ACYL AZIDES: APPLICATION TO THE SYNTHESIS OF VARIOUS HETEROCYCLES

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

BY

ÇAĞATAY DENGİZ

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF MASTER OF SCIENCE
IN
CHEMISTRY

NOVEMBER 2011

Approval of the thesis:

ACYL AZIDES: APPLICATION TO THE SYNTHESIS OF VARIOUS HETEROCYCLES

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Date: 17.11.2011

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

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ABSTRACT

ACYL AZIDES: APPLICATION TO THE SYNTHESIS OF VARIOUS HETEROCYCLES

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November 2011, 185 pages

Pyrazoles, isoindolinones, benzodizepinones and dihydroquinolinones are very important heterocycles for their biological properties. Many pharmaceutical agents include these units as core structures. Reactive molecules such as acyl azides, free radicals and formyl groups are used as key step reactants in these studies. Regiospesific hydrolysis and esterifications are used to reach target starting materials. Two different methodology are used for critical ring closure steps. Benzodiazepinones, and isoindolinones are obtained by base mediated ring closure reactions whereas thionyl chloride mediated procedure is used for dihydroquinolinones. Moreover, chloroacetonylation of the double bonds is also examined. Addition of acetylacetone to various alkenes was performed with in the presence of $Mn(OAc)_3$ and HCl. Removal of one of the acetyl groups with ammonia under very mild conditions provided compounds derived from chloroacetonylation of the double bonds.

Keywords: Acyl azides, pyrazoles, isoindolinones, benzodizepinones, dihydroquinolinones, chloroacetonylation.

ÖZ

AÇİL AZİTLER: ÇEŞİTLİ HETEROSİKLİK BİLEŞİKLERİN SENTEZİNDE UYGULAMALARI

Dengiz, Çağatay

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Balcı

Kasım 2011, 185 sayfa

Pirazoller, izoindolinonlar, benzodiazepinonlar ve dihidrokinolinonlar, biyolojik özellikleri sebebiyle çok önemli heterosiklik bileşiklerdir. Farmasötik ajanların çoğunda bu yapılar ana iskeleti oluşturur. Bu çalışmada, açil azitler, serbest radikaller ve formil grupları gibi reaktif moleküller anahtar basamak reaktantları olarak kullanılır. Hedef başlangıç bileşikleri sentezi için bölge seçici hidroliz ve esterleşme reaksiyonları kullanılmıştır. Kritik halka kapanması basamakları için iki farklı yol seçilmiştir. Benzodiazepinonlar ve izoindolinonlar için baz ortamında halka kapanması reaksiyonları denenirken, tiyonil klorür ortamındaki prosedür dihidrokinolinonlar için kullanıldı. Bunların yanında, çift bağların kloroasetonilasyonu da incelenen konulardandır. Asetilasetonun $Mn(OAc)_3$ ve HCl varlığında çeşitli alkenlere eklenmesi denenmektedir. Asetil gruplarından birinin çıkarılmasıyla ılımlı koşullarda çift bağların kloroasetonilasyonundan türeyen bileşikler sentezlenmiştir.

Anahtar Kelimeler: Açil azitler, pirazoller, izoindolinonlar, benzodiazepinonlar, dihidrokinolinonlar, kloroasetonilasyon.

To my family and Burçak,

ACKNOWLEDGEMENTS

I wish to express my sincere appreciation and thanks to my supervisor Prof. Dr. Metin Balcı for his guidance, valuable advices, moral support and for enlightening my professional and academic vision throughout my study.

I would like to express my sincere thanks to Dr. Sevil Özcan and Murat Kadir Deliömeroğlu for their valuable guidance, discussion and support.

I would like to thank to NMR specialist Zehra Uzunoglu for the NMR experiments.

I would like to express my great thanks to all the members of SYNTHOR Research Group especially to Zeynep, Emrah, Nalan, Yasemin, Merve, Tolga and Serdal for their friendship and helps.

I wish to express my appreciation to the academic staff of METU Department of Chemistry for their professional support and guidance to the students of Department of Chemistry.

I am also indebted to TUBITAK (Scientific and Technological Research Council of Turkey, 2228) for their financial support.

I would like to thank my friends Elif Ertem, Özden Çelikbilek, Şeyma Ekiz and Esra Eroğlu for their precious friendship.

I would like to give the biggest thanks my family who have made everything possible for me with their love, affection, support and guidance throughout my whole life. The completion of this study would not have been possible without them.

Finally, I would like to thank Burçak Dölek for her understanding and patience. It cannot be possible to complete this thesis without her support.

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LIST OF ABBREVIATIONS

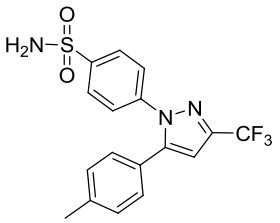
DCM:	Dichloromethane
EtOAc:	Ethyl acetate
CDI:	Carbonyldiimidazole
TMS:	Tetramethylsilane
LDA:	Lithium diisopropylamide
BHT:	Benzotriazole
LiHMDS:	Lithium bis(trimethylsilyl)amide
Fmoc:	Fluorenylmethyloxycarbonyl
Boc:	*N-tert*-butoxycarbonyl
EDC.HCl:	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
THF:	Tetrahydrofuran
NMR:	Nuclear magnetic resonance
IR:	Infrared
J:	Coupling constant
Hz:	Hertz
ppm:	Parts per million
mg:	milligram
mmol:	millimole

CHAPTER 1

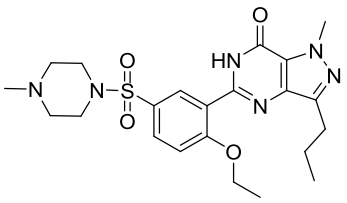
INTRODUCTION

1.1 Pyrazoles

Pyrazoles are known as extensively used heteroaromatic compounds in the pharmaceutical industry.[1] Many pharmaceutical agents include pyrazole units as core structures. Pyrazole skeleton based molecules show antiinflammatorial and antimicrobial properties.[2-4] Two very famous pyrazole-based COX-2 inhibitors are Celecoxib (**1**) and Sildenefil (Viagra) (**2**)**.**[2,5]



Celecoxib (1)

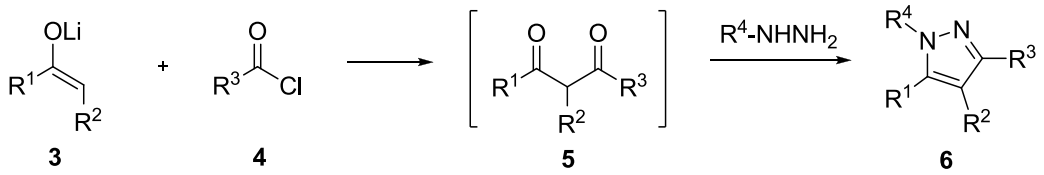


Sildenefil (2)

Importance of the pyrazole based molecules due to their potential bioactivity attracts high attention of scientists.

1.1.1 Synthesis of pyrazoles

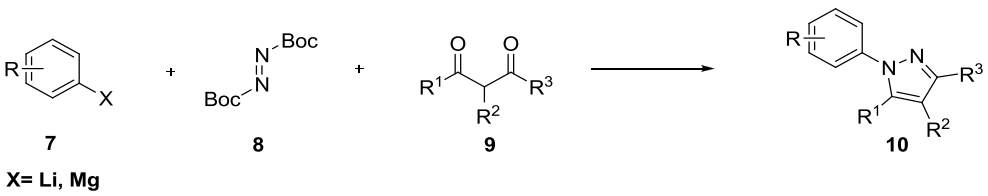
Numerous methods were published for construction of pyrazole based structures. The most classical synthesis of pyrazoles is achieved by the reaction of 1,3-diketones with hydrazine as shown in Scheme 1.[6]



Scheme 1 Synthesis of pyrazole **6**

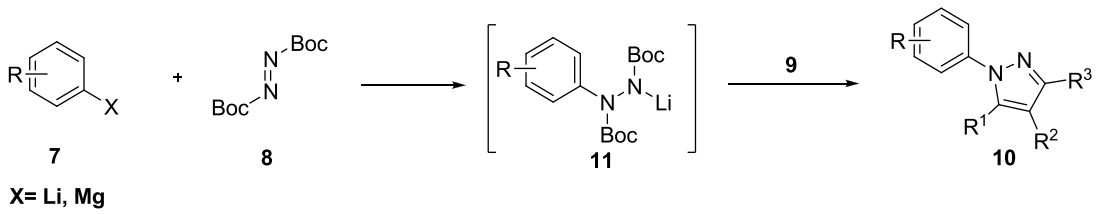
The first step is the synthesis of 1,3-diketones **5** from reaction of the ketones and acid chlorides **4** in the presence of LiHMDS. Formed enolates **3** react efficiently with acid chlorides **4**. After obtaining 1,3-diketones **5** as reaction intermediates, in situ conversion to pyrazoles were obtained by addition of hydrazine derivatives. This procedure is very important because pyrazole containing fused rings can be obtained very easily by using cyclic ketones as starting materials. In addition to these advantages, this method is extremely fast and chemoselective.

More recently, a simple one-pot method was designed to obtain *N*-aryl pyrazoles **10** (Scheme 2).[7] In this study, target pyrazole derivatives were obtained by using aryl nucleophiles **7**, di-*tert*-butylazodicarboxylate **8** and 1,3-dicarbonyl compounds **9**. Although these target molecules are not known natural products, they are very important for pharmaceutical industry.



Scheme 2 Synthesis of *N*-aryl pyrazoles **10**

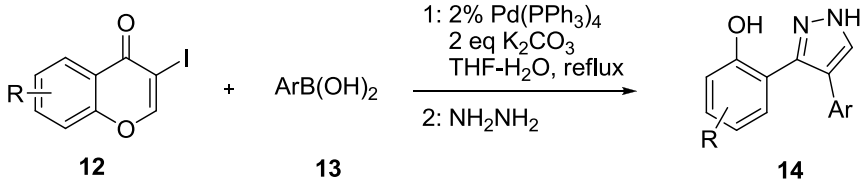
According to proposed mechanism, first step includes the formation of bis-Boc protected aryl hydrazine **11** by the addition of aryl lithium species **7** to di-*tert*-butyl azodicarboxylate **8** (Scheme 3). Then, addition of this intermediate **11** to 1,3-dicarbonyl compounds **9** gives target pyrazole molecules **10**.



Scheme 3 *N*-aryl pyrazole formation mechanism

This quick and simple one-pot method provides an easy access to crucial *N*-aryl pyrazole derivatives. It can be also applied to synthesis of indazole derivatives.

Although there is much interest in synthesis of pyrazole structures, relatively little study has been carried out on 3,4-disubstituted derivatives. Hu *et al.* have reported the synthesis of 1,3,4-substituted pyrazoles **14** via reaction of iodochromone **12**, phenylboronic acid **13**, and hydrazine (Scheme 4).[8] The mechanism includes Suzuki coupling and condensation reactions.



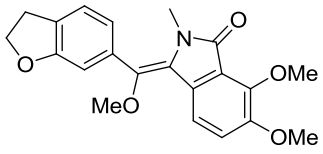
Scheme 4 Synthesis of 1,3,4-substituted pyrazoles

In this process, Suzuki coupling is performed by phenylboronic acid **13** and iodochromone **12**. Then addition of hydrazine to this mixture gives the target pyrazole derivatives **14** as condensation products. By using the same methodology, isoaxole derivatives are also synthesized using hydroxyl amine instead of hydrazine.

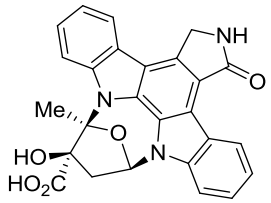
1.2 Isoindolinones

Many natural substances include the isoindolinone skeleton in their structure. One of the most common example of them is pictonamine (**15**) which is isolated from the

Chilean Barberis.[9] Another indolocarbazole structure which is isolated from natural sources is staurosporine (**16**).[10]

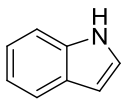


Pictonamine (15)

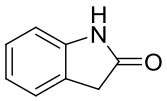


Staurosporine (16)

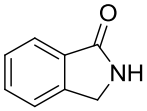
In literature, indolin-2-one (**18**), an oxidation product of indole (**17**), and its derivatives are known as tyrosine kinase inhibitors due to their selectivity towards different receptor tyrosine kinases.[11] Various indolin-2-one (**18**) derivatives was monitored as bioactive compounds in extracts of the herb, *isotis tinctoria.*[12] Active research on bioactivities of indolinones (**18**) explains the increasing number of studies for their synthesis.



Indole (17)



Indolin-2-one (18)



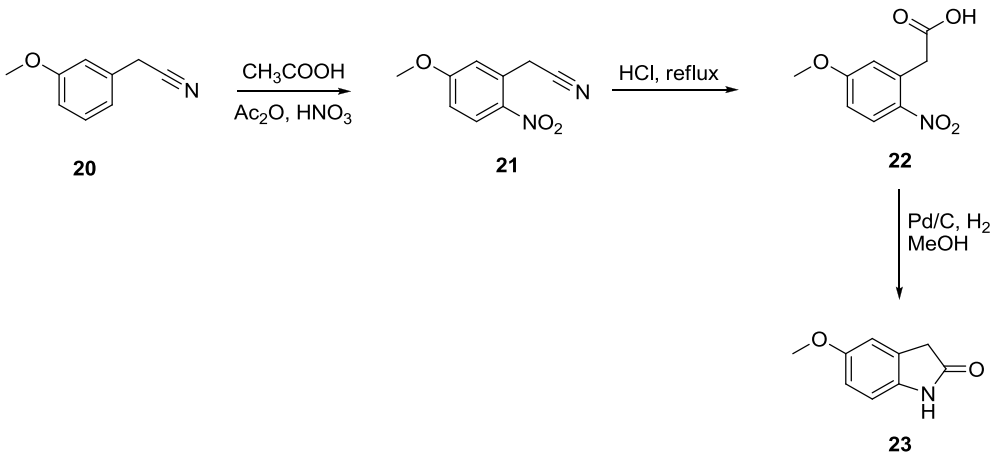
Isoindolin-1-one (19)

Isoindolin-1-one (**19**) structure is also very similar with indolin-2-one (**18**) and indole (**17**) structure. Due to this similarity, isoindolinone derivatives (**19**) attract much interest both in medical chemistry and synthetic organic chemistry. Recently, many isoindolinone derivatives (**19**) were synthesized and screened.[13] Moreover, some substituted isoindolinone structures show potent metabotropic glutamate receptor

antagonist activity.[14] Some derivatives also have antipsychotic-like effects in animals and some other derivatives were selected for treatment of schizophrenia.[15-16]

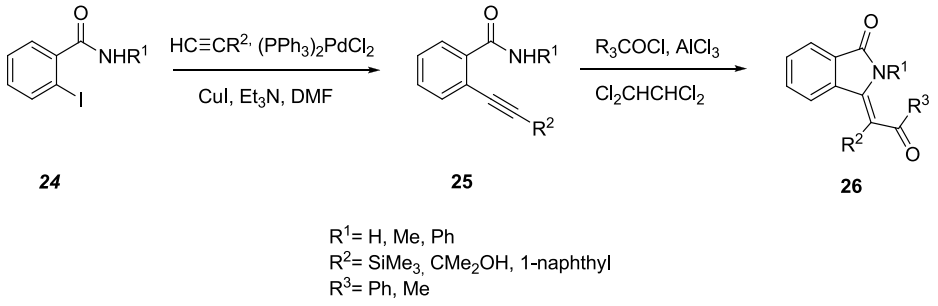
1.2.1 Synthesis of isoindolinones

Several methods have been published for the synthesis of isoindolinones (**19**). Malogni *et al.* have published the synthesis of indolin-2-one derivatives by starting from 2-(3-methoxyphenyl)acetonitrile **20**.



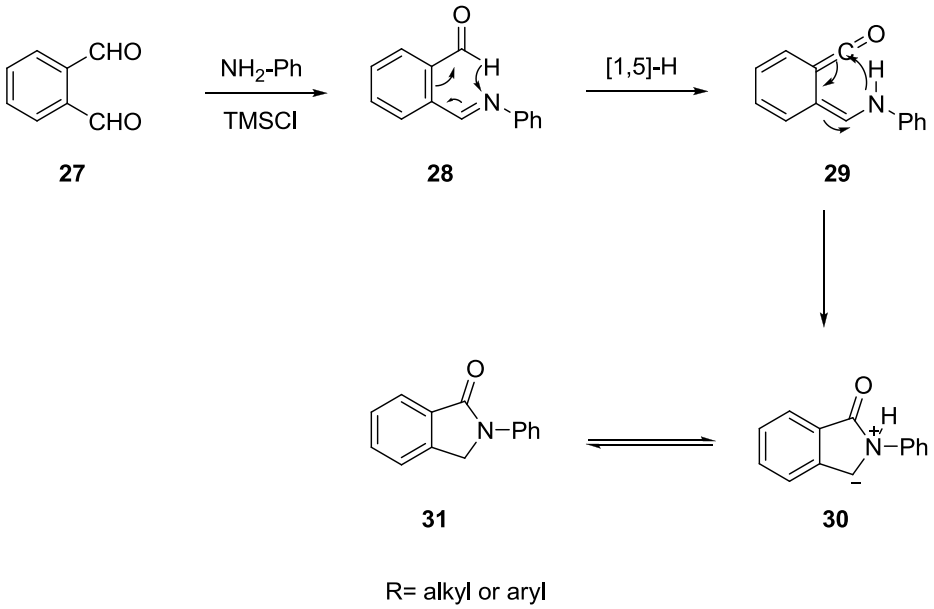
Scheme 5 Synthesis of indolin-2-one derivative **23**

Firstly, 2-(3-methoxyphenyl)acetonitrile **20** was nitrated with electrophilic nitration by using HNO_3, acetic anhydride and acetic acid. Then, subsequent hydrolysis of the nitrile group gave the target carboxylic acid derivative **22.** Finally, reduction of the carboxylic acid derivative **22** formed indolin-2-one derivative **23** (Scheme 5).[17]



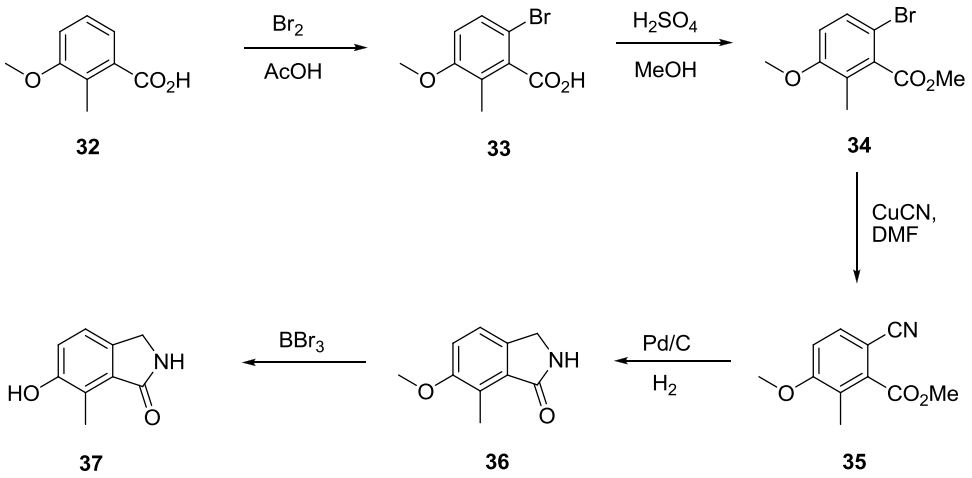
Scheme 6 Palladium catalyzed isoindolinone synthesis

Kundu *et al.* published another methodology for the synthesis isoindolinones by using palladium catalyzed ring closure mechanism. First step includes the Sonogashira coupling reaction between 2-iodobenzamides **24** and acetylene derivatives. Then, ring closure reaction was facilitated by using acylation reagents (Scheme 6).[18]



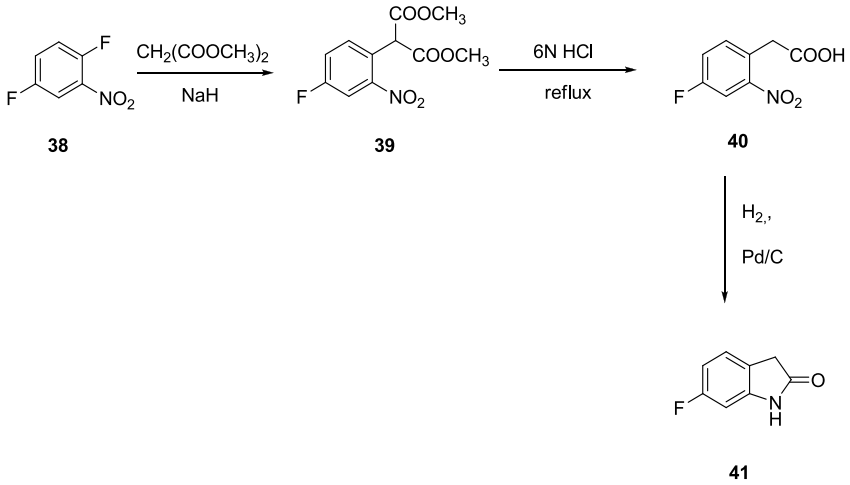
Scheme 7 Rearrangement of *o*-phthalaldehyde

Rearrangement of *o*-phthalaldehyde **27** with primary amines was examined to explore the reaction mechanism (Scheme 7).[19] TMSCl is used as catalyst for this reaction. According to the related information about the reaction mechanism of *o*-phthalaldehyde and primary amines, it is shown that intermediate **28** has crucial role in providing the target compounds based on computational studies.[20] After the formation of the intermediate **28**, [1,5] *H*- sigmatropic rearrangement gave the final isoindolinone derivatives **31**.



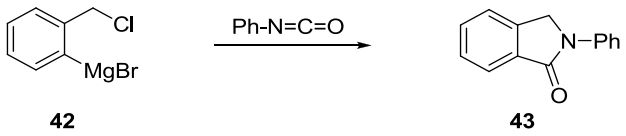
Scheme 8 Synthesis of isoindolin-1-ones **38**

Recently, Pfizer described the preparation of a series of isoidolin-1-ones **37** (Scheme 8).[21] An relatively easy pathway was followed to synthesize them. Starting from the 3-methoxy-2-methyl benzoic acid **32**, regioselective bromination was done by Br_2/AcOH in water. Then, bromoester **34** was obtained by esterification reaction by using MeOH/H_2SO_4. The next step was the cyanation with CuCN. The molecule **35** was reduced by Pd/C, H_2 to afford free amine and spontaneous ring closure gave the isoindolinone product **36**. Treatment of **36** with BBr_3 gave the target molecule **37** in high yield.



Scheme 9 Synthesis of fluoro substituted indolinone **42**

Sun *et al.* described the synthesis of fluoro substituted indolinone compound **41** (Scheme 9).[11] Starting from the 2,5-difluoronitrobenzene **38**, compound **41** was synthesized successfully. First step was the displacement of fluoro group by dimethylmalonate followed by decarboxylation with 6N HCl to obtain compound **40**. Lastly reductive cyclization gave the final product **41**.



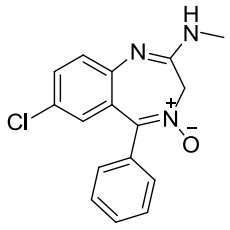
42 **43**

Scheme 10 Synthesis of compound **43**

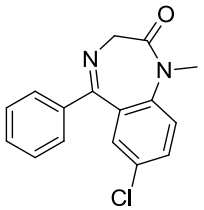
In another study, reaction of phenyl isocyanate and arylmagnesium reagent **42** gave the target molecule **43** in high yield (Scheme 10).[22]

1.3 Benzodiazepinones

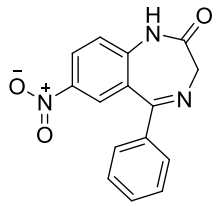
Basically, benzodiazepinones can be defined as seven membered heterocyclic compounds which include the benzene ring and diazepine part. These molecules are very popular due to sedative, tranquilizing effects of diazepam.[23] Studies on this area led to the synthesis of many benzodiazepinone derivatives. Some of them showed important bioactivity towards diseases like cancer, HIV and cardiac arrhythmia.[24]



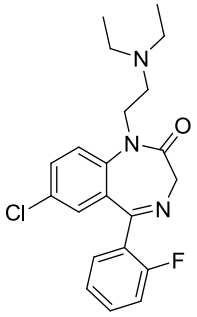
Chlordiazepoxide (44)



Diazepam (45)



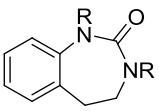
Nitrazepam (46)



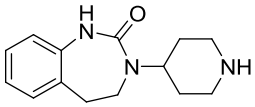
Flurazepam (47)

Leo Sternbach is the scientist who discovered accidentally the first benzodiazepine which is known as chlordiazepoxide (Librium) (**44**). Then diazepam (Valium) (**45**) was accepted as drug due to its better activity results. Another derivative Nitrazepam (**46**) was used against sleeping problems. Lastly, Flurazepam (**47**) was introduced to the literature in 1973.[25]

There are plenty of benzodiazepinone derivatives, which are named as 1,3-, 1,4-, 1,5- 2,4-benzodiazepinones. 1,3-Benzodiazepinones take great interest due to activity results of known examples.



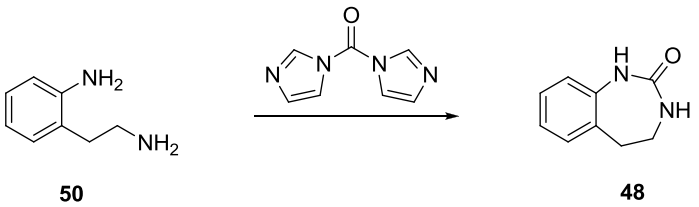
1,3-Benzodiazepin-2-ones 48



49

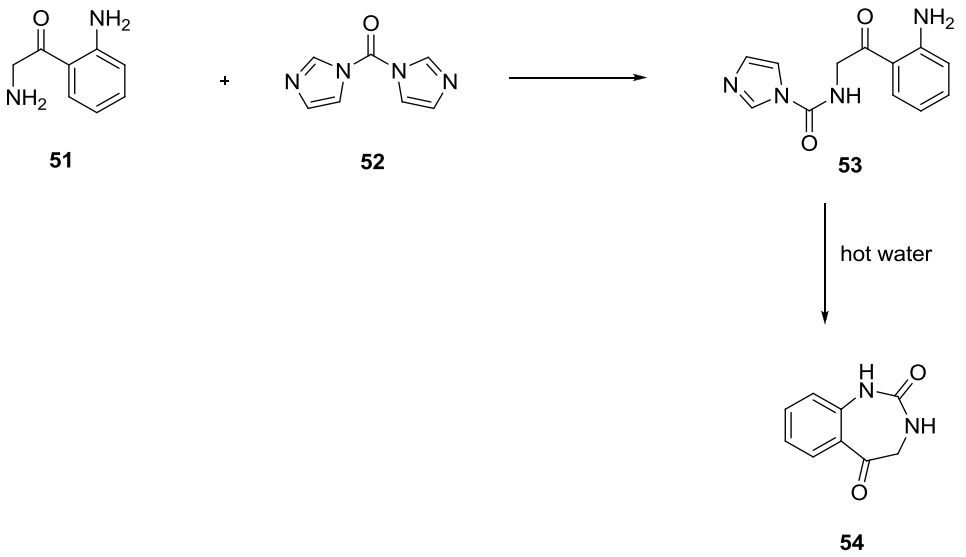
Some derivatives of 1,3-benzodiazepin-2-ones **48**, such as **49** piperidine ring substituted at nitrogen are known as calcitonin gene-related peptide receptor antagonists for the treatment of migraine.[26]

1.3.1 Synthesis of benzodiazepinones



Scheme 11 Synthesis of 1,3-benzodiazepin-2-one by CDI

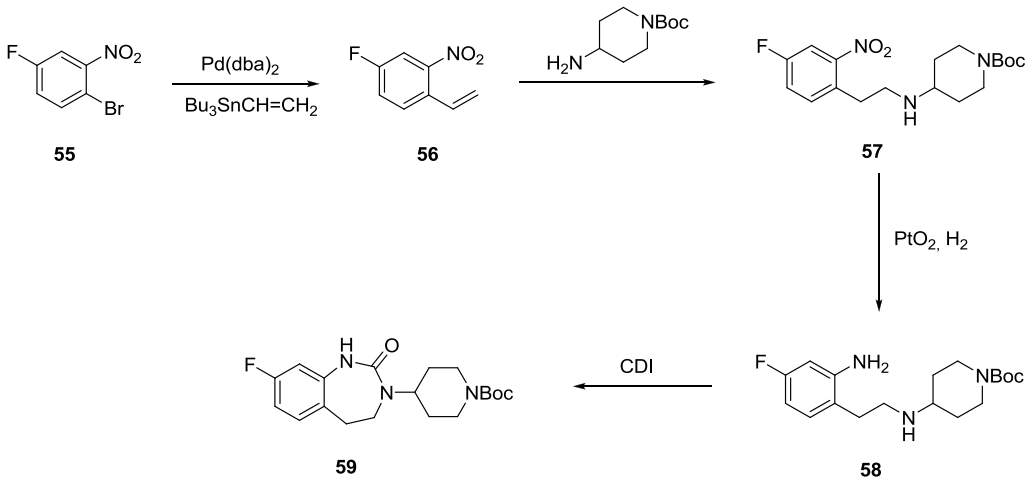
Easiest way to reach 1,3-benzodiazepin-2-one skeleton **48** is treatment of diamine compound **50** with CDI (Scheme 11) .[27]



Scheme 12 Synthesis of benzodiazepine-di-one **54**

In the Scheme 12, Taylor *et al.* used carbonyldiimidazole **52** with diamine molecule **51**. Reaction is very similar to the study in Scheme 11. Only difference is that starting material **51** includes a carbonyl group. Moreover, intermediate **53** could be isolated. Heating compound **53** with water gave the target benzodizepin-di-one molecule **54** (Scheme 12).[28]

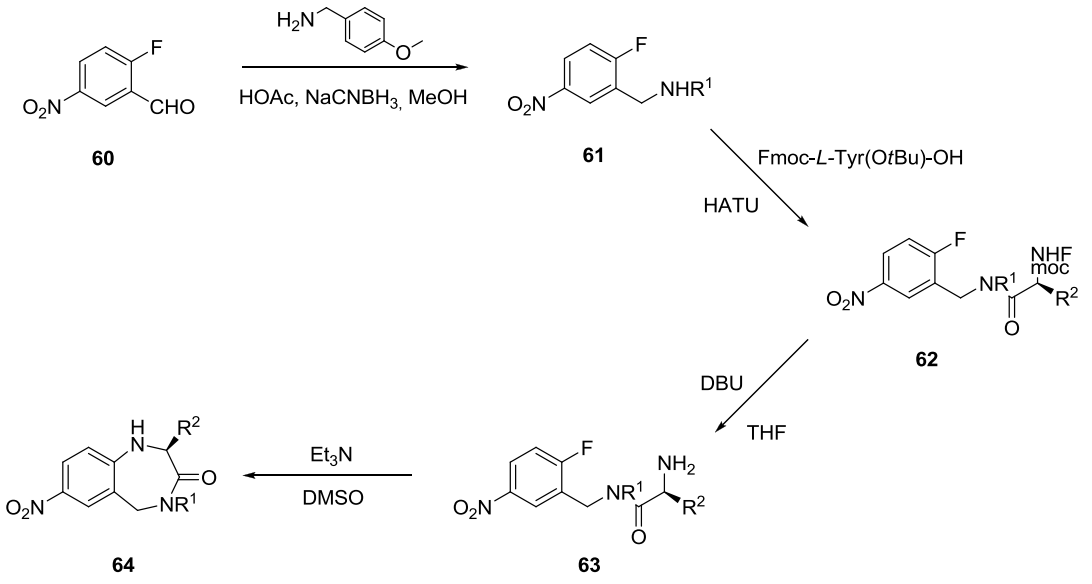
Recently, Han and co-workers successfully synthesized the benzodiazepinone derivatives (Scheme 13).[29] First step is the Stille-coupling reaction of *o*-halonitrobenzene **55**. After that, Michael addition of *tert*-butyl 4-aminopiperidine-1-carboxylate to the activated vinyl compound **56** gave the compound **57**. Then, hydrogenation of the compound **57** with PtO_2/H_2 gave the amine **58** in good yield. Last step of the study was the cyclic urea formation by using CDI. With application of this method, many type of benzodiazepinone derivatives were synthesized. Deprotection of Boc group was done by using HCl at the end of ring closure reaction.



Scheme 13 Synthesis of benzodiazepinone **59**

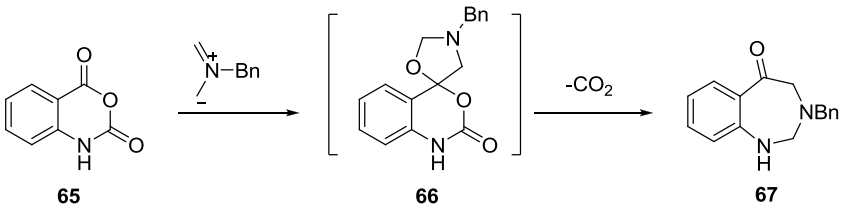
In Scheme 14, Deschrijver *et al.* described the synthesis of 1,4-benzodiazepinone derivatives **64** by four steps starting from 2-fluoro-5-nitro-benzaldehyde **60**.[30] The methodology includes the reductive amination of starting compound **60** with 4-methoxybenzylamine by using sodium cyanoborohydride ($NaCNBH_3$). Reductive amination is a well-known method to synthesize amine compounds from ketones and aldehydes. First step is the formation of hemiaminal intermediate followed by water elimination to give imines. After addition of cyanoborohydride, hydrogenation of imines gives the target amino compounds. Second step of the synthetic pathway includes coupling reaction of fluorenylthyloxycarbonyl (Fmoc) protected amino

acids with secondary amine **61** to give compound **62**. In this step, 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,2,2-tetra-methyl uranium hexafluoro phosphate (HATU) was used as coupling agent. Deprotection was done by using bulky base 8-diazabicyclo[5.4.0]undec-7-ene (DBU) to prevent unwanted nucleophilic aromatic substitution due to activated benzene ring. Final cyclization step is the nucleophillic aromatic substitution by deprotected amine **63** occurred smoothly by Et_3N in DMSO. Nucleophilic aromatic substitution reactions are quite important reactions for organic synthesis. There should be good leaving group such as halide on the aromatic ring and electron withdrawing group is needed to stabilize the intermediate that is formed.



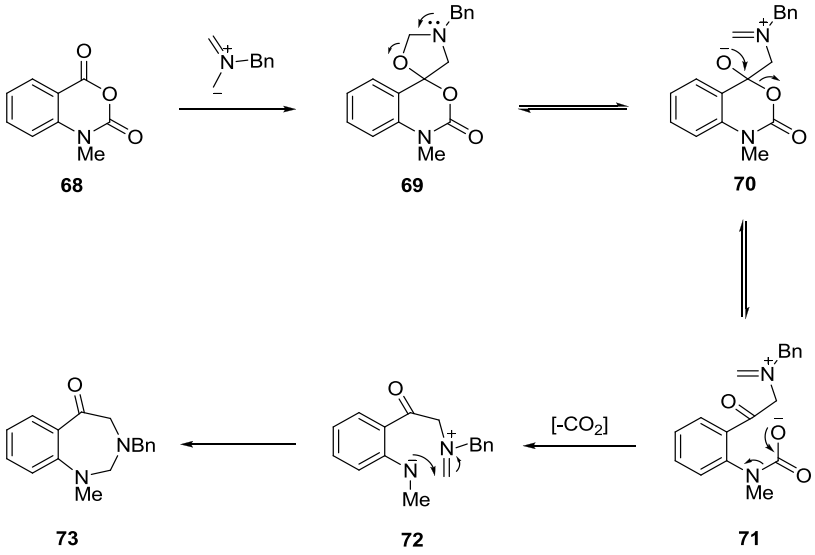
Scheme 14 Synthesis of 1,4-benzodiazepinone derivatives **64**

Ryan *et al.* published an article about benzodiazepinone synthesis by azomethine ylide (Scheme 15).[31]



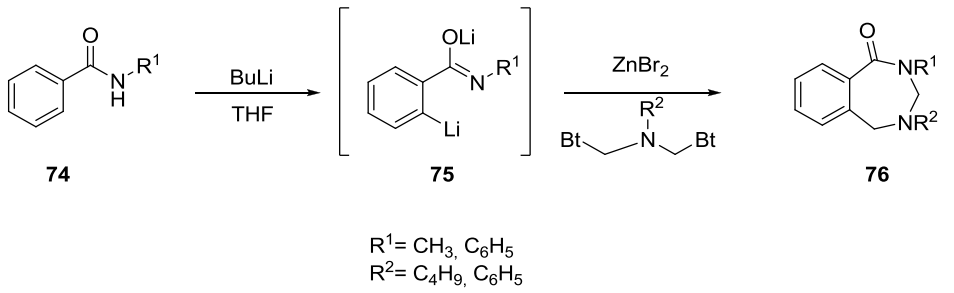
Scheme 15 Synthesis of benzodiazepinone by azomethine ylide

According to the proposed mechanism, azomethine ylides undergo a 1,3-dipolar cycloaddition reaction with anhydride **65** to give oxazolidine intermediate **66** followed by cascade ring opening-decarboxylation-ring closing reactions to obtain benzodiazepinone molecule **67** (Scheme 16).



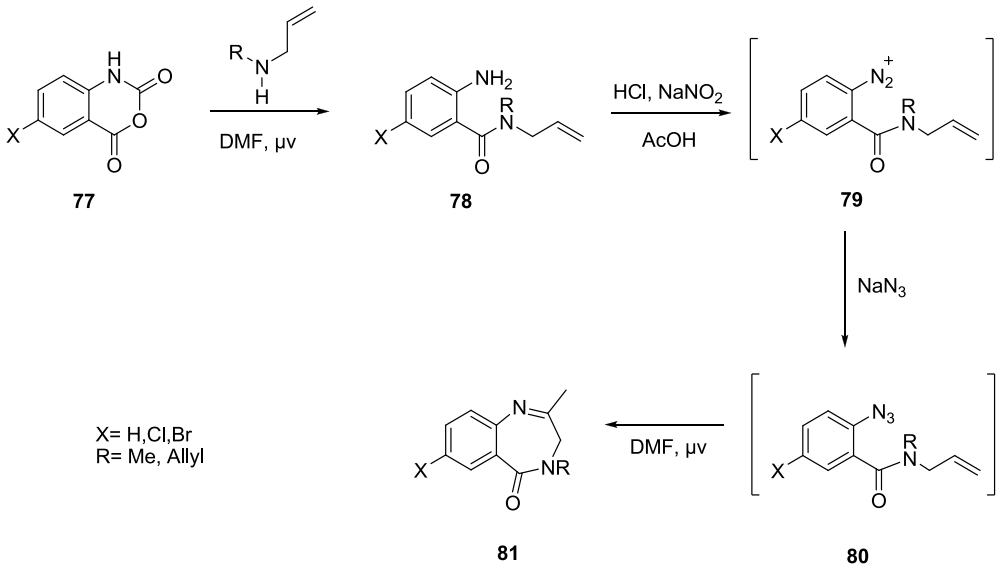
Scheme 16 Synthesis benzodiazepinone **73** by cascade reactions

Katritzky *et al.* showed the formation of 2,4-benzodiazepin-1-ones by one-pot synthesis (Scheme 17).[32]



Scheme 17 Synthesis of 2,4-benzodiazepin-1-ones **76**

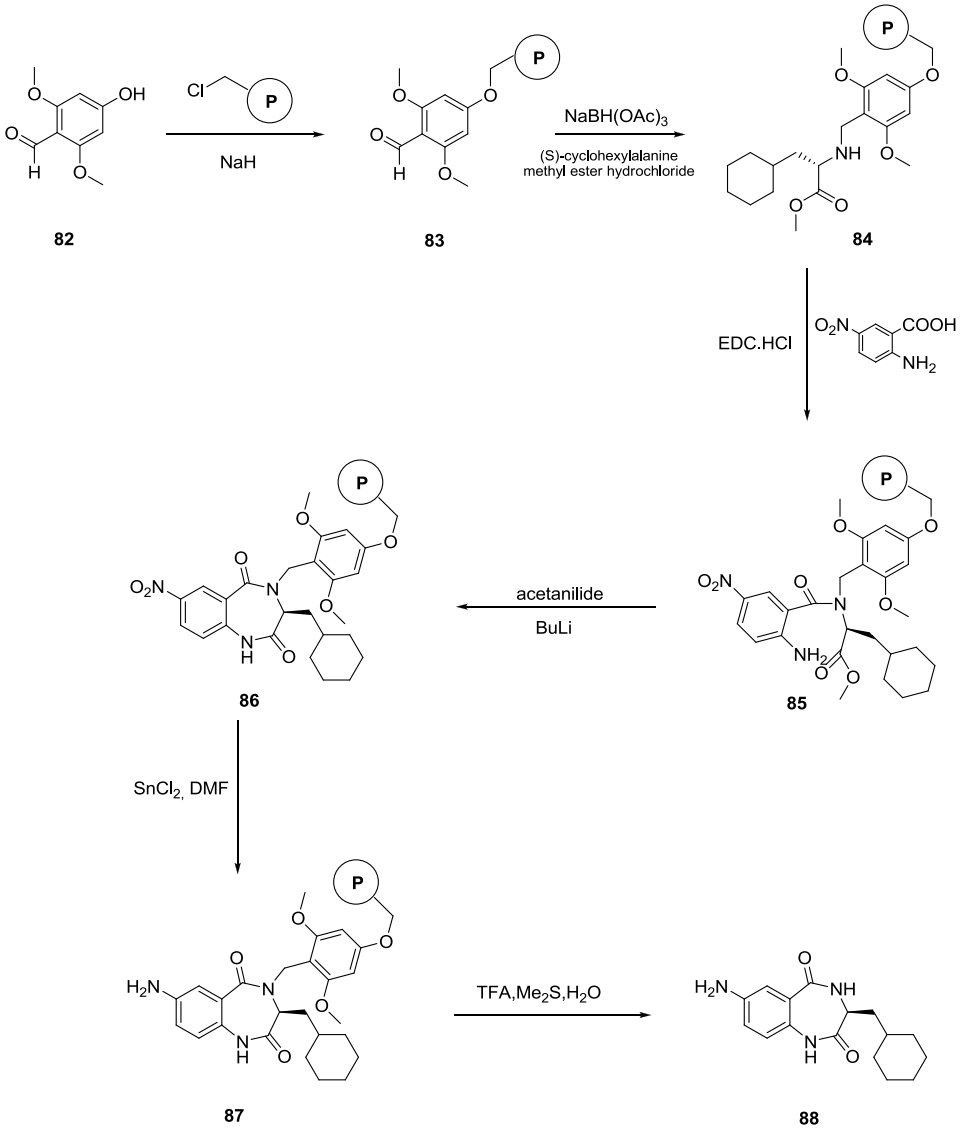
N-alkylbenzamide **74** was used to obtain dianions **75** by orthometalation. Orthometalation is a kind of electrophilic aromatic substitution. Electrophile group attaches itself to ortho position of directing group. In this reaction, lithium is used as electrophile to obtain dianion. Then, reaction of dianion and benzotriazole gives the target benzodiazepinone derivatives **76** in moderate yields. $ZnBr_2$ is very crucial reagent for this reaction, because benzodiazepinone formation was not occurred without $ZnBr_2$. It is used as Lewis acid and activates the benzotriazole compound.



Scheme 18 Synthesis of 1,4-benzodiazepinon-5-one **81**

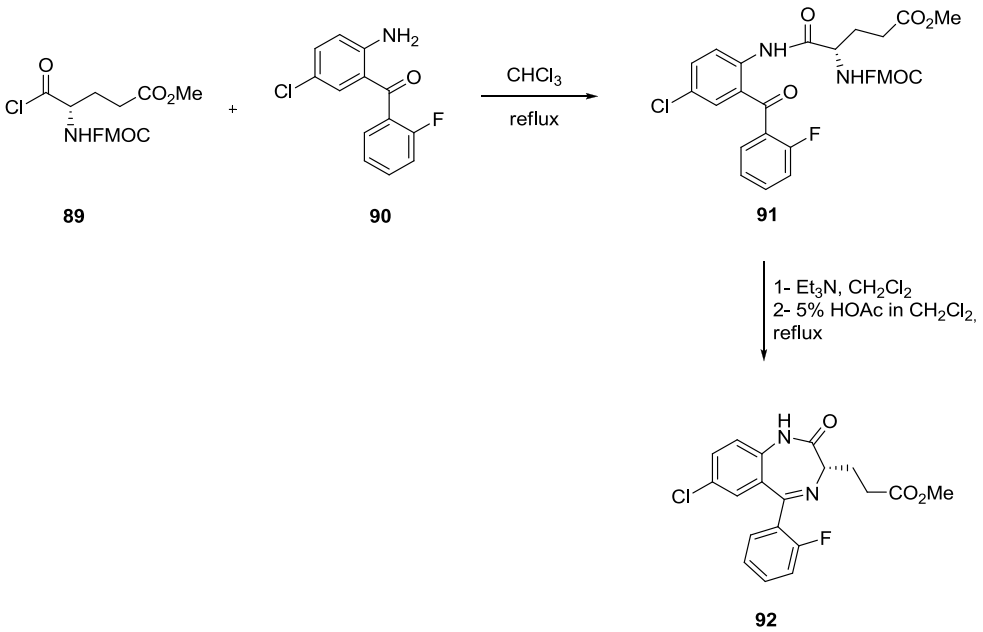
A new method for construction of 1,4-benzodiazepinon-5-one skeleton is described in Scheme 18.[33] Microwave energy mediated synthesis is popular because it

accelerates rates of reactions and improves classical methods. Moreover, it is not always necessary to use organic solvent for all microwave reactions. It is known as green chemistry (more environmentally friendly). In the Scheme 18, reaction of isatoic anhydride **77** with allyl amine in microwave gives the compound **78**. Then, diazotization was done by $NaNO_2$ in acidic medium followed by nucleophillic substitution by sodium azide. Formed intermediate **80** was cyclized to **81** by microvawe radiation. Advantages of this methodology are better yields and cleaner reactions compare to those reactions with conventional heating.



Scheme 19 Solid phase synthesis of 1,4-benzodiazepine-2,5-dione **88**

Ettmayer *et al.* published an article about solid-phase synthesis of 1,4-benzodiazepine-2,5-dione derivatives (Scheme 19).[34] Solid state synthesis can be defined as method; molecules attached to insoluble polymeric material were synthesized in reactant solution . It is easy to remove excess reactants from solution if we compare this method with liquid state synthesis. To attach starting material to polymer, 4-hydroxy-2,6-dimethoxybenzaldhyde **82** was reacted with chloromethylpolystyrene by NaH. Formed product **83** was reacted with (*S*)-cyclohexylalanine methyl ester by free reductive amination to give compound **84**. Then, acylation process was done for the synthesis of **85** by using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC.HCl) and 5-nitroanthranilic acid. Process is quite similar to DCC promoted synthesis of amides from carboxylic acids. For lactamization, lithium acetanilide was used to give compound **86**. Next step was the reduction of nitro group by $SnCl_2$ which gave target polymer bonded benzodiazepinone molecule **87**. To cleave polymer TFA, Me_2S and water mixture was used. This step was only for characterization. Only very small amount of compound **88** was isolated.

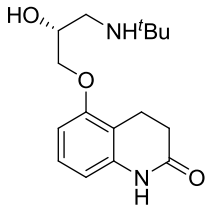


Scheme 20 Synthesis of benzodiazepinone **92**

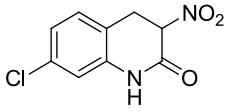
According to the procedure in Scheme 20, synthesis of benzodiazepinone derivatives was achieved by starting from 2-aminobenzophenone derivatives.[35] Condensation reaction of halogen substituted 2-aminobenzophenone **90** and glutamate substituted acid chloride gave the anilide molecule **91** without any racemization problem. Then, protecting group, fluorenylmethyloxycarbonyl chloride (Fmoc) was removed easily by triethyl amine. Fmoc group is generally used for the protection of amines. After removing the protecting group Fmoc, free amine reacted with carbonyl group of benzophenone by cyclodehydration reaction in 5% acetic acid-dichloromethane solution. Target benzodiazepinone molecule **92** was obtained at the end of two step reaction without any significant racemization.

1.4 Dihydroquinolinones

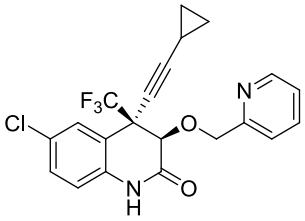
Dihydroquinolinones have great potential in pharmaceutical area due to their important bioactivity results. There are many important known examples in literature. Carteolol (**93**), NMDA antagonist (**94**), HIV-1 reverse transcriptase inhibitor (**95**) and insecticidal antibiotic (**96**) can be given as examples which include dihydroquinolinone framework.[36]



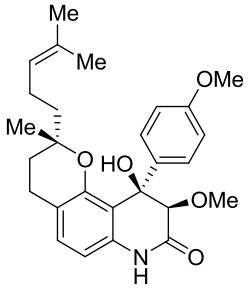
carteolol (93)



NMDA antagonist (94)



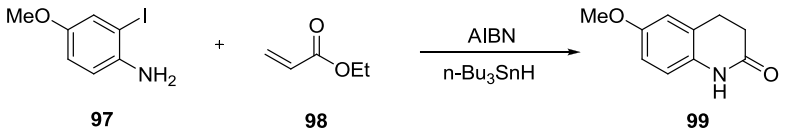
HIV-1 reverse transcriptase inhibitor (95)



insecticidal antibiotic (96)

1.4.1 Synthesis of dihydroquinolinones

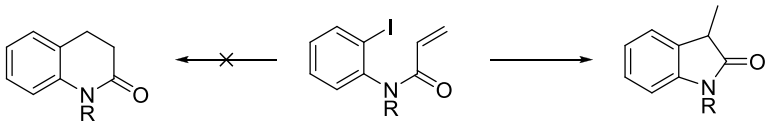
Jiao *et al.* described a tandem methodology which includes radical and ionic processes to synthesize 3,4-dihydroquinolin-2-ones (Scheme 21).[36]



97 **98** **99**

Scheme 21 Synthesis of 3,4-dihydroquinolin-2-one **99**

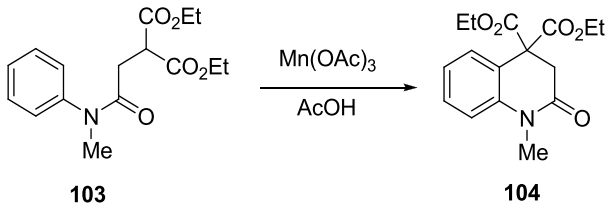
It is known that it is not easy to obtain 3,4-dihydroquinolin-2-ones **100** by intramolecular radical cyclization reactions of compound **101** (Scheme 22) because these reactions favor the formation of 5-*exo* products **102**. To reach 6-*endo* products **100**, a new method was used. Mechanism includes the radical addition and lactamization between compound **97** and **98** (Scheme 21).



100 **101** **102**

Scheme 22 Formation of 5-exo product **102**

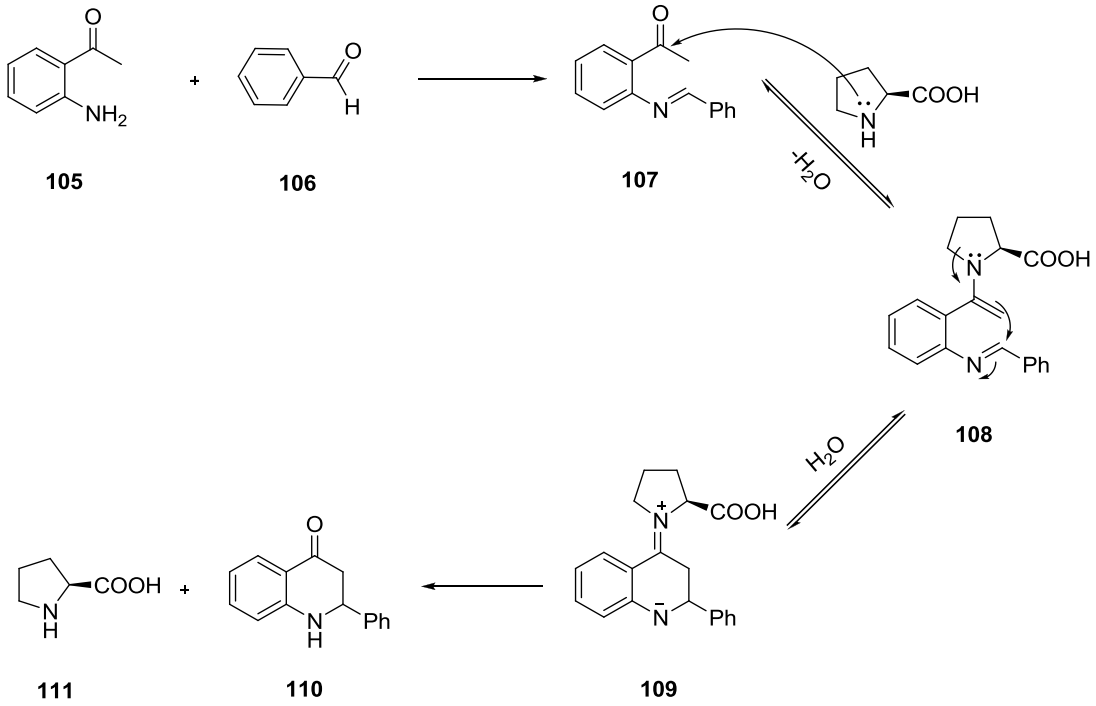
Another approach to dihydroquinolinones is manganese(III) acetate mediated synthesis (Scheme 23).[37] Nishino *et al.* used diethyl 2-[2-(*N*-methyl-*N*-phenylamino) -2-oxoethyl]malonate **103** as starting material for the reaction. Oxidation of malonate compound **103** with manganese (III) acetate in acetic acid gives the desired 3,4-dihydro-2(1*H*)-quinolinone **104** in 60% yield.



103 104

Scheme 23 Manganese(III) acetate mediated dihydroquinolinone synthesis

One pot synthesis of 2-aryl-2,3-dihydroquinolin-4-one **110** was reported by S. Chandrasekhar (Scheme 24).[38] In this reaction, *L*-proline is used as catalyst. Condensation reactions of aryl aldehydes **106** with *o*-aminoacetophenone **105** in the presence of *L*-proline as catalyst gave the target molecule 2-aryl-2,3-dihydroquinolin-4-one **110**.



105 106 107 108 109 111 110

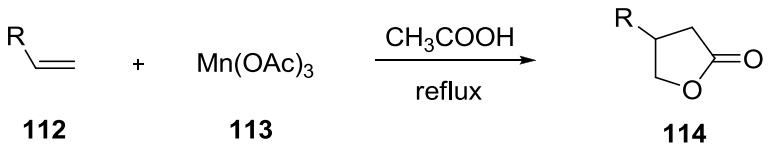
Scheme 24 One pot synthesis of 2-aryl-2,3-dihydroquinolin-4-one **110**

1.5 Chloroacetonylation C=C double bonds

Recently, free radical reactions have gained great popularity in synthetic organic chemistry due to their crucial advantageous abilities like selectivity, specificity and mild reaction conditions. Manganase (III) acetate is a spectacular reagent to obtain carbon radicals which can be easily added to double bonds. C-C bond formation by using manganese (III) acetate is a very effective tool to reach more complex molecules.[39]

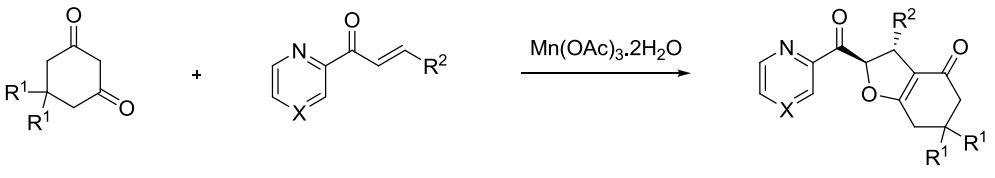
1.5.1 Manganese (III) acetate- oxidative free radical additions

The most classical example of manganese(III) mediated free radical addition is the acetic acid addition to olefins **112**. Manganase(III) acetate **113** in acetic acid at reflux gives γ-lactones **114** as resulted products (Scheme 25).[40]



Scheme 25 Synthesis of γ-lactones **114**

Wang *et al.* described the free radical addition of 1,3-cyclohexanediones **115** to 1-(Pyridin-2-yl)-enones **116** (Scheme 26).[41] Due to the presence of 1,3-diketones, dihydrofuran derivatives **117** were obtained instead of lactone derivatives.

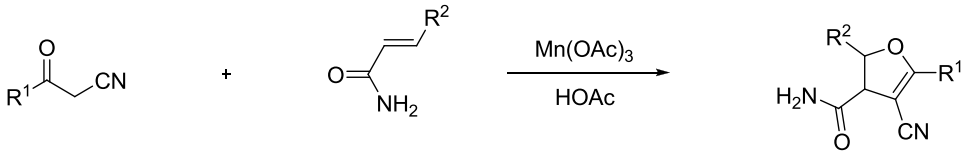


X = CH, N

Scheme 26 Synthesis of dihydrofuran derivatives **117**

First step involves the radical formation on 1,3-cyclohexanediones. Then addition to double bond and successive cyclization by nucleophilic attack of oxygen gives target dihydrofurans. Extremely high diastereoselectivity and regioselectivity are the advantages of this study.

In another study, regio- and stereo-selective synthesis of 4-cyano-2,3-dihydrofuran-3-carboxamides **120** was done by using manganese(III) mediated reaction. Oxidative cyclization of 3-oxopropanenitriles **118** with α,β-unsaturated amides **119** was examined in Scheme 27.[42]

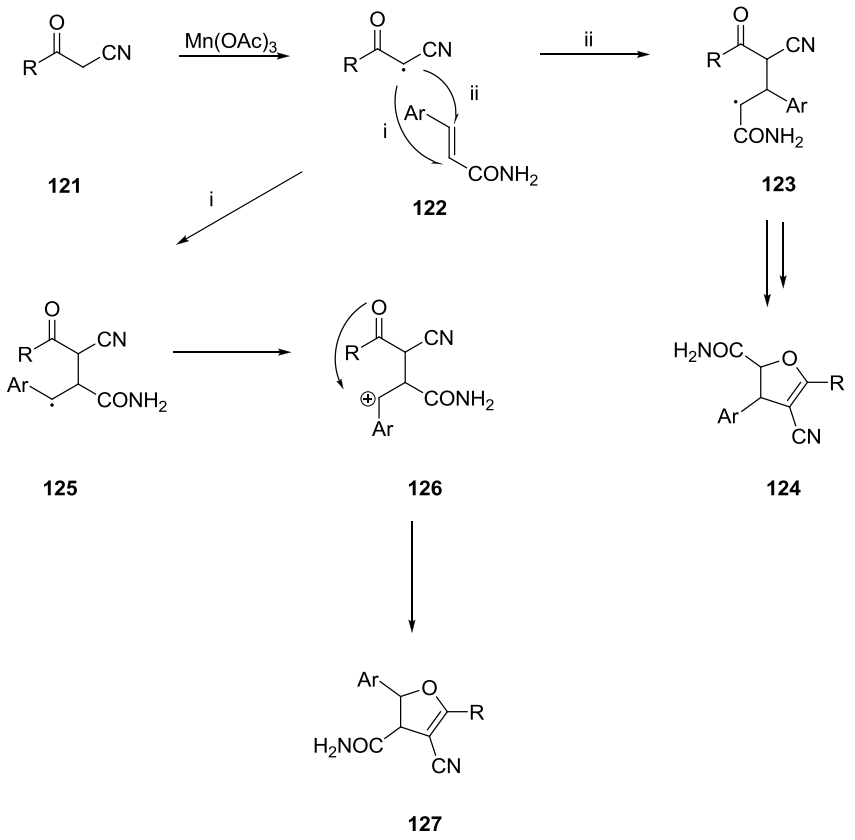


118 **119** **120**

Scheme 27 Synthesis of 4-cyano-2,3-dihydrofuran-3-carboxamides **120**

In this reaction free radical formation occurs on compound **118**. Then addition of free radical to α,β-unsaturated amides **119** gives stereo- and regio-selective products **120**.

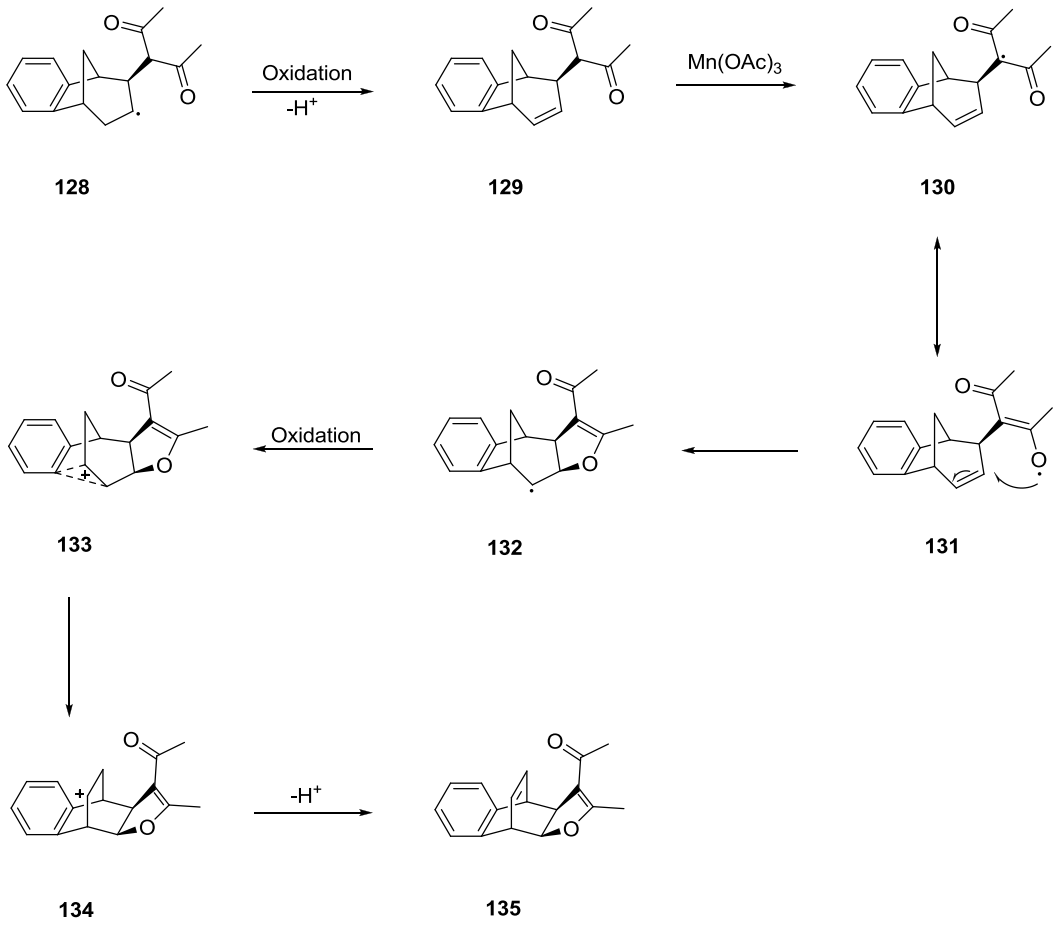
According to proposed mechanism, reaction involves the free radical formation on compound **121.** At that point, there are two different positions on olefin for free radical attack (i, ii). After the formation of addition product, formed radical is oxidized one more time by manganese(III) acetate to give carbocation **126**. Attack of oxygen atom to intermediate **126** gives cyclization product **127** as shown in Scheme 28.



Scheme 28 Mechanism for compounds **124** and **127**

Recently, Balcı *et al.* published a mechanistic study which proves second oxidation mechanism in dihydrofuran formation. Reaction of homobenzonorbornadiene and 1,3-diketones in the presence of manganese(III) acetate and $Cu(OAc)_2$ gave mainly rearranged products having [2.2.2] skeleton and non-rearranged dihydrofuran derivatives (Scheme 29).[43]

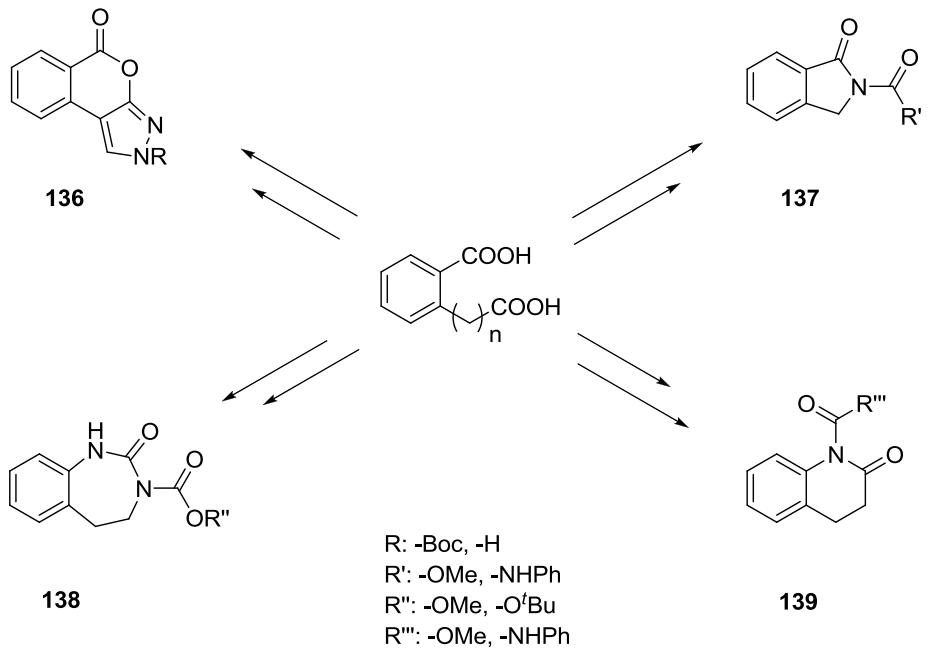
Homobenzonorbornadiene molecule is used because it is capable of generating both classical and non-classical carbocations. Rearranged products proved that formation mechanism includes additional oxidation. On the other hand, radicals are not capable of making rearrangement. Therefore, rearranged product **135** cannot be formed by radical mechanism.



Scheme 29 Mechanism for rearranged product **135** having [2.2.2] skeleton

1.6 Aim of the study

Heterocyclic organic chemistry attracts high attention of scientists due to importance of the heterocyclic compounds. Many drugs include heterocyclic structures in their core skeletons. Many natural processes depend on these heterocyclic compounds. Our aim is to develop new and easy synthetic methods for the construction of the important heterocyclic compound's skeletons. Pyrazoles **136**, isoindolinones **137**, benzodizepinones **138**, dihydroquinolinones **139** and acetonylation products are our targets in this study (Scheme 30). To reach these molecules, acyl azides are used as key compounds in our synthetic methodology. Manganese(III) acetate chemistry is also examined to obtain acetonylation products. One pot synthetic procedure will be used for the synthesis of pyrazole derivatives starting from homophthalic anhydride molecules.



Scheme 30 Target molecules of the study

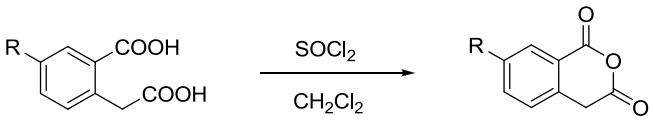
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of pyrazole derivatives

2.1.1 Synthesis of starting compounds: homophthalic anhydrides

Homophthalic anhydrides were synthesized according to the literature starting from homophthalic acid derivatives (Scheme 31).[44-47]



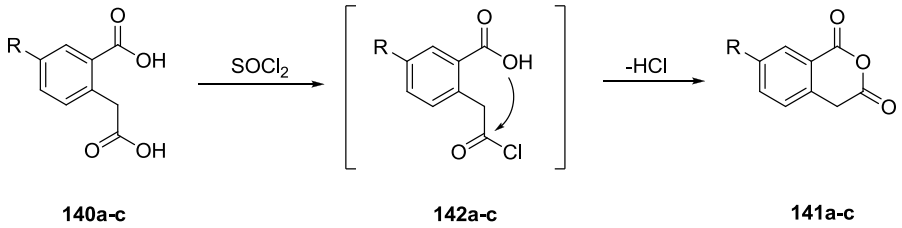
140a-c **141a-c**

a R= H
b R= Br
c R= OCH_3

Scheme 31 Synthesis of homophthalic anhydrides

Addition of thionyl chloride to solution of homophthalic acid in dichloromethane gives homophthalic anhydride derivatives in high yields >95%. Mechanism includes the formation of semi-acyl chlorides as intermediates. Second step is the intramolecular nucleophilic attack of carboxylic acid oxygen to acyl chloride groups. Crucial point is the semi-acyl chloride formation due to reactivity difference of the carbonyl groups. Carbonyl group which is directly bonded to benzene ring is less reactive due to conjugation with benzene. Therefore, acyl chloride formation

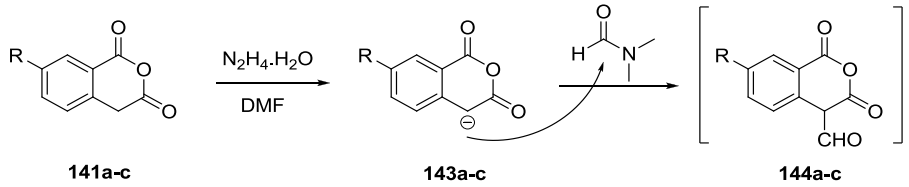
occurs from the carbonyl group which is separated from the benzene ring by -CH_2- group. (Scheme 32).



Scheme 32 Homophthalic anhydride formation mechanism

2.1.2 Synthesis of formylated homophthalic anhydrides

In this study, our strategy was the formyl group addition to methylene group of homophthalic anhydrides by using dimethylformamide both as solvent and reactant. This target molecule was very important because additional formyl group gives a new reactive side for further cascade reactions.

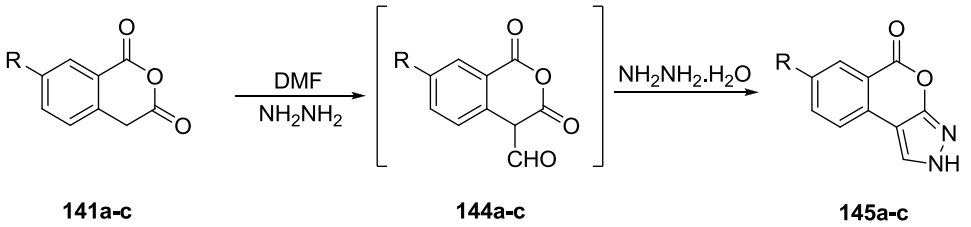


Scheme 33 Synthesis of formylated homophthalic anhydrides

Formyl compounds **144a-c** could not be isolated due to their high reactivities. Formylation of molecules by DMF in the presence of bases is classical method for the introduction of formyl group to reactive sides of the molecules. In our case, hydrazine monohydrate was used as base in this reaction. After proton abstraction from methylene group, nucleophilic attack to dimethylformamide gave intermediates **144a-c**. We proposed these structures based on the structures of the final products **145a-c** (Scheme 33).

2.1.3 Synthesis of isocoumarin- condensed pyrazoles and structure confirmation

According to our strategy, cyclization with excess hydrazine was examined as final step. Formylation and cyclization are the two crucial steps to reach isocoumarin-condensed pyrazoles (Scheme 34).

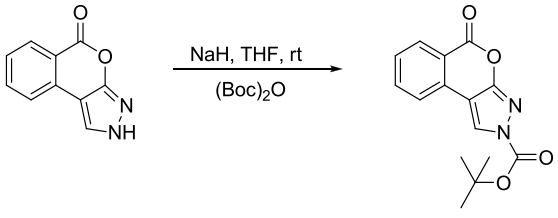


141a-c **144a-c** **145a-c**

Scheme 34 Synthesis of isocoumarin-condensed pyrazoles

To reach these target compounds, we herein reported a novel one-pot, three-component reaction. Homophthalic anhydrides **141a-c** were dissolved in excess dimethylformamide. Then, addition of hydrazine monohydrate to this solution and overnight reflux gave the final products in yields 63-81%.

To confirm structure, NMR techniques were used. There were some problems due to nature of final products. First problem was that structures do not have any important informative proton signal in NMR spectra to elucidate the structures exactly. Secondly, solubility problems prevented us to crystalize molecule for X-ray analysis. To obtain single crystals and to increase solubility, Boc group was introduced to molecule with an easy procedure (Scheme 35).



145a **146**

Scheme 35 Synthesis of Boc-protected isocoumarin-condensed pyrazoles

Confirmation of structure was done after reaction of compound **145a** with di-*tert*-butyl dicarbonate [$(Boc)_2O$] in the presence of NaH. An X-ray analysis on the compound **146** gave exact evidence for the structures of **145a-c** (Figure 1).

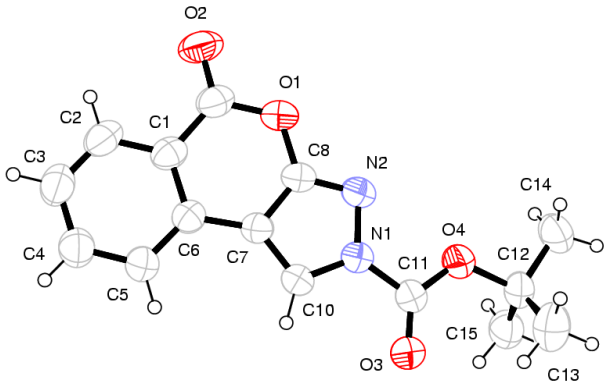
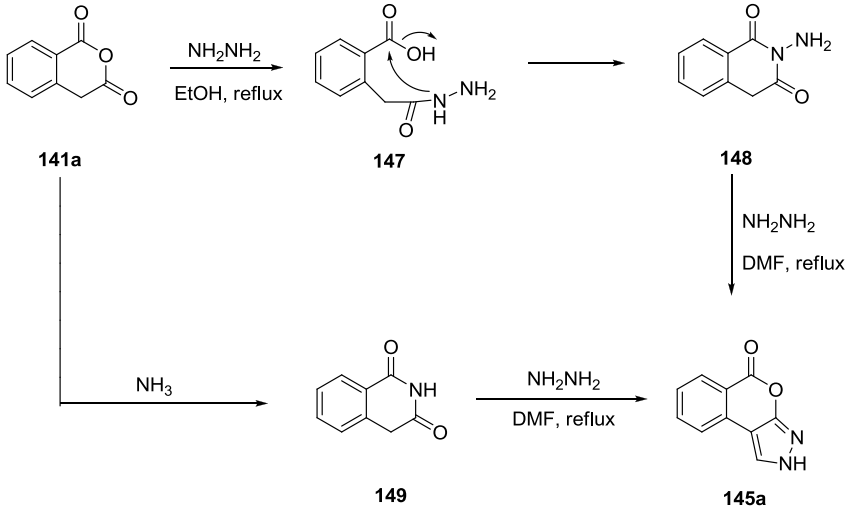


Figure 1 X-ray analysis of compound **146**

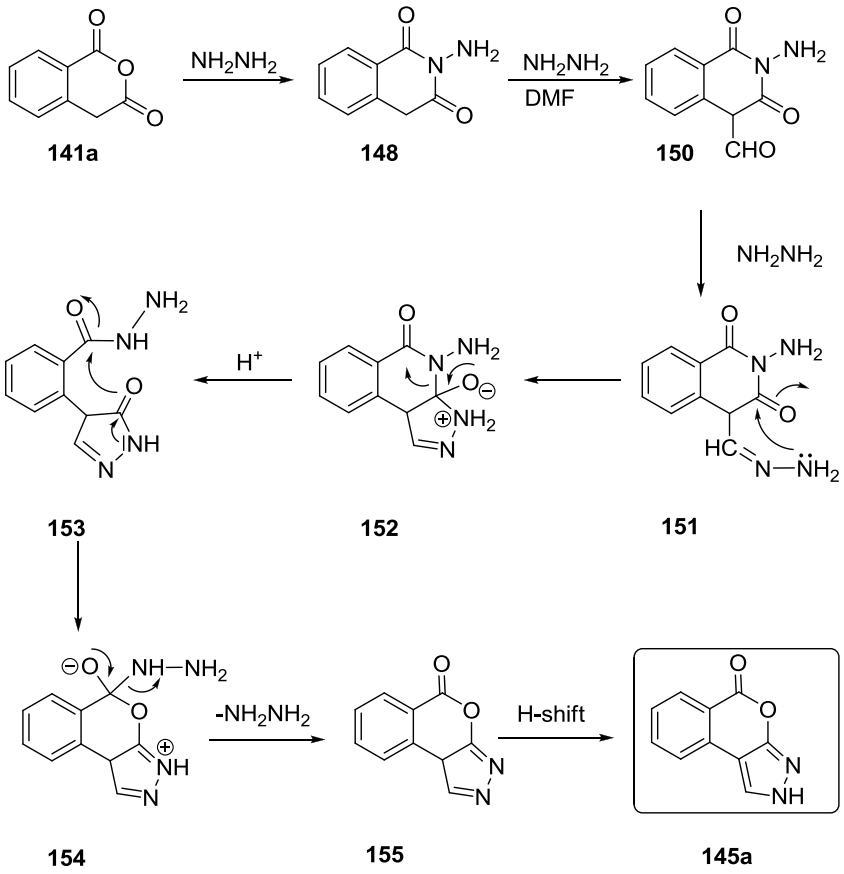
2.1.4 Synthesis of isocoumarin-condensed pyrazoles from hydrazide and imide compounds

To propose a mechanism for isocoumarin-condensed pyrazoles **145a-c** formation, we used independent reactions. While monitoring the reaction medium by GC-MS, the formation of 2-aminoisoquinoline-1,3(*2H*,*4H*)-dione **148** was detected (Scheme 36).



Scheme 36 Synthesis of 2-aminoisoquinoline-1,3(2*H*,4*H*)-dione **148**

To confirm whether compound **148** was formed during the formation of isocoumarin-condensed pyrazoles **145a-c**, hydrazide **148** was synthesized by reaction of homophthalic anhydride and hydrazine monohydride in refluxing ethanol in 85% yield.[48] Although compound **147** has both amide and amine functionality, cyclization occurred surprisingly from less nucleophilic amide nitrogen to form hydrazide molecule **148**. Then, application of the same conditions to hydrazide **148** gave same products as we expected. This results showed that 1*H*-isochromene-1,3(4*H*)-dione **141a** undergoes a ring opening reaction at some step. Imide was also synthesized for further support by reaction of compound **141a** with ammonia.[49] Treatment of imide molecule with hydrazine and DMF also gave the target products in 87% yield.



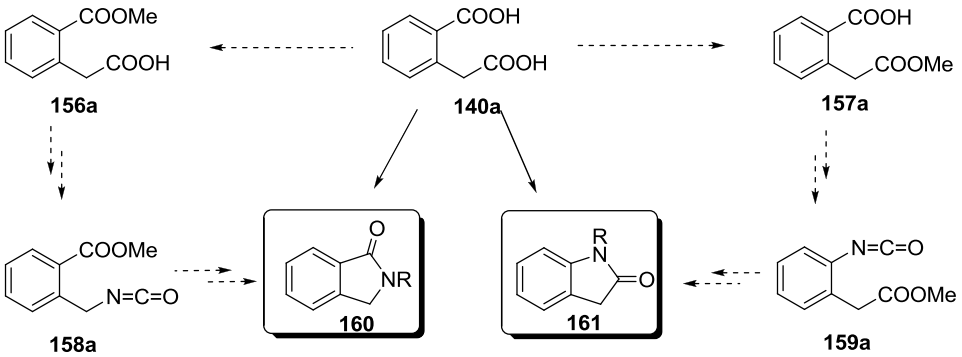
Scheme 37 Proposed mechanism for compound **145a**

After combining all these results, mechanism for the formation of the products **145a-c** was proposed. According to our suggested echanism, first step is the formation of hydrazide molecule **148.** Hydrazide product **148** may undergo formylation reaction. After proton abstraction from methylene group, nucleophilic attack to dimethylformamide gives intermediate molecule **150**. Reaction of hydrazine monohydrate with compound **150** gives the hydrazone **151.** Ring opening reaction by attack of amine group on the carbonyl to produce **153** via intermediate **152**. Further cyclization with the carbonyl oxygen atom of the formed pyrazolone derivative **153** followed by displacement of the hydrazine moiety and a subsequent H-shift in **155** results in formation of the target compound **145a** (Scheme 37).

2.2 Synthesis of isoindolinone derivatives

2.2.1 Synthesis of diester derivatives from homophthalic acid derivatives

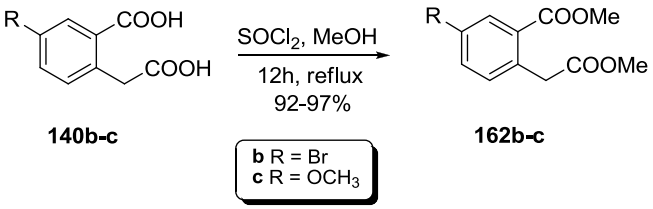
In this study, a new methodology was developed for the synthesis of isoindolinone **160** and indolinones **161** from homophthalic acid derivatives **140a-c** (Scheme 38).



Scheme 38 Synthetic plan for isoindolinones and indolinones

Regiospesific synthesis of the [2-(2-methoxycarbonyl)phenyl] acetic acid **156a** and 2-(2-methoxy-2-oxoethyl)benzoic acid **157a** are the key steps for this study. Regiospesific hydrolysis of diester molecule was used to reach key compound [2-(2-

methoxycarbonyl)phenyl] acetic acid **156a**. Diester molecules were obtained from homophthalic acid derivatives as shown in Scheme 39.

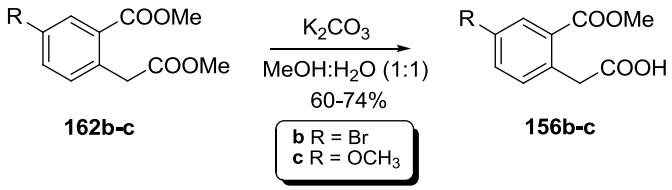


Scheme 39 Synthesis of diester compouds

Esterification reaction was done by refluxing methanol solution of homophthalic acid derivatives **140b-c** in the presence of thionyl chloride. The yields of diester molecules **162b-c** are quite high 92-97%.

2.2.2 Regiospesific synthesis of half esters 156b-c

Recently, Balci *et al.* reported the reactivity of the ester carbonyl groups in similar systems are different.[50] The ester group bonded to methylene group is more reactive than the carbonyl group directly bonded to benzene ring. By using this reactivity advantage, regiospesific hydrolysis of the more reactive side was done (Scheme 40).

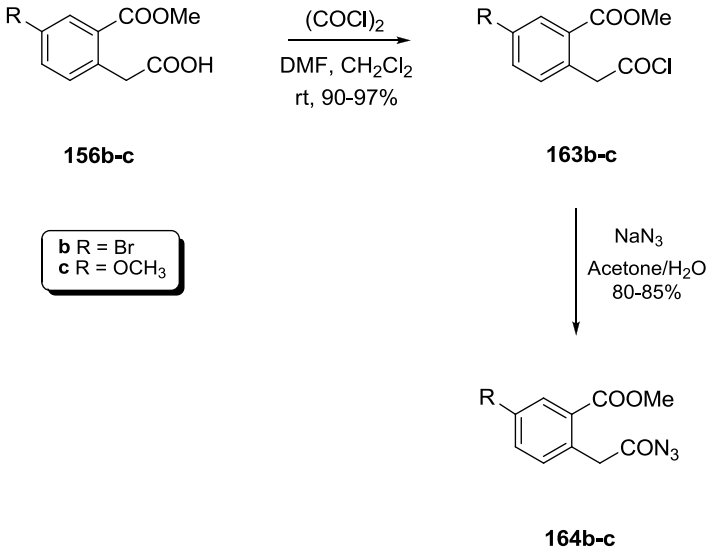


Scheme 40 Hydrolysis of diesters **162b-c**

To reach half ester molecules, regiospesific hydrolysis was done by reaction of compounds **162b-c** with potassium carbonate in solution of water/methanol (1:1). Time dependent reflux of the solution gave target half esters **156b-c** in 60-74% yields.

2.2.3 Synthesis of acyl azides

The half ester molecules reacted with oxalyl chloride in dichloromethane in the presence of catalytic amount of *N,N*-dimethylformamide to give acyl chlorides in quite high yields 90-97% (Scheme 41). By these transformations, better leaving group chlorine attached to molecule to facilitate azide formation.

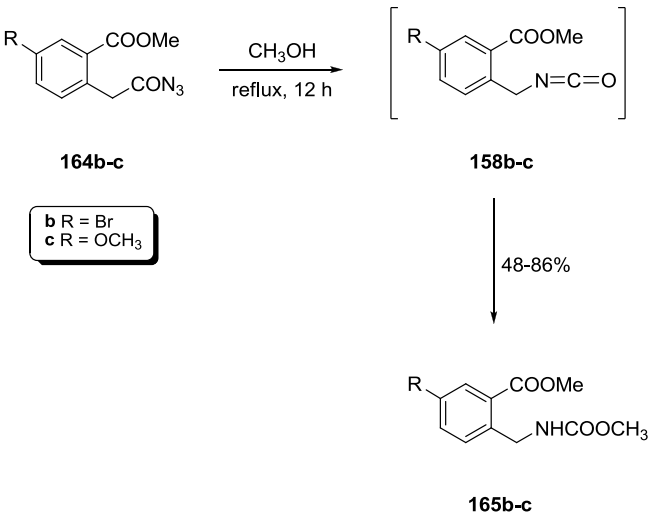


Scheme 41 Synthesis of acyl azides **164b-c**

Common method was used to reach acyl azide molecules **164b-c**. Aqueous solution of sodium azide was added to solution of acyl chlorides **163b-c** in acetone. The acyl azide **164b-c** formation was observed in high yields 80-85%.

