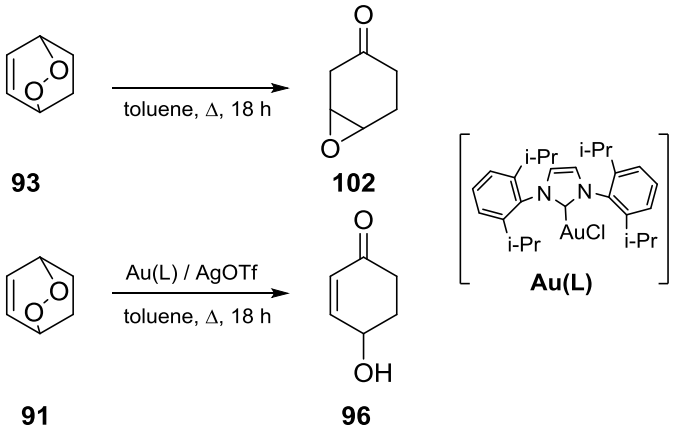
Figure 1: HMBC Spectrum of Compound 95a

For this transformation we suggest the following reaction mechanism. We assume that endoperoxide **93** first undergoes an isomerization reaction to form hydroxyenone **96**. We proved that Au(I) salt catalysizes this transformation. We did two different experiments to prove this transformation. Endoperoxide **93** was heated at the reflux temperature of toluene in the presence of Au(L)/AgOTf and in the absence of Au(L)/AgOTf. Hydroxy enone **96** was formed when the experiment was carried out in the presence of Au(L)/AgOTf catalysis. However, epoxy ketone **102** was formed in the absence of Au(L)/AgOTf catalyst (Sheme 32). Hydoxyl group of enone **96** can attack the alkyne complex formed by interaction of alkyne unit with Au^{1+} to

form an allylinyl ether **98** as the intermediate. The formed compound **98** has a suitable structure to undergo a [3,3] sigmatropic Claisen rearrangement to form the corresponding γ,δ-unsaturated dicarbonyl compound **99**. Ketone carbonyl unit can attack the activated aldehyde carbonyl unit in **100** to generate **101** which has tendency for 1,3-hydrogen shift to form target compound **95** (Scheme 31).

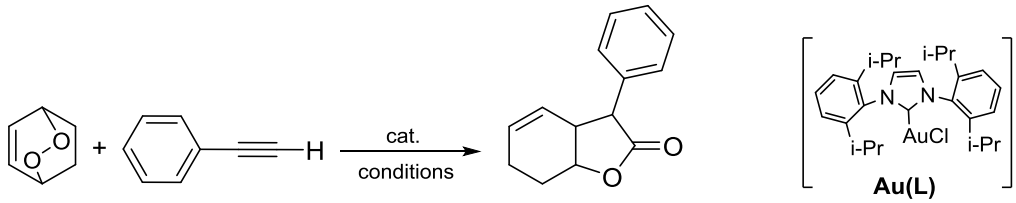


Scheme 32



Scheme 33

We tested five different catalyst in our reaction. Unfortunately, there was no reaction when the reaction was conducted with $AuCl_3$, AuCl, and N-hetereocyclic carbene (NHC) complex of Au(I) and AgOTf in toluene. But, reaction with Au(L)/AgOTf gave product **95d** after 18 h in 66% yield.



93 **94** **95d**

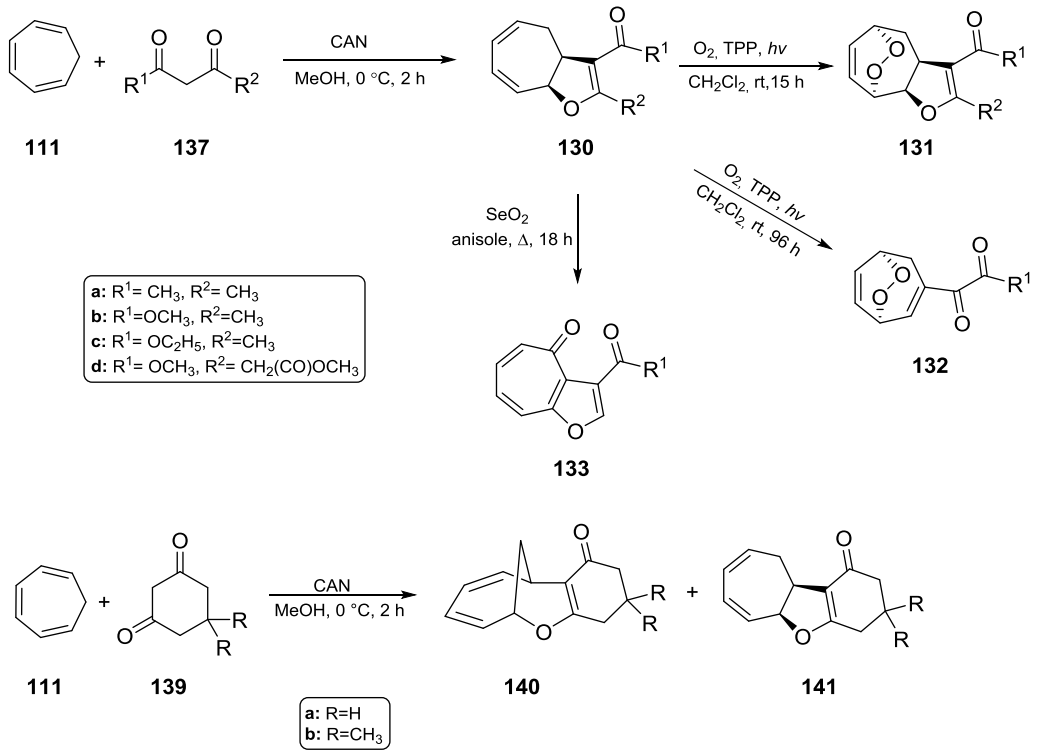
entery	***catalyst***	***solvent***	***condition***	***result***
1.	$AuCl_3$	toluene	18 h heat	no reaction
2.	AuCl	toluene	18 h heat	no reaction
3.	Au(L)	toluene	18 h heat	no reaction
4.	AgOTf	toluene	18 h heat	no reaction
5.	Au(L)/AgOTf	toluene	18 h heat	66%

Figure 2: Catalyst Screening on the Cyclization Reaction of 95d

CHAPTER 4

CONCLUSION

The oxidative free radical cyclization reaction is an important reaction because of fascinating regiochemistry and controversial reaction mechanism. We combined this radical cyclization with photoxygenation reaction and obtained very interesting results in terms of mechanistic studies.



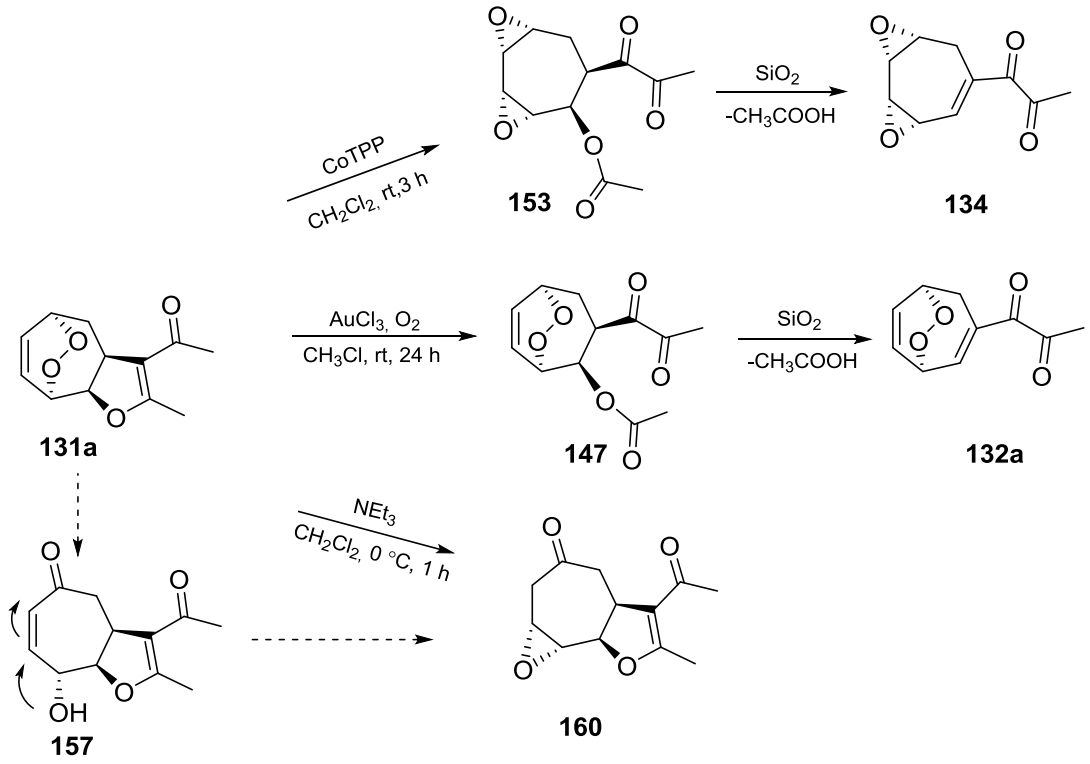
111 137 130 131 132 133 111 139 140 141

Scheme 1

First we synthesized dihydrocyclohepta[*b*]furan derivatives **130** by the reaction of cycloheptatriene (**111**) with various 1,3-dicarbonyl compounds **137**. On the other hand, when cycloheptatriene (**111**) was reacted with cyclic 1,3-diketone **139**, we observed two different ring closure products **140** and **141** (Scheme 1).

We performed three different reactions with dihydrocyclohepta[*b*]furan derivatives **130.** Photoxygenation of dihydrocyclohepta[*b*]furan derivatives **130** gave

endoperoxide derivatives **131**. Furthermore, when we increased the reaction time of photooxygenation of dihydrocyclohepta[*b*]furan derivatives **130**, surprisingly we obtained dicarbonyl compounds **132** where dihydrofuran ring underwent a cleavage reaction. However, the peroxide linkage was intact. Finally, oxidation reaction of dihydrocyclohepta[*b*]furan derivatives **130** with SeO_2 resulted in the formation of tropone derivatives **133** (Scheme 1).

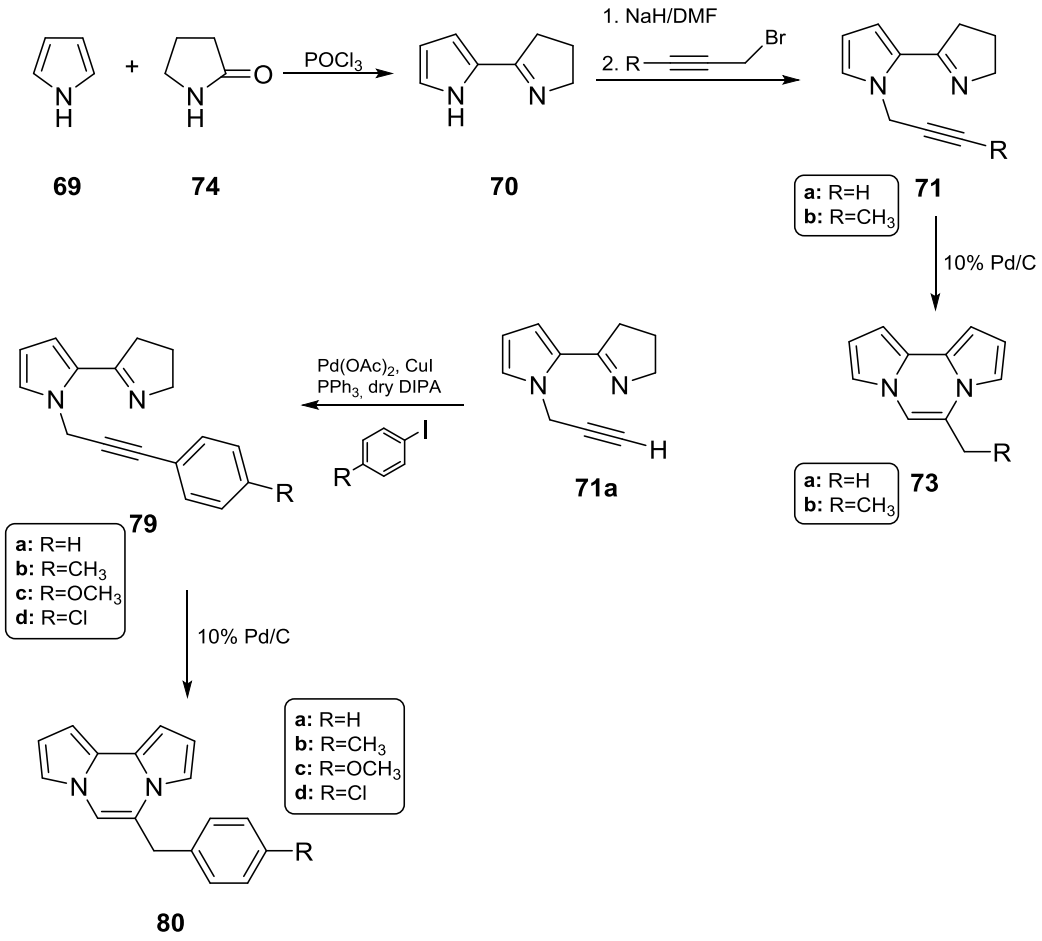


Scheme 2

Endoperoxide **131a** was reacted with CoTPP, $AuCl_3$ and NEt_3. Reaction of endoperoxide **131a** with CoTPP afforded bisepoxide **153** where the dihydrofuran ring underwent a ring-opening reaction. On the other hand, reaction of **131a** with $AuCl_3$ in the presence of oxygen caused an oxidative ring-opening reaction of the five-membered ring. The endoperoxide unit was intact against the $AuCl_3$. Reaction of endoperoxide with triethyl amine afforded compound **160**. We assume that the expected product α,β-unsaturated enone **157** was formed as the intermediate which was transformed into **160** under the reaction conditions. Furthermore, we assume that the suitable conformation of this intermediate was responsible for this transformation (Scheme 2).

In the second part, we synthesized pyrrolo-pyrazino-pyrrole derivatives. Pyrazines ring is an important heterocycle compound due to its various biological activities.

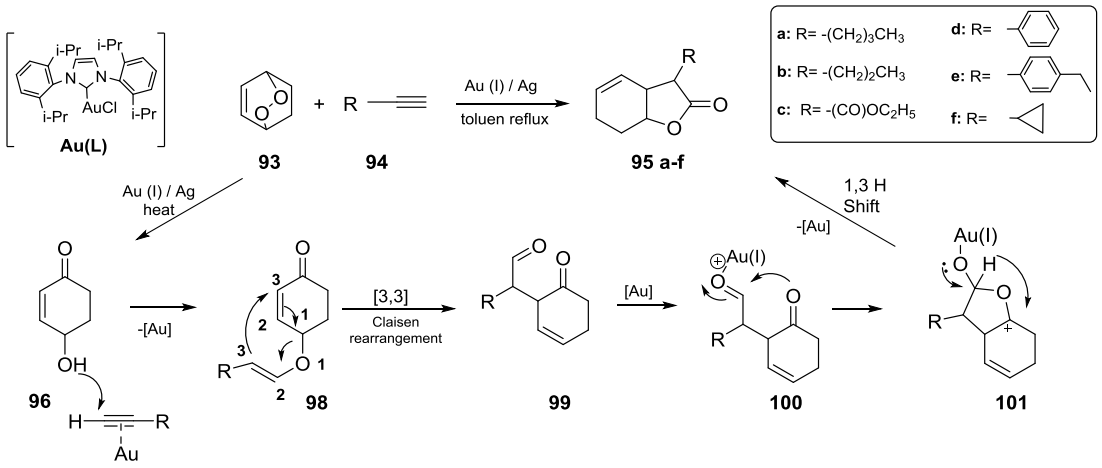
In the first step, we synthesized 2,2'-(1'-pyrrolinyl)pyrrole (**70**) from the reaction of pyrrole (**69**) and 2-pyrrolidinone (**74**). Then,2,2'-(1'-pyrrolinyl)pyrrole (**70**) was reacted with propargyl bromide derivatives to generate propargylated compounds **71**. 1-Prop-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**71a**) was derivatized via Sonogashira cross-coupling reaction. Propargylated compounds **71** and their derivatives **79** were reacted with Pd/C to form the target compounds, pyrrolo-pyrazino-pyrrole derivatives **73** and **80** (Scheme 3).



Scheme 3

In the third part, we developed a new methodology for the synthesis of α-alkylidine-γ-butyrolacton derivatives. Endoperoxide **93** was reacted with alkyne derivatives in the presence of Au(L)/AgOTf and we obtained unexpected product, α-alkylidine-γ-butyrolacton derivatives **95**. Au^{+1} plays an important role in this reaction. We assume

that Au^{+1} catalyzes thermal isomerization of endoperoxide **93** to give enone **96** as an intermediate that adds to the activated alkyne unit to form **98**. This product **98** contains an allyl vinyl ether which is suitable for a [3,3]-sigmatropic rearrangement to give dicarbonyl compound **99**. Cyclization of dicarbonyl compound results in the formation of the final product **95** (Scheme 4)..



Scheme 4

CHAPTER 5

EXPERIMENTAL

5.1 General

^{1}H-NMR and ^{13}C-NMR spectrums were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in $CDCl_3$, CD_3OD, DMSO-d_6, and with TMS as internal reference. Chemical shifts (δ) were reported in units parts per million (ppm). Spin multiplicities were specified as singlet (s), broad singlet (bs), doublet (d), broad doublet (bd), doublet of doublets (dd), doublet of triplets (dt), doublet of quartets (dq), doublet of doublets of doublets (ddd), triplet (t),triplet of doublets (td), quintet (quint), quasi triplet (quasi t) and multiplet (m) and coupling constants (J) were reported in Hertz (Hz).

HRMS data were recorded by Agilent Technologies, 6224 TOF LC/MS-T1200 Series applying the electrospray technique. GC-MS data were recorded by Agilent Technology 7890A using Agilent J&W GC HP-5MS, 30 m x 0.2500 mm x 0.25 μm (190915-433:325 °C)

Infrared spectra were recorded on a Bruker Platinum ATR FT-IR spectrometer in the range of 600-4000 cm^{-1}.

Melting points were reported by operating Gallenkamp electronic melting point apparatus.

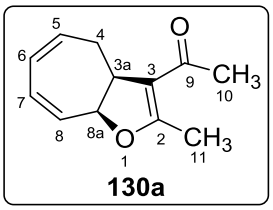
Column chromatography separations were done by using 60-mesh silica gel. Thin layer chromatography (TLC) was performed by using 0.20 mm silica gel 60 F254 aluminum plates.

Names of the compounds were established by using ACD/NMR.

All solvents and chemicals were commercially available and used without further purification.

5.2. 1-[(3a*S*,8a*S*)-2-methyl-4,8a-dihydro-3a*H*-cyclohepta[*b*]furan-3-yl]ethanone (130a)

To a solution of cycloheptatriene (**111**) (0.92 g, 10 mmol) in MeOH (50 mL) was added acetyl acetone **147a** (1.00 g, 10 mmol) and then the reaction mixture was cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise in 45 minutes and the solution was stirred for 75 minutes. After completion of reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:4) to give 1-[(3a*S*,8a*S*)-2-methyl-4,8a-dihydro-3a*H*-cyclohepta[*b*]furan-3-yl]ethanone (**130a**) (1.81 g, 9.52 mmol, 95%) as a colorless oil.



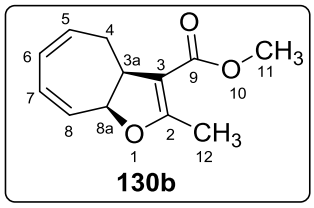
130a

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.21-6.12(m, H_5 and H_8), 6.05 (ddd, *J* = 12.0, 5.4, and 1.1 Hz, H_7), 5.97 (ddd, *J* = 10.1, 5.4, and 1.2 Hz, H_6), 5.01 (bd, *J* = 8.7, H_{8a}), 3.27 (bt, *J* = 10.1 Hz, H_{3a}), 2.35-2.29 (m, H_4), 2.28 (s, CH_3), 2.24 (s, CH_3), 2.03 (dddd, *J* = 16.2, 9.0, 5.3, and 2.0 Hz, H_4) . **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 193.6, 167.1, 134.6, 129.8, 127.2, 126.9, 118.2, 84.6, 51.8, 30.0, 29.1, 15.3. **IR** (ATR, cm^{-1}) 1716, 1609, 1393, 1340, 1217, 1204, 1203, 1066, 1027, 946, 900, 710; **HRMS** Calcd for ($C_{12}H_{14}O_2$) $[M + H]^+$: 191.1066; Found: 191.1065.

5.3 Methyl(3a*S*,8a*S*)-2-methyl-4,8a-dihydro-3a*H*-cyclohepta[*b*]furan-3-carboxylate (130b)

To a solution of cycloheptatriene (**111**) (0.92 g, 10 mmol) in MeOH (50 mL) was added methyl acetoacetate **147b** (1.16 g, 10 mmol) and then the reaction mixture cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise over a period of 45 minutes and the solution was stirred for 75 minutes. After completion of the reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was

washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:1) to give methyl (3a*S*,8a*S*)-2-methyl-4,8a-dihydro-3a*H*-cyclohepta[*b*]furan-3-carboxylate (**130b**) (1.78 g, 8.64 mmol, 86%) as a colorless oil.

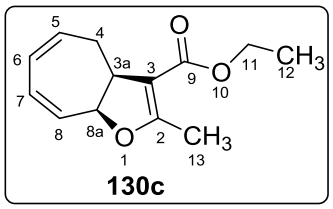


130b

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19-6.11 (m, H_5 and H_8), 6.02 (ddd, J = 11.9, 5.4, and 1.1 Hz, H_7), 5.98-5.93 (m, H_6), 5.03 (bd, J = 8.9 Hz, H_{8a}), 3.73 (s, O-CH_3), 3.22 (bt, J = 10.2 Hz, H_{3a}), 2.38 (ddd, J = 13.3, 8.3, and 1.5 Hz, H_4), 2.20 (s, CH_3), 2.03 (dddd, J = 13.3, 9.5, 5.5, and 1.8 Hz, H_4). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.7, 166.1, 134.5, 130.2, 126.9 (2C), 106.6, 84.5, 51.7, 50.7, 29.8, 14.1. **IR** (ATR, cm^{-1}) 3019, 2161, 1980, 1730, 1435, 1279, 1045, 928, 725, 668; **HRMS** Calcd for ($C_{12}H_{14}O_3$) $[M + H]^+$: 207.1015; Found: 207,1006.

5.4 Ethyl (3a*S*,8a*S*)-2-methyl-4,8a-dihydro-3a*H*-cyclohepta[*b*]furan-3-carboxylate (130c)

To a solution of cycloheptatriene (**111**) (0.92 g, 10 mmol) in MeOH (50 mL) was added ethyl acetoacetate **147c** (1.3 g, 10 mmol) and then the reaction mixture cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise over a period of 45 minutes and the solution was stirred for 75 minutes. After completion of the reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:1) to give ethyl (3a*S*,8a*S*)-2-methyl-4,8a-dihydro-3a*H*-cyclohepta[*b*]furan-3-carboxylate (130c) (1.63 g, 7.4 mmol, 74%) as a colorless oil.



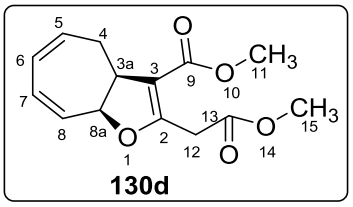
130c

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19-6.11 (m, H_5 and H_8), 6.00 (bdd, J = 11.5 and 5.5 Hz, H_7), 5.95 (bdd, J = 10.1 and 5.5 Hz, H_6), 5.02 (bd, J = 8.9 Hz, H_{8a}), 4.18 (m, CH_2), 3.22 (bt, J =10.1 Hz, H_{3a}), 2.40 (dd, J = 13.2 and 8.3 Hz, H_4), 2.20 (s, CH_3), 2.01 (dt, J = 13.2 and 4.8 Hz, H_4), 1.3 (t, J = 7.1 Hz, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.1, 165.4, 134.4, 130.3 126.9, 126.8, 106.7,

84.3, 59.2, 51.8, 29.8, 14.3, 14.0. **IR** (ATR, cm^{-1}) 2977, 1690, 1638, 1439, 1380, 1340, 1312, 1199, 1102, 1076, 1021, 975, 905, 771; **HRMS** Calcd for ($C_{13}H_{16}O_3$) [M + H]$^+$: 221.1172; Found: 221.1165.

5.5 Methyl (3a*S*,8a*S*)-2-(2-methoxy-2-oxoethyl)-4,8a-dihydro-3a*H*-cyclohepta[*b*]furan-3-carboxylate(130d)

To a solution of cycloheptatriene (**111**) (0.92 g, 10 mmol) in MeOH (50 mL) was added ethyl acetoacetate **147d** (1.74 g, 10 mmol) and then the reaction mixture cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise over a period of 45 minutes and the solution was stirred for 75 minutes. After completion of the reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:4) to give methyl (3a*S*,8a*S*)-2-(2-methoxy-2-oxoethyl)-4,8a-dihydro-3a*H*-cyclohepta[*b*]furan-3-carboxylate(130d) (1.81 g, 6.85 mmol, 68%) as a colorless oil.

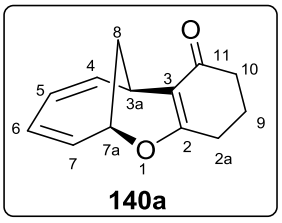


130d

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19-6.15 (m, H_5 and H_8), 6.04 (ddd, J = 12.1, 5.4 and 1.7 Hz, H_7), 5.97 (ddd, J = 10.3, 5.4 and 1.1 Hz, H_6), 5.14 (bd, J = 9.0 Hz, H_{8a}), 3.88 (d, A-part of AB-system, J =16.3 Hz, H_{12}), 3.73 (s, OCH_3), 3.72 (s, OCH_3), 2.62 (d, B-part of AB-system, J = 16.3 Hz, H_{12}), 3.27 (bt, J= 9.7 Hz, H_{3a}), 2.40 (ddd, J = 13.4, 8.2 and 1.9 Hz, H_4), 2.08 (ddd, J = 13.4, 5.0 and 1.9 Hz, H_4),. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.6, 165.3, 162.5, 134.3 129.9, 127.2, 127.1, 109.2, 85.2, 52.2, 51.5, 51.0, 33.8, 29.6. **IR** (ATR, cm^{-1}) 2951, 1743, 1697, 1643, 1435, 1404, 1369, 1319, 1226, 1199, 1163, 1063, 1014, 973, 902, 846, 763, 675, 640; **HRMS** Calcd for ($C_{14}H_{16}O_5$) [M + H]$^+$: 265.1070; Found: 265,1080.

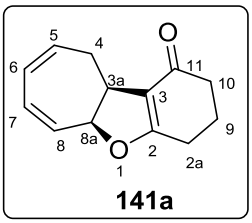
5.6 (2*S*,7*R*)-7,9,10,11-tetrahydro-2,7-methano-1-benzoxonin-8(2*H*)-one (140a) and (5a*R*,10a*R*)-2,3,4,5a,10,10a-hexahydro-1*H*-benzo[*b*]cyclohepta[*d*]furan-1-one (141a)

To a solution of cycloheptatriene (**111**) (0.92 g, 10 mmol) in MeOH (50 mL) was added 1,3-cyclohexanadione (**139a**) (1.12 g, 10 mmol) and then the reaction mixture cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise over a period of 45 minutes and the solution was stirred for 75 minutes. After completion of the reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:1) to give (2*S*,7*R*)-7,9,10,11-tetrahydro-2,7-methano-1-benzoxonin-8(2*H*)-one (140a) (0.65 g, 3.2 mmol, 32%) as a light yellow colored solid from CH_2Cl_2/n-hexane, Mp: 71-73 °C and (5a*R*,10a*R*)-2,3,4,5a,10,10a-hexahydro-1*H*-benzo[*b*]cyclohepta[*d*]furan-1-one (141a) (0.78 g, 3.86 mmol, 38%) as a light yellow colored solid from CH_2Cl_2/n-hexane, Mp: 87-89 °C.



140a

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (dd, J = 10.7 and 8.7 Hz, H_4), 5.95 (ddd, J = 11.8, 7.3, and 0.6 Hz, H_6), 5.79 (dd, J = 11.8 and 6.3 Hz, H_7), 5.68 (dd, J = 10.7 and 7.3 Hz, H_5), 4.92 (ddt, J = 5.9, 4.2, and 2.0 Hz, H_{7a}), 3.39 (bt, J = 6.3 Hz, H_{3a}), 2.32-2.13 (m, 5H), 1.87-1.80 (m, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.5, 169.9, 139.1, 129.6, 128.8, 123.2, 114.5, 72.4, 36.7, 28.4, 28.3, 27.4, 20.6. **IR (ATR, cm^{-1})** 3018, 1606, 1386, 1214, 725, 668; **HRMS** Calcd for ($C_{13}H_{14}O_2$) $[M + H]^+$: 203.1066; Found: 203,1069.

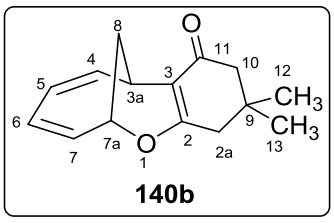


141a

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.16 (m, H_5 and H_8), 5.97 (ddd, J = 11.4, 5.4, and 2.0 Hz, H_7), 5.90 (ddd, J = 10.4, 5.4, and 1.1 Hz, H_6), 5.12 (bd, J = 9.3 Hz, H_{8a}), 3.37 (bt, J = 9.9 Hz, H_{3a}), 2.45 (ddd, J = 13.4, 8.2, and 2.1 Hz, H_4), 2.41-2.34 (m, 2H), 2.30-2.24 (m, 2H), 2.0-1.95 (m, 2H), 1.87 (ddd, J = 13.4, 5.0, and 2.1 Hz, H_4). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.2, 175.0, 133.8, 129.2, 126.4, 126.1, 116.2, 86.3, 49.3, 35.7, 28.5, 22.8, 20.6. **IR** (ATR, cm^{-1}) 1967, 1722, 1615, 1393, 1216, 1066, 725, 668; **HRMS** Calcd for ($C_{13}H_{14}O_2$) $[M + H]^+$: 203.1066; Found: 203,1061.

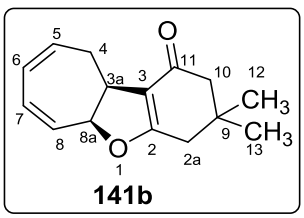
5.7 (2*S*,7*R*)-10,10-dimethyl-7,9,10,11-tetrahydro-2,7-methano-1-benzoxonin-8(2*H*)-one (140b) and (5a*R*,10a*S*)-3,3-dimethyl-2,3,4,5a,10,10a-hexahydro-1*H*-benzo[*b*]cyclohepta[*d*]furan-1-one (141b)

To a solution of cycloheptatriene (**111**) (0.92 g, 10 mmol) in MeOH (50 mL) was added dimedone (**139b**) (1.4 g, 10 mmol) and then the reaction mixture cooled down 0 °C. To this mixture was added a solution of (10.96 g, 20 mmol) CAN in MeOH (100 mL) dropwise over a period of 45 minutes and the solution was stirred for 75 minutes. After completion of the reaction, the reaction mixture was evaporated and the residue was dissolved in EtOAc then the organic phase was washed with water. After evaporation of the solvent the residue was chromatographed on silica gel (50 g), eluting with ethyl acetate/hexane (1:2) to give **(**2*S*,7*R*)-10,10-dimethyl-7,9,10,11-tetrahydro-2,7-methano-1-benzoxonin-8(2*H*)-one (140b) (0.68 g, 2,95 mmol, 29%) as a light white colored solid from CH_2Cl_2/n-hexane, Mp: 83-85 °C and (5a*R*,10a*R*)-2,3,4,5a,10,10a-hexahydro-1*H*-benzo[*b*]cyclohepta[*d*]furan-1-one (141a) (0.75 g, 3.26 mmol, 32%) as a white colored solid from CH_2Cl_2/n-hexane, Mp: 65-68 °C.



140b

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44 (bt, J = 10.5 Hz, H_4), 6.0 (dd, J = 11.8 and 6.2 Hz, H_6), 5.87 (dd, J = 11.8 and 6.1 Hz, H_7), 5.77 (dd, J = 11.0 and 6.2 Hz, H_5), 5.03-4.95 (m, H_{7a}), 3.47 (bt, J = 6.2 Hz, H_{3a}), 2.28-2.22 (m, $CH_{2(10)}$, H_8), 2.21-2.18 (m, $CH_{2(2a)}$), 1.93 (dd, J = 16.0 and 1.1 Hz, H_8), 1.02 (s, CH_3), 1.0 (s, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 196.7, 168.1, 138.8, 129.3, 129.0, 123.1, 113.0, 72.2, 50.4, 42.1, 31.8, 28.8, 27.9, 27.5, 27.3. **IR** (ATR, cm^{-1}) 2987, 2900, 2834, 2159, 2016, 1977, 1650, 1616, 1378, 1082, 1066, 1056; **HRMS** Calcd for ($C_{15}H_{18}O_2$) $[M + H]^+$: 231.1379; Found: 231.1386.



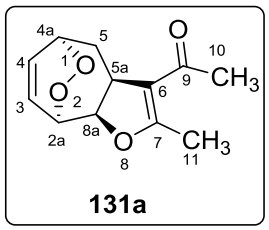
141b

^{1}H NMR (400 MHz, $CDCl_3$) δ, 6.15-6.08 (m, H_5 and H_8), 5.98 (ddd, J = 12.0, 5.4 and 1.7 Hz, H_7), 5.90 (ddd, J = 10.4, 5.4 and 1.1 Hz, H_6), 5.13 (bd, J = 9.1 Hz, H_{8a}), 3.36 (bt, J = 10.2 Hz, H_{3a}), 2.45 (ddd, J = 13.4, 8.4 and 2.0 Hz, H_4), 2.23 (s, $CH_{2(10)}$), 2.23 (d, J = 10.2 Hz , $CH_{2(2a)}$), 1.88 (ddt, J = 13.4, 5.3, and 1.8 Hz, H_4), 1.05 (s, CH_3), 1.02 (s, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 194.2, 175.0, 133.8, 129.2, 126.4, 126.1, 116.2, 86.3, 50.4, 42.1, 31.8, 28.8, 27.9, 27.5, 27.3. **IR** (ATR, cm^{-1}) 2968, 2900, 2834, 2160, 2017, 1977,

1697, 1614, 1455, 1394, 1255, 1049; **HRMS** Calcd for ($C_{15}H_{18}O_2$) $[M + H]^+$: 231.1379; Found: 231.1385.

5.8 1-[(3a*R*,5*S*,8*S*,8a*R*)-2-Methyl-4,8a-dihydro-3a*H*-5,8-epidioxycyclohepta[*b*]furan-3-yl]ethanone (131a)

Dihydro cyclohepta[*b*]furan derivative **130a** (0.380 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg) was dissolved in CH_2Cl_2 (50 mL) in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) overnight while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (2:1) to give 1-[(3a*R*,5*S*,8*S*,8a*R*)-2-methyl-4,8a-dihydro-3a*H*-5,8-epidioxycyclohepta[*b*]furan-3-yl]ethanone **(131a)** (0.351 g, 79%) as a colorless oil.



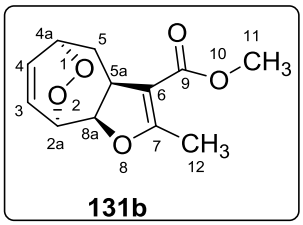
131a

^{1}H NMR (400 MHz, $CDCl_3$) δ), 6.57 (dd, A-part of AB-system, J = 9.10 and 7.1 Hz, H_4), 6.47 (dd, B-part of AB-system, J = 9.10 and 6.8 Hz, H_3), 5.12-5.08 (m, H_{2a}), 5.07 (bt, J = 4.9 Hz, H_{8a}), 4.64 (t, J = 6.8 Hz, H_{4a}), 2.53 (quintet, J = 6.4 Hz, H_{5a}), 2.11 (ddt, J = 15.5 and 12.8 Hz, H_5), 1.65 (dd, J = 15.5 and 6.7 Hz, 1H), H_5), 1.59 (s, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.6, 168.4, 134.2, 124.4, 118.8, 84.5, 76.2, 73.8, 38.2, 35.4, 28.2, 14.8. **IR** (ATR, cm^{-1}) 2988, 2900, 1732, 1715, 1698, 1624, 1416, 1375, 1229, 1188, 1148, 1065; 705 666, 641, 619 **HRMS** Calcd for ($C_{12}H_{14}O_4$) $[M + H]^+$: 223.0964; Found: 223.0961.

5.9 Methyl (3a*R*,5*S*,8*S*,8a*R*)- 2-methyl-4,8a-dihydro-3a*H*-5,8-epidioxycyclohepta[*b*]furan-3-carboxylate (131b)

Dihydro cyclohepta[*b*]furan derivative **130b** (0.412 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg) was dissolved in CH_2Cl_2 (50 mL) in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) overnight while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (1:2) to give methyl (3a*R*,5*S*,8*S*,8a*R*)- 2-

methyl-4,8a-dihydro-3a*H*-5,8-epidioxycyclohepta[*b*]furan-3-carboxylate (**131b**): (0.365 g, 76%) as a colorless oil.

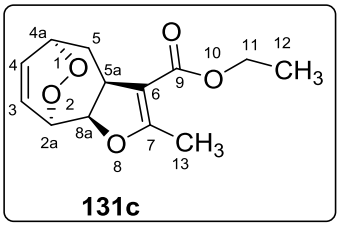


131b

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (dd, A-part of AB-system, J = 9.1 and 7.1 Hz, H_3), 6.42 (ddd, B-part of AB-system, J = 9.1, 6.8 and 0.9 Hz, H_4), 5.09 (dt, J = 6.5 and 2.3 Hz, H_{2a}), 4.96 (bt, J = 6.3 Hz, H_{4a}), 4.66 (dd, J = 9.1 and 2.8 Hz, H_{8a}), 3.75 (s, OCH_3), 3.14 (bq, J = 9.2 Hz, H_{5a}), 2.7 (ddd, J =14.2, 7.7, and 6.4 Hz, H_5), 2.23 (s, CH_3), 2.20-2.14 (m, H_5). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 170.2, 166.1, 135.1, 125.5, 107.9, 85.6, 77.2, 74.9, 50.8, 38.7, 36.5, 14.5. **IR** (ATR, cm^{-1}) 3015, 2988, 2900, 1685, 1637, 1438, 1356, 1333, 1299,1223, 1161, 1089, 1039, 983; 953, 891, 839, 700, 666, 617, **HRMS** Calcd for ($C_{12}H_{14}O_5$) $[M + H]^+$: 239.0914; Found: 239.0912.

5.10 Ethyl (3a*R*,5*S*,8*S*,8a*R*)- 2-methyl-4,8a-dihydro-3a*H*-5,8-epidioxycyclohepta[*b*]furan-3-carboxylate (131c)

Dihydro cyclohepta[*b*]furan derivative **130c** (0.440 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg)was dissolved in CH_2Cl_2 (50 mL) in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) overnight while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (1:4) to give ethyl (3a*R*,5*S*,8*S*,8a*R*)- 2-methyl-4,8a-dihydro-3a*H*-5,8-epidioxycyclohepta[*b*]furan-3-carboxylate (**131c**) (0.352 g, 69%) as a colorless oil.



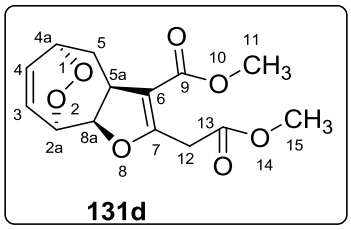
131c

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (dd, A-part of AB-system, J = 9.1 and 7.1 Hz, H_3), 6.42 (ddd, B-part of AB-system, J = 9.1, 7.5, and 0.9 Hz, H_4), 5.09 (bd, J = 6.3, H_{2a}), 4.96 (bt, J = 6.0 Hz, H_{4a}), 4.66 (dd, J = 9.2 and 2.8 Hz, H_{8a}), 4.21-4.12 (m, $CH_{2(11)}$), 3.19-3.14 (m, H_{5a}), 2.70 (ddd, J =14.3, 7.7, and 6.5 Hz, H_5), 2.24 (s, CH_3), 2.23-2.21 (m, H_5) 1.27 (bt, J = 7.1 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 165.7, 135.1, 125.5, 108.1, 85.5, 77.2, 74.9, 59.5, 38.8, 36.6, 14.5, 14.4. IR (ATR, cm^{-1}) 3023, 2953,

1740, 1694, 1645, 1437, 1403, 1321, 1214, 1166, 1108, 1066, 1015, 973, 846, 706, 667; HRMS Calcd for ($C_{13}H_{16}O_5$) $[M + H]^+$: 253.1070; Found: 253.1076.

5.11 Methyl (3a*R*,5*S*,8*S*,8a*R*)- 2-(2-methoxy-2-oxoethyl)-4,8a-dihydro-3a*H*-5,8-epidioxycyclo-hepta[*b*]furan -3-carboxylate (131d)

Dihydro cyclohepta[*b*]furan derivative **130d** (0.530 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg) was dissolved in CH_2Cl_2 (50 mL) in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) overnight while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (1:2) to give methyl (3a*R*,5*S*,8*S*,8a*R*)- 2-(2-methoxy-2-oxoethyl)-4,8a-dihydro-3a*H*-5,8-epidioxycyclo-hepta[*b*]furan -3-carboxylate (**131d**) (0.394 g, 66%) as a colorless oil.



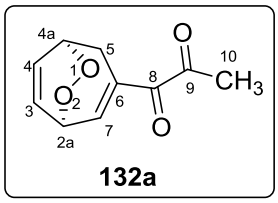
131d

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (dd, A-part of AB-system, J = 9.3 and 7.0 Hz, H_3), 6.43(ddd, B-part of AB-system, J = 9.3, 6.8 and 0.9 Hz, H_4), 5.11 (dt, J = 6.8 and 2.0 Hz, H_8), 4.79 (dd, J = 9.2 and 2.8 Hz, H_{8a}), 4.70 (bt, J = 6.5 Hz, H_{4a}), 4.03 (d, A-part of AB-system, J = 16.5 Hz, H_{12}), 3.73 (s, OCH_3), 3.71 (s, OCH_3), 3.50 (d, B-part of AB-system, J =16.5 Hz, H_{12}), 3.22 (q, J = 8.8 Hz, H_{5a}), 2.70 (ddd, J =15.5, 7.7, and 6.5 Hz, H_5), 2.25 (dd, J =15.5 and 10.5 Hz, H_5). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 168.6, 165.3, 164.9, 135.2, 125.4, 110.4, 86.3, 77.1, 74.7, 52.4, 51.1, 38.6, 36.3, 34.2. **IR** (ATR, cm^{-1}) 2988, 2900, 2159, 2017, 1978, 1743, 1705, 1632, 1435, 1373, 1327, 1194, 1124, 1053; **HRMS** Calcd for ($C_{14}H_{16}O_5$) $[M + H]^+$: 297.0979; Found: 297.0973.

5.12 1-[(1*S*,5*S*)-6,7-Dioxabicyclo[3.2.2]nona-2,8-dien-3-yl]propane-1,2-dione (132a)

Dihydro cyclohepta[*b*]furan derivative **130a** (0.380 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg) was dissolved in 50 mL of CH_2Cl_2 in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) for 96 h while the dry oxygen was bubbled through the

solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (1:2) to give 1-[(1*S*,5*S*)-6,7-dioxabicyclo[3.2.2]nona-2,8-dien-3-yl]propane-1,2-dione (**132a**) (0.320 g, 82%) as a colorless oil.

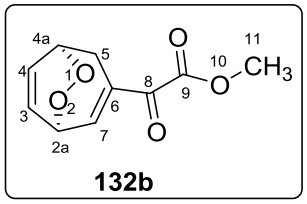


132a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (bd, J = 6.8, H_7), 6.73 (bdt, J = 8.9 and 0.9 Hz, H_3), 6.51 (dt, J = 8.7 and 1.0 Hz, H_4), 5.02-4.94 (m, H_{2a} and H_{4a}), 3.13 (ddd, A-part of AB-system, J = 19.4, 7.04 and 2.0 Hz, H_5), 2.70 (dt, B-part of AB-system, J = 19.4 and 1.3 Hz, H_5), 2.4 (s, CH_3). **^{13}C NMR (**100 MHz, $CDCl_3$) δ 200.1, 193.3, 146.5, 136.6, 131.8, 128.5, 75.0, 72.3, 33.2, 26.6. **IR** (ATR, cm^{-1}) 2159, 2017, 1978, 1743, 1705, 1632, 1435, 1373, 1327, 1254, 1194, 1124, 1084, 1053, 582; **HRMS** Calcd for ($C_{10}H_{10}O_4$) $[M + H]^+$: 195.0651; Found: 195.0658.

5.13 Methyl (1*S*,5*S*)-6,7-dioxabicyclo[3.2.2]nona-2,8-dien-3-yl(oxo)acetate (132b)

Dihydro cyclohepta[*b*]furan derivative **130b** (0.412 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg) was dissolved in 50 mL of CH_2Cl_2 in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) for 96 h while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (1:2) to give methyl (1*S*,5*S*)-6,7-dioxabicyclo[3.2.2]nona-2,8-dien-3-yl(oxo)acetate (**132b**) (0.331 g, 78%) as a colorless oil.



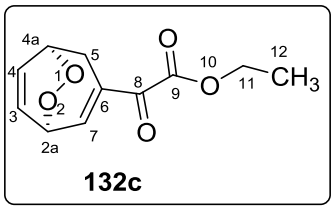
132b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dt, J = 6.8 and 1.6 Hz, H_7), 6.73 (bdd, J = 8.6 and 1.1 Hz, H_3), 6.51 (ddd, J = 8.6, 7.4 and 1.0 Hz, H_4), 5.02-4.95 (m, H_{2a} and H_{4a}), 3.90 (s, OCH_3), 3.14 (ddd, A-part of AB-system, J = 19.3, 4.5 and 1.8 Hz, H_5), 2.74 (dt, B-part of AB-system, J = 19.3 and 1.3 Hz, H_5). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.2, 187.6, 146.6, 137.8, 131.6, 128.6, 74.9, 72.2, 52.8, 33.0. **IR** (ATR, cm^{-1}) 2988, 2900, 2833, 2159, 2017, 1977, 1867, 1688, 1680, 1540, 1521,

1410, 1065, 1046; **HRMS** Calcd for ($C_{10}H_{10}O_5$) $[M + H]^+$: 211.0601; Found: 211.0608.

5.14 Ethyl (1*S*,5*S*)-6,7-dioxabicyclo[3.2.2]nona-2,8-dien-3-yl(oxo)acetate (132c)

Dihydro cyclohepta[*b*]furan derivative **130c** (0.440 g, 2 mmol) and a catalytic amount of tetraphenylporphine (TPP) (20 mg) was dissolved in 50 mL of CH_2Cl_2 in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) for 96 h while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (40 g), eluting with ethyl acetate/hexane (1:2) to give ethyl (1*S*,5*S*)-6,7-dioxabicyclo[3.2.2]nona-2,8-dien-3-yl(oxo)acetate (**132c**) (0.312 g, 69%) as a colorless oil.

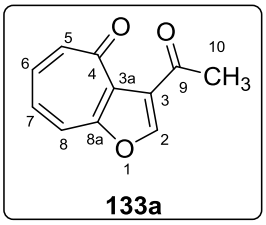


132c

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 6.7 Hz, H_7), 6.73 (bt, J = 8.8, H_3), 6.51 (bt, J = 8.6 Hz, H_4), 5.05-4.95 (m, H_{2a} and H_{4a}), 4.35 (dd, J= 7.2 and 2.0 Hz, $CH_{2\ (11)}$), 3.14 (ddd, A-part of AB-system, J = 19.4, 4.9 and 1.9 Hz, H_5), 2.73 (dd, B-part of AB-system, J = 19.4 and 1.9 Hz, H_5), 1.37 (t, J = 7.2 Hz, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.0, 163.4, 146.4, 137.8, 131.6, 128.6, 74.9, 72.2, 74.9, 72.2, 62.4, 33.0, 14.1. **IR** (ATR, cm^{-1}) 2988, 2900, 2160, 2030, 1978, 1769, 1716, 1682, 1594, 1540, 1476, 1424, 1267, 1148, 1215, 1066;

5.15 3-Acetyl-4*H*-cyclohepta[*b*]furan-4-one (133a)

To a solution of dihydro cyclohepta[*b*]furan derivative **130a** (0.380 g, 2 mmol) in anisole (15 mL) was added SeO_2 (0.888 g, 8 mmol) and the reaction mixture was heated at the reflux temperature for 18 h. After completion of the reaction, the mixture was cooled, filtered and evaporated. The residue was chromatographed on silica gel (45 g), eluting with ethyl acetate/hexane (4:1) to give 3-acetyl-4*H*-cyclohepta[*b*]furan-4-one (**133a**) (0.276 g, 73%) as a light yellow colored solid from CH_2Cl_2/n-hexane, Mp: 87-89 °C.

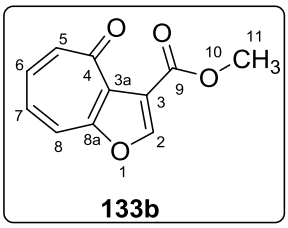


133a

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, J = 11.2 Hz, H_5), 7.64 (dd, J = 11.2 and 8.9 Hz, H_6), 7.54-7.49 (m, H_8), 7.52 (s, H_2), 7.36 (ddd, J = 11.5, 8.5 and 4.0 Hz, H_7), 2.58 (s, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 195.1, 167.6, 159.2, 153.3, 140.8, 136.5, 135.0, 131.7, 120.1, 103.6, 30.1. **IR** (ATR, cm^{-1}) 2988, 2900, 2558, 2017, 1977, 1760, 1732, 1657, 1480, 1468, 1416, 1263.1066; HRMS Calcd for ($C_{11}H_8O_3$) $[M + H]^+$: 189.0546; Found: 189.0551.

5.16 Methyl 4-oxo-4*H*-cyclohepta[*b*]furan-3-carboxylate (133b)

To a solution of dihydro cyclohepta[*b*]furan derivative **130b** (0.412 g, 2 mmol) in anisole (15 mL) was added SeO_2 (0.888 g, 8 mmol) and the reaction mixture was heated at the reflux temperature for 20 h. After the completion of the reaction, the mixture was cooled, filtered and evaporated. The residue was chromatographed on silica gel (45 g), eluting with ethyl acetate/hexane (1:2) to give methyl 4-oxo-4*H*-cyclohepta[*b*]furan-3-carboxylate (**133b**) (0.307 g, 75%) as a light yellow colored solid from CH_2Cl_2/n-hexane, Mp: 84-86 °C.



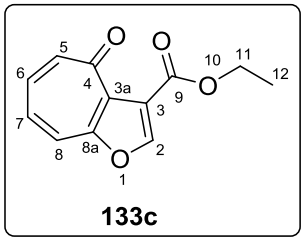
133b

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 11.3 Hz, H_5), 7.65 (dd, J = 11.3 and 8.5 Hz, H_6), 7.53-7.49 (m, H_8), 7.50 (s, H_2), 7.36 (ddt, J = 12.5, 8.2 and 4.4 Hz, H_7), 3.95 (s, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 164.0, 158.7, 154.8, 139.7, 136.1, 134.1, 130.8, 119.3, 96.5, 51.8. IR (ATR, cm^{-1}) 2988, 2900, 2159, 1770, 1747, 1715, 1697, 1537, 1478, 1440, 1268, 1211, 1147, 1065; HRMS Calcd for ($C_{11}H_8O_4$) $[M + H]^+$: 205.0495; Found: 205.0502.

5.17 Ethyl 4-oxo-4*H*-cyclohepta[*b*]furan-3-carboxylate (133c)

To a solution of dihydro cyclohepta[*b*]furan derivative **130c** (0.440 g, 2 mmol) in anisole (15 mL) was added SeO_2 (0.888 g, 8 mmol) and the reaction mixture was heated at the reflux temperature for 20 h. After the completion of the reaction, the mixture was cooled, filtered and evaporated. The residue was chromatographed on silica gel (45 g), eluting with ethyl acetate/hexane (1:2) to give ethyl 4-oxo-4*H*-

cyclohepta[*b*]furan-3-carboxylate (**133c**) (0.293 g, 67%) as a light yellow colored solid from CH_2Cl_2/n-hexane, Mp: 91-93 °C.

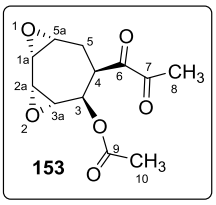


133c

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (d, J = 11.3 Hz, H_5), 7.62 (dd, J = 11.3 and 8.2 Hz, H_6), 7.50-7.45 (m, H_8), 7.47 (s, H_2), 7.36 (ddd, J = 12.5, 8.2 and 4.4 Hz, H_7), 4.40 (q, J = 7.1 Hz, CH_2), 1.40 (t, J = 7.1 Hz, CH_3) . ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 163.6, 158.7, 154.6, 139.4, 135.9, 133.8, 130.7, 118.9, 77.2, 60.7, 14.4. IR (ATR, cm^{-1}) 2987, 2900, 2558, 2159, 2017, 1977, 1771, 1732, 1748, 1688, 1681, 1507, 1488, 1473, 1267, 1208, 1065; HRMS Calcd for ($C_{12}H_{10}O_4$) $[M + H]^+$: 219.0651; Found: 219.0658.

5.18 1-[(1*R*,2*S*,4*S*,8*R*)-3,9-Dioxatricyclo[6.1.0.0^{2,4}]non-6-yl]propane-1,2-dione-5yl acetate (153) and 1-[(1*R*,2*S*,4*S*,8*R*)-3,9-dioxatricyclo[6.1.0.0^{2,4}]non-5-en-6-yl]propane-1,2-dione (134)

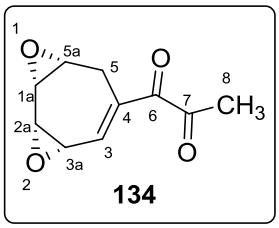
To a stirred solution of 0.22 g (1.0 mmol) endoperoxide (**131a**) in 10 mL of CH_2Cl_2 at room temperature was added 14.0 mg (0.02 mmol) of CoTPP. The resulting mixture was stirred for 3 h, and the solvent was evaporated to give 1-[(1*R*,2*S*,4*S*,8*R*)-3,9-dioxatricyclo[6.1.0.0^{2,4}]non-6-yl]propane-1,2-dione-5yl acetate (**153)** (0. 195 g, 76%) as a white colored solid Mp: 62-64 °C. When (**153)** was chromatographed on silica gel (25 g), eluting with ethyl acetate/hexane (1:1) the compound 1-[(1*R*,2*S*,4*S*,8*R*)-3,9-dioxatricyclo[6.1.0.0^{2,4}]non-5-en-6-yl]propane-1,2-dione (**134**) (0. 141 g, 72%) was formed as a light yellow colored oil.



153

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (dd, J = 4.7 and 2.2 Hz, H_3), 3.78-3.73 (m, H_4), 3.5 (bt J = 3.1, Hz, H_{2a}), 3.40 (dd, J = 3.9 and 2.0 Hz, H_{1a}), 3.20-3.17 (m, H_{3a}), 3.16-3.11 (m, H_{5a}), 2.30 (s, CH_3), 2.19 (t, J = 6.7 Hz, CH_2), 1.99 (s, CH_3).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.5, 196.0, 170.3, 69.5, 58.1, 53.8, 51.6, 50.4, 43.3, 24.0, 23.5, 20.8. **IR** (ATR, cm^{-1}) 2988, 2900, 1685, 1637, 1438, 1356, 1333, 1314, 1305, 1299, 1223, 1192, 1161, 1119, 1089, 1039, 1023, 983, 891, 839, 700, 666, 617; **HRMS** Calcd for ($C_{12}H_{14}O_6$) $[M + H]^+$: 255.0824; Found: 255.0885.

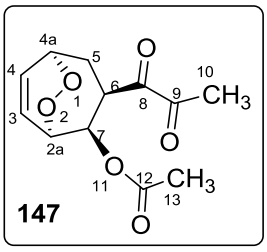
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (dd, J = 4.2 and 1.8 Hz, H_3), 3.75 (dd, , J = 4.2 and 2.3 Hz, H_{2a}), 3.62 (t, J = 4,2 Hz, H_{3a}), 3.17 (dd, J = 4.1 and 2.3 Hz, H_{1a}), 3.13



(d, J = 6.4 Hz, H_5), 3.01 (ddd, J = 6.4, 4.1 and 2.0 Hz, H_{5a}), 2.85 (ddd, J = 8.6, 6.4 and 1.79 Hz, H_5), 2.30 (s, CH_3).**^{13}C NMR** (100 MHz, $CDCl_3$) δ 200.5, 191.8, 114.5, 136.5, 52.8, 52.7, 49.7, 48.1, 26.8, 22.4. **IR** (ATR, cm^{-1}) 3019, 1715, 1621, 1396, 1214, 1044, 928, 750, 668, 627; **HRMS** Calcd for ($C_{10}H_{10}O_4$) $[M + H]^+$: 195.0613; Found: 195.0659.

5.19 (1*R*,2*R*,3*S*,5*R*)-3-Pyruvoyl-6,7-dioxabicyclo[3.2.2]non-8-en-2-yl acetate (147)

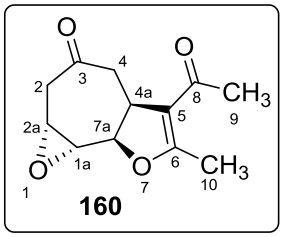
To a stirred solution of 0.22 g (1.0 mmol) endoperoxide (**131a**) in 5 mL of CH_3Cl at was added gold trichloride (3.0 mg, 2.5 mmol %) room temparature under an oxygen atmosphere. The resulting mixture was stirred for 24 h, and the solvent was evaporated to give compound (1*R*,2*R*,3*S*,5*R*)-3-pyruvoyl-6,7-dioxabicyclo[3.2.2]non-8-en-2-yl acetate (**147**) (0. 213 g, 83%) as a white colored solid Mp: 60-62 °C. When **147** was chromatographed on silica gel, eluting with ethyl acetate/hexane gave **132a**.



^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56-6.45 (m, H_3 and H_4), 5.32 (dt, J = 4.8 and 1.0 Hz, H_7), 4.95 (tt, J = 6.4 and 1.0 Hz, H_{2a}), 4.81 (dt, J = 6.7 and 1.2 Hz, H_{4a}), 3.69 (dt, J = 12.6 and 4.8 Hz, H_6), 2.55 (dd, J = 15.6 and 12.6 Hz, H_5), 2.25 (s, CH_3), 1.99 (s, CH_3), 1.95-1.87 (m, H_5). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.1, 196.7, 170.7, 131.9, 126.9, 75.2, 75.1, 72.7, 42.0, 28.8, 23.6, 20.7. **IR** (ATR, cm^{-1}) 2988, 2900, 2884, 1716, 1507, 1405, 1216, 1074, 1066, 1057, 1027, 1016, 891, 668, 625, 601,; **HRMS** Calcd for ($C_{12}H_{14}O_6$) $[M + H]^+$: 255.0824; Found: 255.0890.

5.20 (1a*S*,7b*S*)-5-acetyl-6-methyl-1a,2,4,4a,7a,7b-hexahydro-3*H*-oxireno[6,7]cyclohepta[1,2-*b*]furan-3-one (160):

A solution of triethylamine (45 mg, 0.44 mmol) in 25 mL of $CHCl_3$ was added to a stirred solution of 0.22 g (1.0 mmol) endoperoxide (**131a**) in 50 mL of $CHCl_3$ at 0 °C dropwise over 15 min. The resulting mixture was stirred for 8 h at room temperature, and the solvent was evaporated to give compound (1a*S*,7b*S*)-5-acetyl-6-methyl-1a,2,4,4a,7a,7b-hexahydro-3*H*-oxireno[6,7]cyclohepta[1,2-*b*]furan-3-one (**160**) (0. 181 g, 81%) as a yellow colored solid from EtOAc/n-hexane, Mp: 85-87 °C.

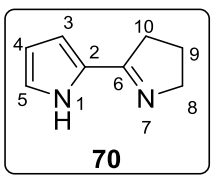


160

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38 (d, J = 2.1 Hz, H_{7a}), 4.79 (dt, J = 5.5 and 2.3 Hz, H_{1a}), 4.55 (dd, J = 7.8 and 5.8 Hz, H_{2a}), 3.13 (ddd, J = 16.1, 7.9 and 1.2 Hz, H_2), 2.84-2.78 (m, H_2 and $CH_{2(4)}$), 2.76-2.71 (m, H_{4a}), 2.09 (s, CH_3), 1.43 (s, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 2019, 197.3, 169.3, 104.2, 76.7, 72.6, 70.9, 45.0, 44.0, 42.5, 19.9, 15.1.

5.21 2,2'-(1'-Pyrrolinyl)pyrrole (70)

Phosphoryl chloride (4.2 mL, 45.0 mmol) was added over a period of 1 h to pyrrole (15.6 mL, 225 mmol) under nitrogen and cooled in an ice bath. To that solution, 2-pyrrolidinone (**74**) (3.9 mL, 51.0 mmol) was added over a period of 2 h under nitrogen and cooled in an ice bath. After the addition was complete, the viscous, amber solution was allowed to warm to room temperature. $CHCl_3$ (25 mL) was added and the solution was transferred to a flask containing water (100 mL) and sodium acetate (40.0 g) cooled in an ice bath. The pH of the turbid, orange solution was adjusted to ~10 with aq KOH (~20 mL, 10 M). The organic layer was separated and saved. The aqueous layer was extracted three times with $CHCl_3$ (~25 mL). The organic extracts were combined with the saved organic layer, and extracted five times with aq. HCl (50 mL, 0.5 M). The pH of each aq. extract was adjusted to ~10 with aq KOH (10 M) to produce a yellow/orange precipitate. The aq. extracts with the precipitate were combined and extracted four times with $CHCl_3$ (100 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to dryness to afford a light orange waxy solid. Crude product **70** was purified by sublimation at 80 °C (100 mTorr) to afford 4.7 g of a white powder. Crystallization from ethanol afforded (**70**) as white crystals (3.6 g, 66%), Mp 162-163 °C.

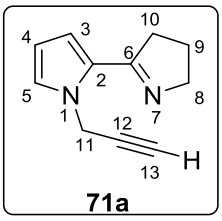


70

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (dd, J = 2.4 and 1.1 Hz, H_5), 6.54 (dd, J = 3.5 and 1.1 Hz, H_3), 6.21 (dd, J = 3.5 and 2.4 Hz, H_4), 4.02 (bt, J = 7.0, Hz, $CH_{2(8)}$), 2.90 (tt, J = 8.2, 1.4 Hz, $CH_{2(10)}$), 2.00 (quintet, J = 8.2 Hz, $CH_{2(9)}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.5, 127.8, 122.2, 113.2, 109.1, 60.5, 35.0, 22.7.

5.22 1-Prop-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (71a)

To a solution of 2,2'-(1'-pyrrolinyl)pyrrole (**70**) (0.201 g, 1.5 mmol) in dry DMF (5 mL) was added NaH (0.040 g, 1.7 mmol) portion wise at 0 °C. The reaction mixture was then stirred at room temperature for 0.5 h. To this solution was added propargyl bromide (0.178 g, 1.5 mmol) drop wise, and the resulting mixture was stirred at room temperature for 2 h. After completion of the reaction (controlled by TLC), water (5 mL) was added, and the solution was extracted with ethyl acetate 6 times. The combined organic extracts were dried over $MgSO_4$. The solvent was evaporated to give the crude product, which was purified by column chromatography eluting with EtOAc/hexane (1:4) to give final product 1-prop-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**71a**) (0.201 g, 77%) as a light yellow colored oil.

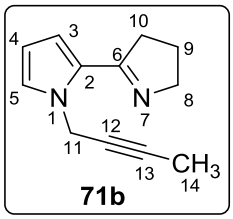


71a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (bdd, J = 2.5 and 1.6 Hz, H_2), 6.50 (dd, J = 3.6 and 1.6 Hz, H_3), 6.17 (dd, J = 3.6 and 2.5 Hz, H_4), 5.41 (d, J = 2.5 Hz, $CH_{2(11)}$), 4.01 (t, J = 7.2 Hz, $CH_{2(8)}$), 2.86 (tt, J = 8.0, 1.4 Hz, $CH_{2(10)}$), 2.37 (t, J = 2.5 Hz, H_{13}), 1.87 (quintet, J = 7.7 Hz, $CH_{2(9)}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.9, 127.3, 125.8, 115.4, 108.3, 79.3, 73.1, 61.8, 38.3, 36.6, 21.8. **IR** (ATR, cm^{-1}) 3001, 2944, 2292, 2252, 1441,1375, 1038, 918, 749; **HRMS** Calcd for ($C_{11}H_{12}N_2$) $[M + H]^+$: 173.1073; Found: 173.1081.

5.23 1-But-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (71b)

To a solution of 2,2'-(1'-pyrrolinyl)pyrrole (**70**) (0.201 g, 1.5 mmol) in dry DMF (5 mL) was added NaH (0.040 g, 1.7 mmol) portion wise at 0 °C. The reaction mixture was then stirred at room temperature for 0.5 h. To this solution was added propargyl bromide (0.200 g, 1.5 mmol) drop wise, and the resulting mixture was stirred at room temperature for 2 h. After completion of the reaction (controlled by TLC), water (5 mL) was added, and the solution was extracted with ethyl acetate 6 times. The combined organic extracts were dried over $MgSO_4$. The solvent was evaporated to give the crude product, which was purified by column chromatography eluting with EtOAc/hexane (1:4) to give final product 1-but-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**71b**) (0.177 g, 63%) as a light yellow colored oil.

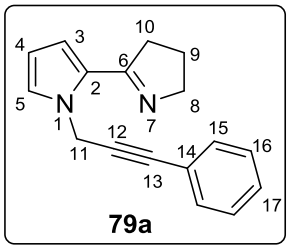


71b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (bdd, J = 2.8 and 1.6 Hz, H_5), 6.51 (dd, J = 3.8 and 1.6 Hz, H_3), 6.17 (dd, J = 3.6 and 2.8 Hz, H_4), 5.32 (q, J = 2.5 Hz, $CH_{2(11)}$), 4.00 (tt, J = 7.2 and 1.6 Hz, $CH_{2(8)}$), 2.88 (tt, J = 7.2 and 1.6 Hz, $CH_{2(10)}$), 1.89 (quintet, J = 7.3 Hz, $CH_{2(9)}$), 1.84 (t, J = 2.5 Hz, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.9, 127.1, 125.9, 115.2, 107.9, 80.9, 74.5, 61.9, 38.7, 36.6, 21.9, 3.7. **IR** (ATR, cm^{-1}) 3164, 3000, 2944, 2292, 2252, 1613,1435, 1375, 1038, 917, 735, 649; **HRMS** Calcd for ($C_{11}H_{12}N_2$) $[M + H]^+$: 187.1229; Found: 187.1223.

5.24 1-(3-Phenylprop-2-ynyl)-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (79a)

A stirred mixture of CuI (17.0 mg, 0.09 mmol), PPh_3 (90.0 mg, 0.34 mmol), and $Pd(OAc)_2$ (17.0 mg, 0.08 mmol) was purged with nitrogen for 30 min and heated to 50 °C. Then a solution of 1-prop-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**71a**) (0.190 g, 1.1 mmol), iodobenzene (0.245 g, 1.2 mmol), and DIPA (diisopropylamine) (2 mL) in THF (15 mL) was added successively. The mixture was heated for 3 h at 70 °C. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with EtOAc/hexane (1:4) to give final product 1-(3-phenylprop-2-ynyl)-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**79a**) (0.240 g, 87%) as a light yellow colored oil.

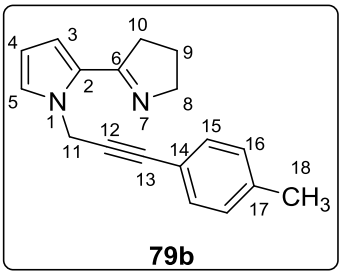


79a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37- 7.33 (m, arom, 2H), 7.23-7.20 (m, arom, 3H), 7.11 (dd, J = 2.9 and 1.6 Hz, H_5), 6.46 (dd, J = 3.6 and 1.6 Hz, H_3), 6.12 (dd, J = 3.6 and 2.9 Hz, H_4), 5.55 (s, $CH_{2(11)}$), 3.95 (tt, J = 7.2 and 1.3 Hz, $CH_{2(8)}$), 2.82 (tt, J = 7.2 and 1.6 Hz, $CH_{2(10)}$), 1.82 (quintet, J = 7.2 Hz, $CH_{2(9)}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.0, 131.8, 128.4, 128.3, 127.3, 125.9, 122.8, 115.3, 108.1, 85.0, 84.6, 61.8, 39.2, 36.6, 21.9. **IR** (ATR, cm^{-1}) 3164, 3001 2292, 2253, 1443, 1375, 1039, 918, 749; **HRMS** Calcd for ($C_{17}H_{16}N_2$) $[M + H]^+$: 249.1386; Found: 249.1397.

5.25 1-[3-(4-Methylphenyl)prop-2-ynyl]-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (79b)

A stirred mixture of CuI (17.0 mg, 0.09 mmol), PPh_3 (90.0 mg, 0.34 mmol), and $Pd(OAc)_2$ (17.0 mg, 0.08 mmol) was purged with nitrogen for 30 min and heated to 50 °C. Then a solution of 1-prop-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**71a**) (0.190 g, 1.1 mmol), 4-iodotoluene (0.261 g, 1.2 mmol), and DIPA (diisopropylamine) (2 mL) in THF (15 mL) was added successively. The mixture was heated for 4 h at 70 °C. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with EtOAc/hexane (1:4) to give final product 1-[3-(4-methylphenyl)prop-2-ynyl]-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**79b**) (0.215 g, 74%) as a light yellow colored oil.



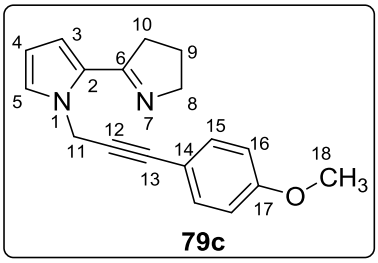
79b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.29 (A-part of AA'BB'-system, arom, 2H), 7.19 (bdd, J = 2.9 and 1.6 Hz, H_5), 7.11-7.06 (B-part of AA'BB'-system, arom, 2H), 6.52 (dd, J = 3.7 and 1.6 Hz, H_3), 6.19 (dd, J = 3.6 and 2.9 Hz, H_4), 5.61 (s, $CH_{2(11)}$), 4.02 (tt, J = 7.2 and 1.7 Hz, $CH_{2(8)}$), 2.88 (tt, J = 7.5 and 1.6 Hz, $CH_{2(10)}$), 2.32 (s, CH_3), 1.88 (quintet, J = 7.6 Hz, $CH_{2(9)}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.0, 138.5, 131.7, 129.0, 127.3, 125.9, 119.7, 115.3, 108.0, 85.1, 83.8, 61.8, 39.2, 36.6, 21.9, 21.5. **IR** (ATR, cm^{-1}) 3001, 2293, 2253, 1632, 1507, 1441, 1375, 1039, 918, 749, 668; **HRMS** Calcd for ($C_{18}H_{18}N_2$) $[M + H]^+$: 263.1542; Found: 263.1560.

5.26 1-[3-(4-Methoxyphenyl)prop-2-ynyl]-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (79c)

A stirred mixture of CuI (17.0 mg, 0.09 mmol), PPh_3 (90.0 mg, 0.34 mmol), and $Pd(OAc)_2$ (17.0 mg, 0.08 mmol) was purged with nitrogen for 30 min and heated to 50 °C. Then a solution of 1-prop-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**71a**) (0.190 g, 1.1 mmol), 4-iodoanisole (0.281 g, 1.2 mmol), and DIPA (diisopropylamine) (2 mL) in THF (15 mL) was added successively. The mixture was heated for 3 h at 70 °C. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with EtOAc/hexane (1:4) to give final product 1-[3-(4-methoxyphenyl)prop-2-ynyl]-

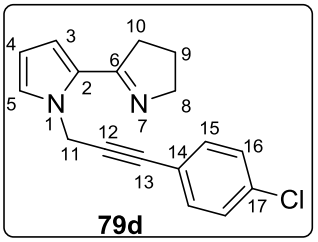
4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**79c**) (0.237 g, 77%) as a light yellow colored oil.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (quasi d, J = 8.8 Hz, arom, 2H), 7.19 (bdd, J = 2.6 and 1.7 Hz, H_5), 6.82 (quasi d, J = 8.8 Hz, arom, 2H), 6.53 (dd, J = 3.7 and 1.7 Hz, H_3), 6.19 (dd, J = 3.7 and 2.6 Hz, H_4), 5.60 (s, $CH_{2(11)}$), 4.03 (tt, J = 7.2 and 1.6 Hz, $CH_{2(8)}$), 3.80 (s, OCH_3), 2.89 (tt, J = 7.6 and 1.6 Hz, $CH_{2(10)}$), 1.90 (quintet, J = 7.6 Hz, $CH_{2(9)}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 166.0, 159.7, 133.2, 127.3, 125.9, 115.3, 114.9, 113.9, 108.0, 84.9, 83.1, 61.8, 55.3, 39.3, 36.7, 21.9. **IR** (ATR, cm^{-1}) 3164, 3001, 2292, 2253, 1443, 1375, 1038, 918, 749; **HRMS** Calcd for ($C_{18}H_{18}N_2O$) [M + H]$^{+}$: 279.1491; Found: 279.1497.

5.27 1-[3-(4-Chlorophenyl)prop-2-ynyl]-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (79d)

A stirred mixture of CuI (17.0 mg, 0.09 mmol), PPh_3 (90.0 mg, 0.34 mmol), and $Pd(OAc)_2$ (17.0 mg, 0.08 mmol) was purged with nitrogen for 30 min and heated to 50 °C. Then a solution of 1-prop-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**71a**) (0.190 g, 1.1 mmol), 1-chloro-4-iodobenzene (0.286 g, 1.2 mmol), and DIPA (diisopropylamine) (2 mL) in THF (15 mL) was added successively. The mixture was heated for 3 h at 70 °C. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with EtOAc/hexane (1:4) to give final product 1-[3-(4-chlorophenyl)prop-2-ynyl]-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**79d**) (0.201 g, 78%) as a light yellow colored oil.

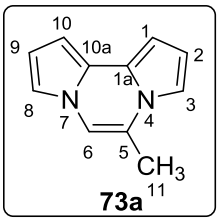


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.27 (m, arom, 5H), 7.14 (dd, J = 2.8 and 1.7 Hz, H_5), 6.54 (dd, J = 3.7 and 1.7 Hz, H_3), 6.20 (dd, J = 3.7 and 2.8 Hz, H_4), 5.63 (s, $CH_{2(11)}$), 4.03 (tt, J = 7.3 and 1.6 Hz, $CH_{2(8)}$), 2.90 (tt, J = 7.3 and 1.6 Hz, $CH_{2(10)}$), 1.91 (quintet, J = 7.3 Hz, $CH_{2(9)}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.9, 131.7, 128.3, 128.2, 127.3, 125.9, 122.7, 115.2, 108.0, 84.9, 84.5, 61.8, 39.2, 36.6, 21.9. **IR** (ATR, cm^{-1}) 3164, 3000,

2292, 2253, 1442, 1375, 1039, 918, 749; **HRMS** Calcd for ($C_{17}H_{15}ClN_2$) $[M + H]^+$: 283.0996; Found: 283.1021.

5.28 5-Methyldipyrrolo[1,2-*a*:2',1'-*c*]pyrazine (73a)

To a 50 mL flask equipped with a condenser was added 1-prop-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**71a**) (0.172 g, 1.0 mmol) and diglyme (5 mL). Nitrogen was directed through a needle so as to continuously bubble through the solution. The solution was warmed to a few degrees below the boiling point of the solvent, and 10% palladium on carbon (0.027 g, 0.025 mmol) was added then the resulting mixture was heated at the reflux temperature for 16 h. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:4) to give pure product 5-Methyldipyrrolo[1,2-*a*:2',1'-*c*]pyrazine (**73a**) (0.135 g, 79%) as a yellow colored solid from EtOAc/n-hexane, Mp: 123-125 ˚C.



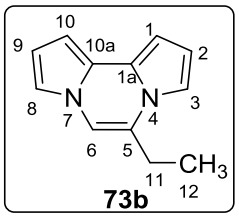
73a

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (bd, J = 2.1 Hz, H_8), 6.92 (bd, J = 2.1 Hz, H_3), 6.90-6.88 (m, H_6), 6.56 (d, J = 2.1 Hz, H_1 and H_{10}), 6.47 (d, J = 2.1 Hz, H_2 and H_9), 2.35 (d, J = 1.2 Hz, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 124.8, 123.9, 118.9, 113.6, 111.9, 111.3, 110.8, 109.1, 99.8, 98.6, 15.6. **IR** (ATR, cm^{-1}), 3164, 3000, 2292, 2253, 1632, 1442, 1375, 1039, 918, 749; **HRMS** Calcd for ($C_{11}H_{10}N_2$) $[M + H]^+$: 171.0916; Found: 171.0918.

5.29 5-Ethyldipyrrolo[1,2-*a*:2',1'-*c*]pyrazine (73b)

To a 50 mL flask equipped with a condenser was added 1-but-2-ynyl-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**71b**) (0.186 g, 1.0 mmol) and diglyme (5 mL). Nitrogen was directed through a needle so as to continuously bubble through the solution. The solution was warmed to a few degrees below the boiling point of the solvent, and 10% palladium on carbon (0.027 g, 0.025 mmol) was added then the resulting mixture was heated at the reflux temperature for 18 h. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:4) to give pure product 5-

ethyldipyrrolo[1,2-*a*:2',1'-*c*]pyrazine (**73b**) (0.130 g, 70%) as a yellow colored solid from EtOAc/n-hexane, Mp: 127-129 ˚C.

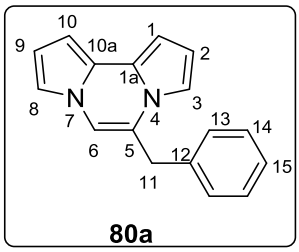


73b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (bt, J = 2.2 Hz, H_8), 6.97 (dd, J = 2.5, 1.6 Hz, H_3), 6.92 (bs, H_6), 6.57-6.55 (m, H_1 and H_{10}), 6.51-6.47 (m, H_2 and H_9), 2.77 (dq, J =7.4 and 1.2 Hz, CH_2), 1.38 (t, J = 7.4 Hz, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 124.8, 124.4, 123.9, 113.8, 111.6, 111.3, 110.9, 108.0, 99.6, 98.5, 22.5, 11.2. **IR** (ATR, cm^{-1}) 3164, 3001, 2944, 2292, 2252, 1632, 1443, 1375, 1038, 918, 749; **HRMS** Calcd for ($C_{12}H_{12}N_2$) $[M + H]^+$: 185.1073; Found: 185.1078.

5.30 5-Benzyldipyrrolo[1,2-*a*:2',1'-*c*]pyrazine (80a)

To a 50 mL flask equipped with a condenser was added 1-(3-phenylprop-2-ynyl)-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**79a**) (0.248 g, 1.0 mmol) and diglyme (5 mL). Nitrogen was directed through a needle so as to continuously bubble through the solution. The solution was warmed to a few degrees below the boiling point of the solvent, and 10% palladium on carbon (0.027 g, 0.025 mmol) was added then the resulting mixture was heated at the reflux temperature for 16 h. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:4) to give pure product 5-benzyldipyrrolo[1,2-*a*:2',1'-*c*]pyrazine (**80a**) (0.185 g, 75%) as a yellow colored solid from EtOAc/n-hexane, Mp: 125-127 ˚C.

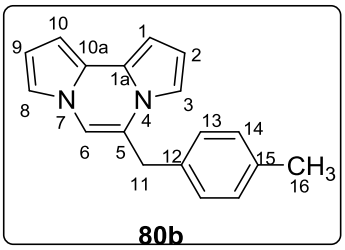


80a

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, arom, 5H), 6.96 (dd, J = 2.8 and 1.4 Hz, H_8), 6.91 (bt, J = 2.2 Hz, H_3), 6.75 (bs, H_6), 6.55 (dd, J = 3.7 and 1.4 Hz, H_{10}), 6.51-6.47 (m, H_1, H_2 and H_9), 4.05 (s, CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 135.8, 128.9, 128.8, 127.2, 124.8, 123.9, 121.9, 114.0, 112.4, 111.3, 111.2, 110.7, 99.7, 98.7, 35.9. **IR** (ATR, cm^{-1}) 3164, 3001, 2292, 2252, 1443, 1375, 1039, 918, 749; **HRMS** Calcd for ($C_{17}H_{14}N_2$) $[M + H]^+$: 247.1229; Found: 247.1241.

5.31 5-(4-Methylbenzyl)dipyrrolo[1,2-*a*:2',1'-*c*]pyrazine (80b)

To a 50 mL flask equipped with a condenser was added product 1-[3-(4-methylphenyl)prop-2-ynyl]-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**79b**) (0.262 g, 1.0 mmol) and diglyme (5 mL). Nitrogen was directed through a needle so as to continuously bubble through the solution. The solution was warmed to a few degrees below the boiling point of the solvent, and 10% palladium on carbon (0.027 g, 0.025 mmol) was added then the resulting mixture was heated at the reflux temperature for 17h. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:4) to give pure product 5-(4-methylbenzyl)dipyrrolo[1,2-*a*:2',1'-*c*]pyrazine (**80b**) (0.167 g, 64%) as a yellow colored solid from EtOAc/n-hexane, Mp: 145-147 ˚C.

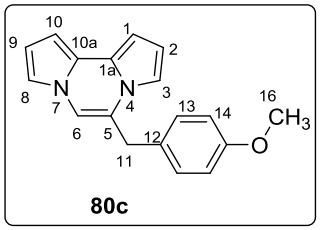


80b

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.14 (AA'BB' system, arom, 4H), 6.97 (dd, J = 2.8 and 1.4 Hz, H_8), 6.92 (bt, J = 2.2, H_3), 6.75 (bs, H_6), 6.55 (dd, J = 3.7 and 1.4 Hz, H_{10}), 6.51-6.47 (m, H_1, H_2 and H_9), 4.02 (s, CH_2), 2.35 (s, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.8, 132.7, 129.5, 128.7, 124.8, 123.9, 122.1, 114.0, 112.3, 111.3, 111.1, 110.6, 99.7, 98.6, 35.5, 21.1. **IR** (ATR, cm^{-1}) 3164, 3001, 2292, 2253, 1442, 1375, 1038, 918, 749; **HRMS** Calcd for ($C_{18}H_{16}N_2$) $[M + H]^+$: 261.1386; Found: 261.1401.

