SYNTHESIS OF NOVEL POTENTIALLY BIOACTIVE *N*-(1,2,4-OXADIAZOLYL METHYL)-3-SUBSTITUTED PHENYL-1,2,4-OXADIAZOL-5(*4H*)-ONES AND 1,2,3,5-OXATHIADIAZOL-2-OXIDES

EMİNE ÖZGE GÖZLÜKAYA

JANUARY 2012

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by

EMİNE ÖZGE GÖZLÜKAYA

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OF

MASTER OF SCIENCE

IN

THE DEPARTMENT OF CHEMISTRY

JANUARY 2012

Approval of the Graduate School of Natural and Applied Science.

Prof. Dr. Nihat ÇELEBİ

Director

I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.

Prof. Dr. Çetin BOZKURT

Head of Department

This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Sciences.

Prof. Dr. Yaşar DÜRÜST

Supervisor

Examining Committee Members

1. Prof. Dr. Yaşar DÜRÜST

2. Prof. Dr. Özdemir ÖZARSLAN

3. Prof. Dr. Mustafa KÜÇÜKİSLAMOĞLU

ABSTRACT

SYNTHESIS OF NOVEL POTENTIALLY BIOACTIVE *N*-(1,2,4-OXADIAZOLYL METHYL)-3-SUBSTITUTED PHENYL-1,2,4-OXADIAZOL-5(*4H*)-ONES AND 1,2,3,5-OXATHIADIAZOL-2-OXIDES

Gözlükaya, Özge

M.Sc., Department of Chemistry

Supervisor: Prof. Dr. Yaşar Dürüst

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This research study presents a simple and practical synthesis of *N*-substituted oxadizolones with respect to a variety of 5-chloromethyl-1,2,4-oxadiazoles. In order to achieve this synthetic sequence, first we prepared arylsubstituted 1,2,4,-oxadiazol-5-ones(or thiones) and 1,2,3,5-oxathiadiazol-2-oxides starting from the substituted aromatic amidoximes using CDI, TCDI, and $SOCl_2$. To our best knowledge of literature survey, some of 1,2,4-oxadiazol-5-ones(or thiones) and all of the 1,2,3,5-oxathiadiazol-2-oxides are novel heterocyclic compounds and not known yet. As the major part of this

work, we have been focused to obtain *N*-(1,2,4-oxadiazolylmethyl)-3-substituted phenyl- [1,2,4]-oxadiazol-5(4*H*)-ones (and thiones) starting from monosubstituted [1,2,4]-Oxadiazol-5(4*H*)-ones (and thiones) and 5-chloromethyl-1,2,4-oxadiazoles using K_2CO_3 in the reaction medium of DMF. The structures of all end products were elucidated by means of IR, NMR (^1H,^{13}C), LC-MS spectra and single crystal X-Ray Diffraction, and physical data (melting points and R_f values). Since the title compounds carry both oxadiazole and oxadiazolone, oxathiadiazole-S-oxide moieties we strongly believe that these compounds would show some remarkable bioactivities against various bacteria species and tumor cells. Therefore, we are getting prepared to examine these activities in collaboration with well-equipped international laboratories in the near future.

Key words: amidoxime, oxadiazole, oxadiazolone, oxadiazole-5-thione, oxathiadiazol-2-oxide, cyclization, spectroscopy.

ÖZET

YENİ POTANSİYEL BİYOAKTİF *N*-SUBSTİTUE (1,2,4-OKSADİAZOL-İL METİL), 1,2,4-OKSADİAZOL-5(*4H*)-ON VE 1,2,3,5-OKSATİYADİAZOL-2-OKSİTLERİN SENTEZİ

Gözlükaya, Emine Özge

Yüksek Lisans Tezi, Kimya Bölümü

Tez Danışmanı: Prof. Dr. Yaşar Dürüst

Ocak 2012, 155 sayfa

Bu araştırma, çeşitli 5-klorometil-1,2,4-oksadiyazoller kullanılarak, *N*-sübstitüe oksadiyazolon (ve tiyon)'ların pratik ve basit sentezini içermektedir. Bu sentetik zinciri tamamlayabilmek için, öncelikle sübstitüe aromatik amidoksimlerin CDI, TCDI ve $SOCl_2$ kullanılarak [1,2,4]-oksadiazol-5(*4H*)-on(tiyon) ve 1,2,3,5-oksatiyadiazol-2-oksit türevleri hazırlanmıştır. Literatür bilgimiz dahilinde, [1,2,4]-oksadiazol-5(4*H*)-on(tiyon) türevlerinin bazıları ve [1,2,3,5]-oksatiyadiazol-2-oksitlerin tamamı henüz bilinmeyen yeni heterohalkasal bileşiklerdir. Bu çalışmanın esas kısmı olarak, mono substitue [1,2,4]-oksadiazol-5(4*H*)-on (tiyon) bileşiklerinin 5-klorometil-(1,2,4)-

oksadiazol'ler ile K_2CO_3 kullanılarak DMF içerisinde *N*-(1,2,4-oksadiazol-ilmetil)-3-substituefenil-[1,2,4]-oksadiazol-5(4*H*)-on (tiyon) türevlerinin elde edilebilmesine odaklanılmıştır. Çalışmanın sonunda, beklenen son ürünler başarıyla sentezlenmiş ve yapıları IR, NMR (^1H ,^{13}C), kütle spektrumu, tek kristal X-ışını kırınımı spektrumları, ve diğer fiziksel sabitler (erime noktası, R_f değerleri..) yardımıyla aydınlatılmıştır. Bu son ürünler hem oksadiyazol, hem oksadiyazolon ve oksatiyadiyazol-S-oksit parçalarını içerdiği için, bu bileşiklerin çeşitli bakteri türlerine ve tümör hücrelerine karşı kaydadeğer biyoaktiflikler gösterebileceğini düşünmekteyiz. Bu nedenle, bu aktivitelerin iyi donanımlı uluslararası laboratuvarlarda yakın zamanda incelenmesi için hazırlanmaktayız.

Anahtar Kelimeler: amidoksim, oksadiazol, oksadiazolon, oksadiazol-5-tiyon, oksatiyadiazol-2-oksit, halkalaşma, spektroskopi.

To my mother and family,

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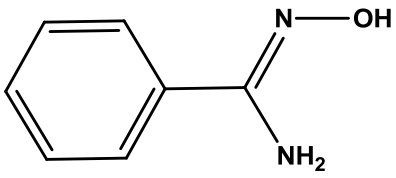
FORMULAE



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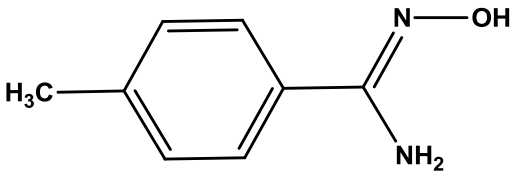

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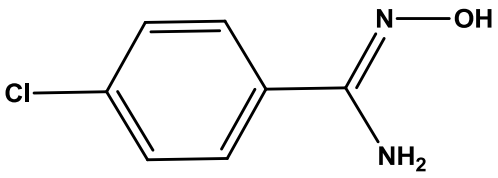

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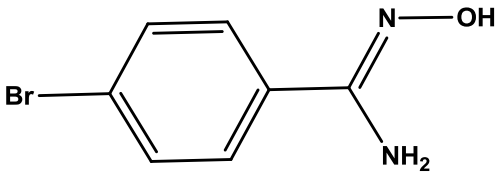

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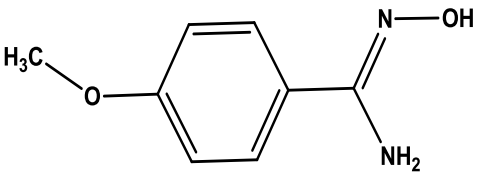

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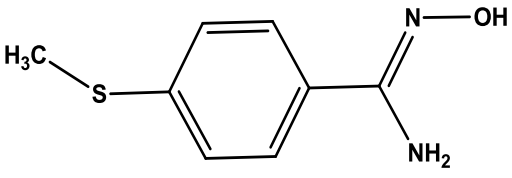

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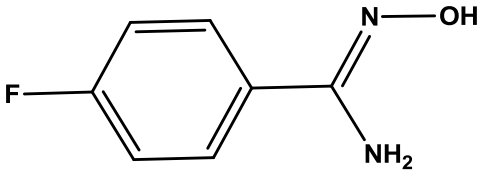

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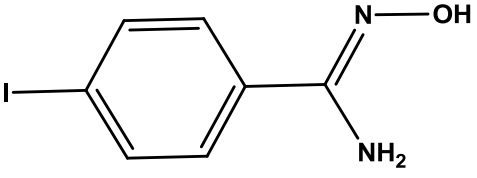

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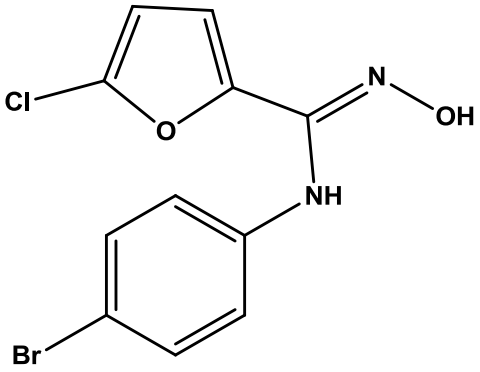

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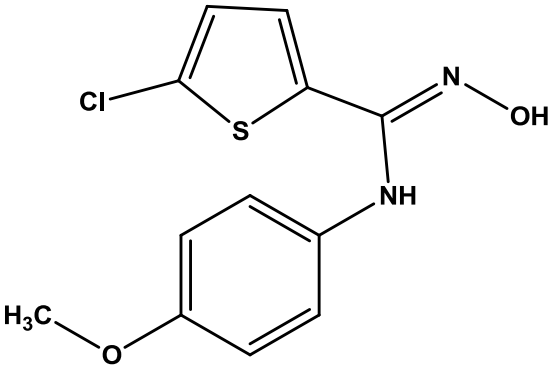

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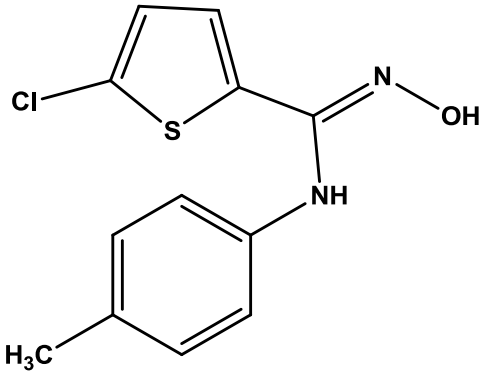

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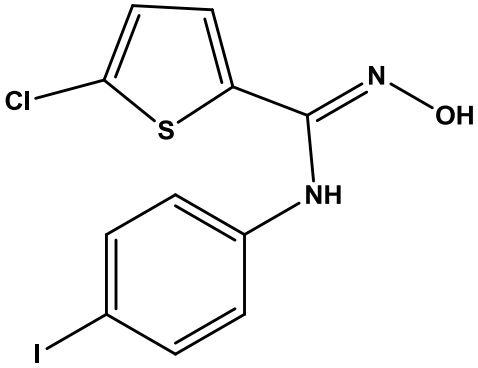

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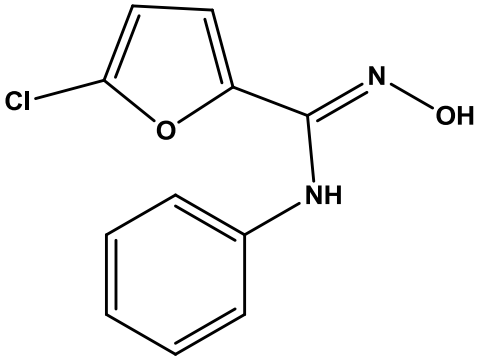

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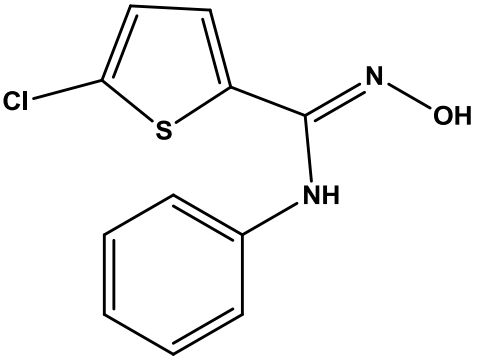

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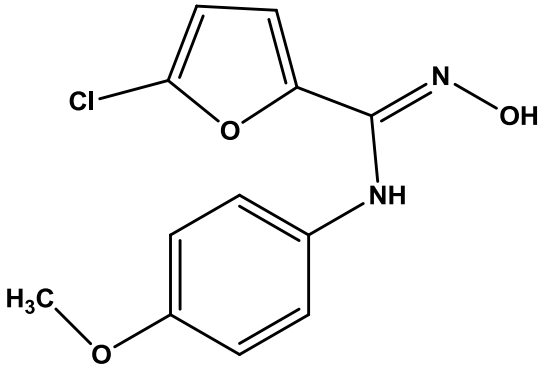

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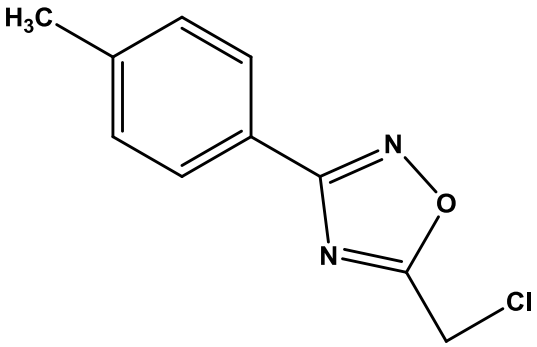

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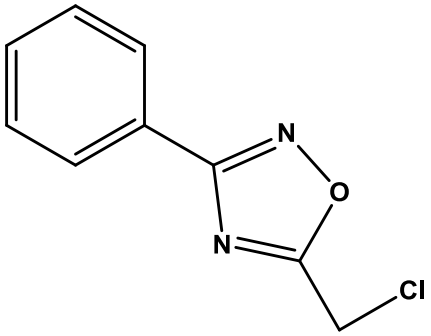

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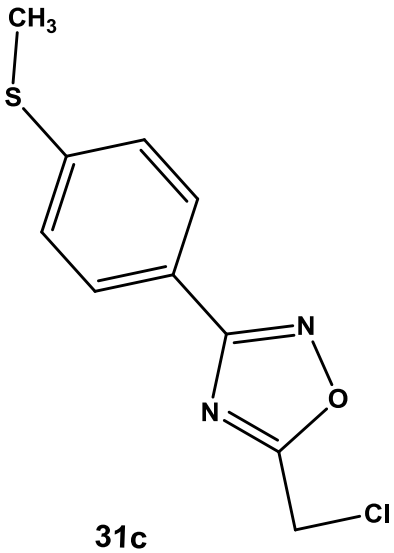

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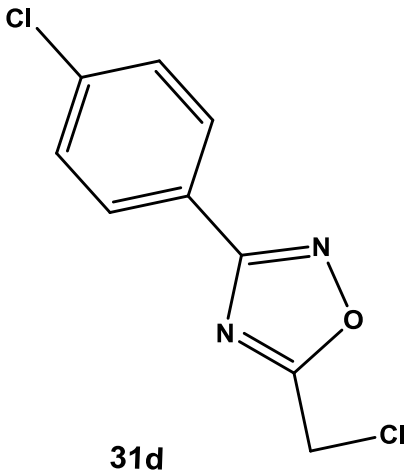

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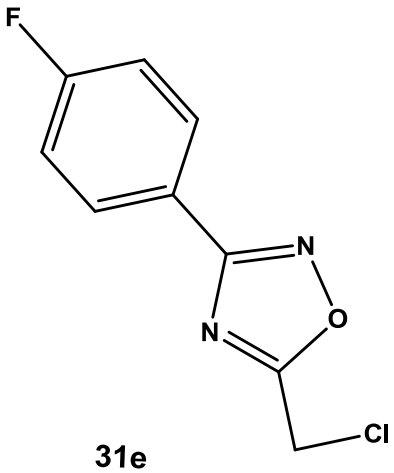

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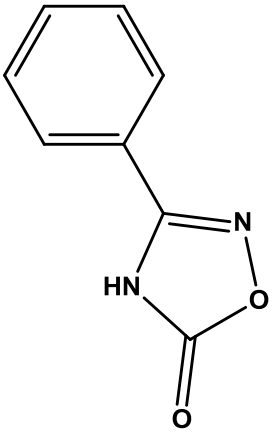

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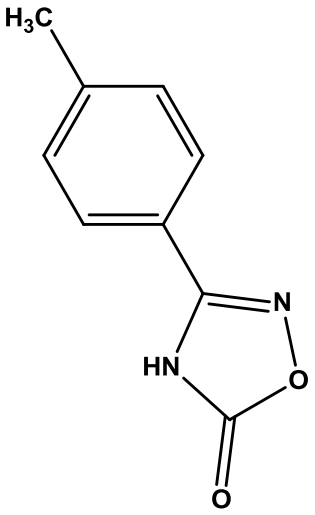

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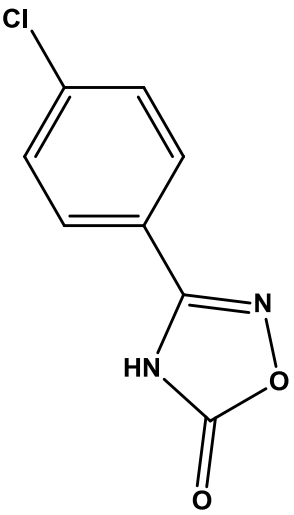

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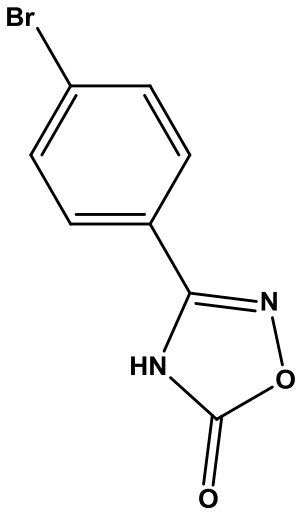

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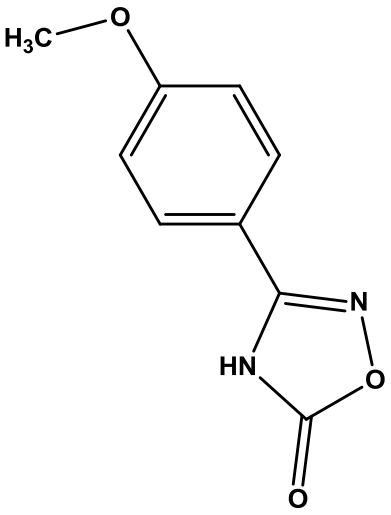

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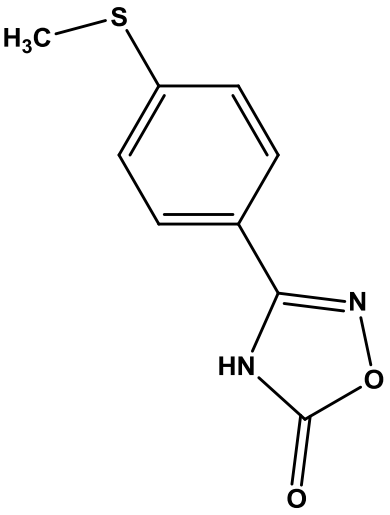

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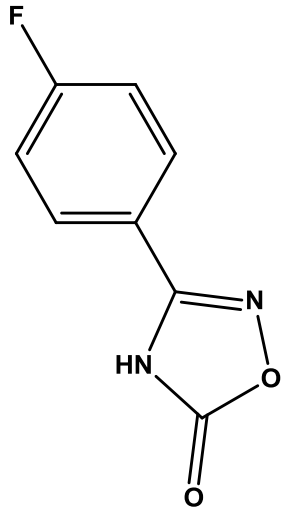

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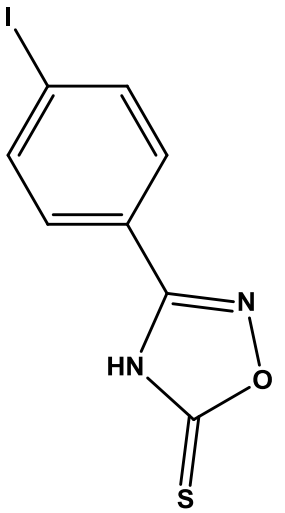

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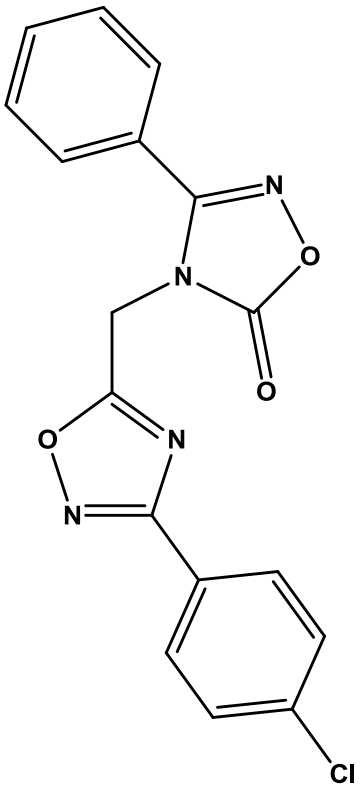

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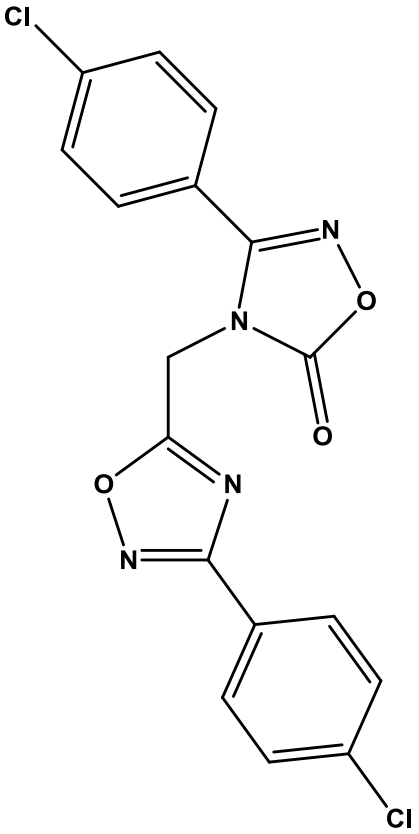

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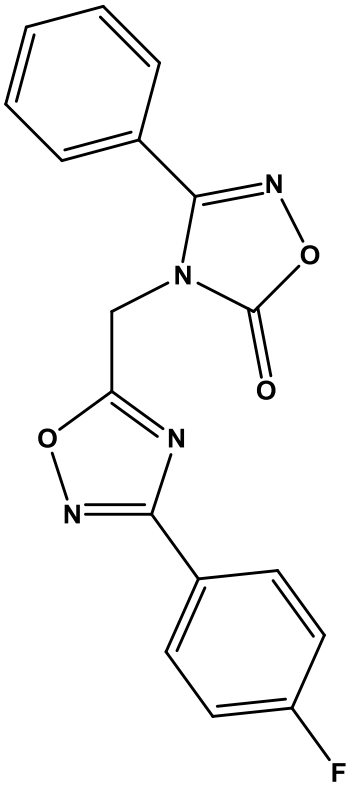

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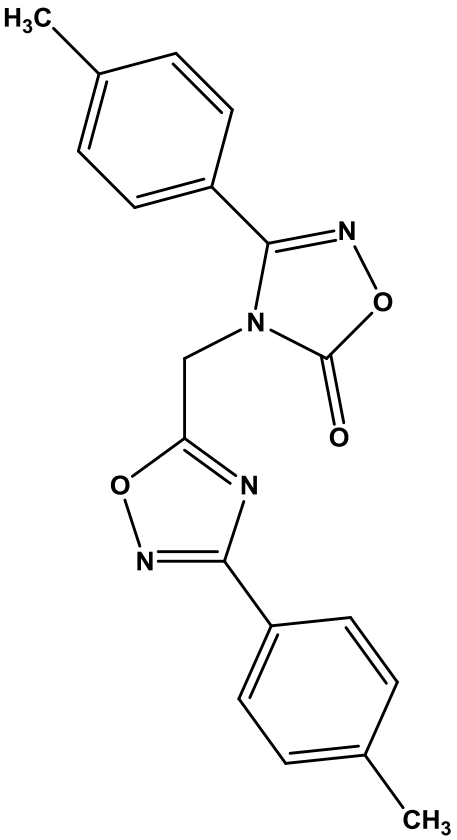

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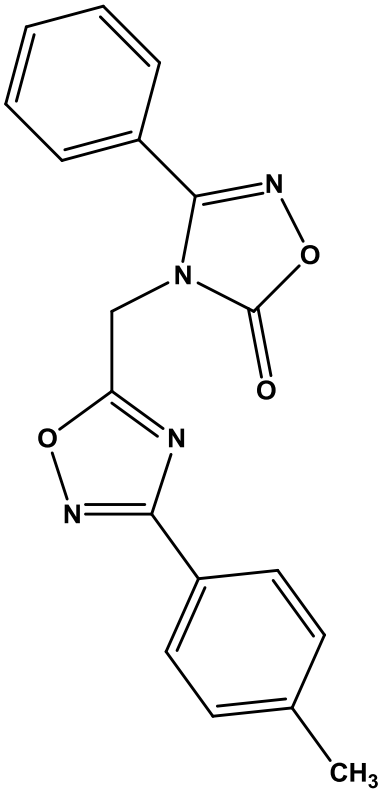

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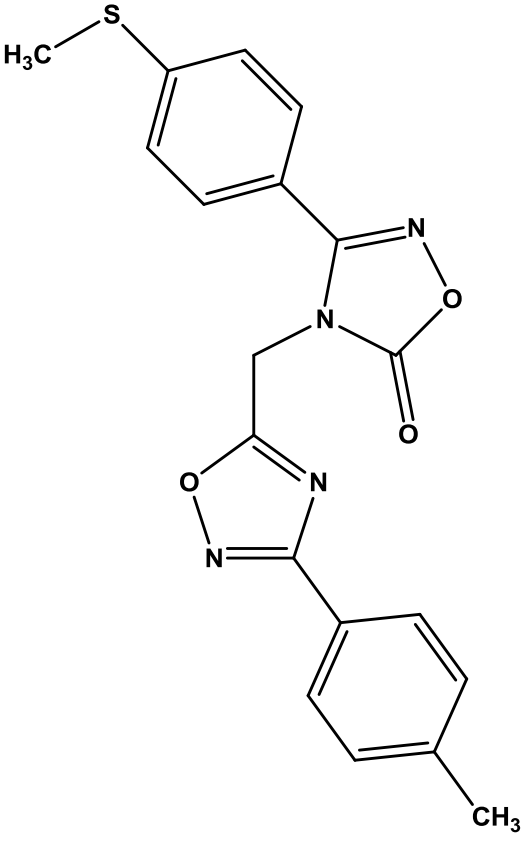

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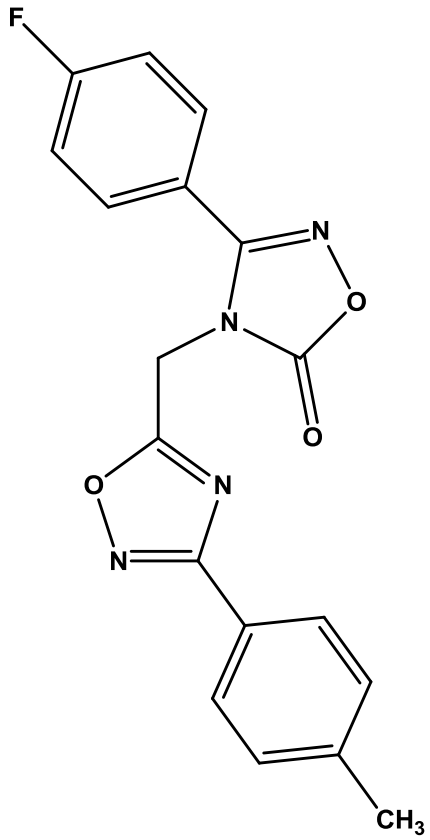

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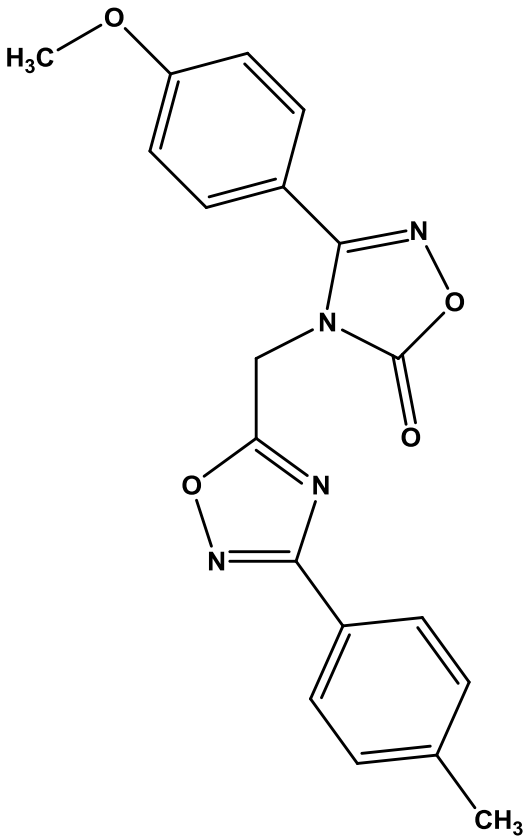

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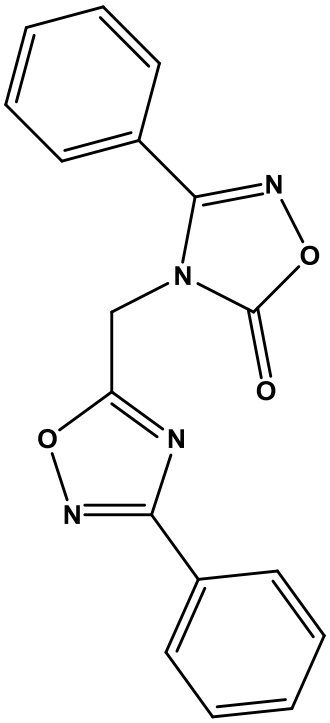

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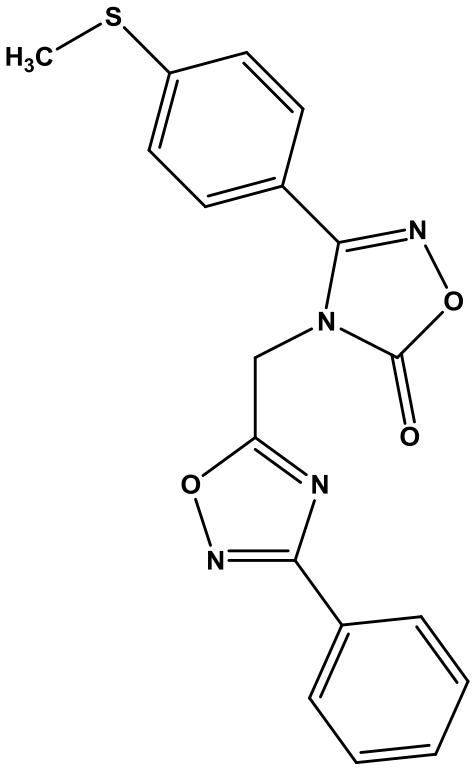

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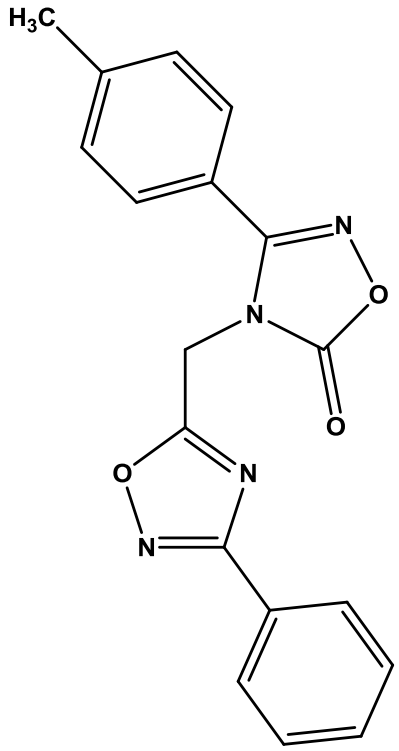

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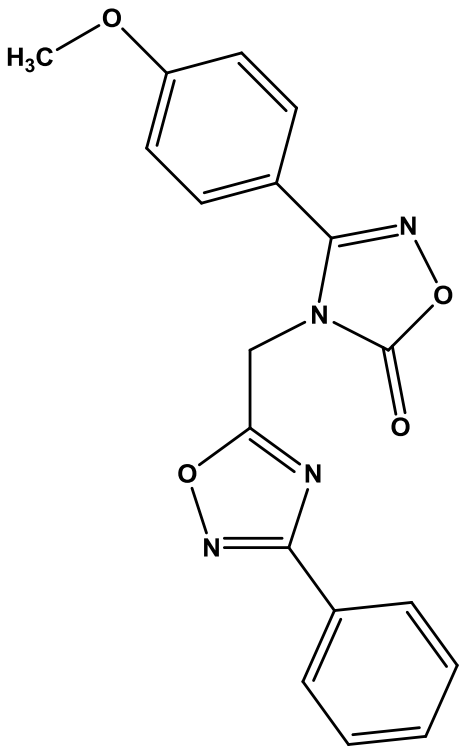

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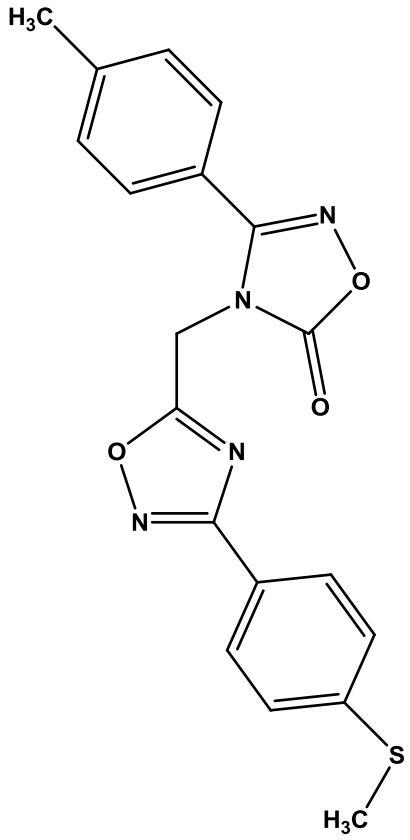

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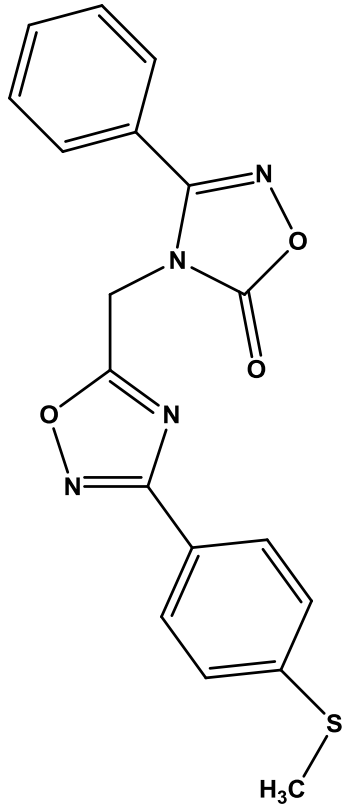

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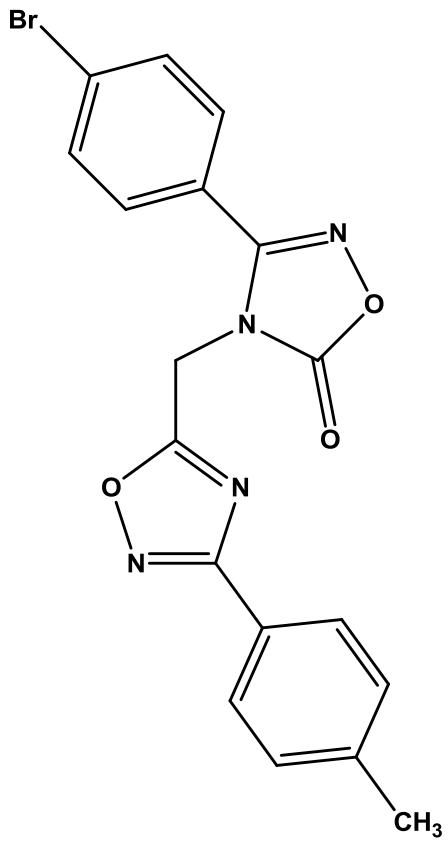

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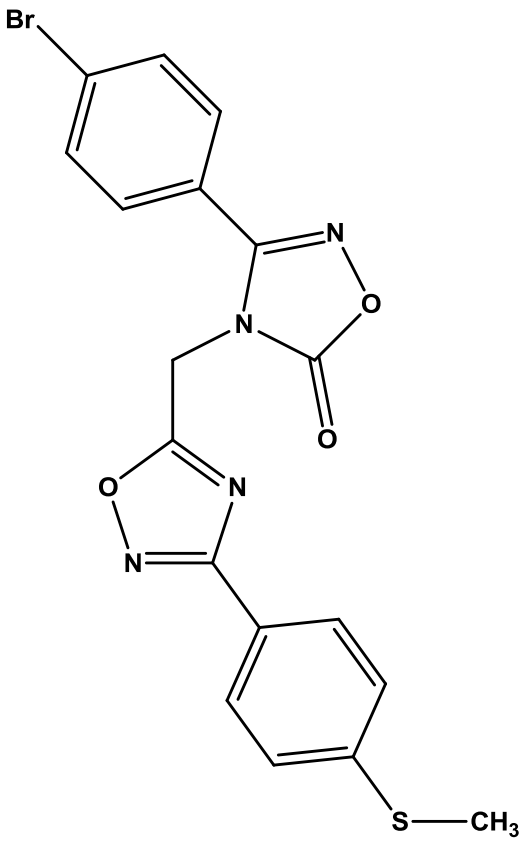

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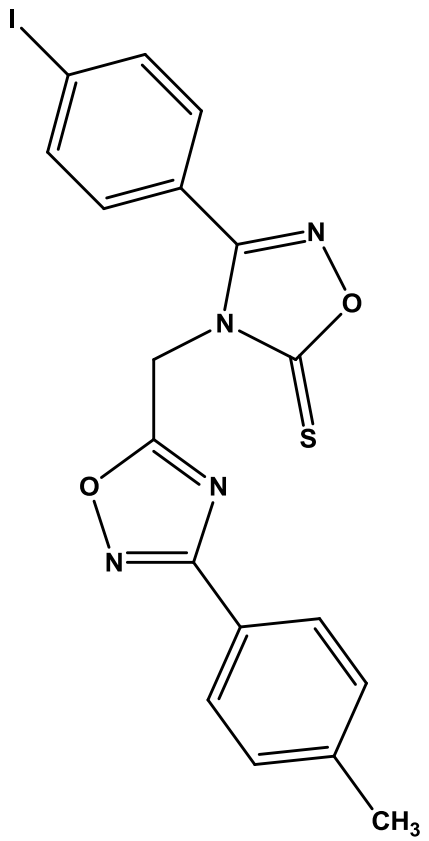

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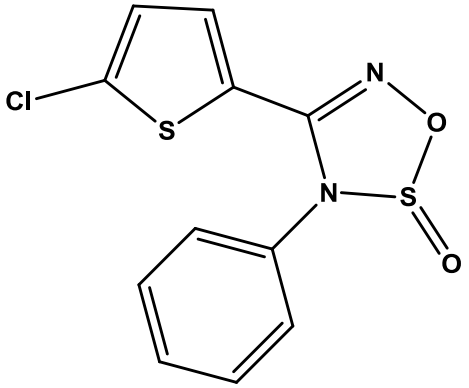

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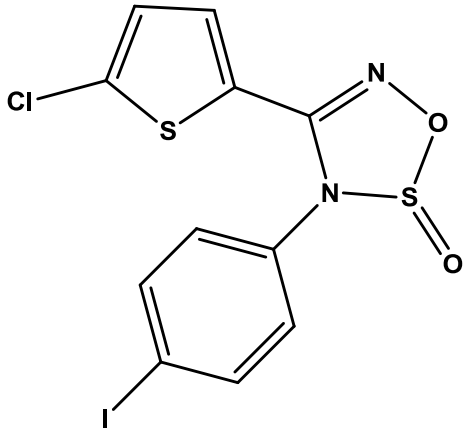

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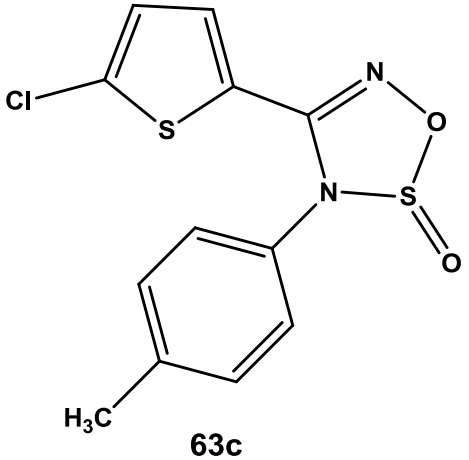

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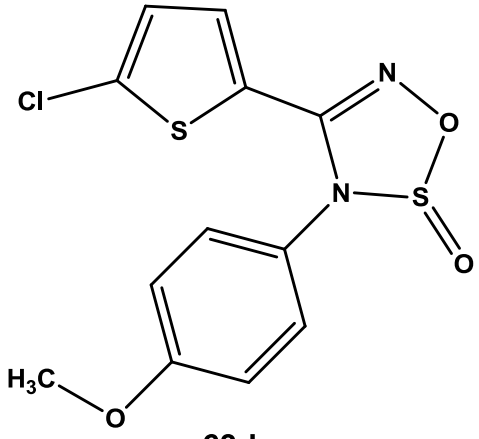

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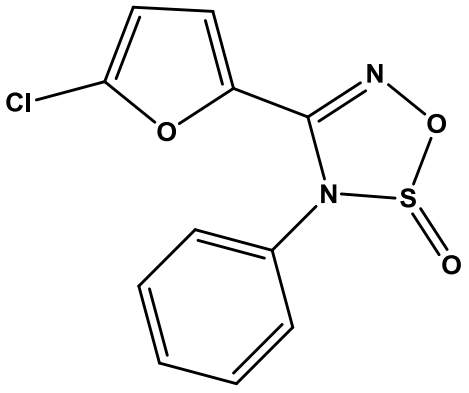

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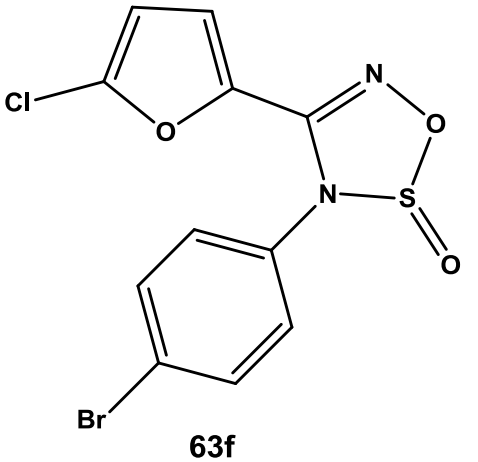

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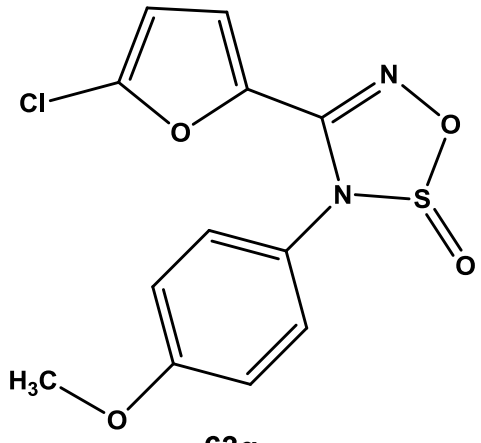

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ABBREVIATIONS

a.q.	Aqueous
cm	Centimeter
d	Doublet (NMR)
DMF	N,N-Dimethylformamide
CDI	1,1-carbonyldiimidazole
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
TCDI	1,1'-thiocarbonyldiimidazole
$SOCl_2$	Thionyl chloride
Et_3N	Triethylamine
EtOAc	Ethyl acetate
CH_2Cl_2	Dichloromethane
MeOH	Methanol
Hz	Hertz
IR	Infrared spectroscopy
J	Coupling constant (NMR)
KBr	Potassium bromide
LC-MS	Liquid Chromatography-Mass Spectroscopy
min	Minutes
h	Hours
m.p.	Melting point
MS	Mass

NMR	Nuclear magnetic resonance
ppm	Parts per million (NMR)
Rf	Retention Factor
r.t.	Room temperature
TLC	Thin Layer Chromatography

CHAPTER 1

INTRODUCTION

1.1. AMIDOXIMES

The amidoxime group can be considered as an amide in which the oxygen atom of the carbonyl group has been replaced by an isonitroso group, or as an amidine whose hydrogen atom of the imido group has been exchanged for a hydroxy radical. For this reason amidoximes are sometimes named oxamidines. They are also related to hydroxamic acids. Although the first amidoxime was prepared in 1873 by Lossen and Schifferdecker [2] from hydrogen cyanide and hydroxylamine, they did not establish the structure of this compound, which they called “isuretin” (Figure 1.1.). The name “amidoxime” was first used by Tiemann [1] , in 1884.

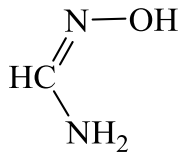
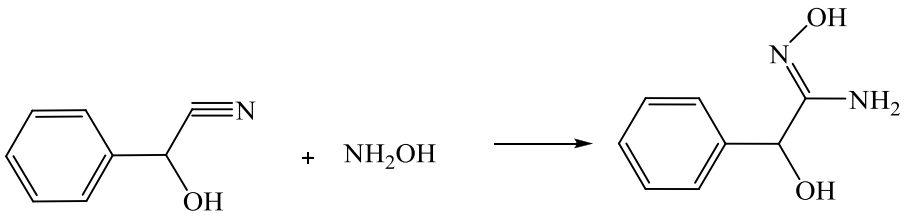


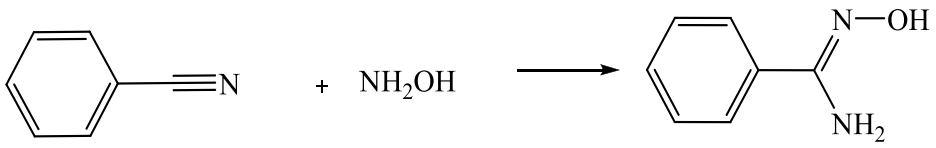
Figure 1.1. Structure of isuretin

Tiemann assigned a structural formula to the novel functional group, naming it “amidoxime.” He prepared two related compounds mandelamidoxime **4** and benzamidoxime **1** by the reaction of hydroxylamine with benzaldehyde cyanohydrin and with benzonitrile (Scheme 1.1.).



2 **3** **4**

Mandelamidoxime

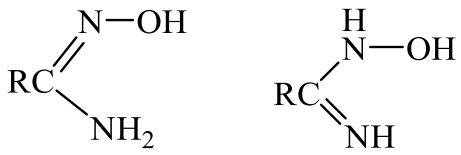


5 **3** **1**

Benzamidoxime

Scheme 1.1. Mandelamidoxime and Benzamidoxime

Tiemann recognized that the amidoximes may be present in two tautomeric forms with **6a** predominant (Figure 1.2.).



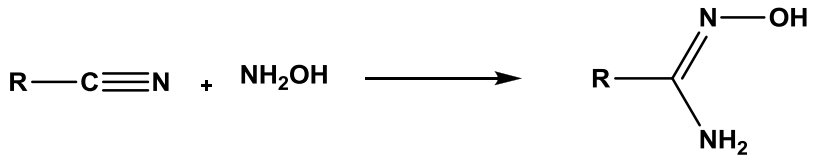
6a **6b**

Figure 1.2. Structures of tautomers

1.1.1 Synthesis of Amidoximes

1.1.1.1 By Action of Hydroxylamines on Nitriles

This is the most used process for the preparation of amidoximes. The experimental procedure recommended by Tiemann and Kruger [1] consists in liberating hydroxylamine from its hydrochloride using sodium carbonate, adding an equivalent amount of nitrile and enough alcohol to obtain a clear solution, and keeping the mixture at 60-80° C during a few hours (Scheme 1.2.).



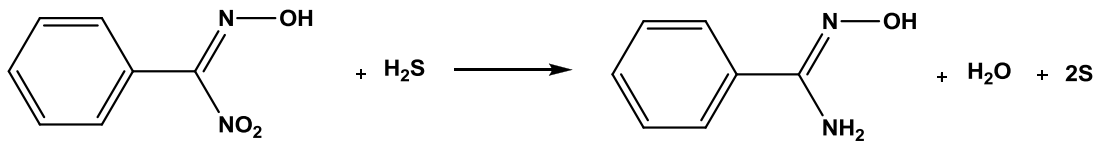
5 **3** **1**

Scheme 1.2. Action of hydroxylamine on nitriles

Aromatic amidoximes generally are obtained with better yields than are aliphatic.

1.1.1.2 By Reduction of Nitrosolic and Nitrolic Acids

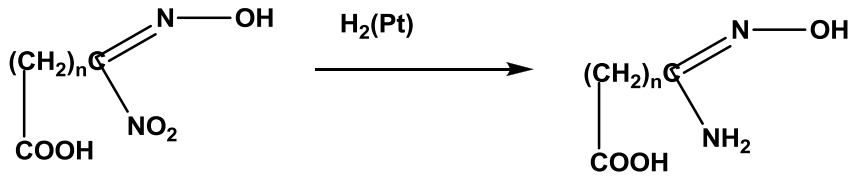
Wieland and Bauer [3] prepared benzamidoxime by reduction of nitrosolic acid **7** by hydrogen sulfide (Scheme 1.3.).



7 **1**

Scheme 1.3. Reduction of Nitrosolic Acid

A general method was found [4] for preparation of monoamidoximes of dicarboxylic acids, by catalytic reaction of nitrolic acids (Scheme 1.4.)

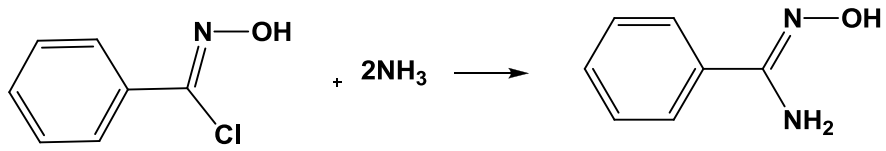


8 **9**

Scheme 1.4. Catalytic Reaction of Nitrolic Acid

1.1.1.3 By Action of Ammonia on Hydroximic Acid Chlorides (Chloroximes)

Hydroximic acid chlorides **10** are formed by chlorination of aldoximes. Werner used ammonia to react with hydroximic acid chlorides to prepare benzamidoximes, *o*-chlorobenzamidoxime [5a,5b], and terephtalomidoxime [6] (Scheme 1.5.).



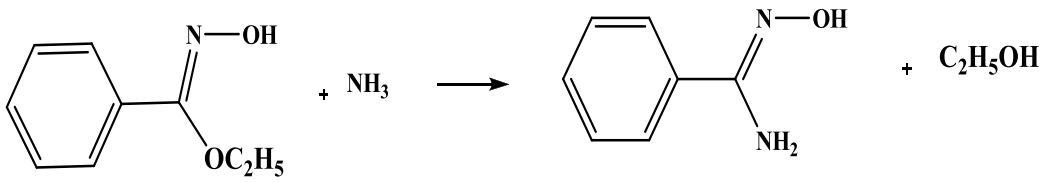
10 **1**

Scheme 1.5. Action of Ammonia on Hydroximic Acid Chloride

1.1.1.4 By Action of Ammonia on Oximinoethers

An alcoholic solution of ammonia and ethyl benzhydroxamic acid yields benzamidoxime, when heated in pressure bottle for 8 hrs. at 175° [7]. This

reaction has not found in general application (Scheme 1.6.).

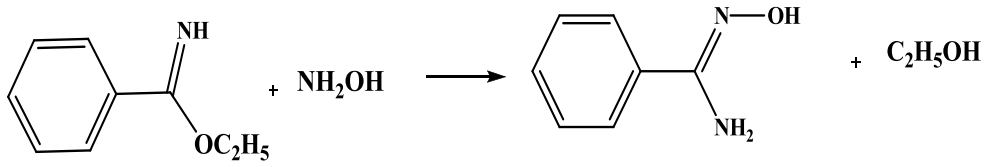


11 **1**

Scheme 1.6. Action of Ammonia on Oxoiminoethers

1.1.1.5 By Action of Hydroxylamine on Iminoethers

Pinner [8] and Lossen [9], who obtained benzamidoxime by treating ethyl iminobenzoate with hydroxylamine, firstly reported this reaction (Scheme 1.7.).



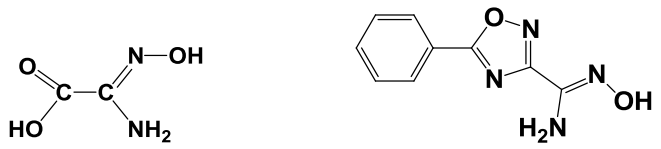
12 **1**

Scheme 1.7. Action of Hydroxylamine on İminoethers

Since the benzonitrile is the starting material for the synthesis of the iminoether, this reaction is not practical method for the synthesis of amidoximes compering with method 1.1.1.1.

1.1.1.6 By Action of Hydroxylamine on Amides or Thioamides

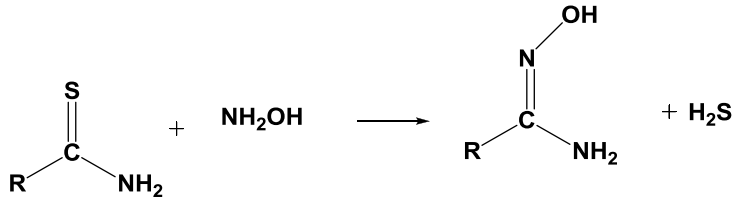
This method has only been reported [10,11] for the preperation of two amidoximes as shown below (Figure 1.3.).



13 **14**

Figure 1.3. Amidoximes which prepared by amides

The procedure for the synthesis of amidoximes from thioamides is same as from nitriles. By this method some aromatic amidoximes have been prepared [12-13].



15 **16**

Scheme 1.8. Action of Hydroxylamine on Thioamides

1.1.2 Properties of Amidoximes

1.1.2.1 Physical Properties of Amidoximes

The amidoximes are colorless, crystalline compounds. Aryl amidoximes which are insoluble in water and soluble in alcohols and some organic solvents are more stable than aliphatic amidoximes. The first member of aliphatic series is soluble in water but their solubilities decrease with increasing molecular weight. The amidoximes are O−H acids, not N−H acids as is brought out by the appreciably higher pKa of o-methyl derivative of benzamidoxime whose pKa value is 26.0. The pKa value of benzamidoxime is 23.0 [14]. Considerable work has been done since 1960 in determining

these properties for simple amidoximes such as benzamidoximes, formamidoxime, and *N,N*-dimethylacetamidoxime. These studies indicate that there is a major configurational difference between unsubstituted amidoximes or their *N*-alkyl anologues and the *N,N*-dialkyl derivatives. The free OH stretching absorption can easily observed in chloroform solution near 3620 cm^{-1} instead solid state. In solution as well as the solid state amidoximes are obviously highly associated. Structure for amidoximes is easily demonstrate by proving the presence of the amine group. The asymetric and symmetric NH_2 stretching modes can be observed as two sharp bands near 3500 and 3400 cm^{-1}, either in chloroform, benzene, acetonitrile, or in the solid state. In addition to these two sharp bands, broad absorption occurs between 2500 and 3300 cm^{-1}, attributable to associated OH and SH stretching frequencies. All of amidoximes exhibit a very strong band between 1650 and 1670 cm^{-1} both in the solid state and in solution.

1.1.2.2 Chemical Properties and Reactions of Amidoximes

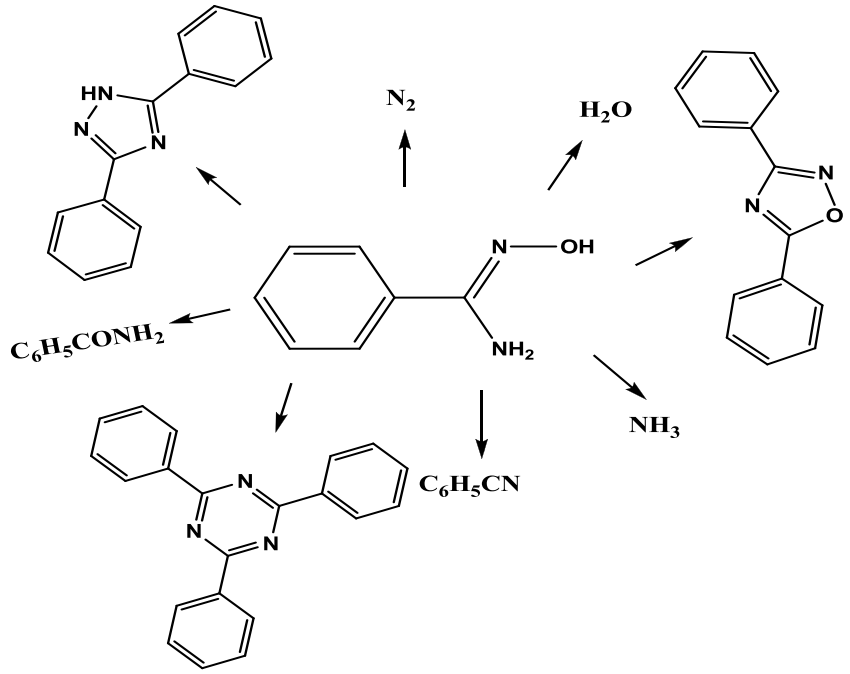
1.1.2.2.1 Salt Formation

The amidoximes are amphoteric substances, soluble in dilute mineralacids as well as in aqueous alkaline solutions [15]. Amidoximes form colored crystalline compounds with the salts of some metals. Werner [16] prepared a great number of such compounds with different amidoximes and proved that they are internal complexes in which the metal atom is linked to the oxime group as well as the amino group. These amidoximes have been used as analytical reagents for various cations [17, 18].

Oxamidedioxime (“Niccolox”), which forms complex salts with Ni^{++}, Cu^{++}, Ag^{+}, Co^{++}, has been applied in quantitative analysis [19, 20, 21, 22]. Nicotinamidoxime can be used for the spectrophotometric determination of uranium [23].

1.1.2.2.2 Thermal Decomposition

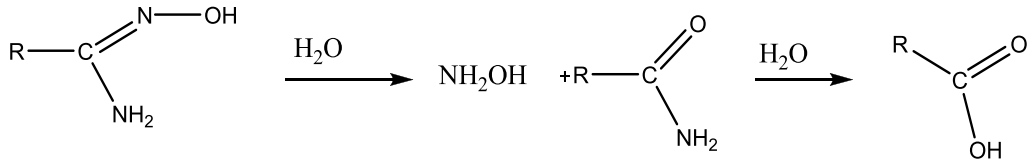
Generally, amidoximes are decomposed when heated in the neighborhood of their melting point. Benzamidoxime is melting at 80℃ and stable up to 170℃. At this temperature it decomposes, yielding several products which were identified [24] as nitrogen, ammonia, water, benzonitrile, benzamide, diphenyl 1, 2, 4-oxadiazole, diphenyl-1, 2, 4-triazole and triphenyl-1, 3, 5-triazine.



Scheme 1.9. Decomposition of Benzamidoxime

1.1.2.2.3 Hydrolysis

Many amidoximes, which at room temperature form soluble salt's with dilute mineral acids and alkalies, are hydrolyzed completely when heated in the same media [25]. Amides and hydroxylamine are formed, and under drastic conditions the amides are hydrolyzed into the corresponding acids.



Scheme 1.10. Hydrolysis of Amidoximes

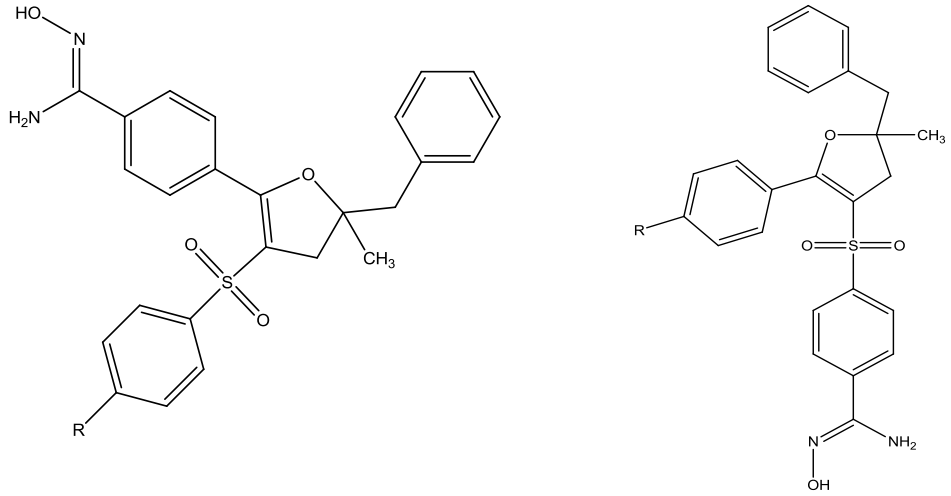
At 200°C, a solution of ammonium hydroxide hydrolyzes benzamidoxime into benzamide and ammonium benzoate [26]. Oxamidedioxime is hydrolyzed by concentrated hydrochloric acid into oxalic acid, ammonia, and hydroxylamine [27, 28].

1.1.2.2.4 Reduction of Amidoximes

The reduction of benzamidoxime with sodium amalgam [15, 29] produces ammonia and benzaldoxime with a yield of only 10 to 12%; most of the amidoxime remains unchanged. Amidines can be prepared by reduction of the corresponding amidoximes [30] in the presence of Raney nickel at 30 atm and 60-80°C. The electrolytic reduction of benzamidoxime in 3.3% HCl also yields benzamidine [30].

1.1.2.3. Biological Properties of Monoamidoximes

Some derivatives of monoamidoximes **17, 18** has been tested for antileishmanial activity (Figure 1.4.). And seen that substituents such as halogen, trifluoromethyl or methoxy groups improve antileishmanial activity on monoamidoximes.



17 **18**

Figure 1.4. Monoamidoximes which tested for activity

The best activities has been obtained for substituents carried on the sulfone moiety with amidoxime carried on the other benzenic moiety. Nitro groups seem to decrease antileishmanial activity. Cytotoxicity seems to be increased by iodo and methoxy substituents when amidoxime is carried on the sulfone moiety [31].

1.2 OXADIAZOLE

Nitrogen-oxygen heterocycles are of synthetic interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities. It is well known that oxadiazole is a

heterocyclic nucleus has attracted a wide attention of the chemist in search for the new therapeutic molecules [32]. There are four possible isomers of oxadiazole (**I, II, III, IV**) depending on the position of nitrogen atom in the ring and are numbered as shown in (Figure 1.5.)[33].

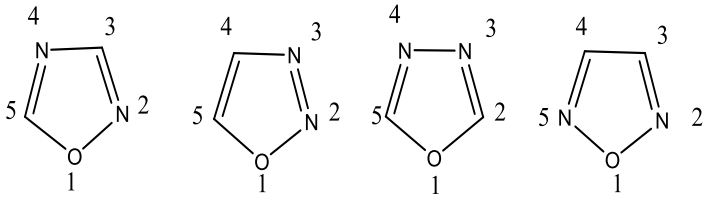


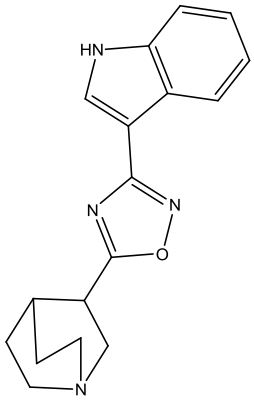
Figure 1.5. Isomers of oxadiazole

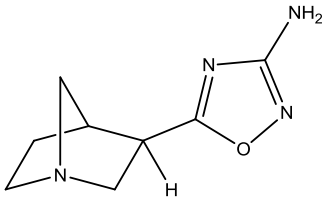
The electrophillic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However the attack of electrophiles occurs at nitrogen, if oxadiazole ring is substituted with electron-releasing groups. Oxadiazole ring is generally resistant to nucleophilic attack. Halogensubstituted oxadiazole, however, undergo nucleophilic substitution with replacement of halogen atom by nucleophiles. Oxadiazole undergo nucleophilic substitution similarly as occurring at an aliphatic sp^2 carbon atom [34].

1.2.1. 1,2,4-Oxadiazole

1,2,4-Oxadiazole rings occur widely in biologically active synthetic compounds, and are often used in drug discovery as hydrolysis-resisting bioisosteric replacements for ester or amide functionalities. Furthermore,

1,2,4-oxadiazoles are well-known nitrogen compounds and sizeable work has been done in this area since their first preparation in 1884 [35]. The synthesis of 1,2,4-oxadiazoles has received much attention and has been the subject of intense studies [36]. Most of surveys indicate that more than half of the original publications concerned the biological activity of these compounds and the basic concept behind developments is that the 1,2,4-oxadiazole ring is a hydrolysis-resisting bioisosteric alternative for an ester moiety. Its derivatives can be found in a vast number of compounds exerting biological activity such as ligands of benzodiazepine receptors, [37,38] anti-inflammatory agents, [39, 40, 41] antiviral agents, [42] inhibitors of protein tyrosine phosphatases, [43] agonists of muscarinic receptors, [44,45] antagonists of histamine HT_3^- receptors (Figure 1.6.) [46].





exo-diastereoisomer

1.Potent 5-HT_3 antagonist 2.Highly efficacious muscarinic antagonist

Figure 1.6. Examples of biologically active 1,2,4-Oxadiazoles

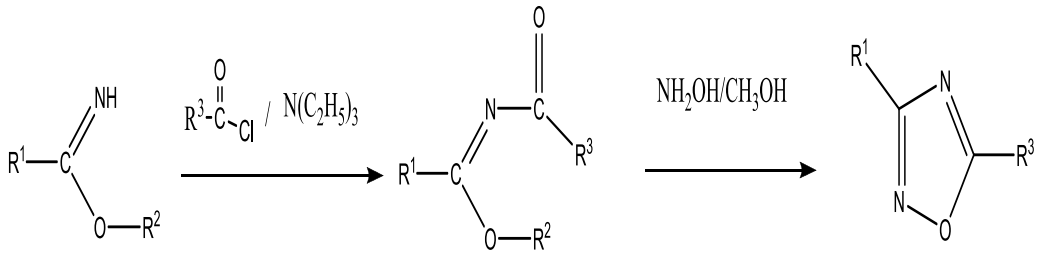
The basicity of the 1,2,4-oxadiazole, a fundamental property that governs many aspects of its chemical reactivity and is an essential factor influencing practical use of compounds. 1,2,4-oxadiazoles are as weak organic bases. Thus, the ability of these heterocycles to form azolium (quaternized) salts has

examined and it has been suggested that the ‘quaternization’ of 5-phenyl-1,2,4-oxadiazoles takes place at N(2) predominantly because of steric reasons [47]. Basicity constants of a series of 1,2,4-oxadiazoles which has determined experimentally has positioned these compounds as weak bases. Protonation of the 1,2,4-oxadiazole ring occurs predominantly at N(4). Ring substituents can have a pronounced effect not only on the basicity constant but also on the regioselectivity of protonation [48]. Five general synthetic methods have been reported for the preparation of 1,2,4-oxadiazole ring systems: condensation of amidoximes with derivatives of carboxylic acids to give *o*-acylamidoximes, which are cyclized to 1,2,4-oxadiazoles; cyclization of *N*-acylamidoximes; 1,3-dipolar cycloaddition of nitrile oxides to nitriles; electrocyclic ring closure of nitrenoids; and oxidation of 4,5-dihydro-1,2,4-oxadiazoles [49]. The most common methods recently reported for the synthesis of 1,2,4-oxadiazoles are cyclization of *o*-acylamidoximes obtained from acylation of amidoximes by carboxylic acids or acid chlorides [50].

