THE SYNTHESIS OF 6- AND 7- MEMBERED HETEROCYCLIC RING SYSTEMS FUSED TO PYRIDINE RING

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

BY

YASEMIN DINCOFLAZ

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

FEBRUARY 2013

Approval of the thesis:

THE SYNTHESIS OF 6- AND 7- MEMBERED HETEROCYCLIC RING SYSTEMS FUSED TO PYRIDINE RING

submitted by **YASEMİN DİNÇOFLAZ** in partial fulfillment of the requirements for the degree of **Master of Sciences in Chemistry Department, Middle East Technical University** by,

Prof. Dr. Canan ÖZGEN
Dean, Graduate School of **Natural and Applied Sciences** _____

Prof. Dr. Ilker OZKAN
Head of Department, **Chemistry** _____

Prof. Dr. Metin BALCI
Supervisor, **Chemistry Dept., METU** _____

Examining Committee Members:

Prof. Dr. Vildan ADAR
Chemistry Dept., Hacettepe University _____

Prof. Dr. Metin BALCI
Chemistry Dept., METU _____

Prof. Dr. Özdemir DOGAN
Chemistry Dept, METU _____

Assoc. Prof. Dr. Adnan BULUT
Chemistry Dept., Kırıkkale University _____

Assist. Prof. Dr. Akın AKDAG
Chemistry Dept., METU _____

Date: 01.02.2013

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

Name, Last name : Yasemin Dinçoflaz

Signature :

ABSTRACT

THE SYNTHESIS OF 6- AND 7- MEMBERED HETEROCYCLIC RING SYSTEMS FUSED TO PYRIDINE RING

Dincoflaz, Yasemin
M.Sc., Department of Chemistry
Supervisor: Prof. Dr. Metin Balcı

February 2013, 87 pages

The synthesis of the nitrogen containing heterocyclic compounds is one of the leading research areas throughout the organic chemistry due to their significant activities in biological systems. Among the various biologically active molecules, pyridine-fused ring systems are of prime importance on the grounds of their proven clinical roles.

The coupling reactions with 6-membered heterocyclic compounds and diazepines gave rise to new pharmalogical compounds in recent years. Therefore, our object was the synthesis of pyridine-fused 6- and 7-membered heterocycles.

Starting from bromopyridine, two different methods were applied for the synthesis of target compounds. In the first part of the this thesis, coupling products were synthesized using Sonogashira coupling reaction. After synthesis of the coupling derivatives, ring-closure under the basic conditions generated the heterocyclic units without using any catalyzer. In the second part of study, nicotinic acid and pyridopyranone derivatives were synthesized by using intramolecular cyclization reactions. The formed products were conscientiously purified and characterized by means of spectroscopics method.

Keywords: bromopyridine, Sonogashira coupling, nicotinic acid, ring-closure reaction

ÖZ

PİRİDİN HALKASINA KENETLENMİŞ 6- ve 7- ÜYELİ HETEROHALKALI SİSTEMLERİN SENTEZİ

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

Şubat 2013, 87 sayfa

Azot içeren heterohalkalı bileşiklerin sentezi, bu yapıların biyolojik sistemler üzerinde gösterdikleri önemli aktivitelerden dolayı organik kimyanın önde gelen çalışma alanlarından birisidir. Biyolojik aktivite gösteren moleküller arasında, klinik etkileri kanıtlanmış piridine kenetlenmiş heterohalkalı sistemlerin sentezi ile ilgili çalışmalar önem kazanmaktadır.

Son yıllarda altı üyeli heterohalkalı bileşikler ile diazepinlere uygulanan kenetlenme reaksiyonları sonucunda önemli farmakolojik etkileri olan yeni bileşikler sentezlenmektedir. Bu nedenle bu çalışma kapsamında piridin halkasına 6- ve 7- üyeli azot ihtiva eden heterohalkaların kenetlenmesi hedeflenmiştir.

Çalışma kapsamında hedef moleküllerin sentezi için bromopiridinden başlayarak iki farklı yöntem uygulandı. Çalışmamızın birinci kısmında Sonogashira kenetlenme yöntemiyle piridin halkasına kenetleme ürünleri sentezlendi. Bu ürünlerin sentezinden sonra, herhangi bir katalizör kullanmadan bazik koşullarda halka kapanma reaksiyonu ile ikili-heterohalkalı yapılar oluşturuldu. Çalışmanın ikinci kısmında ise nikotinik asitin oluşumundan sonra intramoleküler halkalaşma yönteminden faydalanılarak piridopiranon türevleri sentezlendi. Oluşan ürünler özenle saflaştırıldı ve yapıları spektroskopik yöntemler aracılığı ile karakterize edildi.

Anahtar Kelimeler: bromopiridin, Sonogashira kenetlenme reaksiyonu, nikotinik asit, halka kapanma reaksiyonu

To my Family...

ACKNOWLEDGEMENT

I would like to present my special thanks to my supervisor Prof. Dr. Metin Balcı for his guidance, continuous interest, support and encouragement. It was a great chance for me to be a student of Prof. Balcı.

I would like to thank to Dr. Zeynep Ekmekci and Dr. Nurettin Menges for their guidance, support and encouragement throughout my master study.

I would like to thank to NMR specialists Betul Eymur for the NMR experiments.

I would like to express my great thanks to all the members of SYNTHOR, **Nalan**, **Merve Sinem**, **Selbi**, **Serdal**, **Çağatay**, **Merve**, **Yasemin**, Tolga, Erol, Furgan, Sinem, Selin, Fatih, Sultan, Başak for their support and friendship through these years.

I would like to thank to Özlem Sarı for DFT calculation.

I would like to thank to TUBITAK (Scientific and Technological Research Council of Turkey, 110R001) for financial support.

Finally I would like to express sincere thanks to my parents (Mustafa and Emine) and my brothers (Erol and Şenol) very much for tolerating and supporting me in anything and any time.

TABLE OF CONTENTS

LIST OF FIGURES

FIGURES

LIST OF TABLES

TABLES

LIST OF SCHEMES

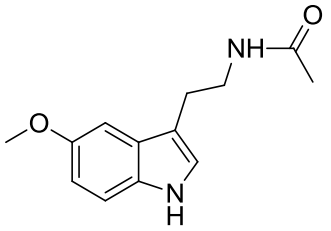
SCHEMES

CHAPTER 1

INTRODUCTION

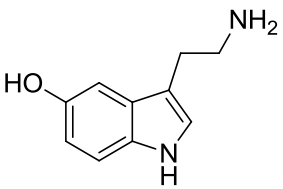
1.1 General introduction to heterocycles in our life

There is chemistry behind all of the biological processes in nature. Basic process of our life such as metabolism, transmission of nerve impulses, consists of chemical reactions involving heterocycles.



melatonin

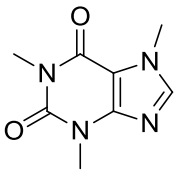
1



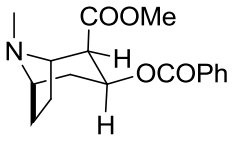
serotonin

2

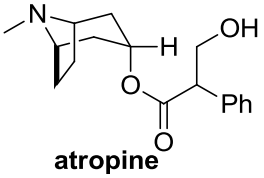
Melatonin (**1**) and seratonin (**2**) well known as neurotransmitters are heterocycles which have different functions on the central nervous system (CNS). Numerous nervous system drugs have lots of different structures from aliphatic to heterocyclic, yet most of them are heterocycles and aromatics.



caffeine
3



cocaine
4

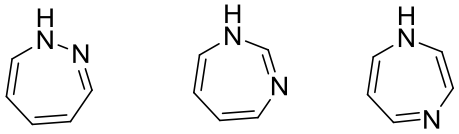


atropine
5

For years, the illnesses were cured with natural products which were obtained from leaves, fruits etc. However, these conventional methods were not known as successful treatment until the last decade. Additionally, it was recognized that this treatment has been the right way to cure in terms of containing various heterocyclic rings, which were extracted from plants, animals, and insects. For instance, humans have extracted plants, containing alkaloids such as caffeine (**3**), cocaine (**4**), atropine (**5**), since ancient times for therapeutic and relaxation purposes. Structures of all of the alkaloids are heterocycles. Especially, atropine alkaloids of the piperidine series were used in medicine as treatment of ophthalmic disease.[1]

1.2 Aromatic ring fused diazepines

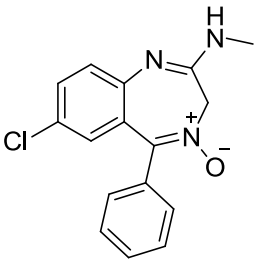
Diazepines are seven membered heterocycles consisting of two nitrogen atoms. Their name and activities change depending on position of nitrogen atoms. For instance, they are named as 1,2-diazepine (**6**), 1,3-diazepine (**7**) or 1,4-diazepine (**8**).



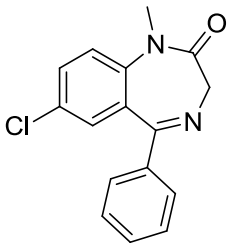
6 **7** **8**

The most common, benzodiazepine is a heterocyclic compound where benzene and diazepine rings are fused. There are different isomers depending on the position of nitrogen atoms. Benzodiazepines are widely used in clinics and for medicinal purposes.[2] So these molecules are very popular since they are used as drugs.[3]

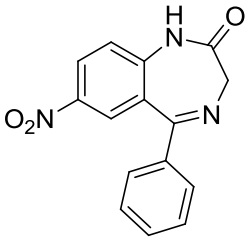
Chlorodiazepoxide (**9**) known as the first benzodiazepine, was coincidentally found by Dr. Leo Henryk Sternbach (Hoffmann-La Roche in Switzerland) was available in markets in 1960. It is very important derivative in terms of hypnotic, anxiolytic and muscle relaxant.[4] Around the same time, diazepam (valium) (**10**) was discovered to show better activity in psychotherapy. Then, another derivative of nitrazepam (**11**) was used against anypnia.[5] Similarly, clonazepam (**12**) has anxiolytic, anticonvulsant, muscle relaxant and hypnotic properties.[6] Additionally, it was recognized by the Food and Drug Administration for treatment of epilepsy.[7,8]



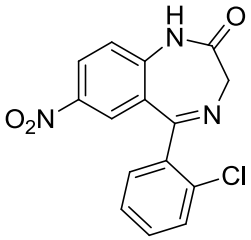
chlordiazepoxide
9



diazepam
10



nitrazepam
11



clonazepam
12

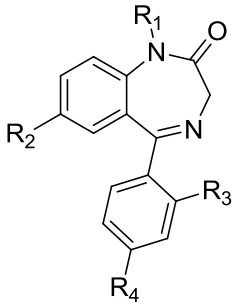


Table 1

	positive effect	*negative effect*
R_1	H, CH_3, Et , i-Bu	t-Bu
R_2	Cl, F , NO_2 ,CF_3	Me, OMe
R_3	F , Cl	
R_4	H	Any substitution

Sternbach also developed a methodology for the synthesis of more impressive and selective benzodiazepines. Furthermore, these benzodiazepines were tested by his group.

They investigated structure-activity relationships of benzodiazepine derivatives. On the other hand, they searched whether they show pharmacophoric effect or not. After investigation, they approved that substitution on the rings brings about different effect on biological activity. If the R_2 on the ring is an electron-withdrawing group such as halogens or nitro groups, it leads to high biological activity. (Tabla 1). Conversely, if the R_2 group is an electron-donating group such as methyl or methoxy, it will lead to a considerable decrease in activity. Similarly, substitution at the R_3 position on benzene ring with halogens gives a rise to activity increase while any substitution at the R_4 causes significantly less anxiolytic activity. Larger groups in R_1 position led to decreased activity.[9,10] To illustrate, they created a new compound, which are CH_3 in R_1 position, NO_2 in R_2 position, F in R_3 position, showing potent hypnotic effect.

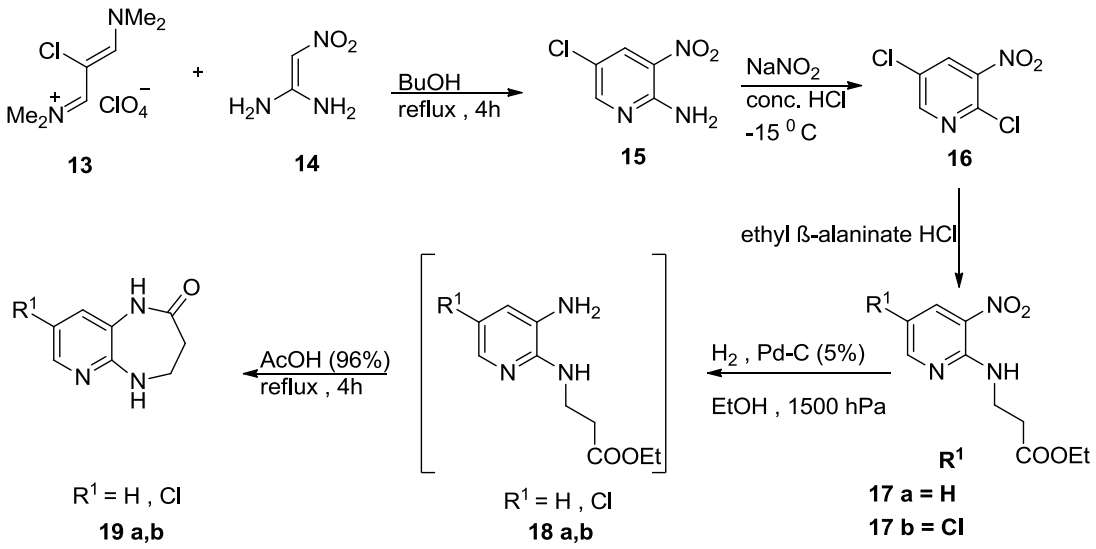
Hence, over 80 derivatives of benzodiazepine were synthesized by changing these groups.

In recent years, thanks to pharmacological properties, the synthesis of many benzodiazepines derivatives and diazepines fused other aromatic rings such as pyridodiazepines is being investigated by scientist.

1.2.1 Pyridodiazepines and their synthesis

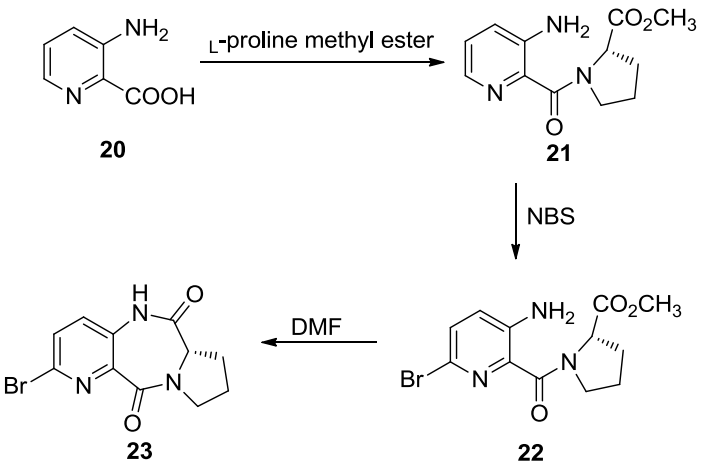
In particular, the recent studies in chemistry and pharmacy are concerned to synthesis of tricyclic and tetracyclic derivatives of benzodiazepine, pyridodiazepine type having effect on the central nervous and vascular systems.[11] Savelli *et al.*[12,13,14] defined that some pyridodiazepinone structures have antipsychotic properties.

Hussenether *et al.*[14] used ***N***-(3-nitropyridin-2-yl)-β-alaninates as starting material to obtain pyridodiazepinone. Initially, to synthesize starting material, they used the condensation reaction of vinamidinium perchlorate (**13**) with 2-nitroethen-1,1-diamine (**14**) in BuOH. Aminopyridine **15** was formed in good yield. Subsequently, the aminopyridine **15** was transformed to dichloronitropyridine **16** using $NaNO_2$ in concentrated HCl. After forming compound **16**, substitution reaction was performed with ethyl β-alaninate to obtain the starting material. Target molecule **19a** and **19b** were formed by intramolecular cyclization after reduction of nitro groups.[15] (Scheme 1).



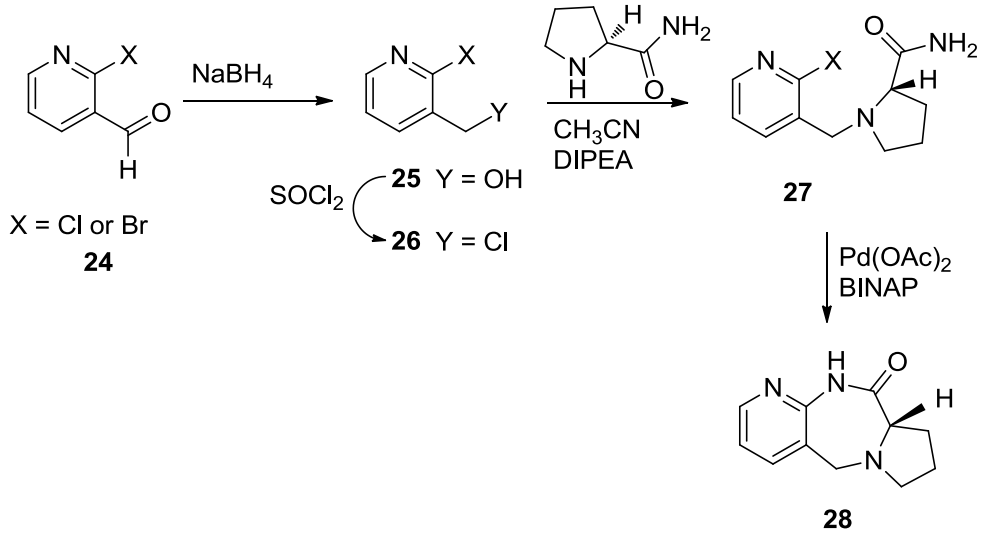
Scheme 1

A new methodology for construction of pyrido-pyrrolo[1,4]diazepine-6,11dione (**23**) skeleton is described in Scheme 2. El Bouakher *et al.*[15] used 3-aminopyridine-2-carboxylic acid (**20**) as a starting material which was reacted with L-proline methyl ester to give compound **21**. After bromination, followed by ring closing reaction, chiral compound **23** was obtained (Scheme 2). [16]



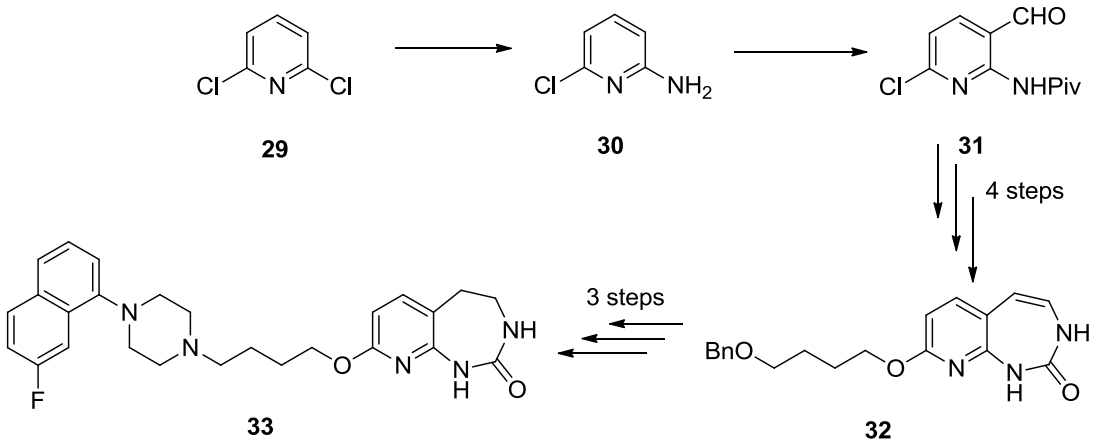
Scheme 2

Another example for cyclization was published by L. Legerén and D. Domínguez. First step of the synthetic route of this method shown in Scheme 3 started with the reduction of 2-halonicotinaldehydes **24** with $NaBH_4$ and then compound **25** was formed. Subsequently, $SOCl_2$ was added to obtain corresponding 3-chloromethyl-2-halopyridine (**26**). Hünig base (N,N-Diisoproylethlyamine) was used for the alkylation of secondary amine, L-prolinamide to tertiary amine **27** by alkyl halide **26**. Finally, the ring closure was achieved for the formation of pyrrolopyridodiazepinone 28 totally in 4 steps by using catalysts such as $Pd(OAc)_2$ and BINAP (Scheme 3).[17]



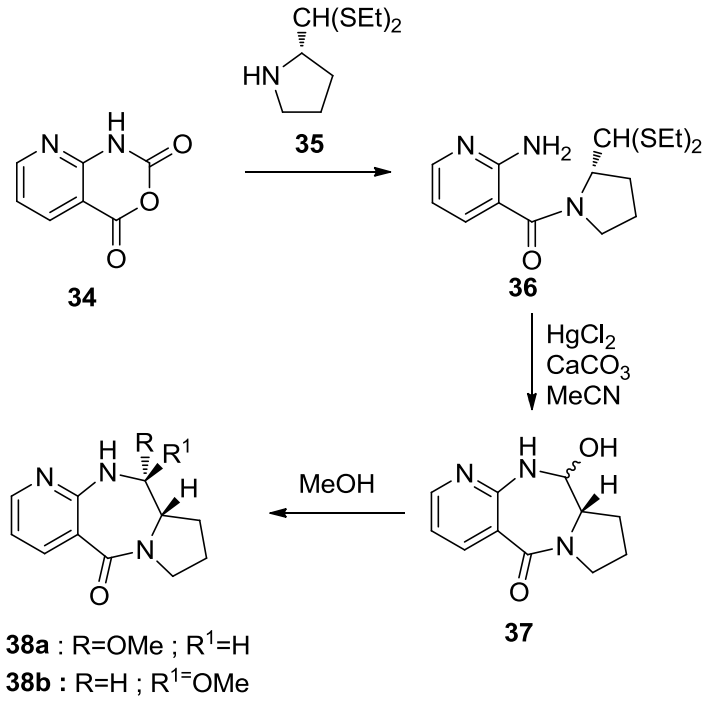
Scheme 3

A medicinal chemistry group[18] was successful to prepare a dopamine D_2 partial agonist **33** in 7 steps and similarly Javier *et al.* inspired this original method and developed similar route with increasing yield and using more safety reagent and conditions (Scheme 4).[18]



Scheme 4

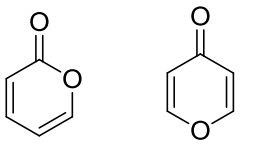
CRC Gene Targeted Drug Design Research Group revealed new methodology for the synthesis of compound **38a** and **38b** using pyridooxazine **34** as starting material. Firstly, they used compound **35** to form amide **36**. After treatment of **36** with $HgCl_2$ and $CaCO_3$, a diastereomeric mixture of carbinolamine **37** was formed**.** Finally, they synthesized the pyrrolopyridodiazepinone **38a** and **38b**. The formed diastereomers were separated by crystallization from dry Et_2O and the diastereomer **38a** was obtained as crystalline compound (Scheme 5).[19]



Scheme 5

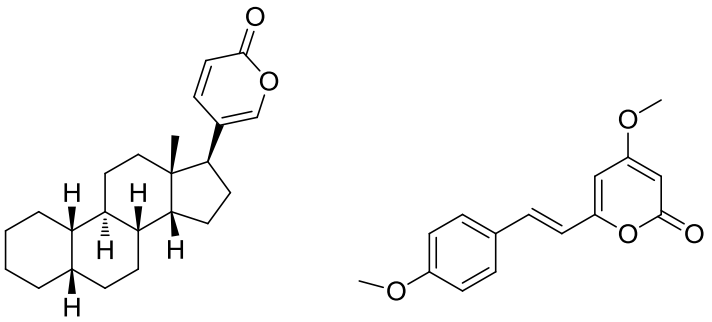
1.3 Pyrone (or pyranone) and their synthesis

Pyrone (or pyranone) is an unsaturated cyclic chemical compound. It has isomers, such as 2-pyrone (**39**) and 4-pyrone (**40**).



2-pyrone **39** 4-pyrone **40**

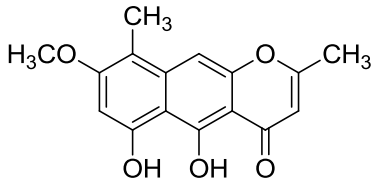
Pyrone is widely distributed in natural compounds and are the structural part of a variety of pharmacologically and biologically active compounds. Comparing these two isomers, 2-pyrone is found in natural products commonly. To illustrate, the bufanolides (**41**) known a kind of steroid and yangonin (**42**) was found in the kava plant.[20]



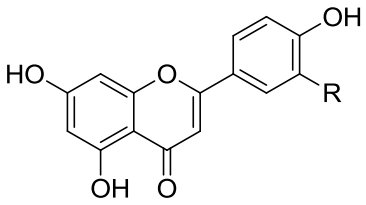
Bufadienolide **41** Yangonin **42**

Pyrones fused aromatic rings are also encountered in nature. The naphtypyrone **43** from *Cassia quinquangulata* exhibit good resistance toward SA and MRSA which are bacteria and result in infection of people who are in hospital.

Benzopyrones are known as coumarins. Correspondingly, benzene fused 4-pyrone, apigenin (**44**) and luteolin (**45**), flavones are excellent towards the same bacterium strains[20]

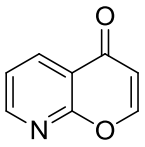


naphthopyrone
43



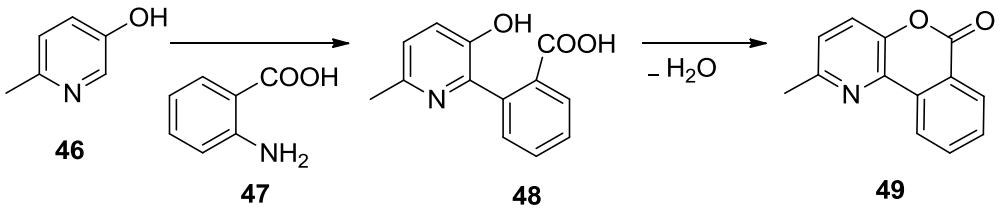
44 R = H , apigenin
45 R = OH , luteolin

In addition to this, even these six-membered heterocycles are commonly found in the natural products. However, pyridine-fused heterocycles such as pyranopyridinones **45** is unknown.



pyranopyridinone
45

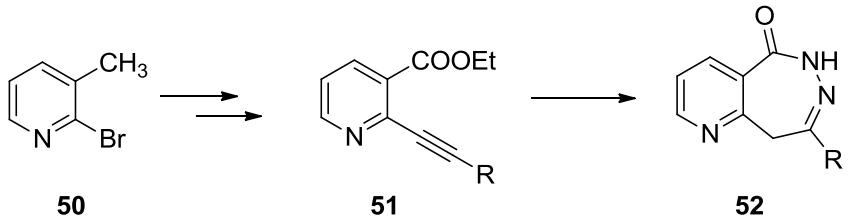
Pyranopyridinones are rarely encountered heterocyclic compound consisting of a pyridine ring fused to six-membered pyranone ring (**39** and **40**).
Katrizky and his co-workers[21] reported the preparation of benzopyranopyridinones. According to this route, 3-hydroxy-6-methylpyridine (**46**) was chosen as starting material**.** Reaction of **46** with anthralinic acid (**47**) used as benzyne precursor and *n*-pentylnitrite, gave the expected product (**49**). Furthermore, they synthesized derivatives of compound **49** starting with analogs of compound **46** (Scheme 6).



Scheme 6

1.4 Aim of Study

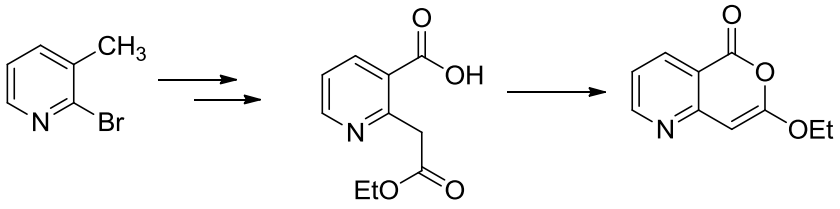
Diazepines especially pyridodizepines have recently attracted the attention of scientists. It was proven that those compounds and their derivatives have shown a various activities in many biologically important processes. Hence, our aim of the first part was to develop a new methodology for the synthesis of pyridodiazepinones. Starting from bromopyridine **50**, our purpose was to convert bromopyridine to alknyl derivatives through Sonogashira coupling reaction. After synthesis of alknyl derivatives **51**, we planned to obtain pyridodiazepinone derivatives **52** (Scheme 7).



50 **51** **52**

Scheme 7

In the second part of the study, the synthesis of pyridopyranone **54** was achieved accidentially. Starting from bromopyridine **50** again, the key compound **53** was synthesized leading to the intramolecular ring closure to form compound **54** (Scheme 8). As a conclusion, a new synthetic methodology was foreseen.



50 **53** **54**

Scheme 8

CHAPTER 2

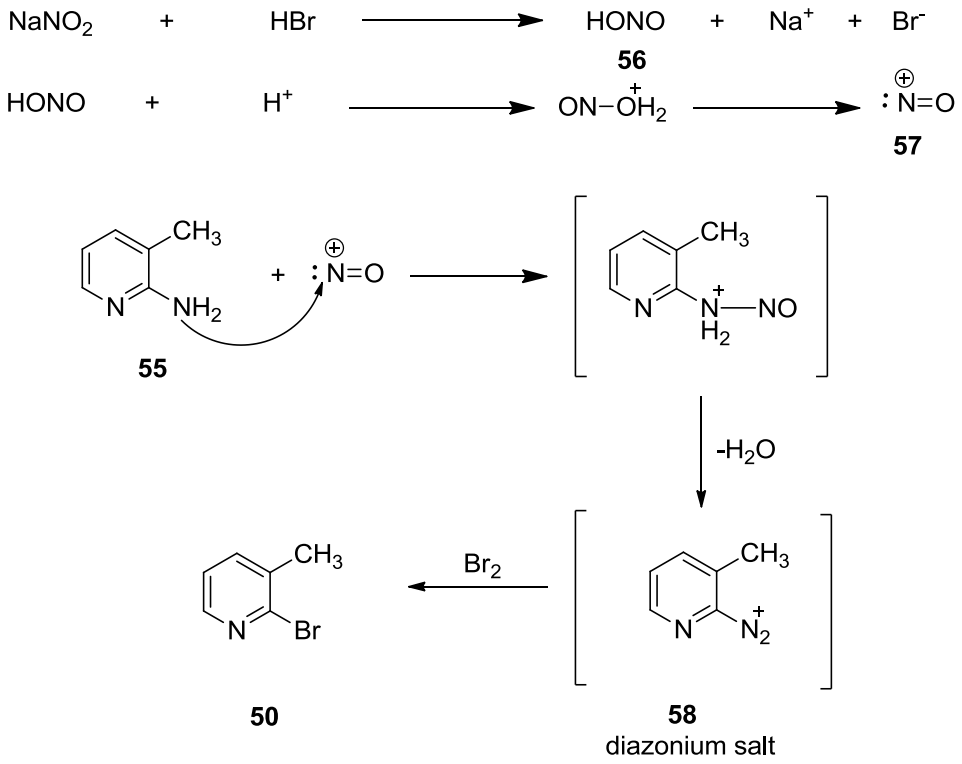
RESULT AND DISCUSSION

2.1 Synthesis of pyridodiazepinone derivatives

To synthesize pyridodiazepinone derivatives; 2-amino-3-methyl pyridine (**55**) was used as starting material, which is commercially available. Our aim was to synthesize bromopyridine as key compound through modified Sandmeyer reaction.

2.1.1 Synthesis of key compound: 2-bromo 3-methylpyridine (**50**)

2-Amino-3-methyl pyridine (**55**) was chosen as a starting material which was submitted to diazotization reaction (modified Sandmeyer reaction) to get to the corresponding bromopyridine **50**.[22]



Scheme 9

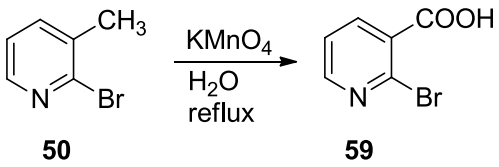
Firstly, nitrous acid **56** was formed through protonation of nitrite ion in acidic medium then dehydration leads to formation of nitrosonium ion **57**. Primary amine with nitrous acid gave highly unstable diazonium salts which spontaneously decompose by losing N_2 to form a carbenium ion. The carbenium ion goes on to produce a aromatic halides as the major product (Scheme 9).

The structure of **50** was determined by ^{1}H and ^{13}C-NMR. In ^{1}H-NMR spectrum, each of pyridine protons resonate at aromatic region as doublet of doublets. Methyl protons resonate at 2.23 ppm as singlet.
The incorporation of bromine atom into the molecule was determined by MS-spectrum where the observed doublet of molecular weight peak was assigned to the isotopes of bromine atom.

In ^{13}C-NMR spectrum, there were six peaks at 146.8, 143.9, 139.2, 135.2, 122.9, 21.8 ppm.

2.1.2 Synthesis of 2-bromopyridine-3-carboxylic acid (59)

According to the literature, treatment of bromomethyl pyridine **50** with potassium permanganate in H_2O at reflux temperature results in oxidation of methyl group to give the 2-bromopyridine-3-carboxylic acid (**59**) (Scheme 10).[23]



50 **59**

Scheme 10

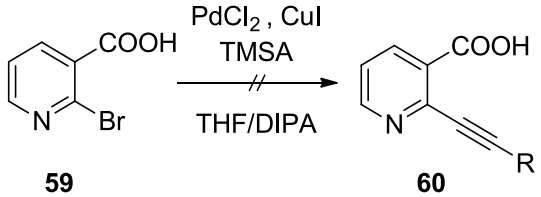
This reaction was completed in 24 h and desired compound **59** was obtained in 44% yield. The structure of compound **59** was proven by ^{1}H and ^{13}C NMR spectra.

In the ^{1}H NMR spectrum, each of the pyridine protons resonate at 7.6-8.4 ppm as doublet of doublets.

The ^{13}C NMR spectrum consisting of six signals at 166.4, 151.8, 139.2, 138.7, 131.1, 123.2 ppm was also in aggrement with the structure.

2.1.3 Synthesis of ethyl 2-bromonicotinate (61)

After successful synthesis of bromopyridine carboxylic acid **59**, we have applied Sonogashira coupling reactions under various conditions. Unfortunately, we were not able to get even any trace of the desired compound **60** (Scheme 11). In some cases, the staring material was recovered or some unidentified products were formed. We assumed that the carboxylic acid functional group was responsible for failure of the coupling reaction. Therefore, we decided to protect the acid functionality as an ester group and synthesized the corresponding ester **61**.



