DEVELOPMENT OF NEW METHODOLOGIES FOR THE SYNTHESIS OF THIENOPYRIDAZINONE AND FURO- AND THIENODIAZEPINEDIONE DERIVATIVES

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DEVELOPMENT OF A NEW METHODOLOGY FOR THE SYNTHESIS OF THIENOPYRIDAZINONE AND FURO- AND THIENODIAZEPINEDIONE DERIVATIVES

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ABSTRACT

DEVELOPMENT OF NEW METHODOLOGIES FOR THE SYNTHESIS OF THIENOPYRIDAZINONE AND FURO- AND THIENODIAZEPINEDIONE DERIVATIVES

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July 2013, 166 pages

Some heterocycles are natural compounds and play a major part in biochemical processes. They also have interesting biological activities and pharmacological properties. In this study, new methodologies were developed to synthesize bicyclic heterocyclic compounds consisting of thiophene and furan fused to six- and seven-membered rings, respectively. In the first part, thienopyridazinone derivatives were synthesized. For this purpose, the starting compound was chosen as methyl 2-(2-methoxy-2-oxoethyl)-3-thienoate, which was oxidized with SeO_2 and then treated with hydrazine derivatives for cyclization. Later, they were converted to isocyanate derivatives which were used to produce the corresponding urethane and/or amine derivatives by treatment with methanol and aqueous HCl, respectively. In the second part, a new synthetic methodology was developed for furo- or thienodiazepinedione derivatives starting from methyl 2-(2-methoxy-2-oxoethyl)-3-furoate or-thionate. First, acyl azides were synthesized. Application of Curtius rearrangement to acyl azides gave the corresponding isocyantes, which was followed by cyclzation rection to produce the desired compound.

Keywords: thienopyridazinone, furodiazepinedione, thienodiazepinedione, acyl azide, isocynate.

ÖZ

TİYENOPİRİDAZİNON VE FURO- VE TİYENODİAZEPİNDİON TÜREVLERİNİN SENTEZİ İÇİN YENİ SENTETİK YÖNTEMLERİN GELİŞTİRİLMESİ

Özer, Merve Sinem

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Balcı

Temmuz 2013, 166 sayfa

Heterosiklik bileşiklerin önemli bir kısmı doğada bulunur ve biyokimyasal süreçlerde rol alırlar. Ayrıca biyolojik aktiviteleri ve farmakolojik özellikleri de bulunmaktadır. Bu çalışmada tiyofen ve furan halkasına altılı ve yedili heterosiklik halkaların kenetlenmesi ile bisiklik yapıda olan organik moleküllerin sentezi için yeni yöntemler geliştirilmiştir. İlk bölümde tiyenopiridazinon türevleri sentezlendi. Bunun için çıkış maddesi olarak metil 2-(2-metoksi-2-oksoetil)-3-tiyonat seçilerek halka oluşturmak için hidrazin ile türevlendirildi. İsosiyanata çevrildikten sonra sırasıyla metanol ve/veya HCl çözeltisi eklenerek üretan ve amin elde edildi. İkinci kısımda ise metil 2-(2-metoksi-2-oksoetil)-3-furanat ve/veya –tiyonattan çıkarak furodiazepindione türevleri sentezi için yeni bir yöntem geliştirildi. Açil azid türevleri elde edildikten sonra Curtius düzenlenmesi ile isosiyanat oluştu ve daha sonra istenen halka kapanma reaksiyonu gerçekleştirildi.

Anahtar kelimeler: tiyenopiridazinon, furodiazepindion, tiyenodiazepindion, açil azid, isosiynat.

The end of a time, a time to begin…

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF ABBREVIATIONS

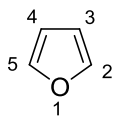
aq.	Aqueous
Ar	Aryl
ATR	Attenuated total reflectance
DMSO	Dimethylsulfoxide
eq.	Equivalent
Et	Ethyl
EtOAc	Ethyl acetate
FT-IR	Fourier-transform infrared spectroscopy
i-Pr	*iso*-Propyl
Me	Methyl
NMR	Nuclear magnetic resonance
Ph	Phenyl
ppm	Parts per million
rt	Room temperature
TLC	Thin layer chromatography
TMS	Trimethylsilyl
δ	Chemical shift

CHAPTER 1

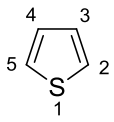
INTRODUCTION

1.1 Furans and Thiophenes

Furan (**1**) and thiophene (**2**) are five-membered heterocyclic compounds and isoelectronic to each other.



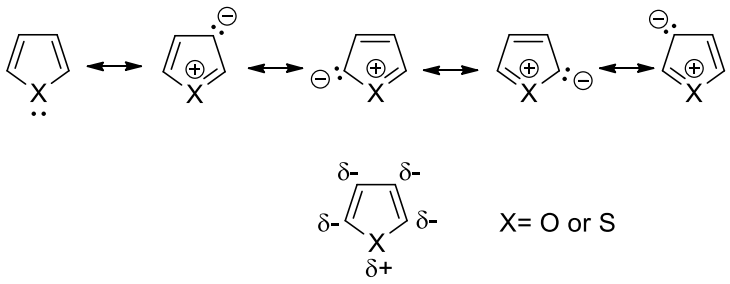
furan (**1**)



thiophene (**2**)

With two lone pairs, one of them participates conjugation with double bonds and the other stays on molecular plane in sp^2 hybrid orbital. Since oxygen is more electronegative than sulfur, lone pair of furan has less tendency to be conjugated so it is less aromatic than thiophene and would react like dienes.

As the resonance structures of furan or thiophene show, all carbon atoms have high electron density especially β-carbon atoms, while heteroatom holds partial positive charge (Scheme 1).



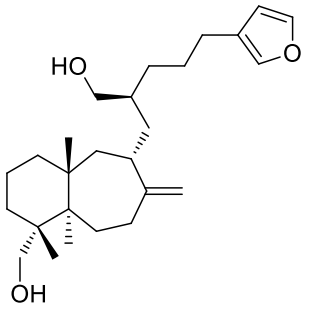
Scheme 1 The resonance structures of furan or thiophene

In the ^{1}H NMR spectra, the resonance signals appearing at lower field belong to α-hydrogens and resonance signals at higher field to β-hydrogens due to the decreased electron density (Table 1).[1]

Table 1 ^{1}H NMR Spectral Data for Furan and Thiophene (in $CDCl_3$)

	Furan	**Thiophene**
H-2	7.29 ppm	7.18 ppm
H-3	6.24 ppm	6.99 ppm
$J_{2,3}$	1.75 Hz	4.90 Hz
$J_{2,4}$	0.85 Hz	1.04 Hz
$J_{2,5}$	1.40 Hz	2.84 Hz
$J_{3,4}$	3.30 Hz	3.50 Hz

Furan skeleton is present in many natural compounds. For example, shinsonefuran (**3**) found in the deep-sea sponge *Stoeba extensa* shows cytotoxicity against HeLa cells with an IC_{50} of 16 mg^{-1}.[2] The new furanocembranolide (**4**) was isolated from the octocorals *Leptogorgia alba* and *Leptogorgia ridida* which were found on the Pacific coast of Panama.[3] A furanoeremophilane compound **5** was identified during chemical and genetic study of *Ligularia tongolensis* in the Hengduan Mountains of China.[4]



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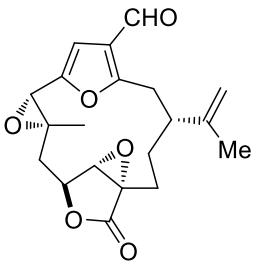

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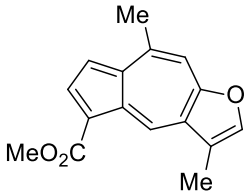
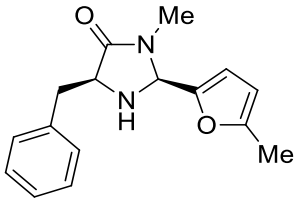


5

On the other hand, furan moiety is present in MacMillan's imidazolidinone catalyst **6** used in enantioselective alkylation of indole resulting in 84% *ee*.[5,6] Some pharmaceuticals also contain furan skeleton; for example, ranitidine (**7**) (Zantac©), a histamine H2-receptor antagonist that inhibits gastric acid secretion.[7]



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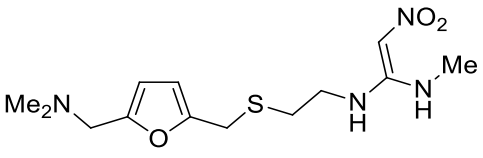
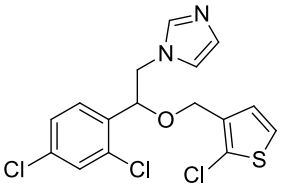
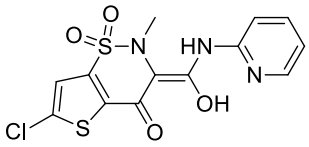


7

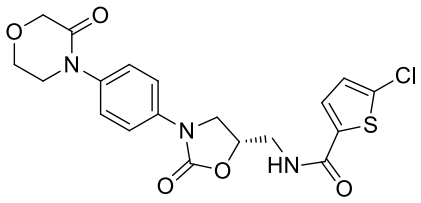
The thiophene moiety is known as toxicophore due to its oxidative bioactivation towards electrophilic species. Tioconazole (**8**), lornoxicam (**9**), and rivaroxaban (**10**) are examples of several drugs containing thiophene.[8] Tioconazole (**8**) is an antifungal mediation known under the brand names Trosyd and Gyno-Trosyd by Pfizer. Lornoxicam (**9**) whose trade name is Xefo is a non-steroidal anti-inflammatory drug. Rivaroxaban (**10**) is an oral anticoagulant marketed by Bayer.



Tioconazole (**8**)



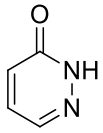
Lornoxicam (**9**)



Rivaroxaban (**10**)

1.2 Pyridazinones

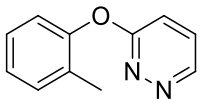
Pyridazinones (**11**) are six-membered heterocycles that contain two adjacent nitrogen atoms and a carbonyl group.



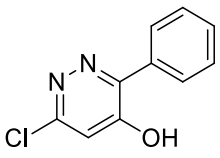
Pyridazinone (**11**)

Pyridazinones have gained importance in terms of biological, medicinal and agricultural reasons. On the other hand, the reason for the low abundance in nature is the difficulty for living organisms to form N-N bonds.[9] Moreover, it has been shown that pyridazinones have prominent potentials as antidepressant,[10] antihypertensive,[11–13] antithrombotic,[14] anticonvulsant,[15] cardiotonic,[16] antibacterial,[17] diuretics,[18] antiHIV,[19] and anticancer reagents.[20]

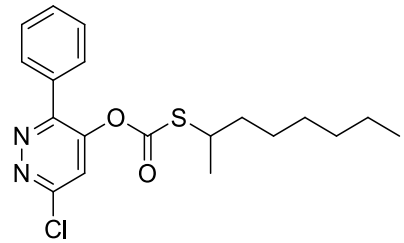
As a class of pyridazinone herbicides, credazine (**12**), pyridafol (**13**) and pyridate (**14**) are the compounds in the Compendium of Pesticide Common Names.[21]



credazine (**12**)



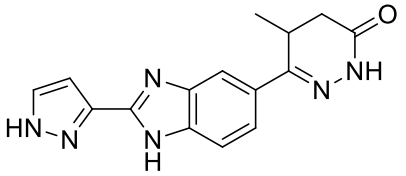
pyridafol (**13**)



pyridate (**14**)

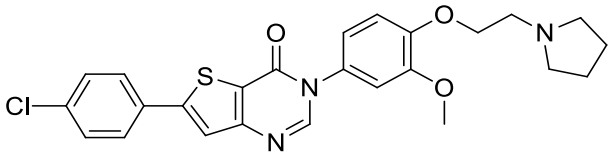
6-Aryl-tetrahydropyridazin-3-one derivatives are known as cardiotonic agents exhibiting inotropic and vasodilator activities. Therefore, synthetic variation of this skeleton has been

examined to inhibit phosphodiesterase type 3 enzyme (PDE3) selectively and meribendan (**15**) has been found to be the most promising derivative.[22]



meribendan (**15**)

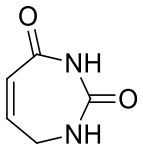
Moreover, thienopyridazinone core **16**, also known as GW3430, is a drug functioning as selective non-peptide antagonist the melanin concentrating hormone receptor MCH1R. This antagonist is efficient for the treatment of obesity in rodents and dogs, anxiety and depression.[23]



GW3430 (**16**)

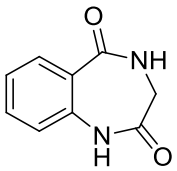
1.3 Diazepinedione

Diazepinedione is a seven membered heterocyclic compound having two nitrogen atoms and two carbonyl functional groups. It has many isomers depending on the place of nitrogen atoms and carbonyl group. 1,3-Diazepine-2,4-dione (**17**) is one of its constitutional isomers.



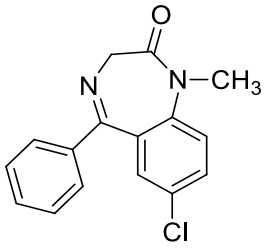
1*H*-1,3-diazepine-2,4(3*H*,7*H*)-dione (**17**)

Compounds having 1,4-benzodiazepine-2,5-dione ring system such as **18** are well-known for their biological utility. They have been studied as anxiolytic,[24] anticonvulsant,[25] antitumor,[26] and anti-HIV agents.[27] These benzodiazepinedione derivatives have been found to inhibit platelet aggregation behaving like the arginine-glycine-aspartic acid (RGD) peptide sequence[28] and as to disrupt the p53-Hdm2 protein-protein interaction inducing cell growth arrest and apoptosis.[29–31]



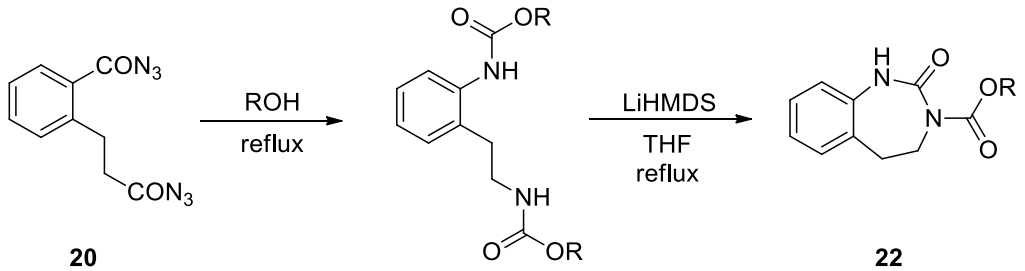
3,4-dihydro-1*H*-benzo[e][1,4]diazepine-2,5-dione (**18**)

On the other hand, diazepinone skeleton has also been found to have interesting activities. Those compounds having pharmacological property attracted the attention in 1960s. Around the same time, diazepam (**19**) was discovered and then used in psychotherapy. Later, research concerning diazepinones showed that they have anticonvulsant, sedative and antitumor properties.[32-34]



Diazepam (**19**)

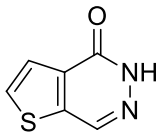
Although diazepinones are pharmacologically well-known heterocyclic compounds, there are not many synthetic approaches described in the literature. Balci and his group developed a methodology for the synthesis of 1,3-benzodiazepine-2-one derivatives (Scheme 2).[35]



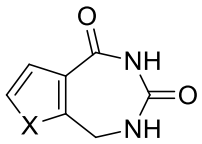
Scheme 2 The synthesis of 1,3-benzodiazepine-2-one derivatives

1.4 Thienopyridazinone and furodiazepinedione derivatives

It is known that many heterocycles play major roles in the areas regarding living things; however, compounds in which thiophene fused to pyridazinone **23** and furan or thiophene fused to diazepinedione **24** or **25** are not well-known in the literature in terms of their synthesis and activities.



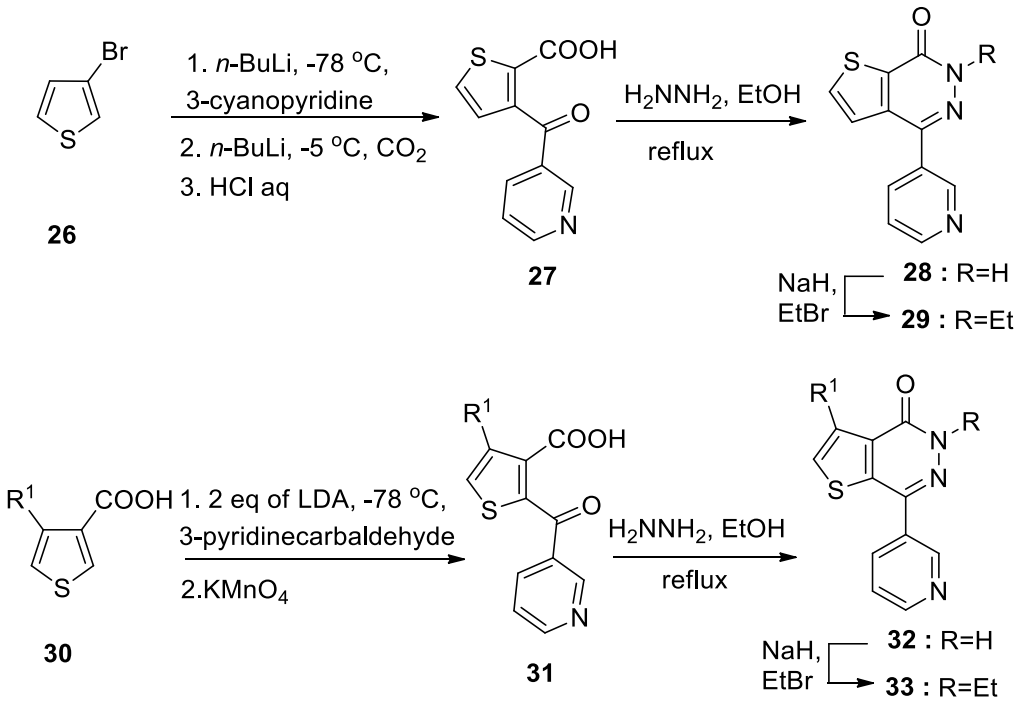
thieno[2,3-d]pyridazin-4(5*H*)-one (**23**)



X = O 7,8-dihydro-4*H*-furo[2,3-e]
[1,3]diazepine-4,6(5*H*)-dione (**24**)

X = S 7,8-dihydro-4*H*-thieno[2,3-e]
[1,3]diazepine-4,6(5*H*)-dione (**25**)

1.4.1 Synthesis of thienopyridazinone derivatives

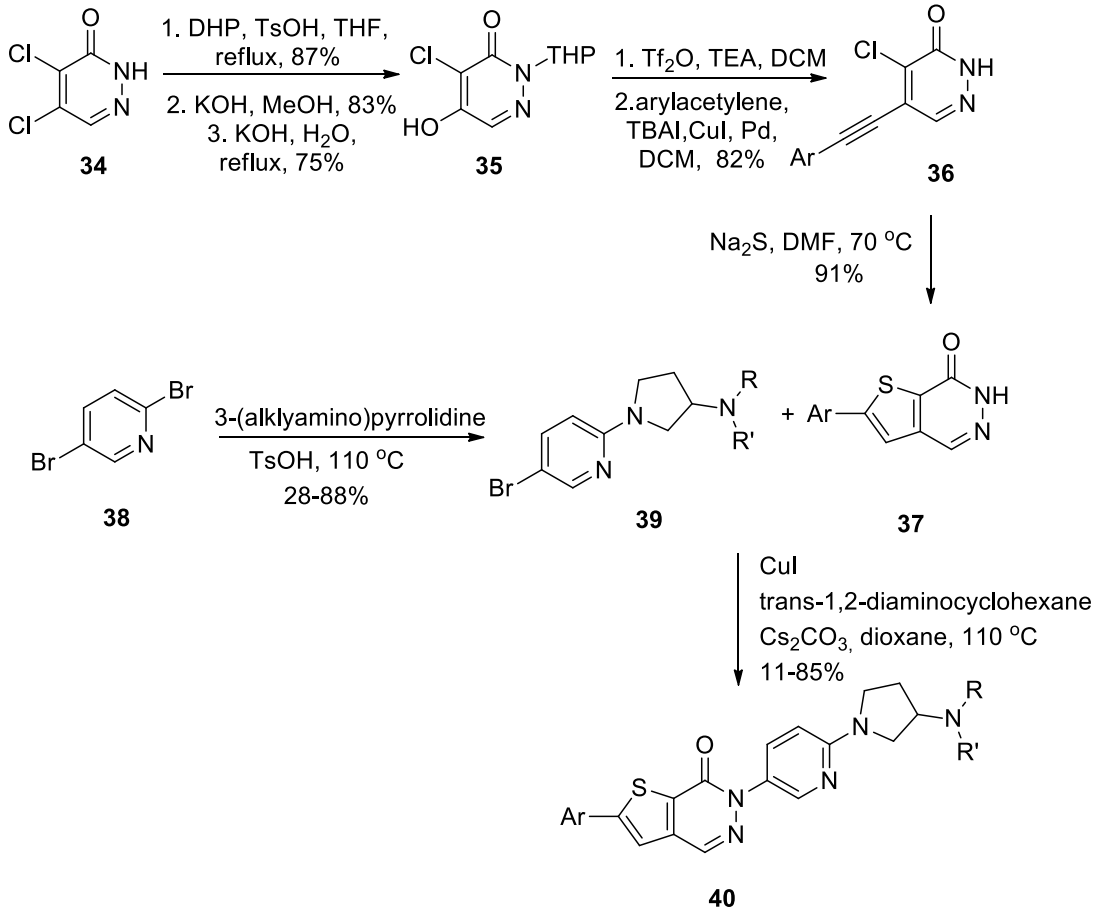


Scheme 3 Synthesis of thienopyridazinone derivatives

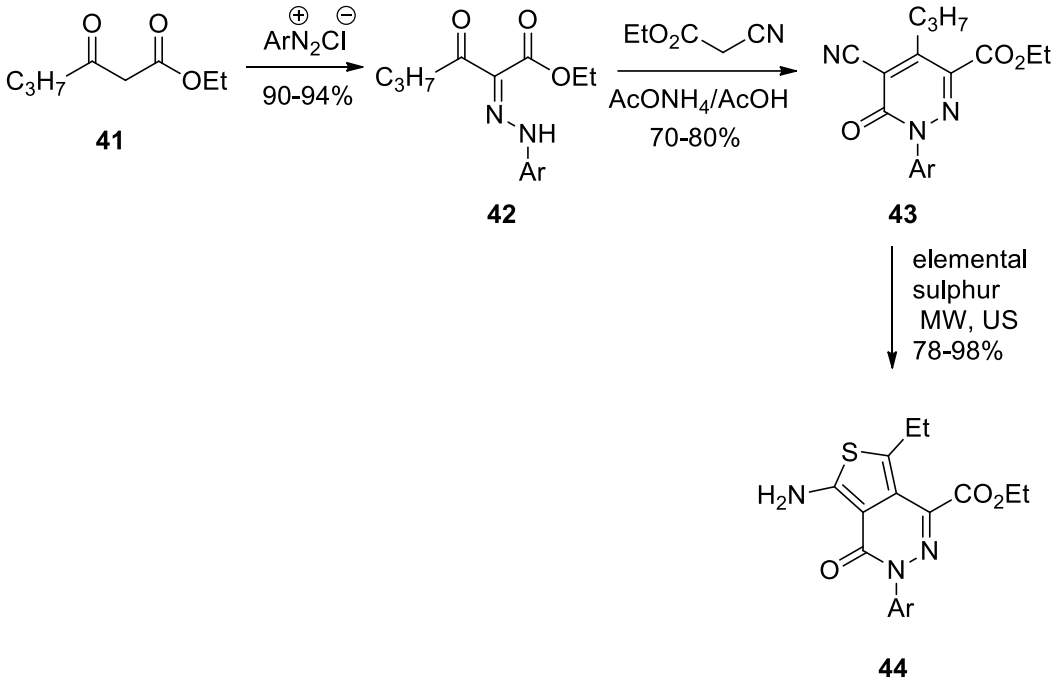
Some thienopyridazinone derivatives are reported in the literature; furthermore, it has been found that they show thromboxane A_2 (TXA_2) synthetase-inhibitory and bronchodilatory activities.[36] For example, thienopyridazinone **29** was obtained in an overall yield of 7% starting from 2-bromothiophene (**26**) whose reaction with one equivalent of *n*-BuLi at -78 °C followed by the reaction with 3-cyanopyride gave an intermediate. Subsequent reaction of this intermediate with one equivalent of *n*-BuLi at higher temperatures followed by reaction with dry ice and then diluted HCl produced 3-(3-pyridinoyl)thiophene-3-carboxylic acid (**27**). Later, hydrazine was added for cyclization to get the compound **28**. Since the desired product was obtained with such a low yield, the synthesis was started with thiophene-3-carboxylic acid (**30**) (Scheme 3). Addition of two equivalents of LDA to **30** followed by treatment of 3-pyridinecarbaldehyde and then oxidation gave compound **31** in 65% yield. Similarly, the ring closure to get thienopridazinone **32** would be achieved by the addition of hydrazine in the overall yield of 58%.

Another thiophene-fused pyridazinone derivative **40** was tested on obese rats and demonstrated to be dose-dependent weight loss effect.[23] The key compound **36** was prepared

from dichloropyridazinone **34** and 2,5-dibromopyridine (**38**) (Scheme 4). In the first part, pyridazinone **34** was protected as THP derivative. The selective substitution of one chlorine atom was carried out in methanol with KOH to give **35**, which was converted to **36** by Sonogashira coupling with arylacetylenes. Later, thiophene-fused pyridazinone **37** was obtained by the treatment with sodium sulfide. In the second part, the more reactive bromine of **38** was replaced with 3-aminopyrolidines to give bromopyridine **39** which was coupled with **37** to form final product **40**.



Scheme 4 Synthesis of thienopyridazinone derivatives

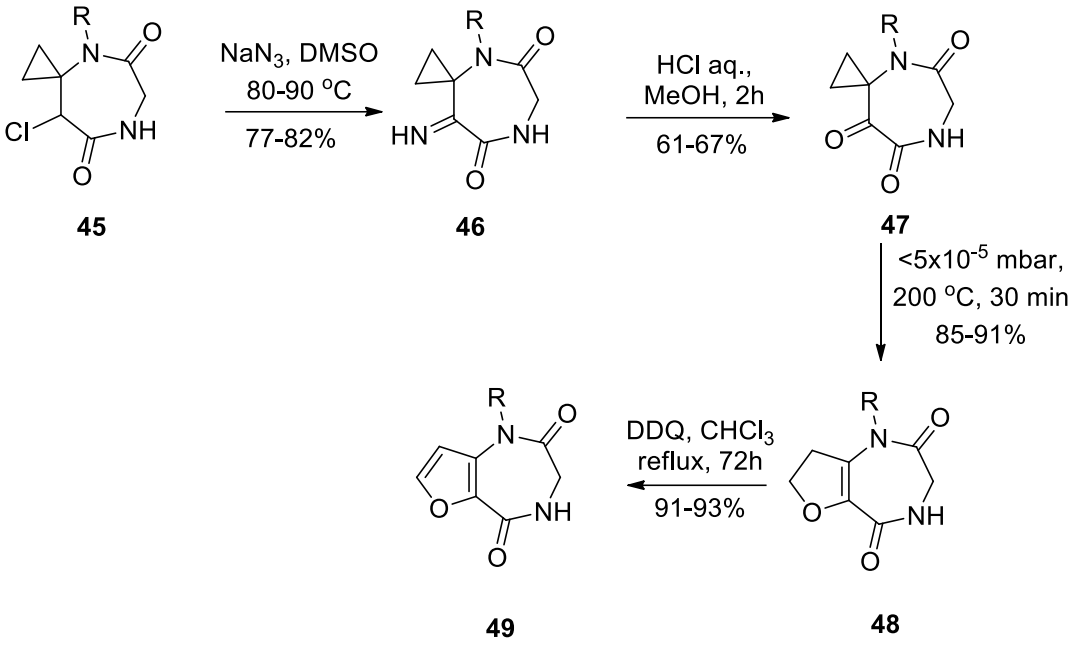


Scheme 5 Synthesis of thienopyridazinone derivatives

A different approach to synthesize thienopyridazinone derivatives was starting from ethyl 3-oxohexanote (**41**) under neat reaction conditions (Scheme 5). Moreover, the help of microwaves and ultrasound resulted in shorter reaction time and better yields.[37] Hydrazone **42** were synthesized by the coupling of starting material **41** with diazonium salts. The reaction of arylhydrazone **42** with ethyl cyanoacetate by heating of neat reagents led to closure of the ring to give **43**. Then, the pyridazinones were reacted with elemental sulphur for the production of desired compound **44**.

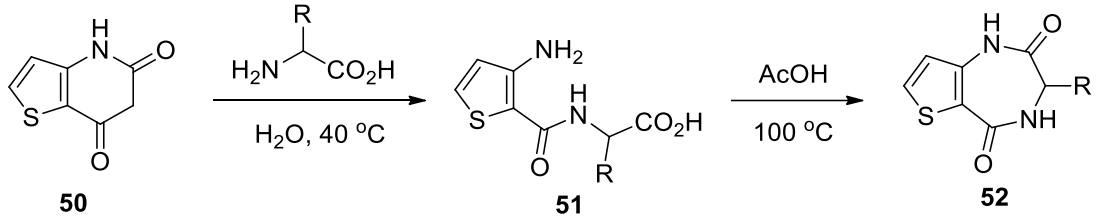
1.4.2 Furodiazepinedione derivatives

The synthesis of seven-membered diazepinedione fused to furan is not well-defined in literature. Starting from chlorolactames **45**,[38] the synthesis of furodiazepinedione **49** was reported in the literature.[39] Addition of sodium azide to **45** in DMSO gave corresponding imine **46** by nucleophilic substitution followed by elimination of nitrogen. Then, imine **46** was hydrolyzed to ketone **47** and the Cloke rearrangement was achieved to give dihydrofuran **48** by heating in sublimation apparatus at 200 °C. Finally, the final product was obtained by oxidation with DDQ at the boiling point of chloroform (Scheme 6).



Scheme 6 Synthesis of furodiazepinedione derivatives

1.4.3 Synthesis of thienodiazepinedione derivatives

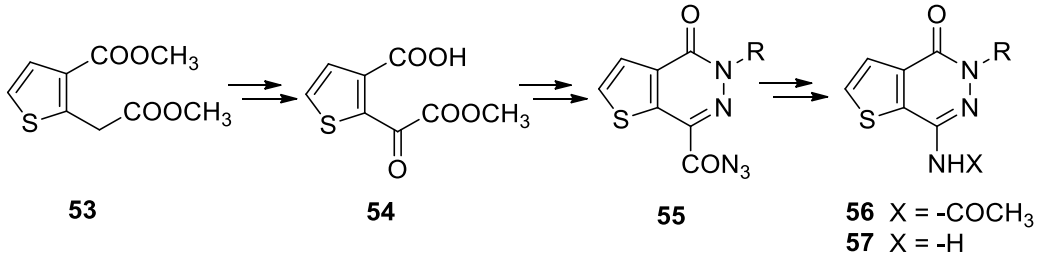


Scheme 7 Synthesis of thienodiazepinedione derivatives

Treatment of thiaisatoic anhydride (**50**) with various aminoacids followed by addition of acetic acid resulted in 3,4-dihydrothieno[3,2-*e*][1,4]diazepine-2,5-dione (**52**) in 41-75% yields (Scheme 7).[40]

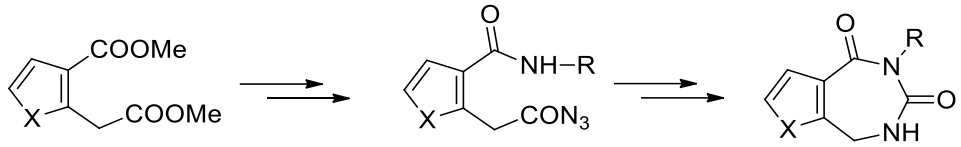
1.5 Aim of the thesis

The aim was to synthesize heterocyclic compounds having bicyclic structure consisting of thiophene- and furan-fused six or seven membered heterocycles.



Scheme 8 Synthetic pathway for thienopyridazinone derivatives

In the first part of this work, we planned to synthesize the new heterocycles where thiophene fused to pyridazinone skeleton. For this purpose, the diester **53** was chosen as the starting material. Then, one of this ester groups should be converted first in the acid functionality to give **54**. After getting the desired intermediates, the ring closure reaction was planned to be carried out with hydrazine to yield **55**. Later, acyl azide functionality in **55** was utilized using Curtius rearrangement as the main reaction. Finally, we degradate the carbonyl group to corresponding amine, since the compounds having –NH or $–NH_2$ groups are more likely to show biological activities (Scheme 8).



X = O **58**
X = S **53**

X = O **59**
X = S **60**

X = O **61**
X = S **62**

Scheme 9 Synthetic pathway for furo- and thienodiazepinedione derivetives

In the second part, the synthesis of furodiazepinediones **61** and **62** was planned. This skeleton is not described in the literature. Acyl azides **59** and **60** will play here a dominating role. Intramolecular cyclization of isocyanates, which will be generated from **59** and **60** with –NH group in **59** and **60** should produce the desired target compound **61** and **62**(Scheme 9).

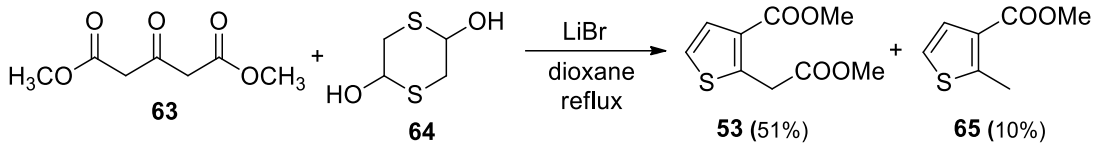
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of thienopyridazinone derivatives

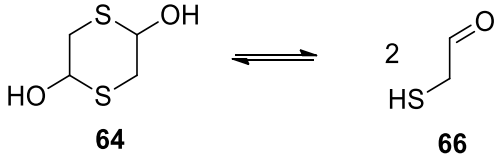
2.1.1 Synthesis of the starting material

For the synthesis of the target compound thienopyridazinone derivatives, it was started with methyl 2-(2-methoxy-2-oxoethyl)-3-thienoate (**53**) which was synthesized according to a literature method.[41] Dimethyl 1,3-acetonedicarboxylate (**63**) and 2,5-dihydroxy-1,4-dithiane (**64**) were reacted in the presence of Lewis acid as LiBr in dioxane to give the starting material **53** in 53% yield beside the side product **65** which was also formed in 10% yield (Scheme 10).



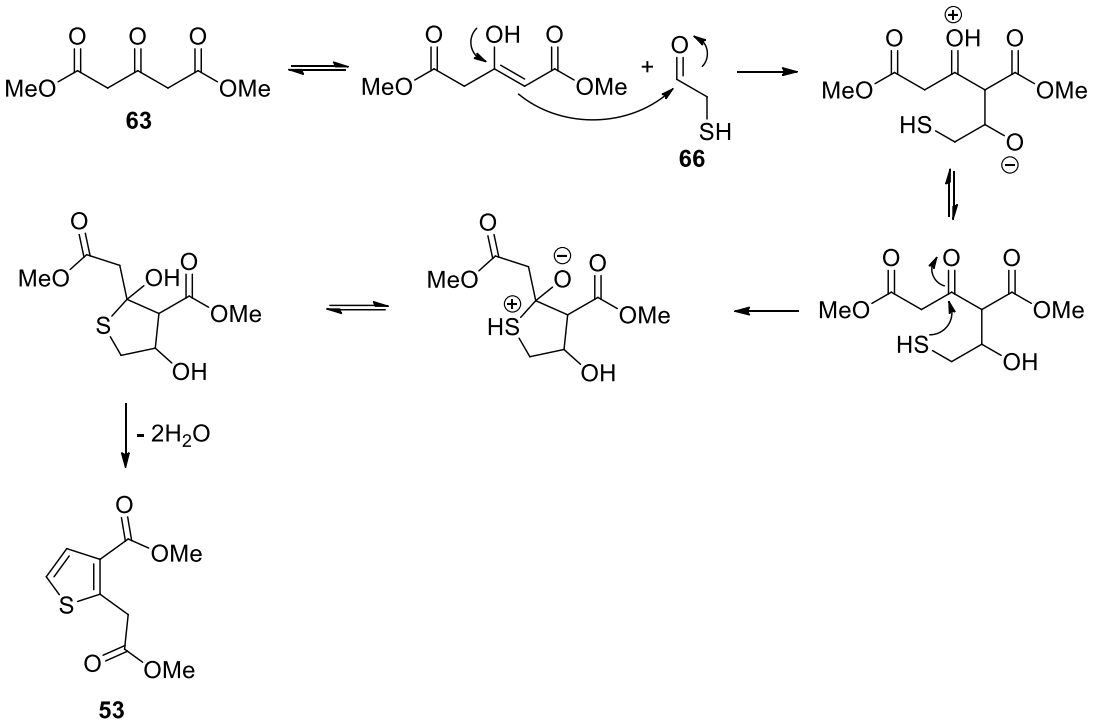
Scheme 10 Synthesis of the starting material **53**

The equivalency of dithiane **64** can be ranged from 0.5 to 1.0 with respect to dimethyl 1,3-acetonedicarboxylate (**63**) since the dithiane **64** is a dimer of mercaptoacetaldehyde (**66**) (Scheme 11).



Scheme 11 Dithiane; a dimer of mercaptoacetaldehyde

According to the mechanism that we proposed for this reaction, aldol-type reaction would firstly take place between the compounds **63** and **66**. Then, the cyclization would be achieved with a nucleophilic attack of sulphur to the most reactive carbonyl group which is a ketone. After elimination of water molecule whose driving force is aromatization, the reaction would be completed (Scheme 12).

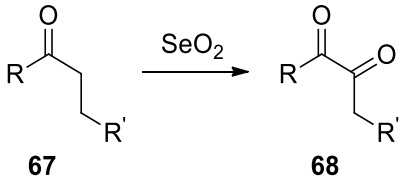


Scheme 12 Proposed mechanism for the formation of **53**

Since this thiophene derivative **53** contains the desired ester functionalities, it was chosen as the starting material. Converting these ester groups to other functionalities are crucial for the establishment of the target heterocyclic skeleton. Previously, Balcı *et al.*[42] utilized thiophenediester **53** successfully for the synthesis of heterocyclic ring systems.

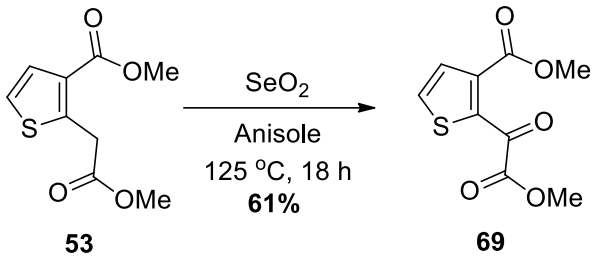
2.1.2 Oxidation with selenium dioxide

A methylene group neighbor to a carbonyl group in **67** can be oxidized to an α-diketone **68** in the presence of SeO_2 (Scheme 13). This oxidation reaction carried out with selenium dioxide is known as Riley oxidation.[43]



Scheme 13 Oxidation with SeO_2

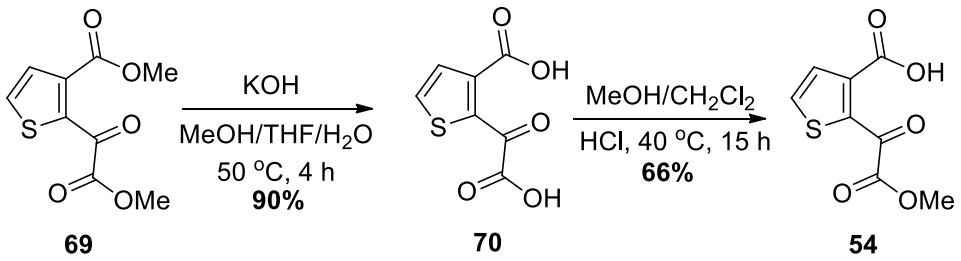
For this study, a methylene group between a thiophene ring and a carbonyl group in compound **53** was successfully oxidized to a ketone **69**. The reaction was first carried out in dioxane as a solvent. However, we found that dioxane was not a suitable solvent for this case since its boiling point was not sufficient for oxidation. Therefore, the solvent was changed to xylene yet the xylene was also oxidized and the compound could not be purified successfully. Also, the yield was low. Finally, we decided to use anisole as a solvent having higher boiling point at 154 °C (Scheme 14).



Scheme 14 Oxidation of methylene group to ketone with SeO_2

2.1.3 Regioselective esterification

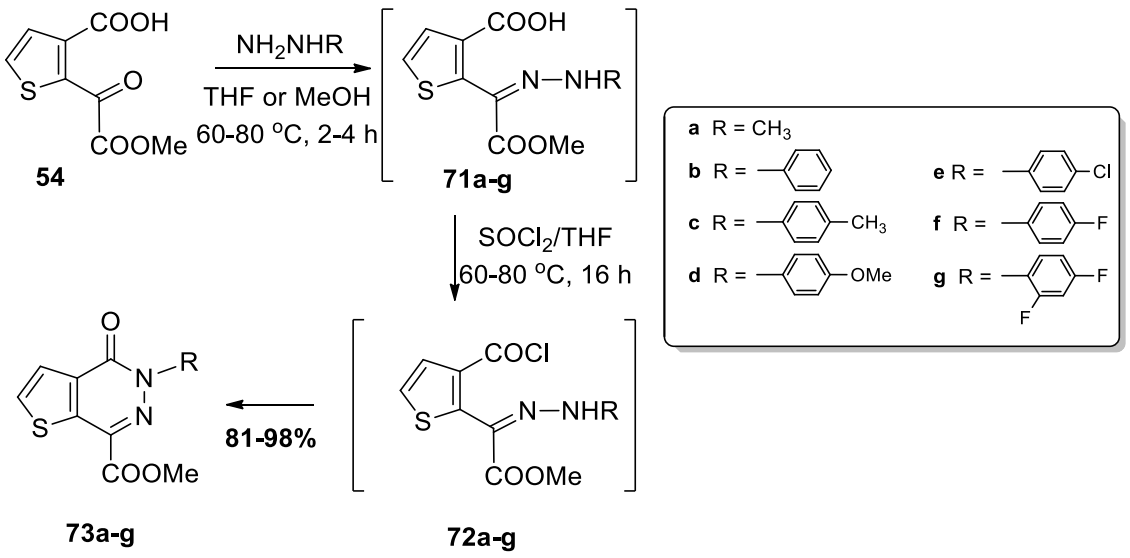
In order to obtain the key compound **54**, the diester **69** firstly was hydrolyzed to diacid **70**. For this purpose, 2M KOH in methanol was used. Disappearance of peaks belonging to ester protons at 3.85 and 3.80 ppm and also appearance of broad singlet belonging to acid peak at 13.50 ppm showed the formation of diacid **70**. Then, regioselective esterification was achieved in methanol/dichloromethane mixture and acidic environment. The fact that one of the acid carbonyl group is in conjugation with aromatic thiophene ring and the other not causes reactivity difference. Due to reactivity difference of two carbonyl groups, one of the acid functional group was converted to ester selectively (Scheme 15).



Scheme 15 Regioselective esterification

2.1.4 Cyclization reaction with hydrazine derivatives

Starting from compound **54**, cyclization was achieved with a very facile way. The ketoester **54** was reacted first hydrazine derivatives to give the desired cyclization compound. For derivatization, seven different hydrazine derivatives were used. THF or methanol was used as a solvent depending on the hydrazine used. THF used for methyhydrazine and phenylhaydrazine. On the other hand, methanol was used for the other derivatives due to solubility problem since the hydrazine derivatives were in the form of salt like $HCl \cdot NH_2NHR$. The hydrazides **71a-g** formed were not isolated. The solvent was evaporated and the acid functionalities were chlorinated with thionylchloride to make it a better leaving group. Then, the lone pair of the nitrogen atom would attack the carbonyl group of the acyl chloride and cyclization would be acquired (Scheme 16).



Scheme 16 Generation of bicyclic system

Formation of the bicyclic compounds **73a-g** was verified by ^{1}H and ^{13}C NMR analysis. Moreover, X-ray analysis of the furan derivative of **73a** was also in agreement with proposed structure.[44]

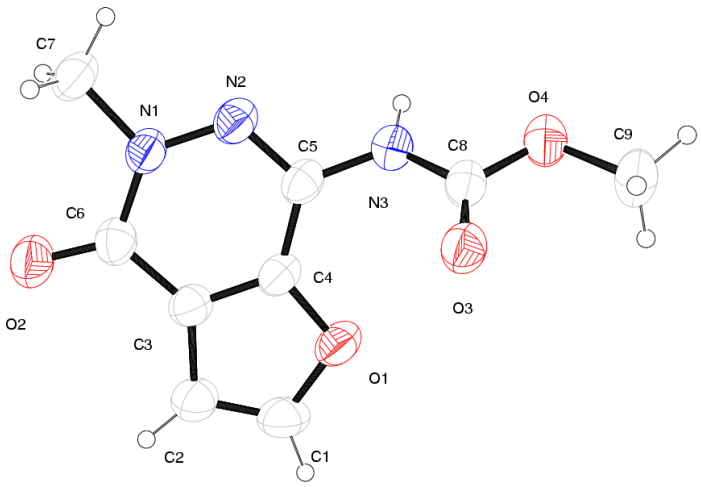


Figure 1 ORTEP drawing of the furan derivative of molecule **73a**

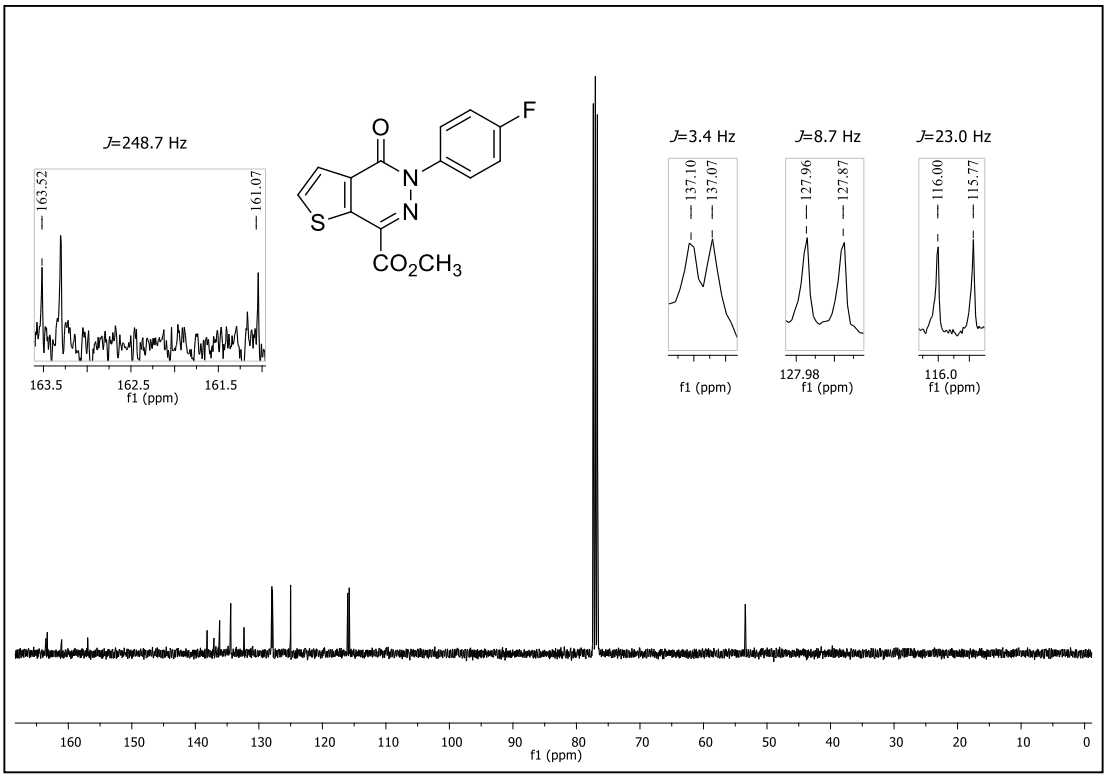


Figure 2 ^{13}C NMR spectrum of compound **73f**

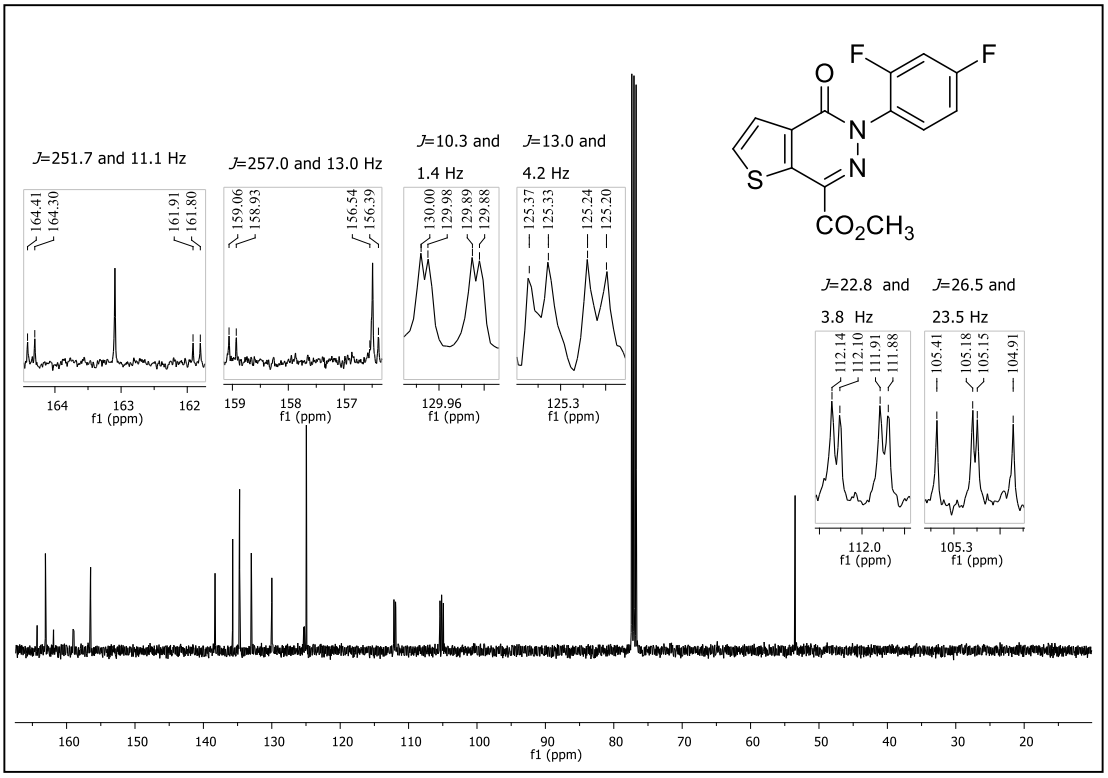


Figure 3 ^{13}C NMR spectrum of compound **73g**

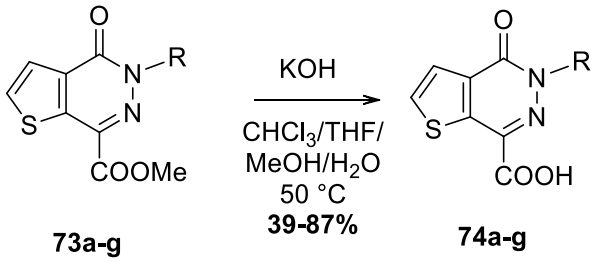
The ^{13}C NMR spectra of the fluorinated derivative were also in agreement with our expectation. Since the spin quantum number (I) of ^{19}F is ½, ^{19}F will couple with ^{13}C and split the ^{13}C signals into doublet according to equation *m=2I+1*. The coupling constant of ^{13}C-^{19}F over one bond ($^{1}J_{C\text{-}F}$) is very large like around 250 Hz. As the distance between ^{13}C and ^{19}F increases, the coupling constant decreases. The coupling constant of ^{13}C-^{19}F over two bonds ($^{2}J_{C\text{-}F}$) is 20-25 Hz.

The compound **73f** contains one fluorine atom attached to the phenyl ring. Therefore, ^{19}F coupled with ^{13}C atoms on the benzene ring as seen in the ^{13}C NMR spectrum (Figure 2). The largest coupling constant is the one with the carbon directly attached to fluorine which is 248.7 Hz. The coupling constants of fluorine with the carbon atoms in *ortho-*, *meta-* and *para*-positions are 23.0, 8.7, and 3.4 Hz, respectively.

On the other hand, the compound **73g** contains two fluorine atoms; therefore, all the carbons are split into doublet of doublets (Figure 3). The carbons directly attached to fluorine have the largest coupling constants (^{1}J) around 251.7 and 257.0 Hz and also they show further couplings of 11.1 and 13.0 Hz, respectively due to fluorine atom in the *meta*-position (^{3}J). Furthermore, the quaternary carbon attached to the nitrogen has coupling constant of 22.8 Hz due to fluorine atom in *ortho*-position. The fluorine in para couples it with ^{4}J = 3.8 Hz.

2.1.5 Hydrolysis of ester functional groups in 73a-g

Thienopyridazinone skeletons having ester functional groups **73a-g** were hydrolyzed under basic conditions. After acidification of the reaction medium with aq. HCl, the acids **74a-g** were formed (Scheme 17). Since the acids **73a-g** formed were not soluble either in organic solvent or in water, they precipitated after filtration of the acids, they were analyzed by ^{1}H and ^{13}C NMR. Peaks belonging to ester protons around 4 ppm in ^{1}H NMR and 53 ppm in ^{13}C NMR spectra disappeared.



73a-g **74a-g**

Scheme 17 Synthesis of acids **74a-g**

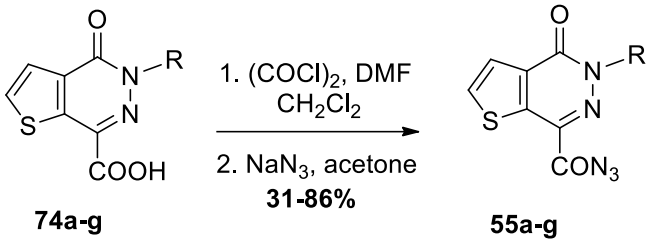
2.1.6 Synthesis of acyl azides 55a-g

For the synthesis of acyl azides **55a-g** starting from corresponding acid **74a-g**, these acid functionalities should be activated by converting them into the corresponding to acyl chlorides. For this purpose, the acids were treated with oxalyl chloride and catalytic amount of DMF. Later, solvents were evaporated and the acyl chlorides formed were treated without

isolation with sodium azide in acetone to give the corresponding acyl azides **55a-g** (Scheme 18).

The formation of acyl azides was established mainly by IR analysis. The wave number around 2150 cm^{-1} typical for azides was observed in all cases. Moreover, disappearance of acid proton around 14 ppm in the ^{1}H NMR spectra also confirmed the consumption of the acids **74a-g**.

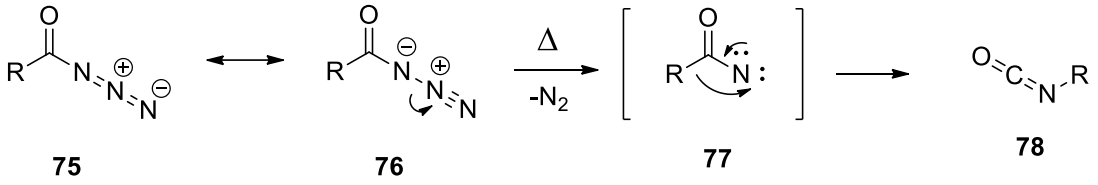
Azides are known to be unstable due to removal of nitrogen gas upon heating. They even decompose when storing at room temperature. However, an interesting feature about these acyl azides is that they are relatively stable due to the conjugation with pyridazine ring.



Scheme 18 Synthesis of acyl azides **55a-g**

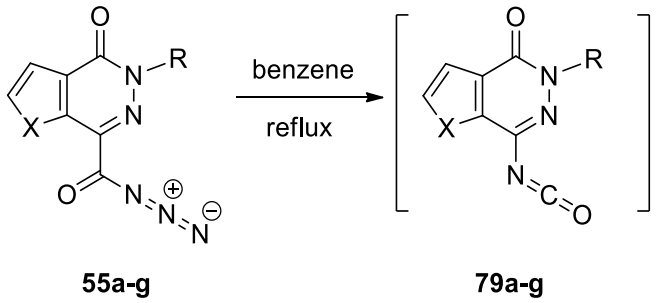
2.1.7 Synthesis of isocyanates via Curtius rearrangement

Heating of an acyl azide **75** forms corresponding isocyanate **78** with the removal of nitrogen gas. First, nitrogen gas is released to form acyl nitrene **77** which is an electron deficient intermediate and it rearranges to obey octet rule (Scheme 19). This reaction is called Curtius rearrangement.[45] To apply the Curtius rearrangement to our compounds, the azides **55a-g** were dissolved in an aprotic solvent and were heated.



Scheme 19 Mechanism of Curtius rearrangement

In general, isocyanates are stable reactive intermediate. They can be isolated and stored; on the other hand, they are quite reactive and can be trapped by nucleophiles because the carbon atom of isocyanate is so electrophilic. In this study, benzene was chosen as the aprotic solvent and the acyl azides **55a-g** were heated at the reflux temperature of benzene. Furthermore, we did not isolate the isocyanates which were directly used for the next step (Scheme 20).

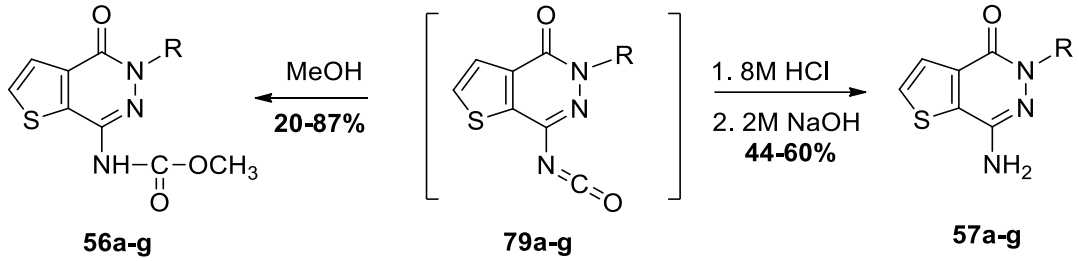


55a-g **79a-g**

Scheme 20 Synthesis of isocyanates **79a-g** via Curtius rearrangement

2.1.8 Synthesis of urethanes 56a-g and amines 57a-g

Without isolation of isocyanates **79a-g**, methanol or 8M HCl were used to trap the isocyanates. Addition of methanol resulted in the formation of urethanes **56a-g** and hydrolysis in acidic environment gave the amine derivatives **57a-g** (Scheme 21).

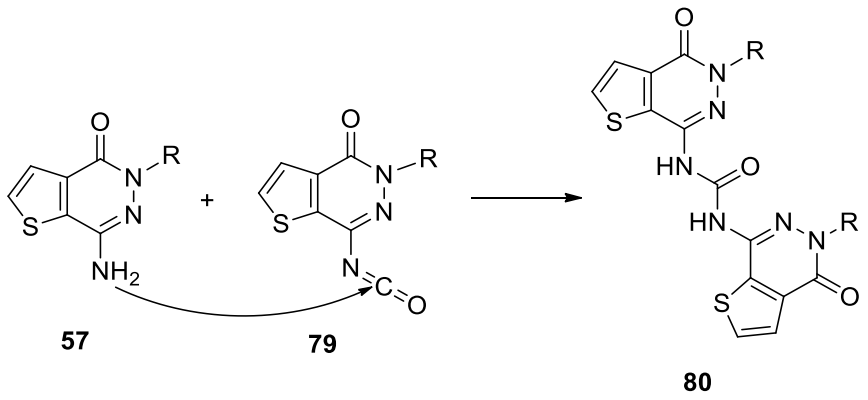


56a-g **79a-g** **57a-g**

Scheme 21 Synthesis of urethanes **56a-g** and amines **57a-g**

The formation of urethanes **56a-g** were shown easily by analysis both NMR and IR spectra. The methyl proton resonances appearing around 3.7 ppm belonging to $–OCH_3$ groups and broad singlets about 7 ppm are arising from –NH protons showing formation of urethane derivatives. Also, no trace of characteristic wave number of isocyanate around 2250 cm^{-1} was present indicating the quantitative consumption of isocyanates.

Hydrolysis of isocyanate was carried out in acidic medium to give corresponding amine derivatives **57a-g** in good yields. Otherwise, we would encounter the dimerized compounds **80** due to the attack of the lone pair of amine **57** to the carbonyl group of isocyante **79** since the rate of reaction of amine **57** with isocyanate **79** (Scheme 22). By hydrolysis in acidic media the amine formed initially is immediately trapped as the salts before reacting with isocyanate.



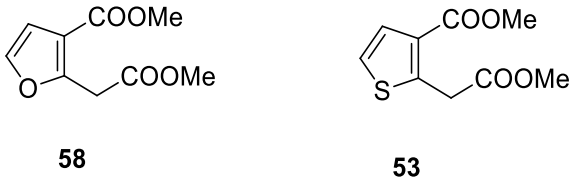
Scheme 22 Dimerization of isocyanates

Amines **57a-g** were analyzed by IR and NMR spectra. Since the solubility of amines were difficult, different solvents were examined for NMR analysis such as acetone-d_6, DMSO-d_6 and $CDCl_3$. Formation of amines **57a-g** was confirmed by the broad singlet resonating around 4.0-5.5 ppm in ^{1}H NMR. ^{13}C NMR spectra were also in agreement with the proposed structure.

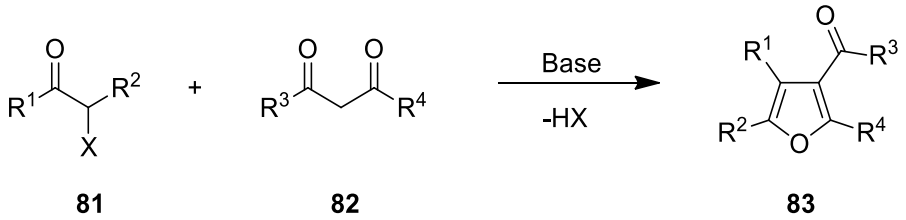
2.2 Synthesis of furo- and thienodiazepinedione derivatives

2.2.1 Synthesis of the starting materials

Furan diester **58** and thiophene diester **53** were chosen as the starting materials. The synthesis of thiophene diester **53** was discussed in section 2.2.1. In this section, synthesis of furan diester **58** will be discussed shortly.

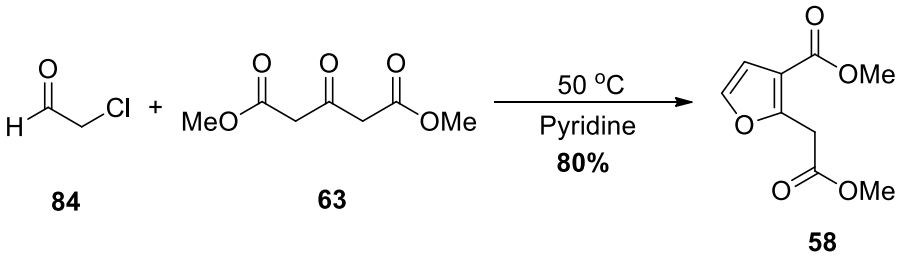


For the synthesis of furan diester **58**, Feist-Benary furan synthesis was utilized.[46,47] As a result of this reaction, substituted furan **83** was obtained (Scheme 23). According to the mechanism, first a condensation reaction takes place and subsequent nucleophilic aliphatic substitution gives the product.



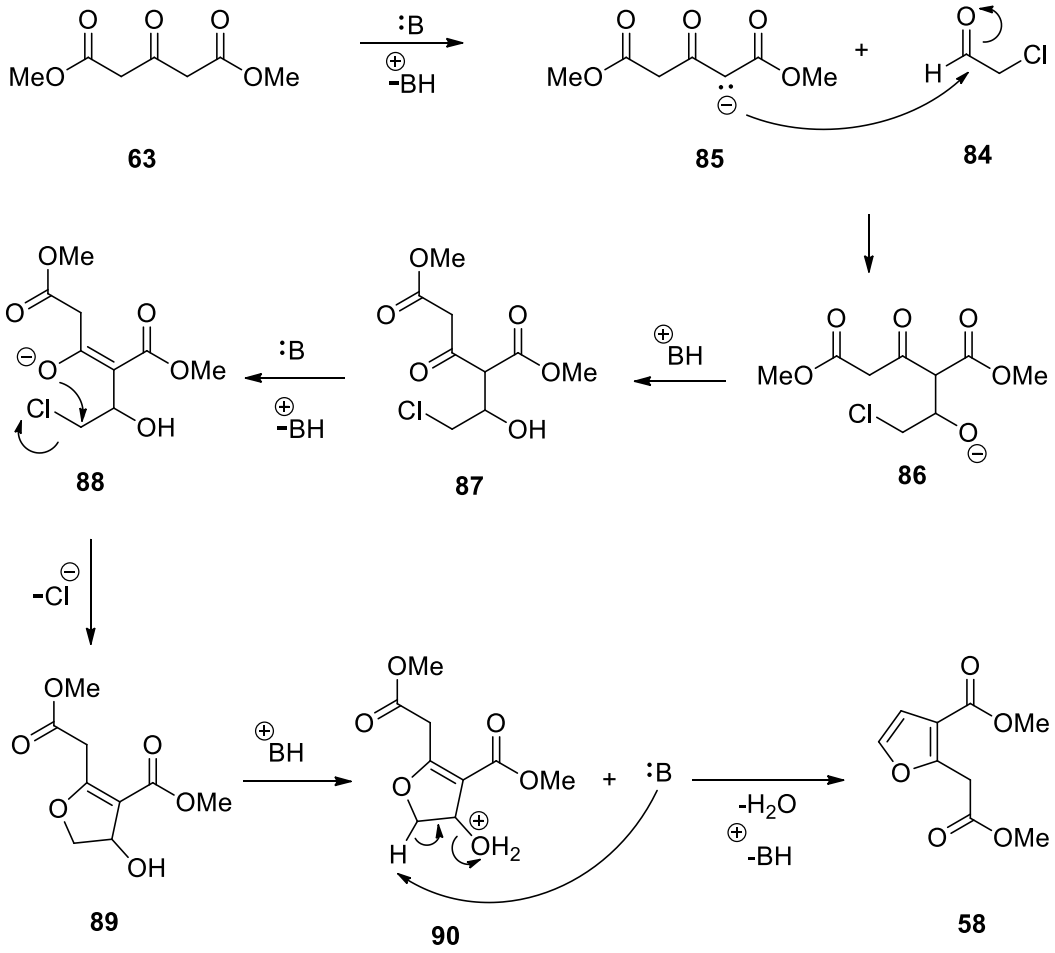
Scheme 23 Feist-Benary furan synthesis

For the synthesis of **58**, the known procedure was applied.[48] The reaction of chloroacetaldehyde (**84**) and 1,3-acetone dicarboxylate (**63**) in pyridine gave the desired starting compound **58** (Scheme 24).



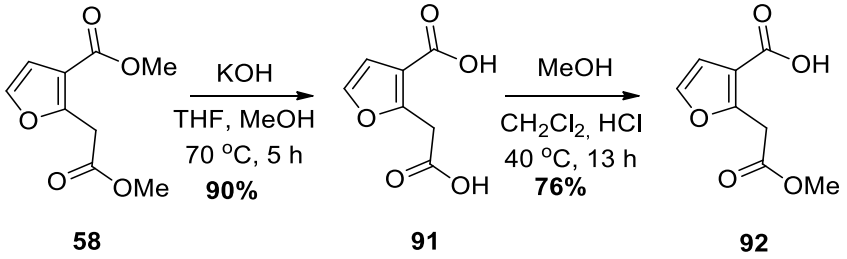
Scheme 24 Synthesis of the starting material **58**

The reaction mechanism starts with the deprotonation of 1,3-acetone dicarboxylate (**63**). The formed carbanion **85** attacks the carbonyl group of chloroacetaldehyde (**84**), an aldol reaction takes place and then enolate **88** is formed. This enolate displaces the chloride and cyclization occurs. Removal of water molecule results in the formation of furan diester **58** (Scheme 25).



Scheme 25 Proposed mechanism for the formation of **58**

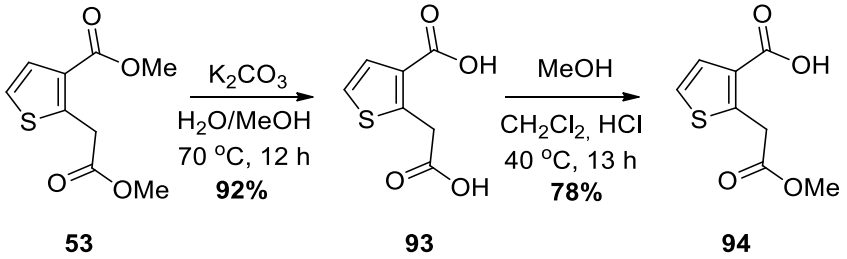
2.2.2 Regioselective esterification



Scheme 26 Regioselective esterification for furan derivative

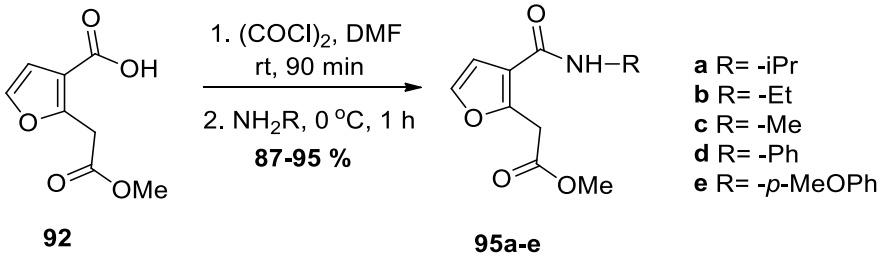
As discussed in part 2.1.3, regioselective esterification of **58** was planned in the same manner as discussed in Scheme 26 and 27. First of all, the ester functionalities in diester **58** and **53** should be hydrolyzed. For furan diester **58**, KOH was used for hydrolysis. However, K_2CO_3 was successively used for the hydrolysis of thiophene diester **53**.

Later, esterification was carried out in the presence of methanol and catalytic amount of acid for both of the diacids **91** and **93** to give the corresponding monoesters **92** and **94**, respectively.



Scheme 27 Regioselective esterification for thiophene derivative

2.2.3 Synthesis of amide derivatives 95a-e and 96a,b

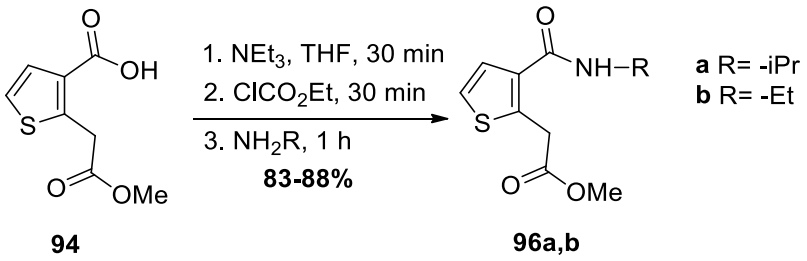


Scheme 28 Synthesis of furan amides **95a-e**

For the synthesis of amide derivatives, we started from acid **92** and **94**. Different approaches were applied to furan and thiophene derivatives.

First of all, furan monoacid **92** was treated with oxalyl chloride in the presence of catalytic amount of DMF for chlorination of acid functional group to make it a better living group. Then, it was treated with several amine derivatives. For this purpose, both amines containing an alkyl group such as isopropyl, ethyl, methyl and aromatic amines such as aniline and *p*-anisidine were used for derivatization. The amides **95a-c** were synthesized with pretty good yields ranging from 87% to 95% (Scheme 28).

On the other hand, the methodology described for the synthesis of furan amides **95a-e** did not work for thiophene amide **96a,b** synthesis because the carboxylic acid group in **95** could not be chlorinated with oxalyl chloride. Later, thionyl chloride was examined yet it was also not successful. Therefore, we turned our attention to another good leaving group like synthesis of anhydride. This time, the proton of carboxylic acid of **94** was abstracted with NEt_3 and then it was treated with ethylchloroformate. Without isolation of anhydride formed, amine derivatives were introduced. Isopropyl amine and ethyl amine were used for the synthesis of the corresponding amides **96a,b** (Scheme 29).

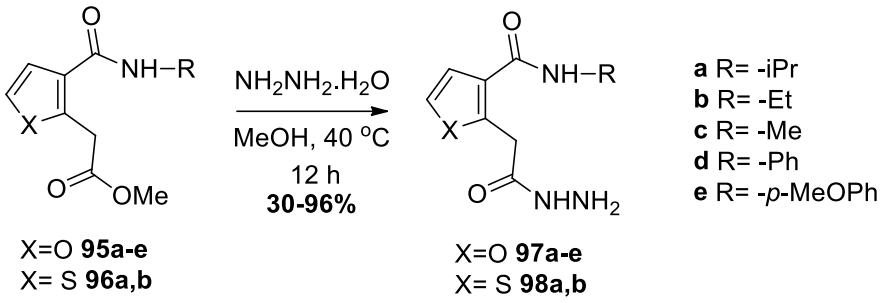


94 **96a,b**

Scheme 29 Synthesis of thiophene amides **96a,b**

2.2.4 Synthesis of hydrazide derivatives 97a-e and 98a,b

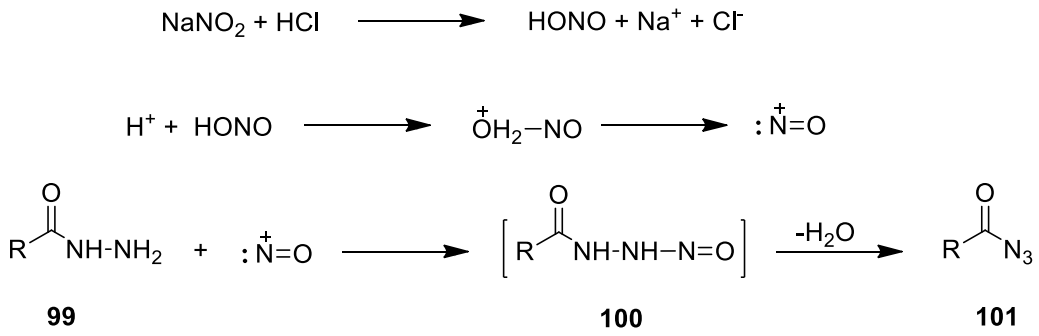
For the next step, we aimed to synthesize hydrazide derivatives **97a-e** and **89a,b**. A mixture of hydrazinemonohydride and **95a-e** or **96a,b** was heated in methanol at 40 °C for 12 hours (Scheme 30). Derivatives of hydrazide where –R group is isopropyl or ethyl were more soluble compared to other derivatives because of the fact that they are branched making them easily soluble. That is why their NMR spectra were recorded in $CDCl_3$ while the others in DMSO-d_6.



Scheme 30 Synthesis of hydrazide derivatives **97a-e** and **98a,b**

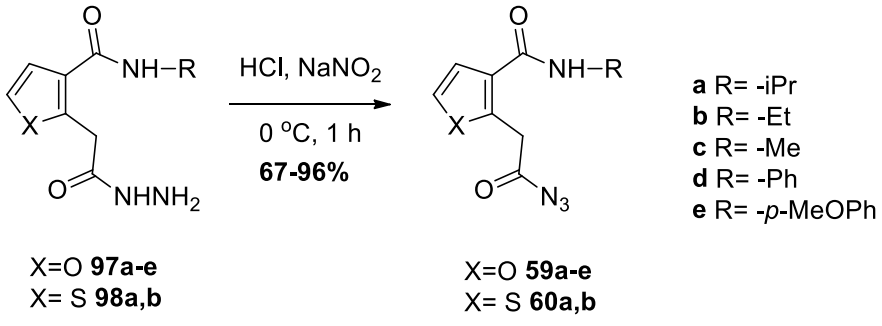
2.2.5 Synthesis of acyl azide derivatives 59a-e and 60a,e

One of the synthetic methods for acyl azide is modified Sandmayer reaction known in the literature.[49] In this reaction, acyl azide **101** is formed starting from hydrazide **99** (Scheme 31).



Scheme 31 Synthetic steps for acyl azide

This approach was utilized to synthesize acyl azide derivatives **59a-e** and **60a,b** which were the key compounds leading us to our target compound via Curtius rearrangement (Scheme 32).



Scheme 32 Synthesis of acyl azides **59a-e** and **60a,e**

The thiophene acyl azides **60a,b** were more stable compared to the furan acyl azides **59a,b**. Still, all azide derivatives were stable enough to be analyzed by ^{13}C and ^{1}H NMR spectra except **59b**. The acyl azide **59b** was fast decomposed to corresponding isocyanate. Right

after the reaction, its IR spectrum was recorded. Both wave number of acyl azide 2137 cm^{-1} and that of isocyanate 2254 cm^{-1} were present in the spectrum. Due to this fast decomposition, we could not get a clean ^{13}C and ^{1}H NMR spectra of compound **59b**.

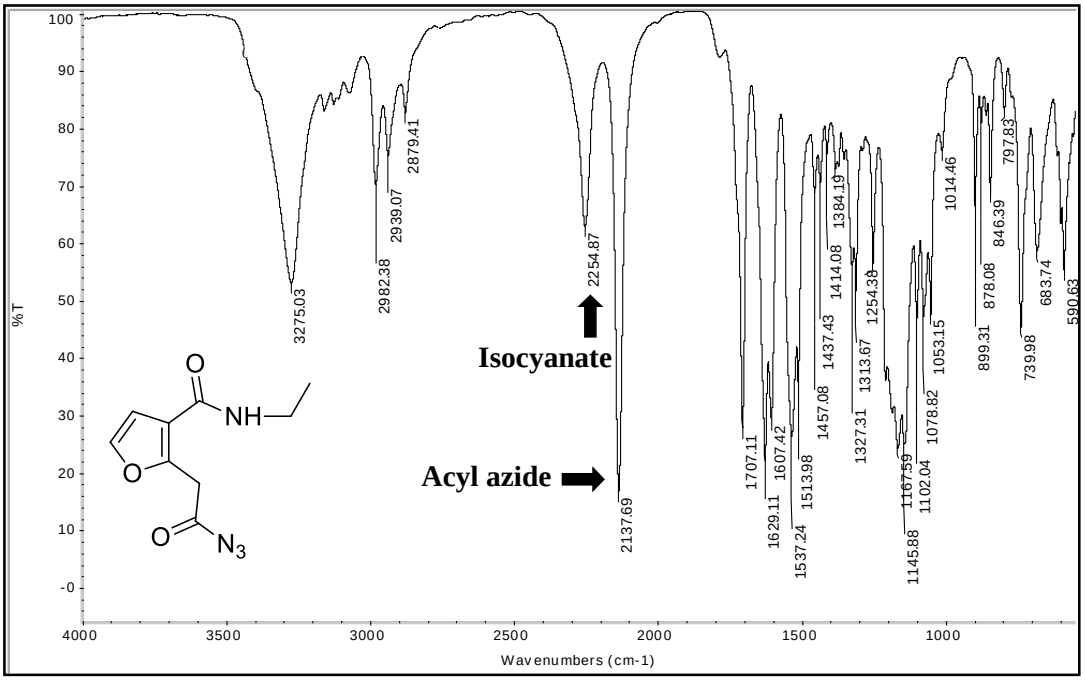
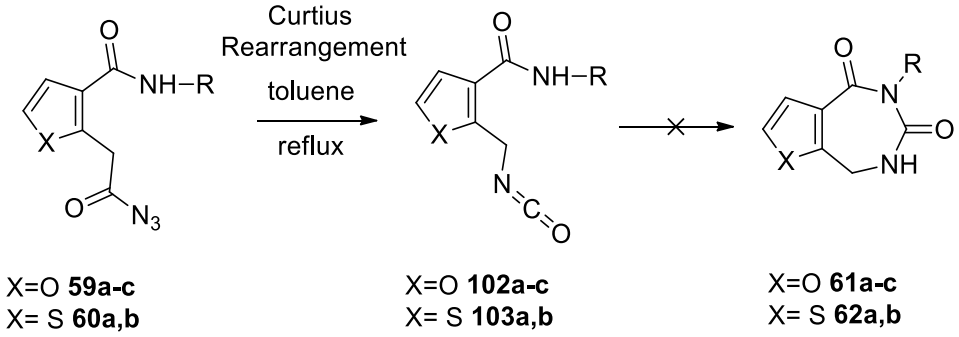


Figure 4 IR spectrum of compound **59b**

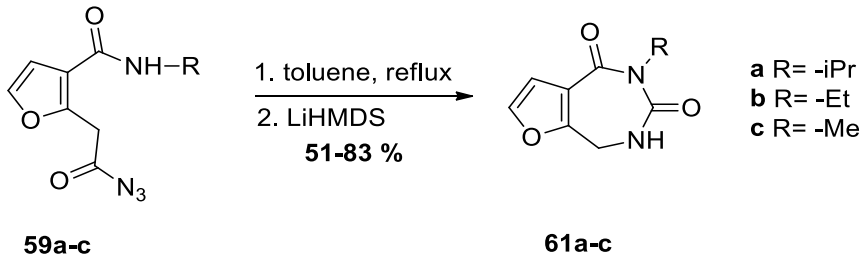
2.2.6 Ring closure reaction

Our idea about cyclization reaction was based on Curtius rearrangement. Starting from acyl azide derivatives **59a-e** and **60a,b**, we aimed to synthesize isocyanates **102a-e** and **103a,b** by heating in an aprotic solvent like toluene. Then, the lone pairs of nitrogen of amide group would attack the carbonyl carbon of isocyanate in **102a-e** and **103a,b** and then ring closure would take place (Scheme 33). However, this expectation failed. We did not observe a cyclization yet we determined the presence of isocyanate at the end of the reaction by IR due to typical absorption wave number of isocyanate around 2250 cm^{-1}.



Scheme 33 Expected intramolecular cyclization

Therefore, we turned our attention to use a non-nucleophilic base such as Lithium hexamethyldisilazide (LiHMDS) in the second step. Firstly, the acyl azides **59a-c** and **60a,b** were heated at the reflux temperature of toluene for the conversion to isocyanate **102a-c** and **103a,b** which were not isolated and characterized. Later, LiHMDS was introduced to the reaction medium to deprotonate the amide proton of isocyanate **102a-c** and **103a,b** to increase the nucleophilicity of the amide nitrogen atoms. Then, the anion formed attacked the carbonyl group and the bicyclic products were formed **61a-c** and **62a,b**.



Scheme 34 Ring closure reaction for furan derivatives

For the furan derivatives, when the alkyl groups were attached to nucleophilic nitrogen atom in acyl azides **59a-c**, the expected products **61a-c** were formed (Scheme 34). The confirmation of the bicyclic products **61a-c** was done with ^{1}H NMR and X-Ray analysis. In ^{1}H NMR, the methylene protons were split into doublet with J = 4-6 Hz due to –NH proton and the –NH proton as broad triplet (Figure 5).

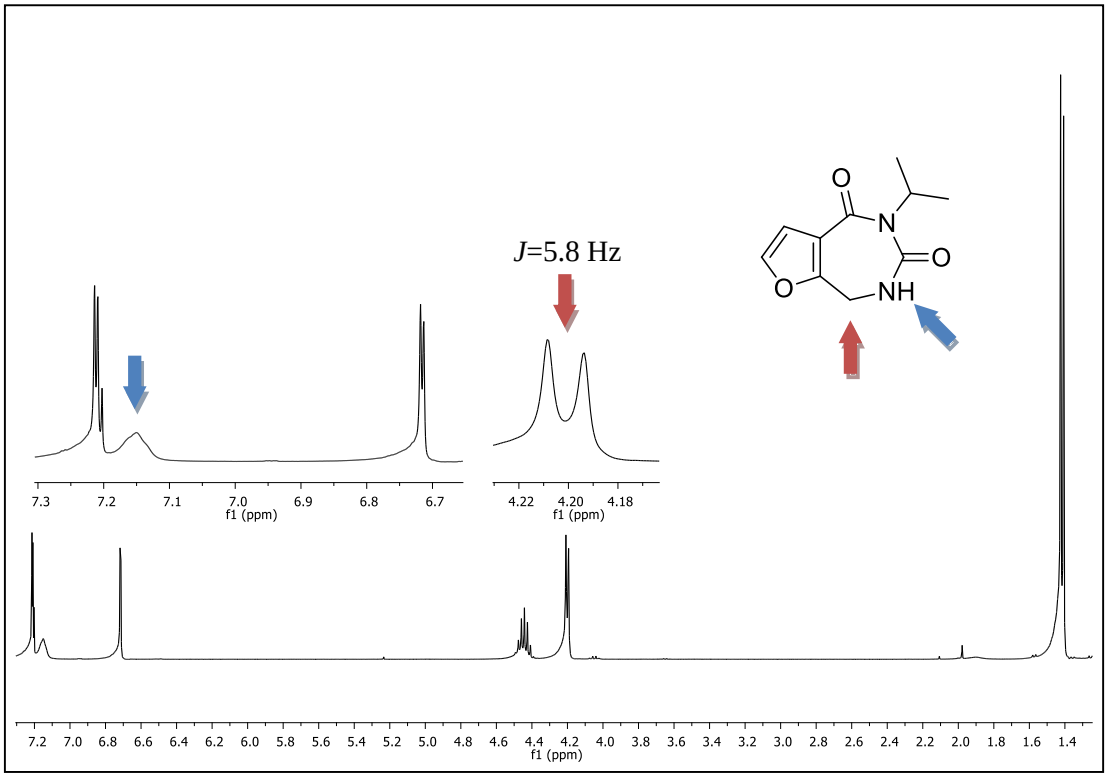
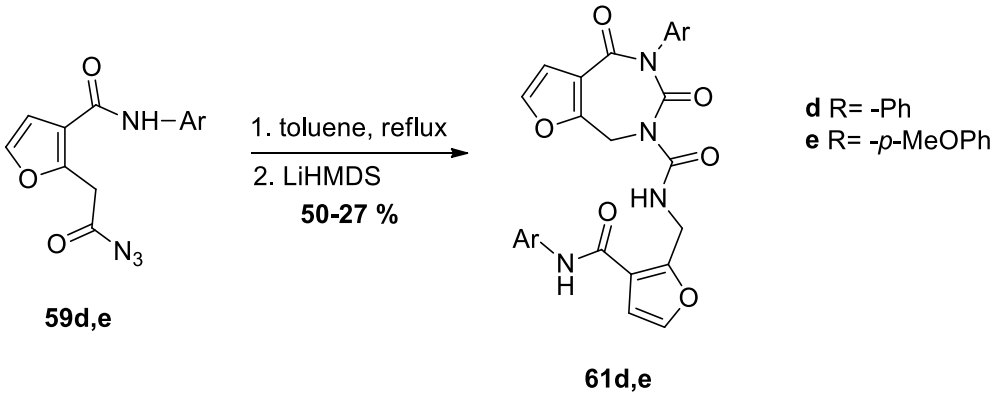


Figure 5 ^{1}HNMR spectrum of compound **61a**

Moreover, X-Ray analysis was carried out to characterize one of the representative structure. The result of X-Ray analysis was in agreement with our expected product **61a** (Figure 6).



59d,e **61d,e**

Scheme 35 Formation of the unexpected dimerization

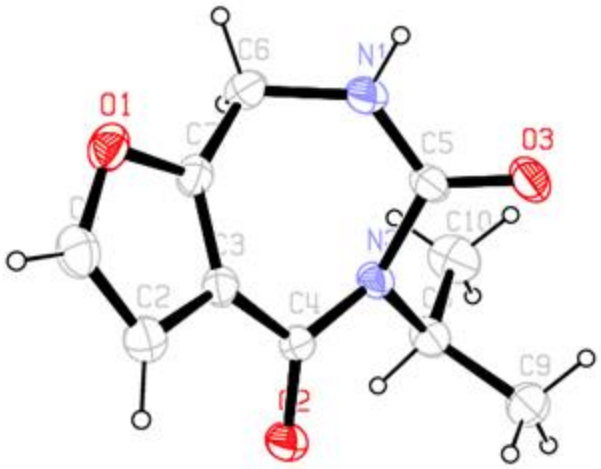
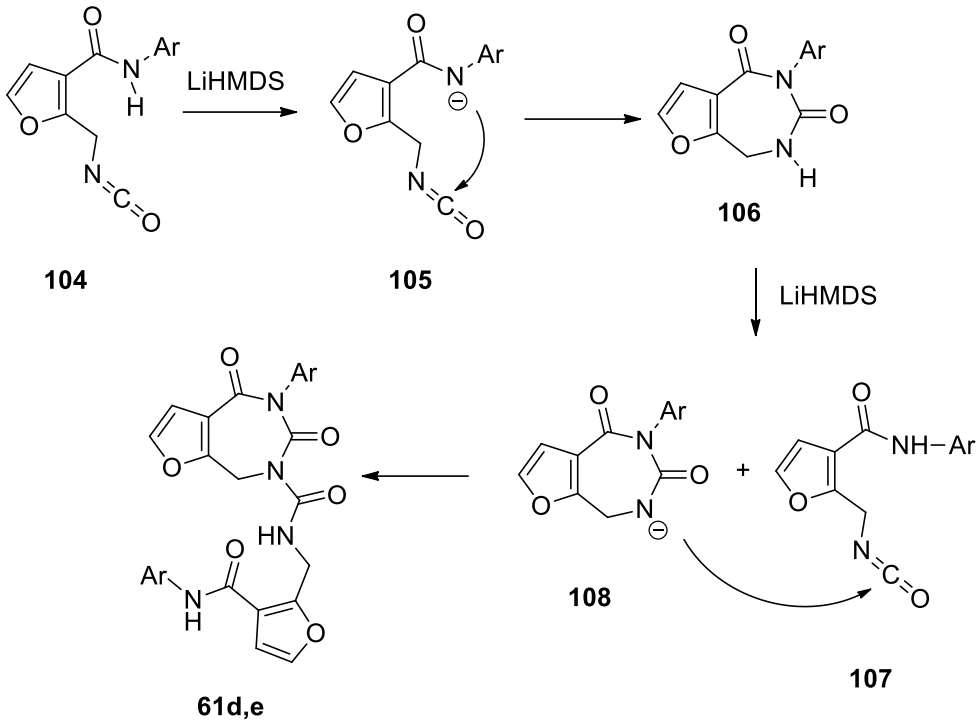


Figure 6 X-Ray Structure of compound **61a**

On the other hand, when an aryl group was attached to the amide nitrogen as in the case of **59c,d**, different products, a kind of dimerized products **61d,e** were formed (Scheme 35). According to mechanism that we proposed, isocyanate **104** will be formed by Curtius rearrangement. Then, the amide proton in **104** will be abstracted by LiHMDS. We assume that the anion **105** formed will be more stabilized due to delocalization over the aromatic ring, making the anion **105** more stable. Now this stable anion can undergo cyclization reaction to form the bicyclic compound **106**. The base cannot abstract the proton on nitrogen atom to produce **108**, which will be stabilized due to the presence of an aromatic ring. This anion can attack an isocyanate group present in the reaction media to form the dimeric compounds **61d,e** as shown in Scheme 36.



Scheme 36 Proposed mechanism for the formation of **61d,e**

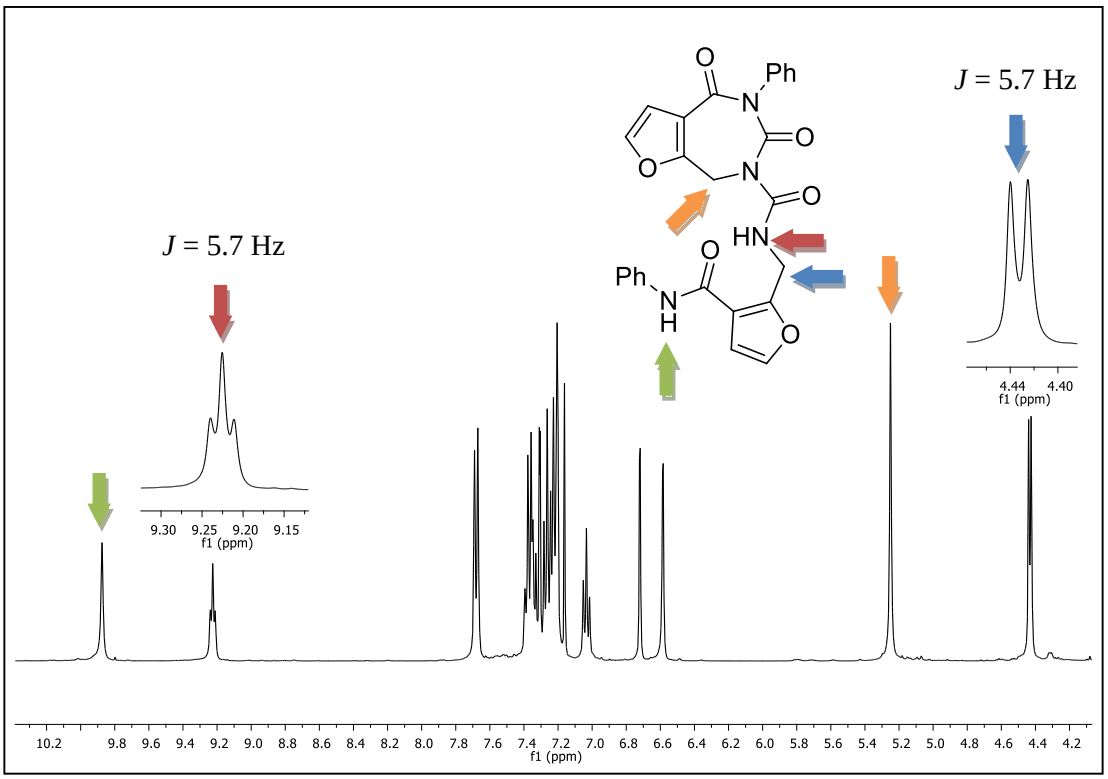
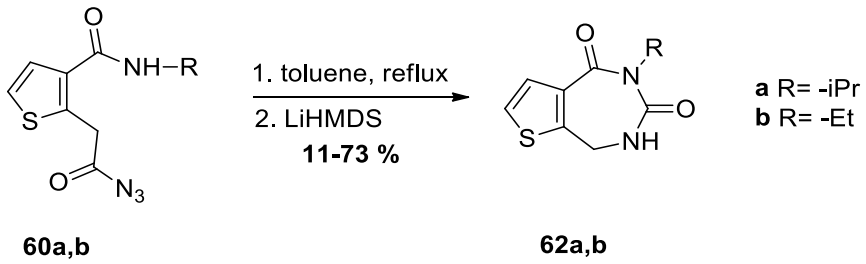


Figure 7 ^{1}H NMR spectrum of compound **61d**

^{1}H NMR spectrum of compound **61d** demonstrated that neighboring –CH_2 and –NH protons coupled each other with a coupling constant of 5.7 Hz (Figure 7).