1.2.2 Synthesis of Oxadiazoles

1.2.2.1 Preparation of 1,2,4-Oxadiazoles by Alkyl *N*-Acylimidates

On the treatment of alkyl *N*-acylimidates **19** with hydroxylamine, a fast attack of the amino group on the imidic carbon is observed at room temperature. The cyclization to the 1,2,4-oxadiazoles **20** is slow under these conditions and, in some instances heating is needed (Scheme 1.10.)[51].

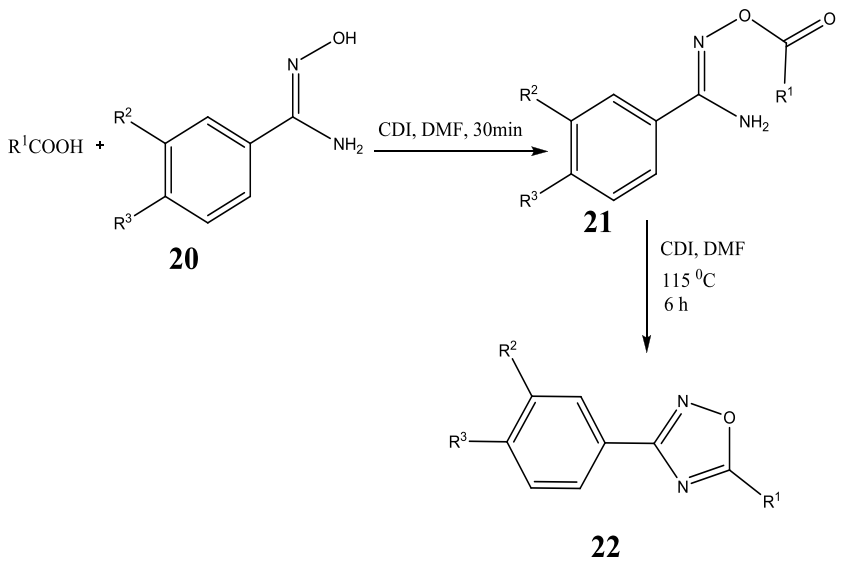


19

Scheme 1.11. The cyclization of 1,2,4-Oxadiazoles

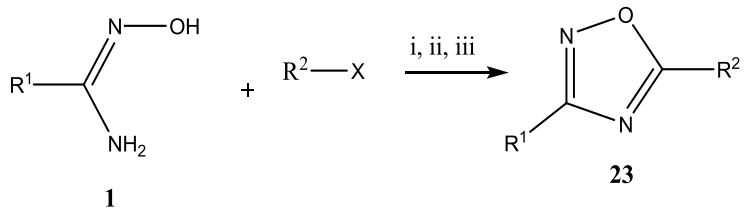
1.2.2.2 Preparation of 1,2,4-Oxadiazole from Acylation of Amidoximes with Derivatives of Carboxylic Acids

The well-known reactions of amidoximes, which have been thoroughly studied since 1920–1930 are those involving their acylation. The majority of publications devoted to the chemistry of amidoximes refer to the synthesis of *o*-acylated amidoximes and 1,2,4-oxadiazoles, which are among the most readily accessible heterocycles inrecent years. The most common method for synthesizing 1,2,4-oxadiazoles involves *o*-acylation of amidoximes followed by cyclodehydratation. Acyl chlorides, anhydrides, esteres, fluorides, and trichloroalkanes are commonly used as acylating agents [45]. Carboxylic acids in the presence of coupling reagents like dicyclohexylcarbodiimide (DCC), 1,1'-carbonyldiimidazole (CDI), or 1-[3(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) are also employed to achieve the same procedure [52]. The general approach to parallel solution-phase synthesis of 1,2,4-oxadiazoles is provided in (Scheme 2.2). Carboxylic acids **20** were activated with CDI in DMF at room temperature and treated with readily available benzamidoximes **1** in DMF (Scheme 1.12.) [53].



Scheme 1.12. Parallel Synthesis of 1,2,4-Oxadiazole using CDI Activation

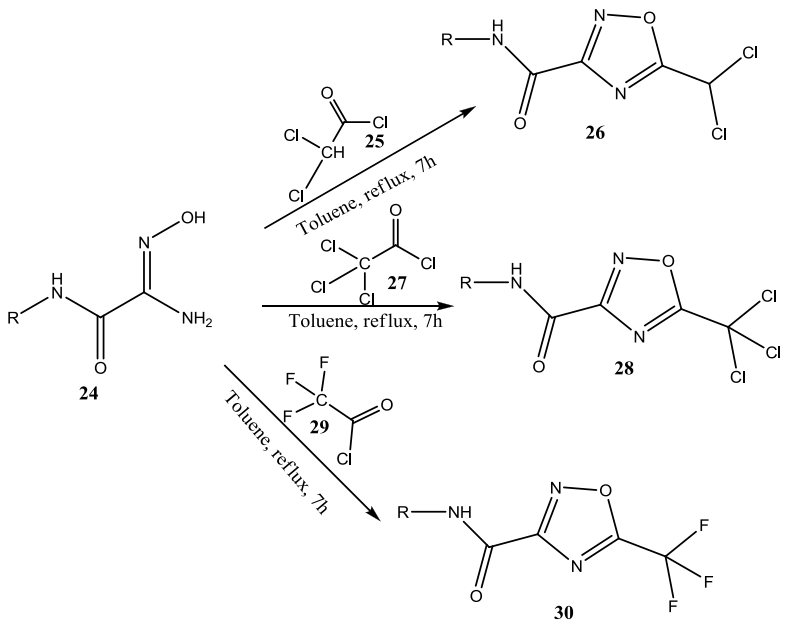
Other methods to obtain 1,2,4-oxadiazoles include reactions of amidoximes with aryl halides in the presence of palladium catalysts, or with aldehydes followed by oxidation (Scheme 1.13)[54].



i: X= -C(O)Cl, -C(O)F, -C(O)O-C(O)R^2
ii: X= -C(O)OH, coupling reagent
iii: X= -Hal (R^2=Ar) , -CHO, -CN

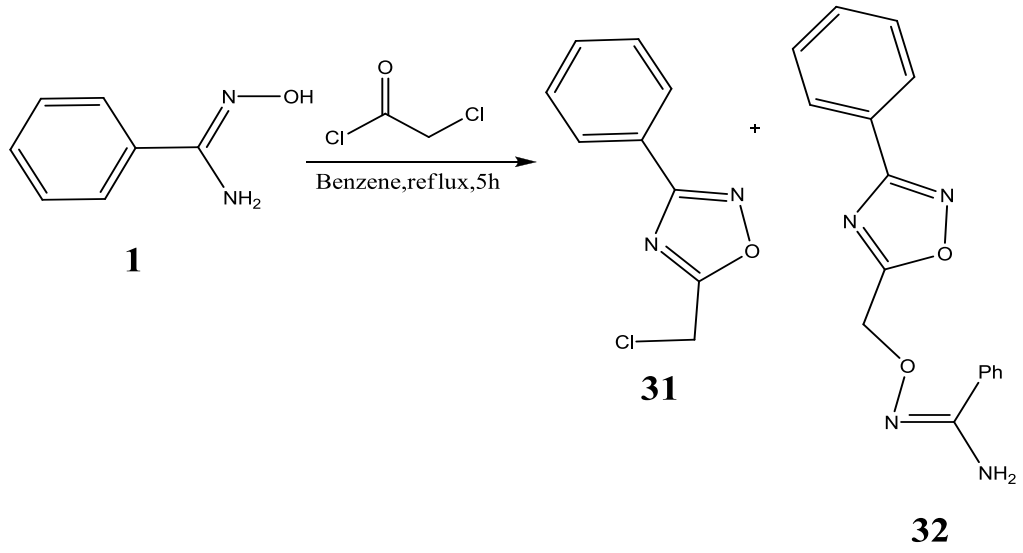
Scheme 1.13 Synthesis of 1,2,4-oxadiazole by oxidation

Yarovenko **et al.** isolated 1,2,4-Oxadiazoles as the only products of reactions between carbamoylamidoximes **24** and chloroanhydrides and anhydrides of halogenoacetic acids (Scheme 1.14.) [55].



Scheme 1.14. Synhtesis of 1,2,4-Oxadiazole from Anhydride of halogenoacetic acid

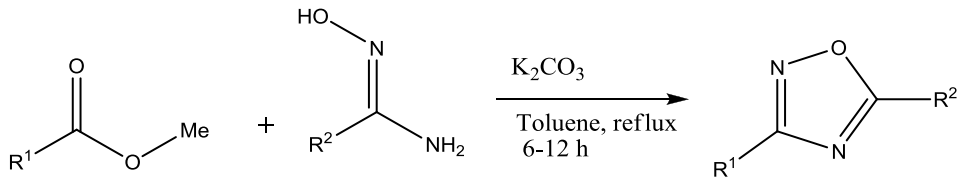
Dürüst **et al**. reported that the reaction of benzamidoxime **1** with chloroacetyl chloride **25** on boiling in benzene led to the formation of 1,2,4-oxadiazole **31** and 3-methyl-*4H*-1,2,4-oxadiazin-5(*6H*)-one **32** (Scheme 1.15.) [56].



Scheme 1.15. Synthesis of 1,2,4-oxadiazole from chloroacetyl chloride

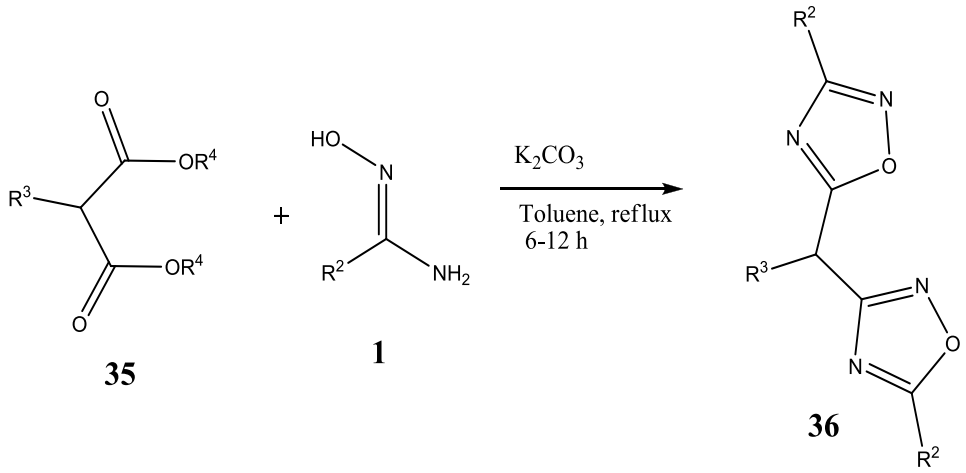
1.2.2.3 Other Methods for Preparation of 1,2,4-Oxadiazole

A convenient one-pot synthesis of 1,2,4-oxadiazoles is described by Kande **et al**. The condensation of carboxylic acid esters and amidoximes in the presence of potassium carbonate to synthesize a variety of mono-, bis- and tris-oxadiazoles in moderate to excellent yields (Scheme 1.16.) (Scheme 1.17.) [57].



33 **1** **34**

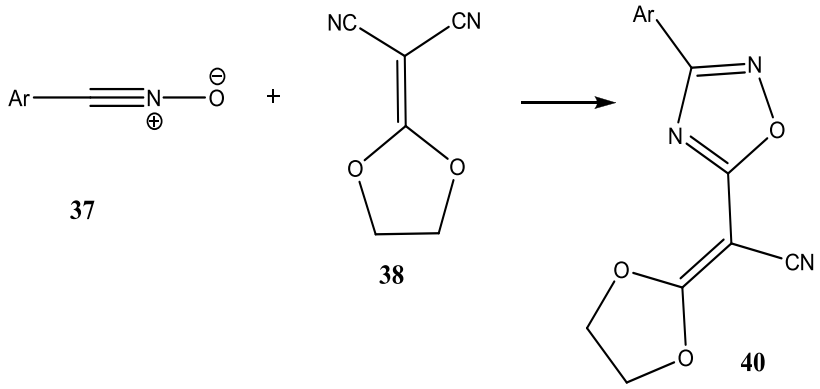
Scheme 1.16. Synthesis of 1,2,4-oxadiazoles



35 **1** **36**

Scheme 1.17. Synthesis of bis-1,2,4-oxadiazoles

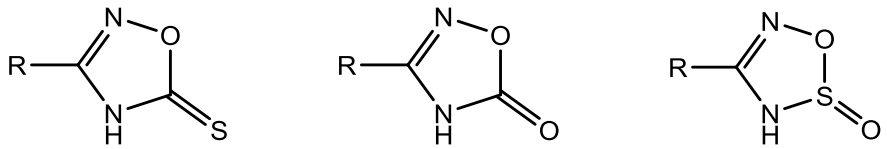
Neidlein **et al**. also developed another method, which is producing 1,2,4-oxadiazole *via* the cycloaddition of nitrile oxides **37** to nitriles **38** (Scheme 1.18.) [58].



Scheme 1.18. Formation of 1,2,4-oxadiazole from nitriles

1.3 OXADIAZOLONES and ANALOGUES

Various acidic heterocycles are classically used by medicinal chemists as carboxylic acid bioisosters. Some examples of acidic heterocycles are 1,2,4-oxadiazol-5-one, 1,2,4-oxadiazol-5-thione, 1,2,3,5-oxathiadiazol-2-oxide rings (Figure1.7). In particular, 1,2,4-oxadiazol-5-one is found in AT1 antagonists, COX inhibitors, PLA2 inhibitors and modulators of GluR. Compounds bearing these heterocycles have different lipophilic properties that may translate into improved bioavailability compared with their tetrazole analogues [59]. All these heterocycles can replace carboxylic acids but display geometrically different protomers and slightly different physico-chemical properties [60].



42 **41** **43**

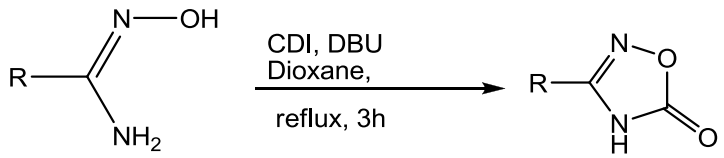
Figure 1.7. Structures of 1,2,4-oxadiazol-5-one, 1,2,4-oxadiazole-5-thione and 1,2,3,5-oxathiadiazol-2-oxide

1.3.1 Synthesis of 1,2,4-Oxadiazol-5-ones

Oxadiazolones are versatile synthetic intermediates that serve as precursors and protecting groups for amidines, an important class of biologic functionality [61].

1.3.1.1 By Cyclization Reactions of Amidoximes

1,2,4-oxadiazol-5(*4H)*-one **41** is obtained by treatment with 1,1'-carbonyldiimidazole (CDI) and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (Scheme 1.19.) [62].

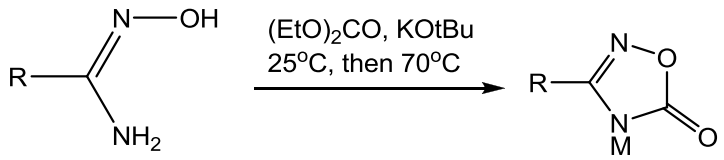


1 **41**

Scheme 1.19. Cyclization of amidoxime to 1,2,4-oxadiazol-5(*4H*)-one

1.3.1.2 Synthesis of Sodium or Potassium Salts of 1,2,4-oxadiazol-5(4*H*)-ones by Cyclization of Amidoximes

Another method defined by Hett, uses amidoximes, diethyl carbonate and KOtBu to form potassium or sodium salts of 1,2,4-oxadiazol-5(*4H*)-ones **44** (Scheme 1.20.) [62].



1 **44**

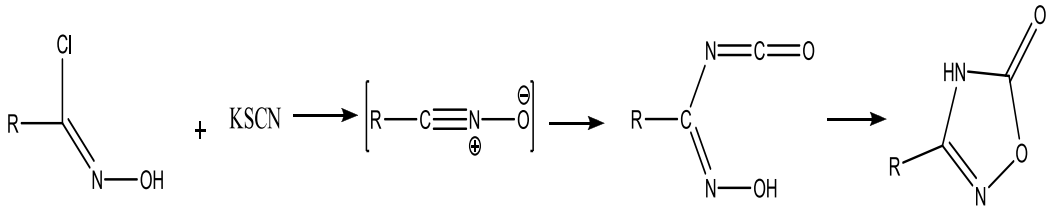
M: K

M: Na

Scheme 1.20. Synthesis of potassium or sodium salts of 1,2,4-oxadiazol-5(*4H*)-ones

1.3.1.3 By Hydroxamoyl Chlorides

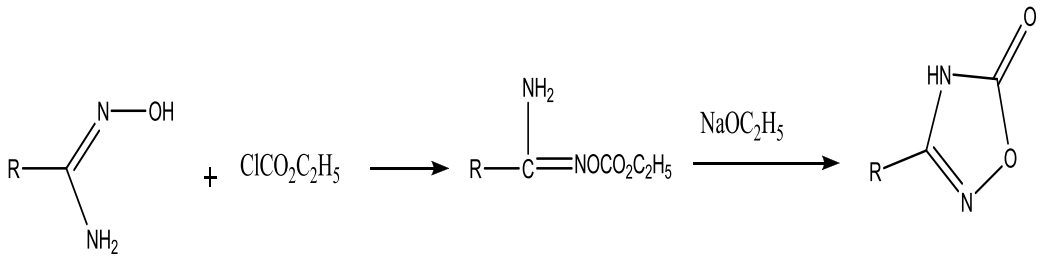
Hussein **et al.** studied that potassium cyanate reacts readily with hydroxamoyl chlorides (precursors of nitrile oxides) under mild conditions to give good yields of the corresponding 1,2,4-oxadiazol-5(*4H*)-ones (Scheme 1.21.) [63].



45 **46** **47** **41**

Scheme 1.21. Synthesis of 1,2,4-oxadiazol-5(*4H*)-one by hydoxyamoyl chloride

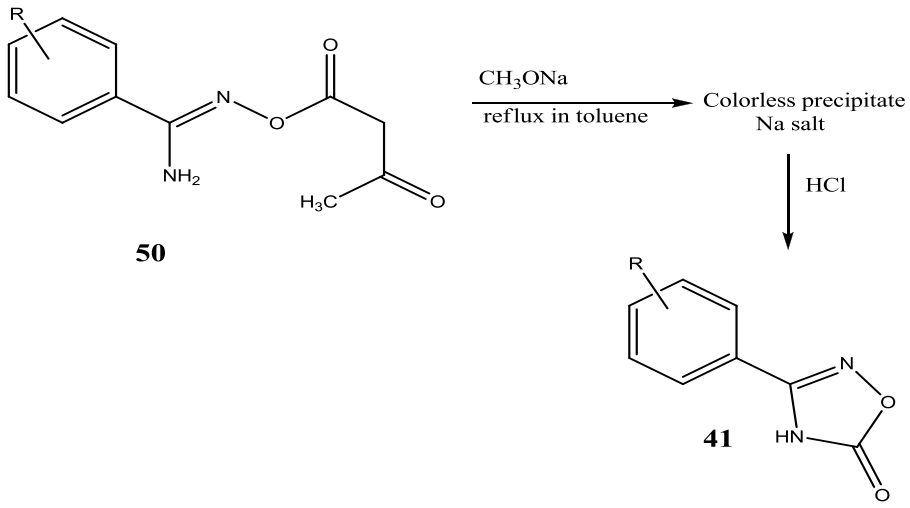
The 1,2,4-oxadiazole-5(*4H*)-ones are also prepared by cyclization of the corresponding *o*-carbethoxyamidoximes with sodium ethoxide (Scheme 1.22.) [63].



1 **48** **49** **41**

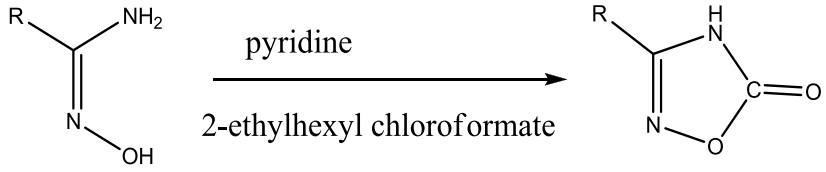
Scheme 1.22. Synthesis of 1,2,4-oxadiazol-5(*4H*)-one by cyclization of *o*-carbethoxyamidoximes

Tabei **et al.** developed a method, cyclization of *o*-Acetoacetylbenzamide oxime **50** derivatives in the presence of a strong base proceed with elimination of acetone to afford, 3-aryl-1,2,4-oxadiazol-5-one derivatives (Scheme 1.23.) [64].



Scheme 1.23. Cyclization of *o*-acetoacetyl benzamide oxime

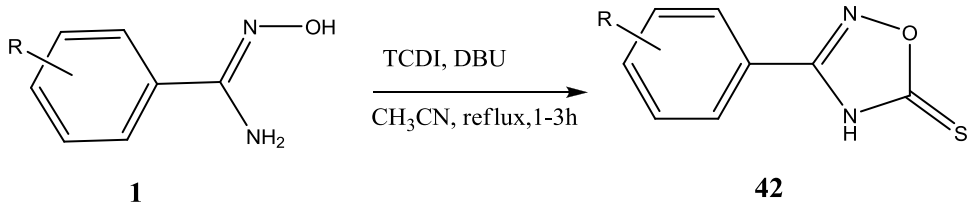
Kohara **et al.**, reported that synthesis of 1,2,4-oxadiazol-5-one by treatment of amidoximes **1** with 2-ethylhexyl chloroformate and cyclization in refluxing xylene followed by saponification (Scheme 1.24.)[65].



Scheme 1.24. Cyclization of amidoximes with 2-ethylhexyl chloroformate

1.3.2 Synthesis of 1,2,4-Oxadiazole-5-thiones

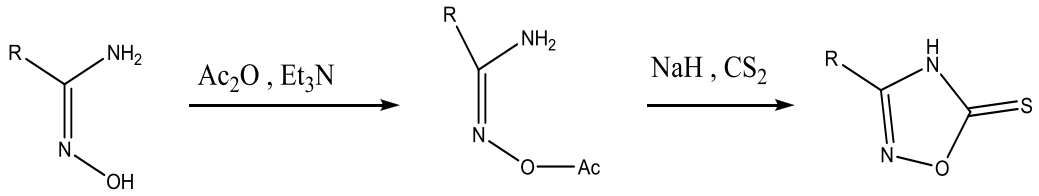
1,2,4-Oxadiazole-5-thione **42** is obtained by treatment with 1,1´ thiocarbonyldiimidazole(TCDI) and DBU(1,8-diazabicyclo[5.4.0]undec-7-ene) by Kohara **et al.** (Scheme 1.25)[65].



1 **42**

Scheme 1.25 Cyclization of amidoxime by TCDI

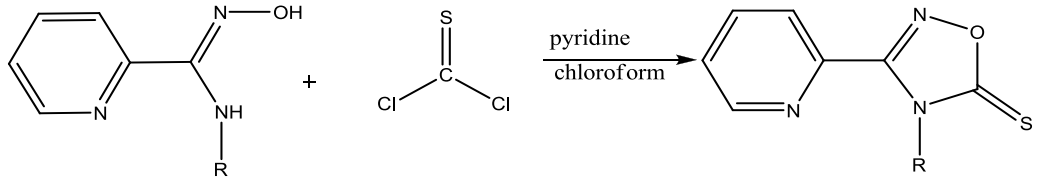
Kohara **et al.**, shows another method for syntesis of 1,2,4-oxadiazole-5-thione from the amidoximes. According to Birr's method, acetylated with acetic anhydride in the presence of triethylamine followed by treatment with carbon disulfide and sodium hydride to give the 1,2,4-oxadiazole-5-thione (scheme 1.26.) [65].



1 **42**

Scheme 1.26. Synthesis of 1,2,4-oxadiazole-5-thione according to Birr's method

Dürüst **et al**. determined that a solution of redistilled thiophosgene in chloroform adding dropwise to an ice-cooled solution of N-substituted carboxamide oxime and pyridine gives 3,4-disubstituted 1,2,4-oxadiazole-5(*4H*)-thiones (scheme 1.27.) [66].

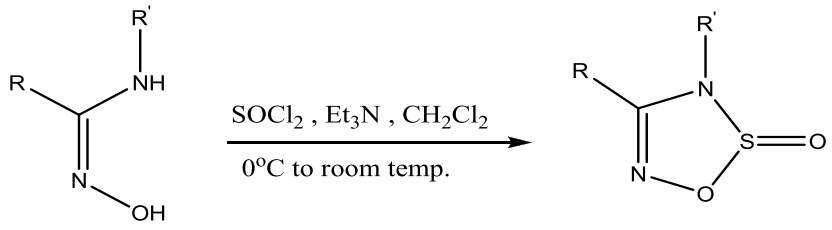


51 **52** **53**

Scheme 1.27. Cyclization of carboxamide oxime to 1,2,4-oxadiazole-5(*4H*)-thiones

1.3.3 Synthesis of 1,2,3,5-oxathiadiazol-2-oxide

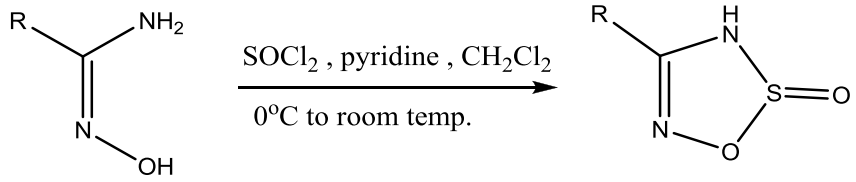
Dondoni shows that preparation of 3,4-disubstituted 1,2,3,5-oxathiadiazol-2-oxides **43** in good yields by cyclization of *N*-alkyl- and *N*-arylamidoximes with thionyl chloride in the presence of triethylamine(scheme 1.28.) [67].



51 **43**

Scheme 1.28. Cyclization of *N*-alkyl or *N*-arylamidoximes

Kohara **et al.** reported another method for synthesis of 1,2,3,5-oxathiadiazol-2-oxide **43** that uses pyridine instead of triethylamine as a base (scheme 1.29.) [65].

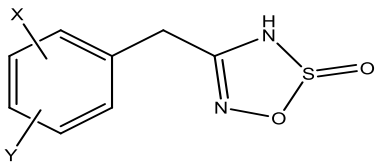


1 **43**

Scheme 1.29. Cyclization of amidoxime to 1,2,3,5-oxathiadiazol-2-oxide

1.3.4 Biological Activity Studies

Several substituted benzyloxathiadiazoles were examined in the postprandial assay in the db/db mouse by Ellingboe **et al.** All of these compounds lowered plasma glucose by less than 15% at a dose of 20 mg/kg (po).However, at the higher dose of 100 mg/kg, four compounds, **54, 55, 56,** and **57,** showed antihyperglycemic activity which was comparable to that of ciglitazone. Alkyl or aryl groups in the 4-position **58, 59, 60** were detrimental (scheme 1.30.) [68].



	X	Y
54	3-CF_3	H
55	3-Cl	H
56	2-F	4-Br
57	4-$PhCH_2O$	H
58	4-$PhCH_2CH_2O$	H
59	3-CH_3	4-CH_3
60	4-tBu	H
	4-Ph	H

Scheme 1.30. Antihyperglycemic activity of some 1,2,3,5-oxathiadiazol-2-oxides

The design, synthesis, and biological activity of benzimidazole-7-carboxylic acids bearing 1,2,4-oxadiazol-5-one, 1,2,4-thiadiazol-5-one, 1,2,4-oxadiazole-5-thione, and 1,2,3,5-oxathiadiazol-2-oxide rings are described by Kohara **et al**. The synthesized compounds were evaluated for in vitro and in vivo angiotensin II (AII) receptor antagonistic activities. Most were found to have high affinity for the AT1 receptor (IC50 value, 10-6-10-7M) and to inhibit the AII-induced pressor response (more than 50% inhibition at 1 mg/kg po). The 1,2,4-oxadiazol-5-one, 1,2,4-thiadiazole-5-one, and 1,2,4-oxadiazol-5-thione derivatives showed stronger inhibitory effects than the corresponding tetrazole derivatives, while their binding affinities were weaker. This might be ascribed to their improved bioavailability by increased lipophilicity. In this study, Kohara **et al.,** showed that the 1,2,4-oxadiazol-5-one ring and its thio analog, the 1,2,4-thiadiazol-5-one ring, could be lipophilic bioisosteres for the tetrazole ring in nonpeptide AII receptor antagonists [65].

CHAPTER II

2.1. RESULTS and DISCUSSION

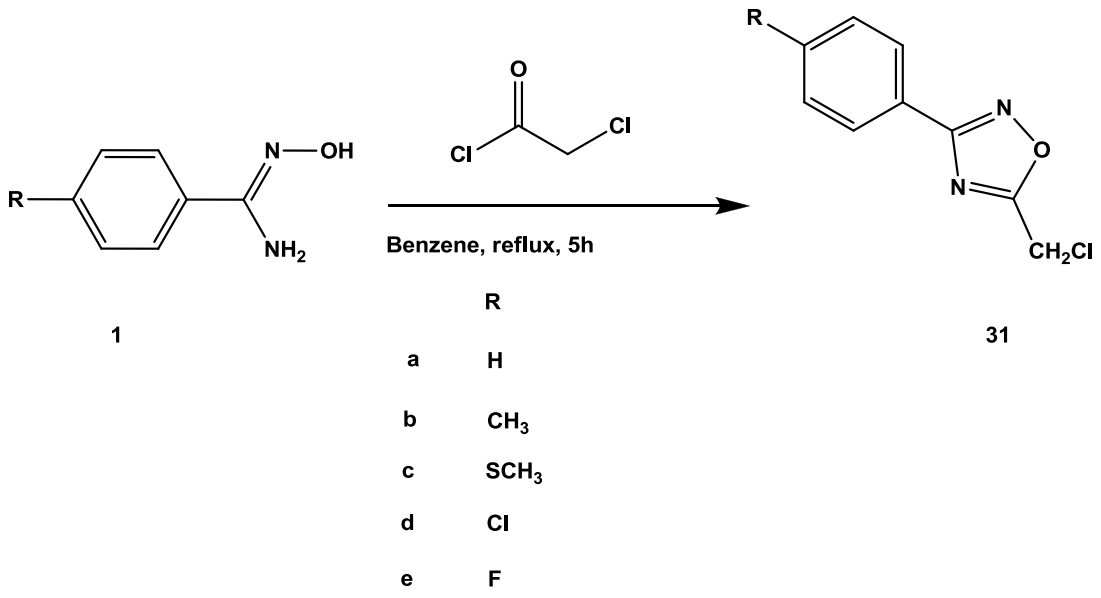
In this study, we attempted to perform *N*-substitution on the 1,2,4-oxadiazol -5(4*H*)-ones and 1,2,5,2-oxathiadiazole-S-oxides. To our best knowledge of literature based on WEB OF KNOWLEDGE, SCI FINDER and REAXYS electronic databases, there is no work related to *N*-substitution of oxadiazolones and oxathiadiazole-S-oxides with respect to 5-chloromethyl oxadiazoles and aryl groups like furyl, thiophene and phenyl moieties. 1,2,4-Oxadiazoles, oxadiazolones and oxathiadiazole-S-oxides are drawing increasing attention in recent decades due to their pharmacological activities [40, 41, 42, 65, 68]. Therefore, importance of these end products carrying both oxadiazolone and oxadiazole rings can be considered promising valuable potential bioactive molecules. In this regard, we are getting prepared to examine their bioactivities against various bacteria species and tumor cells in the near future.

The present research work is basically consisted of six parts.

1) Synthesis of substituted aryl monoamidoximes (**1a-h**) and *N*-aryl substituted furan and thiophene carboxamidoximes (**2a-g**) as primary starting materials,
2) Synthesis of aryl substituted 5-(chloromethyl)-1,2,4-oxadiazoles (**31a-e**) as one of the major starting compounds,
3) Synthesis of 3-aryl substituted-1,2,4-oxadiazol-5(*4H*)-ones (**41a-g**) (as the second component of this study),
4) Synthesis of oxadiazole-5-thiones (**42**) ,
5) Synthesis of the end products carrying both oxadiazolones and oxadiazoles.
6) Synthesis of *N*-aryl substituted oxathiadiazole-S-oxides (**63a-g**).

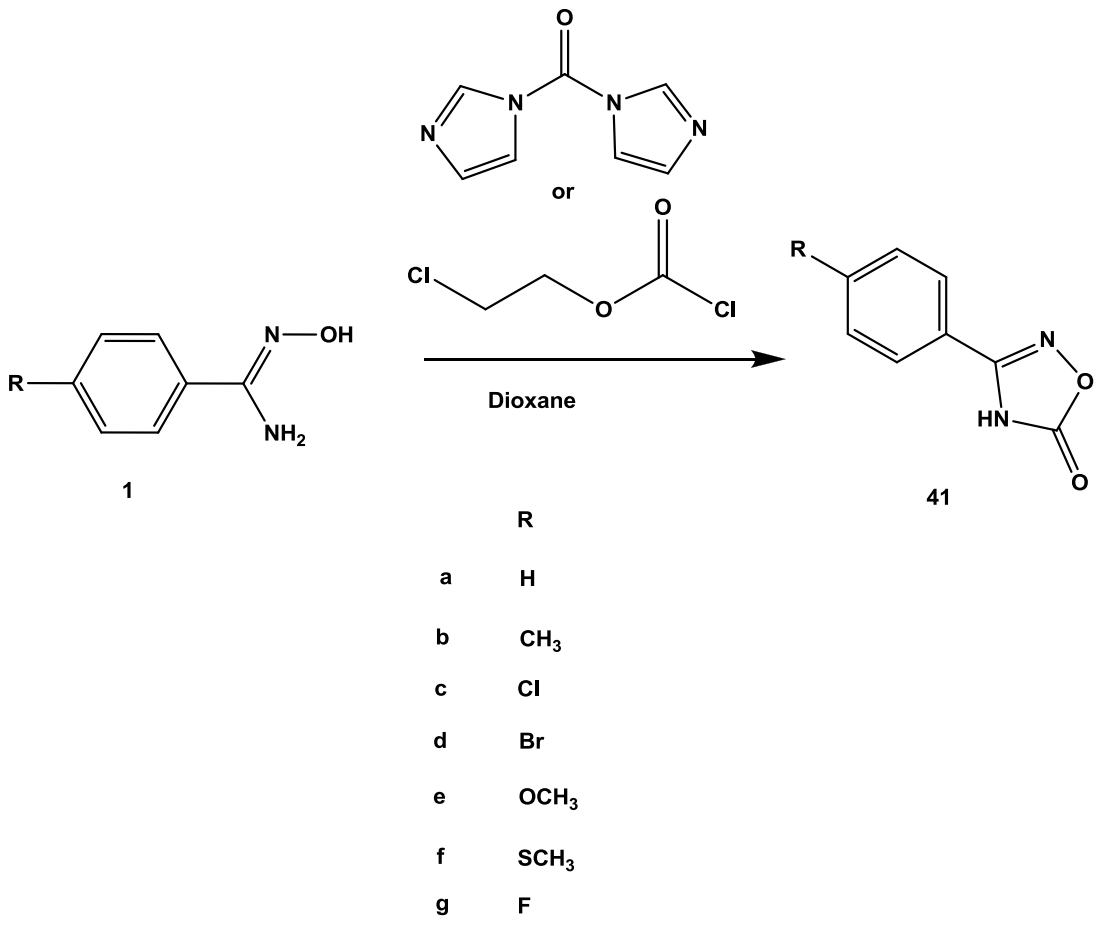
In order to carry out this project, first, aryl monoamidoximes have been prepared starting from appropriate, basically, *p*-substituted benzonitriles. Their physical/spectral data all confirmed these compounds.

Both electron-releasing and electron-withdrawing groups have been selected. After having prepared mono aryl amidoximes, they were reacted with chloroacetylchloride to yield 3-(4-substituted phenyl)-5-chloromethyl-1,2,4-oxadiazoles (**31a-e**), which are one of the major components in this work, according to the literature method described previously in [56]. These compounds are found to be similar registered in literature.

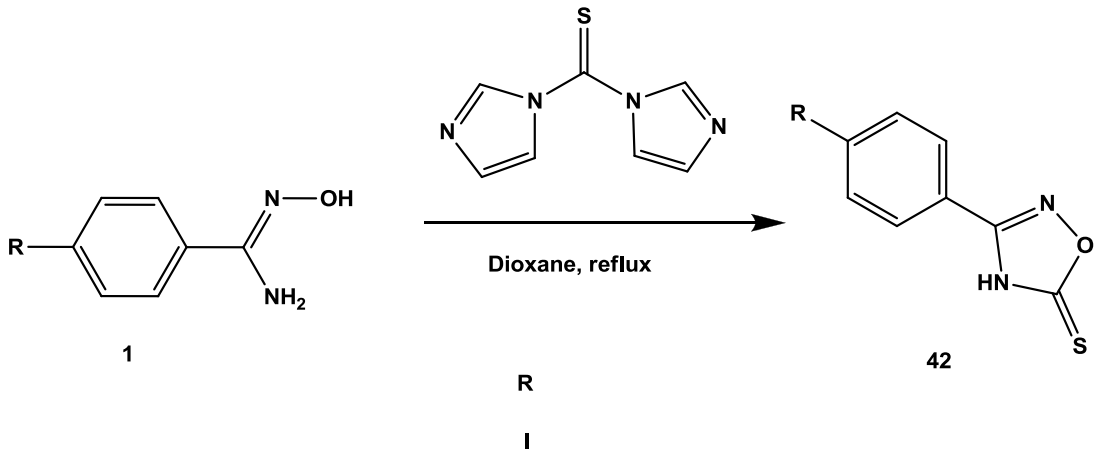


Scheme 2. 2. The synthesis of 3-aryl-5-(chloromethyl)-1,2,4-oxadiazoles **31a-e**.

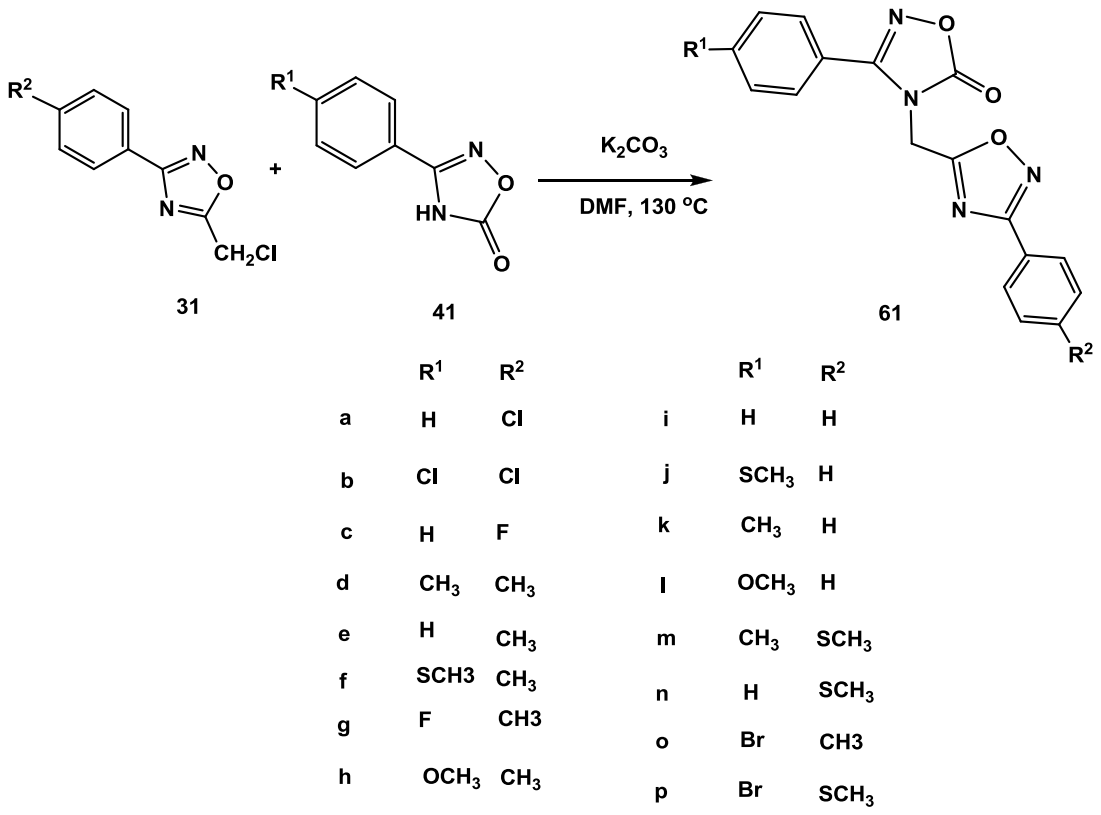
Second key reagent in this research is the 1,2,4-oxadiazolones (thiones) (**41a-g, 42**) which are unsubstituted on nitrogen. Synthesis of these compounds was performed by the reaction of monoamidoximes and 1,1-carbonyldiimidazole (CDI), 2-chloroethylchloroformate or ethylchloroformate (Scheme 2.2). The structures of oxadiazolones have been found to be similar described in literature based on the physical/chemical/spectral data.



Scheme 2.2. Synthesis of 1,2,4-oxadiazole-5(*4H*)-ones **41 a-g**.



Scheme 2.3. Synthesis of 1,2,4-oxadiazole-5(*4H*)-thione **42**.



	R1	R2		R1	R2
a	H	Cl	i	H	H
b	Cl	Cl	j	SCH_3	H
c	H	F	k	CH_3	H
d	CH_3	CH_3	l	OCH_3	H
e	H	CH_3	m	CH_3	SCH_3
f	SCH3	CH_3	n	H	SCH_3
g	F	CH3	o	Br	CH3
h	OCH_3	CH_3	p	Br	SCH_3

Scheme 2.4. Synthesis of oxadiazolyl methyl oxadiazolones **61a-p**.

Oxadiazolyl methyl oxadiazolones were identified by their physical/chemical/spectral data. Typical representative IR, ^{1}H NMR, ^{13}C NMR and MASS spectra were shown below (Figure 2.1.-4.).

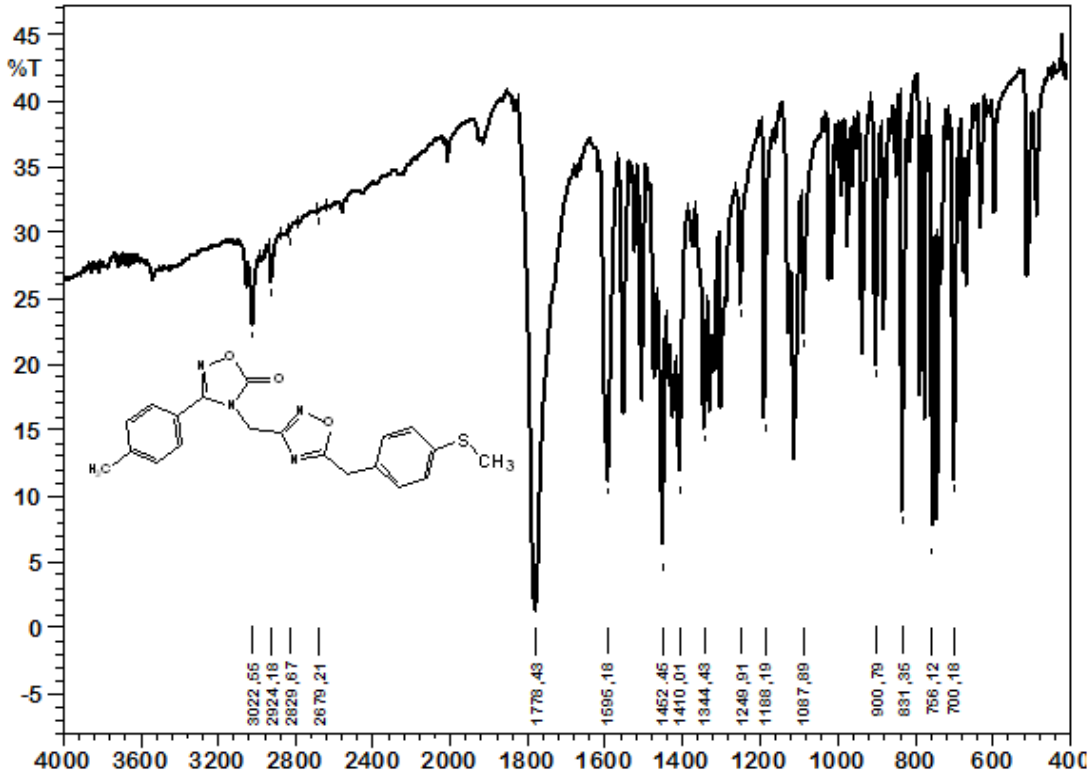


Figure 2.1. IR spectrum of **61m**

Upon investigation of the IR spectrum of the compound **61m**, we see the disappearance of the NH absorptions originated from the oxadiazolone and appearance of the carbonyl which is originally existing in oxadiazolone. Also, the C=N absorption appears at 1596 cm^{-1}.

As for ^{1}H NMR spectra, it is clearly seen the CH_2 protons at around 5.0 ppm as singlet, and SCH_3 and CH_3 protons at around 2.4 ,2.5 ppm respectively. In the ^{13}C NMR spectrum, we can see the aliphatic carbons (CH_2, *p*-tolyl CH_3 and SCH_3) at around 40, 21 and 16 ppm respectively. Carbonyl carbon appeared at around 172 ppm.Iminic carbon of the oxadiazole ring resonates at around 168 ppm, more deshielded due to being located between two sp^2 hybridized nitrogen atoms in comparison with the other imine carbons.

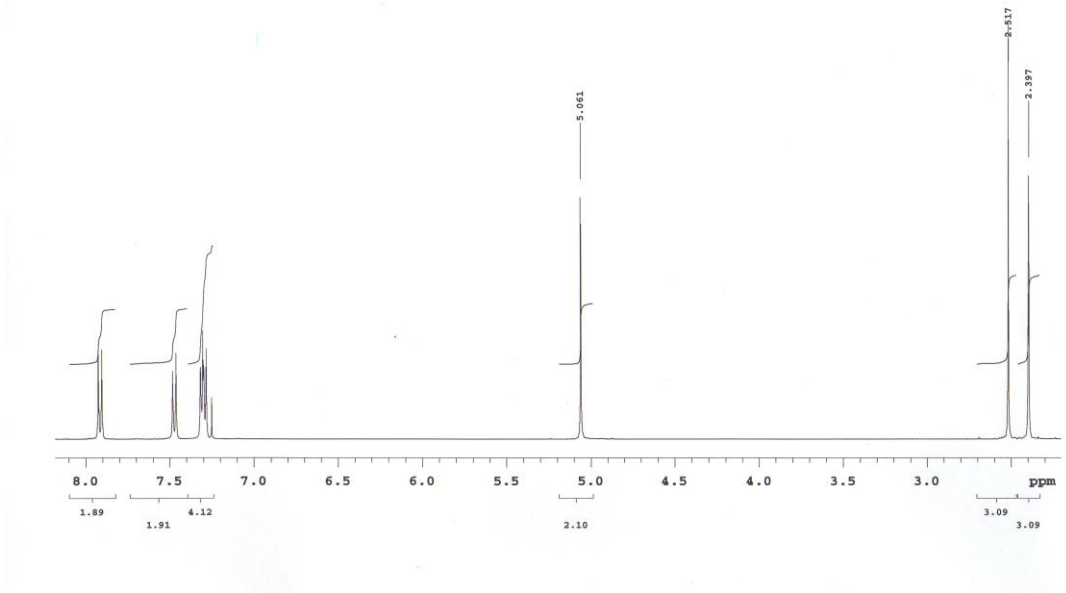


Figure 2.2. ^{1}H NMR spectrum of **61m**

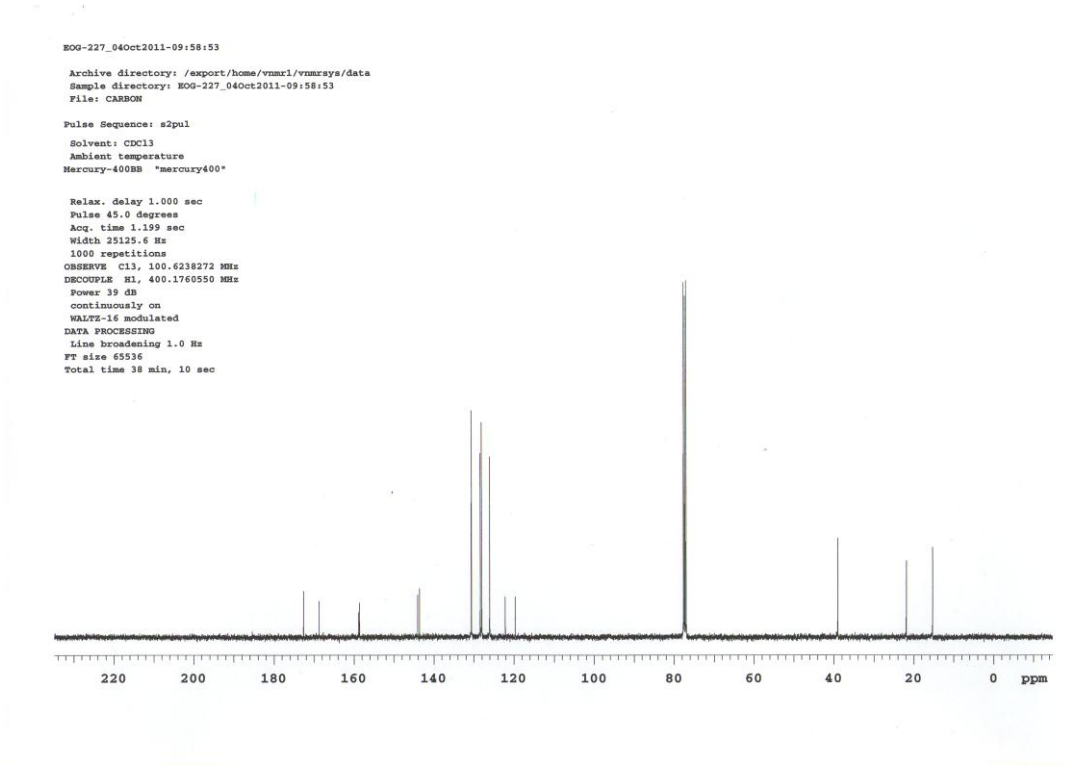


Figure 2.3. ^{13}C NMR spectrum of **61m**

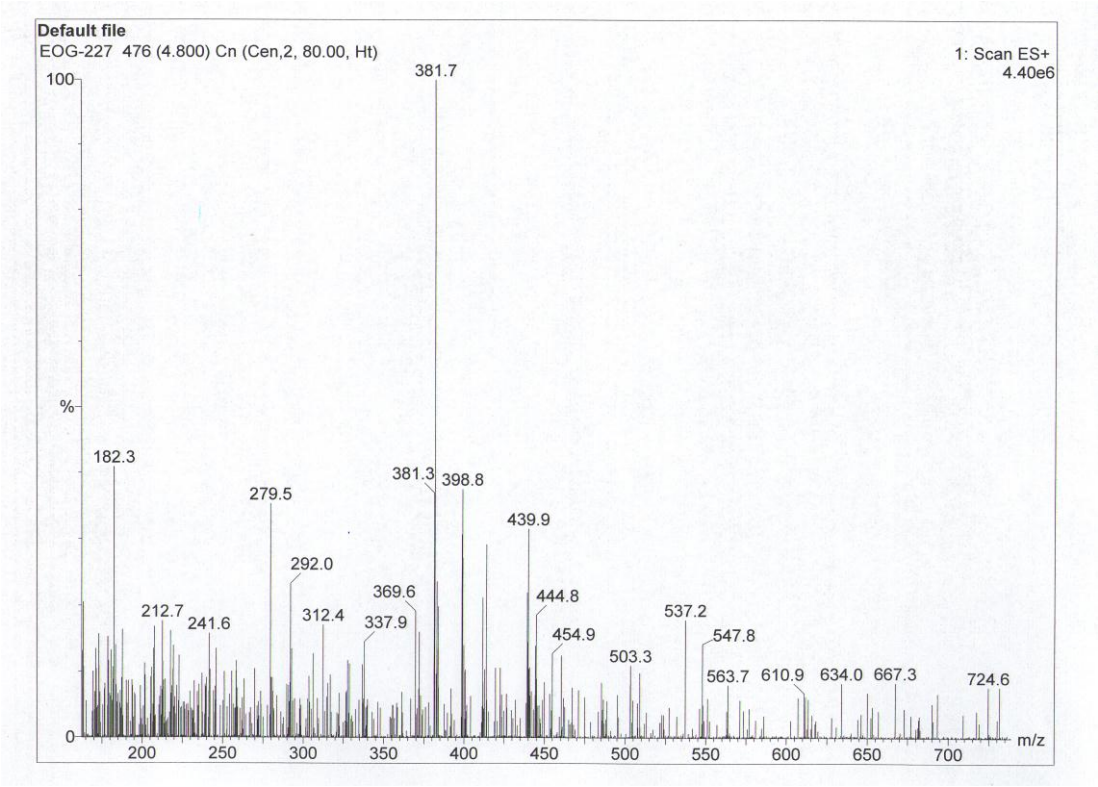
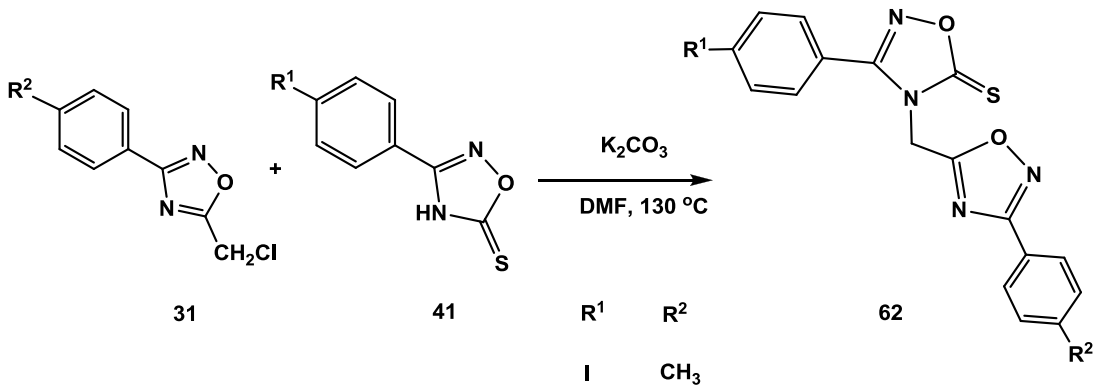


Figure 2.4. LC-MS spectum of **61m**

LC-MS spectrum shows M+H peak as base peak which is another proof of the structure.

We also wanted to obtain a representative *N*-oxadiazolyl-substituted product from 1,2,4-oxadiazole-5(*4H*) thione (Scheme 2.5). 4-Iodo substituted chloromethyl oxadiazole and p-tolyl substituted oxadiazolethione were selected as key reagents.The product was identified by spectral/physical data.



Scheme 2.5. Synthesis of *N*-oxadiazolyl methylsubstituted oxadiazole-thione **62**

All of the end products were identified by IR, NMR, MS and X-Ray Diffraction (**61e** and **61g**) spectra, m.p., and R_f characteristics. Exact structures of the compounds **61e** and **61g** were resolved by single crystal X-Ray diffraction ORTEP views (Figure 2.5. and Figure 2.6.).

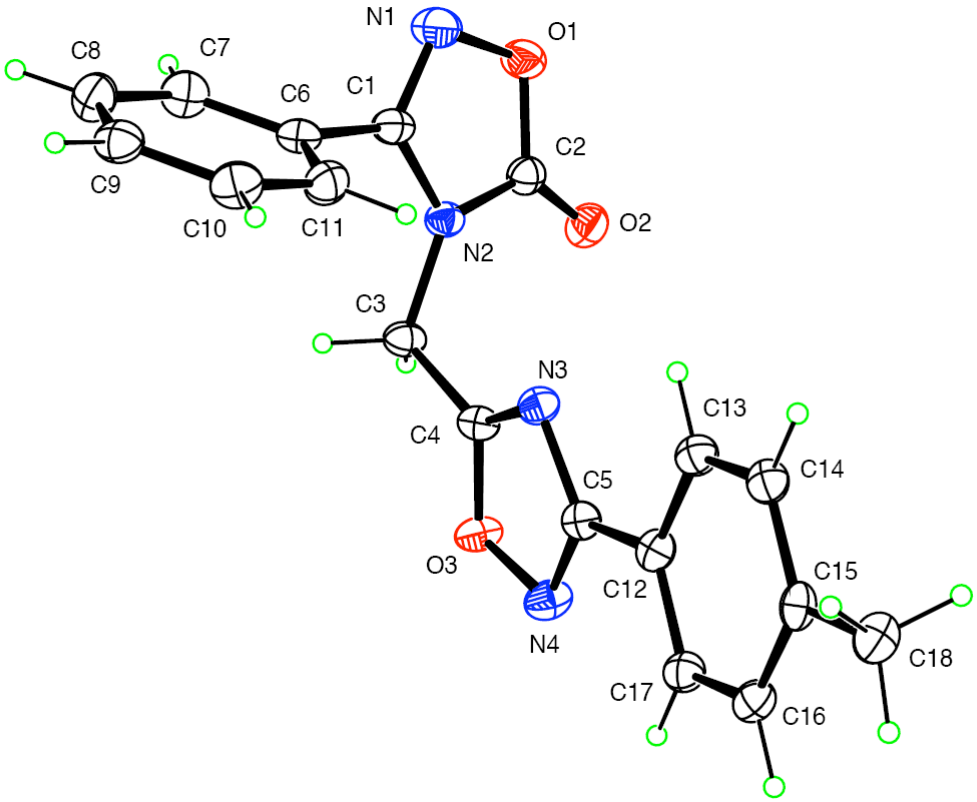


Figure 2.5. X-Ray ORTEP view of compound **61e**

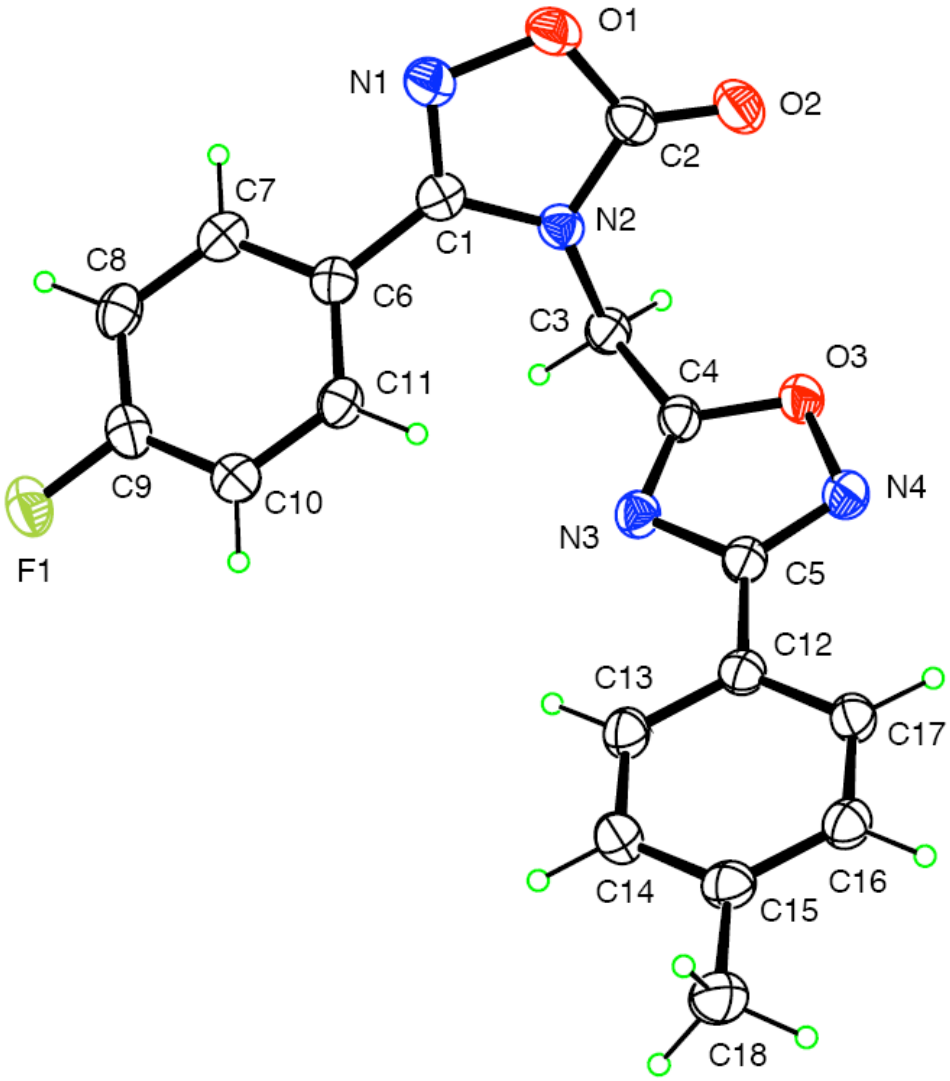
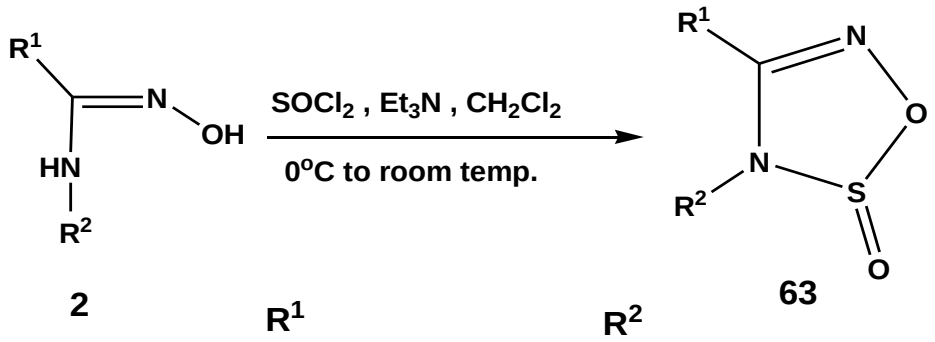


Figure 2.6. X-Ray ORTEP view of compound **61g**

In order to obtain *N*-aryl substituted 1,2,3,5-oxathiadiazole-S-oxides (**63a-g**), we conducted the reactions between the corresponding *N*-substituted 5-chlorothienyl and 5-chlorofuryl amidoximes (**2a-g**) and thionyl chloride in the presence of triethyl amine (Scheme 2.6.).



2 **63**

	R^1	R^2
a	5-chloro-2-thienyl	Ph
b	5-chloro-2-thienyl	4-C_6H_4-I
c	5-chloro-2-thienyl	4-CH_3-C_6H_4
d	5-chloro-2-thienyl	4-CH_3O-C_6H_4
e	5-chloro-2-furyl	Ph
f	5-chloro-2-furyl	4-Br-C_6H_4
g	5-chloro-2-furyl	4-CH_3O-C_6H_4

Scheme 2.6. Synthesis of 4-(5-chloro-2-thienyl and furyl)-3-substituted phenyl-3*H*-1,2,3,5-oxathiadiazole 2-oxides (**63a-g).**

Below it was illustrated the representative spectra of this group of compounds.