5.32 5-(4-Methoxybenzyl)dipyrrolo[1,2-*a*:2',1'-*c*]pyrazine (80c)

To a 50 mL flask equipped with a condenser was added product 1-[3-(4-methoxyphenyl)prop-2-ynyl]-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**79c**) (0.278 g, 1.0 mmol) and diglyme (5 mL). Nitrogen was directed through a needle so as to continuously bubble through the solution. The solution was warmed to a few degrees below the boiling point of the solvent, and 10% palladium on carbon (0.027 g, 0.025 mmol) was added then the resulting mixture was heated at the reflux temperature for 16 h. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:4) to give pure product 5-(4-methoxybenzyl)dipyrrolo[1,2-*a*:2',1'-*c*]pyrazine (**80c**) (0.171 g, 62%) as a light green colored viscous oil.

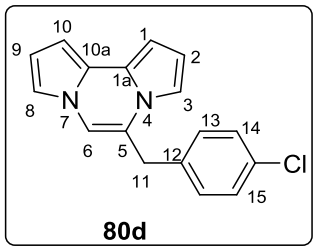


80c

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (quasi d, J = 8.5 Hz, arom, 2H), 6.90 (dd, J = 2.8, 1.4 Hz, H_8), 6.84 (bt, J = 2.0 Hz, H_3), 6.81 (quasi d, J = 8.5 Hz, arom, 2H), 6.65 (bs, H_6), 6.48 (dd, J = 3.7 and 1.3 Hz, H_{10}), 6.44-6.39 (m, H_1, H_2 and H_9), 3.92 (s, CH_2), 3.74 (s, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.8, 129.9, 127.7, 124.8, 123.9, 122.4, 114.3, 114.0, 112.3, 111.3, 111.1, 110.6, 99.7, 98.6, 55.3, 35.0. **IR** (ATR, cm^{-1}) 3164, 3001, 2292, 2252, 1442, 1375, 1038, 918, 749; **HRMS** Calcd for ($C_{18}H_{16}N_2O$) $[M + H]^+$: 277.1335; Found: 277.1340.

5.33 5-(4-Chlorobenzyl)dipyrrolo[1,2-*a*:2',1'-*c*]pyrazine (80d)

To a 50 mL flask equipped with a condenser was added product 1-[3-(4-chlorophenyl)prop-2-ynyl]-4',5'-dihydro-1*H*,3'*H*-2,2'-bipyrrole (**79d**) (0.282 g, 1.0 mmol) and diglyme (5 mL). Nitrogen was directed through a needle so as to continuously bubble through the solution. The solution was warmed to a few degrees below the boiling point of the solvent, and 10% palladium on carbon (0.027 g, 0.025 mmol) was added then was the resulting mixture heated at the reflux temperature for 18 h. After complete conversion (monitored by TLC) solvent was evaporated, and the residue was chromatographed on silica gel eluting with ethyl acetate/hexane (1:4) to give pure product 5-(4-chlorobenzyl)dipyrrolo[1,2-*a*:2',1'-*c*]pyrazine (**80d**) (0.175 g, 62%) as a yellow colored solid form EtOAc/n-hexane, Mp:137-138.

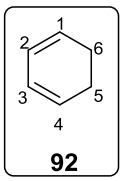


80d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (quasi d, J = 8.3 Hz, arom, 2H), 7.24 (quasi d, J = 8.3 Hz, arom, 2H), 6.93 (bt, J = 1.8 Hz, H_8), 6.90 (dd, J = 2.4 and 1.4 Hz H_3), 6.78 (bs, H_6), 6.57-6.54 (m, H_{10}), 6.53-6.48 (m, H_1, H_2 and H_9), 4.03 (s, CH_2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 134.4, 133.1, 130.1, 129.1, 124.7, 123.8, 121.3, 114.1, 112.5, 111.5, 111.4, 110.8, 99.9, 98.9, 35.3. IR (ATR, cm^{-1}) 3164, 3001, 2292, 2253, 1443, 1375, 1039, 918, 749; **HRMS** Calcd for ($C_{17}H_{13}N_2Cl$) $[M + H]^+$: 281.0767; Found: 281.0862.

5.34 Cyclohexa-1,3-diene (92)

A mixture of 156 mL of cyclohexene (**88**) (127.0 g, 1.55 mol) and N-bromosuccinimide (55.0 g, 0.31 mol) was heated at the reflux temperature for 3h in a round-bottomed flask with a condenser and drying tube. After complete conversion, reaction mixture was filtered into a one round-bottomed flask. Filitrate was evaporated and the residual yellowish oil was purified by vacuum distillation to give 3-bromocyclohex-1-ene (**89**) (209.0 g, 84%). Liquid distilled between T = 51-52 °C. (10 torr) 3-Bromocyclohexene (209.0 g, 1.30 mol) (**89**) and 386 mL of quinoline (422.0 g, 3.27 mol) were added into a round-bottomed flask attached with distilling equipment ending with an oil bubbler. Oil bath was set to maximum power to avoid precipitation. The colorless cyclohexa-1,3-diene (**90**) (88.4 g, 85%) distilled between T = 80-82 °C.[133]

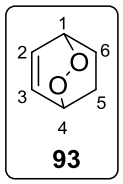


92

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82-5.76 (m, A part of AB system, H_2 and H_3), 5.72-5.65 (m, B part of AB system, H_1 and H_4), 6.93 (bt, J = 1.8 Hz, $CH_{2(5)}$ and $CH_{2(6)}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 124.2 (2C) 122.4 (2C), 20.1 (2C).

54.35 2,3-Dioxabicyclo[2.2.2]oct-5-ene (93)

Cyclohexa-1,3-diene (**92**) (1 g, 1.25 mol) and a catalytic amount of tetraphenylporphine (TPP) (30 mg) was dissolved in 100 mL of CH_2Cl_2 in a flask covered with a water jacket. Then, the mixture was irradiated with a projection lamp (300 W) for 18 h while the dry oxygen was bubbled through the solution with a constant rate at room temperature. After the reaction was complete the solvent was removed by a rotary evaporator at 30 °C. The residue was chromatographed on silica gel (65 g), eluting with ethyl acetate/hexane (1:1) to give 2,3-Dioxabicyclo[2.2.2]oct-5-ene (**93**) (1.26 g, 90%) as a colorless oil.[134]

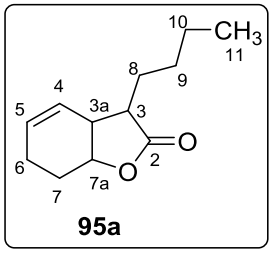


93

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (t, J=4.3, H_2 and H_3), 4.56 (bs, H_1 and H_4), 2.17 (AA' part of AA'BB' system, $CH_{2(6)}$), 1.41 (BB' part of AA'BB' system, $CH_{2(5)}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 131.6 (2C) 70.2 (2C), 21.1 (2C).

5.36 3-Butyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3*H*)-one (95a)

To a solution of 2,3-Dioxabicyclo[2.2.2]oct-5-ene (**93**) (0.112 g, 1 mmol) in toluene (10 mL) was added Au(L) (12.5 mg, 0.02 mmol, 2 mmol %) and AgOTf (7.5 mg, 0.03 mmol, 3 mmol %). Then was added 1-hexyne (0.082 g, 1 mmol) and the resulting mixture was heated at the reflux temperature for 16 h. After complete conversion (monitored by TLC) reaction mixture was filtrated and then evaporated. The residue was chromatographed on silica gel (20 g), eluting with ethyl acetate/hexane (1:2) to give 3-butyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3*H*)-one (**95a**) (0.119 g, 61%) as a colorless oil.



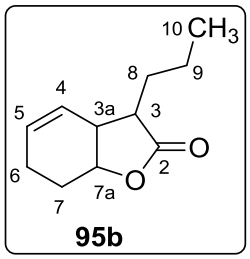
95a

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (ddt, J = 9.9, 3.9 and 1.8 Hz, H_5), 5.50 (ddd, J = 9.9, 3.7 and 1.9 Hz, H_4), 4.64 (td, J = 6.5 and 4.6 Hz, H_{7a}), 2.64-2.61 (m, H_{3a}), 2.26 (dt, J = 8.1 and 6.0 Hz, H_3), 2.17-2.07 (m, H_6), 2.01-1.91 (m, H_6), 1.82 (ddt, J = 9.3, 6.6 and 2.3 Hz, $CH_{2(8)}$), 1.78-1.70 (m, H_7), 1.60-1.53 (m, H_7), 1.43-1.35 (m, $CH_{2(9)}$), 1.33-1.25 (m, $CH_{2(10)}$)), 0.89 (t, J=7.3 Hz, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.1, 127.3, 125.0, 75.2, 45.8, 39.4, 28.8, 28.5, 24.2, 21.5, 19.4, 12.8. **IR** (ATR, cm^{-1}) 3019, 2931, 2858, 2394, 2196, 2025, 1763, 1467, 1214, 1175, 1028, 667; **HRMS** Calcd for ($C_{12}H_{18}O_2$) $[M + H]^+$: 195.1379; Found: 195.1374.

5.37 3-Propyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3*H*)-one (95b)

To a solution of 2,3-dioxabicyclo[2.2.2]oct-5-ene (**93**) (0.112 g, 1 mmol) in toluene (10 mL) was added Au(L) (12.5 mg, 0.02 mmol, 2 mmol %) and AgOTf (7.5 mg, 0.03 mmol, 3 mmol %). Then was added 1-pentyne (0.068 g, 1 mmol) and was heated at the reflux temperature for 16 h. After complete conversion (monitored by TLC) reaction mixture was filtrated and then evaporated. The residue was chromatographed on silica gel (20 g), eluting with ethyl acetate/hexane (1:2) to give 3-propyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3*H*)-one (**95b**) (0.115 g, 63%) as a colorless viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, J = 9.8, 3.7 and 1.9 Hz, H_5), 5.57 (ddd, J = 9.8, 3.4 and 1.7 Hz, H_4), 4.71 (dd, J = 11.2 and 6.5 Hz, H_{7a}), 2.70 (m, H_{3a}), 2.34 (dt, J= 7.8 and 6.1 Hz, H_3), 2.24-2.14 (m, H_6), 2.08-1.98 (m, H_6), 1.93-1.86 (m, $CH_{2(8)}$),

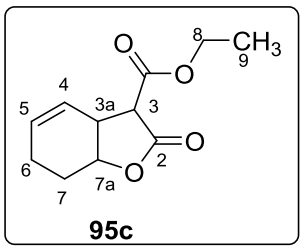


95b

1.79 (ddt, J = 15.0, 8.4 and 5.6, Hz, H_7), 1.66-1.59 (m, H_7), 1.55-1.47 (m, $CH_{2(9)}$), 0.96 (t, J=7.3 Hz, CH_3) . **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.1, 128.4, 126.0, 76.2, 46.6, 40.4, 32.2, 25.2, 20.5, 20.4, 13.9. **IR** (ATR, cm^{-1}) 3019, 2900, 1688, 1393, 1214, 1047, 928, 750, 668, 582; **HRMS** Calcd for ($C_{11}H_{16}O_2$) $[M + H]^+$: 181.1223; Found: 181.1215.

5.38 Methyl 2-oxo-2,3,3a,6,7,7a-hexahydro-1-benzofuran-3-carboxylate (95c)

To a solution of 2,3-dioxabicyclo[2.2.2]oct-5-ene (**93**) (0.112 g, 1 mmol) in toluene (10 mL) was added Au(L) (12.5 mg, 0.02 mmol, 2 mmol %) and AgOTf (7.5 mg, 0.03 mmol, 3 mmol %). Then was added ethyl propiolate (0.098 g, 1 mmol) and was heated at the reflux temperature for 14 h. After complete conversion (monitored by TLC) reaction mixture was filtrated and then evaporated. The residue was chromatographed on silica gel (20 g), eluting with ethyl acetate/hexane (1:2) to give methyl 2-oxo-2,3,3a,6,7,7a-hexahydro-1-benzofuran-3-carboxylate (**95c**) (0.120 g, 57%) as a colorless viscous oil.



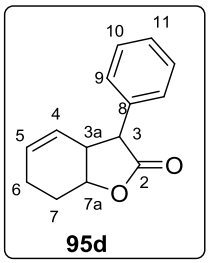
95c

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (bdt, J = 10.2 and 1.2 Hz, H_5), 5.45 (bdt, J = 10.2 and 1.8 Hz, H_4), 4.88 (dt, J = 6.1 and 3.4 Hz, H_{7a}), 4.20 (q, J = 7.2 Hz, $CH_{2(8)}$), 3.31-3.27 (m, H_{3a}), 2.18-2.10 (m, H_3 and H_6), 2.02-1.91 (m, H_6 and H_7), 1.85-1.74 (m, H_7), 1.25 (t, J = 7.2 Hz, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 171.6, 167.3, 129.8, 124.1, 77.5, 62.3, 53.6, 39.0, 24.7, 19.5, 14.1. **IR** (ATR, cm^{-1}) 3018, 2900, 2399, 1730, 1516, 1399, 1214, 1047, 928, 750, 668; **HRMS** Calcd for ($C_{11}H_{14}O_4$) $[M + H]^+$: 211.0964; Found: 211.0973.

5.39 3-Phenyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3*H*)-one (95d)

To a solution of 2,3-dioxabicyclo[2.2.2]oct-5-ene (**93**) (0.112 g, 1 mmol) in toluene (10 mL) was added Au(L) (12.5 mg, 0.02 mmol, 2 mmol %) and AgOTf (7.5 mg, 0.03 mmol, 3 mmol %). Then was added phenylacetylene (0.102 g, 1 mmol) and was heated at the reflux temperature for 18 h. After complete conversion (monitored by TLC) reaction mixture was filtrated and then evaporated. The residue was chromatographed on silica gel (20 g), eluting with ethyl acetate/hexane (1:2) to give

3-phenyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3*H*)-one (**95d**) (0.141 g, 66%) as a light yellow colored oil.

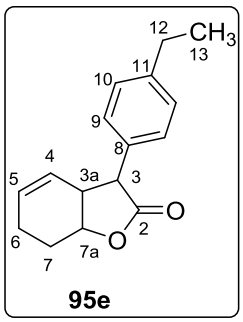


95d

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.20 (m, 3H, arom.), 7.17-7.13 (m, 2H, arom.), 5.82 (dt, J = 10.2 and 5.9 Hz, H_5), 4.88 (ddd, J = 10.4, 2.7 and 1.5 Hz, H_4), 4.81 (bs, H_{7a}), 4.11 (d, J = 8.0, H_3), 3.18-3.11 (m, H_{3a}), 2.30-2.21 (m, H_7), 2.20 (m, H_6) 1.95 (dt, J = 17.7 and 5.7, Hz, H_6), 1.65 (dddd, J = 17.0, 11.9, 6.2 and 2.0 Hz, H_7) . **^{13}C NMR** (100 MHz, $CDCl_3$) δ 175.5, 132.3, 128.9, 128.6, 127.3, 126.5, 121.5, 75.2, 50.8, 39.8, 23.4, 17.6. **IR** (ATR, cm^{-1}) 3018, 2987, 2900, 1770, 1393, 1214, 1066, 929, 750, 668, 626, 589; **HRMS** Calcd for ($C_{14}H_{14}O_2$) $[M + H]^+$: 215.1066; Found: 215.1065.

5.40 3-(4-Ethylphenyl)-3a,6,7,7a-tetrahydro-1-benzofuran-2(3*H*)-one (95e)

To a solution of 2,3-dioxabicyclo[2.2.2]oct-5-ene (**93**) (0.112 g, 1 mmol) in toluene (10 mL) was added Au(L) (12.5 mg, 0.02 mmol, 2 mmol %) and AgOTf (7.5 mg, 0.03 mmol, 3 mmol %). Then was added 1-ethyl-4-ethynylbenzene (0.130 g, 1 mmol) and was heated at the reflux temperature for 18 h. After complete conversion (monitored by TLC) reaction mixture was filtrated and then evaporated. The residue was chromatographed on silica gel (20 g), eluting with ethyl acetate/hexane (1:2) to give 3-(4-ethylphenyl)-3a,6,7,7a-tetrahydro-1-benzofuran-2(3*H*)-one (**95e**) (0.135 g, 56%) as a light yellow colored oil.

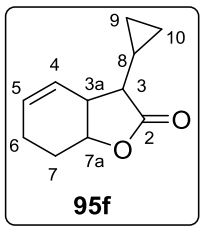


95e

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (quasi d, J = 8.2 Hz, 2H, arom.), 7.13 (quasi d, J = 8.2 Hz, 2H, arom.), 5.80 (dt, J = 10.0 and 5.7 Hz, H_5), 4.99 (ddt, J = 10.0 and 3.0 Hz, H_4), 4.86 (bs, H_{7a}), 4.15 (d, J = 8.1 Hz, H_3), 3.23-3.15 (m, H_{3a}), 2.64 (q, J = 7.7 Hz, $CH_{2(12)}$), 2.35-2.28 (m, H_7), 2.27-2.19 (m, H_6), 2.01 (dt, J = 17.5 and 4.0 Hz, H_6), 1.72 (dddd, J = 17.0, 11.9, 6.3, 2.0 Hz, H_7), 1.23(t, J = 7.7 Hz, CH_3). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 176.8, 143.5, 129.9, 129.5, 127.9, 124.3, 122.7, 76.1, 51.5, 40.8, 28.5, 24.5, 18.6, 15.5. **IR** (ATR, cm^{-1}) 3019, 2965, 2162, 1979, 1770, 1516, 1214, 1038, 929, 750, 626, 581; **HRMS** Calcd for ($C_{16}H_{18}O_2$) $[M + H]^+$: 243.1379; Found: 243.1384.

541 3-Cyclopropyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3*H*)-one (95f)

To a solution of 2,3-dioxabicyclo[2.2.2]oct-5-ene (**93**) (0.112 g, 1 mmol) in toluene (10 mL) was added Au(L) (12.5 mg, 0.02 mmol, 2 mmol %) and AgOTf (7.5 mg, 0.03 mmol, 3 mmol %). Then was added cyclopropylacetylene (0.066 g, 1 mmol) and was heated at the reflux temperature for 18 h. After complete conversion (monitored by TLC) reaction mixture was filtrated and then evaporated. The residue was chromatographed on silica gel (20 g), eluting with ethyl acetate/hexane (1:2) to give 3-cyclopropyl-3a,6,7,7a-tetrahydro-1-benzofuran-2(3*H*)-one (**95f**) (0.121 g, 67%) as a colorless viscous oil.



95f

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (ddt, J = 9.8, 3.9 and 1.9 Hz, H_5), 5.58 (ddd, J = 9.8, 3.7 and 1.8 Hz, H_4), 4.77 (dt, J = 11.0 and 6.2 Hz, H_{7a}), 2.70-2.60(m, H_{3a}), 2.23-2.13 (m, H_6), 2.07-1.99 (m, H_6), 1.92-1.85 (m, H_3 and H_7), 1.85-1.81 (m, H_7), 0.99 (ddt, J = 13.1, 8.3 and 4.8 Hz, H_8), 0.67 (ddt, J = 13.8, 9.1 and 4.9 Hz, H_9), 0.58 (ddt, J = 13.5, 8.1, 4.5 Hz, H_{10}), 0.48 (dt, J = 9.5 and 4.9 Hz, H_9), 0.35 (dt, J=9.4 and 4.7 Hz, H_{10}) . **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.9, 128.3, 125.9, 76.3, 50.9, 41.5, 25.1, 20.3, 11.5, 3.4, 2.8. **IR** (ATR, cm^{-1}) 2988, 2900, 1766, 1405, 1393, 1216, 1066, 1057, 1027, 870, 750, 668; **HRMS** Calcd for ($C_{11}H_{14}O_2$) $[M + H]^+$: 179.1066; Found: 179.1068.

REFERENCES

(1) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339.

(2) Snider, B. B. *Tetrahedron* **2009**, *65*, 10738.

(3) Smith, G. F.; Sillivan, V. R.; Frank, G. *Ind. Eng. Chem. Anal. Ed.* **1936**, *8*, 449.

(4) Nair, V.; Mathew, J.; Nair, L. G. *Synth. Commun.* **1996**, *26*, 4531.

(5)Szumny, A.; Wawrzenczyk, C. *Synlett* **2006**, 1523.

(6) Nair, V.; Suja, T. D.; Mohanan, K. *Synthesis* **2006**, 2335.

(7) Kobayashi, K.; Mori, M.; Umed, T.; Morikawa, O.; Konishi, H. *Chem. Lett.* **1996**, *25*, 451.

(8) Kobayashi, K.; Umakoshi, H.; Hayashi, K.; Morikawa, O.; Konishi, H. *Chem. Lett.* **2004**, *33*, 1588.

(9) Haller, R.; Kohlmorgen, R.; Hansel, W. *Tetrahedron Lett*. **1973**, *14*, 1205.

(10) Snider, B. B.; Kwon, T. *J. Org. Chem.* **1990**, *55*, 4786.

(11) Citterio, A.; Pesce, L.; Sebastiano, R.; Santi, R. *Synthesis* **1990**, 142.

(12) Takemoto, Y.; Ohra, T.; Koike, H.; Furuse, S. I.; Iwata, C. *J. Org. Chem.* **1994**, *59*, 4727.

(13) Takemoto, Y.; Ibuka, T.; Hayase, H.; Iwanaga, A.; Yamagata, S.; Iwata, C.; Tanaka, T. *Tetrahedron Lett.* **1998**, *39*, 7545.

(14) Jamie, J. F.; Rickards, R. W. *J. Chem. Soc., Perkin Trans.* **1996**, *1*, 2603.

(15) Kim, H. J.; Yoon, U. C.; Jung, Y. S.; Park, N. S.; Cederstrom, E. M.; Mariano, P. S. *J. Org. Chem.* **1998**, *63*, 860.

(16) Trahanovsky, W. S.; Robbins, M. D. *J. Am. Chem. Soc.* **1971**, *93*, 5256.

(17) Magnus, P.; Barth, L. *Tetrahedron Lett*. **1992**, *33*, 2777.

(18) Nair, V.; Nair, L. G.; George, T. G.; Augustine, A. *Tetrahedron* **2000**, *56*, 7607.

(19) Roy, S. C.; Adhikari, S. *Indian J. Chem. Sect. B* **1992**, *31B*, 459.

(20) Iranpoor, N.; Kazemi, F.; Salehi, P. *Synth. Commun*. **1997**, *27*, 1247.

(21) Iranpoor, N.; Kazemi, F. *Synth. Commun.* **1999**, *29*, 561.

(22) Iranpoor, N.; Kazemi, F. *Synthesis* **1996**, 821.

(23) Varala, R.; Enugala, R.; Nuvula, S.; Adapa, S. R. *Synlett* **2006**, 1009.

(24) Shaabani, A.; Maleki, A. *Chem. Pharm. Bull*. **2008**, *56*, 79.

(25) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398.

(26) Graham, J. H.; Jones, C. M.; Jui, N. T.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2008**, *130*, 16494.

(27) Jang, H.-Y.; Hong, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2007**, *129*, 7004.

(28) Nair, V.; Nair, L. G.; Balagopal, L.; Rajan, R. *Indian J. Chem. Sect. B* **1999**, *38*, 1234.

(29) Gupta, A. D.; Singh, R.; Singh, V. K. *Synlett* **1996**, 69.

(30) Palomo, C.; Aizpurua, J. M.; Legido, M.; Mielgo, A.; Galarza, R. *Chem. Eur. J.* **1997**, *3*, 1432.

(31) Hwu, J. R.; Jain, M. L.; Tsay, S. C.; Hakemelahi, G. H. *Tetrahedron Lett.* **1996**, *37*, 2035.

(32) Iranpoor, N.; Mothaghineghad, W. *Tetrahedron* **1994**, *50*, 1859.

(33) Wasserman, H. H.; Murray, R. W. *Singlet Oxygen, A Series of Monographs*, Academic Press New York, **1979**; *40*, 13.

(34) Foote, C. S. *Science* **1970**, *162*, 963.

(35) Wilson,T.; Hastings, J. W. *Photophysiyology*, **1970**, *5*, 49.

(36) Ranby, B.; Rabek, J. F. *Photodegradation, Photooxidation and Photostabilization of Polymers*, John Wiley and Sons Ltd, **1975**.

(37) Gorman, A. A. *Chem. Soc. Rev*. **1981**, *10*, 205.

(38) Adam, W. *Chem. Ztg.* **1975**, *3*, 142.

(39) Balci, M. *Chem. Rev.* **1981**, *81*, 91.

(40) Schenck, G. O.; Eggert, H.; Denk, W. *Liebigs Ann. Chem.* **1953**, *584*, 177.

(41) Clennan, E. L. *Chem. Res.* **2001**, *34*, 875.

(42) Coughlin, D. J.; Salomon, R. G. *J. Am. Chem. Soc*. **1977**, *99*, 655.

(43) Schenck, G. O.; Dunlap, E. D. *Angew. Chem.* **1956**, *68*, 248.

(44) Nelson, E. K. *J. Am. Chem. Soc.* **1911**, *33*, 1404.

(45) Boche, J.; Runguist, O. *J. Org. Chem.* **1968**, *33*, 4285.

(46) Wasserman, H. H.; Larsen, D. L. *Chem. Commun.***1972**, 253.

(47) Adam, W.; Erden. I. *Tetrahedron Lett.* **1979,** *20***,** 2781.

(48) Adam, W.; Erden, I. *Angew.Chem., Int. Ed. Engl.* **1978**, *17*, 211.

(49) Yamato, M.; Hashigaki, K.; Yasumoto, Y.; Sakai, J.; Luduena, R.F.; Banerjee,A.Tsukagoshi, S.; Tashiro, T.; Tsuruo, T. *J. Med. Chem.* **1987**, *30*, 1897.

(50) Trust, T.J.; Bartlett, K.H. *Antimicrob. Agents Ch.* **1975**, *8*, 381.

(51) Inamori, Y.; Shinohara, S.; Tsujibo, H.; Okabe, T.; Morita, Y.; Sakagami, Y.; Kumeda, Y.; Ishida, N. *Biol. Pharm. Bull*. **1999**, *22*, 990.

(52) Nozoe, T.; Kitahara, Y.; Ando, T.; Masamune, S. *Proc. Jap. Acad.* **1951**, *27*, 231.

(53) Collington, E. W.; Jones, G. *Chem. Commun*. **1968**, 958.

(54) Cook, J. W.; Gibb, A. R.; Raphael, R. A.; Somerville, A. R. *J. Chem. Soc*. **1951**, 503.

(55) Nozoe, T.; Seto, S.; Kitahara, Y.; Kunori, M.; Nakayama, Y. *Proc. Jap. Acad.* **1950**, *26*, 38.

(56) Nozoe, T. *Progr. Org. Chem.* **1961**, *5*, 141.

(57) Radlick, P. *J.Org. Chem.* **1964**, *29*, 960.

(58) Doering, W. V. E.; Knox, L. H. *J. Am. Chem. Soc.* **1951**, *73*, 828.

(59) Stevens, H. C.; Keich, D. A.; Brandt, D. R.; Fountain, K. R.; Gaughan, E. J. *J. Am. Chem. Soc.* **1965**, *87*, 5257.

(60) Birch, A. J.; Keeton, R. *Aust. J. Chem.* **1971**, *24*, 331.

(61) Thiele, J.; Weitz, E. *Liebigs Ann. Chem*. **1910**, *377*, 1.

(62) Bordwell, F. G.; Winn, M. *J. Org. Chem.* **1967**, *32*, 42.

(63) Guney, M.; Dastan, A.; Balci, M. *Helv. Chim. Acta* **2005**, *88*, 830.

(64) Jonas, R.; Klockow, M.; Lues, I.; Prueche,r H.; Schliep ,H. J.; Wurziger, H. *Eur. J. Med. Chem.* **1993**, *28*, 129.

(65) Daidone, G.; Maggio, B.; Schillaci, D. *Pharmazie* **1990**, *45*, 441.

(66) Meshram, H. M.; Prasad, B. R. V.; Kumar, D. A. *Tetrahedron Lett.* **2010**, *51*, 3477.

(67) Battilocchio, C.; Poce, G.; Alfonso, S.; Porretta, G. C.; Consalvi, S.; Sautebin, L.; Pace, S.; Rossi, A.; Ghelardini, C.; Mannelli, L. D. C.; Schenone, S.; Giordani, A.; Francesco, L. D.; Patrignani, P.; Biava, M. *Bioorg. Med. Chem*. **2013**, *21*, 3695.

(68) Kaiser, D. G.; Glenn, E. M. *J. Pharm. Sci*. **1972**, *61*, 190.

(69) Roth, B. D. *Prog. Med. Chem*. **2002**, *40*, 1.

(70) Etcheverry, S. B.; Barrioa, D. A.; Cortizoa, A. M.; Williams, P. A. M. *J. Inorg. Biochem*. **2002**, *88*, 94.

(71) Papaetis, G. S.; Syrigos, K. N. *BioDrugs* **2009**, *23*, 377.

(72) Giuliani, F. C.; Berbieri, B.; Perroni, G.; Lazzari, E.; Arcamoni, F.; Mongelli, N. *Proc. Am. Assoc. Cancer Res.* **1988**, *29*, 330.

(73) Kros, A.; Van Hovel S. W. F. M.; Nolte R. J. M.; Sommerdijk N. A. J. M. *Sens. Actuators B* **2001**, *80*, 229.

(74) Saito, R.; Matsumura, Y.; Suzuki, S.; Okazaki, N. *Tetrahedron* **2010**, *66*, 8273.

(75) Bobek, M.; Bloch, A. *J. Med. Chem.* **1972**, *15*, 164.

(76) Peresada, V. P.; Medvedev, O. S.; Likhosherstov, A. M.; Skoldinov, A. P. *Khim.-Farm. Zh.* **1987**, *21*, 1054.

(77) Likhosherstov, A. M.; Filippova, O. V.; Peresada, V. P.; Kryzhanovskii, S. A.; Vititnova, M. B.; Kaverina, N. V.; Reznikov, K. *M. Pharm. Chem. J.* **2003**, *37*, 6.

(78) Seredenin, S. B.; Voronina, T. A.; Likhosherstov, A. M.; Peresada,V. P.; Molodavkin, G. M.; Halikas, J. A. *Patent US 5378846*, **1995**.

(79) Seredenin, S. B.; Voronina, T. A.; Beshimov, A.; Peresada, V. P.; Likhosherstov, A. *M. Patent RU 2099055*, **1997**.

(80) Yong, W.; Gloer, J. B.; Scott, J. A.; Malloch, D. *J. Nat. Prod.* **1995**, *58*, 93.

(81) Chill, L.; Aknin, M.; Kashman, Y. *Org. Lett*. **2003**, *5*, 2433.

(82) Huang, S. X.; Powell, E.; Rajski, S. R.; Zhao, L. X.; Jiang, C. L.; Duan, Y.; Xu, W.; Shen, B. *Org. Lett.* **2010**, *12*, 3525.

(83) Zilkowski, B. W.; Bartelt, R. J.; Blumberg, D.; James, D. G.; Weaver, D. K. *J. Chem. Ecol.* **1999**, *25*, 229.

(84) Durán, R.; Zubía, E.; Ortega, M. J.; Naranjo, S.; Salvá, J. *Tetrahedron* **1999**, *55*, 13225.

(85) Masuda, H.; Tanaka, M.; Akiyama, T.; Shibamoto, T. *J. Agric. Food Chem.***1980**, *28*, 244.

(86) Darkins, P.; Groarke, M.; McKervey, M. A.; Moncrieff, H. M.; McCarthy, N.; Nieuwenhuyzen, M. *J. Chem. Soc. Perkin Trans.* **2000**, *1*, 381.

(87) Kobayashi, T.; Miki, K.; Nikacen, B.; Ohta, A. *J. Chem. Soc. Perkin Trans.* **2001**, *1*, 1372.

(88) Kamitori, Y. *J. Heterocyc. Chem.* **2001**, *38*, 773.

(89) Kano, S.; Takahagi, Y.; Shibuya, S. *Synthesis* **1978**, 372.

(90) Bradbury, R. H.; Griffiths, D.; Rivett, J. E. *Heterocycles* **1990**, *31*, 1647.

(91) Raw, S. A.; Wilfred, C. D.; Taylor, R. J. K. *Chem. Commun.***2003**, 2286.

(92) Zhao, Z.; Wisnoski, D. D.; Wolkenberg, S. E.; Leister, W. H.; Wang, Y.; Lindsley, C. W. *Tetrahedron Lett.* **2004**, *45*, 4873.

(93) Blake, K.W.; Porter, A. E. A.; Sammes, P. G. *J. Chem. Soc. Perkin Trans.* **1972**, *1*, 2494.

(94) Adam, I.; Orain, D.; Meier, P. *Synlett* **2004**, 2031.

(95) Dickschat, J. S.; Reichenbach, H.;Wagner-Dobler, I.; Schulz, S. *Eur. J. Org. Chem.* **2005**, 4141.

(96) Matsushita, H.; Lee, S. H.; Yoshida, K.; Clapham, B.; Koch, G.; Zimmermann, J.; Janda, K. D. *Org. Lett.* **2004**, *6*, 4627.

(97) Chandrasekhar, S.; Gopalaih, K. *Tetrahedron Lett.* **2001**, *42*, 8123.

(98) Büchi, G.; Galindo, J. *J.Org. Chem* **1991**, *56*, 2605.

(99) Sato, N.; Ono, M. *J. Heterocyc. Chem.* **2000**, *37*, 419.

(100) Basceken, S.; Balci, M. *J. Org. Chem.* **2015,** *80*, 3806.

(101) Guven, S.; Ozer, M. S.; Kaya, S.; Menges, N.; Balci, M. *Org. Lett.* **2015,** *17*, 2660.

(102) Thoms, H. *Ber. Dtsch. Pharm. Ges.* **1891**, *1*, 241.

(103). Hoffmann, H. M. R.; Rabe, J. *Angew. Chem. Int. Ed. Engl*. **1985**, *24*, 94.

(104) Picman, A. K. *Biochem. Syst. Ecol.* **1986**, *14*, 255.

(105) Chang S. T.; Wang D. S. Y.; Wu C. L.; Shiah S. G.; Kuo Y. H.; Chang C.J. *Phytochemistry* **2000**, *55*, 227.

(106) Chen, F. C.; Peng, C. F.; Tsai, I. L.; Chen, I. S. *J. Nat. Prod*. **2005**, *68*, 1318.

(107) Kuo, S. Y.; Hsieh, T. J.; Wang, Y. D.; Lo, W. L.; Hsui, Y. R.; Chen, C. Y. *Chem. Pharm. Bull*. **2008**, *56*, 97.

(108) Hu, J. F.; Patel, R.; Li, B.; Garo, E.; Hough, G. W.; Goering, M. G.; Yoo, H. D.; Neil-Johnson, M. O; Eldridge, G. R. *J. Nat. Prod.*, **2007**, *70*, 604.

(109) Merten, J.; Hennig, A.; Schwab, P.; Frhlich, R.; Tokalov, S. V.; Gutzeit, H. O.; Metz, P. *Eur. J. Org. Chem.* **2006**, 1144.

(110) Ballini, R.; Marcantoni, E.; Perella, S. *J. Org. Chem.* **1999**, *64*, 2954.

(111) Lee, A. S. Y.; Chang, Y. T.; Wang, S. H.; Chu, S. F. *Tetrahedron Lett*. **2002**, *43*, 8489.

(112) Bachi, M. D.; Bosch, E. *J. Org. Chem*. **1992**, *57*, 4696.

(113) Lertvorachon, J.; Meepowpan, P.; Thebtaranonth, Y. *Tetrahedron* **1998**, *54*, 14341.

(114) Wakamatsu, T.; Miyachi, N.; Ozaki, F.; Shibasaki, M.; Ban, Y. *Tetrahedron Lett.* **1988**, *29*, 3829.

(115) Shie, J. Y.; Zhu, J. L. *Tetrahedron* **2016**, *72*, 1590.

(116) Gagnier, S. V.; Larock, R. C. *J. Org. Chem*. **2000**, *65*, 1525.

(117) Claisen, L. *Chem. Ber.* **1912**, *45*, 3157.

(118) Bergmann, E.; Corte, H. *J. Chem. Soc.* **1935**, 1363.

(119) Hurd, C. D.; Pollack, M. A. *J. Am. Chem. Soc.* **1938**, *60*, 1905.

(120) Carroll, M. F. *J. Chem. Soc.* **1940**, 704.

(121) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta*. **1964**, *47*, 2425.

(122) Johnson, W. S.; Werthemann, L.; Bartlett, W. R; Brockson, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

(123) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897.

(124) Baldwin, J. E.; Walker, J. A. *J. Chem. Soc., Chem. Commun.* **1973**, 117.

(125) Kwart, H.; Schwartz, J. L. *J. Org. Chem.* **1974**, *39*, 1575.

(126) Jolidon, S.; Hansen, H. J. *Helv. Chim. Acta* **1977**, *60*, 978.

(127) Kazmaier, U. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 998.

(128) Ponaras, A. A. *Tetrahedron Lett.* **1980**, *21*, 4803.

(129) Rhoads, S. J.; Cockroft, R. D. *J. Am. Chem. Soc.* **1969**, *91*, 2815.

(130) Reich, N. W.; Yang, C. G.; Shi, Z.; He, C. *Synlett* **2006**, *8*, 1278.

(131) Sherry, B.; Toste, F. *J. Am. Chem. Soc.* **2004,** *126*, 15978.

(132) Peruzzi M. T.; Lee S. J.; Gagne M. R. *Org. Lett.* **2017,** *19*, 6256.

(133) Rosenberg M. G.; Billing P.; Brecker L.; Brinker U. H. *J. Org. Chem.* **2014**, *79*, 8786.

(134) Altun Y.; Dogan D. S.; Balci M. *Tetrahedron* **2014**, *70*, 4884.