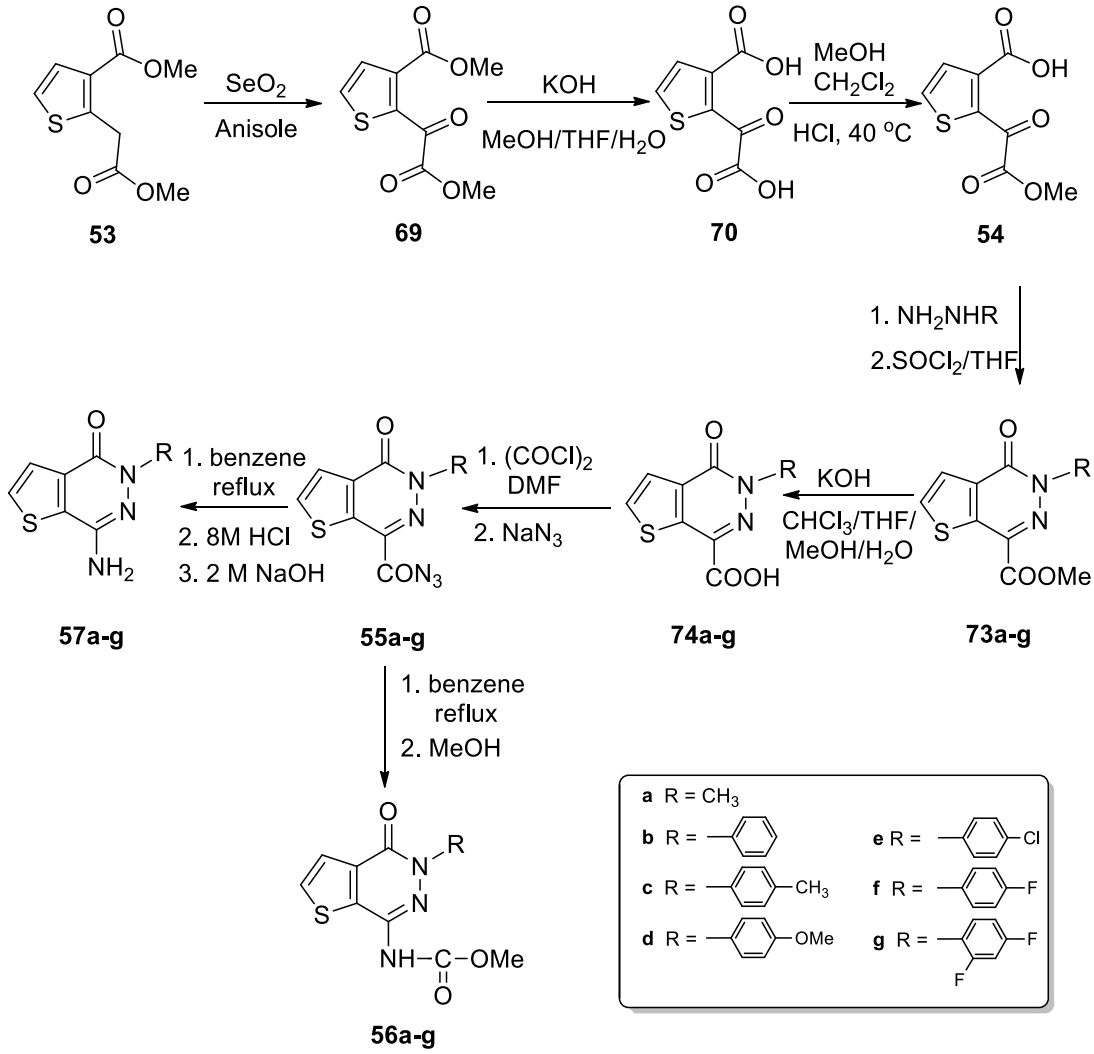
60a,b **62a,b**

Scheme 37 Ring closure reaction for thiophene derivatives

The cyclization method used for the synthesis furan derivatives **61a-c** also worked for thiophene derivatives **62a,b** (Scheme 37).

CHAPTER 3

CONCLUSION

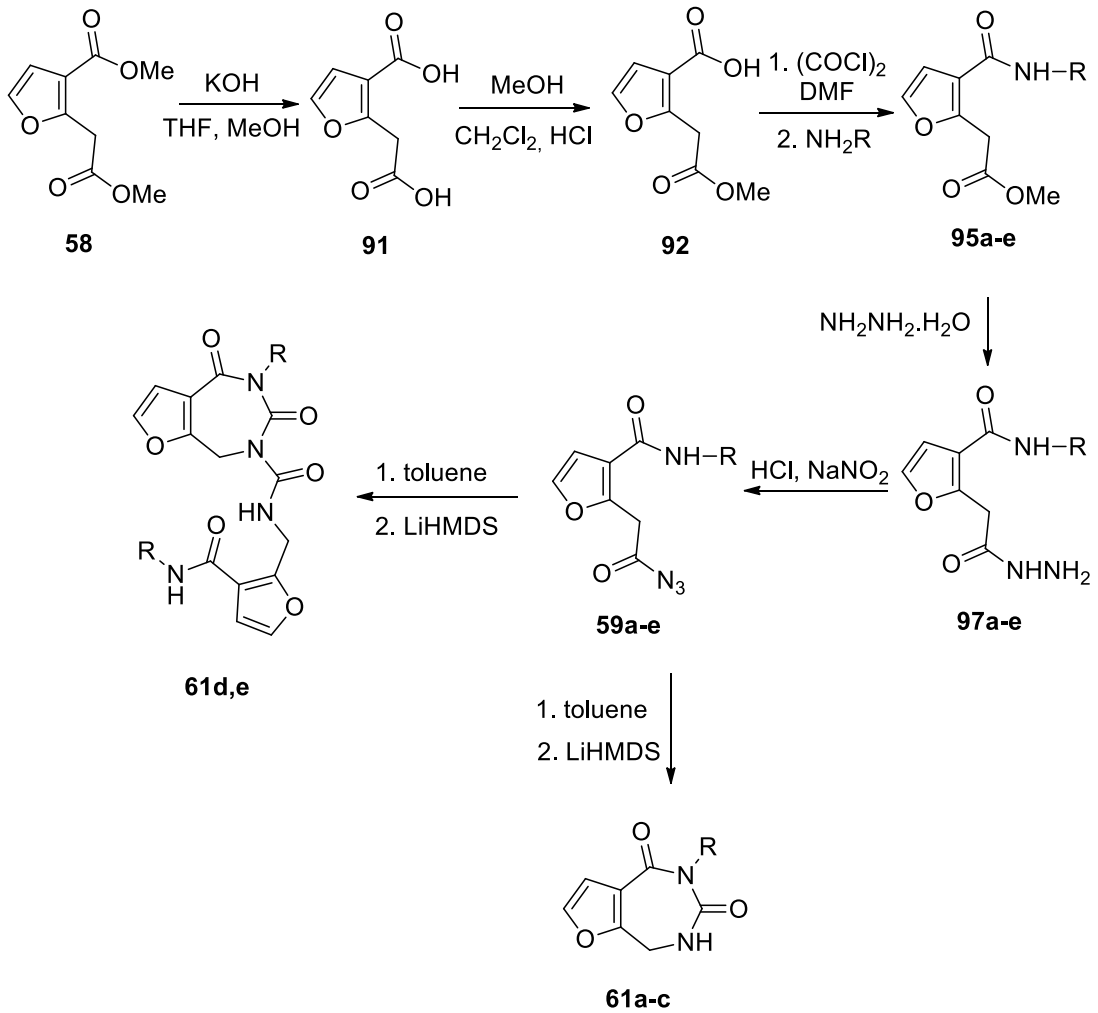


Scheme 38 Synthetic steps for the synthesis of thienopyridazinone derivatives

Knowing that heterocycles are important in terms of pharmacy and biology, we aimed to develop new and facile methodology for the synthesis of heterocyclic compounds skeleton which are not present in the literature. In our study, we synthesized thienopyridazinone and

furo- and thienodiazepinedione derivatives and these compounds have potential for biological activities.

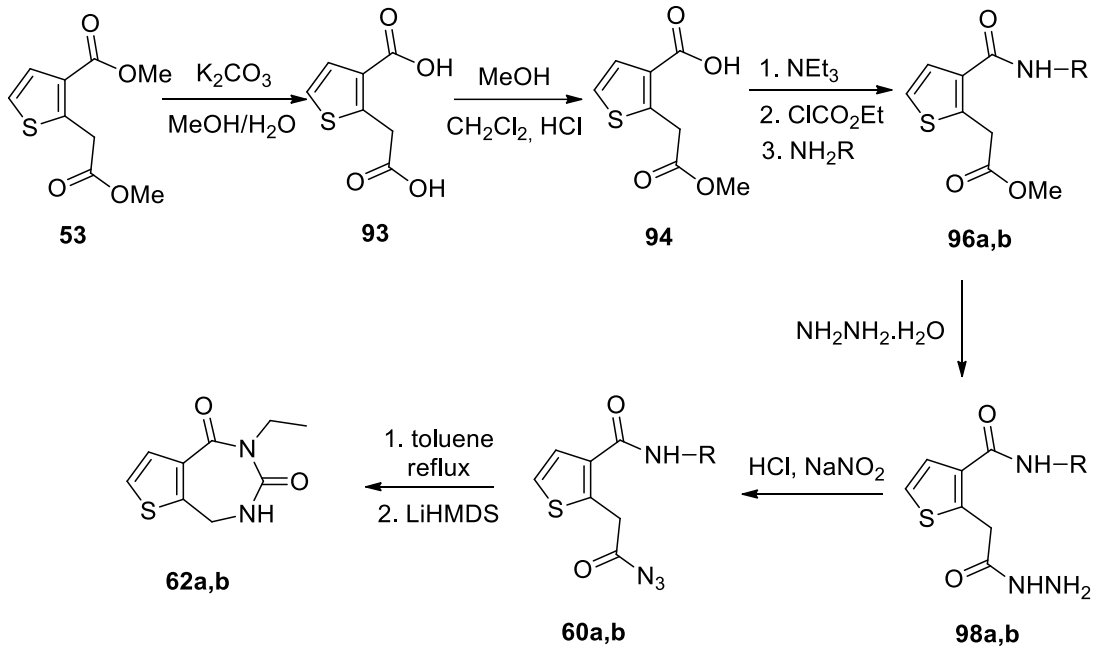
In the first part of the study, we synthesized thienopyridazinone **56a-g** and **57a-g** (Scheme 38). Firstly, methylene group in **53** was oxidized to ketone **69** with SeO_2. Then, esterification was carried out regioselectively to get compound **54**. Cyclization was achieved with seven different hydrazine derivatives. After hydrolysis of ester functionalities in **73a-g**, acyl azides **55a-g** were syntheized as the key compounds. Reaction of acyl azides **55a-g** with methanol at elevated temperature gave urethanes **56a-g**, whereas treatment with 8M HCl furnished the corresponding amino pyridazinones **57a-g**. This part of the work was published in 2013.[44]



Scheme 39 Synthetic steps for the synthesis of furodiazepinedione derivatives

In the second part of the study, the synthesis of furodiazepinedione **611a-c** (Scheme 39) and thienodiazepinedione **62a,b** (Scheme 40) was achieved. Firstly, the starting compound **58** and **53** were hydrolyzed. While furan diester **58** was hydrolyzed with KOH, K_2CO_3 was used

for thiophene diester **53**. Then, one of the carboxylic acid functional group was converted into ester to give **92** and **94**. Then, different procedures were applied to the synthesis of amide derivaties **95a-c** and **96a,b**. Treatment of hydrazinemonohydride gave hydrazide derivatives **97a-c** and **98a,b** which were later used for the synthesis of acyl azides **59a-e** and **60a,b**. Then, intramolecular cyclization was achieved by Curtius rearrangement to give target compounds **61a-c** and **62a,b**. Also, intermolecular cyclization followed by intermolecular addition brought about unexpected products **61d,e**.



Scheme 40 Synthetic steps for the synthesis of thienodiazepinedione derivatives

CHAPTER 4

EXPERIMENTAL

4.1 General

Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in DMSO-$d_6$and $CDCl_3$ with TMS as internal reference. Chemical shifts (δ) were expressed in units parts per million (ppm). Spin multiplicities were specified as singlet (s), doublet (d), doublet of doublets (dd), 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}).

Mass spectra were recorded by Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) LC/MS on Agilent 1200/6530.

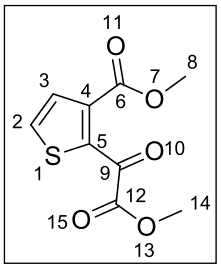
Column chromatographic separations were performed by using Fluka Silica Gel 60 plates with a particle size of 0.063–0.200 mm. Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Fluka.

Compounds were named by using ChemDraw Ultra 11.0.

Solvents were purified as reported in the literature.[50]

4.2 Methyl 2-(2-methoxy-2-oxoacetyl)thiophene-3-carboxylate (69)

SeO_2 (2.6 g, 23.30 mmol) was added to a stirred solution of diester **53** (2.0 g, 9.3 mmol) in anisole (50 mL) and heated at 125 °C for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the mixture was cooled, filtered and washed with ethyl acetate (100 mL). The solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with hexane/ethyl acetate (2:1) to give oxidized diester **69** as a brown oil (1.25 g, 61%).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, $J_{2,3}$=5.1 Hz, 1H, H-2), 7.43 (d, $J_{3,2}$=5.1 Hz, 1H, H-3), 3.85 (s, 3H, -OCH_3), 3.80 (s, 3H, -OCH_3);

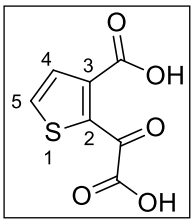
^{13}C NMR (100.6 MHz, $CDCl_3$)δ 179.6, 162.8, 162.1, 142.0, 136.7, 132.9, 129.9, 53.1, 52.5;

IR (ATR, cm^{-1})3110, 2954, 1758, 1717, 1668, 1262, 1170, 1151

Anal. Calcd for $C_9H_8O_5S$: C, 47.36; H, 3.53; S, 14.05 **Found:** C, 46.99; H, 3.54; S, 14.27.

4.3 2-(Carboxycarbonyl)-3-thienoic acid (70)

A solution of KOH (28.3 mL, 56.6 mmol, 2M) in methanol was added to a stirred solution of oxidized diester **69** (4.0 g, 17.5 mmol) in THF (60 mL), MeOH (30 mL) and H_2O (4 mL). The mixture was stirred at 50 °C for 4 h and monitored on TLC. After the completion of the reaction, the mixture was cooled on an ice bath and a solid precipitated. The precipitate was filtered, washed with ethyl acetate and then dissolved in water (30 mL). The solution was acidified with aq. HCl (1M) to pH = 2 and then extracted with ethyl acetate (3 × 400 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated to give diacid **70** as a white solid (3.1 g, 90%), mp 153–155 °C.



^{1}H NMR (400 MHz, DMSO-d_6) δ 13.50 (bs, 2H, -COOH), 8.07 (d, $J_{5,4}$=5.0 Hz, 1H, H-5), 7.47 (d, $J_{4,5}$=5.0 Hz, 1H, H-4);

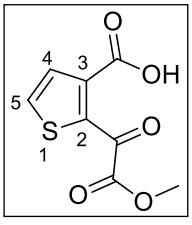
^{13}C NMR (100.6 MHz, DMSO-d_6) δ 181.9, 163.8, 162.8, 140.8, 138.6, 134.2, 129.5;

IR (ATR, cm^{-1}) 3118, 1719, 1685, 1663, 1526, 1402, 1259, 12043;

Anal. Calcd for $C_7H_4O_5S$: C, 42.00; H, 2.01; S, 16.02 **Found:** C, 42.04; H, 2.13; S, 16.02.

4.4 2-[Methoxy(oxo)acetyl]-3-thienoic acid (54)

Conc. HCl (20 drops) was added to a stirred solution of diacid **70** (3.1 g, 15.5 mmol) in MeOH (20 mL) and CH_2Cl_2 (40 mL) and the mixture was stirred at 40 °C for 15 h. The solvents were evaporated and the residue was purified and separated by column chromatography (silica gel) eluting with hexane/ethyl acetate (2:1) and then only with ethyl acetate to give monoester **54** as a white solid (2.2 g, 66%), mp 98–100 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 8.5 (bs, 1H, -COOH), 7.71(d, 1H, $J_{5,4}$=5.1 Hz, H-5), 7.64 (d, $J_{4,5}$=5.1 Hz, 1H, H-4), 3.89 (s, 3H, OCH_3);

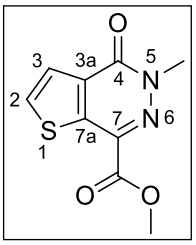
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.6, 166.6, 162.0, 142.5, 136.1, 133.7, 131.2, 53.3;

IR (ATR, cm^{-1})3117, 2960, 1723, 1690, 1664, 1518, 1403, 1312, 1290, 1274, 1172;

Anal. Calcd for $C_8H_6O_5S$: C, 44.86; H, 2.82; S, 14.97 **Found:** C, 44.44; H, 2.76; S, 14.93.

4.5 Methyl 5-methyl-4-oxo-4,5-dihydrothieno[2,3-d]pyridazine-7-carboxylate (73a)

A solution of methyl hydrazine (0.37 mL, 7.07 mmol) in dry THF (5 mL) was added to a stirred solution of the monoester **54** (1.4 g, 6.5 mmol) in dry THF (75 mL) and the mixture was stirred at 50 °C for 2 h. Thionyl chloride (1.03 mL, 14.14 mmol) was added to the reaction mixture and stirred at 50 °C for 16 h. The solvent was evaporated and the residue was purified by column chromatography (silica gel) eluting with ethyl acetate/chloroform/hexane (3:3:2) to give pyridazine **73a** as a white solid (1.43 g, 91%), mp 200–202 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, $J_{2,3}$=5.4 Hz, 1H, H-2), 7.68 (1H, d, $J_{3,2}$=5.4 Hz, H-3), 4.00 (s, 3H, -OCH_3), 3.92 (s, 3H, -NCH_3);

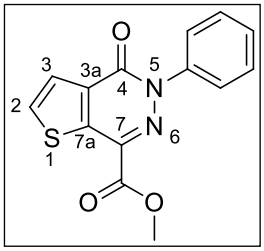
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.2, 157.6, 138.5, 135.3, 133.9, 131.5, 124.3, 53.3, 40.2;

IR (ATR, cm^{-1}) 3085, 3070, 2964, 1710, 1683, 1451, 1432, 1354, 1256, 1211, 1056 ;

Anal. Calcd for $C_9H_8N_2O_3S$: C, 48.21; H, 3.60; N, 12.49; S, 14.30 **Found:** C, 48.42; H, 3.59; N, 12.49; S, 14.68.

4.6 Methyl 4-oxo-5-phenyl-4,5-dihydrothieno[2,3-d]pyridazine-7-carboxylate (73b)

A solution of phenyl hydrazine (0.99 mL, 10.1 mmol) in dry THF (5 mL) was added to a stirred solution of the monoester **70** (2.0 g, 6.3 mmol) in dry THF (40 mL) and dry benzene (40 mL) and the mixture was stirred at 80 °C for 4 h. Thionyl chloride (1.5 mL, 20.2 mmol) was added to the reaction mixture and stirred at 80 °C for 16 h. The solvents were evaporated and the residue was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:1) and then ethyl acetate/dichloromethane (1:1) to give pyridazine **73b** as a white solid (2.1 g, 81%), mp 246–248 °C.



^{1}H NMR (400 MHz, $CDCl_3$)δ 7.74 (s, 2H, H-2 and H-3), 7.58–7.55 (m, 2H, arom.), 7.46–7.42 (m, 2H, arom.), 7.36 (tt, J=7.4, 1.2, Hz, 1H, arom.), 3.98 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.4, 157.0, 141.1, 138.1, 136.2, 134.2, 132.2, 129.0, 128.6, 126.0, 125.0, 53,4;

IR (ATR, cm^{-1}) 3102, 3083, 1709, 1681, 1500, 1453, 1356, 1192, 1155, 1045;

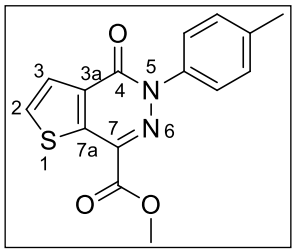
Anal. Calcd for $C_{14}H_{10}N_2O_3S$: C, 58.73; H, 3.52; N, 9.78; S, 11.20 **Found:** C, 58.90; H, 3.67; N, 9.82; S, 11.57.

4.7 General procedure for the synthesis of thienopyridazine derivatives (73c-g)

The monoester **70** (1.0 g, 4.67 mmol) and phenyl hydrazinium chloride derivatives (5.1 mmol) were dissolved in dry MeOH (50 mL) and the mixture was stirred at 50 °C for 2 h. The solvent was evaporated and the residue was dissolved in dry benzene (50 mL). Thionyl chloride (1.0 mL, 14.0 mmol) was added to the reaction mixture and stirred at 50 ºC for 16 h.

The solvent was evaporated and the residue was purified by column chromatography eluting with ethyl acetate/dichloromethane (1:1) to give thienopyridazine derivatives **73c-g** as a white solid.

4.7.1 Methyl 5-(4-methylphenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyridazine-7-carboxylate (73c): (1.33 g, 95%), mp 251–253 °C.



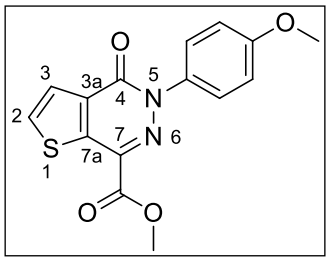
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, $J_{2,3}$=5.5 Hz, 1H, H-2), 7.72 (d, $J_{3,2}$=5.5 Hz, 1H, H-3), 7.45–7.42 (m, A-part of AA'BB' system, 2H, arom.), 7.25–7.22 (m, B-part of AA'BB'system, 2H, arom.), 3.97 (s, 3H, -OCH_3), 2.35 (s, 3H, -CH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.1, 157.7, 139.3, 139.2, 138.7, 136.8, 134.7, 132.7, 130.2, 126.4, 125.6, 53.9, 21.8;

IR (ATR, cm^{-1}) 3102, 3083, 2959, 1746, 1710, 1679, 1487, 1453, 1442, 1405, 1356, 1270, 1145, 1111, 1086, 1046;

Anal. Calcd for $C_{15}H_{12}N_2O_3S$: C, 59.99; H, 4.03; N, 9.33; S, 10.68 **Found:** C, 59.78; H, 4.11; N, 9.43; S, 10.82.

4.7.2 Methyl 5-(4-methoxyphenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyridazine-7-carboxylate (73d): (1.26 g, 85%), mp 189–191 °C.



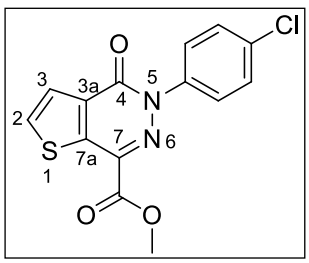
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, $J_{2,3}$=5.5 Hz, 1H, H-2), 7.72 (d, $J_{3,2}$=5.5 Hz, 1H, H-3), 7.50–7.46 (m, A-part of AA'BB'system, 2H, arom.), 6.97–6.91 (m, B-part of AA'BB' system, 2H, arom.), 3.97 (s, 3H, -OCH_3), 3.79 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.5, 159.6, 157.1, 138.1, 136.2, 134.1, 134.0, 132.0, 127.2, 125.0, 114.2, 55.6, 53.3;

IR (ATR, cm^{-1}) 3075, 2954, 2839, 1720, 1671, 1511, 1454, 1437, 1358, 1234, 1175, 1147, 1047;

Anal. Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.82; N, 8.86; S, 10.14 **Found:** C, 56.65; H, 3.81; N, 8.81; S, 9.82.

4.7.3 Methyl 5-(4-chlorophenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyridazine-7-carboxylate (73e): (1.47 g, 98%), mp 195–197 °C.



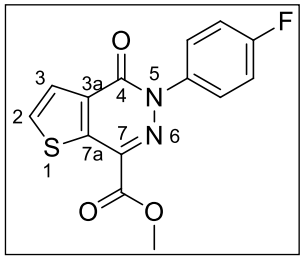
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.73 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.59–7.52 (m, A-part of AA'BB'system, 2H, arom.), 7.44–7.38 (m, B-part of AA'BB' system, 2H, arom.), 3.98 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.2, 156.8, 139.5, 138.1, 136.1, 134.5, 134.3, 132.4, 129.1, 127.3, 125.0, 53.4;

IR (ATR, cm^{-1}) 3103, 3087, 2919, 2849, 1745, 1717, 1686, 1486, 1452, 1405, 1358, 1270, 1143, 1135, 1087, 1011;

Anal. Calcd for $C_{14}H_9ClN_2O_3S$: C, 52.42; H, 2.83; N, 8.73; S, 10.00 **Found:** C, 52.39; H, 3.15; N, 8.44; S, 10.35.

4.7.4 Methyl 5-(4-fluorophenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyridazine-7-carboxylate (73f): (1.26 g, 89%), mp 201–203 °C.



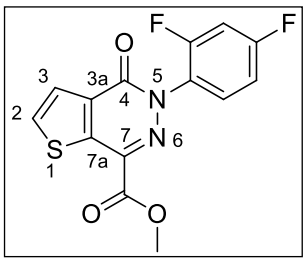
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, $J_{2,3}$=5.3 1H, Hz, H-2), 7.73 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.57 (m, A-part of AA'BB'system, 2H, arom.), 7.55 (m, B-part of AA'BB'system, 2H, arom.), 3.98 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.3, 161.3 (d, J=248.7 Hz), 157.0, 138.1, 137.1 (d, J=3.4 Hz), 136.2, 134.43, 132.3, 127.9 (d, J=8.7 Hz), 125.0, 115.9 (d, J=23.0 Hz), 53.41;

IR (ATR, cm^{-1}) 3105, 3084, 2964, 1746, 1716, 1682, 1453, 1435, 1358, 1235, 1144, 1042;

Anal. Calcd for $C_{14}H_9FN_2O_3S$: C, 55.26; H, 2.98; N, 9.21; S, 10.54 **Found:** C, 55.32; H, 3.04; N, 9.10; S, 11.02.

4.7.5 Methyl 5-(2,4-difluorophenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyridazine-7-carboxylate (73g): (1.46 g, 97%), mp 224–226 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.73 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.48–7.38 (m, 1H, arom.), 7.00–6.92 (m, 2H, arom.), 3.98 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 163.1, 163.0 (dd, J=251.7 and 11.1 Hz), 157.7 (dd, J=257.0 and 13.0 Hz), 156.5, 138.3, 135.7, 134.7, 133.0, 129.9 (dd, J=10.3 and 1.4, Hz), 125.3 (dd, J=13.0 and 4.2 Hz), 125.0, 112.0 (dd, J=22.8 and 3.8, Hz), 105.2 (dd, J=26.5 and 23.5, Hz), 53.5;

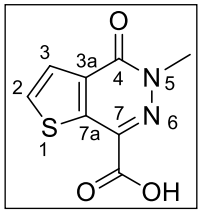
IR (ATR, cm^{-1}) 3104, 3085, 2963, 1746, 1717, 1687, 1485, 1452, 1435, 1359, 1271, 1143, 1110, 1087;

Anal. Calcd for $C_{14}H_8F_2N_2O_3S$: C, 52.17; H, 2.50; N, 8.69; S, 9.95 **Found:** C, 52.17; H, 2.50; N, 8.66; S, 10.35.

4.8 General procedure for the hydrolysis of pyridazine derivatives (73a-g)

A solution of KOH (4.8–3.1 mL, 2 mol eq., 2M) in methanol was added to a stirred solution of esters **73a-g** (1.0 g, 4.8–3.1 mmol) in THF (60 mL), chloroform (80 mL) and H_2O (0.5 mL). The mixture was stirred at 50 °C for 90 min and monitored on TLC. After the completion of the reaction, the mixture was cooled, hexane (50 mL) added and a solid precipitated. The precipitate was filtered, washed with ethyl acetate and then dissolved in water (40 mL). The solution was acidified with aq. HCl (1M) to pH = 2 and a white solid precipitated. The precipitate was filtered on filter paper and allowed to dry at ambient temperature to give acids **74a-g** as white solids.

4.8.1 5-Methyl-4-oxo-4,5-dihydrothieno[2,3-d]pyridazine-7-carboxylic acid (74a): (0. 53g, 57%), mp 276–278 °C.



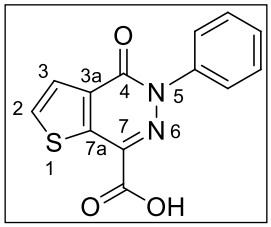
^{1}H NMR (400 MHz, DMSO-d_6) δ 13.90 (bs, 1H, -COOH), 8.15 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.66 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 3.82 (s, 3H, -NCH_3);

^{13}C NMR (100.6 MHz, DMSO-d_6) δ 163.9, 156.8, 138.1, 135.5, 134.6, 131.7, 123.5, 39.6;

IR (ATR, cm^{-1})3073, 2957, 1705, 1619, 1456, 1396, 1189, 1033;

Anal. Calcd for $C_8H_6N_2O_3S$: C, 45.71; H, 2.88; N, 13.33; S, 15.25 **Found:** C, 45.39; H, 2.55; N, 12.97; S, 14.89.

4.8.2 4-Oxo-5-phenyl-4,5-dihydrothieno[2,3-d]pyridazine-7-carboxylic acid (74b): (0.69 g, 73%), mp 245–247 °C.



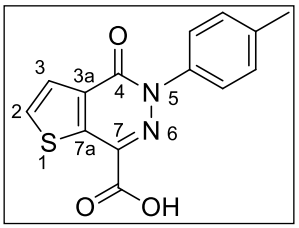
^{1}H NMR (400 MHz, DMSO-d_6) δ 14.20 (bs, 1H, -COOH), 8.22 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.73 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.63–7.47 (m, 5H, arom.);

^{13}C NMR (100.6 MHz, DMSO-d_6) δ 164.6, 157.0, 141.9, 138.5, 136.6, 136.1, 133.1, 129.3, 129.0, 127.1, 124.7;

IR (ATR, cm^{-1}) 3109, 3076, 2959, 2834, 1714, 1536, 1456, 1401, 1393, 1153, 1126, 1036;

Anal. Calcd for $C_{13}H_8N_2O_3S$: C, 57.35; H, 2.96; N, 10.29; S, 11.78 **Found:** C, 57.07; H, 3.09; N, 10.63; S, 12.11.

4.8.3 5-(4-Methylphenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyri- dazine-7-carboxylic acid (74c): (0.83 g, 87%), mp 233–235 °C.



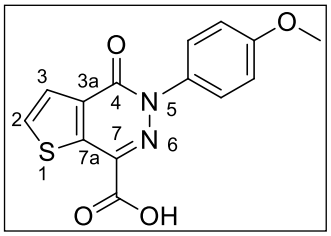
^{1}H NMR (400 MHz, DMSO-d_6) δ 14.10 (bs, 1H, -COOH), 8.20 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.72 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.48 (br d, J=8.3 Hz, 2H, arom.), 7.35 (bd, J=8.3 Hz, 2H, arom.), 2.40 (s, 3H, -CH_3);

^{13}C NMR (100.6 MHz, DMSO-d_6) δ 163.9, 156.4, 138.8, 137.9, 137.8, 135.8, 135.5, 132.4, 129.1, 126.2, 124.1, 20.7;

IR (ATR, cm^{-1}) 3102, 2918, 1746, 1716, 1687, 1623, 1487, 1453, 1434, 1359, 1270, 1146, 1039;

Anal. Calcd for $C_{14}H_{10}N_2O_3S$: C, 58.73; H, 3.52; N, 9.78; S, 11.20 **Found:** C, 58.41; H, 3.59; N, 9.53; S, 11.58.

4.8.4 5-(4-Methoxyphenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyri-dazine-7-carboxylic acid (74d): (0.83 g, 87%), mp 230–232 °C.



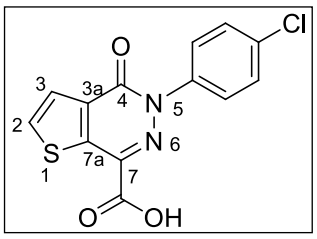
^{1}H NMR (400 MHz, DMSO-d_6) δ 14.05 (bs, 1H, -COOH), 8.20 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.71 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.55–7.49 (m, A-part of AA'BB' system, 2H, arom.), 7.11–7.06 (m, B-part of AA'BB' system, 2H, arom.), 3.83 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, DMSO-d_6) δ 164.0, 158.9, 156.5, 137.8, 135.8, 135.4, 134.1, 132.2, 127.7, 124.1, 113.8, 55.5;

IR (ATR, cm^{-1}) 3111, 3075, 2961, 2834, 1714, 1624, 1609, 1508, 1456, 1330, 1252, 1218, 1155, 1127, 1031;

Anal. Calcd for $C_{14}H_{10}N_2O_4S$: C, 55.62; H, 3.33; N, 9.27; S, 10.61 **Found:** C, 55.28; H, 3.38; N, 9.30; S, 10.61.

4.8.5 5-(4-Chlorophenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyri-dazine-7-carboxylic acid (74e): (0.67 g, 70%), mp 244–246 °C.



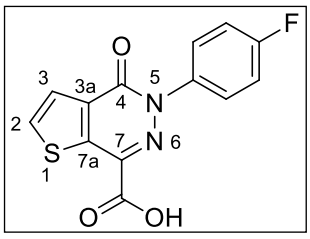
^{1}H NMR (400 MHz, DMSO-d_6) δ 14.10 (bs, 1H, -COOH), 8.22 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.73 (d, $J_{3,2}$=5.3 Hz,1H, H-3), 7.70–7.65 (m, A-part of AA'BB' system, 2H, arom.), 7.65–7.60 (m, B-part of AA'BB' system, 2H, arom.);

^{13}C NMR (100.6 MHz, DMSO-d_6) δ 163.9, 156.3, 140.0, 137.9, 136.1, 135.5, 132.8, 132.7, 128.7, 128.2, 124.1;

IR (ATR, cm^{-1}) 3074, 2956, 1714, 1626, 1492, 1394, 1309, 1217, 1155;

Anal. Calcd for $C_{13}H_7ClN_2O_3S$: C, 50.91; H, 2.30; N, 9.13; S, 10.45 **Found:** C, 50.71; H, 2.29; N, 8.85; S, 11.18.

4.8.6 5-(4-fluorophenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyri-dazine-7-carboxylic acid (74f): (0.58 g, 61%), mp 255–257 °C.



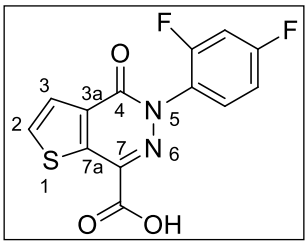
^{1}H NMR (400 MHz, DMSO-d_6) δ 14.10 (bs, 1H, -COOH), 8.22 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.73 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.70–7.64 (m, A-part of AA'BB' system 2H, arom.), 7.43–7.36 (m, B-part of AA'BB' system, 2H, arom.);

^{13}C NMR (100.6 MHz, DMSO-d_6) δ 163.9, 161.4 (d, J=245.4 Hz), 156.4, 137.9, 137.5 (d, J=3.1 Hz), 136.0, 135.5, 132.5, 128.7 (d, J=8.9 Hz), 124,1, 115.5 (d, J=23.1 Hz);

IR (ATR, cm^{-1}) 3112, 3074, 2960, 1716, 1628, 1604, 1510, 1240, 1218, 1157;

Anal. Calcd for $C_{13}H_7FN_2O_3S$: C, 53.79; H, 2.43; N, 9.65; S, 11.05 **Found:** C, 53.27; H, 2.34; N, 9.61; S, 11.38.

4.8.7 5-(2,4-Difluorophenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyridazine-7-carboxylic acid (74g): (0.65 g, 68%), mp 240–242 °C.



^{1}H NMR (400 MHz, DMSO-d_6) δ 14.15 (bs, 1H, -COOH), 8.27 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.76 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.79–7.73 (m, 1H, arom.), 7.58 (ddd, J=10.4, 9.2, and 2.7 Hz, 1H, arom.), 7.37–7.30 (m, 1H, arom.);

^{13}C NMR (100.6 MHz, DMSO-d_6) δ 163.6, 162.3 (dd, J=248.9 and 11.7, Hz), 157.0 (dd, J=252.9 and 13.3, Hz), 156.0, 138.1, 136.6, 134.9, 133.5, 131.0 (d, J=10.3 Hz), 125.5 (dd, J=13.0 and 3.9, Hz), 123.9, 112.2 (dd, J=22.8 and 3.5, Hz), 104.9 (dd, J=27.1 and 24.1 Hz);

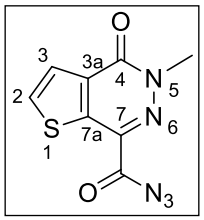
IR (ATR, cm^{-1}) 3079, 2930, 1725, 1639, 1534, 1404, 1278, 1163, 1149, 1134;

Anal. Calcd for $C_{13}H_6F_2N_2O_3S$: C, 50.65; H, 1.96; N, 9.09; S, 10.49 **Found:** C, 50.42; H, 2.03; N, 9.37; S, 10.67.

4.9 General procedure for the synthesis of acyl azide derivatives (55a-g)

Oxalyl chloride (0.70 mL, 8.2 mmol) and then DMF (7 drops) were added to a stirred suspension of the acids **74a-g** (1.0 g, 3.25–4.76 mmol) in dichloromethane (120 mL) and the mixture was stirred at rt for 2 h. The solvent and excess oxalyl chloride were evaporated. The residue was dissolved in acetone (50 mL) and cooled to 2 °C. To this solution, a solution of NaN_3 (0.25 g, 3.85 mmol) in H_2O (3 mL) was added. Precipitation of inorganic salt was immediately observed. The resulting mixture was stirred for 1 h. and then, H_2O (80 mL) was added. The mixture was extracted with ethyl acetate (2 x 150 mL), the combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/dichloromethane/hexane (2:2:1) to give acyl azides **55a-g** as white solids.

4.9.1 5-Methyl-4-oxo-4,5-dihydrothieno[2,3-d]pyridazine-7-carbonyl azide (55a): (0.69 g, 62%), mp 137–139 °C.

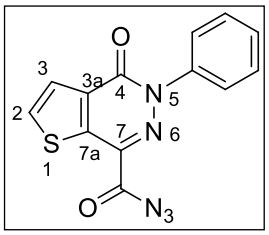


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.68 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 3.91 (s, 3H, -NCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.3, 157.5, 137.6, 135.2, 134.3, 131.9, 124.2, 40.3;

IR (ATR, cm^{-1}) 3117, 3099, 3073, 2155, 1672, 1659, 1349, 1186.

4.9.2 4-Oxo-5-phenyl-4,5-dihydrothieno[2,3-d]pyridazine-7-carbonyl azide (55b): (0.83 g, 75%), mp 152–154 ºC.

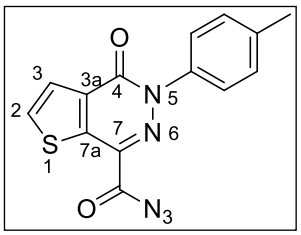


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.75 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.58–7.54 (m, 2H, arom.), 7.49–7.43 (m, 2H, arom.), 7.39 (tt, J= 7.4 and 1.2 Hz, 1H, arom.);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.6, 156.9, 140.9, 137.2, 136.2, 134.6, 132.6, 129.1, 128.8, 125.9, 125.0;

IR (ATR, cm^{-1}) 3098, 3082, 2155, 1694, 1668, 1347, 1165.

4.9.3 5-(4-Methylphenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyridazine-7-carbonyl azide (55c): (0.71 g, 65%), mp 159–161 °C.

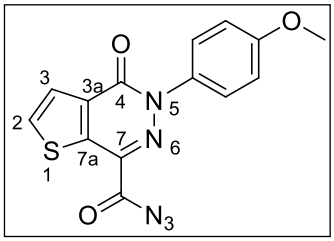


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.74 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.45–7.41 (m, A-part of AA'BB' system, 2H, arom.), 7.26–7.24 (m, B-part of AA'BB' system, 2H, arom.), 2.36 (s, 3H, -CH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.6, 157.0, 138.9, 138.4, 137.2, 136.1, 134.4, 132.4, 129.7, 125.6, 125.0, 21.2;

IR (ATR, cm^{-1}) 3098, 3079, 2960, 2919, 2159, 1690, 1669, 1628, 1509, 1346, 1172.

4.9.4 5-(4-Methoxyphenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyridazine-7-carbonyl azide (55d): (0.66 g, 61%), mp 119–121 °C.

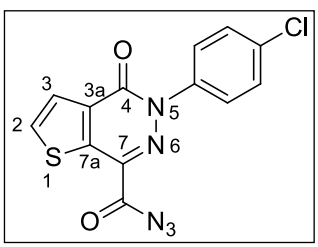


^{1}H NMR (400 MHz, $CDCl_3$)δ 7.76 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.74 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.50–7.45 (m, A-part of AA'BB' system, 2H, arom.), 6.98–6.93 (m, B-part of AA'BB' system, 2H, arom.), 3.80 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.5, 159.7, 157.0, 137.1, 136.0, 134.4, 133.8, 132.3, 127.0, 124.9, 114.3, 55.6;

IR (ATR, cm^{-1}) 3083, 2921, 2835, 2151, 1668, 1507, 1349, 1250, 1166, 1105.

4.9.5 5-(4-Chlorophenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyri-dazine-7-carbonyl azide (55e): (0.93 g, 86%), mp 128–130 °C.

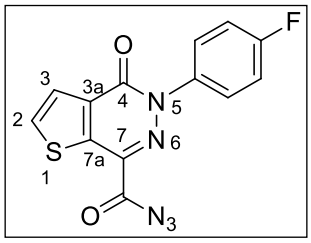


^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.74 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.57–7.52 (m, A-part of AA'BB' system, 2H, arom.), 7.46–7.40 (m, B-part of AA'BB' system, 2H, arom.);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.4, 156.8, 139.3, 137.2, 136,1, 134.9, 134.6, 132.8, 129.2, 127.1, 125.0;

IR (ATR, cm^{-1}) 3118, 3101, 2158, 1692, 1671, 1488, 1350, 1260.

4.9.6 5-(4-Fluorophenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyri-dazine-7-carbonyl azide (55f): (0.85 g, 79%), mp 137–239 °C.

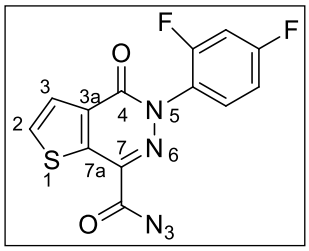


^{1}H NMR(400 MHz, $CDCl_3$) δ 7.78 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.74 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.59–7.53 (m, A-part of AA'BB' system, 2H, arom.), 7.18–7.11 (m, B-part of AA'BB' system, 2H, arom.);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.4, 162.4 (d, J=248.9 Hz), 156.8, 137.2, 136.9 (d, J=3.0 Hz), 136.1, 134.8, 132.7, 127.8 (d, J=8.9 Hz), 125.0, 116.0 (d, J=23.1 Hz);

IR (ATR, cm^{-1}) 3125, 3109, 2155, 1682, 1671, 1506, 1353, 1247, 1160, 1151.

4.9.7 5-(2,4-Difluorophenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyridazine-7-carbonyl azide (55g): (0.83 g, 77%), mp 146–148 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, $J_{2,3}$=5.3 Hz,1H, H-2), 7.74 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.45–7.37 (m, 1H, arom.), 7.02–6.93 (m, 2H, arom.);

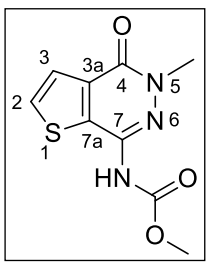
^{13}C NMR (100.6 MHz, $CDCl_3$) δ 169.3, 163.2 (dd, J=252.4 and 11.1 Hz), 157.6 (dd, J=256.1 and 12.6 Hz), 156.4, 137.3, 135.7, 135.1, 133.4, 129.7 (dd, J=10.3 and 1.0 Hz), 125.1 (d, J=4.0 Hz), 124.9, 112.1 (dd, J=22.7 and 3.7 Hz), 105.3 (dd, J=26.4 and 23.4 Hz);

IR (ATR, cm^{-1}) 3107, 3083, 2960, 2163, 1698, 1680, 1613, 1510, 1485, 1173.

4.10 General procedure for the synthesis of urethane derivatives (56a-g)

The acyl azide derivatives **55a-g** (0.20 g, 0.60–0.85 mmol) were dissolved in dry benzene (40 mL) and heated at reflux temperature for 90 min. Dry MeOH (2 mL) was added and stirred at for 6 h and 12 h. The solvent and excess MeOH were evaporated. The crude product was purified by column chromatography (silica gel) eluting with hexane/ethyl acetate/dichloromethane (2:1:1) to give urethane derivatives **56a-g** as a white solid.

4.10.1 Methyl 5-methyl-4-oxo-4,5-dihydrothieno[2,3-d]pyridazin-7-ylcarbamate (56a): (87 mg, 43%), mp 171–173 °C.



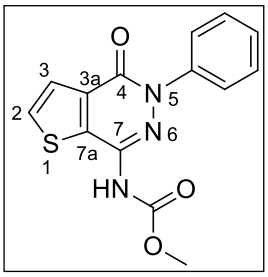
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.60 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.14 (bs, 1H, -NH), 3.76 (s, 3H, -OCH_3), 3.71 (s, 3H, -NCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.2, 154.4, 137.3, 136.3, 135.3, 132.2, 124.9, 53.1, 38.9;

IR (ATR, cm^{-1}) 3236, 3138, 2957, 2922, 2851, 1698, 1640, 1550, 1523, 1462, 1247, 1060;

Anal. Calcd for $C_9H_9N_3O_3S$: C, 45.18; H, 3.79; N, 17.56; S, 13.40 **Found:** C, 45.11; H, 3.91; N, 17.24; S, 13.65.

4.10.2 Methyl 4-oxo-5-phenyl-4,5-dihydrothieno[2,3-d]pyridazin-7-ylcarbamate (56b): (119 mg, 59%), mp 186–188 °C.



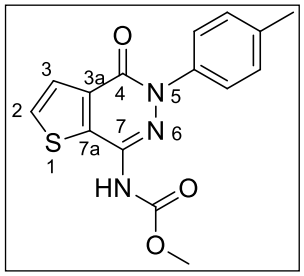
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.67 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.57–7.53 (m, 2H, arom.), 7.42 (bt, J=7.4 Hz, 2H, arom.), 7.32 (tt, J=7.4, 1.2 Hz, 1H, arom.), 6.97 (bs, 1H, -NH), 3.78 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.6, 154.4, 141.1, 138.2, 136.0, 135.9, 132.6, 128.8, 128.0, 125.8, 125.5, 53.2;

IR (ATR, cm^{-1}) 3244, 3107, 2960, 2913, 1724, 1646, 1553, 1488, 1302, 1241, 1046;

Anal. Calcd for $C_{14}H_{11}N_3O_3S$: C, 55.80; H, 3.68; N, 13.95; S, 10.64 **Found:** C, 56.07; H, 3.99; N, 13.88; S, 11.02.

4.10.3 Methyl 5-(4-methylphenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyridazin-7-ylcarbamate (56c): (95 mg, 47%), mp 172–174 °C.



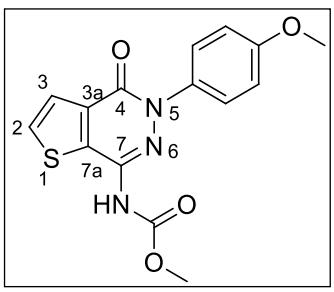
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.65 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.43–7.37 (m, A-part of AA'BB' system, 2H, arom.), 7.20–7.18 (m, B-part of AA'BB' system, 2H, arom.), 7.03 (bs, 1H, -NH), 3.77 (s, 3H, -OCH_3), 2.33 (s, 3H, -CH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.6, 154.5, 138.6, 138.2, 138.0, 135.9, 135.8, 132.4, 129.4, 125.5, 53.2, 21.1;

IR (ATR, cm^{-1}) 3246, 3107, 3087, 3031, 2959, 1725, 1653, 1552, 1481, 1240, 1135, 1044;

Anal. Calcd for $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.16; N, 13.33; S, 10.17 **Found:** C, 56.78; H, 4.27; N, 13.05; S, 10.39.

4.10.4 Methyl 5-(4-methoxyphenyl)-4-oxo-4,5-dihydrothieno-[2,3-d]pyridazin-7-ylcarbamate (56d): (91 mg, 45%), mp 167–169 °C.



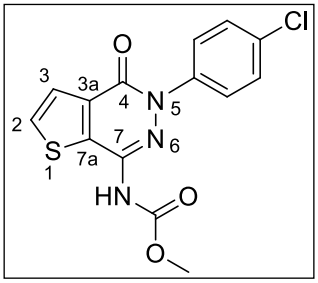
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.66 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.47–7.42 (m, A-part of AA'BB' system, 2H, arom.), 6.99 (bs, 1H, -NH), 6.94–6.89 (m, B-part of AA'BB' system, 2H, arom.), 3.78 (s, 3H, -OCH_3), 3.77 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.8, 154.4, 152.2, 135.9, 133.6, 133.5, 131.8, 130.2, 124.7, 123.2, 111.7, 53.3, 50.9;

IR (ATR, cm^{-1}) 3327, 3105, 3089, 2922, 2850, 1735, 1657, 1560, 1512, 1484, 1456, 1098, 1019;

Anal. Calcd for $C_{15}H_{13}N_3O_4S$: C, 54.37; H, 3.95; N, 12.68; S, 9.68 **Found:** C, 54.25; H, 4.33; N, 12.31; S, 9.59.

4.10.5 Methyl 5-(4-chlorophenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyridazin-7-ylcarbamate (56e): (109 mg, 54%), mp 156–158 °C.



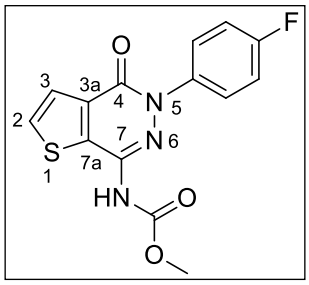
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.67 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.54–7.49 (m, A-part of AA'BB' system, 2H, arom.), 7.37–7.32 (m, B-part of AA'BB' system, 2H, arom.), 7.14 (bs, 1H, -NH), 3.78 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.4, 154.3, 139.5, 138.0, 136.3, 135.9, 133.5, 132.8, 128.8, 126.9, 125.5, 53.3;

IR (ATR, cm^{-1}) 3208, 3103, 3085, 2955, 2922, 1729, 1682, 1556, 1536, 1486, 1262, 1244, 1126;

Anal. Calcd for $C_{14}H_{10}ClN_3O_3S$: C, 50.08; H, 3.00; N, 12.51; S, 9.55 **Found:** C, 50.36; H, 3.18; N, 12.48; S, 10.16.

4.10.6 Methyl 5-(4-fluorophenyl)-4-oxo-4,5-dihydrothieno[2,3-d]pyridazin-7-ylcarbamate (56f): (176 mg, 87%), mp 145–147 °C.



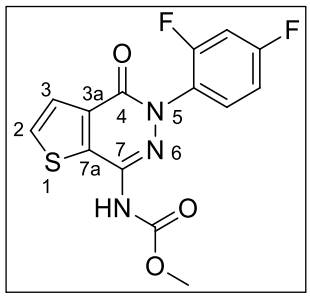
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.66 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.55–7.48 (m, A-part of AA'BB' system, 2H, arom.), 7.16 (bs, 1H, -NH), 7.10–7.03 (m, B-part of AA'BB' system, 2H, arom.), 3.77 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.8 (d, J=248.0 Hz), 156.5, 154.3, 138.0, 137.0 (d, J=3.3 Hz), 136.1, 136.0, 132.7, 127.5 (d, J=8.6 Hz), 125.5, 115.6 (d, J=22.9 Hz), 53.2;

IR (ATR, cm^{-1}) 3280, 3087, 1708, 1660, 1558, 1523, 1495, 1130;

Anal. Calcd for $C_{14}H_{10}FN_3O_3S$: C, 52.66; H, 3.16; N, 13.16; S, 10.04 **Found:** C, 52.35; H, 3.32; N, 12.87; S, 10.50.

4.10.7 Methyl 5-(2,4-difluorophenyl)-4-oxo-4,5-dihydrothieno-[2,3-d]pyridazin-7-ylcarbamate (56g): (129 mg, 64%), mp 199–201 °C.



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, $J_{2,3}$=5.3 Hz, 1H, H-2), 7.69 (d, $J_{3,2}$=5.3 Hz, 1H, H-3), 7.41–7.34 (m, 1H, arom.), 7.00 (bs, 1H, -NH), 6.97–6.88 (m, 2H, arom.), 3.77 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 162.7 (dd, J=251.2 and 11.3 Hz), 157.6 (dd, J=255.7 and 12.6 Hz), 156.3, 154.3, 137.5, 136.5, 136.4, 132.9, 129.8 (dd, J=10.2 and 1.8 Hz), 125.5, 125.2 (dd, J=4.3 and 2.6 Hz), 111.8 (dd, J=22.6 and 3.7 Hz), 105.0 (dd, J=26.3 and 23.5 Hz), 53.7;

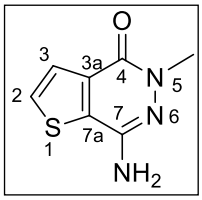
IR (ATR, cm^{-1}) 3197, 3112, 3069, 2990, 2947, 1727, 1651, 1563, 1508, 1246, 1151;

Anal. Calcd for $C_{14}H_9F_2N_3O_3S$: C, 49.85; H, 2.69; N, 12.46; S, 9.51 **Found:** C, 50.16; H, 2.74; N, 12.26; S, 9.57.

4.11 General procedure for the synthesis of aminopyridazinone derivatives (57a-g)

The acyl azide derivatives **55a-g** (0.3 g, 1.0–1.4 mmol) was dissolved in dry benzene (40 mL) and heated at reflux for 90 min. The solution was cooled to 40 °C and HCl (10 mL, 8M) was added. The mixture was stirred at 40 °C for 10 min and then the pH value was adjusted to pH=10 by addition of 10% NaOH solution at 10 °C. The mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. The crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/dichloromethane (1:1) to give amine derivatives **57a-g** as white solids.

4.11.1 7-Amino-5-methylthieno[2,3-d]pyridazin-4(5*H*)-one (57a): (80 mg, 42%), mp 165–167 °C.



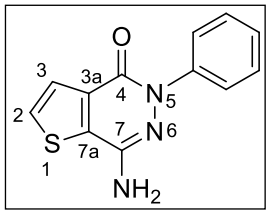
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, $J_{2,3}$=5.2 Hz, 1H, H-2), 7.52 (d, $J_{3,2}$=5.2 Hz, 1H, H-3), 4.13 (bs, 2H, -NH_2), 3.65 (s, 3H, -NCH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.6, 142.2, 137.2, 133.1, 129.6, 126.1, 38.4;

IR (ATR, cm^{-1}) 3325, 3158, 3075, 1610, 1531, 1416, 1330, 1249, 1127, 1041;

Anal. Calcd for $C_7H_7N_3OS$: C, 46.40; H, 3.89; N, 23.19; S, 17.69 **Found:** C, 46.01; H, 3.87; N, 22.98; S, 18.10.

4.11.2 7-Amino-5-phenylthieno[2,3-d]pyridazin-4(5*H*)-one (57b): (94 mg, 46%), mp 187–189 °C.



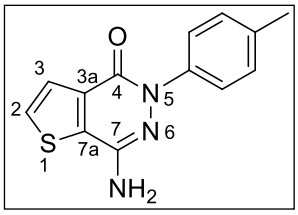
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, $J_{2,3}$=5.1 Hz, 1H, H-2), 7.57 (d, $J_{3,2}$=5.1 Hz, 1H, H-3), 7.58–7.55 (m, 2H, arom.), 7.43–7.37 (m, 2H, arom.), 7.29 (tt, J=7.4 and 1.2 Hz, 1H, arom.), 4.21 (bs, 2H, -NH_2);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.2, 142.6, 141.7, 137.8, 133.4, 129.9, 128.7, 127.6, 126.7, 125.9;

IR (ATR, cm^{-1}) 3336, 3203, 3101, 1632, 1556, 1544, 1403, 1304, 1054;

Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.18 **Found:** C, 59.12; H, 3.85; N, 17.29; S, 13.61.

4.11.3 7-Amino-5-(4-methylphenyl)thieno[2,3-d]pyridazin-4(5*H*)-one (57c): (91 mg, 44%), mp 245–247 °C.



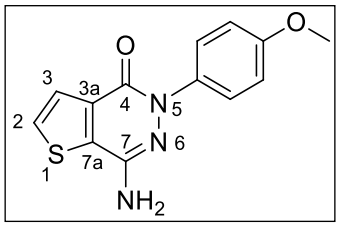
^{1}H NMR (400 MHz, acetone-d_6) δ 7.82 (d, $J_{2,3}$=5.2 Hz, 1H, H-2), 7.54 (d, $J_{3,2}$=5.2 Hz, 1H, H-3), 7.46–7.41 (m, A-part of AA'BB' system, 2H, arom.), 7.13–7.11 (m, B-part of AA'BB' system, 2H, arom.), 5.44 (bs, 2H, -NH_2), 2.24 (s, 3H, -CH_3);

^{13}C NMR (100.6 MHz, DMSO-d_6) δ 155.0, 143.8, 139.5, 136.7, 136.1, 133.6, 132.1, 128.7, 125.8, 125.2, 20.6;

IR (ATR, cm^{-1}) 3351, 3200, 3082, 1629, 1541, 1401, 1324, 1259, 1088;

Anal. Calcd for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33; S, 12.46 **Found:** C, 60.31; H, 4.40; N, 15.98; S, 12.10.

4.11.4 7-Amino-5-(4-methoxyphenyl)thieno[2,3-d]pyridazin-4(5*H*)-one (57d): (100 mg, 48%), mp 208–210 °C.



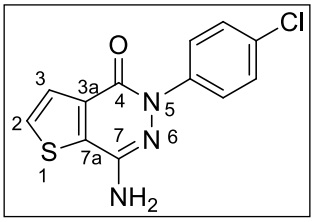
^{1}H NMR (400 MHz, acetone-d_6) δ 7.81 (d, $J_{2,3}$=5.1 Hz, 1H, H-2), 7.54 (d, $J_{3,2}$=5.1 Hz, 1H, H-3), 7.48–7.43 (m, A-part of AA'BB' system, 2H, arom.), 6.89–6.82 (m, B-part of AA'BB' system, 2H, arom.), 5.43 (s, 2H, -NH_2), 3.71 (s, 3H, -OCH_3);

^{13}C NMR (100.6 MHz, DMSO-d_6) δ 157.8, 155.0, 143.7, 136.9, 135.0, 133.5, 132.1, 127.2, 125.2, 113.4, 55.3;

IR (ATR, cm^{-1}) 3326, 3184, 3078, 1630, 1606, 1506, 1325, 1030;

Anal. Calcd for $C_{13}H_{11}N_3O_2S$: C, 57.13; H, 4.06; N, 15.37; S, 11.73 **Found:** C, 56.81; H, 3.99; N, 15.29; S, 12.24.

4.11.5 7-Amino-5-(4-chlorophenyl)thieno[2,3-d]pyridazin-4(5*H*)-one (57e): (119 mg, 57%), mp 230–232 °C.



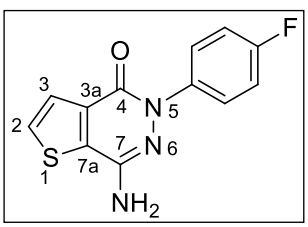
^{1}H NMR (400 MHz, acetone-d_6) δ 7.84 (d, $J_{2,3}$=5.2 Hz, 1H, H-2), 7.68–7.63 (m, A-part of AA'BB' system, 2H, arom.), 7.55 (d, $J_{3,2}$=5.2 Hz, 1H, H-3), 7.38–7.30 (m, B-part of AA'BB' system, 2H, arom.), 5.55 (bs, 2H,-NH_2);

^{13}C NMR (100.6 MHz, DMSO-d_6) δ 155.0, 144.1, 140.7, 136.7, 133.8, 132.3, 130.9, 128.2, 127.5, 125.2;

IR (ATR, cm^{-1}) 3355, 3304, 3202, 3077, 1628, 1539, 1489, 1472, 1322, 1089;

Anal. Calcd for $C_{12}H_8ClN_3OS$: C, 51.90; H, 2.90; N, 15.13; S, 11.55 **Found:** C, 52.27; H, 2.86; N, 15.13; S, 11.68.

4.11.6 7-Amino-5-(4-fluorophenyl)thieno[2,3-d]pyridazin-4(5*H*)-one (57f): (125 mg, 60%), mp 241–243 °C.



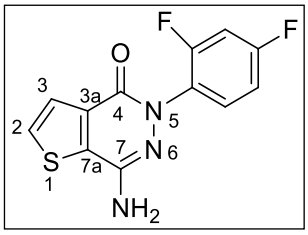
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, $J_{2,3}$=5.2 Hz, 1H, H-2), 7.59 (d, $J_{3,2}$=5.2 Hz, 1H, H-3), 7.57–7.50 (m, A-part of AA'BB'system, 2H, arom.), 7.11–7.04 (m, B-part of AA'BB' system, 2H, arom.), 4.21 (bs, 2H, -NH_2);

^{13}C NMR (100.6 MHz, DMSO-d_6) δ 160.1 (d, J=243.8 Hz), 154.7, 143.7, 137.9 (d, J=2.8 Hz), 136.4, 133.4, 131.9, 127.7 (d, J=8.5 Hz), 124.8, 114.7 (d, J=22.6 Hz);

IR (ATR, cm^{-1}) 3339, 3192, 3095, 3083, 1632, 1541, 1501, 1319, 1216, 1057;

Anal. Calcd for $C_{12}H_8FN_3OS$: C, 55.16; H, 3.09; N, 16.08; S, 12.27 **Found:** C, 55.01; H, 3.03; N, 15.94; S, 12.84.

4.11.7 7-Amino-5-(2,4-difluorophenyl)thieno[2,3-d]pyridazin-4(5*H*)-one (57g): (101 mg, 48%), mp 248–250 °C.



^{1}H NMR (400 MHz, acetone-d_6) δ 7.86 (d, $J_{2,3}$=5.2 Hz, 1H, H-2), 7.54 (d, $J_{3,2}$=5.2 Hz, 1H, H-3), 7.48 (dt, J=8.7 and 6.1 Hz, 1H, arom.), 7.10–6.98 (m, 2H, arom), 5.50 (bs, 2H, -NH_2);

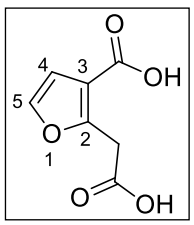
^{13}C NMR (100.6 MHz, DMSO-d_6) δ 161.5 (dd, J=247.3 and 11.6 Hz), 157.0 (dd, J=252.3 and 13.1 Hz), 154.9, 144.3, 136.0, 134.3, 132.5, 130.9 (dd, J=10.3 and 1.7 Hz), 126.4 (dd, J=12.9 and 3.9 Hz), 125.0, 111.7 (dd, J=22.5 and 3.4, Hz), 104.6 (dd, J=26.8 and 24.4, Hz);

IR (ATR, cm^{-1}) 3337, 3187, 3082, 1639, 1611, 1546, 1504, 1336;

Anal. Calcd for $C_{12}H_7F_2N_3OS$: C, 51.61; H, 2.53; N, 15.05; S, 11.48 **Found:** C, 51.51; H, 2.73; N, 14.74; S, 11.21.

4.12 2-(Carboxymethyl)furan-3-carboxylic acid (91)

The diester **58** (10.0 g, 50.6 mmol) was dissolved in THF (100 mL), MeOH (50 mL) and water (5 mL). Then, KOH in MeOH (76 mL) was added and the mixture was stirred at 70 °C for 5 h. The reaction mixture was cooled to rt and the solvent was evaporated. The residue was dissolved in water (50 mL) and the solution was acidified to pH = 2 with HCl. The acid was extracted with EtOAc (400 mL). Later, aqueous layer was re-exracted with EtOAc (2 x 200 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The product was washed with $CHCl_3$ to give white powder (7.7 g, 90%), mp 210-212 °C.

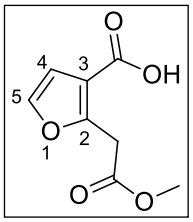


^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.63 (bs, 2H, -OH), 7.63 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 6.66 (d, $J_{4,5}$=1.9 Hz, 1H, H-4), 3.97 (s, 2H, -CH_2);
^{13}C-NMR (100.6 MHz, DMSO-d_6) δ: 170.0, 164.5, 154.8, 142.3, 115.6, 110.9, 33.4.
IR (ATR, cm^{-1}) 3130, 3001, 2930, 2618, 1682, 1461, 1314, 1216, 893, 750;

Anal. Calcd. for $C_7H_6O_5$: C, 49.42; H, 3.55 **Found:** C, 49.43; H, 3.59.

4.13 2-(2-Methoxy-2-oxoethyl)furan-3-carboxylic acid (92)

The diacid **91** (7.0 g, 41.2 mmol) was dissolved in 30 mL MeOH and 75 mL CH_2Cl_2. HCl (10 drops) was added and the mixture was stirred at 40 °C for 13 h. The solvent was evaporated and the residue was purified by column chromatography eluting with hexane/EtOAc (2:1, 1:1, 1:2). It was re-crystallized from ether/hexane (5:1) to give colorless snowflake crystals (5.8 g, 76%), mp 81-83 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.37 (bs, 1H, -OH), 7.37 (d, $J_{5,4}$=1.9 Hz, 1H, H-5), 6.75 (d, $J_{4,5}$=1.9 Hz, 1H, H-4), 4.11 (s, 2H, -CH_2), 3.73 (s, 3H, -OCH_3);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 169.3, 169.0, 155.6, 142.3, 115.3, 111.1, 52.6, 33.7;

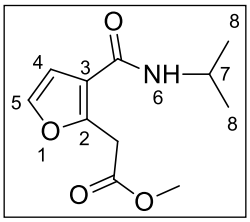
IR (ATR, cm^{-1}) 3127, 2932, 2686, 2615, 1738, 1729, 1679, 1324, 1247, 753;

Anal. Calcd. for $C_8H_8O_5$: C, 52.18; H, 4.38 **Found:** C, 52.41; H, 4.17.

4.14 General procedure for the synthesis of amide derivatives 95a-e

The acid **92** (3.0 g, 16.3 mmol) was dissolved in 40 mL CH_2Cl_2 and oxalyl chloride (2.1 mL, 24.4 mmol) was added at rt. Then, 5 drops of DMF were added and the solution was stirred for 90 min. The solvent and excess oxalyl chloride was evaporated. Later, residue was dissolved in acetone and amine derivatives (48.9 mmol) was added at 0-5 °C and stirred for 1 h. The mixture was extracted with CH_2Cl_2 (150 mL) and 1M HCl. The aqueous layer was re-extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated.

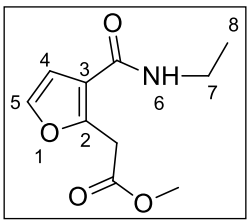
4.14.1 Methyl [3-(propan-2-ylcarbamoyl)furan-2-yl]acetate (95a): The product was re-crystallized from hexane/EtOAc (1:3) to give colorless crystals (salt like) (3.4 g, 94%), mp 84-86 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.31 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 6.50 (d, $J_{4,5}$=2.0 Hz, 1H, H-4), 6.15 (d, J =5.5 Hz, 1H, -NH), 4.20 (dq, J=13.3, 6.6 Hz, 1H, -CH), 4.06 (s, 2H, -CH_2), 3.73 (s, 3H, -OCH_3), 1.21 (d, J=6.5 Hz, 6H, -CH_3);
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 170.1, 162.4, 150.8, 141.6, 118.8, 109.0, 52.5, 41.4, 33.3, 22.8;
IR (ATR, cm^{-1}) 3383, 3112, 2965, 1726, 1644, 1620, 1519, 1210, 1176, 751;

Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22 **Found:** C, 58.02; H, 6.38; N, 6.17.

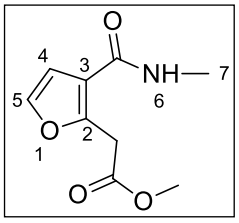
4.14.2 Methyl [3-(ethylcarbamoyl)furan-2-yl]acetate (95b): The product was re-crystallized from hexane/EtOAc (1:3) to give colorless salt like crystals (3.2 g, 94%), mp 73- 75 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 6.51 (d, $J_{4,5}$=2.0 Hz, 1H, H-4), 6.44 (bs, 1H, -NH), 4.08 (s, 2H), 3.71 (s, 3H, -OCH_3), 3.41 – 3.32 (m, 2H, -CH_2), 1.17 (t, J=7.3 Hz, 3H, -CH_3);
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 170.3, 163.2, 151.0, 141.8, 118.6, 109.0, 52.6, 34.4, 33.4, 14.9;
IR (ATR, cm^{-1}) 3385, 3112, 2968, 1716, 1649, 1616, 1530, 1212, 1177, 755;

Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63 **Found:** C, 56.55; H, 6.10; N, 6.51.

4.14.3 Methyl [3-(methylcarbamoyl)furan-2-yl]acetate (95c): The product was re-crystallized from hexane/EtOAc (1:3) to give colorless crystals (salt like) (3.2 g, 98%), mp 110- 112 °C.



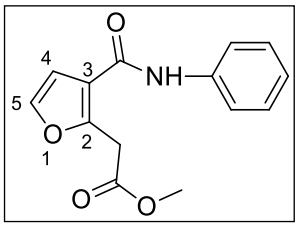
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.31 – 7.28 (m, 1H, H-5), 6.49 (d, $J_{4,5}$=1.9 Hz, 1H, H-4), 6.45 (bs, 1H, -NH), 4.09 (s, 2H, -CH_2), 3.73 (s, 3H, -OCH_3), 2.88 (d, J = 2.6 Hz, 3H, -NCH_3);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 170.4, 164.0, 151.1, 141.8, 118.5, 109.0, 52.6, 33.4, 26.3;

IR (ATR, cm^{-1}) 3385, 3109, 2954, 1720, 1650, 1540, 1210, 1179, 755;

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10 **Found:** C, 54.57; H, 5.43; N, 7.06.

4.14.4 Methyl [3-(phenylcarbamoyl)furan-2-yl]acetate (95d): The product was re-crystallized from hexane/EtOAc (1:3) to give colorless crystals (salt like) (4.0 g, 95%), mp 126- 128 °C.



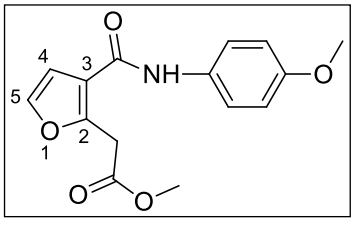
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.51 (bs, 1H, -NH), 7.61 (d, J=8.1 Hz, 2H, arom.), 7.36 – 7.33 (m, 2H, arom.), 7.32 (s, 1H, H-5), 7.12 (t, J=7.4 Hz, 1H, arom.), 6.67 (d, $J_{4,5}$=1.8 Hz, 1H, H-4), 4.09 (s, 2H, -CH_2), 3.79 (s, 3H, -OCH_3);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 170.7, 161.6, 151.1, 141.91, 138.1, 128.9, 124.4, 120.3, 119.4, 109.4, 52.8, 33.5;

IR (ATR, cm^{-1}) 3367, 1719, 1665, 1612, 1593, 1540, 1437, 1334, 1199, 131;

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40 **Found:** C, 65.00; H, 4.62; N, 5.41.

4.14.5 Methyl {3-[(4-methoxyphenyl)carbamoyl]furan-2-yl}acetate (95e): The product was re-crystallized from hexane/EtOAc (1:3) to give colorless crystals (salt like) (4.1 g, 87%), mp 148-150 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.38 (bs, 1H, -NH), 7.51 (d, J=8.9 Hz, 2H, arom.), 7.35 (d, $J_{5,4}$=1.9 Hz, 1H, H-5), 6.90 – 6.84 (m, 2H, arom.), 6.66 (bs, 1H, H-4), 4.09 (s, 2H, -CH_2), 3.80 (s, 3H, -OCH_3), 3.78 (s, 3H, -OCH_3);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 170.7, 161.4, 156.5, 150.7, 142.0, 131.2, 122.1, 119.6, 114.2, 109.5, 55.6, 52.83, 33.5;

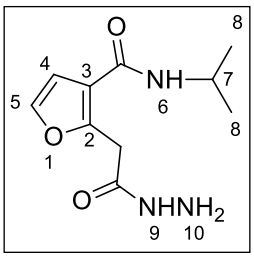
IR (ATR, cm^{-1}) 3380, 3004, 1722, 1656, 1540, 1508, 1345, 1304, 830;

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.28; H, 5.23; N, 4.84 **Found:** C, 62.35; H, 4.88; N,4.84.

4.15 General procedure for the synthesis of hydrazone derivatives 97a-e

The ester **95a-e** (2.7 g) was dissolved in 50 mL MeOH in which 2.5 equivalent hydrazinemonohydrate was added and it was left to react at 40 °C over a night. Then, the MeOH was evaporated. To remove excess hydrazine, it was washed with cold hexane/EtOAc to give white solids.

4.15.1 2-(2-hydrazinyl-2-oxoethyl)-*N*-(propan-2-yl)furan-3-carboxamide (97a): (2.5 g, 92%), mp 135- 137 °C.



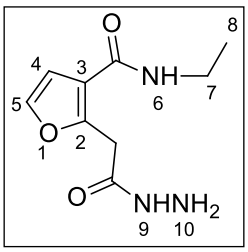
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.81 (bs, 1H, H-9), 7.29 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 6.47 (d, $J_{4,5}$=2.0 Hz, 1H, H-4), 6.28 (d, J=0.6 Hz, 1H, H-6), 4.26 – 4.15 (m, 1H, -CH), 3.84 (bs, 2H, $-NH_2$), 3.82 (s, 2H, $-CH_2$), 1.24 (d, J=6.6 Hz, 6H, $-CH_3$);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 169.3, 163.1, 151.8, 141.6, 118.3, 109.2, 41.7, 34.4, 22.7;

IR (ATR, cm^{-1}) 3254, 3051, 1627, 1605, 1530, 1517, 1353, 1214, 1073, 723;

Anal. Calcd. for $C_{10}H_{15}N_3O_3$: C, 53.32; H, 6.71; N, 18.66 **Found:** C, 52.93; H, 6.55; N, 18.54.

4.15.2 *N*-ethyl-2-(2-hydrazinyl-2-oxoethyl)furan-3-carboxamide (97b): (2.5 g, 91%), mp 141- 143 °C.



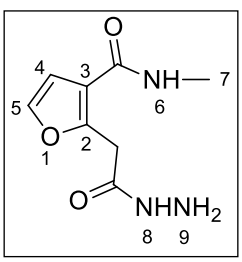
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.82 (bs, 1H, H-9), 7.29 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 6.50 (bs, 1H, H-6), 6.48 (d, $J_{4,5}$=2.0 Hz, 1H, H-4), 3.83 (s, 2H, $-NH_2$), 3.67 (bs, 2H, $-NH_2$), 3.47 – 3.38 (m, 2H, $-CH_2$), 1.23 (t, J=7.3 Hz, 3H, $-CH_3$);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 169.2, 164.0, 152.6, 141.9, 117.7, 108.8, 34.7, 34.7, 14.9;

IR (ATR, cm^{-1}) 3259, 3176, 3144, 3056, 2980, 1613, 1532, 1514, 1078, 751, 707;

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.18; H, 6.20; N, 19.89 **Found:** C, 50.96; H, 5.91; N, 19.70.

4.15.3 2-(2-Hydrazinyl-2-oxoethyl)-*N*-methylfuran-3-carboxamide (97c): (2.5 g, 92%), mp 165- 167 °C.



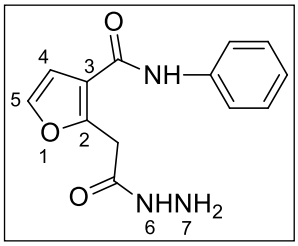
^{1}H-NMR (400 MHz, DMSO-d_6) δ: 9.23 (bs, 1H, H-8), 8.27 (d, J=4.2 Hz, 1H, H-6), 7.57 – 7.55 (m, 1H, H-5), 6.80 (d, $J_{4,5}$=1.9 Hz, 1H, H-4), 4.24 (s, 2H, $-NH_2$), 3.80 (s, 2H, $-CH_2$), 2.72 (d, J=4.6 Hz, 3H, $-CH_3$);

^{13}C-NMR (100.6 MHz, DMSO-d_6) δ: 167.3, 163.1, 152.4, 141.5, 117.7, 109.3, 32.7, 25.6;

IR (ATR, cm^{-1}) 3282, 3194, 3064, 1683, 1618, 1586, 1552, 718;

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.73; H, 5.62; N, 21.31 **Found:** C, 48.34; H, 5.31; N, 21.31.

4.15.4 2-(2-Hydrazinyl-2-oxoethyl)-*N*-phenylfuran-3-carboxamide (97d): (2.6 g, 96%), mp 175- 177 °C.



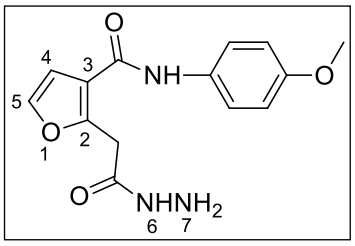
^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.49 (s, 1H, H-6), 9.46 (s, 1H, -NH-Ph), 7.71 (dd, J=8.5, 0.9 Hz, 2H, arom.), 7.66 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 7.38 – 7.31 (m, 2H, arom.), 7.09 (t, J=7.4 Hz, 1H, arom.), 6.99 (d, $J_{4,5}$=2.0 Hz, 1H, H-4), 4.37 (s, 2H, -NH_2), 3.86 (s, 2H, -CH_2);

^{13}C-NMR (100.6 MHz, DMSO-d_6) δ: 167.5, 161.3, 152.6, 141.8, 139.0, 128.7, 123.6, 120.1, 118.8, 110.2, 32.9;

IR (ATR, cm^{-1}) 3324, 3272, 1619, 1594, 1525, 1512, 1326, 749, 687;

Anal. Calcd. for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21 **Found:** C, 60.52; H, 4.80; N, 16.23.

4.15.5 2-(2-Hydrazinyl-2-oxoethyl)-*N*-(4-methoxyphenyl)furan-3-carboxamide (97e):(2.4 g, 90%), mp 192-194 °C.



^{1}H-NMR (400 MHz, DMSO-d_6) δ: 10.29 (bs, 1H, H-6), 9.41 (bs, 1H, -NH-arom.), 7.64 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 7.62 – 7.57 (m, A-part of AA'BB' system, 2H, arom.), 6.97 (d, $J_{4,5}$=1.9 Hz, 1H, H-4), 6.94 – 6.89 (m,B-part of AA'BB' system, 2H, arom.), 4.36 (bs, 2H,

-NH_2), 3.85 (s, 2H, -CH_2), 3.73 (s, 3H, -OCH_3);

^{13}C-NMR (100.6 MHz, DMSO-d_6) δ: 167.4, 160.9, 155.5, 152.5, 141.7, 131.0, 121.7, 118.7, 113.79, 110.0, 55.2, 32.8;

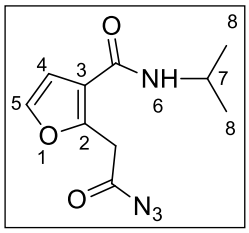
IR (ATR, cm^{-1}) 3328, 3268, 1642, 1620, 1525, 1511, 1242, 825;

Anal. Calcd. For $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53 **Found:** C, 57.50; H, 4.79; N,14.39.

4.16 General procedure for the synthesis of acyl azide derivatives 59a-e

To a stirred a solution of hydrazide **97a-e** (1.5 g) in 1M HCl (40 mL) at 0 °C, a solution of 1.05 eq of $NaNO_3$ in 5 mL of water was added and stirred for 30 min. The mixture was extracted with Et_2O (2 x 60 mL). The combined organic layers were washed with sat. aq Na_2CO_3 solution (40 mL), dried over $MgSO_4$ and concentrated. Column chromatography was done on silica gel (15 g) eluting with DCM/ Et_2O (1:1) to give white solids.

4.16.1 [3-(Propan-2-ylcarbamoyl)furan-2-yl]acetyl azide (59a): (1.5 g, 92%).

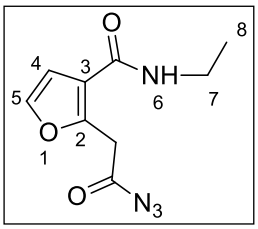


^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, $J_{5,4}$=2.1 Hz, 1H, H-5), 6.47 (d, $J_{4,5}$=2.0 Hz, 1H, H-4), 5.78 (bs, 1H, -NH), 4.21 (dq, J=13.2, 6.6 Hz, 1H, -CH), 4.12 (s, 2H, $-CH_2$), 1.23 (d, J=6.6 Hz, 6H, $-CH_3$);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 176.3, 162.2, 150.8, 142.2, 118.7, 108.6, 41.5, 35.7, 22.9;

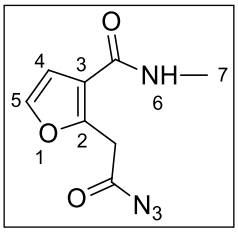
IR (ATR, cm^{-1}) 3254, 2133, 1706, 1620, 1602, 1534, 1514, 1169, 746.

4.16.2 [3-(Ethylcarbamoyl)furan-2-yl]acetyl azide (59b): (1.4 g, 89%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, $J_{5,4}$ = 2.1 Hz, 1H, H-5), 6.42 (d, $J_{4,5}$ = 2.0 Hz, 1H, H-4), 4.06 (s, 2H, $-CH_2$), 3.35 (qd, J = 7.3, 5.7 Hz, 2H, $-NCH_2$), 1.14 (t, J = 7.3 Hz, 3H, $-CH_3$).

4.16.3 [3-(Methylcarbamoyl)furan-2-yl]acetyl azide (59c): (1.3 g, 82%).

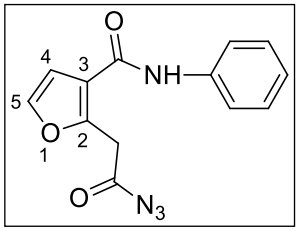


^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, $J_{5,4}$=2.0 Hz, 1H, H-5), 6.47 (s, 1H, H-4), 6.04 (bs, 1H, -NH), 4.13 (s, 2H, $-CH_2$), 2.92 (d, J=4.8 Hz, 3H, $-CH_3$);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 176.5, 163.7, 150.9, 142.2, 118.4, 108.5, 35.6, 26.3;

IR (ATR, cm^{-1}) 3298, 2137, 1706, 1627, 1606, 1544, 1136, 734.

4.16.4 [3-(Phenylcarbamoyl)furan-2-yl]acetyl azide (59d): (0.9 g, 59%).

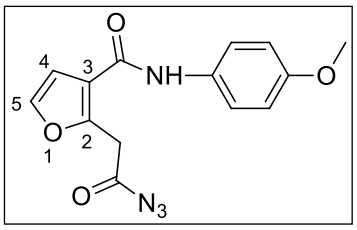


^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.98 (bs, 1H, -NH), 7.57 (dd, J =8.5, 0.9 Hz, 2H, arom.), 7.38 (d, $J_{5,4}$=2.1 Hz, 1H, H-5), 7.37 – 7.30 (m, 2H, arom.), 7.13 (t, J=7.4 Hz, 1H, arom.), 6.64 (d, $J_{4,5}$=1.8 Hz, 1H, H-4), 4.14 (s, 2H, $-CH_2$);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 176.7, 161.3, 151.2, 142.4, 137.7, 129.1, 124.7, 120.5, 119.3, 108.9, 35.7;

IR (ATR, cm^{-1}) 3370, 2141, 1730, 1647, 1610, 1598, 1531, 1491, 1442, 1327, 1061, 723.

4.16.5 {3-[(4-Methoxyphenyl)carbamoyl]furan-2-yl}acetyl azide (59e): (1.5 g, 96%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.81 (bs, 1H, -NH), 7.47 (d, J=8.9 Hz, 2H, arom.), 7.40 (d, $J_{5,4}$=1.4 Hz, 1H, H-5), 6.91 – 6.85 (m, 2H, arom.), 6.63 (d, $J_{4,5}$=1.3 Hz, 1H, H-4), 4.14 (s, 2H, -CH_2), 3.80 (s, 3H, -OCH_3);

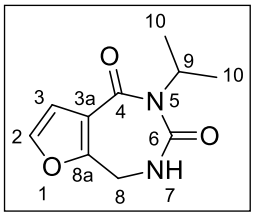
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 176.6, 161.2, 156.8, 151.1, 142.4, 130.7, 122.4, 119.2, 114.3, 108.8, 55.6, 35.7;

IR (ATR, cm^{-1}) 3287, 2152, 1708, 1643, 1621, 1508, 1240, 1185, 1035, 823.

4.17 Genaral procedure for the cyclization reaction 61a-e

Acylazide **59a-e** (0.1 g) was heated to reflux temperature in dry toluene (4 mL) for 3 h under N_2 atmosphere. Then, it was allowed to cool to rt and 1.5 eq of LiHMDS was added. It was left to react at rt for 15 min. When TLC showed that the reaction was completed, the organic layer was extracted with aq NH_4Cl solution (25 mL) and EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. Flash column chromatography was carried out on 10 g silica gel using DCM/EtOAc (2:1) for purification and re-crystallized from hexane and chloroform (1:5) to give colorless needle like crystals for **61a-c**. For **61d,e**, flash column chromatography was done hexane/EtOAc (1:1) and to give colorless solid compounds.

4.17.1 5-(Propan-2-yl)-7,8-dihydro-4*H*-furo[2,3-e][1,3]diazepine-4,6(5*H*)-dione (61a): (45 mg, 52%), mp 156-158 °C.



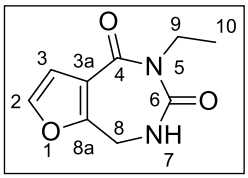
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, $J_{2,3}$=1.9 Hz, 1H, H-2), 7.21 (bs, 1H, -NH), 6.77 (d, $J_{3,2}$=1.9 Hz, 1H, H-3), 4.50 (h, J=6.7 Hz, 1H, -CH), 4.26 (d, , 2H, -CH_2), 1.47 (d, J=6.8 Hz, 6H, -CH_3);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 161.5, 157.6, 157.2, 141.8, 118.4, 111.3, 50.4, 37.2, 20.7;

IR (ATR, cm^{-1}) 3223, 3090, 2979, 2930, 1690, 1646, 1610, 1431, 1396, 1361, 1075, 752;

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45 **Found:** C, 57.63; H, 5.68; N, 13.47.

4.17.2 5-Ethyl-7,8-dihydro-4*H*-furo[2,3-e][1,3]diazepine-4,6(5*H*)-dione (61b): (73 mg, 83 %), mp 159-161 °C.



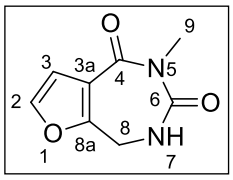
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.29 (d, $J_{2,3}$=1.9 Hz, 1H, H-2), 6.81 (d, $J_{3,2}$=1.9 Hz, 1H, H-3), 6.71 (bs, 1H, -NH), 4.32 (d, J=5.3 Hz, 2H, -CH_2), 3.91 (q, J = 7.0 Hz, 2H, -CH_2), 1.30 (t, J=7.0 Hz, 3H, -CH_3);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 161.3, 157.6, 156.4, 141.9, 118.4, 111.7, 41.0, 37.7, 14.1;

IR (ATR, cm^{-1}) 3240, 3119, 3083, 1663, 1610, 1473, 1437, 1369, 1079, 746;

Anal. Calcd. for$C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43 **Found:** C, 55.20; H, 5.07; N, 14.36.

4.17.3 5-Methyl-7,8-dihydro-4*H*-furo[2,3-e][1,3]diazepine-4,6(5*H*)-dione (61c): (44 mg, 51 %), mp 174-176 °C.



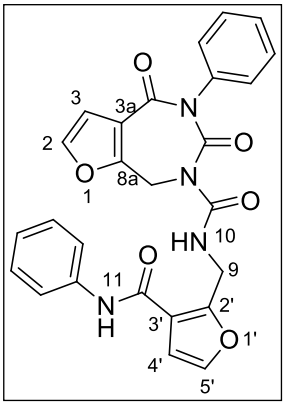
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.41 (bs, 1H, -NH), 7.29 (d, $J_{2,3}$=1.9 Hz, 1H, H-2), 6.81 (d, $J_{3,2}$=1.9 Hz, 1H, H-3), 4.33 (d, J=5.2 Hz, 2H, -CH_2), 3.22 (s, 3H, -CH_3);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 161.9, 158.2, 156.8, 141.9, 117.9, 111.4, 37.6, 33.2;

IR (ATR, cm^{-1}) 3165, 3141, 3066, 2941, 1674, 1617, 1465, 1445, 1368, 1088, 738;

Anal. Calcd. for$C_8H_8N_2O_3$: C, 53.33; H, 4.48; N, 15.55 **Found:** C, 52.66; H, 4.25; N, 15.35.

4.17.4 5-Phenyl-7,8-dihydro-4*H*-furo[2,3-e][1,3]diazepine-4,6(5*H*)-dione (61d): (45 mg, 50%), m.p. 105-107 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.97 (bs, 1H, H-11), 9.32 (t, J=5.7 Hz, 1H, H-10), 7.78 (d, J=7.9 Hz, 2H, arom.), 7.51 – 7.42 (m, 3H, arom.), 7.41 (d, $J_{5',4'}$=1.7 Hz, 1H, H-5'), 7.35 (dd, J=15.3, 7.3 Hz, 4H, arom.), 7.30 (d, $J_{2,3}$=1.9 Hz, 1H, H-2), 7.13 (t, J=7.4 Hz, 1H, arom.), 6.82 (d, $J_{4',5'}$=1.7 Hz, 1H, H-4'), 6.68 (d, $J_{3,2}$=1.5 Hz, 1H, H-3), 5.35 (s, 2H, -CH_2), 4.53 (d, J=5.8 Hz, 2H, -CH_2);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 161.4, 160.4, 157.6, 156.2, 154.3, 149.9, 143.1, 142.4, 138.7, 138.1, 129.6, 129.0, 128.9, 128.8, 124.1, 121.1, 120.0, 118.2, 110.9, 110.7, 38.5, 37.3;

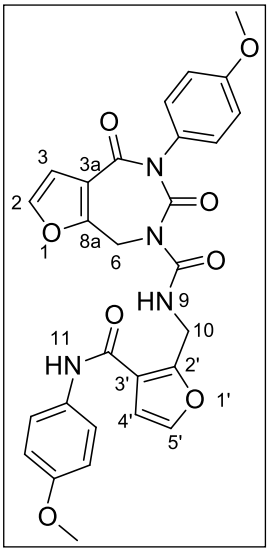
IR (ATR, cm^{-1}) 3296, 3130, 3016, 1705, 1661, 1512, 1442, 1347, 1124, 749;

Calcd HRMS for $C_{26}H_{21}N_4O_6^+$:485.14611 **Found:** 485.15023.

4.17.5 5-(4-Methoxyphenyl)-7,8-dihydro-4*H*-furo[2,3-e][1,3]diazepine-4,6(5*H*)-dione (61e): (24 mg, 27%), m.p. 88-90 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.88 (bs, 1H, H-11), 9.37 (t, J=5.8 Hz, 1H, H-9), 7.70 – 7.68 (m, A-part of AA'BB' system, 2H, arom.), 7.41 (d, $J_{5',4'}$=2.0 Hz, 1H, H-5'), 7.31 (d, $J_{2,3}$=1.8 Hz, 1H, H-2), 7.25 – 7.20 (m, C-part of CC'DD' system, 2H, arom.), 7.00 – 6.95 (m, B-part of AA'BB' system,, 2H, arom.), 6.93 – 6.88 (m, D-part of CC'DD' system, 2H, arom.), 6.83 (d, $J_{4',5'}$=1.9 Hz, 1H, H-4'), 6.68 (d, $J_{3,2}$=1.7 Hz, 1H, H-3), 5.35 (s, 2H, -CH_2), 4.55 (d, J=5.9 Hz, 2H, -CH_2), 3.84 (s, 3H, -OCH_3), 3.82 (s, 3H, -OCH_3);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 161.2, 160.7, 159.8, 157. 7, 156.7, 156.4, 154.4, 149.7, 143.2, 142.6, 132.0, 130.7, 130.7, 121.7, 121.2, 118.4, 114.4, 114.2, 111.0, 110.9, 55.6, 55.6, 38. 6, 37.4;

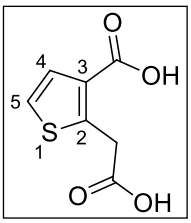


IR (ATR, cm^{-1}) 3296, 3128, 3011, 2933, 2836, 1705, 1659, 1507, 1232, 1125, 734;

Calcd HRMS for $C_{28}H_{25}N_4O_8^+$: 545.16724 **Found:** 545.16881.

4.18 2-(Carboxymethyl)thiophene-3-carboxylic acid (93)

Diester **53** (15.0 g, 70.0 mmol) and K_2CO_3 was dissolved in 100 mL MeOH and 100 mL water and heated at reflux temperature for 12 h. After reaction was completed, MeOH was evaporated and the reaction mixture was acidified to pH = 2. Then, it was exracted with EtOAc (3 x 250 mL). The combined organic layers were evaporated and washed with chloroform to give yellowish solid powder (13.0 g, 92%), mp 208-210 °C.



