# SYNTHESIS OF FUROPYRROLONE AND FUROPYRIDAZINONE DERIVATIVES: A NEW CLASS OF COMPOUNDS

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EMRAH KARAHAN

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Approval of the thesis:

**SYNTHESIS OF FUROPYRROLONE AND FUROPYRIDAZINONE DERIVATIVES: A NEW CLASS OF COMPOUNDS**

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

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Signature:

## ABSTRACT

SYNTHESIS OF FUROPYRROLONE AND FUROPYRIDAZINONE DERIVATIVES: A NEW CLASS OF COMPOUNDS

Karahan, Emrah

M.Sc., Department of Chemistry

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February 2011, 102 pages

Furopyrrolone has a bicyclic structure consisting of furan and a pyrrolone ring. It is isoelectronic with isoindolinone which is also a heterocyclic organic compound. It has a bicyclic structure, consisting of a benzene ring fused to a five-membered nitrogen containing pyrrolone ring. Pyrrolones, pyrrolidines, pyrrolidinones, pyridazines and pyridazinones are precursors to many pharmaceuticals. In this project we developed new synthetic procedures leading to the synthesis of furopyrrolone derivatives. To do this, the starting compound, methyl 2-(2-methoxy-2-oxoethyl)-3-furoate, was converted to isocyanate, regioselectively. This isocyanate was converted into the corresponding urethane and/or urea derivatives by treatment with alcohol and amine, respectively. It is known that acyl chlorides are more reactive than esters and carboxylic acids. Therefore, ester was converted to more reactive compound acyl azide that was used for intramolecular cyclization to get desired furopyrrolone skeletons. In the second part, methyl 2-formylfuran-3-carboxylate was treated with hydrazine and hydrazine salts. Then, intramolecular molecular cyclization caused the formation of desired heterocycles via acyl chloride intermediate.



**Keywords:** Furopyrrolone, isoindolinone, furopyridazinone, isocyanates.

# ÖZ

FUROPİROLON VE FUROPİRİDAZİNON TÜREVLERİNİN SENTEZİ: YENİ İSKELET YAPISINA SAHİP BİLEŞİKLER

Karahan, Emrah

Yüksek Lisans, Kimya Bölümü

Tez Yöneticisi: Prof. Dr. Metin Balcı

Şubat 2011, 102 sayfa

Furopirolon, furan ve pirolon halkalarının kenetlenmesinden oluşan bisiklik yapıya sahip bileşik olup izoindolinon ile izoelektroniktir. İzoindolinon da heterosiklik bir bileşik olup benzene ve pirolon halkalarının kenetlenmesinden oluşmuştur. Pirolon, pirolidin, pirolidinon, piridazin ve piridazinon birçok ilacın temel yapısını oluşturmaktadır. Bu çalışma kapsamında, furopirolon ve furopiridazinon türevlerinin sentezi için yeni bir yöntem geliştirildi. Bunun için çıkış bileşiği olan diester, metil 2-(2-metoksi-2-oksoetil)-3-furoat, regiospesifik olarak izosiyanata çevrildi. Bu izosiyanat alkol ve aminlerle reaksiyona sokularak ürethan ve üre türevleri sentezlendi. İntramoleküler siklizasyonu elde etmek için ester grupları kendilerinden daha reaktif olan asil klorürlere çevrildi. İkinci kısımda ise, aldehit hidrazin ve hidrazin tuzlarıyla reaksiyona sokuldu ve elde edilen bileşikler halkalaşma için kullanıldı. Siklizasyonu sağlamak için ise ester grupları tekrar asil klorürlere çevrildi.

**Anahtar kelimeler:** Furopirolon, izoindolinon, furopiridazinon, izosiyanat.

*To my family and lovely angel…*

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## LIST OF ABBREVIATIONS

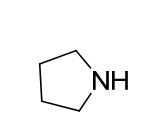
| | |
|---|---|
| **DCM:** | Dichloromethane |
| **TFA:** | Trifluoroaceticacid |
| **THF**: | Tetrahydrofuran |
| **NMR**: | Nuclear magnetic resonance |
| **IR**: | Infrared |
| **J**: | Coupling constant |
| **Hz**: | Hertz |
| **ppm**: | Parts per million |
| **mg**: | miligram |
| **mmol**: | milimol |

# CHAPTER 1

# INTRODUCTION

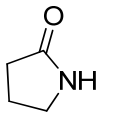
## 1.1 Pyrrolidines, pyrrolidinones, pyrrolones

Pyrrolidine **(1)**, pyrrolidinone **(2)** and pyrrolones **(3)** are five-membered heterocycles containing nitrogen atom. The specificity of these compounds is that they are components of alkaloids.[1] Most of these *N*-containing heterocycles show pharmacological activity.[2]



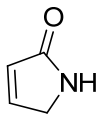

**pyrrolidine**

**1**




**pyrrolidinone**

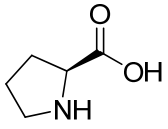
**2**




**pyrrolone**

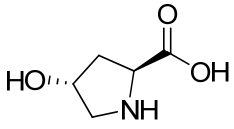
**3**

Several natural products and some amino acids contain pyrrolidine **(1)**, pyrrolidinone **(2)** and pyrrolone **(3)** in their skeleton. Most important ones are two amino acids. Proline **(4)** and 4-hydroxyproline **(5)** have pyrrolidine ring **(1)** as a basic structure. The importance of these amino acids arises from their constitution. They are the only two having a secondary amino group among the 20 natural amino acids. Due to this property, they can behave only as hydrogen bond acceptor, not donor.




**proline**

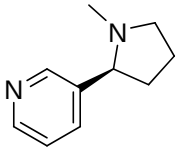
**4**




**4-hydroxyproline**

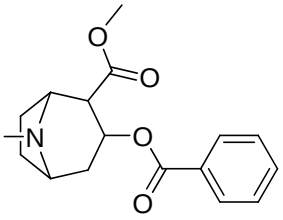
**5**

Nicotine **(6)** is one of the other important pyrrolidine derivatives which also consists an additional heterocycle, pyridine. It is an alkaloid and highly addictive more than the other well-known pyrrolidine derivatives cocaine **(7)**.



**(*S*)-nicotine**

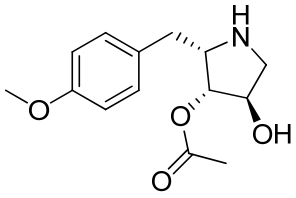
**6**



**cocaine**

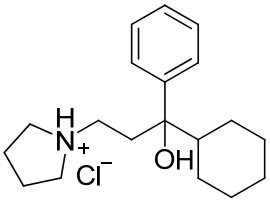
**7**

Nicotine **(6)** can be obtained from the leaves of tobacco, *nicotiana rustica* and *n. tabacum*.[3] (*S*)-nicotine **(6)** has been used as insecticide over decades.[4] On the other hand, it has an significant effect on central nervous system and a wide usage in the treatment of psychotic disorders or intellectual impairment disorders including Parkinson's disease and Alzheimer's disease.[5]



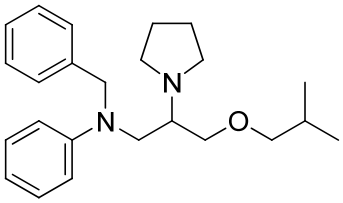
**anisomycin**

**8**



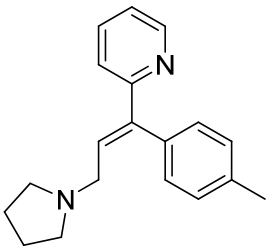
**procyclidine**

**9**



**bepridil**

**10**

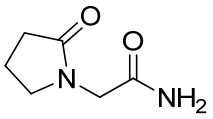


**triprolidine**

**11**

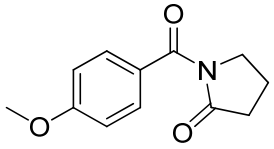
Among the pyrrolidine **(1)** derivatives those are commonly being used as medicine, some of them comes to the fore such as; anisomycin **(8)**, which has antifungal activity[6] and inhibits the protein synthesis,[7] procyclidine **(9)**, which is the pyrrolidine salt being used to treat Pakinson's disease,[8] bepridil **(10)**, one of the calcium channel blocker is used to treat abnormal heart rhythms,[9] and triprolidine **(11)**, which is the active ingredient of A-ferin. Triprolidine **(11)** is used for treatment of allergic rhinitis and can clear the congestion in nose.[10]

Pyrrolidinones **(2)** are other types of important heterocycles that are found in a lot of natural products and biologically active compounds. The most important one is the racetams which have had a long history of vigorous study, because of its toxicology and safety, also its effectiveness. The racetams work by increasing choline in the brain facilitating an increase in memory and cognition so they are called as nootropic drugs.[11] Piracetam **(12)** and aniracetam **(13)** are the famous racetam drugs in the pharmaceuticals.




**piracetam**

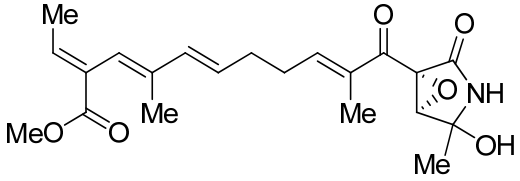
**12**




**aniracetam**

**13**

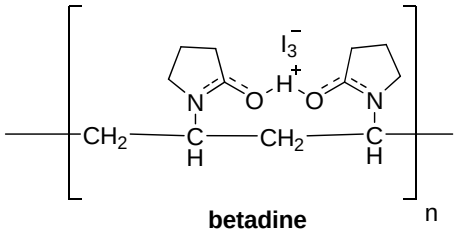
Epolactaene **(14)** is one of the another pyrrolidinone **(2)** derivative which is isolated from *Penicillium* sp. BM 1989-P.[12] It is generally used for induction of neurite outgrowth[13] and also hinders some enzymes such as human DNA topoisomerase II and mammalian DNA polymerases.[14]




**epolactaene**

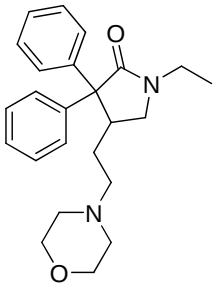
**14**

Pyrrolidinone **(2)** can be utilized as a monomer. The most famous polymer is the povidone iodine, complex of polyvinypyrrolidinone with iodine, known as betadine **(15)**, which is used as an antiseptic.[15] Moreover, doxapram **(16)**, which is familiar with the name Dopram in the market, is another derivative of pyrrolidinones used to treat respiratory infection.[16] In addition to this, they can be in the structure of uncommon amino acid, like pyroglutamic acid **(17)**, generated from the intramolecular cyclization of glutamic acid.[17]



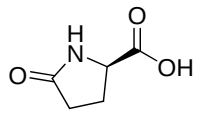
**betadine**

**15**



**doxapram**

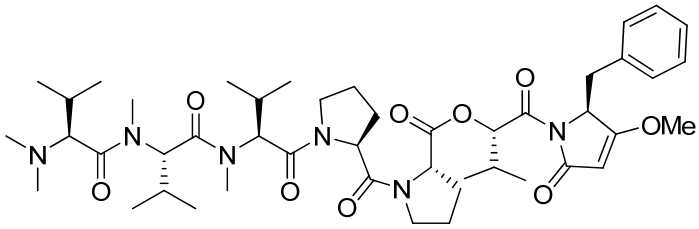
**16**



**pyroglutamic acid**

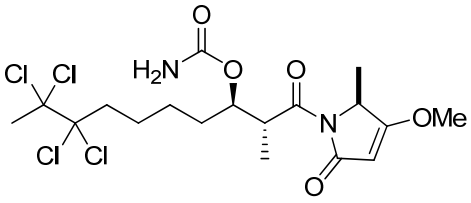
**17**

Dolastatin 15 **(18)** is the polypeptide chain which has pyrrolone **(3)** ring at the end of the peptide that offer target selectivity to compound by providing conformational restriction.[18] Another pharmacologically active pyrrolones derivative is mirabimide E **(19)** which displays solid tumor selective cytotoxicity.[19]



**dolastatin 15**

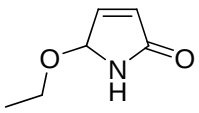
**18**



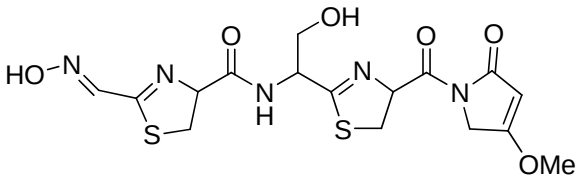
**mirabimide E**

**19**

Pyrrolones **(3)** are also found in the natural products which demonstrate biological activities. Some derivatives can be synthesized by marine cyanobacteria, for instance, *Ageratum conyzoides* produce the 5-ethoxy-*1H*-pyrrol-2(*5H*)-one **(20)** as an alkaloid[20] and naturally occurring antibiotic althiomycin **(21)** was synthesized by *Streptomyces althioticus* and it hinders the protein synthesis.[21]



**20**



**althiomycin**

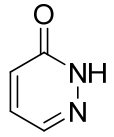
**21**

## 1.2 Pyridazines and pyridazinones

Pyridazine **(22)** and pyridazinone **(23)** are six-membered heterocycles that contain two adjacent nitrogen atoms. They show a wide range of pharmacological activity and are found in a lot of natural compounds having a biological activity. In the literature, it is known that pyridazines have antimicrobial,[22] anti-hypertensive[23] and anticancer activity.[24] In addition, pyridazinones are used for the treatment of platelet aggregation[25] and ulcer.[26]

**pyridazine**

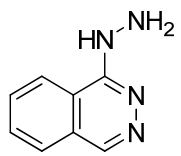
**22**



**pyridazinone**

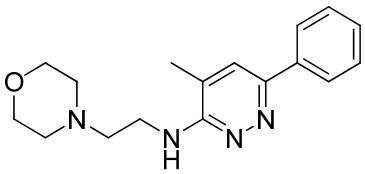
**23**

Pyridazine **(22)** derivatives are found in skeleton of some commercially available drugs. For instance, Apresoline contains hydralazine **(24)** as a pyridazine derivative that is used to treat hypertension for pregnant.[27] Brantur is other drug which is used for the treatment of depression[28] and it includes minaprine **(25)** as an active compound. Azaphen is another medicine including pyridazine ring. It has pipofezine **(26)** structure which is tricyclic anti-depressant having a sedative effect.[29]



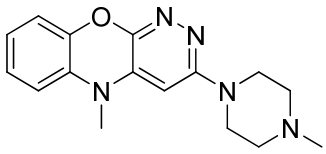
**hydralazine**

**24**



**minaprine**

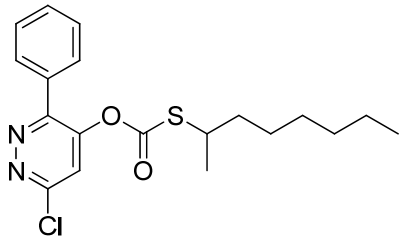
**25**



**pipofezine**

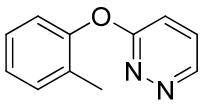
**26**

Pyridazine derivatives are also widely used in agriculture as herbicides in order to kill pests and unwanted plants.[30] These compounds have different functionalities in their structures. For example, pyridate **(27)** has thiocarbonate composition, credazine **(28)** comprises the ether linkage and pyridafol **(29)** consists of alcohol unit.



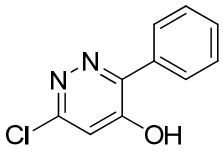
**pyridate**

**27**



**credazine**

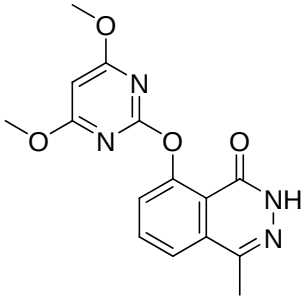
**28**



**pyridafol**

**29**

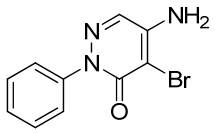
Pyridazinones **(23)** hold considerable interest relative to the preparation of organic intermediates and physiologically active compounds.[31] They are used as 5-$HT_{2c}$ agonists, which play an important role in emesis, mood, sexuality, sleep and appetite.[32] Moreover, it is proven by Yamaguchi *et al.* that pyridazinones **(23)** exhibit bronchodilator activity on the cardiovascular system.[33] Laguna *et. al* show that they inhibit the blood platelet aggregation.[34] Another pharmacological properties of pyridazinone derivatives is the reduction of blood pressure.[35] Pyridazinone derivatives **(23)** are also found as an inhibitor, such as methylphthalazin-1-one **(30)** which is the inhibitor of acetohydroxyacid synthase (AHAS), an enzyme that speeds up the biosynthesis of branched-chain amino acids including leucine and valine.[36] For the case, in the structure of AHAS inhibitor, methylphthalazin-1-one **(30)**, pyridazinone ring is fused to benzene ring, which is called phthalazinone.



**methylphthalazin-1-one**

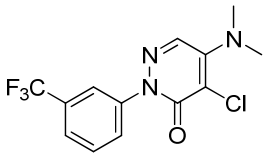
**30**

Pyridazinones **(23)** are widely used as pesticides, such as herbicides and insecticides. Some herbicides including pyridazinone ring in their structure have various functional groups on the pyridazinone ring. For example, brompyrazon **(31)** and metflurazon **(32)** have amine group in their skeleton and also they have halides such as bromine and chlorine, respectively. Several pyridazinone herbicides contain carboxylic acid as a functional group, such as flufenpyr **(33)** and oxapyrazon **(34)**. Another important pyridazinone herbicide is pyridaphenthion **(35)**, which comprises both sulphur and phosphorus.



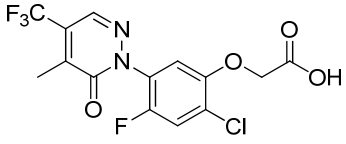
**brompyrazon**

**31**



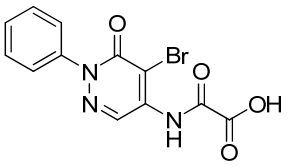
**metflurazon**

**32**



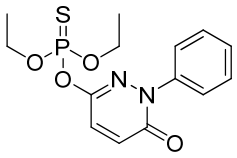
**flufenpyr**

**33**



**oxapyrazon**

**34**



**pyridaphenthion**

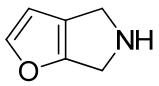
**35**

### 1.3 A new class of compounds; furopyrrolones and furopyridazinones

The majority of essential life-science products contains at least one heterocyclic sub-unit within their structures and therefore heterocyclic chemistry is essential part of the pharmaceutical industry. A wide variety of receptors have precious biological activity due to their rigid structures and functional heterocycles generally possess drug-like belongings, such as a useful solubility profile. In order to further explore chemical space available for pharmaceutical applications, there is a continued demand for the development of new heterocyclic core scaffolds that have novel structures and bear functionality that may be readily transformed into focused libraries of analogues for bioassay and subsequent hit-to-lead medicinal chemistry development.[37]

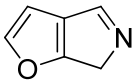
#### 1.3.1 Synthesis of furopyrrolones

The literature shows that pyrrolidines **(1)**, pyrrolidinones **(2)** and pyrrolones **(3)** are widely present in natural compounds and are structural part of a variety of pharmacologically and biologically active compounds.



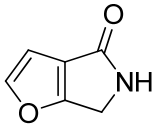

5,6-dihydro-4*H*-furo[2,3-*c*]pyrrole

**36**




6*H*-furo[2,3-*c*]pyrrole

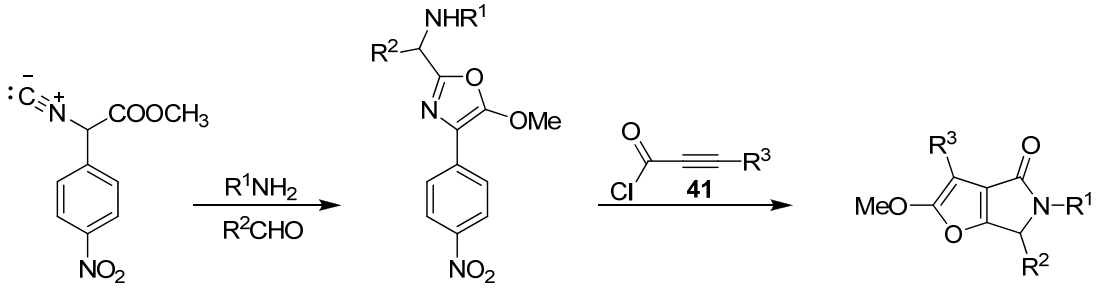
**37**




5,6-dihydro-4*H*-furo[2,3-*c*]pyrrol-4-one

**38**

In addition to this, even these five-membered heterocycles are commonly found in the natural products, furan-fused nitrogen containing heterocycles such as furopyrrole **36** and furopyrrolone **38** are almost unknown. Especially, synthetic methodology of these furan fused five membered heterocycles is absent.



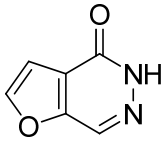

**39** **40** **42**

**Scheme 1**

In the literature, there is only one way of the synthesis of furopyrrolones. Zhu and co-workers developed a four component synthesis of furopyrrolones on the basis of the unique reactivity of methyl α-isocyano-4nitrobenzeneacetate **(39)**. A three component reaction of methyl α-isocyano-4 nitrobenzene acetate **(39)** with aldehyde and amine gave corresponding methoxyoxazole derivative **40**. Reaction of oxazole **40** with propynoyl chloride **41** produced furopyrrolone **42**.[38,39]

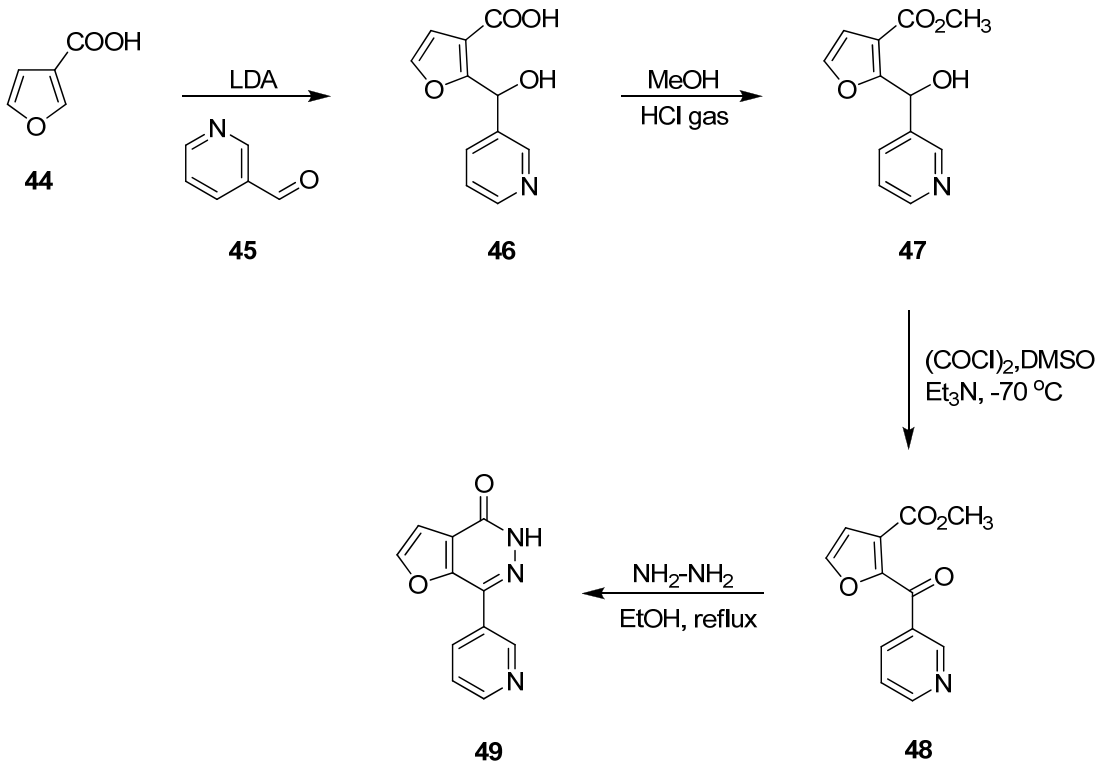
### 1.3.2 Synthesis of furopyridazinones

Furopyridazinone **43** is rarely seen heterocyclic compound consisting of five-membered furan ring fused to six-membered nitrogen containing pyrrolone ring **(3)**. This new class of compound **43** has only two synthetic pathways and both methodology give substituted furopyridazinone derivatives.



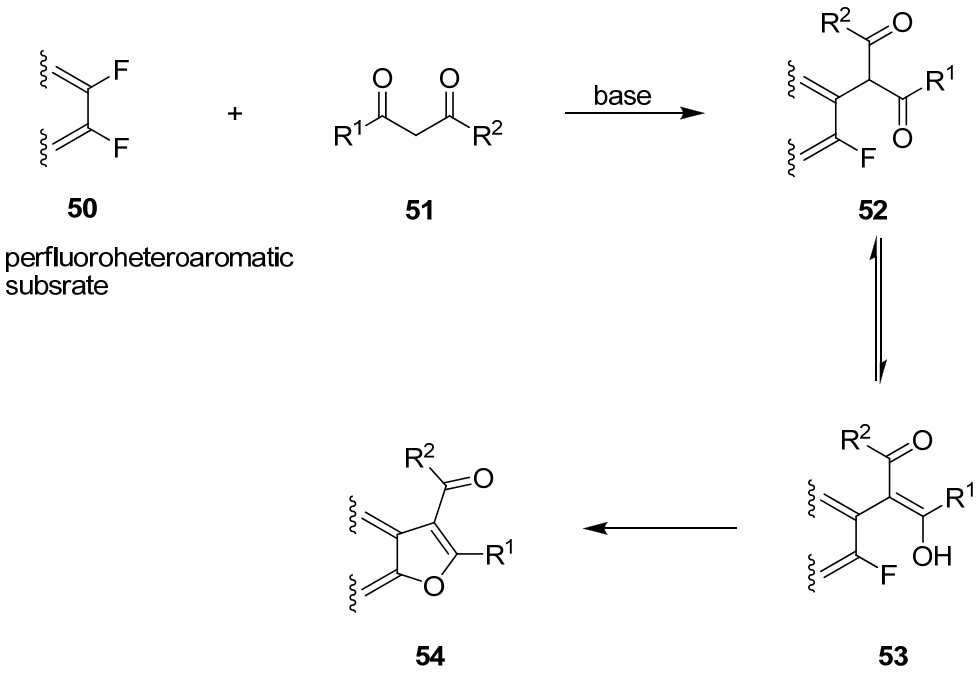

**furopyridazinone**

**43**



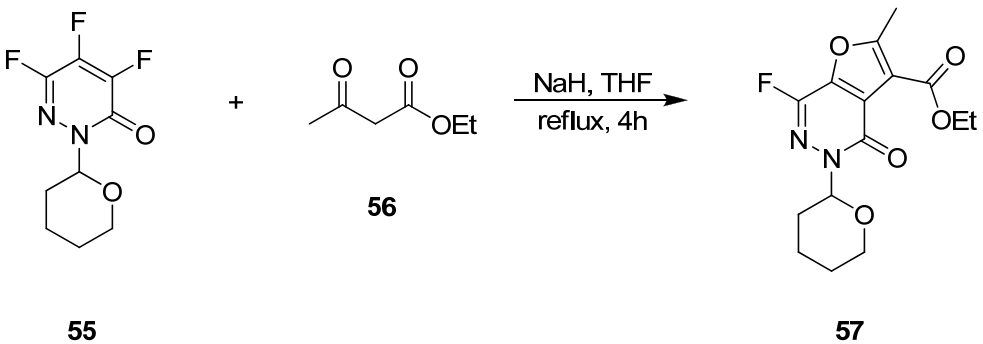

**Scheme 2**

Yamaguchi and co-workers reported the preparation of furopyridazinone **49** which is utilized in the inhibition of thromboxane $A_2$ synthetase and in addition to this it shows bronchodilating activity.[40] According to this method, furan 3-carboxylic acid **(44)** was treated with nicotinaldehyde **(45)** to give carbinol product **46**. After the conversion of carboxylic acid **46** into methylester **47**, alcohol functionality in **47** was oxidized to corresponding ketone **48** by Swern oxidation via treatment with oxalylchloride and DMSO at low temperature. Finally, addition of hydrazine hydrate gave furopyridazinone derivative **49** at reflux temperature of ethanol.




**Scheme 3**

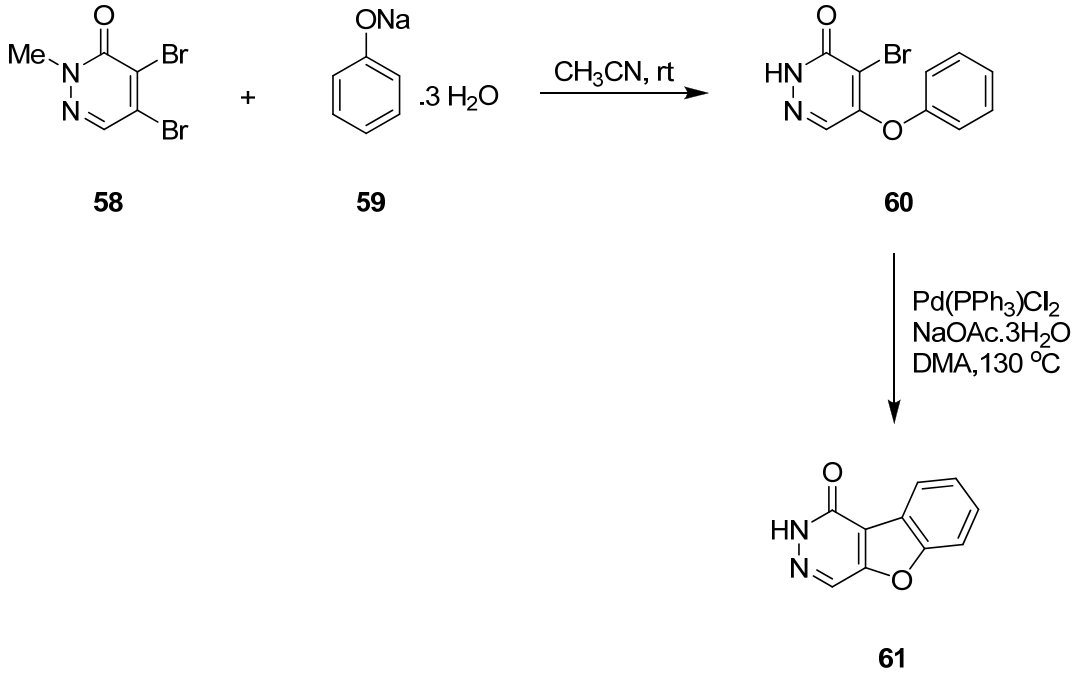
Another effective method for synthesizing furopyridazinone **(43)** derivatives is reaction between a variety of perfluoroheteroaromatic derivatives **50** and representative 1,3-dicarbonyl substrates **51** in the presence of a base.[37] In this method, Cartwright *et al*. have developed similar procedures for the synthesis of furan fused systems starting from tetrafluoropyridazine, tetrafluoropyridine and trifluoropyridazinone derivatives and following reactions of these scaffolds gave the various type heterocycles with different functionality. For the synthesis of furopyridazinone derivatives, protected pyridazinone **55** was reacted with ethyl acetoacetate **56** in the presence of NaH to give corresponding furopyridazinone derivative **57** in high yield.




**Scheme 4**

### 1.3.3 Synthesis of benzofuropyridazinones

Benzofuropyridazinones were synthesized by Matyus *et al*. by using pyridazin-3(2*H*)-one precursor.[41] In this methodology, regioselective nucleophilic substitution reaction of a 2-methyl-4,5-dihalopyridazin-3(2*H*)-one with phenol was performed and followed by an intramolecular Heck-type reaction.




**58** **59** **60** **61**

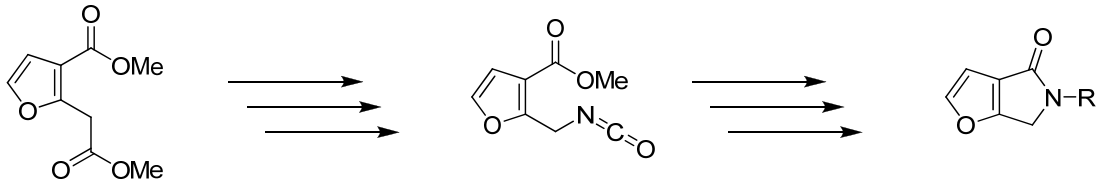
**Scheme 5**

First of all, dibromopyridazinone **58** was reacted with sodium phenoxide **59** in acetonitrile at room temperature to give the corresponding phenoxypyridazinone derivative **60** via nucleophilic substitution reaction. Subsequently, intramolecular Heck-type reaction was performed under the given reaction conditions to obtain the desired heterocycles **61**.

### 1.4 Aim of the thesis

The aim of this thesis was the development of new synthetic methodologies for the synthesis of furopyrrolone **64** and furopyridazinone **67** derivatives starting from the diester **62** and methyl ester **65**. First, the diester **62** will be synthesized by reaction of 1,3-acetone dicarboxylate **(71)** and chloroacetaldehyde **(70)**.

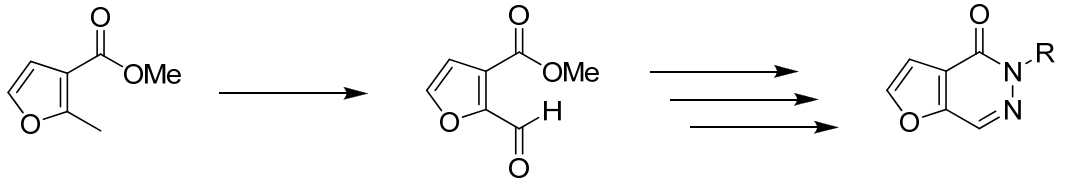
The main idea is the selective conversion of one of the ester groups into corresponding acyl azide, which will be transformed into isocyanate via Curtius rearrangement. Finally, intramolecular cyclization will give desired furopyrrolone derivatives **64**.




**62** **63** **64**

**Scheme 6**

In the second part of study, starting compound **65** will be oxidized to key compound aldehyde **66**. Reactions of aldehyde **66** with hydrazines and hydrazine salts will give the imine moiety and nucleophilic nitrogen atom. Lastly, intramolecular cyclization will provide the furopyridazinone derivatives **67**.




**65** **66** **67**

**Scheme 7**

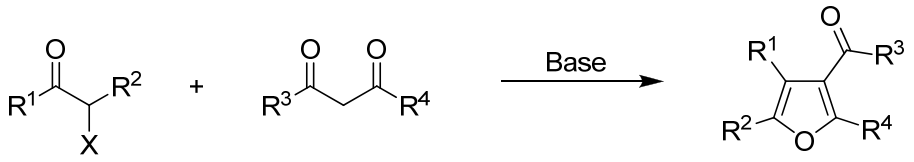
# CHAPTER 2

# RESULTS AND DISCUSSION

## 2.1 Synthesis of furopyrrolone derivatives

### 2.1.1 Synthesis of starting compound: methyl 2-(2-methoxy-2-oxoethyl)furan-3-carboxylate

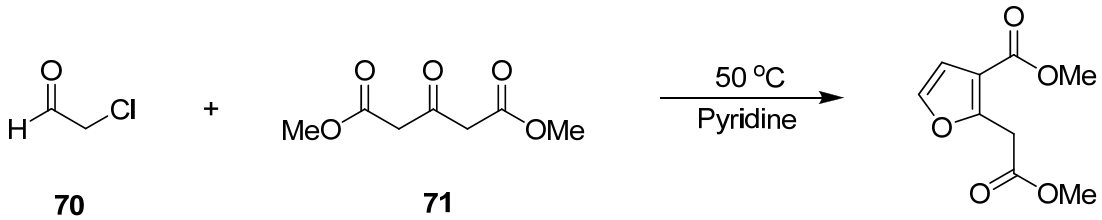
Methyl 2-(2-methoxy-2-oxoethyl)-3-furoate **(62)** was chosen as a starting material which was already synthesized by Tada, Ohtsu and Chiba in 1994,[42] using Feist-Benary furan synthesis. In this synthetic methodology, α-halocarbonyl compound **68** reacts with a β-dicarbonyl **51** in the presence of a base to generate a tetra-substituted furan derivative **69**.[43,44]




**68** **51** **69**

**Scheme 8**

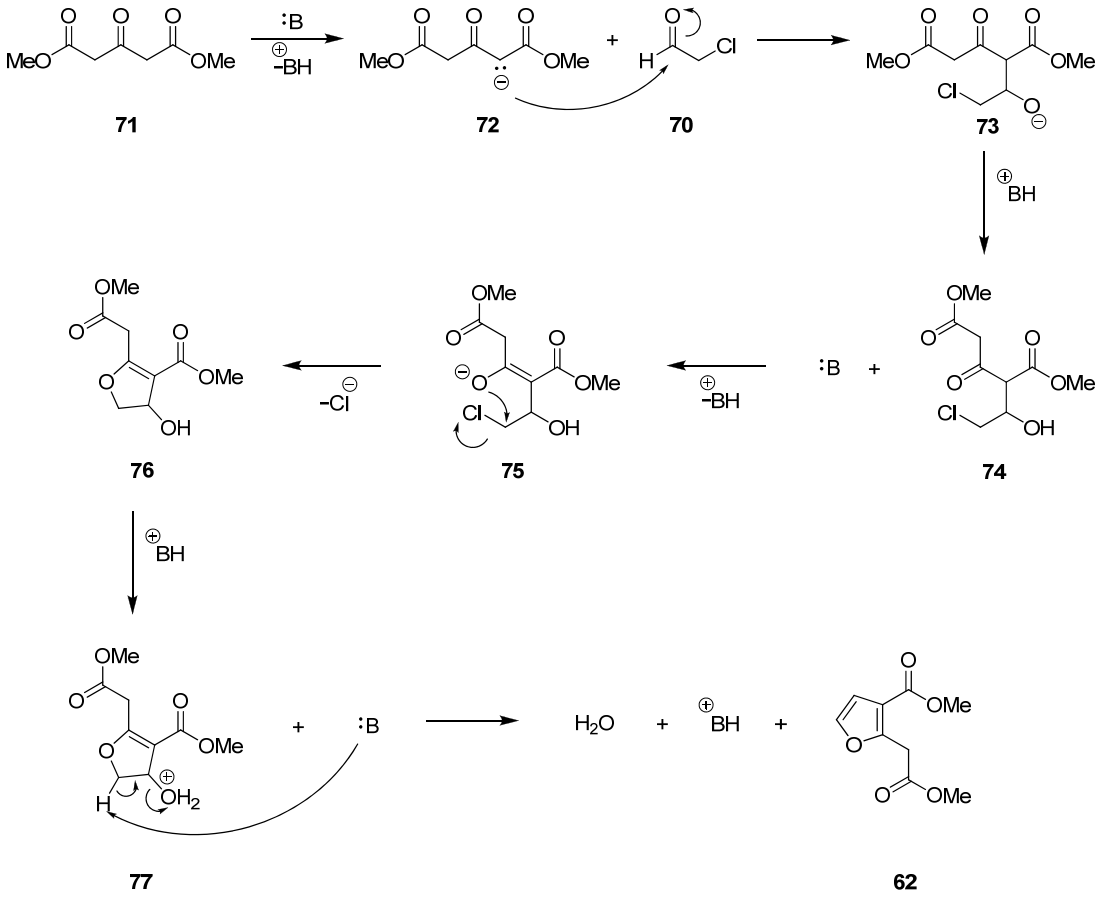
The diester **62** was prepared by condensation of 1,3-acetone dicarboxylate **(71)** and chloroacetaldehyde **(70)** in pyridine at 50 $^{o}$C for 16 hours.




**70** **71** **62**

**Scheme 9**

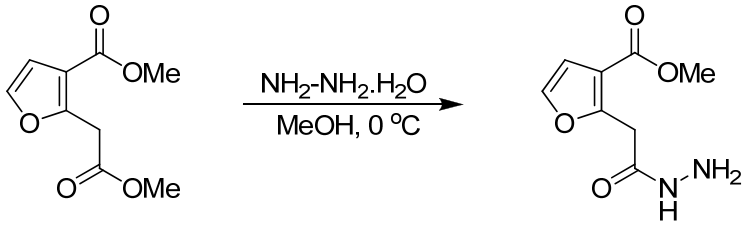
The mechanism involves an aldol reaction followed by an intramolecular *O*-alkylation and dehydration to yield the furan product.[45] Firstly, pyridine abstracts the acidic α-proton of 1,3-acetone dicarboxylate **(71)** to generate anion **72** and this carbanion **72** reacts with chloroacetaldehyde (**70)** to furnish aldol adduct **74**. Second abstraction of α-proton from 1,3-acetone dicarboxylate **(71)** generates the enolate **75**. Intramolecular $S_N2$ reaction between the oxygen nucleophile and the carbon atom bearing the chloride leaving group leads to formation of dihydrofuran **76**. Finally, removal of water gives the starting compound **62**.




**Scheme 10**

### 2.1.2 Synthesis of methyl 2-(2-hydrazinyl-2-oxoethyl)furan-3-carboxylate

For the synthesis of furopyrrolone derivatives, nitrogen atom must be introduced into the diester **62**. Our plan for the construction of the desired heterocyclic ring system **64** involved an intramolecular cyclization reaction of the isocyanate, which can be generated by Curtius rearrangement[46] of the corresponding acyl azide. The most convenient method for synthesis of acyl azide is the conversion of acyl chlorides with $NaN_3$ in aqueous medium. However, we faced with some troubles related to this method and turned our attention into generation of acyl azides via acyl hydrazides.



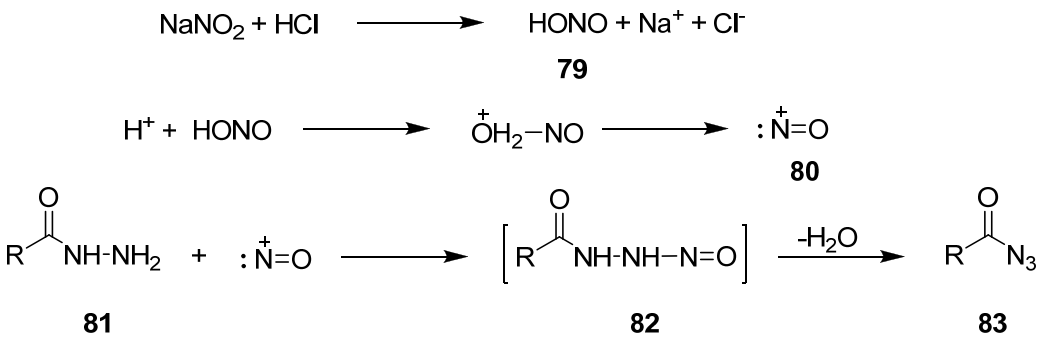

**62** **78**

**Scheme 11**

Recently, Balci *et al*. reported that diester **62** was successfully converted to the corresponding dihydrazide by refluxing in MeOH.[47] However; the reactivity of the ester carbonyl group of **62** is different because conjugation decreases the reactivity of the one of the carbonyl groups. Therefore, the ester functionality connected to the $CH_2$ group is more reactive than the other. By using this reactivity difference, at low temperature we could achieve regioselective hydrazide formation by treatment of diester with hydrazine monohydrate from 0 $^oC$ to 15 $^oC$ for 18 hours. Disappearance of one of the ester peaks in NMR spectrum proved the formation of desired monohydrazide **78**, which was formed in 80% yield.

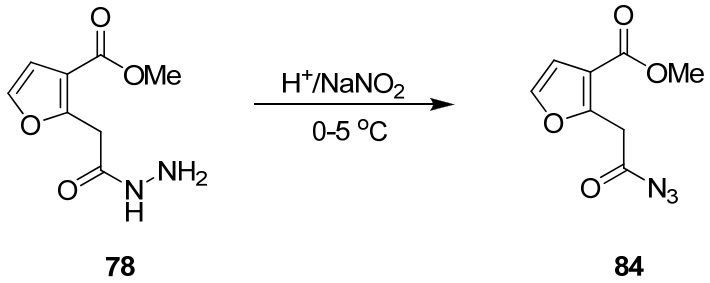
### 2.1.3 Synthesis of methyl 2-(2-azido-2-oxoethyl)furan-3-carboxylate

Modified Sandmeyer reaction was used for conversion of hydrazide **81** into acyl azide **83** via β-nitroso hydrazide **82** intermediate.[48] First of all, nitrous acid **79** was formed by protonation of nitrite ion from the acidic medium then dehydration leads to formation of nitrosonium ion **80**. Probably, the nucleophilic attack of $-NH_2$ group of hydrazide to $NO^+$ forms the corresponding β-nitroso hydrazine intermediate **82** which may finally convert into the product, azide **83**.




**Scheme 12**

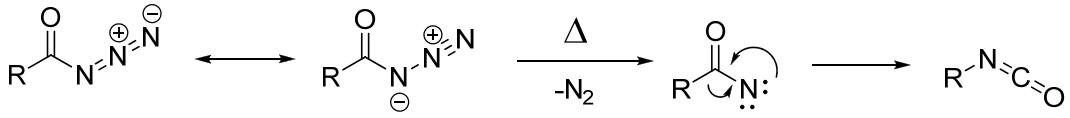
This methodology was used for construction of desired acyl azide **84** which will be the key compound in Curtius rearrangement. Therefore, the hydrazide derivative **78** was treated with $NaNO_2$ and HCl at low temperature to give monoazide derivative **84** in 82% yield. Disappearance of both broad –NH and $-NH_2$ peaks in NMR spectrum and appearance of characteristic frequency of azides at around 2100 $cm^{-1}$ in IR spectrum confirmed the formation of azide **84**.




**Scheme 13**

### 2.1.4 Synthesis of methyl 2-(isocyanatomethyl)furan-3-carboxylate

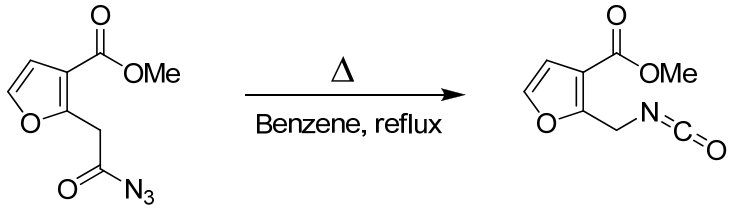
In 1894, Theodor Curtius found a new type of rearrangement which is about conversion of acyl azides into corresponding isocyanate.[49]



**85** **86** **87** **88**

**Scheme 14**

Mechanism of this rearrangement starts with removal of nitrogen gas from the molecule to form the nitrene as a reactive intermediate. Because of the electron deficiency of nitrene, it undergoes a rearrangement to generate isocyanate and this rearrangement is called as Curtius rearrangement.