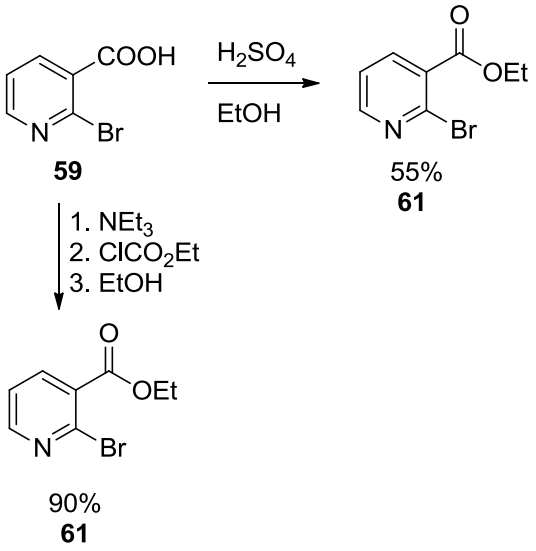
59 **60**

Scheme 11

Initially, we attempted a typical esterification reaction, namely Fisher esterification. According to this reaction, addition of a proton or a Lewis acid increases the reactivity of the carbonyl group. Nucleophilic attack of the alcohol gives a tetrahedral intermediate in which there are two equivalent hydroxyl groups. One of these hydroxyl groups is eliminated after a proton shift (tautomerism) to give water and the ester.

We used H_2SO_4 and ethanol at reflux temperature monitoring on TLC in 2 days to perform this reaction. Ester **61** was successfully obtained at the end of the reaction in 55% isolated yield. However, approximately half quantity of the starting material was not converted.

Accordingly, we preferred to apply different esterification procedures to increase the yield. First of all, to a solution of compound **59** in THF, NEt_3 was added at -5^o C to abstract carboxylic acid's proton. Then, ethylchloroformate was added to obtain nicotinic anhydride. The mixture was stirred at below 0 ^{o}C for 30 minute. Finally, after addition of EtOH, the resulting mixture was heated at reflux temperature over night. The desired ester was formed in 92% yield (Scheme 12).

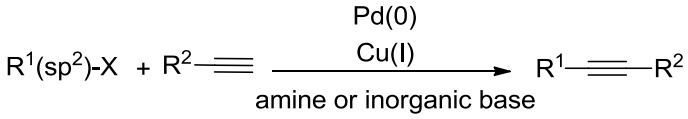


Scheme 12

The structure of **61** was also proven by ^{1}H and ^{13}C NMR spectra and the existence of bromine was supported with GC-MS spectrum.

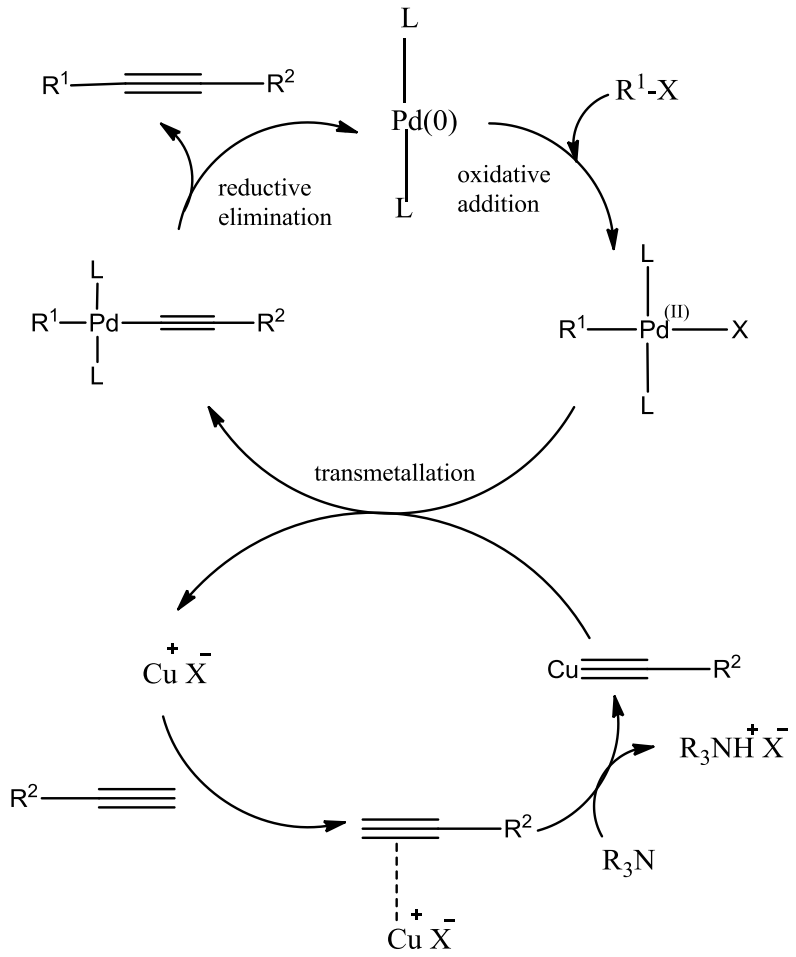
2.1.4 Sonogashira coupling reaction

The Sonogashira reaction is used in organic synthesis to form new carbon-carbon bonds. A palladium catalyst is utilized to form a carbon-carbon bond between a terminal sp hybridized carbon and a sp^2 hybridized C-X such as aryl or vinyl halide (Scheme 13 and 14).[24]



R^1= aryl, hetaroaryl, vinyl
R^2= aryl, alkenyl, hetaroaryl, alkyl, SiR_3
X= I, Br, Cl, OTf

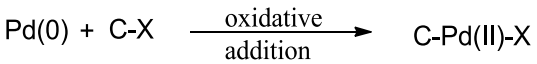
Scheme 13



L= phosphine, base , solvent or alkyne

Scheme 14

Based on the mechanism, oxidative addition is a process that increases both the oxidation state and coordination number of a metal centre. According to Sonogashira reaction, Pd(0) is used as catalyzer and oxidative addition provide that oxidation state of palladium increase from 0 to 2. Additionally, new two covalent bond are formed owing to insertion of Pd^0L_2 to R-X (Scheme 14 and 15).[24]

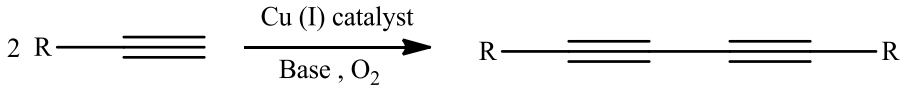


Scheme 15

As to transmetallation, it involves the transfer of ligands from one metal to another. As shown in Scheme 14, after oxidative addition, that complex reacts in a transmetallation with Copper acetylide.

And finally, reductive elimination is occured which is the reverse of oxidative addition. On the other hand, palladium act as catalyzer and becomes again Pd(0).[24]

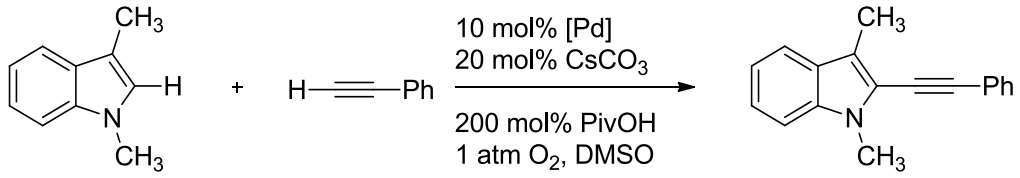
It is suggested that in the copper cycle, the existence of a base brings about formation of pi-alkyne complex, in that terminal proton of alkyne become more acidic. Cu salt is used as a co-catalyzer as well as to increase reaction rate. Even though the copper increases the reactivity, it has some side effects to the system. Evano *et al*. emphasized that homocoupling product is formed owing to the presence of the oxygen according to Hay/Glasser reaction and consequently, it is necessary to run the reaction in an inert atmosphere to avoid formation of the homocoupling product (Scheme 16).[25, 26]



Scheme 16

This problem led the researcher to modify Sonogashira coupling reaction without using copper salt due to formation of homocoupling product.

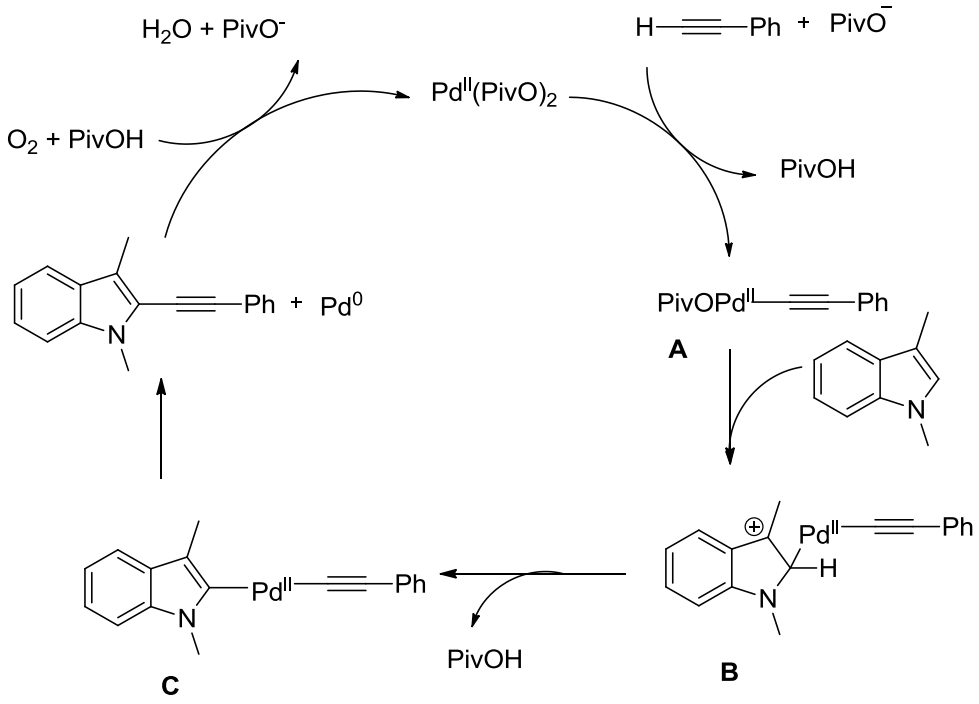
Under O_2 atmosphere without using Cu salt, Yang *et al*. achieved to synthesize only coupling product known as direct oxidative Heck–Cassar–Sonogashira type alkynylation reaction.[27] They optimized reaction conditions. They changed quantity of acid or base, temperature, time and palladium sources (Scheme 17).



62 **63** **64**

Scheme 17

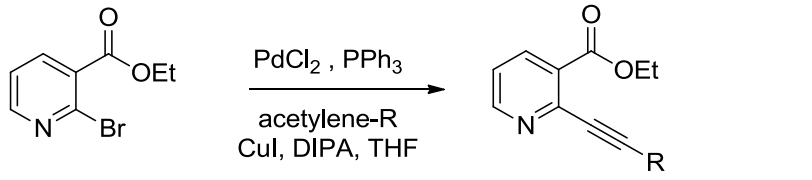
According to proposed mechanism (Scheme 18), firstly, pivalic acid and $CsCO_3$ are neutralized each other which forms CsOPiv. Then, it reacts with Pd^{II} and acetylene group. This intermediate (A) reacts with C_2 position of indole and produces new intermediate (B). After deprotonation by CsOPiv, compound C is formed. Finally, reductive elimination is occured and Pd^0 is reoxidized to Pd^{II} in the precense of O_2 and PivOH.[27] Thus, new copper-free Heck-Cassar-Sonogashira Coupling reaction was developed.



Scheme 18

2.1.5 Synthesis of coupling products (51a-d)

To a solution of compound **61** in THF, diisopropylamine, $PdCl_2$, PPh_3, CuI and acetylene group were added sequentially under N_2 atmosphere to avoid formation of homocoupling product. We optimized these reactions by controlling with TLC and GC-MS. Thus, a suitable reactant was obtained for coupling reaction. According to acetylene groups, reaction temperature and time have been changed (Scheme 19).



61

51(a-d)

51a R=phenyl
51b R=hexanyl
51c R=TMS
51d R=4-methoxyphenyl

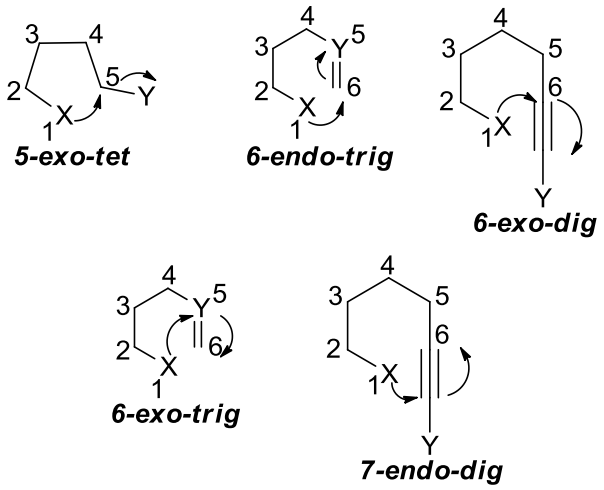
Scheme 19

The ^{1}H and ^{13}C NMR spectra supported the formation of compound **51a-d**. Especially, the presence of two carbon resonances between 80 and 100 ppm clearly indicated incorporation of alkyne functionalities into the molecule.

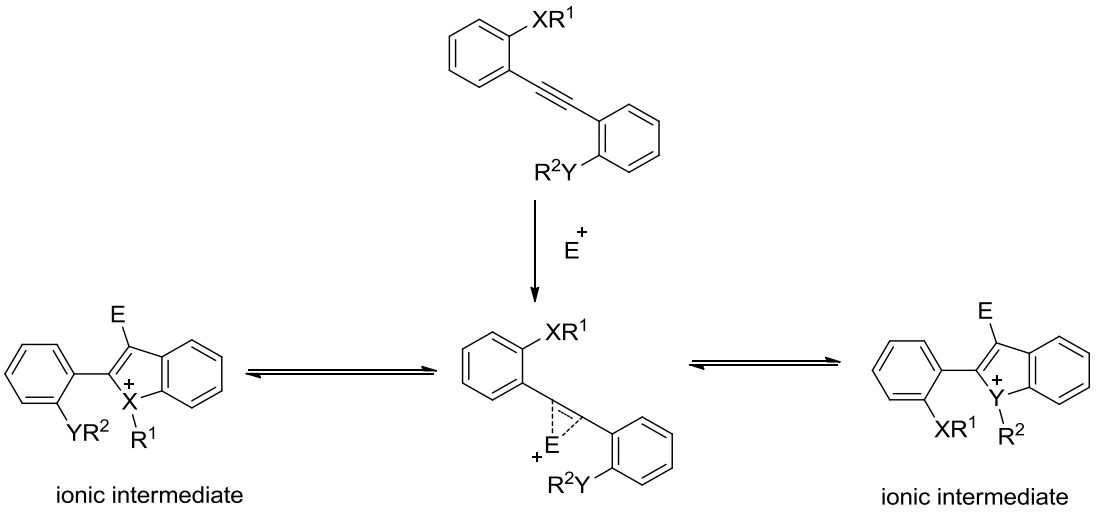
2.1.6 Synthesis of heterocycles via cyclization of alkynes

In recent years, electrophilic heteroatom cyclization is one of the most popular area for the synthesis of functionalized indoles, furans, thiophenes, pyroles and new heterobicyclic compounds using electrophile like I_2, ICI or organochalcogen derivatives such as sellenium, tellurium or Ag, Pd, Au ve Cu salts.[28]

Cyclization type depends on substrate of molecule, nucleophile strength and steric hindrance of molecule (Scheme 20). This rule is called as Baldwin's rule. In digonal systems, *5* to *7 exo-dig* is favored and *5* to *7 endo-dig* is favored.[29] Effects of the substrate and the nucleophile strength on cyclization type are illustrated in Scheme 21.



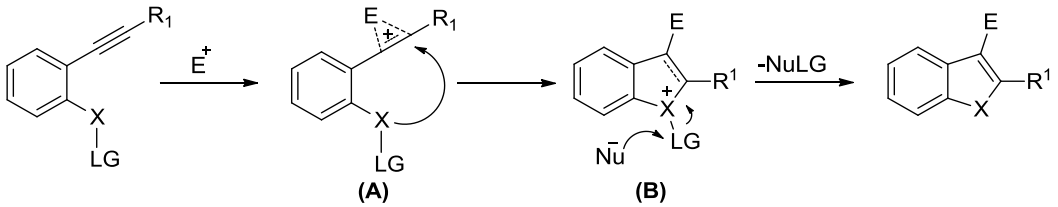
Scheme 20



Scheme 21

First step of electrophilic cyclization includes that an electrophilic source attack the sp^2 or sp hybridized carbon to activate the carbon-carbon multiple bond towards nucleophilic attack (A) and either endo or exo intermediate (B) is formed.

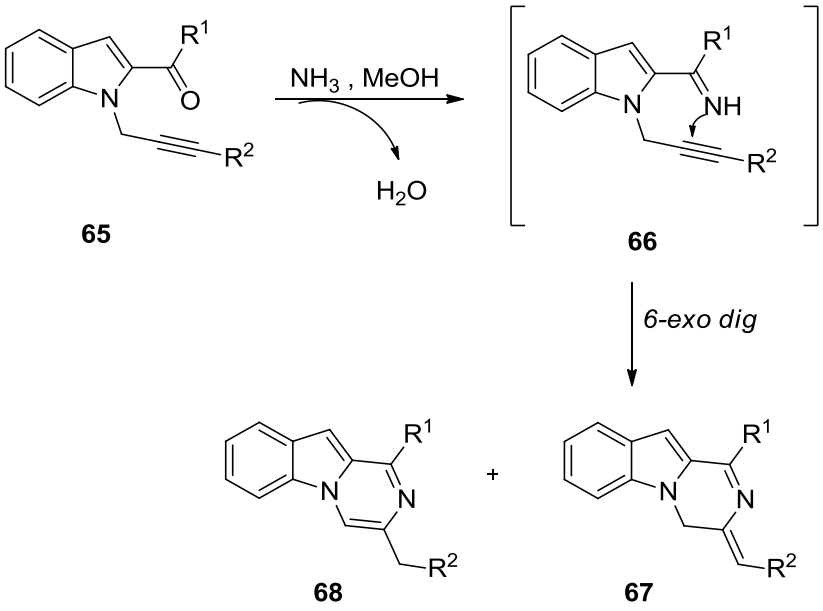
Second step is the removal of group which is attached to heteroatom. Finally, heterocyclic product is generated. (Scheme 22).



Scheme 22

So far, electrophilic cyclization reaction with alkyne was exemplified. Not only electrophile is required to carry out cyclization with alkyne, but also there are some example from literature which is not used catalyzer though rarely seen.

However, without using any electrophile, the intramolecular cyclization reaction with alkyne derivatives was performed by Abbiati and his group in the presence of ammonia (Scheme 23).[30]



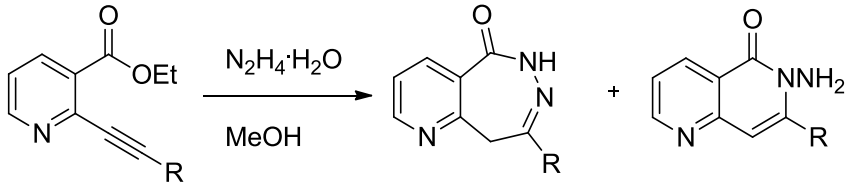
Scheme 23

In this reaction, as a result of the use of ammonia, as intermediate product, imine **66** was formed. Afterwards, pyrazinoindole **67** and isomerization product **68** were synthesized.[30]

2.1.7 Synthesis of pyridodiazepinone derivatives (52a-b)

In recent times, we have been interested in developing new synthetic methodologies for the construction of new heterobicycles from alkynes. Therefore, we preferred to apply the alkyl cyclization reaction without using any electrophile sources in order to synthesize our targeted molecules, pyridodiazepinone derivatives.

Initially, hydrazine monohydrate was added to solution of compound **51a-c** in MeOH and the reaction was monitored by TLC. The reaction time and temperature were changed (Scheme 24).



51 (a-c)

a= phenyl
b= hexanyl
c= H

52(a,b)

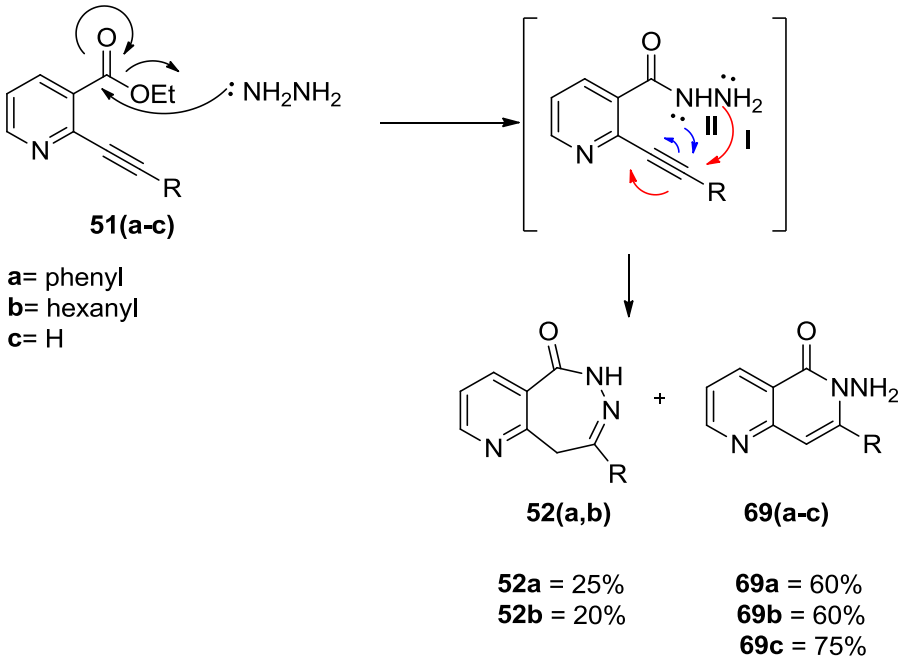
52a = 25%
52b = 20%

69(a-c)

69a = 60%
69b = 60%
69c = 75%

Scheme 24

As expected, the synthesis of pyridodiazepinone derivatives **52** were accomplished by the reaction of hydrazine first with the ester group to give hydrazide and followed by a *7-endo-dig* type cyclization according to Baldwin's rule as mentioned before. Furthermore, napthyridinone derivatives **69** was also formed as *6-endo-dig* type cyclization product. However, exo-dig type cyclic product was not formed (Scheme 25).



Scheme 25

According to proposed mechanism, hydrazine as nucleophile attacks the carbonyl carbon and hydrazide is formed as intermediate product. After that, more nucleophilic nitrogen attacks the alkyne carbon and *7-endo-dig* product, pyridodiazepinone is formed through arrow **I.** Less nucleophilic nitrogen attacks to alkyne carbon and as major product, naphthyridinone is formed through arrow **II** (Scheme 25).

Although it was expected that seven membered ring will be formed as the major product since nitrogen atom non-conjugated with carbonyl carbon is more nucleophilic than the other. However, six membered ring, napthyridinone was formed as the major product.

The characterization of compound **52a** and **69a** was achieved by ^{1}H and ^{13}C-NMR spectra.

The broad -NH peak indicates the presence of amide group and the formation of *7-endo-dig* cyclization product in ^{1}H-NMR. Disappearance of acetylene carbons in ^{13}C-NMR also indicates the ring closure. (Figure 1).

Comparing with compound **69a**, the broad -NH_2 peak at 4.2 ppm shows the presence of amide group and -CH signal at 5.9 ppm indicates the precence of a C=C double bond proton (Figure 2).

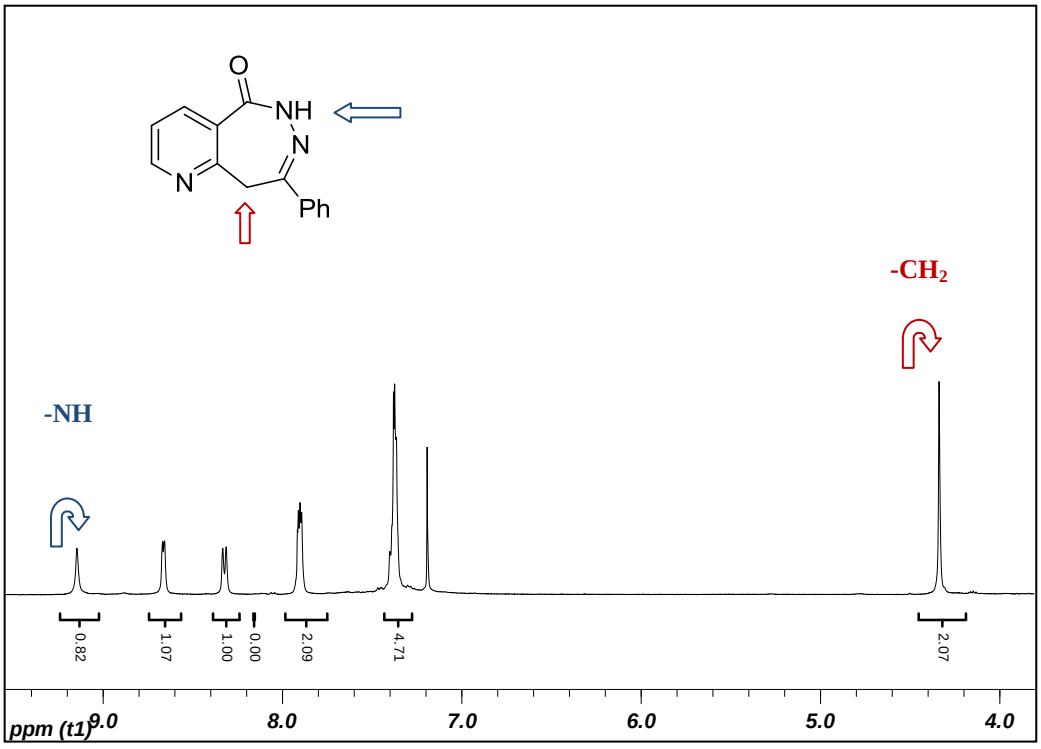


Figure 1 ^{1}H NMR Spectrum of Compound 52a

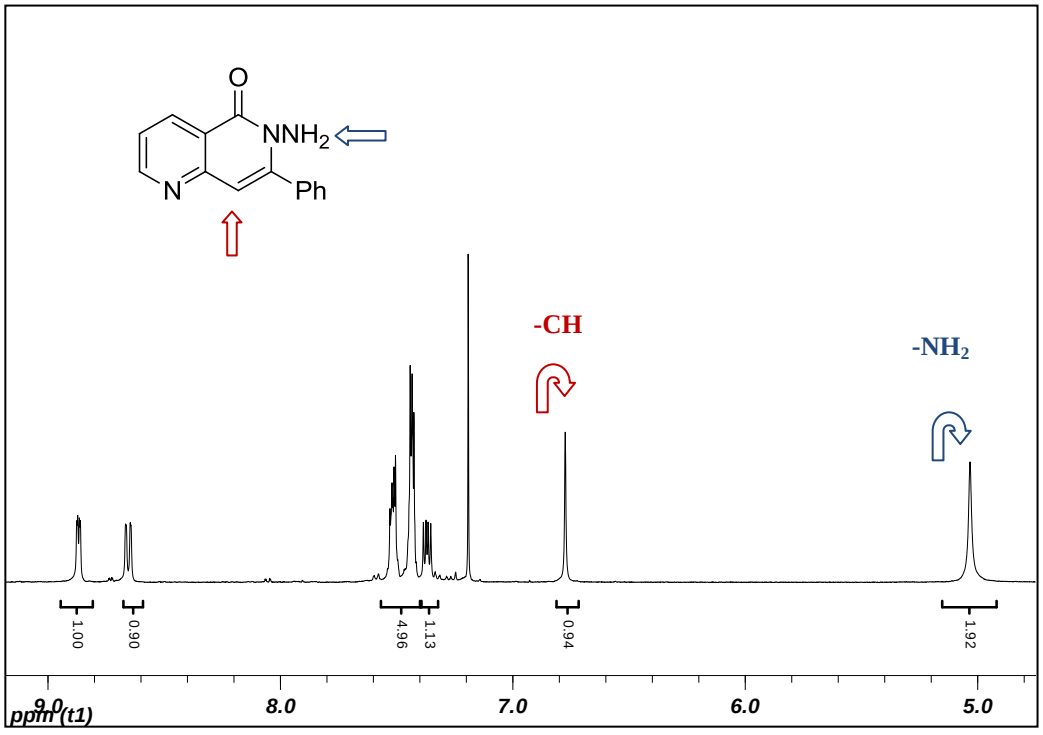


Figure 2 ^{1}H-NMR Spectrum of Compound 69a

Computational studies are in agreement with experimental studies. Computational studies for only one derivative were done by comparing these two compounds (**52a** and **69a**). Computational studies showed that six membered ring is more stable than seven membered ring.

Geometrical parameters of compound **52a** and **69a** were fully optimized at the hybrid density functional[31,32] B3LYP (Becke-3-parameter-Lee-Yang-Parr) method using 6-31+G (d, p) basis set implemented in Gaussian 09[33]. Single point solvation calculations with polarized continuum model[34] (PCM) were carried out at the B3LYP/6-31+G(d, p) level with methanol solvent since it was used in the experimental study. Gibbs free energy corrections calculated for the gas phase stationary points were added to solvation energies in order to compute Gibbs free energy values in the solution phase.

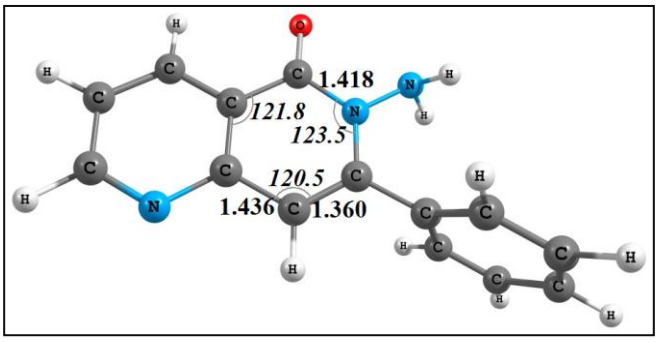


Figure 3 The optimized geometry of compound 69a

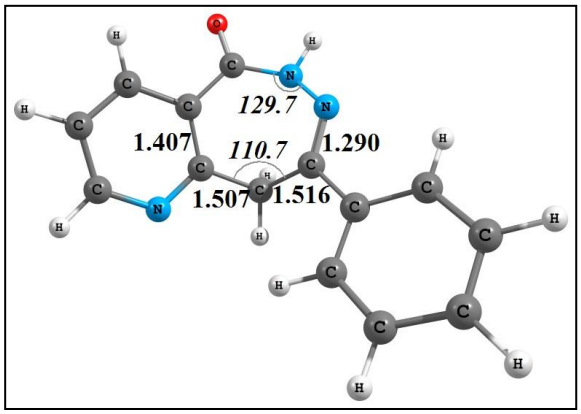


Figure 4 The optimized geometry of compound 52a

As shown in Figure 3, compound **69a** is thought to be closer to the aromatic structure in terms of bond angle, length and planarity of structure after optimization. Bond angle is closer to 120^{o} degree like sp^2-hybridized.

According to **Table 2**, in both gas phase and solvent, the result of calculations indicated that compound **69a** is more stable than compound **52a**. In gas phase, naphthyridinone is 2.74 kcal more stable than pyridodiazepinone. Similarly, naphthyridinone is 2.91 kcal more stable than pyridodiazepinone in methanol. Mechanistic studies are in progress.

Table 2

Gas phase	Eel+ZPE (au)	Eel+H (au)	Eel+G (au)
Compound 69a	-779.396196	-779.381820	-779.437453
Compound 52a	-779.397846	-779.383539	-779.438889

Table 3

Solvent (Methanol)	Eel (au)	correction (H)	Eel+H (au)	correction (G)	Eel+G (au)
Compound 69a	-779.638892	0.239429	-779.399463	0.183796	-779.455096
Compound 52a	-779.635760	0.240666	-779.395094	0.185316	-779.450444

Compound **52b** was purified by crystallization with petroluem ether and chloroform. However, compound **52b** is not isolated yet. On the other hand, the formation of seven-membered ring **52b** was observed in ^{1}H-NMR even though it was a mixture of **52b** and **69b** because similar NMR spectrum was seen for the other derivatives which are compound **52a** and **69a** (Figure 5 and 6).

