SYNTHESIS OF NEW URACIL AND *o*-BENZOSULFIMIDE BASED POTENTIALLY BIOACTIVE HETEROCYCLES

BESRA ÖZER

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SYNTHESIS OF NEW URACIL AND *o*-BENZOSULFIMIDE BASED POTENTIALLY BIOACTIVE HETEROCYCLES

by
BESRA ÖZER

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IN
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Approval of the Graduate School of Natural and Applied Science.

Prof. Dr. Yaşar DÜRÜST
Director

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

Prof.Dr.Nedime DÜRÜST
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.Mustafa ARSLAN

3 Prof.Dr. Mustafa KÜÇÜKİSLAMOĞLU

ABSTRACT

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Özer, Besra
M.Sc., Department of Chemistry
Supervisor: Prof. Dr. Yaşar Dürüst

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The aim of this work is to synthesize a variety of *N*-(5-methyl-1,2,4-oxadiazolyl) substituted *o*-benzosulfimide, *N*,*N'*-(5-methyl-1,2,4-oxadiazolyl) disubstituted uracil, *N*,*N'*-(5-methyl-1,2,4-oxadiazolyl)disubstituted 5-amino uracil, and *N*,*N'*-(5-methyl-1,2,4-oxadiazolyl) disubstituted benzylidene pyrimidinedione. 1,2,4-Oxadiazole related scaffolds have been used for decades in composing a variety of heterocylic compounds with a remarkable potency of bioactivity. In order to perform this, firstly we have prepared, 5-

chloromethyl 1,2,4-oxadiazoles from the *p*-substituted benzamidoximes, which were easily synthesized from the *p*-substituted benzonitriles. To our best knowledge of literature, *N*- oxadiazolylmethyl substituted *O*-benzosulfimide, *N*-oxadiazolylmethyl substituted uracil, *N*-oxadiazolylmethyl substituted 5-amino uracils, and *N* –oxadiazolylmethyl substituted pyrimidines have not been reported so far.

5-Chloromethyl-1,2,4-oxadiazoles were reacted with the above mentioned benzosulfimide, uracil which have N-H, by using K_2CO_3 in DMF.

These structures of all end products were elucidated by means of IR, NMR (^1H, ^{13}C), LC-MS spectra and physical data (melting points and R_f values). Since all of these novel compounds carry potent groups like oxadiazole, bioactivity assessment of these heterocyles are underway in due course.

Keywords: amidoxime, 1,2,4 oxadiazole, o-benzosulfimide, uracil, 5-amino uracil, pyrimidinedione, spectroscopy

ÖZET

YENİ URACİL VE *o*-BENZOSÜLFİMİD ESASLI POTANSİYEL BİYOAKTİF HETEROHALKALARIN SENTEZİ

Özer,Besra
Yüksek Lisans Tezi, Kimya Bölümü
Tez Danışmanı: Prof. Dr. Yaşar Dürüst

Temmuz 2013, 222 sayfa

Bu çalışmanın amacı çeşitli *N*-(5-metil-1,2,4-okzadiazolil) sabstitue *o*-benzosülfimid, *N*,*N'*-(5-metil-1,2,4-okzadiazolil) disubstitue uracil, *N*,*N'*-(5-metil-1,2,4-okzadiazolil) disabstitue 5-amino uracil ve *N*,*N'*-(5-metil-1,2,4-okzadiazolil)disubstitue benziliden pirimidindion sentezidir.Biyoaktif potansiyeli olabilecek çeşitli heterohalkalı bileşikleri oluşturmak için yıllardır 1,2,4, okzadiazol iskelet yapısında bileşikler kullanılmaktadır. Bu çalışmayı gerçekleştirmek için öncelikle *p*-substitue benzonitrillerden kolay bir şekilde elde edilen *p*-substitue benzamidoksimlerden 5-klorometil 1,2,4 okzadiazol

hazırladık. Literatür bilgimiz dahilinde, *N*-okzadiazolilmetil substitute *O*-benzosulfimid, *N*-okzadiazolilmetil substitue uracil, *N*-oksadiazolilmetil substitue 5-amino uracil ve *N*-okzadiazolilmetil substitue pirimidindionlar şimdiye kadar bildirilmemiştir.

Tüm son ürünlerin yapıları IR, NMR (^{1}H, ^{13}C), LC-MS spektrumları ve fiziksel sabitler (erime noktası, Rf değerleri) ile aydınlatıldı. Bu yeni bileşiklerin hepsi okzadiazol gibi gruplar içerdiği için biyoaktiflikleri incelenecektir.

Anahtar Kelimeler: amidoksim, 1,2,4 okzadiazol, *o*-benzosulfimid, uracil, 5-amino uracil, pirimidindion, spektroskopi

TO MY FATHER AND MOTHER

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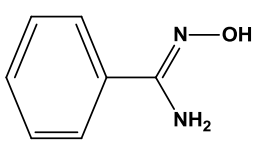
I would like to thank my family especially my brothers and Esra Gül for their strong support and encouragement of my studies and their patience.

FORMULAE



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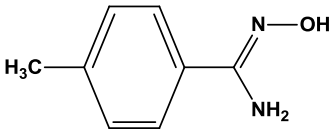

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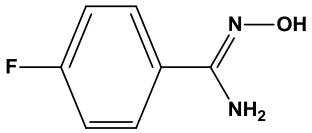

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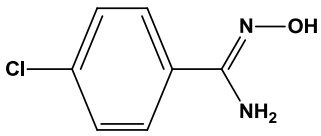

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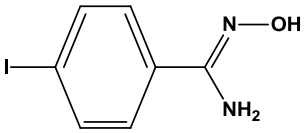

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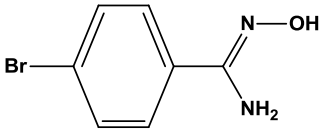

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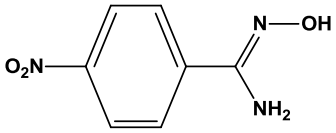

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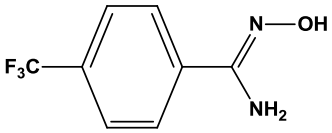

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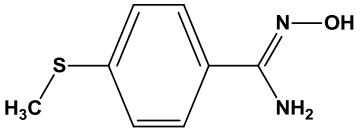

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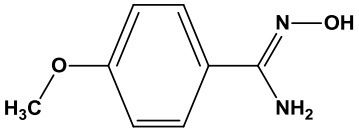

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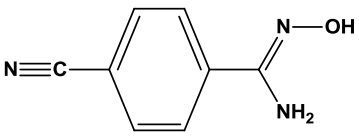

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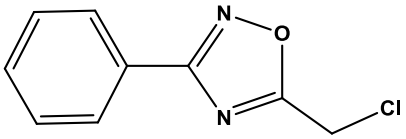

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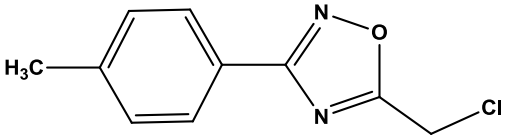

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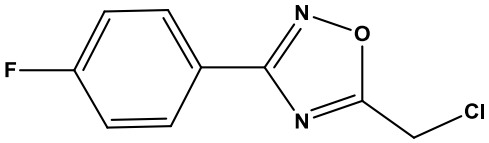

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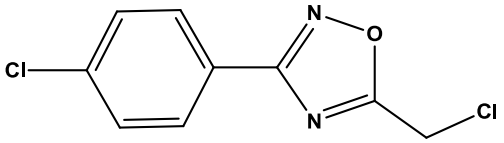

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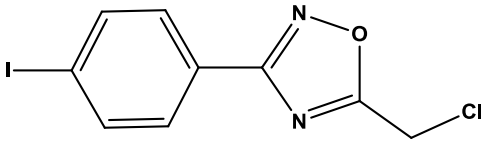

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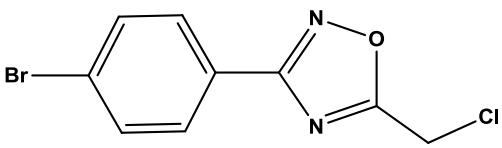

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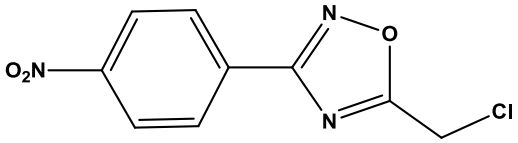

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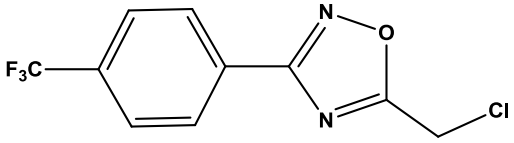

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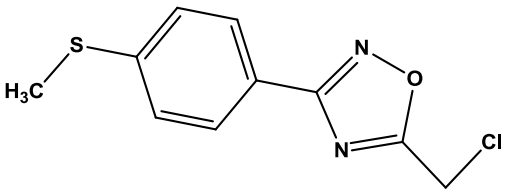

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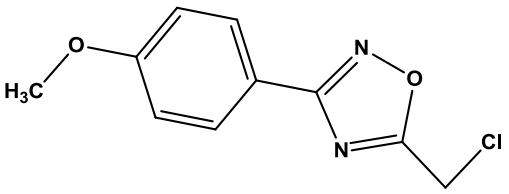

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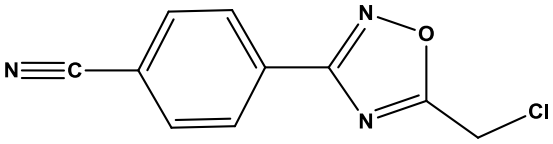

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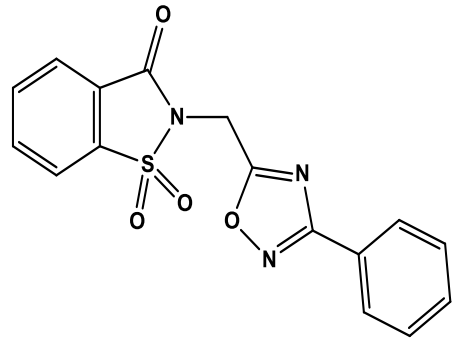

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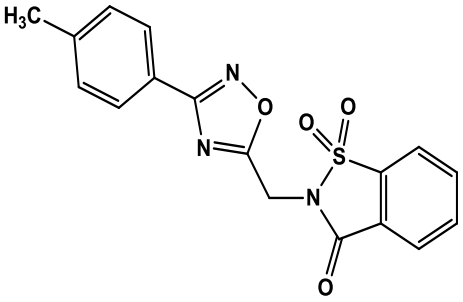

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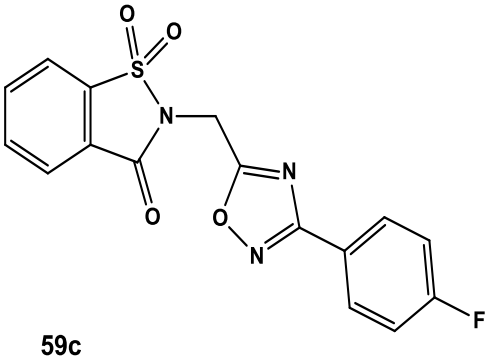

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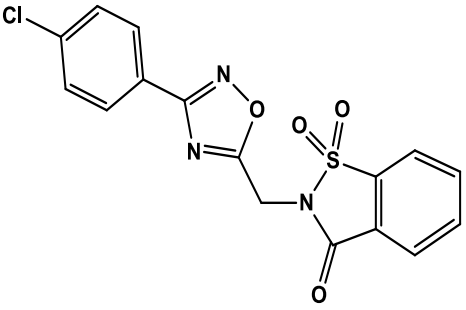

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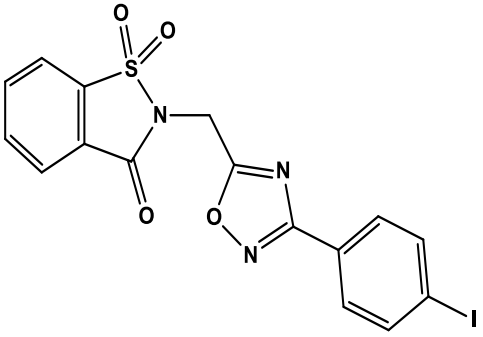

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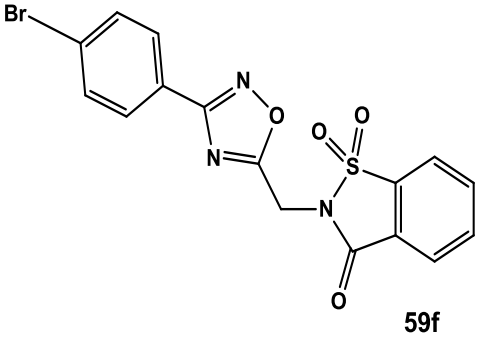

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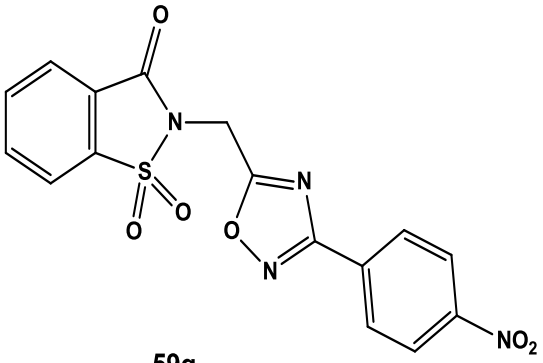

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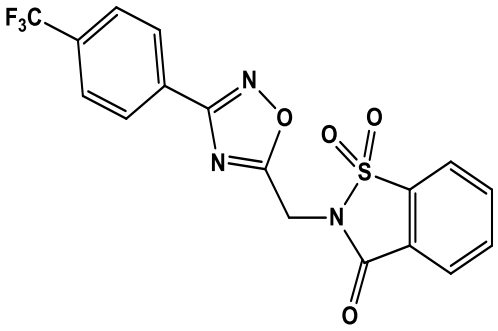

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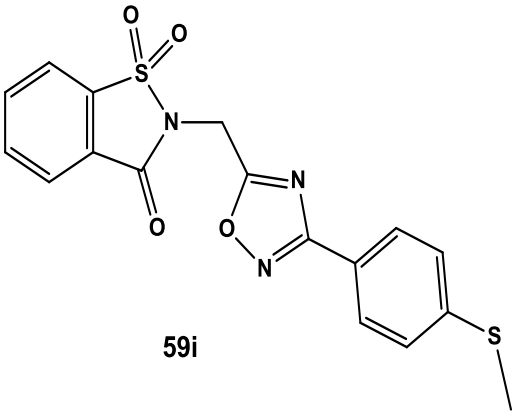

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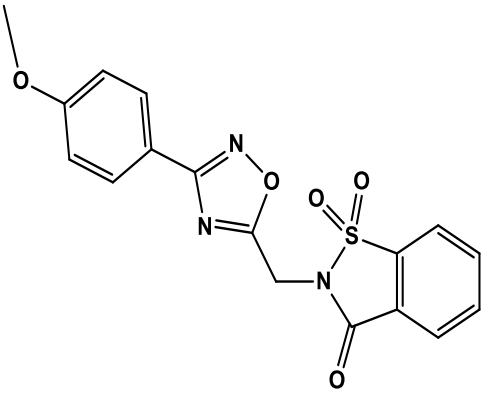

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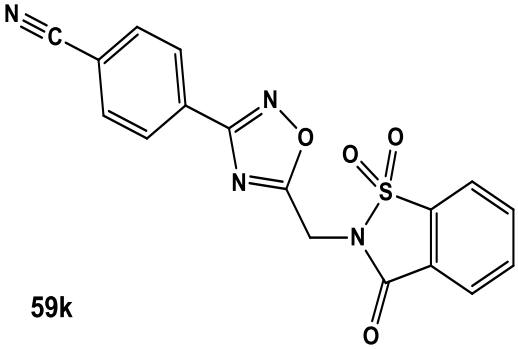

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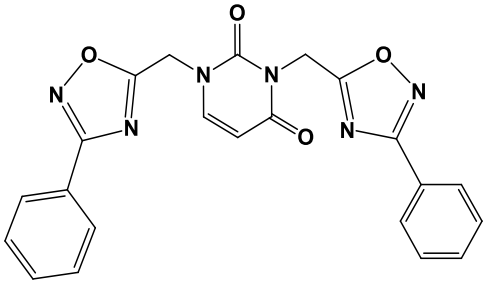

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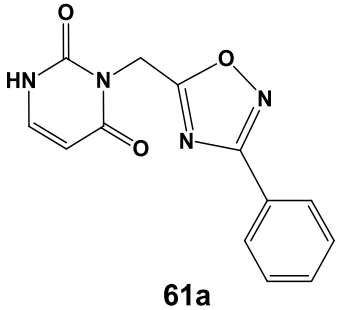

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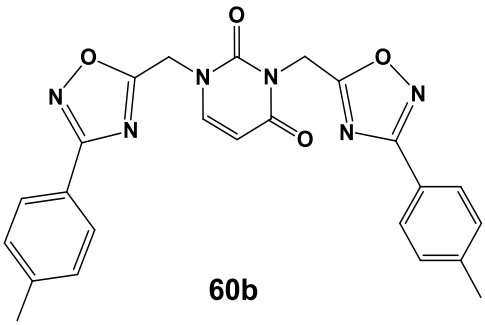

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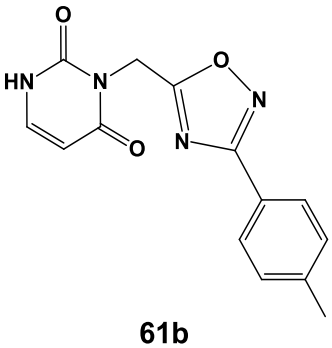

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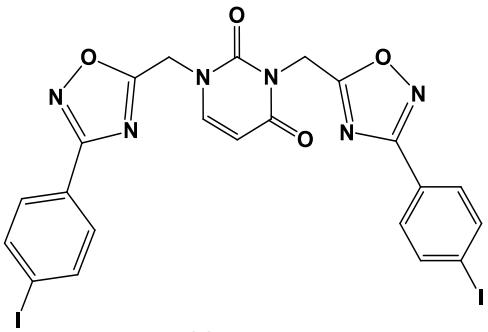

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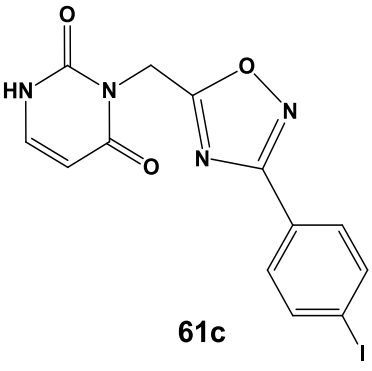

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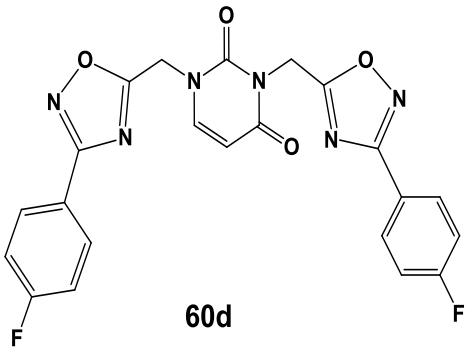

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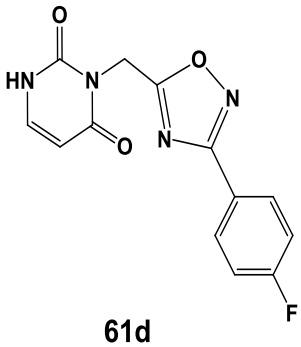

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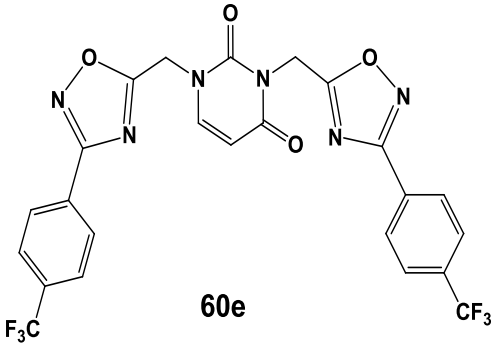

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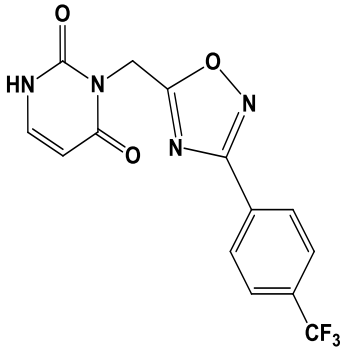

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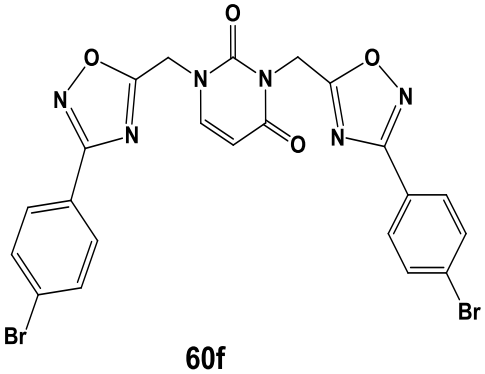

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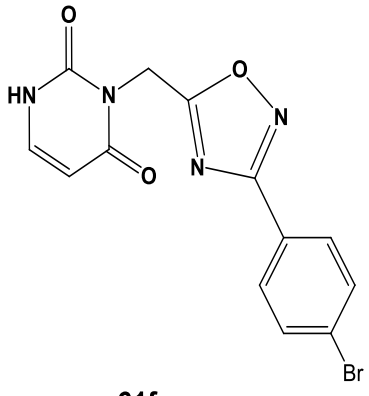

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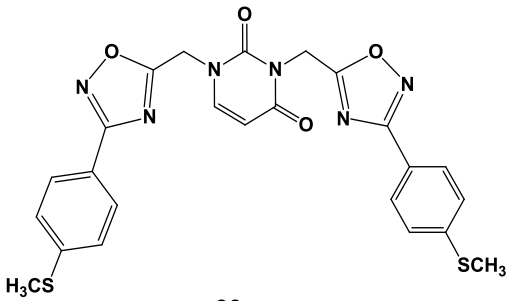

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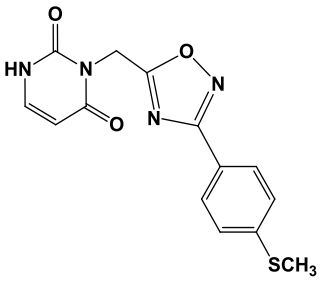

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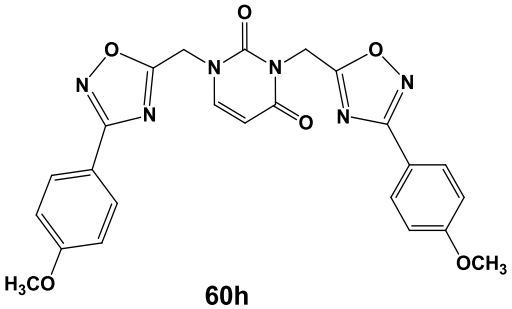

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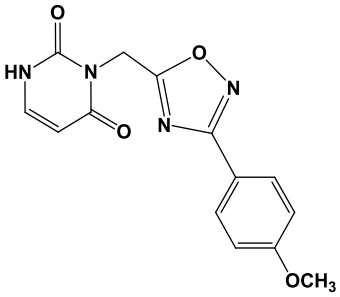

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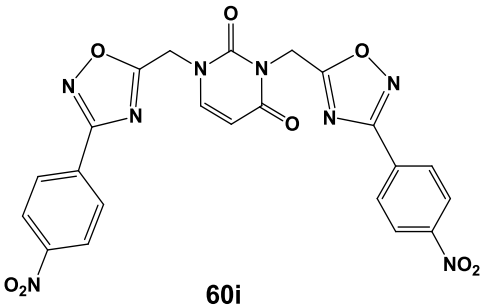

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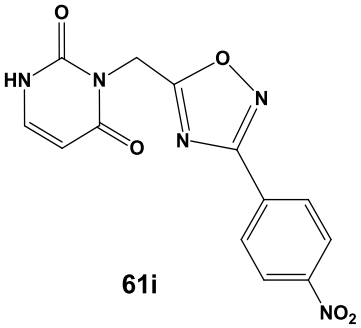

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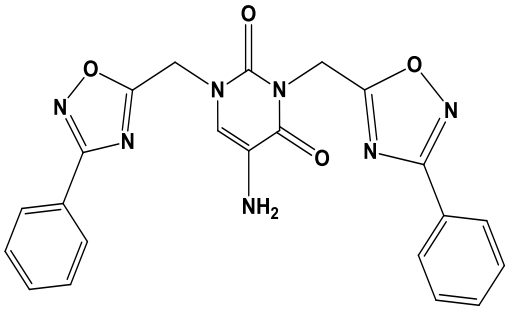

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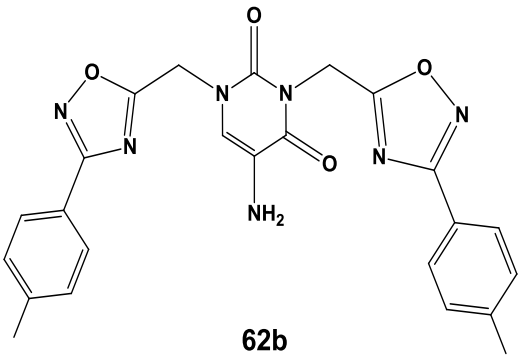

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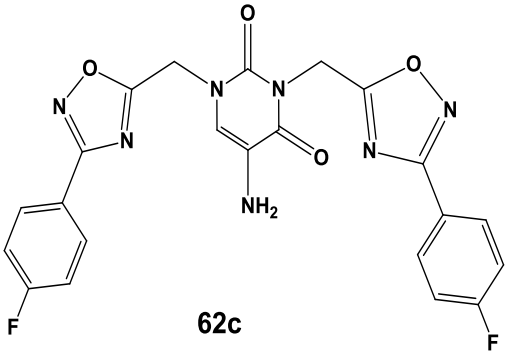

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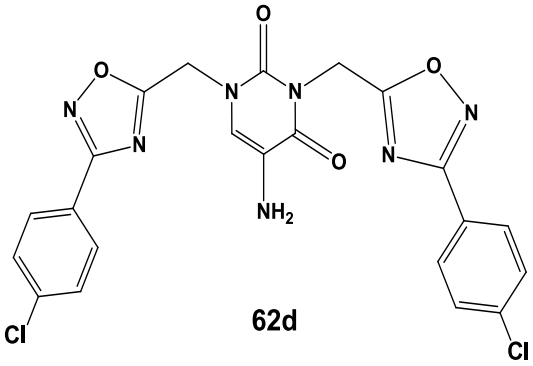

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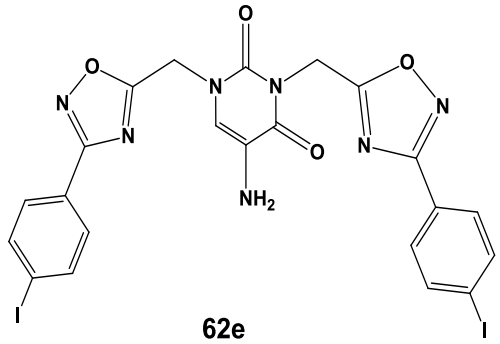

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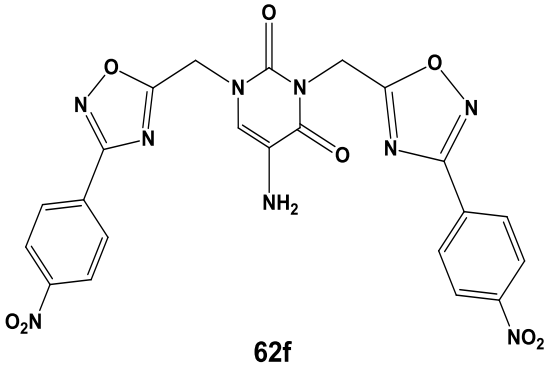

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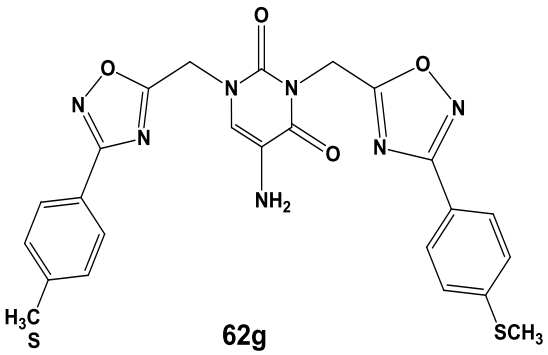

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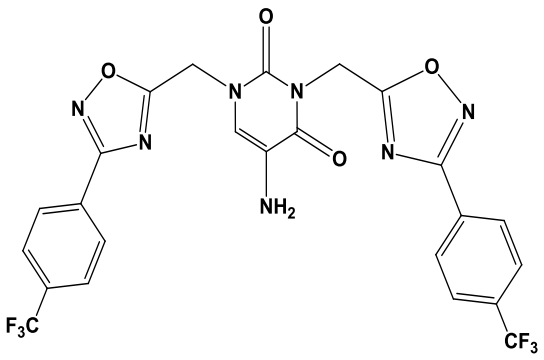

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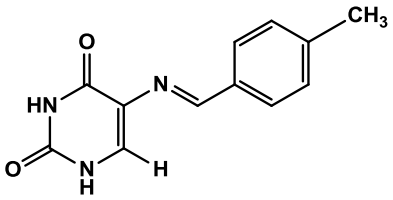

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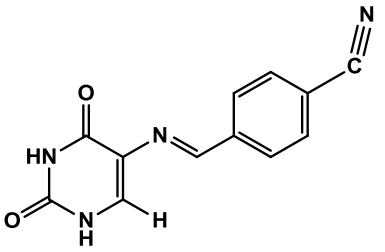

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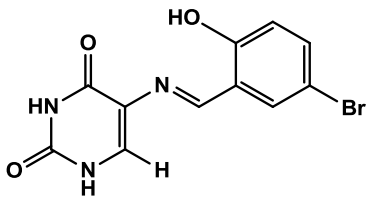

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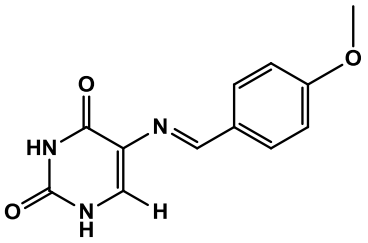

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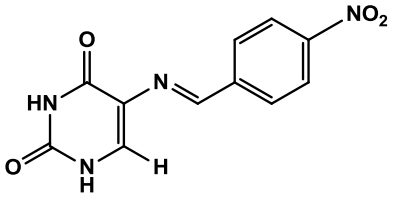

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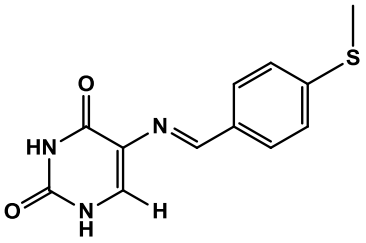

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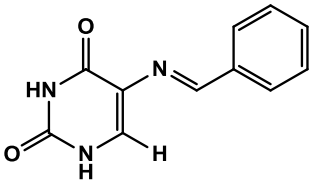

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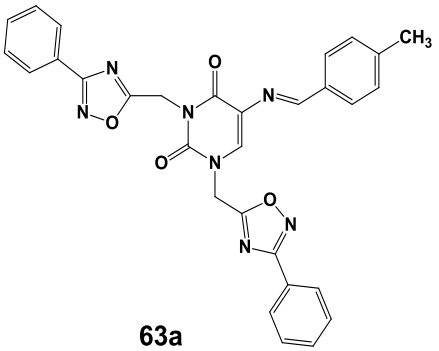

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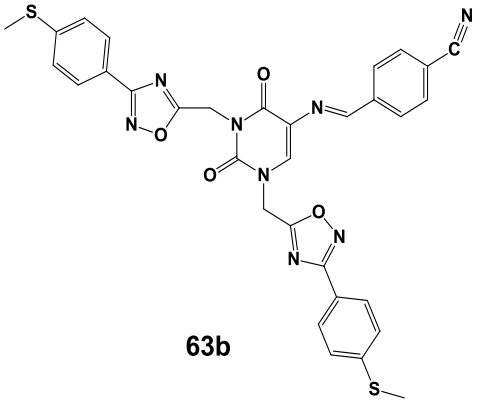

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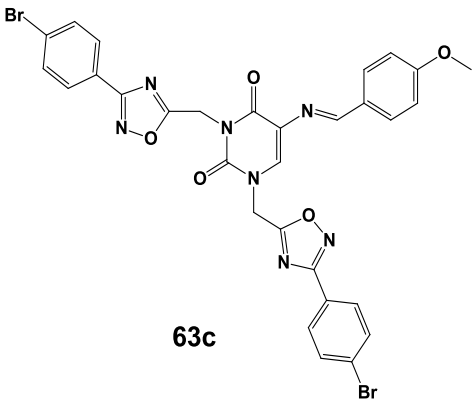

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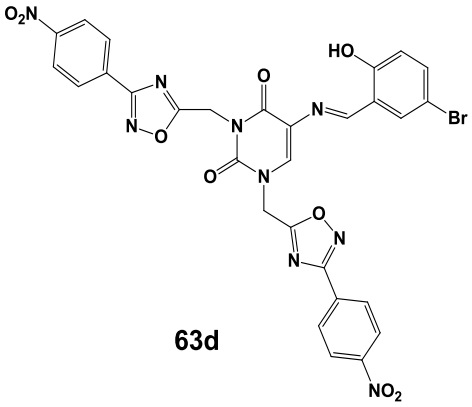

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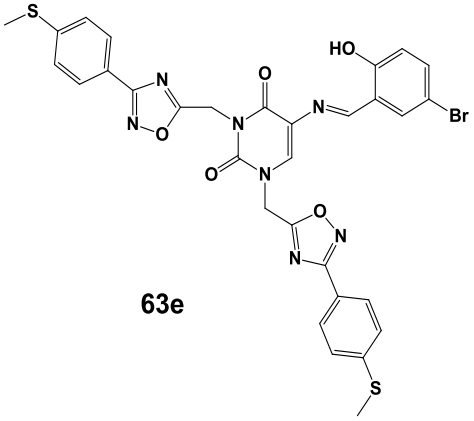

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ABBREVITAIONS

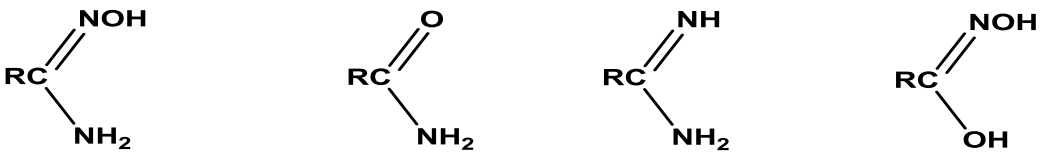
a.q	Aqueous
cm	Centimetre
DCC	Dicyclohexylcarbodiimide
DMF	N,N-Dimethylformamide
DMSO- d_6	Dimethylsulfoxide- d_6
Et_3N	Triethylamine
EtOAc	Ethyl acetate
Hz	Hertz
IR	Infrared spectroscopy
KBr	Potassium bromide
LC-MS	Liquid Chromatography-Mass Spectroscopy
m.p	Melting point
MS	Mass
MW	Microwave
NMR	Nuclear magnetic resonance
Ppm	Parts per million (NMR)
Rf	Retention Factor
r.t	Room temperature
TLC	Thin Layer Chromatography
EDC	3-(dimethylamino)propyl]-3-ethyl carbodiimide)
CDI	carbonyldiimidazole
HOBt	Hydroxybenzotriazole

CHAPTER I

INTRODUCTION

1.1.AMIDOXIMES

Amidoximes carry both amino and hyroximino functionality at the same carbon, due to this property they associate with amidine amides and hydroxamic acids [1]. The amidoxime function **(1a)** can be considered either as an amide **(1b)** in which the oxygen atom of the carbonyl group has been replaced by an isonitroso group, or as an amidine **(1c)** Whose hydrogen atom of the imido group has been exchanged for hydroxy radical. **(1d)** (Figure 1.1)

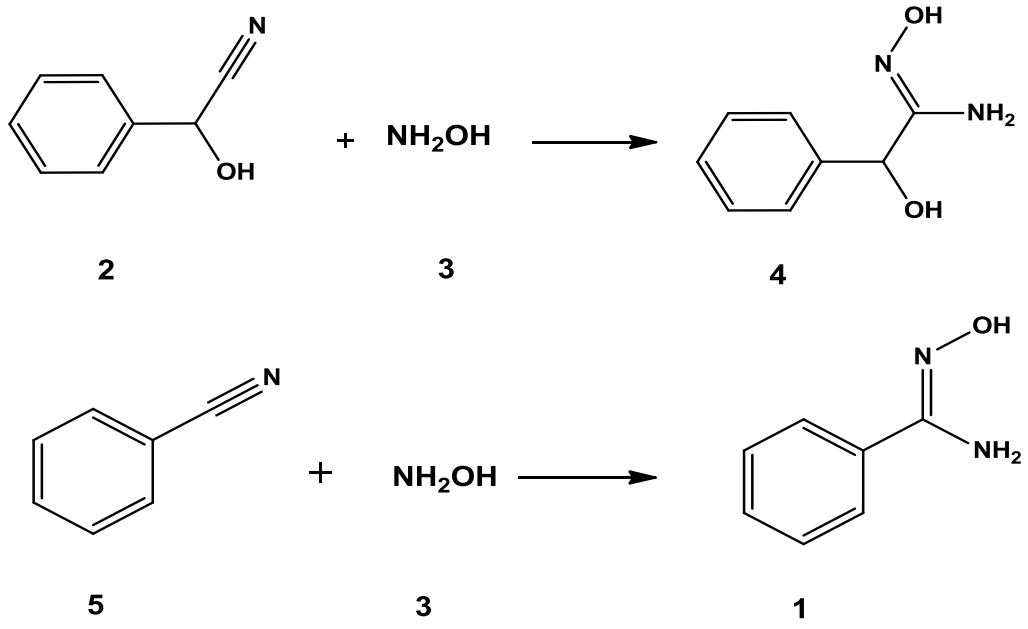


1a **1b** **1c** **1d**

Figure 1.1. Structure of amidoxime function

The name “amidoximes” **1** were first exploited by Tieman who brighten the structure of this class of compounds in 1884. Despite the fact that

Lossen and Schifferdecker first prepared amidoxime in 1873 from hydrogen cyanide and hydroxylamine. These authors didn't determine the structure of these compound which is called "isosuretin". Tieman identified a structural formula, naming it "amidoxime". He formulated two dependent compounds **4** and **1** by the addition reaction of hydroxylamine **3** to benzaldehyde cyanohydrins and benzonitrile [2] (Scheme 1.1).