**84** **63**

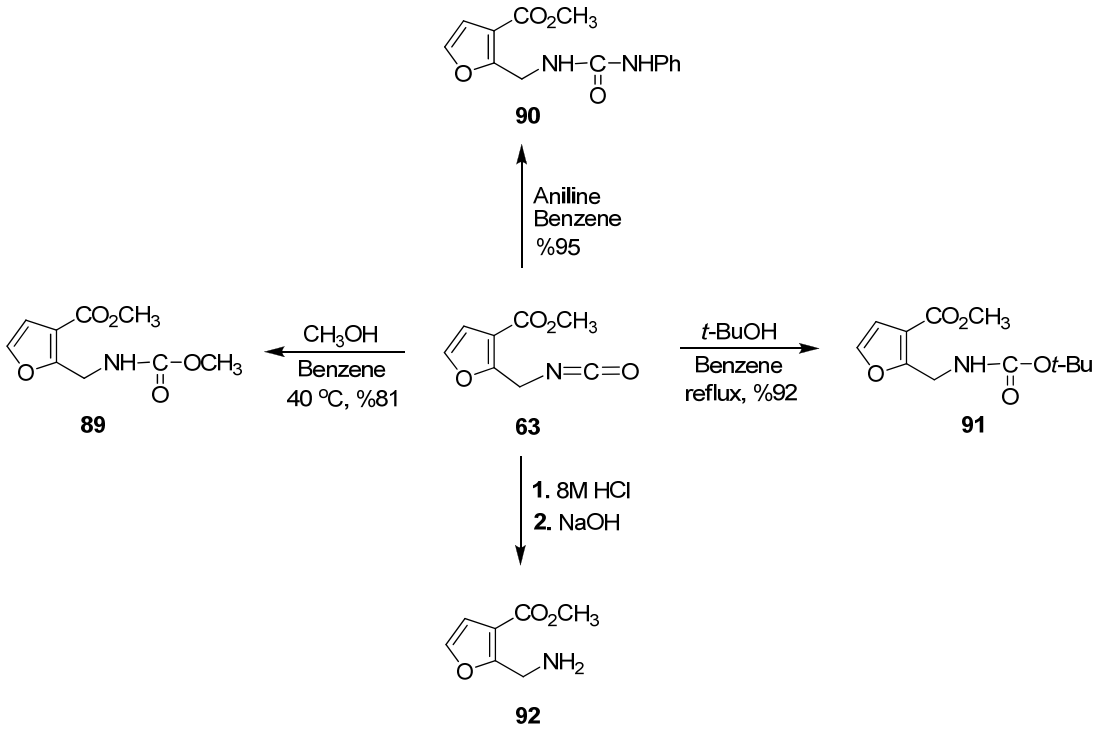
**Scheme 15**

To obtain the target isocyanate **63**, acyl azide **84** was heated at reflux temperature of benzene for one hour then simply removal of solvent gave isocyanate **63**. The difference in chemical shift of $-CH_2$ in $^1H$ NMR and that of carbonyl carbon $^{13}C$ NMR showed the conversion. Moreover, IR spectrum strongly supported this conversion with the appearance of characteristic sharp isocyanate signal at around 2200 $cm^{-1}$.

### 2.1.5 Reaction of isocyanate with different nucleophiles

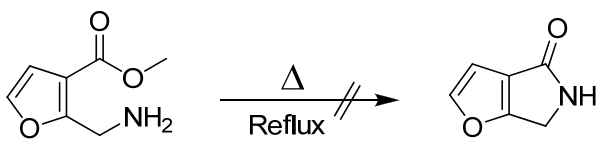
Isocyanate derivative **63** was chosen as a model to explore further reactions. Isocyanates can be trapped by a variety of nucleophiles. Treatment of **63** with MeOH in benzene at 40 $^oC$ for 1 hour gave the urethane derivative **89** in 81% yield. When the reaction was carried out in the presence of t-BuOH at reflux temperature, Boc-

protected amine derivative **91** was generated, which is a useful intermediate[50] in organic synthesis. The urea derivative **90** was obtained from **63** in 95% yield after treatment with aniline in benzene. Hydrolysis of isocyanate **63** in acidic medium and then subsequent treatment with base gave the primary amine **92** as a pale yellow oily liquid.




**Scheme 16**

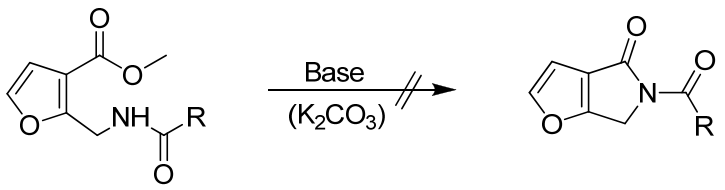
For all these three cases, doublet signals appearing at about 4.6 ppm in $^{1}$H NMR spectra belong to $-CH_2$ group which verify the generation of –NH protons that will be required for cyclization reaction in the following steps. For the amine **92** derivative, broad singlet at 1.62 ppm confirms the formation of $-NH_2$ which can be considered as precursor of the desired furopyrrolone **93**.




**92** **93**

**Scheme 17**

First of all, the primary amine **92** was heated at reflux temperature in THF to obtain the furopyrrolone **93** but the desired compound was not formed. Thus, in order to get higher temperature, benzene and toluene was used as a solvent but for all cases, all efforts to convert **92** into the target compound **93** failed and the starting compound **92** was recovered.




**89** R = OMe
**90** R = NHPh
**91** R = O$^t$Bu

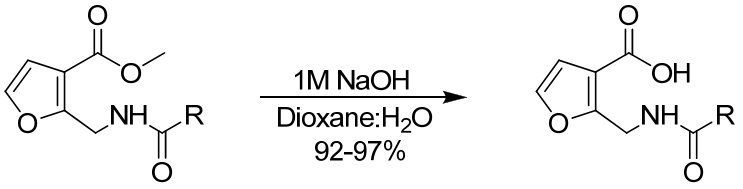
**94** R = OMe
**95** R = NHPh
**96** R = O$^t$Bu

**Scheme 18**

As a second method, abstraction of acidic –NH proton in **89**, **90**, **91** was performed by using different bases such as $K_2CO_3$ and LDA, but also these powerful bases could not achieve the cyclization to construct the target heterocyclic skeleton, furopyrrolones **94**, **95**, **96**.

### 2.1.6 Synthesis of carboxylic acid derivatives

Therefore we turned our attention to increase the reactivity of carbonyl group for cyclization and it is known that acyl chlorides are more reactive than esters and acids. Acyl chlorides can be easily synthesized from carboxylic acids by treatment with thionyl chloride in THF. First of all, the ester derivatives **89**, **90**, **91** were hydrolyzed by treatment with 1M NaOH in dioxane:water mixture at room temperature to get the corresponding acid derivatives **97**, **98**, **99** in high yield.




**89** R = OMe
**90** R = NHPh
**91** R = O$^t$Bu

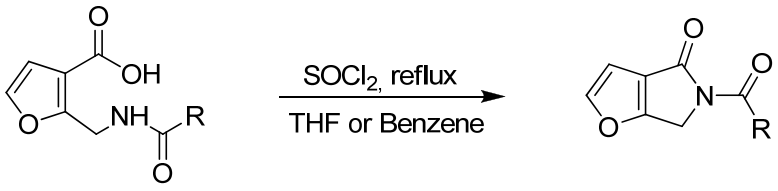
**97** R = OMe
**98** R = NHPh
**99** R = O$^t$Bu

**Scheme 19**

The loss of ester methyl proton signal at around 3.8 ppm and appearance of broad singlets at around 12.7 ppm in NMR spectra confirmed that hydrolysis was completed successfully.

### 2.1.7 Synthesis of furopyrrolone derivatives via acyl chloride intermediates

Carbonyl groups of acyl chlorides are very reactive electrophilic centers, therefore they can easily react with nucleophiles. These nucleophilic attacks can be intermolecular or intramolecular. For the synthesis of target heterocyclic skeleton, this time intramolecular cyclization was designed. So, carboxylic acids **97**, **98**, **99** were treated with $SOCl_2$ in benzene or THF at reflux temperature to get furopyrrolone derivatives **94**, **95**, **96** in high yields.

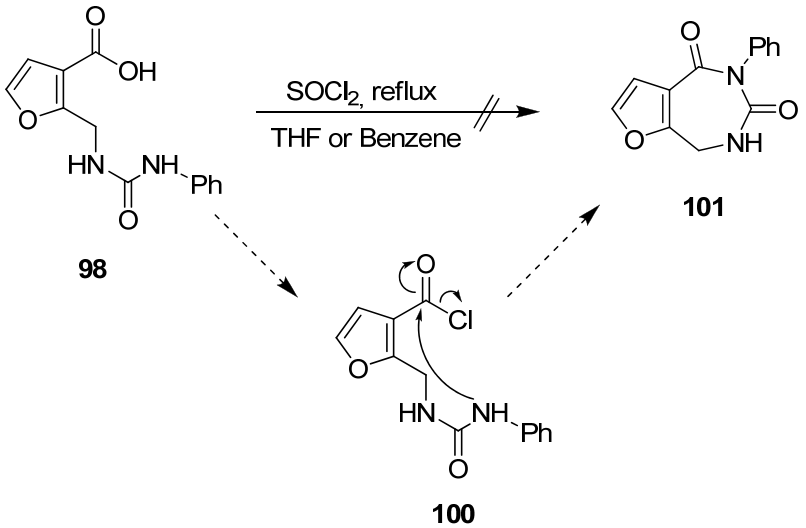



**97** R = OMe
**98** R = NHPh
**99** R = O$^t$Bu

**94** R = OMe
**95** R = NHPh
**96** R = O$^t$Bu

**Scheme 20**

Disappearance of both broad –NH and acid protons and the loss of coupling between the methylenic proton and –NH proton strictly proves the formation of target furopyrrolone derivatives.




**98**

**101**

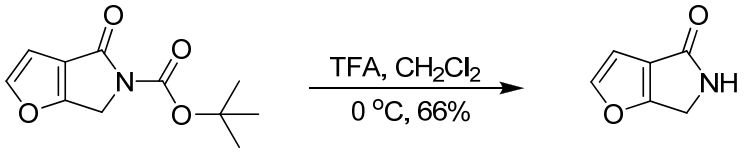
**100**

**Scheme 21**

For the urea derivative **98**, there was also a second possibility for cyclization which creates the seven membered diazepinedione ring fused to furan ring but this furodiazepinedione derivative **101** could not be generated even in traces. The reason is that the conjugation between lone pair of nitrogen atom and the aromatic phenyl ring decreases the nucleophilicity of the nitrogen atom and so it would not attack to carbonyl group. Moreover, the size of the phenyl ring causes the steric hindrance that prevents generation of furodiazepinedione ring.

### 2.1.8 Synthesis of 5,6-dihydro-4*H*-furo[2,3-*c*]pyrrol-4-one

*tert*-Butyl carbamate is a protection group for amines. It has a resistance to nucleophilic attacks and bases. It can be removed from the molecule by treatment with anhydrous strong acids. Therefore, hydrolysis of the cyclization product **96** with $CF_3COOH$ in dichloromethane at 0 $^oC$ gave the target compound "5,6-dihydro-4*H*-furo[2,3-c]pyrrol-4-one" **(93)** in 66% yield. In this way, the basic structure of the furopyrrolone was produced for the first time in the literature. The spectral data of **93** were fully in accordance with the proposed structure.



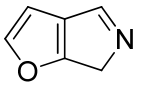

**96** **93**

**Scheme 22**

In the NMR spectrum there is a broad singlet at 5.83 ppm that belongs to –NH proton. Furan protons resonate as doublets with a coupling constant of 2.0 Hz at 6.58 and 7.45 ppm, respectively. Moreover, at 4.29 ppm there is a singlet for $–CH_2$ protons.

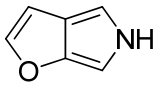
### 2.1.9 Synthesis of *tert*-butyl (3-(hydroxymethyl)furan-2-yl)methylcarbamate

With the purpose of bringing in the new types of heterocycles for the literature, such as 6*H*-furo[2,3-*c*]pyrrole **102** and 5*H*-furo[2,3-*c*]pyrrole **103**, new synthetic pathway was designed. The interesting thing for these structures was that it could be easy to convert **102** into **103** due to the fact that after the conversion, the formed product **103** would have a full conjugation and so it could be more stable. To obtain the imine structure in desired molecule **102**, reaction between aldehyde and amine was searched.




6*H*-furo[2,3-*c*]pyrrole

**102**

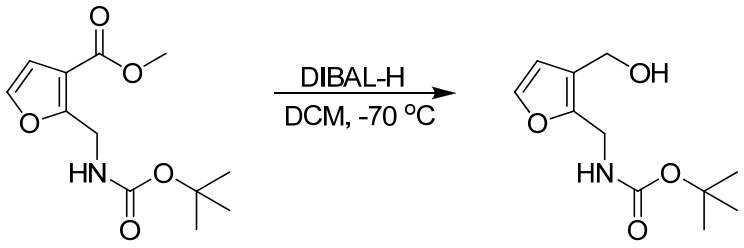



5*H*-furo[2,3-*c*]pyrrole

**103**

**Scheme 23**

Boc-protected ester **91** was tried to reduce to corresponding aldehyde **108** by treatment with DIBAL-H at -70 $^{o}$C in nitrogen atmosphere; however, the ester **91** was reduced to corresponding alcohol **104** even at that temperature.



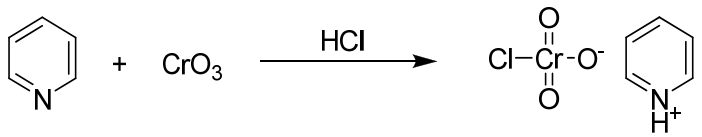

**91** **104**

**Scheme 24**

Formation of alcohol **104** was confirmed by both appearance of new broad –OH and –$CH_2$ signals in the $^{1}$H NMR spectrum and disappearance of ester carbonyl from the $^{13}$C NMR spectrum. Moreover, the absence of the both characteristic ester methyl peak around 3.70 ppm and aldehyde peak in the region of 9-10 ppm made a contribution to prove formation of alcohol **104**.

### 2.1.10 Synthesis of *tert*-butyl (3-formylfuran-2-yl)methylcarbamate

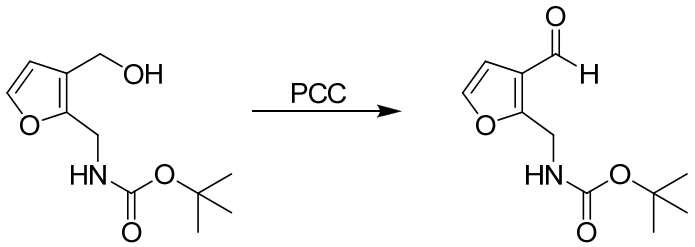
Pyridinium chlorochromate **(107)**, PCC, is a mild oxidizing agent. Its advantage is that it does not totally oxidize the alcohols to corresponding acids as does the other oxidizing agents such as Jones reagent. It is prepared by the reaction of pyridine **(105)** with chrominium(VI)oxide **(106)** in the presence of HCl.




**105** **106** **107**

**Scheme 25**

Therefore, the desired aldehyde **108** was created by treatment of alcohol **104** with PCC **107** in dichloromethane at room temperature for 2 hours. Removal of the broad –OH signal from the $^{1}$H NMR spectrum and appearance of the characteristic aldehyde peak in the region of 9-10 ppm confirmed that alcohol **104** was oxidized the aldehyde **108**, not carboxylic acid.

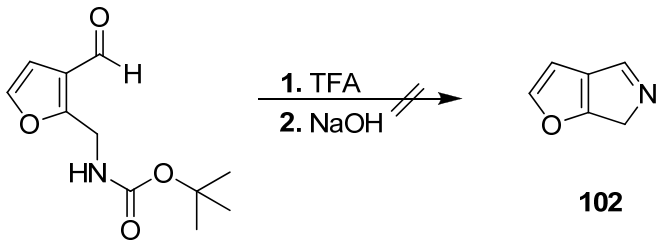



**104** **108**

**Scheme 26**

### 2.1.11 Synthesis of 6*H*-furo[2,3-*c*]pyrrole

The desired heterocyclic skeleton **102** was tried to be synthesized by nucleophilic attack on nitrogen atom. To do this, Boc-protection group was removed by acidic hydrolysis and treated with base to generate amine in the reaction medium. However, all efforts to convert **108** into the target compound **102** were failed.




**108** **102**

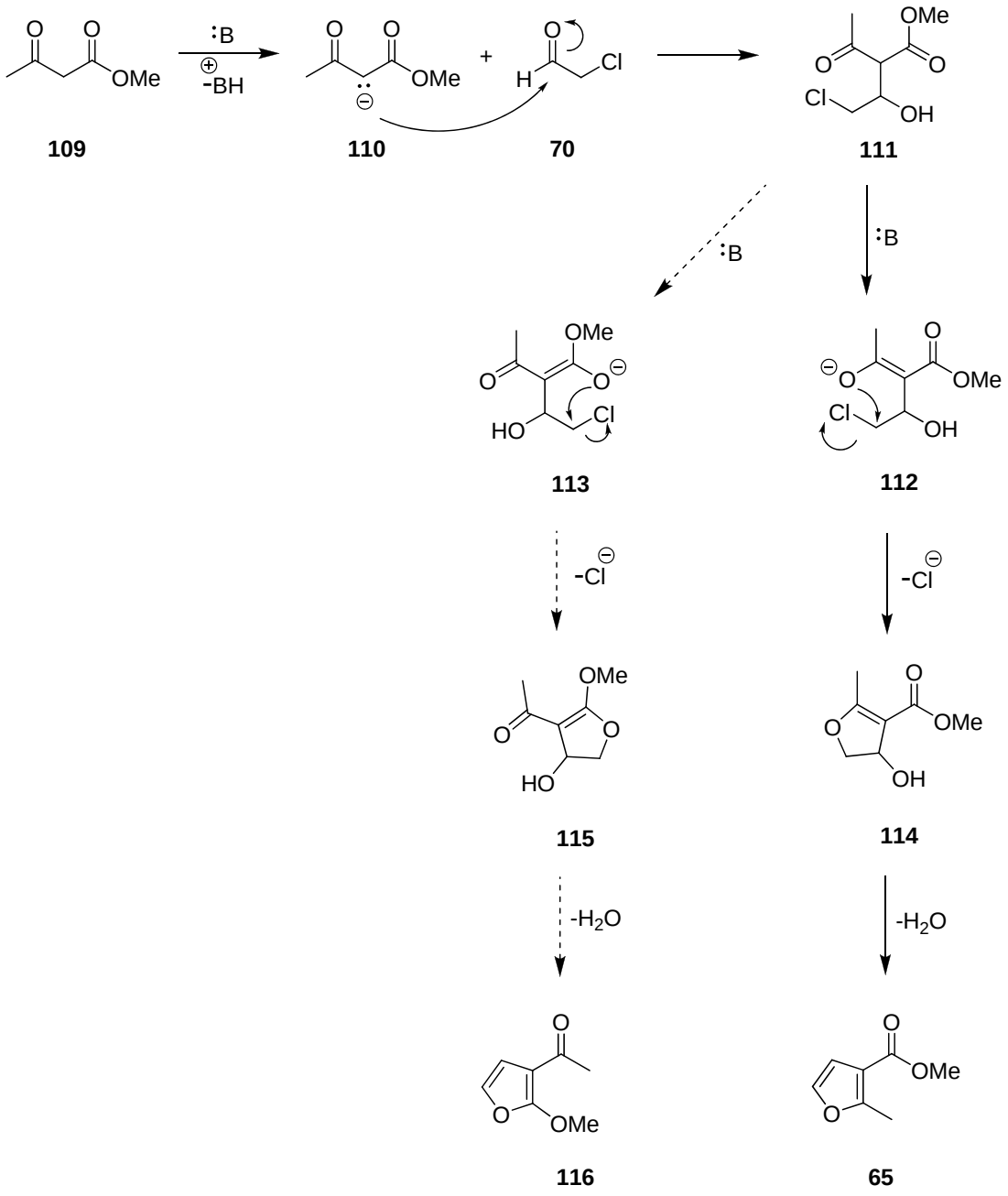
**Scheme 27**

During the course of the reaction, all aldehyde **108** was used however; the product **102** could not be isolated from the reaction mixture.

## 2.2 Synthesis of furopyridazinones derivatives

### 2.2.1 Synthesis of starting compound: methyl 2-methylfuran-3-carboxylate

For the synthesis of furopyridazinone **(67)** skeleton, methyl 2-methyl furoate **65** was chosen as a starting compound. In order to obtain furan moiety in the desired skeleton, again Feist-Benary furan synthesis was applied. This time, methylacetoacetate **(109)** and chloroacetaldehyde **(70)** was used as β-dicarbonyl and α-halocarbonyl, respectively. The ester **65** was synthesized by treatment with methyl acetoacetate **(109)** with chloroacetaldehyde **(70)** in the presence of pyridine at 50 $^{o}$C for 16 hours. Methyl acetoacetate **(109)** has two different carbonyl groups; according to mechanism there can be two types of intramolecular *O*-alkylation leading to the products **65**, **116**. However, the reactivity difference between ester and ketone carbonyls plays an important role in the reaction mechanism. Due to more reactivity of ketone carbonyl, the reaction proceeds from the ketone carbonyl, so at the end of the reaction, there is only one product **65** formed.

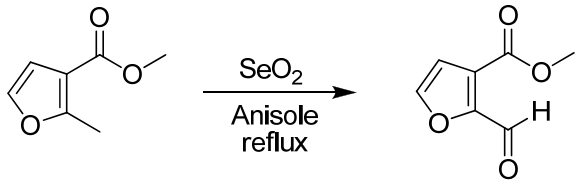



**Scheme 28**

Doublets with a coupling constant 2 Hz in the aromatic range prove the formation of furan ring and characteristic ester singlet at 3.82 ppm and the singlet at 2.57 ppm confirm the structure of the compound **65**. If the other molecule **116** would be formed, a ketone carbonyl signal in the region of 190-200 ppm in $^{13}C$ NMR spectrum should be observed. However, there is only a characteristic ester carbonyl signal around 160 ppm.

### 2.2.2 Synthesis of methyl 2-formylfuran-3-carboxylate

Imine part of the pyridazinone ring can be obtained from the reaction between aldehyde and primary amine. In order to get this structure, furfural derivative **66** was synthesized from the starting compound **65** by treatment with $SeO_2$ in anisole at reflux temperature. Dioxane is always used as a solvent for this oxidation reaction, but this time it did not work, because its boiling point is not high enough to oxidize the starting compound **65**. Consequently, *o*-xylene was used as a solvent due to its high boiling point; however, *o*-xylene was also oxidized by selenium dioxide so this decreased the reaction yield. Finally, anisole, methoxybenzene, was preferred as a solvent for this oxidation reaction.




**65** **66**

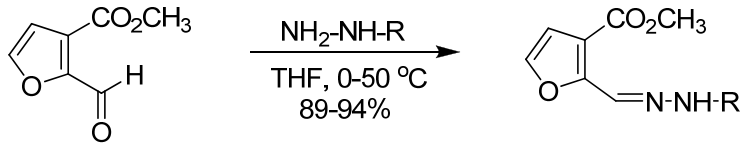
**Scheme 29**

In the $^1H$ NMR spectrum, the signal at 10.23 ppm shows the formation of aldehyde. This aldehyde peak resonates as doublet $J = 0.7$ Hz due to the coupling with the low field furan proton (H-2) over five bonds. Therefore, this furan proton (H-2) resonates as doublet of doublets.

### 2.2.3 Synthesis of imine part of furopyridazinones: Addition of hydrazines to aldehyde

Furopyridazinones **(63)** have nitrogen-nitrogen bond. Hydrazine derivatives were used to get this skeleton. Aldehyde **66** was treated with hydrazines in order to generate both imine structure and nitrogen-nitrogen bond. For the cyclization, there should be nucleophilic center in the molecule; therefore single substituted hydrazines were used. Initially, aldehyde **66** was reacted with phenylhydrazine in THF at room temperature to get **117**.

Secondly, *tert*-butylcarbazate was used as hydrazine with the purpose of generation of Boc-protected amide **118** and finally methylhydrazine was preferred to create imine compound **119** with nucleophilic center without conjugation with carbonyl and phenyl group.




**66**

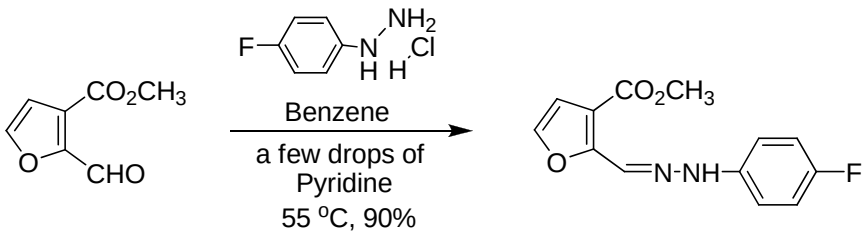
**117** R = Ph
**118** R = Boc
**119** R = $CH_3$

**Scheme 30**

In condensation step, there were always *cis*- and *trans*-products in a ratio of 5:1. On the other hand, this was not significant because in the hydrolysis step the *cis*-*trans* mixture of ester gave only one product.

### 2.2.4 Addition of hydrazinium chloride hydrazine salt: "4-Fluorophenyl hydrazinium chloride"

Treatment of aldehyde **66** with hydrazine salts in THF did not work. The ionic structure did not permit the hydrazine to behave as a nucleophile. In order to get rid of this situation, the reaction was carried out in the presence of a few drops of pyridine in benzene. In this way, free hydrazine derivative was generated in the reaction medium to acquire the condensation product **120**. The characterization of compound was made by $^{1}H$ and $^{13}C$ NMR spectroscopy. Once more, appearance of a signal at 8.24 ppm in $^{1}H$ NMR proves the imine formation. Moreover, all of the phenyl carbons resonate as doublets with different coupling constants, in the range of 2 Hz to 230 Hz, arising from the coupling with fluorine atom.

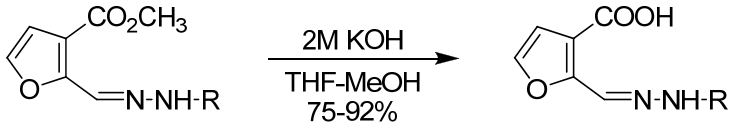



**66** **120**

**Scheme 31**

### 2.2.5 Synthesis of carboxylic acid derivatives

Hydrolysis of the ester derivatives **117**, **118**, **120** was performed by treatment with 2M KOH in THF-MeOH mixture. Phenyl **117**, fluorophenyl **120** and carbamate derivative **118** were hydrolyzed at 75 °C respectively; however, no cyclization reaction was observed. Hydrolysis was confirmed by $^{1}$H NMR spectrum. Removal of the ester signal from the spectrum and the rise of broad singlet around 12.8-13.0 ppm proves the formation of carboxylic acid derivatives **121**, **122**, **123**.

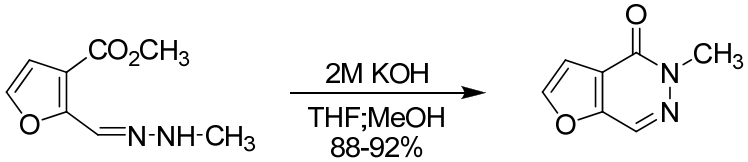



**117** R = Ph
**118** R = Boc
**120** R = ϕ–F

**121** R = Ph
**122** R = Boc
**123** R = ϕ–F

**Scheme 32**

On the other hand, for methylhydrazine derivative **119**, when the hydrolysis was performed even at 0 °C, an intramolecular cyclization reaction took place to form furopyridazinone derivative **124**.



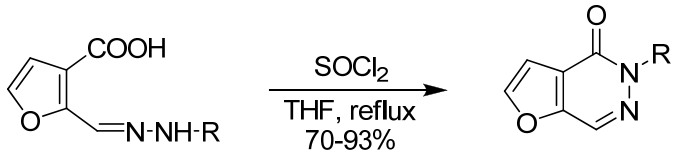

**119** **124**

**Scheme 33**

Disappearance of both –NH and ester signal from $^1$H NMR spectrum demonstrate that desired furopyridazinone skeleton **124** was synthesized for the first time. The reason of this cyclization reaction is that methylhydrazine derivative **119** has no conjugation so intramolecular attack of nitrogen atom was easier. On the other hand, for the carbamate and phenyl derivatives, there was a conjugation between lone pair of nitrogen and carbonyl and aromatic phenyl groups. Hence, this conjugation causes the decrease in the nucleophilicity of the nitrogen atom.

### 2.2.6 Synthesis of furopyridazinone derivatives via acyl chloride intermediate

Finally, like in the furopyrrolone case, the reactivity of the carbonyl group should be increased in order to get the furopyridazinone derivatives and it is known that acyl chlorides are much more reactive than other carbonyl groups. Then, these acids **121**, **122**, **123** were treated with $SOCl_2$ at reflux temperature in THF to produce the target furopyridazinone derivatives **125**, **126**, **127** in high yields.




**121** R = Ph
**122** R = Boc
**123** R = ϕ–F

**125** R = Ph
**126** R = H
**127** R = ϕ–F

**Scheme 34**

As a consequence of high temperature chlorination with $SOCl_2$, Boc protection group was hydrolyzed during the course of the reaction and in this way, the basic skeleton of the furopyridazinone **126** was synthesized for the first time in the literature.

# CHAPTER 3

# EXPERIMENTAL

## 3.1 General

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

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

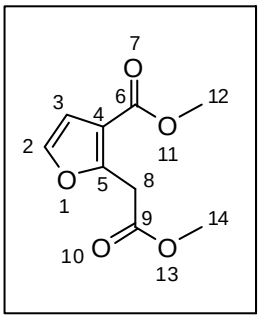
Column chromatographic separations were performed by using Fluka Silica Gel 60 plates with a particle size of 0.063–0.200 mm. Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Fluka.

Compounds were named by using ChemDraw Ultra 11.0.

Solvents were purified as reported in the literature.[51]

### 3.2 Synthesis of methyl 2-(2-methoxy-2-oxoethyl)furan-3-carboxylate (62)

1,3-Acetone dicarboxylate **71** (25 g, 143.5 mmol) was dissolved in pyridine (50 mL). To this mixture, a solution of chloroacetaldehyde **70** (45%, 26.5 mL) was added dropwise at room temperature, and then stirred at 50 $^{o}$C 16 h. The reaction was monitored on TLC. After the completion of the reaction, the mixture was extracted with water (200 mL) and ethyl acetate (3 x 200 mL). The combined organic extracts were washed with 2M of HCl (250 mL), 5% $NaHCO_3$ (250 mL), 10% NaOH (250 mL) and brine (250 mL) (saturated NaCl solution) one by one and dried over $Mg_2SO_4$. Removal of the solvent gave the crude product, which was then purified by column chromatography eluting with hexane/EtOAc (3:1). Eluted solvent was evaporated to yield oily colorless diester **62** (19.4 g, 68.5%).



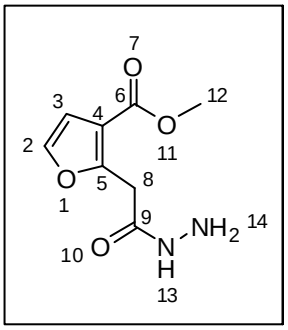

**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.26 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 6.63 (d, $J_{3,2}$ = 2.0 Hz, 1H, H-3), 4.01 (s, 2H, -$CH_2$), 3.76 (s, 3H, -$OCH_3$), 3.66 (s, 3H, -$OCH_3$).

**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 169.0, 163.8, 154.1, 141.8, 115.5, 110.8, 52.3, 51.5, 33.5.

**IR** (ATR) 3340, 2880, 1040, 1000, 980.

### 3.3 Synthesis of methyl 2-(2-hydrazinyl-2-oxoethyl)furan-3-carboxylate (78)

To a stirred solution of diester **62** (10.0 g, 50.5 mmol) in methanol (100 mL) was added hydrazine monohydrate (7.4 mL, 151.5 mmol) at 0 ºC and followed by stirring without removing the ice bath for 18 h. The solvent was evaporated and the crude product was purified by extraction with chloroform (200 mL) and water (40 mL). The aqueous layer was reextracted with chloroform (2 x 70 mL) and the combined organic extracts were washed with water (40 mL), dried over $MgSO_4$ and the solvent was evaporated to give monohydrazide **78** as a white solid (8.0 g, 80%) (m.p. 143-144 °C).




**$^{1}$H-NMR** (400 MHz, DMSO-$d_6$) $\delta$: 9.03 (br s, 1H, -NH), 7.45 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 6.48 (d, $J_{3,2}$ = 2.0 Hz, 1H, H-3), 4.24 (br s, 2H, -$NH_2$), 3.60 (s, 2H, -$CH_2$), 3.53 (s, 3H, -$OCH_3$).

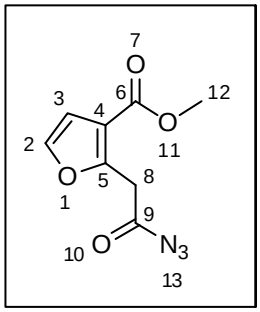
**$^{13}$C-NMR** (100.6 MHz, DMSO-$d_6$) $\delta$: 166.4, 163.3, 155.9, 142.4, 114.4, 110.3, 51.4, 32.7.

**IR** (KBr, $cm^{-1}$) 3301, 1712, 1644, 1540, 1439, 1312, 1205, 1068, 755.

**Anal. Calcd. for** $C_8H_{10}N_2O_4$ (198.18): C 48.48, H 5.09, N 14.14; Found: C 48.51, H 5.05, N 14.12

### 3.4 Synthesis of methyl 2-(2-azido-2-oxoethyl)furan-3-carboxylate (84)

To a stirred solution of monohydrazide **78** (2.5 g, 12.6 mmol) in aq. HCl (40 mL, 1M) at 0 ºC was added dropwise a solution of sodium nitrite (0.91 g, 13.3 mmol) in water (10 mL) followed by stirring at 0-5 ºC for 30 min. The mixture was extracted with EtOAc (2 x 60 mL). The combined organic phases were washed with sat. aq. solution of $Na_2CO_3$ (50 mL) and then brine (50 mL), dried over $MgSO_4$ and the solvent was evaporated to give acyl azide **84** as a colorless oil (2.16 g, 82%).



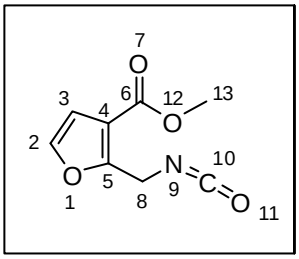

**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.29 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 6.64 (d, $J_{3,2}$ = 2.0 Hz, 1H, H-3), 4.02 (s, 2H, -$CH_2$), 3.77 (s, 3H, -$OCH_3$).

**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 175.3, 163.7, 153.1, 142.2, 116.1, 110.8, 51.6, 35.7.

**IR** (KBr, $cm^{-1}$) 2956, 2143, 1718, 1613, 1443, 1315, 1205, 1158, 1034.

### 3.5 Synthesis of methyl 2-(isocyanatomethyl)furan-3-carboxylate (63)

The acyl azide **84** (2.1 g, 10.0 mmol) was dissolved in dry benzene (30 mL) and heated at reflux temperature for 1 h. The solvent was evaporated to give isocyanate **63** as colorless oil (1.72 g, 95%).



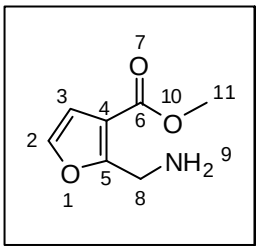

**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.32 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 6.64 (d, $J_{3,2}$ = 2.0 Hz, 1H, H-3), 4.67 (s, 2H, -$CH_2$), 3.80 (s, 3H, -$OCH_3$).

**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 163.3, 155.1, 142.3, 125.3, 115.1, 111.0, 51.8, 38.6.

**IR** (KBr, $cm^{-1}$) 2956, 2258, 1720, 1612, 1515, 1414, 1312, 1081.

### 3.6 Synthesis of methyl 2-(aminomethyl)furan-3-carboxylate (92)

A solution of isocyanate **63** (4.0 g, 22.1 mmol) in HCl (8M, 20 ml) was stirred for 2 h at room temperature. After the completion of the reaction, the reaction mixture was washed with petroleum ether (80 ml), and the pH value of the aqueous phase was adjusted to 10 by the addition of 10% NaOH solution at 5 $^{o}$C. The mixture was extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and the solvent was evaporated to give yellow oily amine **92** (2.5 g, 73%).




**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.22 (d, $J_{2,3}$= 2.0 Hz, 1H, H-2), 6.59 (d, $J_{3,2}$= 2.0 Hz, 1H, H-3), 4.03 (s, 2H, H-8), 3.77 (s, 3H, -$OCH_3$), 1.62 (br s, 2H, -$NH_2$).

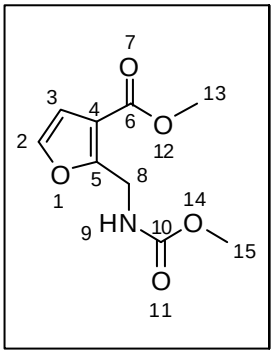
**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 164.1, 162.7, 140.9, 113.1, 110.8, 51.5, 38.6.

**IR** (KBr, $cm^{-1}$) 3381, 3154, 2953, 1716, 1597, 1441, 1306, 1201, 1148, 1053.

**Anal. Calcd. for** $C_7H_9NO_3$ (155.15): C 54.19, H 5.85, N 9.03; Found: C 54.49, H 6.09, N 9.29

### 3.7 Synthesis of methyl 2-((methoxycarbonylamino)methyl)furan-3-carboxylate (89)

To a stirred solution of isocyanate **63** (0.42 g, 2.3 mmol) in dry benzene (20 mL) at 40 ºC was added methanol (0.6 mL, 14.7 mmol) and stirred for 1 h. The solvent was evaporated to give the crude product, which was then purified by column chromatography eluting with ethyl acetate/hexane (2:1) to give urethane **89** as a white solid (0.4 g, 81%) (m.p. 60-62 °C).




**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.33 (d, $J_{2,3}$ = 1.8 Hz, 1H, H-2), 6.69 (d, $J_{3,2}$ = 1.8 Hz, 1H, H-3), 5.51 (br s, 1H, -NH), 4.68 (d, $J_{8,9}$ = 5.6 Hz, 2H, -$CH_2$), 3.87 (s, 3H, -$OCH_3$), 3.71 (s, 3H, -$OCH_3$).

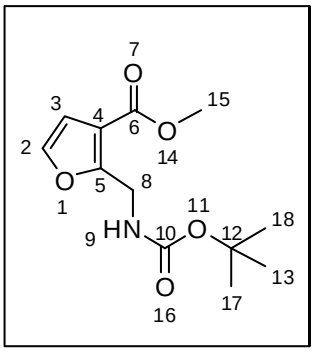
**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 164.0, 158.1, 156.9, 141.5, 114.7, 110.8, 52.3, 51.7, 37.5.

**IR** (KBr, $cm^{-1}$) 3338, 3150, 2938, 1694, 1601, 1540, 1433, 1353, 1310, 1260, 1199, 1144, 1087.

**Anal. Calcd. for** $C_9H_{11}NO_5$ (213.19): C 50.70, H 5.20, N 6.57; Found: C 50.75, H 5.13, N 6.59

### 3.8 Synthesis of methyl 2-((*tert*-butoxycarbonylamino)methyl)furan-3-carboxylate (91)

To a stirred solution of isocyanate **63** (2.81 g, 15.5 mmol) in dry benzene (40 mL) was added excess *tert*-butanol (25 mL) and the resulting mixture was heated at reflux temperature for 2 days. The solvent and excess *tert*-butanol were evaporated to give urethane **91** as a white solid (3.2 g, 92%) (m.p. 93-95°C).



**$^1$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.23 (d, $J_{2,3}$ = 1.9 Hz, 1H, H-2), 6.59 (d, $J_{3,2}$ = 1.9 Hz, 1H, H-3), 5.19 (br s, 1H, -NH), 4.53 (d, $J_{8,9}$ = 5.6 Hz, 2H, -$CH_2$), 3.78 (s, 3H, -$OCH_3$), 1.37 (s, 9H, -$C(CH_3)_3$).

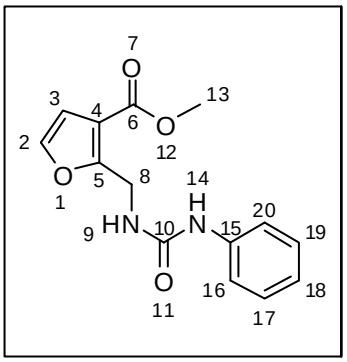
**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 165.0, 159.3, 156.5, 142.3, 115.4, 111.7, 80.7, 52.6, 38.0, 29.3.

**IR** (KBr, $cm^{-1}$) 3360, 3155, 2996, 1716, 1687, 1604, 1524, 1432, 1405, 1315, 1266, 1251, 1199, 1164, 1126, 1088, 1034.

**Anal. Calcd. for** $C_{12}H_{17}NO_5$ (255.27): C 56.46, H 6.71, N 5.49;Found: C 56.56, H 6.80, N 5.56

### 3.9 Synthesis of methyl 2-((3-phenylureido)methyl)furan-3-carboxylate (90)

To a stirred solution of isocyanate **63** (1.7 g, 9.4 mmol) in dry benzene (25 mL) was added aniline (1.2 mL, 13.3 mmol) at room temperature and stirred for 5 min. The precipitate was filtered and washed with a mixture of hexane (30 mL) and dichloromethane (25 mL) to give urethane **90** as a white solid (2.45 g, 95%) (m.p. 153-154 °C).



**$^1$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.24 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 7.19-7.29 (m, 4H, H-16,17,19,20), 7.00 (tt, $J_{18,17} = J_{18,19}$ = 7.2 Hz, $J_{18,16} = J_{18,20}$ = 1.4 Hz, 1H, H-18), 6.72 (br s, 1H, -NH), 6.58 (d, $J_{3,2}$ = 2.0 Hz, 1H, H-3), 5.56 (br t, $J_{9,8}$ = 6.4 Hz, 1H, H-9), 4.64 (d, $J_{8,9}$ = 6.4 Hz, 2H, -$CH_2$), 3.77 (s, 3H, -$OCH_3$).

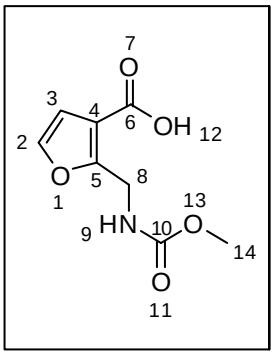
**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 164.6, 158.8, 155.7, 141.6, 138.6, 129.1, 123.6, 120.7, 114.5, 110.6, 51.8, 36.7.

**IR** (KBr, $cm^{-1}$) 3305, 3155, 2955, 1709, 1636, 1597, 1568, 1519, 1498, 1313, 1241, 1196, 1130, 1088.

**Anal. Calcd. for** $C_{14}H_{14}N_2O_4$ (274.27): C 61.31, H 5.14, N 10.21; Found: C 61.18, H 5.25, N 10.26

### 3.10 Synthesis of 2-((methoxycarbonylamino)methyl)furan-3-carboxylic acid (97)

To a stirred solution of ester **89** (0.94 g, 4.4 mmol) in dioxane (45 ml) and $H_2O$ (20 ml) was added dropwise aq. solution of NaOH (8.83 ml, 8.83 mmol, 1M) and the resulting mixture was stirred at 30 $^oC$ for 2 h. The reaction was monitored on TLC. After the completion of the reaction, the solution was acidified to pH 2 with 1M HCl and then extracted with EtOAc (3 x 70 mL). The combined organic extracts were washed with brine (80 mL) and dried over $MgSO_4$. The solvent was evaporated to give crude product, which was purified by crystallization from $CH_2Cl_2$/EtOAc (1:1) (80 mL) to give the acid **97** as a white solid (0.85 g, 97%) (m.p. 183-185°C).




**$^1$H-NMR** (400 MHz, DMSO-$d_6$) $\delta$: 12.76 (br s, 1H, -COOH), 7.66 (d, $J_{2,3}$ = 1.9 Hz, 1H, H-2), 7.63 (t, $J_{9,8}$ = 5.8 Hz, 1H, -NH), 6.65 (d, $J_{3,2}$ = 1.9 Hz, 1H, H-3), 4.52 (d, $J_{8,9}$ = 5.8 Hz, 2H, -$CH_2$), 3.54 (s, 3H, -$OCH_3$).

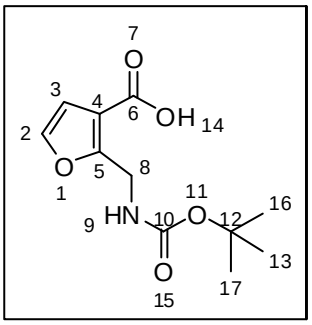
**$^{13}$C-NMR** (100.6 MHz, DMSO-$d_6$) $\delta$: 164.5, 157.7, 157.0, 142.4, 114.8, 111.1, 51.7, 36.8.

**IR** (KBr, $cm^{-1}$) 3324, 3154, 2983, 1680, 1594, 1543, 1518, 1429, 1310, 1261, 1221, 1181, 1145, 1122, 1982, 1022.

**Anal. Calcd. for** $C_8H_9NO_5$ (199.16): C 48.25, H 4.55, N 7.03; Found: C 48.03, H 4.44, N 7.05

### 3.11 Synthesis of 2-((*tert*-butoxycarbonylamino)methyl)furan-3-carboxylic acid (99)

To a stirred solution of ester **91** (6.0 g, 23.5 mmol) in dioxane (80 mL) and water (40 mL) was added aq. NaOH (47 mL, 47 mmol, 1M) dropwise and stirred at 30 ºC for 2 h. The reaction was monitored on TLC. After the completion of the reaction, the solution was acidified with 1N HCl to pH 2 and extracted with EtOAc (3 x 100 mL). The combined organic extracts were washed with brine (80 mL) and dried over $MgSO_4$. The solvent was evaporated to give crude product, which was purified by crystallization from EtOAc/hexane (1:1) to give the acid **99** as a white solid (5.47 g, 96%) (m.p. 142-144 °C).




**$^1$H-NMR** (400 MHz, DMSO-$d_6$) $\delta$: 12.72 (br s, 1H, -COOH), 7.65 (d, $J_{2,3}$ = 1.8 Hz, 1H, H-2), 7.30 (t, $J_{9,8}$ = 5.7 Hz, 1H, -NH), 6.64 (d, $J_{3,2}$ = 1.8 Hz, 1H, H-3), 4.46 (d, $J_{8,9}$ = 5.7 Hz, 2H, -$CH_2$), 1.38 (s, 9H, -$C(CH_3)_3$).

**$^{13}$C-NMR** (100.6 MHz, DMSO-$d_6$) $\delta$: 164.3, 157.8, 155.5, 142.0, 114.3, 110.8, 78.0, 36.3, 28.1.

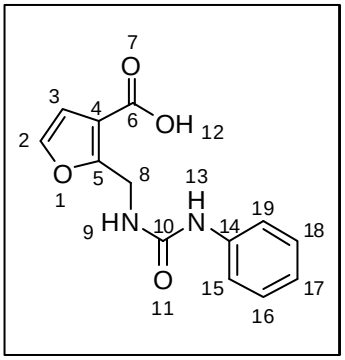
**IR** (KBr, $cm^{-1}$) 3379, 3152, 2988, 1680, 1600, 1519, 1464, 1436, 1367, 1321, 1280, 1251, 1160, 1125, 1086, 1029.