APPENDICIES

A. SPECTRAL DATA

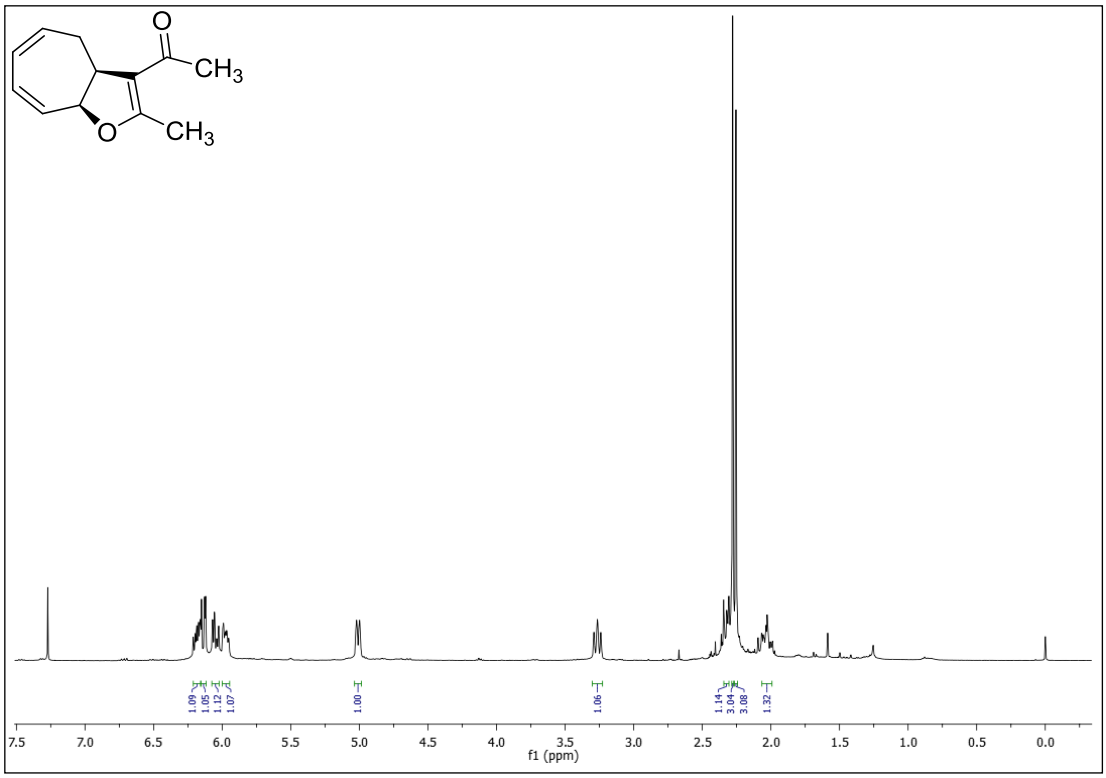


Figure 3 ^{1}H NMR Spectrum of Compound **130a** in $CDCl_3$

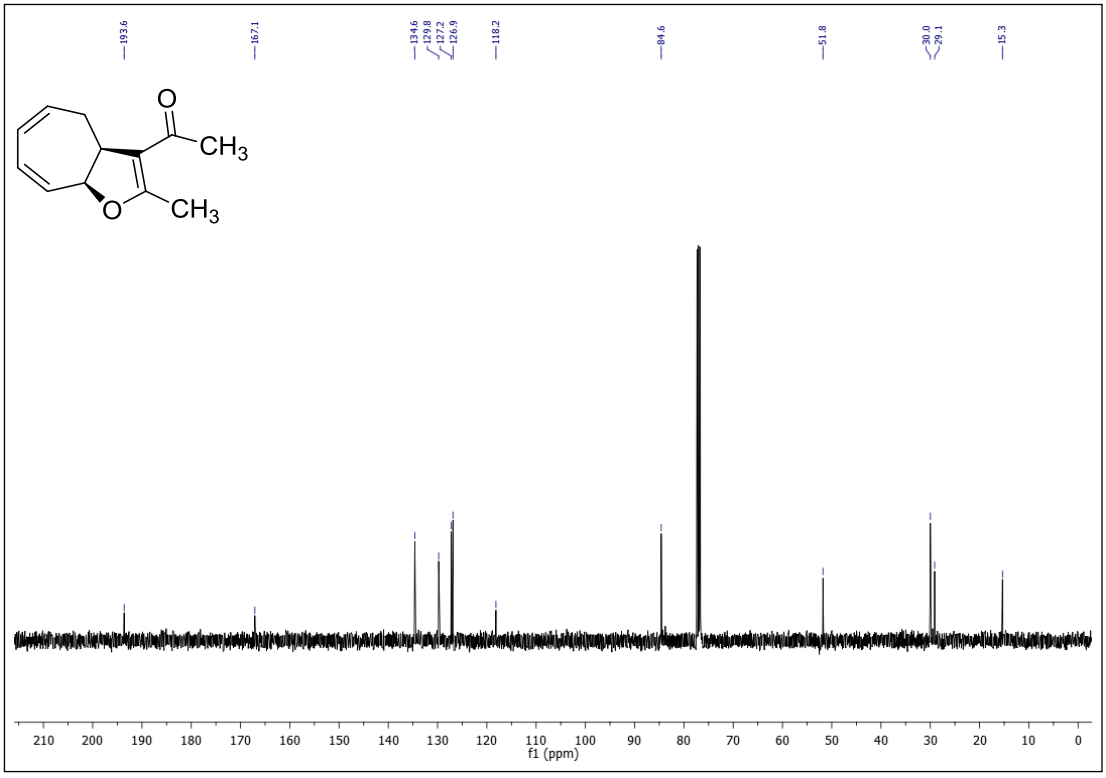


Figure 4 ^{13}C NMR Spectrum of Compound **130a** in $CDCl_3$

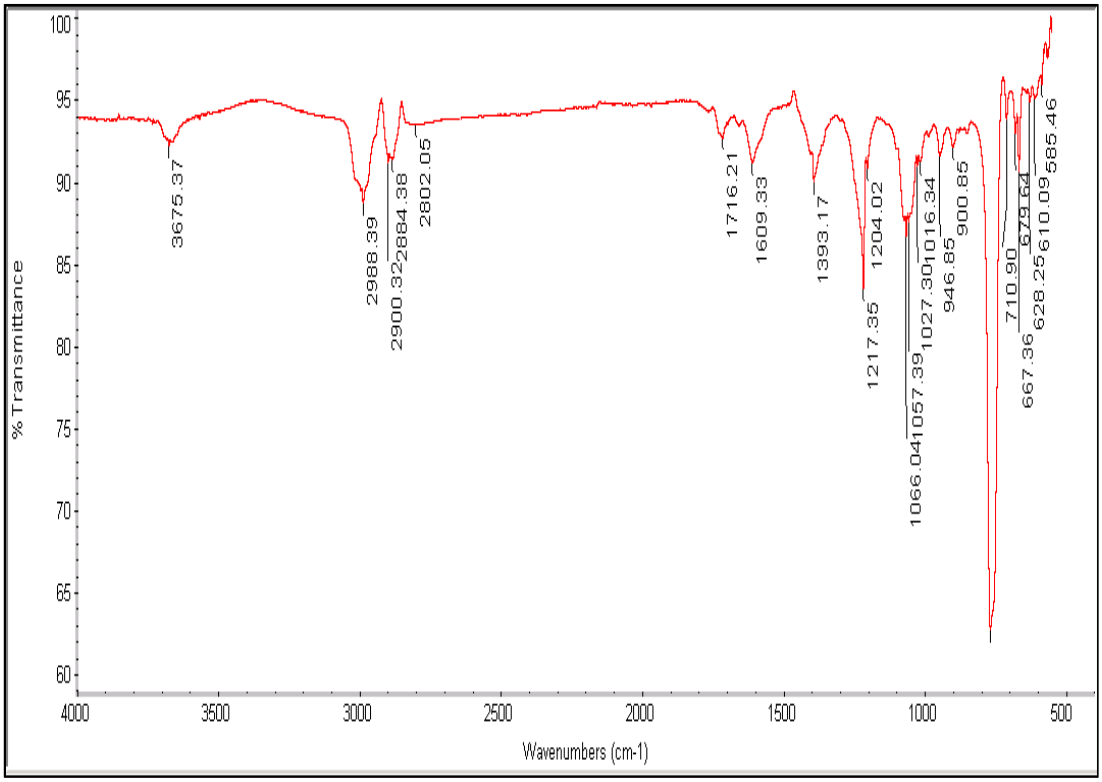


Figure 5 IR Spectrum of Compound **130a**

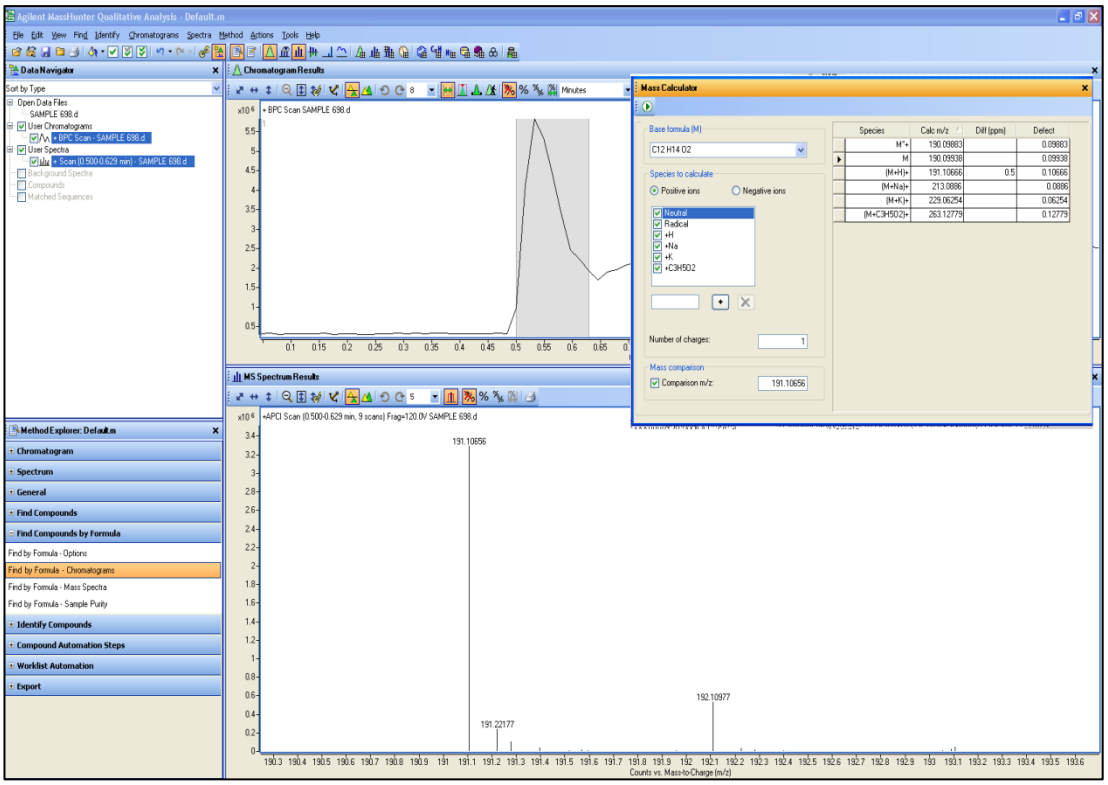


Figure 6 HRMS Spectrum of Compound **130a**

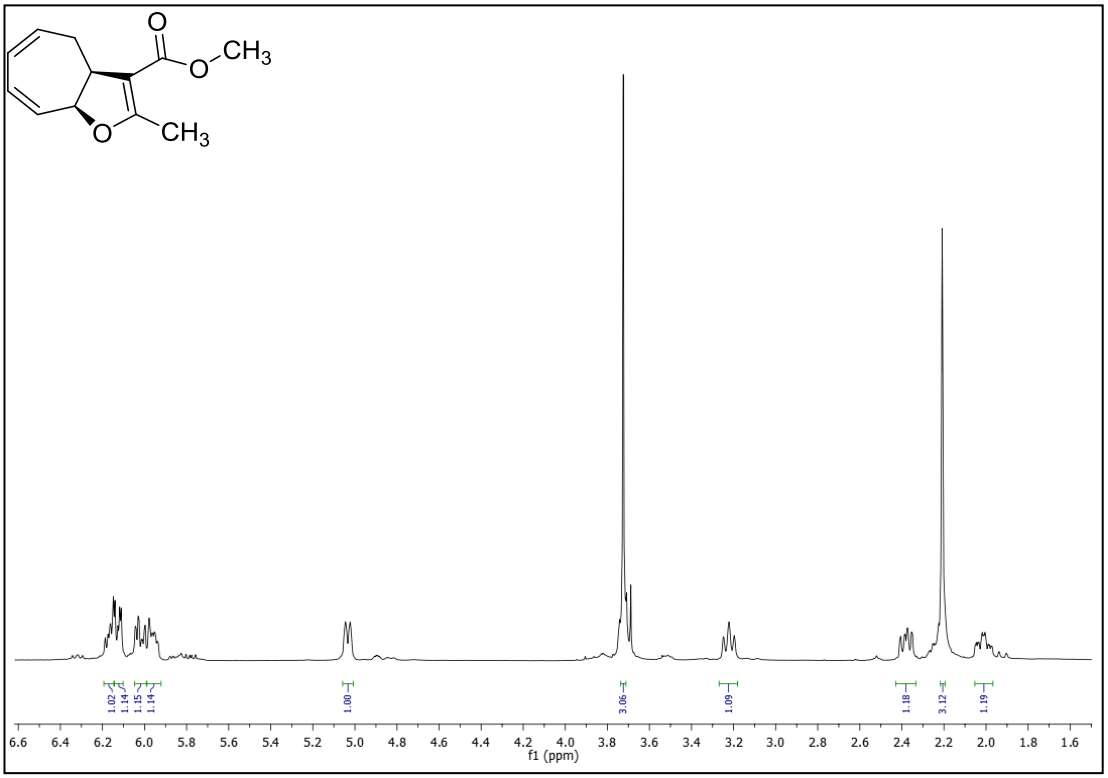


Figure 7 ^{1}H NMR Spectrum of Compound **130b** in $CDCl_3$

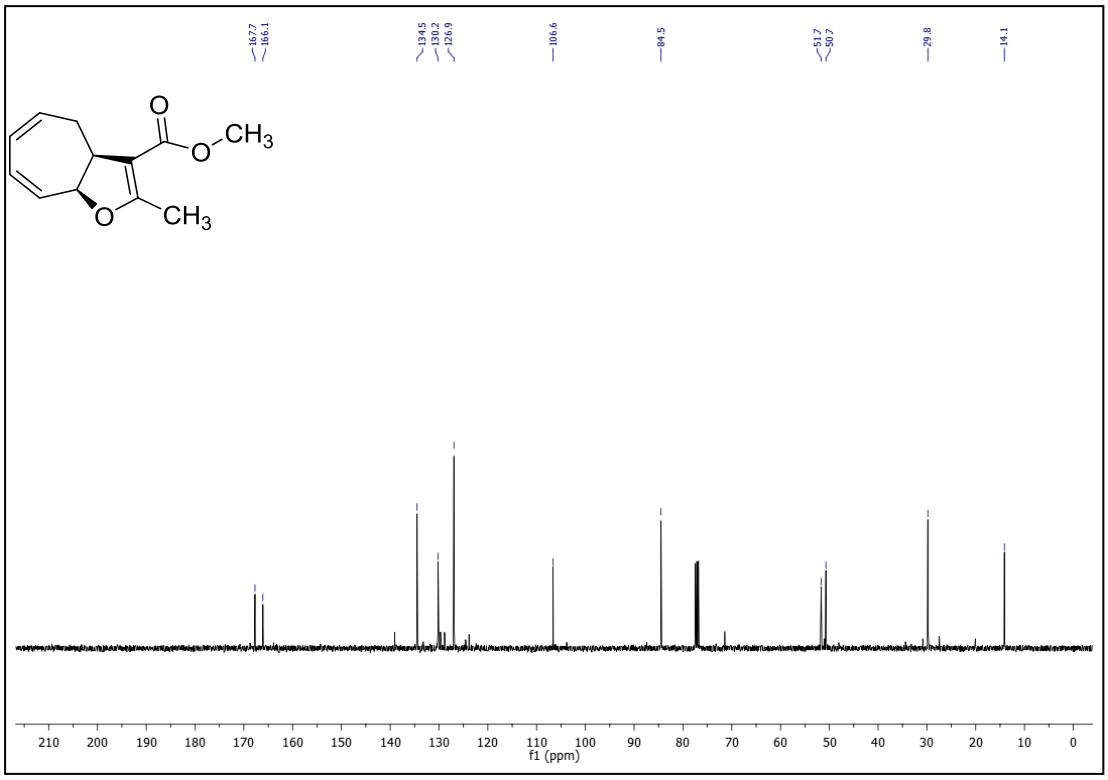


Figure 8 ^{13}C NMR Spectrum of Compound **130b** in $CDCl_3$

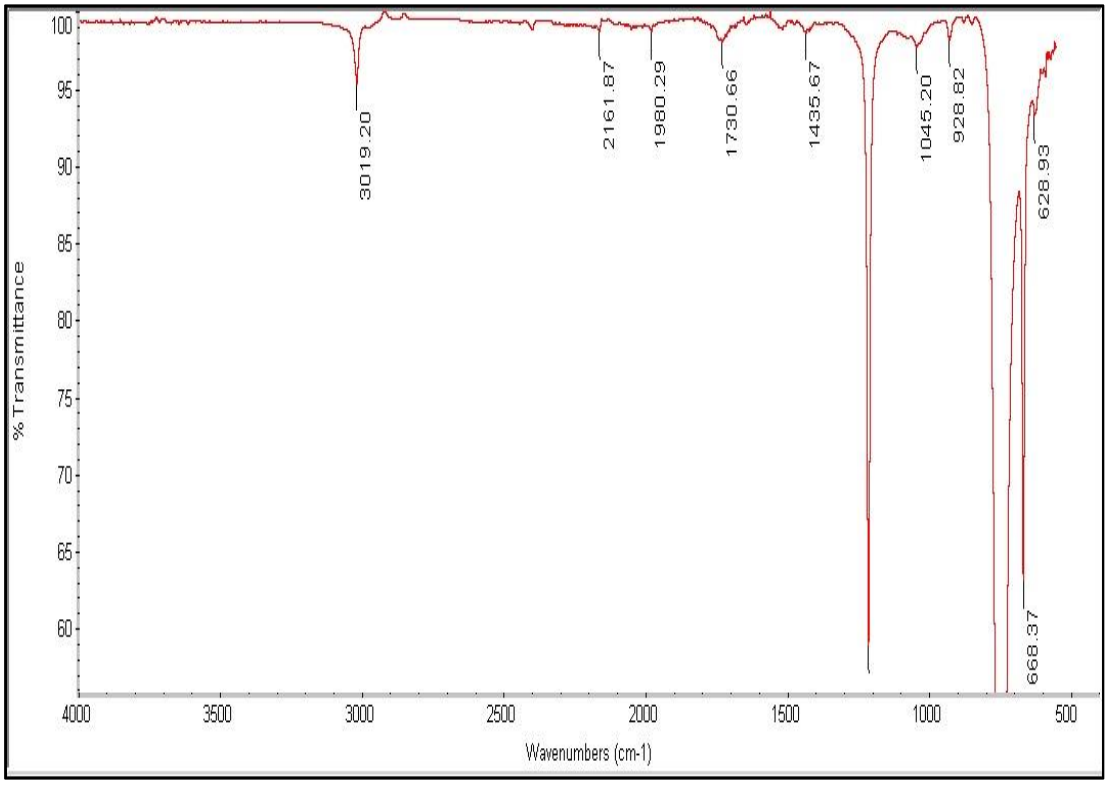


Figure 9 IR Spectrum of Compound **130b**

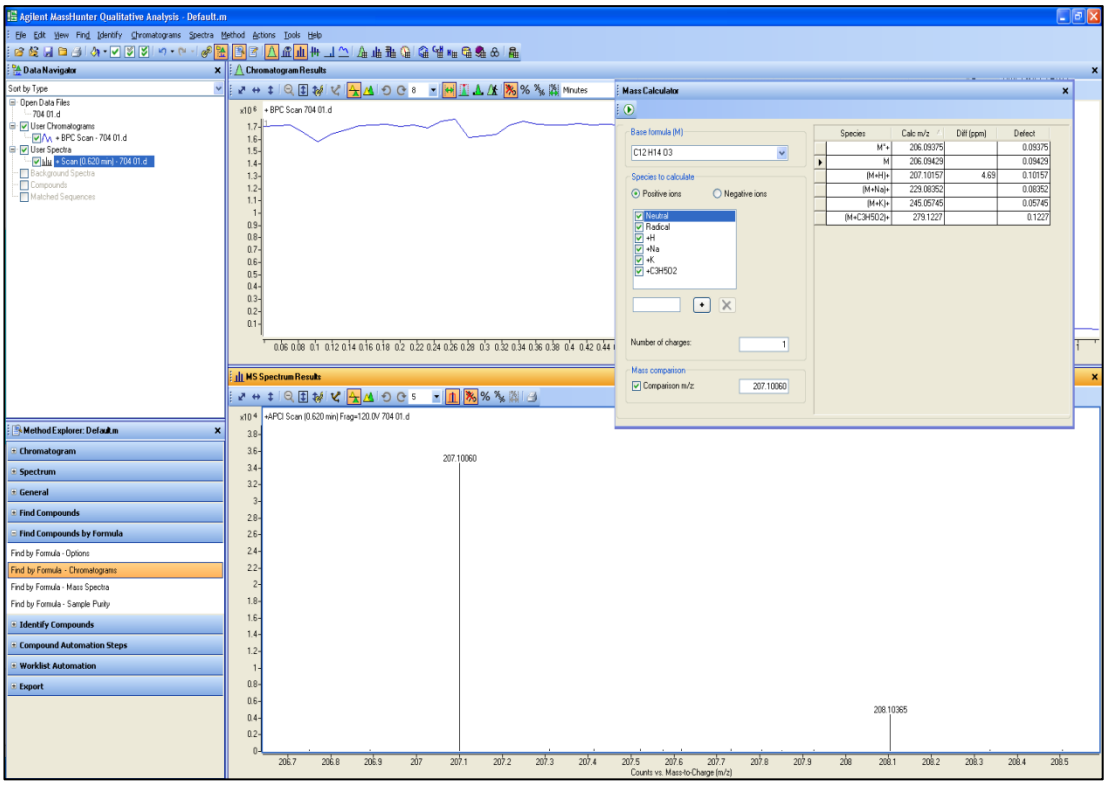


Figure 10 HRMS Spectrum of Compound **130b**

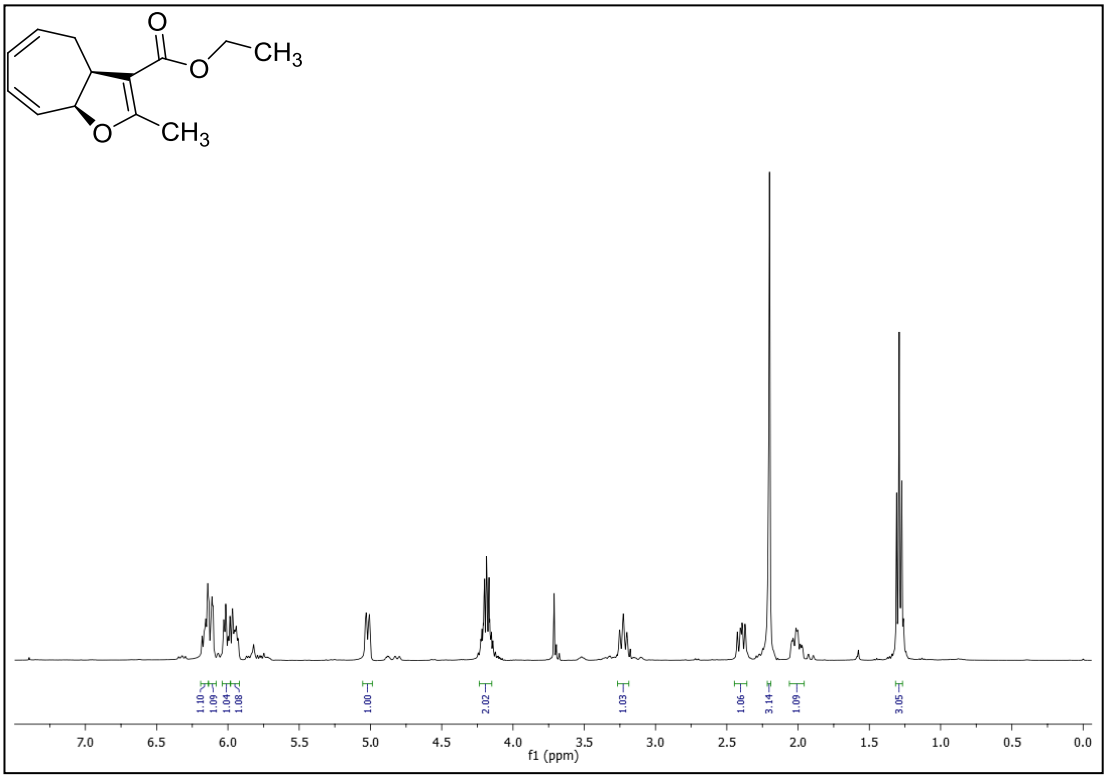


Figure 11 ^{1}H NMR Spectrum of Compound **130c** in $CDCl_3$

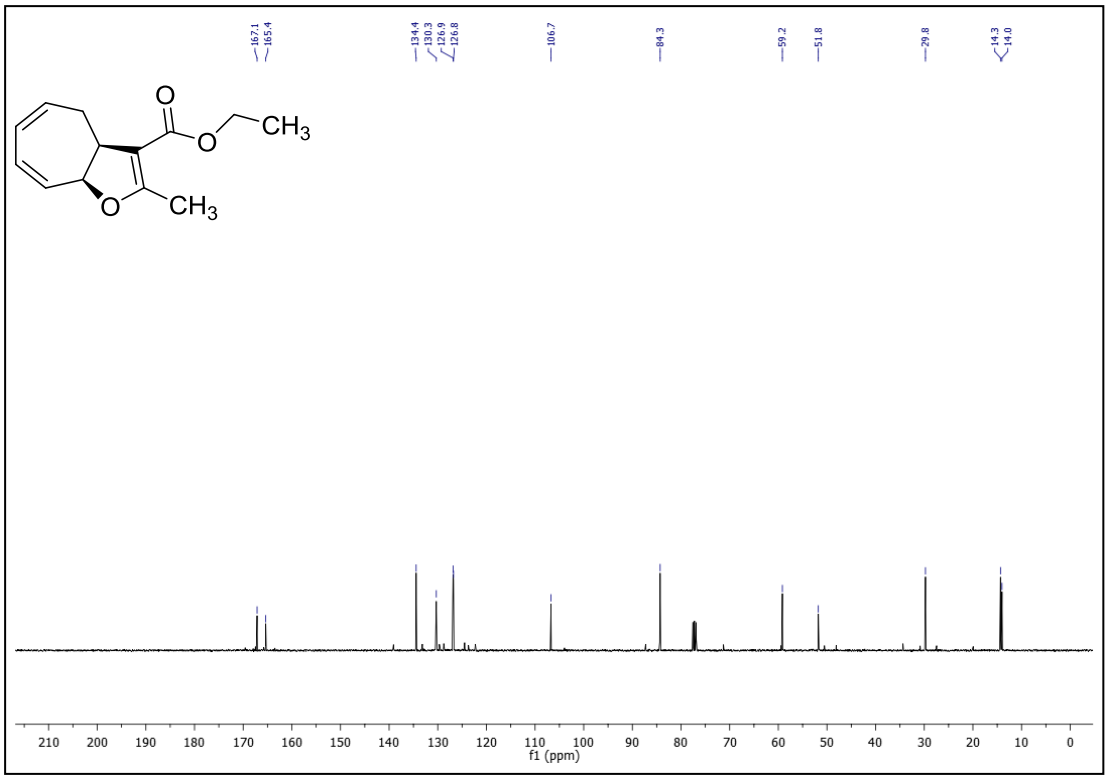


Figure 12 ^{13}C NMR Spectrum of Compound **130c** in $CDCl_3$

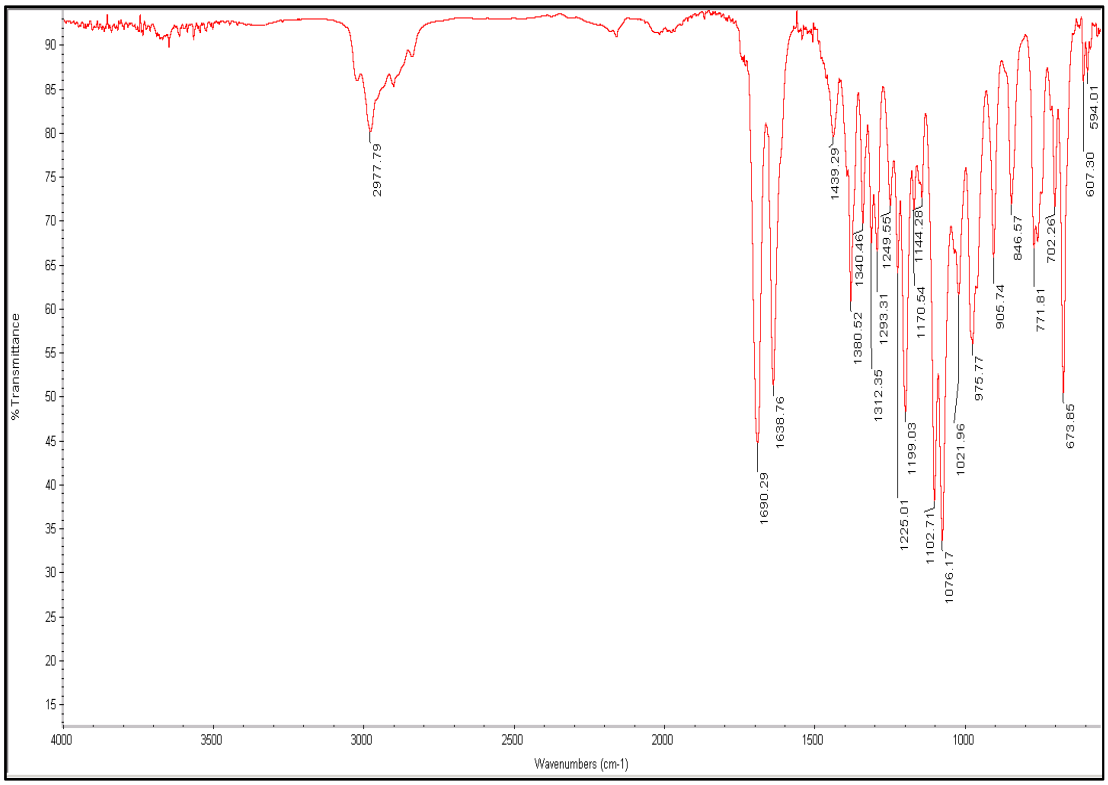


Figure 13 IR Spectrum of Compound **130c**

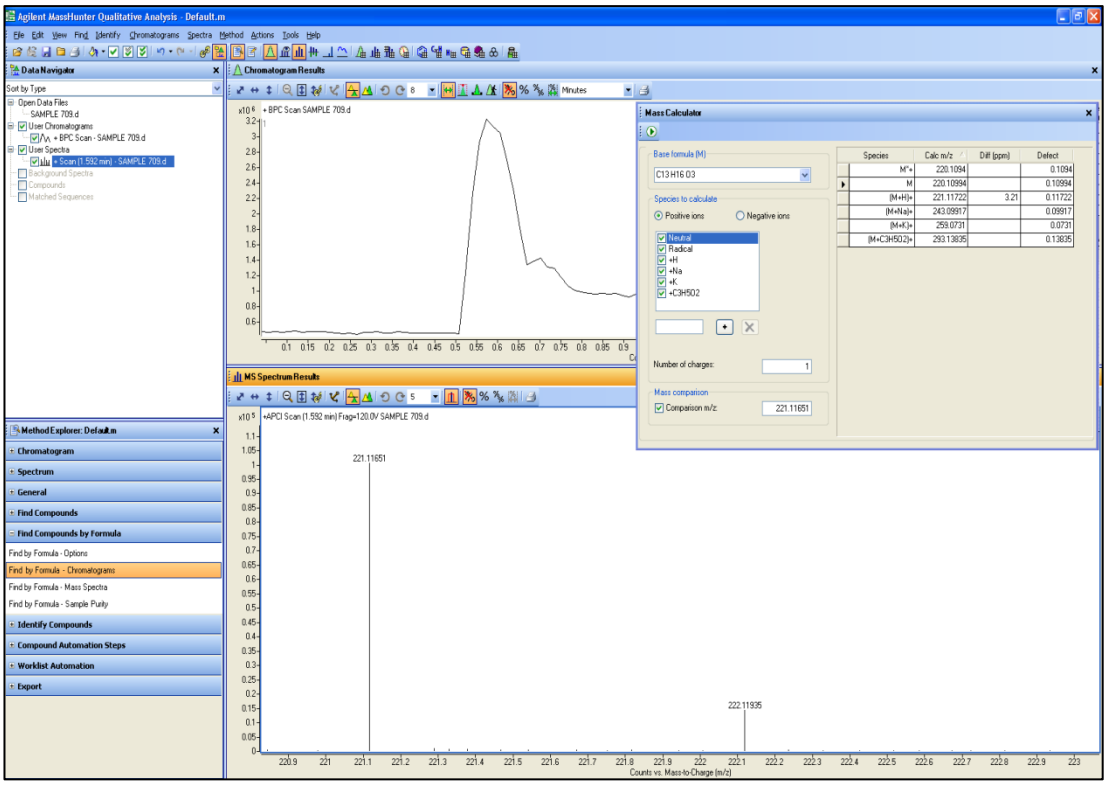


Figure 14 HRMS Spectrum of Compound **130c**

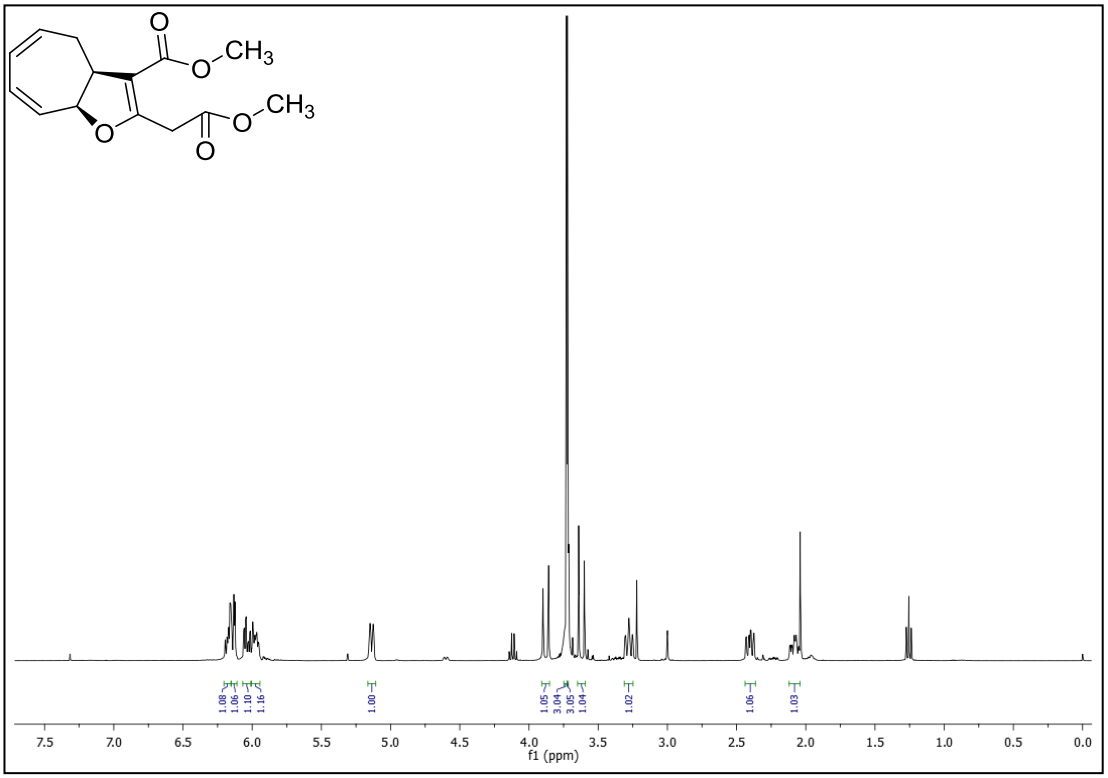


Figure 15 ^{1}H NMR Spectrum of Compound **130d** in $CDCl_3$

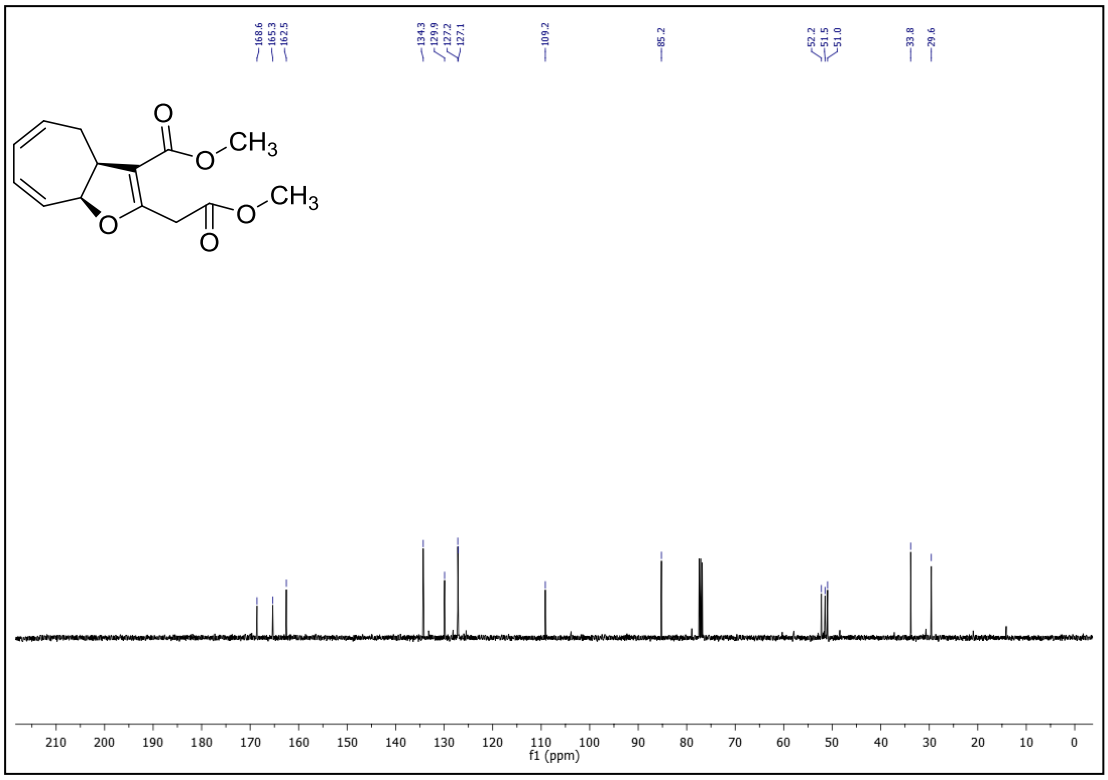


Figure 16 ^{13}C NMR Spectrum of Compound **130d** in $CDCl_3$

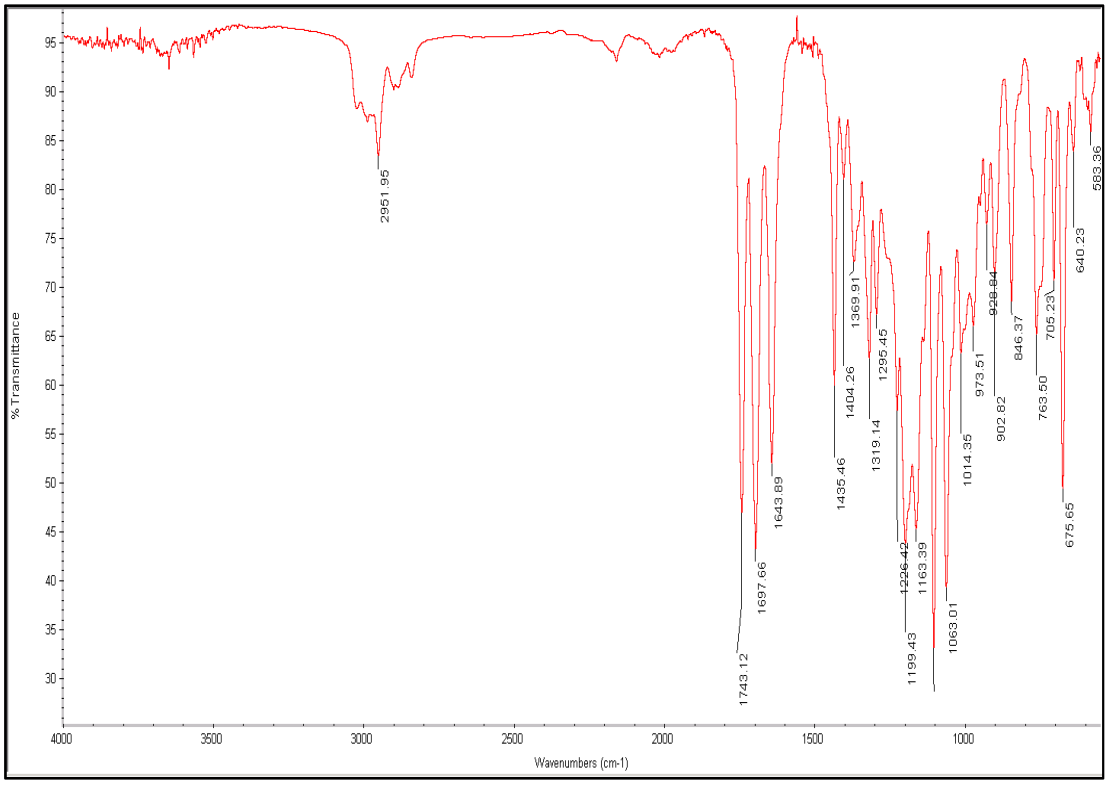


Figure 17 IR Spectrum of Compound **130d**

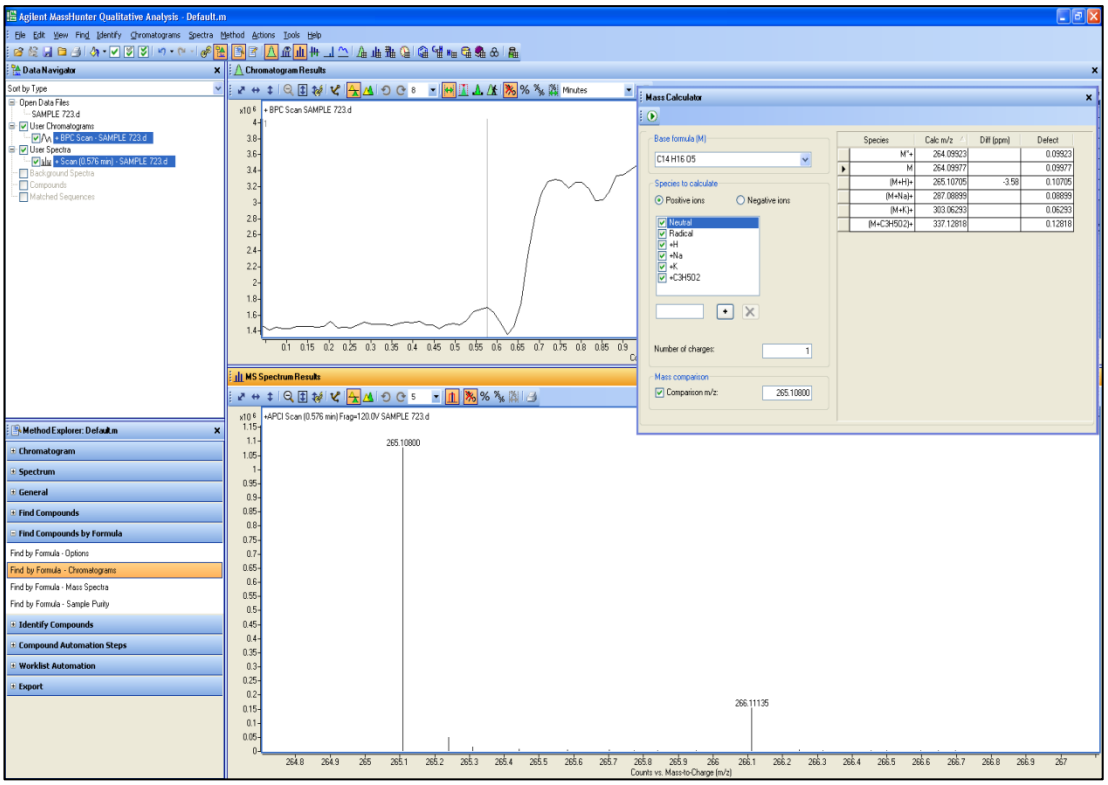


Figure 18 HRMS Spectrum of Compound **130d**

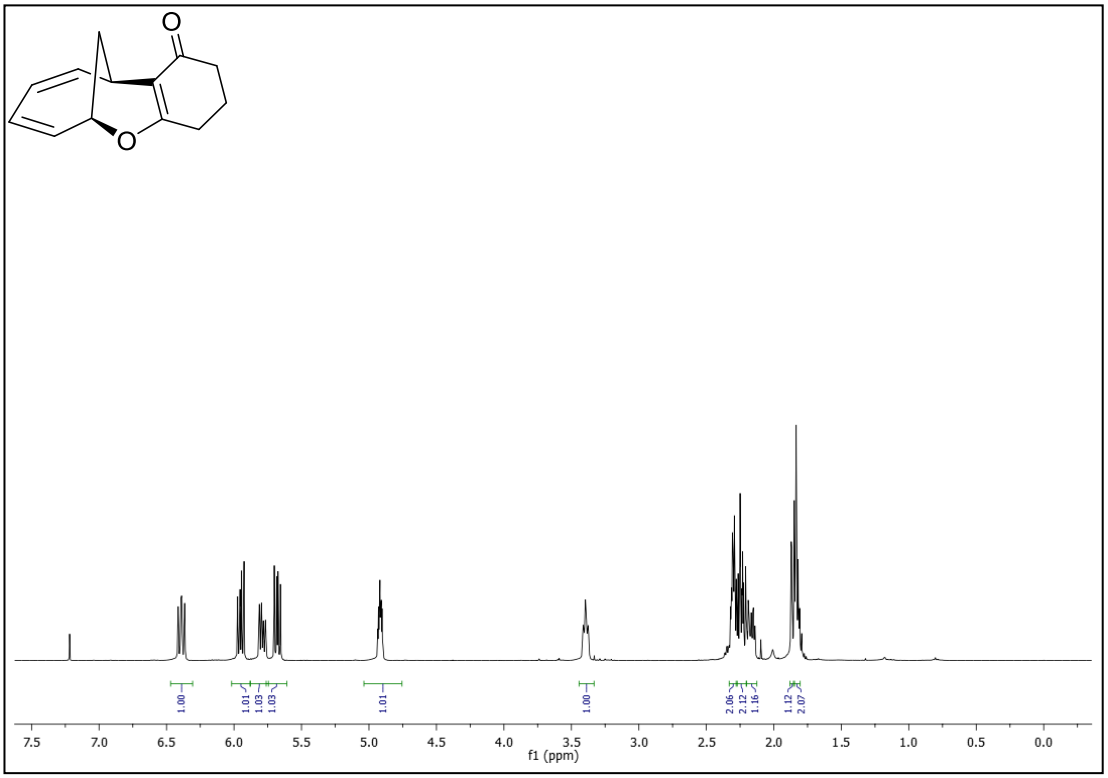


Figure 19 ^{1}H NMR Spectrum of Compound **140a** in $CDCl_3$

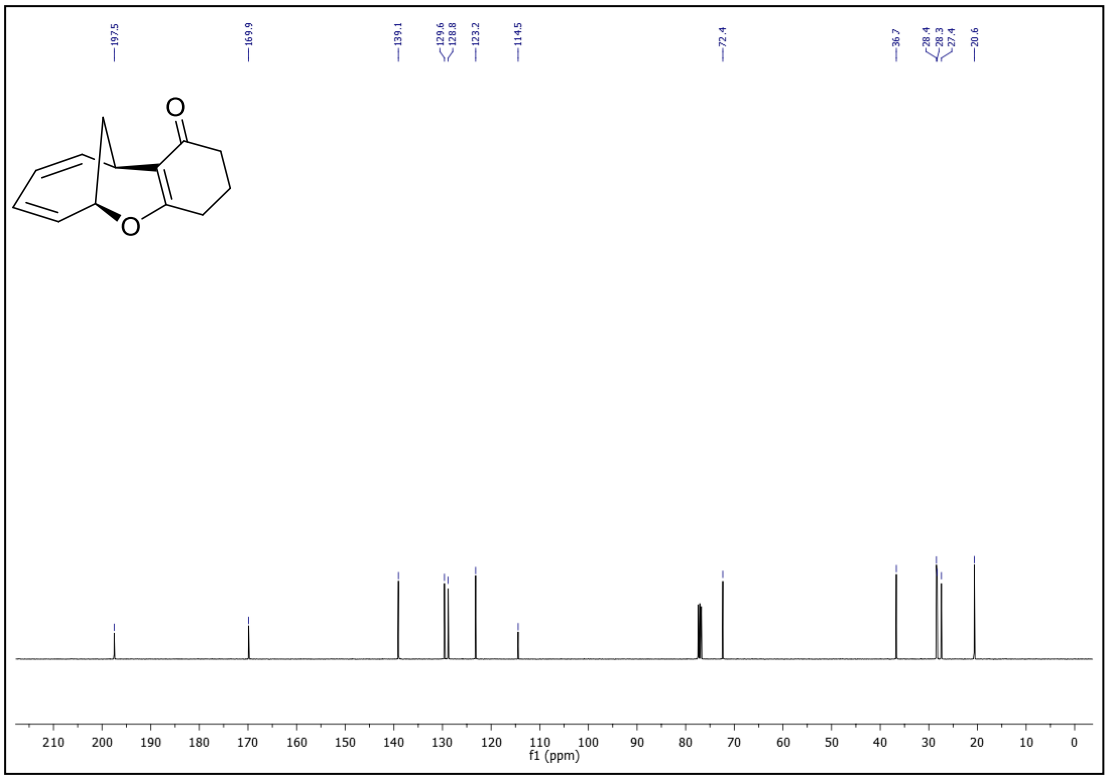


Figure 20 ^{13}C NMR Spectrum of Compound **140a** in $CDCl_3$

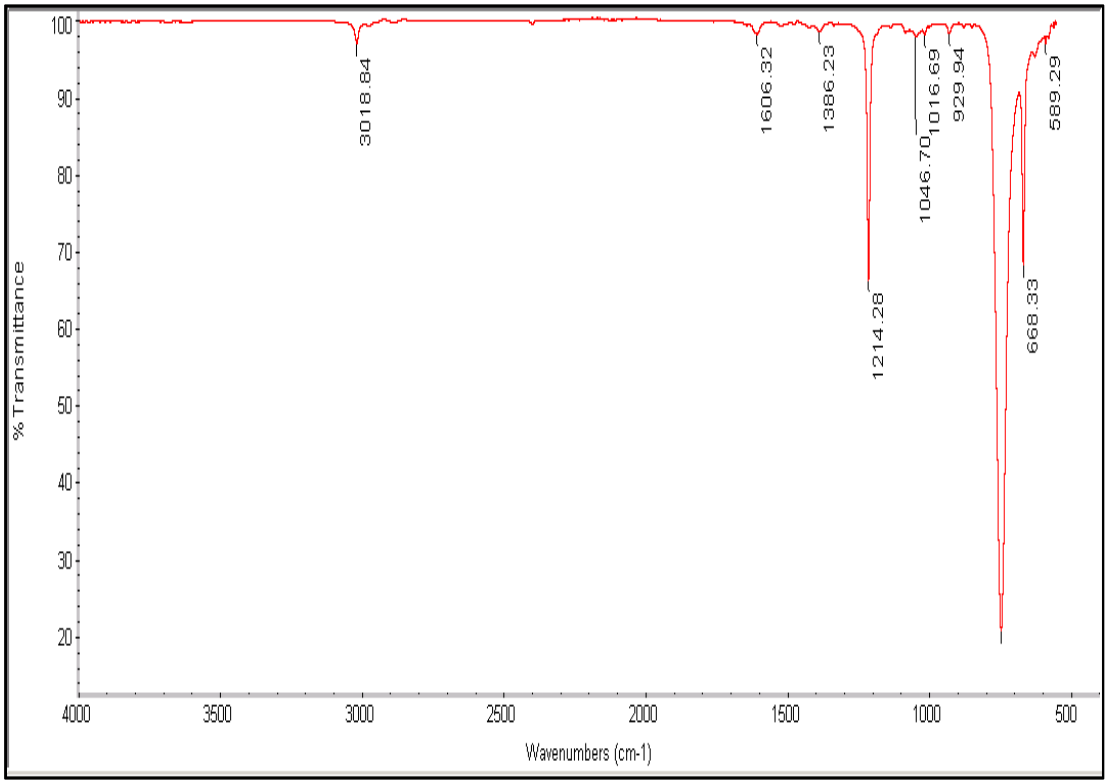


Figure 21 IR Spectrum of Compound **140a**

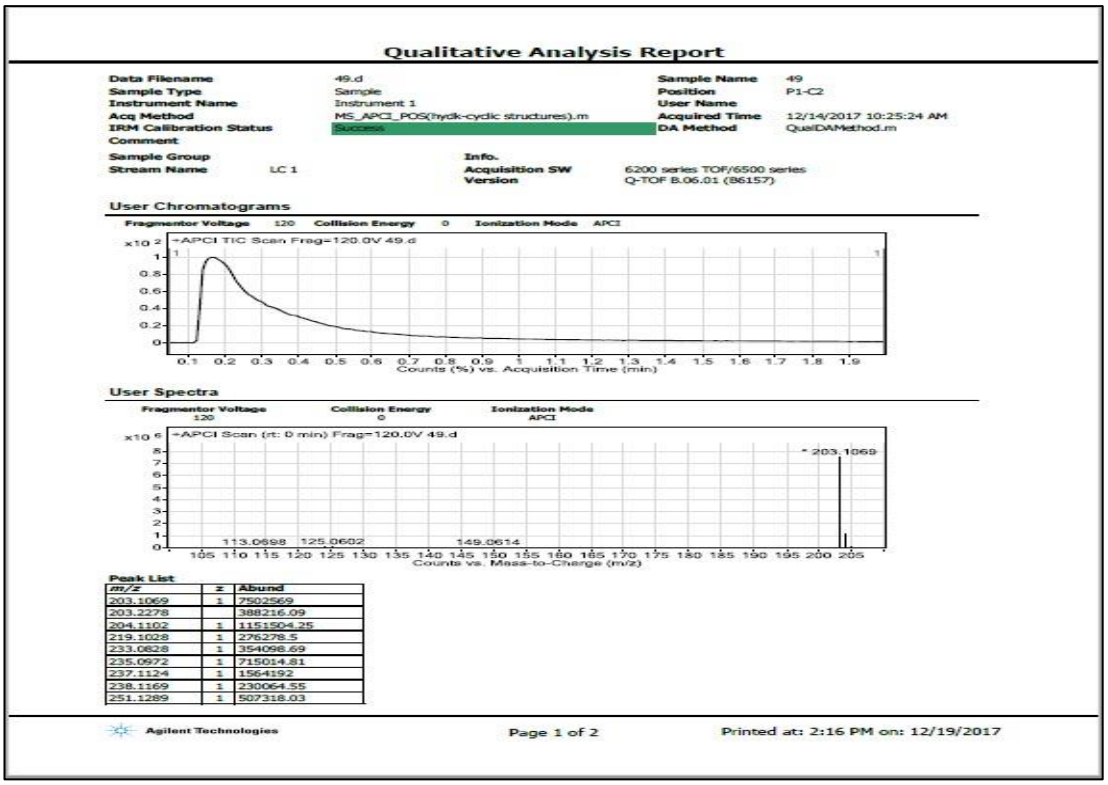


Figure 22 HRMS Spectrum of Compound **140a**

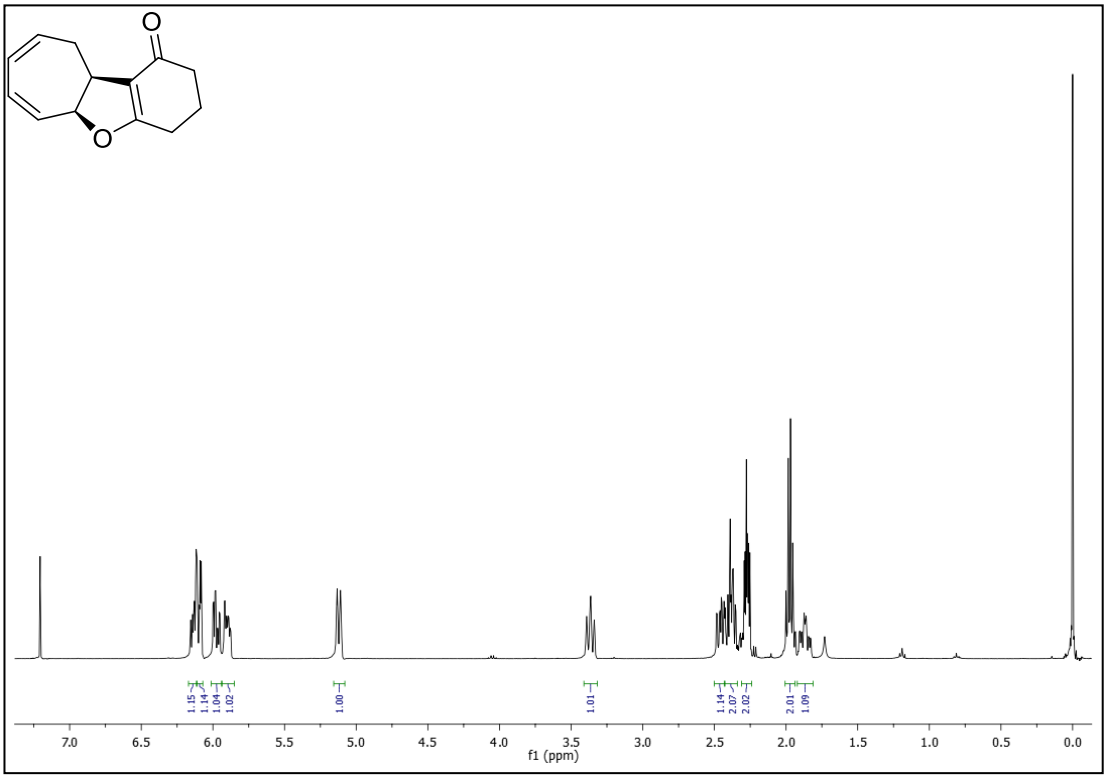


Figure 23 ^{1}H NMR Spectrum of Compound **141a** in $CDCl_3$

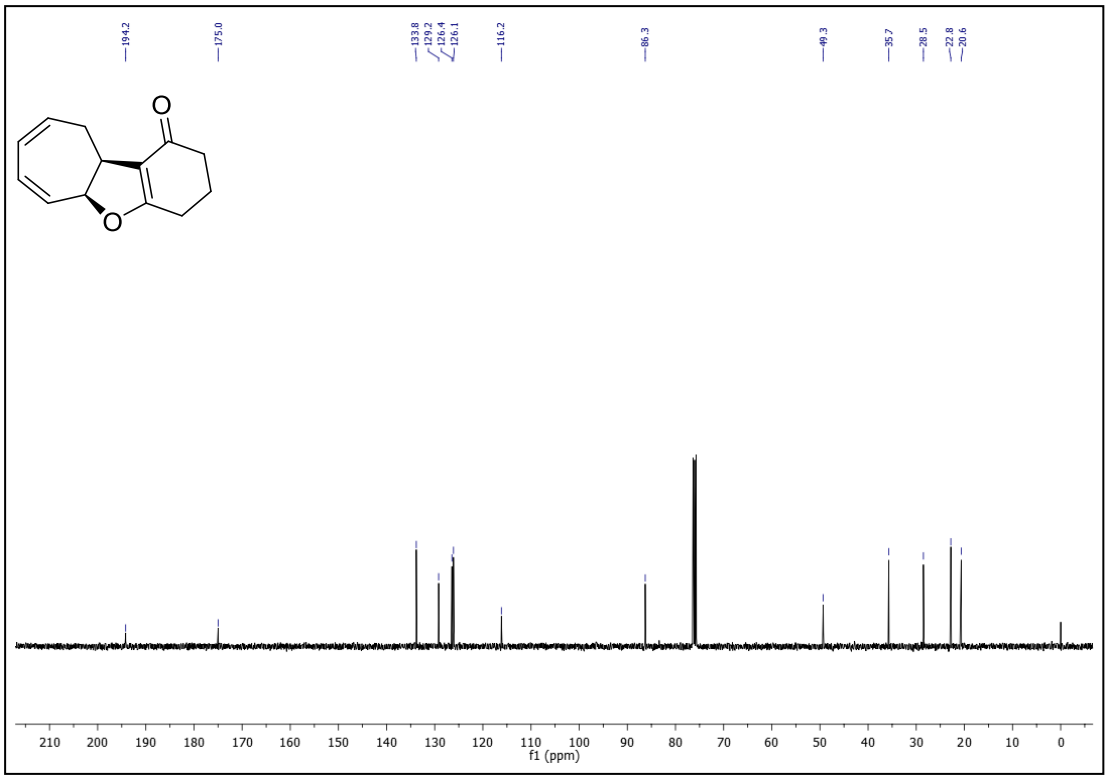


Figure 24 ^{13}C NMR Spectrum of Compound **141a** in $CDCl_3$

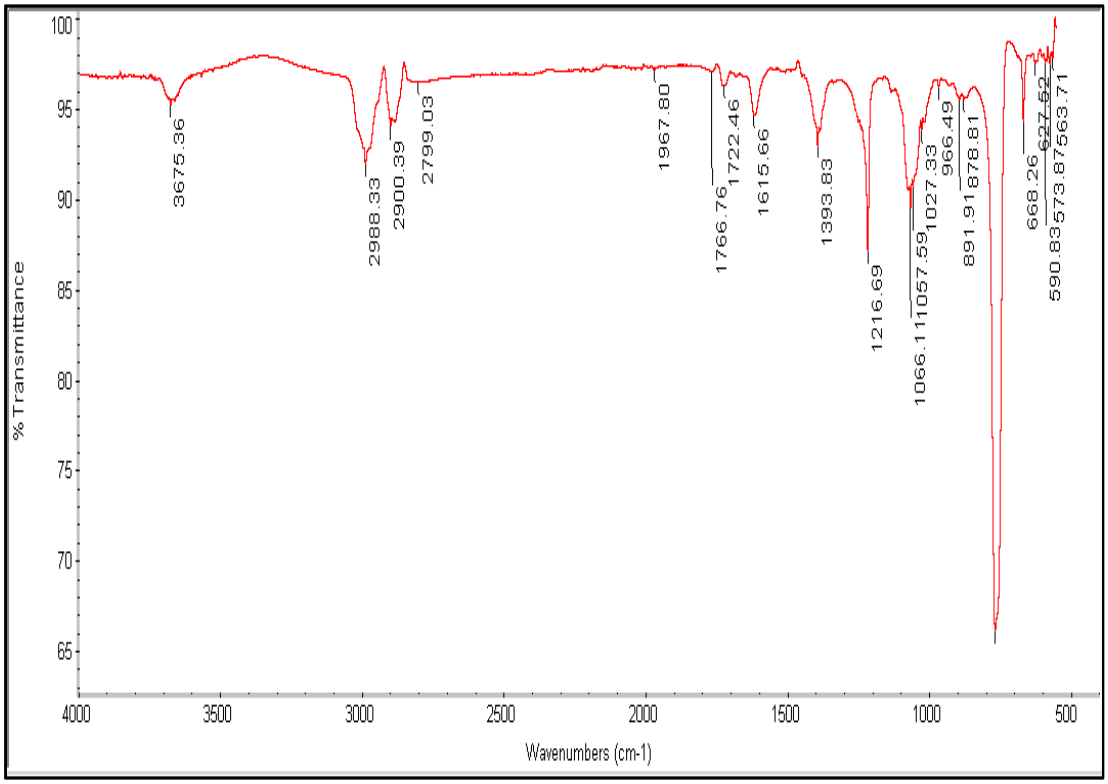


Figure 25 IR Spectrum of Compound **141a**

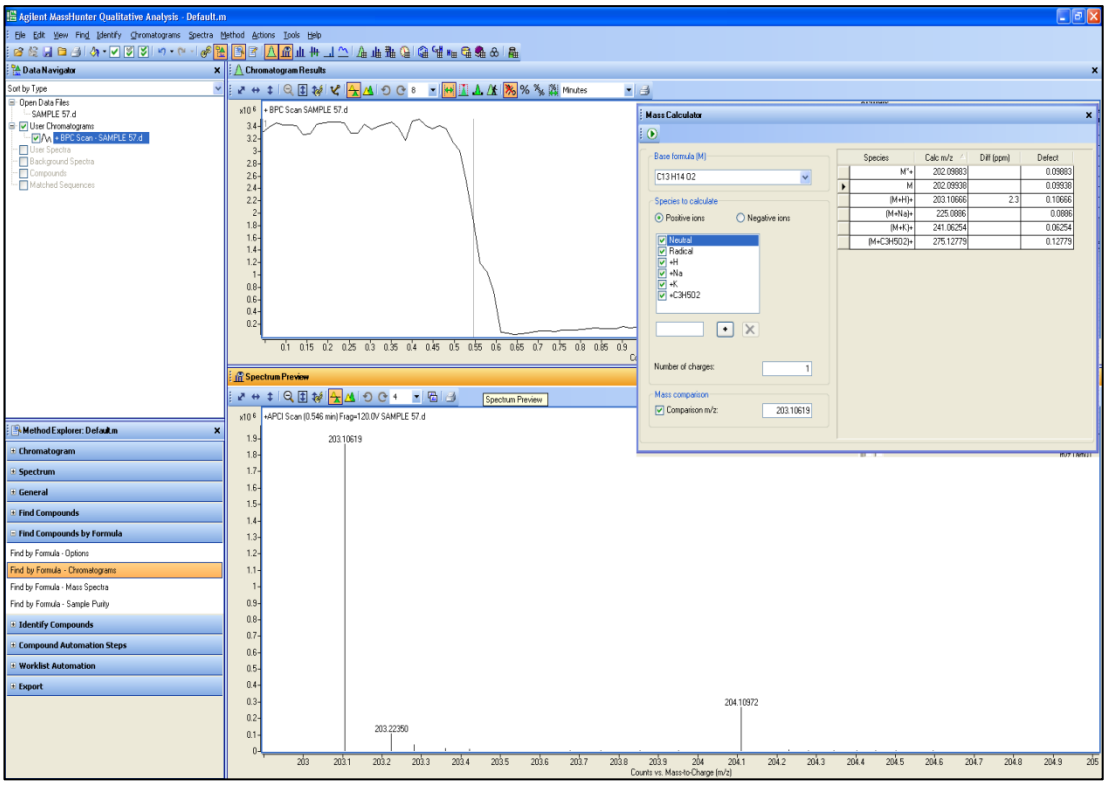


Figure 26 HRMS Spectrum of Compound **141a**

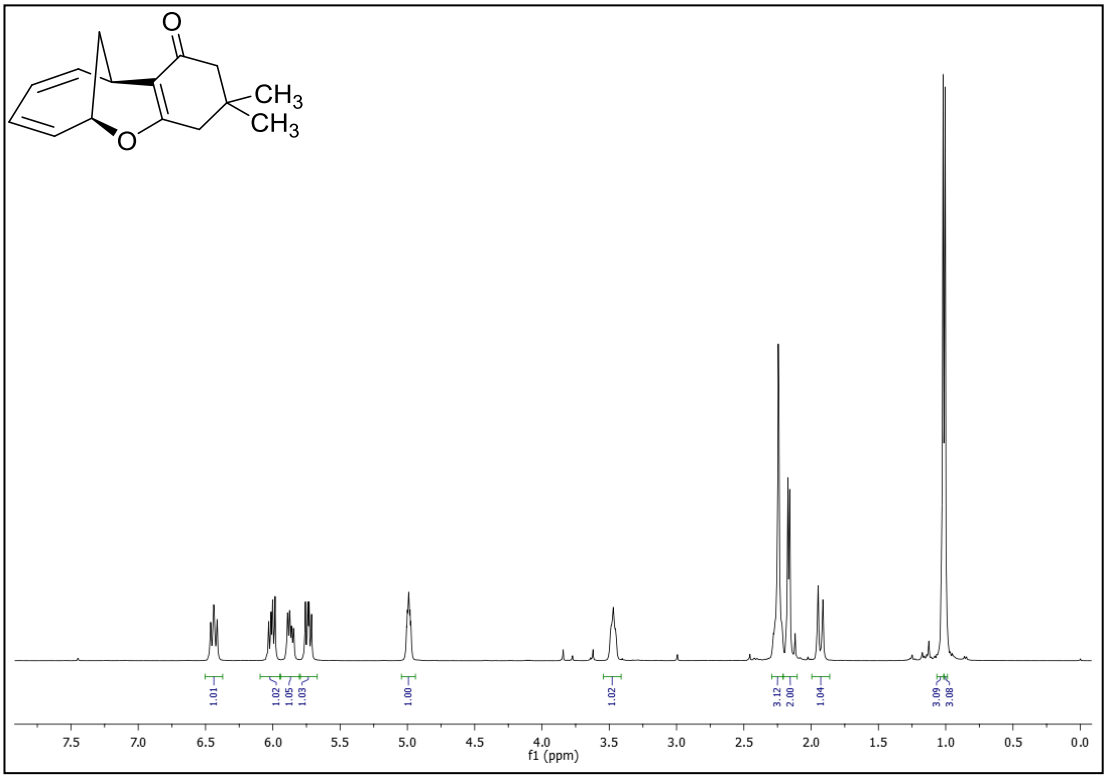


Figure 27 ^{1}H NMR Spectrum of Compound **140b** in $CDCl_3$

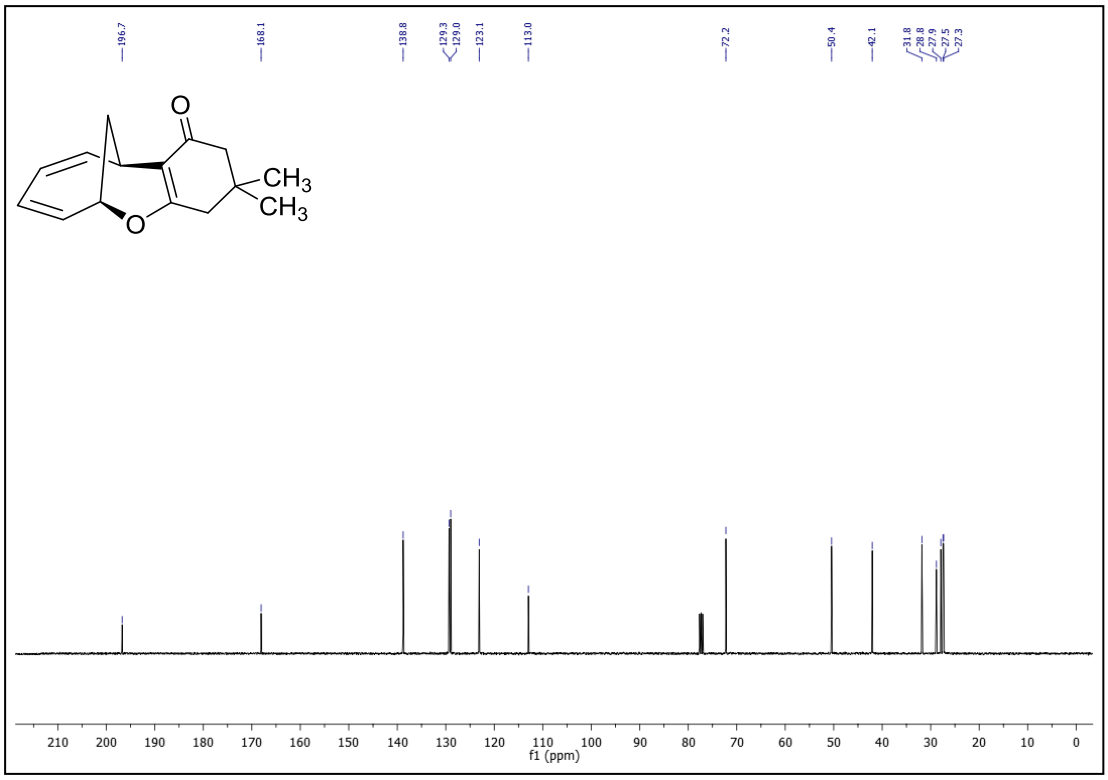


Figure 28 ^{13}C NMR Spectrum of Compound **140b** in $CDCl_3$

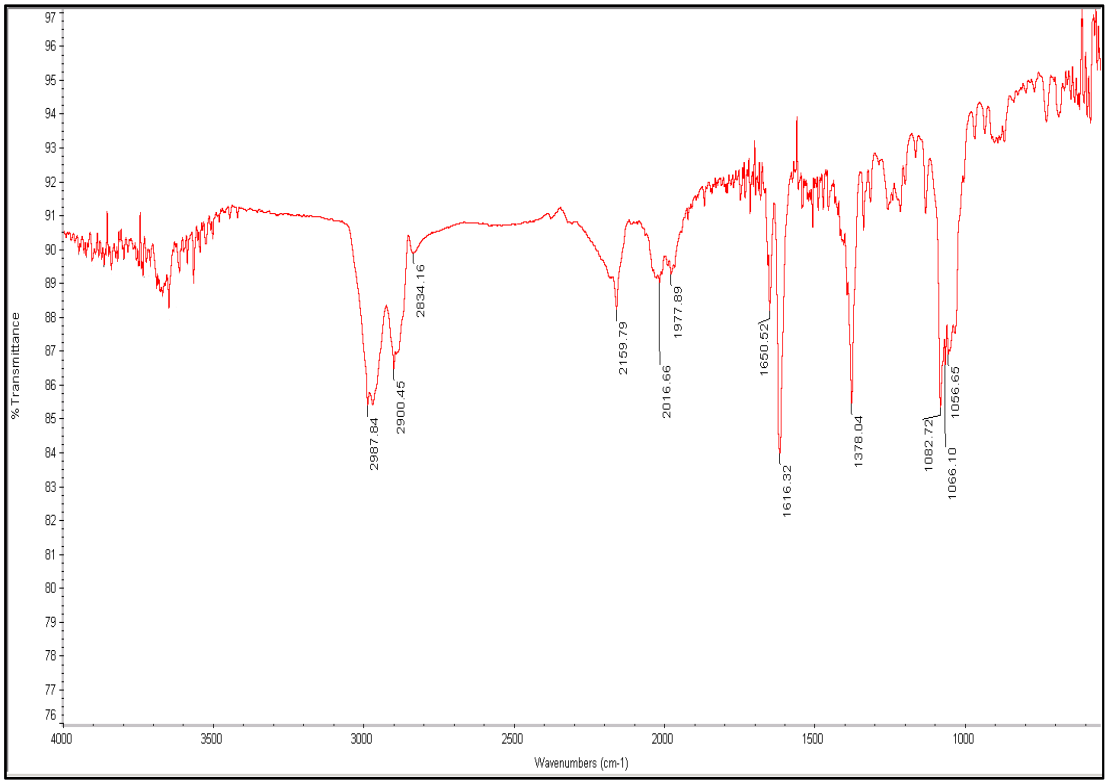


Figure 29 IR Spectrum of Compound **140b**

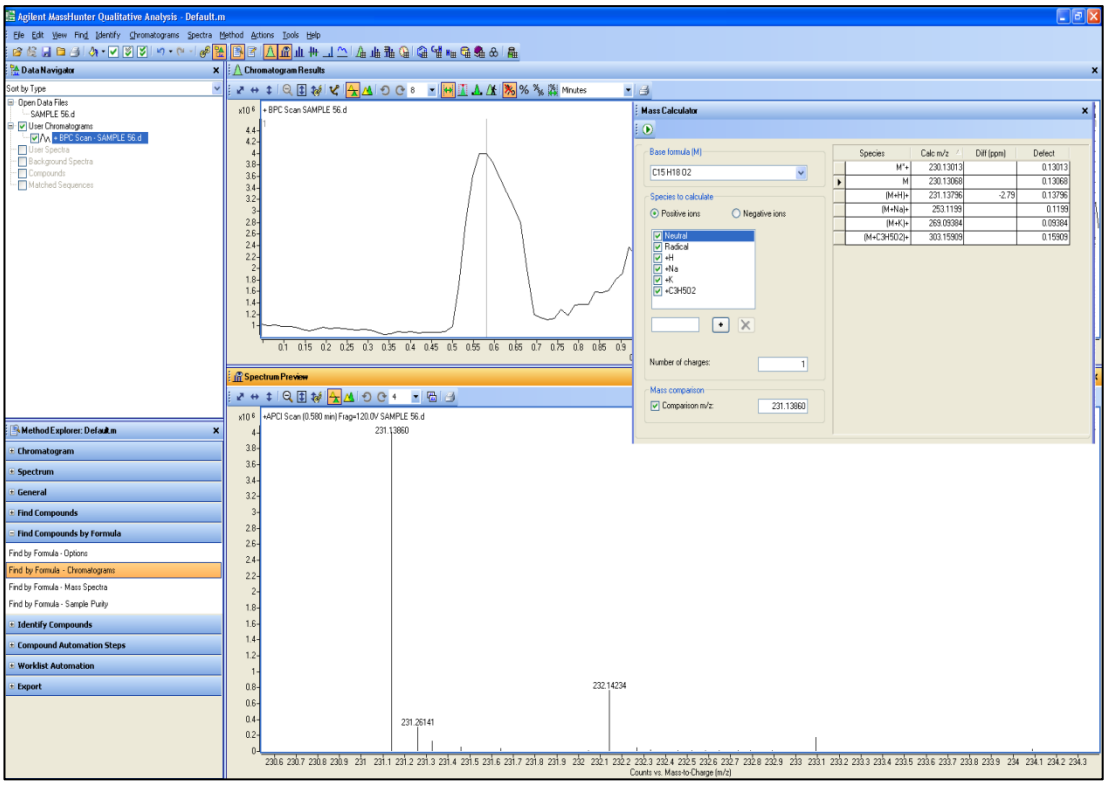


Figure 30 HRMS Spectrum of Compound **140b**

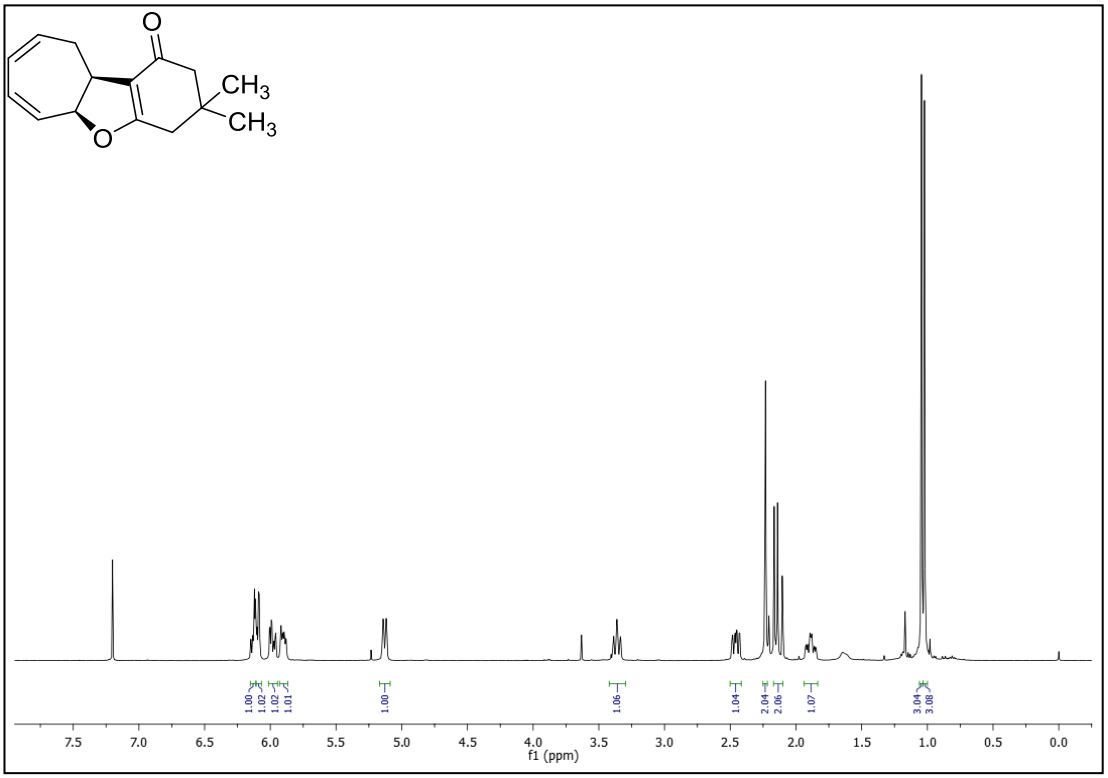


Figure 31 ^{1}H NMR Spectrum of Compound **141b** in $CDCl_3$

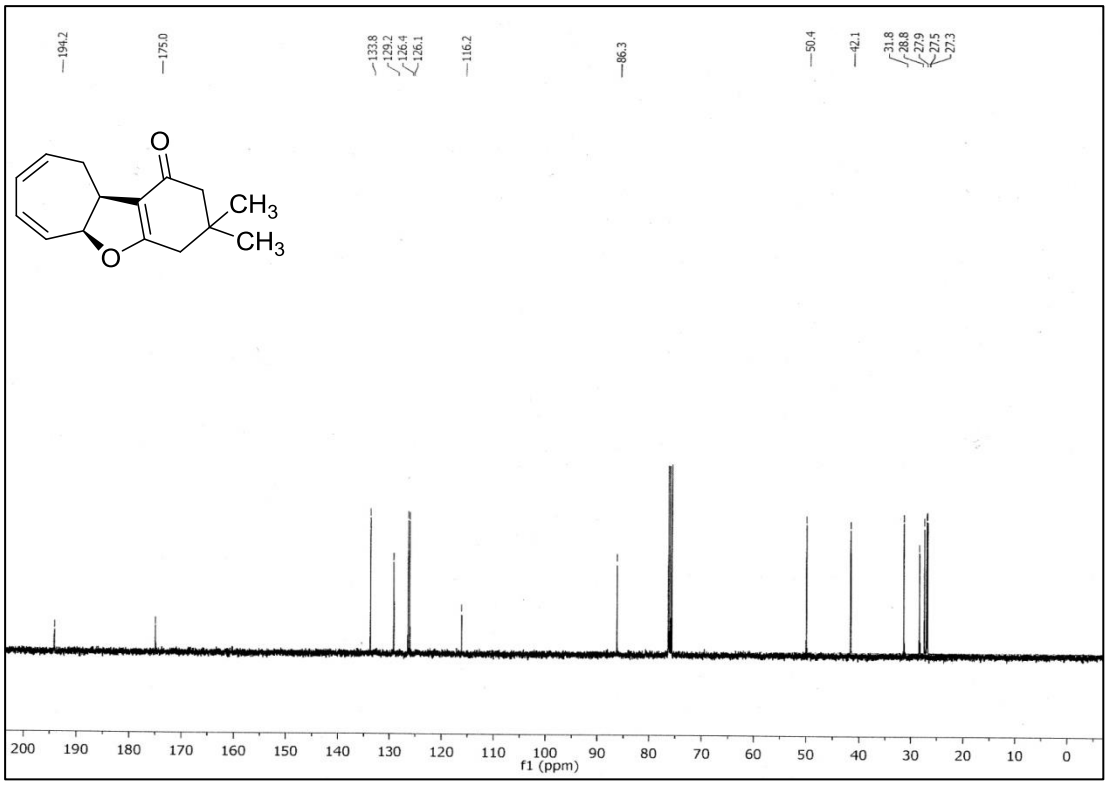


Figure 32 ^{13}C NMR Spectrum of Compound **141b** in $CDCl_3$

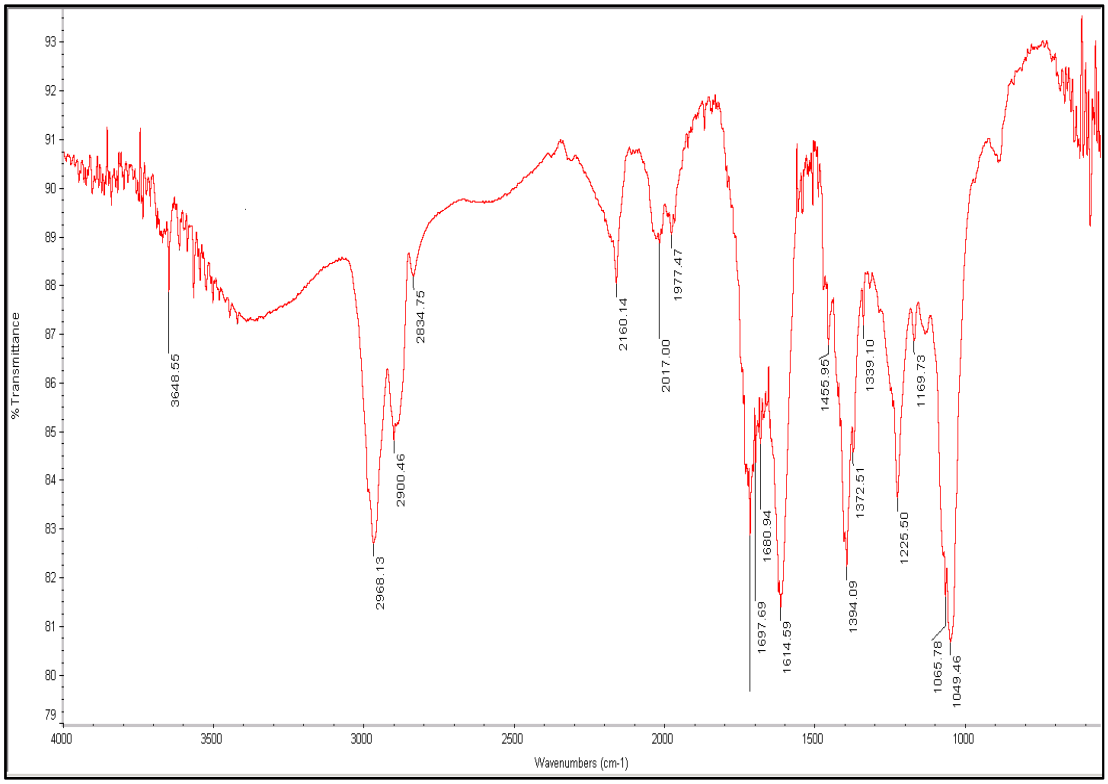


Figure 33 IR Spectrum of Compound **141b**

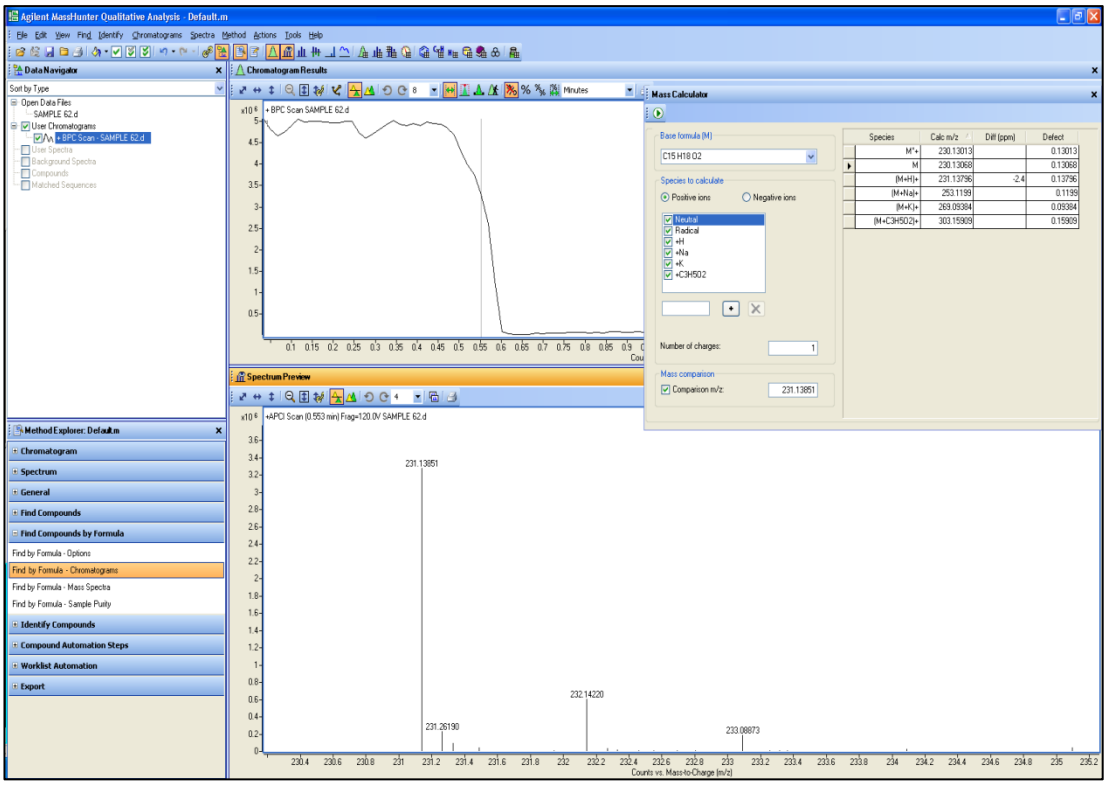


Figure 34 HRMS Spectrum of Compound **141b**

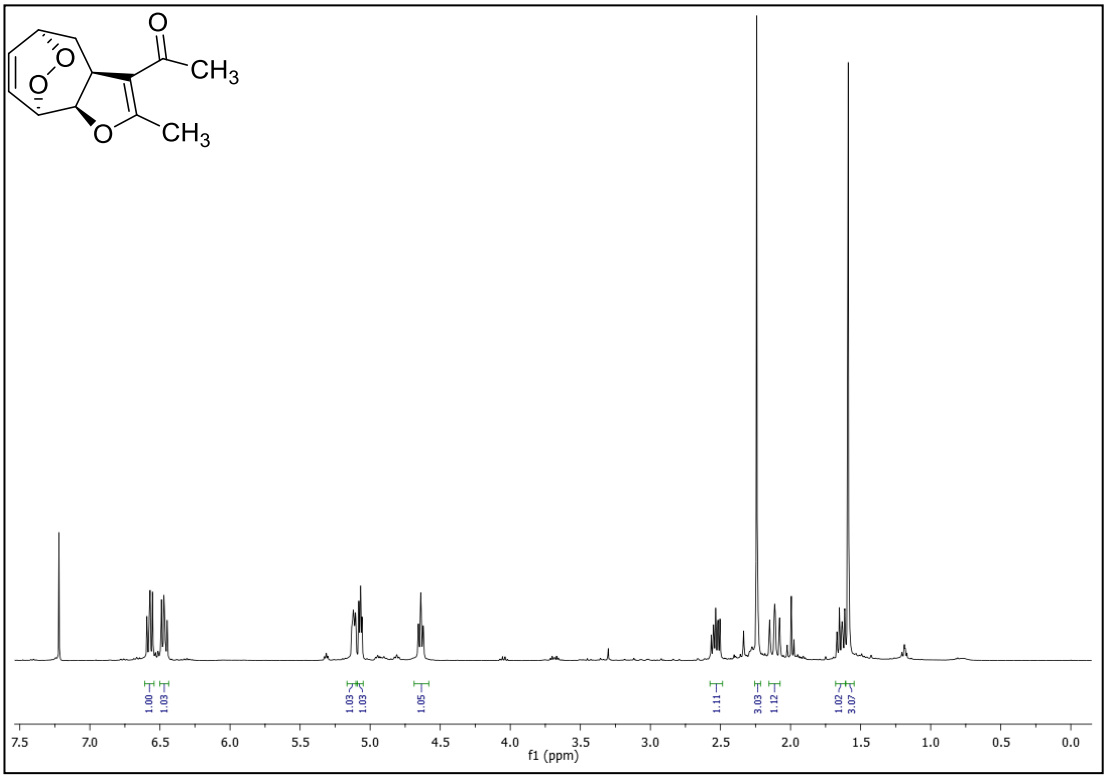


Figure 35 ^{1}H NMR Spectrum of Compound **131a** in $CDCl_3$

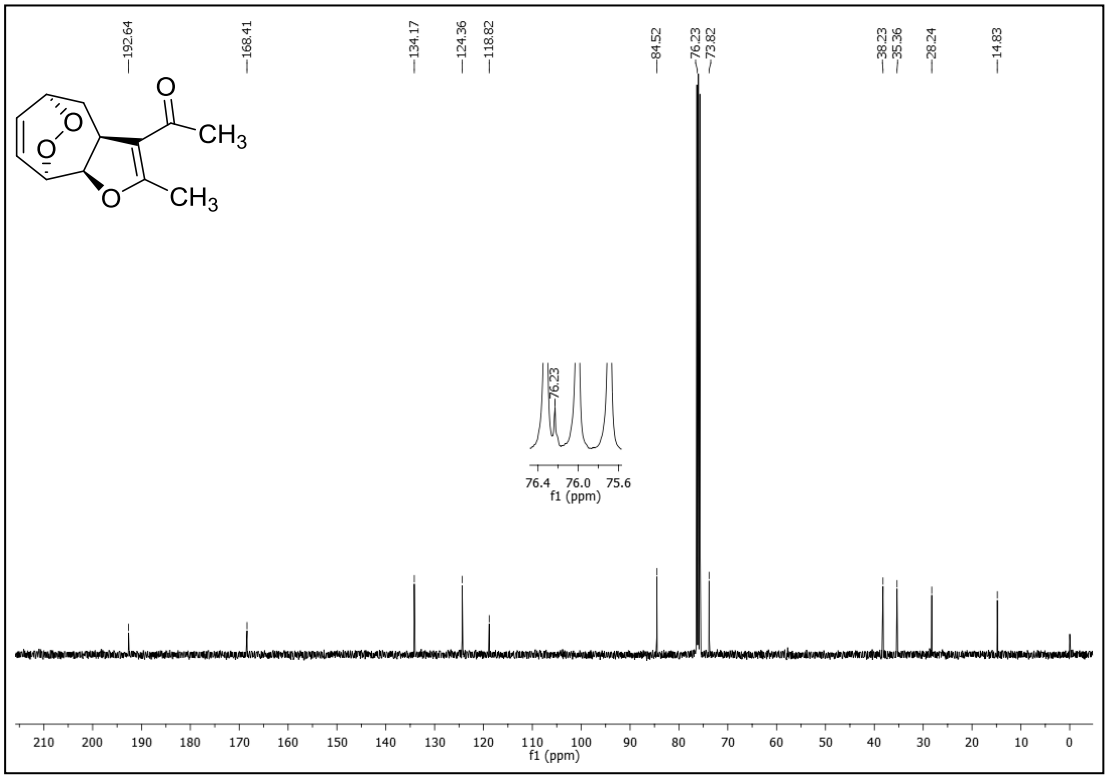


Figure 36 ^{13}C NMR Spectrum of Compound **131a** in $CDCl_3$

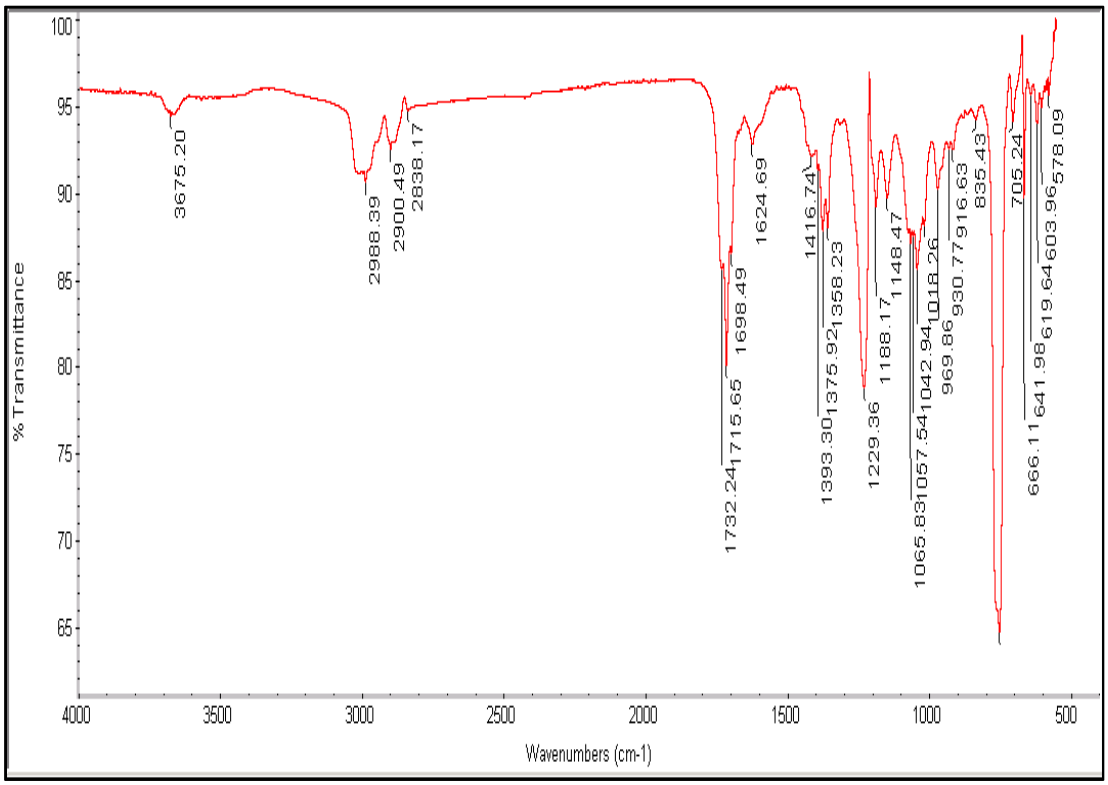


Figure 37 IR Spectrum of Compound **131a**

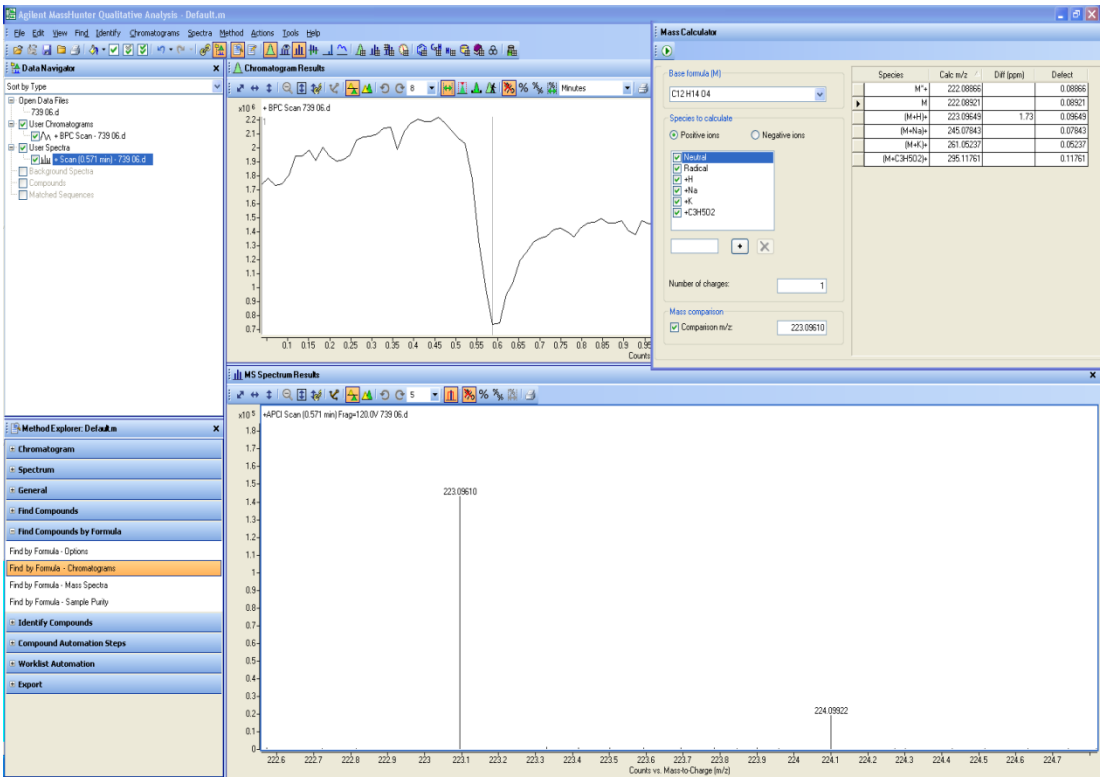


Figure 38 HRMS Spectrum of Compound **131a**