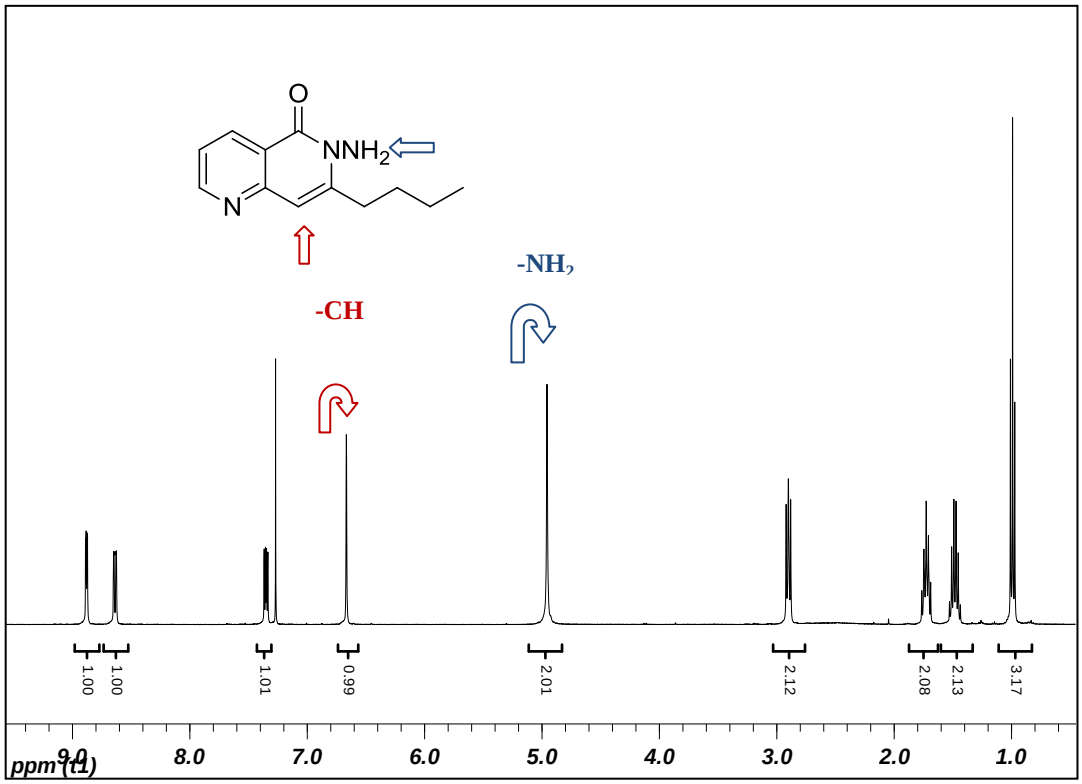


Figure 5 ^{1}H NMR Spectrum of Compound 69b

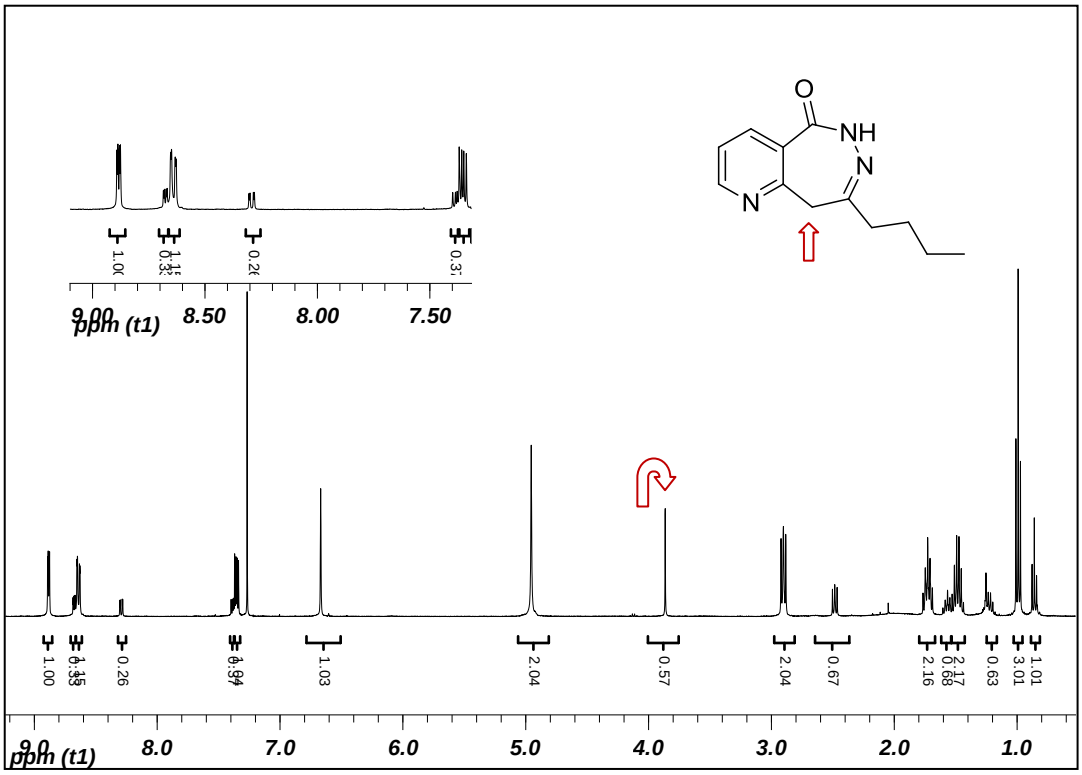


Figure 6 [1]H-NMR Spectrum of the mixture of Compound 69b and 52b

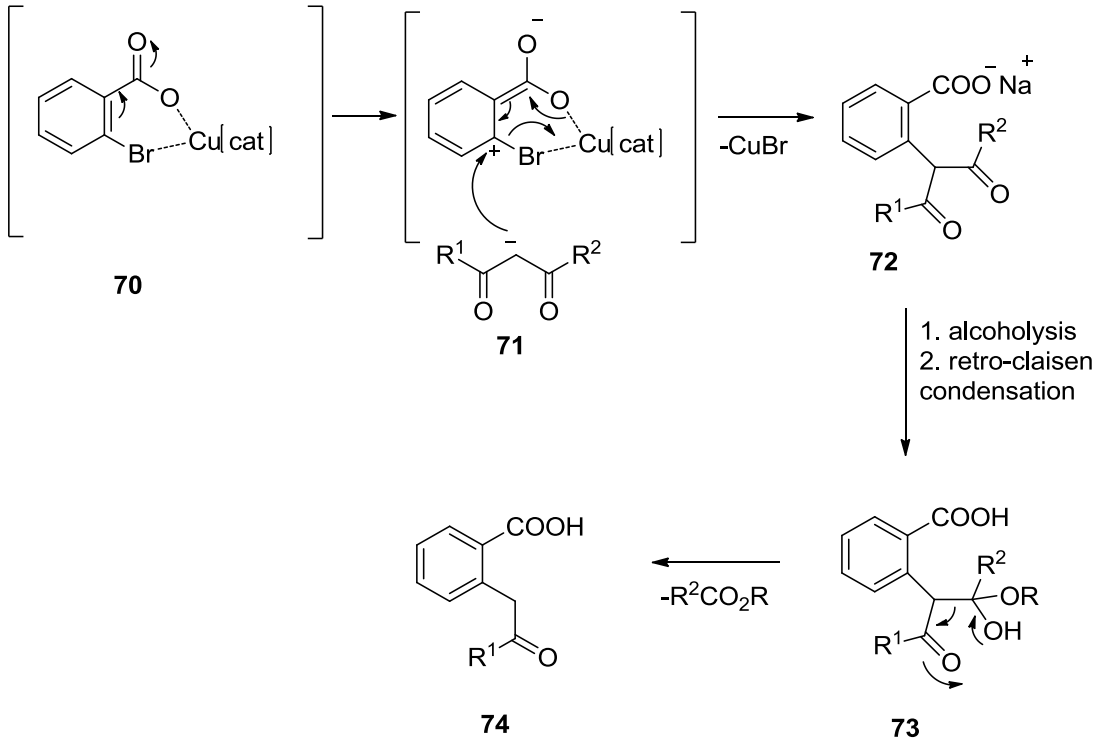
2.2 Synthesis of pyranopyridinone (54)

As mentioned before, compound **50** and **59** were used as starting materials for the synthesis of pyranopyridinone.

2.2.1 Synthesis of 2-(2-ethoxy-2-oxoethyl) nicotinic acid (53)

Hurtley [35] showed that the halide ion can be displaced with anion from dicarbonyl compounds by copper catalyzed reaction under basic conditions (Scheme 26). After heating of the substitution product under the same reaction condition, elimination of one acyl have been occurred through alcoholysis reaction and retro-Claisen condensation[36,37]. Order of elimination are these; acyl > benzoyl > ethoxycarbonyl group. General mechanism for this reaction is given in Scheme 26.

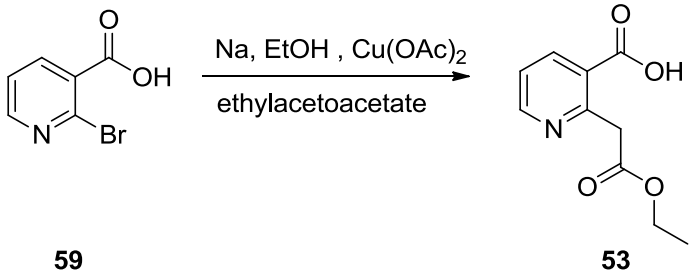
Firstly, chelated copper **70** is formed and then the rearrangement is occurred. Simultaneously, anion of dicarbonyl compound **71** attacks the carbon atom bearing the brom atom. After formation of compound **72**, sequentially alcoholysis and retro-Claisen condensation take place. After elimination of acyl group compound **74** is formed.



Scheme 26

We applied this reaction to bromo nicotinic acid (**59**) according to literature[38] and compound **53** was obtained (Scheme 27).

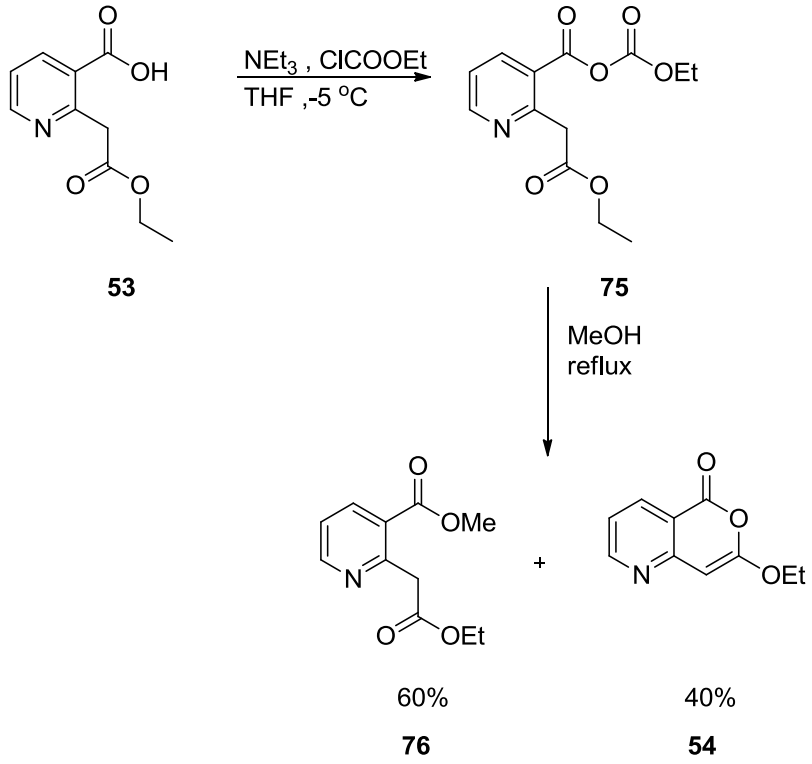
The ^{1}H and ^{13}C NMR spectra supported the formation of the compound **53**.



Scheme 27

2.2.2 Synthesis of the 7-ethoxy-5H-pyrano[4,3-b]pyridin-5-one (54)

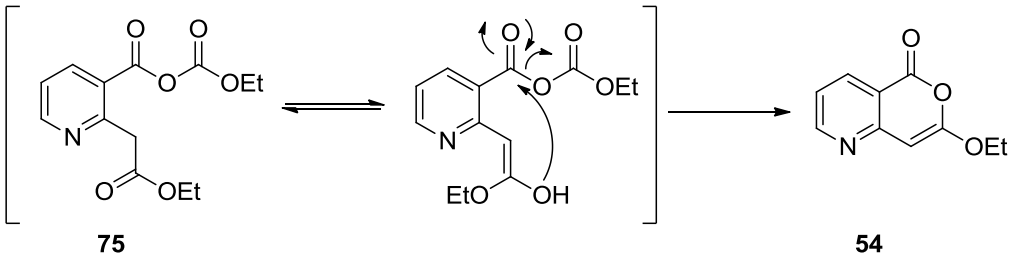
For esterification reaction, nicotinic acid **53** was treated with ethylchloroformate as described before to get diester **75**. Heating of **75** in MeOH under reflux temperature resulted in the formation of esterification product **76** and the cyclization product **54**. Pyranopyridinone **54** was actually an unexpected product (Scheme 28).



53 **75** **76** **54**

Scheme 28

The mechanism of formation for **54** is shown in Scheme 29.



75 **54**

Scheme 29

The structure of **54** is consistent with ^{1}H and ^{13}C-NMR spectral data.

In ^{1}H-NMR spectrum, olefine proton resonate at 4.8 ppm. In ^{13}C-NMR spectrum, double bond carbons resonate at 81.9 and 113.4 ppm. Additionally, high resolution mass spectroscopy verify the mass of **54**.

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).

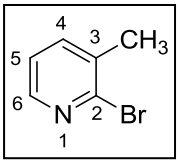
Column chromatographic separations were performed by using Fluka Silica Gel 60 plates with a particle size of 0.063–0.200 mm. Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Fluka.

Compounds were named by using ChemDraw Ultra 12.0 and ACD NMR.

Solvents were purified as reported in the literature.[39]

3.2 Synthesis of 2-bromo-3-methylpyridine (50)

2-Amino-3-methlypyridine (50 g, 0.46 mol) was added to the stirred solution of 48% HBr (230 mL). Then, Br_2 (70 mL, 1.36 mole) was added dropwise to the solution in 90 min while keeping the temperature below -5 ^{o}C and the formation of reddish-brown precipitate was observed. Then, 150 mL of $NaNO_2$ solution (80 g, 1.16 mol) was added dropwise in 2 hours and it was allowed to react for additional 30 minutes. It was followed by the addition of 40% of NaOH to adjust the pH to 10. It was extracted with diethylether (4 x 200 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated to give 2-bromo-3-methylpiridine **2** as orange oil (74 g, 92%).



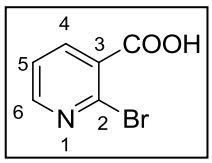
^{1}H NMR(400 MHz, *$CDCl_3$*): δ 8.6 (dd, *J*=4.3 ;1.6 Hz, 1H), 8.2 (dd, *J*=7.6 ; 4.8 Hz, 1H), 7.5 (dd, *J*=7.6 ; 1.2 Hz, 1H), 2.20 (s, 3H)

^{13}C NMR (400 MHz, *$CDCl_3$*) :δ 146.8, 143.9, 139.2, 135.2, 122.9, 21.8

IR (ATR cm^{-1}) **:** 2467, 2412, 1655, 1608, 1442, 1384, 1335, 1112, 1045, 994, 774

3.3 Synthesis of 2-bromopyridin-3-carboxylic acid (59)

2-Bromo-3-methylpyridine (**55**) (50 g, 290 mmol) and $KMnO_4$ (46.2 g, 292 mmol) was heated to reflux temperature in H_2O (800 mL) for 4 hours. After cooling the reaction mixture to room temperature, $KMnO_4$ (46.2 g, 292 mmol) was added and it was refluxed for 20 hours. The reaction mixture was filtered with celite in gauch kroze and the liquid part was extracted with EtOAc (2 x 100 mL) to remove impurities. Then, the aqueous layer was acidified with aq. HCl (1M) to pH = 2. After filtering white precipitate with gauch kroze, it was washed with H_2O (100 mL) and CH_2Cl_2 (200 mL) to give 2-bromopyridine-3-carboxylic acid (**59**) (26 g, 44%).



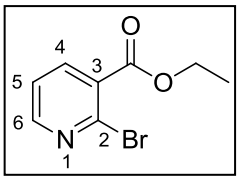
^{1}H NMR(400 MHz, *DMSO*) : δ 8.4 (dd, J=4.8 ; 2.0 Hz, 1H), 8.1 (dd, J=7.6 ; 4.8 Hz, 1H), 7.6 (dd, J=7.6 ; 2.0 Hz, 1H)

^{13}C NMR (400 MHz, *DMSO*): δ 166.4, 151.8, 139.2, 138.7, 131.1, 123.2

IR (ATR, cm^{-1}) : 2746, 1714, 1578, 1403, 1270, 1159, 1122, 1057, 963, 817, 764, 703, 543

3.4 Synthesis of ethyl 2-bromonicotinate (61)

2-Bromopyridine-3-carboxylic acid (**59**) (10 mmol, 2 g) was dissolved in dry THF and cooled at -5 ^oC by ice-salt bath. A cold solution of triethylamine (20 mmol, 2 g) in THF (3 mL) was added to this solution drop by drop in 10 min and the reaction mixture was stirred for 0.5 h without removing ice bath. After that, a solution of ethyl chloroformate (15 mmol, 1,7 g) in 3 ml of THF was added as dropwise in 10 min while maintaining the same temperature and stirred for 0.5 h. Then ethanol (15 mL) was added to the reaction mixture and stirred for 0.5h at room temperature. After 0.5 h, the mixture was heated to the reflux temperature overnight. The reaction was monitored on TLC. After completion of reaction the mixture extracted with EtOAc (2 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and evoporated. The crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:1). After evoporation of solvent, ethyl 2-bromonicotinate (**61**) was obtained as light yellow oil (90%, 2.05 g).



^{1}H NMR (400 MHz, *$CDCl_3$*): δ ppm 8.41 (dd, *J* = 4.75, 2.01 Hz, 1H), 8.00 (dd, *J* = 7.64, 2.01 Hz, 1H), 7.28 (dd, *J* = 7.69, 4.76 Hz, 1H), 4.36 (q, *J* = 7.15 Hz, 2H), 1.35 (t, *J* = 7.14 Hz, 3H)

^{13}C NMR (400 MHz, *$CDCl_3$*): δ 164.9, 151.8, 140.4, 139.4, 129.9, 122.3, 62.1, 14.1

IR (ATR, cm^{-1}) : 2981, 1728, 1575, 1556, 1394, 1366, 1298, 1272, 1242, 1138, 1048

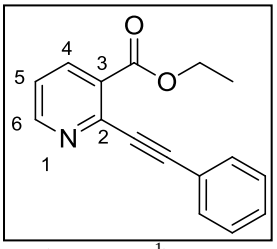
3.5 General procedure for coupling products 61a-d

Ethyl 2-bromonicotinate (0.8 g, 3.5 mmol) was dissolved the mixture of THF (11 mL) and DIPA (4 mL) at room temperature. Then alkyne derivatives (1.2 eq) were added while purged with N_2 gas atmosphere 15 min. Sequentially, $PdCl_2$ (0.02 mmol, 3.5 mg), PPh_3 (0.06 mmol, 16.0 mg) and CuI (0.015 mmol, 3.0 mg) were added. Reactions were monitored on TLC. After completion of reaction, it was extracted with EtOAc (2 x 100 mL) and dried over $MgSO_4$. The solvent was evaporated. The crude products were purified by column chromatography (silica gel) eluting with suitable solvent mixture to give coupling product derivatives as oil. According to acetylene derivatives, the reaction time, temperature, yield were changed.

Table 4

	Compound 61	Temperature	Time	Crude Yield	Column Solvent --------- EtOAc:Hexane	color
a	-phenyl	45 ^{0}C	5 h	85%	1:4	Light yellow
b	1-hexanyl	65 ^{0}C	24 h	95%	1:5	Light yellow
c	-$SiMe_3$	40 ^{0}C	5 h	92%	1:4	brown
d	-4-methoxyphenyl	55 ^{o}C	6h	87%	1:4	yellow

3.5.1 Synthesis of ethyl 2-(phenylethynyl)nicotinate (61a)

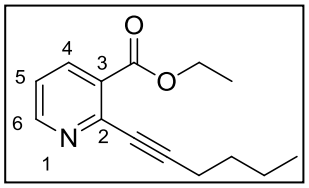


^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.62 (dd, *J* = 4.77, 1.76 Hz, 1H), 8.15 (dd, *J* = 7.97, 1.77 Hz, 1H), 7.59-7.50 (m, 2H), 7.30-7.18 (m, 4H), 4.34 (q, *J* = 7.15 Hz, 2H), 1.30 (t, *J* = 7.14 Hz, 3H)

^{13}C NMR (400 MHz, *$CDCl_3$*): δ 162.6, 150.0, 140.1, 135.7, 129.7, 129.7, 126.8, 126.3, 125.9, 125.9, 119.9, 119.8, 91.6, 85.5, 59.2, 11.8

IR (ATR, cm^{-1}) : 2981, 2224, 1708, 1559, 1491, 1428, 1267, 1136, 1076, 776, 756, 689.

3.5.2 Synthesis of methyl 2-hex-1-ynylnicotinate (61b)



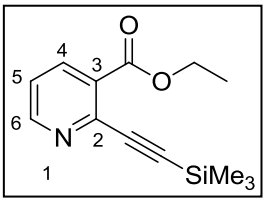
^{1}H NMR (400 MHz, *$CDCl_3$*) δ ppm 8.67 (dd, *J* = 4.78, 1.77 Hz, 1H), 8.18 (dd, *J* = 7.96, 1.77 Hz, 1H), 7.27 (dd, *J* = 7.94, 4.79 Hz, 1H), 4.41 (q, *J* = 7.17 Hz, 2H), 2.52 (t, *J* = 7.15 Hz, 2H), 1.66 (q, 2H), 1.52 (h, 7.19 Hz, 2H), 1.42 (t, *J* = 7.14 Hz, 3H)

^{13}C NMR (400 MHz, *$CDCl_3$*): δ 165.4, 152.1, 142.9, 137.8, 128.5, 121.6, 96.4, 79.4, 61.4, 30.3, 22.0, 19.4, 14.2, 13.5

IR (ATR, cm^{-1}) 2933, 2872, 2231, 1711, 1579, 1559, 1428, 1366, 1264, 1134, 1082, 1052, 777, 730

HRMS Spectrum: Found: 232.1335 ; Calculated $[M+H]^+$ = 232.1332

3.5.3 Synthesis of ethyl 2-((trimethylsilyl)ethynyl)nicotinate (61c)

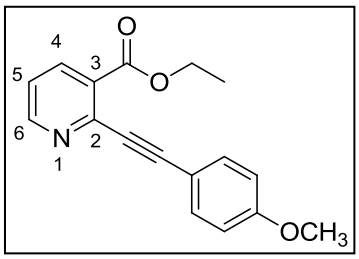


^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 7.13 (dd, *J* = 8.85, 5.82 Hz, 1H), 8.01 (dd, *J* = 7.99, 1.65 Hz, 1H), 8.60-8.42 (m, 1H), 4.24 (q, *J* = 7.10 Hz, 2H), 1.24 (t, *J* = 7.15 Hz, 3H), 0.11 (s, 9H)

^{13}C NMR (400 MHz, *CDCl$_3$*): δ ppm 165.7, 152.6, 142.2, 138.3, 129.6, 122.8, 102.8, 102.7, 100.5, 62.1, 14.6, 0.00

IR (ATR, cm^{-1}) : 2979, 2935, 2221, 1724, 1708, 1557, 1508, 1428, 1247, 1155, 1075, 1025, 831, 775, 532

3.5.4 Synthesis of ethyl 2-((4-methoxyphenyl)ethynyl)nicotinate (61d)



^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.72 (dd, *J* = 4.76, 1.74 Hz, 1H), 8.25 (dd, *J* = 7.95, 1.74 Hz, 1H), 7.64-7.55 (m, 2H), 7.30 (dd, *J* = 7.95, 4.77 Hz, 1H), 6.93-6.87 (m, 2H), 4.45 (q, *J* = 7.15 Hz, 2H), 3.84 (s, 3H), 1.42 (t, *J* = 7.14 Hz, 3H)

^{13}C NMR (400 MHz, *CDCl$_3$*): δ ppm 165.3, 160.4, 152.4, 143.0, 138.1, 138.1, 133.8, 128.4, 121.8, 121.8, 114.4, 114.1, 94.5, 87.1, 61.6, 55.3, 14.3

IR (ATR, cm^{-1}) : 2960, 1732, 1714, 1558, 1422, 1002, 1249, 1135, 1078, 841, 778

HRMS Spectrum: Found: 281.1163 ; Calculated $[M+H]^+$ = 282,1125

3.6 General procedure for pyridodiazepinone derivatives 52a-b

The hydrazine monohydrate (0.50-0.55 g, 10-11 mmol) was added to the solution of coupling products **61** (0.5 g, 2-2.2 mmol) in MeOH (15 mL). Reaction mixture was heated to reflux temperature. Reaction was monitored on TLC. After completion of reaction, it was extracted with mixture of EtOAc (2 x 50 mL) and H_2O, dried over $MgSO_4$ and the solvent was evaporated in vacuo and separated by column chromatography with suitable solvent mixture to give pyridodiazepinone and naphthyridinone derivatives as light yellow solid.

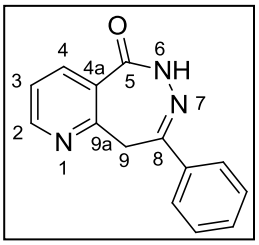
Table 5

	Pyridodiazepinone derivatives(52a-b)	Temperature	Time	Crude Yield	Column Solvent EtOAc:Hexane
a	-phenyl	50 ^{o}C	24 h	25%	2:5
b	-1-hexanyl	65 ^{o}C	48 h	20%	Not yet isolated

Table 6

	Naphthyridinone Derivatives (**69**)	Temperature	Time	Crude Yield	Column Solvent ---------- EtOAc:Hexane
a	-phenyl	50 ^{o}C	24 h	60%	2:5
b	1-hexanyl	65 ^{o}C	48 h	60%	1:2
c	-H	45 ^{o}C	24 h	75%	1:6

3.6.1 Synthesis of 8-phenyl-6,9-dihydro-5H-pyrido[3,2-d][1,2]diazepin-5-one (52a)



^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.91 (s, 1H -NH), 8.66 (dd, *J* = 4.95, 1.67 Hz, 1H), 8.33 (dd, *J* = 7.83, 1.33 Hz, 1H), 8.04-7.54 (m, 2H), 7.42-7.34 (m, 4H), 4.35-4.34 (s, 2H)

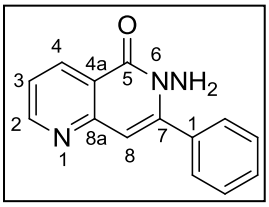
^{13}C NMR (400 MHz, *CDCl$_3$*): δ 164.4, 157.9, 152.9, 151.3, 137.8, 133.3, 129.1, 129.1, 127.1, 125.7, 125.7, 125.6, 121.6, 37.0

IR (ATR, cm^{-1}) : 2917, 2849, 1651, 1607, 1581, 1458, 1436, 1361, 1260, 1018, 801, 750, 684

HRMS Spectrum: Found: 238.0996; Calculated $[M+H]^{+}$ = 238.0975

Melting Point (^{0}C): 164.7-165.8 ^{0}C

3.6.2 Synthesis of 6-amino-7-phenyl-1,6-naphthyridin-5(6H)-one (69a)



^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.87 (dd, *J* = 4.51, 1.61 Hz, 1H), 8.65 (dd, *J* = 8.07, 1.13 Hz, 1H), 7.55-7.40 (m, 5H), 7.37 (dd, *J* = 8.11, 4.57 Hz, 1H), 6.77 (s, 1H), 5.03 (s, 2H)

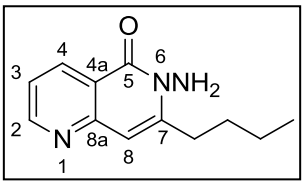
^{13}C NMR (400 MHz, *CDCl$_3$*): δ 159.6, 152.9, 150.3, 145.4, 134.7, 132.4, 127.8, 127.6, 127.6, 126.7, 126.7, 119.9, 118.3, 106.8

IR (ATR, cm^{-1}) : 3182, 1644, 1608, 1583, 1430, 1391, 1295, 1021, 838, 776, 698

Melting point : 210.6-212.2 ^{o}C

HRMS Spectrum: Found: 238.0996; Calculated $[M+H]^{+}$ = 238.0981

3.6.3 Synthesis of 6-amino-7-butyl-1,6-naphthyridin-5(6H)-one (69b)



^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.88 (dd, *J* = 4.54, 1.74 Hz, 1H), 8.64 (dd, *J* = 8.45, 1.24 Hz, 1H), 7.35 (dd, *J* = 8.07, 4.55 Hz, 1H), 6.67 (s, 1H), 4.96 (s, 2H, -NH), 2.93-2.87 (dt, 2H), 1.73 (q, *J* = 15.25, 7.53 Hz, 2H), 1.59-1.31 (h, 2H), 0.99 (t, *J* = 7.34 Hz, 3H)

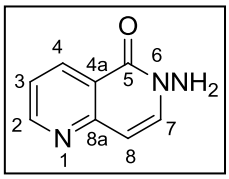
^{13}C NMR (400 MHz, *CDCl$_3$*): δ 162.2, 154.4, 152.3, 135.5, 149.3, 136.2, 120.7, 119.1, 105.5, 32.3, 30.2, 22.3, 13.8

IR (ATR, cm^{-1}) : 3288, 3129, 2958, 2870, 1603, 1582, 1558, 1465, 1453, 1393, 1298, 1242, 1100, 816, 770, 713

Melting Point : 120.8-121 ^{o}C

HRMS Spectrum: Found: 218.1286 ; Calculated $[M+H]^+$ = 218.1288

3.6.4 Synthesis of 6-amino-1,6-naphthyridin-5(6H)-one (69c)



^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.93 (dd, *J* = 4.55, 1.79 Hz, 1H), 8.70 (dd, *J* = 8.09, 1.38 Hz, 1H), 7.63 (d, *J* = 7.72 Hz, 1H), 7.43 (dd, *J* = 8.13, 4.57 Hz, 1H), 6.78 (d, *J* = 7.73 Hz, 1H), 5.14 (s, 2H, -NH)

^{13}C NMR (400 MHz, *CDCl$_3$*): δ 160.8, 153.4, 152.2, 135.5, 135.1, 120.7, 120.3, 106.1

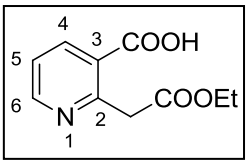
IR (ATR, cm^{-1}): 3296, 3189, 1637, 1612, 1578, 1555, 1479, 1399, 1306, 1242, 1089, 796, 710, 623

Melting Point: 189-191 ^{o}C

HRMS Spectrum: Found: 162.0666 ; Calculated $[M+H]^+$ = 162.0667

3.7 Synthesis of 2-(2-ethoxy-2-oxoethyl)nicotinic acid (53)

Na (1.44 g, 62 mmol) in small portions was dissolved in dry EtOH (30 mL) and ethylacetoacetate (4,78 mL, 37.5 mmol) was added. It was followed by the addition of 2-bromopiridine-3-carboxylic acid **(59)** (5 g, 18.5 mmol) and 0.2 g $Cu(OAc)_2$ and heated to reflux temperature for 2 hours. Then, it was cooled to room temperature and 25 mL of acetic acid. After the solvent of the reaction mixture was evaporated, 25 mL of water was added and it was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. It was purified with column chromatography on silica gel eluting with hexane:EtOAc (1:1) and re-crystallized with hexane:EtOAc (1:10) to give 2-(2-ethoxy-2-oxoethyl)nicotinic acid (**53)** as snowflake white crystals (2.84 g, 55%).



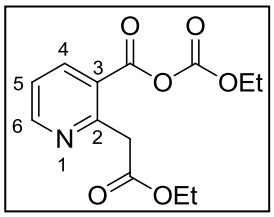
^{1}H NMR(400 MHz, *CDCl$_3$*) : δ 13.1 (s, 1H), 8.8 (dd, J=5.2 ; 2.0 Hz, H_6), 8.4 (dd, J=8.0 ; 5.2 Hz, H_4), 7.4 (dd, J=8.0 ;2.0 Hz, H_5), 4.25 (s, 2H), 4.13 (q,J=7.2 Hz, 2H), 1.25 (t,J=7.2 Hz, 3H)

^{13}C NMR (400 MHz, *CDCl$_3$*): δ 170.4, 169.1, 155.9, 151.2, 140.4, 126.7, 122.8, 61.0, 42.8 14.1.

IR (ATR, cm^{-1}) : 2375, 1724, 1585, 1244, 1089, 1025, 936, 801, 755, 740, 591

3.8 Synthesis of 2-(2-ethoxy-2-oxoethyl)nicotinic (ethyl carbonic) anhydride (75)

2-(2-ethoxy-2-oxoethyl)nicotinic acid (3 mmol, 0.6 g) (**53**) was dissolved in dry THF (10 mL) and cooled at -5 ^{o}C by ice-salt bath. A cold solution of triethylamine (3.6 mmol, 0.36 g) in THF (3 mL) was added to this solution drop by drop in 10 min and the reaction mixture was stirred for 0.5h without removing ice bath. After that, a solution of ethyl chloroformate (3.6 mmol, 0.39 g) in 3 mL of THF was added as dropwise in 10 min while maintaining the same temperature and stirred for 0.5 h. Then the reaction mixture was stirred over night at room temperature. After completion of reaction, for extraction of organic phase, EtOAc (100 x 2 mL) and mixture of water and HCl (1 mL) were used. Then combined organic phase dried over $MgSO_4$. After evaporation, light yellow solid was obtained (0,73 g, 90%).



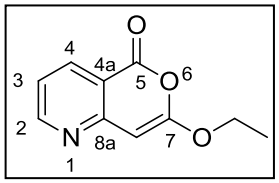
^{1}H-NMR (400 MHz, *CDCl$_3$*) δ ppm 8.63 (dd, *J* = 4.86, 1.75 Hz, 1H), 8.22 (dd, *J* = 7.98, 1.75 Hz, 1H), 7.28 (dd, *J* = 7.97, 4.85 Hz, 1H), 4.19 (s, 2H), 4.29 (q, *J* = 7.14 Hz, 2H), 4.06 (q, *J* = 7.14 Hz, 2H), 1.28 (t, *J* = 7.15 Hz, 3H), 1.13 (t, *J* = 7.14 Hz, 3H)

^{13}C NMR (400 MHz, *CDCl$_3$*) : δ 169.8, 160.4, 157.3, 153.2, 148.4, 139.1, 123.4, 122.4, 66.1, 60.8, 43.6, 13.9, 13.7

IR (ATR, cm^{-1}) : 2984, 1718, 1582, 1445, 1244, 1182, 1139, 1088, 1024, 742

3.9 Synthesis of methyl 2-(2-ethoxy-2-oxoethyl)nicotinate (76) and 7-ethoxy-5H-pyrano[4,3-b]pyridin-5-one (54)

Methanol (15 mL) was added to 2-(2-ethoxy-2-oxoethyl)nicotinic (ethyl carbonic) anhydride (**75**) (1.8 mmol, 0.5 g) and heated to reflux temperature overnight. The reaction was monitored on TLC. After completion of reaction the mixture extracted with EtOAc (2 x 100 ml). The combined organic extracts were dried with $MgSO_4$ and evaporated. The crude products was separated by column chromatography (silica gel) eluting with ethylacetate/hexane (7:3). 7-ethoxy-5H-pyrano[4,3-b]pyridin-5-one (**54**) was obtained. (40%, 0.14 g) and methyl 2-(2-ethoxy-2-oxoethyl)nicotinate (**76**) was obtained (60%, 0.24 g)



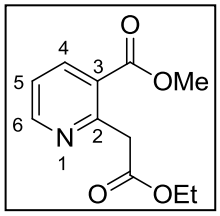
^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.72 (dd, *J* = 4.74, 1.79 Hz, 1H), 8.35 (dd, *J* = 7.99, 1.76 Hz, 1H), 7.17 (dd, *J* = 7.95, 4.75 Hz, 1H), 5.79 (s, 1H), 4.18 (q, *J* = 7.05 Hz, 2H), 1.42 (t, *J* = 7.05 Hz, 3H)

^{13}C NMR (400 MHz, *CDCl$_3$*) : δ 161.8, 160.5, 157.3, 156.3, 138.1, 120.4, 113.4, 81.9, 65.7, 14.2

IR (ATR, cm^{-1}) **:** 3085, 2987, 1740, 1632, 1596, 1558, 1441, 1316, 1214, 1180, 1009, 994, 796

HRMS Spectrum: Found: 192.0669; Calculated $[M+H]^{+}$ = 192,0667

Melting point : 109.2-109.9 ^{o}C



^{1}H NMR (400 MHz, *CDCl$_3$*) δ ppm 8.60 (dd, *J* = 4.83, 1.74 Hz, 1H), 8.22 (dd, *J* = 7.90, 1.76 Hz, 1H), 7.25 (dd, *J* = 7.91, 4.84 Hz, 1H), 4.21 (s, 2H), 4.10 (q, *J* = 7.13 Hz, 2H), 3.82 (s, 3H), 1.17 (t, *J* = 7.13 Hz, 3H)

^{13}C NMR (400 MHz, *CDCl$_3$*) : δ 170.5, 166.2, 155.9, 151.9, 138.6, 125.7, 122.2, 60.7, 52.2, 43.7, 14.1

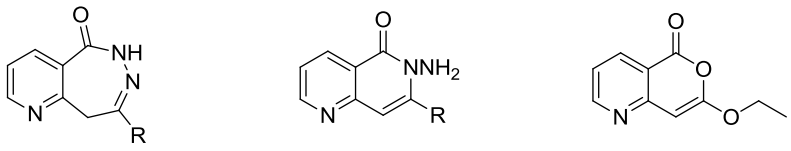
Melting point : 88-90 ^{o}C

IR (ATR, cm^{-1}) : 2975, 1734, 1716, 1570, 1559, 1269, 1242, 1174, 1131, 1086, 1028, 744

CHAPTER 4

CONCLUSION

In this study, we developed new synthetic methodologies for the synthesis of pyridodiazepinone **52,** naphthyridinone **69** and pyranopyridinone **54** derivatives (Scheme 30). These compounds show potential for possessing biological activity since there are many biologically active compounds in the literature having the similar framework with these molecules.