**Anal. Calcd. for** $C_8H_9NO_5$ (199.16): C 48.25, H 4.55, N 7.03; Found: C 48.03, H 4.44, N 7.05

### 3.12 Synthesis of 2-((3-phenylureido)methyl)furan-3-carboxylic acid (98)

To a stirred solution of ester **90** (1.1 g, 4.01 mmol) in dioxane (45 ml) and $H_2O$ (20 ml) was added dropwise aq. solution of NaOH (8.0 ml, 8.0 mmol, 1M) and the resulting mixture was stirred at 35 $^oC$ for 2.5 h. The reaction was monitored on TLC. After the completion of the reaction, the solution was acidified with 1M HCl to pH 2 and then extracted with EtOAc (3 x 70 mL). The combined organic extracts were washed with brine (80 mL) and dried over $MgSO_4$. The solvent was evaporated to

give crude product, which was purified by crystallization from acetone/EtOAc (1:1) (150 ml) to give the acid **98** as a white solid (0.96 g, 92%) (m.p. 153-154 °C).



**$^1$H-NMR** (400 MHz, DMSO-$d_6$) $\delta$: 12.82 (br s, 1H, -COOH), 8.63 (br s, 1H, H-13), 7.66 (d, $J_{2,3}$ = 1.9 Hz, 1H, H-2), 7.38 (br d, $J_{15,16} = J_{19,18}$ = 7.6 Hz, 2H, H-15,19), 7.23 (br t, $J_{16,15} = J_{16,17} = J_{18,17} = J_{18,19}$ = 7.9 Hz, 2H, H-16,18), 6.90 (br t, $J_{17,18} = J_{17,16}$ = 7.3 Hz, 1H, 17), 6.68 (d, $J_{3,2}$ = 1.9 Hz, 1H, H-3), 6.59 (t, $J_{9,8}$ = 6.0 Hz, 1H, -NH), 4.60 (d, $J_{8,9}$ = 6.0 Hz, 2H, -$CH_2$).

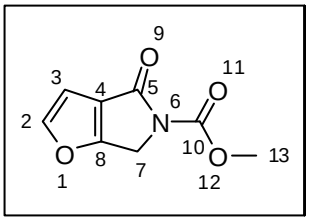
**$^{13}$C-NMR** (100.6 MHz, DMSO-$d_6$) $\delta$: 164.7, 158.8, 155.2, 142.3, 140.5, 128.9, 121.5, 118.0, 114.8, 111.2, 35.8.

**IR** (KBr, cm$^{-1}$) 3330, 3146, 2970, 1680, 1637, 1595, 1563, 1513, 1435, 1423, 1309, 1220, 1128, 1083, 1021.

**Anal. Calcd. for** $C_{13}H_{12}N_2O_4$ (260.25): C 60.00, H 4.65, N 10.76; Found: C 60.21, H 4.78, N 10.81

### 3.13 Synthesis of methyl 4-oxo-4*H*-furo[2,3-*c*]pyrrole-5(*6H*)-carboxylate (94)

To a stirred solution of the acid **97** (0.2 g, 1.0 mmol) in dry THF (15 mL) was added thionyl chloride (0.15 mL, 2.0 mmol) and heated at reflux temperature for 3 h. The reaction was monitored on TLC. After one hour, the solvent and excess thionyl chloride were evaporated. The residue was dissolved in dry benzene (20 mL) and heated at reflux temperature for 18 h. The solvent was evaporated and the crude product was purified by column chromatography eluting with EtOAc/hexane (1:1) to give furopyrrolone derivative **94** as a white solid (0.14 g, 78%) (m.p. 173-175 °C).



**$^1$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.49 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 6.61 (d, $J_{3,2}$ = 2.0 Hz, 1H, H-3), 4.66 (s, 2H, -$CH_2$), 3.86 (s, 3H, -$OCH_3$).

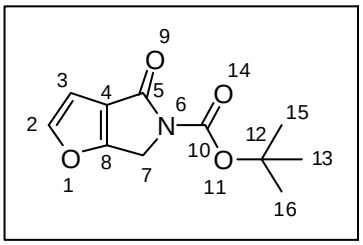
**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 167.5, 161.2, 152.5, 149.3, 120.7, 106.3, 53.7, 45.8.

**IR** (KBr, $cm^{-1}$) 3135, 2973, 1764, 1691, 1607, 1437, 1393, 1325, 1255, 1194, 1130, 1074.

**Anal. Calcd. for** $C_8H_7NO_4$ (181.15): C 53.04, H 3.89, N 7.73; found: C 53.21, H 3.86, N 7.82

### 3.14 Synthesis of *tert*-butyl 4-oxo-4*H*-furo[2,3-*c*]pyrrole-5(*6H*)-carboxylate (96)

To a stirred suspension of the acid **99** (1.24 g, 5.14 mmol) in dry THF (25 mL) was added thionyl chloride (0.79 mL, 10.78 mmol) and heated at reflux temperature for 3 h. The reaction was monitored on TLC. After one hour, the solvent and excess thionyl chloride were evaporated. The residue was dissolved in dry benzene (30 mL) and heated at reflux temperature for 2 days. The solvent was evaporated and the crude product was purified by column chromatography eluting on silica gel with hexane/EtOAc (3:1) to give furopyrrolone derivative **96** as a white solid (0.72 g, 63%) (m.p. 82-84 °C).




**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.47 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 6.59 (d, $J_{3,2}$ = 2.0 Hz, 1H, H-3), 4.59 (s, 2H, $-CH_2$), 1.50 (s, 9H, $-C(CH_3)_3$).

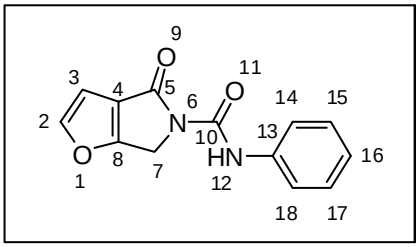
**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 167.3, 161.7, 150.2, 149.0, 121.0, 106.2, 83.0, 45.7, 28.1.

**IR** (KBr, $cm^{-1}$) 3127, 2980, 1770, 1703, 1616, 1495, 1459, 1369, 1323, 1257, 1152, 1067.

**Anal. Calcd. for** $C_{11}H_{13}NO_4$ (223.23): C 59.19, H 5.87, N 6.27; found: C 59.31, H 5.87, N 6.18

### 3.15 Synthesis of 4-oxo-N-phenyl-4*H*-furo[2,3-*c*]pyrrole-5(*6H*)-carboxamide (95)

To a stirred solution of the acid **98** (0.45 g, 1.75 mmol) in dry THF (50 mL) was added thionyl chloride (0.25 mL, 3.46 mmol) and heated at reflux temperature for 4 h. The reaction was monitored on TLC. After the completion of the cyclization, the solvent was evaporated and the crude product was purified by column chromatography eluting with ethyl acetate/hexane/dichloromethane (1:1:1) to give furopyrrolone derivative **95** as a white solid (0.37 g, 89%) (m.p. 172-174 °C).




**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 10.40 (br s, 1H, -NH), 7.53 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 7.49 (br d, $J_{14,15} = J_{18,17}$ = 7.6 Hz, 2H, H-14,18), 7.28 (br t, $J_{15,14} = J_{15,16} = J_{17,16} = J_{17,18}$ = 7.9 Hz, 2H, H-15,17), 7.05 (tt, $J_{16,15} = J_{16,17}$ = 7.4 Hz, $J_{16,14} = J_{16,18}$ = 1.1 Hz, 1H, H-16), 6.63 (d, $J_{3,2}$ = 2.0 Hz, 1H, H-3), 4.77 (s, 2H, -$CH_2$).

**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 168.2, 165.3, 150.5, 149.5, 137.5, 129.0, 124.1, 120.6, 120.1, 106.0, 45.0.

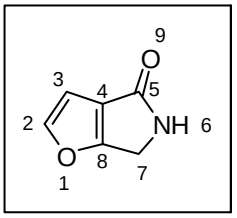
**IR** (KBr, $cm^{-1}$) 3135, 2973, 1764, 1691, 1607, 1437, 1393, 1325, 1255, 1194, 1130, 1074.

**Anal. Calcd. for** $C_{13}H_{10}N_2O_3$ (242.23): C 64.46, H 4.16, N 11.56; found: C 64.23, H 4.16, N 11.63

### 3.16 Synthesis of 5,6-dihydro-4*H*-furo[2,3-*c*]pyrrol-4-one (93)

To a stirred solution of Boc-protected amide **96** (0.30 g, 1.35 mmol) in DCM (30 mL) at 0 ºC was added trifluoroacetic acid (1 mL, 13 mmol) dropwise and stirred for 1 h at room temperature. The reaction was monitored on TLC. After the completion of the reaction, aq. NaOH (6.5 mL, 2M) was added to remove excess acid. Then, the mixture was extracted with DCM (2 x 50 mL) and the combined organic extracts were dried over $MgSO_4$. The solvent was evaporated and the crude product was

purified by column chromatography eluting with ethyl acetate to give *5,6-dihydro-4H-furo[2,3-c]pyrrol-4-one* **93** as a white solid (0.1 g, 63%) (m.p. 141-143 °C).




**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.45 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 6.58 (d, $J_{3,2}$ = 2.0 Hz, 1H, H-3), 5.83 (br s, 1H, -NH), 4.29 (s, 2H, -$CH_2$).

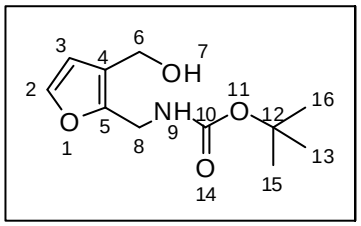
**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 169.0, 167.7, 148.5, 121.1, 105.9, 42.4.

**IR** (KBr, $cm^{-1}$) 3185, 3093, 1726, 1677, 1462, 1443, 1296, 1262, 1173, 1117, 1059, 1037.

**Anal. Calcd. for** $C_6H_5NO_2$ (123.11): C 58.54, H 4.09, N 11.38; found: C 58.46, H 4.09, N 11.28

### 3.17 Synthesis of *tert*-butyl (3-(hydroxymethyl)furan-2-yl)methylcarbamate (104)

The ester **91** (0.5 g, 1.96 mmol) was dissolved in dry DCM (20 mL) and cooled to -70 $^{o}$C under $N_2$. DIBAL-H was added dropwise at -70 $^{o}$C and the mixture was stirred for 90 min at that temperature then 30 min at room temperature. Then, methanol (10 mL) and satd. aq. solution $NH_4Cl$ was added. After that, HCl (8M) was added dropwise to the stirred solution and the reaction mixture was filtered on the bed of celite and washed with DCM. The filtrate was extracted with DCM (3 x 60 mL) and water. The combined organic extracts were dried over $Mg_2SO_4$. Removal of the solvent gave yellow oily alcohol **104** (0.4 g, 90%).



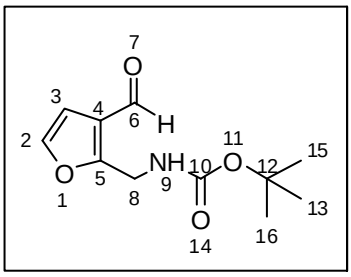

**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.27 (d, $J_{2,3}$ = 1.9 Hz, 1H, H-2), 6.33 (d, $J_{3,2}$ = 1.9 Hz, 1H, H-3), 5.46 (br s, 1H, -NH), 4.50 (br s, 2H, H-6), 4.24 (d, $J_{8,9}$ = 6.1 Hz, 2H, H-8), 3.95 (br s, 1H, -OH), 1.40 (s, 9H, -$C(CH_3)_3$).

**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 156.3, 148.6, 141.4, 122.1, 111.4, 80.2, 55.9, 35.6, 28.3.

**IR** (ATR) 3350, 2977, 2932, 1693, 1510, 1366, 1250, 1163, 1046, 1010, 733, 603.

### 3.18 Synthesis of *tert*-butyl (3-formylfuran-2-yl)methylcarbamate (108)

To a stirred solution of the PCC (9.4 g, 43.6 mmol) in DCM (40 mL) was added alcohol **104** (3.96 g, 17.4 mmol) in DCM (20 mL) and stirred for 2 h at room temperature. The reaction was monitored on TLC. After the completion of the reaction, ether was added (white brown color appeared) and stirred 15 minutes more. Then the solution was filtered from a bed of silica. Removal of the solvent gave the crude product, was then purified by column chromatography eluting with hexane/EtOAc (1:1). Eluted solvent was evaporated to yield aldehyde **108** as a white solid (3.05 g, 78%) (m.p. 100-101 °C).




**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 10.04 (s, 1H, H-6), 7.36 (d, $J_{2,3}$ = 1.9 Hz, 1H, H-2), 6.73 (d, $J_{3,2}$ = 1.9 Hz, 1H, H-3), 5.19 (br s, 1H, -NH), 4.57 (d, $J_{8,9}$ = 5.8 Hz, 2H, H-8), 1.42 (s, 9H, -C($CH_3$)$_3$).

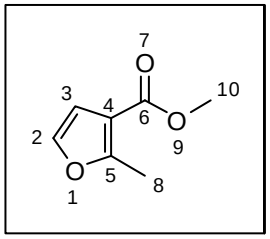
**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 185.3, 159.9, 155.4, 142.7, 123.2, 108.7, 80.2, 36.4, 28.3.

**IR** (ATR) 3353, 2981, 2936, 2826, 2733, 1737, 1681, 1590, 1393, 1301, 1251, 1159, 890, 772, 628.

**Anal. Calcd. for** $C_{11}H_{15}NO_4$ (225.24): C 58.66, H 6.71, N 6.22; Found: C 58.25, H 6.60, N 6.24

### 3.19 Synthesis of methyl 2-methylfuran-3-carboxylate (65)

Methylacetoacetate **109** (30.0 g, 258.4 mmol) was dissolved in pyridine (100 mL). To this mixture, a solution of chloroacetaldehyde **70** (45%, 46.5 mL, 322.9 mmol) was added dropwise at room temperature, and then stirred at 50 $^{o}$C 16 h. The reaction was monitored on TLC. After the completion of the reaction, the mixture was extracted with water (200 mL) and ethyl acetate (3 x 200 mL). The combined organic extracts were washed with 2M of HCl (250 mL), 5% $NaHCO_3$ (250 mL), 10% NaOH (250 mL) and brine (250 mL) (saturated NaCl solution) one by one, dried over $Mg_2SO_4$. Removal of the solvent gave the crude product, which was then purified by column chromatography eluting with hexane/EtOAc (4:1). Eluted solvent was evaporated to yield ester **65** as an oily colorless liquid (23.5 g, 65%).



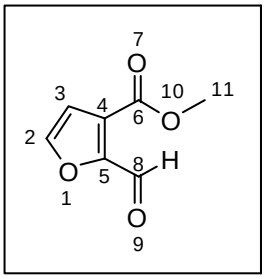

**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.22 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 6.63 (d, $J_{3,2}$ = 2.0 Hz, 1H, H-3), 3.82 (s, 3H, -$OCH_3$), 2.57 (s, 3H, -$CH_3$).

**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 164.5, 159.3, 140.3, 113.2, 110.6, 51.2, 13.6.

**IR** (ATR) 2954, 1819, 1720, 1668, 1438, 1383, 1302, 1120, 1044, 967, 835, 757.

### 3.20 Synthesis of methyl 2-formylfuran-3-carboxylate (66)

The ester **65** (1.0 g, 7.14 mmol) was dissolved in anisole (15 mL). To this solution, $SeO_2$ (1.58 g, 14.28 mmol) was added and stirred for overnight at 160 $^{o}$C. The reaction was monitored on TLC. After the completion of the reaction, the reaction mixture filtered and extracted with water (50 mL) and ethyl acetate (3 x 70 mL). Then the combined organic extract was dried over $Mg_2SO_4$. Removal of the solvent gave the crude product, which was then purified by column chromatography eluting with hexane/EtOAc (5:1). Eluted solvent was evaporated to yield aldehyde **66** as a yellow solid (0.44 g, 40%) (m.p. 77-78 °C).




**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 10.23 (d, $J_{8,2}$ = 0.7 Hz, 1H, H-8), 7.64 (dd, $J_{2,3}$ = 1.8 Hz, $J_{2,8}$ = 0.7 Hz, 1H, H-2), 6.89 (d, $J_{3,2}$ = 1.8 Hz, 1H, H-3), 3.95 (s, 3H, -$OCH_3$).

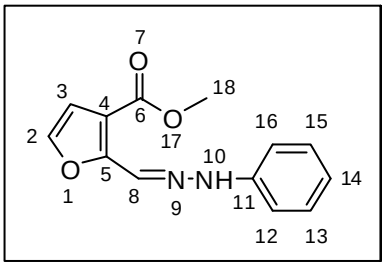
**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 178.8, 162.0, 152.4, 146.6, 126.2, 112.9, 52.5.

**IR** (ATR) 3153, 3130, 3014, 2960, 2882, 2846, 1715, 1671, 1575, 1480, 1435, 1403, 1365, 1303, 1264, 1211, 1180.

**Anal. Calcd. for** $C_7H_6O_4$ (154.12): C 54.55, H 3.92; Found: C 54.33, H 3.91

### 3.21 Synthesis of methyl 2-((2-phenylhydrazono)methyl)furan-3-carboxylate (117)

Aldehyde **66** (1.0 g, 6.49 mmol) was dissolved in THF (20 mL). To this solution, phenylhydrazine (0.64 mL, 6.49 mmol) was added dropwise at room temperature and stirred for 2 h. The reaction was monitored on TLC. After the completion of the reaction, removal of the solvent gave the crude product, which was washed with hexane-EtOAc (4:1) and filtrate was evaporated and again washed with same solvent. This procedure repeated for three times to get yellow solid imine **117** (1.5 g, 95%) (m.p. 133-134 °C).




**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 8.24 (s, 1H, H-8), 8.04 (br s, 1H, -NH), 7.40 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 7.29 (br t, $J_{13,12} = J_{13,14} = J_{15,14} = J_{15,16}$ = 7.9 Hz, 2H, H-13,15), 7.13 (br d, $J_{12,13} = J_{16,15}$ = 7.6 Hz, 2H, H-12,16), 6.92 (tt, $J_{14,13} = J_{14,15}$ = 7.3 Hz, $J_{14,12} = J_{14,16}$ = 1.0 Hz, 1H, H-14), 6.73 (d, $J_{3,2}$ = 2.0 Hz, 1H, H-3), 3.87 (s, 3H, -$OCH_3$).

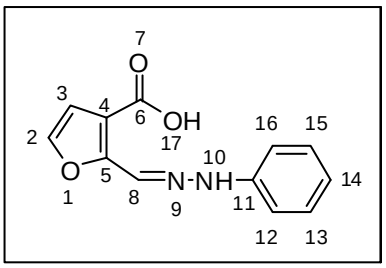
**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 163.7, 154.0, 143.5, 142.3, 129.2, 126.3, 120.9, 114.9, 113.1, 114.4, 51.6.

**IR** (ATR) 3275, 3127, 3068, 3022, 2951, 1687, 1587, 1494, 1306, 1254, 1206, 1170, 1058, 747, 730.

**Anal. Calcd. for** $C_{13}H_{12}N_2O_3$ (244.25): C 63.93, H 4.95, N 11.47; Found: C 63.81, H 4.94, N 11.29

### 3.22 Synthesis of 2-((2-phenylhydrazono)methyl)furan-3-carboxylic acid (121)

Ester **117** (0.66 g, 2.7 mmol) was dissolved in THF (20 mL), methanol (7.5 mL) and water (0.75 mL). To this mixture; KOH (3.0 mL, 2M in methanol) was added and stirred for 3 h at room temperature. The reaction was monitored on TLC. After the completion of the reaction, removal of the solvent gave crude product, which was extracted with water (3 x 50 mL) and EtOAc. The combined aqueous phase was acidified with 1 N HCl. Then, aq. phase was extracted with EtOAc (3 x 50 mL) and water. The combined organic phase was dried over $Mg_2SO_4$. Removal of the solvent gave the acid **121** as a brown solid (0.57 g, 92%) (m.p. 196-197 °C).




**$^1$H-NMR** (400 MHz, DMSO-$d_6$) $\delta$: 12.88 (br s, 1H, -COOH), 10.88 (s, 1H, -NH), 8.36 (s, 1H, H-8), 7.73 (d, $J_{2,3}$ = 1.9 Hz, 1H, H-2), 7.23 (br t, $J_{13,12}$ = $J_{13,14}$ = $J_{15,14}$ = $J_{15,16}$ = 7.9 Hz, 2H, H-13,15), 7.04 (br d, $J_{12,13}$ = $J_{16,15}$ = 7.6 Hz, 2H, H-12,16), 6.80 (br t, $J_{14,13}$ = $J_{14,15}$ = 7.3 Hz, 1H, H-14), 6.75 (d, $J_{3,2}$= 1.9 Hz, 1H, H-3).

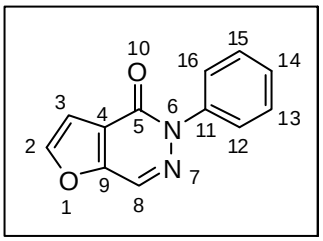
**$^{13}$C-NMR** (100.6 MHz, DMSO-$d_6$) $\delta$: 164.0, 153.7, 144.4, 142.8, 129.1, 125.9, 119.6, 115.1, 112.3, 111.7.

**IR** (ATR) 3301, 3124, 2997, 2874, 2676, 2573, 1670, 1583, 1498, 1277, 1255, 1130, 1050, 752.

**Anal. Calcd. for** $C_{12}H_{10}N_2O_3$ (230.22): C 62.60, H 4.38, N 12.17; Found: C 62.21, H 4.40, N 11.82

### 3.23 Synthesis of 5-phenylfuro[2,3-*d*]pyridazin-4(*5H*)-one (125)

To a stirred solution of the acid **121** (0.44 g, 1,91 mmol) in dry THF (20 mL) was added thionyl chloride (0.28 mL, 3.82 mmol) and heated at reflux temperature overnight. After the completion of the reaction, removal of the solvent gave the crude product, which was then purified by column chromatography eluting with hexane/EtOAc (1:1). Eluted solvent was evaporated to yield furopyridazinone derivative **125** as a brown solid (0.38 g, 93%) (m.p. 93-94 °C).



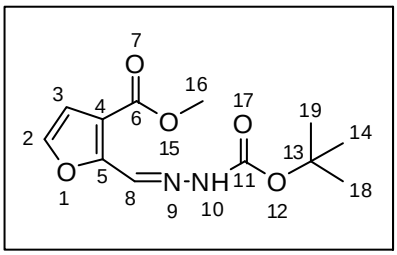

**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 8.35 (d, $J_{8,3}$ = 0.7 Hz, 1H, H-8), 7.73 (d, $J_{2,3}$ =1.9 Hz, 1H, H-2), 7.58 (br d, $J_{12,13} = J_{16,15}$ = 8.6 Hz, 2H, H-12,16), 7.49 (br t, $J_{13,12} = J_{13,14} = J_{15,14} = J_{15,16}$ = 7.7 Hz, 2H, H-13,15), 7.40 (tt, $J_{14,13} = J_{14,15}$ = 7.4 Hz, $J_{14,12} = J_{14,16}$ = 1.2 Hz, 1H, H-14), 7.13 (dd, $J_{3,2}$ = 1.9 Hz, $J_{3,8}$ = 0.7 Hz, 1H, H-3).

**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 158.4, 152.6, 146.9, 141.7, 128.8, 128.1, 127.0, 126.0, 123.5, 107.8.

**IR** (ATR) 3156, 3105, 3057, 1674, 1581, 1493, 1456, 1379, 1297, 1266, 1152, 1116, 871, 758, 693.

### 3.24 Synthesis of *tert*-butyl 2-((3-(methoxycarbonyl)furan-2-yl)methylene) hydrazinecarboxylate (118)

Aldehyde **66** (0.3 g, 1.95 mmol) was dissolved in THF (5 mL). To this solution, tert-butylcarbazate (0.26 mL, 1.95 mmol) was added at room temperature and stirred for 3 h at 50 $^{o}$C. The reaction was monitored on TLC. After the completion of the reaction, removal of the solvent gave the crude product, which was extracted with EtOAc (3 x 20 mL), dried over $Mg_2SO_4$. Removal of the solvent gave imine **118** as a yellow solid (0.51 g, 98%) (m.p. 122-123 °C).



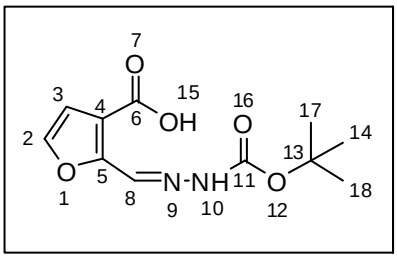
**$^1$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 8.44 (br s, 1H, -NH), 8.28 (br s, 1H, H-8), 7.42 (d, $J_{2,3}$ = 1.9 Hz, 1H, H-2), 6.73 (d, $J_{3,2}$ = 1.9 Hz, 1H, H-3), 3.85 (s, 3H, -$OCH_3$), 1.53 (s, 9H, -$C(CH_3)_3$).

**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 163.3, 152.6, 152.3, 143.3, 132.4, 114.7, 111.4, 81.7, 51.8, 28.1.

**IR** (ATR) 3201, 2977, 1701, 1536, 1498, 1367, 1276, 1248, 1154, 1038, 862, 751.

### 3.25 Synthesis of 2-((2-(*tert*-butoxycarbonyl)hydrazono)methyl)furan-3-carboxylic acid (122)

Ester **118** (0.52 g, 1.96 mmol) was dissolved in THF (10 mL), methanol (5 mL) and water (0.5 mL). To this mixture; KOH (1.96 mL, 2M in methanol) was added and stirred for 3 h at 75 $^o$C. The reaction was monitored on TLC. After the completion of the reaction, removal of solvent gave the crude product, which was extracted water (3 x 30 mL) and EtOAc. The combined aqueous phase was acidified with 1 N HCl to pH 2. Then, aq. phase was extracted with EtOAc (3 x 40 mL) and water. The combined organic extracts were dried over $Mg_2SO_4$. Removal of the solvent gave the acid **122** as a brown solid (0.43 g, 87%) (m.p. 164-165 °C).



**$^1$H-NMR** (400 MHz, DMSO-$d_6$) $\delta$: 13.03 (br s, 1H, -COOH), 11.19 (br s, 1H, -NH), 8.47 (s, 1H, H-8), 7.81 (d, $J_{2,3}$ = 1.9 Hz, 1H, H-2), 6.78 (d, $J_{3,2}$ = 1.9 Hz, 1H, H-3), 1.45 (s, 9H, -$C(CH_3)_3$).

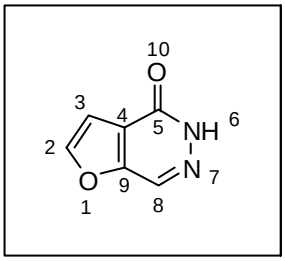
**$^{13}$C-NMR** (100.6 MHz, DMSO-$d_6$) $\delta$: 163.7, 152.3, 152.2, 144.3, 132.6, 118.6, 112.2, 80.1, 28.1.

**IR** (ATR) 3100, 2978, 2930, 1696, 1669, 1483, 1440, 1391, 1280, 1162, 1050, 1035, 856, 757,737.

**Anal. Calcd. for** $C_{11}H_{14}N_2O_5$ (254.24): C 51.97, H 5.55, N 11.02; Found: C 51.69, H 5.40, N 10.64

### 3.26 Synthesis of furo[2,3-*d*]pyridazin-4(*5H*)-one (126)

To a stirred solution of the acid **122** (0.27 g, 1.06 mmol) in dry THF (10 mL) was added thionyl chloride (0.15 mL, 2.12 mmol) and heated gently at reflux temperature overnight. After the completion of the reaction, removal of the solvent gave the crude product, which was washed with n-hexane/EtOAc (4:1) and filtered to get furopyridazinone derivative **126** as a brown solid (0.1 g, 70%) (m.p. 203-204 °C).



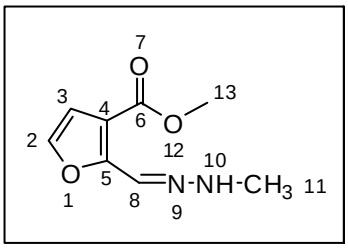

**$^{1}$H-NMR** (400 MHz, DMSO-$d_6$) $\delta$: 12.93 (br s, 1H, -NH), 8.53 (d, $J_{8,3}$ = 0.7 Hz, 1H, H-8), 8.20 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 7.13 (dd, $J_{3,2}$ = 2.0 Hz, $J_{3,8}$ = 0.7 Hz, 1H, H-3).

**$^{13}$C-NMR** (100.6 MHz, DMSO-$d_6$) $\delta$: 159.3, 153.0, 147.9, 127.2, 122.1, 106.5.

**IR** (ATR) 3241, 3155, 3128, 3101, 2970, 2922, 1655, 1572, 1501, 1422, 1380, 1183, 863, 752, 609.

### 3.27 Synthesis of methyl 2-((2-methylhydrazono)methyl)furan-3-carboxylate (119)

Aldehyde **66** (0.62 g, 4.02 mmol) was dissolved in THF (10 mL). To this solution, methylhydrazine (0.22 mL, 4.02 mmol) was added dropwise and stirred for 3 h in ice bath. The reaction was monitored on TLC. After the completion of the reaction, removal of the solvent gave the crude product, which was extracted with EtOAc (3 x 30 mL), dried over $Mg_2SO_4$. Removal of the solvent gave yellow oily imine **119** (0.70 g, 96%).



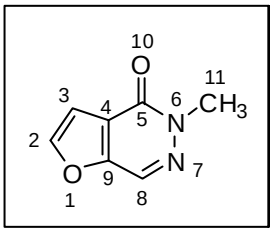

**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 7.91 (s, 1H, H-8), 7.30 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 6.68 (d, $J_{3,2}$ = 2.0 Hz, 1H, H-3), 6.14 (br s, 1H, -NH), 3.83 (s, 3H, -$OCH_3$), 3.02 (s, 3H, -$NCH_3$).

**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 163.8, 155.4, 141.3, 122.4, 113.1, 111.0, 51.3, 33.7.

**IR** (ATR) 3394, 3210, 2951, 1701, 1589, 1437, 1319, 1290, 1196, 1167, 1058, 1031, 739, 597.

### 3.28 Synthesis of 5-methylfuro[2,3-*d*]pyridazin-4(*5H*)-one (124)

Ester **119** (0.65 g, 3.57 mmol) was dissolved in THF (15 mL), methanol (7 mL) and water (1.0 mL). To this mixture; KOH (3.57 mL, 2M in methanol) was added and stirred for 3 h at 40 $^{o}$C. The reaction was monitored on TLC. After the completion of the reaction, removal of solvent gave the crude product, which was then purified by column chromatography eluting with hexane/EtOAc (2:1). Eluted solvent was evaporated to yield furopyridazinone derivative **124** white solid (0.32 g, 60%) (m.p. 107-108 °C).




**$^{1}$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 8.18 (d, $J_{8,3}$ = 0.7 Hz, 1H, H-8), 7.67 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 7.04 (dd, $J_{3,2}$ = 2.0 Hz, $J_{3,8}$ = 0.7 Hz, 1H, H-3), 3.85 (s, 3H, -$NCH_3$).

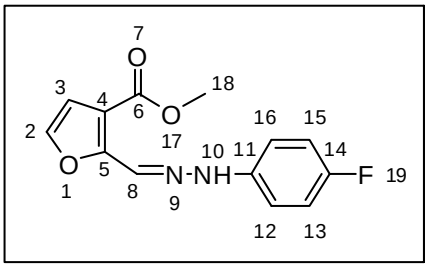
**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 158.9, 153.0, 146.6, 126.0, 122.6, 107.2, 39.6.

**IR** (ATR) 3118, 3101, 3054, 3039, 1647, 1575, 1502, 1379, 1274, 1142, 1004, 804, 766.

**Anal. Calcd. for** $C_7H_6N_2O_2$ (150.13): C 56.00, H 4.03, N 18.66; Found: C 55.98, H 4.04, N 18.49

### 3.29 Synthesis of methyl 2-((2-(4-fluorophenyl)hydrazono)methyl)furan-3-carboxylate (120)

Aldehyde **66** (0.50 g, 3.24 mmol) was dissolved in benzene (15 mL) and 5 drops of pyridine. To this solution, 4-fluorophenylhydraziniumchloride (0.53 g, 3.24 mmol) was added and stirred for 3 h at room temperature. The reaction was monitored on TLC. After the completion of the reaction, removal of the solvent gave the crude product, which was extracted with EtOAc (3 x 60 mL), dried over $Mg_2SO_4$. Removal of the solvent gave imine **120** as a brown solid (0.77 g, 90%) (m.p. 135-136 °C).



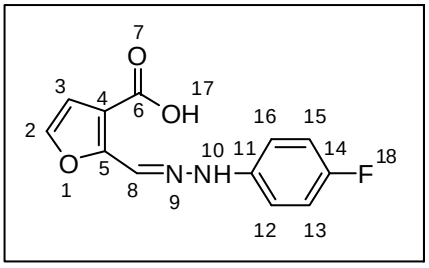
**$^1$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 8.24 (s, 1H, H-8), 8.06 (br s, 1H, -NH), 7.40 (d, $J_{2,3}$ = 1.9 Hz, 1H, H-2), 7.15-6.97 (m, 4H, H-12,13,15,16), 6.73 (d, $J_{3,2}$ = 1.9 Hz, 1H, H-3), 3.86 (s, 3H, -$OCH_3$).

**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 163.6, 157.8 (d, $^1J_{CF}$ = 231.4 Hz), 153.9, 142.4, 139.9 (d, $^4J_{CF}$ = 1.8 Hz), 126.5, 115.9 (d, $^2J_{CF}$ = 22.8 Hz), 115.2, 114.2 (d, $^3J_{CF}$ = 7.5 Hz), 111.5, 51.7.

**IR** (ATR) 3278, 3138, 3020, 2955, 1686, 1589, 1534, 1505, 1439, 1272, 1257, 1060, 1039, 831, 744.

### 3.30 Synthesis of 2-((2-(4-fluorophenyl)hydrazono)methyl)furan-3-carboxylic acid (123)

Ester **120** (0.69 g, 2.63 mmol) was dissolved in THF (20 mL), methanol (10 mL) and water (1.0 mL). To this mixture; KOH (2.63 mL, 2M in methanol) was added and stirred for 4 h at 75 $^oC$. The reaction was monitored on TLC. After the completion of the reaction, removal of solvent gave the crude product, which was extracted water (3 x 60 mL) and EtOAc. The combined aqueous phase was acidified with 1 N HCl to pH 2. Then, aq. phase was extracted with EtOAc (3 x 60 mL) and water. The combined organic extracts were dried over $Mg_2SO_4$. Removal of the solvent gave the acid **123** as a brown solid (0.49 g, 75%) (m.p. 199-200 °C).



**$^1$H-NMR** (400 MHz, DMSO-$d_6$) $\delta$: 12.87 (br s, 1H, -COOH), 10.89 (s, 1H, -NH), 8.34 (s, 1H, H-8), 7.73 (d, $J_{2,3}$ = 1.9 Hz, 1H, H-2), 7.11-7.01 (m, 4H, H-12,13, 15,16), 6.75 (d, $J_{3,2}$ = 1.9 Hz, 1H, H-3).

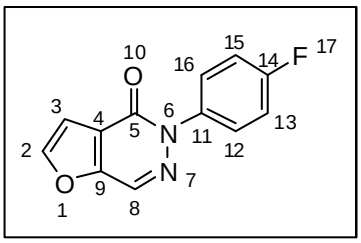
**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 164.1, 156.4 (d, $^1J_{CF}$ = 234.9 Hz), 153.7, 142.9, 141.0 (d, $^4J_{CF}$ = 1.0 Hz), 125.9, 115.7 (d, $^2J_{CF}$ = 22.5 Hz), 115.2, 113.4 (d, $^3J_{CF}$ = 7.6 Hz), 111.8.

**IR** (ATR) 3241, 3213, 3041, 2961, 2562, 1696, 1556, 1505, 1455, 1316, 1223, 1189, 1076, 1025, 825, 737.

**Anal. Calcd. for** $C_{12}H_9FN_2O_3$ (248.21): C 58.07, H 3.65, N 11.29; Found: C 58.16, H 3.87, N 10.21

### 3.31 Synthesis of 5-(4-fluorophenyl)furo[2,3-*d*]pyridazin-4(5*H*)-one (127)

To a stirred solution of the acid **123** (0.40 g, 1.61 mmol) in dry THF (15 mL) was added thionyl chloride (0.23 mL, 3.22 mmol) and heated at reflux temperature overnight. After the completion of the reaction, removal of the solvent gave the crude product, which was then purified by column chromatography eluting with hexane/EtOAc (2:1). Eluted solvent was evaporated to yield furopyridazinone derivative **127** as a white solid (0.26 g, 70%) (m.p. 122-123 °C).




**$^1$H-NMR** (400 MHz, $CDCl_3$) $\delta$: 8.35 (d, $J_{8,3}$ = 0.6 Hz, 1H, H-8), 7.74 (d, $J_{2,3}$ = 2.0 Hz, 1H, H-2), 7.59-7.54 (m, 2H, H-12,16), 7.20-7.15 (m, 2H, H-13,15), 7.13 (dd, $J_{3,2}$ = 2.0 Hz, $J_{3,8}$ = 0.6 Hz, 1H, H-3).

**$^{13}$C-NMR** (100.6 MHz, $CDCl_3$) $\delta$: 163.2, 159.6 (d, $^1J_{CF}$ = 228.3 Hz), 152.6, 147.1, 137.6 d, ($^4J_{CF}$ = 3.2 Hz), 127.8 (d, $^3J_{CF}$ = 8.5 Hz), 127.2, 123.5, 115.7 (d, $^2J_{CF}$ = 22.8 Hz), 107.8.

**IR** (ATR) 2922, 1739, 1688, 1507, 1496, 1381, 1262, 1216, 1141, 1106, 1060, 1012, 1012, 832, 742, 610.

**Anal. Calcd. for** $C_{12}H_7FN_2O_2$ (230.19): C 62.61, H 3.07, N 12.17; Found: C 62.44, H 3.00, N 12.05

# CHAPTER 4

# CONCLUSION

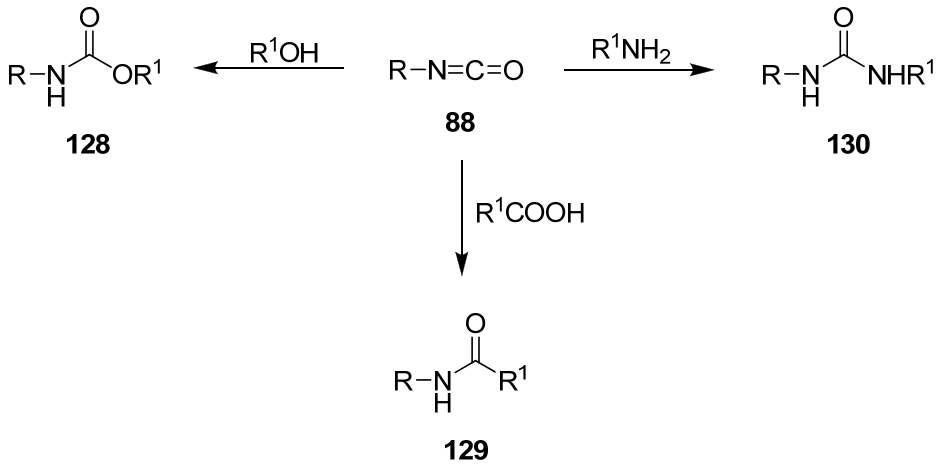
In this work, we developed a new synthetic methodology for the synthesis of new classes of compounds, such as furopyrrolones **64** and furopyridazinones **67**. The presented results established that intramolecular cyclization of acyl chlorides is a valuable method for the synthesis of heterocyclic compounds with new skeletons. Furthermore, this work showed that controlling the number of the $CH_2$ groups separating the ester functionalities from the furan ring can be a useful approach for the synthesis of six- and seven-membered heterocycles fused to a furan ring.


**64** **67**

**Scheme 35**

In the first part of this work, furan ring with two ester functionality was synthesized by using Feist-Benary method. The most important step of this method was the synthesis of monoisocyanate. To do this, regioselective formation of hydrazide was performed under given conditions and by using the modified Sandmeyer reaction corresponding acyl azide was created. This acyl azide was easily converted to corresponding isocyanate with high yield via Curtius rearrangement. The importance of isocyanate was that they were used as derivative generator. Reaction of isocyanates with a diverse number of nucleophiles enables production of different urethane **128**, amide **129** or urea **130** derivatives which may lead to construct various furopyrrolone derivatives.

Especially, Boc-protected amide was synthesized by treatment of isocyanate with *tert*-butanol because it was crucial for the synthesis of basic structure of furopyrrolone.




**Scheme 36**

Proton abstraction with base from the generated carbamate and urea derivatives did not lead to intramolecular cyclization. Therefore, we changed the strategy and we tried to increase the reactivity of the carbonyl group. It is known that acyl chlorides are much more reactive than other carbonyl groups, such as esters and carboxylic acids so they can easily undergo intramolecular cyclization. For that reason, the ester derivatives were first hydrolyzed to carboxylic acids and treatment with thionyl chloride gave the corresponding furopyrrolone derivatives via acyl chloride intermediate. These new types of compounds can show some biological and pharmaceutical properties like other pyrrolidinone and pyrrolone derivatives. Therefore this work was published in Helvetica Chimica Acta last year.[52]

In the second part, furopyridazinone derivatives were synthesized again by using acyl chloride intermediate. Initially, once more Feist-Benary method was used to synthesize starting furan derivative. Functionalization of methyl group was crucial to obtain the imine moiety in pyridazinone ring. To do this, oxidation of methyl group in the starting compound **65** to aldehyde was achieved by $SeO_2$ with some difficulties.

Then, both imine structure and nitrogen-nitrogen double bond was acquired by treatment of aldehyde with hydrazine derivatives. Finally, increasing the reactivity of carbonyl group caused the intramolecular cyclization to give the new class of compounds, furopyridazinones **67**.