^{1}H-NMR (400 MHz, DMSO-d_6) δ: 12.60 (s, 2H, -OH), 7.41 (d, $J_{5,4}$=5.3 Hz, 1H, H-5), 7.33 (d, $J_{4,5}$=5.3 Hz, 1H, H-4), 4.14 (s, 2H, -CH_2);

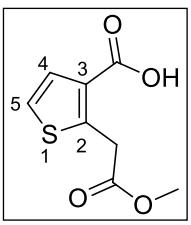
^{13}C-NMR (100.6 MHz, DMSO-d_6) δ: 171.2, 164.3, 144.5, 130.3, 128.9, 123.9, 34.1;

IR (ATR, cm^{-1}) 2627, 1662, 1536, 1447, 1395, 1283, 1215, 917, 717, 535;

Anal. Calcd for $C_9H_8O_5S$: C, 45.16; H, 3.25; S, 17.22 **Found:** C, 44.84; H, 3.23; S 16.86.

4.19 2-(2-Methoxy-2-oxoethyl)thiophene-3-carboxylic acid (94)

The diacid **93** (7.0 g, 37.6 mmol) was dissolved in 30 mL MeOH and 75 mL CH_2Cl_2. HCl (10 drops) was added and the mixture was stirred at 40 °C for 13 h. The solvent was evaporated and the residue was purified by column chromatography on 280 g silica gel eluting with hexane/EtOAc (2:1, 1:1). The product was re-crystallized from hexane/ether (1:3) to give colorless needles (5.9 g, 78%), mp 111-113 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 11.24 (s, 1H, -OH), 7.51 (d, $J_{5,4}$=5.4 Hz, 1H, H-5), 7.20 – 7.17 (m, 1H, H-4), 4.26 (s, 2H, -CH_2), 3.75 (s, 3H, -OCH_3).

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 170.5, 168.7, 145.9, 129.6, 129.1, 123.6, 52.5, 34.5.

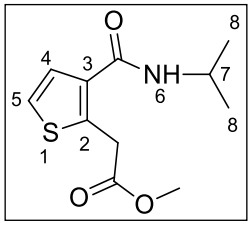
IR (ATR, cm^{-1}) 2547, 1740, 16633, 1533, 1445, 1348, 1287, 1179, 943, 736, 538

Anal. Calcd for $C_9H_8O_5S$: C, 47.99; H, 4.03; S, 16.02 **Found:**C, 47.73;H, 4.02; S15.96.

4.20 General procedure for the synthesis of amide derivatives 96a,b

The acid **94** (1.5 g, 16.3 mmol) was dissolved in 20 mL CH_2Cl_2 at 0 °C and NEt_3 (1.6 mL, 11.2 mmol) was added and the resulting mixture was stirred for 30 min followed by the addition of ethylchloroformate (1.6 mL, 17.2 mmol) and stirred for additional 30 min. Then, 2.5 equivalents of the amine derivatives were added to reaction medium. The progress of the reaction was controlled by TLC and approximately 1h later, the reaction was completed. After that, the solvent was evaporated. The mixture was extracted with EtOAc (100 mL) and 1M HCl. The aqueous layer was re-extracted with EtOAc(2 x 50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated.

4.20.1 Methyl [3-(propan-2-ylcarbamoyl)thiophen-2-yl]acetate (96a): For purification, flash column chromatography was done on 60 g silica gel eluting with hexane/EtOAc (3/1) to give reddish brown oil (1.6 g, 88%).



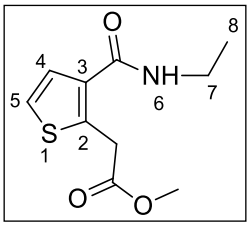
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.20 – 7.15 (m, 2H, H-5 and H-4), 6.53 (bs, 1H, -NH), 4.21 (td, J = 13.2, 6.6 Hz, 1H, -CH), 4.10 (s, 2H, $-CH_2$), 3.75 (s, 3H, $-OCH_3$), 1.23 (d, J = 6.6 Hz, 6H, $-CH_3$);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 171.60, 163.41, 137.35, 135.26, 127.14, 124.13, 52.62, 41.74, 34.02, 22.87;

IR (ATR, cm^{-1}) 3264, 2976, 1738, 1622, 1558, 1522, 1145, 1002, 711;

Calcd HRMS for $C_{11}H_{16}NO_3S^+$: 242,08509 **Found:** 242,08632.

4.20.2 Methyl [3-(ethylcarbamoyl)thiophen-2-yl]acetate (96b): For purification, flash column chromatography was done on 60 g silica gel eluting with hexane/EtOAc (2/1) to give brownish oil (1.4 g, 83%).



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.15 (d, $J_{5,4}$=5.4 Hz, 1H, H-5), 7.11 (d, $J_{4,5}$=5.4 Hz, 1H, H-4), 6.77 (bs, 1H, -NH), 4.10 (s, 2H, $-CH_2$), 3.70 (s, 3H, $-OCH_3$), 3.37 (qd, J = 7.3, 5.6 Hz, 2H, H-7), 1.17 (t, J = 7.3 Hz, 3H, $-CH_3$);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 171.4, 164.0, 138.1, 134.3, 126.8, 123.7, 52.3, 34.4, 33.8, 14.6;

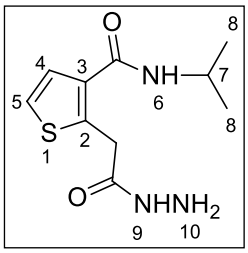
IR (ATR, cm^{-1}) 3328, 2974, 2951, 1734, 1628, 1549, 1514, 1435, 1283, 1174, 1000, 728, 708;

Calcd HRMS for $C_{10}H_{13}NNaO_3S^+$: 250,05138 **Found:** 250,05322.

4.21 General procedure for the synthesis of hydrazide derivatives 98a,b

The esters **96a,b** (1.0 g) were dissolved in 20 mL MeOH in which 2.5 equivalent hydrazinemonohydrate was added and it was left to react at 40 °C over a night. Then, the solvent was evaporated.

4.21.1 2-(2-Hydrazinyl-2-oxoethyl)-*N*-(propan-2-yl)thiophene-3-carboxamide (98a): The crude product was washed with cold EtOAc to give white powder (0.7 g, 95%), mp 151-153 °C.



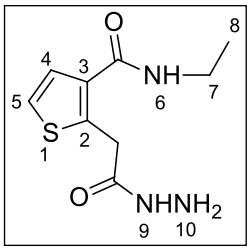
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.04 (s, 1H, -NNH), 7.14 – 7.10 (m, 2H, H-5 and H-4), 6.63 (d, J=6.0 Hz, 1H, -NH), 4.26 – 4.16 (m, 1H, -CH), 3.92 (s, 2H, $-CH_2$), 3.71 (bs, 2H, $-NH_2$), 1.25 (d, J = 6.6 Hz, 6H, $-CH_3$);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 170.7, 164.0, 140.7, 133.6, 126.5, 124.2, 42.1, 35.1, 22.9;

IR (ATR, cm^{-1}) 3274, 2971, 1629, 1553, 1519, 1291, 1146, 992, 693, 556;

Calcd HRMS for $C_{10}H_{16}N_3O_2S^+$: 242,09632 **Found:** 242,09772.

4.21.2 *N*-ethyl-2-(2-hydrazinyl-2-oxoethyl)thiophene-3-carboxamide (98b): The crude material was extracted with DCM (3 x 100 mL) to give balck crystals (0.3 g, 30%), mp 100-102 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.97 (s, 1H, -NNH), 7.16 (d, $J_{5,4}$=5.4 Hz, 1H, H-5), 7.11 (d, $J_{4,5}$=5.4 Hz, 1H, H-4), 6.46 (bs, 1H, -NH), 3.95 (s, 2H, $-CH_2$), 3.50 – 3.41 (m, 2H, H-7), 3.30 (bs, 2H, $-NH_2$) 1.25 (t, J=7.3 Hz, 3H, $-CH_3$);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 170.7, 164.9, 140.6, 133.5, 126.6, 124.2, 34.9, 14.9;

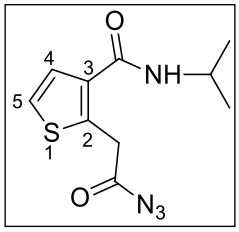
IR (ATR, cm^{-1}) 3231, 3058, 2977, 1668, 1614, 1547, 1518, 1438, 1354, 1297, 992, 690;

Calcd HRMS for $C_9H_{13}N_3NaO_2S^+$: 250,06262 **Found:** 250,06417.

4.22 General procedure for the synthesis of acyl azide derivatives 60a,b

To a stirred a solution of hydrazide **98a,b** (0.5 g) in 1M HCl (20 mL) at 0 °C, a solution of 1.05 eq of $NaNO_3$ in 2 mL of water was added and stirred for 30 min. The mixture was extracted with Et_2O (2 x 60 mL). The combined organic layers washed with sat. aq Na_2CO_3 solution (40 mL), dried over $MgSO_4$ and concentrated. Column chromatography was done on silica gel (10 g) eluting with Et_2O to give corresponding acyl azides.

4.22.1 [3-(Propan-2-ylcarbamoyl)thiophen-2-yl]acetyl azide. (60a): (0.4 mg, 67 %).

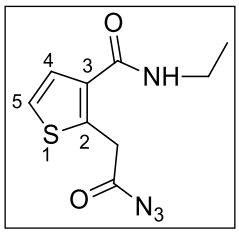


^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.21 (dt, $J_{5,4}$=5.3, 1.5 Hz, 1H, H-5), 7.14 (d, $J_{4,5}$=5.3 Hz, 1H, H-4), 6.03 (bs, 1H, -NH), 4.22 (tt, J = 12.3, 5.5 Hz, 1H, -CH), 4.17 (s, 2H, -CH_2), 1.24 (d, J = 6.6 Hz, 6H, -CH_3);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 177.5, 163.1, 137.9, 134.4, 126.3, 124.4, 41.6, 36.3, 22.8;

IR (ATR, cm^{-1}) 3294, 2975, 2145, 1700, 1626, 1549, 1519, 1154, 693.

4.22.2 [3-(Ethylcarbamoyl)thiophen-2-yl]acetyl azide (60b): (0.5 mg, 90 %).



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.22 (d, $J_{5,4}$=5.4 Hz, 1H, H-5), 7.15 (d, $J_{4,5}$=5.4 Hz, 1H, H-4), 6.18 (bs, 1H, -NH), 4.18 (s, 2H, -CH_2), 3.44 (qd, J = 7.3, 5.6 Hz, 2H, -NCH_2), 1.23 (t, J = 7.3 Hz, 3H, -CH_3);

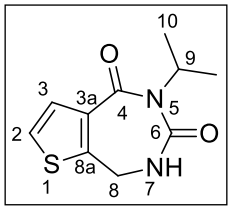
^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 181.9, 168.1, 142.4, 138.4, 130.4, 128.8, 40.6, 38.9, 19.2;

IR (ATR, cm^{-1}) 3316, 2974, 2934, 2136, 1711, 1625, 1550, 1514, 1289, 1146, 1062, 707.

4.23 Genaral procedure for the cyclization reaction 62a,b

A solution of acylazide **60a** or **60b** (0.1 g) in dry toluene (5 mL) was heated to reflux temperature for 3h under N_2 atmosphere. Then, it was allowed to cool to rt and 1.5 eq of LiHMDS was added. It was left to react at rt for 30 min. After completion of the reaction, the organic layer was extracted with aq NH_4Cl solution (25 mL) and EtOAc (3 x 50 mL). The organic layers were dried over $MgSO_4$ and evaporated.

4.23.1 5-(Propan-2-yl)-7,8-dihydro-4*H*-thieno[2,3-e][1,3]diazepine-4,6(5*H*)-dione (62a): For purification, flash column chromatography on 10 g silica gel eluting with hexane/EtOAc (3/1) to give white snowflake crystals (10 mg, 11%), mp 175-177 °C.

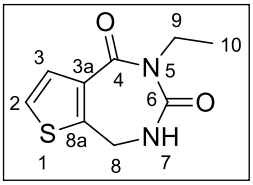


^{1}H NMR (400 MHz, $CDCl_3$) δ7.46 (d, $J_{2,3}$=5.2 Hz, 1H, H-2), 7.11 (d, $J_{3,2}$=5.2 Hz, 1H, H-3), 6.38 (br s, 1H, -NH), 4.60 (septet, J=6.8 Hz, 1H, -CH), 4.33 (d, J=6.4 Hz, 2H, -CH_2), 1.50 (d, J=6.8 Hz, 6H, -CH_3);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ161.4, 157.0, 144.6, 135.3, 130.3, 123.2, 50.1, 37.9, 20.6.

IR (ATR, cm^{-1})3344, 3080, 2972, 2925, 1691, 1630, 1439, 1362, 1105, 1022, 755, 722;

4.23.2 5-Ethyl-7,8-dihydro-4*H*-thieno[2,3-e][1,3]diazepine-4,6(5*H*)-dione (62b): The crude product was re-crystallized in $CHCl_3$ under petrolium ether atmosphere to give brownish snowflake crystals (10 mg, 11%), mp 178-180 °C.



^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.46 (d, $J_{2,3}$=5.2 Hz, 1H, H-2), 7.11 (d, $J_{3,2}$=5.2 Hz, 1H, H-3), 6.96 (bs, 1H, -NH), 4.35 (d, J=6.0 Hz, 2H, H-8), 3.95 (q, J=7.0 Hz, 2H, H-9), 1.32 (t, J=7.0 Hz, 3H, -CH_3);

^{13}C-NMR (100.6 MHz, $CDCl_3$) δ: 161.5, 157.7, 144.3, 135.0, 130.4, 123.2, 41.0, 37.9, 14.1;

IR (ATR, cm^{-1}) 3216, 3079, 1674, 1637, 1545, 1375, 1320, 1261, 1097, 1050, 771;

Anal. Calcd for $C_9H_{10}N_2O_2S$: C, 51.41; H, 4.79; N, 13.32; S, 15.25 **Found:**C, 51.22; H, 4.65; N,13.18; S,14.94.