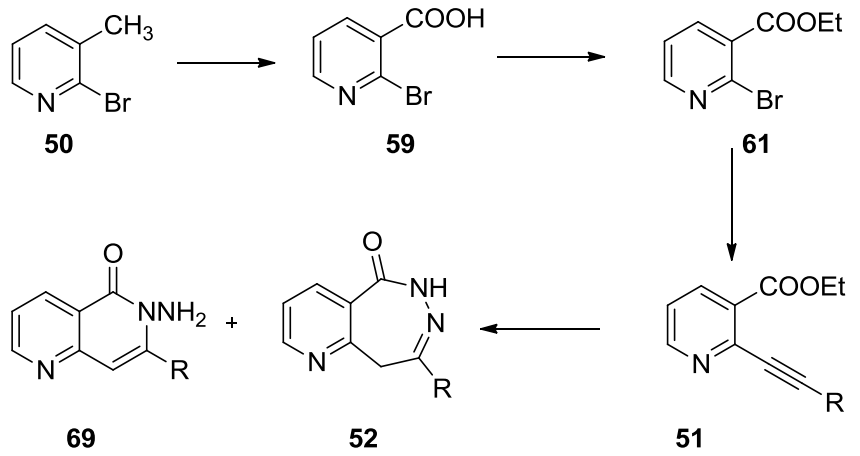


52 **69** **54**

Scheme 30

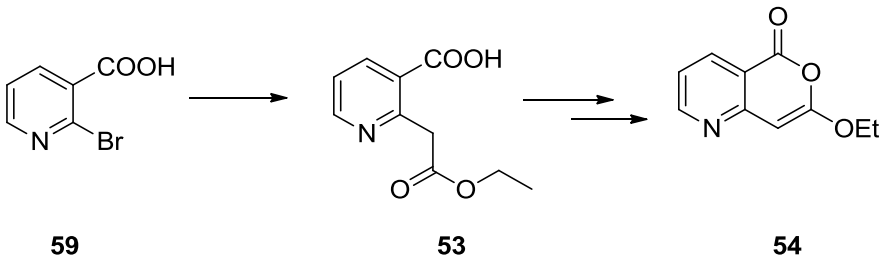
We have divided our studies into two parts. In the first part of our study, we focused on the synthesis of pyridodiazepinone derivatives.

Bromopyridine **50** was synthesized by using modified Sandmeyer reaction. Then, to obtain ester **61**, sequentially oxidation and esterification reaction were performed. After the synthesis of bromonicotinate **61**, Sonogashira coupling reaction was applied and coupling products **51** were obtained. Finally, to obtain pyridodiazepinone **54**, the coupling product **51** was reacted with hydrazine monohydrate and alkyl cyclization without using any electrophile was achieved. However, unexpected product naphthyridinone derivatives **69** were obtained as the major product. Therefore, the new synthetic method was revealed for the synthesis of pyridodiazepinone **52** and naphthyridinone **69** in a facile way (Scheme 31).



Scheme 31

Second part of this study includes the synthesis of pyranopyridinone **54**. The first two steps were the same with the first part. Then, Hurtley condensation reaction was applied using copper acetate to obtain corresponding compound **53**. Treating with nicotinic acid **53** with triethylamine and ethylchloroformate and following treatment with methanol gave pyranopyridinone **54** using intramolecular cyclization (Scheme 32).



Scheme 32

REFERENCES

(1) Pozharskii, A. F.; Soldatenkov, A. T.; Katrizky, A. R. *Heterocycles Life and Society*; Wiley, 2011; pp. 162–167.

(2) Tan, K. R.; Brown, M.; Labouebe, G.; Yvon, C.; Creton, C.; Fritschy, J.-M.; Rudolph, U.; Lüscher, C. *Nature* **2010**, *463*, 769–775.

(3) Archer, G. A.; Sternbach, L. H. *Chem. Rev.* **1968**, *68*, 747–784.

(4) Cooper, J. R.; Bloom, F. E.; Robert, H. R. *The Complete Story of Benzodiazepines*; 7th ed.; USA: Oxford University Press, 1996.

(5) Sternbach, L. H. *Agent Actions* **1972**, *2*, 193–196.

(6) Cowen, P. J.; Green, A. R.; Nutt, D. J. *Nature* **1981**, *290*, 54–55.

(7) Ståhl, Y.; Persson, A.; Petters, I.; Rane, A.; Theorell, K.; Walson, P. *Epilepsia* **1983**, *24*, 225–231.

(8) Browne, T. R. *Arch. Neurol.* **1976**, *33*, 326–332.

(9) Sternbach, L. H. *J. Med. Chem.* **1979**, *22*, 1–7.

(10) Sternbach, L. H.; Garantini, S.; Mussini, E.; Randall, L. O. *The benzodiazepines*; Raven Press: New York, 1973; pp. 685–687.

(11) Verdecia Reyes, Y.; Ochoa Rodriguez, E.; Ruiz Reyes, A.; Nunez Figueredo, Y.; Carillo Dominguez, C.; Tacoronte Morales, J. E.; Alba Gutierrez, L. L.; Pardo Andreu, G. L. 12.pdf, WO 2011041989 A2 **2011**.

(12) Savelli, F.; Boido, A.; Vazzana, I.; Sparatore, F. J. *J. Heterocycl. Chem.* **1987**, *24*, 1709–1716.

(13) Savelli, F.; Boido, A.; Satta, M.; Peana, A.; Marzano, C. *Farmaco.* **1994**, *49*, 259–265.

(14) Savelli, F.; Boido, A.; Damonte, G. J. *Heterocycl. Chem.* **1996**, *33*, 1737–1742.

(15) Hussenether, T.; Hübner, H.; Gmeiner, P.; Troschütz, R. *Bioorg. Med. Chem.* **2004**, *12*, 2625–2637.

(16) El Bouakher, A.; Prié, G.; Aadil, M.; Lazar, S.; Akssira, M.; Viaud-Massuard, M.-C. *Tetrahedron* **2012**, *68*, 9572–9577.

(17) Legerén, L.; Domínguez, D. *Tetrahedron Lett.* **2010**, *51*, 4053–4057.

(18) Magano, J.; Acciacca, A.; Akin, A.; Collman, B. M.; Conway, B.; Waldo, M.; Chen, M. H.; Mennen, K. E. *Org. Proc. R&D* **2009**, *13*, 555–566.

(19) Thurston, D. E.; Bose, D. S.; Howard, X. P. W.; Jenkins, T. C.; Leoni, A.; Baraldi, P. G.; Guiotto, A.; Cacciari, B.; Kelland, L. R.; Foloppe, M.; Rault, S. *J. Med. Chem.* **1999**, *42*, 1951–1964.

(20) Gibbons, S. *Nat. Prod. Rep.* **2004**, *21*, 263–277.

(21) Dennis, N.; Katritzky, A. R.; Parton, S. K. *J. Chem. Soc. Perkin Trans. I* **1974**, *0*, 750–754.

(22) Mandal, A. B.; Augustine, J. K.; Quattropani, A.; Bombrun, A. *Tetrahedron Lett.* **2005**, *46*, 6033–6036.

(23) Meier, P.; Legraverant, S.; Müller, S.; Schaub, J. *Synthesis* **2003**, *4*, 551–554.

(24) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46–49.

(25) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084–5121.

(26) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131.

(27) Yang, L.; Zhao, L.; Li, C.-J. *Chem. Comm* **2010**, *46*, 4184–4186.

(28) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937–2980.

(29) Baldwin, J. *J.C.S. Chem. Comm.* **1976**, 734–736.

(30) Abbiati, G.; Arcadi, A.; Bellinazzi, A.; Beccalli, E.; Rossi, E.; Zanzola, S. *J. Org. Chem.* **2005**, *70*, 4088–4095.

(31) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

(32) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

(33) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Cossi, P. G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A. J.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, T.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. M.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. . J. *Gaussian 09, Revision B.01, Gaussian, Inc., Wallingford CT* **2010**.

(34) Miertus, S.; Scrocco, E.; Tomasi, J. *J. Chem. Phys.* **1981**, *55*, 117–129.

(35) Hurtley, W. H. R. *J. Chem. Soc.* **1929**, *0*, 1870–1873.

(36) Lindley, J. *Tetrahedron* **1983**, *40*, 1433–1456.

(37) Aalten, H. L.; Koten, G. V; Goubitz, K.; Stam, C. S. *Organomet.* **1989**, *8*, 2293–2299.

(38) Ames, D. E.; Dodds, W. D. *J. Chem. Soc. Perkin Trans. I* **1972**, 705–710.

(39) Furniss, B. S.; Hannaford, A. C.; Smith, G. S. W.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; 5th ed.; Wiley and Sons, 1994.