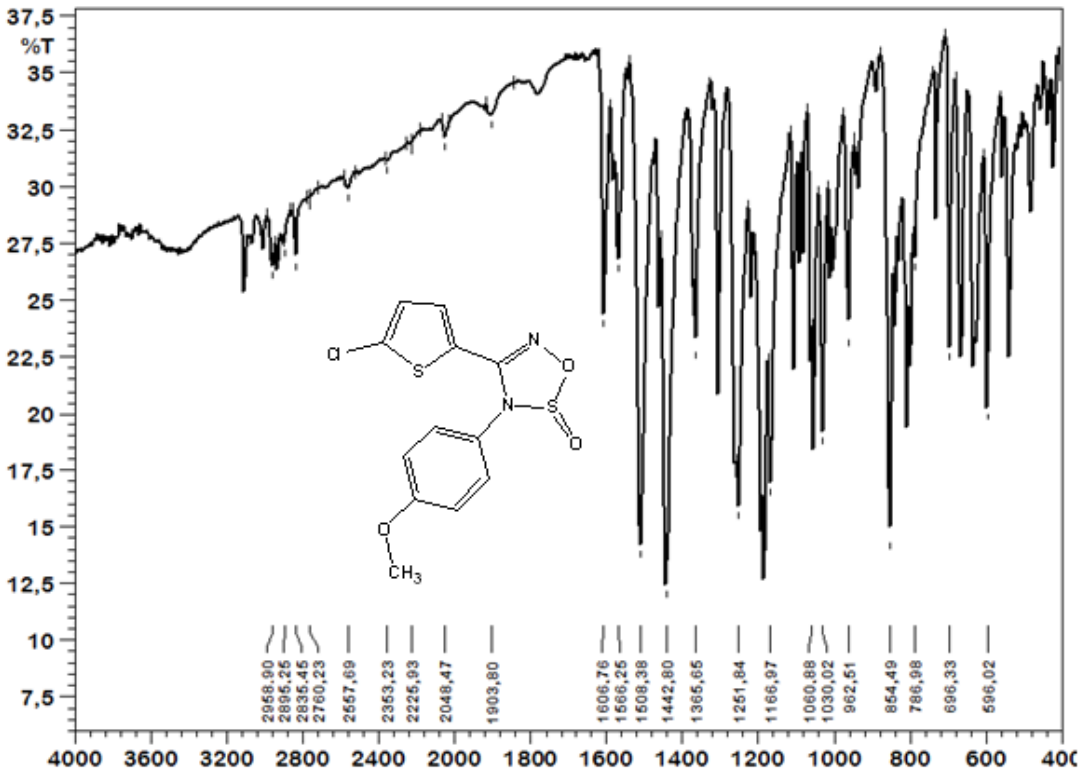


Figure 2.7. IR spectrum of compound **63d**

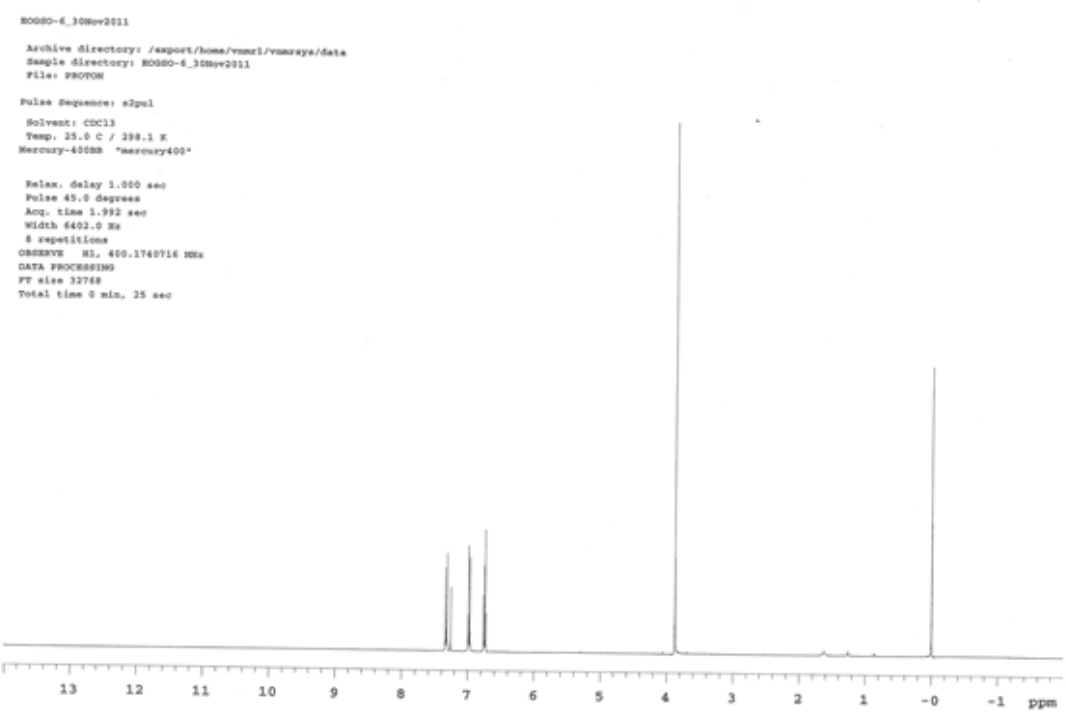


Figure 2.8. ^{1}H NMR spectrum of **63d**

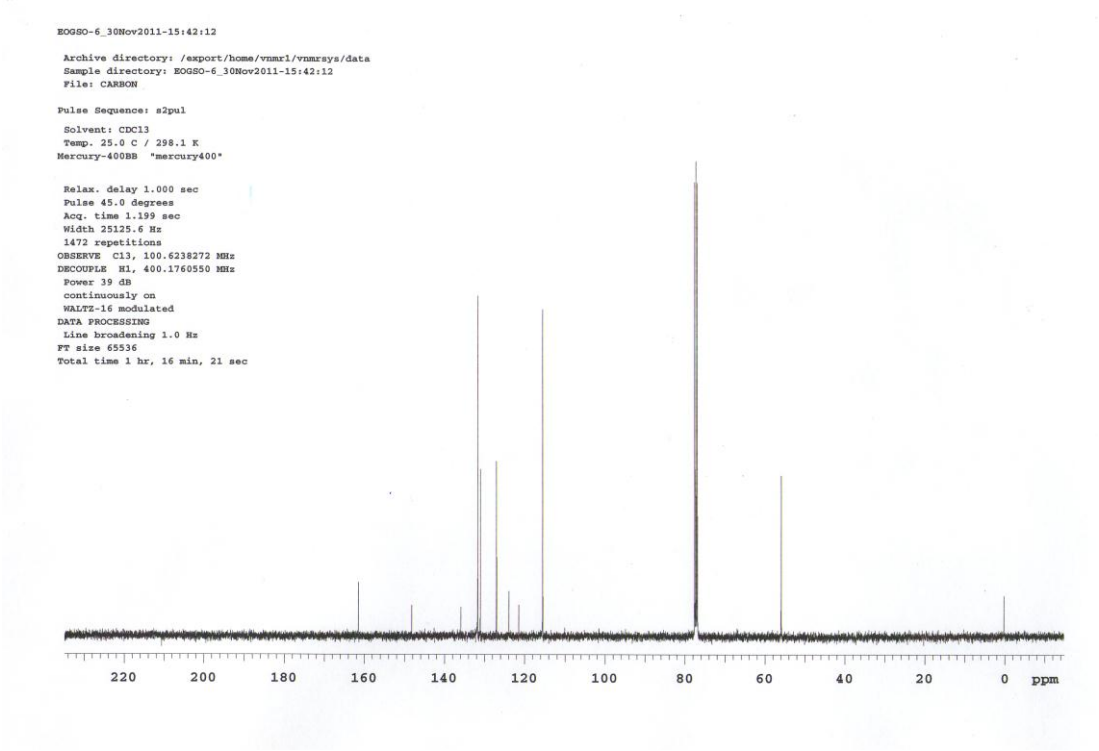


Figure 2.9. ^{13}C NMR spectrum of **63d**

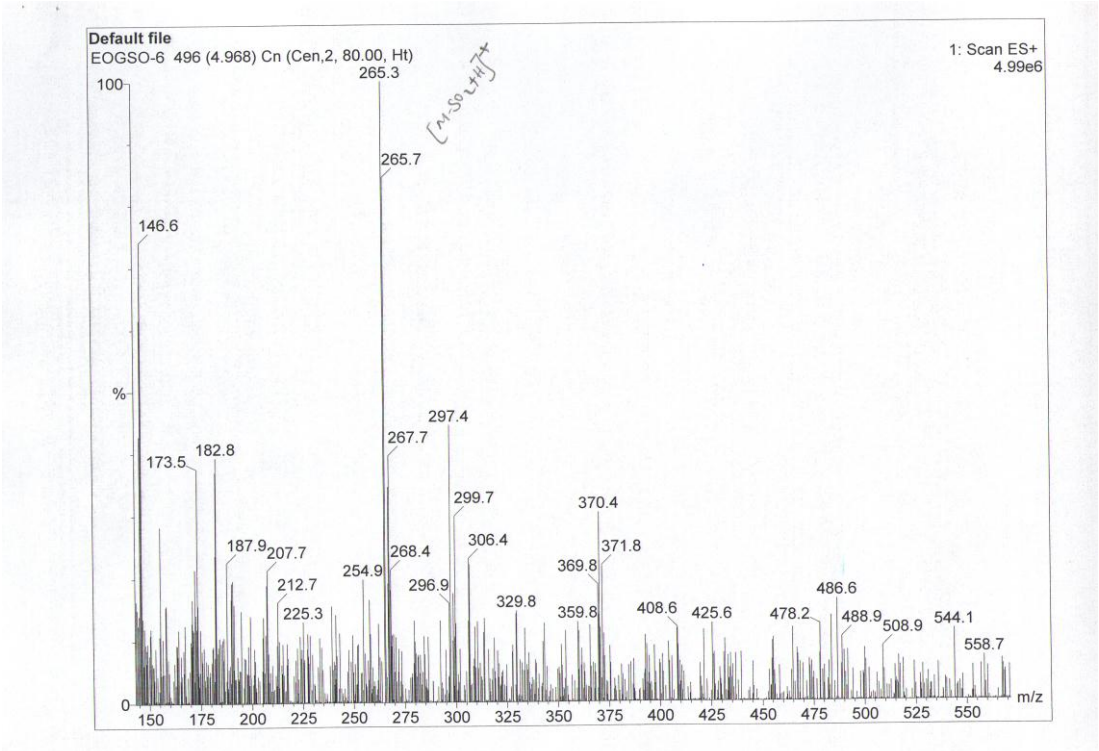
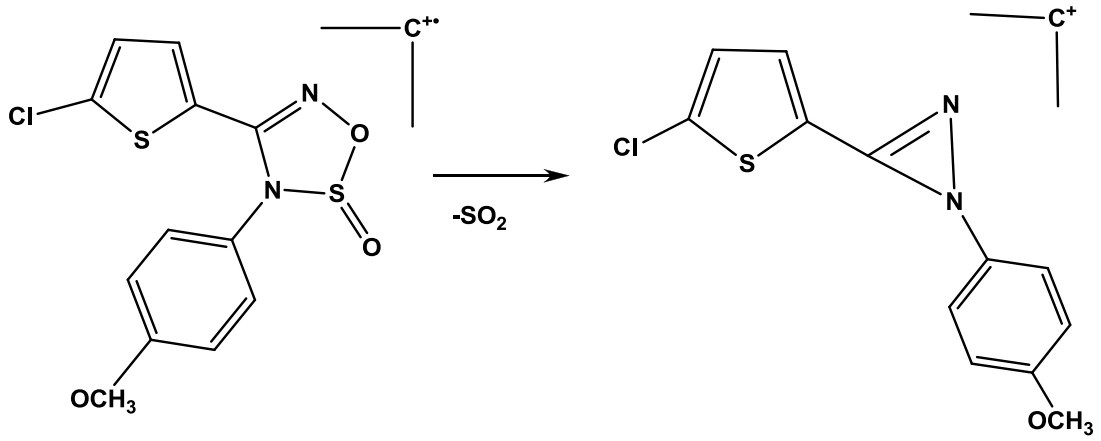


Figure 2.10. LC-MS spectrum of compound **63d**

Spectral data were found to be in accord with the expected structures. In this regard, it is clearly seen that amidoxime-related NOH and NH absorptions in the IR spectrum disappeared. Instead absorption regarding the S=O strechings came out. In the proton NMR, we see the aromatic protons both from phenyl and thienyl or furyl groups and also methyls where available. Moreover, an interesting fragmentation arose in the LC-MS spectra which reveals the SO_2 ejection from the compounds in LC-MS inlet (Scheme 2.11). The produced cation is stabilized aromatic diaziridine species and shows as base peak.



m/z 327

M+H 328

m/z 265

M+H 266

Scheme 2.7. Mass spectral fragmentation of compound **63d**.

2.2. CONCLUSION

In summary, we have introduced a simple and practical method to obtain novel *N*-subtituted products of the 1,2,4-oxadiazolones and oxathiadiazole-S-oxides. Thus, 17 *N*-chloromethyloxadiazolyl-substituted 1,2,4-oxadiazolones have been obtained. In addition to these compounds, we have also prepared 7 *N*-aryl substituted 1,2,4-oxathiadiazole-S-oxides carrying furan and thiophene moieties. All of these 24 compounds are novel and we expect they would show bioactivity against various bacteria species and tumor cells.

CHAPTER III

EXPERIMENTAL

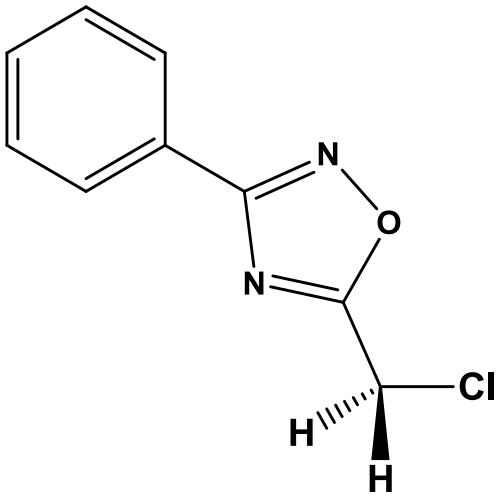
^{1}H and ^{13}C NMR spectra were recorded on a BRUKER AVANCE (400 MHz for proton and 100 MHz for carbon) and VARIAN MERCURY (300 MHz for proton and 75 MHz for carbon) spectrometers. IR spectra were recorded on a SHIMADZU FTIR-8400S instruments (KBr pellet). Mass spectra were recorded on an Agilent LC-MS instrument. Flash column chromatography was performed on Silica Gel (Merck, 230-400 Mesh ASTM). Melting points were determined on a MELTEMP apparatus and were uncorrected. TLC was done using precoated plates with fluorescent indicator (Merck 5735). The stain solutions of permanganate and iodine were used for visualization of the TLC spots.

PART I

This part includes synthesis of aromatic amidoximes and 1,2,4-oxadiazoles. Amidoximes **1a-h** were synthesized according to the methods described in the literature [69-70]. 1,2,4-oxadiazoles **31a-e** were synthesized according to the methods described in the literature [56].

Synthesis of Oxadiazoles (31a-e)

5-(Chloromethyl)-3-phenyl-1,2,4-oxadiazole (31a)



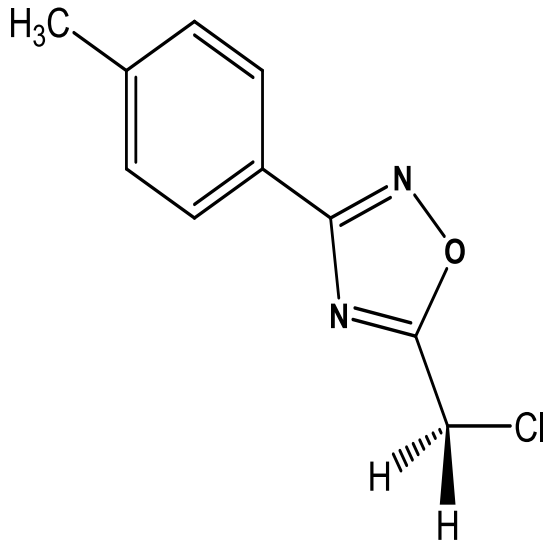
To a solution of chloroacetylchloride (0.813 g, 7.2 mmol) in benzene (10 mL) was added dropwise to a solution of benzamidoxime **(1a)** (2.448 g, 18.0 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(31a)** as a white solid. (1.250g, 90%)

Mp:39-40℃.

R_f: 0.93 (n-Hexane: Ethyl acetate; 1:1)

IR (KBr, ν : cm^{-1}): 3034 (Arom. C-H), 1599, 1573 (C=N), 1476, 1444, 1361, 1300, 922, 711 (C-Cl).

5-(Chloromethyl)-3-p-tolyl-1,2,4-oxadiazole (31b)



To a solution of chloroacetylchloride (0.407 g, 3.60 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-tolyl-benzamidoxime **(1b)** (1.350 g, 9.00 mmol) in benzene (100 mL) and the mixture was heated under reflux for10h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(31b)** as a white solid.

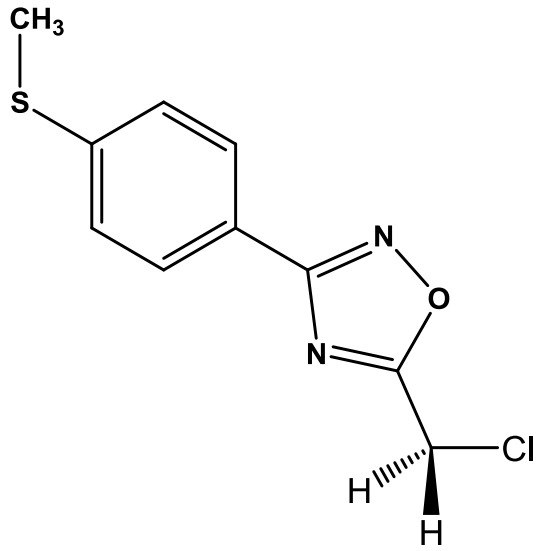
(0.710 g, 94.8 %).

M.p.:46-47 ˚C.

R_f: 0.84 (*n*-Hexane: Ethyl acetate; 1:1)

IR (KBr, ν :cm^{-1}): 3028 (Arom. C-H), 1620, 1597 (C=N), 1479, 1413, 1342, 1284, 1151, 829, 746 (C-Cl).

5-(Chloromethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole (31c)



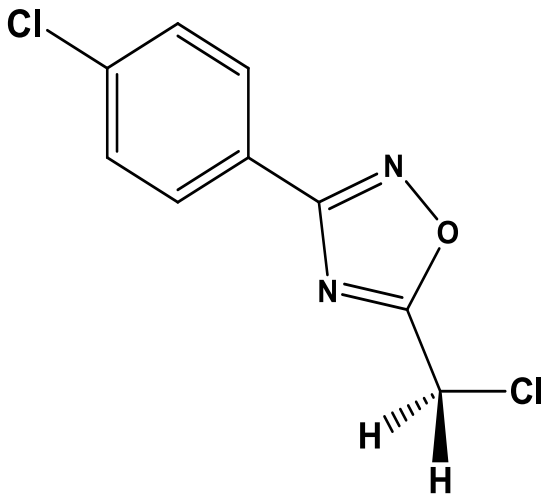
To a solution of chloroacetylchloride (0.261 g, 2.31 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-methylthio-benzamidoxime **(1f)** (1.056 g, 5.79 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 5:1) to give **(31c)** as a light yellow solid. (0.550 g, 99 %).

M.p.:58-60 ˚C.

R_f: 0.88 (*n*-Hexane: Ethyl acetate; 1:1)

IR (KBr, ν :cm^{-1}): 3020 (Arom. C-H), 1664, 1595 (C=N), 1467, 1408, 1361, 1294, 1118, 825, 740 (C-Cl).

5-(Chloromethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (31d)



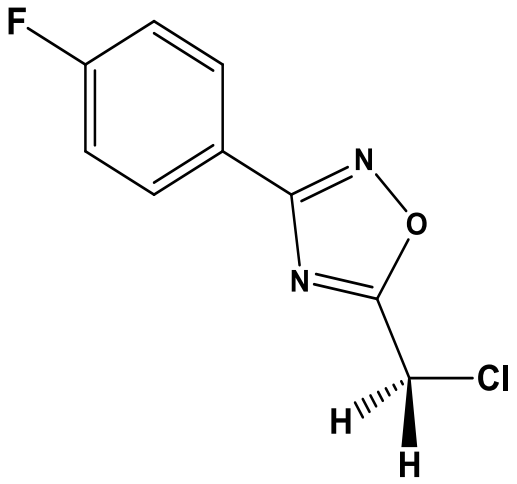
To a solution of chloroacetylchloride (0.813 g, 7.2 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-chloro-benzamidoxime **(1c)** (3.070 g, 18.0 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 3:1) to give **(31d)** as a white solid. (1.448 g, 88 %).

M.p.:61-63 ˚C

R_f: 0.93 (*n*-Hexane: Ethyl acetate; 1:1)

IR (KBr, ν : cm^{-1}): 3022 (Arom. C-H), 1593, 1566 (C=N), 1473, 1410, 1354, 1091, 839, 740 (C-Cl).

5-(Chloromethyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (31e)



To a solution of chloroacetylchloride (0.438 g, 3.88 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-fluoro-benzamidoxime **(1g)** (1.50 g, 9.73 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The progress of the reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 5:1) to give **(31d)** as a yellow oil (0.786 g, 95%).

Rf: 0.69 (*n*-Hexane: Ethyl acetate; 1:1)

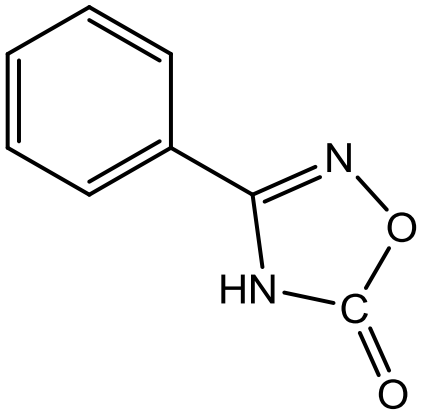
IR (KBr, ν : cm^{-1}): 3032 (Arom. C-H), 1610, 1583 (C=N), 1481, 1417, 1356,1234, 1157, 844, 754 (C-Cl).

PART II

This part includes synthesis of 1,2,4-oxadiazol-5-ones **(41a-g)**, 1,2,4-oxadiazole- 5-thiones **(42)**, according to two methods described in the literature [60, 67].

Synthesis of 1,2,4-oxadiazol-5(4*H*)-ones

3-Phenyl-[1,2,4]-oxadiazol-5(*4H*)-one (41a)



Method I

In a round-bottom flask, benzamidoxime **1a** (1 eq, 0.136g), DBU (1.1 eq, 0.167g), CDI (1.5 eq, 0.243 g) and dioxane (5 mL/ mmol) were added. The resulting mixture was stirred at 110°C 1-1.5 h. The progress of the reaction monitored by TLC (CH_2Cl_2/MeOH, 95/5). Dioxane was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with HCl 1N. Organic layers were dried over Na_2SO4 and filtered before evaporation *in vacuo*. The product was **41a** white solid.(0.112 g, 69%)

Method II

Benzamidoxime **1a** (1 mmol, 0.136 g) was solved in dioxane (2 mL), then

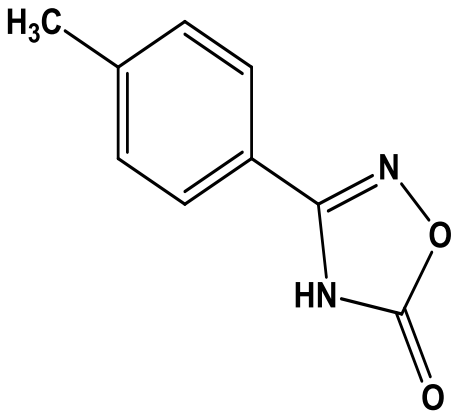
Et_3N (2 mmol, 0.202 g) added to the benzamidoxime solution and stirred about 10 min in ice-bath. And 2-chloroethyl chloroformate (1 mmol, 0.143 g) solution in dioxane (1 mL) was added dropwise at about 15 min to the cooled solution.After dropping they were transferred to the oil bath and stirred at about 72℃ overnight. The progress of the reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo.* The mixture in CH_2Cl_2 was washed 3 times with distilled water. Organic layers were dried over Na_2SO_4 and filtered before evaporation *in vacuo*. The crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 2:1) to give **(41a)** as a light yellow solid. (0.096 g, 69%)

Mp.:199.2-200℃.

R_f: 0.31(in *n*-Hexane/Ethyl acetate 1:1)

IR (KBr, ν :cm^{-1}): 3477.77(N-H), 3113.21(Aromatic C-H), 1770.71(C=O), 1616.40(C=N), 1556(C=C), 1257.21,1467.88, 1111.03, 997.23, 950.94, 893.07, 783.13

3-*p*-Tolyl-[1,2,4]-oxadiazol-5(*4H*)-one (41b)



Method I

In a round-bottom flask, *p*-tolyl-benzamidomidoxime **1b** (1 eq, 0.300 g, 2

mmol), DBU (1.1 eq, 0.334 g, 2.2 mmol), CDI (1.5 eq, 0.486 g, 3 mmol) and dioxane (5 mL/ mmol) were added. The resulting mixture was stirred at 110°C 1-1.5 h . The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). Dioxane was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with HCl 1N.Organic layers were dried over Na_2SO_4 and filtered before evaporation *in vacuo*. The product **41b** was white solid. (0.310g, 88%)

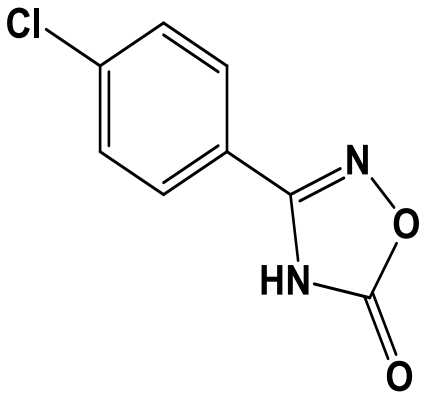
Method II

p-Tolyl-benzamidoxime **1b** (1 mmol, 0.150 g) was solved in dioxane (2 mL), then Et_3N (2 mmol, 0.202 g) added to the amidoxime solution and stirred about 10 min in ice-bath. And 2-chloroethyl chloroformate (1 mmol, 0.143 g) solution in dioxane (1 mL) was added dropwise at about 15 min to the cooled solution.After dropping they were transferred to the oil bath and stirred at about 72℃ overnight. The progress of the reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo.* The mixture in CH_2Cl_2 was washed 3 times with distilled water. Organic layers were dried over Na_2SO_4 and filtered before evaporation *in vacuo*. The crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 2:1) to give **41b** as a yellow solid. (0.095 g, 54%) Mp.: 217.2-219.4℃

R_f: 0.20(in *n*-Hexane/Ethyl acetate 1:1)

IR (KBr, ν :cm^{-1}): 3477.77 (N-H), 3109.35(Aromatic C-H), 1764.93(C=O), 1600.97(C=N), 1462.09, 1400.37, 1255.70(C-O), 999.16, 952.87, 887.28, 663.53

3-(4-Chlorophenyl)-[1,2,4]-oxadiazol-5(*4H*)-one (41c)



Method I

In a round-bottom flask, *p*-chlorobenzamidomidoxime **1c** (1 eq, 0.121 g, 1 mmol), DBU (1.1 eq, 0.167 g, 1.1 mmol), 1,1-carbonyldiimidazole (CDI) (1.5 eq, 0.243 g, 1.5 mmol) and dioxane (5 mL/ mmol) were added. The resulting mixture was stirred at 110°C 1-1.5 h . The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). Dioxane was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with HCl 1N.Organic layers were dried over Na_2SO_4 and filtered before evaporation *in vacuo*. The product **41c** was beige solid.(0.305g, 74%)

Method II

4-Chlorobenzamidoxime **1c** (1 mmol, 0.171 g) was dissolved in dioxane (2 mL), then Et_3N (2 mmol, 0.202 g) added to the amidoxime solution and stirred about 10 min in ice-bath. And 2- chloroethyl chloroformate (1 mmol, 0.143 g) solution in dioxane (1 mL) was added dropwise at about 15 min to the cooled solution. After dropping they were transferred to the oil bath and stirred at about 75℃ overnight. The progress of the reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo.* The mixture in

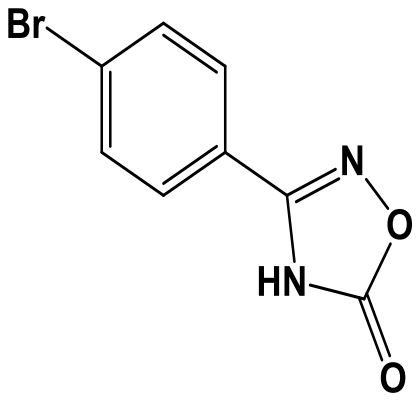
CH_2Cl_2 was washed 3 times with distilled water. Organic layers were dried over Na_2SO_4 and filtered before evaporation *in vacuo*. The crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 2:1) to give **41c** as a slightly yellow solid. (0.095 g, 54%)

Mp.: 274-276℃

R_f: 0.26 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν : cm^{-1}): 3068.85(C-H), 1745.64(C=O), 1593.25(C=N), 1469.81, 1410.01, 1251.84(C-O), 1093.67, 954.80, 839.06, 748.41

3-(4-Bromophenyl)-[1,2,4]-oxadiazol-5(*4H*)-one (41d)



Method I

In a round-bottom flask, *p*-bromobenzamidomidoxime **1d** (1 eq, 0.388 g, 1.8 mmol), DBU (1.1 eq, 0.301 g,1.98 mmol), CDI (1.5 eq, 0.437 g, 2.7 mmol) and dioxane (5 mL/ mmol) were added. The resulting mixture was stirred at 110°C 1-1.5 h. The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). Dioxane was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with HCl 1N.Organic layers were dried over Na_2SO_4 and filtered before evaporation *in vacuo*. The product **41d** was white solid. (0.319 g,75%)

Method II

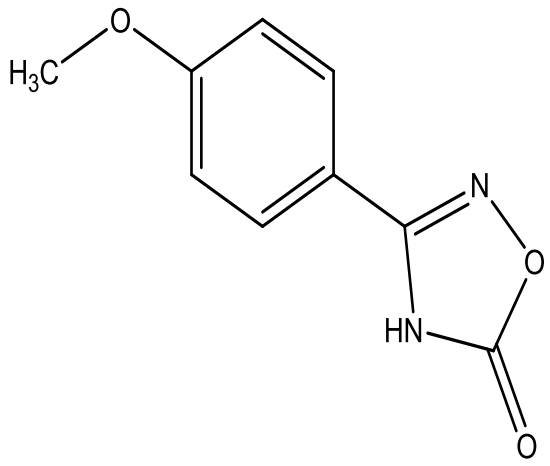
p-Bromobenzamidoxime **1d** (1 mmol, 0.215 g) was solved in dioxane (2 mL), then Et_3N (2 mmol, 0.202 g) added to the amidoxime solution and stirred about 10 min in ice-bath. And 2- chloroethyl chloroformate (1 mmol, 0.143 g) solution in dioxane (1 mL) was added dropwise at about 15 min to the cooled solution. After dropping they were transferred to the oil bath and stirred at about 75℃ overnight. The progress of the reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo.* The mixture in CH_2Cl_2 was washed 3 times with distilled water. Organic layers were dried over Na_2SO_4 and filtered before evaporation *in vacuo*. The crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 2:1) to give pure solid product **41d.** (0.182 g, 40%)

Mp.:206-207℃

R_f: 0.15 (*n*-hexane: ethyl acetate; 2:1)

IR (KBr, ν : cm^{-1}): 3203.87(Aromatic -NH), 2929.97(Aromatic C-H), 1712.85(C=O), 1656.91(C=N), 1604.81, 1492.95, 1253.77, 1118.75, 1070.53, 1010.73, 842.92, 761.19

3-(4-Methoxyphenyl)-[1,2,4]-oxadiazol-5(*4H*)-one (41e)



Method I

In a round-bottom flask, *p*-methoxy-benzamidomidoxime **1e**(1eq,0.332g, 2 mmol), DBU (1.1eq,0.334g,2.2 mmol), CDI (1.5eq, 0.486g, 3 mmol) and dioxane (5 mL/ mmol) were added. The resulting mixture was stirred at 110°C 1-1.5 h. The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). Dioxane was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with HCl 1N.Organic layers were dried over Na_2SO_4 and filtered before evaporation *in vacuo*. The product **41e** was white solid.(0.269 g, 70%)

Method II

p-Methoxybenzamidoxime **1e** (1 mmol, 0.166 g) was solved in dioxane(2 mL), then Et_3N (2 mmol, 0.202 g) added to the amidoxime solution and stirred about 10 min in ice-bath. And 2- chloroethyl chloroformate (1 mmol, 0.143 g) solution in dioxane(1 mL) was added dropwise at about 15 min. to the cooled solution. After dropping they were transferred to the oil bath and stirred at about 75℃ overnight. The progress of the reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo.* The mixture in

CH_2Cl_2 was washed 3 times with distilled water. Organic layers were dried over Na_2SO_4 and filtered before evaporation *in vacuo*. The crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 2:1) to give pure solid product **41e.**

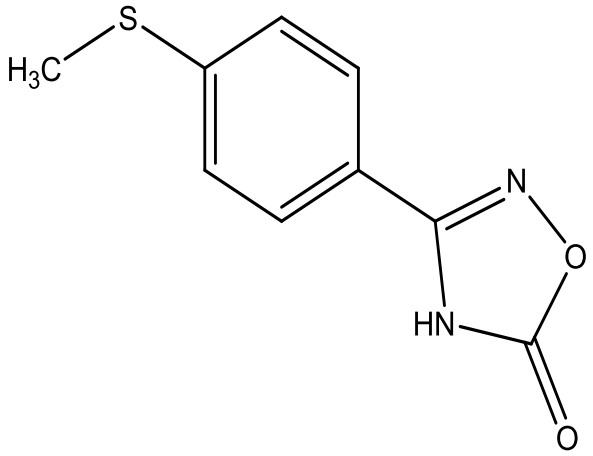
(0.115 g, 60%)

Mp.: 190℃.

R_f: 0.16 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν :cm^{-1}): 3487.42(-NH), 3124.79(Aromatic –CH), 1770.71(C=O), 1612.54(C=N), 1479.45, 1444.73, 1309.71, 1251.84, 1033.88, 995.30, 949.01, 846.78, 761.91

3-(4-(Methylthio)phenyl)-[1,2,4]-oxadiazol-5(*4H*)-one (41f)



Method I

In a round-bottom flask, *p*-methylthio-benzamidomidoxime **1f** (1 eq, 0.728 g, 4 mmol), DBU (1.1 eq, 0.668 g,4.4 mmol), CDI (1.5 eq, 0.972 g, 6 mmol) and dioxane (5 mL/ mmol) were added. The resulting mixture was stirred at 110°C 1-1.5 h. The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). Dioxane was removed under reduced pressure. The

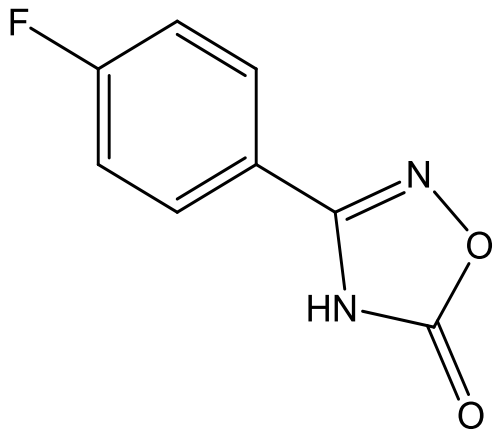
mixture in CH_2Cl_2 was washed 3 times with HCl 1N.Organic layers were dried over Na_2SO_4 and filtered before evaporation *in vacuo*. The product **41f** was beige solid.(0.332 g, 40%)

Mp.: 211-213℃

R_f: 0.10 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν :cm^{-1}): 3468.13(-NH), 3032.20(Aromatic –CH), 1774.57(C=O), 1599.04(C=N), 1462.08, 1253.77, 1195.91, 1091.75, 950.52

3-(4-Fluorophenyl)-[1,2,4]-oxadiazol-5(*4H*)-one (41g)



Method I

In a round-bottom flask, *p*-fluoro-benzamidomidoxime **1g** (1 eq, 0.154 g, 1 mmol), DBU (1.1 eq, 0.167 g, 1.1 mmol), CDI (1.5 eq, 0.243 g, 1.5 mmol) and dioxane (5 mL/ mmol) were added. The resulting mixture was stirred at 110°C 1-1.5 h. The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). Dioxane was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with HCl 1N.Organic layers were dried over Na_2SO_4 and filtered before evaporation *in vacuo.* The product **41g** was white solid.(0.144 g, 80%)

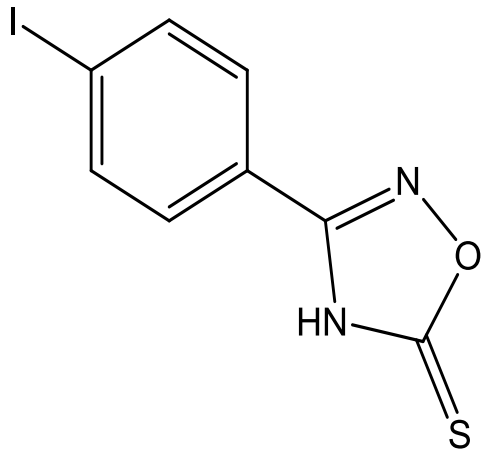
Mp.:237-238℃

R_f: 0.18 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν :cm^{-1}): 3173.01(Aromatic -CH), 1735.99(C=O), 1608.69(C=N), 1473.66,1236.41(C=N), 1170.83, 956.72, 852.56

Synthesis of 1,2,4-Oxadiazole-5(4*H*)-thione 42

3-(4-Iodophenyl)-[1,2,4]-oxadiazole-5(*4H*)-thione (42)



In a round-bottom flask, *p*-iodo-benzamidoxime **1h** (1 eq, 0.262 g, 1 mmol), DBU (4 eq, 0.608 g, 4 mmol), 1,1'-thiocarbonyldiimidazole (TCDI) (1.5 eq, 0.267 g, 1.5 mmol) and dioxane (5 mL/ mmol) were added. The resulting mixture was stirred at 110°C (1-1.5 h). The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). Dioxane was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with HCl 1N. The solvent was removed under reduced pressure. The product **42a** is yellow powder. (0.213 g, 70%)

Mp.: >300℃

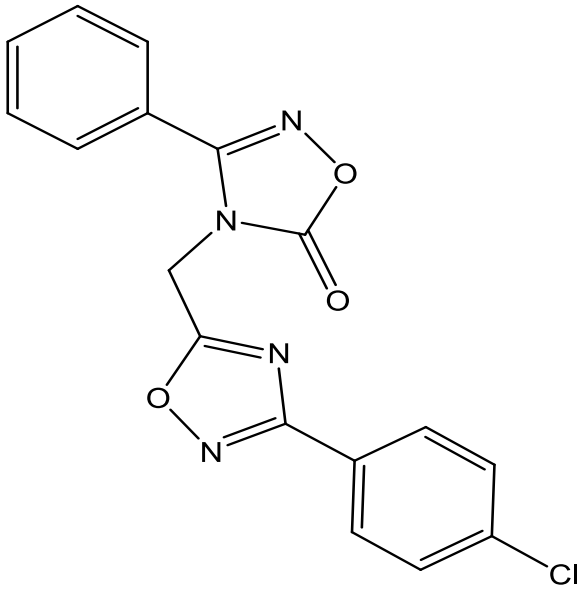
R_f: 0.58(in CH_2Cl_2/MeOH, 95/5%)

IR (KBr, ν :cm^{-1}): 3194.23(Aromatic –CH), 1643.41, 1600.97, 1548.89, 1462.09, 1265.35, 1157.33, 974.08, 825.56, 717.54

PART III

Synthesis of *N*-substituted [1,2,4]-Oxadiazol-5-ones 61a-t, 62 and [1,2,3,5]-Oxathiadiazol-2-oxides (63a-g)

4-((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-3-phenyl-[1,2,4]-oxadiazol-5(*4H*)-one (61a)



A mixture of 5-(chloromethyl)-3-(*p*-chlorophenyl)-1,2,4-oxadiazole **31d** (1 eq, 0.057 g, 0.25 mmol) and 3-phenyl-[1,2,4]-oxadiazol-5(*4H*)-one **41a** (1 eq, 0.041 g, 0.25 mmol) with K_2CO_3 (0.5 eq, 0.017 g, 0.125 mmol) in 5 mL of DMF was heated at 130 ℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61a)** as a yellow solid.

(40 mg, yield: 45%)

Mp.: 136-137℃

R_f: 0.675 (*n*-hexane: ethyl acetate; 1:1)

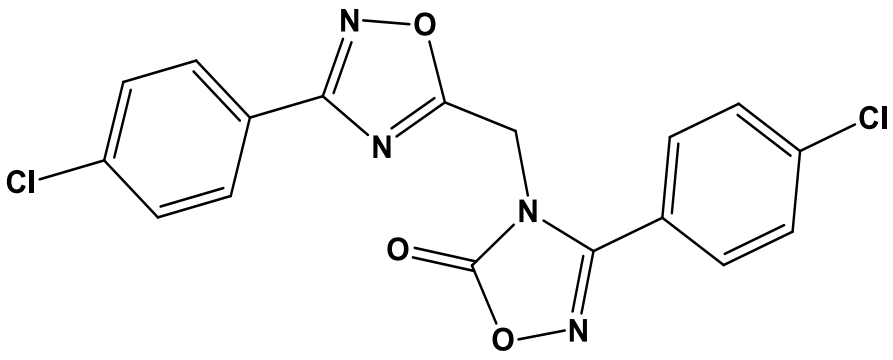
IR (KBr, ν :cm^{-1}): 3095.85 (Aromatic –CH), 1766.85(C=O), 1608.69(C=N), 1556.61, 1425.45, 1330.53, 1226.77, 1159.26, 945.15, 844.85, 767.69

^{1}H NMR (δ_H, 300 MHz, $CDCl_3$): 8.0(d, J=8.4 Hz, 2H), 7.6(t, J= 8.7 Hz, 3H), 7.5(d, J=15 Hz, 2H), 7.4(d, J=8.4 Hz, 2H), 5.0(s,2H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$):172.894(C=O), 168.210(C=N), 158.772(C=N), 158.455(C=N), 138.242(C-Cl), 132.885(-CH), 129.945, 129.575, 129.109, 128.495(-CH), 124.413(-C-), 122.603(-C-), 38.988($-CH_2$)

MS (*m/z*, %)=355.0 $[M]^+$(100), 340.0(5), 318.0(8), 281.0(8), 237.0(7)

3-(4-Chlorophenyl)-4-((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-[1,2,4]-oxadiazol-5(*4H*)-one (61b)



A mixture of 5-(chloromethyl)-3-(*p*-chlorophenyl)-1,2,4-oxadiazole **31d** (1 eq, 0.048 g, 0.21 mmol) and 3-(*p*-chlorophenyl)-[1,2,4]-oxadiazol-5(*4H*)-one **41c** (1 eq, 0.041 g, 0.21 mmol) with K_2CO_3 (0.5 eq, 0.014 g, 0.105 mmol) in 5 mL of DMF was heated at 130 ℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61b)** as

a yellow solid. (25 mg, yield: 30%)

Mp.: 106℃

R_f: 0.7 (*n*-hexane: ethyl acetate; 1:1)

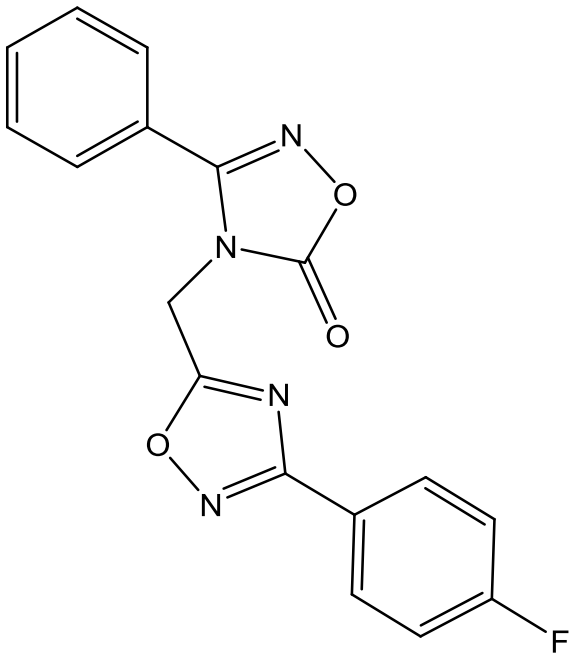
IR (KBr, ν :cm^{-1}): 3088.14 (Aromatic –CH), 1782.29(C=O), 1599.04(C=N), 1444.70, 1400.37, 1093.67, 943.27, 839.06, 775.41

^{1}H NMR (δ_H, 300 MHz, $CDCl_3$): 8.0(d, J=8.4 Hz, 2H), 7.5(m, J= 42 Hz, 6H), 5.0(s,2H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 172.715(C=O), 168.244(C=N), 139.605(C=N), 138.355(C=N), 130.602(-C-), 130.419, 129.816, 129.629, 129.105 (-CH), 124.299(-C-), 121.000(-C-), 38.958(-CH_2)

MS (*m/z*, %)=154.7 $[M+H]^+$(100), 381.1(30), 355.1(20), 318(25), 313.0(12), 281.0(10), 210.0(10), 172.8(8), 164.9(12), 156.9(32)

4-((3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-3-phenyl-1,2,4-oxadiazol-5(*4H*)-one (61c)



A mixture of 5-(chloromethyl)-3-(*p*-fluorophenyl)-1,2,4-oxadiazole **31e** (1 eq, 0.053 g, 0.25 mmol) and 3-phenyl-[1,2,4]-oxadiazol-5(4H)-one **41a** (1 eq, 0.041 g, 0.25 mmol) with K_2CO_3 (0.5 eq, 0.017 g, 0.125 mmol) in 5 mL of DMF was heated at 130 ℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61c)** as a white solid. (75 mg, yield: 88%)

Mp.: 108℃

R_f: 0.625 (*n*-hexane: ethyl acetate; 1:1)

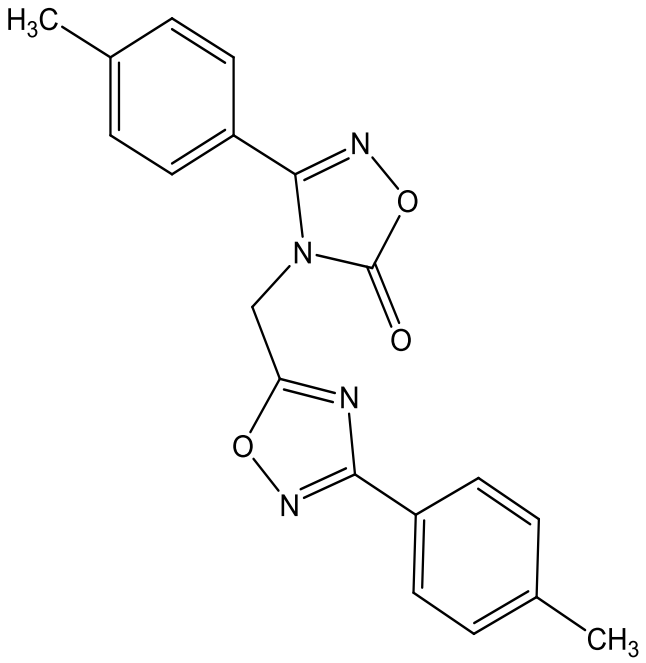
IR (KBr, ν : cm^{-1}): 2943.47(Aromatic –CH), 1766.85(C=O), 1608.69(C=C), 1556.61, 1425.45, 1330.93, 1226.77(C-O), 945.15, 844.85, 767.69

^{1}H NMR (δ_H, 300 MHz, $CDCl_3$): 8.0(d, J= 14.1, 2H), 7.6(m, J= 35.7 Hz, 5H), 7.2(d, J= 17.4 Hz, 2H), 5.0(s,2H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 172.795 (C=O), 168.160 (C=N), 158.787(C=N), 158.485(C=N), 132.885(-CH), 129.942 (-CH), 129.502(-CH), 130.160(-C-), 163.422(C-F), 130.106 (-CH), 122.603(-CH), 116.628(-C-), 116.334(-C-), 38.992($-CH_2$)

MS (m/z,%)= 339.7 $[M+H]^+$(100), 229.8(39), 309.8(15), 305.8(18), 295.7(18), 256.9(19), 191.7(30), 183.8(39), 172.6(35)

3-*p*-tolyl-4-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-[1,2,4]-oxadiazol-5(4H)-one (61d)



A mixture of 5-(chloromethyl)-3-(*p*-tolyl)-1,2,4-oxadiazole **31b** (1 eq, 0.209 g, 1 mmol) and 3-(*p*-tolyl)-[1,2,4]-oxadiazol-5(*4H*)-one **41b** (1 eq, 0.176 g,1 mmol) with K_2CO_3 (0.5 eq, 0.069 g, 0.5 mmol) in 5 mL of DMF was heated at 130℃ for 2 h and monitored by TLC. The reaction mixture was concentrared in vacuo, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61d)** as a yellow solid. (40 mg, yield: 46%)

Mp.: 103-105℃

R_f: 0.7 (*n*-hexane: ethyl acetate; 1:1)

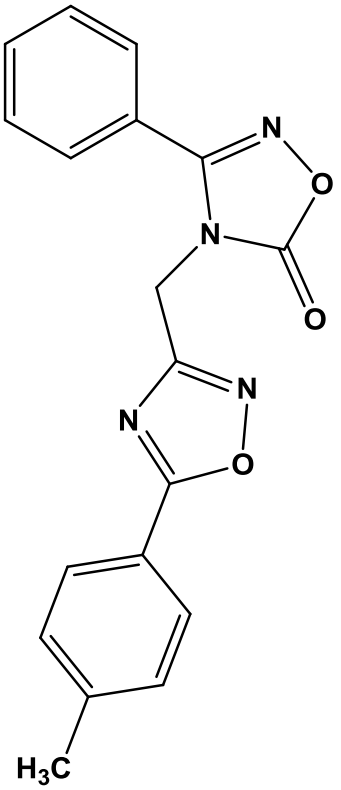
IR (KBr, ν :cm-1): 3032.20(Aromatic –CH), 1786.14(C=O), 1600.97(C=C), 1257.67(C-O), 1444.70, 1107.18, 823.63,761.91

^{1}H NMR (δ_H, 300 MHz, $CDCl_3$): 7.9(d, J=7.8 Hz, 2H), 7.5 (d, J= 7.8 Hz, 2H), 7.2(t, J= 20.4 Hz, 4H), 5.0(s, 2H), 2.4(s,6H)

^{13}C NMR (δ c, 100 MHz, $CDCl_3$): 172.536(C=O), 168.958(C=N), 158.994(C=N), 158.615(C=N), 143.530(-C-), 142.423(-C-), 130.572, 129.900, 128.388, 127.731 (-CH), 123.149(-C-), 119.656(-C-), 39.004($-CH_2$), 21.846($-CH_3$), 21.819($-CH_3$)

MS (m/z,%)= 349.8 $[M+H]^+$ (100), 305.8(9), 188.8(7)

4-((3-(4-tolyl)-1,2,4-oxadiazol-5-yl)methyl)-3-phenyl-[1,2,4]-oxadiazol-5(*4H*)-one (61e)



A mixture of 5-(chloromethyl)-3-(*p*-tolyl)-1,2,4-oxadiazole **31b** (1 eq, 0.062 g,0.30 mmol) and 3-phenyl-[1,2,4]-oxadiazol-5(*4H*)-one **41a** (1 eq, 0.048 g,0.30 mmol) with K_2CO_3 (0.5 eq, 0.021 g, 0.15 mmol) in 5 mL of DMF was heated at 130 ℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61e)** as a white solid.

(40 mg, 40%)

Mp.: 108-109℃

Rf: 0.675 (*n*-hexane: ethyl acetate; 1:1)

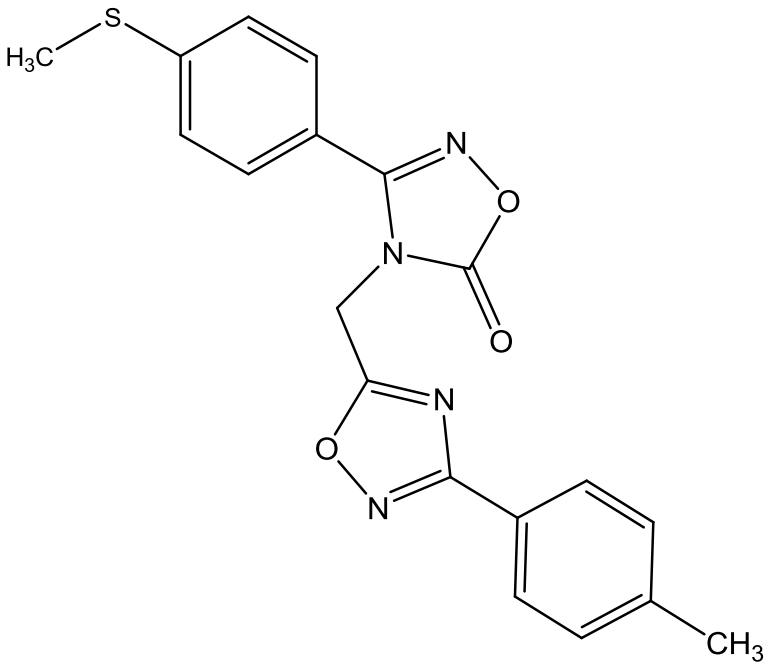
IR (KBr, ν :cm-1): 3034.13(Aromatic –CH), 1770.71(C=O), 1604.83(C=C), 1452.45, 1332.45(C-O), 943.22, 797.77

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.9(d, J=8.1 Hz, 2H), 7.6(m, J= 40.8 Hz, 5H), 7.2(t, J= 12.3 Hz, 2H), 5.0(s,2H), 2.4(s,3H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 172.429(C=O), 168.977(C=N), 158.798(C=N), 158.516(C=N), 142.450(-C-), 132.813(-C-), 129.896(-CH), 128.529(-CH), 127.735(-CH), 123.115(-C-), 122.672(-C-), 39.015($-CH_2$), 21.838($-CH_3$)

MS (m/z, %)= 335.8 $[M+H]^+$(100), 321.5(5), 203.4(9), 233.6(5)

3-(4-(Methylthio)phenyl)-4-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-[1,2,4]-oxadiazol-5(*4H*)-one (61f)



A mixture of 5-(chloromethyl)-3-(*p*-tolyl)-1,2,4-oxadiazole **31b** (1 eq, 0.048 g, 0.23 mmol) and 3-(*p*-methylthiophenyl)-[1,2,4]-oxadiazol-5(4H)-one **41f** (1 eq, 0.048 g, 0.23 mmol) with K_2CO_3(0.5 eq, 0.017 g, 0.12 mmol) in 5 mL of DMF was heated at 130℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61f)** as a yellow solid. (50 mg, yield: 57%)

Mp.: 108-109℃

Rf: 0.625 (*n*-hexane: ethyl acetate; 1:1)

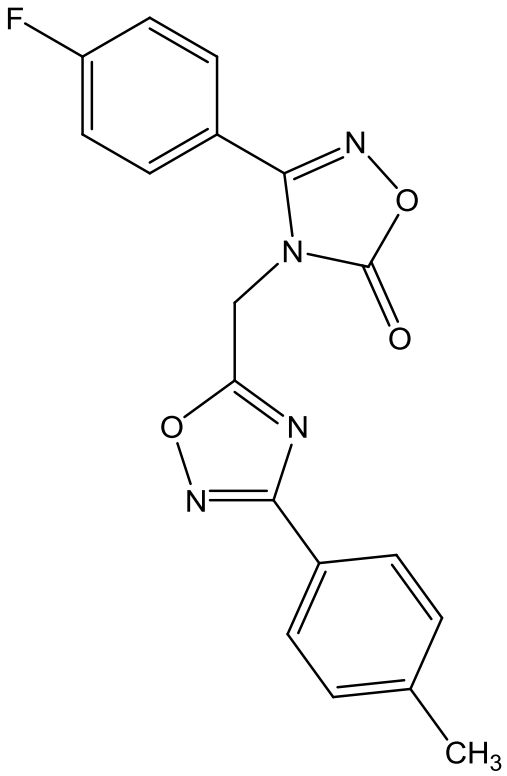
IR (KBr, ν :cm-1): 3055.35(Aromatic –CH), 1782.29(C=O), 1600.97(C=C), 1444.73, 1111.03, 937.44, 738.76

^{1}H NMR (δ_H, 300 MHz, $CDCl_3$): 7.9(d, J= 7.8 Hz, 2H), 7.5(d, J= 8.7 Hz, 2H), 7.2(t, J= 20.7 Hz, 4H), 5.1(s,2H), 2.4(s,3H), 2.4(s,3H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 172.494(C=O), 168.977(C=N), 158.844(C=N), 158.264(C=N), 145.794(-C-), 142.461(-C-), 129.907, 128.594, 127.735, 126.372(-CH), 123.104(-C-), 118.251(-C-), 39.038($-CH_2$), 21.849($-CH_3$), 14.992($-CH_3$)

MS(m/z, %)= 381.8 $[M+H]^+$(100), 337.6(15), 309.7(50), 291.6(27), 206.6(24)

3-(4-Fluorophenyl)-4-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-[1,2,4]-oxadiazol-5(*4H*)-one (61g)



A mixture of 5-(chloromethyl)-3-(*p*-tolyl)-1,2,4-oxadiazole **31b** (1 eq, 0.042 g, 0.2 mmol) and 3-(*p*-fluorophenyl)-[1,2,4]-oxadiazol-5(*4H*)-one **41g** (1 eq, 0.036 g, 0.2 mmol) with K_2CO_3(0.5 eq, 0.014 g, 0.1 mmol) in 5 mL of DMF was heated at 130℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61g)** as a yellow crystals in diethylether. (0.045 g, 60%)

Mp.: 109℃

Rf: 0.6 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν :cm-1): 2960.83(Aromatic –CH), 1793.86(C=O), 1608.63(C=C), 1518.00, 1448.59, 1215.19(C-O), 846.78, 758.05

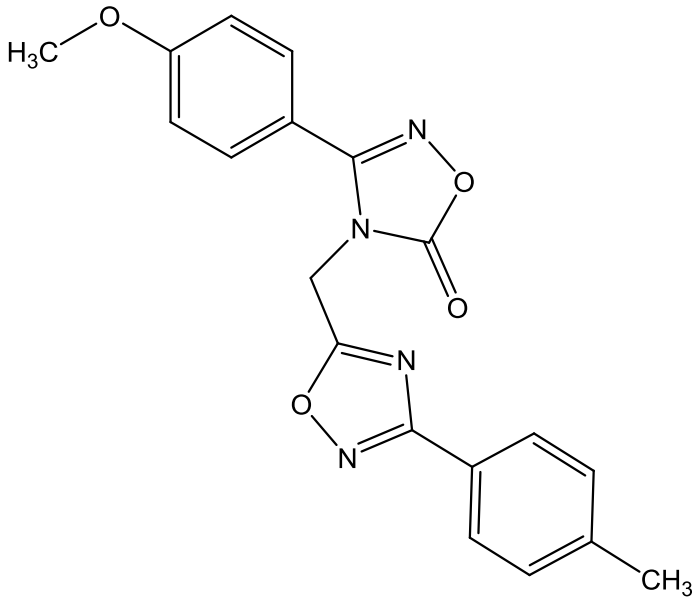
^{1}H NMR (δ_H, 300 MHz, $CDCl_3$): 7.9(d, J= 7.8 Hz, 2H), 7.6(d, J=9 Hz, 2H),

7.2(m, J= 22.5 Hz, 4H), 5.0(s, 2H), 2.4(s, 3H)

^{13}C NMR (δ c, 100 MHz, $CDCl_3$): 172.345(C=O), 168.985(C-F), 158.665(C=N), 157.760(C=N), 142.560(C=N), 131.049(-C-), 130.931(-CH), 129.949(-CH), 127.716(-CH), 123.000(-CH), 117.579(-C-), 117.281(-C-), 38.966($-CH_2$), 21.865($-CH_3$)

MS(m/z, %)= 353.8$[M+H]^+$(100), 339.0(10), 221.9(30), 182.8(33)

3-(4-Methoxyphenyl)-4-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-[1,2,4]-oxadiazol-5(*4H*)-one (61h)



A mixture of 5-(chloromethyl)-3-(*p*-tolyl)-1,2,4-oxadiazole **31b** (1 eq, 0.140 g, 0.67 mmol) and 3-(*p*-methoxyphenyl)-[1,2,4]-oxadiazol-5(*4H*)-one **41e** (1 eq, 0.128 g, 0.67 mmol) with K_2CO_3(0.5 eq, 0.054 g, 0.39 mmol) in 5 mL of DMF was heated at 130℃ for 2 h and monitored by TLC. The reaction mixture was concentrared in vacuo, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61h)** as a yellow solid. (105 mg, yield:44%)

Mp.: 106-107℃

R_f: 0.55 (*n*-hexane: ethyl acetate; 1:1)

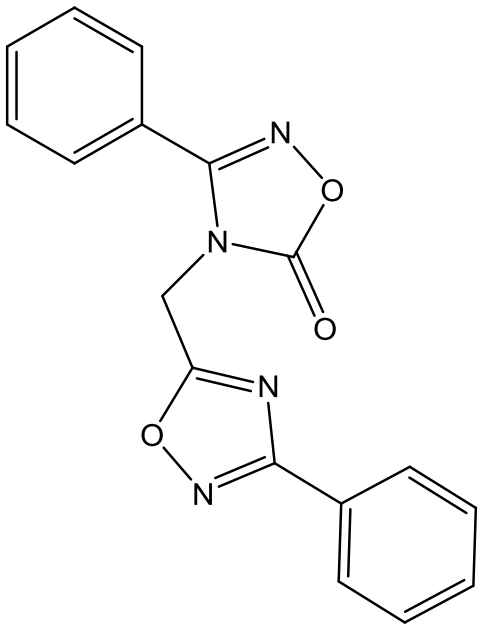
IR (KBr, ν :cm-1): 3020.63(Aromatic –CH), 1778.43(C=O), 1612.54(C=C), 1516.10, 1263.42, 1180.47, 933.58, 835.21, 738.76

^{1}H NMR (δ_H, 300 MHz, $CDCl_3$): 7.9(d,J= 10.8 Hz, 2H), 7.5(d, J=8.7 Hz, 2H), 7.3(d, J= 9 Hz, 2H), 7.0(d, J= 8.7 Hz, 2H), 5.1(s, 2H), 3.8(s, 3H), 2.4 (s, 3H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 172.623(C=O), 168.970(C=N), 163.033(C-O), 158.928(C=N), 158.405(C=N), 142.423(-C-), 130.155, 129.896, 127.735(-CH), 123.161(-C-), 115.364(-CH), 114.486(-C-), 55.750($-CH_2$), 39.015($-CH_3$), 21.834($-CH_3$)

MS (m/z, %)= 365.8$[M+H]^+$(100), 321.8(8), 293.8(35)

3-Phenyl-4-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-1,2,4-oxadiazol-5(*4H*)-one (61i)



A mixture of 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole **31a** (1 eq, 0.065 g, 0.33 mmol) and 3-phenyl-[1,2,4]-oxadiazol-5(*4H*)-one **41a** (1 eq, 0.054 g,

0.33 mmol) with K_2CO_3 (0.5 eq, 0.023 g, 0.17 mmol) in 5 mL of DMF was heated at 130 ℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61i)** as a yellow solid. (55 mg, yield: 53%)

Mp.: 115-117℃

Rf: 0.65 (*n*-hexane: ethyl acetate; 1:1)

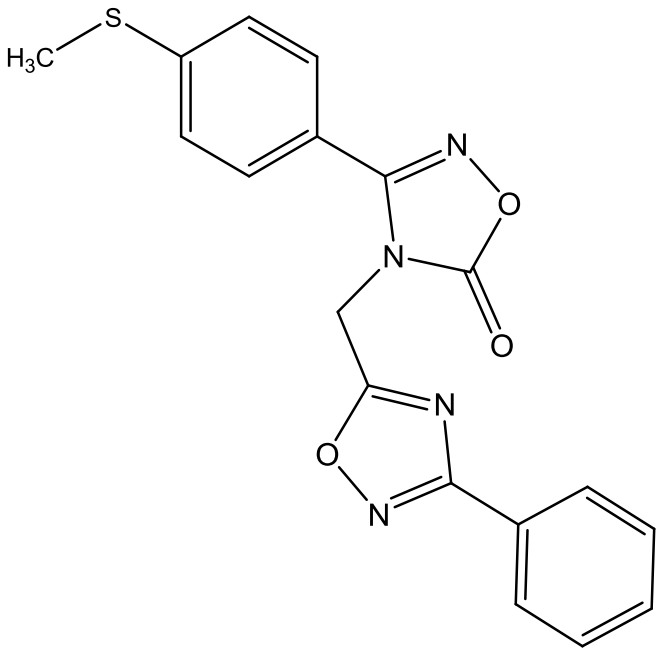
IR (KBr, ν :cm-1): 3061.13(Aromatic –CH), 1790.00(C=O), 1595.18(C=N), 1288.49(C-O), 1072.46, 902.72, 754.19

^{1}H NMR (δ_H, 300 MHz, $CDCl_3$): 8.0(d, J= 10 Hz, 2H), 7.6(d, J= 13.6 Hz, 2H), 7.5(m, J= 34.8 Hz, 6H), 5.1(s,2H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 172.646(C=O), 168.980(C=N), 158.800(C=N), 158.510(C=N), 132.861(-C-), 131.999(-C-), 129.927, 129.218, 128.525, 127.808 (-CH), 125.934(-C-), 122.634(-C-), 39.025($-CH_2$)

MS (m/z, %)= 321.7$[M+H]^+$(100), 309.6(18), 225.5(12), 173.5(25)

3-(4-(Methylthio)phenyl)-4-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-1,2,4-oxadiazol-5(*4H*)-one (61j)



A mixture of 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole **31a** (1 eq, 0.080 g, 0.41 mmol) and 3-(*p*-thiomethylphenyl)-[1,2,4]-oxadiazol-5(*4H*)-one **41f** (1 eq, 0.085 g,0.41 mmol) with K_2CO_3(0.5 eq, 0.028 g, 0.20 mmol) in 5 mL of DMF was heated at 130℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61j)** as a white solid. (30 mg, yield:20%)

Mp.: 128℃

R_f: 0.675 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν :cm-1): 3055.35(Aromatic C-H), 1788.07(C=O), 1604.83(C=C), 1444.73, 1132.25, 900.79, 812.06, 759.98

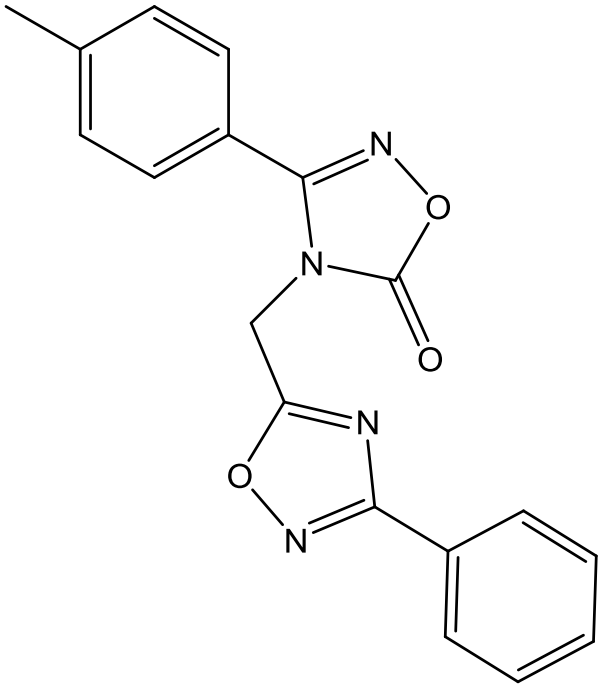
^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 8.0(d, J= 10 Hz, 2H), 7.5(m, J= 20 Hz, 5H), 7.3(d, J= 8.4 Hz, 2H), 5.1(s, 2H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 172.668(C=O), 168.980(C=N),

158.823(C=N), 158.221(C=N), 145.838(C-S), 131.999(-C-), 129.210, 128.578, 127.808, 126.368(-CH), 125.919(-C-), 118.222(-C-), 39.033($-CH_2$), 14.991($-CH_3$)

MS (m/z,%)= 367.7$[M+H]^+$(100), 338.7(92), 321.5(90), , 241.5(68), 207.9(50), 192.8(60)

4-((3-Phenyl-1,2,4-oxadiazol-5-yl)methyl)-3-*p*-tolyl-[1,2,4]-oxadiazol-5(*4H*)-one (61k)



A mixture of 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole **31a** (1 eq, 0.097 g, 0.50 mmol) and 3-(*p*-tolyl)-[1,2,4]-oxadiazol-5(*4H*)-one **41b** (1 eq, 0.087 g, 0.50 mmol) with K_2CO_3 (0.5 eq, 0.035 g, 0.25 mmol) in 5 mL of DMF was heated at 130 ℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61k)** as a yellow solid. (75 mg, yield: 45%)