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APPENDIX A

SPECTRAL DATA

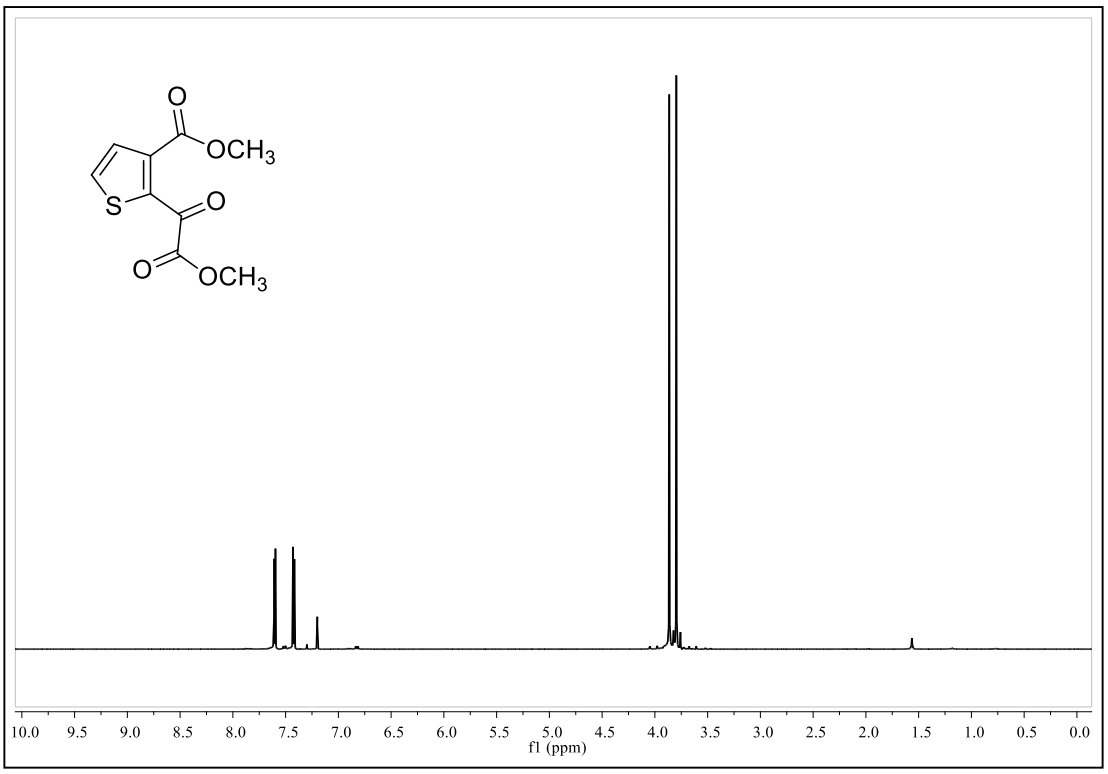

Figure A 1 ^{1}H NMR spectrum of compound **69**

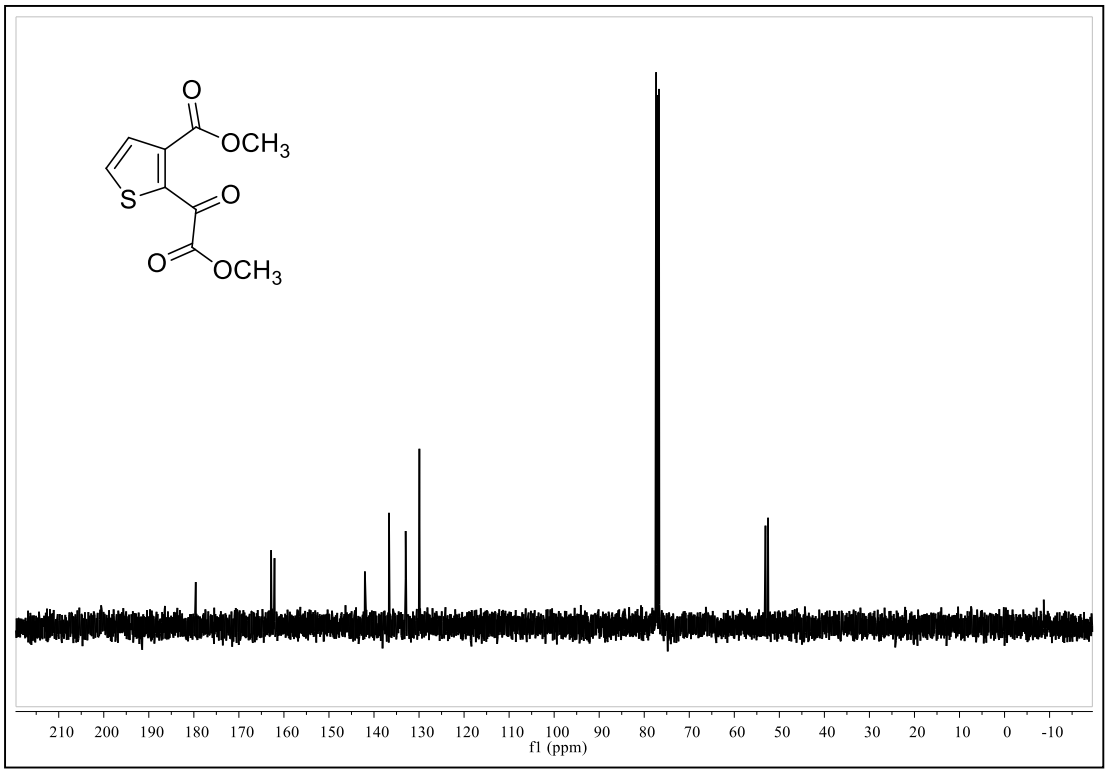

Figure A 2 ^{13}C NMR spectrum of compound **69**

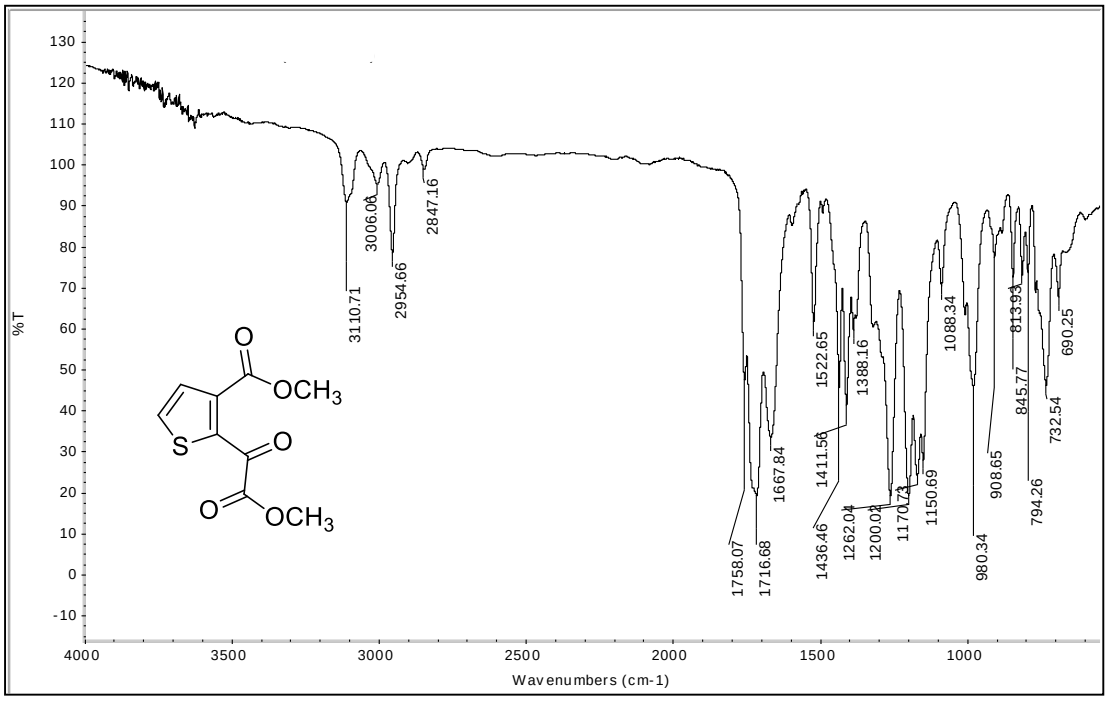

Figure A 3 IR spectrum of compound **69**

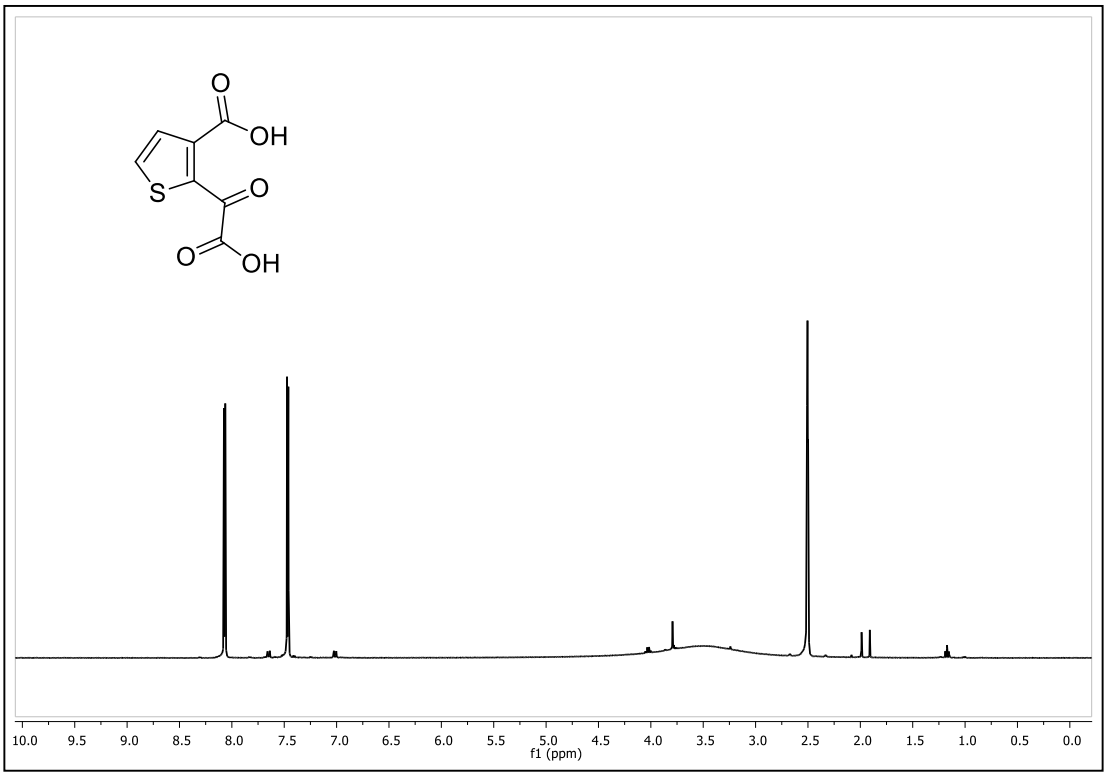

Figure A 4 ^{1}H NMR spectrum of compound **70**

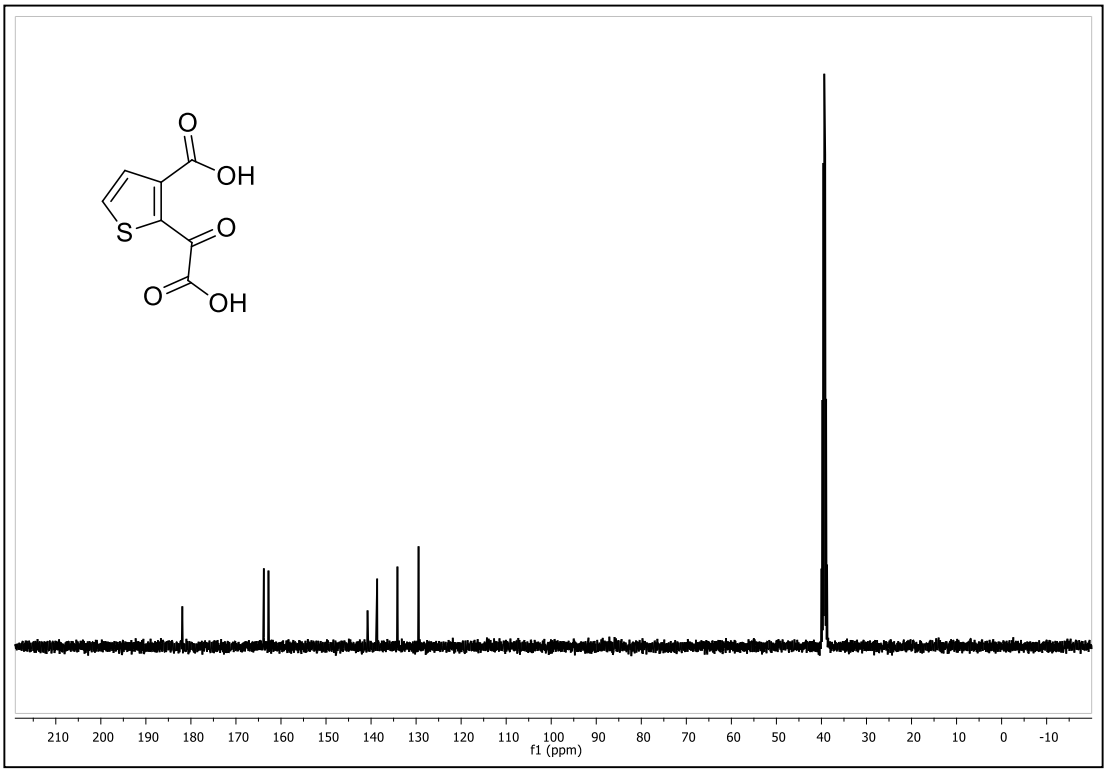

Figure A 5 ^{13}C NMR spectrum of compound **70**

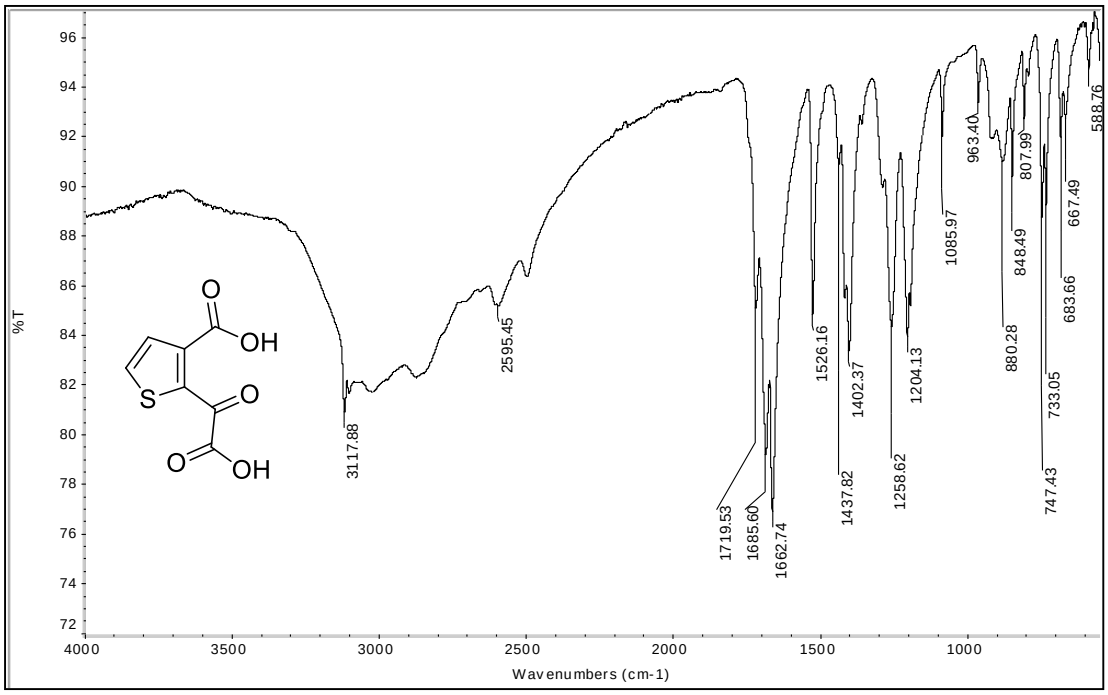

Figure A 6 IR spectrum of compound **70**

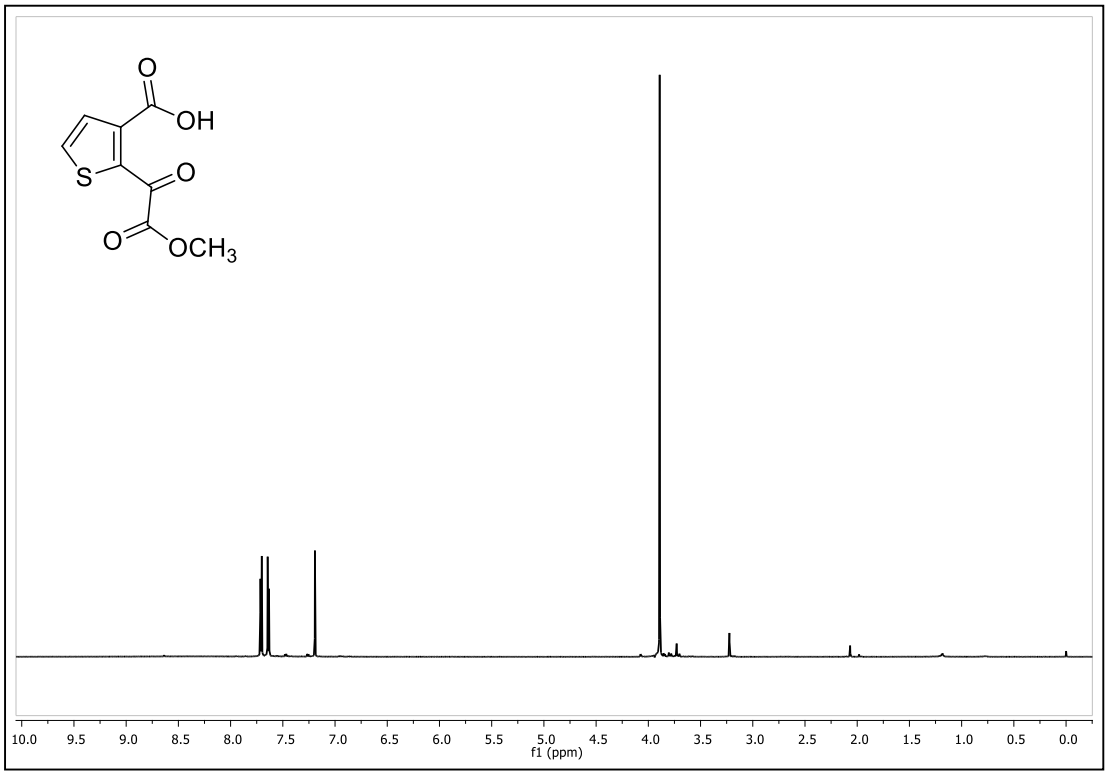

Figure A 7 ^{1}H NMR spectrum of compound **54**

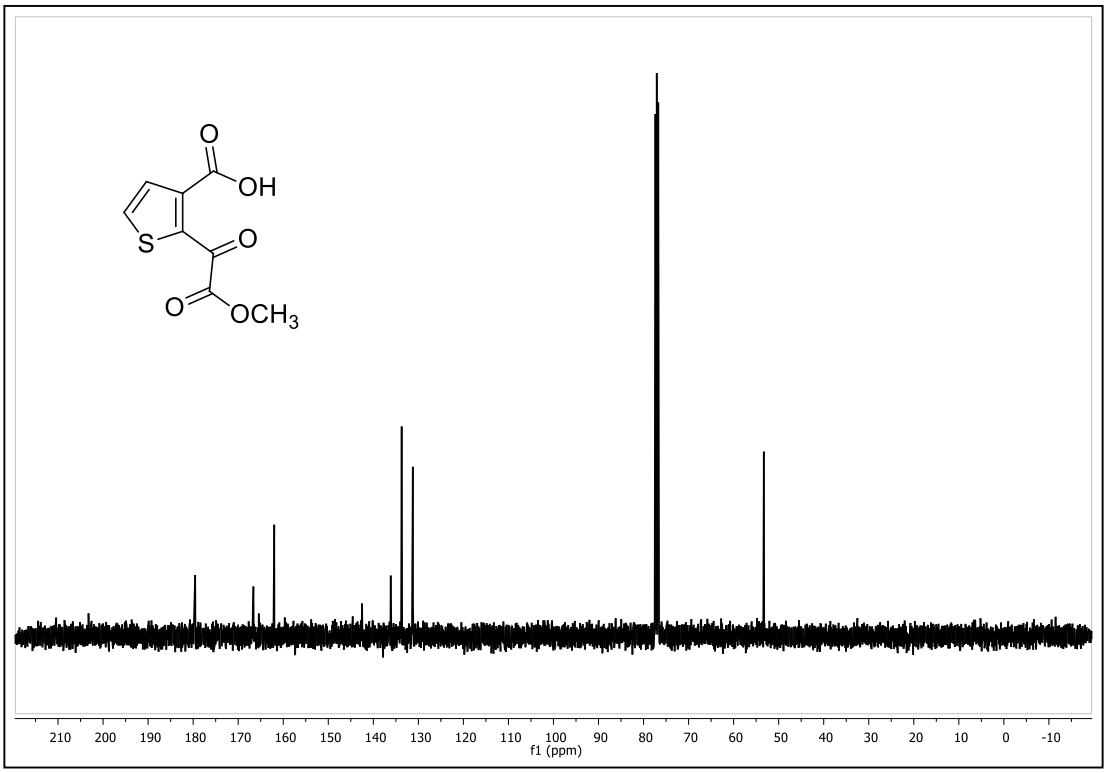

Figure A 8 ^{13}C NMR spectrum of compound **54**

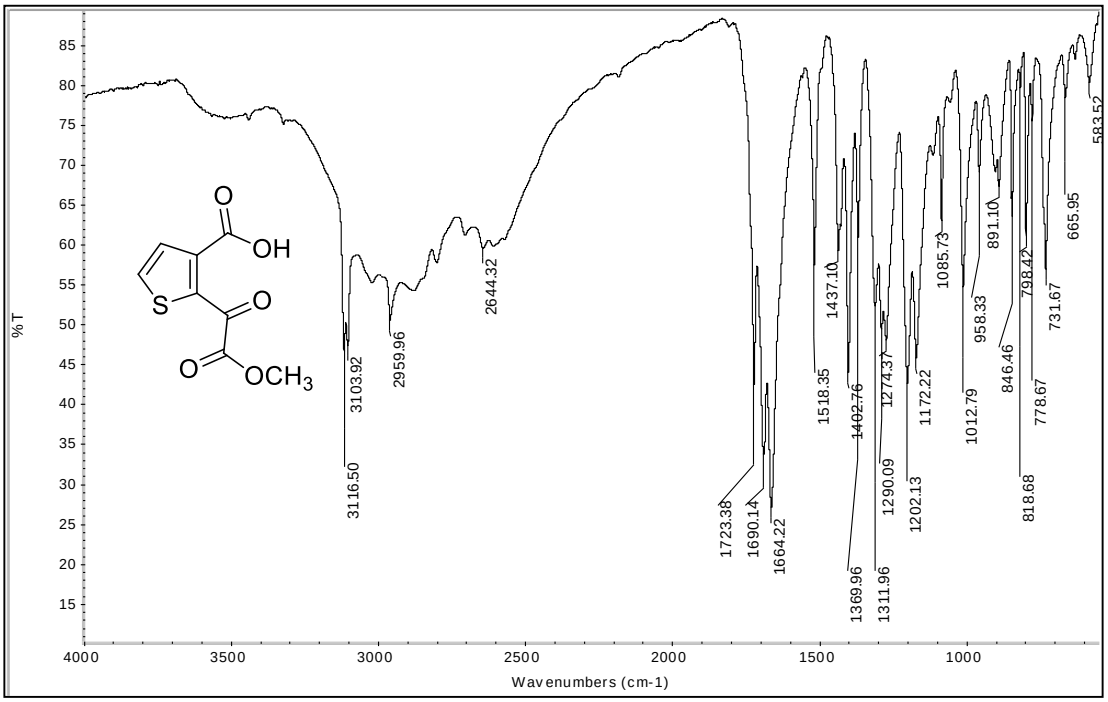

Figure A 9 IR spectrum of compound **54**

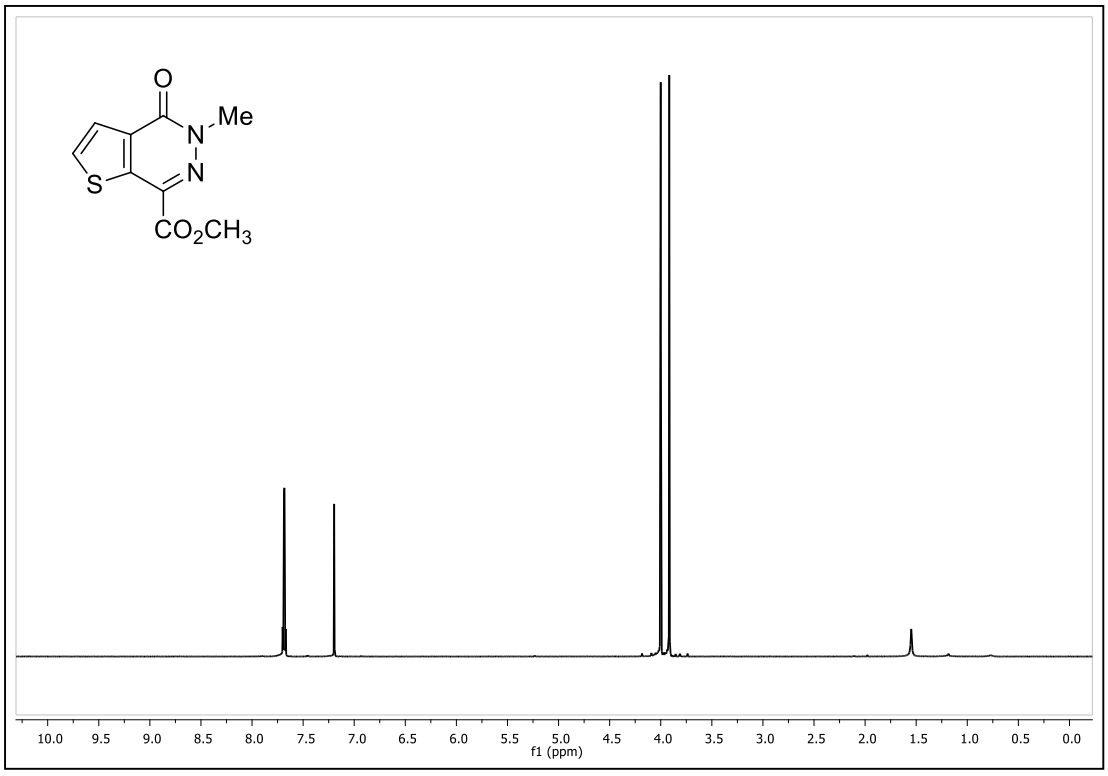

Figure A 10 ^{1}H NMR spectrum of compound**73a**

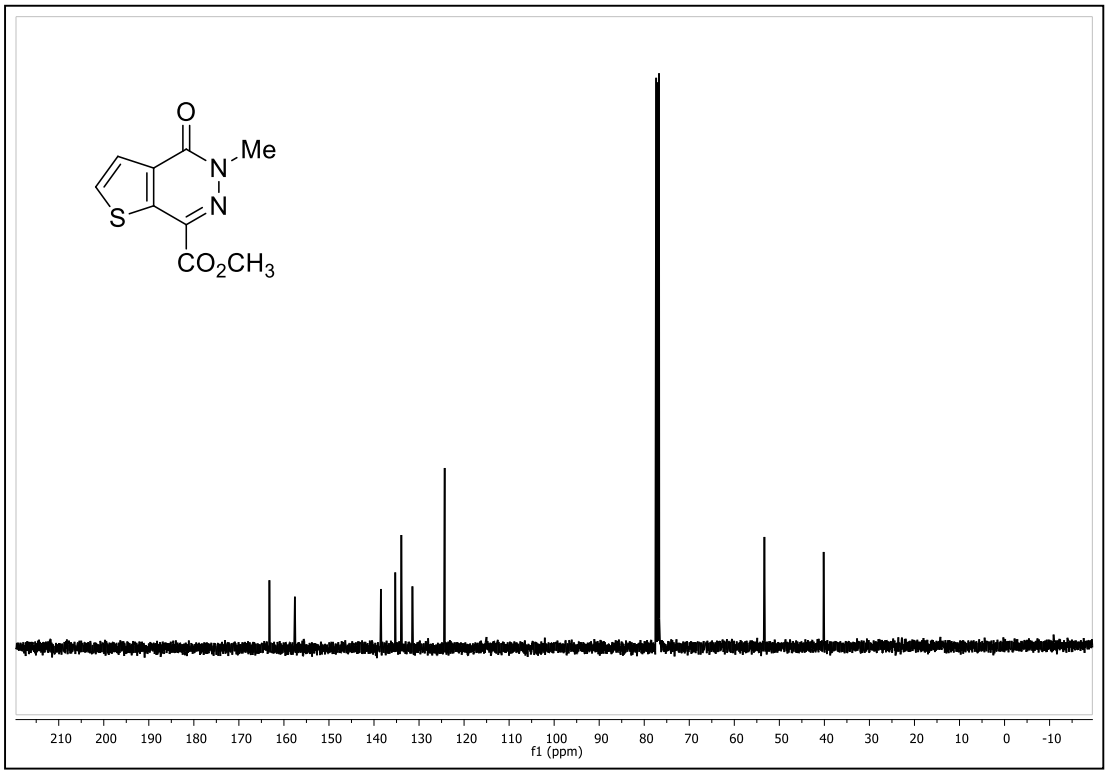

Figure A 11 ^{13}C NMR spectrum of compound**73a**

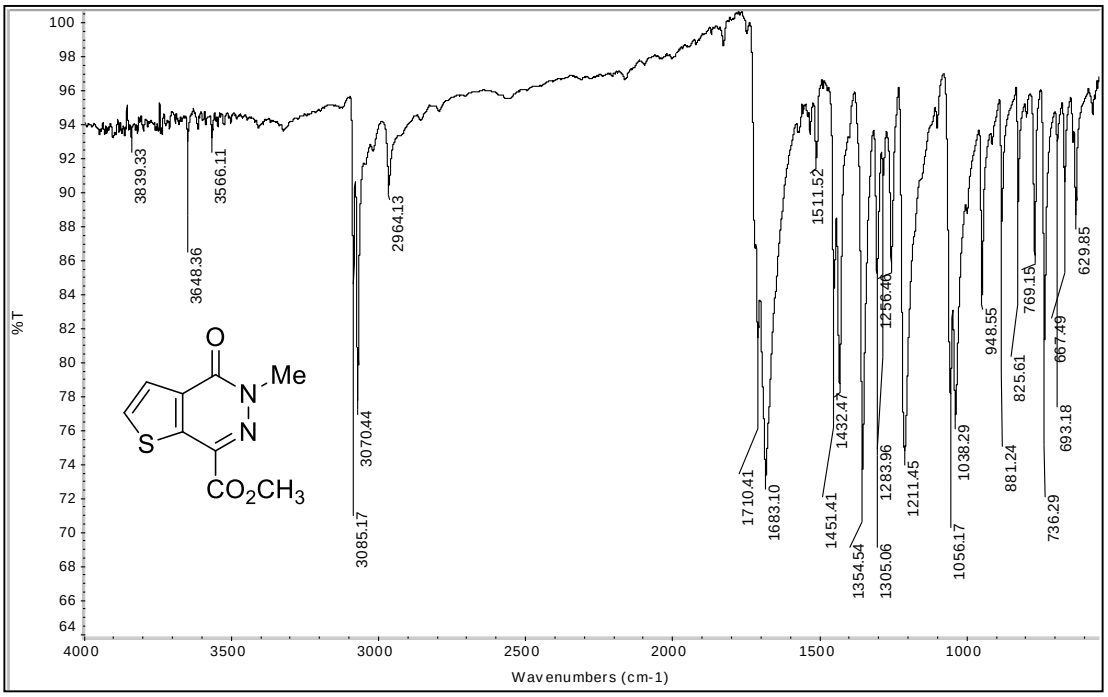

Figure A 12 IR spectrum of compound **73a**

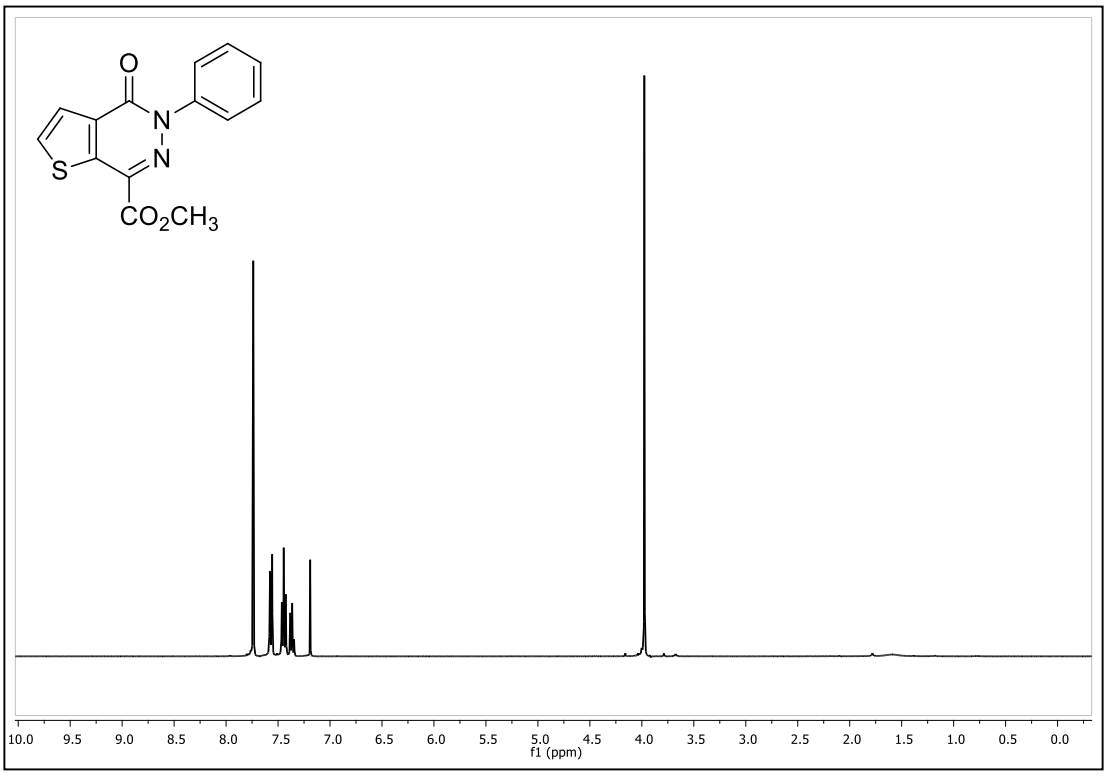

Figure A 13 ^{1}H NMR spectrum of compound**73b**

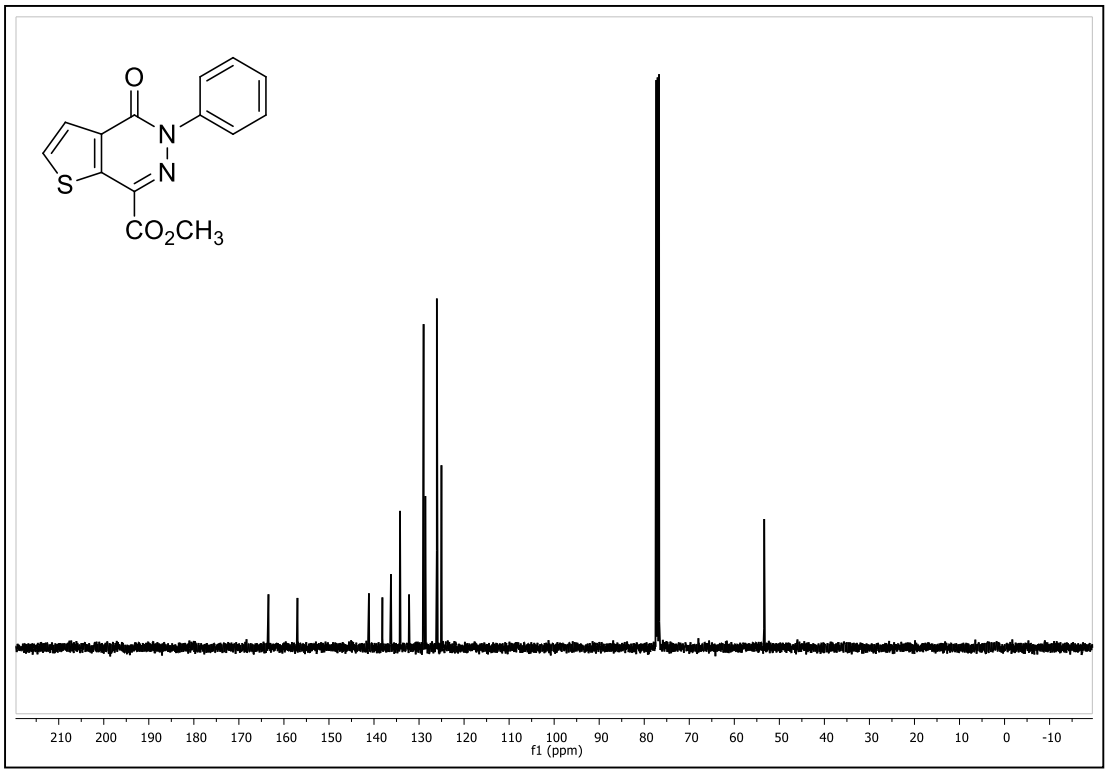

Figure A 14 ^{13}C NMR spectrum of compound **73b**

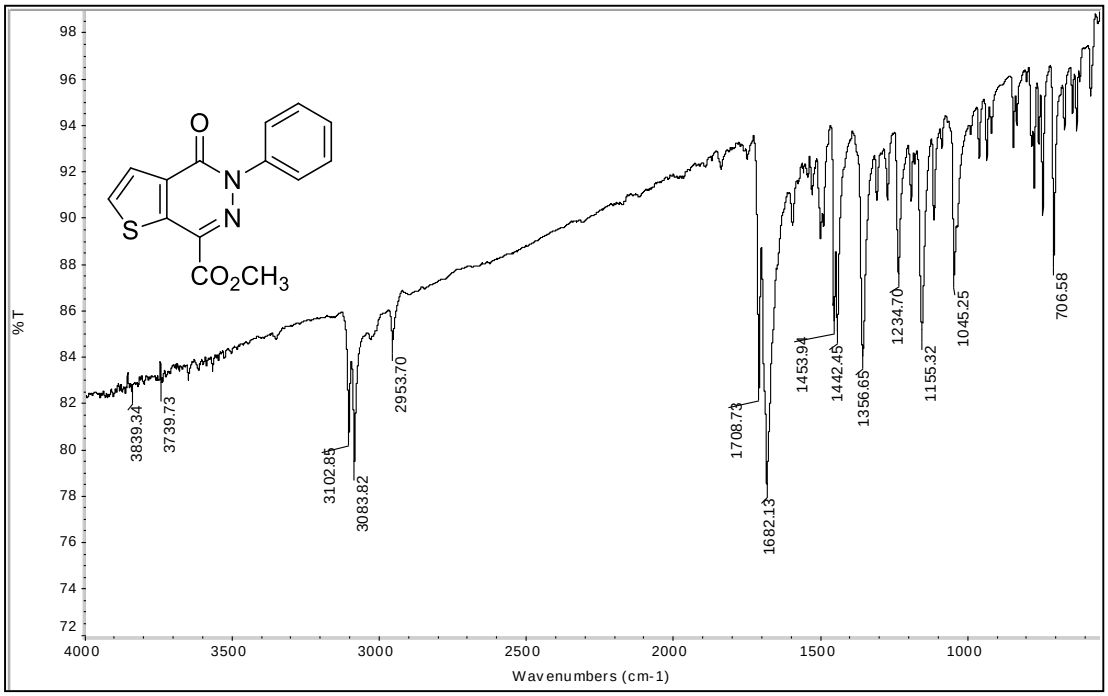

Figure A 15 IR spectrum of compound **73b**

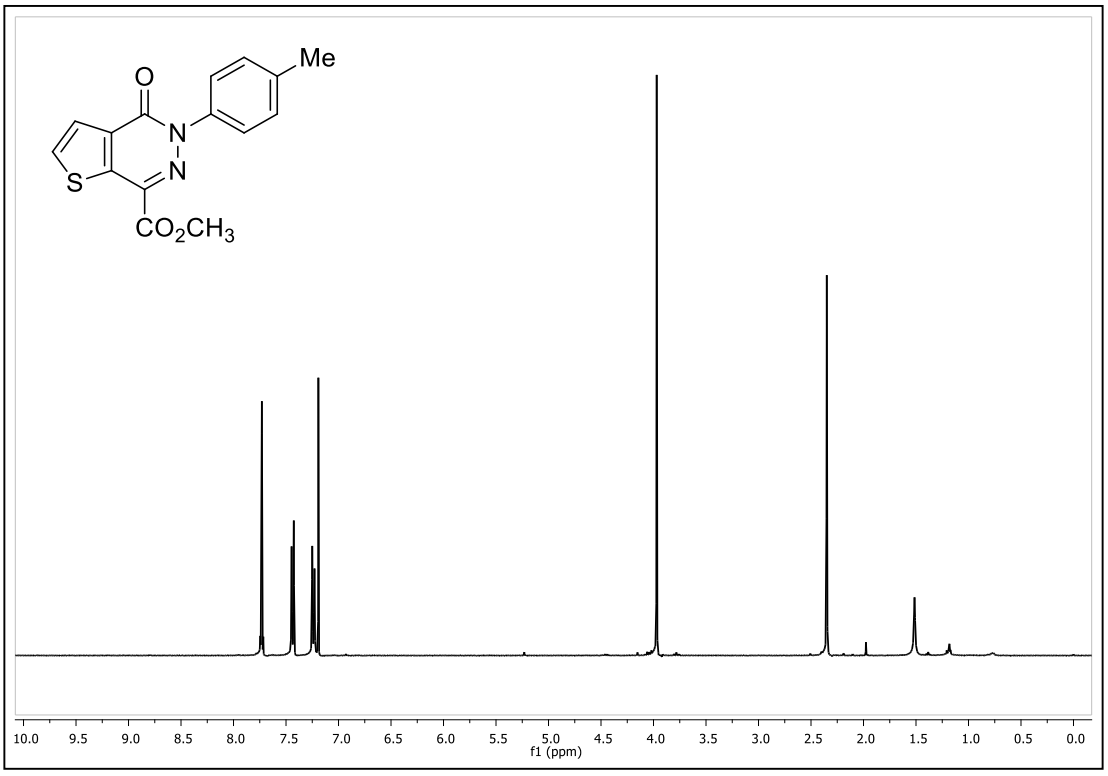

Figure A 16 ^{1}H NMR spectrum of compound**73c**

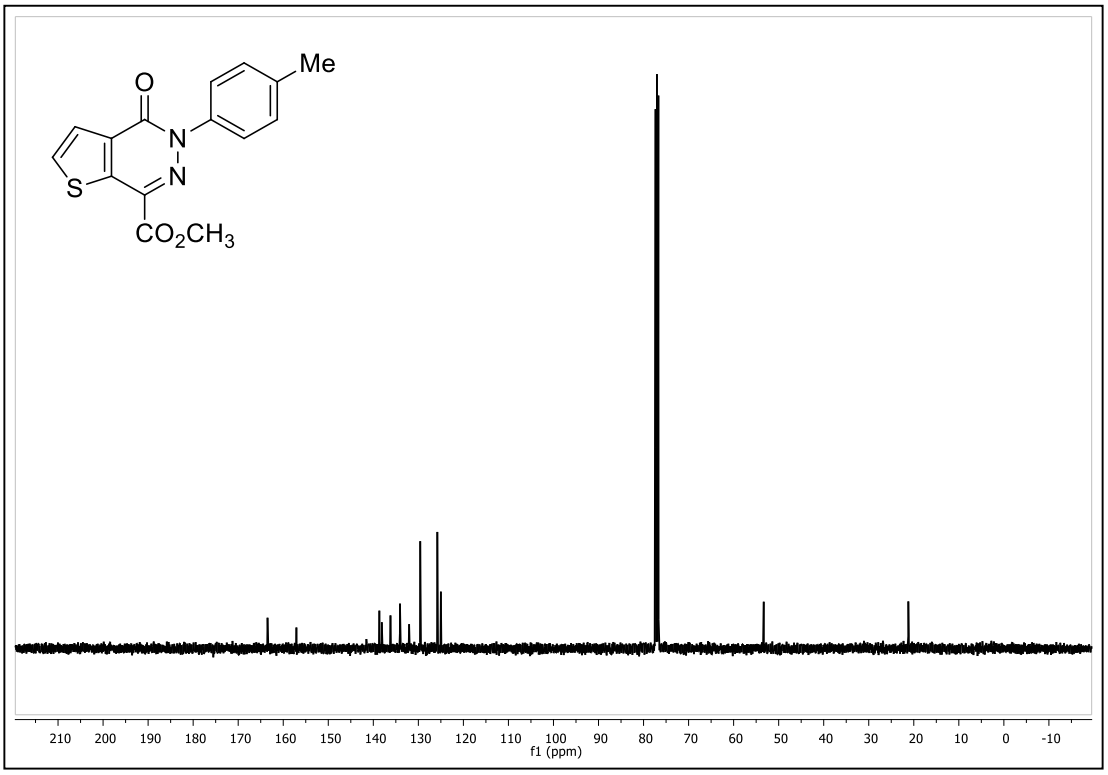

Figure A 17 ^{13}C NMR spectrum of compound**73c**

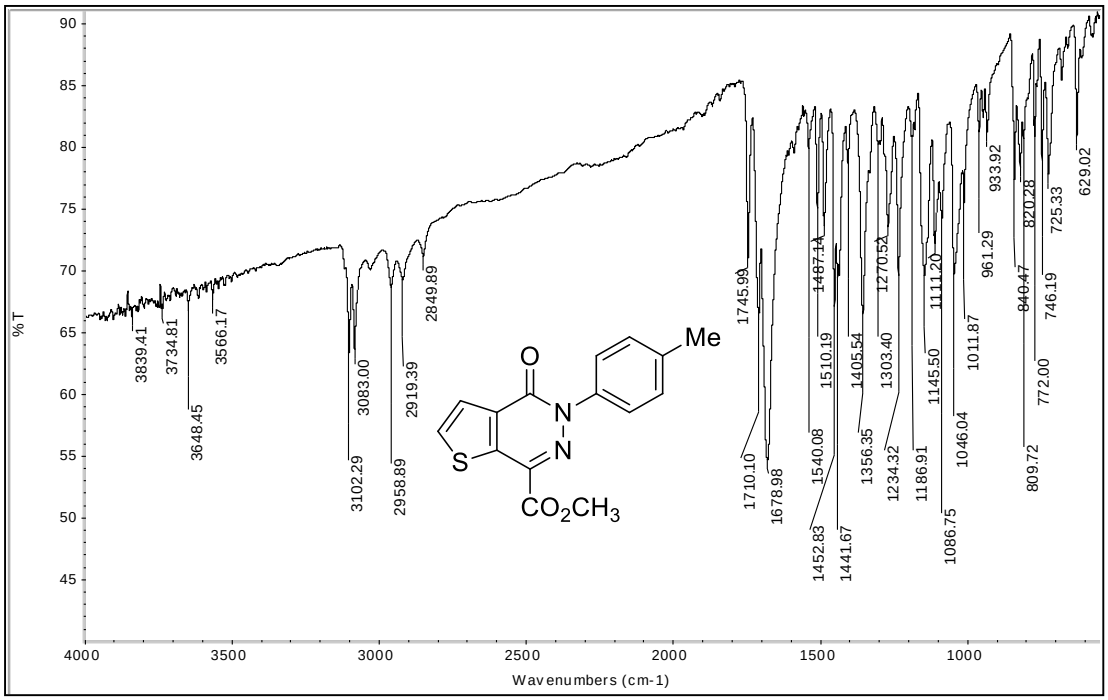

Figure A 18 IR spectrum of compound **73c**

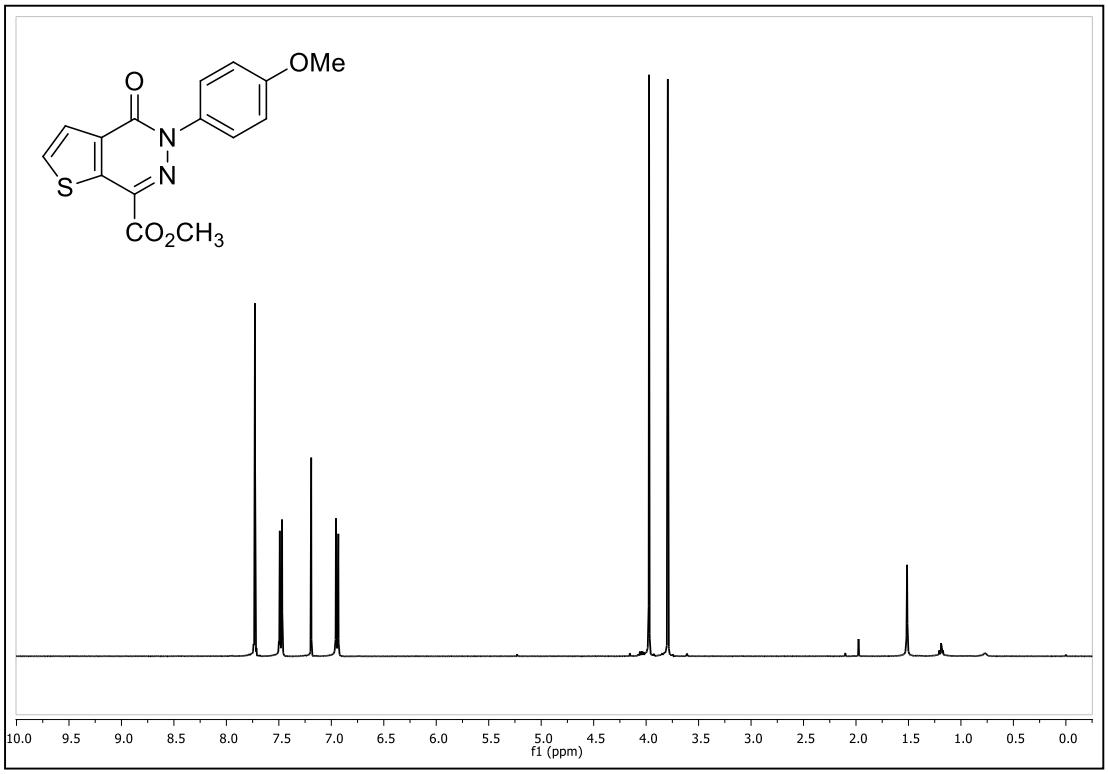

Figure A 19 ^{1}H NMR spectrum of compound**73d**

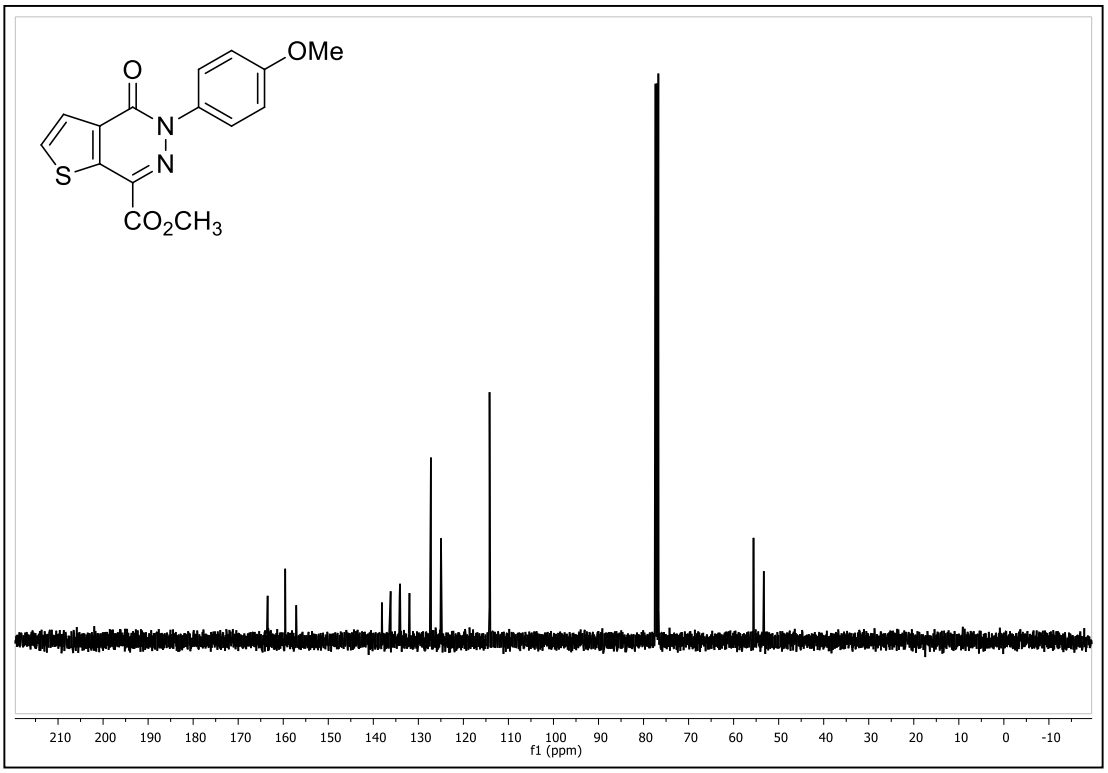

Figure A 20 ^{13}C NMR spectrum of compound **73d**

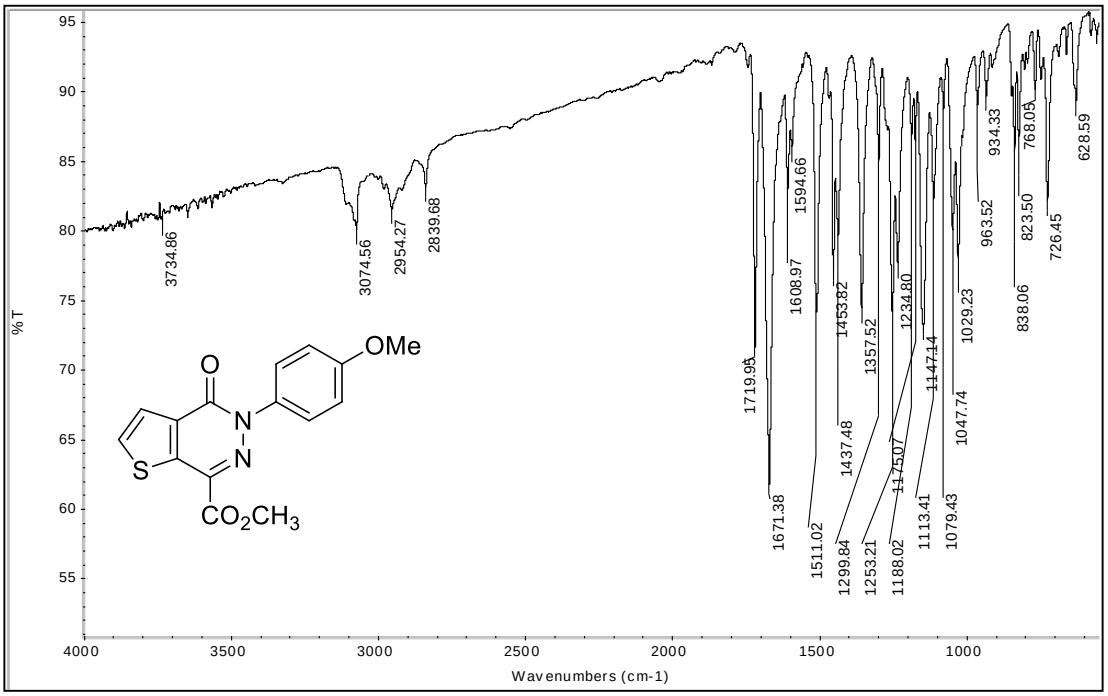

Figure A 21 IR spectrum of compound **73d**

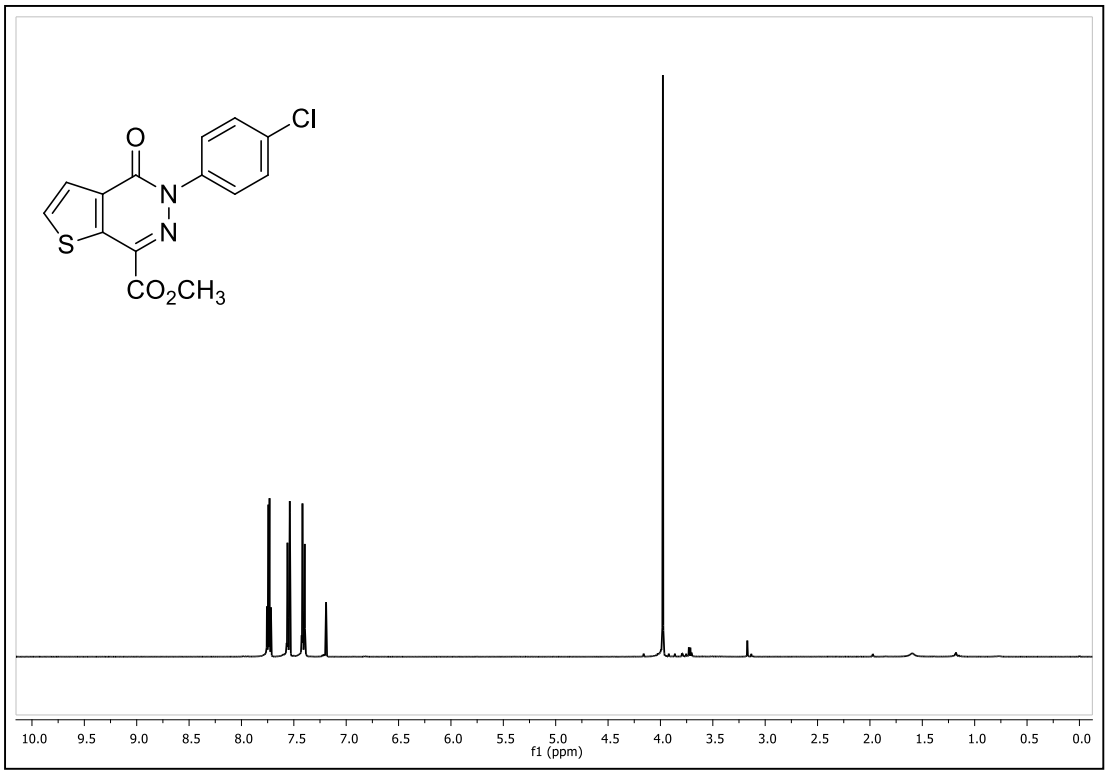

Figure A 22 ^{1}H NMR spectrum of compound**73e**

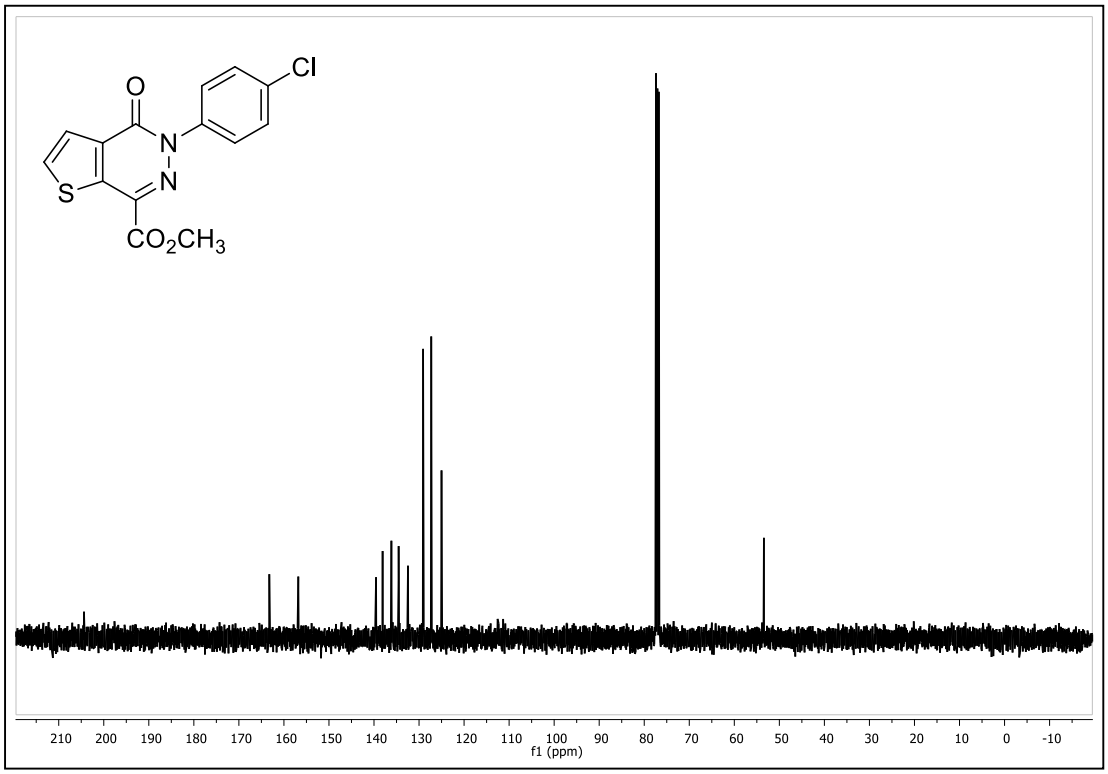

Figure A 23 ^{13}C NMR spectrum of compound**73e**

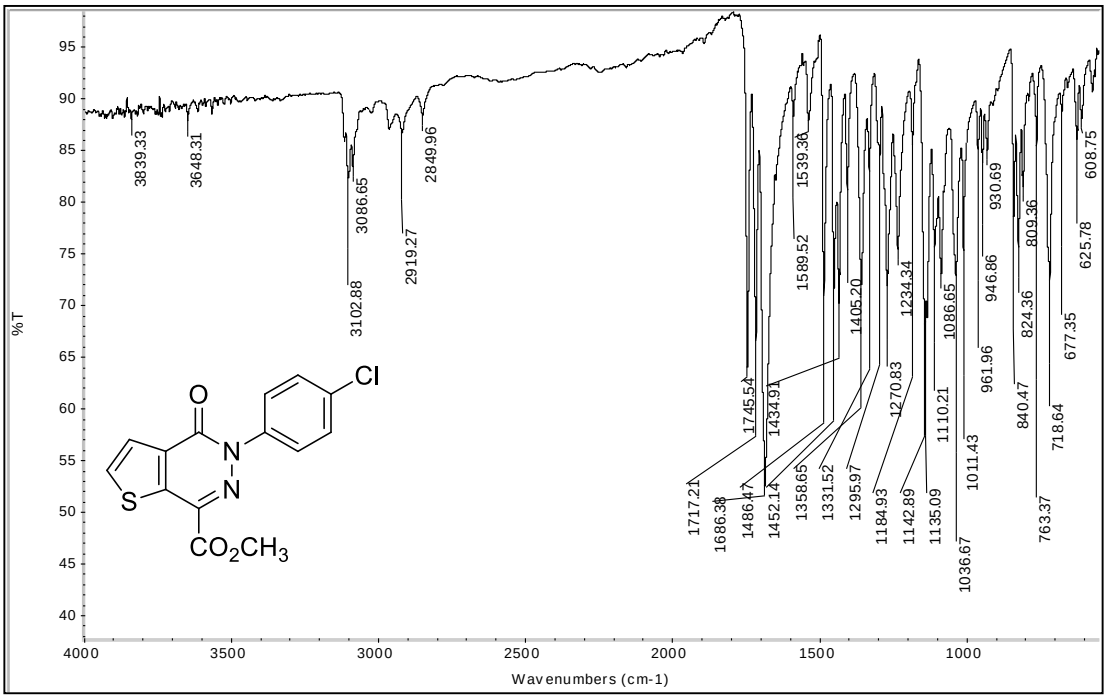

Figure A 24 IR spectrum of compound **73e**

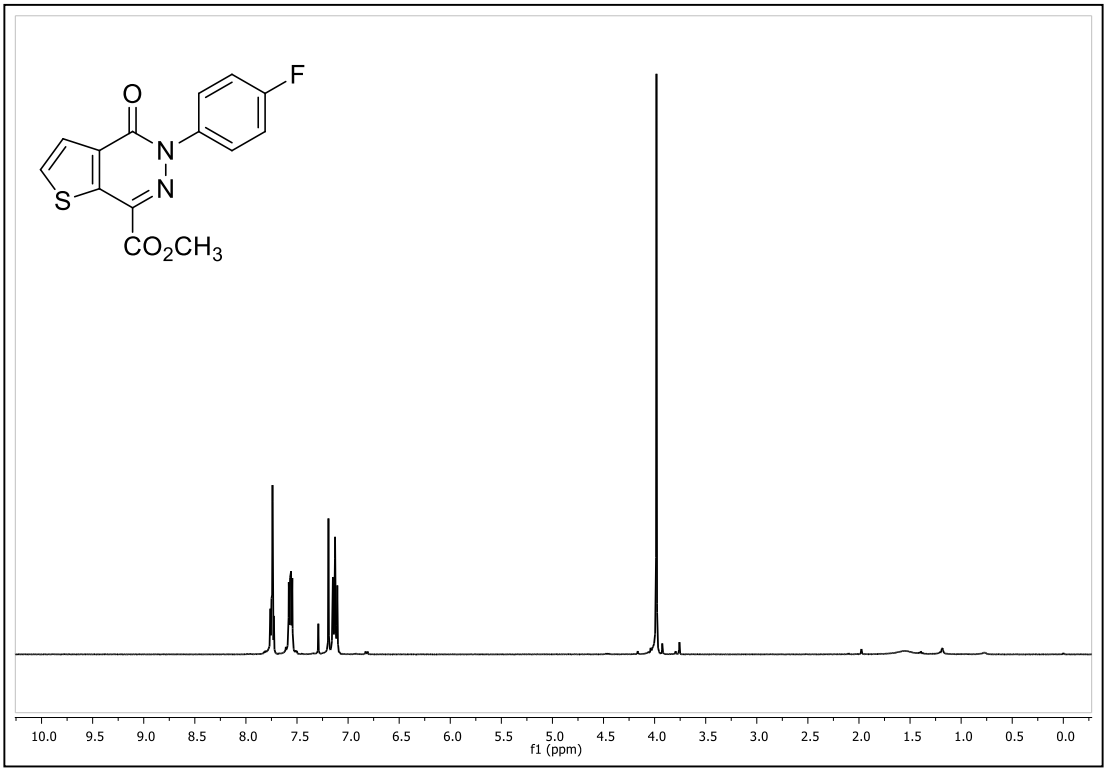

Figure A 25 ^{1}H NMR spectrum of compound**73f**

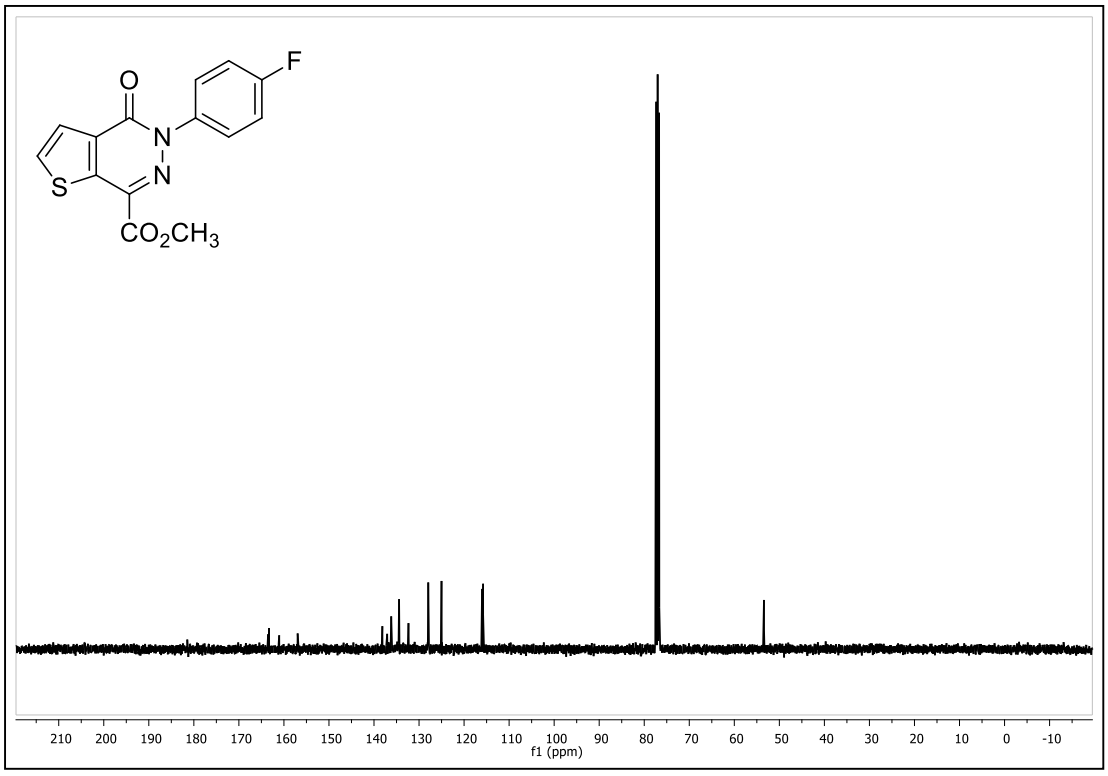

Figure A 26 ^{13}C NMR spectrum of compound**73f**

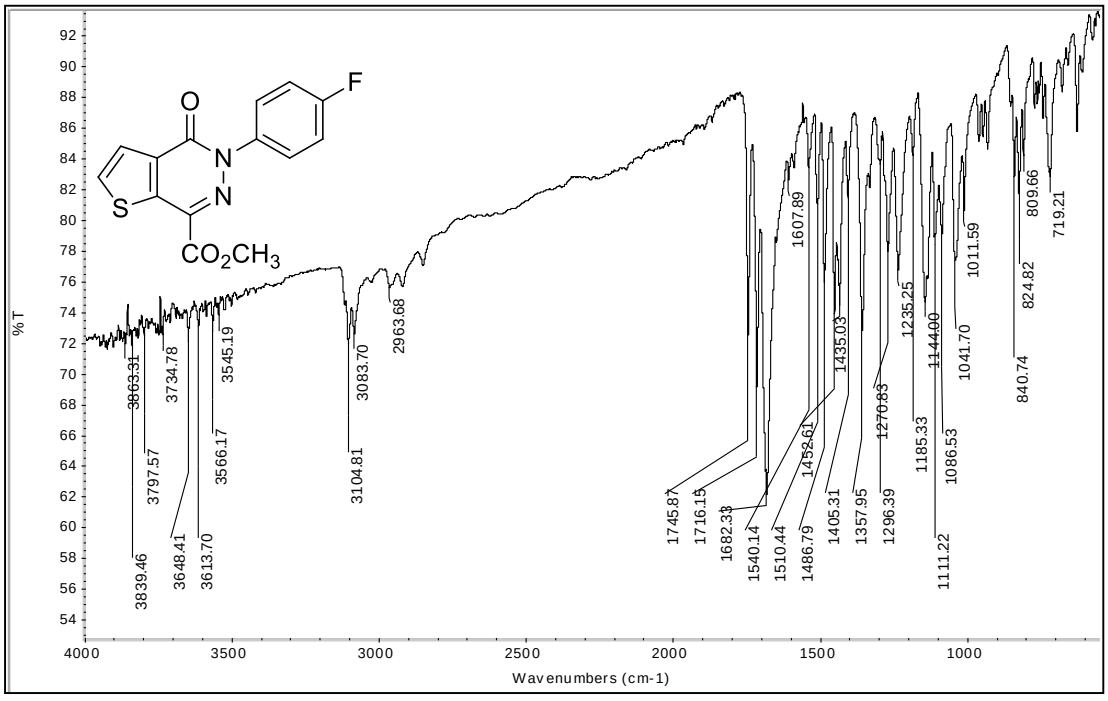

Figure A 27 IR spectrum of compound **73f**

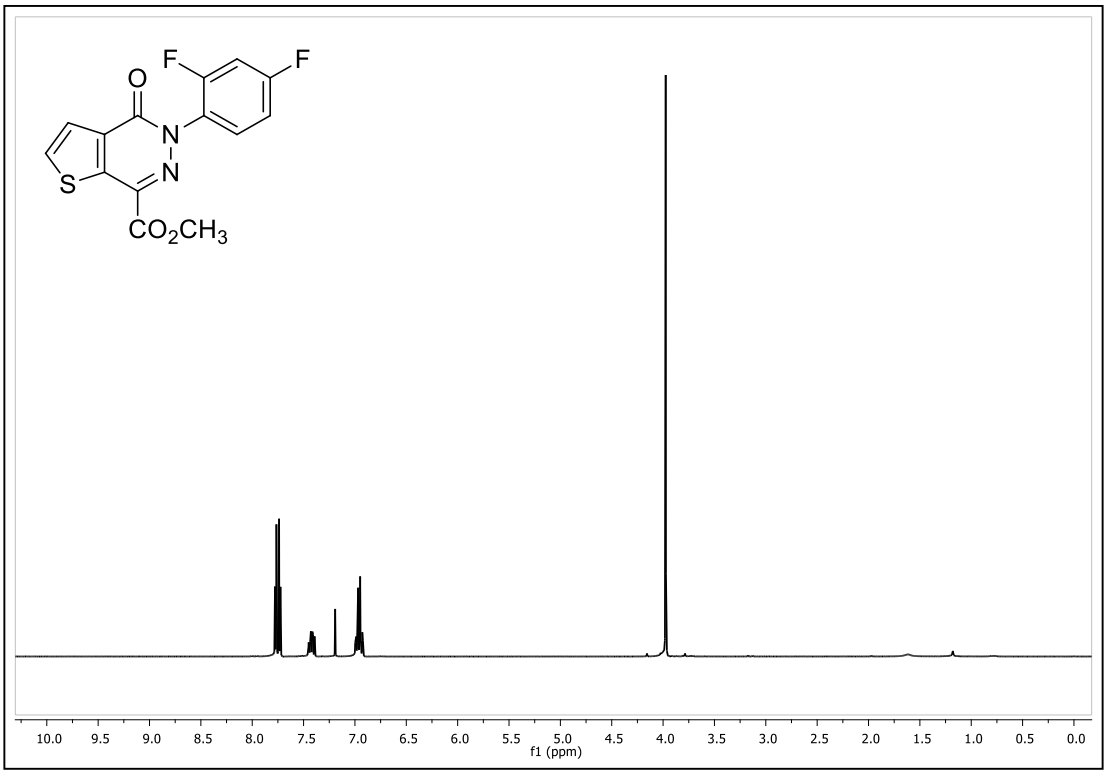

Figure A 28 ^{1}H NMR spectrum of compound**73g**

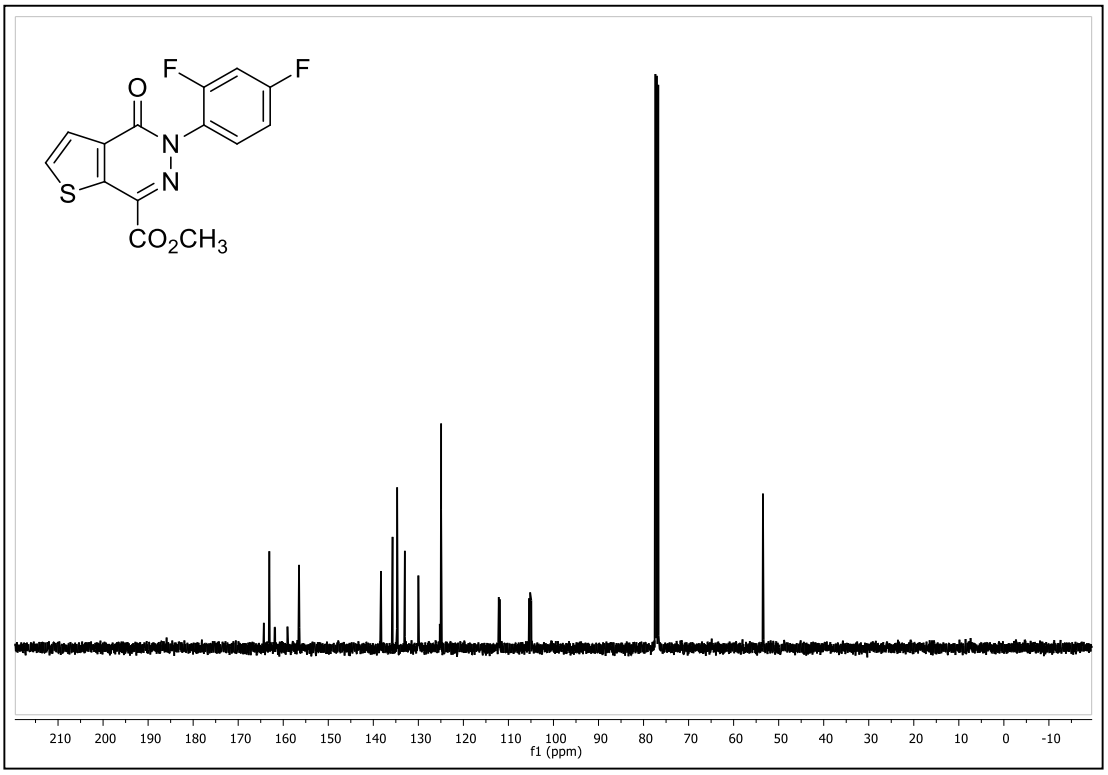

Figure A 29 ^{13}C NMR spectrum of compound**73g**

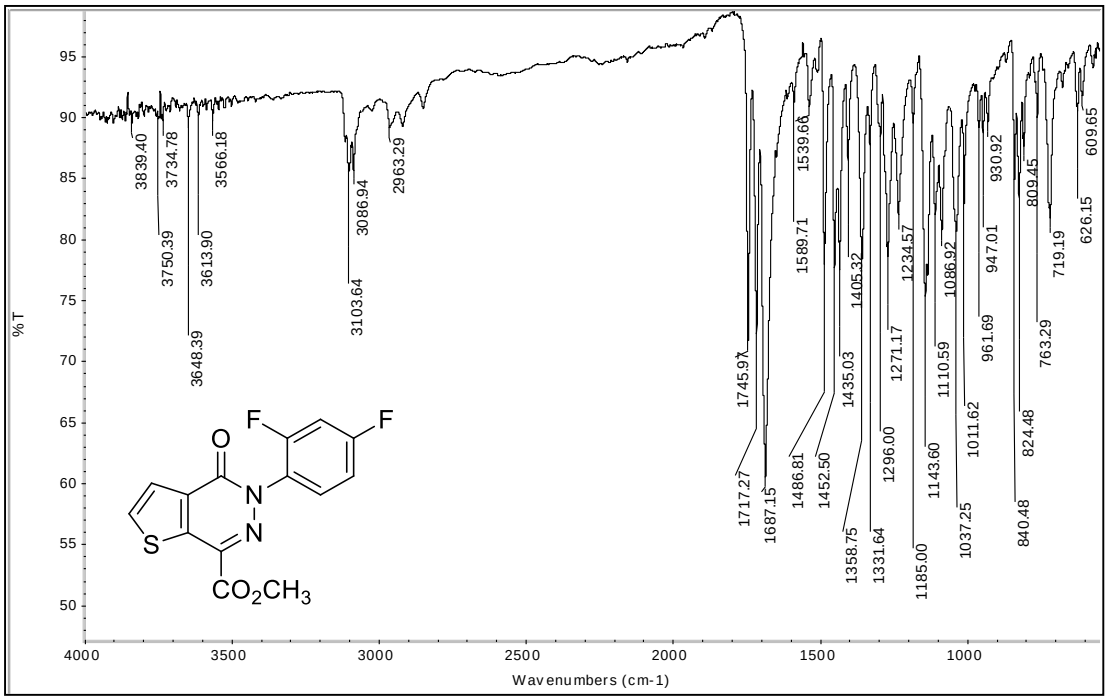

Figure A 30 IR spectrum of compound **73g**

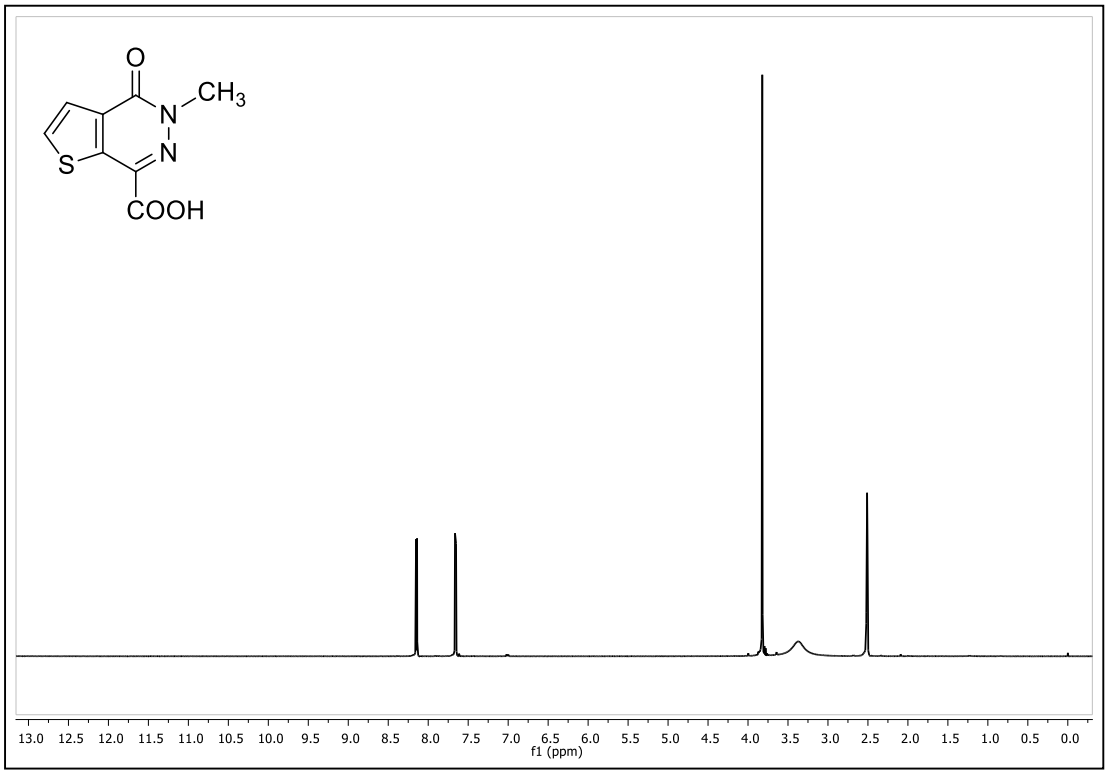

Figure A 31 ^{1}H NMR spectrum of compound**74a**

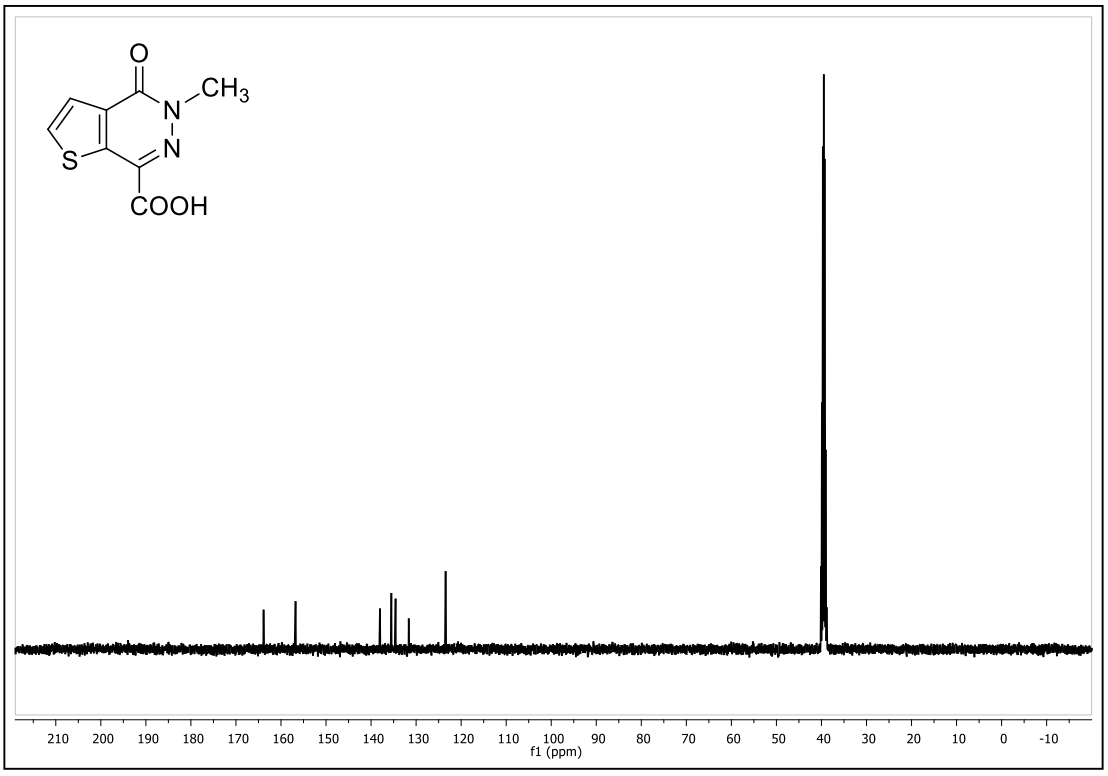

Figure A 32 ^{13}C NMR spectrum of compound**74a**

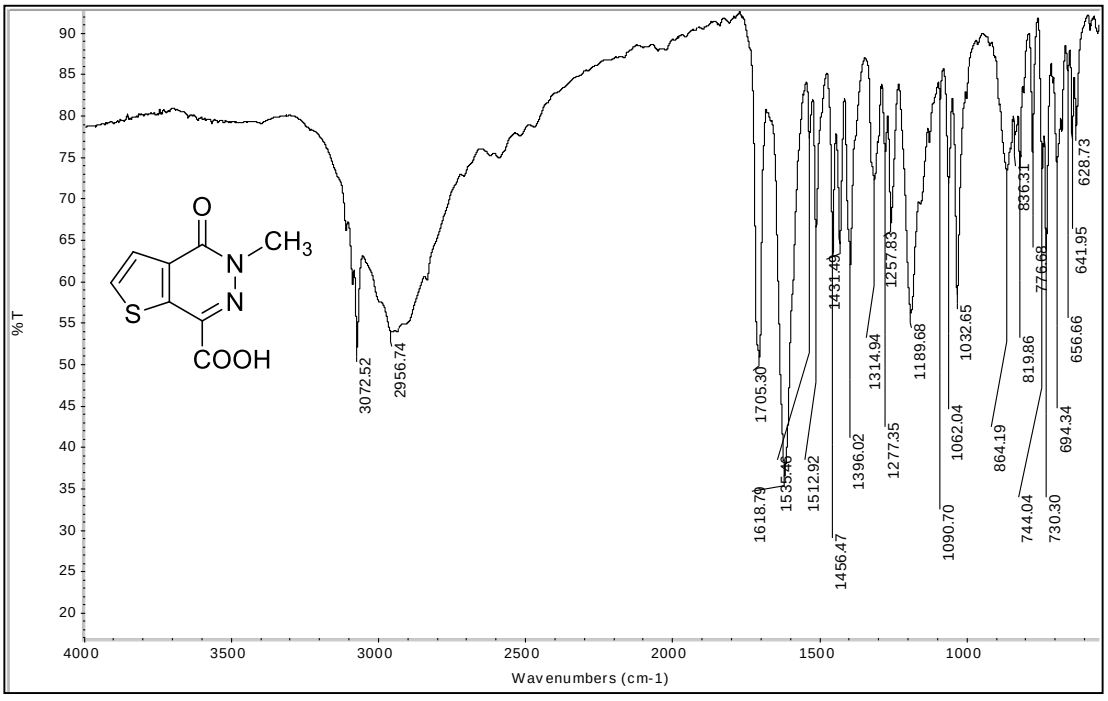

Figure A 33 IR spectrum of compound **74a**

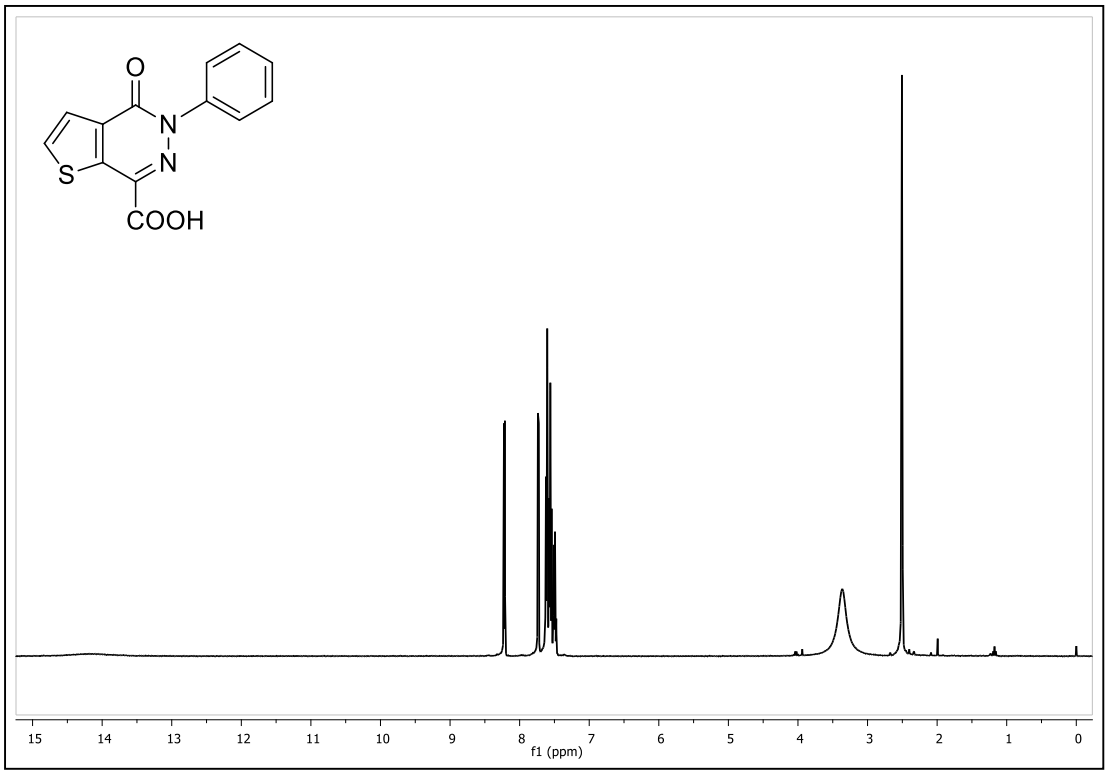

Figure A 34 ^{1}H NMR spectrum of compound**74b**

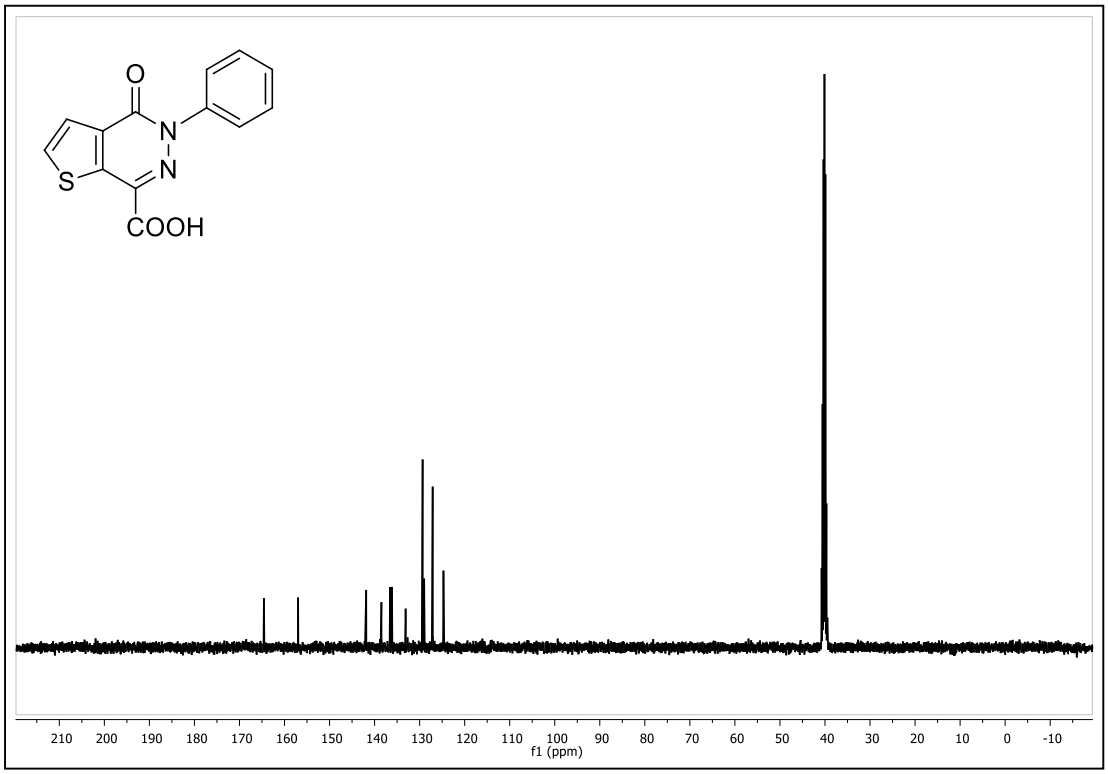

Figure A 35 ^{13}C NMR spectrum of compound **74b**

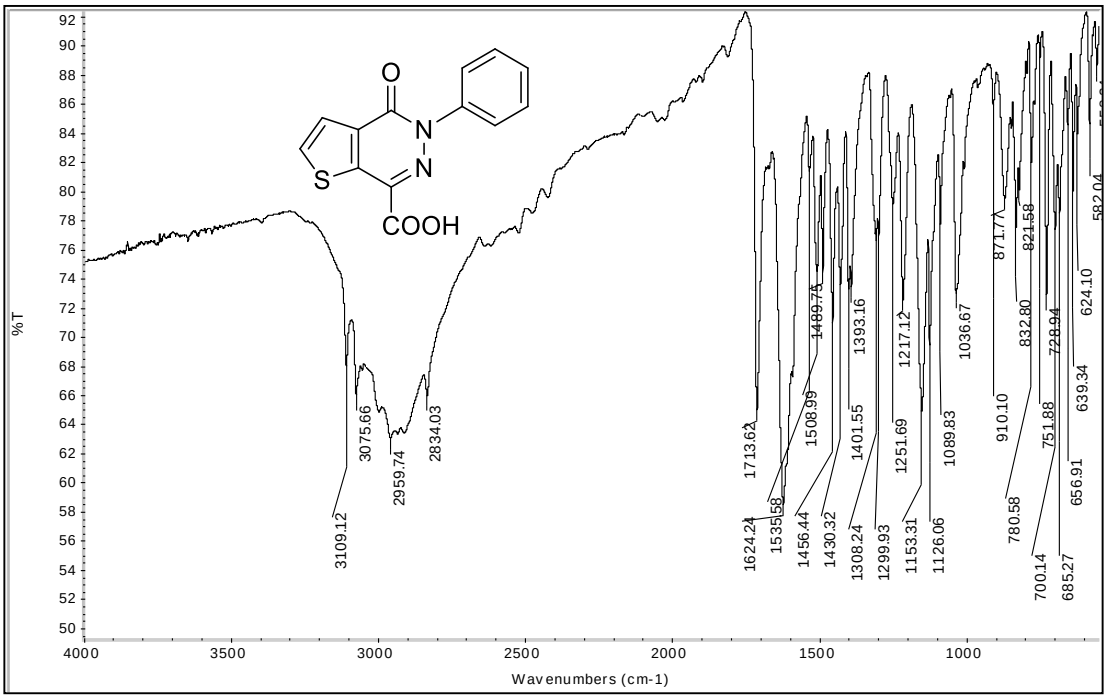

Figure A 36 IR spectrum of compound **74b**

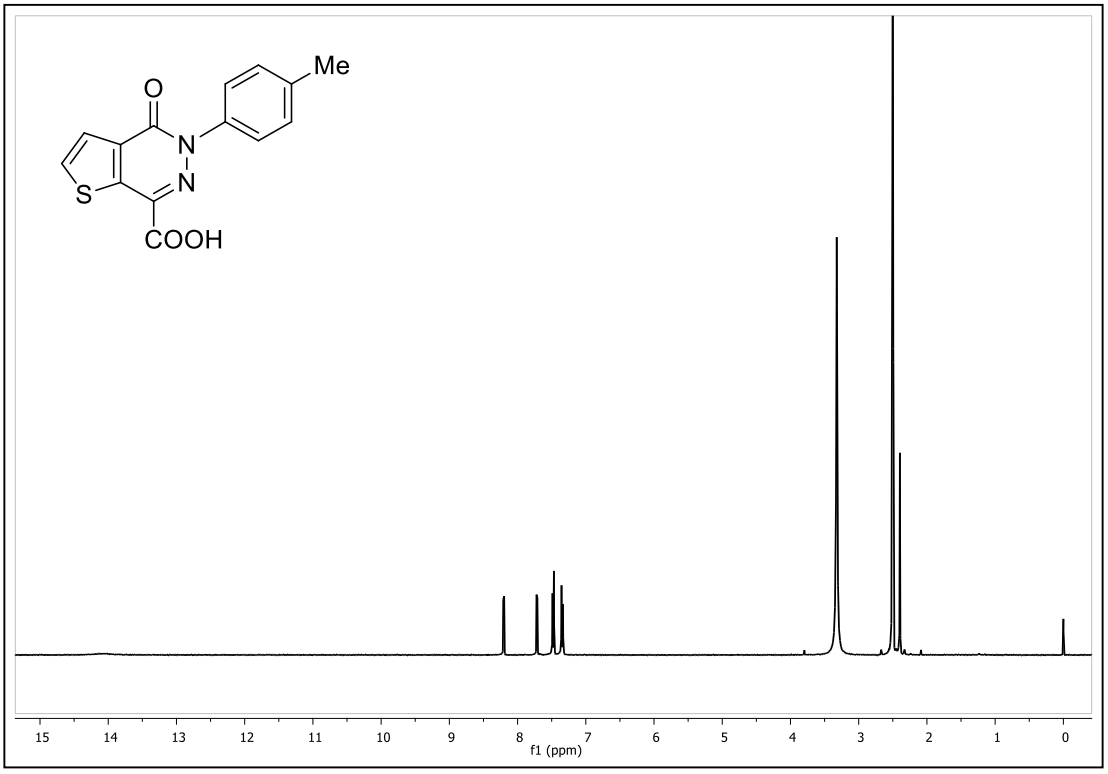

Figure A 37 ^{1}H NMR spectrum of compound **74c**

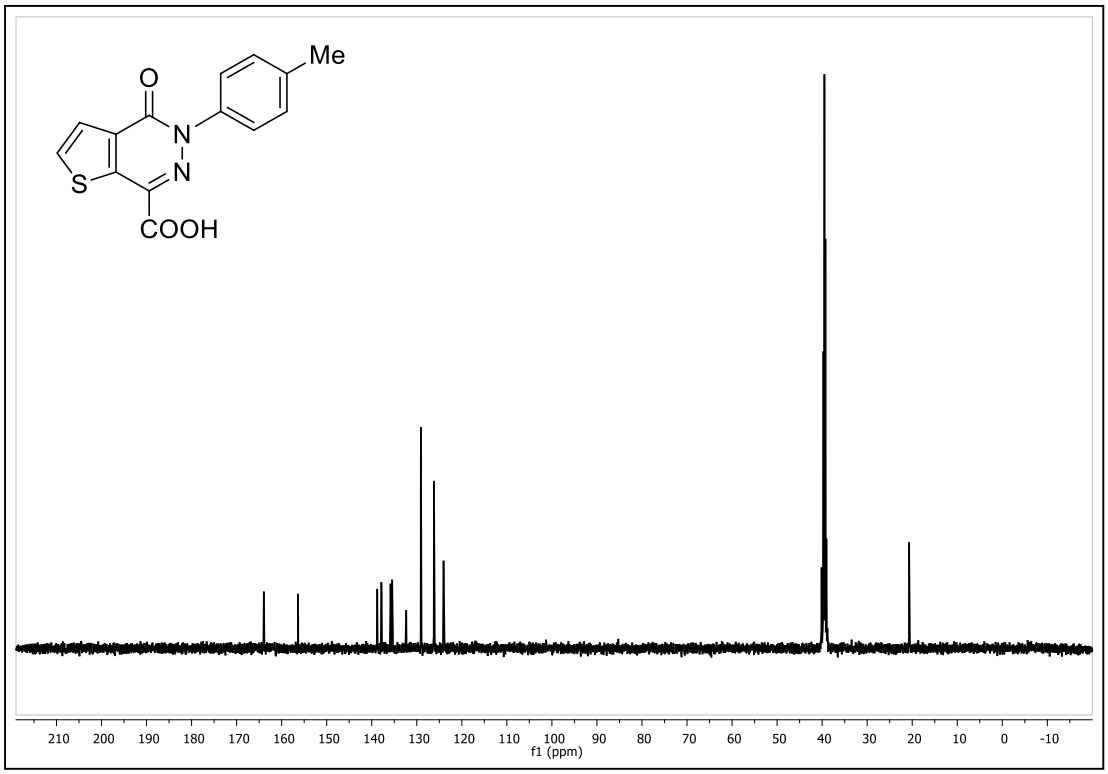

Figure A 38 ^{13}C NMR spectrum of compound **74c**

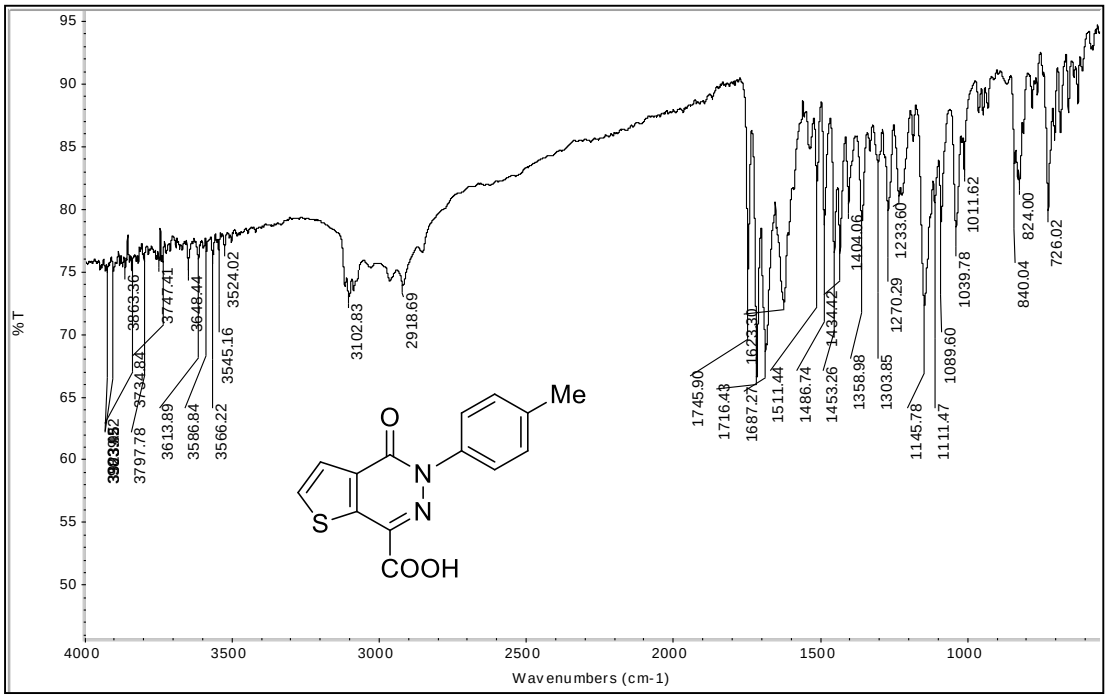

Figure A 39 IR spectrum of compound **74c**

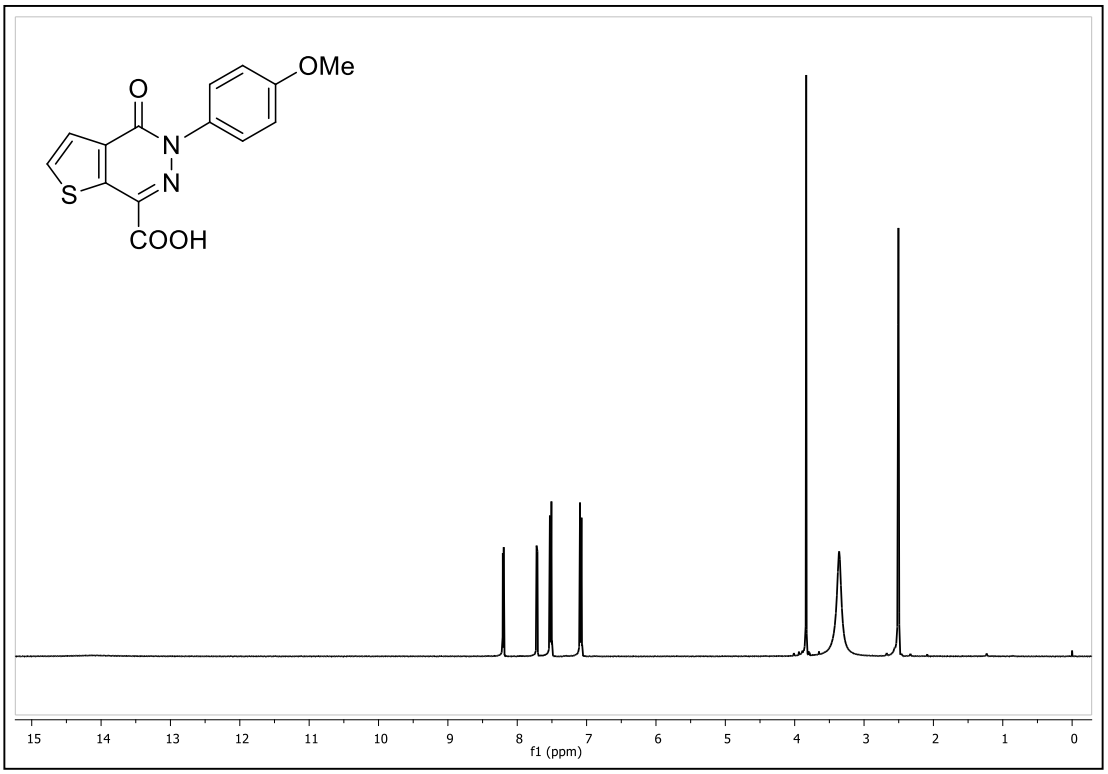

Figure A 40 ^{1}H NMR spectrum of compound **74d**

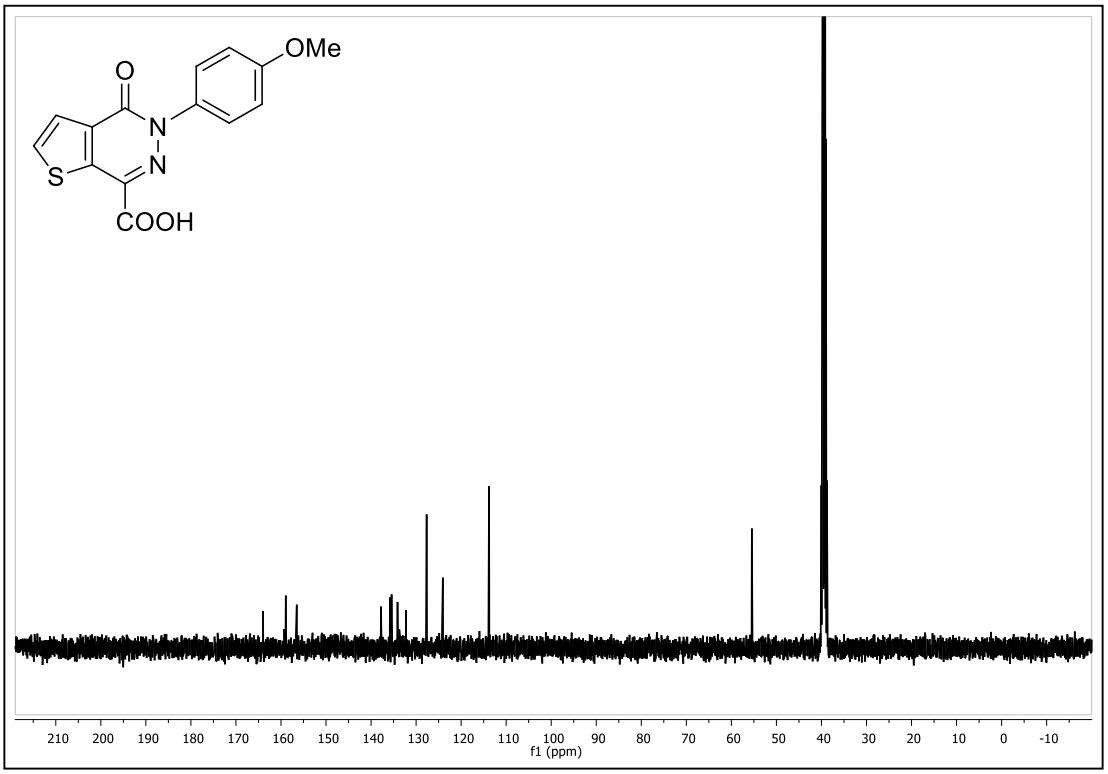

Figure A 41 ^{13}C NMR spectrum of compound **74d**