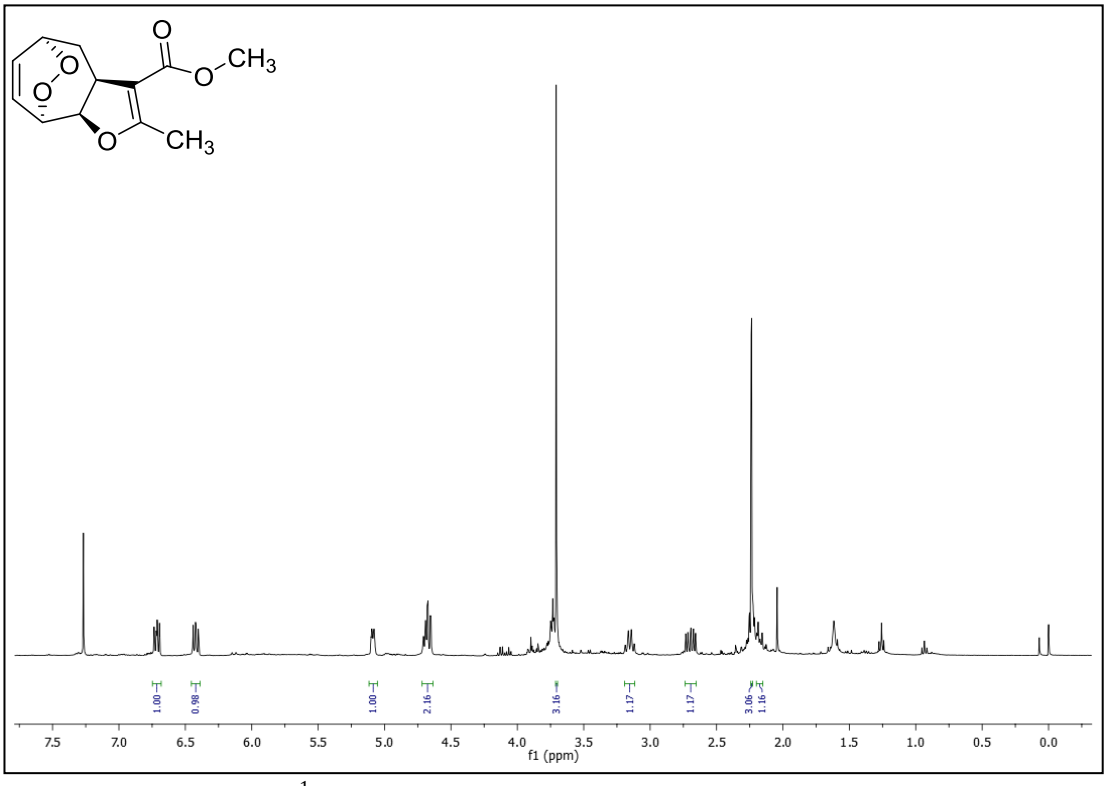


Figure 39 ^{1}H NMR Spectrum of Compound **131b** in $CDCl_3$

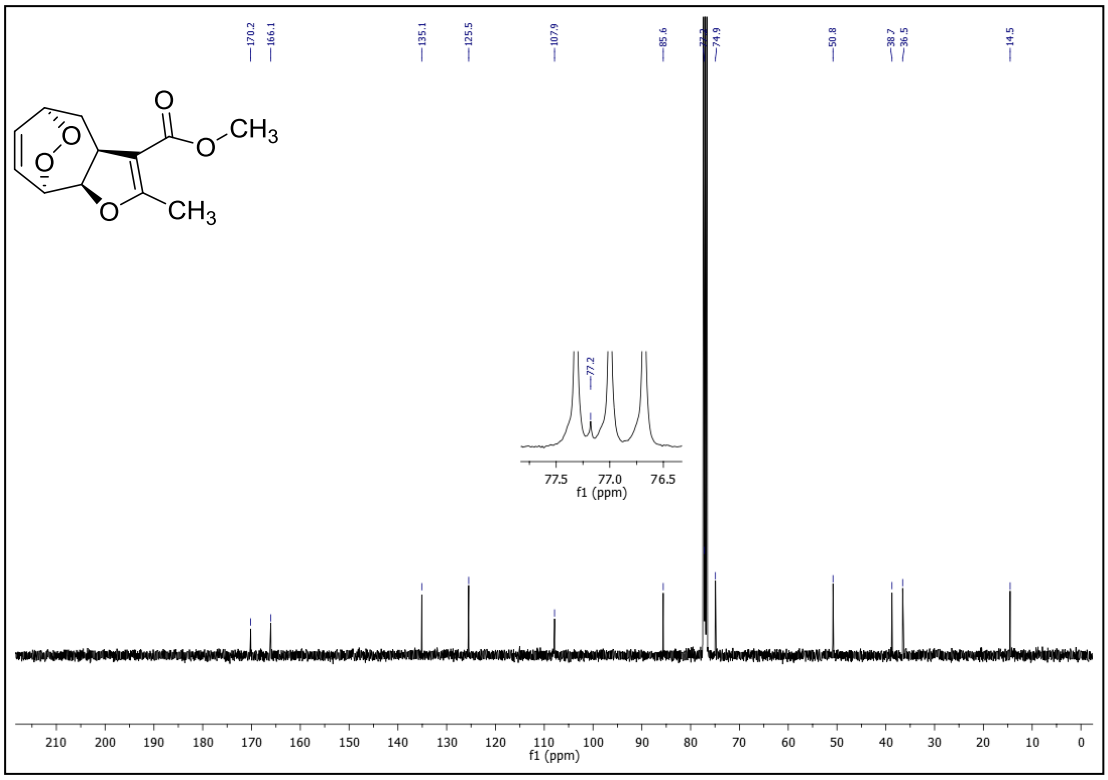


Figure 40 ^{13}C NMR Spectrum of Compound **131b** in $CDCl_3$

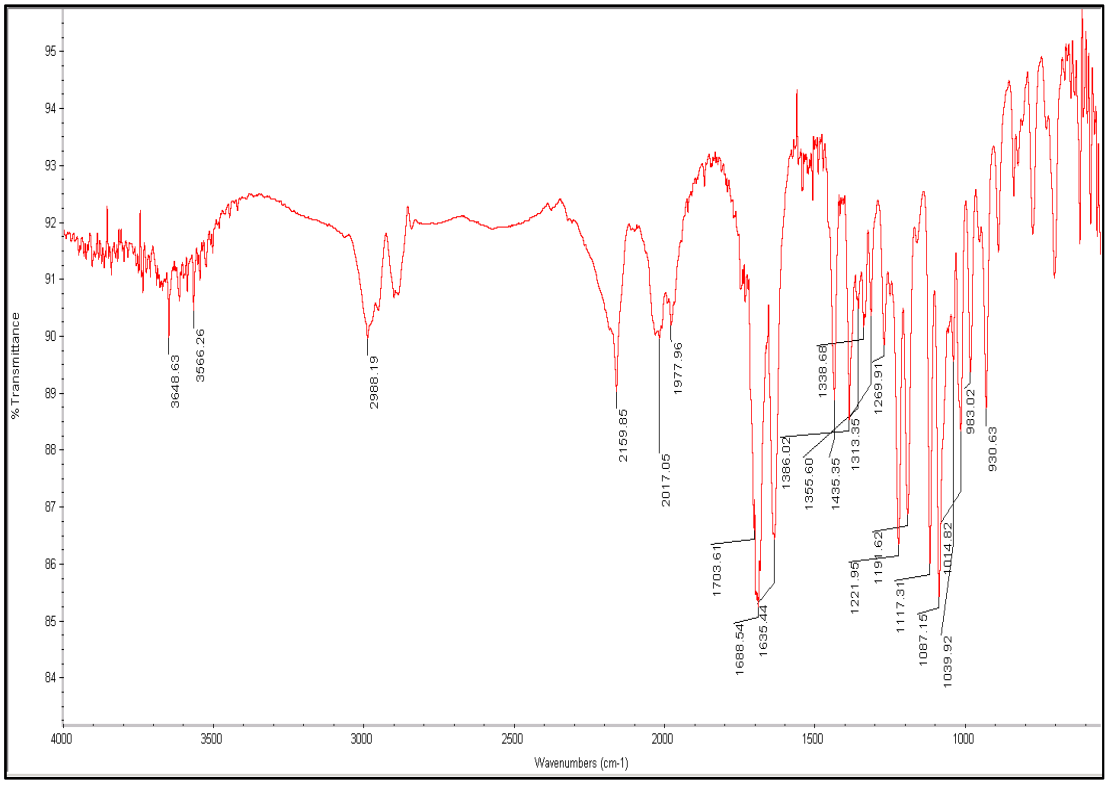


Figure 41 IR Spectrum of Compound **131b**

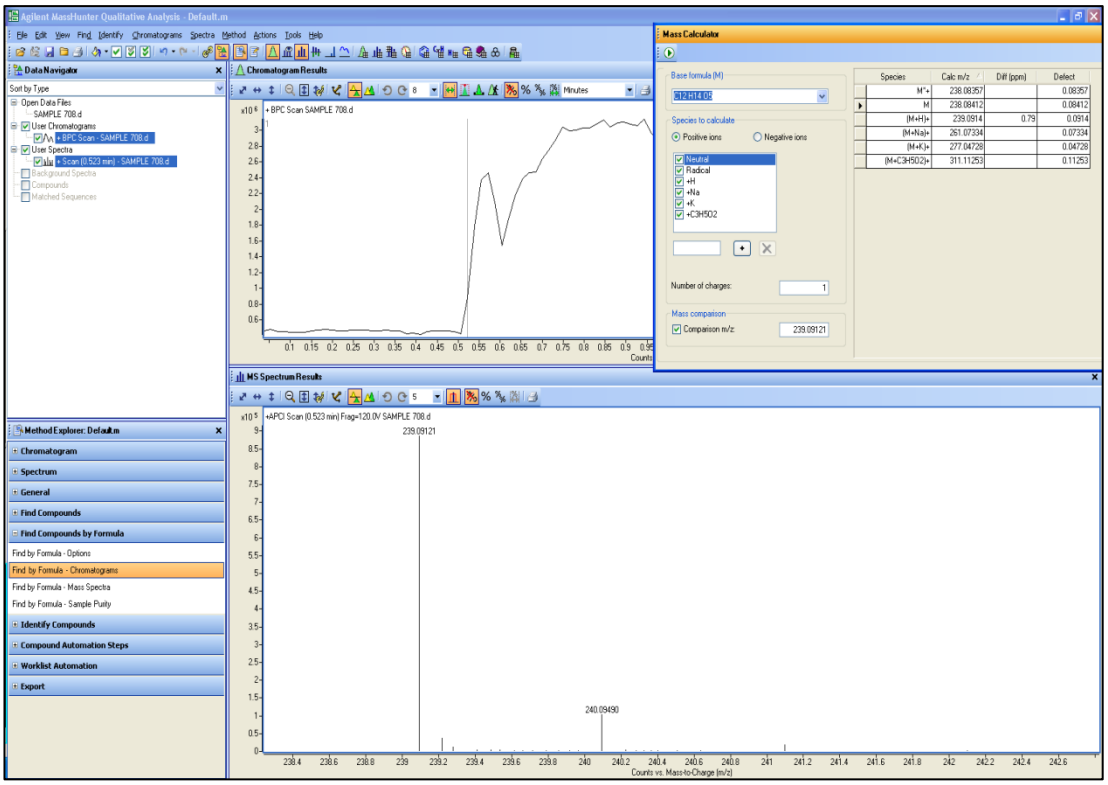


Figure 42 HRMS Spectrum of Compound **131b**

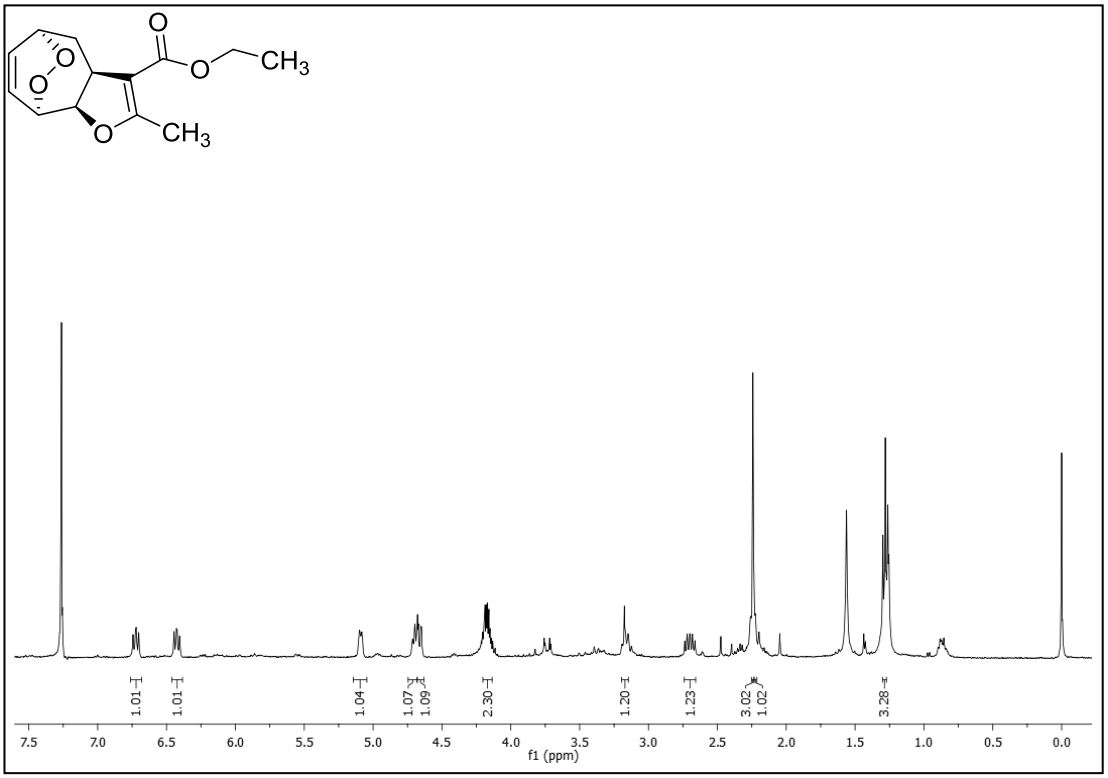


Figure 43 ^{1}H NMR Spectrum of Compound **131c** in $CDCl_3$

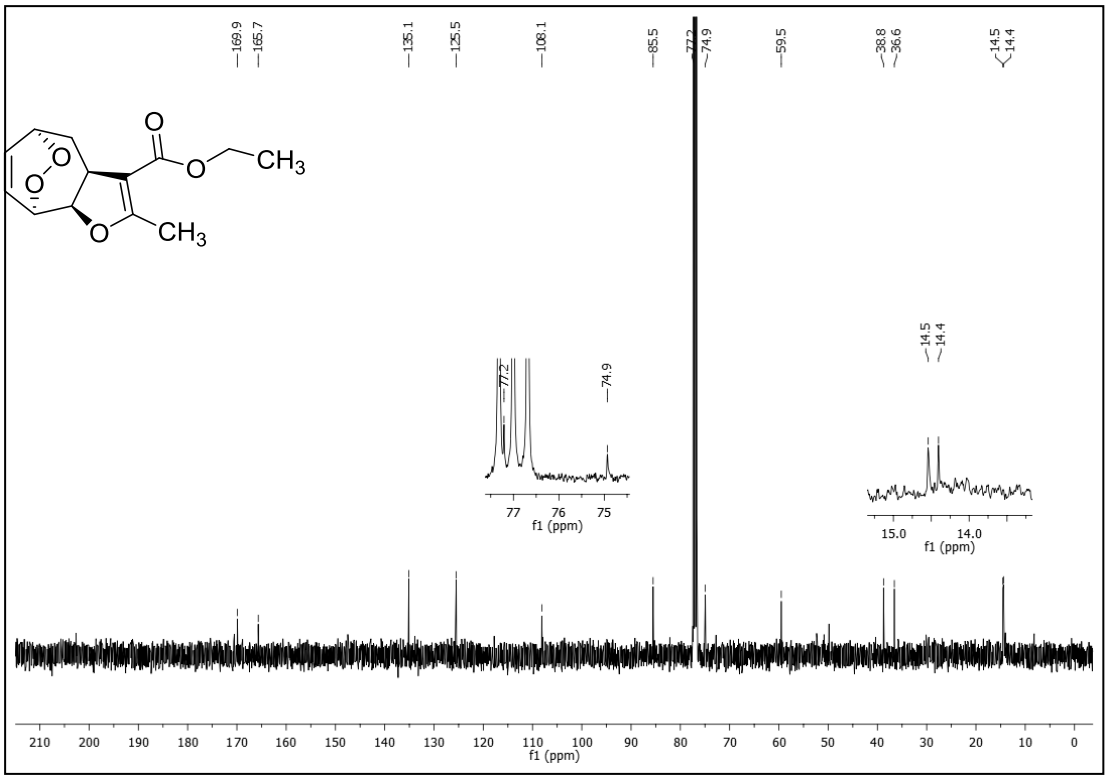


Figure 44 ^{13}C NMR Spectrum of Compound **131c** in $CDCl_3$

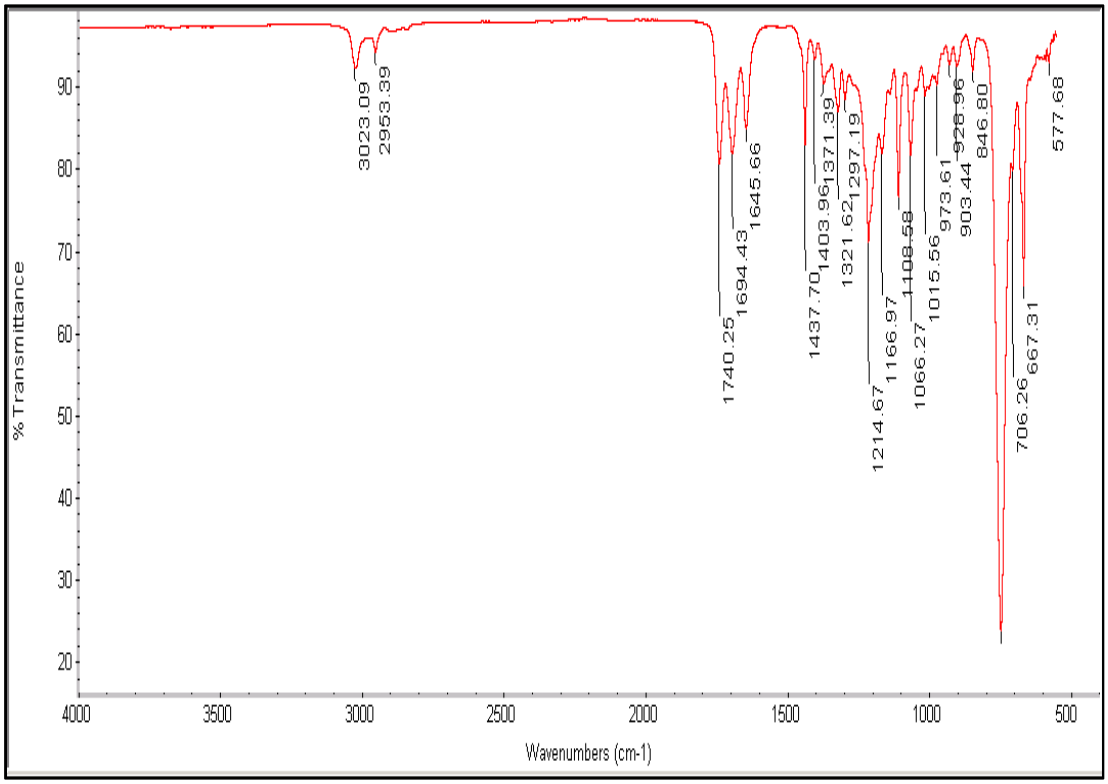


Figure 45 IR Spectrum of Compound **131c**

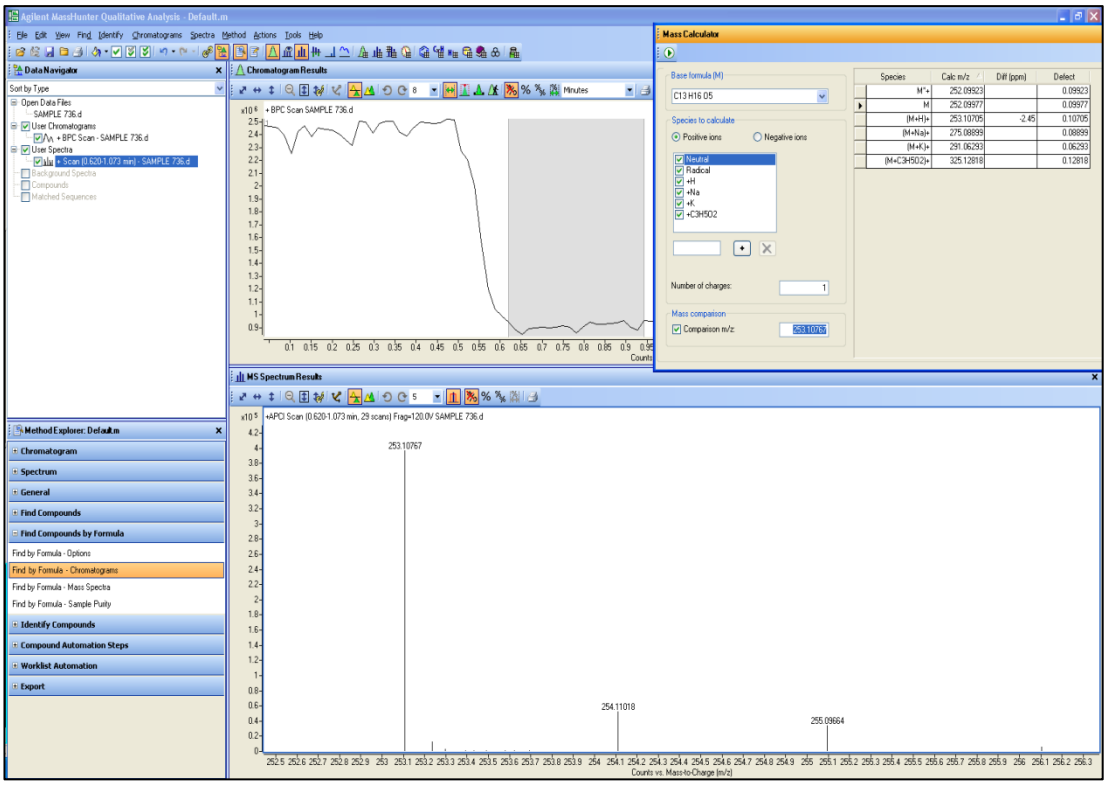


Figure 46 HRMS Spectrum of Compound **131c**

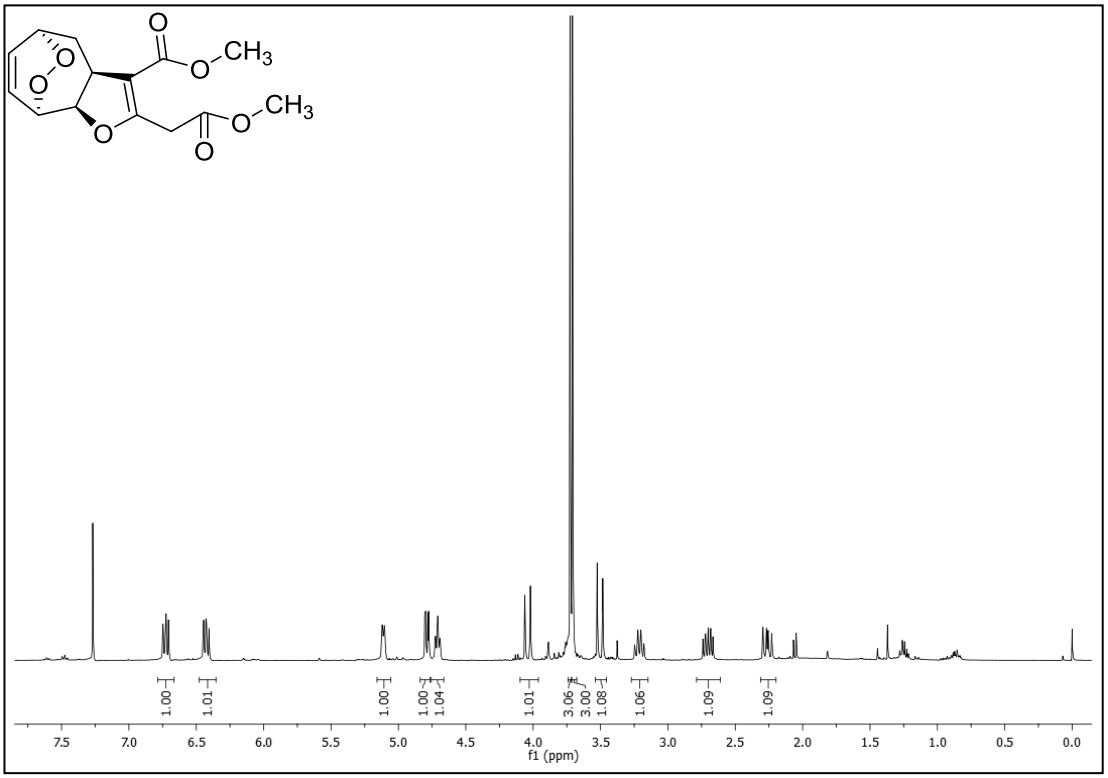


Figure 47 ^{1}H NMR Spectrum of Compound **131d** in $CDCl_3$

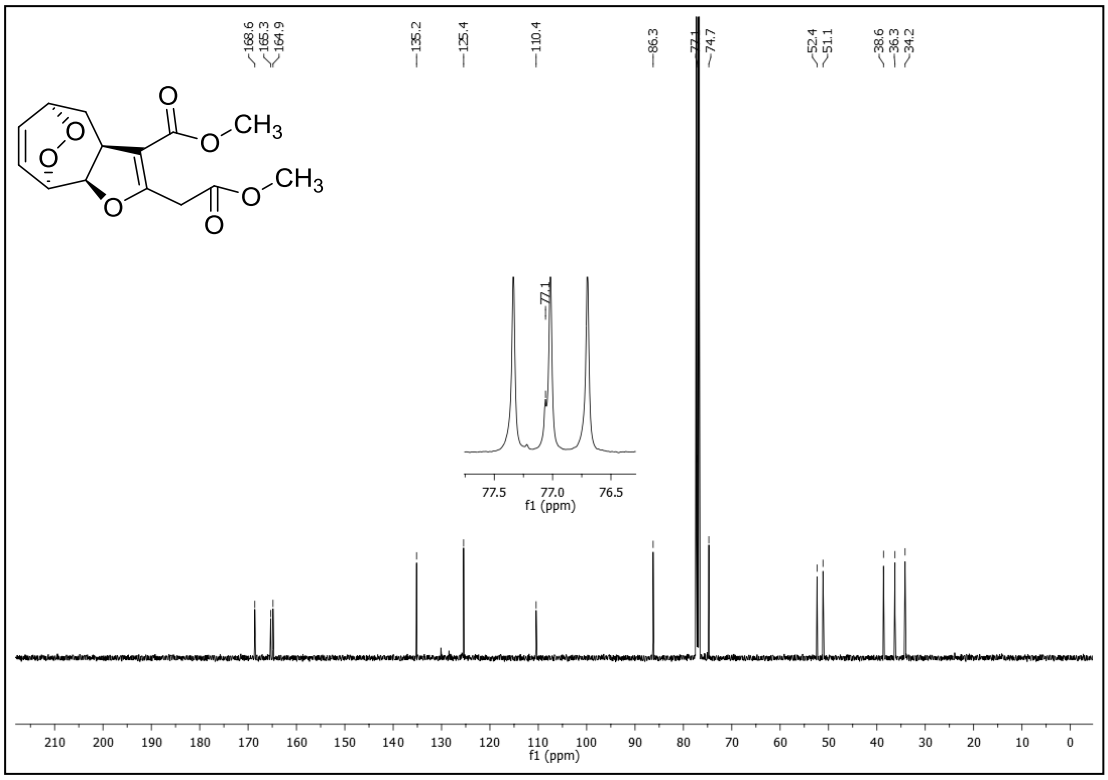


Figure 48 ^{13}C NMR Spectrum of Compound **131d** in $CDCl_3$

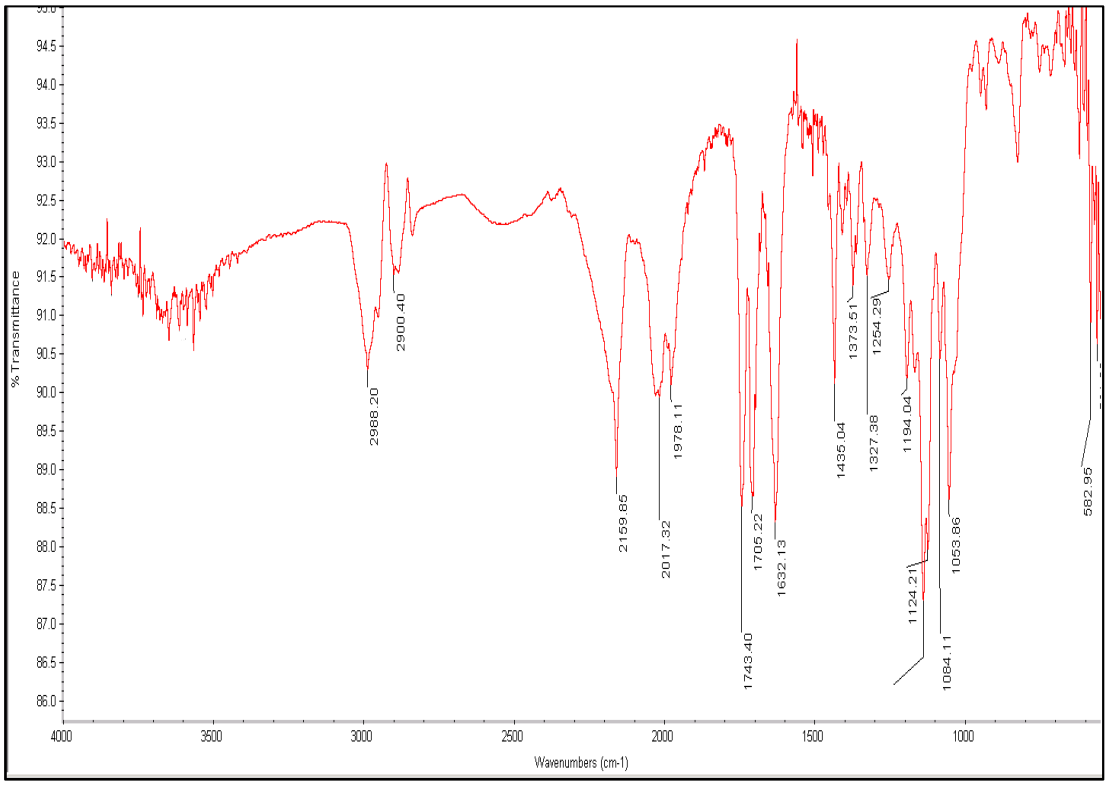


Figure 49 IR Spectrum of Compound **131d**

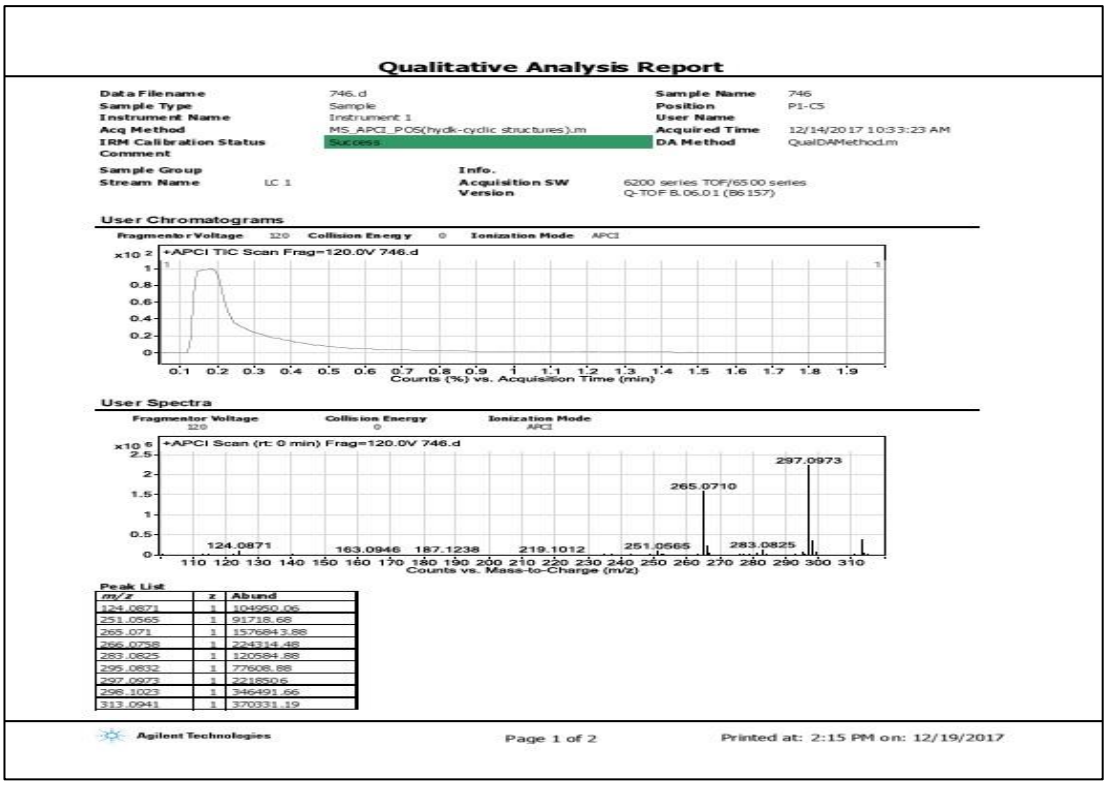


Figure 50 HRMS Spectrum of Compound **131d**

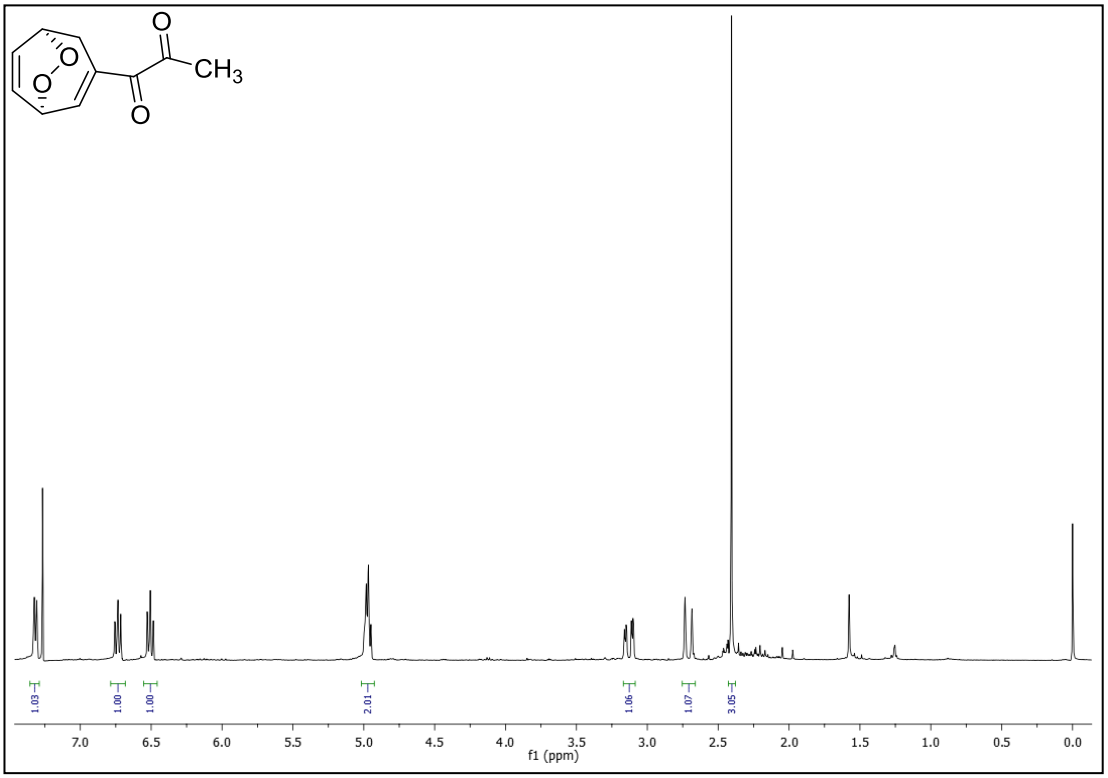


Figure 51 ^{1}H NMR Spectrum of Compound **132a** in $CDCl_3$

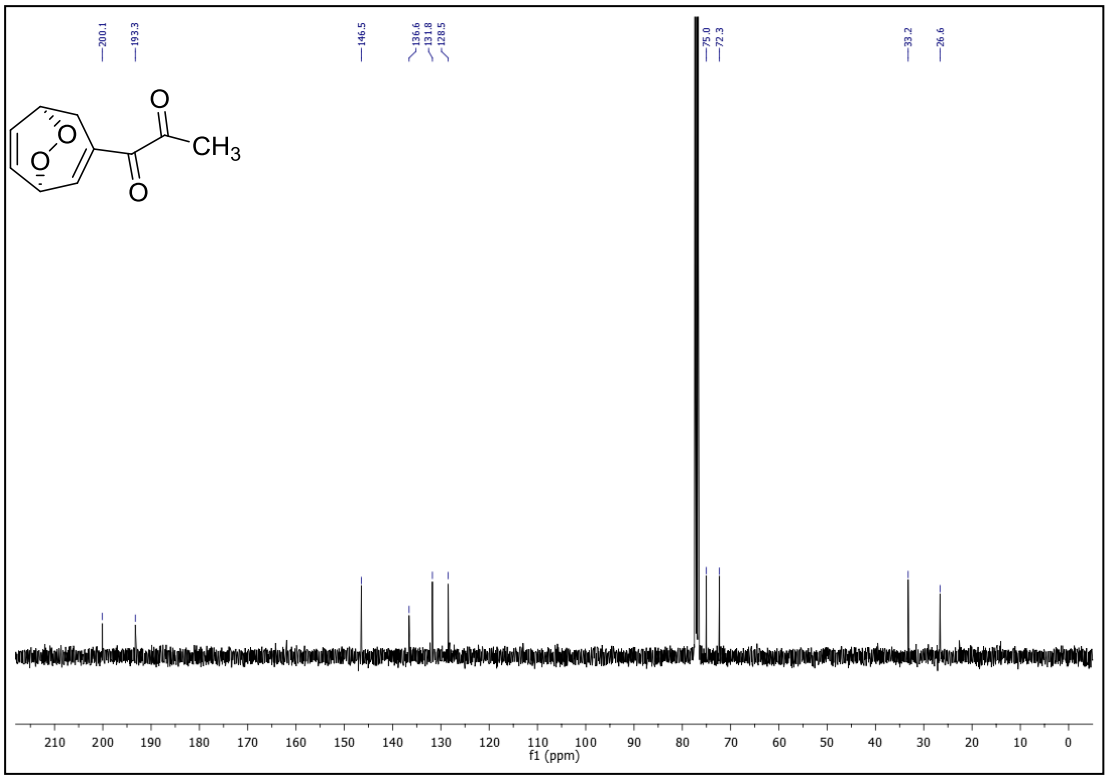


Figure 52 ^{13}C NMR Spectrum of Compound **132a** in $CDCl_3$

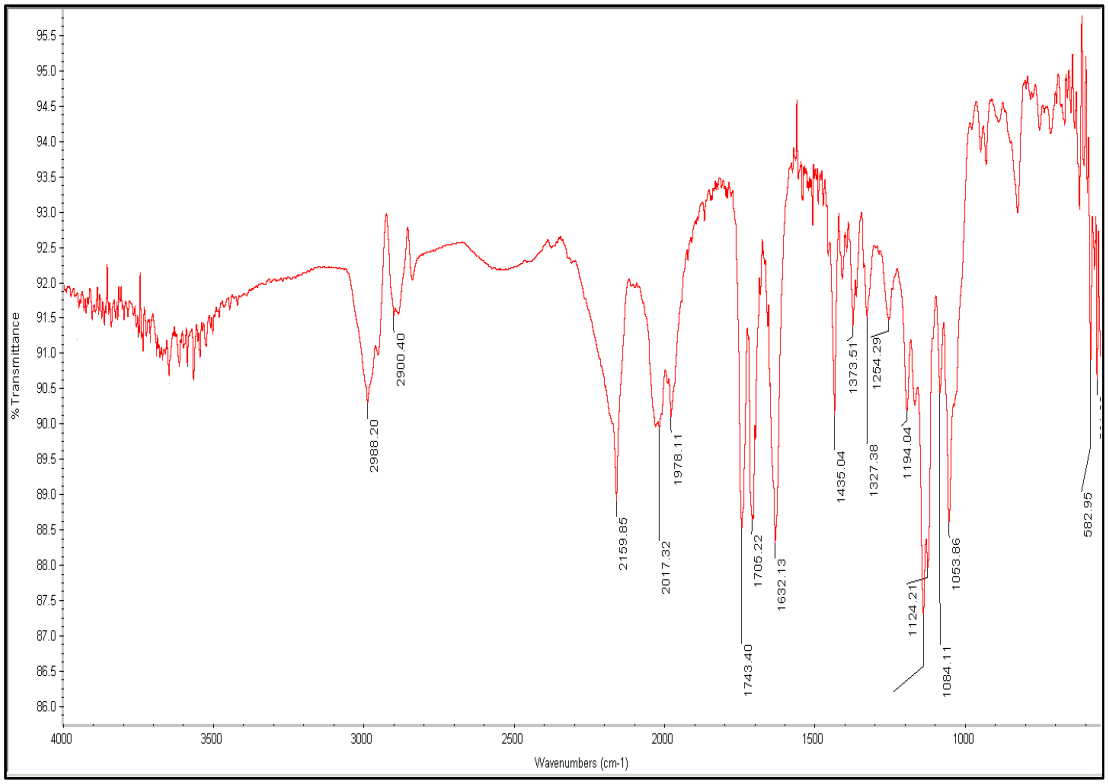


Figure 53 IR Spectrum of Compound **132a**

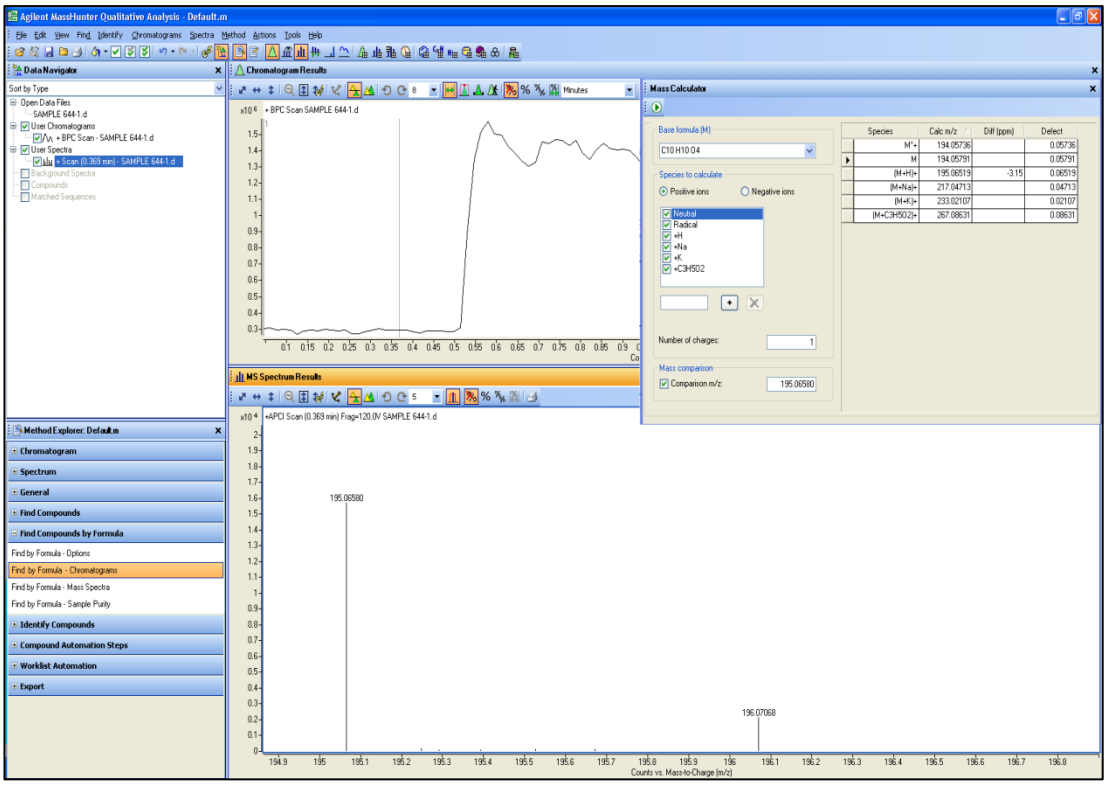


Figure 54 HRMS Spectrum of Compound **132a**

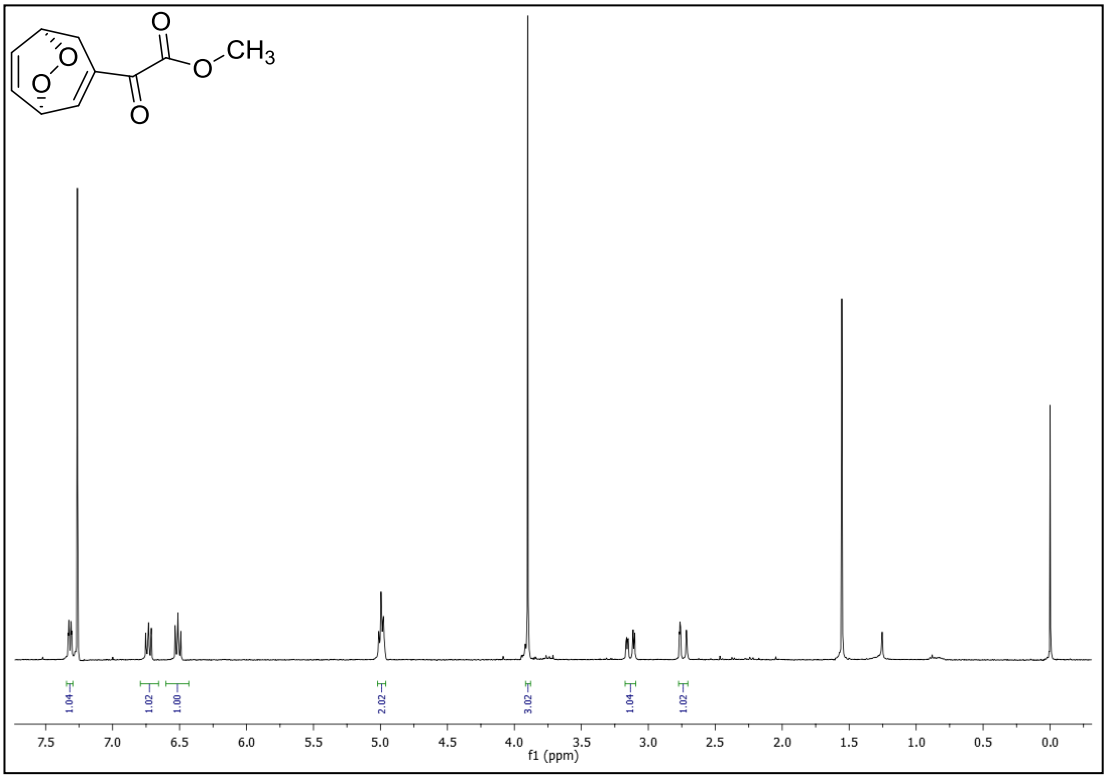


Figure 55 ^{1}H NMR Spectrum of Compound **132b** in $CDCl_3$

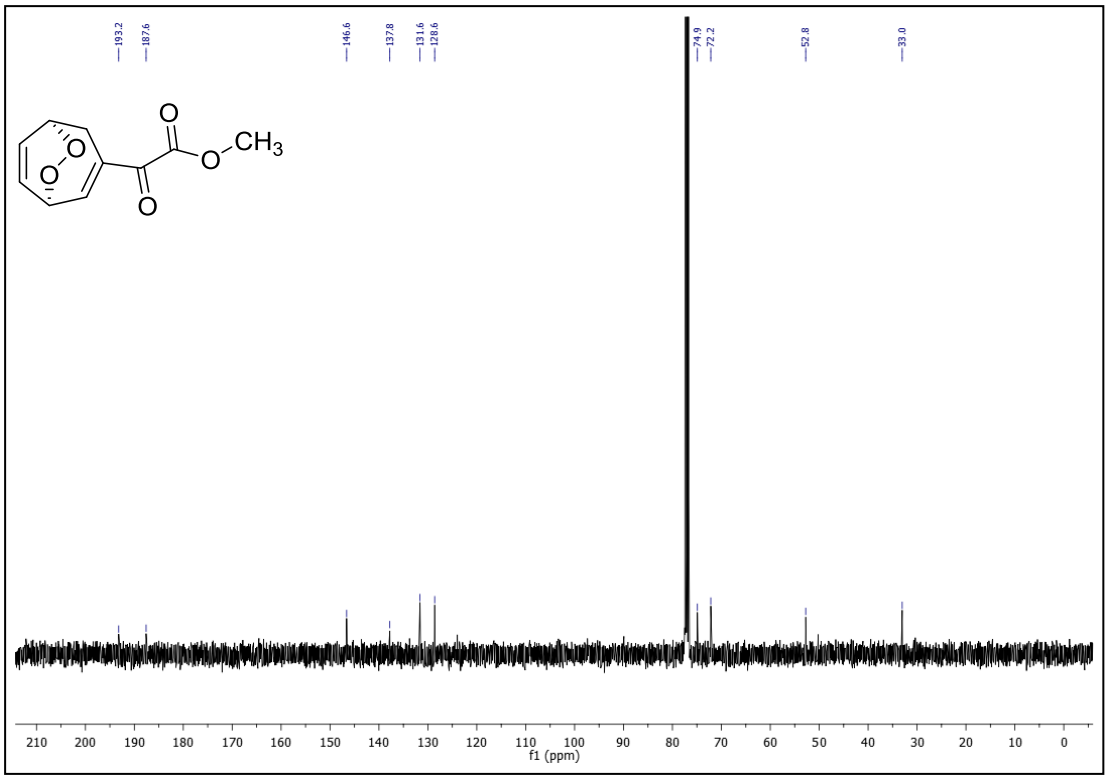


Figure 56 ^{13}C NMR Spectrum of Compound **132b** in $CDCl_3$

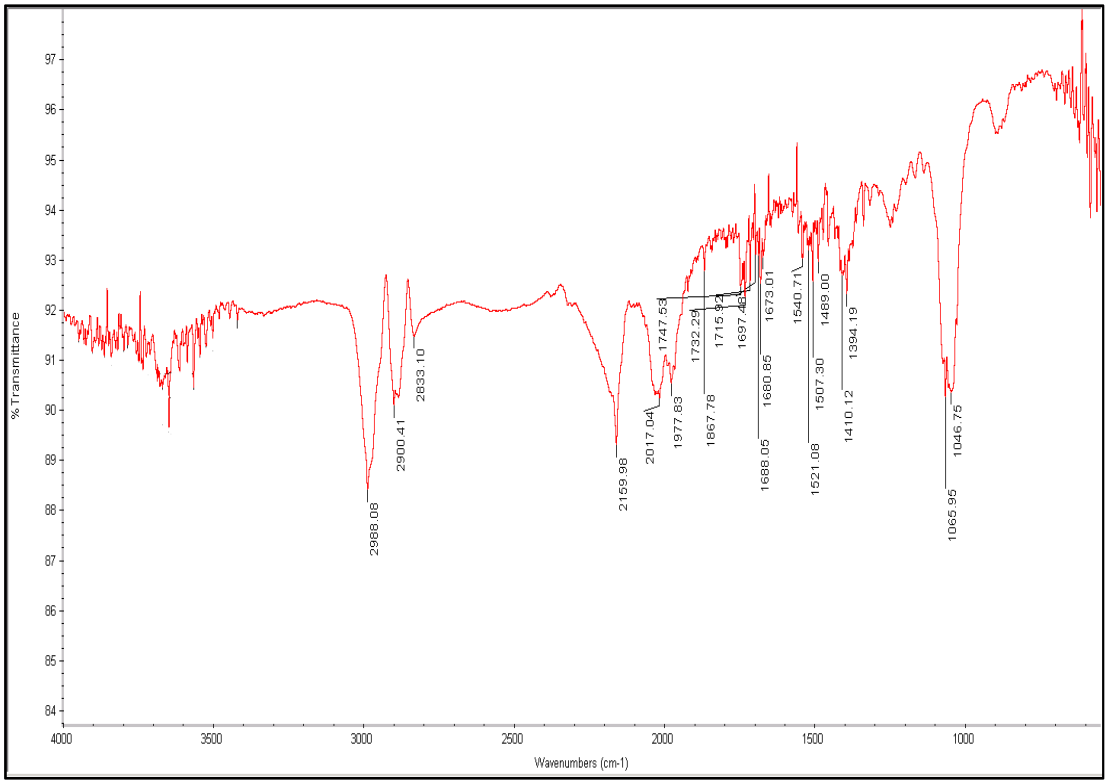


Figure 57 IR Spectrum of Compound **132b**

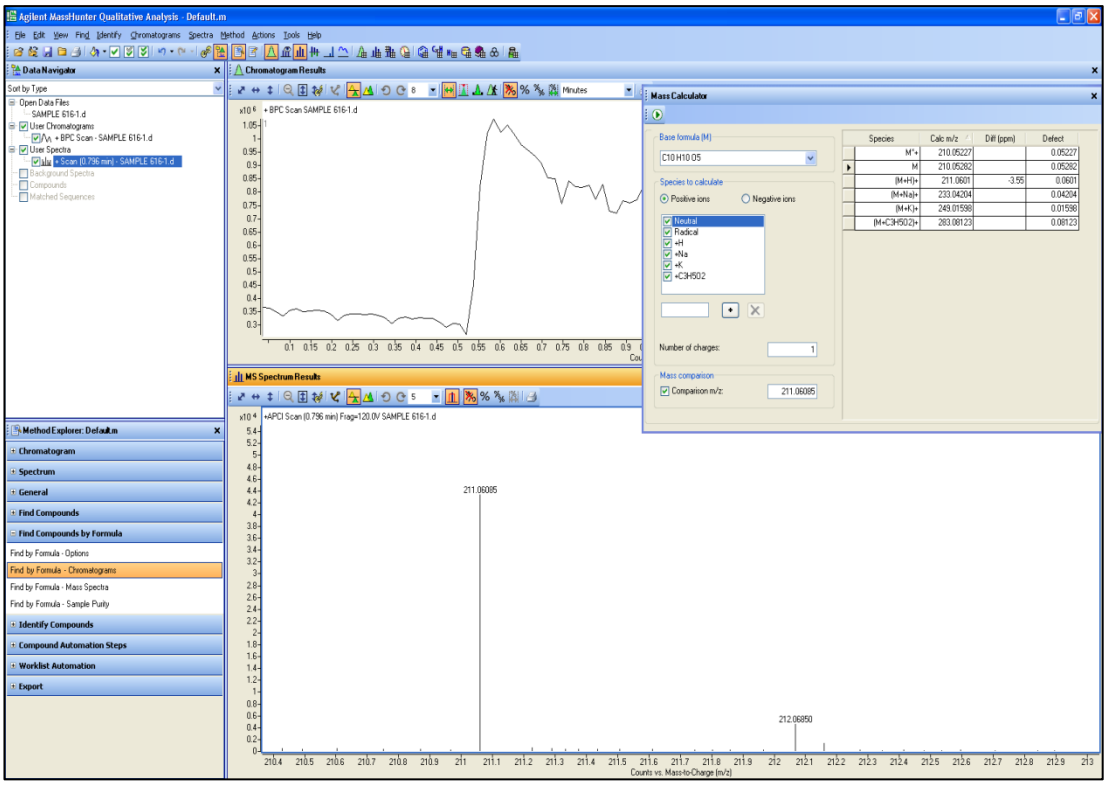


Figure 58 HRMS Spectrum of Compound **132b**

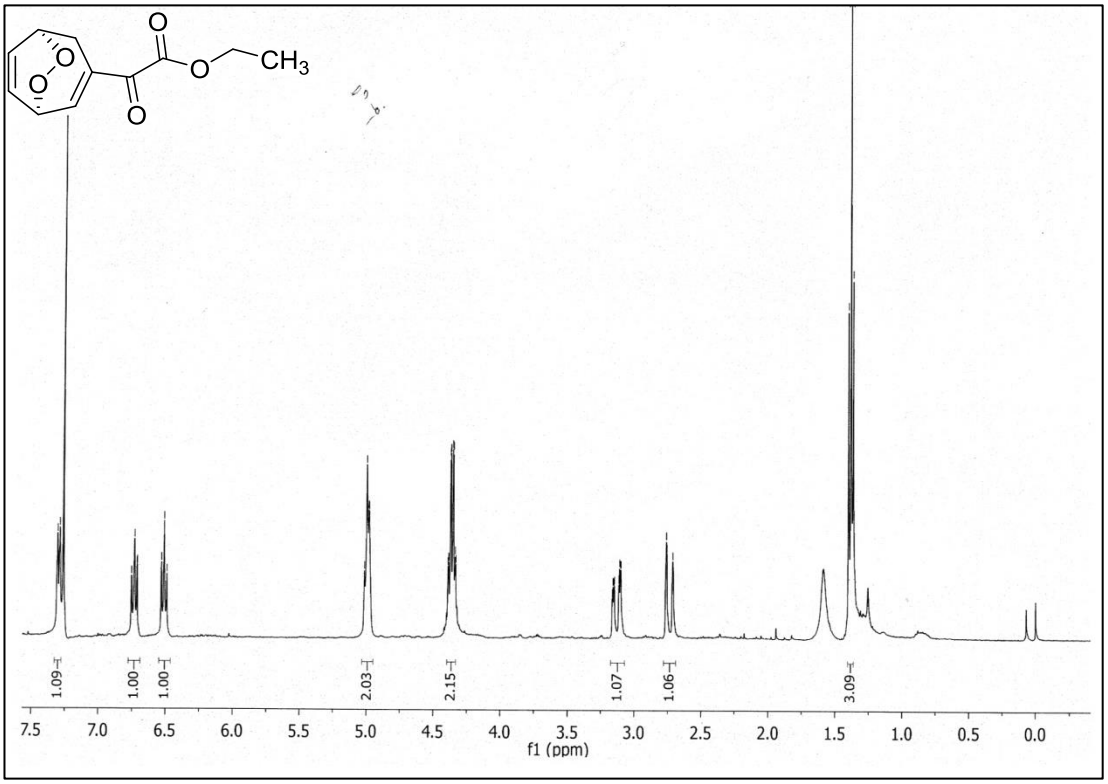


Figure 59 ^{1}H NMR Spectrum of Compound **132c** in $CDCl_3$

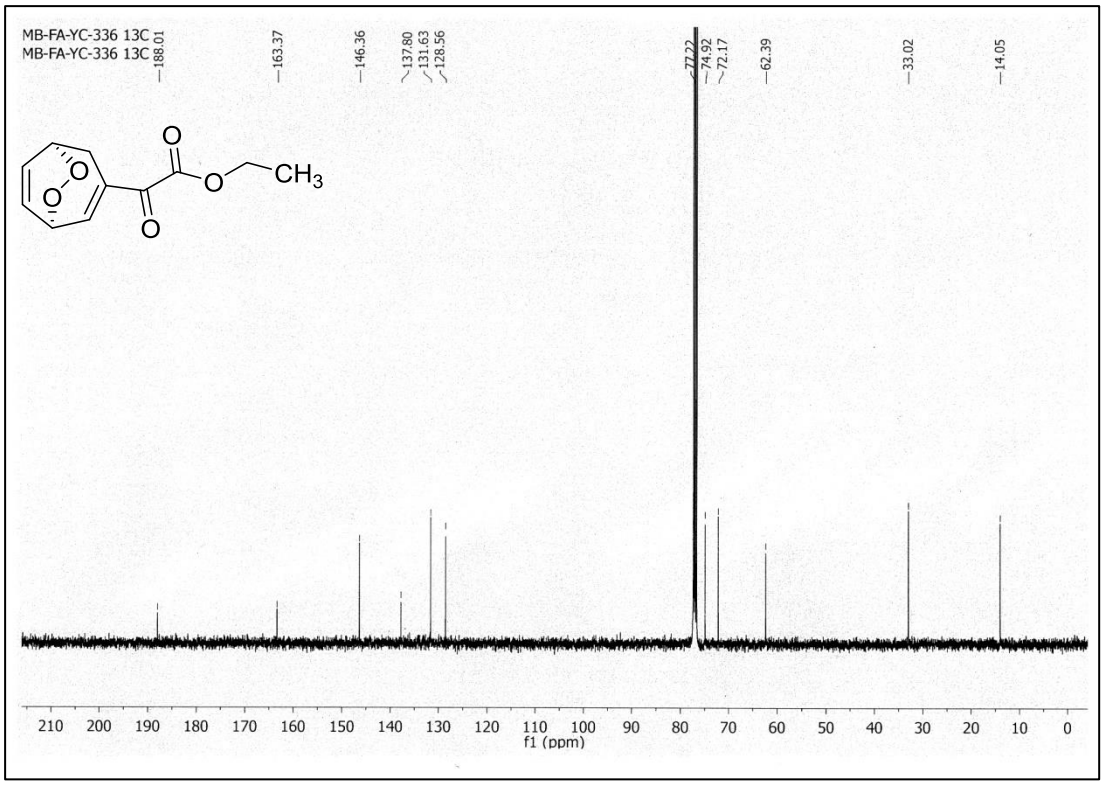


Figure 60 ^{13}C NMR Spectrum of Compound **132c** in $CDCl_3$

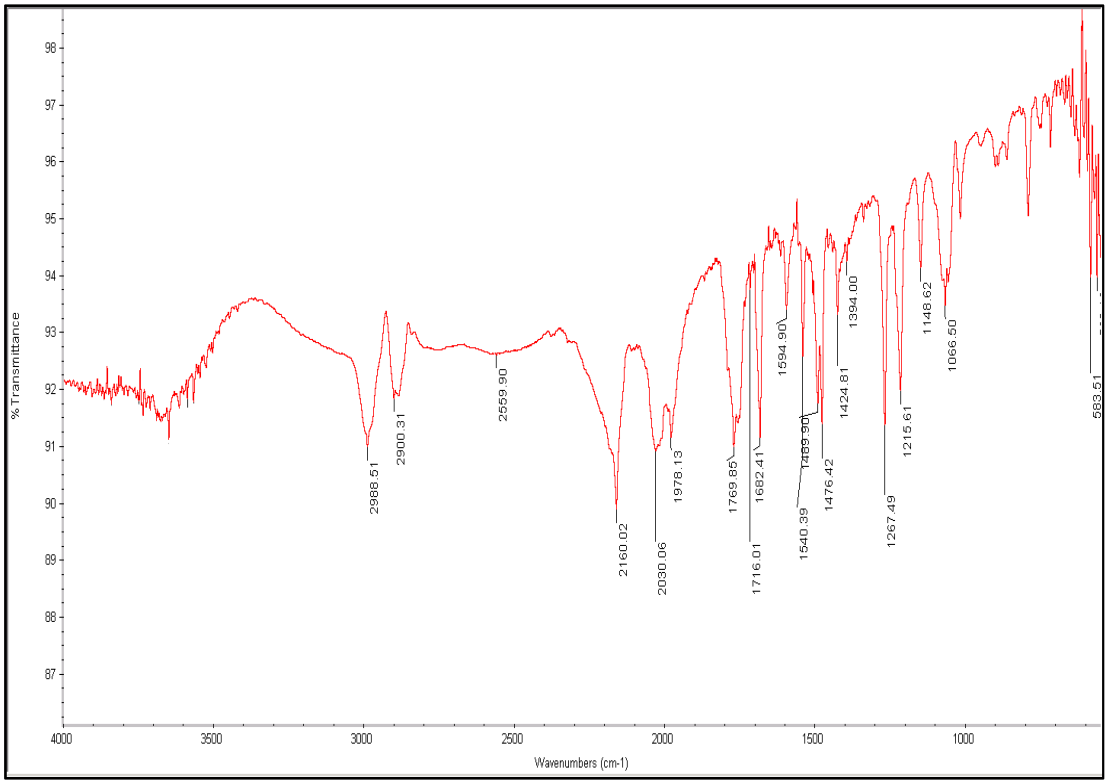


Figure 61 IR Spectrum of Compound **132c**

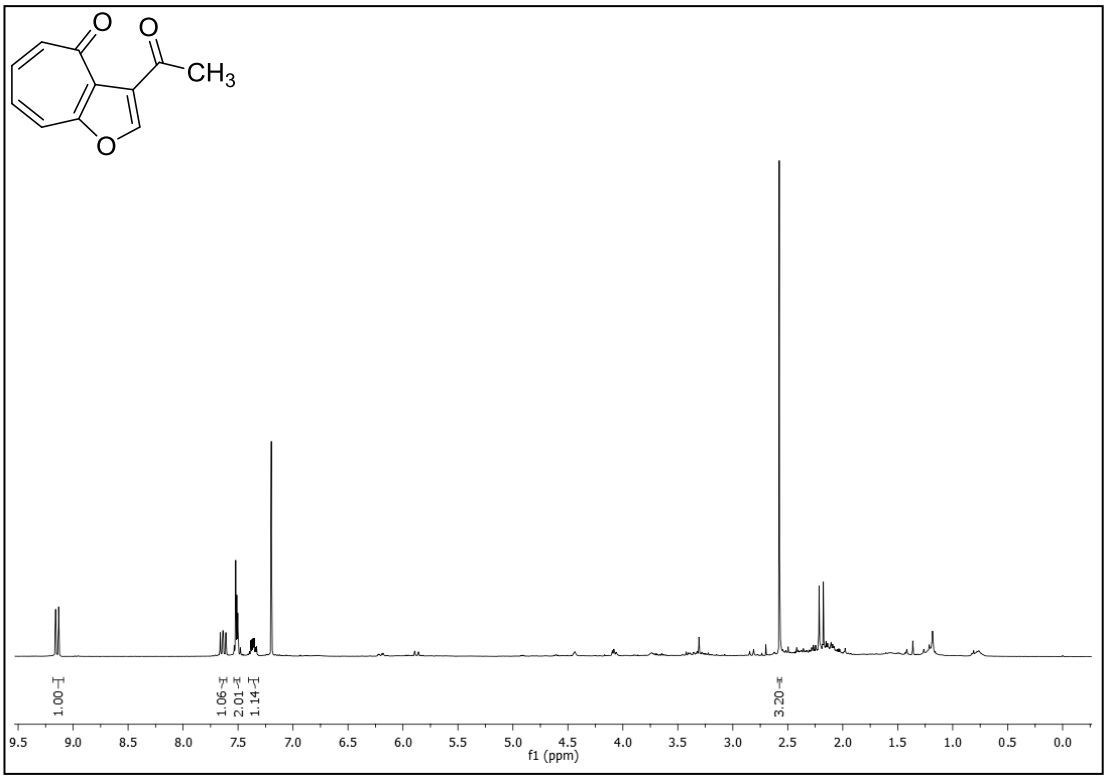


Figure 62 ^{1}H NMR Spectrum of Compound **133a** in $CDCl_3$

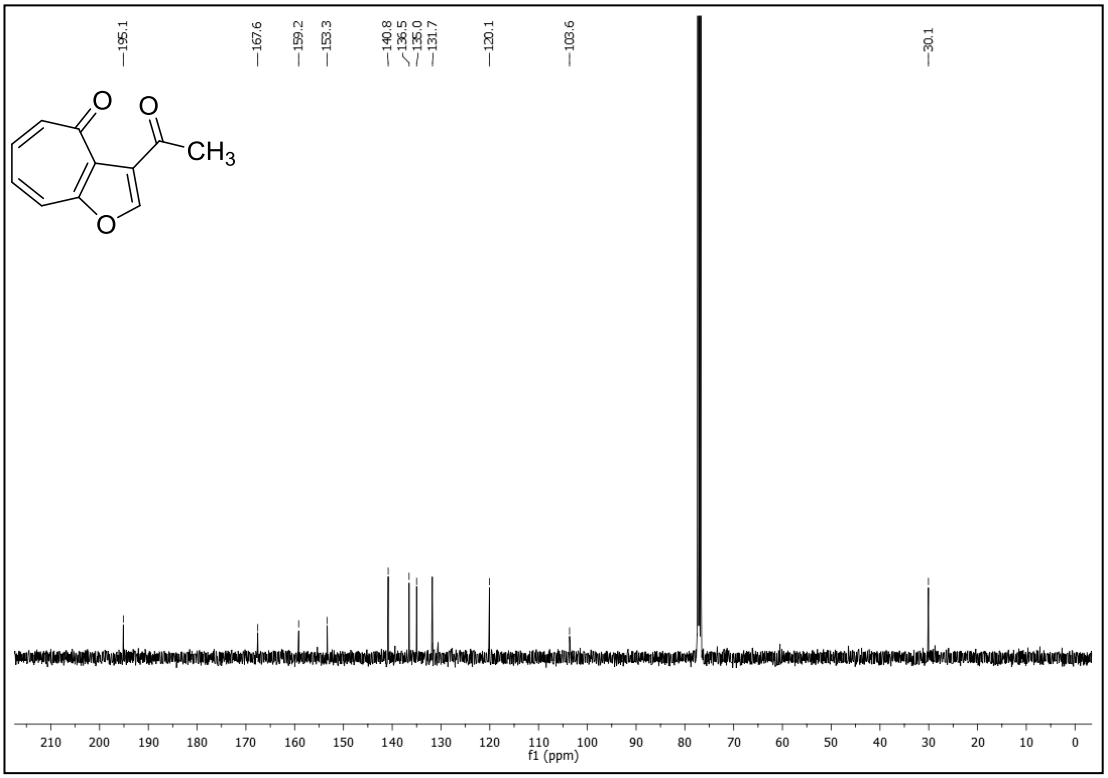


Figure 63 ^{13}C NMR Spectrum of Compound **133a** in $CDCl_3$

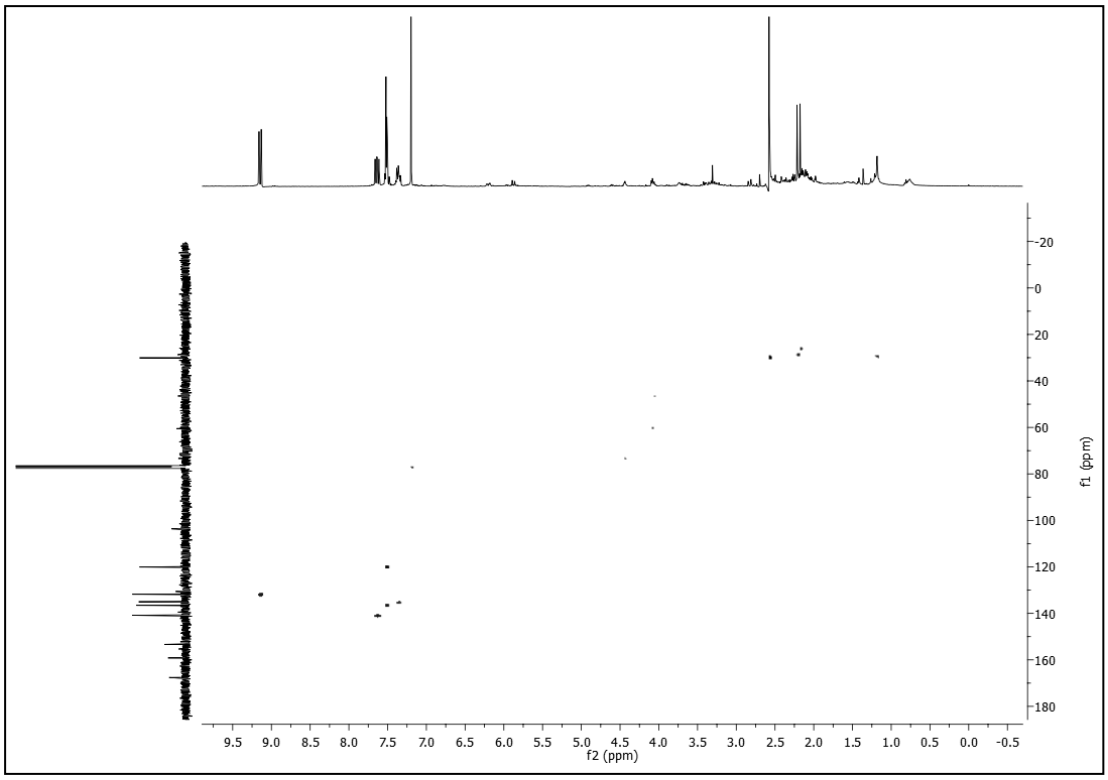


Figure 64 HSQC Spectrum of Compound **133a** in $CDCl_3$

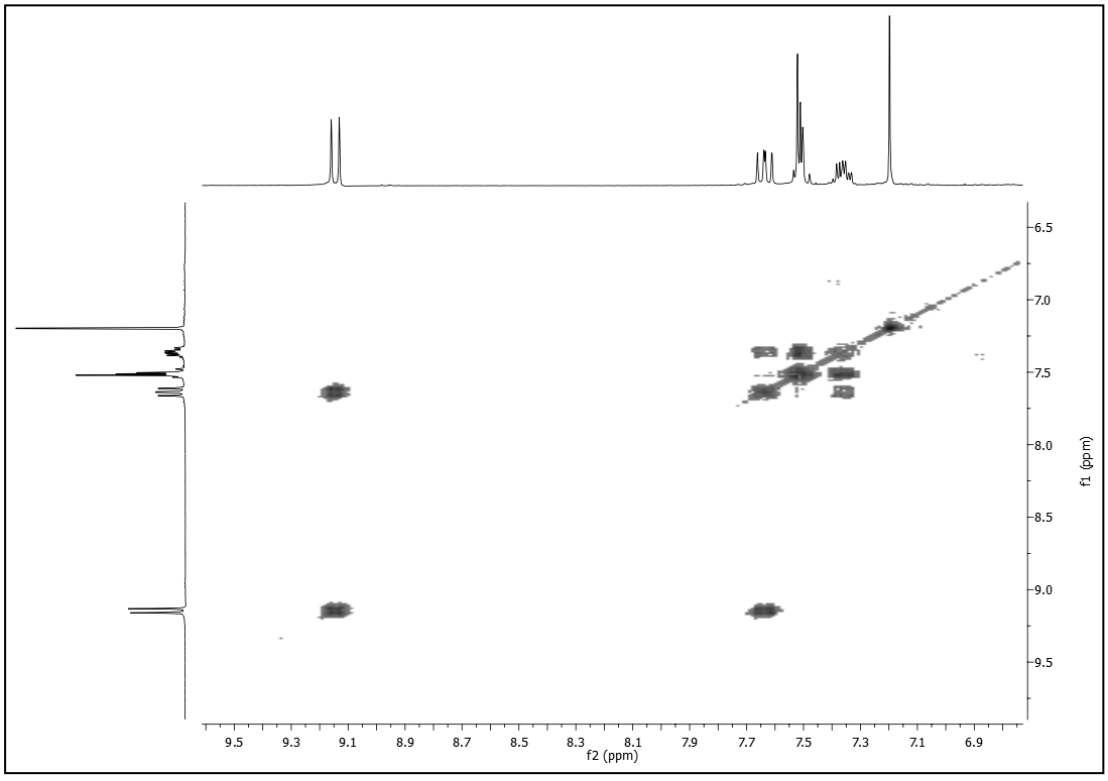


Figure 65 COSY Spectrum of Compound **133a** in $CDCl_3$

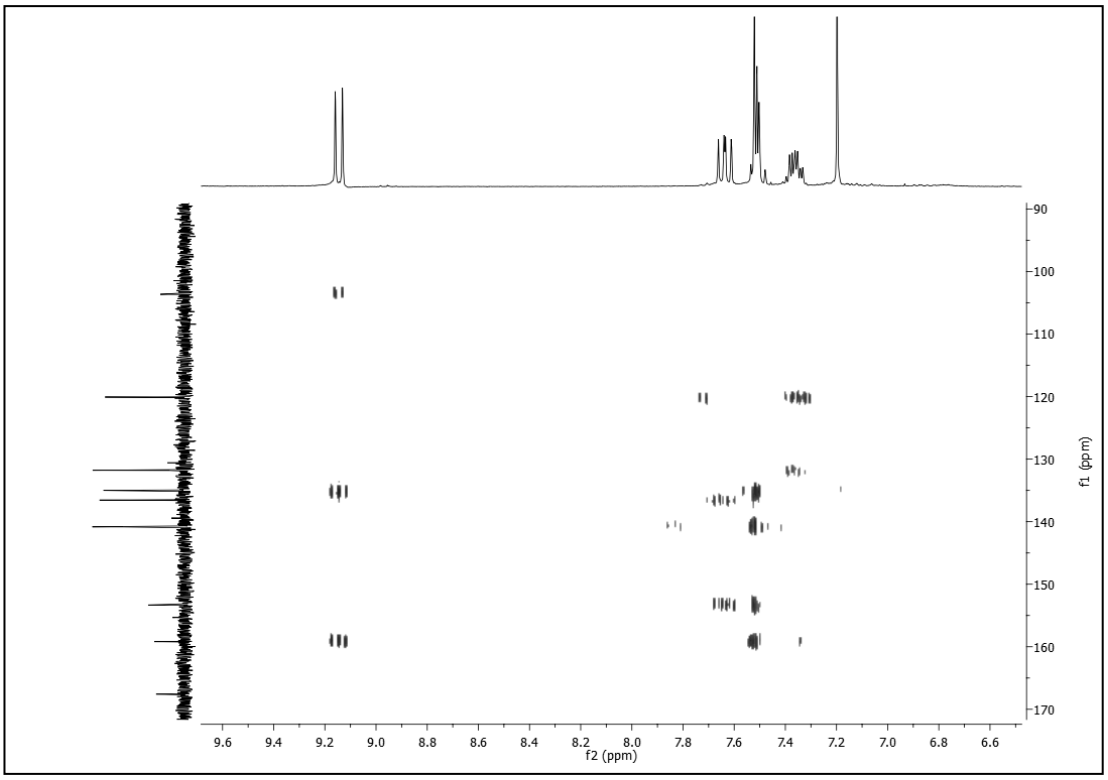


Figure 66 HMBC Spectrum of Compound **133a** in $CDCl_3$

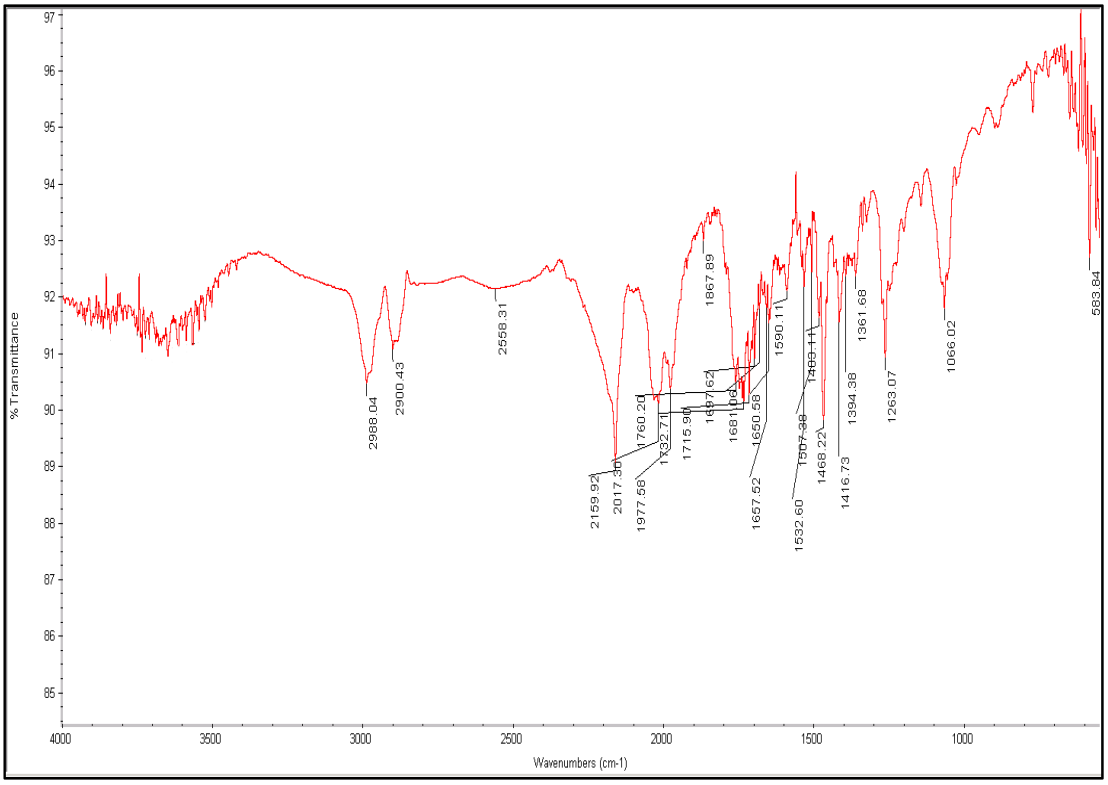


Figure 67 IR Spectrum of Compound **133a**

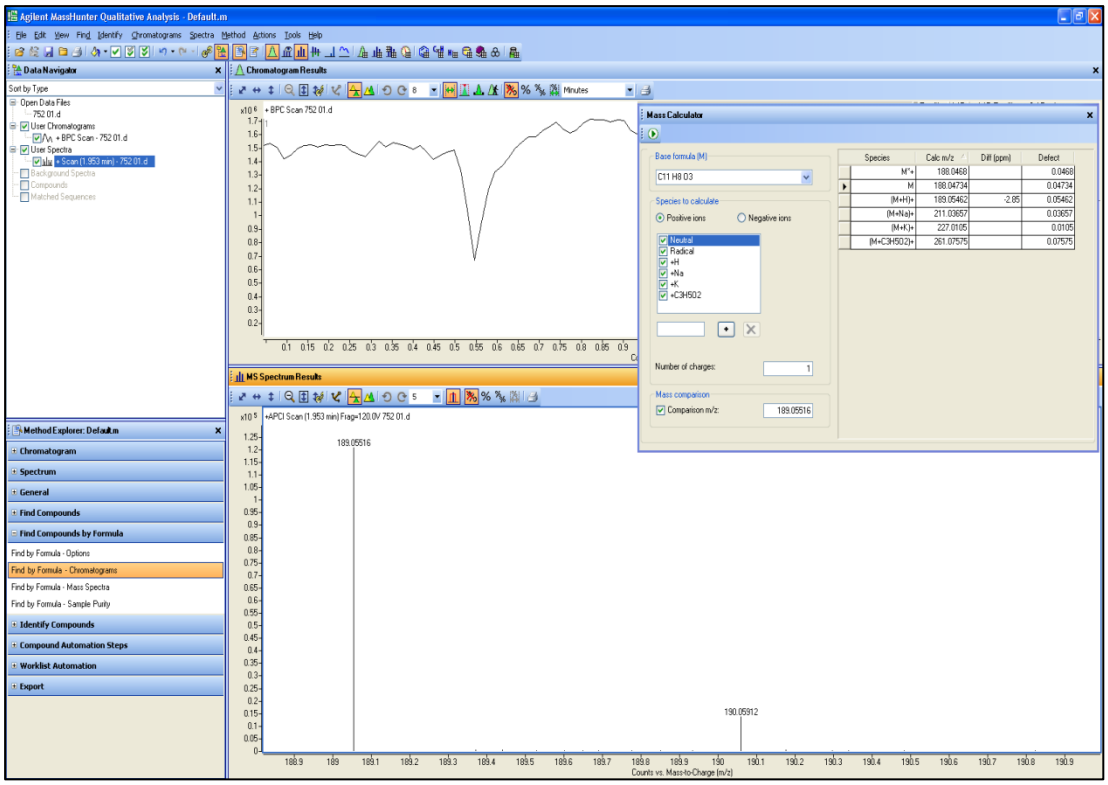


Figure 68 HRMS Spectrum of Compound **133a**

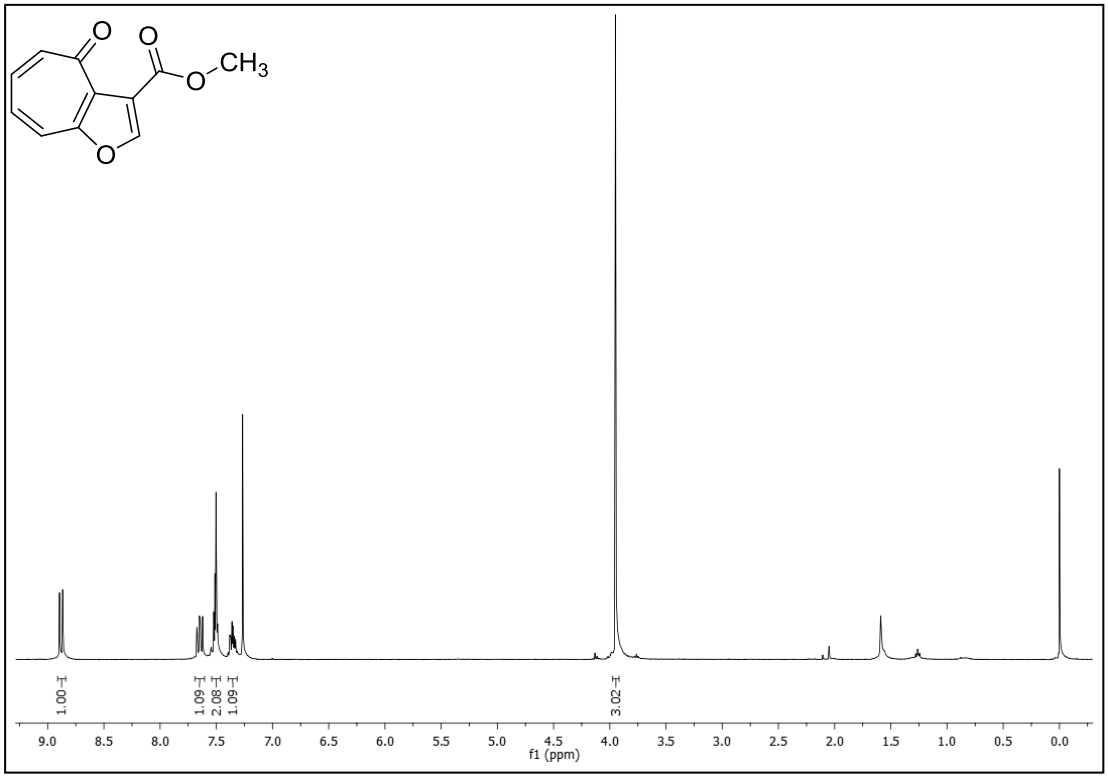


Figure 69 ^{1}H NMR Spectrum of Compound **133b** in $CDCl_3$

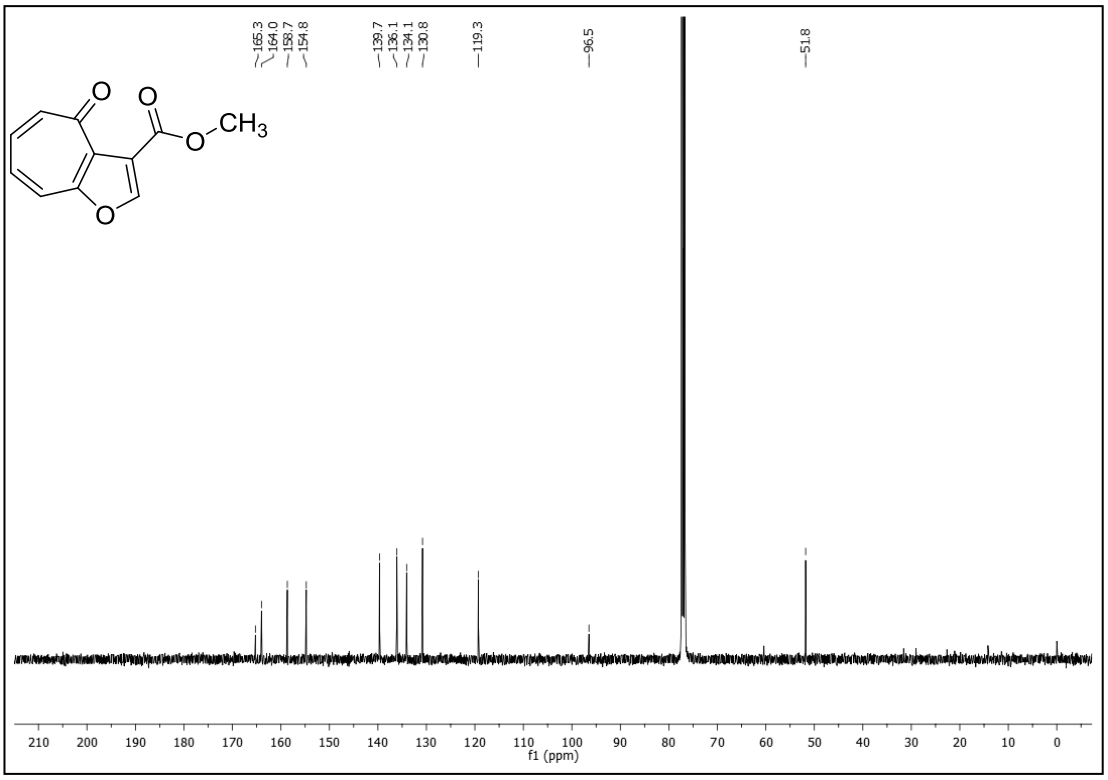


Figure 70 ^{13}C NMR Spectrum of Compound **133b** in $CDCl_3$

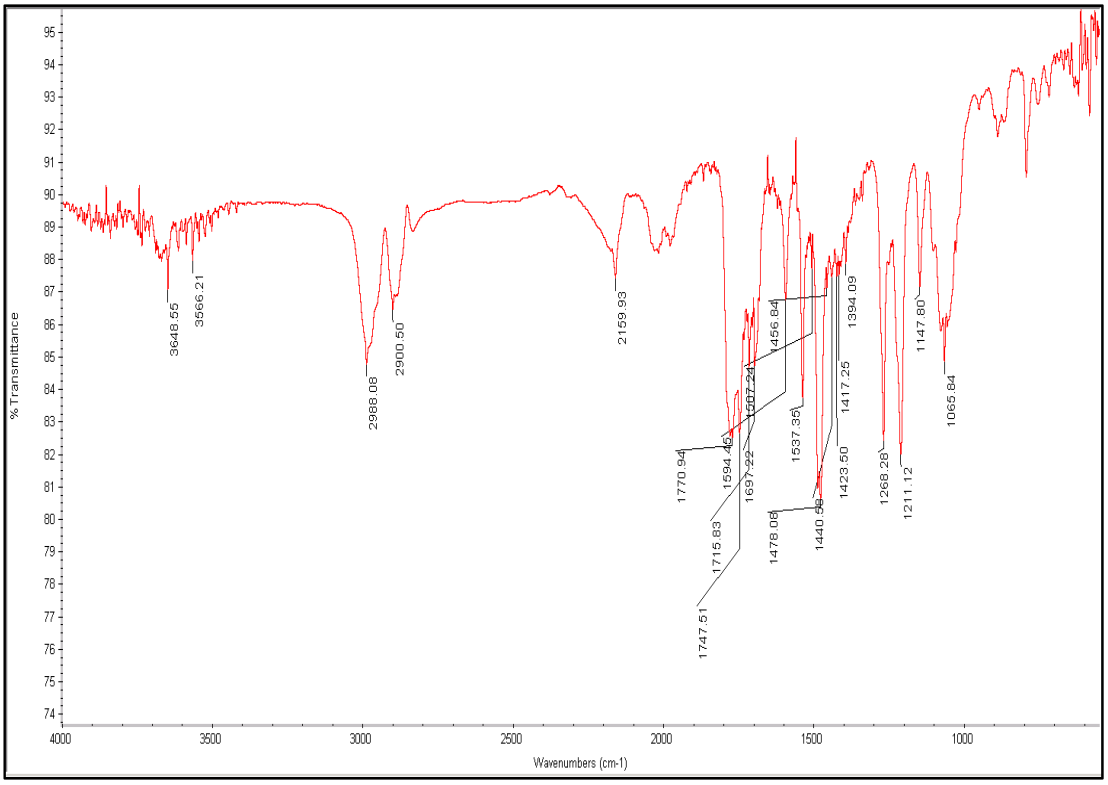


Figure 71 IR Spectrum of Compound **133b**

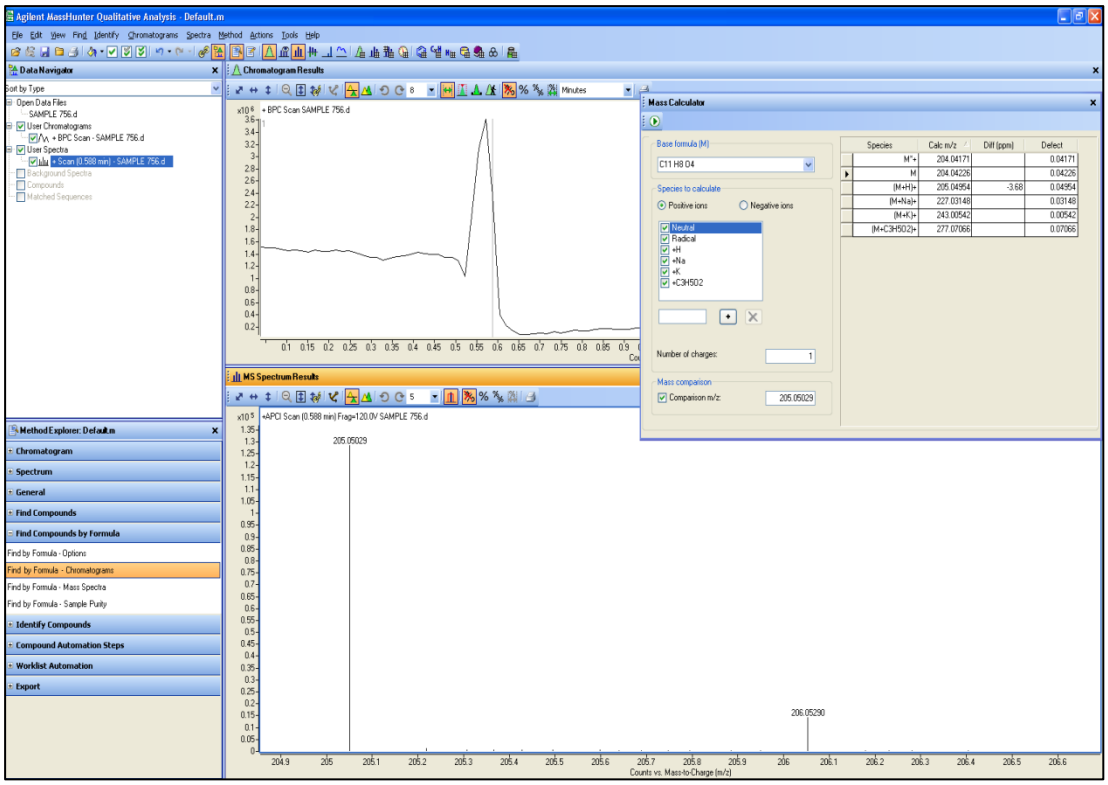


Figure 72 HRMS Spectrum of Compound **133b**

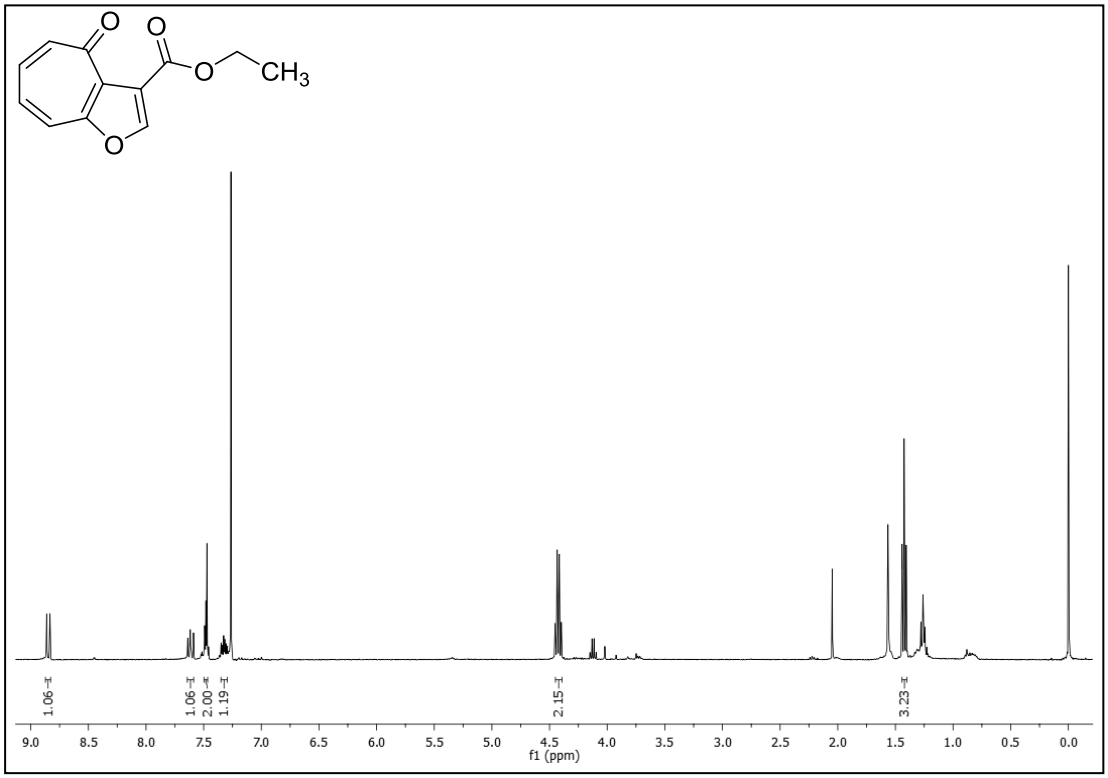


Figure 73 ^{1}H NMR Spectrum of Compound **133c** in $CDCl_3$

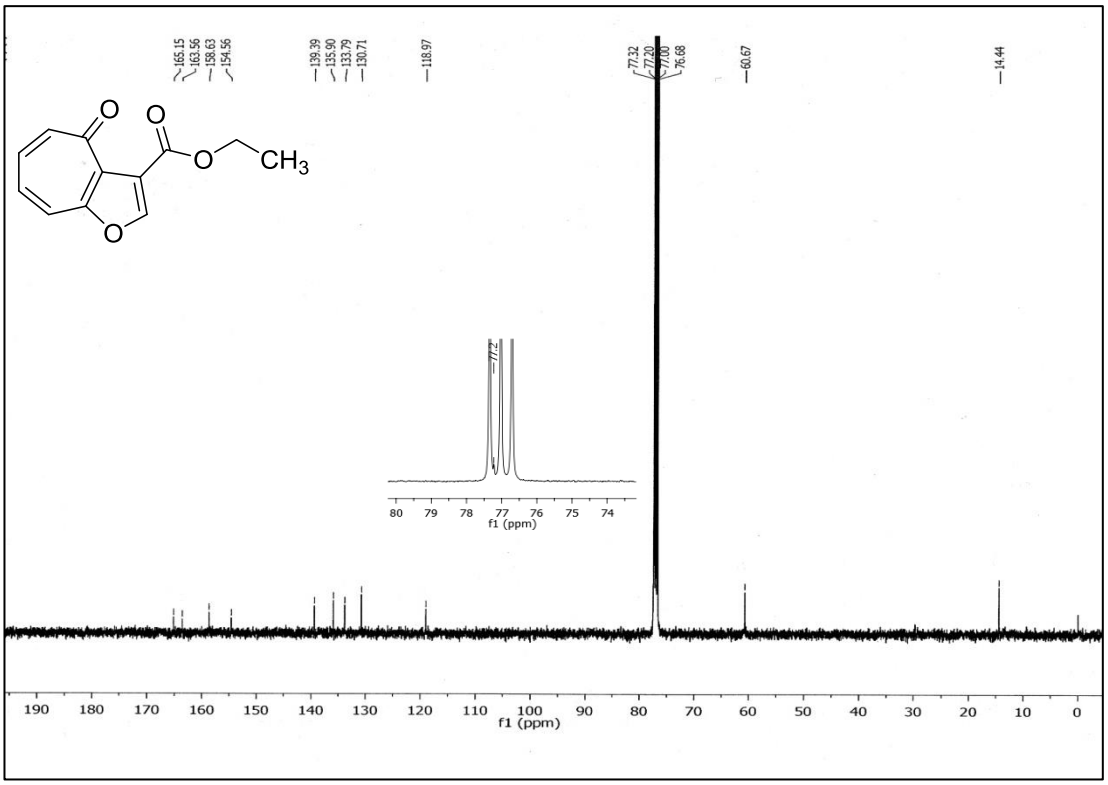


Figure 74 ^{13}C NMR Spectrum of Compound **133c** in $CDCl_3$