Scheme 1.1. Synthesis of mandelamidoxime and benzamidoxime

Tautomerism is important characteristics associated with amidoximes. Although amidoximes have been known since the late 1800's, a review by Eloy and Lenaers in 1962 only briefly mentioned the tautomeric questions [3]. Amidoximes can be existed in two tautomeric forms [4].Structure **1e** has been accepted as the correct structure of amidoximes.

Figure 1.2. Structures of tautomers of amidoxime

Depending on the nature of substitution at their amido nitrogen, amidoximes can adopt a *Z* **1g** or an *E* **1h** configuration. *Z* form is more stable [5] in the case of unsubstituted (R^2=R^3) and N-monosubstituted (R^3=H) amidoximes. The relative stability of the *Z* form is believed to be a consequence of intramolecular hydrogen bonding together with the fact that interaction of oxygen and amido nitrogen lone pairs should destabilize the *E* configuration. (Figure 1.3)

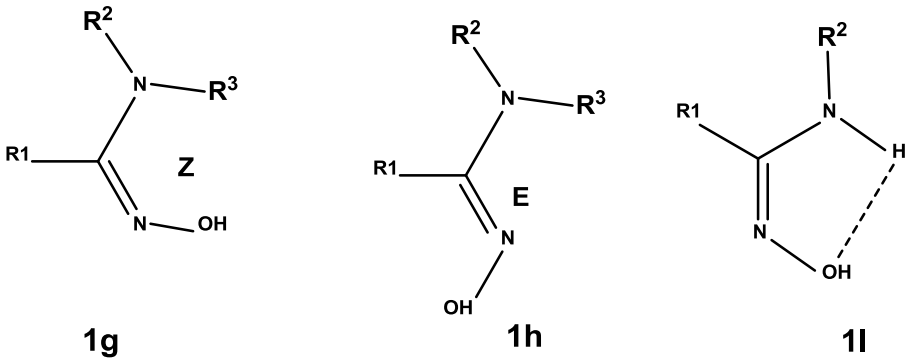


Figure 1.3. *Z* (g) and *E* (h) configurations of an amidoxime and hydrogen bonding within an N-monosubstituted *Z* amidoxime (I).

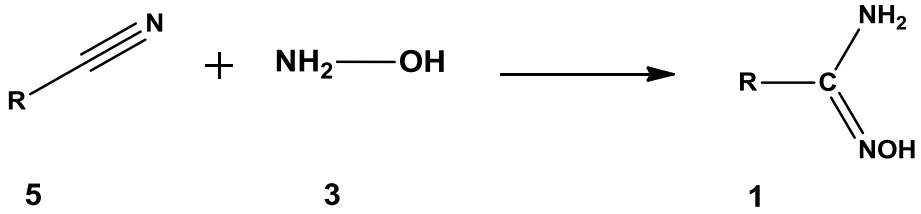
Amidoximes constitute an important class of compound in their own right and have been employed for the synthesis of a variety of valuable compounds. Their importance in chemistry, along with their rich biology, makes amidoximes an attractive target for medicinal chemists, biochemists and biologists [6].

1.1.1.Synthesis of Amidoximes

1.1.1.1.By Action of Hydroxylamines on Nitriles

This is the most used process by Tieman and Krüger [7] due to obtained amidoximes by using hydroxylamine hydrochloride. (Scheme 1.2)

Nucleophilic addition to nitriles **5**, RC≡N, represents an attractive route to new organic compounds [8]. Barros *et al.* reported that nitriles undergo addition reactions with ammonia, hydroxylamine **3**, and hydrazine which is used for preparation of amidoximes, amidrazones amidine and hydroxamic acid in organic synthesis.



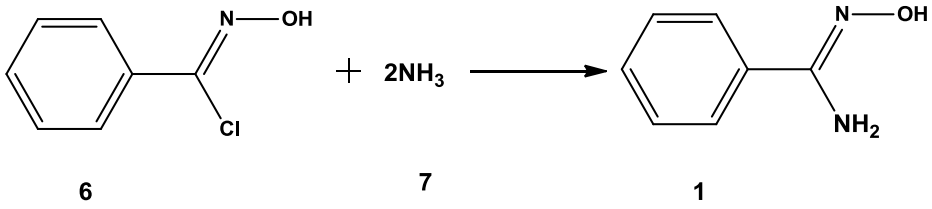
Scheme 1.2. Action of hydroxylamine on nitriles

The experimental procedure consists liberating hydroxylamine from its hydrochloride by 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.

1.1.1.2.By action of Ammonia on Hydroximic Acid Chlorides(chloroximes)

Chlorination of aldoximes leads to hydroximoyl chlorides **6** (Hydroximic acid chloride). These compounds react easily with ammonia **7** to prepare amidoximes. By using this method, Werner prepared benzamidoxime, *o*-chlorobenzamidoxime [9] and terephthalamidoxime [10] (Scheme1.3).

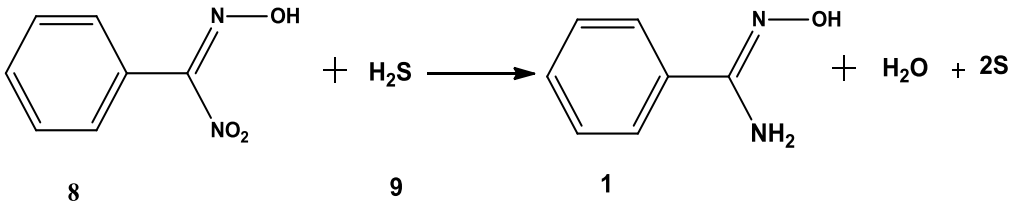


6 7 1

Scheme 1.3. Action of ammonia on hydroximic acid chlorides

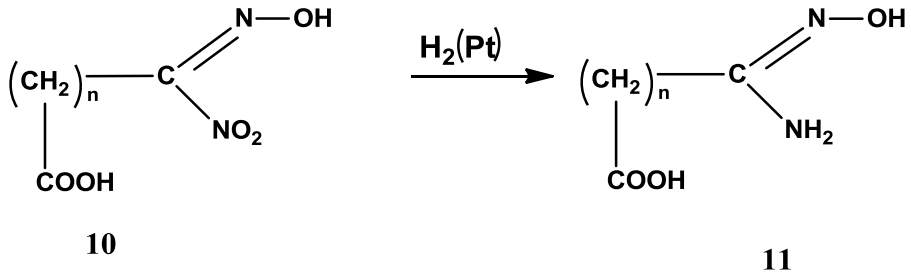
1.1.1.3.By Reduction of Nitrosolic and Nitrolic Acid

Wieland and Bauer [11] prepared benzamidoxime by reduction of nitrosolic acid **8** with using hydrogen sulfide **9**.



Scheme 1.4. Reduction of nitrolic acids to amidoximes

The preparation of monoamidoximes of dicarboxylic acids was found by using a general method [12] by catalytic reaction of nitrolic acids (Scheme1.5).

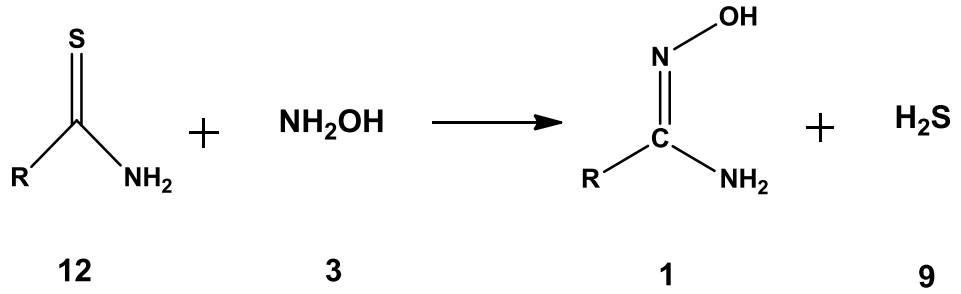


Scheme 1.5. Catalytic reduction of nitrolic acids to amidoximes

1.1.1.4.By Action of Hydroxylamine on Amides or Thioamides

Some aromatic amidoximes have been prepared by the action of hydroxylamine **3** on thioamides **12**.The procedure for synthesis amidoximes **1** from nitriles is the same as the procedure for synthesis from thioamides.

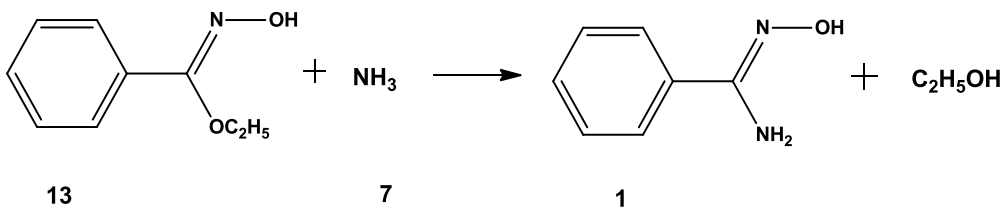
Due to the fact that hydroxylamine is liberated from its hydrochloride by an equivalent amount of aqueous sodium carbonate. The thioamide is then introduced and ethanol is added until the mixture is clear. The solution is refluxed for a few hours and the amidoxime isolate



Scheme 1.6. Action of hydroxylamine on thioamides.

1.1.1.5.By Action of Ammonia on Oximinoethers

Ethyl benzhydroxamic acid and an alcoholic solution of ammonia **7** are heated in pressure bottle for 8 hrs. at 175°C to yields benzamidoximes [13].This reactions are not found in general applications.(Scheme 1.7)



Scheme 1.7. Action of ammonia on oxoiminoethers

1.1.1.6.By Action of Hydroxylamine on Iminoethers

Ethylimino benzoate **14** is threated with hydroxylamine by Pinner [14] to obtained benzamidoximes.

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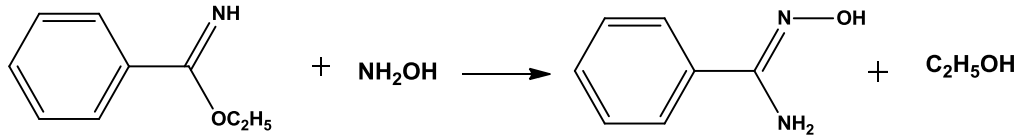


14 3 1

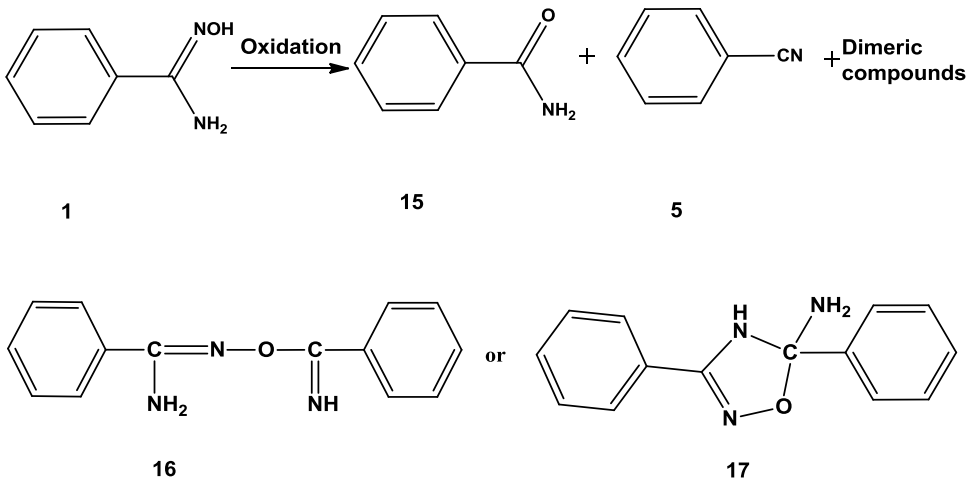
Scheme 1.8. Action of hydroxylamine on iminoethers

1.1.2.Properties of Amidoximes

1.1.2.1.Chemical Properties and Reactions of Amidoximes

1.1.2.1.1.Oxidation

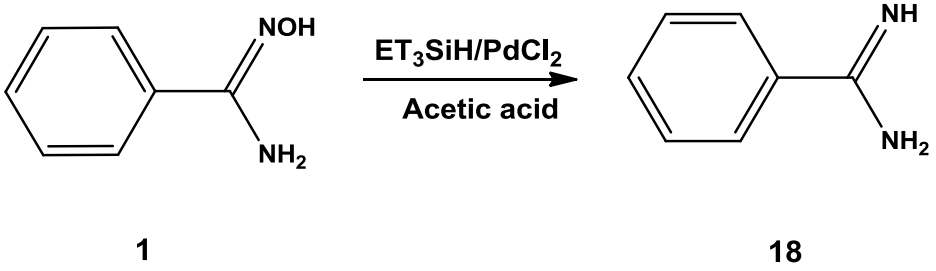
The oxidation of amidoximes generally leads to a mixture of compounds, including the corresponding amide **15** and nitrile **5** as well as "dimeric" products **16** (or **17**) with a formula corresponding to **16** arylamidoximes [NH_2OH] [15] (Scheme1.9). Stieglitz were first reported in 1889 [16]. He concerned with the oxidation of benzamidoxime with potassium ferricyanide in KOH. A cyclic dimeric structure was initially proposed for the main product of this reaction. Later, formation of the same product has been reported to occur during oxidation of benzamidoxime by acidic solutions of Cl_2 or Br_2, and by iodine in aqueous bicarbonate.



Scheme 1.9. The oxidation of arylamidoximes

1.1.2.1.2.Reduction

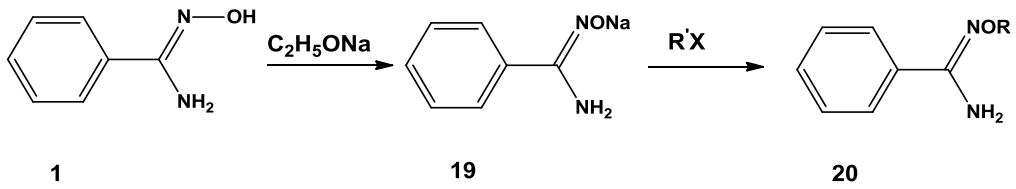
Amidoximes have been directly reduced to amidine **18** by transition metal catalyzed method. Catalytic hydrogenation with palladium on charcoal proceeds well in the presence of acetic anhydride as an acylating agent [17]. The reduction of amidoximes with potassium formate [18] or ammonium formate in acetic acid using Pd/C reduction proceeded only with 100% by weight of catalyst(Scheme 1.10).



Scheme 1.10. Reduction of amidoxime.

1.1.2.1.3.*o*-Alkylation

Salts of amidoximes, obtained from sodium alcoholate, treated with aliphatic halogen compounds yield to *o*-alkyl ethers **20** [19] (Scheme1.11).



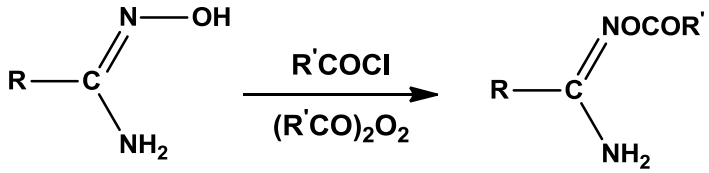
1 **19** **20**

Scheme 1.11. *o*-Alkylation of amidoxime

Potassium or sodium hydroxide in aqueous alcoholic solution can be used instead of sodium ethoxide [20].

1.1.2.1.4.Acylation

Acid chlorides or anhydrides. Acylated the amidoximes readily at room temperature (Scheme 1.12).



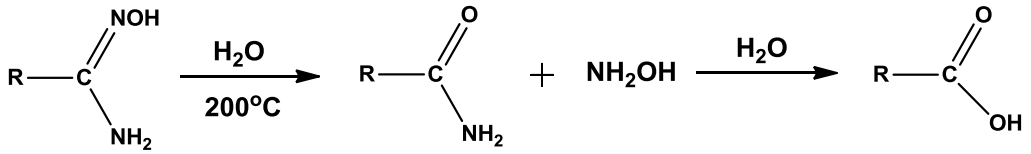
1 **21**

Scheme 1.12. Acylation of amidoxime

Also the infrared spectra of the acyl derivatives show the presence of the NH_2 and -O-CO-groups and the absence of the broad OH-absorption band at about 3.2m [21].

1.1.2.1.5.Hydrolysis

Many amidoximes hydrolyzed completely when heated in the same media. Amides and hydroxylamine formed, and under drastic conditions the amides hydrolyzed into the corresponding acids [22].



1 15 3 22

Scheme 1.13. Hydrolysis of amidoximes

At 200°C, a solution of ammonium hydroxide hydrolyzes benzamidoxime into benzamide and ammonium benzoate [23]. Oxamidedioxime is hydrolyzed by concentrated hydrochloric acid into oxalic acid, ammonia, and hydroxylamine [24].

1.1.2.1.6.Salt Formation

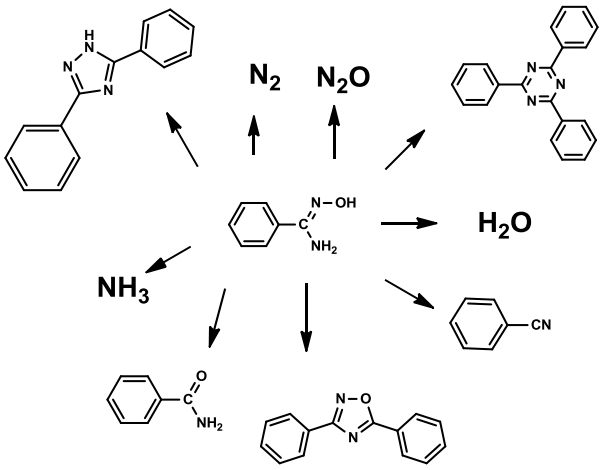
The amidoximes are amphoteric substances, soluble in dilute mineral acids as well as in aqueous alkaline solutions [25].

The hydrogen atom of the NOH group can be substituted, as in the case of oximes, by a metal and many sodium and silver salts have been described. On the other hand the amino groups in the amidoximes show basic properties.

Salts of amidoximes with mineral or organic acids are crystallize easily and have well defined melting points [26]. In addition to this, amidoximes form colored crystalline compounds with the salts of some metals [27]. A great number of such compounds with different amidoxime was prepared and proved that they are internal complexes where the metal atom is linked to the oxime group as well as to the amino group by Werner [28].

1.1.2.1.7.Thermal Decomposition

Generally, amidoximes decomposed when heated in the neighborhood of their melting point. Benzamidoxime, that is melting at 80°C stable up to 170 ^{o}C. At this temperature it decomposes, producing several products which were identified [29] as nitrogen, nitrous oxide, ammonia, water, benzonitrile, benzamide, diphenyl-1,2,4-oxadiazole, diphenyl-1,2-Ptriazole and triphenyl- 3,5- triazine (Scheme 1.14).



Sheme 1.14. Thermal decomposition of benzamidoxime

1.1.2.2.Physical Properties

The amidoximes are colorless, crystalline compounds. Aryl amidoximes, which are soluble in alcohols and some organic solvents and insoluble in water, are more stable than aliphatic amidoximes.The solubility of aliphatics in water decrease with increasing molecular weight, but the first series are soluble [30].

When amidoximes identified by IR spectra the free OH strecthing absorbtion can easily observed in chloroform solution near 3600 cm^{-1}. The asymetric and symmetric NH_2 stretching modes can be observed as two sharp band near 3500 and 3400 cm^{-1} either in chloroform, benzene acetonitrile, or in solid state. At last all amidoximes exhibit a very strong band between 1650 and 1670 cm^{-1} both in solid state and solution.

1.1.2.3.Biological Properties

The importance of amidoximes in chemistry, along with their rich biology [31] makes amidoximes an attractive target for medicinal chemists, biochemists and biologists.

Amidoximes have exhibited important biological activities for example as antitumor agents [32] antibacterial [33] and antifungal [34].

A number of amidoximes have already been used as prodrugs in clinical trials [35].

Many recent pharmaceutical applications have been enriched, with some of their mechanistic pathways converted to amidines, as well as clarification of their ability to release NO providing insight into their mode of action and allowing the design of new therapeutic agents.The nitrogen oxide generated functions as mediator in regulating diverse physiological processes such as blood pressure, neurotransmission, learning, memory, and immunomodulation [36].

1.2.OXADIAZOLE

Nitrogen, oxygen heterocycles are synthetic interest because they generate an important class of natural and non-natural products many of which exhibit useful biological activities [37].

This is particularly true for five-membered ring, like oxadiazole heterocyclic compounds which emerged as the nucleous components of a large number

of muscarinic agonists, benzodiazepine receptor partial agonists, growth hormone secretagogous [38].

There are four possible isomers of oxadiazole **(I,II, III, IV)** which relate with the position of nitrogen atom in the ring and are numbered as shown in (Figure 1.4) [39].

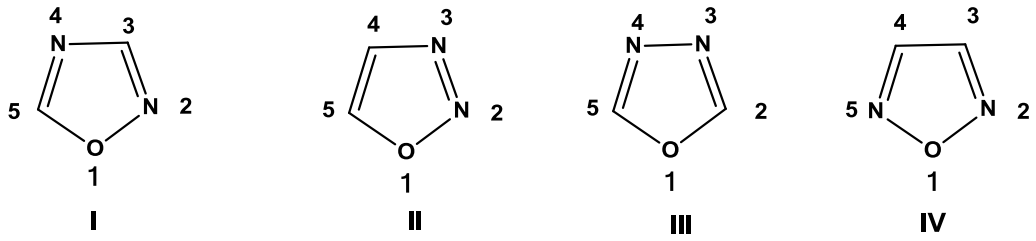
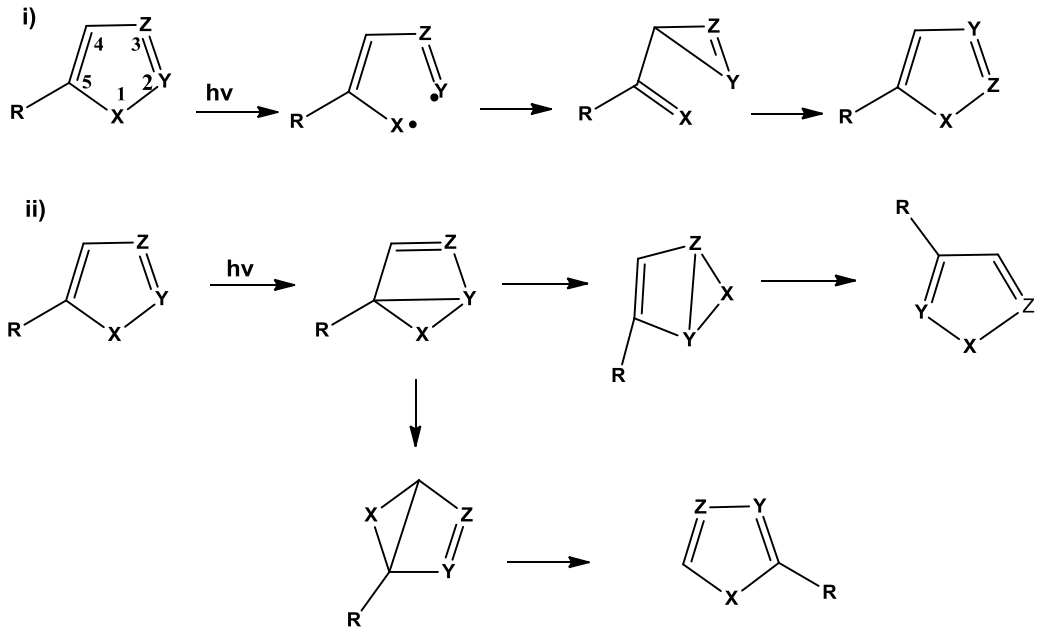


Figure 1.4. Isomers of oxadiazole

A wide class of reactions symbolized by photoinduced ring rearrangements of five-membered heterocycles which received a lot of attention for the development of synthetic procedure and the description of their mechanisms [40].

Among these, two generally observed pathways are represented by **(i)** The ring contraction-ring expansion mechanism explaining the interchange of two adjacent ring atoms and involves a three-membered ring intermediate, and **(ii)** the internal cyclization–isomerization route (also named as electrocyclic ring closure-heteroatom migration route), which involves an initial bicyclic isomer (the Dewar isomer) through the formation of a bond between positions **2** and **5** of the starting ring, followed by a sigmatropic shift to form the rearranged ring [41] (Scheme 1.15).



Scheme 1.15. The photoisomerization of five-membered heterocycles

1.2.1.1,2,4- Oxadiazole

1,2,4-Oxadiazoles (Figure1.5) are a class of heterocyclic compounds that have been well studied in the literature. This class of heterocycles have attracted widespread attention due to their important biological activities such as antiviral [42], fungicide [43], herbicide [44], analgesic and anti-inflammatory [45] .

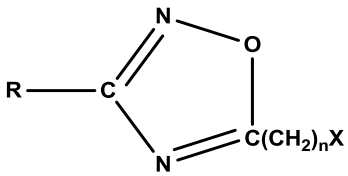


Figure 1.5. Structure of 1,2,4-oxadiazole

This motif have been used as heterocyclic amide and ester bioisoester in the synthesis of peptide building blocks and in the formation of dipeptidomimetics [46].

The 1,2,4-oxadiazole presents a high tendency to rearrange into other more stable heterocyclic systems [47]. This reactivity depends on several factors such as **(i)** The presence of a labile O-N bond [48] **(ii)** The low aromaticity [49] **(iii)**The eventual presence of a participating side-chain at C(3), **(iv)** the electrophilic character of N(2) which stems from the ability of the oxygen to act as a good internal leaving group and [50] **(v)** the electrophilic character of C(5) induced by the presence of electron-withdrawing substituents [51].

Several models can be prescribed where a common primary photoprocess involves the cleavage of the O-N bond which supposedly generates an open-chain intermediate with either a zwitterionic (**II**), diradical (**III**), or nitrene-like (**IV**) character [52] (Figure.1.6).

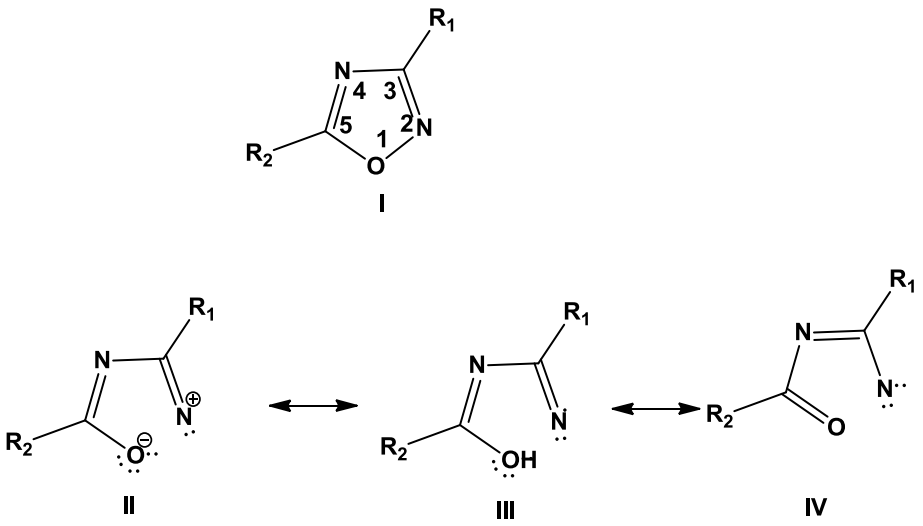


Figure 1.6. 1,2,4-Oxadiazole and its proposed first-formed photolytic intermediates

The basicity of the 1,2,4-oxadiazole ring leads many sight of its chemical reactivity and is an essential factor influencing practical use of compounds. 1,2,4-oxadiazoles are weak organic bases, therefore the ability of these

heterocycles to form azolium (‘quaternized’) salts has examined it has been suggested that the ‘quaternization’ of 5-phenyl-1,2,4-oxadiazoles takes place at N(2) predominantly because of steric reasons [53]. Brown and Ghosh undertook pK_{BH}^{+} values for 3-methyl- and 3,5-dimethyl-1,2,4- oxadiazoles in 1969 [54].This try has been failed because in both cases protonation of the heterocycle produced too little spectral change. But pK_{BH}^{+} values of representative 3,5-disubstituted 1,2,4 oxadiazoles been determined experimentally in aqueous H_2SO_4 using ^{1}H-NMR and UV spectroscopy in presents.

Several methods have been reported for the synthesis of 1,2,4-oxadiazoles. Between those the condensation of amidoximes with carboxylic acids [55] take place in two step. In the first step the amidoxime was prepared by the addition of hydroxylamine to a nitrile compound is *o*-acylated by an activated carboxylic acid derivative [56].

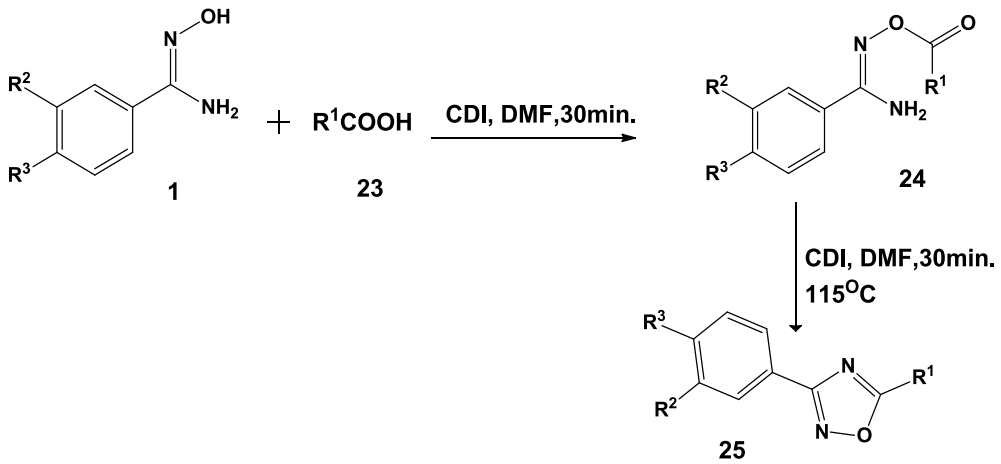
The heterocycle is subsequently formed by 1,3-dipolar cycloaddition of nitrile oxides to nitriles [57].

1.2.2.Synthesis of Oxadiazoles

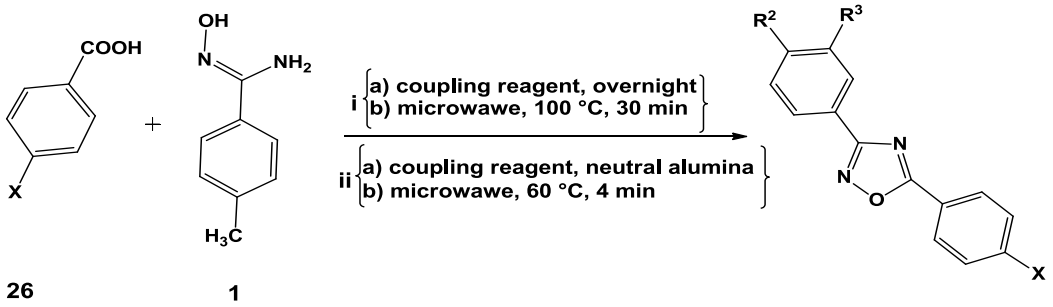
1.2.2.1.Preparation of 1,2,4-Oxadiazole from Acylation of Amidoximes with Derivatives of Carboxylic Acids

Several methods have been reported in the literature for the synthesis of these useful heterocycles. Most commonly, they have been prepared by a two-step process involving *o*-acylation of an amidoxime with an activated carboxylic acid [58]. Classically, the activated acid derivatives are esters [59]. acid chlorides [60]. Symmetrical [61], Unsymmetrical [62], anhydrides and

orthoesters [63]. In addition, carboxylic acids need a coupling reagent such as dicyclohexylcarbodiimid(DCC), 1-[3-(dimethylamino)propyl]-3-ethyl, carbodiimide(EDC), 1,1'-carbonyldiimidazole (CDI), Hydroxybenzotriazole (HOBt) or 2-(1H-Benzotriazole-1-yl)-1,1,3,3- tetramethyluronium hexa fluorophosphate(HBTU) to react [64] with amidoximes.The general approach to parallel solution-phase synthesis of 1,2,4-oxadiazoles is provided in (Scheme 1.16). Carboxylic acids **20** were activated with CDI in DMF at room temperature and treated with readily available benzamidoximes **1** in DMF. In addition to this synthesis of 1,2,4-oxadiazoles have been reported in different methods very recently. Some of them include formation of these compounds under microwave irradiation in the presence of solvent or under solvent-free conditions in which amidoximes are required as starting materials [65]. Shortening reaction times and/or improving yields, as well as to promote new reactions were investigated in the presence of solvent, the *o*-acylation of an amidoxime with a few carboxylic acids mediated by some peptide coupling reagents and the subsequent cyclization reaction [38] (Scheme 1.17).