Mp.: 130-132℃

Rf: 0.675 (*n*-hexane: ethyl acetate; 1:1)

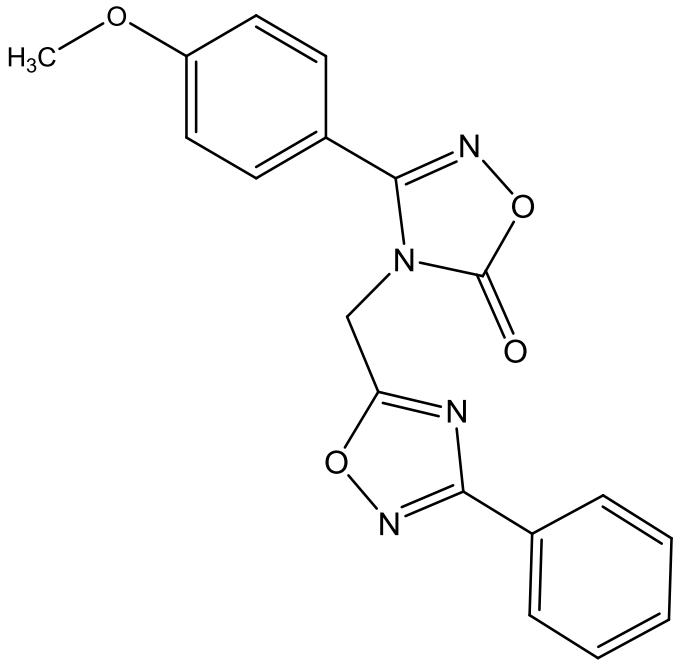
IR (KBr, ν :cm-1): 3072.71(Aromatic C-H), 1786.14(C=O), 1595.18(C=C), 1444.73, 1350.22, 829.42, 758.05, 715.61

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 8.0(d, J= 10 Hz, 2H), 7.5(m, J= 21.2 Hz, 5H), 7.3(d, J= 8 Hz, 2H), 5.1(s,2H), 2.4(s,3H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 172.699(C=O), 168.965(C=N), 158.868(C=N), 158.563(C=N), 143.552(-C-), 131.961(-CH), 130.582(-CH), 129.195(-CH), 128.372(-CH), 127.801(-CH), 125.964(-C-), 119.640(-C-), 38.995($-CH_2$), 21.819($-CH_3$)

MS(m/z, %)= 335.8$[M+H]^+$(100), 309.9(10), 291.6(20), 263.7(15)

3-(4-Methoxyphenyl)-4-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-[1,2,4]-oxadiazol-5(*4H*)-one (61l)



A mixture of 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole **31a** (1 eq, 0.078 g, 0.40 mmol) and 3-(*p*-methoxyphenyl)-[1,2,4]-oxadiazol-5(*4H*)-one **41e** (1 eq, 0.077 g, 0.40 mmol) with K_2CO_3(0.5 eq, 0.028 g, 0.20 mmol) in 5 mL of DMF was heated at 130℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61l)** as a yellow solid. (25 mg, yield: 18%)

Mp.: 92℃

Rf: 0.7(*n*-hexane: ethyl acetate; 1:1)

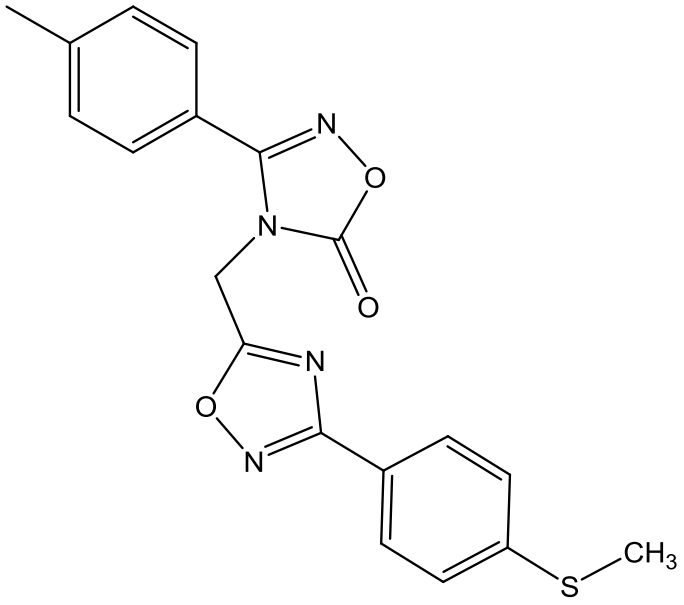
IR (KBr, ν :cm-1): 3036.06(Aromatic C-H), 1766.85(C=O), 1600.97(C=C), 1518.03, 1346.36, 1263.42(C-O), 1176.62, 844.85, 758.05, 715.61

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 8.0(d, J= 10 Hz, 2H), 7.5(m, J= 35.6 Hz, 5H), 7.0(d, J= 8.4 Hz, 2H), 5.1(s, 2H), 3.8(s,3H)

^{13}C NMR(δ_C, 100 MHz, $CDCl_3$): 172.775(C=O),168.973(C=N),163.029(C=N) 158.906(C=N), 158.350(C=N), 131.969, 130.140, 129.203, 127.808(-CH), 125.957(-C-), 115.380(-CH), 114.458(-C-), 55.759($-CH_2$), 39.018($-CH_3$)

MS (m/z, %)= 351.8$[M+H]^+$(100), 321.6(15), 307.8(17), 279.7(45), 209.0(33)

4-((3-(4-(Methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-3-*p*-tolyl-[1,2,4]-oxadiazol-5(*4H*)-one (61m)



A mixture of 5-(chloromethyl)-3-(*p*-thiomethylphenyl)-1,2,4-oxadiazole **31c** (1 eq, 0.075 g, 0.31 mmol) and 3-(p-tolyl)-[1,2,4]-oxadiazol-5(*4H*)-one **41b** (1 eq, 0.054 g, 0.31 mmol) with K_2CO_3(0.5 eq, 0.021 g, 0.15 mmol) in 5 mL of DMF was heated at 130 ℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61m)** as a yellow solid. (35 mg, yield: 30%)

Mp.: 142-144℃

Rf: 0.76 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν :cm-1): 3020.63 (Aromatic C-H), 1774.57(C=O), 1593.25(C=C), 1448.59, 1186.26(C-O), 829.42

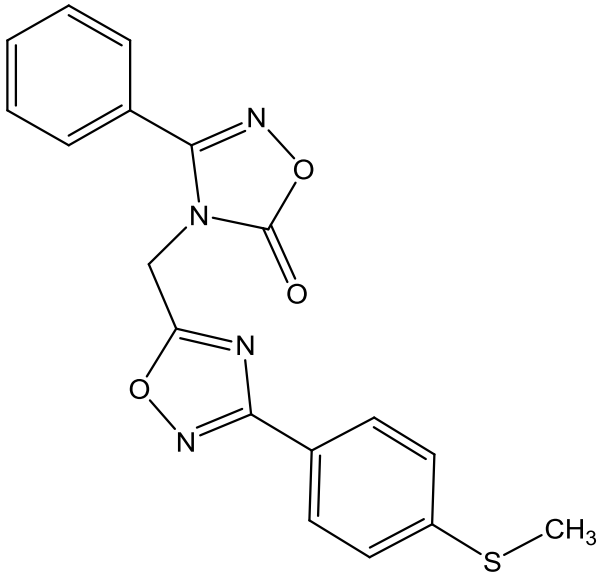
^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.9(d, J= 8.4 Hz, 2H), 7.4(d, J= 8 Hz, 2H), 7.3(m, J= 26.4 Hz, 4H), 5.0(s, 2H), 2.5(s, 3H), 2.4(s,3H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 172.592(C=O), 168.630(C=N),

158.861(C=N), 158.571(C=N), 144.017(-C-), 143.544(C-S), 130.574, 128.357, 128.014, 125.995(-CH), 122.124(-C-), 119.652(-C-), 38.987($-CH_2$), 21.819($-CH_3$), 15.220($-CH_3$)

MS (m/z,%)= 381.7$[M+H]^+$(100),337.9(15), 279.5(37), 182.3(42)

4-((3-(4-(Methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-3-phenyl-1,2,4-oxadiazol-5(*4H*)-one (61n)



A mixture of 5-(chloromethyl)-3-(*p*-thiomethylphenyl)-1,2,4-oxadiazole **31c** (1 eq, 0.242 g, 1 mmol) and 3-phenyl-[1,2,4]-oxadiazol-5(*4H*)-one **41a** (1 eq, 0.162 g, 1 mmol) with K_2CO_3 (0.5 eq, 0.069 g, 0.5 mmol) in 5 mL of DMF was heated at 130 ℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61n)** as a yellow solid. (233 mg, 70%)

Mp.: 108℃

Rf: 0.64 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν :cm-1): 3022.55(Aromatic –CH), 1778.43(C=O), 1595.18(C=C),

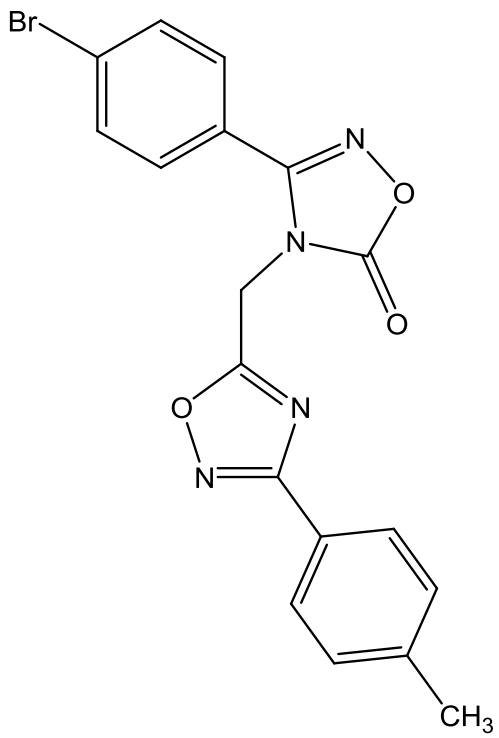
1452.45, 1189.19(C-O), 900.79, 831.35, 756.12, 700.18

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.9(d, J= 10.8 Hz, 2H), 7.6(m, J= 14 Hz, 3H), 7.5(d, J= 7.6 Hz, 2H), 7.3(d, J= 10.8 Hz, 2H), 5.1(s,2H), 2.5(s, 3H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 172.516(C=O), 168.630(C=N), 158.784(C=N), 158.510 (C=N), 144.055(C-S), 132.838(-C-), 129.904, 128.509, 128.006, 125.995 (-CH), 122.619(-C-), 122.070(-C-), 39.003($-CH_2$), 15.212($-CH_3$)

MS (m/z, %)= 367.7 $[M+H]^+$(100), 289.3(35), 227.8(52), 182.2(82),

3-(4-Bromophenyl)-4-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-1,2,4-oxadiazol-5(*4H*)-one (61o)



A mixture of 5-(chloromethyl)-3-(*p*-tolyl)-1,2,4-oxadiazole **31b** (1 eq, 0.121 g, 0.58 mmol) and 3-(*p*-bromophenyl)-[1,2,4]-oxadiazol-5(*4H*)-one **41d** (1 eq, 0.140 g, 0.58 mmol) with K_2CO_3(0.5 eq, 0.041 g, 0.30 mmol) in 5 mL of DMF was heated at 130℃ for 1 h and monitored by TLC. The reaction mixture was

concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 5:1) to give **(61o)** as a yellow solid. (48 mg, yield: 20%)

Mp.: 121-122℃

R_f: 0.70 (*n*-hexane: ethyl acetate; 1:1)

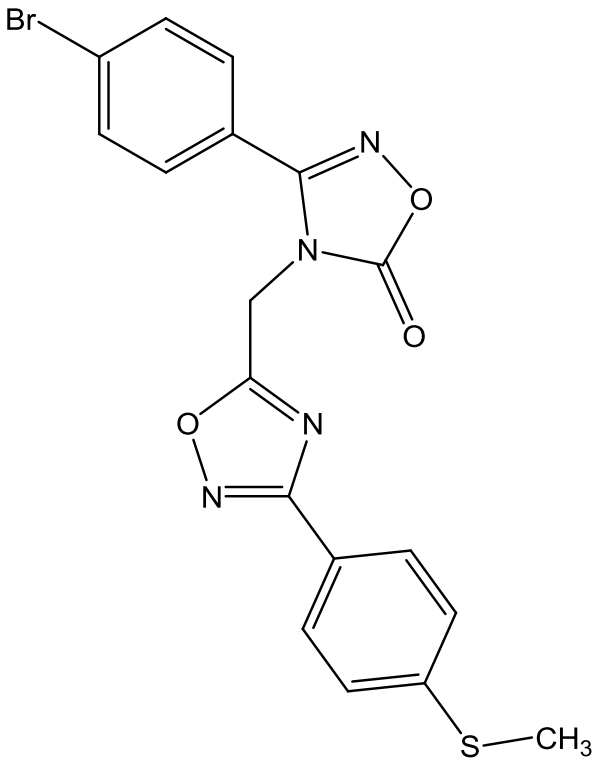
IR (KBr, ν :cm-1): 3053.42 (Aromatic –CH), 1788.07 (C=O), 1602.90 (C=C), 1516.10, 1413.87, 1265.35 (C-O), 1028.09, 933.58, 835.21, 738.76

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.9(d, J= 8.0 Hz, 2H), 7.7(d, J= 13.2 Hz, 2H), 7.5(d, J= 10.8 Hz, 2H), 7.3(d, J= 8.4 Hz, 2H), 5.0(s,2H), 2.4(s,3H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 172.034(C=O), 168.764(C=N), 158.386(C-Br), 157.570(C=N), 142.322(-C-), 133.087, 129.719, 129.734, 127.493(-CH), 127.661(-C-), 122.761(-C-), 121.291(-C-), 38.749($-CH_2$), 21.634($-CH_3$)

MS (m/z, %)= 415.6$[M+H]^+$(50), 413.6$[M]^+$(30), 389.6(70), 334.5(100), 257.0(40)

3-(4-Bromophenyl)-4-((3-(4-(methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-[1,2,4]-oxadiazol-5(*4H*)-one (61p)



A mixture of 5-(chloromethyl)-3-(*p*-thiomethylphenyl)-1,2,4-oxadiazole **31c**(1 eq, 0.065 g, 0.27 mmol) and 3-(*p*-bromophenyl)-[1,2,4]-oxadiazol-5(*4H*)-one **41d** (1 eq, 0.065 g, 0.27 mmol) with K_2CO_3 (0.5 eq, 0.019 g, 0.14 mmol) in 5 mL of DMF was heated at 130℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(61p)** as a white solid. (40 mg, yield: 33%)

Mp.: 140℃

R_f: 0.70 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν :cm-1): 3016.77 (Aromatic –CH), 1780.36(C=O), 1599.04(C=C), 1444.73, 1024.24, 835.21, 759.98

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.8(m, J= 20.4 Hz, 4H), 7.6(d, J= 8.4 Hz, 2H) 7.3(d, J= 8.4 Hz, 2H), 5.3(s,2H), 2.5(s,3H)

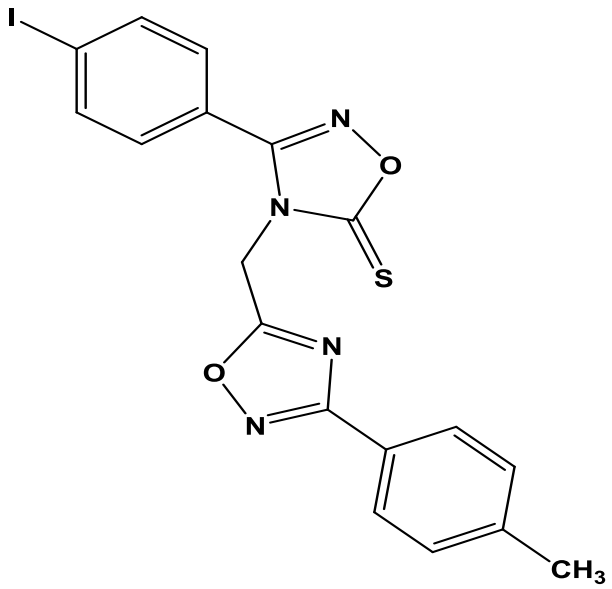
^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 174.573(C=O), 168.088(C=N),

158.906(C=N), 158.754(C=N), 144.192(C-S), 133.241, 131.253, 128.113, 126.482(-CH), 127.008(C-Br), 122.246(-C-), 122.032(-C-), 39.422($-CH_2$), 14.718($-CH_3$)

MS (m/z,%)= 468.6$[M+Na]^+$(50), 321.5(28), 293.6(28), 145.9(15)

Synthesis of *N*-substituted [1,2,4]-Oxadiazol-5-thiones

3-(4-Iodophenyl)-4-((3-(4-(*p*-tolyl)-1,2,4-oxadiazol-5-yl)methyl)-[1,2,4]-oxadiazol-5(*4H*)-thione (62)



A mixture of 5-(chloromethyl)-3-(*p*-tolyl)-1,2,4-oxadiazole **31b** (1 eq, 0.065 g, 0.27 mmol) and 3-(*p*-iodophenyl)-[1,2,4]-oxadiazol-5(*4H*)-one **42a** (1 eq, 0.065 g, 0.27 mmol) with K_2CO_3(0.5eq, 0.019 g, 0.14 mmol) in 5 mL of DMF was heated at 130℃ for 2 h and monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 4:1) to give **(62)** as a white solid. (40 mg, yield: 33%)

Mp.: 140℃

Rf: 0.56 (*n*-hexane: ethyl acetate, 1:1)

IR (KBr, ν :cm-1): 2972.76 (Aromatic –CH), 1654.62(C=N), 1593.25, 1502.60, 1398.44(C-O), 1273.06, 1174.69, 1008.80, 885.36, 827.45, 738.76

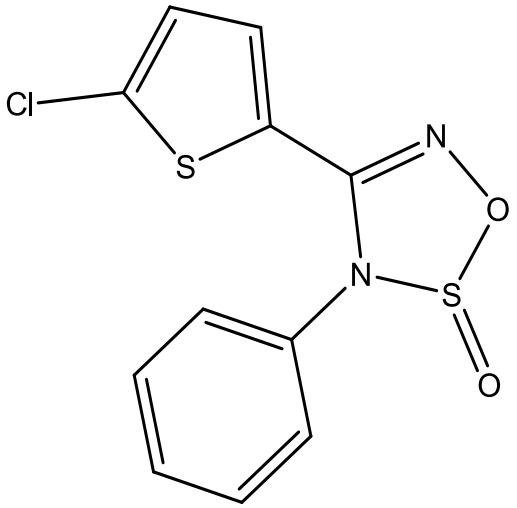
^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.8(m, J= 20.4 Hz, 4H), 7.6(d, J= 8.4 Hz, 2H) 7.3(d, J= 8.4 Hz, 2H), 5.3(s,2H), 2.5(s,3H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 174.573(C=S), 168.088(C=N), 158.906(C=N), 158.754(C=N), 144.192(C-S), 133.241, 131.253, 128.113, 126.482(-CH), 127.008(C-Br), 122.246(-C-), 122.032(-C-), 39.422($-CH_2$), 14.718($-CH_3$)

MS (m/z,%)= 468.6 $[M+Na]^+$(50), 321.5(28), 293.6(28), 145.9(15)

Synthesis of *N*-substituted 1,2,3,5-oxathiadiazole-2-oxide (63a-g)

4-(5-chloro-*2*-thienyl)-*N*-phenyl-[1,2,3,5]-oxathiadiazole-2-oxide (63a)



In a round-bottom flask, 5-chloro-*N*-phenylthiophene-2-carboxamidoxime **2f** (1 eq, 0.128 g, 0.5 mmol), pyridine (2 eq, 0.079 g, 1 mmol) and THF (3 mL/ mmol) were added. At 0°C was added $SOCl_2$ (1.5 eq, 0.089 g, 0.75 mmol) in CH_2Cl_2. The resulting mixture was stirred at room temperature (45 min). The

progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). THF was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with water. Organic layers were dried over Na_2SO_4 and filtered before evaporation in vacuo. The crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 6:1) to give **(63a)** as a brown solid. (35 mg, yield: %24)

Mp.: 82℃

R_f: 0.83 (*n*-hexane: ethyl acetate; 1:1)

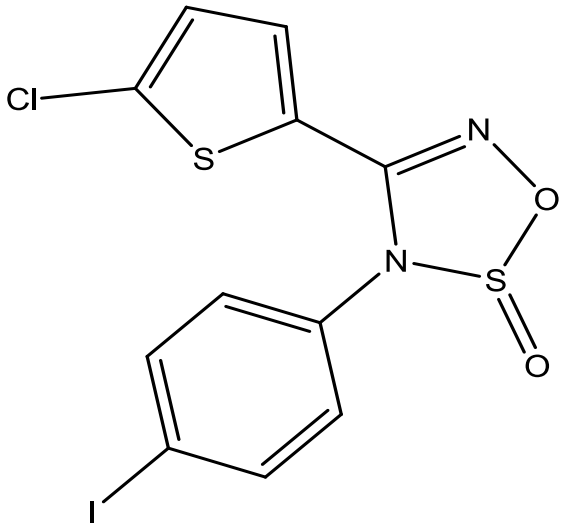
IR (KBr, ν :cm^{-1}): 3063.06 (Aromatic –CH), 1548.89(C=N), 1525.74, 1491.02, 1431.23, 1305.85, 1193.98, 1060.88, 1004.95, 864.14, 767.69, 696.33

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.5(m, J= 28.8 Hz, 3H), 7.4(d, J= 9.2 Hz, 2H), 6.75(d, J= 4 Hz, 1H), 6.6(d, J= 4 Hz, 1H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$):147.603(C=N), 135.685(-C-), 131.738(C-Cl), 130.854(-CH), 130.580(-CH), 129.612(-CH), 130.161(-CH), 129.612(-CH), 126.800(-C-), 120.993(-CH)

MS (*m/z*, %)= 235.7 $[M-SO_2+H]^+$(100), 146.2(12), 105.1(17)

4-(5-Chloro-2-thienyl)-*N*-(*p*-iodophenyl)-[1,2,3,5]-oxathiadiazole-2-oxide (63b)



In a round-bottom flask, 5-chloro-*N*-(*p*-iodophenyl)thiophene-2-carboxamidoxime **2d** (1 eq, 0.095 g, 0.25 mmol), pyridine (2 eq, 0.040 g, 0.50 mmol) and THF (3 mL/ mmol) were added. At 0°C was added $SOCl_2$ (1.5 eq, 0.045 g,0.38 mmol) in CH_2Cl_2. The resulting mixture was stirred at room temperature (45 min). The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). THF was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with water. Organic layers were dried over Na_2SO_4 and filtered before evaporation in vacuo. The crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 6:1) to give **(63b)** as a light brown solid.(20 mg, yield: 19%)

Mp.: 88-90℃

R_f: 0.87 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν :cm^{-1}): 3086.21 (Aromatic –CH), 1566.25(C=C), 1481.38, 1442.80, 1195.91, 1008.80, 856.42, 804.34

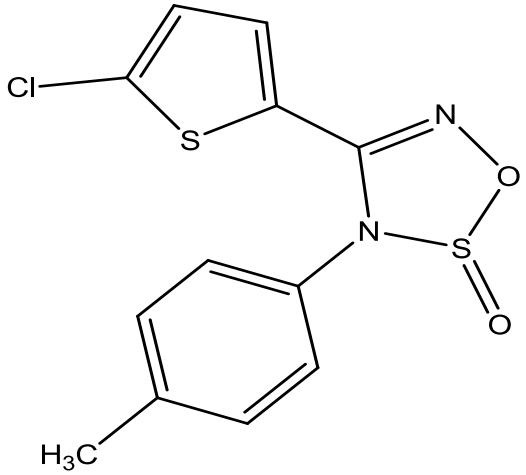
^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.8(d, J=6.8 Hz, 2H), 7.1(d, J=6.8 Hz, 2H), 6.8(d, J=4.4 Hz, 1H), 6.7(d, J=4 Hz, 1H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 147.575(C=N),139.650(-CH),136.206(-C-)

,135.230(CH), 131.778(C-Cl), 131.207(-CH), 127.176(-CH), 96.741(C-I)

MS (*m/z*, %)= 359.9[M-SO_2+H]$^+$(50), 296.9(100), 280.8(18), 230.1(12), 229.8(19),207.7(19)

4-(5-Chloro-2-thienyl)-*N*-(*p*-tolyl)-[1,2,3,5]-oxathiadiazole-2-oxide (63c)



In a round-bottom flask, 5-chloro-*N*-(*p*-tolyl)thiophene-2-carboxamidoxime **2c** (1 eq, 0.067 g, 0.25 mmol), pyridine (2 eq, 0.040 g,0.50 mmol) and THF (3 mL/ mmol) were added. At 0°C was added $SOCl_2$ (1.5eq, 0.045 g,0.38 mmol) in CH_2Cl_2. The resulting mixture was stirred at room temperature (45 min). The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). THF was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with water. Organic layers were dried over Na_2SO_4 and filtered before evaporation in vacuo. The crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 6:1) to give **(63c)** as a brown solid. (30 mg, yield: 40%)

Mp.: 80℃

R_f: 0.85 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν :cm^{-1}): 3109.35(Aromatic –CH), 1604.83(C=N), 1508.38, 1444.73,

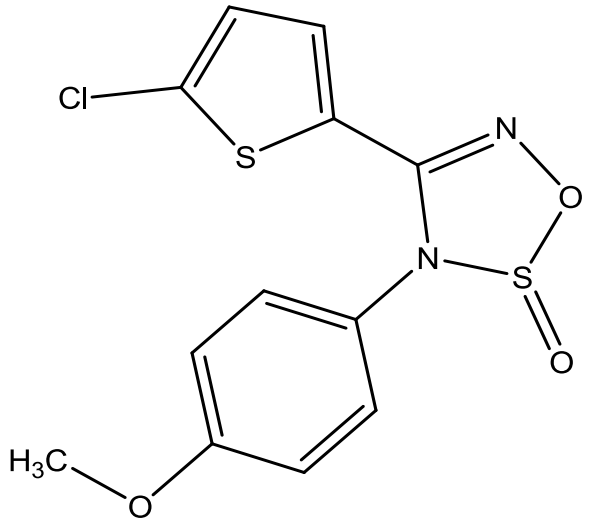
1369.50, 1190.12, 1057.03, 854.49

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$):7.3(d,4H), 7.1(d, J=4 Hz, 1H), 6.8(d, J=4,4 Hz, 1H), 2.3(s,3H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$):148.124(C=N), 141.456(-C-), 134.438(-C-), 132.457(C-Cl), 131.428(C-H), 130.239(C-H), 129.005(-CH), 128.829(-CH), 121.148(-C-), 21.499($-CH_3$)

MS (*m/z*, %)=251.5$[M-SO_2+H]^+$(100), 173.2(8), 146.4(12)

4-(5-Chloro-2-thienyl)-*N*-(*p*-methoxyphenyl)-[1,2,3,5]-oxathiadiazole-2-oxide (63d)



In a round-bottom flask, 5-chloro-*N*-(*p*-methoxyphenyl)thiophene-2-carboxamidoxime **2b** (1 eq, 0.071 g, 0.25 mmol), pyridine (2 eq, 0.040 g, 0.50 mmol) and THF (3 mL/ mmol) were added. At 0°C was added $SOCl_2$ (1.5 eq, 0.045 g,0.38 mmol) in CH_2Cl_2. The resulting mixture was stirred at room temperature (45 min). The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). THF was removed under reduced pressure. The

mixture in CH_2Cl_2 was washed 3 times with water. Organic layers were dried over Na_2SO_4 and filtered before evaporation in vacuo. The crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 6:1) to give **(63d)** as a brown solid. (25 mg, yield: 32%)

Mp.: 79℃

R_f: 0.78 (*n*-hexane: ethyl acetate; 1:1)

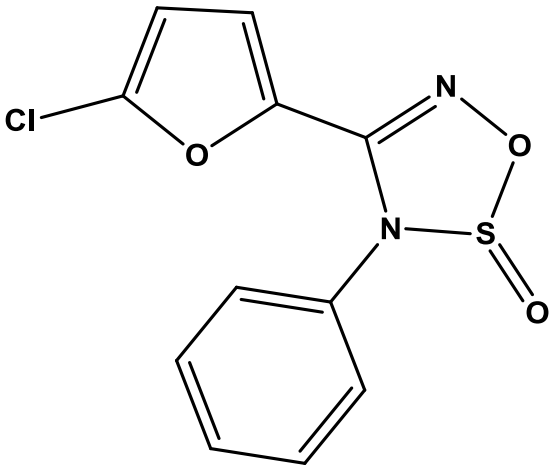
IR (KBr, ν :cm^{-1}): 3101.64(Aromatic –CH), 1606.76(C=C=), 1566.25, 1508.38, 1442.80, 1365.65, 1251.84(C-O), 1166.97, 1060.88, 854.49

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.3(d, J= 8.8 Hz, 2H), 6,9(d, J= 12.2 Hz,2H), 6.7(d, J= 14.4 Hz, 2H), 3.9(s, 3H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$):161.497(C=N), 148.185(-C-Cl), 135.893(-C-) 131.664(-CH), 131.009(-CH), 126.970(-CH), 123.892(-C-), 121.415(-C-), 115.486(-CH), 55.889($-CH_3$)

MS (*m/z*, %)= 266.5$[M-SO_2+H]^+$(100), 229.4(8),217.6(5), 182.3(8), 164.6(10), 146.1(27)

4-(5-Chloro-2-furyl)-*N*-Phenyl-[1,2,3,5]-oxathiadiazole-2-oxide (63e)



In a round-bottom flask, 5-chloro-*N*-phenylfuran-2-carboxamidoxime **2e** (1 eq, 0.118 g, 0.50 mmol), pyridine (2 eq,0.079 g,1 mmol) and THF (3 mL/ mmol) were added. At 0°C was added $SOCl_2$ (1.5 eq, 0.089 g,0.75 mmol) in CH_2Cl_2. The resulting mixture was stirred at room temperature (45 min). The progress of the reaction monitored by TLC (CH_2Cl_2/MeOH, 95/5). THF was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with water. Organic layers were dried over Na_2SO_4 and filtered before evaporation in vacuo. The crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 6:1) to give **(63e)** as a beige solid. (30 mg, 20%)

Mp.: 118-120℃

R_f: 0.76 (*n*-hexane:ethyl acetate; 1:1)

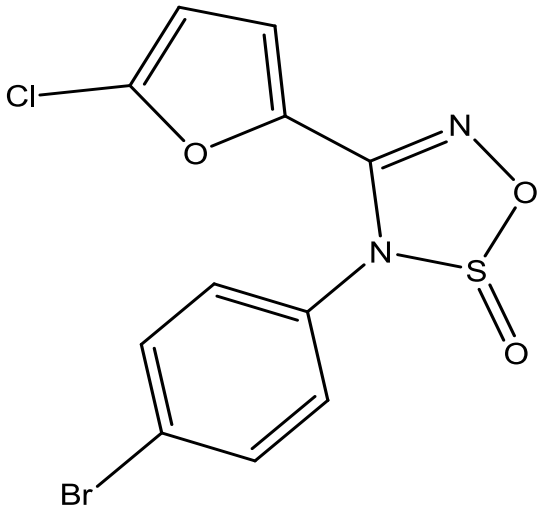
IR (KBr, ν :cm^{-1}): 3153.72(Aromatic –CH), 1608.78(C=N), 1485.24, 1383.01, 1267.27, 1199.76, 1126.47, 941.29, 850.64, 750.84

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.5(m, J= 8 Hz, 3H), 7.4(d, J= 10 Hz, 2H), 6.6(d, J= 4 Hz, 1H), 6.3(d, J= 3.6 Hz, 1H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 145.076(C=N), 140.062(-C-), 131.308(-CH), 131.207(-CH), 130.818(-CH), 129.790(-CH), 119.312(-C-), 110.198(-C-)

MS (*m/z*, %)=248.7(25), 247.6$[M]^+$(100), 221.6(7), 151.7(3)

4-(5-Chloro-2-furyl)-*N*-(*p*-bromophenyl)-[1,2,3,5]-oxathiadiazole-2-oxide (63f)



In round-bottom flask, 5-chloro-*N*-(*p*-bromophenyl)furan-2-carboxamidoxime **2a** (1 eq 0.079 g, 0.25 mmol), pyridine (2 eq, 0.040 g, 0.50 mmol) and THF (3 mL/ mmol) were added. At 0°C was added $SOCl_2$ (1.5 eq, 0.045 g,0.375 mmol) in CH_2Cl_2. The resulting mixture was stirred at room temperature (45 min). The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). THF was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with water. Organic layers were dried over Na_2SO_4 and filtered before evaporation in vacuo. The crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 6:1) to give **(63f)** as a light brown solid. (30 mg, 34%)

Mp.: 96℃

R_f: 0.85 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν :cm^{-1}): 3088.21(Aromatic –CH), 1608.69(C=N), 1491.02, 1383.01, 1271.12, 1197.83, 1128.47, 983.77, 868.00, 789.91

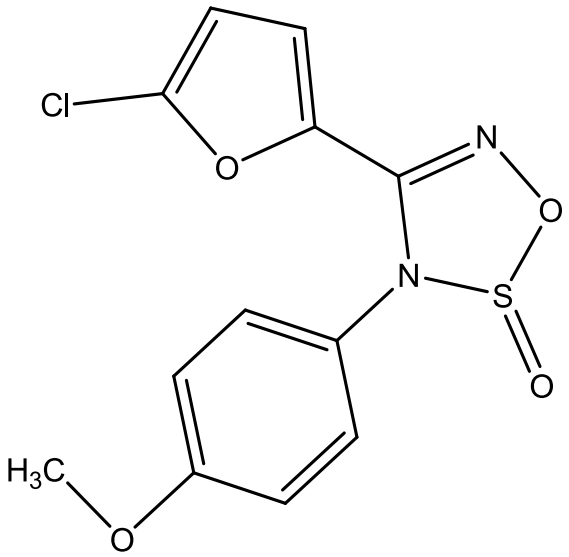
^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.7(d,J= 12 Hz, 2H), 7.4(d, J= 11.6 Hz), 6.6(d, J= 3.6 Hz, 1H), 6.4(d, J= 3.6 Hz, 1H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 144.893(C=N), 140.123(-C-), 136.434(-C-),

133.775(-CH), 131.756(-CH), 131.367(-C-), 124.440(-C-), 119.624(-CH), 110.335(-CH)

MS (*m/z*, %)=300.6[M-SO_2+H]$^+$(100), 285.4(20), 241.9(28), 207.7(22), 190.6(20), 182.7(15)

4-(5-Chloro-2-furyl)-*N*-(*p*-meyhoxyphenyl)-[1,2,3,5]-oxathiadiazole-2-oxide (63g)



In a round-bottom flask, 5-chloro-*N*-(*p*-methoxyphenyl)furan-2-carboxamidoxime **2g** (1 eq 0.079 g, 0.25 mmol), pyridine (2 eq, 0.040 g, 0.50 mmol) and THF (3 mL/ mmol) were added. At 0°C was added $SOCl_2$ (1.5 eq, 0.045 g,0.375 mmol) in CH_2Cl_2. The resulting mixture was stirred at room temperature (45 min). The progress of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 95/5). THF was removed under reduced pressure. The mixture in CH_2Cl_2 was washed 3 times with water. Organic layers were dried over Na_2SO_4 and filtered before evaporation in vacuo. The crude residue was purified by flash column chromatography (*n*-hexane: ethyl acetate; 6:1) to give **(63g)** as a light brown solid. (35 mg, 45%)

Mp.: 79℃

R_f: 0.73 (*n*-hexane: ethyl acetate; 1:1)

IR (KBr, ν :cm^{-1}): 3130.57(Aromatic –CH), 1604.83, 1508.38, 1483.31, 1381.08, 1253.77, 1201.69, 1120.68, 1026.16, 858.35

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.3(d,J=12.4 Hz, 2H), 6.9(d, J=12.4 Hz, 2H), 6.1(d, J=3.6 Hz, 1H), 6.0(d, J=3.6 Hz, 1H), 3.8(s, 3H)

^{13}C NMR (δ_C, 100 MHz, $CDCl_3$): 161.164(C=N), 144.961(-C-), 140.928(-C-), 136.856(-C-), 131.092(-CH), 123.833(-C-), 117.639(-CH), 115.126(-CH), 108.432(-CH), 55.675($-CH_3$)

MS (*m/z*, %)= 251.7$[M^+-SO_2+H]^+$(100), 115.3(6), 101.3(50), 104.6(8)