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## APPENDIX A

## SPECTRAL DATA

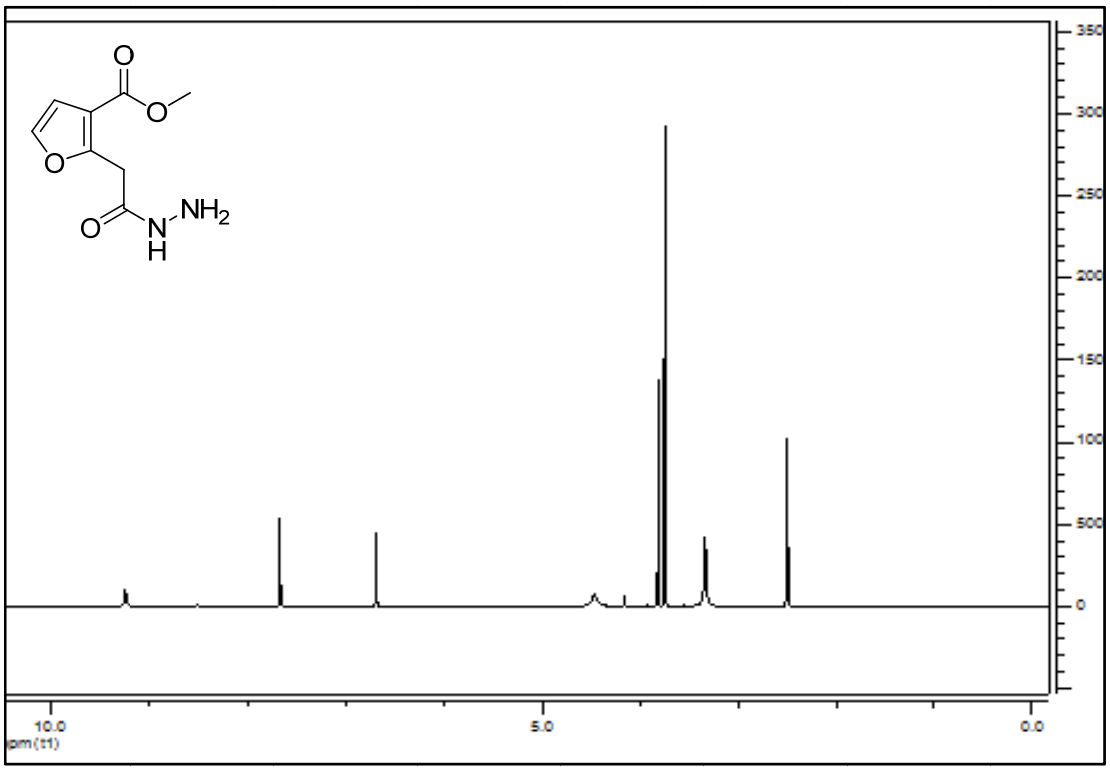


**Figure 1** $^{1}$H-NMR Spectrum of Compound **78**

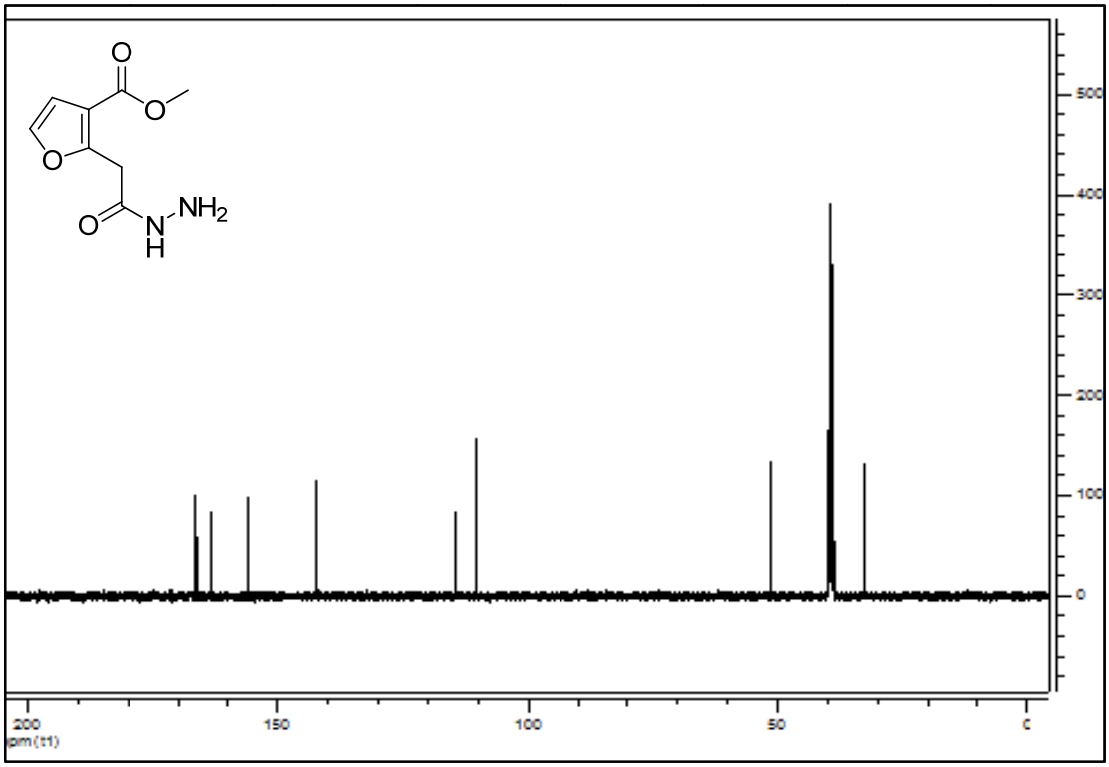


**Figure 2** $^{13}$C-NMR Spectrum of Compound **78**

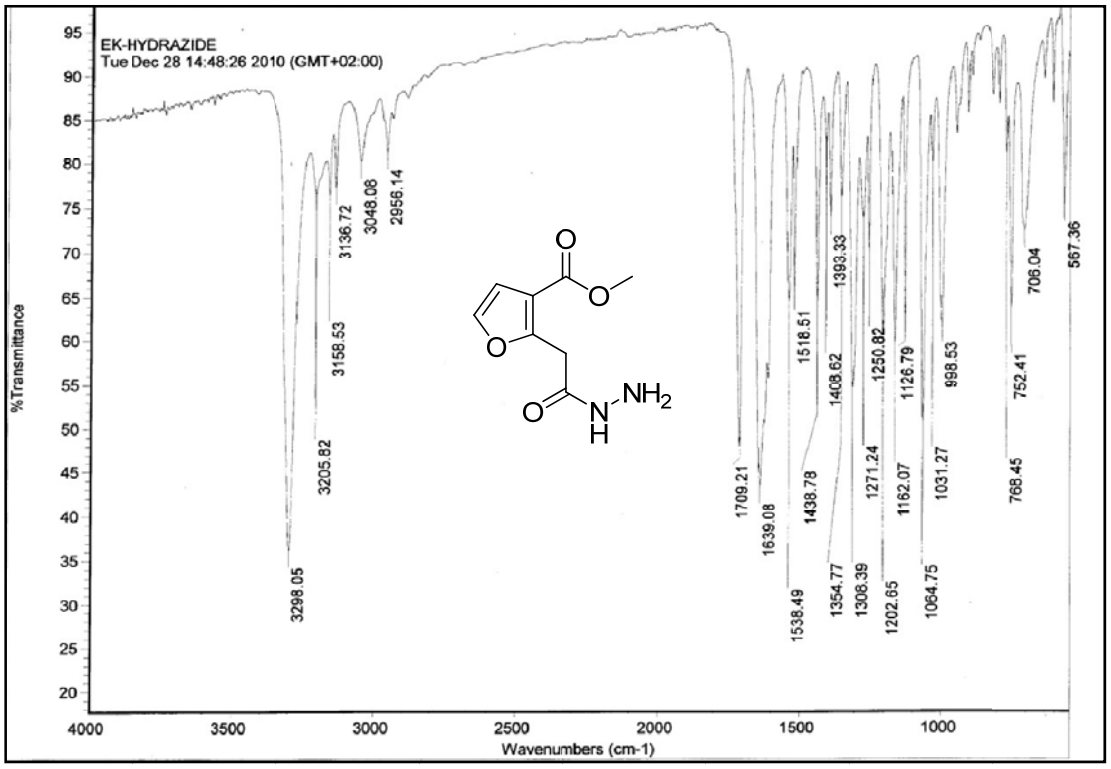


**Figure 3** IR Spectrum of Compound **78**

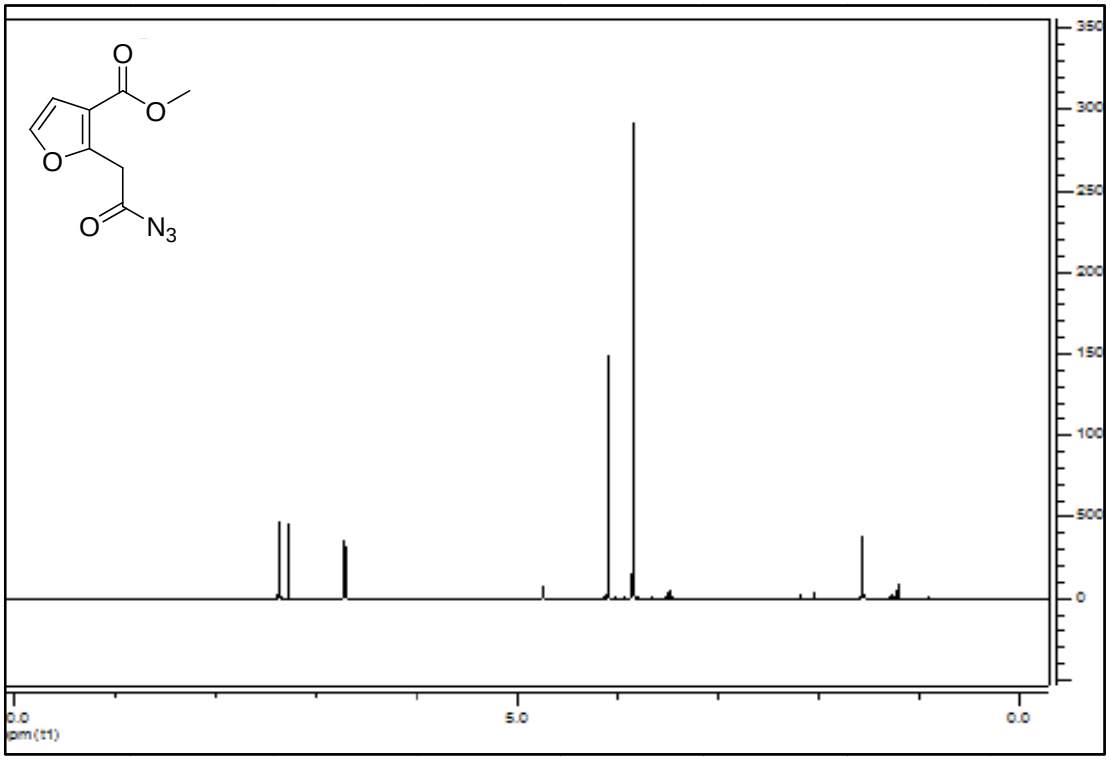


**Figure 4** $^{1}$H-NMR Spectrum of Compound **84**

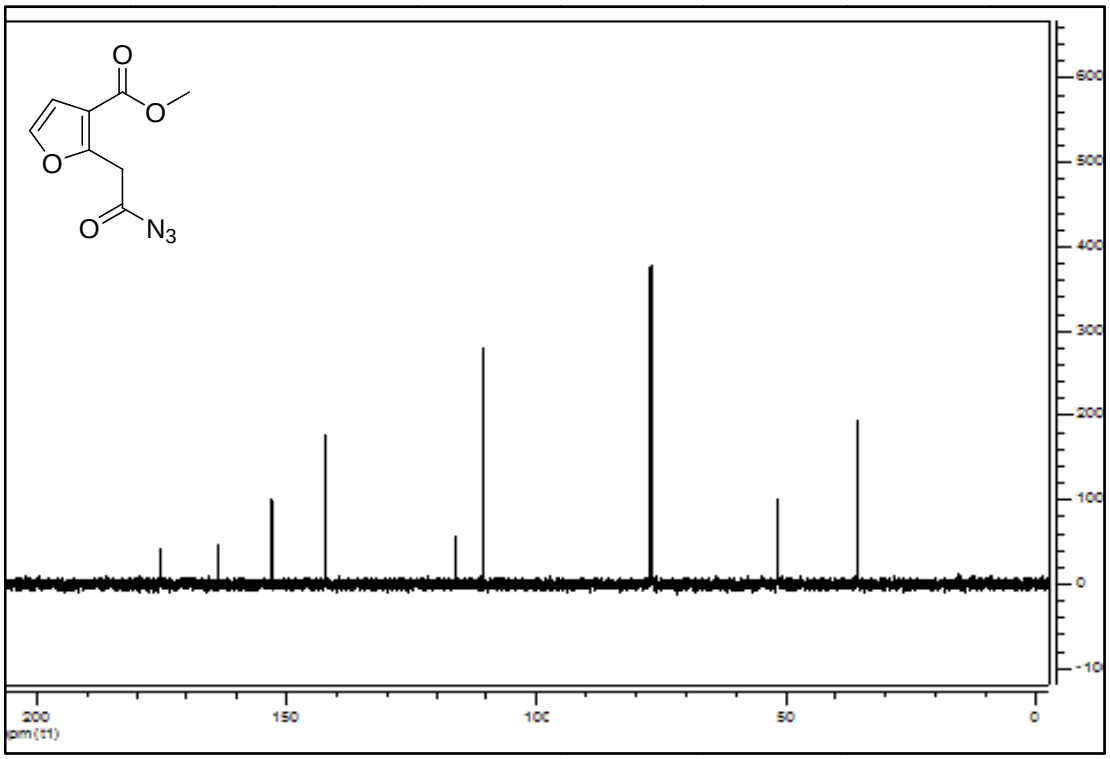


**Figure 5** $^{13}$C -NMR Spectrum of Compound **84**

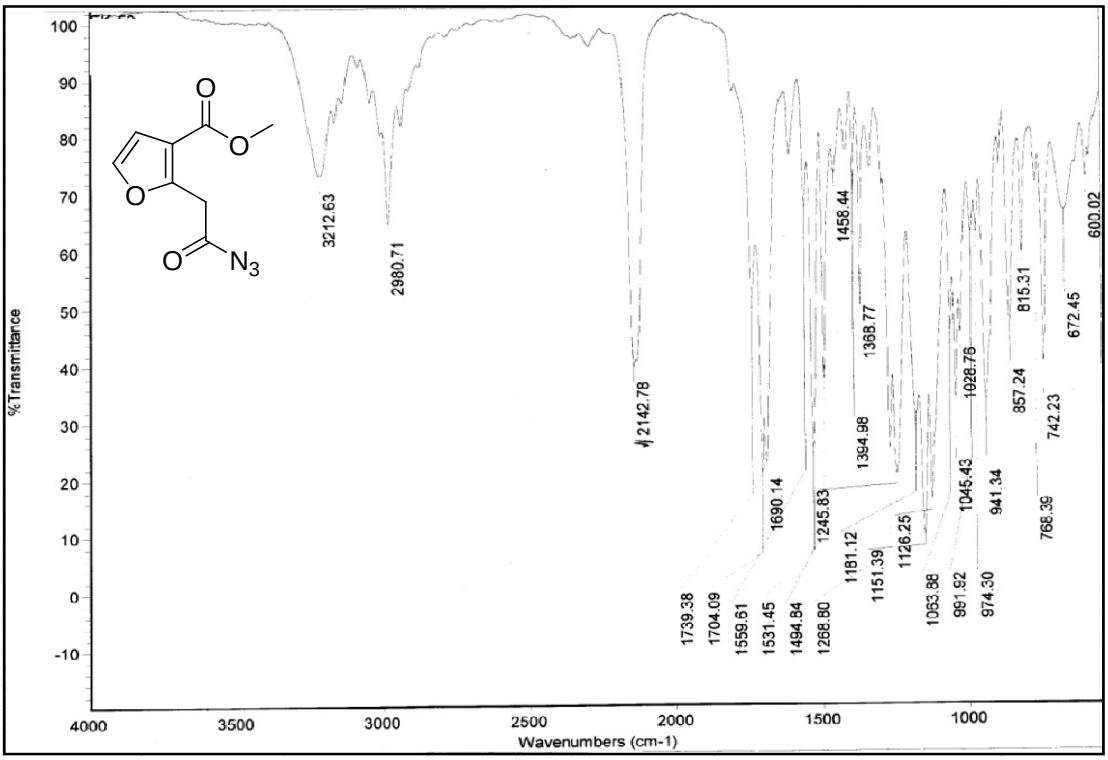


**Figure 6** IR Spectrum of Compound **84**

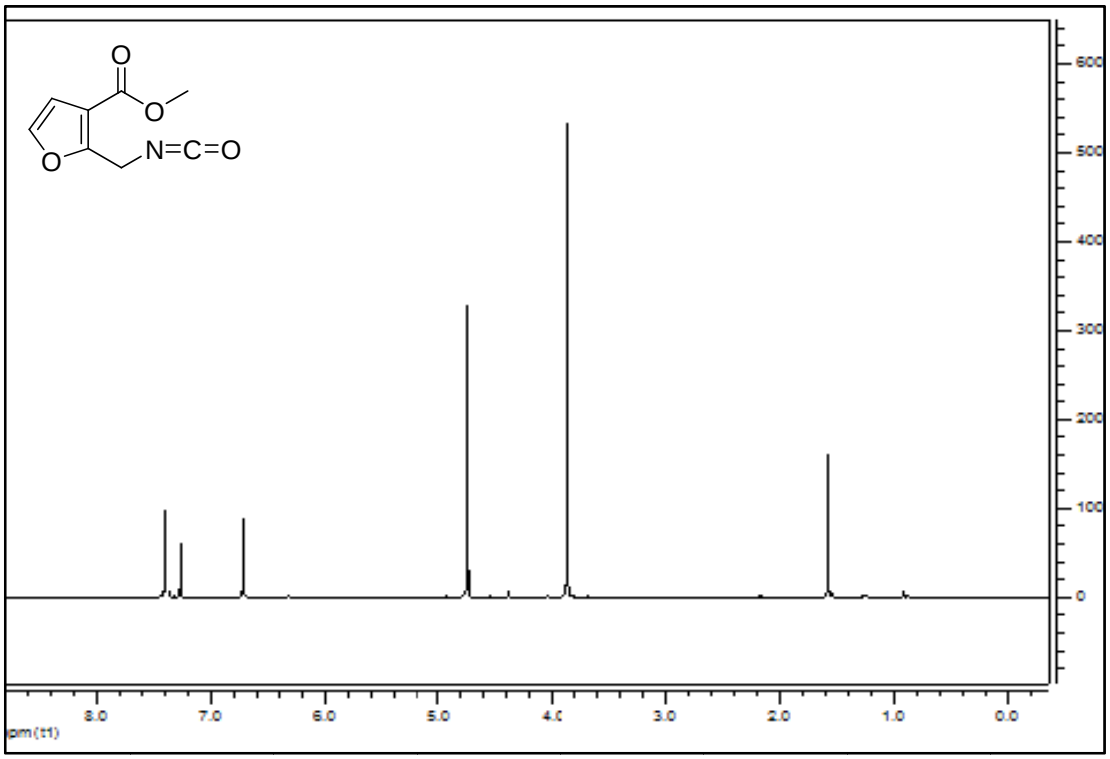


**Figure 7** $^{1}$H-NMR Spectrum of Compound **63**

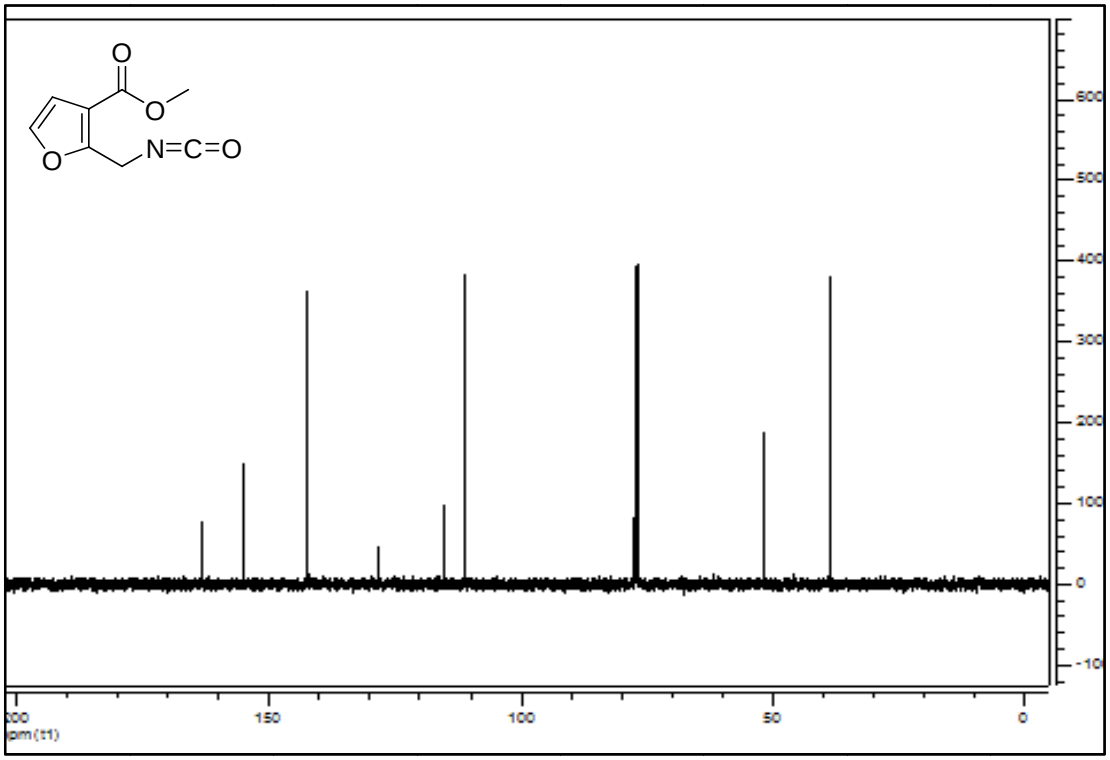


**Figure 8** $^{13}C$ -NMR Spectrum of Compound **63**

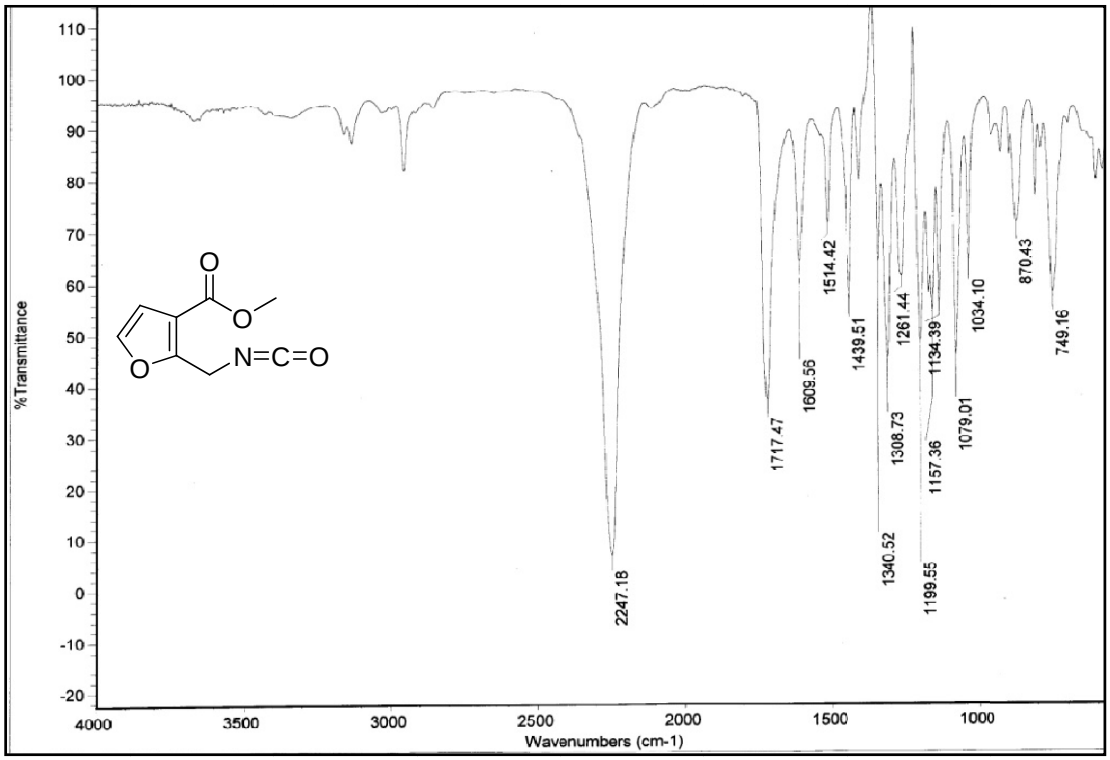


**Figure 9** IR Spectrum of Compound **63**

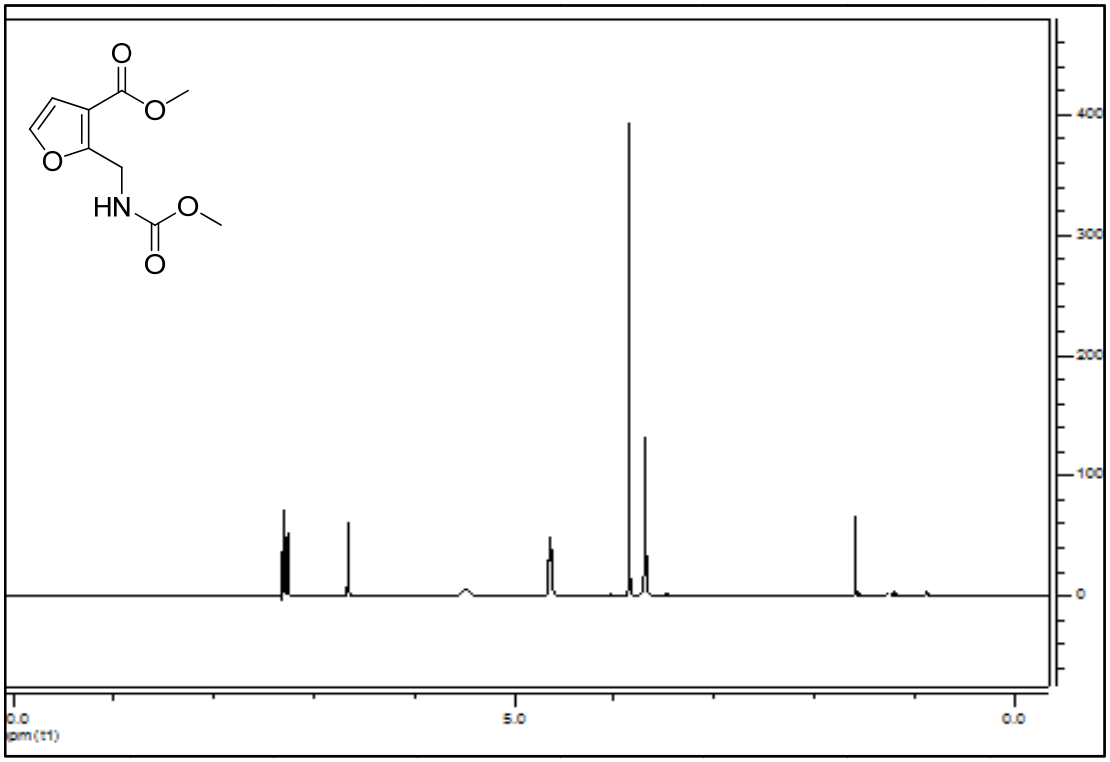


**Figure 10** $^{1}$H-NMR Spectrum of Compound **89**

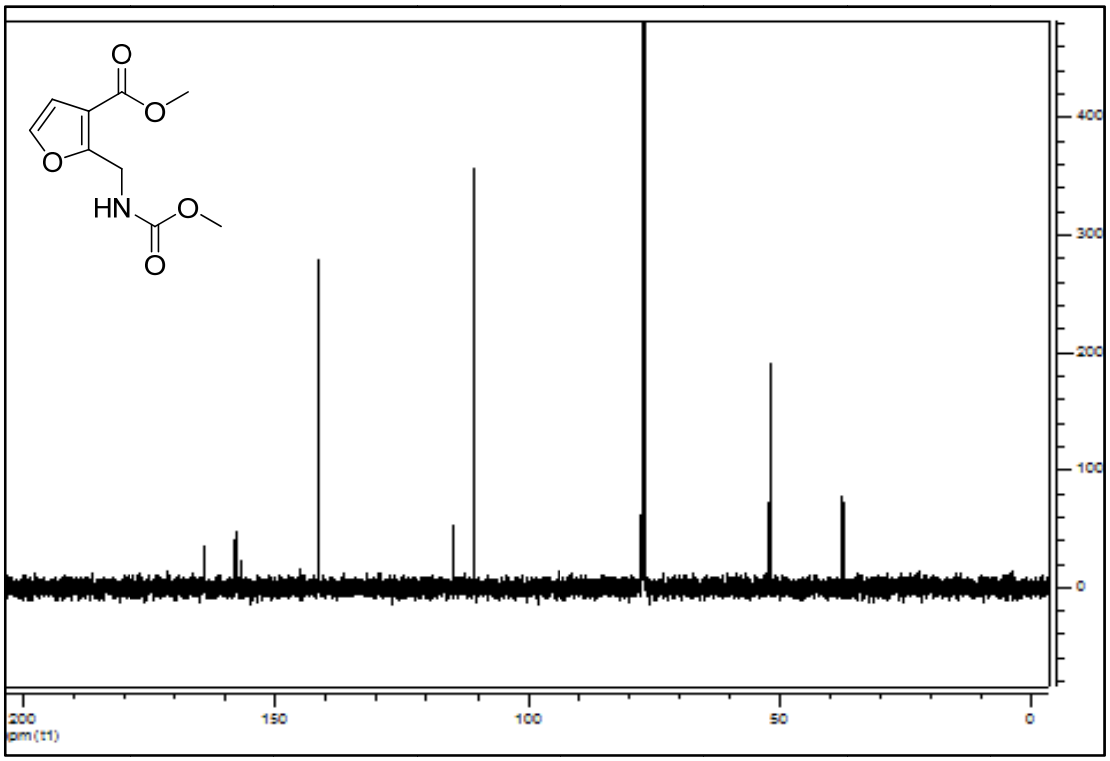


**Figure 11** $^{13}$C -NMR Spectrum of Compound **89**

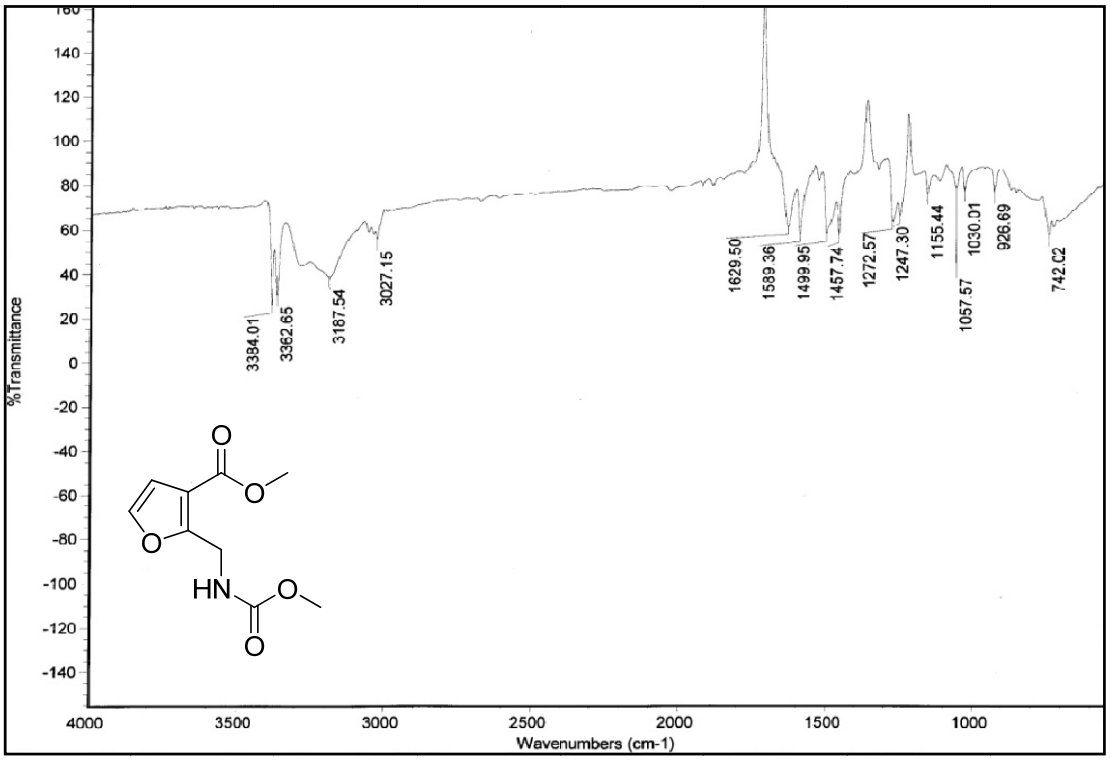


**Figure 12** IR Spectrum of Compound **89**

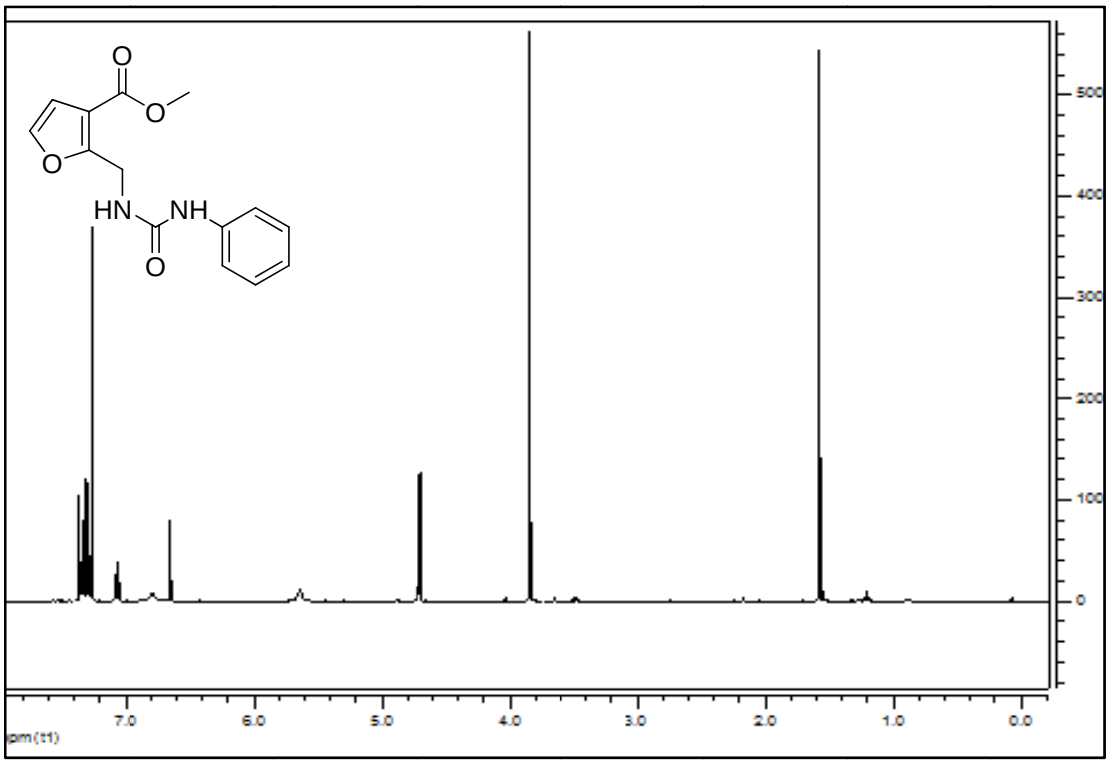


**Figure 13** $^{1}$H-NMR Spectrum of Compound **90**

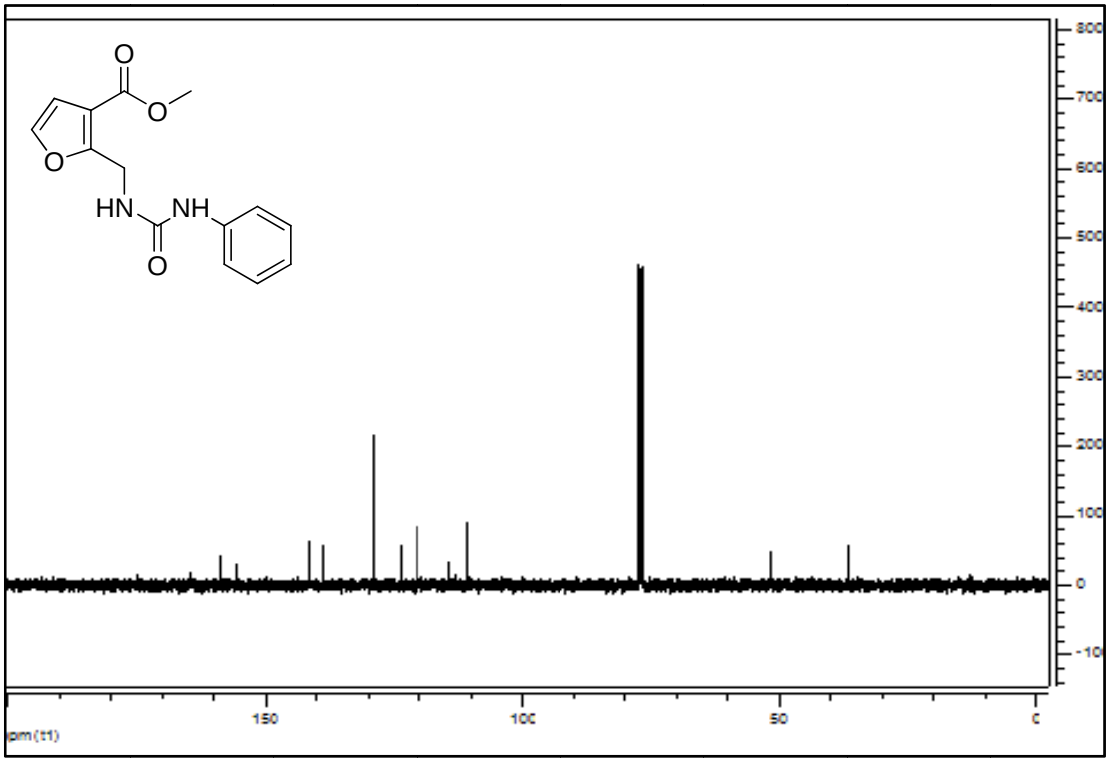


**Figure 14** $^{13}$C -NMR Spectrum of Compound **90**

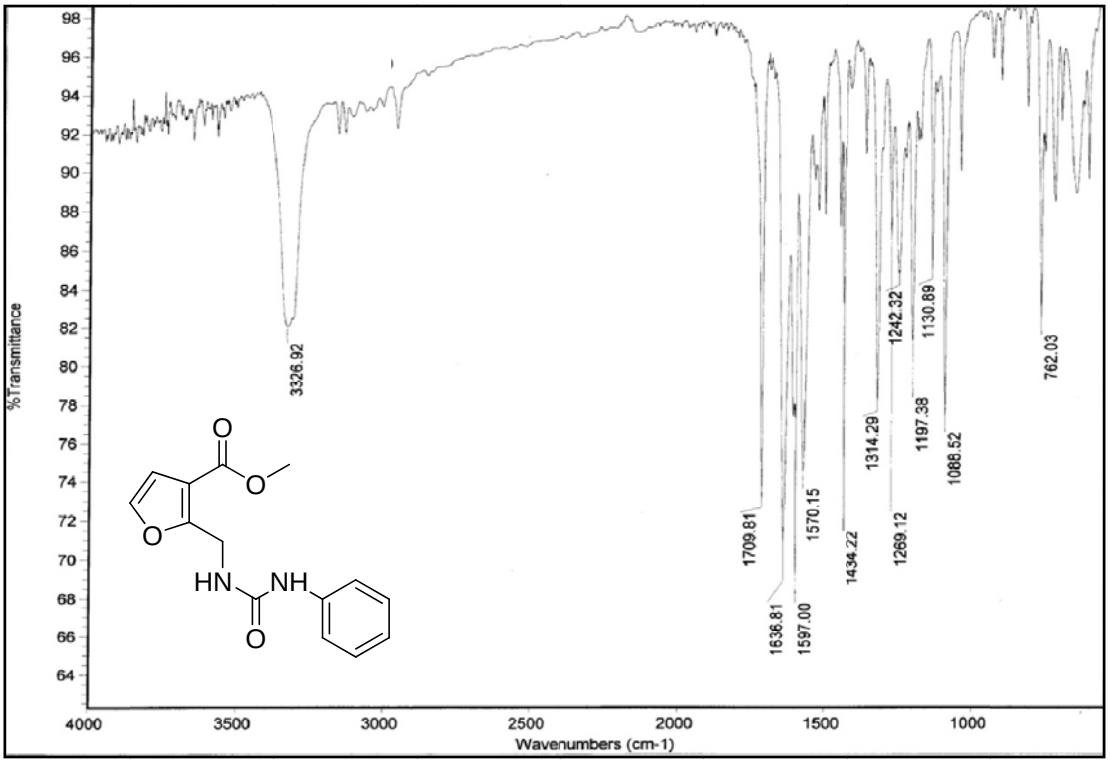


**Figure 15** IR Spectrum of Compound **90**

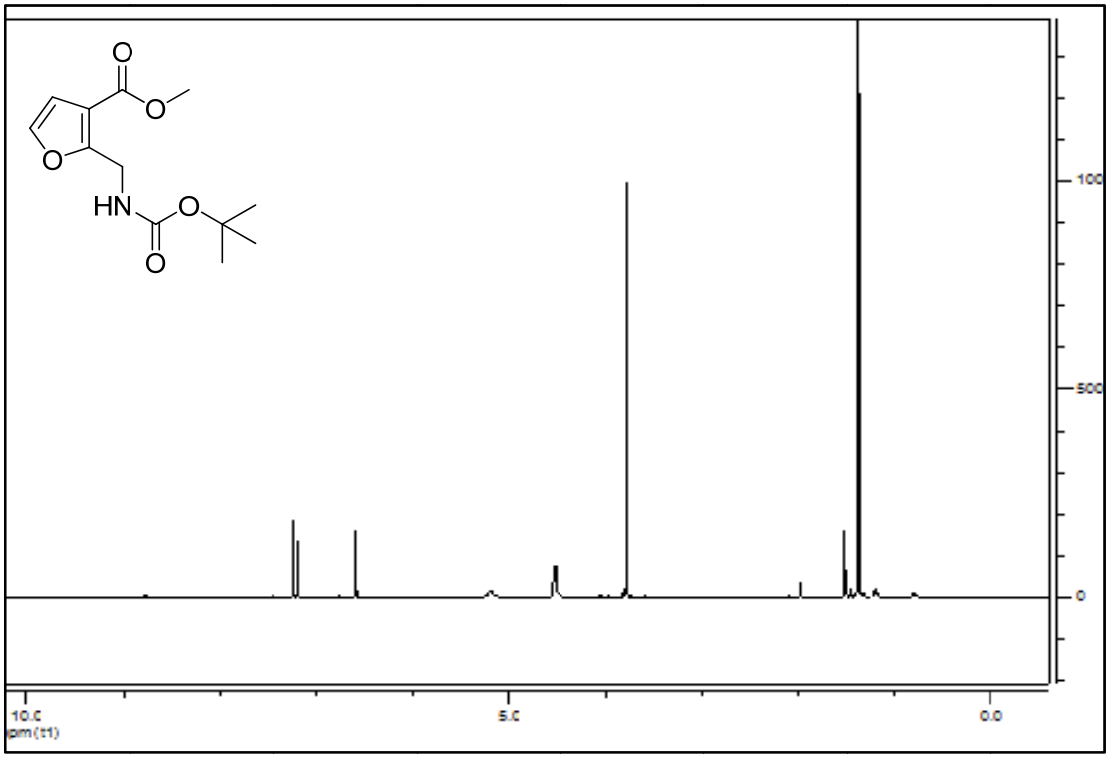


**Figure 16** $^{1}$H-NMR Spectrum of Compound **91**

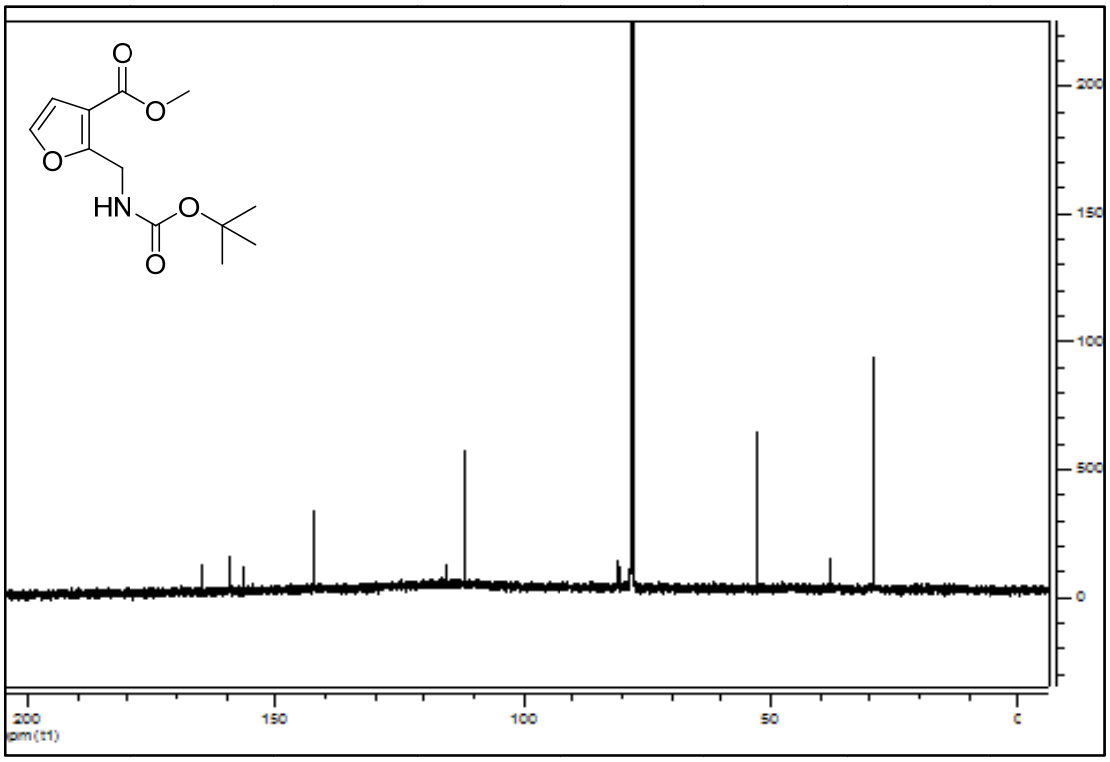