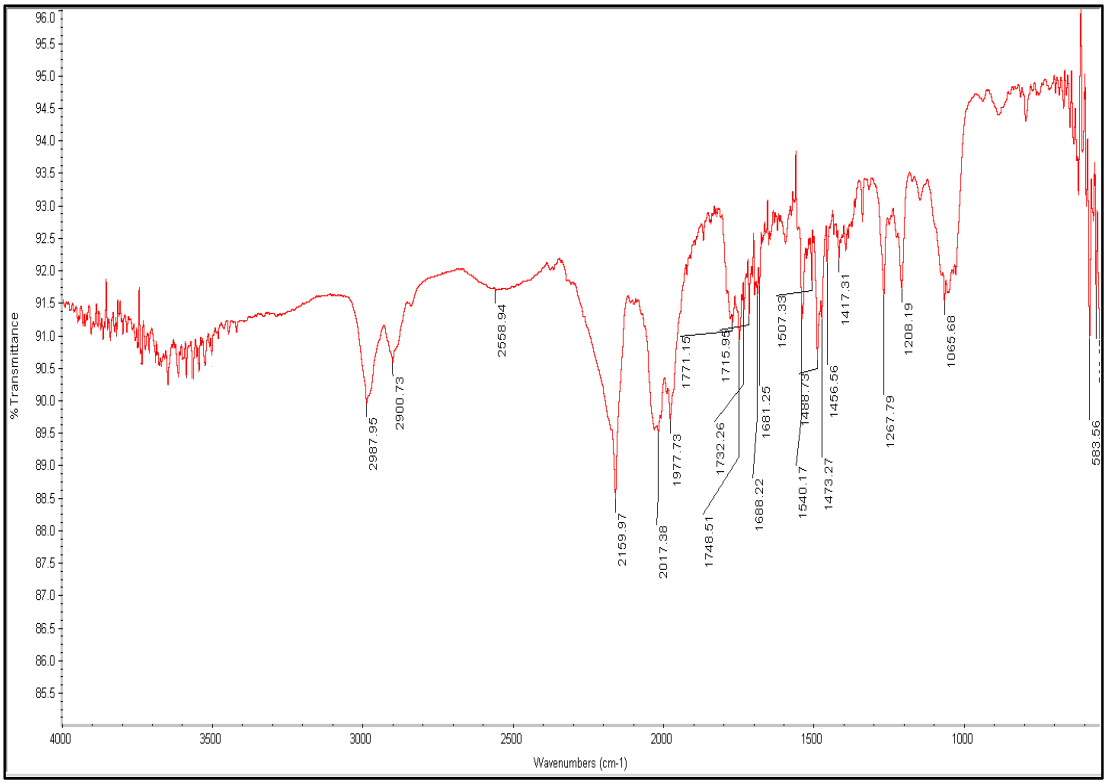


Figure 75 IR Spectrum of Compound **133c**

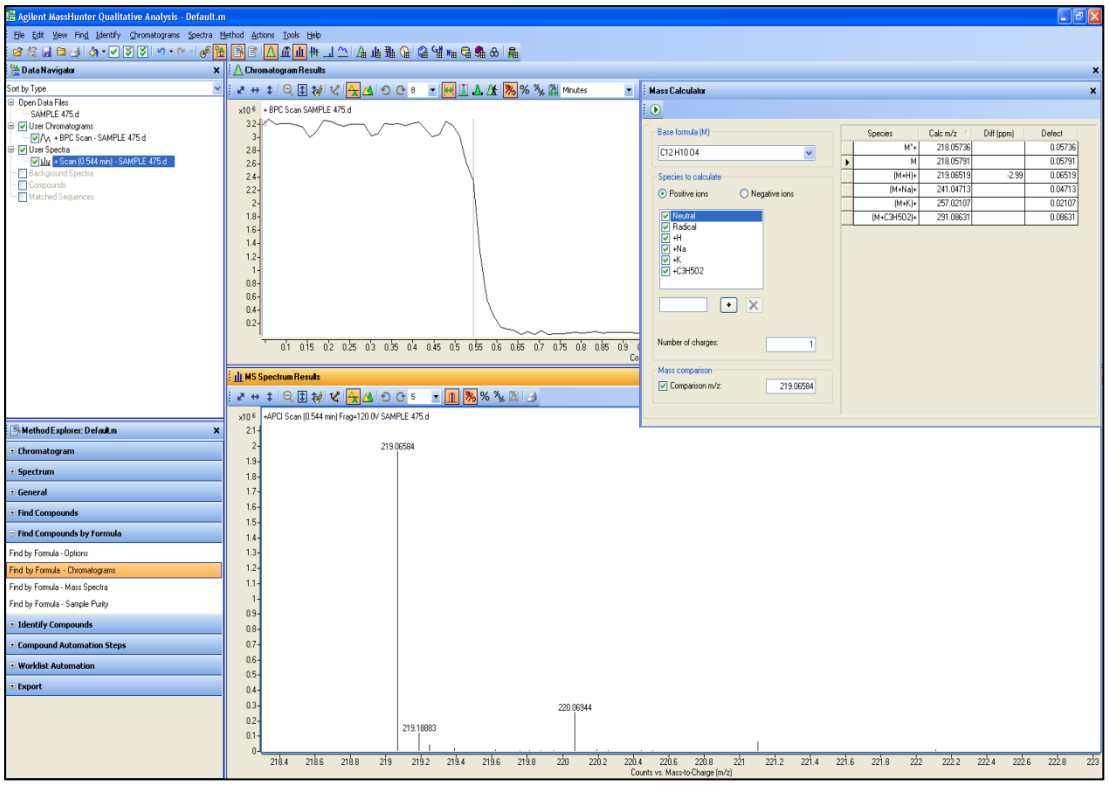


Figure 76 HRMS Spectrum of Compound **133c**

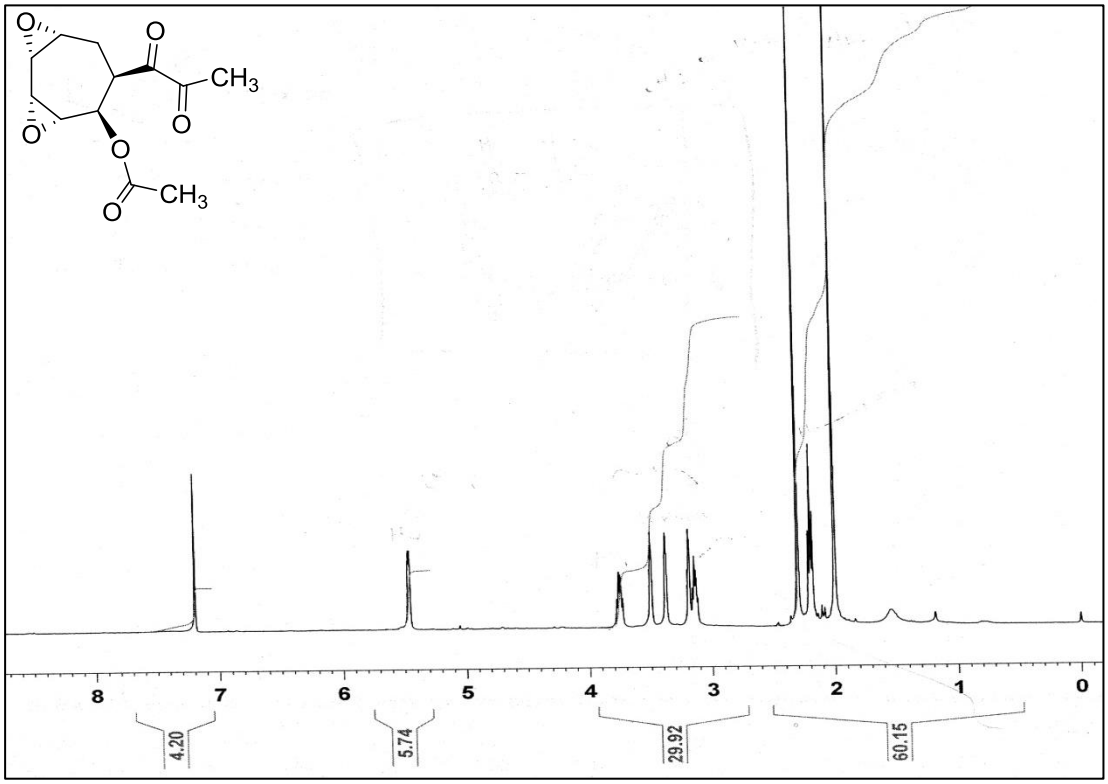


Figure 77 ^{1}H NMR Spectrum of Compound **153** in $CDCl_3$

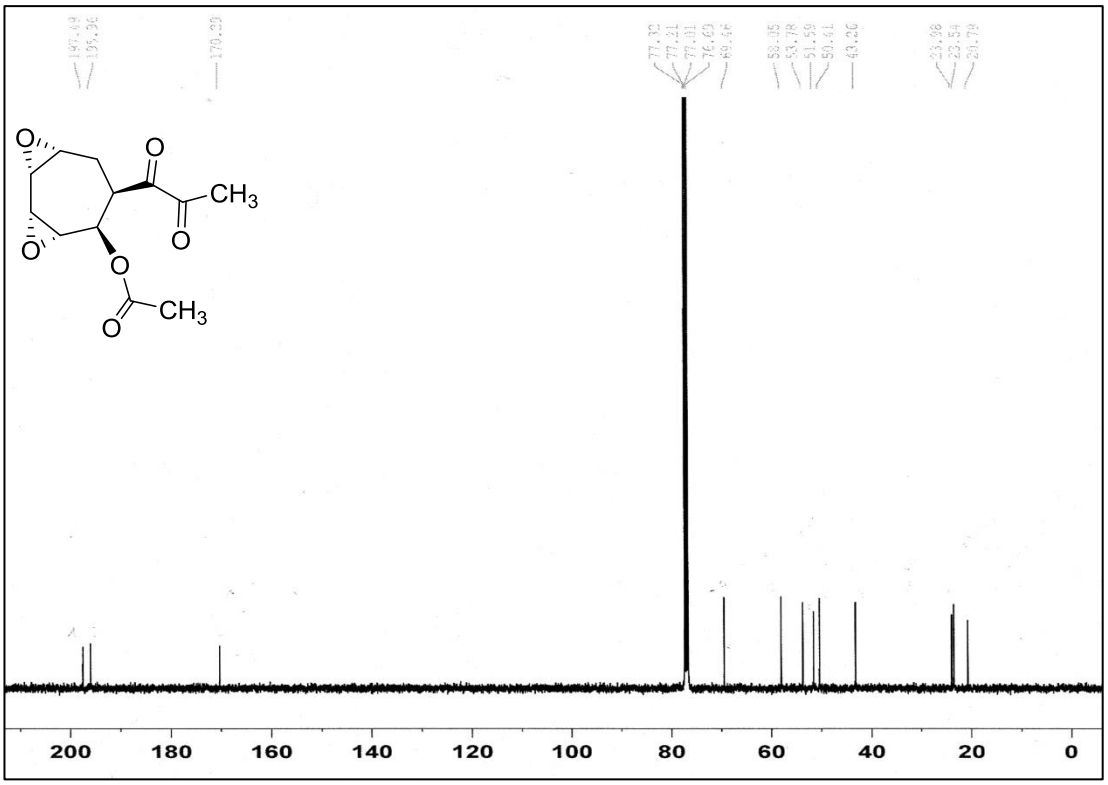


Figure 78 ^{13}C NMR Spectrum of Compound **153** in $CDCl_3$

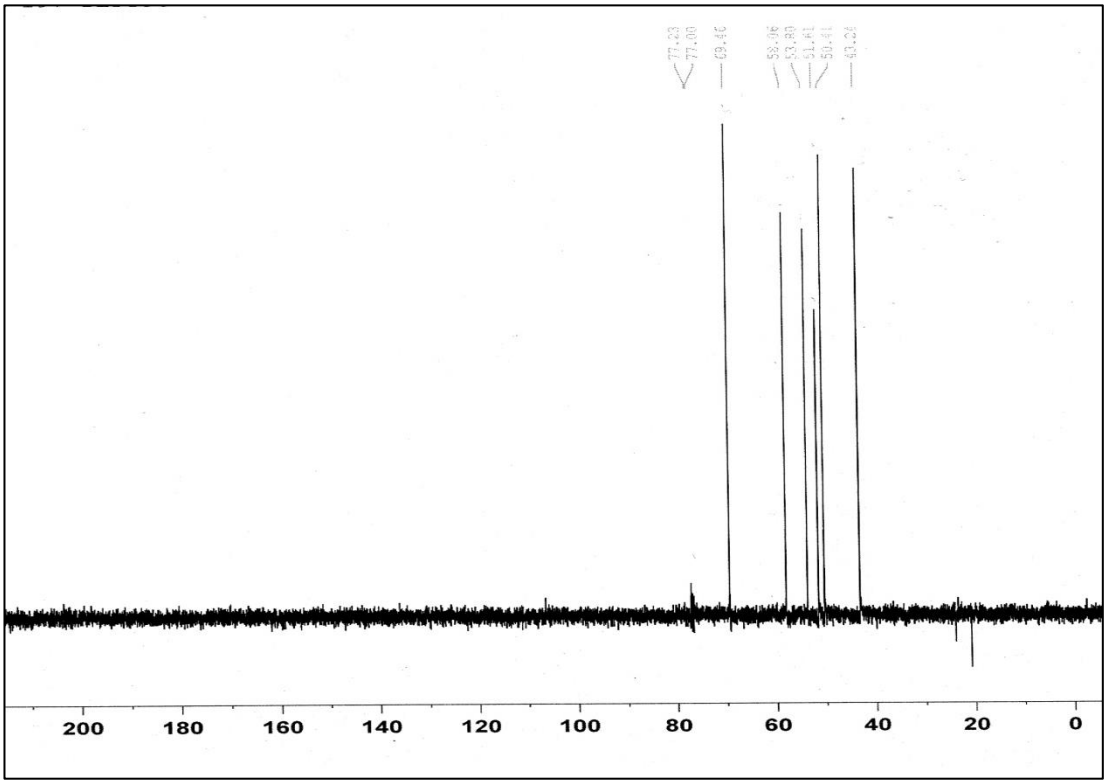


Figure 79 DEPT90 Spectrum of Compound **153** in $CDCl_3$

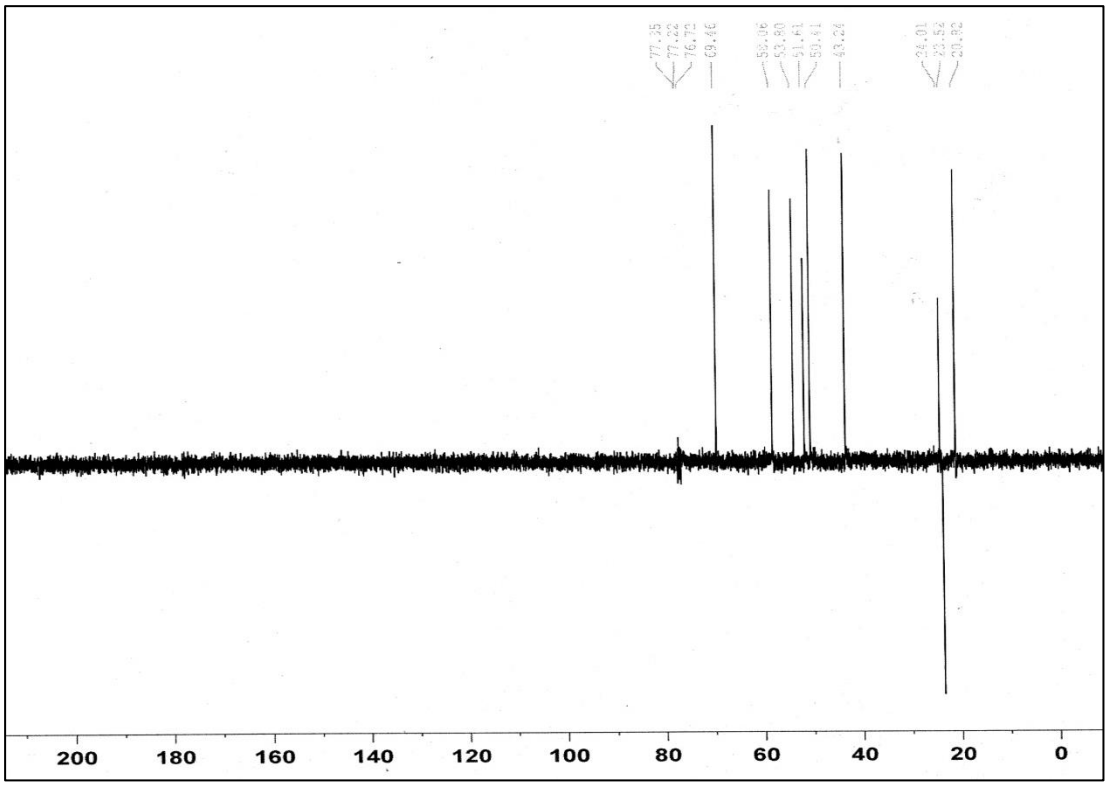


Figure 80 DEPT135 Spectrum of Compound **153** in $CDCl_3$

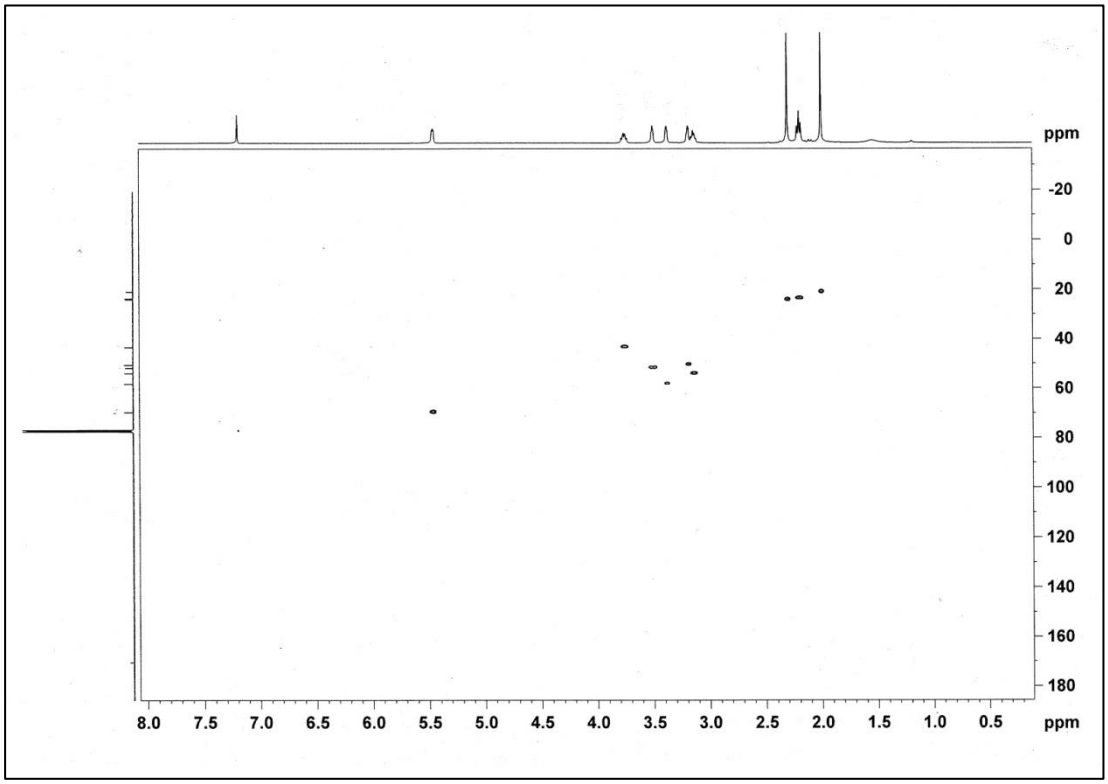


Figure 81 HSQC Spectrum of Compound **153** in $CDCl_3$

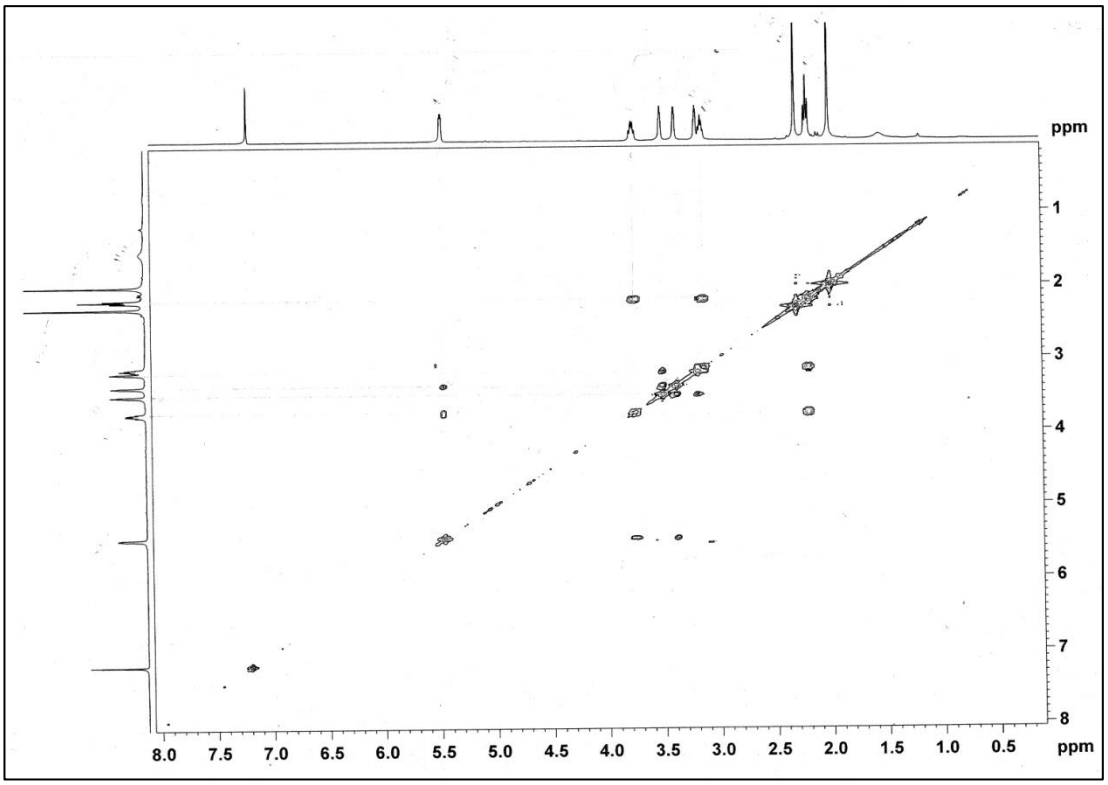


Figure 82 COSY Spectrum of Compound **153** in $CDCl_3$

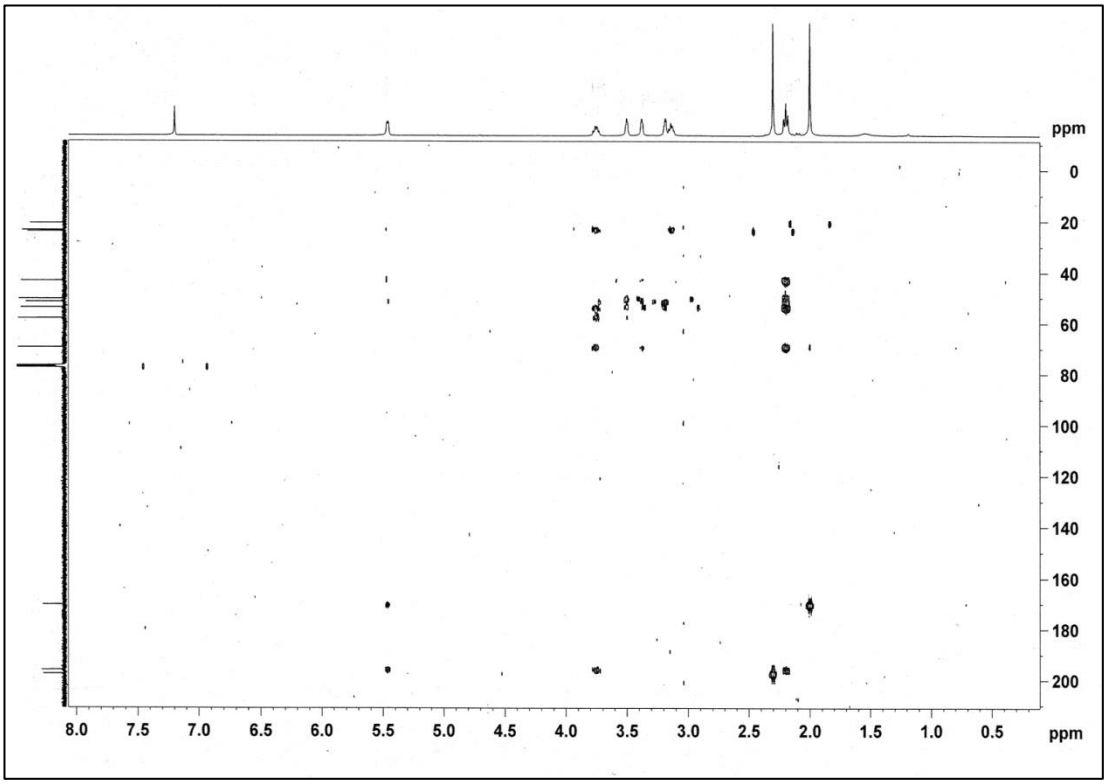


Figure 83 HMBC Spectrum of Compound **153** in $CDCl_3$

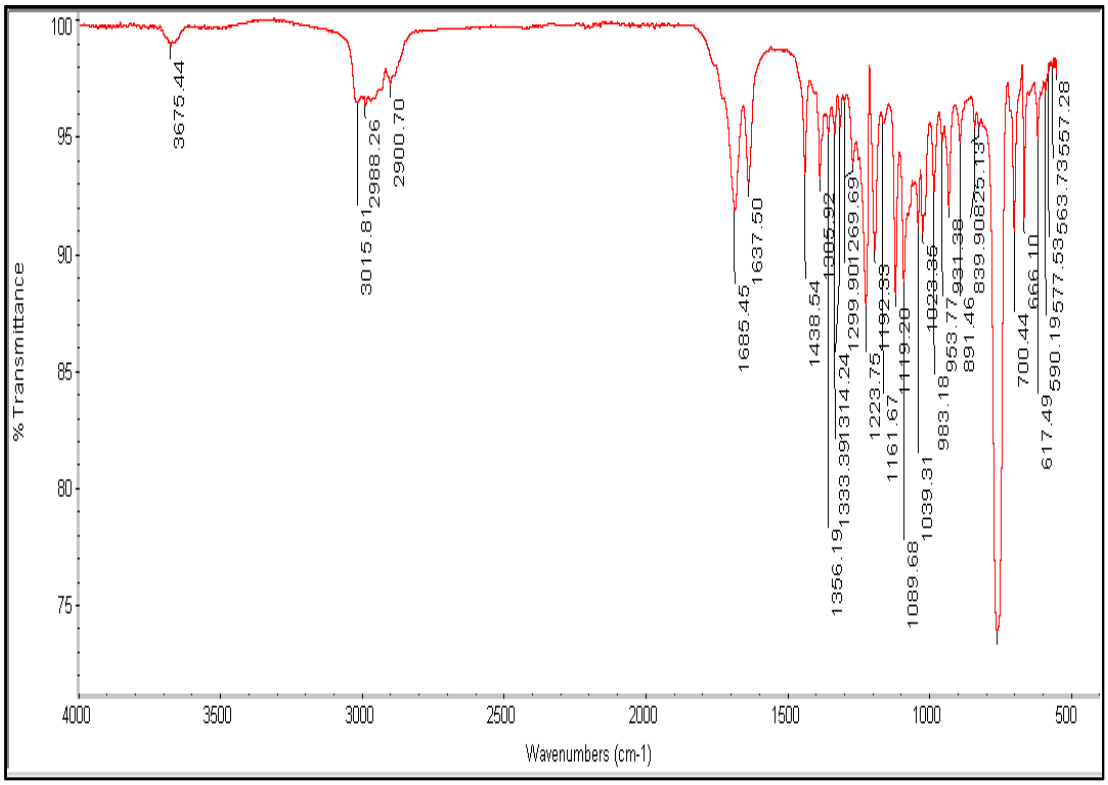


Figure 84 IR Spectrum of Compound **153**

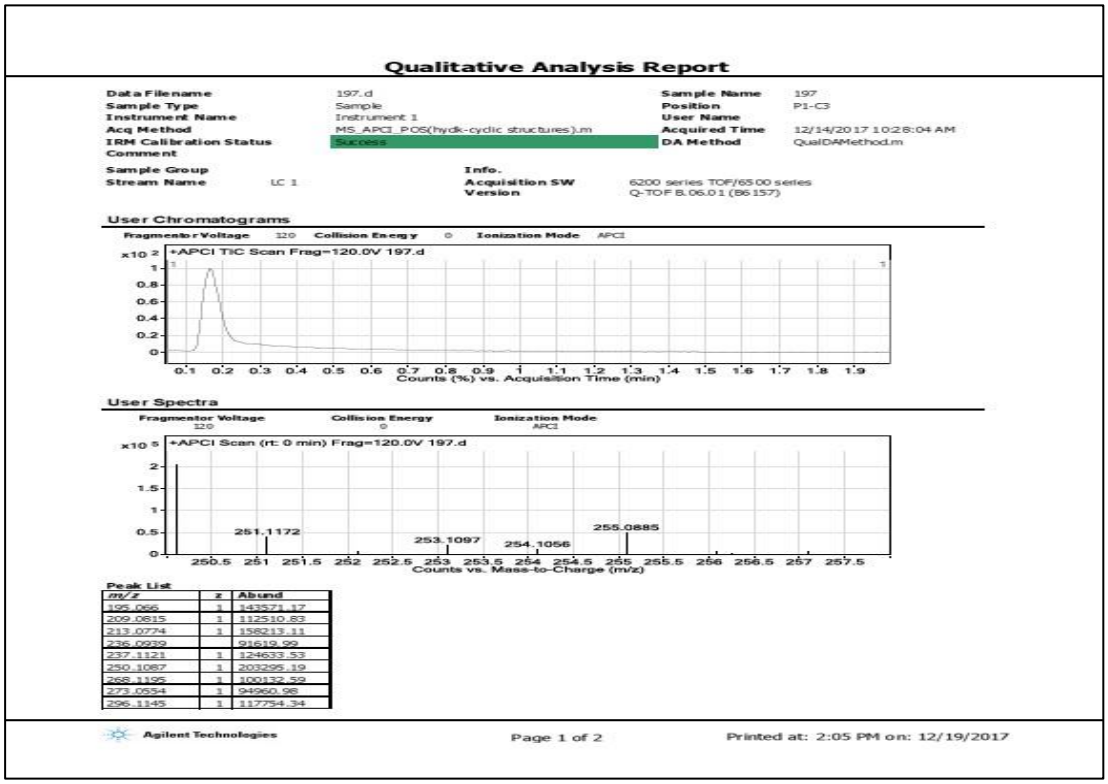


Figure 85 HRMS Spectrum of Compound **153**

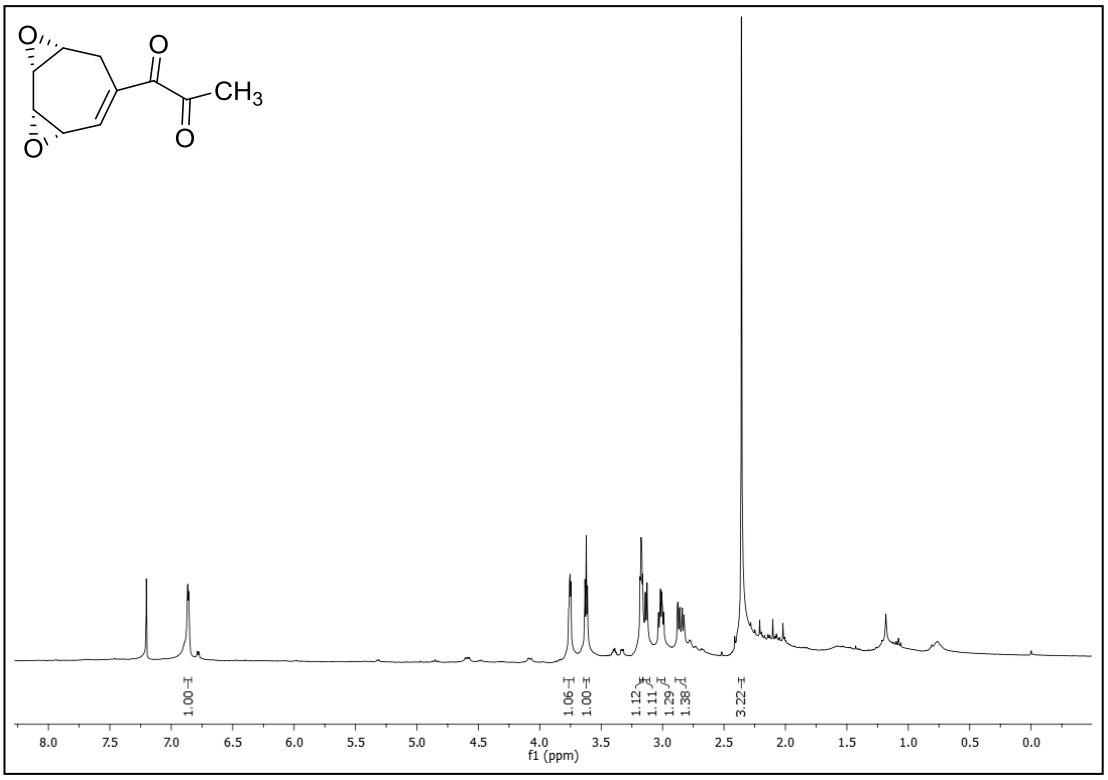


Figure 86 ^{1}H NMR Spectrum of Compound **134** in $CDCl_3$

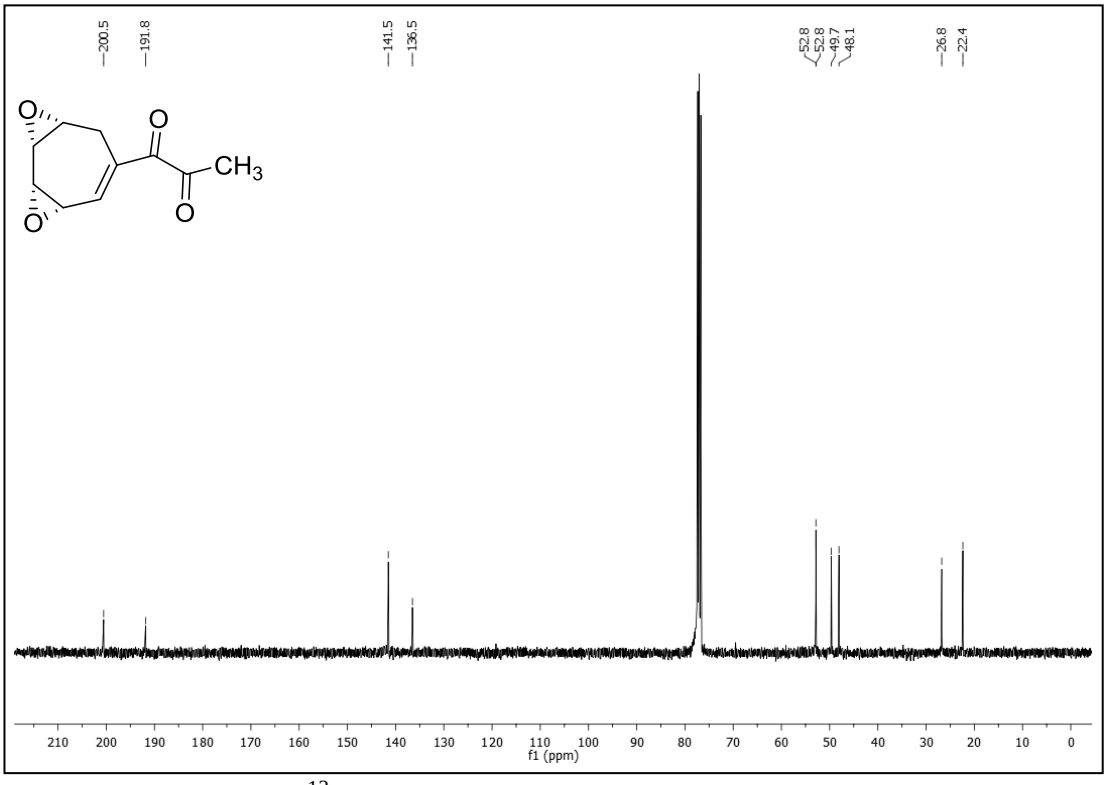


Figure 87 ^{13}C NMR Spectrum of Compound **134** in $CDCl_3$

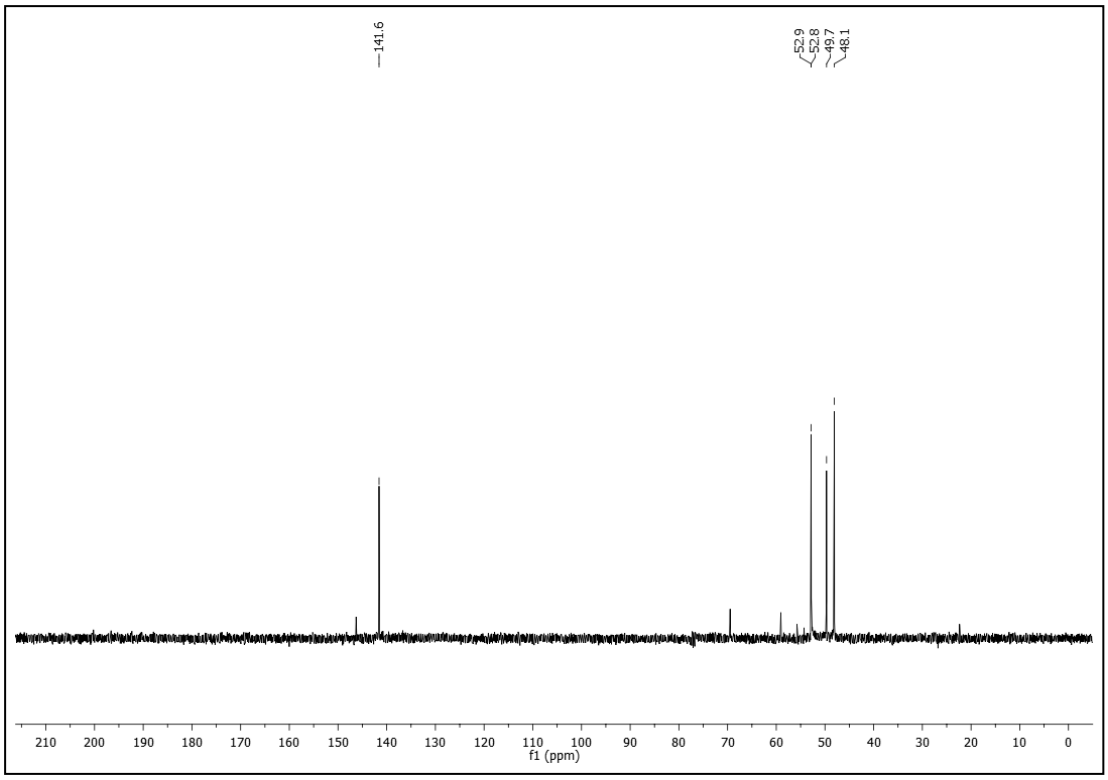


Figure 88 DEPT90 Spectrum of Compound **134** in $CDCl_3$

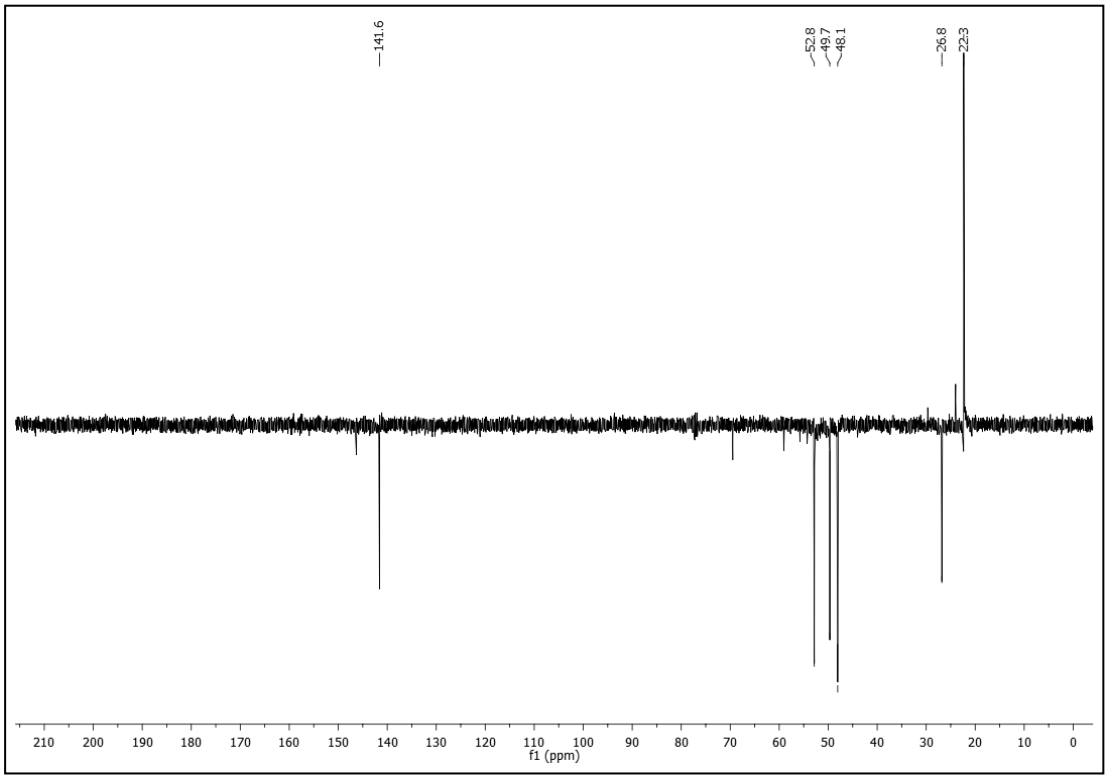


Figure 89 DEPT135 Spectrum of Compound **134** in $CDCl_3$

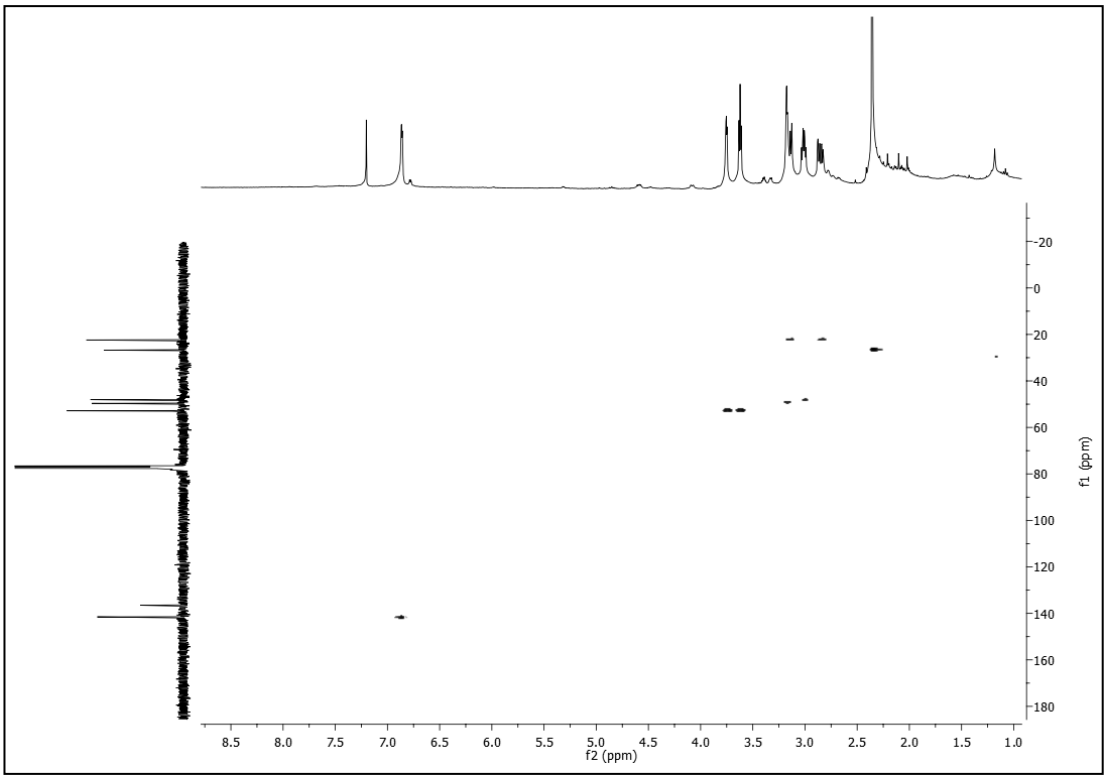


Figure 90 HSQC Spectrum of Compound **134** in $CDCl_3$

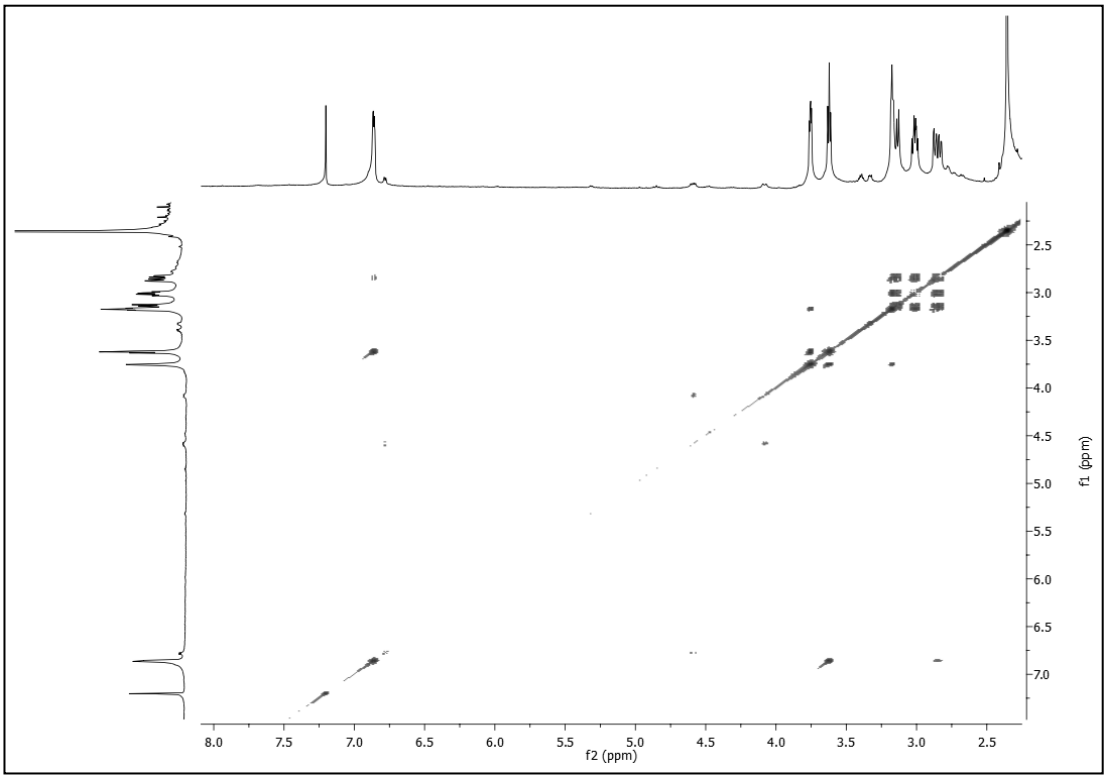


Figure 91 COSY Spectrum of Compound **134** in $CDCl_3$

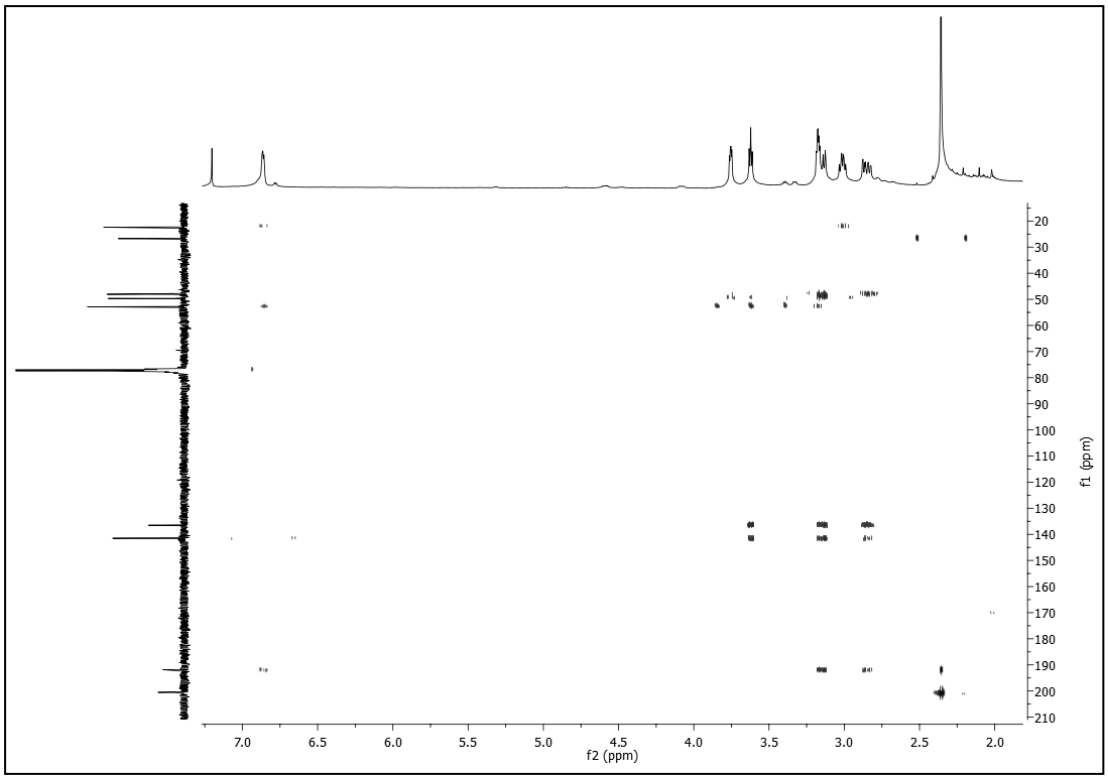


Figure 92 HMBC Spectrum of Compound **134** in $CDCl_3$

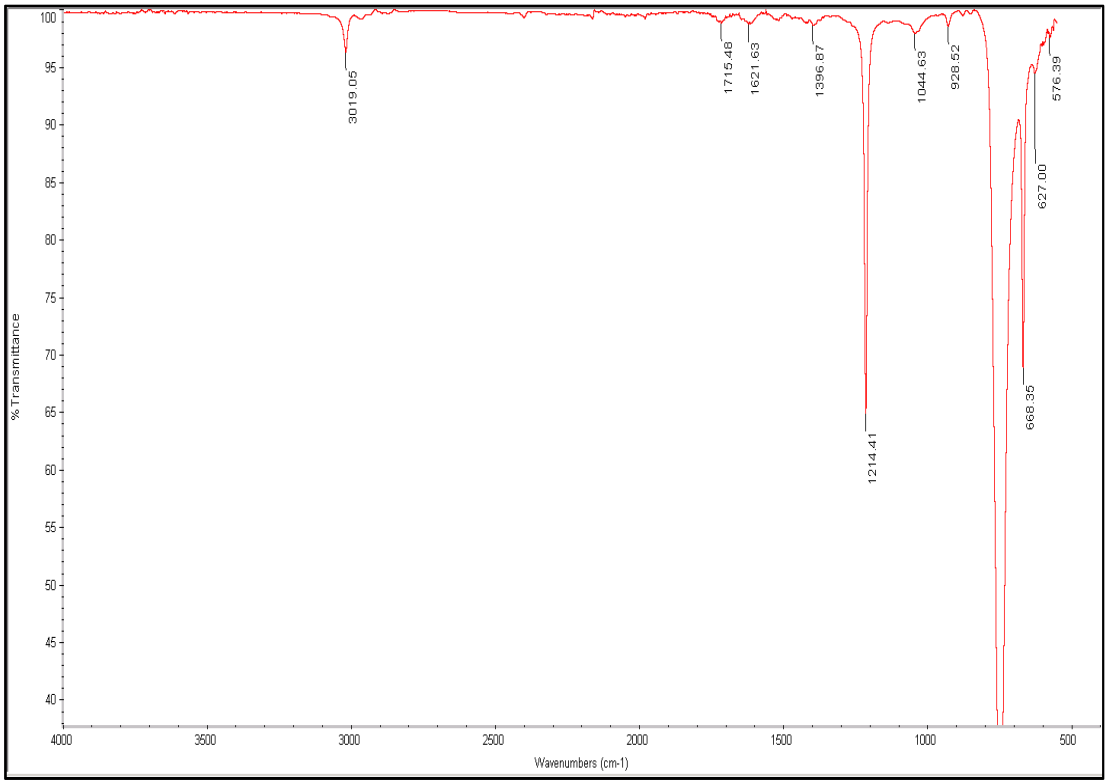


Figure 93 IR Spectrum of Compound **134**

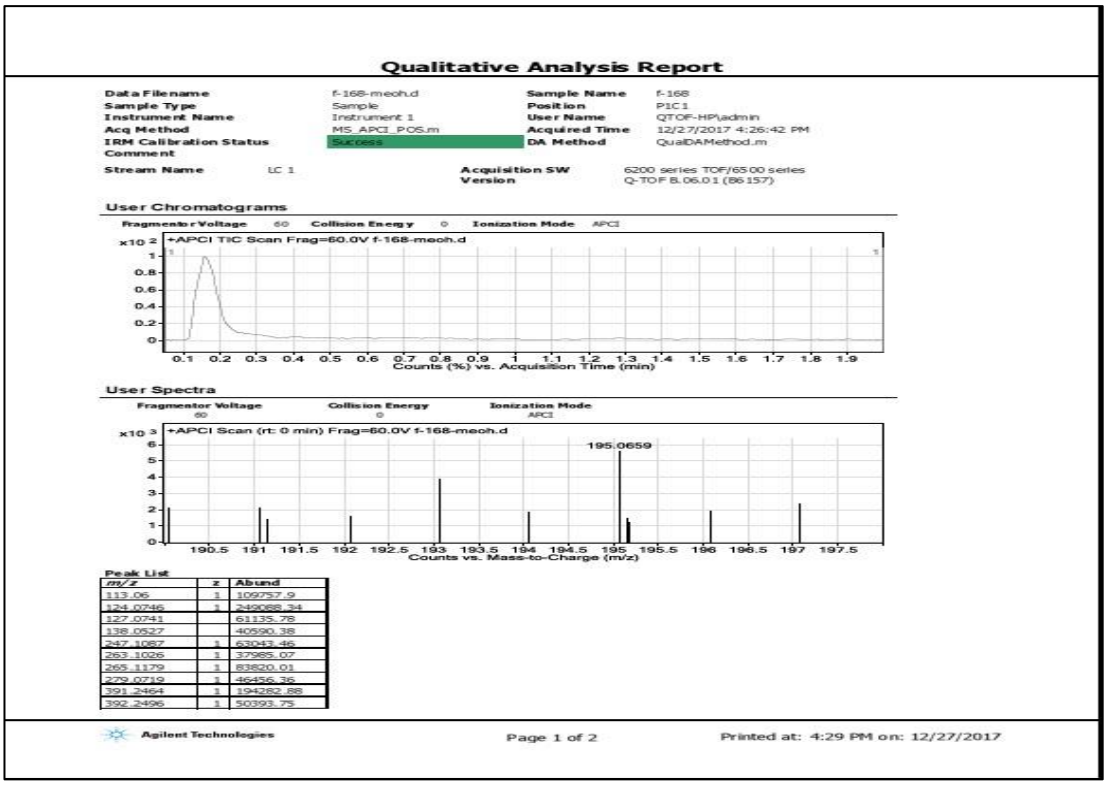


Figure 94 HRMS Spectrum of Compound **134**

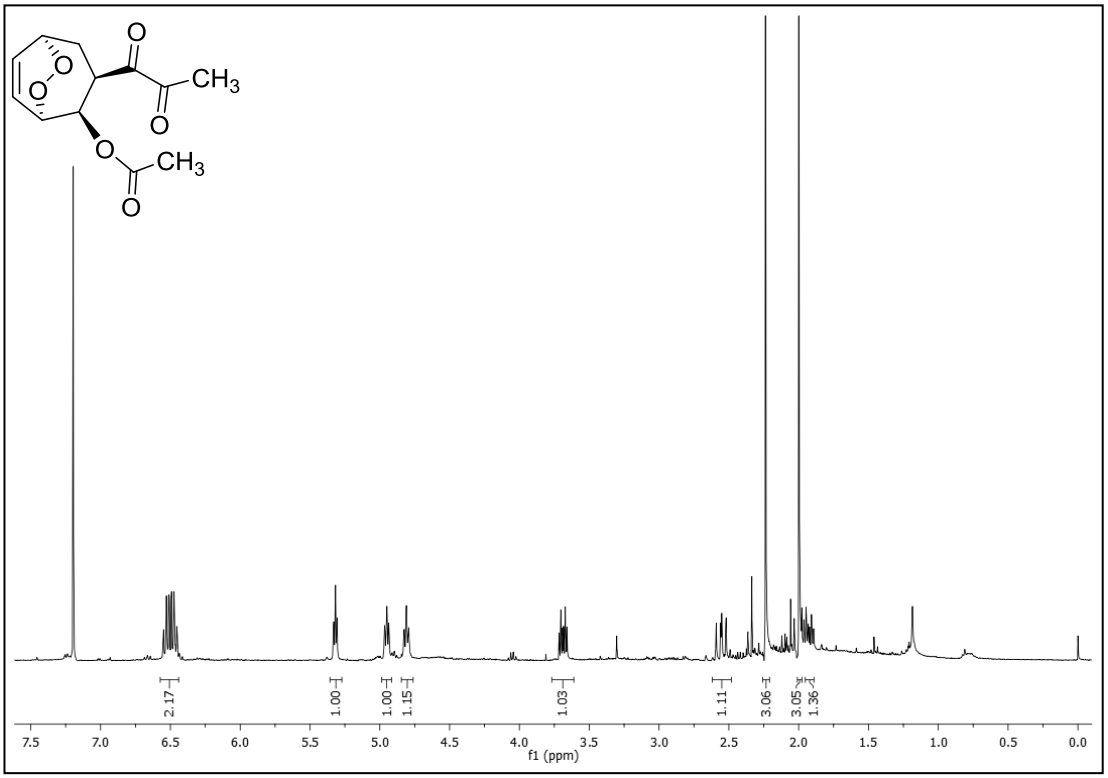


Figure 95 ^{1}H NMR Spectrum of Compound **147** in $CDCl_3$

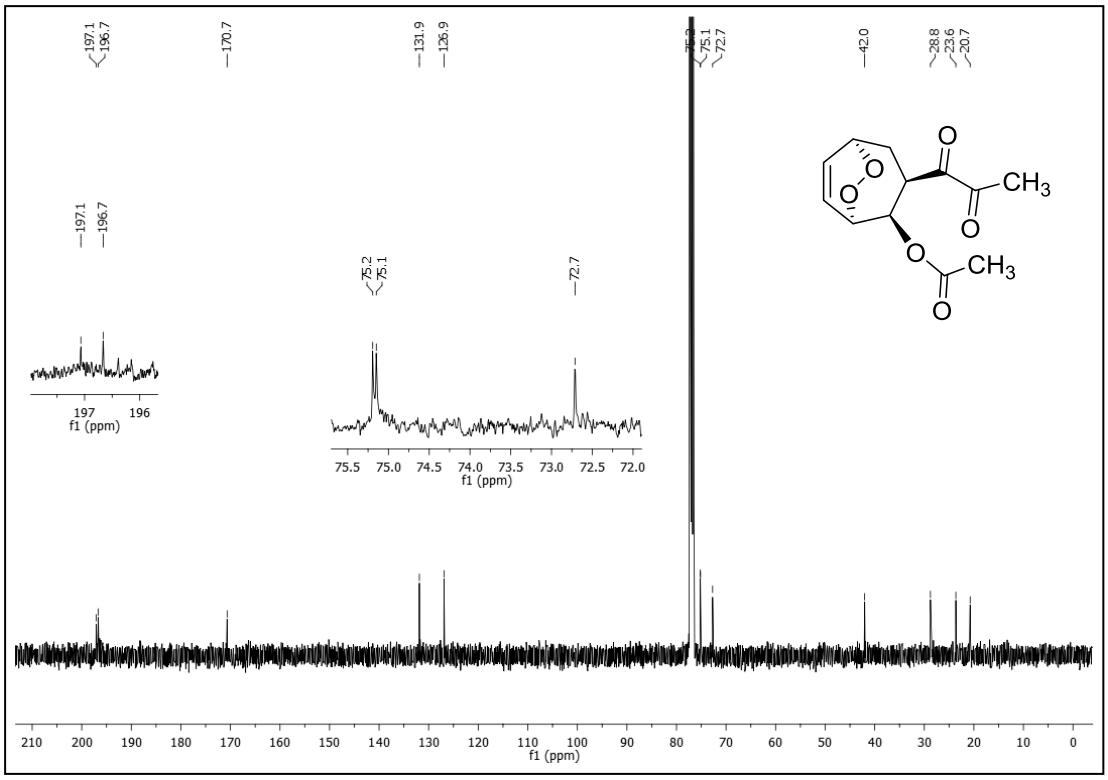


Figure 96 ^{13}C NMR Spectrum of Compound **147** in $CDCl_3$

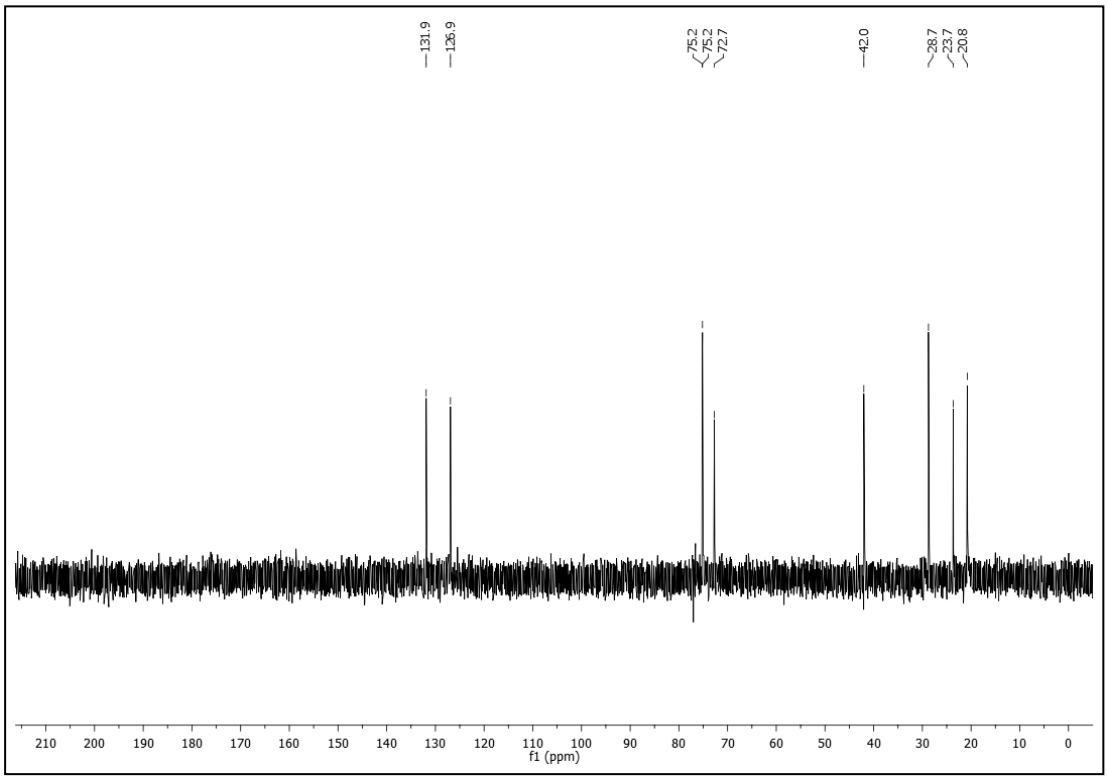


Figure 97 DEPT90 Spectrum of Compound **147** in $CDCl_3$

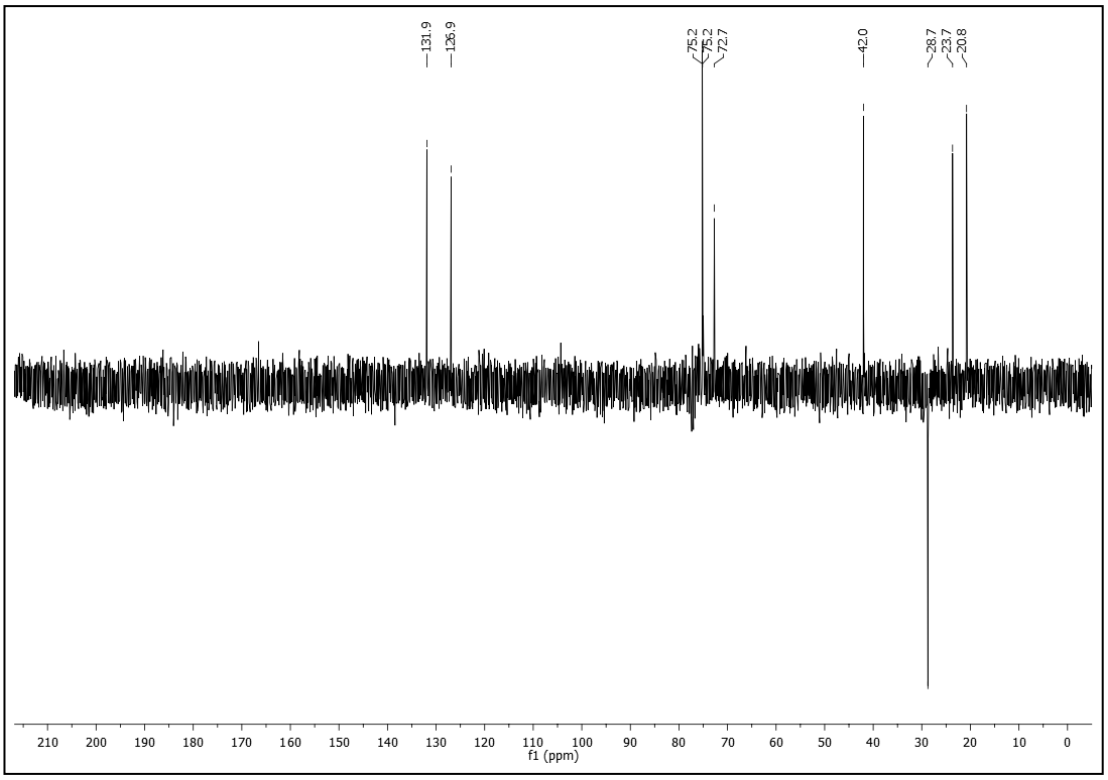


Figure 98 DEPT135 Spectrum of Compound **147** in $CDCl_3$

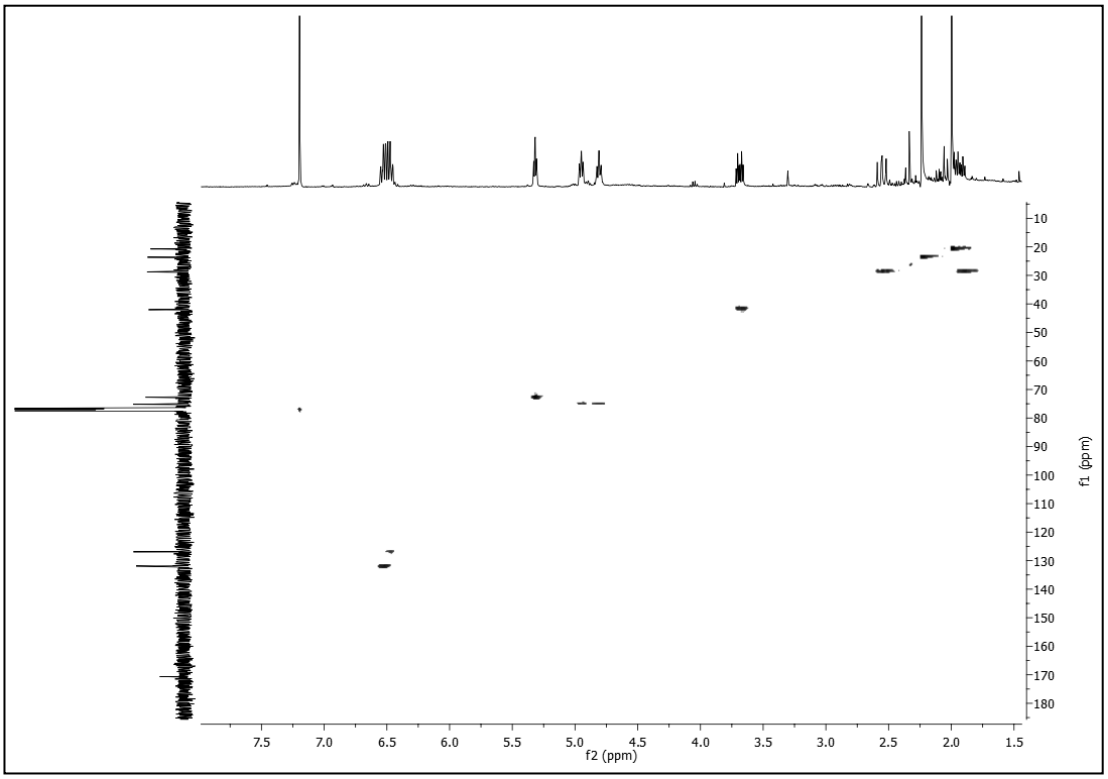


Figure 99 HSQC Spectrum of Compound **147** in $CDCl_3$

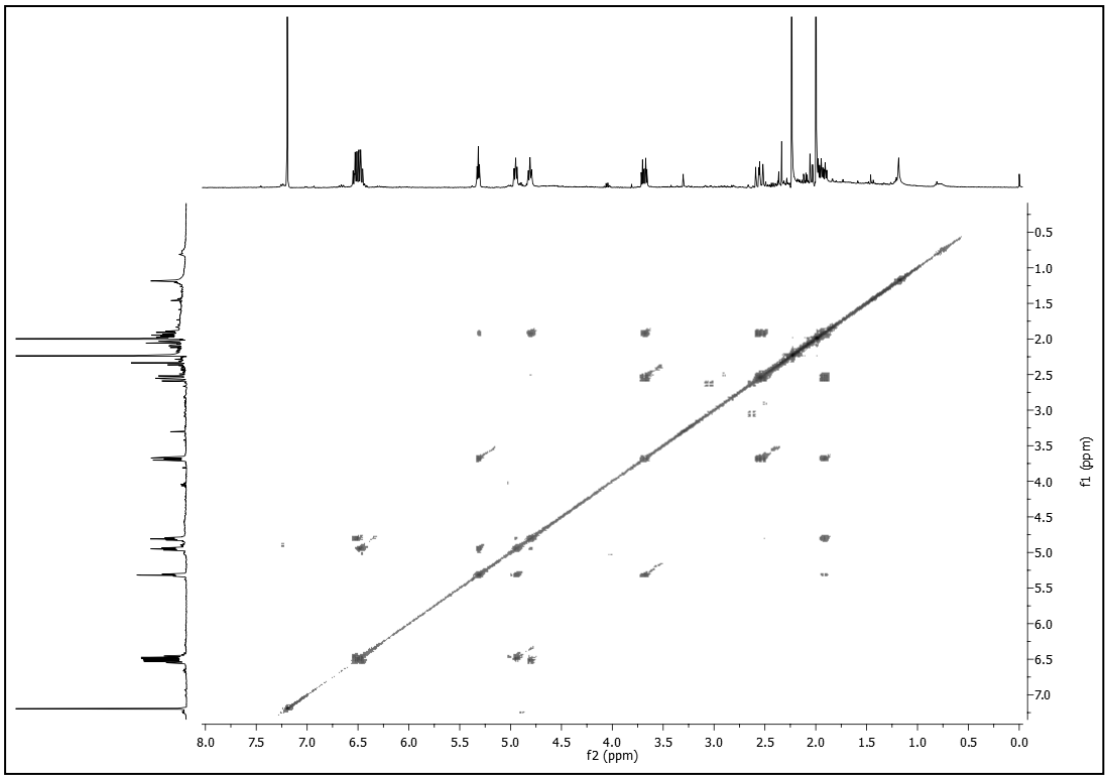


Figure 100 COSY Spectrum of Compound **147** in $CDCl_3$

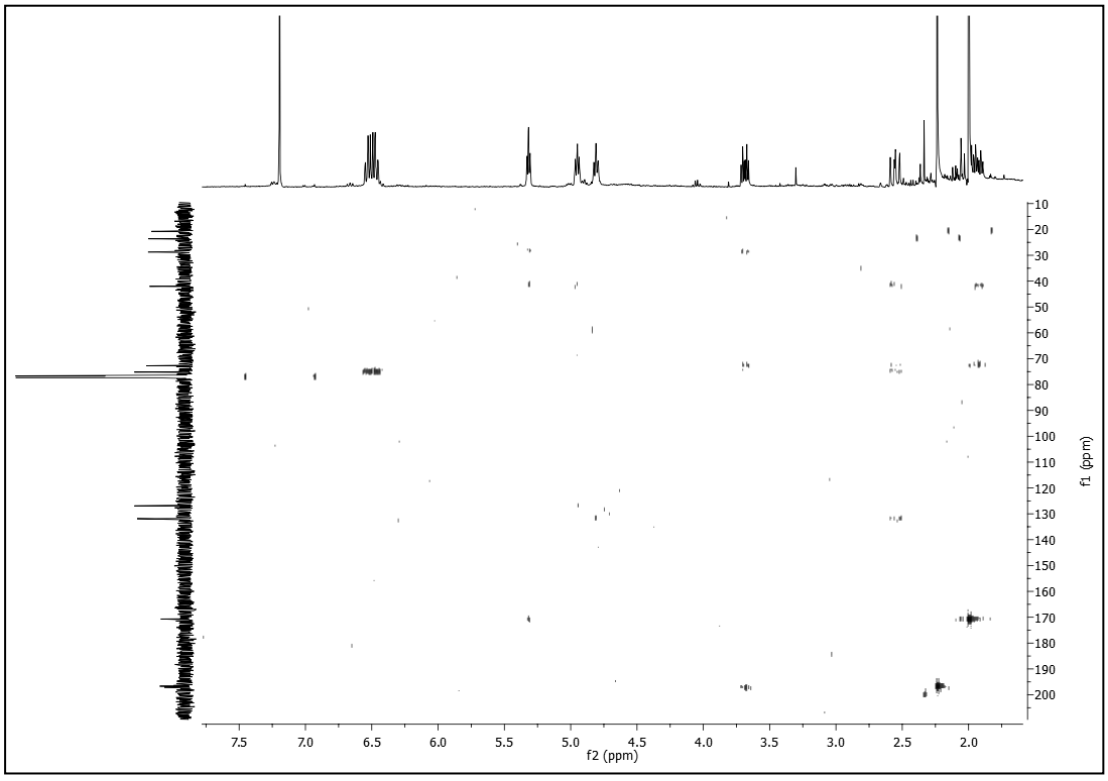


Figure 101 HMBC Spectrum of Compound **147** in $CDCl_3$

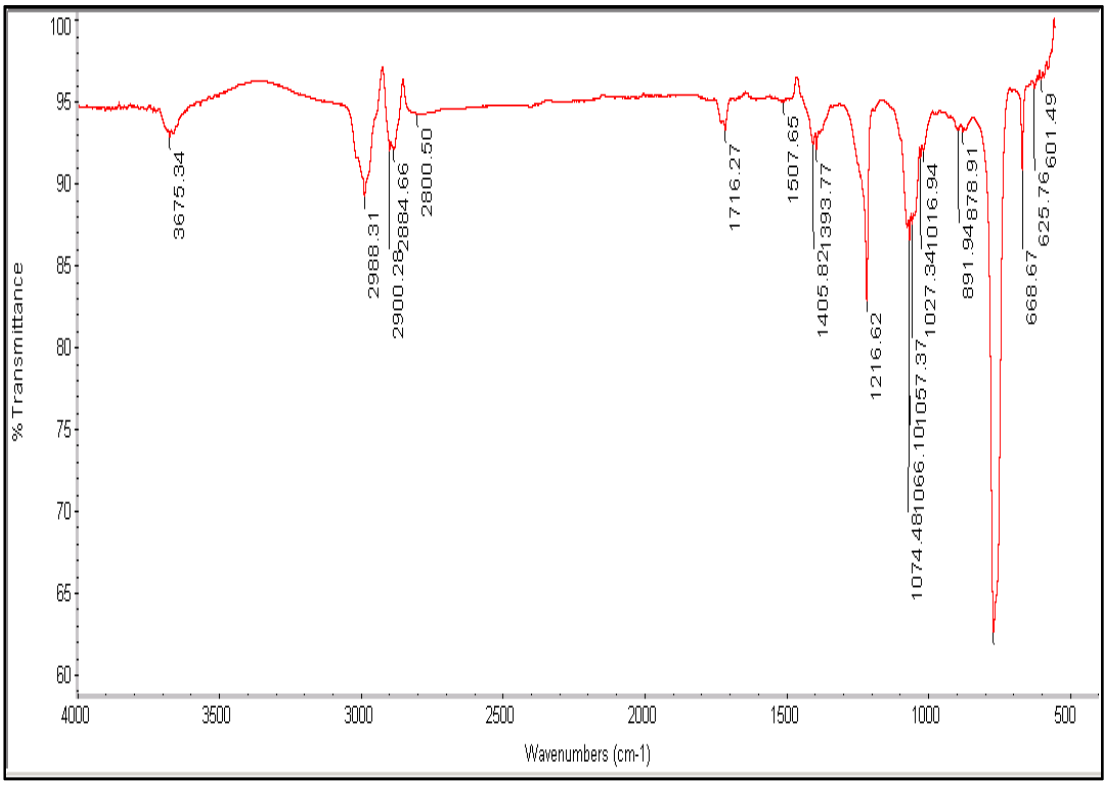


Figure 102 IR Spectrum of Compound **147**

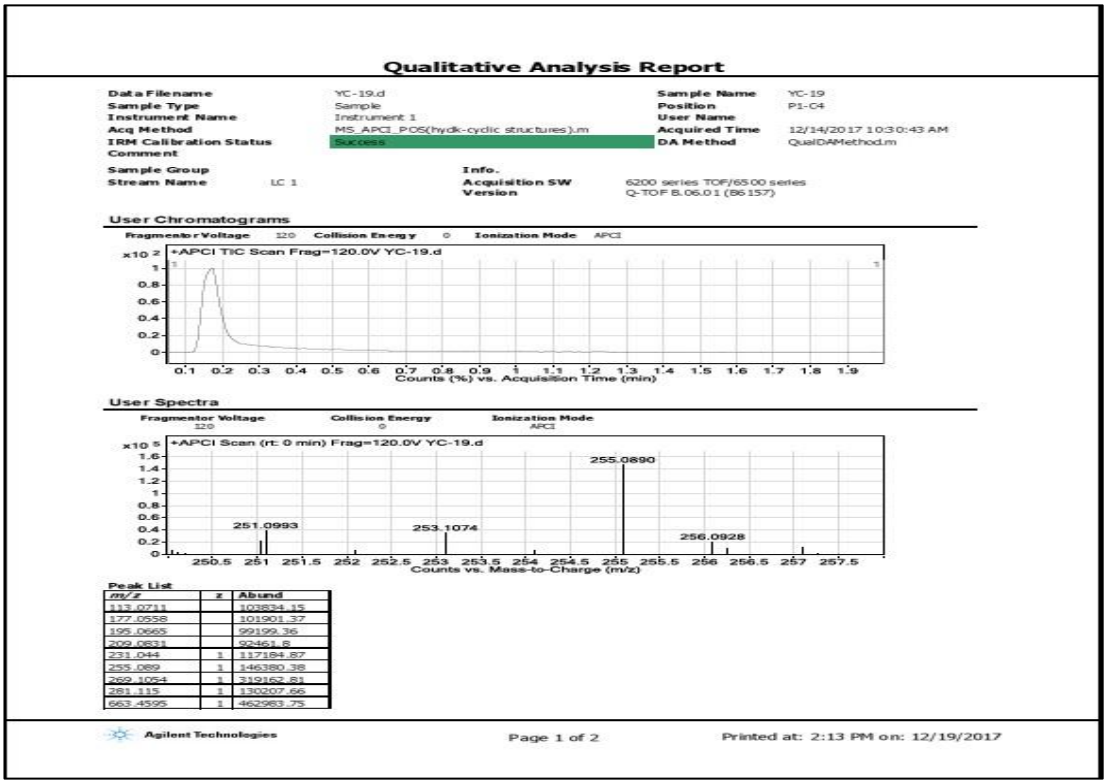


Figure 103 HRMS Spectrum of Compound **147**

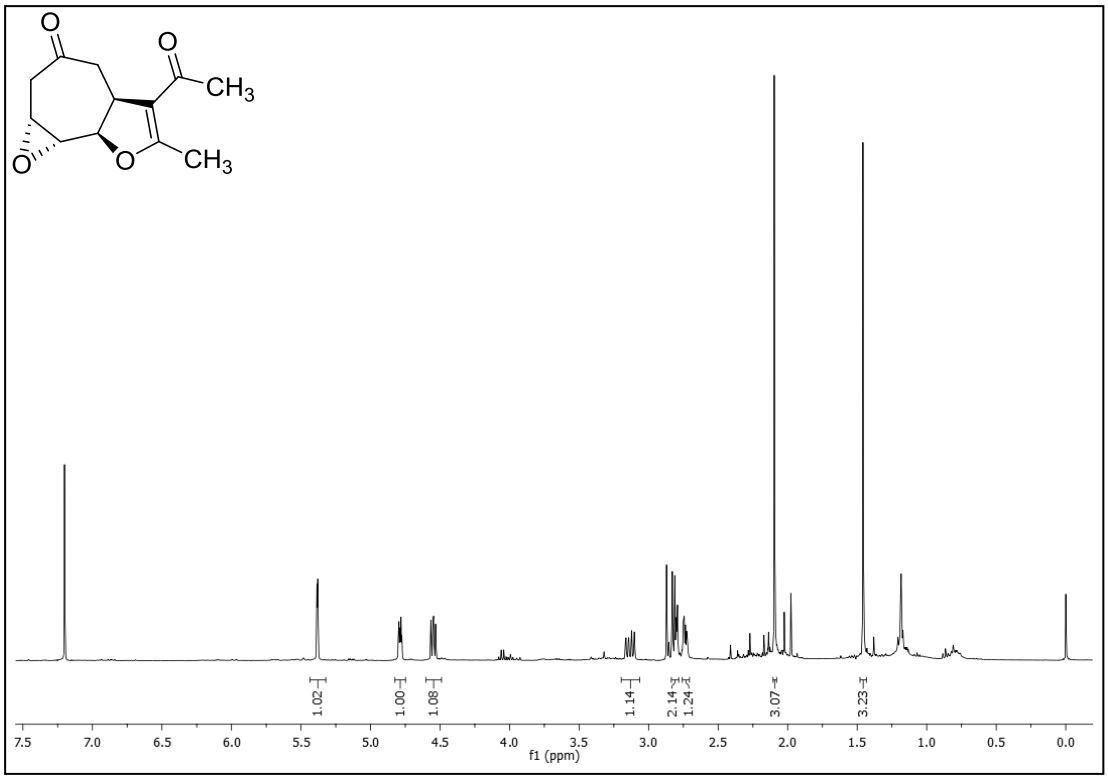


Figure 104 ^{1}H NMR Spectrum of Compound **160** in $CDCl_3$

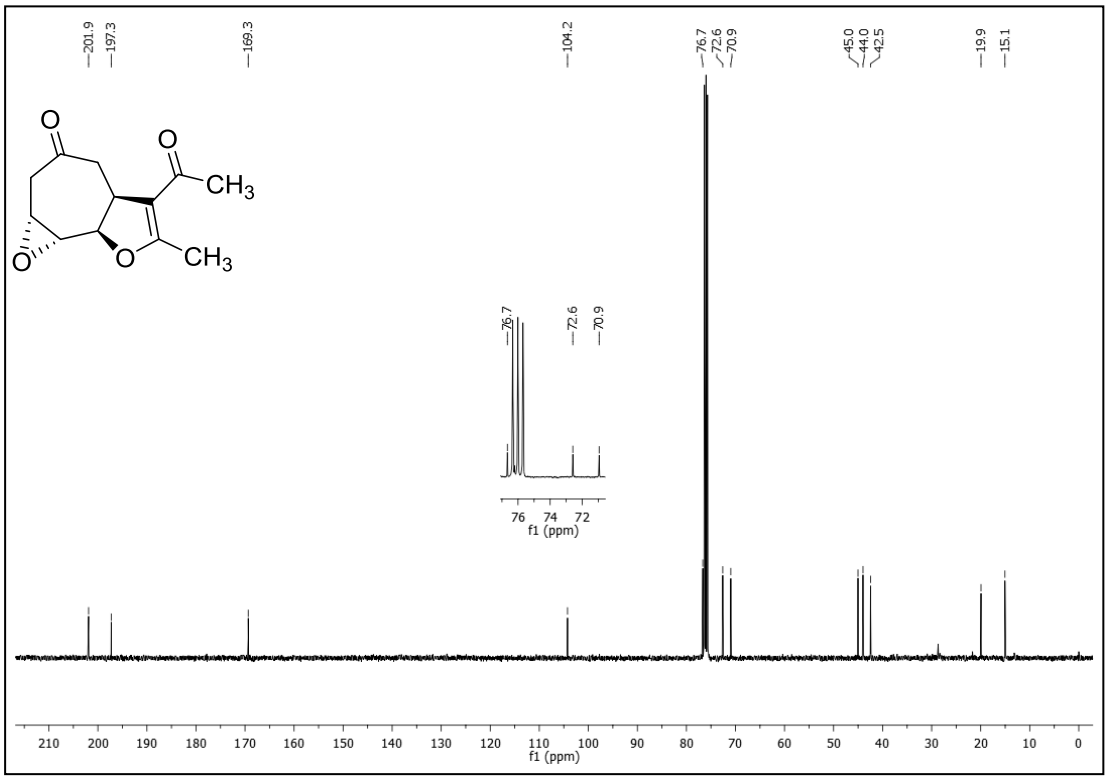


Figure 105 ^{13}C NMR Spectrum of Compound **160** in $CDCl_3$

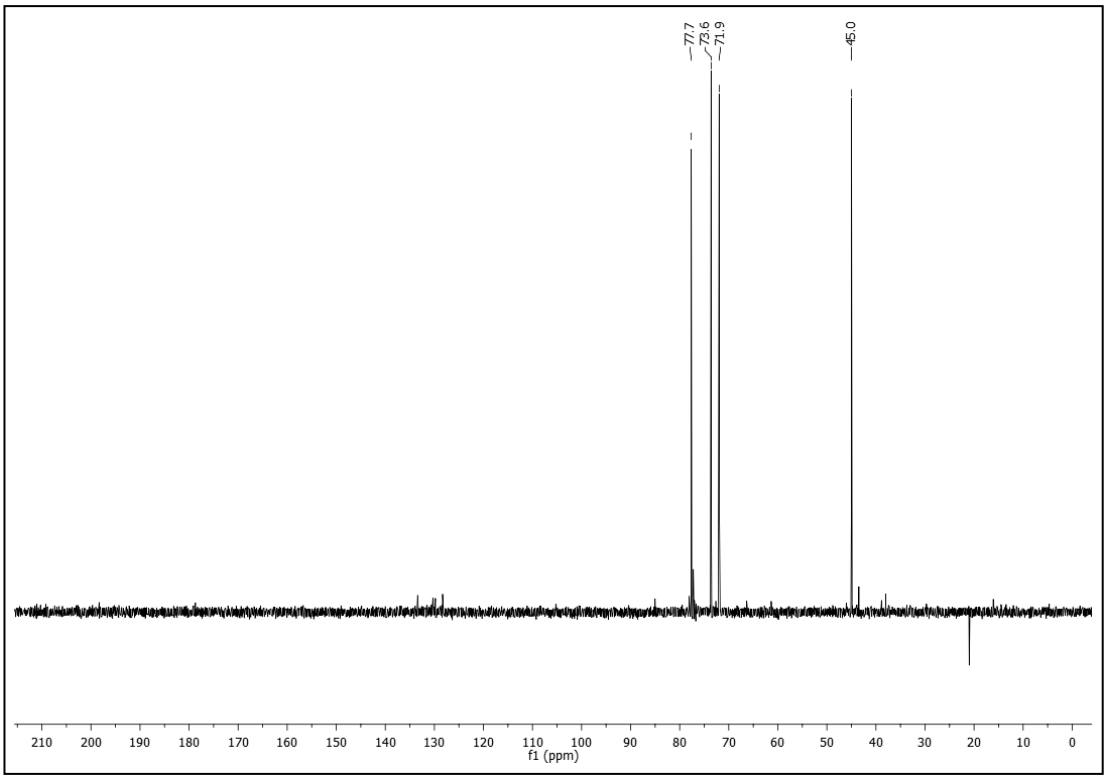


Figure 106 DEPT90 Spectrum of Compound **160** in $CDCl_3$

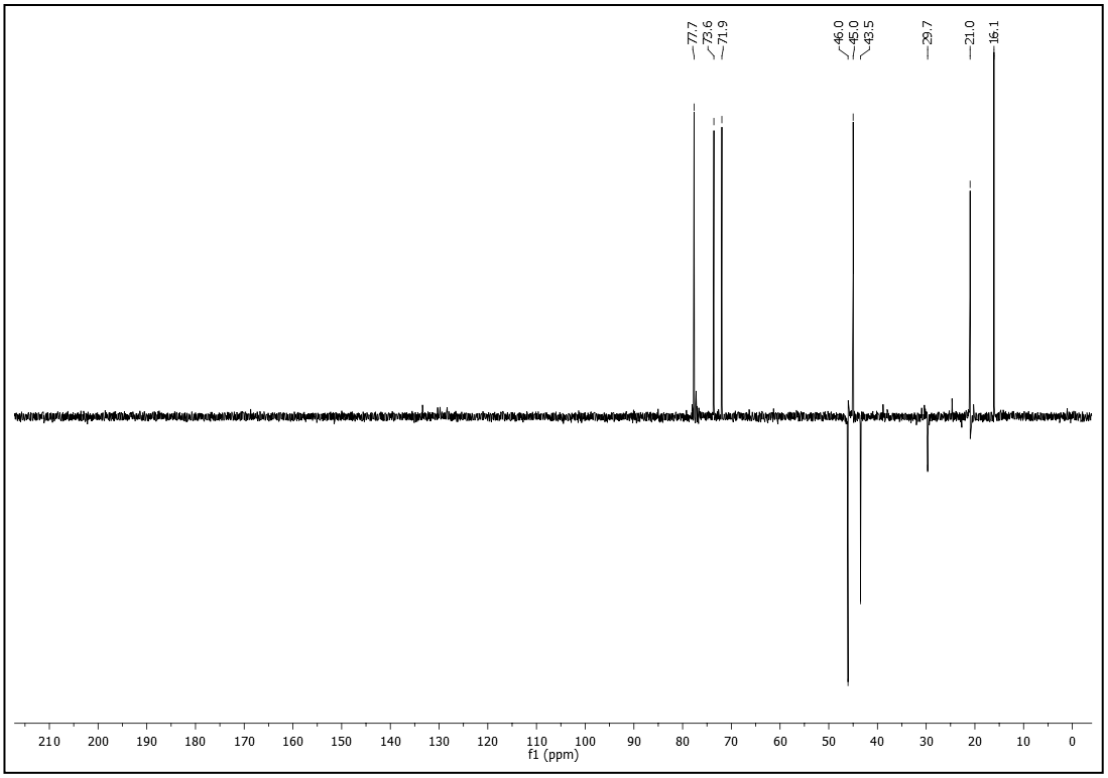


Figure 107 DEPT135 Spectrum of Compound **160** in $CDCl_3$

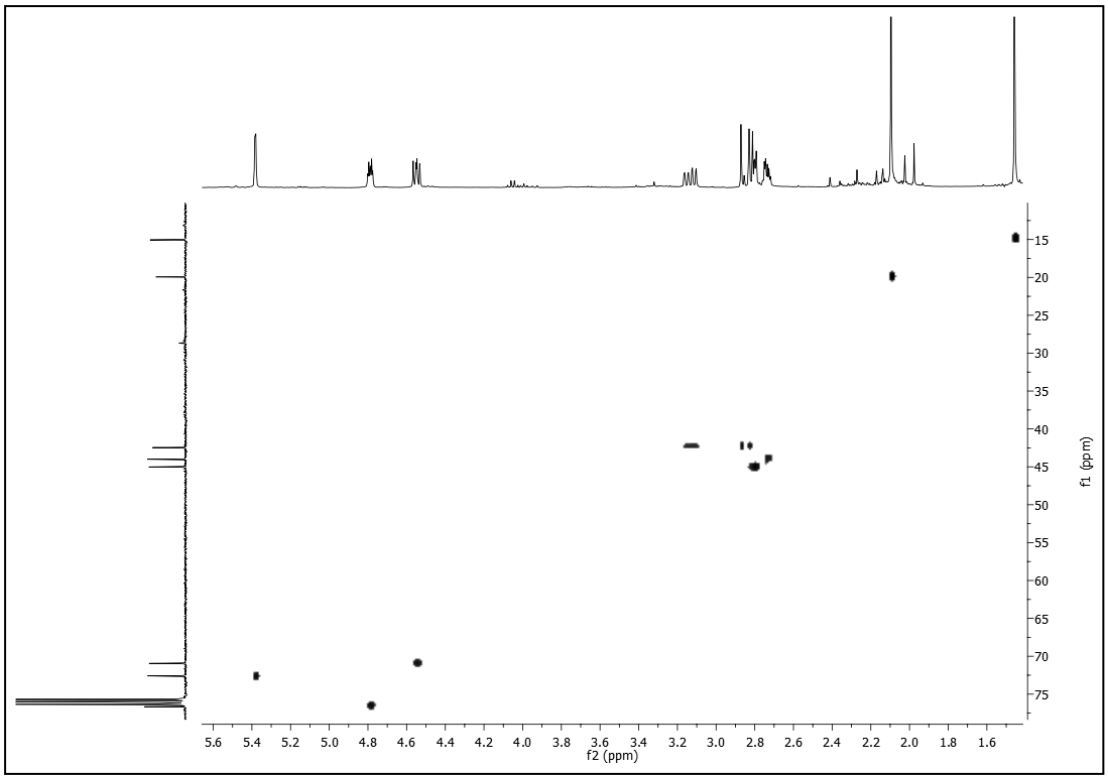


Figure 108 HSQC Spectrum of Compound **160** in $CDCl_3$

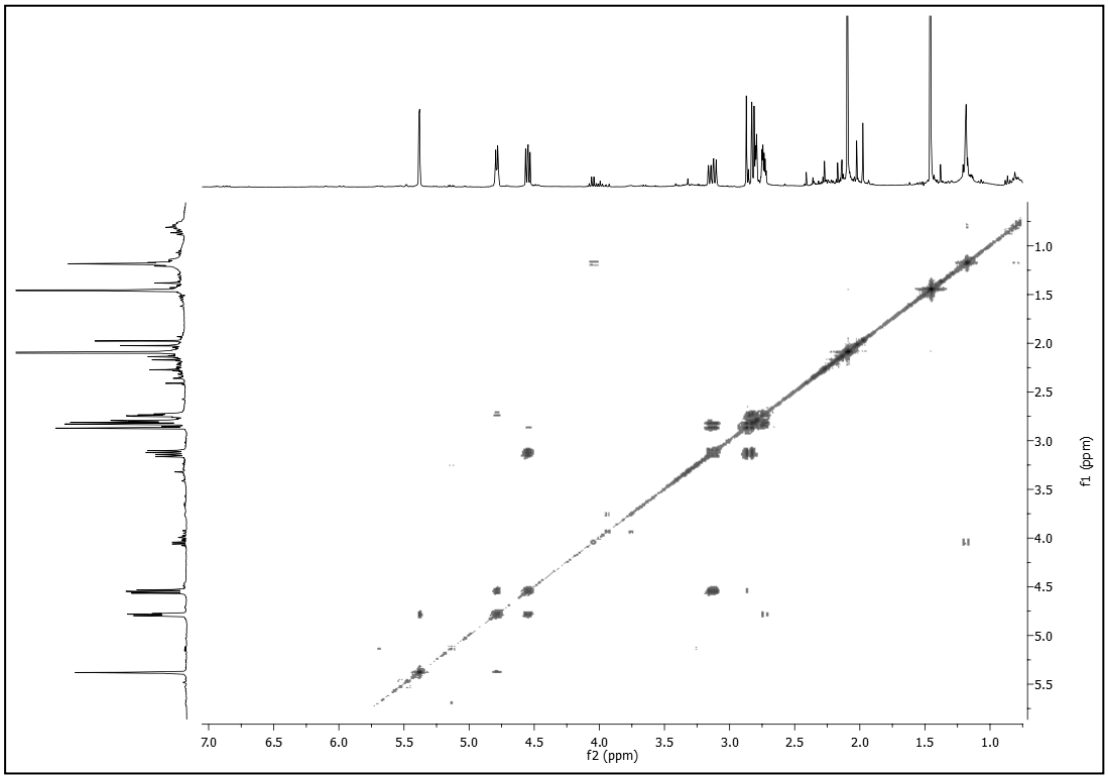


Figure 109 COSY Spectrum of Compound **160** in $CDCl_3$

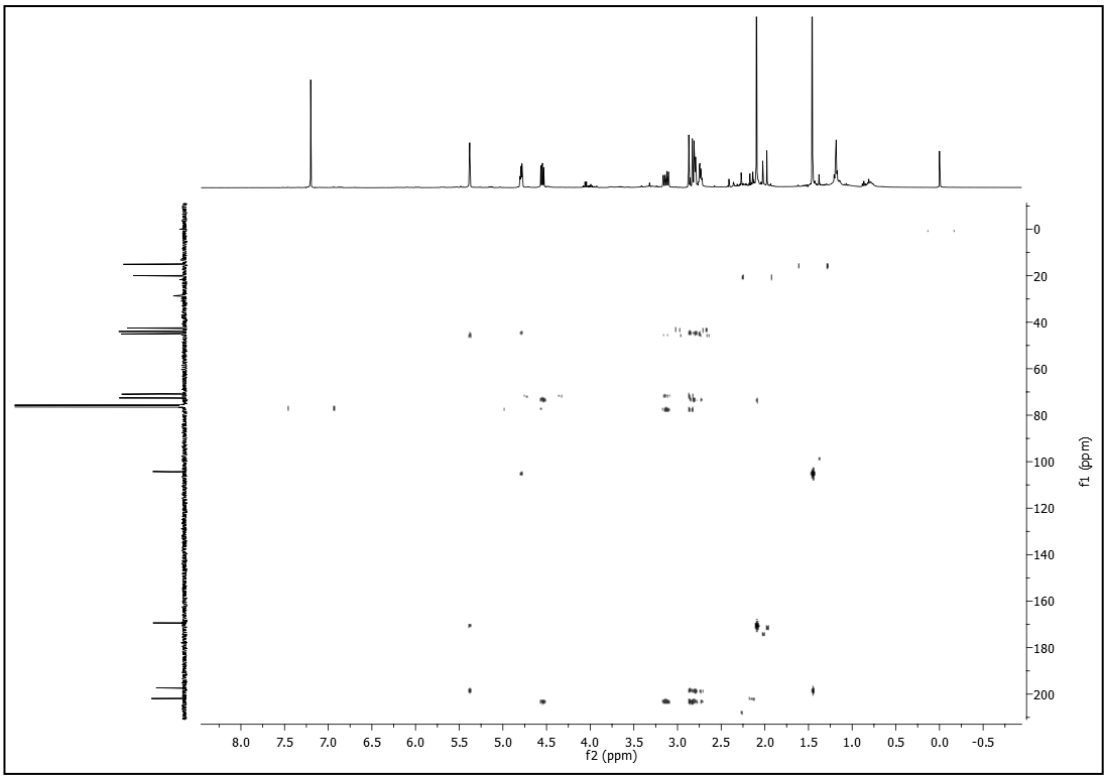


Figure 110 HMBC Spectrum of Compound **160** in $CDCl_3$