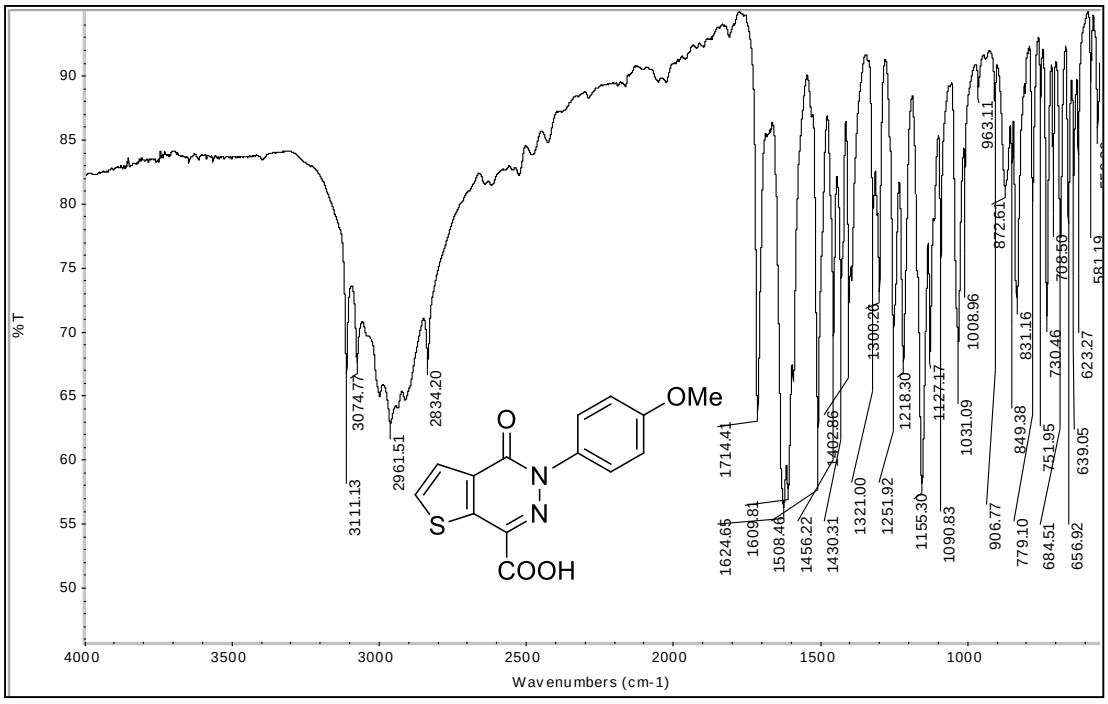

Figure A 42 IR spectrum of compound **74d**

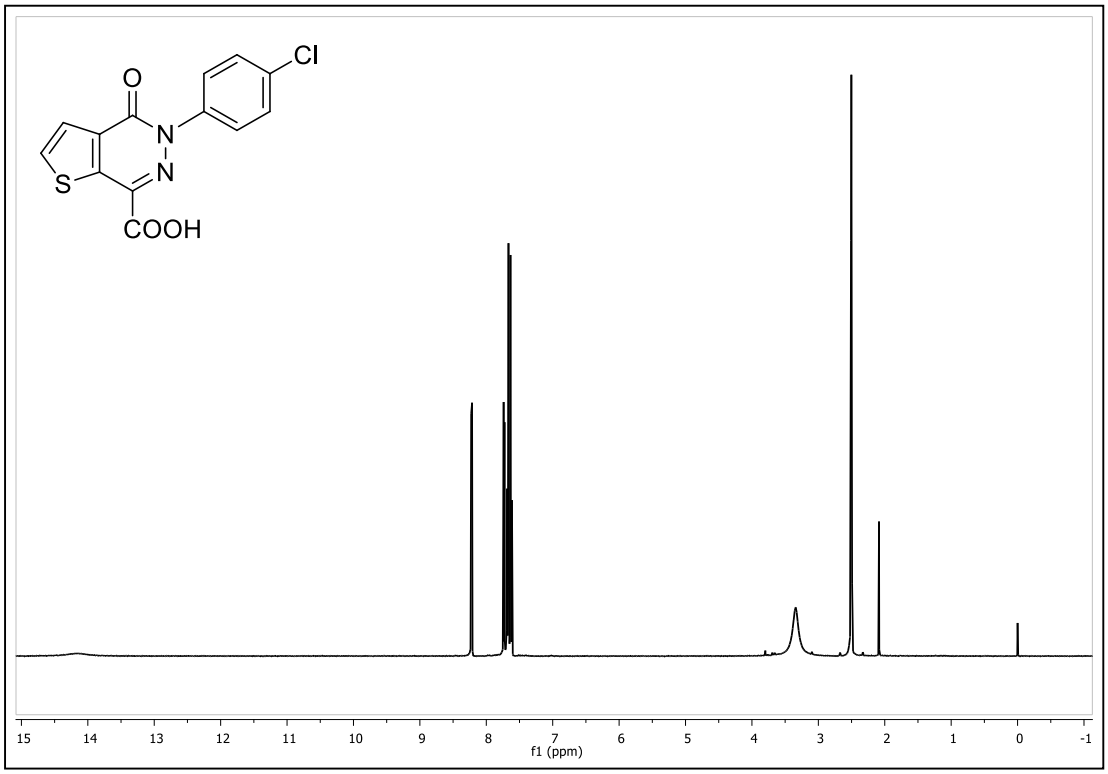

Figure A 43 ^{1}H NMR spectrum of compound **74e**

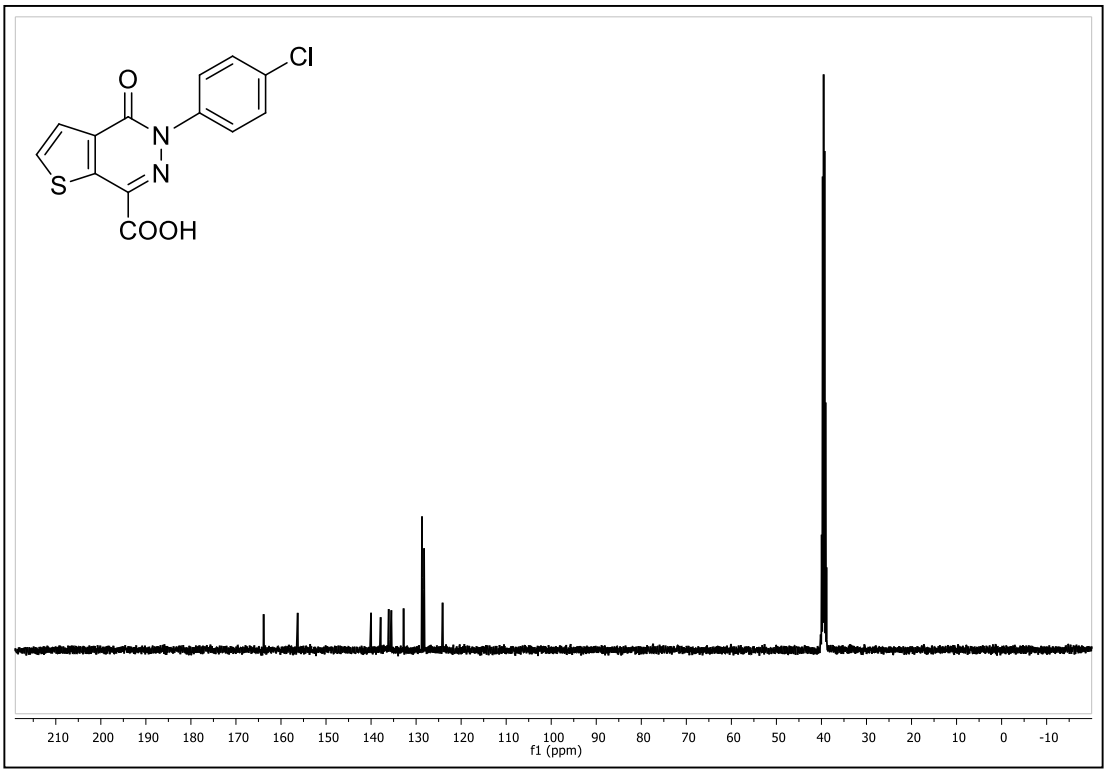

Figure A 44 ^{13}C NMR spectrum of compound **74e**

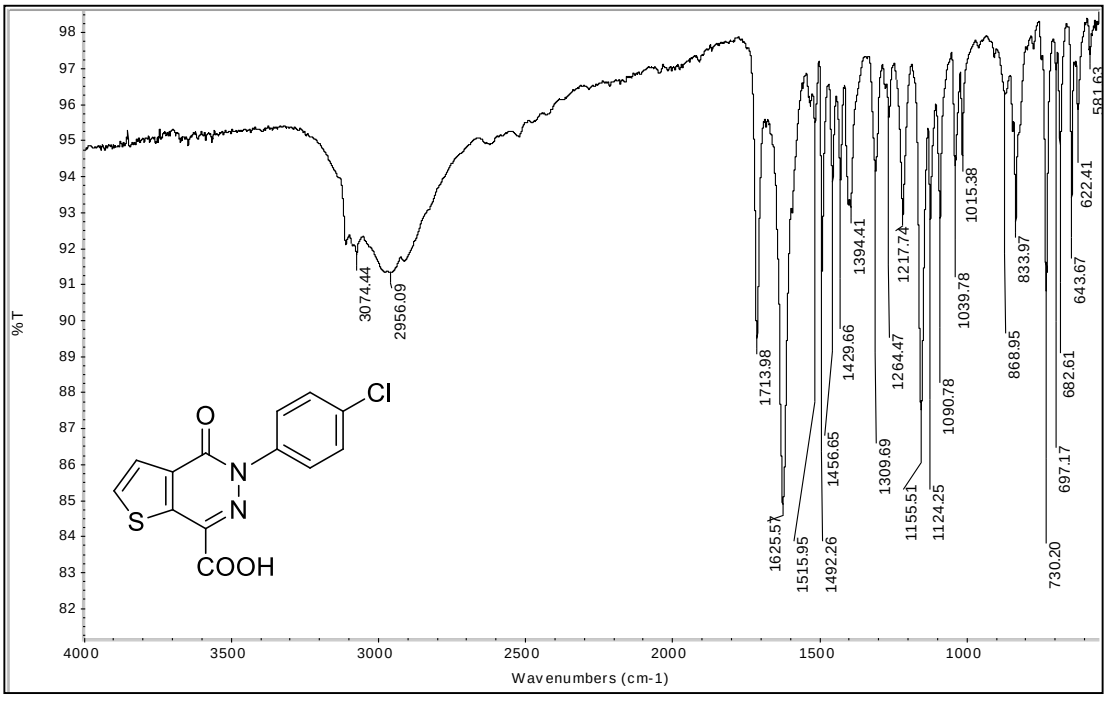

Figure A 45 IR spectrum of compound **74e**

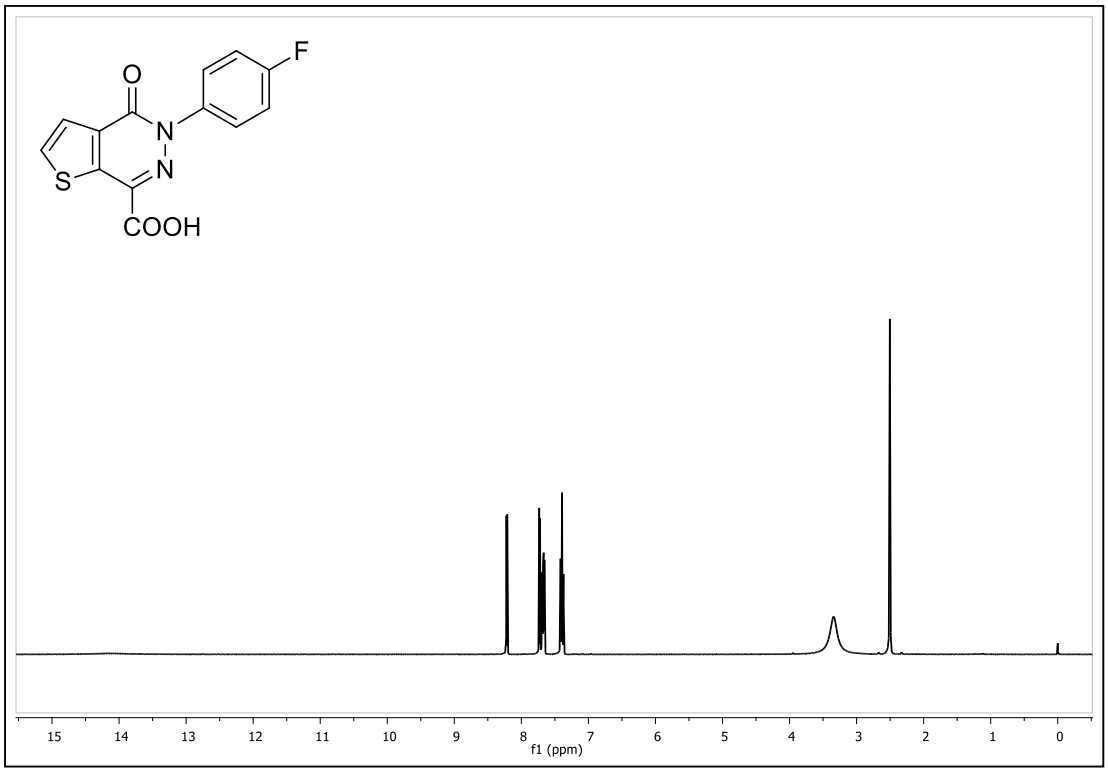

Figure A 46 ^{1}H NMR spectrum of compound **74f**

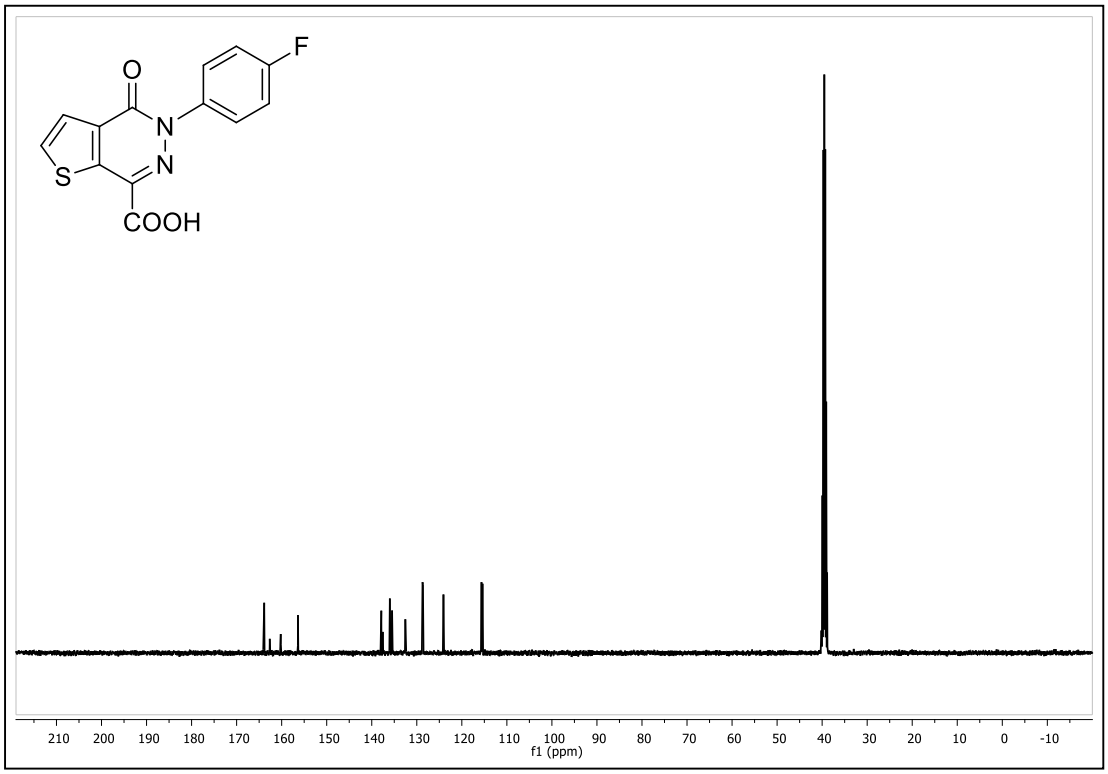

Figure A 47 ^{13}C NMR spectrum of compound **74f**

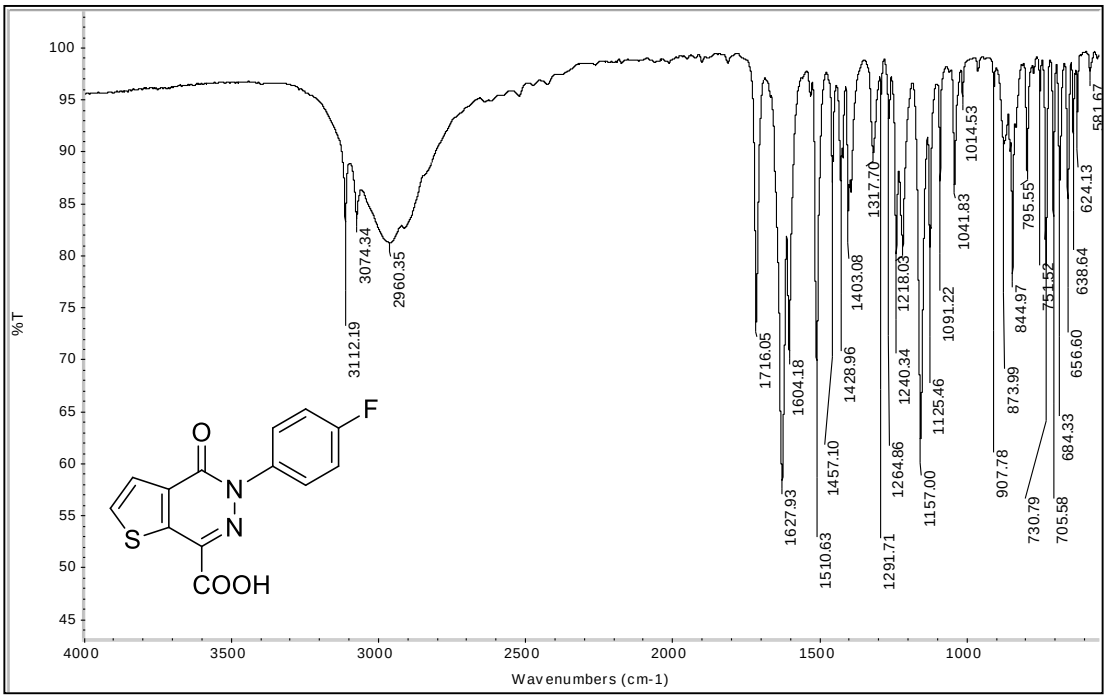

Figure A 48 IR spectrum of compound **74f**

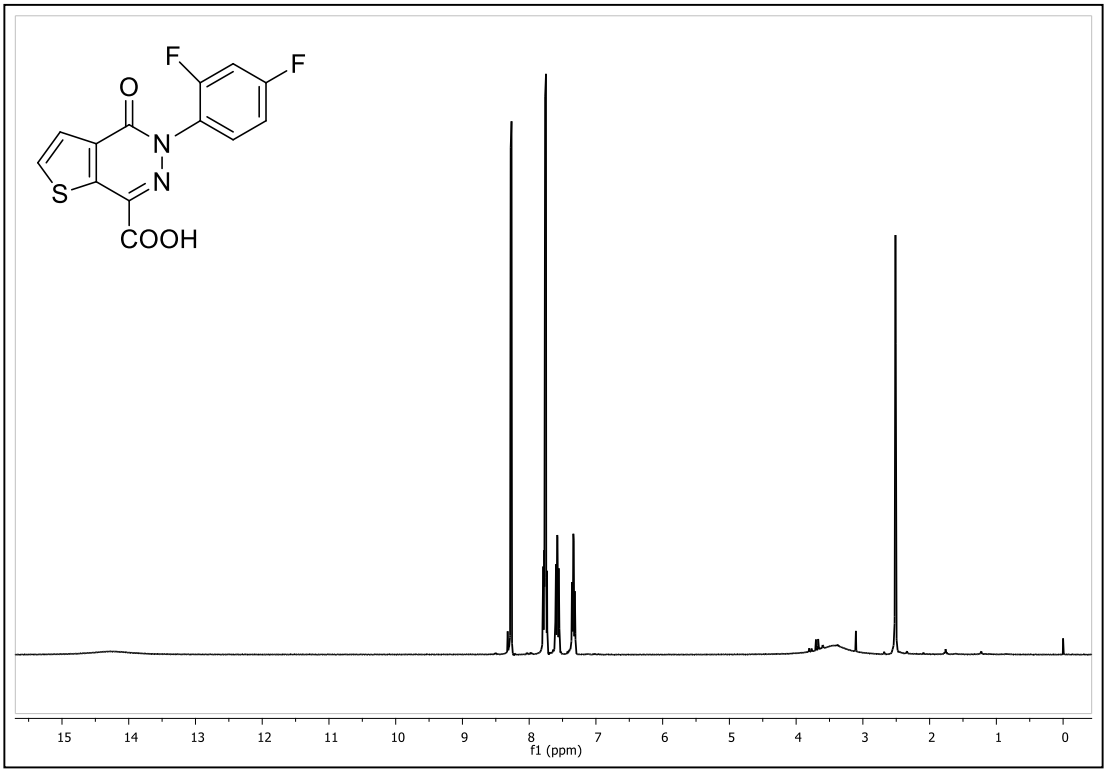

Figure A 49 ^{1}H NMR spectrum of compound **74g**

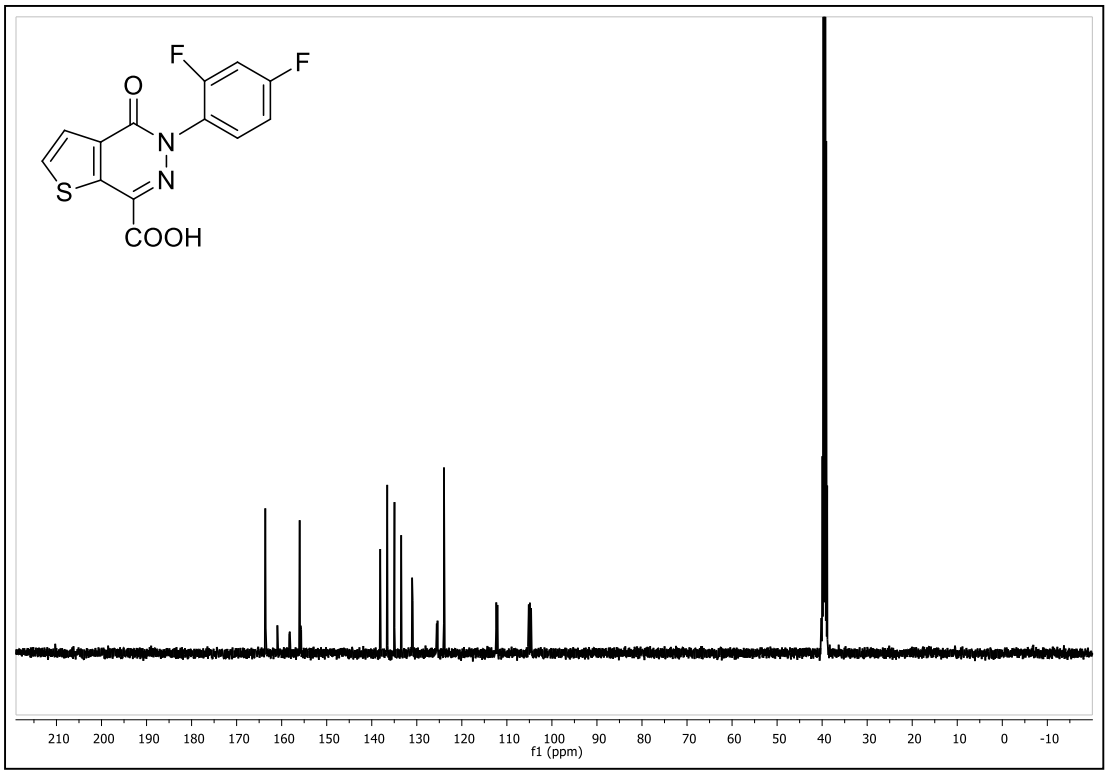

Figure A 50 ^{13}C NMR spectrum of compound **74g**

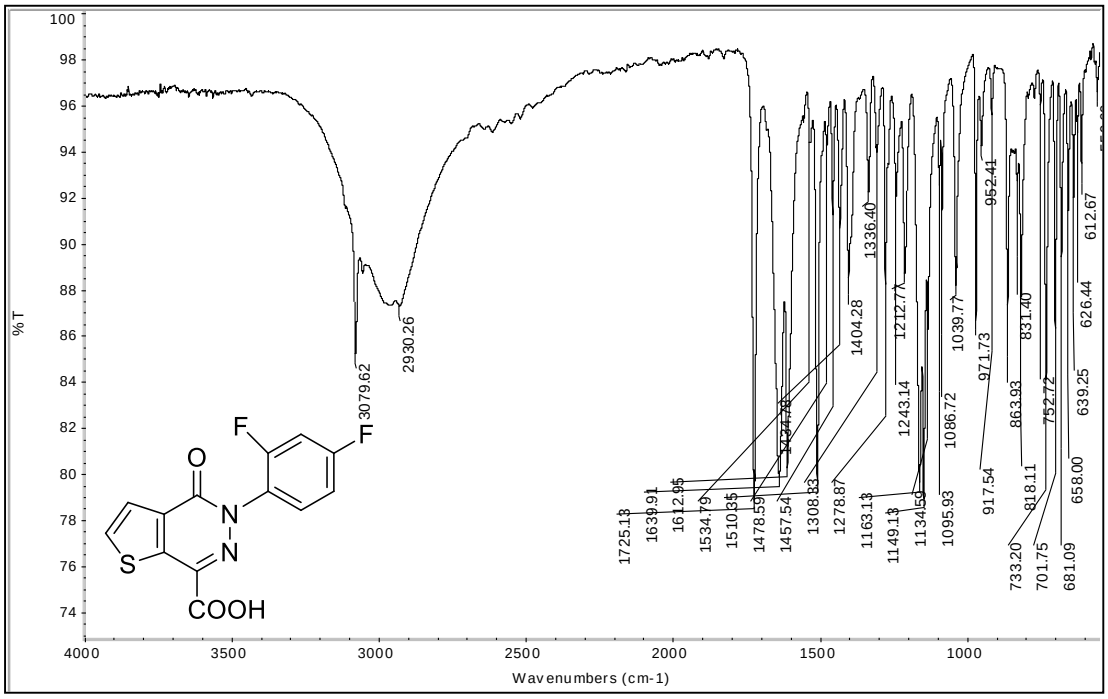

Figure A 51 IR spectrum of compound **74g**

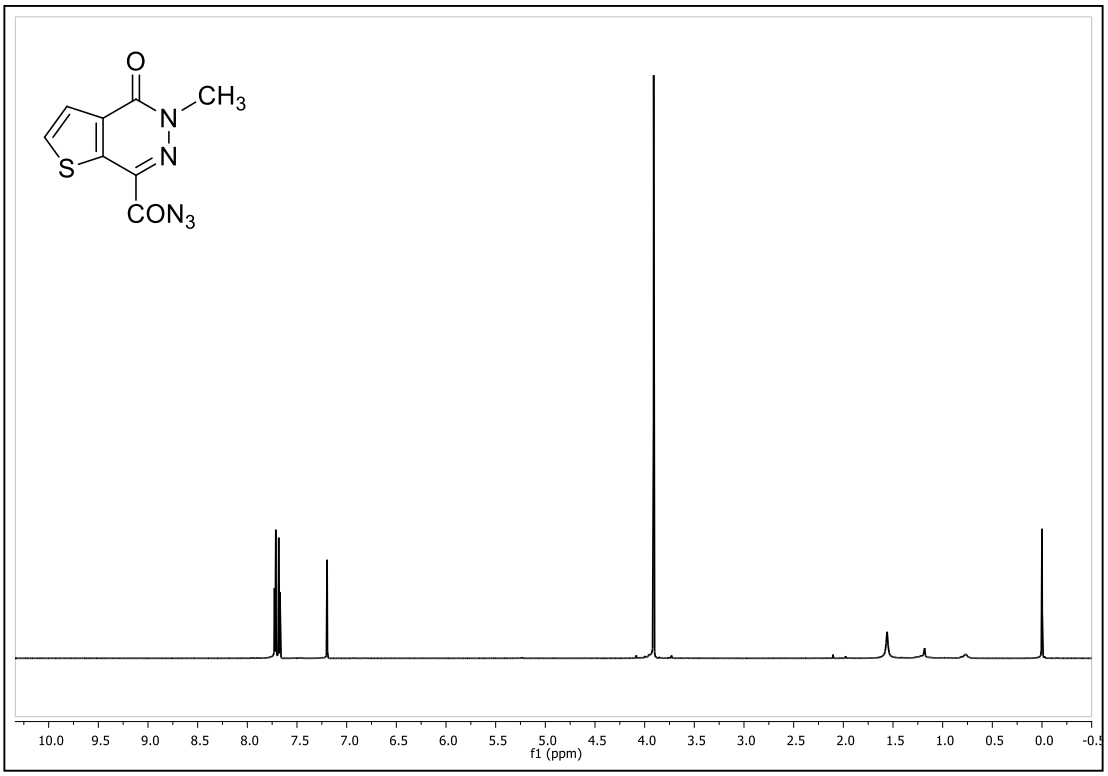

Figure A 52 ^{1}H NMR spectrum of compound **55a**

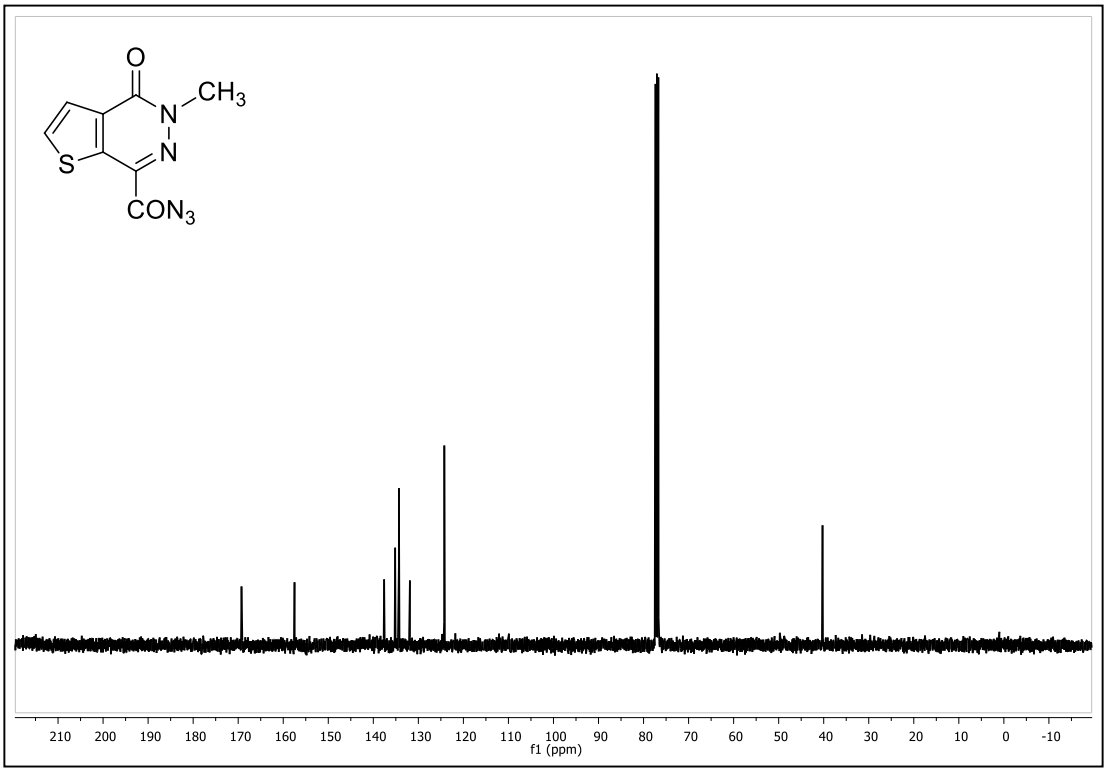

Figure A 53 ^{13}C NMR spectrum of compound **55a**

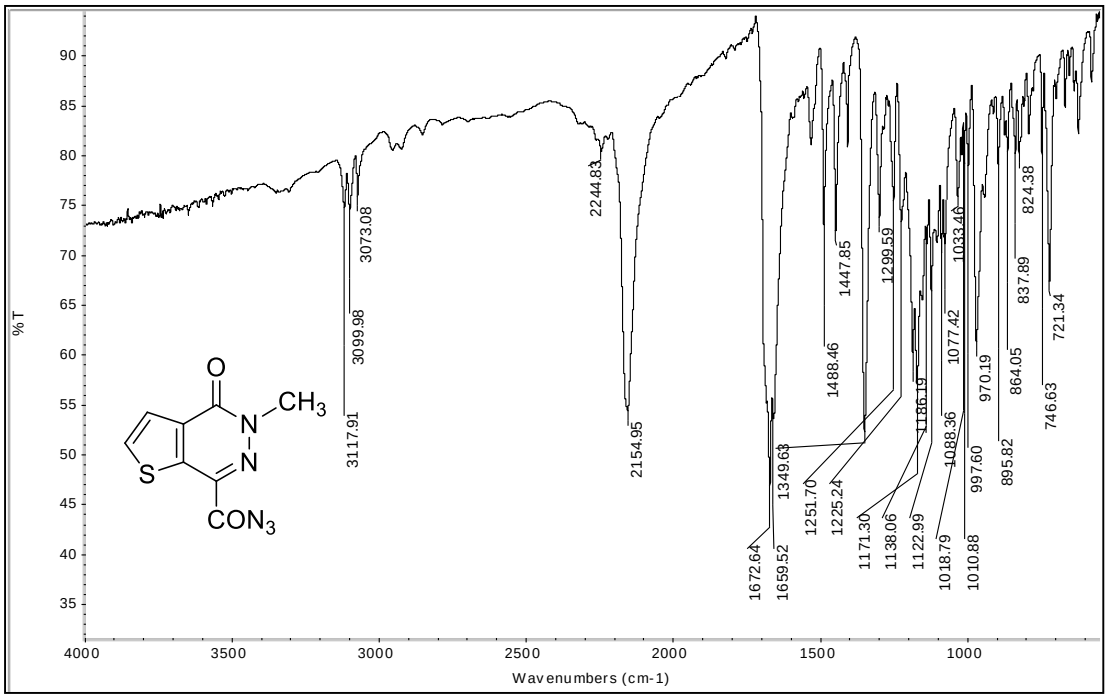

Figure A 54 IR spectrum of compound **55a**

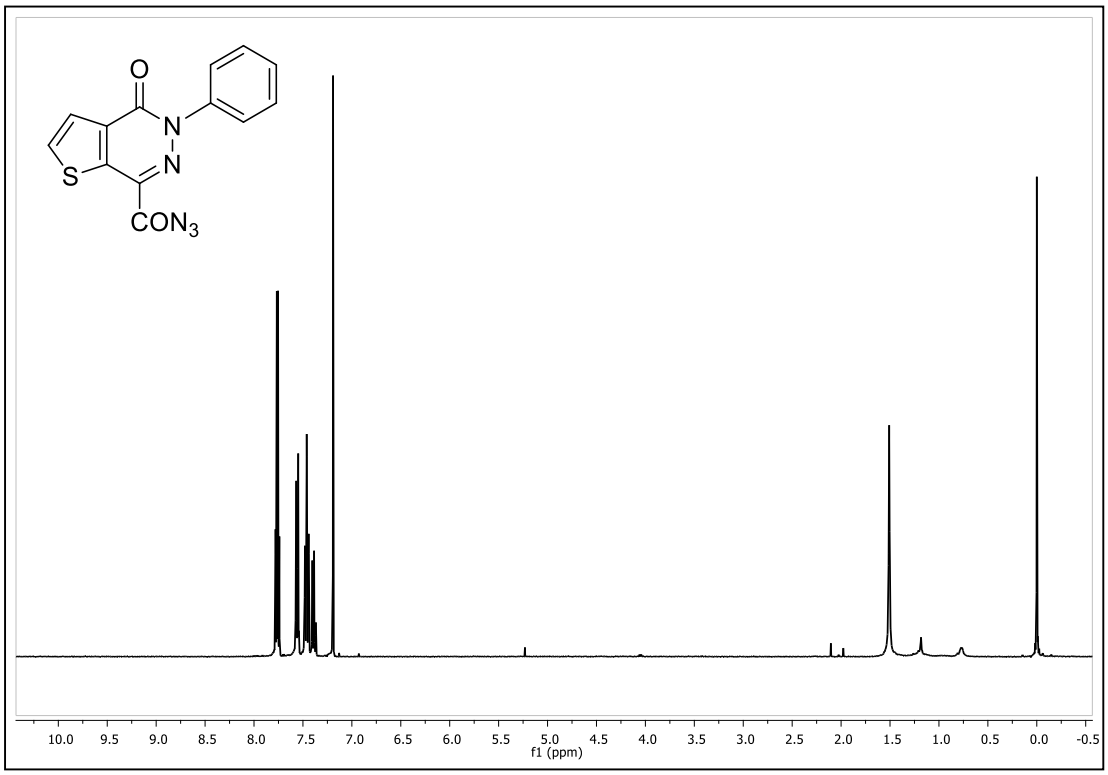

Figure A 55 ^{1}H NMR spectrum of compound **55b**

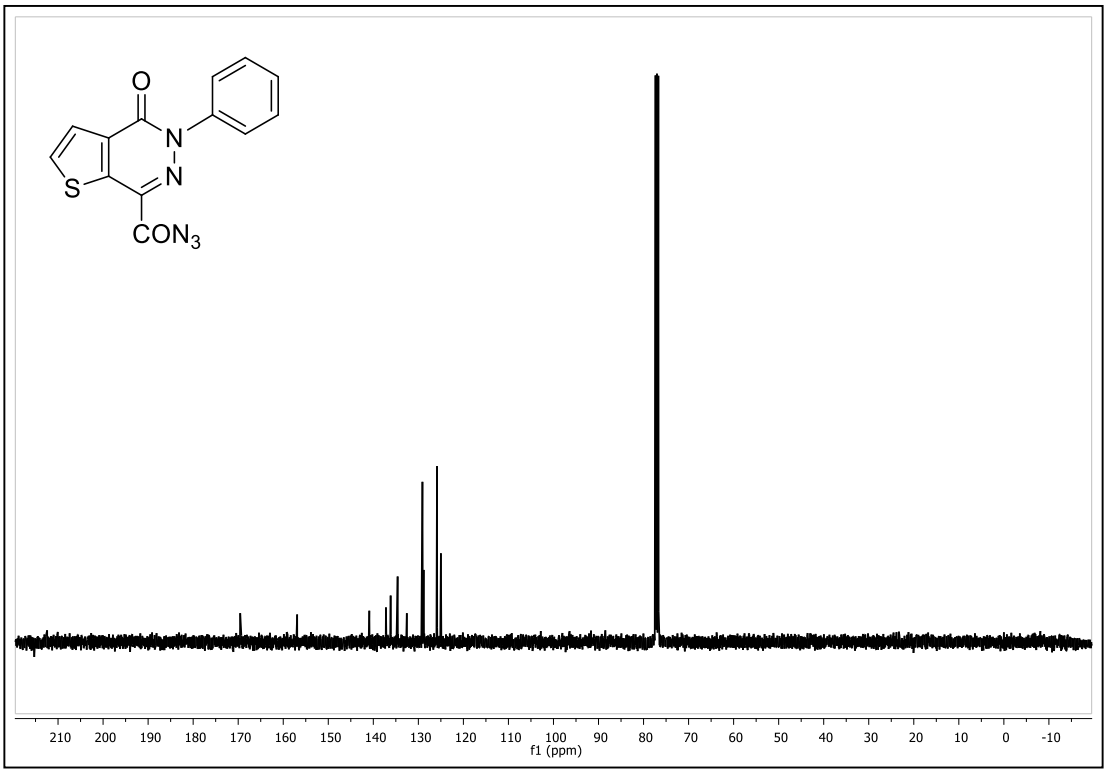

Figure A 56 ^{13}C NMR spectrum of compound **55b**

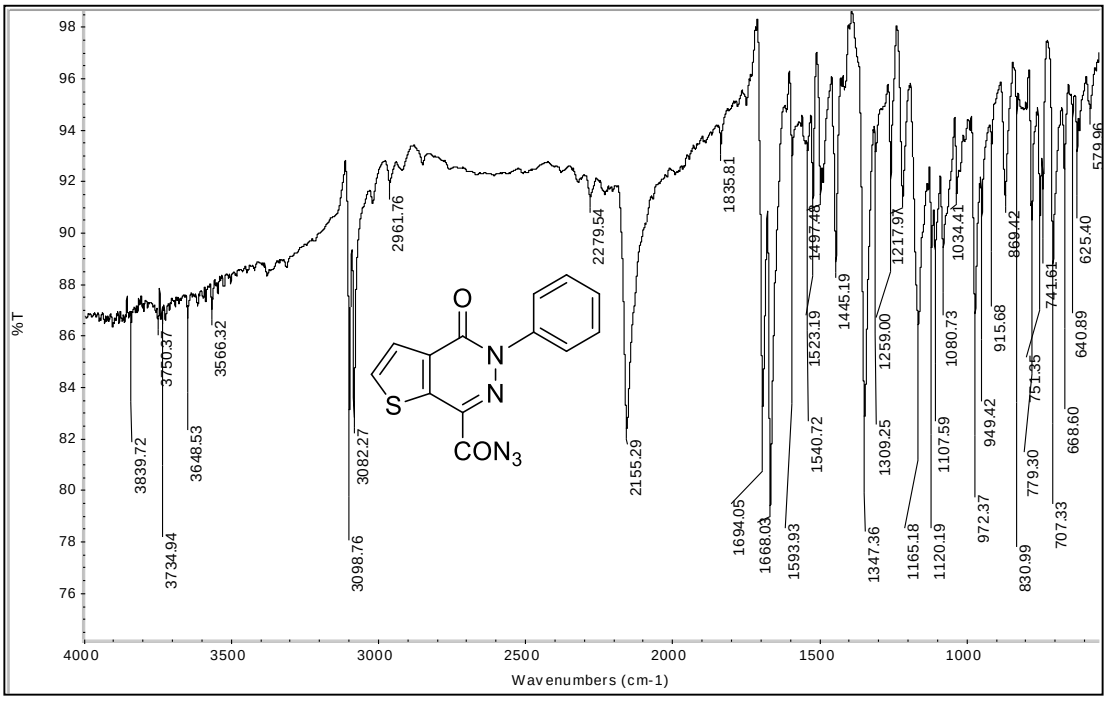

Figure A 57 IR spectrum of compound **55b**

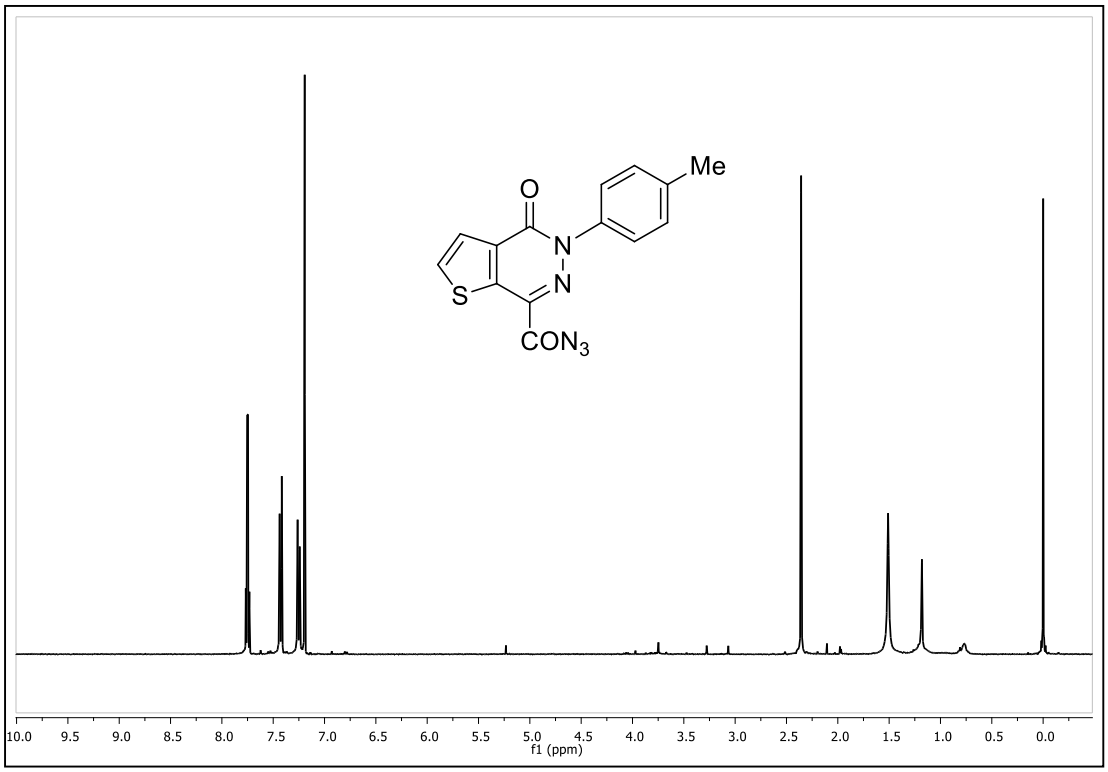

Figure A 58 ^{1}H NMR spectrum of compound **55c**

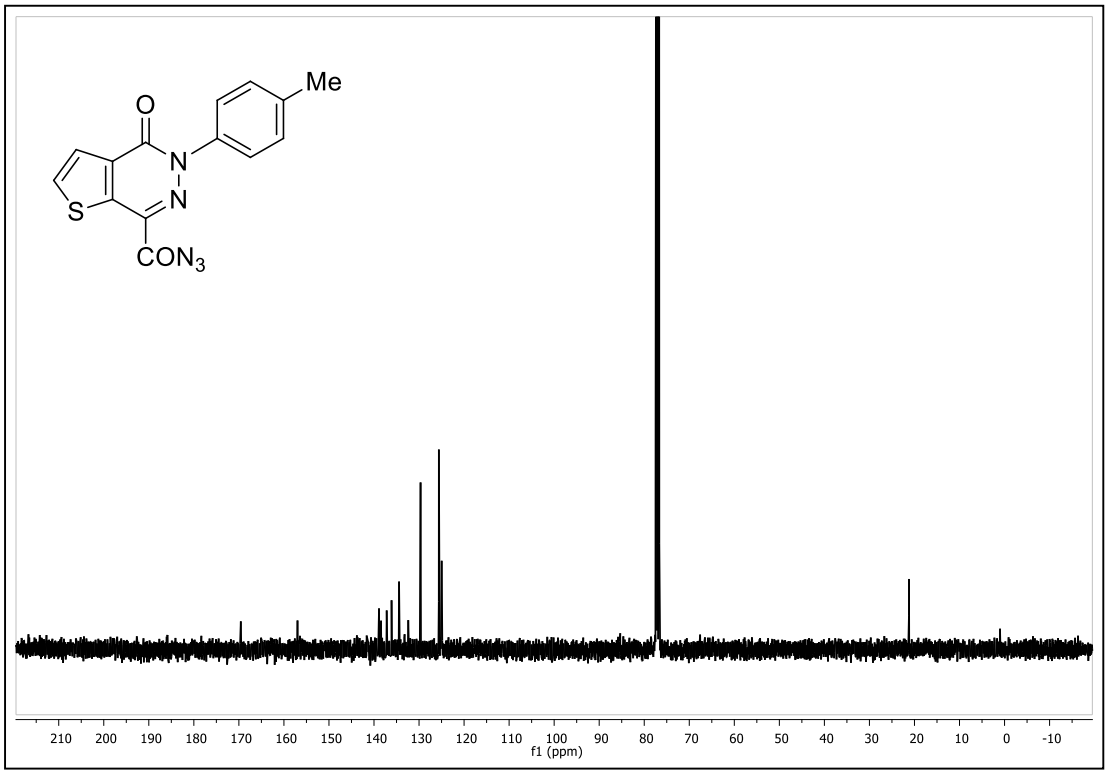

Figure A 59 ^{13}C NMR spectrum of compound **55c**

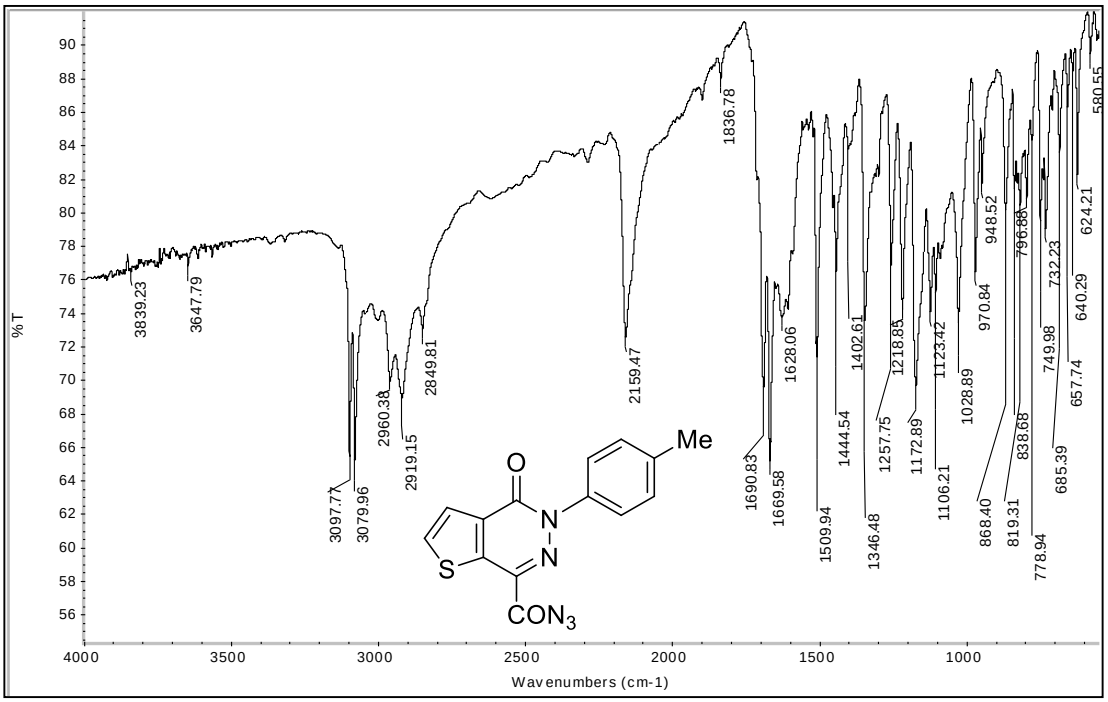

Figure A 60 IR spectrum of compound **55c**

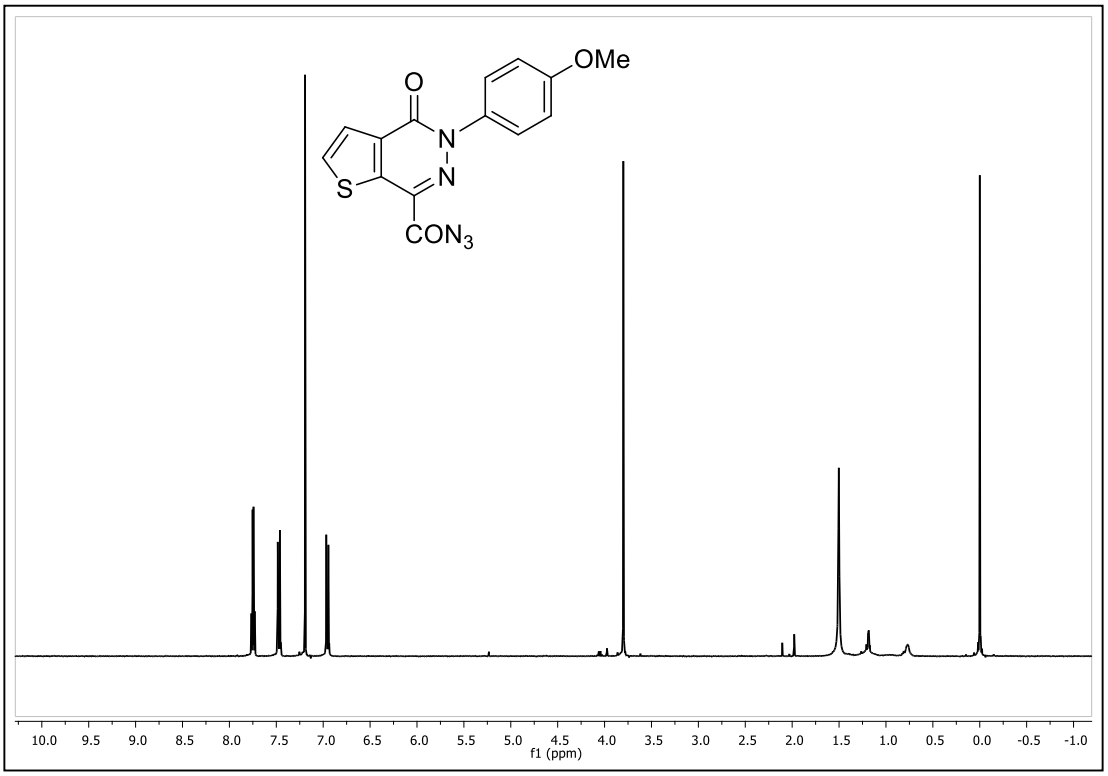

Figure A 61 ^{1}H NMR spectrum of compound **55d**

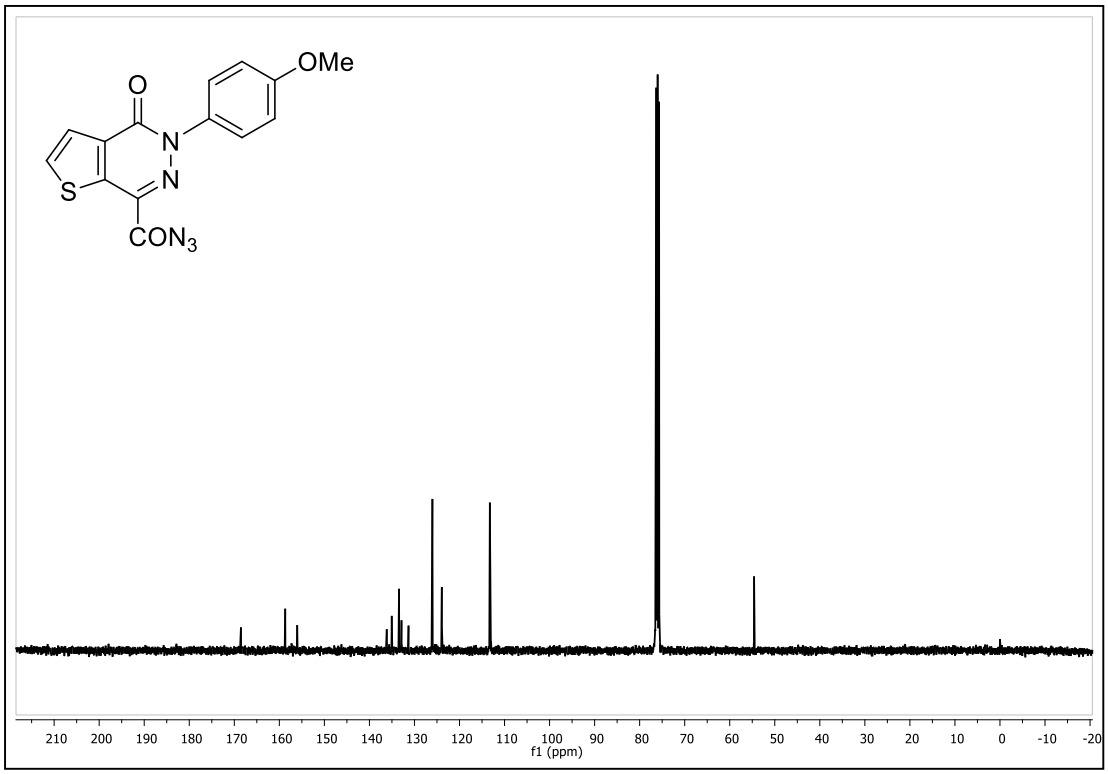

Figure A 62 ^{13}C NMR spectrum of compound **55d**

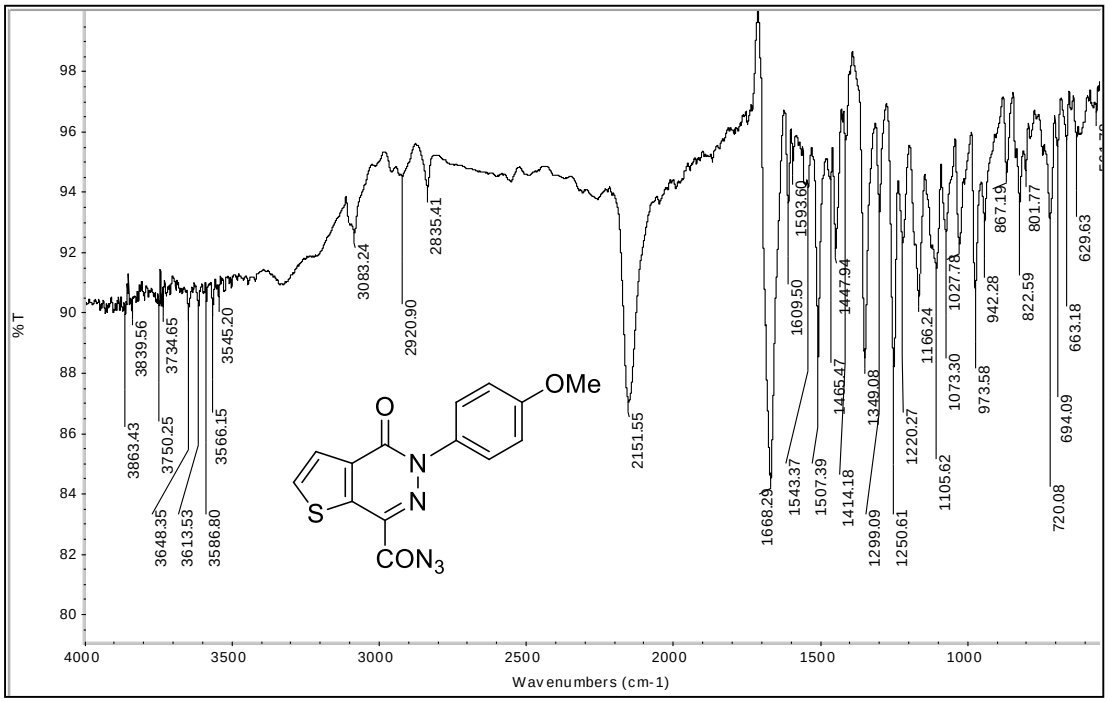

Figure A 63 IR spectrum of compound **55d**

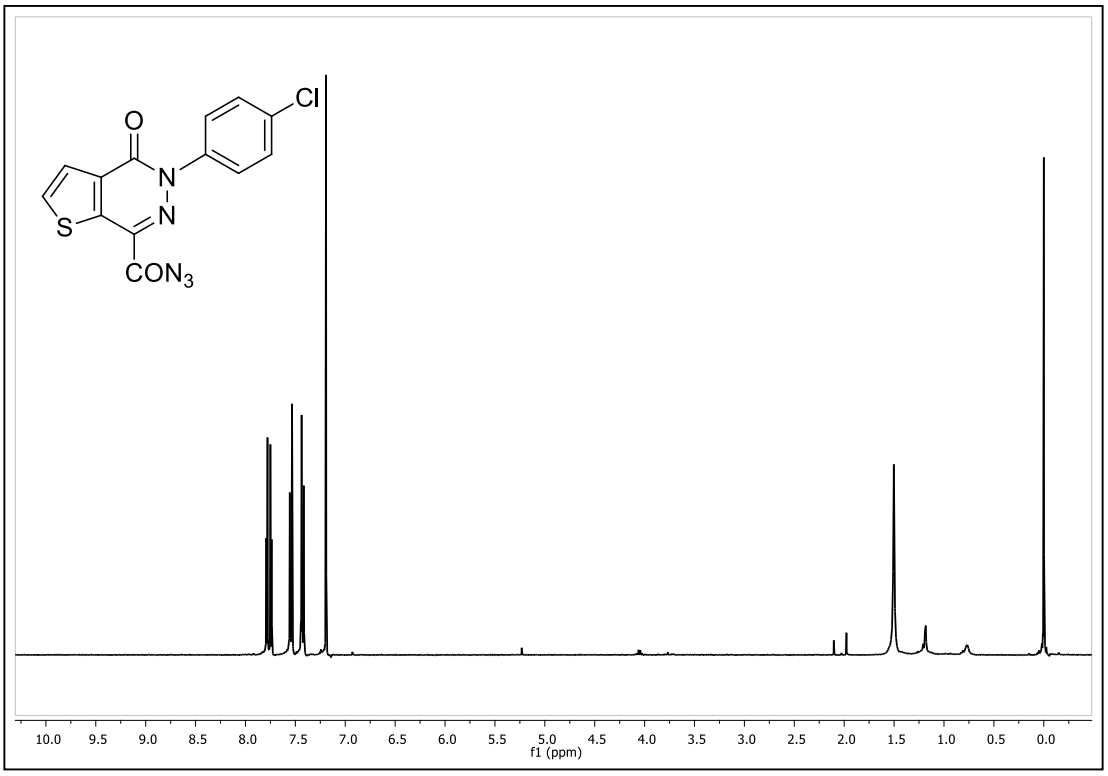

Figure A 64 ^{1}H NMR spectrum of compound **55e**

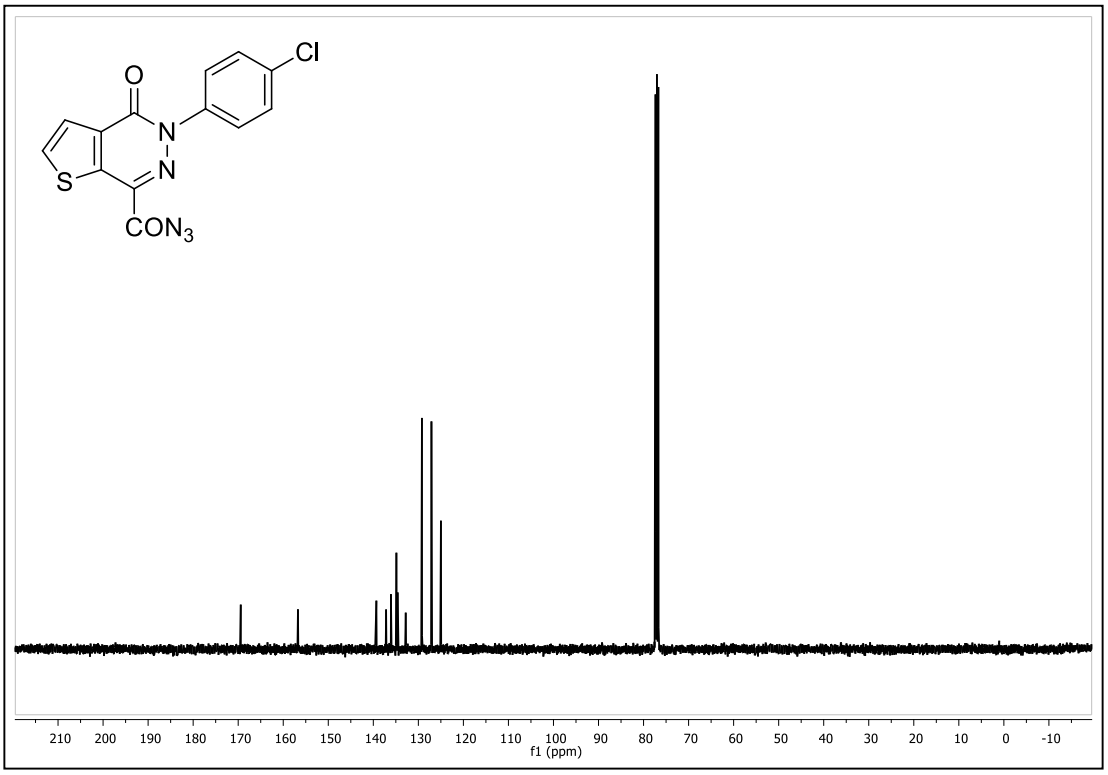

Figure A 65 ^{13}C NMR spectrum of compound **55e**

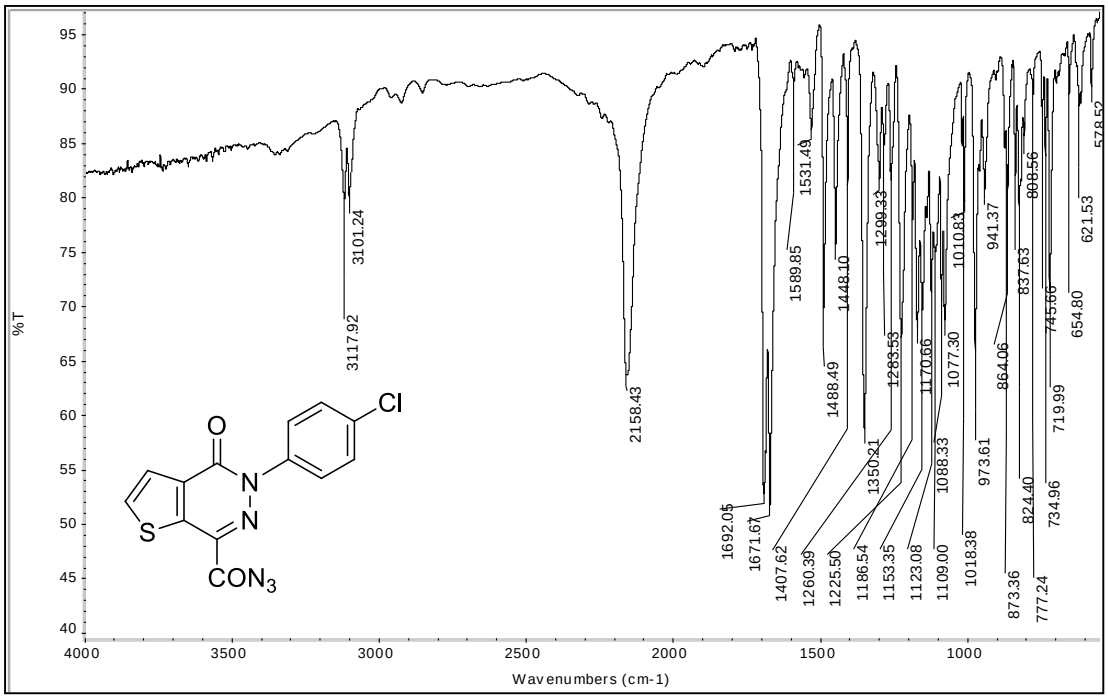

Figure A 66 IR spectrum of compound **55e**

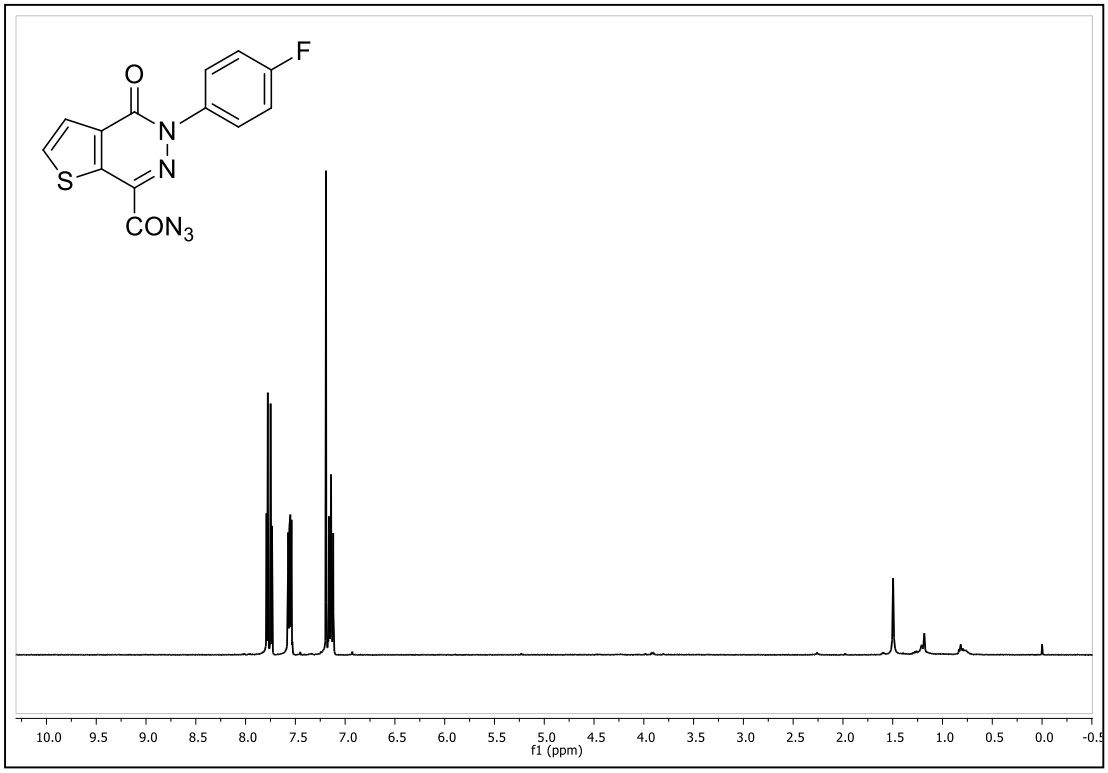

Figure A 67 ^{1}H NMR spectrum of compound **55f**

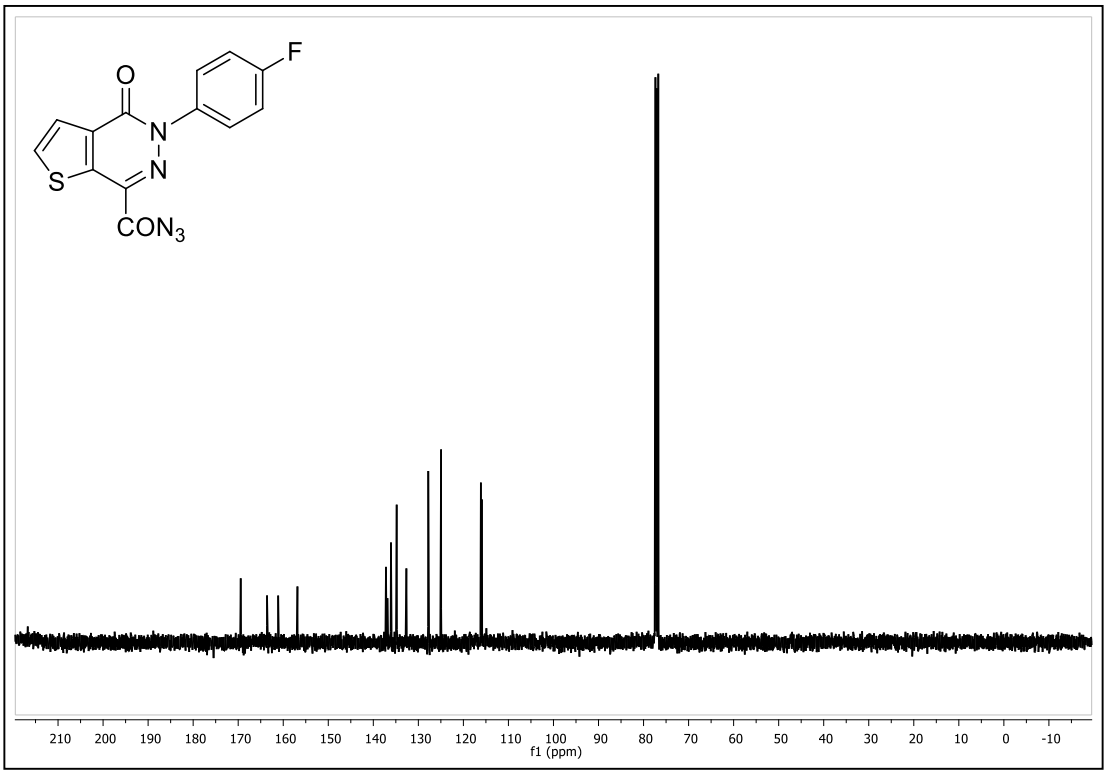

Figure A 68 ^{13}C NMR spectrum of compound **55f**

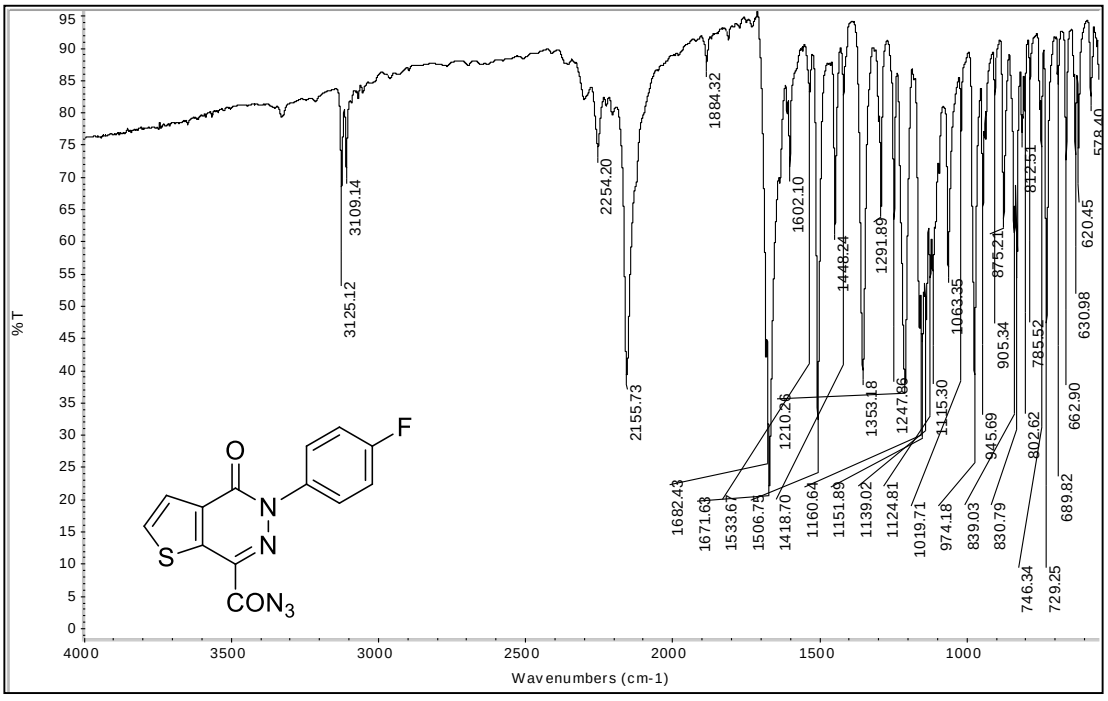

Figure A 69 IR spectrum of compound **55f**

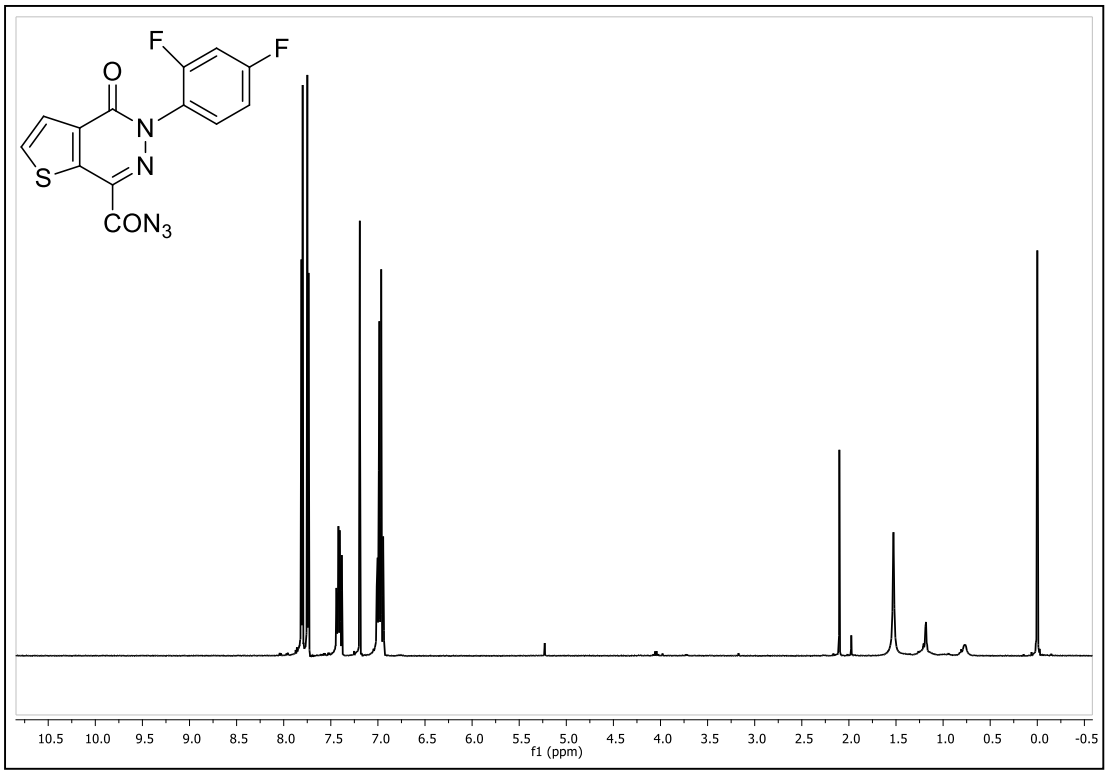

Figure A 70 ^{1}H NMR spectrum of compound **55g**

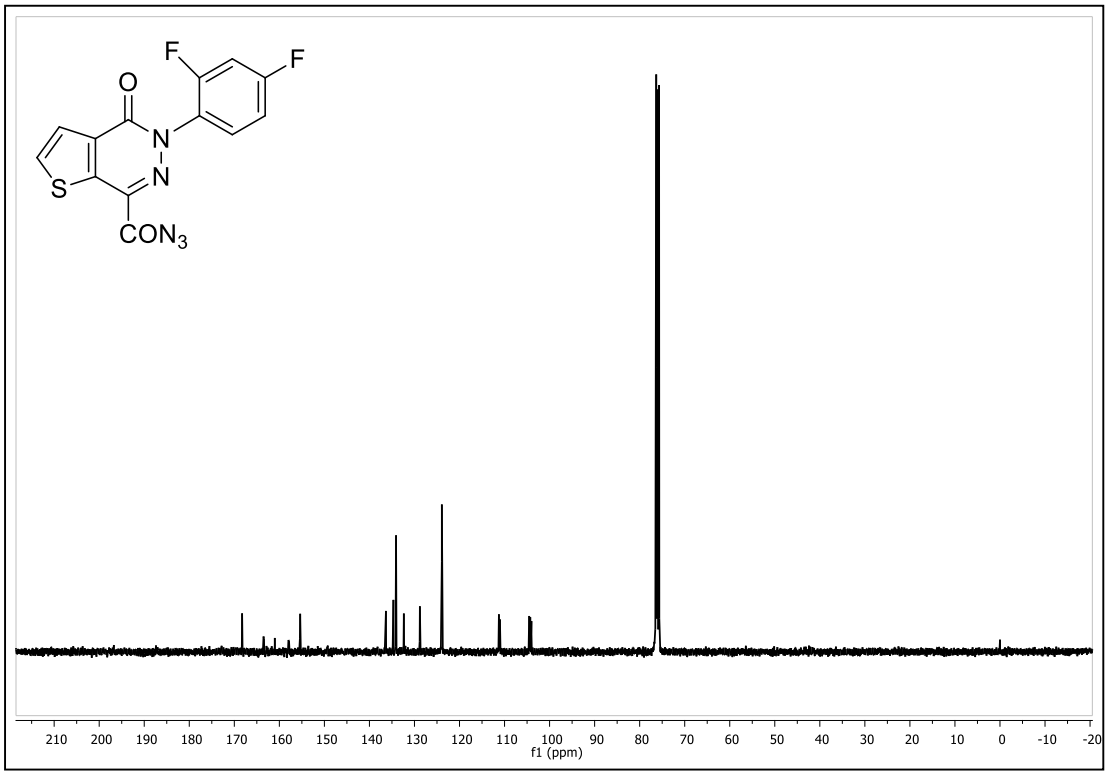

Figure A 71 ^{13}C NMR spectrum of compound **55g**

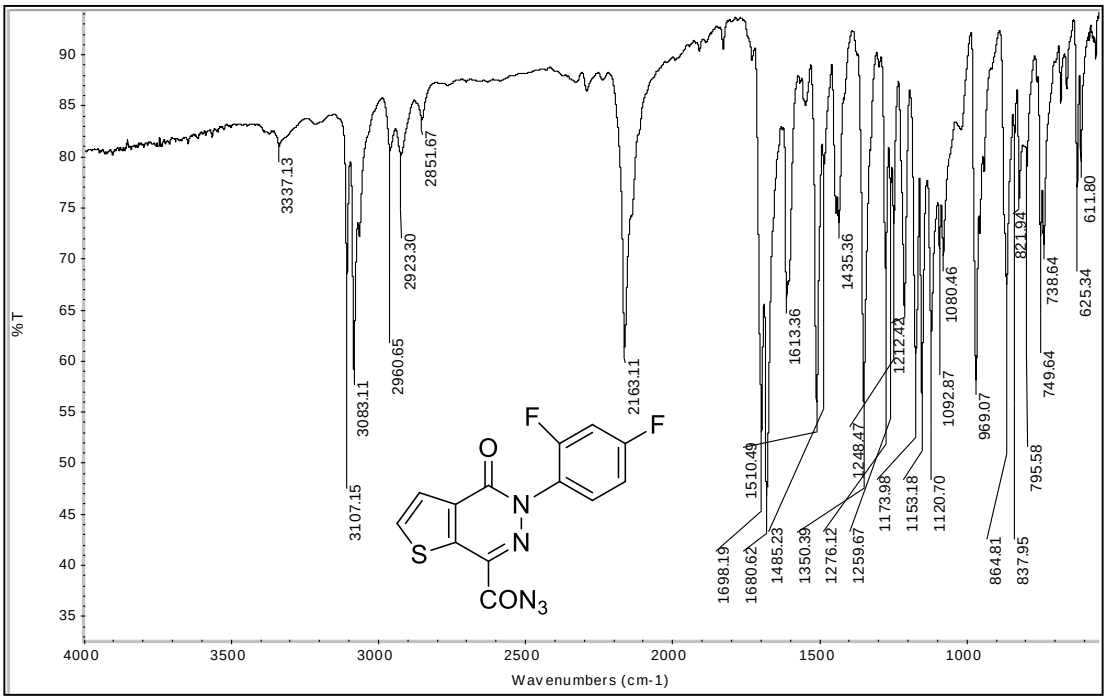

Figure A 72 IR spectrum of compound **55g**

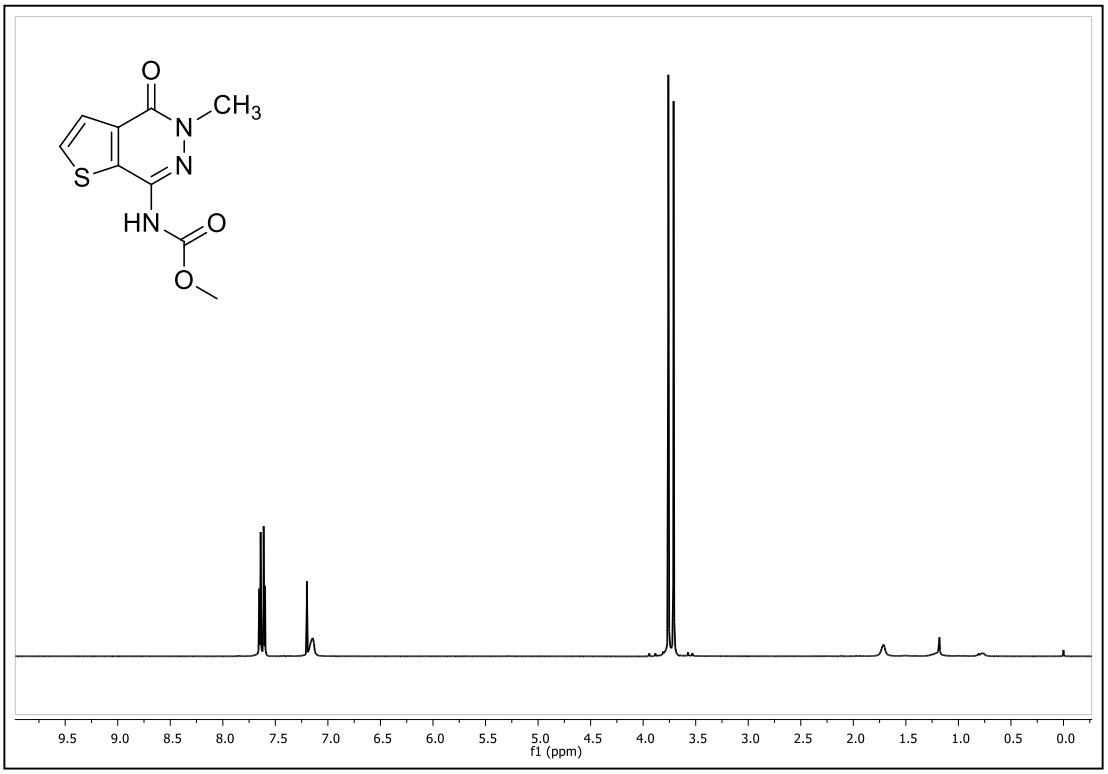

Figure A 73 ^{1}H NMR spectrum of compound **55a**

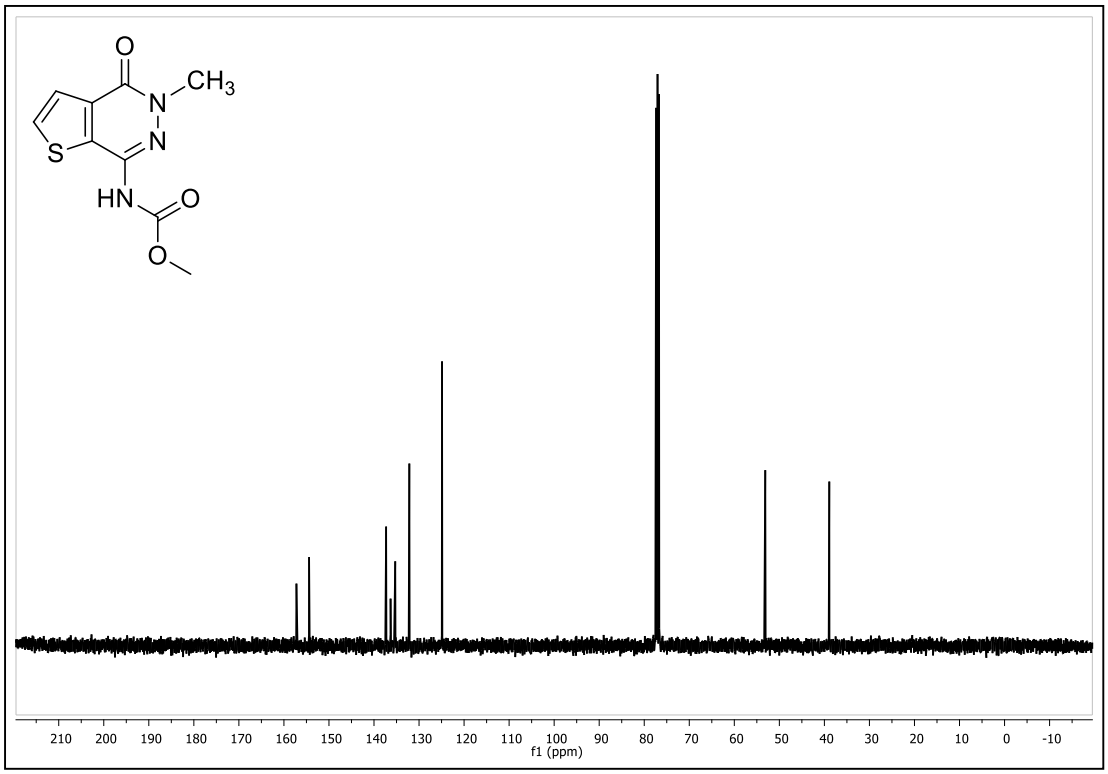

Figure A 74 ^{13}C NMR spectrum of compound **56a**

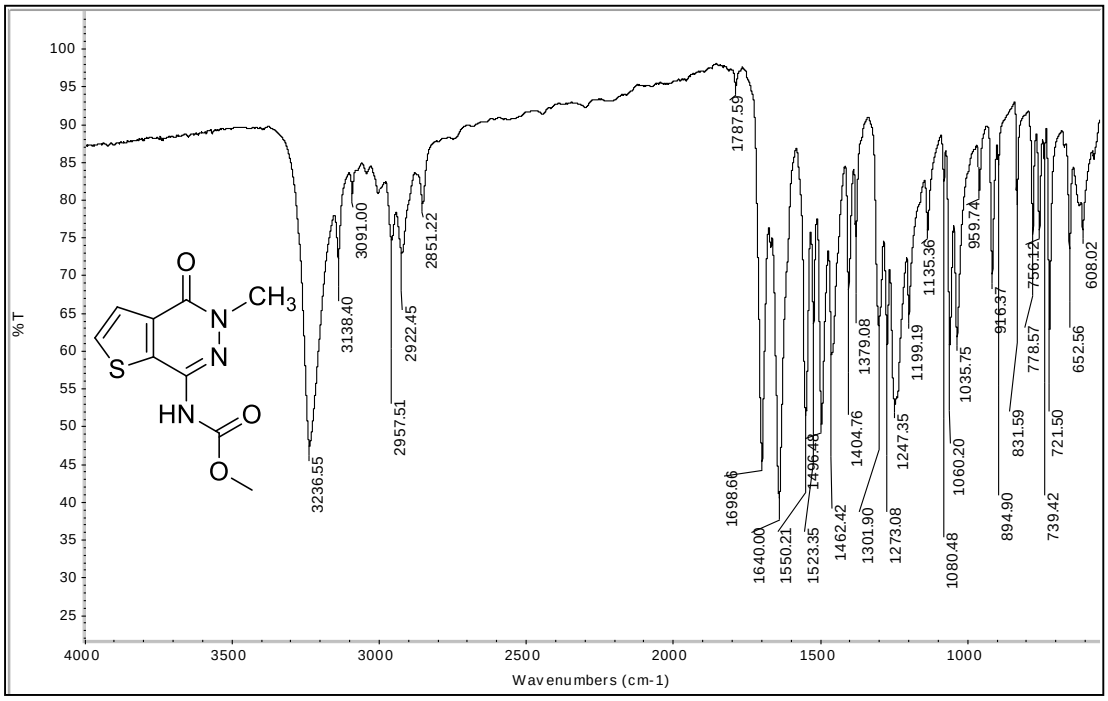

Figure A 75 IR spectrum of compound **56a**

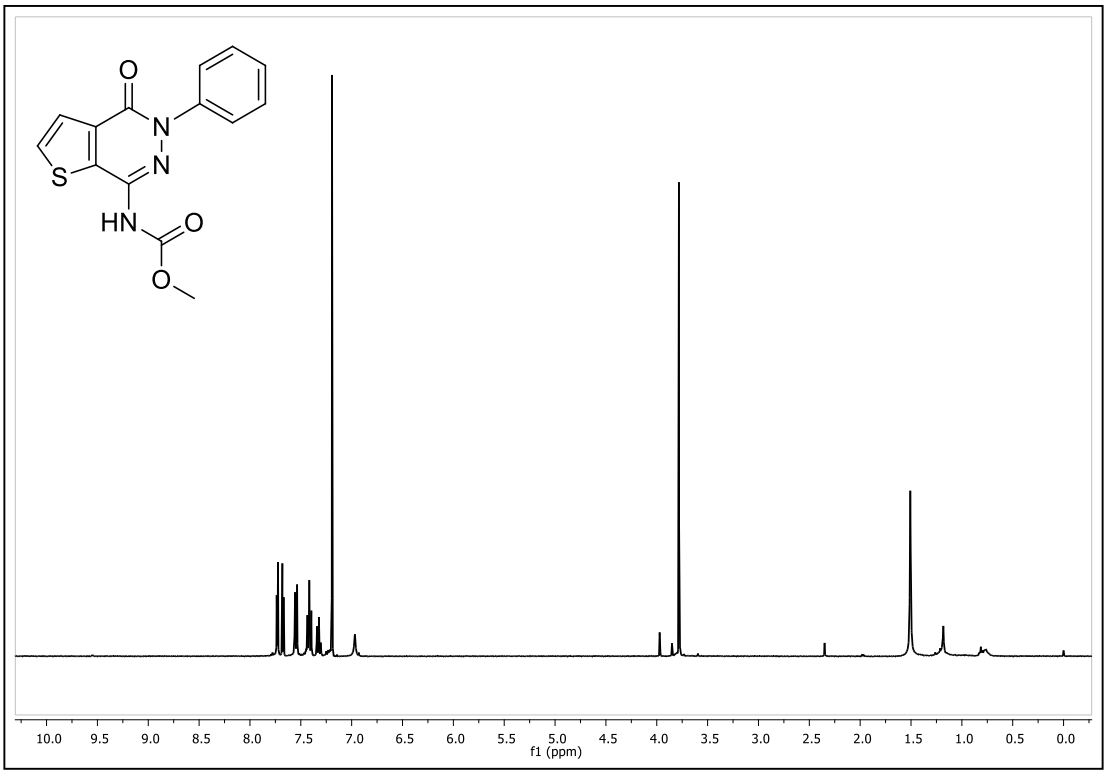

Figure A 76 ^{1}H NMR spectrum of compound **56b**

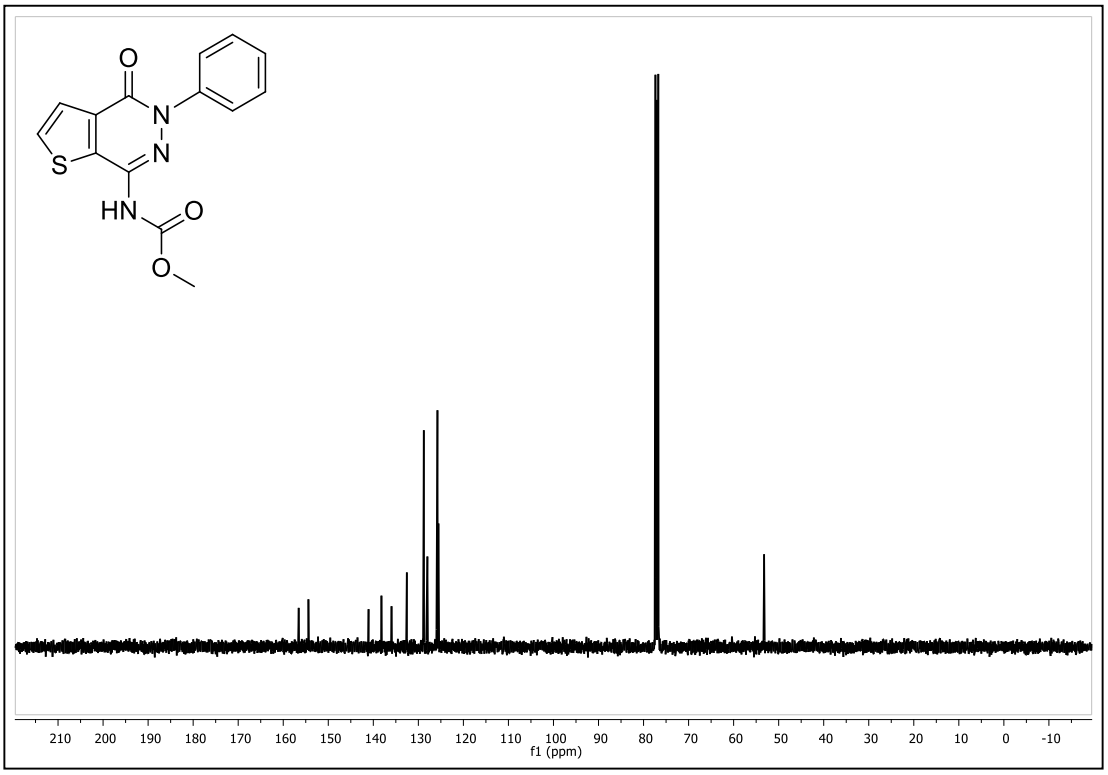

Figure A 77 ^{13}C NMR spectrum of compound **56b**

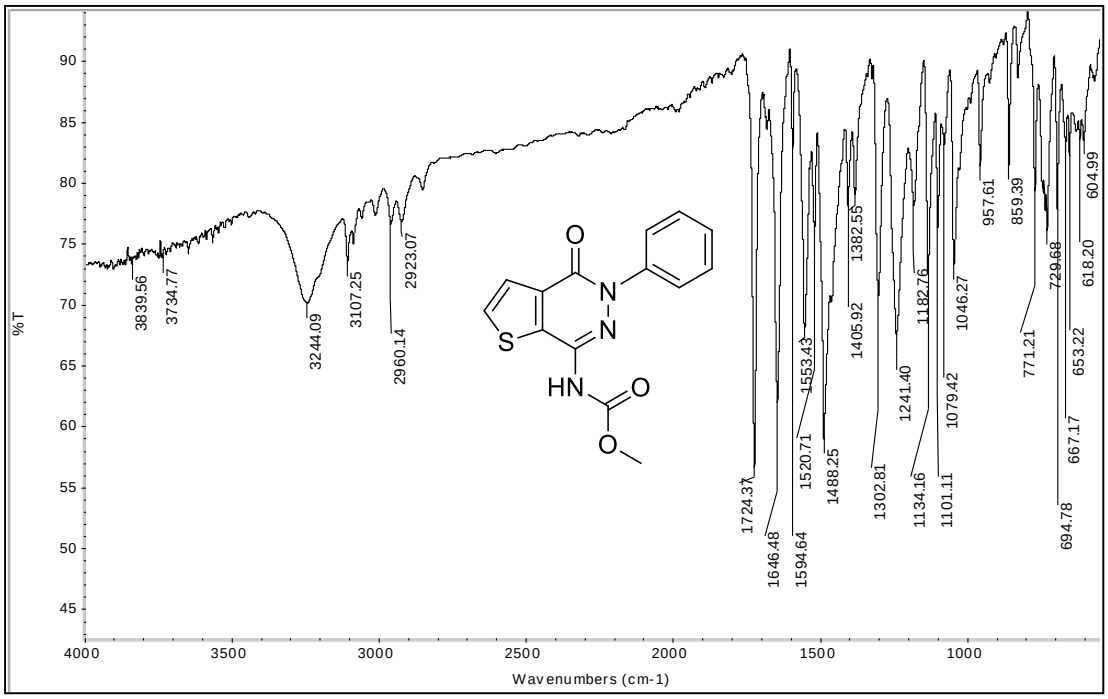

Figure A 78 IR spectrum of compound **56b**

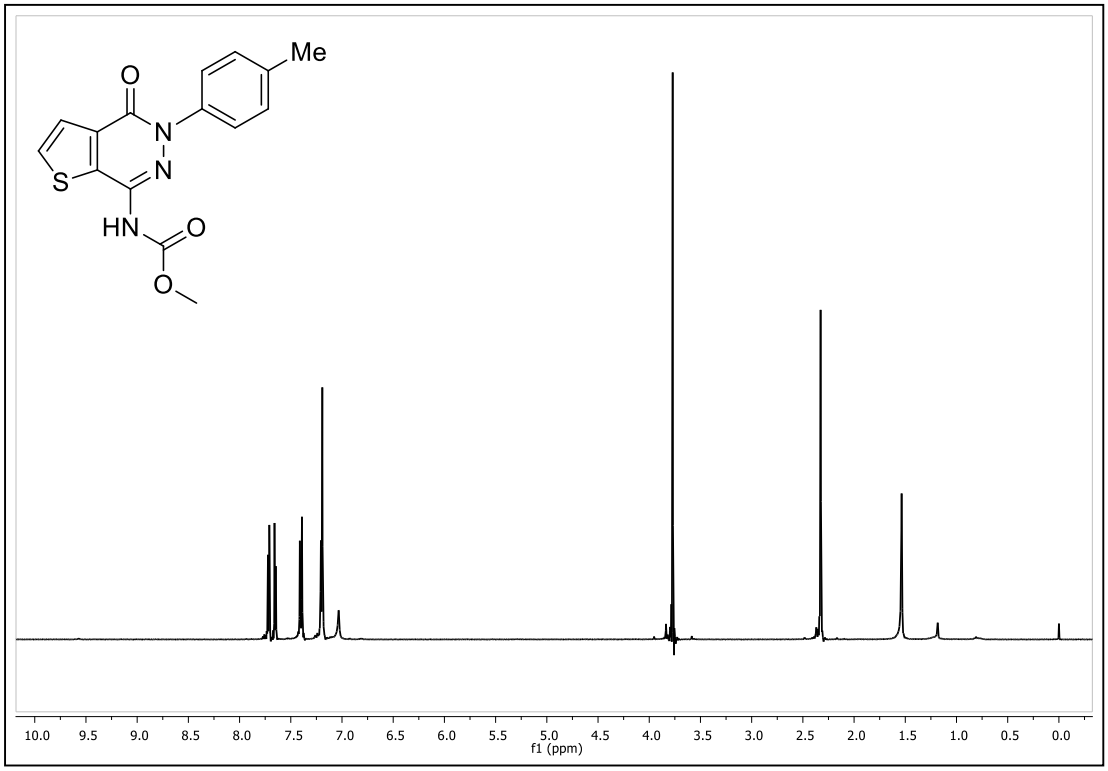

Figure A 79 ^{1}H NMR spectrum of compound **56c**

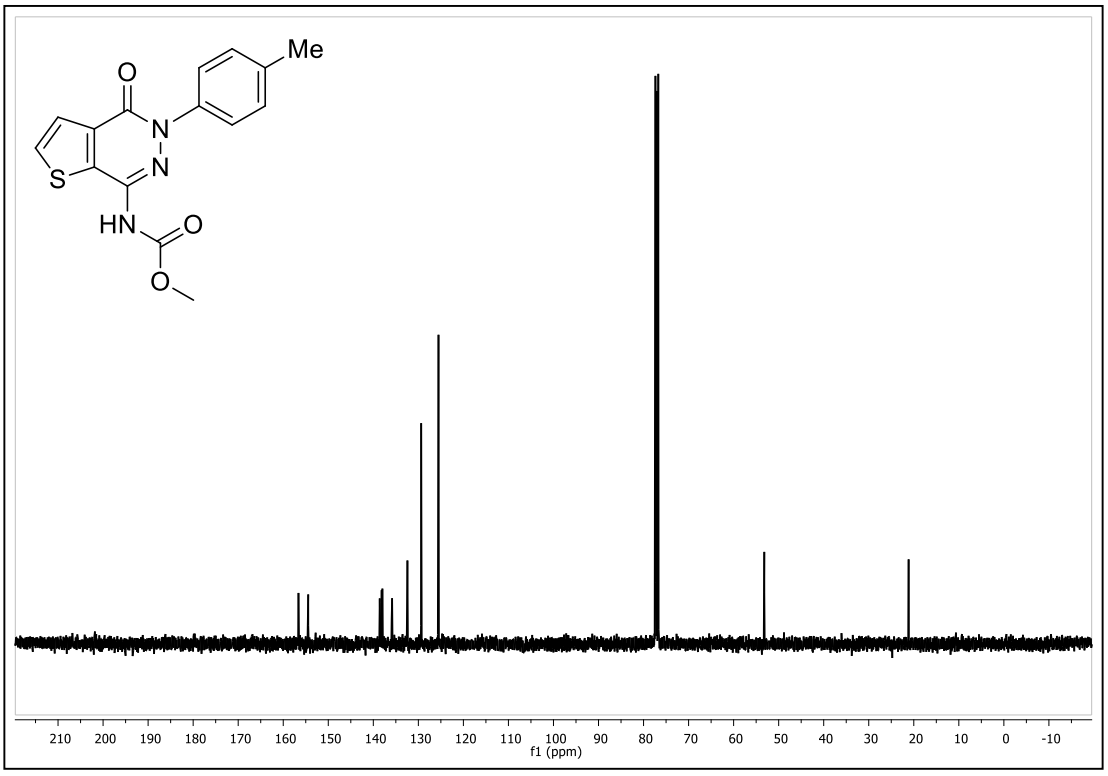

Figure A 80 ^{13}C NMR spectrum of compound **56c**

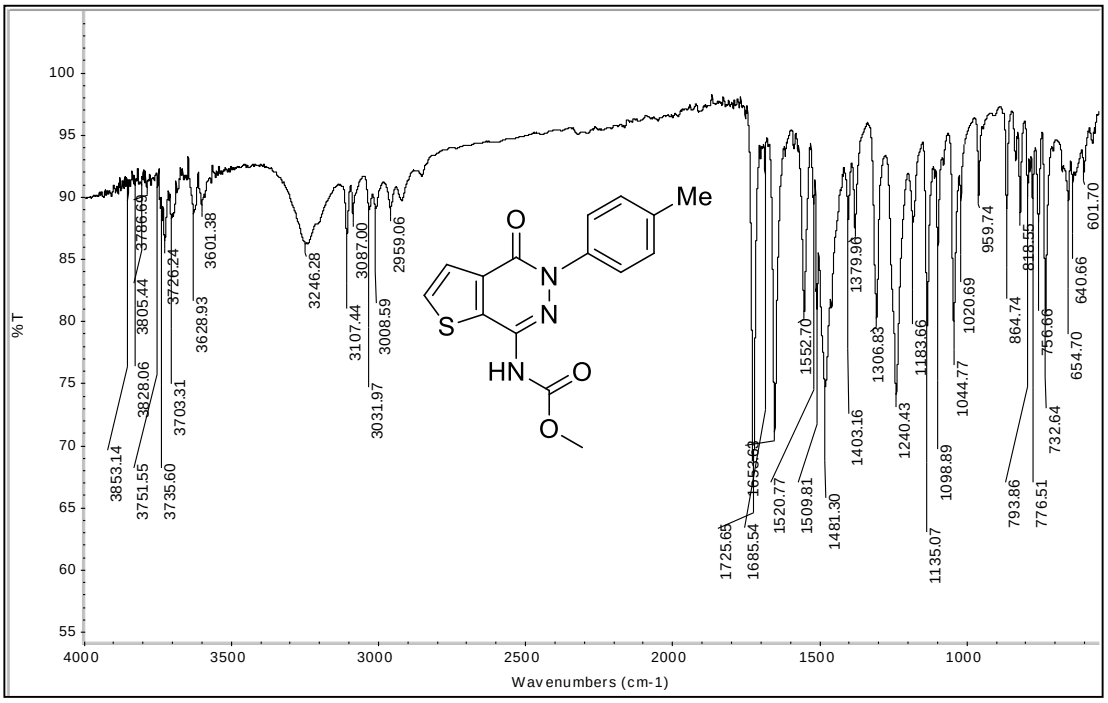

Figure A 81 IR spectrum of compound **56c**

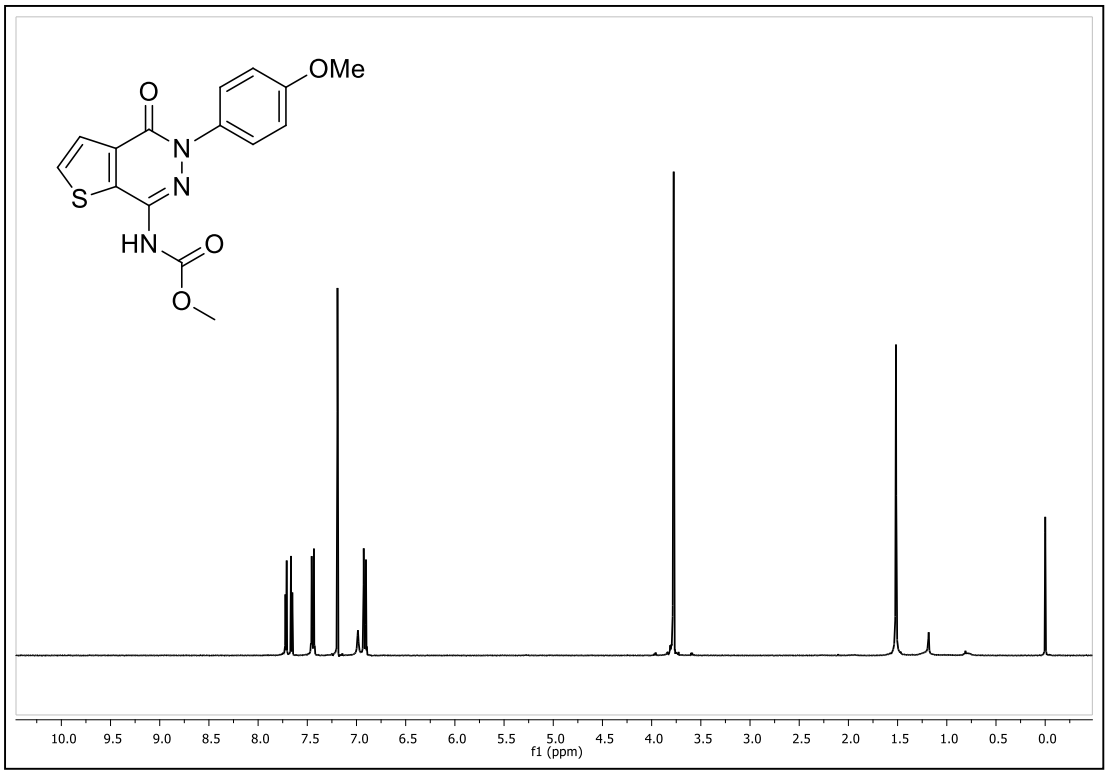

Figure A 82 ^{1}H NMR spectrum of compound **56d**

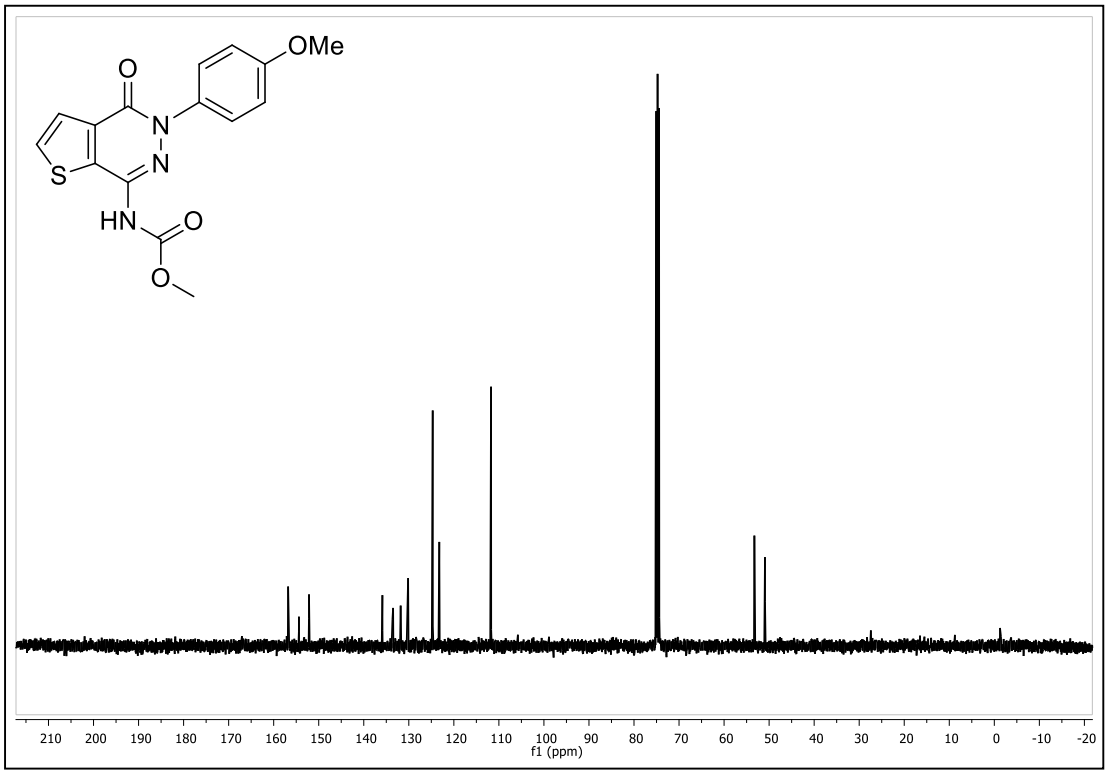

Figure A 83 ^{13}C NMR spectrum of compound **56d**