APPENDIX A

SPECTRAL DATA

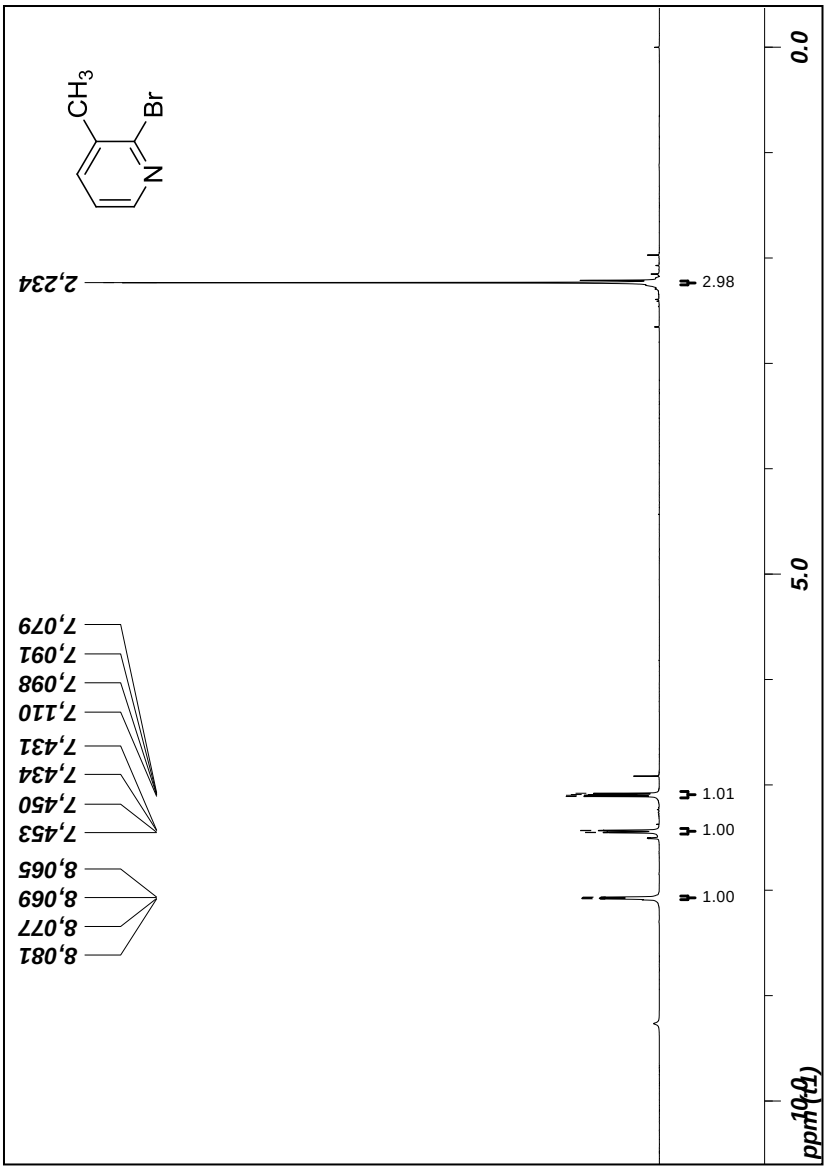


Figure 7 ^{1}H-NMR Spectrum of Compound **50**

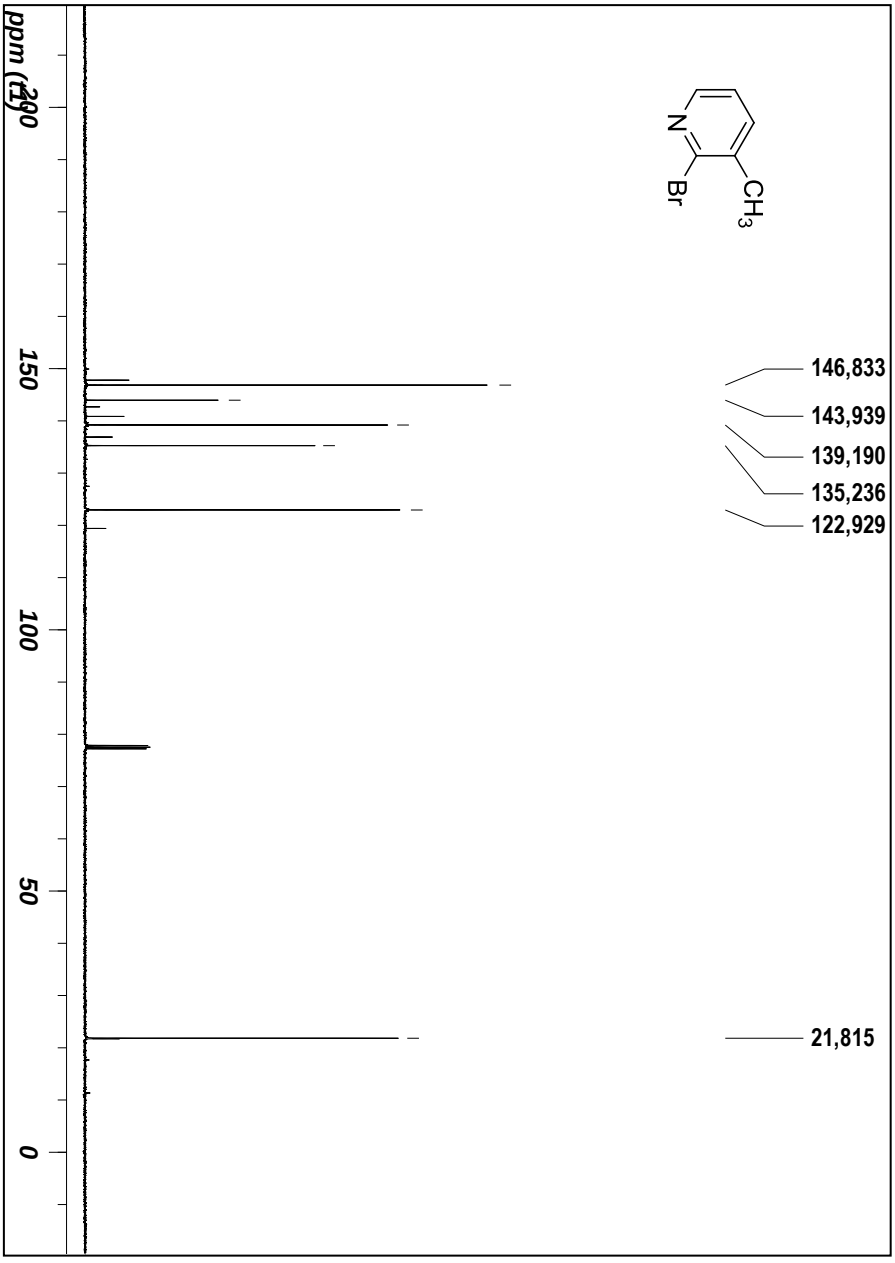


Figure 8 ^{13}C NMR Spectrum of Compound 50

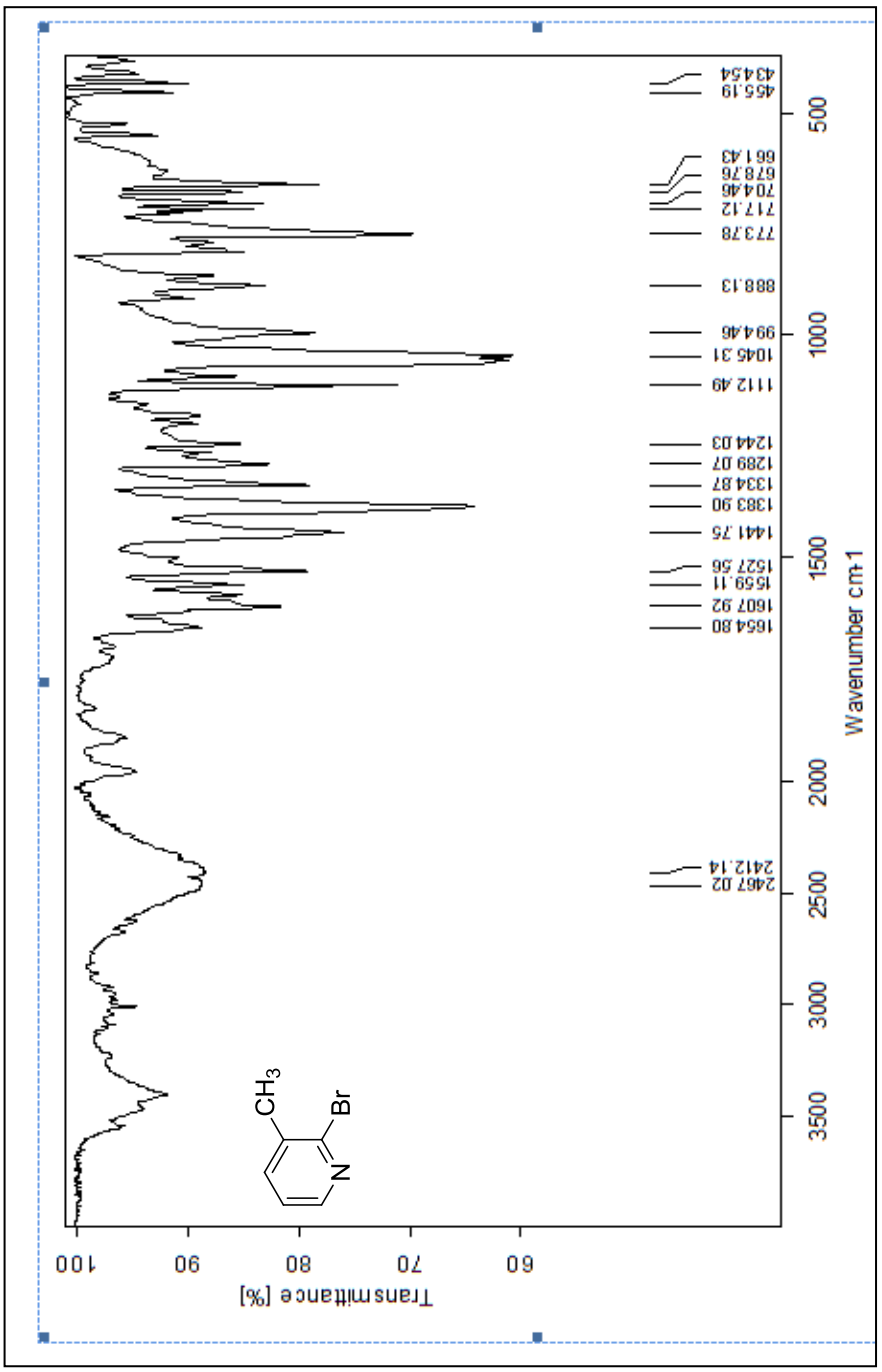


Figure 9 IR (ATR cm^{-1}) Spectrum of Compound 50

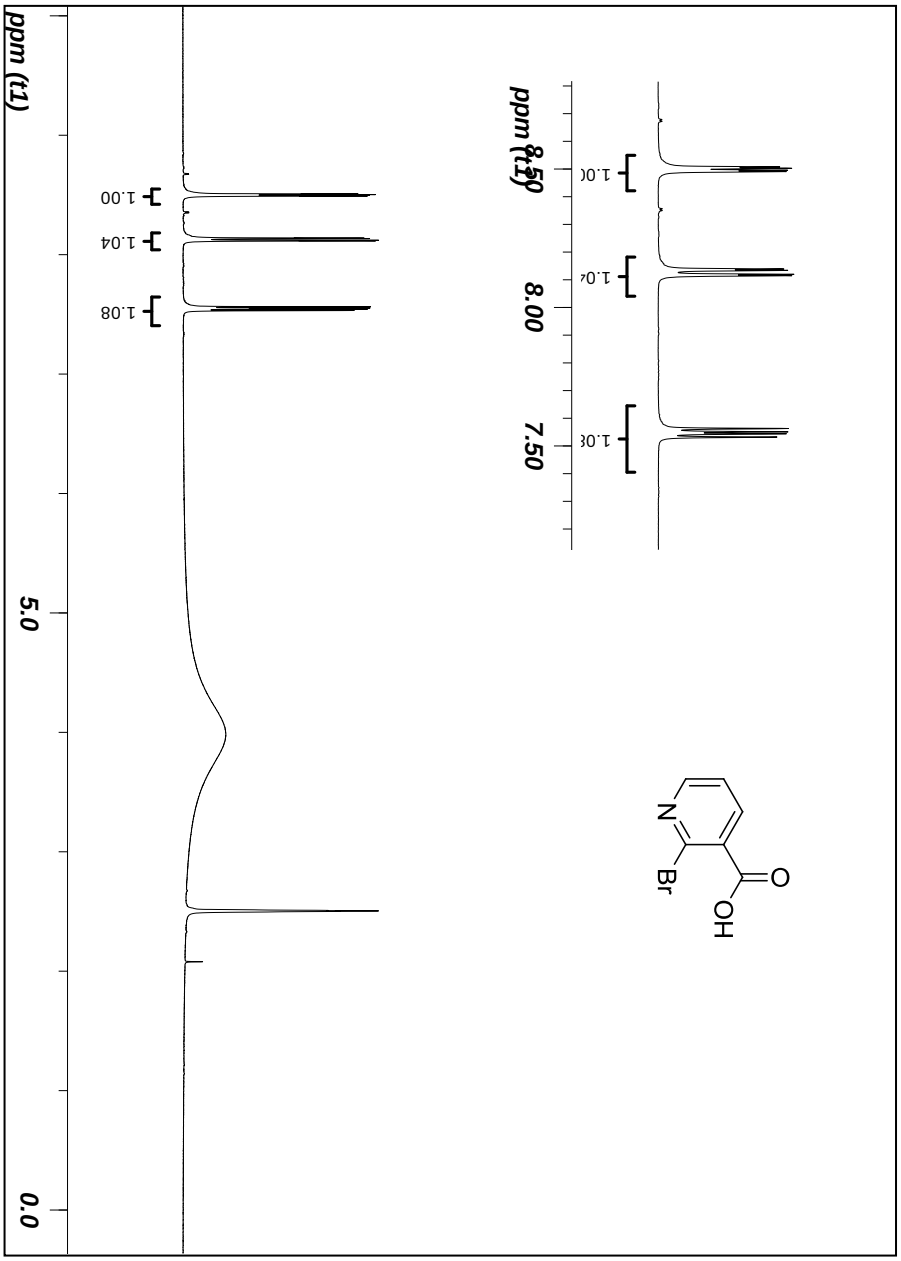


Figure 10 ^{1}H-NMR Spectrum of Compound 59

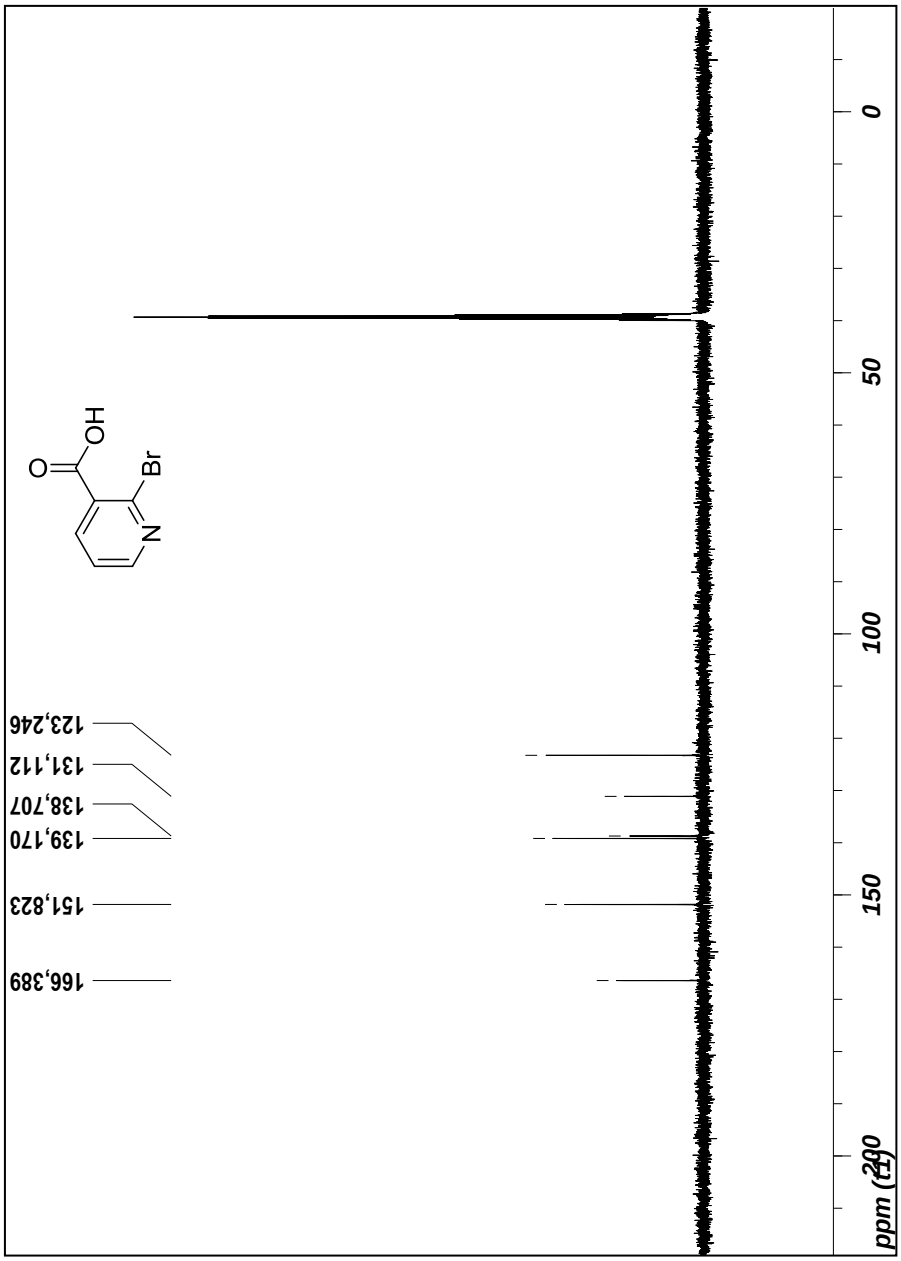


Figure 11 ^{13}C-NMR Spectrum of compound 59

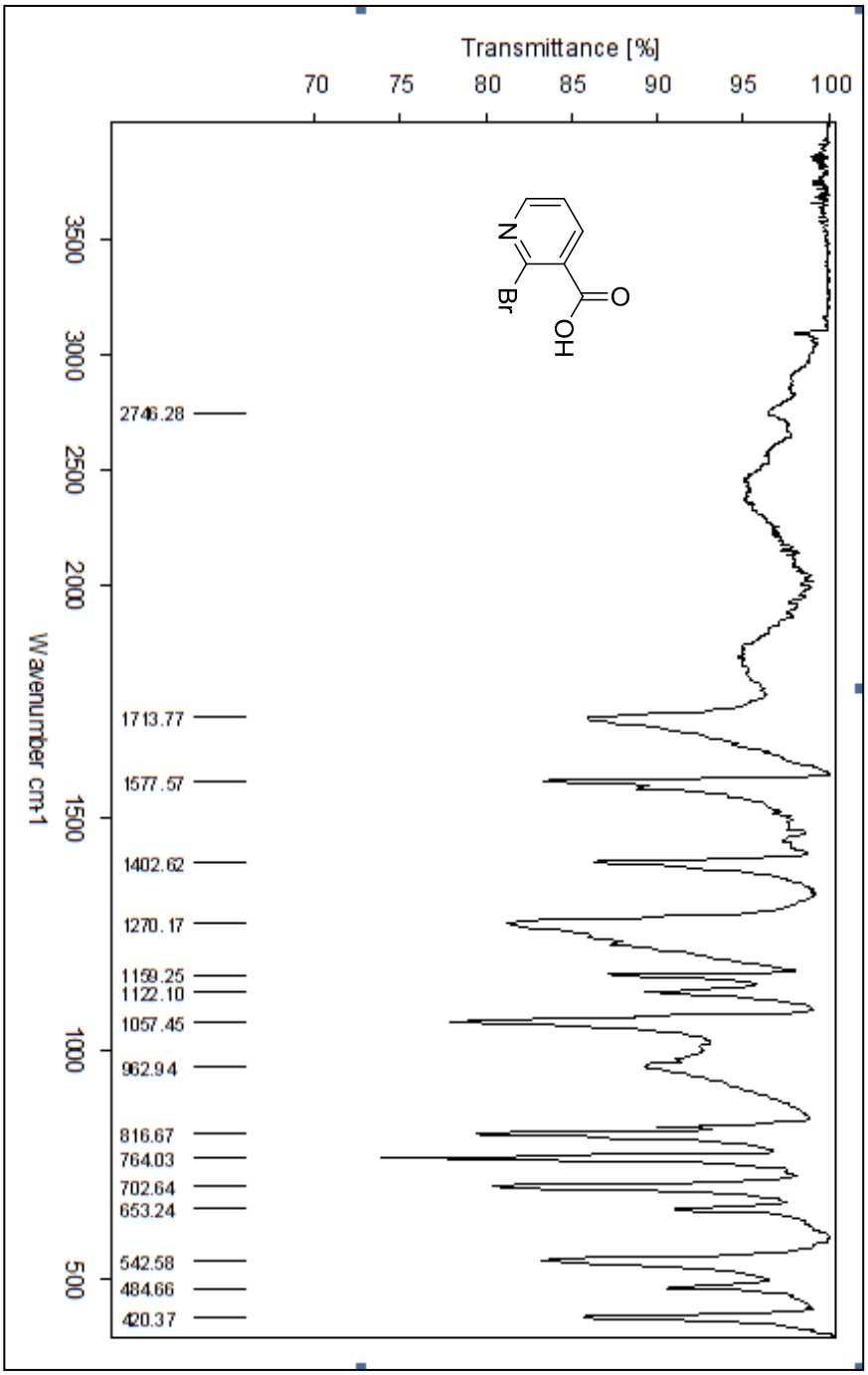


Figure 12 IR (ATR cm^{-1}) Spectrum of Compound 59

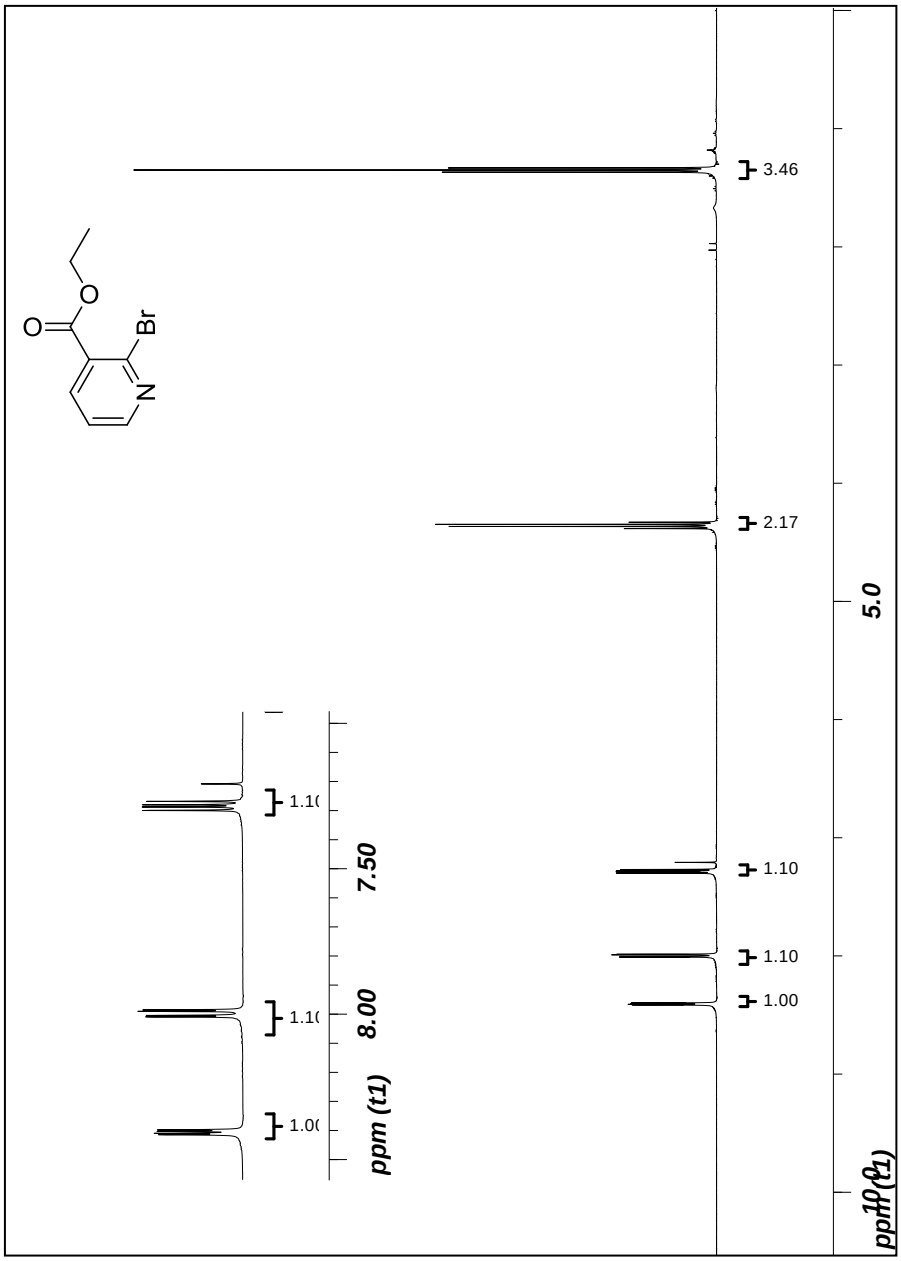


Figure 13 ^{1}H-NMR Spectrum of compound 61

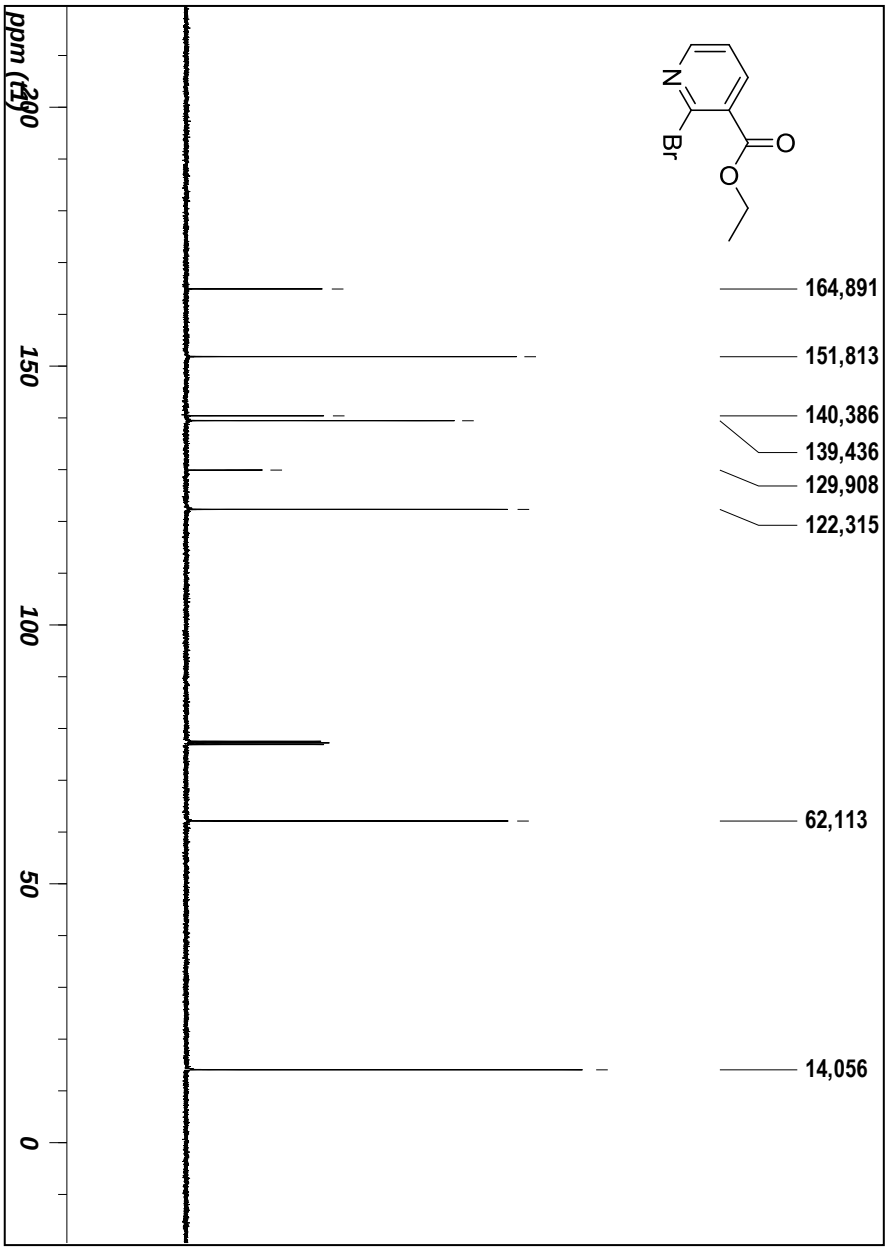


Figure 14 ^{13}C-NMR Spectrum of Compound 61

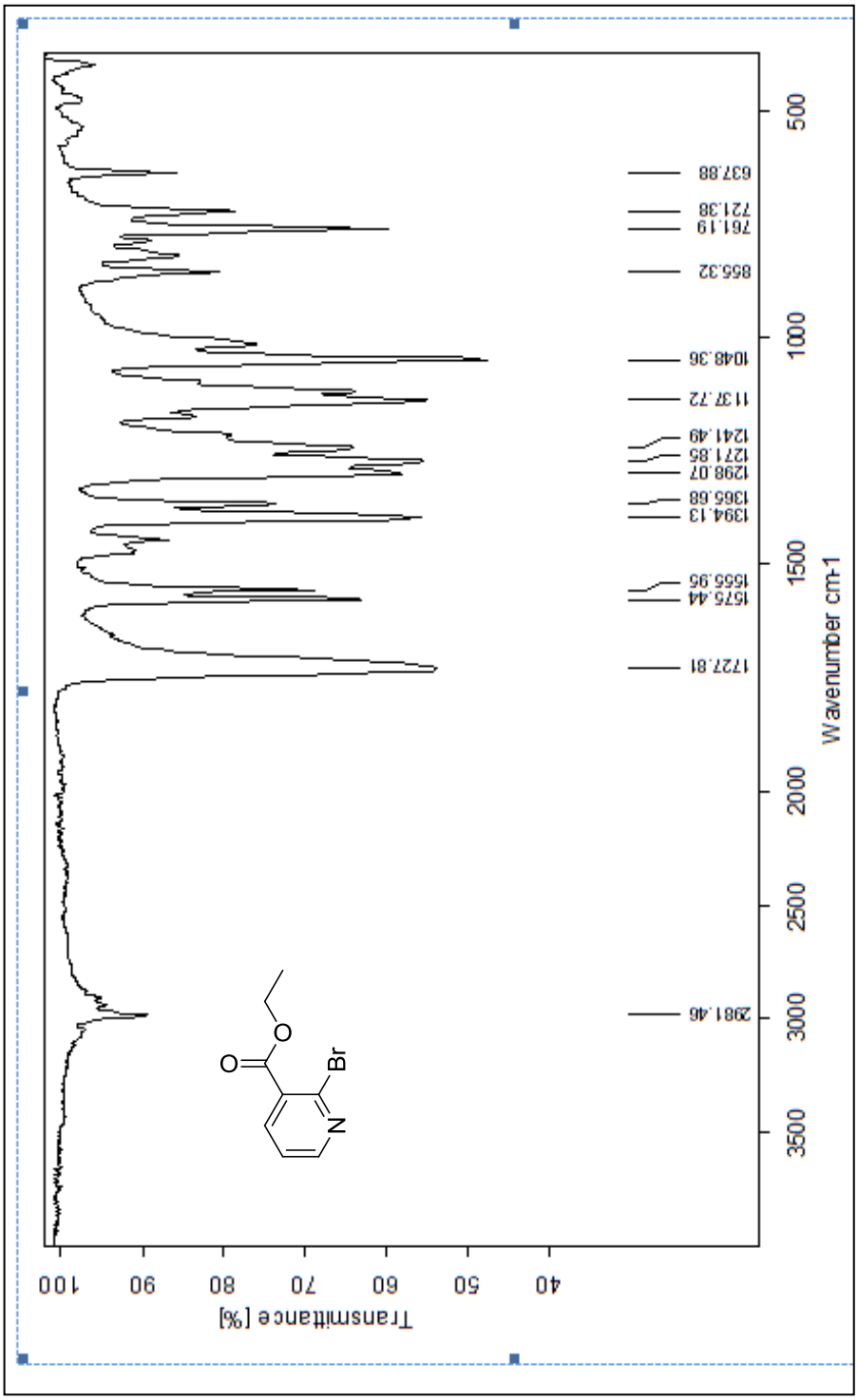


Figure 15 IR (ATR cm^{-1}) Spectrum of Compound 61

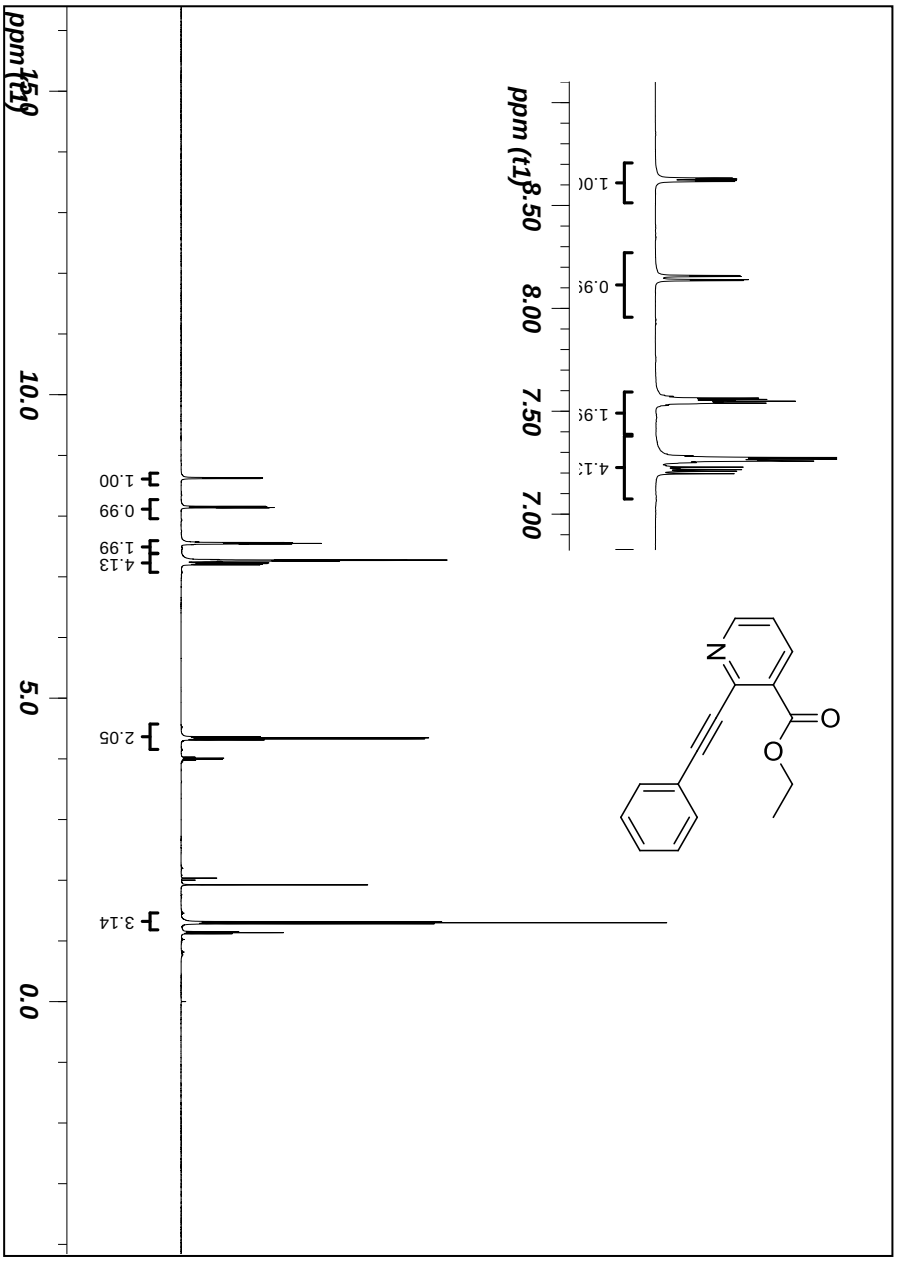


Figure 16 ^{1}H-NMR Spectrum of Compound 51a

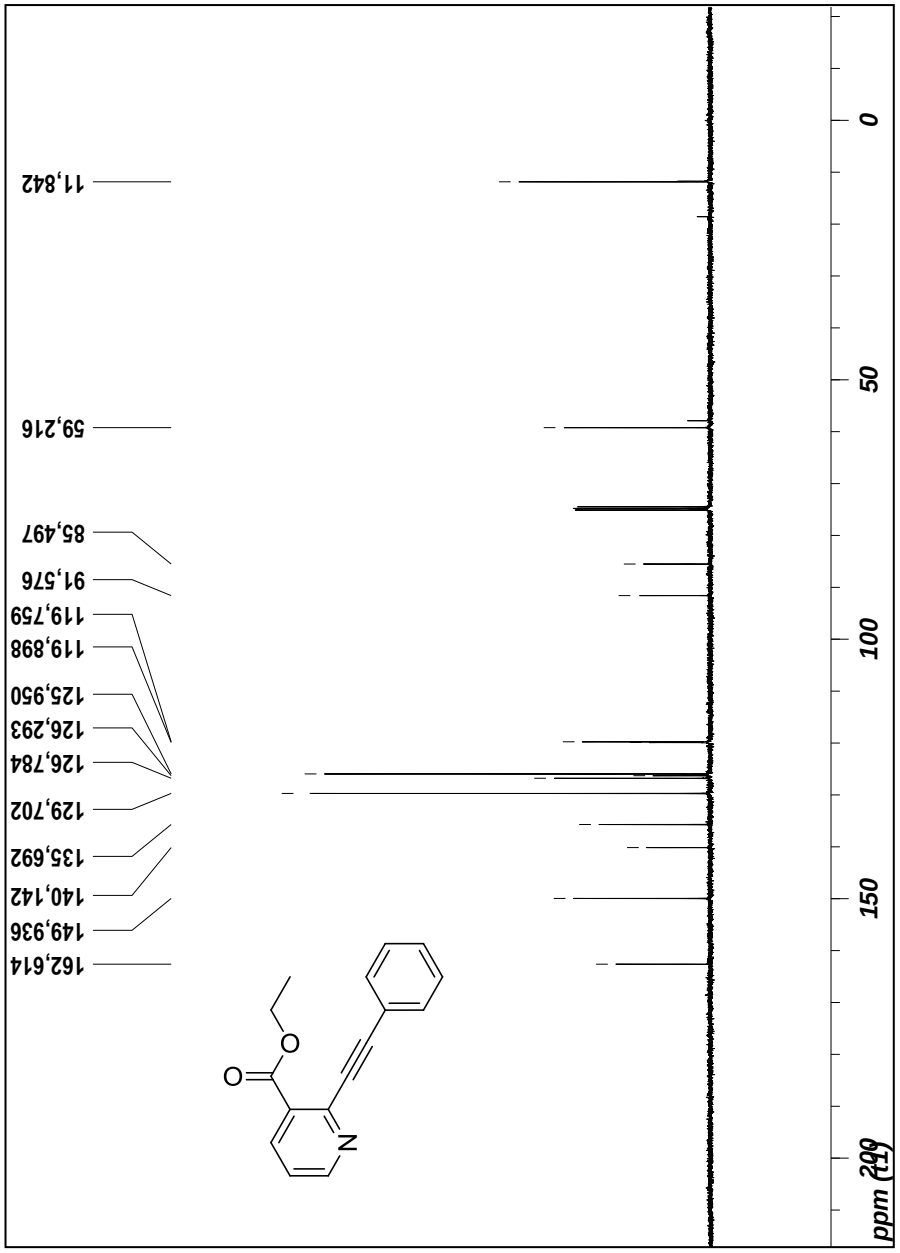


Figure 17 ^{13}C-NMR Spectrum of Compound 51a

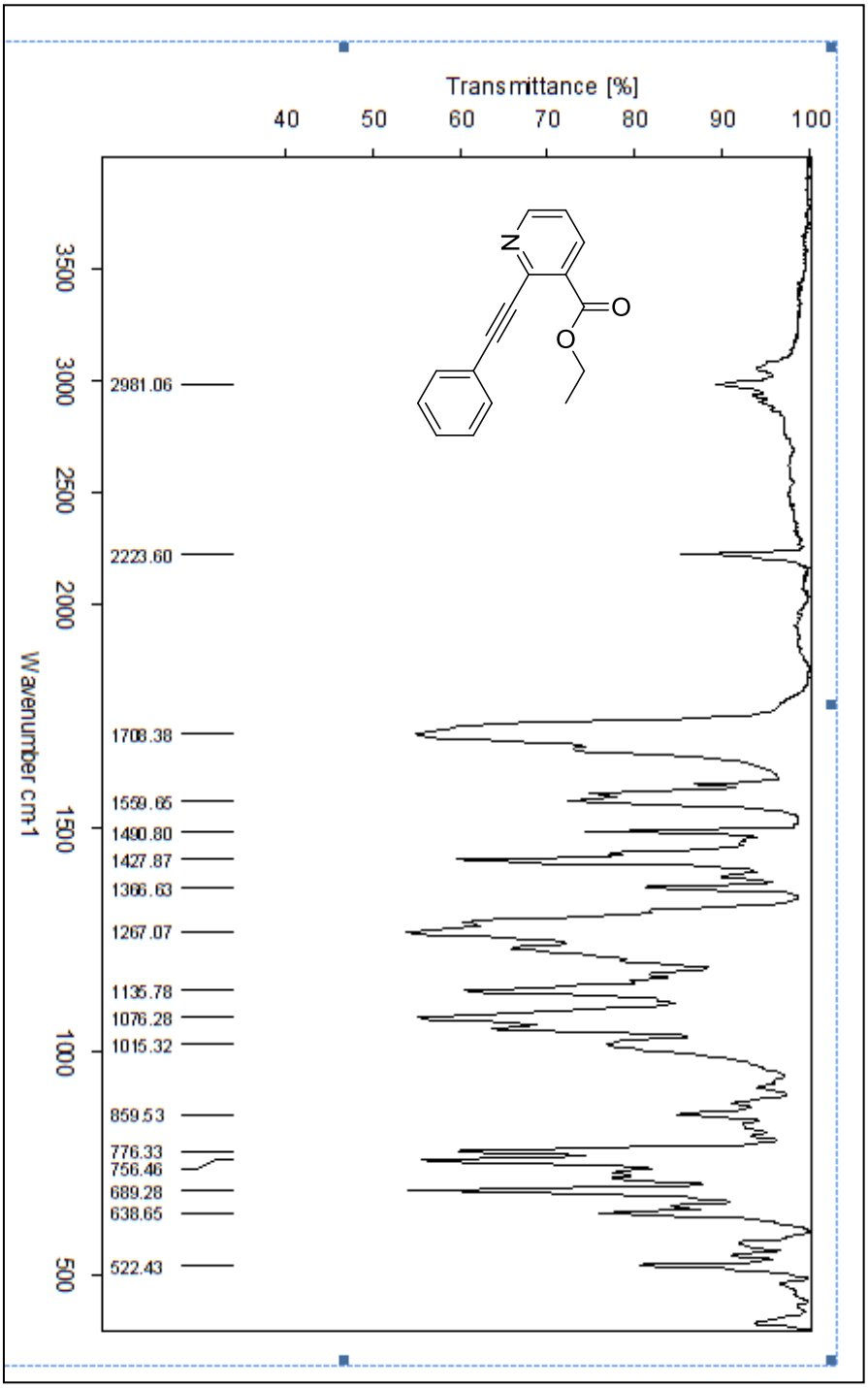


Figure 18 IR (ATR cm^{-1}) Spectrum of Compound 51a

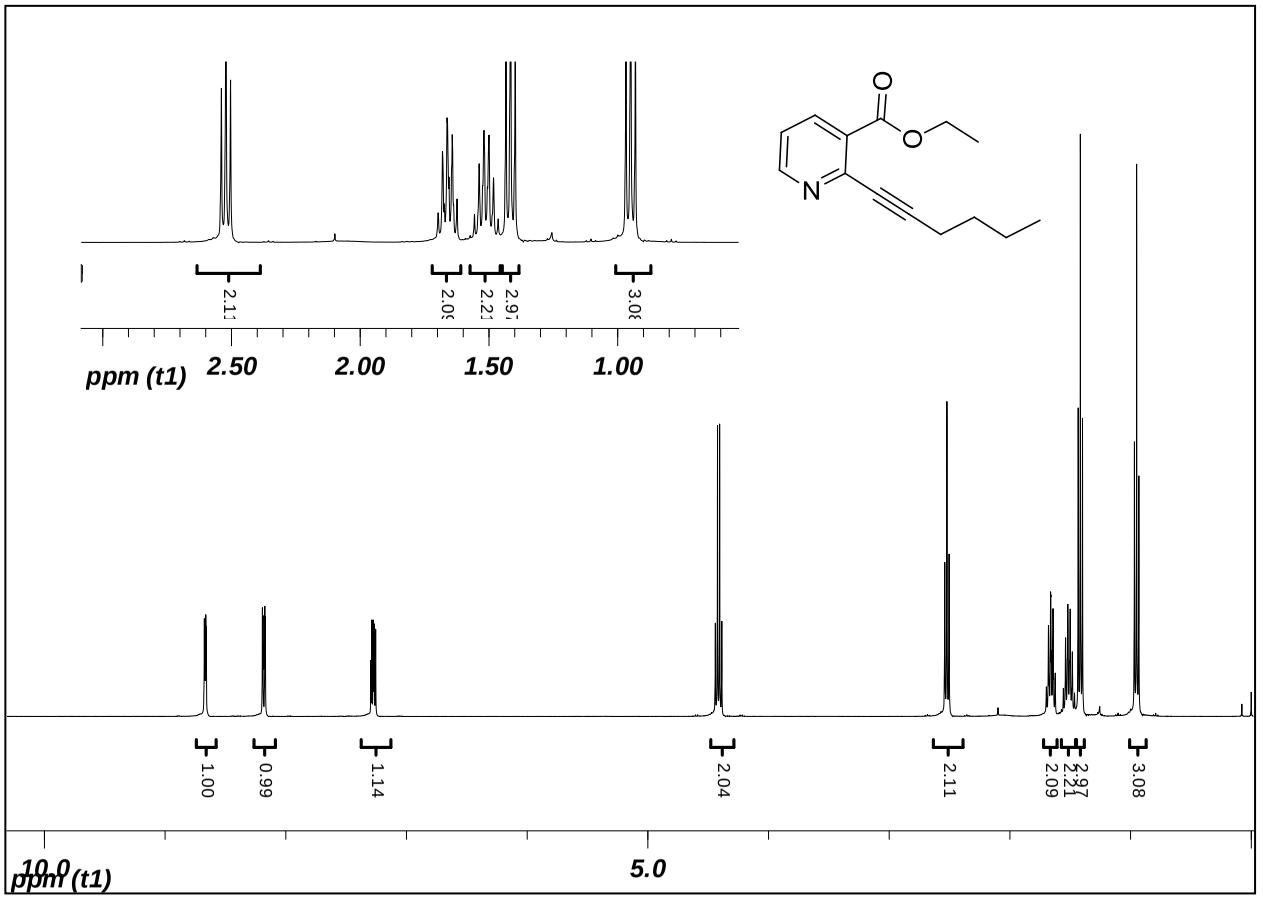


Figure 19 ^{1}H-NMR Spectrum of Compound 51b

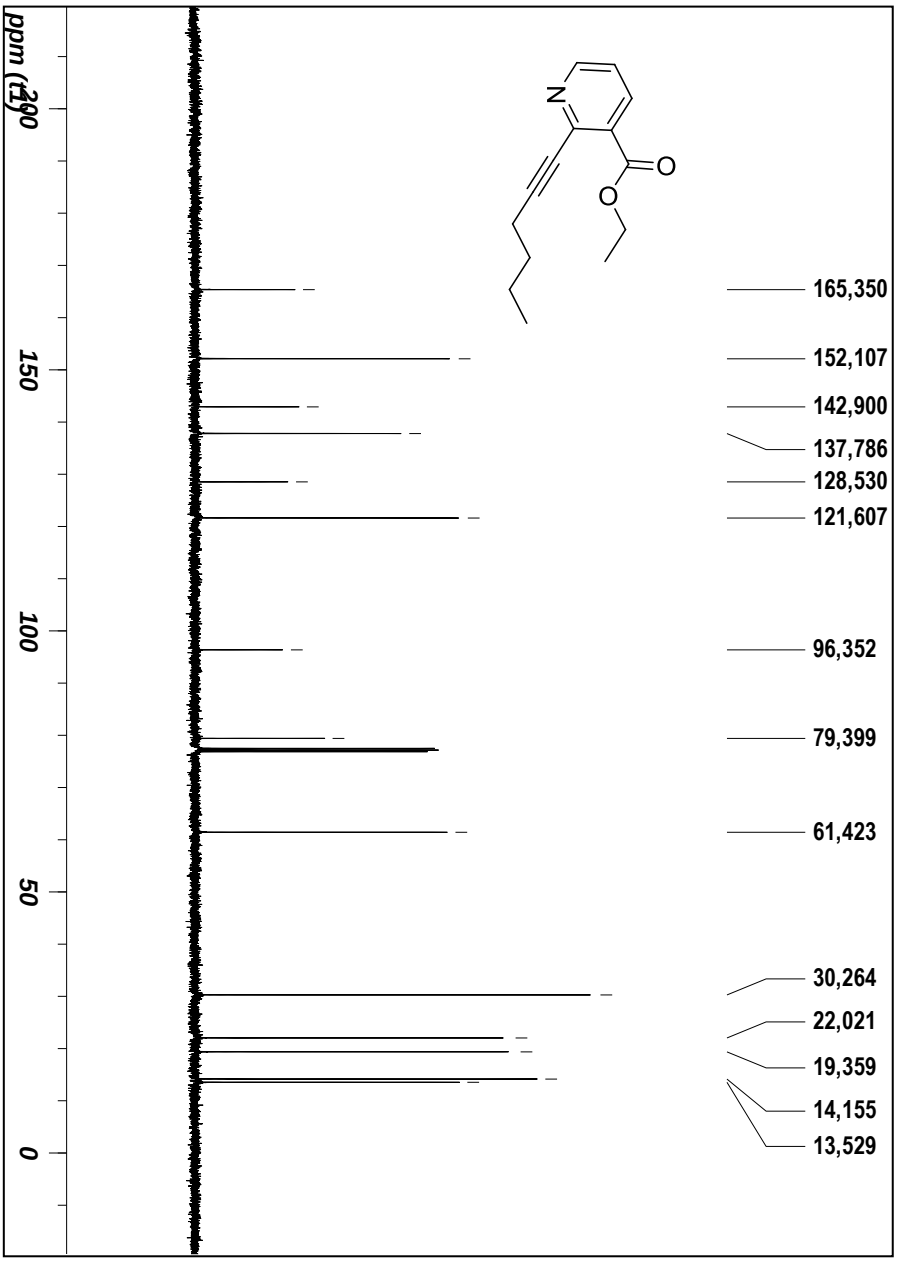


Figure 20 ^{13}C-NMR Spectrum of Compound 51b

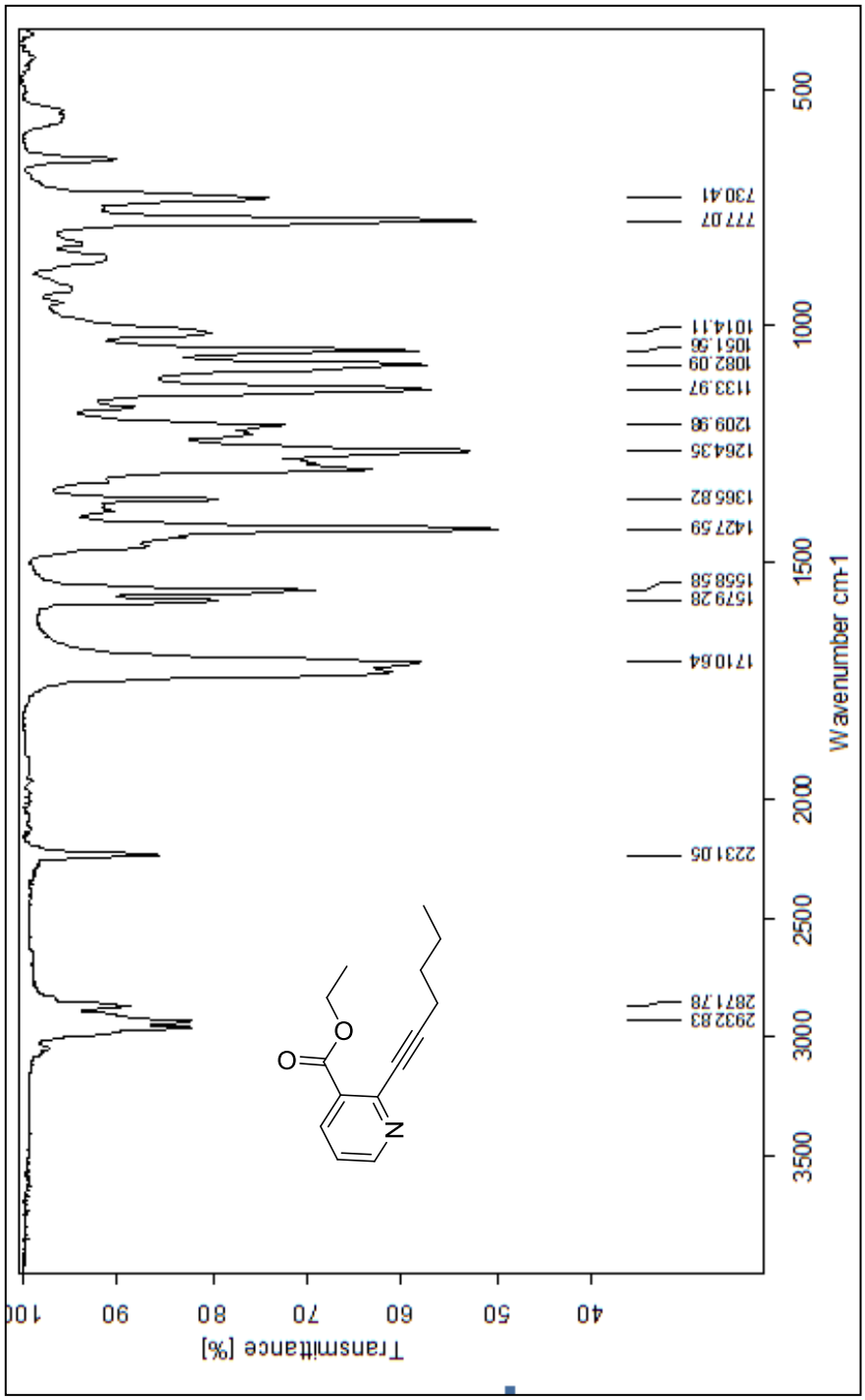


Figure 21 IR (ATR cm^{-1}) Spectrum of Compound 51b

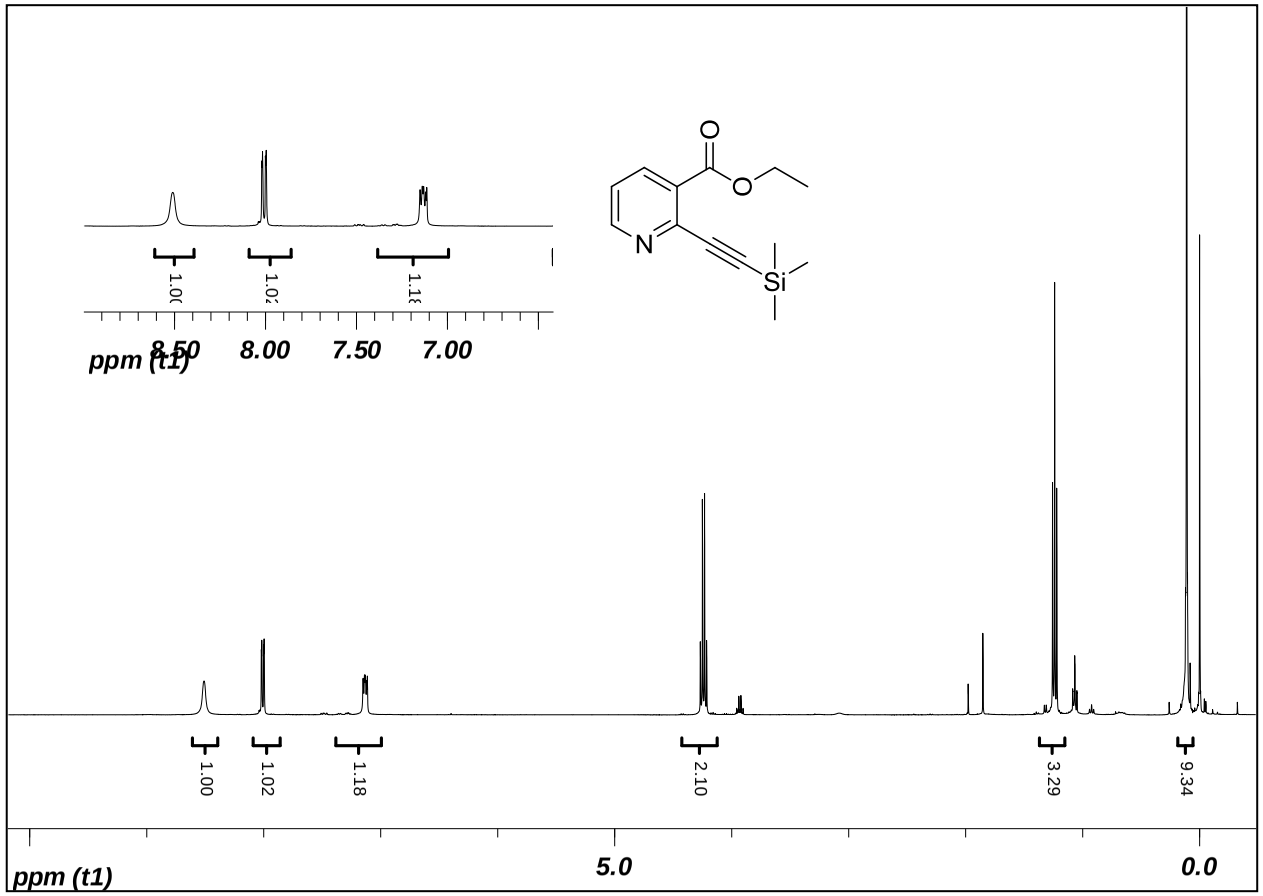


Figure 22 [1]H-NMR Spectrum of Compound 51c

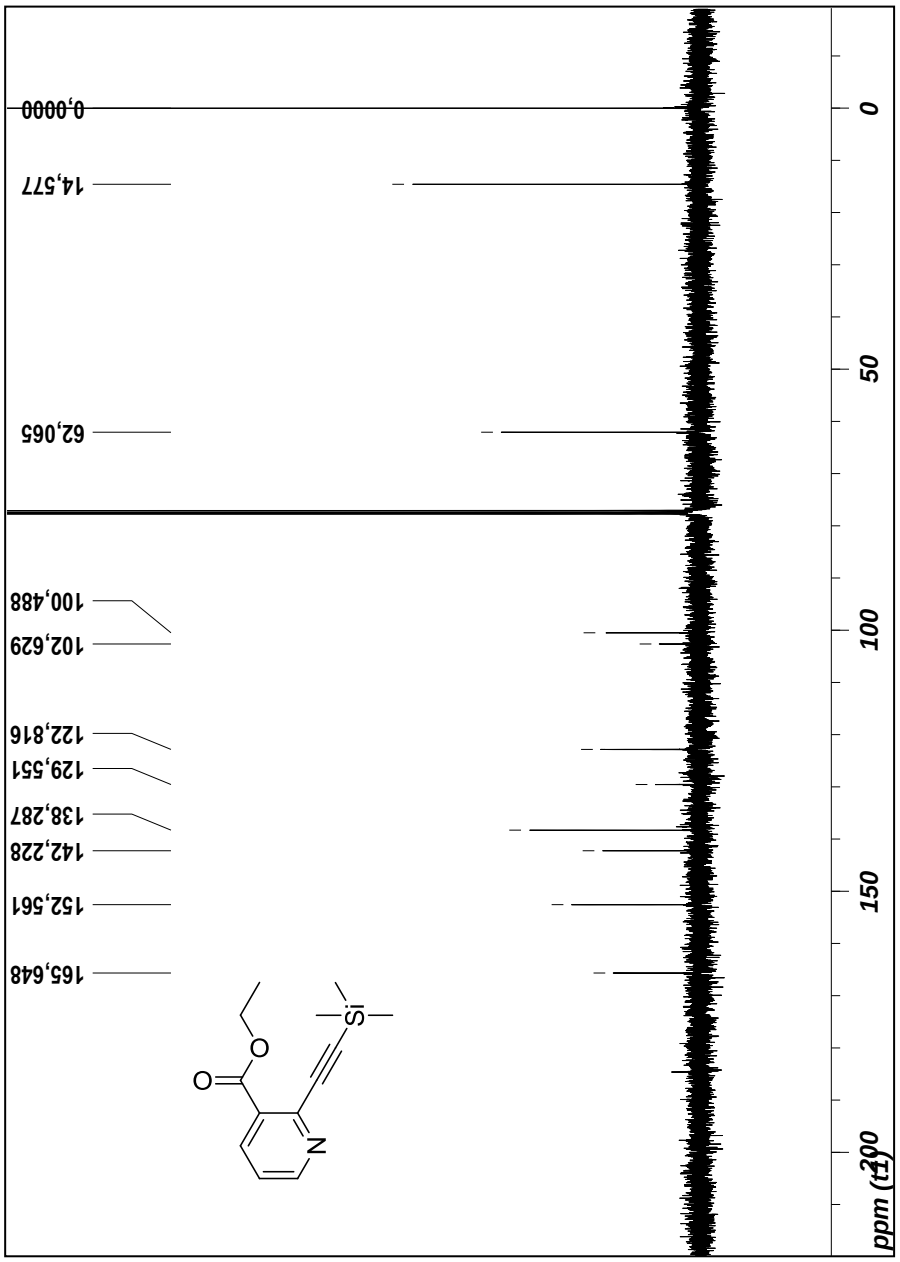


Figure 23 ^{13}C-NMR Spectrum of Compound 51c

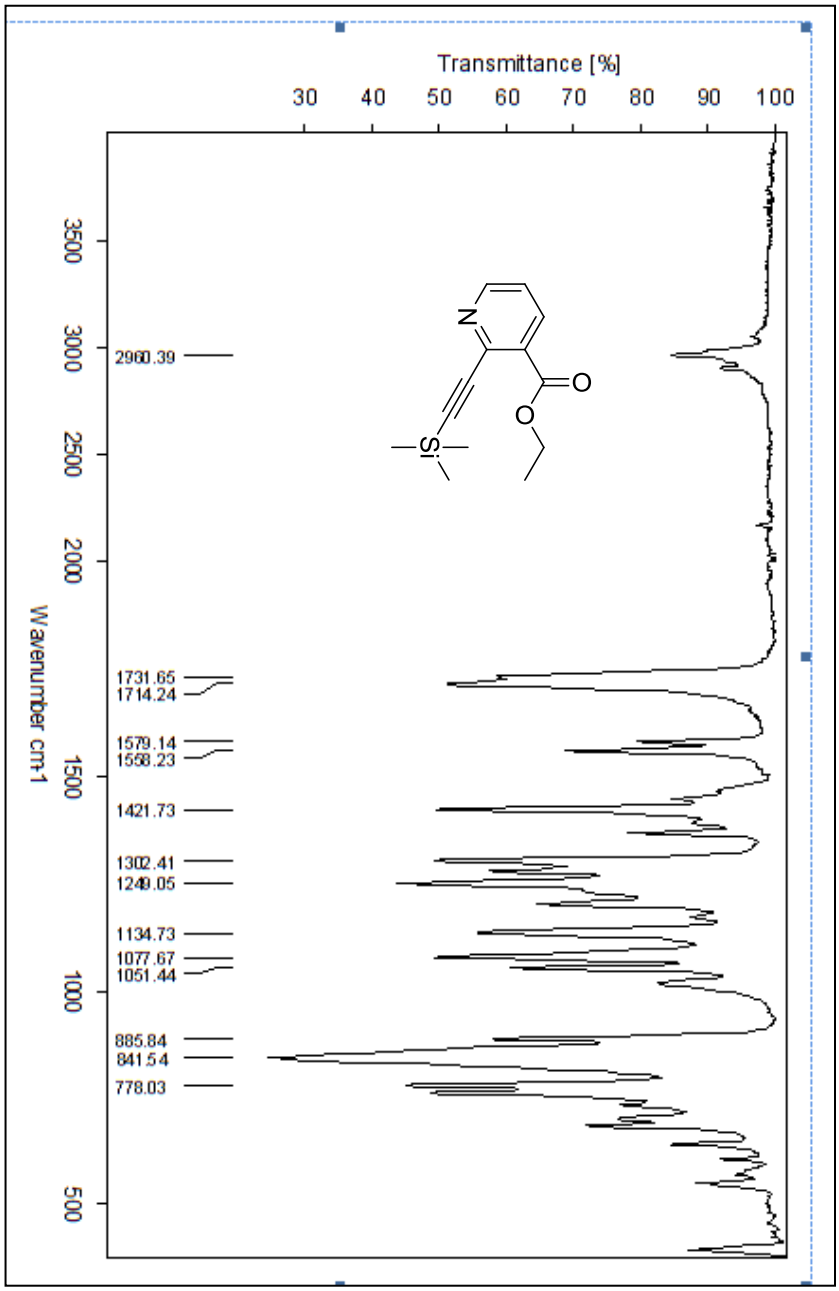


Figure 24 IR (ATR cm^{-1}) Spectrum of Compound 51c

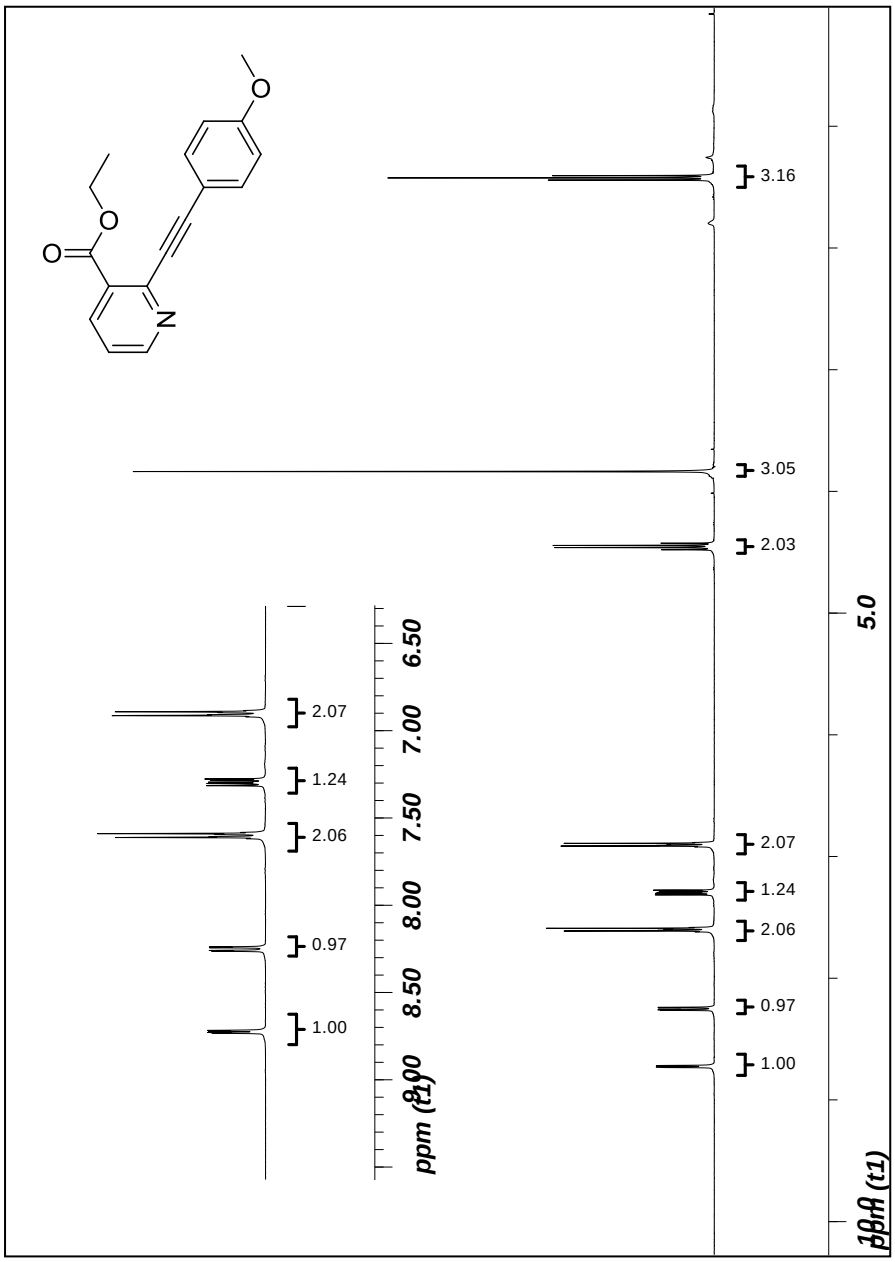


Figure 25 ^{1}H-NMR Spectrum of Compound 51d

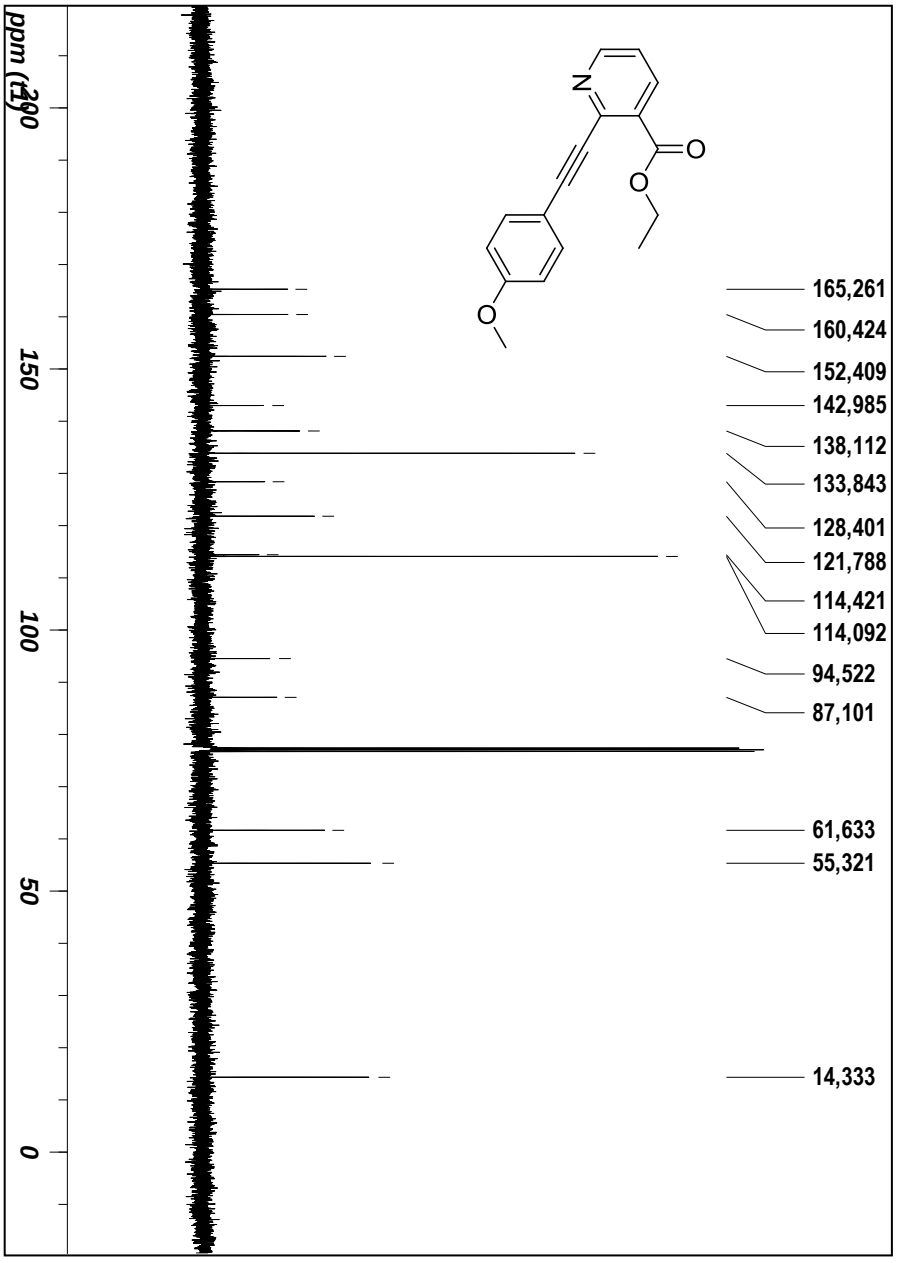


Figure 26 ^{13}C-NMR Spectrum of Compound 51d

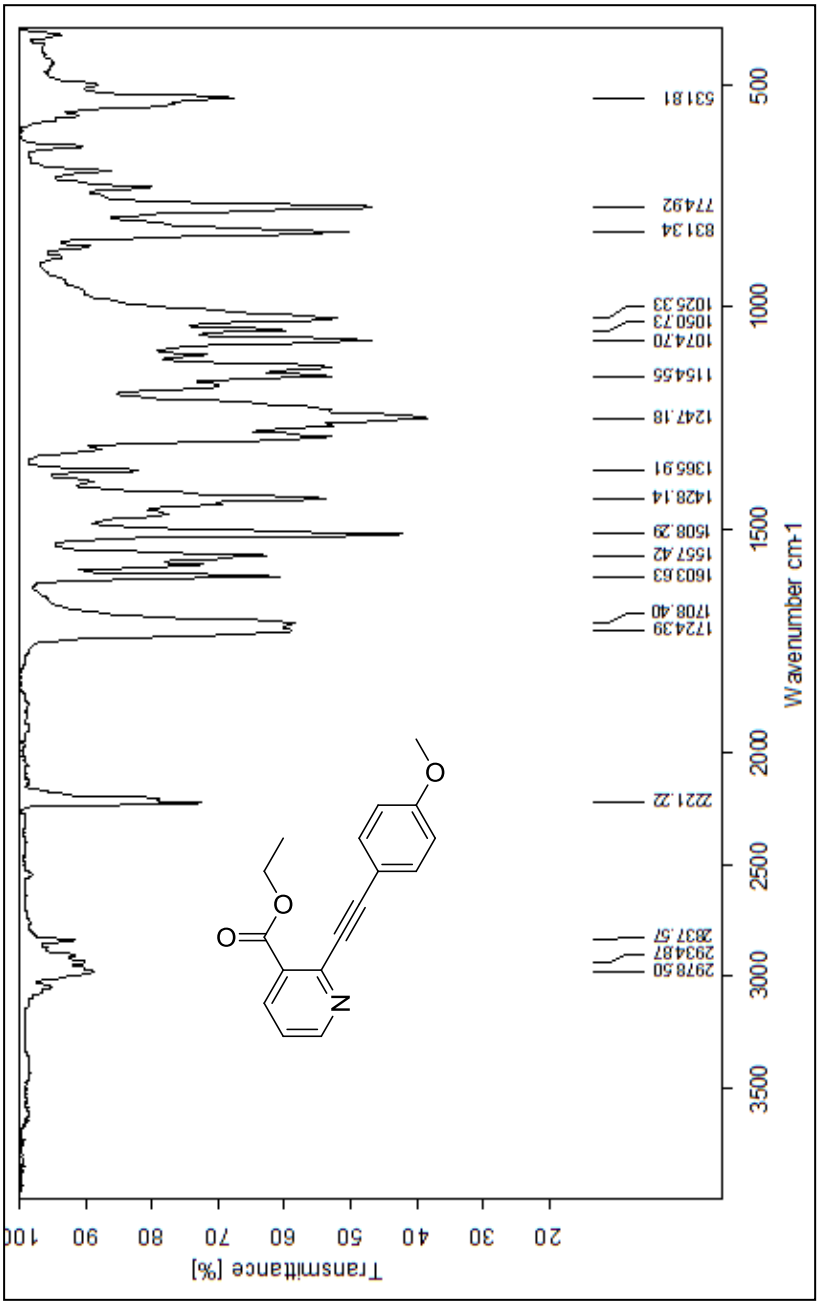


Figure 27 IR (ATR cm^{-1}) Spectrum of Compound 51d

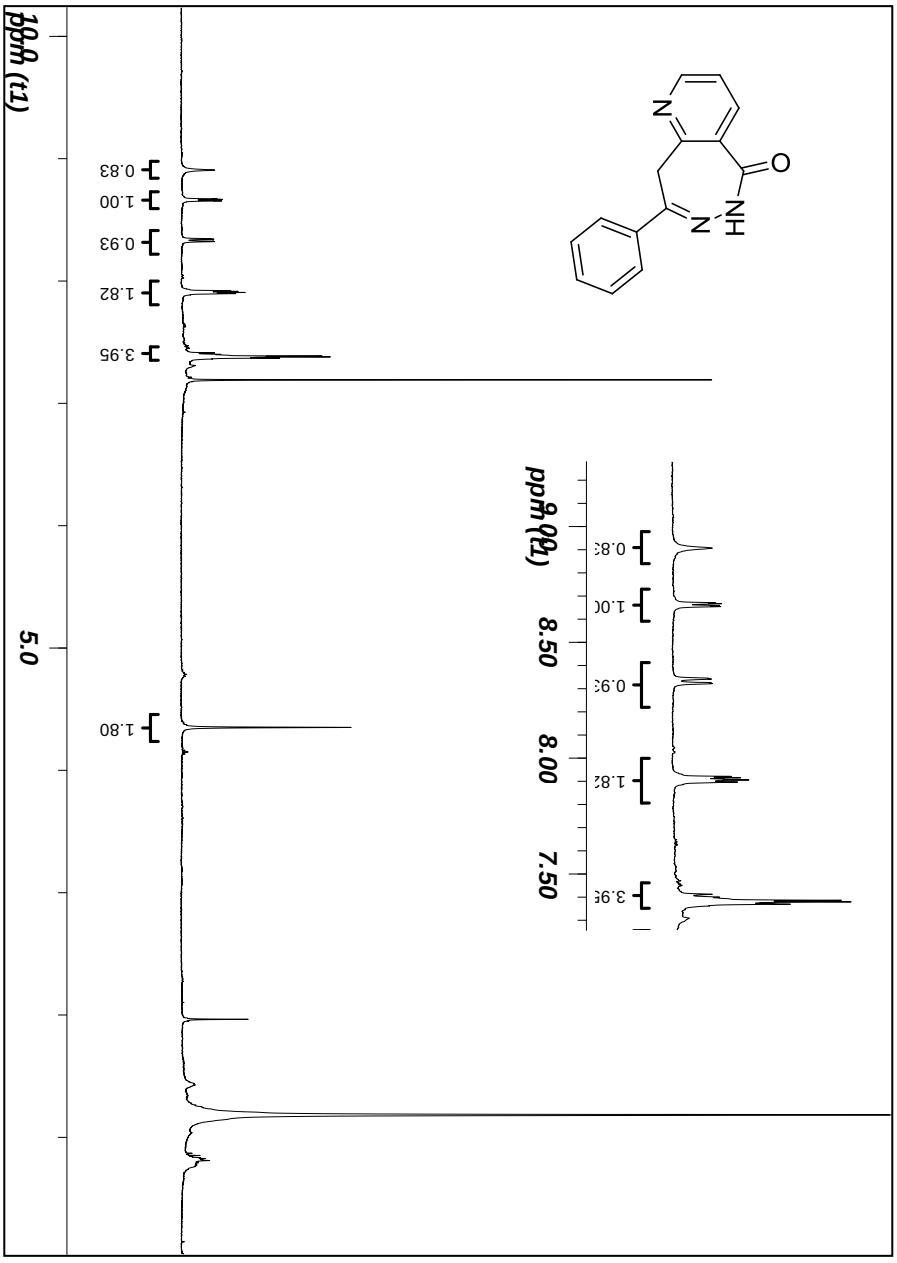


Figure 28 ^{1}H-NMR Spectrum of Compound 52a