Scheme 1.16. Parallel synthesis of 1,2,4-oxadiazole using CDI activation



26 **1** **27**

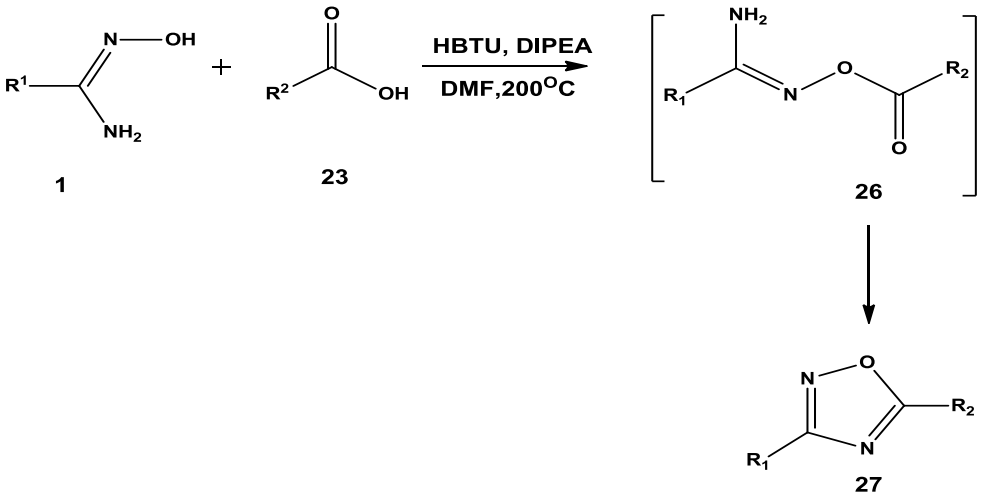
X= H, NO_2,OCH_2CH_3

i=solution method

ii=solvent free method

Scheme 1.17. General synthetic procedure of 1,2,4-oxadiazole derivatives

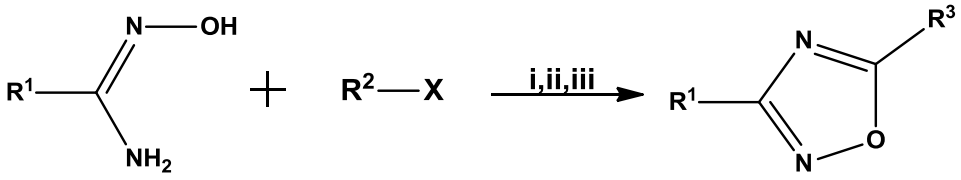
An existing synthetic way involves the coupling of amidoximes with carboxylic acids in the presence of *O*-benzotriazol-1-yl-*N*,*N*,*N*_,*N*_tetramethyluronium tetrafluoroborate(TBTU), 1-hydroxybenzotriazole hydrate(HOBt) and excess *N*,*N*-diisopropylethylamine (DIPEA) followed by in situ thermal cyclization at 110°C [66] (Scheme 1.18).



1 **23** **26** **27**

Scheme 1.18. Synthesis of 1,2,4 oxadiazole by coupling agent

Other methods to obtain 1,2,4 oxadiazoles which include reactions of amidoximes with aryl halides in the presence of palladium catalysts, or with aldehydes followed by oxidation (Scheme1.19)



1 27

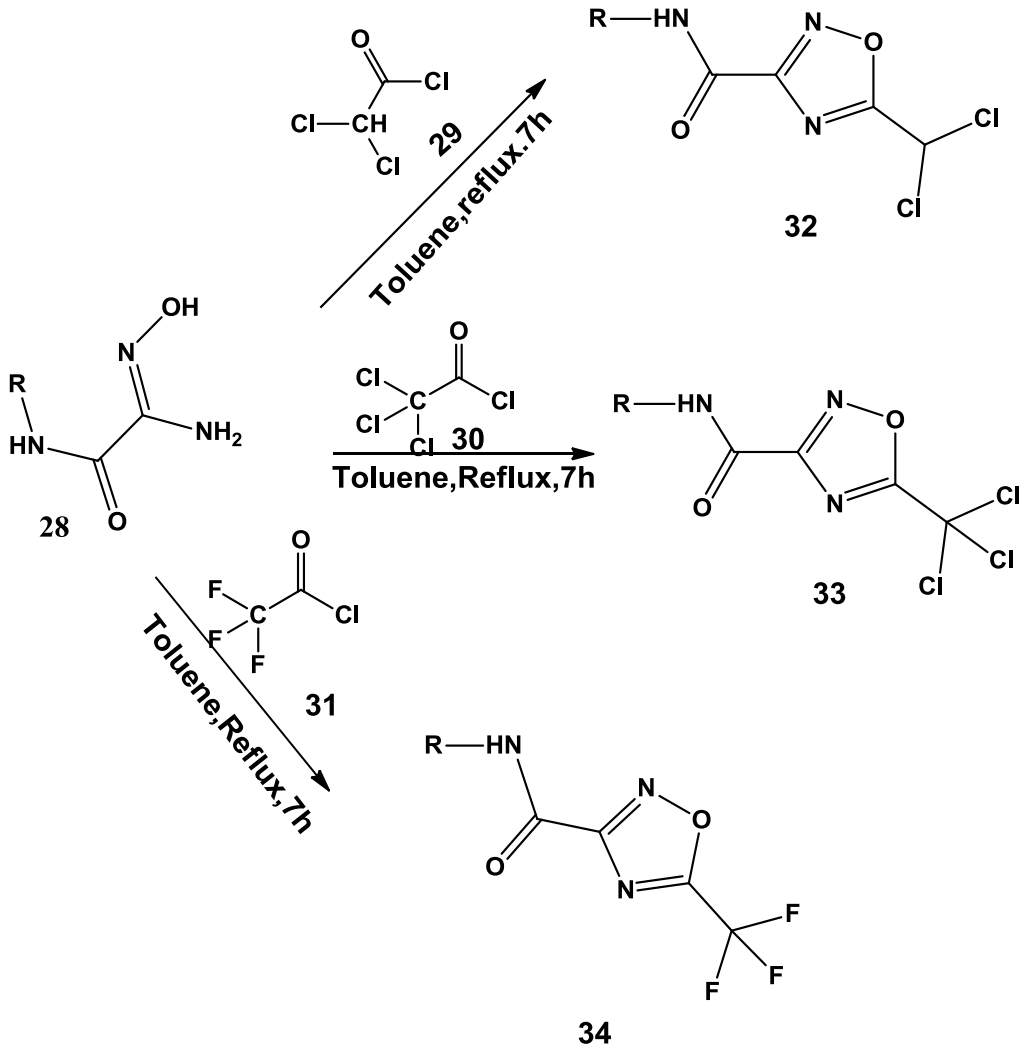
i:X= -C(O)Cl, -C(O)F, -C(O)O-C(O)R^2

ii:X= -C(O)OH, coupling reagent

iii:X=-Hal(R^2=Ar), -CHO, -CN

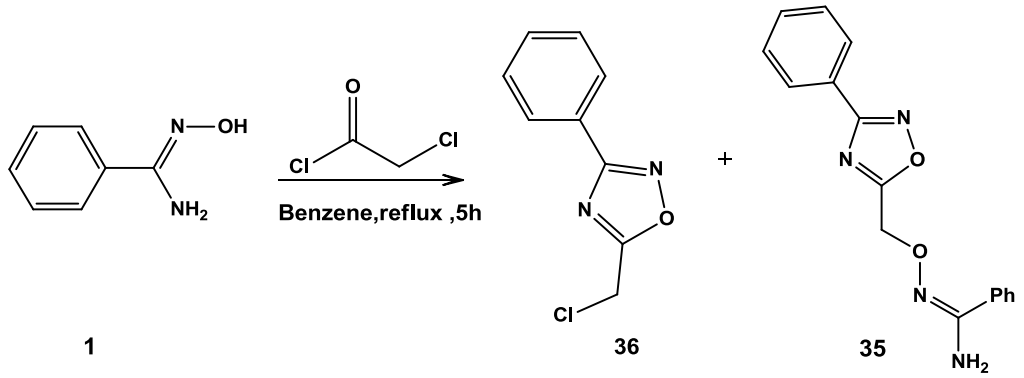
Scheme 1.19. Synthesis of 1,2,4-oxadiazole by oxidation

Yarovenko *et al.* isolated 1,2,4-Oxadiazoles as the only products of reactions between carbamoylamidoximes and chloroanhydrides and anhydrides of halogenoacetic acids [67] (Scheme1.20).



Scheme 1.20. Synhtesis of 1,2,4-oxadiazole from anhydride of halogenoacetic acid.

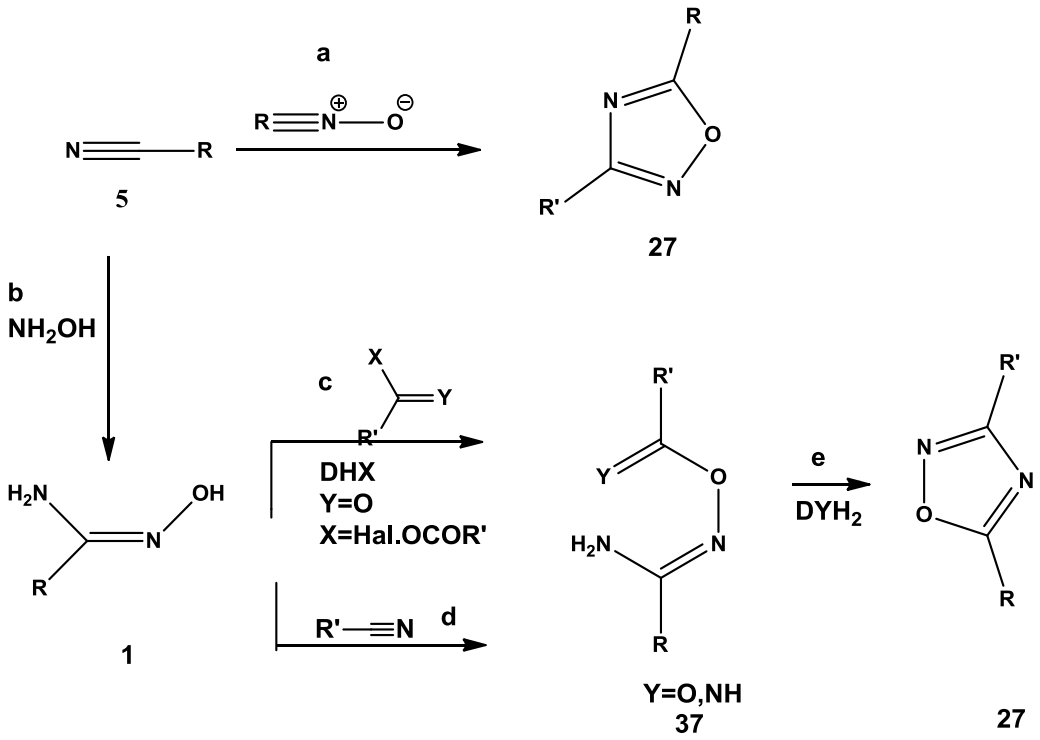
Aliphatic and aromatic amidoximes participate equally as well. By using chloroacetyl chloride in the acylation of amidoximes **1** on boiling point in benzene for formation of 1,2,4-oxadiazole **24** and 3-methyl-4H-1,2,4-oxadiazin-5(6H)-one **33** were reported by Dürüst *et al* [68].



Scheme 1.21. Synthesis of 1,2,4-oxadiazole from chloroacetyl chloride

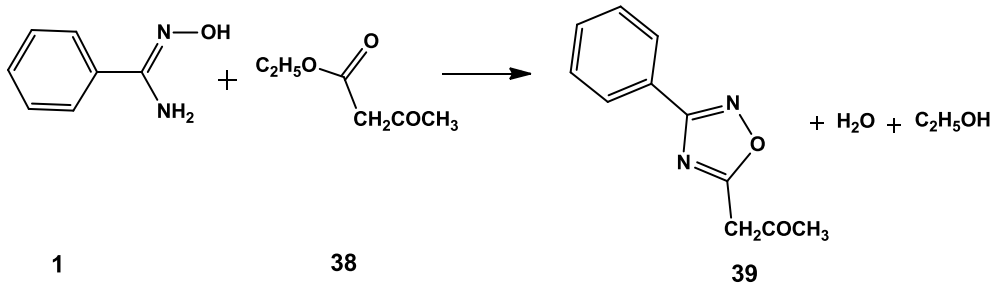
1.2.2.2.Other Methods for Preparation of 1,2,4-Oxadiazole

1,2,4-oxadiazolines have also been prepared by 1,3-dipolar cycloaddition of nitrile oxides to nitriles(Scheme1.22) (path a) and the reaction of amidoximes with activated carboxylic acids and a wide variety of their derivatives (path c and e) or nitriles (path d and e) The boxed intermediate with Y=NH shown in (Scheme1.22) has never been observed in the past, although it is known for Y=O peported by Dmitrii *et al.*



Scheme 1.22. Synthetic strategies for the generation of 1,2,4-oxadiazole derivatives

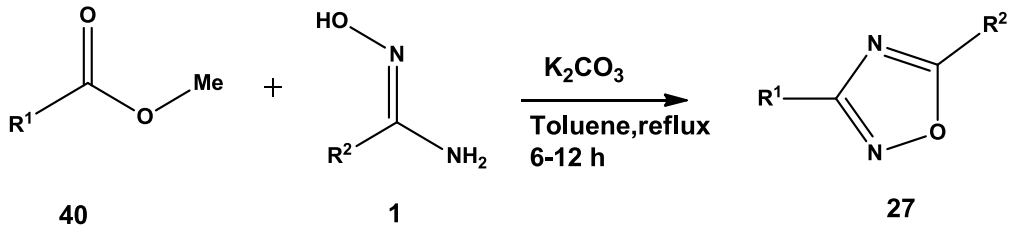
Furthermore amidoximes react on heating with an excess of ethyl acetoacetate. Although they are indifferent toward nonactivated esters. Water and ethanol are eliminated and 5-aryl-3-acetonyl 1,2,4-oxadiazoles reformed(Scheme1.23). Other *p*-ketocarboxylic esters such as ethyl benzoylacetate, *o*-methoxybenzoylacetate, and acetonedicarboxylate react similarly with aromatic amidoximes [69].



1 38 39

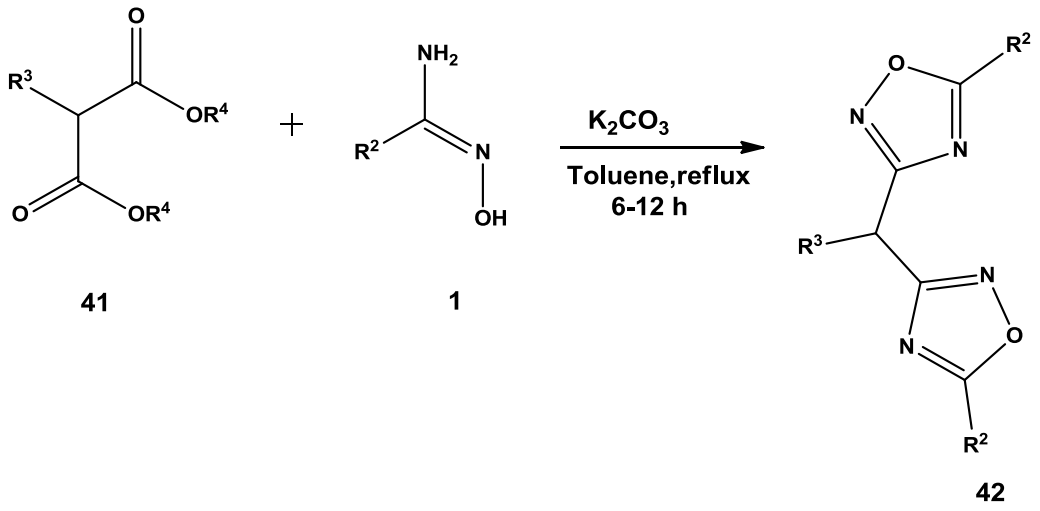
Scheme1.23. Synthesis of 1,2,4-oxadiazole reacted with, β ketocarboxylic ester

Another 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 pottasium carbonate to synthesize a variety of mono, bis, and tris oxadiazoles in moderate to excellent yields [70](Scheme 1.24), (Scheme1.25).



40 1 27

Scheme 1.24. Synthesis of 1,2,4-Oxadiazoles



Scheme 1.25. Synthesis of bis -1,2,4-oxadiazoles

1.3. IMINE

Imines are chemical compounds with carbon-nitrogen double bond where the nitrogen is also bonded to a hydrogen or a carbon chain (Figure 1.7)

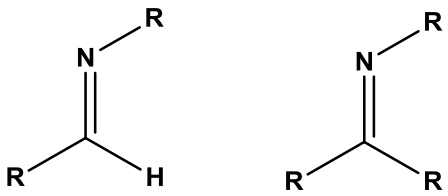
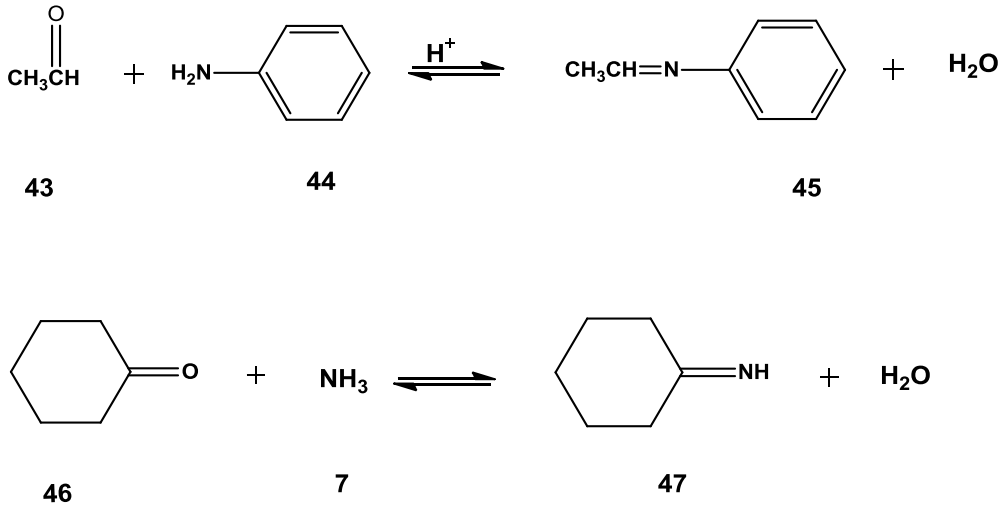


Figure 1.7. Structure of imıne functions

Imines can be prepared by various methods they can be obtained from, gem-dibromomethylaryl derivates [71] formamides [72] palladium catalyzed amination [73] as well as by polymer-supported [74] but the most common one is probably the reaction of aldehydes and ketones with amines.

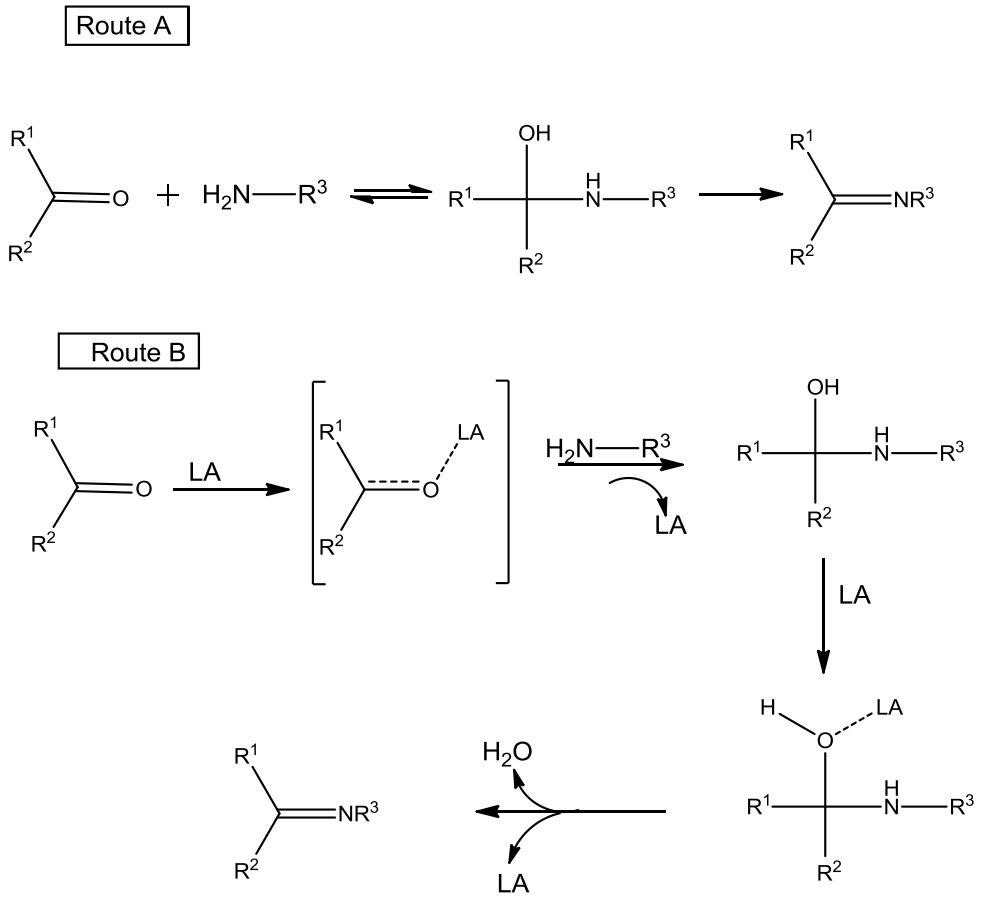
Primary aliphatic amines (RNH_2) and primary aromatic amines ($ArNH_2$) that called ammonia react with the carbonyl group of aldeyhde and ketone to give an ımıne often attribute to shiff base [75].



Scheme 1.26. Formation of imine from an aldehyde and ketone

Furthermore the condensation of amines with carbonyl compounds is a venerable and useful organic transformation as the resultant imines are used as versatile components in nucleophilic addition with organometallic reagents in cycloaddition reactions and have potential for therapeutic aplications such as lipoxygenase inhibitors, anti inflammatory agents. Various synthetic routes for the synthesis of imines are depicted. The classical synthesis of imine, originally reported by Schiff, involves condensation of carbonyl compound with an amine under azeotropic distillation to separate the liberated water.The condensation reaction has been carried out in the presence of $ZnCl_2$, $TiCl_4$, $MgSO_4$, PPTS alumina K-10 under microwave irritation which acts as a Lewis acid catalyzing nucleophilic attack on carbonyl group by the

amine as well as serving as dehydrating agents to facilitate the removal of water in the final step [76]. As the nucleophilic attack by the amine at the carbonyl carbon in the first step is reversible. The feasibility of imine formation largely depends on the rates of removal of water in the final step of (route A) Subsequently, removal of water was facilitated by the use of molecular sieve. In an alternative approach, route B is given(Scheme 1.27).



Scheme1.27. Synthetic routes for imine formation

Consequently imines have enormous application in organic and medicinal chemistry. They possess a wide spectrum of biological activities; they act as

lipoxygenase inhibitors, anti-inflammatory agents [77] and anti-cancer agents [78]. Due to their impressive pharmacological and therapeutic properties in addition to the usage in organic synthesis the development of simple efficient and environmentally friendly synthesis of imines is of great importance.

1.3.1. Aldimine

Aldimines (Figure 1.8) are the simplest of all Schiff bases, aldehyde-derived and contain a C=N group and they are important class of organic compounds [79] which are both not stable at room temperature as a solid [80] and as a high boiling liquid [81].

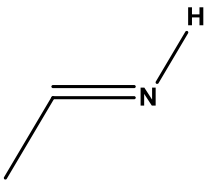


Figure 1.8. Structure of acetaldimine.

The barrier to E-Z-isomerization about a carbon- nitrogen double bond is very sensitive to the nature of the substituent. Bjorgo *et al.* illustrated that *Z*-aldimines which may be observed as transient intermediates after U.V. irradiation spontaneously revert to the *E*-configuration and thus corroborate the independent observations of an exclusive preference for the *E*-aldimine configuration at equilibrium [82].

In addition to this *N*-substituted aldimines adopt the more stable *E* form [83].

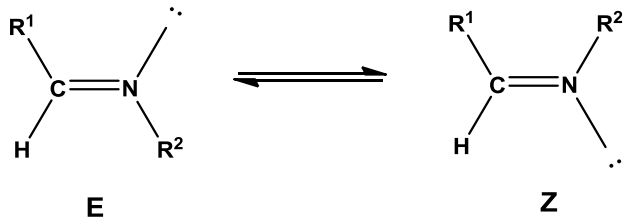
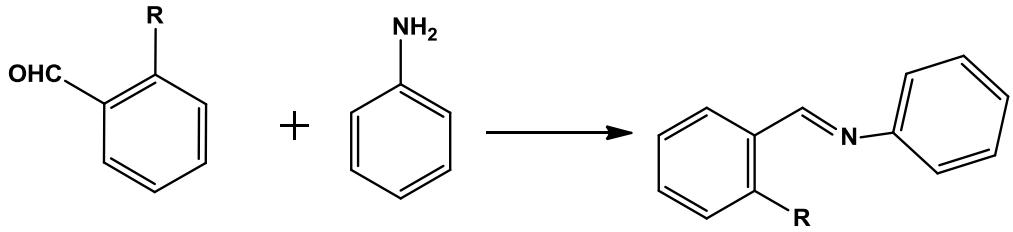


Figure 1.9. *E, Z* Form of aldimines

When an imine is formed from an aldehyde and a primary amine, one molecule of water is liberated per molecule of imine [84]. Dehydrating solvents, or Lewis acid catalysts have been shown to remove water as well as facilitate nucleophilic attack on the carbonyl compound [85]. In many experimental procedures, water-removing techniques or reagents are employed (Scheme1.28).



48a R=H
48b R=OH

44

45a R=H
45b R=O

Scheme 1.28. The reaction of aldehydes with an amine such as aniline to give imines

Aldimines are important electrophiles in organic synthesis and addition reactions to this electrophiles constitute some of the most useful and fundamental organic transformations [86]. So they have been used

successfully in the production of a large number of industrial compounds also in drug preparation.

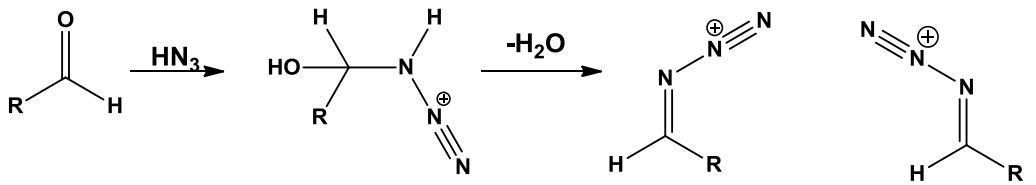
The aldimines are valuable starting materials not only for different *o*- and/or *N*-containing heterocycles [87] but also for diverse secondary heteroaromatic amines [88].

In addition to this aldimines are versatile synthetic reagents and numerous examples of addition reactions of electrophiles to them have been reported as the Mannich type reaction [89].

1.3.1.1.Synthesis of Aldimine

1.3.1.1.1.By Action of Hydrazoic acid

The reaction between equimolar quantities of hydrazoic acid and carbonyl compounds in the presence of a strong mineral acid has become known as the Schmidt reaction [90]. The mechanisms of reactions of aldehyde with hydrazoic acid begin with addition of HN_3 to the carbonyl group to form adizohydrin intermediate **I** Elimination of water from the azidohydrin affords isomeric diazoiminium ions **II** [91].

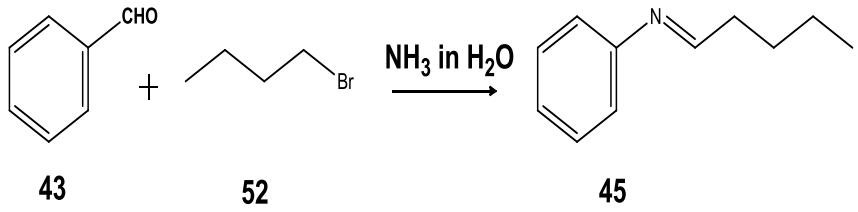


43 **50** **51**

Scheme 1.29. Synthesis of isomeric diazoiminium

1.3.1.1.2.By Action of Alkyl Bromide

Huang *et al.* reported that the reaction of benzaldehyde and 1-bromobutane was initially investigated in aqueous ammonia at room temperature. However, there was no imine observed. When the reaction was carried out at 60 ^{o}C, desired imine was obtained [92].



Scheme 1.30. Formation of imines from aldehydes and bromides in aqueous ammonia.

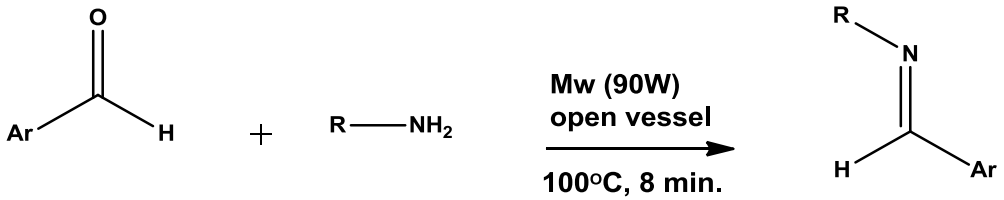
1.3.1.1.3.By Action of Amine via Direct and Indirect Process

The condensation of aldehydes and heteroaromatic amines provides a widely popular class, the aryl-hetarylaldimines.

Reductive amination of carbonyl compounds where the reaction of amines with aldehydes in the presence of a reducing agent. In this reductive amination the overall process involves the formation of an imine or iminium intermediate followed by reduction to alkylatedamines.

Two synthetic methods are commonly used for reductive amination of carbonyl. One of this is the direct reductive amination (Scheme 1.30) in which a mixture of carbonyl compound and amine are treated directly with suitable reducing agents in a single operation without formation of an intermediate imine or iminium salt.

Neat non-volatile amines react with various aromatic aldehydes in the absence of any catalyst, solid support, or solvent, to give imines after a reaction time of eight minutes under microwave irradiation by a clean and very efficient process. In the case of volatile amine, methylamine, 1,3-dimethylurea dispersed on montmorillonite is used as an amine precursor to prepare the corresponding imines [88].

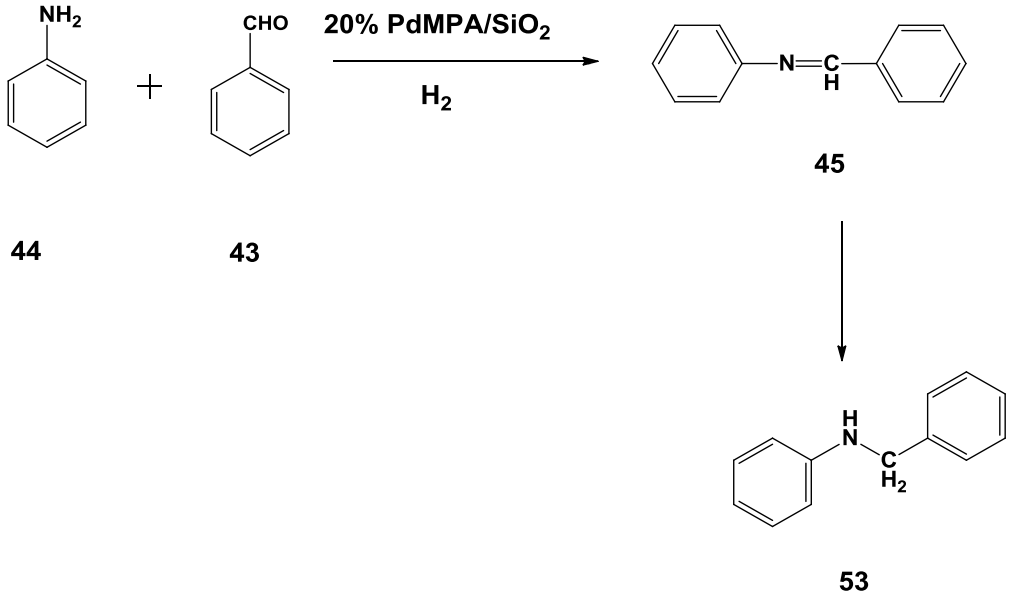


43 44 45

Scheme1.31. Synthesis of imine under microwave irradiation using amine

The other one is a stepwise or indirect reaction, in which the first step is the conversion of amine into imine and further reduction of imine reduced into higher alkylated amine. Direct reductive amination is performed under anhydrous conditions in order to avoid decomposition of the reducing agents or catalysts, and at the same time to enhance the generation of the intermediate imines or iminium salts.

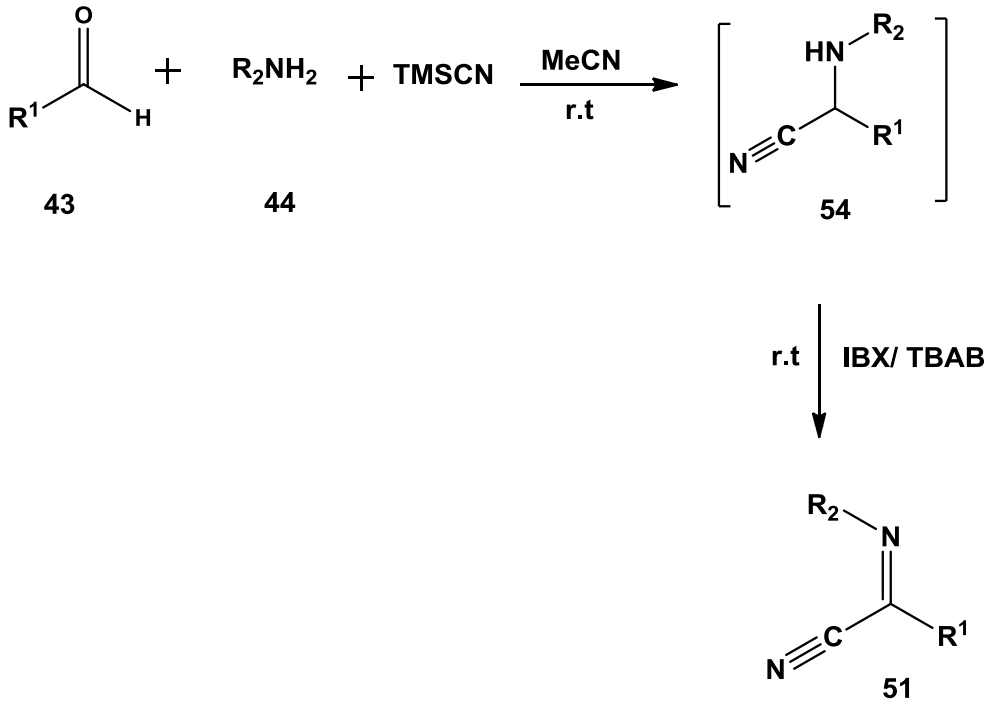
There are several reagents and catalysts reported in the literature for reductive amination of carbonyl. In most of these methods are used acid catalyst/reagent along with a reducing age like $NaBH_4$. Pd and In based homogeneous catalysts are reported for the direct reductive amination [93].



Scheme 1.32. Synthesis of imine and further reduction of imine into higher alkylated amine.