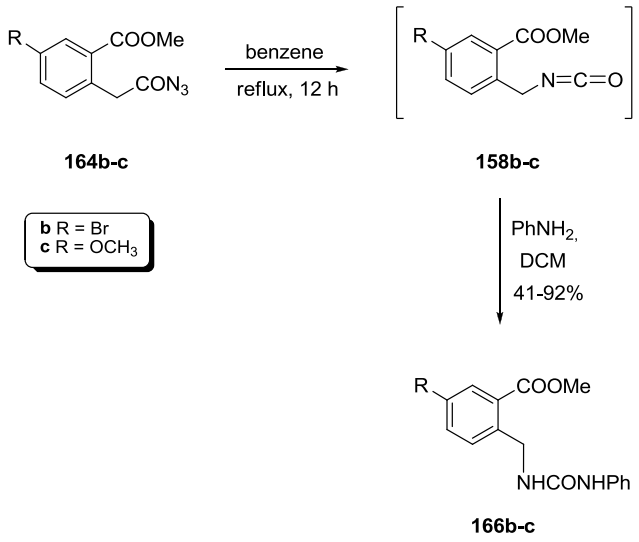
2.2.4 Synthesis of urea and urethane derivatives from acyl azides

Acyl azides **164b-c** are very reactive molecules. By using this advantage, urethane derivatives were obtained by heating acyl azides in methanol. This process involves the intermediate molecule isocyanates **158b-c**. First step is the Curtius rearrangement of the acyl azide molecules and then, nucleophilic attack of the methanol to reactive intermediate isocyanates gave target urethane molecules **165b-c** in yields of 48-86% (Scheme 42).



Scheme 42 Synthesis of urethane derivatives **165b-c**

Similarly, urea derivatives **166b-c** were also synthesized. Acyl azides are very versatile reactants. If these molecules are heated in non-nucleophilic medium, reactive isocyanate molecules can also be isolated. Although this isolation is possible, many studies prefer to use them as reactive intermediates to continue successive reactions instead of isolation of the unstable isocyanates. In our case, we synthesized isocyanates **158b-c** and characterization was done by using especially IR spectrum. After this evidence, we continued next reaction without any purification.



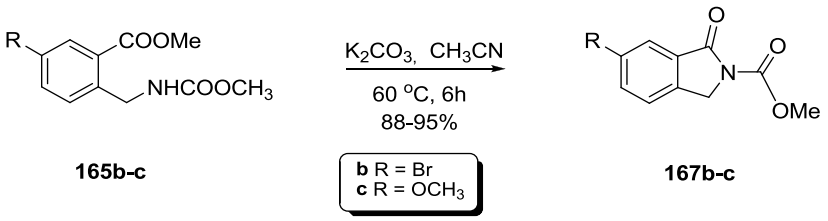
Scheme 43 Synthesis of urea derivatives **166b-c**

Both urea derivatives in Scheme 43 and urethane derivatives in Scheme 42 were our last building blocks for the synthesis of target isoindolinone derivatives. Our methodology is quite useful and functional to obtain substrate molecules urea and urethanes in quite overall high yields. Structure of the ureas and urethanes were characterized by NMR spectroscopy.

Formed urea **166b-c** and urethane derivatives **165b-c** were purified by using column chromatography before final cyclization step.

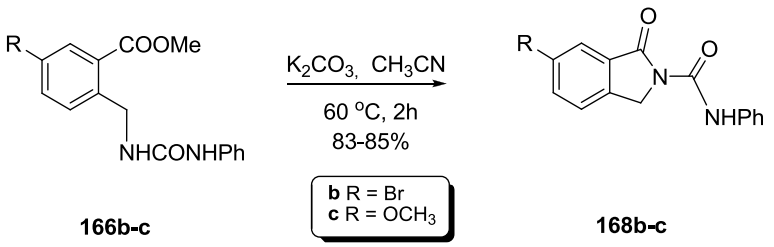
2.2.5 Synthesis of target isoindolinones

After the synthesis of ureas **166b-c** and urethanes **165b-c**, we turned our attention to ring closure of these systems. Treatment of urethanes **165b-c** with potassium carbonate in acetonitrile gave the target isoindolinone derivatives **167b-c** in quite good yields 88-95% (Scheme 44). These smooth transformations are another advantageous part of our methodology. Structure elucidation was done by analysis of elemental analysis, ^{1}H and ^{13}C-NMR data. All these information were in consistent with each other.



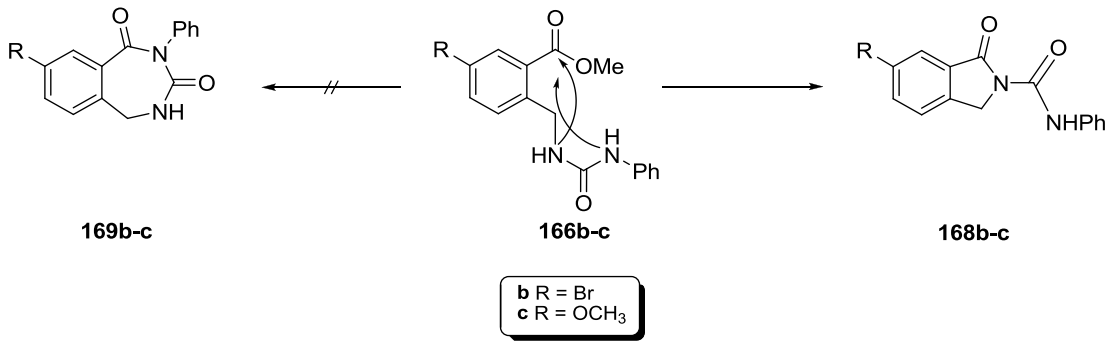
Scheme 44 Synthesis of isoindolinones **167b-c**

Similarly, we applied the same condition to urea derivatives to reach target isoindolinone derivatives. Treatment of urea derivatives **166b-c** with potassium carbonate in acetonitrile also gave the target isoindolinone derivatives **168b-c** in quite good yields 83-85% (Scheme 45).



Scheme 45 Synthesis of isoindolinones **168b-c**

In the cyclization reaction of **166b-c,** there were two different amide functionalities in the molecule. Therefore, two different products were expected due to two different attack possibilities of the different amide groups (Scheme 46).



Scheme 46 **Formation mechanism of** 168b-c

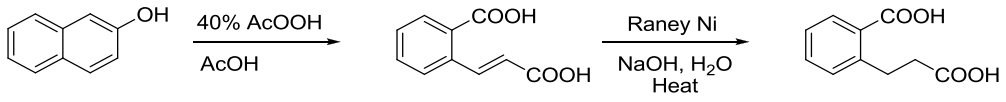
No trace of compounds **169b-c** was detected in reaction mixture. The reason is that formation of five membered ring compounds **168b-c** was preferred over the seven membered ring compounds **169b-c**.

All these results proved that cyclization by using acyl azides is a very advantageous methodology to reach important heterocycles.

2.3 Synthesis of benzodiazepinone derivatives

2.3.1 Synthesis of starting compound: 2-(2-carboxyethyl)benzoic acid

2-(2-carboxyethyl)benzoic acid **172** was prepared according to the description in the literature.[51] This molecule is very important for this study because it served as a building block for benzodiazepinone molecules (Scheme 47).



170 **171** **172**

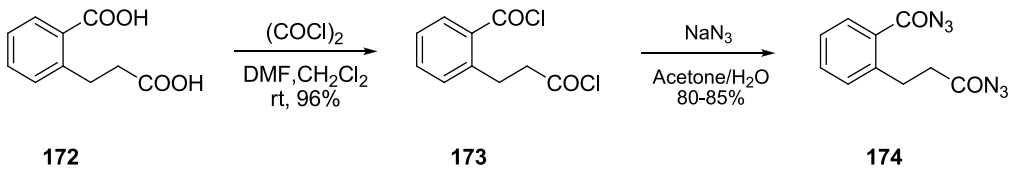
Scheme 47 Synthesis of 2-(2-carboxyethyl)benzoic acid

2-(2-Carboxyethyl)benzoic acid **172** was synthesized starting from β-naphthol **170**. First step was the oxidation of β-naphthol **170** to *o*-carboxycinnamic acid **171** by reaction of peroxyacetic acid. Then successive hydrogenation with Raney nickel in basic aqueus solution gave the target starting material, 2-(2-carboxyethyl)benzoic acid **172**.

Although it was not reported in the literature, exact structure of the *o*-carboxycinnamic acid **171** was determined as *trans* according to the coupling constant of double bond protons which is approximately 16 Hz. Exact structure of the molecule was quite important for this study. According to our synthetic plan, *trans*-configuration could be problematical for cyclization steps. Therefore, we decided to reduce double bond in the presence of Raney nickel. Otherwise, geometry of the molecule could prevent the formation of the diazepinone rings.

2.3.2 Synthesis of bis(acyl azide) compounds

A method for acyl azide formation was described in isoindolinone part 2.2.3. In this study, we also used the same procedures to reach our target bis(acyl azide) compound **174** (Scheme 48).



172 **173** **174**

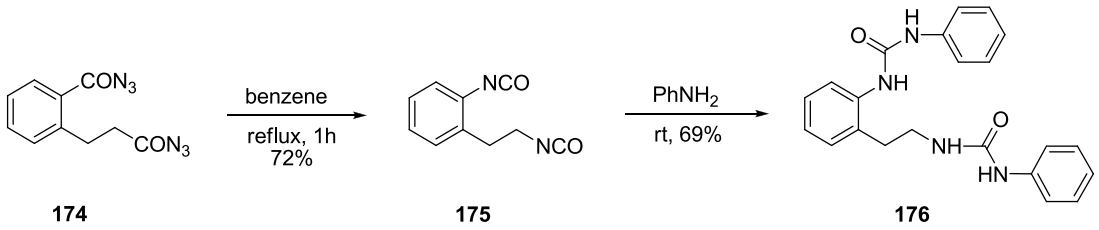
Scheme 48 Synthesis of acyl azide **174**

First step includes the chlorination of the 2-(2-carboxyethyl)benzoic acid **172**. 2-(2-carboxyethyl)benzoic acid **172** was dissolved in dichloromethane and treated with oxalyl chloride in the presence of catalytic amount of *N*,*N*-dimethylformamide. Reaction medium was monitored and reaction was stopped according to the change in solution. At room temperature, solubility of 2-(2-carboxyethyl)benzoic acid **172** is very low in dichloromethane. Reaction was stopped after all the 2-(2-carboxyethyl)benzoic acid **172** had dissolved in dichloromethane.

Bis(acyl azide) compound **174** was synthesized with a common method which we described previously in isoindolinone part 2.2.3. Aqueous solution of sodium azide was added to solution of bis(acyl chloride) **173** in acetone. The bis(acyl azide) **174** formation was observed in 79% yield. After formation of the key bis(acyl azide) molecule, we turned our attention to intramolecular ring closure reactions of the diisocyanate **175**. Curtius rearrangement of the bis(acyl azide) **174** to disocyanate **175** was examined. As we described earlier, this methodology is quite easy and useful to reach important urea and urethane derivatives. In the next part, synthesis of the urea and urethane derivatives are described.

2.3.3 Synthesis of urea from bis(acyl azide) and its ring closure reactions

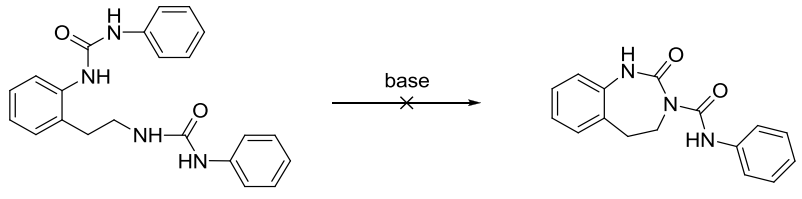
Curtius reaarrengement of the bis(acyl azide) **174** was used to obtain target diisocyanate **175** (Scheme 49). Addition of the nucleophiles to disocyanate **175** gave target urea and urethanes.



174 **175** **176**

Scheme 49 Synthesis of urea **176**

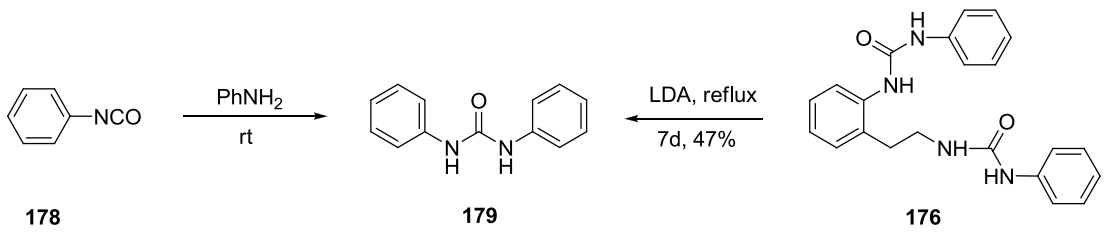
Diisocyanate **175** was isolated and characterized by using IR, ^{1}H and ^{13}C-NMR spectroscopy. To facilitate rearrangement, bis(acyl azide) solution in benzene was heated to reflux for 1 hour. Then, treatment of the diisocyanate with aniline in dichloromethane at room temperature gave the target urea derivative **176**. Precipitation was used to reach clean urea product **176** without any further purification in 69% yield. Until this point, we synthesized our target urea compound without any problem. After directing our efforts to ring closure reactions of this formed urea derivative **176**, we faced with the biggest disappointment of the project (Scheme 50). At first glance, we were very hopeful for ring closure reaction of the urea because it includes four different amide functionalities inside the molecule.



176 **177**

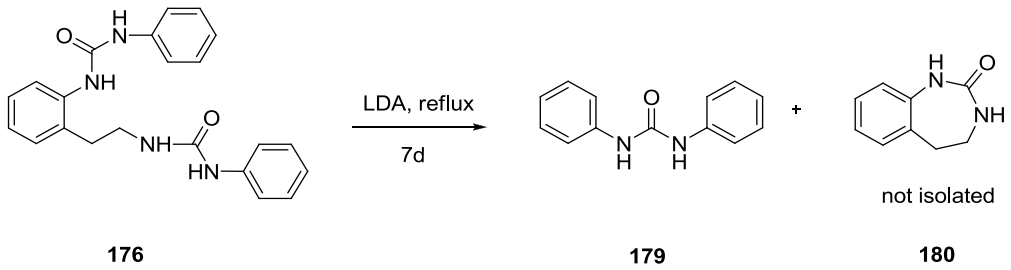
Scheme 50 Ring closure reactions of compound **176**

All efforts to the ring closure reaction of urea derivative **176** were failed. Various bases, such as, pyridine, potassium carbonate, cesium carbonate were tried to facilitate ring closure reactions. None of them revealed the formation of the ring closure product **177**. However, treatment of the urea derivative **176** with lithium diisopropylamide under reflux for one week afforded *N,N'*-diphenylurea[52] (**179**) in 47% yield (based on consumed starting material) as only isolable product. To confirm the structure of the formed *N,N'*-diphenylurea **179**, we conducted an independent experiment. Reaction of phenyl isocyanate **178** with aniline also gave the same product *N,N'*-diphenylurea **179** (Scheme 51). Comparison of the all spectroscopic data showed complete agreement.

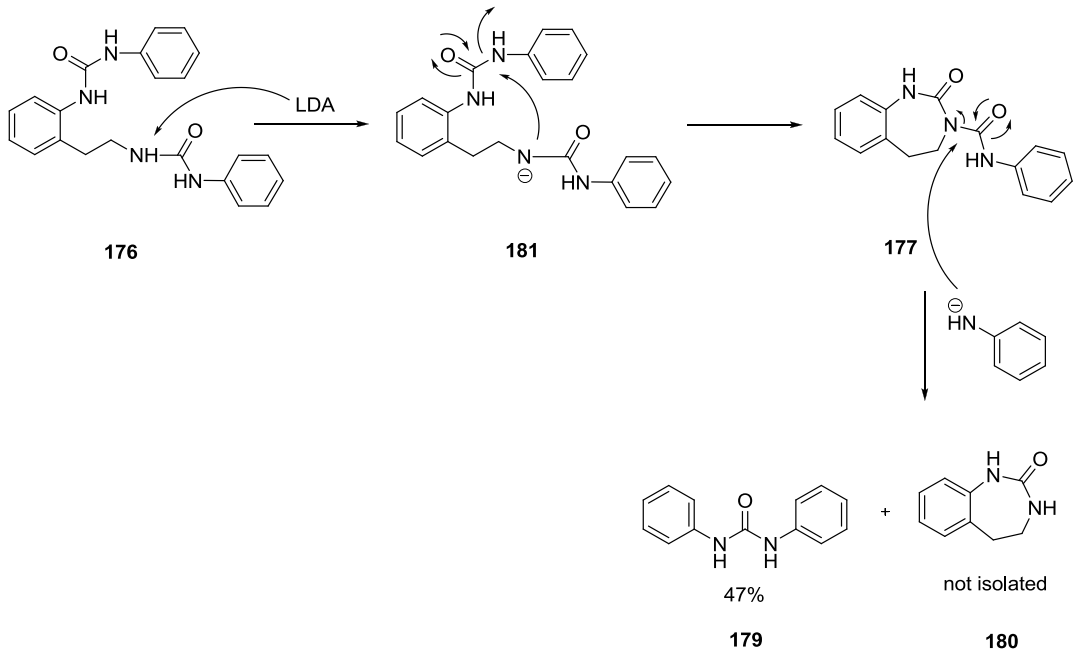


Scheme 51 Synthesis of *N,N'*-diphenylurea **179**

Due to complex reaction medium and solubility problems, we could not isolate any other products. Actually, we expected the formation of **180** based on the mechanism of fragmentation of *N,N'*-diphenylurea (**179**) (Scheme 52) as depicted in Scheme 53.



Scheme 52 Reaction of urea **176** with LDA



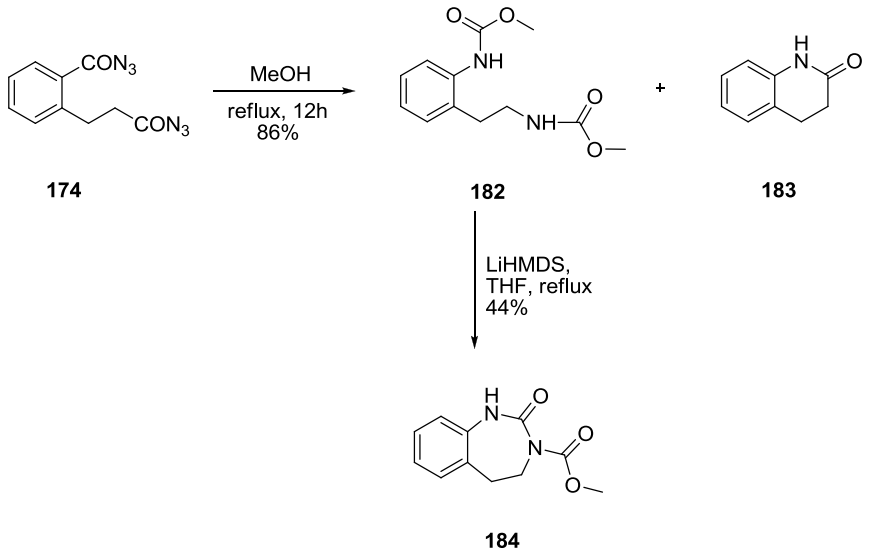
Scheme 53 Proposed mechanism for compound **180**

According to the proposal, first step includes the abstraction of the proton from the amide bonded to methylene group of the compound **176**. Then, nucleophilic attack to carbonyl group gives the target benzodiazepinone molecule **177**. At this point, reaction continues with the attack of the leaving aniline anion to compound **177**. It gives hydrolyzed benzodiazepinone **180** and fragmentation product **179**. This proposal could not be supported any further evidence due to isolation problems.

2.3.4 Synthesis of urethanes from bis(acyl azide) and their ring closure reactions

After the failure of the ring closure reactions of compound **176**, we turned our attention to increase reactivity of carbonyl groups in **176**. Therefore, we synthesized urethane derivatives starting from bis(acyl azide) **174**. Bis(acyl azide) **174** was reacted with alcohols such as methanol and *tert*-buthyl alcohole to give corresponding urethane derivatives. At the reflux temperature of methanol, two different products were observed. One was the target urethane **182** and the other one was the ring closure product **183** due to semi rearrangement of the compound 1**74** to isocyanate. Reactions of urethane **182** with various bases were also failed. No ring

closure product was detected at the end of the reactions. However, treatment of the urethane **182** with lithium hexamethyldisilazide for 30 minutes gave the target 1,3-benzodiazepinone derivative **184** in 44% yield (Scheme 54). Prolonged reaction time resulted in a decreased amount of the desired product.



174 **182** **183** **184**

Scheme 54 Synthesis of benzodiazepinone **184**

Structure confirmation was done at first glance by using IR, ^{1}H and ^{13}C- NMR spectroscopy. Exact confirmation of the structure was provided by X-ray analysis of the compound **184**.

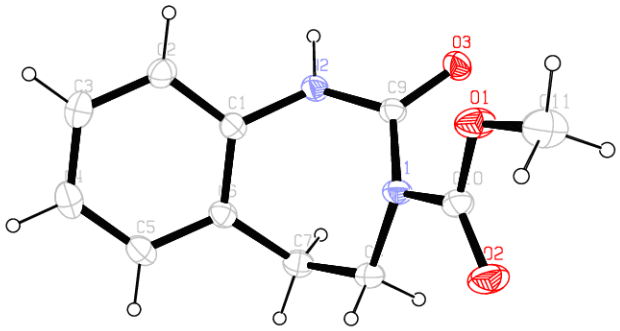
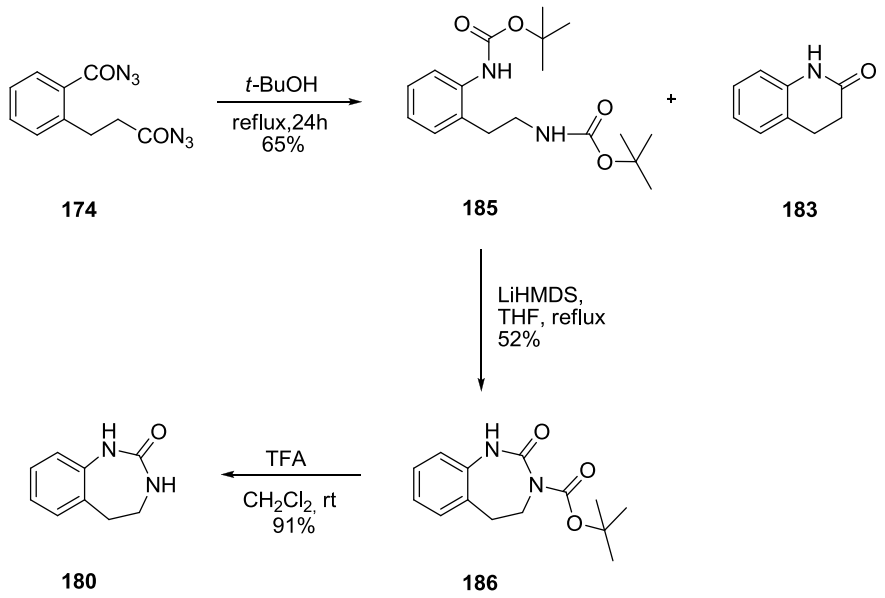


Figure 2 X-ray analysis of compound **184**

Similarly we applied same reaction conditions to *tert*-butyl urethane derivative **185**. In this case, target urethane derivative **185** was obtained in 65% yield (Scheme 55).



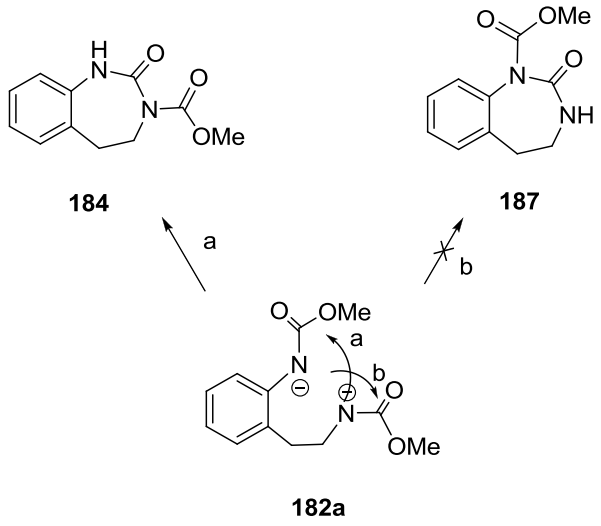
Scheme 55 Synthesis of benzodiazepinone **186**

After the isolation of the urethane **185**, we applied ring closure reaction conditions. Treatment of the urethane **185** with lithium hexamethyldisilazide for 30 minutes gave the target 1,3-benzodiazepinone derivative **186** in 52% yield. Structure confirmation was done by using IR, ^{1}H and ^{13}C- NMR spectroscopy. We also compared ^{1}H and ^{13}C- NMR spectra of compounds **184** and **186**. Both spectra showed same characteristics. Finally, the exact structure of **186** was confirmed by single crystal X-ray analysis.

Hydrolysis of the compound **186** was also done by using trifluoroacetic acid in dichloromethane at room temperature. This reaction gave the 1,3-benzodizepinon-2-one **180** in 91% yield. The spectroscopic data of 1,3-benzodizepinon-2-one **180** was fully in accordance with those reported in the literature.[53]

Careful analysis of the reaction mixture did not reveal the formation of any other product. Actually in the reaction of **182** as well as of **185**, two isomers were expected

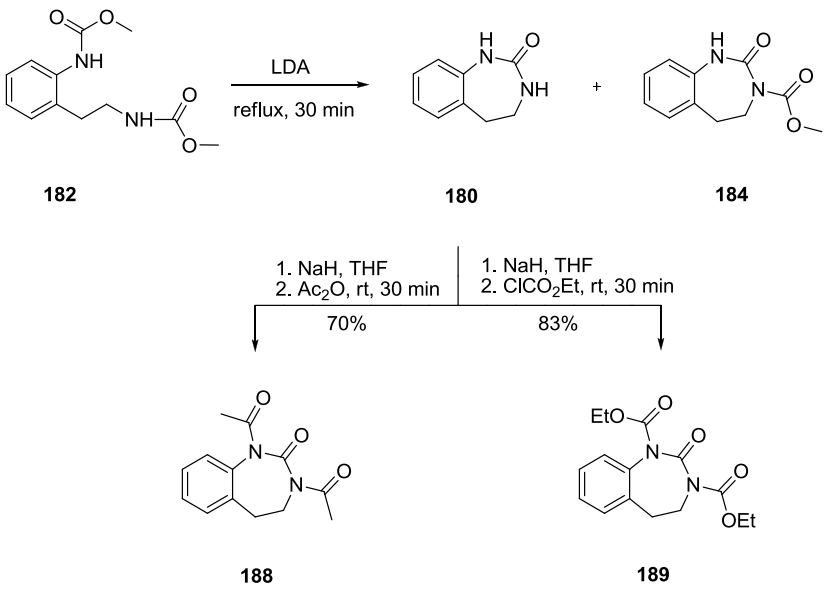
as a result of the attack of the amide functionalities to the two different carbonyl groups (Scheme 56). Because of the increased acidity of the NH attached directly to benzene ring, one would expect compound **187** as a sole major product. Surprisingly, the isomer **184** was formed as sole product. We assume that the abstraction of the more acidic -NH proton in diurethane **182** is hindered by the bulky base which is used, or the nucleophilicity of the amide functionality conjugated with the benzene ring may also be reduced due to the conjugation.



Scheme 56 Mechanism for the synthesis of **184** and **187**

After the proposal for the regiospesific product formation, we used another base for further reaction. Lithium diisopropylamide was freshly prepared from diisopropylamine and butyl lithium. Tetrahydrofuran solution of the lithiumdiisopropylamide was reacted with the compound **182**. Two products were formed. After isolation, products were identified as the cyclization products **184** and 1,3-benzodizepinon-2-one **180** (Scheme 57).

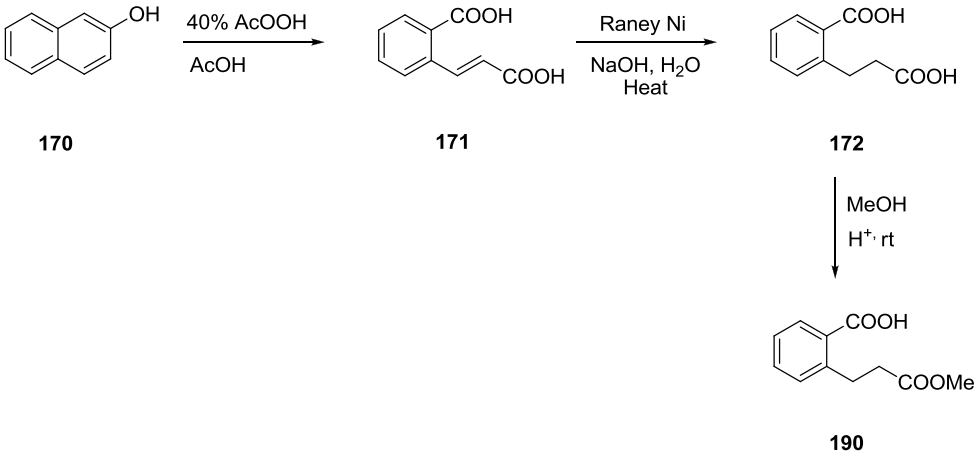
For further derivatization of the 1,3-benzodiazepin-2-one **180**, we used sodium hydride for proton abstraction and addition of acetic anhydride or ethyl chloroformate to this mixture as quenching reagent gave the diacetylated compound **188** and diester compound **189** in yields 70% and 83% respectively.



Scheme 57 Derivatization of benzodiazepinone**180**

2.4 Synthesis of dihydroquinolinone derivatives

2.4.1 Synthesis of starting compound: mono methyl ester



Scheme 58 Syntheis of mono methyl ester **190**

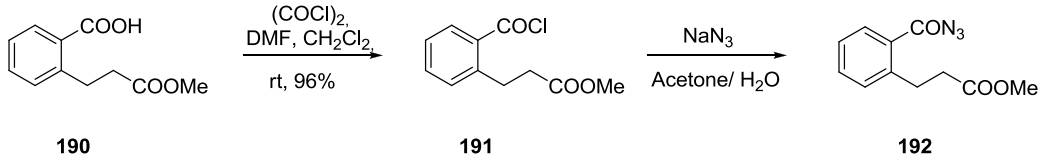
In the benzodiazepinone part, we described the synthesis of the starting material 2-(2-carboxyethyl)benzoic acid **172**. Carboxylic acid derivative **172** was synthesized

from β-naphthol **170**. Oxidation of β-naphthol **170** by reaction of peroxyacetic acid gave *o*-carboxycinnamic acid **171**. Then successive hydrogenation with Raney nickel in basic aqueus solution gave the target starting material, 2-(2-carboxyethyl)benzoic acid **172**. In this case, we needed to go one step further. Mono methyl ester compound **190** was obtained by esterification reaction at room temperature (Scheme 58).[54]

In this study, most important step was the regiospesific synthesis of mono methyl ester compound **190**. There are two reactive site inside the molecule for esterification reaction. After 30 minutes at room temperature, only the carboxylic acid which is bonded to -CH_2- group undergoes esterification. The reason is obvious; this carboxylic acid is more reactive than the carboxylic acid which is directly bonded to benzene ring. If we compare the carboxylic acid groups, one of the groups is bonded directly to the benzene ring. This conjugation decreases reactivity of carboxylic acid. For the carboxylic acid bonded to CH_2- group, there are two methylene groups between benzene and carboxylic acid, which prevent conjugation. Therefore, this part is more reactive and esterification occurs exclusively at this position.

2.4.2 Synthesis of acyl azide compound

As we described in earlier, the mono methyl ester **190** was reacted with oxalyl chloride in dichloromethane in the presence of catalytic amount of *N*,*N*-dimethylformamide to give acyl chloride **191** in quite high yield 96% (Scheme 59). By using this chlorination reaction, a better leaving group, chlorine atom was attached to molecule for next step. This methodology was used to reach desired acyl azide **192** which is key compound in Curtius rearrangement.

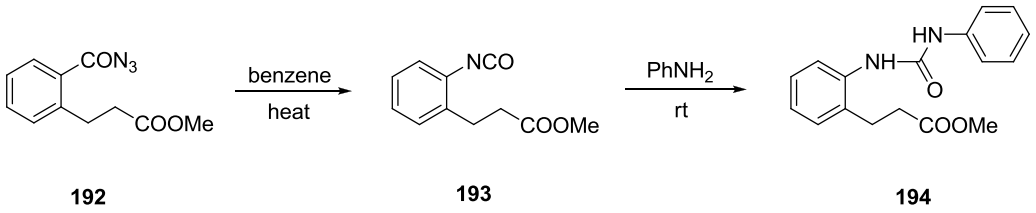


Scheme 59 Synthesis of acyl azide **192**

An aqueous solution of sodium azide was added to solution of acyl chloride **191** in acetone. The formation of acyl azide **192** was observed and proved by characteristic frequency of azide functionality at around 2100 cm^{-1} in IR spectrum.

2.4.3 Synthesis of urea derivative from acyl azide

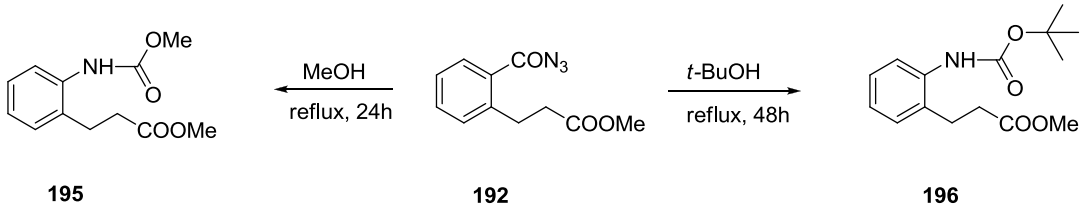
For the synthesis of target urea derivative **194**, acyl azide **192** was heated in benzene to give corresponding isocyanate **193** by Curtius rearrangement. Treatment of isocyanate molecule **193** with aniline in dichloromethane at room temperature gave the target urea derivative **194** (Scheme 60).



Scheme 60 Synthesis of urea **194**

2.4.4 Synthesis of urethane derivatives from acyl azide

We also synthesized urethane derivatives to expand our substrate molecules for ring closure reactions. Urethane derivatives were synthesized by heating acyl azide compound **192** in alcohols such as methanol and *tert*-butyl alcohol. This transformation includes in situ formation of isocyanate molecule **193**. In situ formed isocyanate **193** was reacted with nuclephiles to give target urethane derivatives **195** and **196** (Scheme 61).

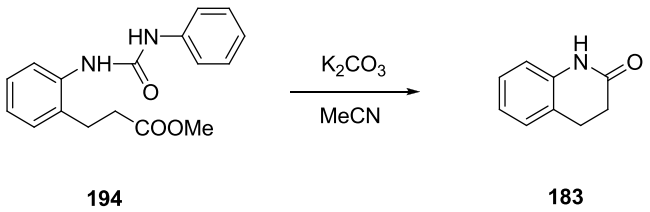


Scheme 61 Synthesis of urethanes **195** and **196**

After the successful synthesis of target urea and urethane derivatives, we focused on hydrolysis reactions of the formed urea and urethane substrates.

2.4.5 Hydrolysis of urea and urethane derivatives

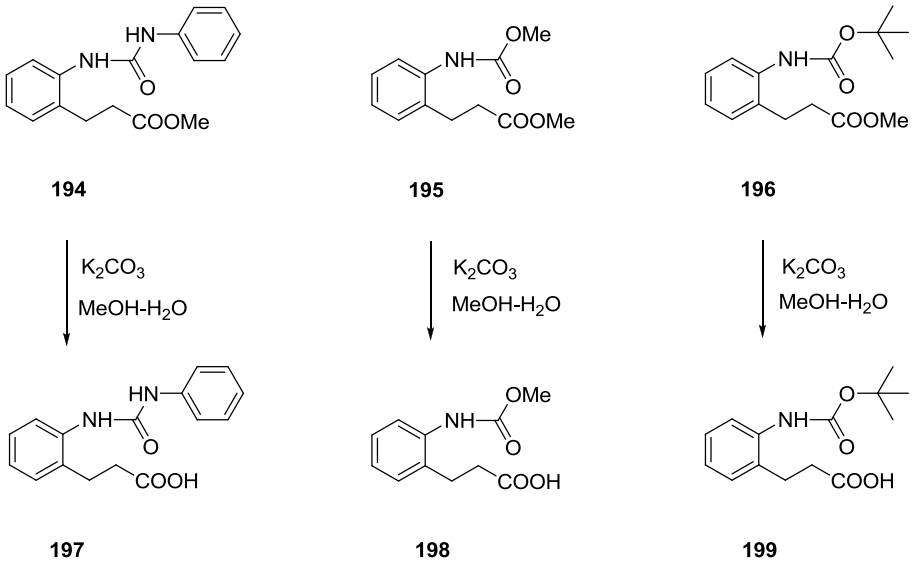
Base mediated ring closure reaction of urea derivative **194** was failed. We isolated the hydrolyzed product **183** at the end of the reaction as sole product (Scheme 62). Therefore, we turned our attention to a new ring closure methodology. A mild ring closure conditions were provided by this technique.



194 **183**

Scheme 62 Ring closure reaction of urea **194** with base

This method depends on the reactivity increase of the ester groups in urea and urethane molecules. We hydrolyzed all three ester molecules by potassium carbonate in refluxing methanol-water mixture (1:1) (Scheme 63).



194 **195** **196**

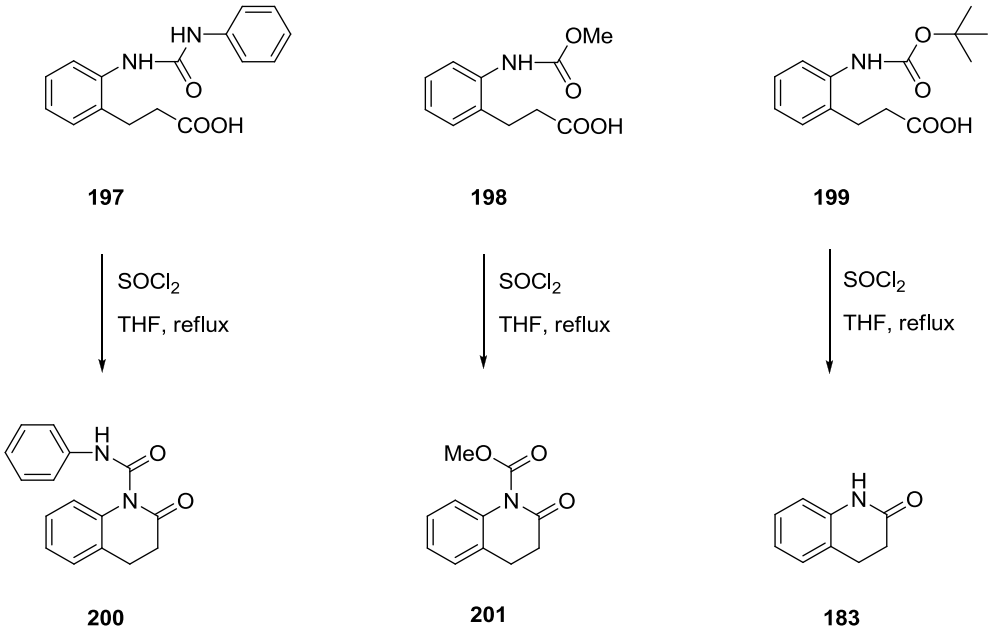
197 **198** **199**

Scheme 63 Synthesis of hydrolyzed urea and urethanes

Carboxylic acid derivatives **197-199** were used for the ring closure reactions to reach dihydroquinolinones.

2.4.6 Ring closure of the hydrolyzed urea and urethane derivatives

As explained earlier, base mediated ring closure reactions were failed. Then we decided to increase reactivity of the carbonyl groups by transforming ester groups to acyl chlorides. To use this methodology, we hydrolyzed all urea and urethane derivatives' ester groups in Scheme 58. Acyl chloride formation was described in earlier chapters by oxalyl chloride in dichloromethane at room temprature. In this study, we used another chlorination process to force ring closure reactions by reactive acyl chlorides. Treatment of carboxylic acid derivatives with thionyl chloride in tetrahydrofuran gave the target dihydroquinolinone molecules **200** and **201** (Scheme 64).

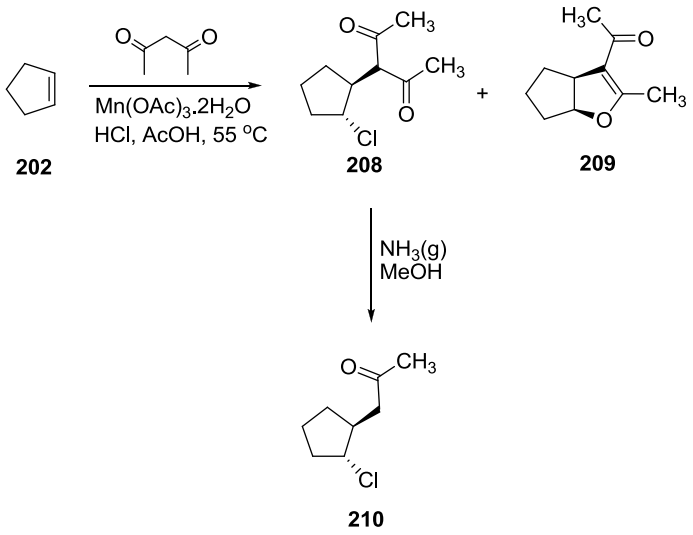


Scheme 64 Ring closure reactions of urea and urethanes by thionyl chloride

Acyl chloride molecules were not isolated. In situ formed acyl chloride molecules spontaneously transformed to dihydroquinoline products **200**, **201** and **183**. For the Boc protected molecule **199**, hydrolyzed dihydroquinolinone **183** was obtained as sole product. Boc groups are not very stable in acidic medium. After ring closure, medium was acidic due to formed hydrochloric acid.

2.5 Chloroacetonylation of C=C double bonds

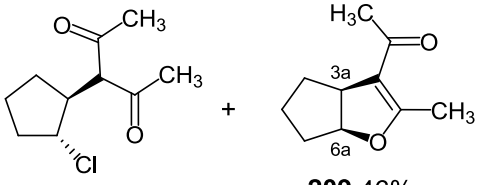
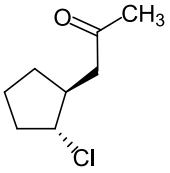
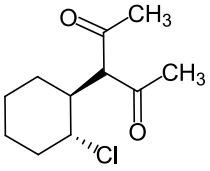
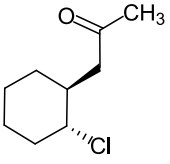
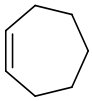
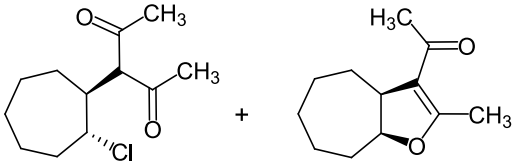
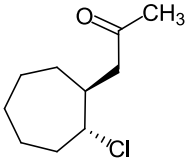
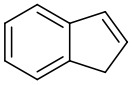
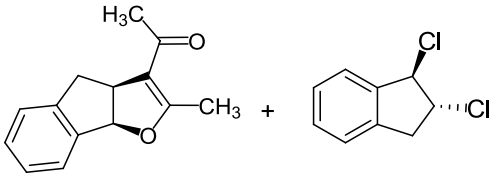
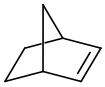
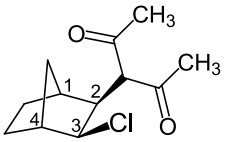
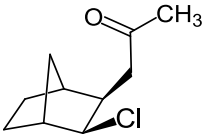
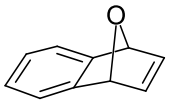
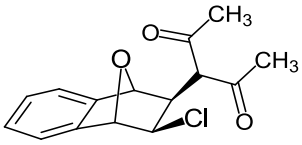
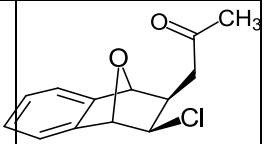
2.5.1 Reaction of acetylacetone with C=C double bonds in the presence of $Mn(OAc)_3$ and HCl



Scheme 65 Chlorocetonylation of cyclopentene

In this study, we were interested in addressing the question whether the carbocation generated by reaction of 1,3-dicarbonyl compounds in the presence of $Mn(OAc)_3$ can be trapped with a nucleophile or not. As a nucleophile, we used conc. HCl solution. Therefore, we searched the reaction of $Mn(OAc)_3$ with various alkenes in the presence of HCl to incorporate chlorine atom into the molecule (Table 1 & Scheme 65).

Table 1 Reaction of various alkenes with acetylacetone in the presence of conc. HCl

Entry	Compound	Addition products	Acetonyl Product
1	 **202**	 **208** 31% + **209** 46%	 **210** (87%)
2	 **203**	 **211** (85%)	 **212** (92%)
3	 **204**	 **213** (53%) + **214** (35%)	 **215** (87%)
4	 **205**	 **216** (75%) **217** (13.5%)	--
5	 **206**	 **218** (65%)	 **219 (**95%)
6	 **207**	 **220** (87%)	 **221** (95%)

Acetylacetone was chosen as 1,3-dicarbonyl compound to explore addition reactions. The purpose of choosing acetyl acetone will be shown in second part of this study. Treatment of cyclopentene **202** and $Mn(OAc)_3.2H_2O$ in acetic acid with acetylacetone and HCl at 55 ^oC for 24 hours gave the dihydrofuran adduct **209** in a 46% yield, whereas the desired trapping product **208** was formed in 31% yield (Entry 1, Table 1). The structures of the compounds **208** and **209** were characterized by their NMR spectra. The *cis* configuration of dihydrofuran ring was determined by comparison with similar systems[55] and measuring the coupling constant between protons H-3a and H-6a (*J = 8.*0 Hz*)*, which supports *cis*-configuration of the coupled protons. Furthermore, we performed a restricted hybrid HF-DFT SCF calculation using the basis set 6-31G** as implemented in the Spartan'08 V111 package program and shown that the *cis*-isomer **209** 15.3 kcal/mol more stable than the corresponding *trans*-isomer. The *trans*-configuration in **208** was also assigned by same calculations. It was shown that *trans*-isomer **208** is about 6.76 kcal/mol more stable than the *cis*-isomer.

Reaction of cyclohexene with acetyl acetone in the presence of $Mn(OAc)_3.2H_2O$ gave the adduct **211**[56] as sole product, in 85% yield (Entry 2, Table 1). Interestingly, we have not detected any amount of dihydrofuran derivative as in the case of cyclopentene **202**. On the other hand, cycloheptene **204** surprisingly afforded cyclization product **214** in 35% yield beside the expected product **213** which was formed in 53% yield (Entry 3, Table 1)

For entry 4, the reaction of indene **205** with $Mn(OAc)_3$, having a strained double bond, did not form the expected addition product. Mainly, cyclization product **216** was formed in a yield of 75%, whereas *trans*-1,2-dichloroindene (**217**) formed by addition of in situ generated chlorine to the double bond of indene, wasformed as the minor product.

Reaction of acetylacetone with bicyclic olefins such as norbornene **206** and oxabenzonorbornadiene **207** proceeded smoothly; the desired addition products **218** and **220** were isolated in 65 and 87% yields, respectively. The *exo*-configuration of the substituents was confirmed by measuring the coupling constants between the

bridgehead protons and protons adjacent to the substituents. The bridgehead protons in **220** resonate as two separate singlets at 5.24 and 4.85 ppm. The absence of any coupling between the protons H1-H2 and H3-H4 confirms the *endo*-orientation of the protons, a high value of J_{12} (J_{34}) about 3.5-5.0 Hz would be expected in case of *endo*-orientation of the substituents. In the case of norbornene system, the observed small couplings J_{12} = 1.1 and J_{34} = 1.3 Hz also support the *exo*-configuration of the substituents in **219**. The isolated adducts were again converted to the corresponding acetonyl derivatives **219** and **221** in a yield of 95%.

2.5.2 Removal of acetyl group from addition products by ammonia

In the last part of our study, we used a method to reach our target chloroacetonylation products. Reaction of addition products with gaseous ammonia in methanol gave target chloroacetonylation products with quite high yields (Scheme 65). Acetyl group was removed under very mild reaction conditions. Room temperature was enough for removal of acetyl group from the molecules.

Addition product **208** was reacted with NH_3 and desired chloroacetonylation product **210** was obtained in 87% yield (Scheme 65). We also performed same reaction for the other addition products (Entry, 1,2,3,5,6, Table 1).

As a result, we developed simple and short method for chloroacetonylation of the various double bonds in two subsequent steps.

CHAPTER 3

EXPERIMENTAL

3.1 General

Nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in DMSO-$_{d6}$ and $CDCl_3$ with TMS as internal reference. Chemical shifts (δ) were expressed in units parts per million (ppm). Spin multiplicities were specified as singlet (s), doublet (d), doublet of doublets (dd), triplet (t) and multiplet (m) and coupling constants (J) were reported in Hertz (Hz).

Infrared spectra were recorded on a Matson 1000 FT-IR spectrometer and Vertex 70 series FT-IR spectrometer. Band positions were reported in reciprocal centimeters (cm^{-1}).

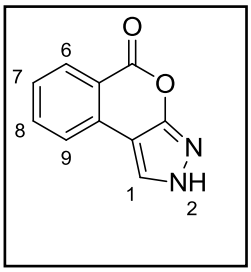
Column chromatographic separations were performed by using Fluka Silica Gel 60 plates with a particle size of 0.063–0.200 mm. Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Fluka.

Compounds were named by using ChemDraw Ultra 11.0 and ACD NMR.

Solvents were purified as reported in the literature.[57]

3.2 Synthesis of isochromeno[3,4-*c*]pyrazol-5(2*H*)-one (145a)

To a solution of homophthalic anhydride **141a** (0.60 g, 3.7 mmol) in DMF (5 mL), an excess amount of hydrazine monohydrate (1.0 mL, 14.2 mmol) was added at room temperature and the resulting mixture was refluxed overnight. After cooling to room temperature, the residue was triturated with H_2O (50 mL), filtered and dried to give an analytically pure sample of **145a**. (isolated yield: 0.56 g, 81%); mp 263–264 ^oC.



^{1}H-NMR (400 MHz, DMSO-d_6) δ 13.14 (br s, 1H, –NH), 8.46 (br s, 1H, H-1), 8.17 (br d, $J_{6,7}$ = 7.9 Hz, 1H, H-6), 7.92 (br d, $J_{9,8}$ = 7.7 Hz, 1H, H-9), 7.92 (br dd, $J_{8,9}$ = 7.7 Hz, $J_{8,7}$ = 7.5 Hz, 1H, H-8), 7.49 (br dd, $J_{7,8}$ = 7.5 Hz, $J_{7,6}$ = 7.9 Hz, 1H, H-7).

^{13}C NMR (100 MHz, DMSO-d_6) δ 161.8, 157.3, 135.9, 133.3, 131.2, 127.2, 125.6, 123.7, 118.7, 100.0.

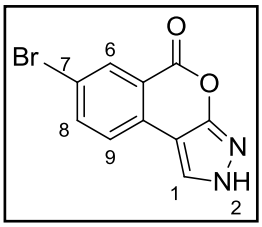
IR (KBr, cm^{-1}) 3218, 2958, 1733, 1705, 1685, 1625, 1590, 1496,1434, 1318, 1242, 1187, 1076, 1053, 942, 871, 757.

Anal. Calcd for $C_{10}H_6N_2O_2$: C, 64.52; H, 3.25; N, 15.05. Found: C, 64.25; H, 3.45; N, 16.03.

HRMS m/z $(M+H)^+$ Calcd for $C_{10}H_7N_2O_2$: 187.0508; found: 187.0506.

3.3 Synthesis of 7-bromoisochromeno[3,4-*c*]pyrazol-5(2*H*)-one (145b)

To a solution of homophthalic anhydride **141b** (1.44g, 6.0 mmol) in DMF (12 mL), an excess amount of hydrazine monohydrate (2.4 mL, 34.1 mmol) was added at room temperature and the resulting mixture was refluxed overnight. After cooling to room temperature, the residue was triturated with H_2O (50 mL), filtered and dried to give an analytically pure sample of **145b**. (isolated yield: (1.16 g, 73%), mp 322–324 ^oC.



^{1}H-NMR (400 MHz, DMSO-d_6) δ 13.27 (br s, 1H, NH), 8.57 (br s, 1H, H-1), 8.28 (d, $J_{6,8}$ = 2.1 Hz, 1H, H-6), 8.09 (dd, $J_{8,9}$ = 8.4, $J_{8,6}$ = 2.1 Hz, 1H, H-8), 7.95 (d, $J_{9,8}$ = 8.4 Hz, 1H, H-9).

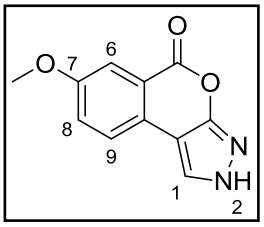
^{13}C NMR (100 MHz, DMSO-d_6) δ 160.2, 156.7, 138.0, 132.6, 132.0, 125.5, 125.1, 120.2, 118.7, 99.0.

IR (ATR, cm^{-1}) 3216, 1735, 1622, 1586, 1485, 1231, 1177, 1072, 822.

HRMS m/z $(M+H)^+$ Calcd for $C_{10}H_5N_2O_2Br$: 264.9613; found: 264.9611.

3.4 Synthesis of 7-methoxyisochromeno[3,4-*c*]pyrazol-5(2*H*)-one (145c)

To a solution of homophthalic anhydride **141c** (0.34 g, 1.8 mmol) in DMF (2 mL), an excess amount of hydrazine monohydrate (0.5 mL, 7.1 mmol) was added at room temperature and the resulting mixture was refluxed overnight. After cooling to room temperature, the residue was triturated with H_2O (50 mL), filtered and dried to give an analytically pure sample of **145c** with 63% yield, mp 275–276 ^oC.



^{1}H-NMR (400 MHz, DMSO-d_6) δ 13.04 (br s, 1H, NH), 8.39 (d, $J_{1,2}$ = 1.8 Hz, 1H, H-1), 7.87 (d, $J_{8,9}$ = 8.6 Hz, 1H, H-9), 7.60 (d, $J_{6,8}$ = 2.7 Hz, 1H, H-6), 7.47 (dd, $J_{8,9}$ = 8.6 Hz, $J_{6,8}$ = 2.8 Hz, 1H, H-8), 3.86 (s, 3H, H-10, –OCH_3).

^{13}C NMR (100 MHz, DMSO-d_6) δ 161.2, 157.8, 156.3, 126.2, 124.5, 124.1, 123.9, 119.3, 112.5, 99.4, 55.5.

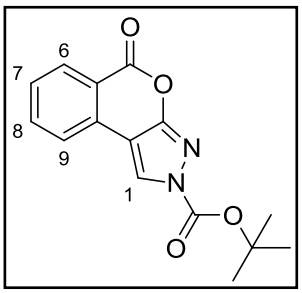
IR (ATR, cm^{-1}) 3649, 3446, 1734, 1653, 998.

HRMS m/z $(M+H)^+$ Calcd for $C_{11}H_9N_2O_3$: 217.0613; found: 217.0612.

3.5 Synthesis of *tert*-butyl 5-oxoisochromeno[3,4-*c*]pyrazole-2(5*H*)-carboxylate (146)

Isochromeno[3,4-*c*]pyrazol-5(2*H*)-one **145a** (0.38g, 2.0 mmol) was dissolved in 10 ml THF and temperature cooled down to 0°C. To this mixture was added NaH (0.09 g, 2.3 mmol, (%60)) and reaction mixture was mixed for 30 min. Then, Boc_2O (2.3

mmol, 0.49 g) was added at room temperature and reaction mixture was mixed another 30 min with TLC control. After the completion of the reaction, excess NaH was quenched with dropwise addition of water. The reaction crude was obtained by extraction with 3x50ml EtOAc and concentration at vacuo. Finally, *tert*-butyl 5-oxoisochromeno[3,4-c]pyrazole-2(*5H*)-carboxylate **146** (0.53g, 91%, mp 270.0–271.5 ^{o}C) was obtained with flash chromatography with DCM.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H, H-1), 8.36 (br d, $J_{6,7}$ = 7.9, 1H, H-6), 7.85–7.70 (m, 2H), 7.53 (dt, *J* = 7.5, *J* = 1.6 Hz, 1H, H-8), 1.69 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 159.0, 147.4, 135.3, 131.9, 130.6, 128.5, 125.0, 123.1, 120.2, 105.2, 86.7, 27.9.

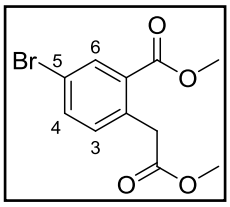
IR (ATR, cm^{-1}) 3649, 3446, 1734, 1653, 998.

HRMS m/z $(M+Na)^+$ Calcd for $C_{15}H_{14}N_2O_4Na$: 309.0850; found: 309.0851.

X-ray Crystallographic data (excluding structure factors) for structure **146** have been deposited (CCDC 800464) with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: (+44) 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk).

3.6 Synthesis of methyl 5-bromo-2-(2-methoxy-2-oxoethyl)benzoate (162b)

To a solution of 5-bromo-2-(carboxymethyl)benzoic acid **140b** (2.43g, 9.4 mmol) in MeOH (50 mL) was added $SOCl_2$ (1.70 ml, 23.5 mmol) dropwise at room temperature; the mixture was refluxed for 12 h. After completion of the reaction, the solvent was evaporated to give methyl 5-bromo-2-(2-methoxy-2-oxoethyl)benzoate **162b**. Chromatography of the residue over a short column (silica gel, CH_2Cl_2) gave pure diester (yield: 2.48 g (92%); mp 101–103 °C).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (d, $J_{6,4}$ = 2.1 Hz, 1H, H-6), 7.51 (dd, $J_{4,3}$ = 8.1 Hz, $J_{4,6}$ = 2.1 Hz, 1H, H-4), 7.05 (d, $J_{3,4}$ = 8.2 Hz, 1H, H-3), 3.88 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.61 (s, 3H,

OCH_3).

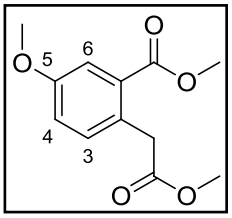
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 166.1, 135.2, 134.9, 133.9, 133.8, 131.3, 121.1, 52.3, 52.0, 39.8.

IR (KBr, cm^{-1}) 2991, 2951, 1723, 1591, 1288, 1254, 1167.

Anal. Calcd for $C_{11}H_{11}BrO_4$: C, 46.02; H, 3.86. Found: C, 46.23; H, 3.75.

3.7 Synthesis of methyl 5-methoxy-2-(2-methoxy-2-oxoethyl)benzoate (162c)

2-(carboxymethyl)-5-methoxybenzoic acid **140c** (2.84g, 13.5mmol) was dissolved in 50 ml MeOH and was added $SOCl_2$ (2.45ml, 33.8mmol) dropwise at room temperature; mixture was refluxed for 12 hours. After the completion of the reaction, the solvent was evaporated to give diester **162c**. Chromatography of the residue over a short column (silica gel, CH_2Cl_2) gave pure **162c** (3.12g, 97%) as colorless oil.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.47 (br d, $J_{6,4}$ = 2.8 Hz, 1H, H-6), 7.09 (br d, $J_{3,4}$: 8.4 Hz, 1H, H-3), 6.95 (br dd, $J_{4,3}$ = 8.4 Hz and J_{46}: 2.8 Hz, 1H, H-4), 3.86 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 3.62 (s, 3H,OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 167.3, 158.6, 133.3, 130.5, 128.0, 118.4, 115.9, 55.5, 52.0, 51.9, 39.7.

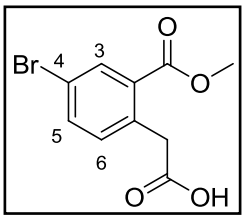
IR (KBr, cm^{-1}) 2951, 2835, 1736, 1712, 1286, 1213, 1044, 793.

HRMS m/z $(M+H)^+$ Calcd for $C_{12}H_{15}O_5$: 239.0914; found: 239.0865.

3.8 Synthesis of [4-bromo-2-(methoxycarbonyl)phenyl]acetic acid (156b)

To a solution of diester **162b** (2.82 g, 9.8 mmol) in MeOH–H_2O (1:1, 50mL) was added K_2CO_3 (2.31 g, 16.7 mmol) and the mixture was refluxed for 45 min. The mixture was cooled to r.t. and H_2O was added. To remove the unreacted diester **162b**, the aqueous phase was extracted with EtOAc. The aqueous phase was acidified with 1 M HCl and extracted with EtOAc. Evaporation of the solvent gave

pure **156b** as a white solid; yield: 1.75 g (73% based on consumed diester **162b**); mp 161–163 °C.



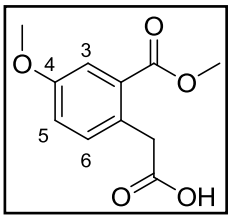
^{1}H-NMR (400 MHz, $CDCl_3$) δ 11.00–10.20 (br s, 1H, OH), 8.07 (d, $J_{3,5}$ = 2.2 Hz, 1H, H-3), 7.52 (dd, $J_{5,6}$ = 8.2 Hz, $J_{5,3}$ = 2.2 Hz, 1H, H-5), 7.05 (d, $J_{6,5}$ = 8.2 Hz, 1 H, H-6), 3.90 (s, 2 H, CH_2), 3.80 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 165.4, 134.5, 133.3, 133.0, 132.9, 130.1, 120.5, 51.5, 39.0.

IR (KBr, cm^{-1}) 3500, 2953, 1706, 1435, 1288, 1255, 1080.

3.9 Synthesis of [4-methoxy-2-(methoxycarbonyl)phenyl]acetic acid acid (156c)

To a solution of diester **162c** (1.45 g, 6.1 mmol) in MeOH–H_2O (1:1, 50mL) was added K_2CO_3 (1.43 g, 10.4 mmol) and the mixture was refluxed for 45 min. The mixture was cooled to r.t. and H_2O was added. To remove the unreacted diester **162c**, the aqueous phase was extracted with EtOAc. The aqueous phase was acidified with 1 M HCl and extracted with EtOAc. Evaporation of the solvent gave pure **156c** as a white solid; yield: 0.82 g (60% based on consumed diester **162c**); mp 136–137 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 14.00-8.00 (br s, 1H, OH), 7.54 (d, $J_{3,5}$ = 2.8 Hz, 1H, H-3), 7.22 (part of AB system d, J_{65} = 8.4 Hz, 1H, H-6), 7.05 (part of AB system, dd, J_{53} = 2.8 and J_{56} = 8.4 Hz, 1H, H-5), 3.94 (s, 2H, CH_2), 3.91 (s, 3H,OMe), 3.84 (s, 3H, OMe).

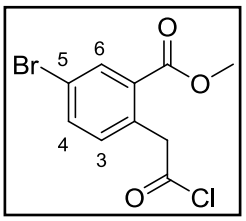
^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 168.0, 158.8, 133.4, 130.3, 127.4, 118.8, 116.0, 55.5, 52.4, 39.9.

IR (KBr, cm^{-1}) 2953, 1714, 1691, 1610, 1287, 1231, 1072, 781.

3.10 Synthesis of methyl-5-bromo-2-(2-chloro-2-oxoethyl)benzoate (163b)

To a stirred suspension of half ester **156b** (0.82 g, 3.0 mmol) in CH_2Cl_2 (25 mL) was added oxalyl chloride (0.28 ml, 3.3 mmol) and DMF (2 drops) as catalyst. The

resulting solution was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was evaporated to give **163b** (0.85 g, 97%) as a yellowish viscous oil.



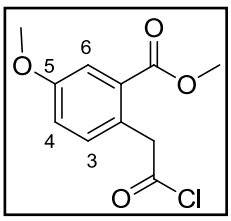
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 (d, $J_{6,4}$ = 2.2 Hz, 1H, H-6), 7.58 (dd, $J_{4,3}$ = 8.1 Hz, $J_{4,6}$ = 2.2 Hz, 1H, H-4), 7.06 (d, $J_{3,4}$ = 8.2 Hz,1H, H-3), 4.42 (s, 2 H, CH_2), 3.84 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 165.7, 135.8, 134.4, 133.7, 132.9, 130.7, 122.5, 52.6, 51.9.

IR (KBr, cm^{-1}) 2953, 1799, 1721, 1259, 963, 752.

3.11 Synthesis of methyl 2-(2-chloro-2-oxoethyl)-5-methoxybenzoate (163c)

To a stirred suspension of half ester **156c** (0.79 g, 3.5 mmol) in CH_2Cl_2 (25 mL) was added oxalyl chloride (0.36ml, 4.2 mmol) and DMF (2 drops) as catalyst. The resulting solution was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was evaporated to give **163c** (0.81 g, 95%) as a yellowish viscous oil.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.61 (d, $J_{6,4}$ = 2.8 Hz, 1H, H-6), 7.16 (d, $J_{3,4}$ = 8.5 Hz, 1H, H-3), 7.06 (dd, $J_{4,3}$ = 8.5 Hz, $J_{4,6}$ = 2.8 Hz, 1H, H4), 4.46 (s, 2 H, CH_2), 3.91 (s, 3 H, OMe), 3.85 (s, 3 H, OMe).

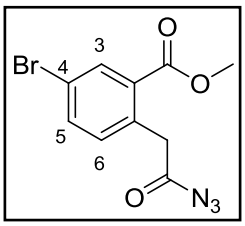
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 166.8, 159.4, 133.3, 130.1, 126.0, 118.7, 116.3, 55.6, 52.4, 51.9.

IR (KBr, cm^{-1}) 2954, 1799, 1716, 1287, 904.

3.12 Synthesis of methyl 2-(2-azido-2-oxoethyl)-5-bromobenzoate (164b)

To a solution of acyl chloride **163b** (1.54 g, 5.3 mmol) in acetone (30 mL) was added a solution of NaN_3 (0.69 g, 10.56 mmol) in H_2O (10 mL) dropwise at 0 °C and the mixture was stirred at 0 °C for 1 h. After the addition of H_2O (25 mL) the mixture was extracted with EtOAc (3 × 25 mL), and the combined extracts were washed with

sat. $NaHCO_3$ and H_2O, and dried ($MgSO_4$). After concentration of the solvent, acyl azide **164b** (1.34 g, 85%), unstable at room temperature, was obtained as yellowish oil, which was used for the next step without purification.



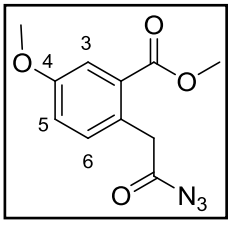
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.12 (d, $J_{3,5}$ = 2.2 Hz, 1H, H-3), 7.56 (dd, $J_{5,6}$ = 8.1 Hz, $J_{5,3}$ = 2.2 Hz, 1H, H-5), 7.05 (d, $J_{6,5}$ = 8.2 Hz, 1H, H-6), 3.92 (s, 2 H, CH_2), 3.83 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 164.9, 134.5, 133.1, 133.0, 132.9, 130.0, 120.7, 51.4, 41.3.

IR (KBr, cm^{-1}) 2952, 2316, 1716, 1640, 1289, 1254, 1064, 833.

3.13 Synthesis of methyl 2-(2-azido-2-oxoethyl)-5-methoxybenzoate (164c)

To a solution of acyl chloride **163c** (1.51 g, 6.2 mmol) in acetone (30 mL) was added a solution of NaN_3 (0.81 g, 12.4 mmol) in H_2O (10 mL) dropwise at 0 °C and the mixture was stirred at 0 °C for 1 hour. After the addition of H_2O (25 mL) the mixture was extracted with EtOAc (3 × 25 mL), and the combined extracts were washed with sat. $NaHCO_3$ and H_2O, and dried ($MgSO_4$). After concentration of the solvent, acyl azide **164c** (1.39 g, 89%), unstable at room temperature, was obtained as yellowish oil, which was used for the next step without purification.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.57 (d, $J_{3,5}$ = 2.6 Hz, 1H, H-3), 7.16 (d, $J_{6,5}$ = 8.4 Hz, 1H, H-6), 7.05 (dd, $J_{5,6}$ = 8.4 Hz, $J_{5,3}$ = 2.6 Hz, 1H, H-5), 3.96 (s, 2H, CH_2), 3.89 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3).

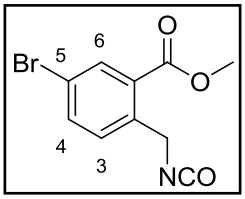
^{13}C NMR (100 MHz, $CDCl_3$) δ 178.7, 167.1, 158.9, 133.5, 130.2,127.1, 118.6, 116.1, 55.5, 52.2, 42.2.

IR (KBr, cm^{-1}) 2953, 2254, 2138, 1716, 1610, 1504, 1275, 905, 728.

3.14 Synthesis of 5-bromo-2-(isocyanatomethyl)benzoate (158b)

Acyl azide **164b** (0.30g, 1.0 mmol) was dissolved in dry benzene (50 mL) and refluxed for 1 hour. After completion of the reaction, the reaction mixture was concentrated at vacuo to give 5-bromo-2-(isocyanatomethyl)benzoate **158b** (0.27 g,

99%) as yellowish oil which was directly used for the next steps without further purification.



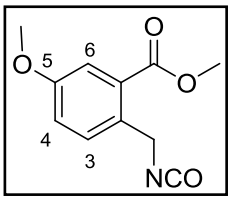
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J_{64}: 2.2 Hz, 1H, H-6), 7.60 (dd, J_{43} = 8.3 Hz and J_{46} = 2.2 Hz, 1H, H-4), 7.38 (d, 1H, J_{34} = 8.3 Hz, H-3), 4.81 (s, 2H, CH_2), 3.84 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 137.9, 136.0, 134.2, 130.4, 129.5, 125.2, 121.8, 52.7, 45.5

IR (KBr, cm^{-1}) 2264, 1720, 1642, 1292, 1255, 907,730.

3.15 Synthesis of methyl 2-(isocyanatomethyl)-5-methoxybenzoate (158c)

Acyl azide **164c** (1.39g, 5.6 mmol) was dissolved in dry benzene (50 mL) and refluxed for 1 hour. After completion of the reaction, the reaction mixture was concentrated at vacuo to give methyl 2-(isocyanatomethyl)-5-methoxybenzoate **158c** (1.20 g, 98%) as yellowish oil which was directly used for the next steps without further purification.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J_{64} = 2.8 Hz, 1H, H-6), 7.37 (part of AB system d, J_{34} = 8.5 Hz, 1H, H-3), 7.03 (part of AB system dd, J_{43} = 8.5 Hz and J_{46} =2.8 Hz, 1H, H-4), 4.75 (s, 2H, CH_2), 3.89 (s, 3H, OMe), 3.80 (s, 3H, OMe).

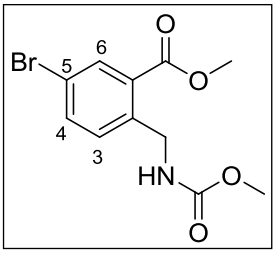
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 159.0, 130.6, 130.3, 128.9, 128.3, 118.4, 116.2, 55.4, 52.2, 45.2.

IR (KBr, cm^{-1}) 2255, 1716, 1504, 1436, 1231, 904.

3.16 Synthesis of methyl 5-Bromo-2-{[(methoxycarbonyl)amino]methyl} benzoate (165b)

A solution of acyl azide **164b** (1.54 g, 5.17 mmol) in MeOH (150 mL) was refluxed for 12 h with TLC monitoring. After completion of reaction,the solvent was removed

under vacuum. Chromatography of the residue (silica gel, 50 g, EtOAc–hexane–CH_2Cl_2, 1:1:2) afforded **165b** (0.75 g, 48%) as a colorless solid; mp: 82-83 ^oC.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.05 (d, $J_{6,4}$ = 1.9 Hz, 1H, H-6), 7.55 (dd, $J_{4,3}$ = 8.2 Hz, $J_{4,6}$ = 2.2 Hz, 1H, H-4), 7.35 (d, $J_{3,4}$ = 8.2 Hz, 1H, H-3), 5.73 (br s, 1H, NH), 4.43 (d, $J_{(CH2)(NH)}$ = 6.8 Hz, 2 H, CH_2), 3.85 (s, 3 H, OCH_3), 3.56 (s, 3 H, OCH_3).

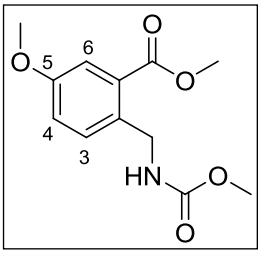
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 157.0, 139.5, 135.7, 133.9, 132.8, 130.2, 121.4, 52.5, 52.1, 43.6.

IR (KBr, cm^{-1}) 3442, 2952, 1708, 1497, 1447, 1246, 996.

HRMS m/z $(M+Na)^+$ Calcd for $C_{11}H_{12}NO_4Na$: 323.9842; found: 323.9842.

3.17 Synthesis of methyl 5-methoxy-2 {[(methoxycarbonyl) amino]methyl} benzoate (165c)

A solution of acyl azide **164c** (1.15 g, 4.61 mmol) in MeOH (150 mL) was refluxed for 12 h with TLC monitoring. After completion of reaction, the solvent was removed under vacuum. Chromatography of the residue (silica gel, 50 g, EtOAc–hexane, 1:2) afforded **165c** (0.88 g, 75%) as a colorless oil.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (d, $J_{4,6}$ = 2.7 Hz, 1H, H-6), 7.45 (d, $J_{3,4}$ = 8.5 Hz, 1H, H-3), 7.03 (dd, $J_{3,4}$ = 8.5 Hz, $J_{4,6}$ = 2.7 Hz, 1H, H-4), 5.82 (br s, 1H, NH), 4.47 (br d, $J_{(CH2)(NH)}$ = 6.6 Hz, 2H, CH_2), 3.91 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3).

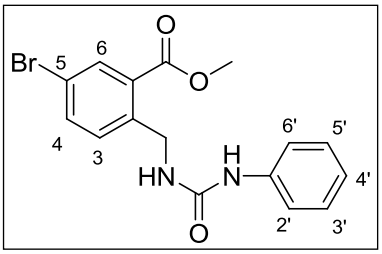
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 158.8, 157.0, 132.8, 129.6, 118.4, 116.1, 55.5, 52.3, 51.9, 43.6.

IR (KBr, cm^{-1}) 3349, 2952, 1707, 1608, 1500, 1217, 1074, 1036.

HRMS m/z $(M+Na)^+$ Calcd for $C_{12}H_{15}NO_5Na$: 276.0842; found: 276.0843.

3.18 Synthesis of methyl 2-{[(Anilinocarbonyl)amino]methyl}-5-bromo benzoate (166b)

A solution of acyl azide **164b** (1.5 g, 13.4 mmol) in benzene (50 mL) was refluxed for 1 hour. After completion of the reaction, the mixture was cooled to room temperature and the solvent was removed under vacuum. The formed isocyanate **158b** was dissolved in CH_2Cl_2 (50 mL). A solution of aniline (1.25 g, 13.4 mmol) in CH_2Cl_2 (5 mL) was added dropwise at room temperature. The resulting mixture was stirred at 25 °C for 2 hours. The organic phase was extracted with 10% HCl soln and H_2O. Evaporation of the solvent gave urea derivative **166b** (0.84 g, 46%).Crystallization (EtOAc–n-hexane, 10:2) gave analytical pure **166b**; mp 170-172 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (d, $J_{6,4}$ = 2.1 Hz, 1H, H-6), 7.52 (dd, $J_{4,3}$ = 8.2 Hz, $J_{4,6}$ = 2.1 Hz, 1H, H-4), 7.39 (d, $J_{3,4}$ = 8.2 Hz, 1H, H-3), 7.30–7.10 (m, 4H), 7.05–6.90 (m, 1H), 6.51 (br s, 1H, NH), 5.94 (br t, J = 6.3 Hz, 1H, NH), 4.50 (d, J = 6.5 Hz, 2H, CH_2), 3.81 (s, 3 H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 155.8, 139.9, 138.6, 135.7, 133.8, 133.7, 130.2, 129.2, 123.6, 121.5, 120.7, 52.5, 42.6.

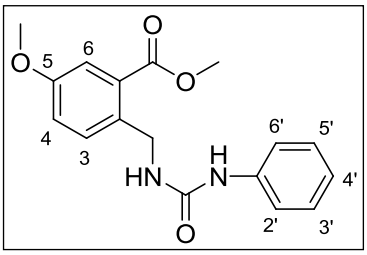
IR (KBr, cm^{-1}) 3303, 1709, 1626, 1557, 1247, 1073.

HRMS m/z $(M+Na)^+$ Calcd for $C_{16}H_{15}BrN_2O_3Na$: 385.0164; found: 385.0168.

3.19 Synthesis of methyl 2-{[(anilinocarbonyl)amino]methyl}-5-methoxy benzoate (166c)

A solution of acyl azide **164c** (0.65 g, 2.6 mmol) in anhydrous benzene (50 mL) was refluxed for 1 hour. After completion of the reaction, the mixture was cooled to room temperature and the solvent was removed under vacuum. The formed isocyanate **158c** was dissolved in CH_2Cl_2 (50 mL). A solution of aniline (0.24 g, 2.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise at room temperature. The resulting mixture was stirred at room temperature for 2 hours. The organic phase was extracted with 10%

HCl soln and H_2O. Evaporation of the solvent gave urea derivative **166c** (0.336 g, 41%). Crystallization (EtOAc–n-hexane, 10:2) gave analytical pure **166c**; mp 142–144 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49 (d, $J_{3,4}$ = 8.5 Hz, 1H, H-3), 7.46 (d, $J_{6,4}$ = 2.8 Hz, 1H, H-6), 7.40–7.20 (m, 4H), 7.10–6.90 (m, 2H), 6.58 (br s, 1 H, NH), 6.03 (br s, 1 H, NH), 4.55 (br d, J = 5.62 Hz, 2 H, CH_2), 3.87 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3).

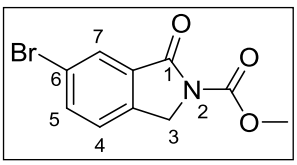
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 158.7, 155.4, 138.7, 133.1, 133.0, 129.7, 129.1, 123.5, 120.7, 118.4, 116.1, 55.5, 52.3, 42.7.

IR (KBr, cm^{-1}) 3310, 3056, 1718, 1627, 1597, 1357, 1177, 1066, 784.

HRMS m/z $(M+Na)^+$ Calcd for $C_{17}H_{18}N_2O_4Na$: 337.1159; found: 337.1141.

3.20 Synthesis of methyl 6-bromo-1-oxo-1,3-dihydro-2*H*-isoindole-2-carboxylate (167b)

To a solution of urethane **165b** (0.48 g, 1.59 mmol) in MeCN (40 mL) was added excess K_2CO_3 (0.66 g, 4.77 mmol) and the resulting mixture was stirred at 60 °C for 6 hours. After completion of the reaction, excess K_2CO_3 was filtered off and washed with MeCN (10 mL). After evaporation of the solvent, the residue was purified by column chromatography (silica gel, 20 g, EtOAc–hexane, 8:2) to give **167b** (0.41 g, 95%) as a colorless solid; mp 164–165 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (d, $J_{7,5}$ = 1.7 Hz, 1H, H-7), 7.77 (dd, $J_{5,4}$ = 8.1 Hz, $J_{5,7}$ = 1.7 Hz, 1H, H-5), 7.39 (d, $J_{4,5}$ = 8.1 Hz, 1H, H-4), 4.78 (s, 2H, CH_2), 3.97 (s, 3H, OCH_3).

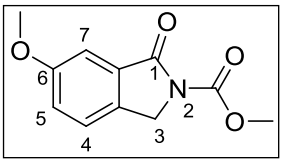
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 152.3, 139.4, 136.8, 133.0, 128.2, 124.8, 122.7, 53.9, 48.9.

IR (KBr, cm^{-1}) 2949, 1767, 1695, 1438, 1363, 1320, 1208, 842.

HRMS m/z $(M+Na)^+$ Calcd for $C_{10}H_8NO_3Na$: 291.9585; found: 2919587.

3.21 Synthesis of methyl 6-methoxy-1-oxo-1,3-dihydro-2*H*-isoindole-2-carboxylate (167c)

To a solution of urethane **165c** (0.42 g, 1.66 mmol) in MeCN (40 mL) was added excess K_2CO_3 (0.69 g, 4.98 mmol) and the resulting mixture was stirred at 60 °C for 6 hours. After completion of the reaction, excess K_2CO_3 was filtered off and washed with MeCN (10 mL). After evaporation of the solvent, the residue was purified by column chromatography (silica gel, 20 g, EtOAc–hexane, 8:2) to give **167c** (0.34 g, 92%) as a white solid; mp 161–163 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.37 (d, $J_{4,5}$ = 8.3 Hz, 1H, H-4), 7.36 (d, $J_{7,5}$ = 2.5 Hz, 1H, H-7), 7.22 (dd, $J_{5,4}$ = 8.3 Hz, $J_{5,7}$ = 2.5 Hz, 1H, H-5), 4.75 (s, 2 H, CH_2), 3.97 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3).

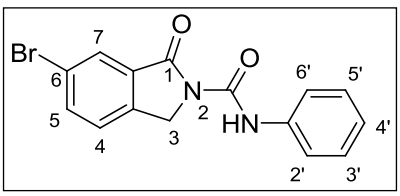
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 160.3, 152.5, 133.2, 132.2, 124.0, 122.8, 107.1, 55.7, 53.7, 48.7.

IR (KBr, cm^{-1}) 1771, 1690, 1494, 1423, 1272, 1250, 1002, 779.

HRMS m/z $(M+Na)^+$ Calcd for $C_{11}H_{11}NO_4Na$: 244.0580; found: 244.0580.

3.22 Synthesis of 6-bromo-1-oxo-*N*-phenyl-1,3-dihydro-2*H*-isoindole-2-carboxamide (168b)

To a solution urea derivative **166b** (0.60 g, 1.65 mmol) in MeCN (150 mL) was added K_2CO_3 (0.68 g, 4.95 mmol). The resulting mixture was stirred at 60 °C for 2 hours. After completion of the reaction, excess K_2CO_3 was filtered and washed with MeCN (10 mL). The solvent was evaporated and the residue was chromatographed (silica gel, EtOAc–hexane, 1:1) to give **168b** (0.47 g, 85%) as a white powder; mp 241–243 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.55 (br s, 1 H, NH), 8.00 (d, $J_{7,5}$ = 1.7 Hz, 1H, H-7), 7.74 (dd, $J_{5,4}$ =

8.1 Hz, $J_{5,7}$ = 1.7 Hz, 1H, H-5), 7.53 (d, J = 7.6 Hz, 2H), 7.40 (d, $J_{4,5}$ = 8.1 Hz, 1H), 7.29 (t, J = 7.4 Hz, 2H), 7.07 (t, J = 7.4 Hz, 1H), 4.83 (s, 2H, CH_2).

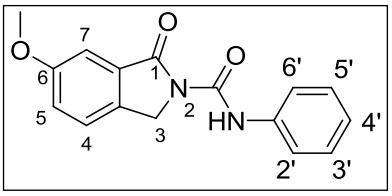
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 149.9, 139.7, 137.3, 137.0, 133.0, 129.1, 127.9, 125.0, 124.3, 122.7, 120.2, 48.4.

IR (KBr, cm^{-1}) 1702, 1678, 1444, 1368, 1311.

Anal. Calcd for $C_{15}H_{11}BrN_2O_2$: C, 54.40; H, 3.35; N, 8.46. Found: C, 54.09; H, 3.41; N, 8.35.

3.23 Synthesis of 6-methoxy-1-oxo-*N*-phenyl-1,3-dihydro-2*H*-isoindole-2-carboxamide (168c)

To a solution of urea derivative **166c** (0.32 g, 1.02 mmol) in MeCN (150 mL) was added K_2CO_3 (0.42 g, 3.06 mmol). The resulting mixture was stirred at 60 °C for 2 hours. After completion of the reaction, excess K_2CO_3 was filtered and washed with MeCN (10 mL). The solvent was evaporated and the residue was chromatographed (silica gel, EtOAc–hexane, 1:1) to give **168c** (0.24 g, 83%) as a white powder; mp 193–195 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.7 (br s, 1H, NH), 7.53 (d, J = 7.6 Hz, 2H), 7.38 (br d, $J_{4,5}$ = 8.3 Hz, 1H, H-4), 7.33–7.25 (m, 3 H), 7.18 (dd, $J_{5,4}$ = 8.4, $J_{5,7}$ = 2.5 Hz, 1H, H-5), 7.05 (br t, J = 7.4 Hz, 1 H), 4.79 (s, 2H, CH_2), 3.82 (s, 3H, OCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 159.3, 149.3, 136.5, 132.5, 131.1, 128.1, 123.3, 123.1, 121.8, 119.1, 105.9, 54.7, 47.2.

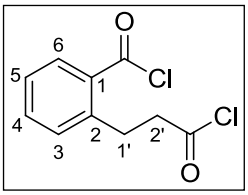
IR (KBr, cm^{-1}) 3242, 3220, 3034, 1710, 1674, 1339, 1257, 1145, 749.

HRMS m/z $(M+Na)^+$ Calcd for $C_{16}H_{14}N_2O_3Na$: 305.0902; found: 305.0926.