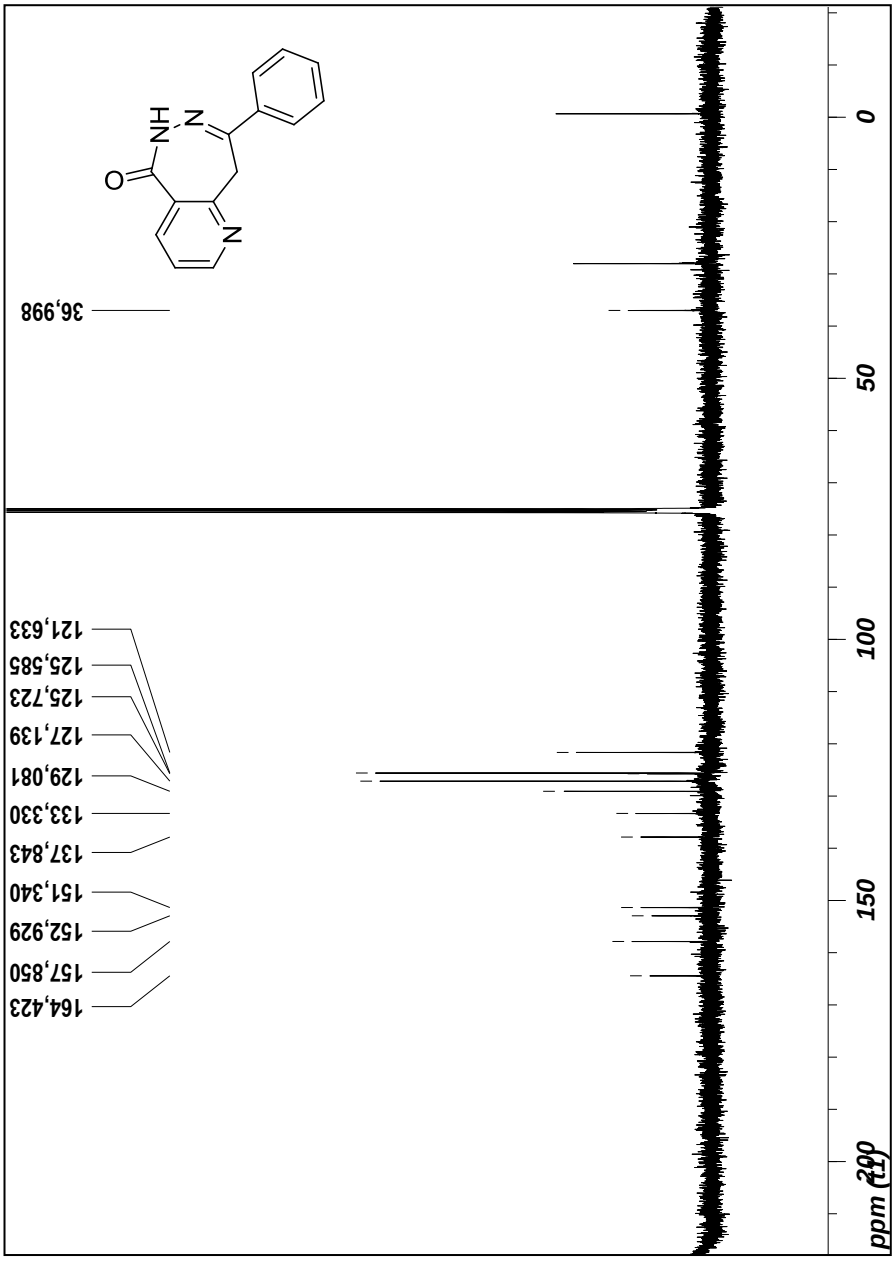


Figure 29 ^{13}C-NMR Spectrum of Compound 52a

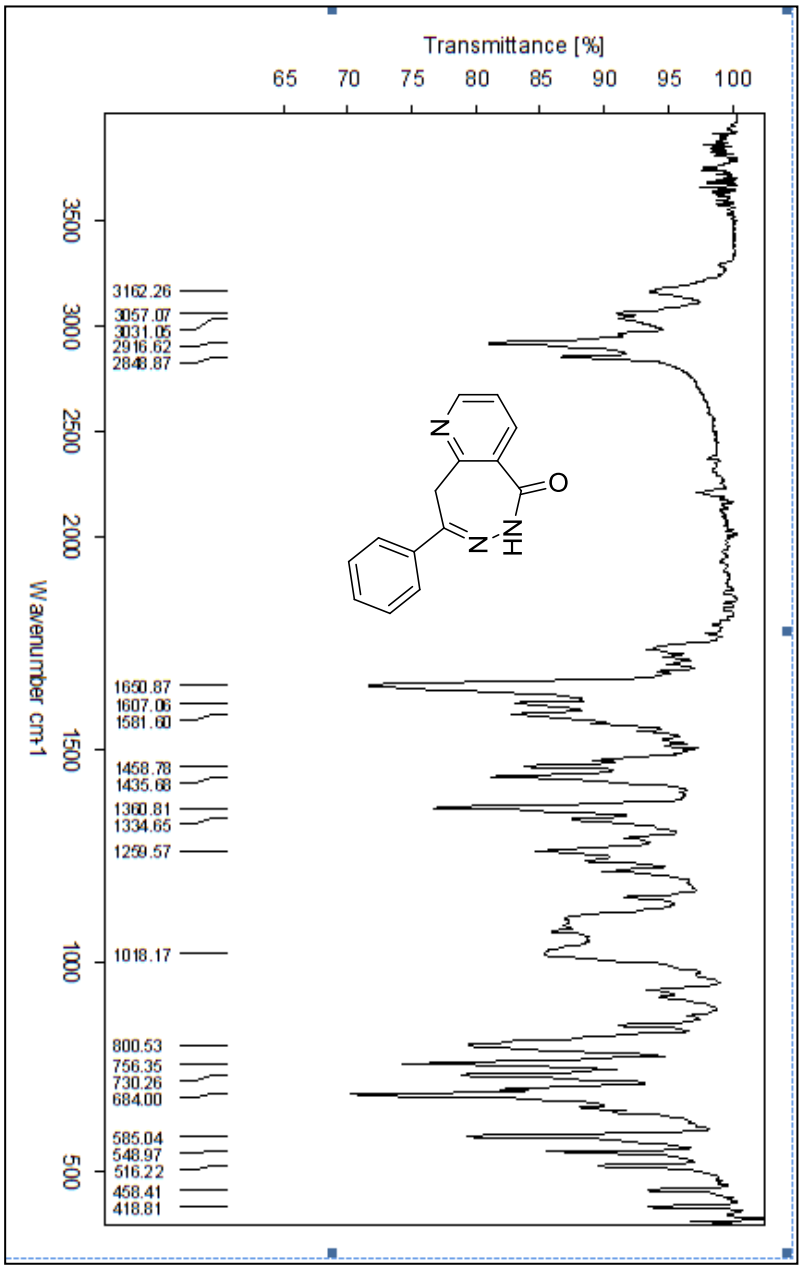


Figure 30 IR (ATR cm^{-1}) Spectrum of Compound 52a

	X	Y	Z
C	-1.365254	0.719521	0.563878
C	-2.279935	-0.138720	-0.074510
C	-3.360584	0.433098	-0.758332
C	-3.469824	1.818147	-0.810654
C	-2.494553	2.583468	-0.164739
N	-1.467671	2.055418	0.512701
H	-4.087344	-0.220087	-1.229946
H	-4.286645	2.299909	-1.337925
H	-2.539878	3.670125	-0.187054
C	-2.199287	-1.626114	-0.014528
C	-0.215471	0.140936	1.347856
C	0.694433	-0.667422	0.444740
H	-0.602263	-0.553703	2.107660
H	0.314767	0.943313	1.856755
O	-3.194655	-2.331746	-0.172283
N	-0.973147	-2.244684	0.216410
H	-1.047206	-3.242099	0.047587
N	0.315638	-1.794200	-0.056441
C	2.069102	-0.204883	0.130615
C	3.043094	-1.121635	-0.310095
C	2.424416	1.149302	0.254733
C	4.335117	-0.695121	-0.604588
H	2.771091	-2.166186	-0.412122
C	3.719526	1.574873	-0.051390
H	1.688011	1.883173	0.565468
C	4.679881	0.655829	-0.476670
H	5.077257	-1.417103	-0.932893
H	3.973451	2.626660	0.041787
H	5.688299	0.986558	-0.707643

Figure 31 Cartesian Coordinates of Compound **52a**

	X	Y	Z
C	-1.762419	-0.973029	0.000543
C	-2.272041	0.345962	-0.000104
C	-3.662511	0.530546	-0.000173
C	-4.483121	-0.586882	0.000398
C	-3.880955	-1.858867	0.001046
N	-2.567600	-2.064605	0.001128
H	-4.055907	1.541833	-0.000669
H	-5.564343	-0.495228	0.000369
H	-4.501753	-2.753239	0.001515
C	-1.382312	1.524210	-0.000717
N	0.001314	1.215064	-0.000850
O	-1.789531	2.677125	-0.001082
C	-0.339103	-1.164915	0.000634
H	0.056927	-2.172571	0.001277
C	0.500758	-0.095455	0.000025
N	0.865655	2.327603	-0.002297
H	1.453205	2.306309	0.825807
H	1.455456	2.302223	-0.828668
C	1.985236	-0.266606	0.000159
C	2.689616	-0.358757	1.210091
C	2.689097	-0.364654	-1.209599
C	4.075249	-0.538304	1.209344
H	2.148334	-0.302461	2.150554
C	4.074752	-0.544177	-1.208563
H	2.147402	-0.312869	-2.150080
C	4.770666	-0.627410	0.000448
H	4.608696	-0.614073	2.152314
H	4.607802	-0.624491	-2.151381
H	5.847364	-0.768843	0.000570