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APPENDICES

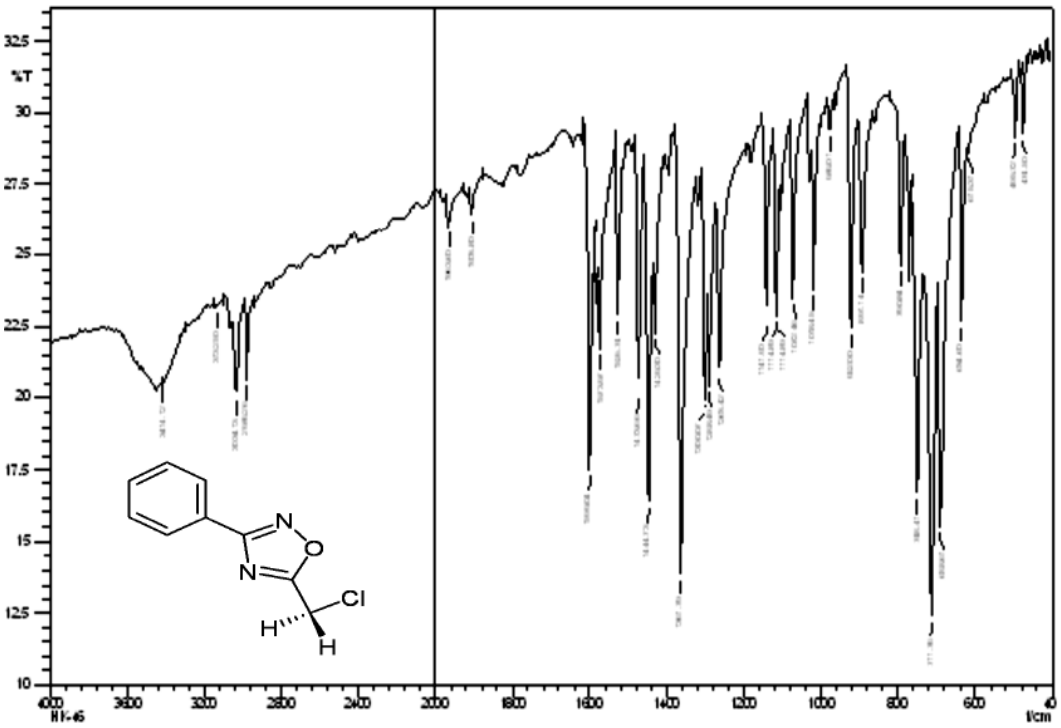

Figure 4.1. IR spectrum of compound **31a**

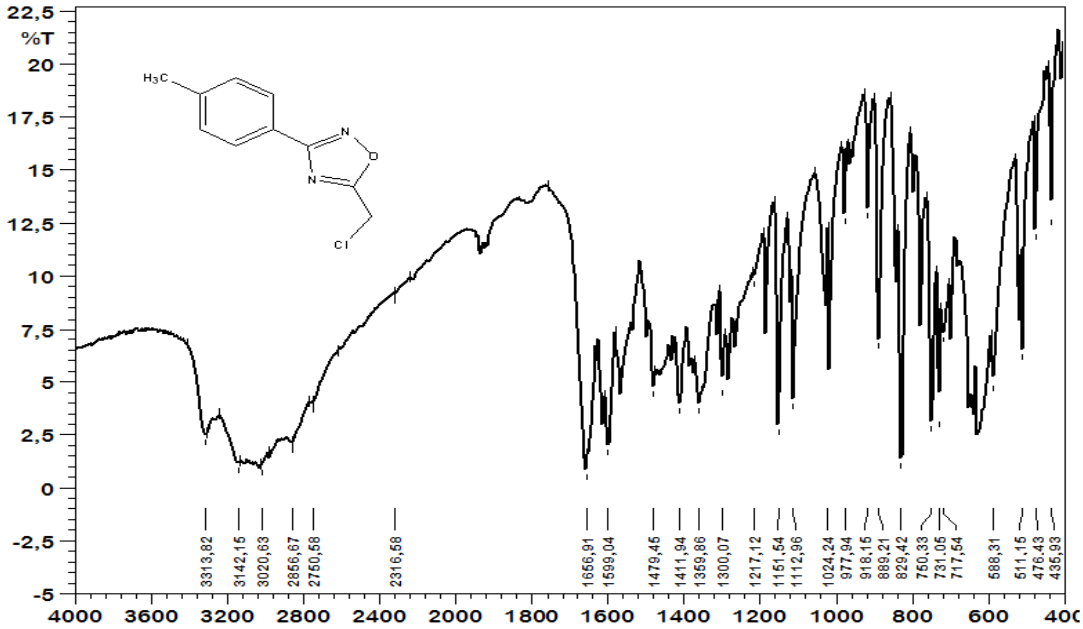

Figure 4.2. IR spectrum of compound **31b**

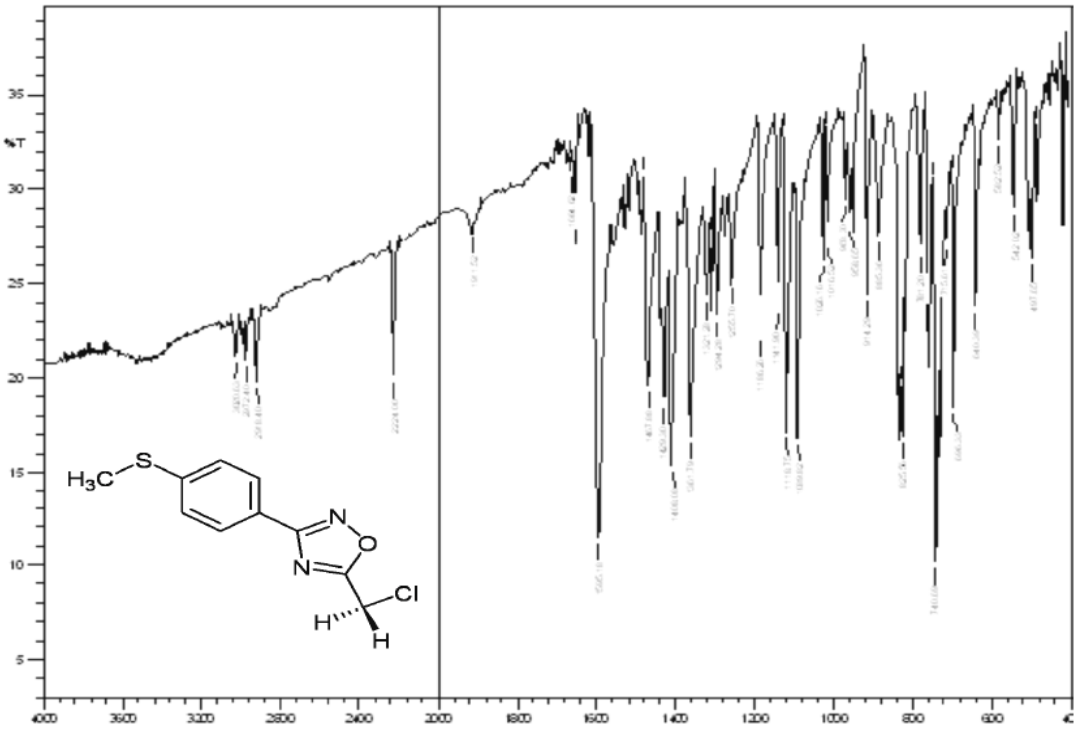

Figure 4.3. IR spectrum of comound **31c**

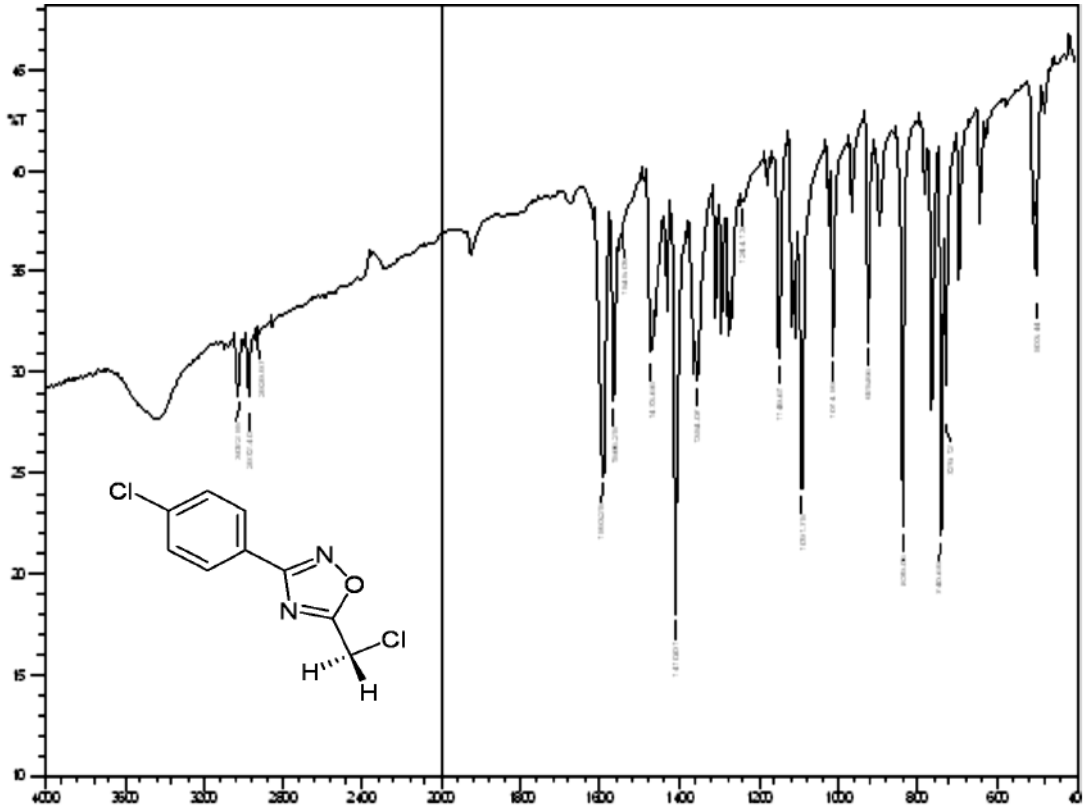

Figure 4.4. IR spectrum of compound **31d**

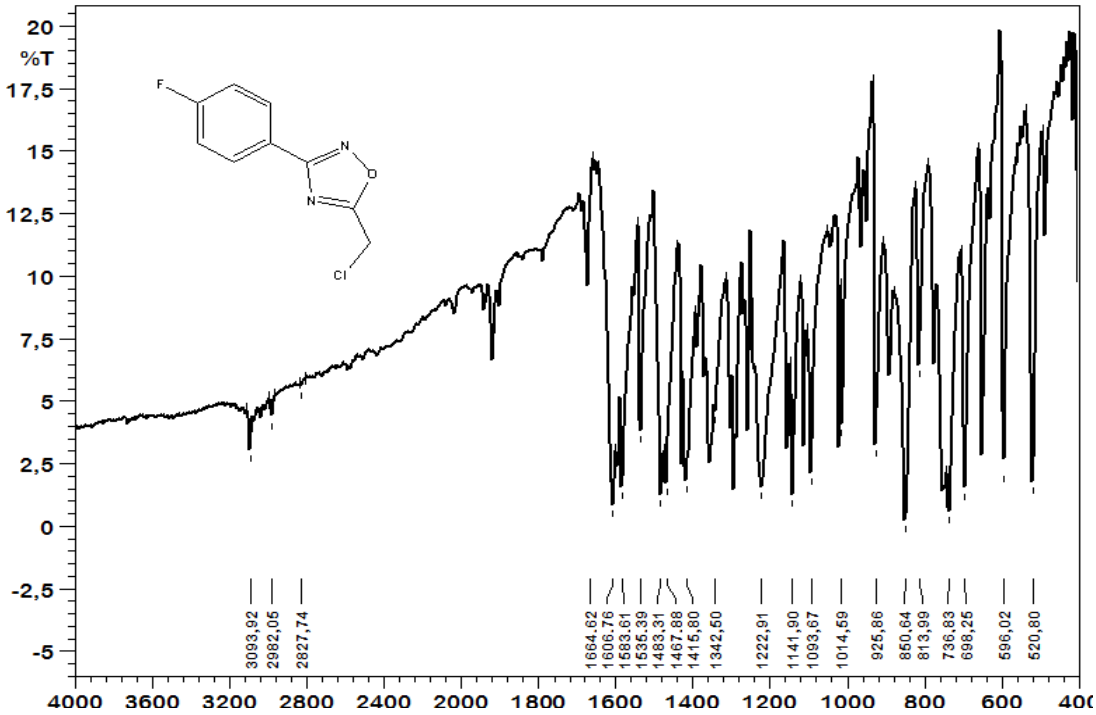

Figure 4.5. IR spectrum of compound **31e**

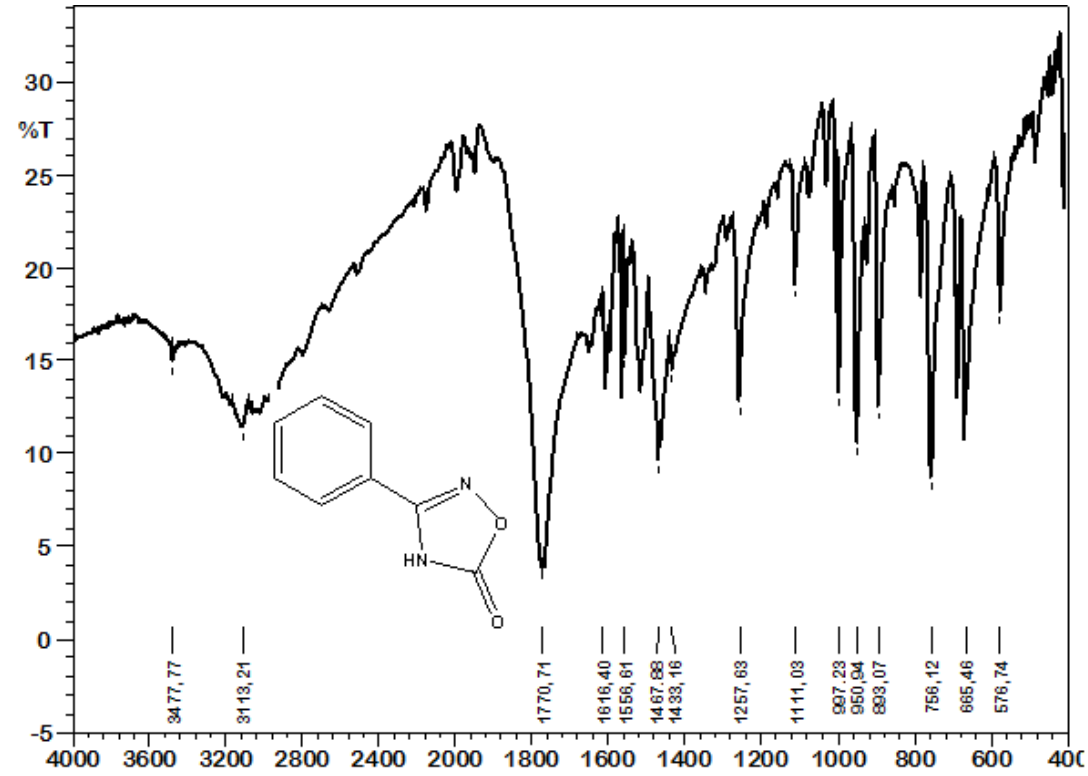

Figure 4.6. IR spectrum of compound **41a**

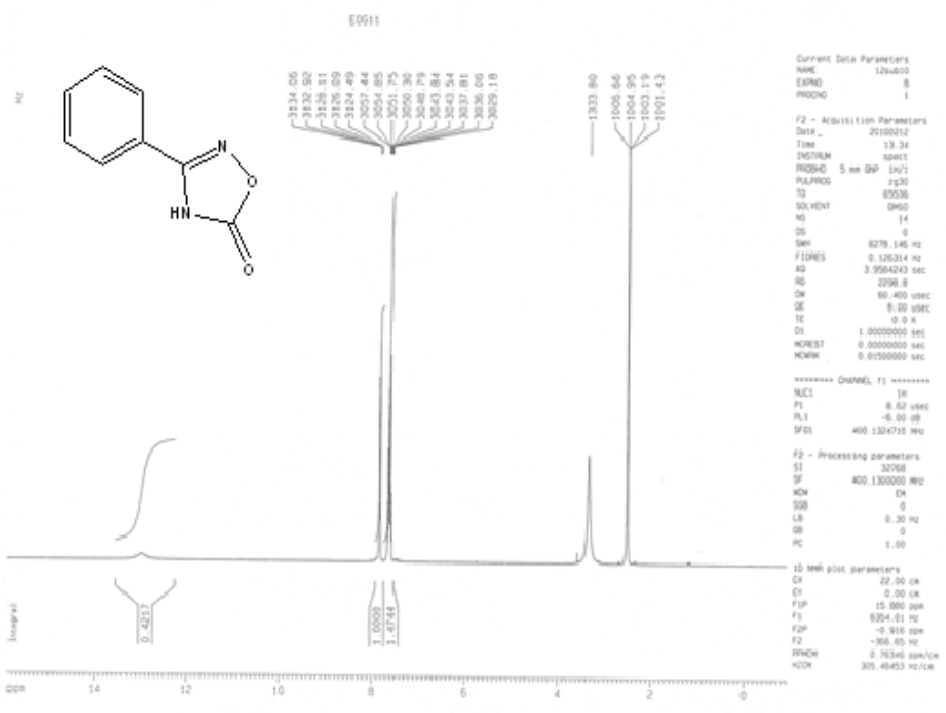

Figure 4.7. ^{1}H NMR spectrum of compound **41a**

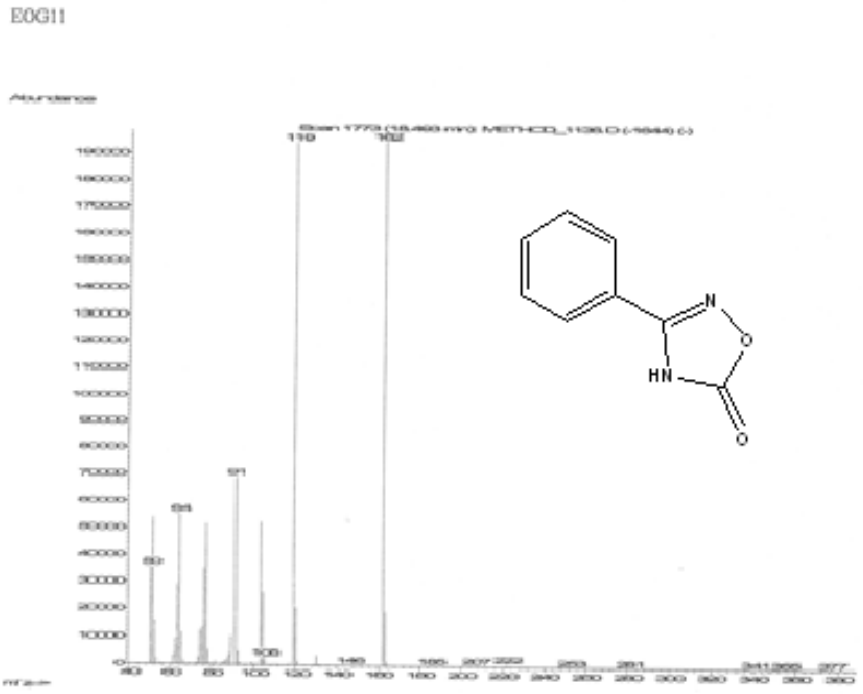

Figure 4.8. LC-MS spectrum of compound **41a**

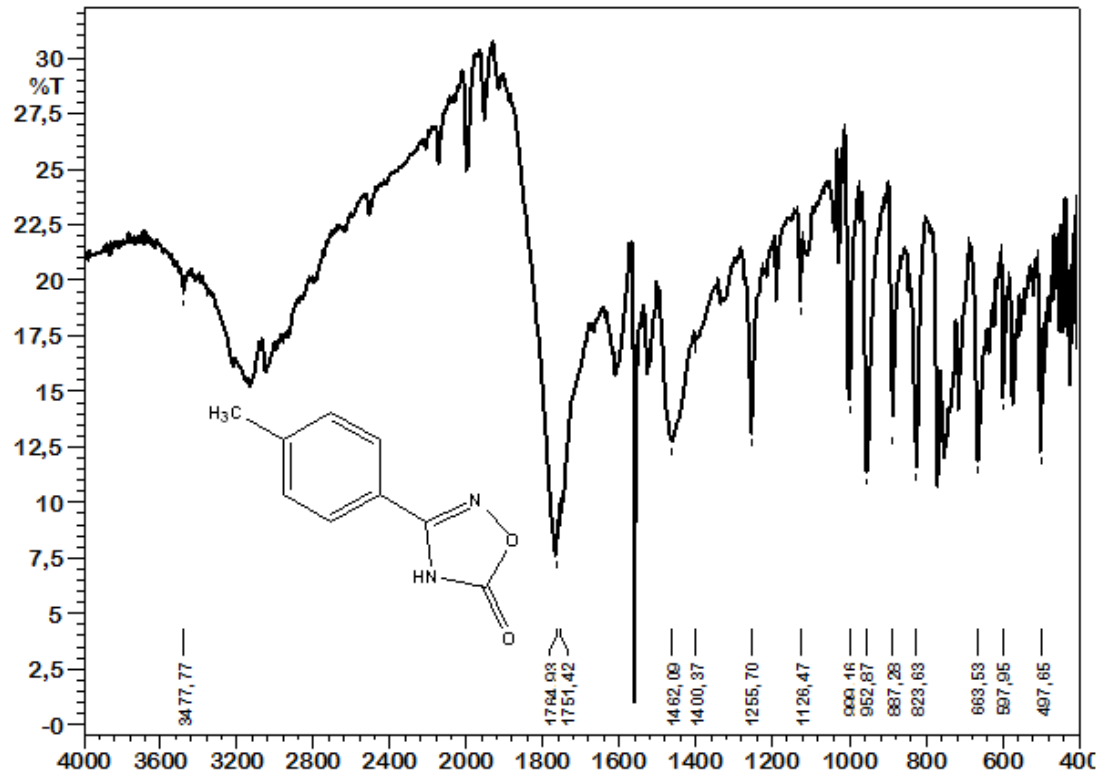

Figure 4.9. IR spectrum of compound **41b**

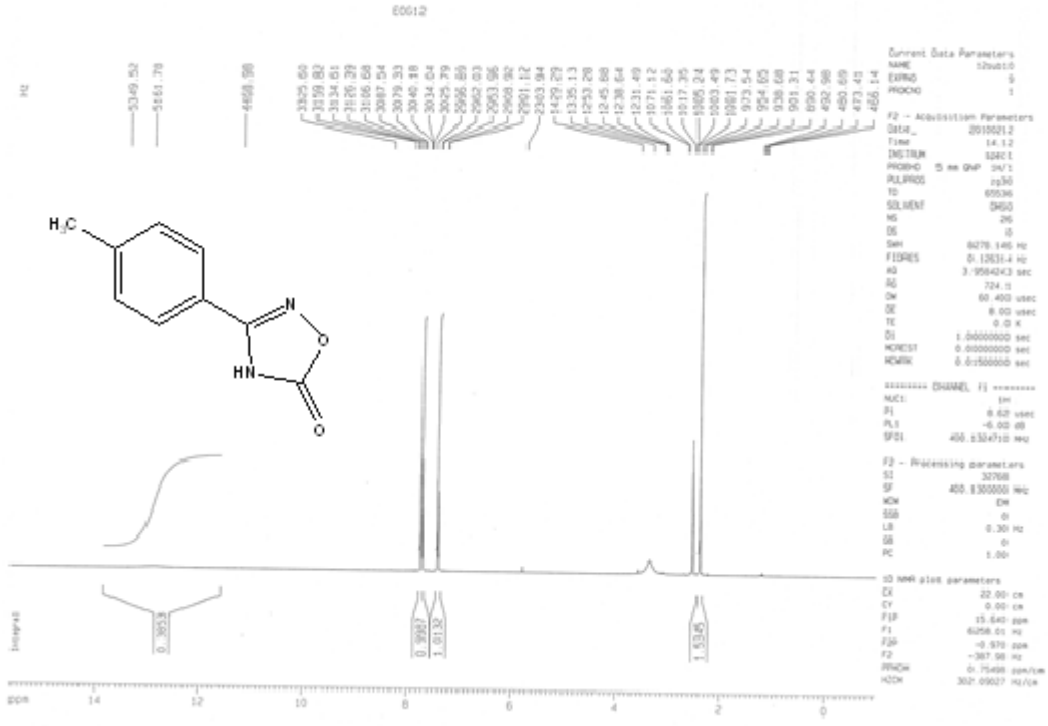

Figure 4.10. ^{1}H NMR spectrum of compound **41b**

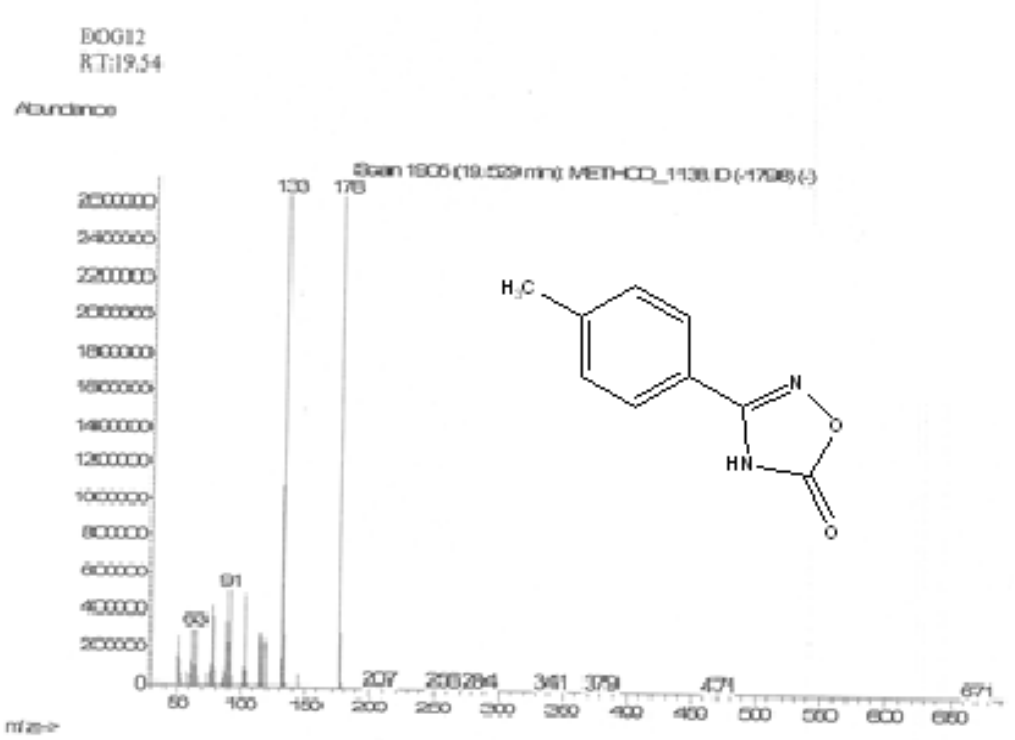

Figure 4.11. LC-MS spectrum of compund **41b**

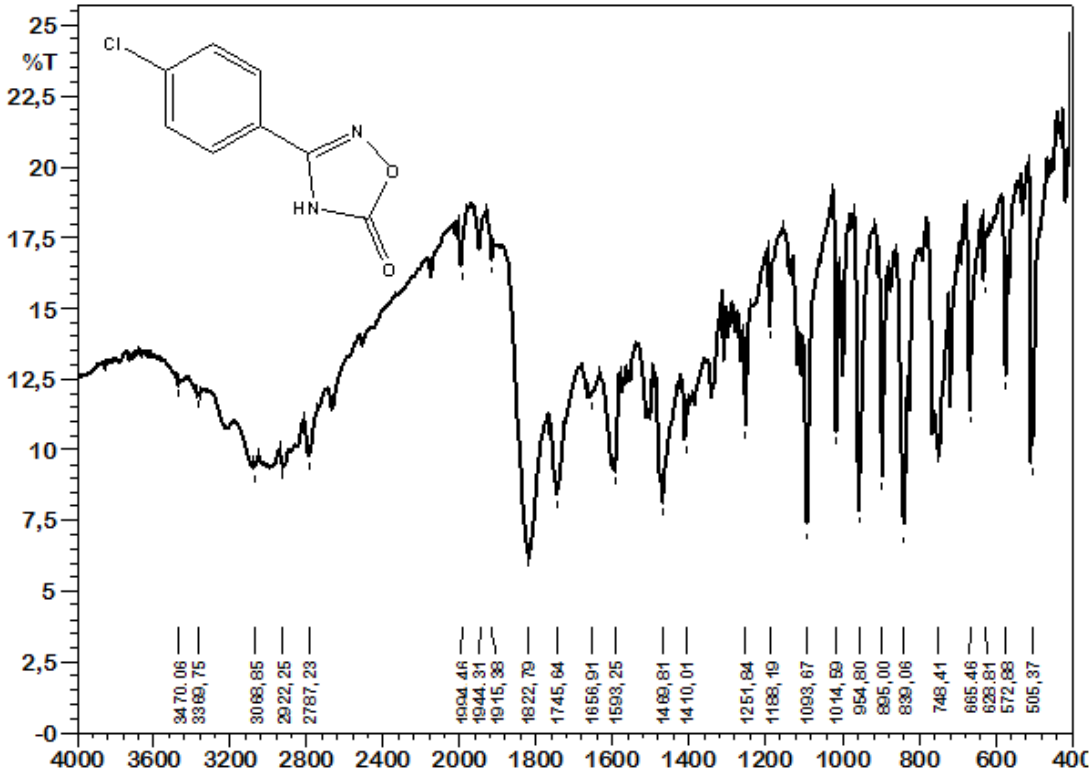

Figure 4.12. IR spectrum of compound **41c**

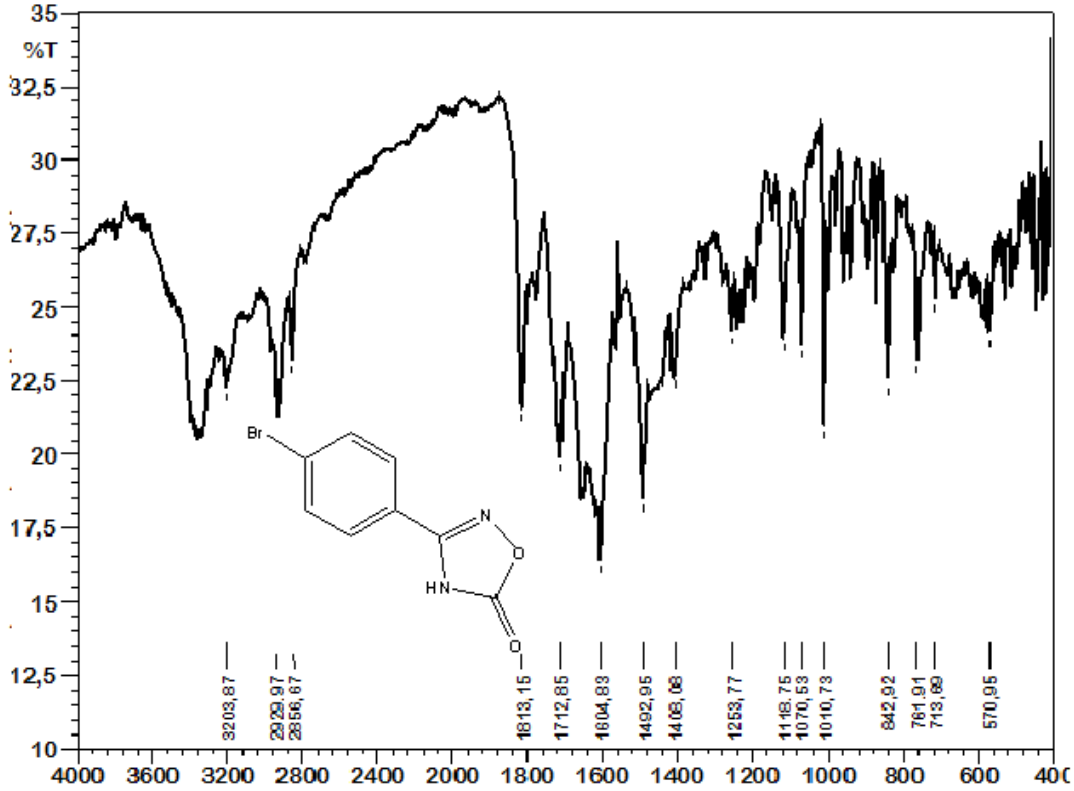

Figure 4.13. IR spectrum of compound **41d**

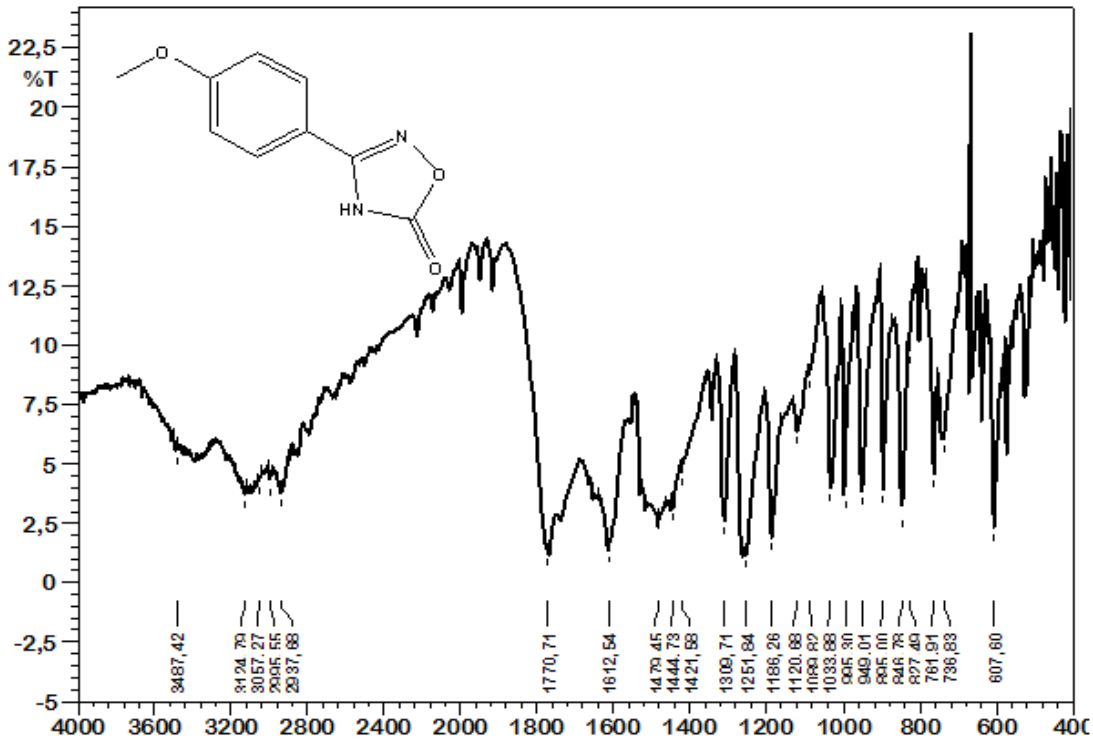

Figure 4.14. IR spectrum of compound **41e**

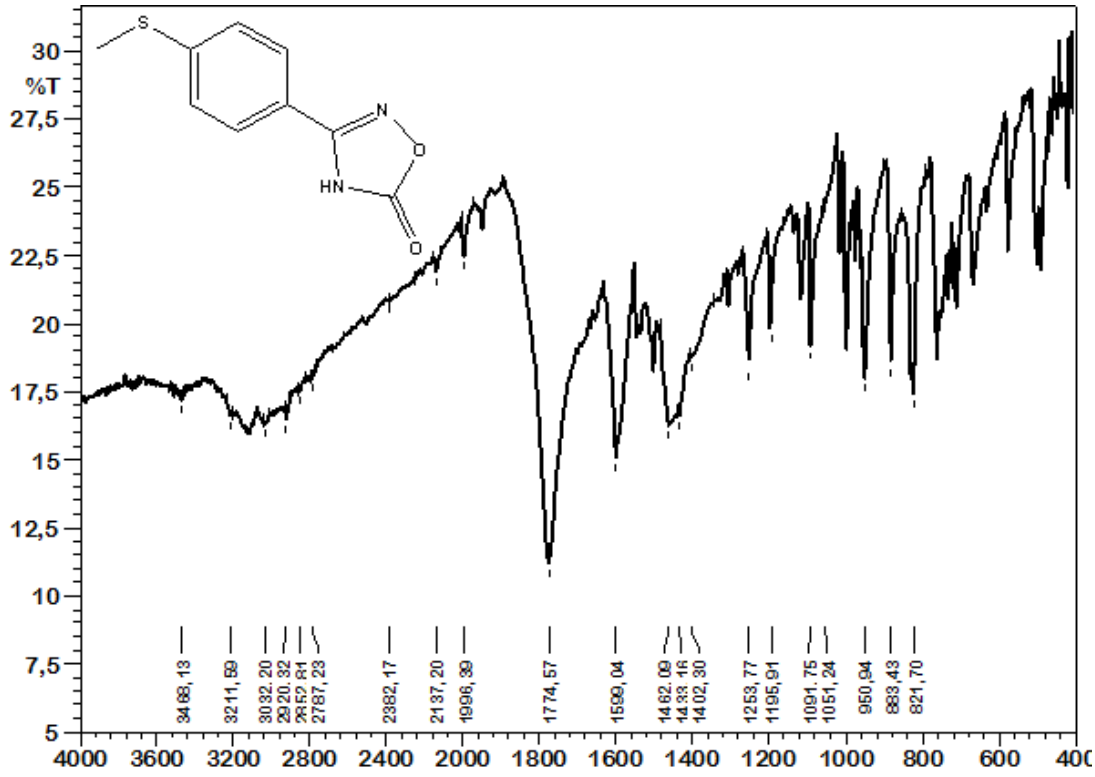

Figure 4.15. IR spectrum of compound **41f**

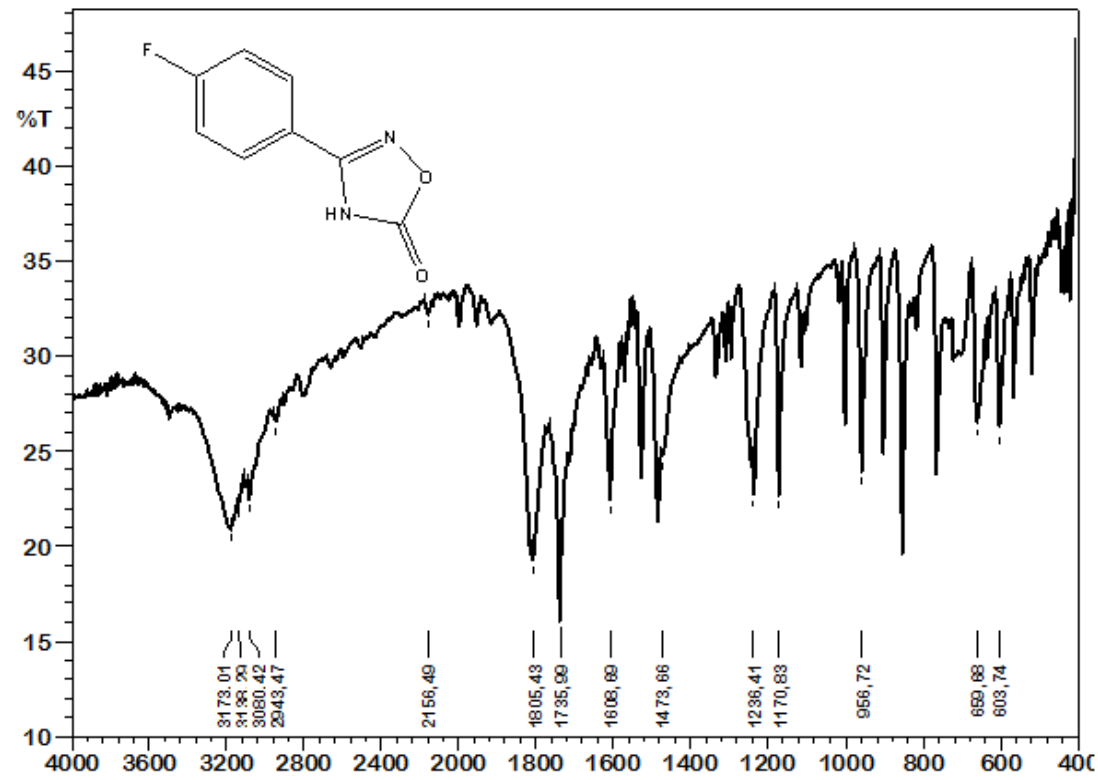

Figure 4.16. IR spectrum of compound **41g**

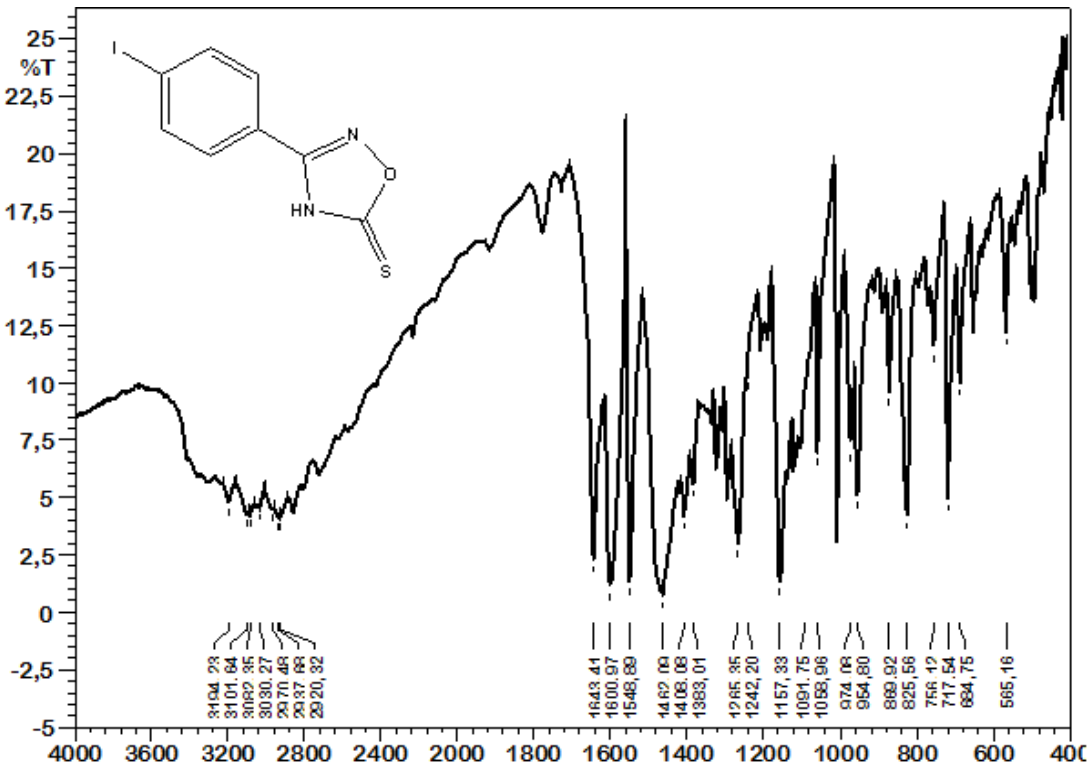

Figure 4.17. IR spectrum of compound **42a**

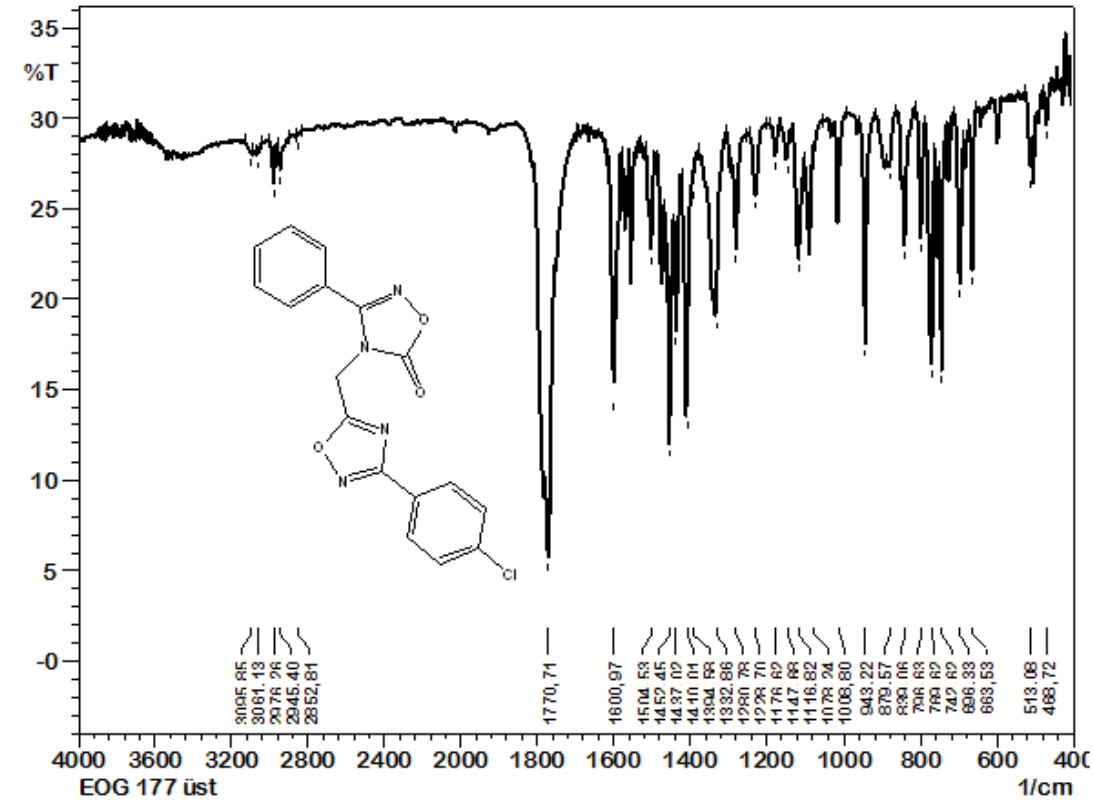

Figure 4.18. IR spectrum of compound **61a**

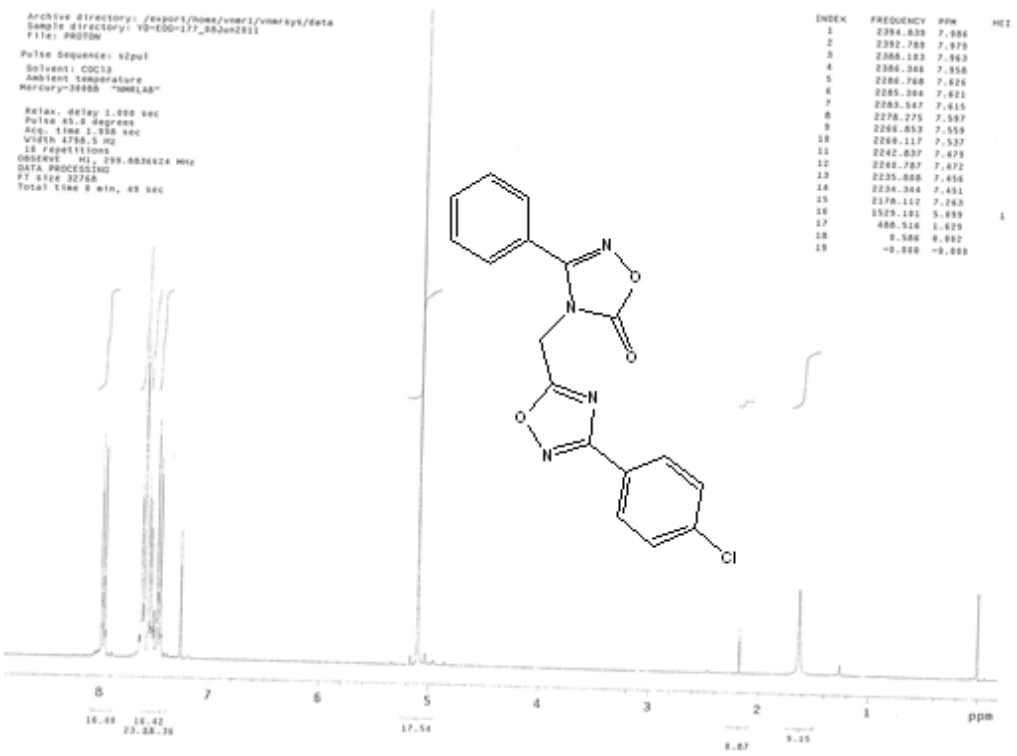

Figure 4.19. ^{1}H NMR spectrum of compound **61 a**

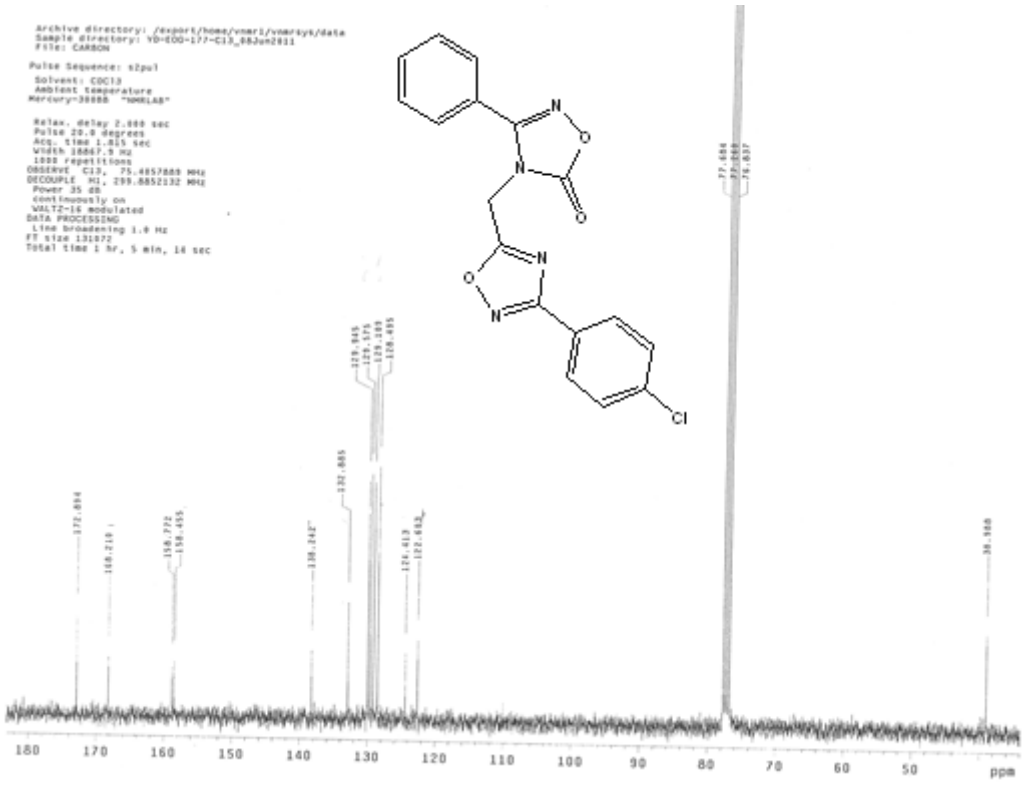

Figure 4.20. ^{13}C NMR spectrum of compound **61a**

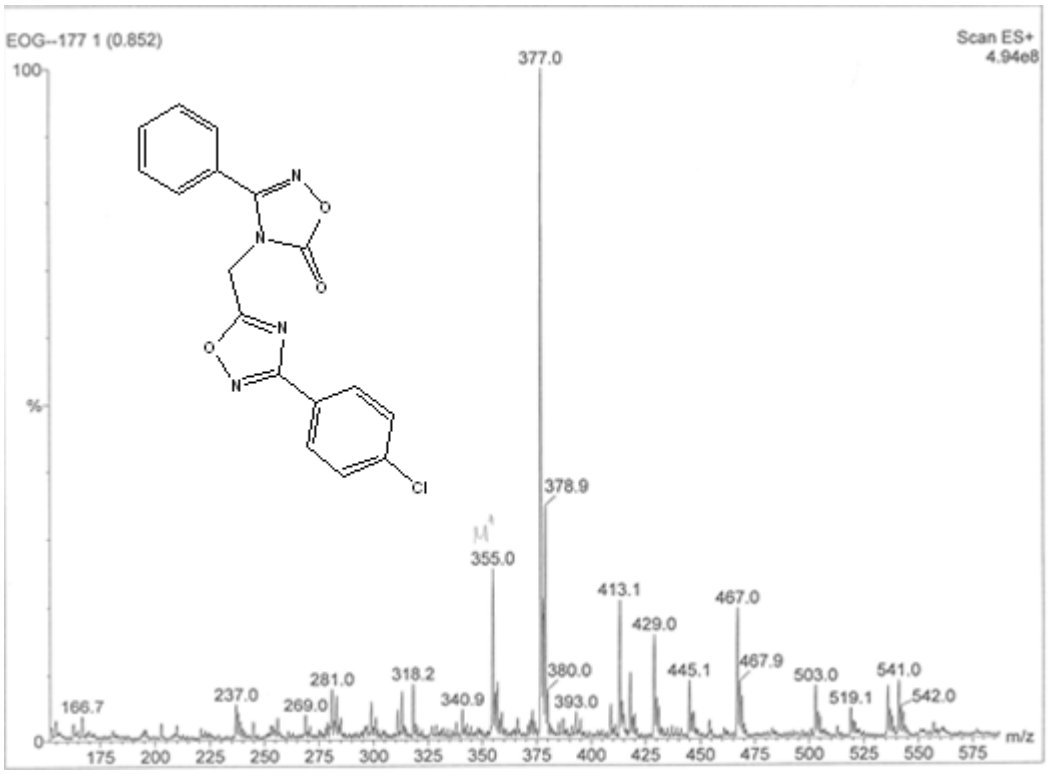

Figure 4.21. LC-MS spectrum of compound **61a**

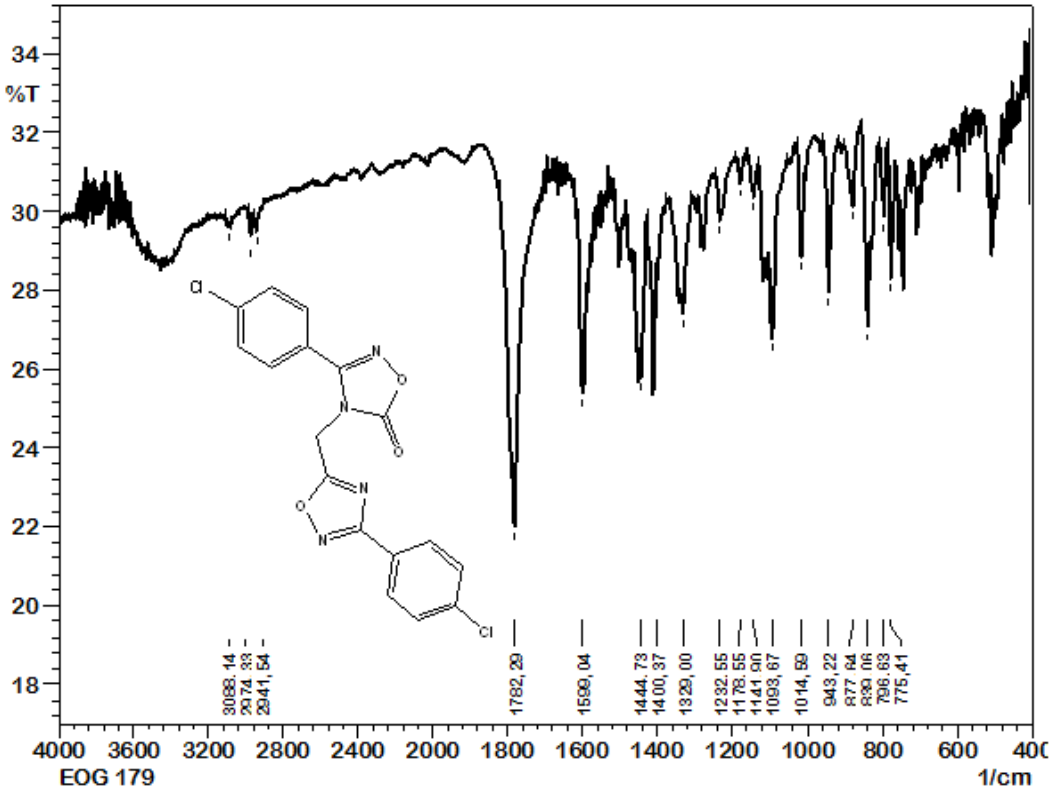

Figure 4.22. IR spectrum of compound **61b**

Figure 4.23. ^{1}H NMR spectrum of compound **61b**

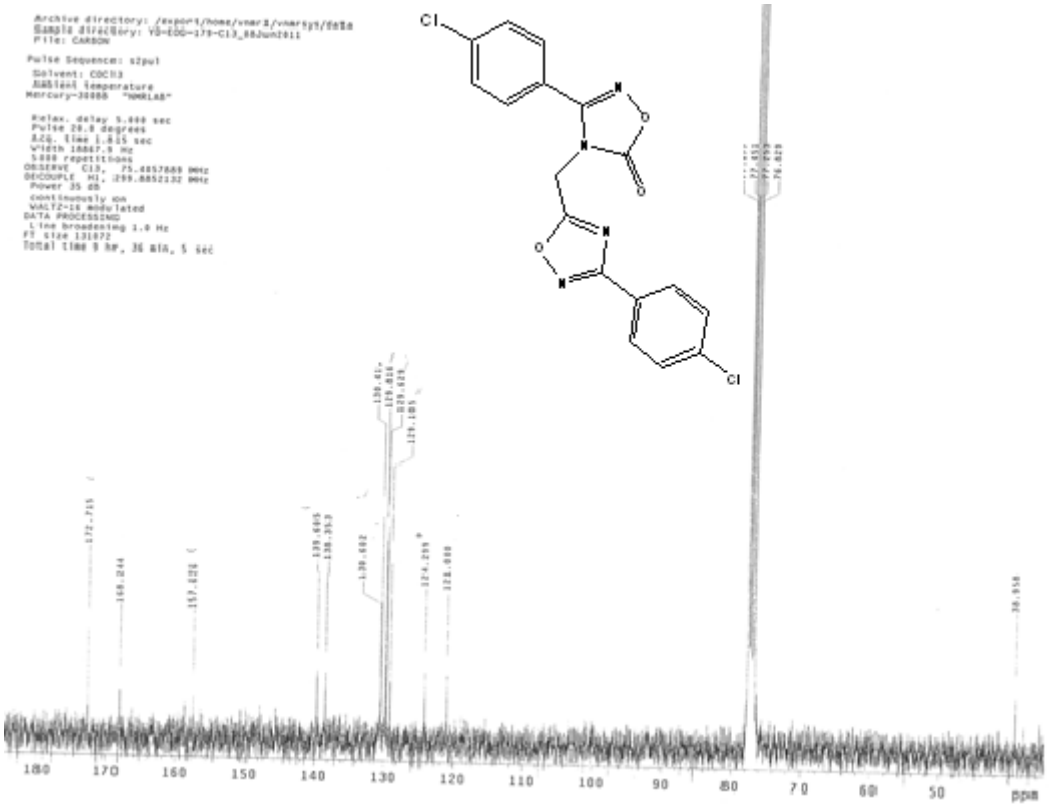

Figure 4.24. ^{13}C NMR spectrum of compound **61b**

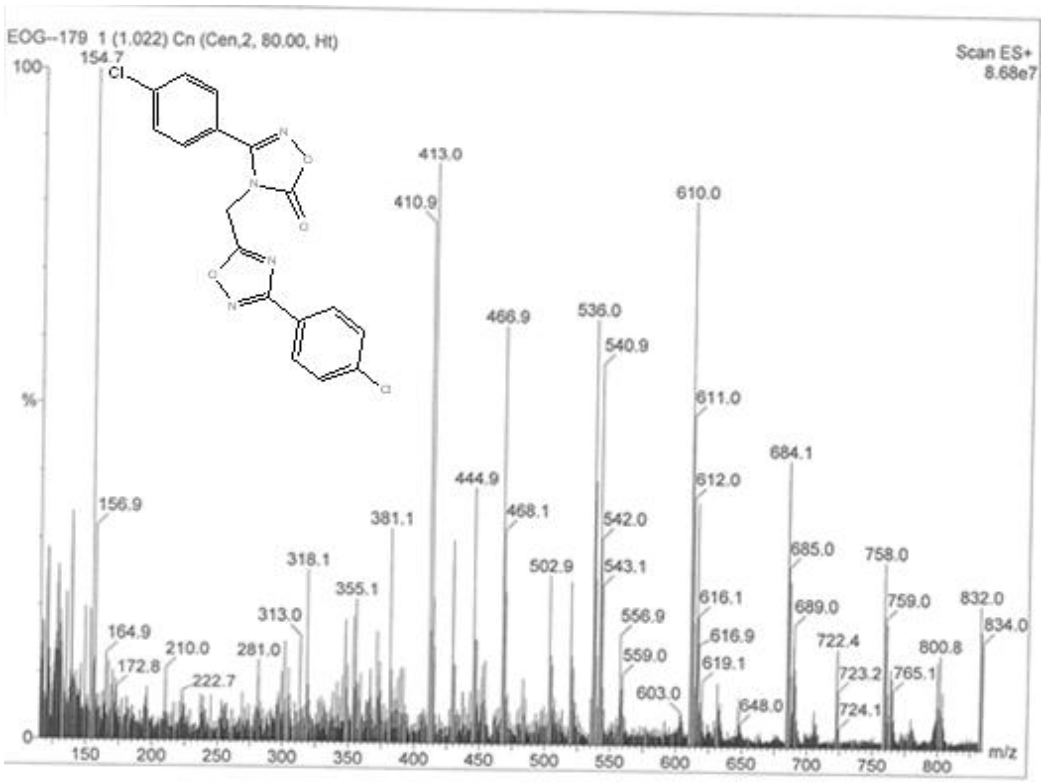

Figure 4.25. LC-MS spectrum of compound **61b**

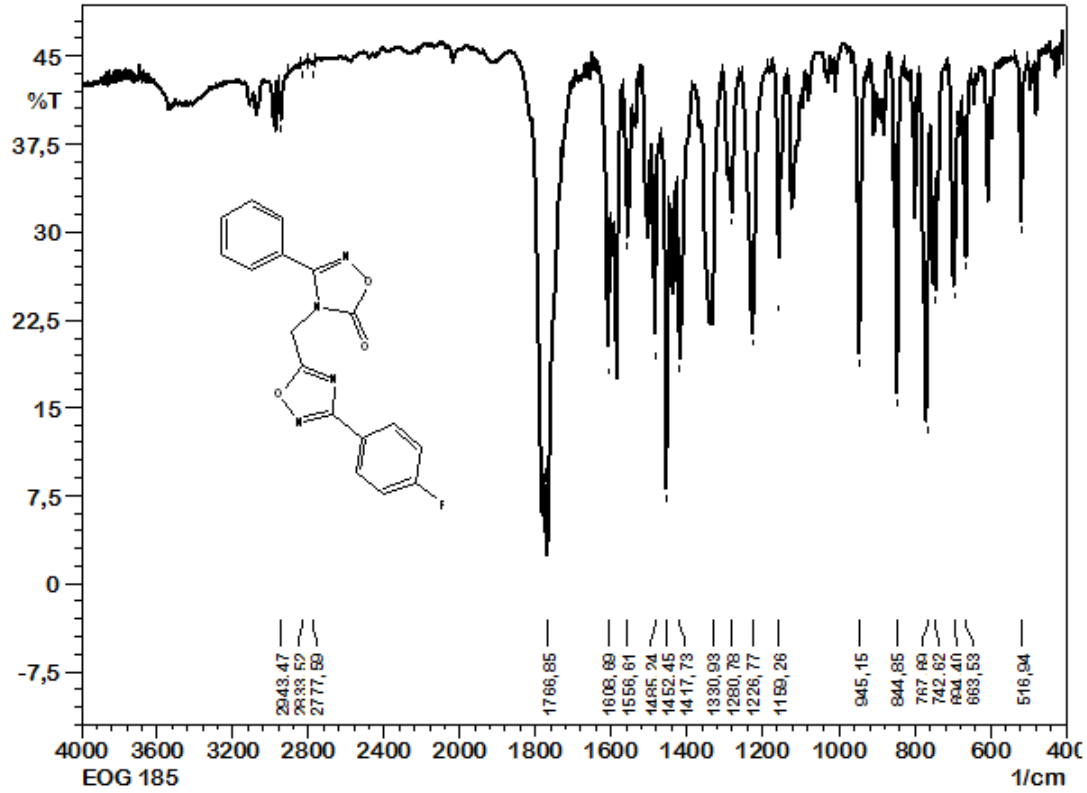

Figure 4.26. IR spectrum of compound **61c**

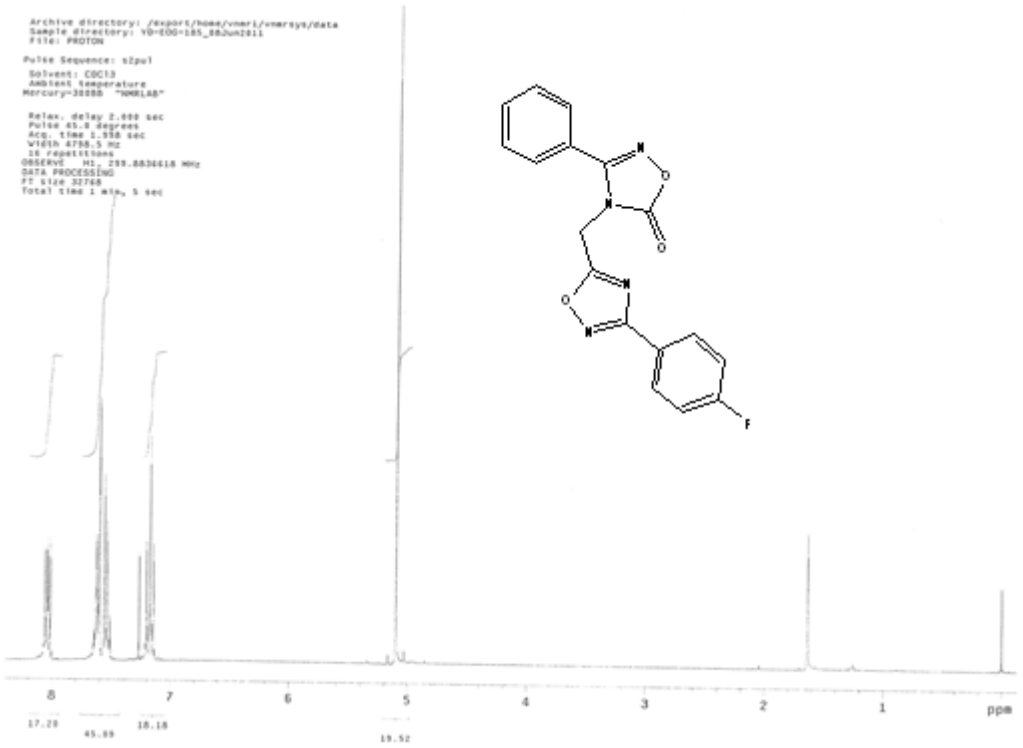

Figure 4.27. ^{1}H NMR spectrum of compound **61c**

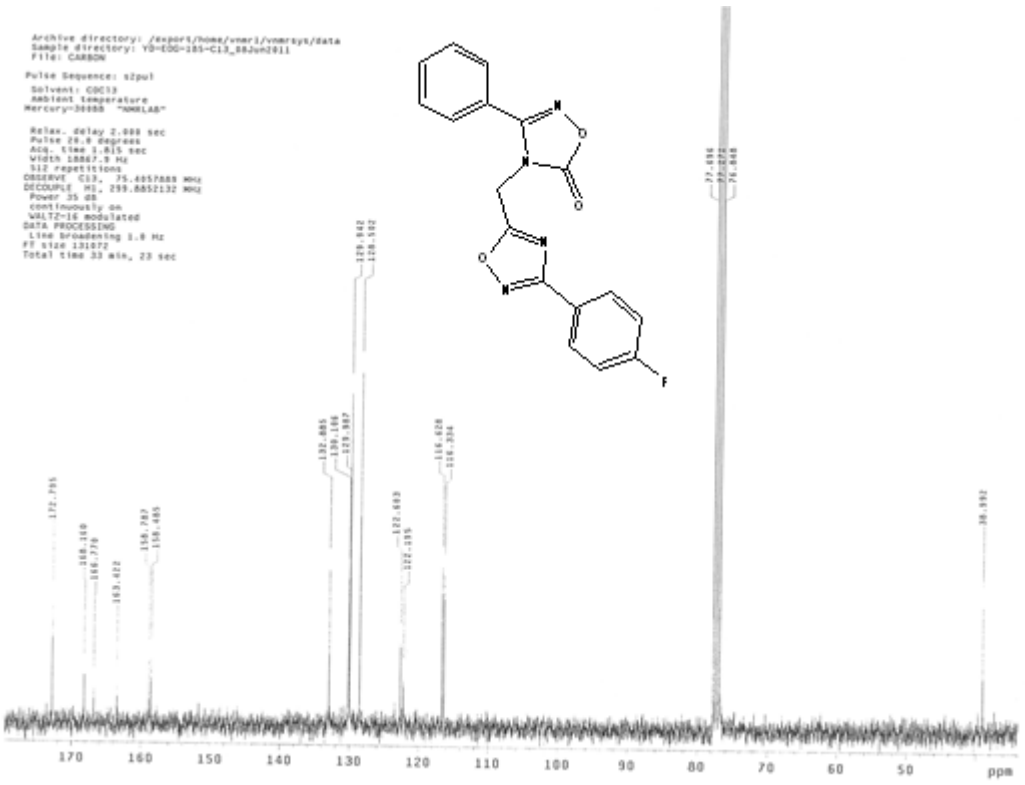

Figure 4.28. ^{13}C NMR spectrum of compound **61c**

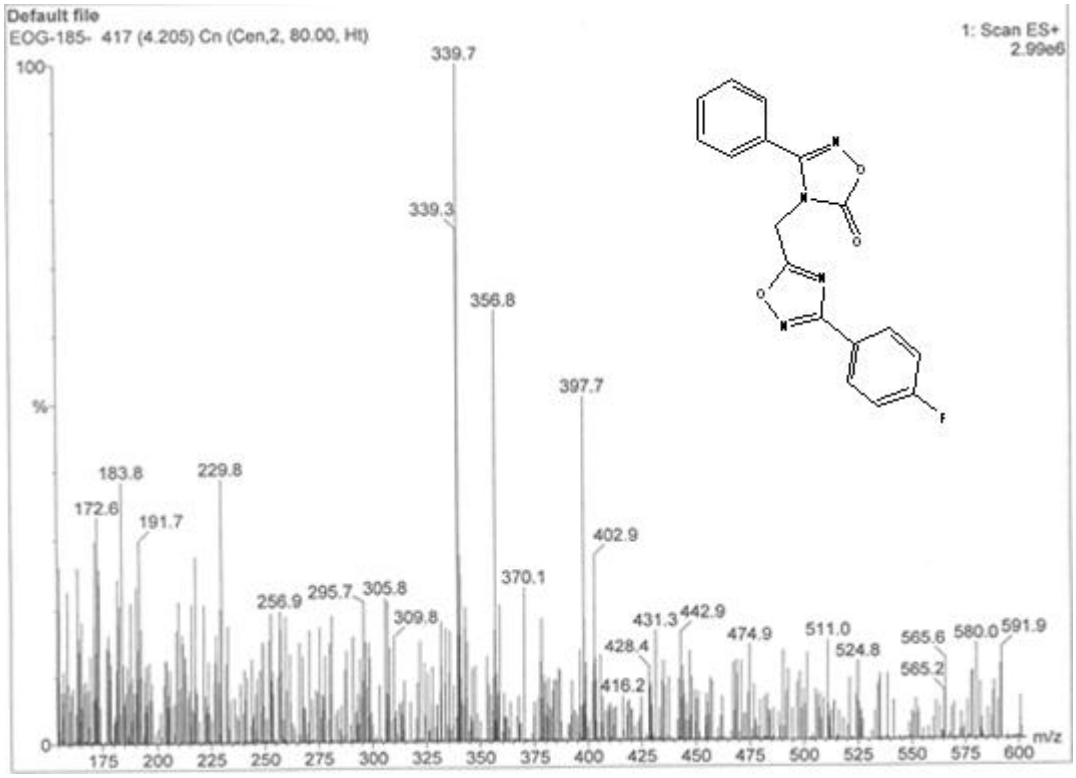

Figure 4.29. LC-MS spectrum of compound **61c**