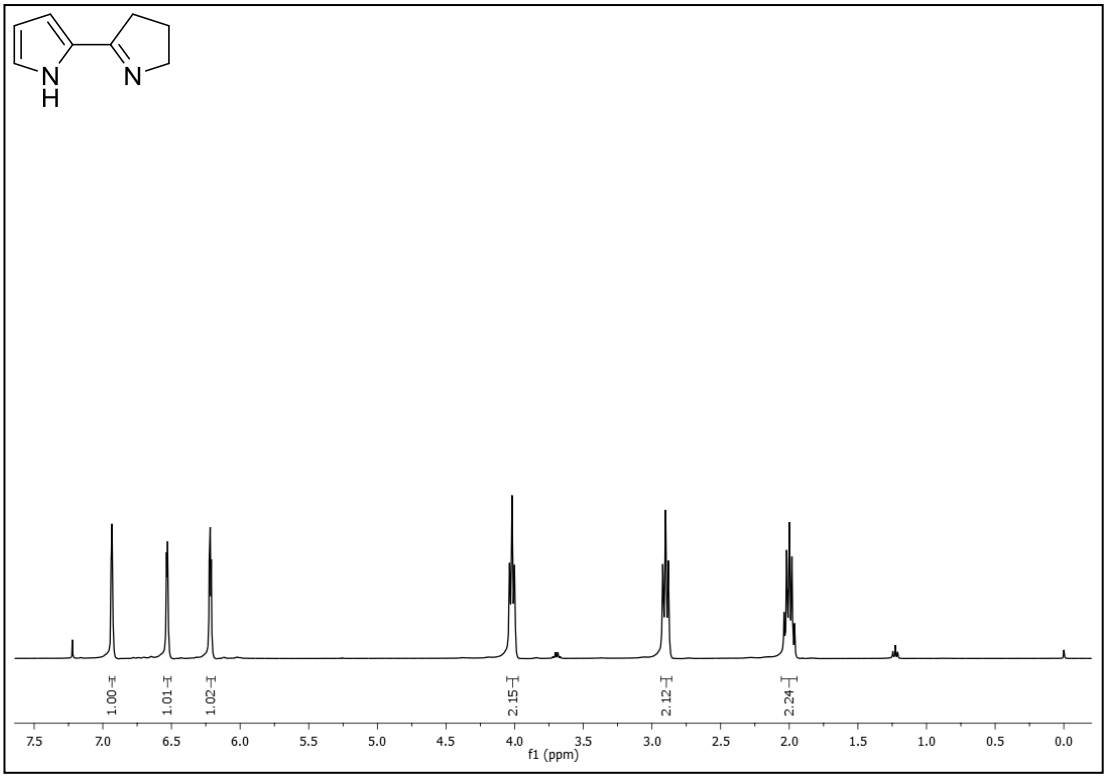


Figure 111 ^{1}H NMR Spectrum of Compound **70** in $CDCl_3$

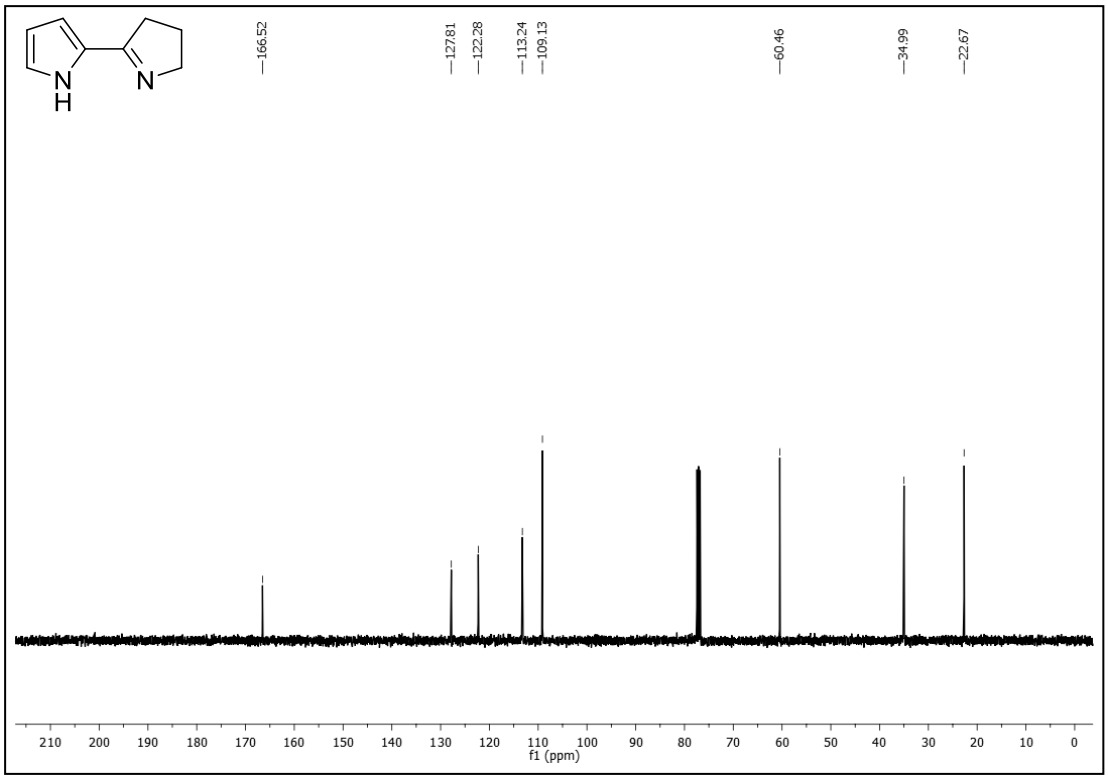


Figure 112 ^{13}C NMR Spectrum of Compound **70** in $CDCl_3$

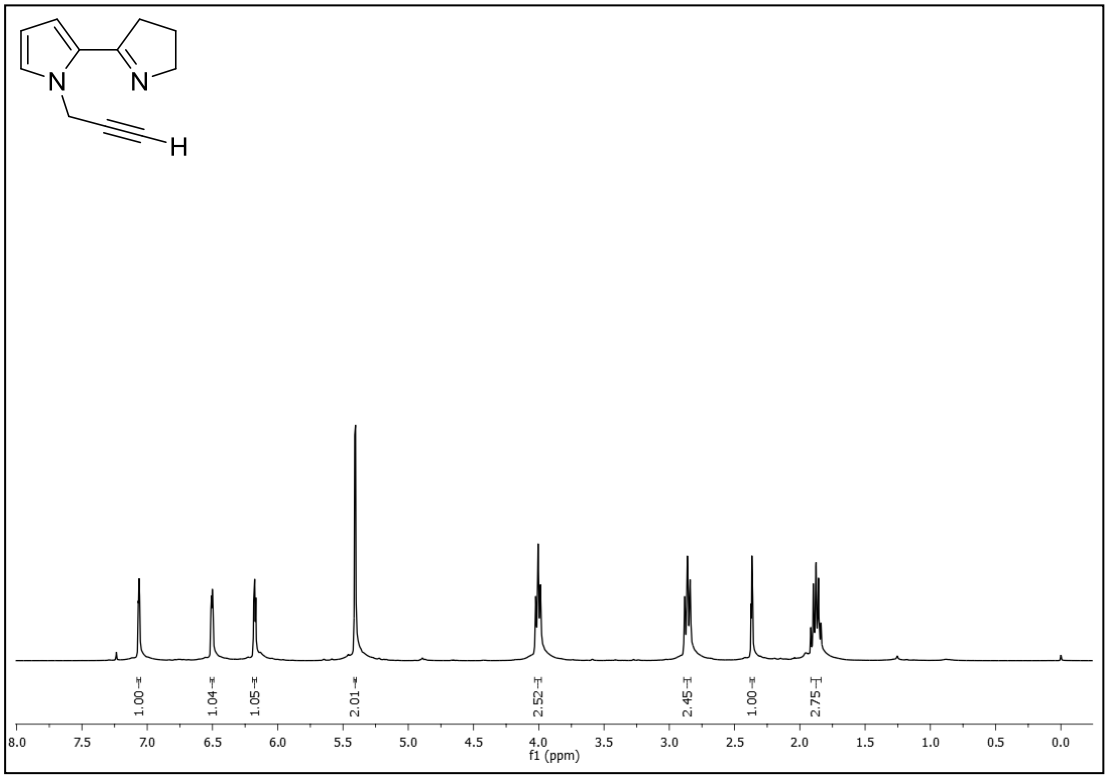


Figure 113 ^{1}H NMR Spectrum of Compound **71a** in $CDCl_3$

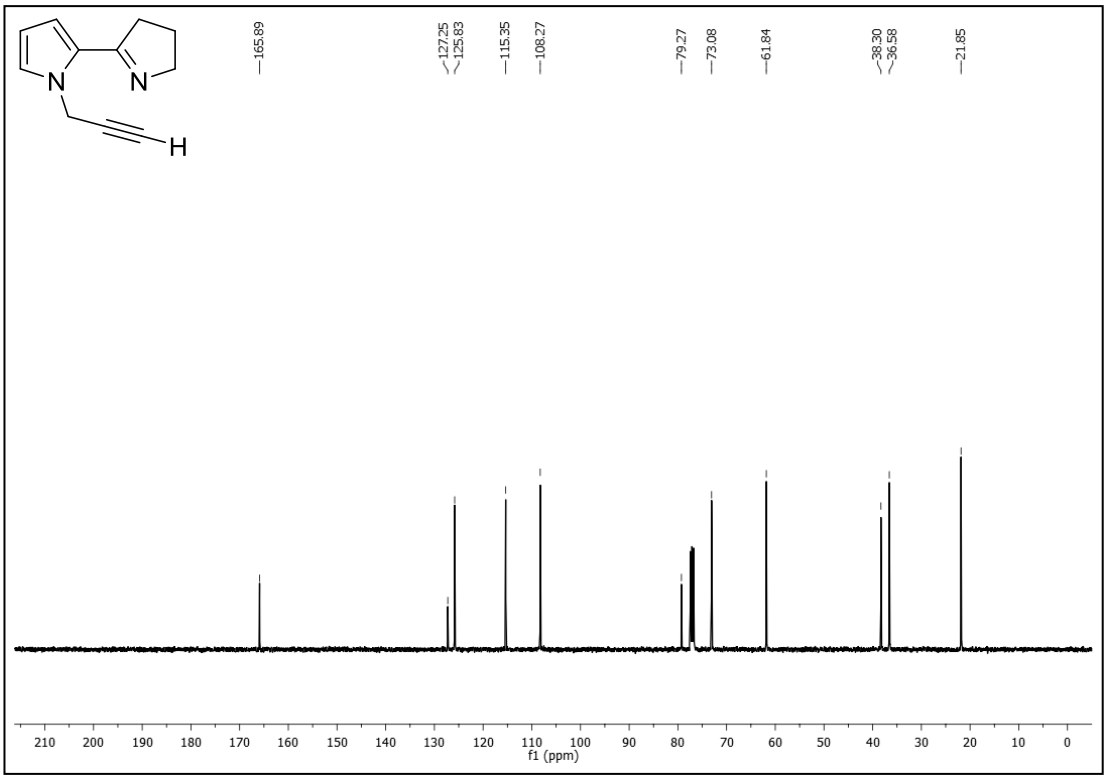


Figure 114 ^{13}C NMR Spectrum of Compound **71a** in $CDCl_3$

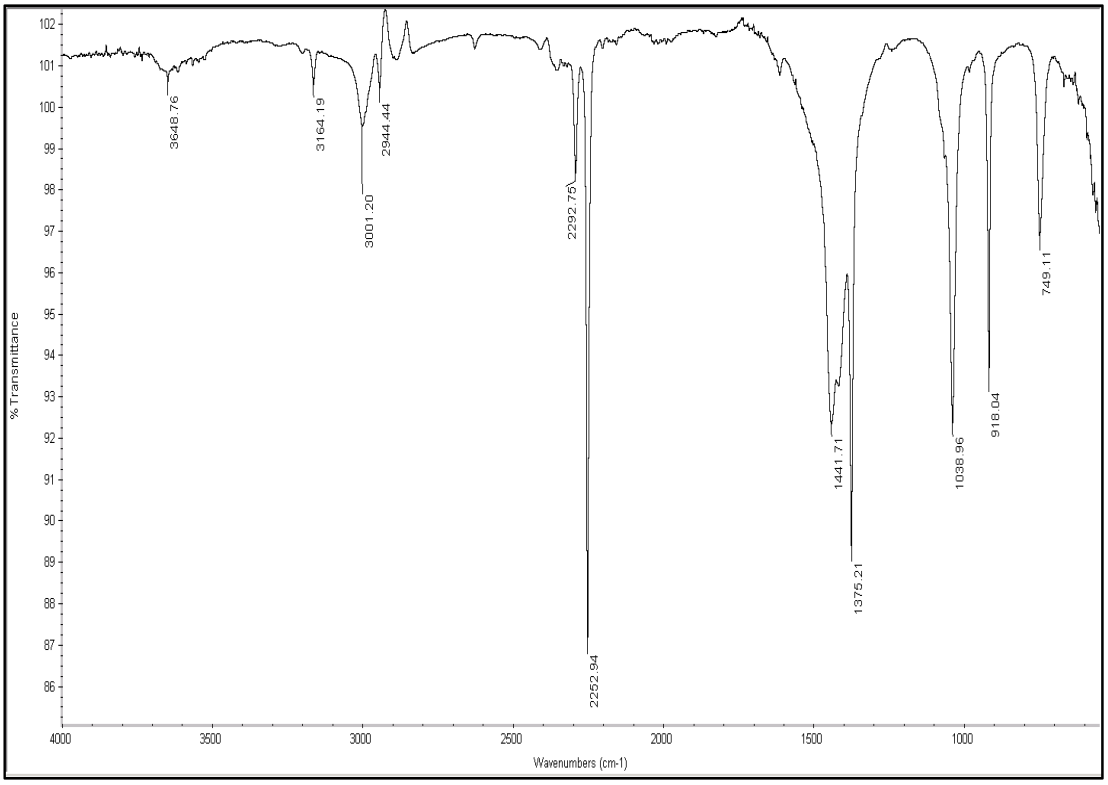


Figure 115 IR Spectrum of Compound **71a**

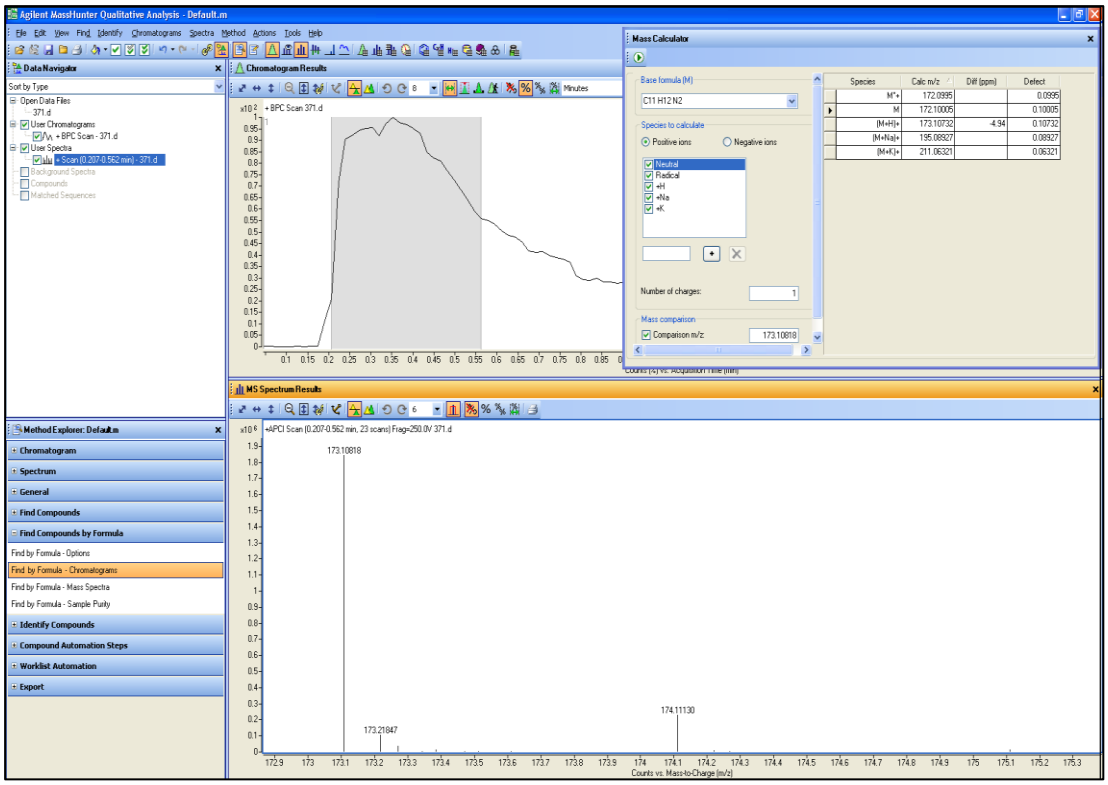


Figure 116 HRMS Spectrum of Compound **71a**

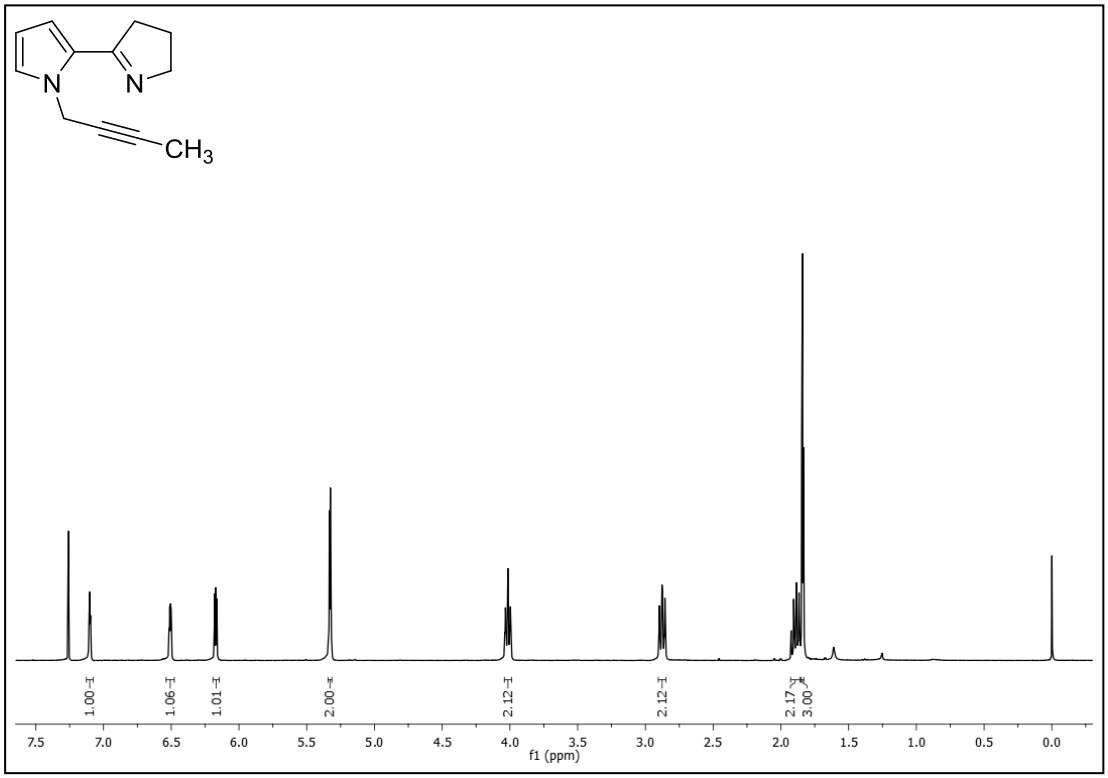


Figure 117 ^{1}H NMR Spectrum of Compound **71b** in $CDCl_3$

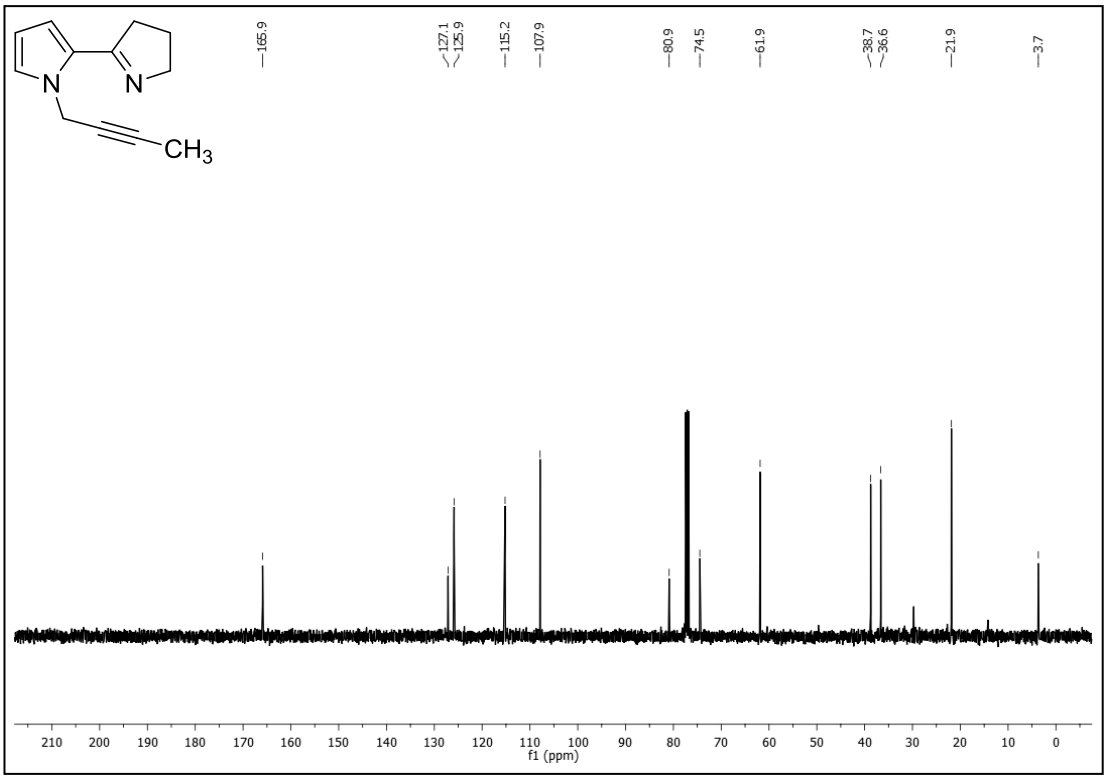


Figure 118 ^{13}C NMR Spectrum of Compound **71b** in $CDCl_3$

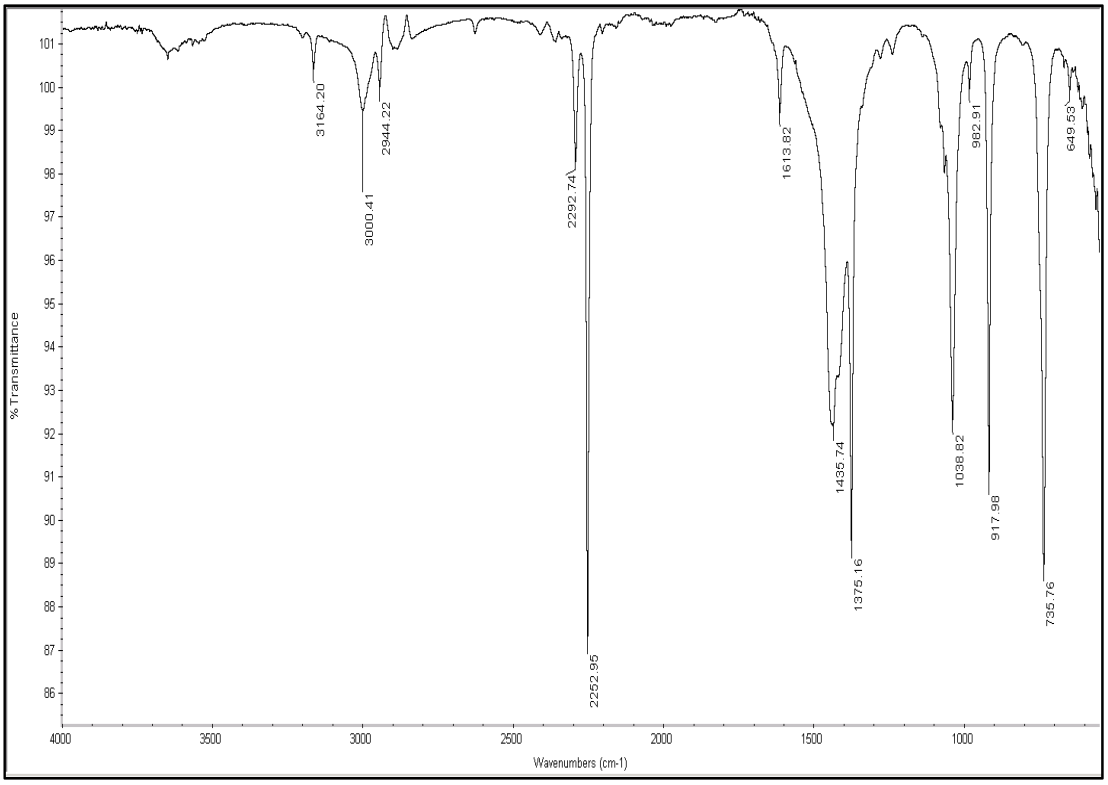


Figure 119 IR Spectrum of Compound **71b**

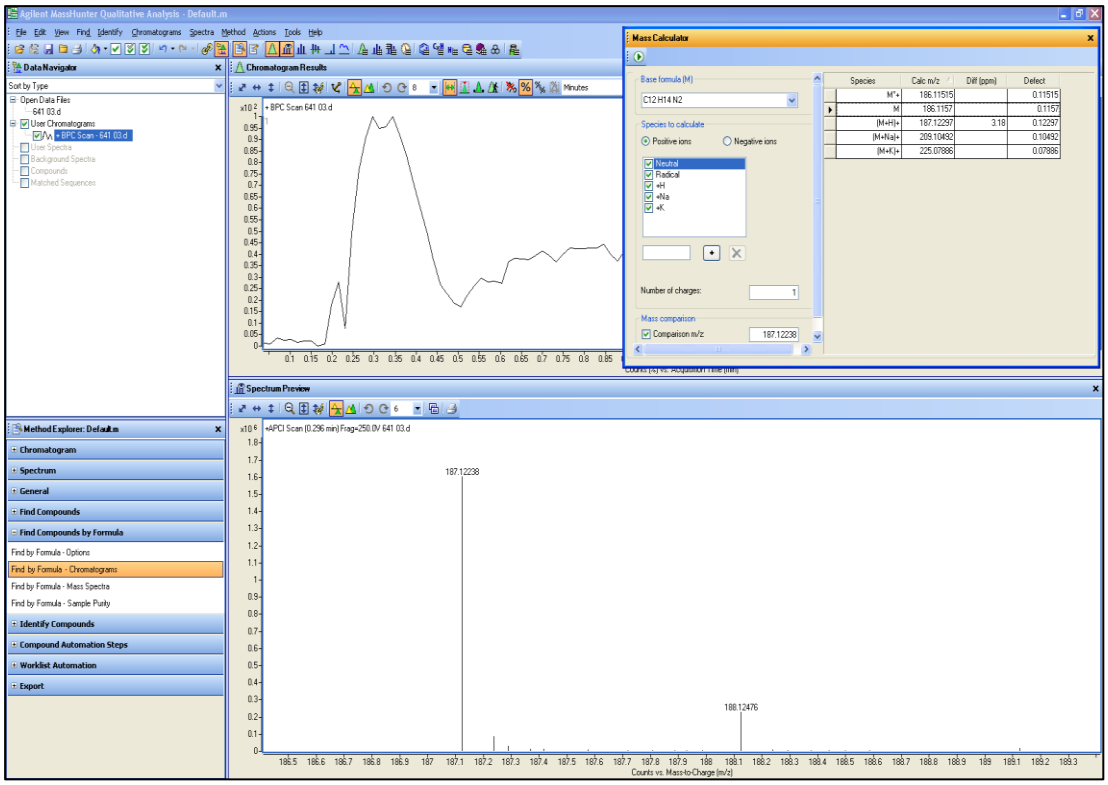


Figure 120 HRMS Spectrum of Compound **71b**

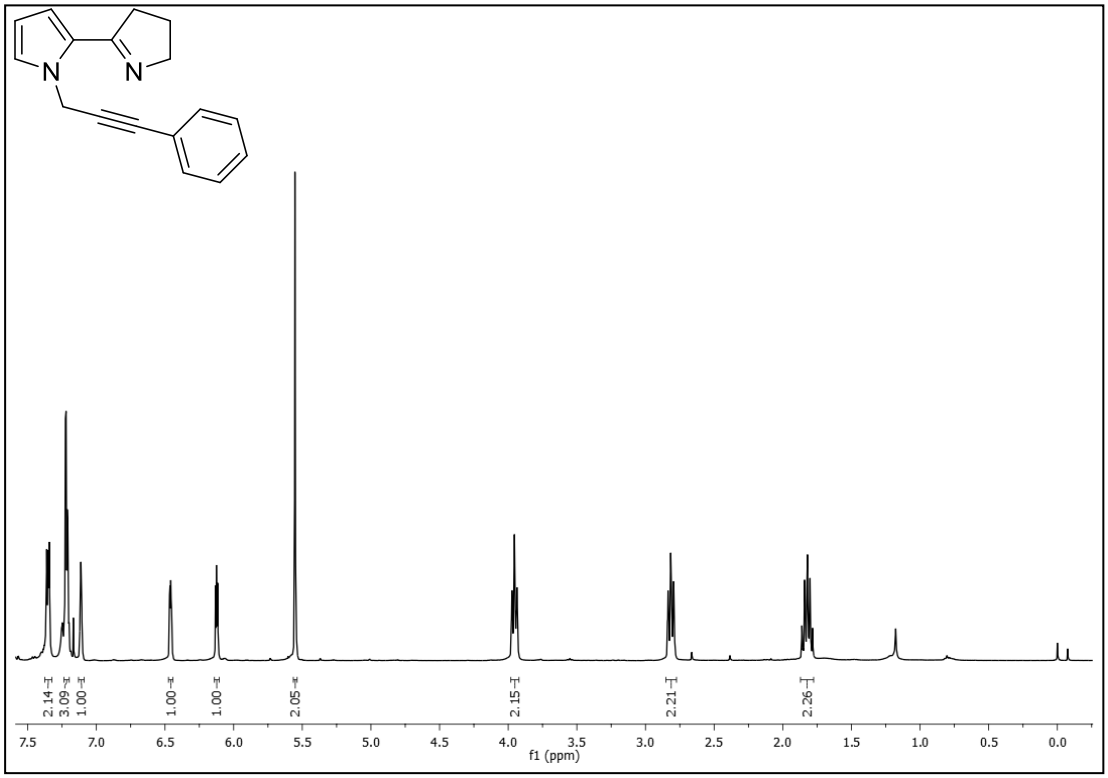


Figure 121 ^{1}H NMR Spectrum of Compound **79a** in $CDCl_3$

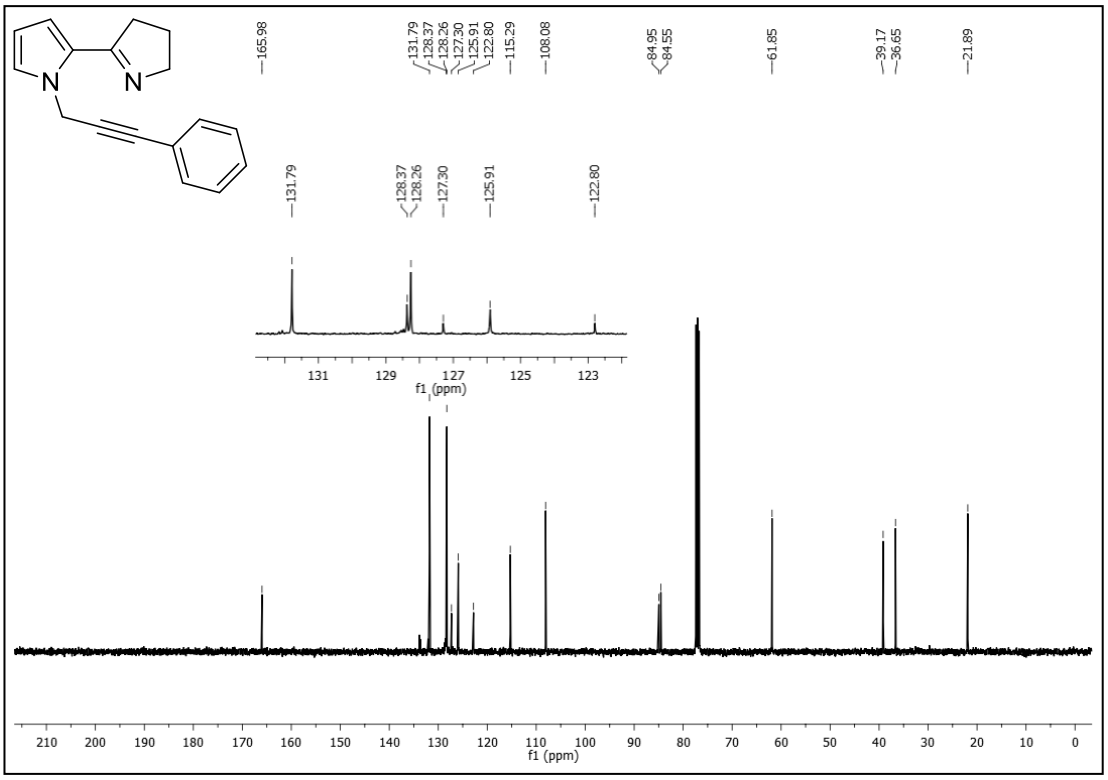


Figure 122 ^{13}C NMR Spectrum of Compound **79a** in $CDCl_3$

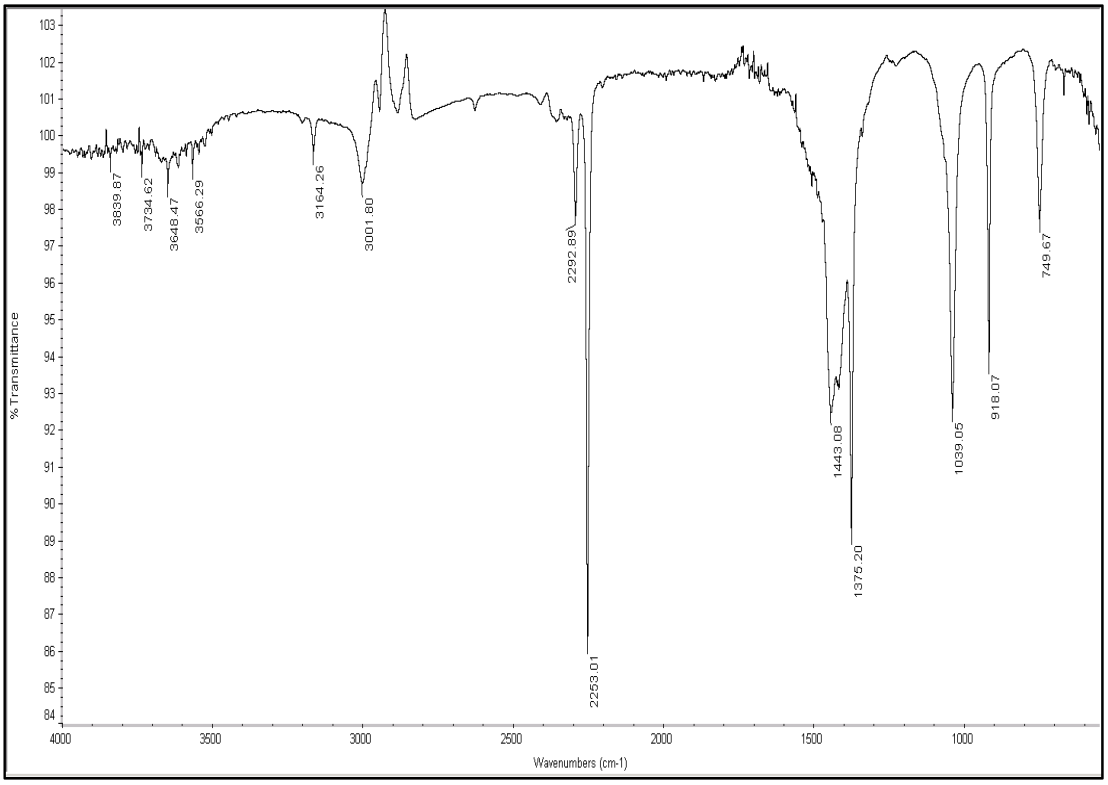


Figure 123 IR Spectrum of Compound **79a**

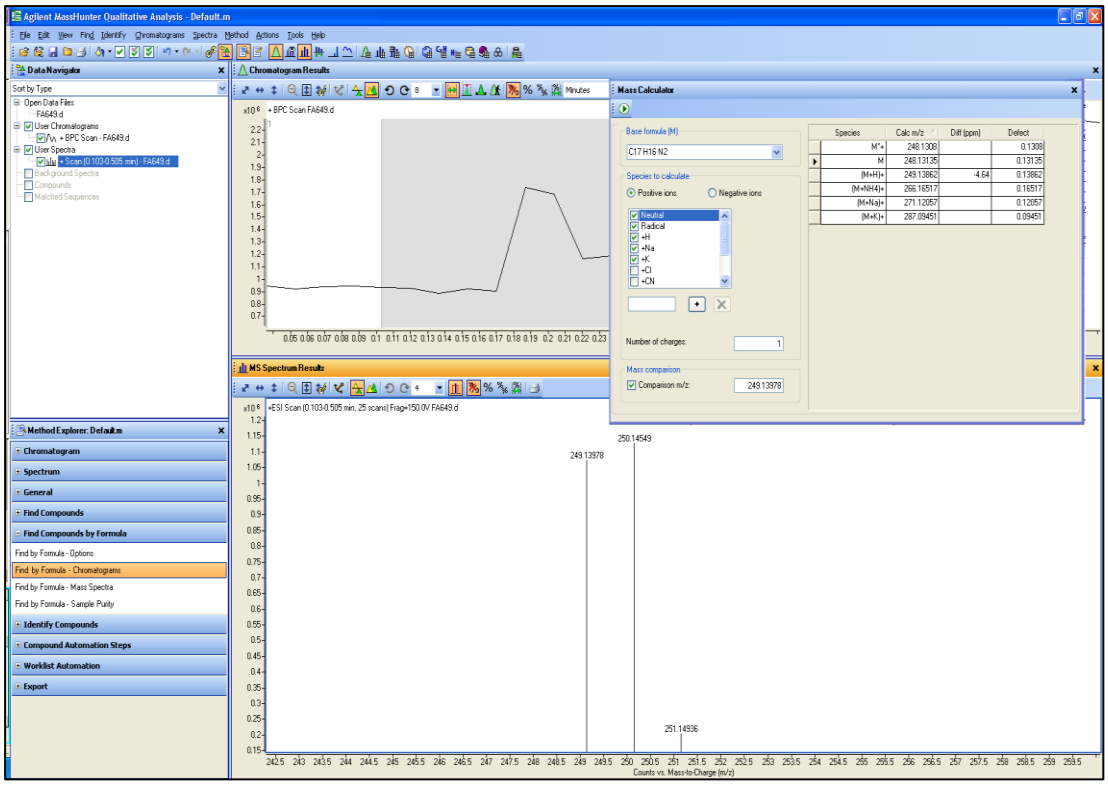


Figure 124 HRMS Spectrum of Compound **79a**

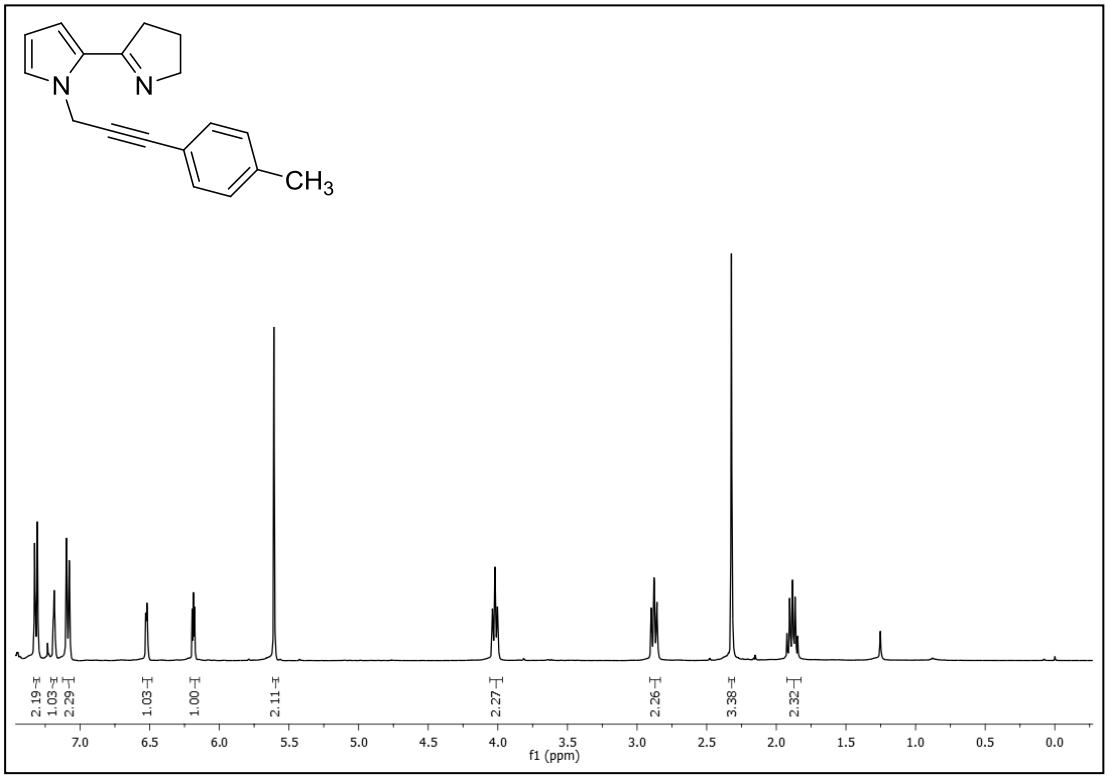


Figure 125 ^{1}H NMR Spectrum of Compound **79b** in $CDCl_3$

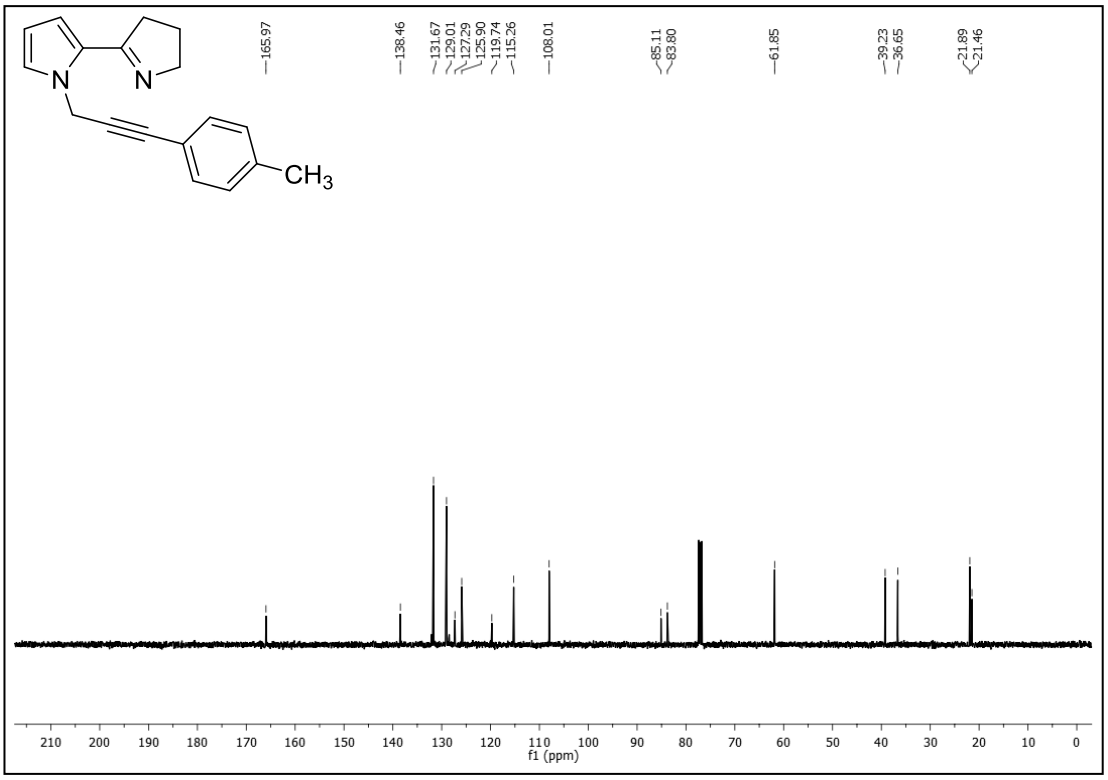


Figure 126 ^{13}C NMR Spectrum of Compound **79b** in $CDCl_3$

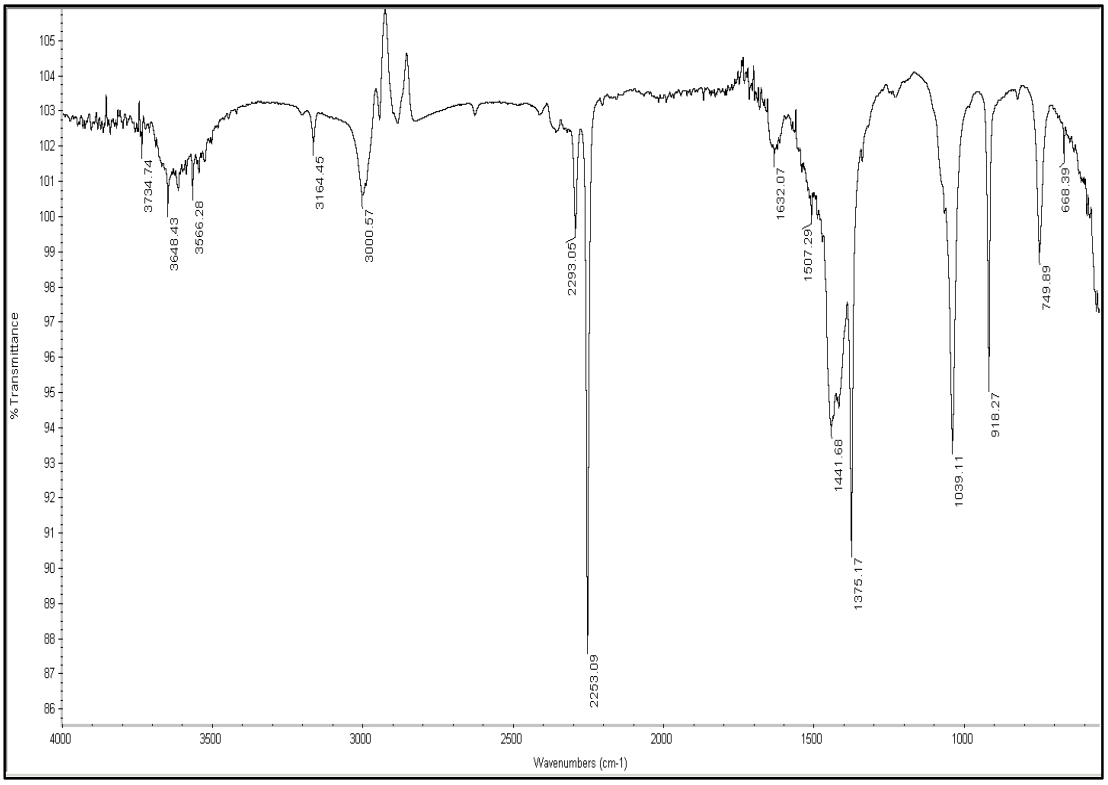


Figure 127 IR Spectrum of Compound **79b**

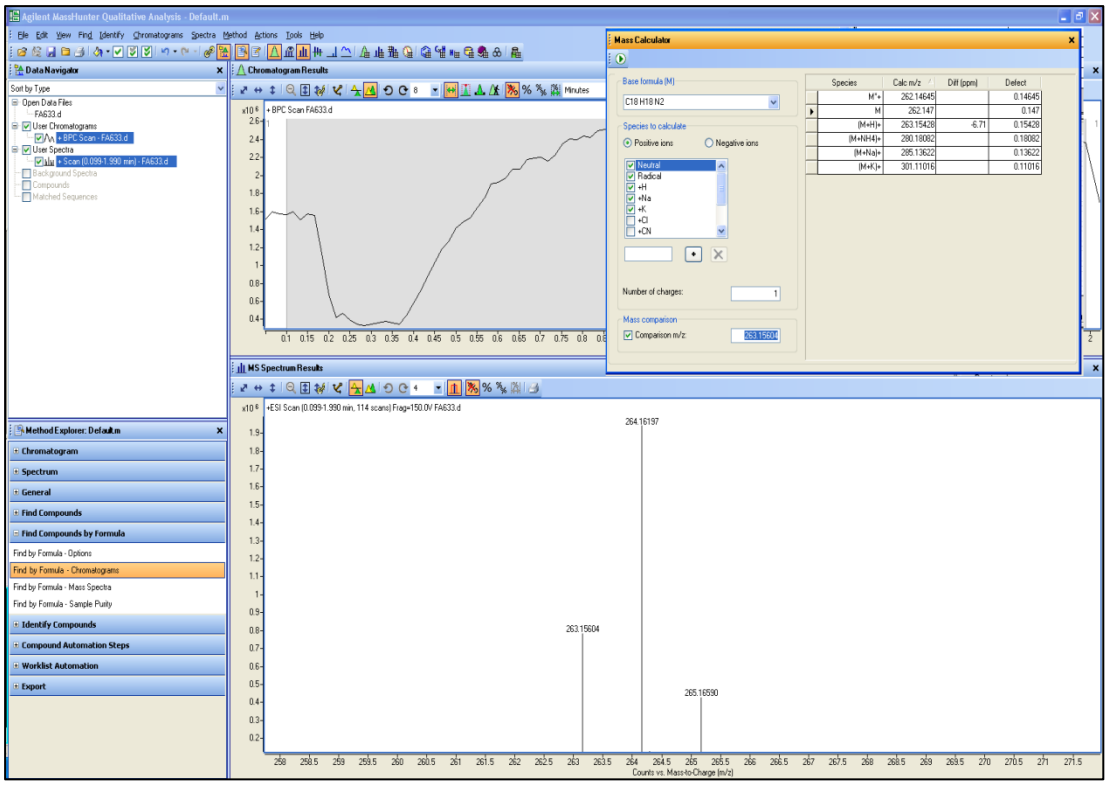


Figure 128 HRMS Spectrum of Compound **79b**

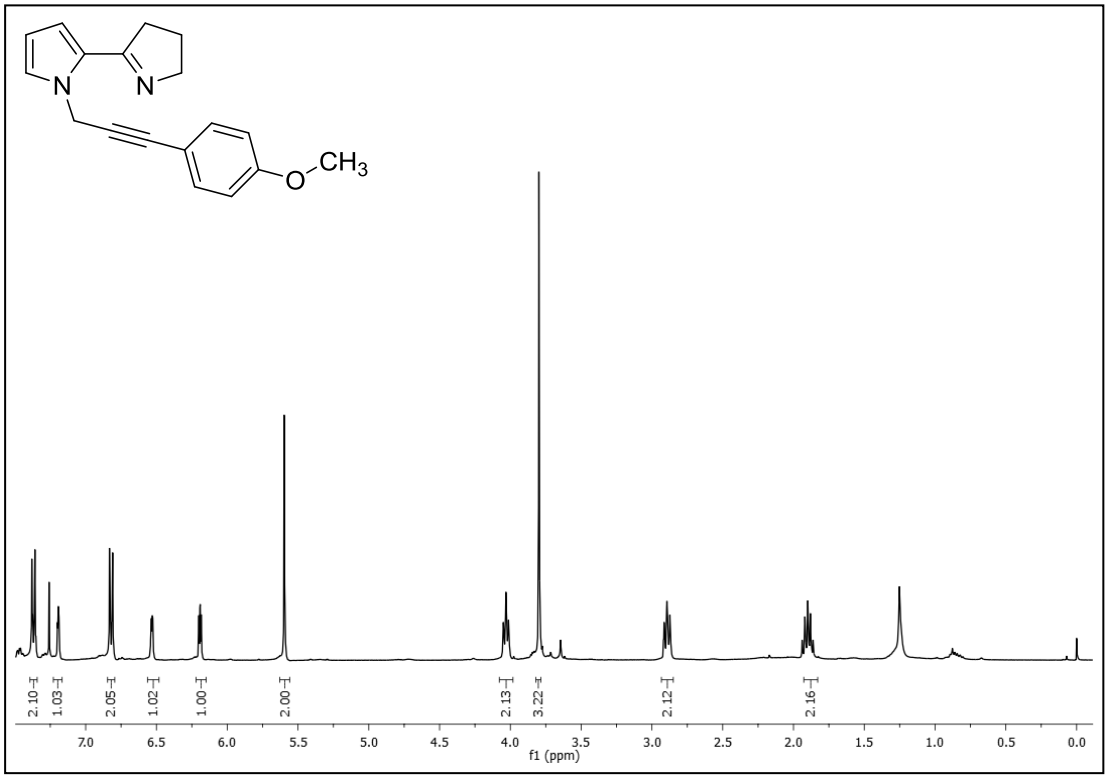


Figure 129 ^{1}H NMR Spectrum of Compound **79c** in $CDCl_3$

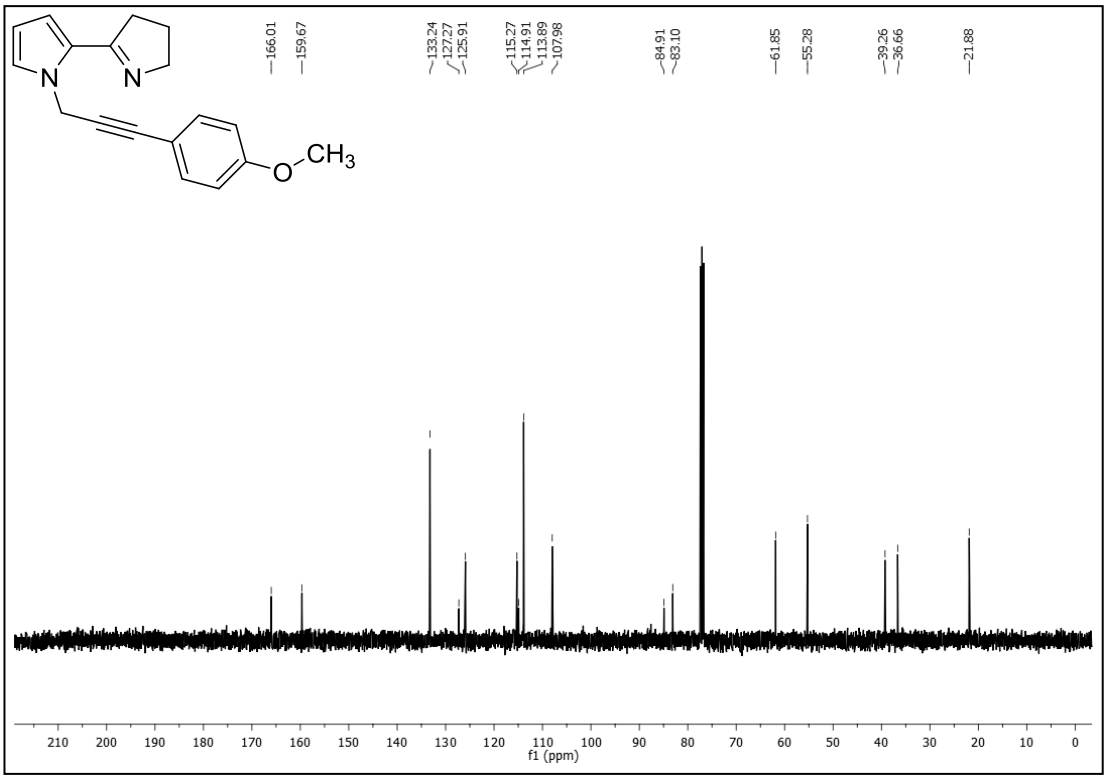


Figure 130 ^{13}C NMR Spectrum of Compound **79c** in $CDCl_3$

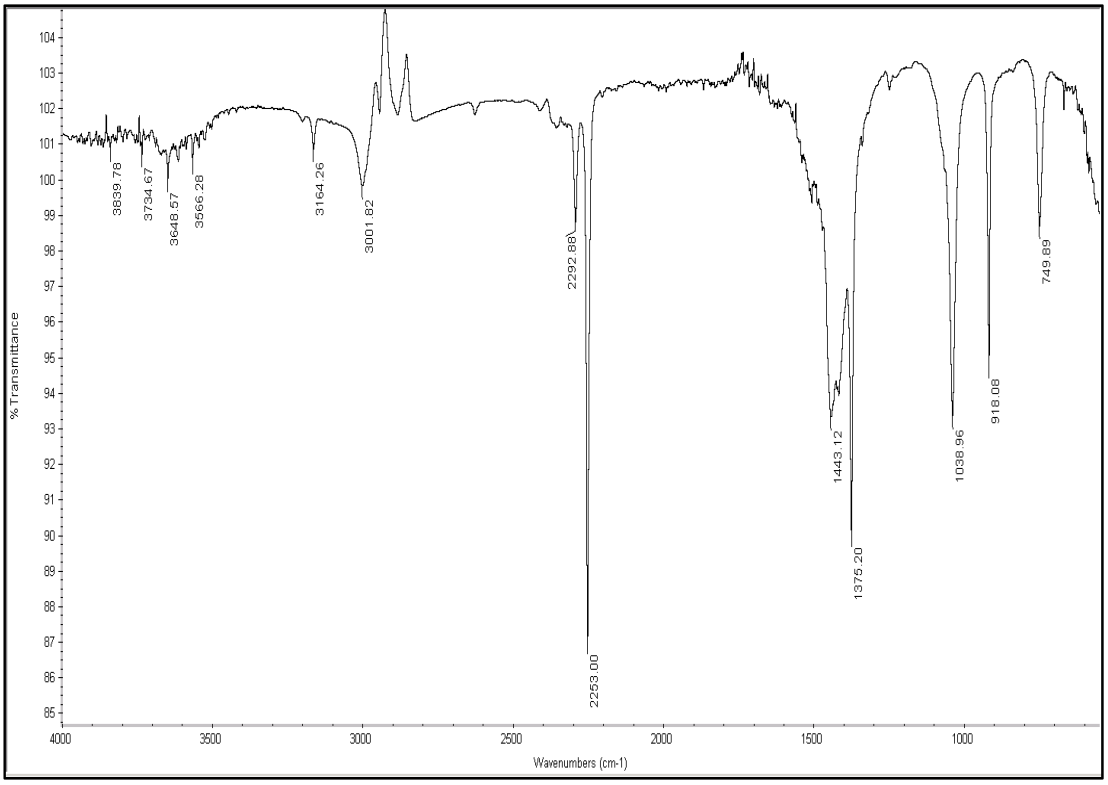


Figure 131 IR Spectrum of Compound **79c**

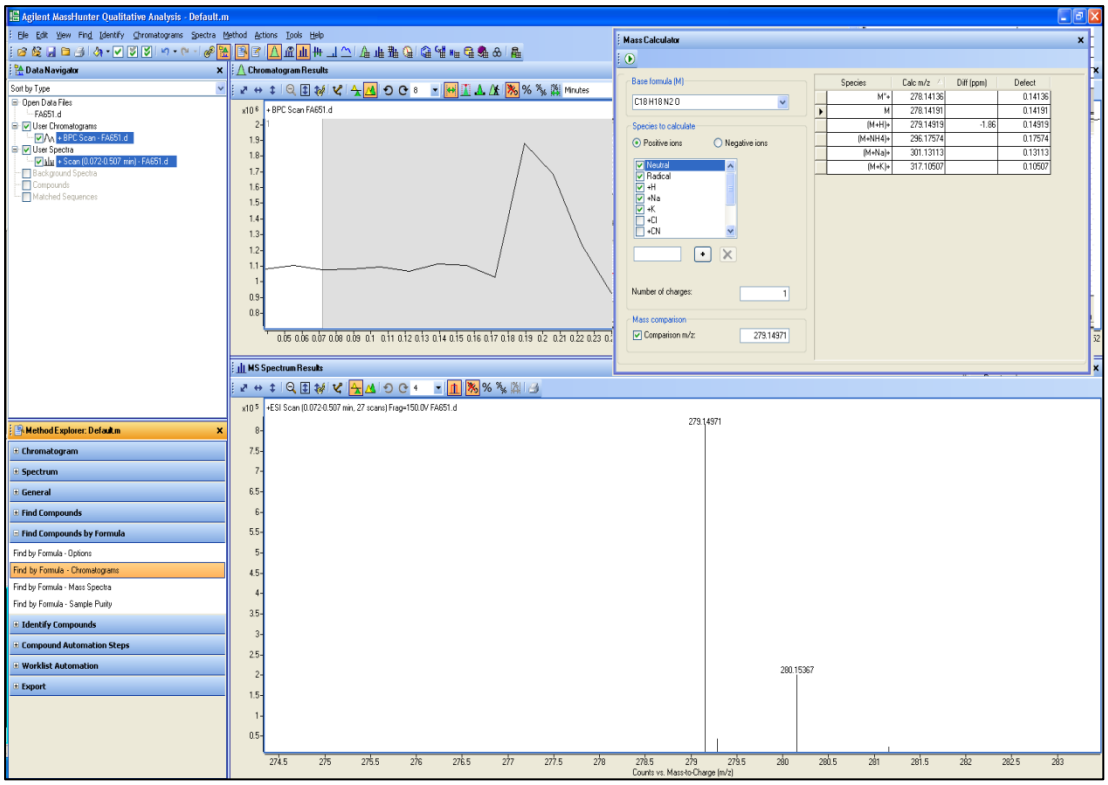


Figure 132 HRMS Spectrum of Compound **79c**

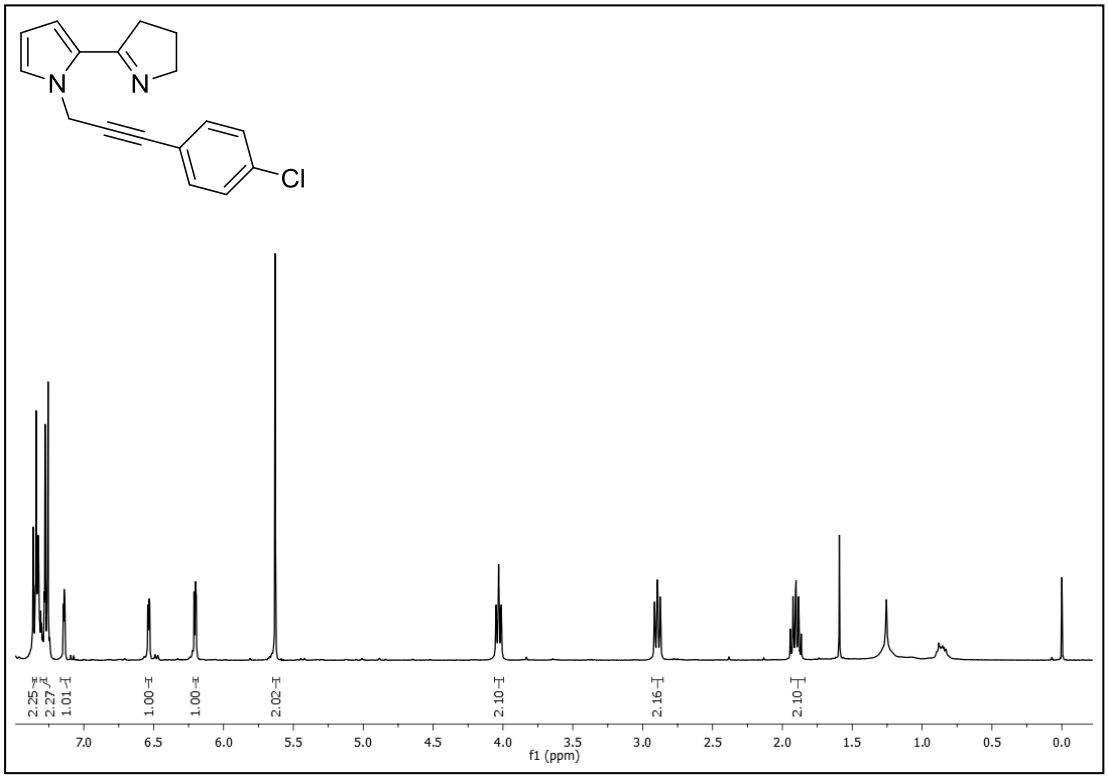


Figure 133 ^{1}H NMR Spectrum of Compound **79d** in $CDCl_3$

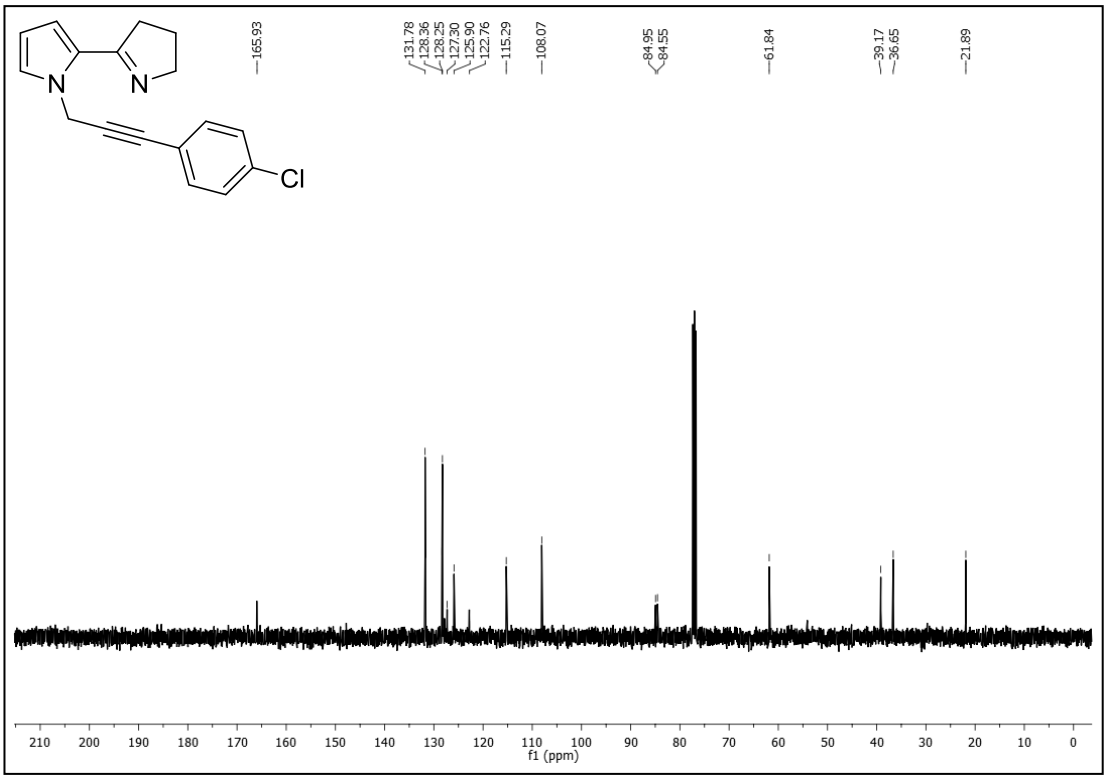


Figure 134 ^{13}C NMR Spectrum of Compound **79d** in $CDCl_3$

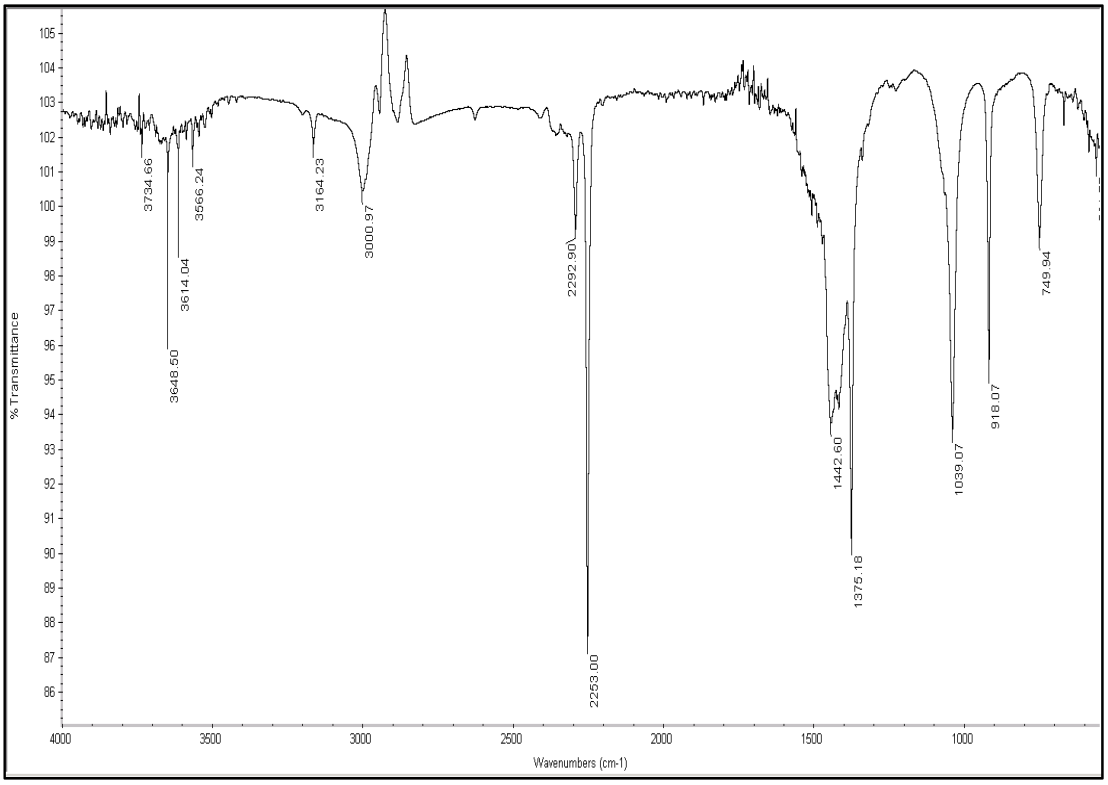


Figure 135 IR Spectrum of Compound **79d**

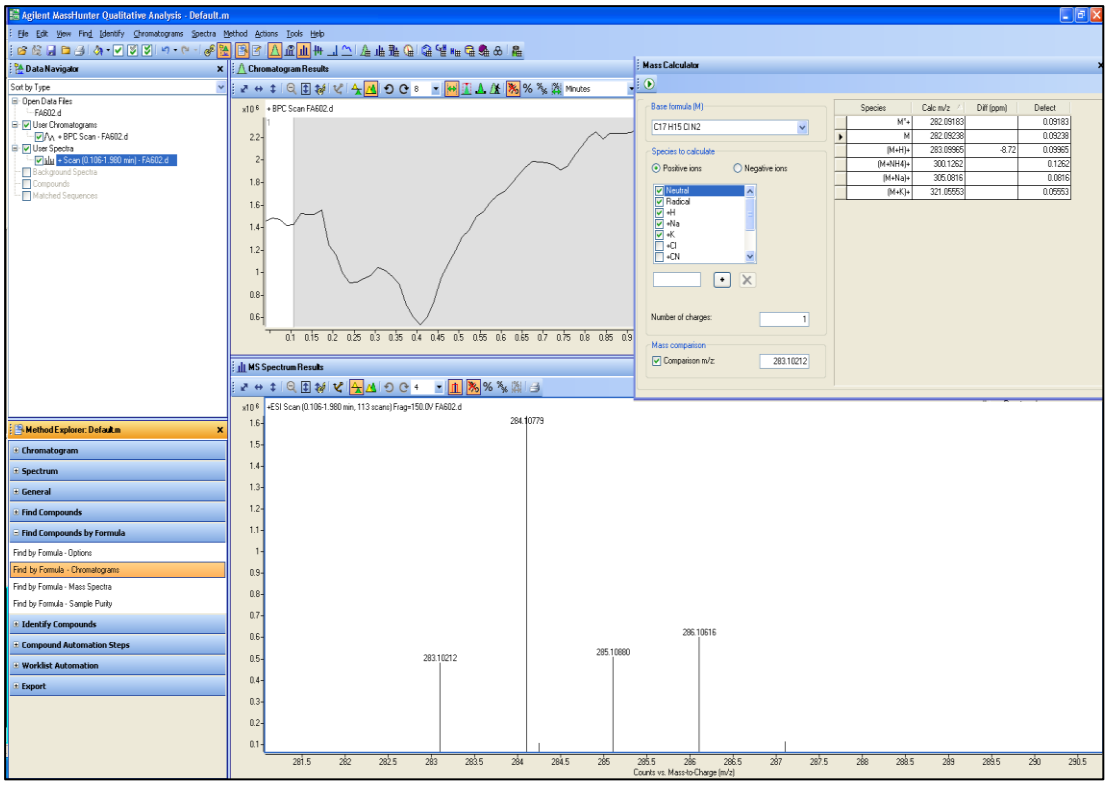


Figure 136 HRMS Spectrum of Compound **79d**

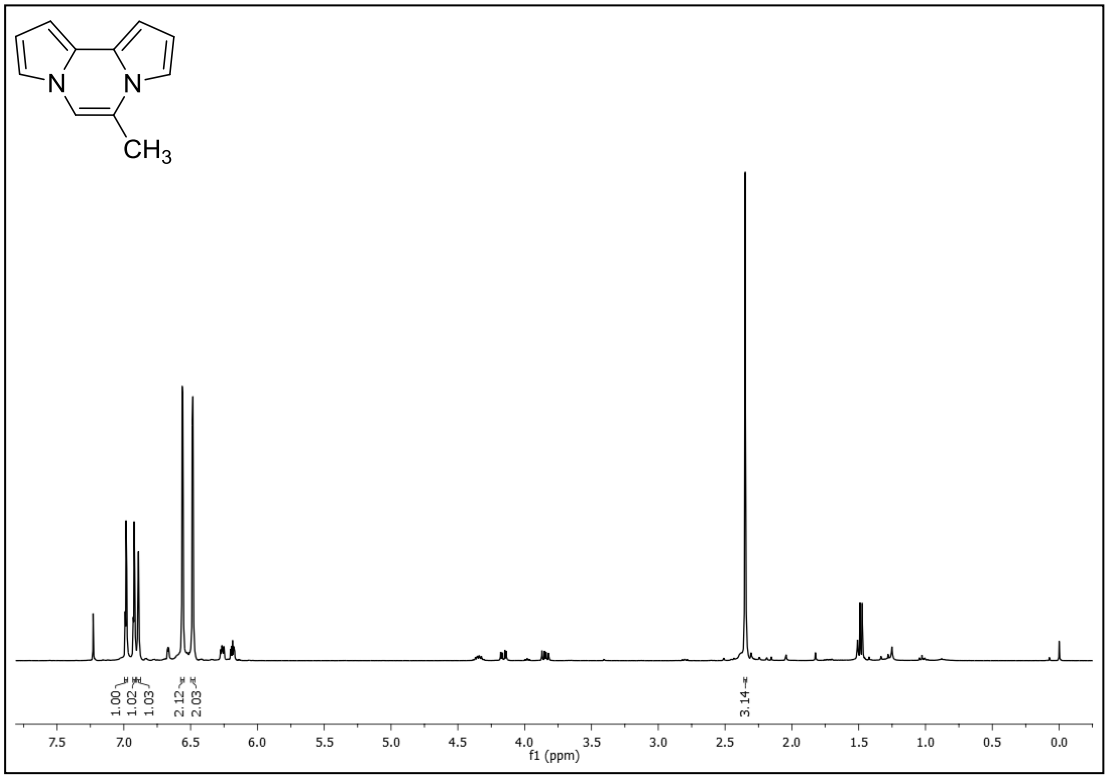


Figure 137 ^{1}H NMR Spectrum of Compound **73a** in $CDCl_3$

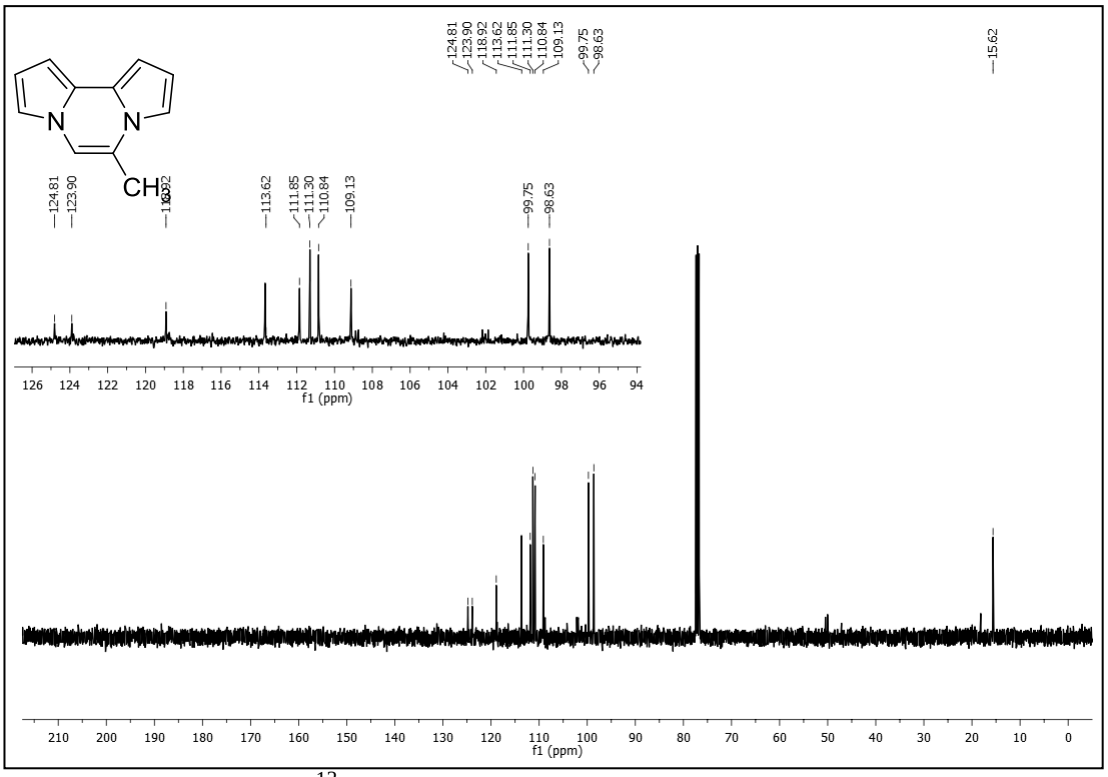


Figure 138 ^{13}C NMR Spectrum of Compound **73a** in $CDCl_3$

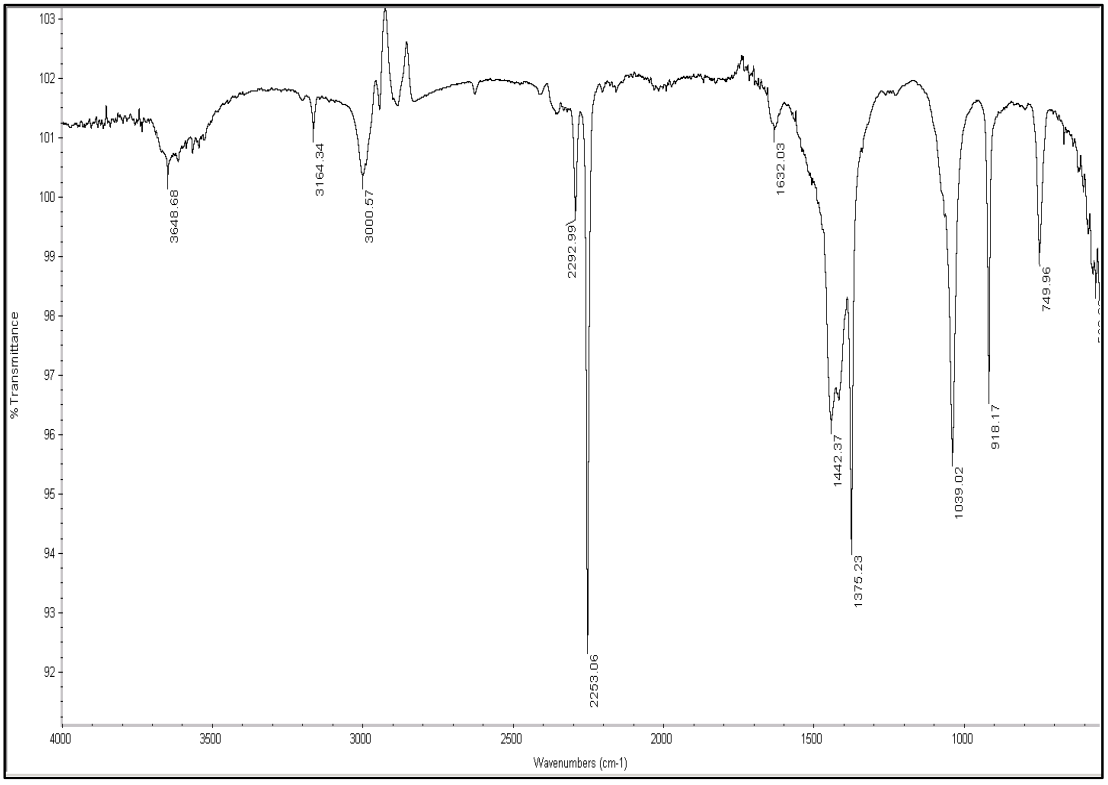


Figure 139 IR Spectrum of Compound **73a**

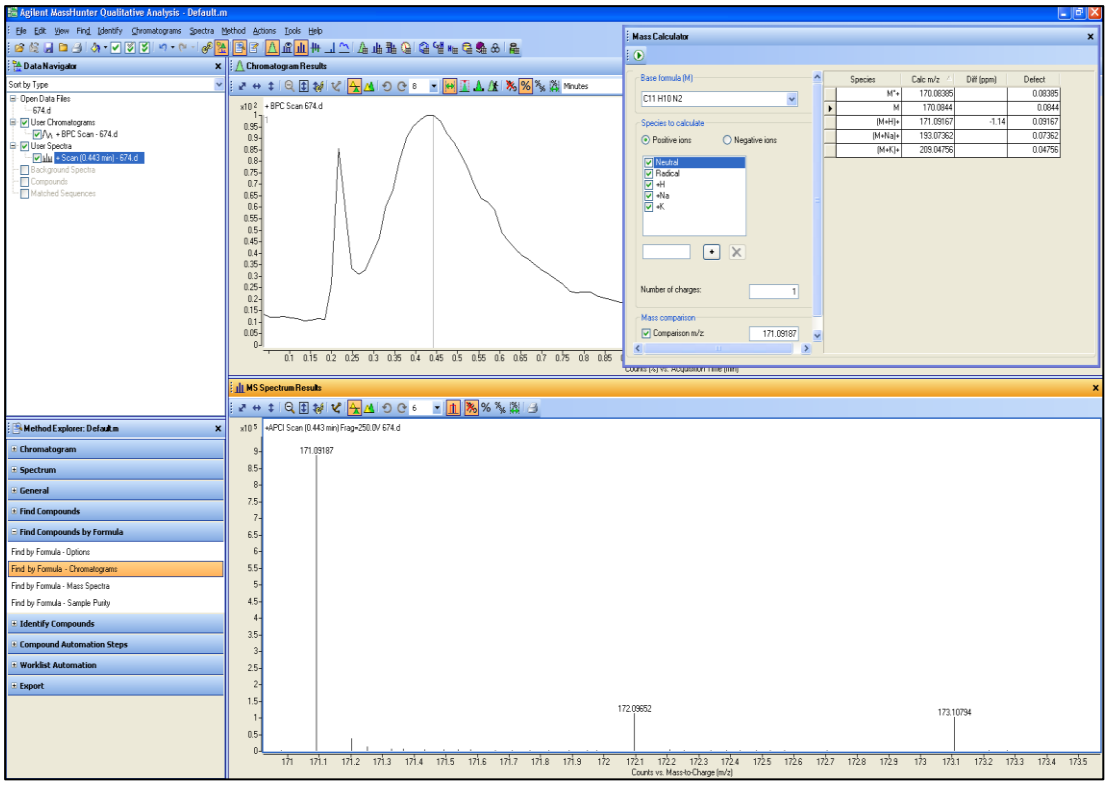


Figure 140 HRMS Spectrum of Compound **73a**

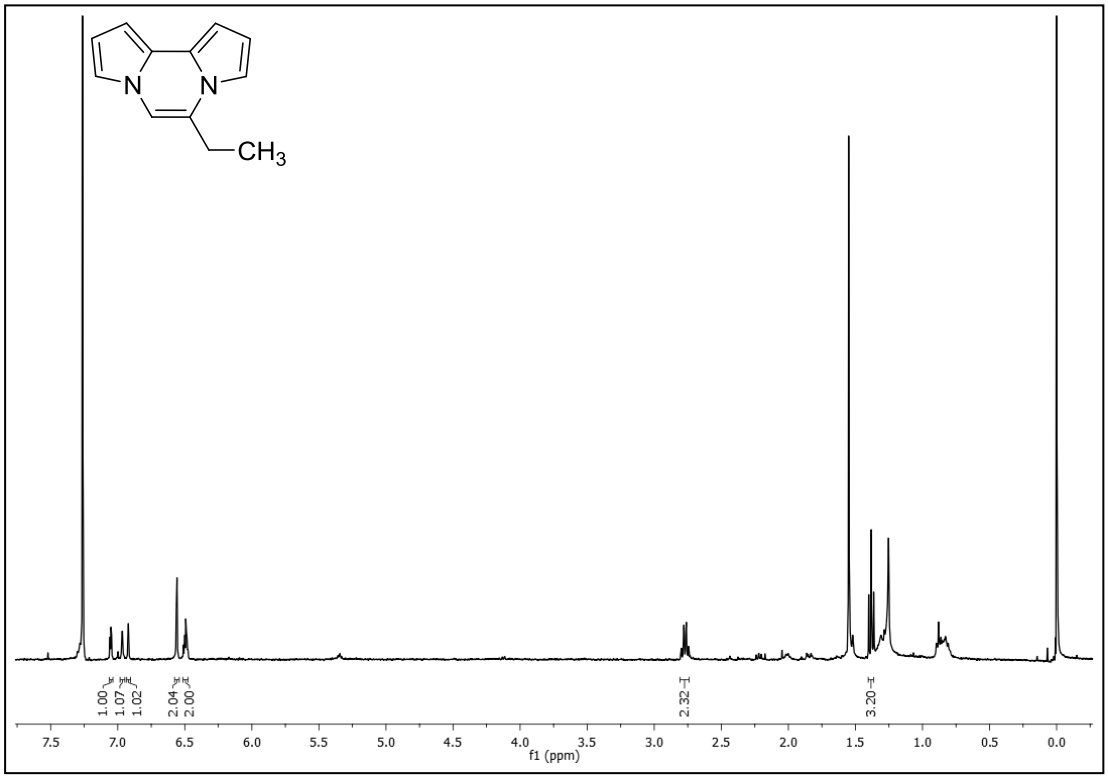


Figure 141 ^{1}H NMR Spectrum of Compound **73b** in $CDCl_3$

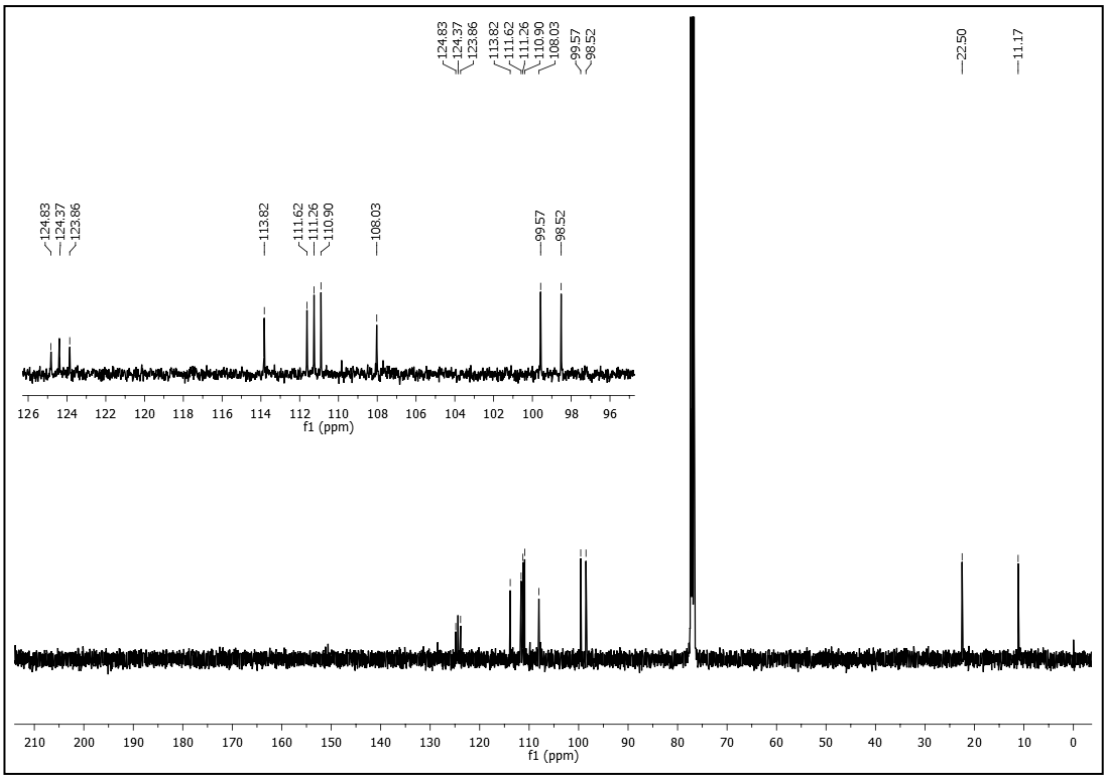


Figure 142 ^{13}C NMR Spectrum of Compound **73b** in $CDCl_3$

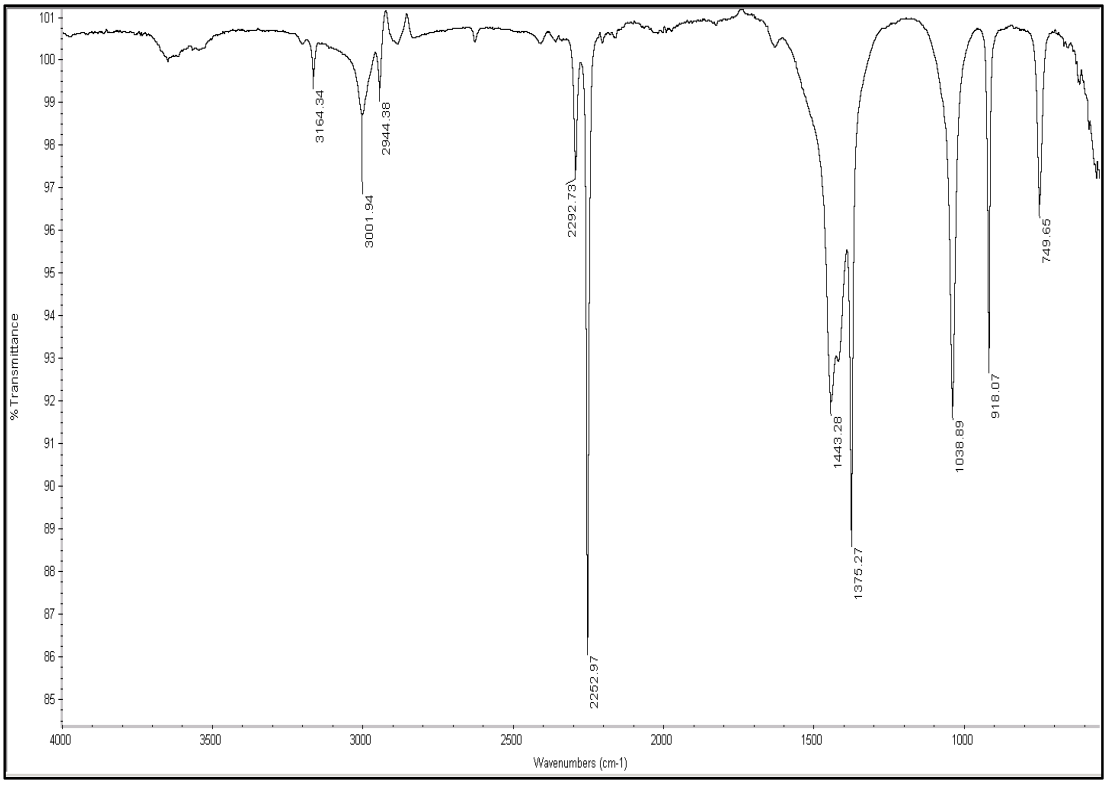


Figure 143 IR Spectrum of Compound **73b**

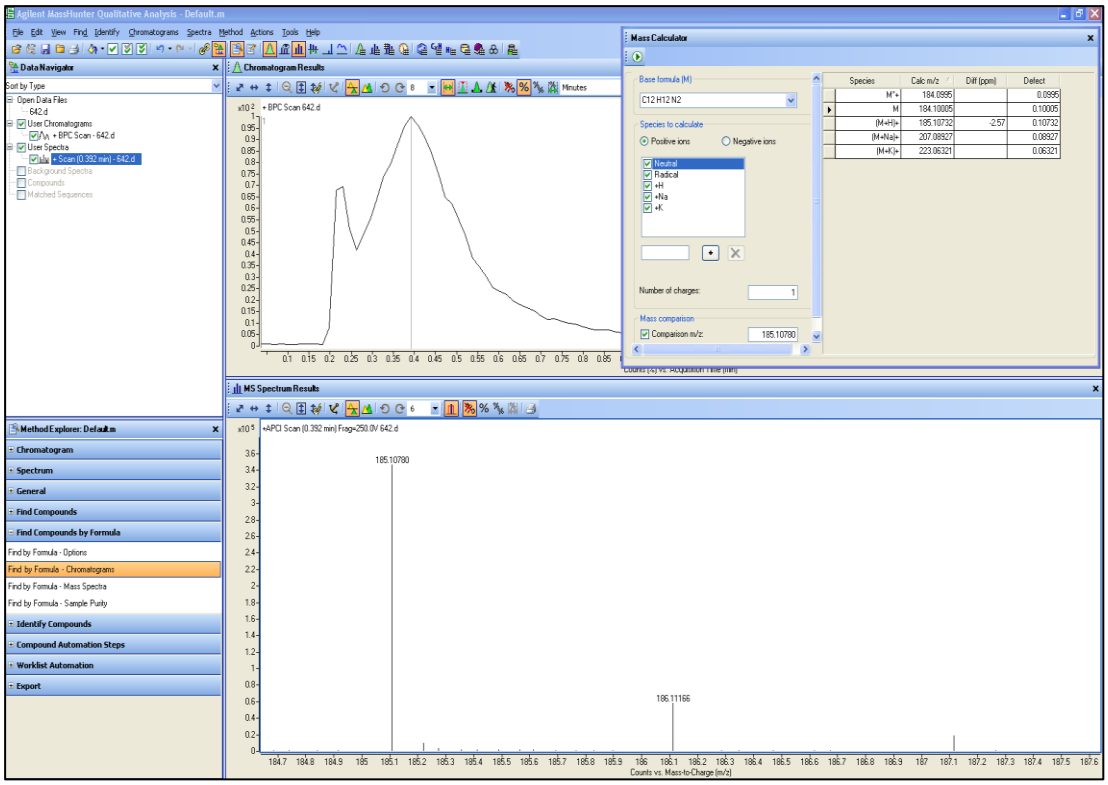


Figure 144 HRMS Spectrum of Compound **73b**

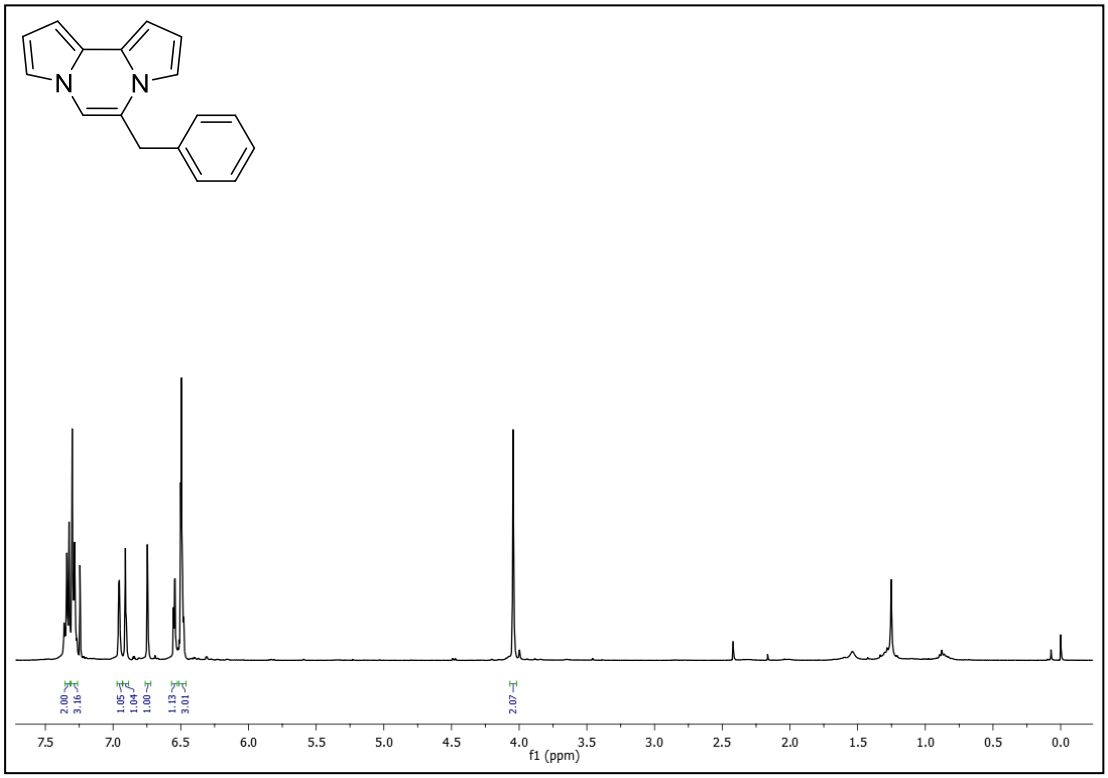


Figure 145 ^{1}H NMR Spectrum of Compound **80a** in $CDCl_3$

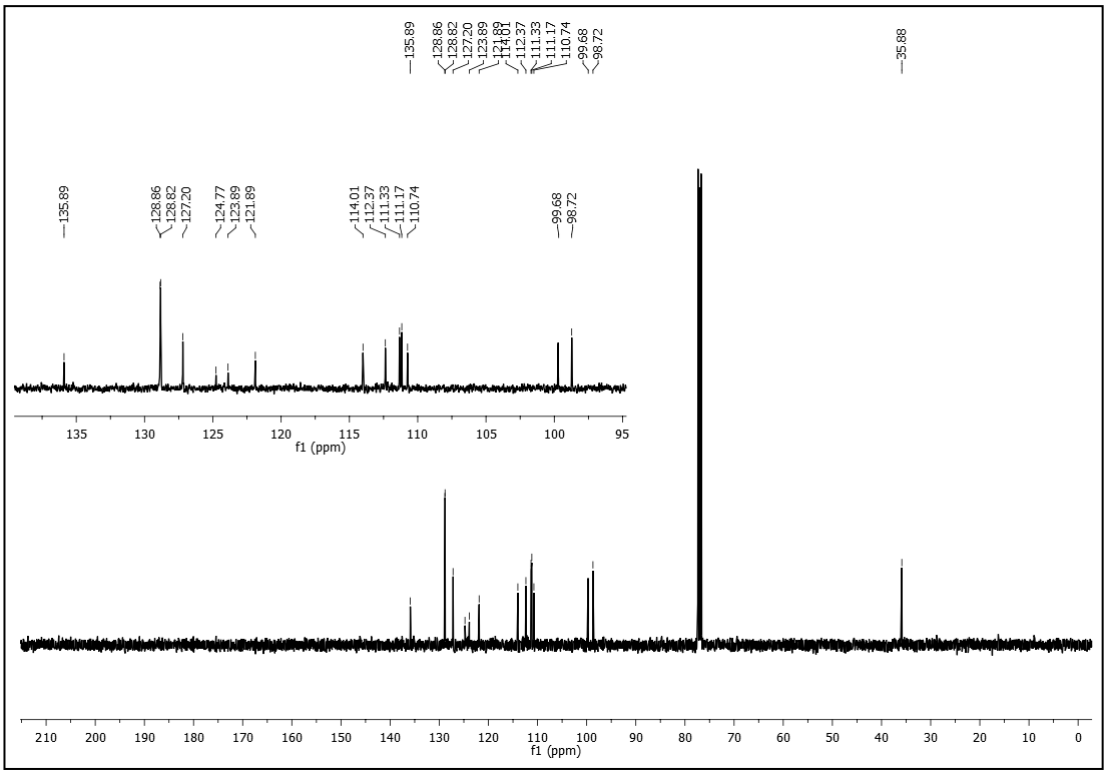


Figure 146 ^{13}C NMR Spectrum of Compound **80a** in $CDCl_3$