3.24 Synthesis of 1-chloro-3-[2-(chlorocarbonyl)phenyl]propan-1-one (173)

To a suspension of 2-(2-carboxyethyl)benzoic acid **172** (1.0 g, 5.15 mmol) in CH_2Cl_2 (50 mL), oxalyl chloride (1.77 mL, 20.6 mmol) was added quickly at room temperature. This was followed by the addition of DMF (2 drops) as catalyst, and the reaction mixture was stirred for 4 hours at room temperature. The reaction was

completed after all the starting material had dissolved in the CH_2Cl_2. The reaction mixture was concentrated under reduced pressure to afford dichloride **173** as a colorless oil; yield: 1.14 g (96%).



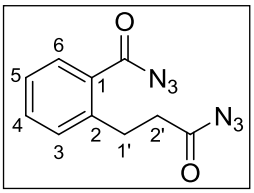
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.0 Hz, 1H, H-6), 7.59 (t, *J* = 7.2 Hz, 1H, H-5), 7.43 (t, *J* = 7.7 Hz, 1H, H-4), 7.37 (d, *J* = 7.7 Hz, 1H, H-3), 3.27–3.19 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 168.1, 141.4, 134.9, 134.5, 132.2, 131.7, 127.8, 47.5, 30.0.

IR (KBr, cm^{-1}) 2922, 1797, 1771, 1451, 1275, 1188, 750.

3.25 Synthesis of 1-azido-3-[2-(azidocarbonyl)phenyl]propan-1-one (174)

To a solution of dichloride **173** (1.14 g, 4.93 mmol) in acetone (10 mL) at 0 °C, a solution of NaN_3 (1.28 g, 19.7 mmol) in H_2O (5 mL) was added. Precipitation of inorganic salt was immediately observed. After completion of the addition, the resulting mixture was stirred for 1 hour and H_2O (25 mL) was added. The mixture was extracted with EtOAc (3 × 75 mL). The organic extracts were dried ($MgSO_4$). After removal of the solvent under reduced pressure, bis(acyl azide) **174** was obtained as a colorless oil which was directly used for the next step without further purification; yield: 0.948 g (79%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 7.8, 1.2 Hz, 1H, H-6), 7.43 (dt, J = 7.5, 1.4 Hz, 1H, H-4), 7.25–7.21 (m, 2 H, H-3 and H-5), 3.23 (t, J = 7.6 Hz, 2H, H-2'), 2.63 (t, J = 7.6 Hz, 2H, H-1').

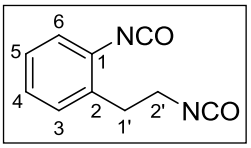
^{13}C NMR (100 MHz, $CDCl_3$) δ 180.3, 173.7, 143.5, 134.4, 132.3, 132.0, 129.6, 127.5, 38.5, 30.2.

IR (KBr, cm^{-1}) 2979, 2275, 2137, 1715, 1692, 1229, 1082, 913, 748.

3.26 Synthesis of 1-isocyanato-2-(2-isocyanatoethyl)benzene (175)

Bis(acyl azide) **174** (0.59 g, 2.4 mmol) was dissolved in anhyd benzene (50 mL) and the mixture was refluxed for 1 hour. After completion of the reaction, the reaction

mixture was concentrated under reduced pressure to give the diisocyanate **175** as a colorless oil which was directly used for the next step without further purification; yield: 0.33 g (72%).



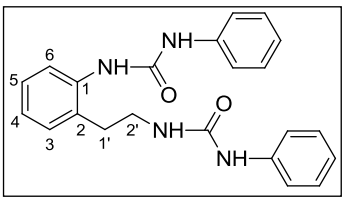
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.18–7.13 (m, 2H, H-4 and H-5), 7.10 (br dd, J = 7.3, 1.4 Hz, H-3 or H-6), 7.06 (br dd, J = 7.9, 1.2 Hz, H-3 or H-6), 3.46 (t, J = 6.8 Hz, 2H, H-2'), 2.87 (t, J = 6.8 Hz, 2 H, H-1').

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.4, 133.7, 132.6, 130.3, 128.3, 128.0, 127.3, 124.3, 44.7, 35.8.

IR (KBr, cm^{-1}) 2968, 2274, 2146, 1713, 1513, 1226, 756.

3.27 Synthesis of *N*-(2-{2-[(anilinocarbonyl)amino]ethyl}phenyl)-N'-phenyl urea (176)

A solution of aniline (1.2 g, 12.9 mmol) in benzene (5 mL) was added dropwise to a stirred solution of diisocyanate **175** (1.0 g, 5.32 mmol) in anhyd CH_2Cl_2 (50 mL) at room temperature and the mixture was stirred for 12 hours. The formed diurea **176** was collected by filtration and washed with CH_2Cl_2 (5–10 mL) to give a colorless powder; yield: 1.36 g (69%); mp 207–208.5 °C.



^{1}H-NMR (400 MHz, acetone-d_6) δ 8.84 (s, NH), 8.63 (s, NH), 8.33 (s, NH), 7.87 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.46 (br d, *J* = 7.6 Hz, 2H), 7.40 (br d, *J* = 7.6 Hz, 2H), 7.28 (br t, *J* = 7.6 Hz, 2H), 7.23 (br t, *J* = 7.5 Hz, 2H), 7.21–7.18 (m, 2H), 7.01 (dt, *J* = 7.4, 1.1 Hz, 1H), 6.98 (br t, *J* = 7.4 Hz, 1H), 6.92 (br t, *J* = 7.3 Hz, 1H), 6.35 (t, *J* = 5.6 Hz, NH), 3.38–3.26 (m, 2H), 2.79 (t, *J* = 8.0 Hz, 2H).

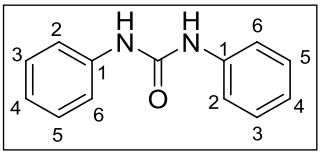
^{13}C NMR (100 MHz, acetone-d_6) δ 155.8, 152.8, 140.2, 139.8, 137.4, 129.5, 129.2, 128.8, 128.6, 126.7, 122.9, 121.74, 121.69, 121.3, 118.1, 117.9, 39.1, 31.7.

IR (KBr, cm^{-1}) 3347, 3218, 3043, 1648, 1620, 1565, 1317, 1179, 893, 709, 691

Anal. Calcd for $C_{22}H_{22}N_4O_2$: C, 70.57; H, 5.92; N, 14.96. Found: C, 70.22; H, 5.88; N, 15.03.

3.28 Synthesis of *N,N'*-Diphenylurea (179)

LDA solution was prepared by the addition of 1.6 M *n*-BuLi in hexane (3.67 mL, 5.9 mmol) to a solution of freshly distilled *i*-Pr_2NH (0.83 mL, 5.9 mmol) in THF (5 mL) at –78 °C, followed by stirring for 30 min. Diurea **176** (0.5 g, 1.34 mmol) was added to the solution. The mixture was refluxed for 7 days. The reaction was monitored by TLC. After completion of the reaction, aq NH_4Cl solutionn (20 mL) was added, the mixture was extracted with EtOAc (3 × 50 mL) and the extracts were dried ($MgSO_4$). Removal of EtOAc gave a mixture (0.35 g). Chromatography of this mixture over silica gel (EtOAc–hexane, 1:2) gave *N,N'*-diphenylurea **179**; yield: 99 mg (35%; 47% based on the consumed starting material); as the second fraction, unreacted starting material **176** was isolated (130 mg, 0.35 mmol).

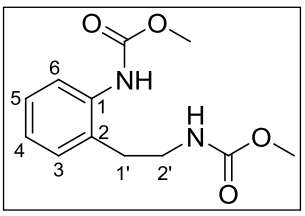


^{1}H-NMR (400 MHz, DMSO-d_6) δ 8.72 (s, 2H, NH), 7.50 (br d, J = 7.6 Hz, 4H), 7.32 (br t, J = 7.6 Hz, 4 H), 7.00 (br t, J = 7.6 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 152.5, 139.7, 128.7, 121.8, 118.2.

3.29 Synthesis of methyl 2-{2 [(methoxycarbonyl)amino]ethyl}phenyl carbamate (182)

Bis(acyl azide) **174** (2.87 g, 11.75 mmol) was dissolved in MeOH (150 mL) and the mixture was refluxed for 6 hours. The reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. Chromatography of the residue on silica gel (50 g; EtOAc–CH_2Cl_2, 1:3) afforded the known 3,4-dihydroquinolin-2(1H)-one[58] (**183**) as the first fraction; yield: 0.092 g (5.4%). The second fraction was identified as diurethane **182**; yield: 2.55 g (86%); colorless crystals (EtOAc); mp 82–84 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.79 (br s, 1H), 7.42 (br s, 1H, NH), 7.18 (t, J = 7.7 Hz, 1H), 7.06 (d, J = 7.3 Hz, 1H), 6.99 (t, J = 7.3 Hz, 1H), 4.98 (br s, 1 H, NH), 3.72 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3), 3.23 (dt, J = 7.4, 6.2 Hz, 2H), 2.75 (t, J = 7.2 Hz, 2H).

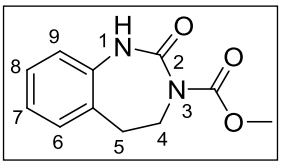
^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 155.1, 136.1, 129.9, 129.2, 127.6, 124.5, 122.6, 52.5, 52.3, 41.3, 31.8.

IR (KBr, cm^{-1}) 3324, 3015, 2953, 1704, 1533, 1242, 1068, 757.

Anal. Calcd for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.43; H, 6.43; N, 11.12.

3.30 Synthesis of methyl 2-oxo-1,2,4,5-tetrahydro-3*H*-1,3-benzodiazepine-3-carboxylate (184)

Diurethane **182** (500 mg, 1.98 mmol) was dissolved in THF (25 mL) under N_2 atmosphere and reacted with LiHMDS as described for the reaction of **185** below. After reaction workup, the residue was chromatographed on silica gel (EtOAc–CH_2Cl_2, 1:1) to give **184** as colorless crystals (EtOAc–n-hexane); yield: 176 mg (44%); mp 145–147 °C. Prolonged reaction time resulted in decreased yield of the product; the hydrolysis product was formed.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.21 (br s, 1 H, NH), 7.15–7.11 (m, 2H), 7.02 (dt, J = 7.4, 1.3 Hz, 1H, H-7), 6.82 (br dd, J = 7.9, 1.4 Hz, 1H, H-6), 3.95 (t, J = 6.1 Hz, 2H, H-4), 3.73 (s, 3 H, OCH_3), 3.03 (t, J = 6.1 Hz, 2H, H-5).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 154.4, 135.8, 130.7, 128.6, 127.6, 124.9, 121.2, 53.8, 46.5, 31.6.

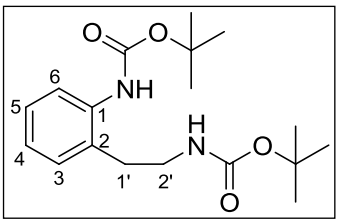
IR (KBr, cm^{-1}) 3245, 2956, 2916, 1700, 1403, 1309, 1219, 772.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.62; H, 5.49; N, 12.70.

3.31 Synthesis of *tert*-butyl 2-{2-[(*tert*-butoxycarbonyl)amino]ethyl}phenyl carbamate (185)

Bis(acyl azide) **174** (2.37 g, 9.7 mmol) was dissolved in *t*-BuOH (200 mL) and the mixture was refluxed for 12 hours. The reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. Chromatography of the residue on silica gel (50 g; EtOAc–*n*-hexane, 1:3) afforded

diurethane **185**; yield: 2.12 g (65%); colorless crystals (EtOH–*n*-hexane); mp 90-92 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.78 (br d, J = 7.4 Hz, 1H), 7.43 (br s, 1H, NH), 7.14 (dt, J = 7.2, 1.6 Hz, 1H), 7.01 (br d, J = 6.7 Hz, 1H), 6.93 (br t, J = 7.3 Hz, 1H), 4.80 (br s, 1H, NH), 3.16 (dt, J = 7.8, 6.5 Hz, 2H, H-2'), 2.70 (t, J = 7.8 Hz, 2H), 1.45 [s, 9H, $OC(CH_3)_3$], 1.39 [s, 9H, $OC(CH_3)_3$].

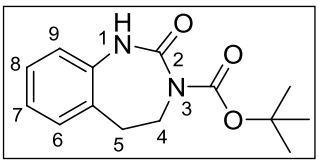
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 153.8, 136.8, 129.7, 128.7, 127.4, 123.7, 122.2, 80.0, 79.7, 41.1, 32.1, 28.4, 28.0.

IR (KBr, cm^{-1}) 3333, 2979, 2934, 1690, 1520, 1166, 744.

Anal. Calcd for $C_{18}H_{28}N_2O_4$: C, 64.26; H, 8.39; N, 8.33. Found: C, 64.01; H, 8.25; N, 8.62.

3.32 Synthesis of *tert*-butyl 2-oxo-1,2,4,5-tetrahydro-3*H*-1,3-benzodiazepine 3-carboxylate (186)

Diurethane **185** (1.14 g, 3.4 mmol) was dissolved in THF (25 mL) under N_2 atmosphere. A solution of 1 M LiHMDS in THF (5.1 mL, 5.1 mmol) was added dropwise and the resulting mixture was refluxed for 1 hour. After completion of the reaction, aq NH_4Cl solution (25 mL) was added, the mixture was extracted with EtOAc (3 × 50 mL) and the extracts were dried ($MgSO_4$). After evaporation of the solvent, the residue was crystallized (EtOAc–n-hexane) to give **186** as colorless crystals; yield: 462 mg (52%); mp 177–179 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.49 (br s, 1H, NH), 7.19 (br d, J = 7.3 Hz, 1 H, H-9), 7.17 (br d, J = 7.0 Hz, 1H, H-6), 7.08–7.03 (m, 2 H, H-7 and H-8), 3.98 (t, J = 6.0 Hz, 2H, H-4), 3.09 (t, J = 6.0 Hz, 2H, H-5), 1.51 [s, 9 H, $OC(CH_3)_3$].

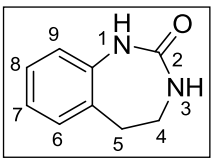
^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 152.5, 136.4, 130.7, 128.1, 127.3, 124.2, 121.3, 82.4, 45.3, 32.3, 28.1.

IR (KBr, cm^{-1}) 3243, 3162, 3003, 2989, 2901, 1702, 1156, 759.

Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.10; H, 6.92; N, 10.68. Found: C, 63.89; H, 6.92; N, 10.70.

3.33 Synthesis of 1,3,4,5-Tetrahydro-2*H*-1,3-benzodiazepin-2-one (180)

1,3-Benzodiazepine-3-carboxylate **186** (80 mg, 0.3 mmol) was dissolved in CH_2Cl_2 (10 mL). TFA (235 mg, 2 mmol) was added dropwise at 0 °C and the mixture was stirred for 1 hour at room temperature. After completion of the reaction, H_2O (20 mL) was added and the resulting mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with H_2O (25 mL) and dried ($MgSO_4$). Removal of the solvent gave the crude product **180** [yield: 45 mg (91%)] which was crystallized (EtOAc–n-hexane) to give colorless crystals; mp 170–172 °C.

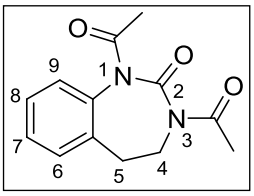


^{1}H-NMR (400 MHz, CD_3OD) δ 7.00 (br t, J = 7.4 Hz, 1H, H-8), 6.94 (br d, J = 7.5 Hz, 1H, H-9), 6.85 (br d, J = 8.0 Hz, 1H, H-6), 6.80 (br t, J = 7.5 Hz, 1H, H-7), 4.75 (br s, 2H, NH), 3.26–3.24 (m, 2H, H-4), 2.89–2.87 (m, 2H, H-5).

^{13}C NMR (100 MHz, CD_3OD) δ 159.2, 138.4, 130.5, 130.2, 127.8, 123.0, 119.7, 43.2, 35.3.

3.34 Synthesis of 1,3-Diacetyl-1,3,4,5-tetrahydro-2*H*-1,3-benzodiazepin-2-one (188)

1,3-Benzodiazepin-2-one **180** (120 mg, 0.74 mmol) was dissolved in THF (10 mL) and the solution was cooled to 0 °C. NaH (60%; 150 mg, 3.75 mmol) was added and the reaction mixture was allowed to warm to room temperature and was stirred for 30 min. Then, Ac_2O (500 mg, 4.9 mmol) was added and the mixture was stirred for an additional 30 min at room temperature. After completion of the reaction, excess NaH was quenched by the dropwise addition of H_2O. The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (2 × 25 mL), dried ($MgSO_4$) and the solvent was evaporated to give the crude diacetyl derivative **188**. Chromatography of the residue over a short silica gel column (EtOAc–CH_2Cl_2, 1:1) gave pure **188** as a colorless oil; yield: 127 mg (70%).



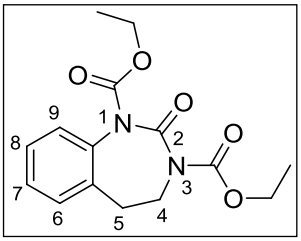
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.24–7.17 (m, 4H), 4.01 (br s, 2H, H-4), 3.00 (t, J = 6.8 Hz, 2H, H-5), 2.34 (s, 3H, CH_3), 2.24 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 168.5, 154.7, 132.9, 130.8, 128.2, 127.02, 126.97, 125.4, 42.0, 27.8, 23.2, 22.3.

Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.02; H, 5.56; N, 11.61.

3.35 Synthesis of diethyl 2-oxo-4,5-dihydro-1*H*-1,3-benzodiazepine-1,3(2*H*) dicarboxylate (189)

1,3-Benzodiazepin-2-one **180** (120 mg, 0.74 mmol) was carboxylated by adding NaH as described above, then adding ethyl chloroformate (540 mg, 5 mmol). Chromatography of the residue over a short silica gel column (EtOAc–CH_2Cl_2, 1:1) gave pure diester derivative **189**; yield: 188 mg (83%); mp 62–64 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.34–7.15 (m, 4H), 4.23 (q, J = 7.0 Hz, 2H, OCH_2), 4.13 (q, J = 7.0 Hz, 2H, OCH_2), 3.97 (t, J = 6.5 Hz, 2H, H-4), 3.03 (t, J = 6.5 Hz, 2H, H-5), 1.23 (t, J = 7.0 Hz, 3H, CH3), 1.18 (t, J = 6.5 Hz, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 152.9, 152.2, 135.2, 132.5, 129.7, 128.6, 128.5, 127.2, 63.5, 63.4, 46.1, 30.0, 14.23, 14.16.

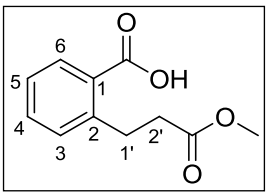
IR (KBr, cm^{-1}) 2984, 1791, 1728, 1370, 1220, 773.

Anal. Calcd for $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15. Found: C, 58.51; H, 6.12; N, 9.16.

3.36 Synthesis of 2-(2-Methoxycarbonylethyl)benzoic acid (190)

2-(2-carboxyethyl)benzoic acid **172** (4.98 g, 25.6 mmol) was dissolved in methanol (100 mL), concentrated sulphuric acid (2.5 mL) was added and the solution stirred at room temperature for 30 minutes. The solution was concentrated at 30 ^{o}C to about 1/10 of the solution. The residue was dissolved in water (60 mL), and 1 M NaOH (60 mL) was added while stirring. The pH was brought to 8 by saturated $NaHCO_3$ and more 1 M NaOH. The aqueous solution was washed with diethylether (2x100 mL)

and the ether phases were discarded. The aqueous phase was acidified with concentrated HCl to pH 1-2 and the acidic product extracted four times with diethylether. The combined organic layers were dried over Na_2SO_4 and the solvents removed by a rotary evaporator at 30 ^oC to give (**190**) (5.04 g, 95%) was obtained as a colourless solid.[49]

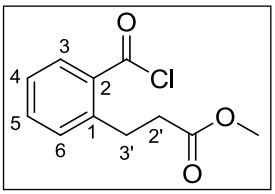


^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 7.9, 1.4 Hz, 1H, H-6), 7.43 (dt, *J* = 7.5, 1.4 Hz, 1H, H-4), 7.30-7.20 (m, 2H), 3.60 (s, 3H, OCH_3), 3.28 (t, *J* = 7.6 Hz, 2H, H-2'), 2.65 (t, *J* = 7.6 Hz, 2H, H-1').

^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 171.6, 142.4, 132.2, 130.9, 130.4, 127.1, 125.6, 50.6, 34.5, 28.9.

3.37 Synthesis of methyl 3-[2-(chlorocarbonyl)phenyl]propanoate (191)

To a stirred suspension of half ester **190** (0.96 g, 4.61 mmol) in CH_2Cl_2 (50 mL) was added oxalyl chloride (0.44ml, 5.07 mmol) and DMF (2 drops) as catalyst. The resulting solution was stirred at room temperature for 1 hour. After completion of the reaction, the solvent was evaporated to give **191** (0.97 g, 93%) as a viscous oil.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.13 (δ, *J* = 8.0 Hz, 1H, H-3), 7.47 (t, *J* = 7.5 Hz, 1H, H-4), 7.31 (t, *J* = 7.7 Hz, 1H, H-5), 7.27 (d, J = 7.7 Hz, 1H, H-6), 3.57 (s, 3H, OCH_3), 3.13 (t, *J* = 7.6 Hz, 2H, H-3'), 2.54 (t, J = 7.6 Hz, 2H, H-2').

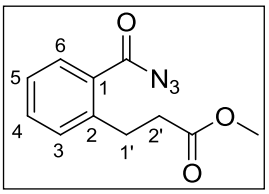
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 167.8, 143.3, 134.5, 134.1, 132.3, 131.4, 127.1, 51.7, 34.8, 29.7.

IR (ATR, cm^{-1}) 2952, 1770, 1736, 1437, 1188, 868, 650.

3.38 Synthesis of 1-[2-(3-methoxy-3-oxopropyl)benzoyl]triaza-1,2-dien-2-ium (192)

To a solution of acyl chloride **191** (0.90 g, 3.97 mmol) in acetone (25 mL) was added a solution of NaN_3 (0.52 g, 7.94 mmol) in H_2O (10 mL) dropwise at 0 °C and the

mixture was stirred at 0 °C for 1 hour. After the addition of H_2O (25 mL) the mixture was extracted with EtOAc (3 × 25 mL), and the combined extracts were washed with sat. $NaHCO_3$ and H_2O, and dried ($MgSO_4$). After concentration of the solvent, acyl azide **192** (0.82 g, 89%), unstable at room temperature, was obtained as colorless oil, which was used for the next step without purification.



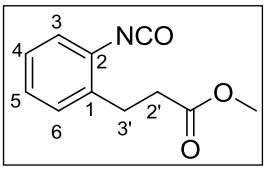
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.6 Hz, 1H, H-6), 7.42 (t, *J* = 7.3 Hz, 1H, H-4), 7.30-7.10 (m, 2H), 3.58 (s, 3H, OCH_3), 3.23 (t, J = 7.8 Hz, 2H, 2'), 2.59 (t, J = 7.8 Hz, 2H, 1').

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 173.1, 143.6, 133.7, 131.7, 131.3, 129.1, 126.7, 51.6, 35.3, 29.9.

IR (ATR, cm^{-1}) 2952, 2277, 2133, 1736, 1689, 1436, 1224, 1175, 976.

3.39 Synthesis of methyl 3-(2-isocyanatophenyl)propanoate (193)

Acyl azide **192** (0.5 g, 2.14mmol) was dissolved in anhydrous benzene (50 mL) and the mixture was refluxed for 1 hour. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to give the isocyanate **193** as a colorless oil which was directly used for the next step without further purification; yield: 0.37 g (83%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.15-6.95 (m, 4H), 3.58 (s, 3H, OCH_3), 2.88 (t, *J* = 7.6 Hz, 2H, H-2'), 2.54 (t, *J* = 7.6 Hz, 2H, H-3').

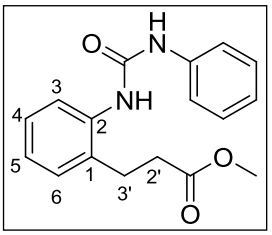
^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 134.6, 132.1, 130.0, 128.4, 127.7, 126.1, 125.0, 51.7, 34.1, 27.4.

IR (ATR, cm^{-1}) 2952, 2268, 1736, 1510, 1158, 754.

3.40 Synthesis of methyl 3-{2-[(anilinocarbonyl)amino]phenyl}propanoate (194)

A solution of aniline (0.34 g, 3.70mmol) in benzene (5 mL) was added dropwise to a stirred solution of isocyanate **193** (0.69 g, 3.36mmol) in anhydrous CH_2Cl_2 (50 mL)

at room temperature and the mixture was stirred for 12 hours. The formed urea **194** was collected by filtration and washed with CH_2Cl_2 (5–10 mL) to give a white solid; yield: 0.79 g (79%); mp 138.5–140 °C.



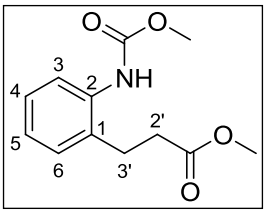
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.68 (s, 1H, NH), 7.54 (br d, J = 8.0 Hz, 1H), 7.24 (br d, J = 7.5 Hz, 2H), 7.20-7.05 (m, 5H), 7.00 (dt, J = 7.5, 1.1 Hz, 1H), 6.93 (t, J = 7.3 Hz, 1H), 3.52 (s, 3H, OCH_3), 2.81 (t, J = 7.1 Hz, 2H, H-3'), 2.56 (t, J = 7.1 Hz, 2H, H-2').

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 154.2, 138.6, 135.9, 133.7, 129.8, 129.0, 127.5, 125.4, 125.2, 123.3, 120.2, 52.0, 34.5, 25.9.

IR (ATR, cm^{-1}) 3275, 1739, 1638, 1547, 1451, 1209, 1155,753.

3.41 Synthesis of methyl 3-{2-[(metoxycarbonyl)amino]phenyl}propanoate (195)

A solution of acyl azide **192** (0.53 g, 2.27 mmol) in MeOH (100 mL) was refluxed for 12 hours with TLC monitoring. After completion of reaction,the solvent was removed under vacuum. Chromatography of the residue (silica gel, 50 g, EtOAc–hexane, 1:1.5) afforded **195** (0.46 g, 86%) as a white solid; mp 69–71 °C.



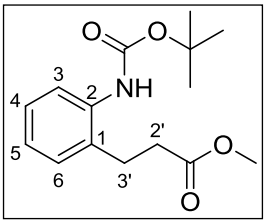
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 1H, NH), 7.71 (br s, 1H, H-3), 7.24 (dt, J = 7.9, 1.7 Hz, 1H, H-4), 7.16 (dd, J = 7.7, 1.6 Hz, 1H, H-6), 7.09 (dt, J = 7.5, 1.0 Hz, 1H, H-5), 3.80 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 2.90 (t, J = 6.7 Hz, 2H, H-3'), 2.71 (t, J = 6.7 Hz, 2H, H-2').

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 155.0, 135.7, 131.8, 129.6, 127.3, 124.8, 123.5, 52.3, 52.0, 34.9, 25.3.

IR (ATR, cm^{-1}) 3290, 1743, 1693, 1527, 1453, 1252, 1151, 754.

3.42 Synthesis of methyl 3-{2-[(*tert*-butoxycarbonyl)amino]phenyl}propanoate (196)

A solution of acyl azide **192** (0.67 g, 2.87 mmol) in t-BuOH (100 mL) was refluxed for 48 hours with TLC monitoring. After completion of reaction,the solvent was removed under vacuum. Chromatography of the residue (silica gel, 50 g, EtOAc–hexane, 1:2) afforded **196** (0.66 g, 82%) as a colorless oil.

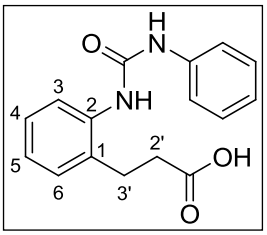


^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.52 (br d, J = 8.0 Hz, 1H), 7.18-7.07 (m, 2H), 7.06 (dd, J = 7.6, 1.6 Hz, 1H), 6.98 (dt, J = 7.5, 1.2 Hz, 1H), 3.60 (s, 3H, OCH_3), 2.82 (t, J = 7.1 Hz, 2H, H-3'), 2.61 (t, J = 7.1 Hz, 2H, H-2'), 1.46 [s, 9H, $OC(CH_3)_3$]. **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.0, 153.7, 136.0, 131.5, 129.3, 127.1, 124.4, 123.4, 80.2, 51.9, 34.6, 28.4, 25.6.

IR (ATR, cm^{-1}) 3343, 1720, 1589, 1516, 1447, 1233, 1153, 752.

3.43 Synthesis of 3-{2-[(anilino-carbonyl)amino]phenyl}propanoic acid (197)

To a solution of ester **194** (0.72 g, 2.41 mmol) in MeOH–H_2O (1:1, 50mL) was added K_2CO_3 (0.40 g, 2.89 mmol) and the mixture was refluxed for 45 min. The mixture was cooled to r.t. and H_2O was added. To remove the unreacted ester **194**, the aqueous phase was extracted with EtOAc. The aqueous phase was acidified with 1 M HCl and extracted with EtOAc. Evaporation of the solvent gave pure **197** as a pale yellow solid; yield: 0.62 g (91%); mp 159.5–161 °C.



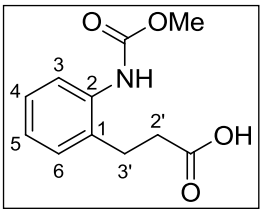
^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.21 (br s, 1H), 9.01 (br s, 1H), 7.97 (br s, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.47 (d, J = 8.3 Hz, 2H), 7.29 (t, J = 7.9 Hz, 2H), 7.22-7.05 (m,2H), 7.02-6.88 (m, 2H), 2.84 (t, J = 7.8 Hz, 2H), 2.55 (t, J = 7.8 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 173.8, 152.9, 139.9, 136.8, 131.4, 128.9, 128.8, 126.4, 123.3, 122.6, 121.7, 118.1, 33.6, 25.9.

IR (ATR, cm^{-1}) 3283, 3037, 1699, 1639, 1548, 1443, 1236,748.

3.44 Synthesis of 3-{2-[(methoxycarbonyl)amino]phenyl}propanoic acid (198)

To a solution of ester **195** (0.51 g, 2.15 mmol) in MeOH–H_2O (1:1, 50mL) was added K_2CO_3 (0.36 g, 2.58 mmol) and the mixture was refluxed for 45 min. The mixture was cooled to r.t. and H_2O was added. To remove the unreacted ester **195**, the aqueous phase was extracted with EtOAc. The aqueous phase was acidified with 1 M HCl and extracted with EtOAc. Evaporation of the solvent gave pure **198** as a white solid; yield: 0.46 g (95%); mp 158–159 °C.



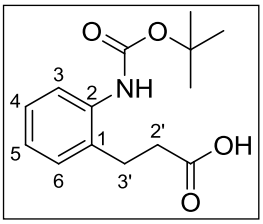
^{1}H-NMR (400 MHz, DMSO-d_6) δ 12.20 (br s, 1H), 8.93 (br s, 1H), 7.32 (d, J = 7.7 Hz, 1H), 7.25-7.15 (m, 2H), 7.11 (d, J = 7.4 Hz, 1H), 3.64 (s, 3H, OCH_3), 2.80 (t, J = 7.7 Hz, 2H), 2.48 (t, J = 7.7 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 172.8, 153.8, 134.6, 133.6, 127.9, 125.1, 124.3, 123.9, 50.4, 32.6, 24.5.

IR (ATR, cm^{-1}) 3290, 2949, 1710, 1692, 1533, 1246, 1067.

3.45 Synthesis of 3-{2-[(*tert*-butoxycarbonyl)amino]phenyl}propanoic acid (199)

To a solution of ester **196** (0.42 g, 1.50 mmol) in MeOH–H_2O (1:1, 50mL) was added K_2CO_3 (0.25 g, 1.80 mmol) and the mixture was refluxed for 45 min. The mixture was cooled to r.t. and H_2O was added. To remove the unreacted ester **196**, the aqueous phase was extracted with EtOAc. The aqueous phase was acidified with 1 M HCl and extracted with EtOAc. Evaporation of the solvent gave pure **199** as a white solid; yield: 0.36 g (89%); mp 112.5–114 °C.



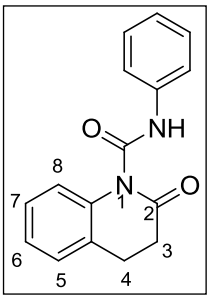
^{1}H-NMR (400 MHz, $CDCl_3$) δ 12.00-10.00 (br s, 1H), 7.65 (br s, 1H), 7.25-7.15 (m, 3H), 7.09 (t, J = 7.5 Hz, 1H), 2.93 (t, J = 7.2 Hz, 2H), 2.80-2.65 (m, 2H), 1.53 [s, 9H, $OC(CH_3)_3$].

^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 154.6, 135.8, 132.0, 129.4, 127.1, 124.9, 124.0, 80.9, 34.4, 28.3, 25.6.

IR (ATR, cm^{-1}) 3394, 2983, 1702, 1523, 1458, 1157, 742.

3.46 Synthesis of 2-oxo-*N*-phenyl-3,4-dihydroquinoline-1(2*H*)-carboxamide (200)

To a solution of the 3-{2-[(anilino-carbonyl)amino]phenyl}propanoic acid **197** (0.50 g, 1.76 mmol) in 50 ml dry THF was added thionyl chloride (0.26ml, 3.52 mmol) and refluxed for 12 hours. The reaction medium was checked by TLC. After the completion of the reaction, evaporation of the solvent gave crude product which was purified by chromatography (silica gel, 50 g, EtOAc–hexane, 1:2) afforded **200** (0.39 g, 84%) as a white solid; mp 117–119 °C.



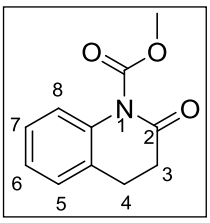
^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.82 (br s, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.40 (d, J = 8.2 Hz, 1H), 7.33-7.00 (m, 6H), 2.84 (t, J = 6.7 Hz, 2H), 2.70 (t, J = 6.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 150.7, 137.5, 135.9, 130.2, 129.1, 127.2, 126.8, 125.7, 124.5, 124.2, 120.5, 35.8, 25.0.

IR (ATR, cm^{-1}) 3180, 2916, 1717, 1592, 1548, 1445, 1160, 751.

3.47 Synthesis of methyl 2-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (201)

To a solution of the 3-{2-[(methoxycarbonyl)amino]phenyl}propanoic acid **198** (0.50 g, 2.24 mmol) in 50 ml dry THF was added thionyl chloride (0.33ml, 4.48 mmol) and refluxed for 8 hours. The reaction medium was checked by TLC. After the completion of the reaction, evaporation of the solvent gave crude product which was purified by chromatography (silica gel, 50 g, EtOAc–hexane, 1:1.5) afforded **201** (0.35 g, 76%) as a white solid; mp 149–151 °C.



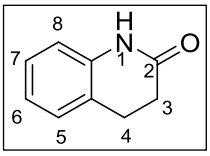
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.30-7.18 (m, 2H), 7.11 (dt, J = 7.4, 1.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 4.01 (s, 3H, OCH_3), 2.97 (t, J = 7.1 Hz, 2H), 2.71 (t, J = 7.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 154.0, 136.8, 127.9, 127.4, 127.0, 124.8, 118.6, 54.9, 33.0, 25.5.

IR (ATR, cm^{-1}) 3336, 2954, 1701, 1526, 1460, 1237, 758.

3.48 Synthesis of methyl 2-oxo-3,4-dihydroquinoline-1(2*H*)-carboxylate (183)

To a solution of the 3-{2-[(*tert*-butoxycarbonyl)amino]phenyl}propanoic acid **199** (0.45 g, 1.70 mmol) in 50 ml dry THF was added thionyl chloride (0.25ml, 3.39 mmol) and refluxed for 8 hours. The reaction medium was checked by TLC. After the completion of the reaction, evaporation of the solvent gave crude product which was purified by chromatography (silica gel, 50 g, EtOAc–hexane, 1:1) afforded **183** (0.17 g, 68%) as a white solid.



^{1}H-NMR (400 MHz, DMSO-d_6) δ 10.08 (br s, 1H, NH), 7.25–7.05 (m, 2H), 6.90 (t, J = 7.4 Hz, 1H), 6.84 (d, J = 7.9 Hz, 1H), 2.86 (t, J = 7.5 Hz, 2H), 2.44 (t, J = 7.5 Hz, 2H).

^{13}C NMR (100 MHz, DMSO-d_6) δ 170.2, 138.2, 127.7, 127.0, 123.5, 121.9, 114.9, 30.4, 24.7.

3.49 General Procedure for oxidative addition of acetylacetone to alkenes in the presence of $Mn(OAc)_3$ and HCl

A solution of alkene (5 mmol) and acetylacetone (0.50 g, 5 mmol) in 15 mL of glacial acetic acid was added to a solution of $Mn(OAc)_3{\cdot}2H_2O$ (2.68 g, 10 mmol) and HCl (1,5 mL, 37%) in 50 mL of glacial acetic acid. The resulting mixture was stirred under N_2 at 55 °C for 24 h. When the reaction was complete, the solution was concentrated in vacuo and quenched with 2x75ml saturated $NaHCO_3$ solution. The solution was extracted with dichloromethane. The combined organic layers were washed several times with water and dried ($MgSO_4$). Evaporation of the solvent gave the crude compound, which was purified by column chromatography.

3.50 General Procedure for conversion of diacyl derivatives to acetonyl compounds with ammonia

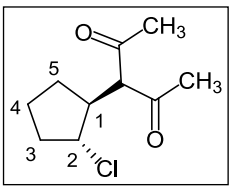
1,3-Diacetyl compound (3 mmol) was dissolved in 50 mL of methanol. The mixture was stirred magnetically for 24 h at room temperature while passing NH_3(g) through this solution. The solvent was removed under reduced pressure to give the hydrolysis

products. To obtain analytical sample, the crude product was subjected to column chromatography (SiO_2 Hexane/EtOAc, 4:1).

3.51 Synthesis of *rel*-(1*R*,2*S*)-3-(2-chlorocyclopentyl)pentane-2,4-dione (208) & *rel*-(1-((3a*R*,6a*R*)-(2-methyl - 4,5,6,6a - tetrahydro- 3a*H*- cyclopenta[*b*]furan-3 yl) ethanone (209)

Acetylacetone (2.21 g, 22.02 mmol), cyclopentene (1.5 g, 22.02 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (11.81 g, 44.04 mmol) in 220 mL of glacial acid was reacted as described above. Chromatography of the residue on silica gel (hexane/EtOAc, 4:1) gave **208** as the first fraction. The dihydrofuran derivative **209** was isolated as the second fraction.

***rel*-(1*R*,2*S*)-3-(2-chlorocyclopentyl)pentane-2,4-dione (208)** Colorless oil (1.38 g, 31%).



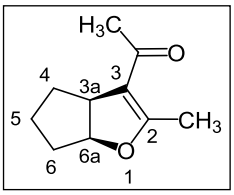
^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.50 (br t, *J* = 4.0 Hz, 1H), 4.03 (d, *J* = 10.7 Hz, 1H), 2.76 (dddd, *J* = 11.2, 10.8, 7.4 and 4.1 Hz, 1H), 2.29 (s, 3H), 2.23 (s, 3H), 2.13-2.05 (m, 2H), 2.03-1.88 (m, 1H), 1.80-1.63 (m, 2H), 1.58-1.40 (m, 1H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.1, 202.4, 71.4, 65.8, 45.6, 35.9, 30.7, 29.3, 26.1, 21.2.

IR (ATR, cm^{-1}): 2959, 1734, 1698, 1421, 1358, 1266, 735;

HRMS: Calcd. for $C_{10}H_{15}ClO_2$: 203.0833. Found: 203.0796.

***rel*-(1-((3a*R*,6a*R*)-(2-methyl - 4,5,6,6a - tetrahydro- 3a*H*- cyclopenta[*b*]furan-3 yl) ethanone (209)** Pale yellow oil (1.68 g, 46%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.04 (br dt, *J* = 8.0 and 2.9 Hz, 1H), 3.59 (br t, *J* = 8.0 Hz, 1H), 2.19 (s, 3H), 2.17 (d *J* = 1.2 Hz,, 3H), 2.00-1.90 (m, 1H), 1.80-1.58 (m, 4H), 1.56-1.40 (m, 1H).

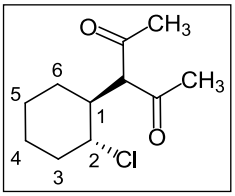
^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.8, 167.0, 116.3, 88.6, 47.2, 35.1, 33.7, 29.2, 23.0, 15.2.

IR (ATR, cm^{-1}): 2970, 1720, 1604, 1376, 1239, 1016, 953.

HRMS: Calcd. for $C_{10}H_{15}O_2$: 167.10666 Found: 167.10700.

3.52 Synthesis of *rel*-(1*R*,2*S*)-3-(2-chlorocyclohexyl)pentane-2,4-dione (211).

Acetylacetone (0.61 g, 6.09 mmol), cyclohexene (0.5 g, 6.09 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (3.26 g, 12.08 mmol) in 120 mL of glacial acid was reacted as described above. Chromatography of the residue on silica gel (30 g, hexane/EtOAc, 4:1) gave the addition product **211**; colorless oil (1.12 g, 85%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.25 (br s, 1H), 3.95 (d, *J* = 10.7 Hz, 1H), 2.48 (tt, *J* = 10.7 and 2.9 Hz, 1H), 2.20 (s, 3H), 2.13 (s, 3H), 2.00-1.93 (m, 1H), 1.80-1.55 (m, 3H), 1.50-1.33 (m, 2H), 1.30-1.15 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.0, 202.5, 72.9, 61.9, 42.3, 34.1, 31.4, 29.5, 25.3, 24.1, 19.3.

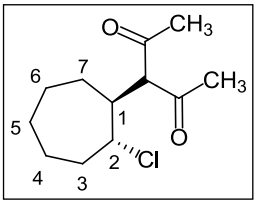
IR (ATR, cm^{-1}): 2937, 1733, 1697, 1358, 1201, 1170, 735.

HRMS (M-HCl), Calcd. for $C_{11}H_{16}O_2$: 181.12231. Found: 181.12232.

3.53 Synthesis of *rel*-(1*R*,2*S*)-3-(2-chlorocycloheptyl)pentane-2,4-dione (213) & *rel*-1-((3a*R*,8a*R*)-2-methyl-4,5,6,7,8,8a-hexahydro-3a*H*-cyclohepta[*b*]furan-3-yl) ethanone (214).

Acetylacetone (0.52 g, 5.2 mmol), cycloheptene (0.5 g, 5.2 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (2.79 g, 10.4 mmol) in 120 mL of glacial acid was reacted as described above. Chromatography of the residue on silica gel (hexane/EtOAc, 4:1) gave **213** as the first fraction. The dihydrofuran derivative **214** was isolated as the second fraction.

***rel*-(1*R*,2*S*)-3-(2-chlorocycloheptyl)pentane-2,4-dione (213)** Colorless oil (635 mg, 53%.



^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.23-4.15 (m, 1H), 4.01 (d, *J* = 10.9 Hz, 1H), 2.59 (tt, *J* = 10.9 and 2.4 Hz, 1H), 2.19 (s, 3H),

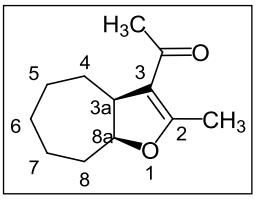
2.10 (s, 3H), 2.00-1.80 (m, 2H), 1.75-1.25 (m, 7H). 1.08-1.02 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 203.5, 202.6, 73.9, 64.6, 45.0, 37.1, 31.2, 29.1, 27.4, 26.6, 25.8, 22.0.

IR (ATR, cm^{-1}): 2929, 1733, 1696, 1420, 1357, 1158, 952.

HRMS: Calcd. for $C_{12}H_{19}ClNaO_2$: 253.0966 Found: 253.0964.

***rel*-1-((3a*R*,8a*R*)-2-methyl-4,5,6,7,8,8a-hexahydro-3a*H*-cyclohepta[*b*]furan-3-yl) ethanone (214).** Pale yellow oil (355 mg, 35%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.67 (dt, *J* = 9.9 Hz and 4.7 Hz, 1H), 3.18 (br t, *J* = 9.7 Hz, 1H), 2.16 (s, 3H), 2.12 (d, *J* = 1.1 Hz, 3H), 2.05-1.90 (m, 1H), 1.85-1.10 (m, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 194.1, 167.4, 117.8, 86.4, 47.4, 31.13, 31.1, 29.1, 28.8, 28.4, 23.7, 15.4

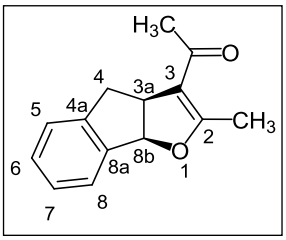
IR (ATR, cm^{-1}): 2926, 1713, 1605, 1388, 1223, 948, 734.

HRMS: Calcd. for $C_{12}H_{19}O_2$: 195.1380. Found: 195.1360.

3.54 Synthesis of *rel*-1-((3a*R*,8b*S*)-(2-methyl-4,8b-dihydro-3a*H*-indino[1,2-*b*] furan-3-yl)ethanone (216). & *rel*-(1*S*,2*S*)-1,2-Dichloro-2,3-dihydro-1*H*-indene (217)

Acetylacetone (0.86 g, 8.61 mmol), 1*H*-indene (1.0 g, 8.61 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (4.62 g, 17.22 mmol) in 170 mL of glacial acid was reacted as described above. Chromatography of the residue on silica gel (hexane/EtOAc, 5:1) gave **217** as the first fraction. The dihydrofuran derivative **216** was isolated as the second fraction.

***rel*-1-((3a*R*,8b*S*)-(2-methyl-4,8b-dihydro-3a*H*-indino[1,2-*b*] furan-3-yl)ethanone (216).** White powder, m.p. 81.5-83.5 °C (1.38 g, 75%).



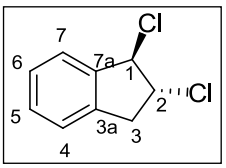
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.0Hz, 1H), 7.35-7.15 (m,3H), 5.95 (d, *J* = 9.2 Hz, 1H), 4.08-4.02 (m, 1H), 3.35 (dd, A-part of AB system, dd, *J* = 17.0 and 8.5Hz, 1H), 3.00 (dd, B-part of AB system, *J* = 17.0 and 2.8 Hz, 1H), 2.21 (s, 3H), 2.12 (d, *J* = 1.2 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 192.9, 166.2, 142.0, 139.0, 128.6, 126.0, 124.7, 124.3, 116.4, 88.9, 44.6, 38.5, 28.3, 14.3

IR (ATR, cm^{-1}) 2957, 1616, 1343, 1216, 957, 752

HRMS: Calcd. for $C_{14}H_{15}O_2$: 215.1067 Found: 215.1041.

***rel*-(1*S*,2*S*)-1,2-Dichloro-2,3-dihydro-1*H*-indene (217)** Colorless oil (217 mg, 13.5%).



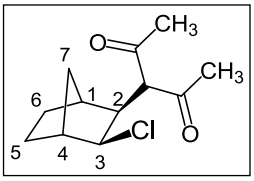
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (m,1H), 7.30-7.15 (m,3H), 5.27 (d, *J* = 3.0 Hz, 1H), 4.58 (dt, *J* = 6.1 and 3.2 Hz, 1H), 3.63 (dd, A-part of AB system, *J* = 16.8 and 6.1 Hz, 1H), 3.11 (dd, B-part of the AB system, *J* = 16.8 Hz and 3.4 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.8 (2C), 128.6, 126.9, 124.4, 124.0, 66.6, 63.4, 39.7.

IR (ATR, cm^{-1}): 3030, 1475, 1463, 1327, 964, 715, 658.

3.55 Synthesis of *rel*-3((1*R*,2*R*,3*R*,4*S*)-(3-chlorobicyclo[2.2.1]hept-2-yl) pentane-2,4-dione (218).

Acetylacetone (0.53 g, 5.31 mmol), norbornene **206** (0.5 g, 5.31 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (2.85 g, 10.62 mmol) in 120 mL of glacial acid was reacted as described above. Chromatography of the residue on silica gel (hexane/EtOAc, 5:1) gave the product **218**. White crystalls, m.p. 50-52 °C (793 mg, 65%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.11 (dd, *J* = 7.1 and 1.3 Hz, 1H), 3.93 (d, *J* = 12.1 Hz, 1H), 2.72 (ddd, *J* = 12.1, 7.1 and 1.1 Hz, 1H), 2.36 (br d, *J* = 4.8 Hz, 1H), 2.16 (s, 3H), 2.10 (s, 3H), 1.83-1.68 (m, 2H), 1.65-1.55 (m, 1H), 1.50-1.38 (m, 1H), 1.25-1.08 (m, 3H)

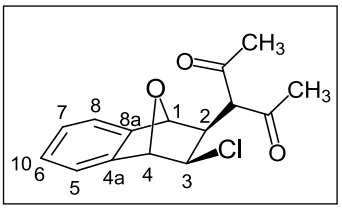
^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.9, 202.7, 72.3, 66.6, 47.8, 46.7, 39.4, 33.4, 29.6, 28.2, 25.8

IR (ATR, cm^{-1}): 2968, 1693, 1357, 1241, 1176, 1158, 893

HRMS: Calcd. for $C_{12}H_{17}ClNaO_2$: 251.0809. Found: 203.0781.

3.56 Synthesis of *rel*-3-((1*S*,2*R*,3*R*,4*S*)-3-chloro-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-yl)pentane-2,4-dione (220).

Acetylacetone (0.35 g, 3.47 mmol), oxa-benzonorbornadiene **207** (0.5 g, 3.47 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (1.86 g, 6.94 mmol) in 120 mL of glacial acid was reacted as described above. Chromatography of the residue on silica gel (hexane/EtOAc, 5:1) gave the product **220**. White powder, m.p. 113-115 °C (843 mg, 87%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.00 (m, 4H), 5.24 (s, 1H), 4.85 (s, 1H), 4.33 (d, *J* = 11.9 Hz, 1H), 4.13 (d, *J* = 7.0 Hz, 1H), 2.98 (dd, *J* = 11.9 Hz and 7.0 Hz, 1H), 2.27 (s, 3H), 2.24 (s, 3H).

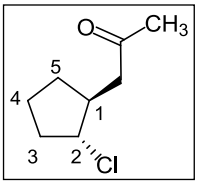
^{13}C-NMR (100 MHz, $CDCl_3$) δ 202.2, 201.8, 145.7, 141.1, 128.2, 127.4, 120.8, 119.2, 87.1, 81.8, 70.8, 61.5, 46.2, 30.2.

IR (ATR, cm^{-1}): 3022, 1717, 1694, 1354, 1215, 956, 854, 759.

HRMS: Calcd. for $C_{15}H_{16}ClO_3$: 279.07825. Found: 279.07893.

3.57 Synthesis of *rel*-1-((1*R*,2*S*)-2-chlorocyclopentyl)propan-2-one (210)

1,3-Diacetyl compound **208** (547 mg, 3.7 mmol) was reacted with NH_3 in 50 mL of methanol as described above. Analytical sample **210** was obtained by silica gel column chromatography. Colorless oil, (377 mg, 87%).



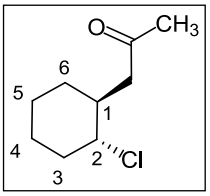
^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.47 (dt, *J* = 3.3 and 1.2 Hz, 1H), 2.75 (dd, A-part of AB-system, *J* = 18.0 Hz and 7.8 Hz, 1H), 2.50 (dd, B-part of AB-system, *J* = 18.0 Hz and 5.9 Hz, 1H), 2.45-2.30 (m, 1H), 2.10 (s, 3H), 2.05-1.95 (m, 2H), 1.90-1.70 (m, 2H), 1.65-1.55 (m, 1H), 1.50-1.30 (m,1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.0, 67.3, 45.1, 41.2, 36.3, 30.4, 28.0, 21.1.

IR (ATR, cm^{-1}): 2958, 1716, 1406, 1356, 1260, 1170, 914.

3.58 Synthesis of *rel*-1-((1*R*,2*S*)-2-chlorocyclohexyl)propan-2-one (212).

1,3-Diacetyl compound **211** (624 mg, 2.88 mmol) was reacted with NH_3 in 50 mL of methanol for 72 h as described above. Analytical sample **212** was obtained by silica gel column chromatography. Colorless oil, (490 mg, 92%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.35 (br s, 1H), 2.60 (dd, A-part of AB-system, *J* = 17.8 Hz and 7.0 Hz, 1H), 2.30 (B-part of AB-system, dd, *J* = 17.8 Hz and 6.1 Hz, 1H), 2.25-2.13 (m, 1H), 2.08 (s, 3H), 2.00-1.90 (m, 1H), 1.80-1.55 (m, 3H), 1.50-1.20 (m, 4H).

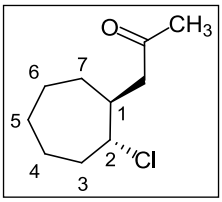
^{13}C-NMR (100 MHz, $CDCl_3$) δ 207.8, 64.6, 47.6, 37.4, 34.2, 30.8, 26.5, 25.2, 19.8

IR (ATR, cm^{-1}) 1710, 1445, 1360, 1270, 1227, 1159, 684.

HRMS: Calcd. for $C_9H_{15}ClO$: 174.0811 Found: 174.1066.

3.59 Synthesis of *rel*-1-((1*R*,2*S*)-2-chlorocycloheptyl)propan-2-one (215).

1,3-Diacetyl compound **213** (150 mg, 0.65 mmol) was reacted with NH_3 in 20 mL of methanol for 48 h as described above. An analytical sample **215** was obtained by silica gel column chromatography. Colorless oil, (105 mg, 87%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.35-4.28 (m, 1H), 2.65 (dd, *J* = 17.3 Hz and 6.2 Hz, 1H), 2.45-2.25 (m, 2H), 2.09 (s, 3H), 2.00-1.88 (m, 2H), 1.75-1.25 (m, 8H).

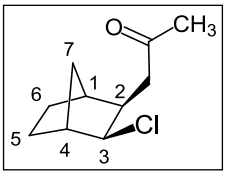
^{13}C-NMR (100 MHz, $CDCl_3$) δ 208.0, 67.7, 48.7, 40.3, 36.9, 30.7, 28.8, 27.1, 26.0, 22.7.

IR (ATR, cm^{-1}): 2927, 1713, 1457, 1359, 1165, 757.

HRMS (M-HCl), Calcd. for $C_{10}H_{16}O$: 153.12739 Found: 153.12841.

3.60 Synthesis of *rel*-1-((1*R*,2*R*,3*R*,4*S*)-3-chlorobicyclo[2.2.1]hept-2yl)acetone (219).

1,3-Diacetyl compound **218** (100 mg, 0.65 mmol) was reacted with NH_3 in 25 mL of methanol for 48 h as described above. An analytical sample **219** was obtained by silica gel column chromatography. Colorless oil, (77 mg, 95%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.08 (dd, *J* = 7.0 Hz and 1.4 Hz, 1H), 2.78 (dd, *J* = 19.4 and 10.5 Hz, 1H), 2.40-2.25 (m, 3H), 2.10 (s, 3H), 1.90-1.85 (m, 1H), 1.73-1.65 (m, 1H), 1.60-1.50 (m, 1H), 1.48-1.35 (m,1H), 1.25-1.05 (m, 3H).

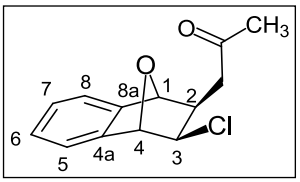
^{13}C-NMR (100 MHz, $CDCl_3$) δ 207.9, 67.5, 47.1, 46.2, 43.3, 42.0, 33.2, 30.0, 29.4, 26.2;

IR (ATR, cm^{-1}): 2957, 1716, 1408, 1353, 1168, 804;

HRMS (M-HCl), Calcd. for $C_{10}H_{14}O$: 151.11174. Found: 151.11242.

3.61 Synthesis of *rel*-1-(1*S*,2*R*,3*R*,4*S*)-3-chloro-1,2,3,4-tetrahydro-1,4-epoxynaphthalen-2-ylpropan-2-one (221).

1,3-Diacetyl compound **220** (133 mg, 0.48 mmol) was reacted with NH_3 in 20 mL of methanol for 48 h as described above. An analytical sample **221** was obtained by silica gel column chromatography. White crystals, m.p. 64-66 °C (77 mg, 95%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.25-7.18 (m, 2H), 7.16-7.08 (m, 2H), 5.24 (s, 1H), 4.97 (s, 1H), 4.10 (d, J = 7.1 Hz, 1H), 3.00 (dd, A-part of AB-system, *J* = 18.5 Hz and 7.1 Hz, 1H), 2.71 (dd, *J* = 18.5 Hz and 7.1 Hz, 1H), 2.51 (q, *J* = 7.1 Hz, 1H), 2.15 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 207.4, 145.9, 141.6, 128.0, 127.2, 120.5, 119.4, 87.3, 83.8, 62.0, 45.1, 40.5, 30.2.

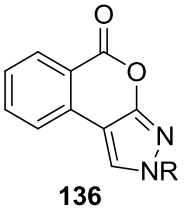
IR (ATR, cm^{-1}): 2915, 1710, 1362, 1154, 980, 770.

HRMS: Calcd. for $C_{13}H_{14}ClO_2$: 237.06768 Found: 237.06928.

CHAPTER 4

CONCLUSION

In this study, new synthetic methodologies for the synthesis of important heterocyclic compounds were developed. Pyrazoles **136**, isoindolinones **137**, benzodizepinones **138**, dihydroquinolinones **139** and acetonyl derivatives **222** were synthesized successfully.



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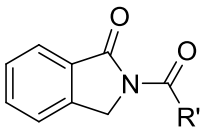
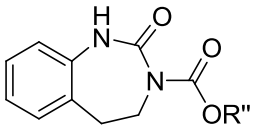
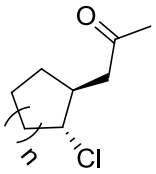


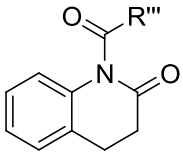
137



138



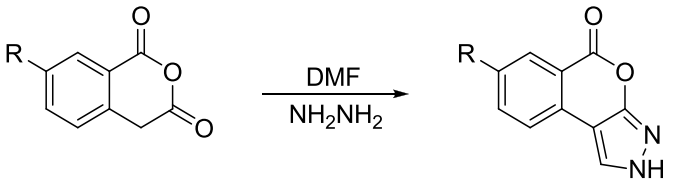
222



139

Reactive molecules such as acyl azides, free radicals and formyl groups are used as key steps in these studies. Moreover, we used advantage of reactivity difference of the similar carbonyl groups for regiospesific reactions. Controlling the number of -

CH_2- groups separating the carbonyl groups from benzene ring can be useful approach for synthesis of five-, six-, and seven membered heterocycles fused to benzene ring. In the first part of the study, we described one-pot, three-component reaction of substituted homophthalic anhydrides with hydrazine in DMF as solvent and reactant, at reflux temperature, to afford isochromeno[3,4-*c*]pyrazole-5(2*H*)-one derivatives **136** in high yields (Scheme 66).

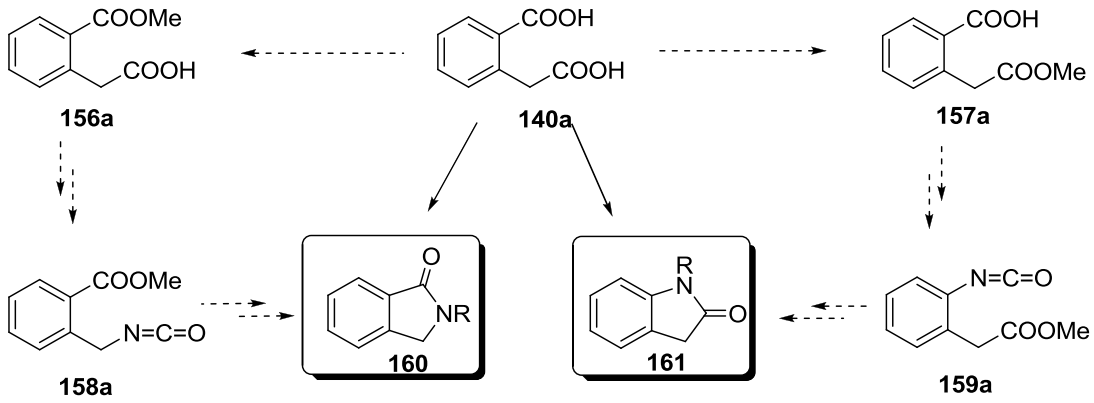


141a-c **145a-c**

Scheme 66 Outline for isocoumarin-condensed pyrazoles **145a-c**

These compounds are very important due to potential biological properties. Therefore, this study was published in *Tetrahedron Letters* in this year.[59]

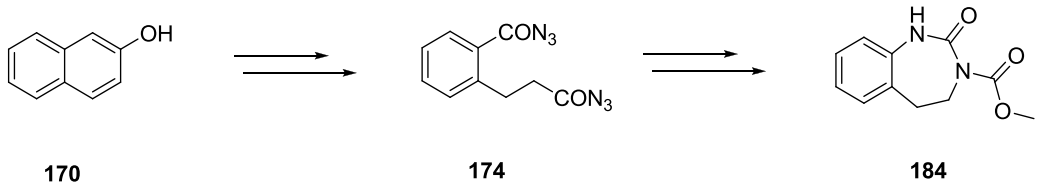
In the second part, synthesis of isoindolinone derivatives was described. The most crucial step is the regiospesific synthesis of semi esters. Then, isoindolinone skeleton was obtained by using acyl azide chemistry.



Scheme 67 Outline for isoindolinone and indolinones **160** and **161**

Preparation of indolin-2-one and isoindolin-1-one and their derivatives starting from 2-(carboxymethyl) benzoic acid, which was first regiospecifically converted into the isomeric half esters (Scheme 67). Transformation of the acid functionalities to the acyl azides followed by Curtius rearrangement gave the regioisomeric isocyanates. Reaction of the isocyanates with aniline produced urethane derivatives. This study was also published by *Synthesis* in this year.[60]

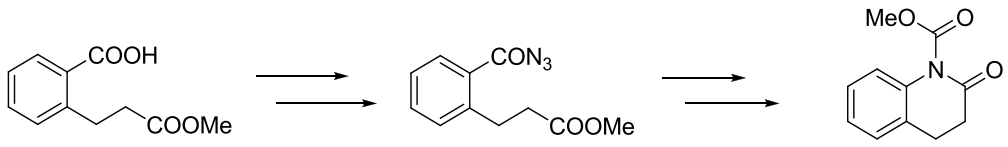
We also report a new synthetic methodology for construction of the 1,3,4,5-tetrahydro-2*H*-1,3-benzodiazepin-2-one skeleton. 2-(2-Carboxyethyl) benzoic acid was converted into the corresponding bis(acyl azide). Curtius rearrangement of the diazide followed by reaction with alcohols provided diurethane derivatives. Ring-closure reaction of the diurethanes with base resulted in formation of the 1,3-benzodiazepin-2-one skeleton (Scheme 68). This study was published in *Synthesis* last year.[61]



170 **174** **184**

Scheme 68 Outline for benzodiazepinone **184**

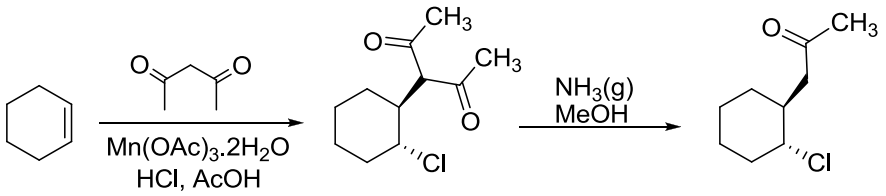
We applied similar methodologies to the synthesis of dihydroquinolinone derivatives starting from 2-(2-carboxyethyl)benzoic acid **170**. Acyl azide formation was followed by urea and urethane transformation. Then successive hydrolysis of esters and ring closure reactions by thionyl chloride were achieved (Scheme 69).



190 **192** **201**

Scheme 69 Outline for dihydroquinolinone **201**

Finally, we described addition of acetylacetone to various alkenes was performed with in the presence of $Mn(OAc)_3{\cdot}2H_2O$ and HCl. Removal of one of the acetyl groups with ammonia under very mild conditions provided compounds derived from chloroacetonylation of the double bonds. This study was also accepted by *Tetrahedron Letters.*