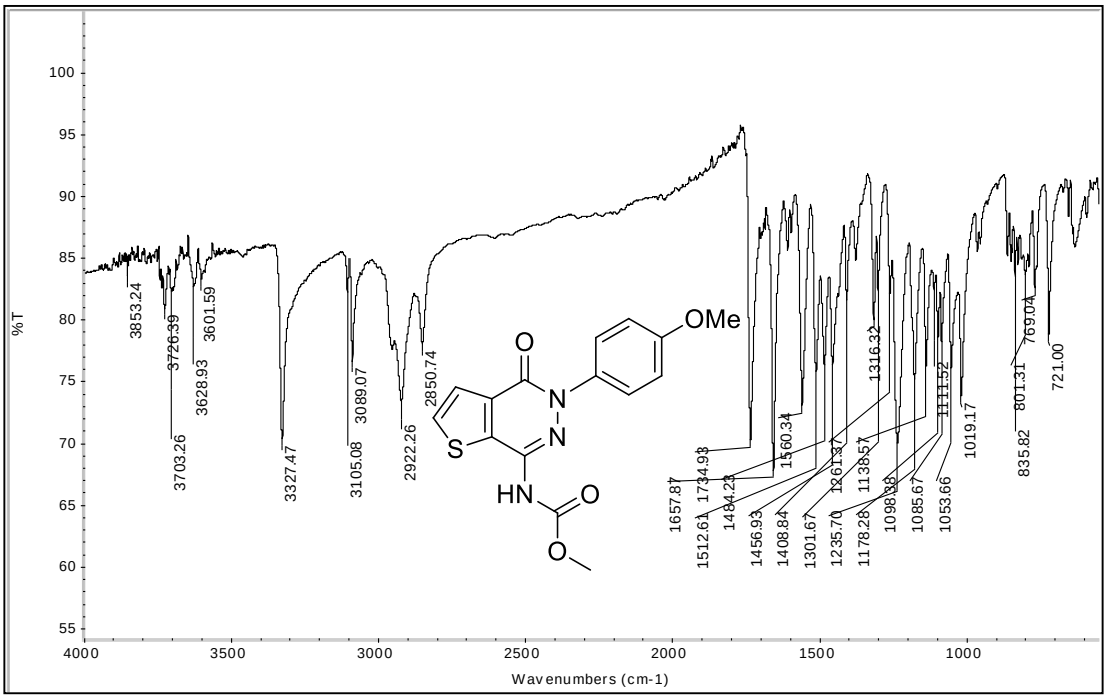

Figure A 84 IR spectrum of compound **56d**

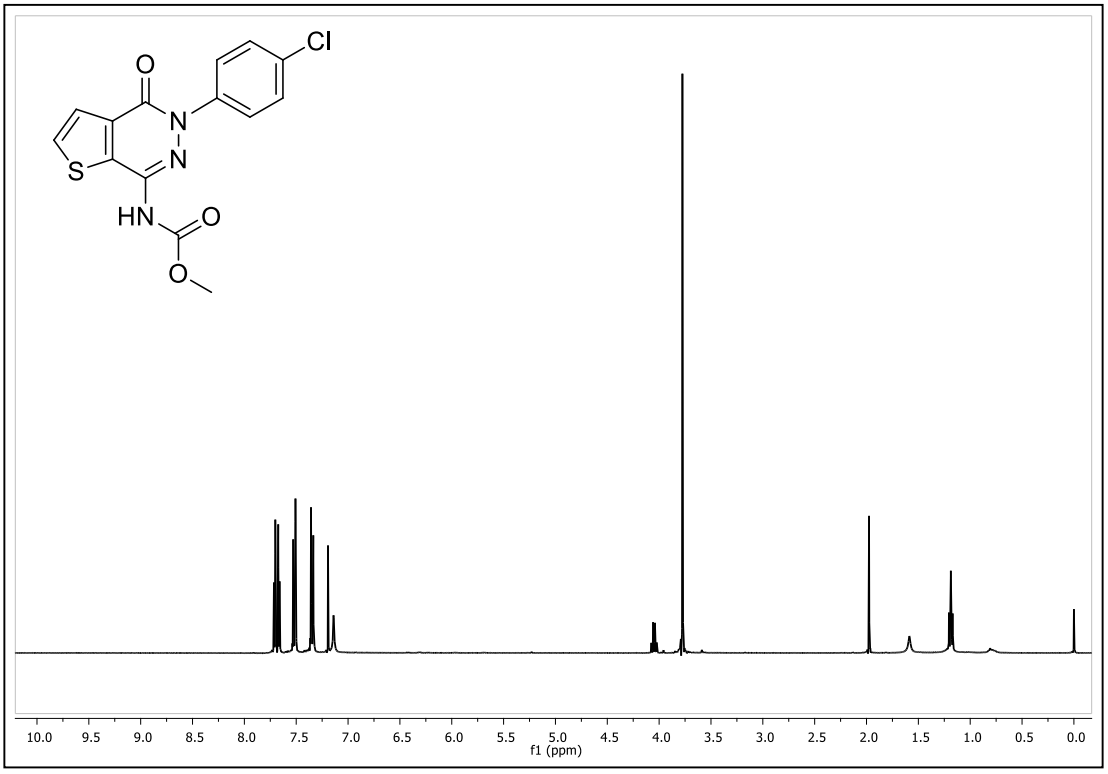

Figure A 85 ^{1}H NMR spectrum of compound **56e**

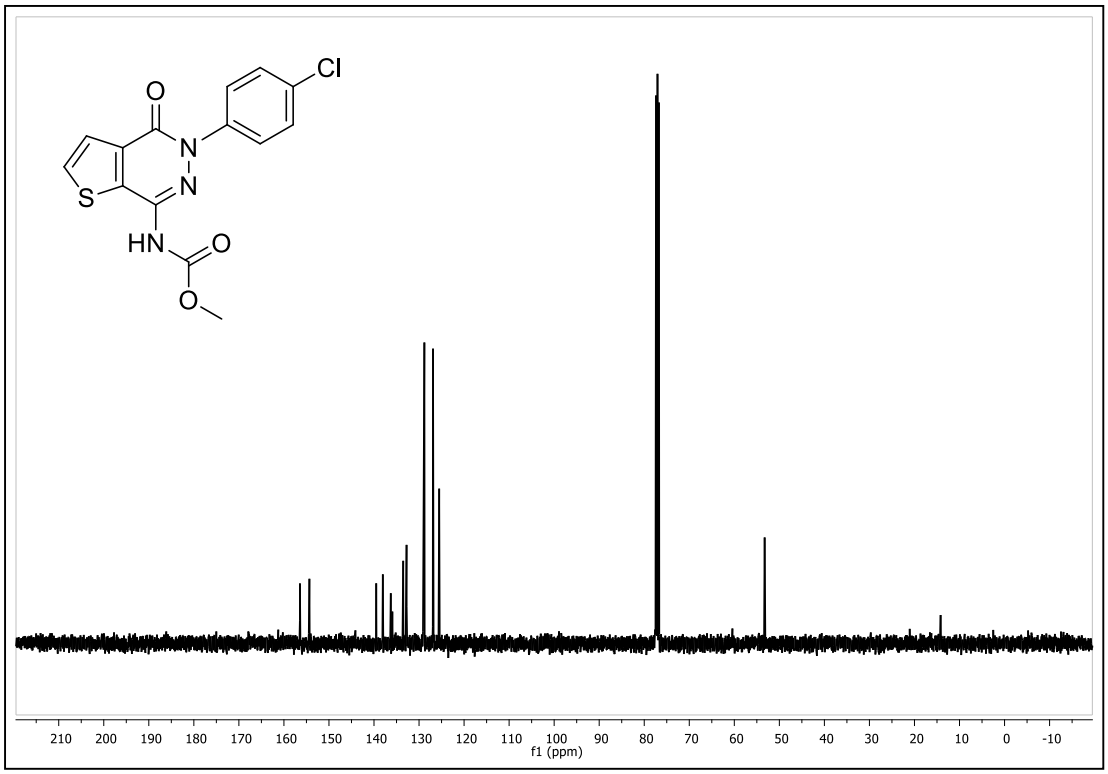

Figure A 86 ^{13}C NMR spectrum of compound **56e**

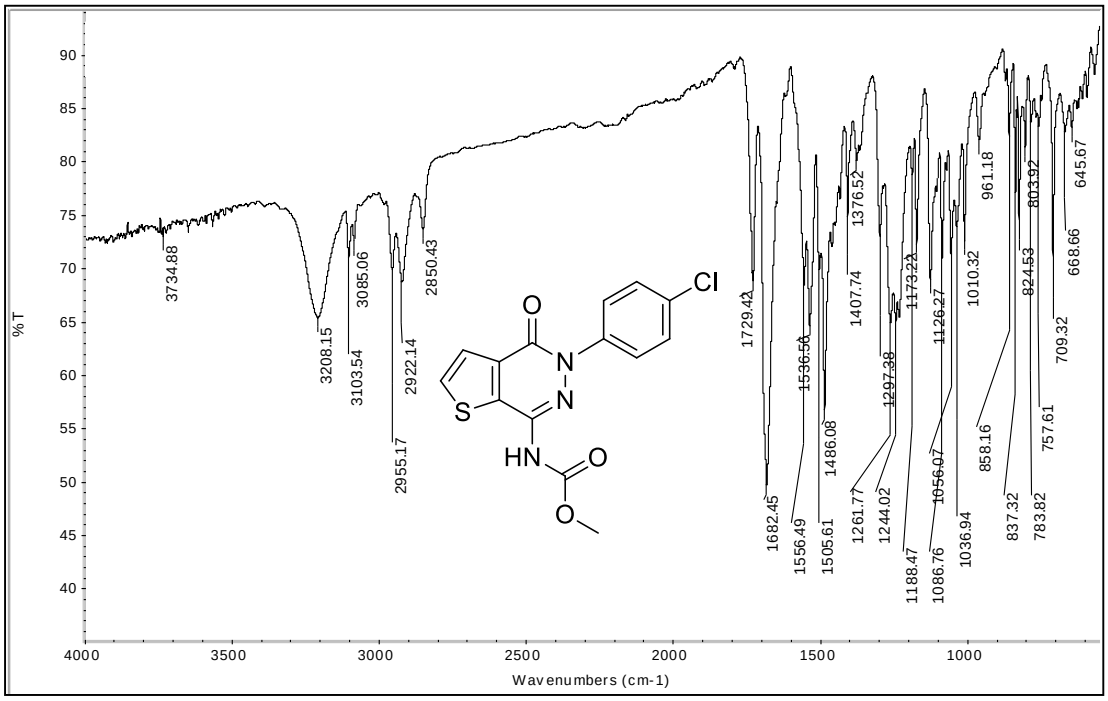

Figure A 87 IR spectrum of compound **56e**

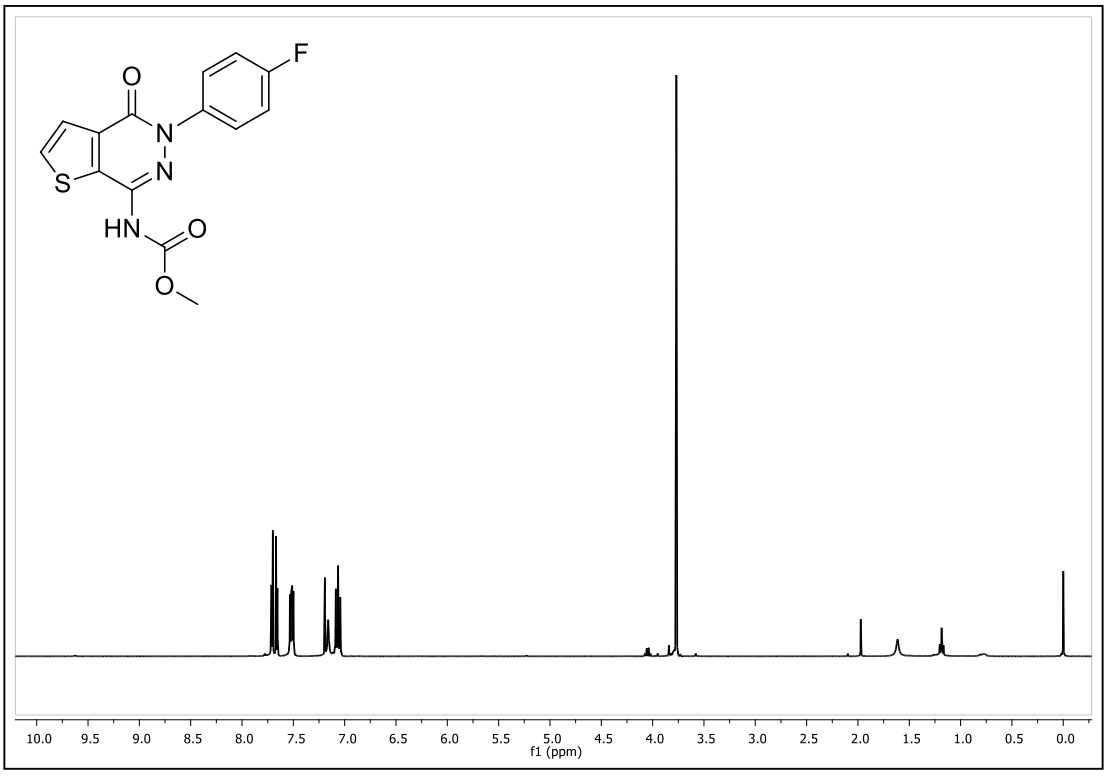

Figure A 88 ^{1}H NMR spectrum of compound **56f**

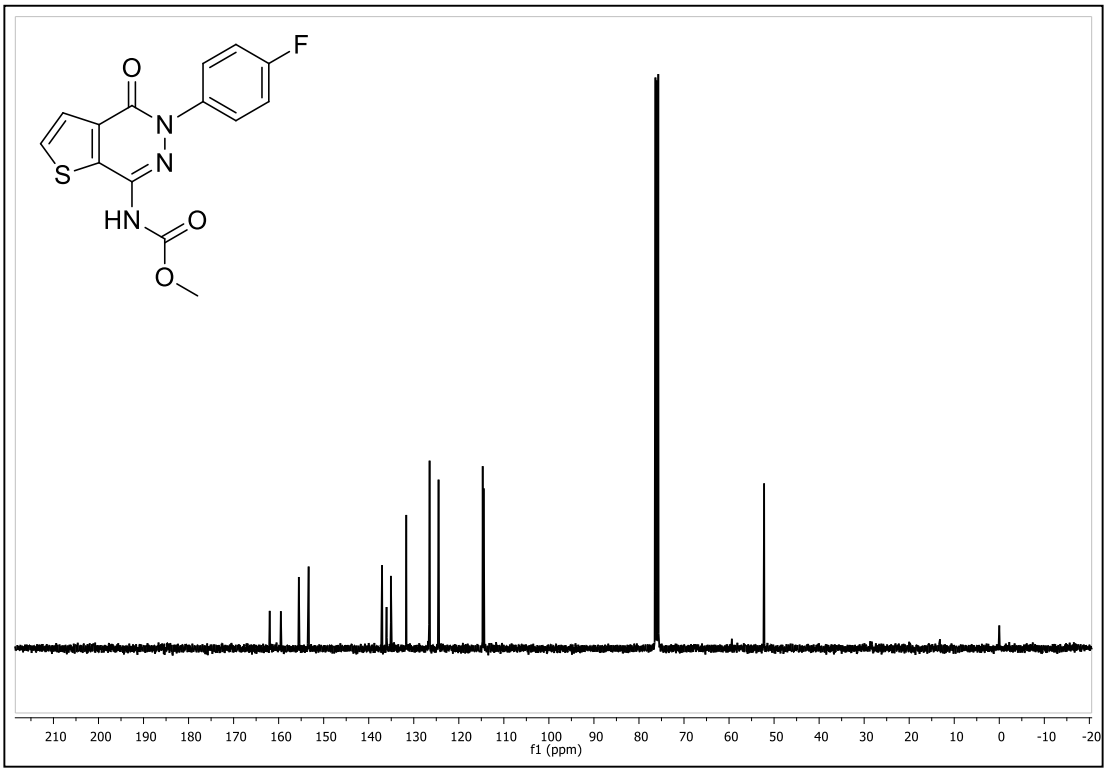

Figure A 89 ^{13}C NMR spectrum of compound **56f**

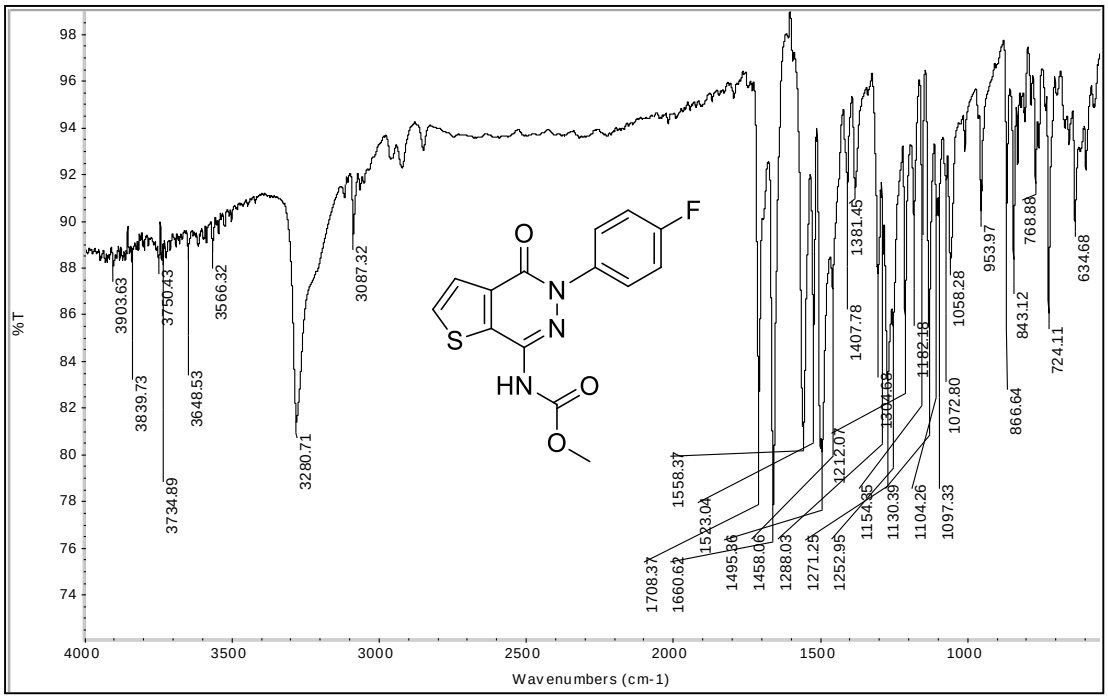

Figure A 90 IR spectrum of compound **56f**

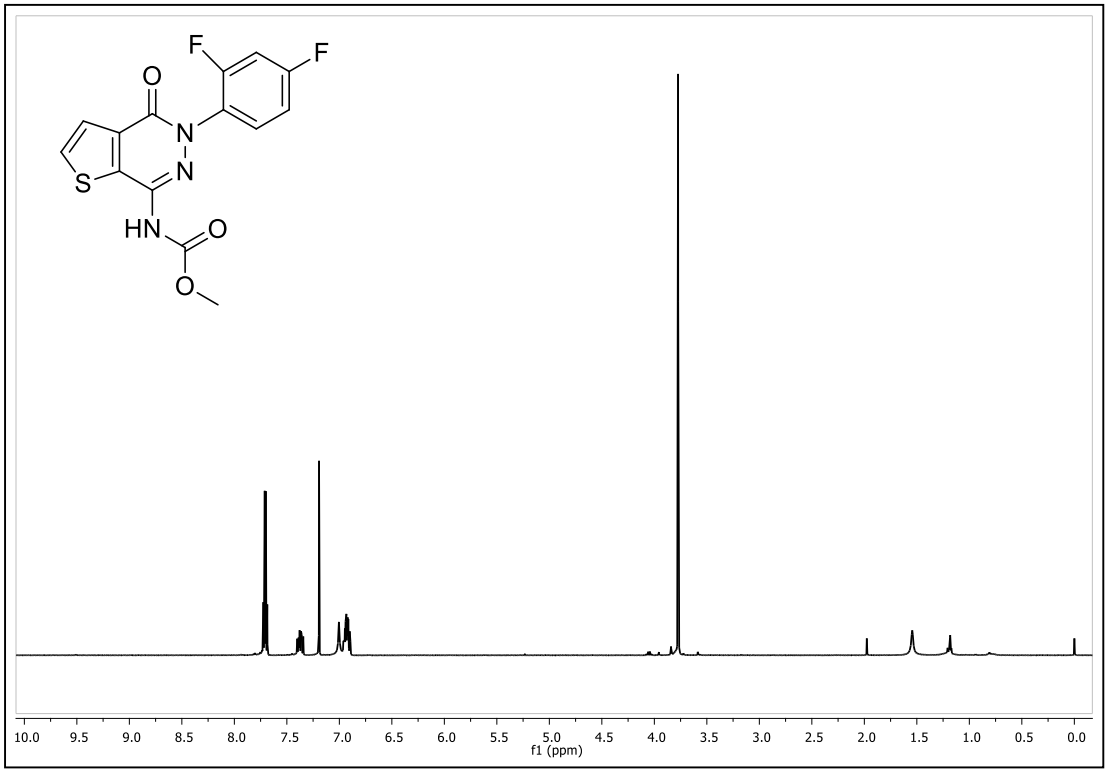

Figure A 91 ^{1}H NMR spectrum of compound **56g**

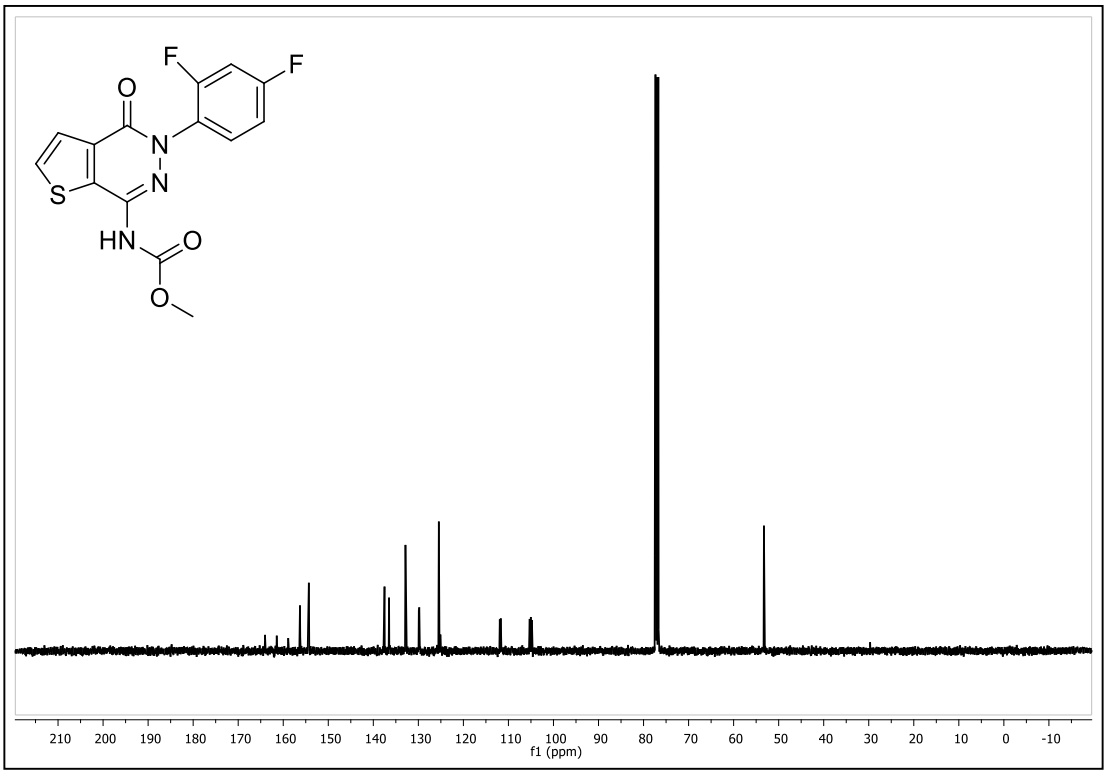

Figure A 92 ^{13}C NMR spectrum of compound **56g**

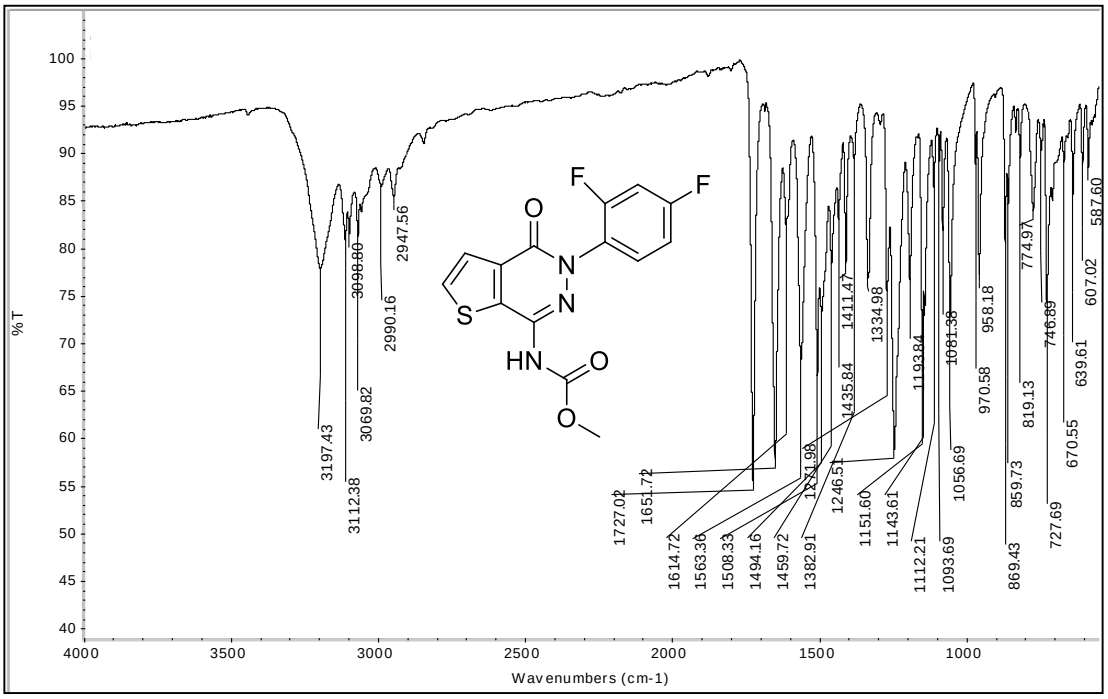

Figure A 93 IR spectrum of compound **56g**

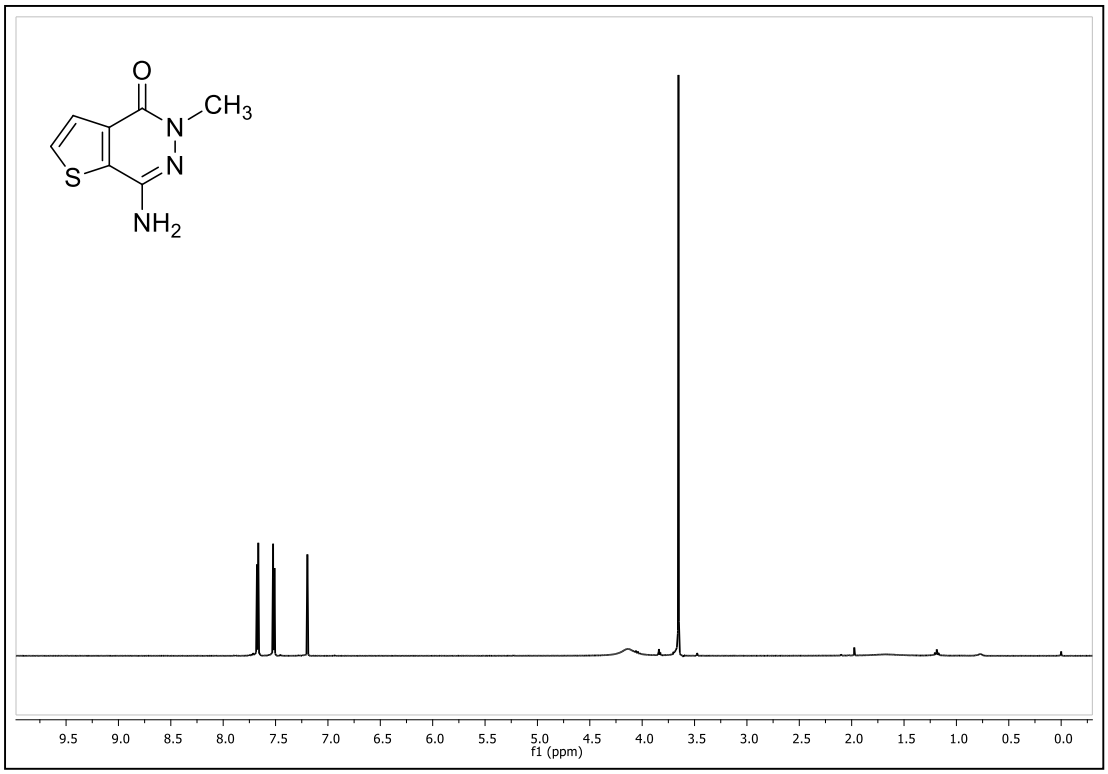

Figure A 94 ^{1}H NMR spectrum of compound **57a**

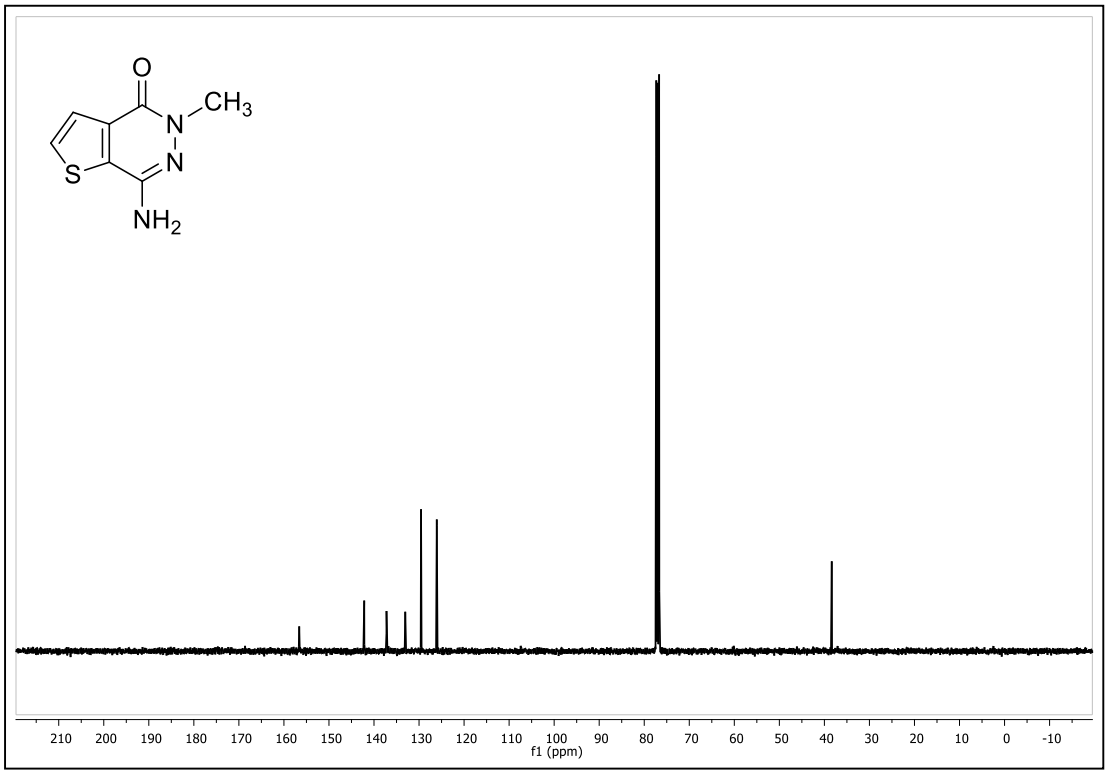

Figure A 95 ^{13}C NMR spectrum of compound **57a**

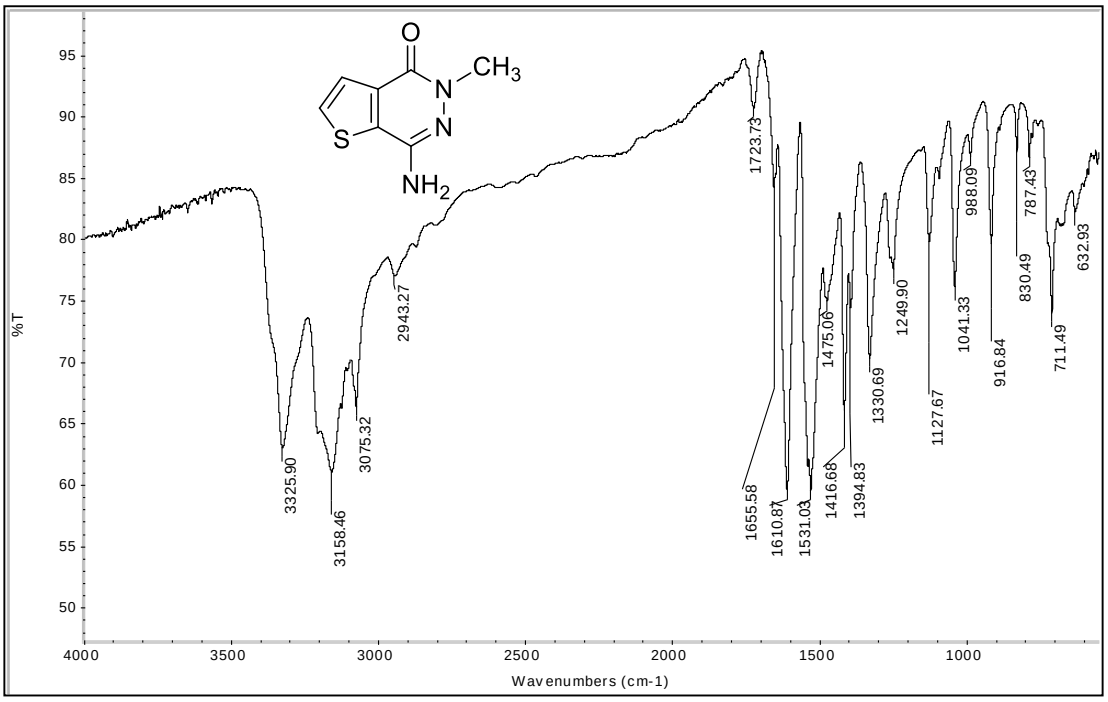

Figure A 96 IR spectrum of compound **57a**

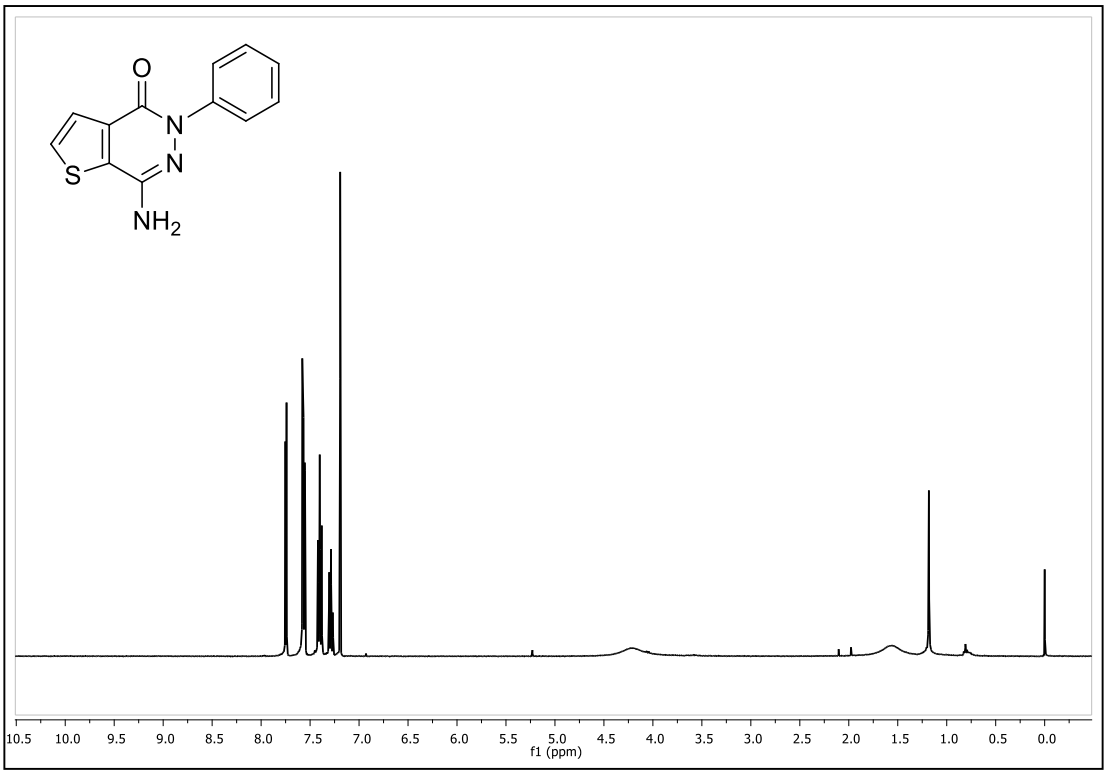

Figure A 97 ^{1}H NMR spectrum of compound **57b**

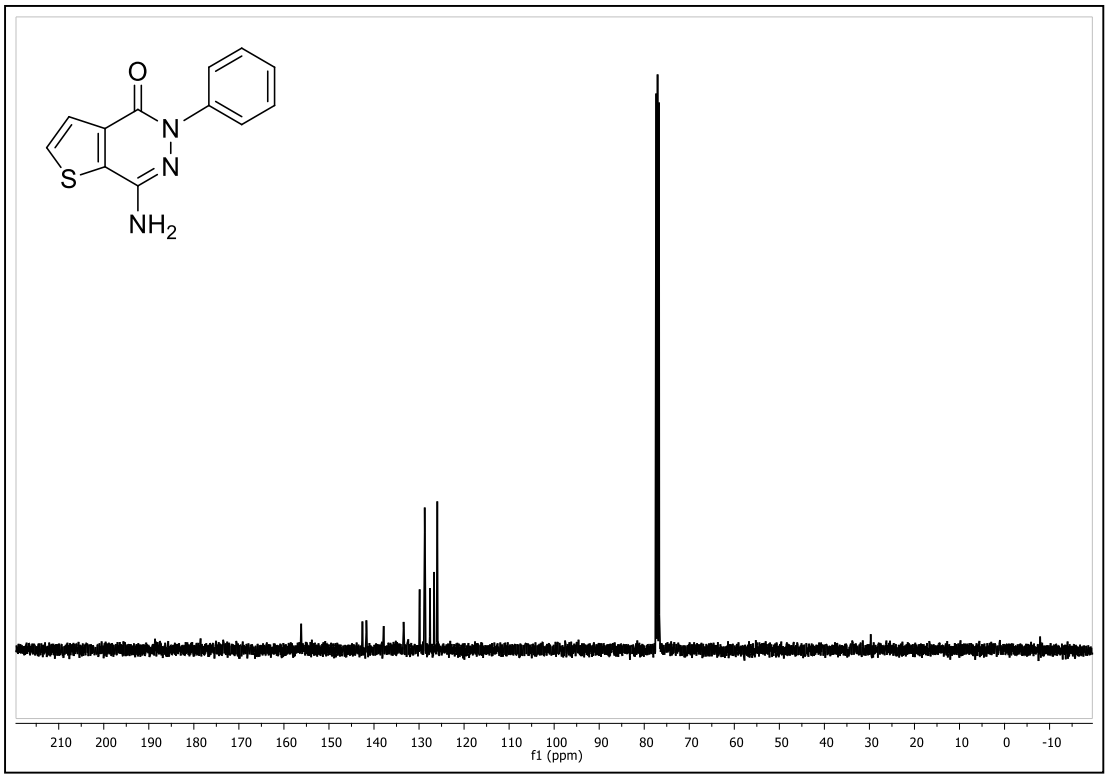

Figure A 98 ^{13}C NMR spectrum of compound **57b**

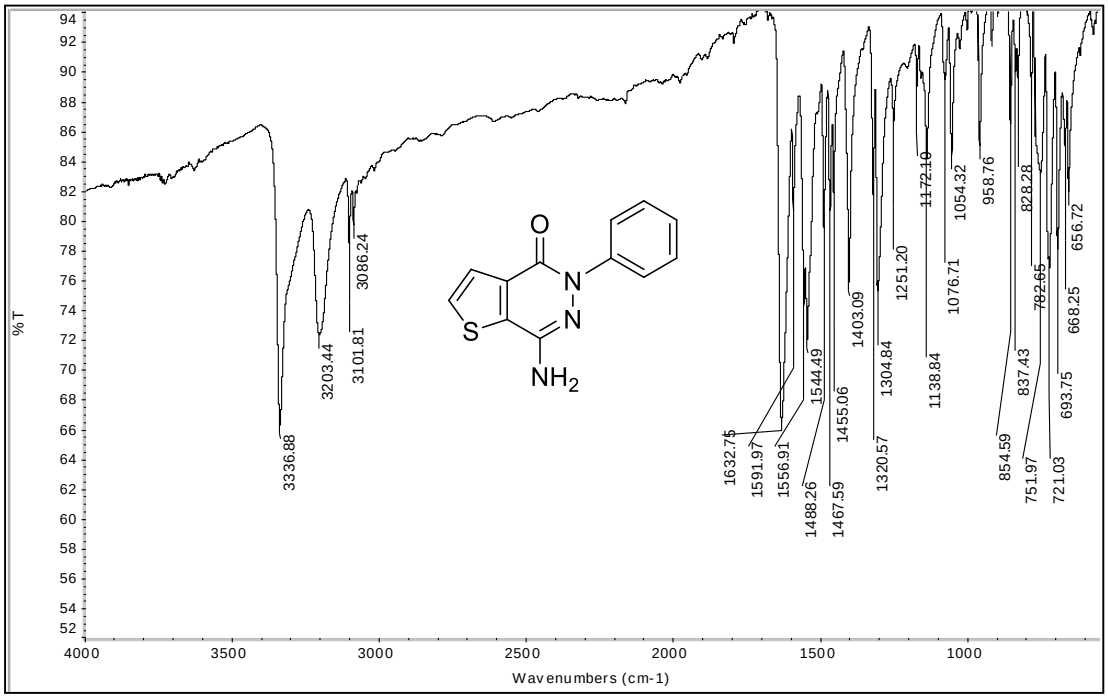

Figure A 99 IR spectrum of compound **57b**

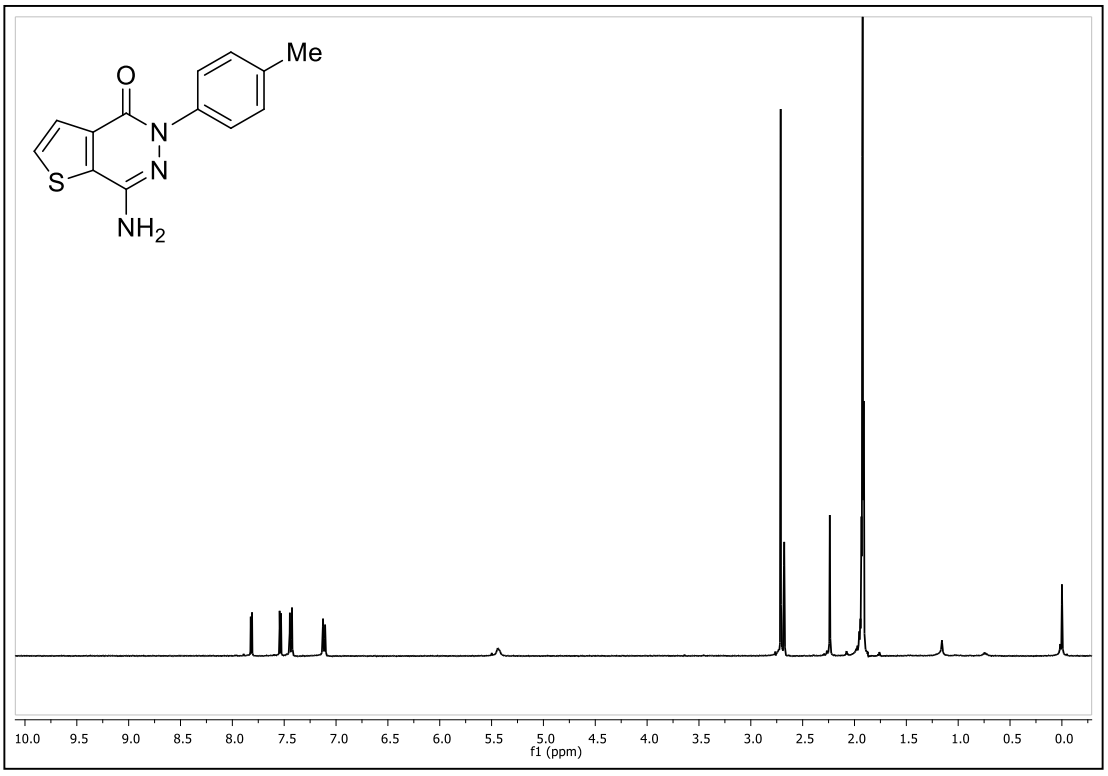

Figure A 100 ^{1}H NMR spectrum of compound **57c**

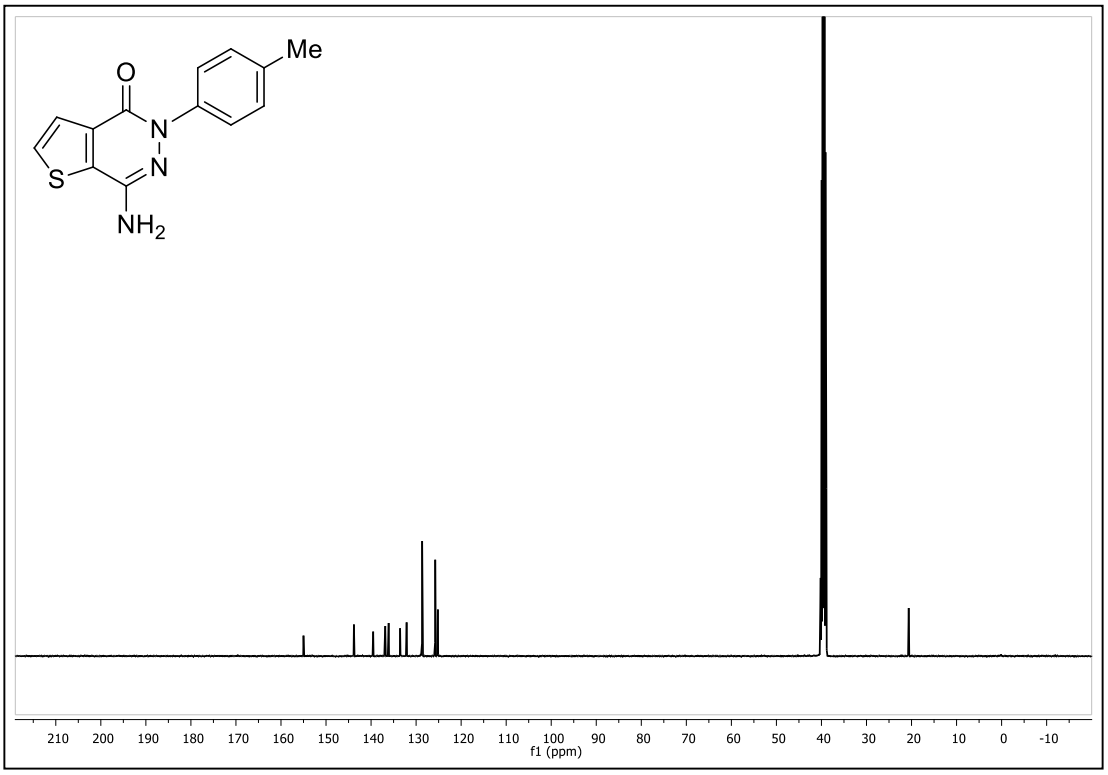

Figure A 101 ^{13}C NMR spectrum of compound **57c**

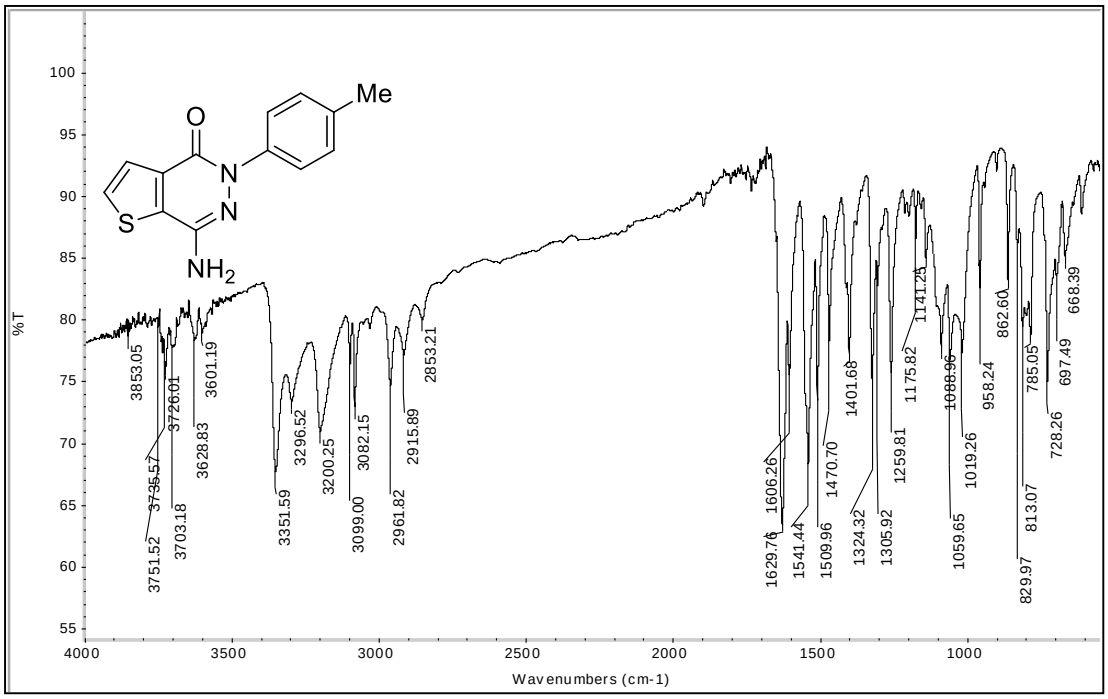

Figure A 102 IR spectrum of compound **57c**

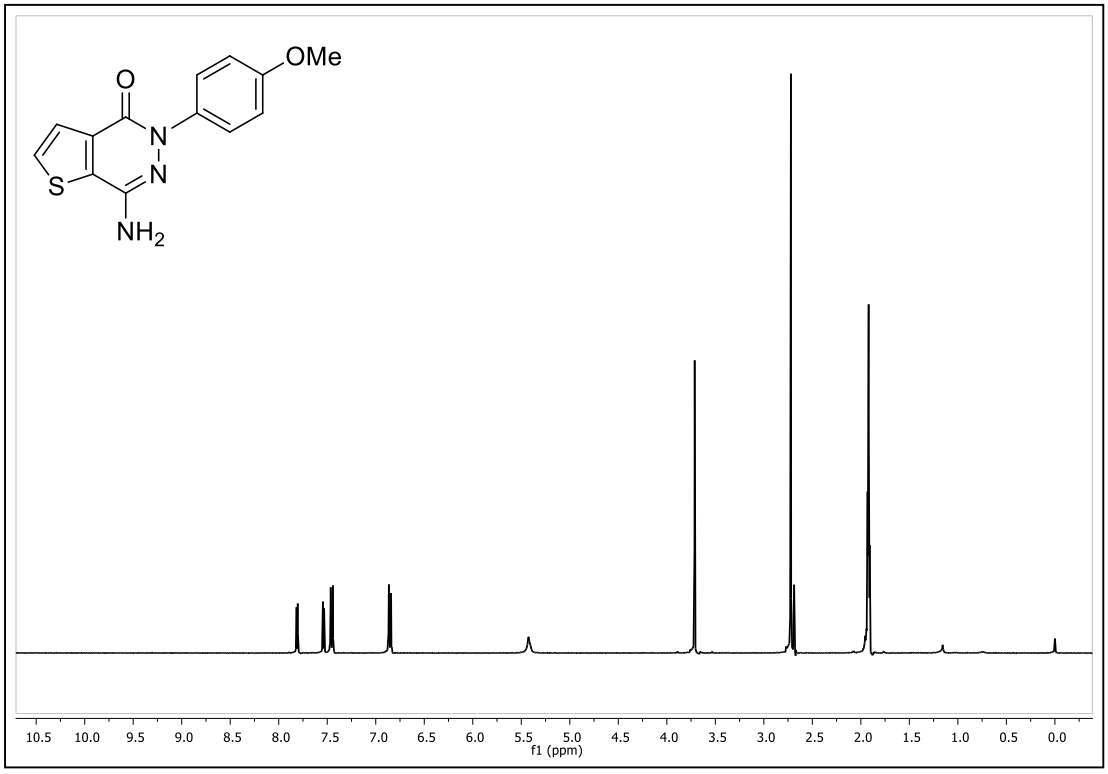

Figure A 103 ^{1}H NMR spectrum of compound **57d**

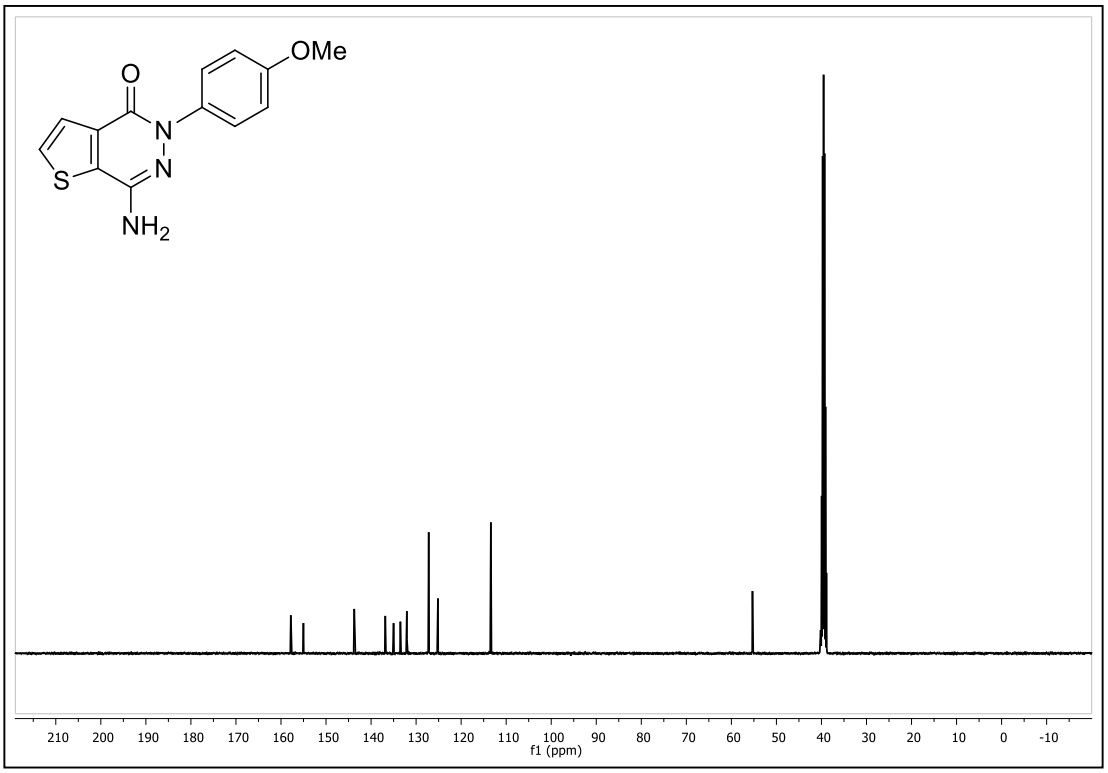

Figure A 104 ^{13}C NMR spectrum of compound **57d**

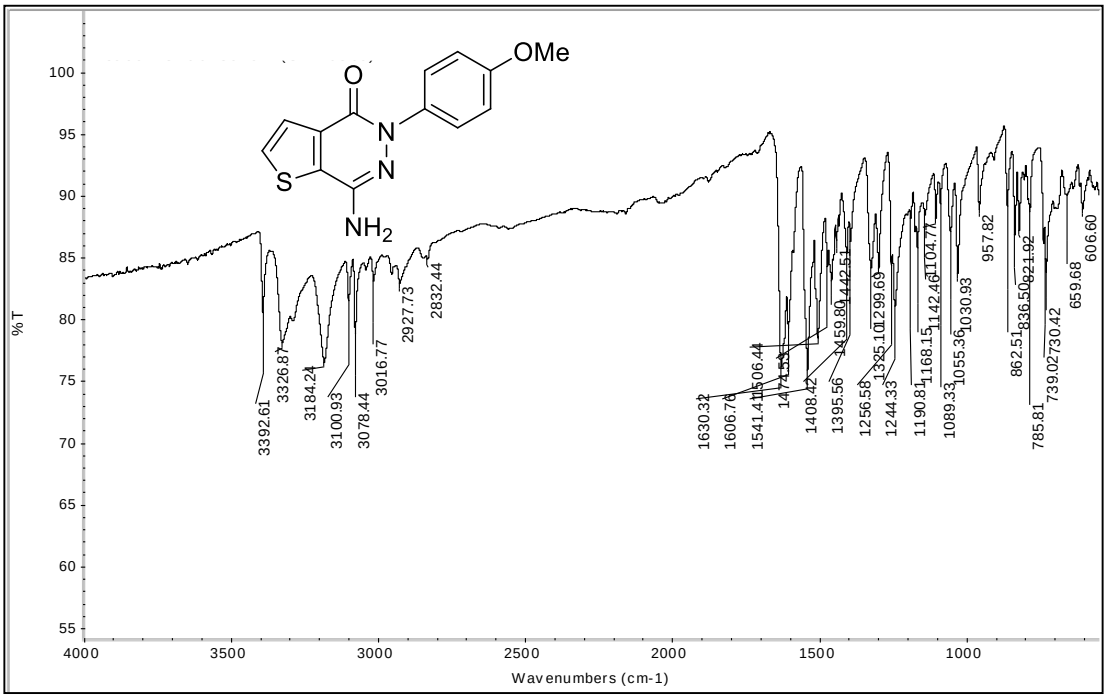

Figure A 105 IR spectrum of compound **57d**

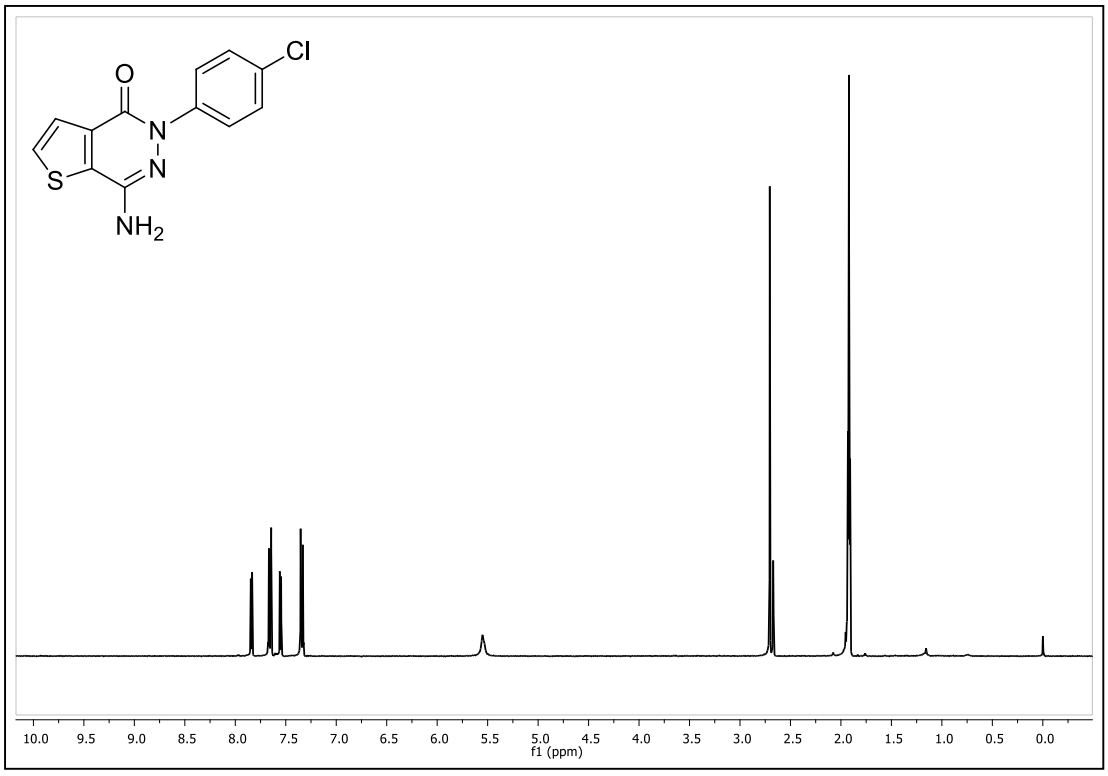

Figure A 106 ^{1}H NMR spectrum of compound **57e**

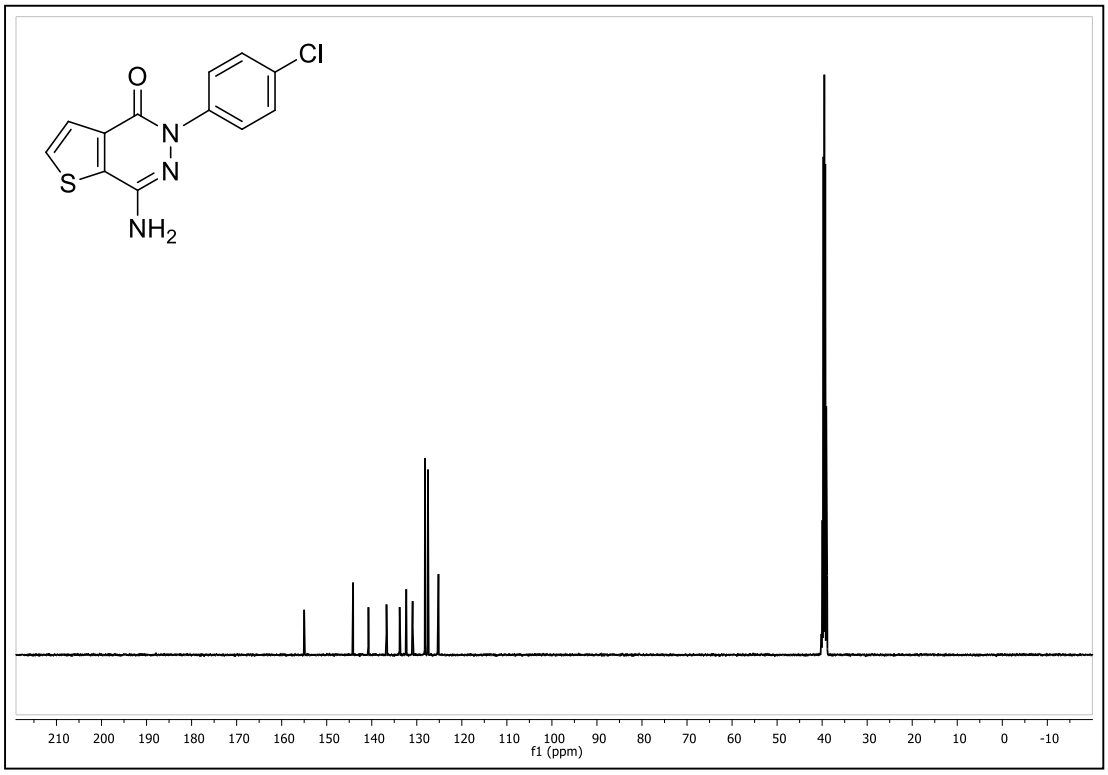

Figure A 107 ^{13}C NMR spectrum of compound **57e**

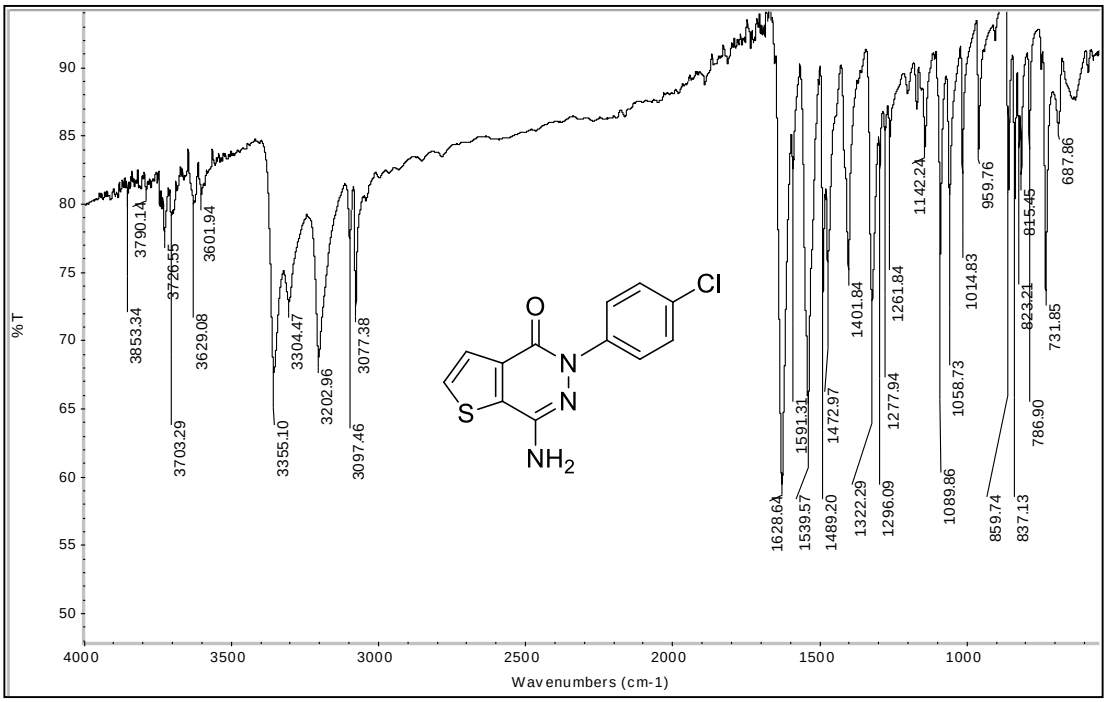

Figure A 108 IR spectrum of compound **57e**

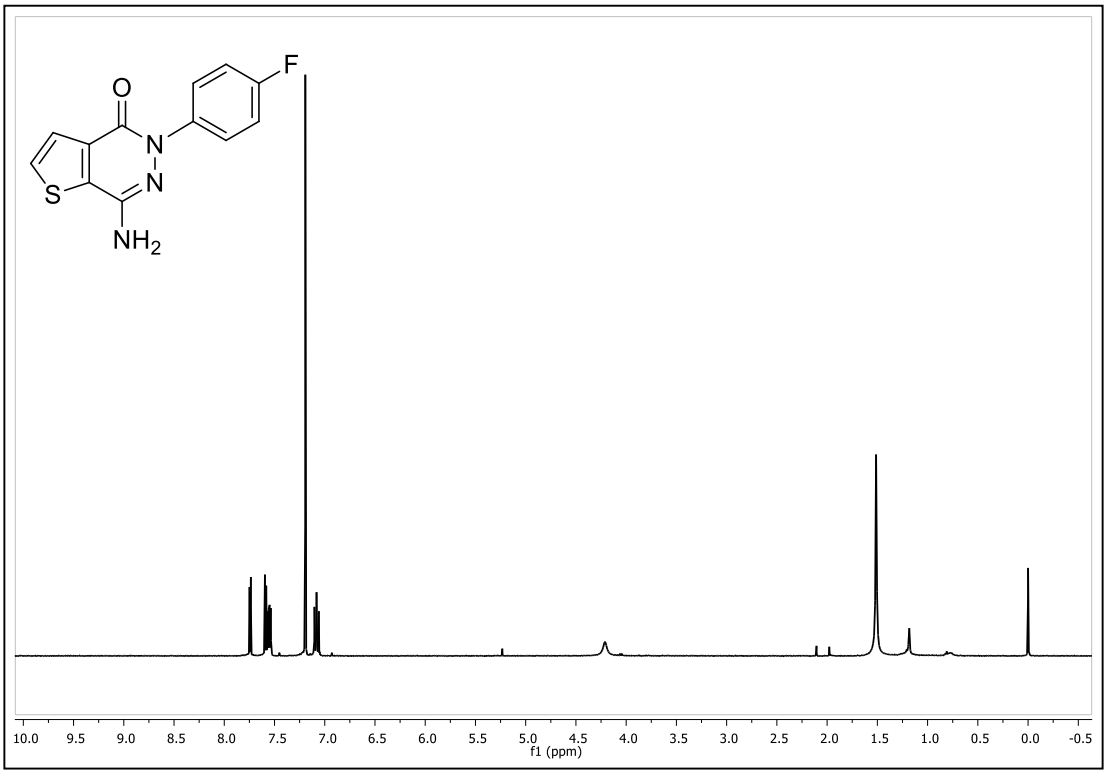

Figure A 109 ^{1}H NMR spectrum of compound **57f**

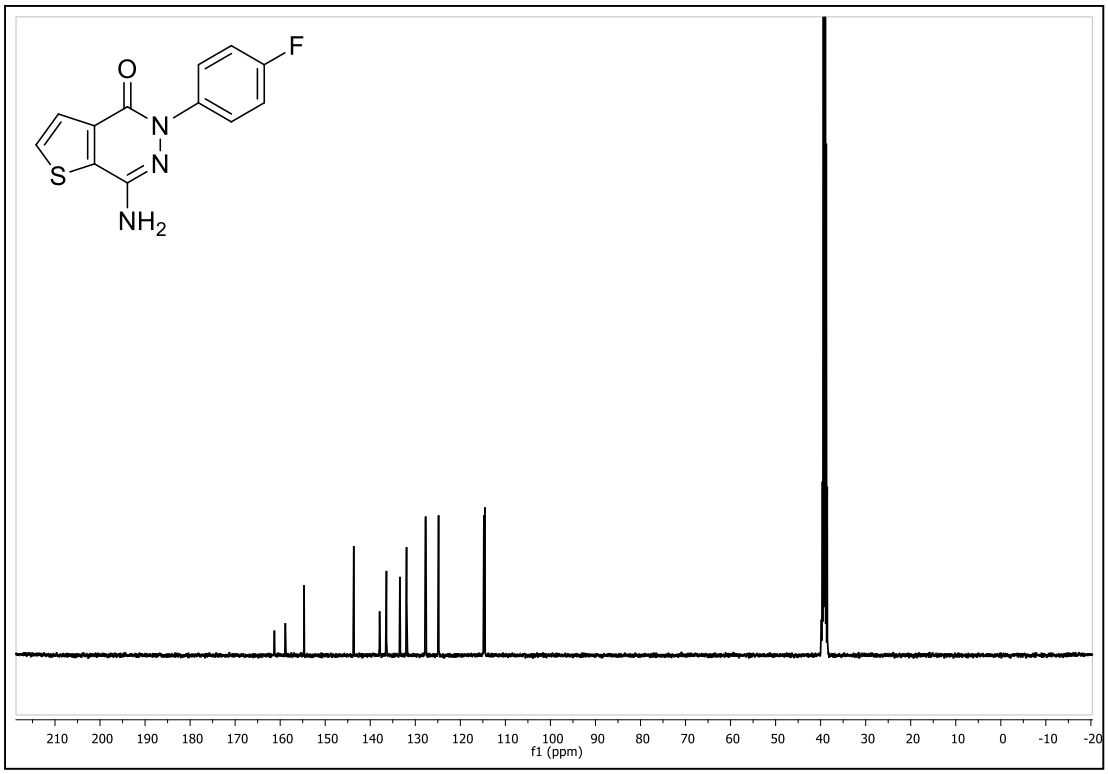

Figure A 110 ^{13}C NMR spectrum of compound **57f**

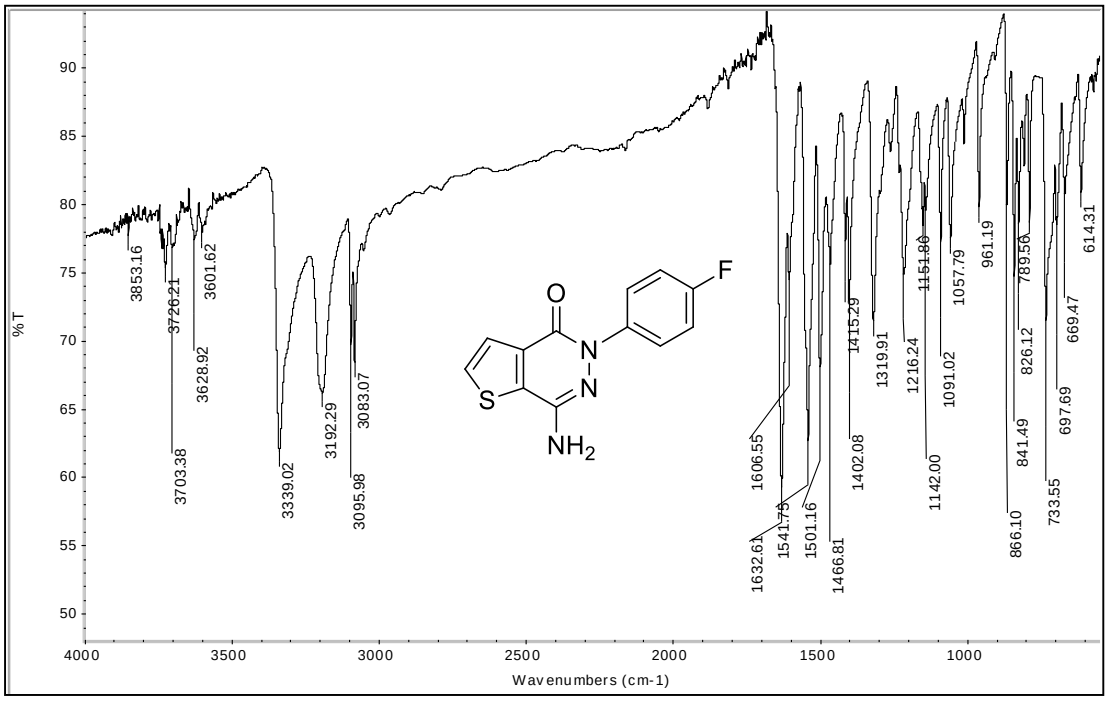

Figure A 111 IR spectrum of compound **57f**

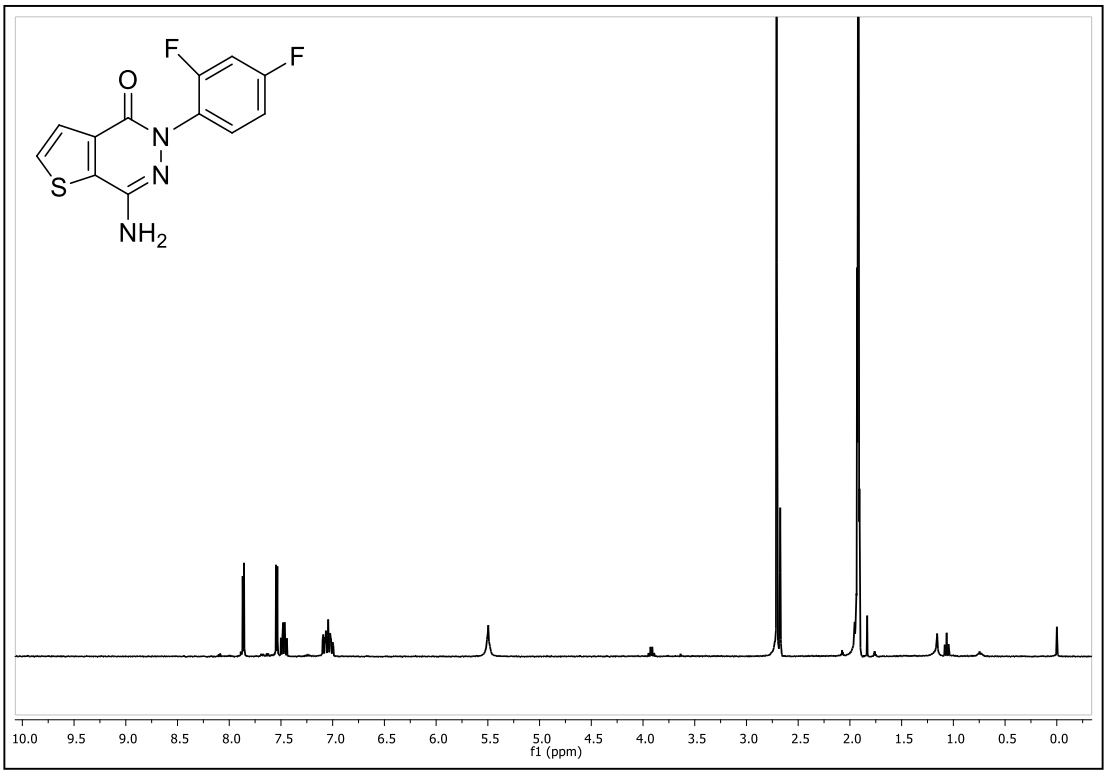

Figure A 112 ^{1}H NMR spectrum of compound **57g**

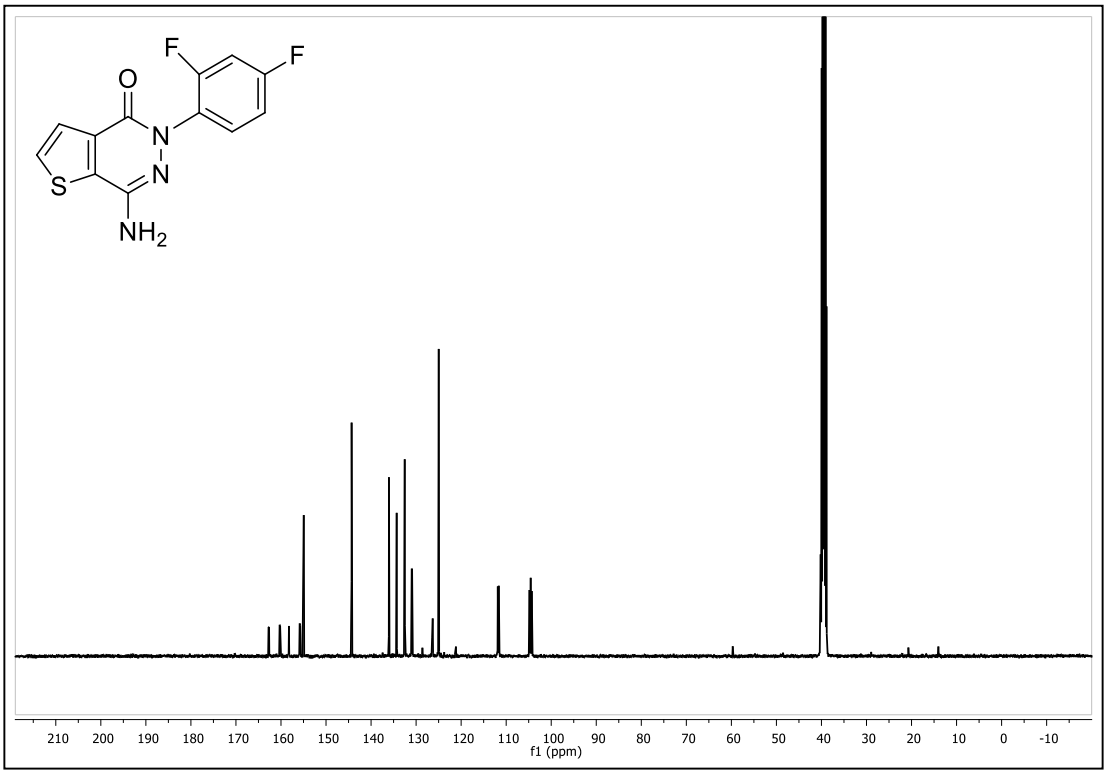

Figure A 113 ^{13}C NMR spectrum of compound **57g**

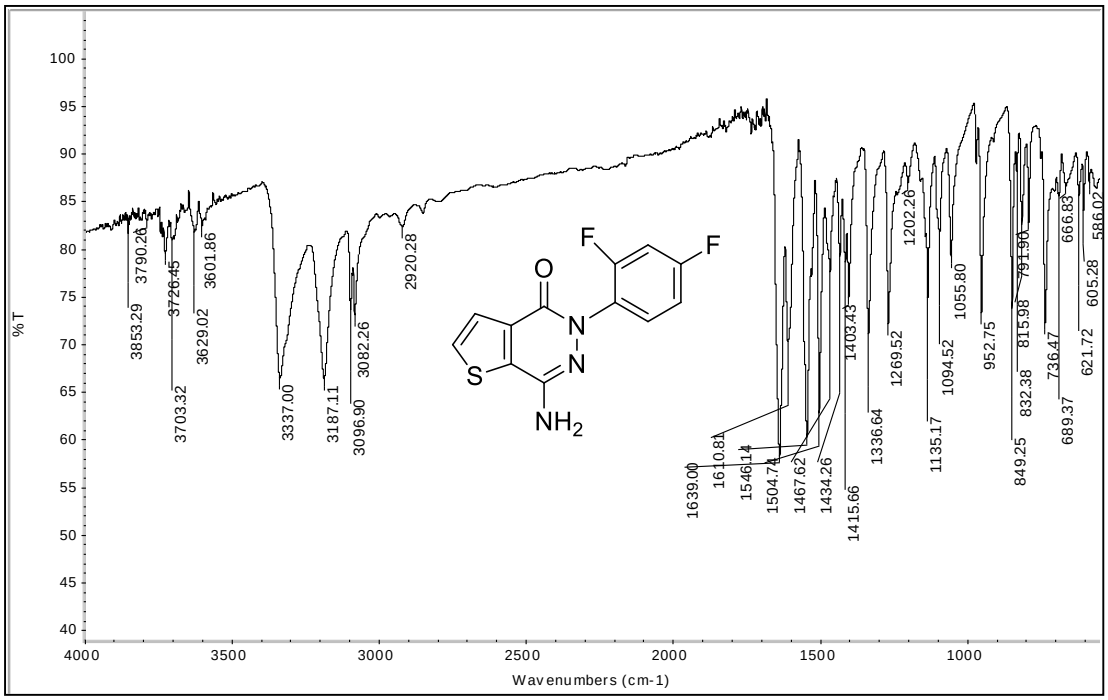

Figure A 114 IR spectrum of compound **57g**

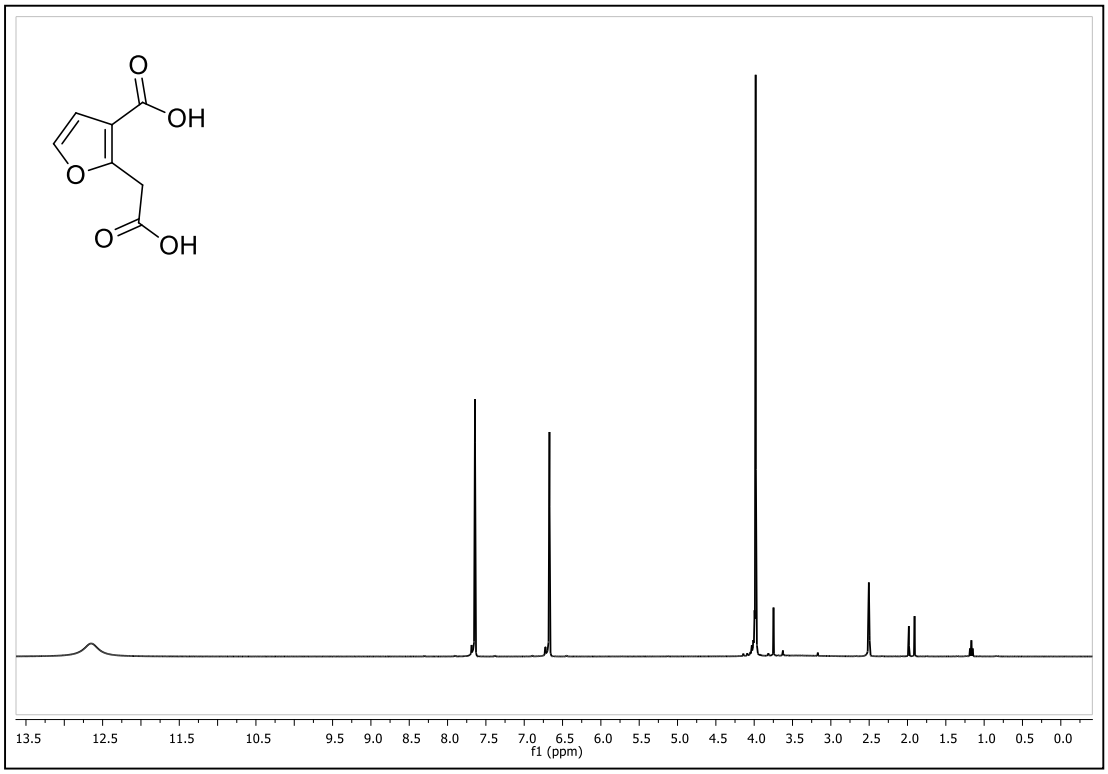

Figure A 115 ^{1}H NMR spectrum of compound **91**

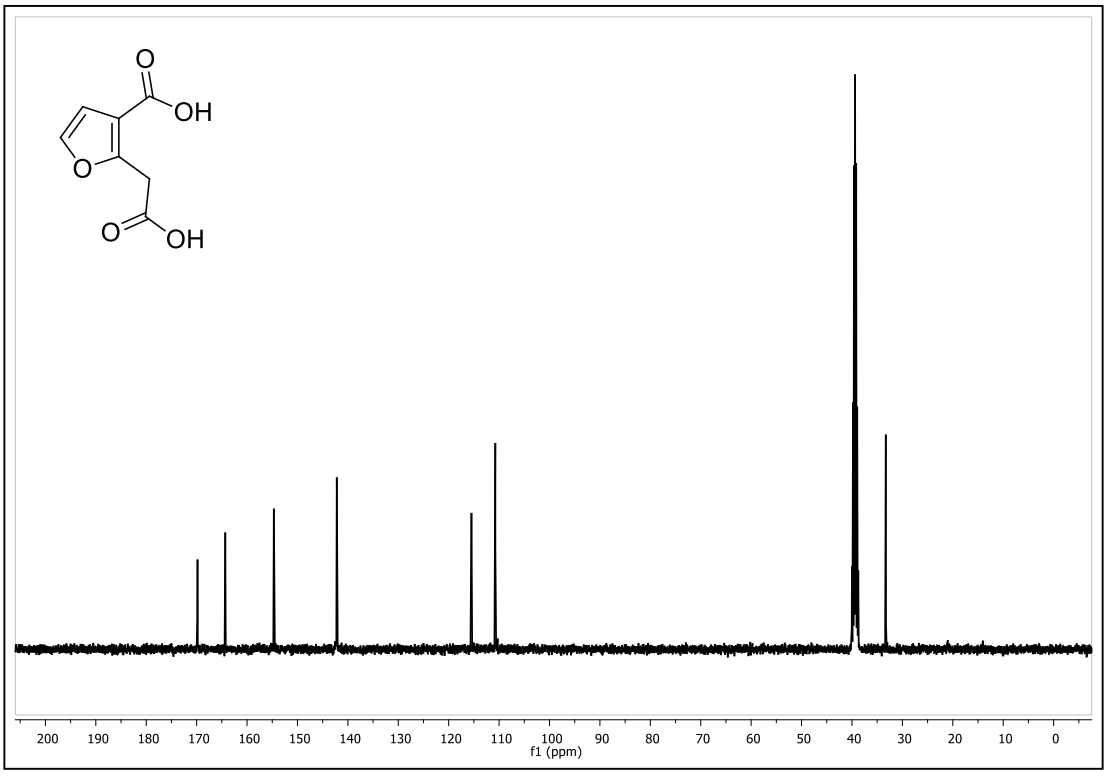

Figure A 116 ^{13}C NMR spectrum of compound **91**

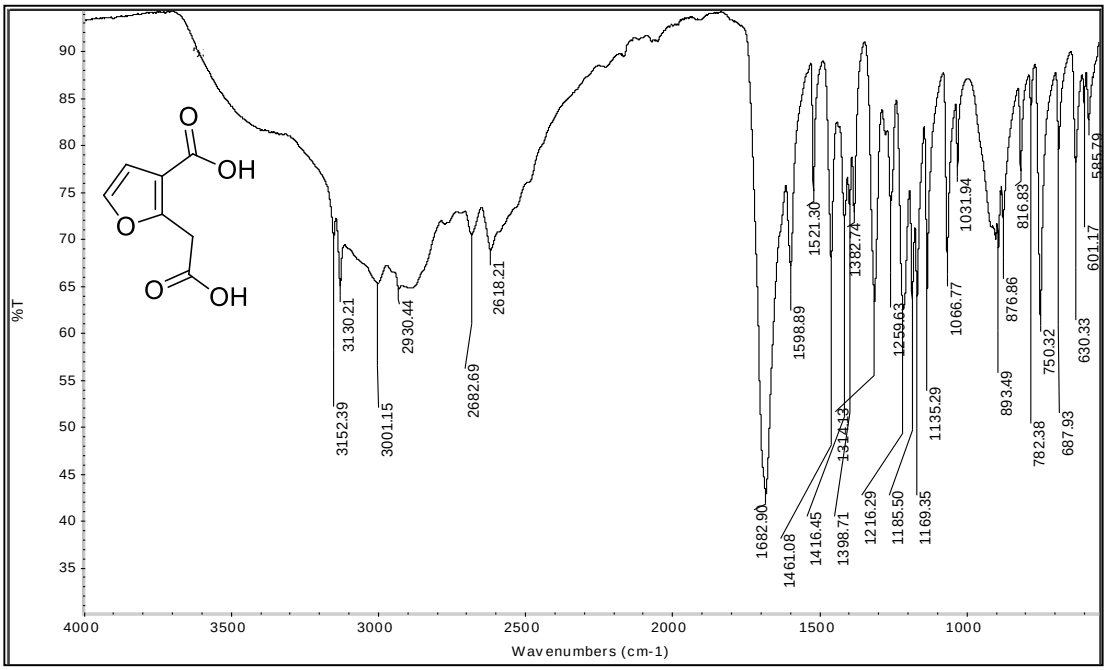

Figure A 117 IR spectrum of compound **91**

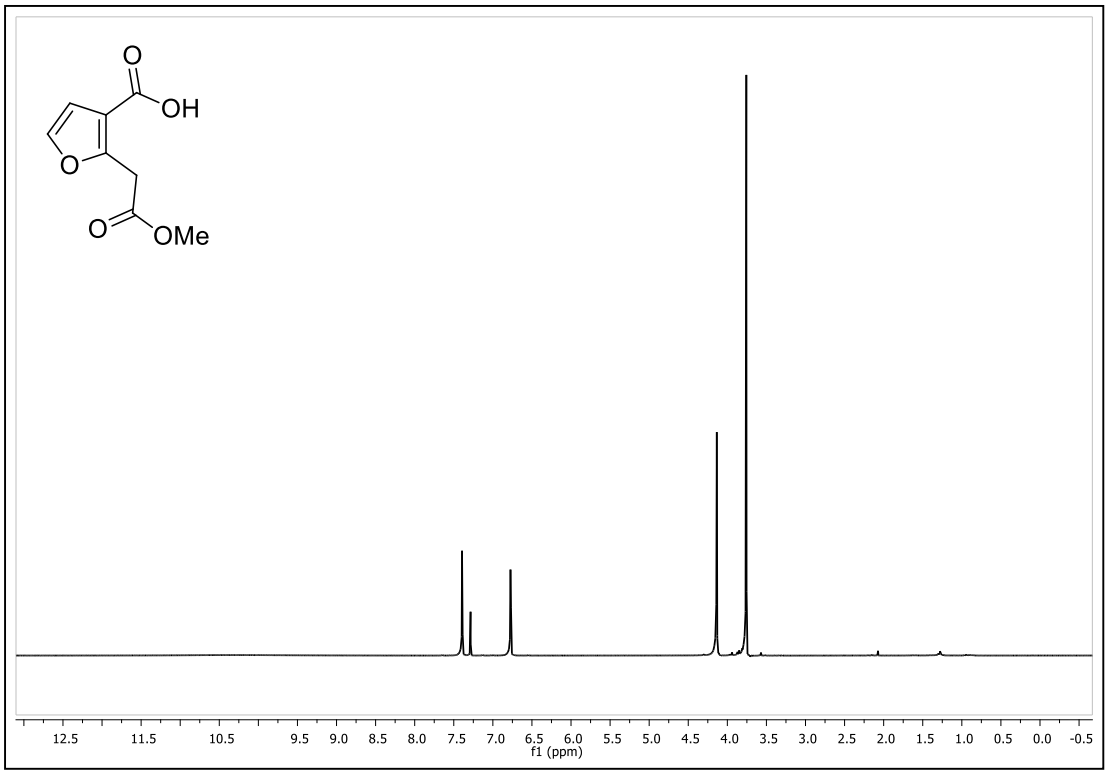

Figure A 118 ^{1}H NMR spectrum of compound **92**

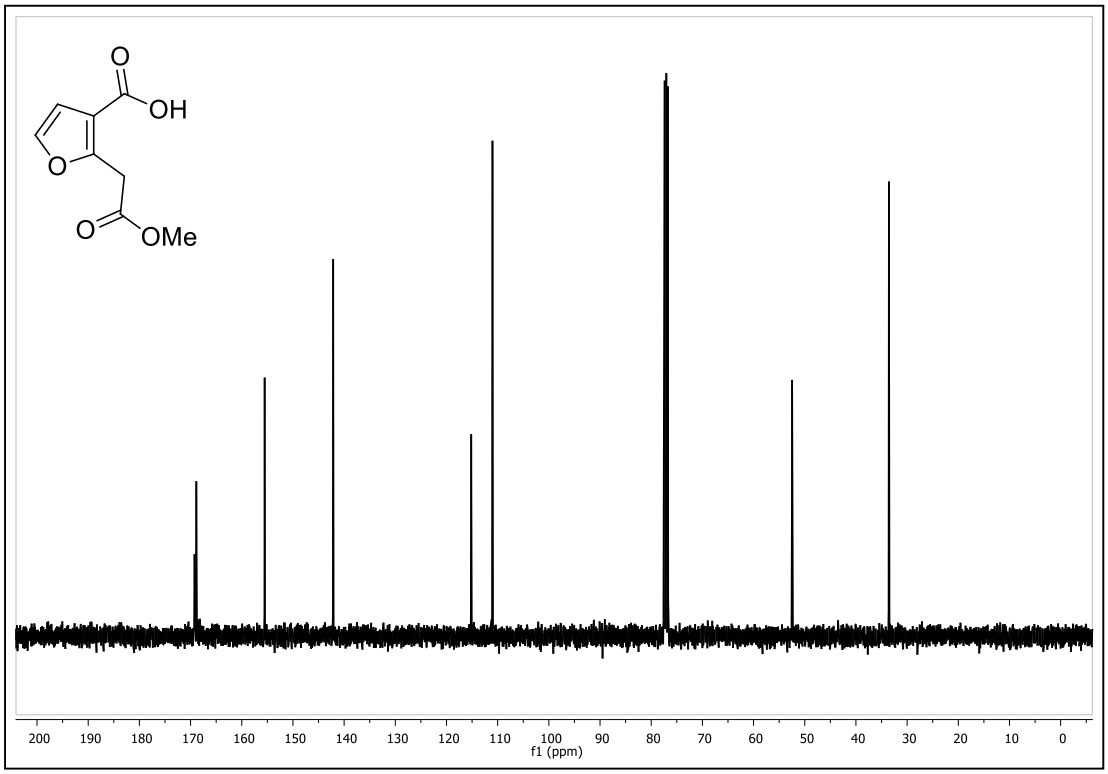

Figure A 119 ^{13}C NMR spectrum of compound **92**

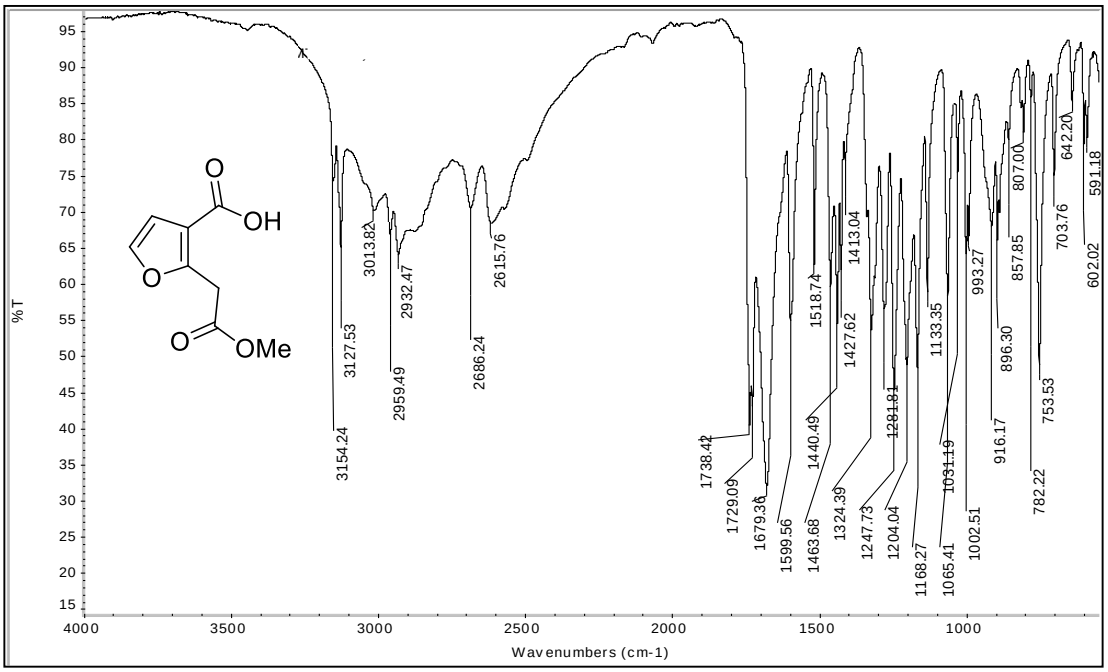

Figure A 120 IR spectrum of compound **92**

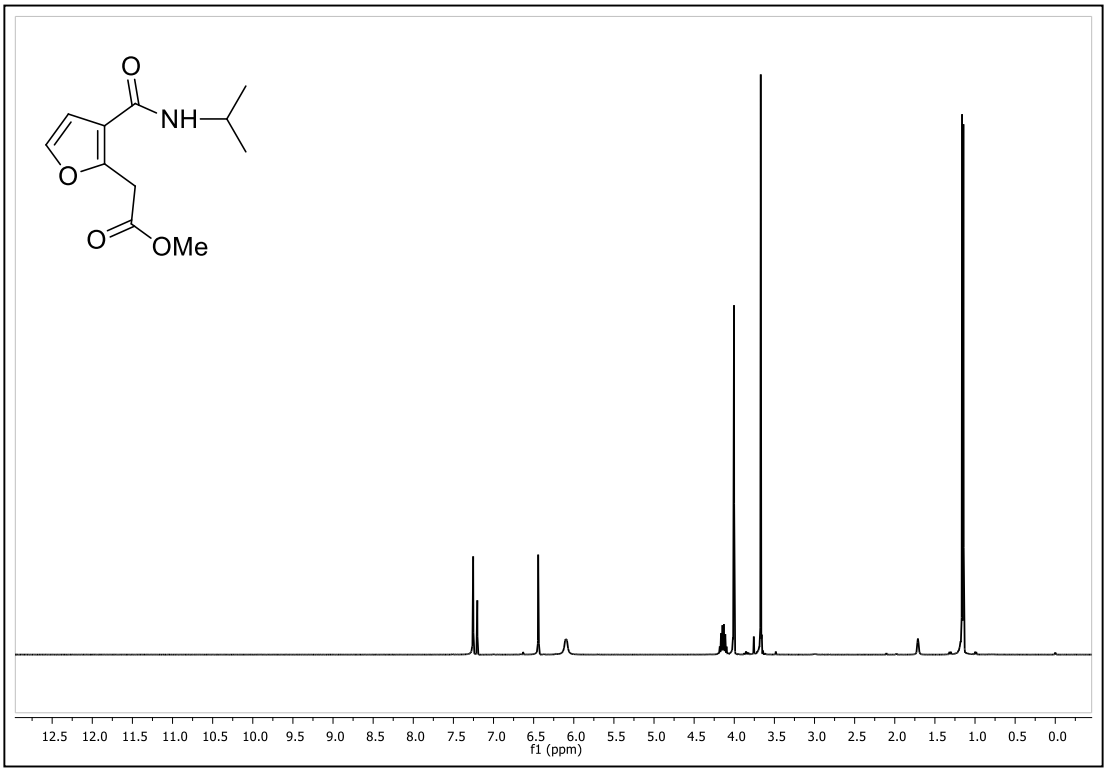

Figure A 121 ^{1}H NMR spectrum of compound **95a**

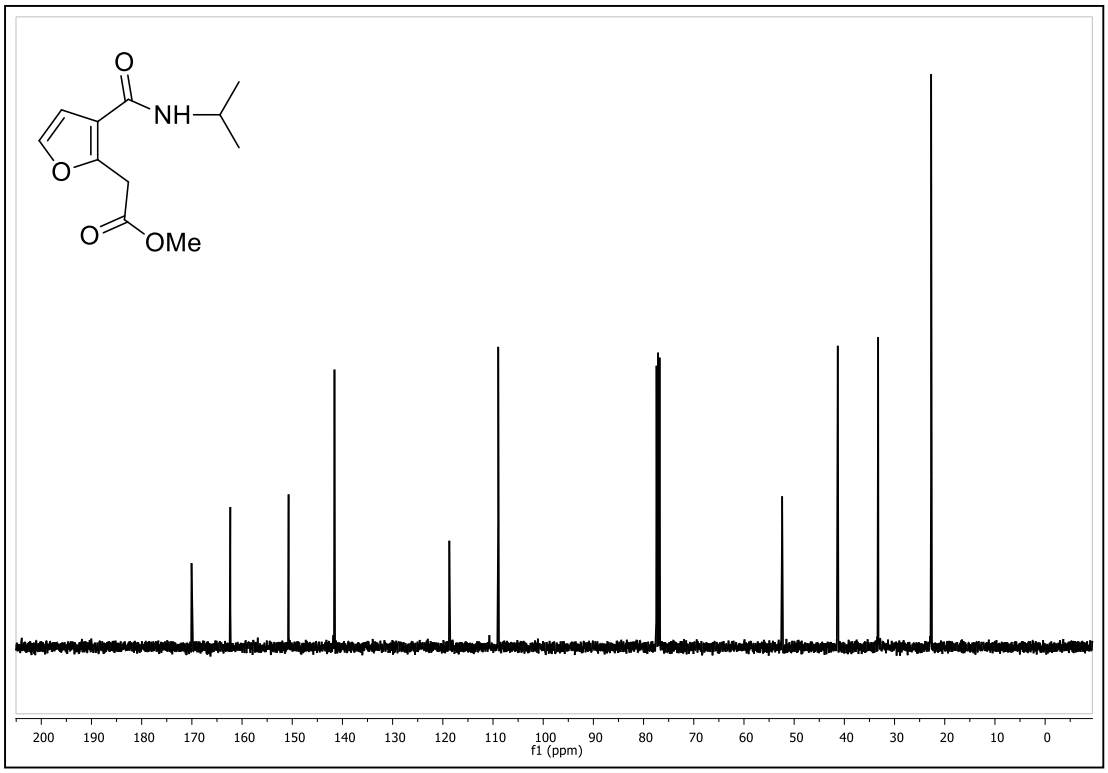

Figure A 122 ^{13}C NMR spectrum of compound **95a**

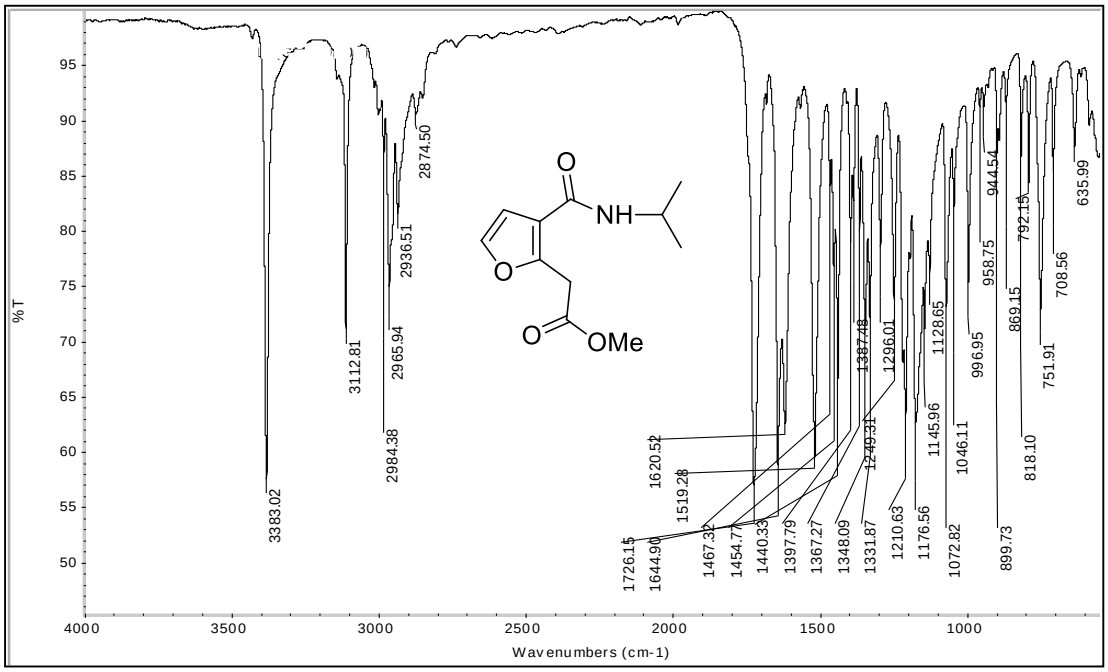

Figure A 123 IR spectrum of compound **95a**

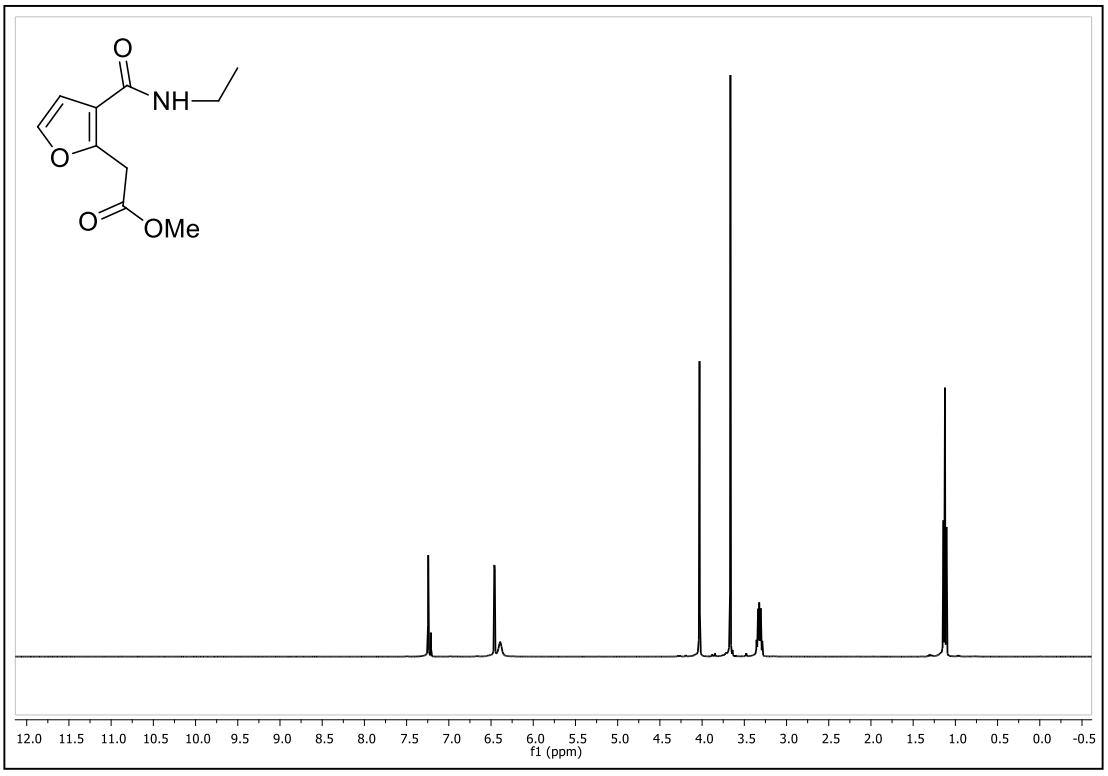

Figure A 124 ^{1}H NMR spectrum of compound **95b**

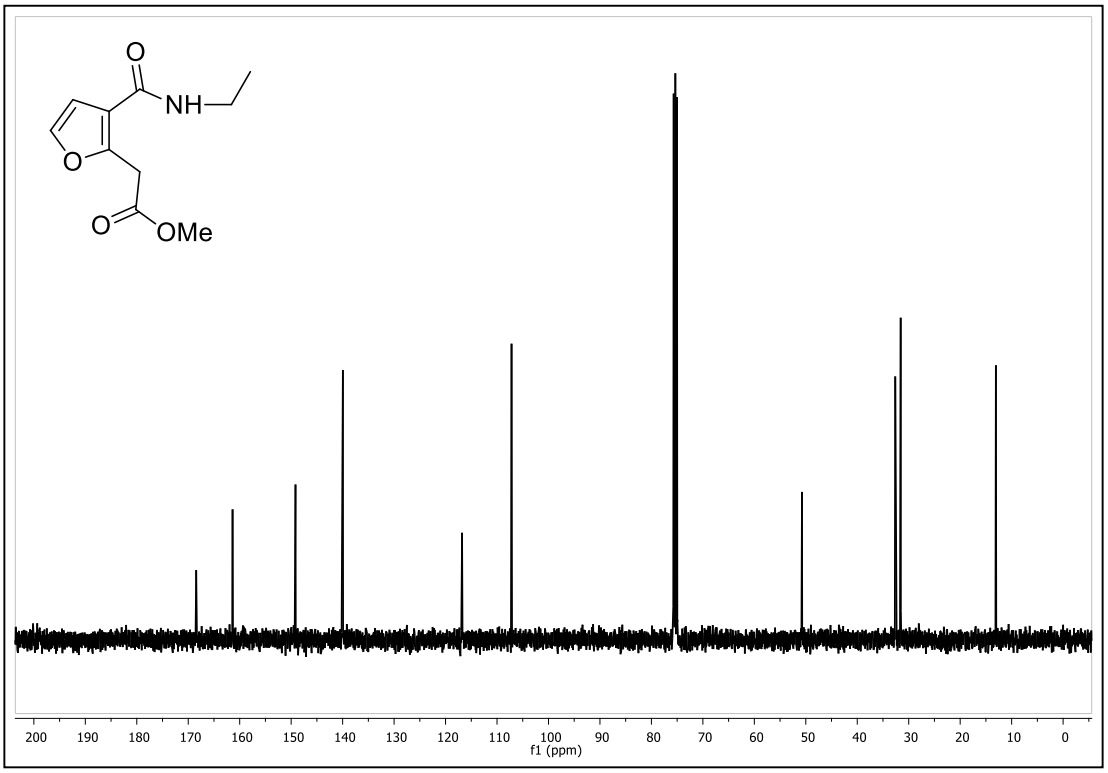