1.3.1.1.4.By action of IBX/TBAB-Mediated Oxidative Strecker Reaction

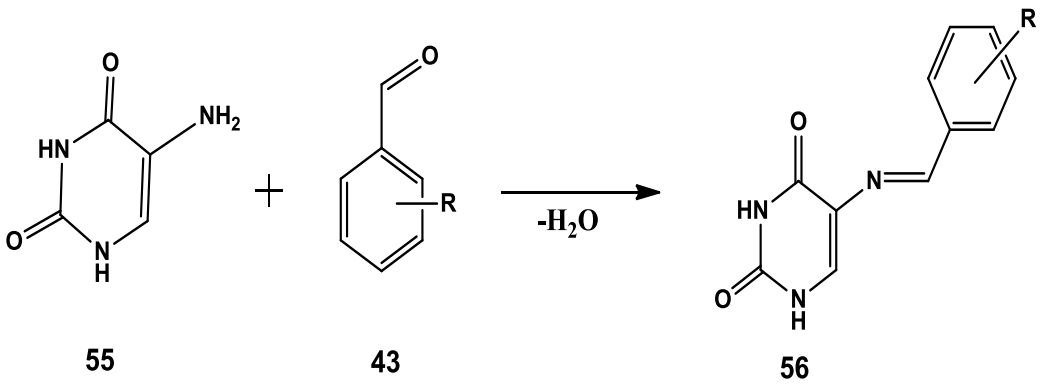
Synthesis of R-iminonitriles derived from aliphatic aldehydes, far less accessible than their aromatic counter parts. Aliphatic aldehydes whether linear or R-branched, participate effectively in oxidative condensation process in the presence of a stoichiometric amount of TBAB. In addition, chiral nonracemic *N,N*-dibenzyl-O-TBS-serinal successfully transformed into the corresponding R-iminonitrile [94].



Scheme 1.33. Synthesis of R-iminonitriles **51** by IBX/TBAB-mediated oxidative strecker reaction.

1.3.1.1.5.By action of 5-aminopyrimidine-2,4(*1H,3H*)-dione

Krutikov *et. al.* reported that the reaction of 5-aminouracil with aryl aldehyde at room temperature in water led to the formation of (*E*)-5-(benzylideneamino)pyrimidine-2,4-(*1H,3H*)-dione (Scheme 1.33) [95].



Scheme 1.34. Synthesis of pyrimidine-2,4-dione from 5-amino uracil.

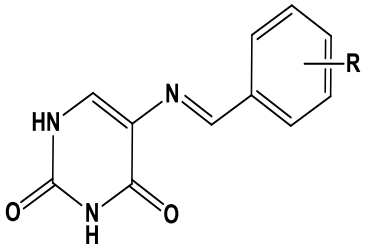
1.3.1.2.Biological Activity Studies

The nitrogen-containing units of these molecules play important roles for their bioactivities. Imines both aldimines and ketimines because of presence of carbon-nitrogen double bond in their molecules ensure potential site for chemical as well as biologicalactivity. To investigate the effect of nature of the substituent and its position on the phenyl rings of aromatic aldimines on the biological activity has been carried out with lots of work. The extent of conjugation in the molecule and length of spacer between two phenyl rings in aromaticimines play a vital role in determining biological potential and evaluation for biological activity [96].

The pyrimidine which was synthesized and an important starting material for our study is designated mainly for use as antiviral, immune-stimulating, antichlamydial, antituberculus, physchodepressant, analgesic, and hepatoprotective remedies. Also these compounds maybe used for treating malignant neoplasms and also in veterinary.The objective of the invention is

obtaining new chemical substances possessing pronounced biological activity of wide range.

The proposed objective is achieved by synthesis of 2,4-dioxo-5 arylidenimine-1,3-pyrimidines of the general formula [97].

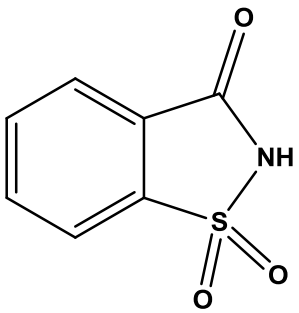


56

Figure 1.10. General formula of 2,4-dioxo-5 arylidenimine-1,3-pyrimidines

1.4.SACCHARIN

Saccharin (o-benzoic sulfimide, $C_6H_4COSO_2NH$) **57** was discovered accidentally by Remsen and Fahlberg at Johns Hopkins University in 1879 during an academic study of the oxidation of o-toluenesulphonamides. The structure of saccharin is shown in (Fig.1.11)



57

Figure1.11. Chemical structures for Hsac.

Afterwards it was discovered that saccharin was slowly absorbed and not metabolized by the human organism being consequently an appropriate artificial sweetener for diabetics [98].

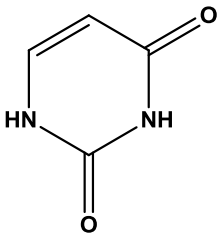
It is a well known heterocyclic compound and has been used as a sweetener in the form of its sodium salt since 1885 [99]. It is a noncaloric sweetener and its action mechanism in humans is controversial, as it is intensely sweet but may also have a bitter taste [100].

Saccharin has been widely incorporated into a variety of biologically active compounds. The saccharin moiety has been identified as an important molecular component in various classes of 5-HT1a antagonists, human leukocyte elastase inhibitors, analgesics, human mast cell tryptase inhibitors, a1a and a1c adrenergic receptor antagonists, aldehyde dehydrogenase inhibitors, and bactericides [101].

In organic and bioorganic synthesis, saccharin and saccharyl derivatives are known as cheap and versatile starting materials for the preparation of related heterocycles and as useful synthetic intermediates [102].

1.4.URACIL AND 5-AMINO URACIL

Uracil, unique constituent of RNA is a naturally occurring pyrimidine analogue [103]. Of the nucleic acid pyrmidines, uracil **58** and isolated from beef spleen, have been found in the free form [104].



58

Figure1.12. Structure of uracil

It was produced in a laboratory in 1900-1901. Many substituted uracil derivatives have registered their importance in pharmaceuticals [105] drug delivery, enzyme synthesis,polysaccharides, transportation, allosteric regulators, coenzymes and pesticides [106]. Uracil undergoes amide-imidic acid tautomeric shifts because any nuclear instability the molecule may have from the lack of formal aromaticity is compensated by the cyclic-amidic stability. In uracil, for example, the following six tautomers are possible [107].

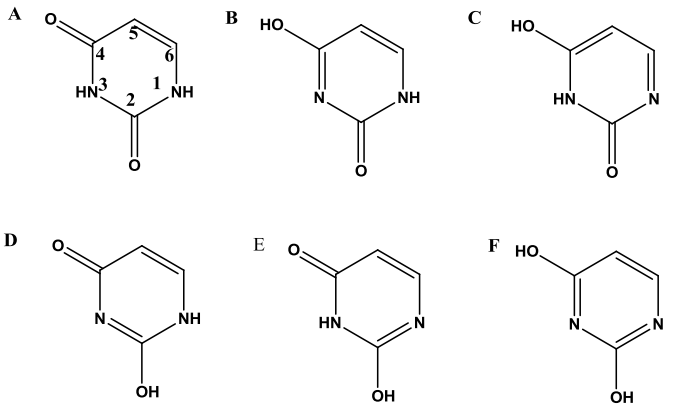


Figure 1.13. Keto-Enol form of uracil

A is the 2,4-diketo tautomer, B-E are keto-enol tautomers, and F is the 2,4-dienol tautomer.

CHAPTER II

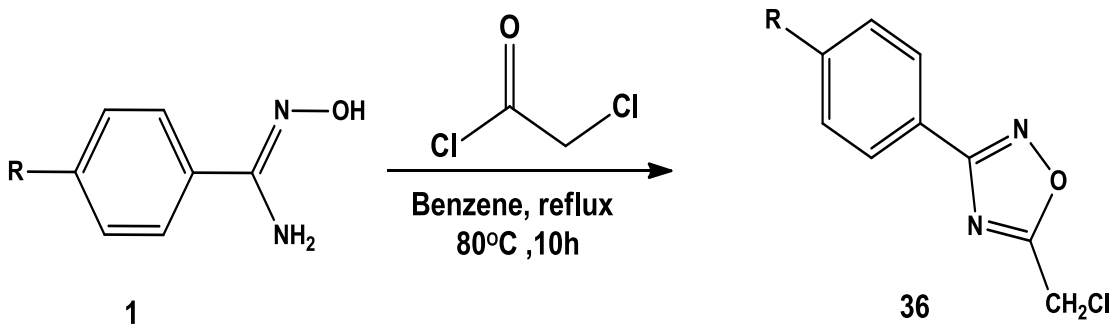
2.1.RESULTS and DISCUSSION

In this study, *N*-substitution on *o*-benzosulfimide, uracil, 5-amino uracil, and aryl substituted 5-benzylideneamino pyrimidinedione with 5-chloromethyl-3-substituted-phenyl-1,2,4-oxadiazoles, respectively, have been introduced. To our best knowledge of literature, there is no report, on the basis of WEB OF KNOWLEDGE, SCIFINDER and REAXYS electronic databases, regarding *N*-substitution of *O*-benzosulfimide, uracil, 5-aminouracil, and 5-benzylideneamino pyrimidinediones with 5-chloromethyl 1,2,4-oxadiazoles. On the other hand, there is an increasing attention on the synthesis of heterocyclic compounds carrying oxadiazole moieties due to their diverse pharmacological activities [42-45]. Therefore, importance of these end products carrying 1,2,4-oxadiazole ring can be considered as promising and intriguing valuable potential bioactive molecules. In this regard, bioactivity assessment of these heterocyles are underway in due course.

The present research work is basically consisted of six parts.

1. Synthesis of substituted aryl amidoximes from benzonitriles **(1a-k)** and aryl substituted 5-(chloromethyl)-1,2,4-oxadiazoles **(36a-k)** as primary starting materials according to well-known literature procedures.
2. Synthesis of 2-[(3-(*p*-substitutedphenyl-1,2,4-oxadiazol-5-yl)methyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxides **(59 a-k).**
3. Synthesis of 1,3-bis[(3-(*p*-substitutedphenyl)-1,2,4-oxadiazol-5-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-diones **(60a-i)** and 3-[(3-(*p*-substitutedphenyl-1,2,4-oxadiazol-5-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-diones **(61a-i).**
4. Synthesis of 5-amino-1,3-bis[(3-(*p*-substitutedphenyl)-1,2,4-oxadiazol-5-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-diones **(62a-h).**
5. Synthesis of aryl substituted 5-(benzylideneamino)pyrimidine-2,4-diones **(56a-g).**
6. Synthesis of *N*-1,2,4-oxadiazolylmethyl substituted 5-(benzylideneamino) pyrimidine-2,4-diones **(63a-e).**

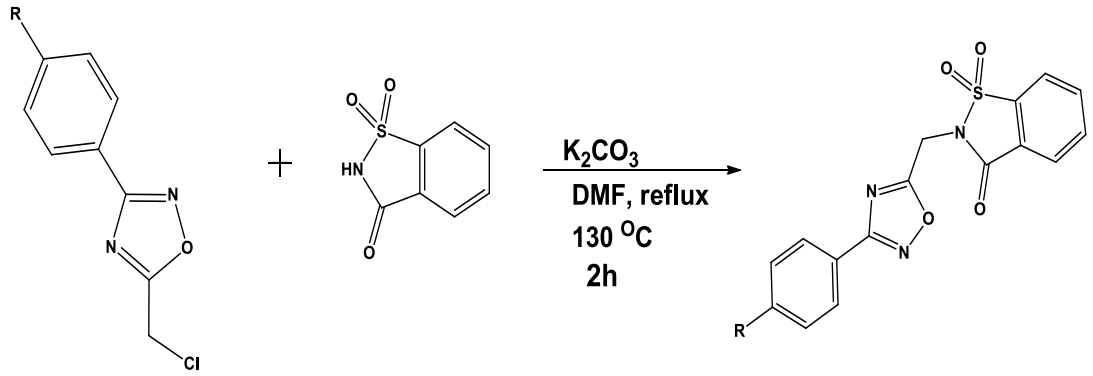
In the first part, aryl substituted monoamidoximes were synthesized according to literature procedures [6-8]. Then, they were reacted with chloroacetyl chloride under the reflux temperature in benzene to give 5-(chloromethyl)-1,2,4-oxadiazoles (**36a-k)** (Scheme1.21) [68]. Their structures were confirmed on the basis of IR spectrum, M.p. and R_f values reported in literature.



R	R
a H	g NO_2
b CH_3	h CF_3
c F	i SCH_3
d Cl	j OCH_3
e I	k CN
f Br	

Scheme 2.1. Synthesis of 3-aryl-5-chloromethyl-1,2,4-oxadiazoles **(36a-k).**

In the second part, 5-(chloromethyl)-1,2,4-oxadiazoles were reacted with *o*-benzosulfimide under reflux in DMF to give 2-[(3-(*p*-substituted phenyl-1,2,4-oxadiazol-5-yl)methyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxides (**59a-k)** (Scheme 2.2).



36 57 59

R	R
a H	g NO_2
b CH_3	h CF_3
c F	i SCH_3
d Cl	j OCH_3
e I	k CN
f Br	

Scheme 2.2. Synthesis of 2-[(3-(*p*-substitutedphenyl)-1,2,4-oxadiazol-5-yl) methyl]-1,2-benzisothiazol-3(2*H*)-one 1,1-dioxides **(59 a-k).**

The structures of these novel compounds were determined by their physical (Mp and R_f values) and spectral data, namely, IR, NMR (^{1} H, ^{13}C) and HRMS measurements. Primary indicative evidence of this series is the disappearance of NH absorption in the IR spectra of compounds.In addition, carbonyl absorption bands which came out from one of starting compounds and i.e. *o*-benzosulfimide, at around 1735-1753 cm^{-1} (Figure 2.1). In the

proton NMR spectra, typical peak is that for methylene protons resonating at around 5.20 ppm quite deshielded due to being adjacent both to benzosulfimide nitrogen and oxadiazole imine carbon. As for carbon-13 NMR spectra it can be seen that most deshielded ones are oxadiazole ring number 3 carbon, fluorine bounded carbon, benzosulfimide carbonyl carbon and oxadiazole ring number 5 carbons respectively. Representative spectra (IR, ^{1}H NMR, ^{13}C NMR, LC-MS) are shown below.

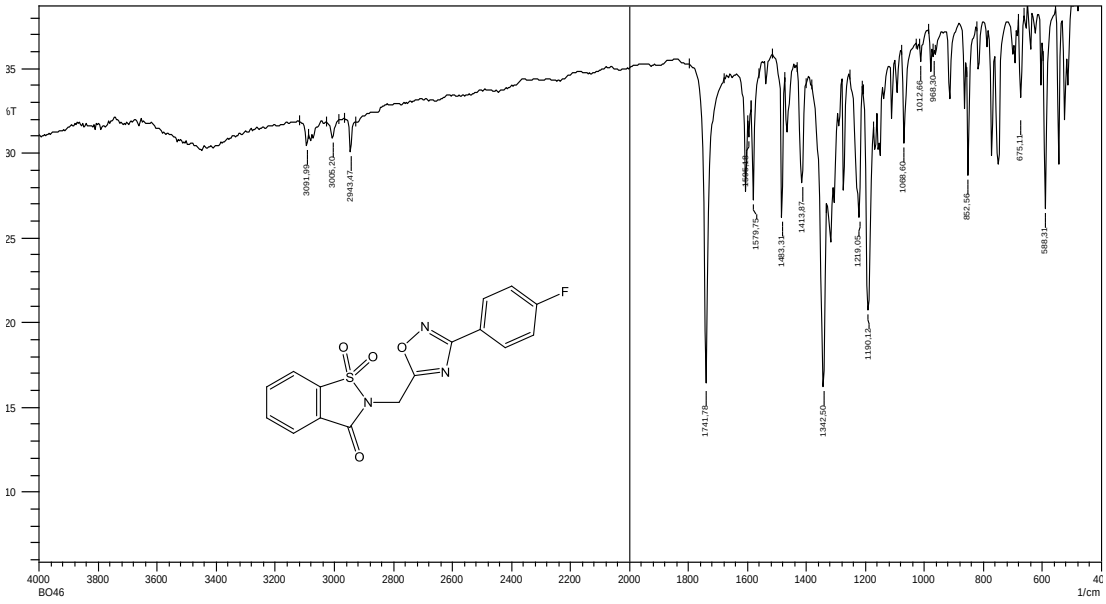


Figure 2.1. The IR spectrum of **59c.**

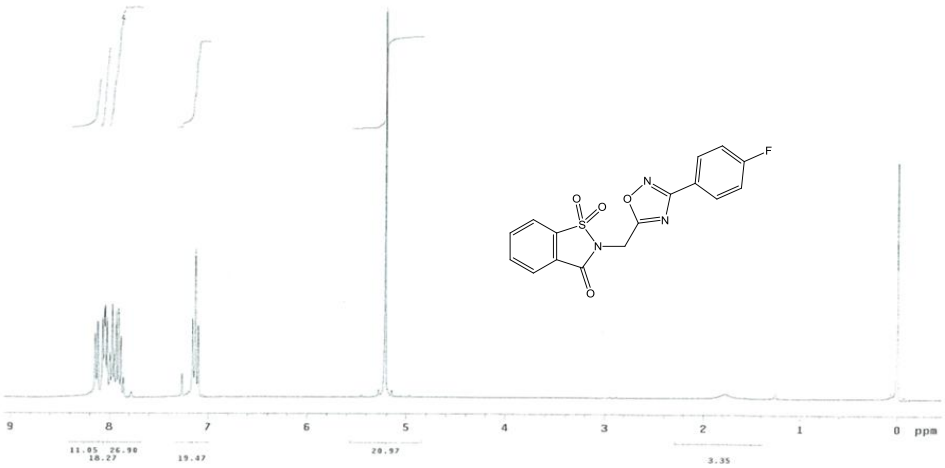


Figure 2.2. ^{1}H NMR Spectrum of **59c.**

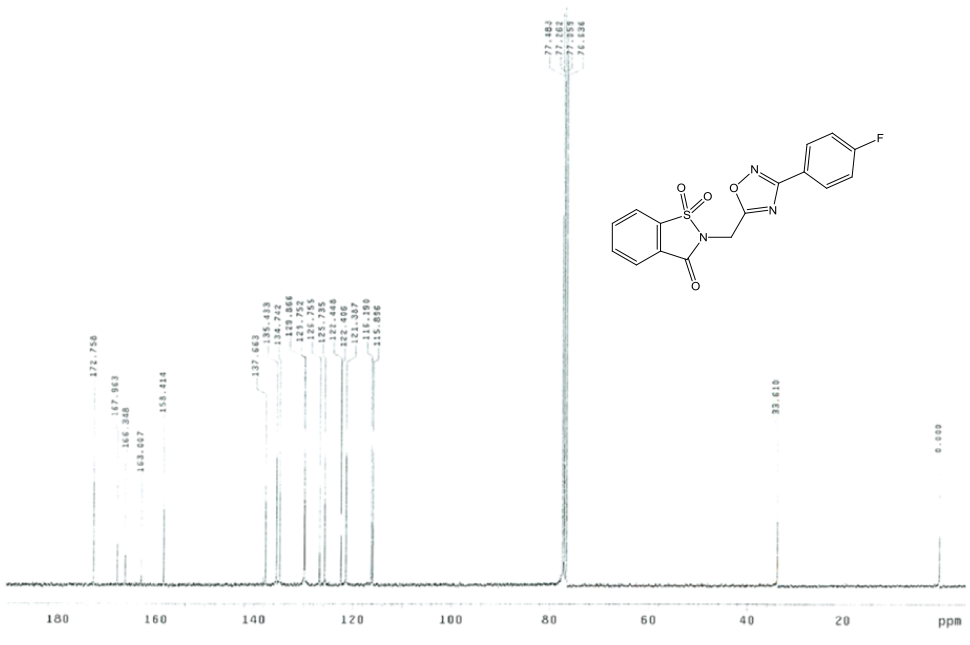
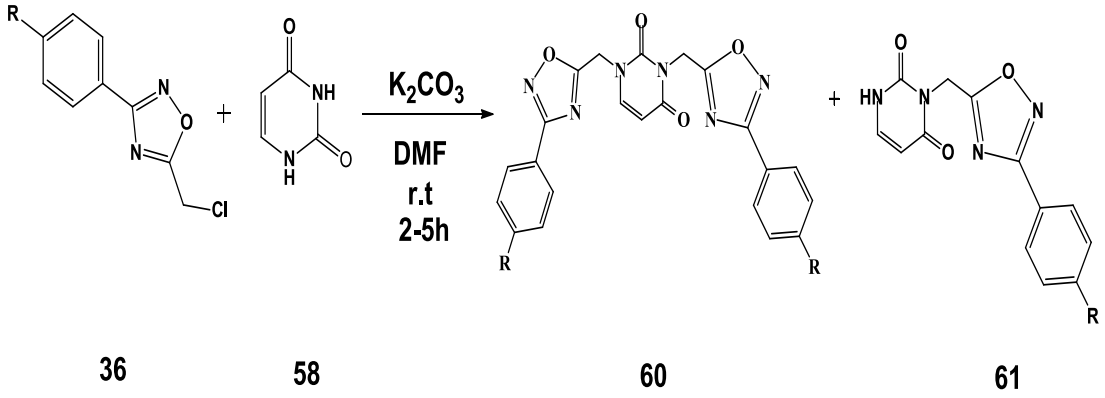


Figure 2.3. ^{13}C NMR spectrum of **59c.**

In the third part, we are involved in *N*-substitution of uracil by 5-chloromethyl-1,2,4- oxadiazoles. The reaction has been found to give rise a mixture of both disubstituted and monosubstituted products. First one, which is less polar and eluted first through chromatography column is the *N*-substituted 1,3-bis[(3-(*p*-substitutedphenyl)-1,2,4-oxadiazol-5-yl)methyl]pyrimidine2,4 (1*H*,3*H*)-diones **(60a-i)** and the other is 3-[(3-(p-substitutedphenyl)-1,2,4-oxadiazol-5-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-diones **(61a-i)** (Scheme 2.3).



36 **58** **60** **61**

R	R
a H	f NO_2
b CH_3	g CF_3
c F	h SCH_3
d I	i OCH_3
e Br	

Scheme 2.3. Synthesis of bis and mono *N*-1,2,4-oxadiazolylmethyl substituted uracils **(60/61a-i).**

Bis *N*-substituted uracils show no NH absorptions in the IR spectra. But however, monosubstituted ones showed NH absorption at around 3500 cm^{-1}. We observed carbonyl absortptions in both compounds at around 1732 cm^{-1}. The disappearance of the NH and appearance of the carbonyl absorbtions originated from the uracil are the indicative properties. Also, the C=N absorption appears at around 1620 cm^{-1}.

In the LC-MS spectra, we see $[M+H]^+$ as base peak and the other confirming data regarding the structure are ^{13}C and ^{1}H NMR chemical shifts. In this regard, upon examination of ^{1}H NMR spectra, it is clearly seen aliphatic CH_2 protons at around 5.48 and 5.41 ppm as singlet and double bond carbon of the uracil, one of the CH protons which is closer to oxygen atom gives doublet at around 8.1 while the other resonates at 6.1 ppm.7 In the ^{13}C NMR spectrum, we can see two aliphatic carbons at around 44 and 36 ppm. Carbonyl carbons arose at around 176 (N-CO-N) and 168 (N-CO) ppm, respectively.Iminic carbons of the oxadiazole rings resonates at around 164 ppm, more dishielded due to being located between two sp^2 hbridized nitrogen atoms in comparison with the other imine carbons. Double bond carbons of the uracil resonated at around 126 and 102 ppm.

Upon investigation of the IR, NMR, LC-MS spectrum for the compound **(61a)** (mono substituted uracils) NH, carbonyl and C=N absorptions arose at around 3400, 1720,1586 cm^{-1} , respectively.These indications are also supported by $[M+H]^+$ at 271 m/z in LC-MS spectra.

In the proton NMR spectra of monosubtituted uracils, typical peaks are observed for aliphatic methylene hydrogens at around 5.2 and NH, which is quite deshielded, as singlets at around 11.6 ppm. Alkenic carbon of uracil

which is quite dishielded have been found to 7.8 ppm due to resonates structure of which double bond move to adjacent of oxygen atom, and the other resonates at around 5.7ppm. As for ^{13}C NMR, carbonyl compounds appeared at around 176 (NH-CO-N), 168 (N-CO) ppm, iminic carbons of the oxadiazole resonated at around 164 and 151ppm and aliphatic CH_2 is seen at around 44 ppm.

Representative spectra of these group of heterocycles are shown below:

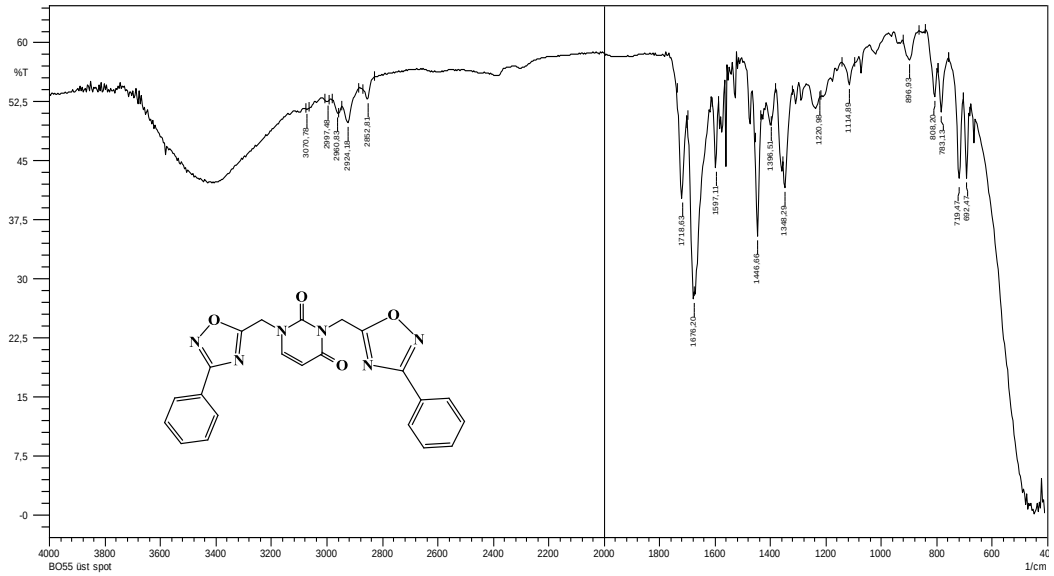


Figure 2.4. The IR spectrum of **60a.**

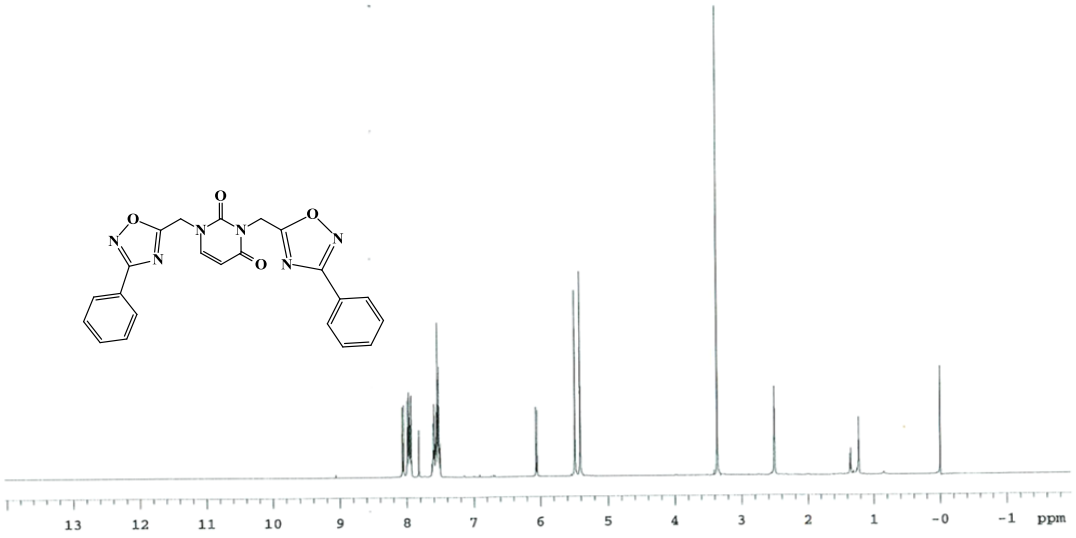


Figure 2.5.[1]H NMR spectrum of **60a.**

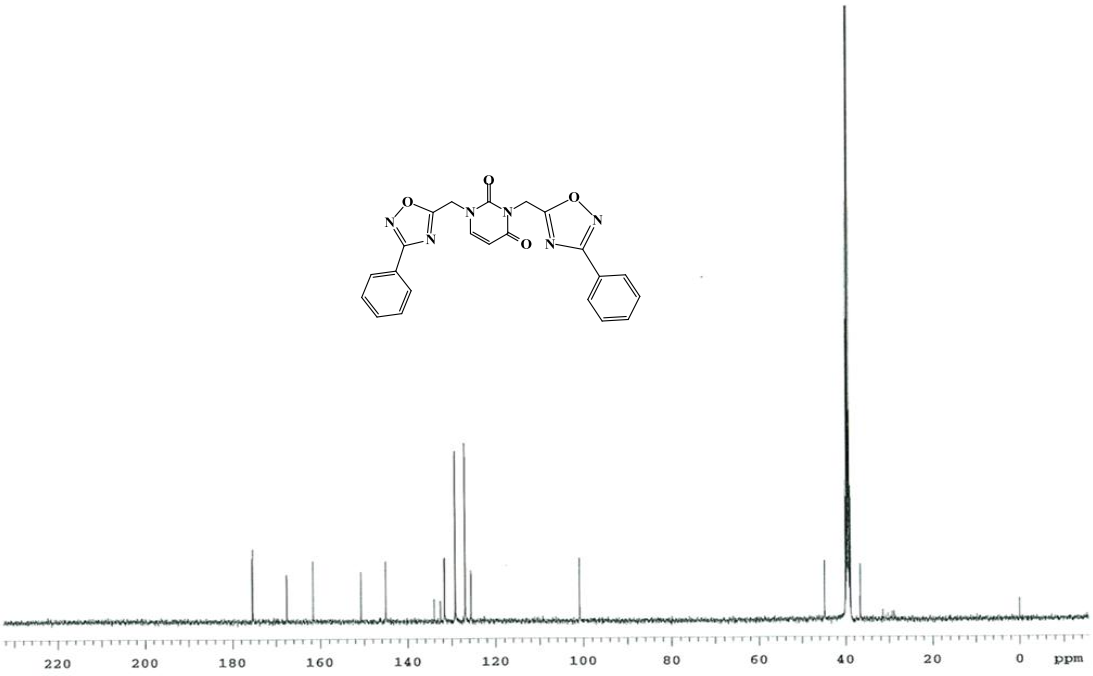


Figure 2.6. [13]C NMR spectrum of **60a.**

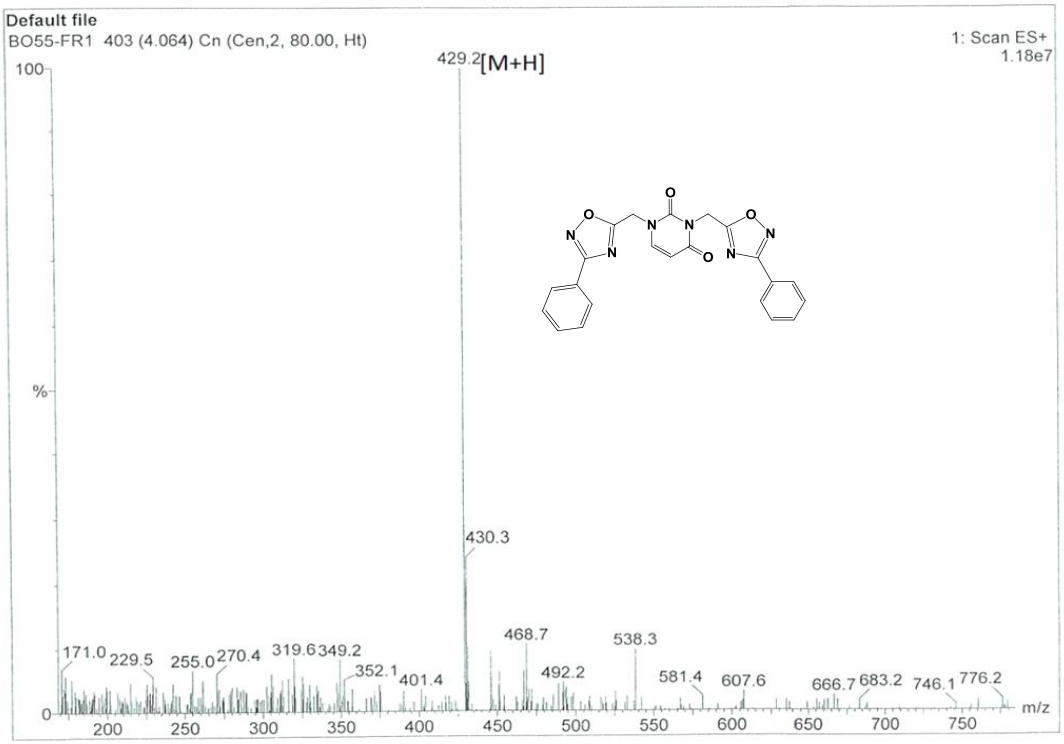


Figure 2.7. LC-MS spectrum of **60a.**

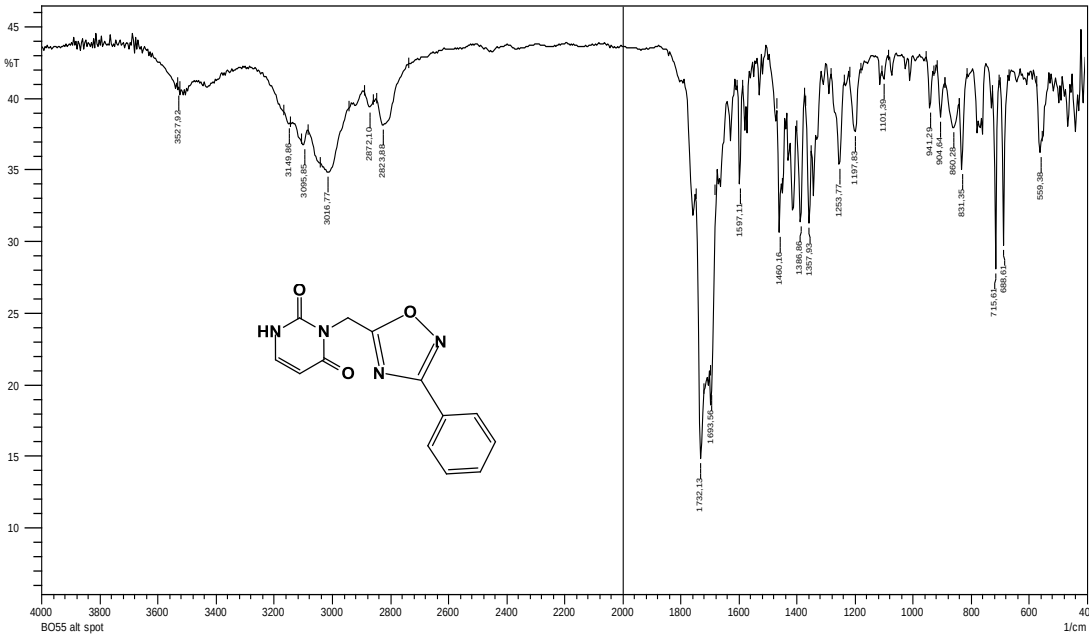


Figure 2.8. IR spectrum of compound **61a.**

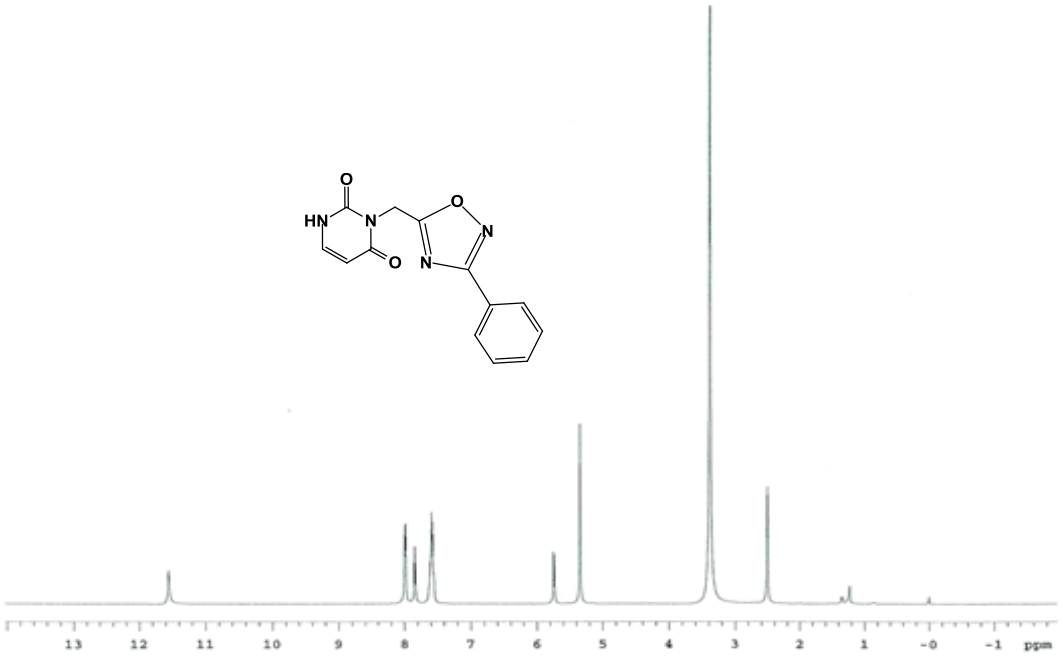


Figure 2.9. ^{1}H NMR spectrum of **61a.**

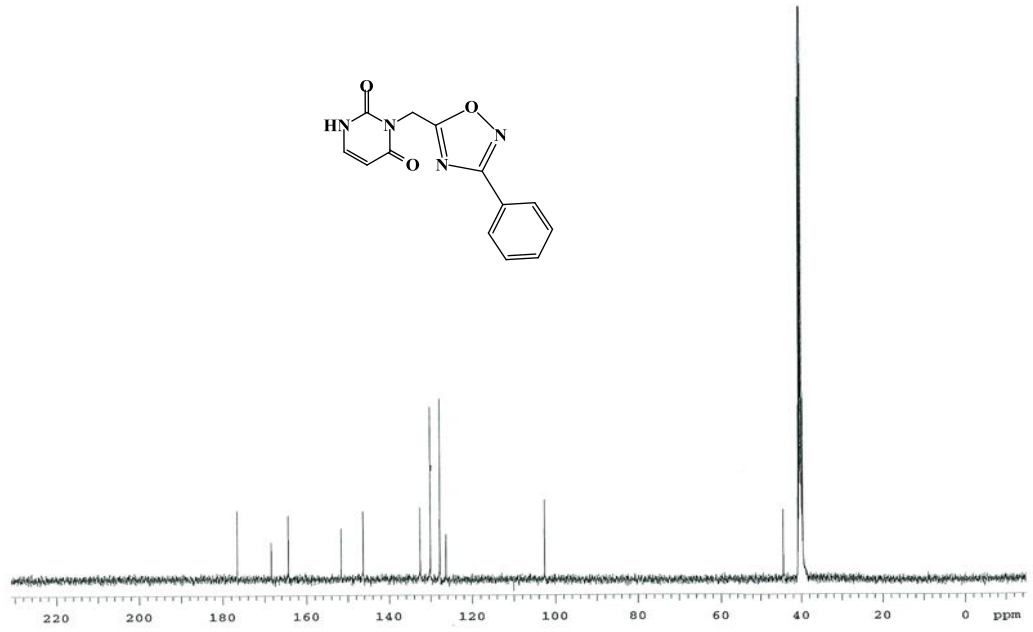


Figure 2.10. ^{13}C NMR spectrum of **61a**

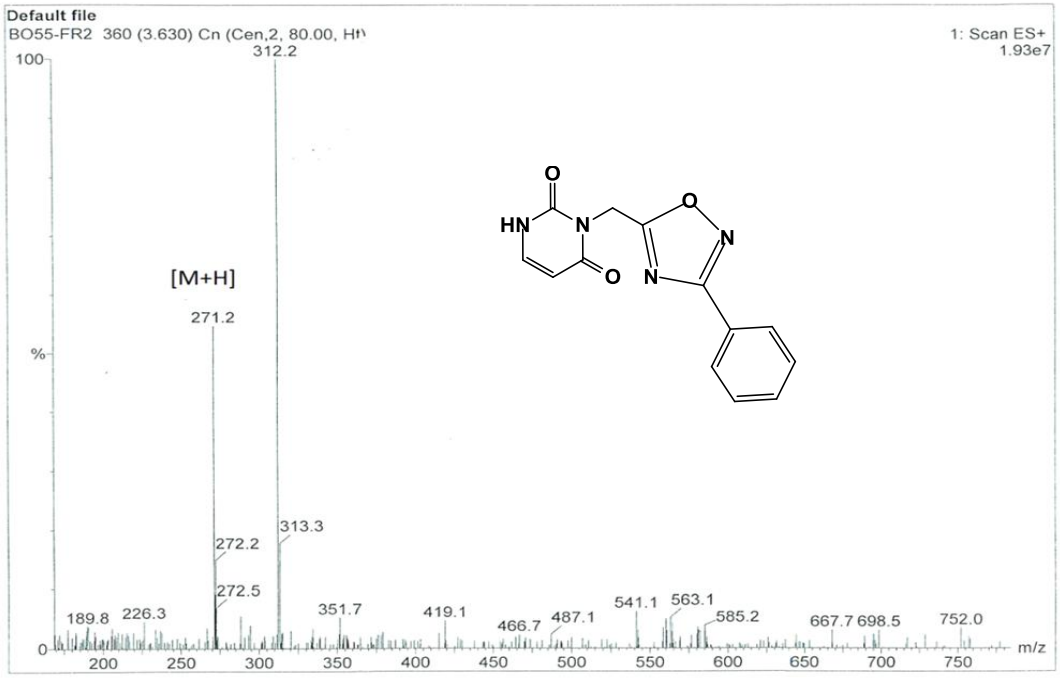
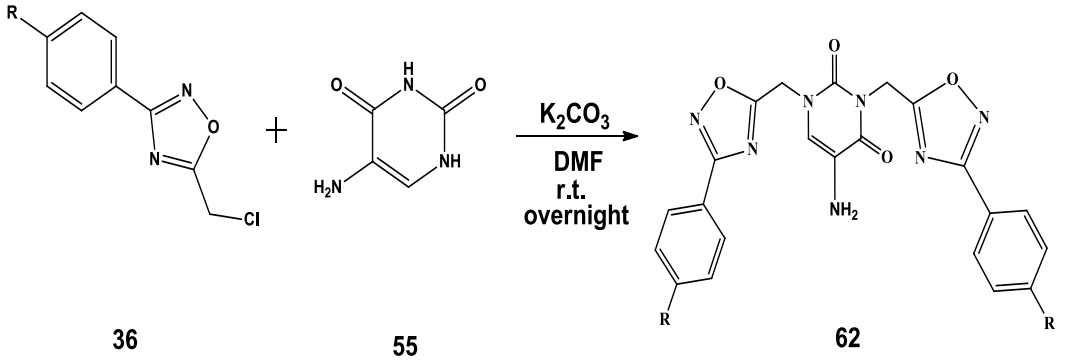


Figure 2.11. LC-MS spectrum of **61a.**

In this part, 5-amino-1,3-bis[(3-(*p*-substitutedphenyl)-1,2,4-oxadiazol-5-yl)methyl]pyrimidine-2,4(1*H*,3*H*)-diones **63a-h** were obtained by the treatment of chloromethyloxadiazole **36** and 5-amino uracil **62** at room temperature in dimethyl formamide (Scheme 2.4). Thus, eight novel compounds are introduced.



36 **55** **62**

R	R
a H	e I
b CH_3	f NO_2
c F	g SCH_3
d Cl	h CF_3

Scheme 2.4. Synthesis of *N*-oxadiazolylmethyl substituted 5-amino uracils (**62a-h).**

The structural elucidation of the *N*-oxadiazolylmethyl substituted 5-amino uracils **(62a-h)** were performed by IR, NMR (^{1}H, ^{13}C,) and LC-MS spectra.

This compounds are quite polar due to NH_2. Therefore, we were able to record their NMR spectra in DMSO-d_6 .^{1}H NMR spectra showed the typical

methylene and amino protons. Particularly, NH_2 protons appeared at 4.6 ppm as a broad singlet and methylene protons at around 5.4 ppm as doublets. ^{13}C NMR spectra revealed that most deshielded carbons are oxadiazole ring number 3 carbons. Structure elucidation is also supported by LC-MS spectrum at which base peak was observed at m/z 444.

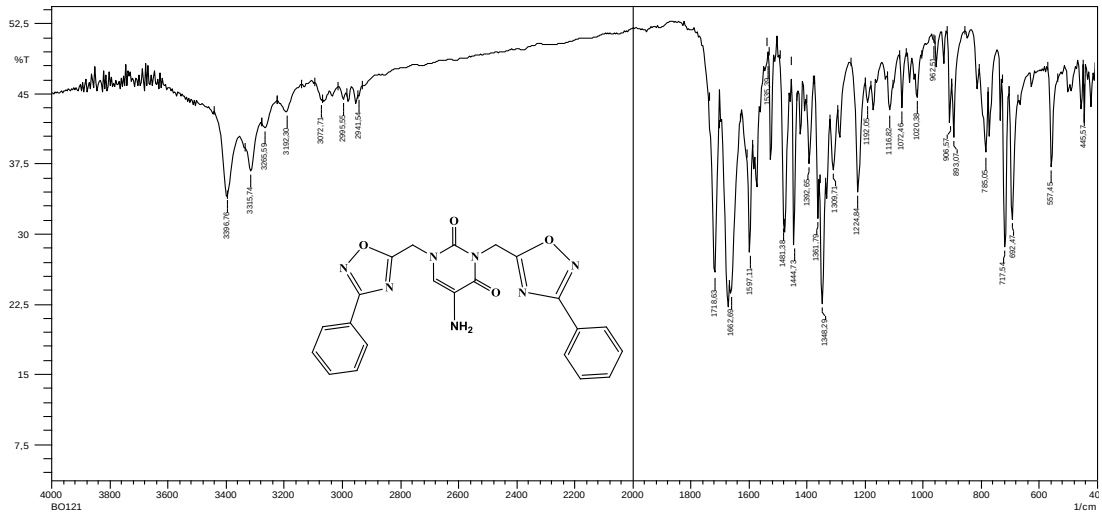


Figure 2.12. IR spectrum of compound **62a.**

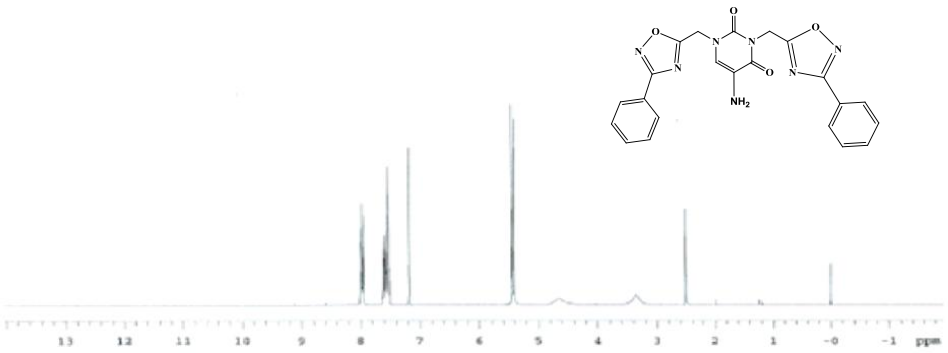


Figure 2.13. ^{1}H NMR spectrum of **62a.**

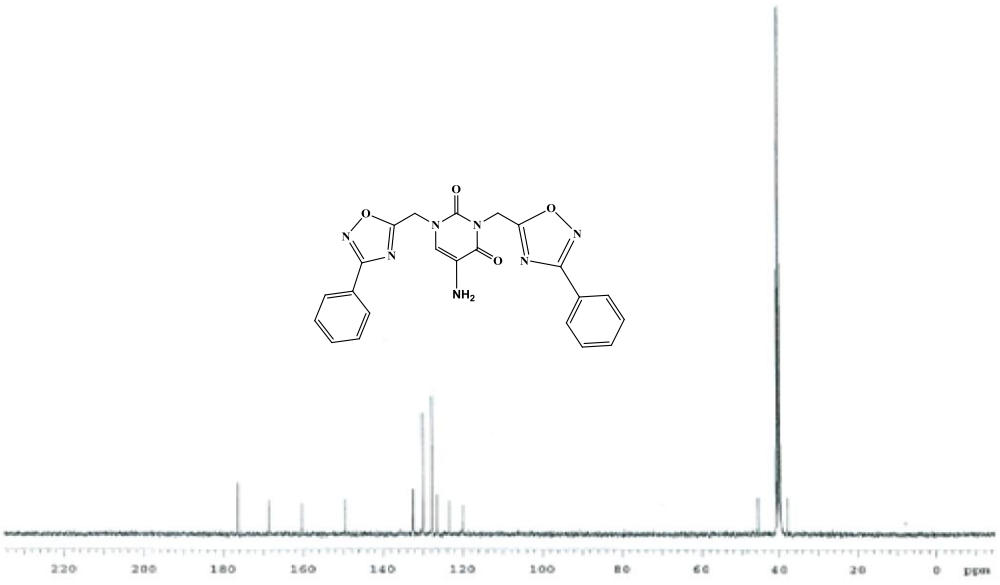


Figure 2.14. ^{13}C NMR spectrum of **62a.**

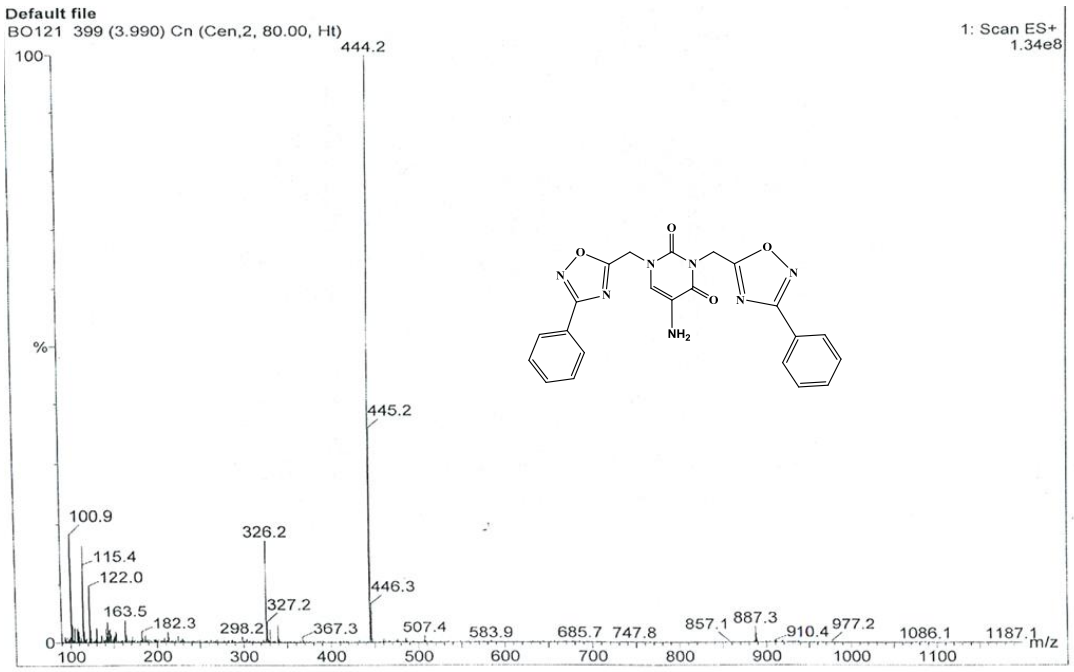
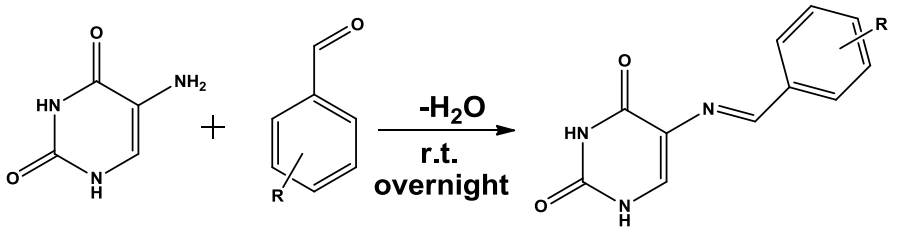


Figure 2.15. LC-MS spectrum of **62a.**

In the last part; in order to perform the synthesis of *N*-oxadiazolylmethyl substituted benzylideneamino pyrimidinediones, we prepared imines of uracil **(56a-g)** by condensation with subsituted benzaldehydes according to the literature procedure [97]**.**



55 **43** **56**

	R		R
a	**CH_3**	**e**	**NO_2**
b	**CN**	**f**	**SCH_3**
c	**5-Br, 2-OH**	**g**	**H**
d	**OCH_3**		

Scheme 2.5. Synthesis of (*E*)-5-(benzylideneamino)pyrimidine-2,4(*1H,3H*)-diones (**56a-g).**

The exact structures of these 7 molecules were identified by IR, m.p., and R_f values by support information from the literature, and three of them were supported by NMR(^{1}H, ^{13}C), LC-MS, characteristics. In the IR spectra the dissappearence of the NH_2 at around 3400 and 3375 cm^{-1} is an evidence and the structural elucidation were proofed by ^{1}H NMR. For the compound **(56e)** This spectra exhibited the two NH protons respectively at around 11.5, 7.5 ppm, one iminic proton at around 9.6 ppm and proton of (-C=C-H) at 7.8 ppm (Figure 2.17). In the ^{13}C NMR carbonyl carbons appeared at around 155.8 and 150.6 ppm and iminic carbon at around 161.9 ppm (Figure 2.18).

This molecule was supported by LC-MS spectra with 261 m/z as a base peak (Figure 2.16).

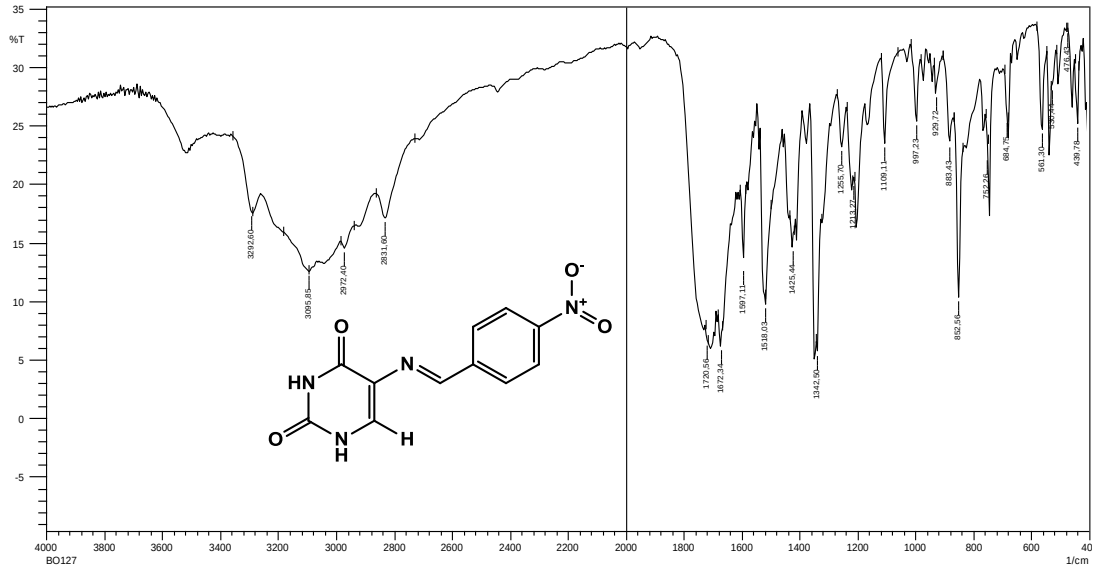


Figure 2.16. IR spectrum of compound **56e.**

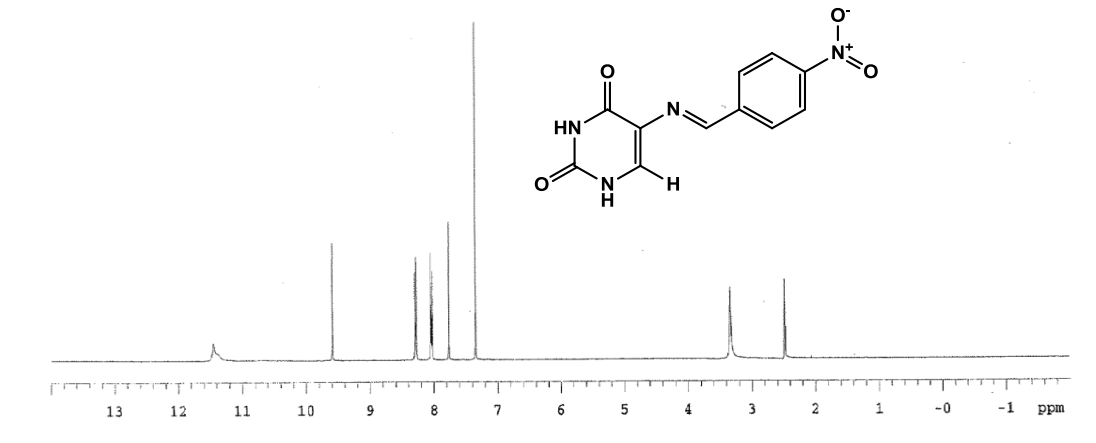


Figure 2.17. ^{1}H NMR spectrum of **56e.**

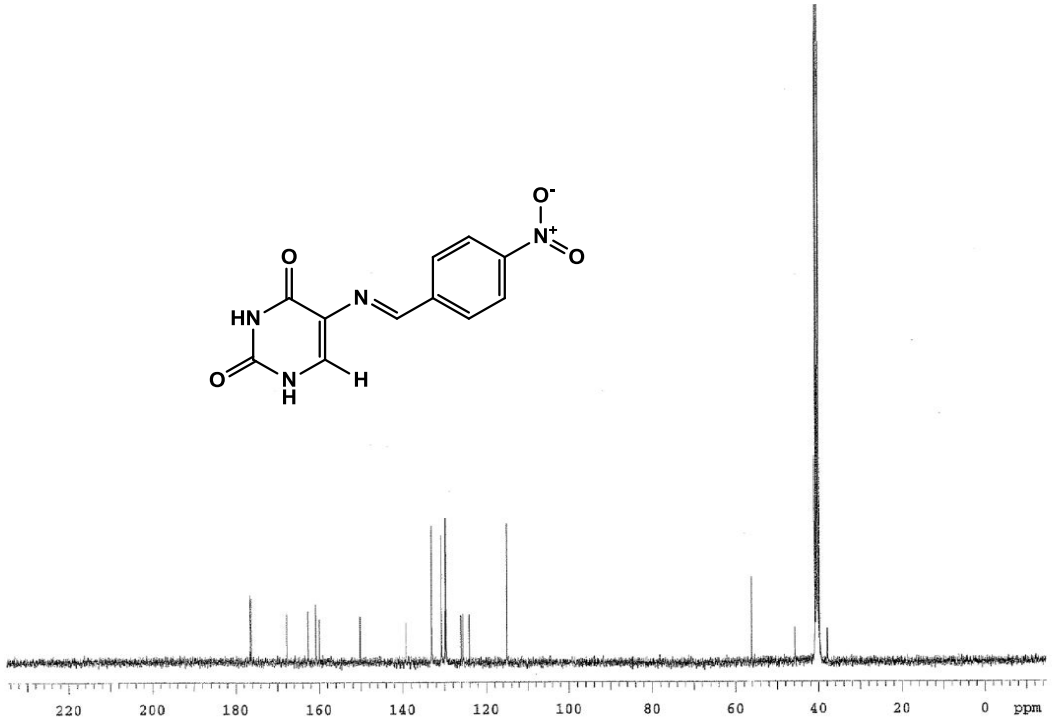


Figure 2.18. ^{13}C NMR spectrum of **56e.**

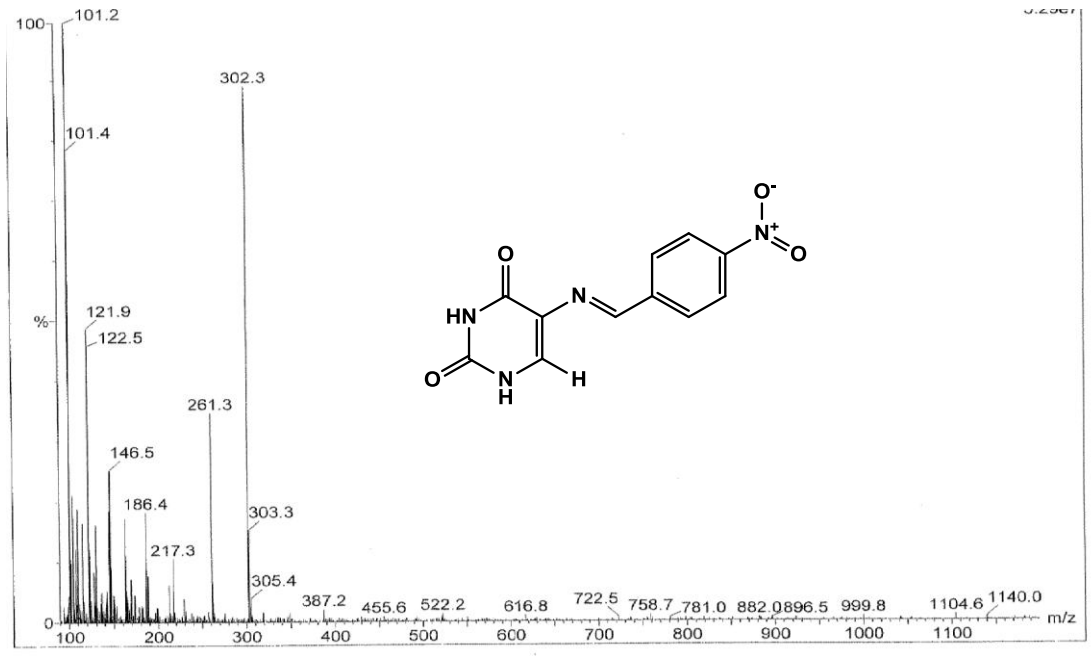
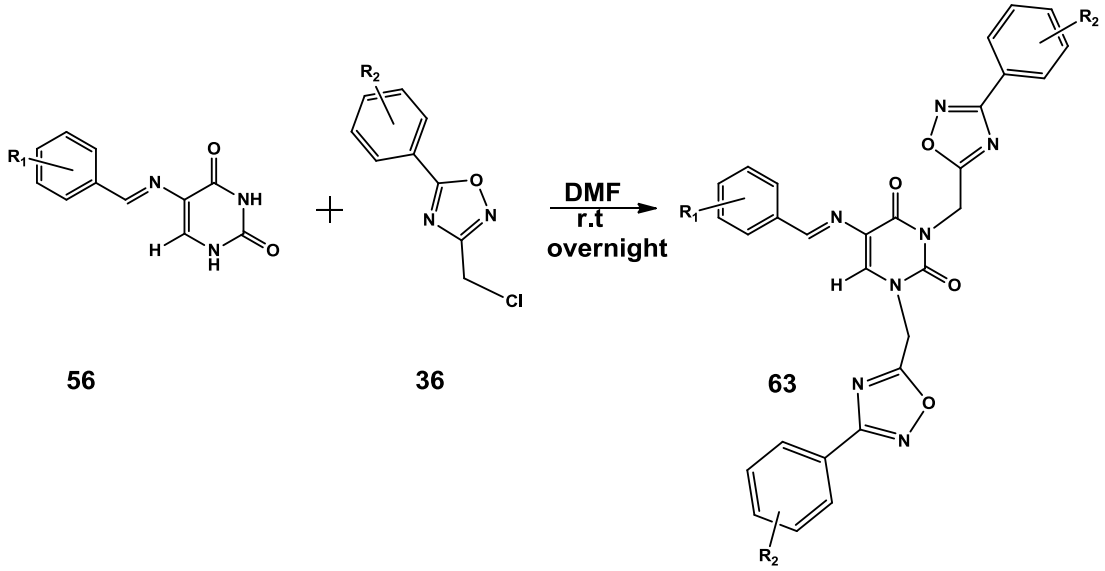


Figure 2.19. LC-MS spectrum of **56e.**

The aryl substituted benzylideneamino pyrimidine diones were then reacted with 5-chloromethyl -1,2,4-oxadiazoles in DMF at room temperature for overnight.



56 36 63

	R_1	R_2
a	CH_3	H
b	CN	SCH_3
c	OCH_3	Br
d	2-OH,5-Br	NO_2
e	2-OH,5-Br	SCH_3

Scheme 2.6. Synthesis of *N*-oxadiazolylmethyl substituted benzylideneamino pyrimidinediones (**63a-e)**.

Their exact structures were identified by spectral and physical methods. Datas were in accord with the specified structures. But, we were not able to separate two of them; **63d** and **63e.** They seems to be a mixture which

includes the starting material benzylideneamino pyrimidine dione and the anticipated molecule. We will try to purify by preparative HPLC in the near future. As a representative compound; **63b** showed one iminic proton of the pyrimidinedione and alkenic proton, -C=C-H, at around 9.54 and 8.52 ppm, respectively, in the ^{1}H NMR spectrum.Two aliphatic CH_2 and SCH_3 protons were found to resonate at around 5.58, 5.48 and 2.51 ppm, respectively, as singlet and quartet signals, whilst ^{13}C NMR spectra exhibited six different carbons between 150-180 ppm. Two of them are assigned to two carbonyl between 180-170 ppm. The other two carbon signals were assigned to the iminic carbons; C=N at the oxadiazole ring.The other iminic carbon is of the pyrimidinedione part of the molecule. The sixth one is nitrile.The other specific carbons are two CH_2 at around 45.9 and 37.9 ppm and the two SCH_3 carbons are at 14.7 which are at the oxadiazole ring. LC-MS data confirmed the molecular ions of the compounds; 649 m/z as a base peak for the compound **63b**. The representative spectra are illustrated for this class of heterocycles below.

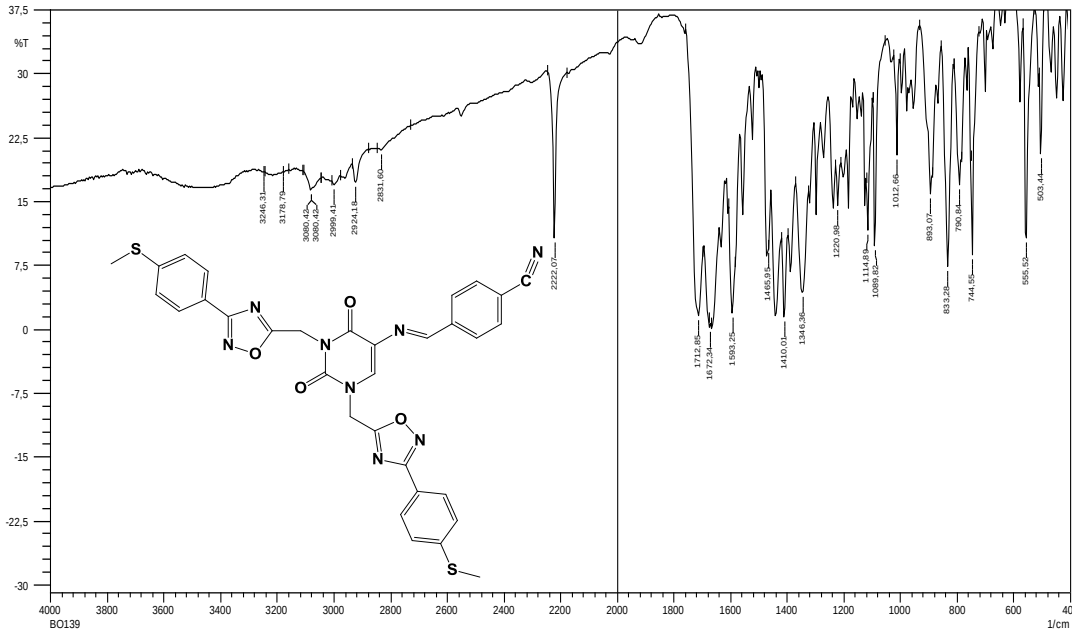


Figure 2.20. IR spectrum of compound **63b.**

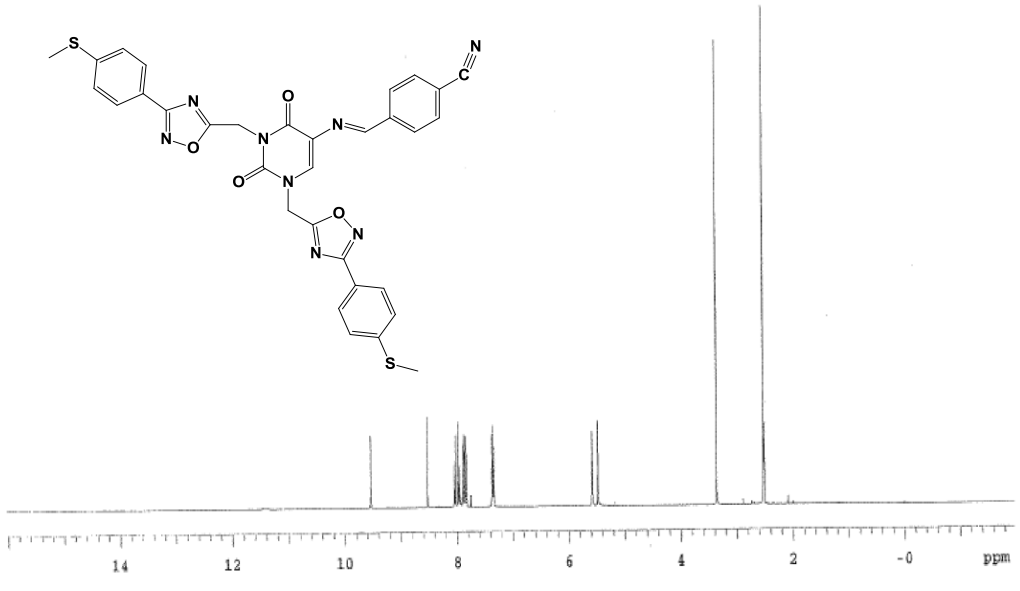


Figure 2.21. ^{1}H NMR spectrum of compound **63b.**

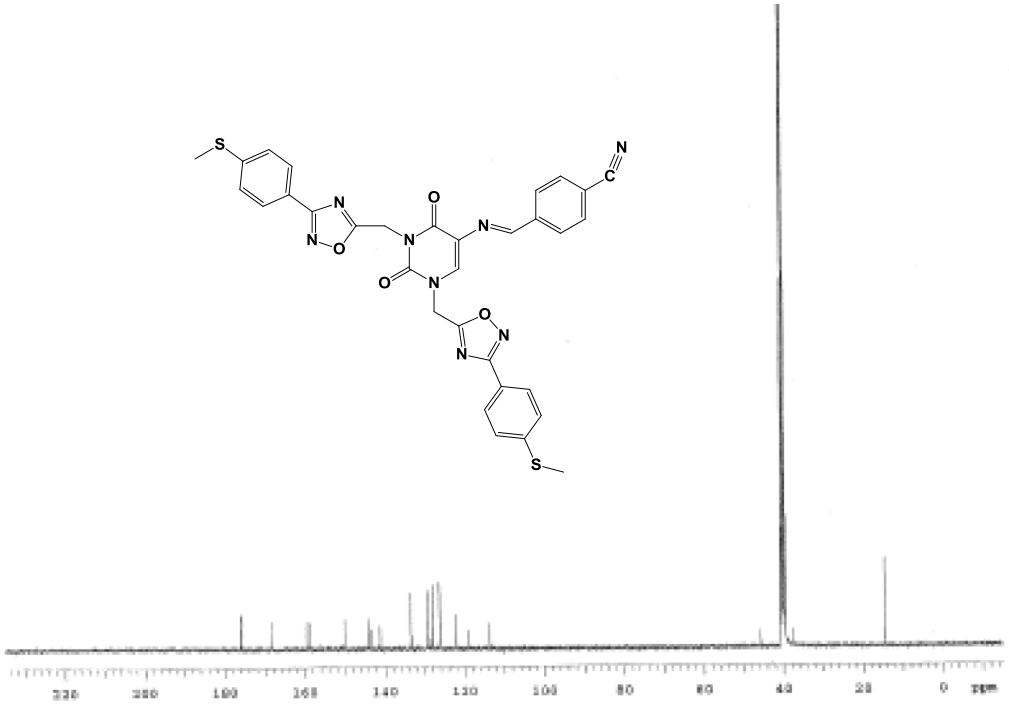


Figure 2.22. ^{13}C NMR spectrum of compound **63b.**

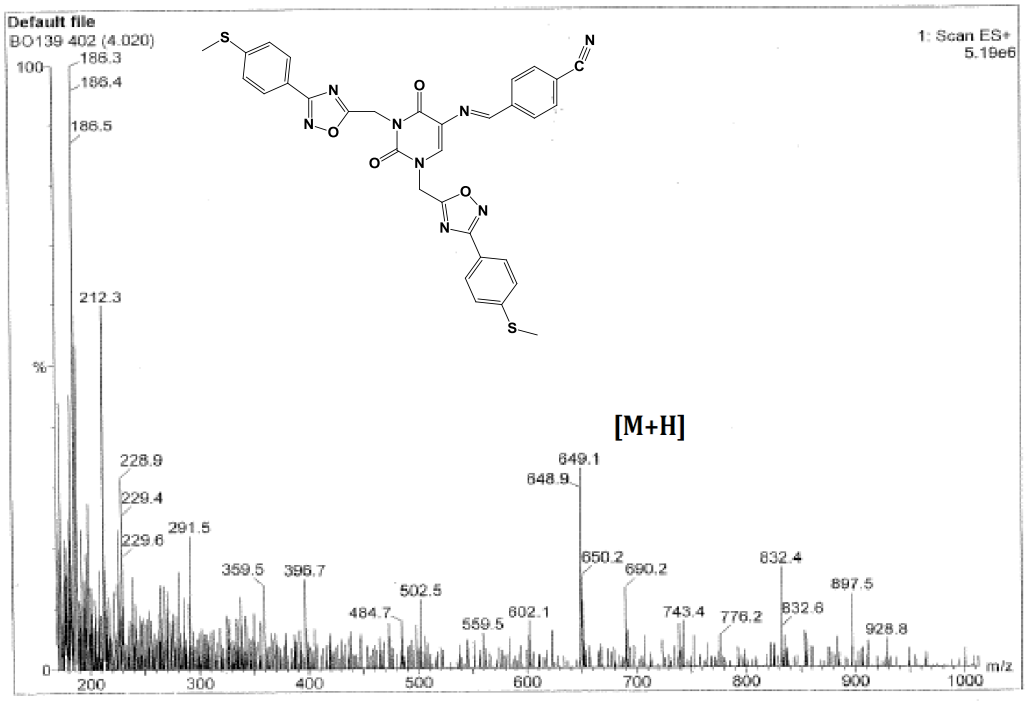


Figure 2.23. LC-MS spectrum of compound **63b.**

2.2. CONCLUSION

In this work we have demonstrated a one-pot and practical synthesis of 11 novel *N*-oxadiazolylmethyl substituted *O*-benzosulfimides,18 novel *N*-oxadiazolylmethyl substituted uracils and 8 novel 1,2,4 chloro methyloxadiazol substituted 5-aminouracil were described. Finally, 4 novel *N*-oxadiazolylmethyl substituted benzylideneamino pyrimidinediones have been synthesized. The structures of the all compounds were fully determined by using spectral/physical data. All of these 41 compounds are novel and since they carry oxadiazole, uracil, amino uracil and benzosulfimide groups, they are considered as potential bioactive heterocycles. For this reason, in the near future, they will be assayed for a series of biological activities such as anti-tumoral, anti-protozoal and antimicrobial in collaboration with international well-equipped and organized laboratories which are competent for such studies.