203 **211** **212**

Scheme 70 Outline for chloroacetonylation product **212**

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APPENDIX A

SPECTRAL DATA

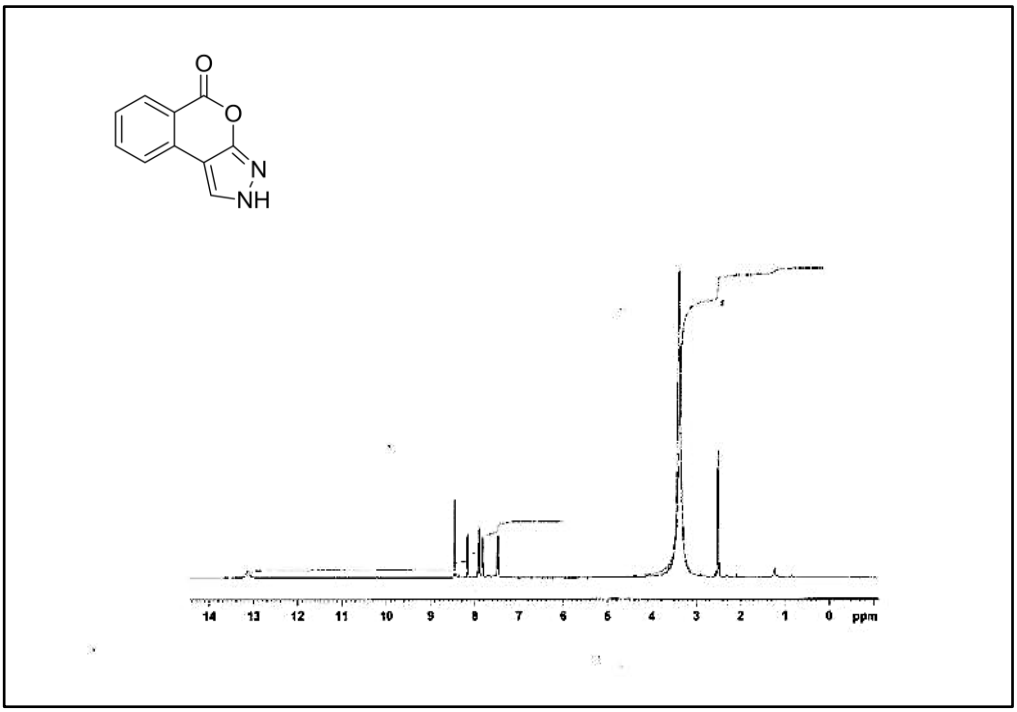

Figure 3 ^{1}H-NMR Spectrum of Compound **145a**

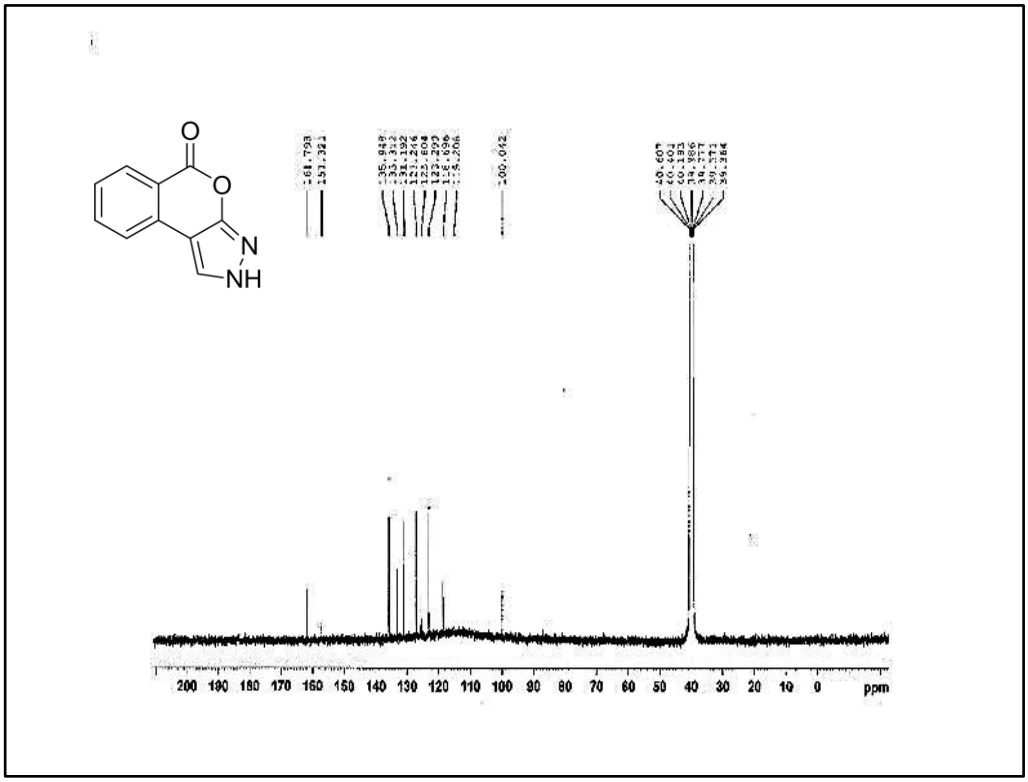

Figure 4 ^{13}C-NMR Spectrum of Compound **145a**

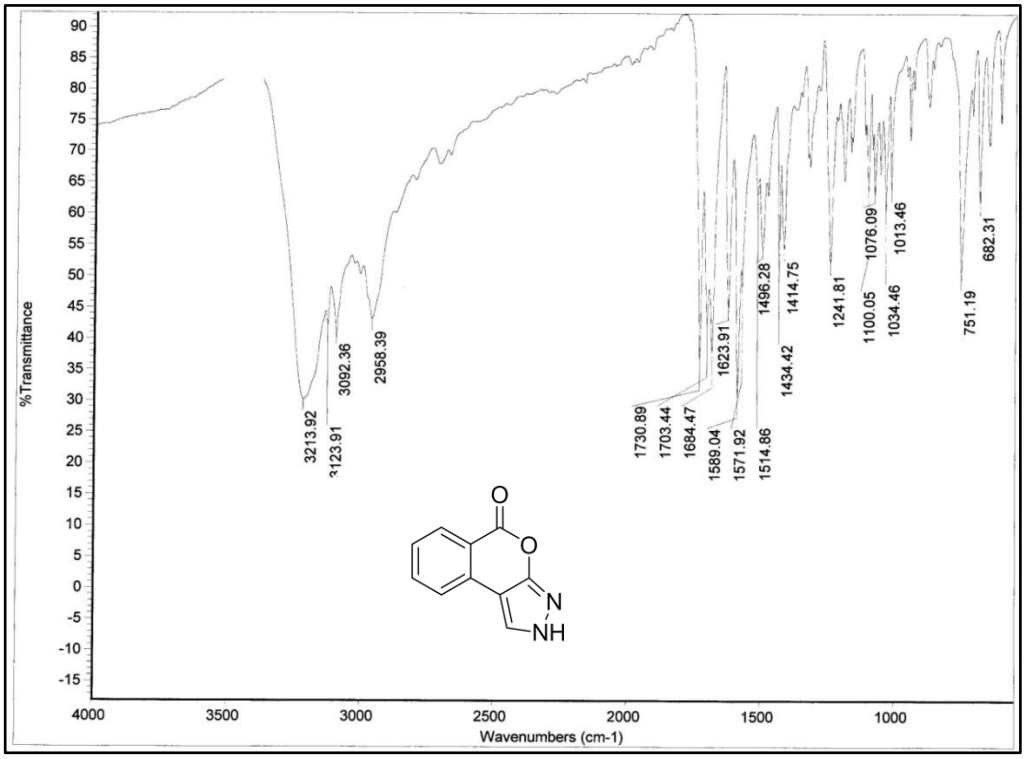

Figure 5 IR Spectrum of Compound **145a**

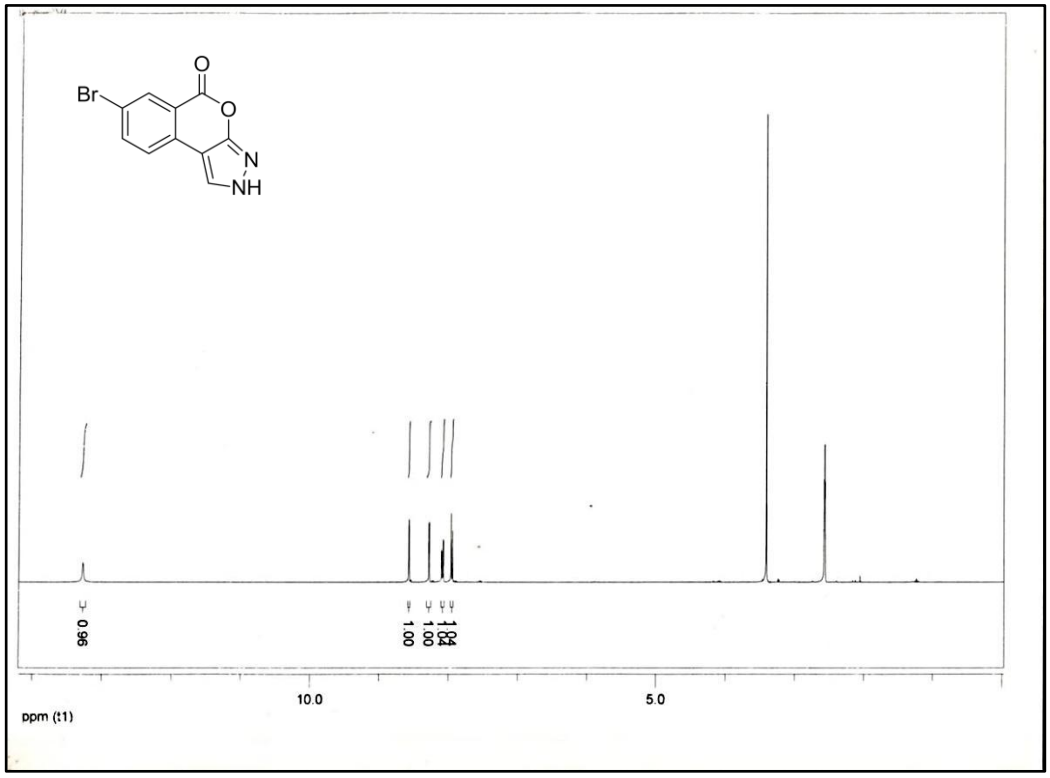

Figure 6 ^{1}H-NMR Spectrum of Compound **145b**

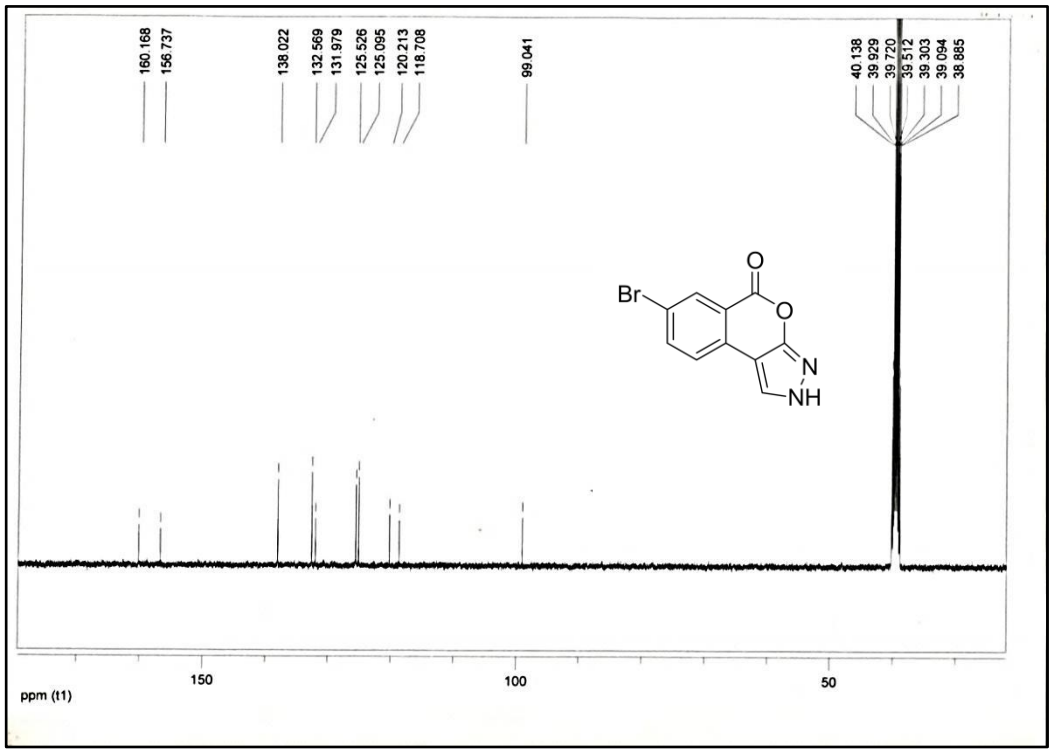

Figure 7 ^{13}C-NMR Spectrum of Compound **145b**

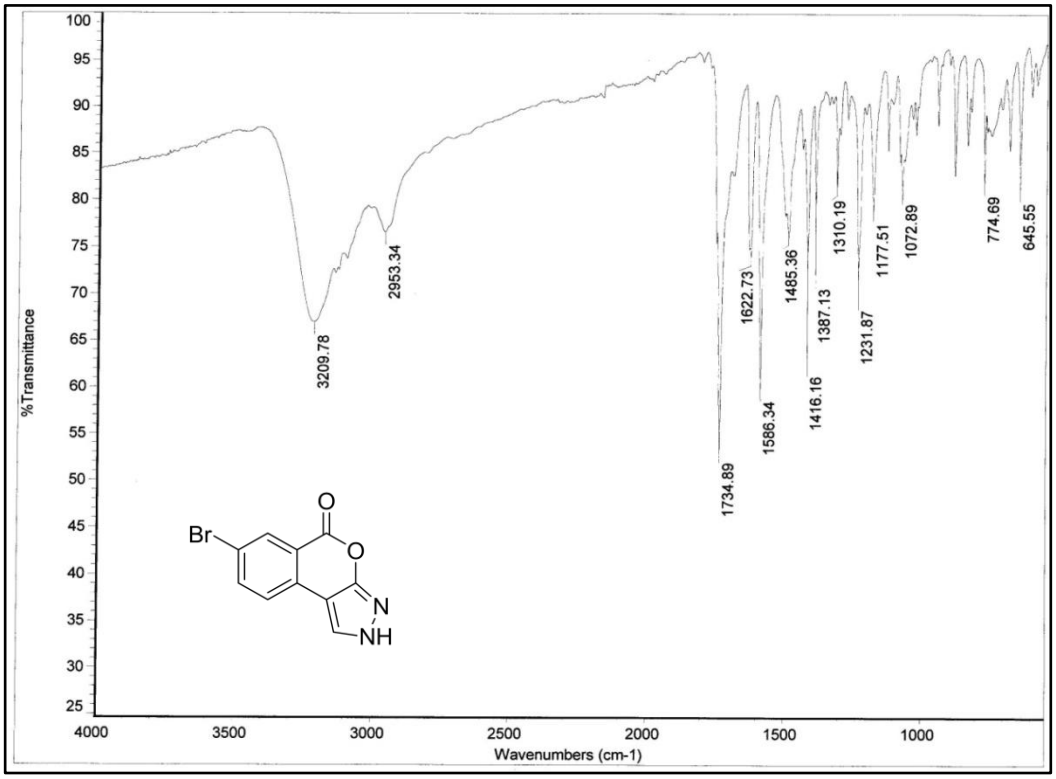

Figure 8 IR Spectrum of Compound **145b**

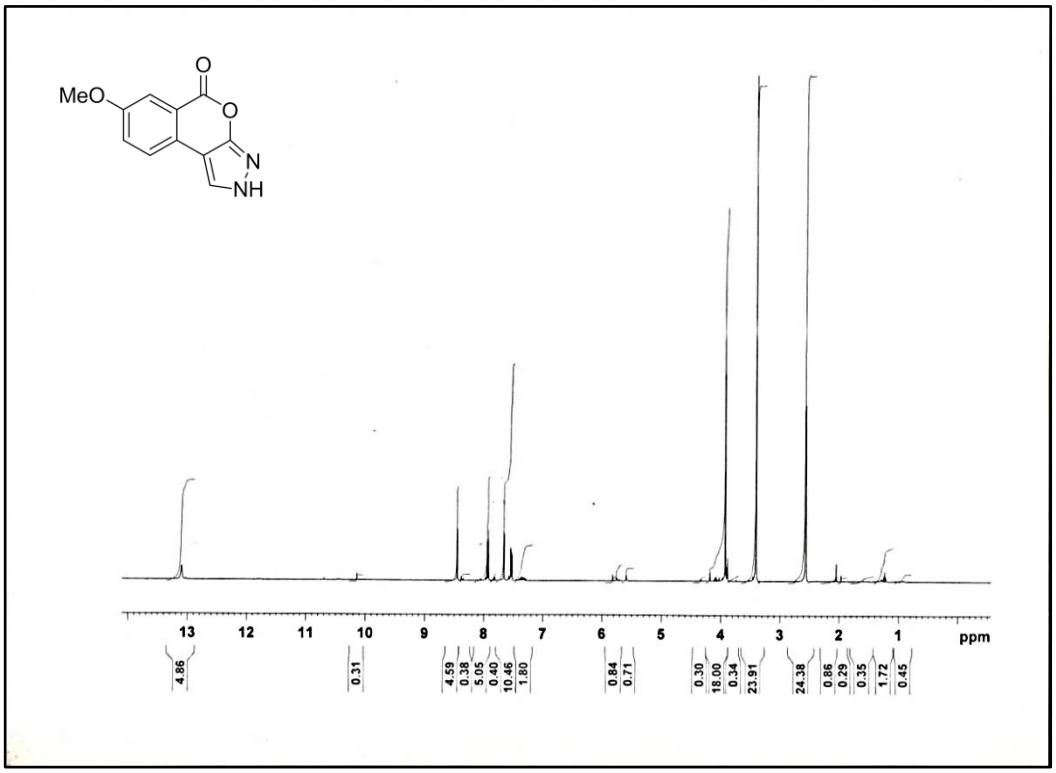

Figure 9 ^{1}H-NMR Spectrum of Compound **145c**

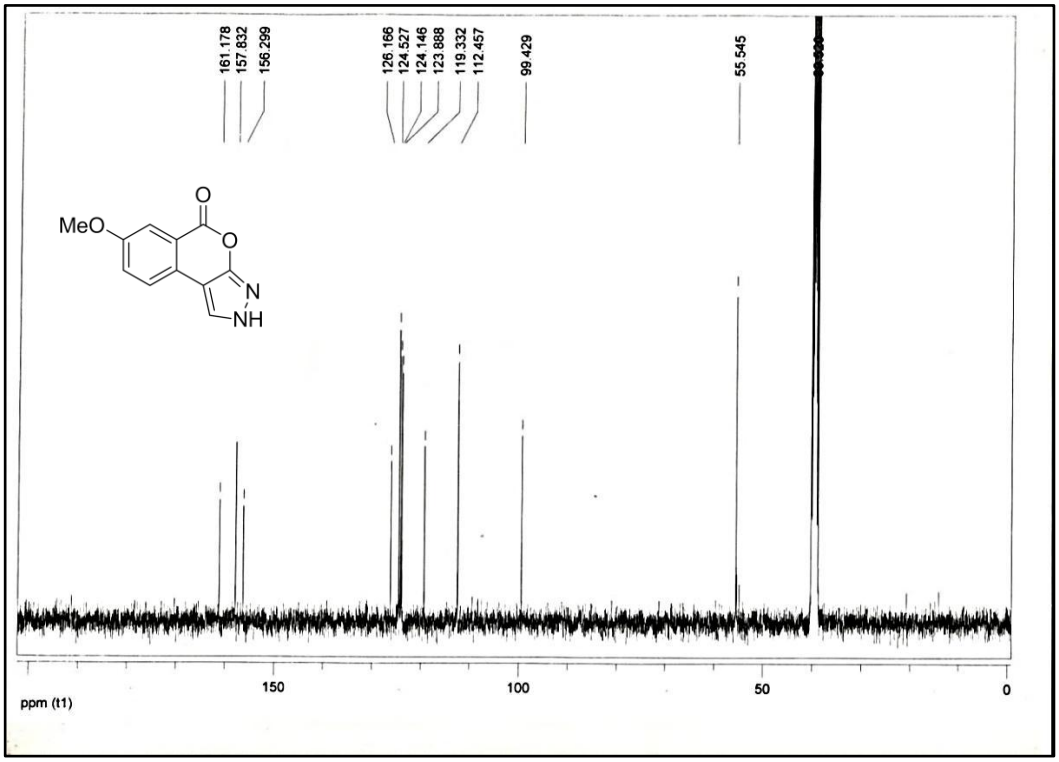

Figure 10 ^{13}C-NMR Spectrum of Compound **145c**

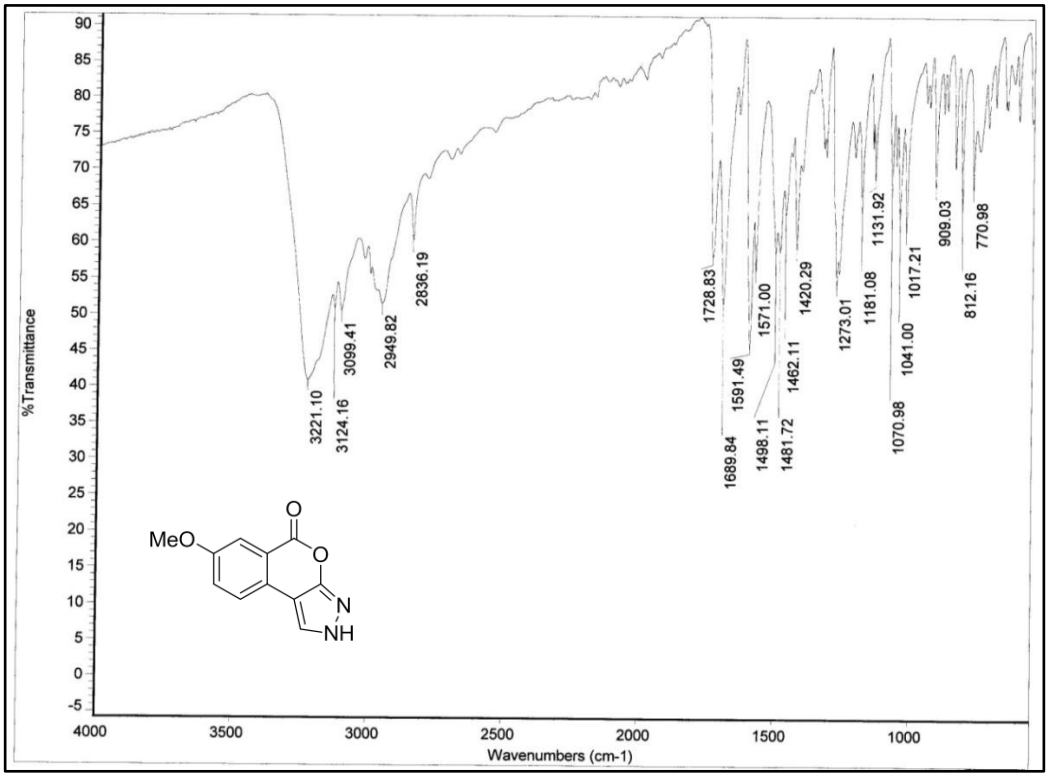

Figure 11 IR Spectrum of Compound **145c**

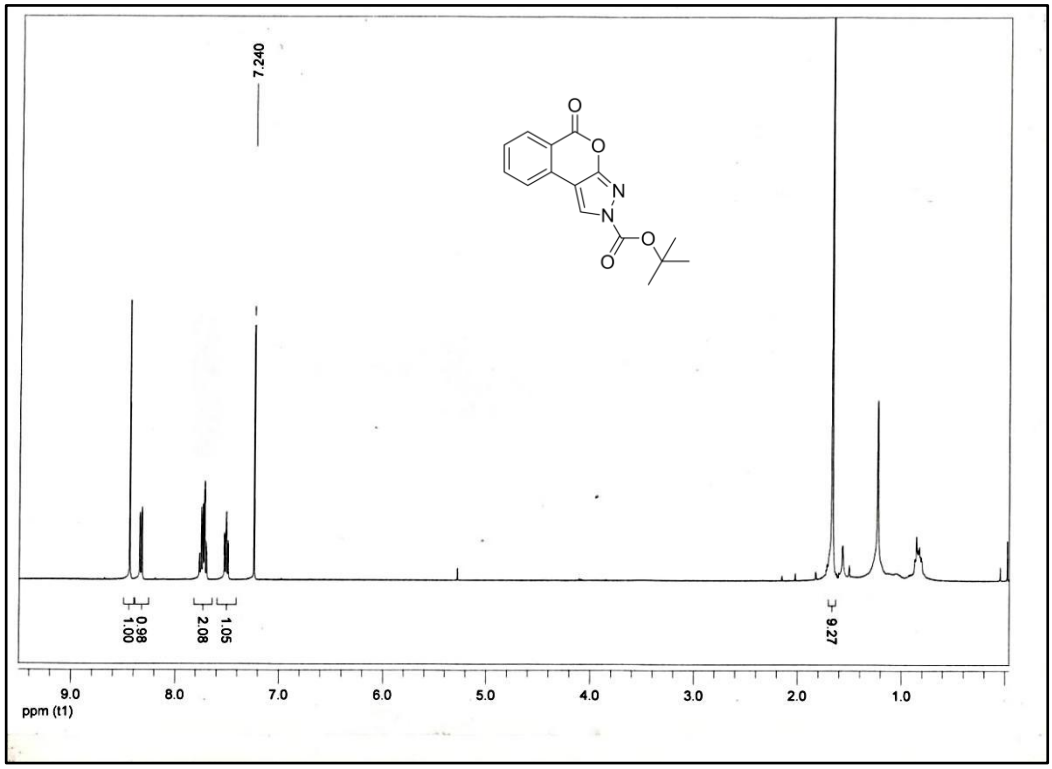

Figure 12 ^{1}H-NMR Spectrum of Compound **146**

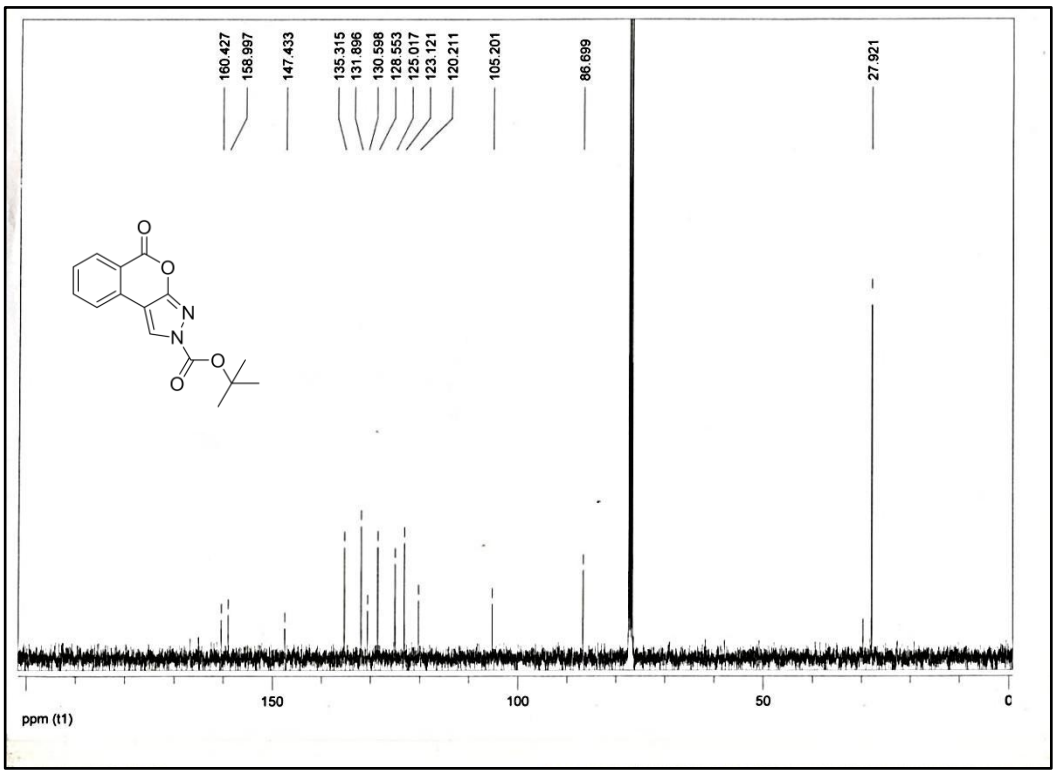

Figure 13 ^{13}C-NMR Spectrum of Compound **146**

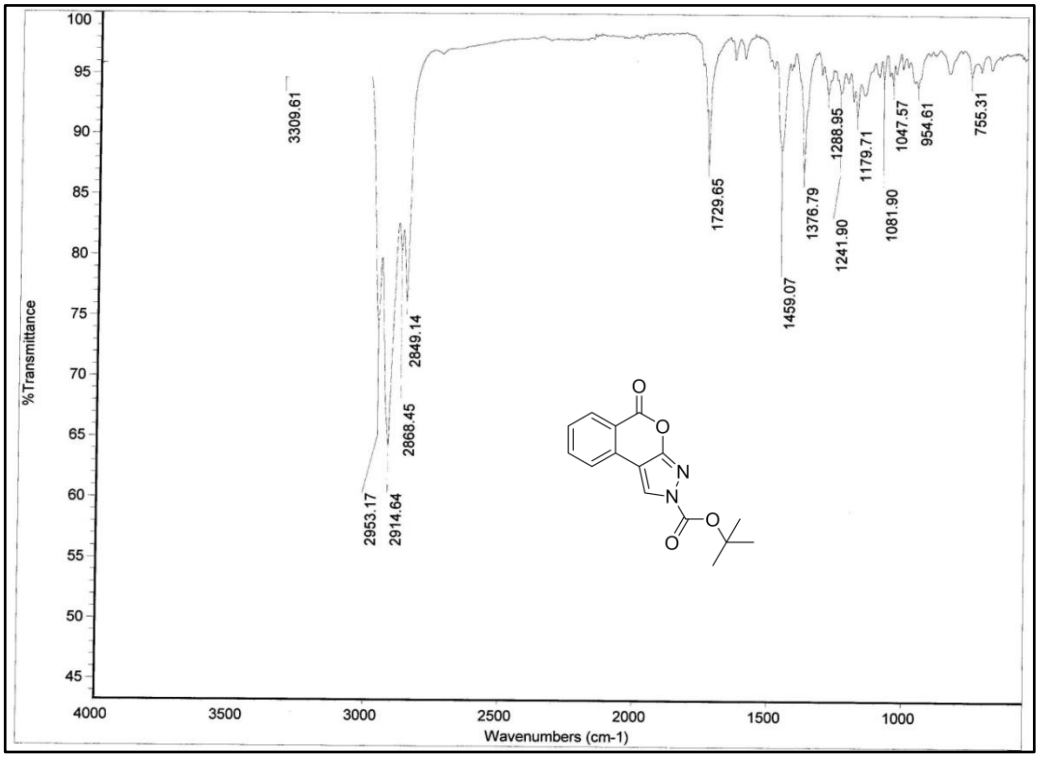

Figure 14 IR Spectrum of Compound **146**

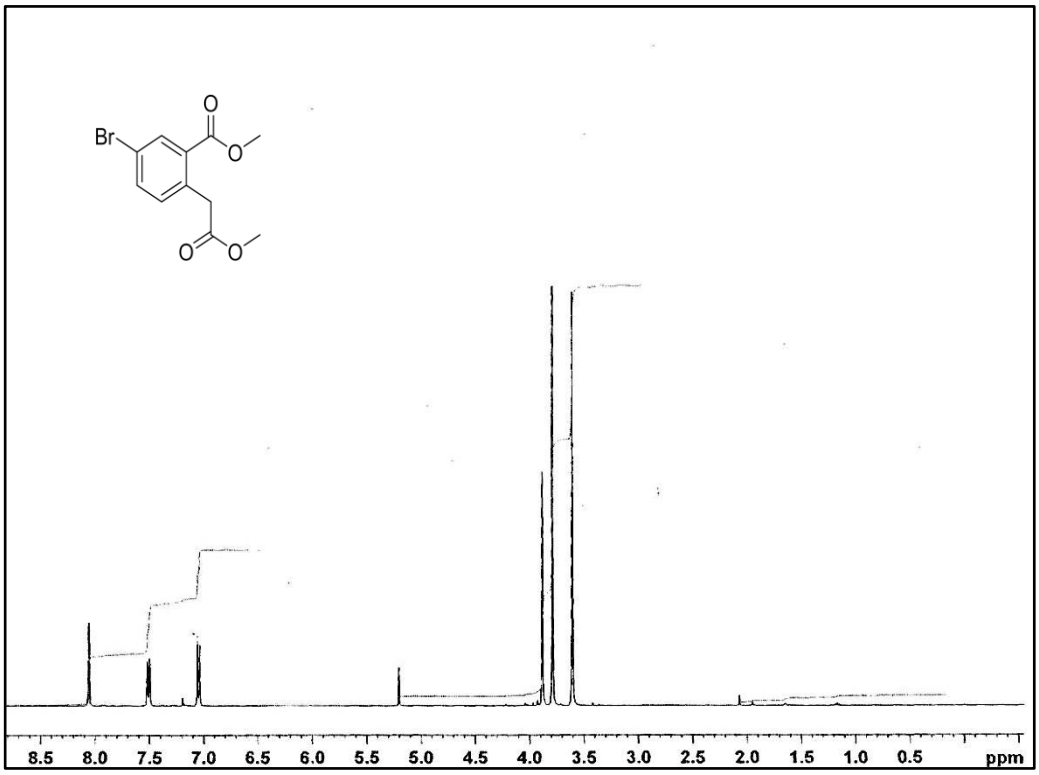

Figure 15 ^{1}H-NMR Spectrum of Compound **162b**

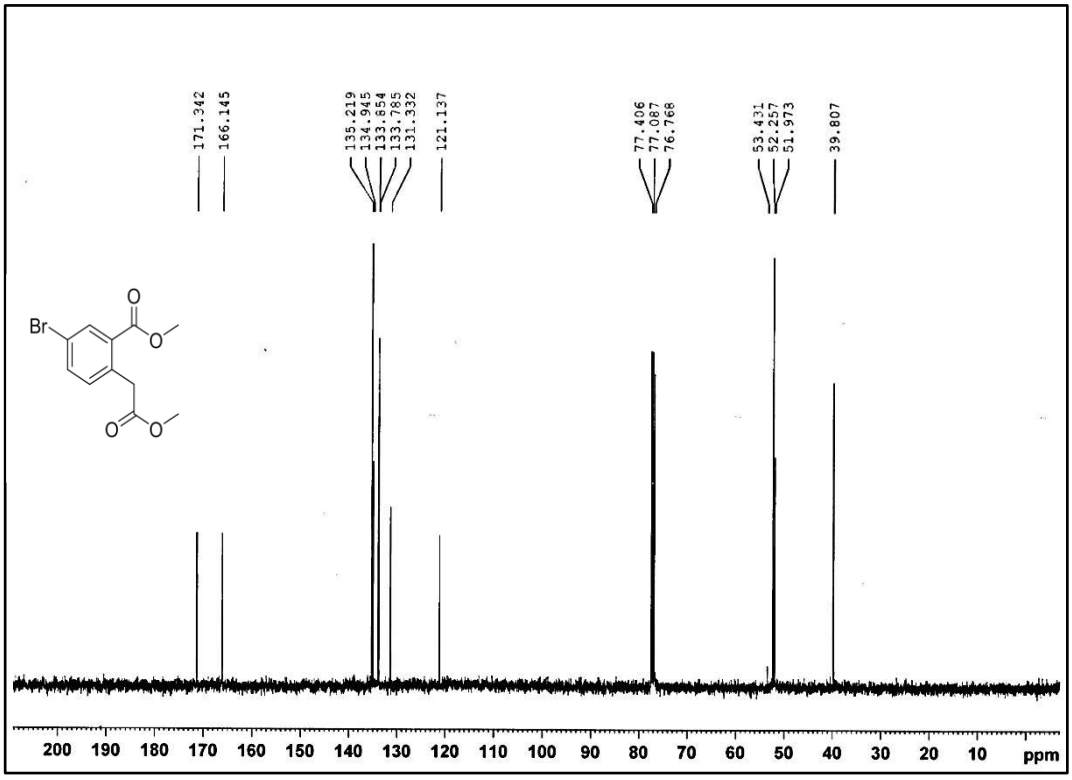

Figure 16 ^{13}C-NMR Spectrum of Compound **162b**

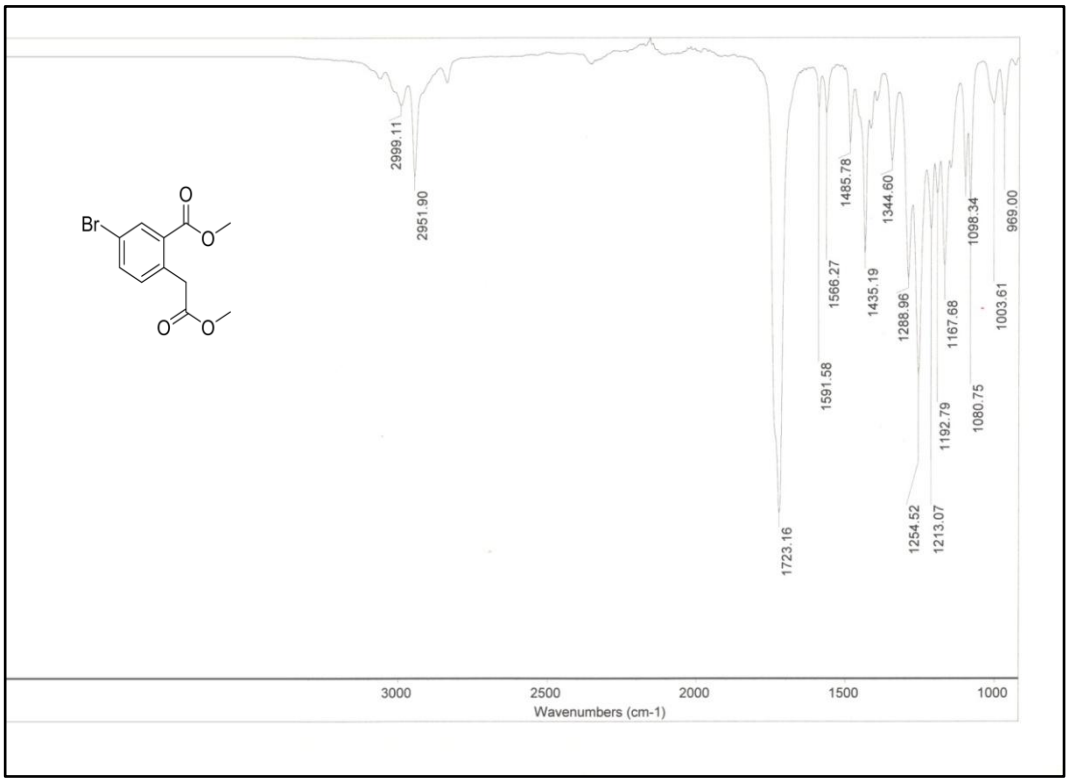

Figure 17 IR Spectrum of Compound **162b**

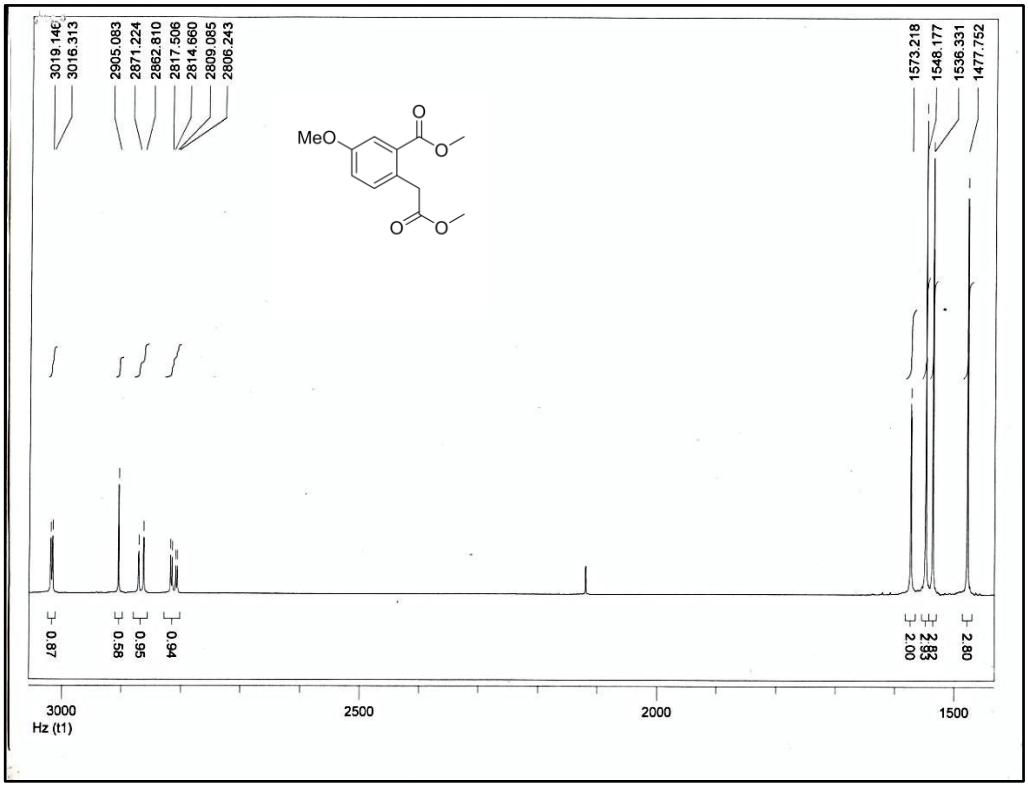

Figure 18 ^{1}H-NMR Spectrum of Compound **162c**

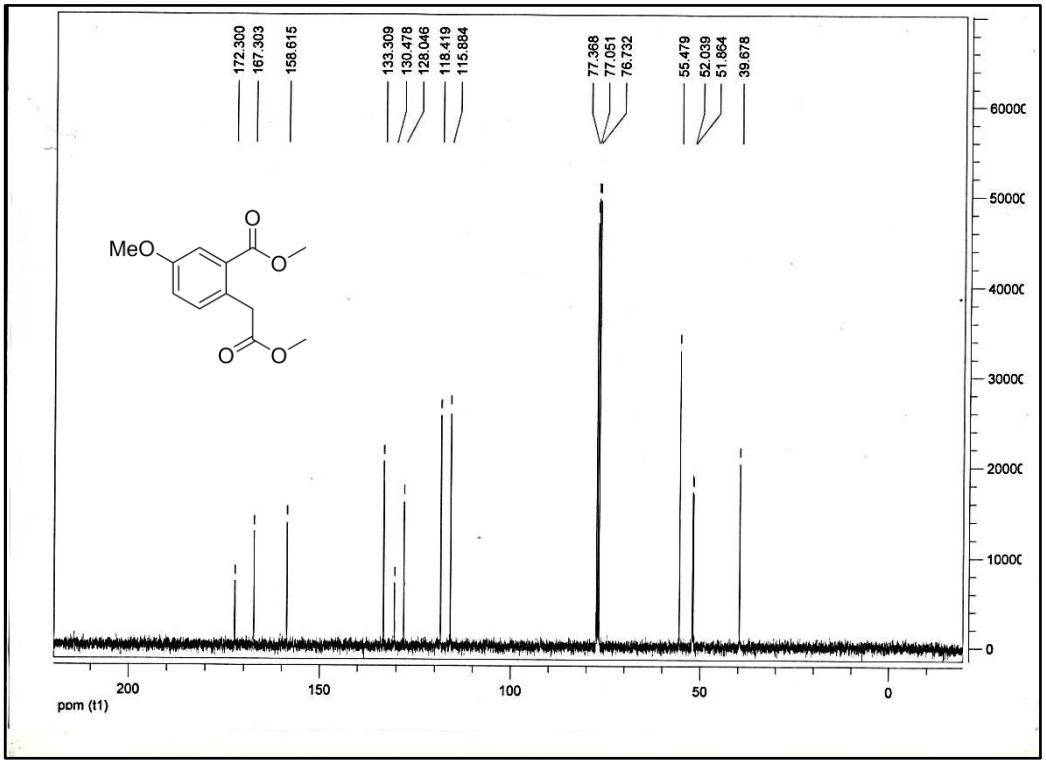

Figure 19 ^{13}C-NMR Spectrum of Compound **162c**

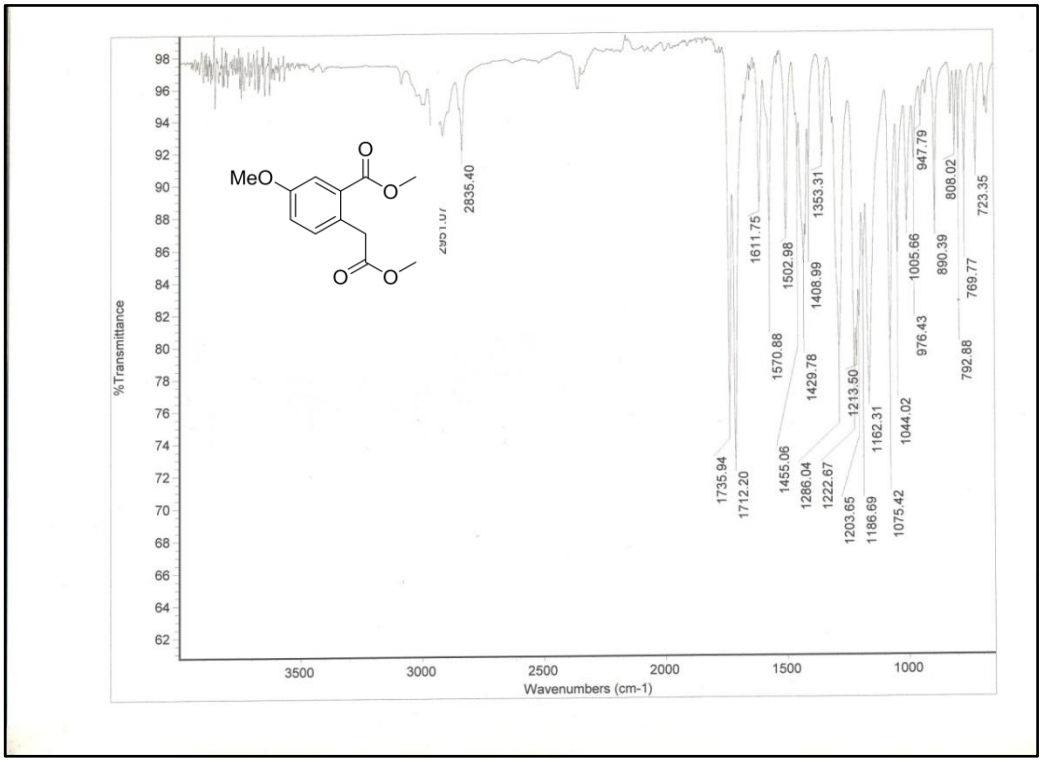

Figure 20 IR Spectrum of Compound **162c**

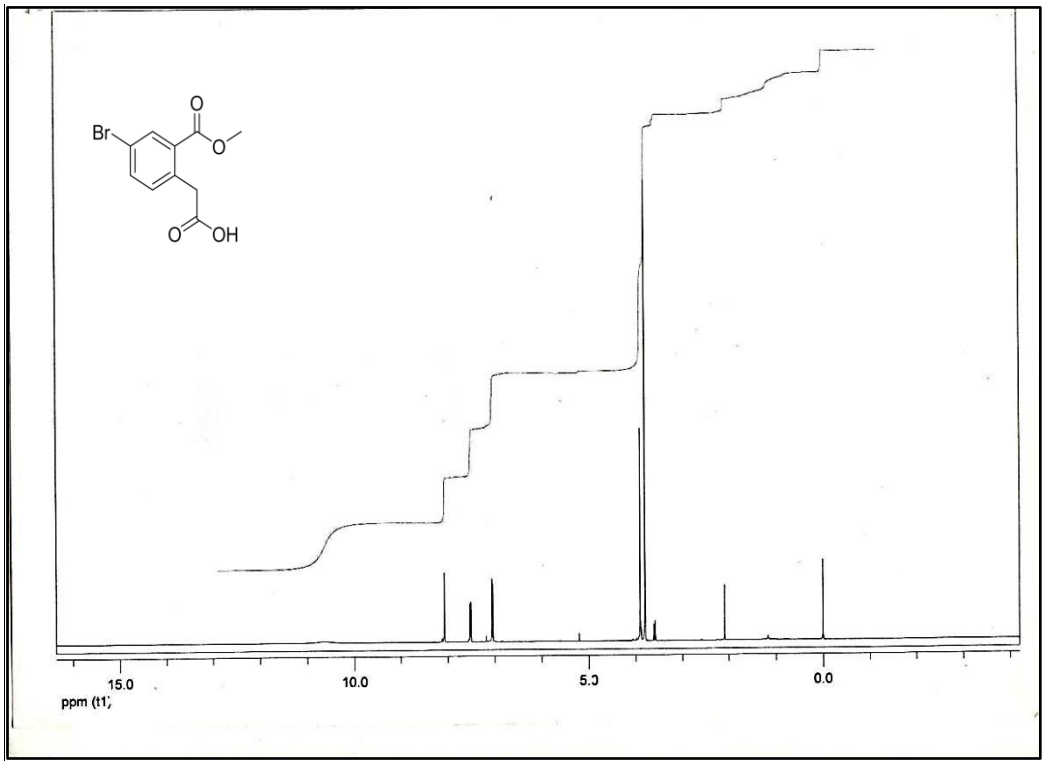

Figure 21 ^{1}H-NMR Spectrum of Compound **156b**

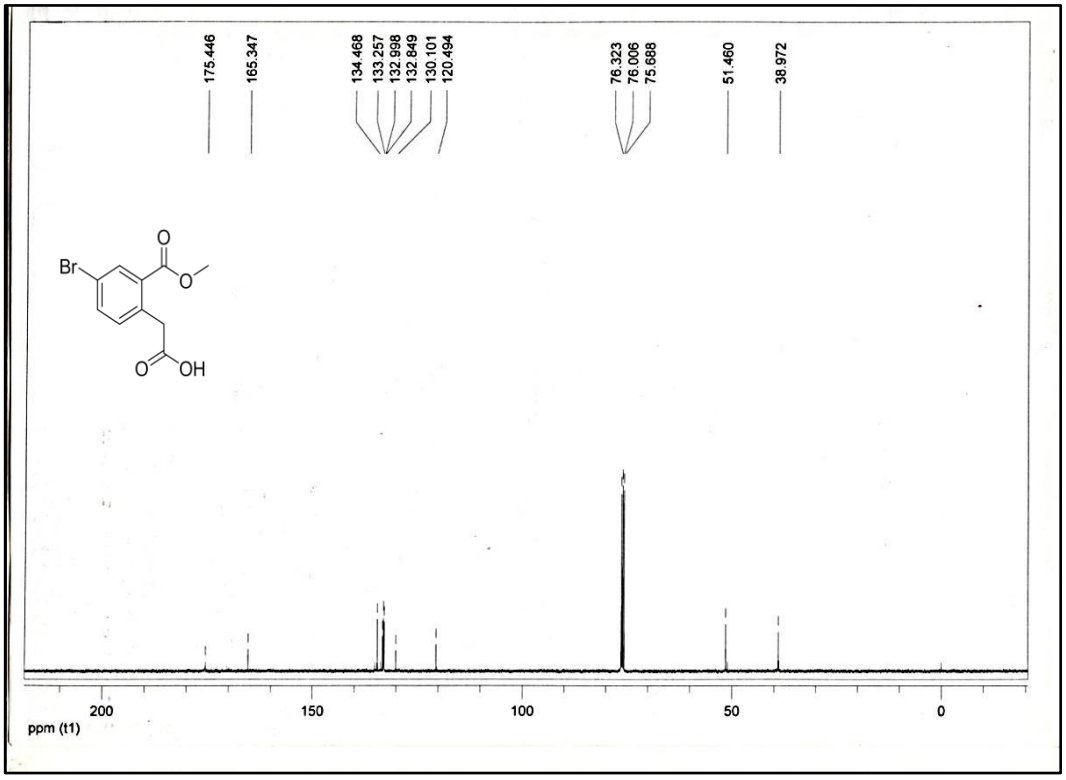

Figure 22 ^{13}C-NMR Spectrum of Compound **156b**

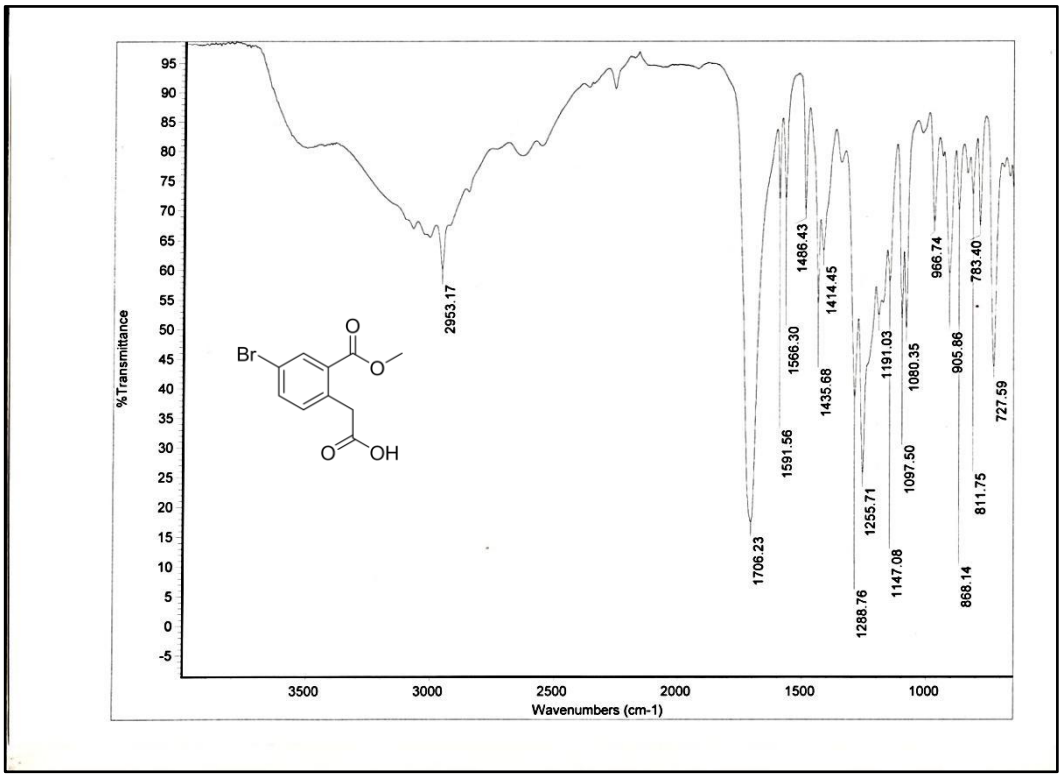

Figure 23 IR Spectrum of Compound **156b**

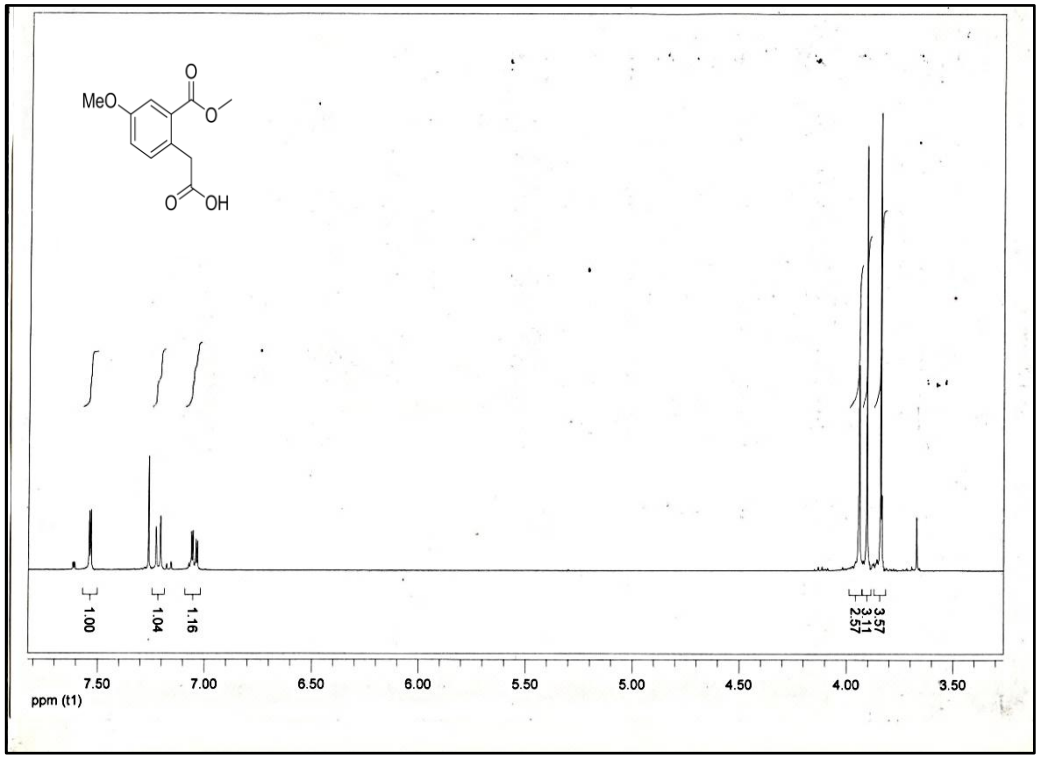

Figure 24 ^{1}H-NMR Spectrum of Compound **156c**

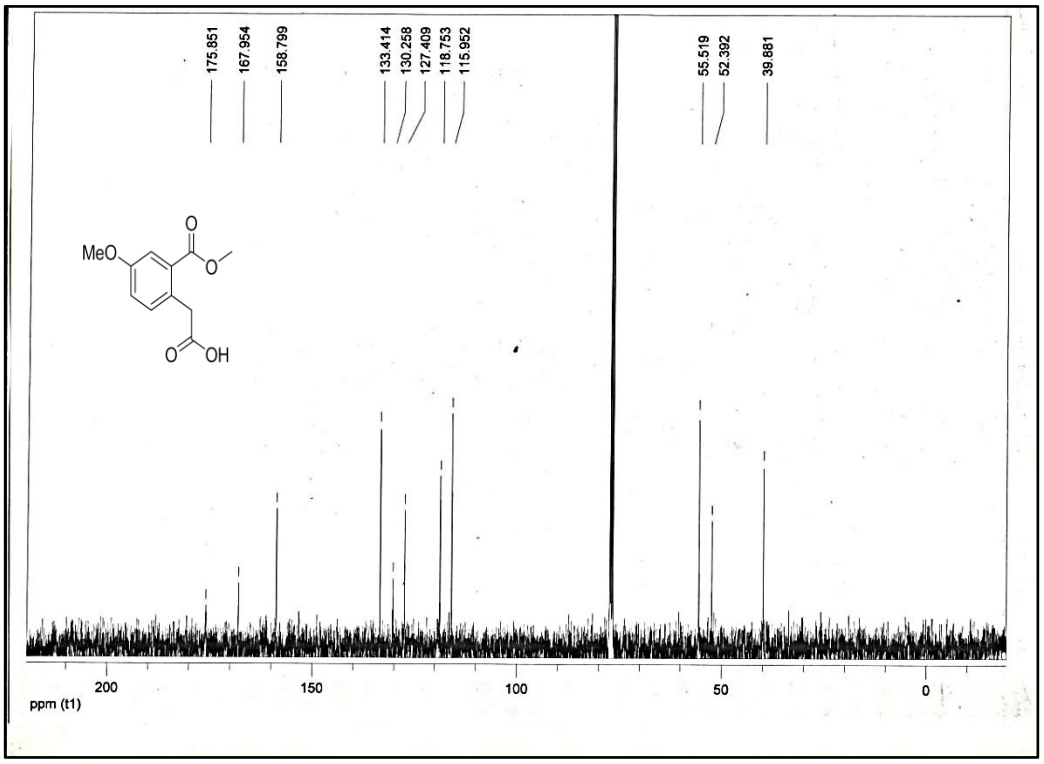

Figure 25 ^{13}C-NMR Spectrum of Compound **156c**

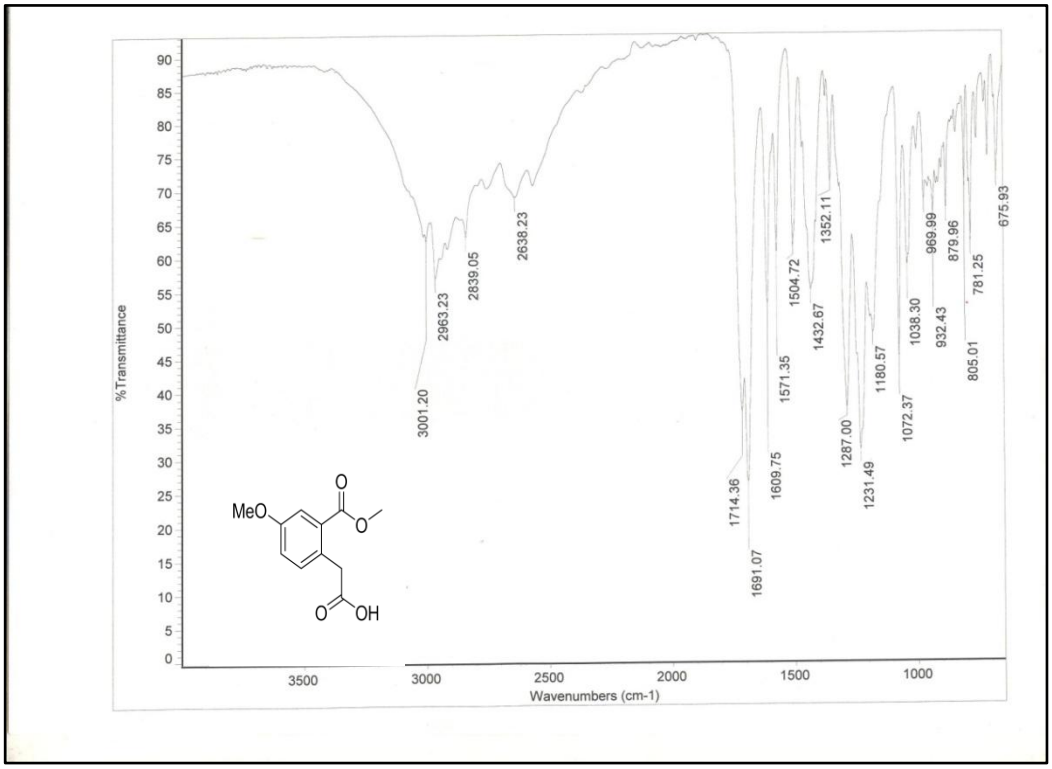

Figure 26 IR Spectrum of Compound **156c**

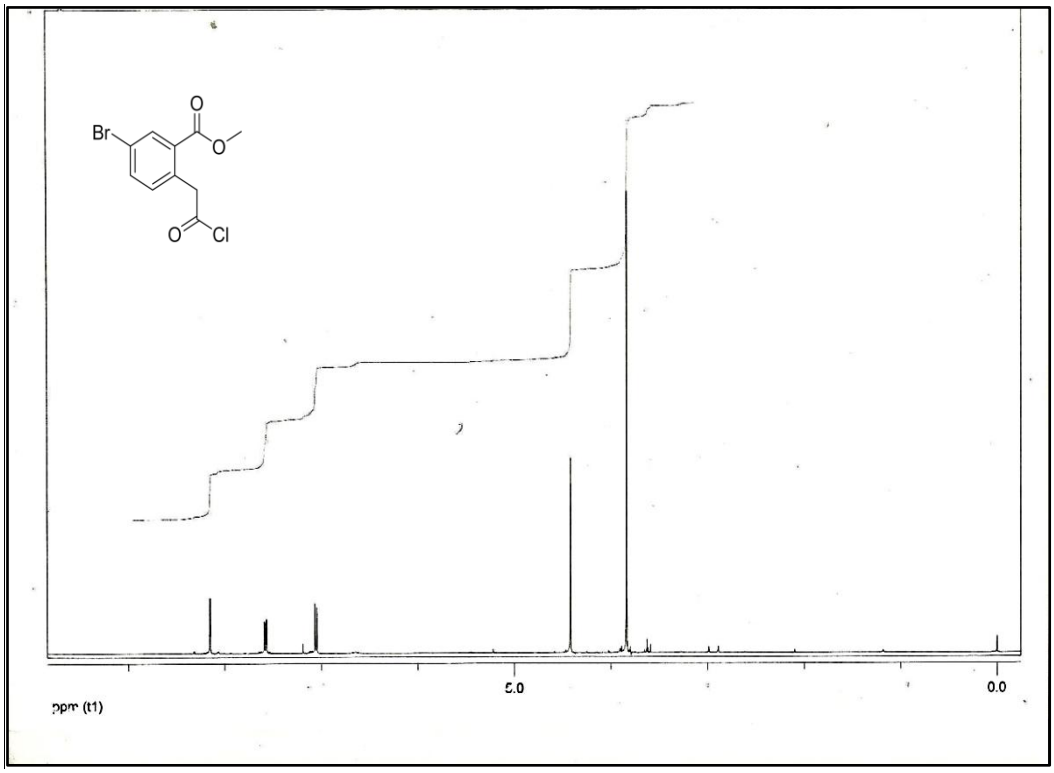

Figure 27 ^{1}H-NMR Spectrum of Compound **163b**

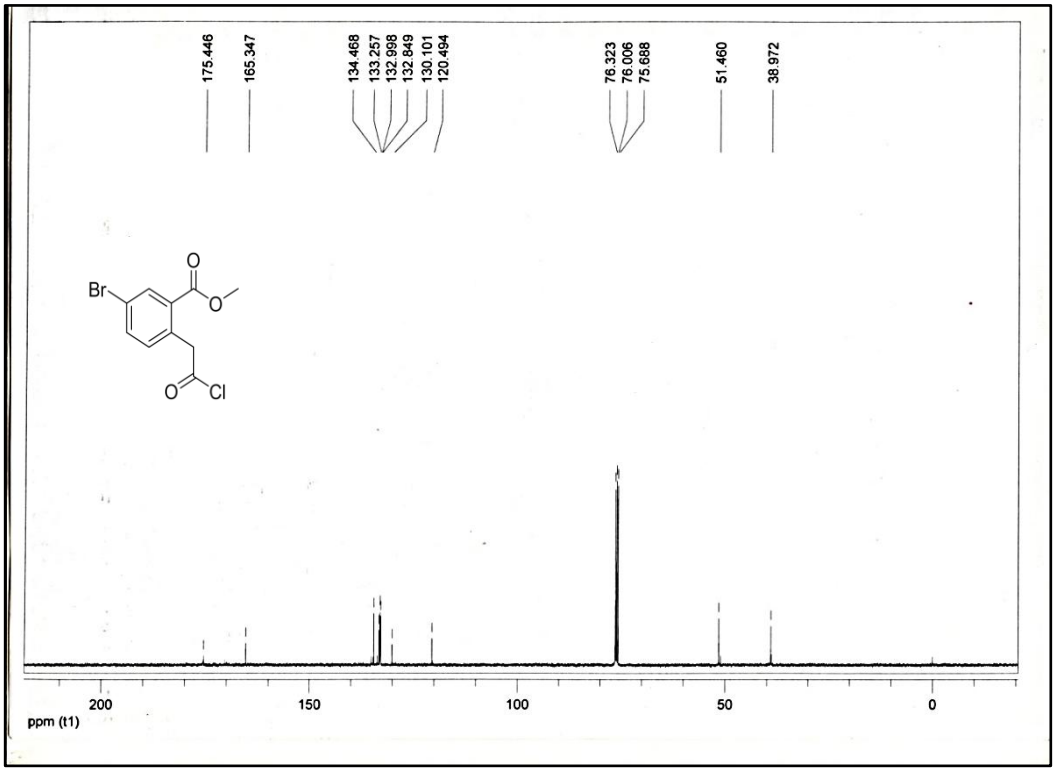

Figure 28 ^{13}C-NMR Spectrum of Compound **163b**

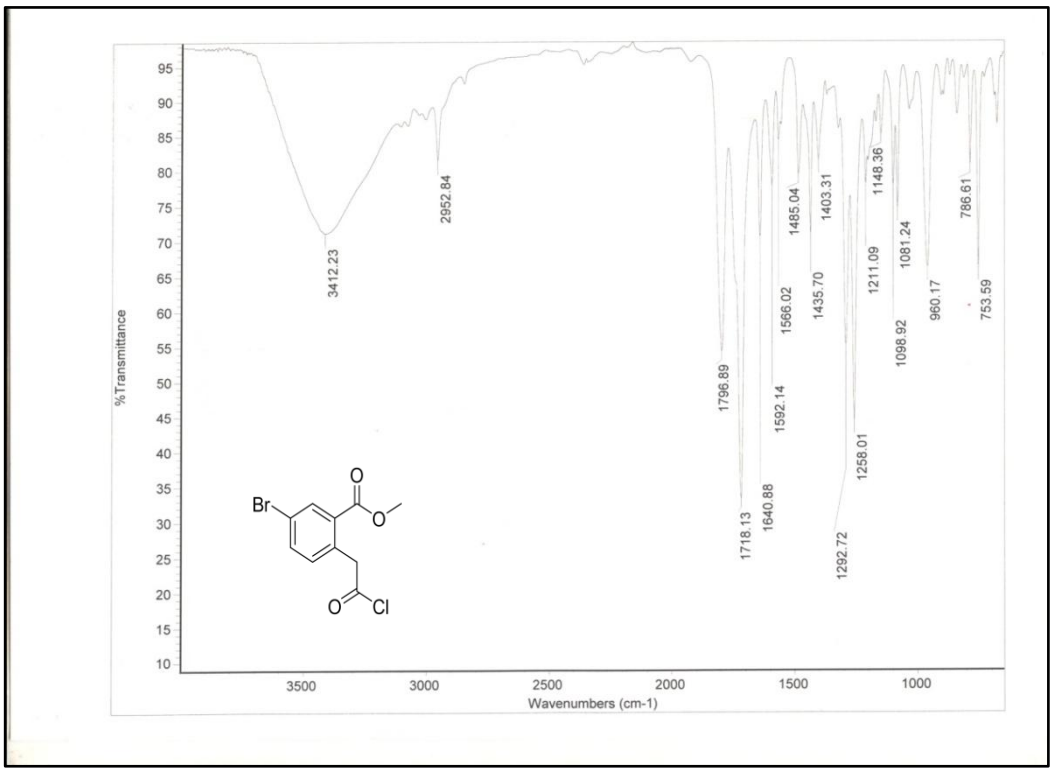

Figure 29 IR Spectrum of Compound **163b**

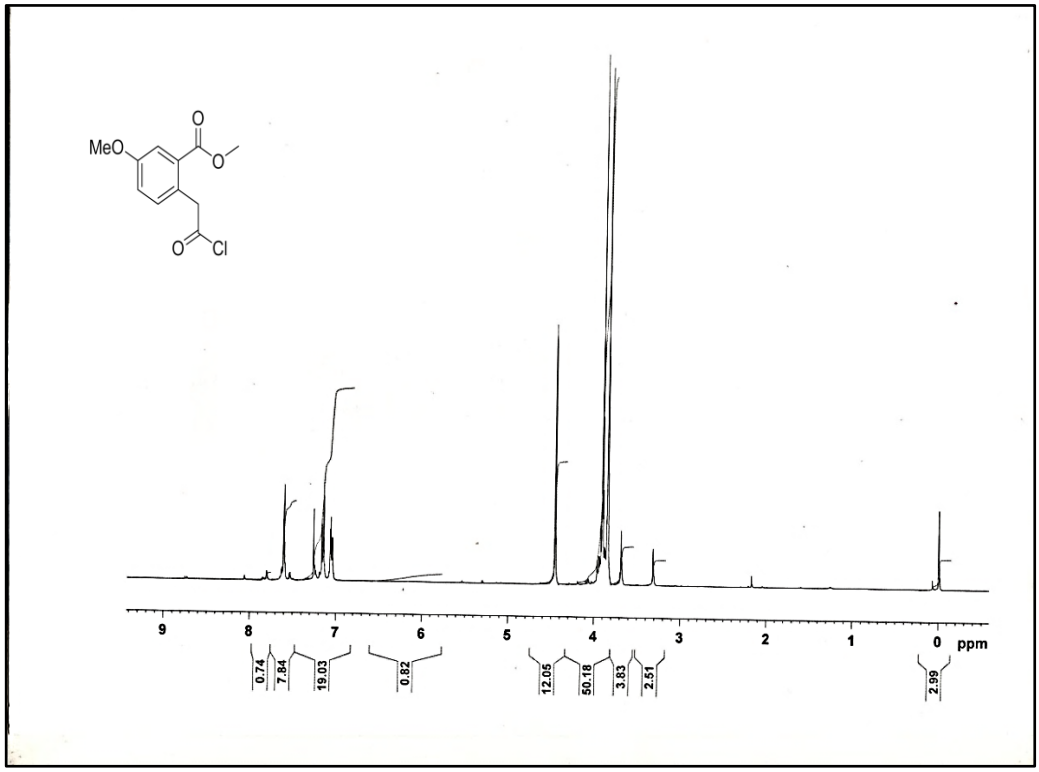

Figure 30 ^{1}H-NMR Spectrum of Compound **163c**

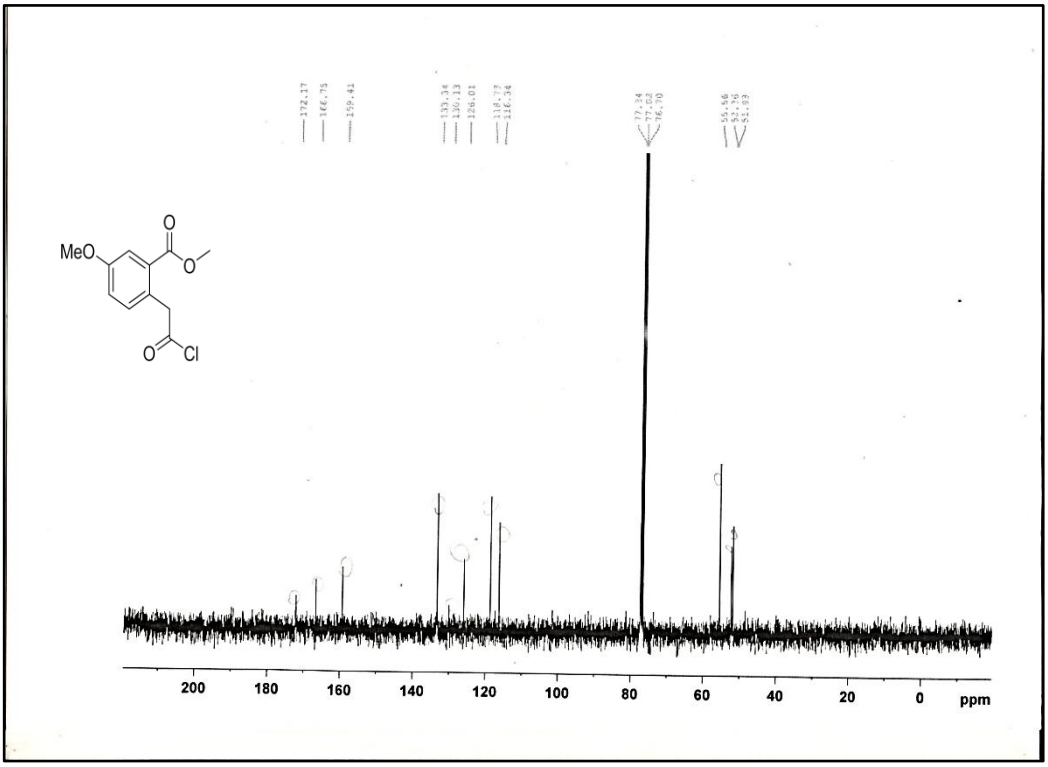

Figure 31 ^{13}C-NMR Spectrum of Compound **163c**

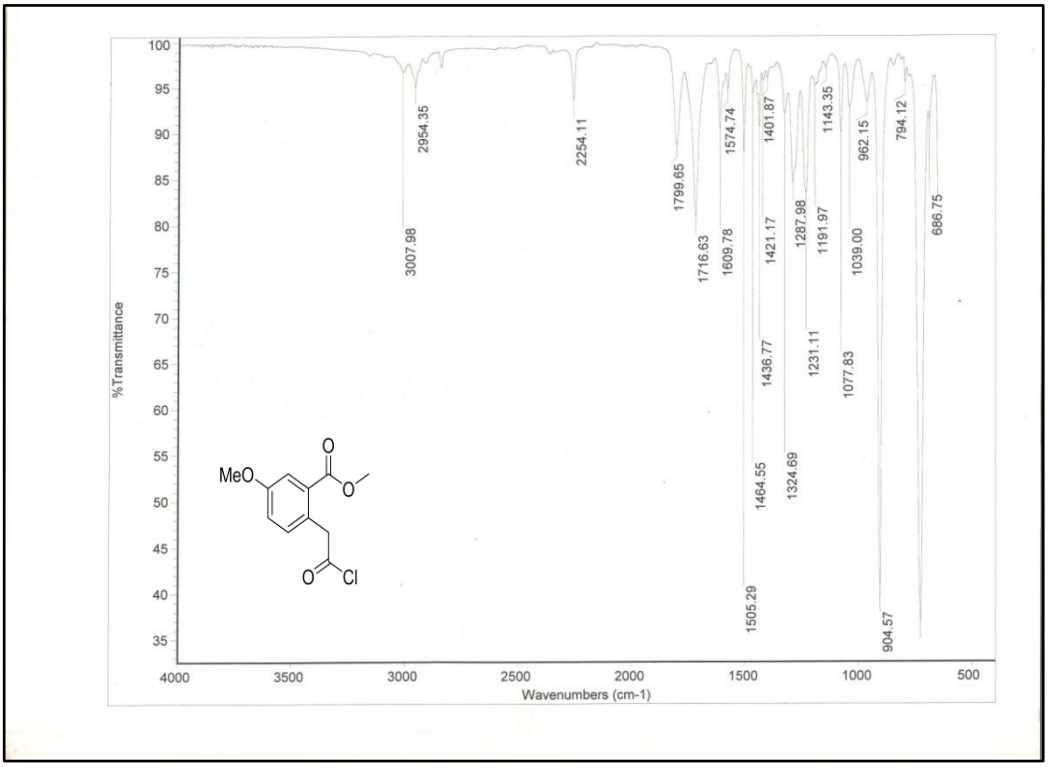

Figure 32 IR Spectrum of Compound **163c**

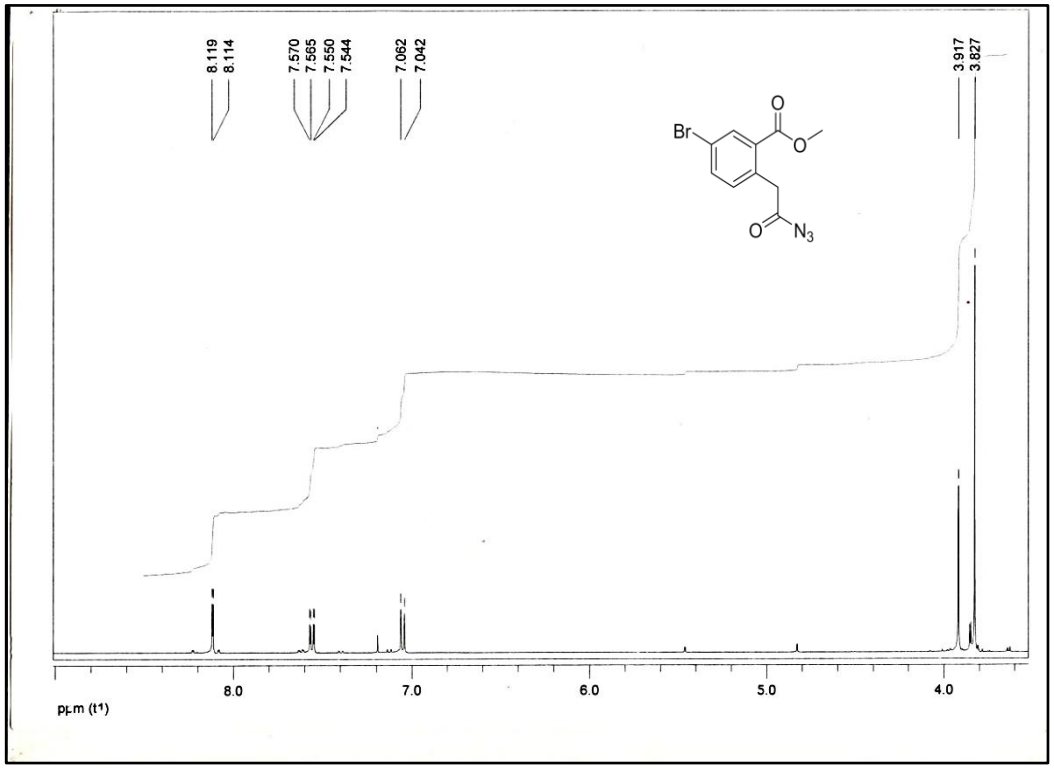

Figure 33 ^{1}H-NMR Spectrum of Compound **164b**

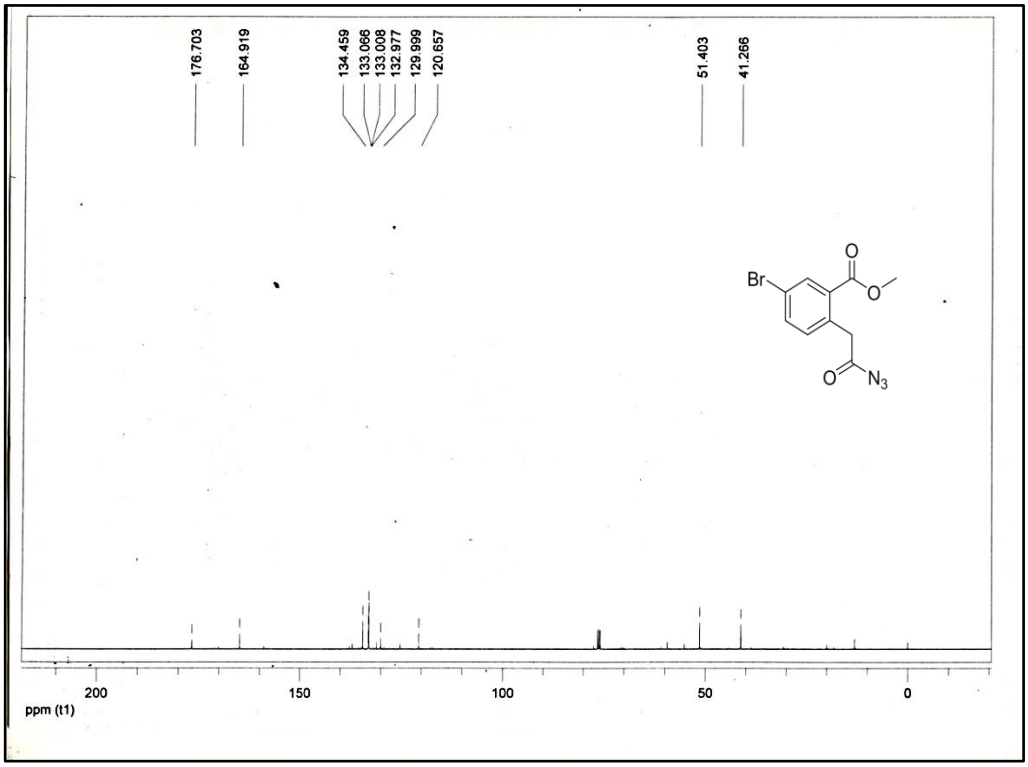

Figure 34 ^{13}C-NMR Spectrum of Compound **164b**

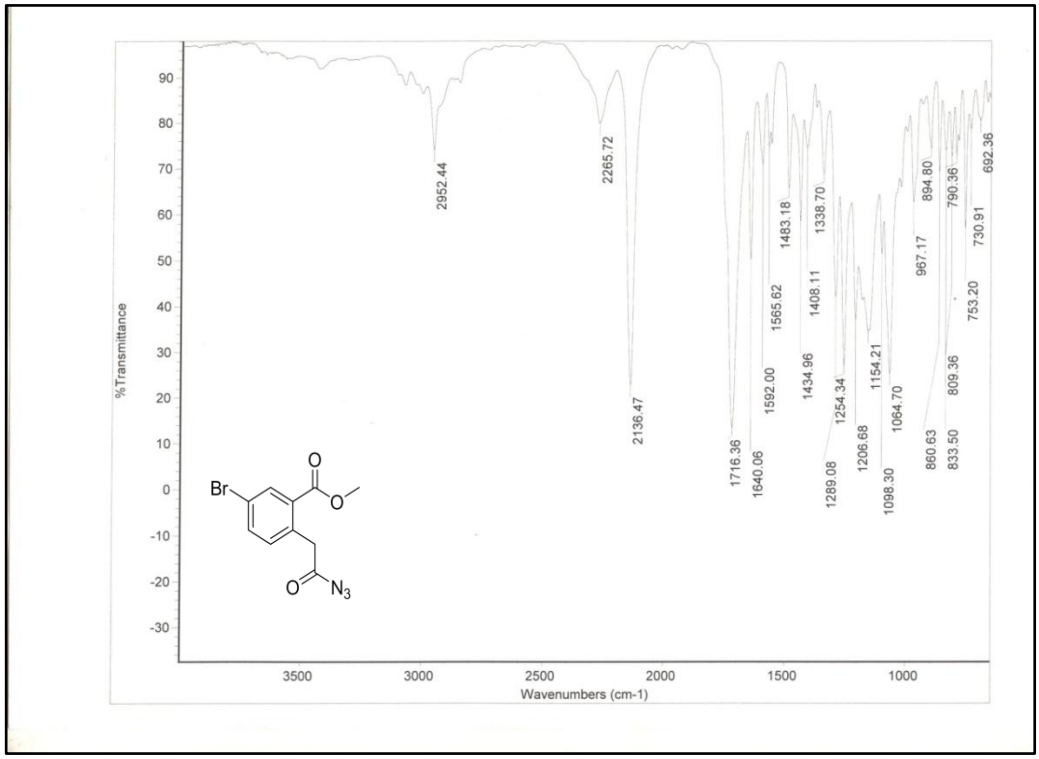

Figure 35 IR Spectrum of Compound **164b**

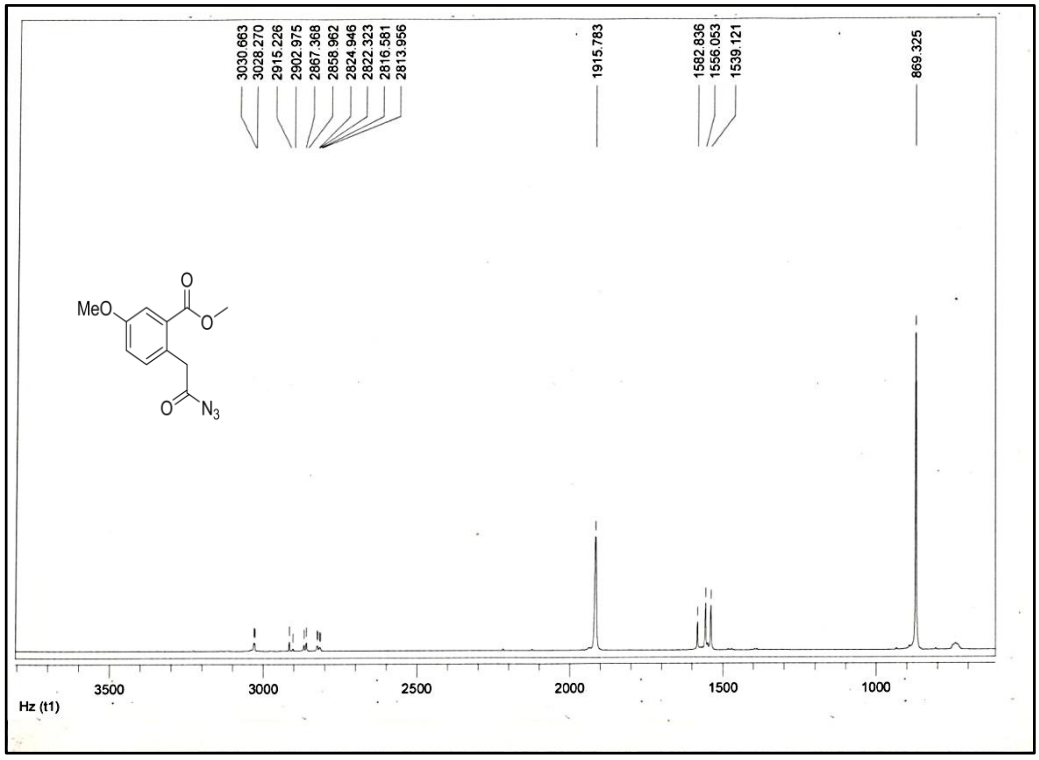