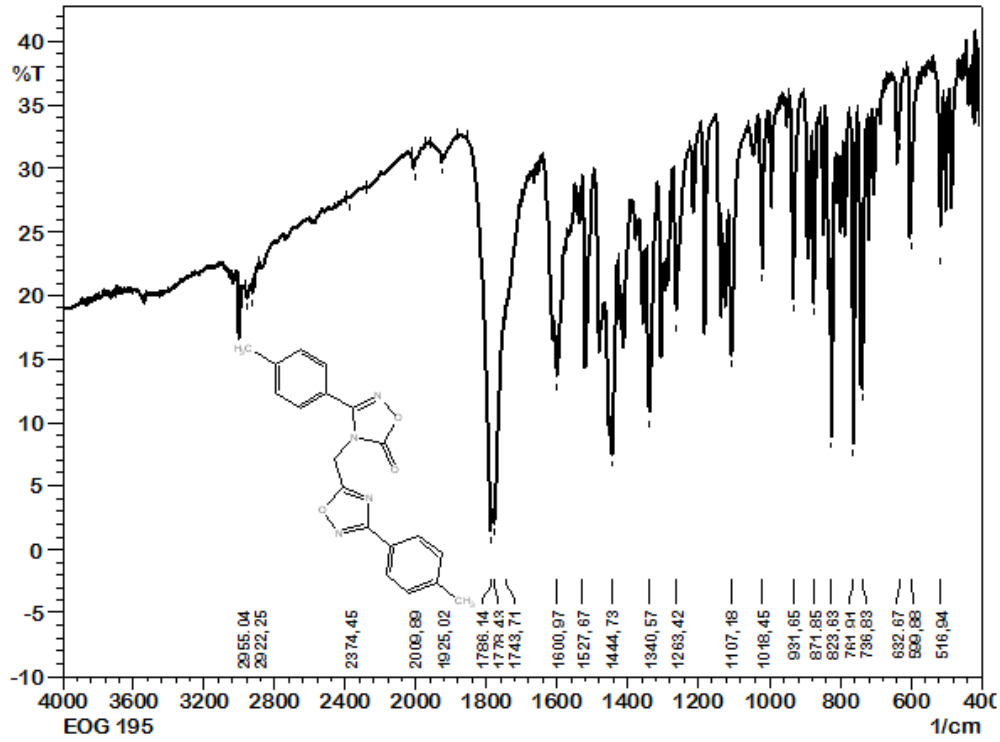

Figure 4.30. IR spectrum of compound **61d**

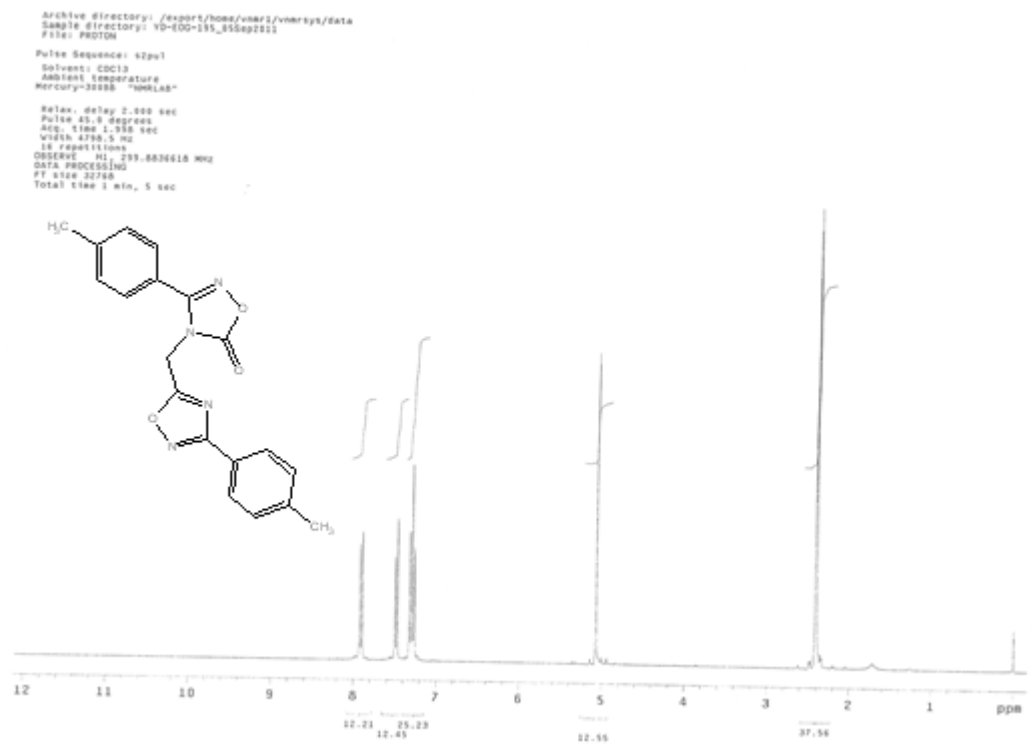

Figure 4.31. ^{1}H NMR spectrum of compound **61d**

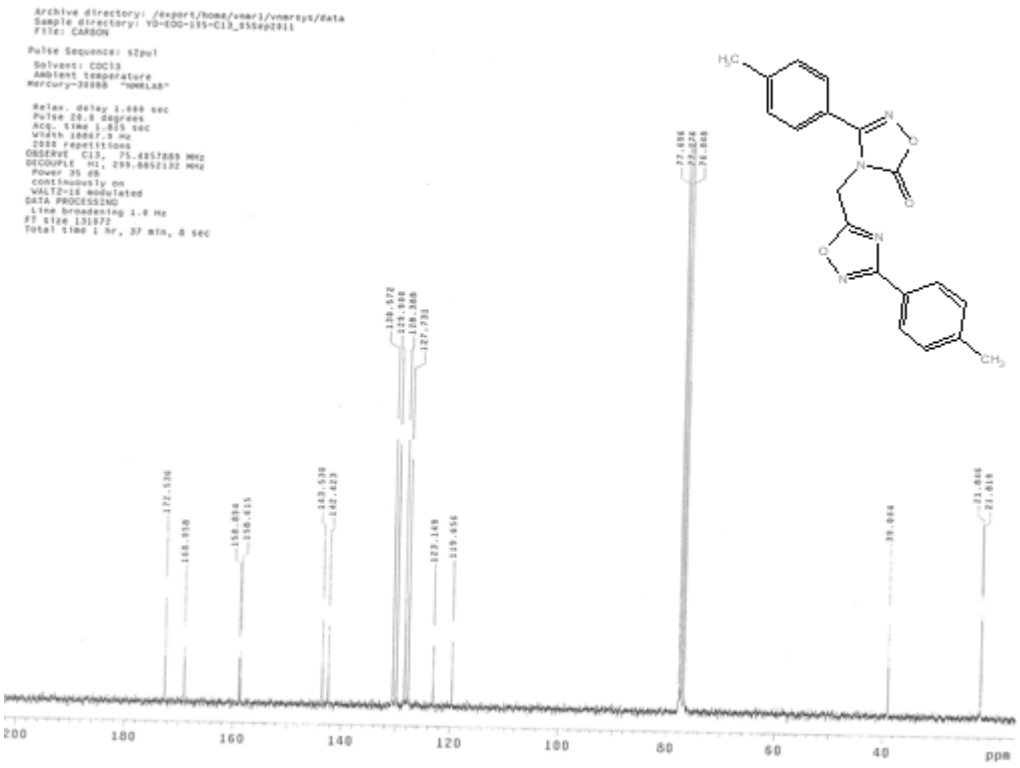

Figure 4.32. ^{13}C NMR spectrum of compound **61d**

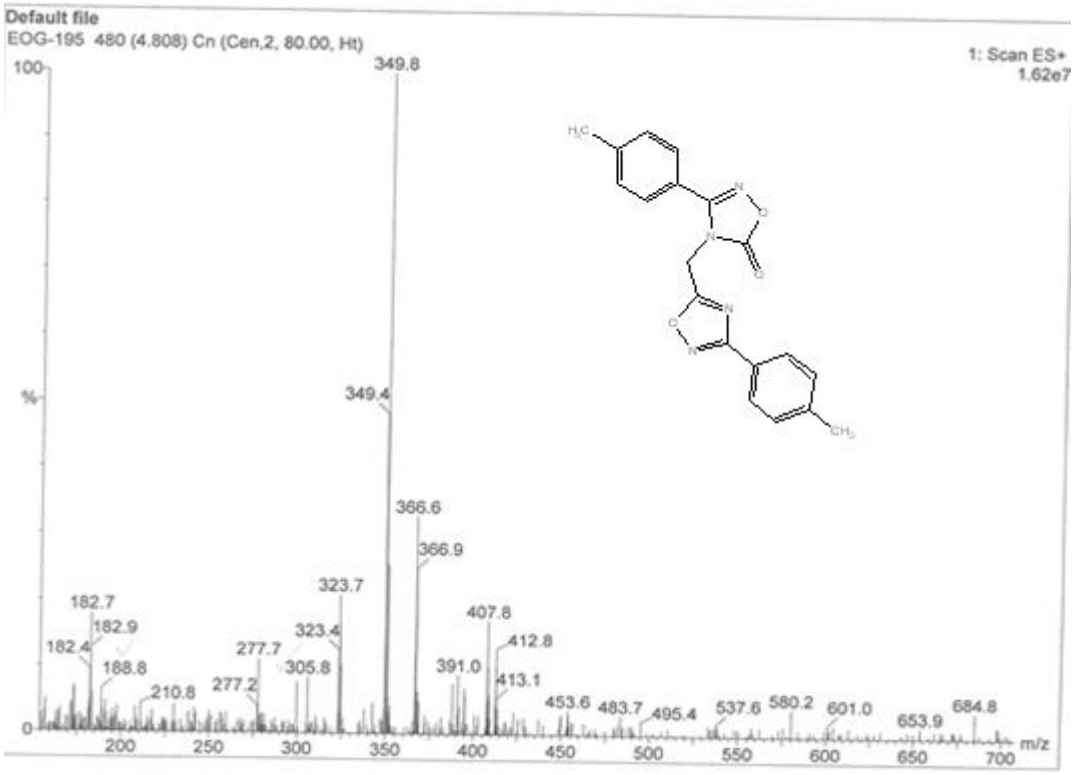

Figure 4.33. LC-MS spectrum of compound **61d**

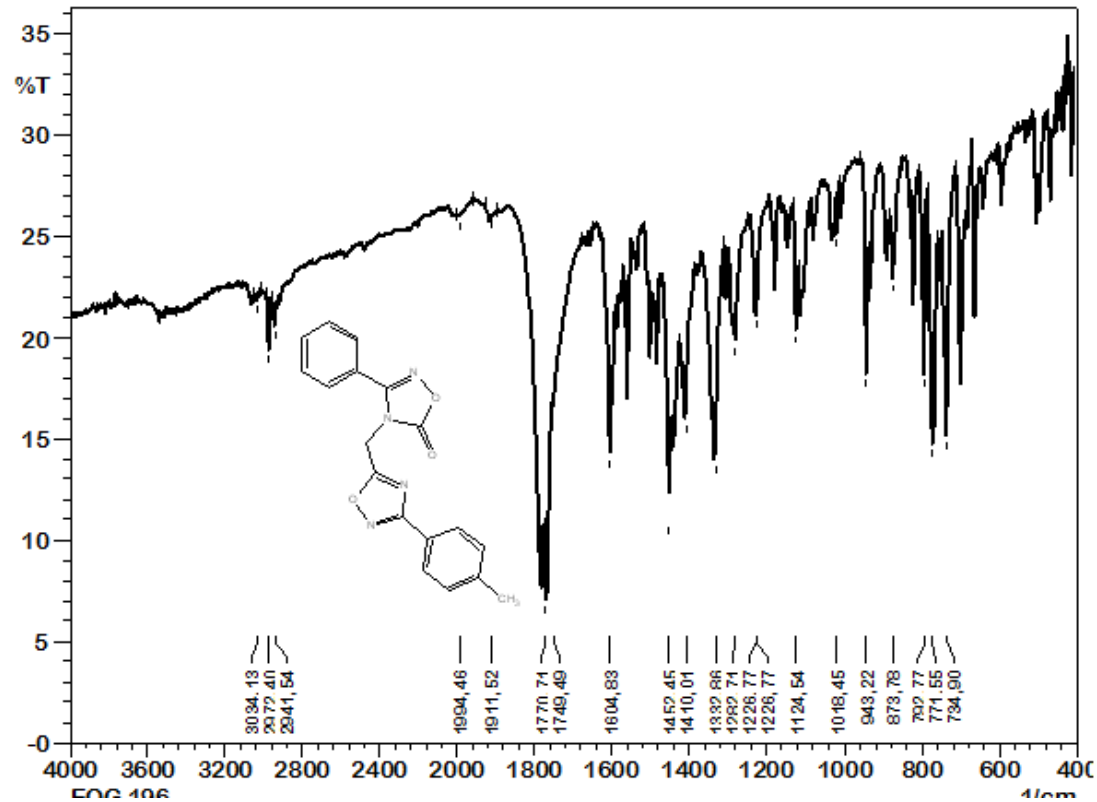

Figure 4.34. IR spectrum of compound **61e**

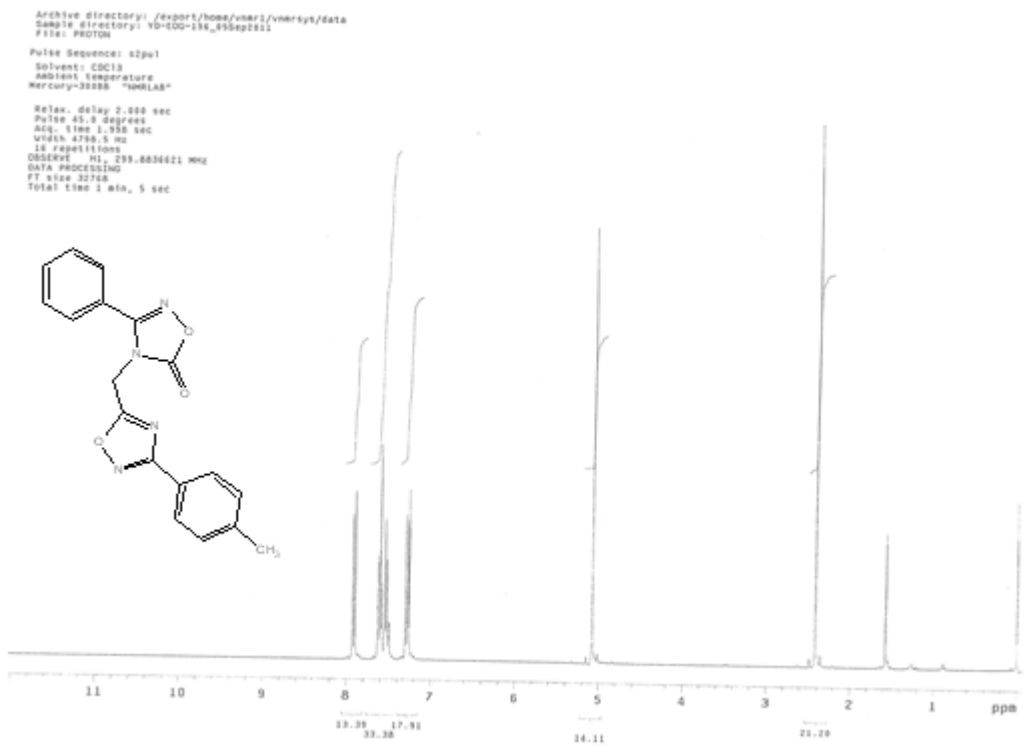

Figure 4.35. ^{1}H NMR spectrum of compound **61e**

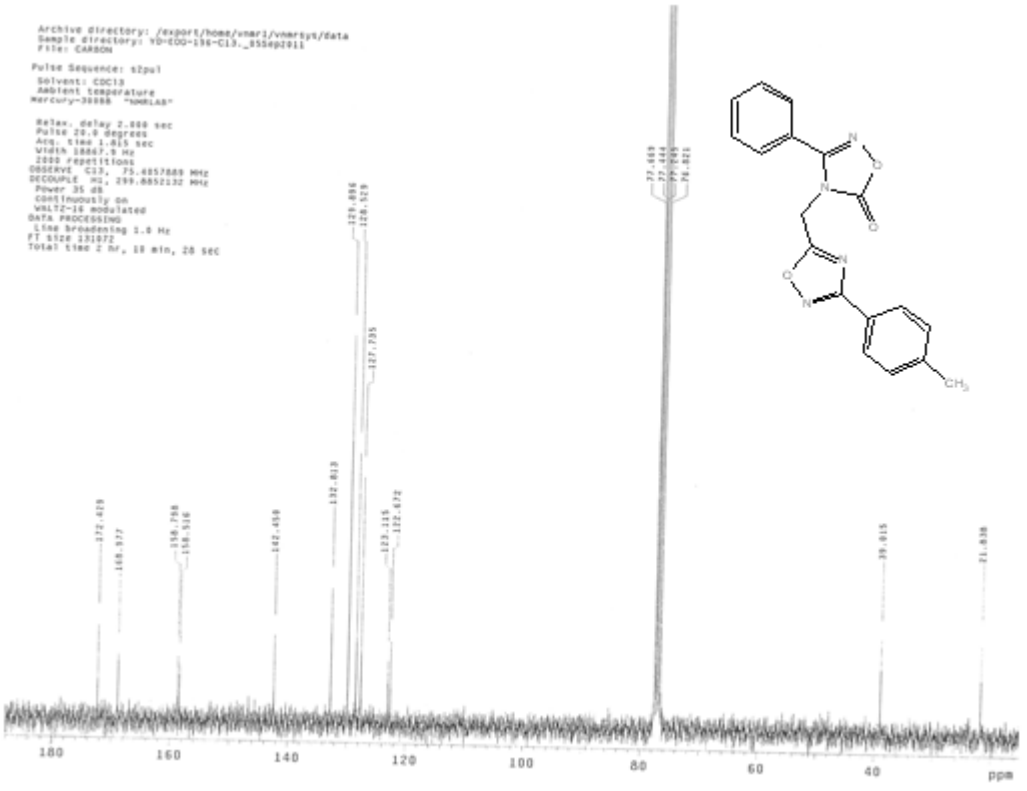

Figure 4.36. ^{13}C NMR spectrum of compound **61e**

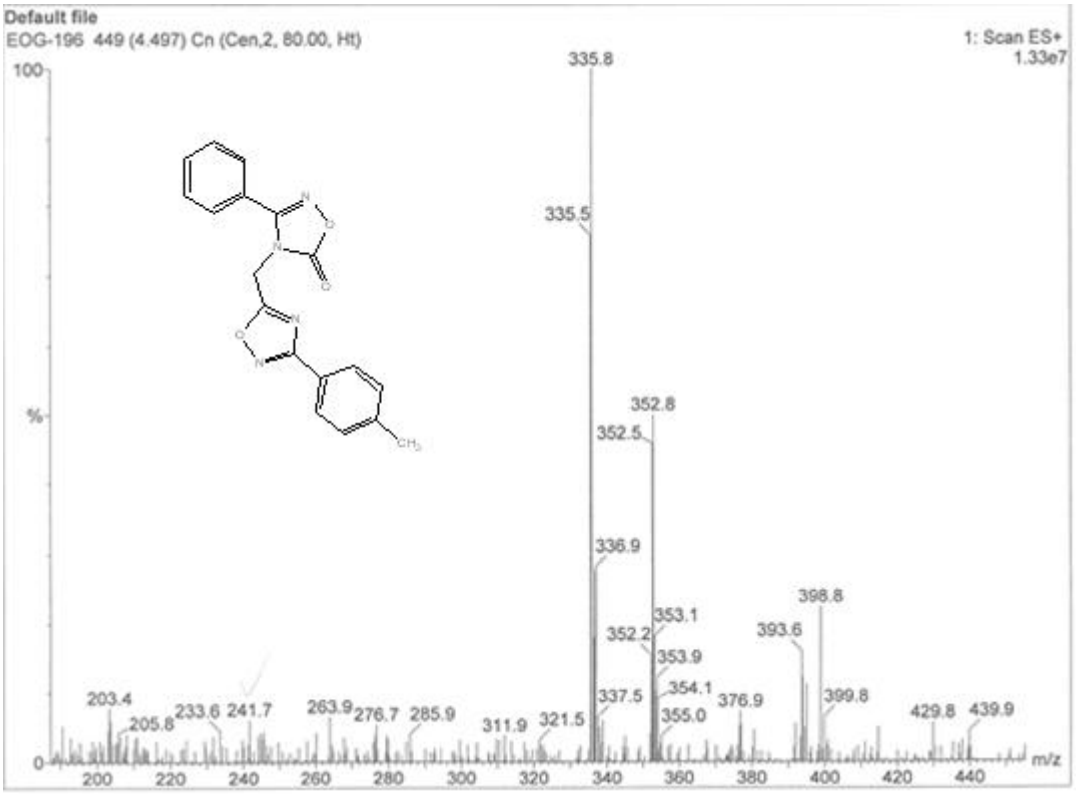

Figure 4.37. LC-MS spectrum of compound **61e**

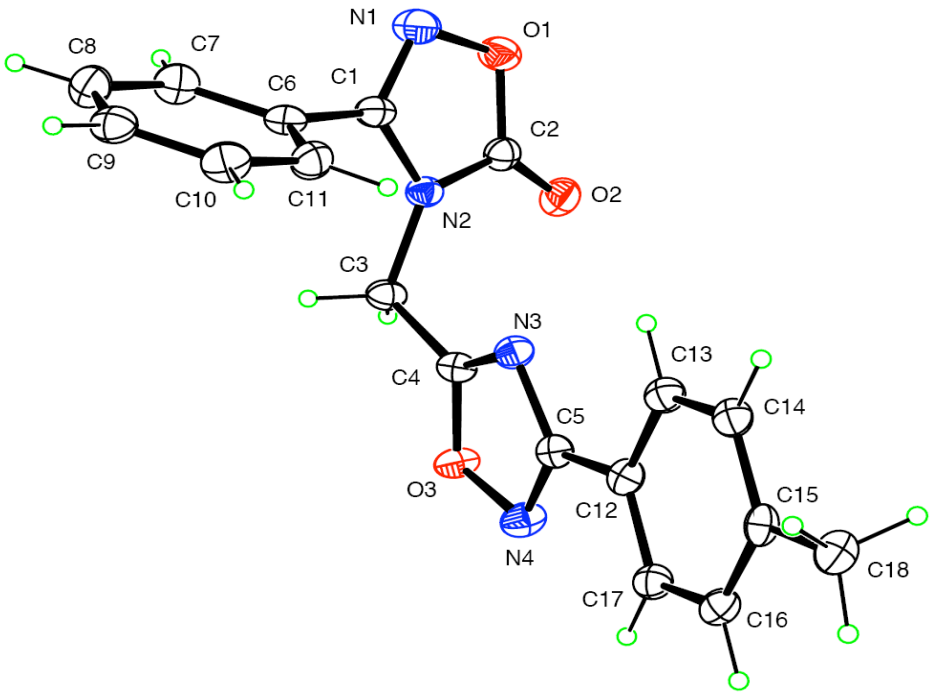

Figure 4.38. X-Ray diffraction spectrum of compound **61e**

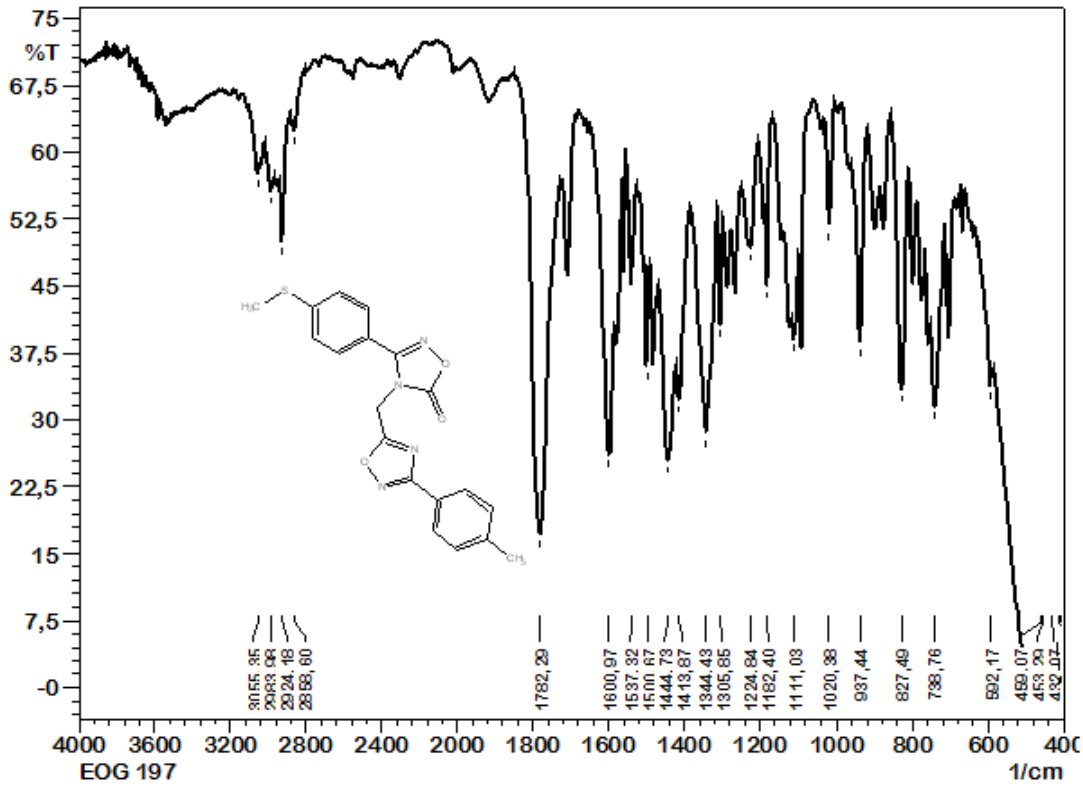

Figure 4.39. IR spectrum of compound **61f**

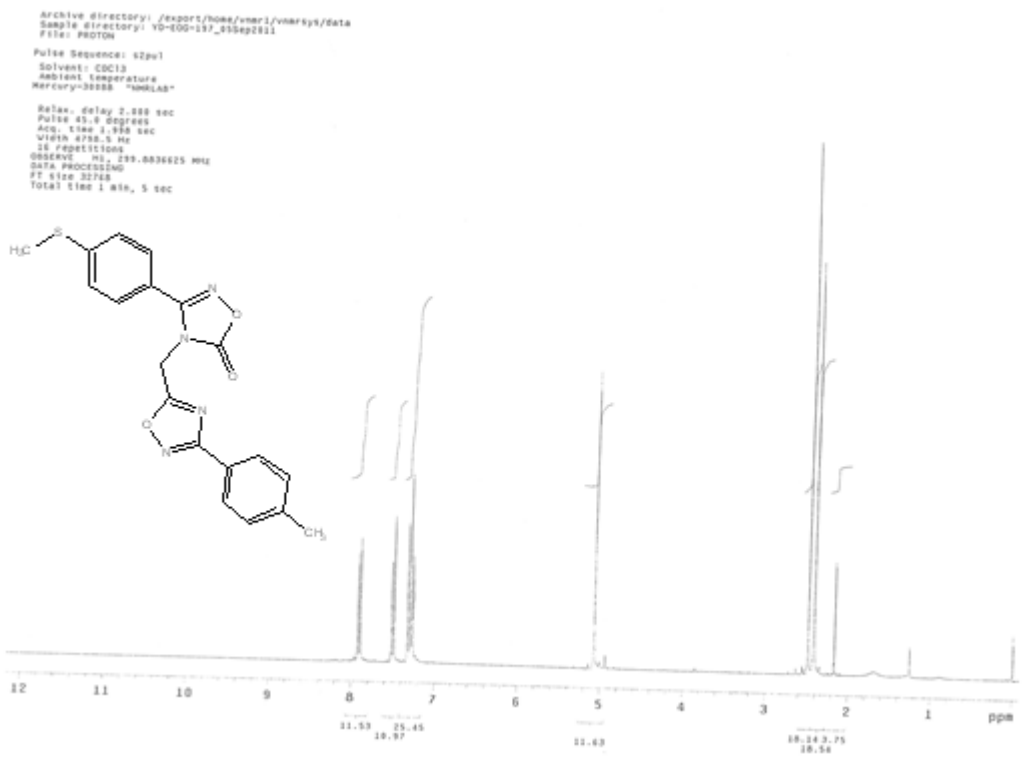

Figure 4.40. ^{1}H NMR spectrum of compound **61f**

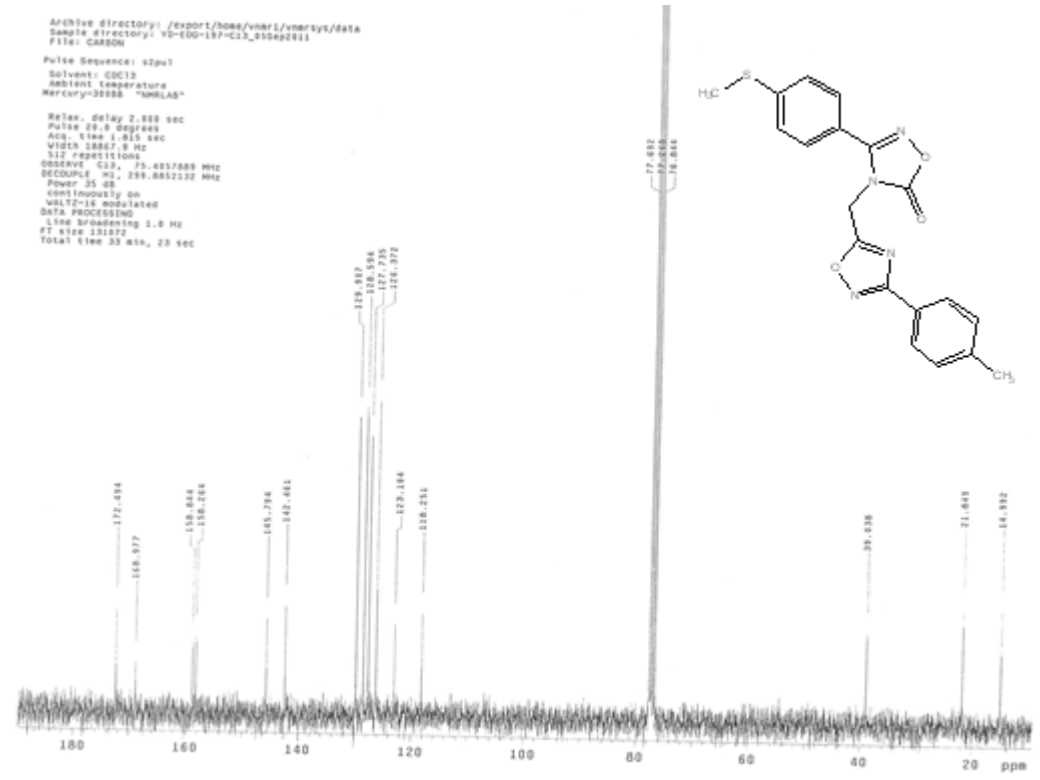

Figure 4.41. ^{13}C NMR spectrum of compound **61f**

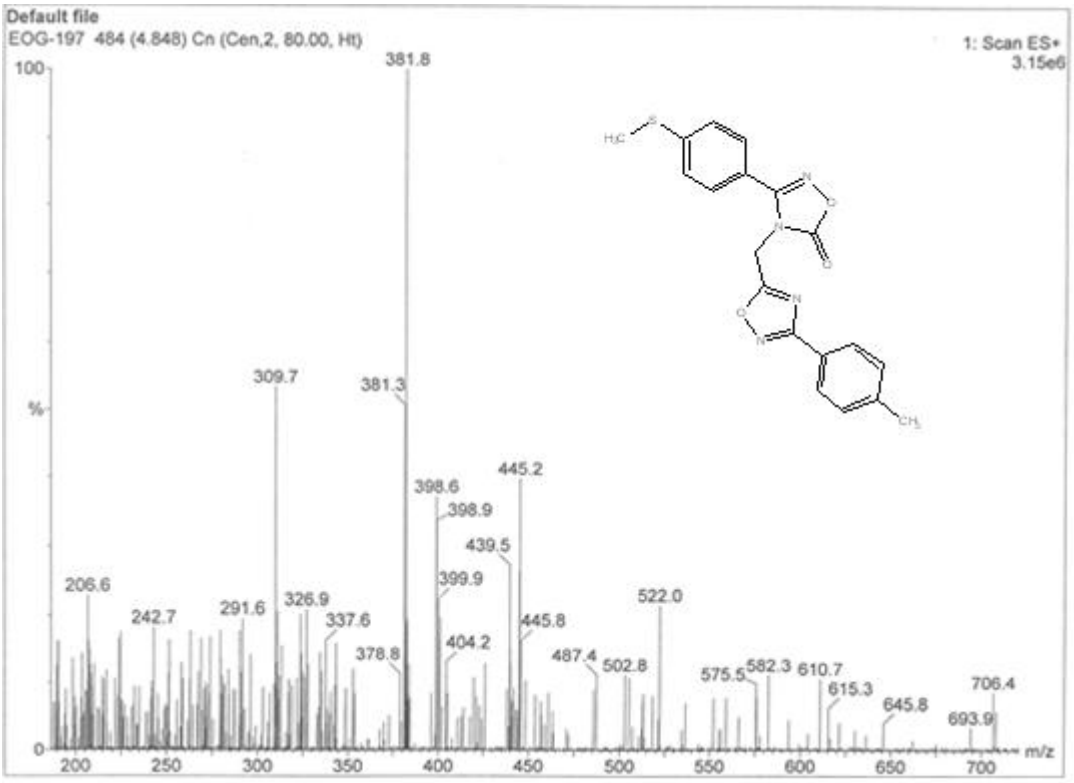

Figure 4.42. LC-MS spectrum of compound **61f**

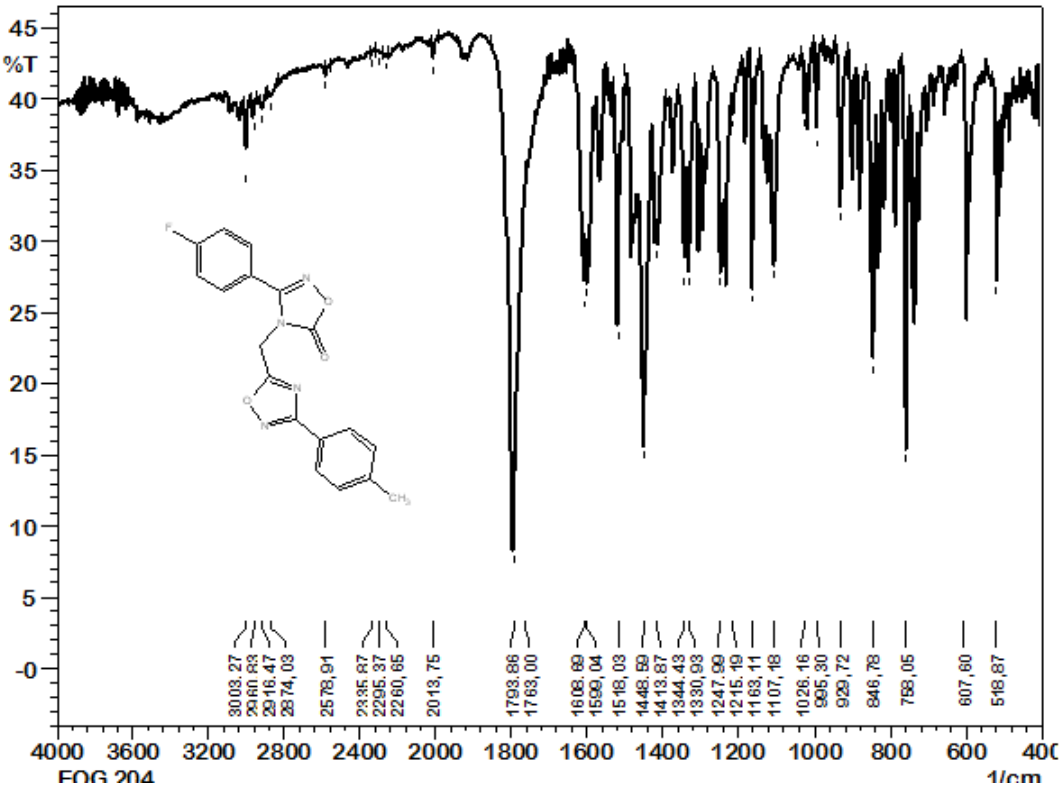

Figure 4.43. IR spectrum of compound **61g**

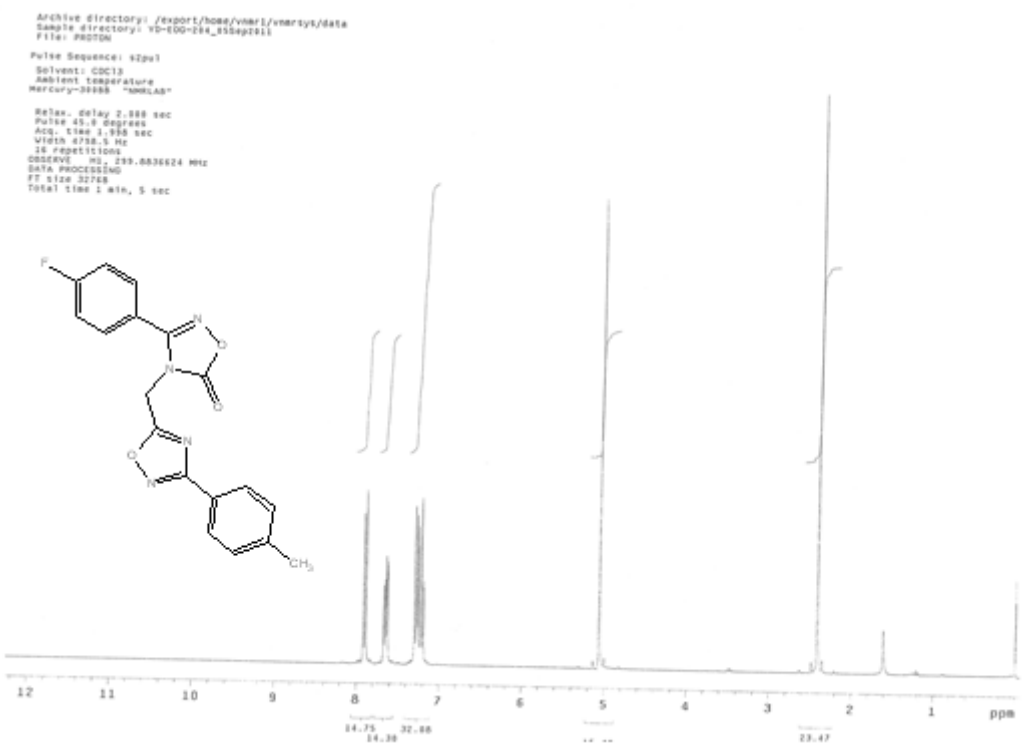

Figure 4.44. ^{1}H NMR spectrum of compound **61g**

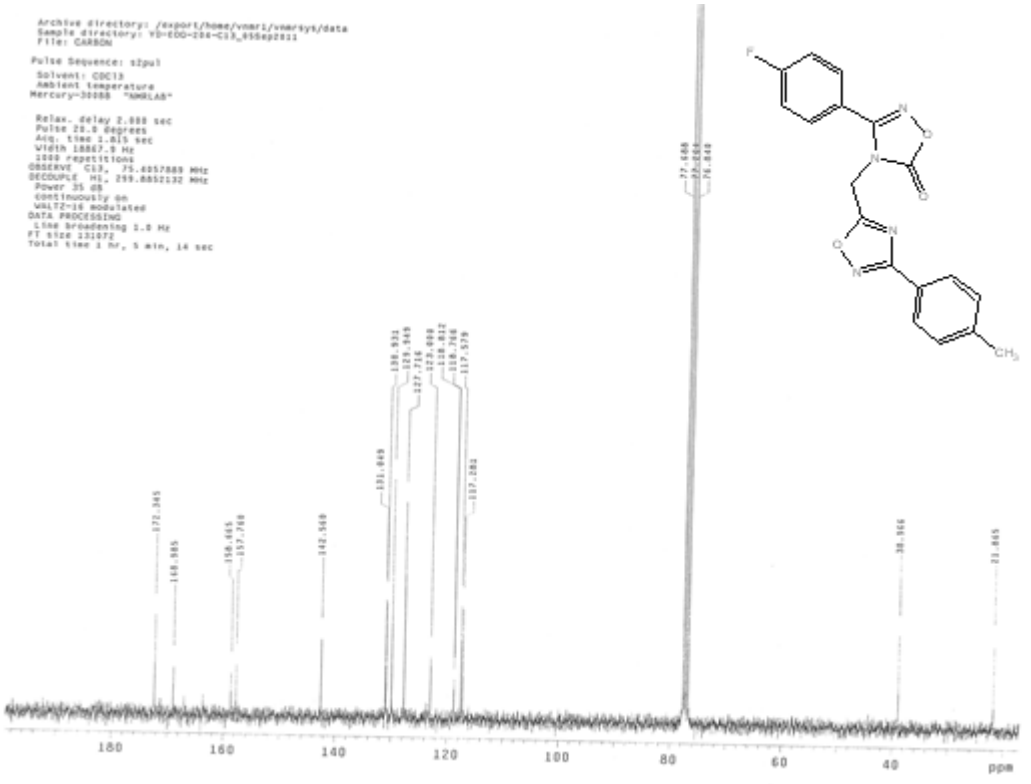

Figure 4.45. ^{13}C NMR spectrum of compound **61g**

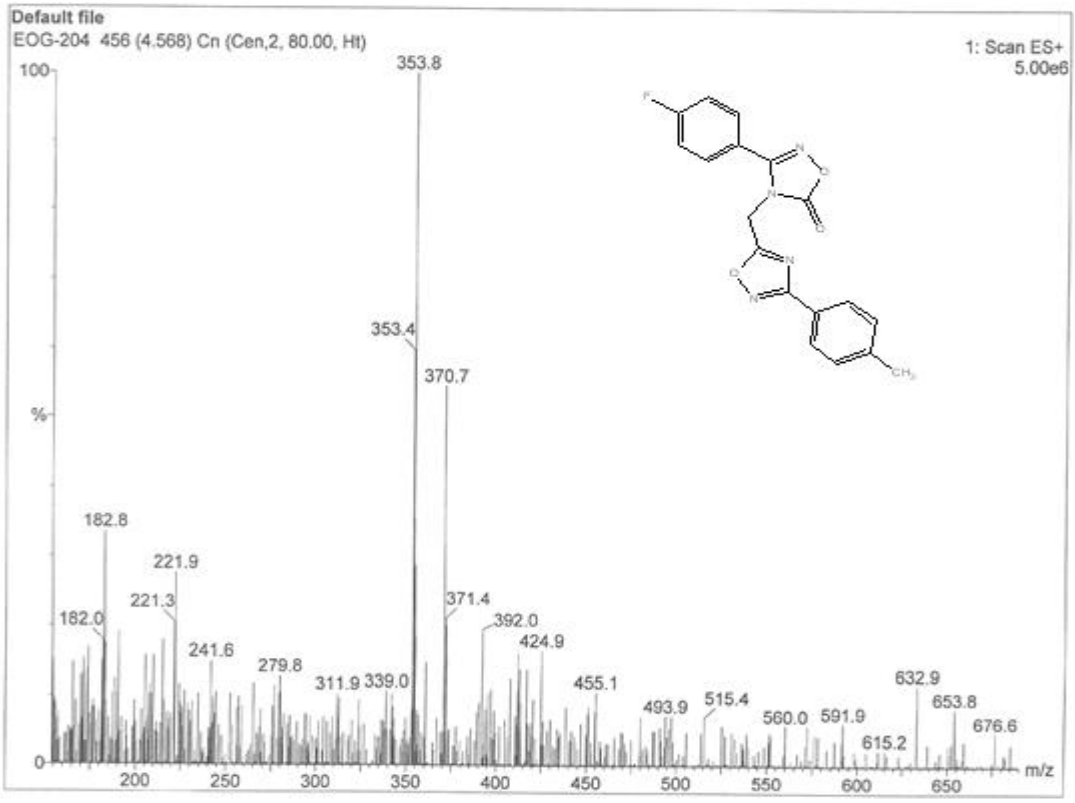

Figure 4.46. LC-MS spectrum of compound **61g**

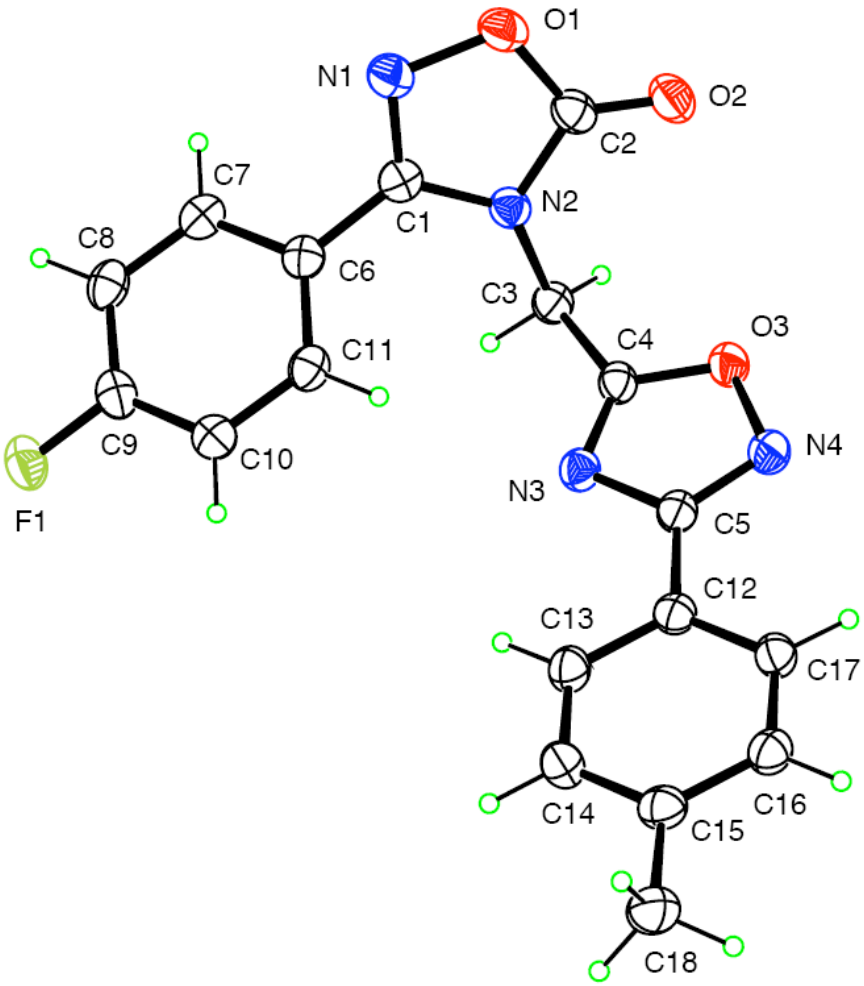

Figure 4.47. X-Ray diffraction spectrum of compound **61g**

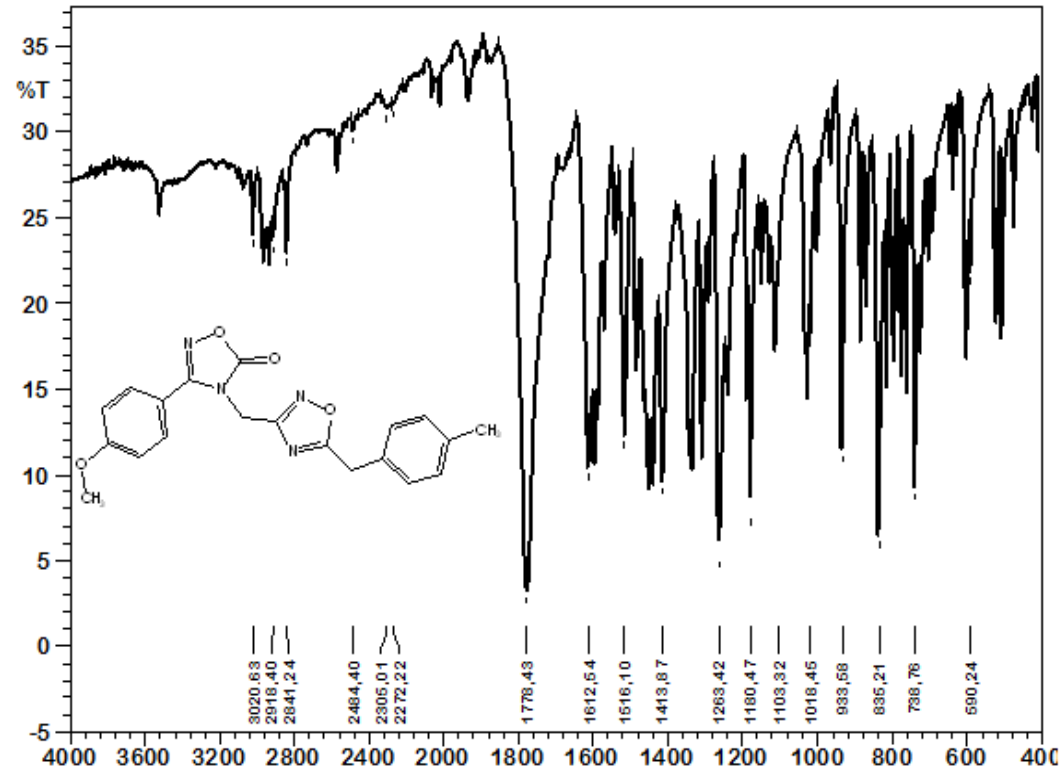

Figure 4.48. IR spectrum of compound **61h**

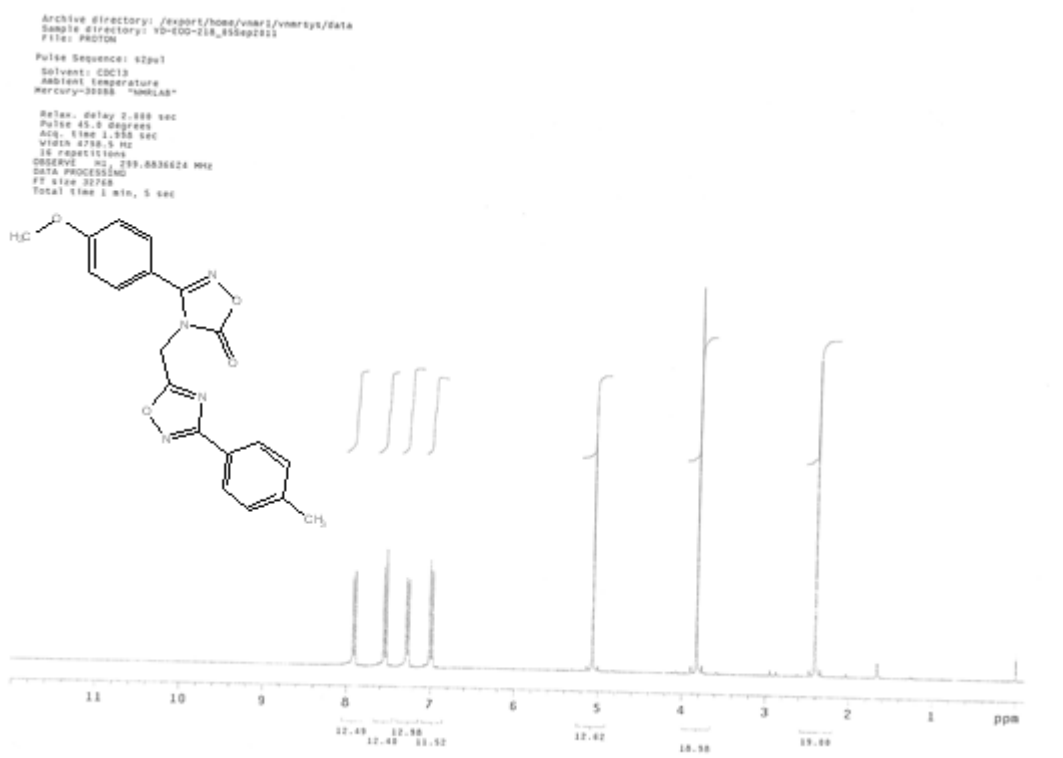

Figure 4.49. ^{1}H NMR spectrum of compound **61h**

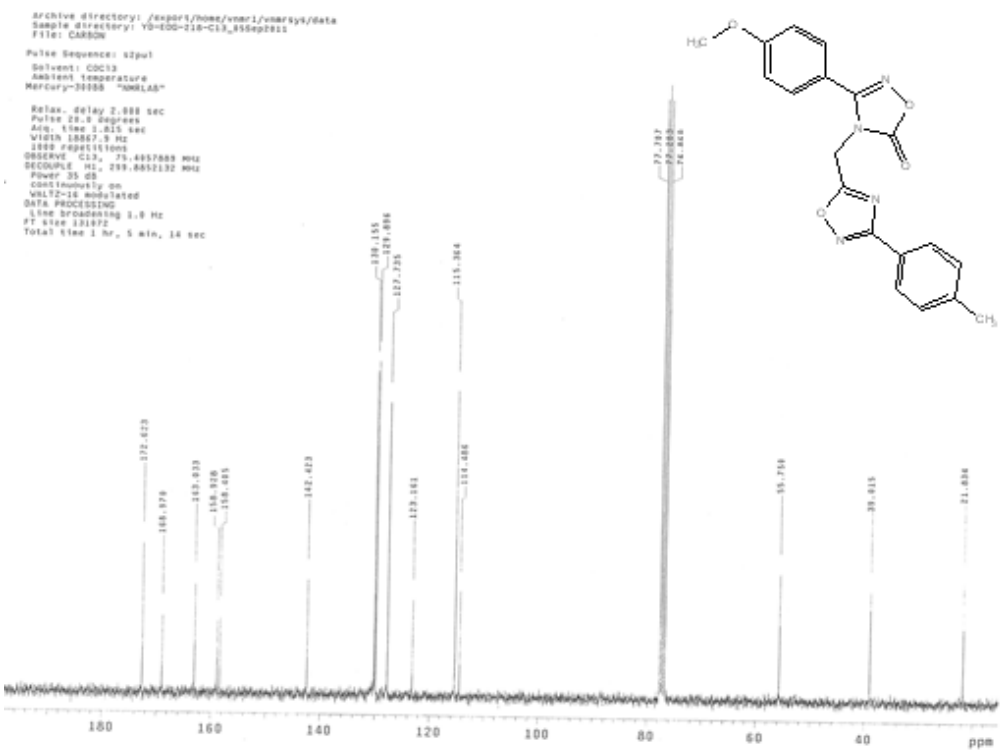

Figure 4.50. ^{13}C NMR spectrum of compound **61h**

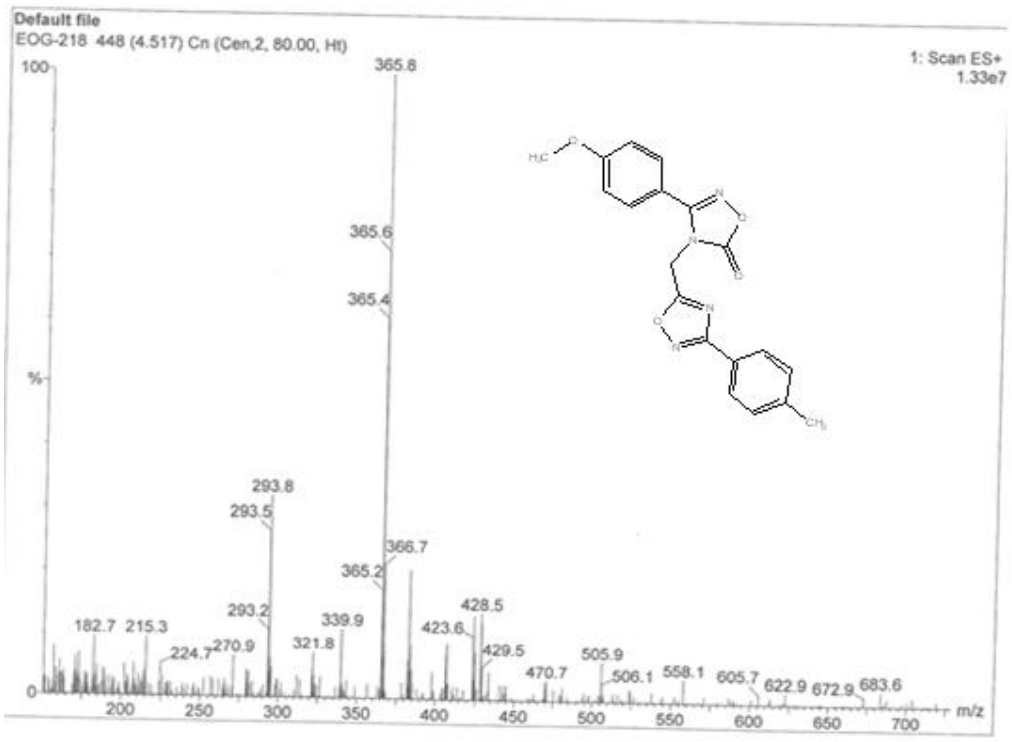

Figure 4.51. LC-MS spectrum of compound **61h**

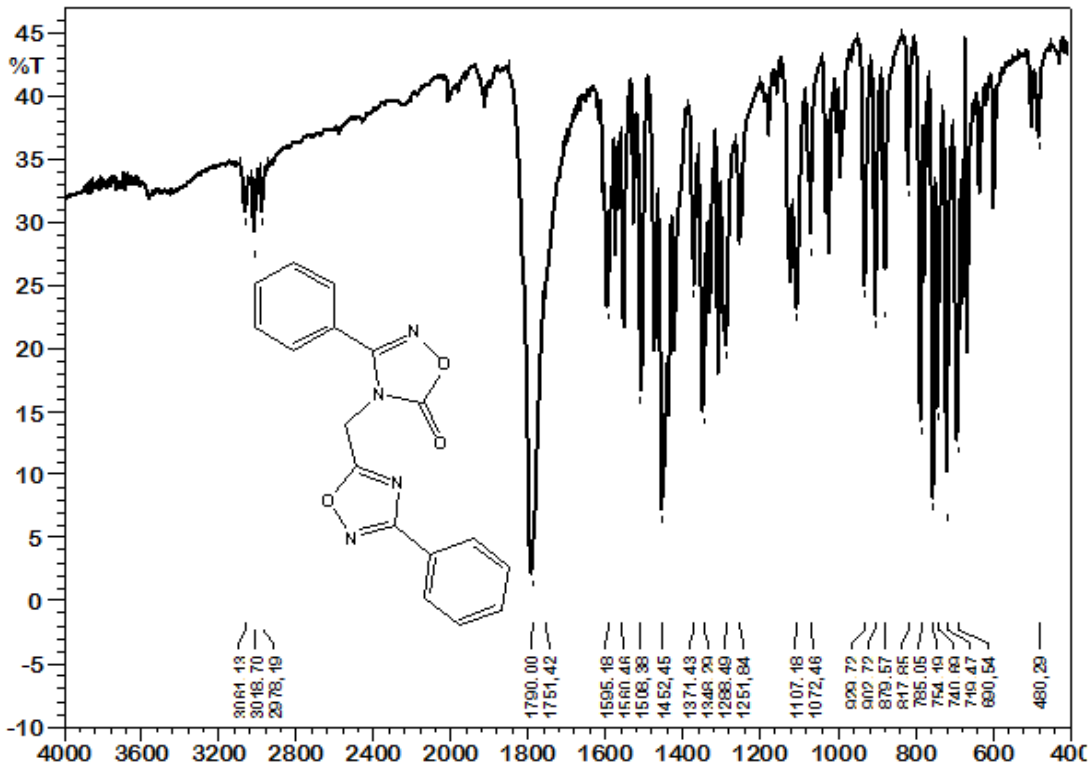

Figure 4.52. IR spectrum of compound **61i**

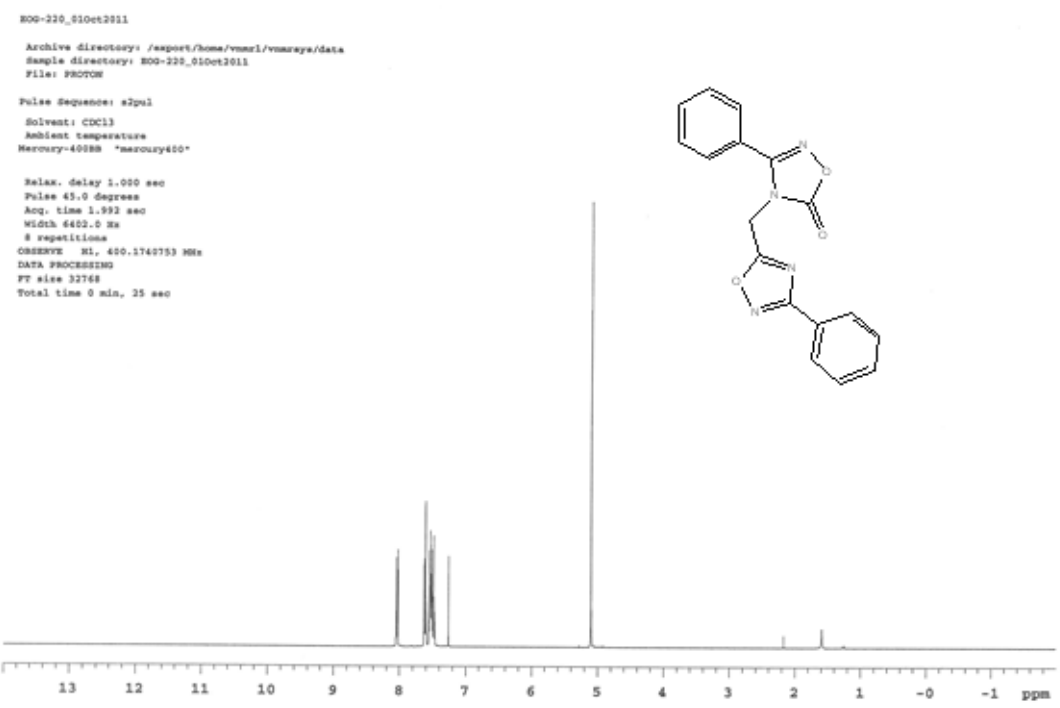

Figure 4.53. ^{1}H NMR spectrum of compound **61i**

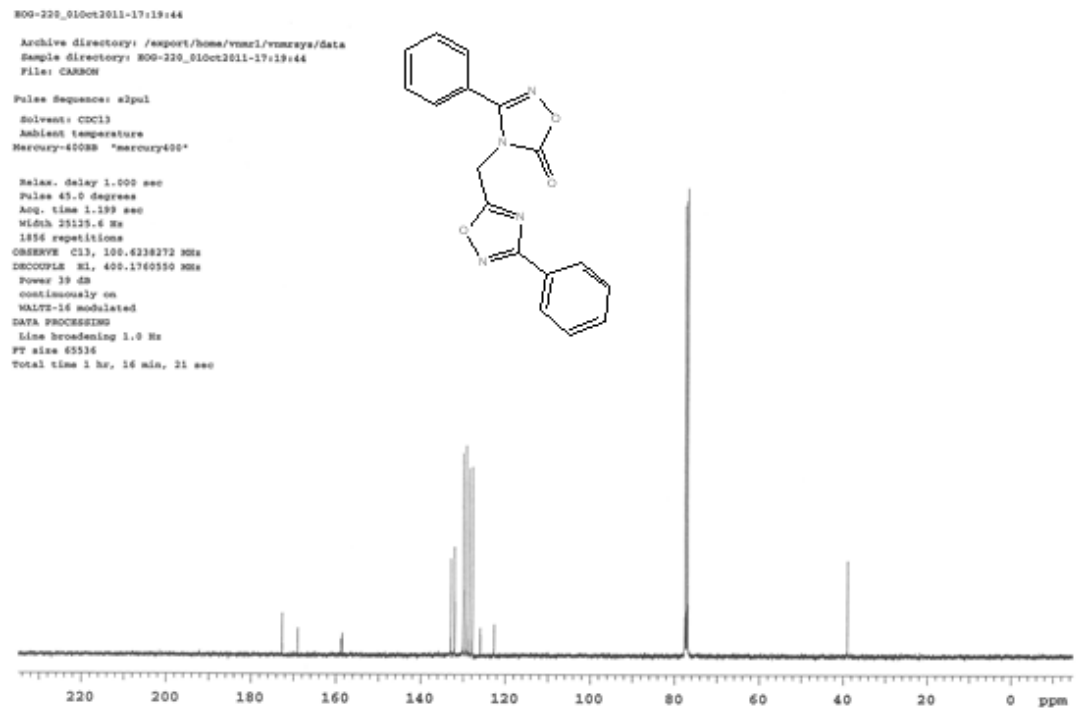

Figure 4.54. ^{13}C NMR spectrum of compound **61i**

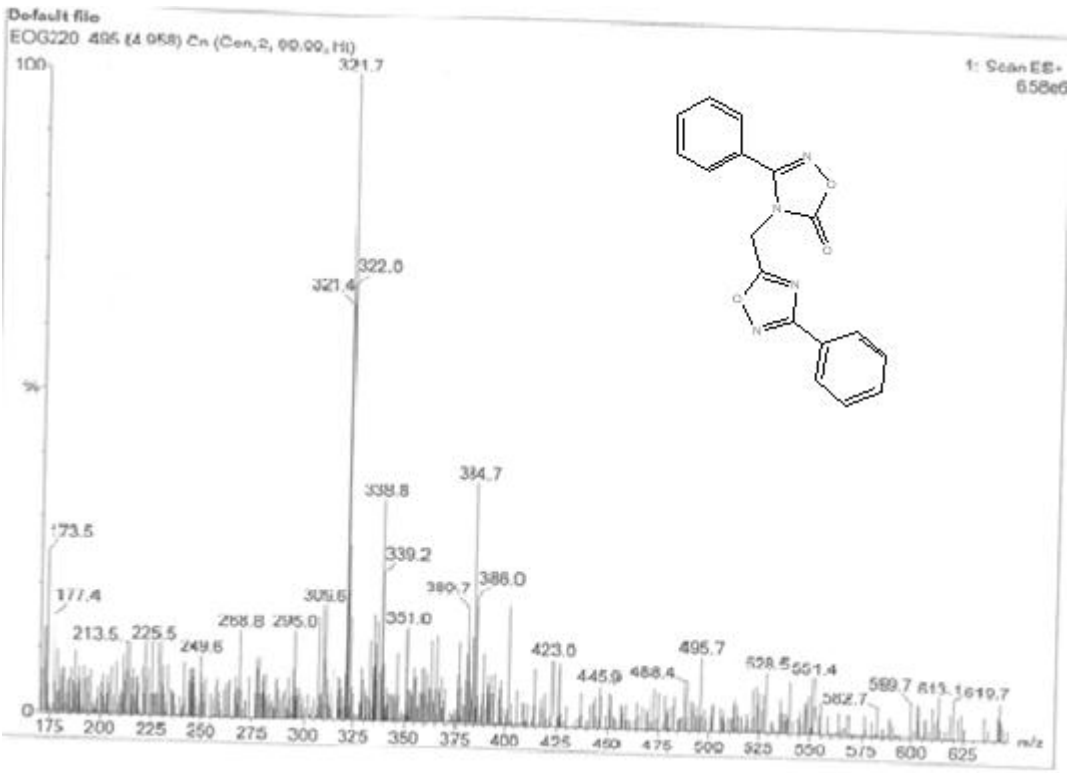

Figure 4.55. LC-MS spectrum of compound **61i**

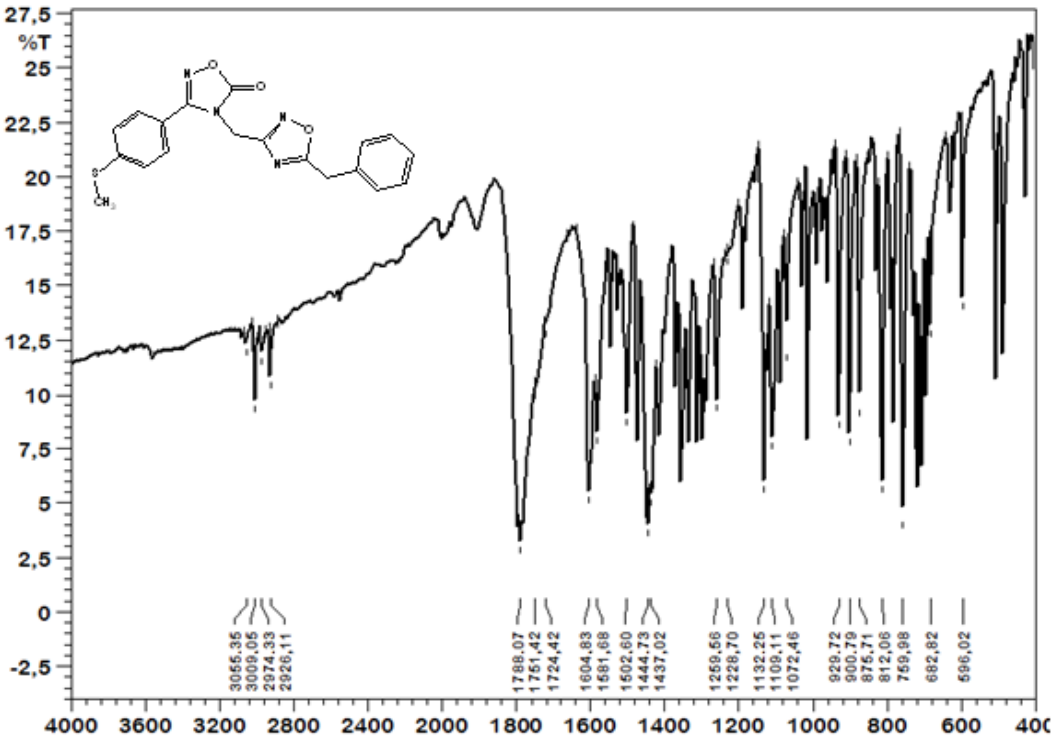

Figure 4.56. IR spectrum of compound **61j**

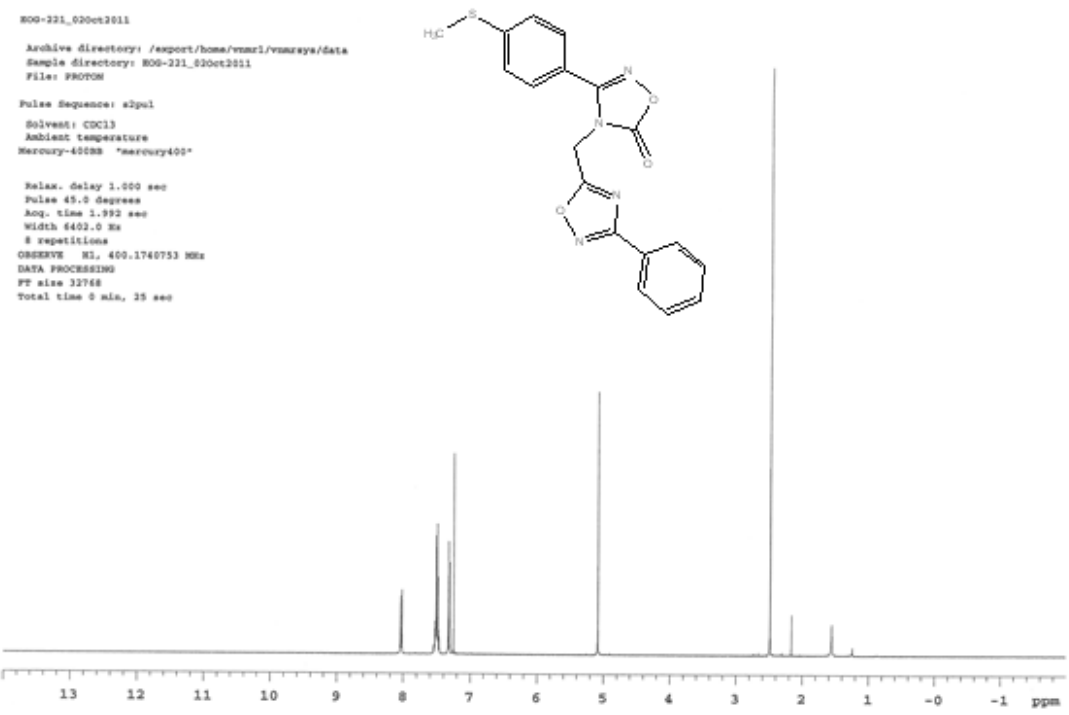

Figure 4.57. ^{1}H NMR spectrum of compound **61j**

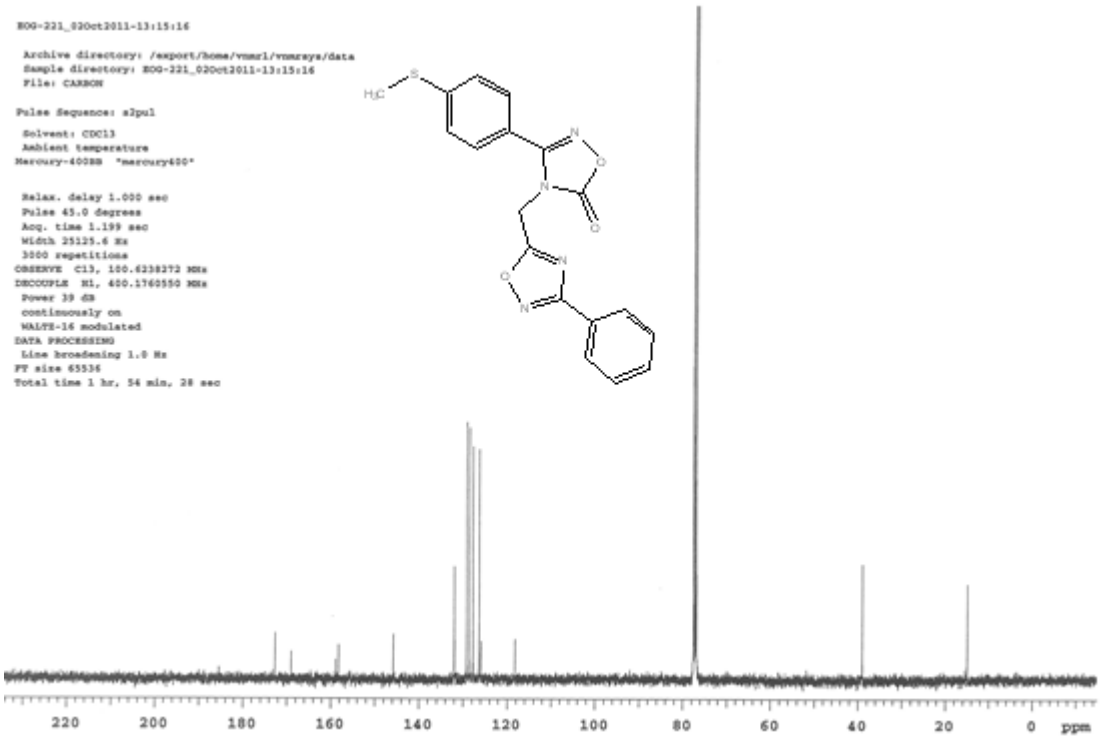