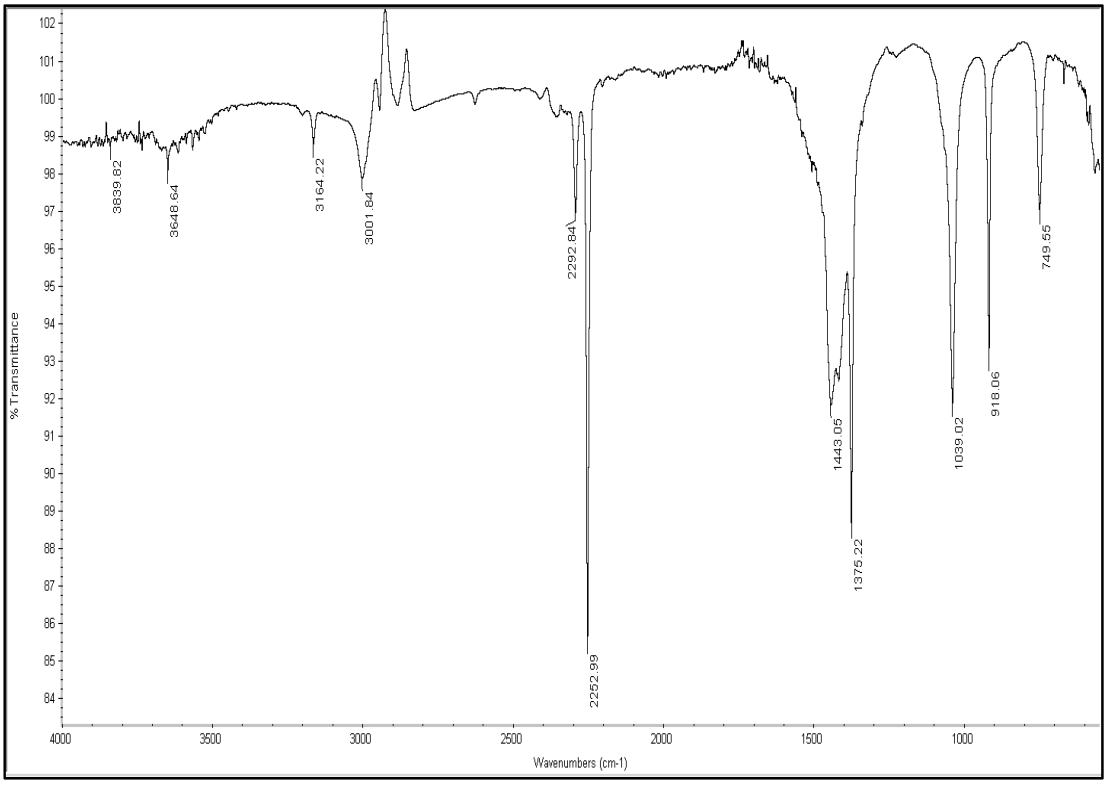


Figure 147 IR Spectrum of Compound **80a**

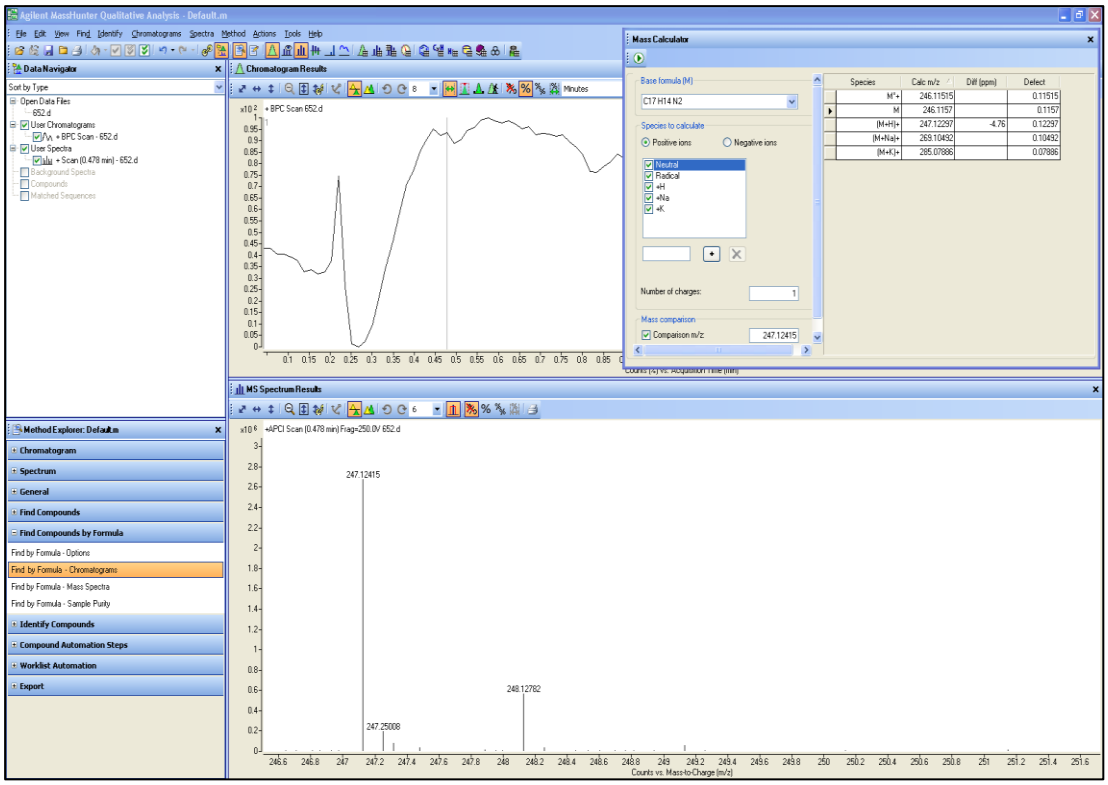


Figure 148 HRMS Spectrum of Compound **80a**

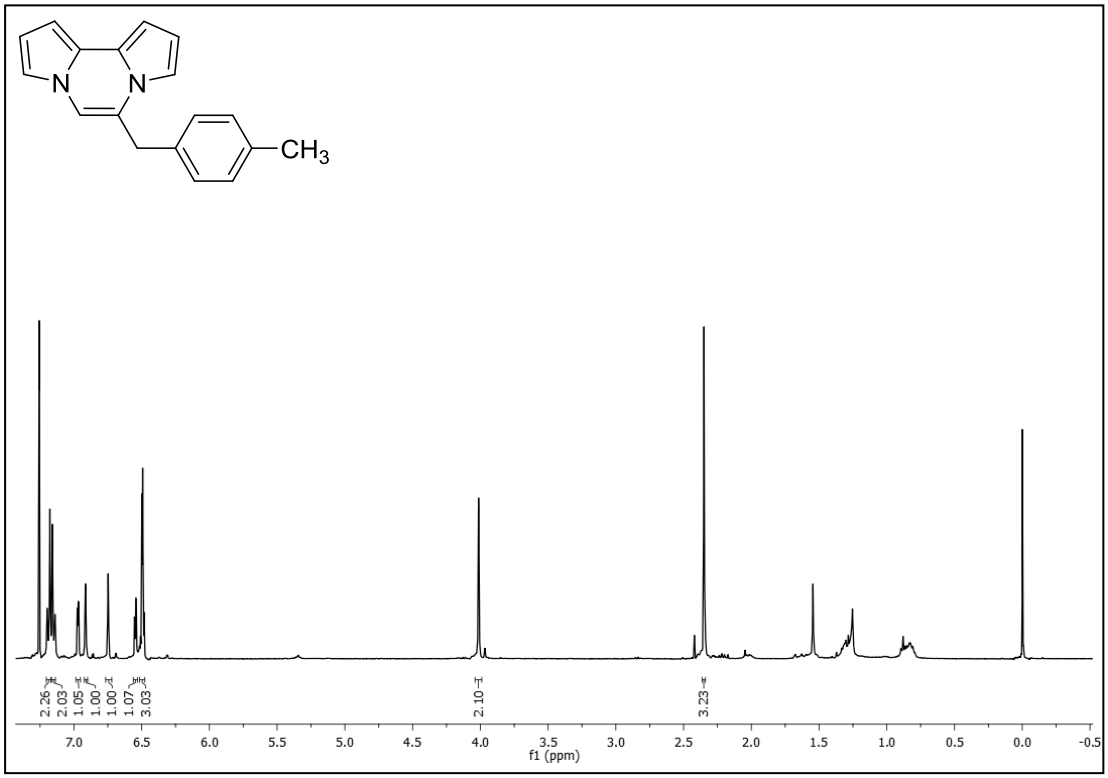


Figure 149 ^{1}H NMR Spectrum of Compound **80b** in $CDCl_3$

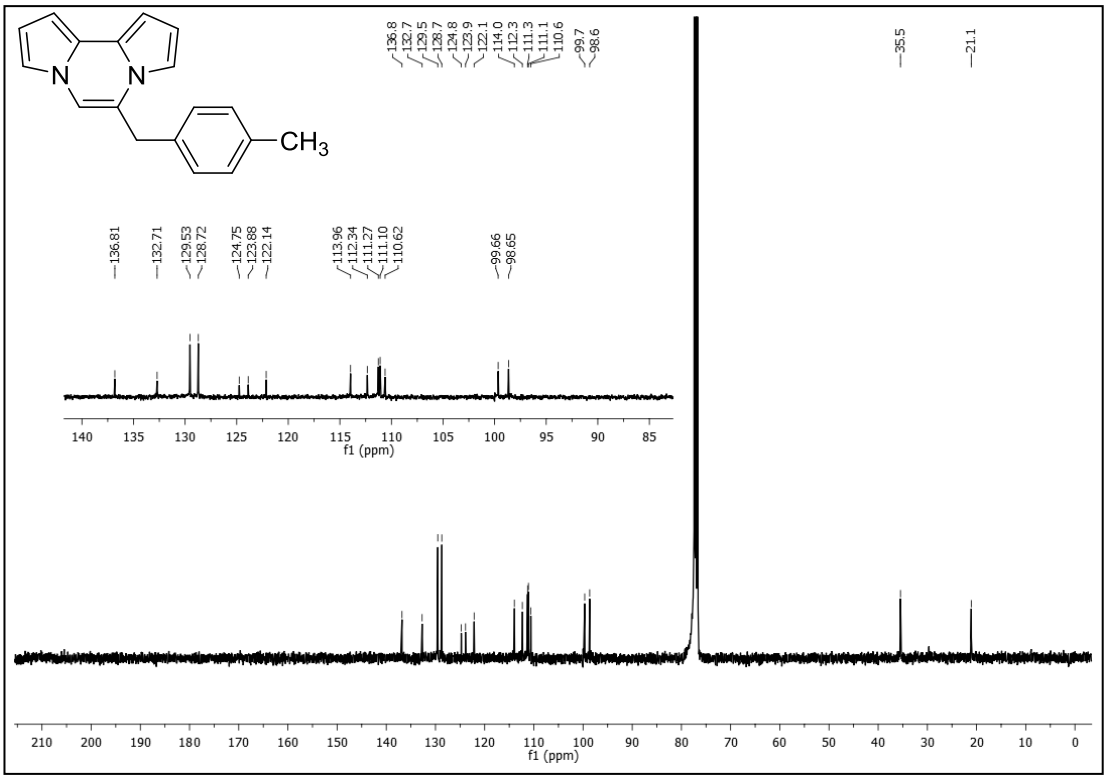


Figure 150 ^{13}C NMR Spectrum of Compound **80b** in $CDCl_3$

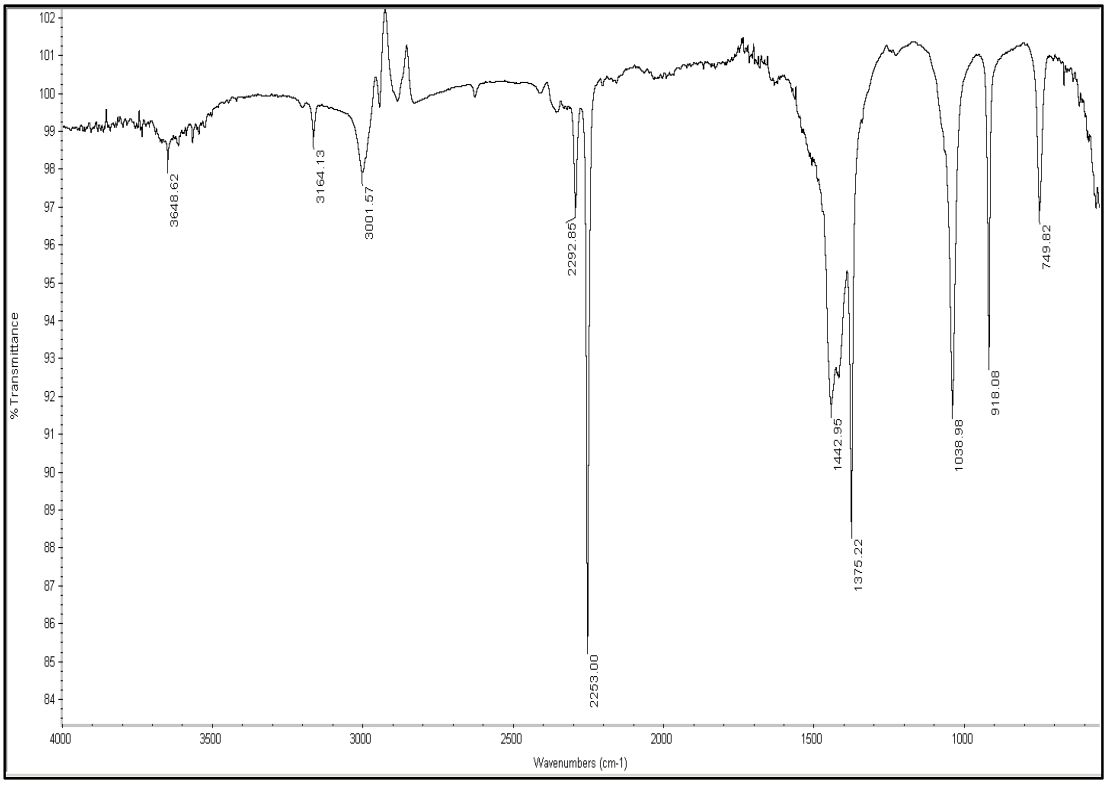


Figure 151 IR Spectrum of Compound **80b**

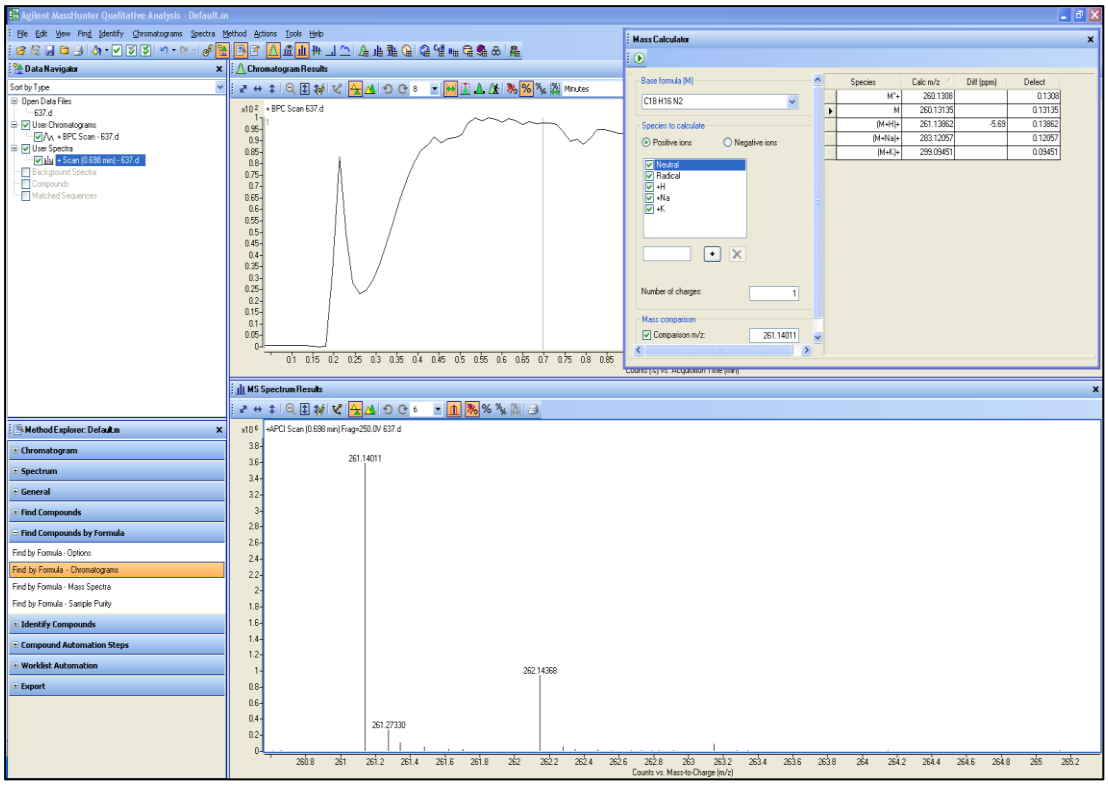


Figure 152 HRMS Spectrum of Compound **80b**

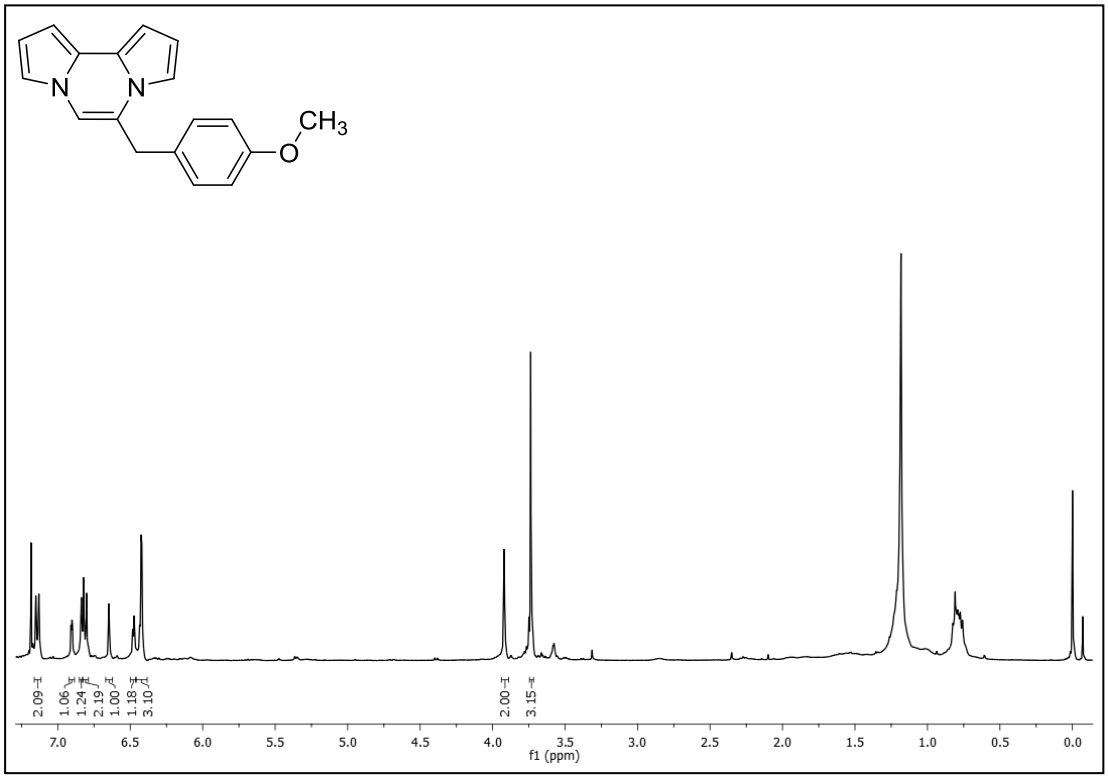


Figure 153 ^{1}H NMR Spectrum of Compound **80c** in $CDCl_3$

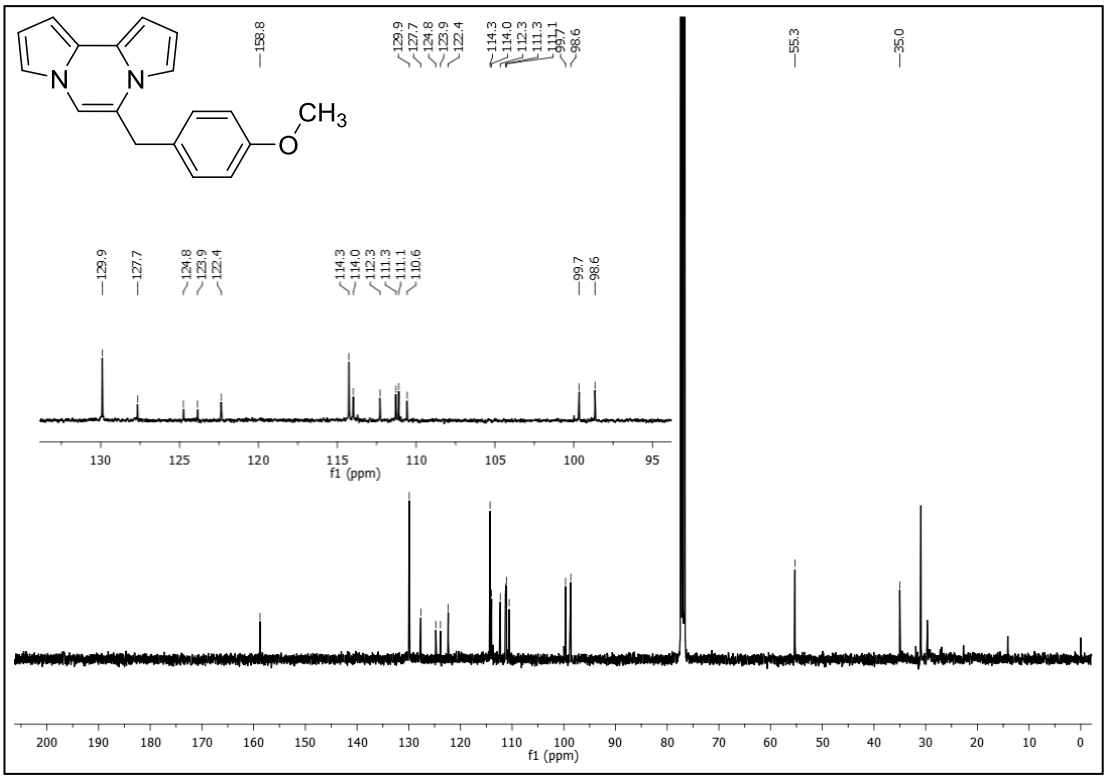


Figure 154 ^{13}C NMR Spectrum of Compound **80c** in $CDCl_3$

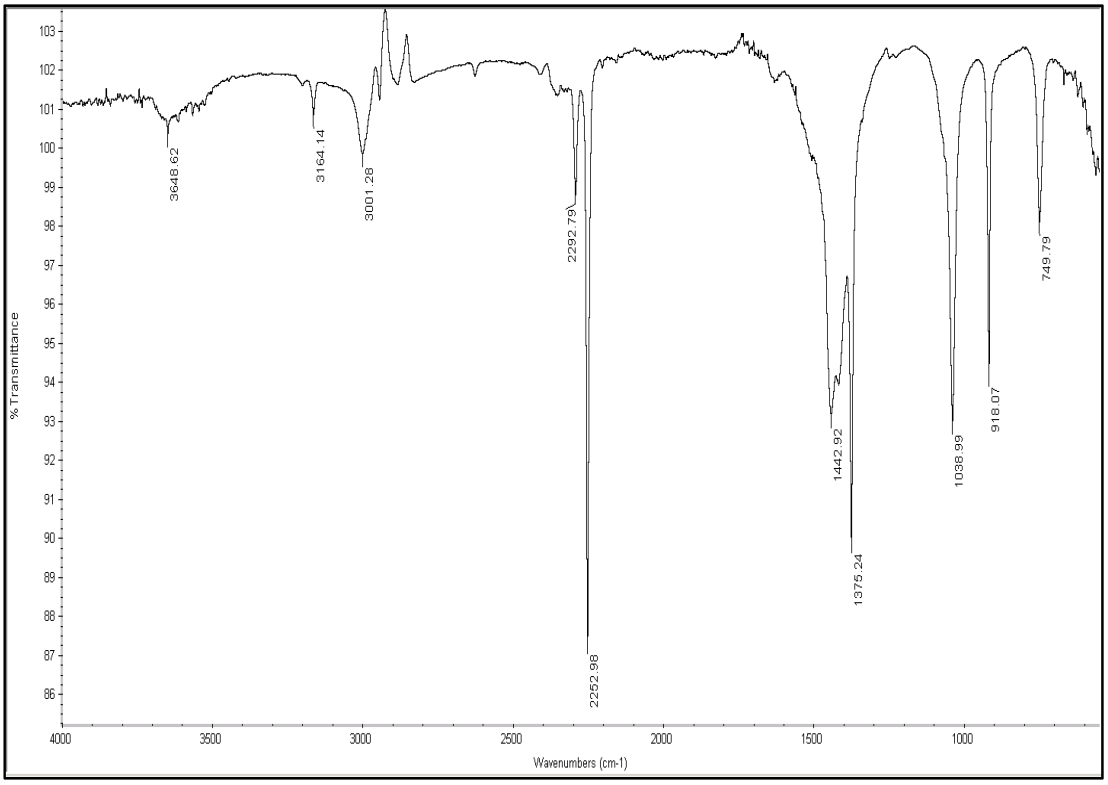


Figure 155 IR Spectrum of Compound **80c**

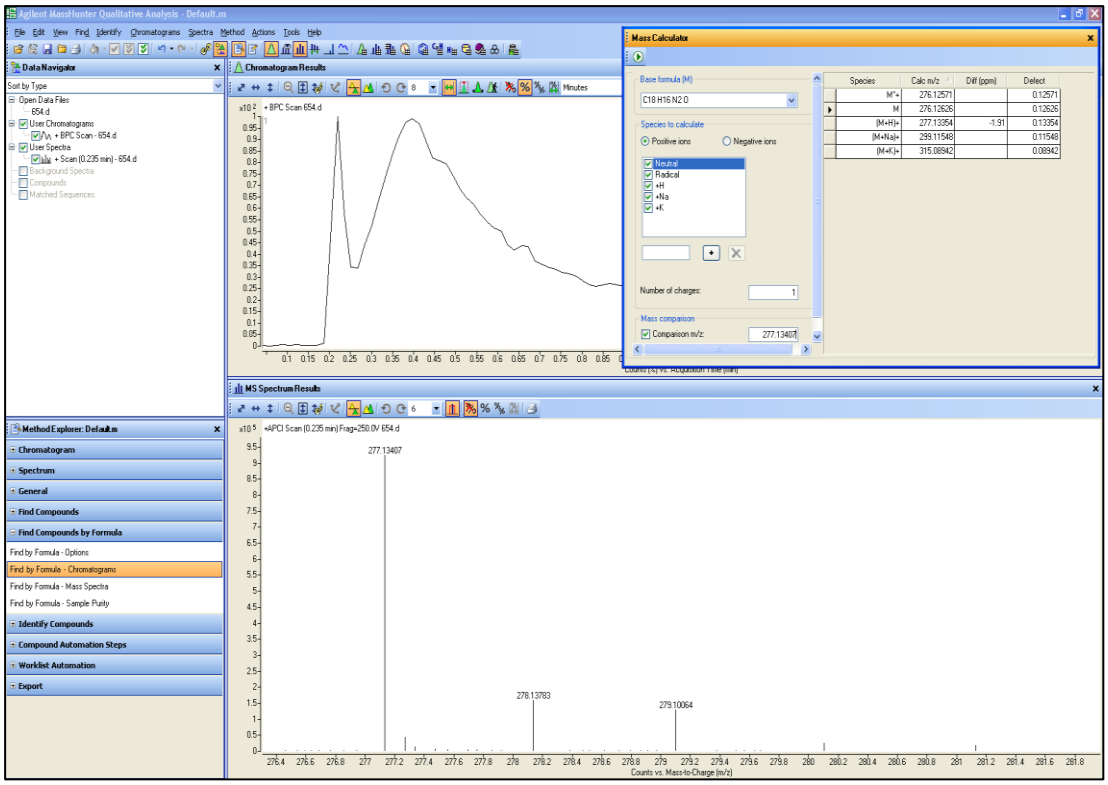


Figure 156 HRMS Spectrum of Compound **80c**

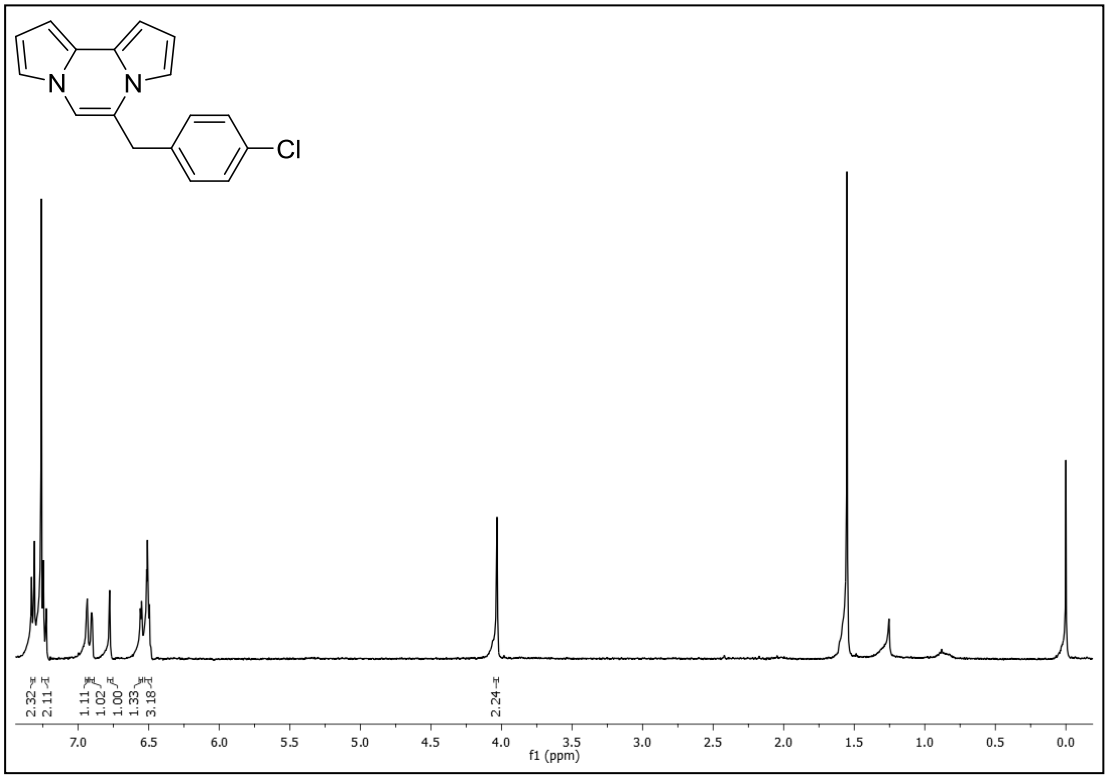


Figure 157 ^{1}H NMR Spectrum of Compound **80d** in $CDCl_3$

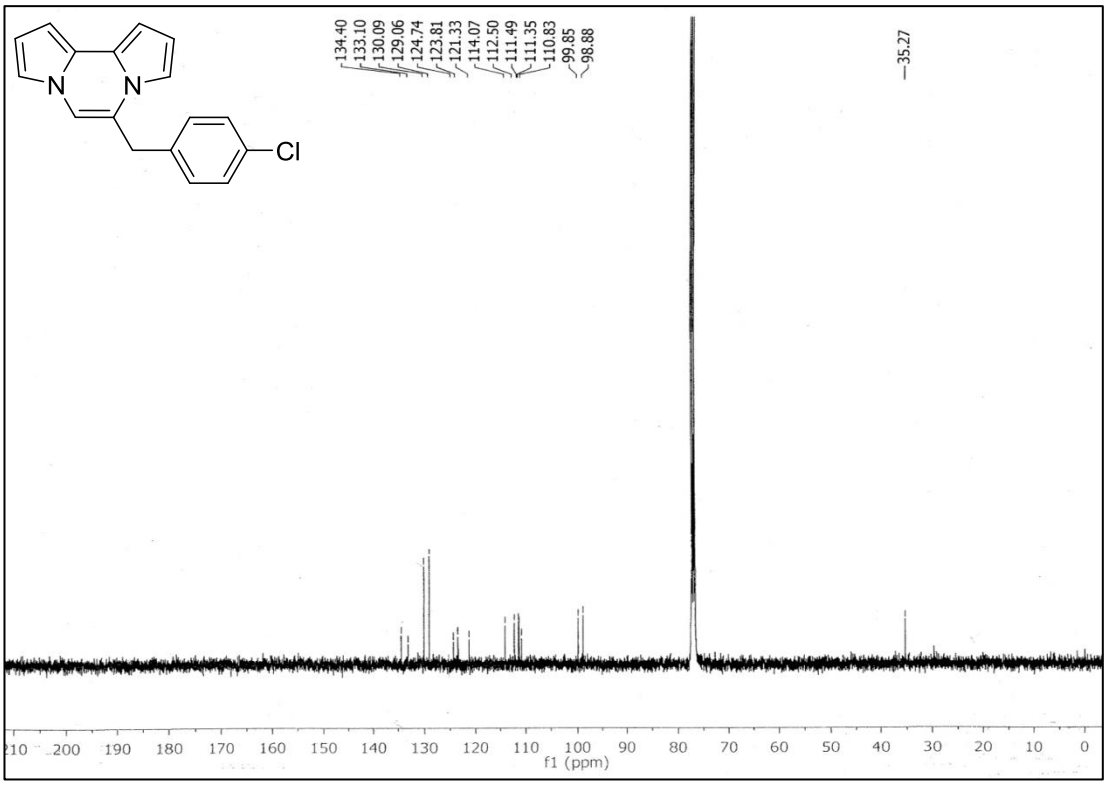


Figure 158 ^{13}C NMR Spectrum of Compound **80d** in $CDCl_3$

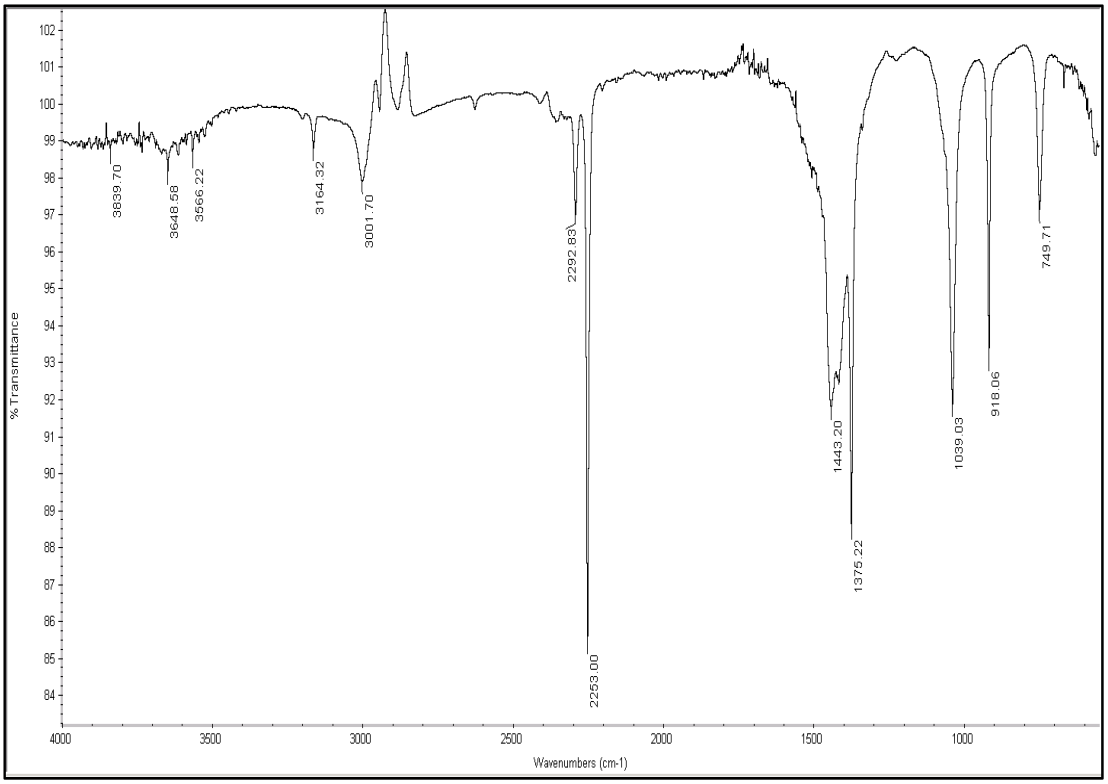


Figure 159 IR Spectrum of Compound **80d**

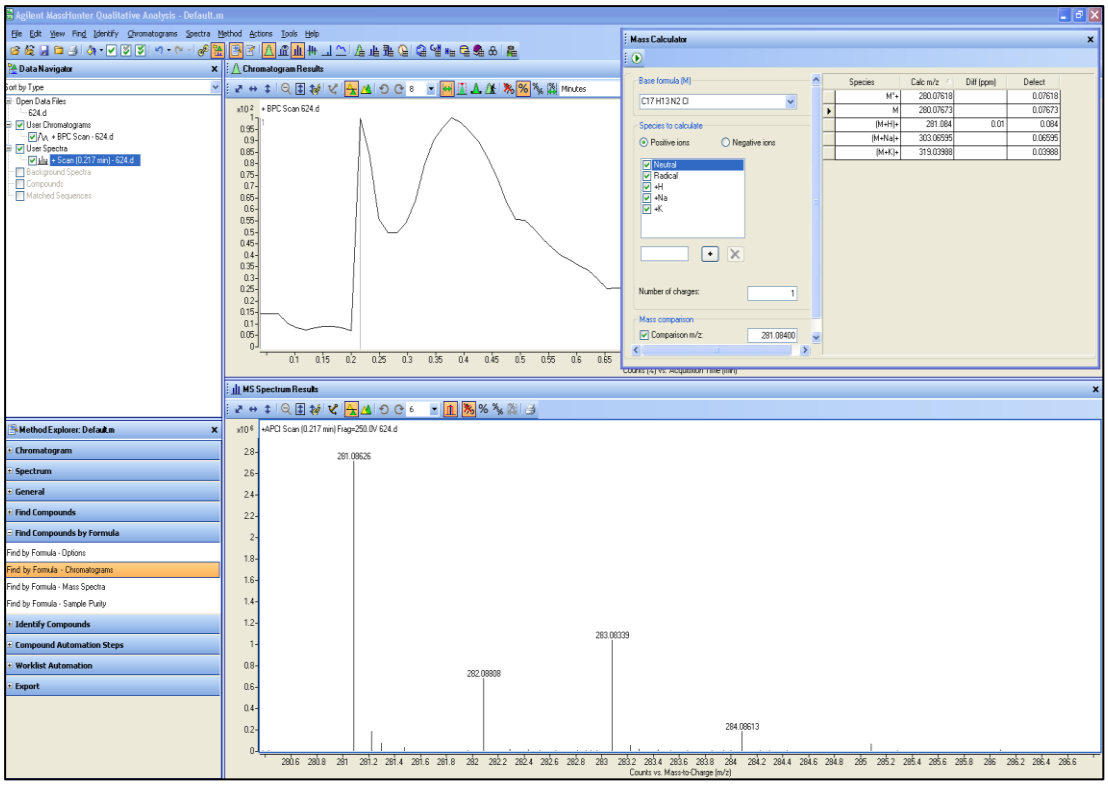


Figure 160 HRMS Spectrum of Compound **80d**

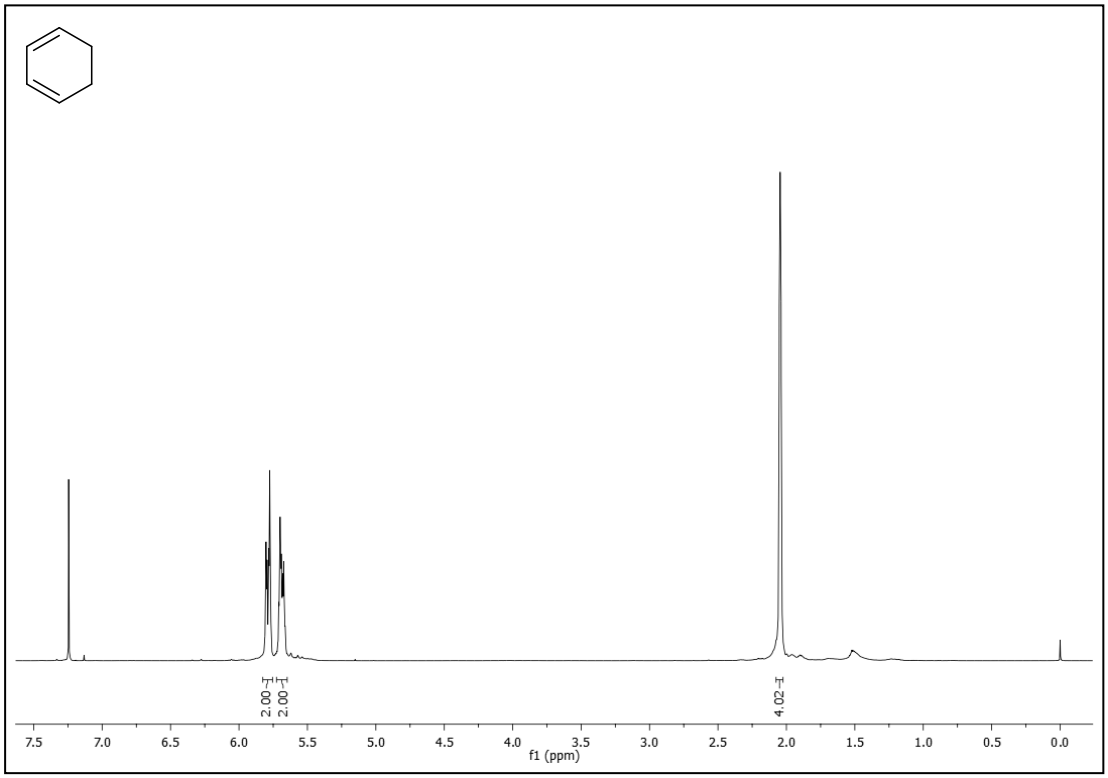


Figure 161 ^{1}H NMR Spectrum of Compound **92** in $CDCl_3$

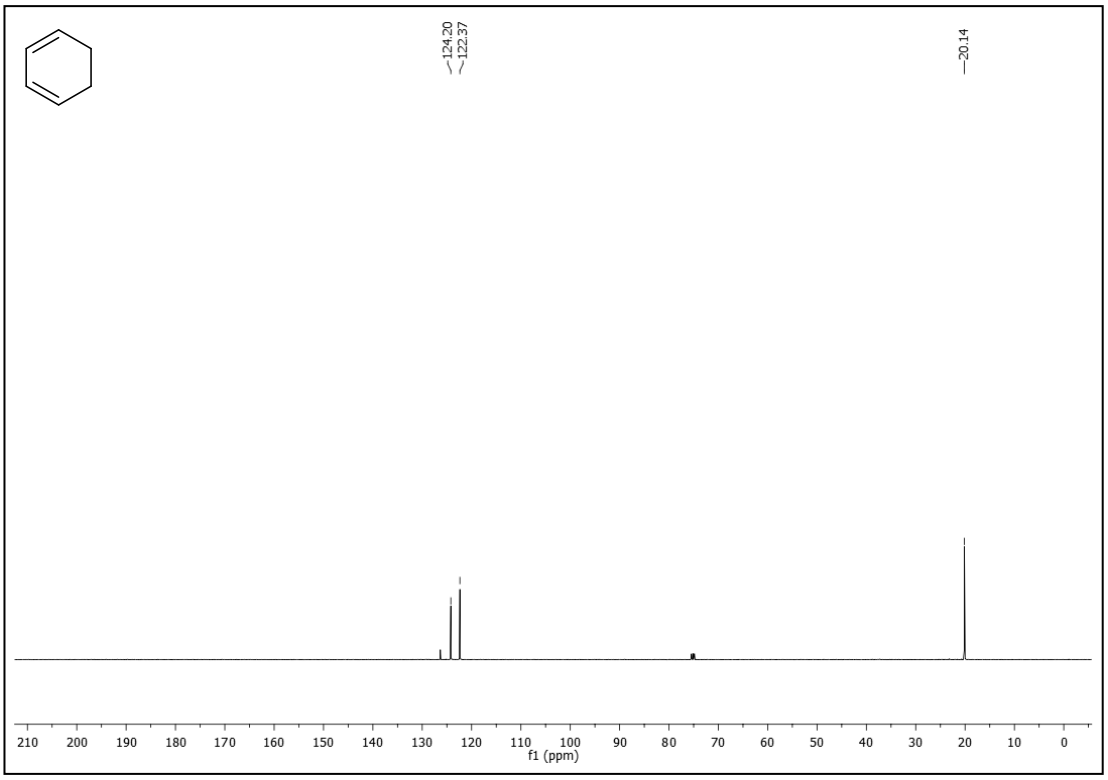


Figure 162 ^{13}C NMR Spectrum of Compound **92** in $CDCl_3$

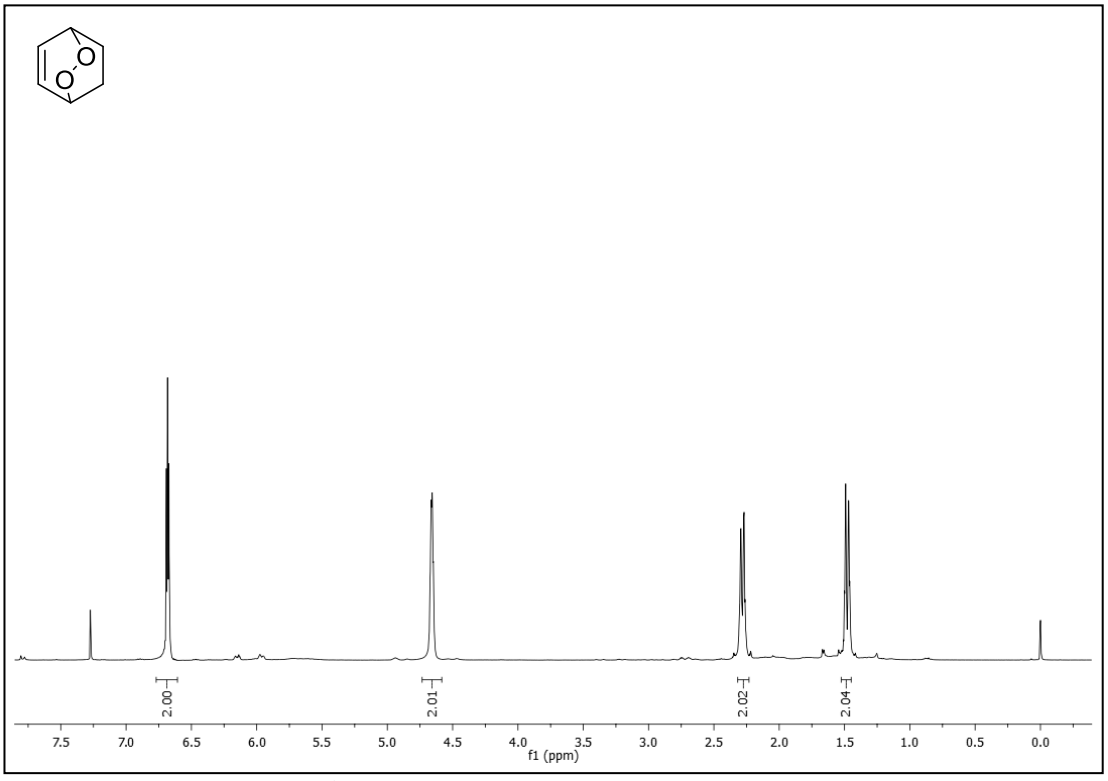


Figure 163 ^{1}H NMR Spectrum of Compound **93** in $CDCl_3$

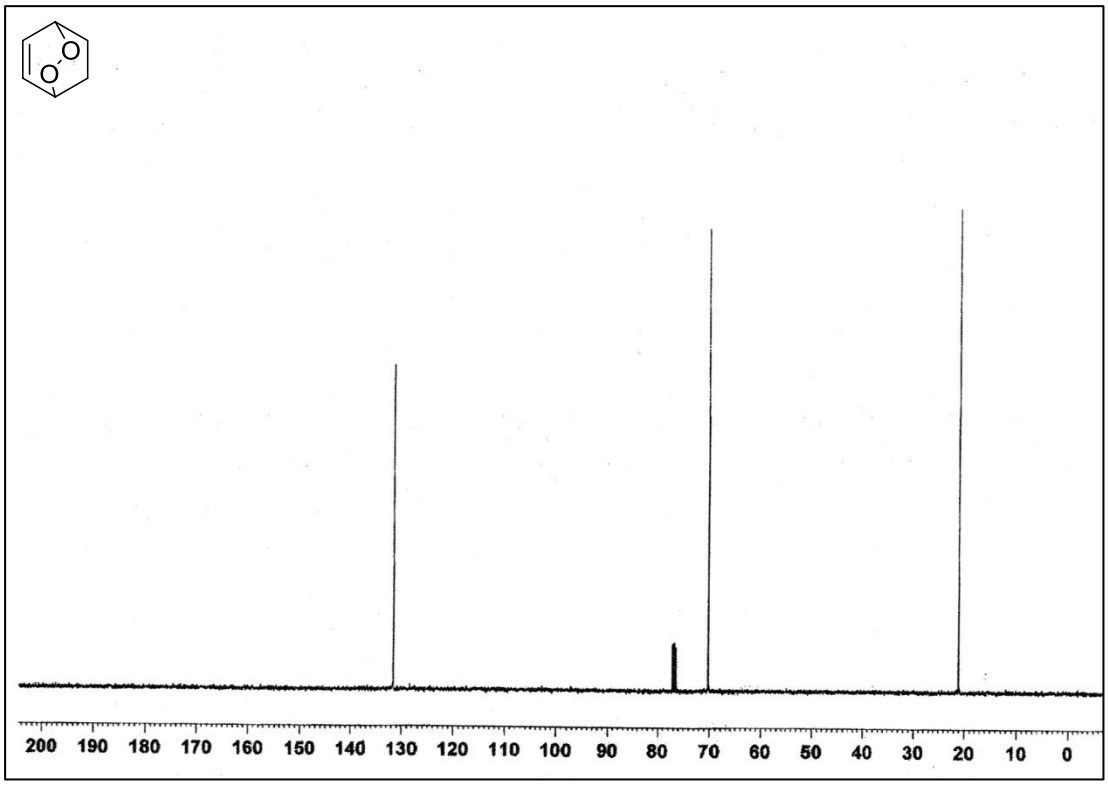


Figure 164 ^{13}C NMR Spectrum of Compound **93** in $CDCl_3$

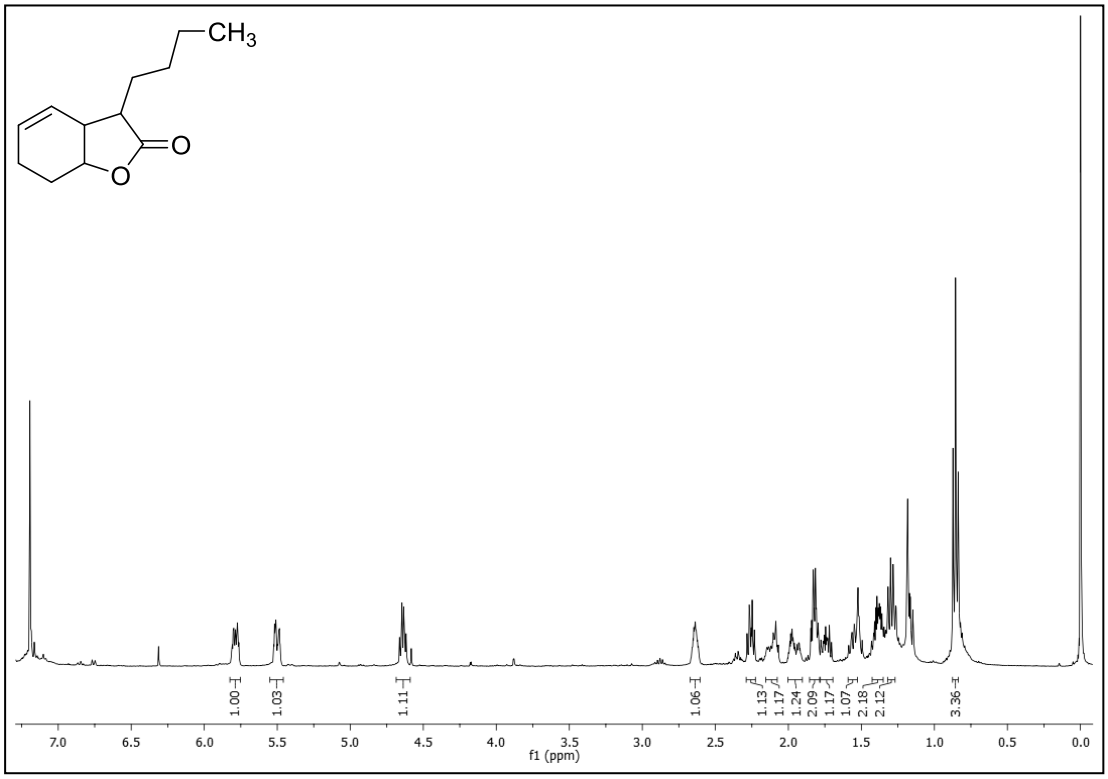


Figure 165 ^{1}H NMR Spectrum of Compound **95a** in $CDCl_3$

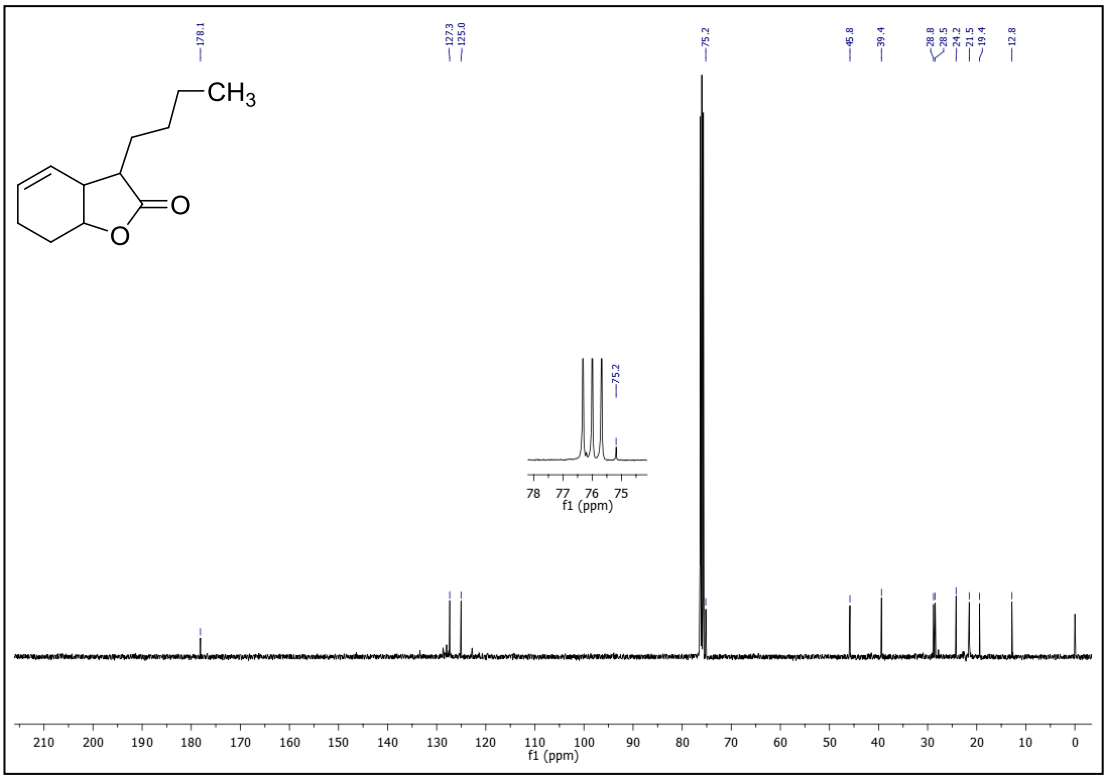


Figure 166 ^{13}C NMR Spectrum of Compound **95a** in $CDCl_3$

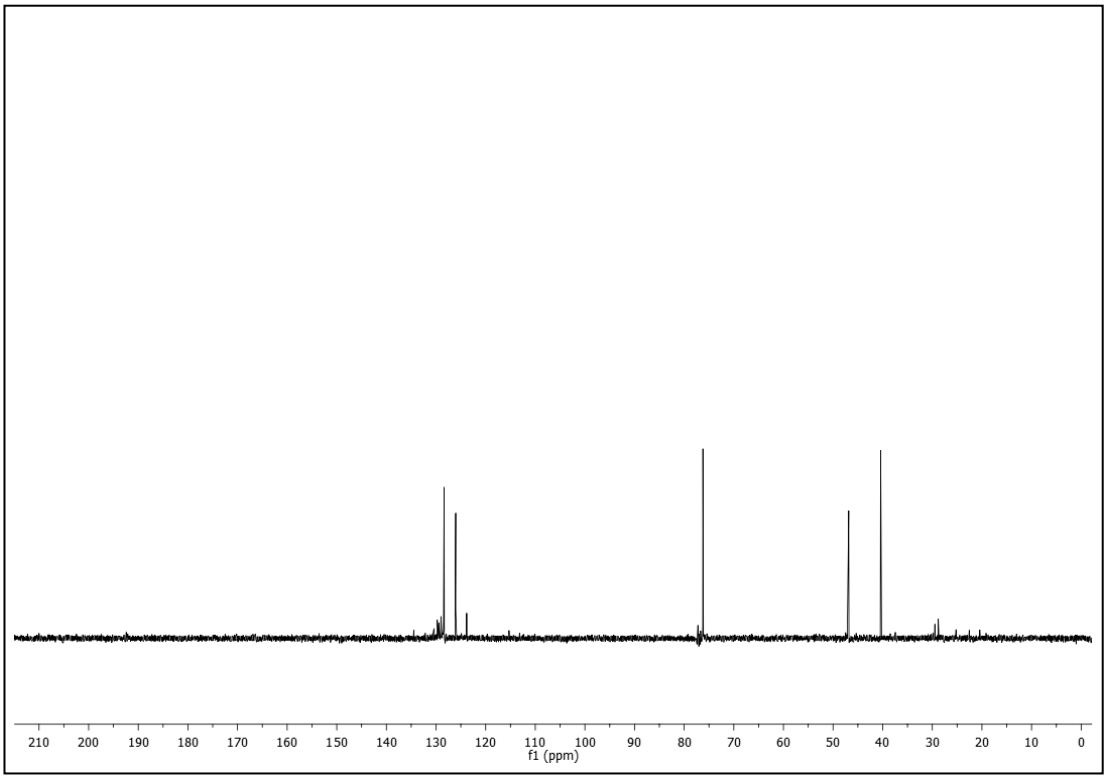


Figure 167 DEPT90 Spectrum of Compound **95a** in $CDCl_3$

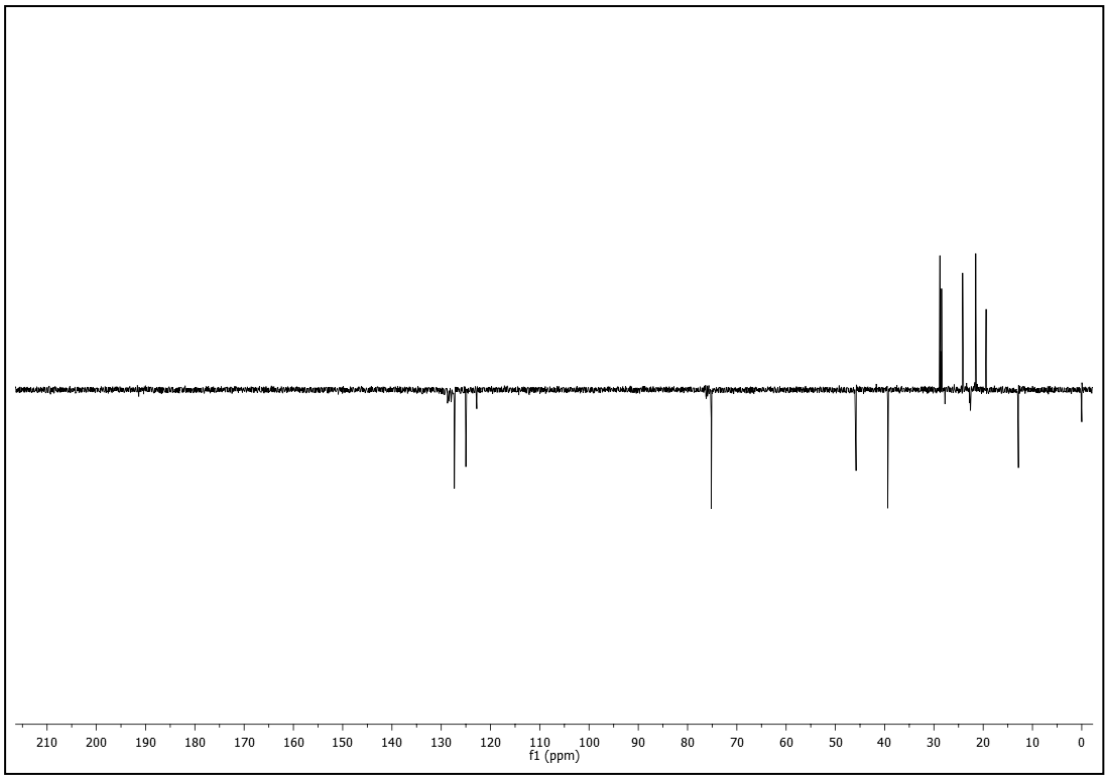


Figure 168 DEPT135 Spectrum of Compound **95a** in $CDCl_3$

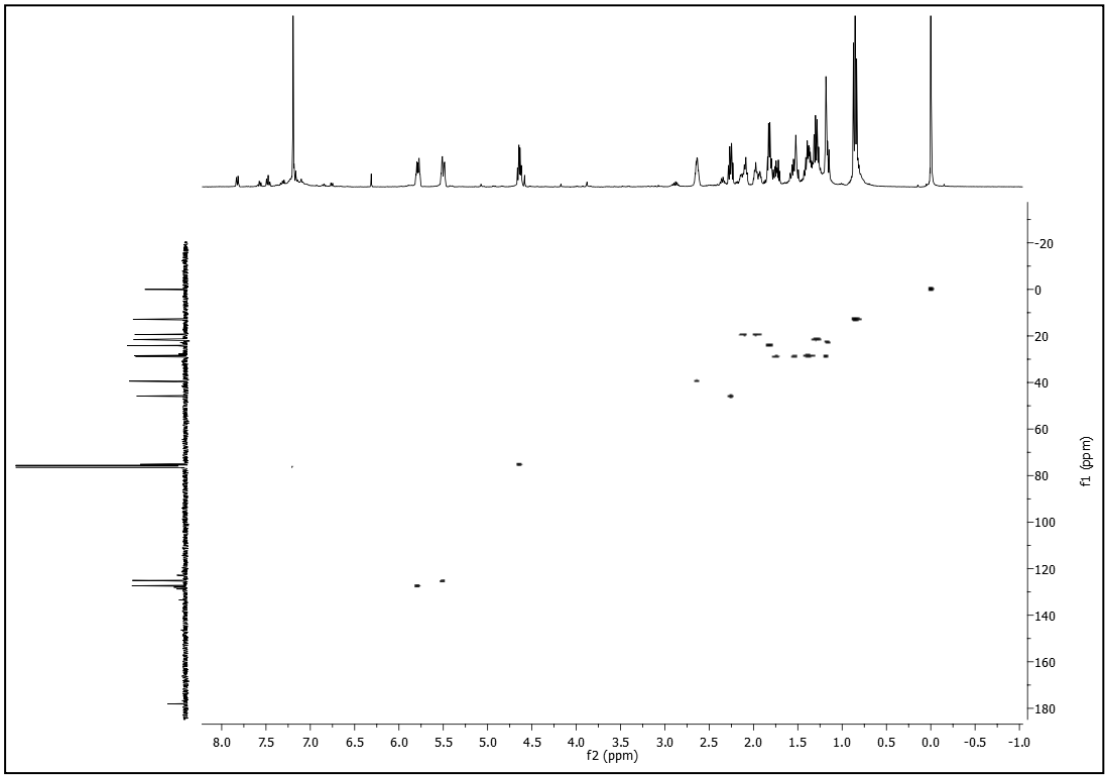


Figure 169 HSQC Spectrum of Compound **95a** in $CDCl_3$

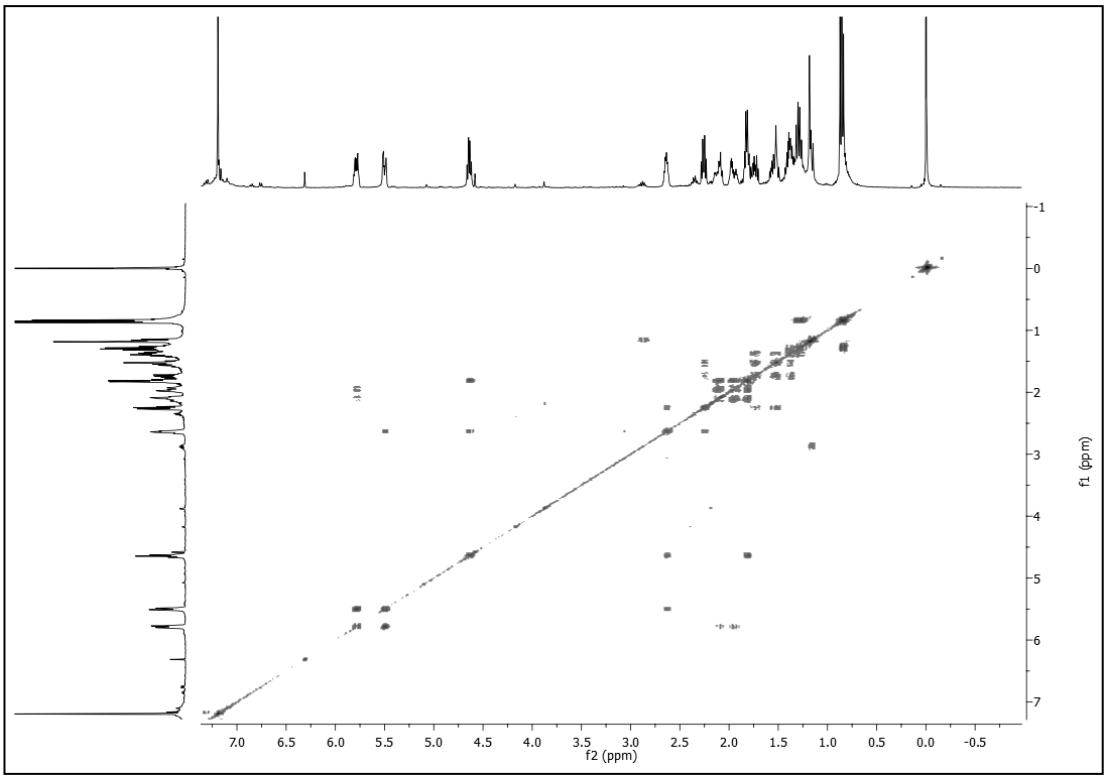


Figure 170 COSY Spectrum of Compound **95a** in $CDCl_3$

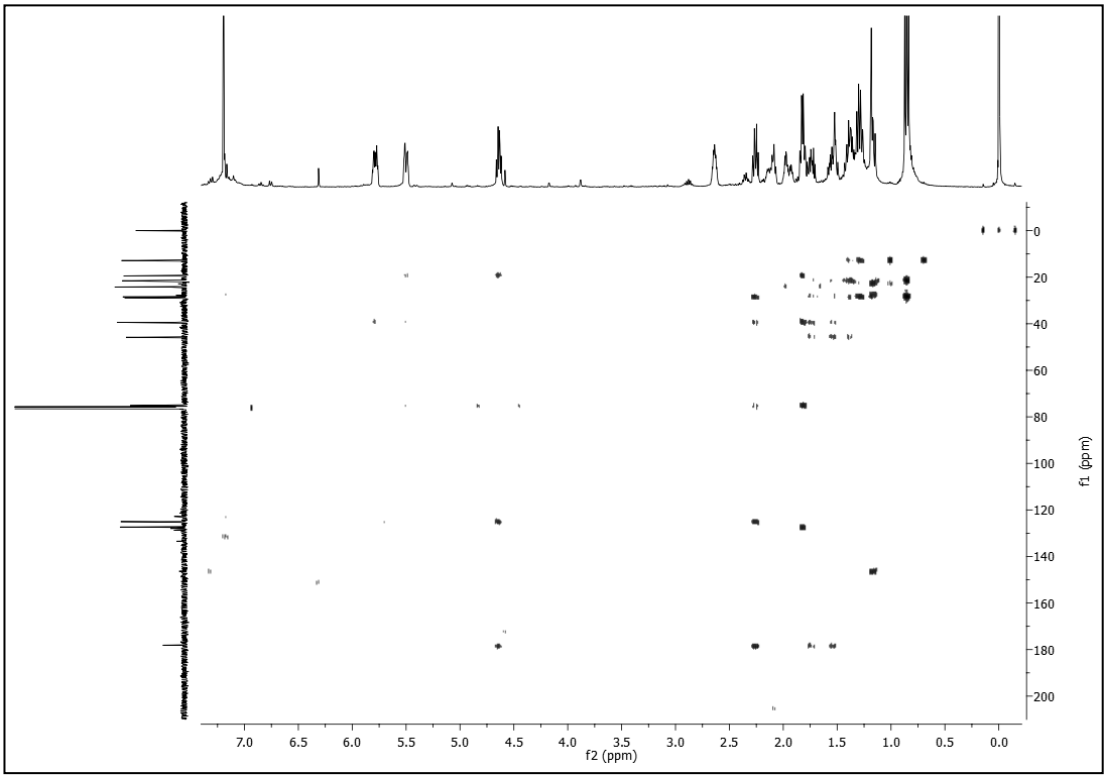


Figure 171 HMBC Spectrum of Compound **95a** in $CDCl_3$

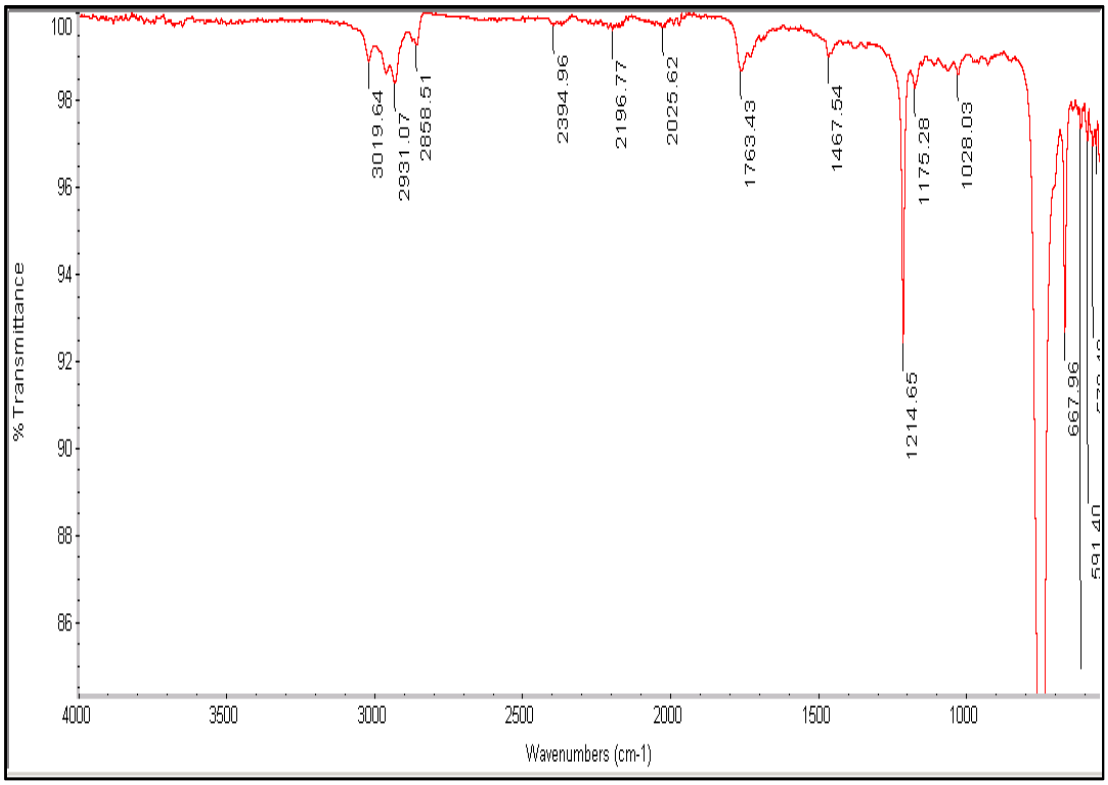


Figure 172 IR Spectrum of Compound **95a**

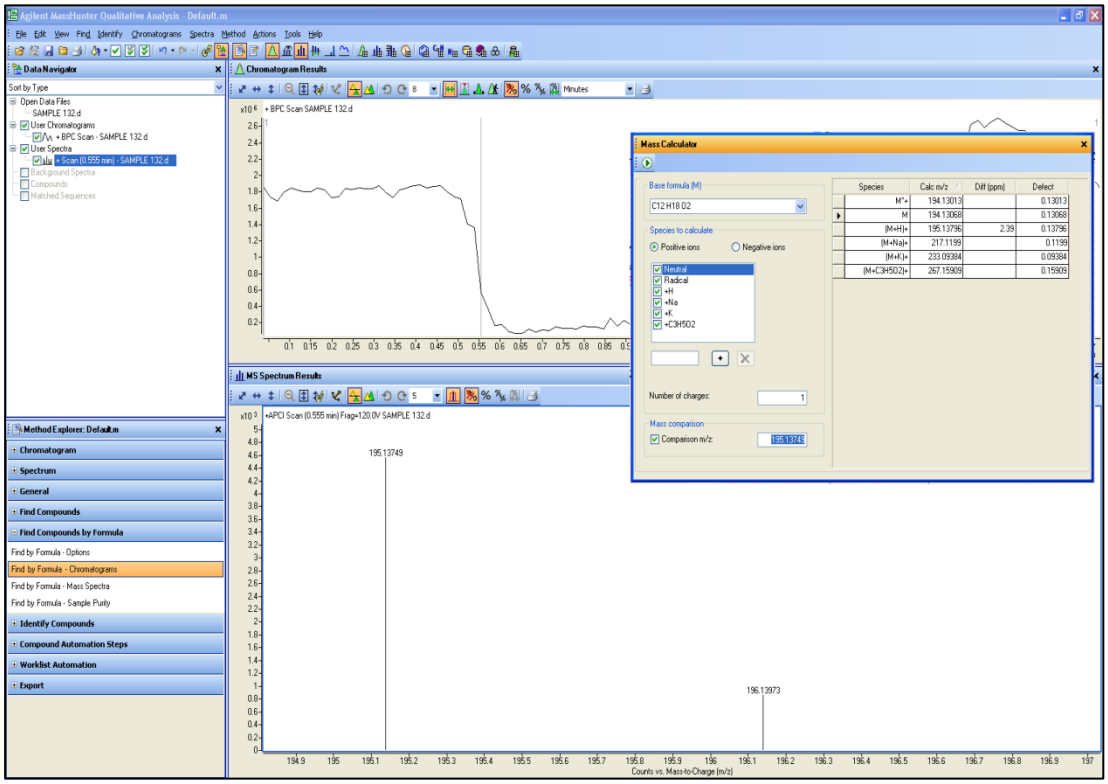


Figure 173 HRMS Spectrum of Compound **95a**

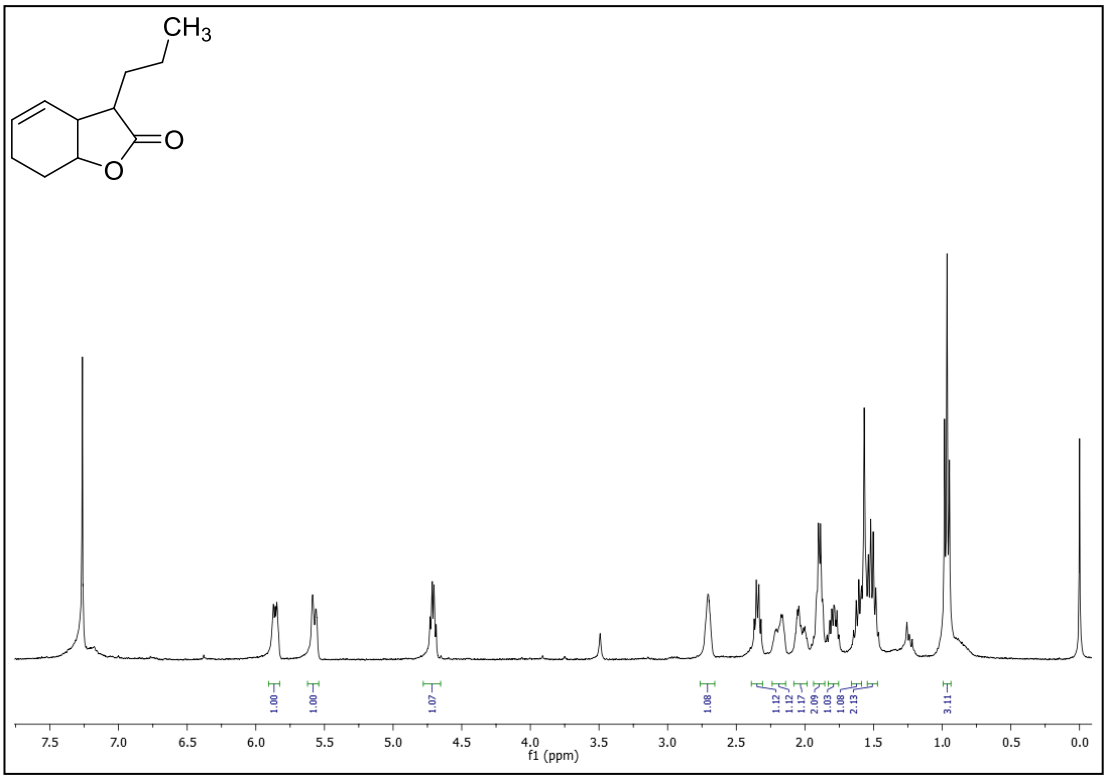


Figure 174 ^{1}H NMR Spectrum of Compound **95b** in $CDCl_3$

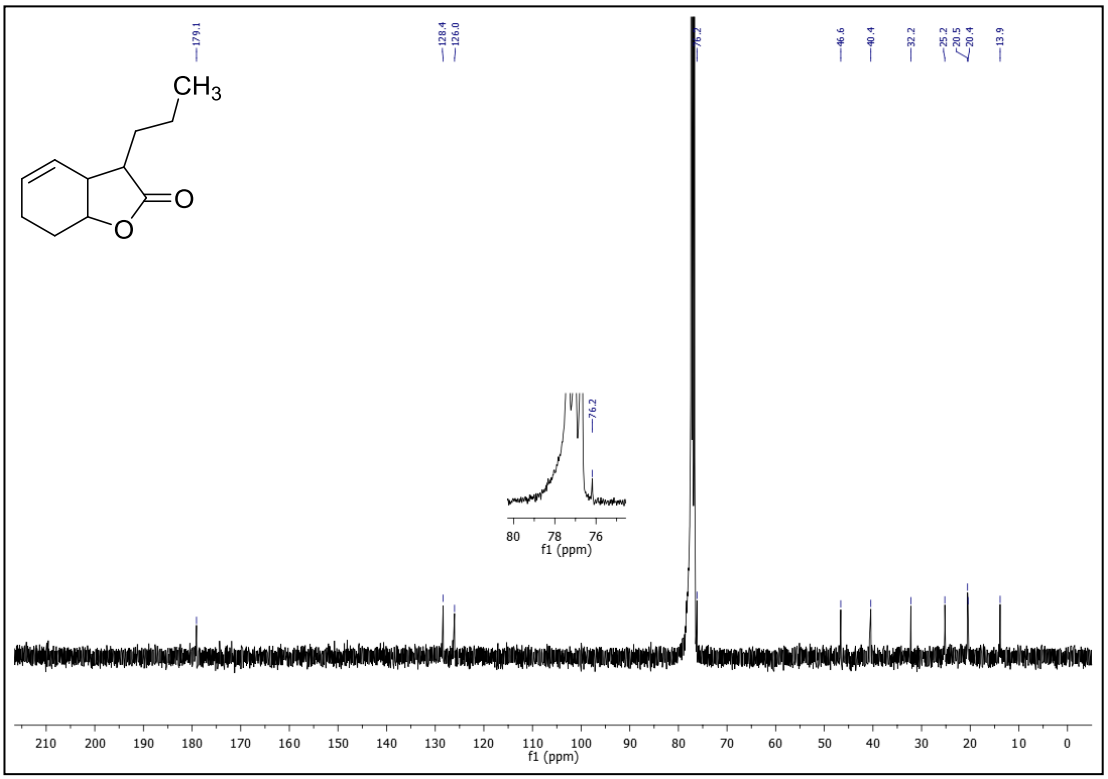


Figure 175 ^{13}C NMR Spectrum of Compound **95b** in $CDCl_3$

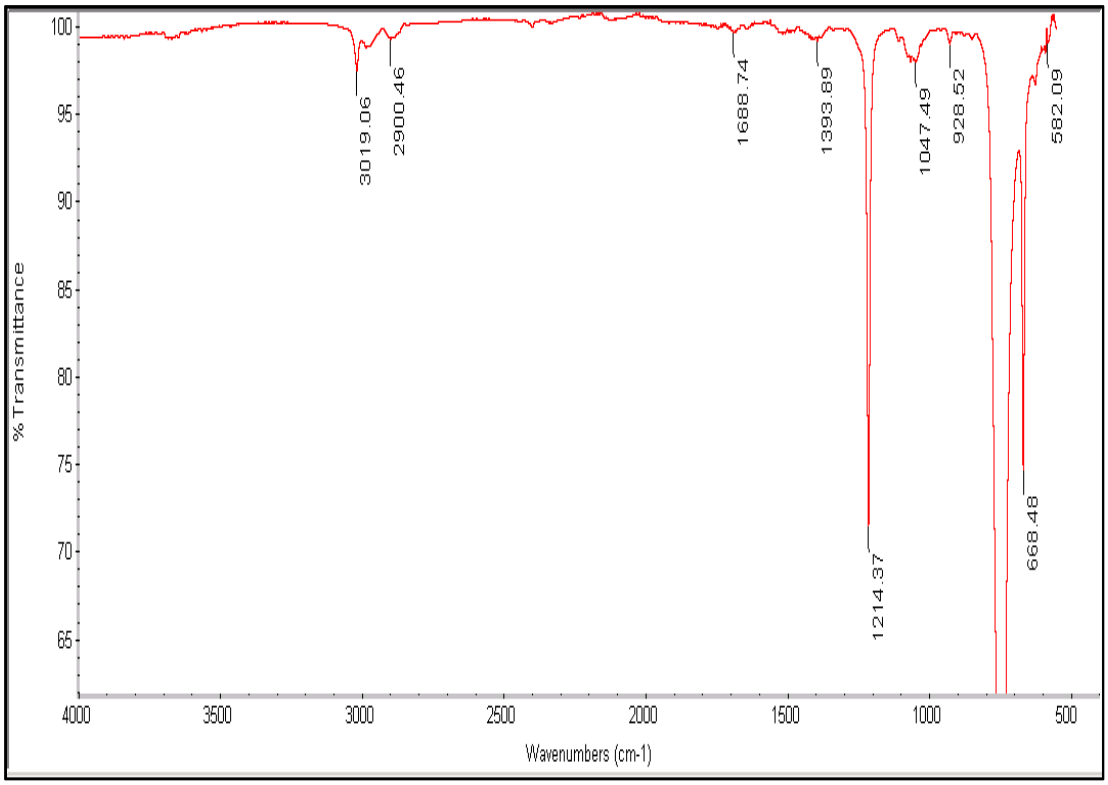


Figure 176 IR Spectrum of Compound **95b**

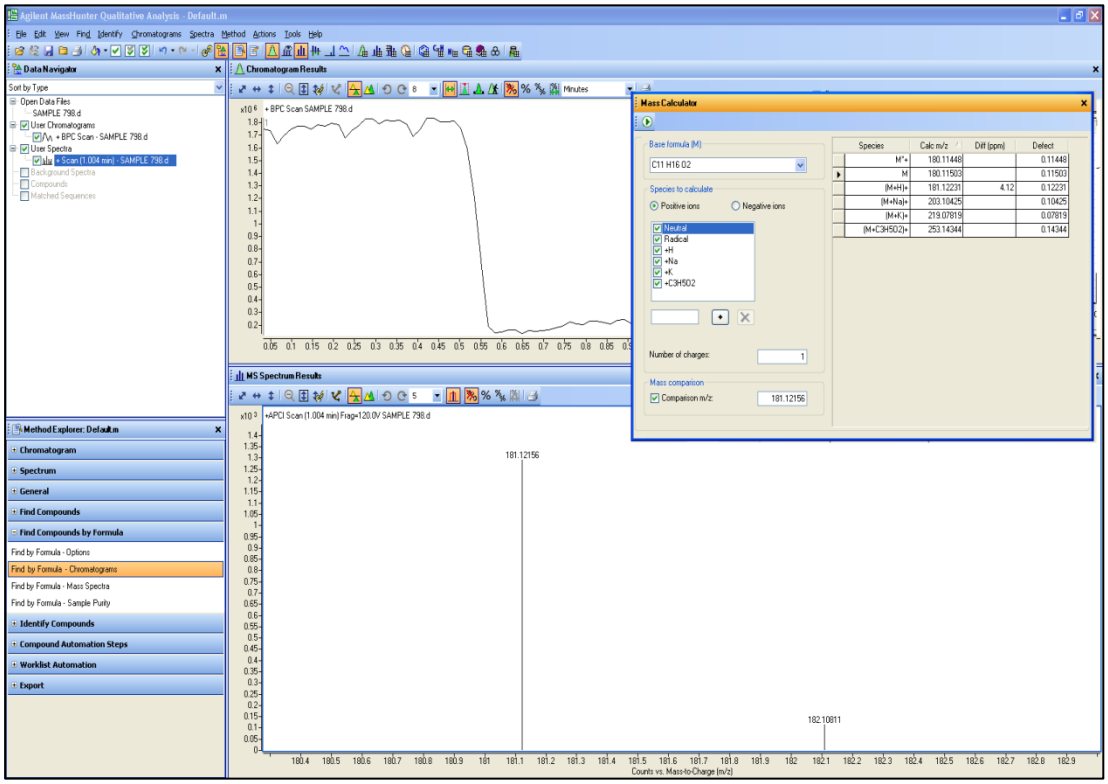


Figure 177 HRMS Spectrum of Compound **95b**

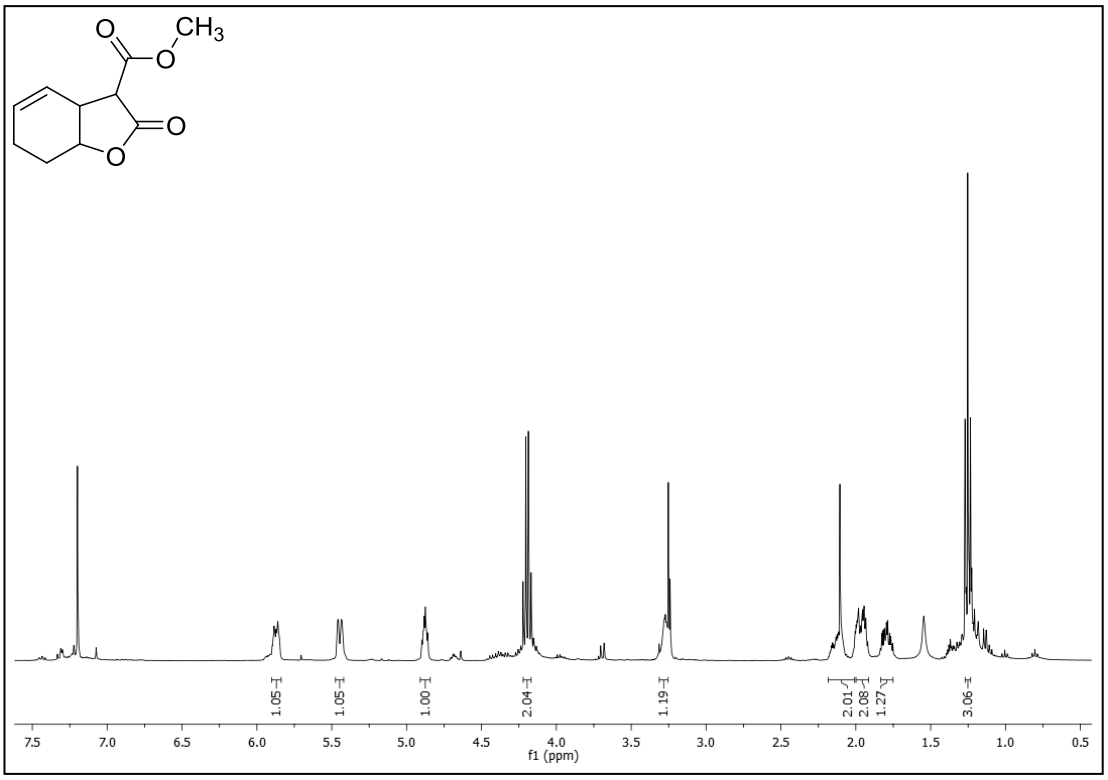


Figure 178 ^{1}H NMR Spectrum of Compound **95c** in $CDCl_3$

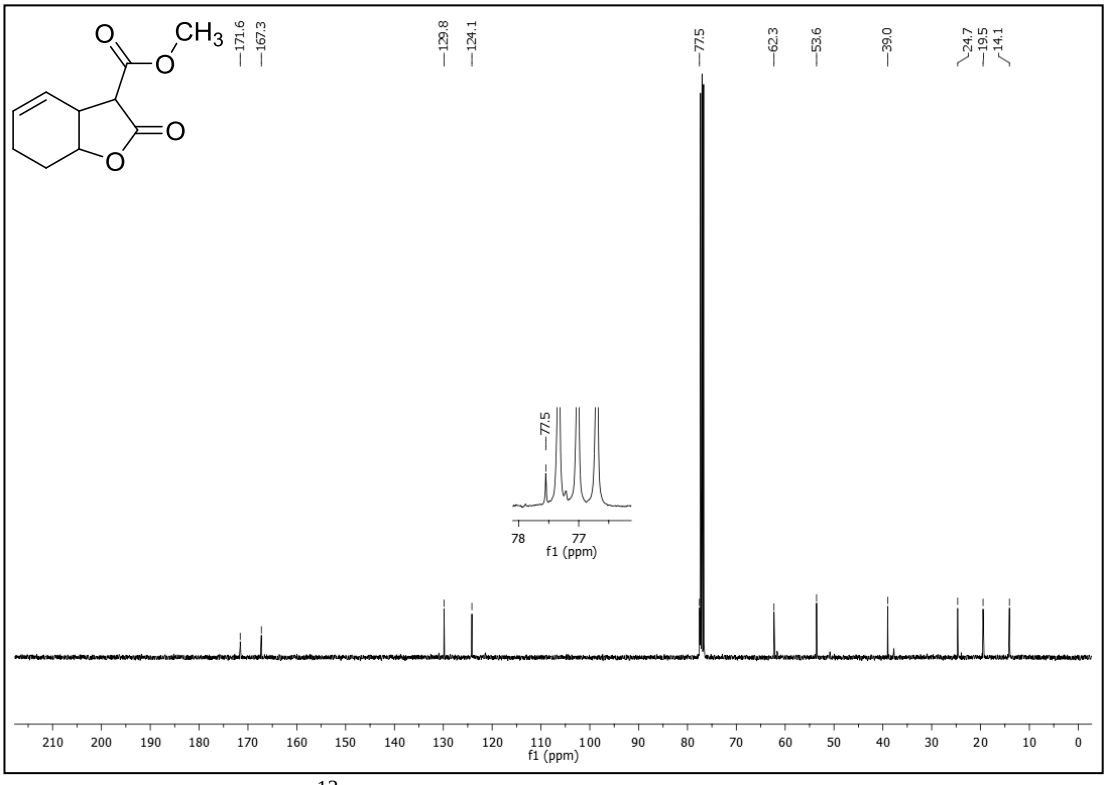


Figure 179 ^{13}C NMR Spectrum of Compound **95c** in $CDCl_3$

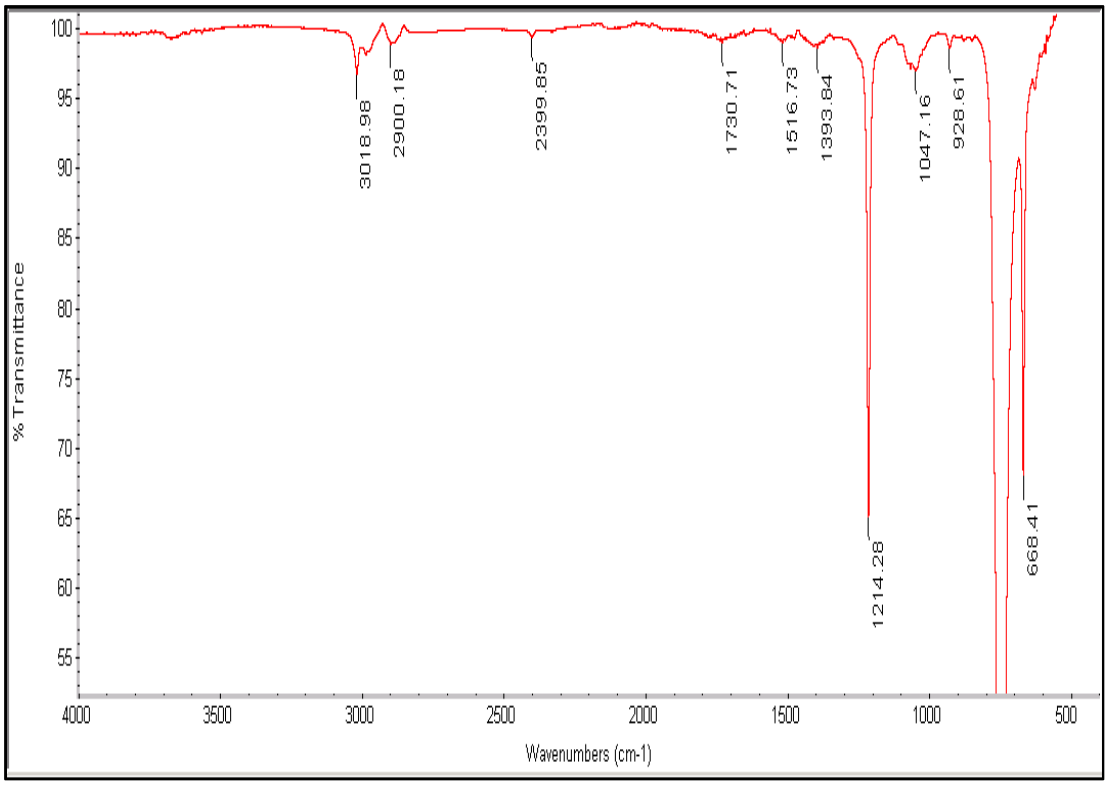


Figure 180 IR Spectrum of Compound **95c**

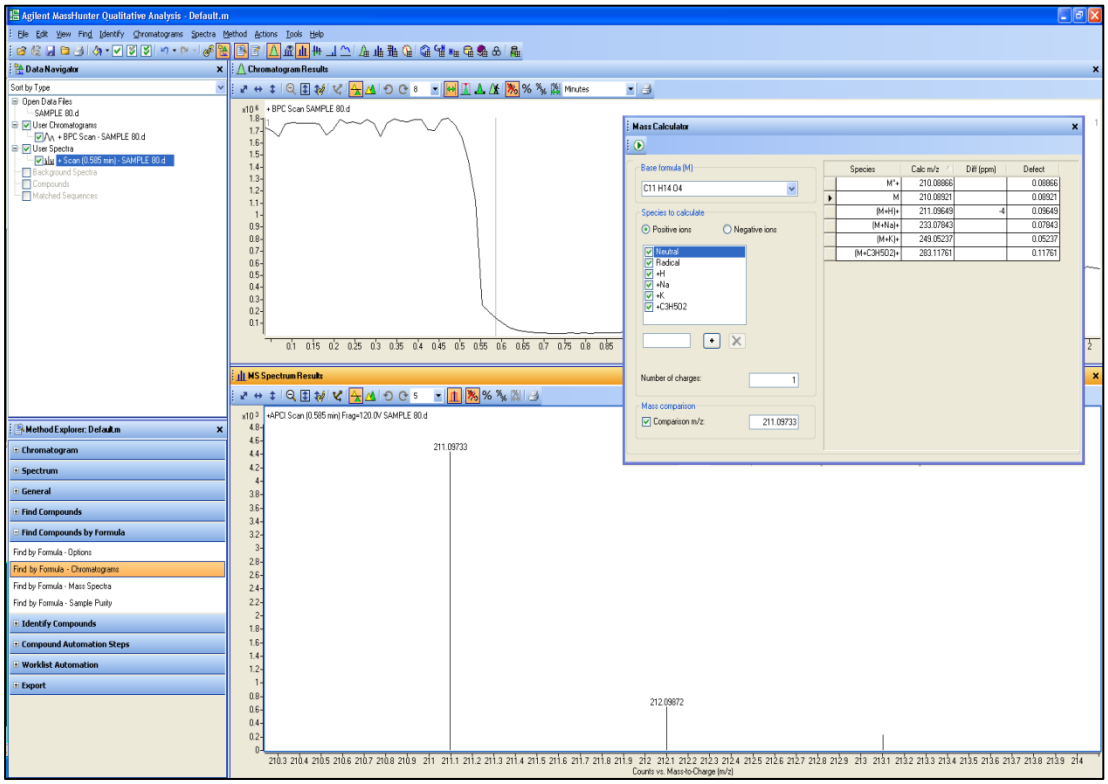


Figure 181 HRMS Spectrum of Compound **95c**

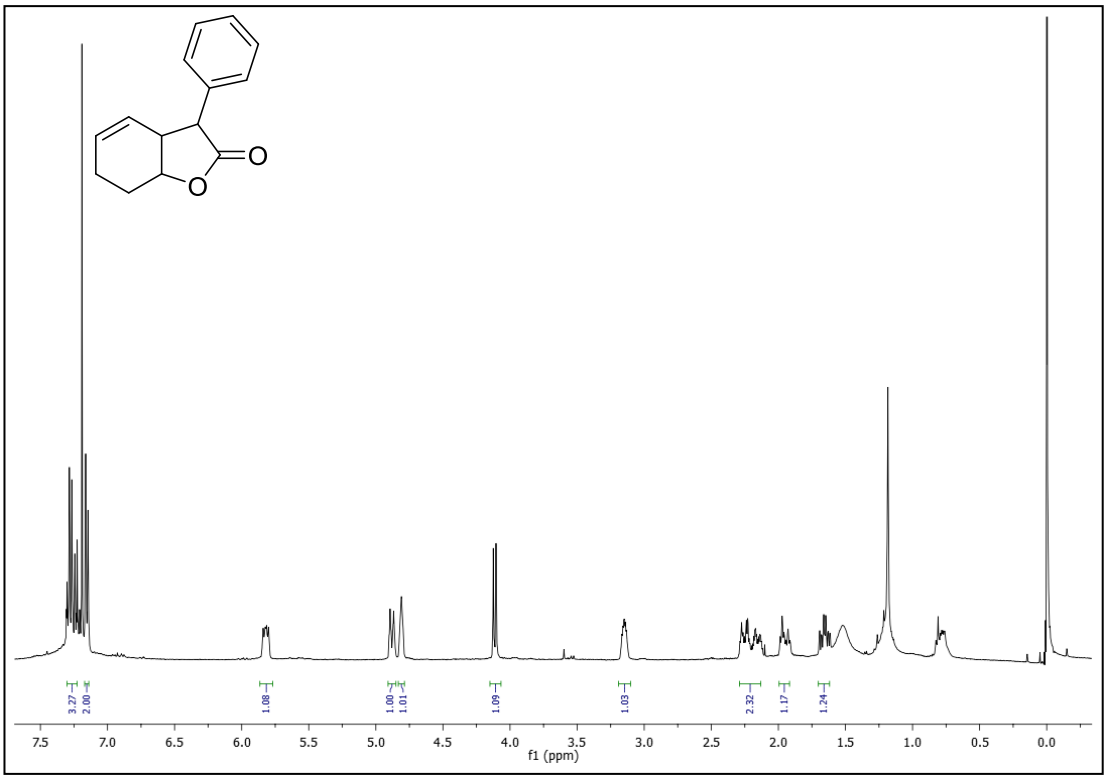