Figure 36 ^{1}H-NMR Spectrum of Compound **164c**

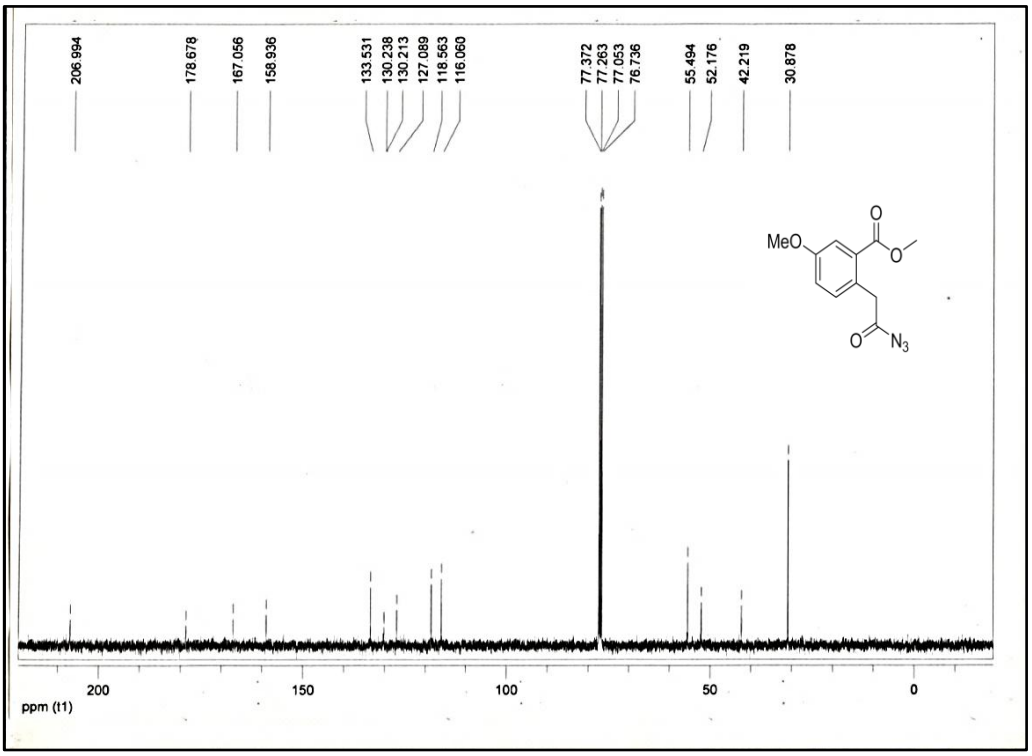

Figure 37 ^{13}C-NMR Spectrum of Compound **164c**

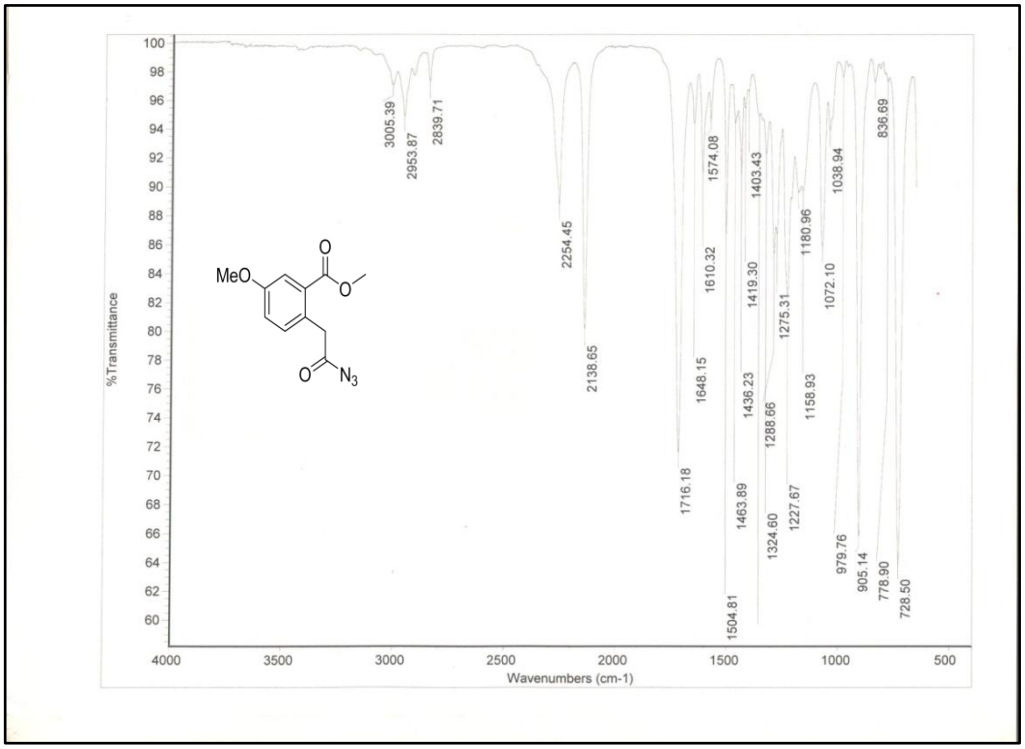

Figure 38 IR Spectrum of Compound **164c**

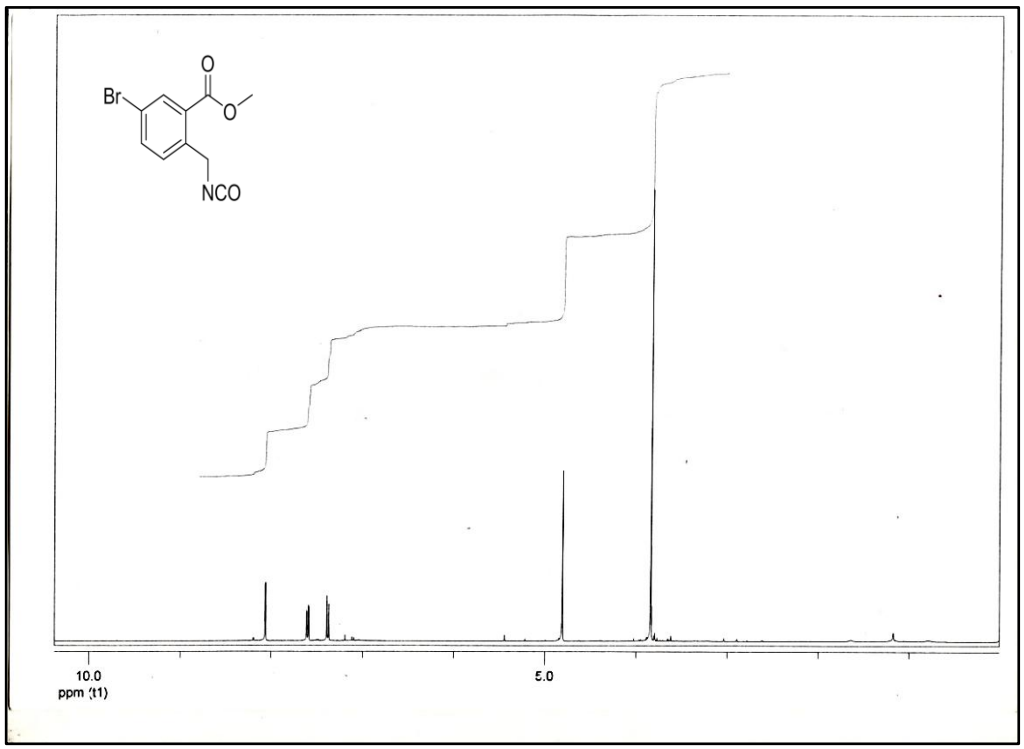

Figure 39 ^{1}H-NMR Spectrum of Compound **158b**

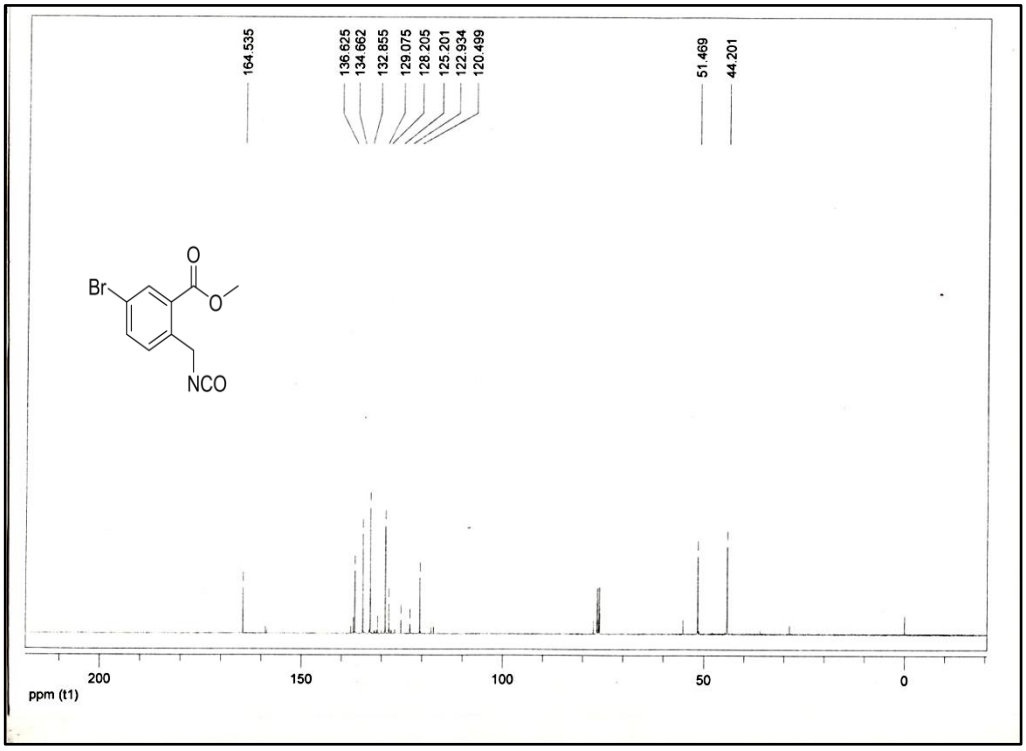

Figure 40 ^{13}C-NMR Spectrum of Compound **158b**

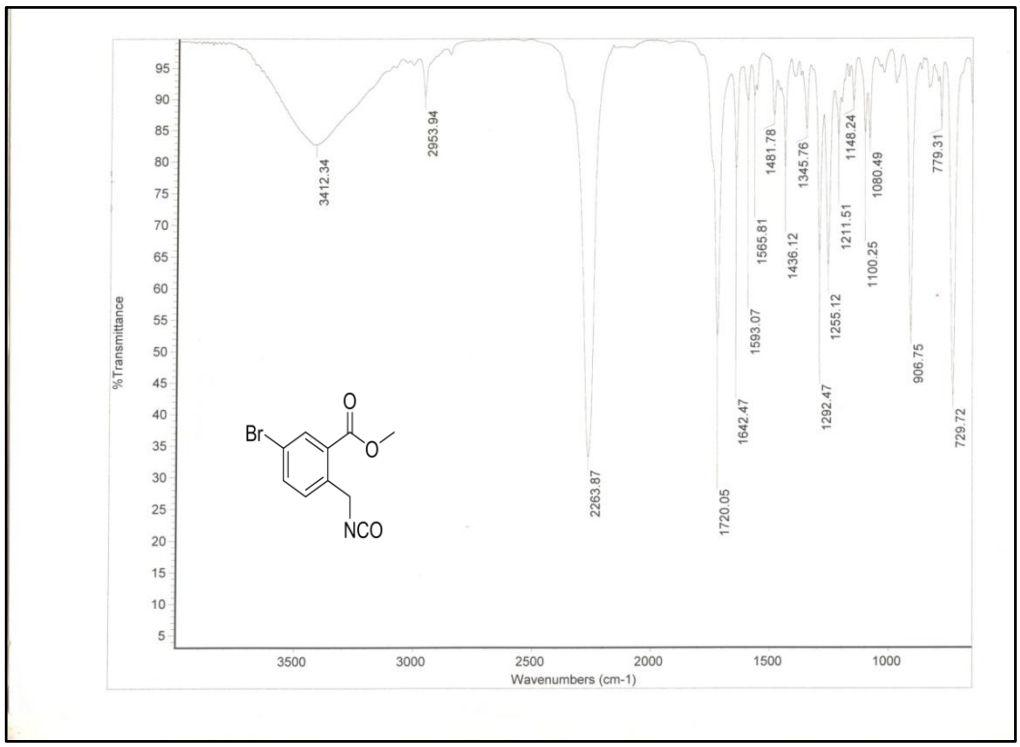

Figure 41 IR Spectrum of Compound **158b**

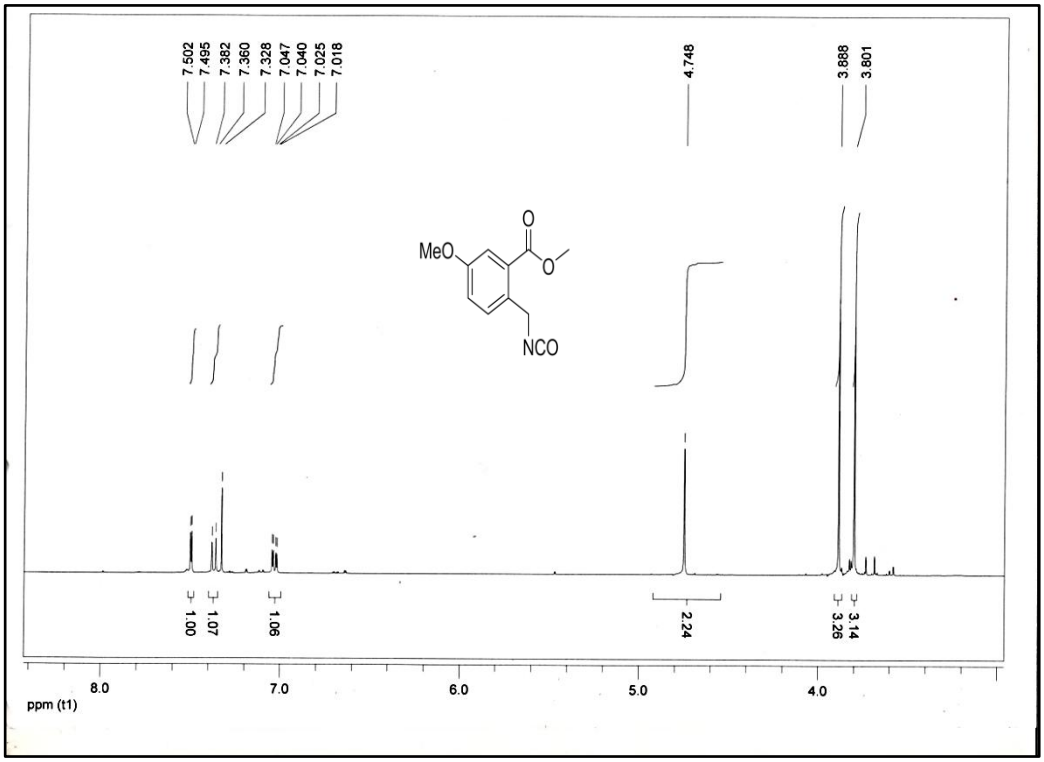

Figure 42 ^{1}H-NMR Spectrum of Compound **158c**

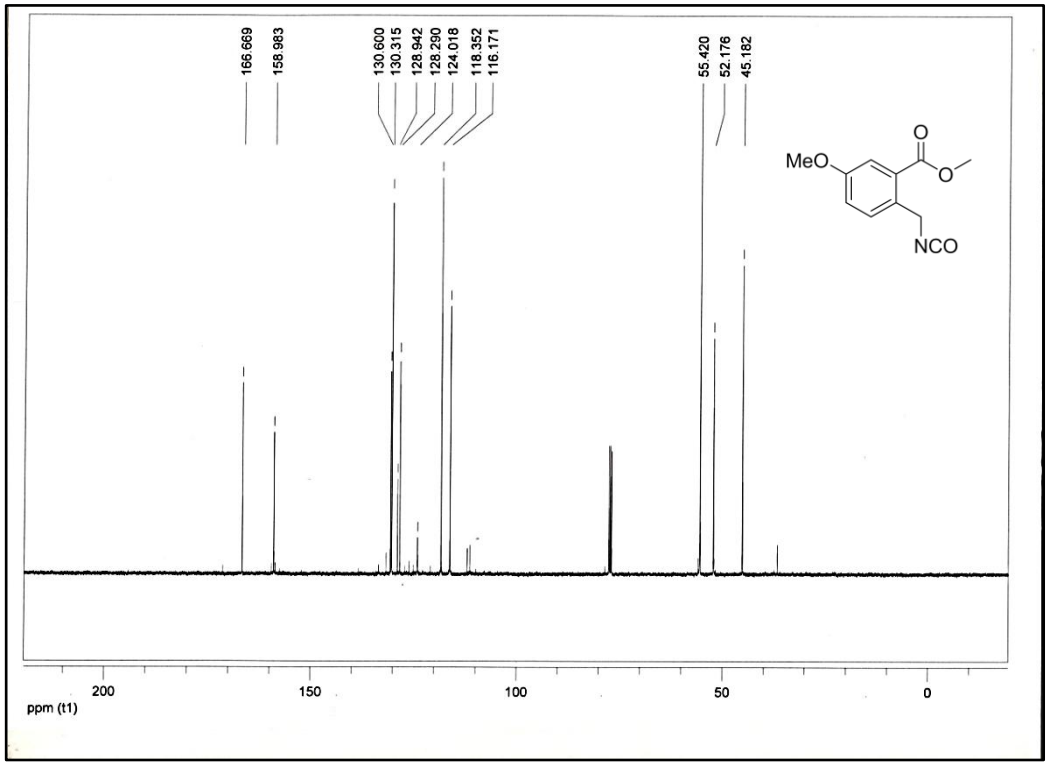

Figure 43 ^{13}C-NMR Spectrum of Compound **158c**

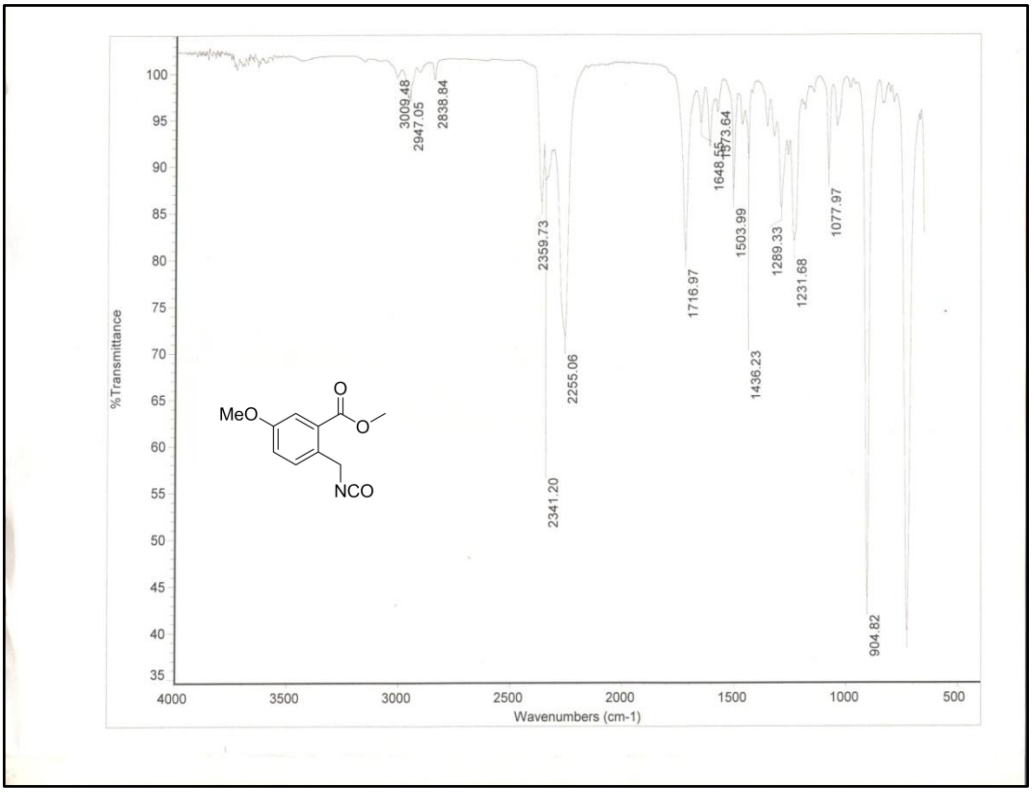

Figure 44 IR Spectrum of Compound **158c**

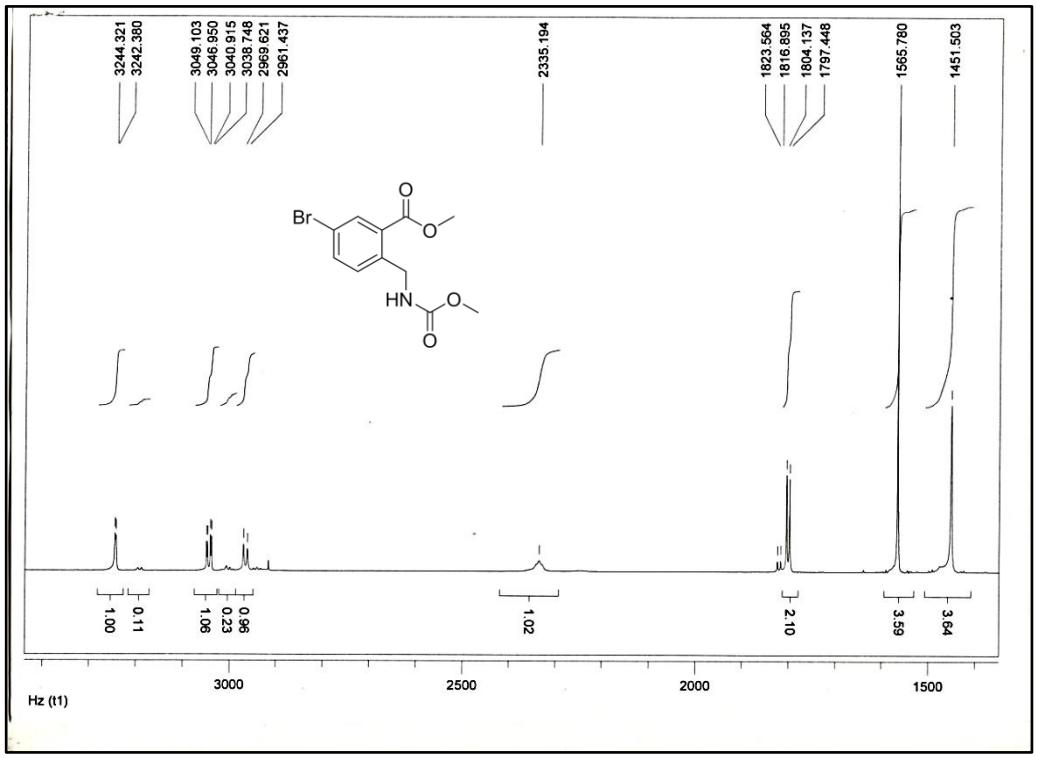

Figure 45 ^{1}H-NMR Spectrum of Compound **165b**

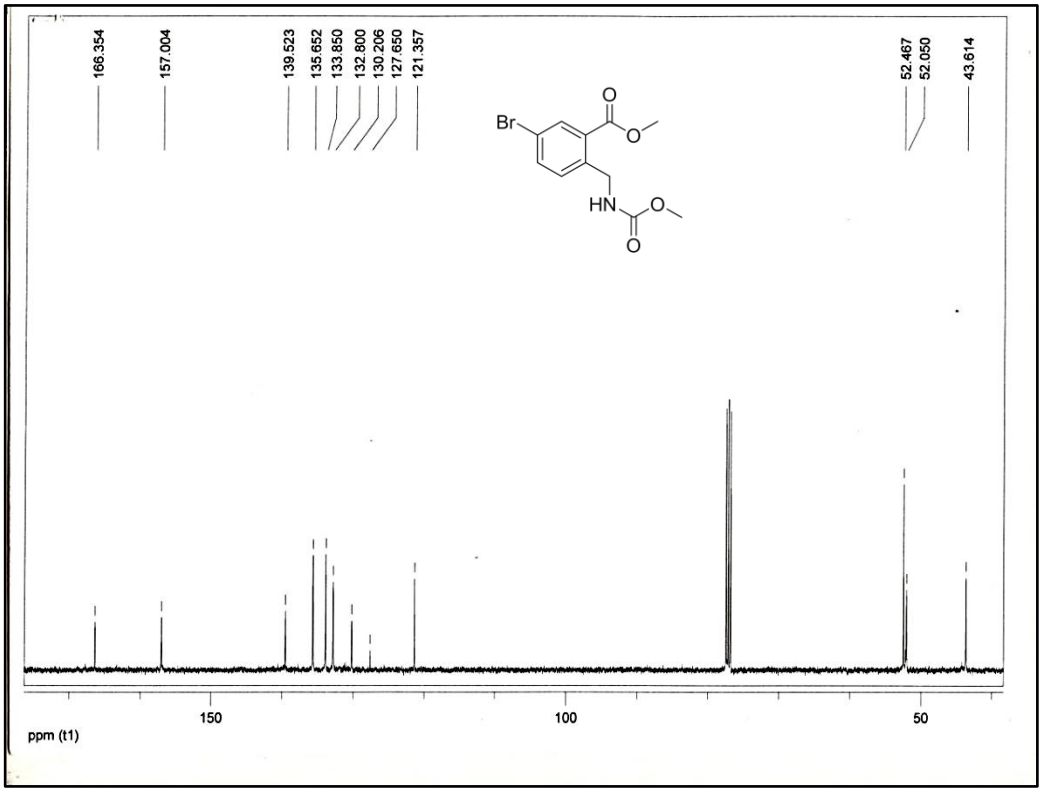

Figure 46 ^{13}C-NMR Spectrum of Compound **165b**

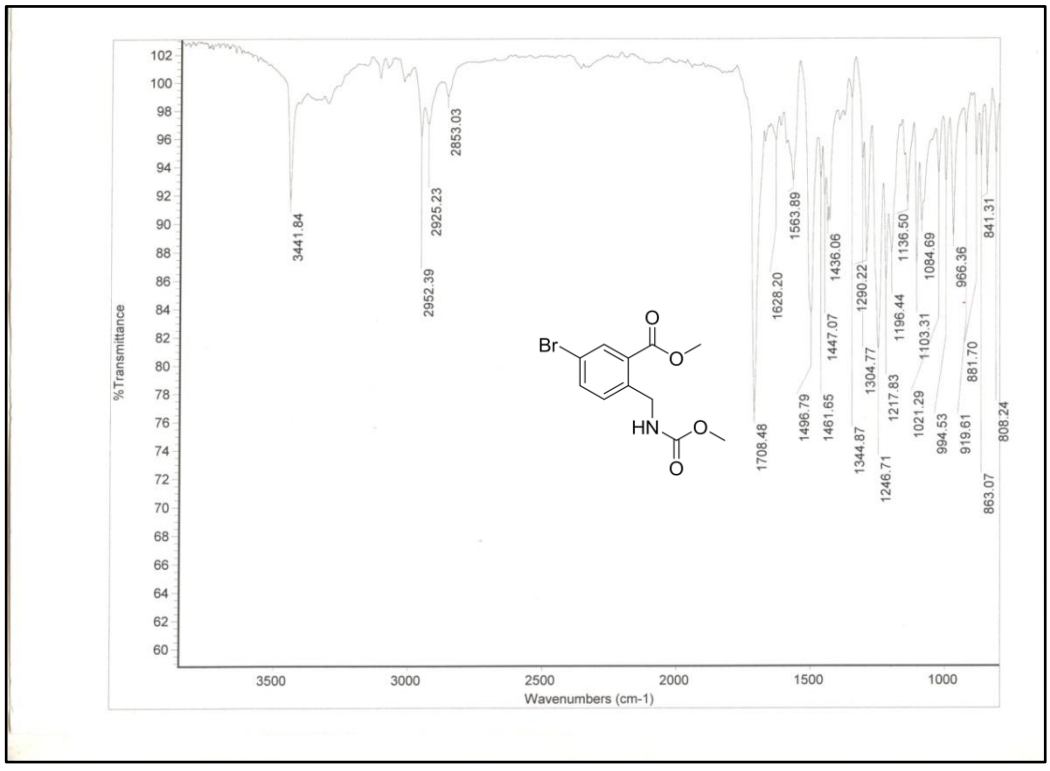

Figure 47 IR Spectrum of Compound **165b**

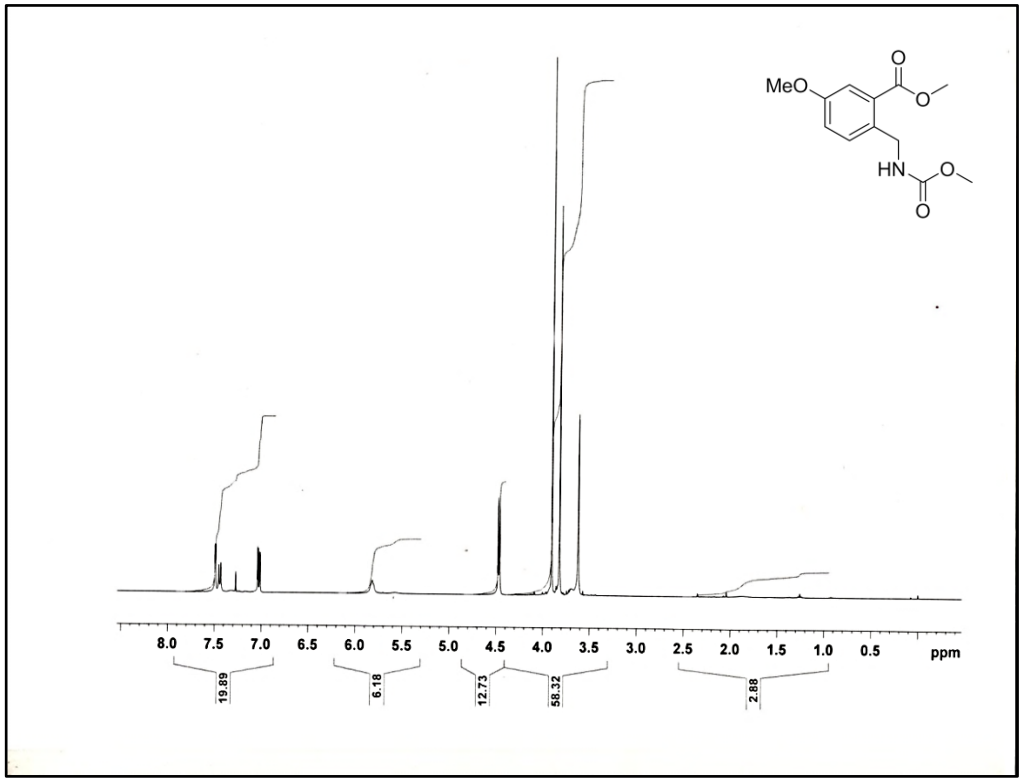

Figure 48 ^{1}H-NMR Spectrum of Compound **165c**

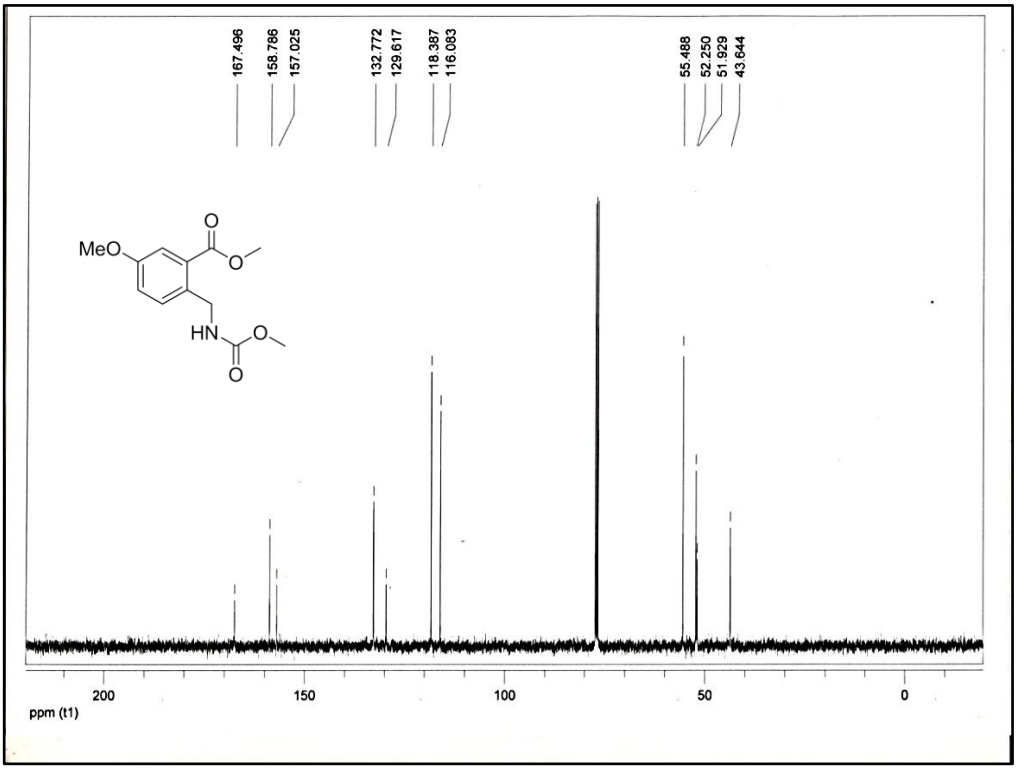

Figure 49 ^{13}C-NMR Spectrum of Compound **165c**

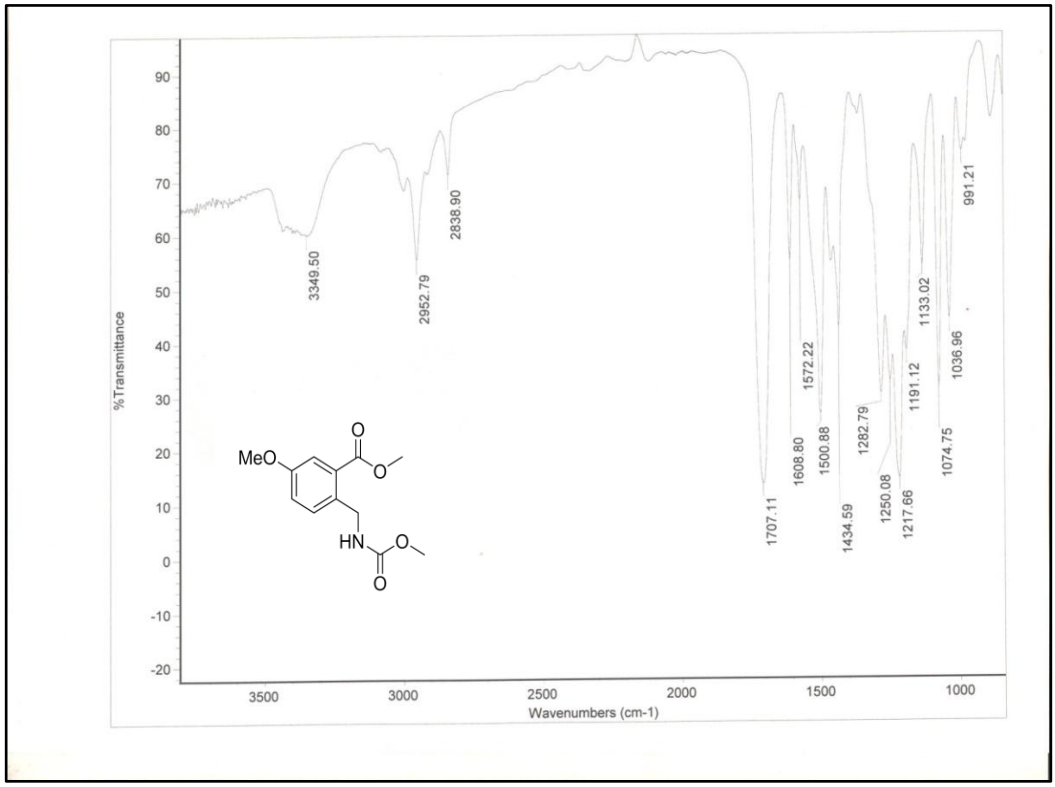

Figure 50 IR Spectrum of Compound **165c**

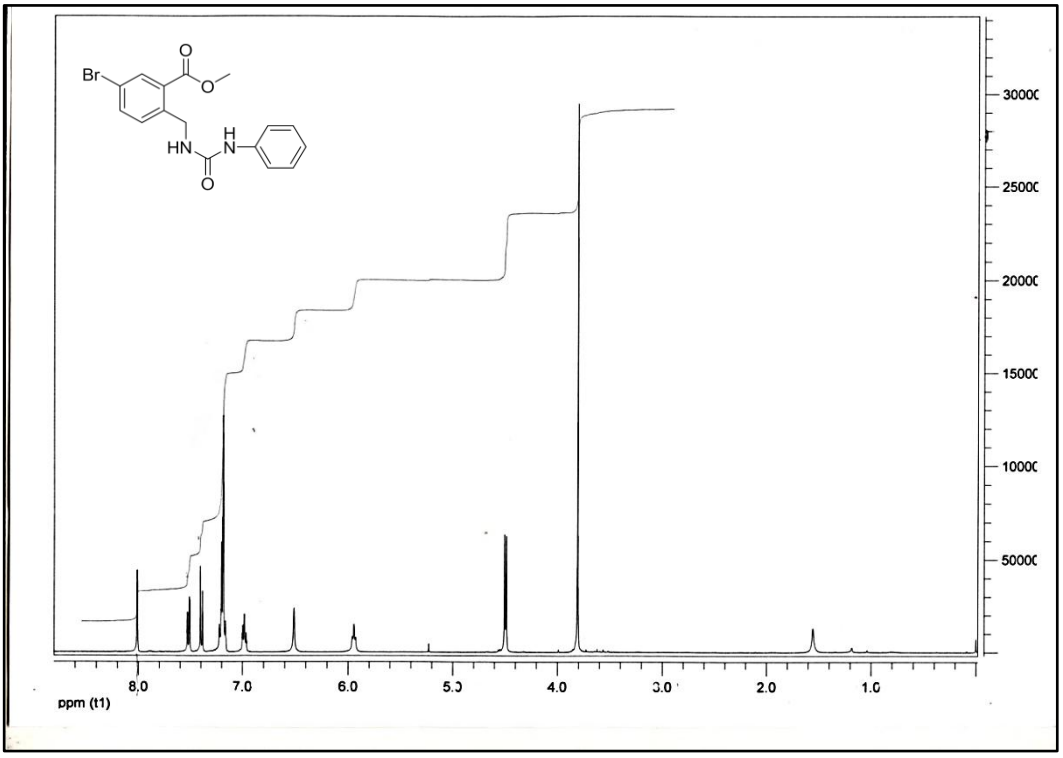

Figure 51 ^{1}H-NMR Spectrum of Compound **166b**

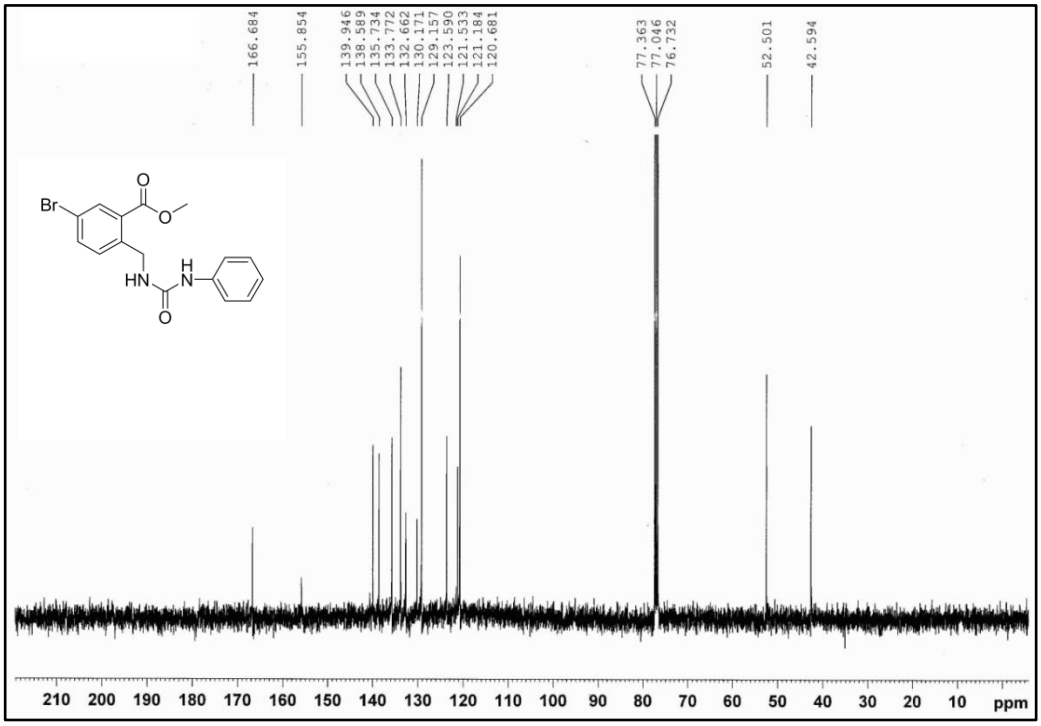

Figure 52 ^{13}C-NMR Spectrum of Compound **166b**

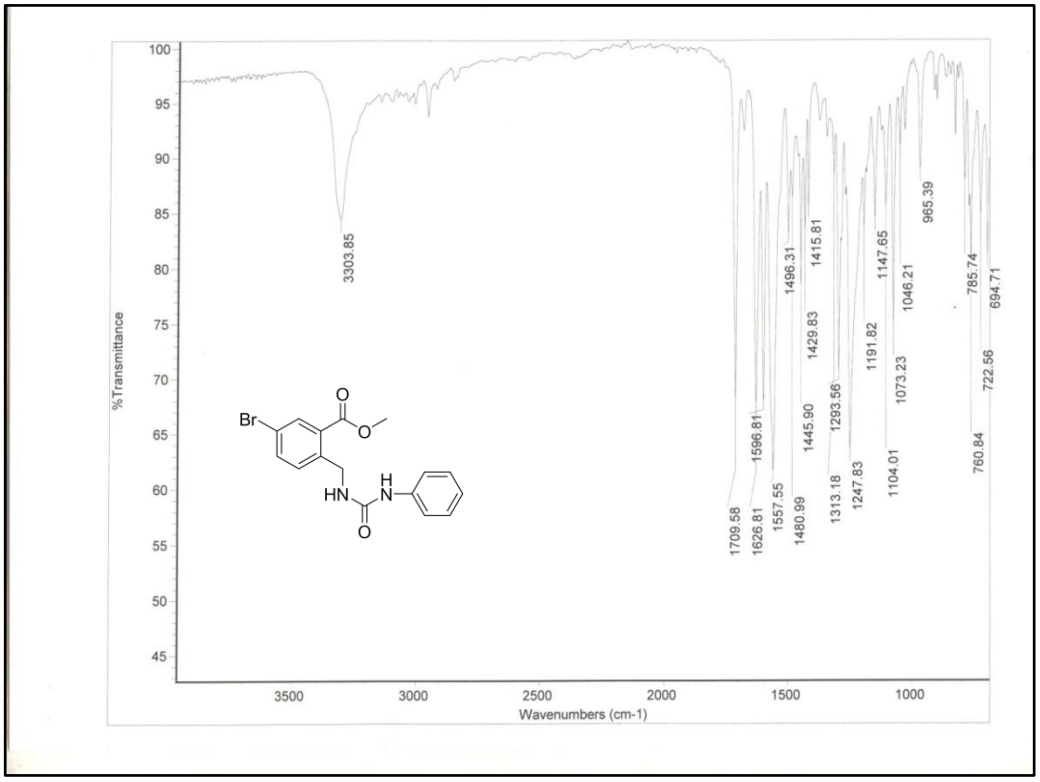

Figure 53 IR Spectrum of Compound **166b**

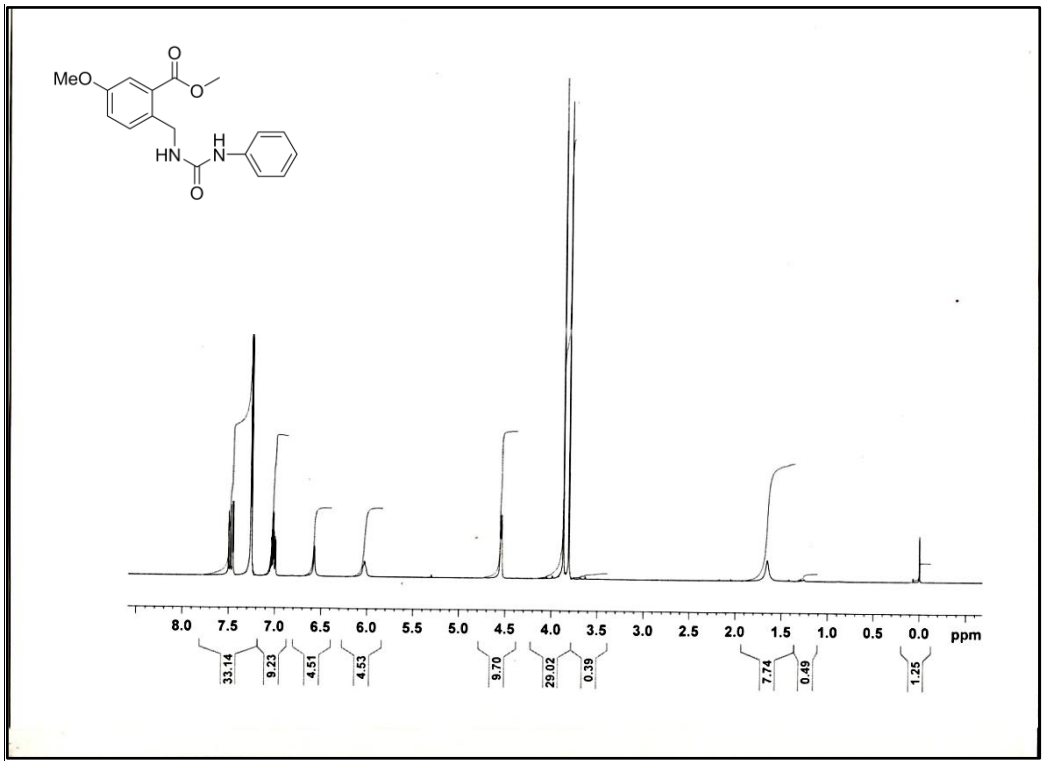

Figure 54 ^{1}H-NMR Spectrum of Compound **166c**

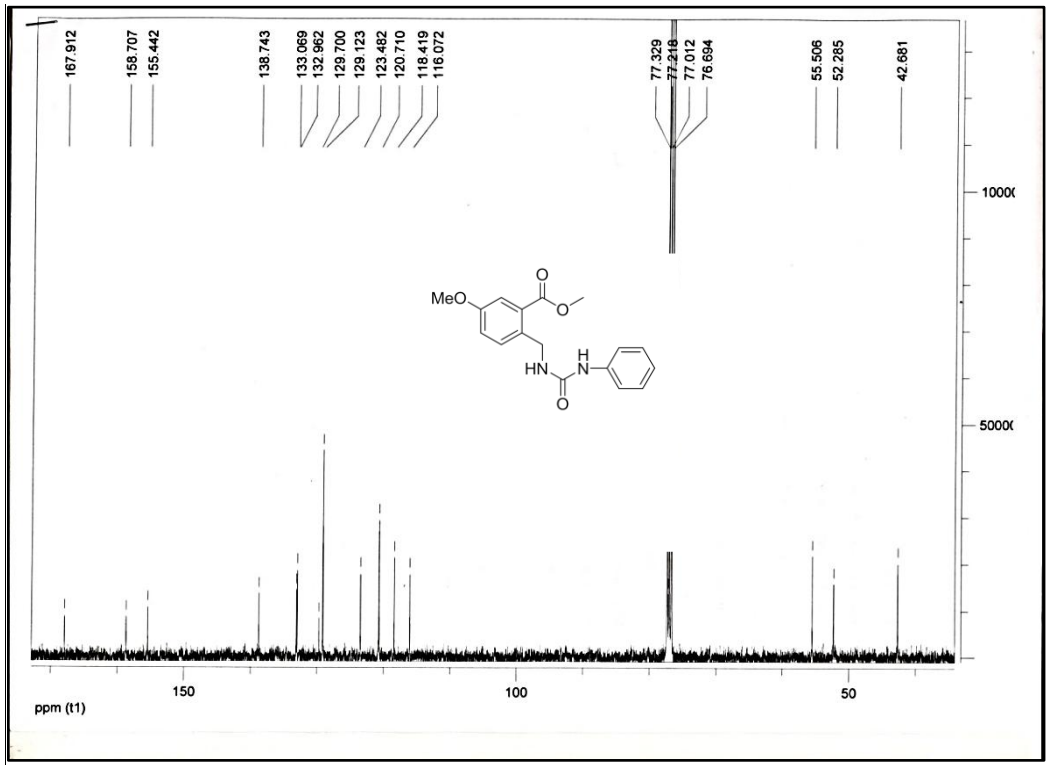

Figure 55 ^{13}C-NMR Spectrum of Compound **166c**

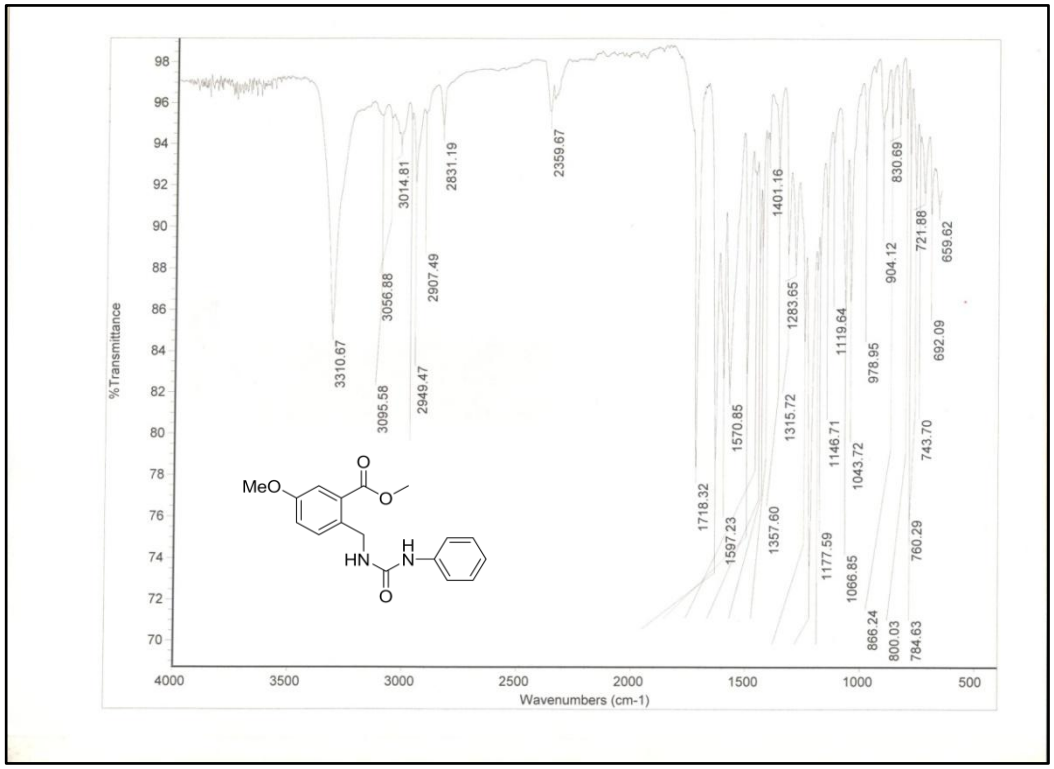

Figure 56 IR Spectrum of Compound **166c**

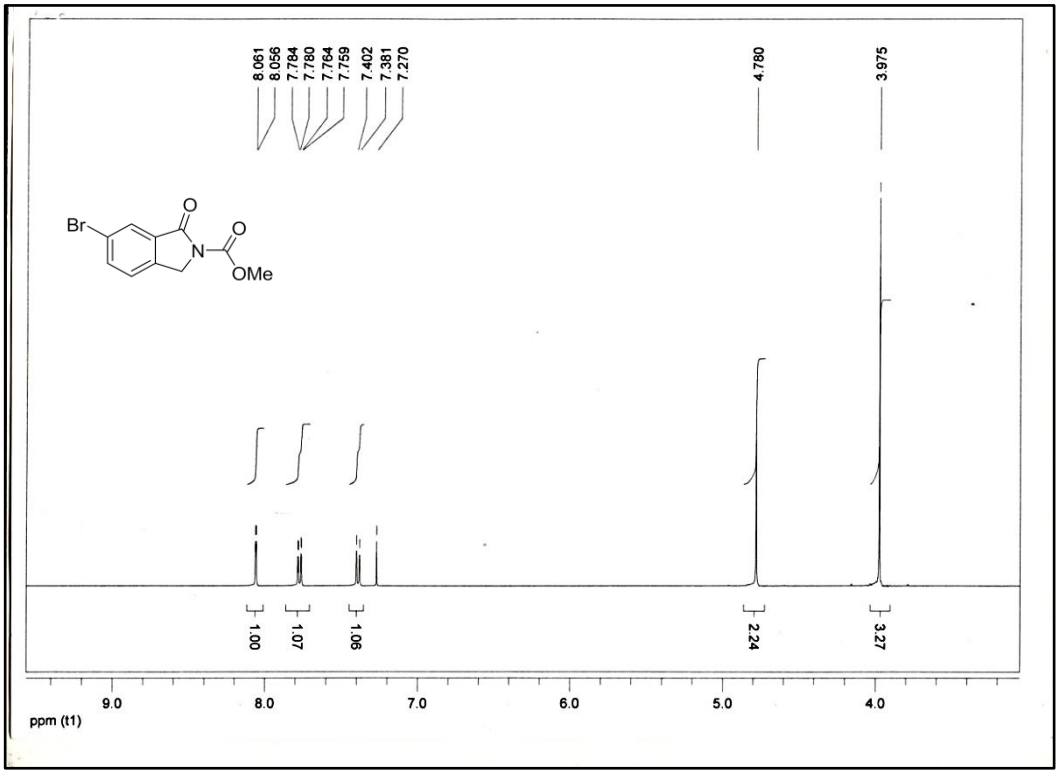

Figure 57 ^{1}H-NMR Spectrum of Compound **167b**

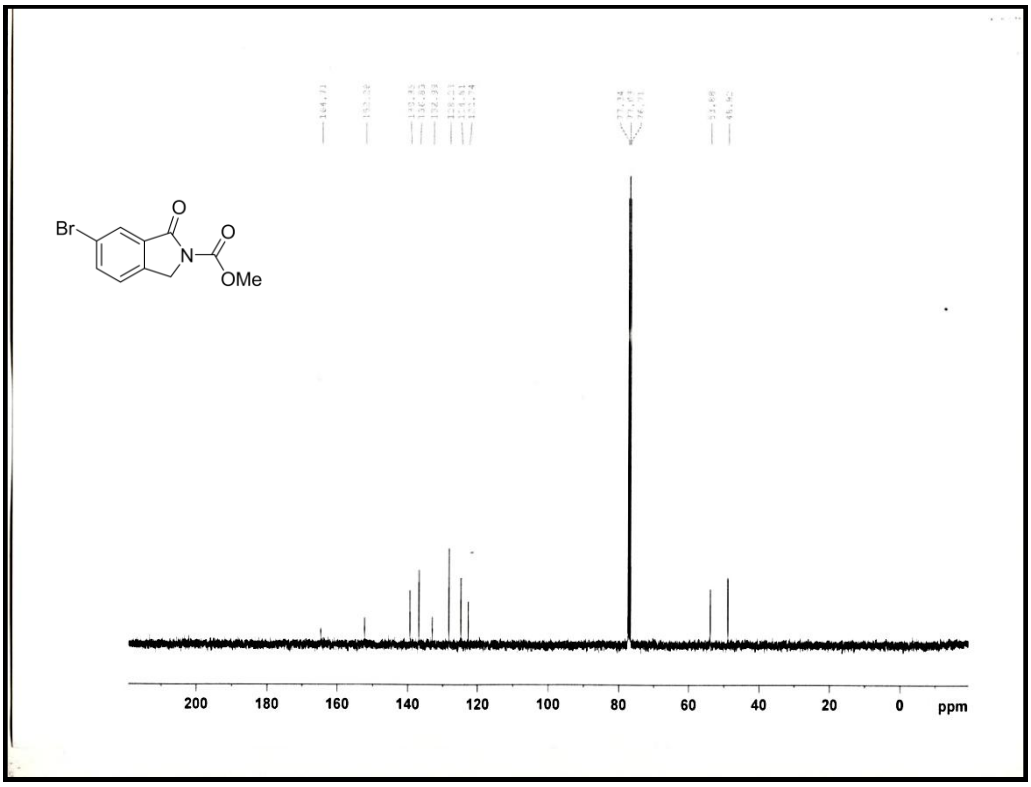

Figure 58 ^{13}C-NMR Spectrum of Compound **167b**

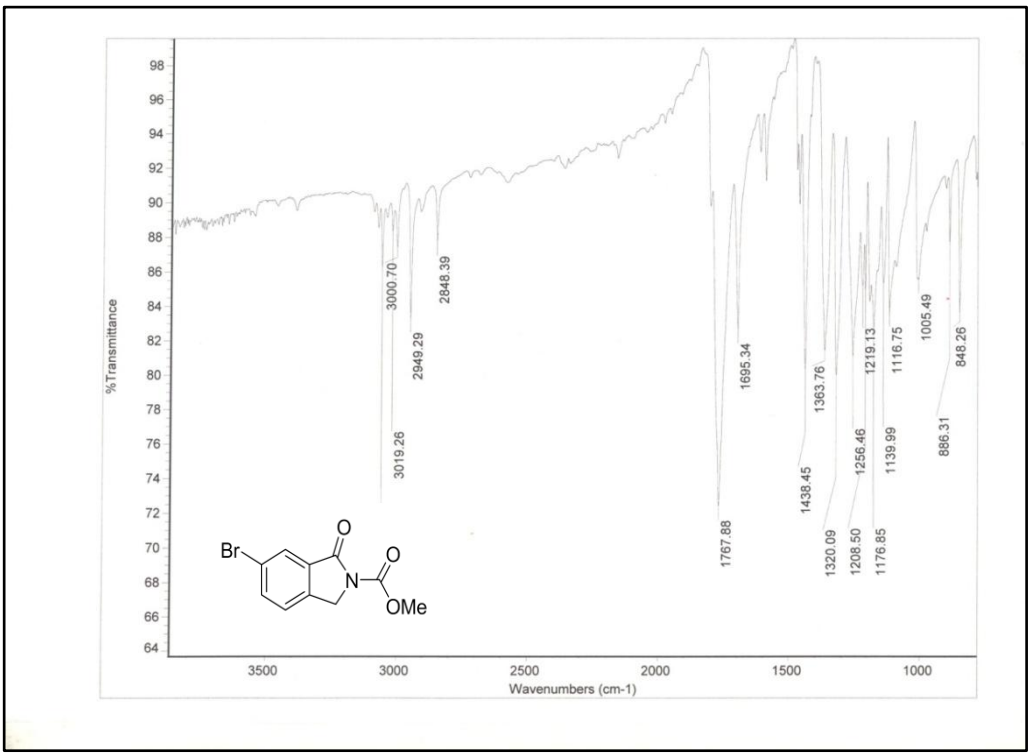

Figure 59 IR Spectrum of Compound **167b**

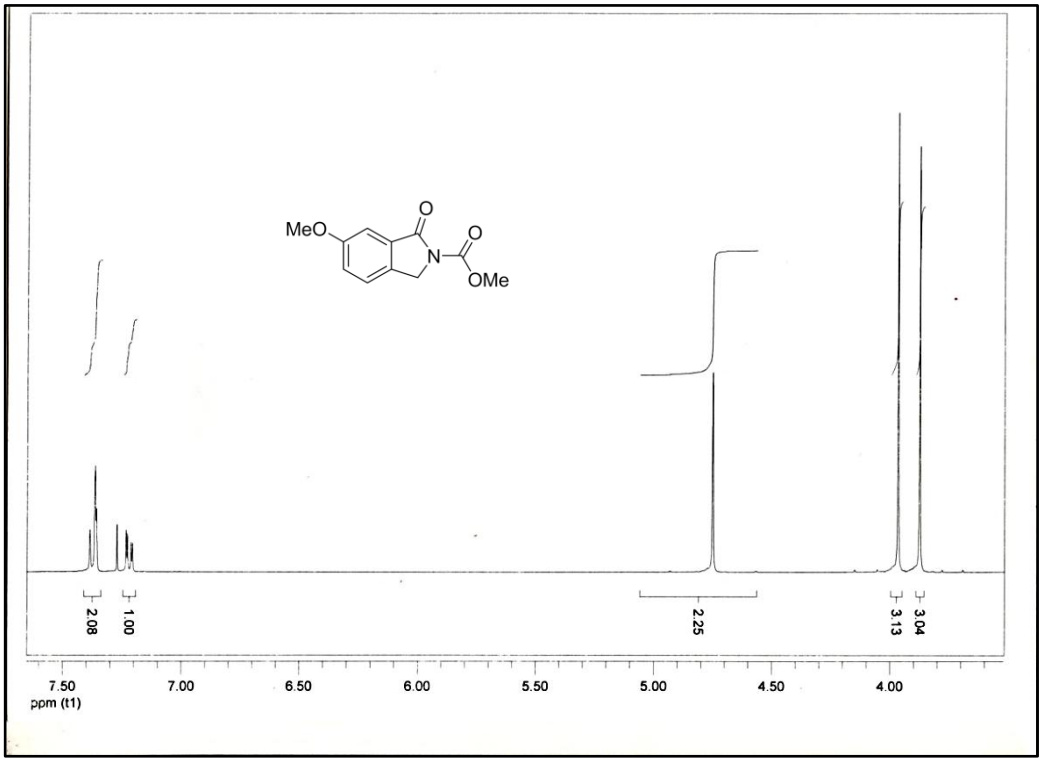

Figure 60 ^{1}H-NMR Spectrum of Compound **167c**

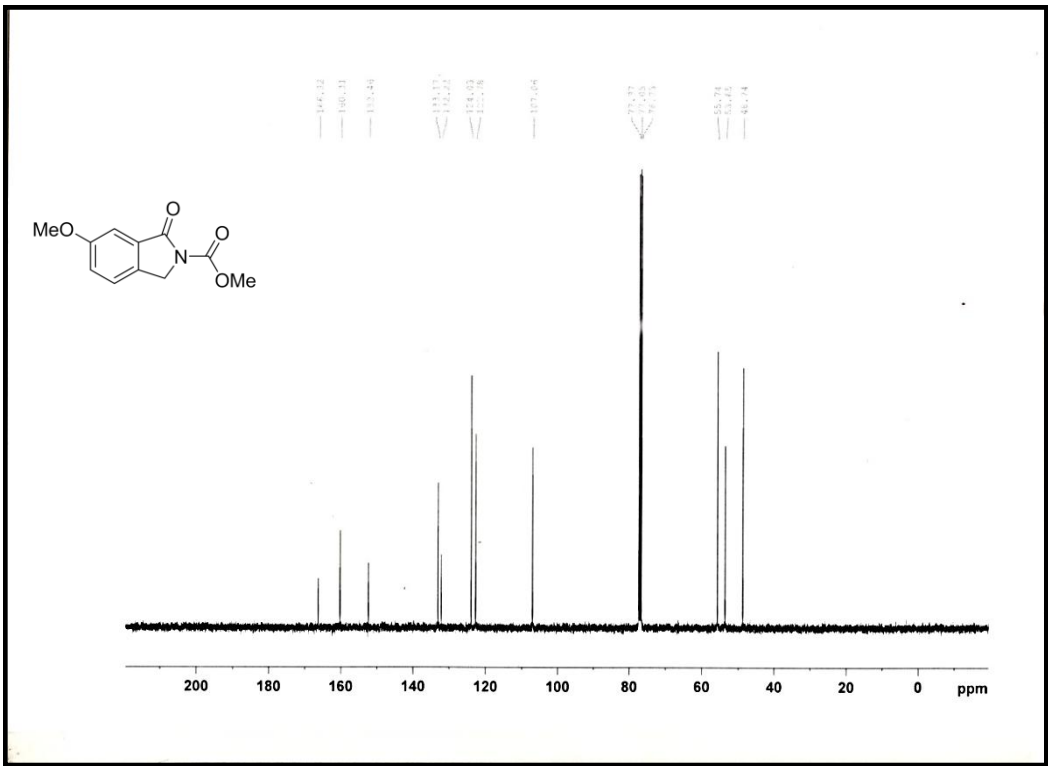

Figure 61 ^{13}C-NMR Spectrum of Compound **167c**

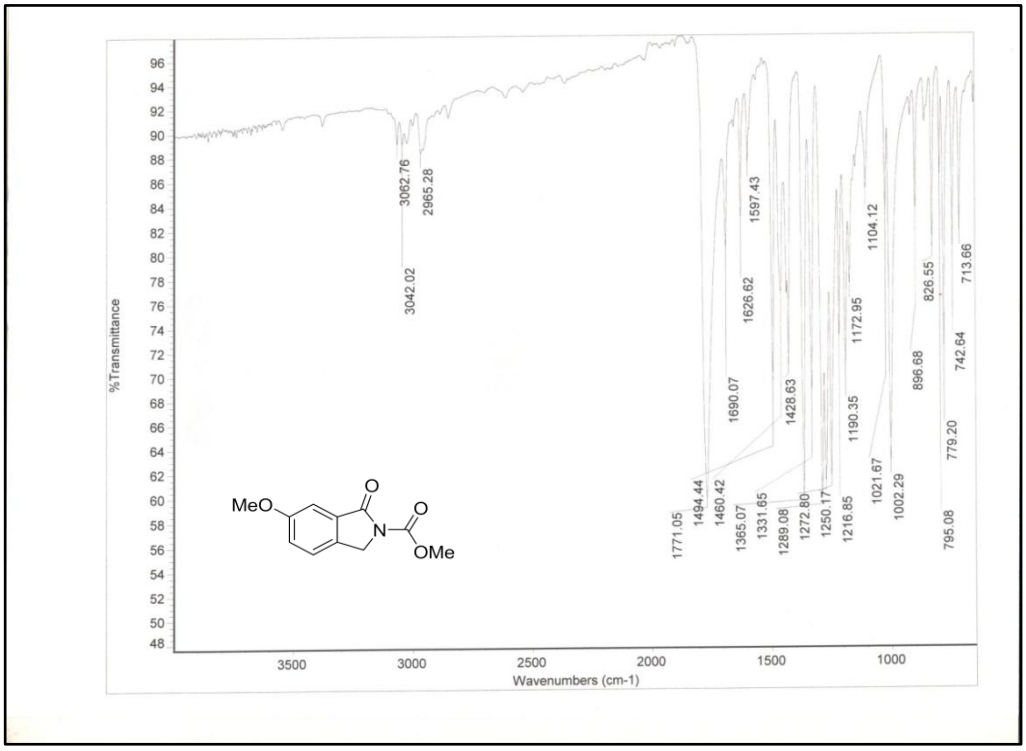

Figure 62 IR Spectrum of Compound **167c**

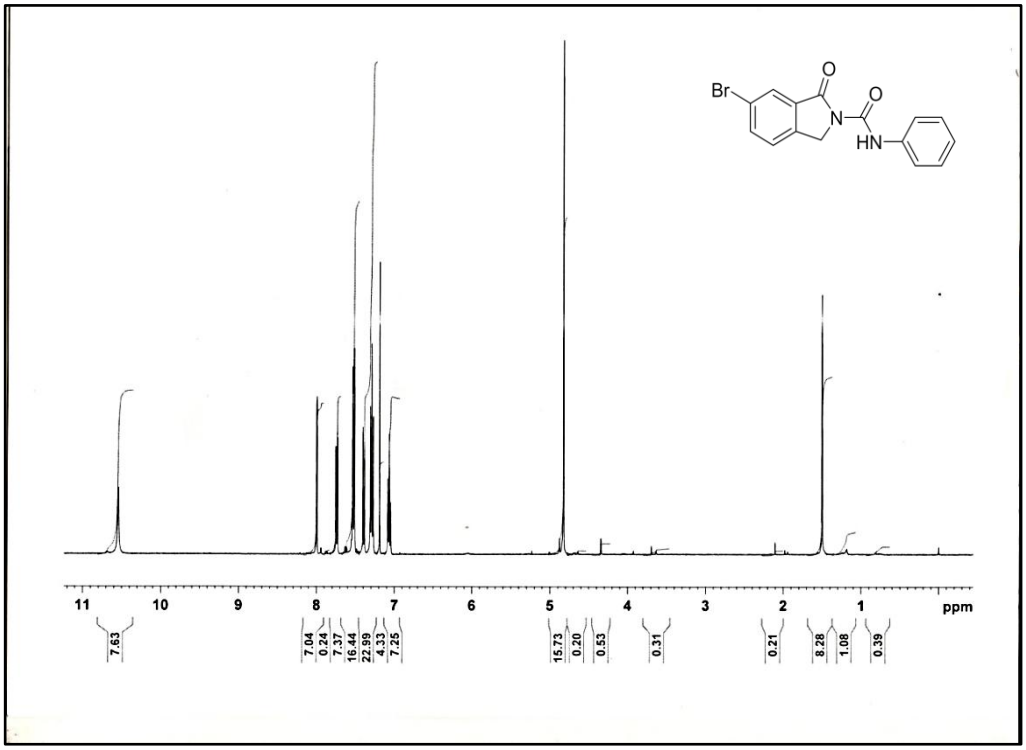

Figure 63 ^{1}H-NMR Spectrum of Compound **168b**

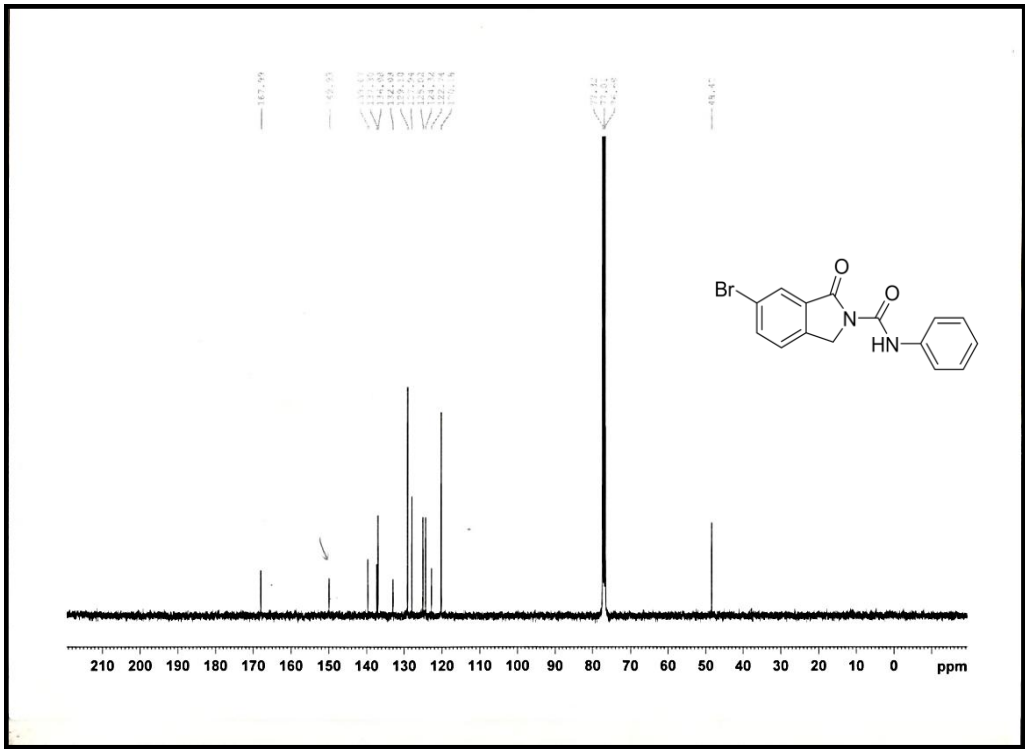

Figure 64 ^{13}C-NMR Spectrum of Compound **168b**

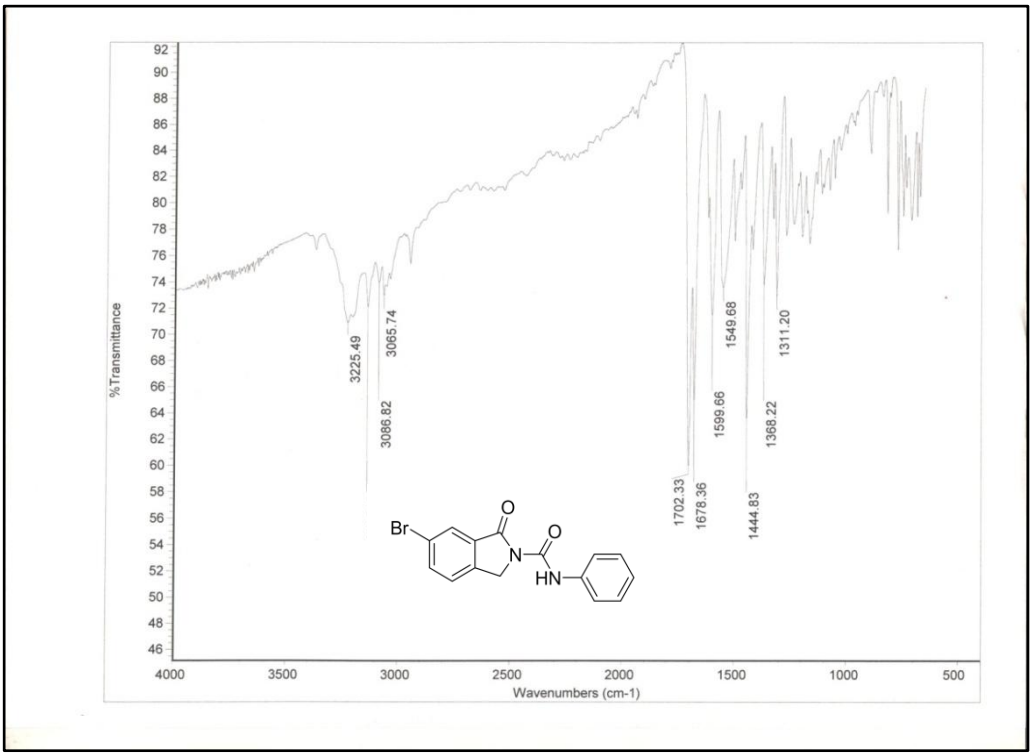

Figure 65 IR Spectrum of Compound **168b**

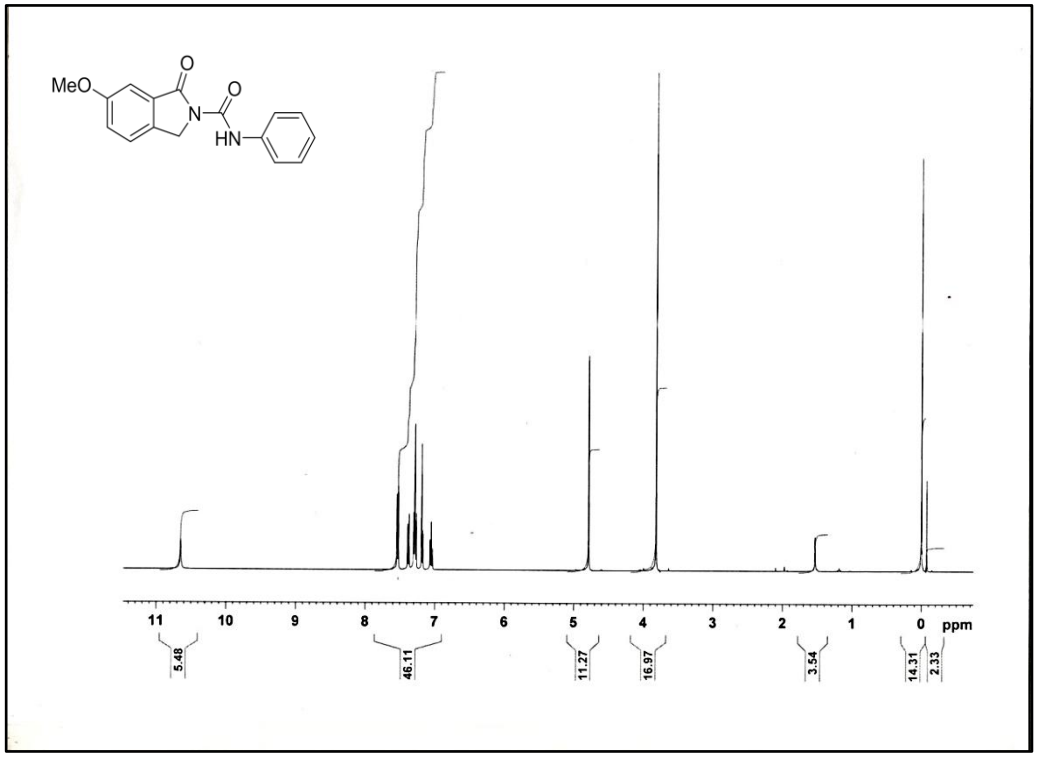

Figure 66 ^{1}H-NMR Spectrum of Compound **168c**

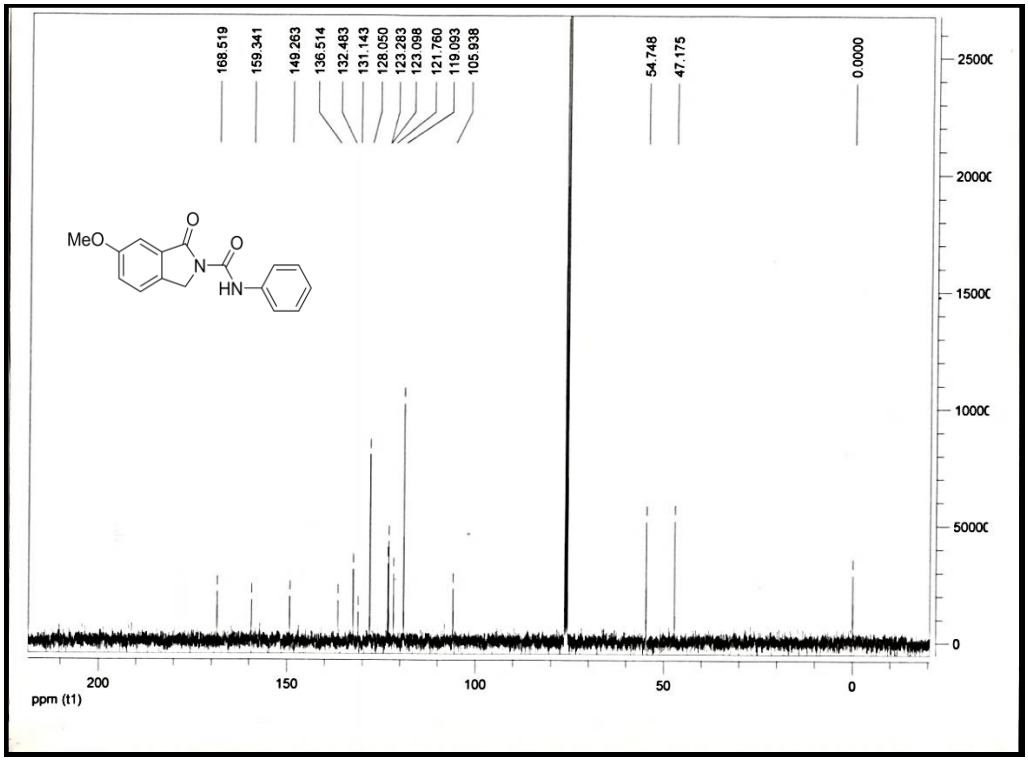

Figure 67 ^{13}C-NMR Spectrum of Compound **168c**

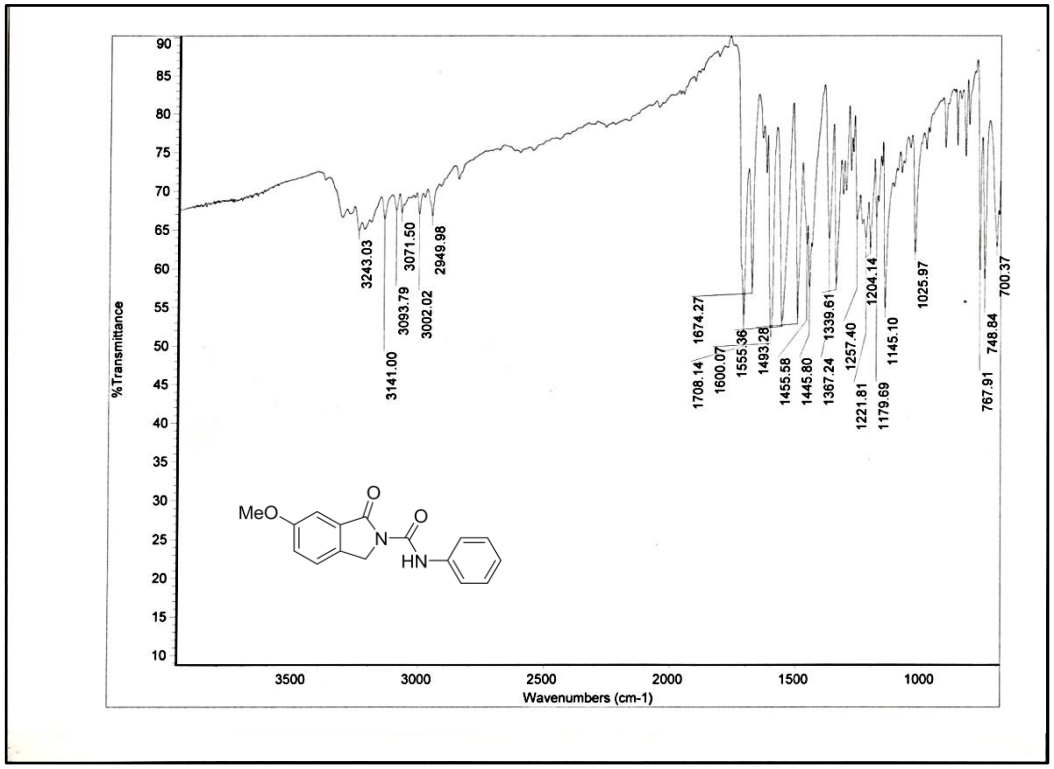

Figure 68 IR Spectrum of Compound **168c**

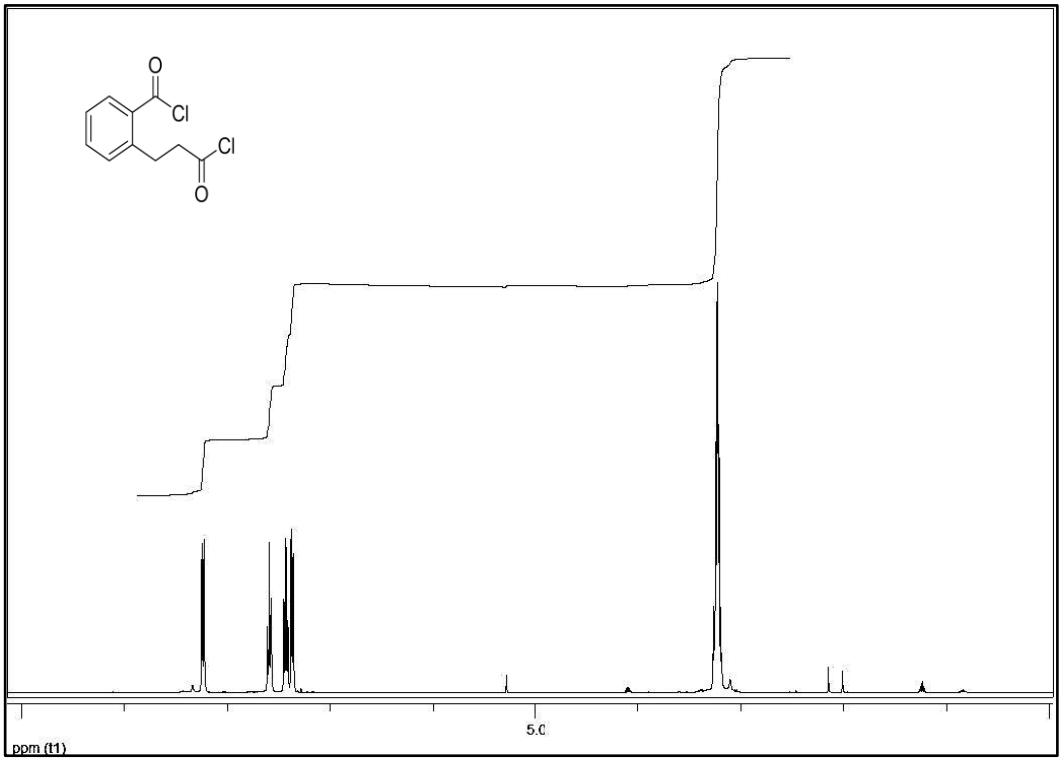

Figure 69 ^{1}H-NMR Spectrum of Compound **173**

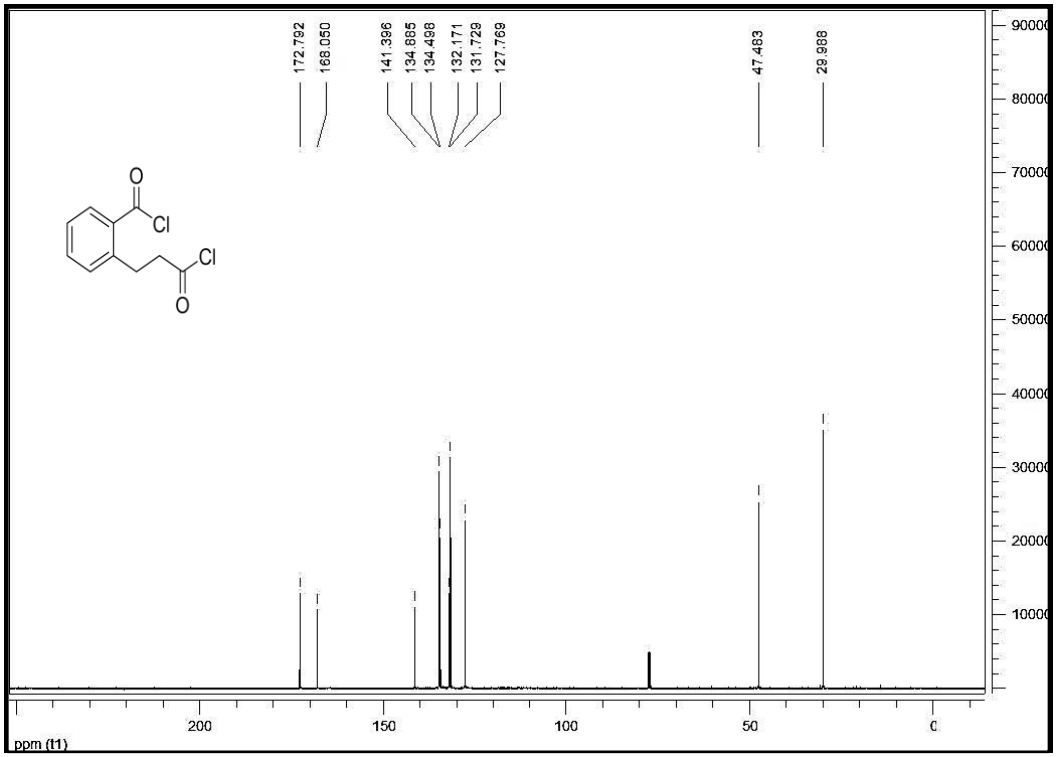

Figure 70 ^{13}C-NMR Spectrum of Compound **173**

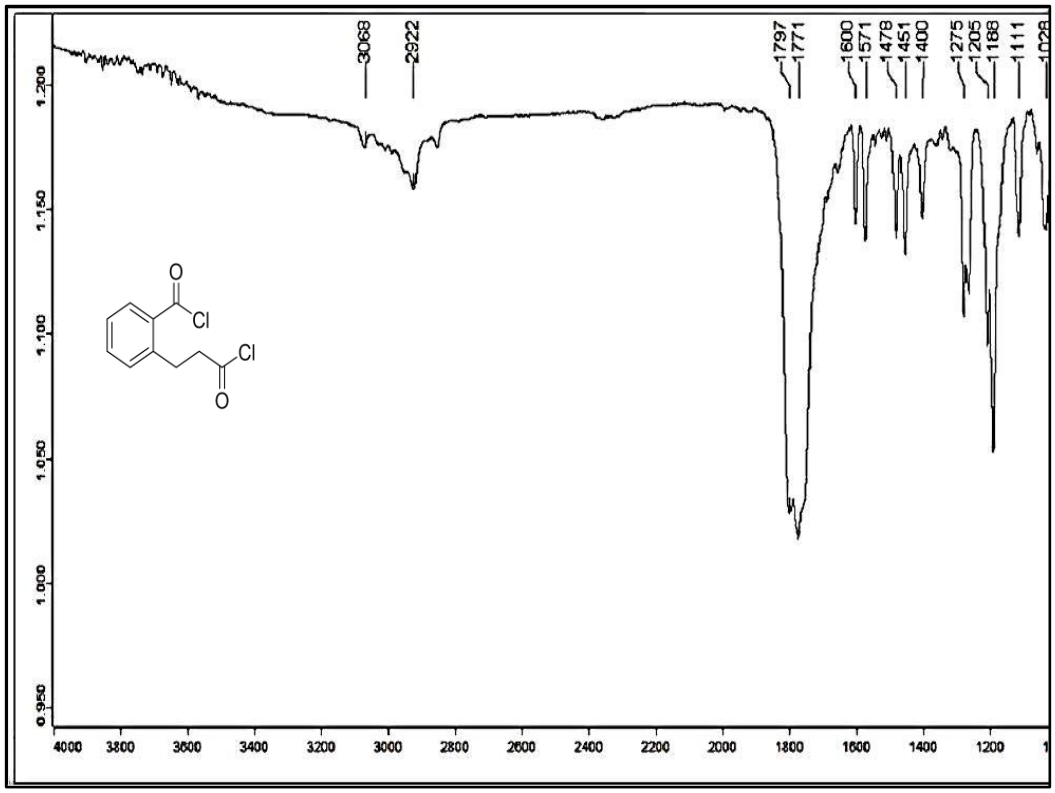

Figure 71 IR Spectrum of Compound **173**