Figure A 125 ^{13}C NMR spectrum of compound **95b**

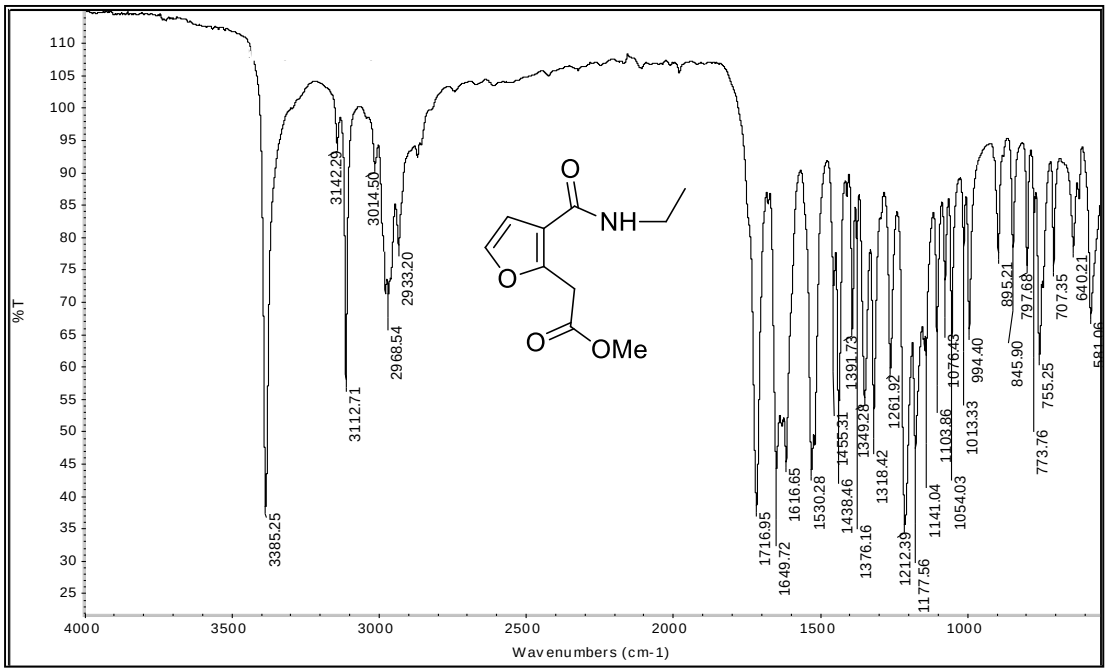

Figure A 126IR spectrum of compound **95b**

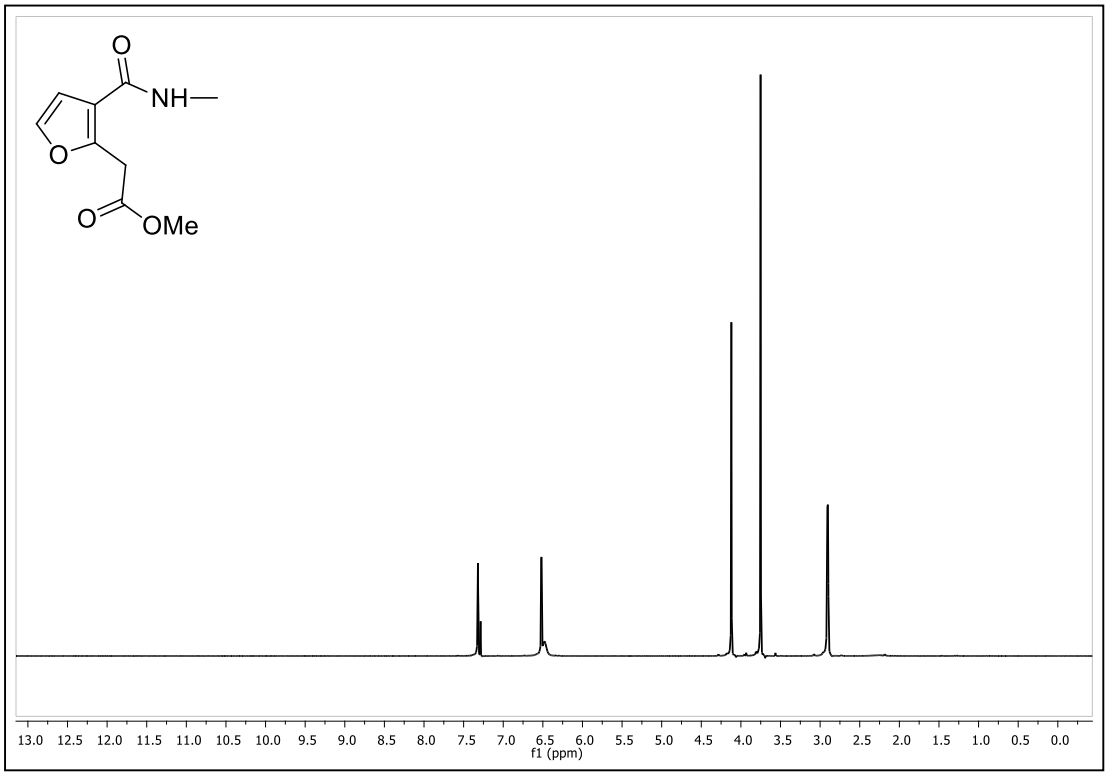

Figure A 127 [1]H NMR spectrum of compound **95c**

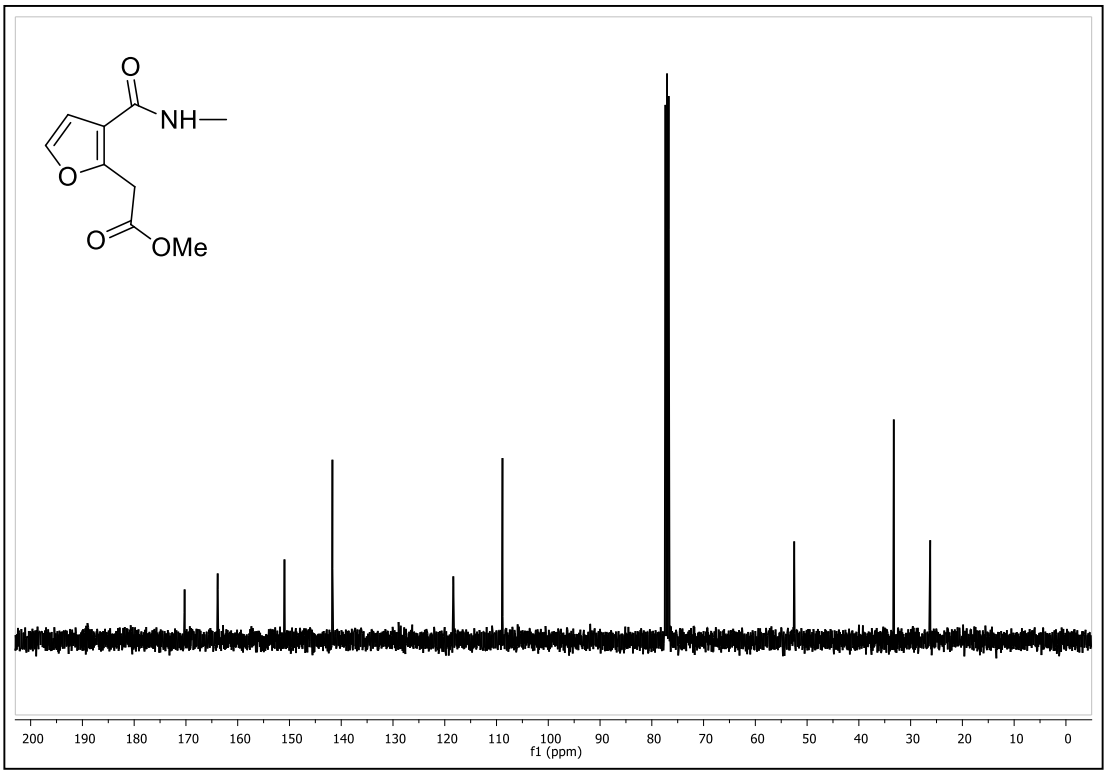

Figure A 128 ^{13}C NMR spectrum of compound **95c**

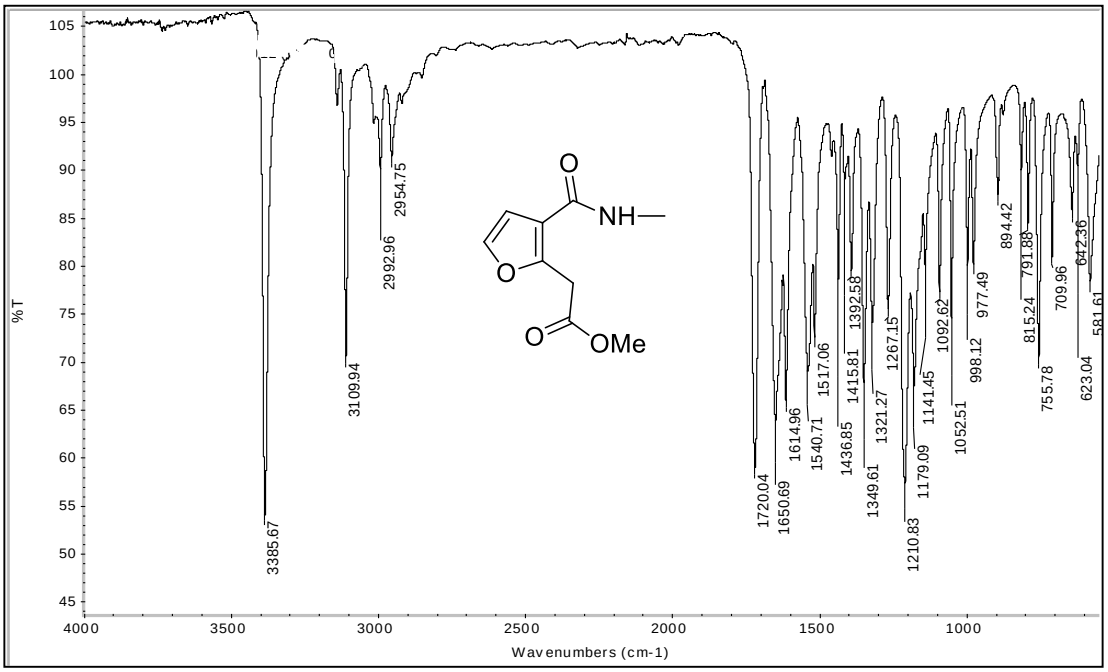

Figure A 129 IR spectrum of compound **95c**

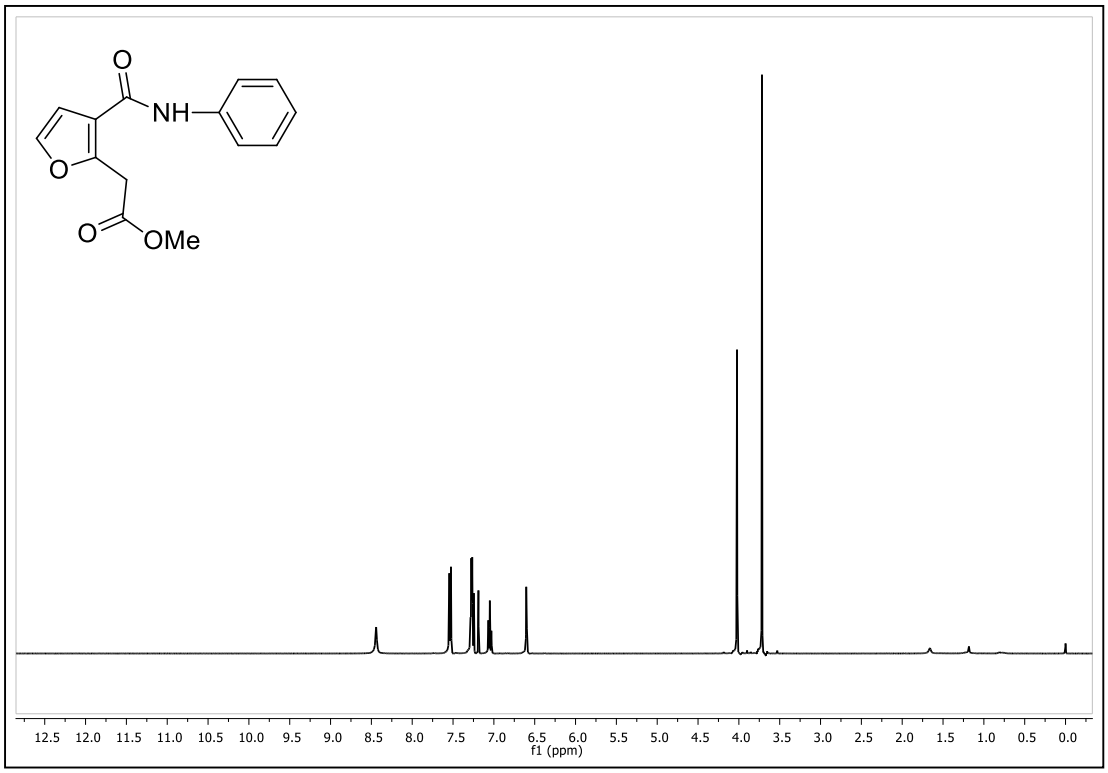

Figure A 130 ^{1}H NMR spectrum of compound **95d**

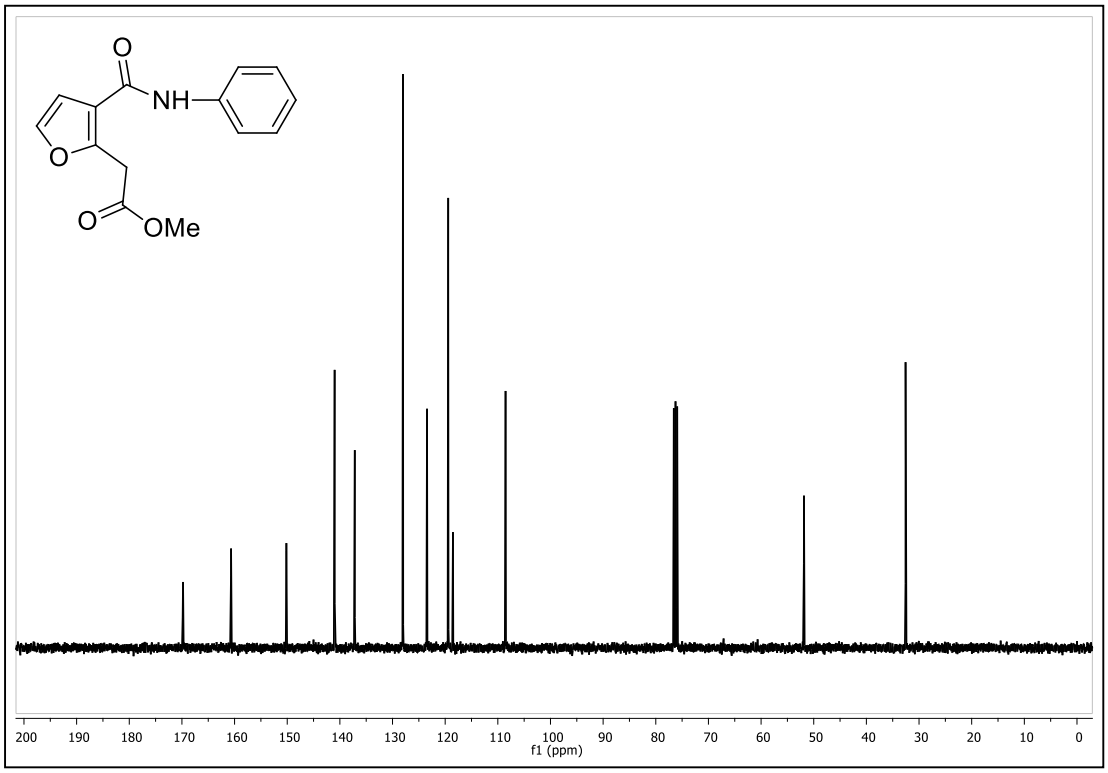

Figure A 131 ^{13}C NMR spectrum of compound **95d**

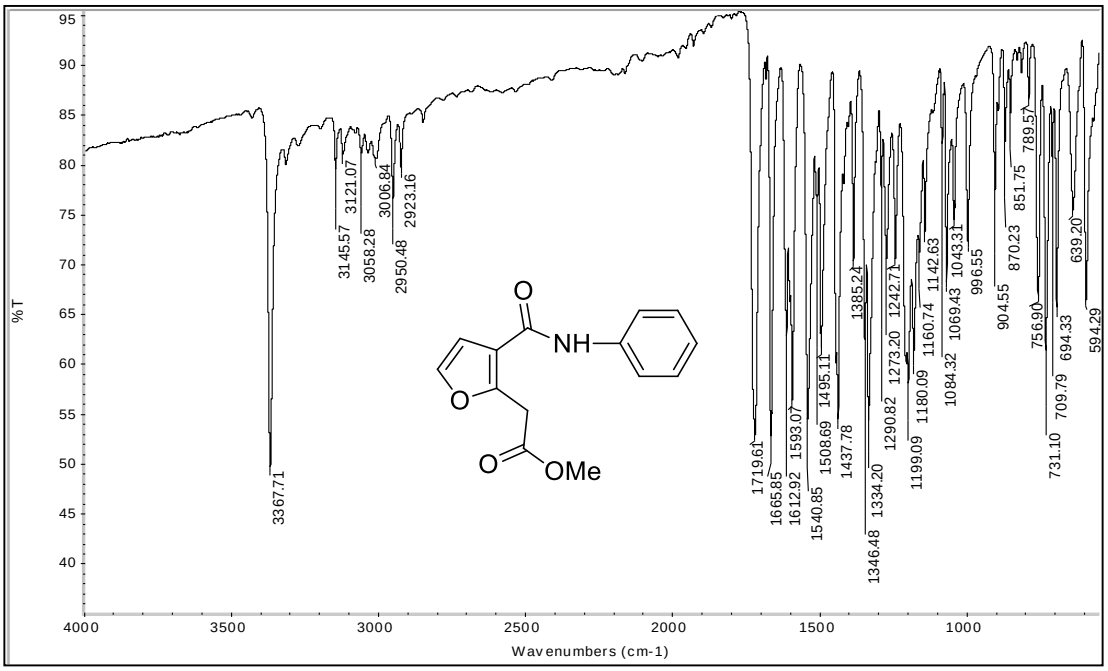

Figure A 132 IR spectrum of compound **95d**

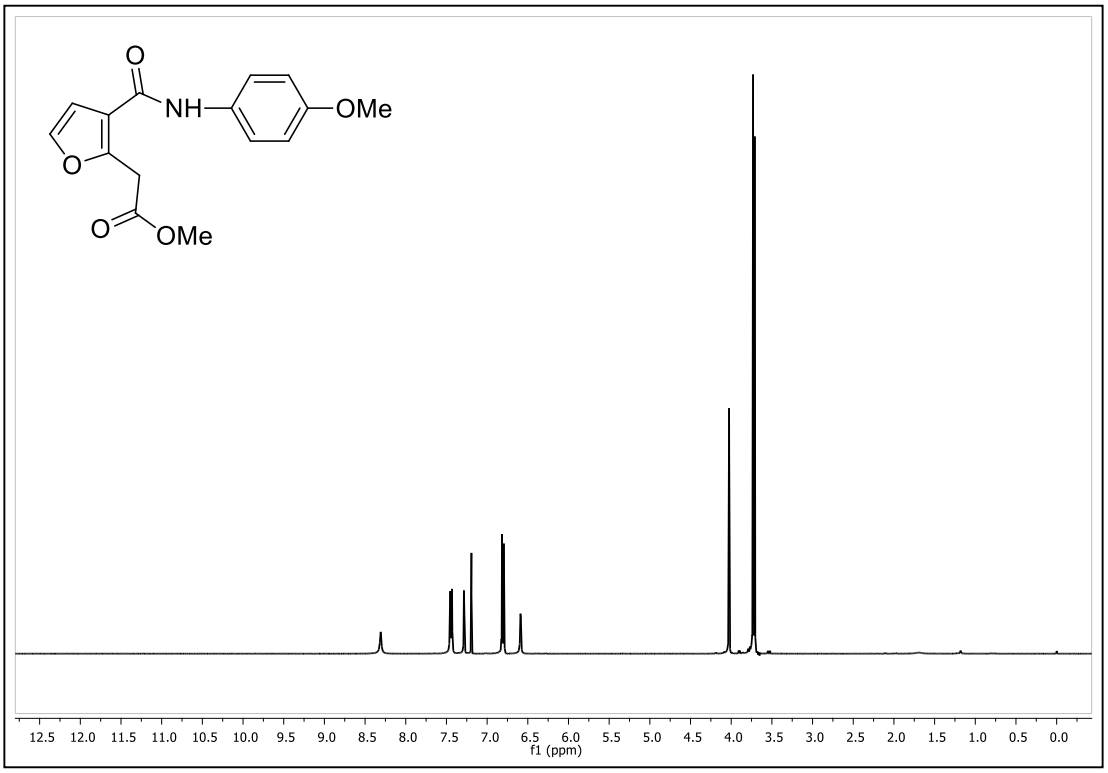

Figure A 133 ^{1}H NMR spectrum of compound **95e**

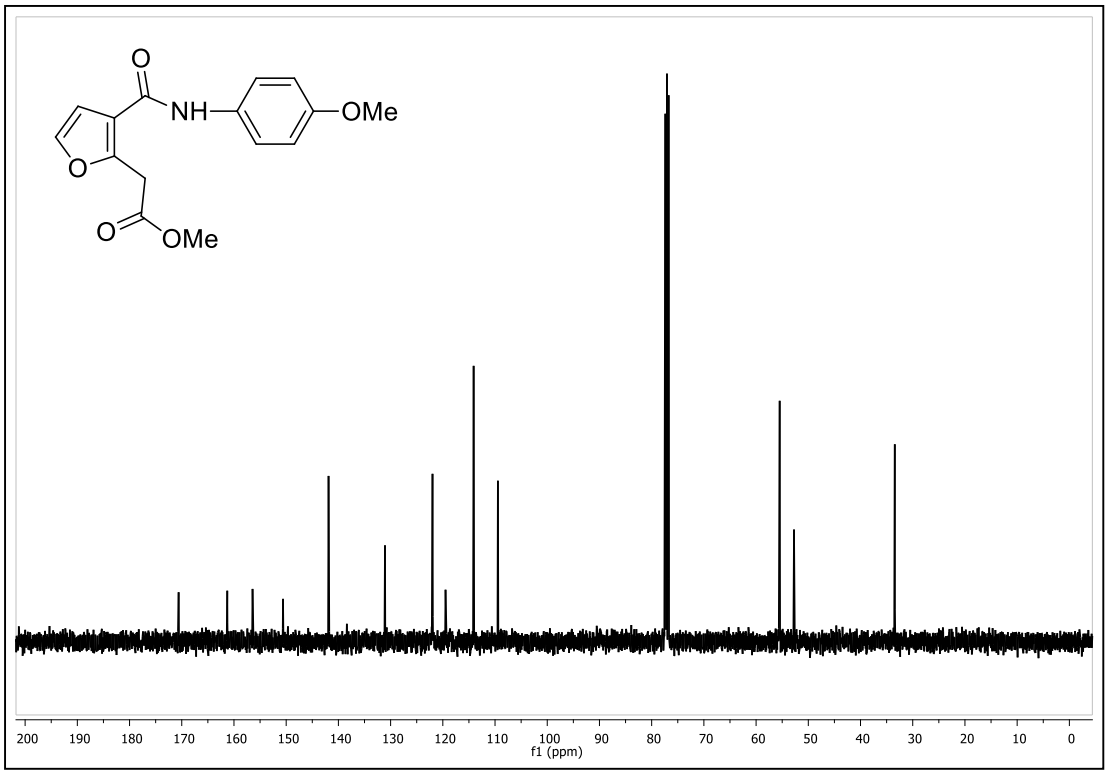

Figure A 134 ^{13}C NMR spectrum of compound **95e**

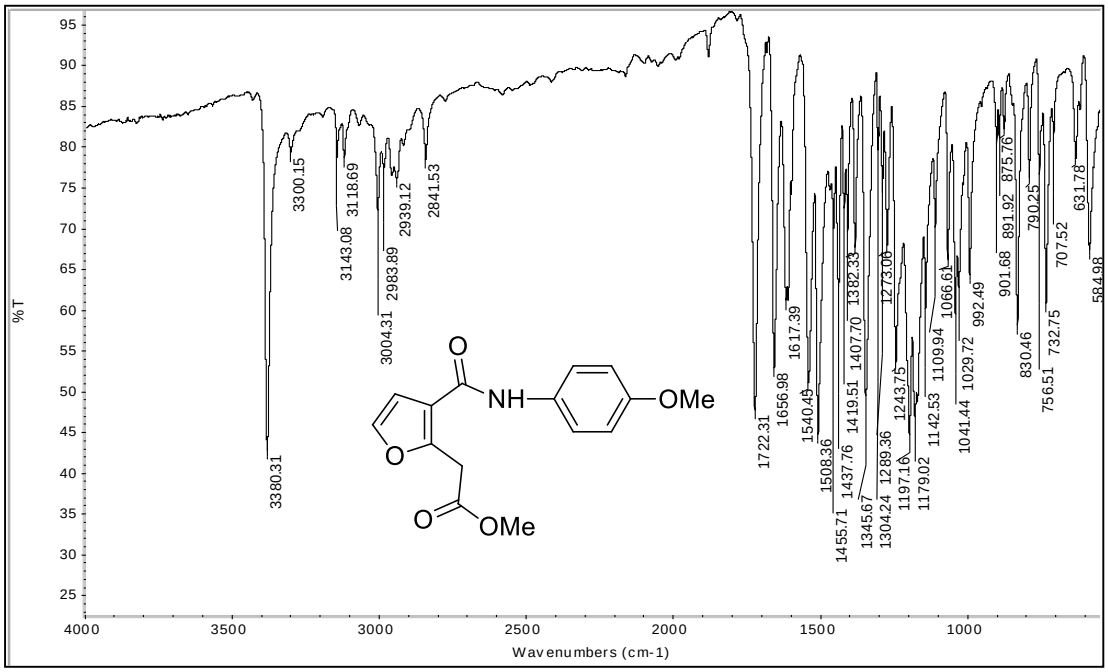

Figure A 135 IR spectrum of compound **95e**

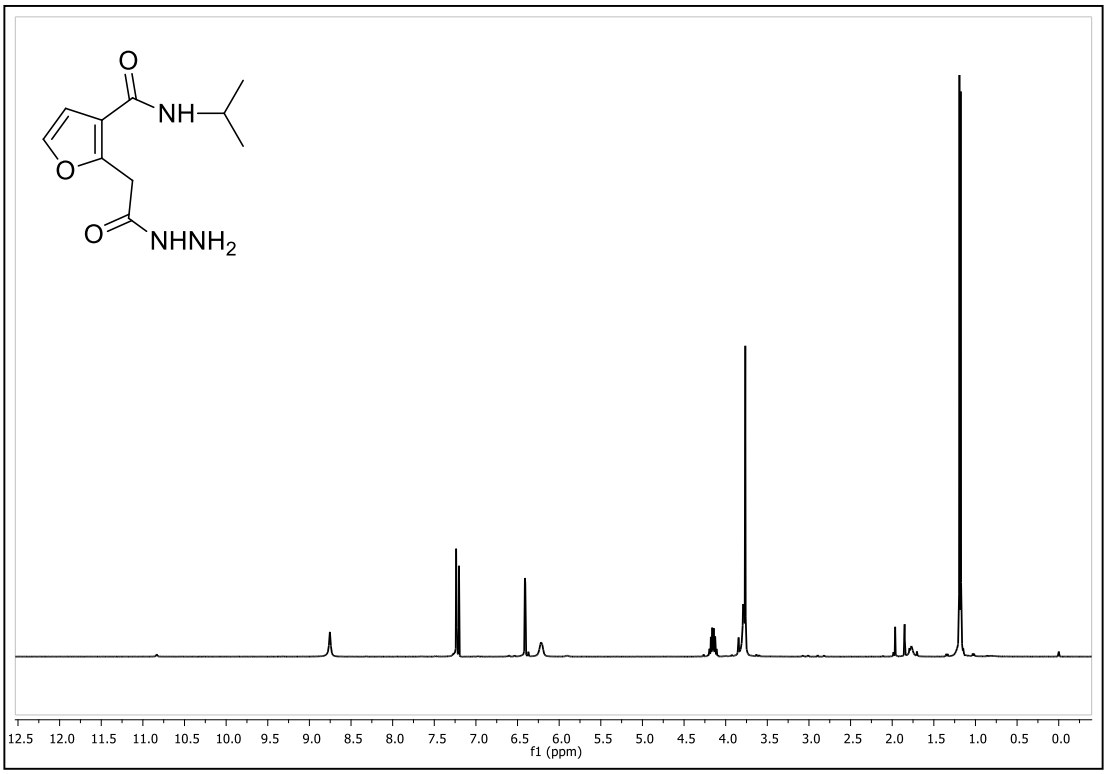

Figure A 136 ^{1}H NMR spectrum of compound **97a**

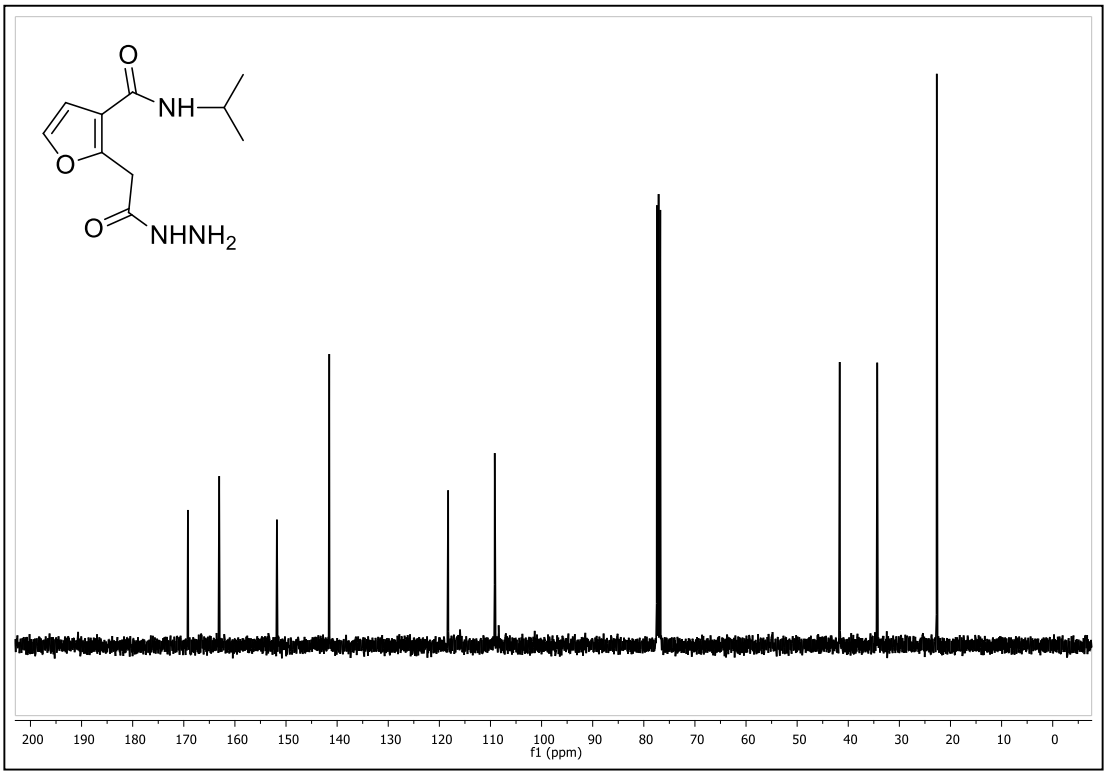

Figure A 137 ^{13}C NMR spectrum of compound **97a**

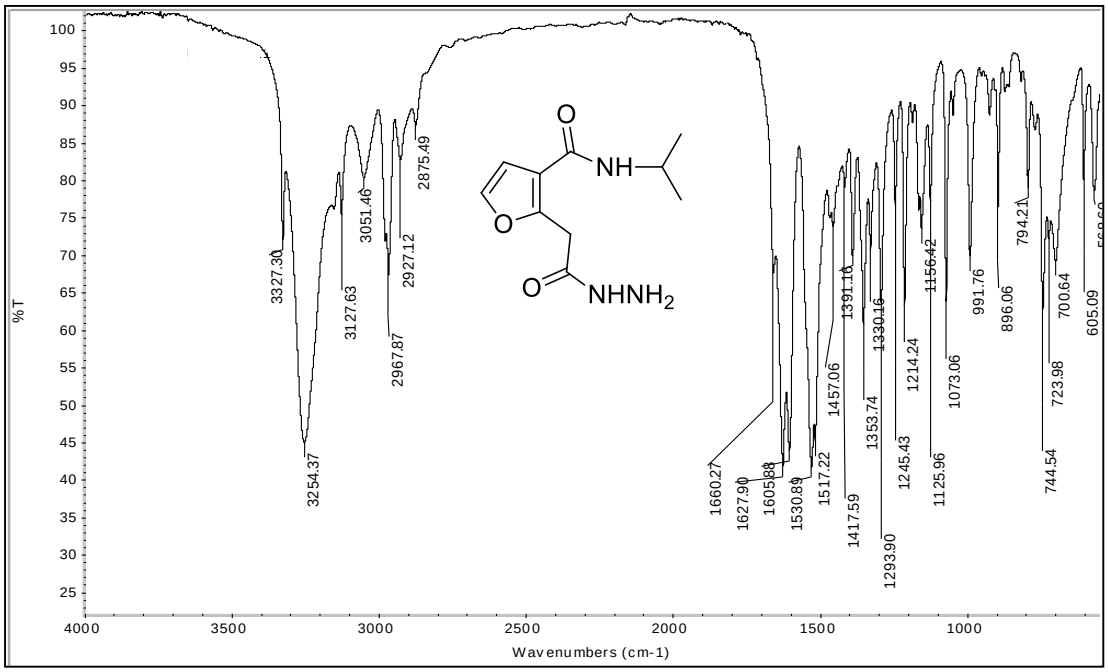

Figure A 138 IR spectrum of compound **97a**

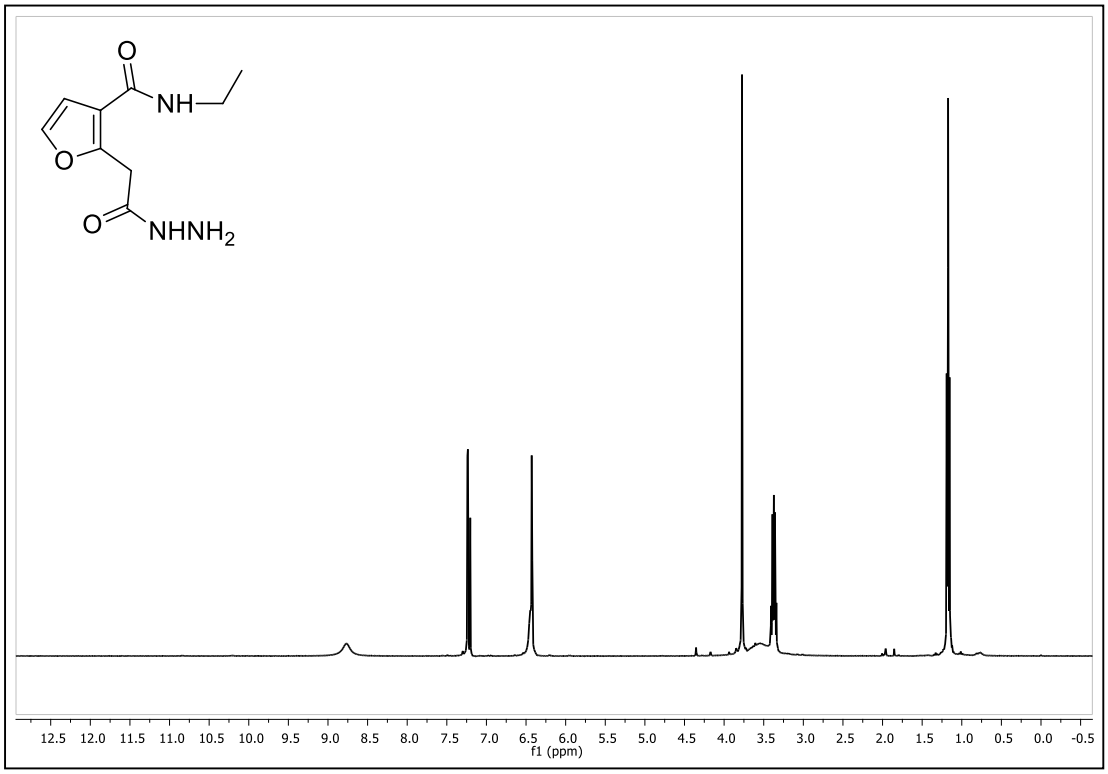

Figure A 139 ^{1}H NMR spectrum of compound **97b**

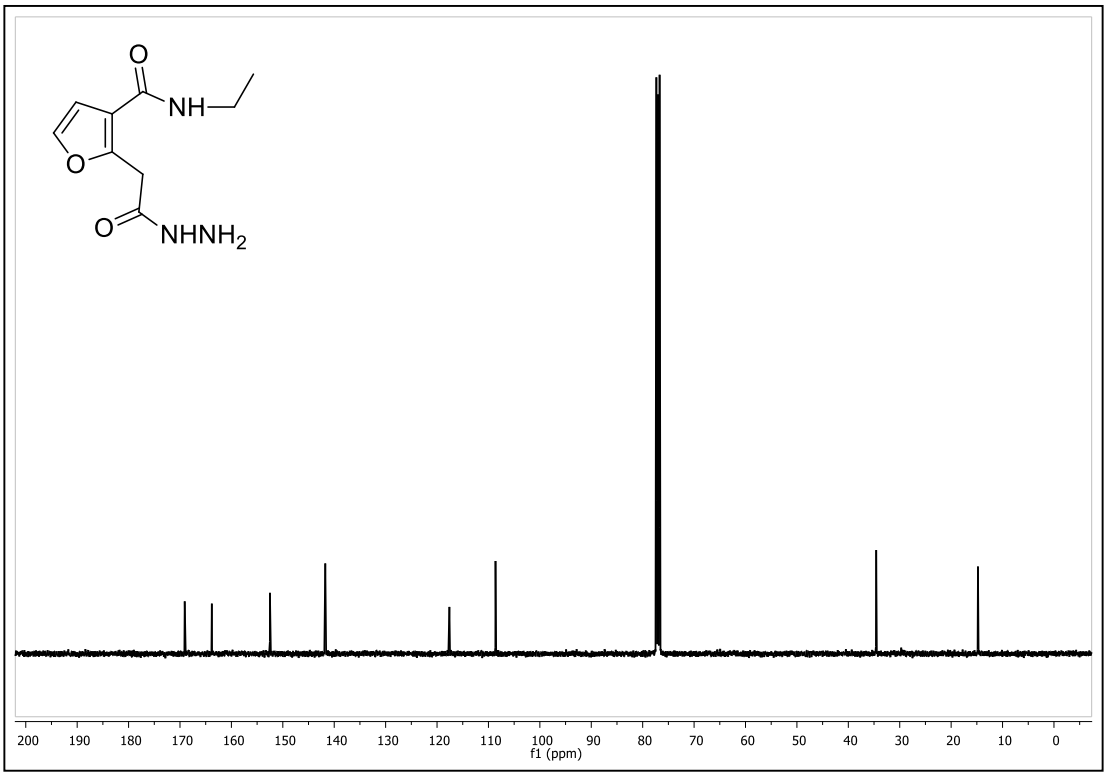

Figure A 140 ^{13}C NMR spectrum of compound **97b**

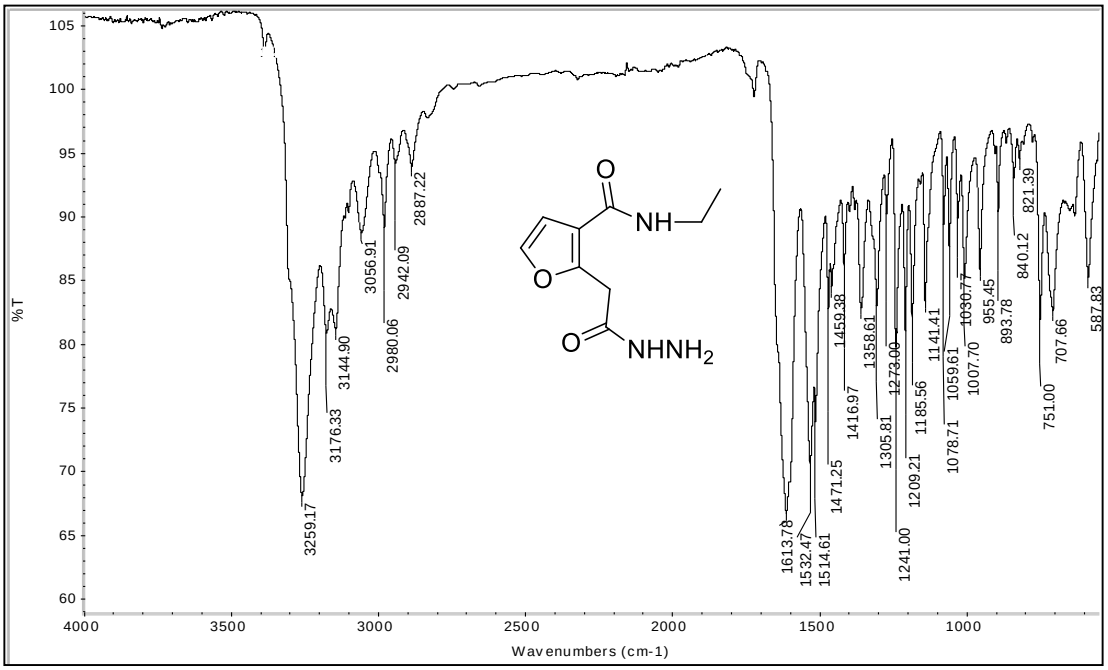

Figure A 141 IR spectrum of compound **97b**

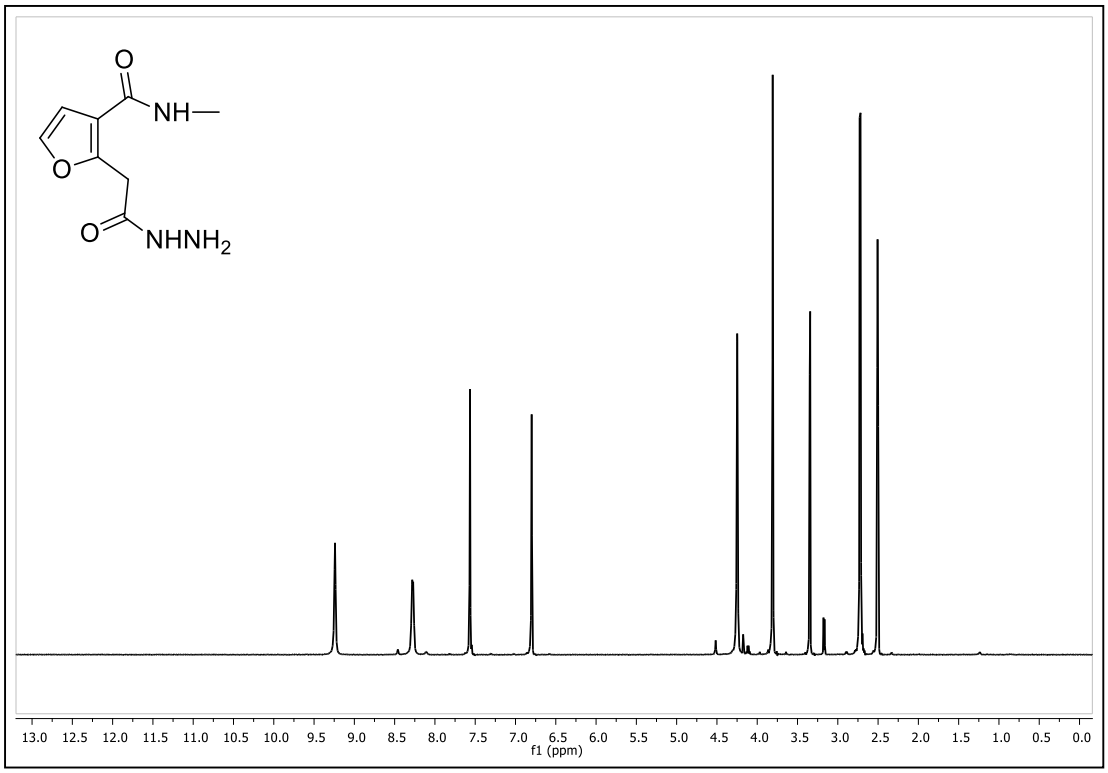

Figure A 142 ^{1}H NMR spectrum of compound **97c**

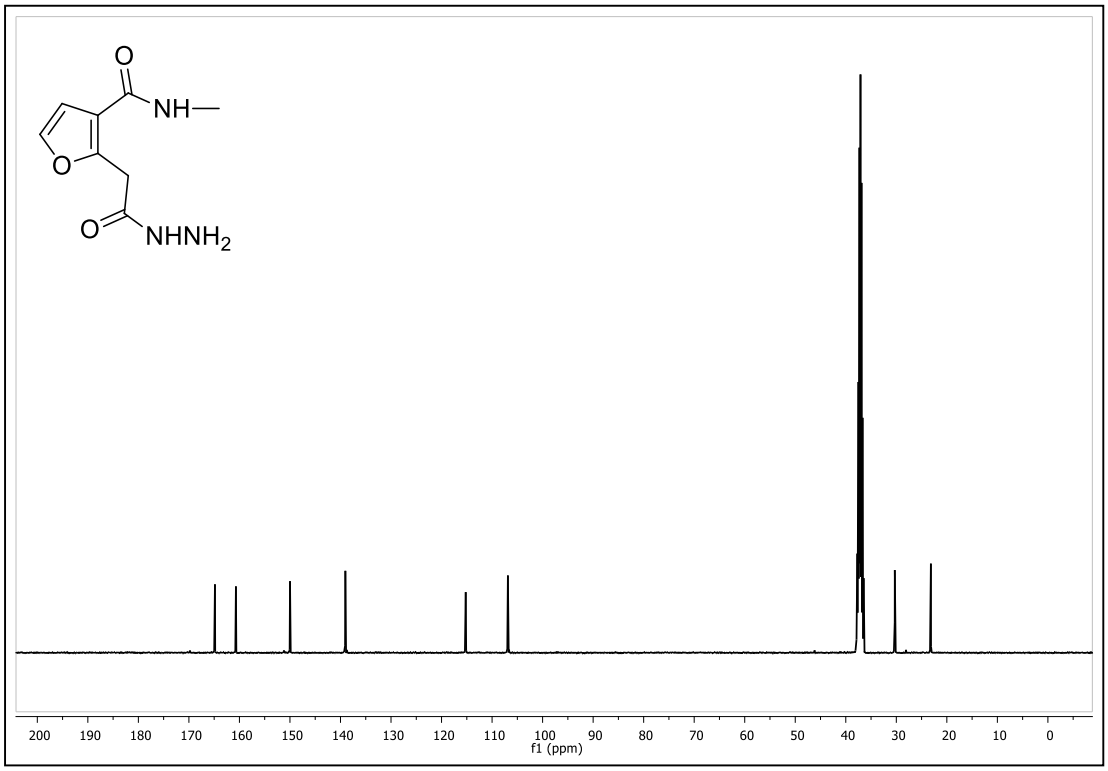

Figure A 143 ^{13}C NMR spectrum of compound **97c**

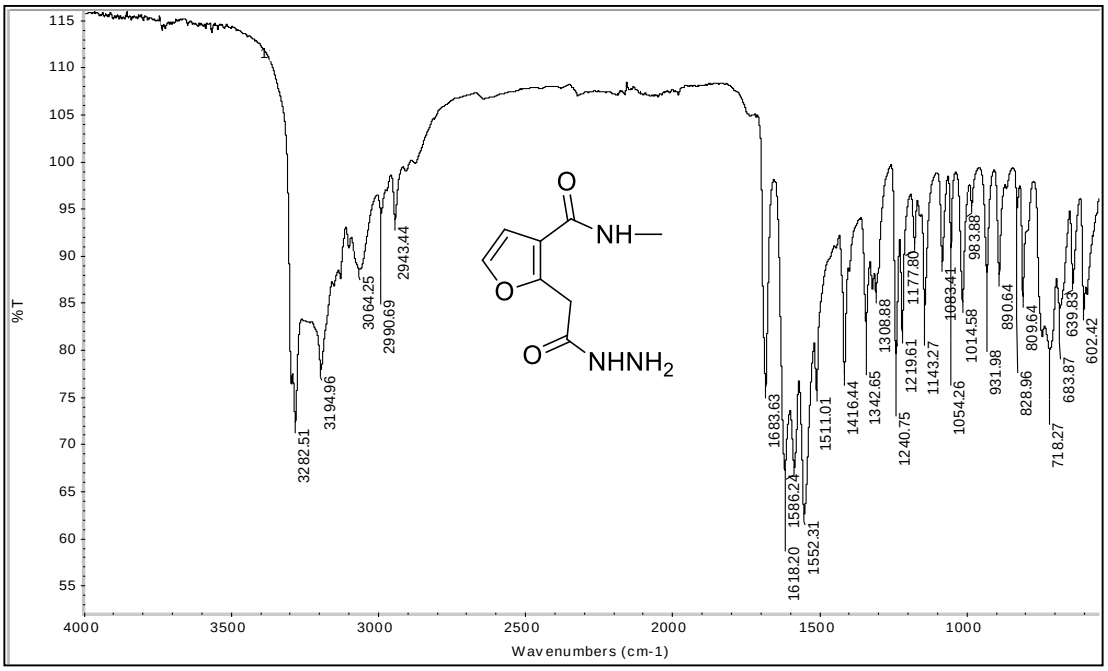

Figure A 144 IR spectrum of compound **97c**

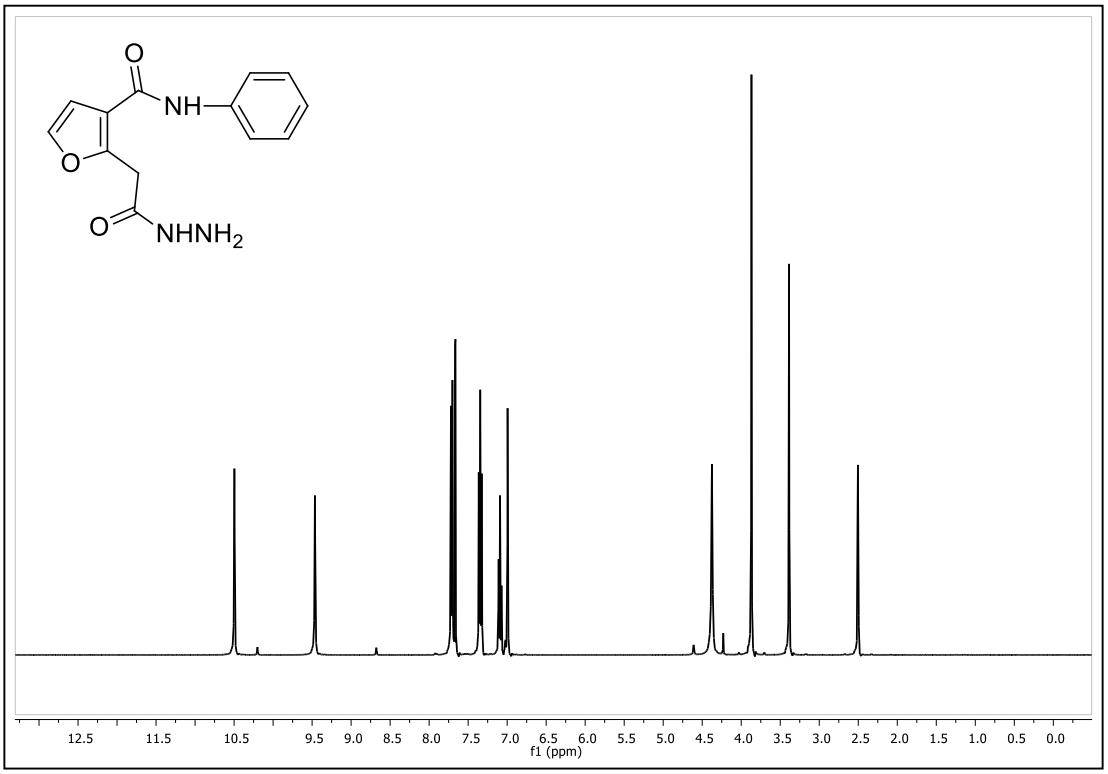

Figure A 145 ^{1}H NMR spectrum of compound **97d**

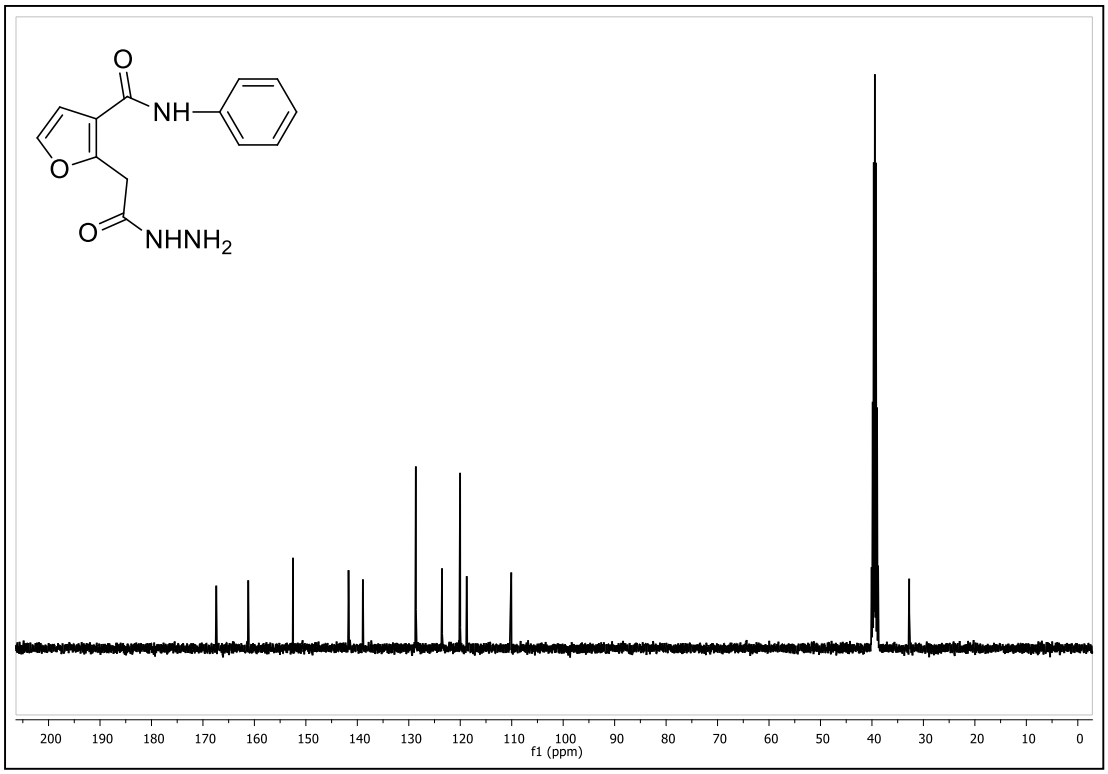

Figure A 146 ^{13}C NMR spectrum of compound **97d**

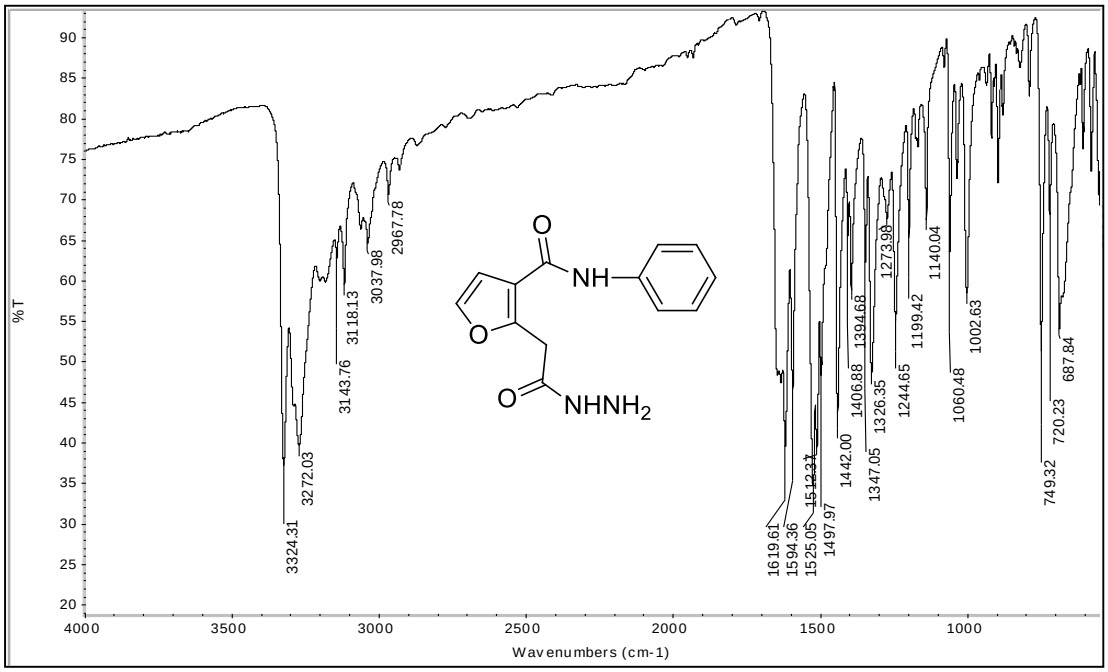

Figure A 147 IR spectrum of compound **97d**

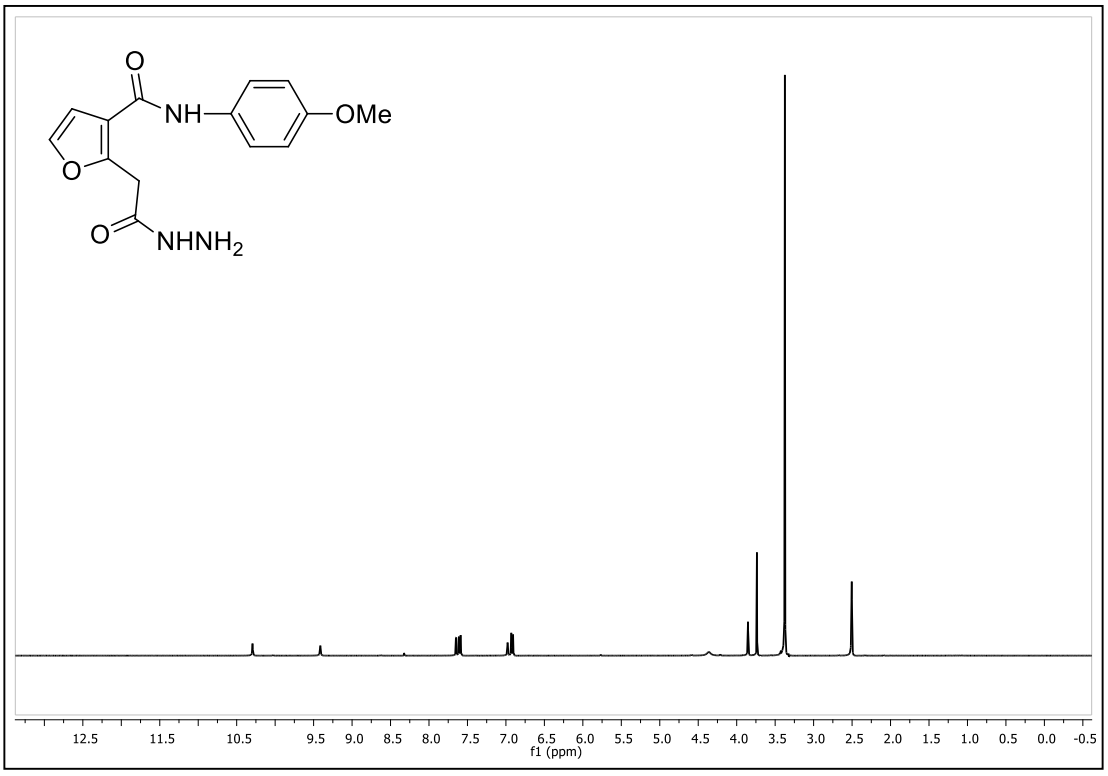

Figure A 148 ^{1}H NMR spectrum of compound **97e**

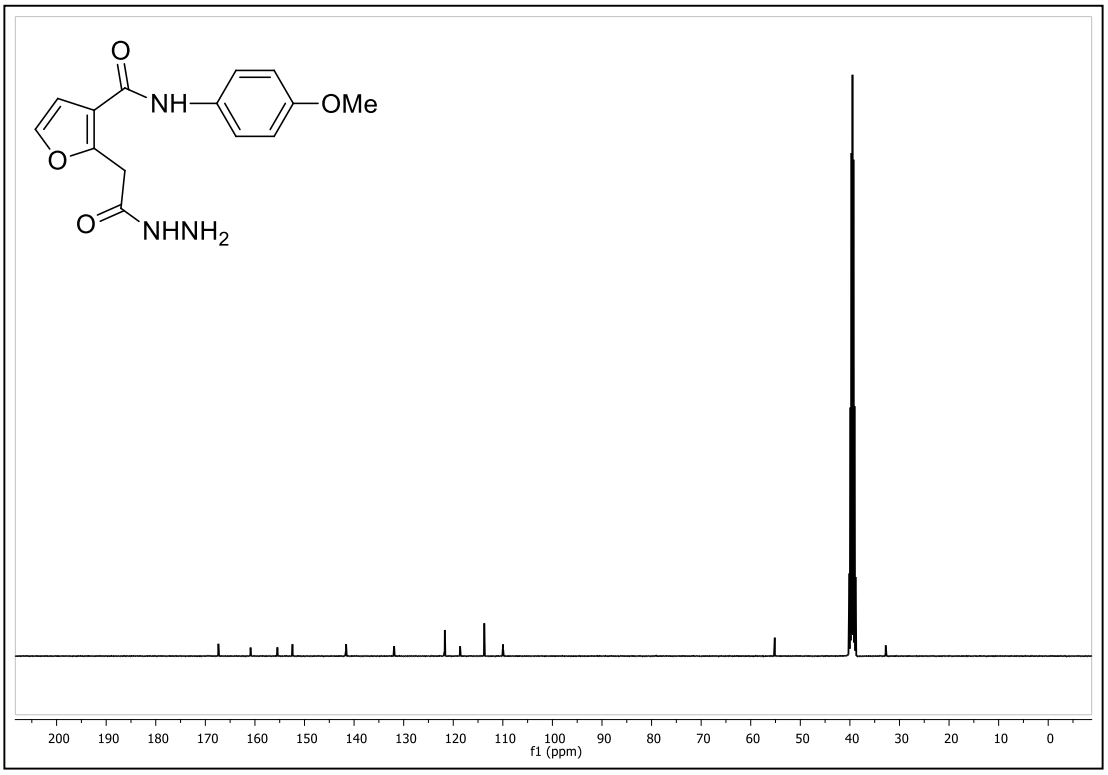

Figure A 149 ^{13}C NMR spectrum of compound **97e**

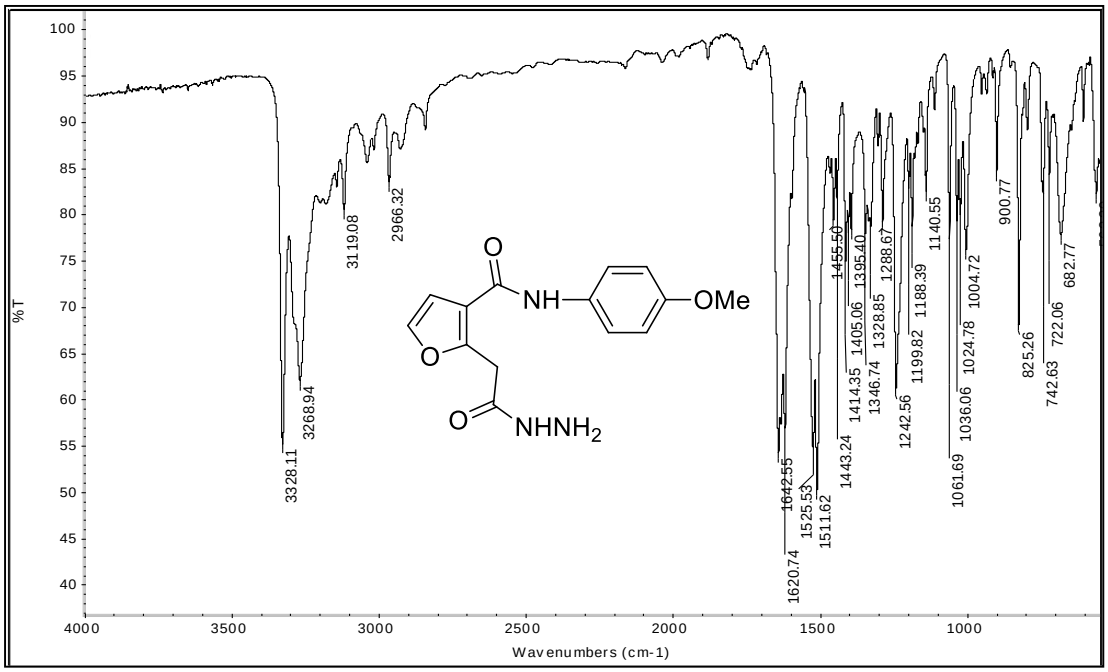

Figure A 150 IR spectrum of compound **97e**

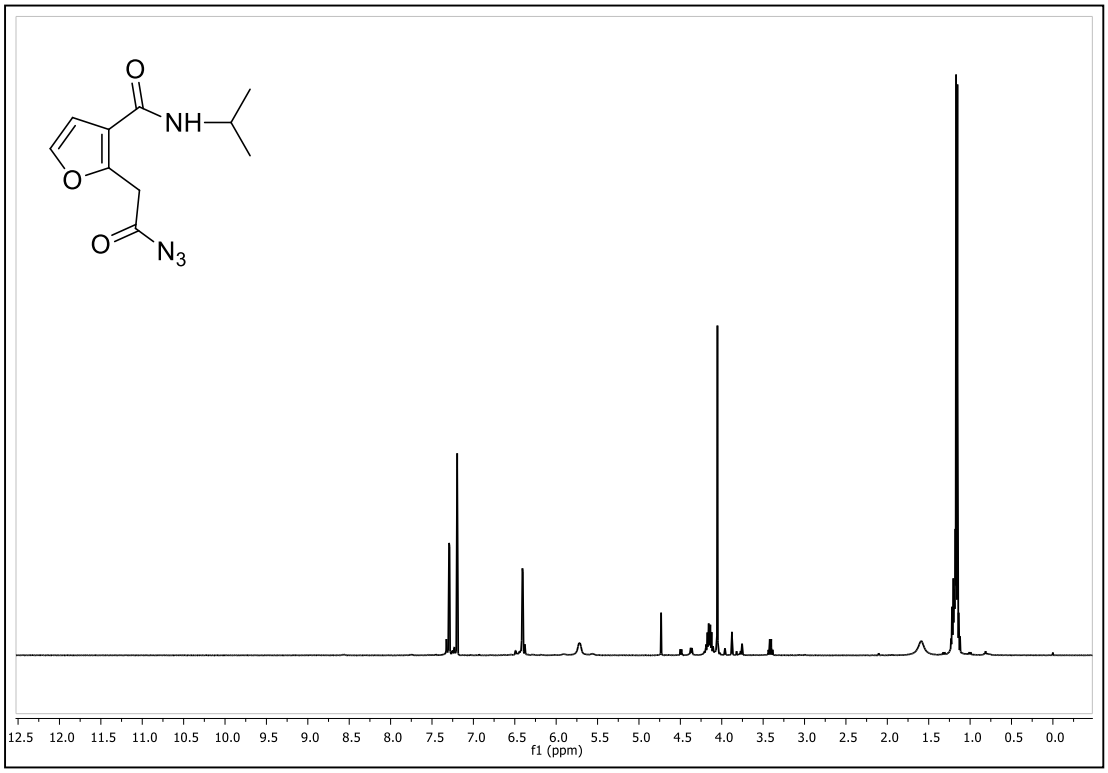

Figure A 151 ^{1}H NMR spectrum of compound **59a**

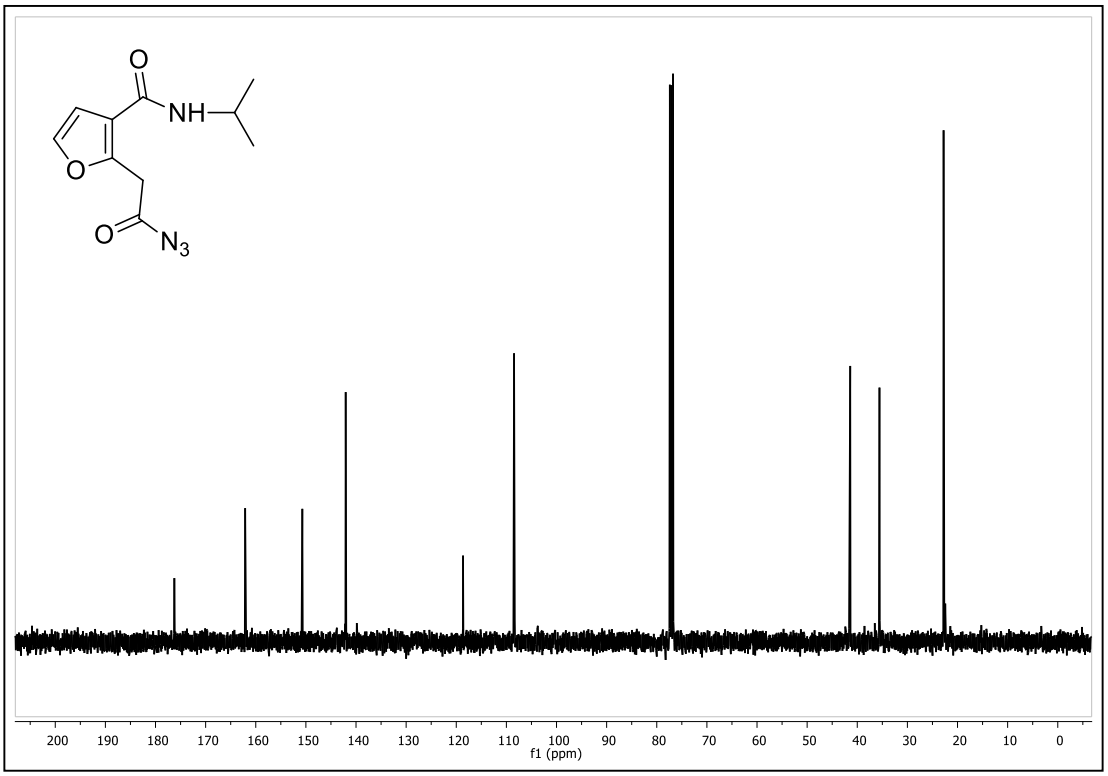

Figure A 152 ^{13}C NMR spectrum of compound **59a**

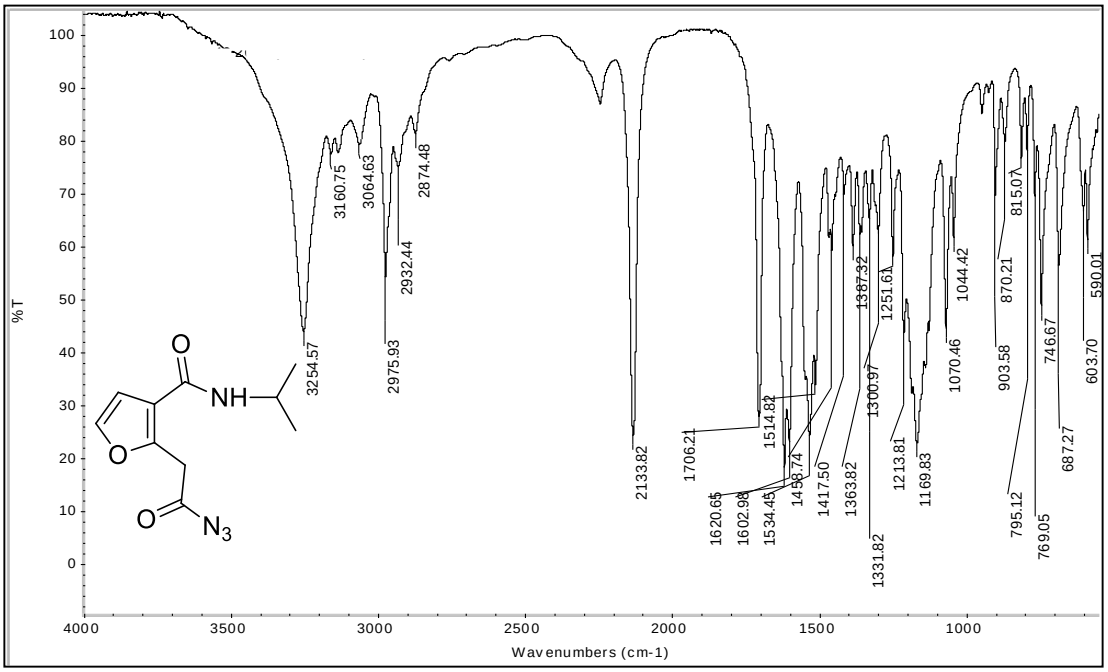

Figure A 153 IR spectrum of compound **59a**

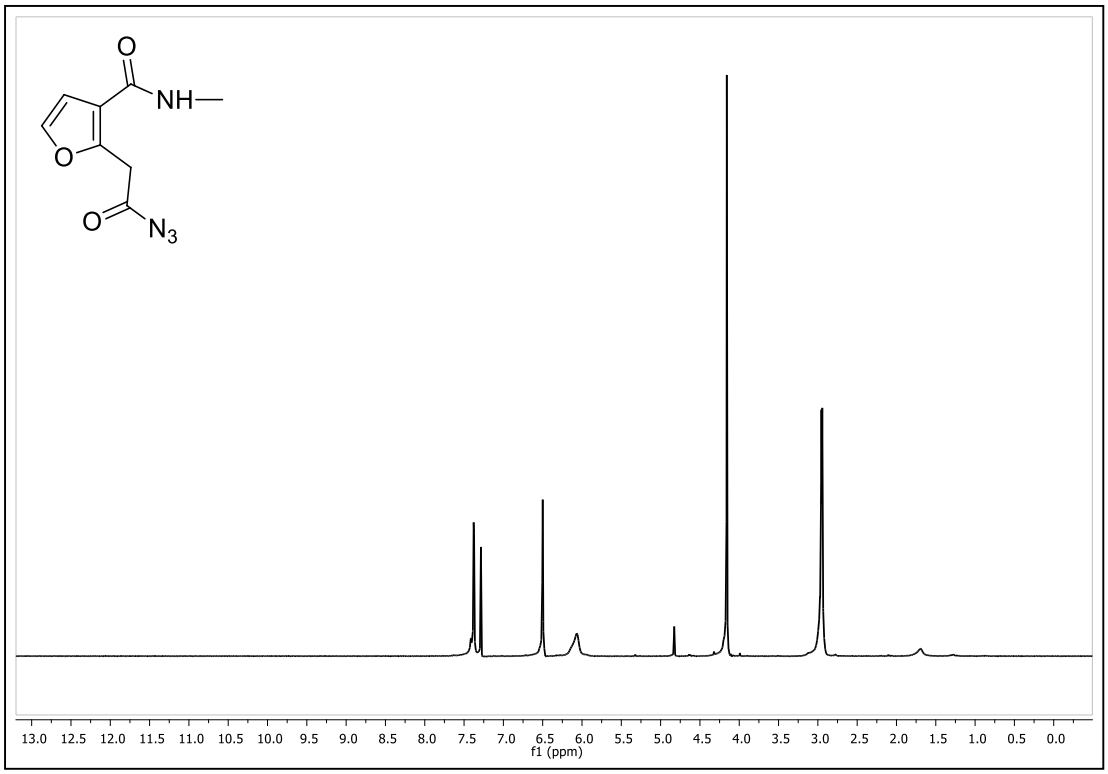

Figure A 154 ^{1}H NMR spectrum of compound **59c**

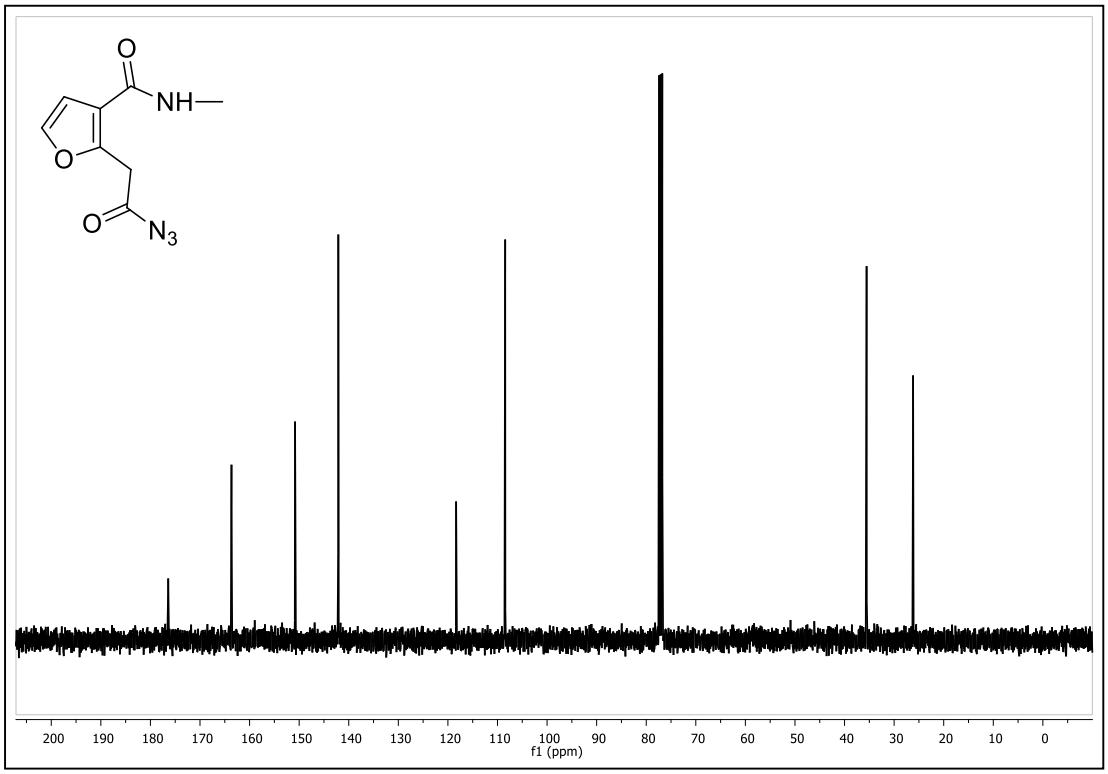

Figure A 155 ^{13}C NMR spectrum of compound **59c**

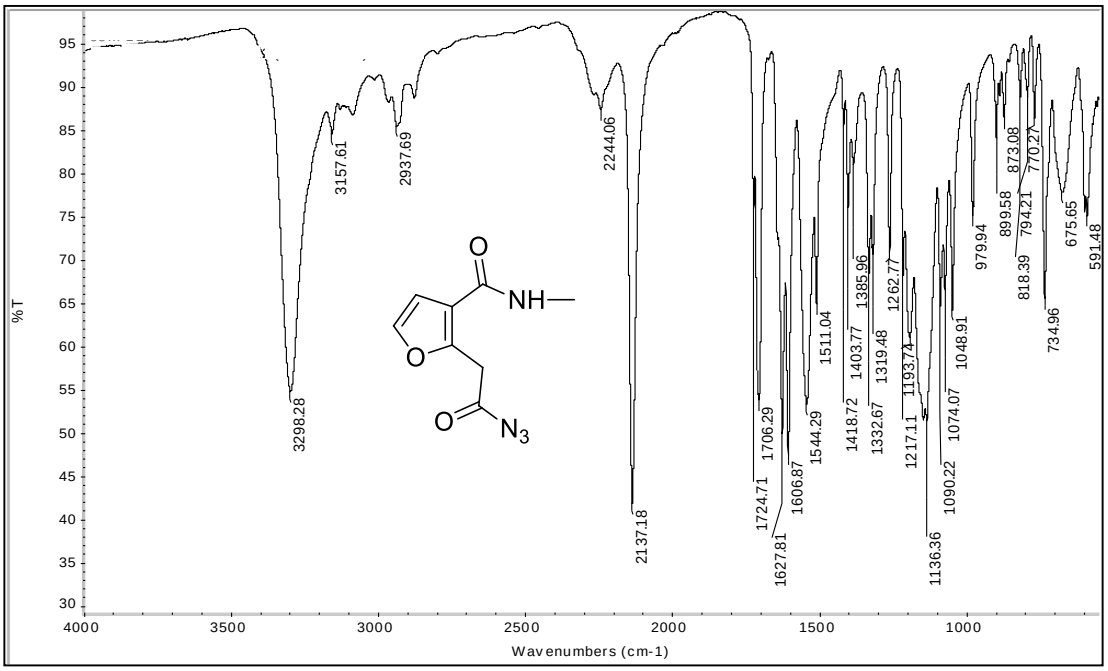

Figure A 156 IR spectrum of compound **59c**

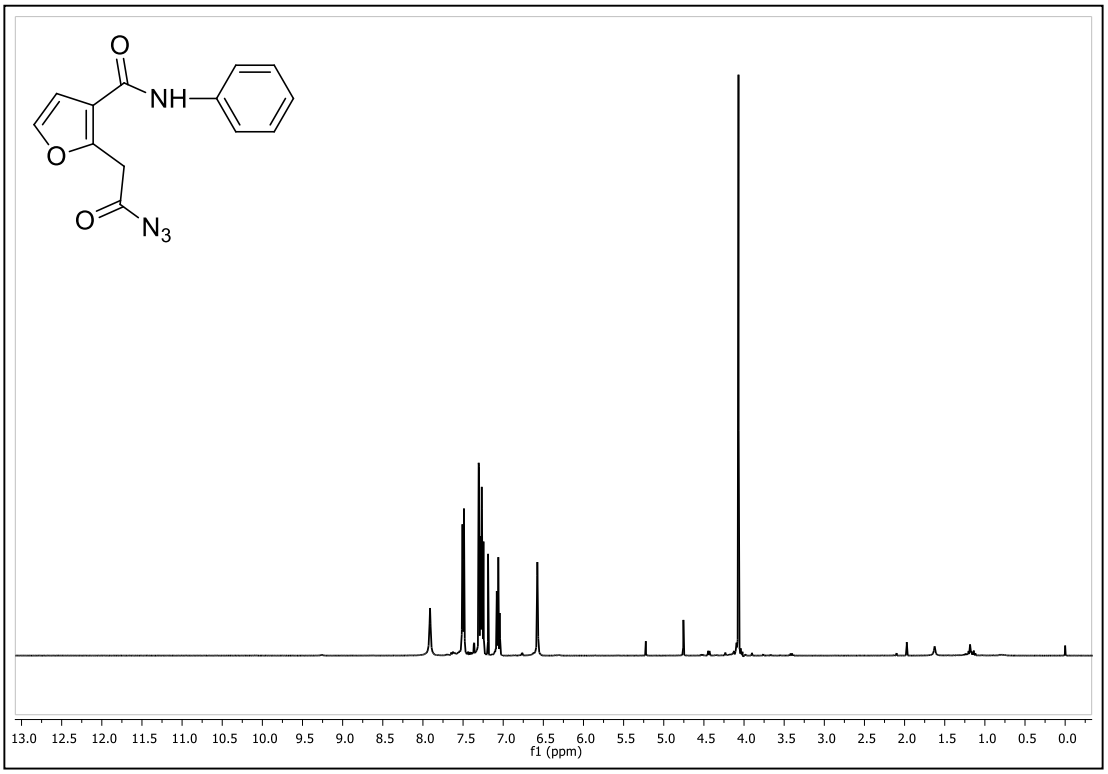

Figure A 157 ^{1}H NMR spectrum of compound **59d**

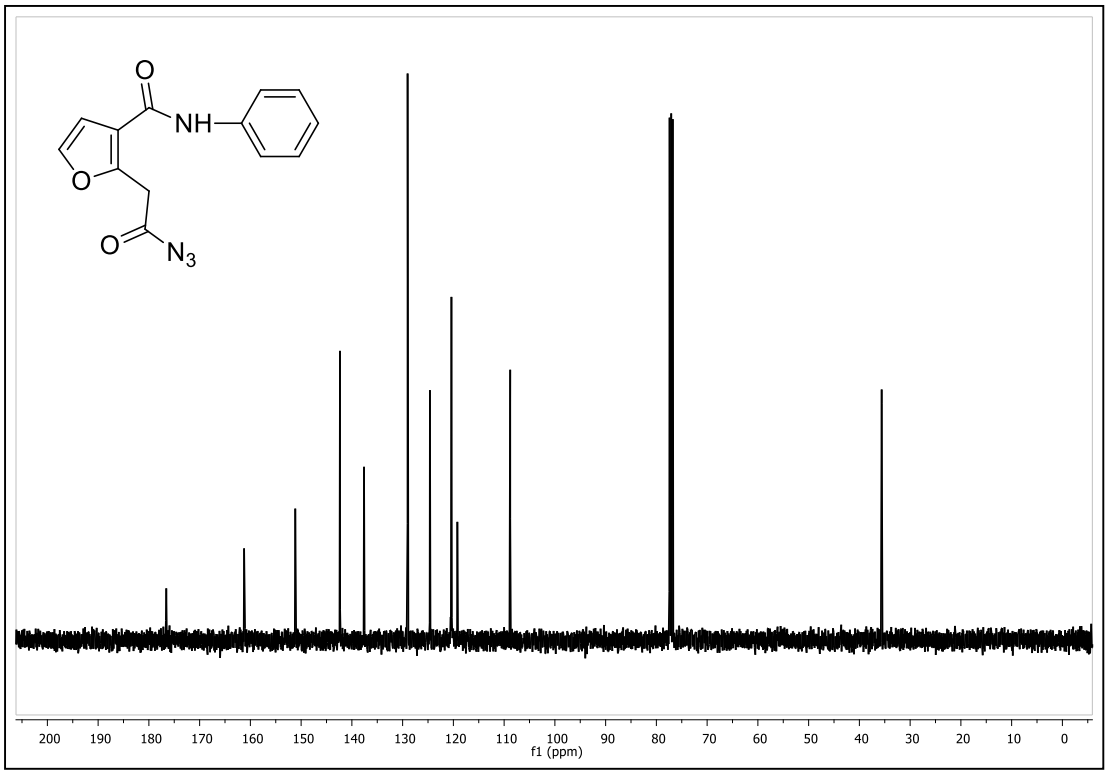

Figure A 158 ^{13}C NMR spectrum of compound **59d**

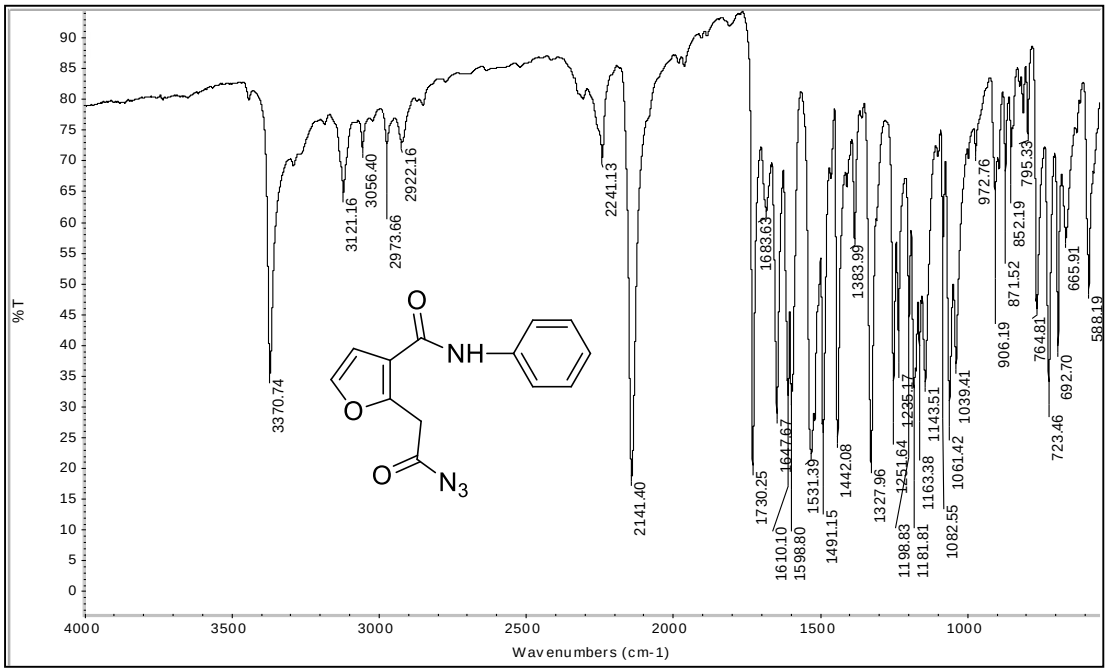

Figure A 159 IR spectrum of compound **59d**

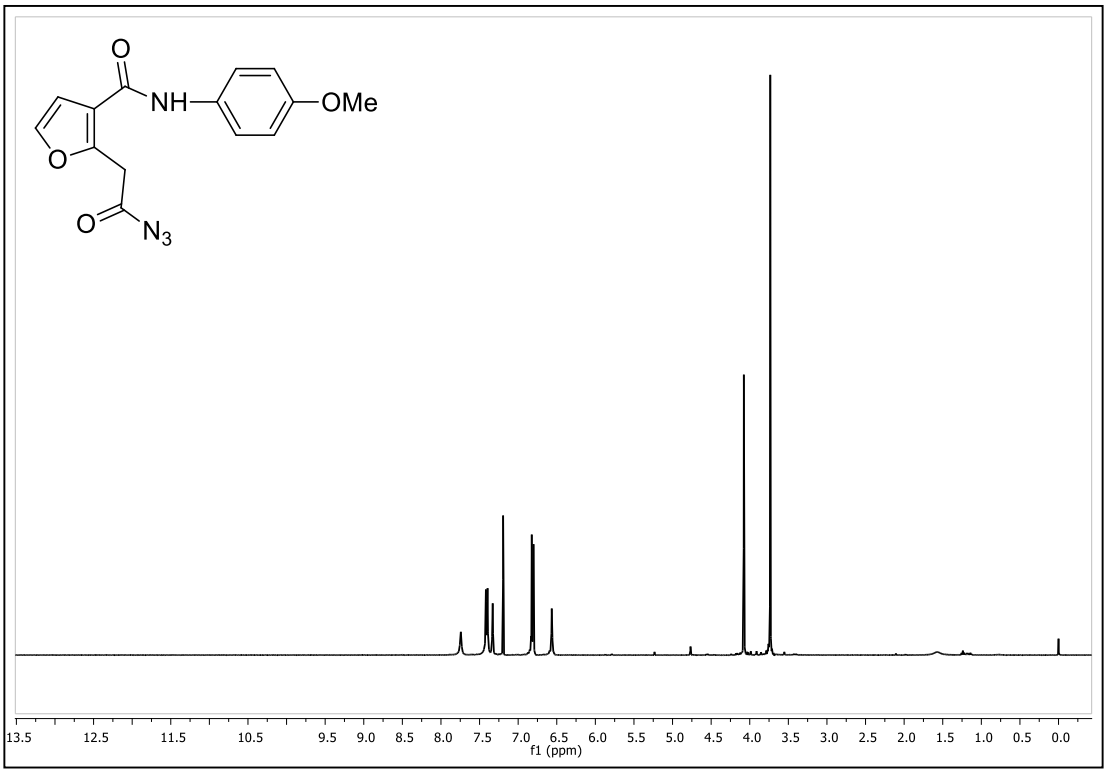

Figure A 160 ^{1}H NMR spectrum of compound **59e**

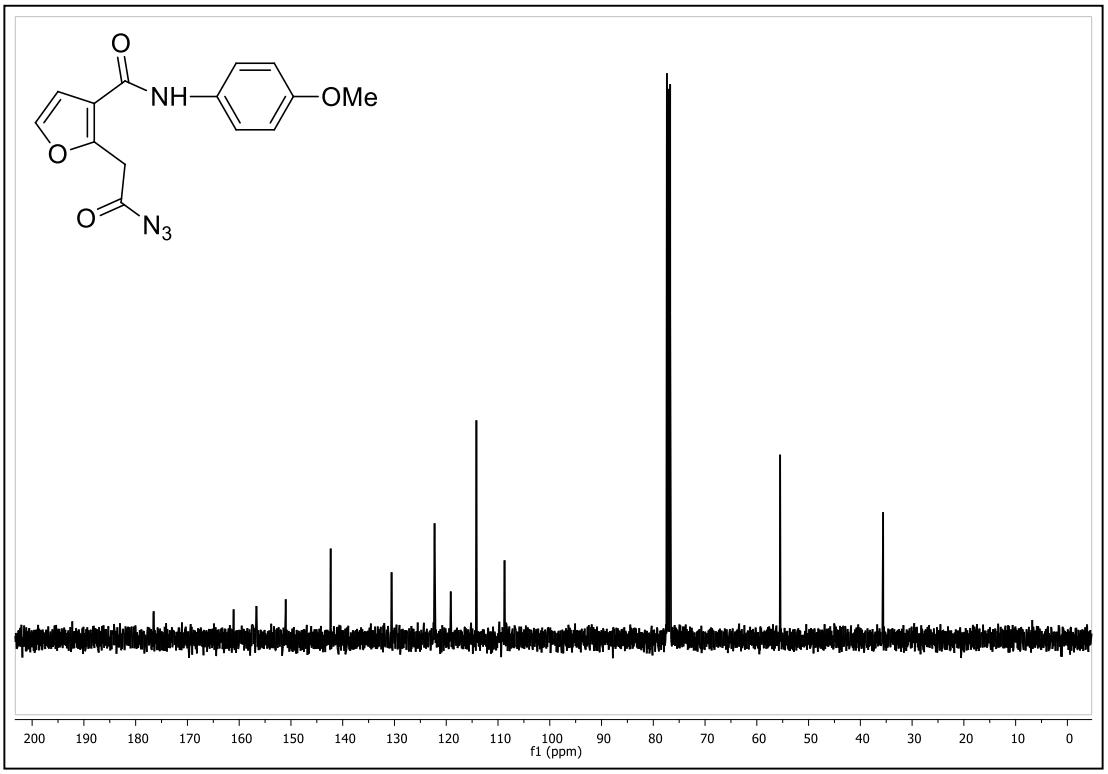

Figure A 161 ^{13}C NMR spectrum of compound **59e**

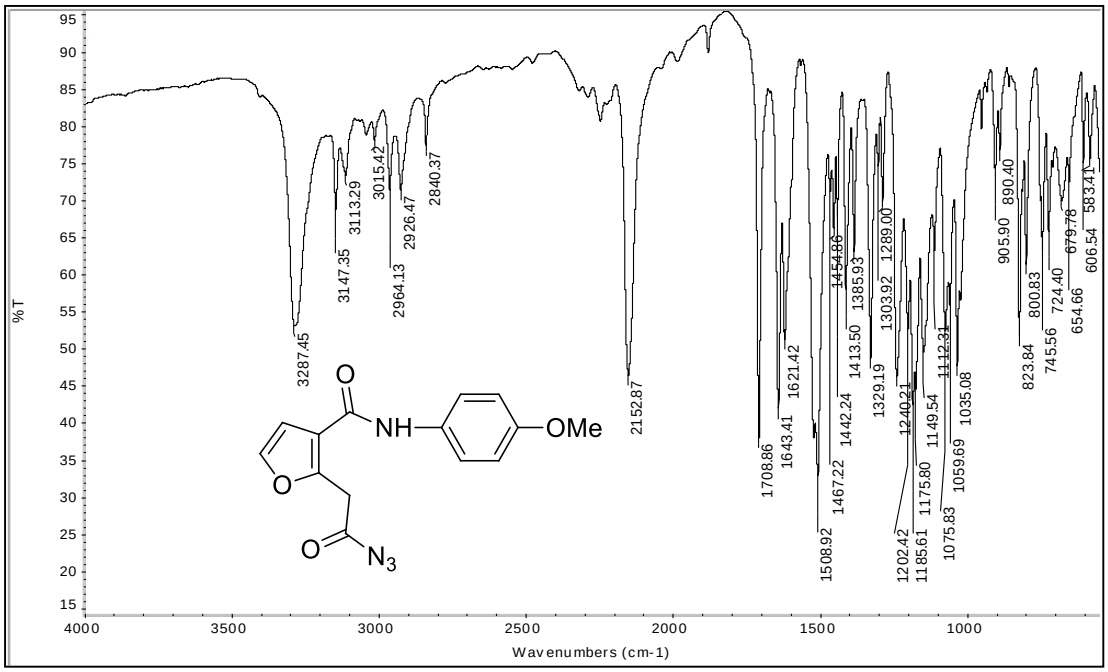

Figure A 162 IR spectrum of compound **59e**

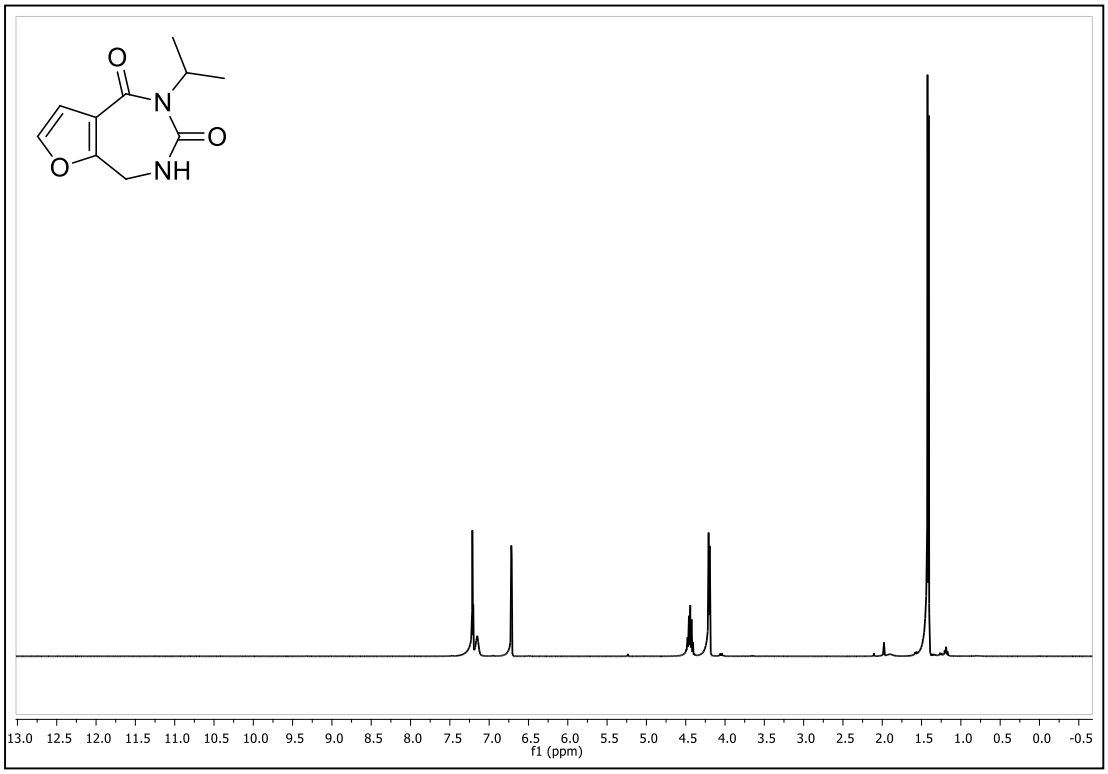

Figure A 163 ^{1}H NMR spectrum of compound **61a**

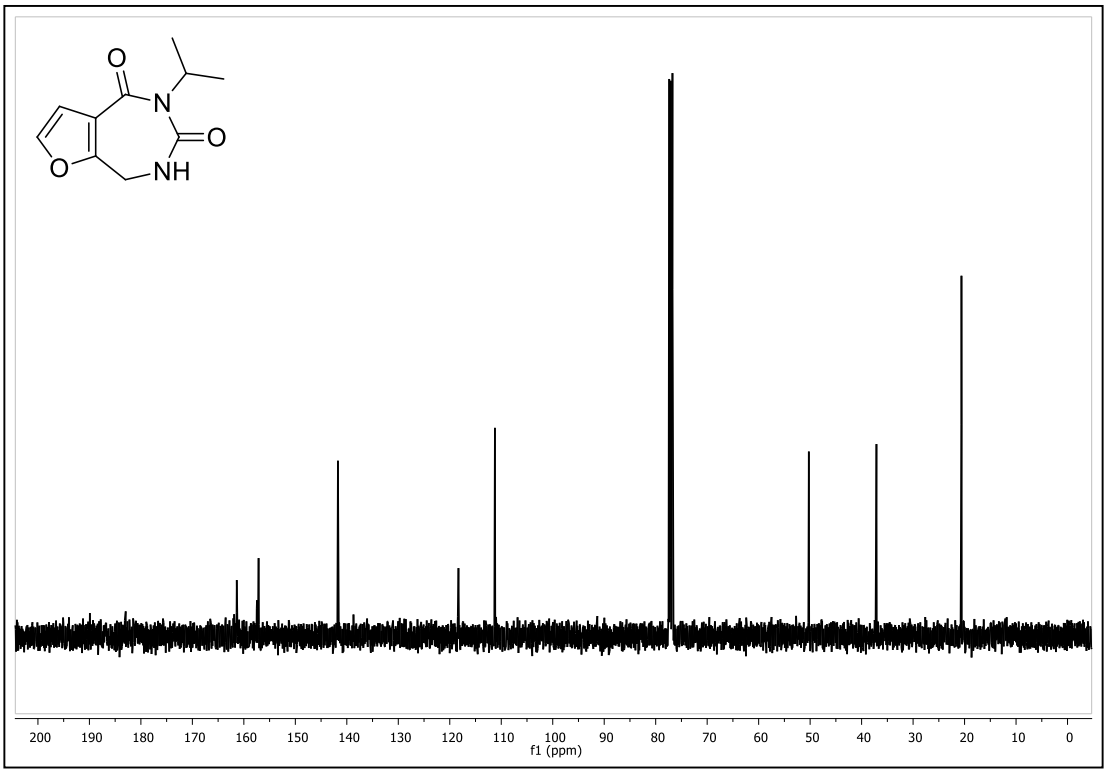

Figure A 164 ^{13}C NMR spectrum of compound **61a**

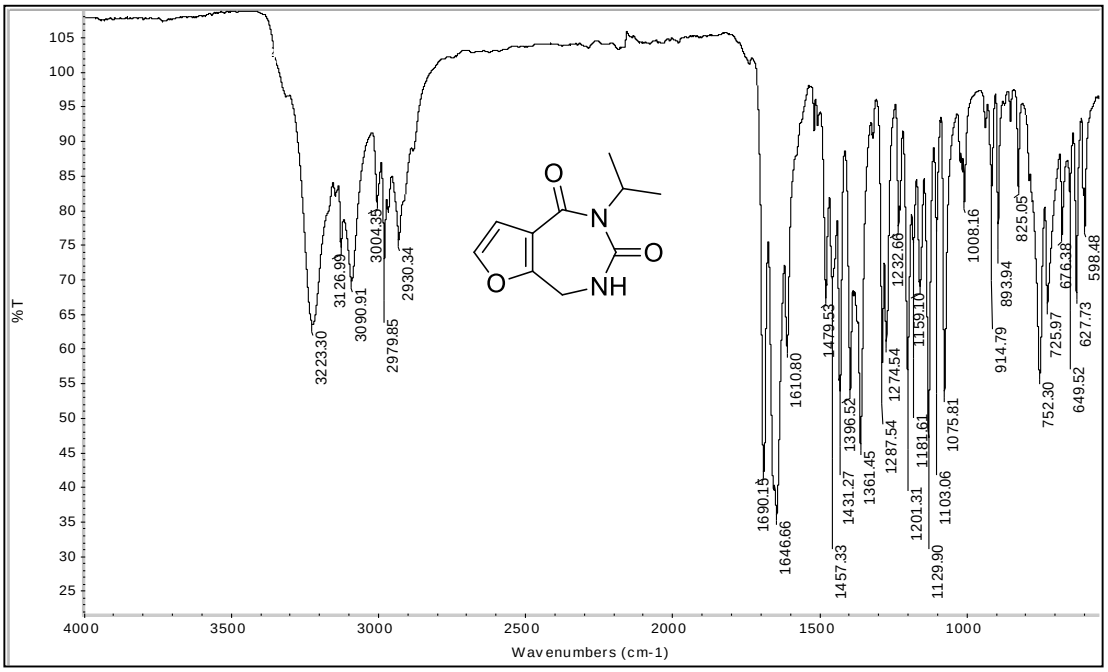

Figure A 165 IR spectrum of compound **61a**

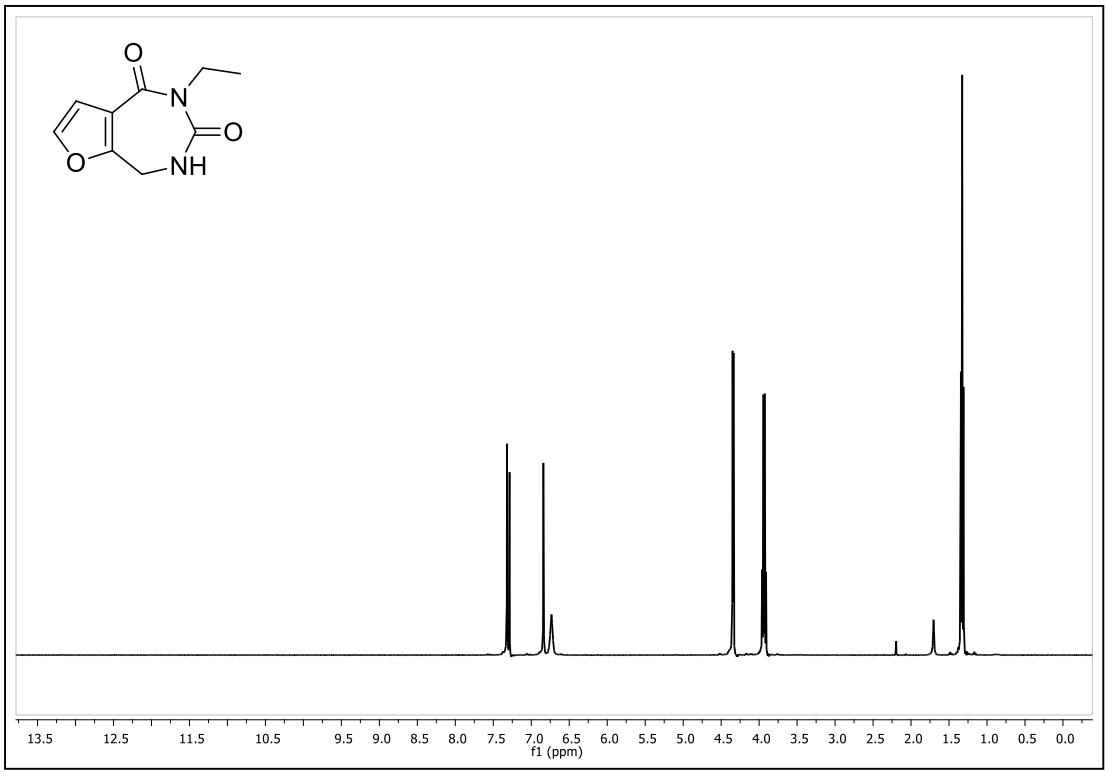