CHAPTER III

EXPERIMENTAL

^{1}H and ^{13}CNMR spectra were recorded on VARIAN and BRUKER spectrometers (300 and 400 MHz for ^{1}H; 75 and 100 MHz for ^{13}C). IR spectra were recorded on a SHIMADZU FTIR 8400-S instrument (KBr pellet). LC-MS spectra were run on Waters 2695 Alliance Micromass ZQ.Melting points were determined on a MELTEMP apparatus and uncorrected. Flash column chromatography was performed on Silica Gel (Merck, 230-400 Mesh ASTM). TLC was done by using precoated plates with fluorescent indicator (Merck 5735). The stain solutions of permanganate and iodine were used for visualization of the TLC spots.

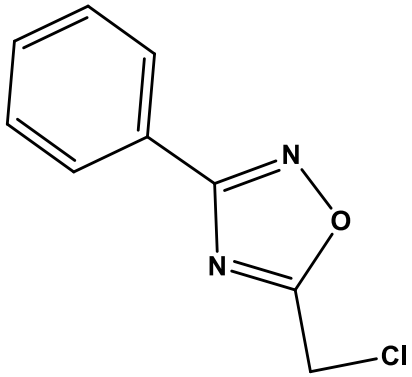
PART 1

In this part the synthesis of aromatic amidoximes and 1,2,4-oxadiazoles are examined. Amidoximes **(1a-j)** were synthesized according to the methods

described in literature [6-8]. 1,2,4-Oxadiazoles **(36a-j)** were synthesized according to the methods described in the literature [70].

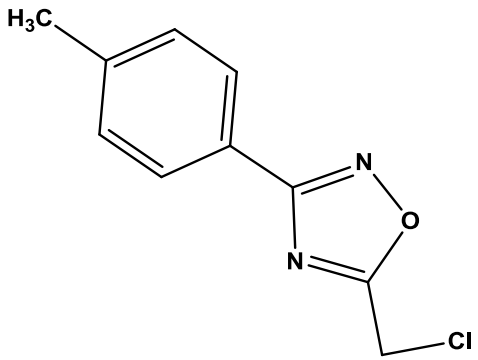
Synthesis of oxadiazoles(36a-j)

5-(Chloromethyl)-3-phenyl-1,2,4-oxadiazole (36a)



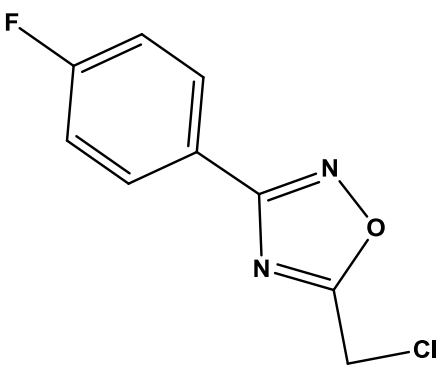
A solution of chloroacetylchloride (0.813 g, 7.2 mmol) in benzene (10 mL) was added dropwise to a solution of benzamidoxime **(1a)** (2.448 g, 18.0 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate;4:1) to give **(36a)** as a white solid. (1.145g, 82%). Mp: 39-40, Rf:0.875(n-Hexane:Ethyl acetate;1:1). IR (KBr, v:cm^{-1}): 3036 (Arom. C-H), 1573, 1518 (C=N), 1473, 1446, 1361,1288, 922,711(C-Cl).

5-(Chloromethyl)-3-(4-tolyl)-1,2,4-oxadiazole (36b)



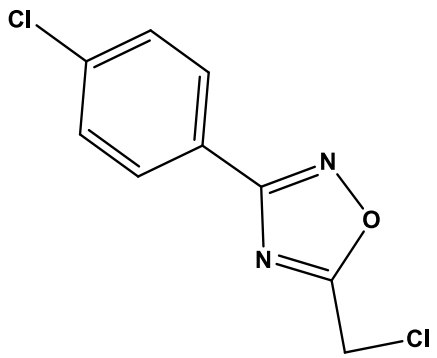
A solution of chloroacetylchloride (0.855g, 7.60 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-tolylbenzamidoxime **(1b)** (2.585 g, 17.00 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(36b)** as a white solid. (1.282 g, 82%). M.p.:46-46 ˚C. $R_{f.}$: 0.84 (n-Hexane:Ethyl acetate; 1:1). IR (KBr, v:cm^{-1}): 3028 (Arom. C-H), 1672, 1597 (C=N), 1473, 1411, 1361, 1300,1284, 1151,968, 827, 757(C-Cl).

5-(Chloromethyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (36c)



A solution of chloroacetylchloride (0.999 g, 8.88 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-fluorobenzamidoxime **(1c)** (1.700 g, 11 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. 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 **(36c)** as a yellow oily. (1.451 g, 78 %). $R_{f.}$: 0.853 (n-Hexane:Ethyl acetate; 1:1). IR (KBr, v:cm^{-1}): 3030 (Arom. C-H), 1606, 1583 (C=N), 1481, 1417, 1356, 1288, 1157,1014, 844, 754 (C-Cl).

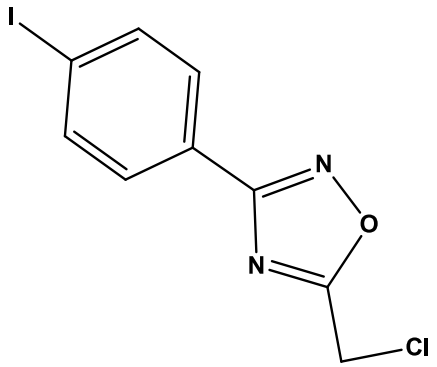
5-(Chloromethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (36d)



A solution of chloroacetylchloride (0.175 g, 1.55 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-chlorobenzamidoxime **(1d)** (0.633 g, 3.72 mmol) in benzene (50 mL) and the mixture was heated under reflux for 10h. 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 **(36d)** as a white solid.

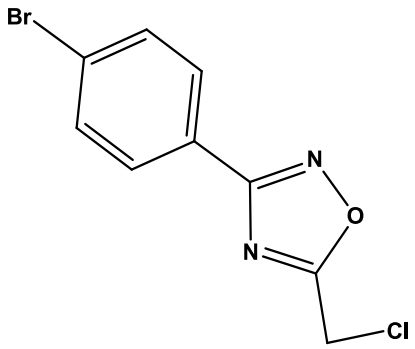
(0.376 g, 96 %). M.p:59-60 ˚C, R_f: 0.818 (n-Hexane:Ethyl acetate; 1:1). IR (KBr, v:cm^{-1}): 3022 (Arom. C-H), 1593, 1566 (C=N), 1473, 1410, 1354, 1149, 839, 740 (C-Cl).

5-(Chloromethyl)-3-(4-iodophenyl)-1,2,4-oxadiazole (36e)



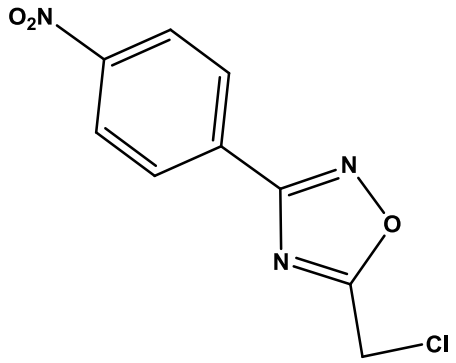
A solution of chloroacetylchloride (0.525 g, 4.56 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-iodobenzamidoxime **(1e)** (1.500 g, 5.73 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(36e)** as a yellow solid. (1.142 g, 79%). M.p.:71-73˚C. R_f: 0.743 (Eluant: n-Hexane:Ethyl acetate; 1:1). IR (KBr, v:cm^{-1}): 3157 (Arom. C-H), 1695, 1562 (C=N), 1467, 1404, 1352, 1273, 1141, 846, 729 (C-Cl).

5-(Chloromethyl)-3-(4-bromophenyl)-1,2,4-oxadiazole (36f)



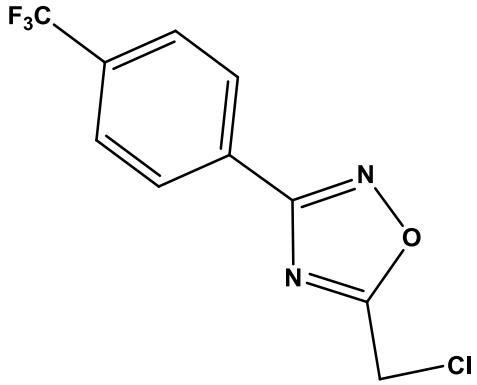
A solution of chloroacetylchloride (0.542 g, 4.84 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-bromobenzamidoxime **(1f)** (2.481 g, 11.64 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give **(36f)** as a white solid. (1.309 g, 98 %), M.p.:59-61˚C. $R_{f.}$: 0.794 (n-Hexane:Ethyl acetate; 1:1). IR(KBr, v:cm^{-1}): 3026 (Arom. C-H), 1653, 1593 (C=N), 1467, 1406, 1359, 1147, 835, 736(C-Cl).

5-(Chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (36g)



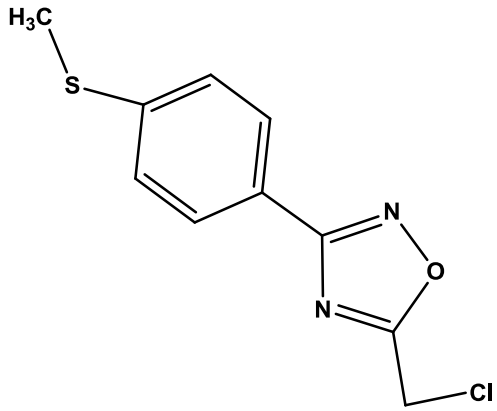
A solution of chloroacetylchloride (0.288 g, 2.57 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-nitrobenzamidoxime **(1g)** (0.579 g, 3.19 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give **(36g)** as a white solid. (0.476g, 77 %). M.p.:84-85˚C. R_f: 0.91 (n-Hexane:Ethyl acetate; 1:1). IR (KBr, v:cm^{-1}): 3080 (Arom. C-H), 1612, 1577 (C=N), 1514 (N=O), 1415, 1354, 1294, 1107, 854, 723 (C-Cl).

5-(Chloromethyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (36h)



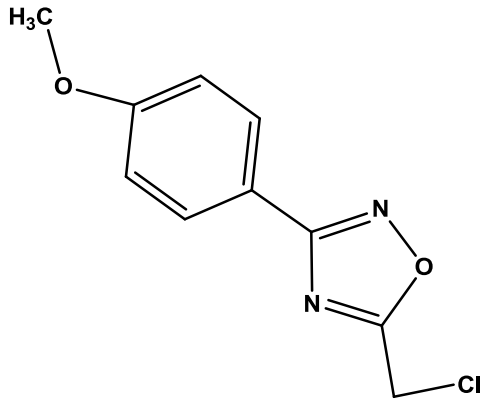
A solution of chloroacetylchloride (0.705 g, 6.30 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-trifluoromethylbenzamidoxime **(1h)** (1.600 g, 7.83 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give **(36h)** as a yellow oily. (1.09 g, 66 %). R_f: 0.83 (n-Hexane:Ethyl acetate; 1:1). IR (KBr, v:cm^{-1}): 3028 (Arom. C-H), 1626, 1597 (C=N), 1577, 1541, 1485, 1325, 1018, 854, 758(C-Cl).

5-(Chloromethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole (36i)



A solution of chloroacetylchloride (0.554 g, 4.94 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-methylthiobenzamidoxime **(1i)** (2.235 g, 12.28 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. 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; 6:1) to give **(36i)** as a white solid. (1.029 g, 87 %). M.p.:63-65 ˚C. R_f: 0.829 (n-Hexane:Ethyl acetate; 1:1). IR (KBr, v:cm^{-1}): 3039 (Arom. C-H), 1664, 1591 (C=N), 1469, 1410, 1359, 1294, 1186, 827, 740 (C-Cl).

5-(Chloromethyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (36j)

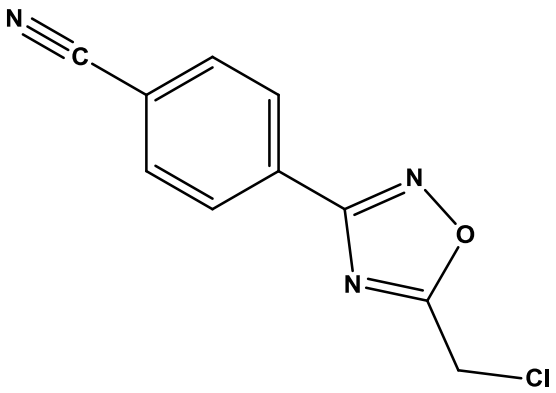


A solution of chloroacetylchloride (0.540 g, 4.82 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-methoxybenzamidoxime **(1j)** (1.00 g, 6.02 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(36j)** as a light yellow solid.

(0.843, 78 %). M.p.:39-40 ˚C. R_f: 0.794 (n-Hexane:Ethyl acetate; 1:1).

IR (KBr, v:cm^{-1}): 3063 (Arom. C-H), 1612, 1587 (C=N), 1481, 1460, 1259, 1253, 1170, 896, 750(C-Cl).

4-(5-(Chloromethyl)-1,2,4-oxadiazol-3-yl)benzonitrile (36k)



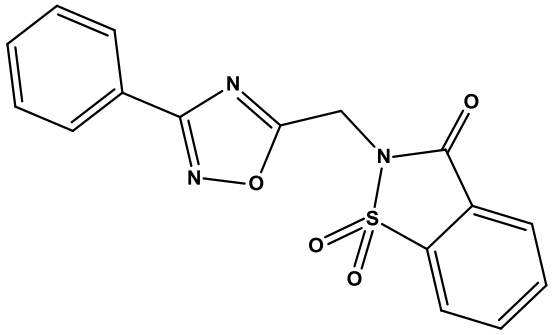
A solution of chloroacetylchloride (0.702 g, 6.26 mmol) in benzene (10 mL) was added dropwise to a solution of terephthalamidoxime **(1k)** (1.00 g, 6.18 mmol) in benzene 100 mL and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(36k)**as a light yellow solid.

(0.173, 13 %). M.p.:58-59˚C. $R_{f.}$: 0.743 (n-Hexane:Ethyl acetate; 1:1). IR (KBr, v: cm^{-1}): 3003 (Arom. C-H), 2200 (C≡N), 1612, 1597 (C=N), 1483, 1423, 1292, 1253, 1181, 842, 754 (C-Cl).

PART2

This part include synthesis of N-substituted O-benzosulfimide on chloromethyl oxadiazole **(59a-k)**

2-((3-Phenyl-1,2,4-oxadiazole-5-yl)methyl)benzo[d]isothiazol-3(*2H*)-one1,1-dioxide (59a)

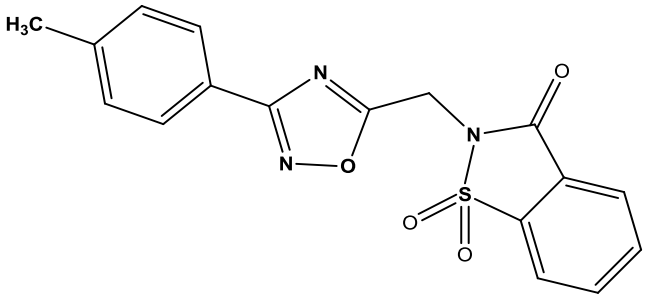


A mixture of 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (**36a)** (1 eq, 0.030 g, 0.18 mmol) and benzo[*d*]isothiazol-3(*2H*)-one 1,1-dioxide **57** (1 eq , 0,032 g, 0.18 mmol) with K_2CO_3 (0.5 eq, 0.0122 g ,0.125 mmol) in 5ml of DMF was heated at 130˚C for 2h and monitored by TLC.The reaction mixture was extracted with (ethyl acetate: cold water 1:1L)x4 and concentrared *in vacuo*, then the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(59a)** as a light yellow solid.

(38mg, %68). Mp.;158-160˚C. Rf: 0.625(n-Hexane:Ethyl acetate; 1:1).

IR(KBr,v:cm^{-1}): 3084(Ar. C-H) ,2924,2864(Aliph.C-H stretching), 1739 (C=O), 1340(asymmetric-SO_2-stretch), 1167(symmetric-SO_2-stretch), 1649, 1599 (C=N), 1460,1300, 1062. ^{1}H NMR(δ_H, 300MHz, $CDCl_3$): 8.15 (d, *J*=1.8Hz, 3H), 8.13-7.90 (m, 3H), 7.54-7.46 (m,3H), 5.30 (s ,2H). ^{13}C NMR($\delta_{C,}$ 100MHz, $CDCl_3$): 172,8 (C=O) ,168.8 (C=N), 158.8 (C=N), 137.9, 135.6, 134.9, 131.6, 129.1,127.8, 127.1,126.4, 125.9, 121.6, 33.9 (CH_2)

2-((3-(*p*-Tolyl)-1,2,4-oxadiazole-5-yl)methyl)benzo[*d*]isothiazol-3(*2H*)-one1,1-dioxide (59b)

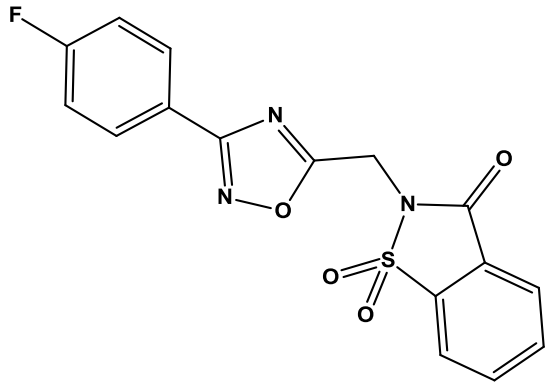


A mixture of 5-(chloromethyl)-3-(4-tolyl)-1,2,4-oxadiazole **(36b**) (1 eq,0.050 g, 0.24mmol) and benzo[d]isothiazol-3(*2H*)-one 1,1-dioxide **57** (1 eq , 0,049 g, 0.24mmol) with K_2CO_3 (0.5 eq, 0.027 g ,0.12 mmol) in DMF (5 mL) was heated at 130˚C for 2h and monitored by TLC. The reaction mixture was extracted with (ethyl acetate: cold water1: 1)x4 and concentrared *in vacuo*, then the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give (**59b**) as a lightwhite solid.

(35mg, %41). Mp;143-144˚C. Rf: 0.600(n-Hexane:Ethyl acetate; 1:1)

IR(KBr,v:cm^{-1}): 3101(Ar. C-H) 2987,2922(Aliph.C-H stretching), 1741 (C=O),1338(asymmetric-SO_2-stretch),1190(symmetric-SO_2-stretch), 1654, 1591 (C=N) ,1465,1298,1057, 902,827.^{1}H NMR (δ_H, 400MHz, DMS-d_6): 8.42(d, *J*=7.6Hz ,1H) , 8.21(d, *J*=7.6Hz, 1H), 8.13(dt, *J*=7.6Hz, 1H), 8.06(dt, *J*=7.6Hz, 1H), 8.07(dt,*J*=7.6Hz 2H), 7.87(d, *J*=8.4Hz,1H), 7.38(d, *J*=8Hz, 1H), 5.48(s, 2H) ,2.38(s, 3H).^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO): 174,0(C=O) ,167,7 (C=N) , 158.2 (C=N), 1421.8, 136.7, 136.3, 129.8, 126.9,125.7, 125.5, 122.9, 125.9, 33.4(CH_2) 21.0(CH_3).

2-((3-(4-Fluorophenyl)-1,2,4-oxadiazole-5-yl)methyl)benzo[*d*]isothiazol-3(*2H*)-one1,1-dioxide (59c)



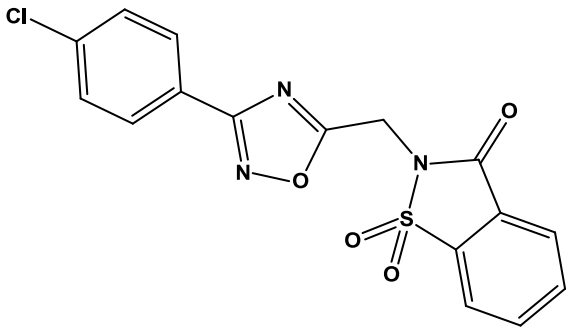
A mixture of 5-(chloromethyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole **(36c)** (1 eq,0.150 g, 0.80 mmol) and benzo[*d*]isothiazol-3(*2H*)-one 1,1-dioxide **57**(1 eq , 0,146 g, 0.80 mmol) with K_2CO_3 (0.5 eq, 0.055 g ,0.40 mmol) in of DMF (5mL) was heated at 130˚C for 2h and monitored by TLC. The reaction mixture was extracted with ethyl acetate: cold water (25mL:25mL)x4 and concentrared *in vacuo*, then the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(59c)** as a light white solid.

(166mg, %58). Mp.:134-135˚C. Rf: 0.484(n-Hexane:Ethyl acetate; 1:1)

IR(KBr,v:cm^{-1}): 3091, 3005 (Ar. C-H) 294(Aliph.C-H stretching), 1741(C=O), 1342(asymmetric -SO_2- stretch), 1190 (symmetric -SO_2- stretch), 1595,1579 (C=N) ,1483 ,1413,1068, 852. ^{1}H NMR (δ_H, 300MHz, $CDCl_3$): 8.13(d, *J*=10Hz, 1H), 8.07-7.91(m,5H), 7.13(t, *J*=8.6Hz, 2H), 5.21(s,2H). ^{13}C NMR ($\delta_{C,}$ 100MHz, $CDCl_3$): 172,8(C=O) ,167,9 (C=N) ,158.4 (C=N), 137.6, 135.6,

135.4, 129.8, 126.7, 125.7, 122.4, 122.5, 122.4, 122.4, 121.4, 116.2, 115.9, 33.6 (CH_2)

2-((3-(4-Chlorophenyl)-1,2,4-oxadiazole-5-yl)methyl)benzo*[d]*isothiazol-3(*2H*)-one1,1-dioxide (59d)



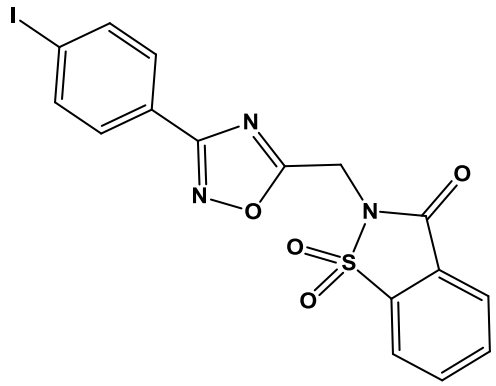
A mixture of 5-(Chloromethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole **(36d)** (1 eq,0.080g, 0.35mmol) and benzo[*d*]isothiazol-3(*2H*)-one 1,1-dioxide **57** (1 eq, 0,064g, 0.35mmol) with K_2CO_3 (0.5eq, 0.024g ,0.17mmol) in 5ml of DMF was heated at 130˚C for 2h and monitored by TLC. The reaction mixture was extracted with (ethyl acetate: cold water 1:1)x4 and concentrared *in vacuo*, then the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(59d)** as a light yellow solid.

(130mg, %99). Mp.;142-143˚C.Rf: 0.571(n-Hexane: Ethyl acetate; 1:1).

IR(KBr,v:cm^{-1}):3091, 3009 (Ar. C-H) 2943,2918 (Aliph.C-H stretching), 1739(C=O), 1342(asymmetric-SO_2- stretch),1192(symmetric -SO_2- stretch), 1664,1595 (C=N) ,1568, 1467,1410, 1271,1165, 1066.^{1}H NMR (δ_H, 300MHz, $CDCl_3$): 8.86(d, *J*=20Hz, 1H), 8.15-7.80(m, 5H), 7.97(d, *J*=66.8Hz, 2H), 5.20(s, 2H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-*d_6*):173,1(C=O) ,168,3 (C=N)

,158.7(C=N), 137.8, 135.7, 135.4, 129.4, 126.9, 124.9, 121.6, 122.5,33.8(CH_2).

2-((3-(4-Iodophenyl)-1,2,4-oxadiazole-5-yl)methyl)benzo[*d*]isothiazol-3(*2H*)-one1,1-dioxide (59e)

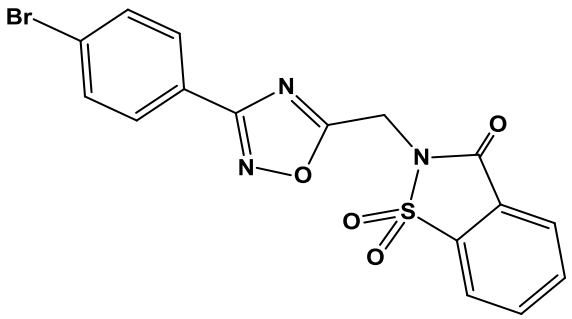


A mixture of 5-(chloromethyl)-3-(4-iodophenyl)-1,2,4-oxadiazole **36e** (1 eq, 0.100 g, 0.31 mmol) and benzo[*d*]isothiazol-3*(2H)*-one 1,1-dioxide **57** (1 eq , 0,062g, 0.31mmol) with K_2CO_3 (0.5eq, 0.021g ,0.16mmol) in 5ml of DMF was heated at 130˚C for 2h and monitored by TLC. The reaction mixture was extracted with (ethyl acetate: cold water 1:1)x4 and concentrared in vacuo, then the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(59e)** as a light yellow solid.

(74mg, %54). Mp.;161-162˚C. Rf: 0.500(n-Hexane:Ethyl acetate; 1:1). IR(KBr,v:cm^{-1}): 3088, (Ar. C-H) 2943,1922, (Aliph.C-H stretching), 1739 (C=O), 1342(asymmetric –SO_2- stretch),1190(symmetric –SO_2- stretch), 1593,1552 (C=N) ,1467,1404,1315,1057. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$):

8.43(d, *J*=7.6Hz, 1H), 8.21-7.80(m, 7H), 5.5(s, 2H).^{13}C NMR ($\delta_{C,}$100 MHz, DMSO-d_6): 173,1(C=O) ,168,5 (C=N) ,158.6(C=N), 138.3, 137.8, 135.7, 135.0, 129.3, 126.9, 125.9,125.9, 121.6, ,33.8 (CH_2).

2-((3-(4-Bromophenyl)-1,2,4-oxadiazole-5-yl)methylbenzo[*d*]isothiazol-3 (*2H*)-one1,1-dioxide (59f)



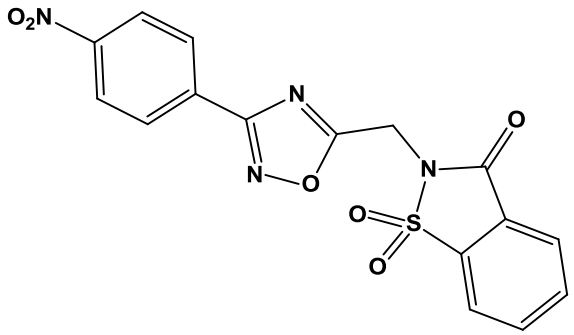
A mixture of 5-(chloromethyl)-3-(4-bromophenyl)-1,2,4-oxadiazole **(36f)** (1 eq,0.150g, 0.55 mmol) and benzo[*d*]isothiazol-3*(2H)*-one 1,1-dioxide **57** (1 eq, 0,100 g, 0.55 mmol) with K_2CO_3 (0.5 eq, 0.038 g ,0.27 mmol) in DMF (5 mL) was heated at 130˚C for 2h and monitored by TLC. The reaction mixture was extracted with (ethyl acetate cold water 1:1L)x4 and concentrared *in vacuo*, then the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(59f)** as a light white solid.

(74mg, %78). Mp.;163-164˚C. Rf: 0.606(n-Hexane:Ethyl acetate; 1:1).

IR(KBr, v:cm^{-1}): 3090, 3007 (Ar. C-H) 2943, 2918(Aliph.C-H stretching), 1739 (C=O), 1342 (asymmetric -SO_2- stretch),1192 (symmetric -SO_2- stretch), 1595,1566(C=N), 1469, 1408, 1271, 1165, 1066. ^{1}H NMR (δ_H, 300MHz, $CDCl_3$): 8.13(d, *J*=7.5Hz,1H), 7.99-7.86(m,5H), 7.58(d, *J*=8.4Hz,

2H), 5.22(s,2H). ^{13}C NMR ($\delta_{C,}$ 300MHz, $CDCl_3$): 172,9(C=O) ,168,1 (C=N) ,158.4(C=N), 137.6, 135.4, 134.7, 132.1, 129.1, 126.9, 126.7,125.7, 121.4, ,33.6 (CH_2).

2-((3-(4-Nitrophenyl)-1,2,4-oxadiazole-5-yl)methyl)benzo[*d*]isothiazol-3(*2H*)-one1,1-dioxide (59g)

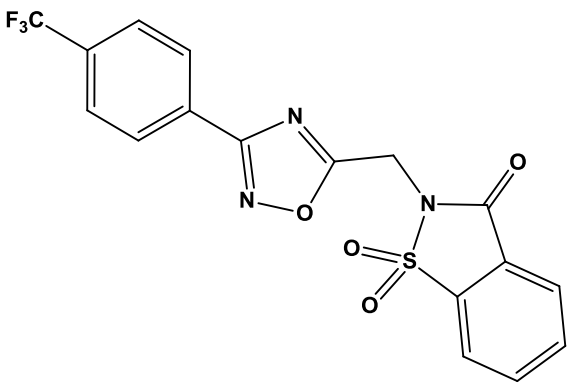


A mixture of 5-(chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole **(36g)** (1 eq, 0.100 g, 0.42 mmol) and benzo[*d*]isothiazol-3(*2H*)-one 1,1-dioxide **57** (1 eq, 0,076 g, 0.42 mmol) with K_2CO_3 (0.5 eq, 0.029 g ,0.21mmol) in of DMF (5mL) was heated at 130˚C for 2h and monitored by TLC. The reaction mixture was extracted with (ethyl acetate: cold water 1:1)x4 and concentrared *in vacuo*, then the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(59g)** as a light white solid.

(74mg, %40). Mp.;223-224 ˚C (dec.). Rf: 0.606(n-Hexane:Ethyl acetate; 1:1). IR(KBr, v:cm^{-1}): 3095, 3005 (Ar. C-H) 2945,2850 (Aliph.C-H stretching), 1739 (C=O), 1338(asymmetric-SO_2-stretch), 1190(symmetric-SO_2-stretch),

1585,1566 (C=N) , 1465,1413, 1271,1105,1068. ^{1}H NMR (δ_H, 300MHz, $CDCl_3$): 8.25(dt, *J*=25.3, 8.1Hz,3H), 7.96(dd, *J*=13.4, 7.6Hz,3H), 7.26(s, 1H), 6.99(s, 1H), 5.24(s,2H). ^{13}C NMR ($\delta_{C,}$ 100MHz, $CDCl_3$):173.5(C=O), 167.3(C=N), 149.6, 137.7, 135.5, 134.8, 132.0, 128.6, 126.7,125.8, 124.1, 121.5, 33.6(CH_2).