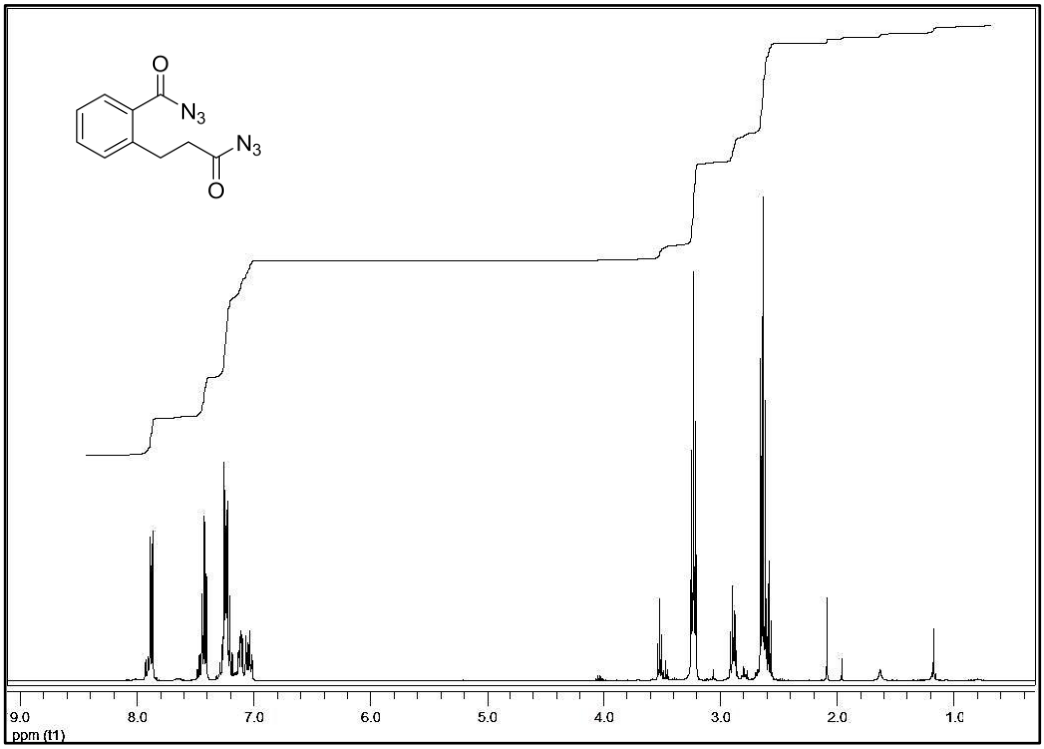

Figure 72 ^{1}H-NMR Spectrum of Compound **174**

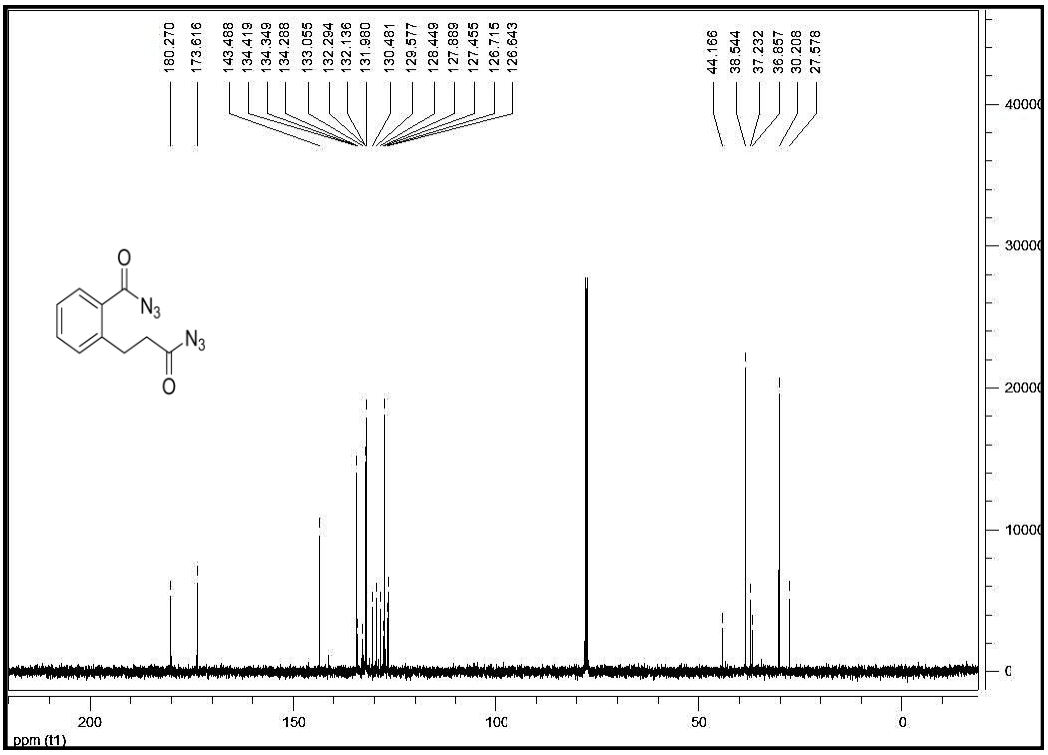

Figure 73 ^{13}C-NMR Spectrum of Compound **174**

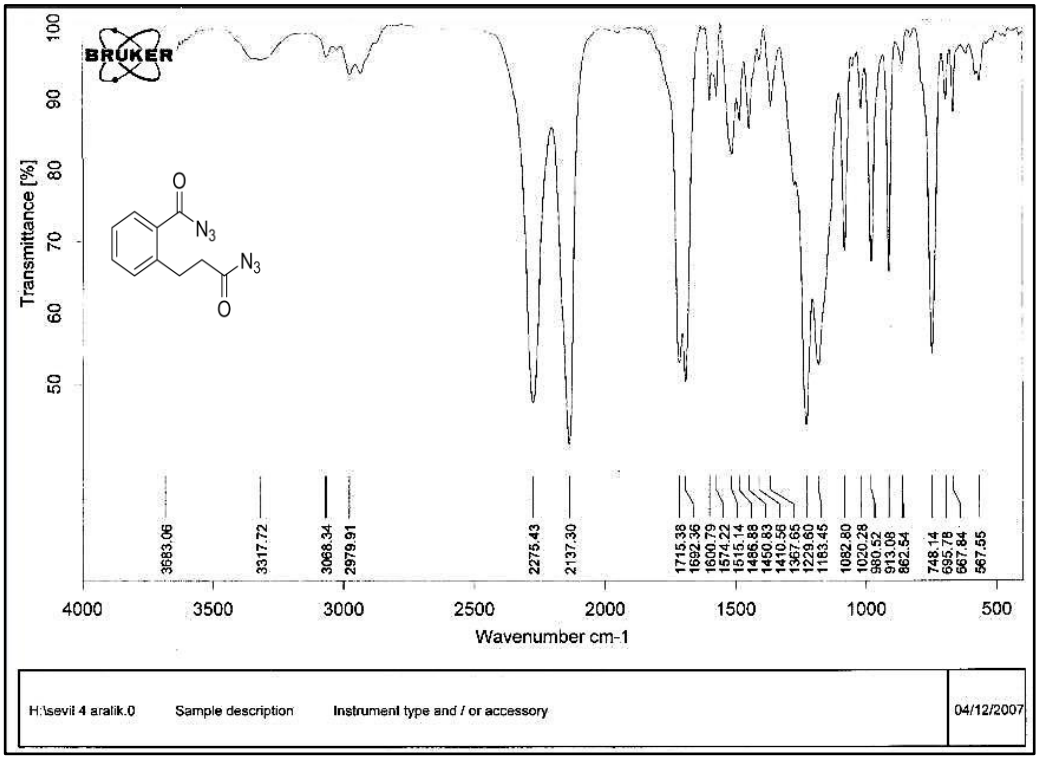

Figure 74 IR Spectrum of Compound **174**

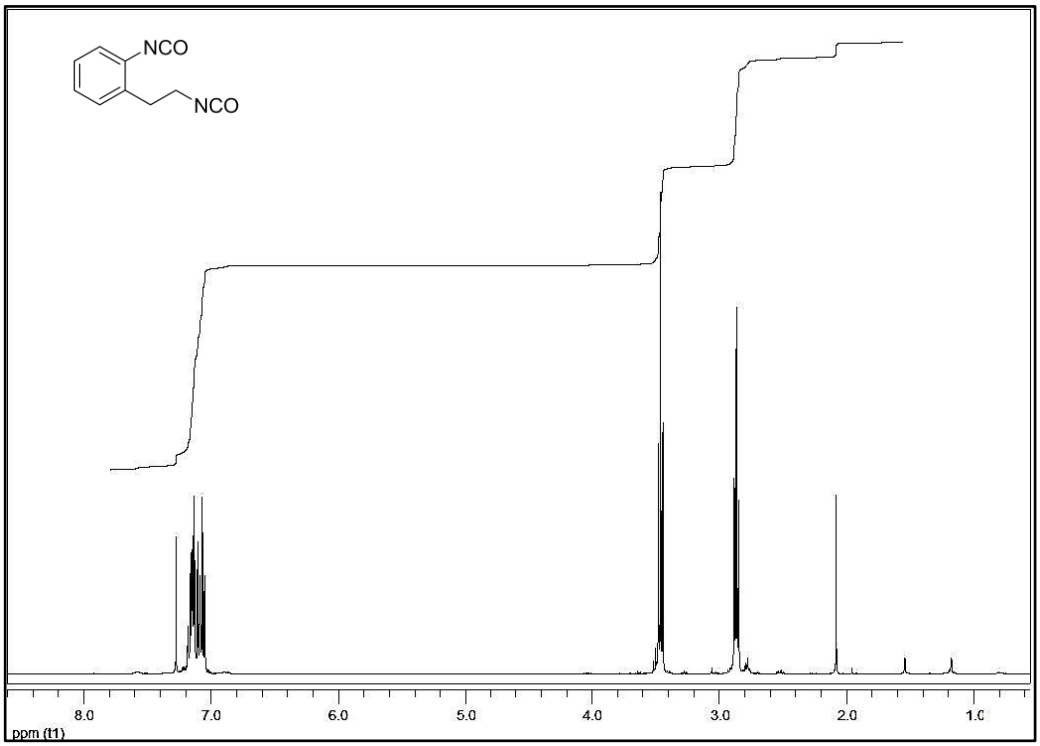

Figure 75 ^{1}H-NMR Spectrum of Compound **175**

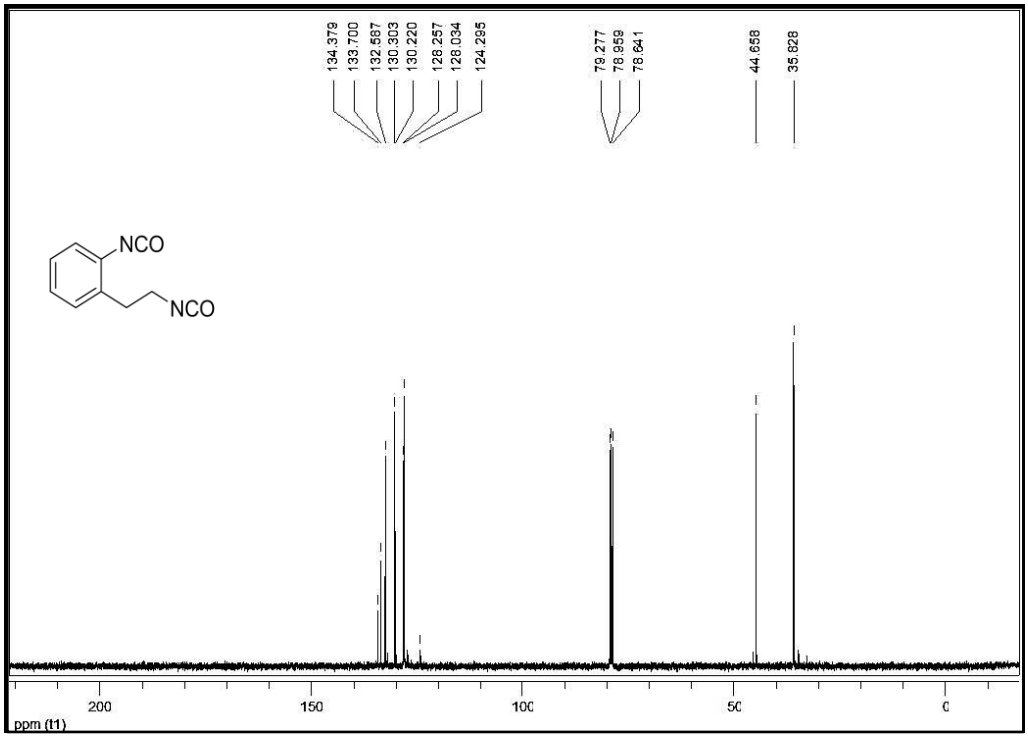

Figure 76 ^{13}C-NMR Spectrum of Compound **175**

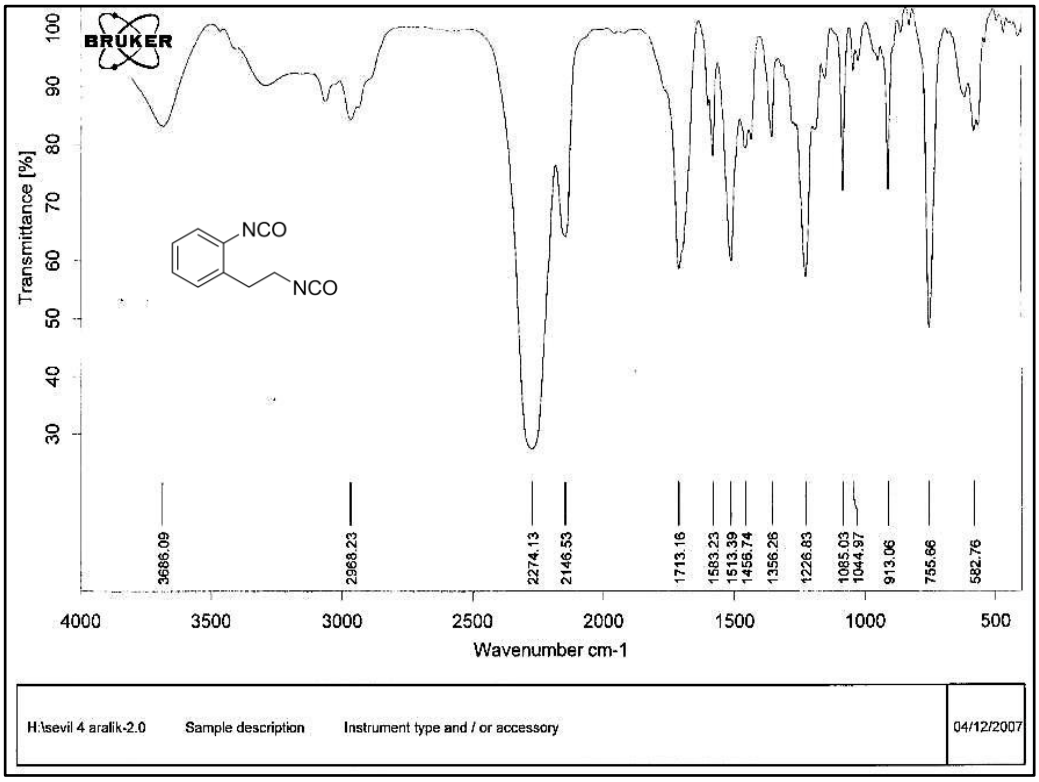

Figure 77 IR Spectrum of Compound **175**

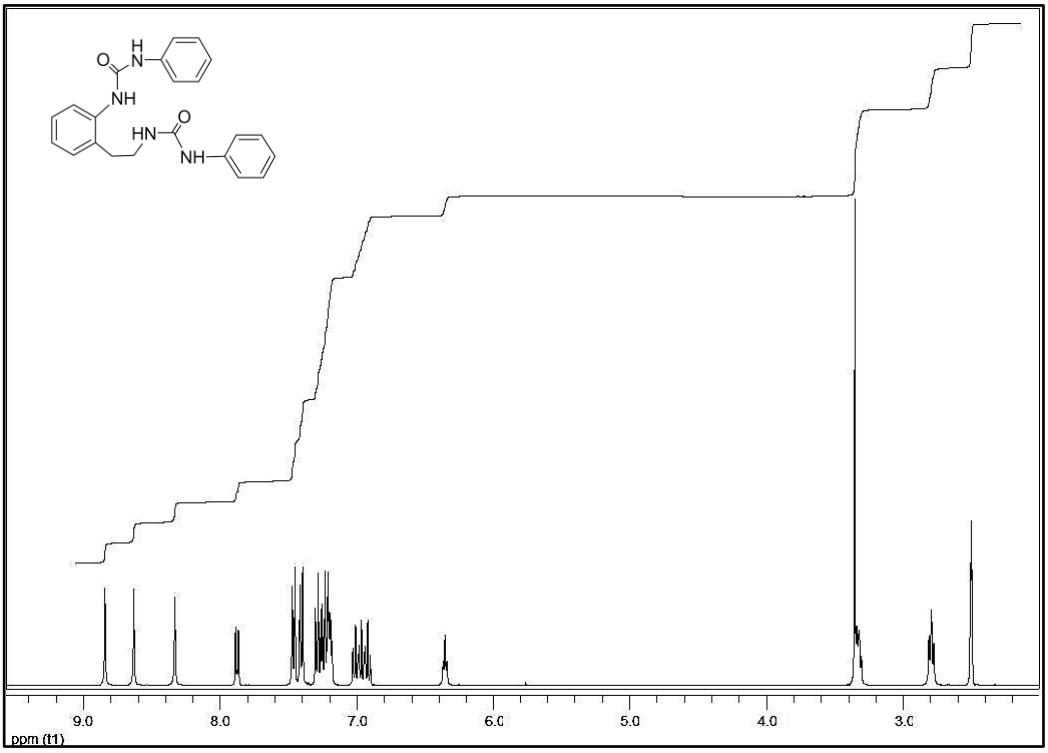

Figure 78 ^{1}H-NMR Spectrum of Compound **176**

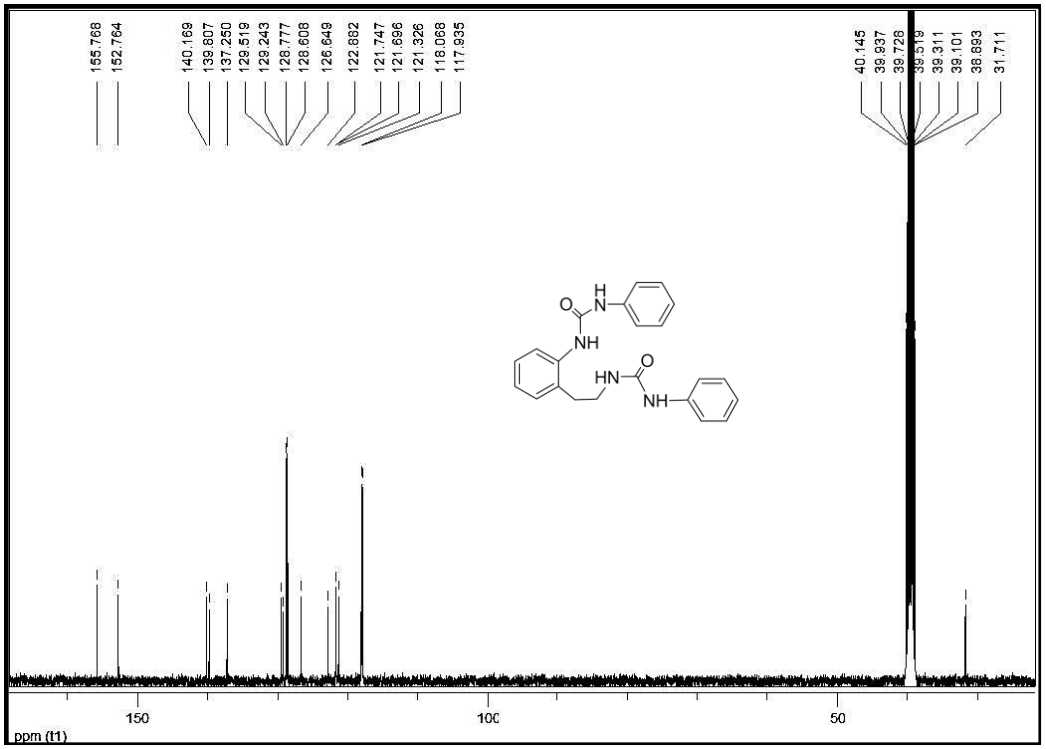

Figure 79 ^{13}C-NMR Spectrum of Compound **176**

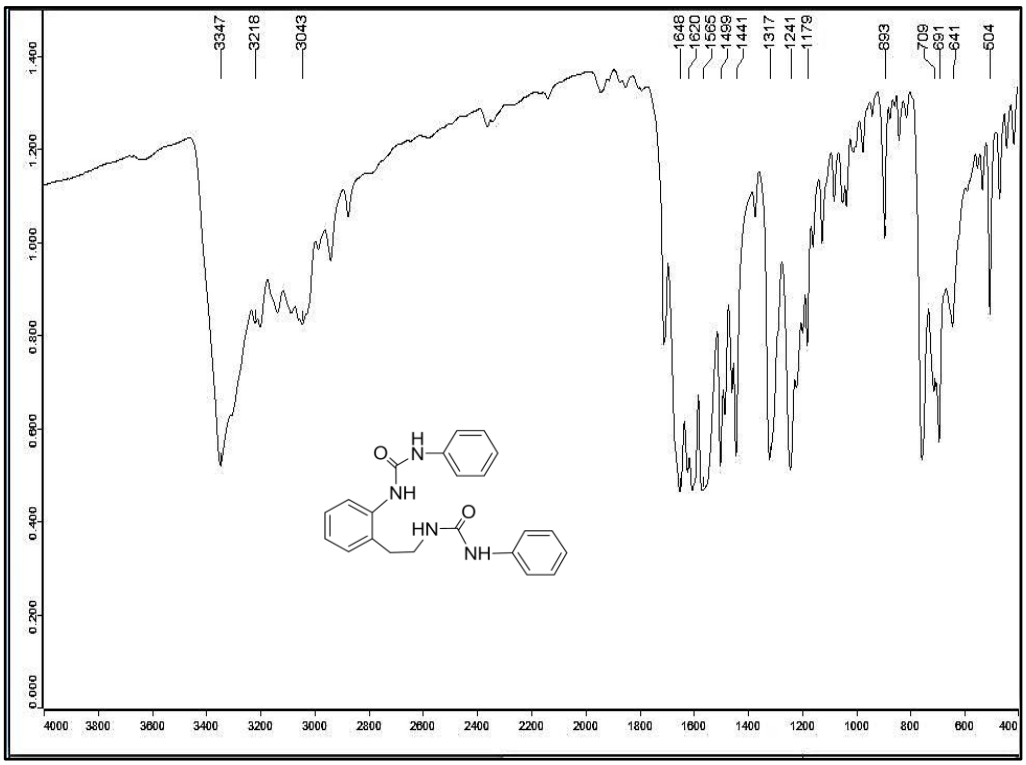

Figure 80 IR Spectrum of Compound **176**

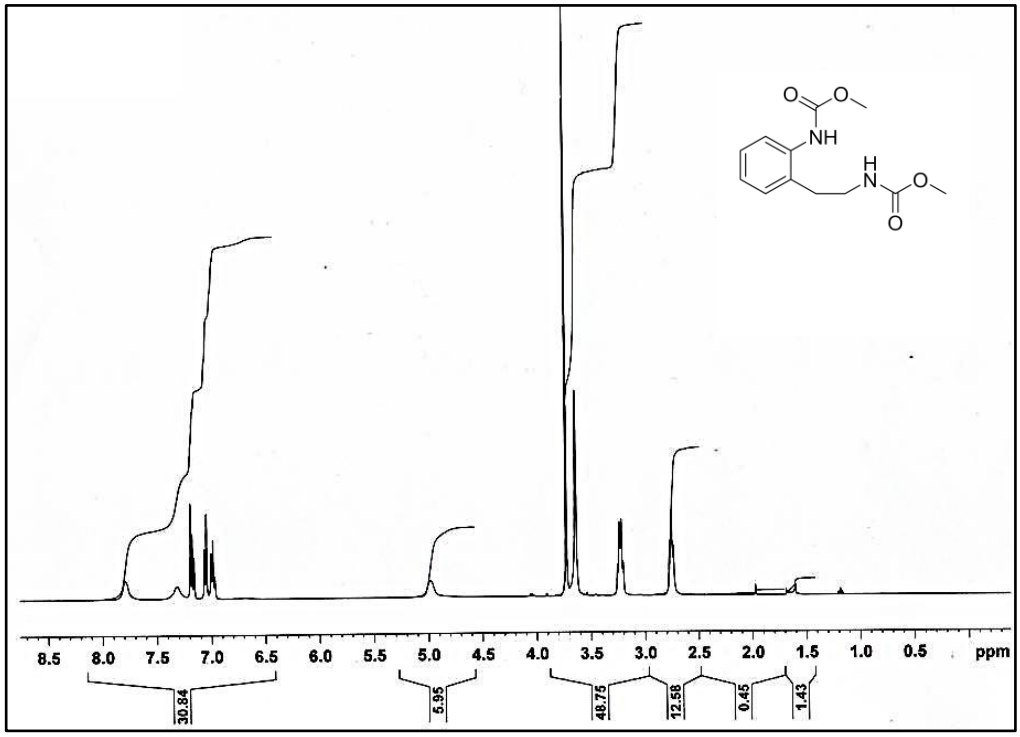

Figure 81 ^{1}H-NMR Spectrum of Compound **182**

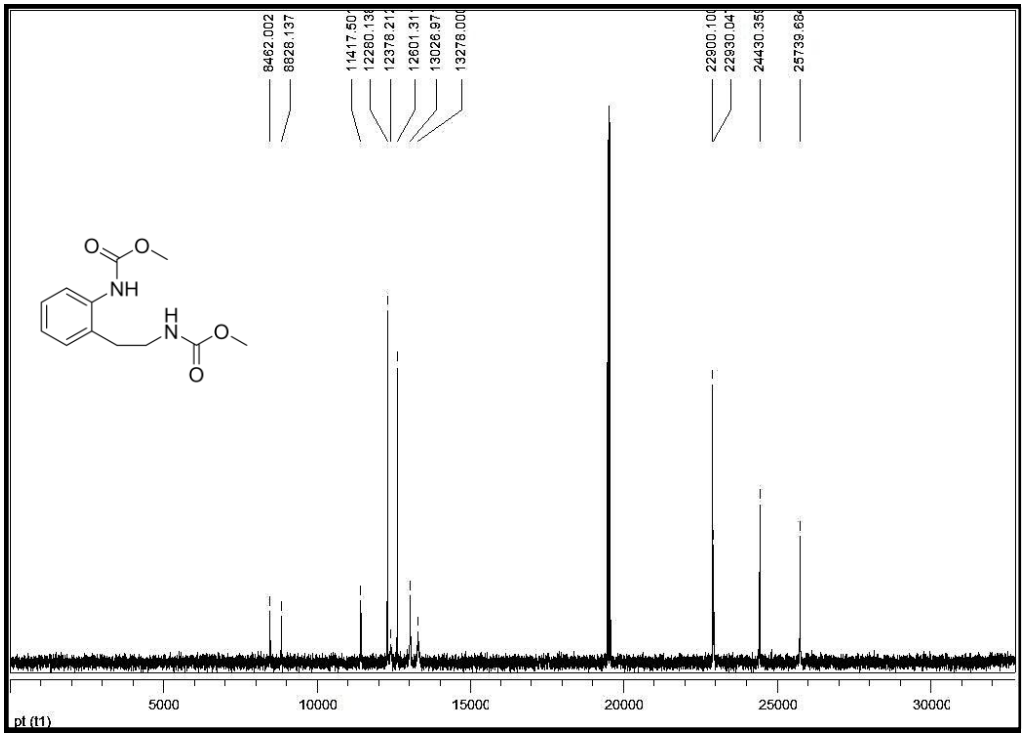

Figure 82 ^{13}C-NMR Spectrum of Compound **182**

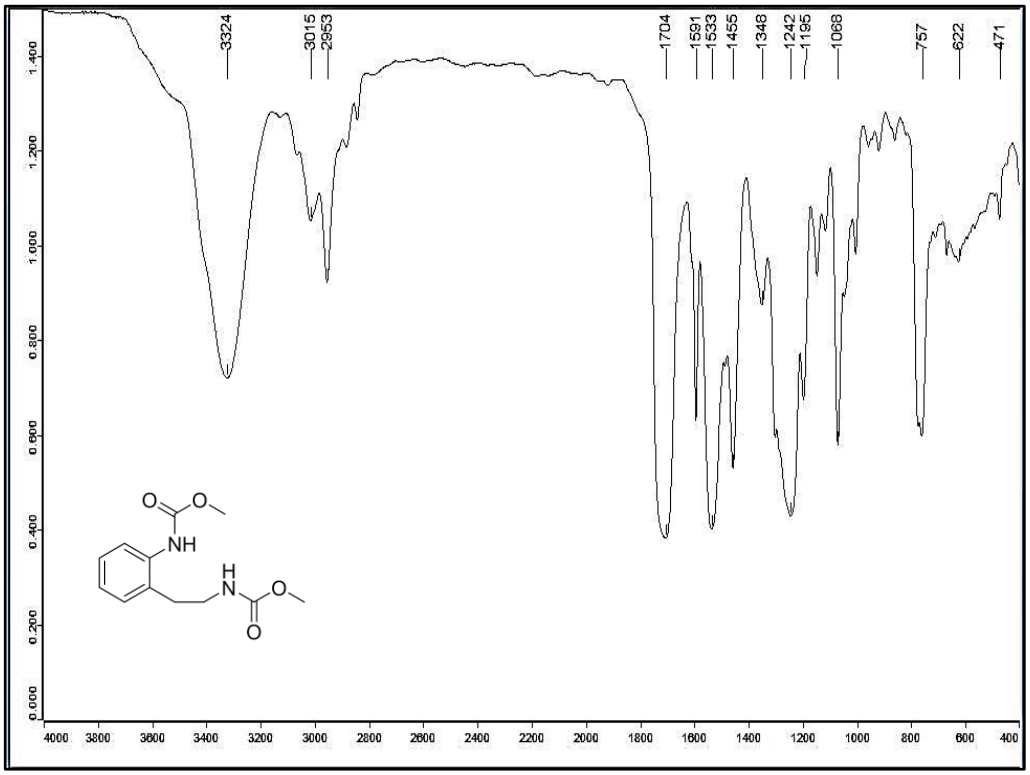

Figure 83 IR Spectrum of Compound **182**

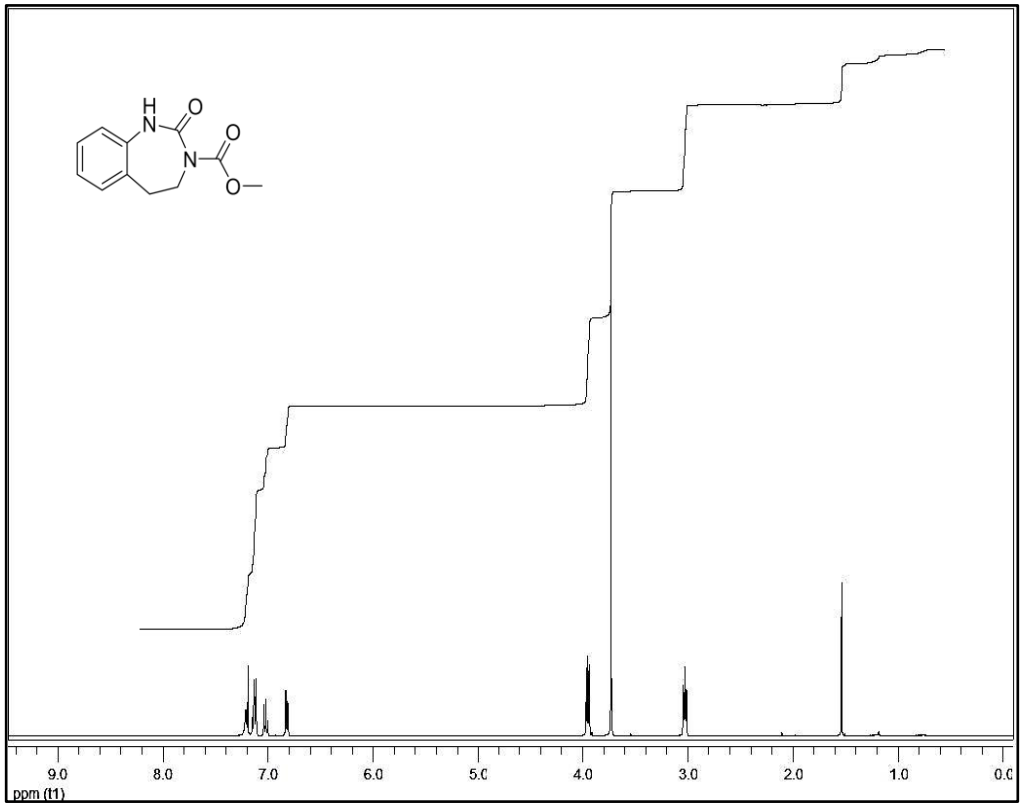

Figure 84 ^{1}H-NMR Spectrum of Compound **184**

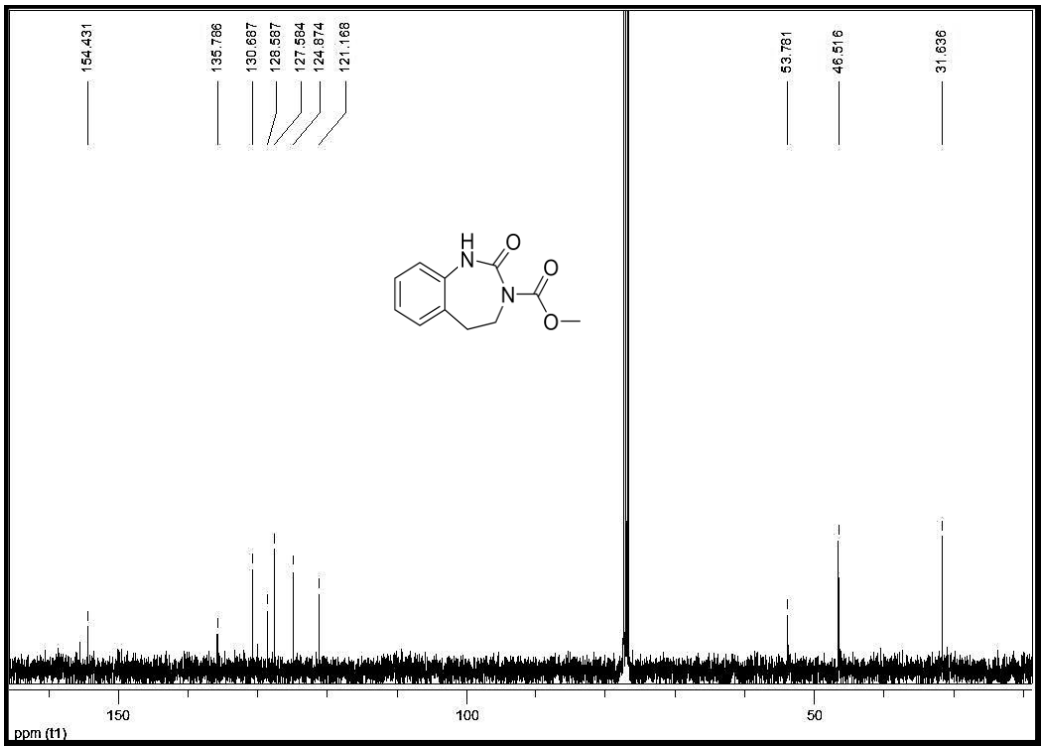

Figure 85 ^{13}C-NMR Spectrum of Compound **184**

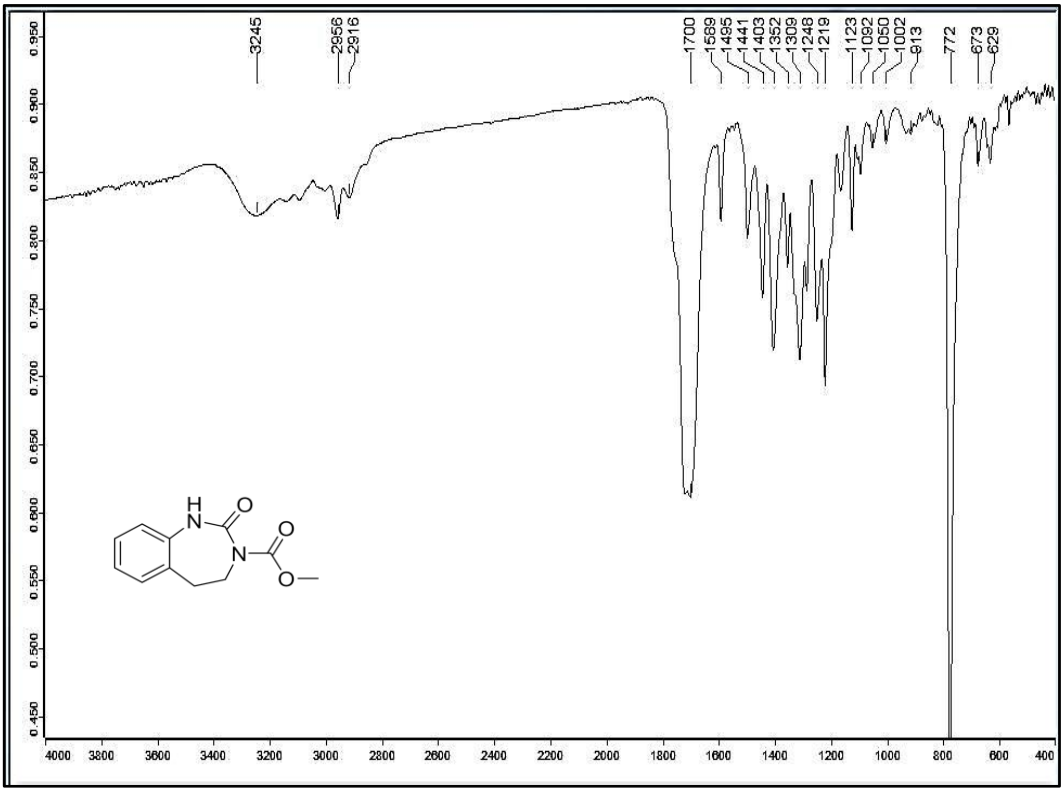

Figure 86 IR Spectrum of Compound **184**

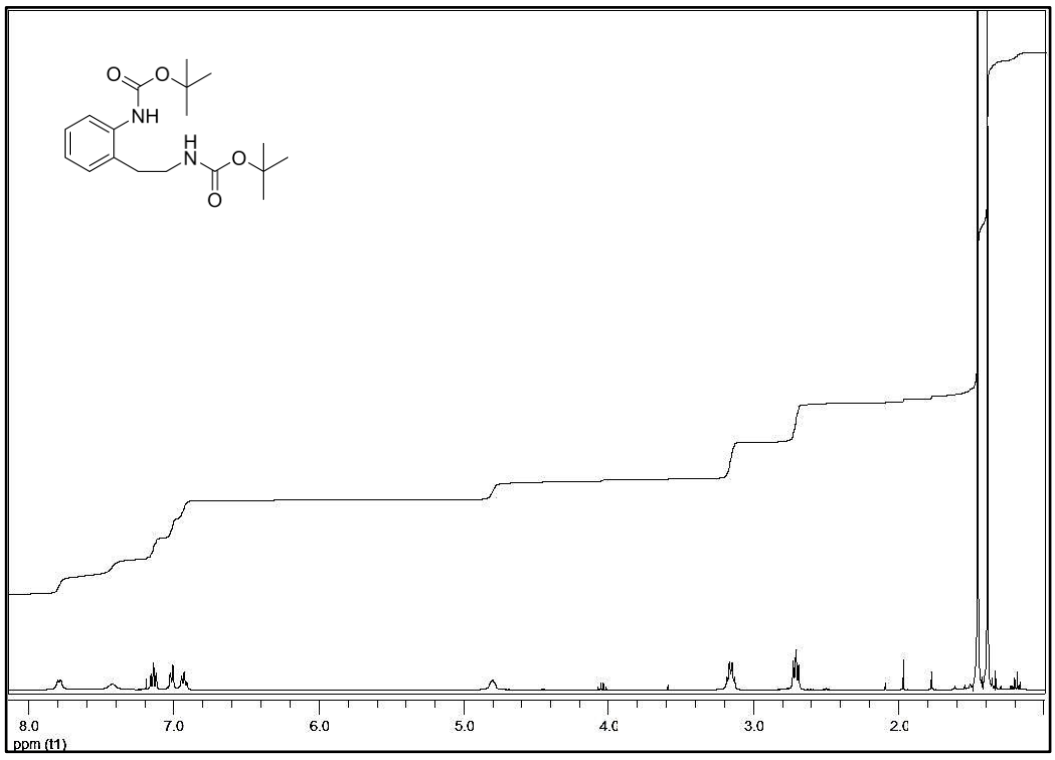

Figure 87 ^{1}H-NMR Spectrum of Compound **185**

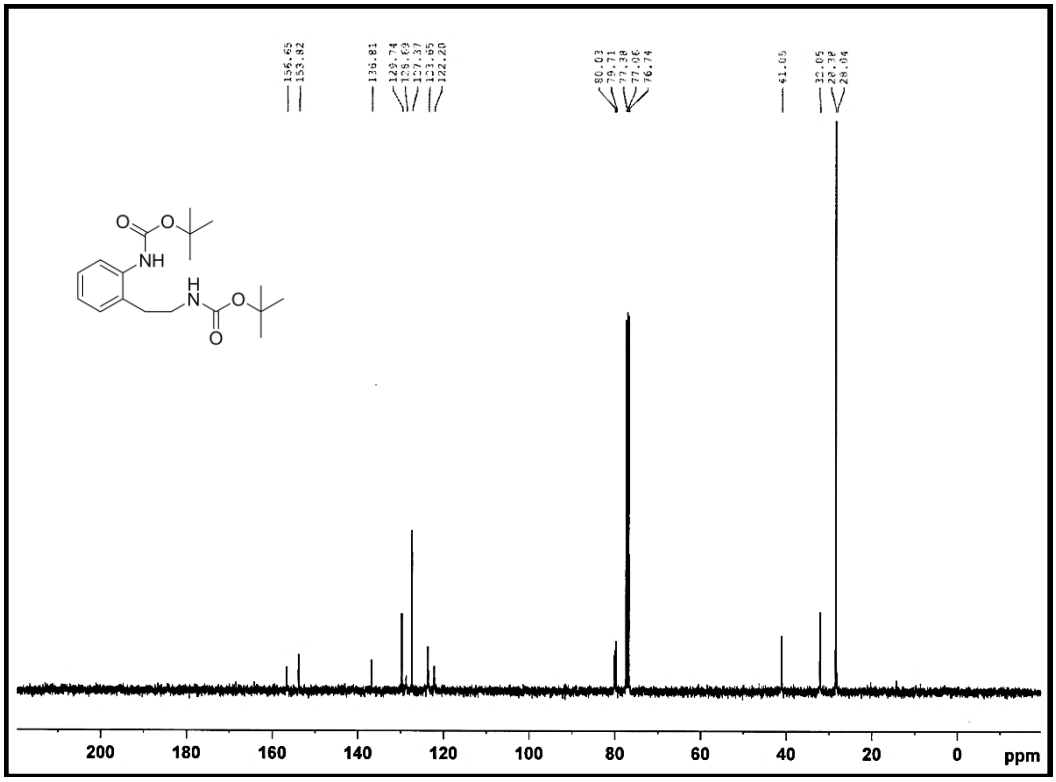

Figure 88 ^{13}C-NMR Spectrum of Compound **185**

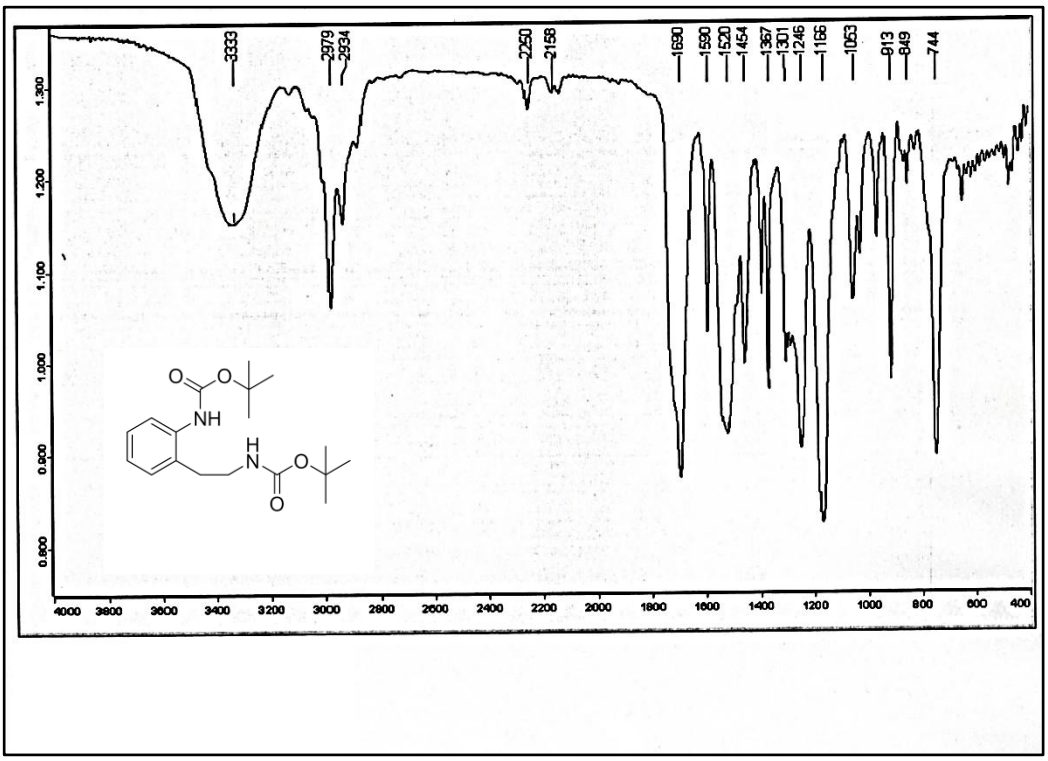

Figure 89 IR Spectrum of Compound **185**

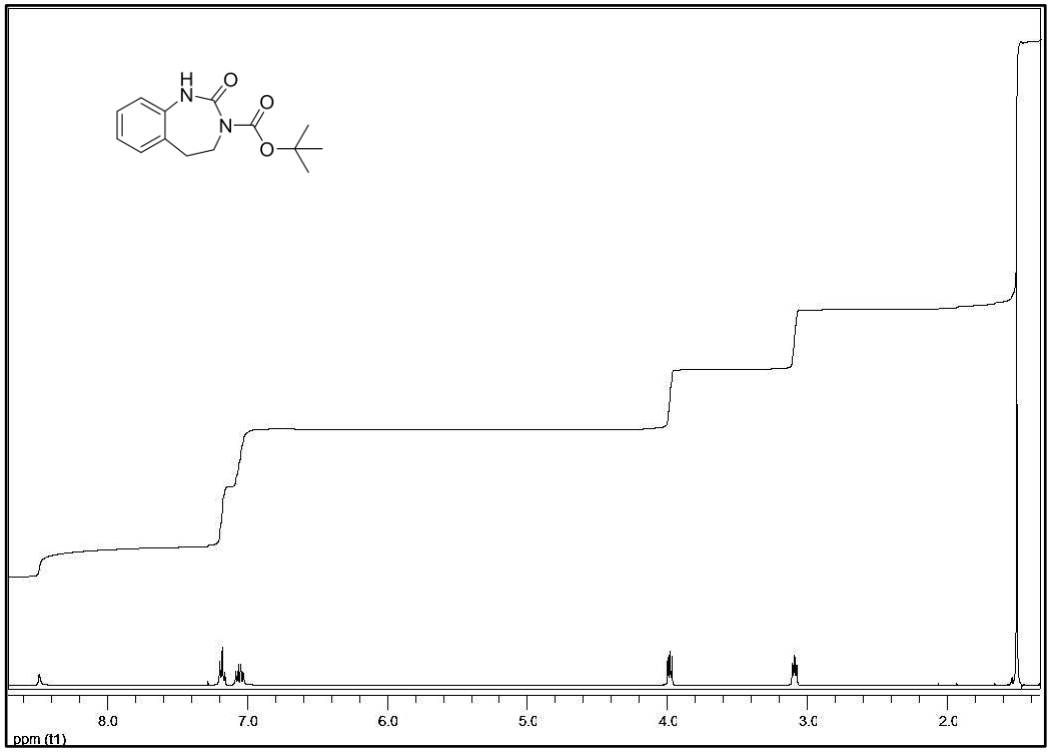

Figure 90 ^{1}H-NMR Spectrum of Compound **186**

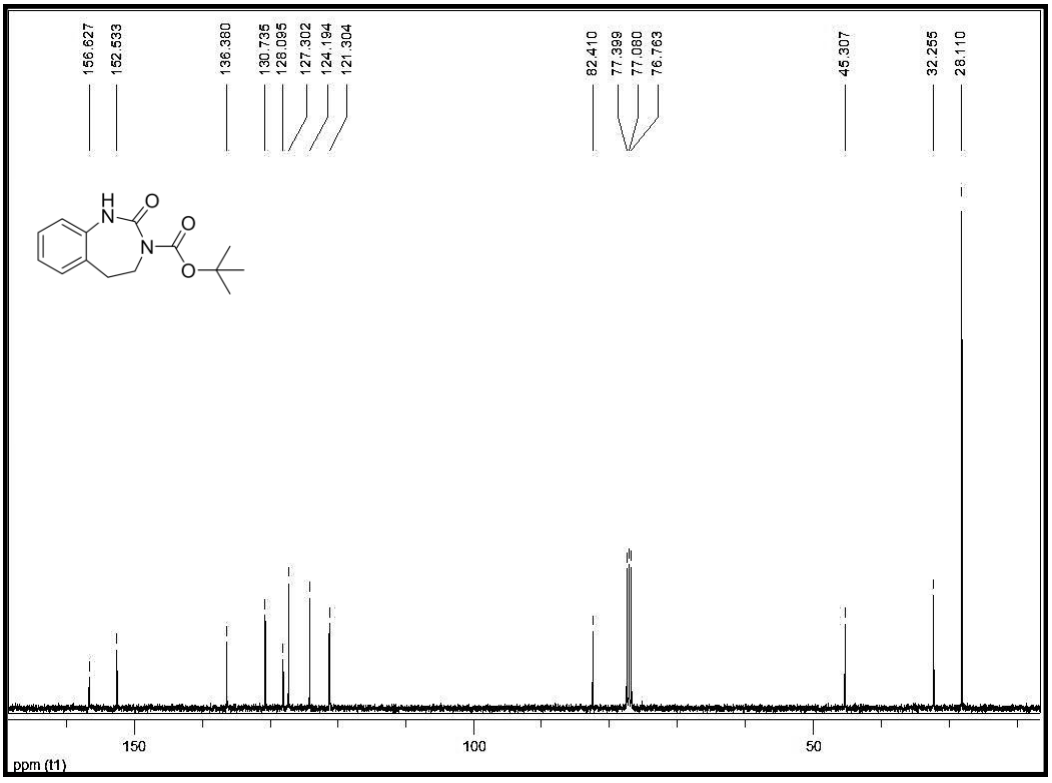

Figure 91 ^{13}C-NMR Spectrum of Compound **186**

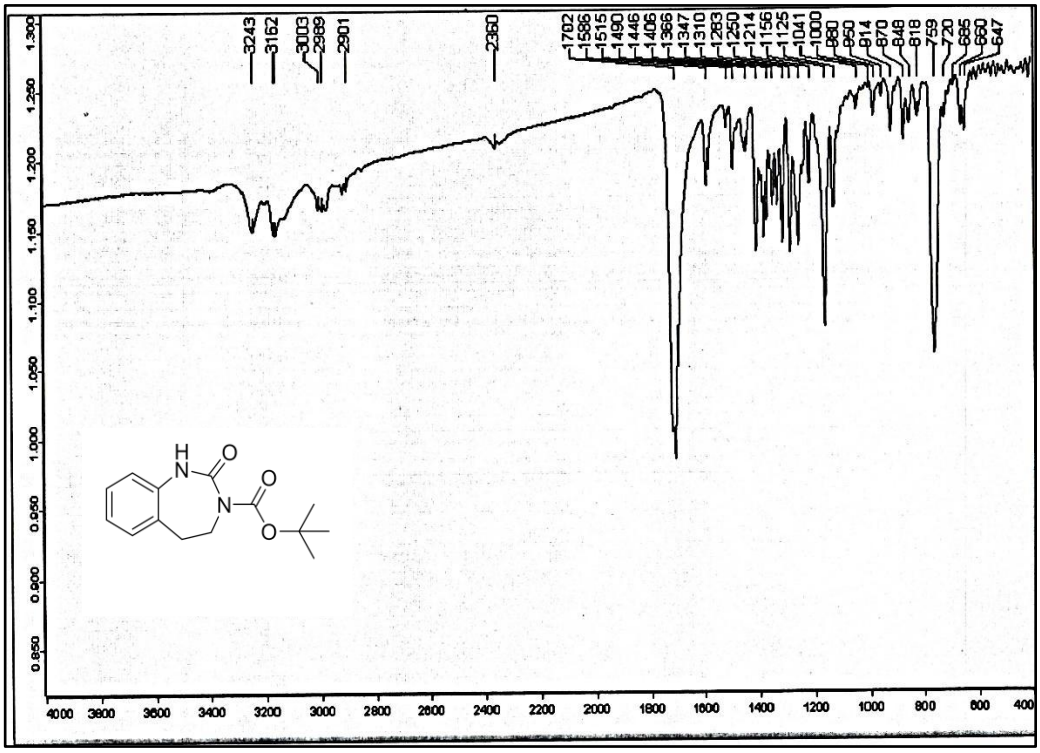

Figure 92 IR Spectrum of Compound **186**

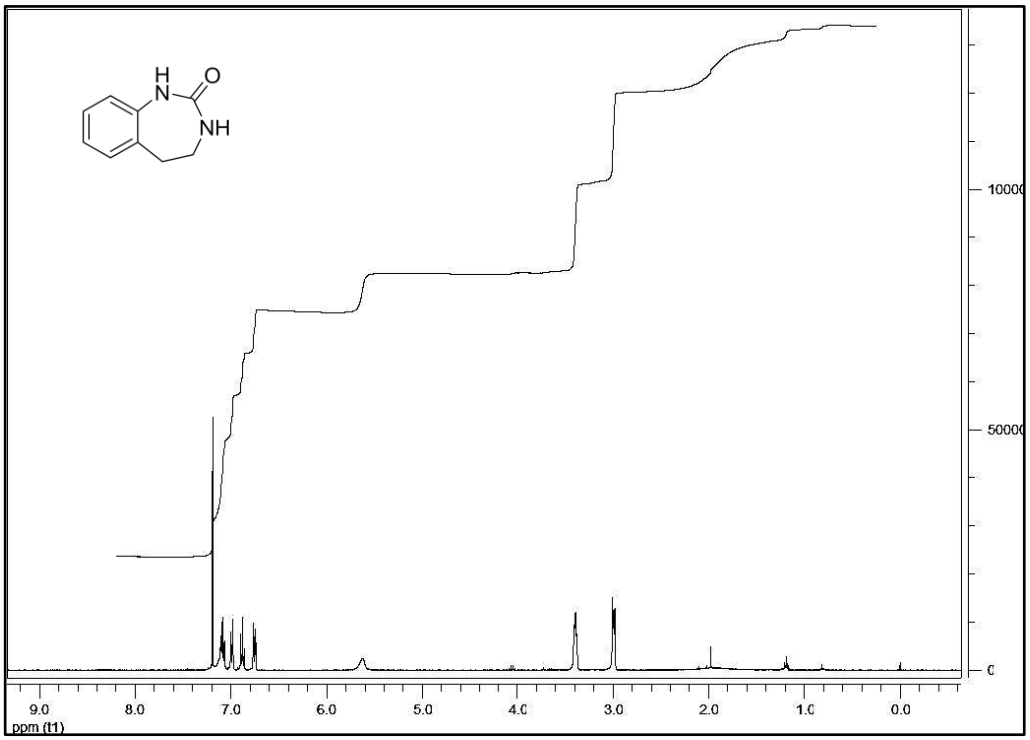

Figure 93 ^{1}H-NMR Spectrum of Compound **180**

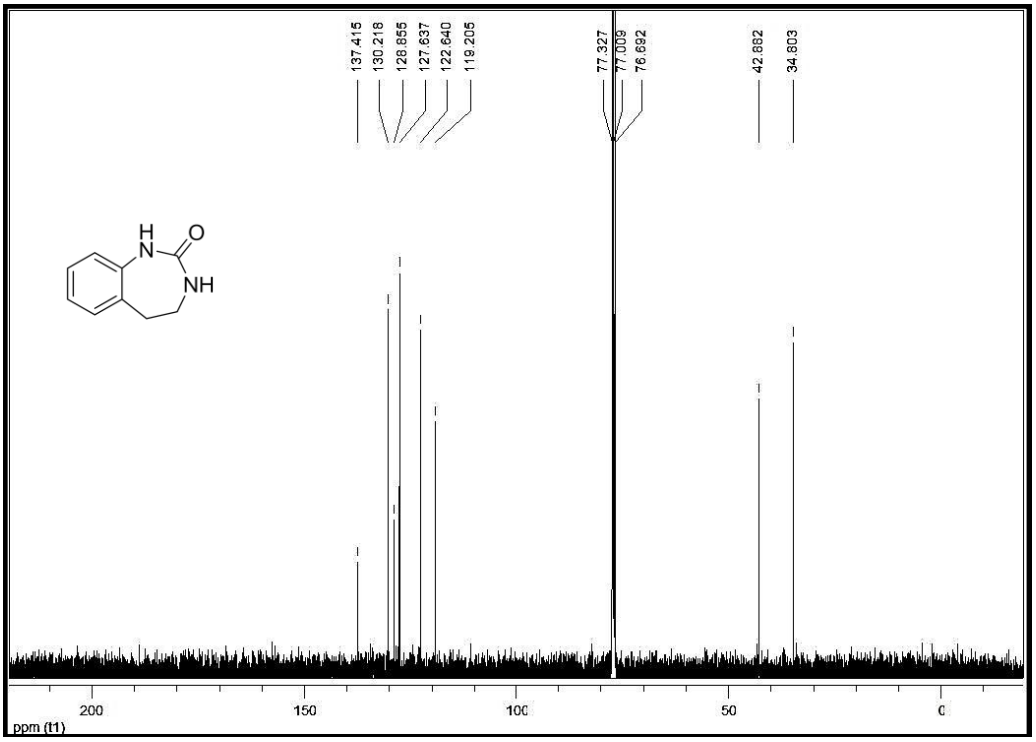

Figure 94 ^{13}C-NMR Spectrum of Compound **180**

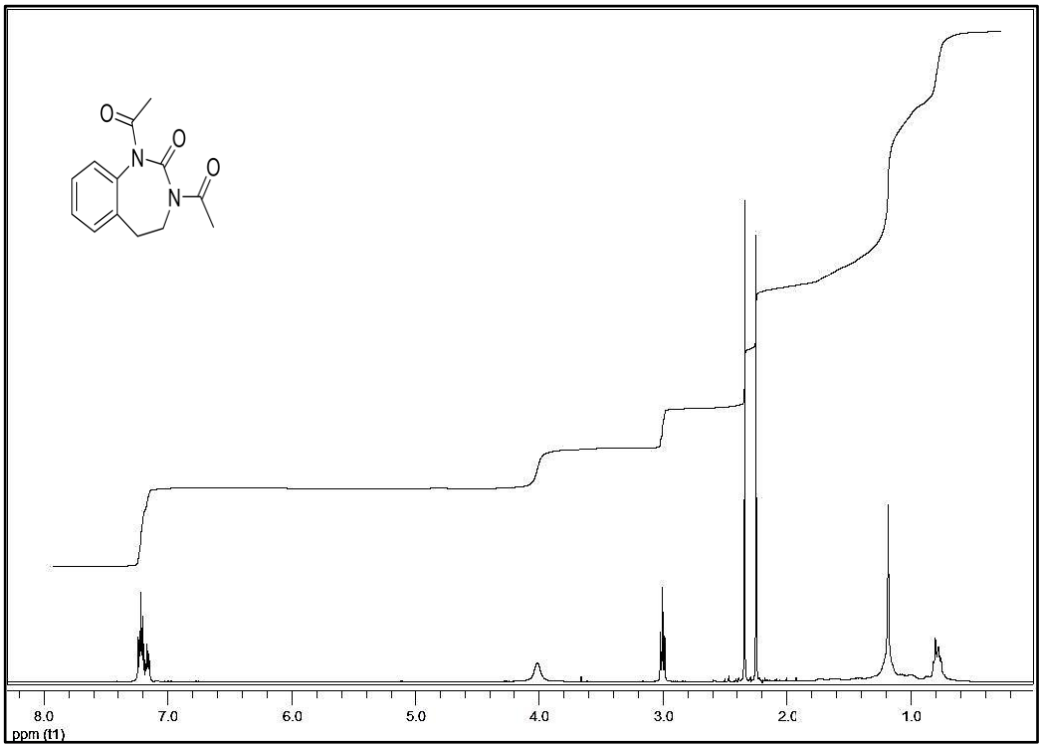

Figure 95 ^{1}H-NMR Spectrum of Compound **188**

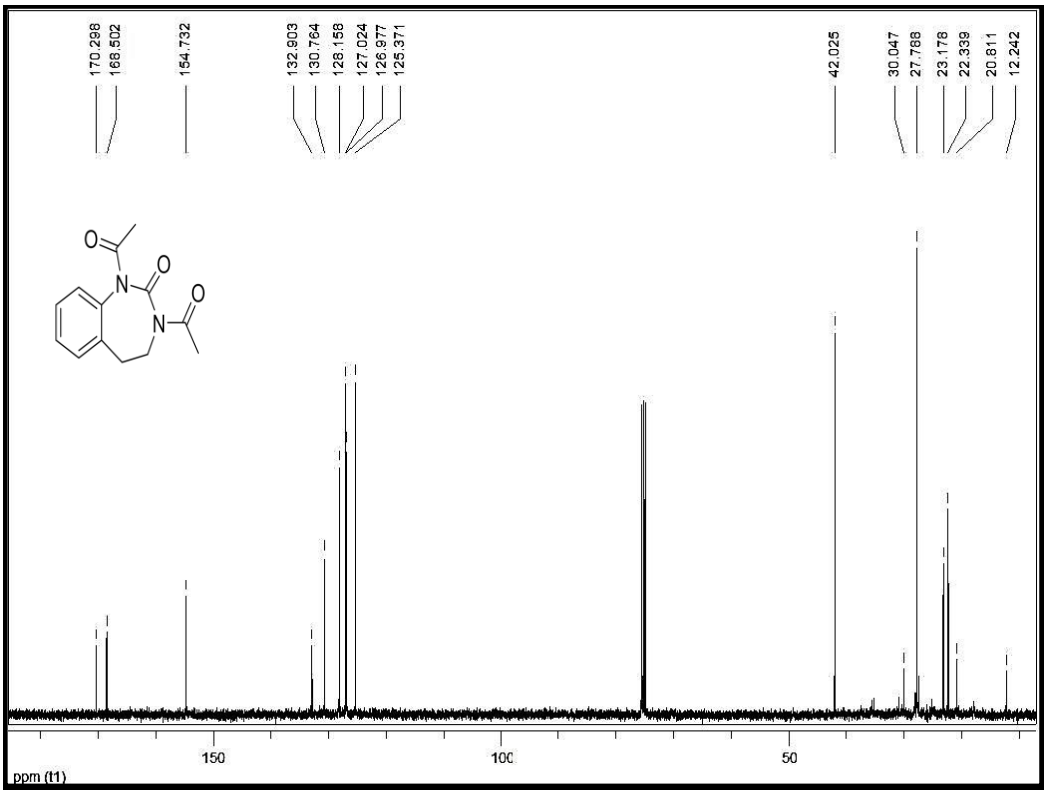

Figure 96 ^{13}C-NMR Spectrum of Compound **188**

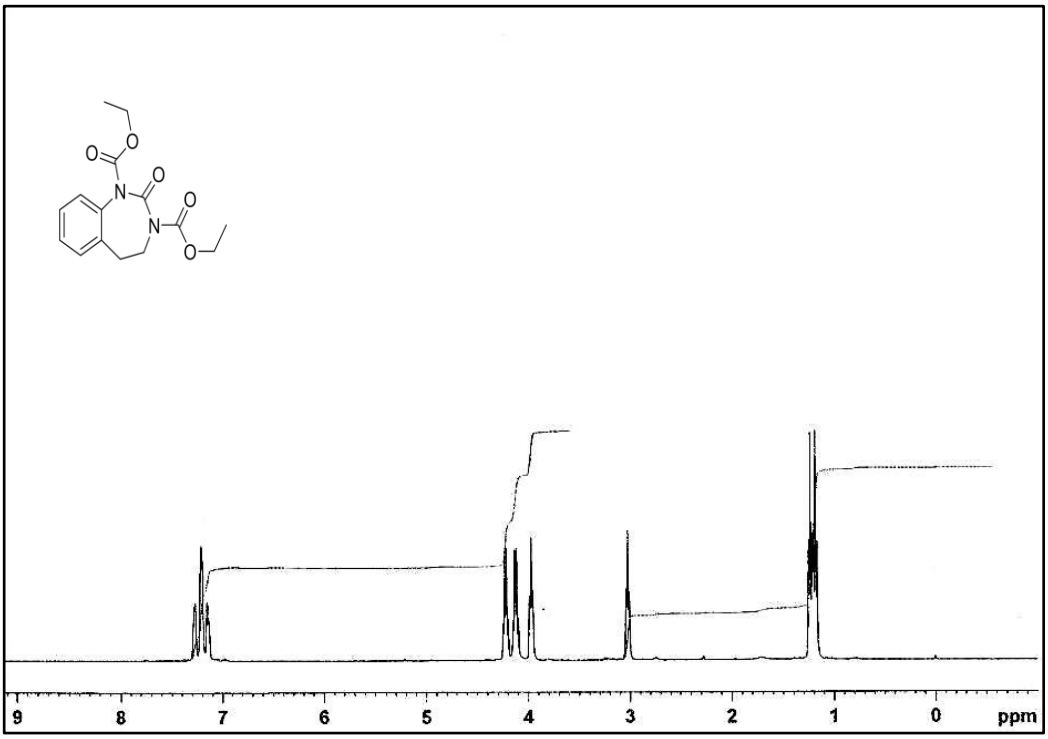

Figure 97 ^{1}H-NMR Spectrum of Compound **189**

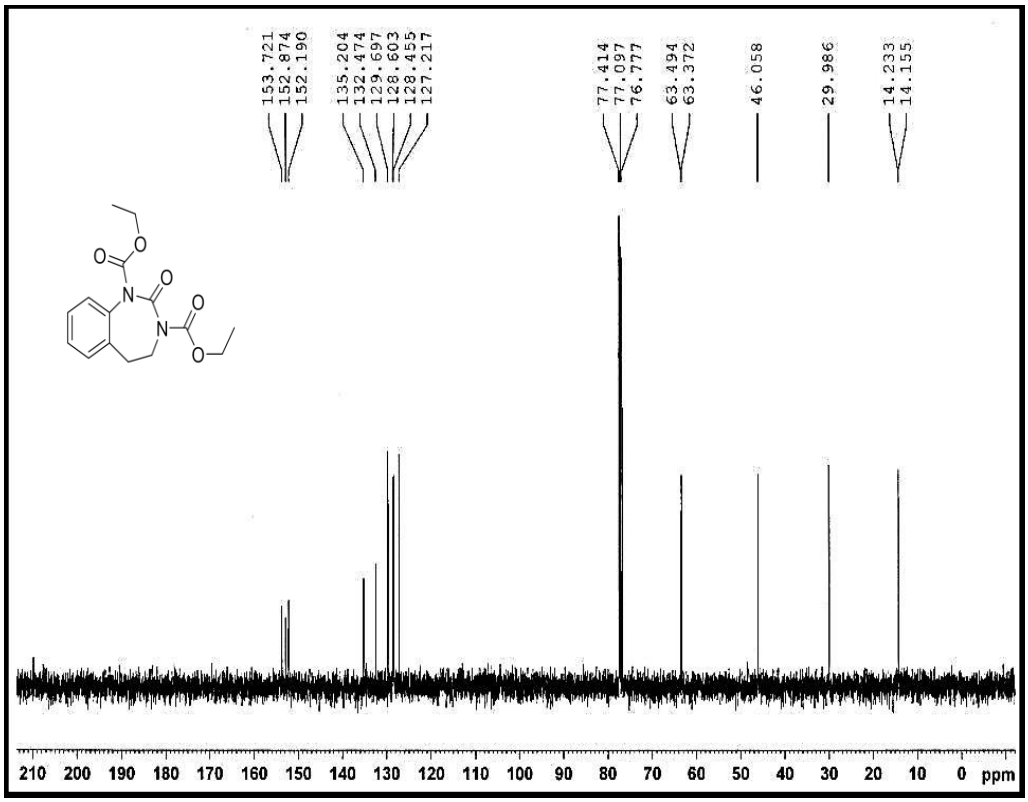

Figure 98 ^{13}C-NMR Spectrum of Compound **189**

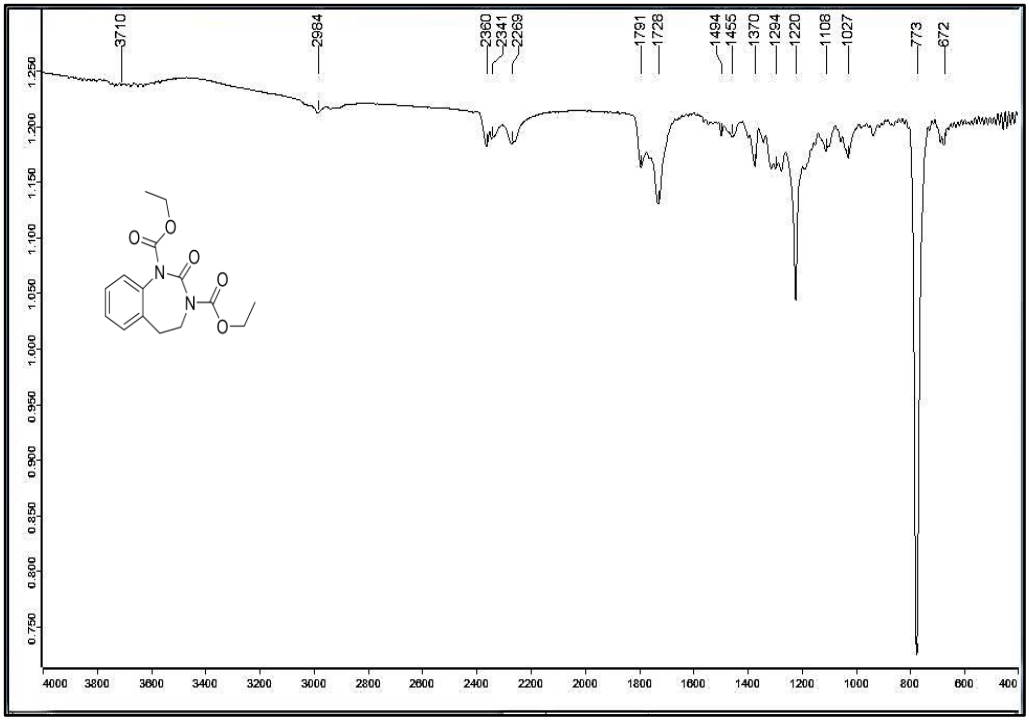

Figure 99 IR Spectrum of Compound **189**

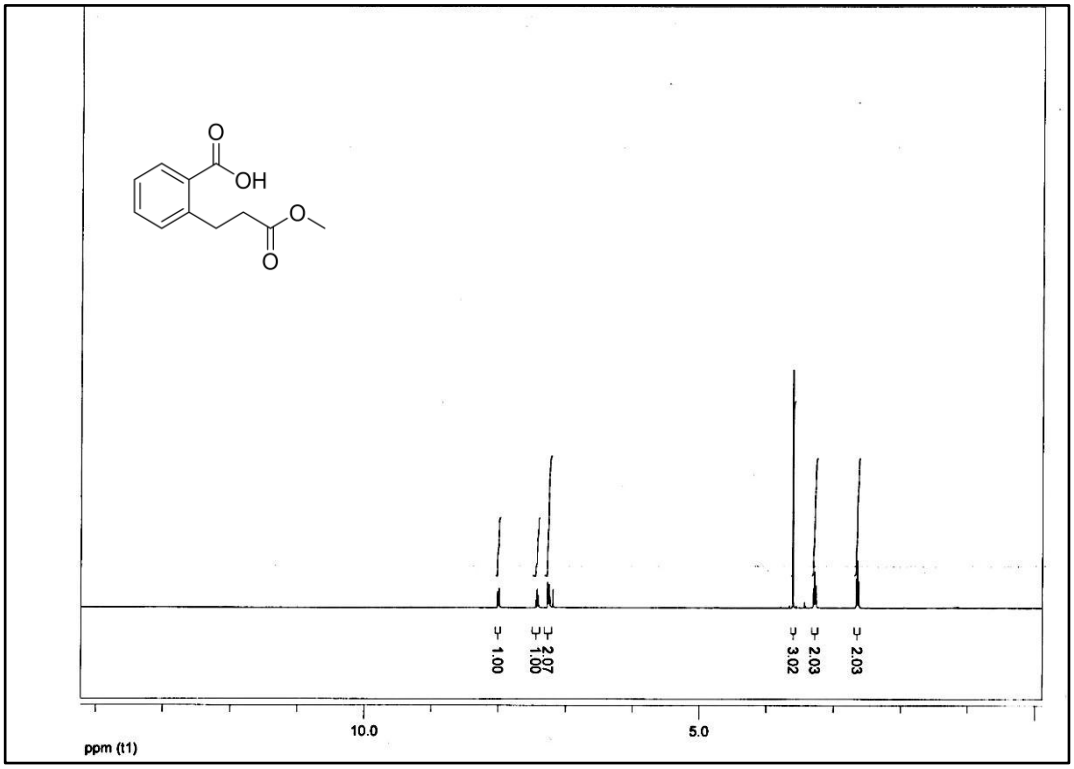

Figure 100 [1]H-NMR Spectrum of Compound **190**

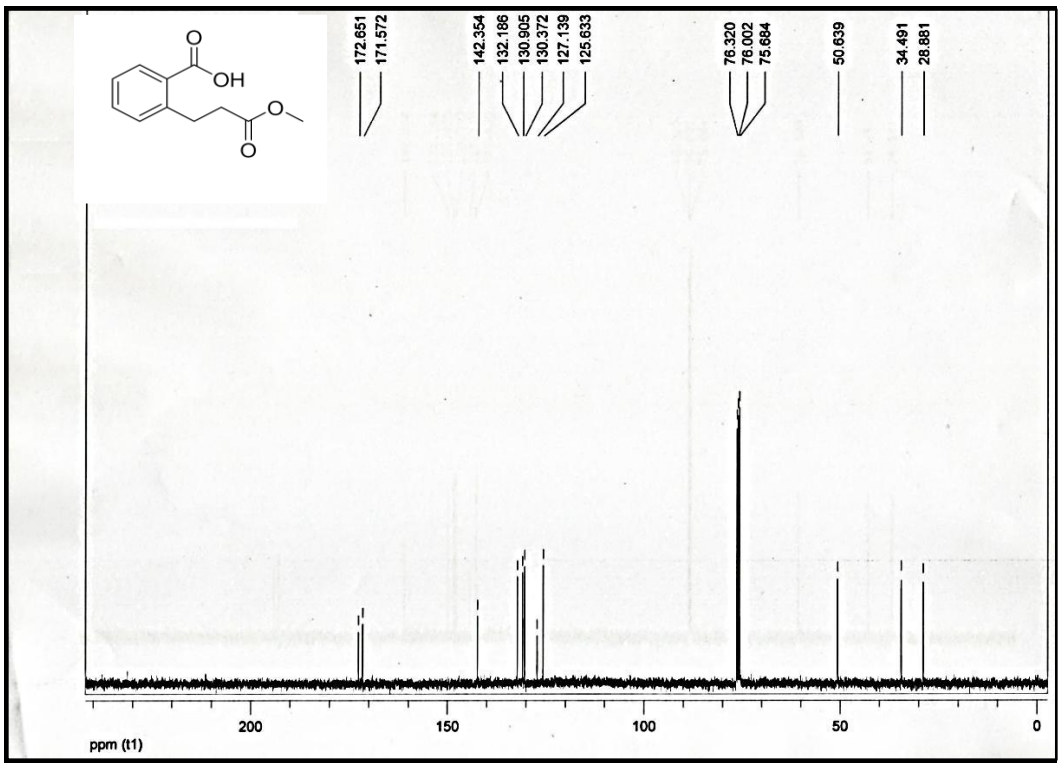

Figure 101 [13]C-NMR Spectrum of Compound **190**

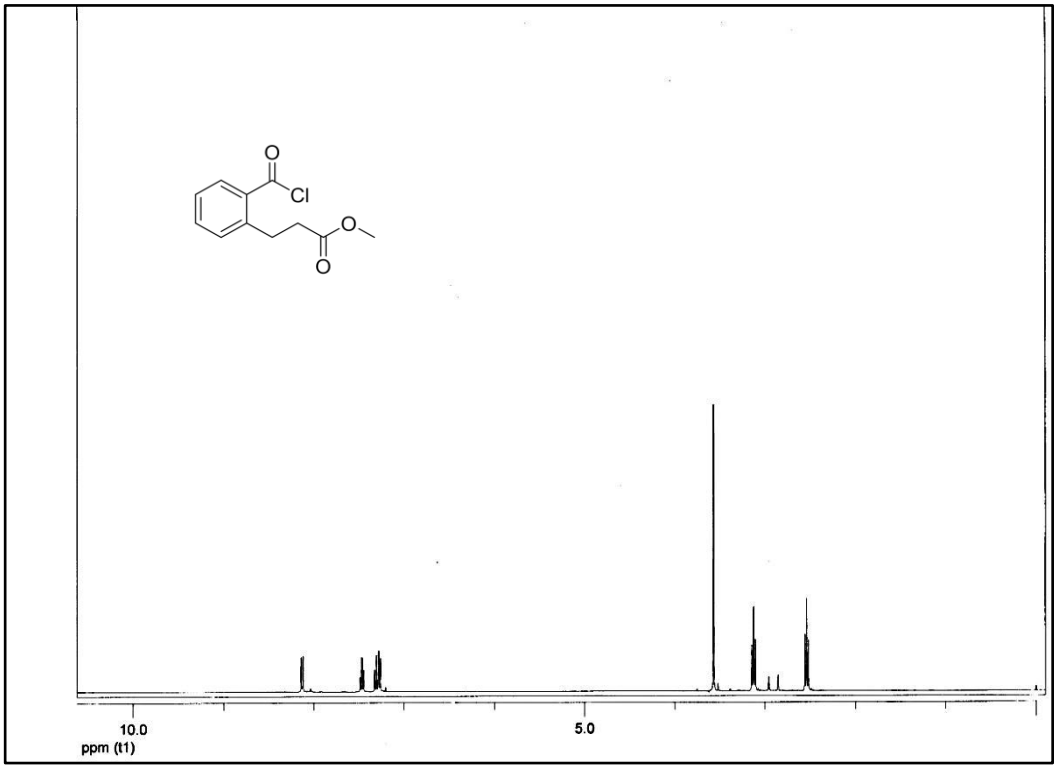

Figure 102 ^{1}H-NMR Spectrum of Compound **191**

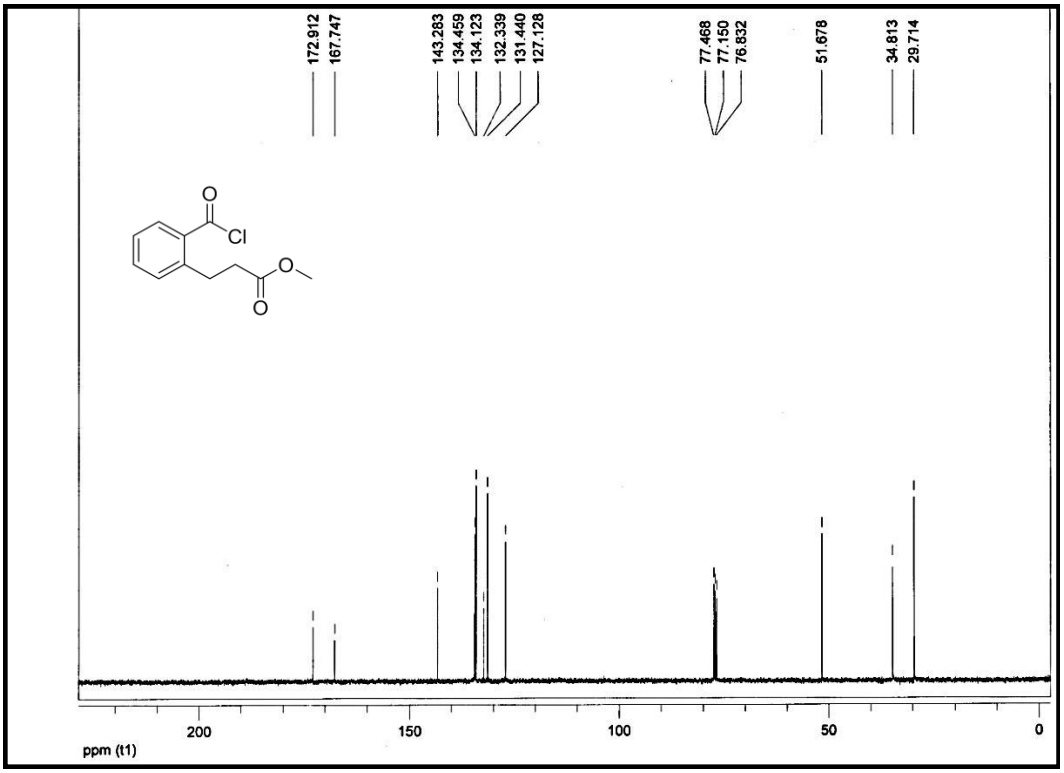

Figure 103 ^{13}C-NMR Spectrum of Compound **191**

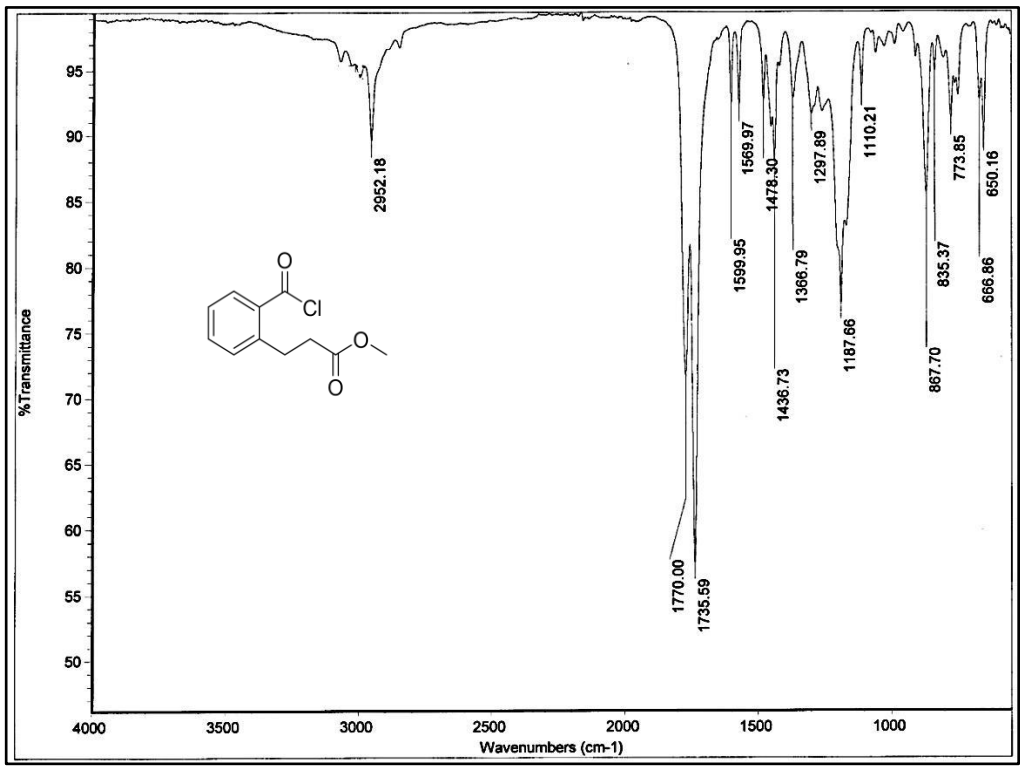

Figure 104 IR Spectrum of Compound **191**

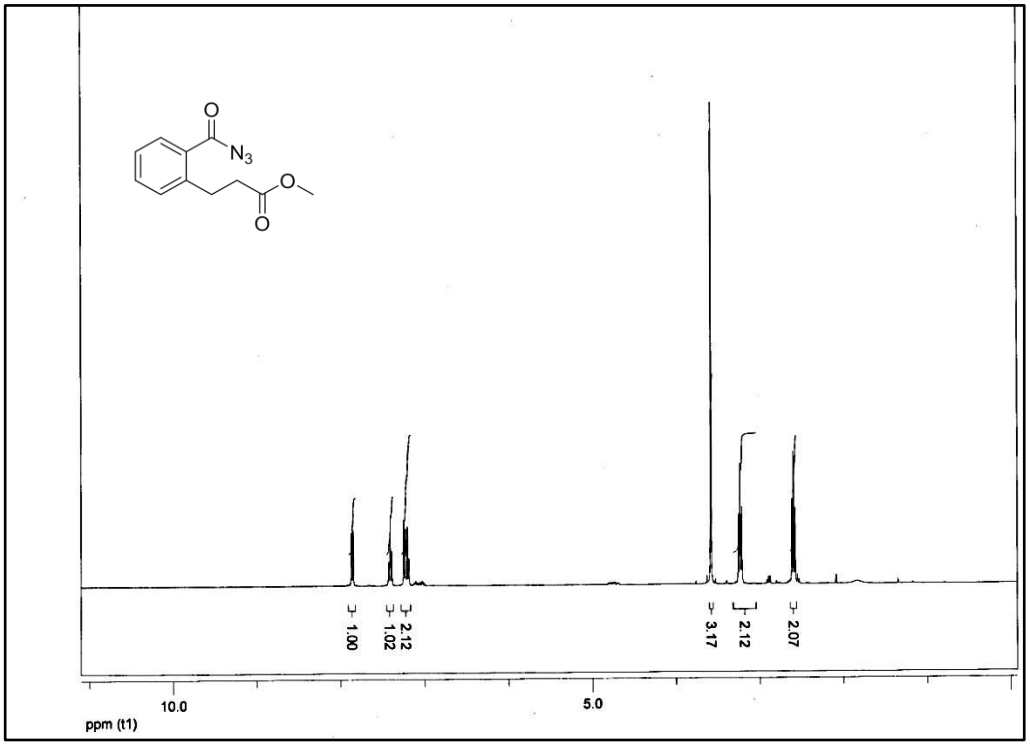

Figure 105 ^{1}H-NMR Spectrum of Compound **192**

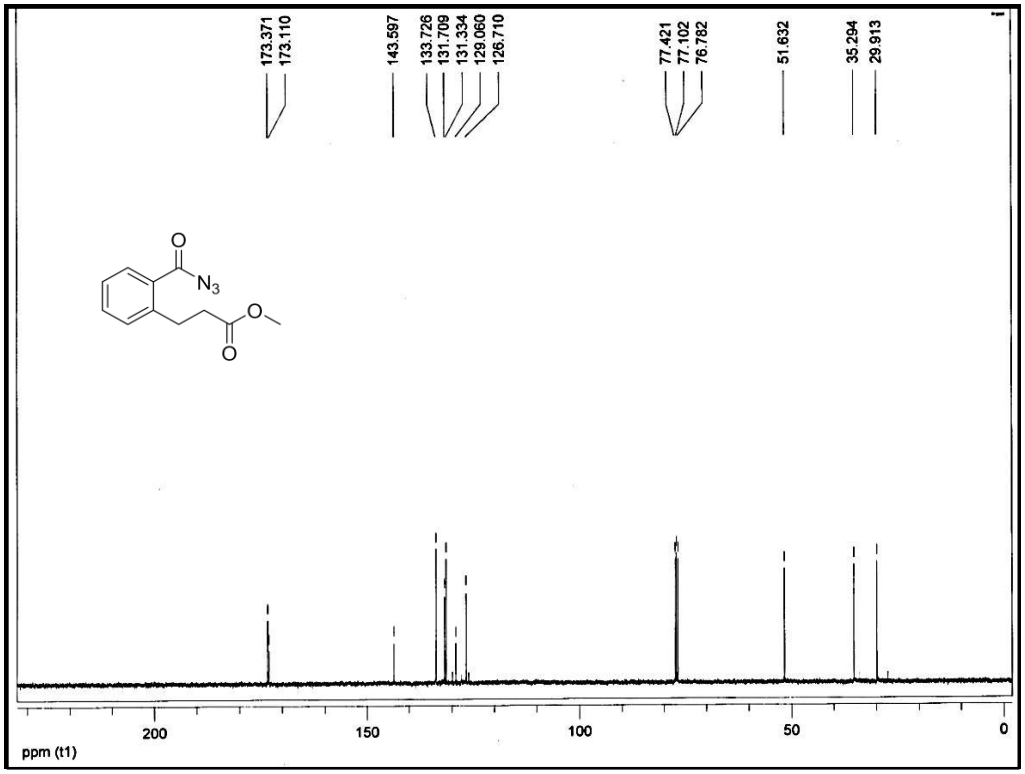

Figure 106 ^{13}C-NMR Spectrum of Compound **192**

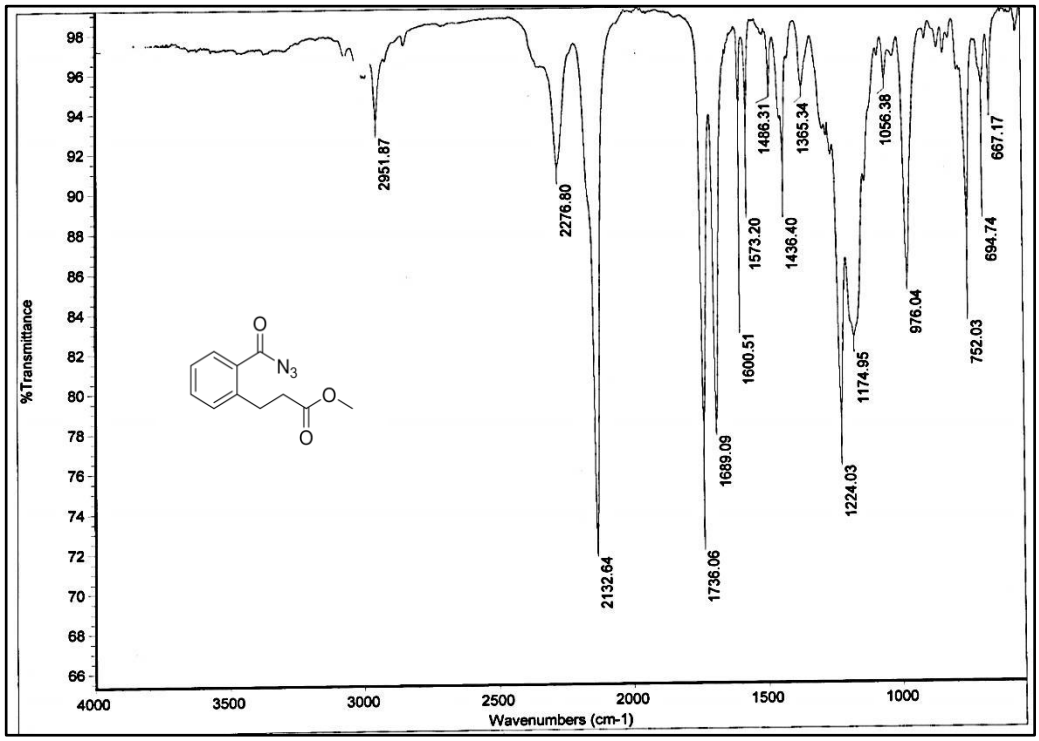