**Figure 17** $^{13}$C -NMR Spectrum of Compound **91**

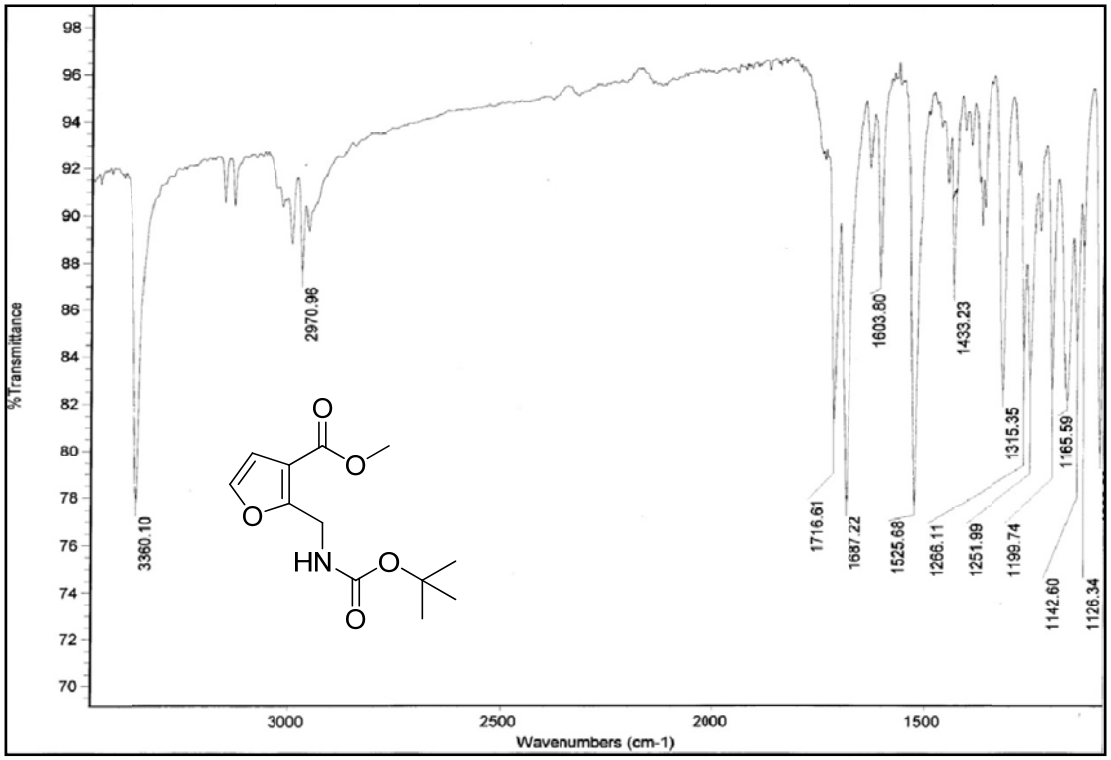


**Figure 18** IR Spectrum of Compound **91**

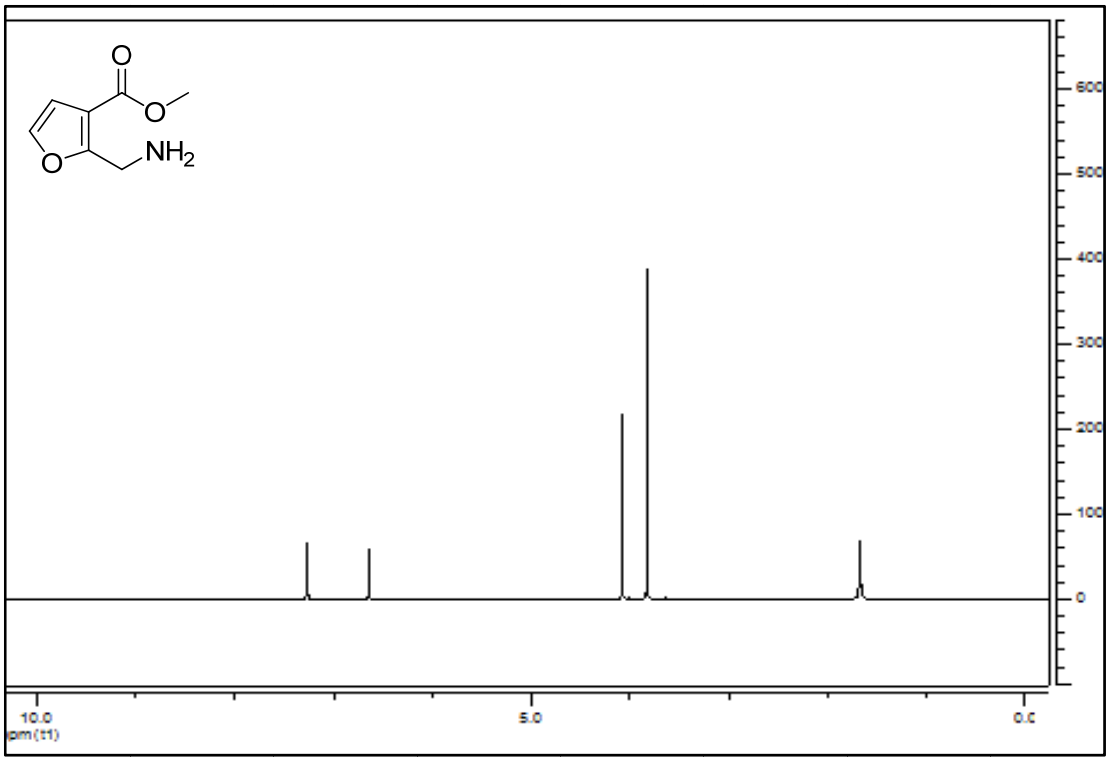


**Figure 19** $^{1}$H-NMR Spectrum of Compound **92**

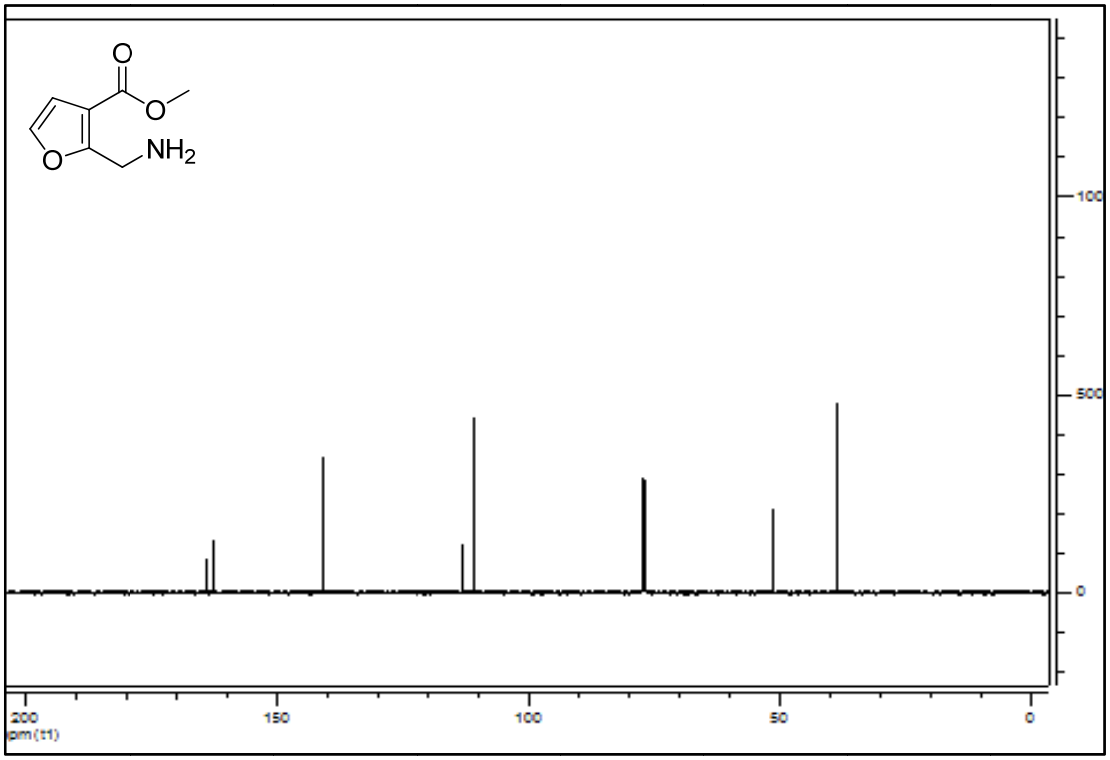


**Figure 20** $^{13}$C -NMR Spectrum of Compound **92**

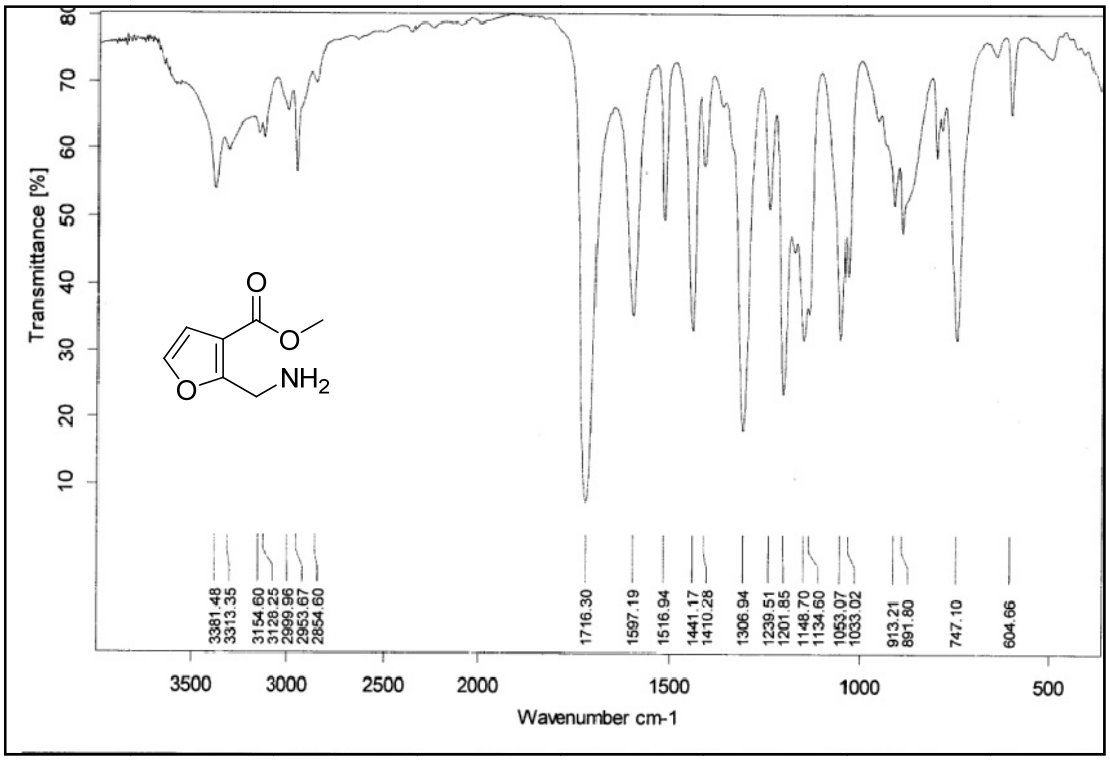


**Figure 21** IR Spectrum of Compound **92**

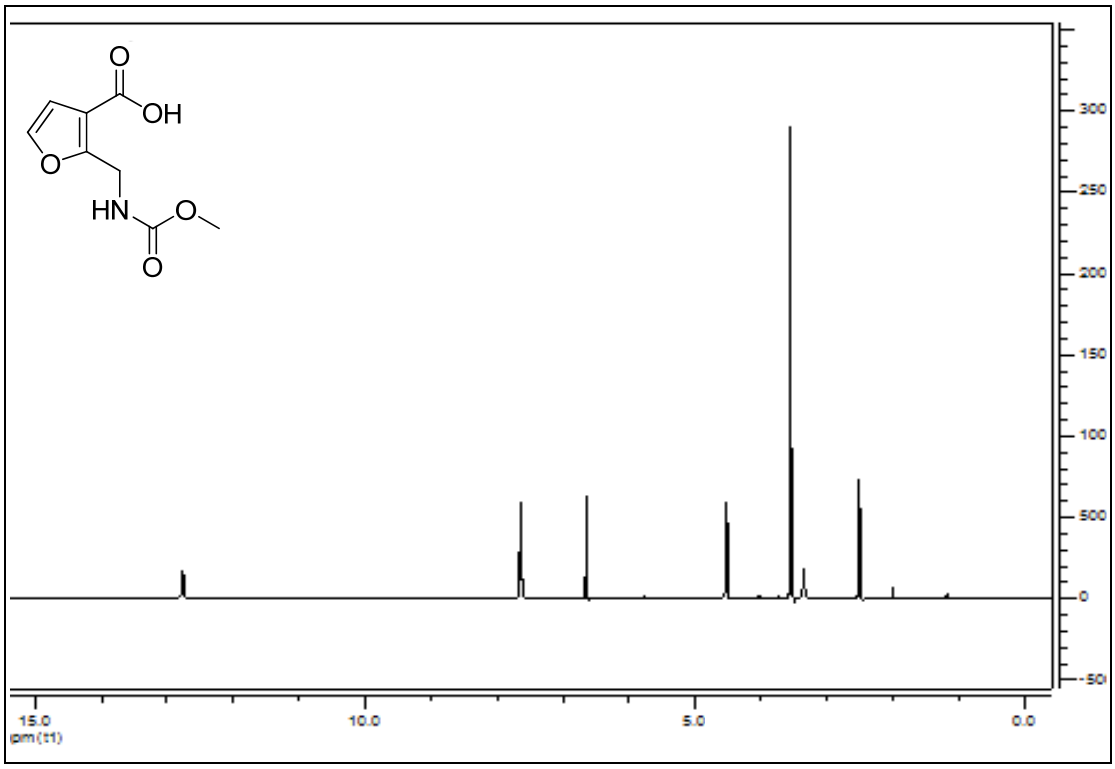


**Figure 22** $^{1}$H-NMR Spectrum of Compound **97**

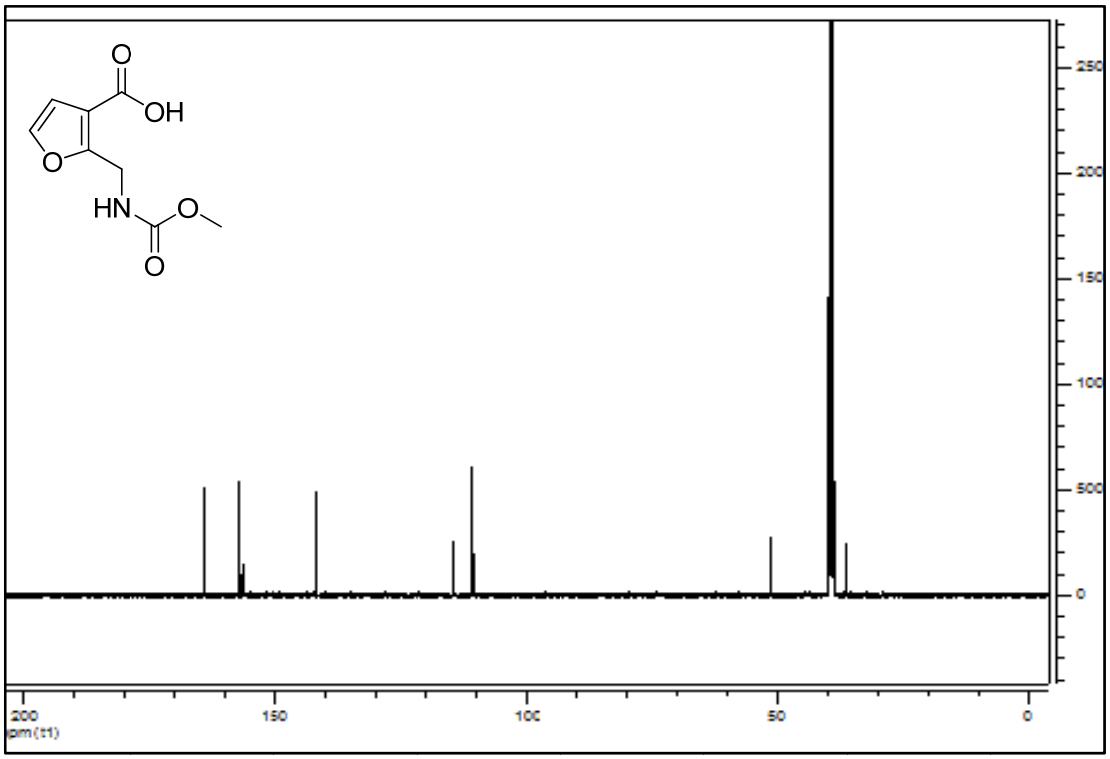


**Figure 23** $^{13}$C -NMR Spectrum of Compound **97**

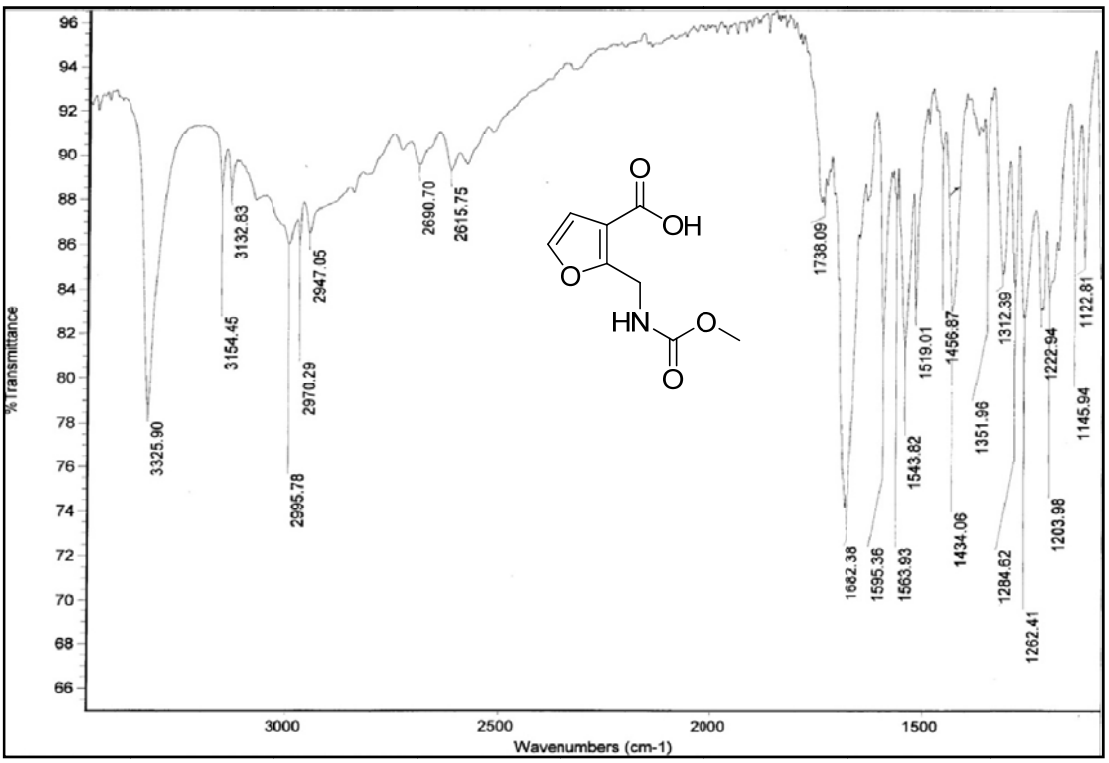


**Figure 24** IR Spectrum of Compound **97**

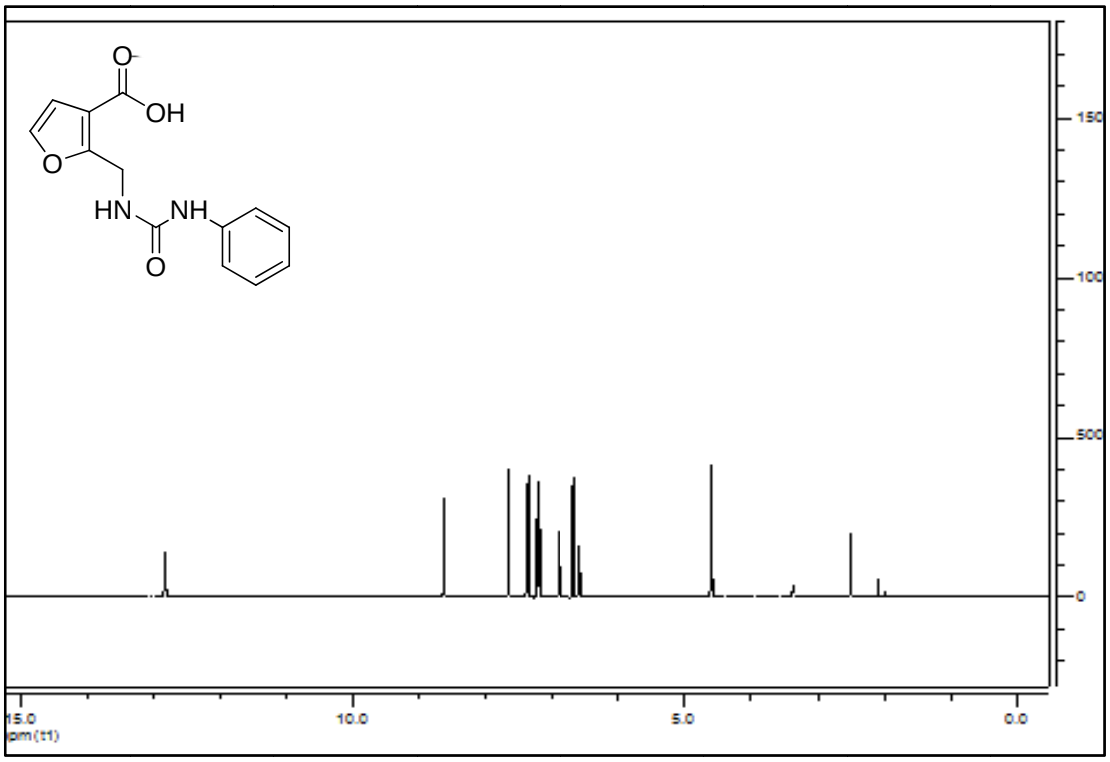


**Figure 25** [1]H-NMR Spectrum of Compound **98**

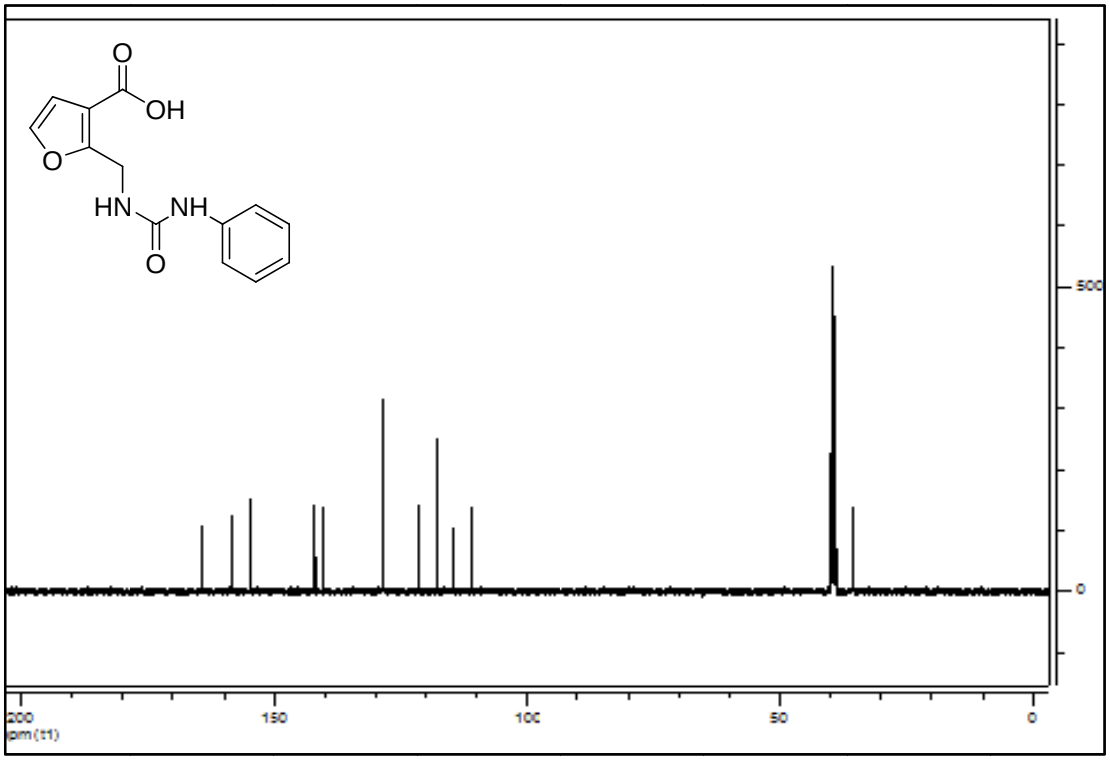


**Figure 26** $^{13}$C -NMR Spectrum of Compound **98**

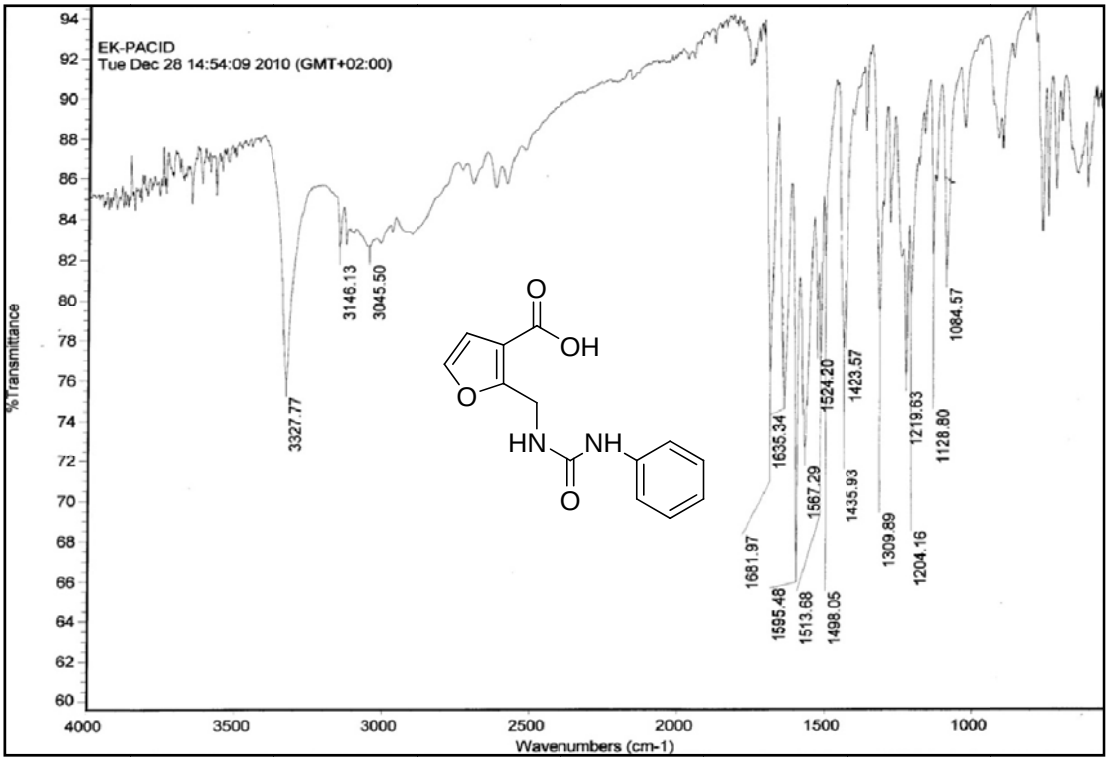


**Figure 27** IR Spectrum of Compound **98**

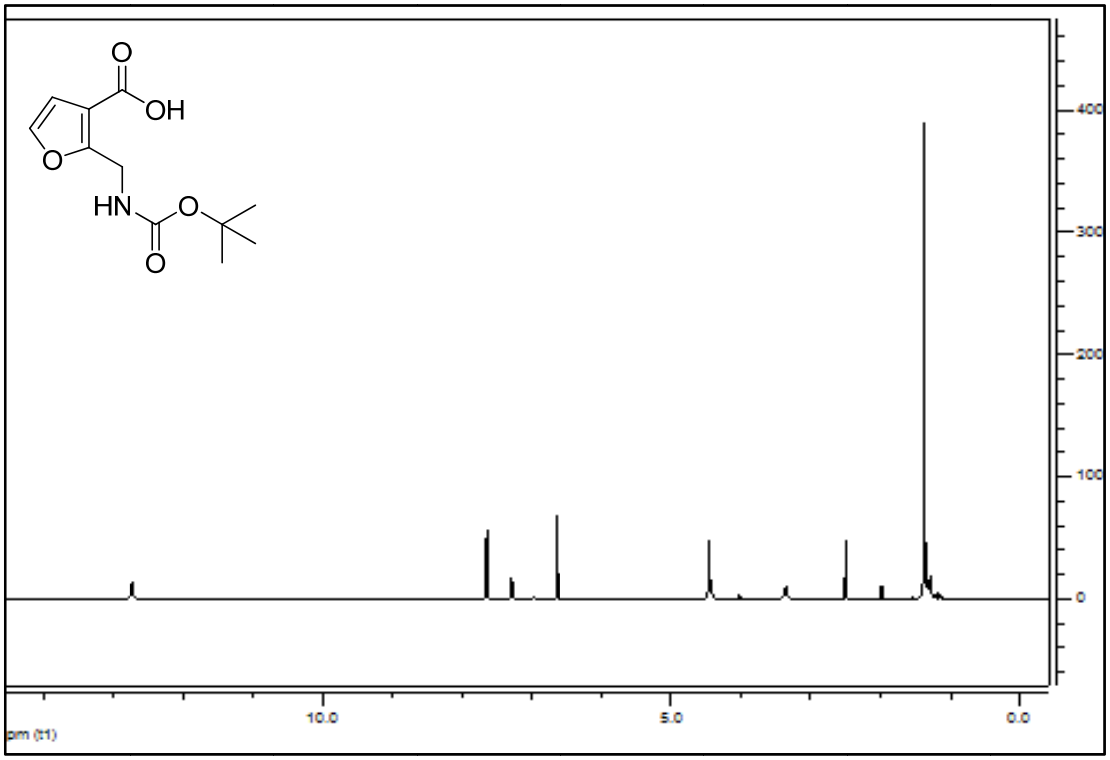


**Figure 28** $^{1}$H-NMR Spectrum of Compound **99**

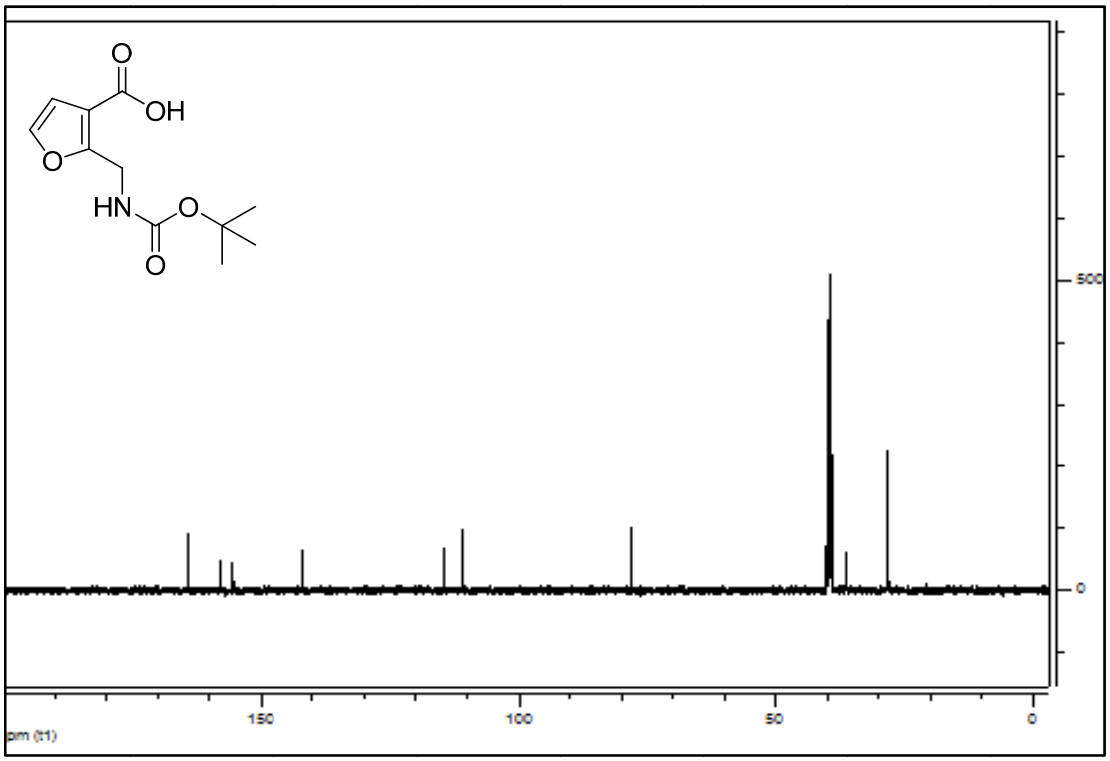


**Figure 29** $^{13}$C -NMR Spectrum of Compound **99**

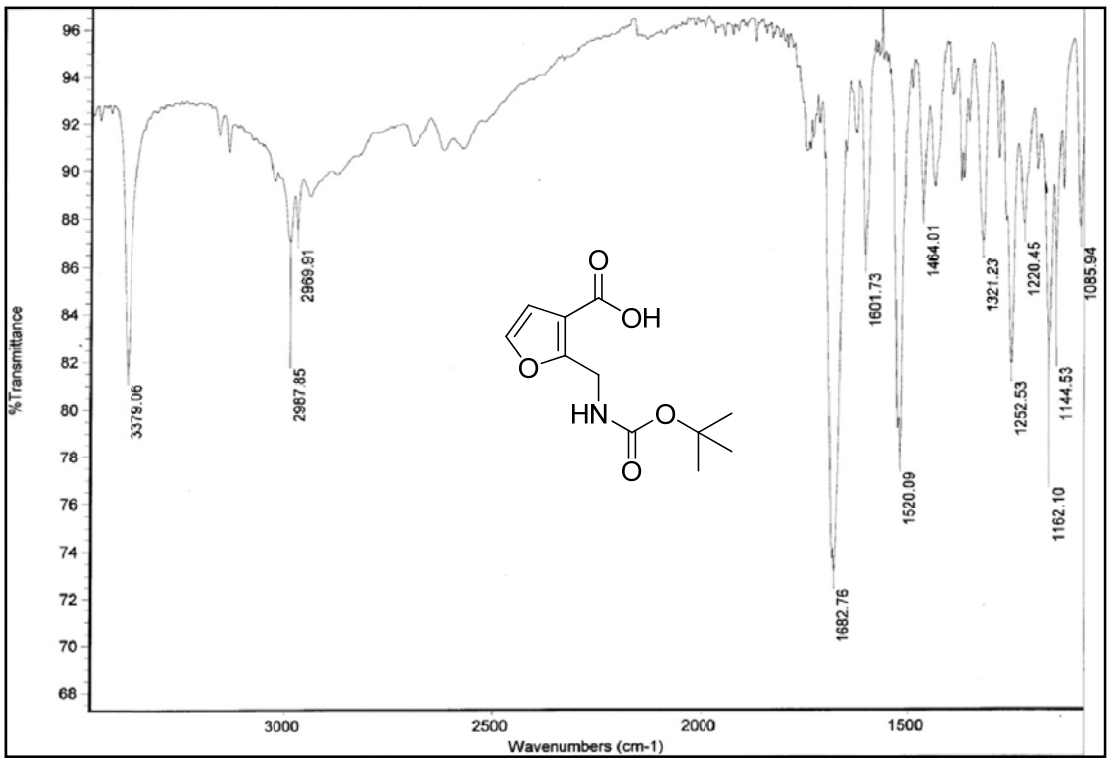


**Figure 30** IR Spectrum of Compound **99**

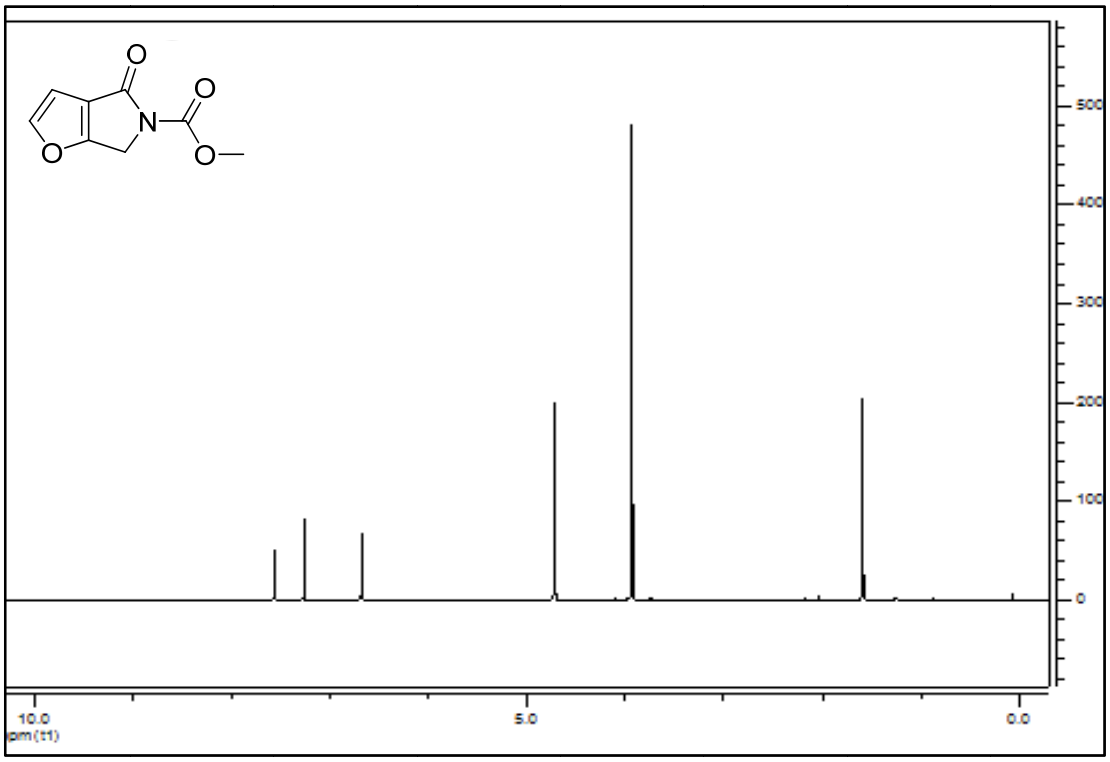


**Figure 31** $^{1}$H-NMR Spectrum of Compound **94**

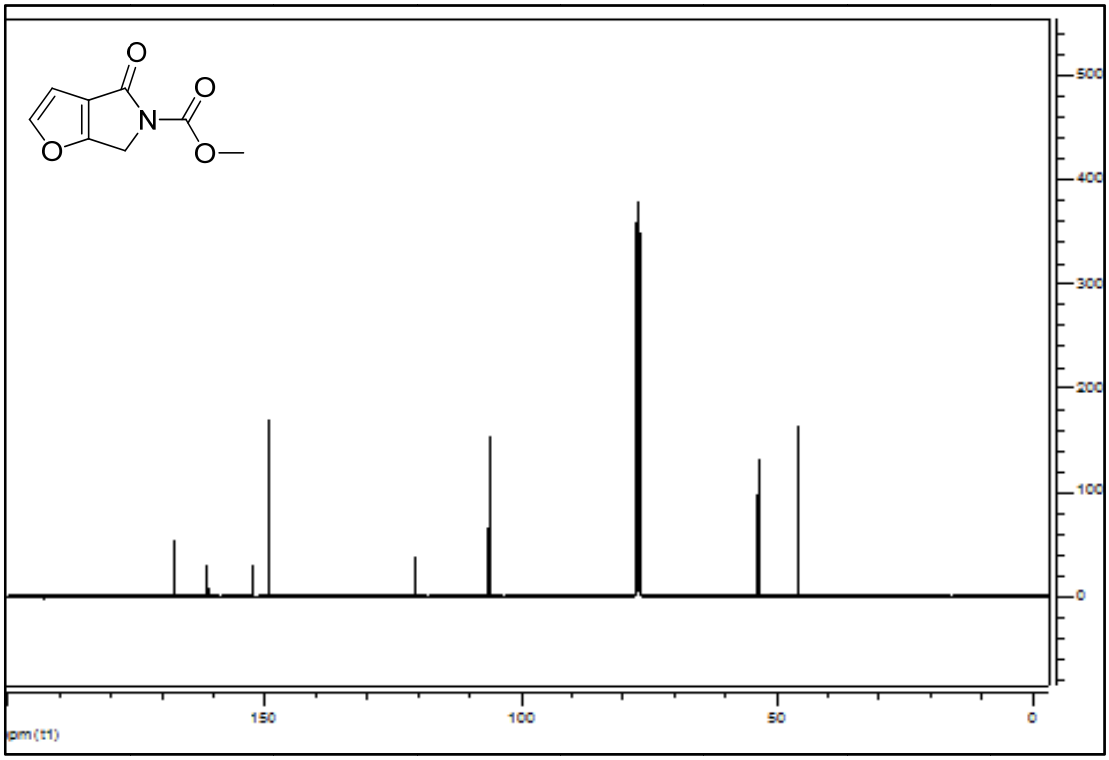


**Figure 32** $^{13}$C -NMR Spectrum of Compound **94**

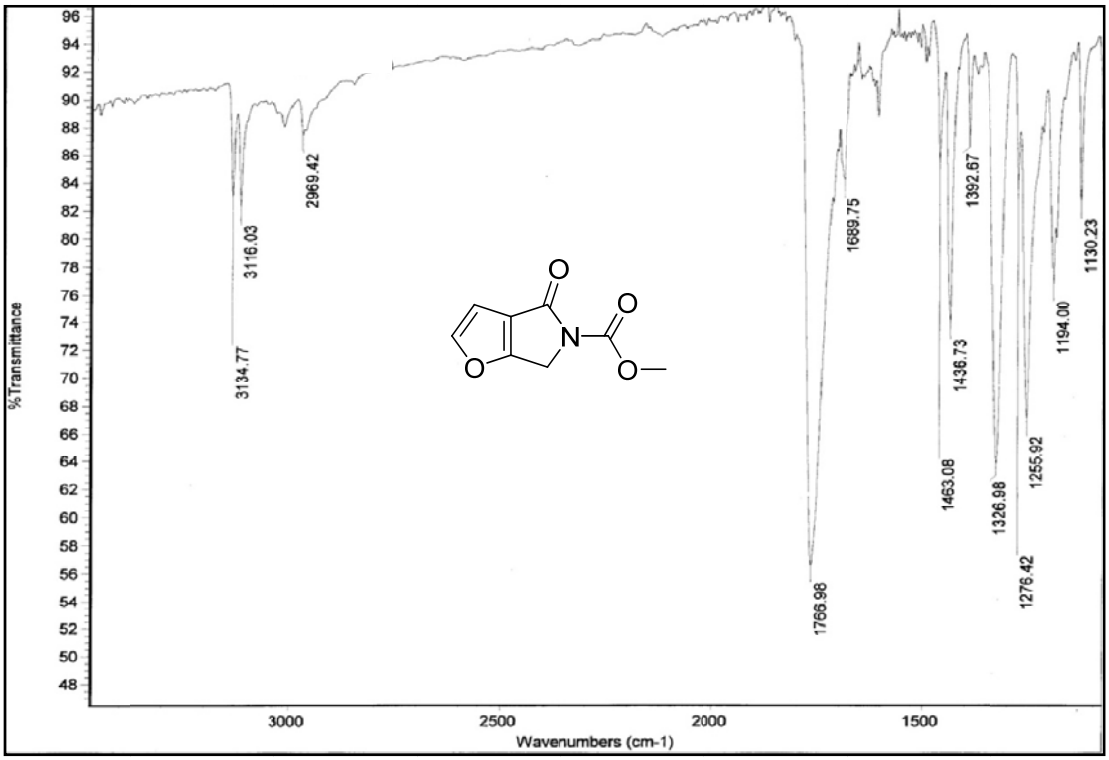


**Figure 33** IR Spectrum of Compound **94**

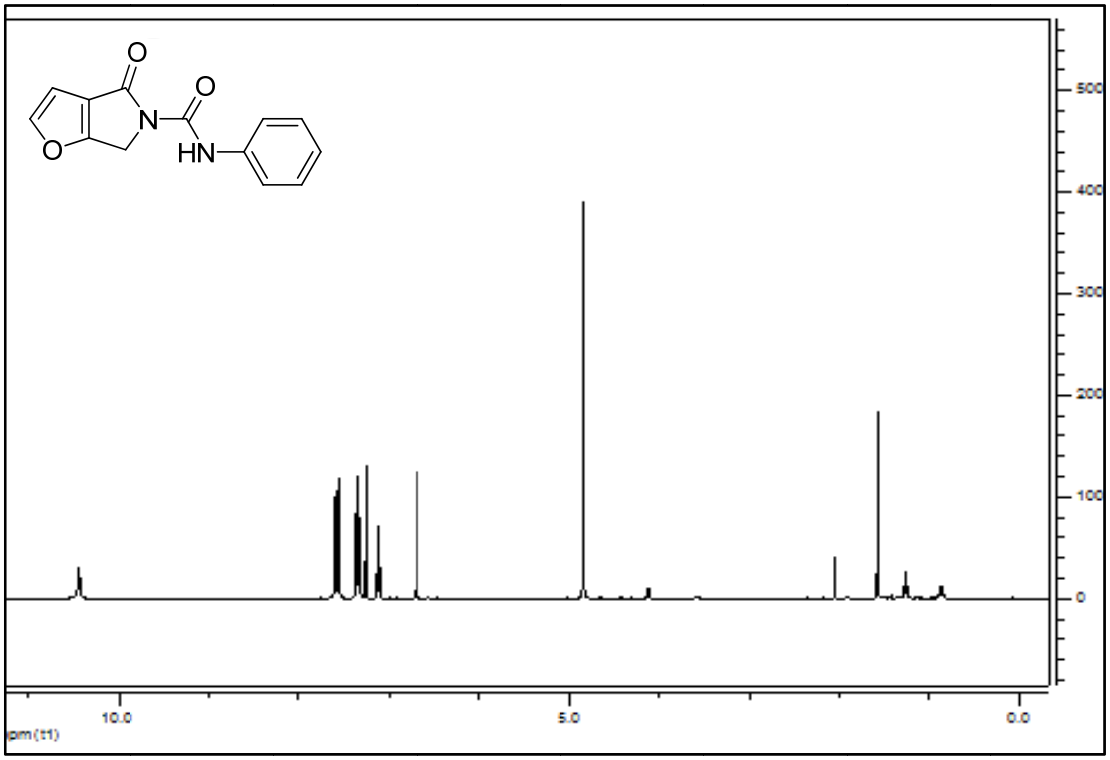


**Figure 34** $^{1}$H-NMR Spectrum of Compound **95**

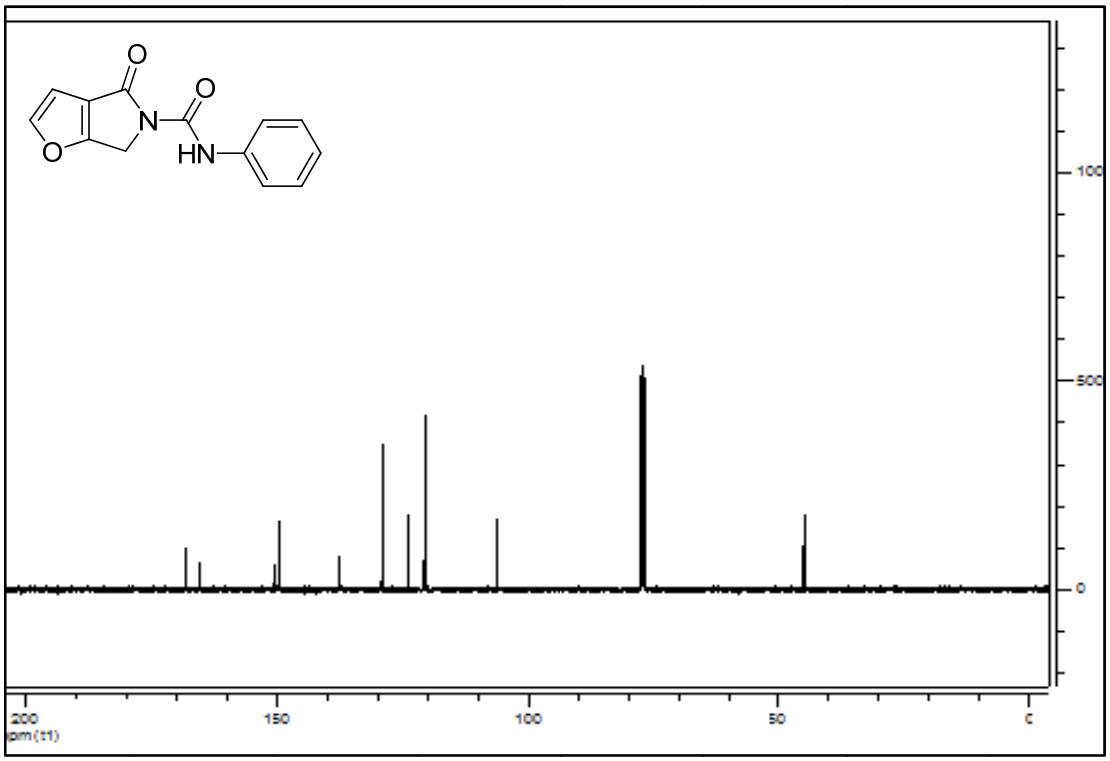