2-((3-(4-Trifluoromethylphenyl)-1,2,4-oxadiazole-5-yl) methyl) benzo [*d*] isothiazol-3(*2H*)-one1,1-dioxide (59h)

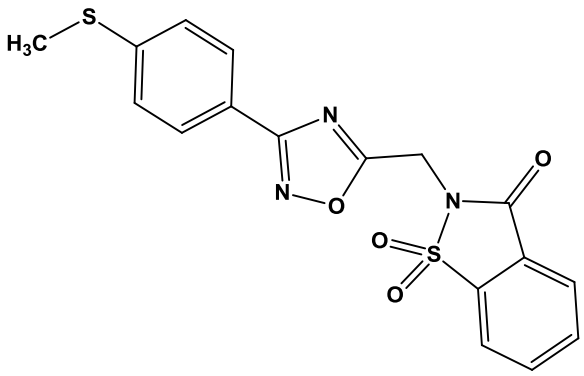


A mixture of 5-(chloromethyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole **(36h)** (1 eq, 0.150 g, 0.57 mmol) and benzo[d]isothiazol-3(*2H*)-one 1,1-dioxide **57**(1 eq , 0,105 g, 0.42 mmol) with K_2CO_3 (0.5 eq, 0.039 g ,0.28 mmol) in of DMF (5mL) was heated at 130˚C for 2h and monitored by TLC. The reaction mixture was extracted with (ethyl acetate: cold water 1:1)x4 and concentrared *in vacuo*, then the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(59h)** as a light yellow solid.

(219 mg, %93). Mp.;166-167˚C. Rf: 0.697(n-Hexane:Ethyl acetate; 1:1)

IR(KBr, v:cm^{-1}): 3093, 3005(Ar. C-H), 2945,2850(Aliph.C-H stretching), 1737(C=O), 1338 (asymmetric-SO_2-stretch), 1190 (symmetric-SO_2- stretch), 1585,1566 (C=N) ,1487,1417, 1273,1170,1114. ^{1}HNMR(δ_H, 300MHz, $CDCl_3$):8.16(t,*J*=7.9Hz,3H),8.01-7.87(m,3H), 7.7(d, *J*=8.1Hz, 2H), 5.24(s,2H). ^{13}C NMR ($\delta_{C,}$ 100MHz, $CDCl_3$): 173,7(C=O), 168,0(C=N), 158.7(C=N), 162.0(CF_3), 161.7, 137,9, 135.7, 133.5, 129.8, 126.9, 125.9, 122.1, 121.6, 33.8 (CH_2).

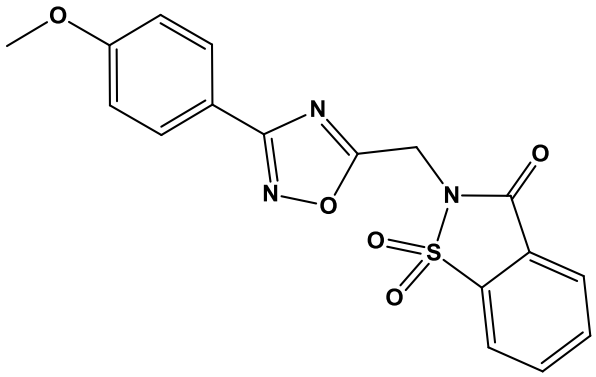
2-((3-(4-(Methylthio)phenyl)-1,2,4-oxadiazole-5-yl)methyl)benzo[*d*] isothiazol-3(*2H*)-one1,1-dioxide (59i)



A mixture of 5-(Chloromethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole **(36i)** (1 eq,0.100 g, 0.41mmol) and benzo[*d*]isothiazol-3(*2H*)-one 1,1-dioxide **57** (1eq, 0,076 g, 0.41 mmol) with K_2CO_3 (0.5 eq, 0.029 g ,0.20 mmol) in of DMF (5mL) was heated at 130˚C for 2h and monitored by TLC. The reaction mixture was extracted with (ethyl acetate: cold water 1:1)x4 and concentrared *in vacuo*, then the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(59i)** as a light yellow solid.

(105 mg, %65). Mp.;153-154 ˚C . Rf: 0.471(n-Hexane:Ethyl acetate; 1:1) IR(KBr, v:cm^{-1}): 3176, 3086 (Ar. C-H) 2916,2868 (Aliph.C-H stretching), 1747 (C=O), 1329 (asymmetric-SO_2-stretch), 1186 (symmetric-SO_2-stretch), 1658,1595 (C=N), 1467, 1294,1126,970. ^{1}H NMR (δ_H, 400MHz, DMSO-*d_6*): 8.22(d,*J*=25Hz,1H), 8.00-7.81(m,5H), 7.34(d,*J*=24Hz,2H), 5.25(s,2H), 2.56(s,3H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-*d_6*): 173.5(C=O), 171.1(C=N), 159.6(C=N), 157.3, 143.7, 126.9, 126.0, 121.6, 34.0 (CH_2), 15.3(CH_3).

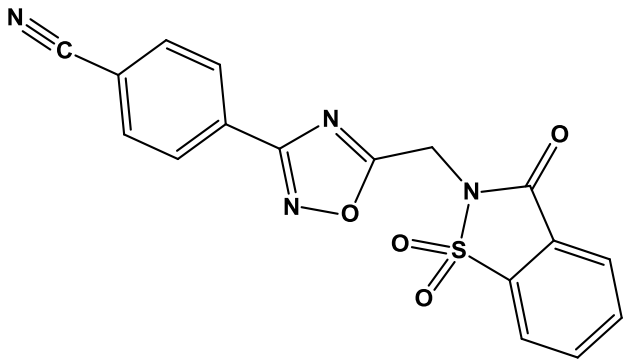
2-((3-(4-(Methoxy)phenyl)-1,2,4-oxadiazole-5-yl)methyl)benzo[*d*] isothiazol-3(*2H*)-one1,1-dioxide (59j)



A mixture of 5-(Chloromethyl)-3-(4-(methoxy)phenyl)-1,2,4-oxadiazole **(36j)** (1 eq, 0.080g, 0.36mmol) and benzo[*d*]isothiazol-3(*2H*)-one 1,1-dioxide **57**(1 eq , 0,065 g, 0.36 mmol) with K_2CO_3 (0.5 eq, 0.025 g ,0.18 mmol) inof DMF (5mL) was heated at 130˚C for 2h and monitored by TLC. The reaction mixture was extracted with (ethyl acetate: cold water 1:1)x4 and concentrared in vacuo, then the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give **(59j)** as a light white solid.

(57 mg, %43). Mp.;154-55 ˚C. Rf: 0.457n-Hexane:Ethyl acetate; 1:1). IR(KBr, v:cm^{-1}): 3090(Ar. C-H) 2997,2916 (Aliph.C-H stretching), 1753 (C=O), 1329 (asymmetric -SO_2- stretch),1188 (symmetric -SO_2-stretch),1602,1572(C=N), 1483, 1425, 1305, 1255, 1172, 1105, 1064. ^{1}H NMR (δ_H, 400 MHz,DMSO-d_6) : 8.4(d,*J*=8.6Hz,1H), 8.2(d,*J*=7,6Hz, 1H), 8.1(dt, *J*=7.6, 6.4Hz, 1H), 8.03(dt, *J*=7.6,6.8Hz, 1H), 7.88(td, *J*=8.8Hz, 2H), 7.1(q, *J*=9.2Hz,2H), 5.4(s,2H),3.8(d, *J*=4Hz, 3H). ^{13}C NMR ($\delta_{C,}$100MHz, $CDCl_3$): 172,5(C=O), 135.6, 126,4, 125.9, 121.5, 118.8, 114.4,55.6 (CH_3).

4-(5-((1,1-Dioxido-3-oxobenzo[*d*]isothiazol-2(*3H*)-yl)methyl)-1,2,4-oxadiazol-3-yl)benzonitrile (59k)



A mixture of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)benzonitrile **(36k)** (1 eq,0.040 g, 0.18 mmol) and benzo[*d*]isothiazol-3(*2H*)-one 1,1-dioxide **57** (1 eq , 0,033 g, 0.18 mmol) with K_2CO_3 (0.5 eq, 0.013 g ,0.009 mmol) in DMF (5mL) was heated at 130˚C for 2h and monitored by TLC. The reaction mixture was extracted with (ethyl acetate: cold water 1:1)x4 and concentrared *in vacuo*, then the crude residue was purified by flash column

chromatography (n-hexane:ethyl acetate; 4:1) to give **(59k)** as a light yellow solid.

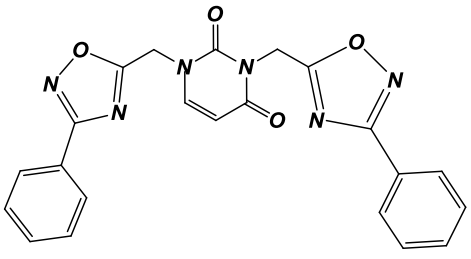
(0.040 mg, %60). Mp.;154-155 ˚C. Rf: 0.457n-Hexane:Ethyl acetate; 1:1) IR(KBr, v:cm^{-1}): 3074 (Ar. C-H) 2956, 2924 (Aliph.C-H stretching), 1735 (C=O), 1342(asymmetric -SO2- stretch),1186 (symmetric -SO2- stretch), 1664,1597(C=N), 2231(C≡N),1467, 1413, 1301, 1263, 1186, 1062, 854. ^{1}H NMR (δ_H, 300 MHz, $CDCl_3$): 8.17-7.28(m, 8H), 5.30(s,2H).^{13}C NMR ($\delta_{C,}$100MHz, $CDCl_3$): 176,4(C=O), 167.7(C=N), 158.7(C=N),162.0, 159.8, 135.6, 128,9, 128.3, 121.5, 115.1(C=N), 29.6(CH_2)

PART 3

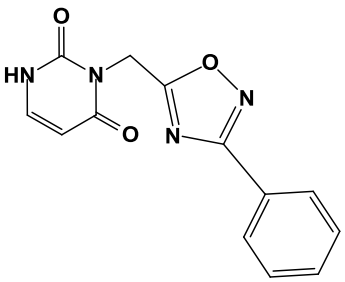
Synthesis of N-subtituted of uracil on chloromethyl oxadiazole **(60a-h)** and **(61a-h)**

1,3-Bis((5-phenyl-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4 (*1H,3H*)

dione (60a) and 3-((5-Phenyl-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(*1H,3H*)-dione (61a)



60a



61a

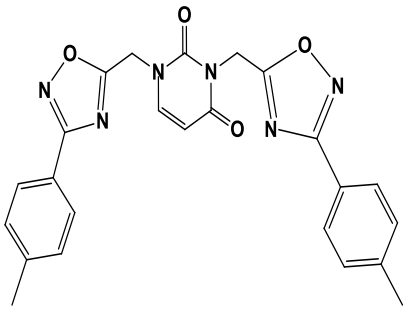
A mixture of uracil **58** (1 eq, 0.020 g ,0.179 mmol) and 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole **(36a)** (2 eq, 0.080 g , 0.359 mmol) with K_2CO_3 (1 eq, 0.025 g, 0.179 mmol) in DMF (5mL) was mixed at room temperature for 5h and monitored by TLC. The reaction mixture was extracted with (Diethyl ether:cold water; 1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(60a)** yellow oily and white **(61a)**solid.

60a: (0.030mg, %39). Rf: 0.428, (n-Hexane:Ethyl acetate; 1:3). IR(KBr, v:cm^{-1}):3070(Ar. C-H) 2997, 2960, 2924, 2857(Aliph.C-H stretching),1718(C=O), 1676, 1597(C=N), 1446, 1483, 1425, 1305, 1255, 1172, 1105, 1064. ^{1}H NMR (δ_H, 400 MHz, DMSO-d_6): 8.06(d, *J*=7.6Hz, 1H), 7.98-7.93(m,4H), 7.82(s,1H), 7.61-7.52(m,6H), 6.05(d, *J*=8.4Hz, 1H), 5.49(s,2H), 5.41(s,2H). ^{13}C NMR ($\delta_{C,}$ 100 MHz, DMSO-d_6): 175.5, 175.4 (C=O), 167.7, 167.4 (C=O), 161.6(C=N), 150.6 (C=N), 125.5(C=C), 100.8(C=C), 44.8(CH_2), 36.6(CH_2), 145.1, 134.0, 132.6, 131.7, 131.6, 129.2, 129.2, 126.9, 125.6. LC-MS (80 eV) (*m/z*, %): 429 (100) $[M+H]^+$, 285(9), 270(5).

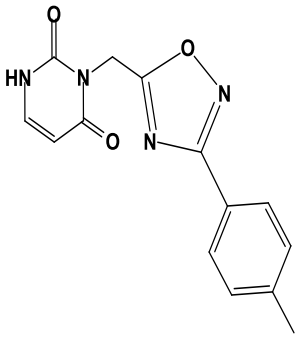
61a: (0,012mg, %24). Mp.**:** 193-195 ˚C. Rf: 0.171. (n-Hexane:Ethyl acetate; 1:3). IR(KBr,v:cm^{-1}): 3527(N-H),3149, 3095(Ar.C-H) 2823, 2872,2 (Aliph.C-H stretching), 1728, 1714(C=O), 1693, 1597(C=N), 1460, 1386, 1357, 1253, 1197, 1101, 941, 904. ^{1}H NMR (δ_H, 400 MHz, DMSO-d_6): 11.56(s, NH), 7.99(d, *J*=6.8Hz, 2H), 7.84(d, *J*=8,1Hz, 1H), 7.58(q, *J*=8.5Hz, 3H), 5.74(s,1H), 5.34(s,2H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-d_6): 176.5(C=O),

168.4(C=O), 164.3(C=N), 151.5(C=N), 126.3(C=C), 102.5(C=C), 44.4(CH_2),146.2,132.5, 130.0, 127.7. LC-MS (80 eV) (*m/z*, %): 271 (64) $[M+H]^+$.

1,3-Bis((5-(*p*-tolyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4*(1H,3H)*-dione (60b) and 3-((5-Phenyl-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(*1H,3H*)-dione (61b)



60b



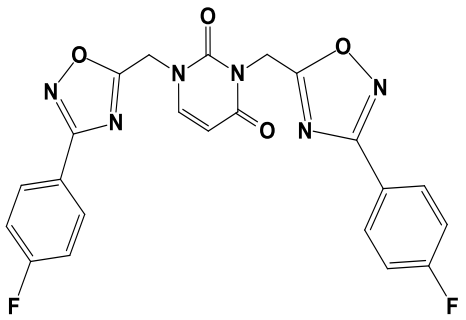
61b

A mixture of uracil **58** (1 eq, 0.027 g ,0.239 mmol) and 5-(chloromethyl)-3-(4-p-tolyl)-1,2,4-oxadiazole **(36b)** (2 eq, 0.100 g , 0.479 mmol) with K_2CO_3 (1 eq, 0.033 g,0.239 mmol) in DMF (5 mL) was mixed at room temperature for 5h and monitored by TLC.The reaction mixture was extracted with (Diethyl ether:cold water; 1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared in vacuo, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(60b)** white solid and **(61b)** white solid.

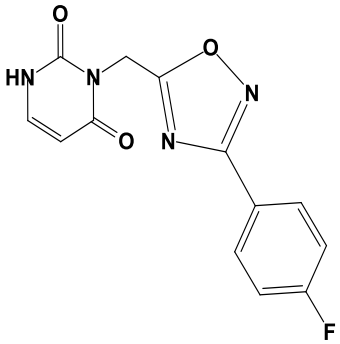
60b: (0,038mg, %34), Rf:0.486 (n-Hexane:Ethyl acetate; 1:3). Mp:133-134˚C. IR(KBr,v:cm^{-1}): 3078, 3034(Ar.,C-H) 2985, 2949, 2922, 2854, 281 (Aliph.C-Hstretching), 1730,(C=O), 1672, 1597,1(C=N), 5351481, 1454, 1411, 1361, 1340, 1242, 943, 891, 746. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 8.04(d, *J*=8Hz, 1H), 7.86-781(m,4H), 7.32(t, *J*=8, 1H), 6.05(d, *J*=8Hz ,1H), 5.46(s,2H), 5.39(s,2H), 2.51(t, *J*=1.6Hz,1H), 2.37(d, *J*=3.2Hz, 6H). ^{13}C NMR (δ_C, 100MHz, DMSO-d_6): 176.1, 175,9(C=O), 168.4,168.3(C=O), 162.4(C=N), 151.4(C=N), 123.6(C=C), 101.6(C=C),145.8, 142.4, 142.3, 130.5, 127.7, 127.6, 123.5, 37.3(CH_2), 21.8(CH_3). LC-MS (80 eV) (*m/z*, %): 457(100) $[M+H]^+$, 154(6).

61b: (0,024 mg, %35). Rf:0.273(n-Hexane:Ethyl acetate; 1:3). Mp:201-202˚C. IR(KBr,v:cm^{-1}): 3446(N-H), 2982, 2941, 2922,(Aliph.C-Hstretching), 1735 (C=O), 1678, 1595 (C=N), 1485, 1344, 1107, 895, 736. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6):11.54(s, NH), 7.86(dd, *J*=8.4, 8 Hz 3H), 7.37(d, *J*=8,4Hz, 1H), 5.73(d, *J* = 8Hz,1H), 5.32(s,1H), 5.34(s,2H), 2.38(s,3H). ^{13}C NMR (δ_C, 100MHz,DMSO-d_6):176.3(C=O), 168.4(C=O), 164.3(C=N), 151.5(C=N) ,123.6(C=C),102.5(C=C),44.4(CH_2),21.7(CH_3),146.2,142.5,130.6, 127.7

1,3-Bis((3-(4-fluorophenyl)-1,2,4-oxadiazol-5ylmethyl)pyrimidine-2,4 (*1H,3H*)-dione (60c) and 3-((5-(4-Fluorophenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(*1H,3H*)-dione (61c)



60c



61c

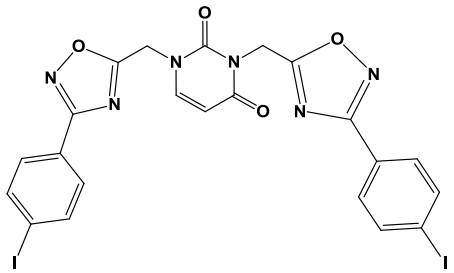
A mixture of uracil **58** (1 eq, 0.026 g ,0.260 mmol) and 5-(chloromethyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole **(36c)** (2 eq, 0.100 g , 0.470 mmol) with K_2CO_3 (1 eq, 0.033 g, 0.260 mmol) in DMF (5 mL) was mixed at room temperature for 5h and monitored by TLC.The reaction mixture was extracted with (Diethyl ether:cold water (1:1)x4 and) and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(60c)** white solid and **(61c)** white solid.

60c: (0.038mg, %31). Rf:0.555 (n-Hexane:Ethyl acetate; 1:3). Mp**:**123-124 ˚C. R(KBr, v:cm^{-1}): 3080, 3018(Ar. C-H) 2951, 2924, 2850, 2762 (Aliph.C-Hstretching),1730(C=O), 1604, 1581(C=N), 1672, 1483, 1450, 1419, 1359, 1342, 1240, 893(C-F). ^{1}H NMR(δ_H, 400MHz, DMSO-d_6): 8.06-7.98(m,5H),

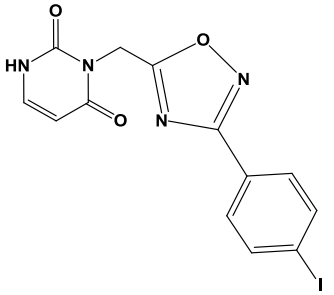
7.41-7.34(m,4H), 6.02(d,*J*=8.4Hz,1H), 5.49(s,2H), 5.41(s, 2H). ^{13}C NMR ($\delta_{C,}$ 100 MHz, DMSO-d_6): 176.4, 176,3(C=O), 167.6, 167.6(C=O), 165.9(C=N), 163.4(C=N),122.9(C=C), 117.3(C=C),145.8, 130.4, 130.3, 130.2, 122.8, 117.1, 37.3(CH_2). LC-MS (80 eV) (*m/z*, %): 465 (100)$[M+H]^+$.

61c: (0,024mg, %29). Rf: 0.444 (n-Hexane:Ethyl acetate; 1:3). Mp**:** 226-1227 ˚C (dec). IR(KBr,v:cm^{-1}): 3537(N-H),3109, 3016(Ar.C-H) 2999, 2926,2872(Aliph.C-H stretching), 1712,(C=O), 1664,1608(C=N), 1483 1460, 1417,1348, 1242, 1165, 943, 844,817. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 11.55(s, NH), 8.06-8.03(m, 2H), 7.84(d, *J*=8Hz, 1H), 7.41(t, *J*=8.8Hz, 2H), 5.74(d, *J*=7.6Hz, 1H), 5.34(s,2H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-d_6): 175.8(C=O), 166.9(C=O), 165.2(C=N), 163.5(C=N), 122.2(C=C), 101.8(C=C), 45.6(CH_2),162.7, 150.7, 145.4, 129.6, 116.6. LC-MS (80 eV) (*m/z*, %): 289(100) $[M+H]^+$.

1,3-Bis((3-(4-iodophenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrimidine2,4 (*1H,3H*)-dione (60d) and 3-((5-(4-Iodophenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4 (*1H,3H*)-dione (61d)



60d



61d

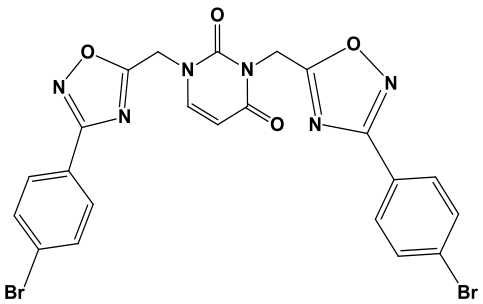
A mixture of uracil **58** (1 eq, 0.017 g ,0.156 mmol) and 5-(Chloromethyl)-3-(4-ıodophenyl)-1,2,4-oxadiazole **(36e)** (2 eq, 0.100 g ,0.312 mmol) with K_2CO_3 (1 eq, 0.022 g, 0.156 mmol) in DMF (5mL) was mixed at room temperature for 5h and monitored by TLC. The reaction was The reaction mixture was extracted with (Diethyl ether:cold water1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(60d**) white solid and **(61d)**white solid.

60d: (74 mg, %49). Rf: 0.645(n-Hexane:Ethyl acetate; 1:3). Mp**:** 82-83 ˚C IR(KBr, v:cm^{-1}): 3091(Ar. C-H),2956, 2852,2802,2754, (Aliph.C-H stretching),1757,1701(C=O),1664(C=N),1591,1558(C=N),1452,1400, 1329,1298,1247,1180,1107,1057,833,786(C-I). ^{1}H NMR(δ_H, 400MHz, DMSO-d_6):7.99(d, J=8.4Hz,1H), 7.86(t,*J*=8.2Hz,4H), 7.70-7.47(m,4H), 6.00(d, *J*=8.4Hz, 1H), 5.43(s,2H), 5.36(s,2H). ^{13}CNMR (δ_C, 100 MHz, DMSO-d_6): 176.5, 176,4(C=O), 167.9,167.8(C=O), 162.3(C=N), 151.4(C=N), 125.2,125.7(C=C), 101.6(C=C), 145.8, 138.5, 138.9, 129.4, 45.5(CH_2). LC-MS (80 eV) (*m/z*, %): 681(35) $[M+H]^+$, 441(21).

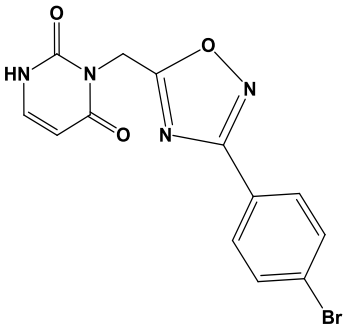
61d: (0.25mg, %29), Rf **:** 0.290(n-Hexane:Ethyl acetate; 1:3). Mp:210-211˚C. IR(KBr,v:cm^{-1}): 3441(N-H), 3090(Ar.C-H), 2956, 2920(Aliph.C-H stretching),1722(C=O), 1666, 1591(C=N),1562,1450,1402,1336,1273, 1234, 1180,1107,1006,808,740(C-I). ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 11.547(s,1H),7.95(d, *J*=8.4Hz,2H), 7.80(dd, *J*=8.4, 8Hz,3H)

5.75(d, *J*=7.6Hz,1H), 5.34(s,2H). ^{13}C NMR ($\delta_{C,}$ 100 MHz, DMSO-d_6):): 176.8 (C=O), 167.9C=O), 164.3C=N), 151.5(C=N), 125.8(C=C), 102.5(C=C), 44,4(CH_2),146.2,139.0, 129.5,100.0.

1,3-Bis((3-(4-bromophenyl)-1,2,4-oxadiazol-5yl)methyl)pyrimidine-2,4 (*1H,3H*)-dione (60e) and 3-((5-(4-Bromophenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4 (*1H,3H*)-dione (61e)



60e



61e

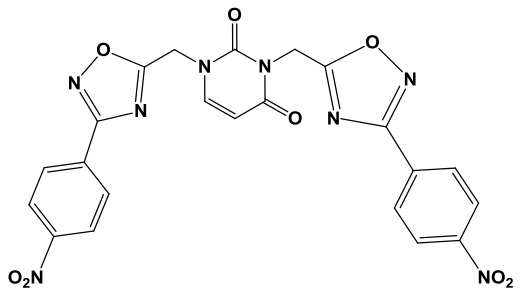
A mixture of uracil **58** (1 eq, 0.018 g ,0.165 mmol) and 5-(chloromethyl)-3-(4-bromophenyl)-1,2,4-oxadiazole **(36f)** (2 eq, 0.090 g , 0.329 mmol) with K_2CO_3 (1 eq, 0.023 g, 0.165 mmol) in (DMF 5mL) was mixed at room temperature 5h and monitored by TLC. The reaction was The reaction mixture was extracted with (Diethyl ether:cold water 1:1)x4 and) and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was

purified by flash column chromatography (n-hexane:ethyl acetate; 6:1)to give **(60e**) white solid and **(61e)**white solid.

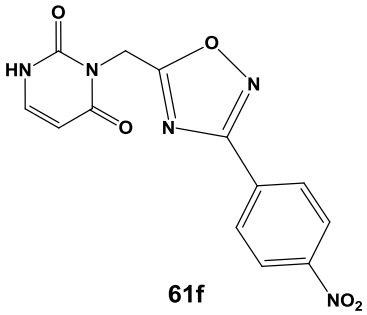
60e: (45mg, %46). Rf**:** 0.633(n-Hexane:Ethyl acetate; 1:3). Mp**:**151-152˚C. IR(KBr, v:cm^{-1}): 3095, 3057(Ar. C-H), 2985, 2929, (Aliph.C-H stretching), 1722(C=O), 1672, 1649,(C=N), 1597, 1566, 1471, 1448,1406,1359, 1342, 1265, 1109, 1012, 808, 740(C-Br). ^{1}H NMR (δ_H, 400MHz, DMSO-*d_6*): 8.053(d, *J*=8Hz, 1H), 7.88(q, *J*=22Hz, 4H), 7.72(t, *J*=16Hz, 4H), 6.06(d, *J*=8Hz, 1H), 5.49(s, 2H), 5.42(s, 2H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-*d_6*):176.6, 176.4(C=O), 167.7,167.6(C=O), 162.3(C=N), 151.4(C=N), 145.8, 133.1, 129.6, 126.1, 125.9, 125.5, 125.4, 101.6, 45.5(CH_2), 37.1(CH_2). LC-MS :(80 eV): (*m/z*, %): 587.1 (100) $[M+H]^+$.

61e: (0.10mg, %18). Rf:0.466 (n-Hexane:Ethyl acetate; 1:3). Mp**:**255-256˚C. (dec.). IR(KBr, v:cm^{-1}):3423(N-H),3090, 3039, 3016(Ar.C-H), 298, 2924(Aliph.C-Hstretching),1703,1664,(C=O),1602,1552(C=N),1465,1421, 1334, 1249, 1199, 1114, 1008, 949, 732 (C-Br). ^{1}H NMR (δ_H, 400MHz, DMSO-*d_6*): 11.55(s, 1H), 7,84(dd, *J*=32, 8.4Hz,2H), 7.83(d, *J*=8.4Hz, 1H), 7,79-7.77(m,2H), 5.73(d, *J*=7,6Hz, 1H), 5.34(s, 2H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO): 176.8(C=O), 167.7(C=O), 164.3(C=N), 151.5(C=N) ,125.5(C=C),102.5(C=C), 146.1, 133.2, 129.7, 126,1, 44.4(CH_2). LC-MS: (80 eV): (*m/z*, %): 351 (100) $[M+H]^+$.

1,3-Bis((3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrimidine-2,4 (*1H,3H*)-dione (60f) and 3-((5-(4-Nitrophenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(*1H,3H*)-dione (61f)



60f



61f

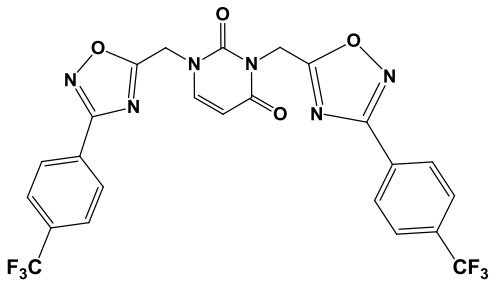
A mixture of uracil **58** (1 eq, 0.023 g ,0.209 mmol) and 5-(chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole **(36g)** (2 eq, 0.100 g , 0.417 mmol) with K_2CO_3 (1 eq, 0.028 g,0.209 mmol) in DMF (5mL) was for 5h mixed at room temperature and monitored by TLC. The reaction mixture was extracted with (Diethyl ether:cold water 1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(60f**) white solid and **(61f)**white solid

60f: (40mg, %37). Rf : 0.300(n-Hexane:Ethyl acetate; 1:3). Mp:192-193˚C IR(KBr, v: cm^{-1}): 3099, 3053, 3009(Ar. C-H), 2958, 2808, 2789, (Aliph.C-H stretching),1720, (C=O),1672, 1583,(C=N), 1516,(NO_2), 1417, 1388, 1336, 1313, 1292, 1103, 966, 794, 707. ^{1}H NMR (δ_H, 400 MHz, DMSO-d_6): 8.33-8.29(m, 4H), 8,19-8.15(m,4H), 8.02(d, *J*=8.4Hz, 1H), 6.03(d,*J*=8.4Hz, 1H),

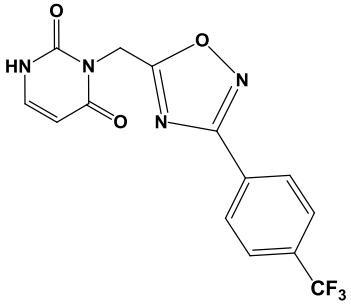
5.45(d,*J*=29.6Hz ,4H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-d_6): 177.2,176.9(C=O), 167.1,167.0(C=O), 162.3(C=N), 158.3,(C=N), 125.2,125.1(C=C), 101.7(C=C) 157.8, 157.3, 156.2, 154.5, 154.0, 152.6, 151.4, 149.9, 149.8, 145.8, 129.2, 129.1, 49.9,48.4 (CH_2), 48.2, 45.6(CH_2).

61f: (0.10 mg ,%15**)**, Rf : 0.166 (n-Hexane:Ethyl acetate; 1:3). Mp:277-278˚C (dec.). IR(KBr, v:cm^{-1}): 3456(N-H), 3155, 3124, 3097, 3051(Ar.C-H), 2958, 2854(Aliph.C-Hstretching), 1707(C=O), 1680, 1579(C=N), 1514 (NO_2), 1462,1404, 1338, 1278, 1103, 1008, 935, 869, 771. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 11.57(s,1H), 8.41(t, *J*=8.4Hz,2H), 8.26(t, *J*=8.8Hz,2H), 7.84(d, *J*=8Hz, 1H), 5.75(dd, *J*=2Hz, 1H), 5.38(s,2H). ^{13}C NMR ($\delta_{C,}$ 100 MHz, DMSO-d_6): 17.6(C=O), 166.4(C=O), 163.5(C=N), 150.7(C=N), 124.5(C=C), 101.8(C=C), 149,3, 145.4, 131.3, 128.5, 43.6(CH_2). LC-MS (80 eV) (*m/z*, %): 271 (100) [M-NO_2], 315 (20) $[M]^+$.

1,3-Bis((3-(4-(trifluoromethyl)phenyl)1,2,4oxadiazolyl)methyl) pyrimidine -2,4(*1H,3H*)-dione (60g) and 3-((5-(4-(Trifluoromethyl)phenyl)-1,2,4-oxadiazol-3-yl)methyl) pyrimidine-2,4 (*1H,3H*)-dione (61g)



60g



61g

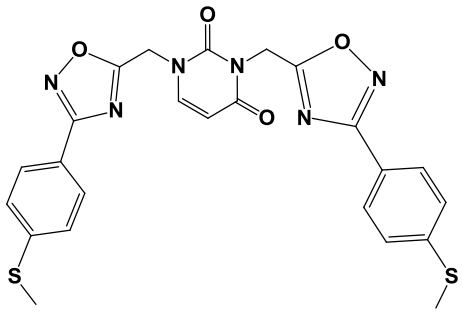
A mixture of uracil **58** (1 eq, 0.020g ,0.190 mmol) and 5-(chloromethyl)-3-(4-triflоromethylphenyl)-1,2,4-oxadiazole **(36h)** (2 eq,0.100 g ,0.381 mmol) with K_2CO_3 (1 eq, 0.026 g,0.190 mmol) in DMF (5mL) was mixed at room temperature for 5h and monitored by TLC.The reaction was The reaction mixture was extracted with (Diethyl ether:cold water 1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(60g)** white solid and **(61g)** white solid.

60g: (61mg, %55). Rf : 0.625(n-Hexane:Ethyl acetate; 1:3). Mp**:**190-191˚C. IR(KBr, v:cm^{-1}): 3095, 3064, 3001(Ar. C-H), 2968, 2928, 2852 (Aliph.CHstretching),1726,1680,(C=O),1604,1579,(C=N),1535,1446,1419, 1327, 1157,1103,962,815,758. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 8.16(q, *J*=11.2Hz ,3H), 8.09(d, *J*=8Hz, 2H), 7.87(t, *J*=8.8Hz,4H), 6.09(d, *J*=8.4Hz,1H), 5.53(s,2H), 5.46(s,2H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-d_6): 176.3, 176.2(C=O), 166.8, 166.7(C=O), 161.6(C=N),157.8(C=N), 129.5, 129.4(CF_3),126.2(C=C), 100.9(C=C) 145.1, 132.1, 131.7, 131.4, 131.1, 127.9, 44.9(CH_2), 36.6(CH_2). LC-MS: (80 eV): (*m/z*, %): 565 (50) $[M+H]^+$.

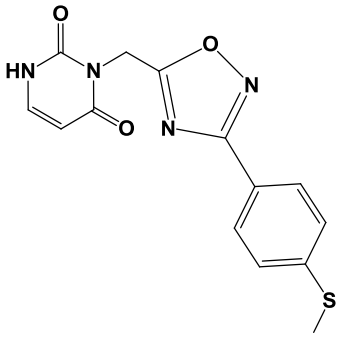
61g: (0.10mg, %15). Rf :0.406 (n-Hexane:Ethyl acetate; 1:3). Mp:247-248˚C (dec.). IR(KBr, v:cm^{-1}): 3410 (N-H), 3097, 3007, (Ar.C-H), 2956, 2854, 2808, (Aliph.C-H stretching), 1737 (C=O), 1695,1656(C=N),1514, 1462,1417, 1329, 1259, 1180, 1010, 941, 850, 758. ^{1}H NMR (δ_H, 400MHz, DMSO-): $d_6$11.55,(s,1H), 8.21(d, J=8.4Hz, 2H), 7.95(d,*J*=8Hz, 2H), 7.84(d, *J*=8,1Hz,

1H), 5.74(d, *J*=7.6Hz, 1H), 5.37(s,1H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO): 176.4(C=O), 166.7(C=O), 163.5(C=N), 150.7(C=N), 129.9(CF_3), 126.2 (C=C), 101.8(C=C), 145.4,127.9, 43.6(CH_2). LC-MS: (80 eV): (*m/z*, %): 339(100) [M+H], 223(45).