Figure 107 IR Spectrum of Compound **192**

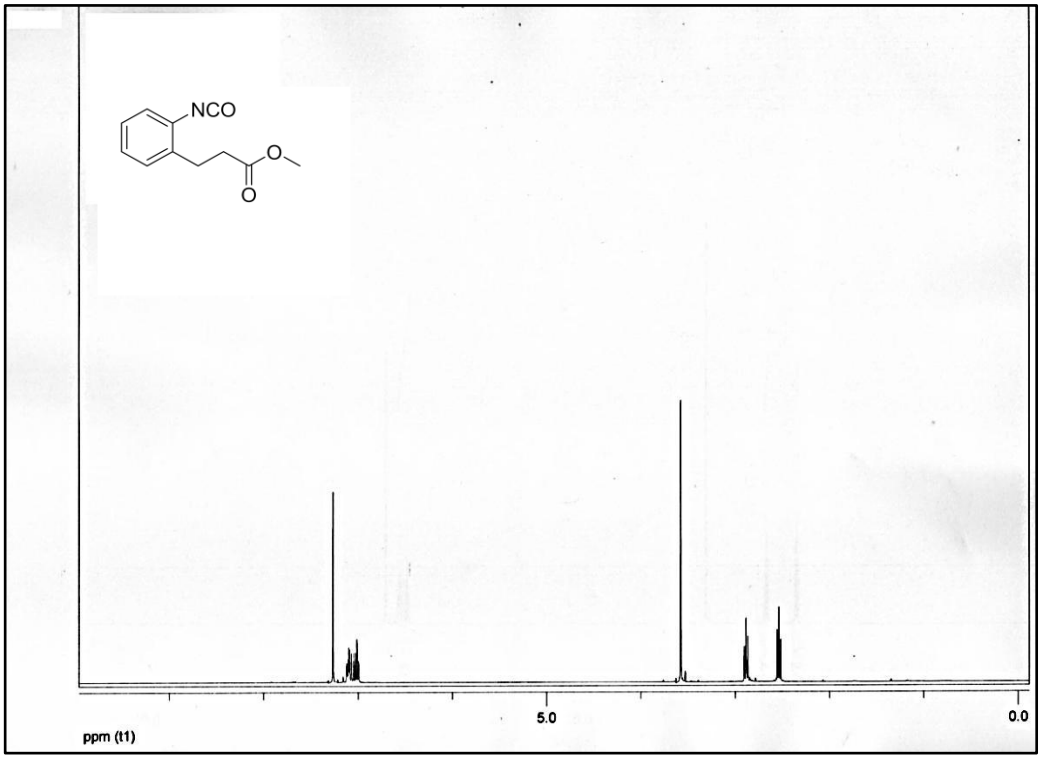

Figure 108 ^{1}H-NMR Spectrum of Compound **193**

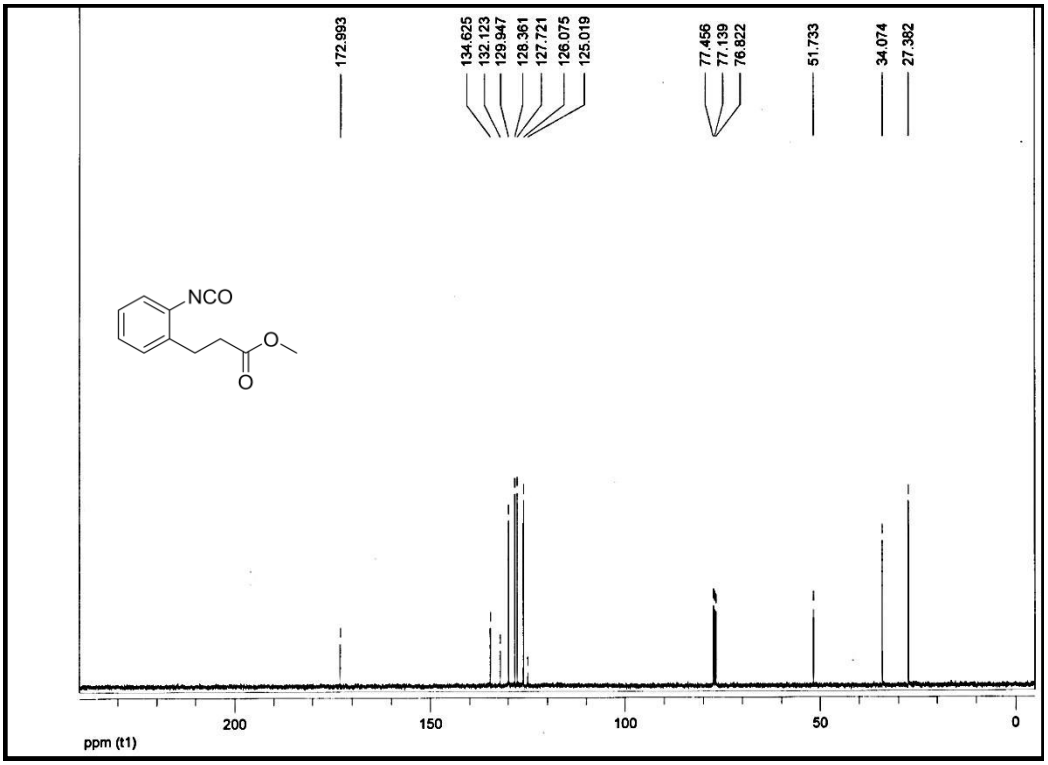

Figure 109 ^{13}C-NMR Spectrum of Compound **193**

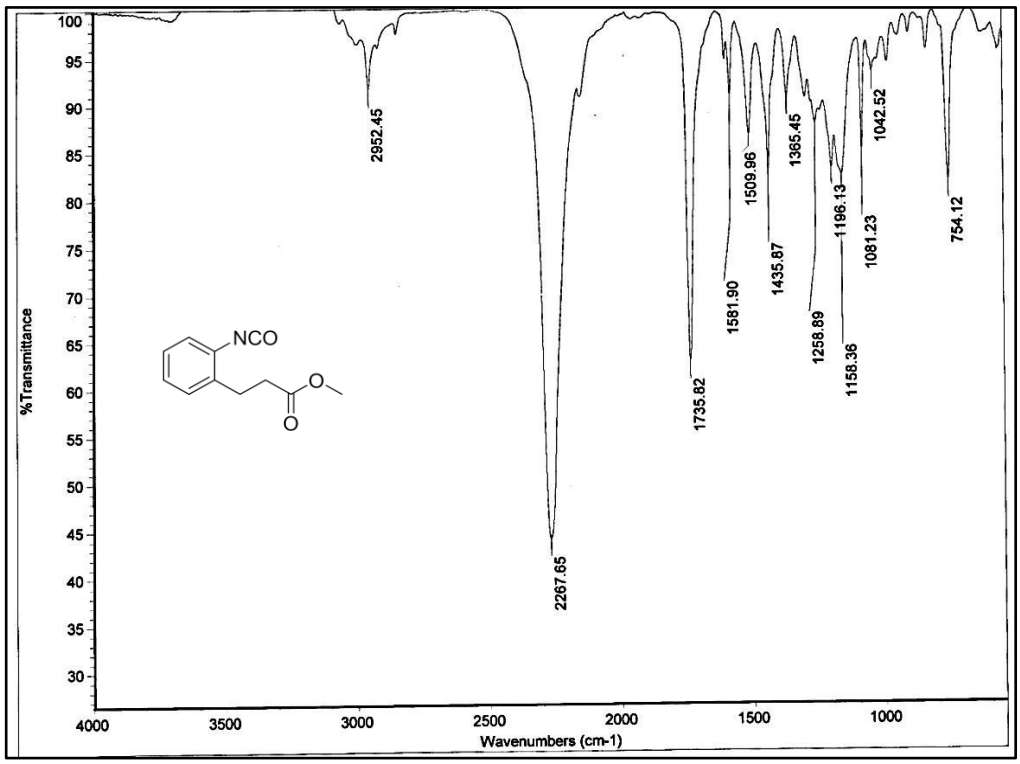

Figure 110 IR Spectrum of Compound **193**

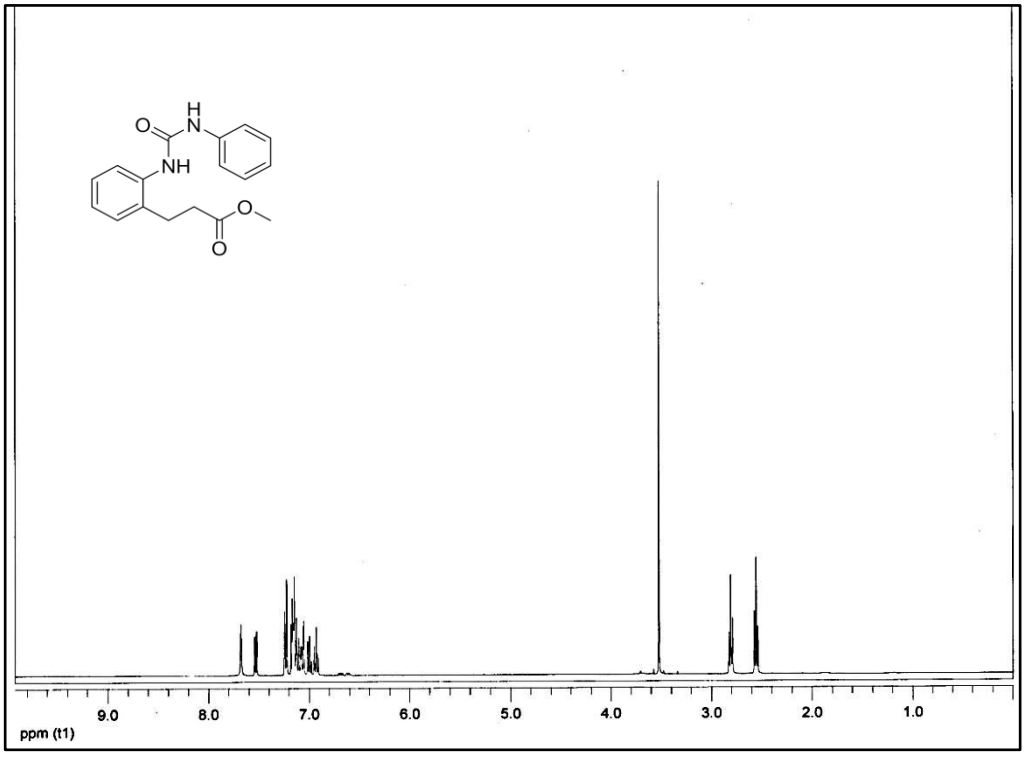

Figure 111 ^{1}H-NMR Spectrum of Compound **194**

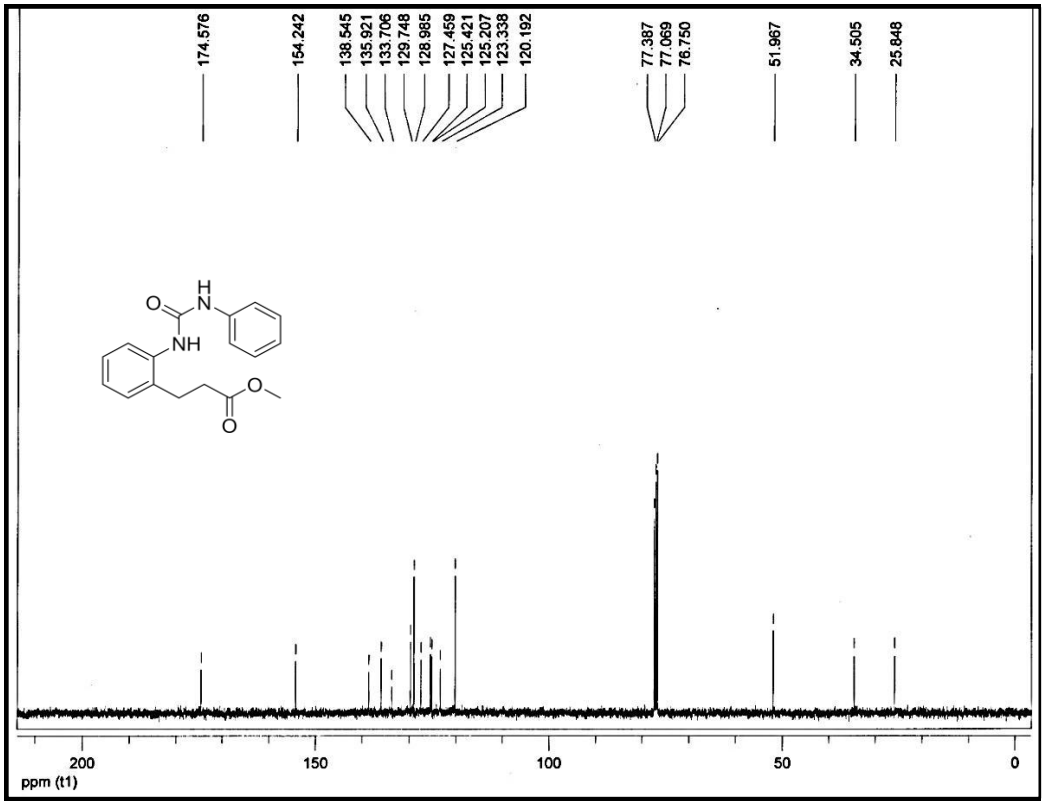

Figure 112 ^{13}C-NMR Spectrum of Compound **194**

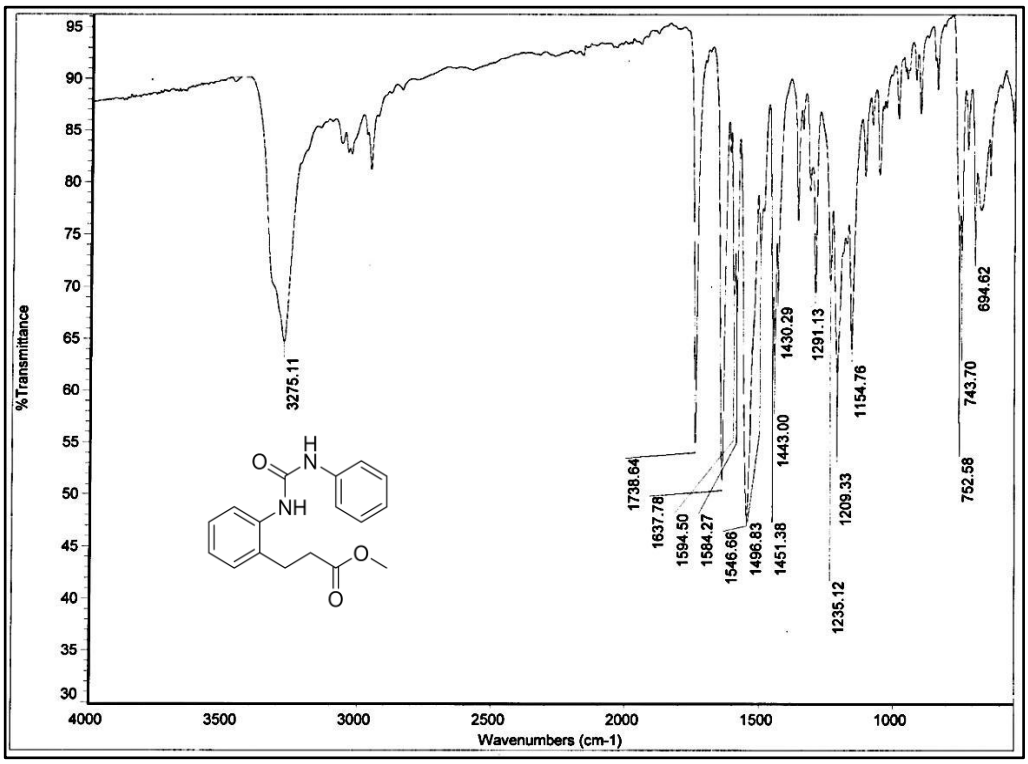

Figure 113 IR Spectrum of Compound **194**

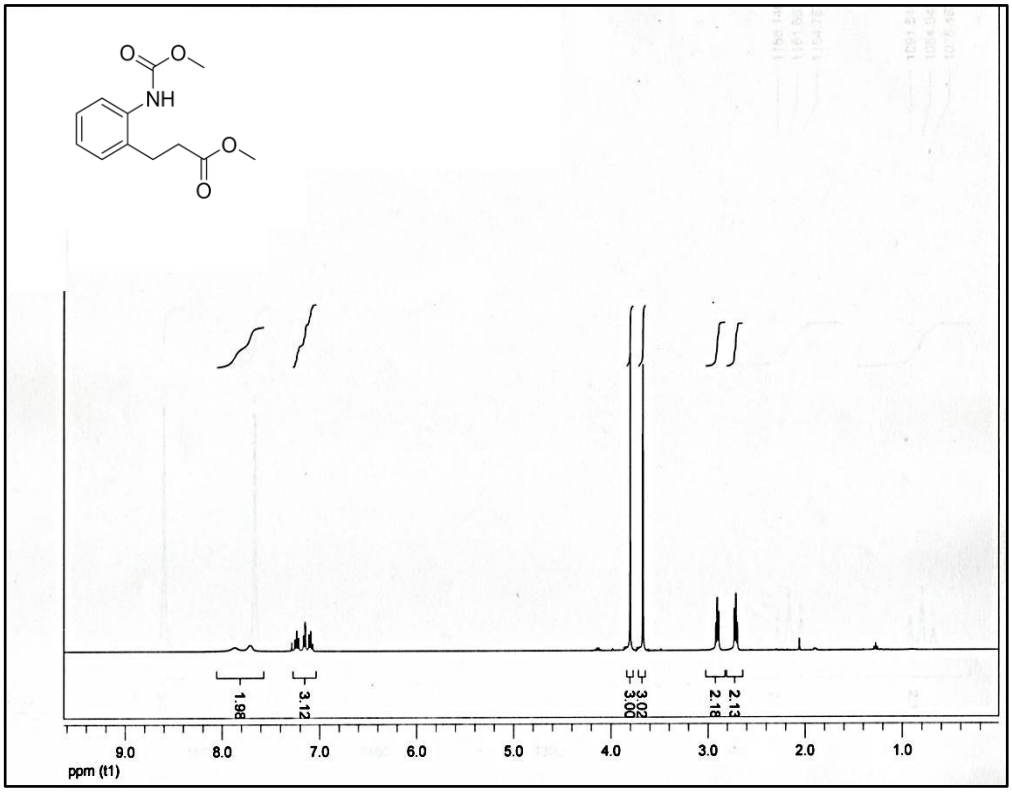

Figure 114 ^{1}H-NMR Spectrum of Compound **195**

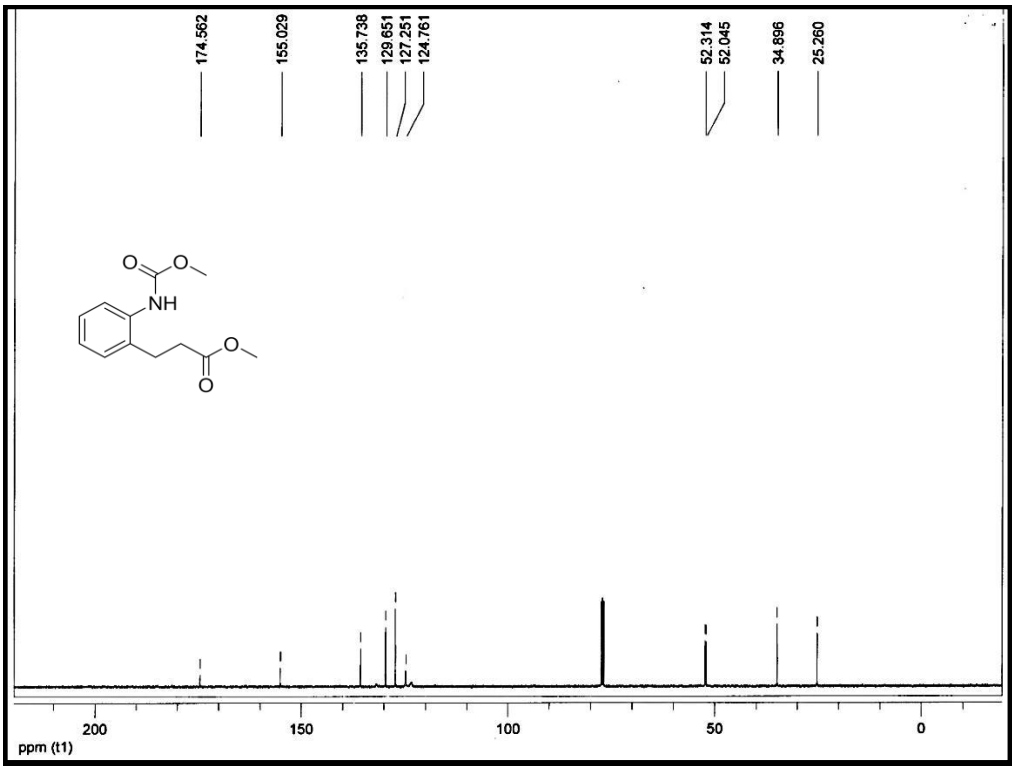

Figure 115 ^{13}C-NMR Spectrum of Compound **195**

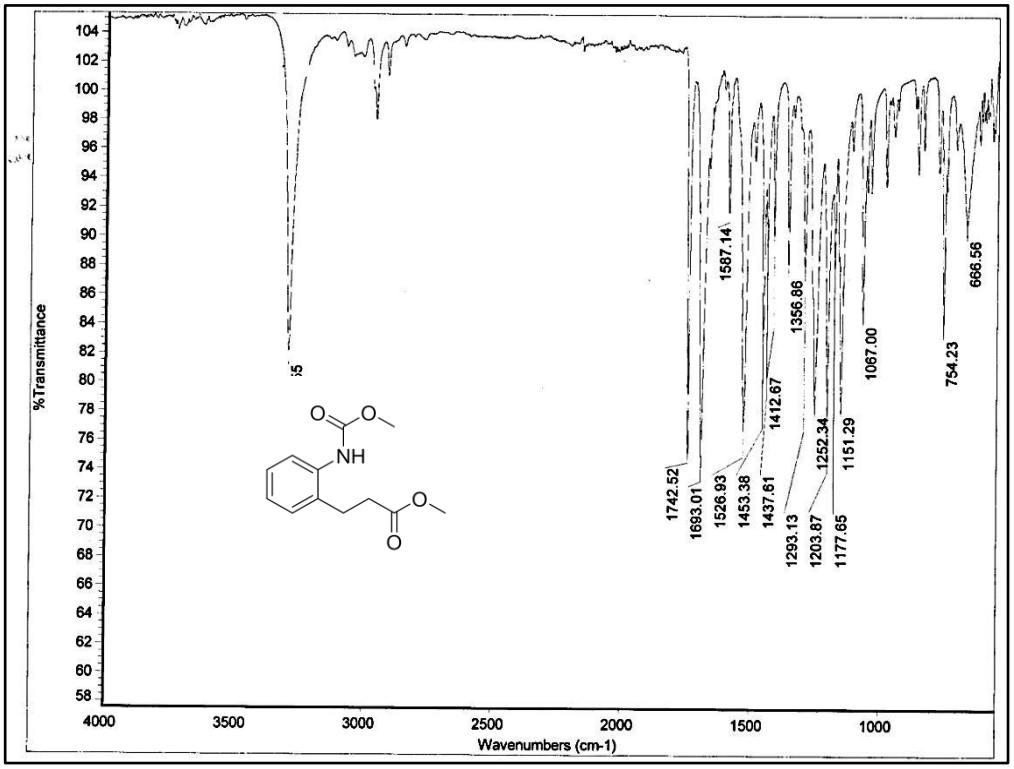

Figure 116 IR Spectrum of Compound **195**

Figure 117 ^{1}H-NMR Spectrum of Compound **196**

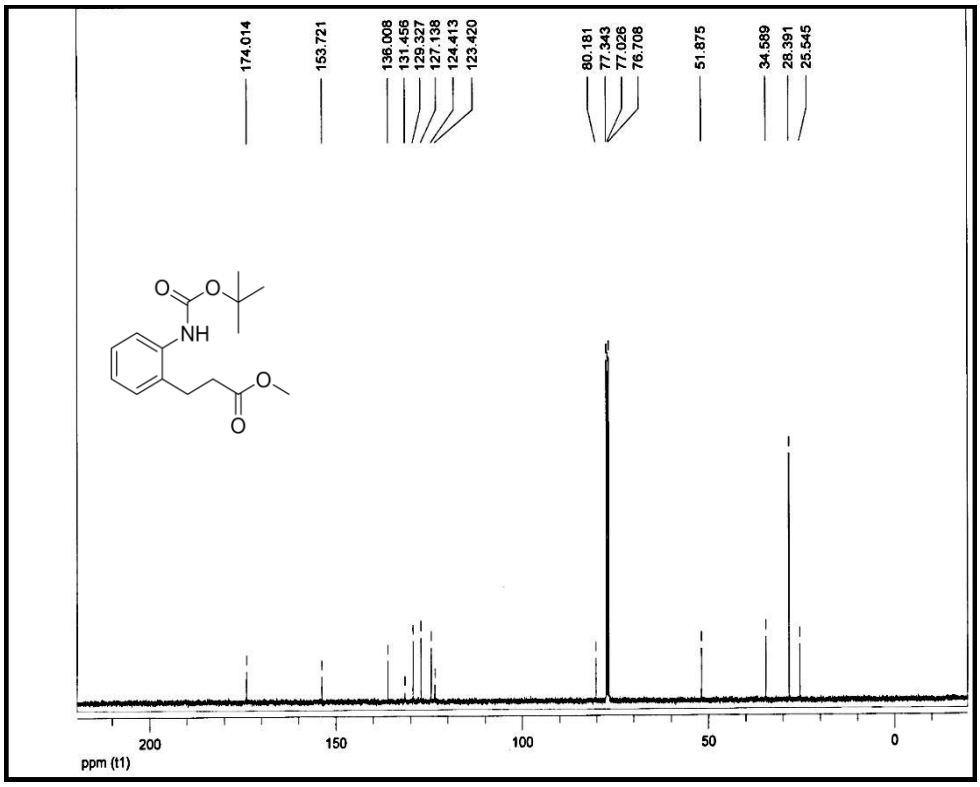

Figure 118 ^{13}C-NMR Spectrum of Compound **196**

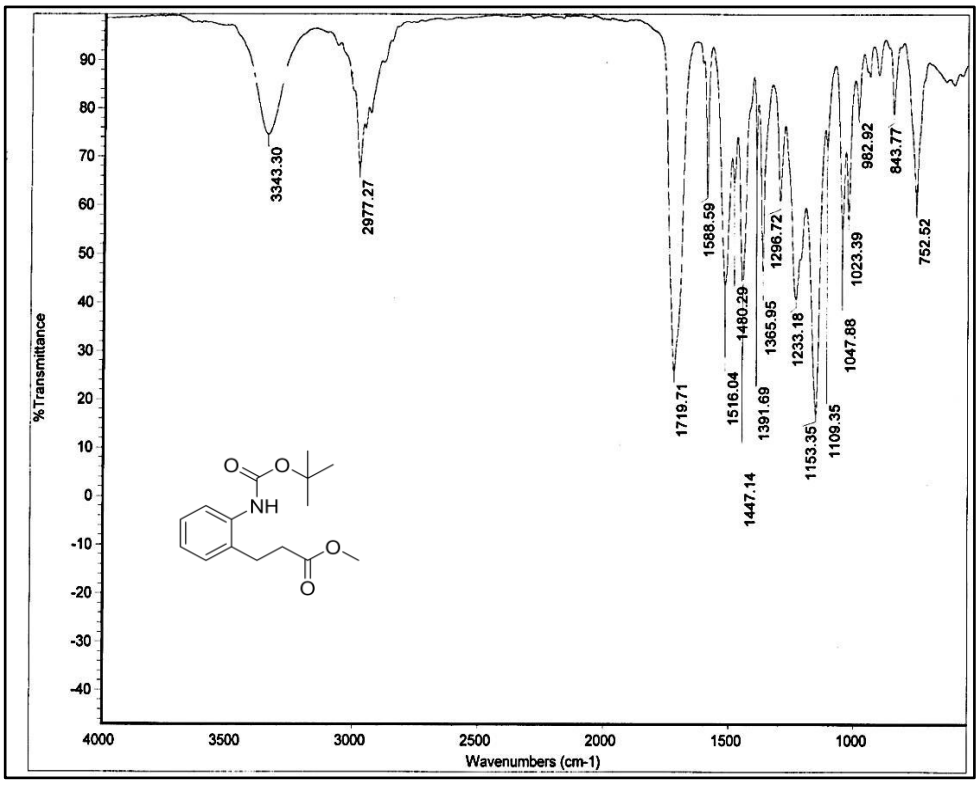

Figure 119 IR Spectrum of Compound **196**

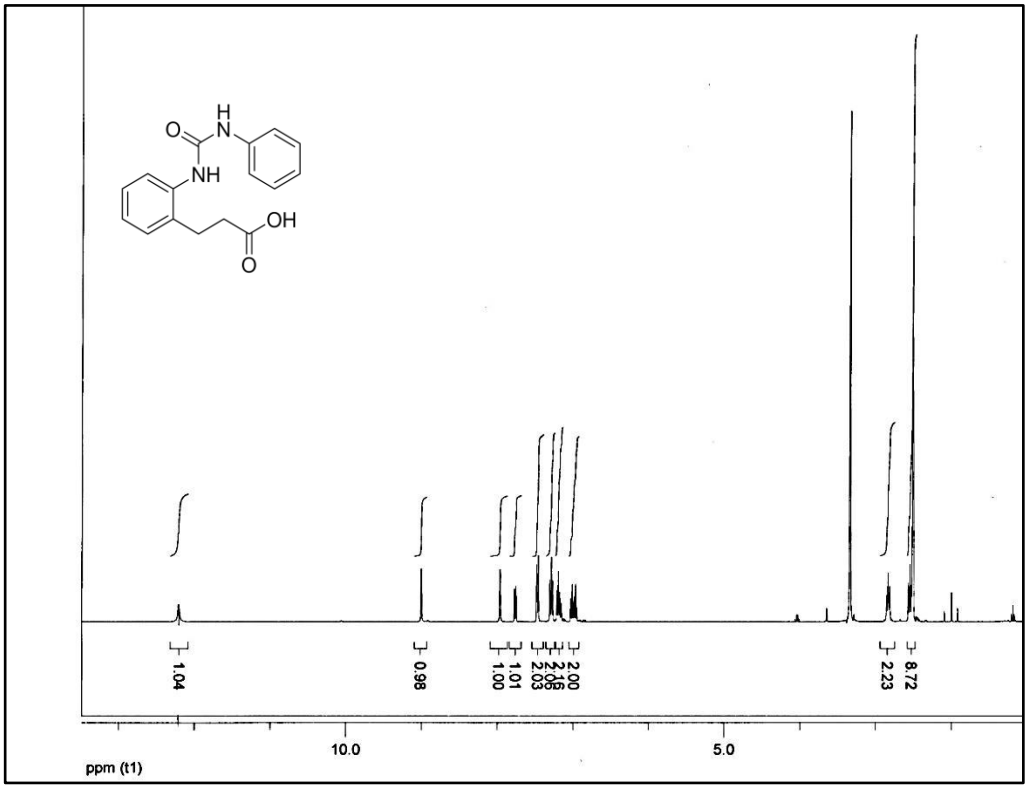

Figure 120 ^{1}H-NMR Spectrum of Compound **197**

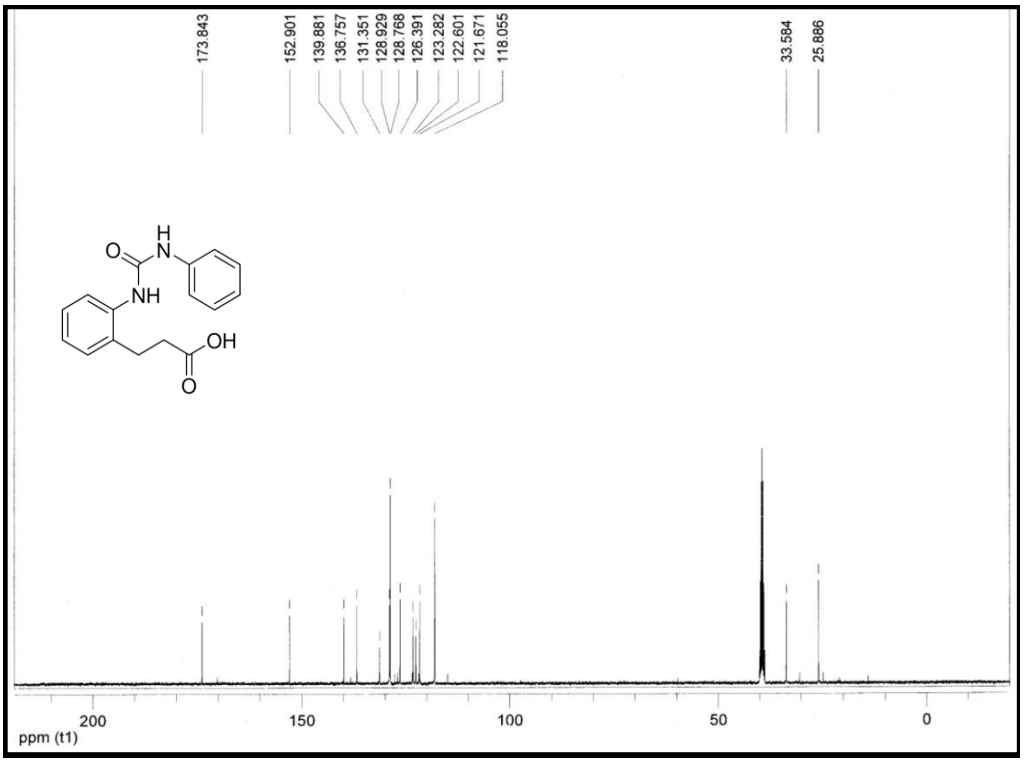

Figure 121 ^{13}C-NMR Spectrum of Compound **197**

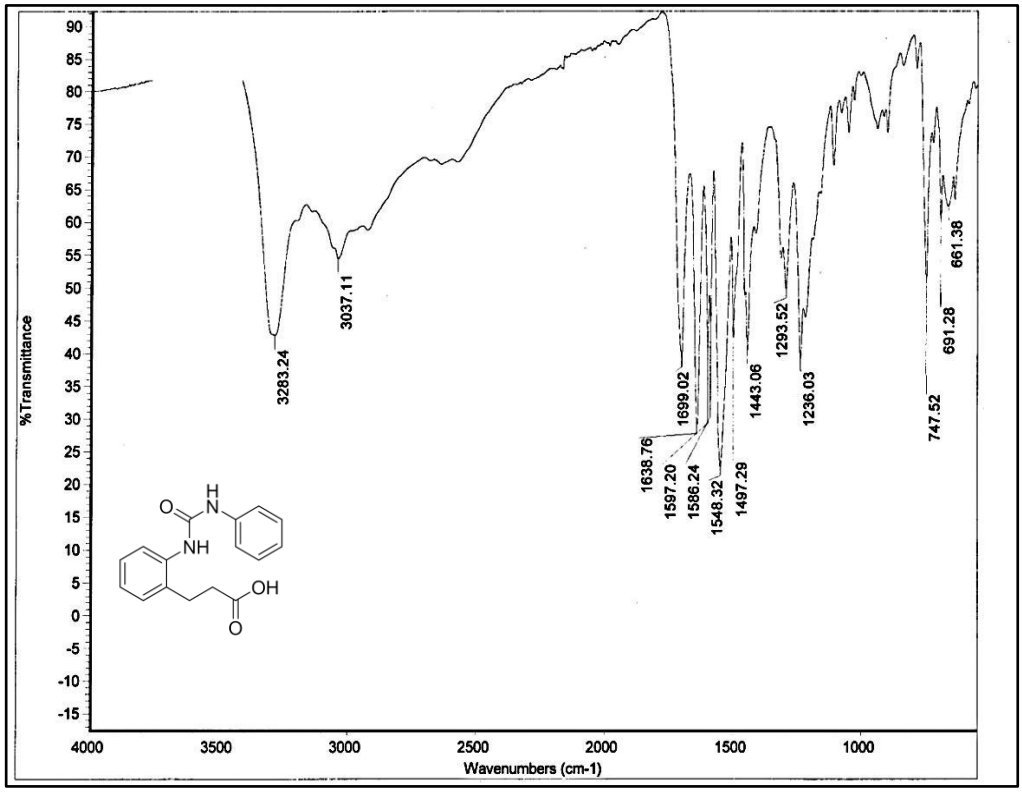

Figure 122 IR Spectrum of Compound **197**

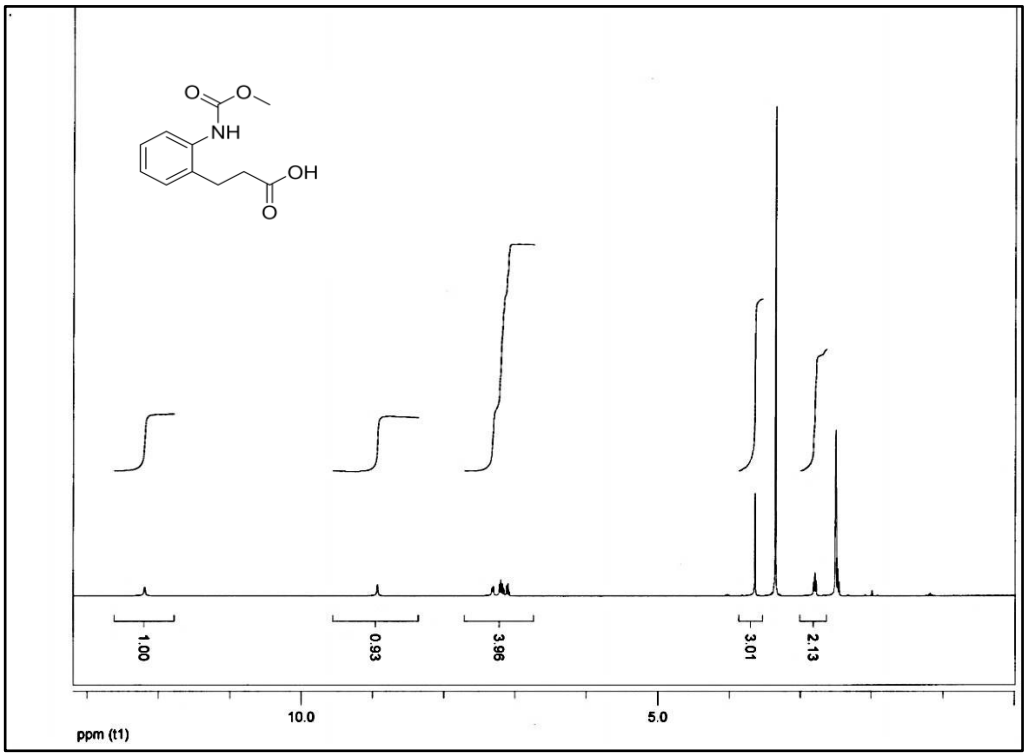

Figure 123 ^{1}H-NMR Spectrum of Compound **198**

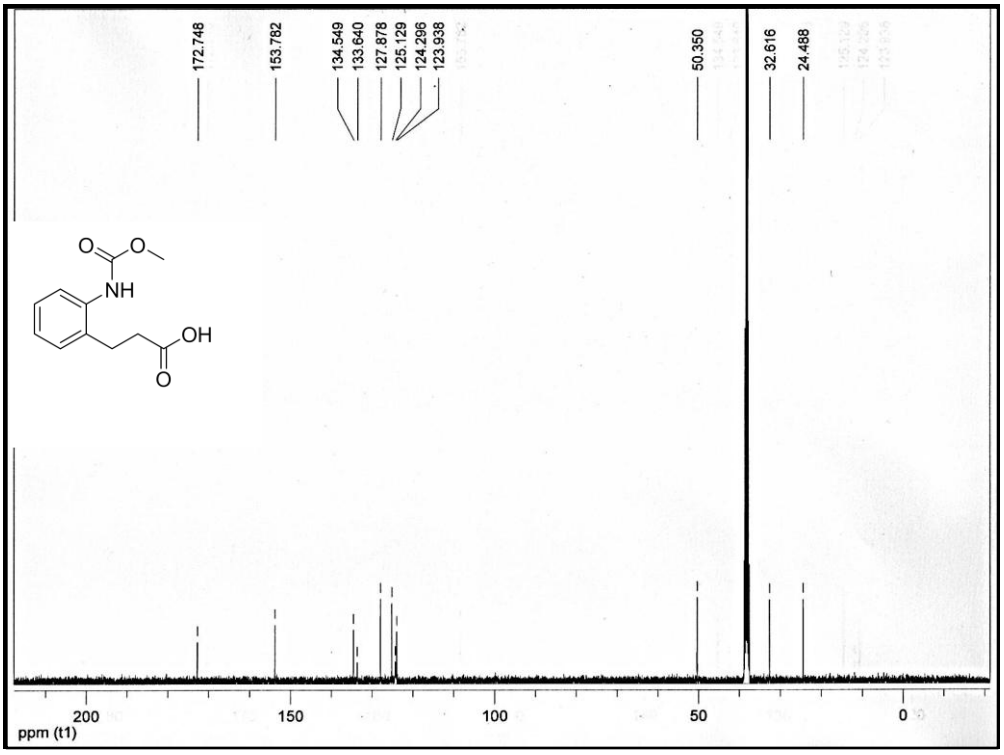

Figure 124 ^{13}C-NMR Spectrum of Compound **198**

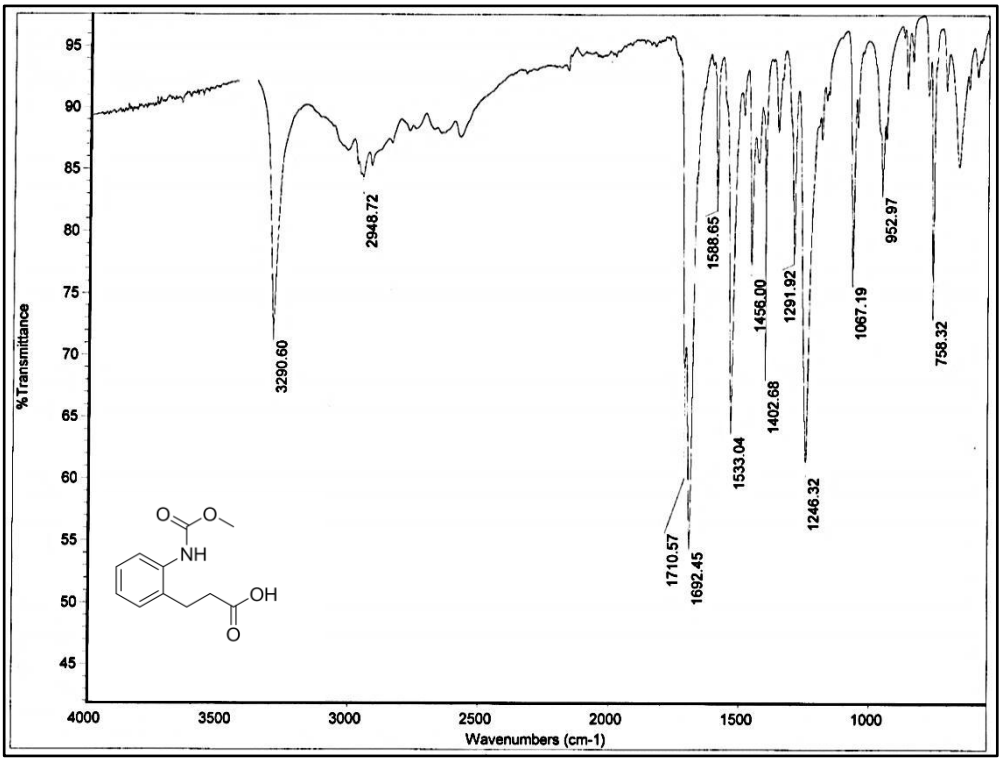

Figure 125 IR Spectrum of Compound **198**

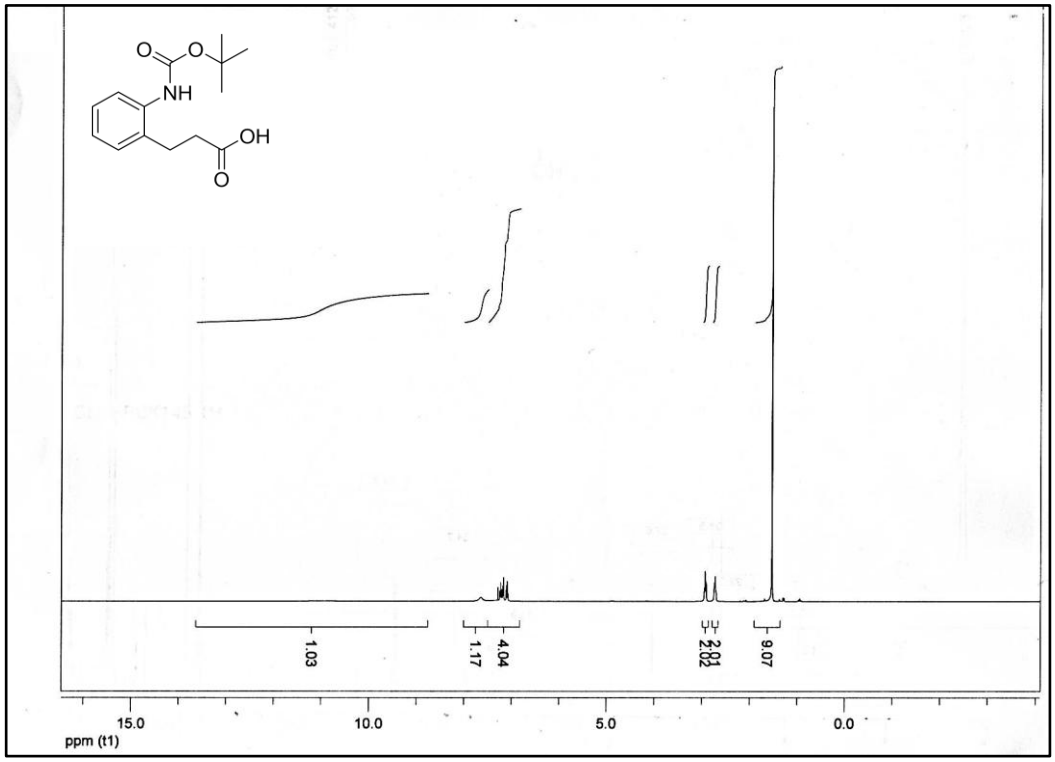

Figure 126 ^{1}H-NMR Spectrum of Compound **199**

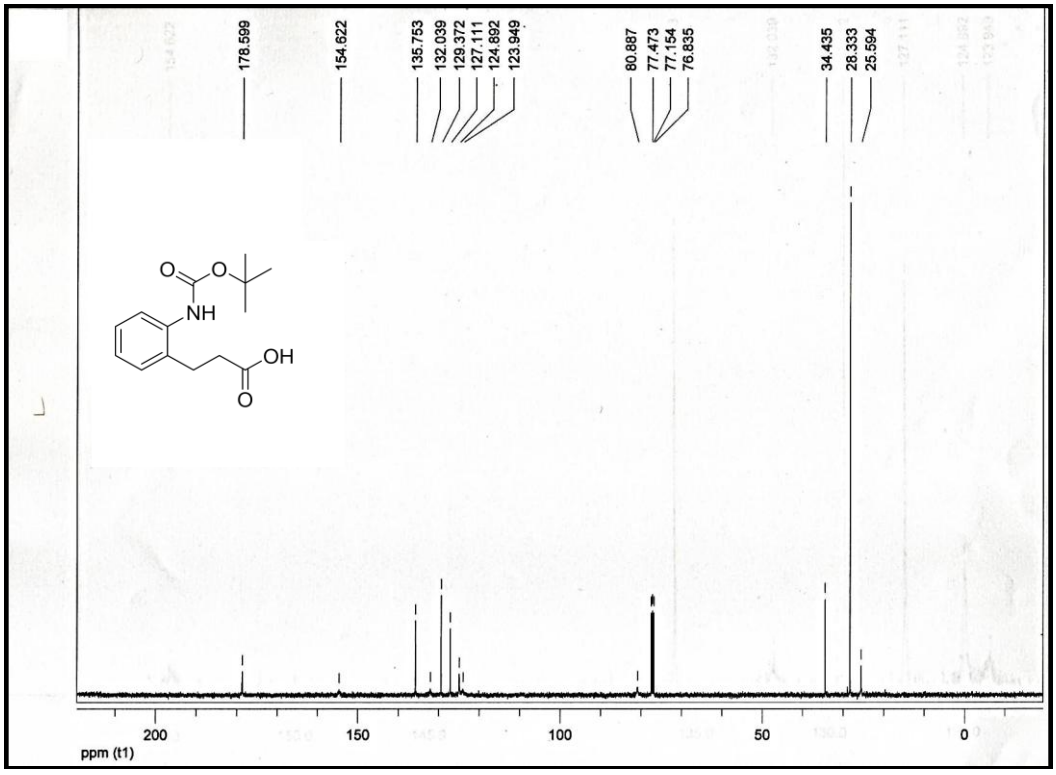

Figure 127 ^{13}C-NMR Spectrum of Compound **199**

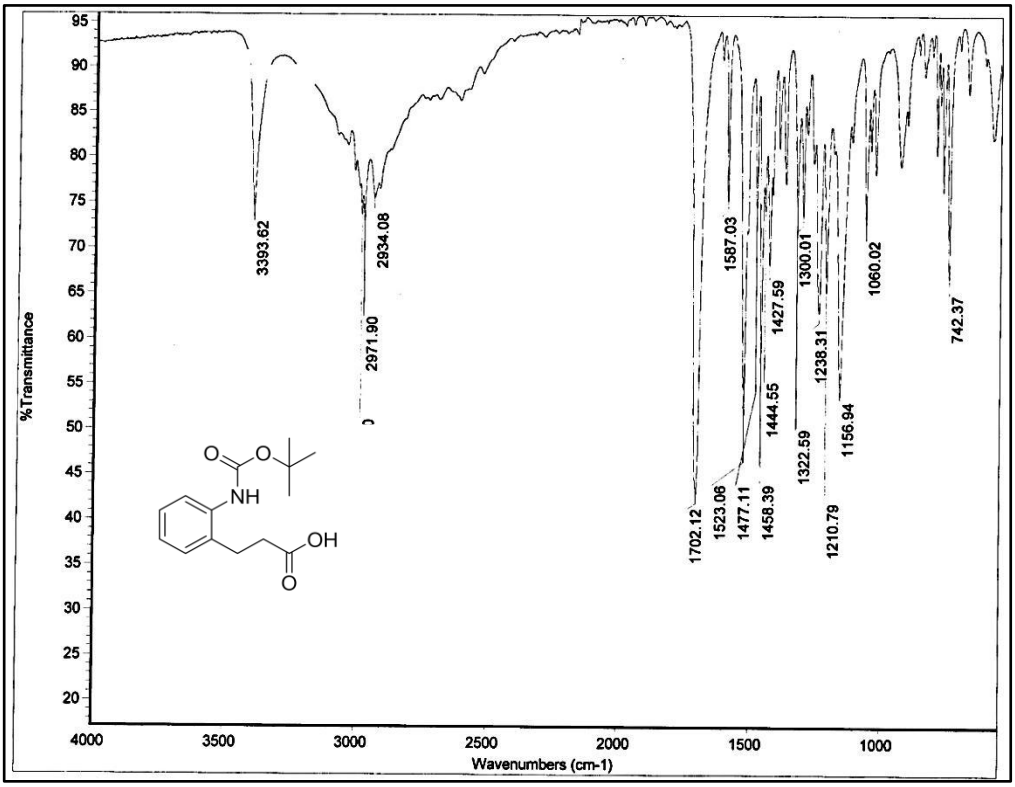

Figure 128 IR Spectrum of Compound 199

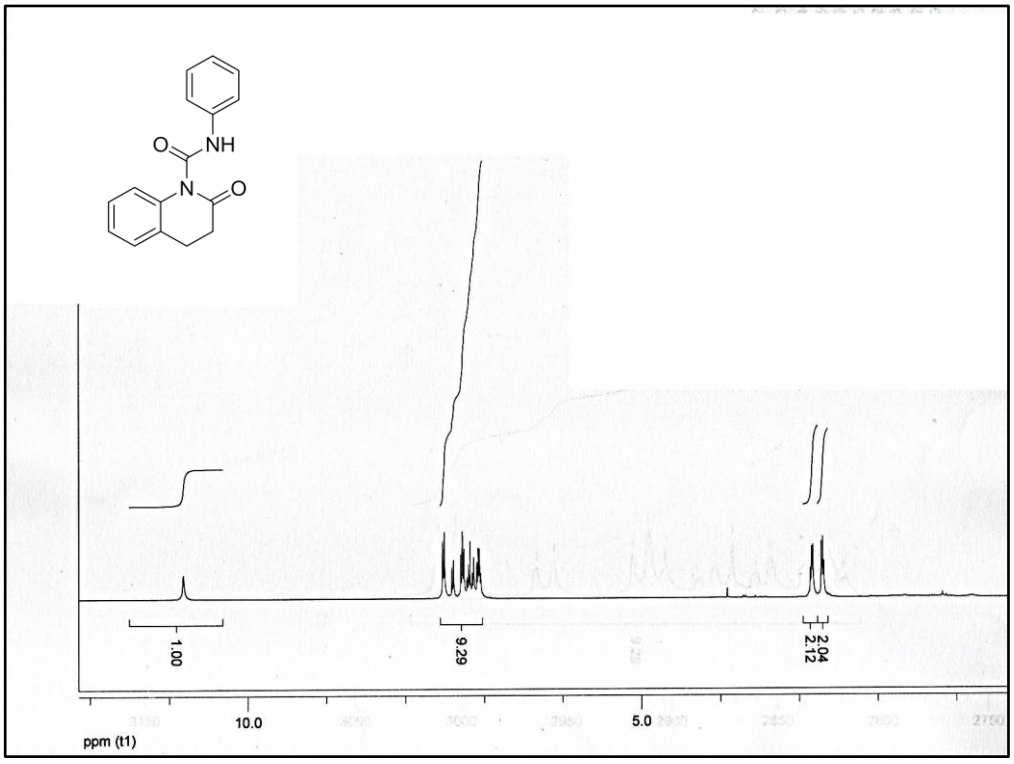

Figure 129 ^{1}H-NMR Spectrum of Compound **200**

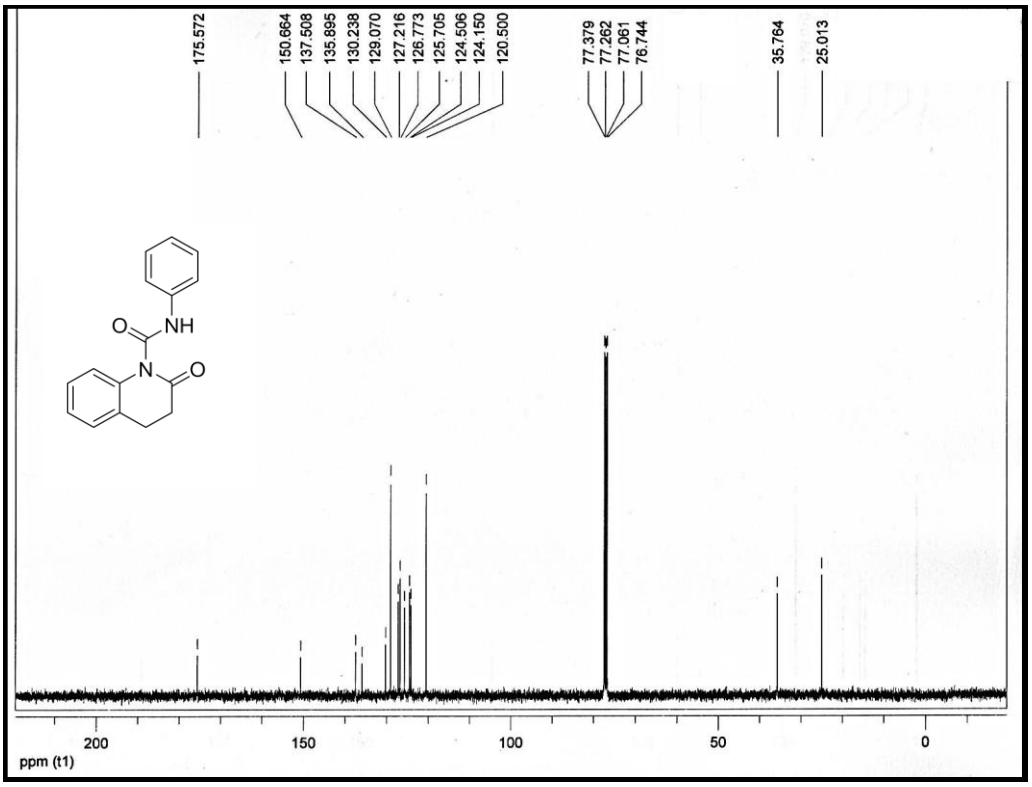

Figure 130 ^{13}C-NMR Spectrum of Compound **200**

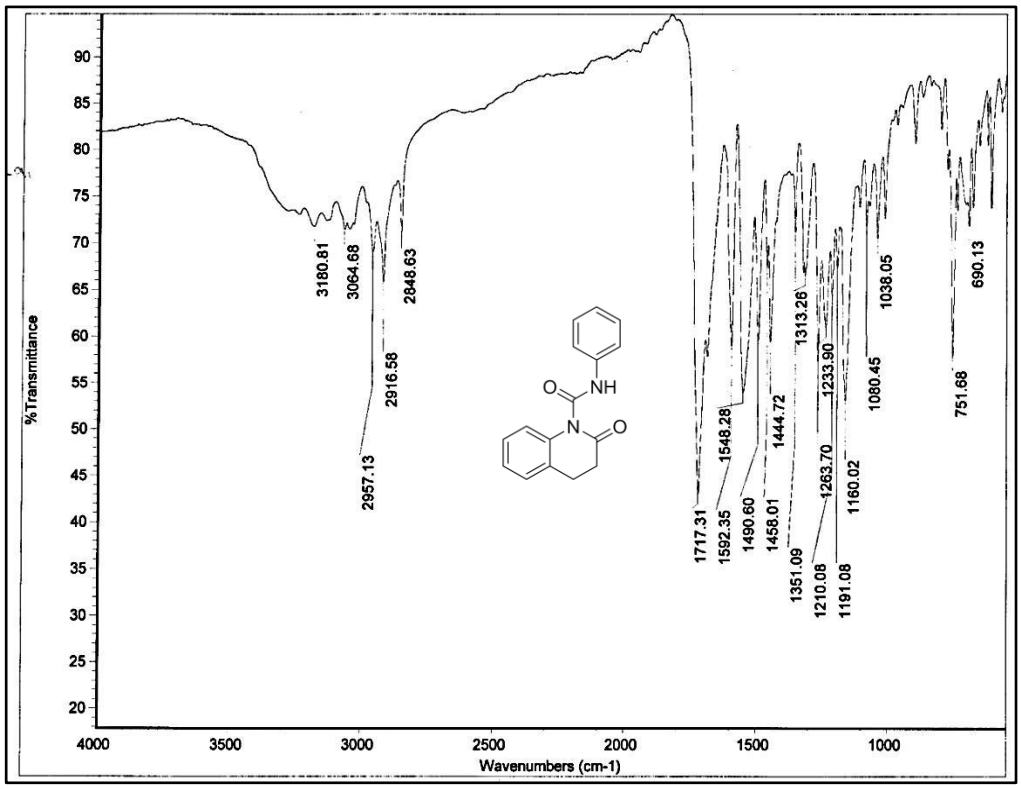

Figure 131 IR Spectrum of Compound **200**

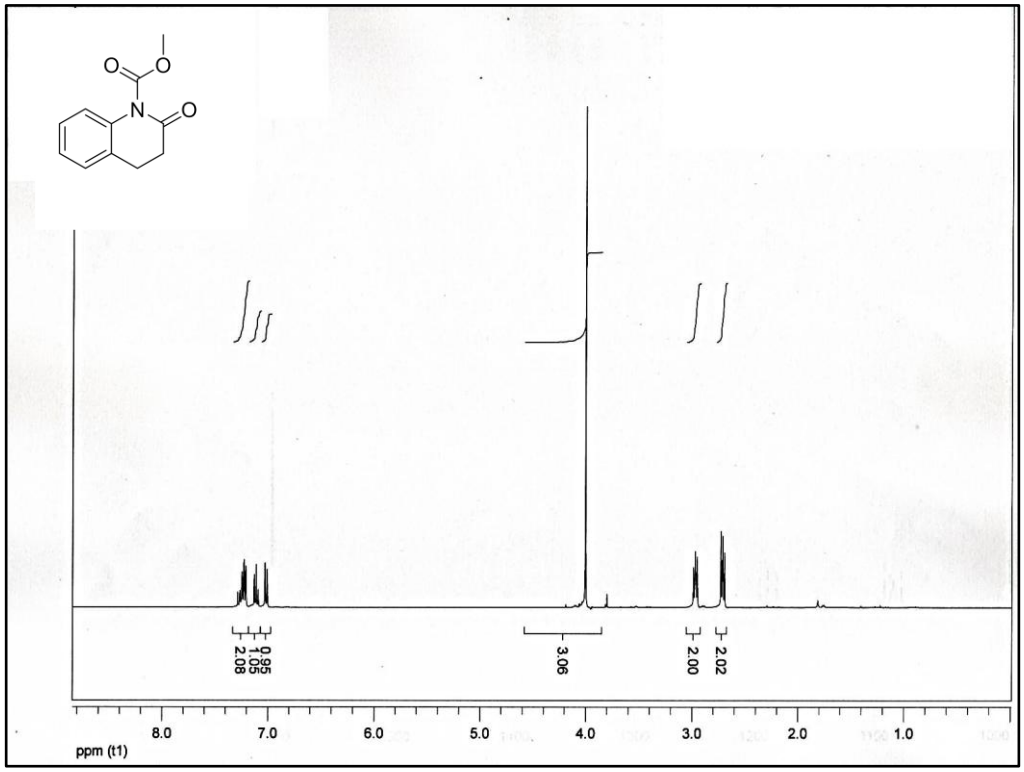

Figure 132 ^{1}H-NMR Spectrum of Compound **201**

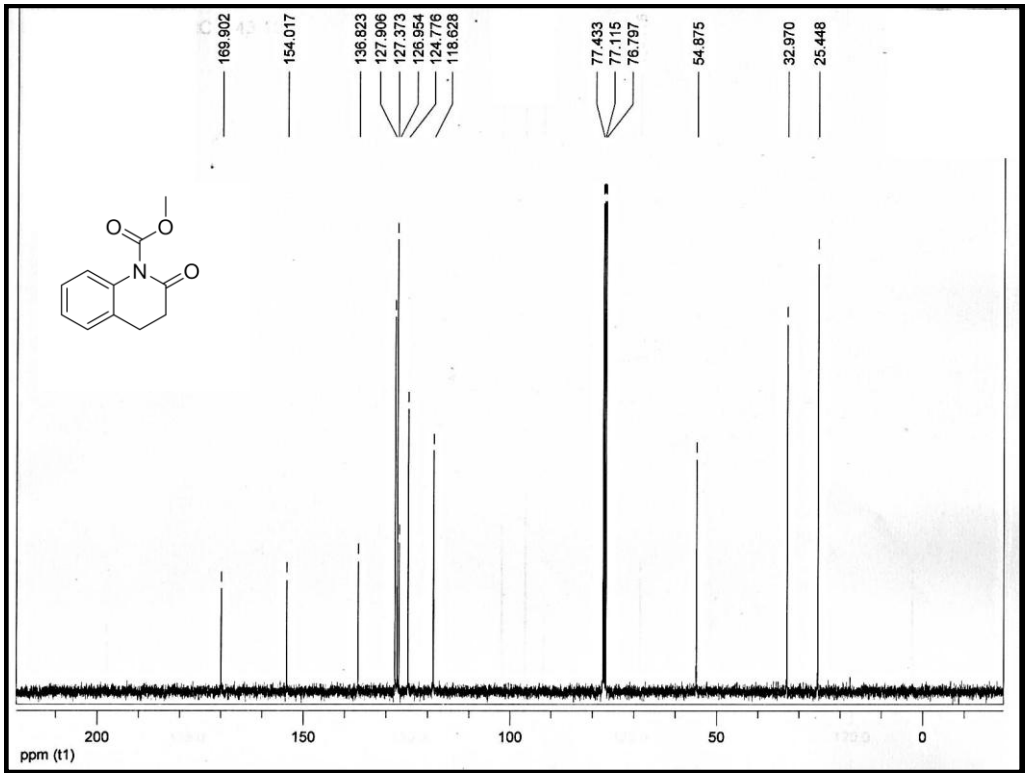

Figure 133 ^{13}C-NMR Spectrum of Compound **201**

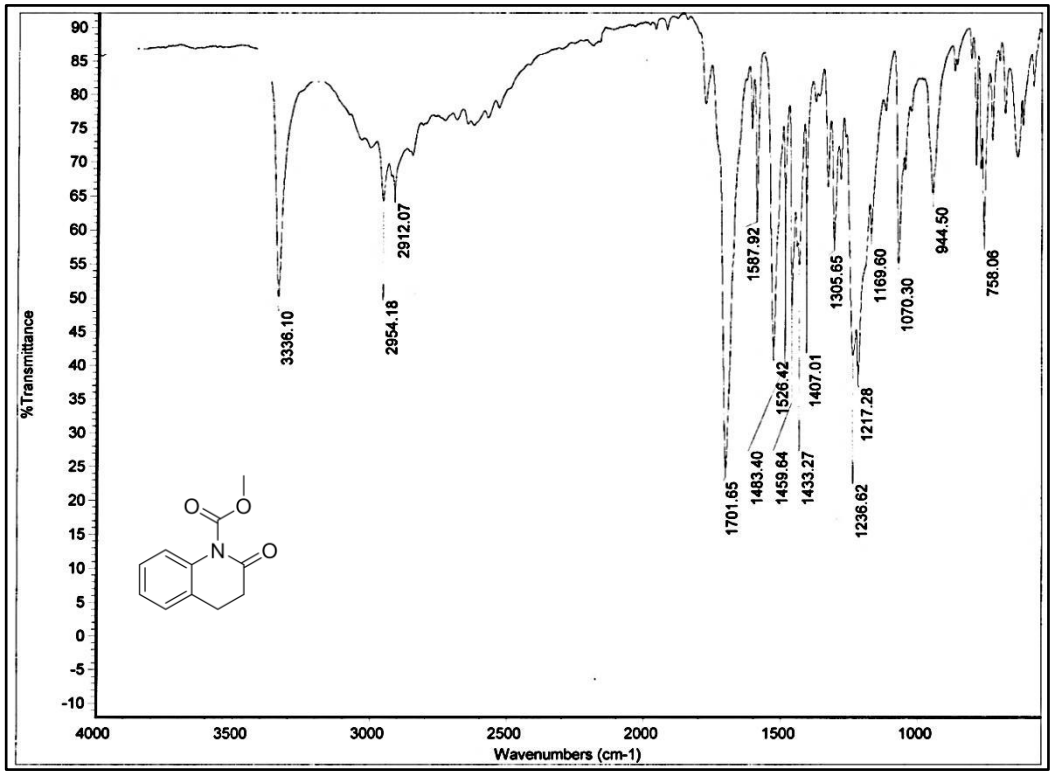

Figure 134 IR Spectrum of Compound **201**

Figure 135 ^{1}H-NMR Spectrum of Compound **183**

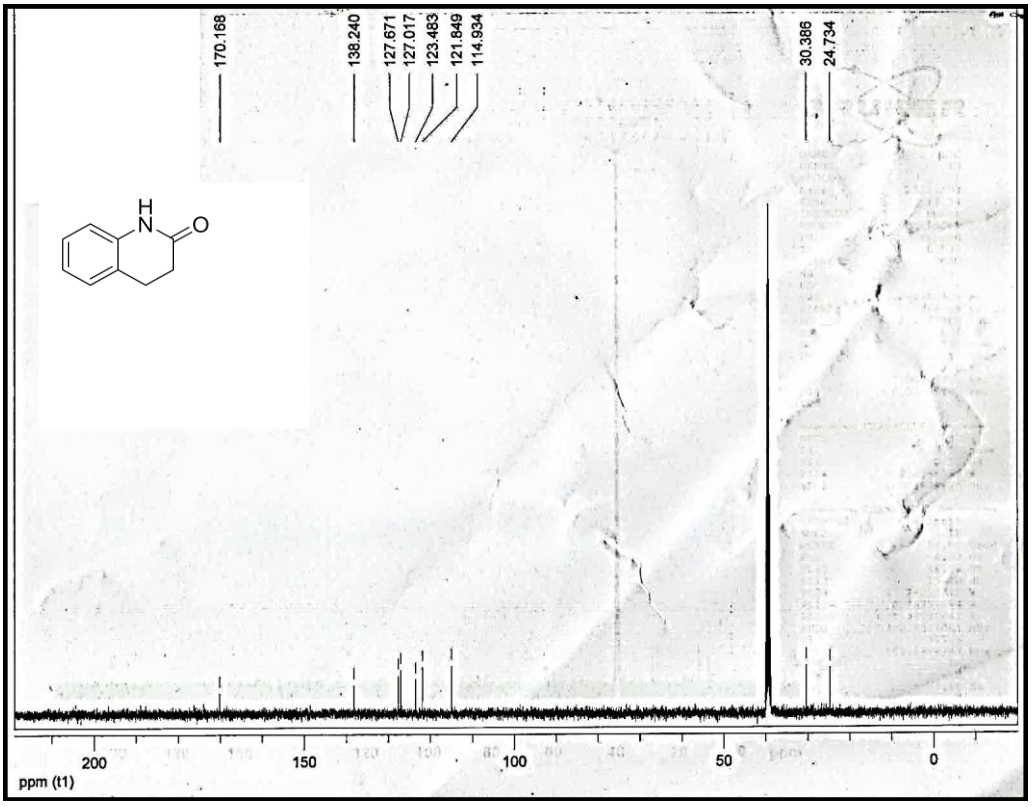

Figure 136 ^{13}C-NMR Spectrum of Compound **183**

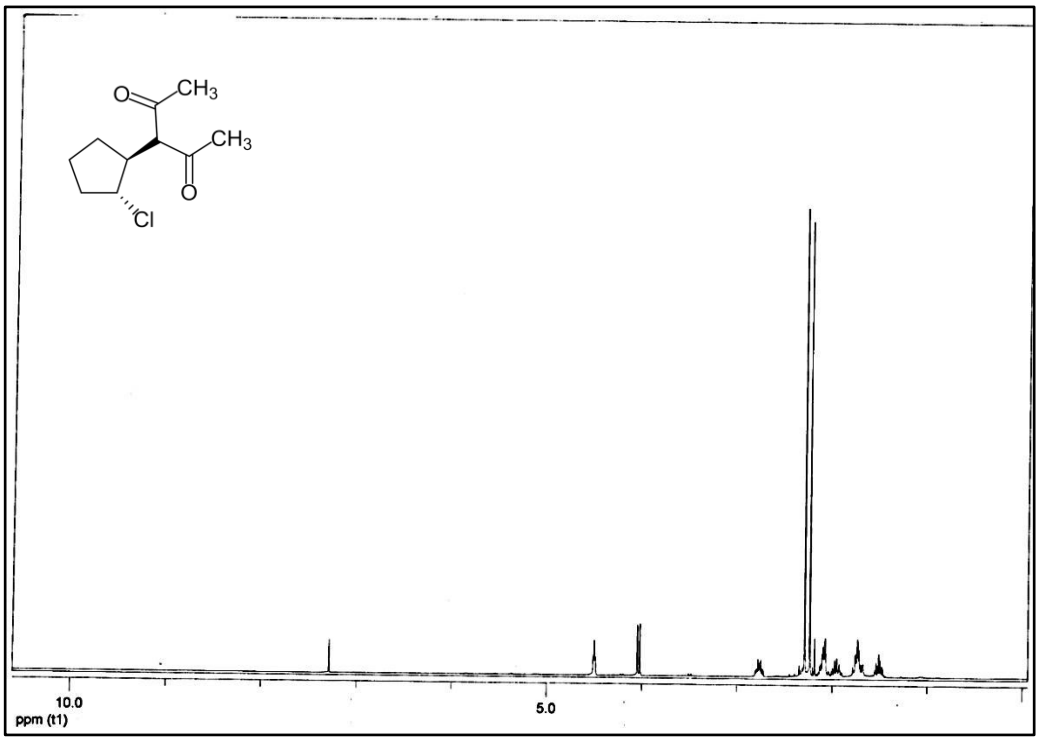

Figure 137 ^{1}H-NMR Spectrum of Compound **208**

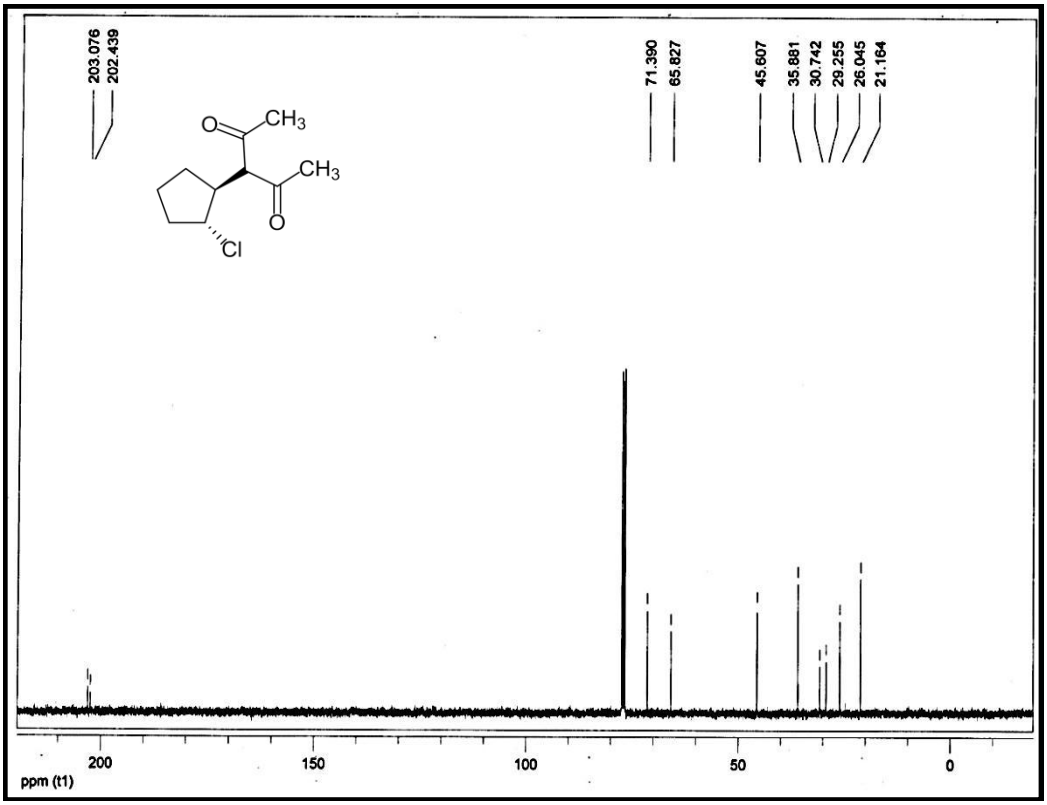

Figure 138 ^{13}C-NMR Spectrum of Compound **208**

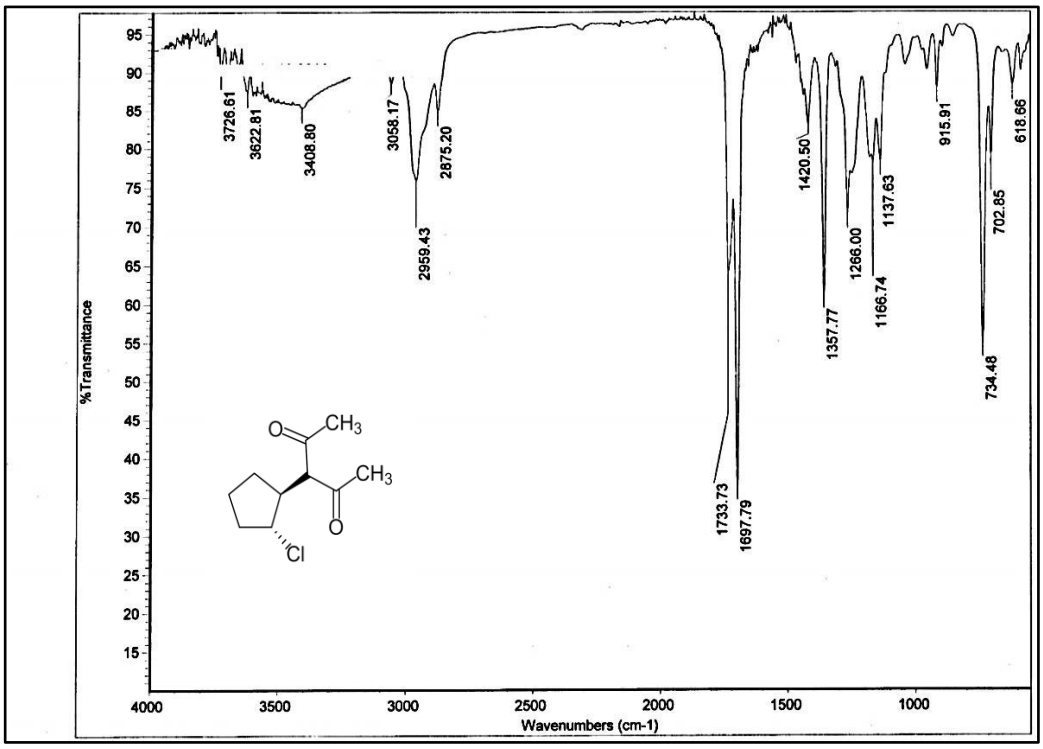

Figure 139 IR Spectrum of Compound **208**

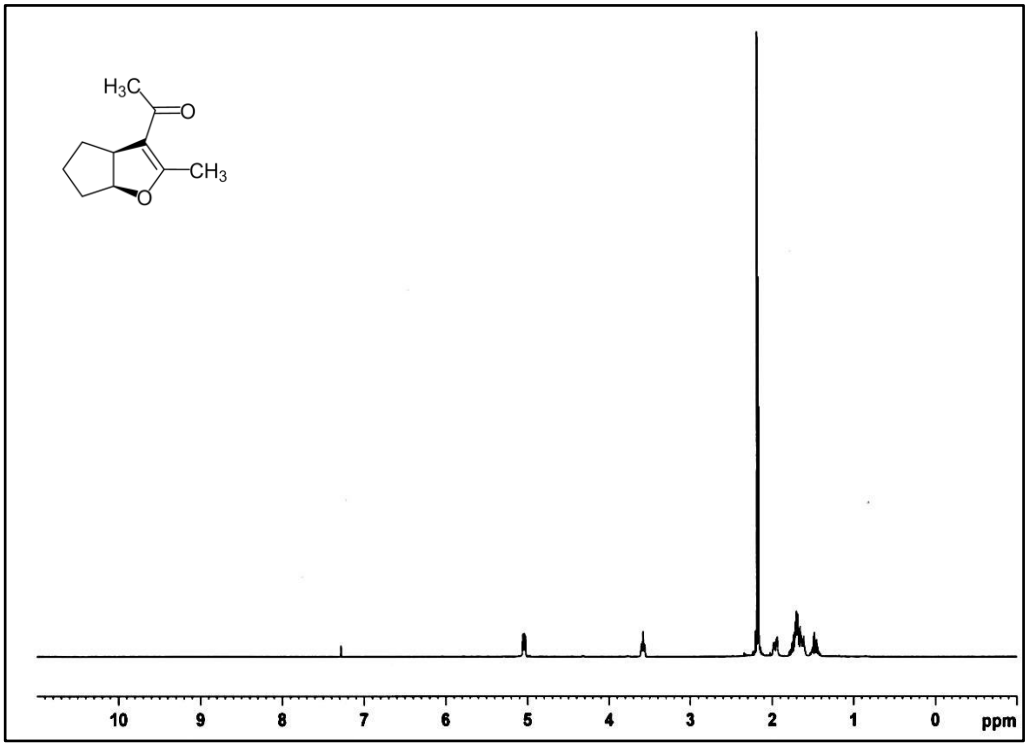

Figure 140 [1]H-NMR Spectrum of Compound **209**

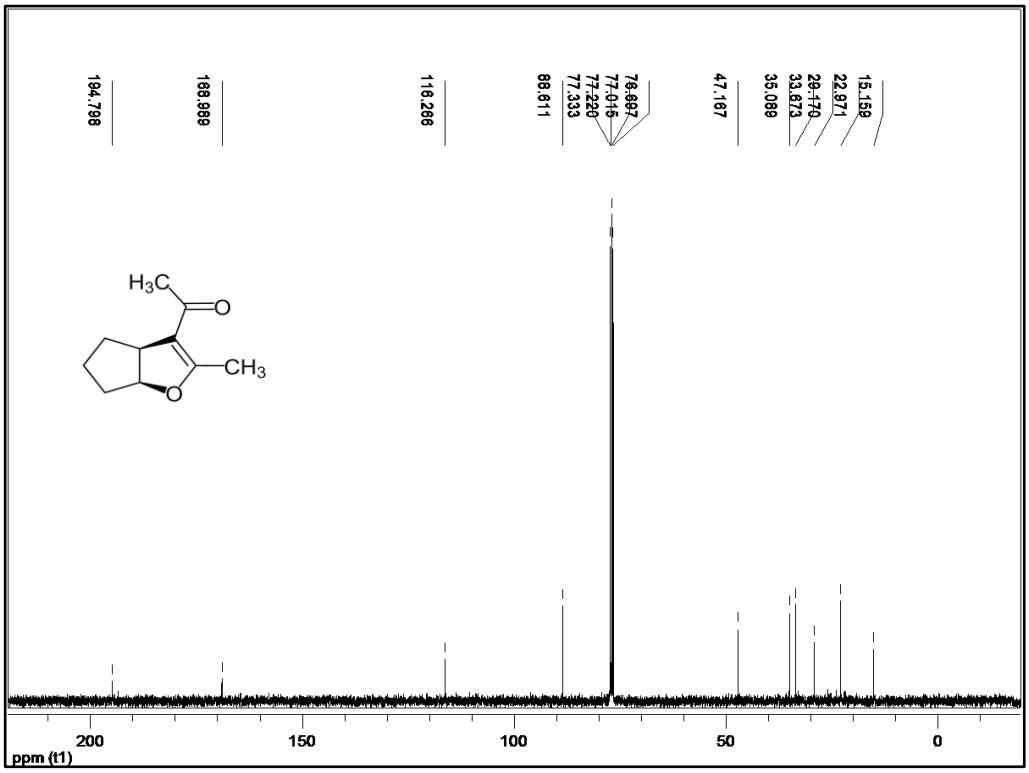

Figure 141 [13]C-NMR Spectrum of Compound **209**

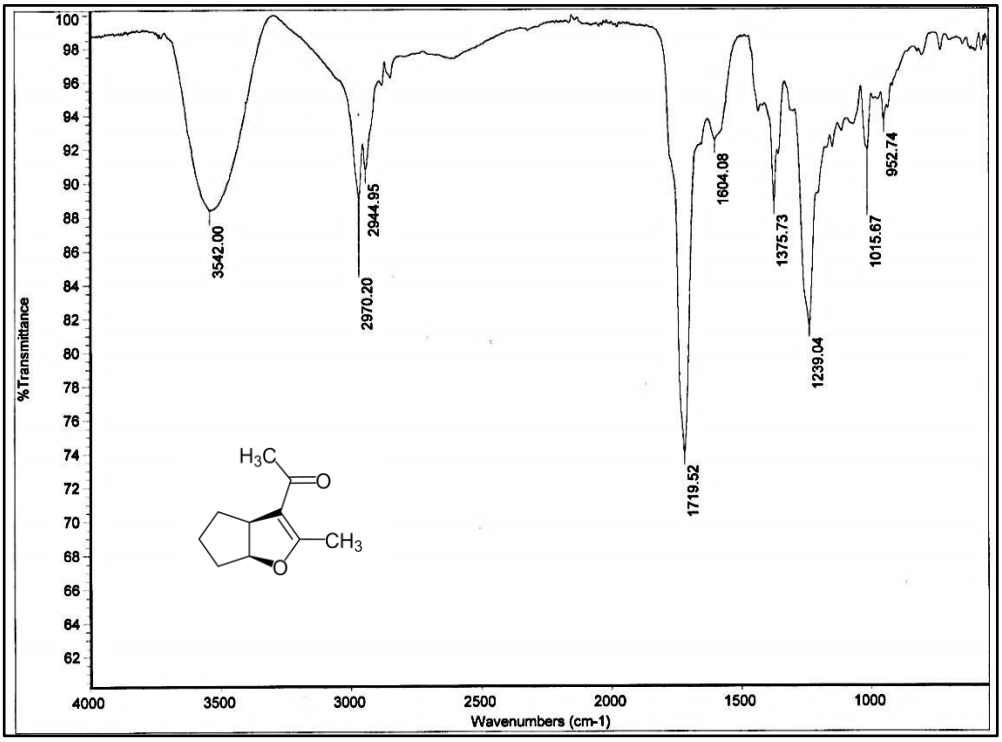

Figure 142 IR Spectrum of Compound **209**

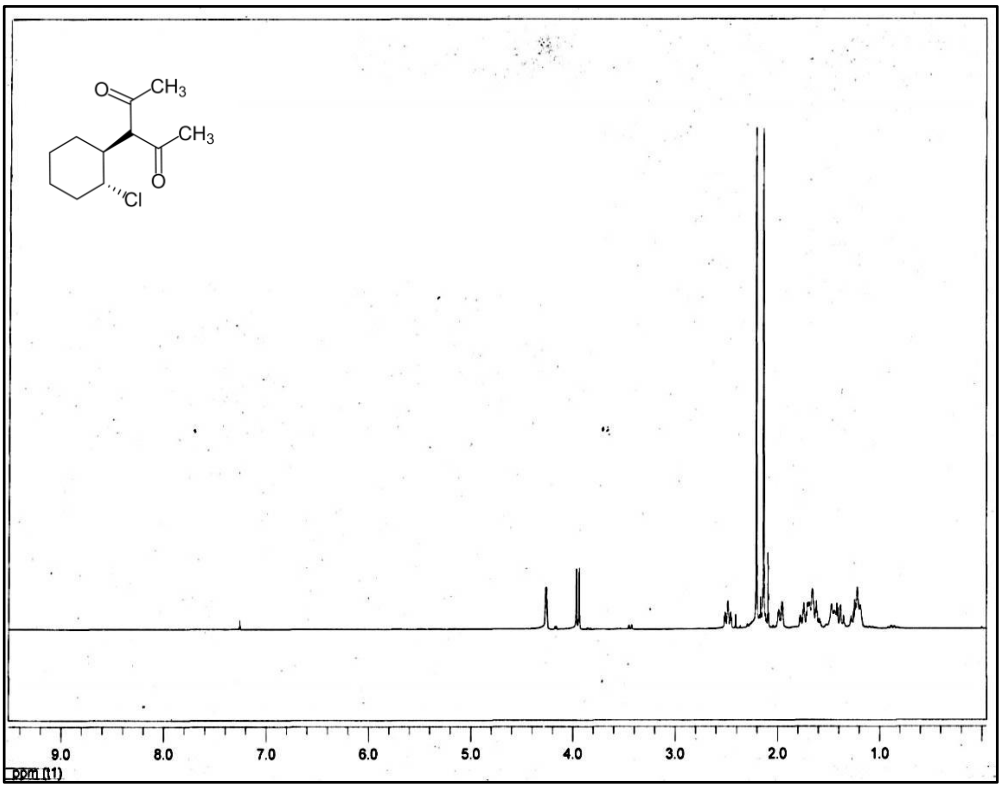