Figure 32 Cartesian Coordinates of Compound **69a**

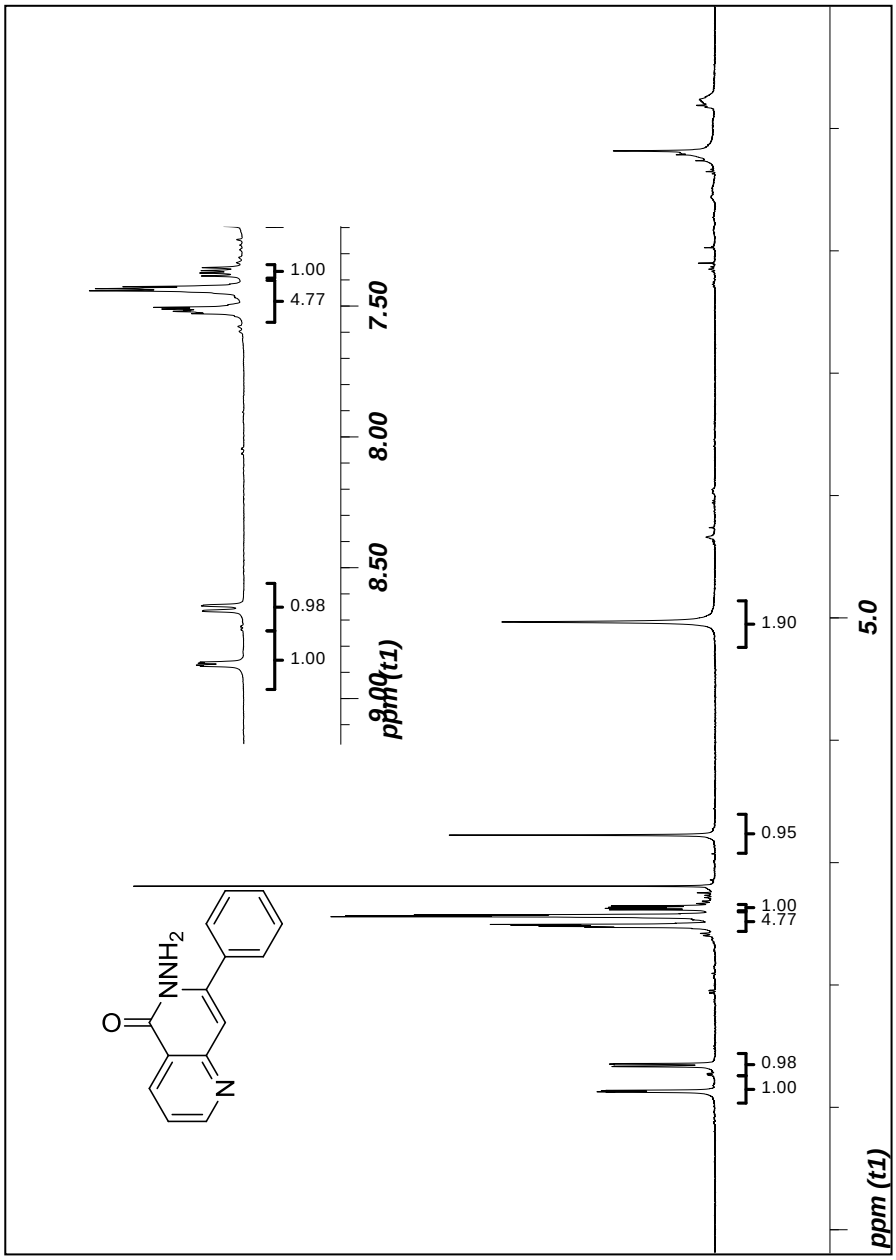


Figure 33 ^{1}H-NMR Spectrum of Compound 69a

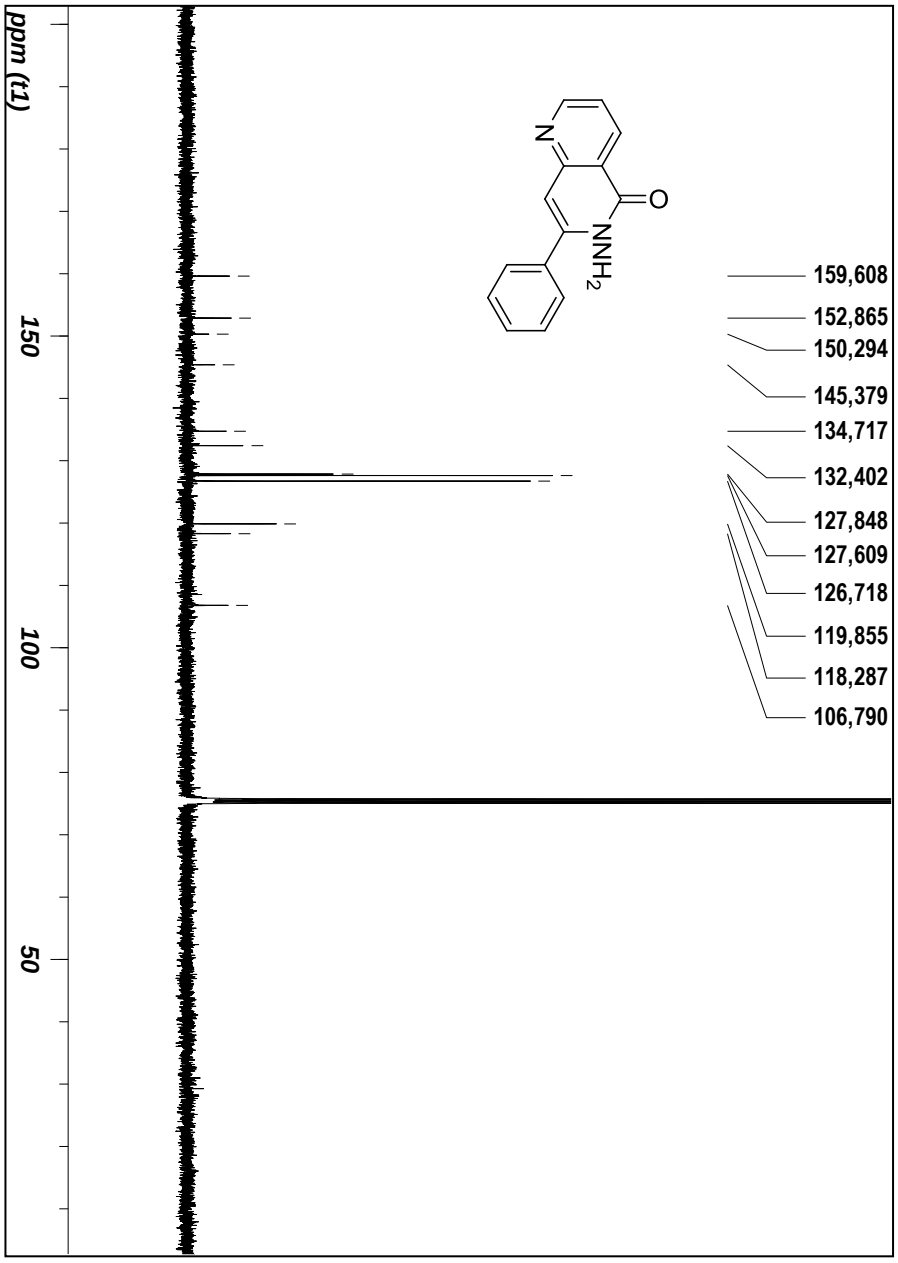


Figure 34 ^{13}C-NMR Spectrum of Compound 69a

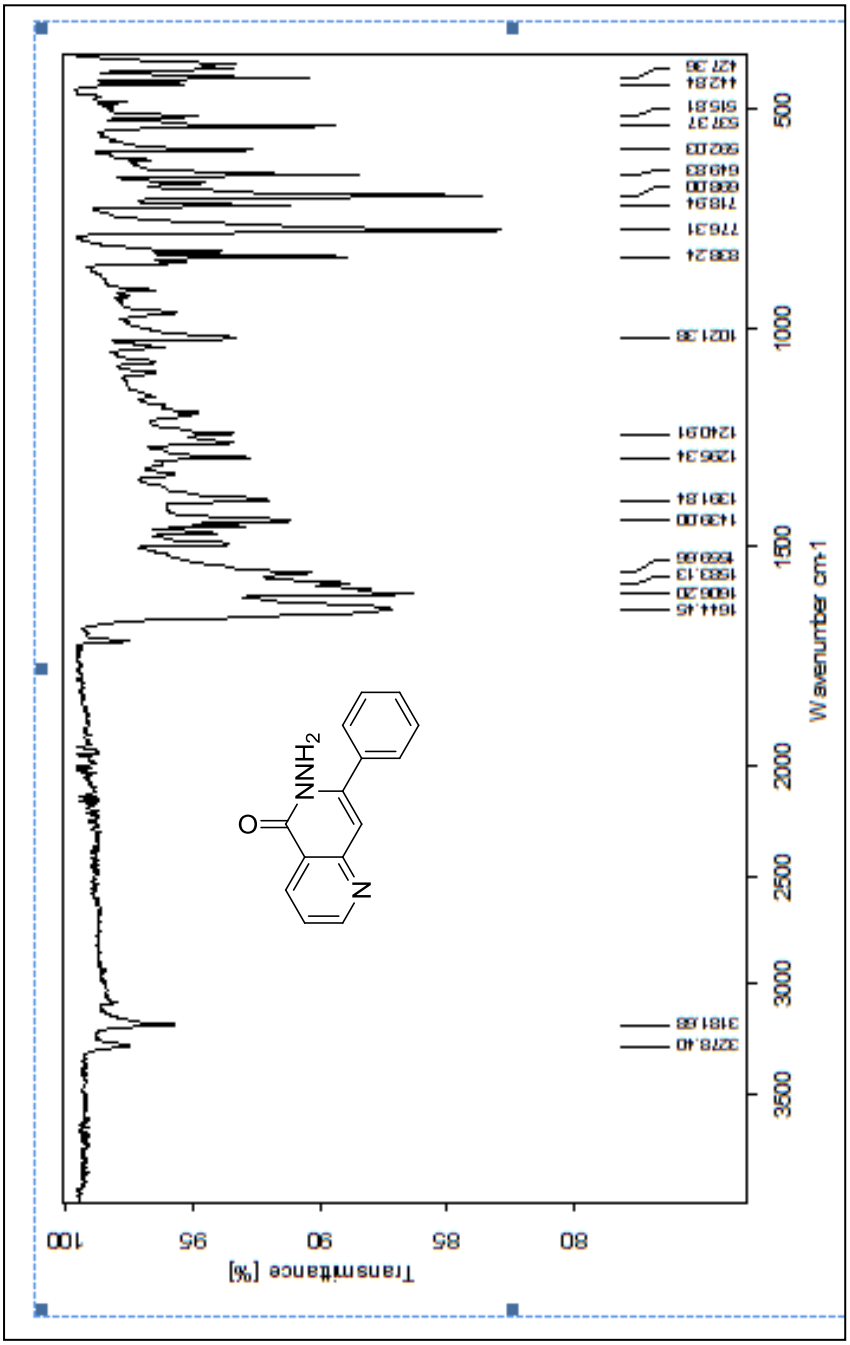


Figure 35 IR (ATR cm^{-1}) Spectrum of Compound 69a

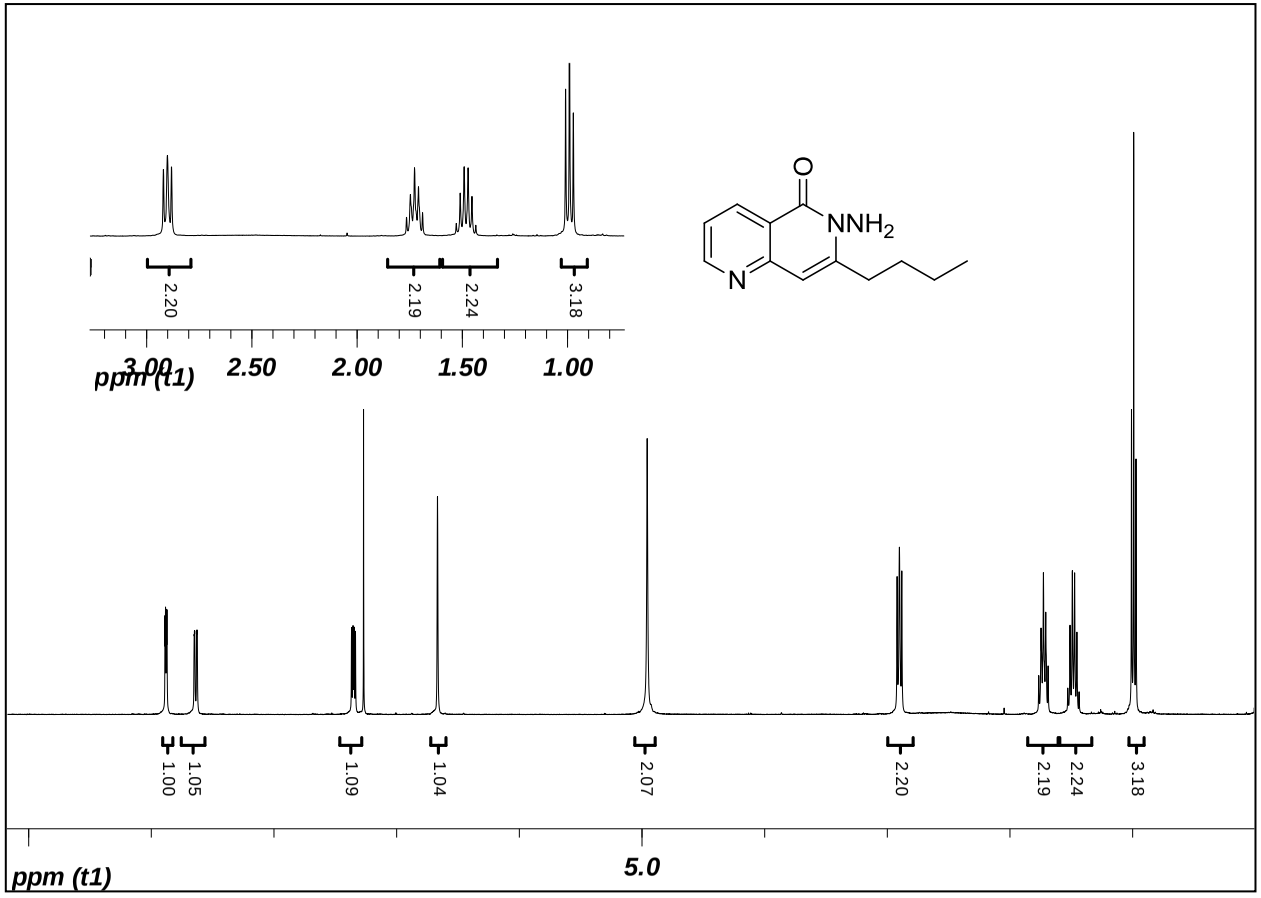


Figure 36 ^{1}H-NMR Spectrum of Compound 69b

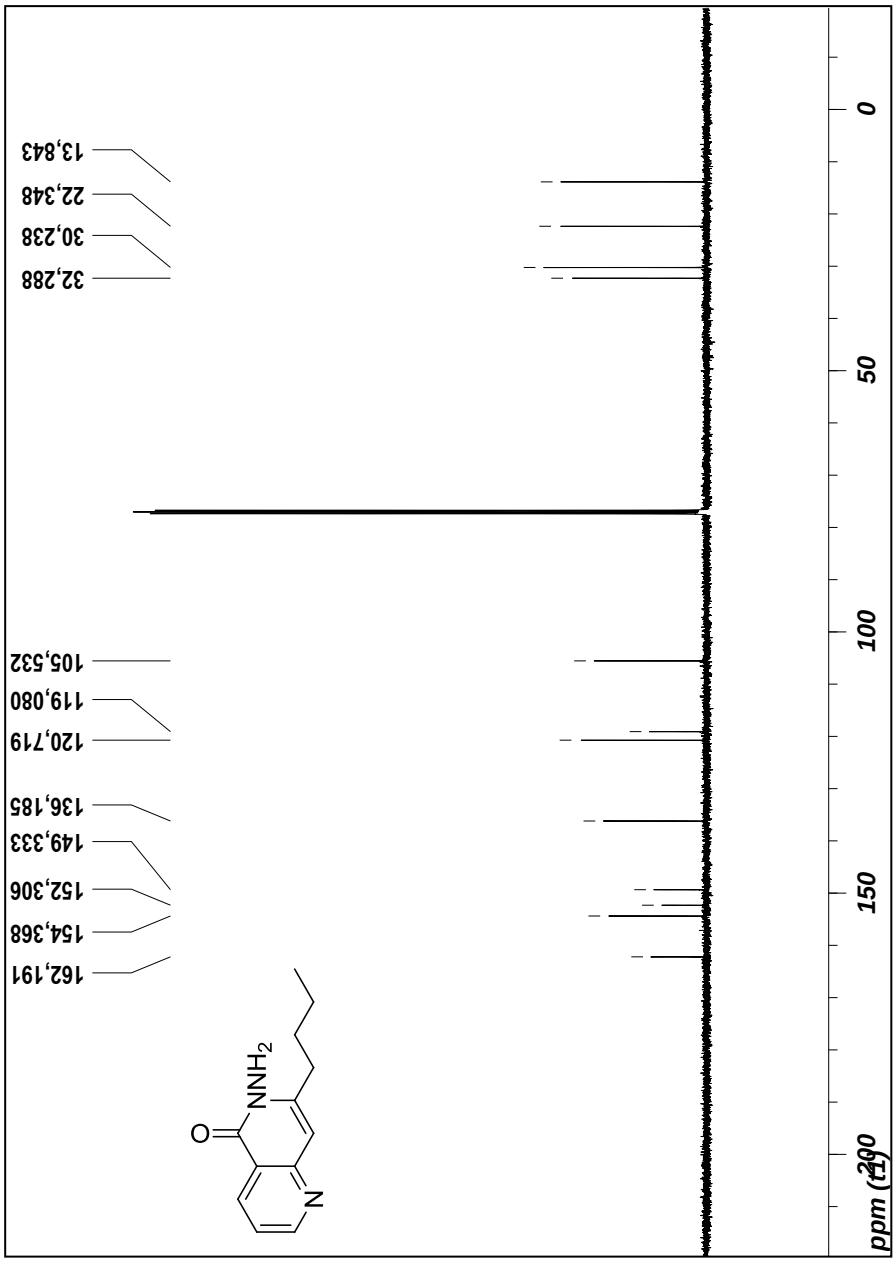


Figure 37 ^{13}C-NMR Spectrum of Compound 69b

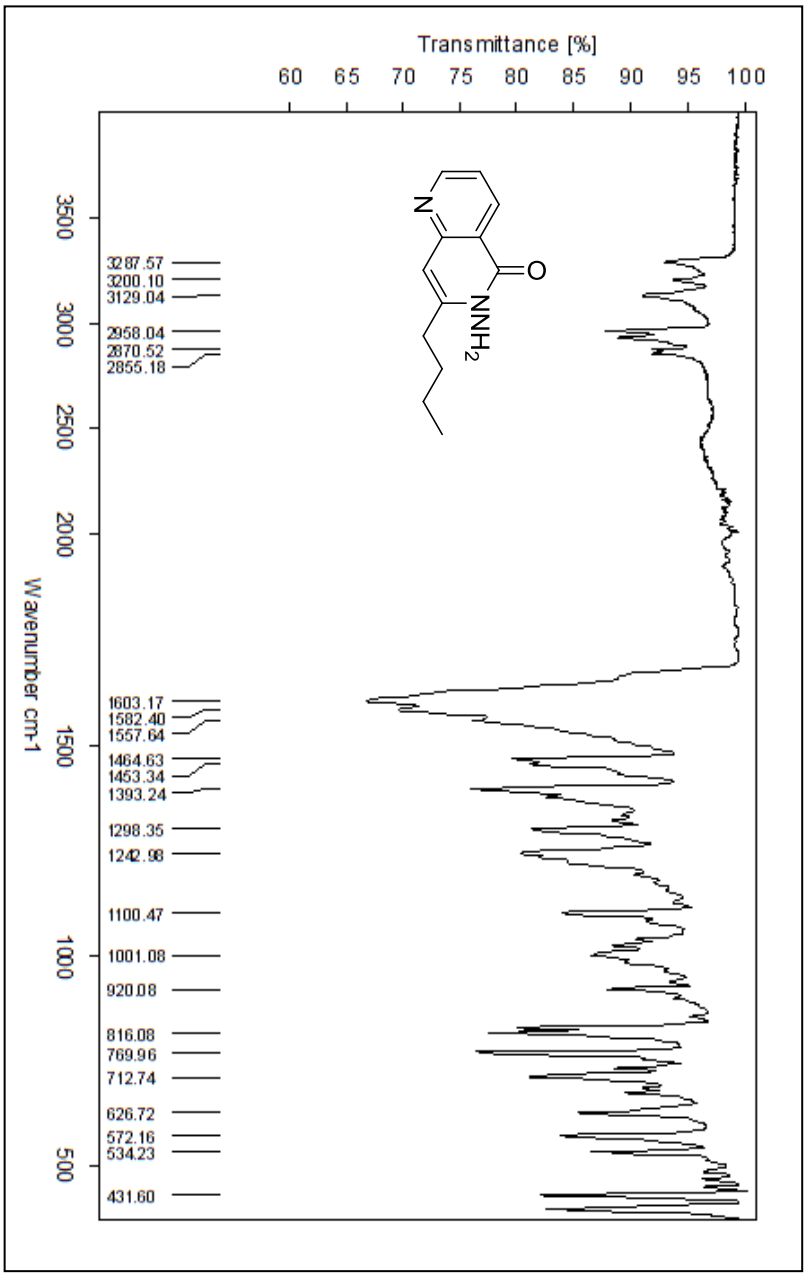


Figure 38 IR (ATR cm^{-1}) Spectrum of Compound 69b

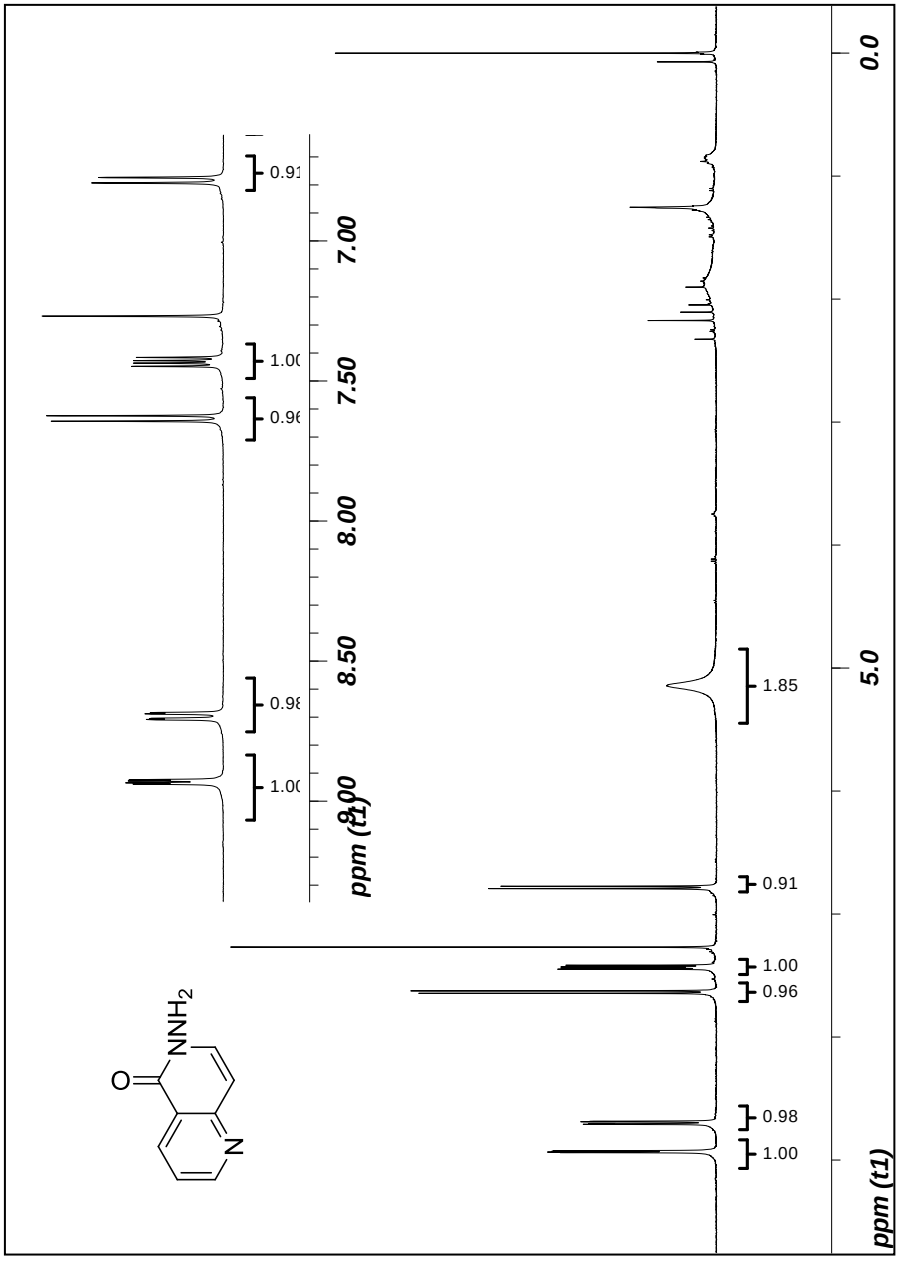


Figure 39 ^{1}H-NMR Spectrum of Compound 69c

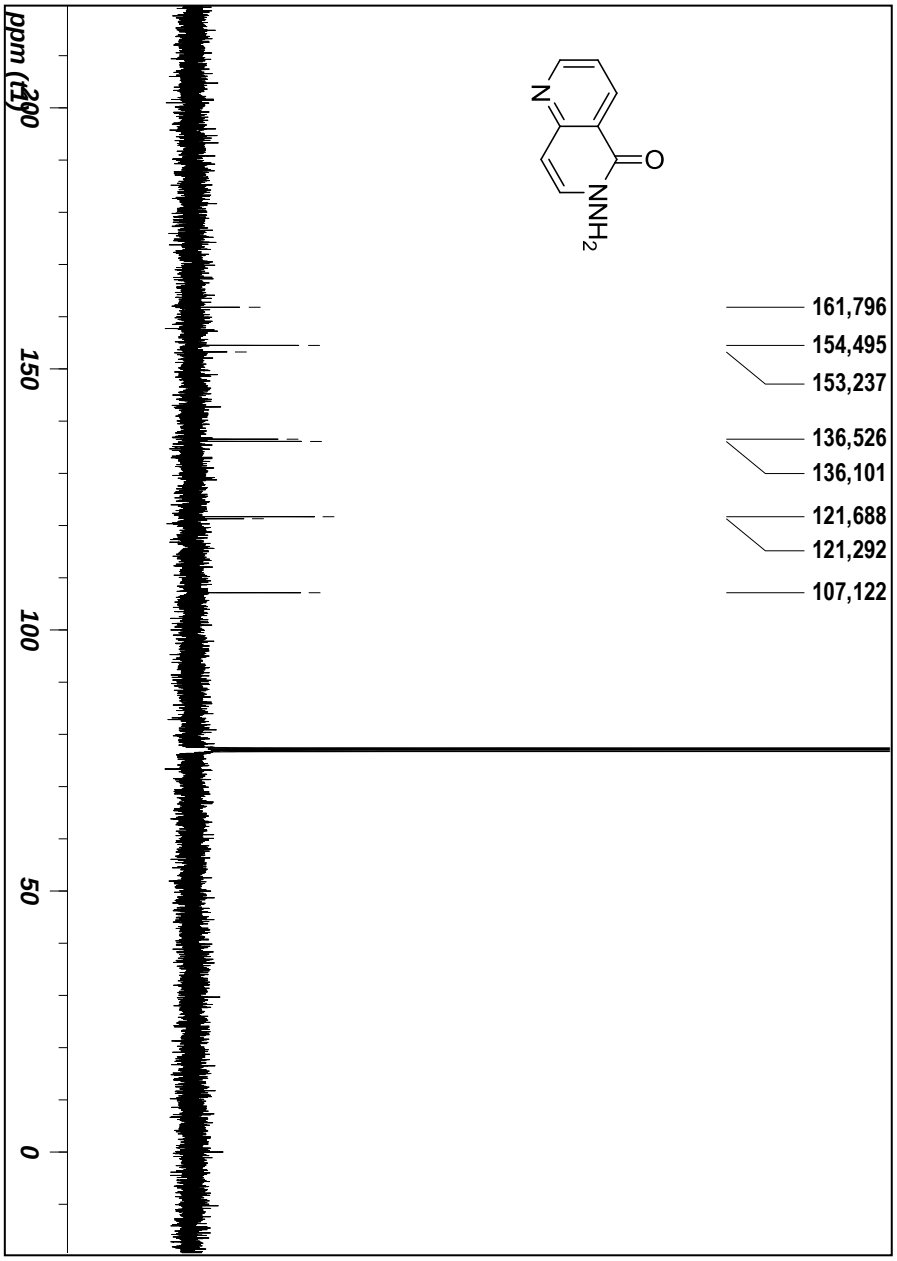


Figure 40 ^{13}C-NMR Spectrum of Compound 69c

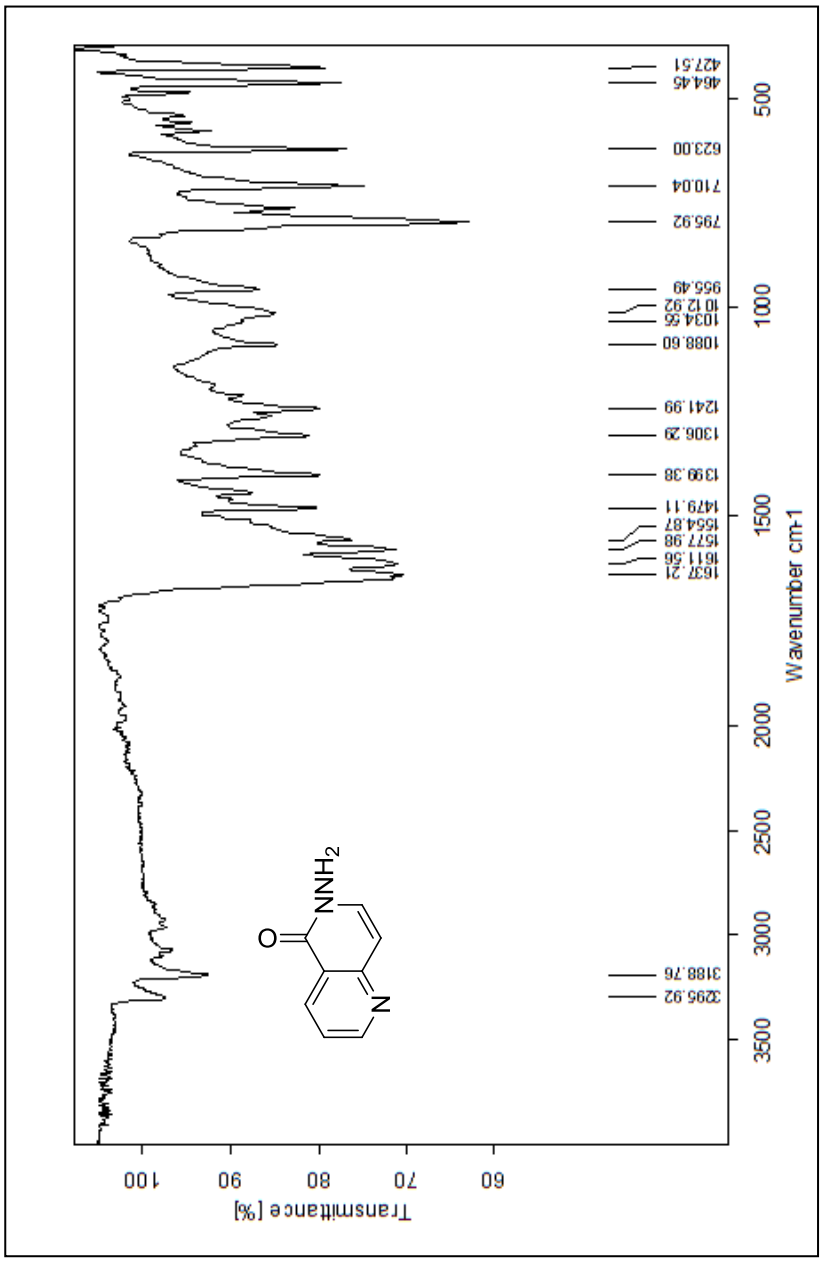


Figure 41 IR (ATR cm^{-1}) Spectrum of Compound 69c

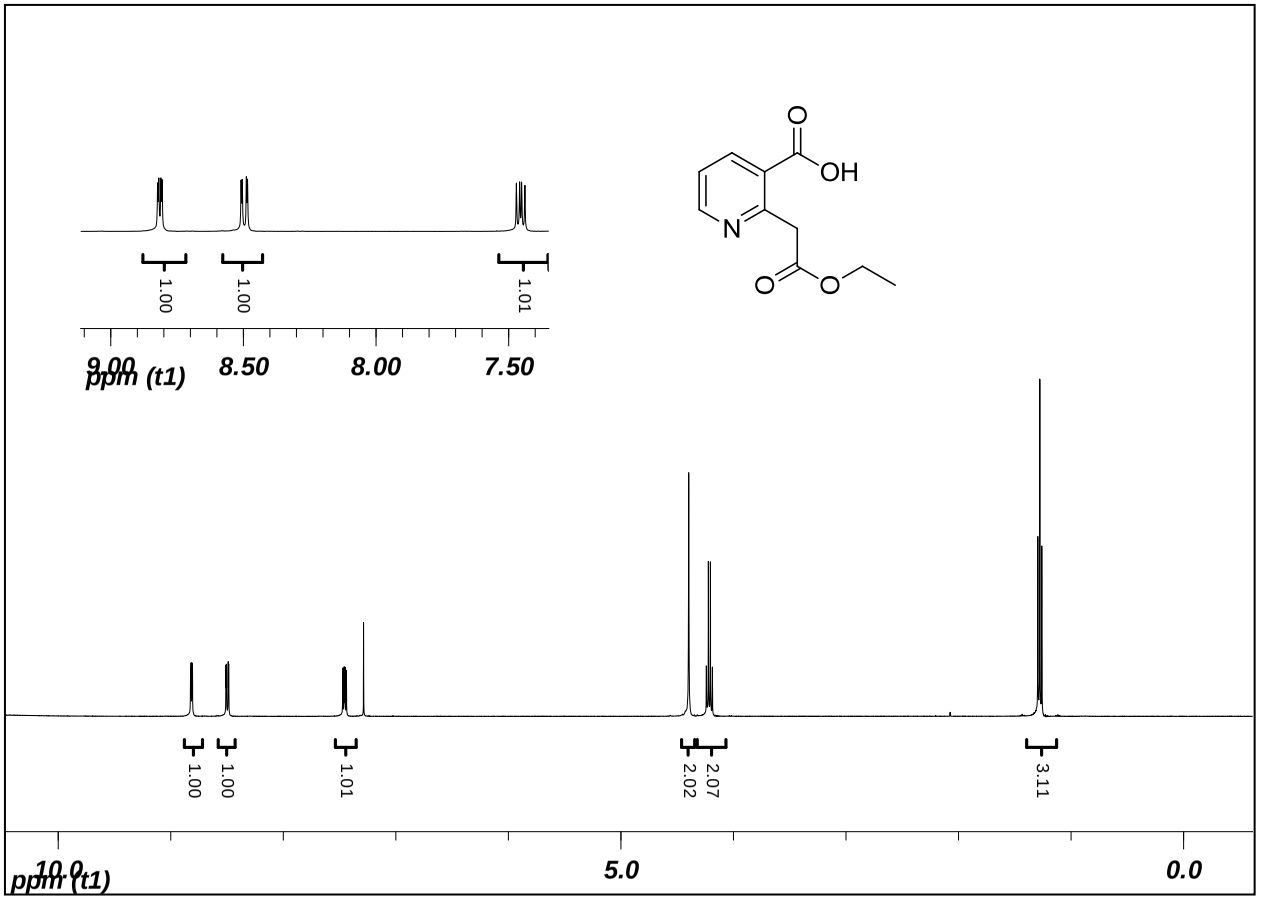


Figure 42 [1]H-NMR Spectrum of Compound 53