Figure 182 ^{1}H NMR Spectrum of Compound **95d** in $CDCl_3$

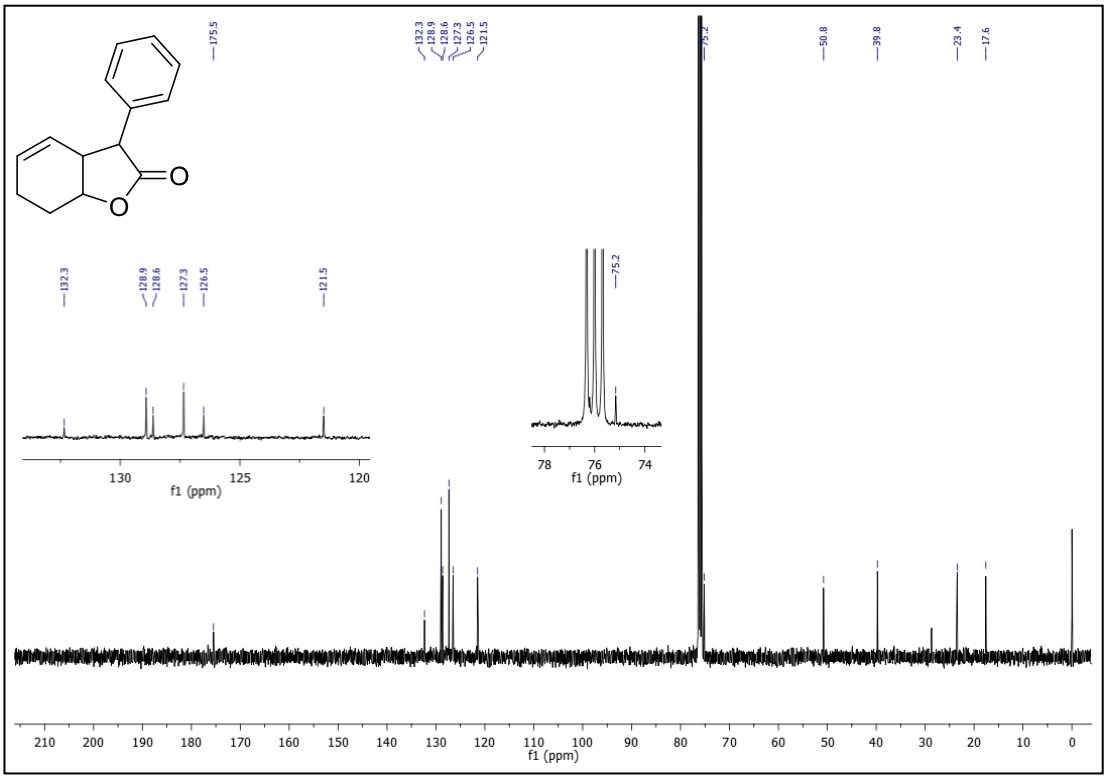


Figure 183 ^{13}C NMR Spectrum of Compound **95d** in $CDCl_3$

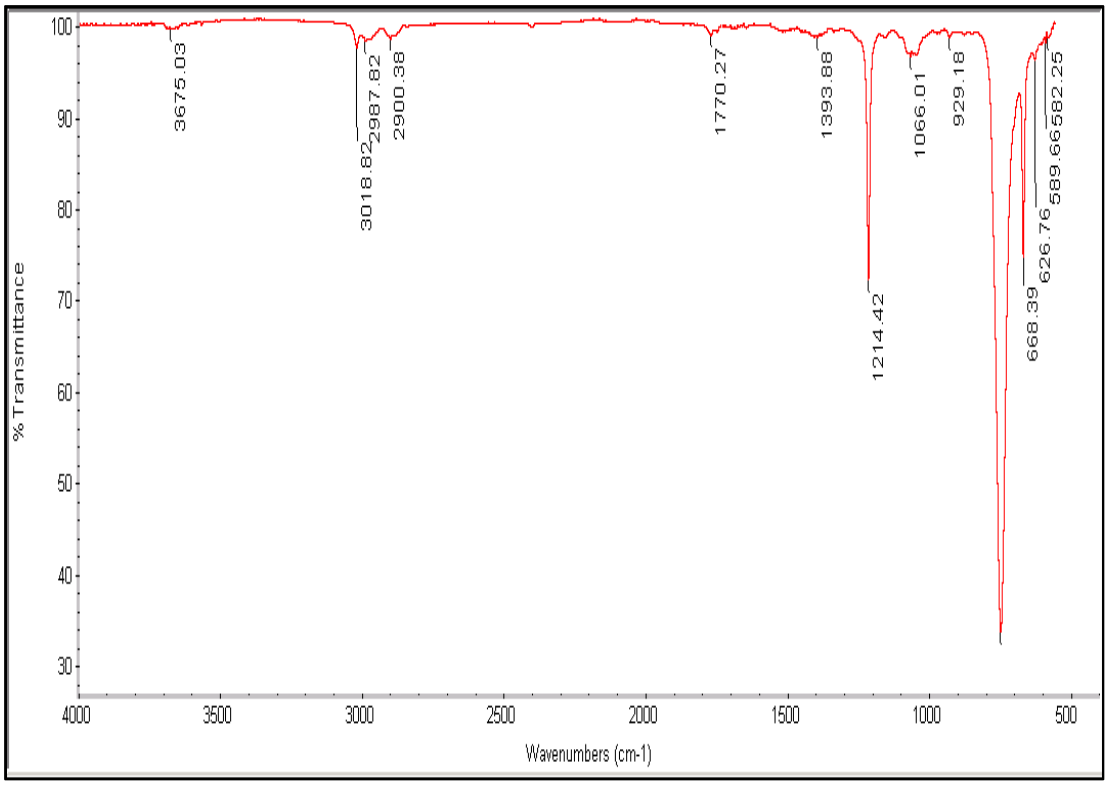


Figure 184 IR Spectrum of Compound **95d**

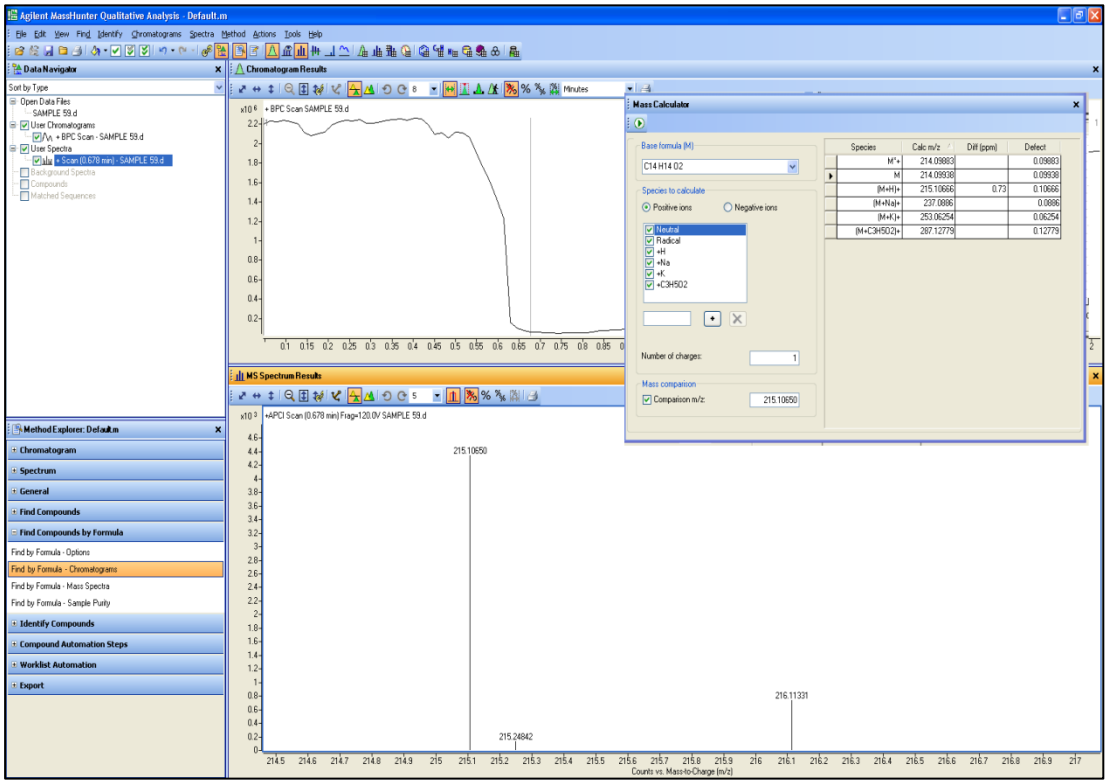


Figure 185 HRMS Spectrum of Compound **95d**

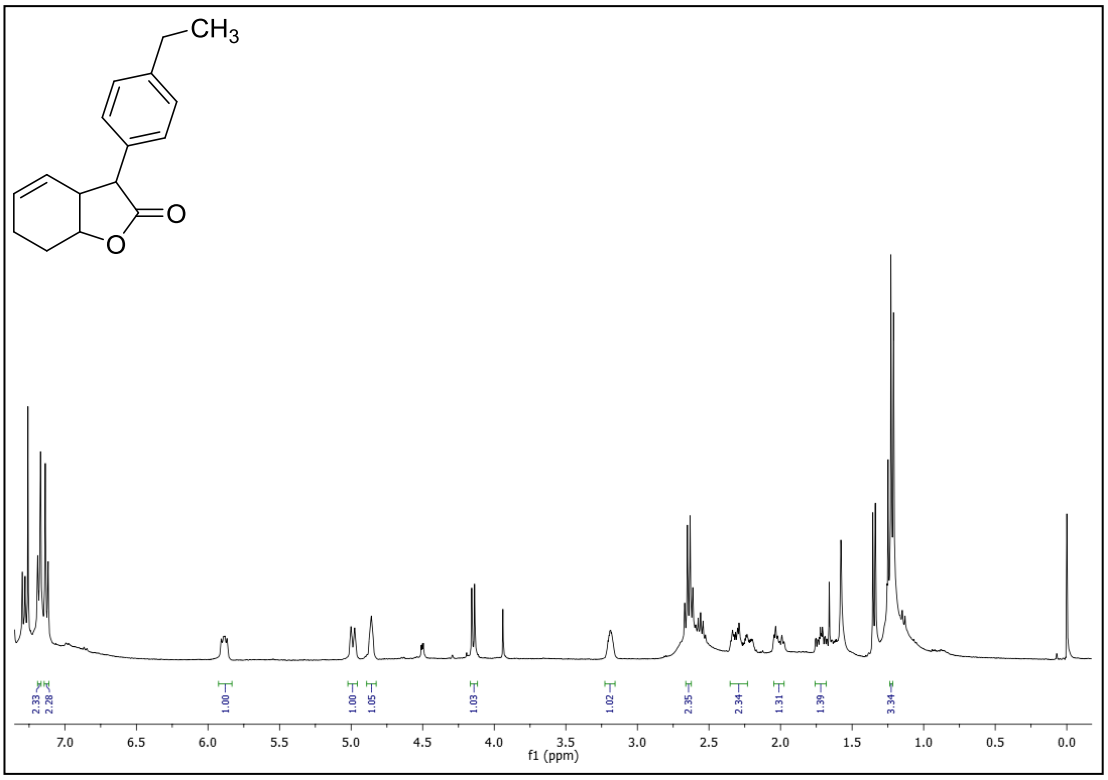


Figure 186 ^{1}H NMR Spectrum of Compound **95e** in $CDCl_3$

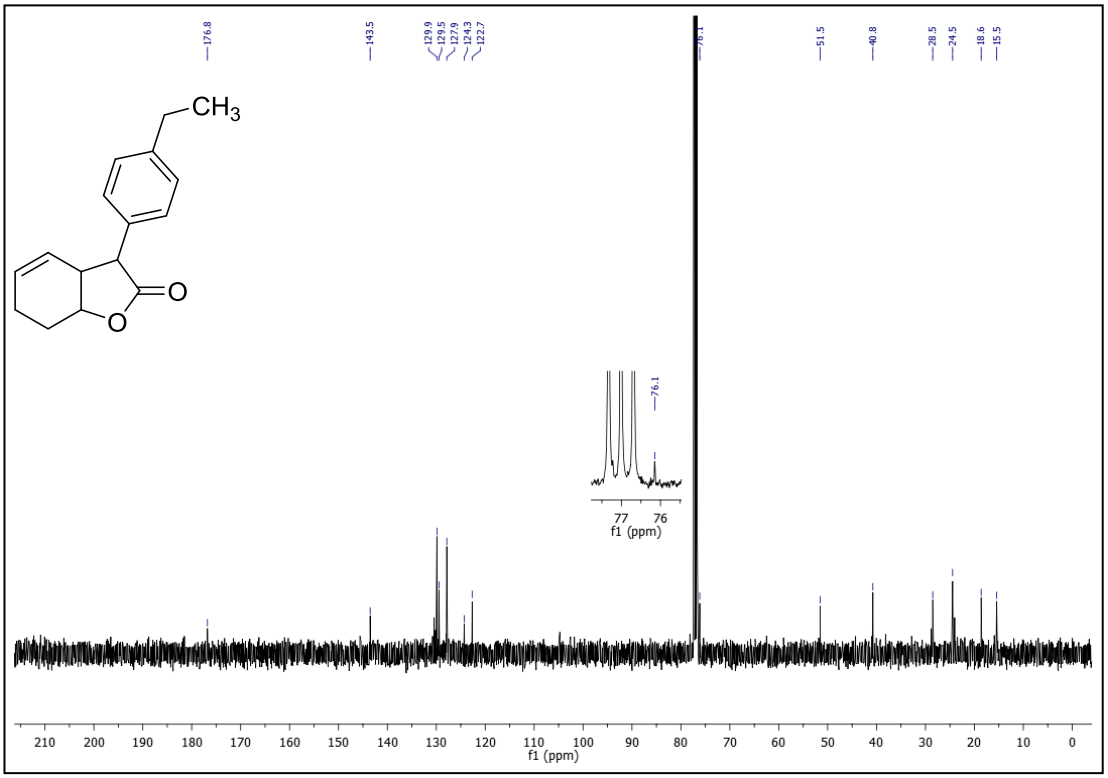


Figure 187 ^{13}C NMR Spectrum of Compound **95e** in $CDCl_3$

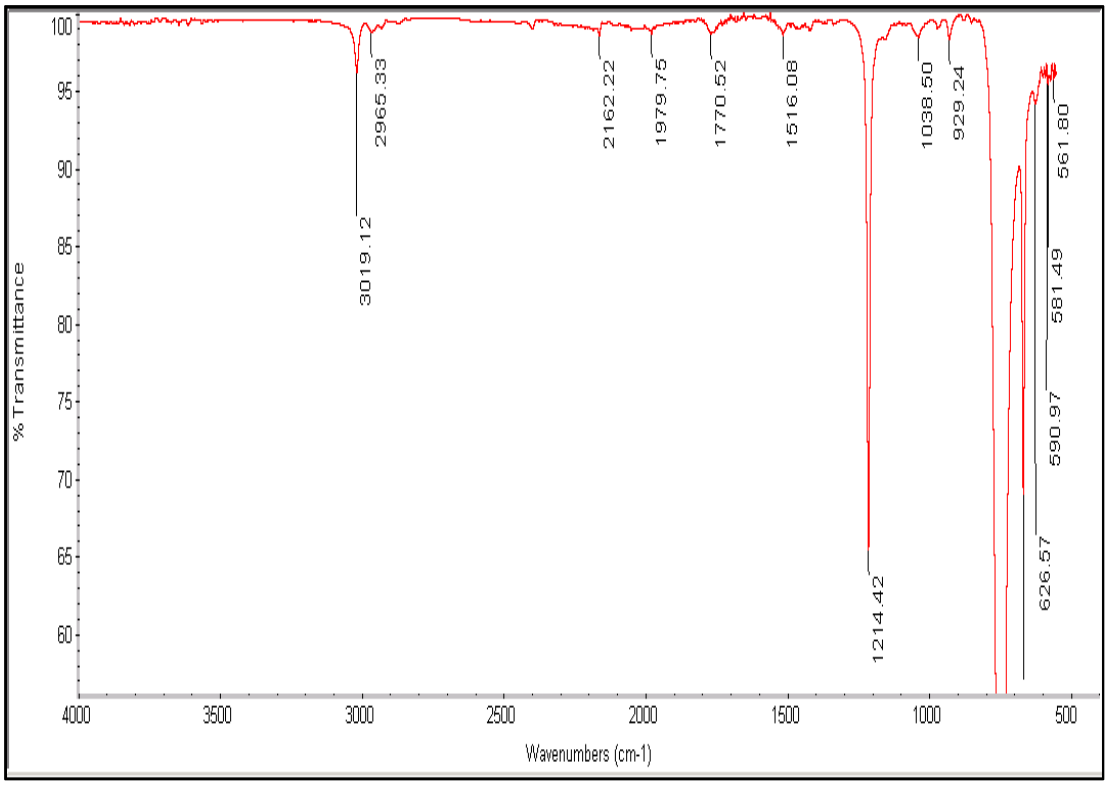


Figure 188 IR Spectrum of Compound **95e**

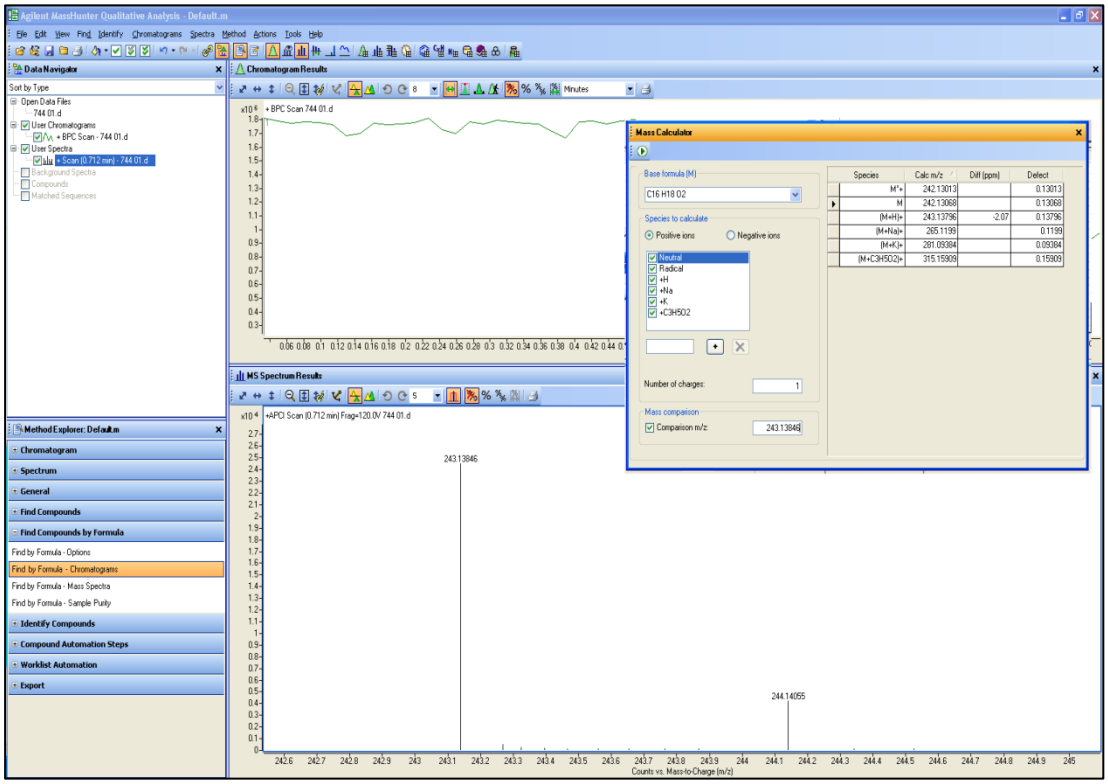


Figure 189 HRMS Spectrum of Compound **95e**

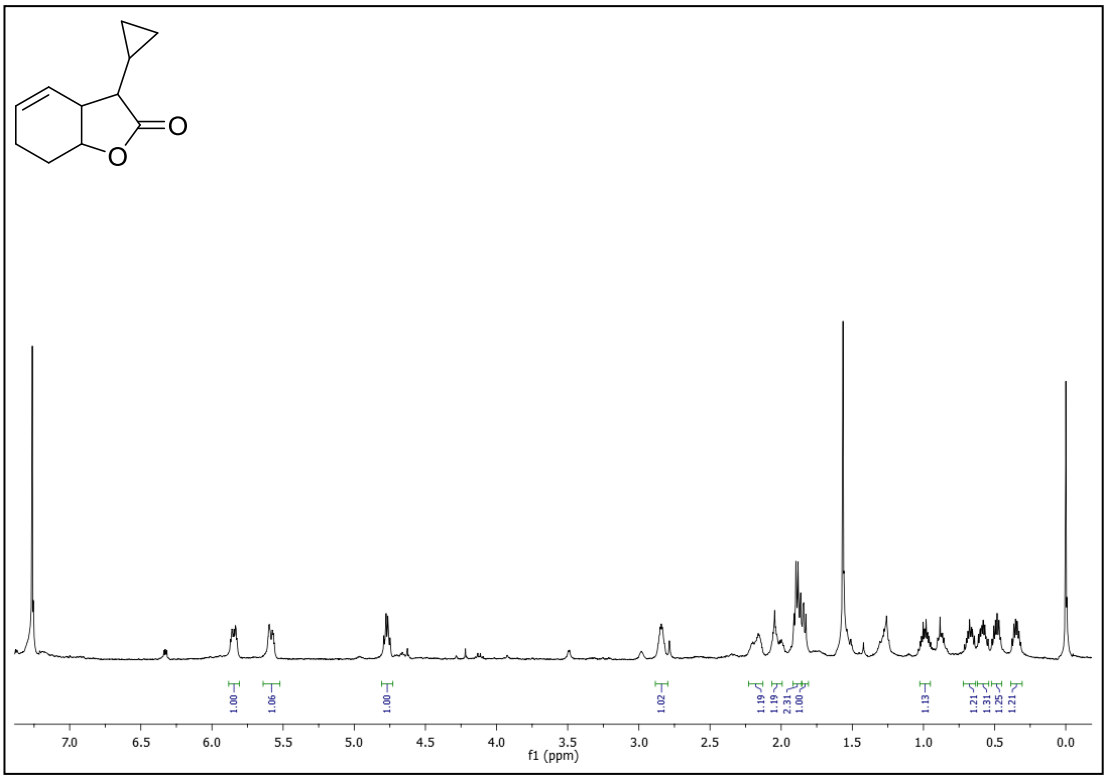


Figure 190 ^{1}H NMR Spectrum of Compound **95f** in $CDCl_3$

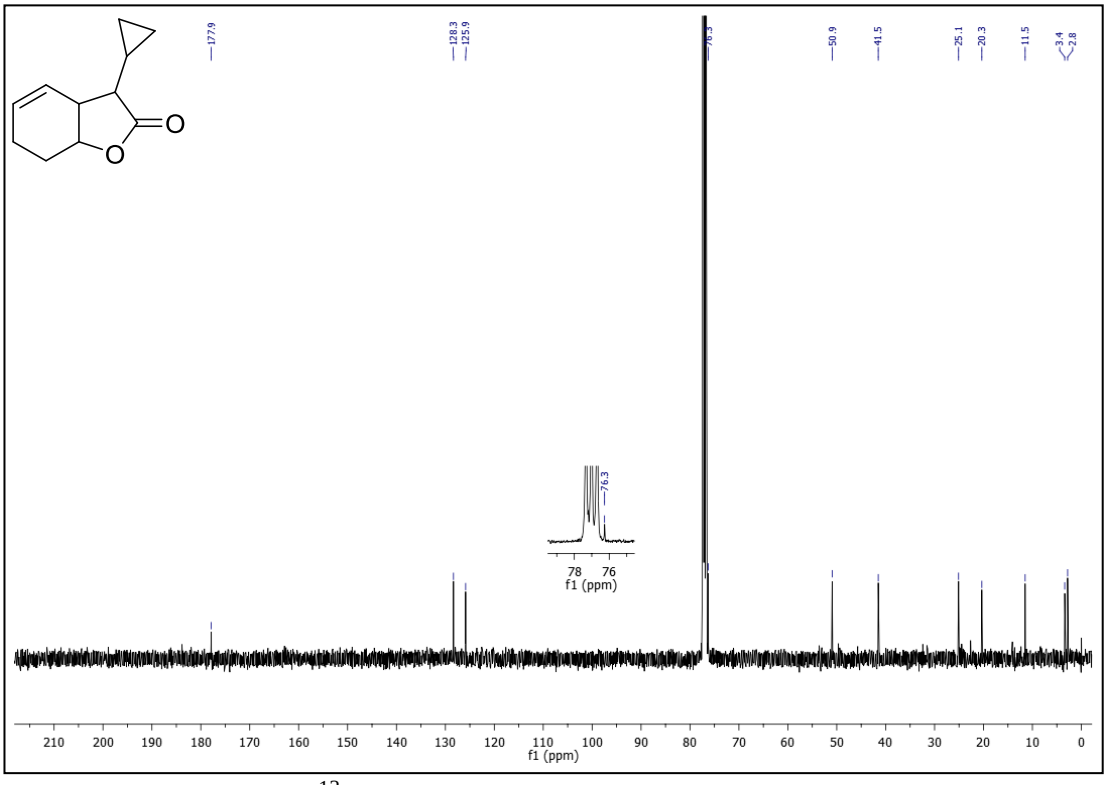


Figure 191 ^{13}C NMR Spectrum of Compound **95f** in $CDCl_3$

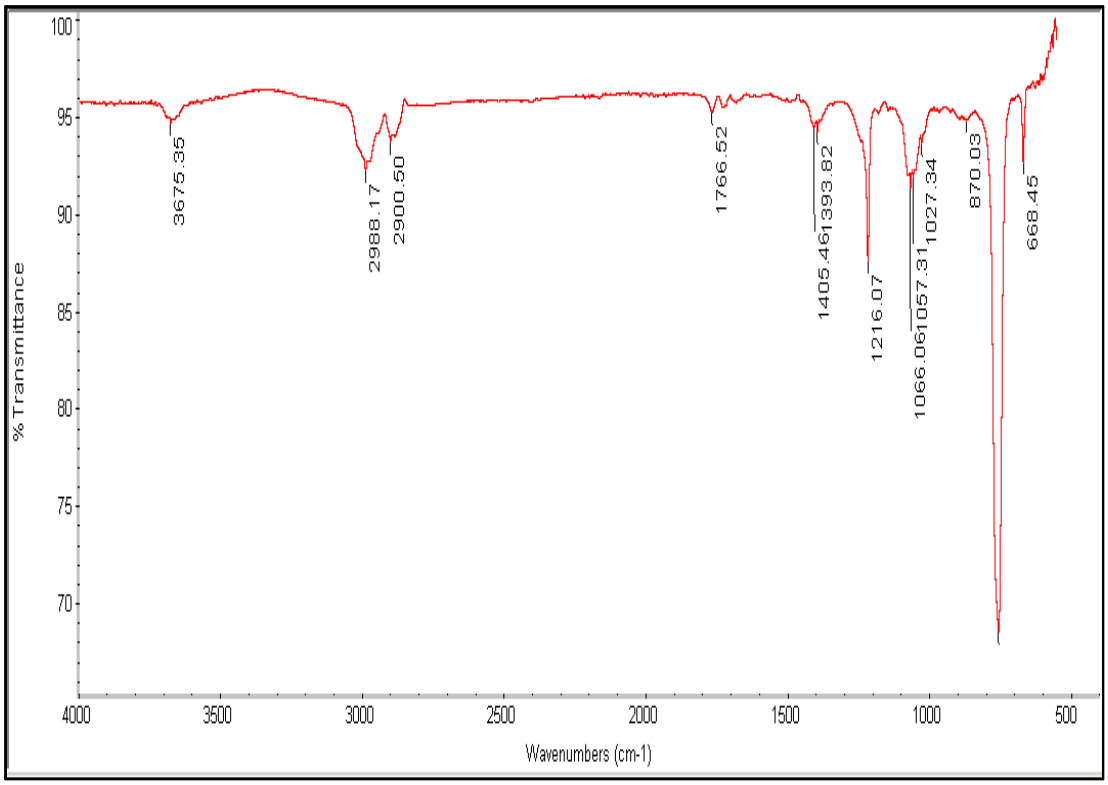


Figure 192 IR Spectrum of Compound **95f**

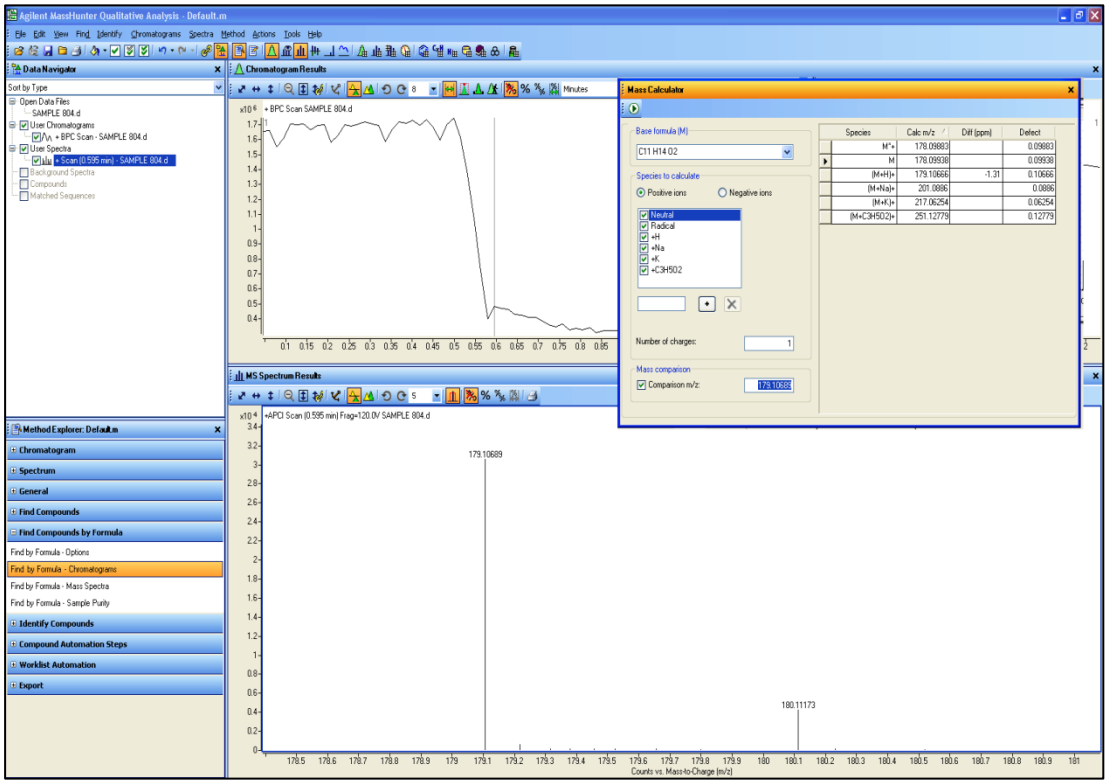


Figure 193 HRMS Spectrum of Compound **95f**

CURRICULUM VITAE

Personal Information

Name Surname	Furgan Aslanoğlu
Nationality:	Turkish (TC)
Date and Place of Birth:	20 September 1981, Van
Marital Status:	Married
Email:	f.aslanoglu@hotmail.com

Education

Degree	Institution	Year of graduation
PhD	METU	2018
MS	YYU	2007
BS	YYU	2004

Foreign Language

English (fluent)

Work Experience

Year	Place	Enrollment
2016−Present	MSU	Research and Teaching Assistant
2009−2016	METU	Research and Teaching Assistant

Publications

1 Akbaş, E.; **Aslanoğlu, F**.; Syntheses of Some New 1H-Pyrazole, Pyridazin-3(2H)-one, and Oxazin-4-one Derivatives, *Heteroatom Chemistry* **2006**, *17*, 8.

2. **Aslanoğlu, F.**; Akbaş, E.; Sönmez, M.; Anıl B.; Studies on Reactions of Pyrimidine Compounds: Synthesis and Reactions of 5-Benzoyl-4,6-Diphenyl-1,2,3,4-Tetrahydro-2-Thioxopyrimidine, *Phosphorus, Sulfur, and Silicon and the Related Elements* **2007**, *182*, 1589.

3. Akbaş, E.; **Aslanoğlu, F.**; Anıl, B.; Şener, A.; A Simple One Pot Synthesis 1,2,3,4,-Tetrahydro-2-thioxopyrimidine Derivatives., *Journal of Heterocyclic Chemistry*, **2008**, *45*, 1457.

4. Akbaş, E.; **Aslanoğlu, F.**; Studies on Reactions of Pyrimidine Compounds. 21. Microwave-Assisted Synthesis of 1,2,3,4-Tetrahydro-2-Thioxopyrimidine Derivatives., *Phosphorus, Sulfur, and Silicon and the Related Elements* **2008**, *183*, 82.
5. Akbaş, E.; Sonmez, M.; Anıl, B.; **Aslanoğlu, F.**; Synthesis and Spectral Studies of Pyranone Derivative and Its Cu(II), Co(II), Ni(II) and Zn(II) Complexes1, *Russian Journal of General Chemistry* **2008**, *78*, 1277.
6. Akbaş, E.; Sonmez, M.; Celebi, M.; **Aslanoğlu, F.**; Synthesis of some transition metal complexes of ligands derived from 5-phenyl-2,3-dihydro-2,3-furandione, *Journal of Chemical Research* **2008**, *5*, 256.

National Conference Proceeding

1. Akbaş, E., **Aslanoğlu, F.**, Sönmez, M., Bazı 5-benzoil-1,2,3,4-tetrahidro-2-tiyoksopirimidin Türevlerinin Sentezi, XX. Ulusal Kimya Kongresi, OKP-61, Kayseri, Türkiye, 4-8 Eylül 2006.
2. Sönmez, M., Akbaş, E., Çelebi, M., **Aslanoğlu, F.**, Bazı Yeni Enamid Ligandlar ile Ni(II) Ve Co(II) Komplekslerinin Sentezi, I. Ulusal Anorganik Kimya Günleri, Adana, Türkiye, 20-23 Nisan 2007.
3. **Aslanoglu F.**, Sudemen B., Balci M., Mn(OAc)3 ve Seryum Amonyum Nitrat Varlığında Sikloheptatrienin 1,3 Dikabonil Bileşikleriyle Reaksiyonlarının İncelenmesi, XXV. Ulusal Kimya Kongresi, Erzurum, Türkiye, 27 Temmuz-2 Eylül 2011.