Figure 143 ^{1}H-NMR Spectrum of Compound **211**

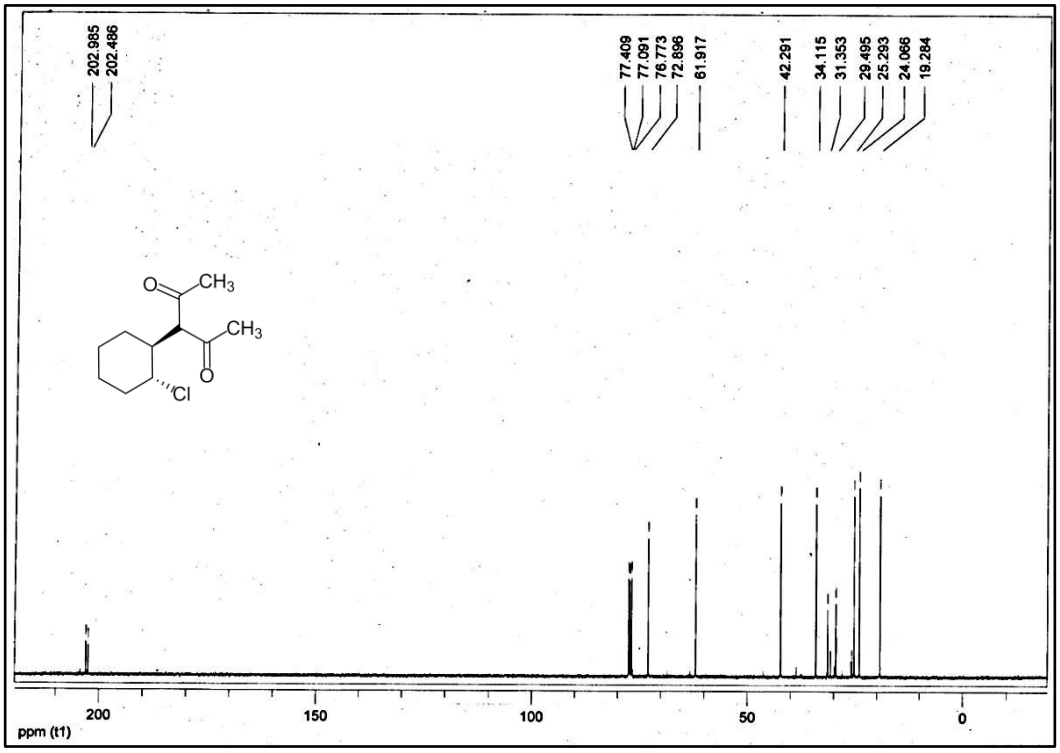

Figure 144 ^{13}C-NMR Spectrum of Compound **211**

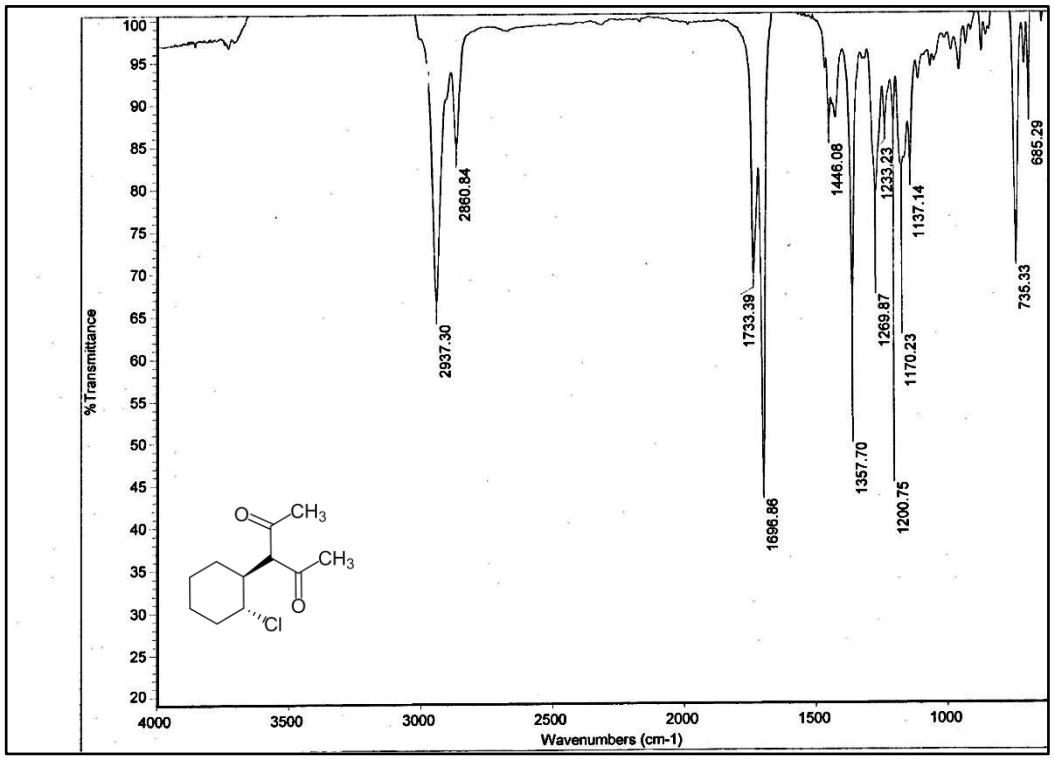

Figure 145 IR Spectrum of Compound **211**

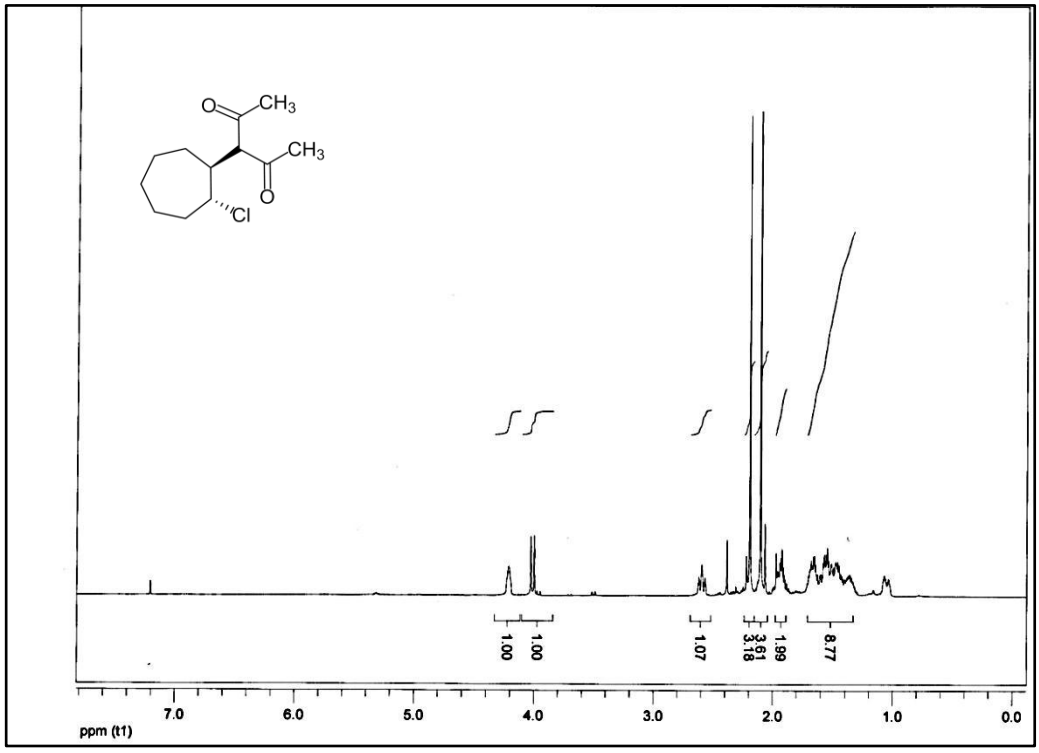

Figure 146 ^{1}H-NMR Spectrum of Compound **213**

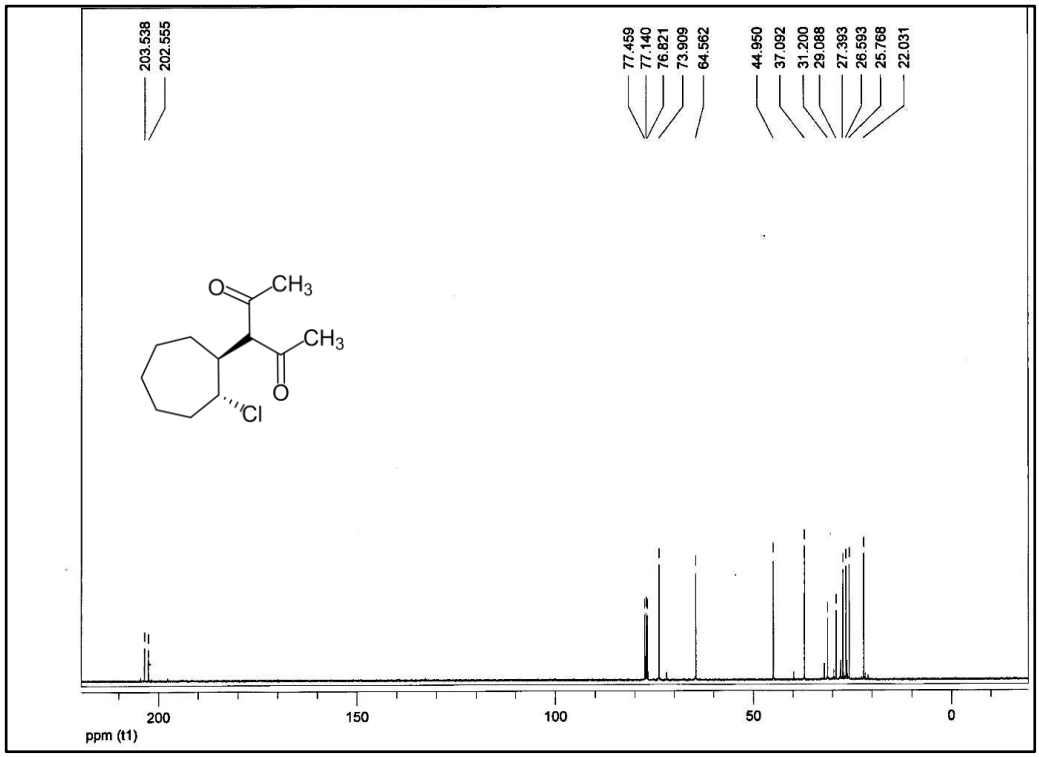

Figure 147 ^{13}C-NMR Spectrum of Compound **213**

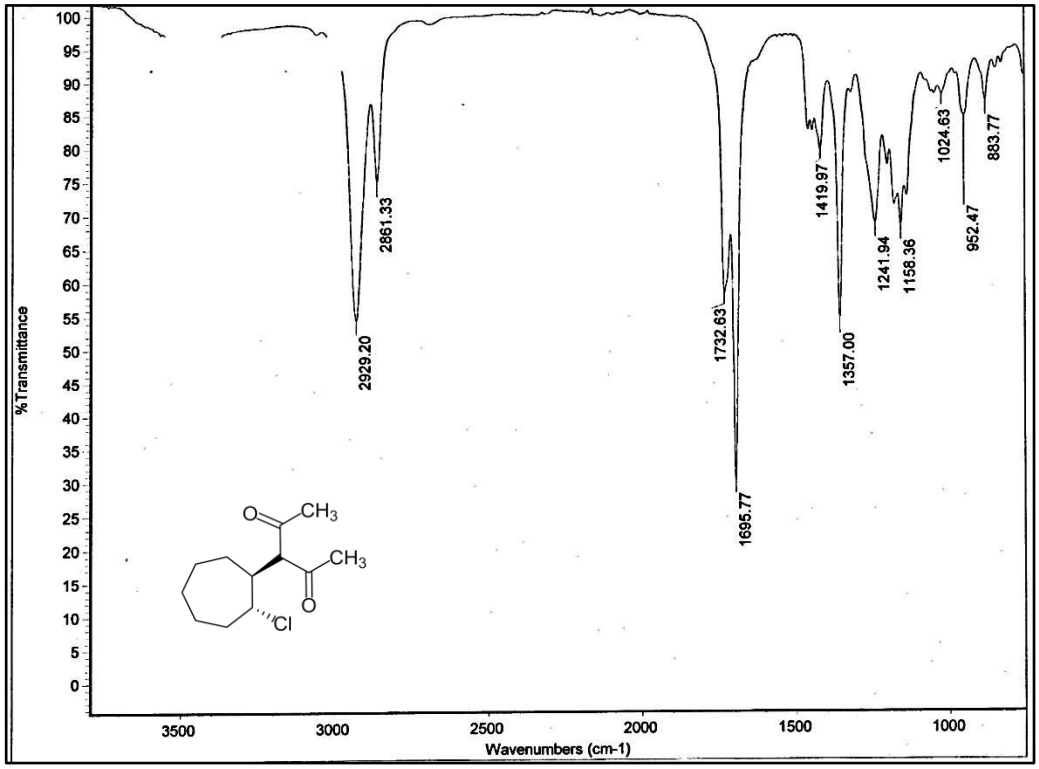

Figure 148 IR Spectrum of Compound **213**

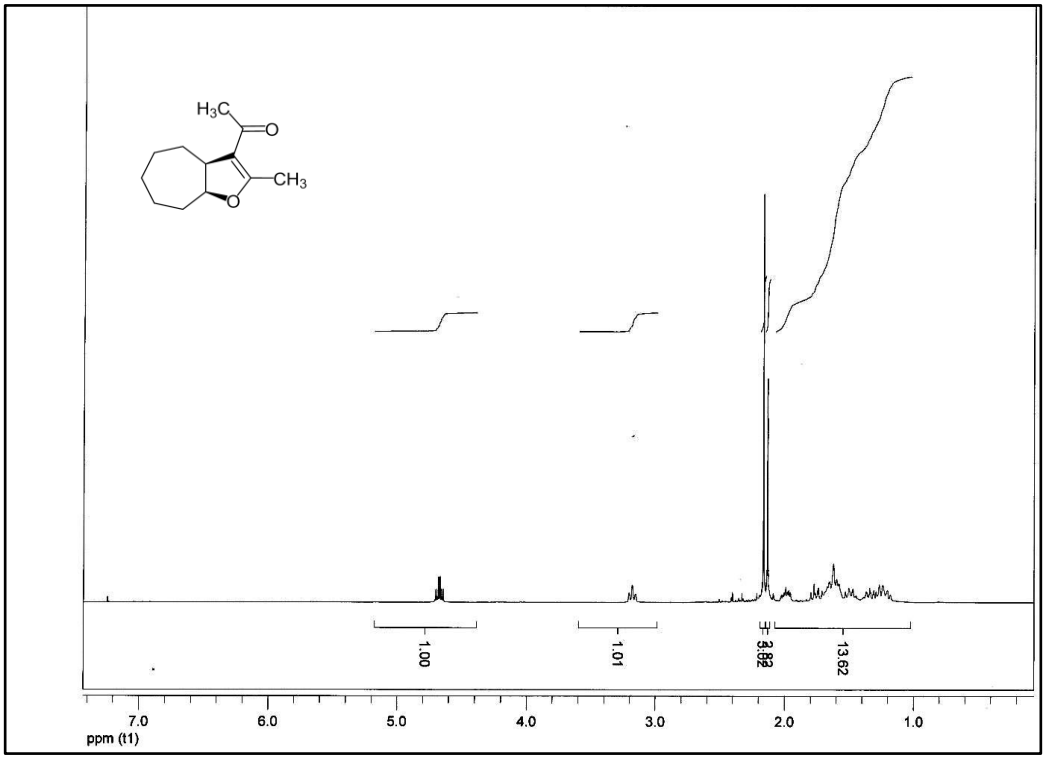

Figure 149 ^{1}H-NMR Spectrum of Compound **214**

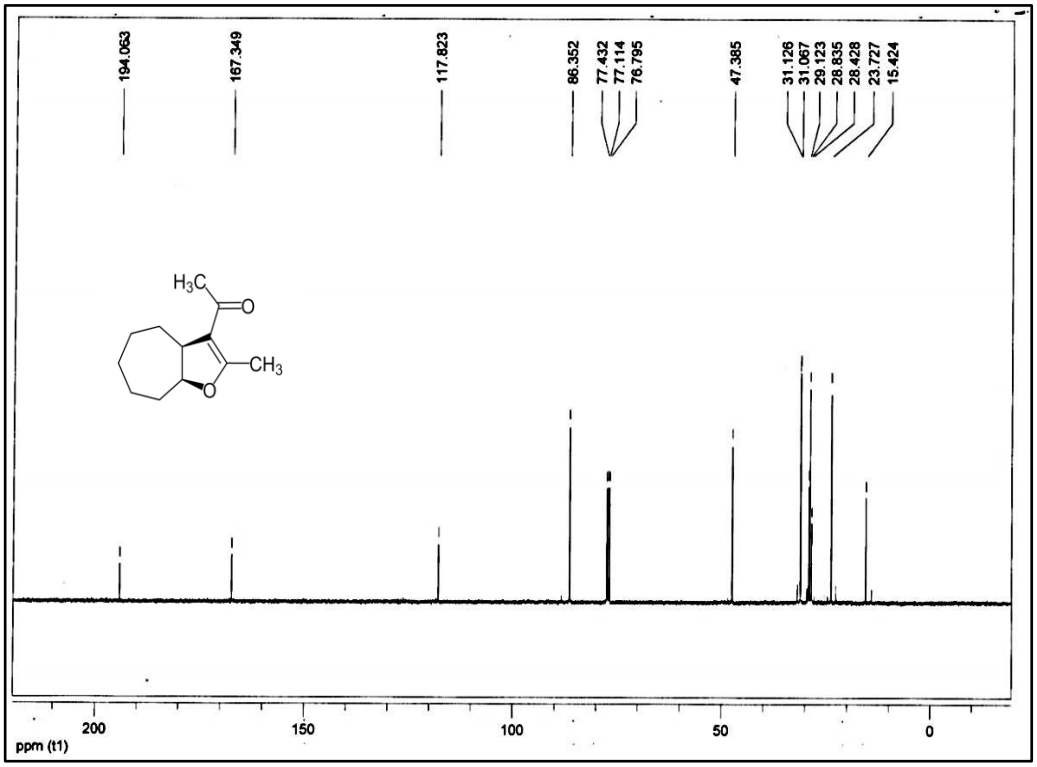

Figure 150 ^{13}C-NMR Spectrum of Compound **214**

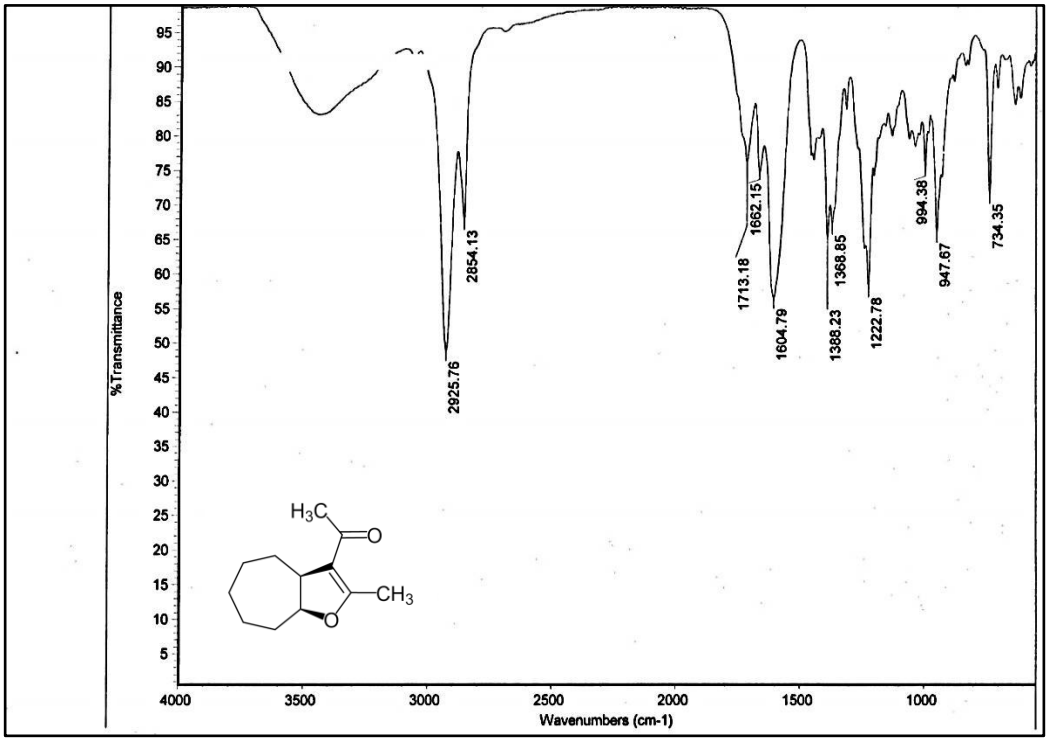

Figure 151 IR Spectrum of Compound **214**

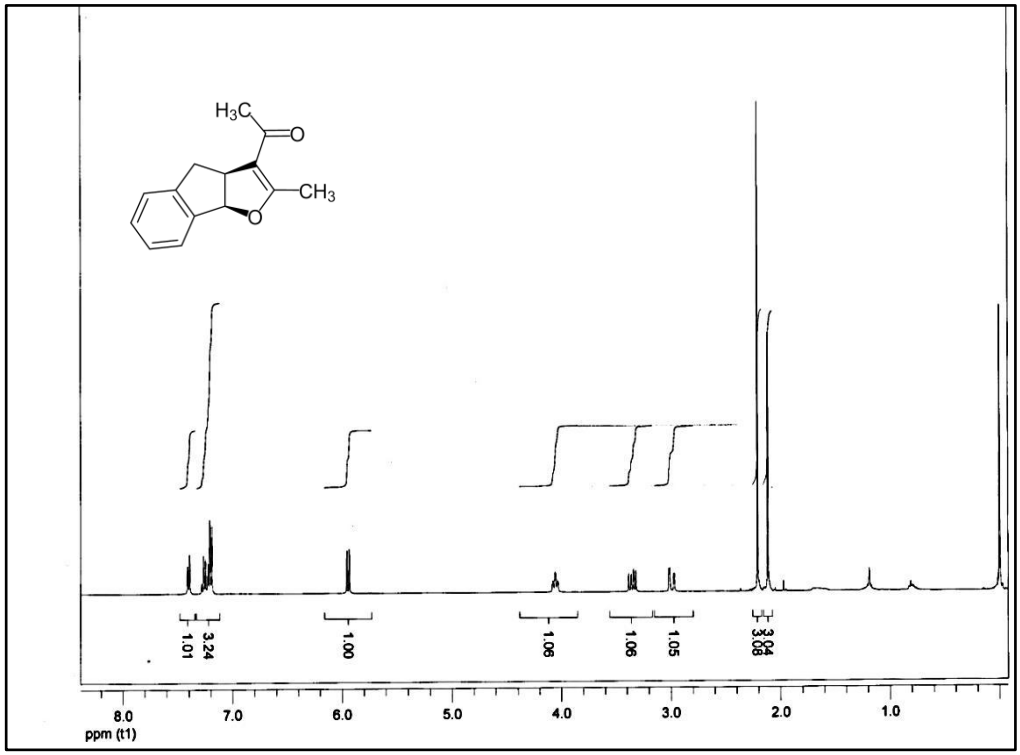

Figure 152 ^{1}H-NMR Spectrum of Compound **216**

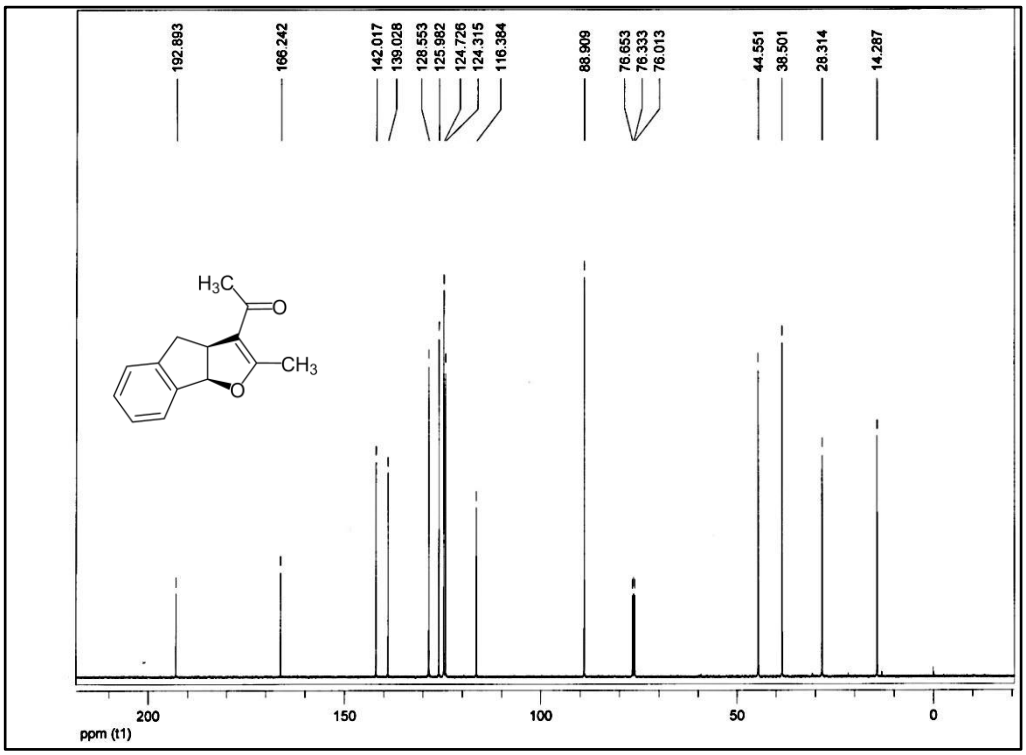

Figure 153 ^{13}C-NMR Spectrum of Compound **216**

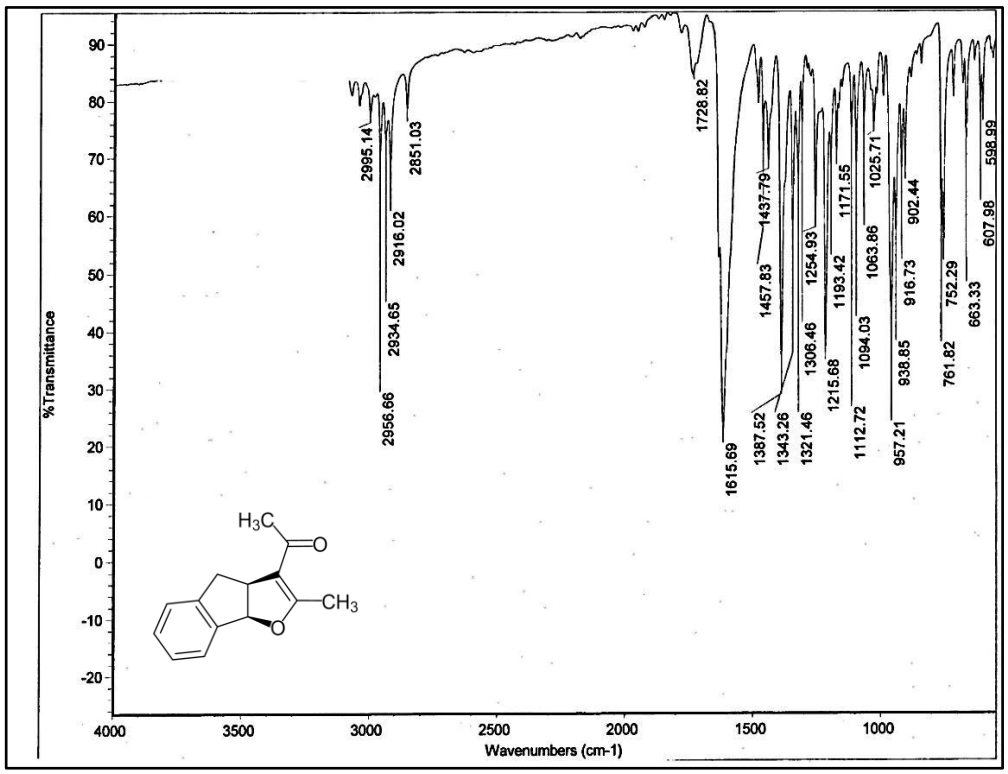

Figure 154 IR Spectrum of Compound **216**

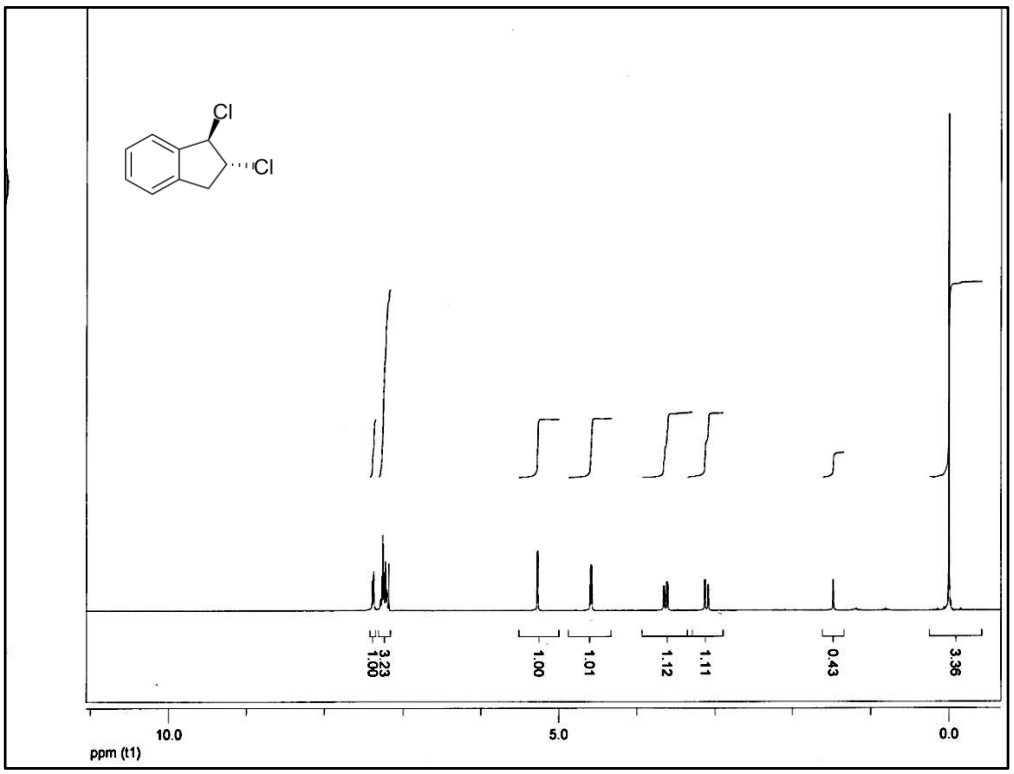

Figure 155 ^{1}H-NMR Spectrum of Compound **217**

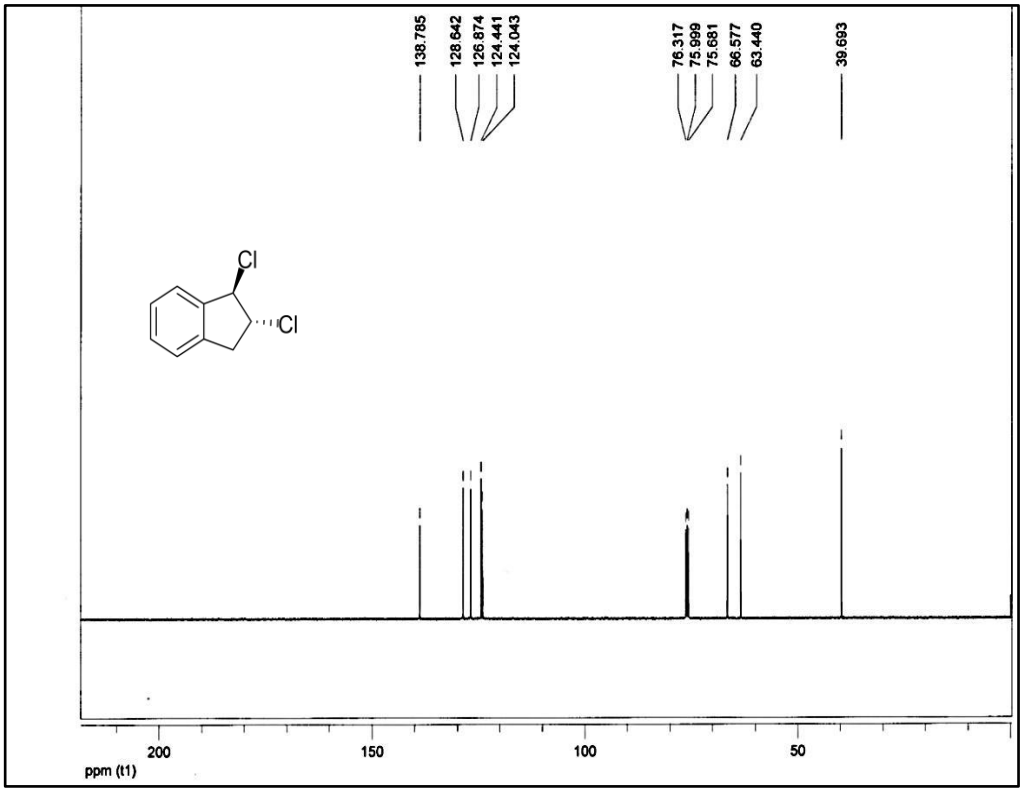

Figure 156 ^{13}C-NMR Spectrum of Compound **217**

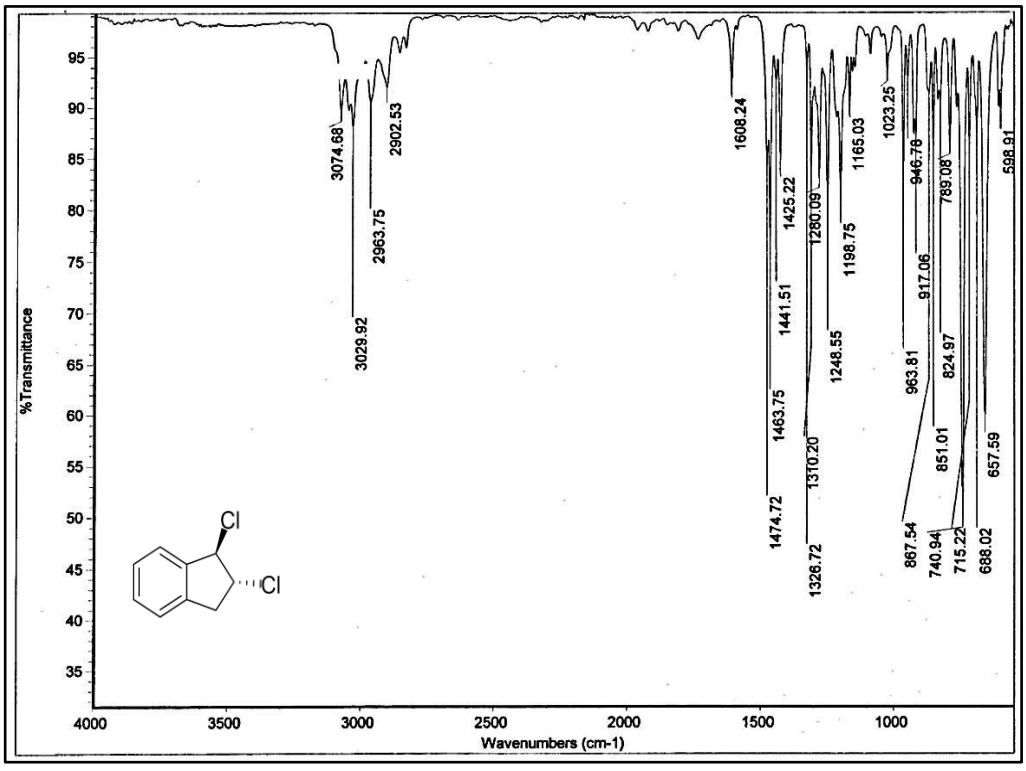

Figure 157 IR Spectrum of Compound **217**

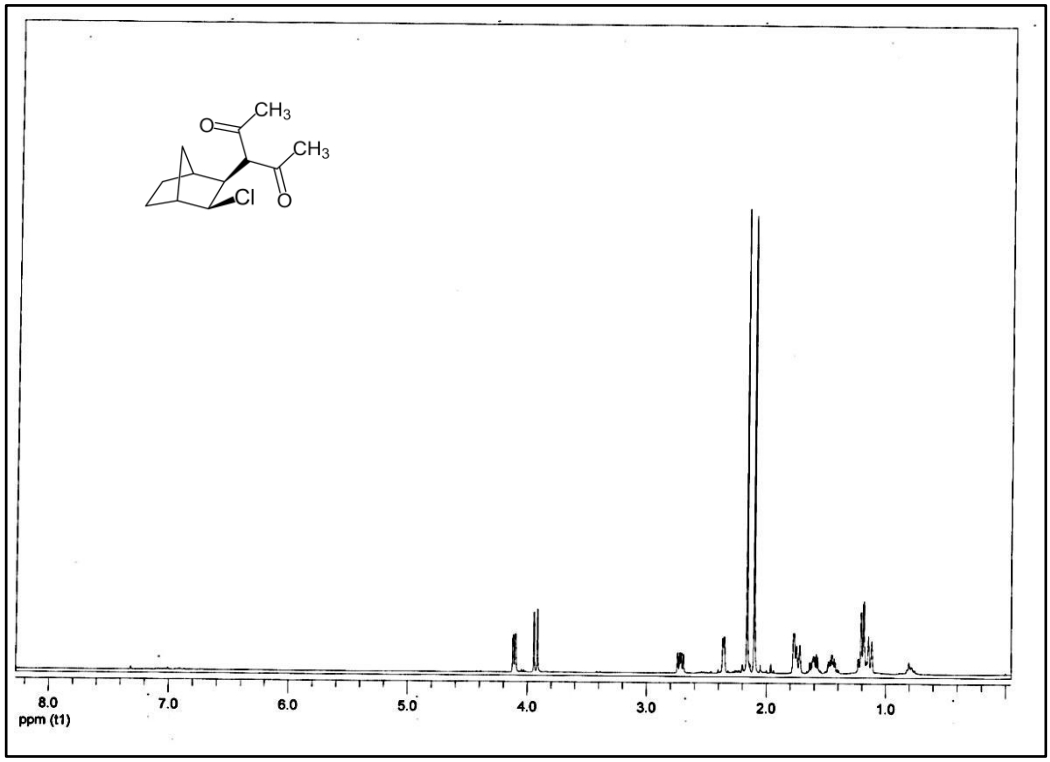

Figure 158 ^{1}H-NMR Spectrum of Compound **218**

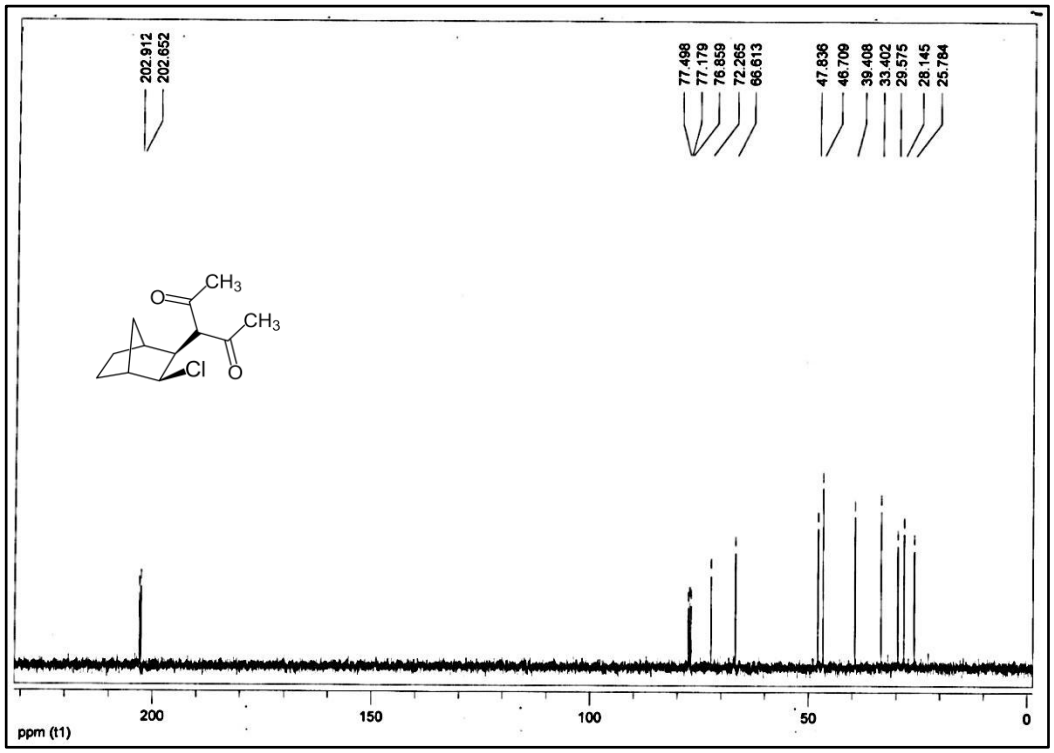

Figure 159 ^{13}C-NMR Spectrum of Compound **218**

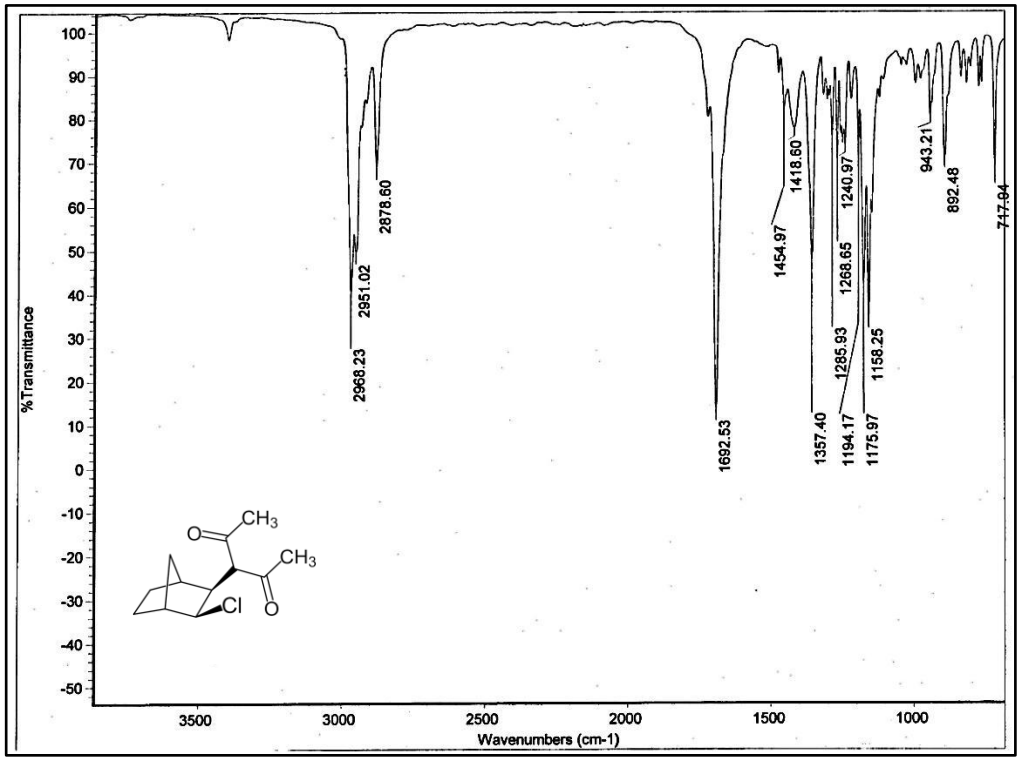

Figure 160 IR Spectrum of Compound **218**

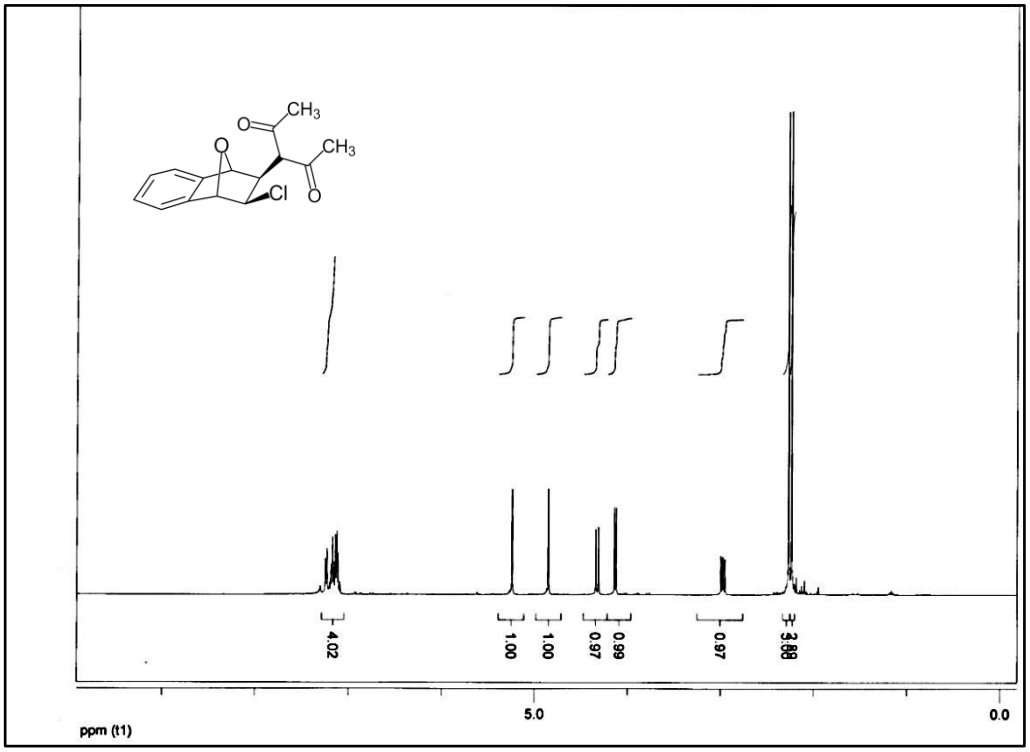

Figure 161 ^{1}H-NMR Spectrum of Compound **220**

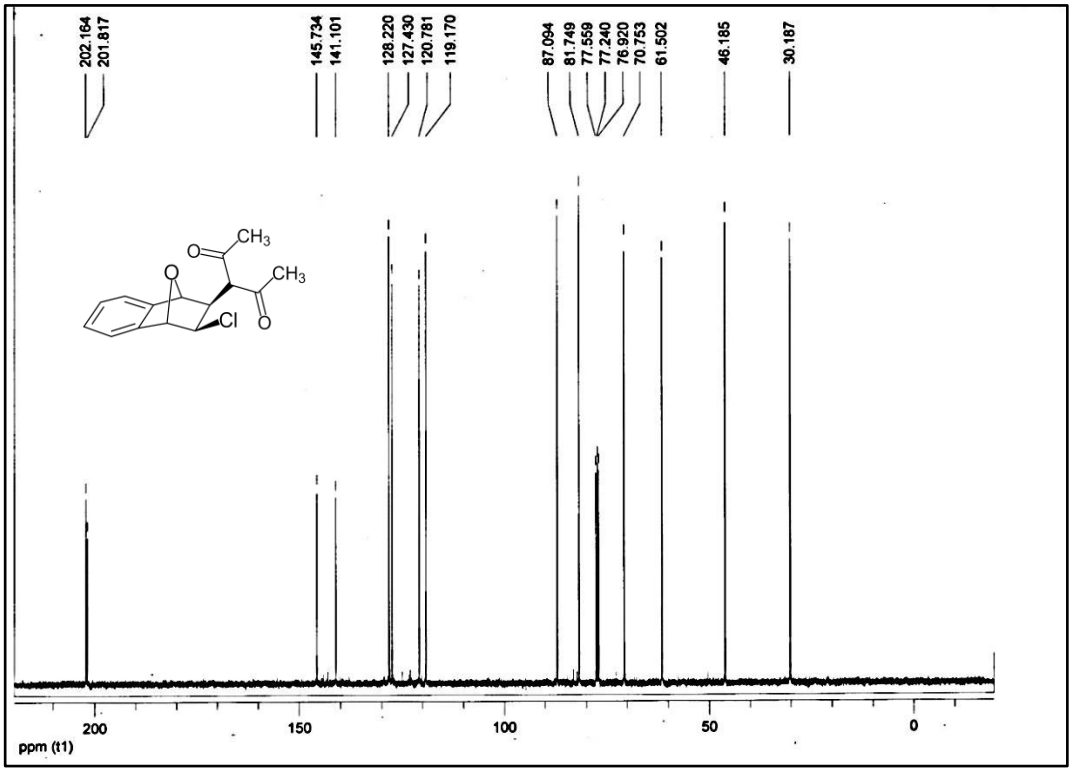

Figure 162 ^{13}C-NMR Spectrum of Compound **220**

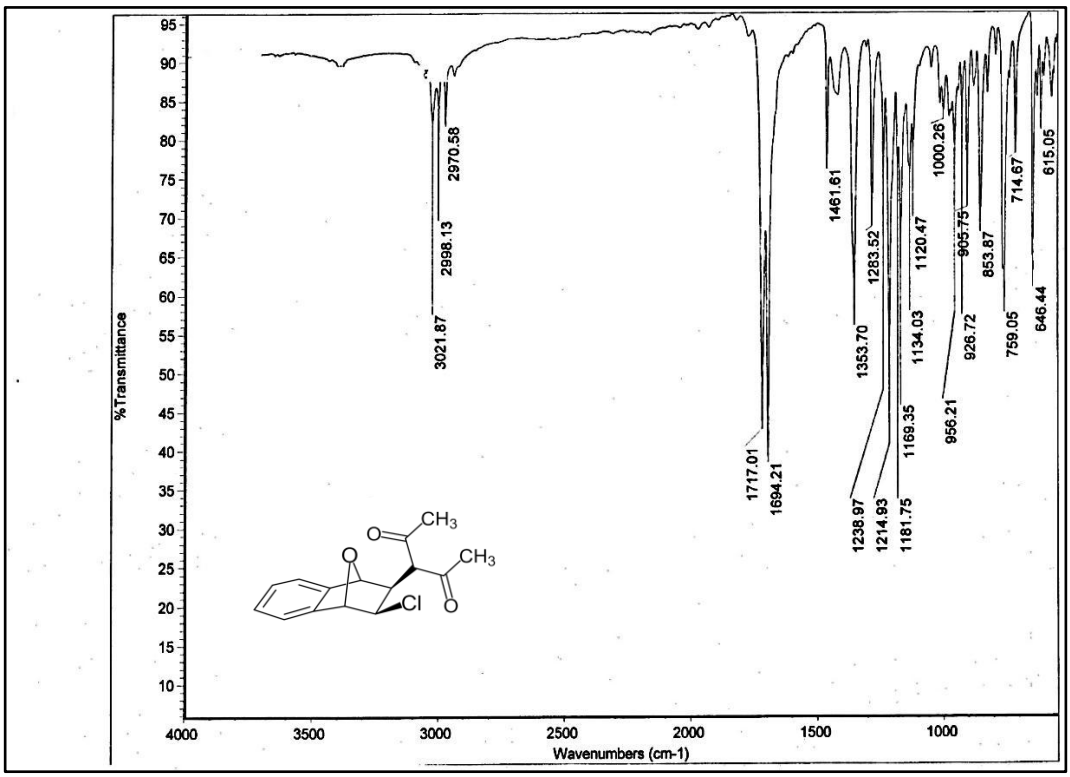

Figure 163 IR Spectrum of Compound **220**

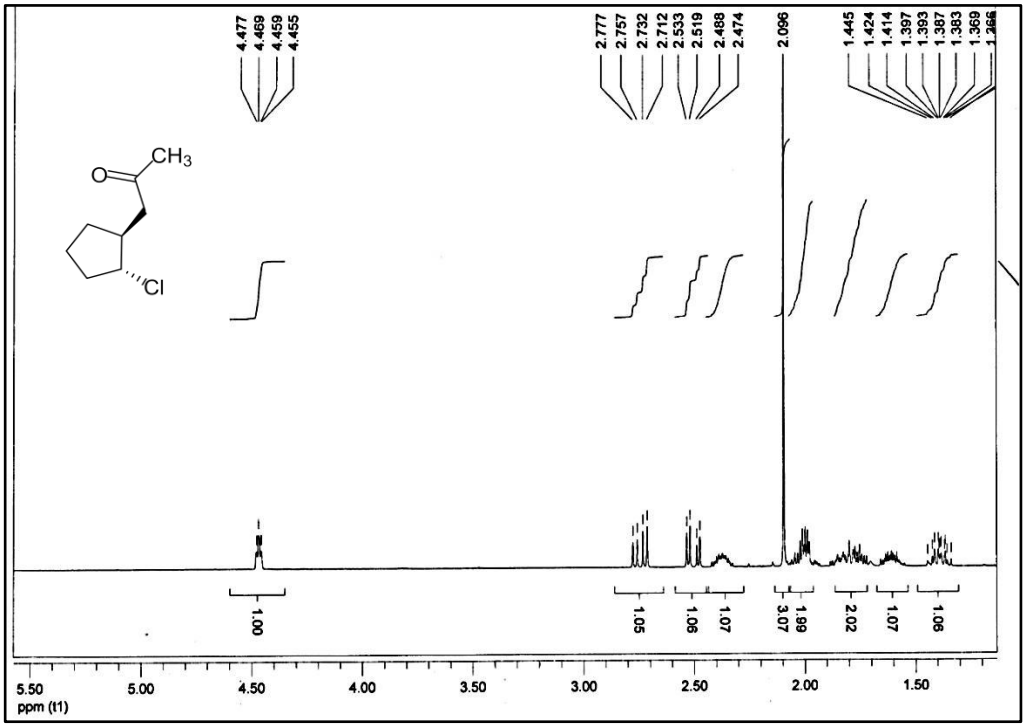

Figure 164 ^{1}H-NMR Spectrum of Compound **210**

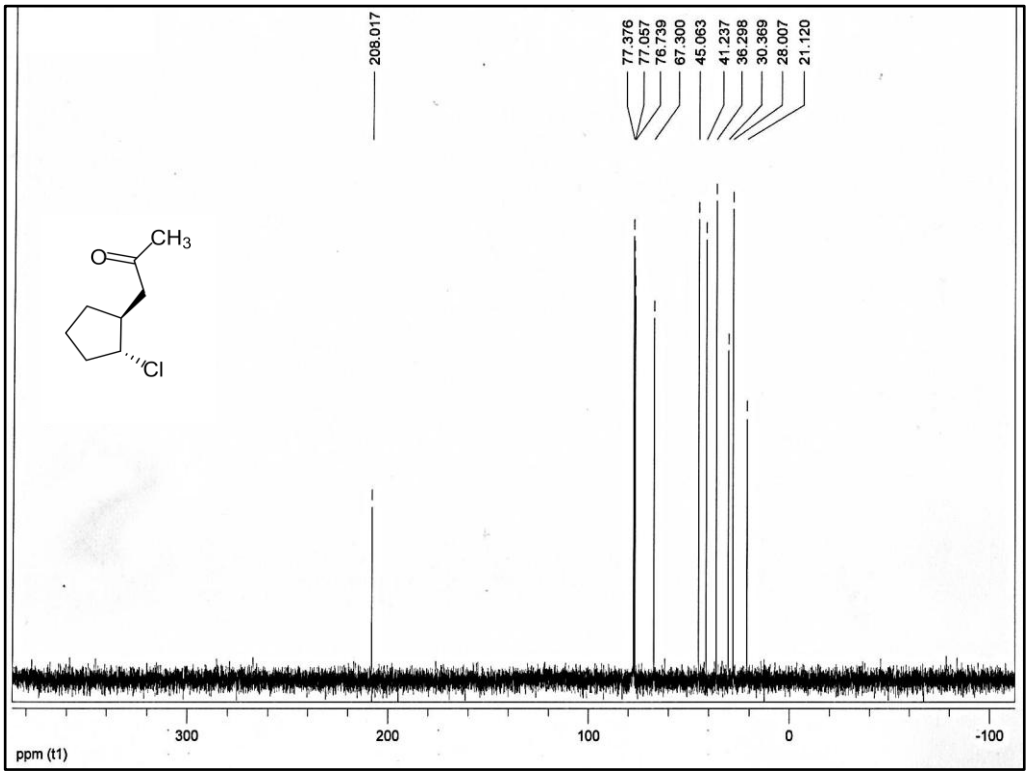

Figure 165 ^{13}C-NMR Spectrum of Compound **210**

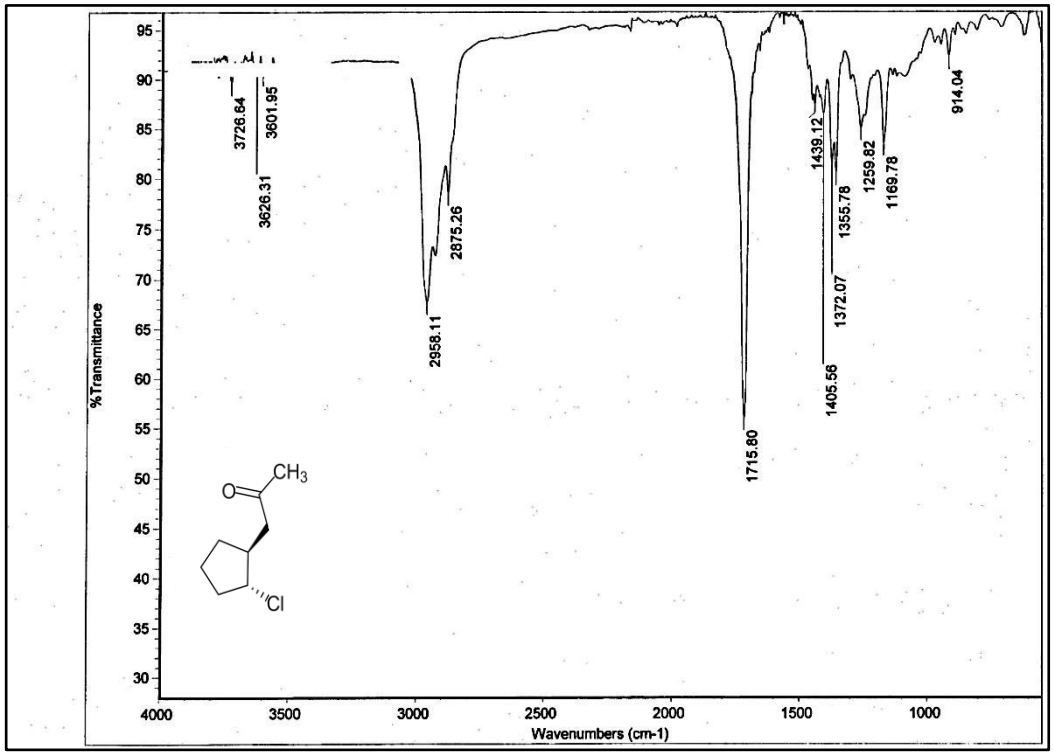

Figure 166 IR Spectrum of Compound **210**

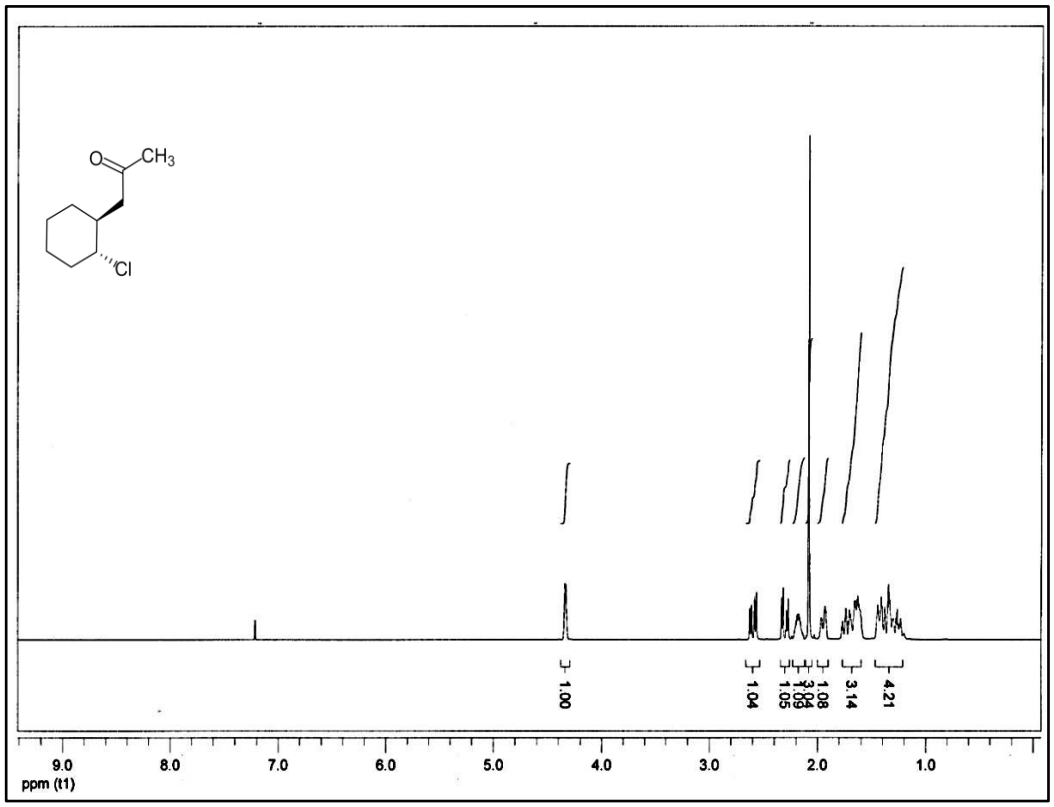

Figure 167 ^{1}H-NMR Spectrum of Compound **212**

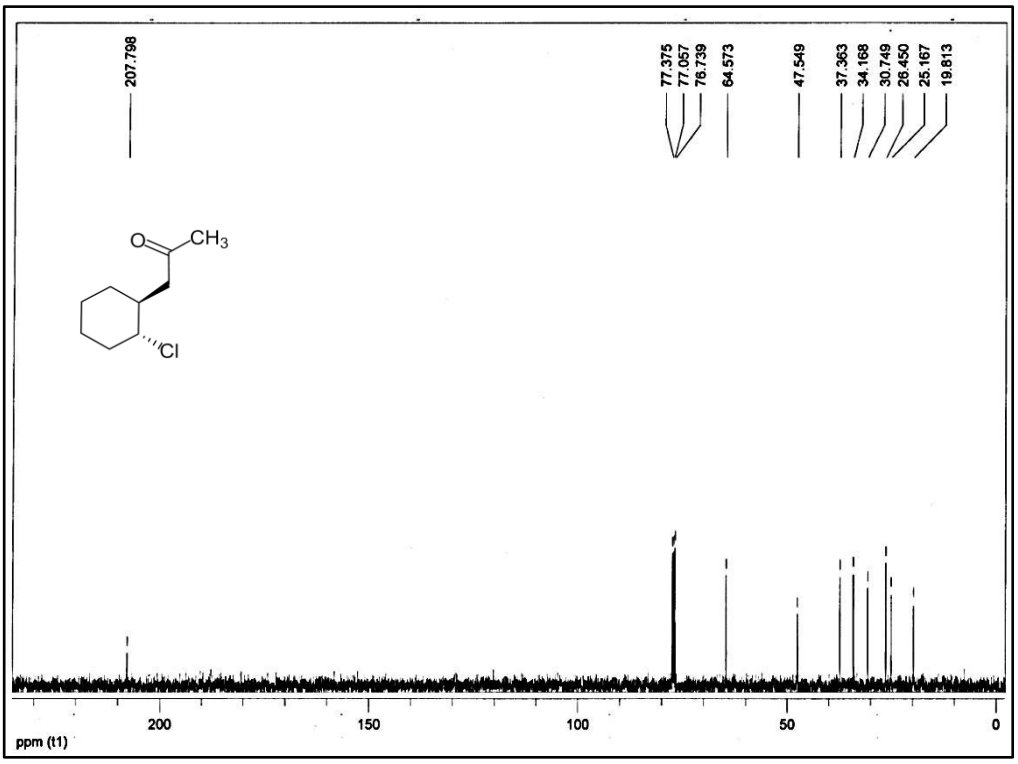

Figure 168 ^{13}C-NMR Spectrum of Compound **212**

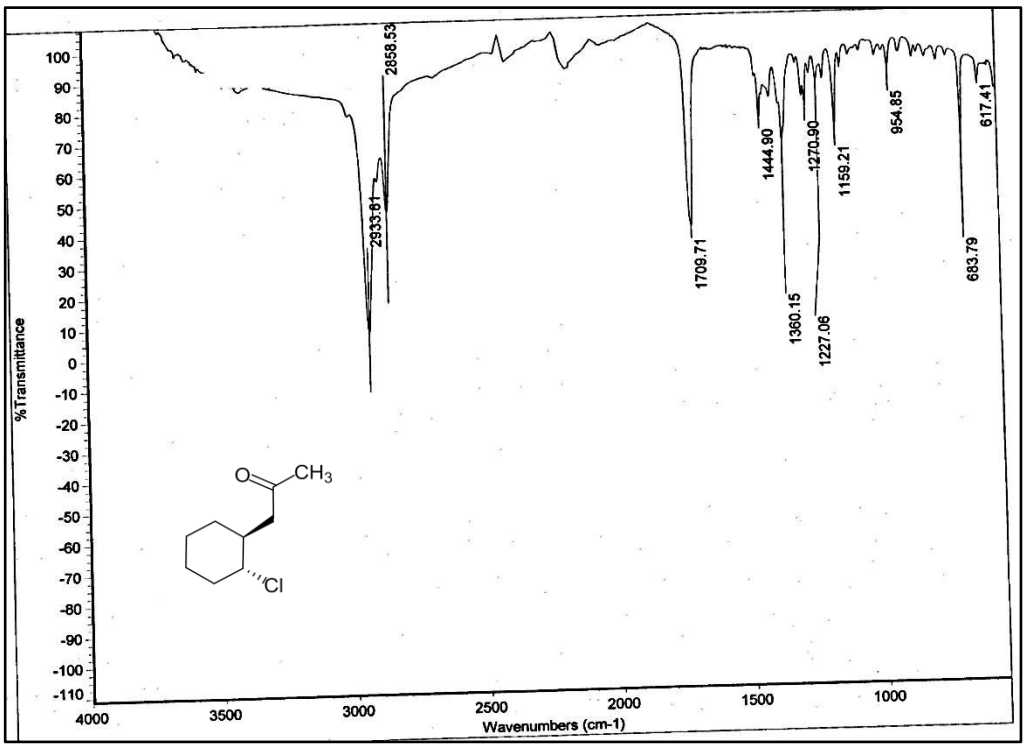

Figure 169 IR Spectrum of Compound **212**

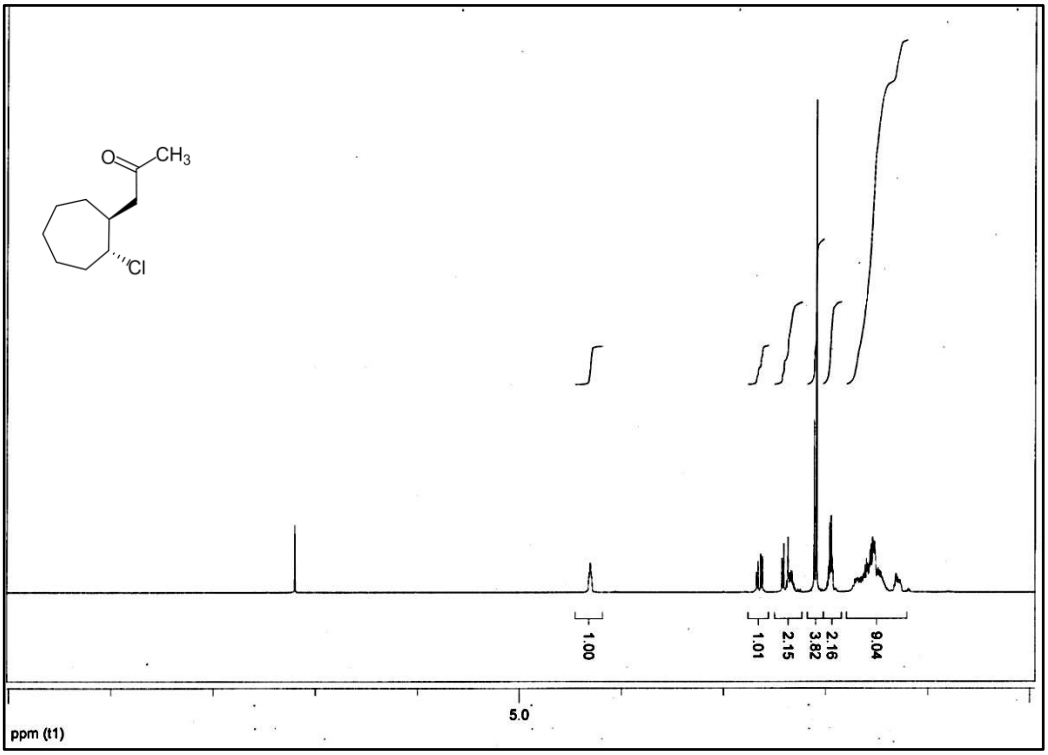

Figure 170 ^{1}H-NMR Spectrum of Compound **215**

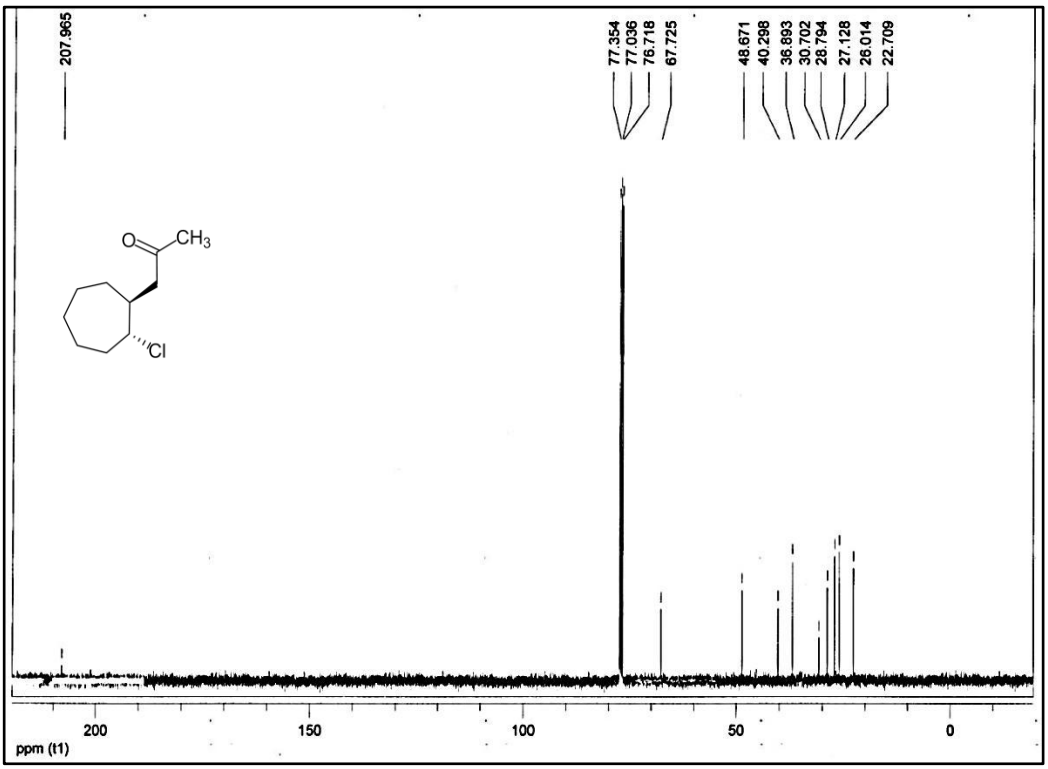

Figure 171 ^{13}C-NMR Spectrum of Compound **215**

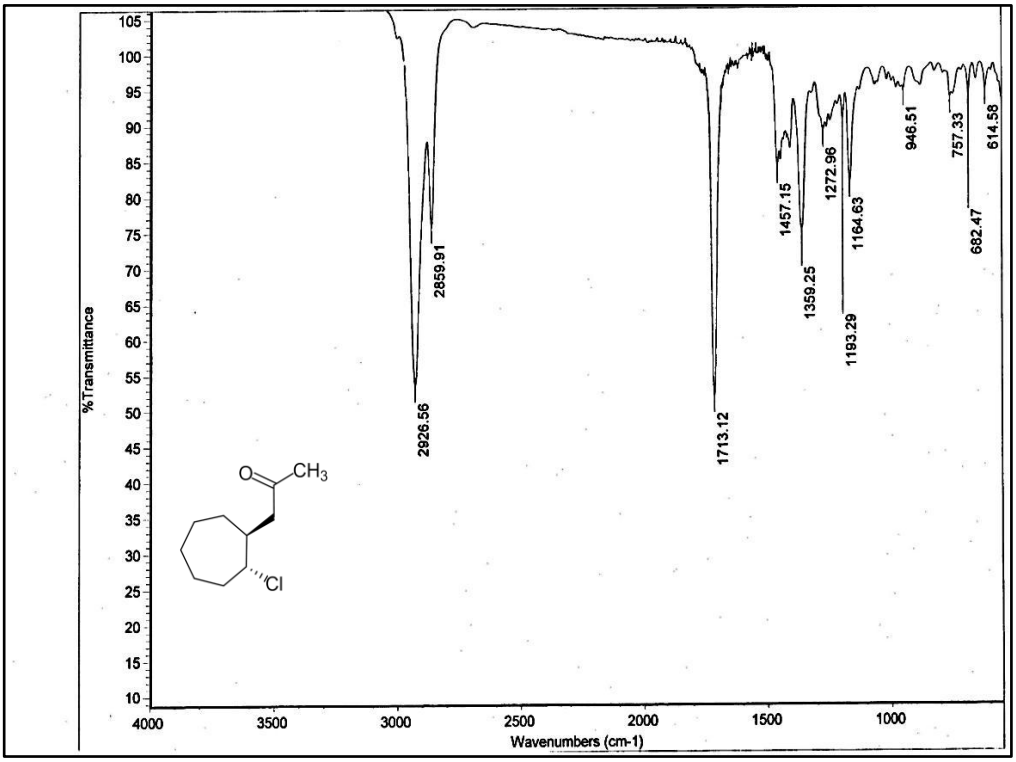

Figure 172 IR Spectrum of Compound **215**

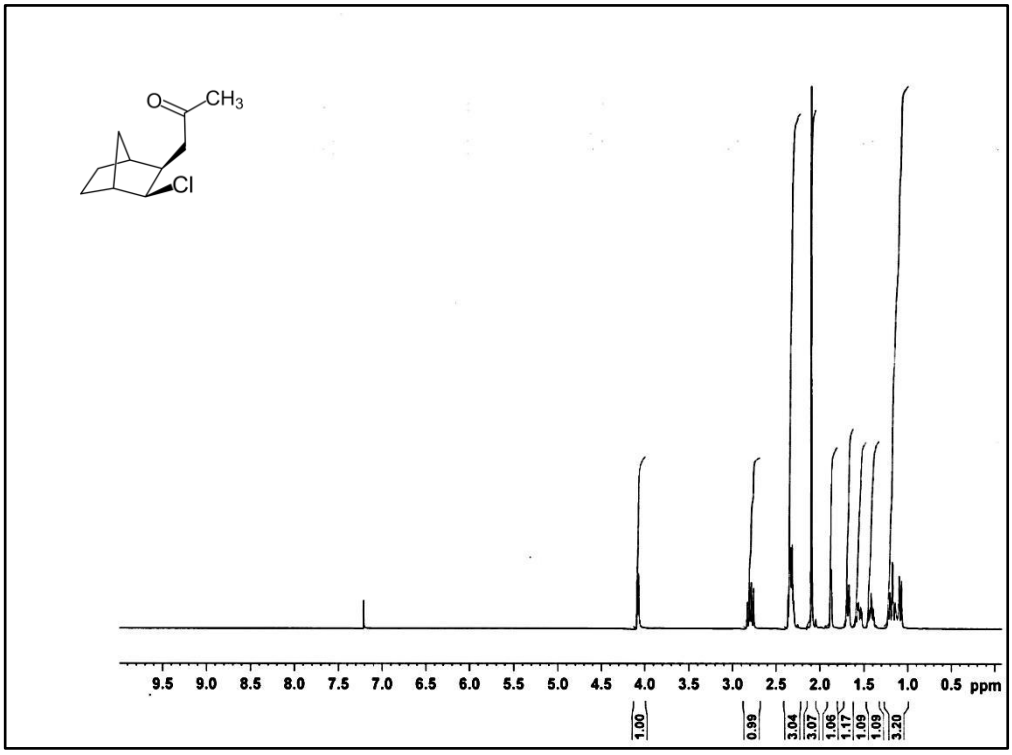

Figure 173 ^{1}H-NMR Spectrum of Compound **219**

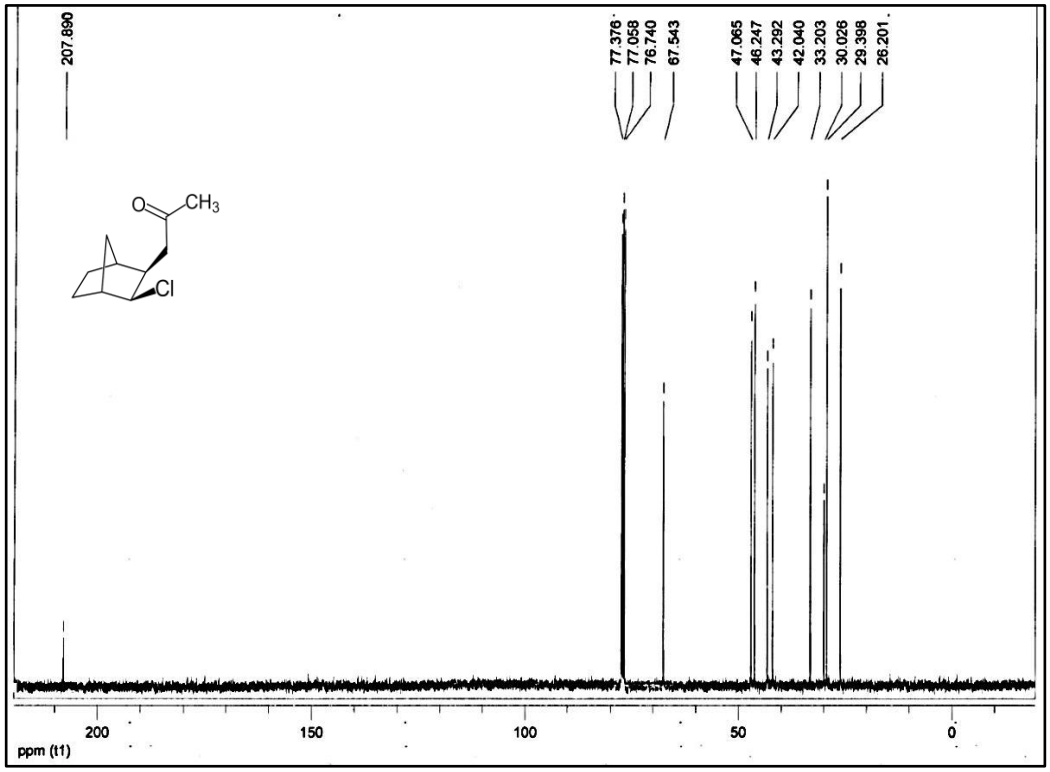

Figure 174 ^{13}C-NMR Spectrum of Compound **219**

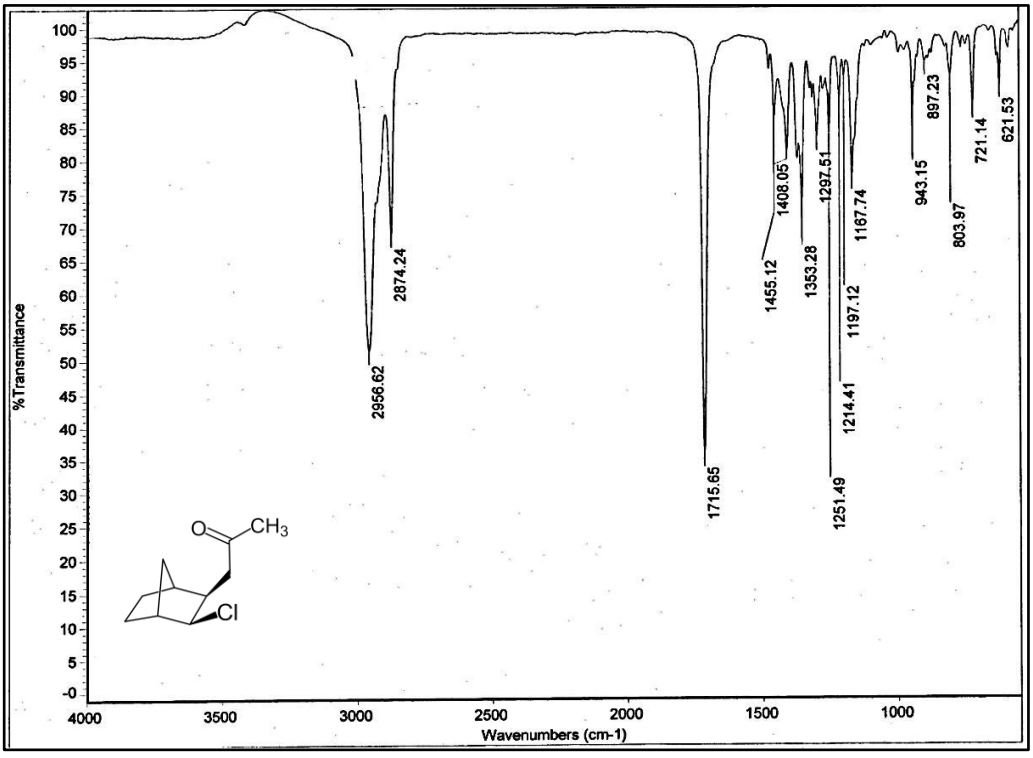

Figure 175 IR Spectrum of Compound **219**

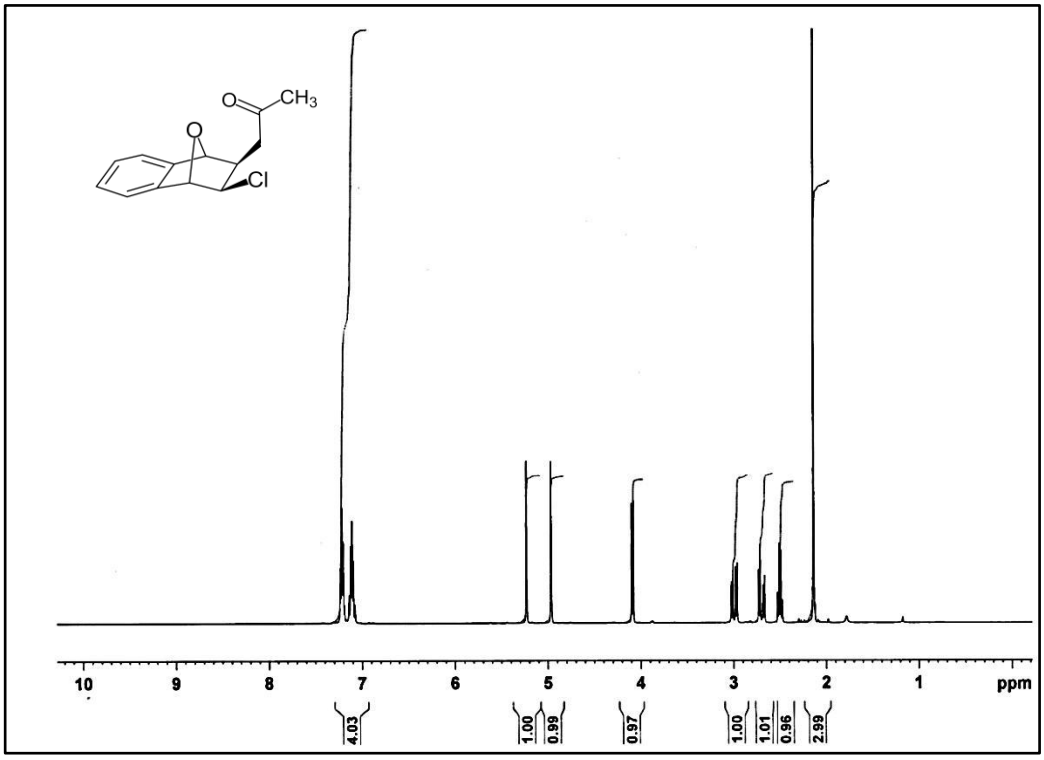

Figure 176 ^{1}H-NMR Spectrum of Compound **221**

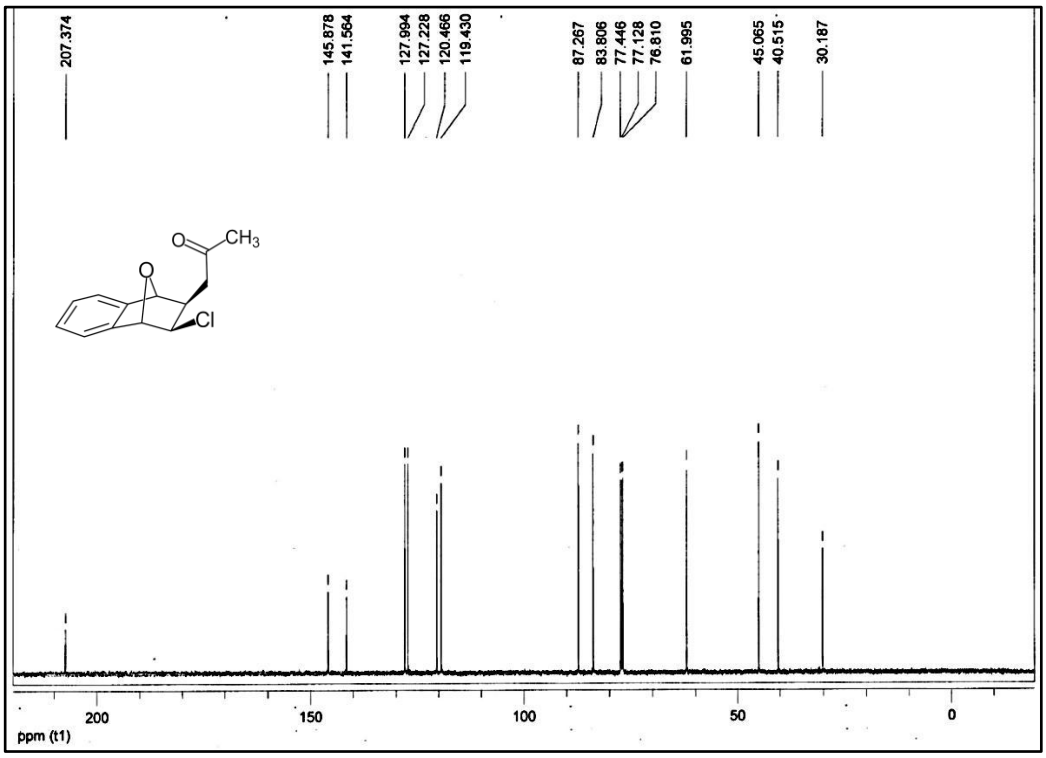

Figure 177 ^{13}C-NMR Spectrum of Compound **221**

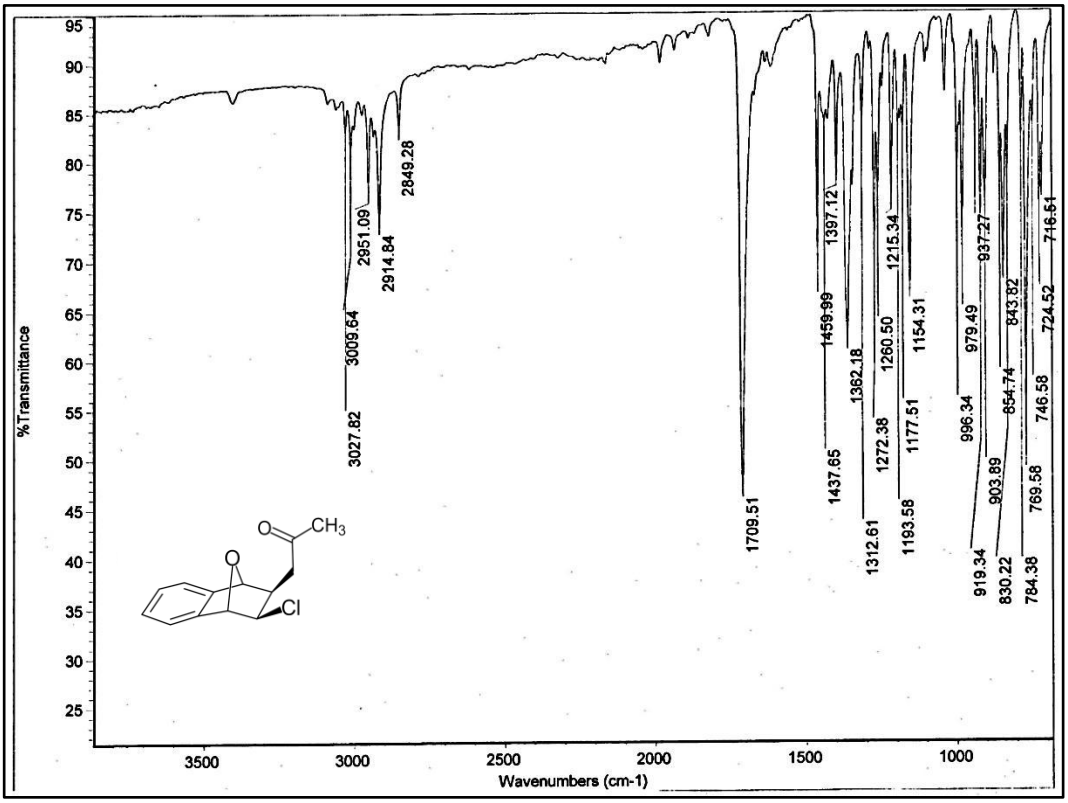

Figure 178 IR Spectrum of Compound **221**