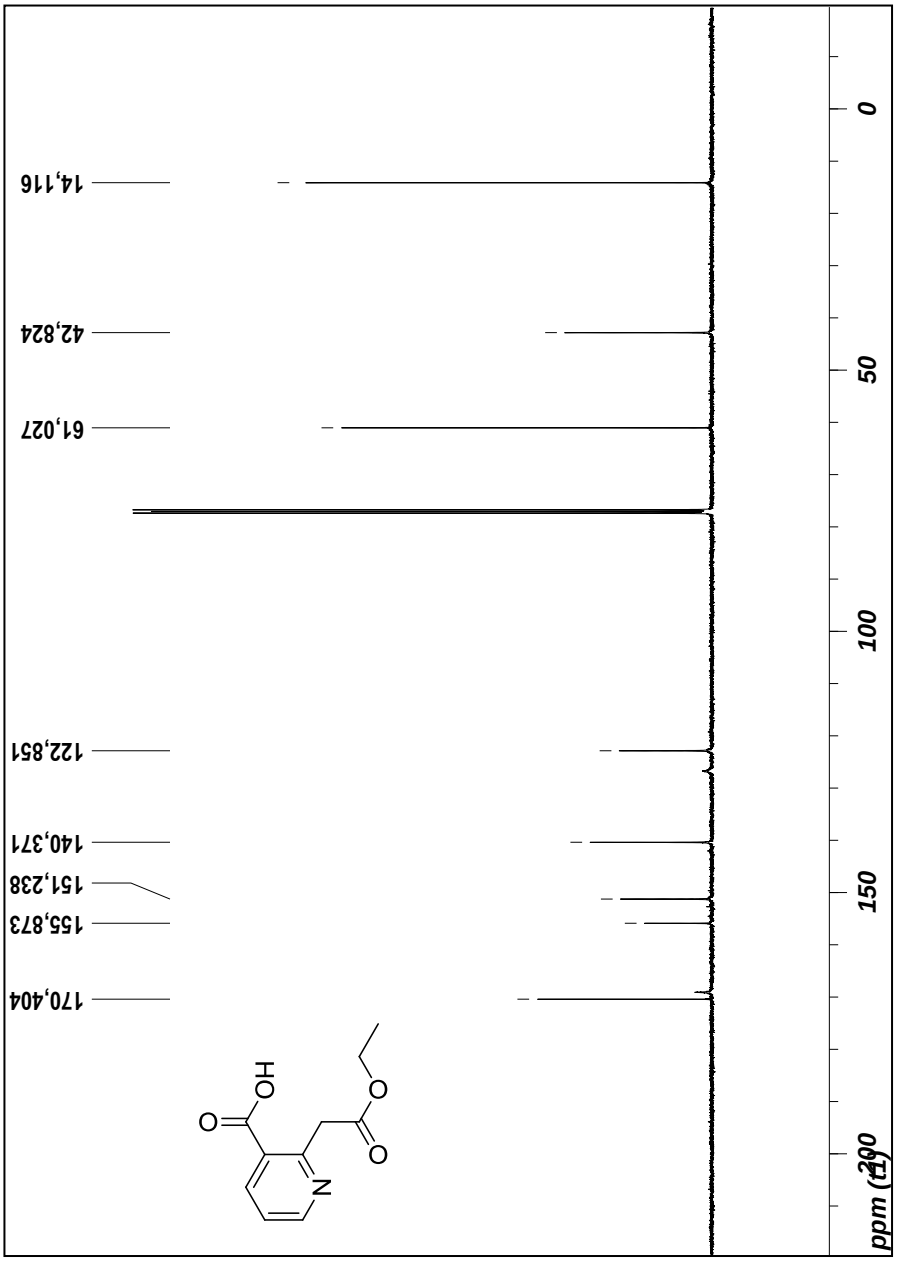


Figure 43 ^{13}C-NMR Spectrum of Compound 53

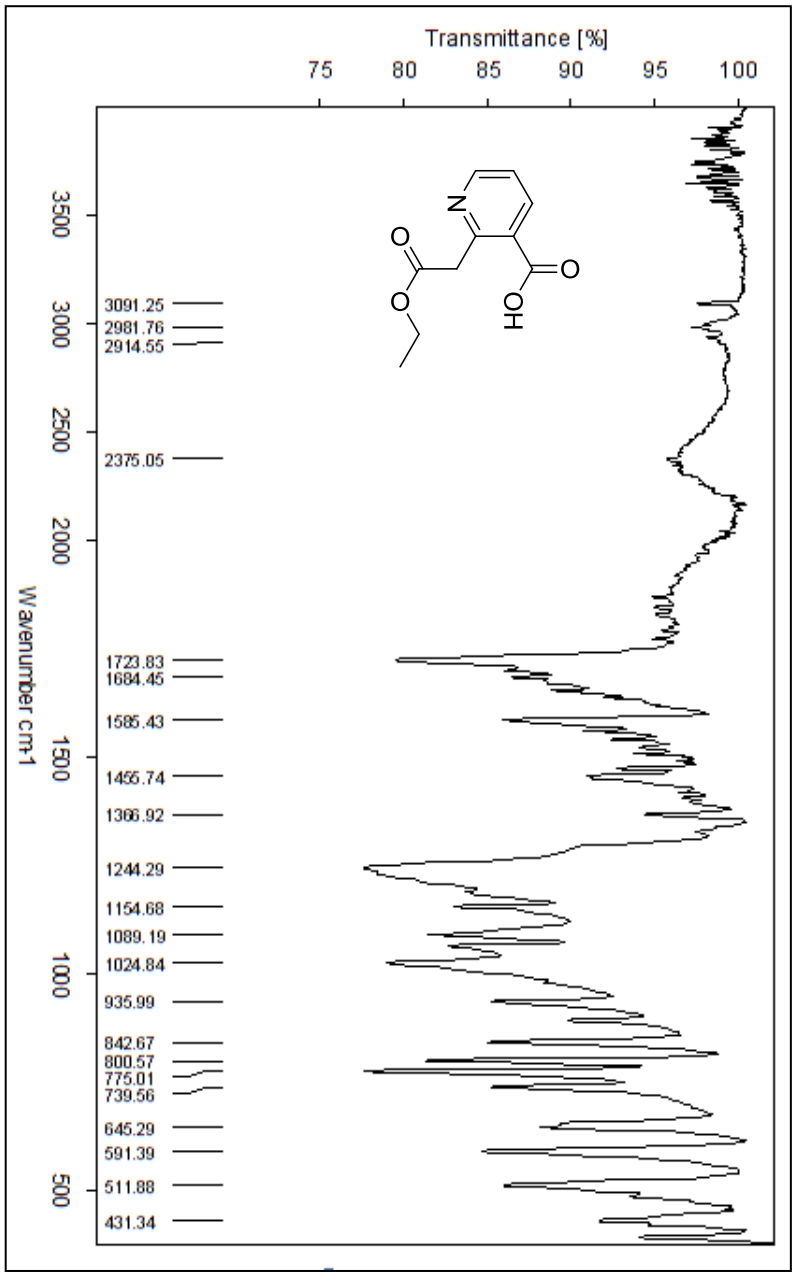


Figure 44 IR (ATR cm^{-1}) Spectrum of Compound 53

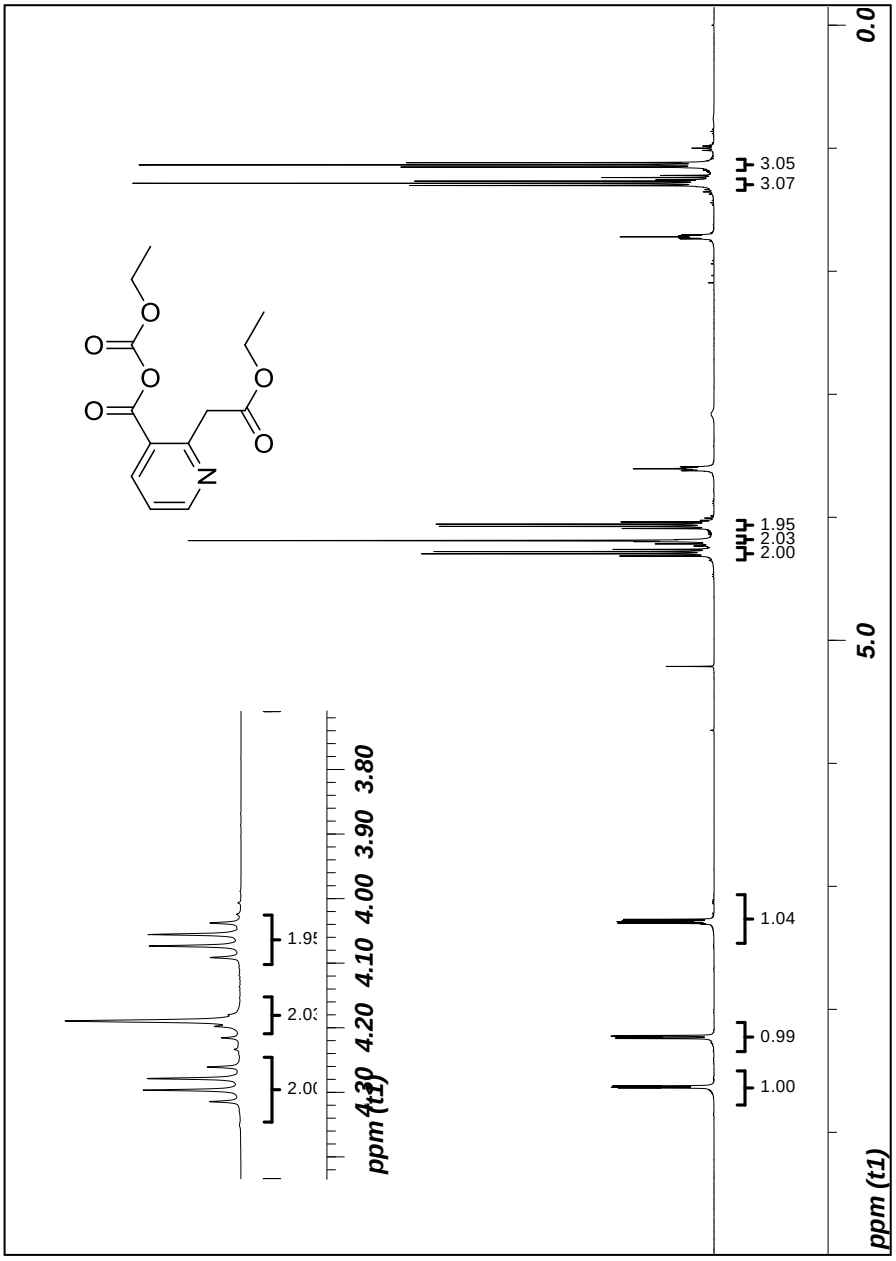


Figure 45 ^{1}H-NMR Spectrum of Compound 75

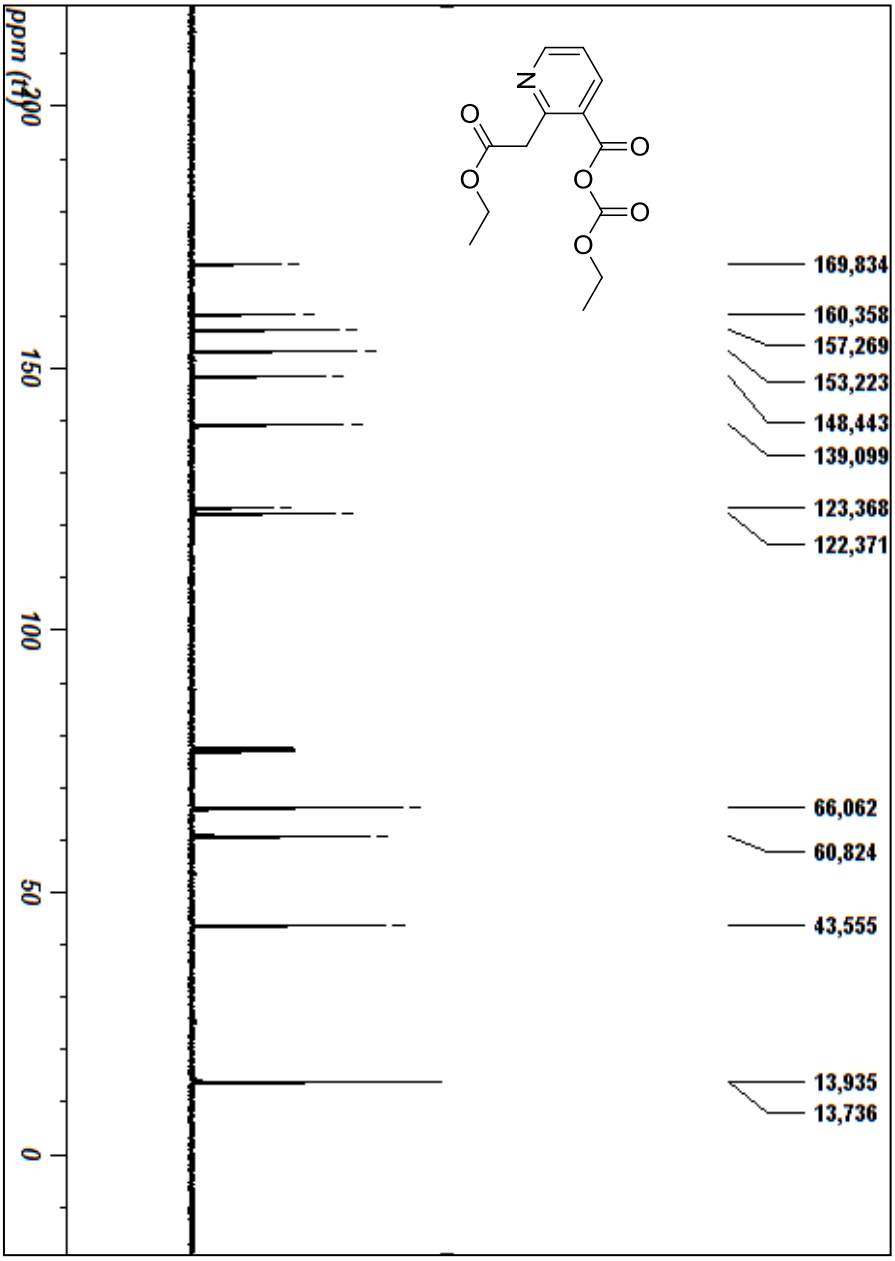


Figure 46 ^{13}C-NMR Spectrum of Compound 75

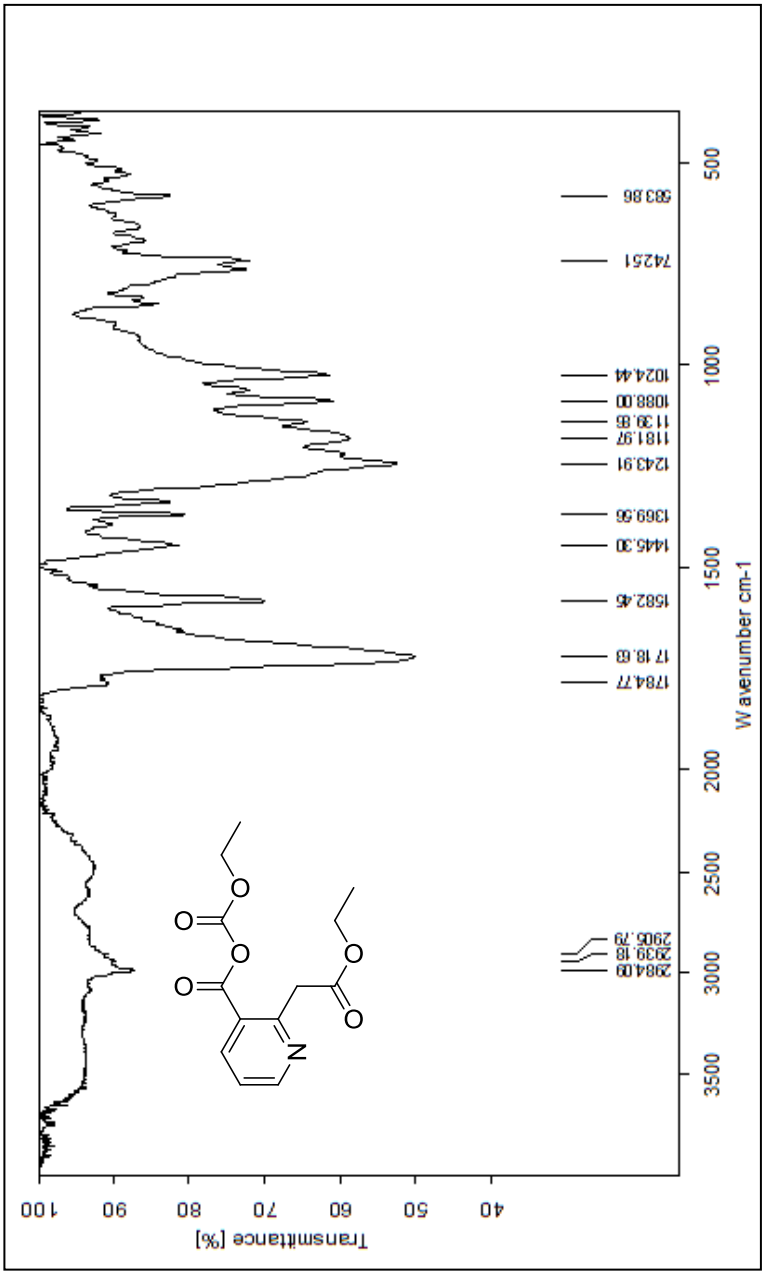


Figure 47 IR (ATR cm^{-1}) Spectrum of Compound 75

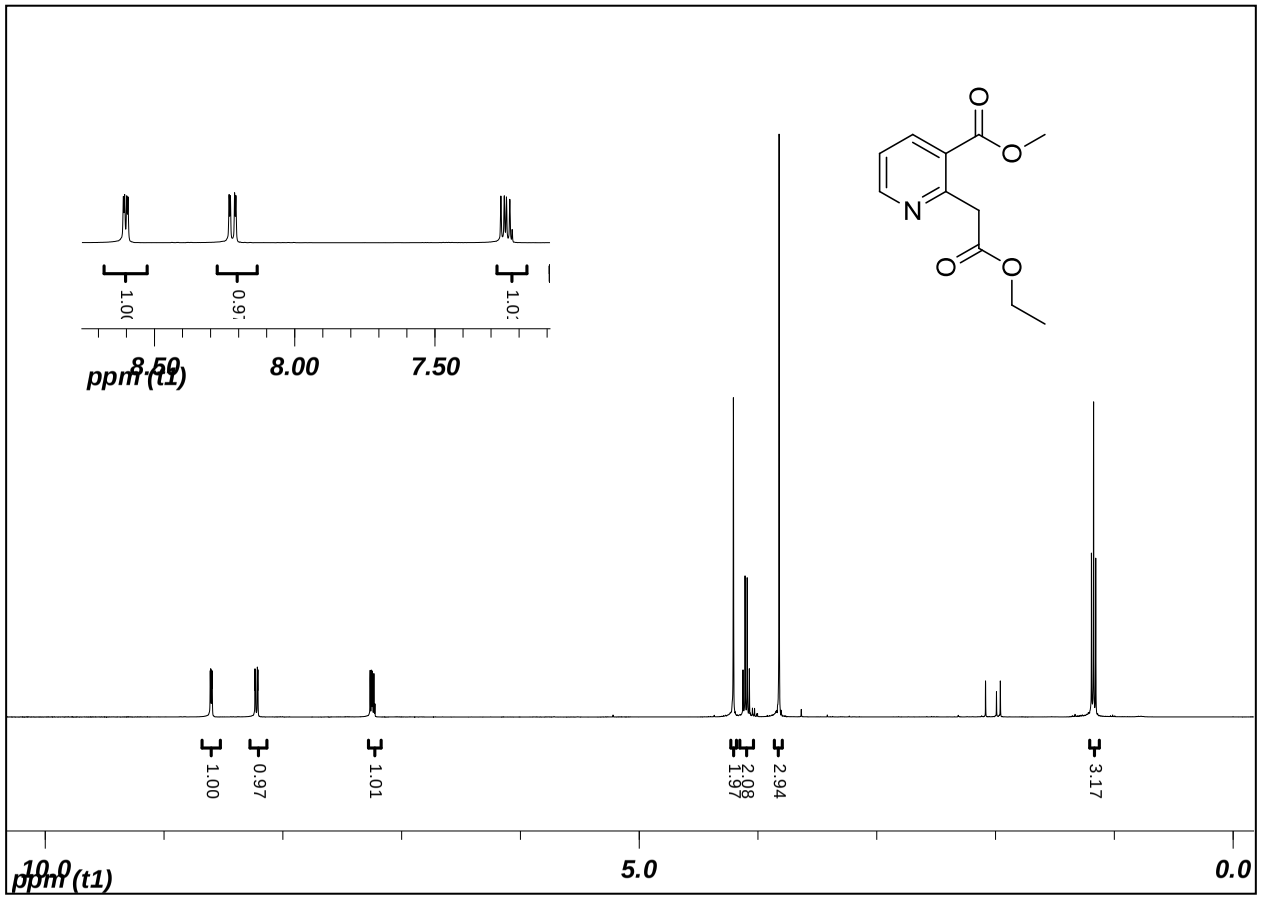


Figure 48 [1]H-NMR Spectrum of Compound 76

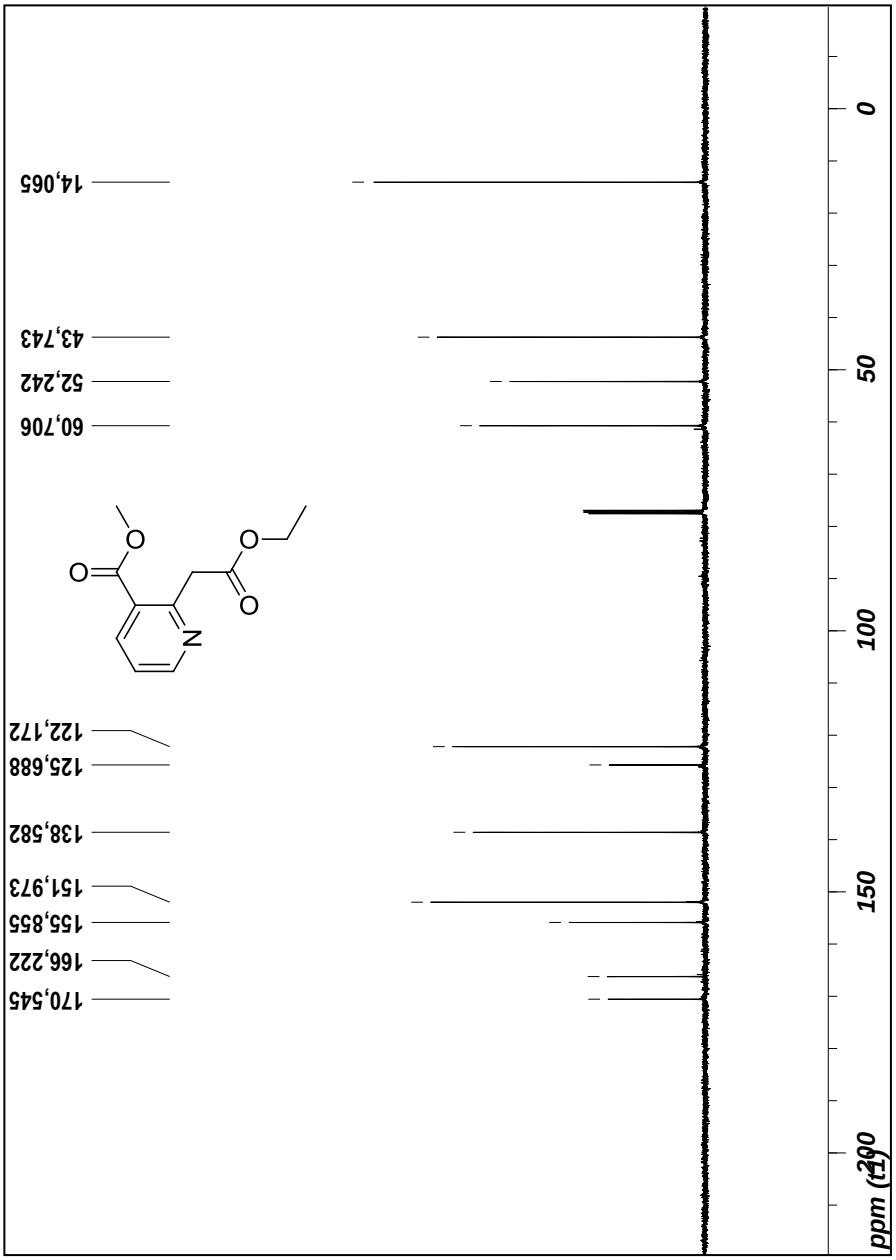


Figure 49 ^{13}C-NMR Spectrum of Compound 76

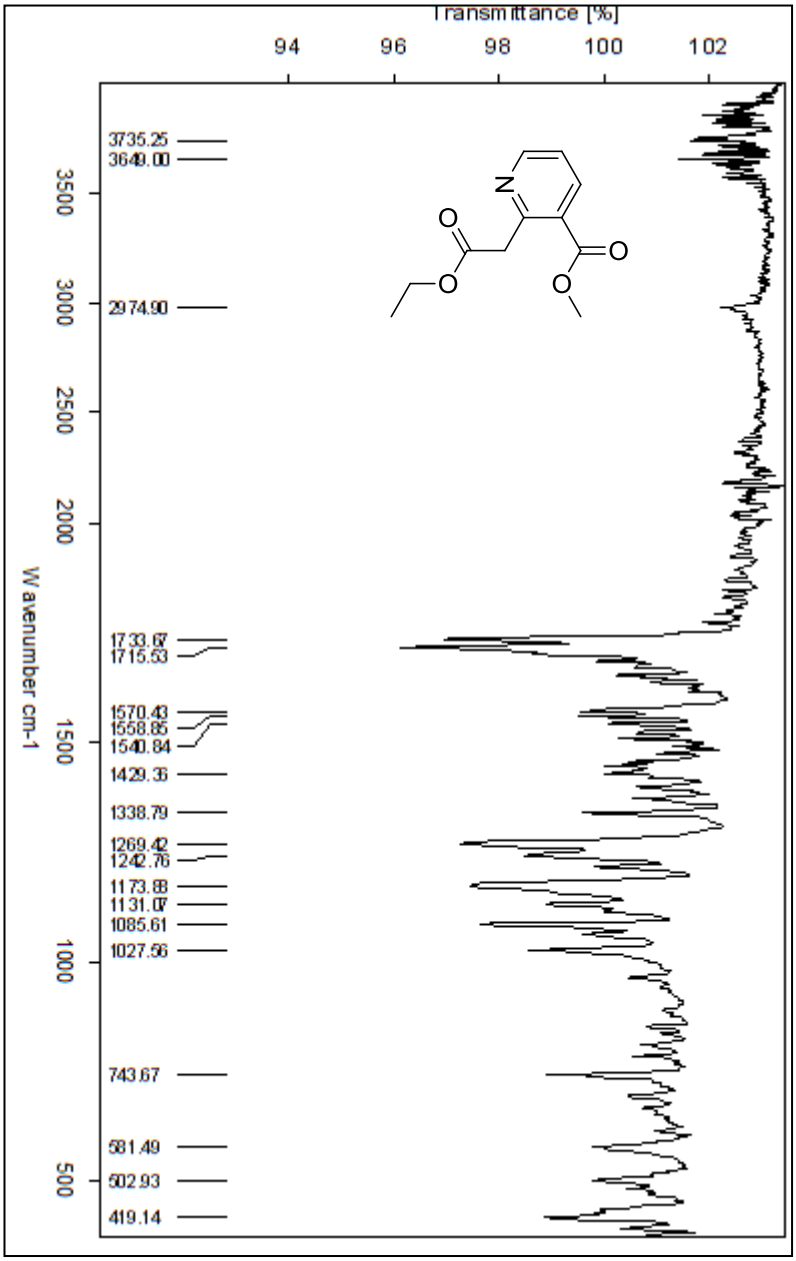


Figure 50 IR (ATR cm^{-1}) Spectrum of Compound 76

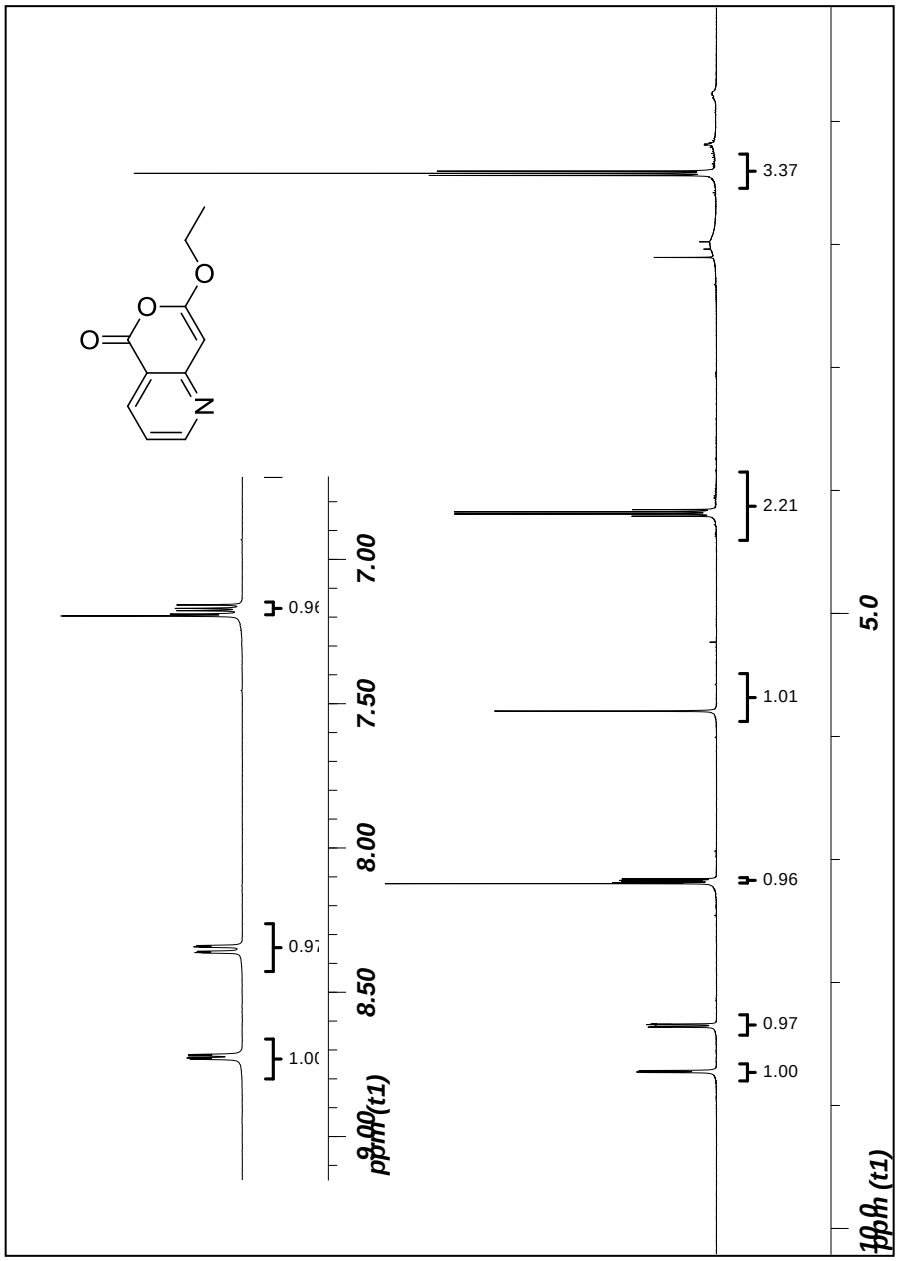


Figure 51 ^{1}H-NMR Spectrum of Compound 54

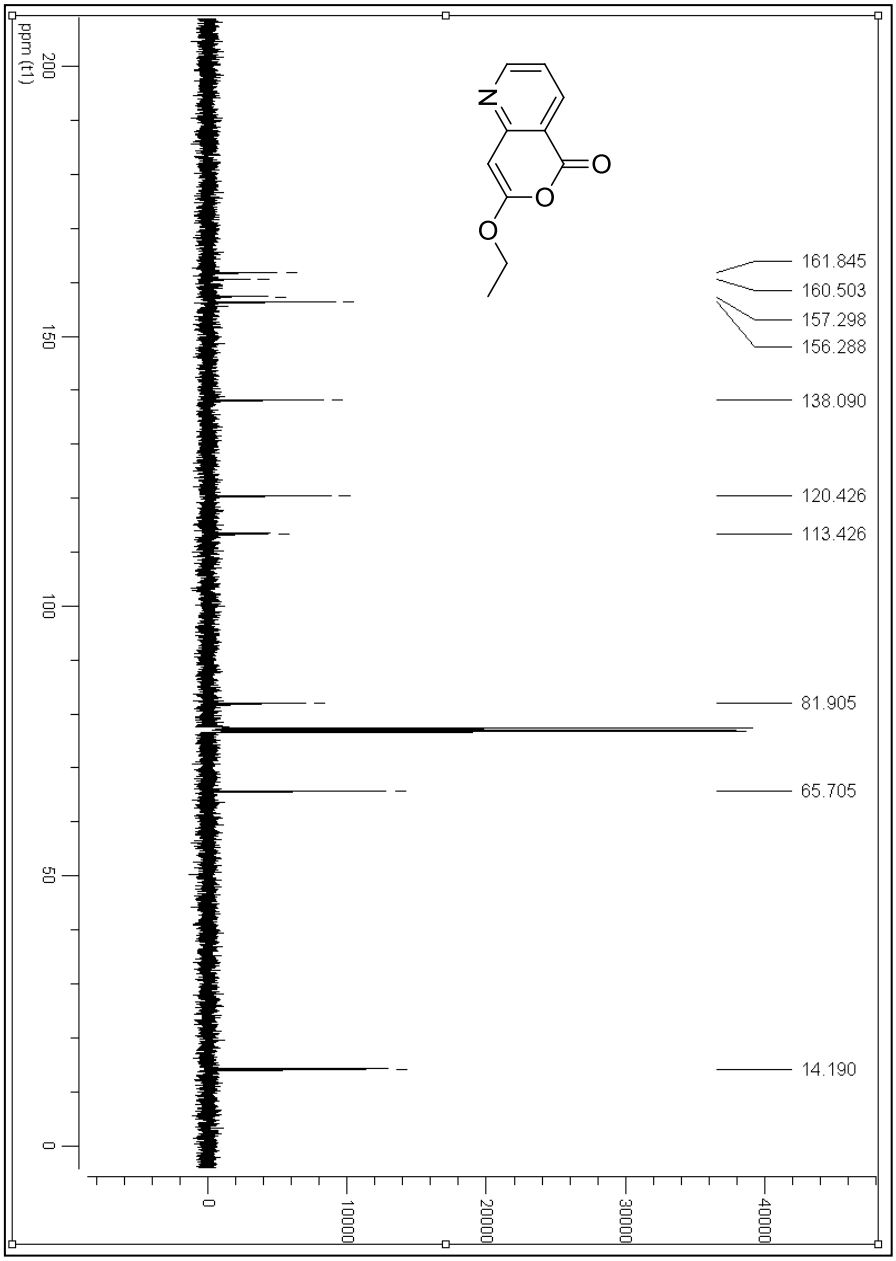


Figure 52 ^{13}C-NMR Spectrum of Compound 54

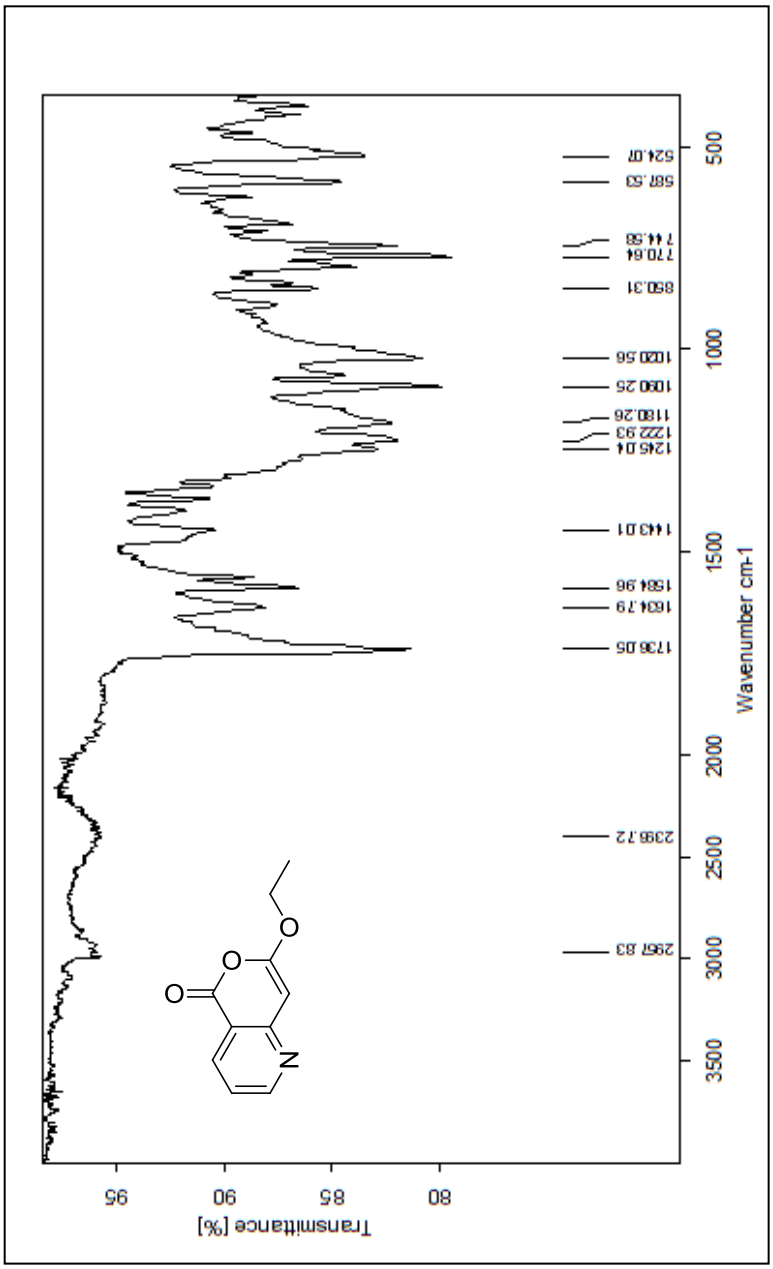


Figure 53 IR (ATR cm^{-1}) Spectrum of Compound 54