**Figure 35** $^{13}$C -NMR Spectrum of Compound **95**

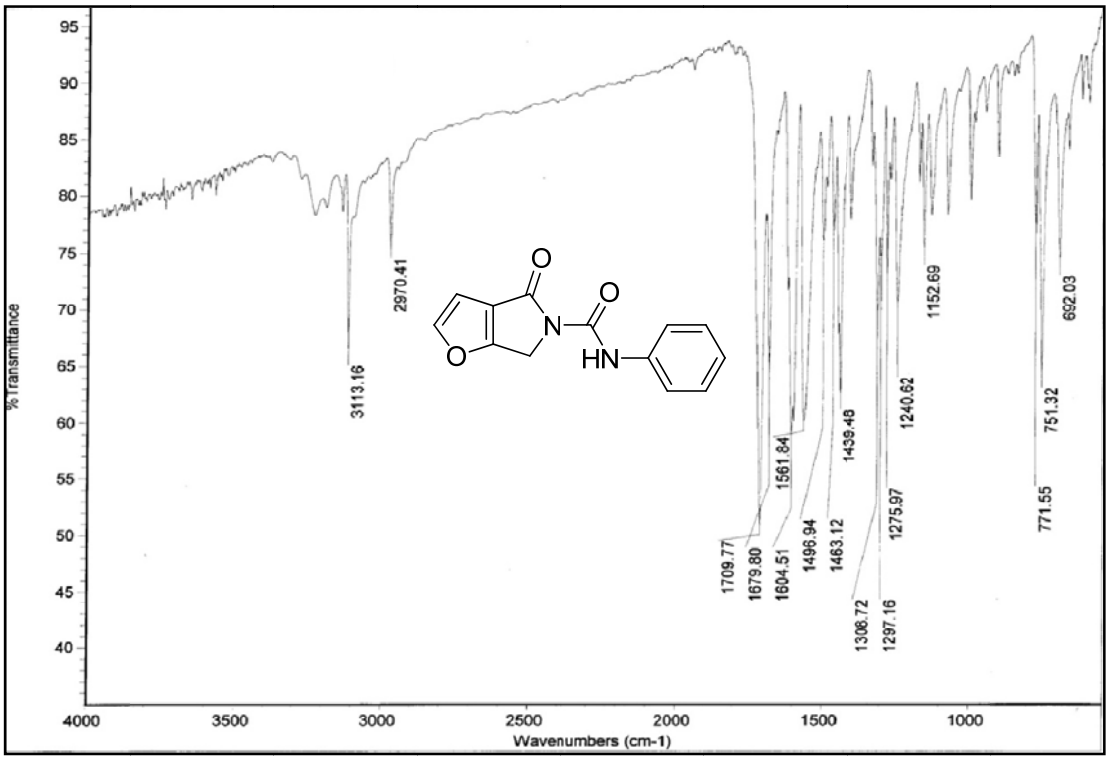


**Figure 36** IR Spectrum of Compound **95**

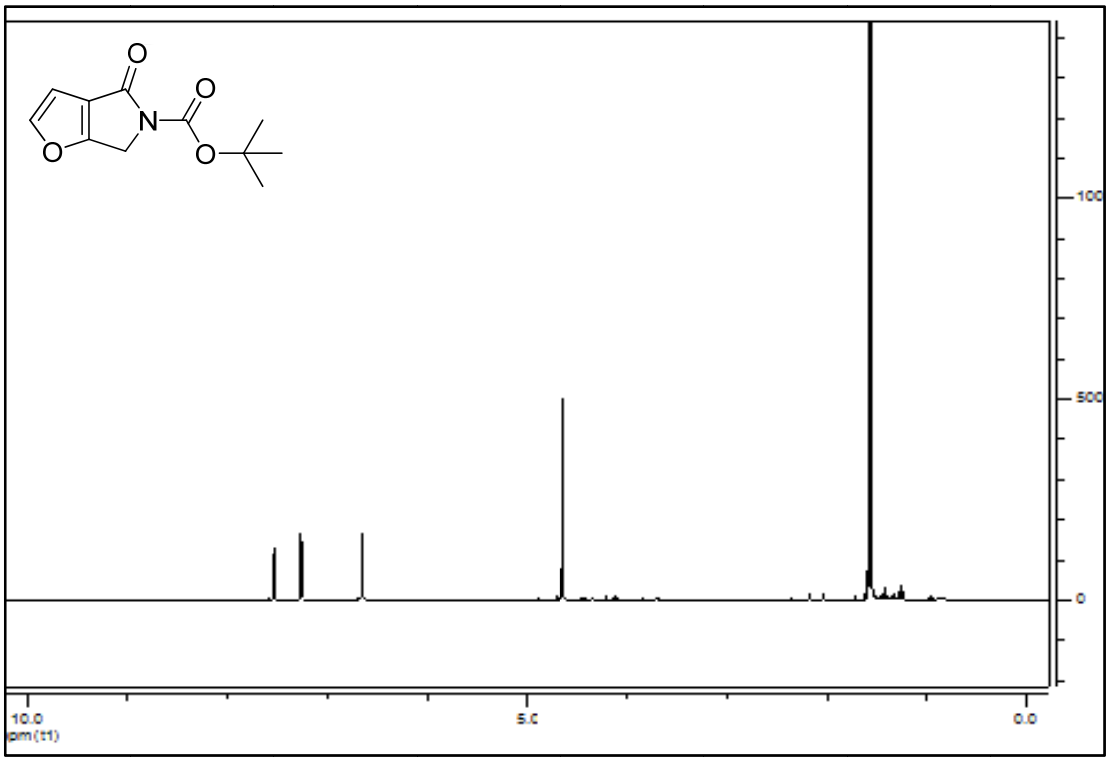

**Figure 37** $^{1}$H-NMR Spectrum of Compound **96**

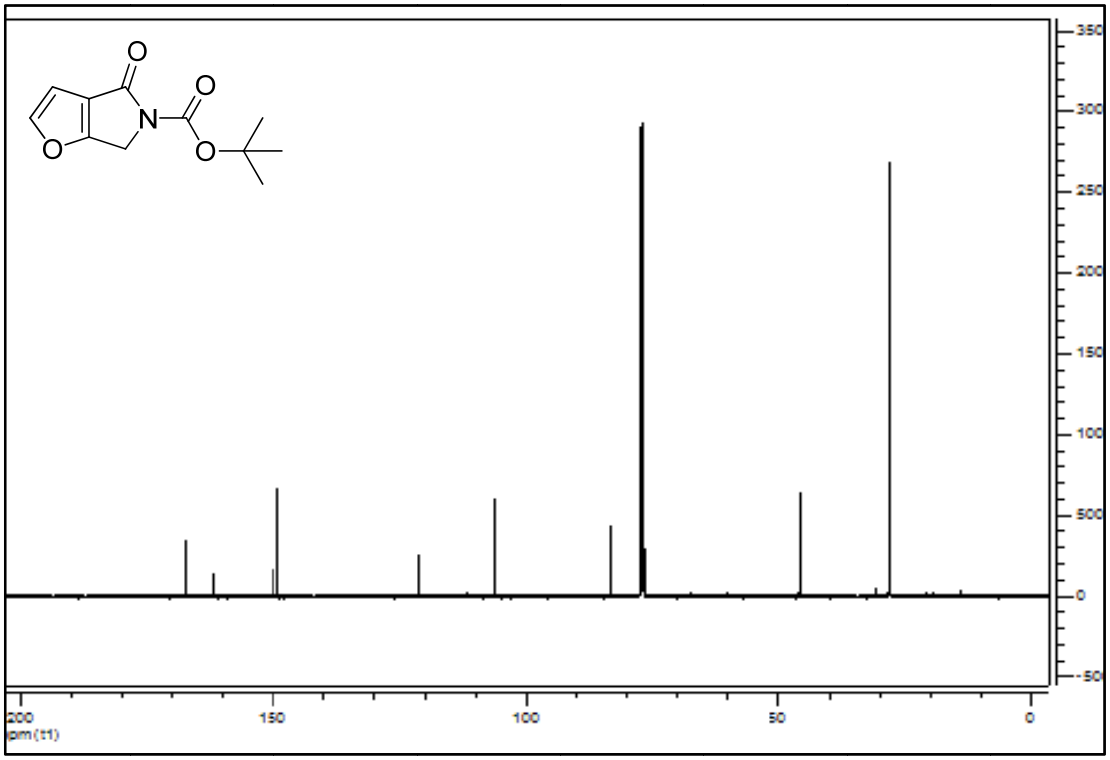


**Figure 38** $^{13}$C -NMR Spectrum of Compound **96**

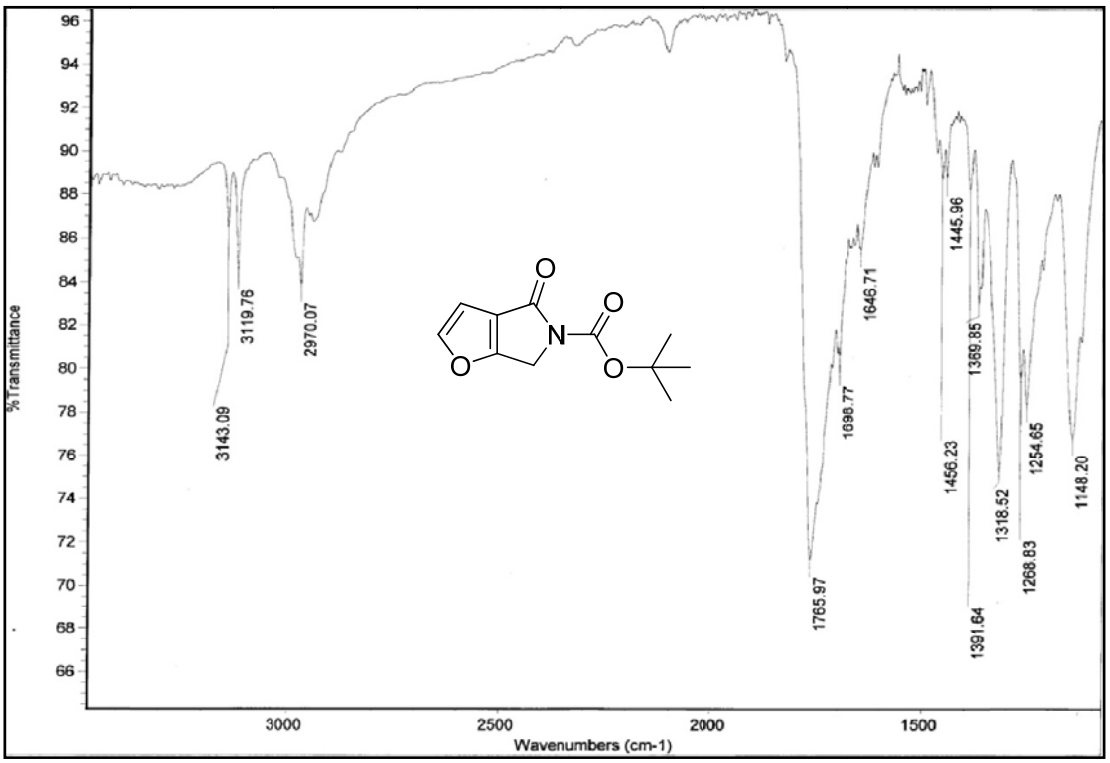


**Figure 39** IR Spectrum of Compound **96**

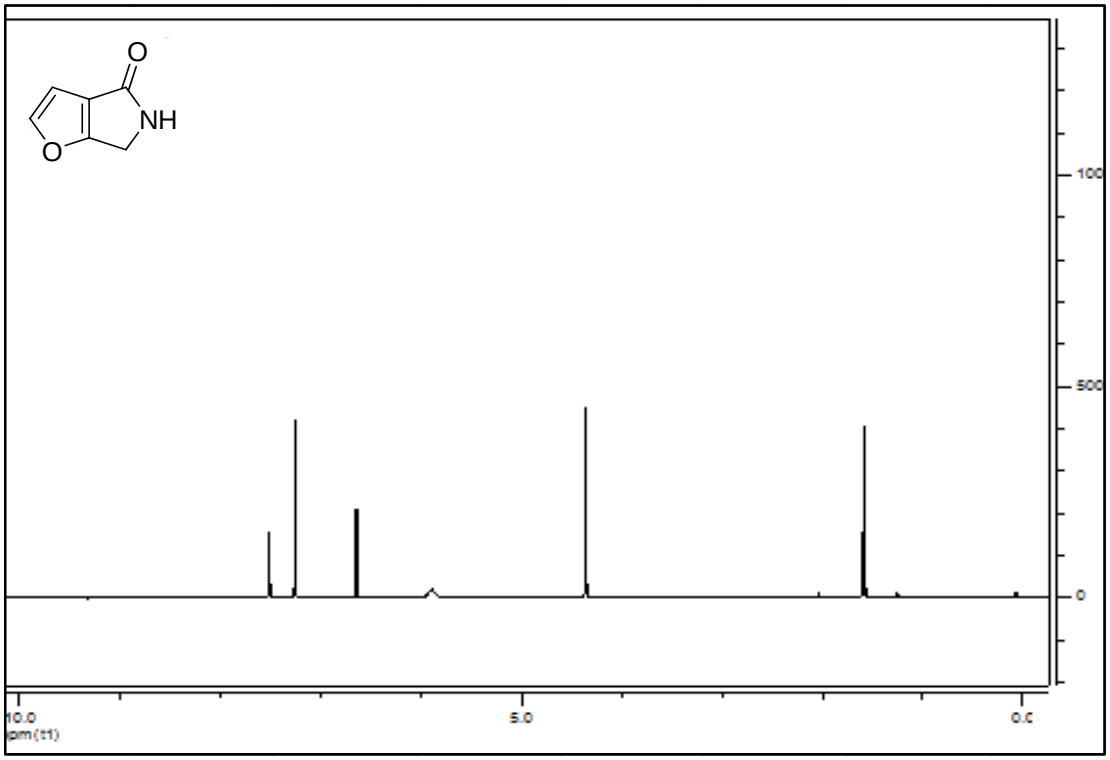


**Figure 40** $^{1}$H-NMR Spectrum of Compound **93**

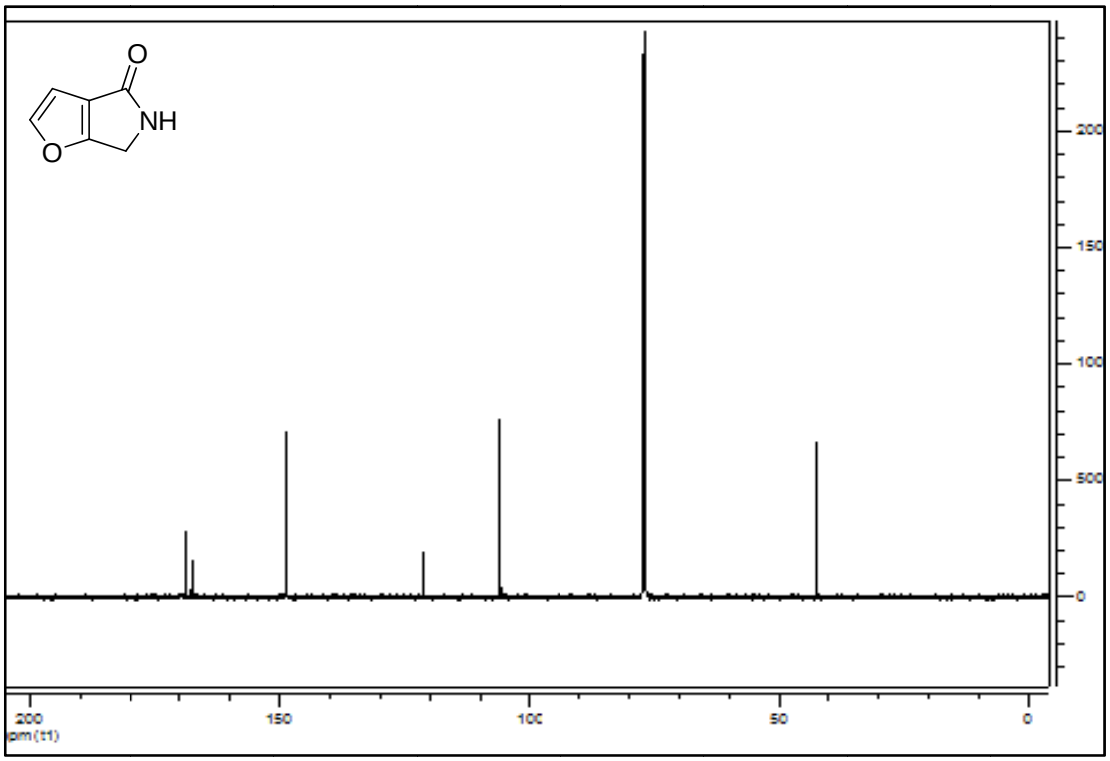


**Figure 41** $^{13}$C -NMR Spectrum of Compound **93**

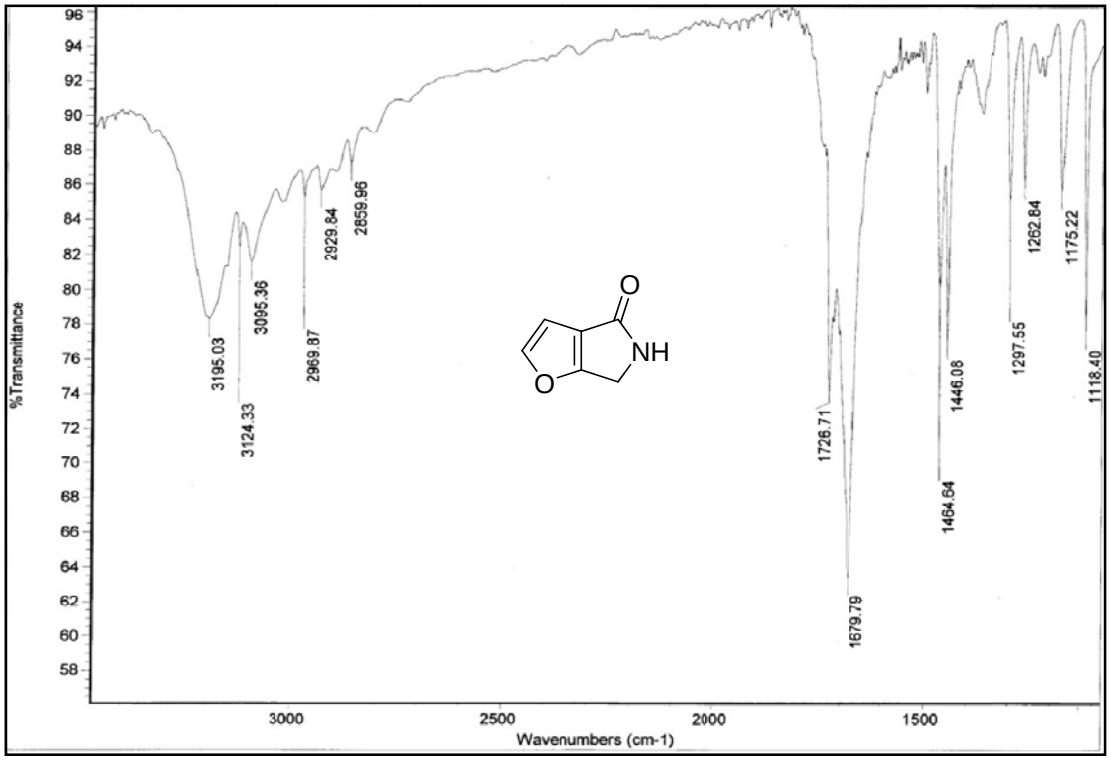


**Figure 42** IR Spectrum of Compound **93**

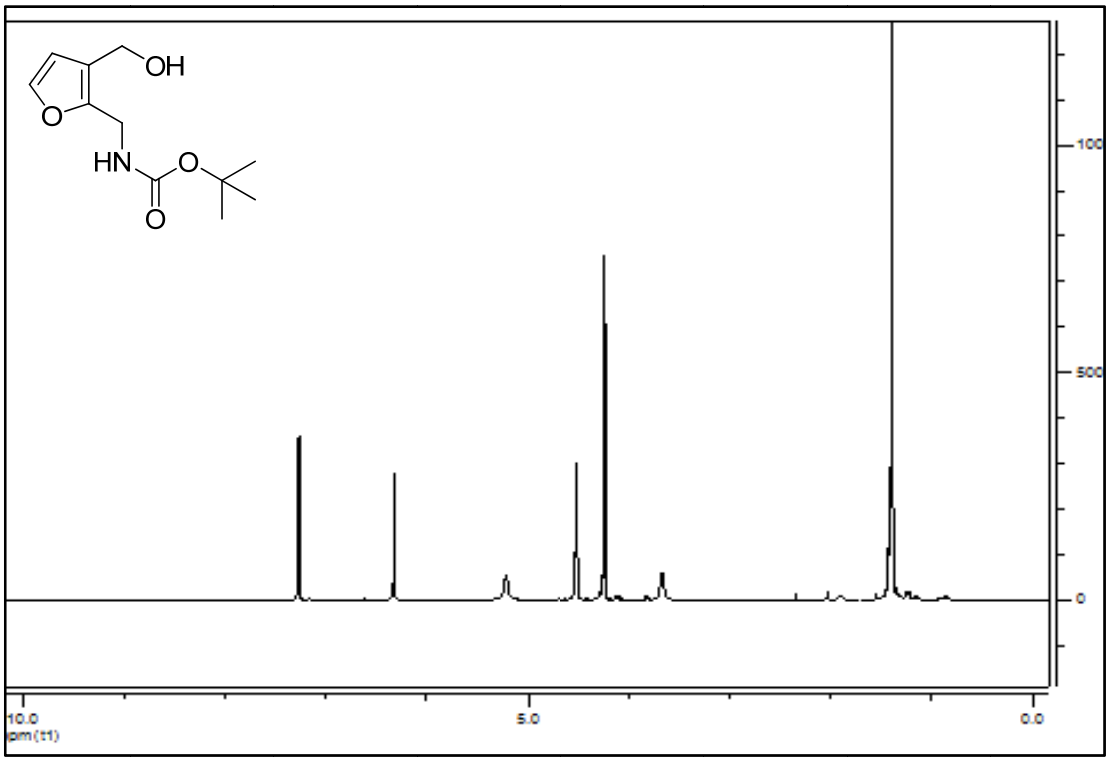


**Figure 43** $^{1}$H-NMR Spectrum of Compound **104**

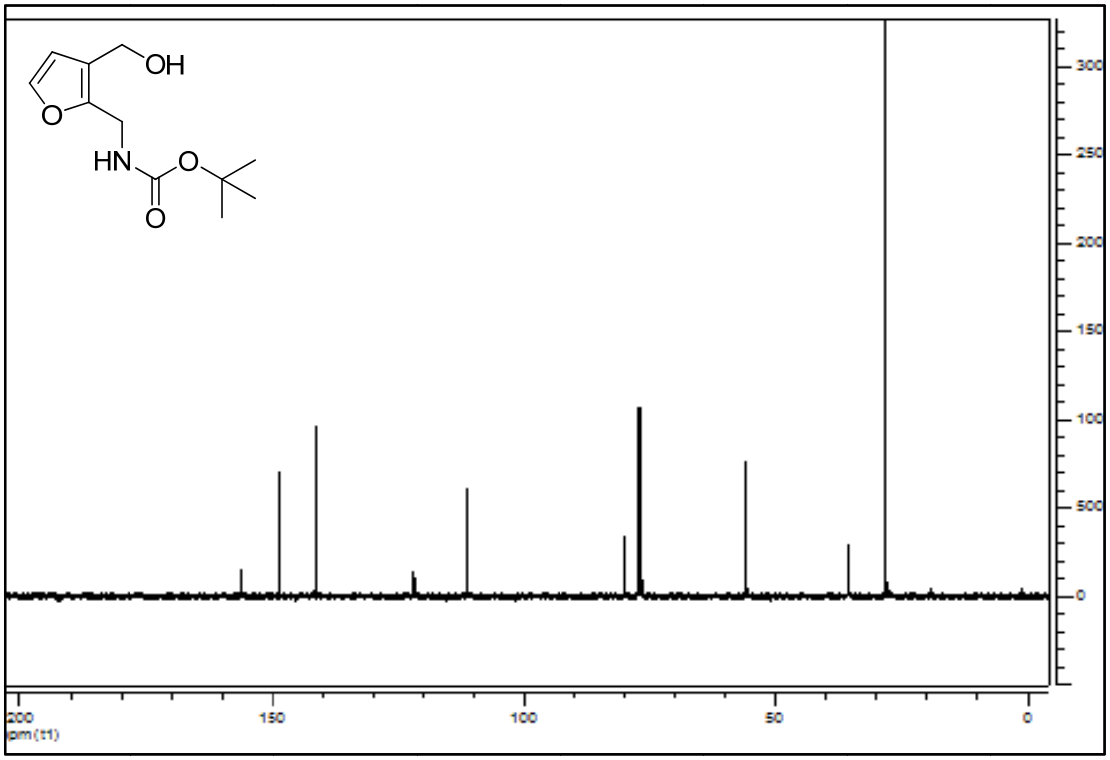


**Figure 44** $^{13}$C -NMR Spectrum of Compound **104**

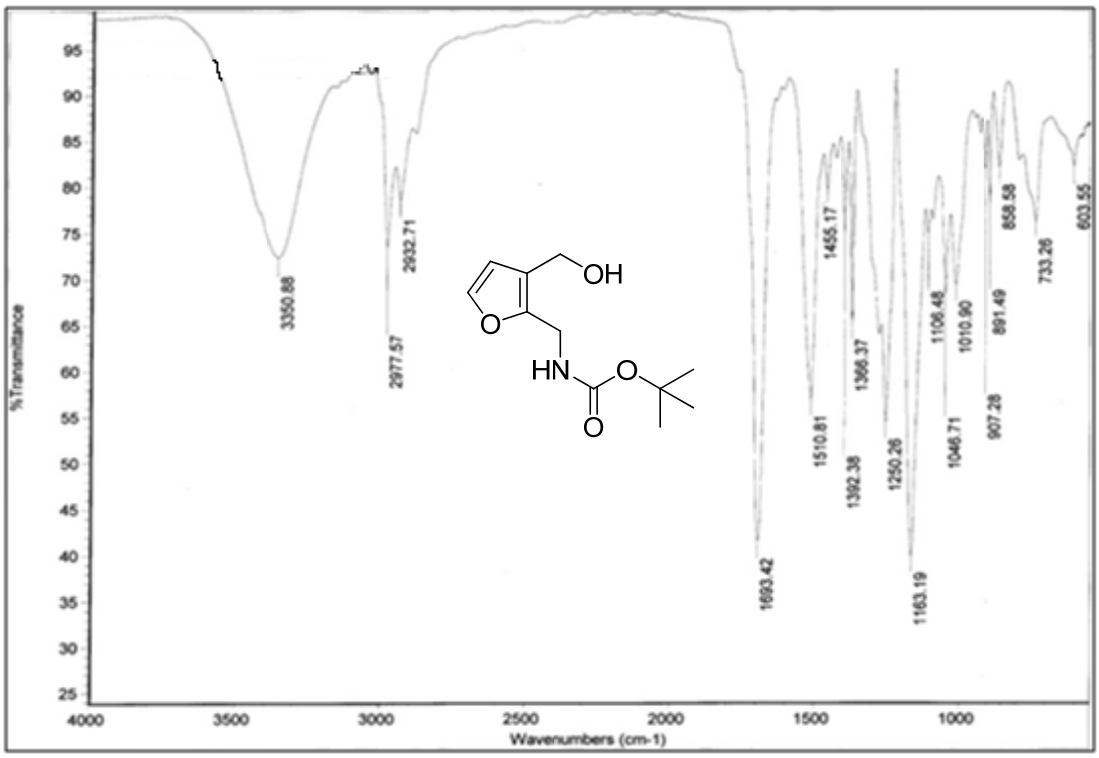


**Figure 45** IR Spectrum of Compound **104**

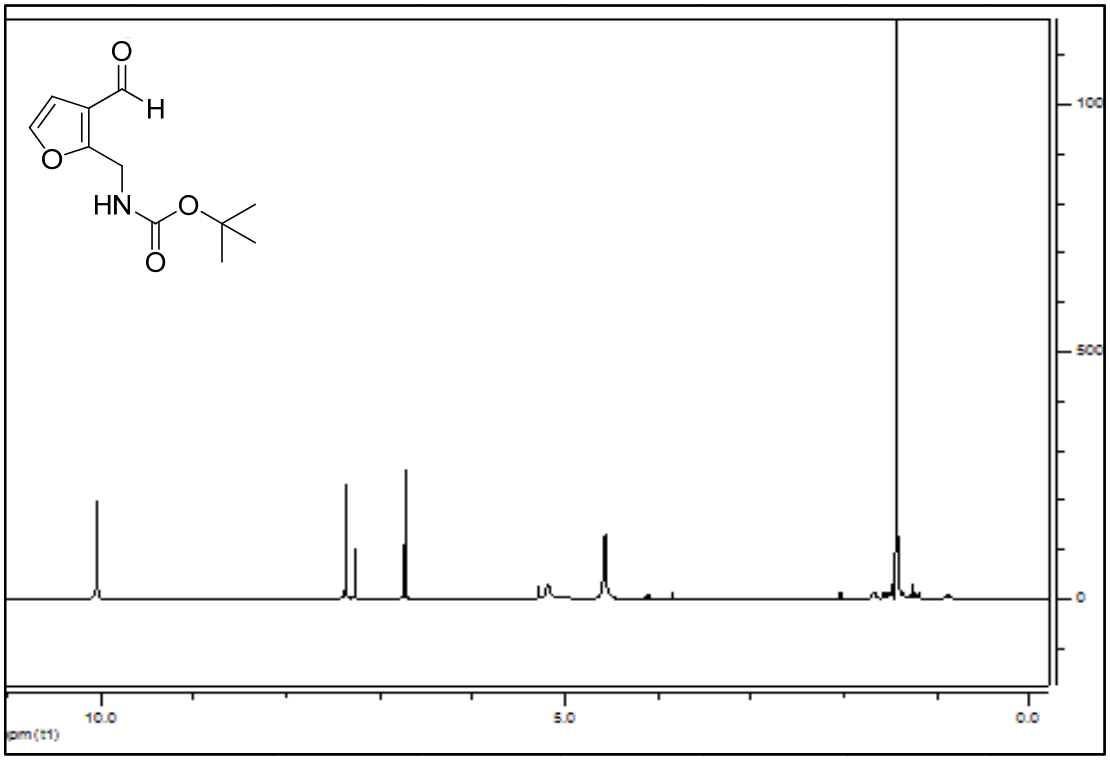


**Figure 46** $^{1}$H-NMR Spectrum of Compound **108**

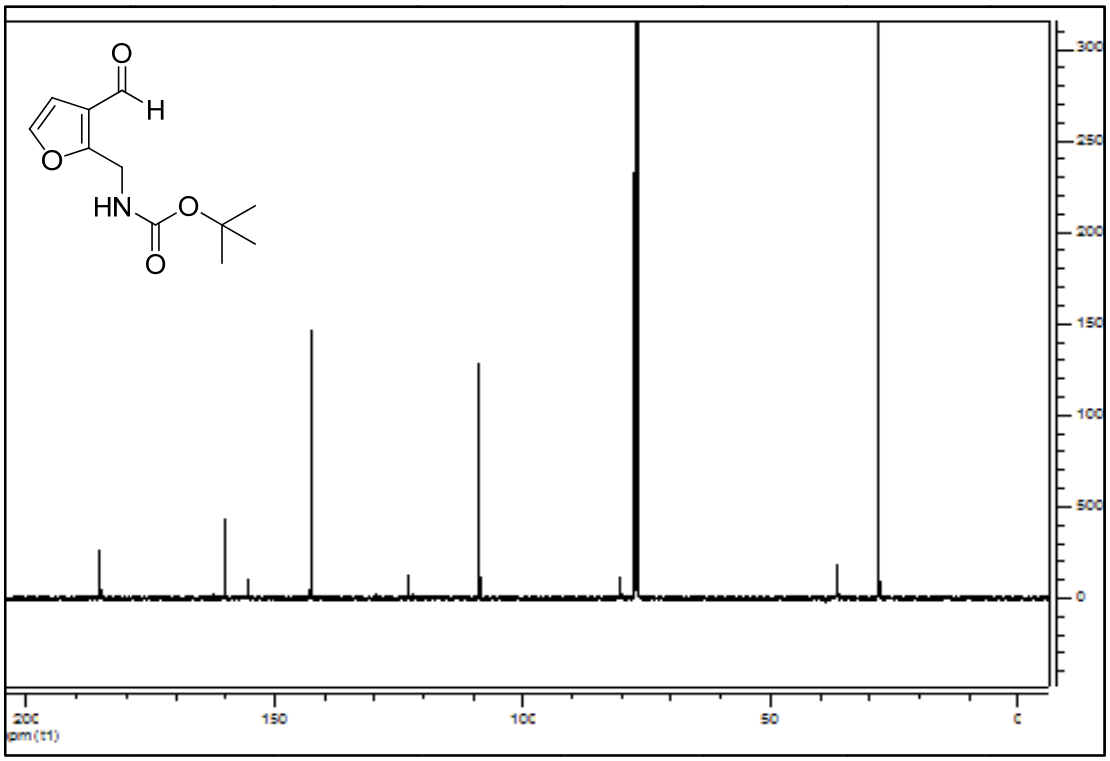


**Figure 47** $^{13}$C -NMR Spectrum of Compound **108**

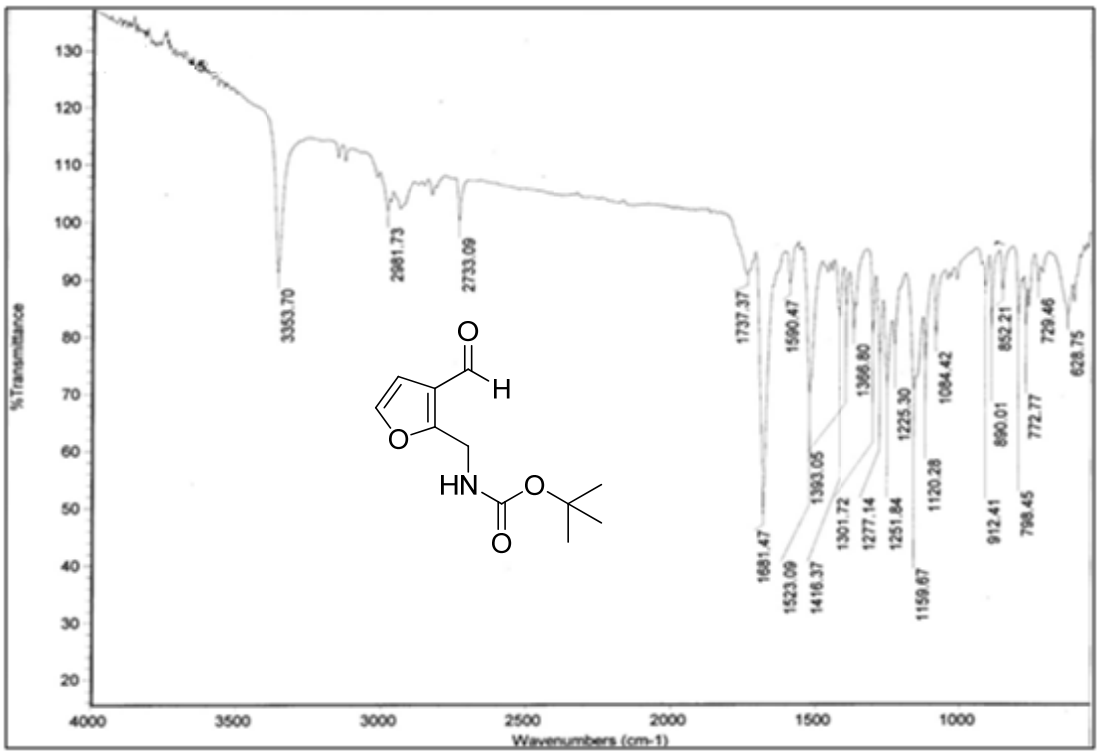


**Figure 48** IR Spectrum of Compound **108**

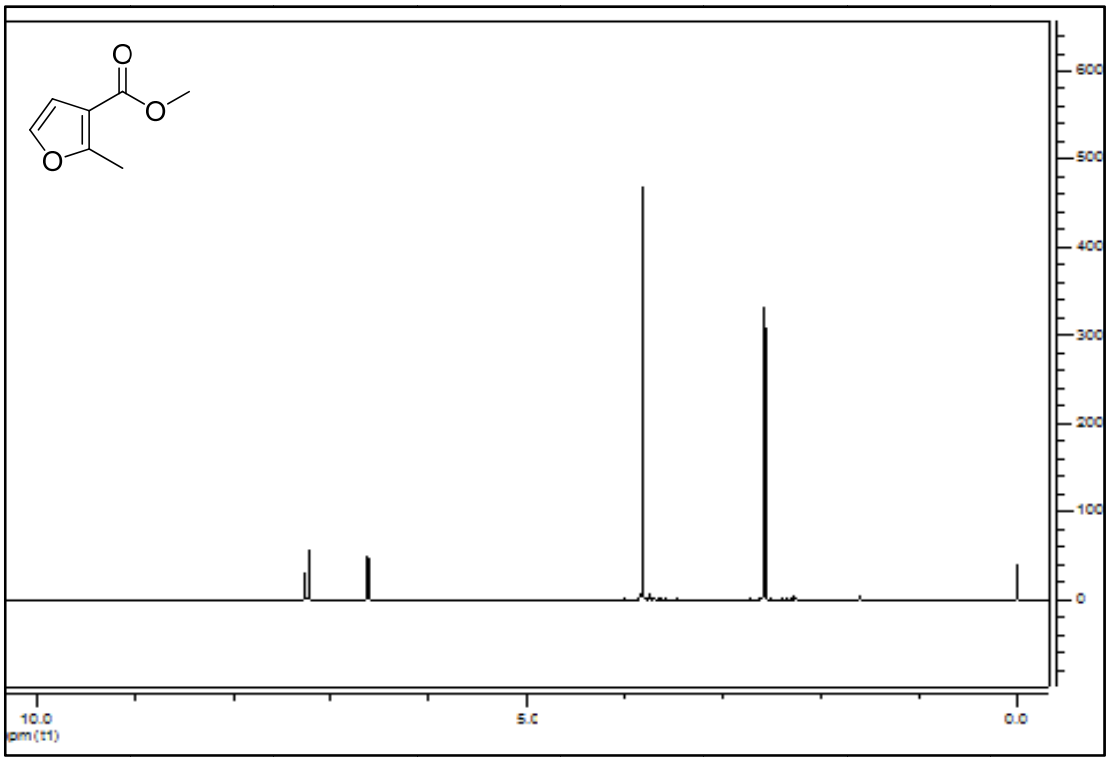


**Figure 49** $^{1}$H-NMR Spectrum of Compound **65**

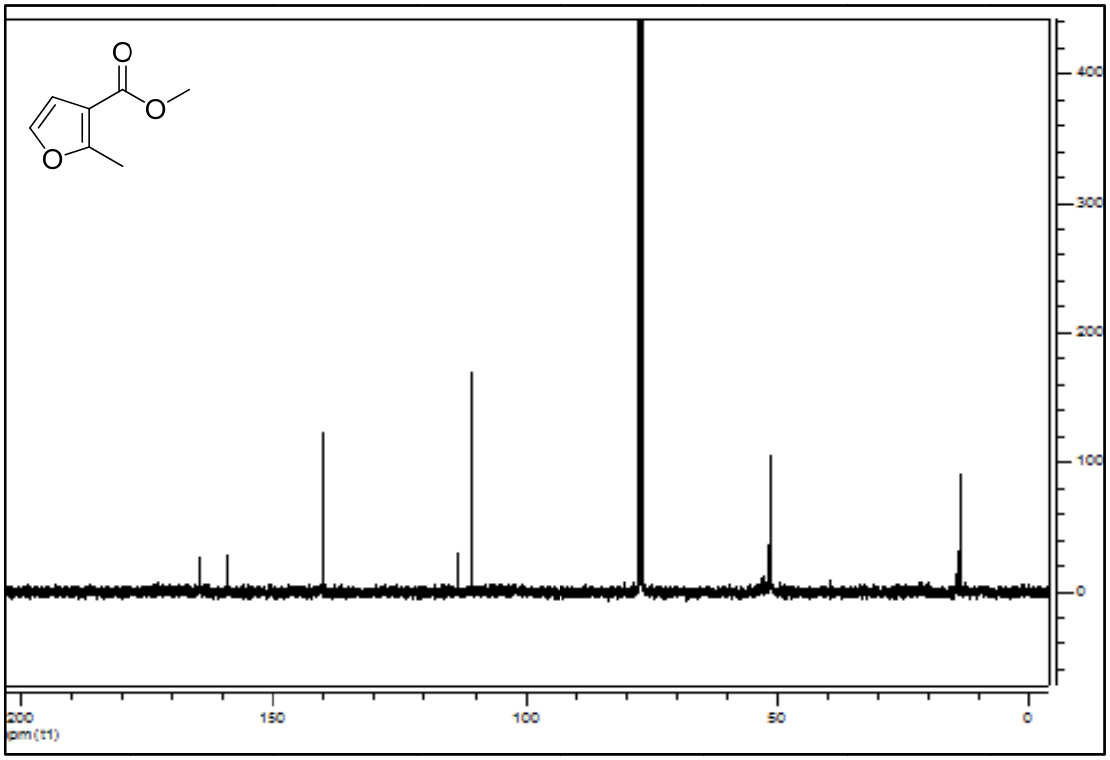


**Figure 50** $^{13}$C -NMR Spectrum of Compound **65**

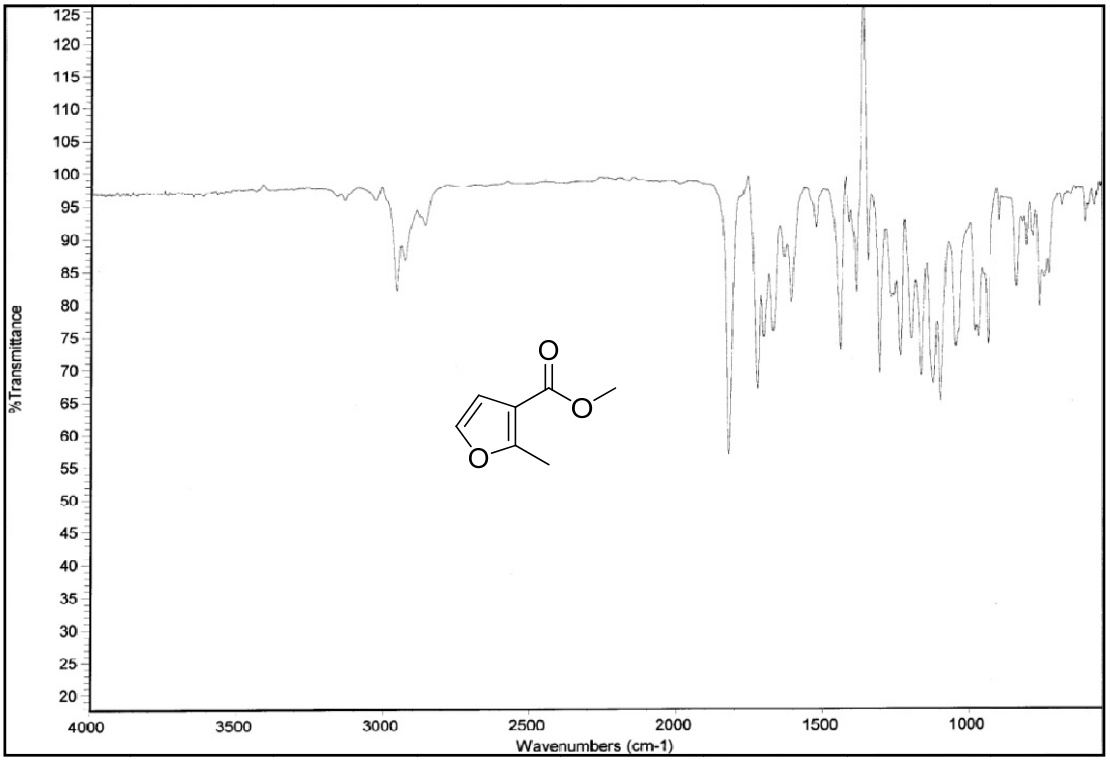


**Figure 51** IR Spectrum of Compound **65**

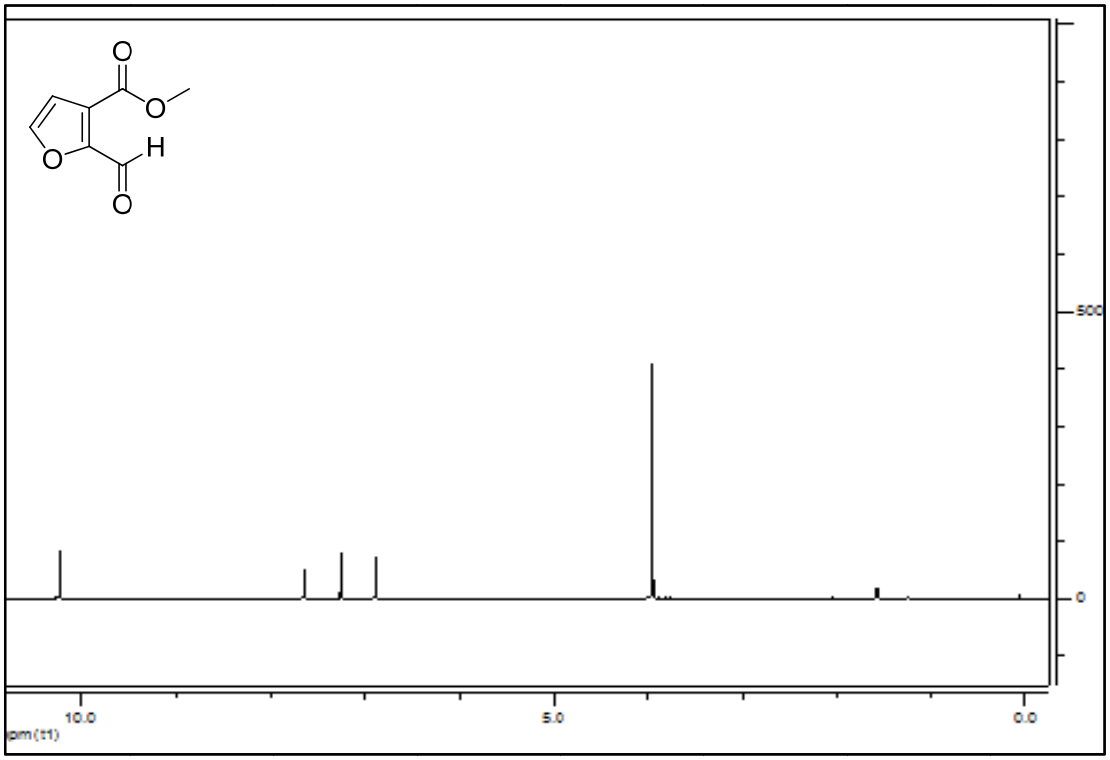


**Figure 52** $^{1}$H-NMR Spectrum of Compound **66**

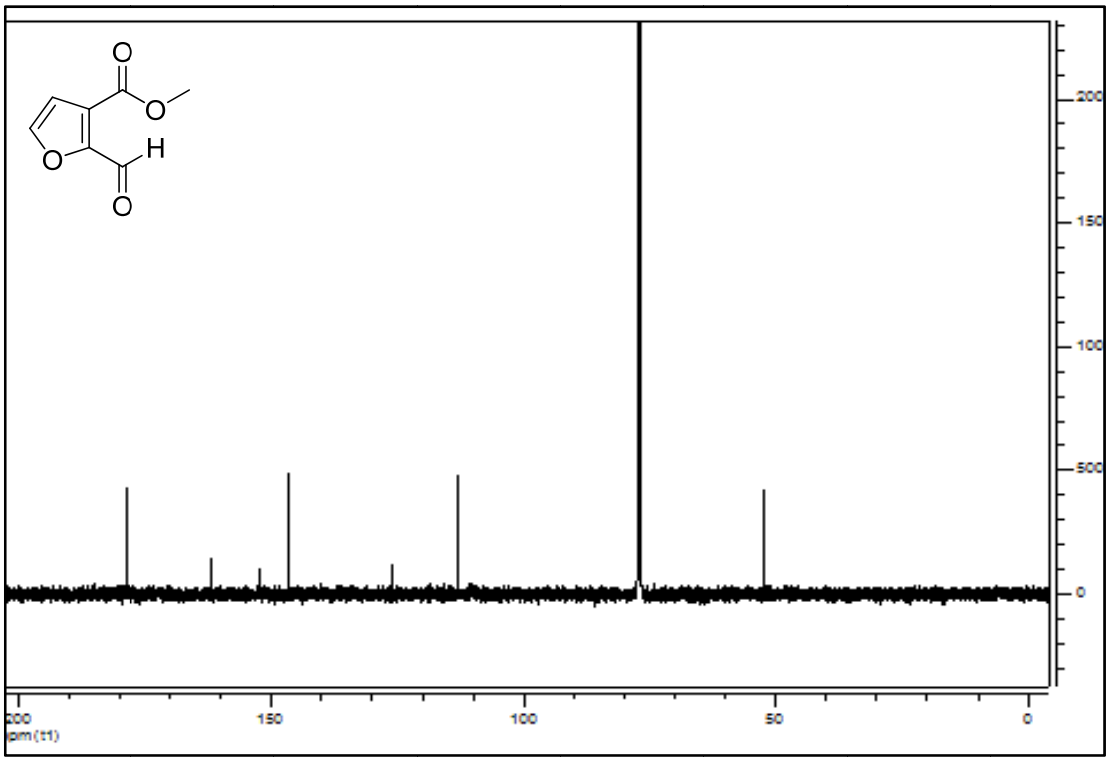