Figure A 166 ^{1}H NMR spectrum of compound **61b**

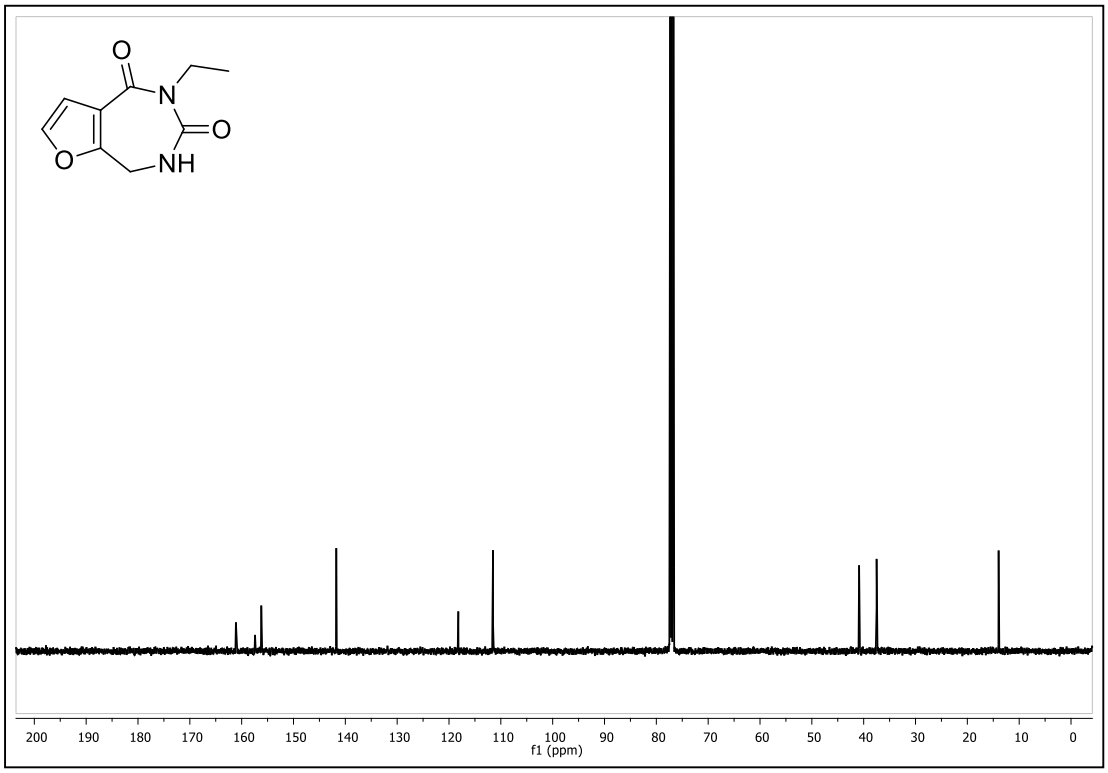

Figure A 167 ^{13}C NMR spectrum of compound **61b**

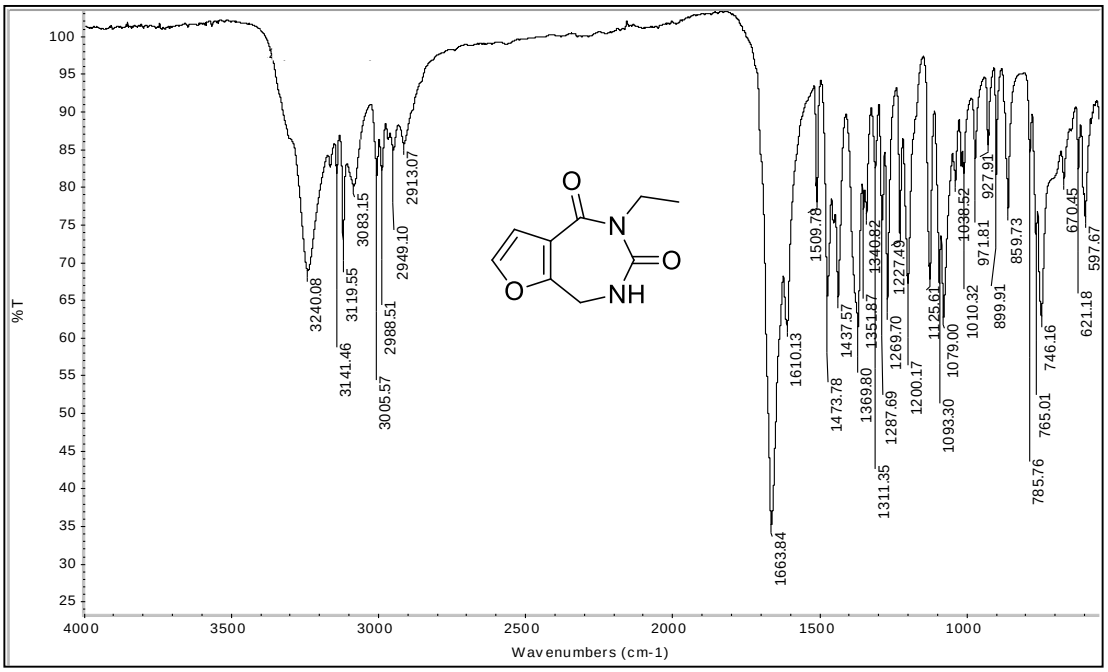

Figure A 168 IR spectrum of compound **61b**

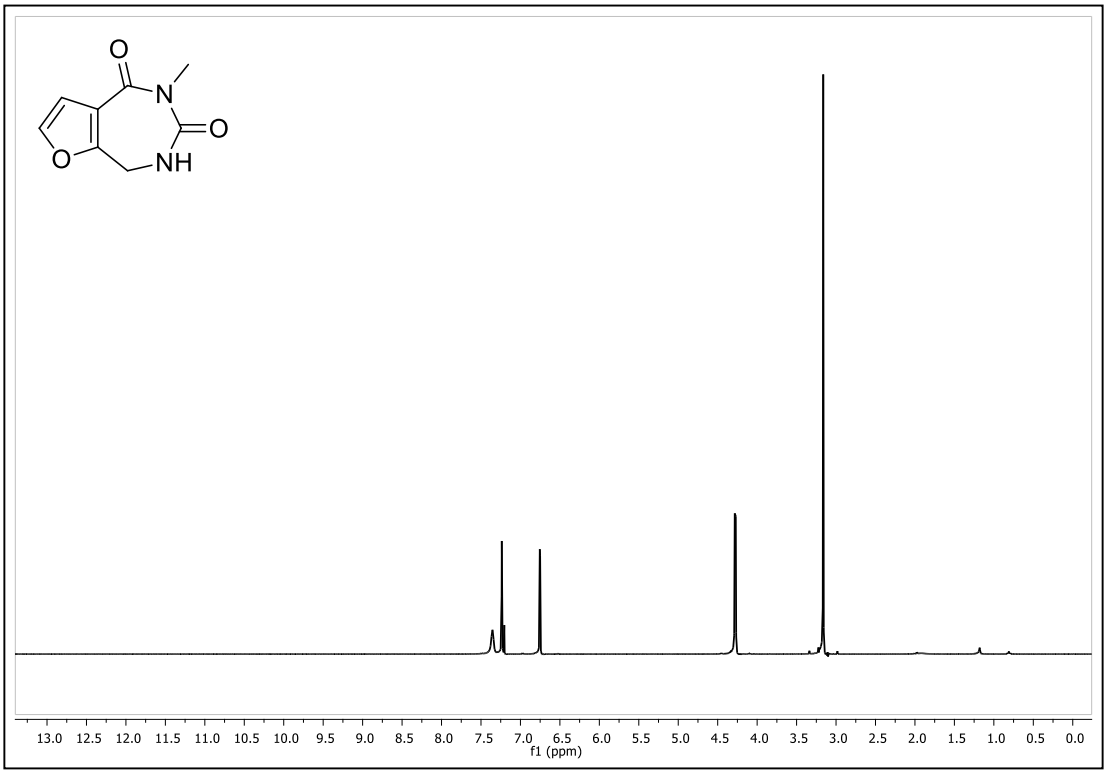

Figure A 169 ^{1}H NMR spectrum of compound **61c**

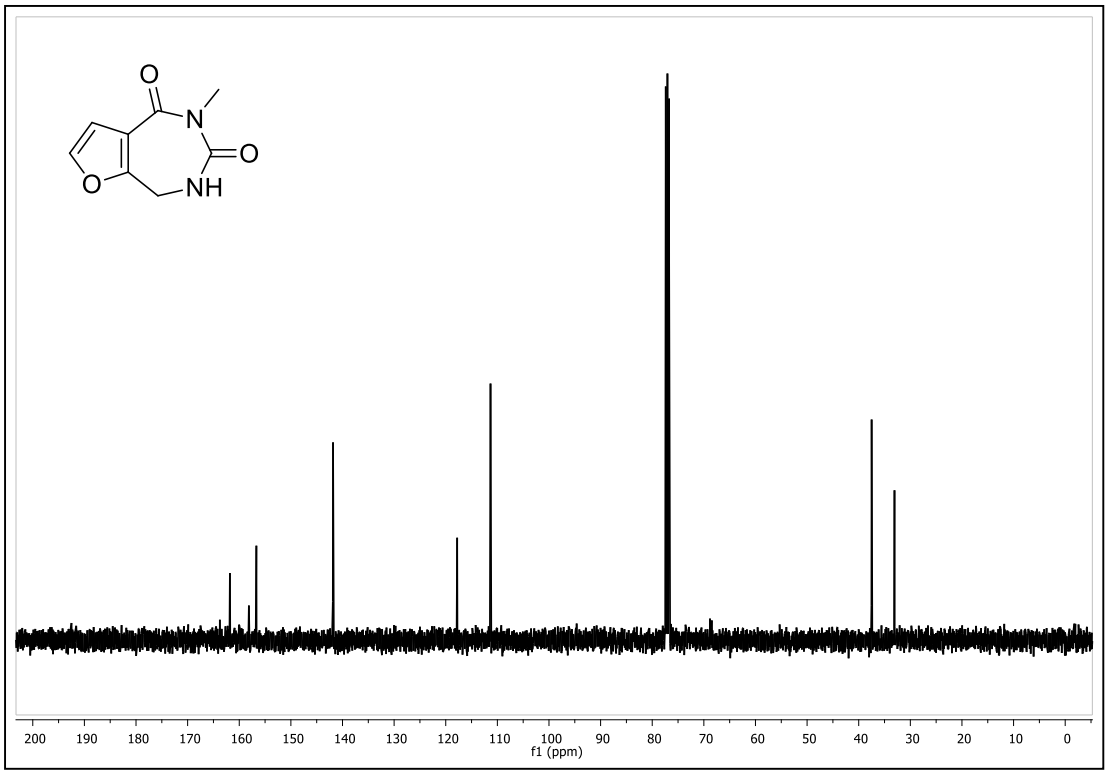

Figure A 170 ^{13}C NMR spectrum of compound **61c**

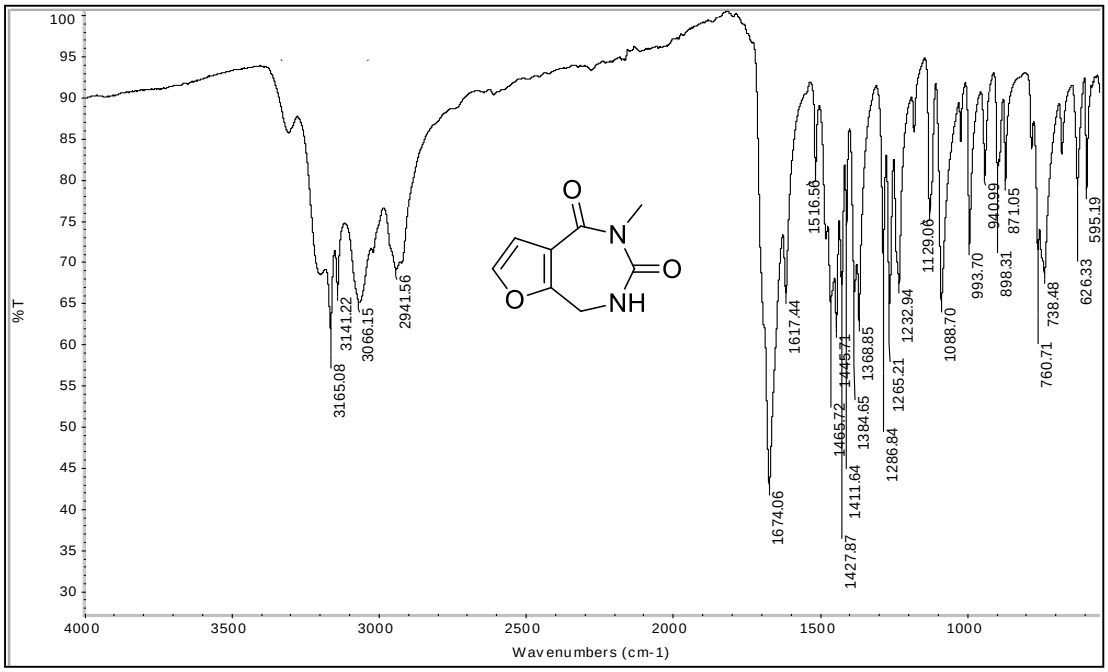

Figure A 171 IR spectrum of compound **61c**

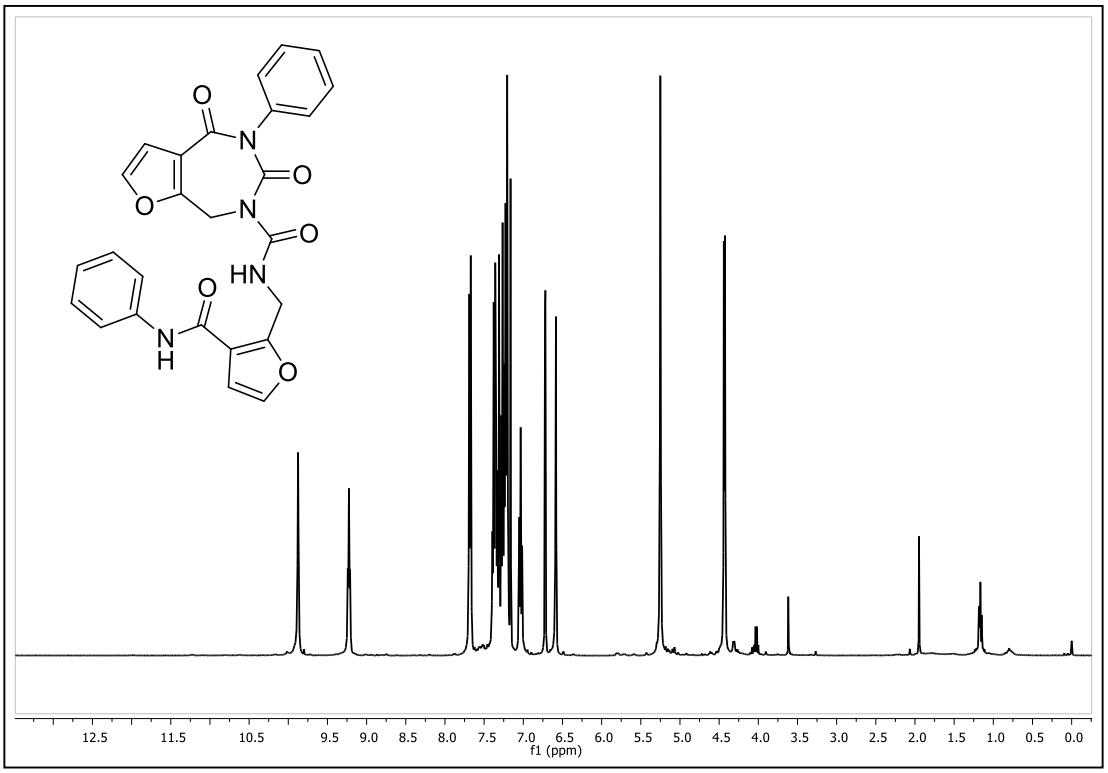

Figure A 172 ^{1}H NMR spectrum of compound **61d**

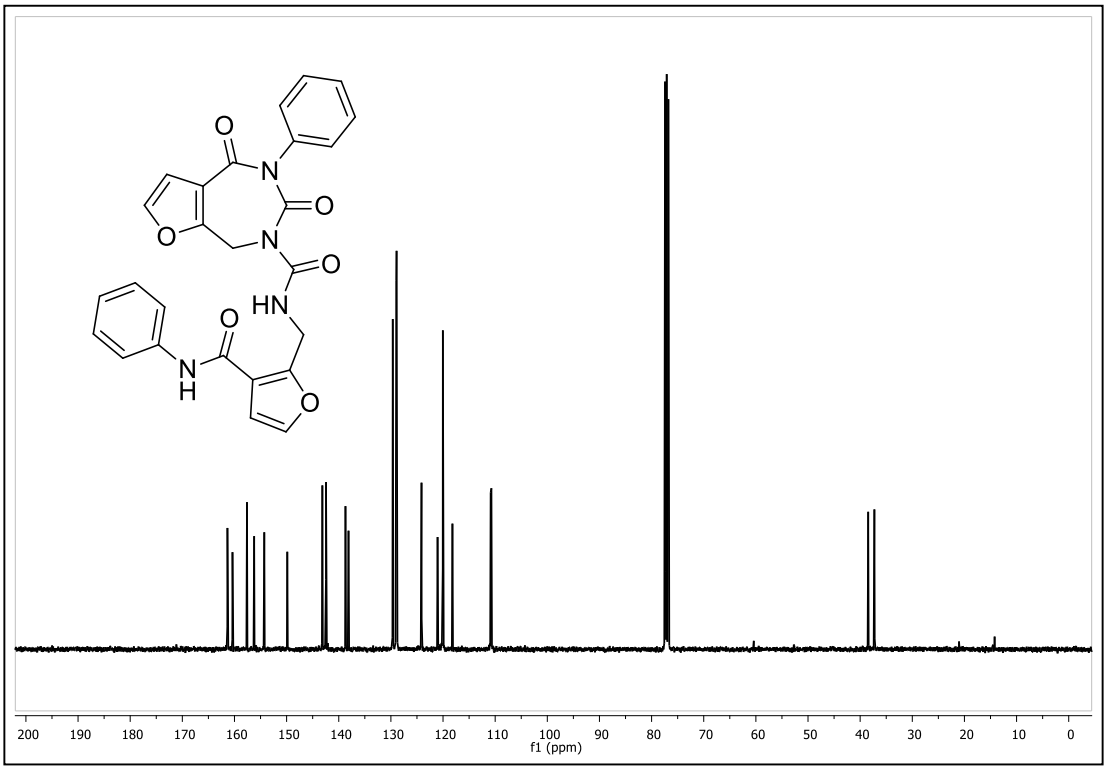

Figure A 173 ^{13}C NMR spectrum of compound **61d**

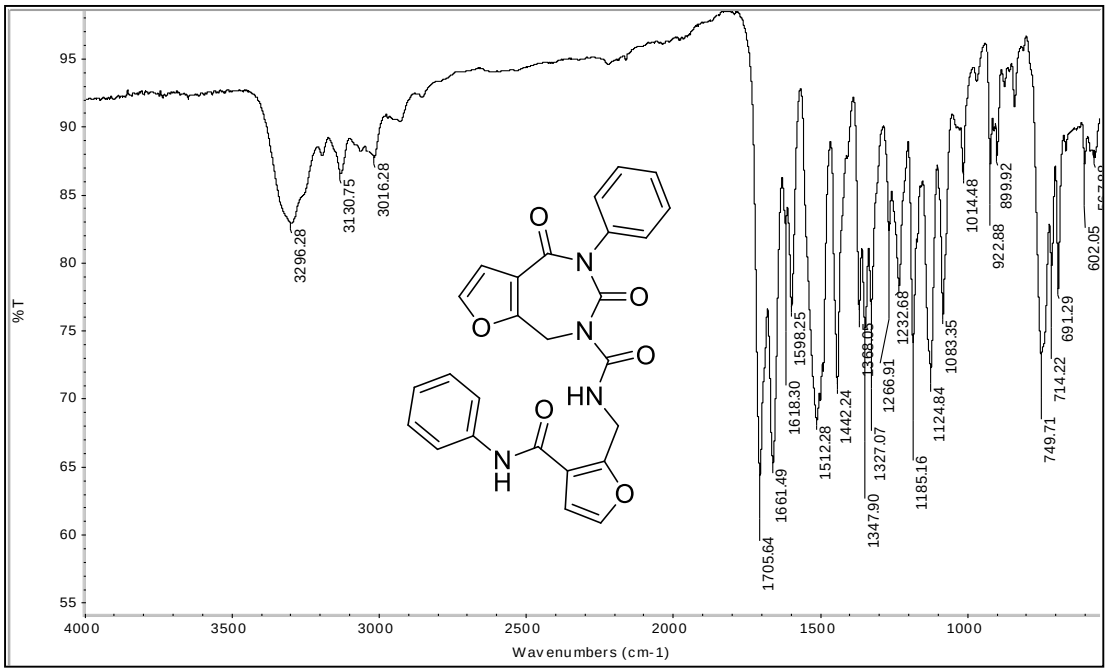

Figure A 174 IR spectrum of compound **61d**

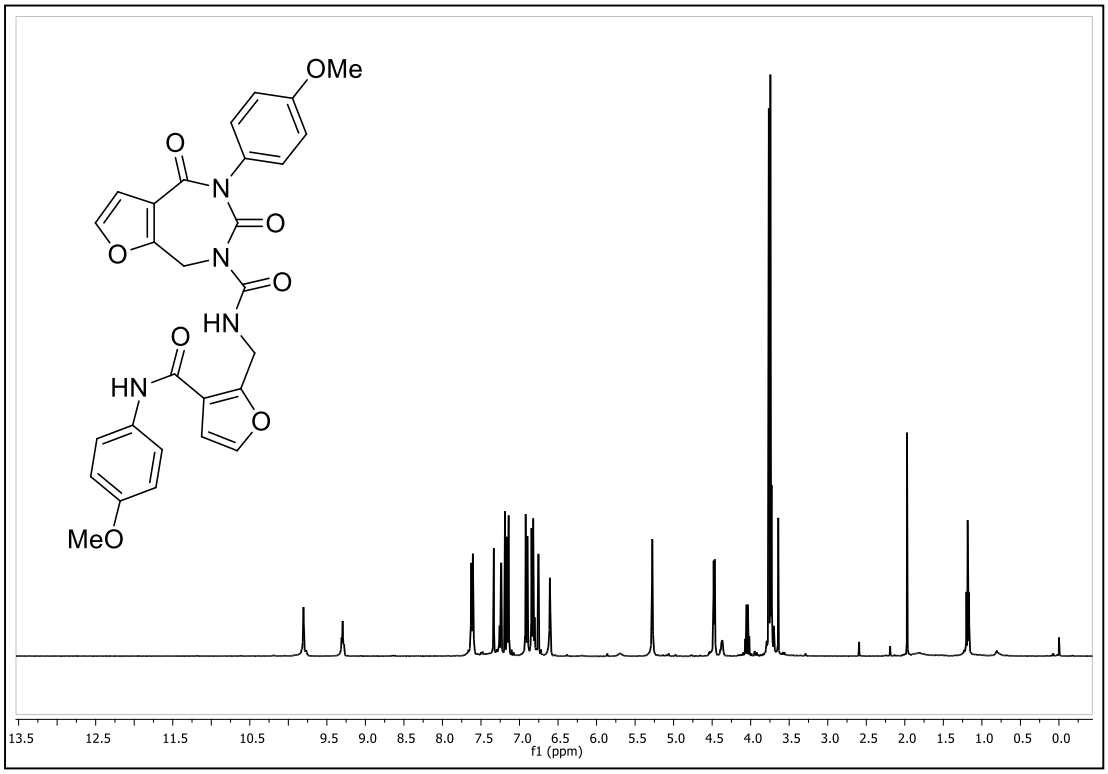

Figure A 175 ^{1}H NMR spectrum of compound **61e**

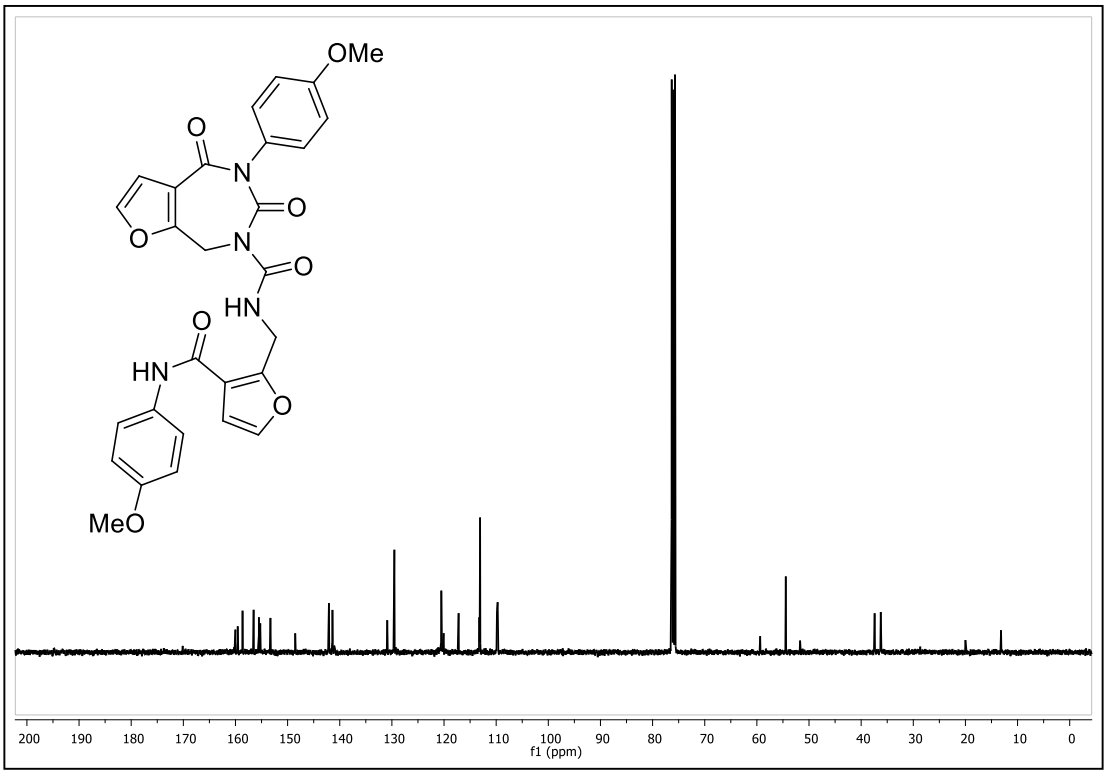

Figure A 176 ^{13}C NMR spectrum of compound **61e**

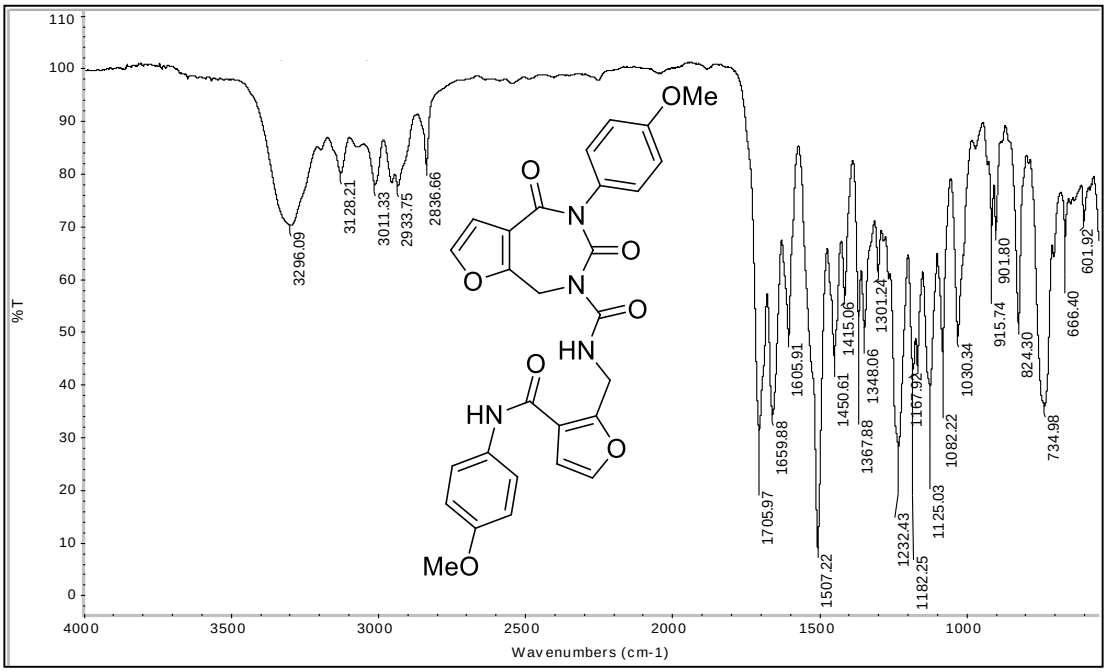

Figure A 177 IR spectrum of compound **61e**

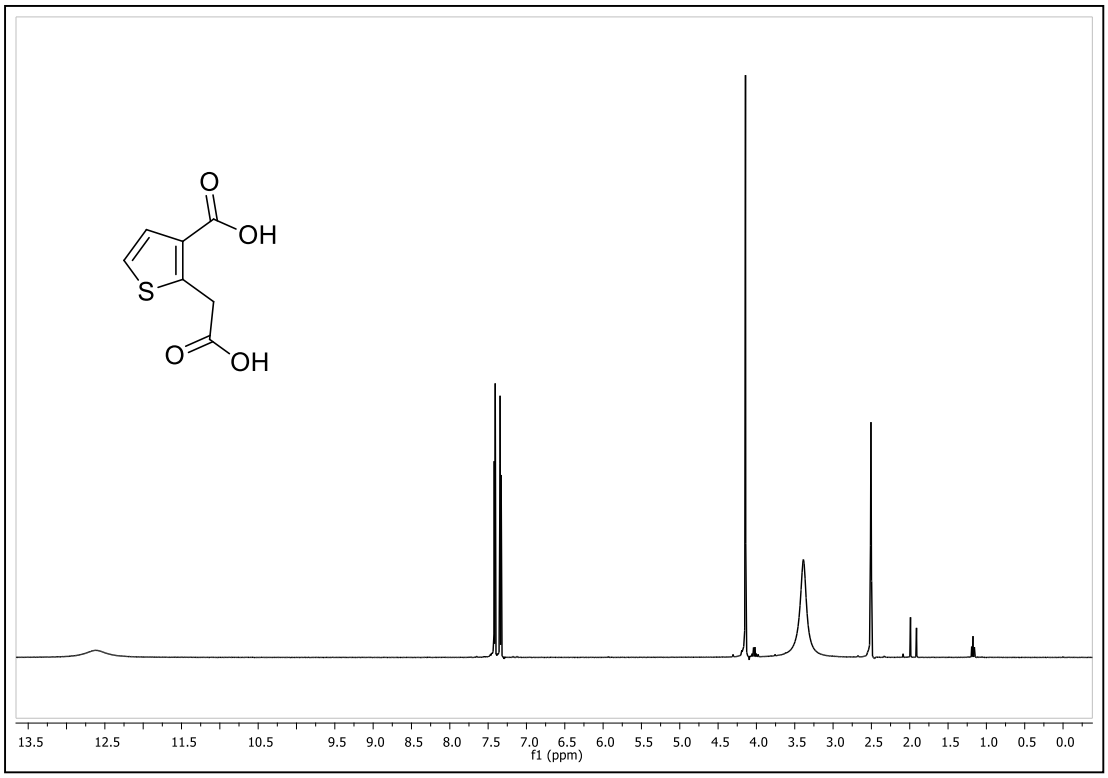

Figure A 178 ^{1}H NMR spectrum of compound **93**

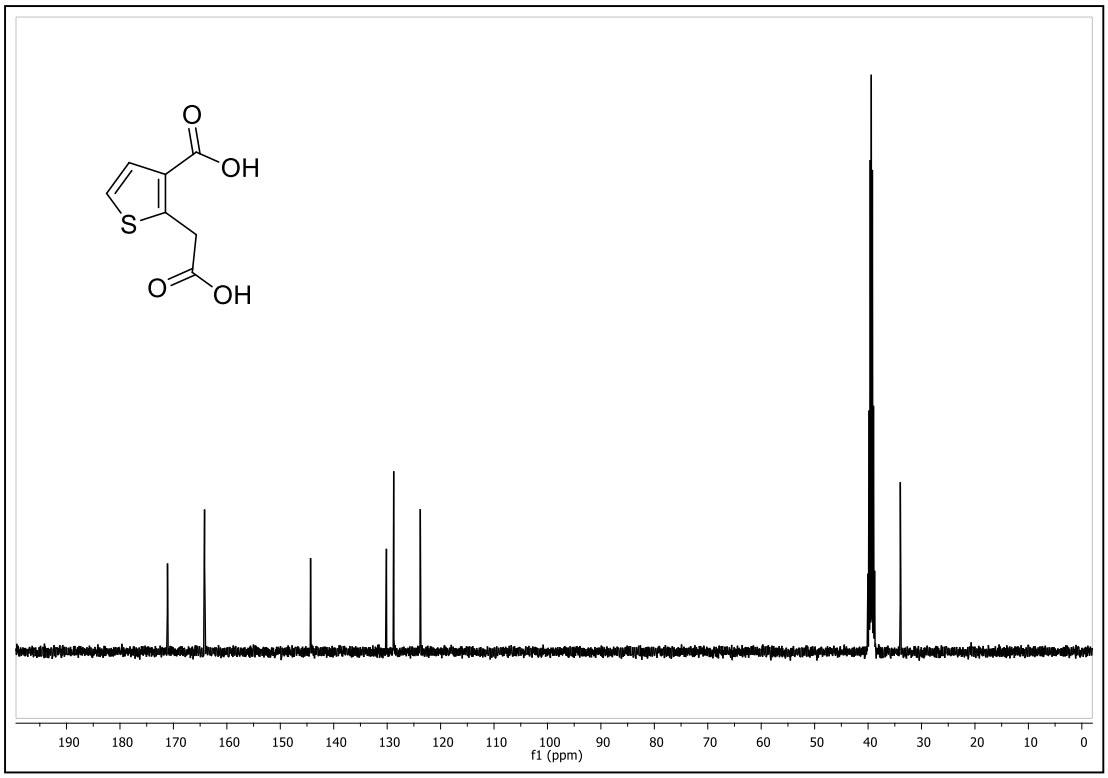

Figure A 179 ^{13}C NMR spectrum of compound **93**

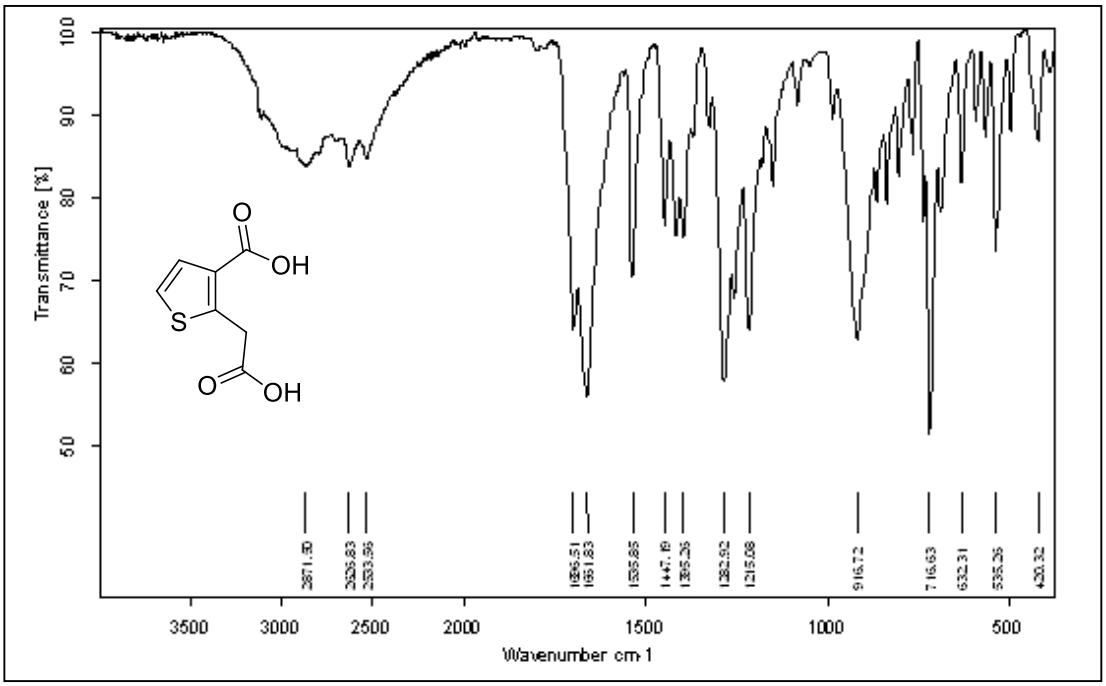

Figure A 180IR spectrum of compound **93**

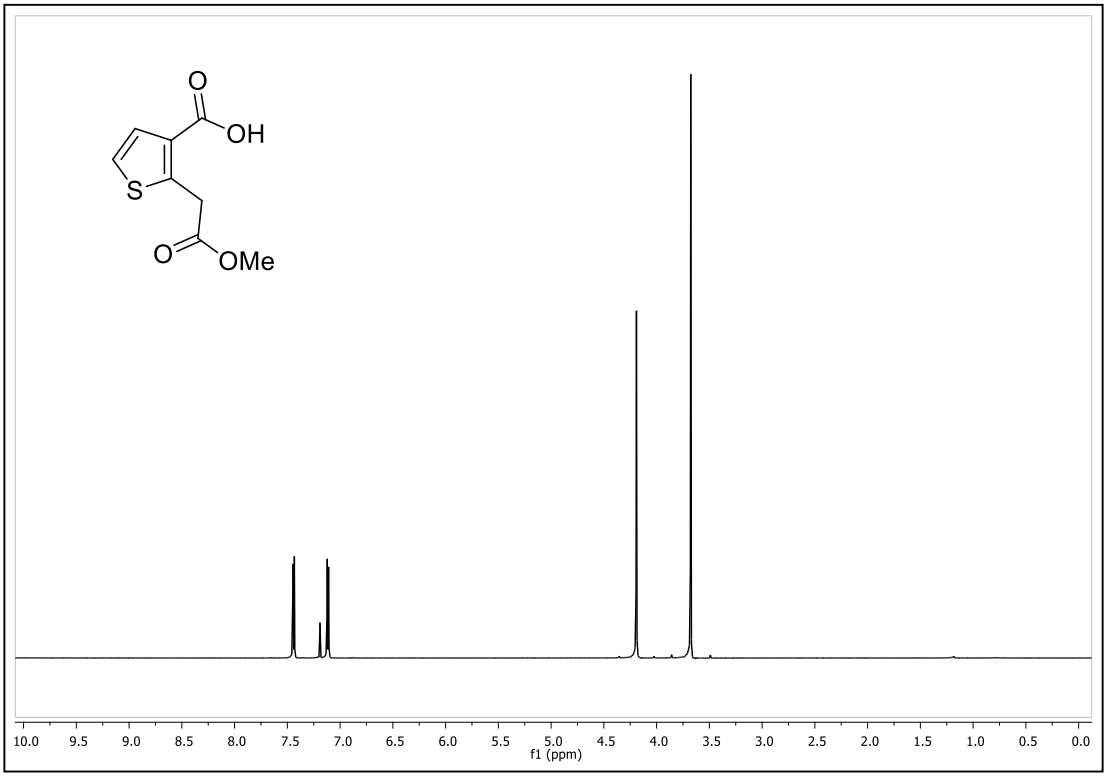

Figure A 181 ^{1}H NMR spectrum of compound **94**

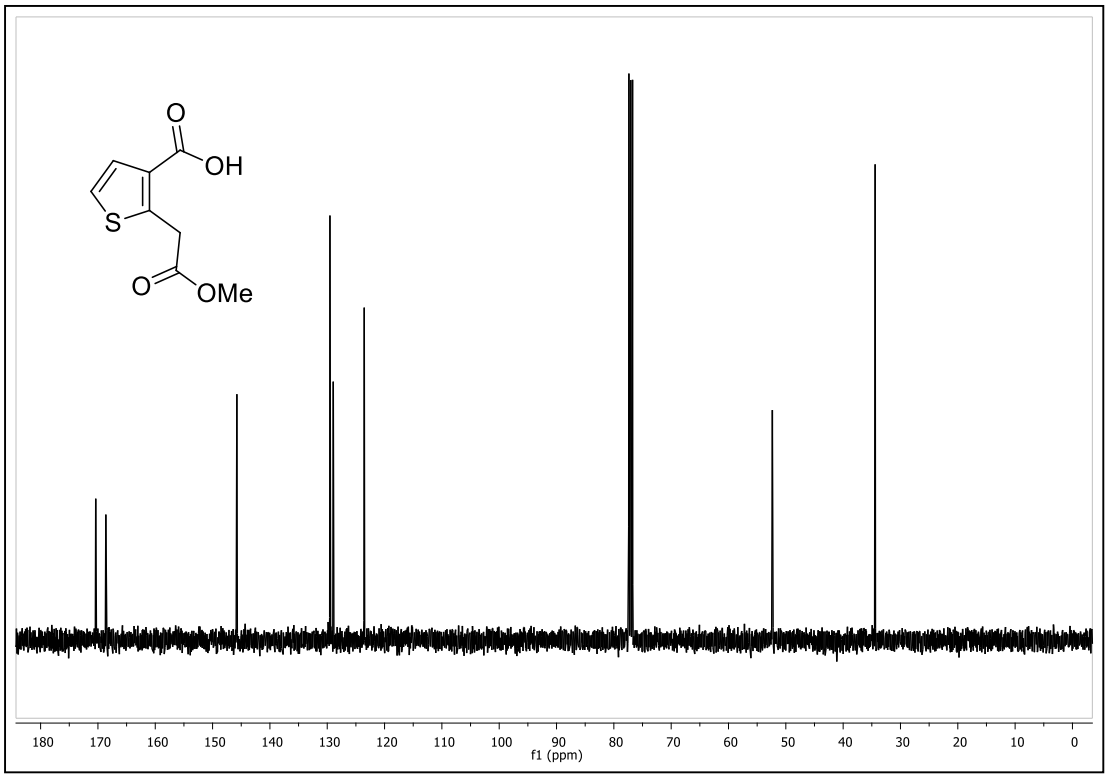

Figure A 182 ^{13}C NMR spectrum of compound **94**

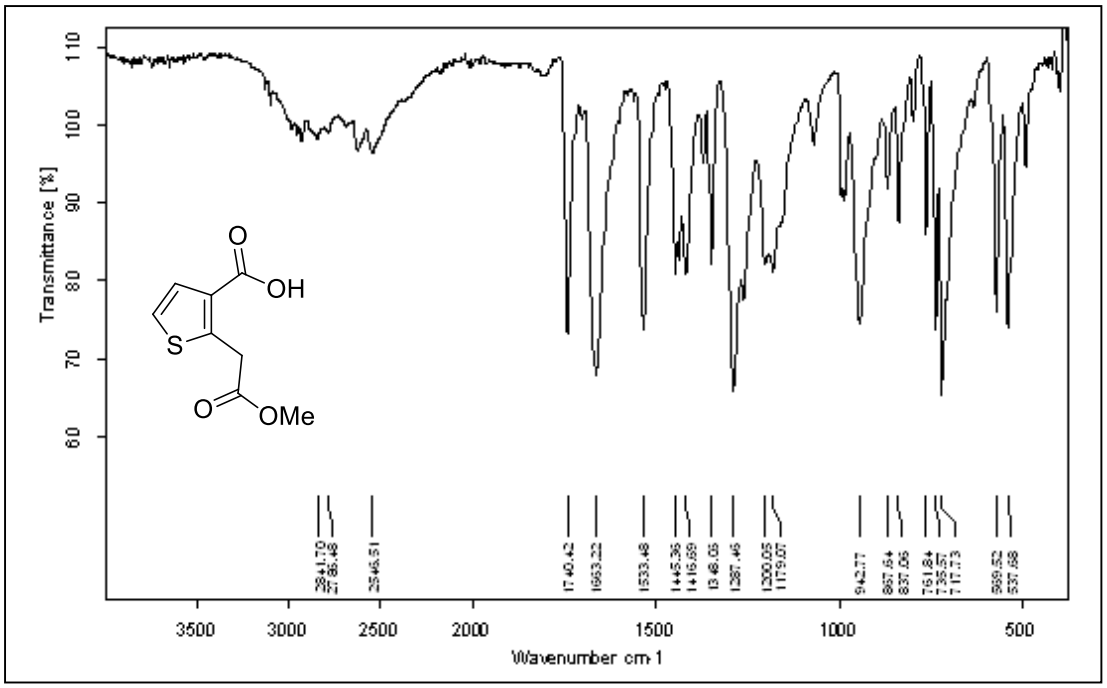

Figure A 183 IR spectrum of compound **94**

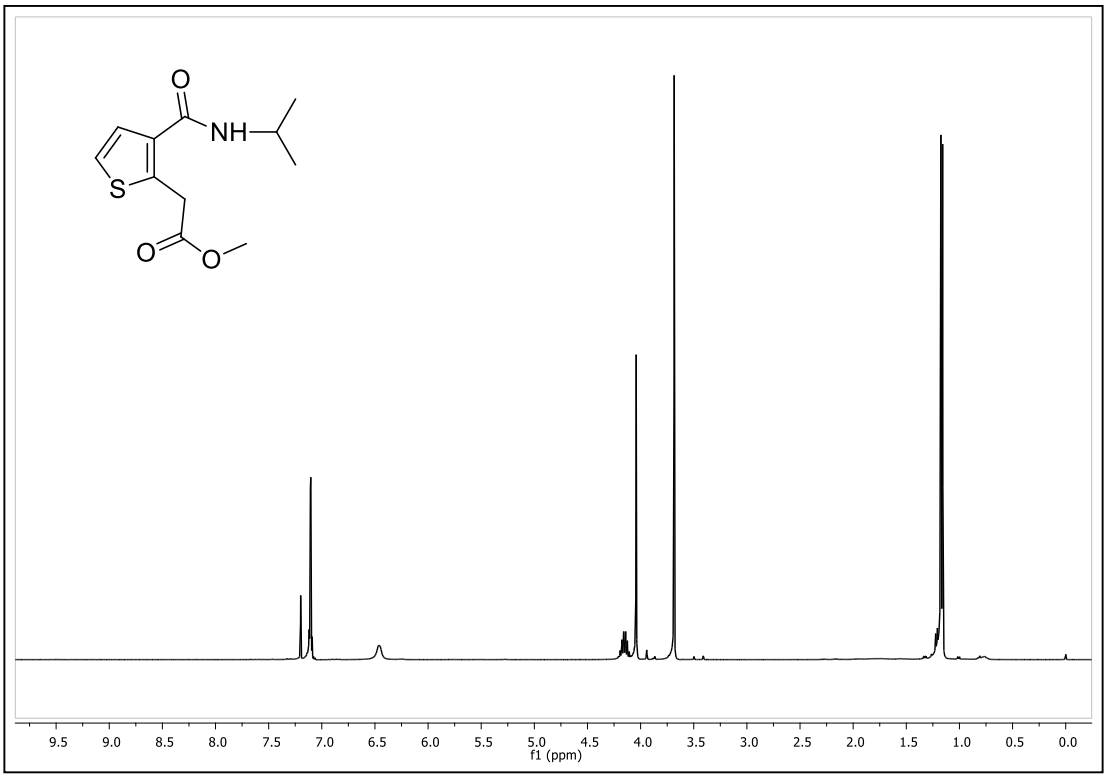

Figure A 184 ^{1}H NMR spectrum of compound **96a**

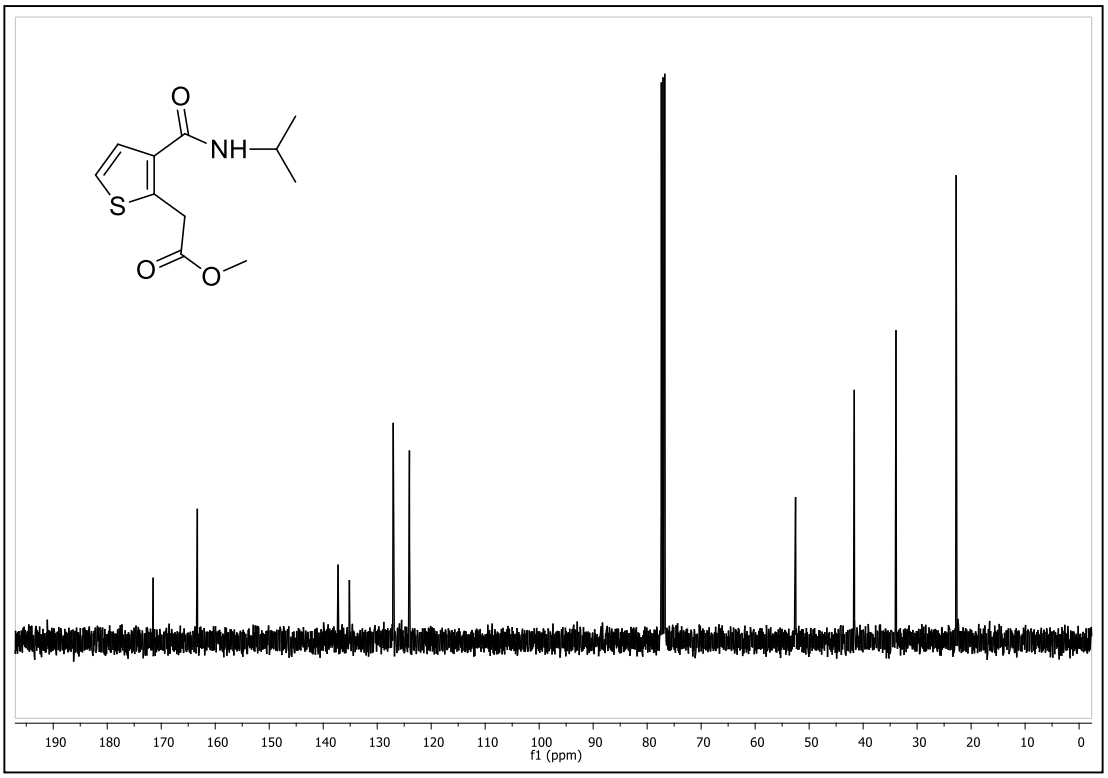

Figure A 185 ^{13}C NMR spectrum of compound **96a**

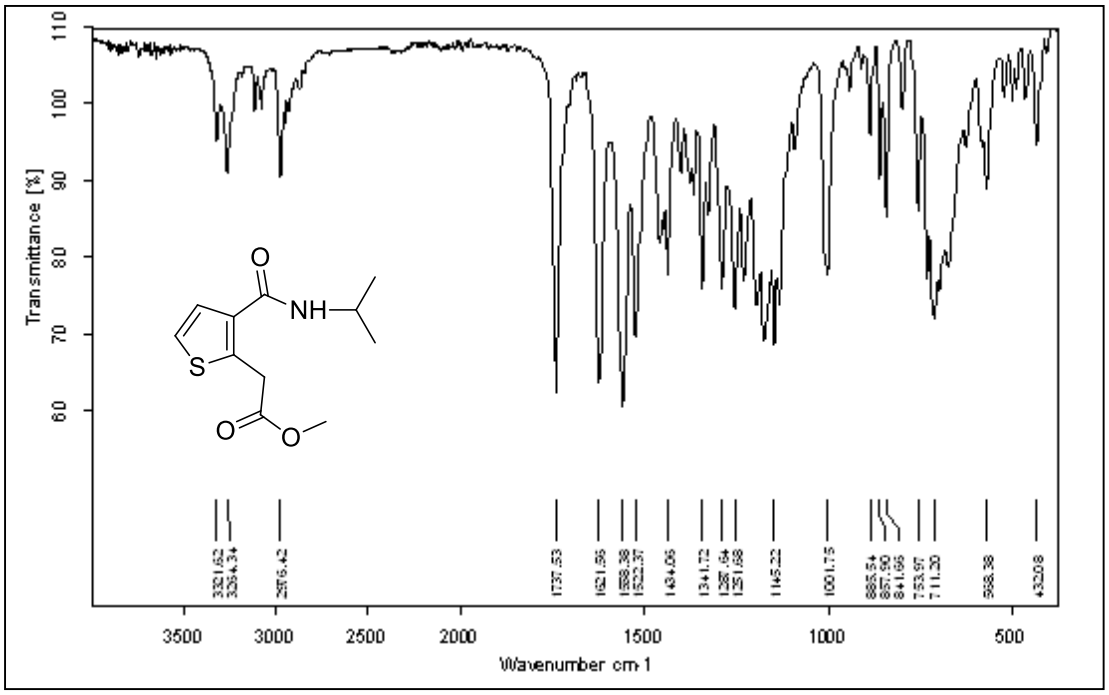

Figure A 186 IR spectrum of compound **96a**

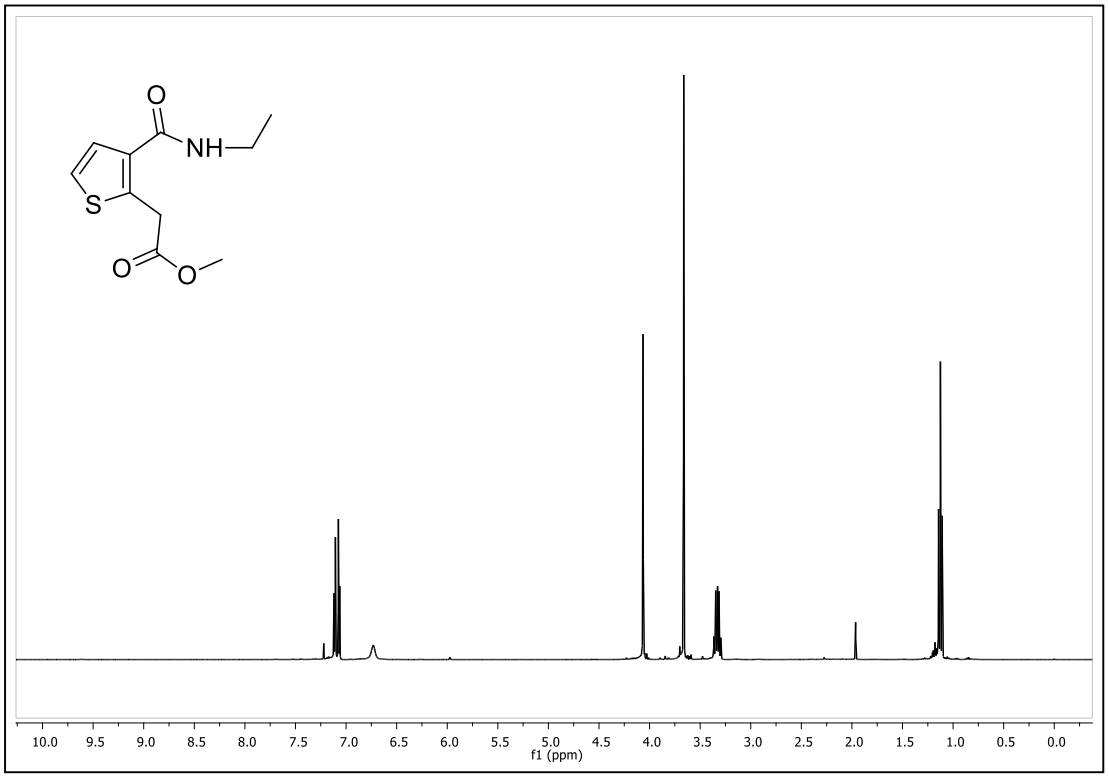

Figure A 187 ^{1}H NMR spectrum of compound **96b**

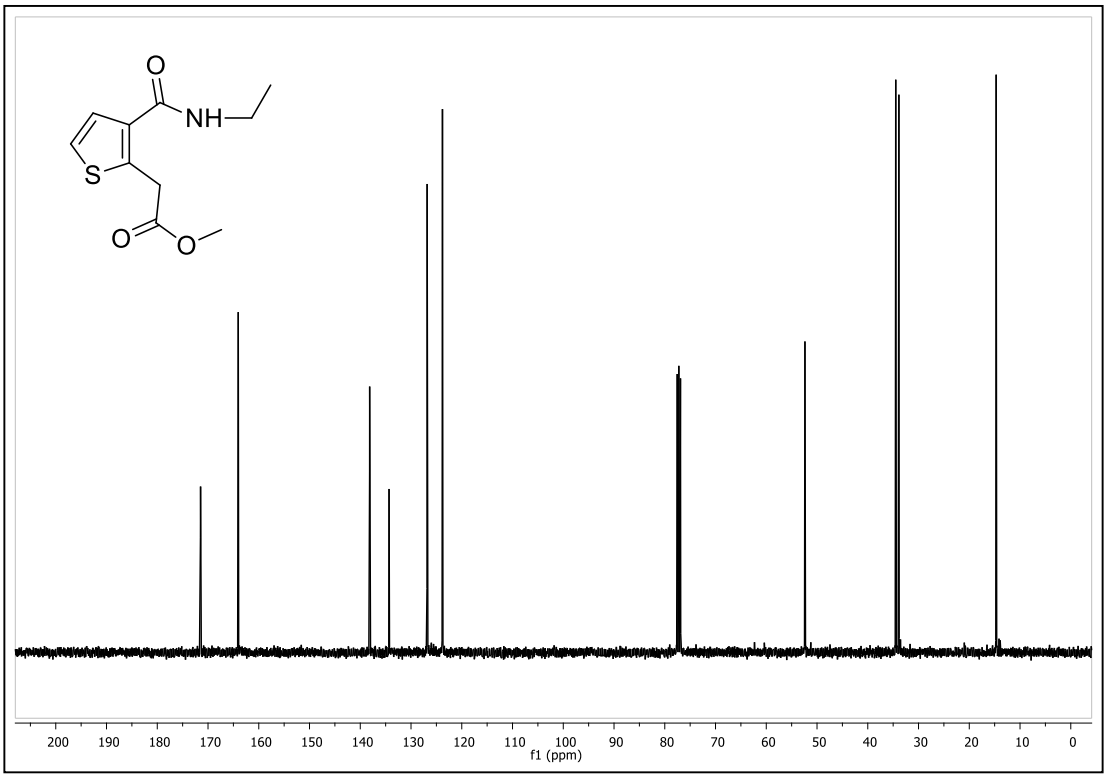

Figure A 188 ^{13}C NMR spectrum of compound **96b**

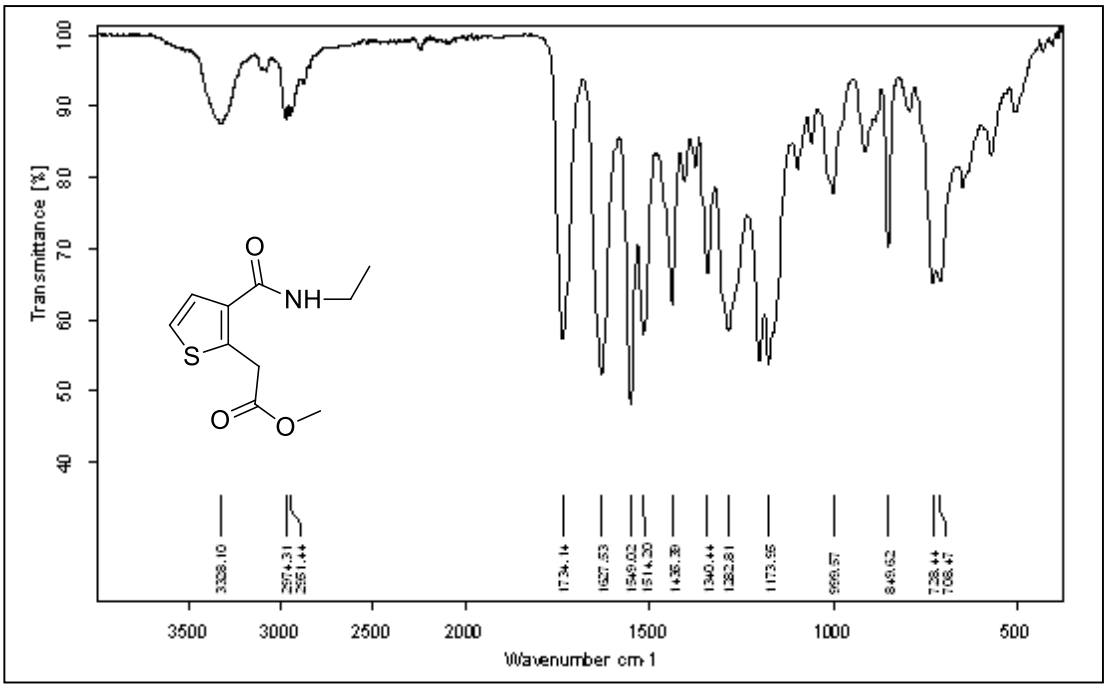

Figure A 189 IR spectrum of compound **96b**

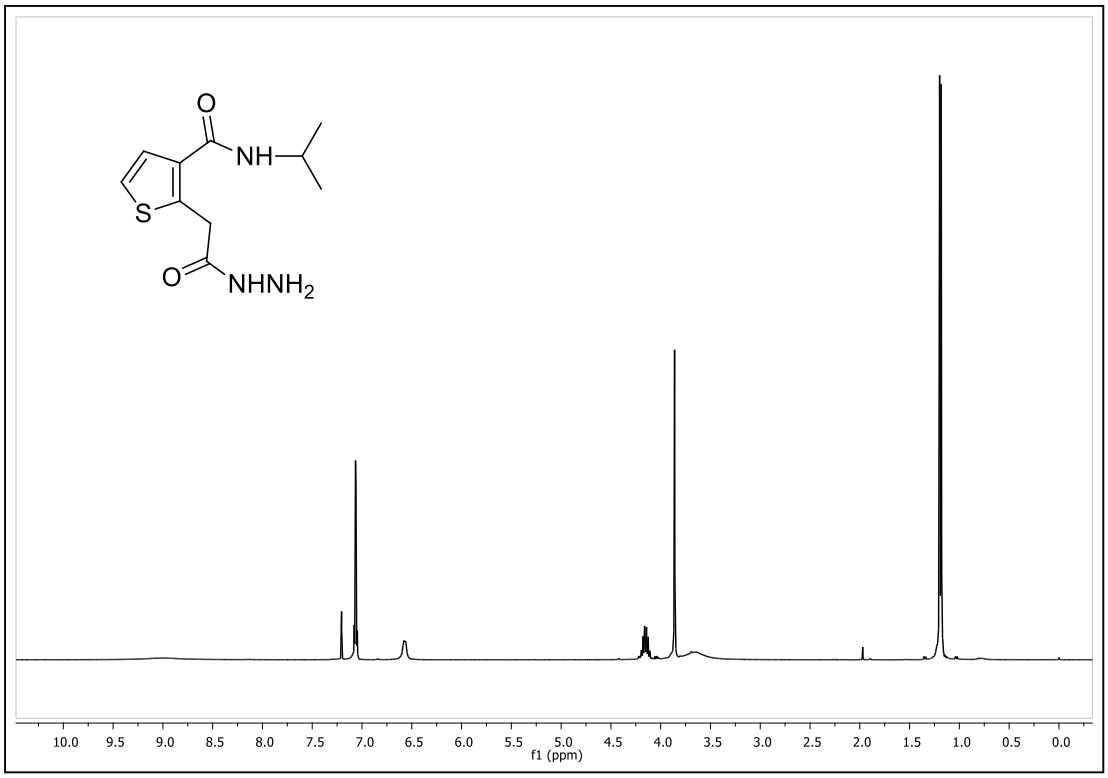

Figure A 190 ^{1}H NMR spectrum of compound **98a**

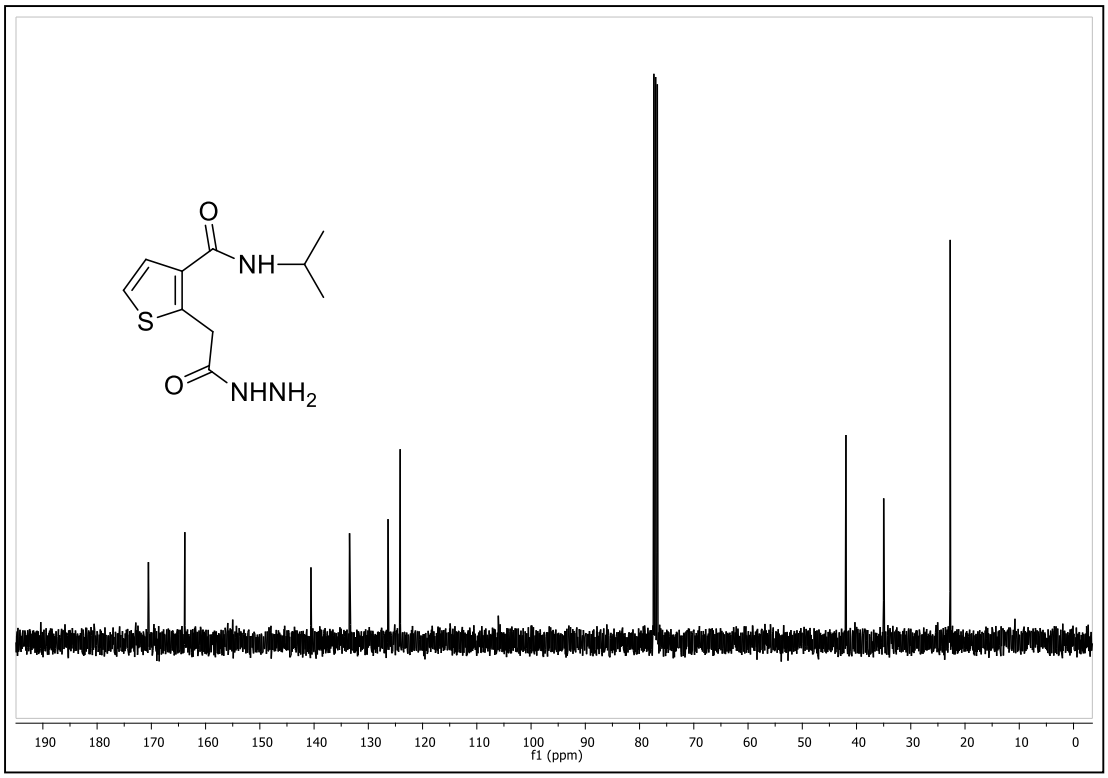

Figure A 191 ^{13}C NMR spectrum of compound **98a**

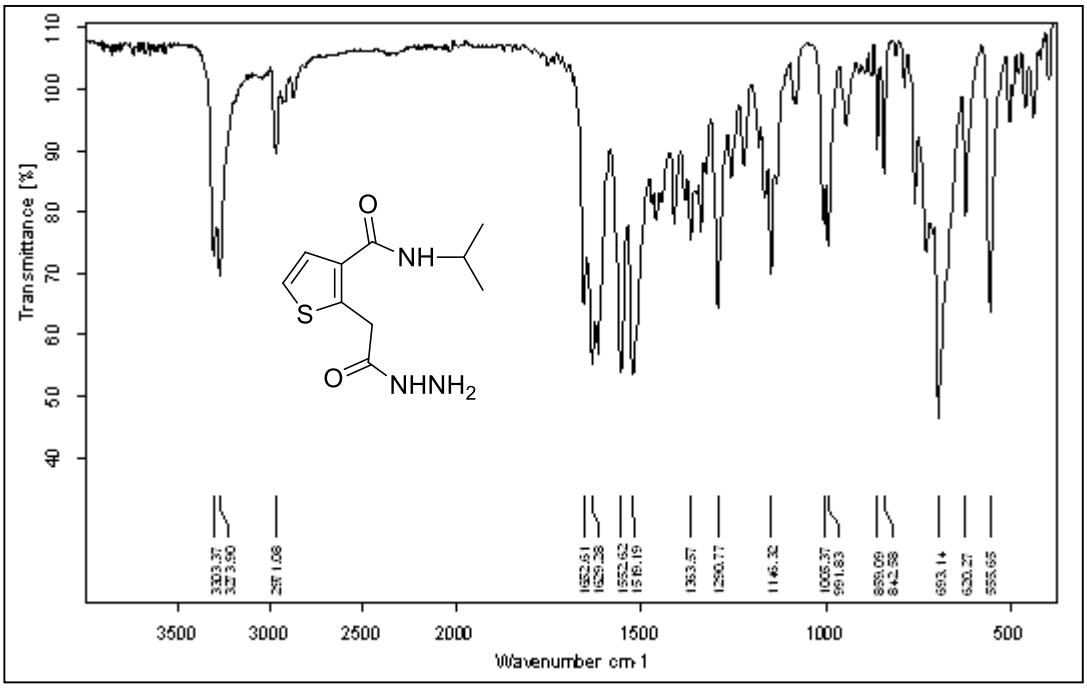

Figure A 192 IR spectrum of compound **98a**

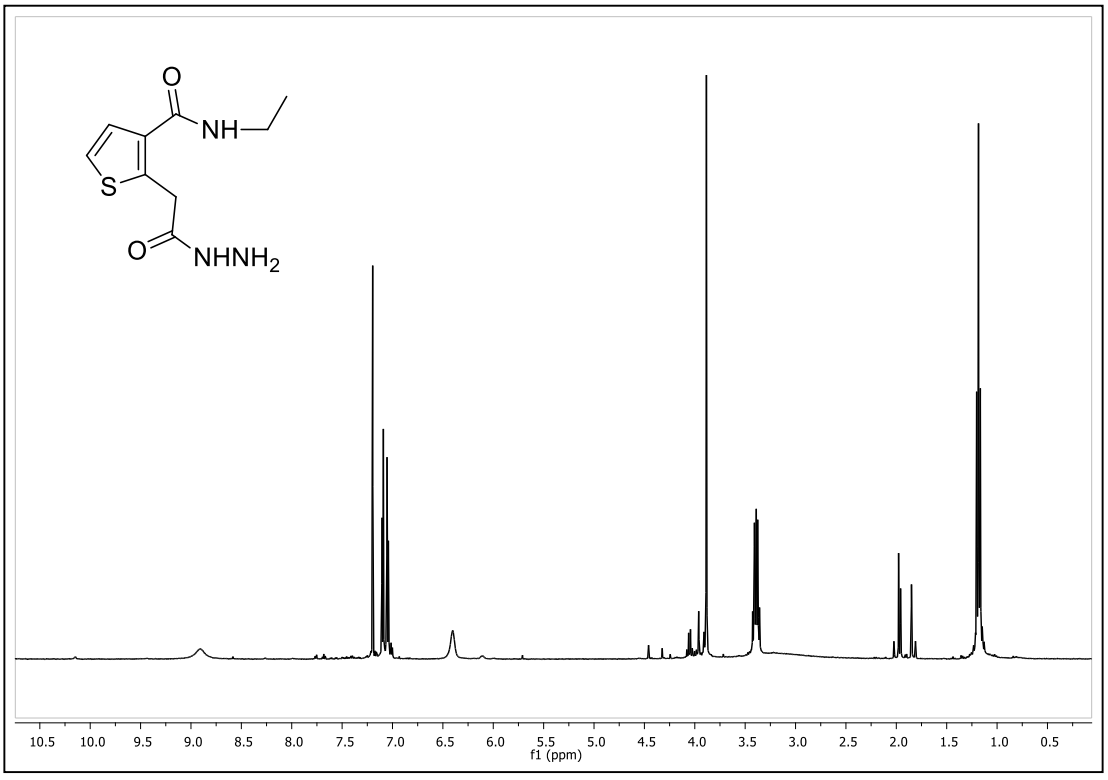

Figure A 193 ^{1}H NMR spectrum of compound **98b**

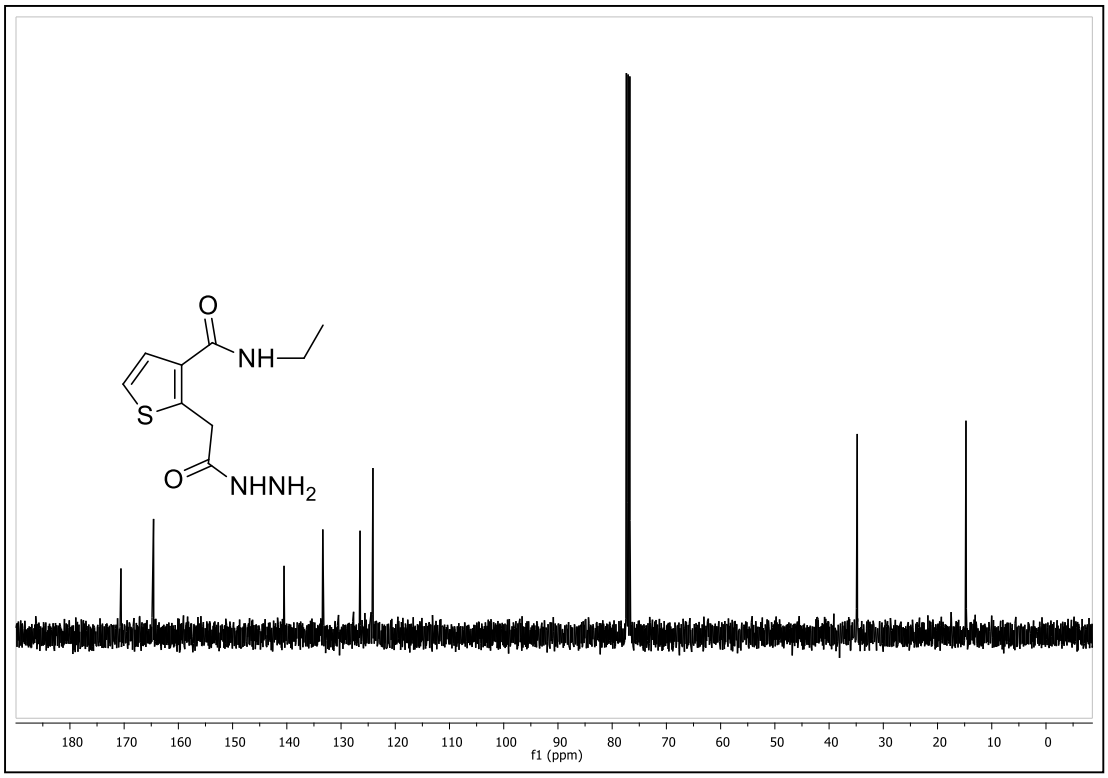

Figure A 194 ^{13}C NMR spectrum of compound **98b**

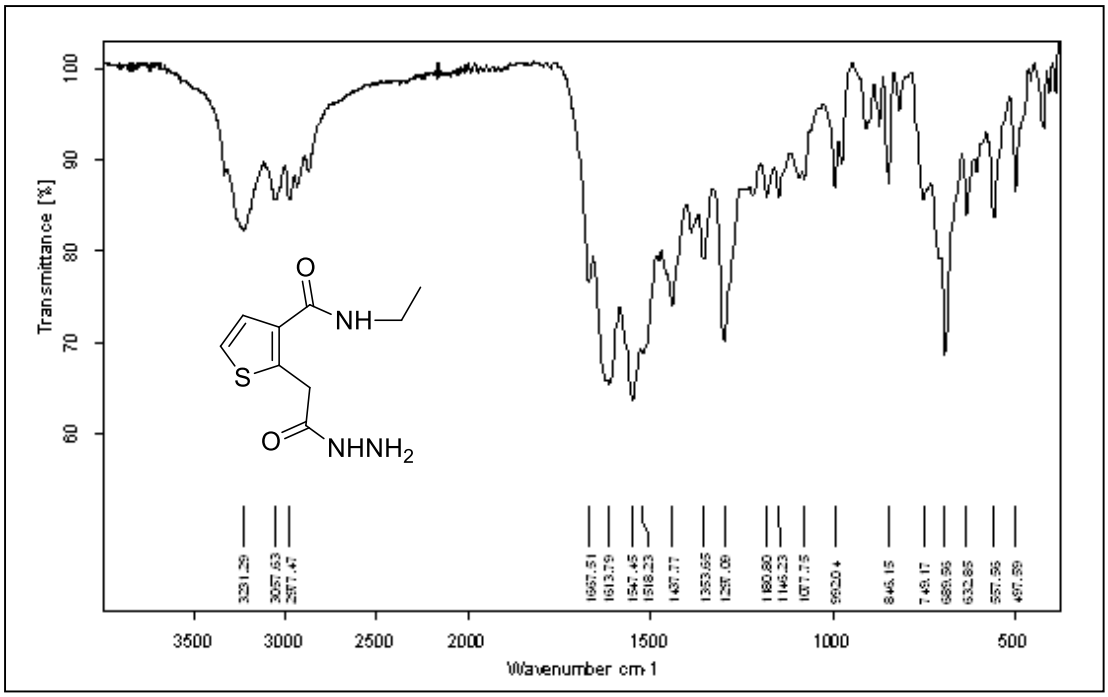

Figure A 195 IR spectrum of compound **98b**

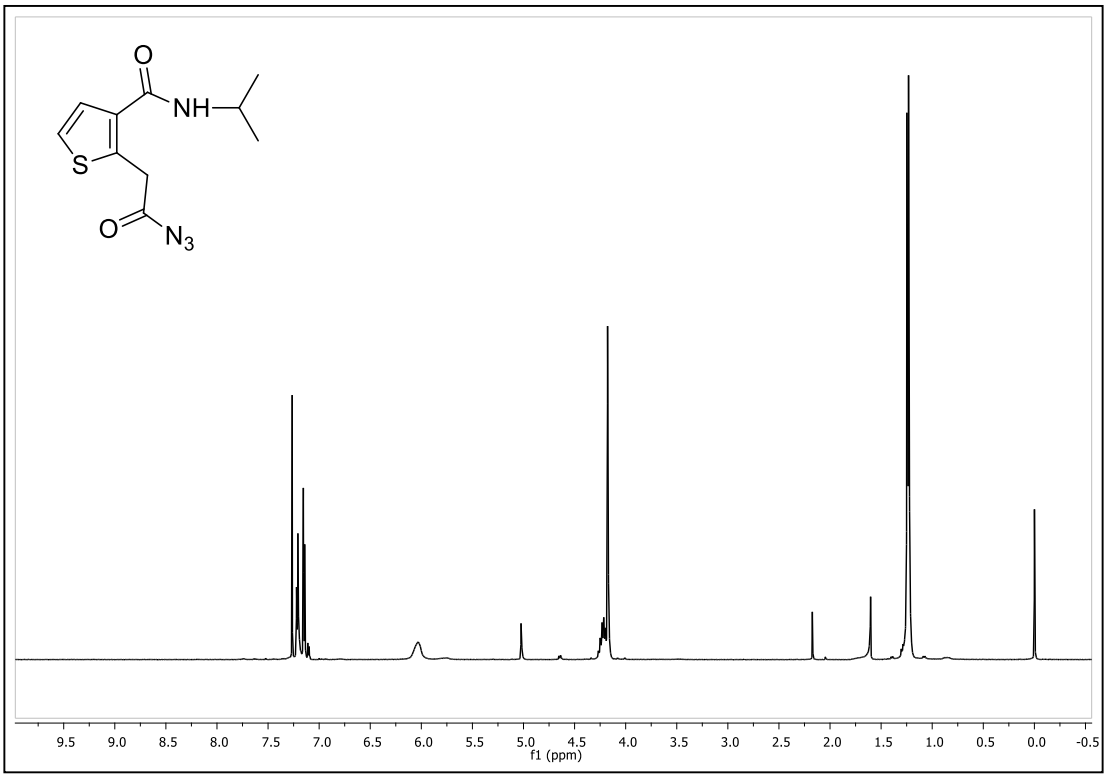

Figure A 196 ^{1}H NMR spectrum of compound **60a**

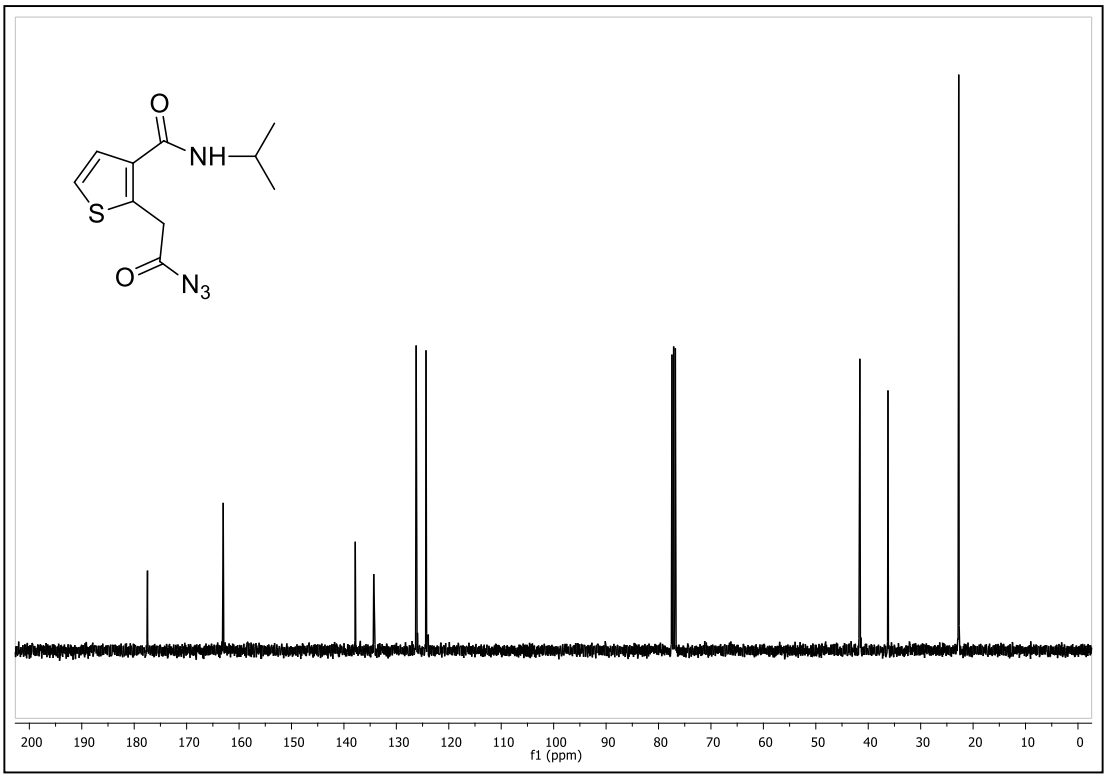

Figure A 197 ^{13}C NMR spectrum of compound **60a**

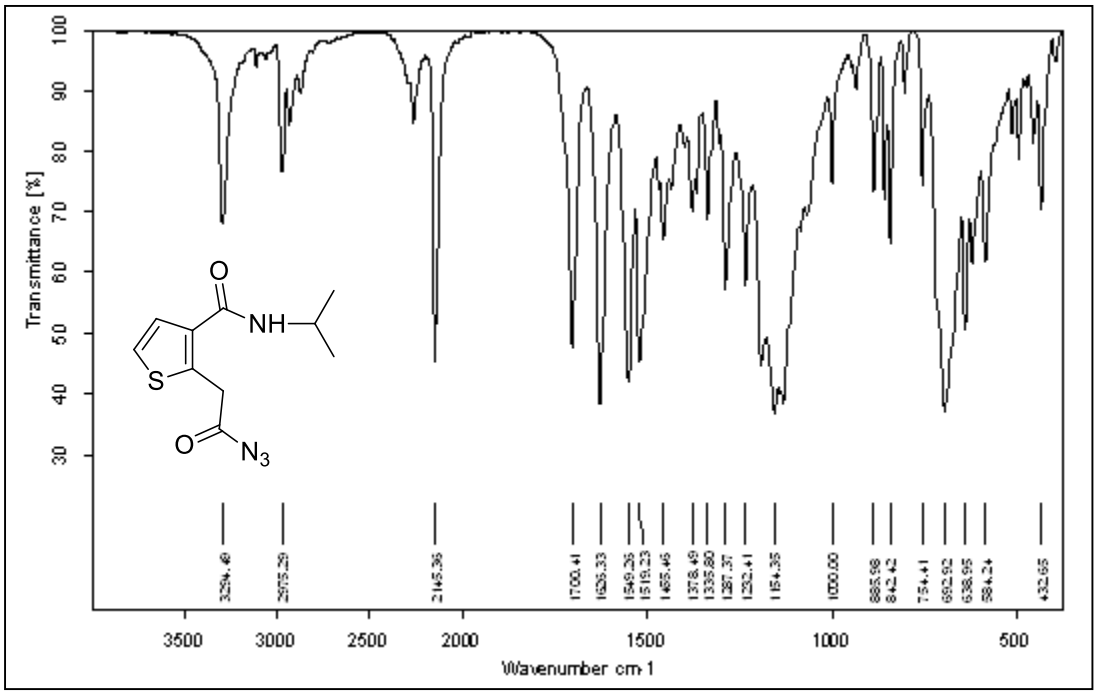

Figure A 198 IR spectrum of compound **60a**

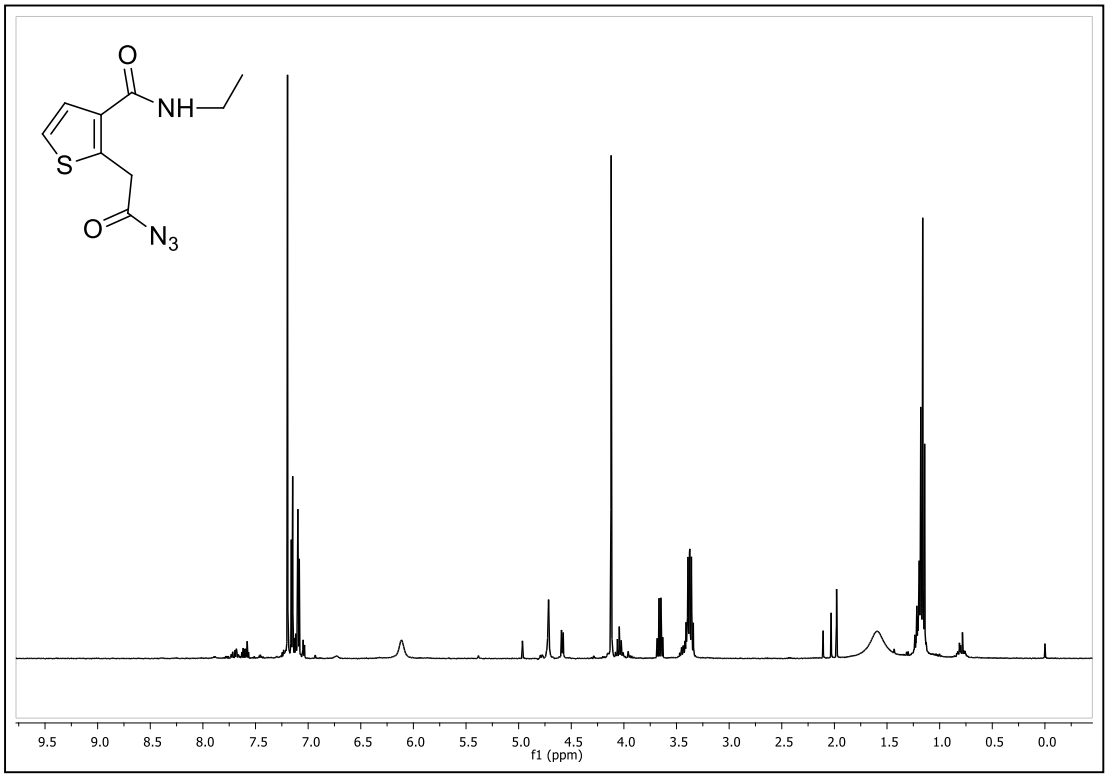

Figure A 199 ^{1}H NMR spectrum of compound **60b**

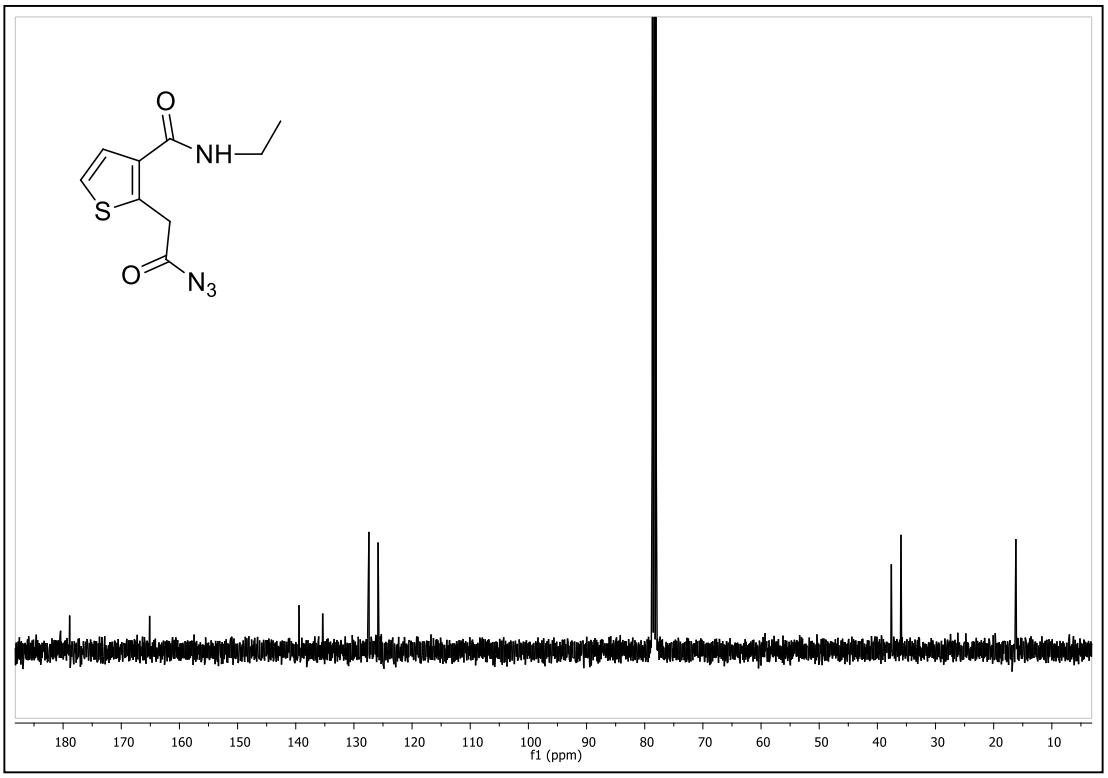

Figure A 200 ^{13}C NMR spectrum of compound **60b**

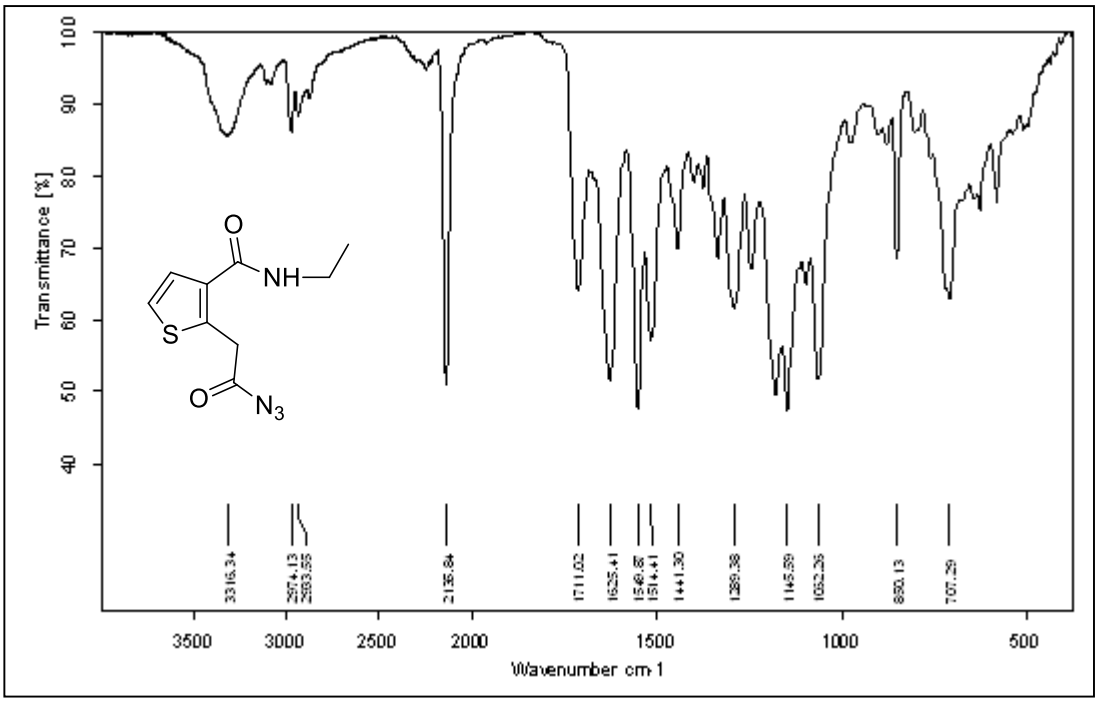

Figure A 201 IR spectrum of compound **60b**

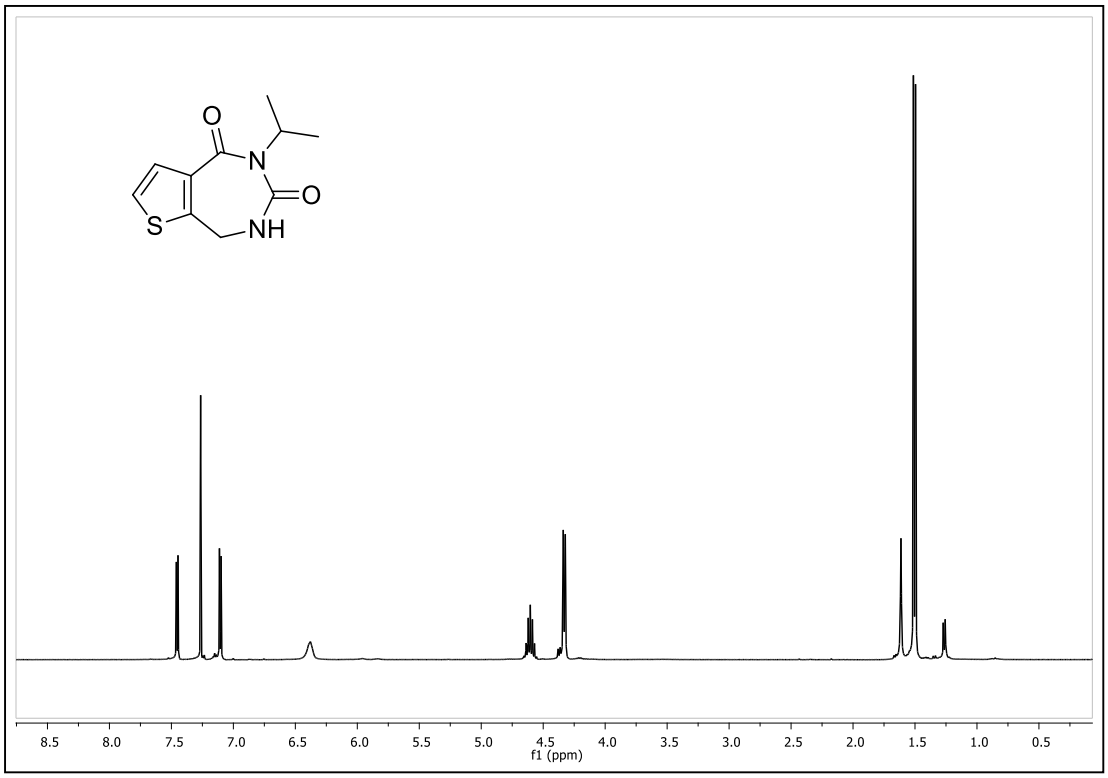

Figure A 202 ^{1}H NMR spectrum of compound **62a**

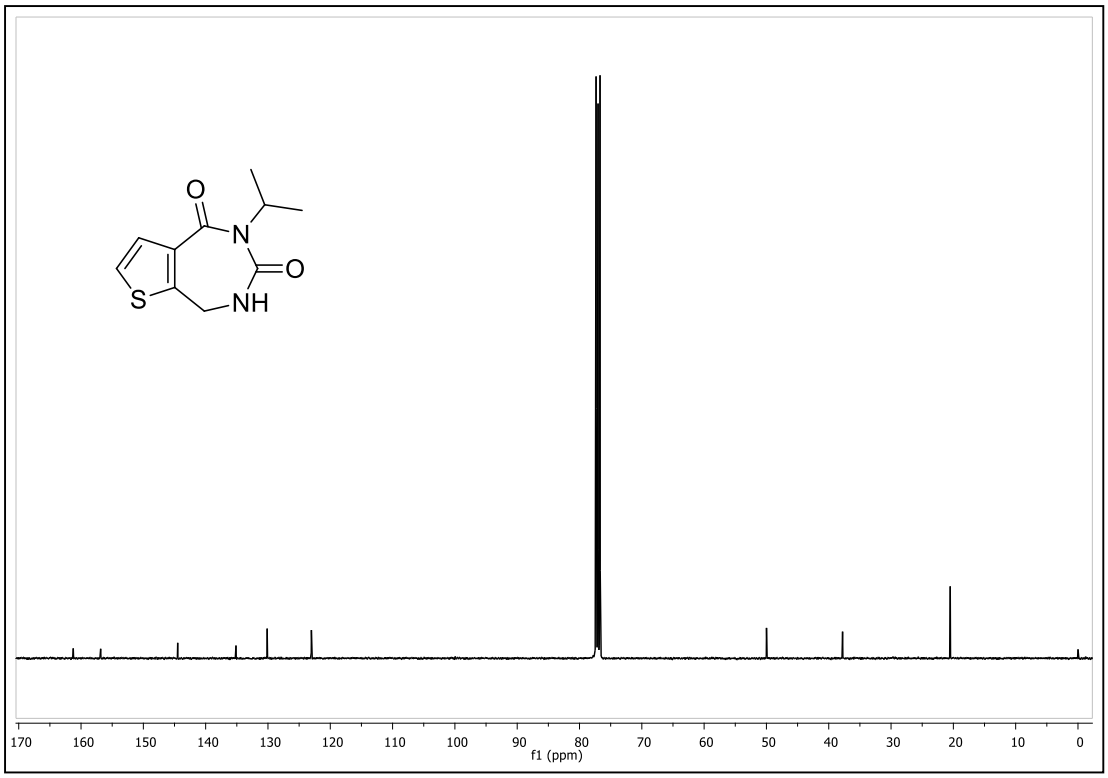

Figure A 203 ^{13}C NMR spectrum of compound **62a**

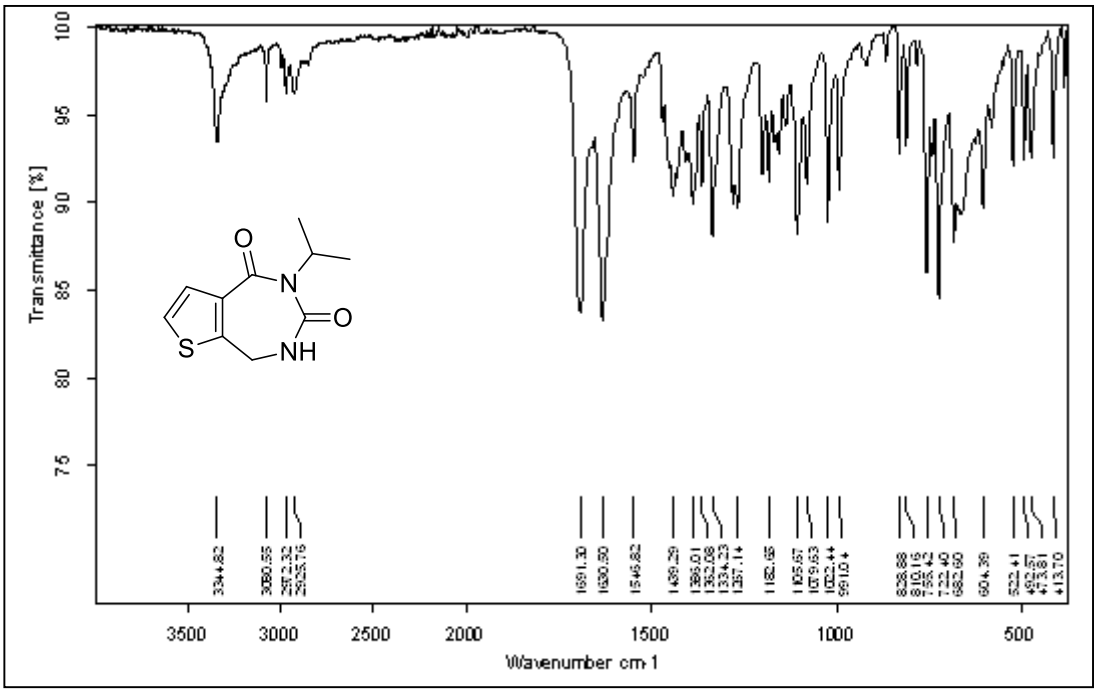

Figure A 204 IR spectrum of compound **62a**

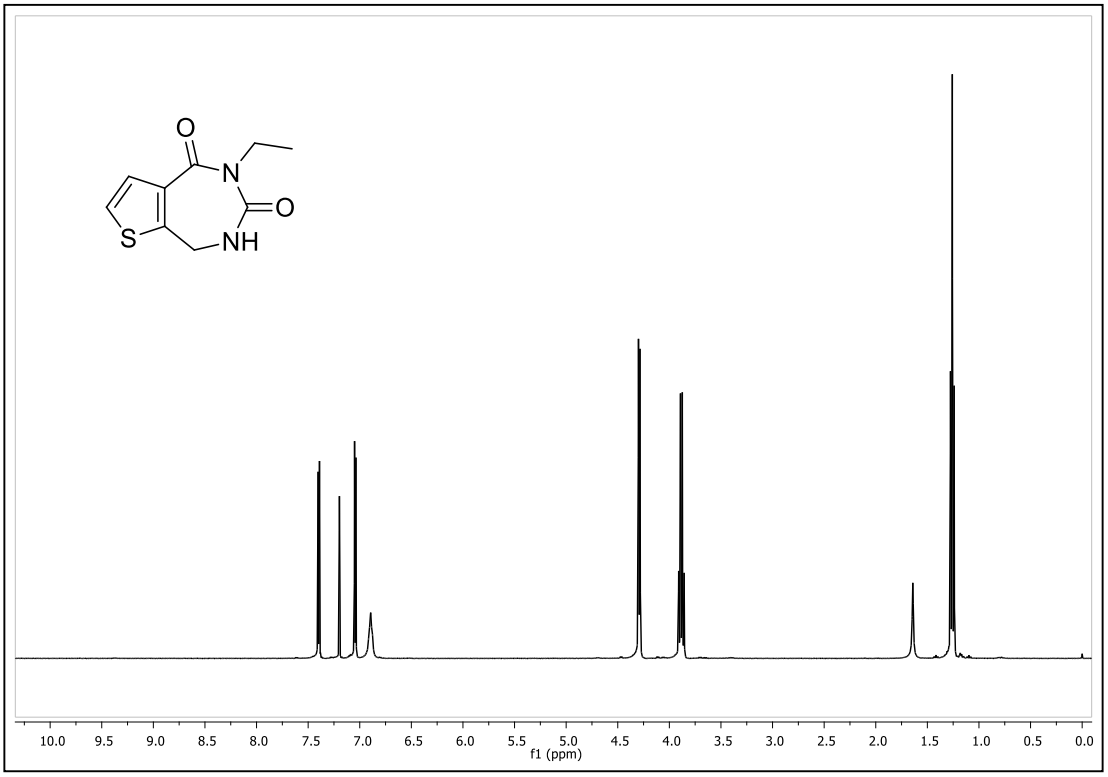

Figure A 205 ^{1}H NMR spectrum of compound **62b**

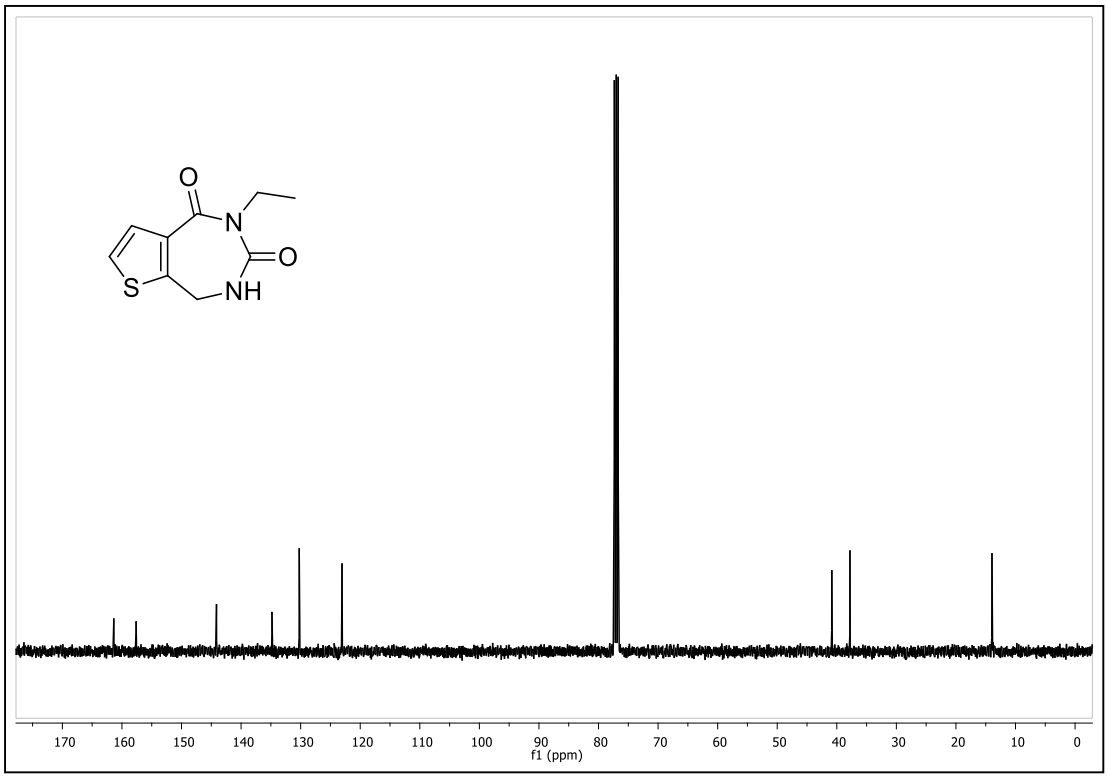

Figure A 206 ^{13}C NMR spectrum of compound **62b**

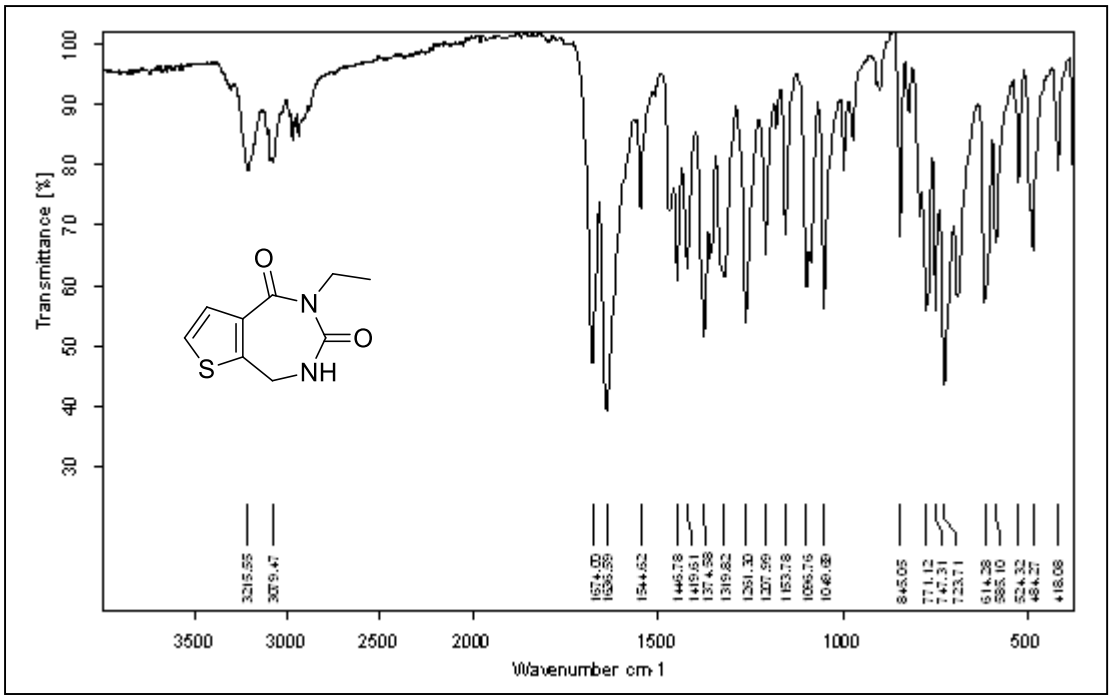

Figure A 207 IR spectrum of compound **62b**