Figure 4.58. ^{13}C NMR spectrum of compound **61j**

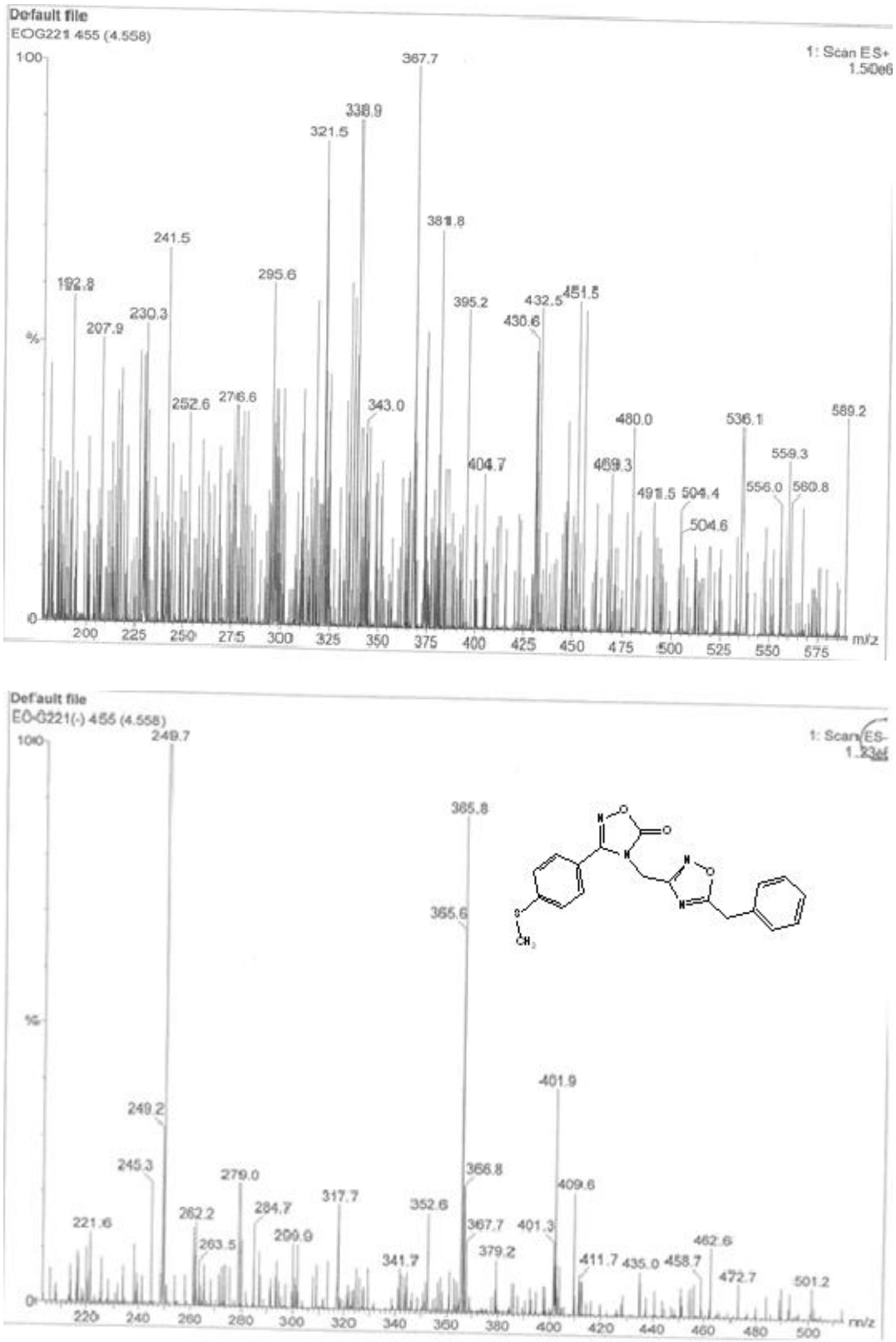

Figure 4.59. LC-MS spectrum of compound **61j**

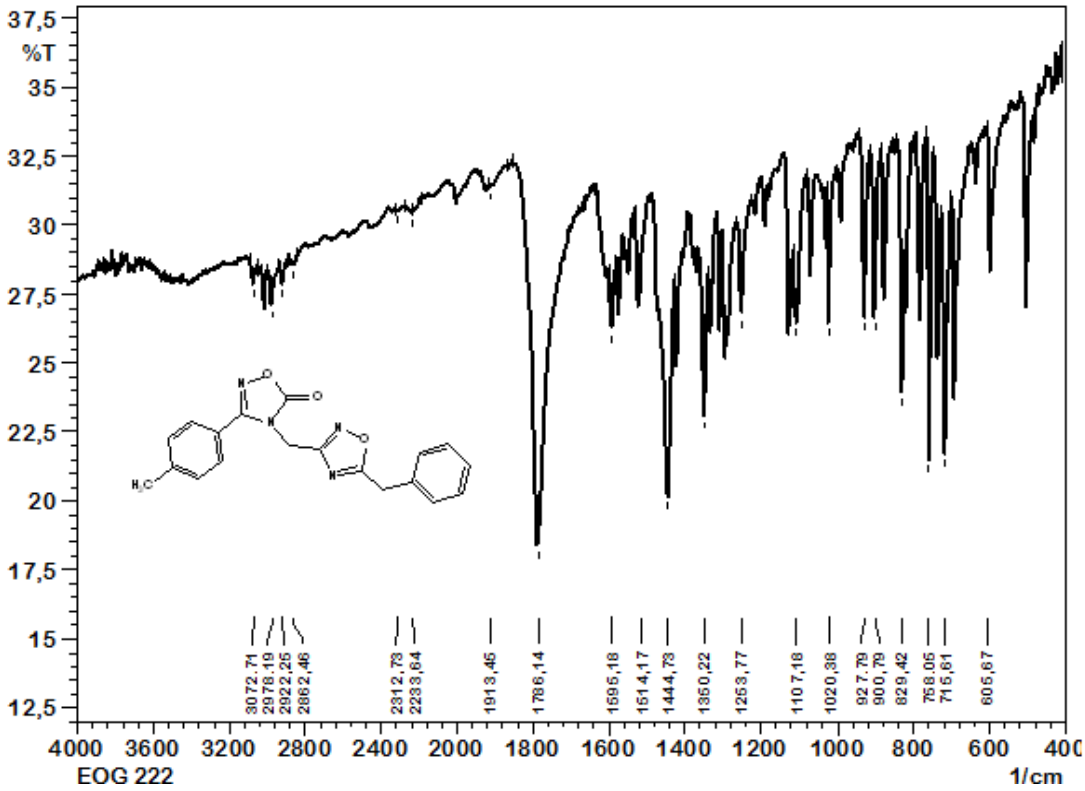

Figure 4.60. IR spectrum of compound **61k**

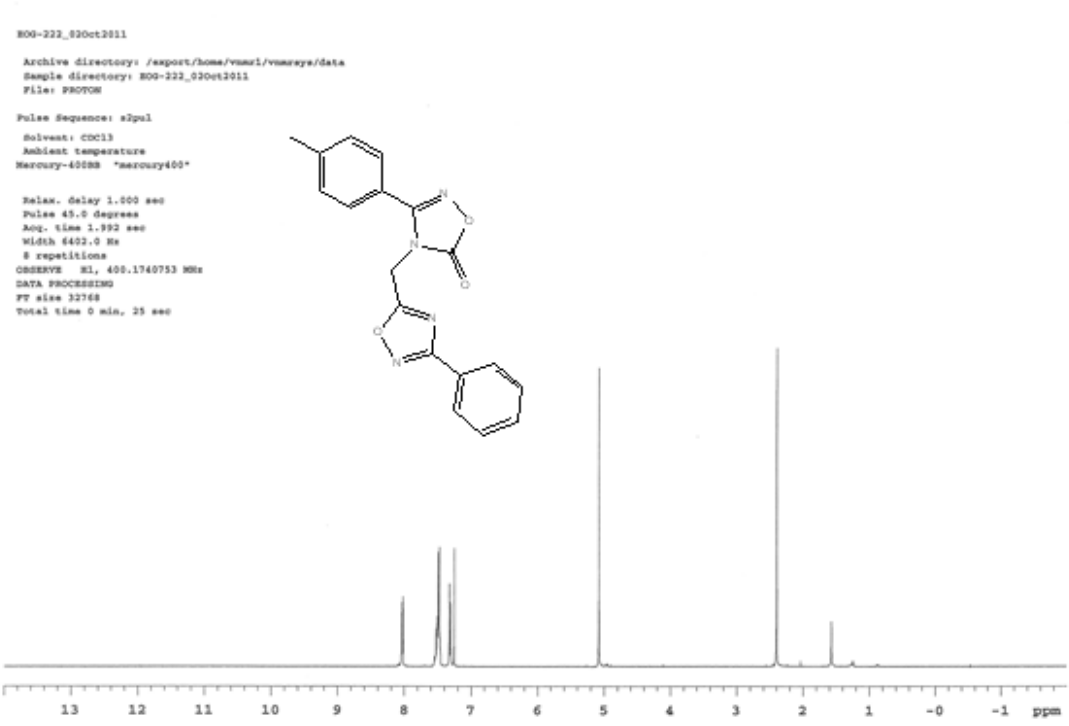

Figure 4.61. ^{1}H NMR spectrum of compound **61k**

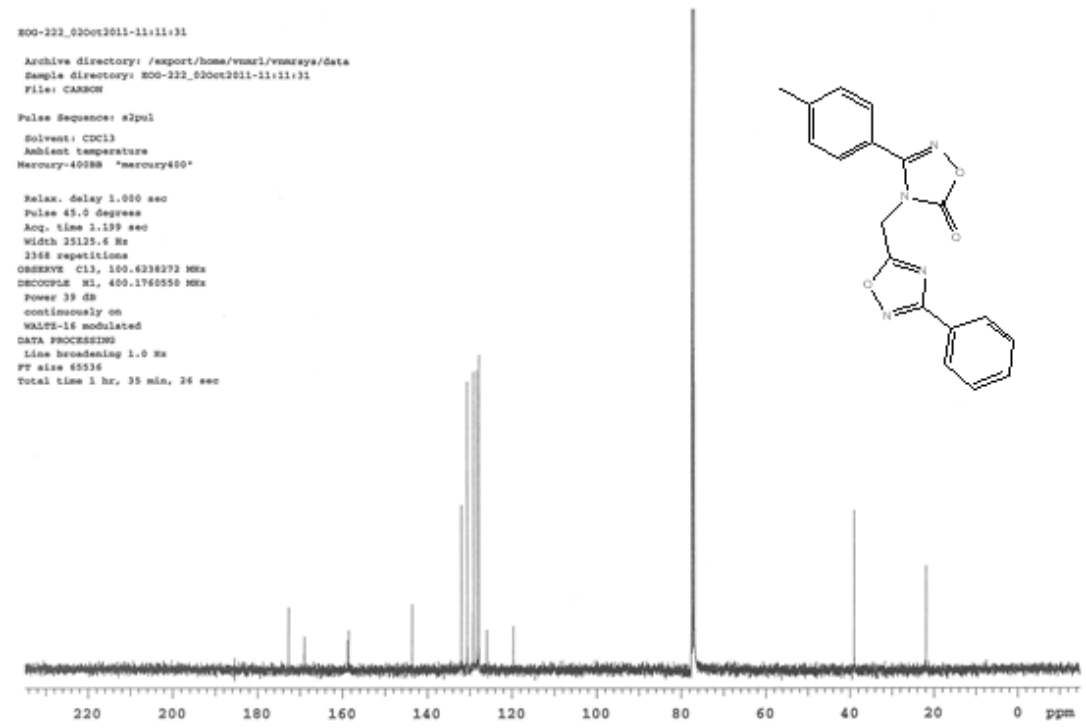

Figure 4.62. ^{13}C NMR spectrum of compound **61k**

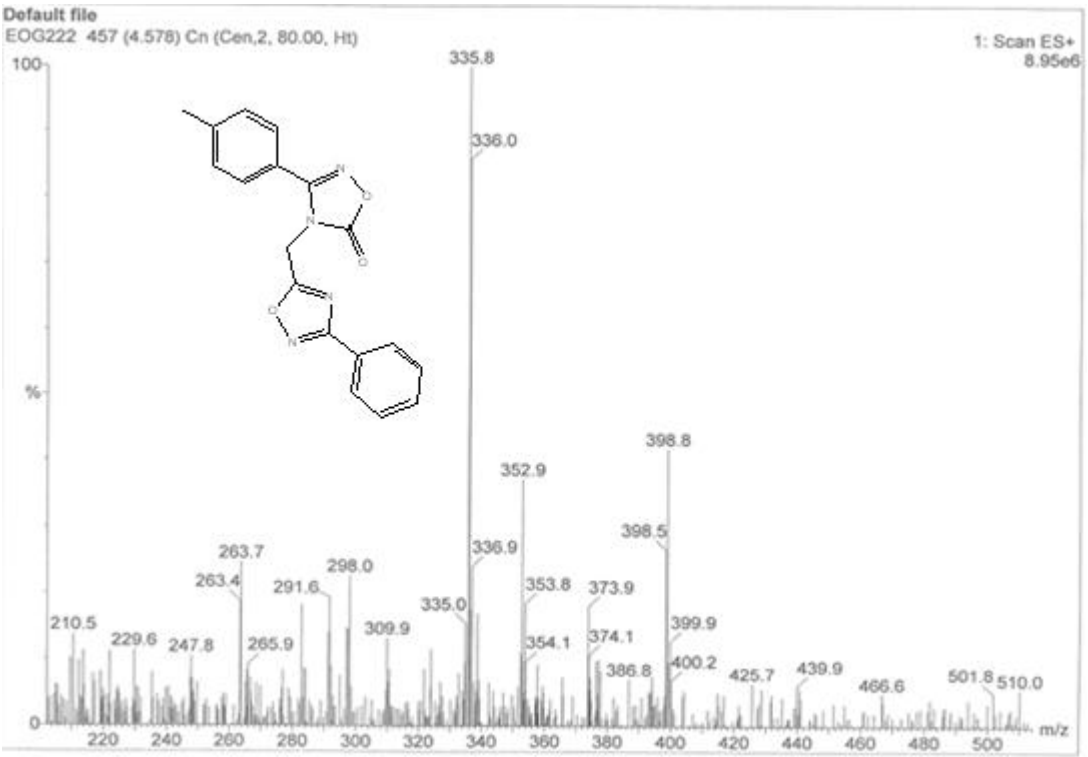

Figure 4.63. LC-MS spectrum of compound **61k**

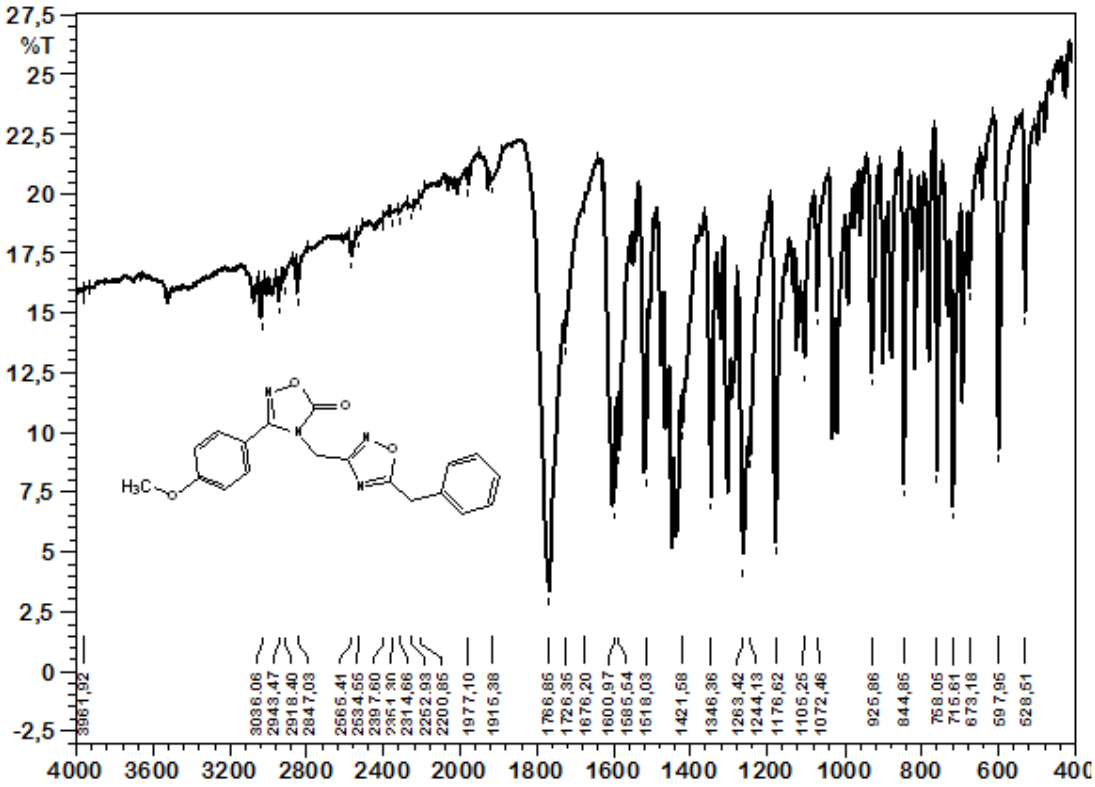

Figure 4.64. IR spectrum of compound **61l**

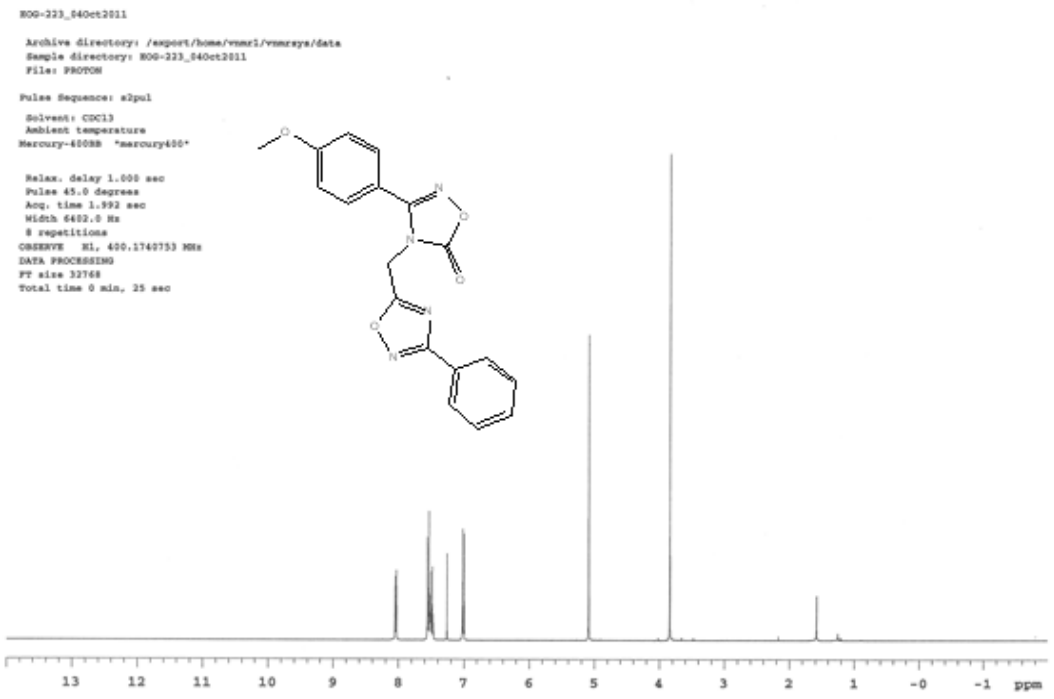

Figure 4.65. ^{1}H NMR spectrum of compound **61l**

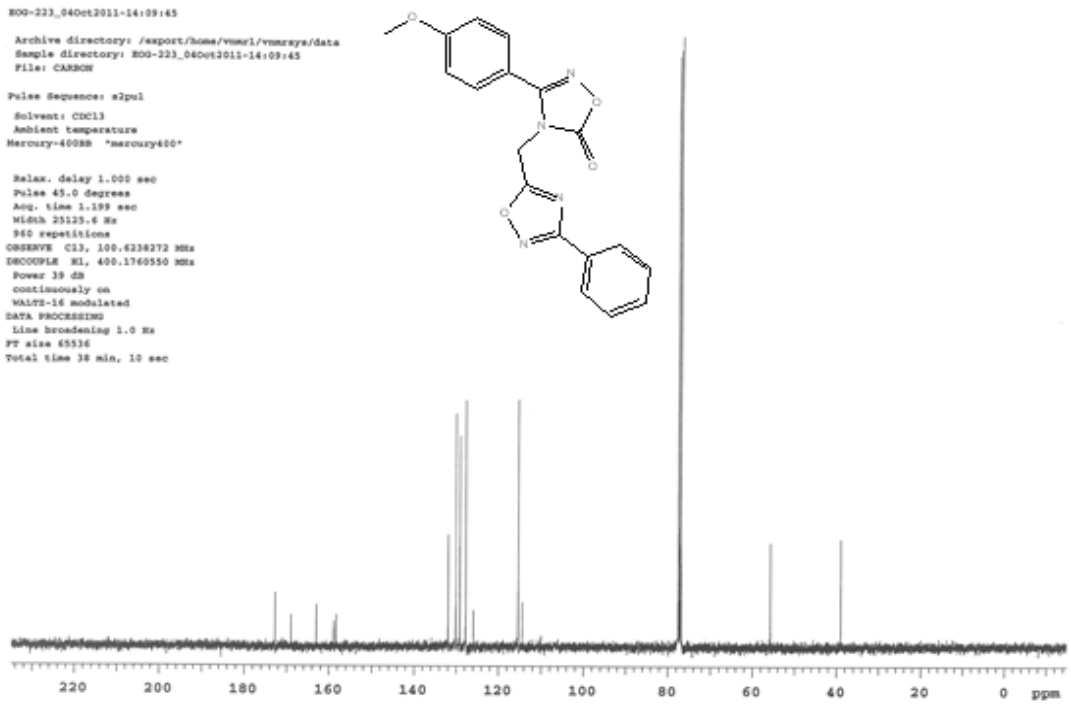

Figure 4.66. ^{13}C NMR spectrum of compound **61l**

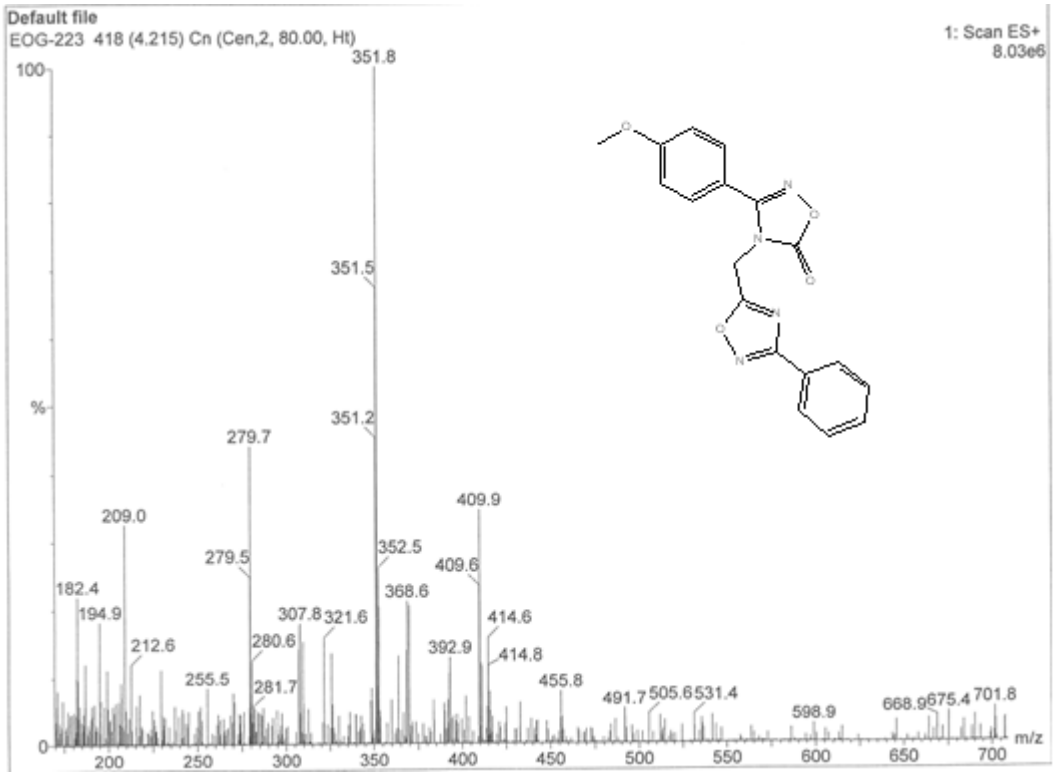

Figure 4.67. LC-MS spectrum of compound **61l**

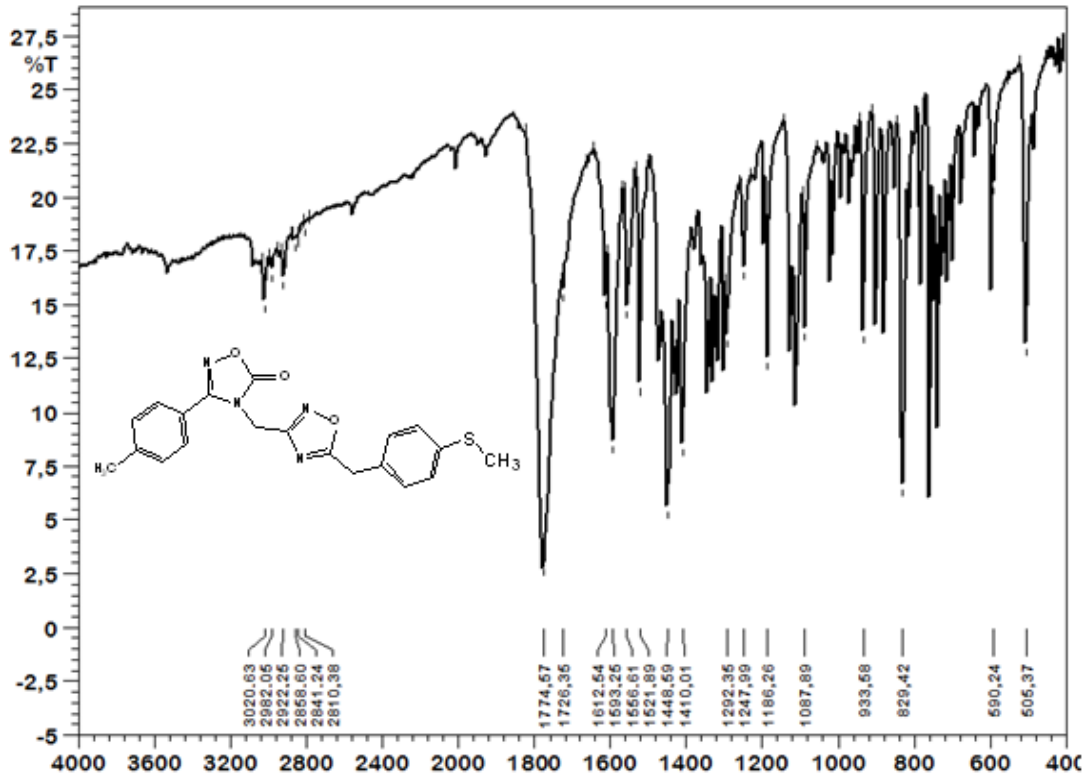

Figure 4.68. IR spectrum of compound **61m**

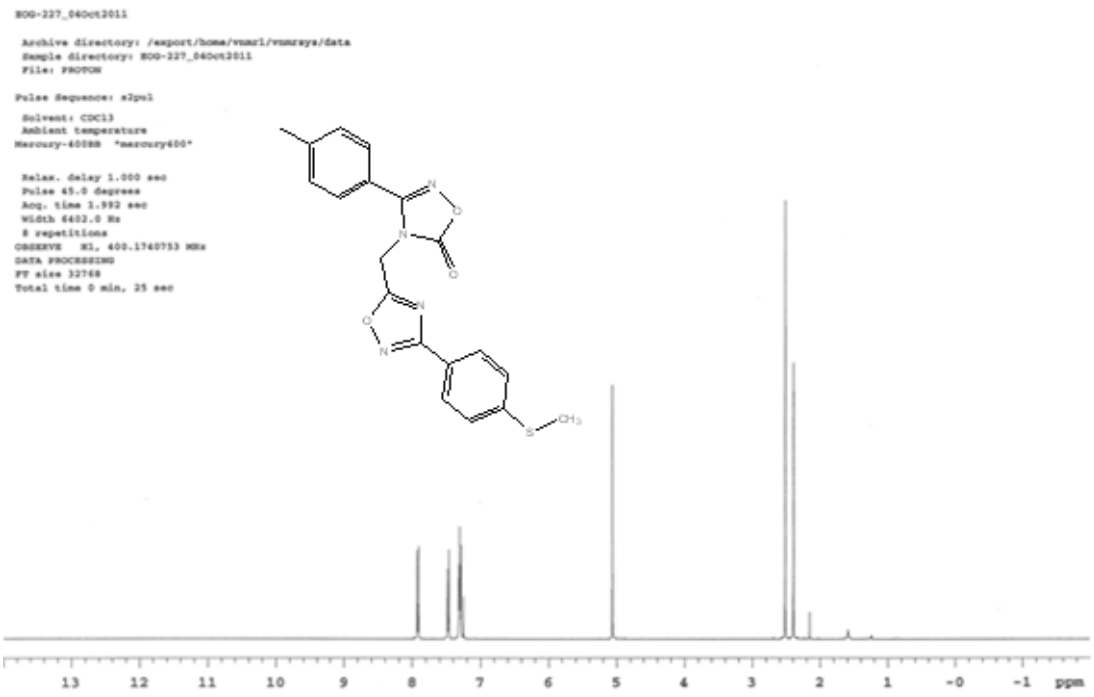

Figure 4.69. ^{1}H NMR spectrum of compound **61m**

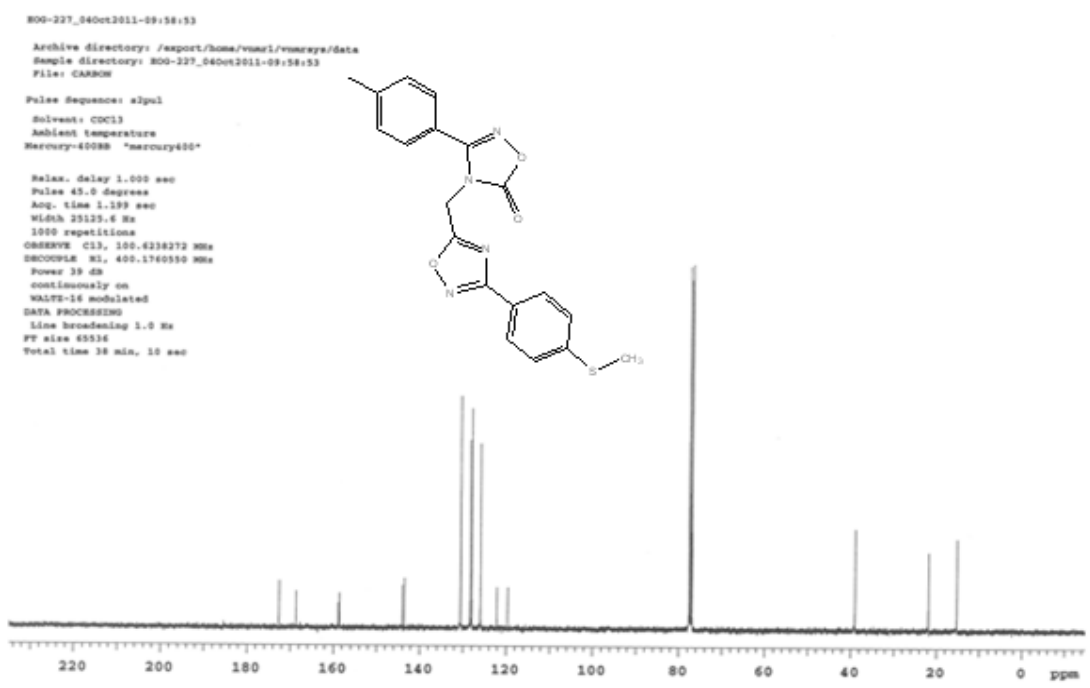

Figure 4.70. ^{13}C NMR spectrum of compound **61m**

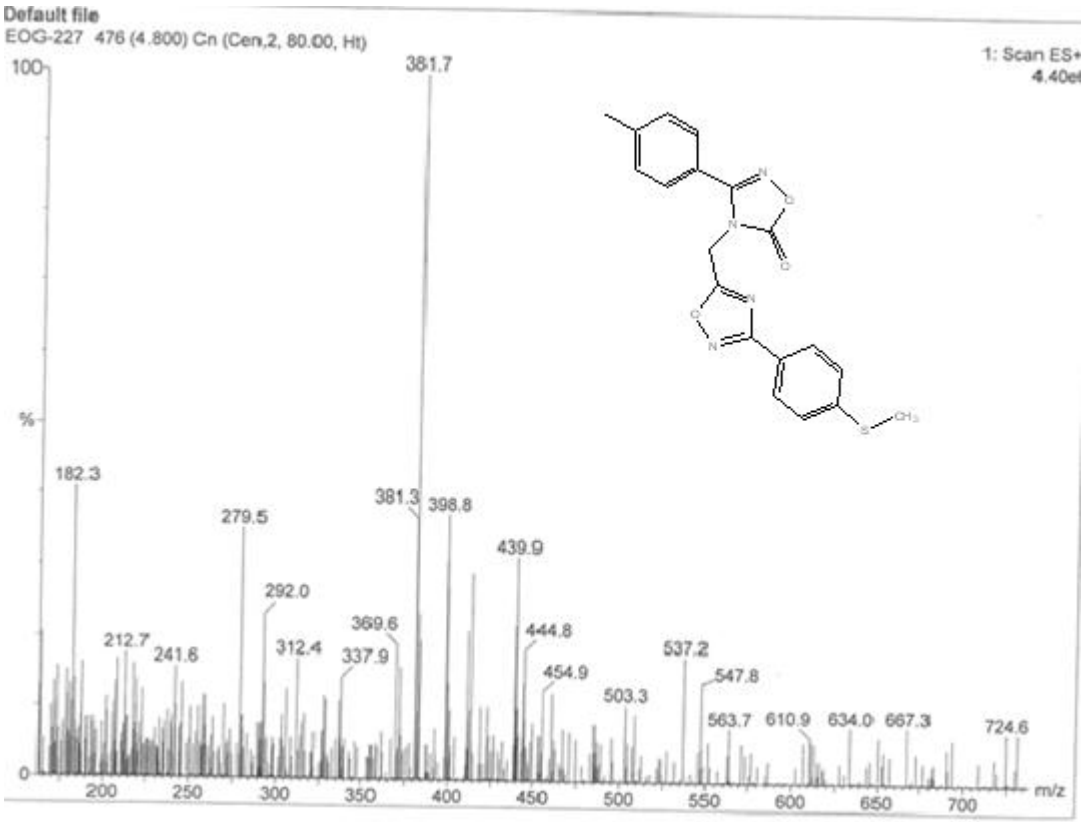

Figure 4.71. LC-MS spectrum of compound **61m**

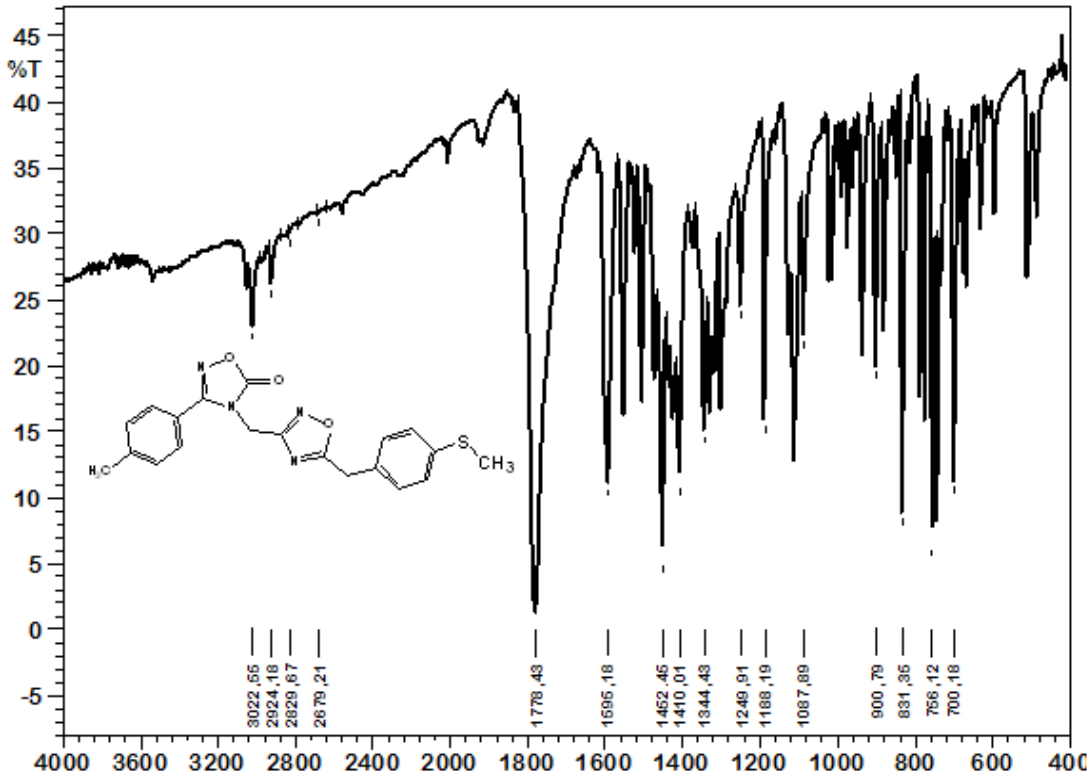

Figure 4.72. IR spectrum of compound **61n**

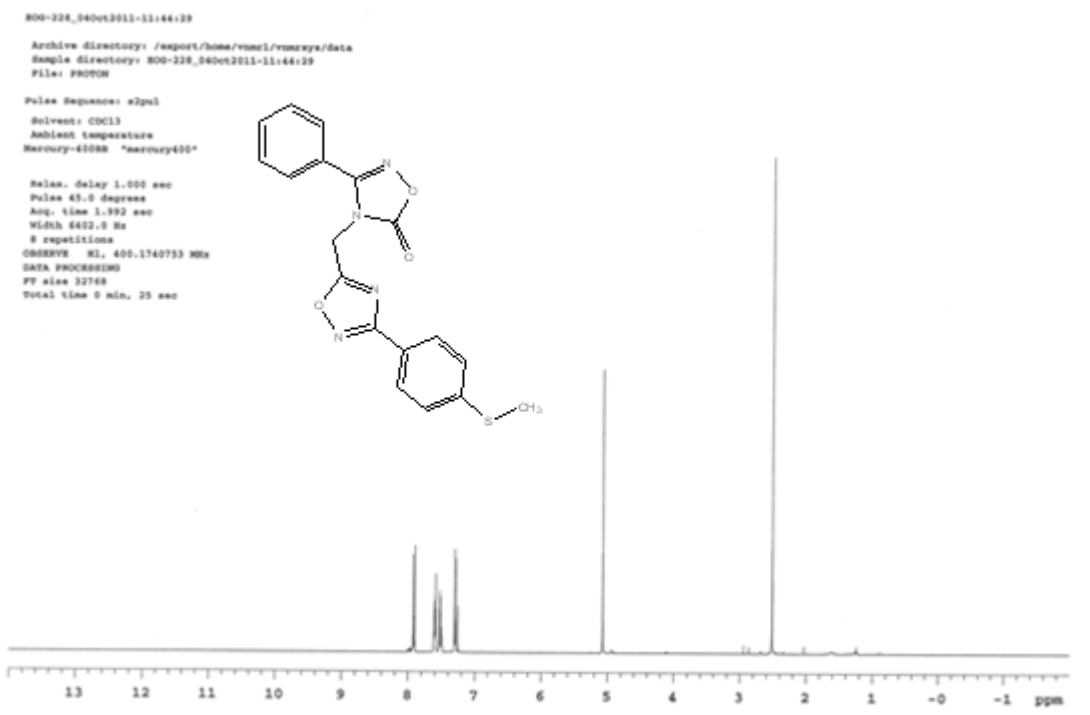

Figure 4.73. ^{1}H NMR spectrum of compound **61n**

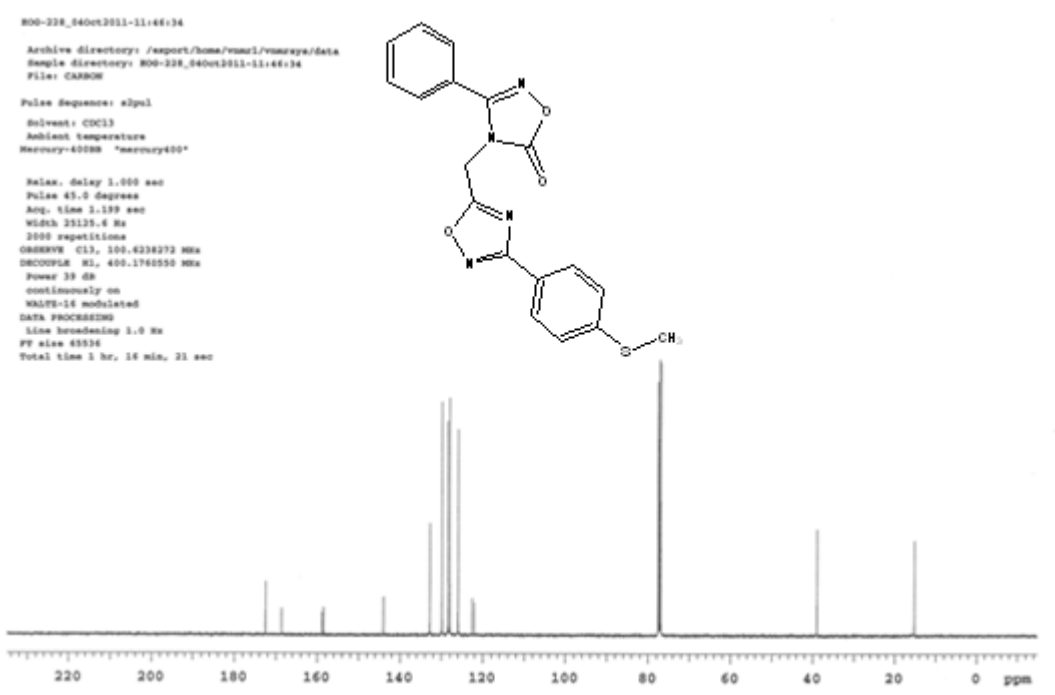

Figure 4.74. ^{13}C NMR spectrum of compound **61n**

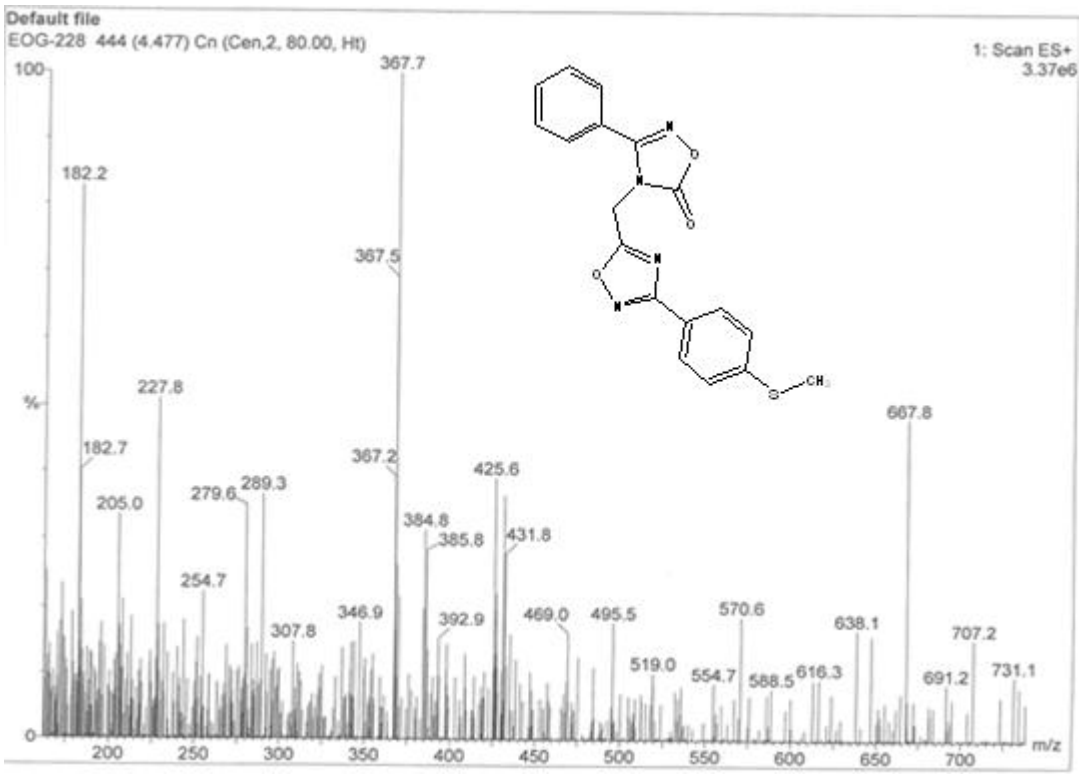

Figure 4.75. LC-MS spectrum of compound **61n**

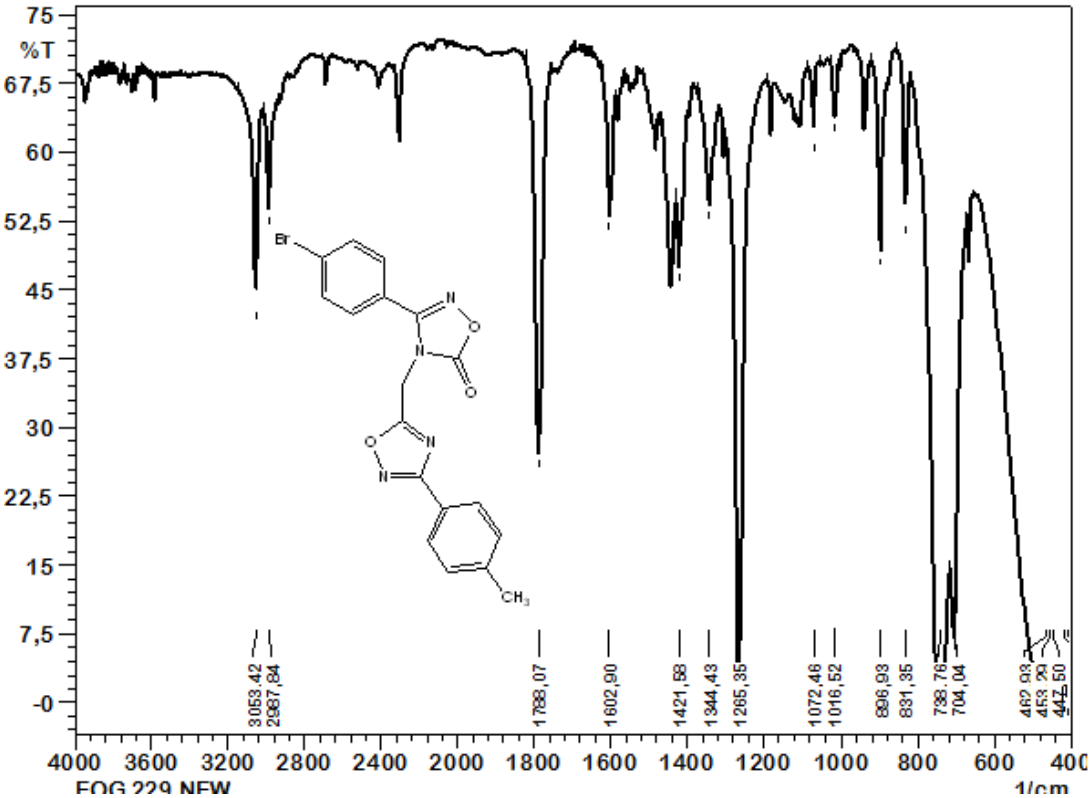

Figure 4.76. IR spectrum of compound **61o**

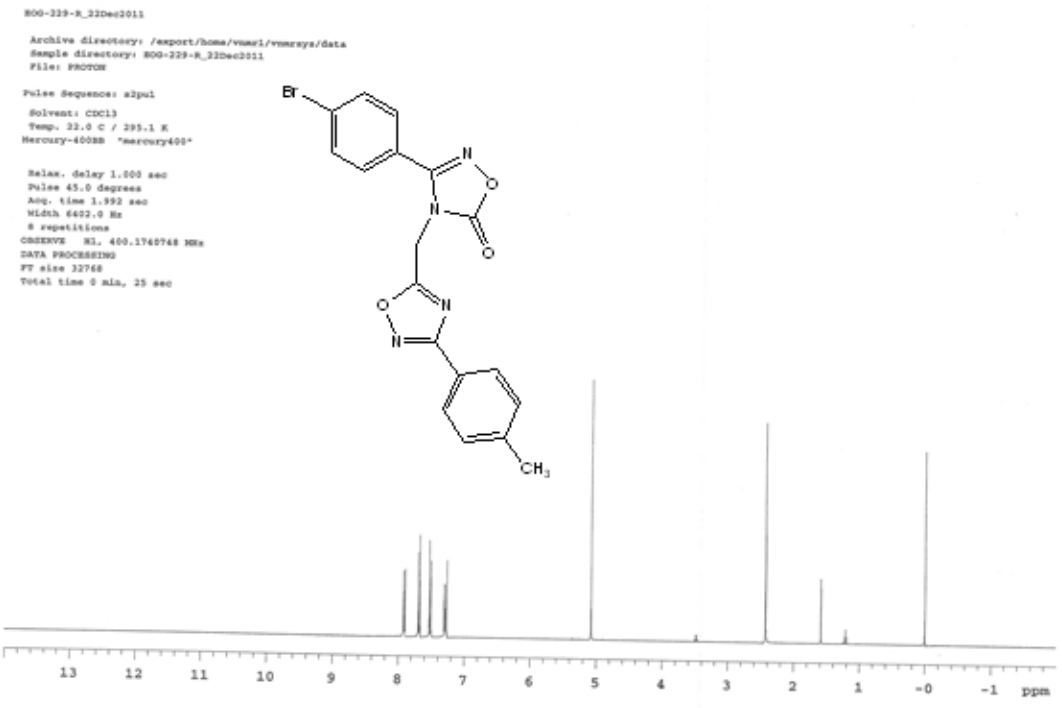

Figure 4.77. ^{1}H NMR spectrum of compound **61o**

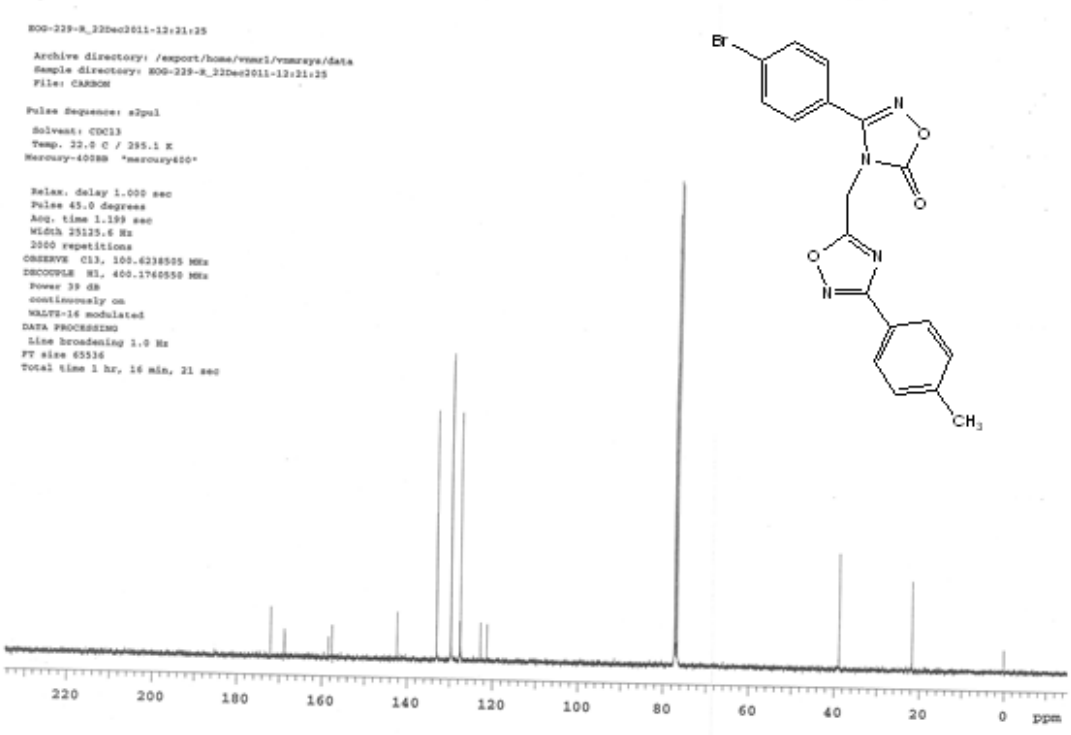

Figure 4.78. ^{13}C NMR spectrum of compound **61o**

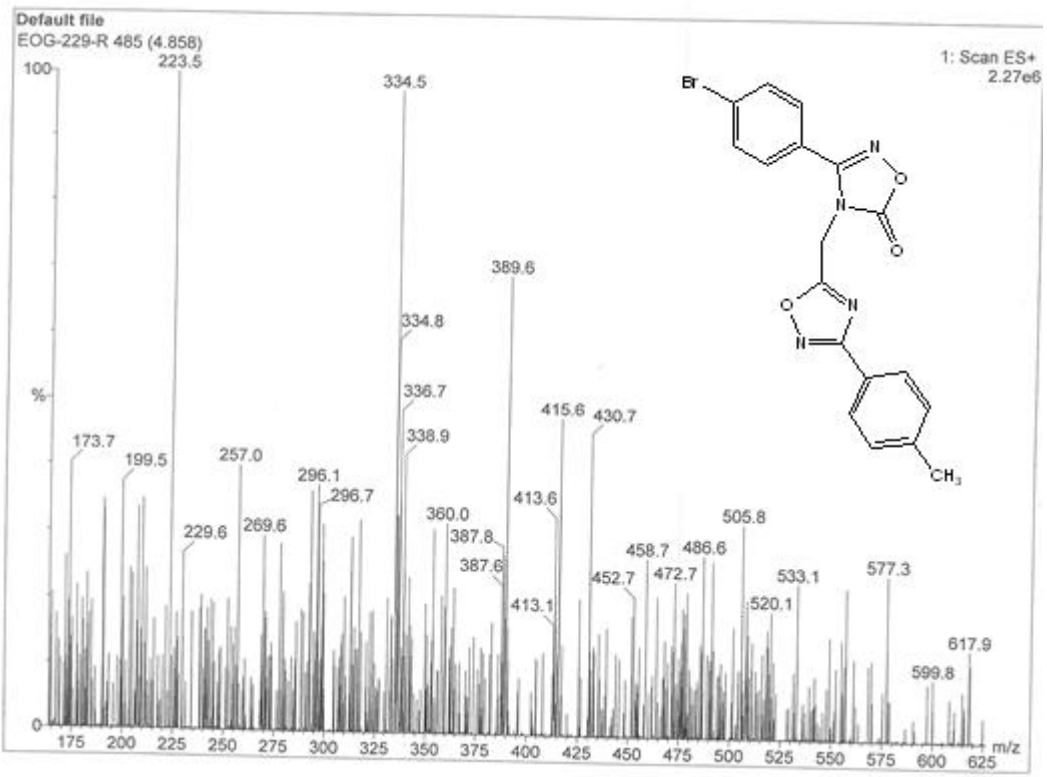

Figure 4.79. LC-MS spectrum of compound **61o**

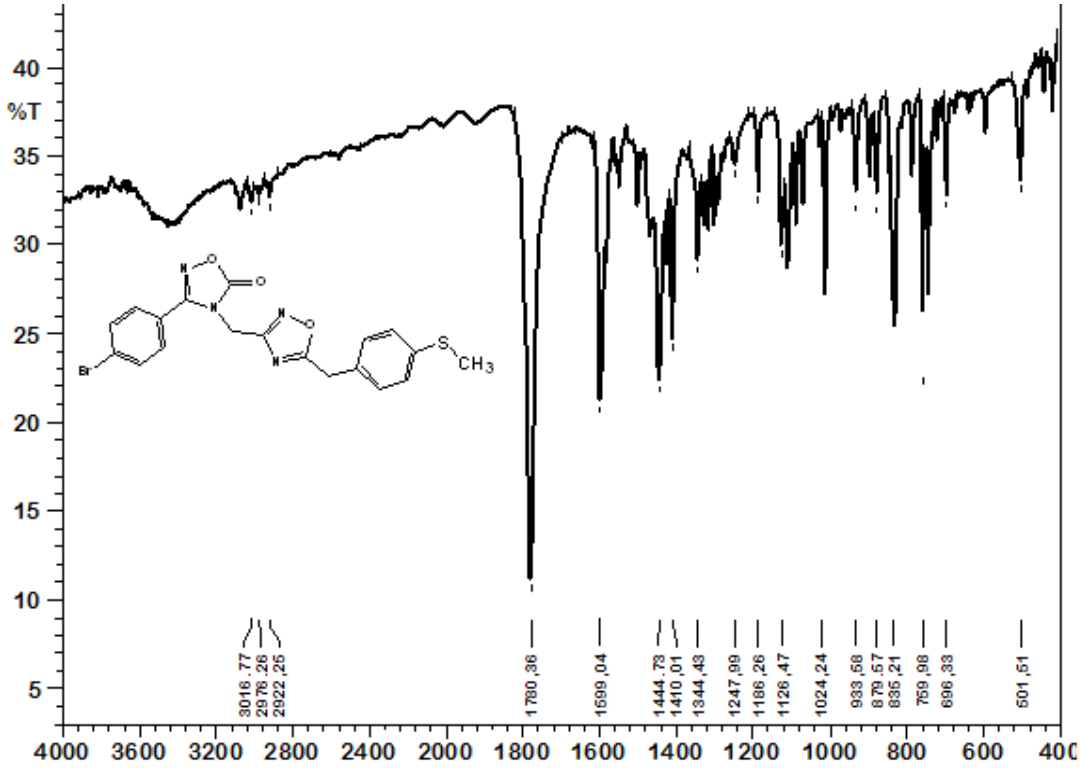

Figure 4.80. IR spectrum of compound **61p**

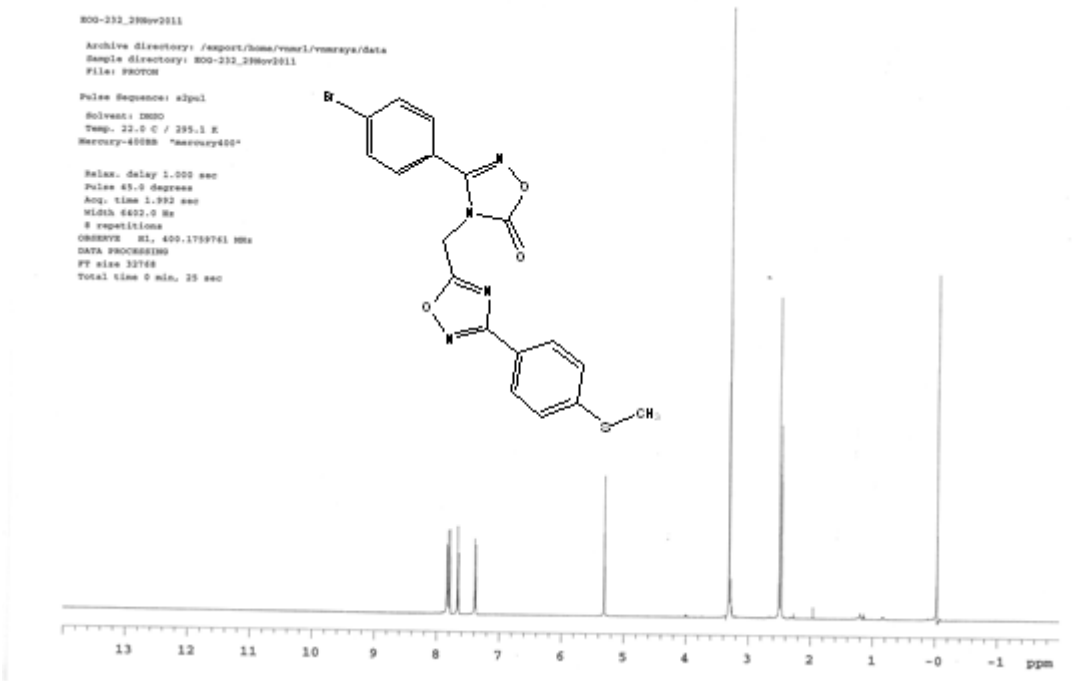

Figure 4.81. ^{1}H NMR spectrum of compound **61p**

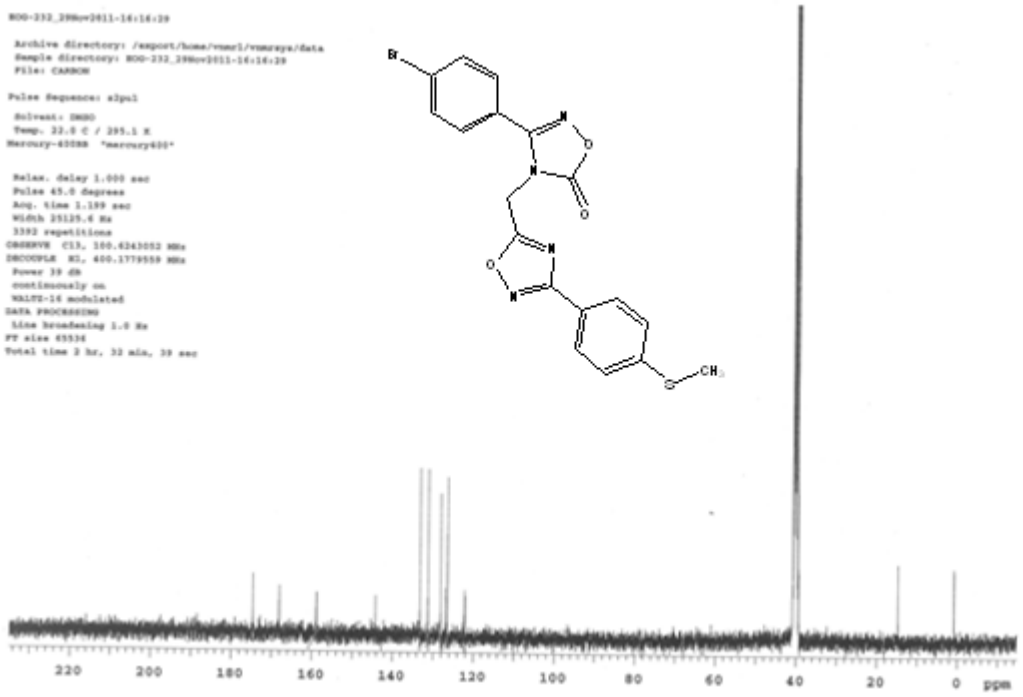

Figure 4.82. ^{13}C NMR spectrum of compoun **61p**

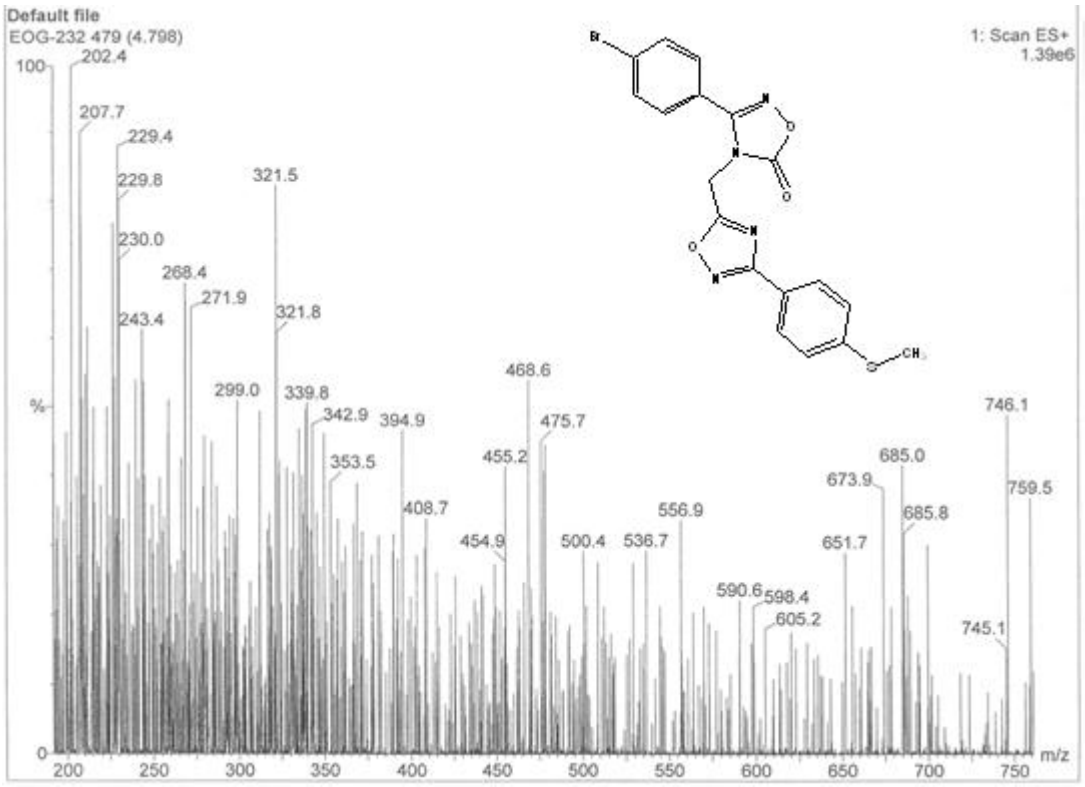

Figure 4.83. LC-MS spectrum of compound **61p**

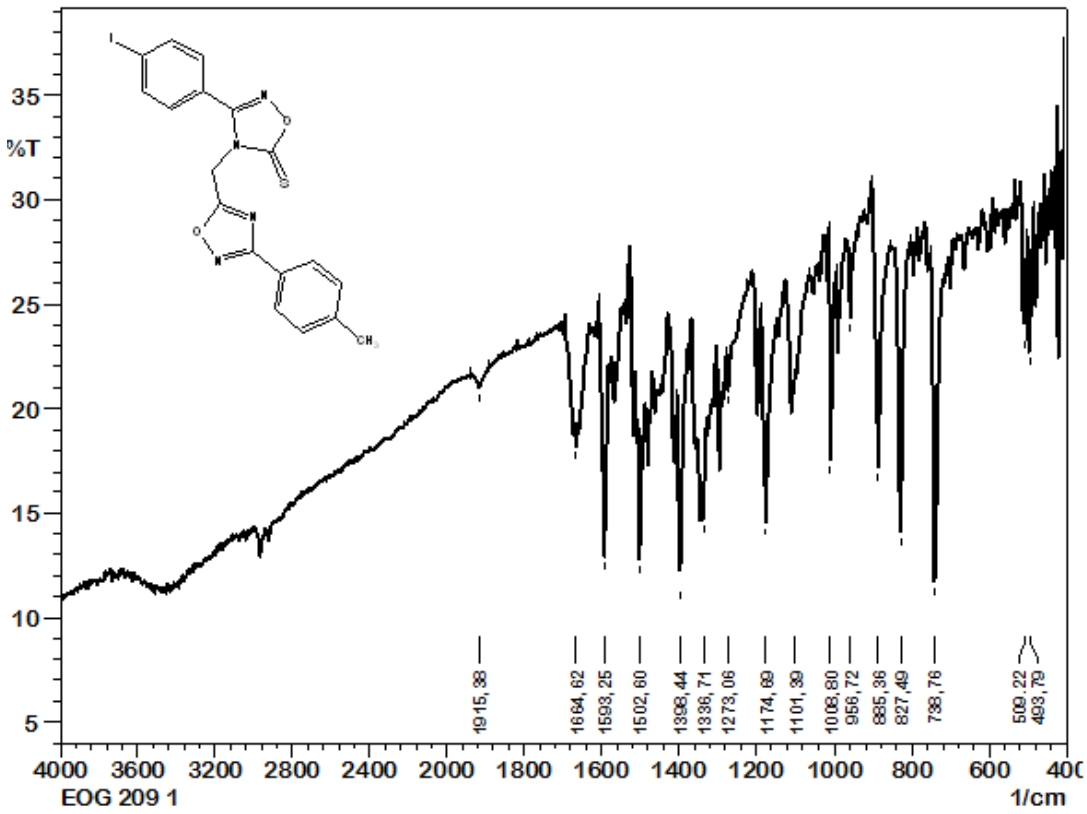

Figure 4.84. IR spectrum of compound **62**

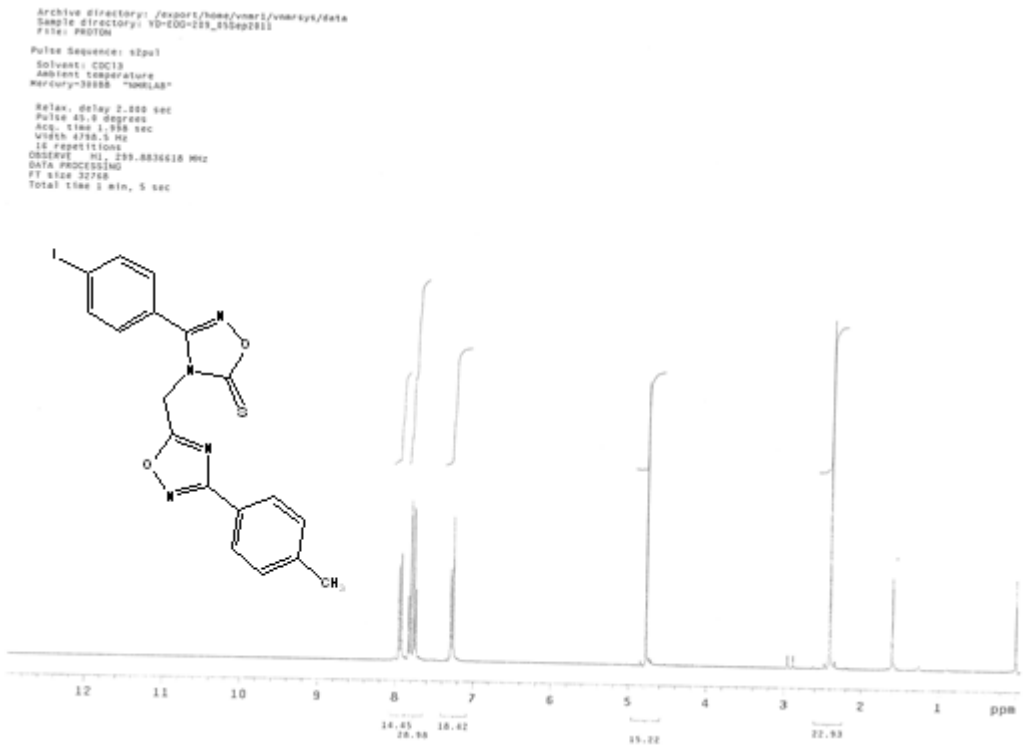

Figure 4.85. ^{1}H NMR spectrum of compound **62**

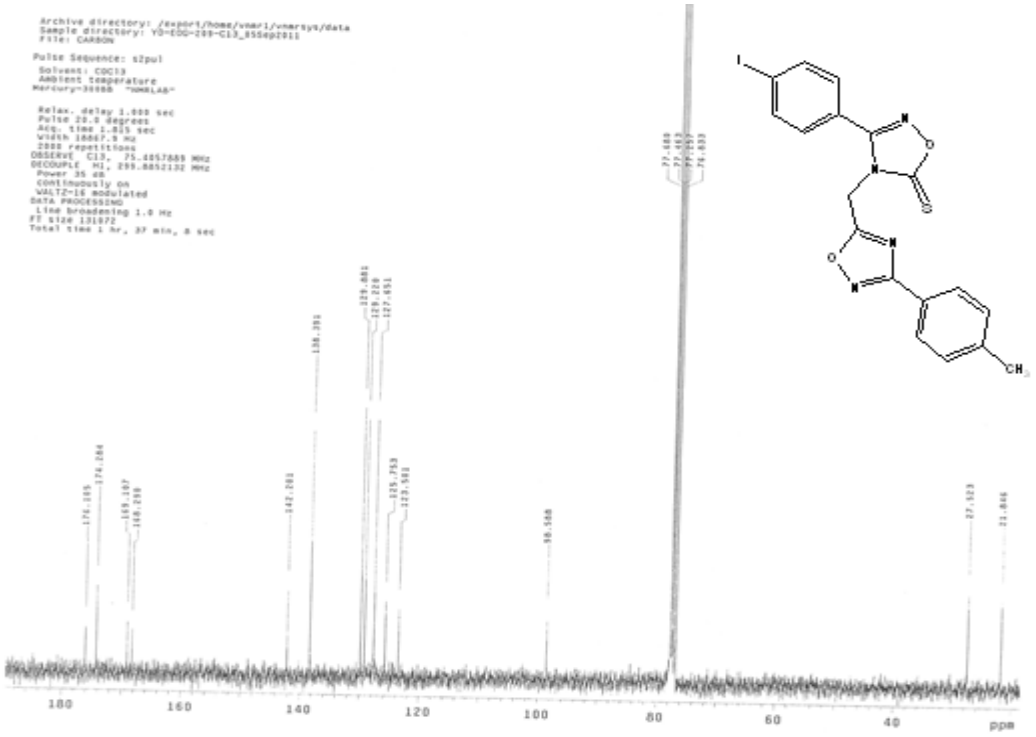

Figure 4.86. ^{13}C NMR spectrum of compound **62**

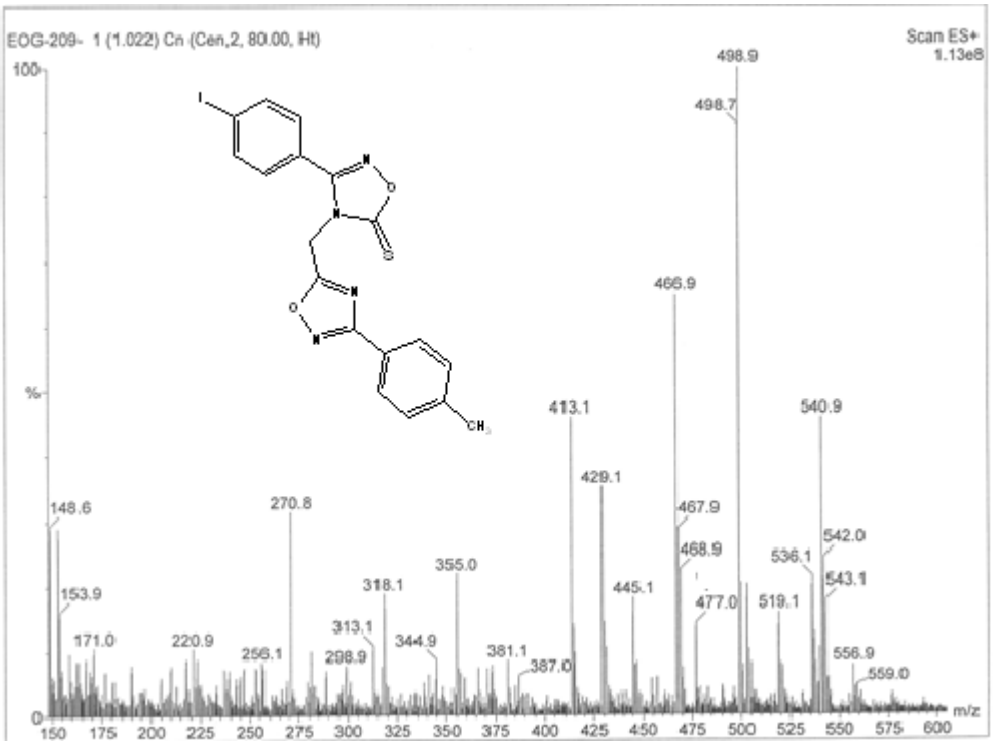