**Figure 53** $^{13}$C -NMR Spectrum of Compound **66**

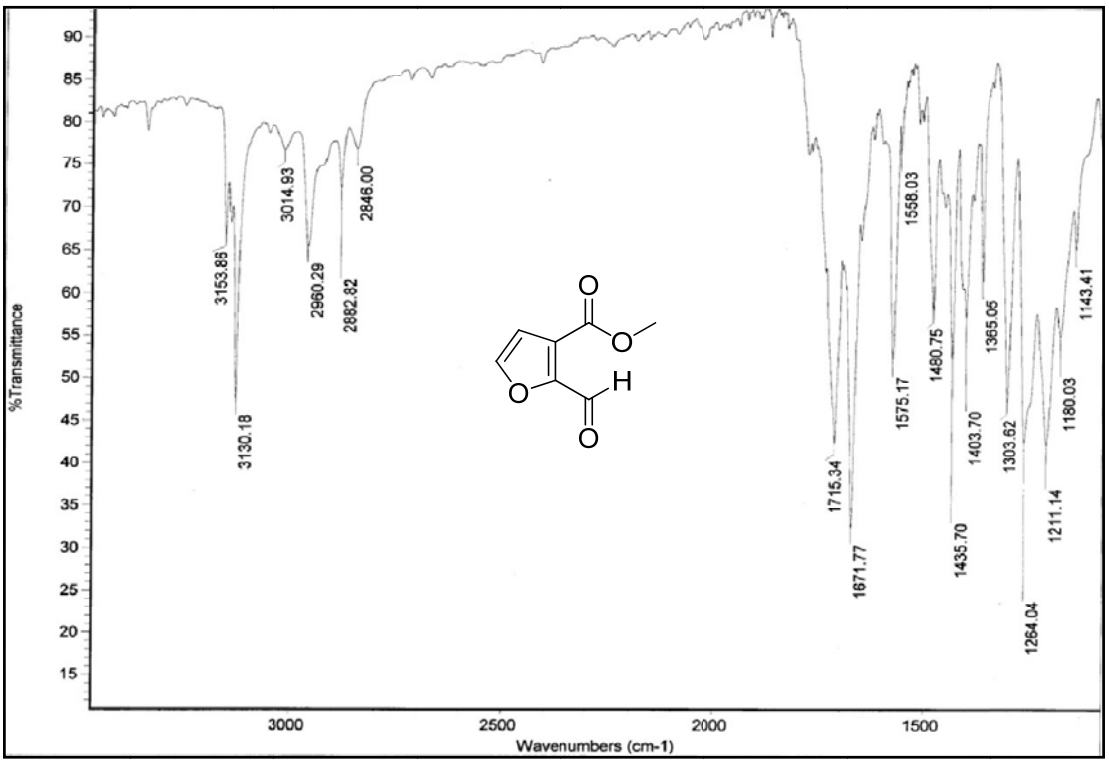


**Figure 54** IR Spectrum of Compound **66**

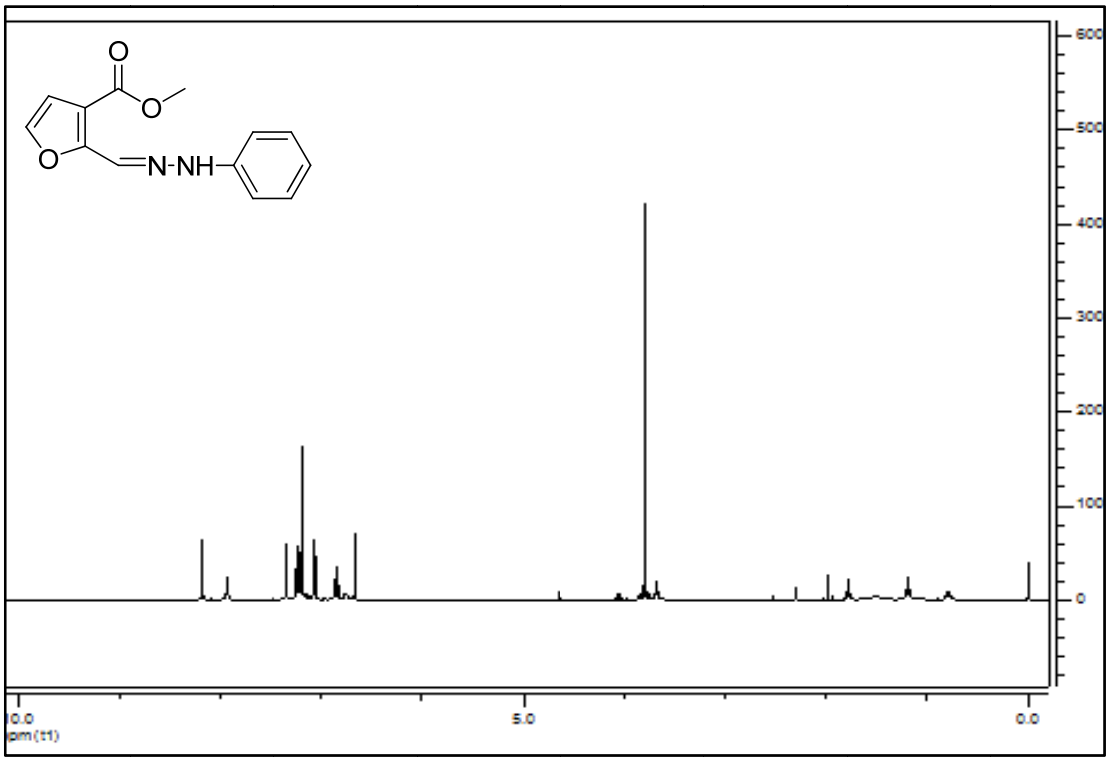


**Figure 55** $^{1}$H-NMR Spectrum of Compound **117**

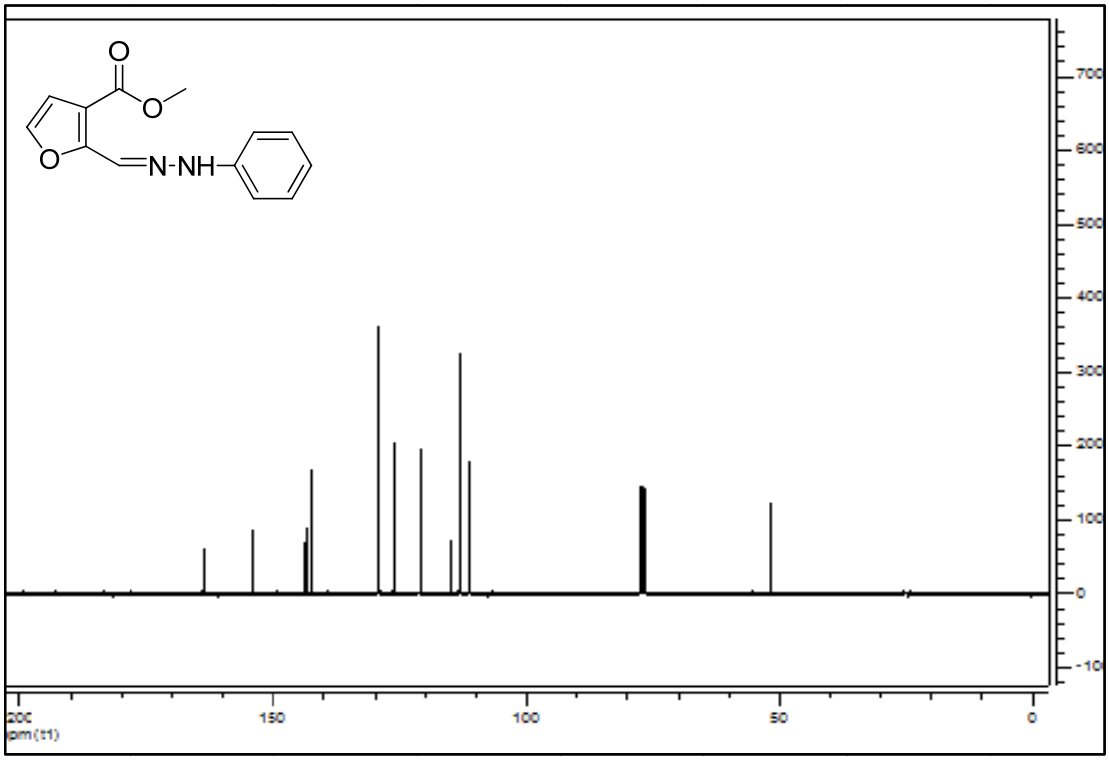


**Figure 56** $^{13}$C -NMR Spectrum of Compound **117**

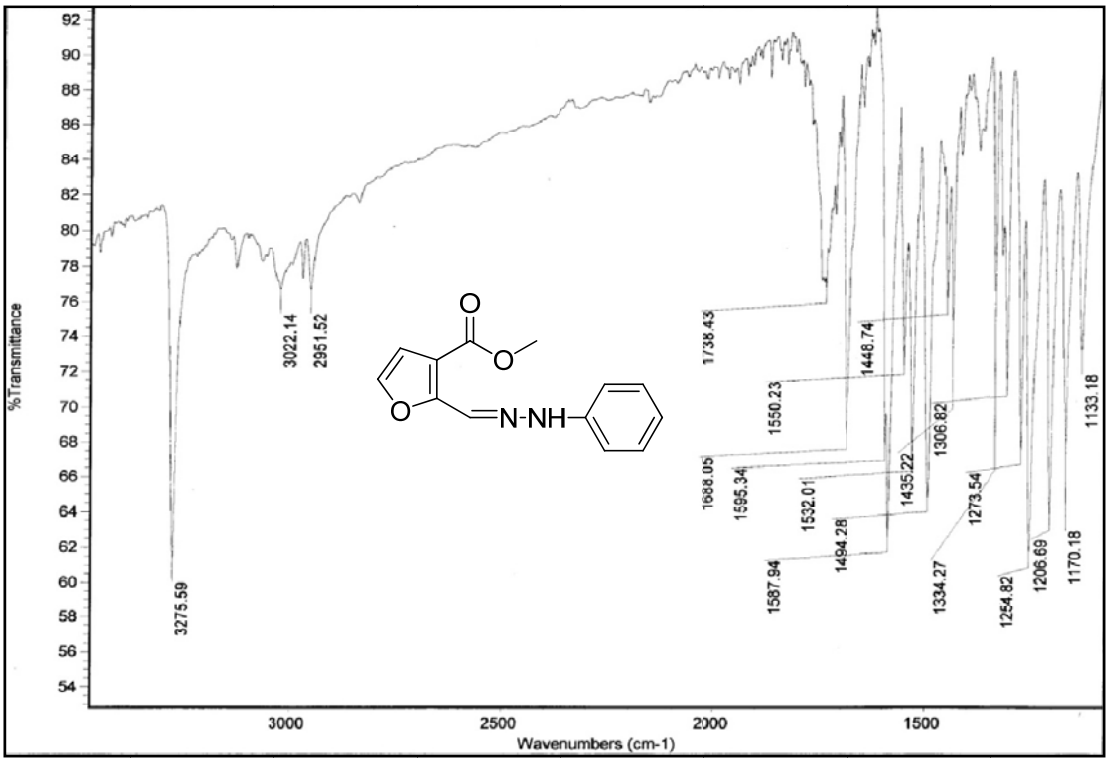


**Figure 57** IR Spectrum of Compound **117**

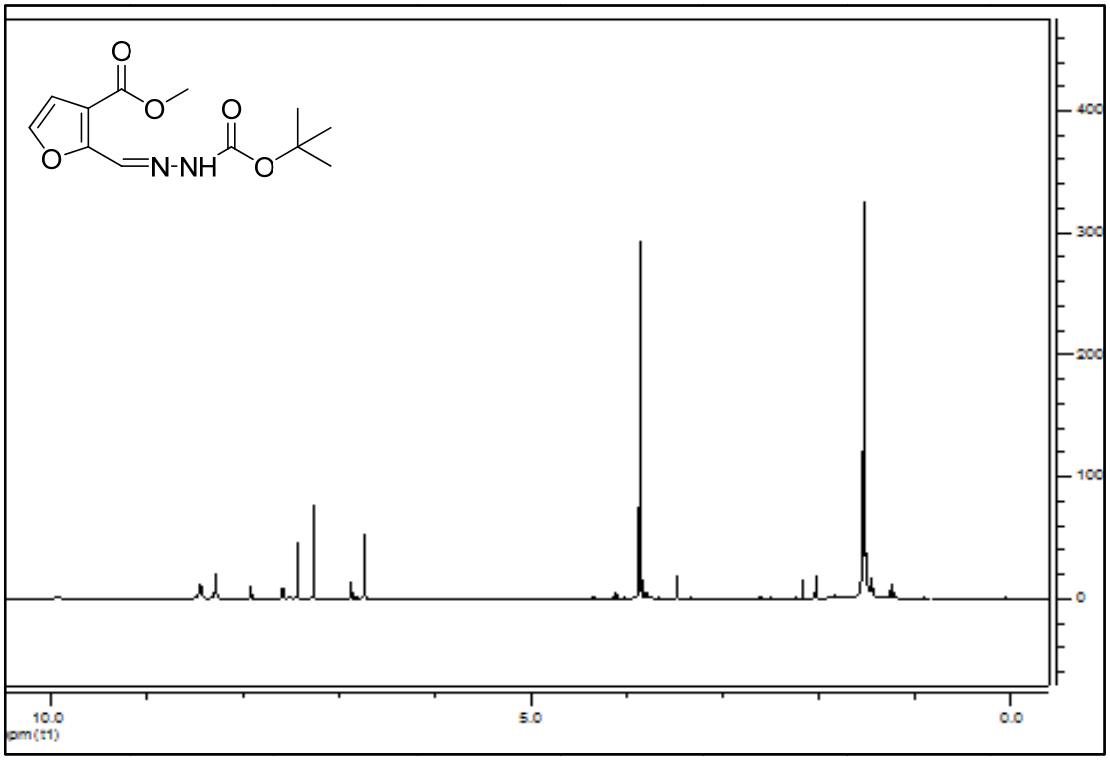


**Figure 58** $^{1}$H-NMR Spectrum of Compound **118**

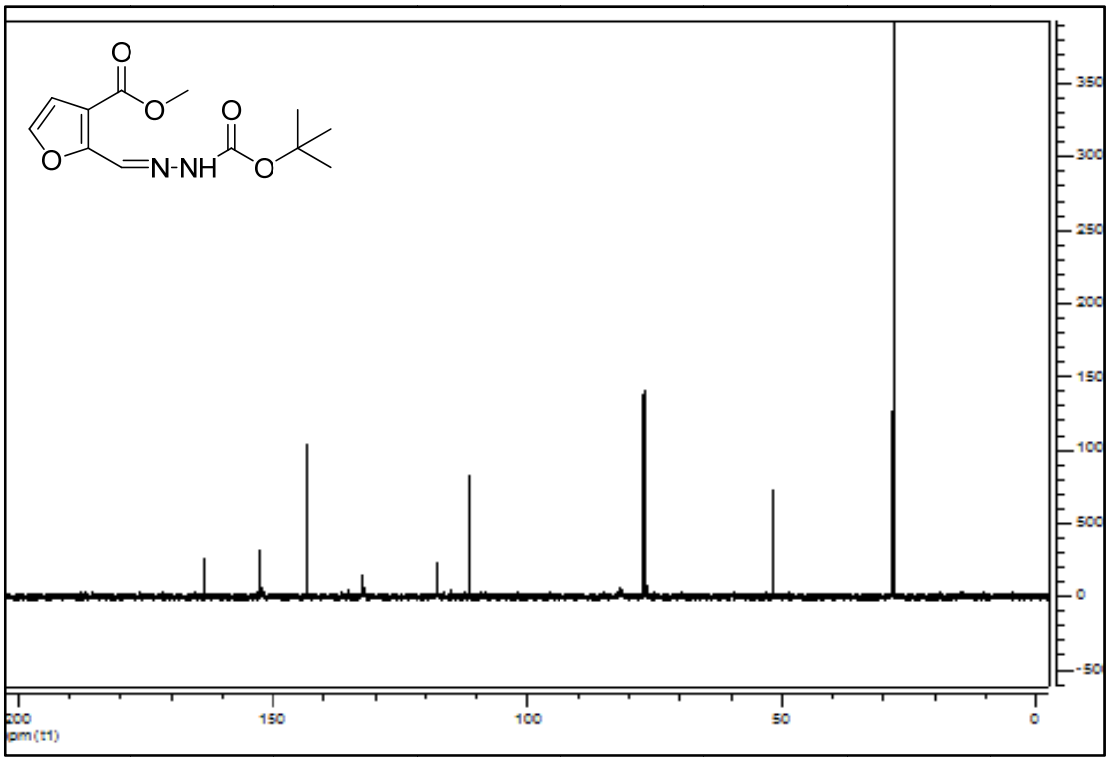


**Figure 59** $^{13}$C -NMR Spectrum of Compound **118**

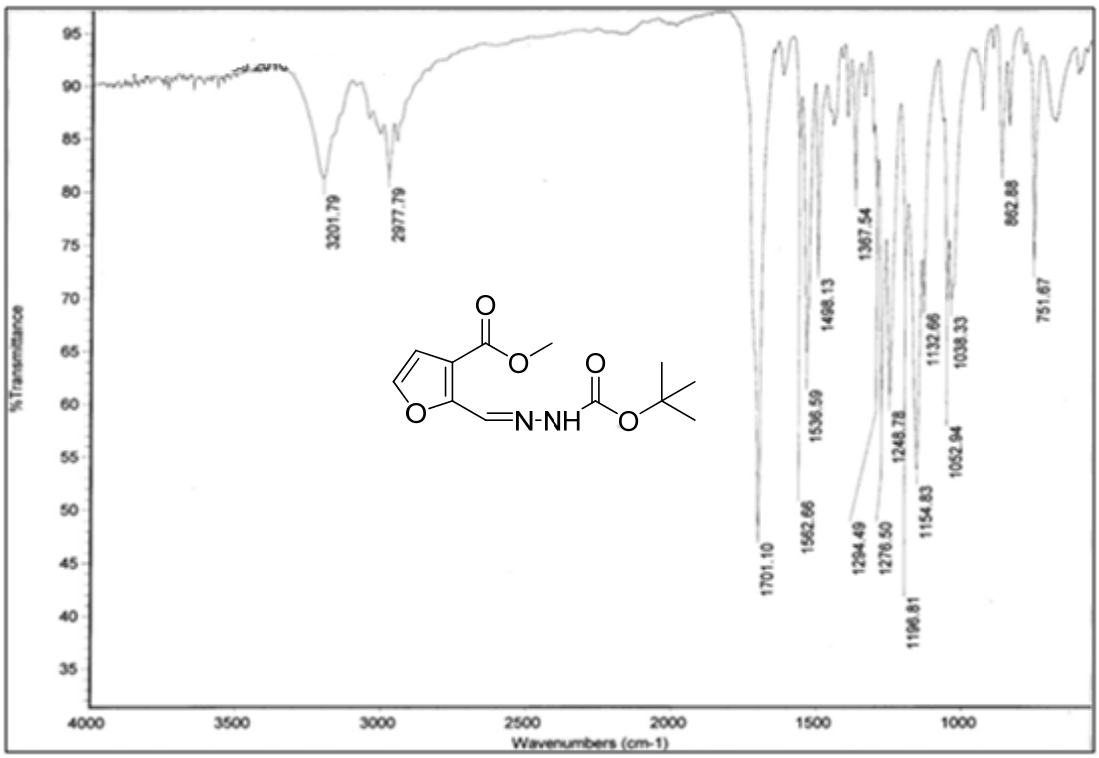


**Figure 60** IR Spectrum of Compound **118**

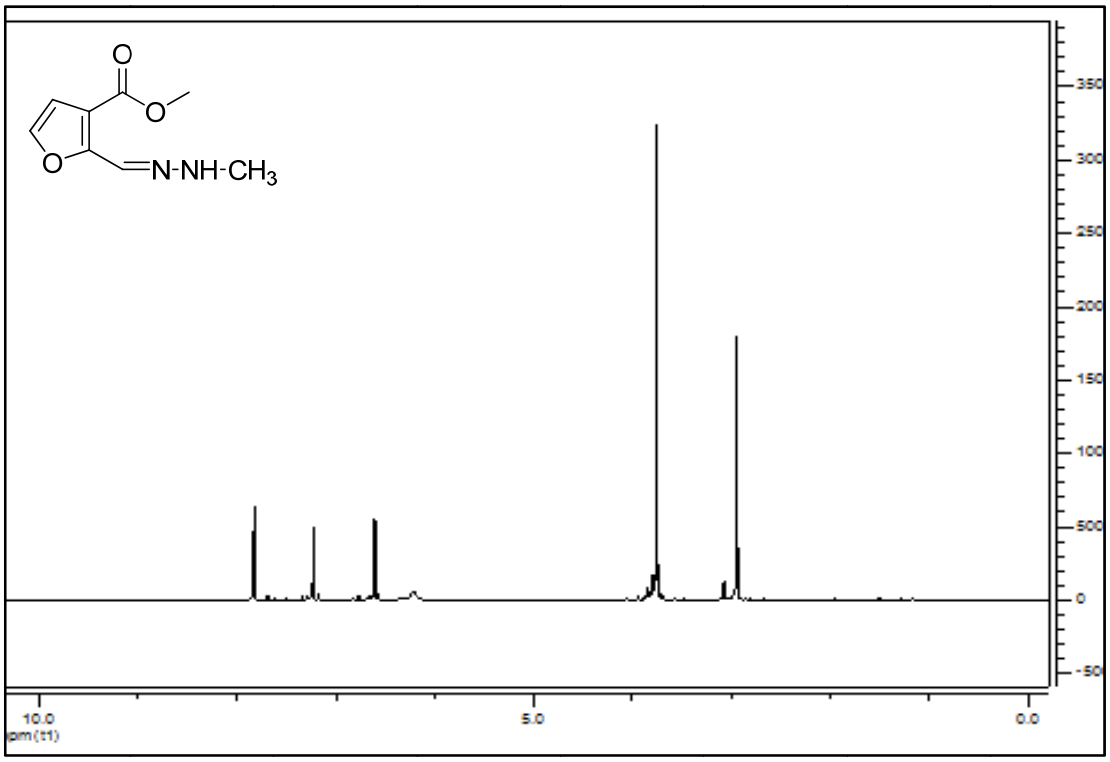


**Figure 61** $^{1}$H-NMR Spectrum of Compound **119**

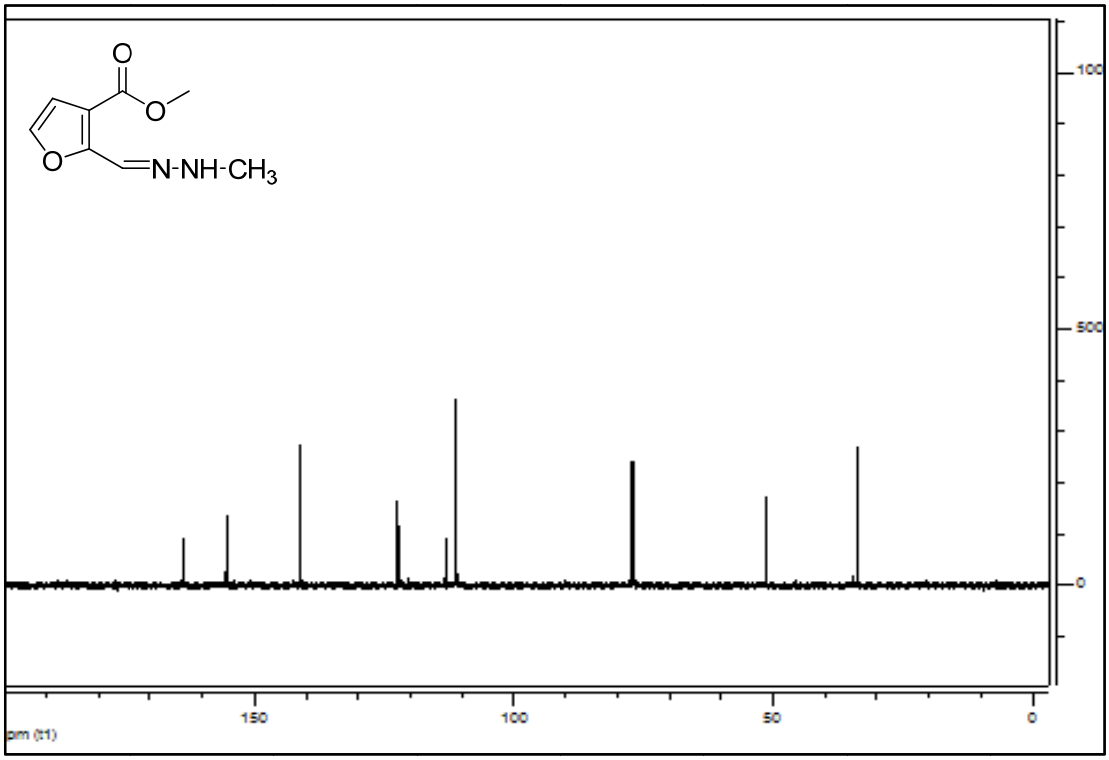


**Figure 62** $^{13}$C -NMR Spectrum of Compound **119**

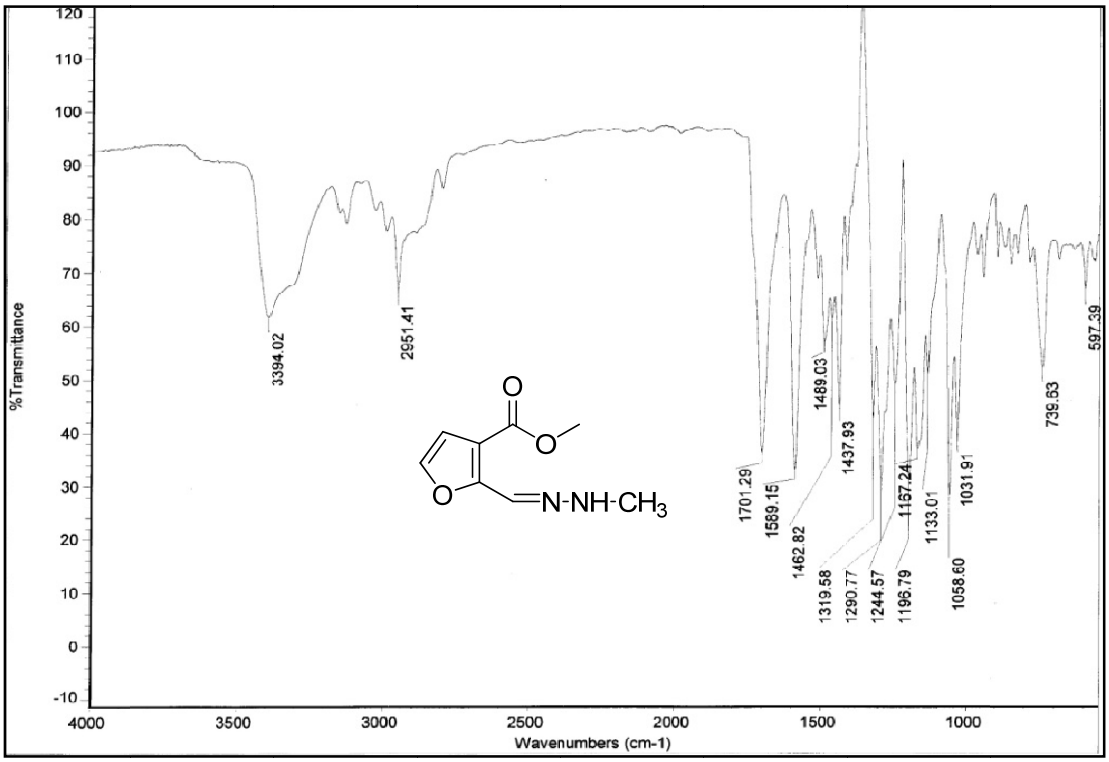


**Figure 63** IR Spectrum of Compound **119**

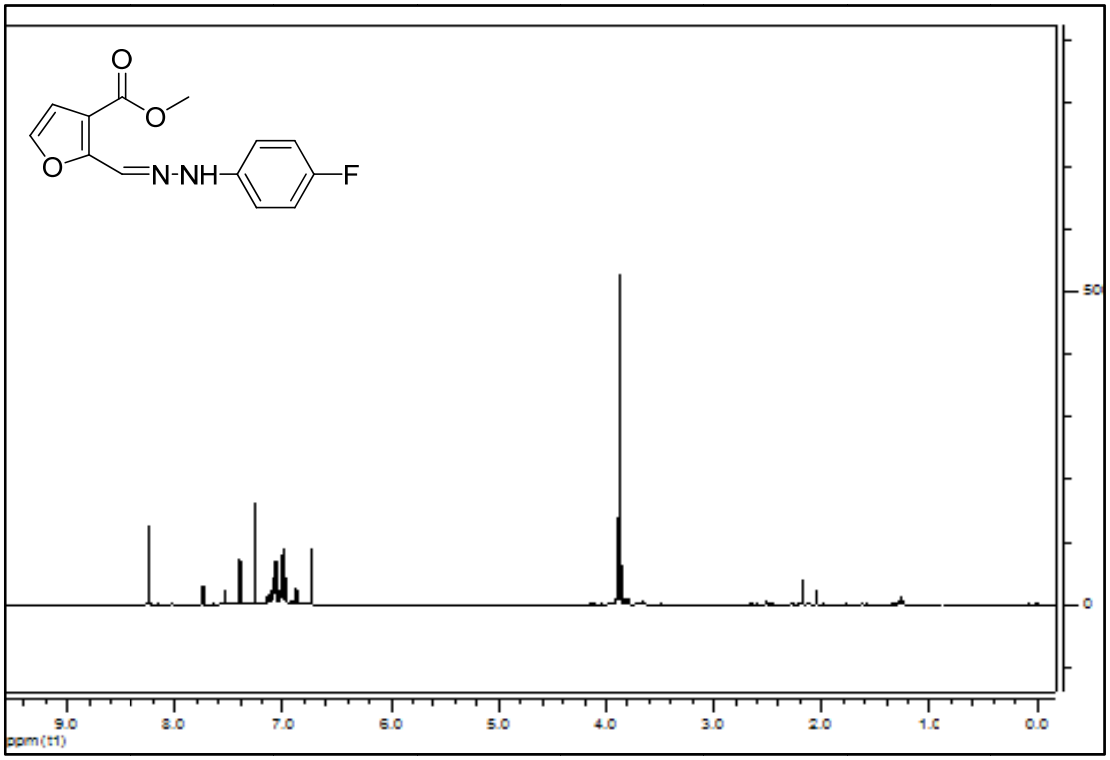


**Figure 64** $^{1}$H-NMR Spectrum of Compound **120**

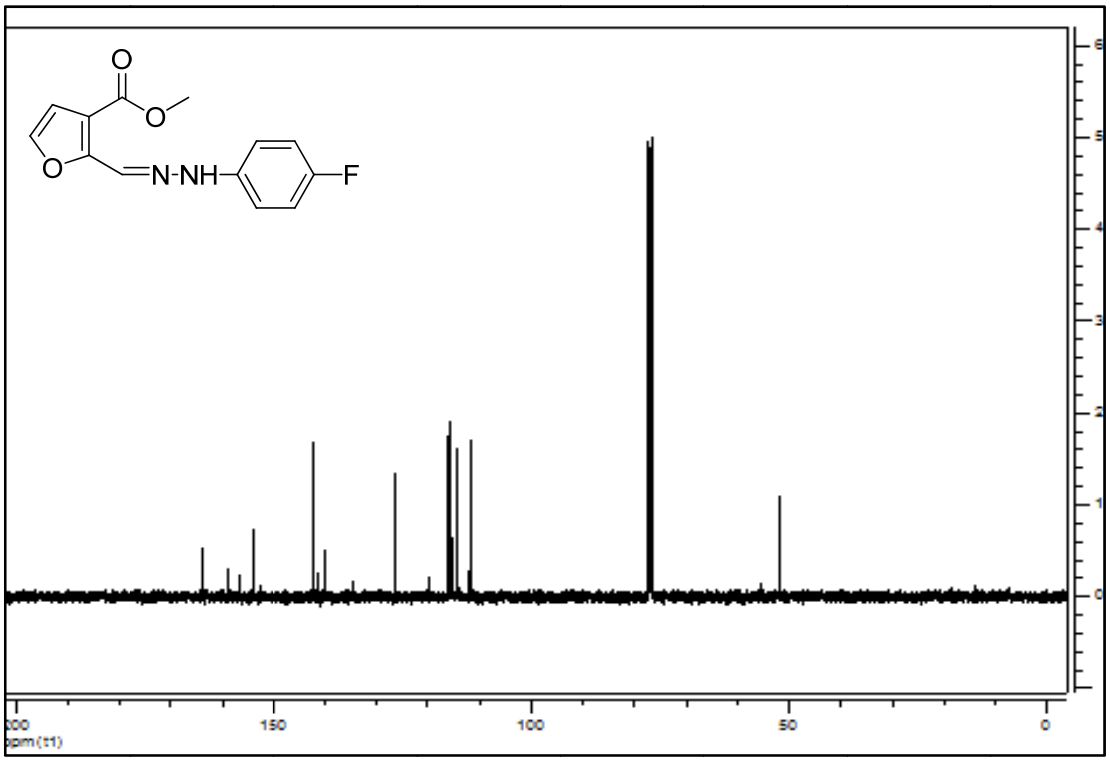


**Figure 65** $^{13}$C -NMR Spectrum of Compound **120**

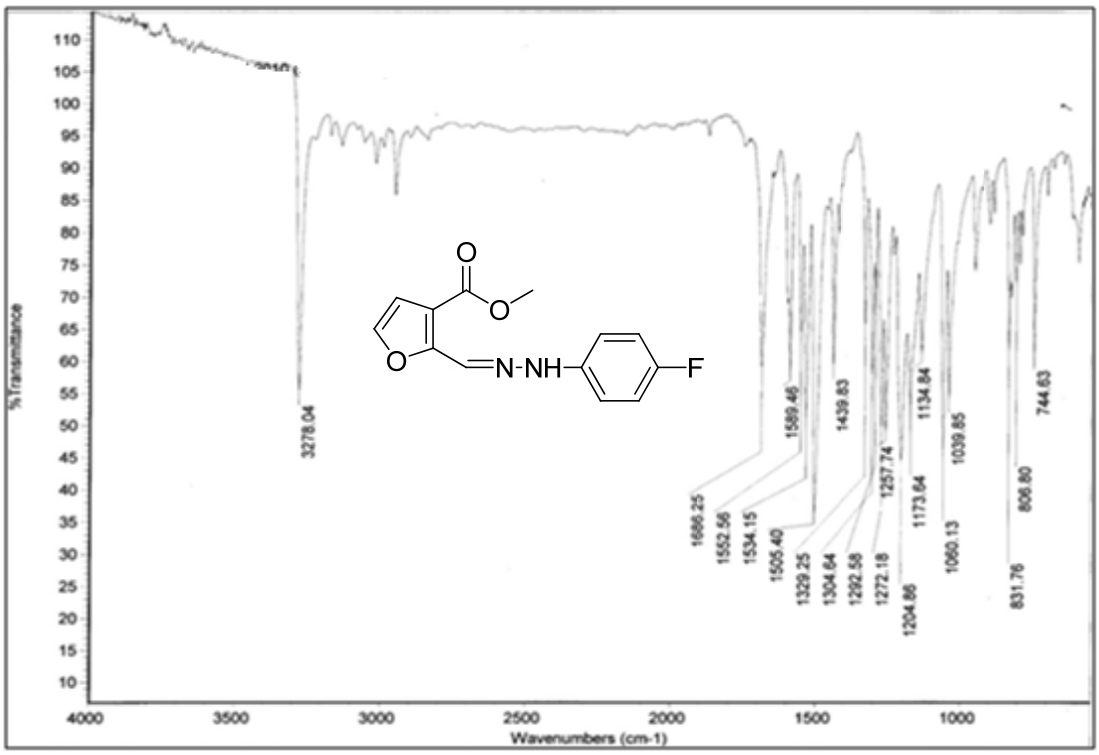


**Figure 66** IR Spectrum of Compound **120**

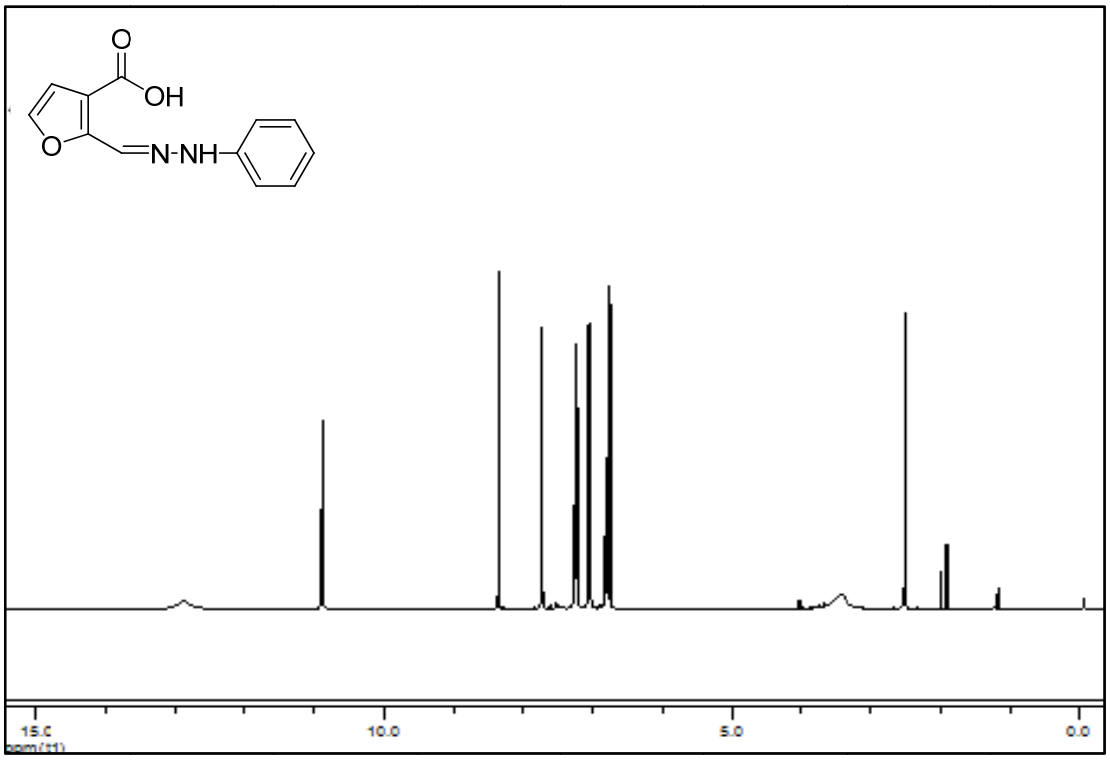


**Figure 67** $^{1}$H-NMR Spectrum of Compound **121**

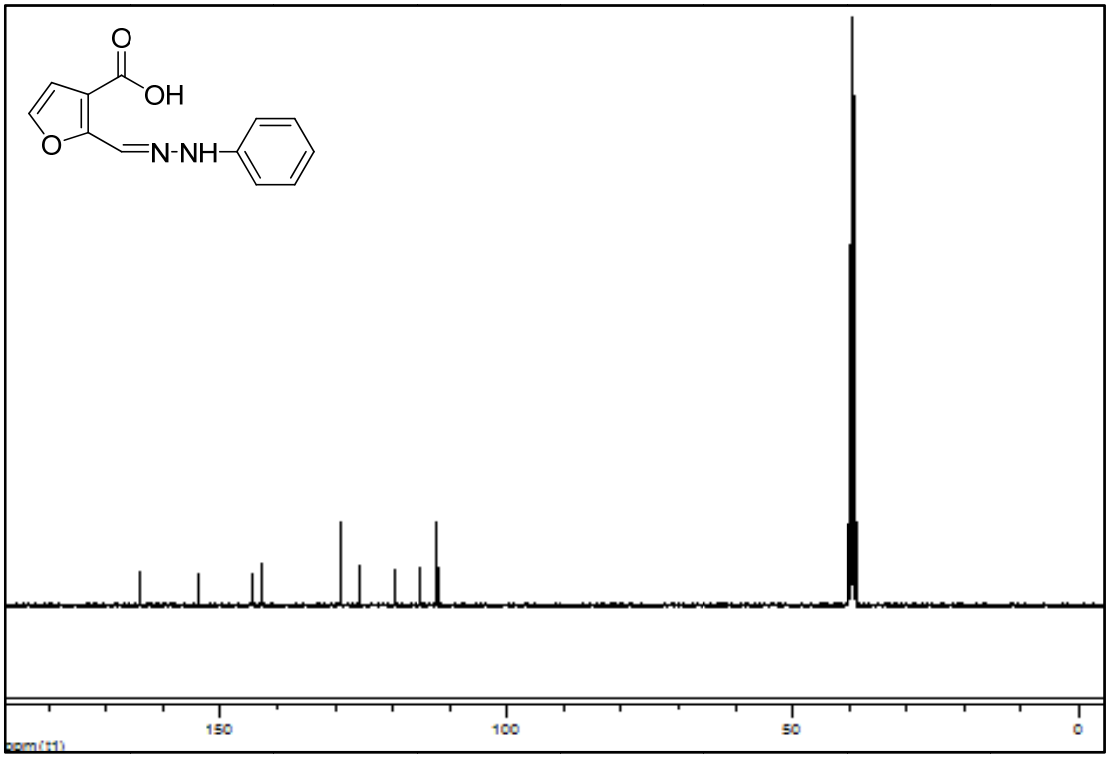


**Figure 68** $^{13}$C -NMR Spectrum of Compound **121**

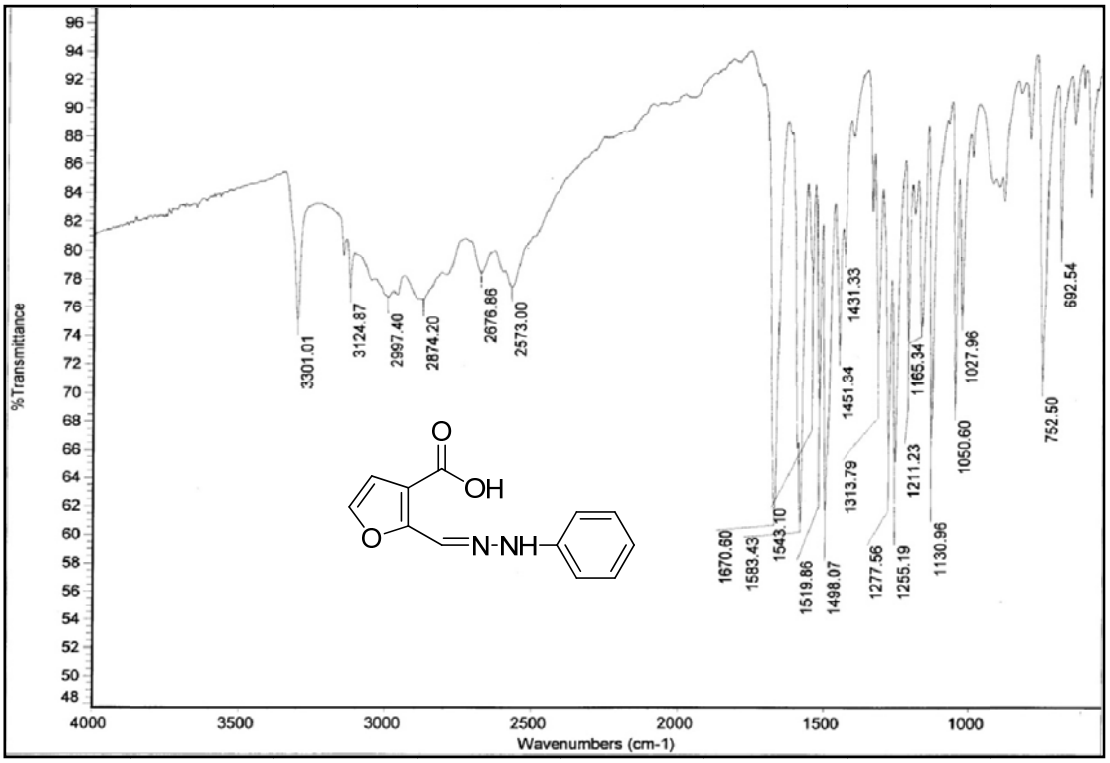


**Figure 69** IR Spectrum of Compound **121**

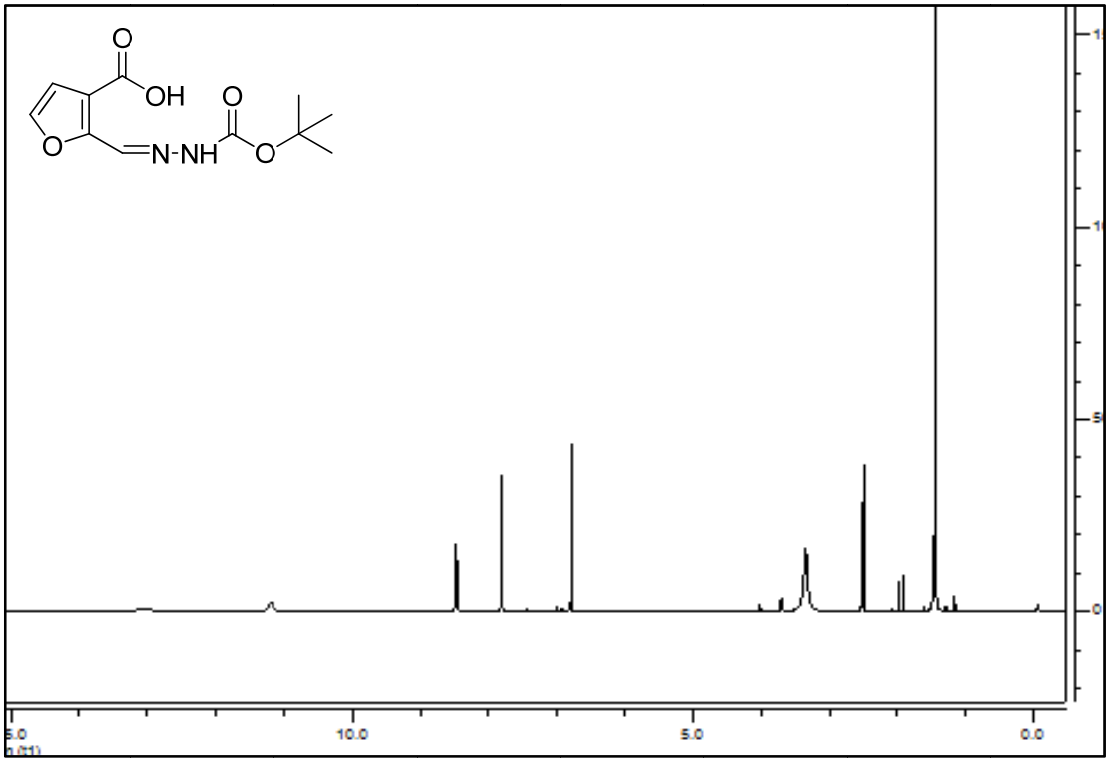


**Figure 70** [1]H-NMR Spectrum of Compound **122**

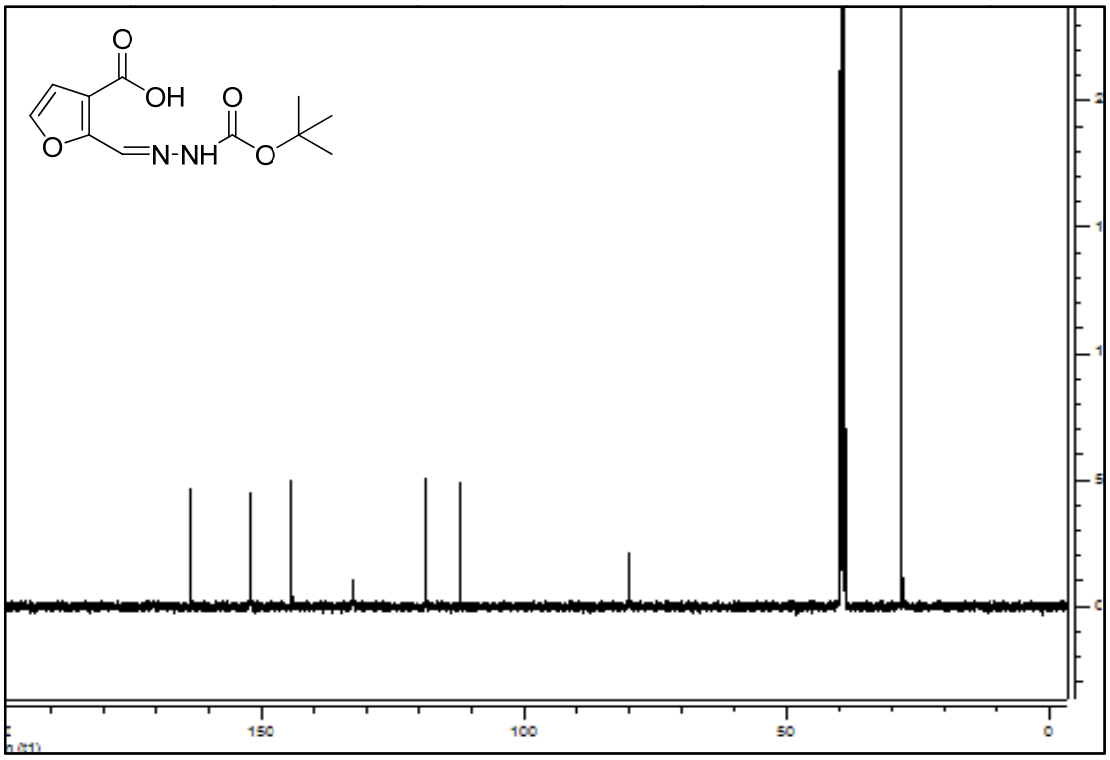


**Figure 71** [13]C -NMR Spectrum of Compound **122**

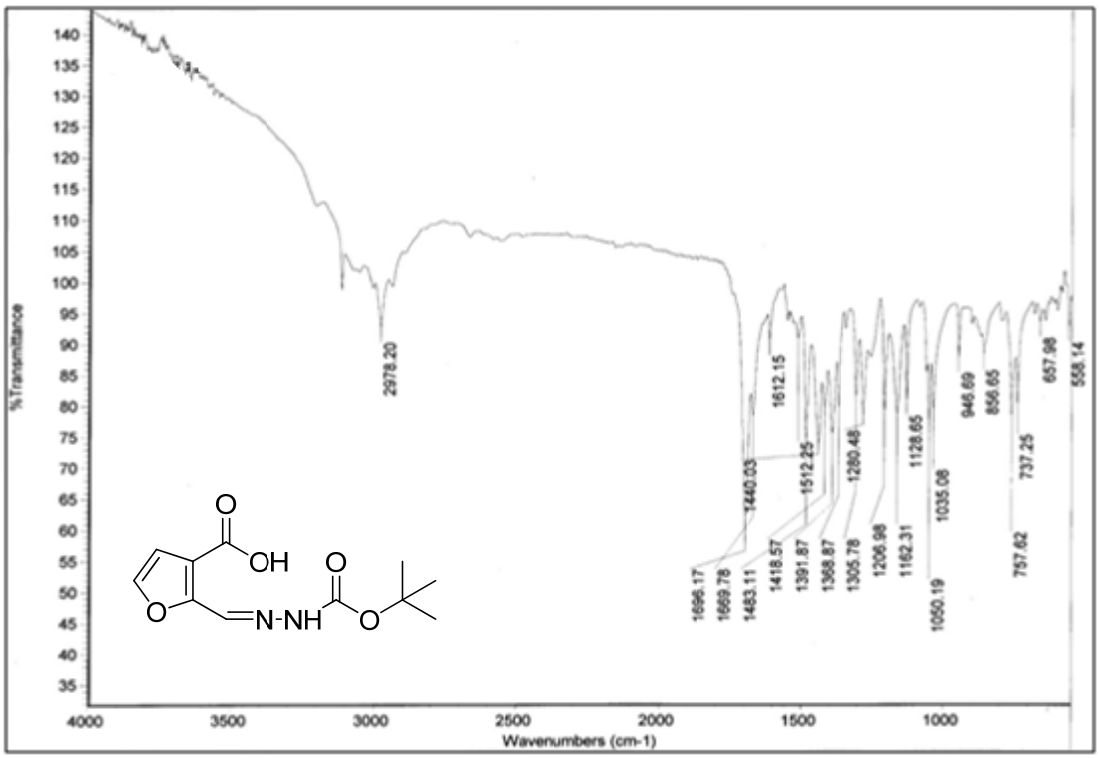


**Figure 72** IR Spectrum of Compound **122**

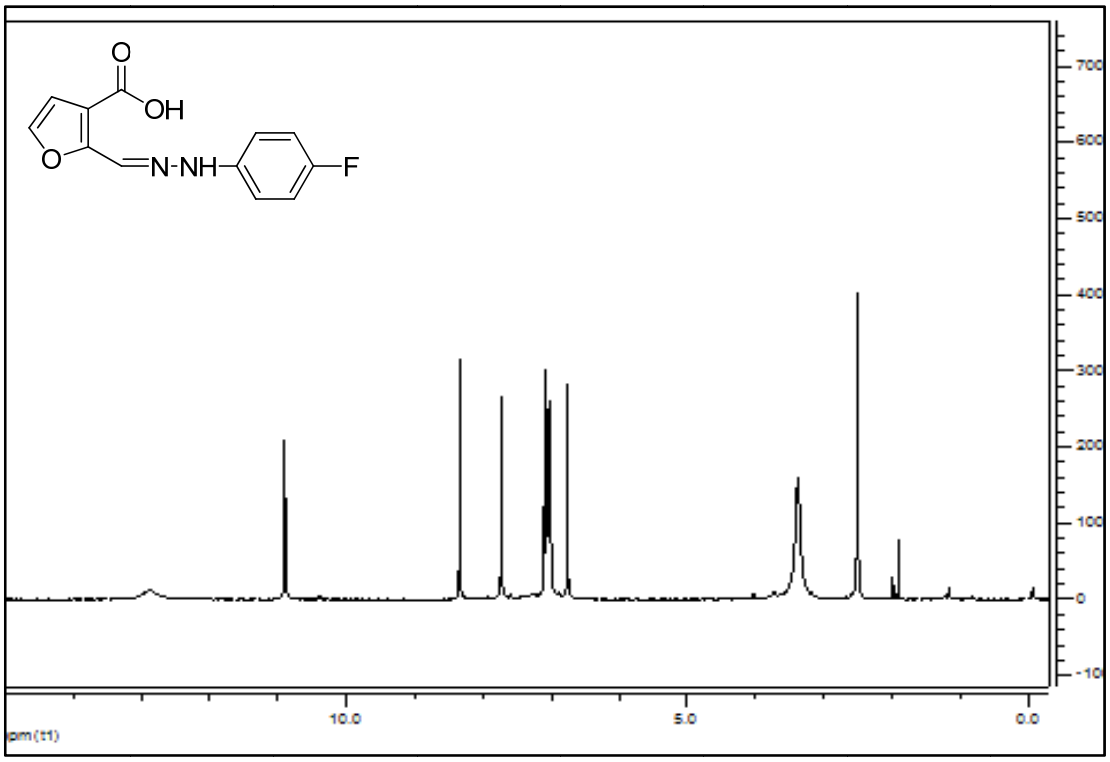


**Figure 73** $^{1}$H-NMR Spectrum of Compound **123**

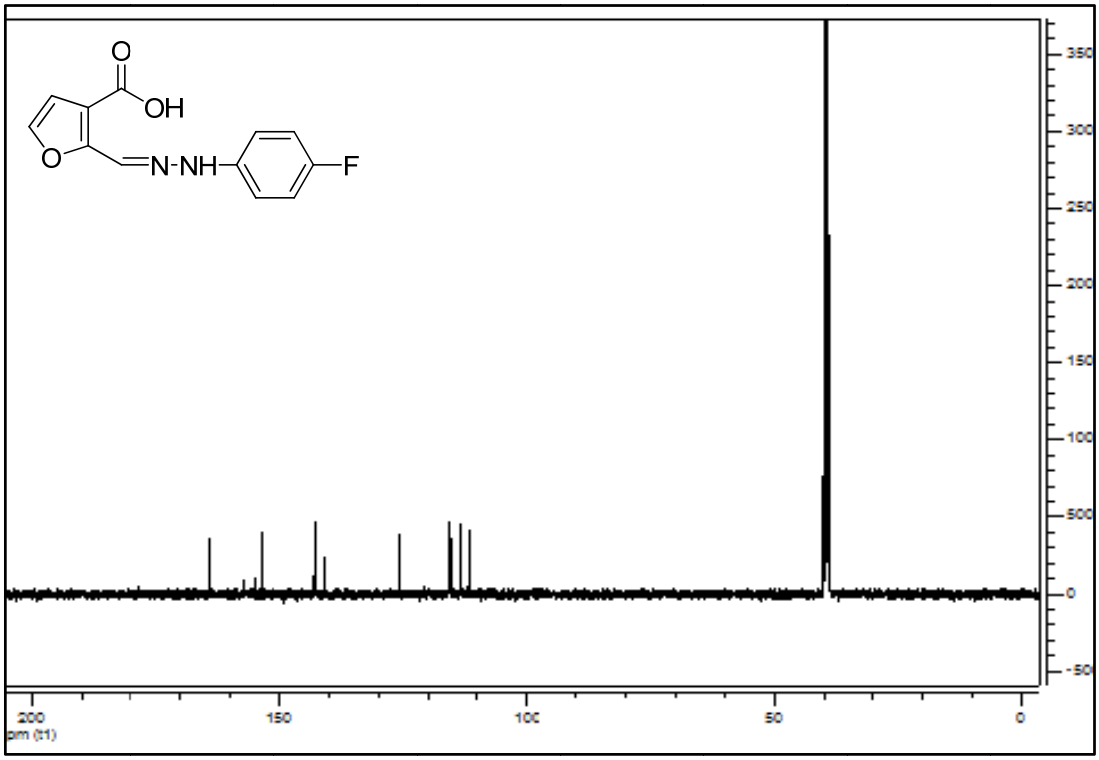


**Figure 74** $^{13}$C -NMR Spectrum of Compound **123**

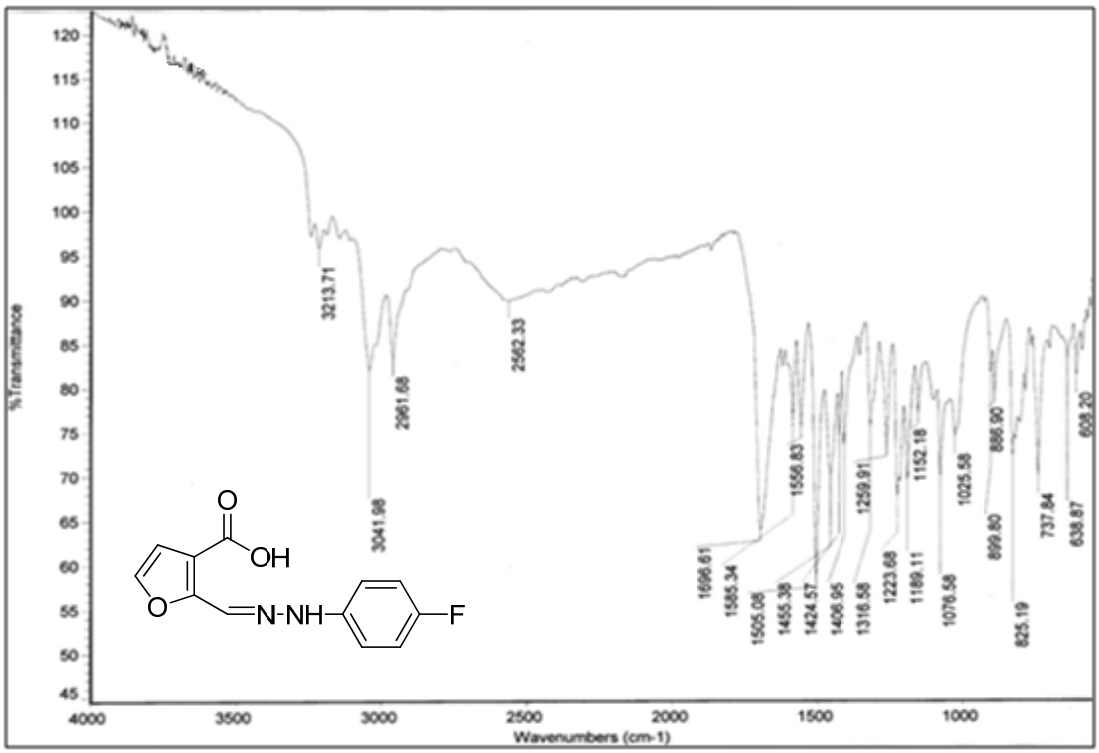


**Figure 75** IR Spectrum of Compound **123**

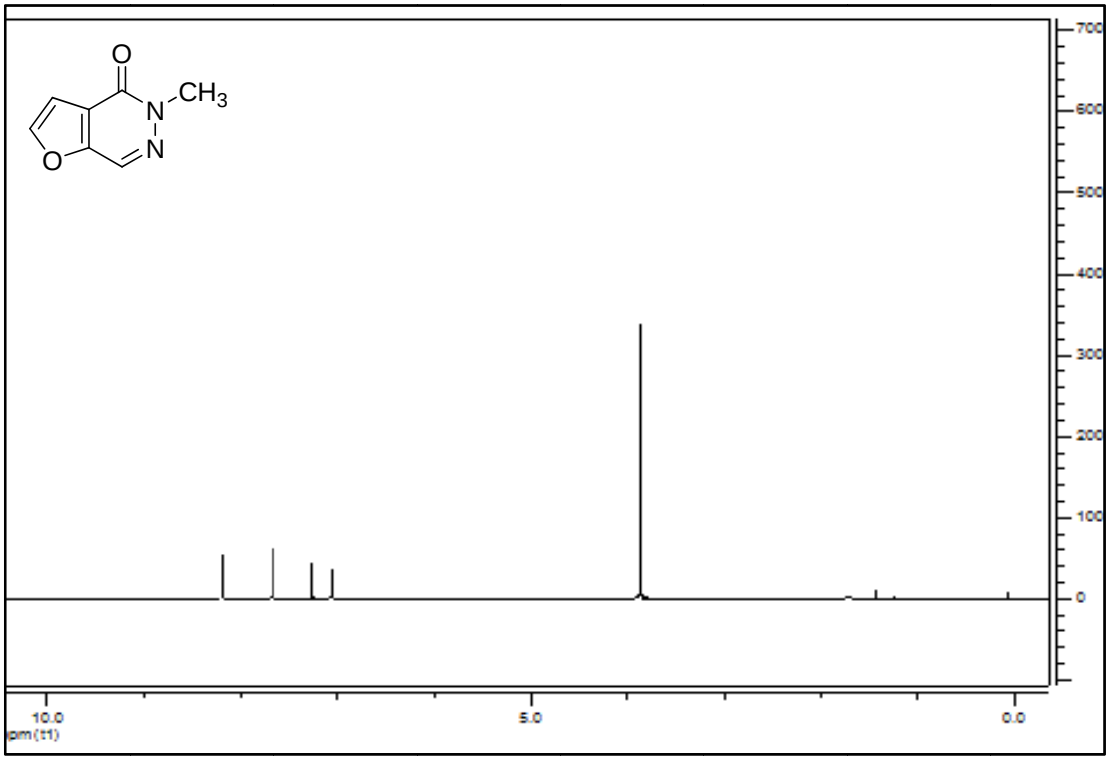


**Figure 76** $^{1}$H-NMR Spectrum of Compound **124**

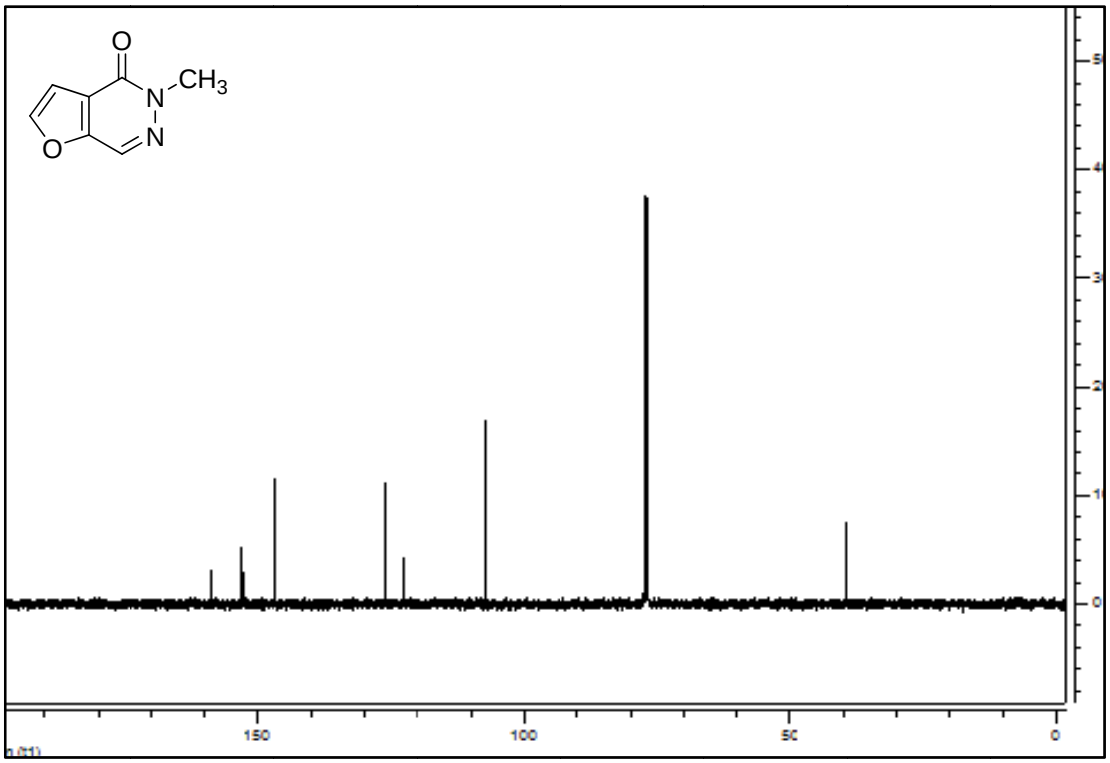


**Figure 77** $^{13}$C -NMR Spectrum of Compound **124**

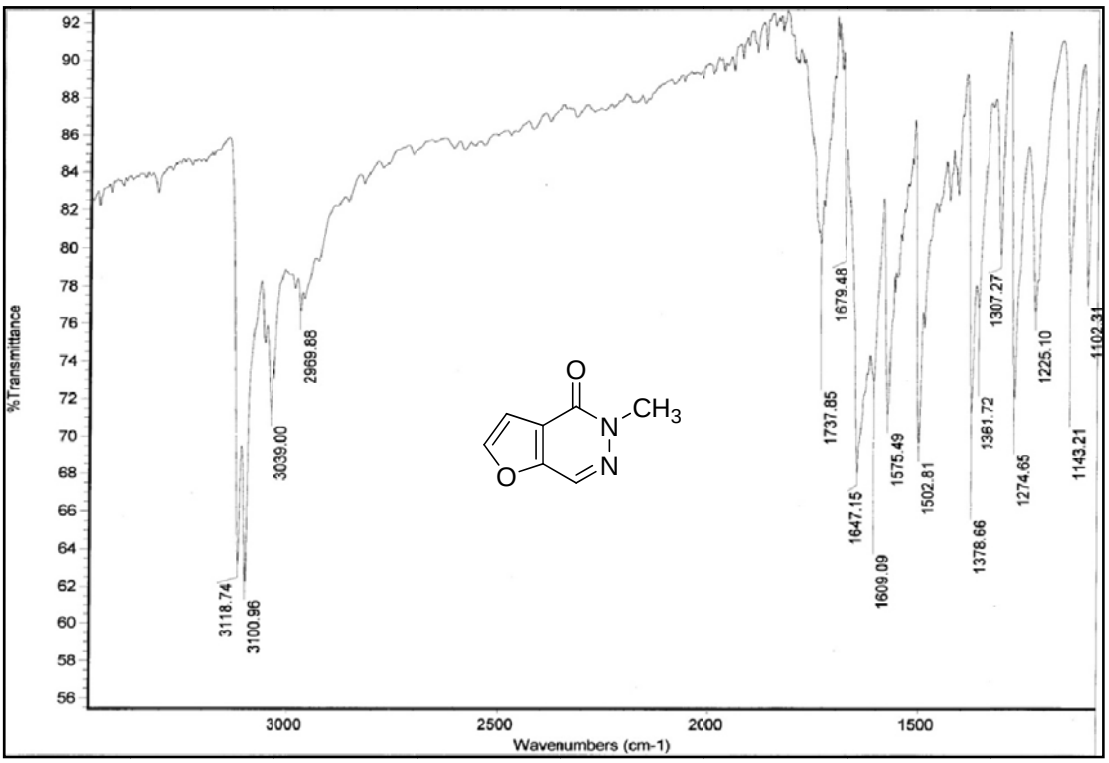


**Figure 78** IR Spectrum of Compound **124**

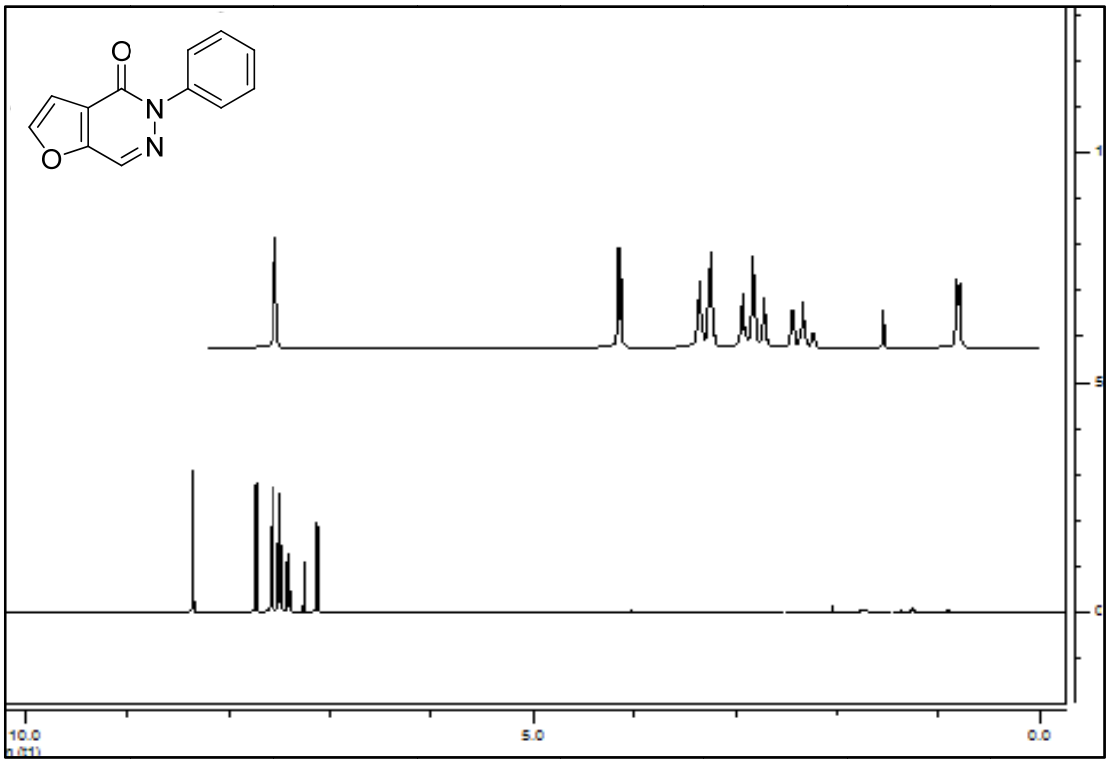


**Figure 79** $^{1}$H-NMR Spectrum of Compound **125**

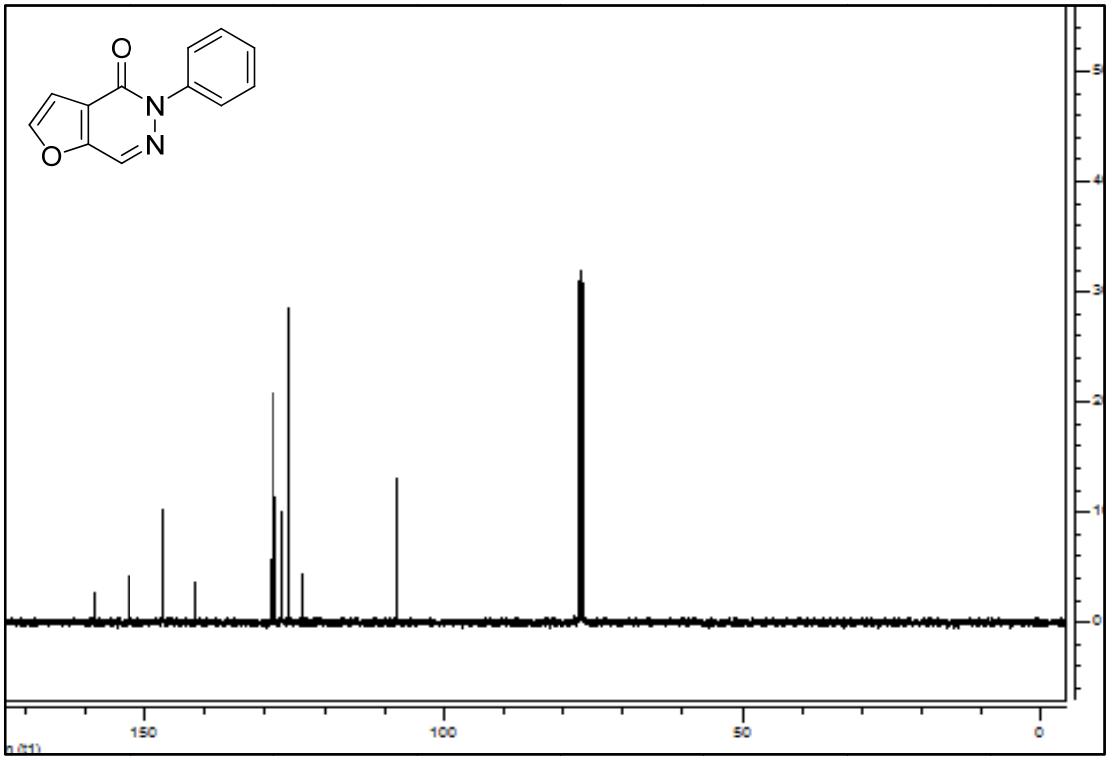


**Figure 80** $^{13}C$ -NMR Spectrum of Compound **125**

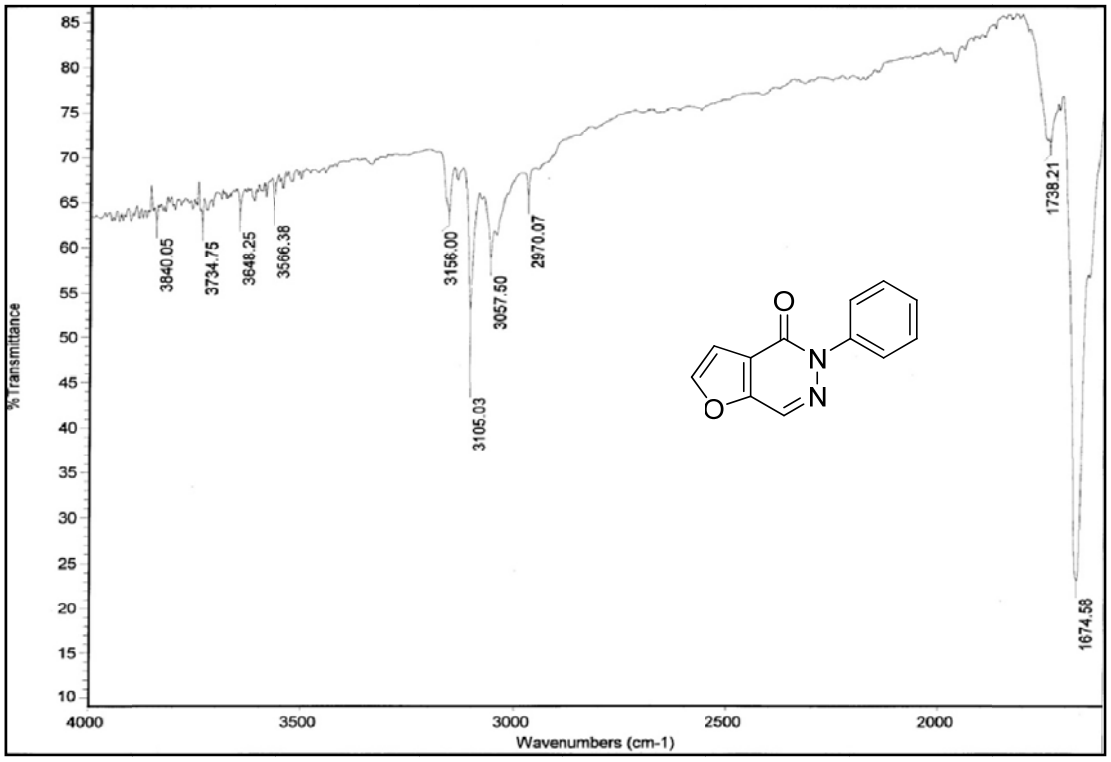


**Figure 81** IR Spectrum of Compound **125**

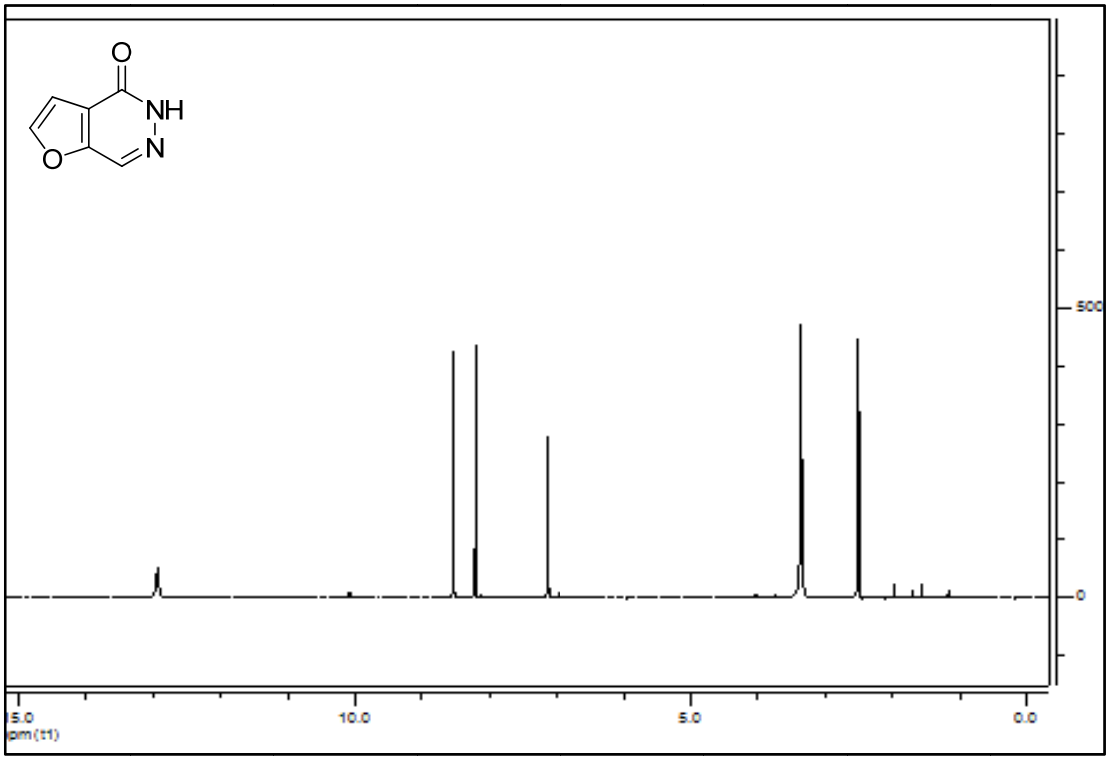


**Figure 82** $^{1}$H-NMR Spectrum of Compound **126**

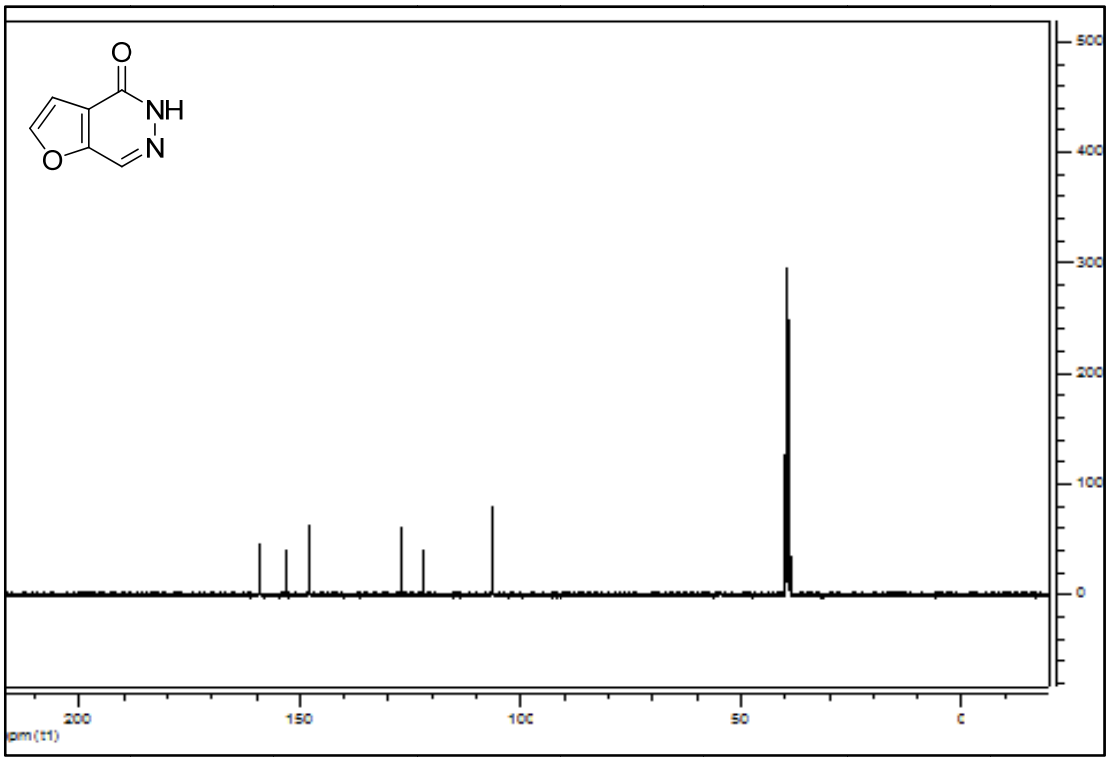


**Figure 83** $^{13}$C -NMR Spectrum of Compound **126**

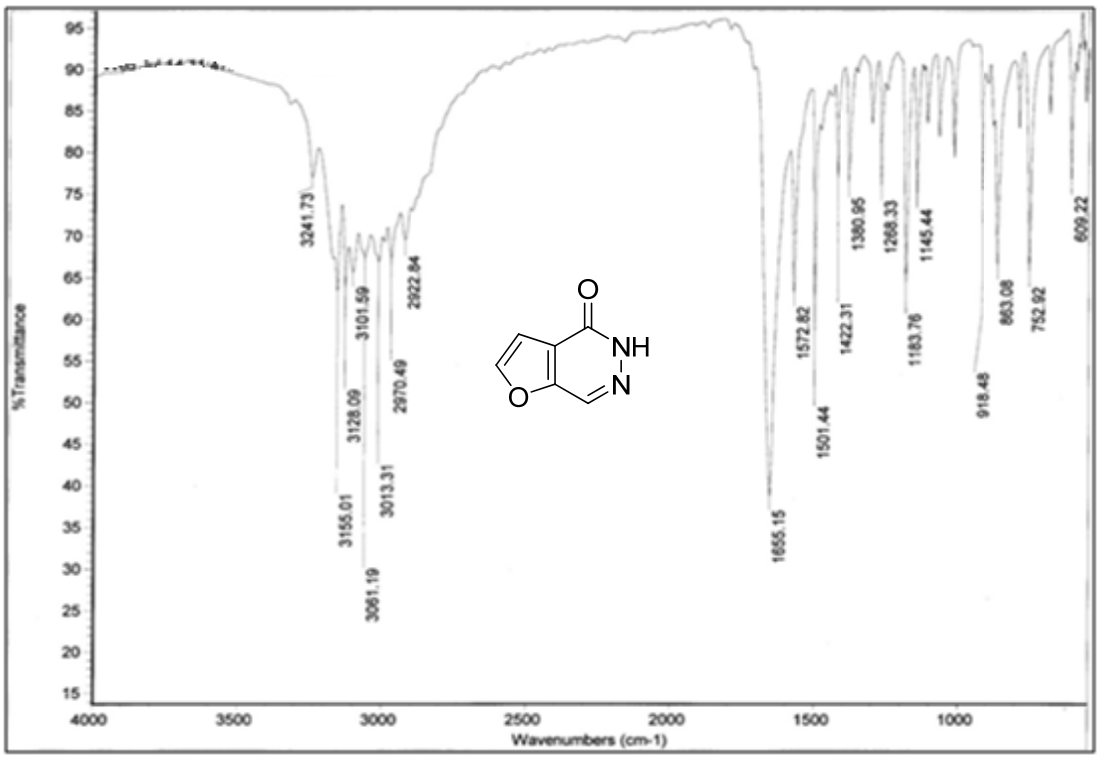


**Figure 84** IR Spectrum of Compound **126**

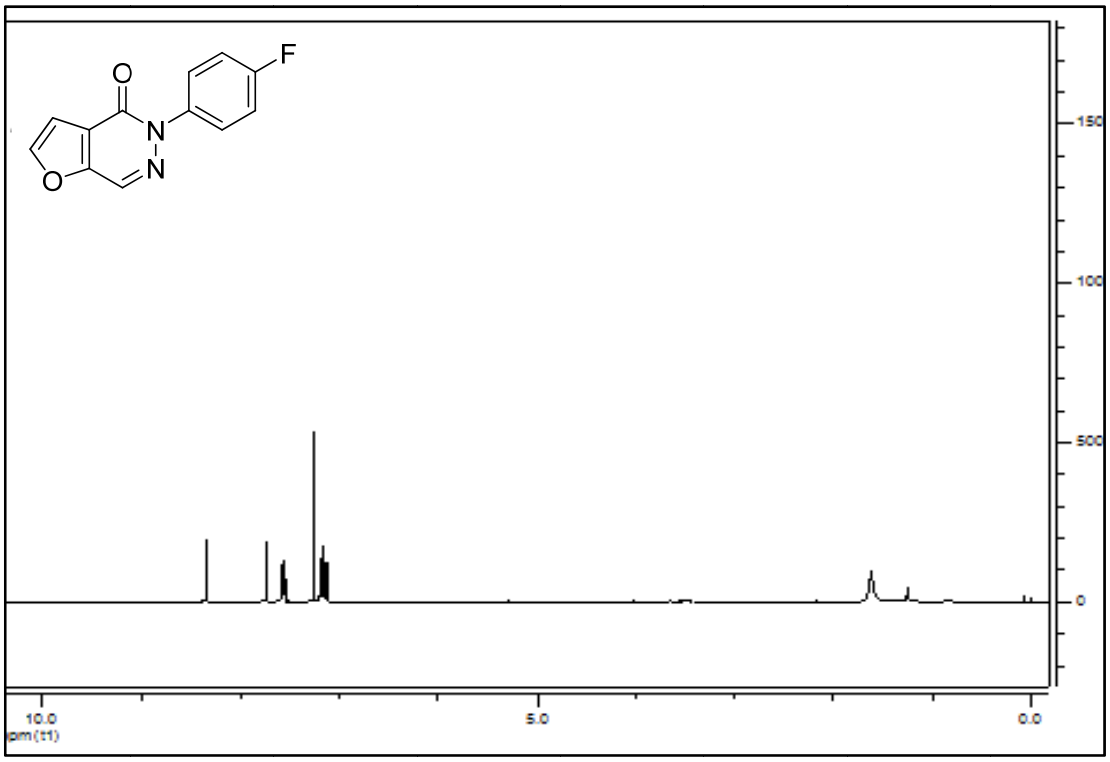


**Figure 85** $^{1}$H-NMR Spectrum of Compound **127**

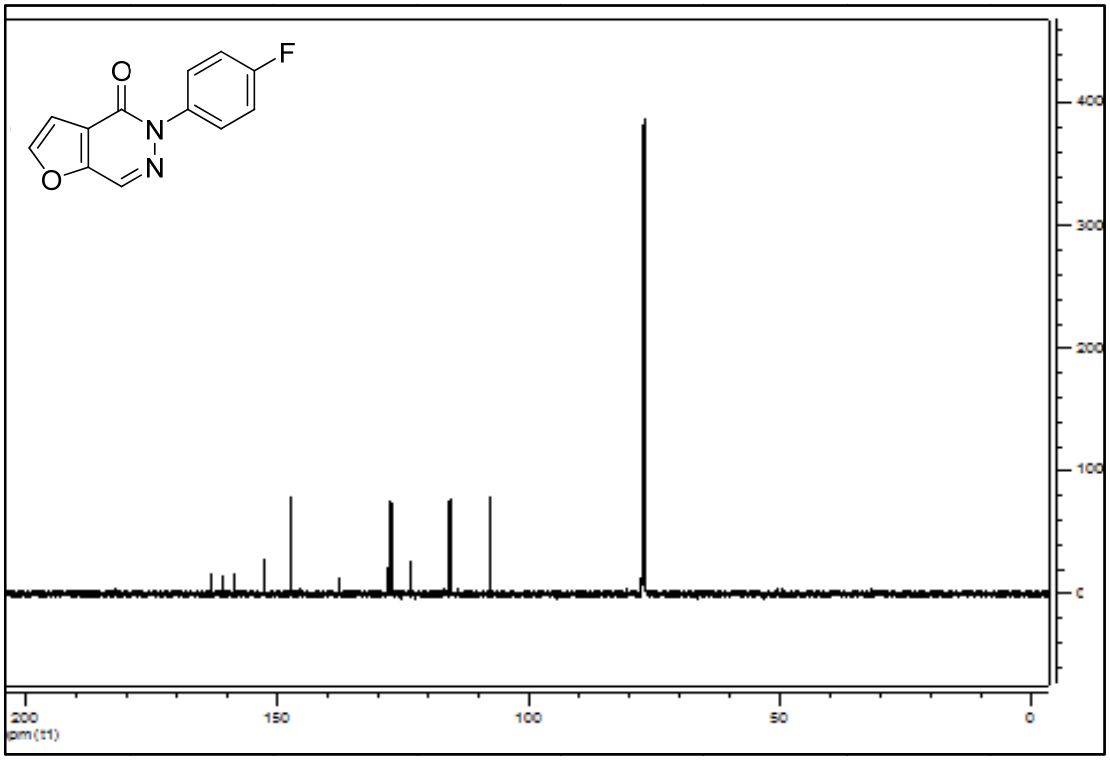


**Figure 86** $^{13}$C -NMR Spectrum of Compound **127**

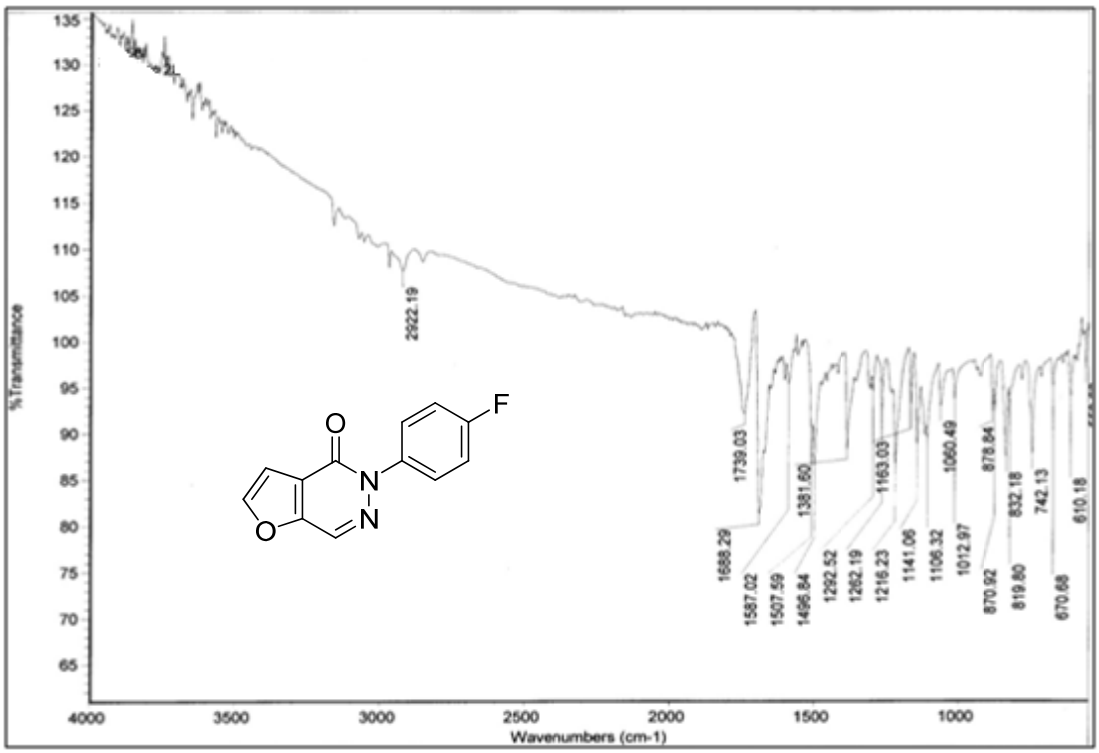


**Figure 87** IR Spectrum of Compound **127**