Figure 4.87. LC-MS spectrum of compound **62**

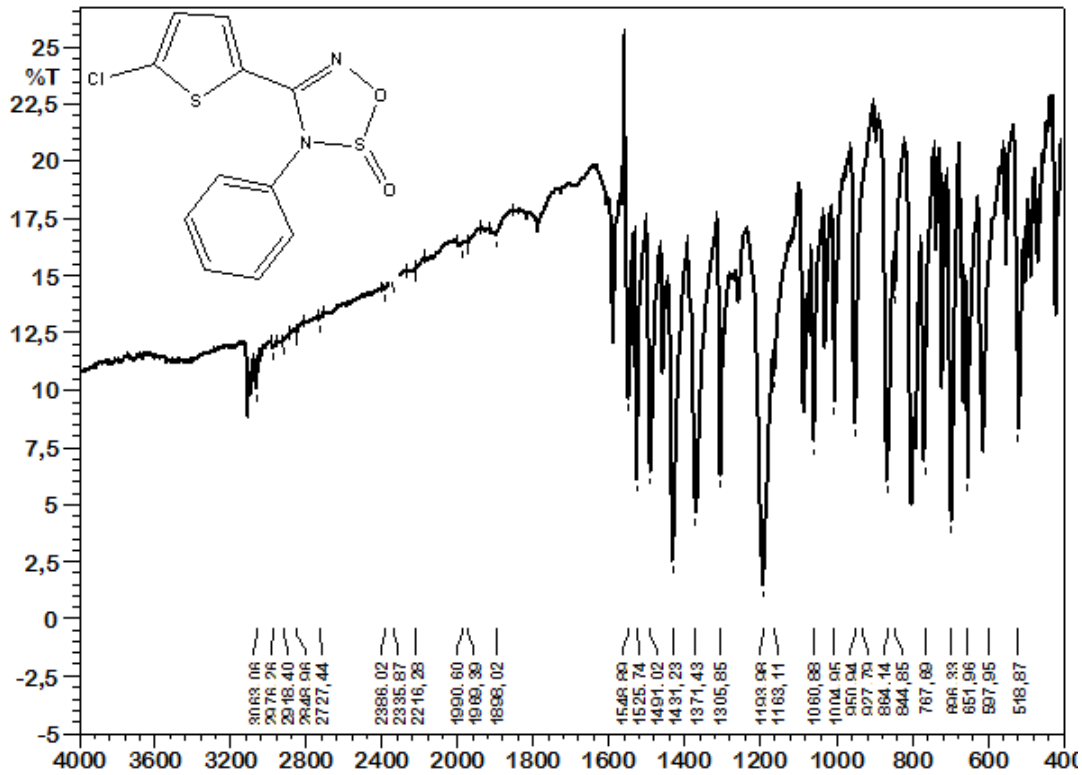

Figure 4.88. IR spectrum of compound **63a**

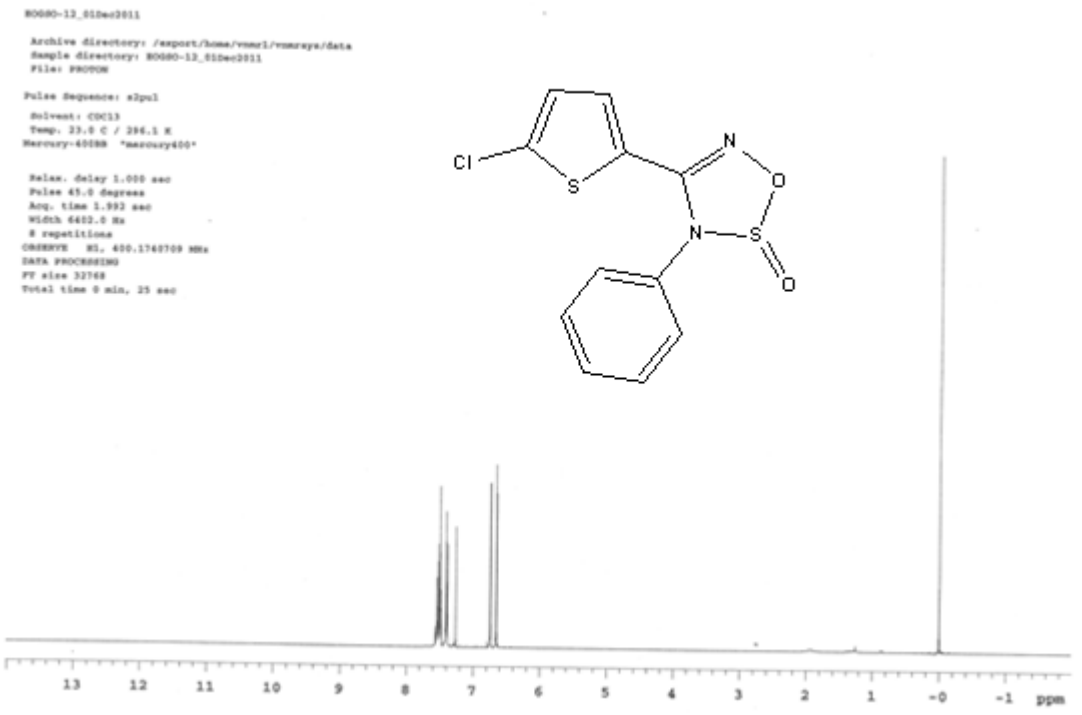

Figure 4.89. ^{1}H NMR of compound **63a**

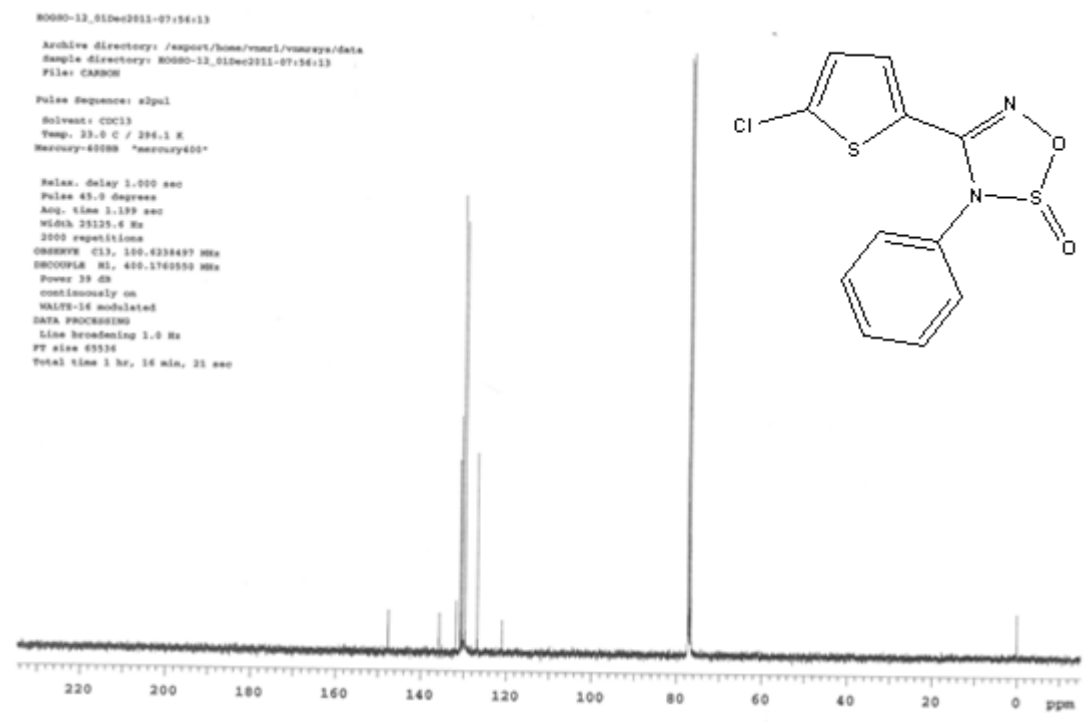

Figure 4.90. ^{13}C NMR of compound **63a**

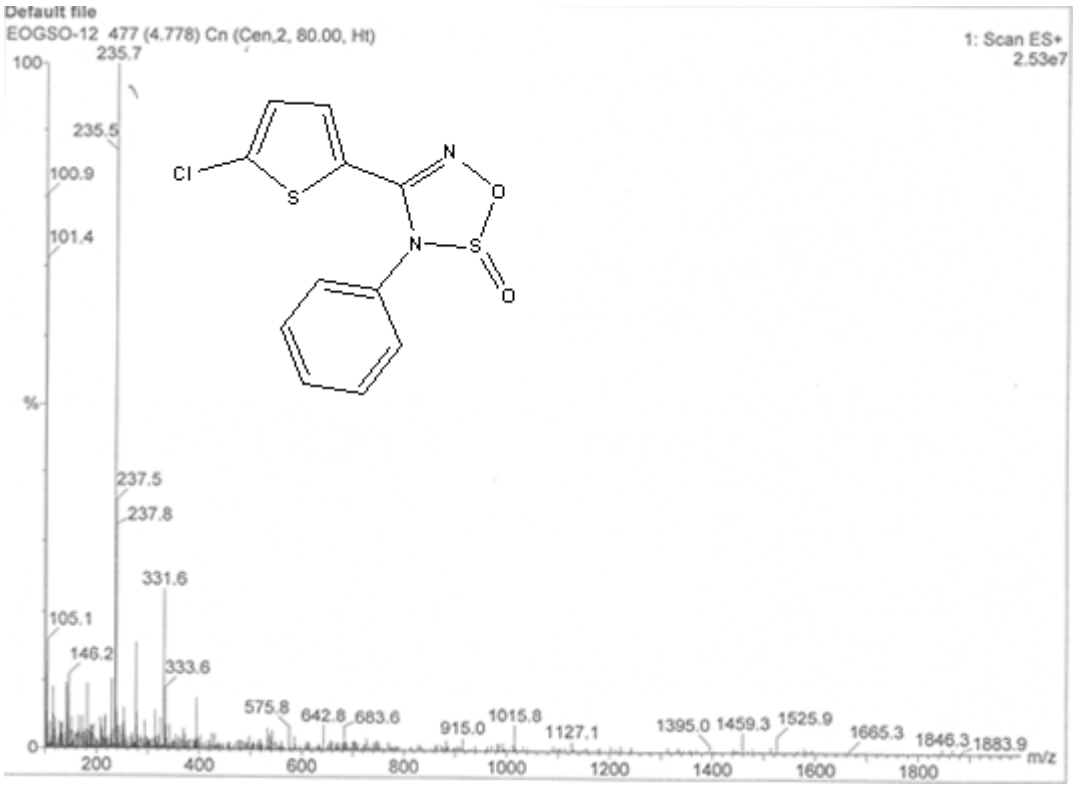

Figure 4.91. LC-MS spectrum of compound **63a**

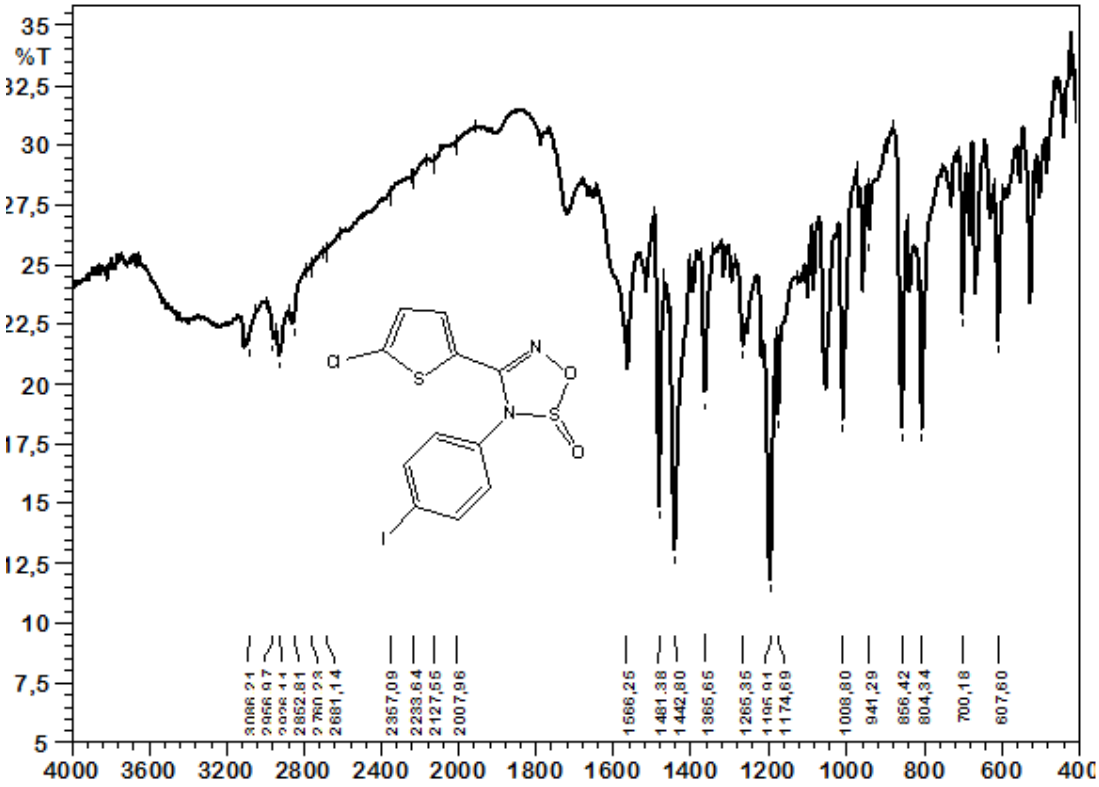

Figure 4.92. IR spectrum of compound **63b**

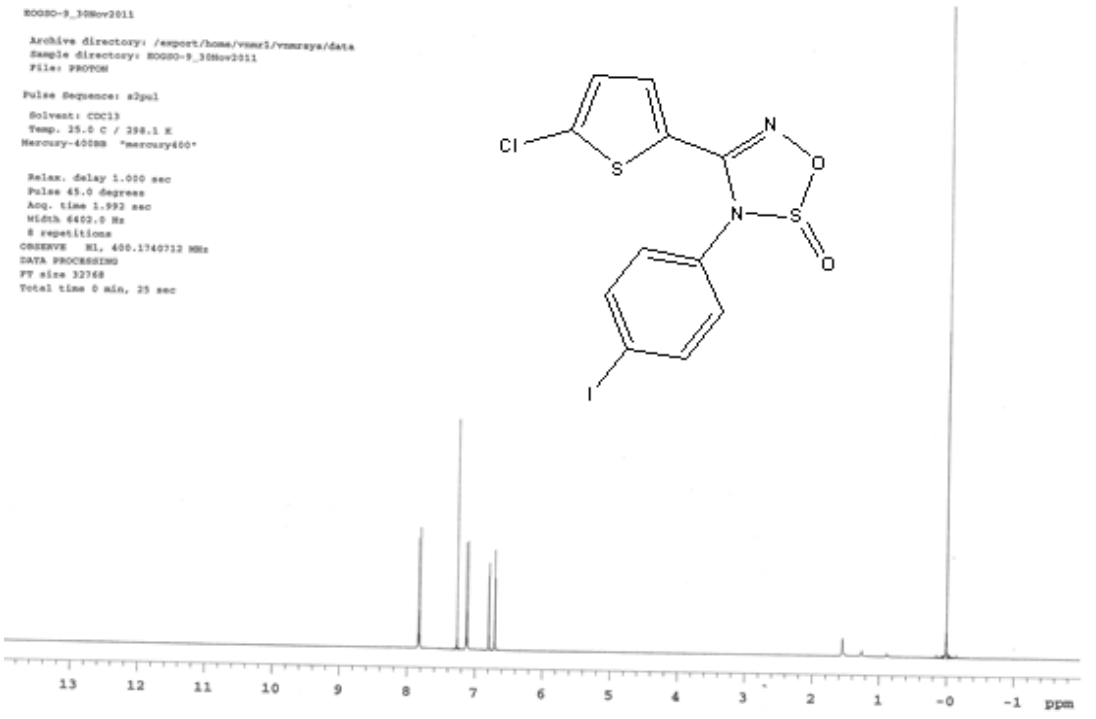

Figure 4.93. ^{1}H NMR spectrum of compound **63b**

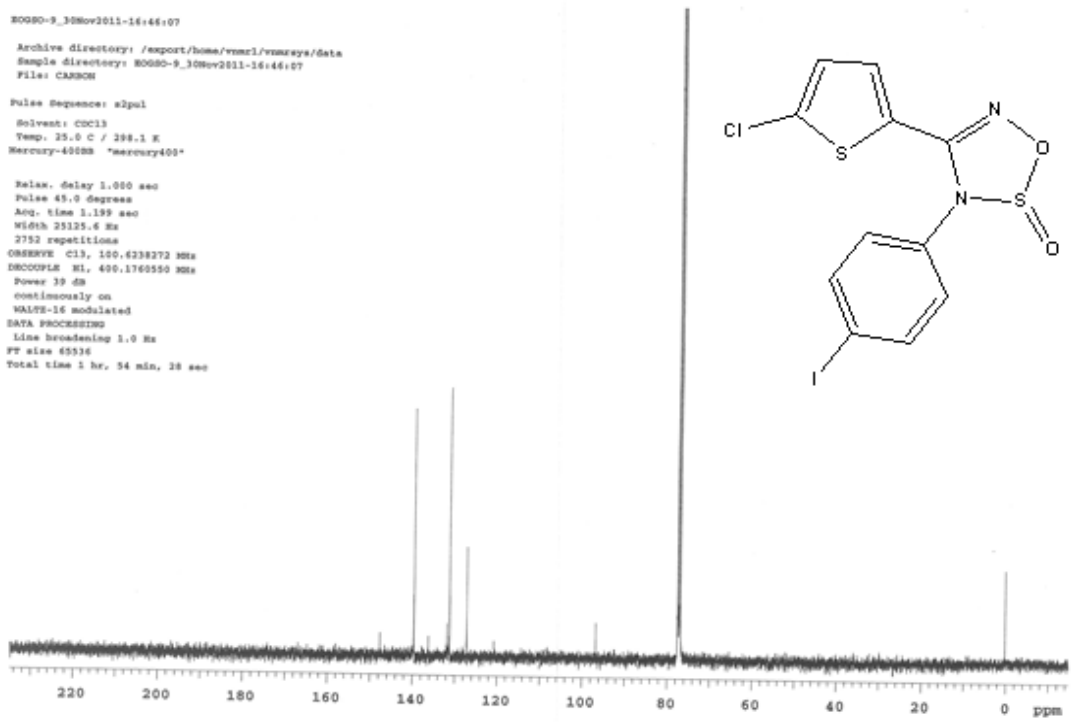

Figure 4.94. ^{13}C NMR spectrum of compound **63b**

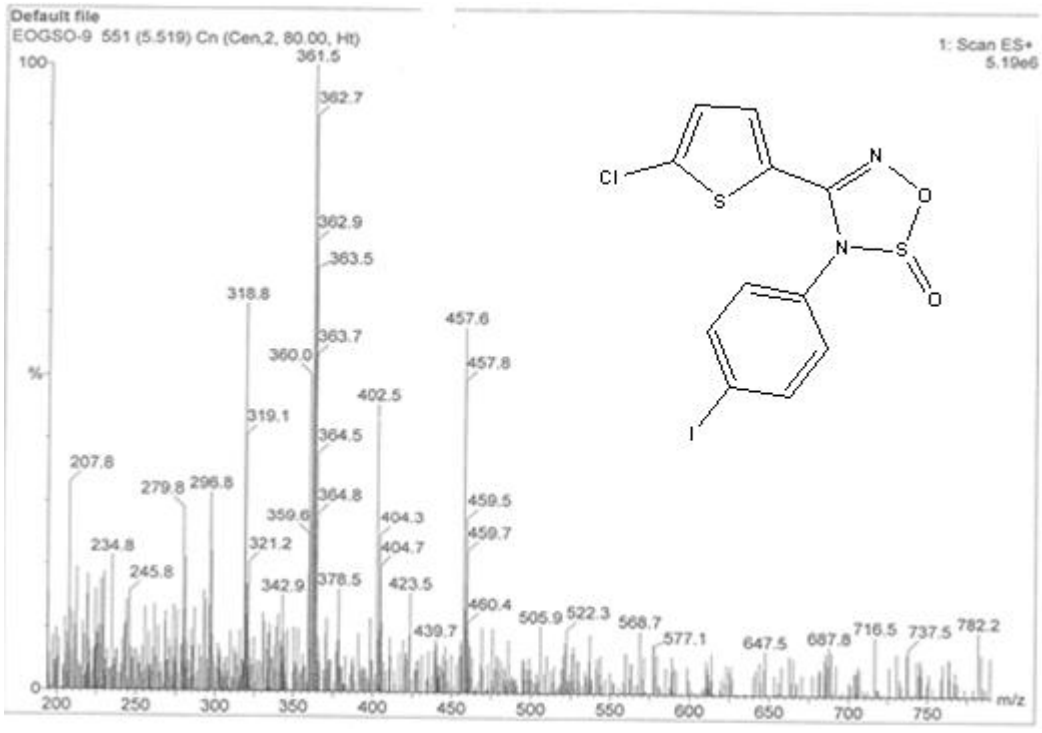

Figure 4.95. LC-MS spectrum of compound **63b**

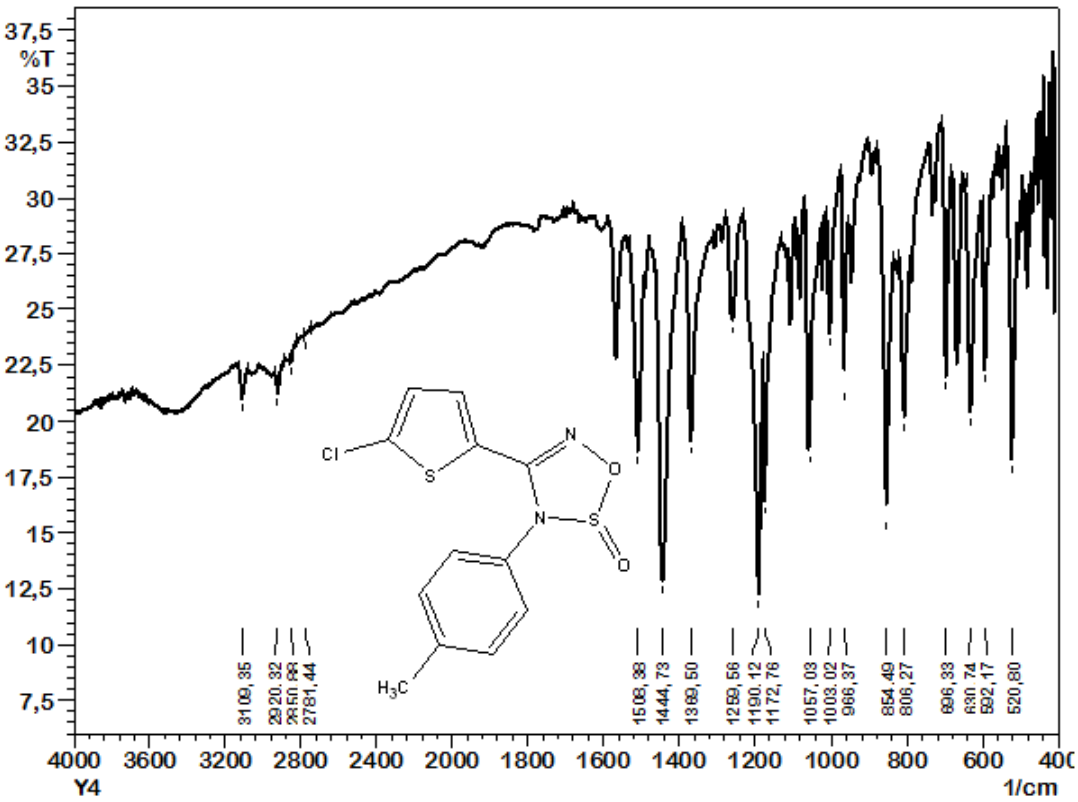

Figure 4.96. IR spectrum of compound **63c**

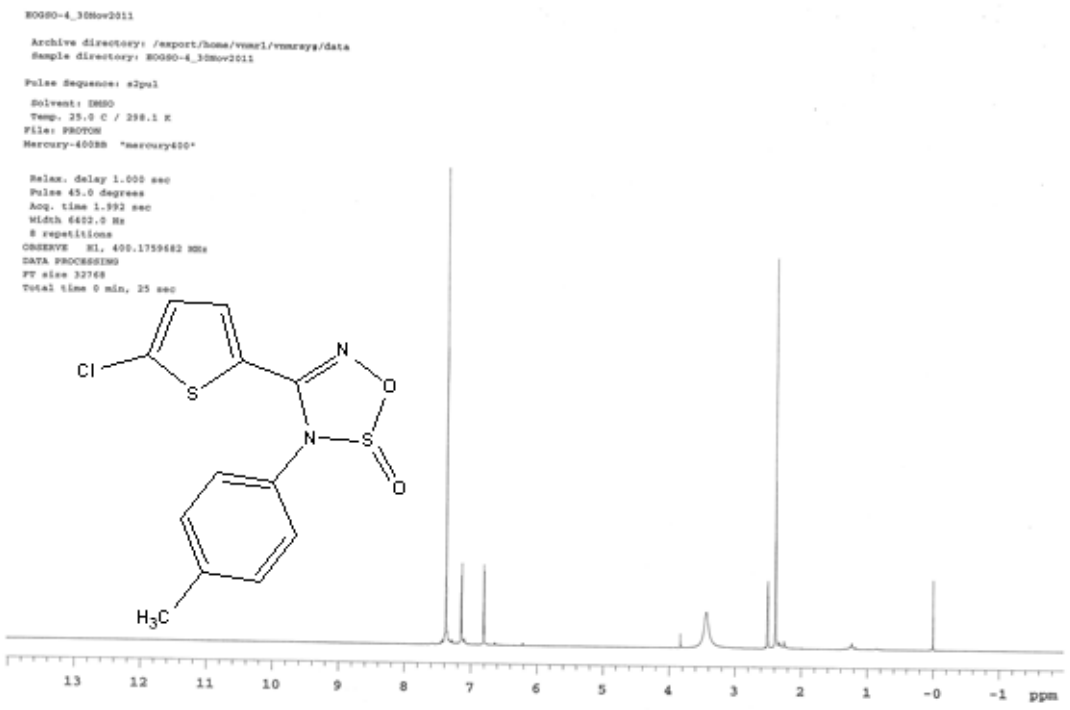

Figure 4.97. ^{1}H NMR spectrum of compound **63c**

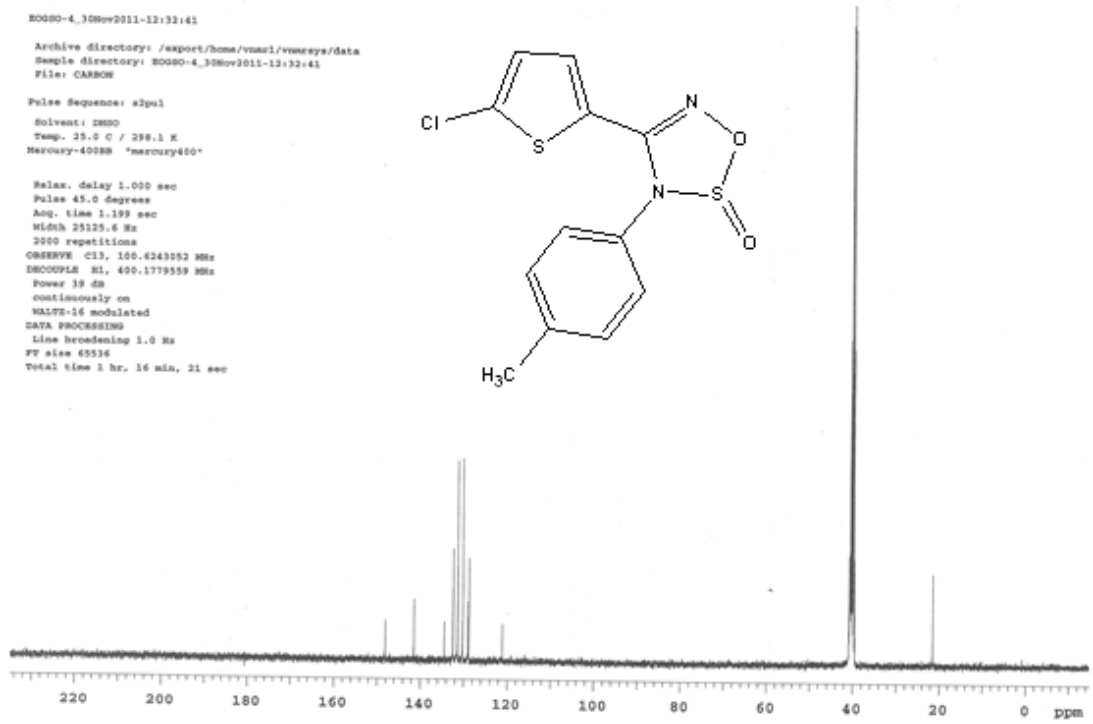

Figure 4.98. ^{13}C NMR spectrum of compound **63c**

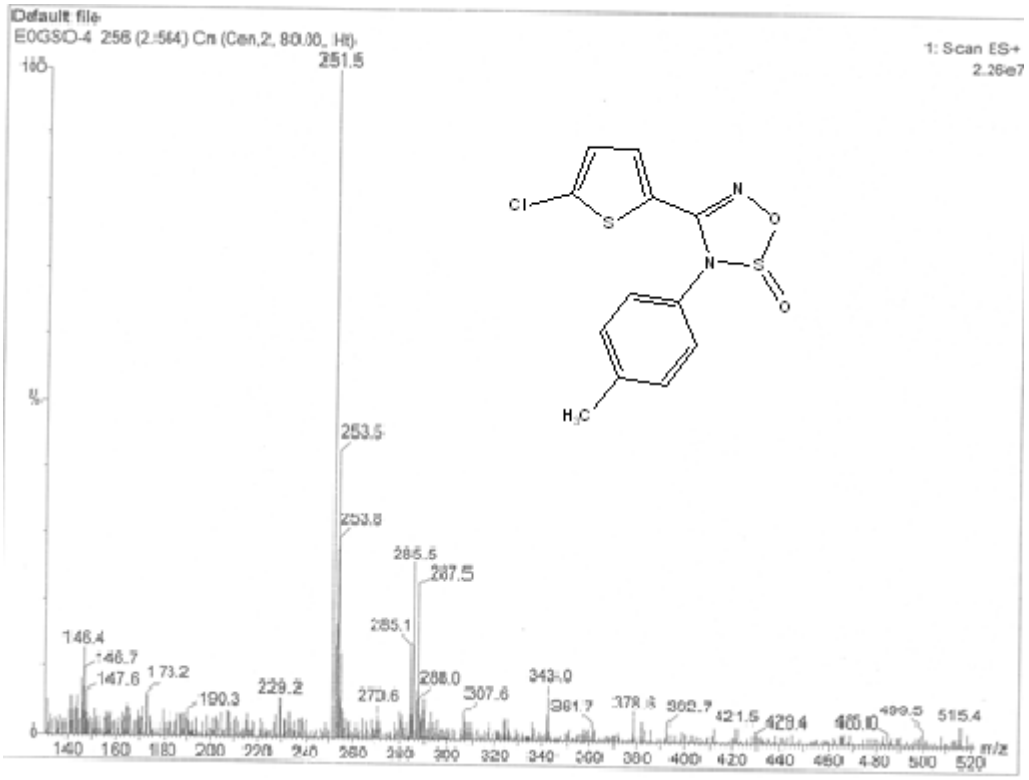

Figure 4.99. LC-MS spectrum of compound **63c**

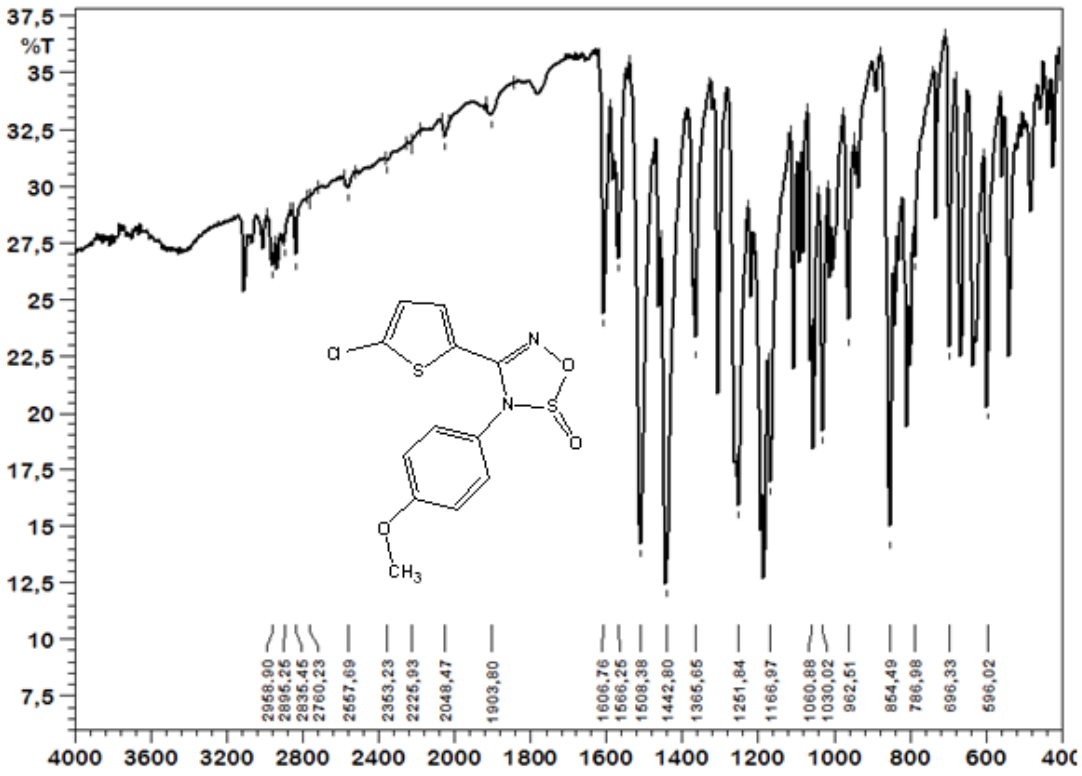

Figure 4.100. IR spectrum of compound **63d**

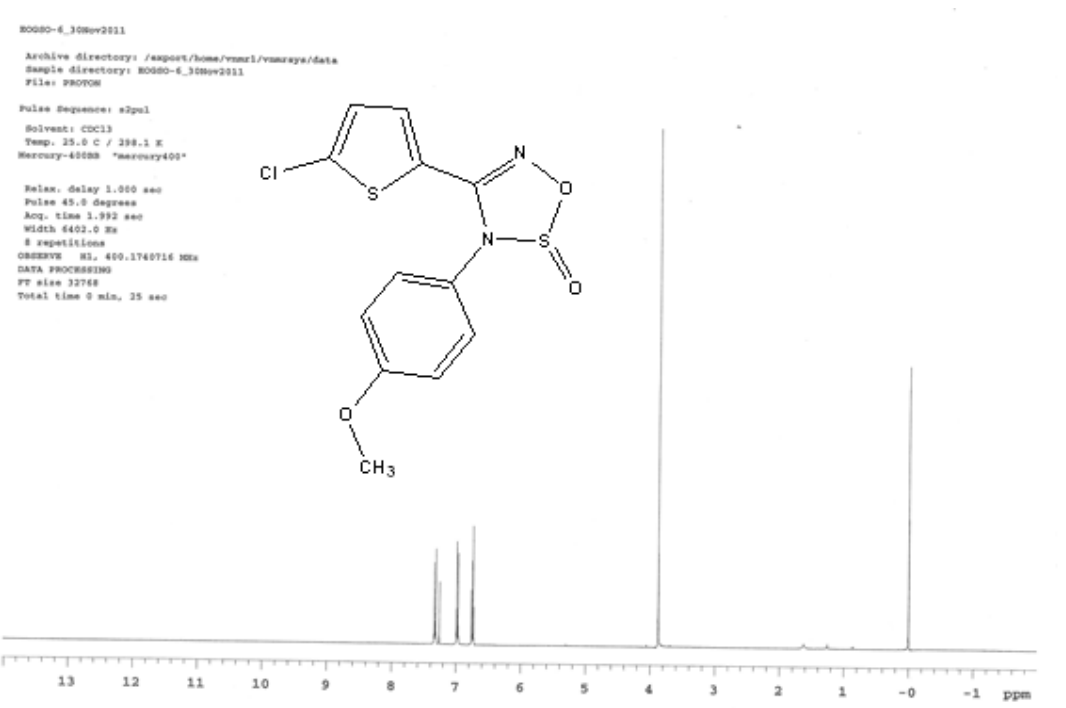

Figure 4.101. ^{1}H NMR spectrum of compound **63d**

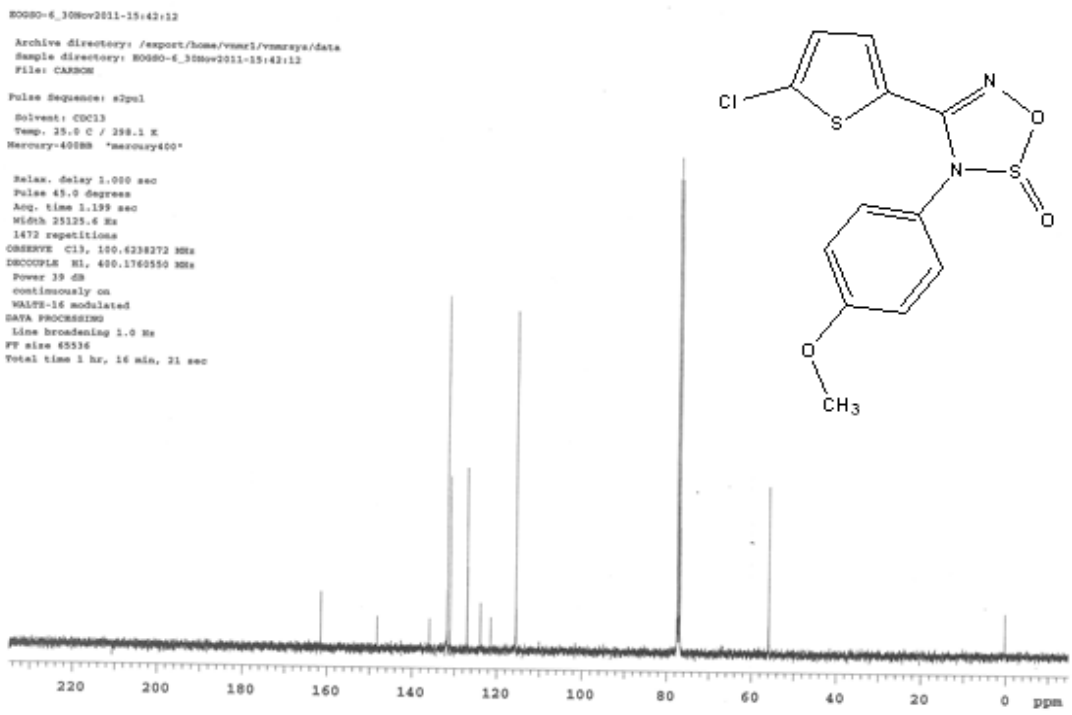

Figure 4.102. ^{13}C NMR spectrum of compound **63d**

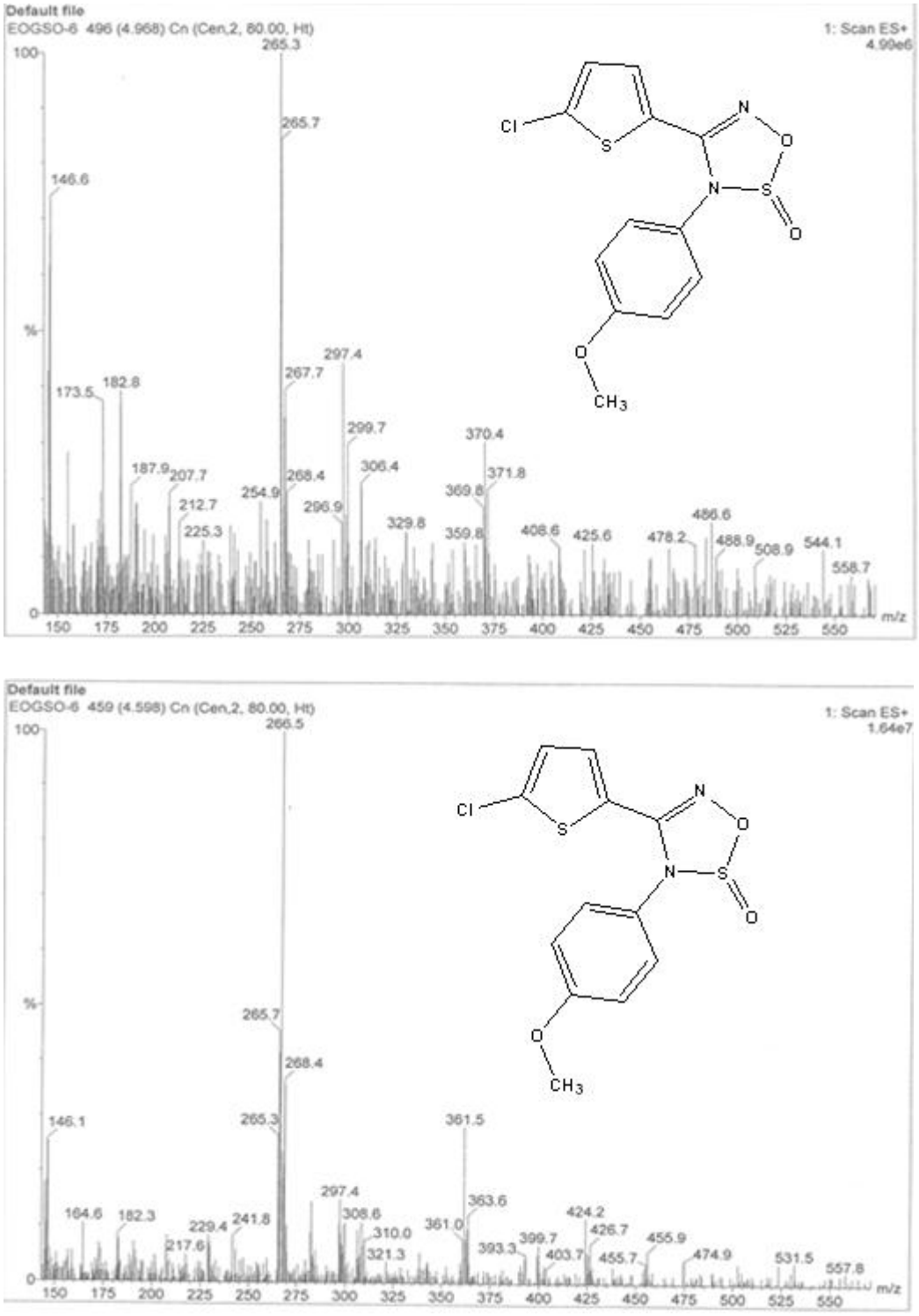

Figure 4.103. LC-MS spectrum of compound **63d**

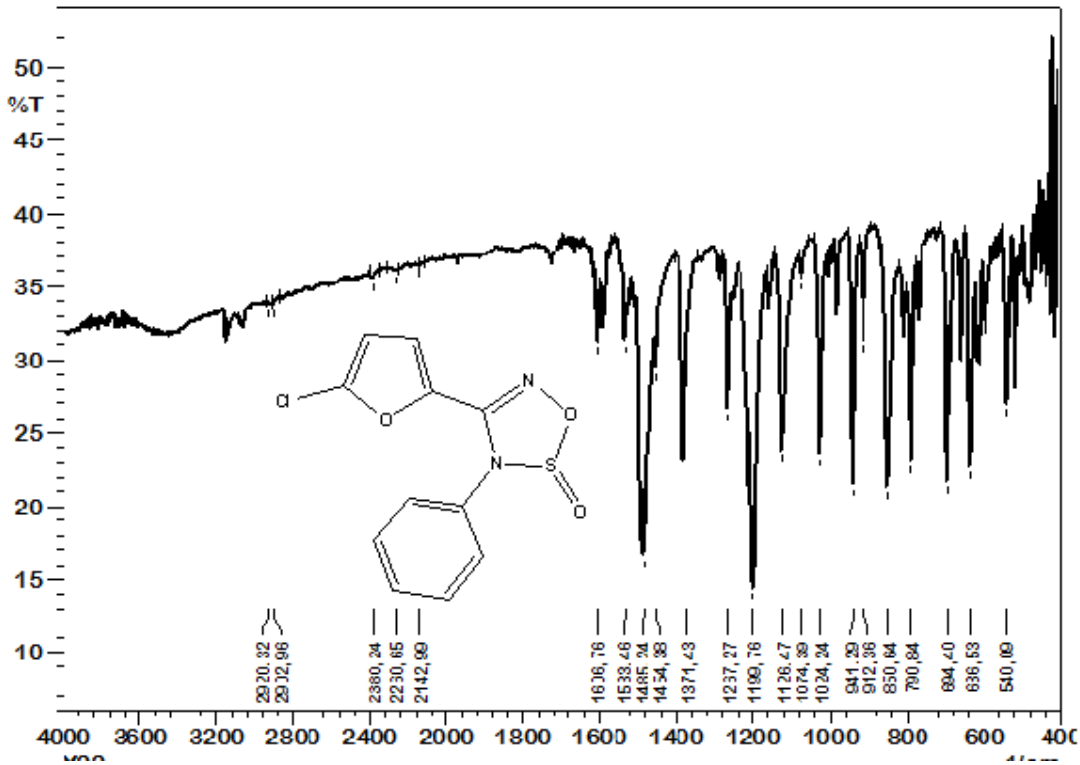

Figure 4.104. IR spectrum of compound **63e**

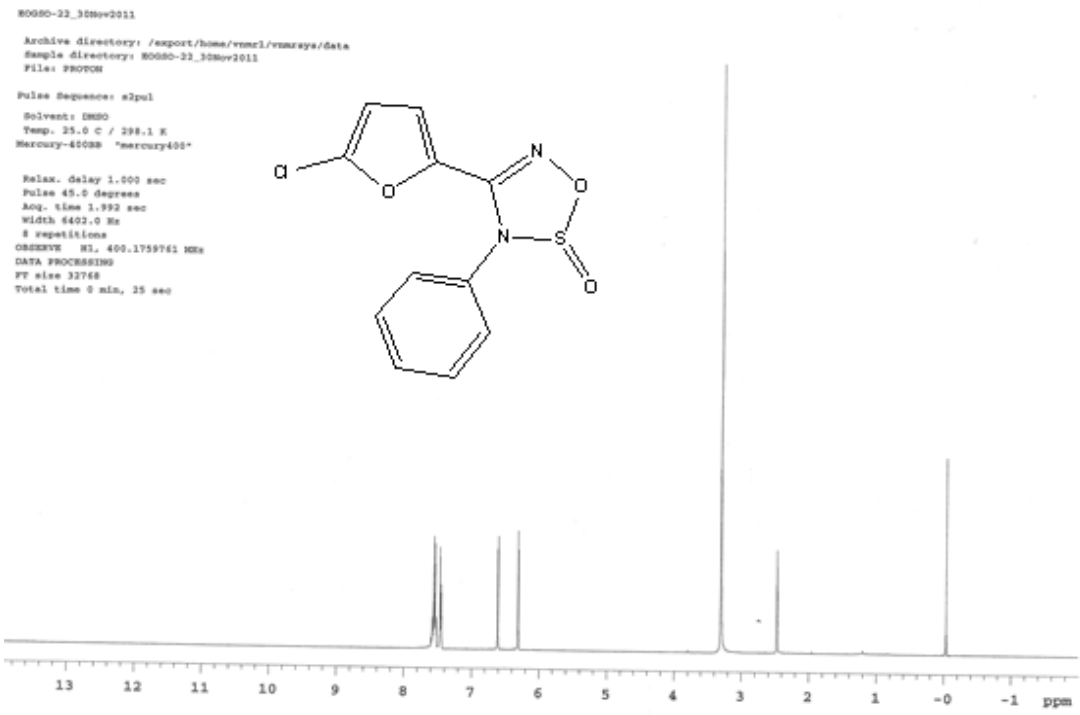

Figure 4.105. ^{1}H NMR spectrum of compound **63e**

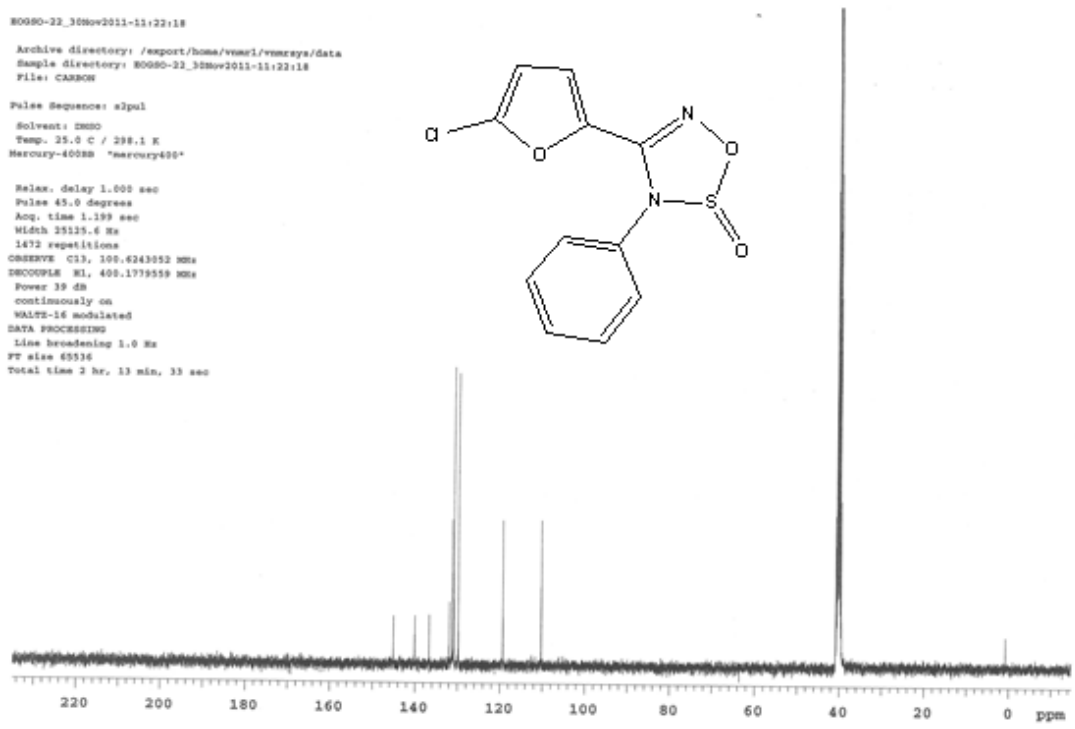

Figure 4.106. ^{13}C NMR spectrum of compound **63e**

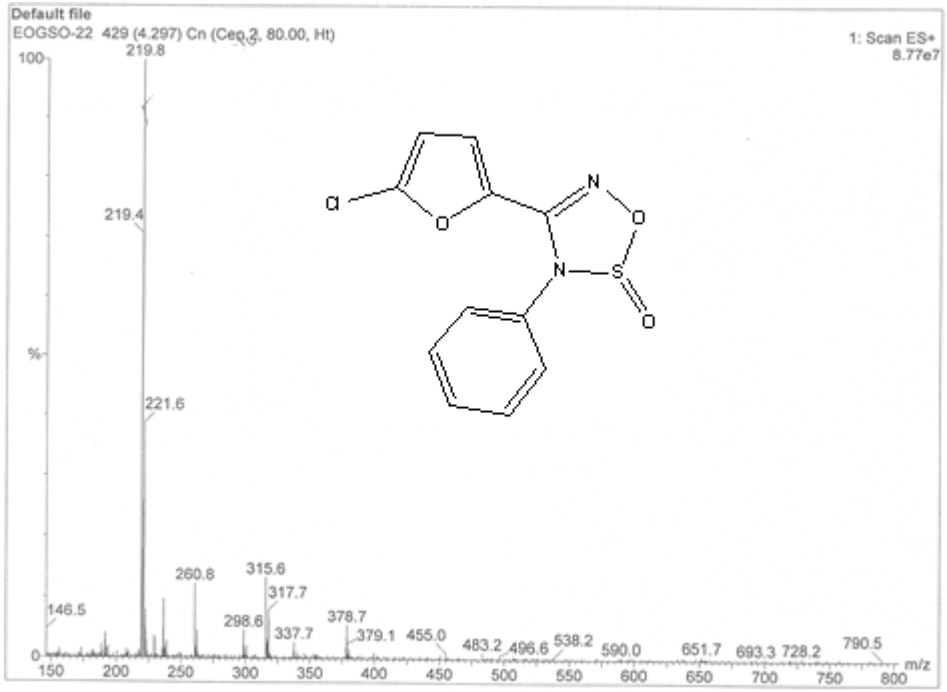

Figure 4.107. LC-MS spectrum of compound **63e**

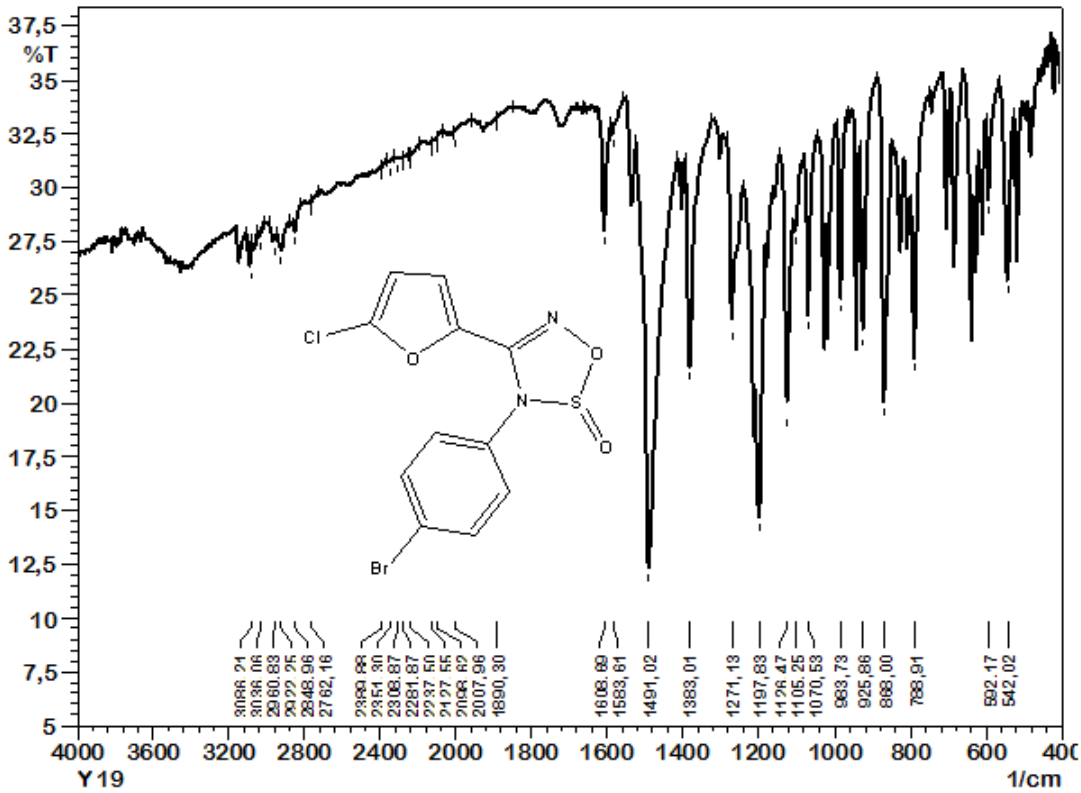

Figure 4.108. IR spectrum of compound **63f**

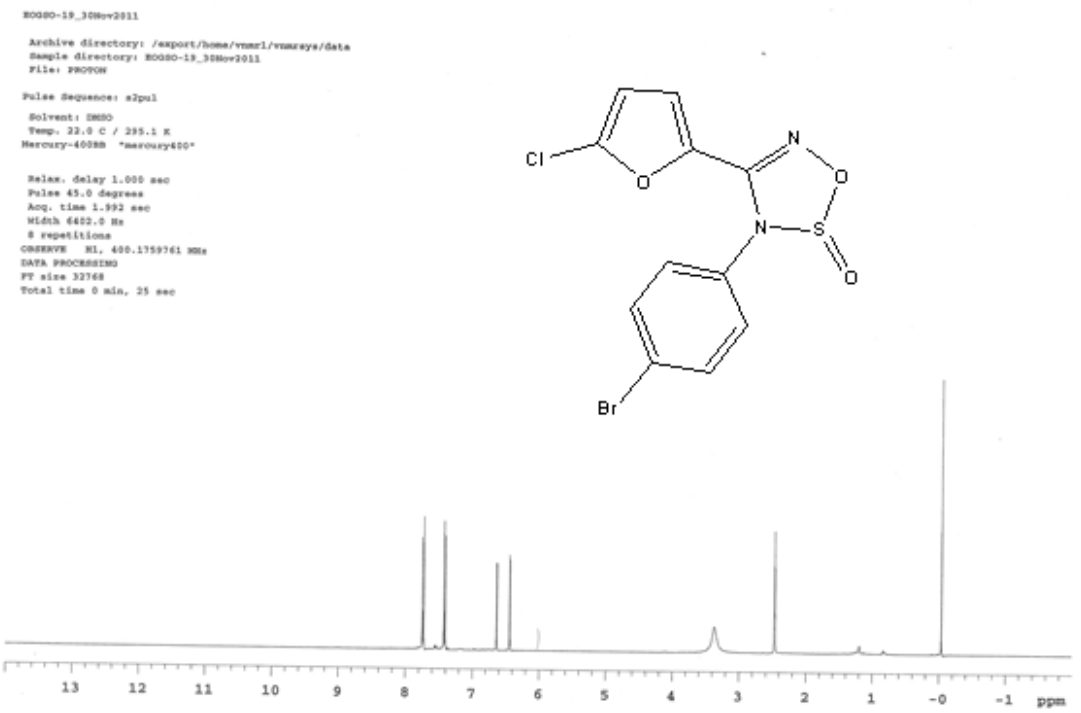

Figure 4.109. ^{1}HNMR spectrum of compound **63f**

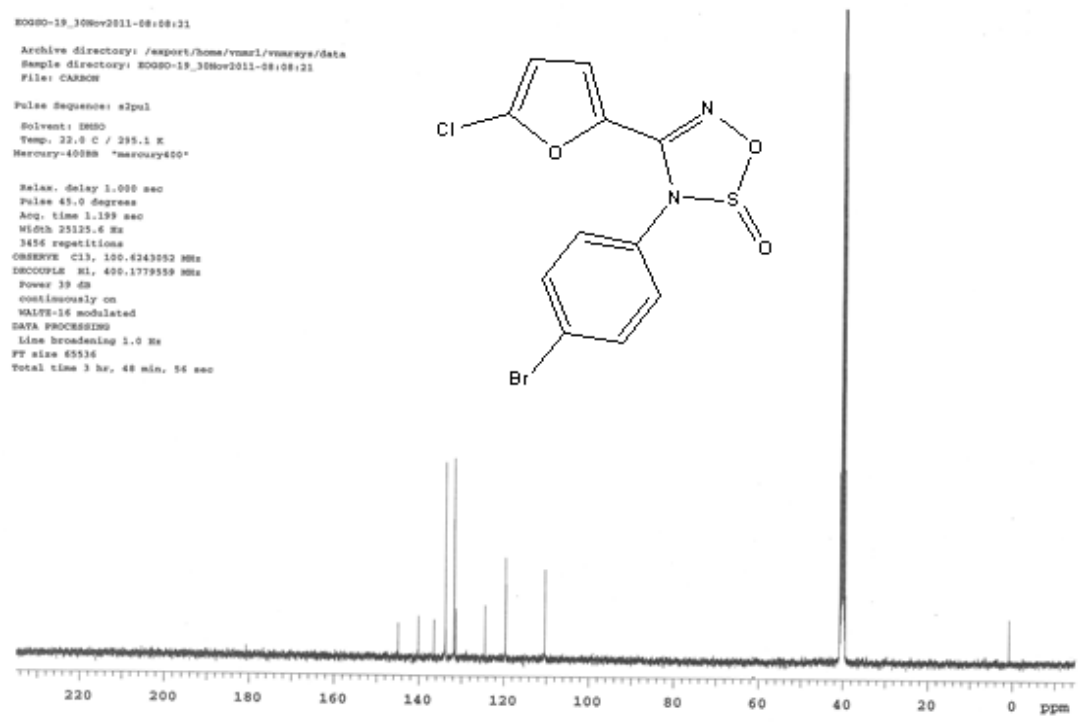

Figure 4.110. ^{13}C NMR spectrum of compound **63f**

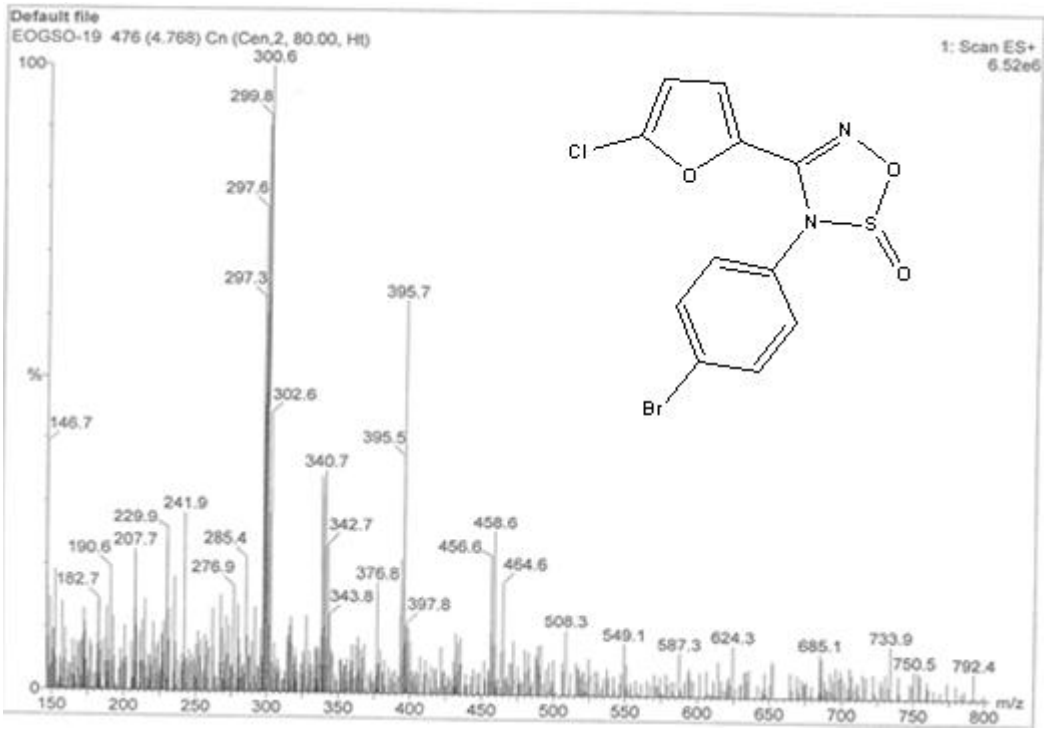

Figure 4.111. LC-MS spectrum of compound **63f**

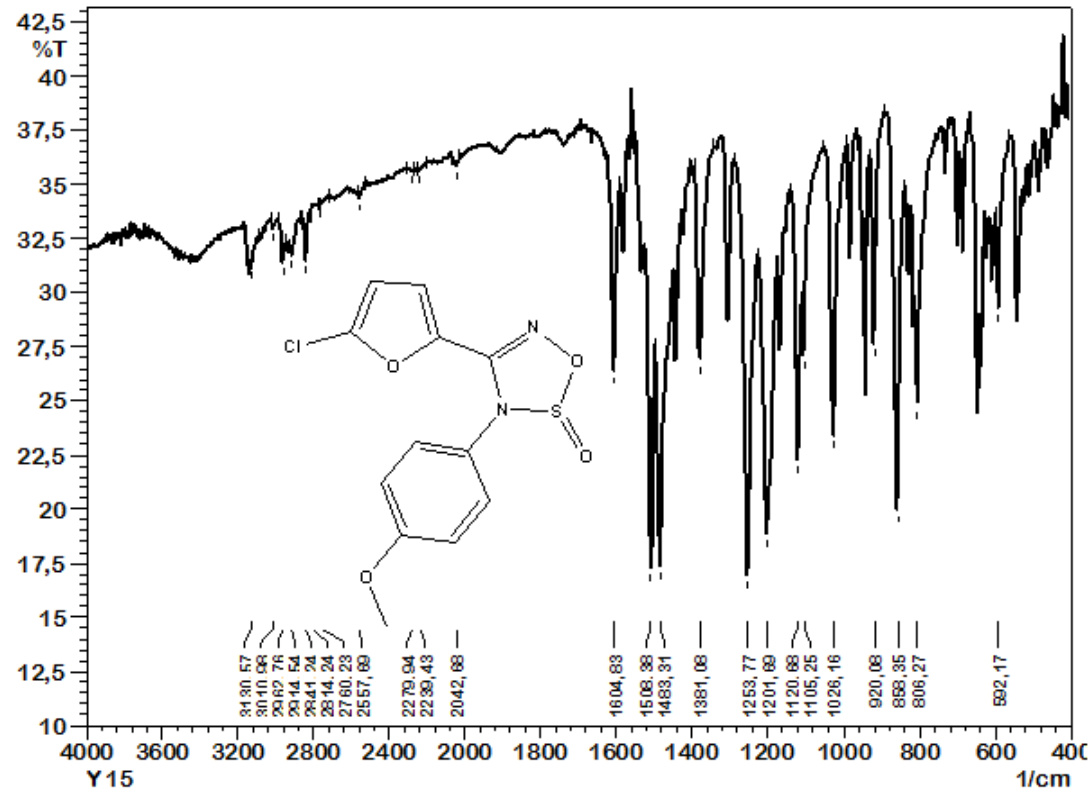

Figure 4.112. IR spectrum of compound **63g**

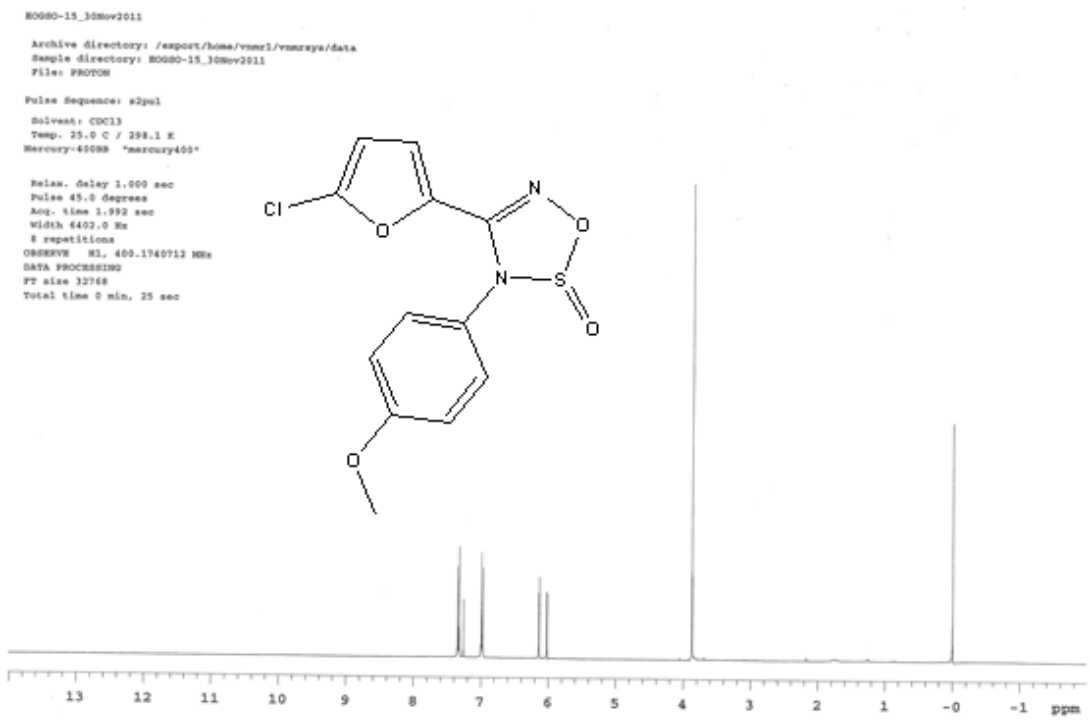

Figure 4.113. ^{1}H NMR spectrum of compound **63g**

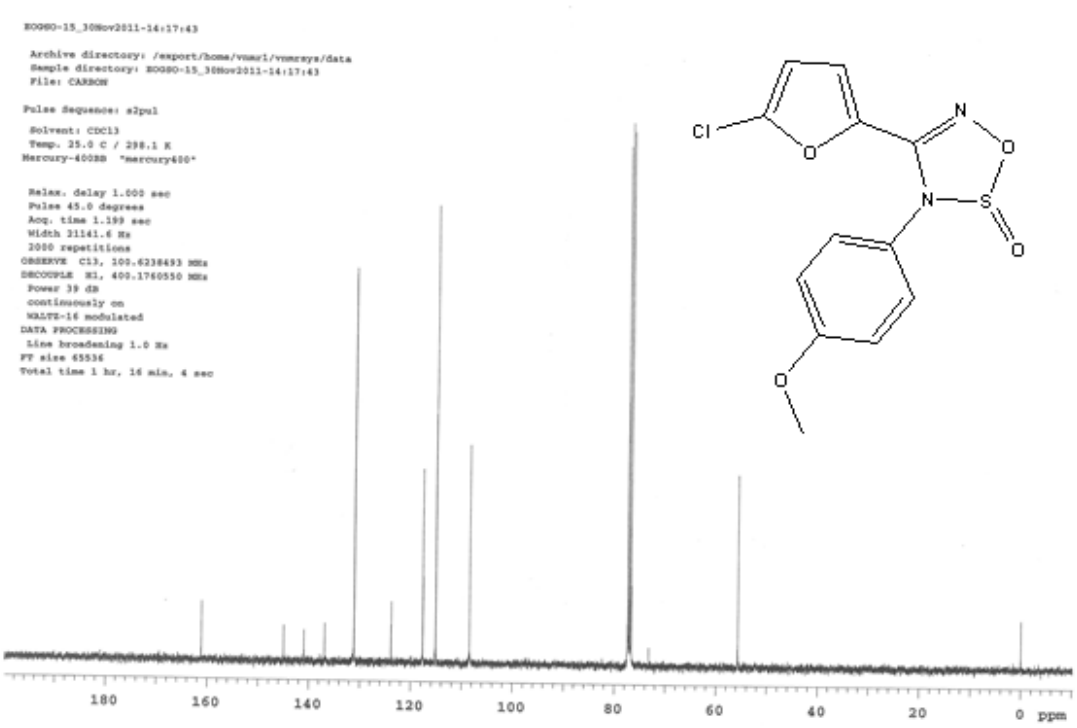

Figure 4.114. ^{13}C NMR spectrum of compound **63g**

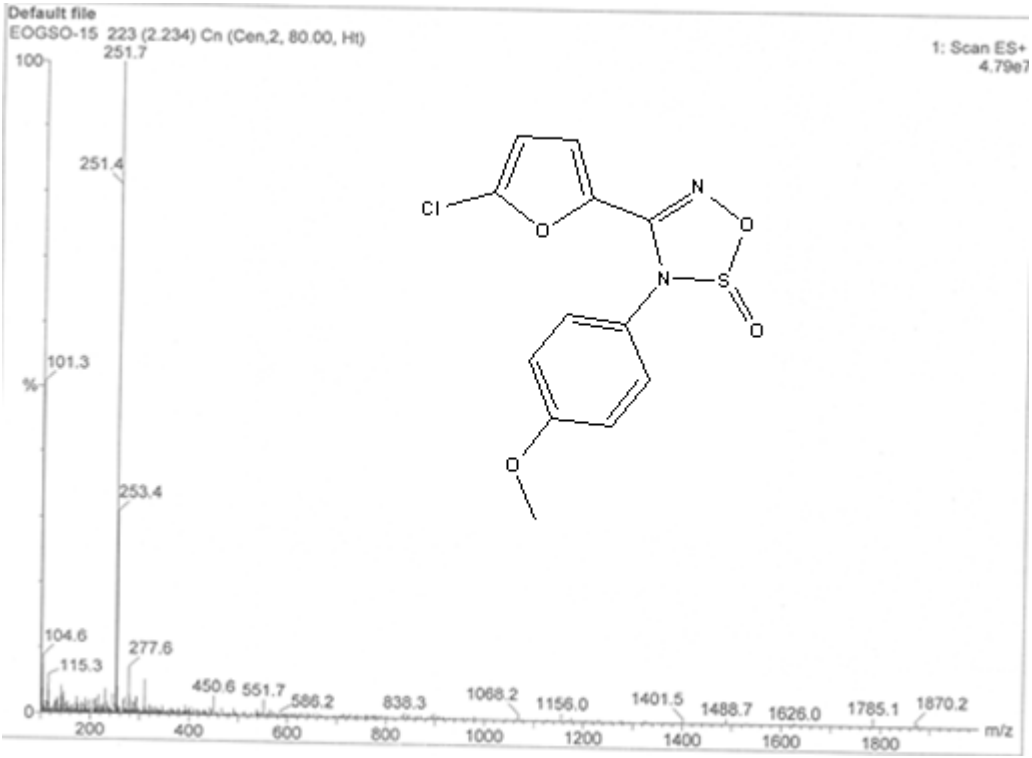

Figure 4.115. LC-MS spectrum of compound **63g**