1,3-Bis((3-(4-(methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl) pyrimidine -2,4(*1H,3H*)-dione (60h) and 3-((5-(4-(Methylthio)phenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(*1H,3H*)-dione (61h)



60h



61h

A mixture of uracil **58** (1 eq, 0.023 g ,0.207 mmol) and 5-(chloromethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole **(36i)** (2 eq, 0.100 g , 0.415 mmol) with K_2CO_3 (1 eq, 0.029 g,0.207 mmol) in DMF(5mL) was mixed at room temperature for 5h and monitored by TLC.The reaction mixture was extracted with (Diethyl ether:cold water 1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column

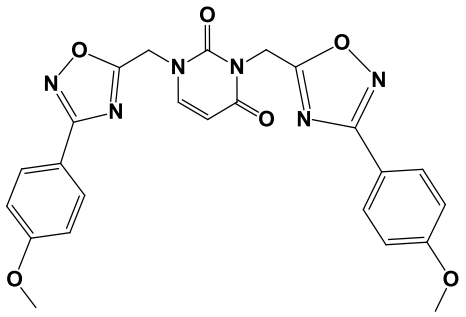
chromatography (n-hexane:ethyl acetate; 6:1) to give **(60h)** yellow oily and **(61h)** white solid.

60h: (40mg, %7). Rf **:** 0.625(n-Hexane:Ethyl acetate; 1:3). IR(KBr, v:cm^{-1}): 3091, 3055,(Ar. C-H), 2989, 2924, (Aliph.C-H stretching), 1718(C=O), 1668, 1595(C=N), 1558,1473,1408, 1344,1240, 1186, 1089, 962, 808,786. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 8.08(d, *J*=8Hz,1H), 7.90(q, *J*=22.8Hz, 4H), 7.40 (t, *J*=16.8Hz, 4H), 6.08(d, *J*=8.4Hz, 1H), 5.45(d, *J*=30Hz,4H), 3.38(s,6H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-d_6): 176.2, 176.0(C=O), 168.1, 168.0(C=O), , 162.3(C=N), 151.4(C=N), 122.4, 122.3(C=C), 101.6(C=C) 145.8, 144.0, 143.9, 128.0, 127.9, 126.4, 45,5(CH_2),37.3(CH_2) 14.7 (CH_3). LC-MS: (80 eV): (*m/z*, %): 521(100) $[M+H]^+$, 276(20), 194(41) 611,45.

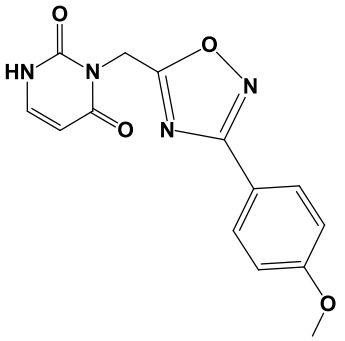
61h: (0.27mg, %8). Rf**:** 0.531 (n-Hexane:Ethyl acetate; 1:3). Mp**:** 228-229˚C. IR(KBr, v:cm^{-1}): 3425(N-H), 3136, 3113,(Ar.C-H), 2958,2924, 2872, 2806,(Aliph.C-Hstretching), 1703,(C=O), 1656, 1597(C=N), 15581467, 1383, 1298, 1251, 1199, 1085, 900, 827, 738. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 11.54(s, 1H), 7.86(dd, *J*=8.4,8Hz, 2H), 7.83(d, *J*=8.4Hz, 2H), 7.42(d, *J*=8.8Hz, 2H), 5.73(dd, *J*= 0.8, 1.6Hz, 1H), 5.32(s, 2H), 2.52(s, 3H)

^{13}C NMR ($\delta_{C,}$ 100 MHz, DMSO-d_6): 175.6,(C=O), 167.3(C=O), 163.5(C=N), 150.7(C=N), 121.5(C=C), 101.7 (C=C),145.4, 143.2, 127.3, 125.7, 43.6 (CH_2), 13.9(CH_3). LC-MS :(80 eV) :(*m/z*, %): 317.2 (100) [M+H], 194.1(30).

1-((3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-3-((3-(4-(methyl thio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrimidine-2,4(*1H,3H*)-dion (60i) and 3-((5-(4-Methoxyphenyl)-1,2,4-oxadiazol-3-yl)methyl)pyrimidine-2,4(*1H,3H*)-dione (61i)



60i



61i

A mixture of uracil **58** (1 eq, 0.025g ,0.223 mmol) and 5-(chloromethyl)-3-(4-(methoxy)phenyl)-1,2,4-oxadiazole **(36j)** (2 eq, 0.100 g , 0.445 mmol) with K_2CO_3 (1 eq, 0.031 g, 0.223 mmol) in DMF (5mL) was mixed at room temperature for 5h and monitored by TLC.The reaction mixture was extracted with (Diethyl ether:cold water 1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(60i)** white solid and, **(61i)**white solid.

60i: (35 mg, %10) Rf: 0.482(n-Hexane:Ethyl acetate; 1:3). Mp **:**137-138˚C. IR(KBr, v:cm^{-1}): 3055(Ar.C-H), 2982, 2941,2839(Aliph.C-H stretching),1735(C=O), 1573, 1678,(C=N),1485, 1446, 1357,1303, 1255 ,1089, 945, 898, 777. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 8.03(d, *J*=8.4Hz,

1H), 7.91-7.85(m, 4H), 7.06(dt, *J*=8.4, 6.8Hz 4H), 6.04(d, *J*=7.6Hz, 1H), 5.41(d, *J*=30Hz, 4H), 3.82(d, *J*=2.4Hz, 6H).

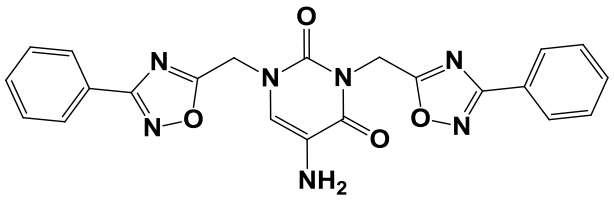
^{13}C NMR ($\delta_{C,}$ 100 MHz, DMSO-d_6): 175.9, 175.8(C=O), 168.1, 168.0(C=O), 162.5, 162.4(C=N), 151.4(C=N), 115.4,115.3 (C=C), 101.6(C=C)145.8, 129.4, 118.7, 118.6, 56.1,(CH_3), 45.5(CH_2), 37.3(CH_2). LC-MS: (80 eV) :(*m/z*, %):489 (100) $[M+H]^+$.

61i: (55mg, %26). Rf: 0.241 (n-Hexane:Ethyl acetate; 1:3). Mp**:**174-175˚C. IR(KBr, v:cm^{-1}): 3448(N-H), 3174, 3080, (Ar.C-H), 2958, 2924, 2852, (Aliph.C-Hstretching), 1734(C=O), 1689, 1612(C=N) , 1579, 1483, 1431, 1383, 1344, 1257, 1174, 1030, 895, 839. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 11.54(s,1H), 7.91(dt, *J*=6.8,6.4Hz, 2H), 7.83(d, *J*=8Hz, 1H), 7.12-7.07(m, 2H), 5.74(dd, *J*=1.6, 1.2Hz,1H), 5.30(d, *J*=5.6Hz, 2H), 4.90(s, 3H). ^{13}C NMR ($\delta_{C,}$ 100 MHz, DMSO-d_6):): 175,5, 175.4(C=O),168.7(C=O),167.3 (C=N), 163.5(C=N), 117.8(C=C), 101,7(C=C), 161.5, 161.7, 150.9, 150.7, 145.4, 128.7,114.6, 99.4, 55.3(CH_3), 43.6(CH_2). LC-MS: (80 eV): (*m/z*, %): 301 (60) [M+H], 208(60) ,193(45).

PART4

Synthesis of N-substituted 5-aminouracil on chloromethyl oxadiazole **(63a-h)**

5-Amino-1,3-bis((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)pyrimidine-2,4(*1H,3H*)-dione (62a)

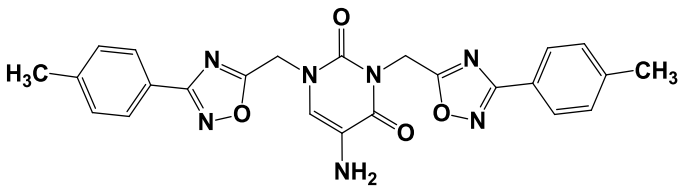


A mixture of 5-aminouracil **55** (1.05 eq, 0.181 g,1.43 mmol) and K_2CO_3 (1.08 eq, 0.203 g,1.47 mmol) in DMF (5mL) was mixed at room temperature for 2h till a change of color observed and 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole **(36a)** (1.1 eq, 0.291 g,1.50 mmol) was added in one portion and stirring was continued overnight and monitored by TLC. The reaction mixture was extracted with (Diethyl ether:cold water; 1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give (**62a)** as a white solid.

(0.73mg %11). Mp**:** 181-182˚C. Rf :0.625 (Eluant: Ethyl acetate). IR(KBr, v:cm^{-1}): 3396, 3315,3265, (NH_2), 3192, 3072, (Ar.C-H), 2995, 2941 (Aliph.C-Hstretching),1718(C=O), 1662, 1597, 1535(C=N), 1481, 1444, 1392, 1309, 1224, 1116, 1072, 962, 893, 717, 557. ^{1}H NMR (δ_H ,400MHz, DMSO-*d_6*): 7.99-7.94(m,4H), 7.61-7.51(m, 6H), 7.18(s, 1H), 5.43(d, *J*=13.2Hz, 4H), 3.36(s, 2H). ^{13}C NMR ($\delta_{C,}$ 100 MHz, DMSO-*d_6*): 123.3(C=C), 120.1(C=C),

132.5, 132.4, 129.9 . 127.7, 126.4, 45.2(CH_2), 37.8(CH_2). LC-MS: (80 eV): (*m/z*, %): 444 (100) $[M+H]^+$.

5-Amino-1,3-bis((3-(p-tolyl)-1,2,4-oxadiazol-5-yl)methyl)pyrimidine-2,4 (*1H,3H*)-dione (62b)

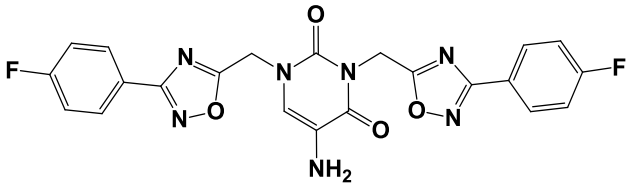


A mixture of 5-aminouracil **55** (1 eq, 0.127 g,1 mmol) and NaOH (2.1 eq,0.084 g,2.1 mmol) in EtOH (20mL) was mixed at room temperature for 2h till a change of color observed and 5-(chloromethyl)-3-(p-tolyl)-1,2,4-oxadiazole **(36b)** (2.1 eq, 0.417 g,1.50 mmol) was added in one portion and stirring was continued overnight and monitored by The reaction mixture was extracted with (Diethyl ether:cold water; 1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(62b)**as a white solid.

(0.50mg %11). Mp**:**194-195˚C. Rf :0.531 (Eluant: Ethyl acetate). IR(KBr, v:cm^{-1}): 3385, 3311, 3257(NH_2), 3194, 3153, (Ar.C-H),2953, 2852,(Aliph.C-Hstretching), 1720(C=O), 1664, 1612, (C=N), 1597, 1477, 1410, 1359, 1220, 1018, 954, 895, 779, 677. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 7.84(q, *J*=7.9Hz, 4H), 7.33(t, *J*=16.8Hz, 4H), 7.16(s, 1H), 5.42(s, 2H), 5.38(s, 2H),

4.56(s, 2H), 2.38(d, *J*=3.2Hz, 6H). ^{13H}C NMR ($\delta_{C,}$ 100MHz, DMSO-d_6): 176,3(C=O), 168.4, 168,3(C=O), 160.4(C=N), 149.6(C=N), 123.6, 123.5(C=C), 119.8(C=C), 149.6, 142.4, 142.3, 130.5, 127.7, 127.6, 45.2(CH_2), 37.8(CH_2), 21.8(CH_3). LC-MS: (80 eV): (*m/z*, %): 472 (100) $[M+H]^+$.

5-Amino-1,3-bis((3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl) pyrimidine-2,4(*1H,3H*)-dione (62c)

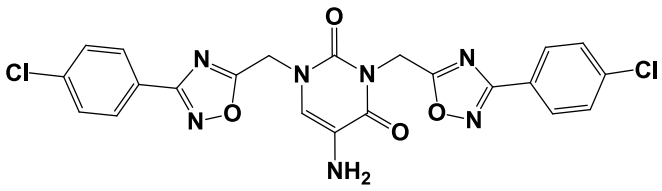


A mixture of 5-aminouracil **55** (1.05 eq, 0.133 g,1.05 mmol) and K_2CO_3 (1.08 eq,0.149 g,1.08 mmol) in DMF (5mL) was mixed at room temperature for 2h till a change of color observed and 5-(chloromethyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole **(36c)** (1.1 eq, 0.233 g, 1.1 mmol) was added in one portion and stirring was continued overnight and monitored by TLC. The reaction mixture was extracted with (Diethyl ether:cold water; 1mL:1mL)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(62c)** as a white solid.

(0.35mg %10). Mp**:** 199-200˚C (dec.). Rf : 0.593 (Eluant: Ethyl acetate)

IR(KBr, v:cm^{-1}): 3433, 3342(NH_2), 3192, 3088, 3022(Ar.C-H),2989, 2881 (Aliph.C-Hstretching),1708(C=O), 1647, 1639(C=N), 1606, 1581,1481, 1417,1352,1234,1157,1095, 910,750(C-F). ^{1}H NMR(δ_H,400MHz, DMSO-d_6): 8.05-7.98(m, 4H), 7.38(q, *J*=8.6Hz, 4H), 7.16(s, 1H), 5.42(d, *J*=14Hz, 4H), 4.56(s, 2H). ^{13}C NMR (δ_C, 100 MHz, DMSO-d_6): 176.6 (C=O), 167.6(C=O), 165.9(C=N), 163.5(C=N), 123.0, 122.9(C=C), 119.7(C=C), 160.4, 149.6, 130.4, 130.3, 123.5, 117.3, 117.2,117.1, 117.O, 45.2 (CH_2), 37.9(CH_2). LC-MS: (80 eV): (*m/z*, %):480 (100) $[M+H]^+$.

5-Amino-1,3-bis((3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl) pyrimidine-2,4(*1H,3H*)-dione (62d)

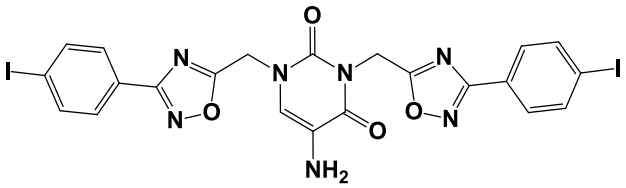


A mixture of 5-aminouracil **55** (1.05eq, 0.200g,1.58mmol) and K_2CO_3(1.08 eq,0.162 g,1.62 mmol) in DMF (5mL) was mixed at room temperature for 2h till a change of color observed and 5-(chloromethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole **(36d)** (1.1eq, 0.377 g, 1.65 mmol) was added in one portion andstirring was continued overnight and monitored by TLC. The reaction mixture was extracted with (Diethyl ether:cold water;1:1L)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4.

Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(62d)** as a white solid

(0.50mg %10). Mp**:** 199-200˚C. Rf : 0.628 (Eluant: Ethyl acetate). IR(KBr, v:cm^{-1}): 3429, 3340(NH_2), 3194, 3082, 3026(Ar.C-H), 2989, 2958, 2929(Aliph.C-Hstretching), 1701(C=O), 1604, 1593,(C=N), 1568, 1473, 1408, 1350, 1311, 1276, 1213, 1091, 954, 746. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 7.96(q, *J*=7.2Hz, 4H), 7.60(t, *J*=17.2Hz, 4H), 7.15(s, 1H), 5.42(t, *J*=30.8Hz, 4H), 3.39(s,1H). ^{13}C NMR ($\delta_{C,}$ 100 MHz, DMSO):176.8 (C=O), 167.6(C=O), 160.3(C=N), 149.6(C=N), 123.5 (C=C), 119.7(C=C),137.2, 137.1, 130.2, 130.1, 129.5, 125.2, 45.2 (CH_2), 37.8(CH_2). LC-MS (80 eV) (*m/z*, %): 512(100) $[M+H]^+$.

5-Amino-1,3-bis((3-(4-iodophenyl)-1,2,4-oxadiazol-5-yl)methyl) pyrimidine-2,4(*1H,3H*)-dione (62e)



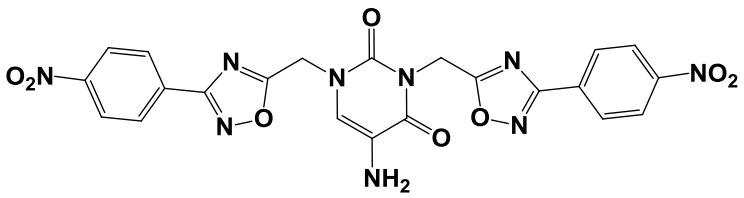
Amixture of 5-aminouracil **55** (1.05 eq, 0.200 g,1.58 mmol) and K_2CO_3 (1.08 eq,0.150 g,1.08 mmol) in 5ml DMFwas mixed at room temperature for 2h till a change of color observed and 5-(chloromethyl)-3-(4-ıodophenyl)-1,2,4-oxadiazole **(36e)** (1.1 eq, 0.352 g,1.1 mmol) was added in one portion and stirring was continued overnight and monitored by TLC. The reaction mixture

was extracted with (Diethyl ether:cold water; 1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(62e)** as a white solid.

(0.76 mg %10). Mp**:** 224-225˚C (dec.). Rf :0.667 (Eluant: Ethyl acetate) IR(KBr, v:cm^{-1}): 3431, 3340(NH_2), 3194, 3086(Ar.C-H),2989, 2958, 2852, (Aliph.C-Hstretching), 1708(C=O), 1672, 1643(C=N), 1589, 1467,1402, 1344, 1269, 1168, 1105, 910, 742. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 7.89(t, *J*=18Hz,4H), 7.70(q, *J*=7.7Hz, 4H), 7.13(s, 1H), 5.41(s, 2H), 5.37(s, 2H)

^{13}C NMR ($\delta_{C,}$ 100 MHz, DMSO-d_6): 176.7(C=O), 167.9 (C=O), 160.3(C=N), 149.5(C=N), 119.7(C=C), 100.0, 99.9(C=C), 138.9,,138.8, 129.4,125.3, 125.7,123.5, 74.4(CH_2), 45.2(CH_2). LC-MS: (80 eV) :(*m/z*, %): 696(20) $[M+H]^+$ 695(62).

5-Amino-1,3-bis((3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl) pyrimidine-2,4(1H,3H)-dione (62f)



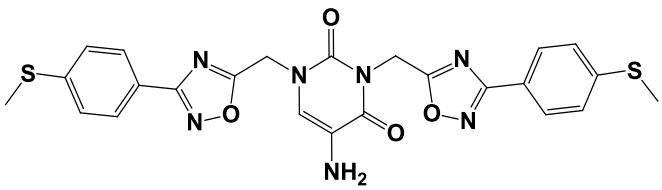
A mixture of 5-aminouracil **55** (1.05 eq, 0,160 g,1.24 mmol) and K_2CO_3(1.08 eq,0.179 g,1.30 mmol) in 5ml DMFwas mixed at room temperature for 2h till a change of color observed and 5-(chloromethyl)-3-(4-nitrophenyl)-1,2,4-

oxadiazole **(36g)** (1.1eq, 0.316 g,1.32 mmol) was added in one portion and stirring was continued overnight and monitored by TLC. The reaction mixture was extracted with (Diethyl ether:cold water; 1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(62f)** as a orange solid.

(0.80mg %12). Mp**:** 113-114˚C. Rf : 0.589 (Eluant: Ethyl acetate). IR(KBr,v:cm^{-1}) 3454, 3362(NH_2), 309, 3036(Ar.C-H), 2953(Aliph.C-Hstretching), 1708(C=O), 1649, 1591, 1521(C=N), 1415, 1342, 1301, 1220, 1103, 1014,854,725. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 8.35(td, *J*=8.8,8Hz, 4H), 8.23-8.18(m, 4H), 7.18(s, 1H), 5.76(s, 1H), 5.46(s, 4H), 3.40(s, 2H)

^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-d_6): 177.3(C=O), 167.2, 167.1(C=O), 160.3(C=N),149.9, 149.6 (C=N), 123.6(C=C), 119.7(C=C), 132.1, 129.2, 129.1, 125.2, 125.1, 55.6(CH_2), 45.3(CH_2). LC-MS :(80 eV): (*m/z*, %): 534(100) $[M+H]^+$.

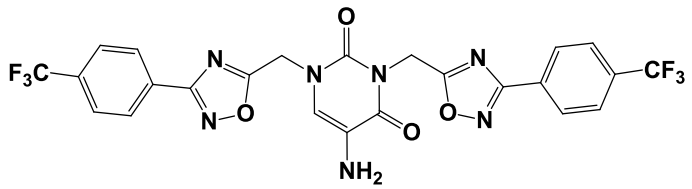
5-Amino-1,3-bis((3-(4-(methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl) pyrimidine-2,4(*1H,3H*)-dione (62g)



A mixture of 5-aminouracil **55** (1.05 eq, 0,133 g,1.05 mmol) and K_2CO_3 (1.08 eq,0.150 g,1.08 mmol) in DMF(5mL) was mixed at room temperature for 2h till a change of color observed and 5-(chloromethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole **(36i)** (1.1 eq, 0.264 g,1.1 mmol) was added in one portion andstirring was continued overnight and monitored by TLC. The reaction mixture was extracted with (Diethyl ether:cold water 1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(62g)** as a white solid.

(0.45mg %10). Mp**:** 187-188˚C. Rf : 0.705 (Eluant: Ethyl acetate). IR(KBr, v:cm^{-1}): 3389 3313(NH_2), 3194, 3072,(Ar.C-H), 2949, 2866, 2835,(Aliph.C-Hstretching),1716,(C=O),1662, 1593(C=N), 1473, 1408,1359, 1230, 1217, 1089, 1016, 885, 788. ^{1}H NMR(δ_H, 400MHz, DMSO-d_6): 7.86(q, *J*=8Hz, 4H), 7.37(t, *J*=18Hz, 4H), 7.15(s, 1H), 5.42(s, 2H), 5.38(s, 2H), 4.55(s, 2H), 2.54-2.50(m, 6H). ^{13}C NMR ($\delta_{C,}$ 400MHz, DMSO-d_6): 176.4, 176.3(C=O), 168.1(C=O), 160.4(C=N), 149.6(C=N), 122.4(C=C), 119.8(C=C),143.9, 128.1, 126.4, 123.5, 45.2(CH_2), 37.8CH_2), 14.7(CH_3). LC-MS: (80 eV) :(*m/z*, %):536(100) $[M+H]^+$.

5-Amino-1,3-bis((3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl) methyl)pyrimidine-2,4(*1H,3H*)-dione (62h)



A mixture of 5-aminouracil **55** (1.05 eq, 0,133 g,1.05 mmol) and K_2CO_3(1.08 eq,0.150 g,1.08 mmol) in DMF (5mL) was mixed at room temperature for 2h till a change of color observed and 5-(chloromethyl)-3-(4-trifloromethyl)phenyl)-1,2,4-oxadiazole **(36h)** (1.1 eq,0.288 g , 1.1 mmol) was added in one portion andstirring was continued overnight and monitored by TLC. The reaction mixture was extracted with (Diethyl ether:cold water; 1:1)x4 and washed with brine solution (15 mL). The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo,* and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(62h)** as a white solid.

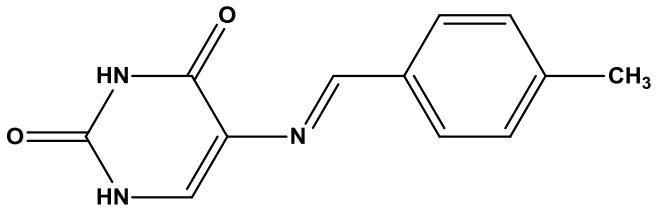
(70mg %11). Mp**:** 221-222˚C. Rf : 0.457 (Eluant: Ethyl acetate). IR(KBr, v:cm^{-1}): 3435, 3344(NH_2), 3192, 3090(Ar.C-H), 2987,2943, (Aliph.C-Hstretching), 1710(C=O), 1647, 1599(C=N) 1483, 1431, 1136, 1332, 1018, 866, 759. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 8.17(q, *J*=7.6Hz, 4H), 7.88(q, *J*=9.4Hz, 4H), 7.18(s, 1H), 5.46(d, *J*=15.6Hz, 4H), 4.58(s,2H).

^{13}C NMR ($\delta_{C,}$ 100 MHz, DMSO-*d_6*): 177.1(C=O), 167.4(C=O), 160.4(C=N), 149.6(C=N),126.9(C=C),123.5,123.1,119.8(C=C),132.4,132.3,132.1,132.0, 130.2, 128.7, 128.6, 125.8, 45.3(CH_2), 37.8(CH_2). LC-MS :(80 eV): (*m/z*, %): 580(100) $[M+H]^+$.

PART 5

In this part synthesis of aryl substituted 5-(benzylideneamino)pyrimidine-2,4-dione **(56a-g)** and its substituents were elucidated as described in the literature [97].

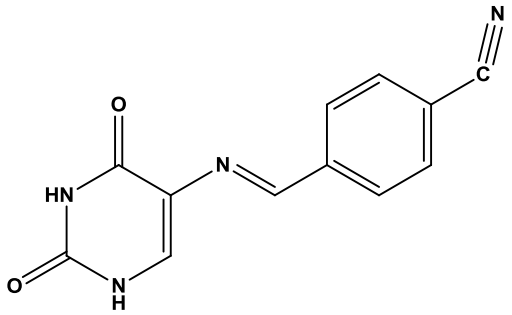
(*E*)-5-((4-Methylbenzylidene)amino) pyrimidine-2,4(*1H,3H*)-dione(56a)



5-aminouracil **55** (1 eq, 0,381 g, 3 mmol) was dissolved in water with heating until the complete dissolution of the parent substance.Then the mixture which was containing 15mL Ethanol and *p*-tolylbenzaldehyde **43a** (1 eq, 0.318 g, 3 mmol) started to added in the mixture of 5-aminouracil by dropwise.White precipitate started to occur . After 5 min. later It was put under reflux at about 1h. Then reaction mixture was left overnight. The light yellow precipitate was filtered off and washed with warm water and Ethanol to give **(56a)** as a white solid.

(200mg %31). Mp**:** 334-335˚C. Rf : 0.613 (Eluant: Ethyl acetate). IR(KBr, v:cm^{-1}): 3215(N-H), 3161, 3066, 3022(Ar.C-H), 2956, 2918, 2814 (Aliph.C-Hstretching), 1712(C=O), 1666,(C=N) , 1597, 1492,1444, 1421, 1329, 1172, 875, 813, 765.

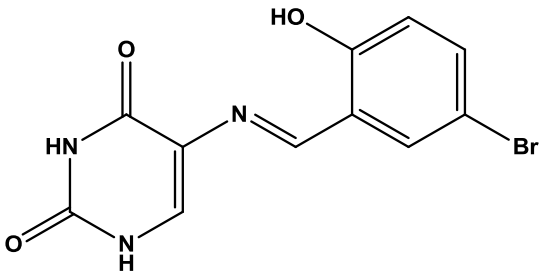
***(E)*-4-(((2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-5yl)imino)methyl) benzonitrile (56b)**



5-aminouracil **55** (1 eq,0,508 g, 4 mmol) was dissolved in water with heating until the complete dissolution of the parent substance.Then the mixture Which was containing 15mL Ethanol and 4-formylbenzonitrile **(43b)** (1 eq,0.524 g, 4 mmol) started to added in the mixture of 5-aminouracil by dropwise adding.White precipitate started to occur. After 5 min. later put it under reflux at about 1h. Then reaction mixture was left overnight. The light yellow precipitate was filtered off and washed with warm water and ethanol to give **(56b)** as a white solid

(200mg, %31). Mp**:** 334-335˚C. Rf : 0.500 (Eluant: Ethyl acetate). IR (KBr, v:cm^{-1}): 3198(N-H), 3163, 3068, 3018 (Ar.C-H), 2918, 2823 (Aliph.C-H stretching), 2229(C≡N), 1708(C=O),1666,(C=N) , 1587, ,1444, 1421, 1292, 1199, 877, 761.

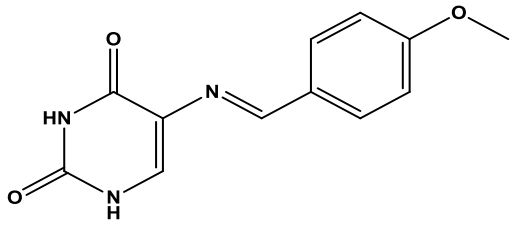
(*E*)-5-((5-Bromo-2-hydroxybenzylidene)amino)pyrimidine-2,4(*1H,3H*)-dione (56c)



5-aminouracil **55** (1eq, 0,508 g, 4 mmol) was dissolved in water with heating until the complete dissolution of the parent substance.Then the mixture which was containing 15mL Ethanol and 5-bromo-2-hydroxybenzaldehyde **(43c)** (1 eq, 0.804 g, 4 mmol) started to added in the mixture of 5-aminouracil by dropwise adding.white precipitate started to occur . After 5 min. later put it under reflux at about 1h. Then reaction mixture was left overnight. The light yellow precipitate was filtered off and washed with warm water and ethanol to giv e(**56c)** as a yellow solid.

(1000mg %80). Rf: 0.567 (Eluant: Ethyl acetate). Mp**:** 345-346˚C. IR(KBr, v:cm^{-1}): 3427(OH), 3178(N-H), 3057, (Ar.C-H),2958, 2739, 2806 (Aliph.C-H stretching), 1705 (C=O), 1651(C=N) , 1473, 1242, 860, 765, 553.

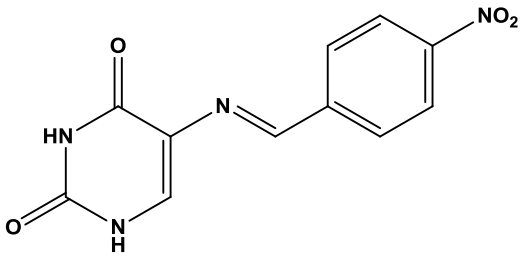
(*E*)-5-((4-Methoxybenzylidene)amino)pyrimidine-2,4(*1H,3H*)-dione (56d)



5-aminouracil **55** (1 eq,0,508 g, 4 mmol) was dissolved in water with heating until the complete dissolution of the parent substance.Then the mixture which was containing 15mL Ethanol and 4-methoxybenzaldehyde **(43d)** (1 eq, 0.544 g, 4 mmol) started to added in the mixture of 5-aminouracil by dropwise adding.White precipitate started to occur . After 5 min. later put it under reflux at about 1h. Then reaction mixture was left overnight. The light yellow precipitate was filtered off and washed with warm water and Ethanol to give **(56d)** as a white solid.

(496 mg %28). Mp**:** 306-307˚C. Rf : 0.500 (Eluant: Ethyl acetate). IR (KBr, v:cm^{-1}): 3373, 3215(N-H), 3165, 3099, 3024(Ar.C-H), 2966, 2837, 2017 (Aliph.C-H stretching), 1774(C=O), 1651(C=N) , 1512, 1247, 1172, 1030, 877,752.

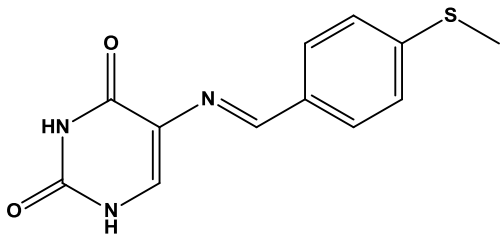
(*E*)-5-((4-Nitrobenzylidene)amino)pyrimidine-2,4(*1H,3H*)-dione (56e)



5-aminouracil **55** (1 eq,0,508 g ,4 mmol) was dissolved in water with heating until the complete dissolution of the parent substance.Then the mixture which was containing 15mL Ethanol and 4-nitrobenzaldehyde **(43e)** (1 eq, 0.604 g, 4 mmol) started to added in the mixture of 5-aminouracil by dropwise adding.white precipitate started to occur. After 5 min. later put it under reflux at about 1h. Then reaction mixture was left overnight. The light yellow precipitate was filtered off and washed with warm water and Ethanol to give (**56e)** as a yellow solid.

(322 mg %30). Mp**:** 331-332˚C. Rf : 0.542 (Eluant: Ethyl acetate). IR (KBr, v:cm^{-1}): 3198, 3169 (N-H), 3072, 3037 (Ar.C-H), 2985, 2960, 2825 (Aliph.C-H stretching), 1716(C=O), 1666(C=N), 1552, 1489, 1440(NO_2), 1330, 1276, 817, 763, 538,466. ^{1}H NMR (δ_H,400MHz, DMSO-d_6): 11.45(s, N-H), 9.59(s, 1H) ,7.90-7.72 (m, 3H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-d_6): 161.8(C=O), 155.9(C=O), 150,7(C=N), 121.9(C=C), 148.9, 143.5, 141.9, 129.3, 129.0, 125.7, 124.7. LC-MS :(80 eV): (*m/z*, %) 261(49) $[M+H]^+$.

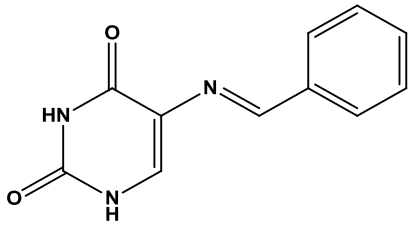
(*E*)-5-((4-(Methylthio)benzylidene)amino)pyrimidine-2,4(*1H,3H*)-dione (56f)



5-aminouracil **55** (1 eq, 0,508 g, 4 mmol) was dissolved in water with heating until the complete dissolution of the parent substance.Then the mixture which was containing 15mL Ethanol and 4-(methylthio)benzaldehyde **(43f)** (1 eq, 0.608 g, 4 mmol) started to added in the mixture of 5-aminouracil by dropwise adding.White precipitate started to occur . After 5 min. later put it under reflux at about 1h. Then reaction mixture was left overnight. The light yellow precipitate was filtered off and washed with warm water and Ethanol to give (**56f)** as a white solid.

(932mg %89). Mp**:**337-340˚C. Rf: 0.502 (Eluant: Ethyl acetate). IR(KBr, v:cm^{-1}): 3514, 3292(N-H), 3095(Ar.C-H), 2972, 2831(Aliph.C-H stretching), 1720(C=O), 1672 (C=N) , 1342, 1213, 852, 752. ^{1}H NMR(δ_H,400MHz, DMSO-d_6):11.37(s, N-H), 9.30(d,J=12.8Hz 1H) ,8.35 (s, 1H), 7.90-77.27(m,3H), 7.59(s,N-H), 2.51(s, 3H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-d_6): 176.1, 176.9(C=O), 168.1, 168.1(C=O), 162.1(C=N), 122.2(C=C), 158.3, 144.0, 143.9, 129.9, 128.9,14.8,14.7(CH_3).LC-MS:(80 eV): (*m/z*, %) 262(100) $[M+H]^+$.

***(E)*-5-(Benzylideneamino)pyrimidine-2,4*(1H,3H)*-dione (56g)**



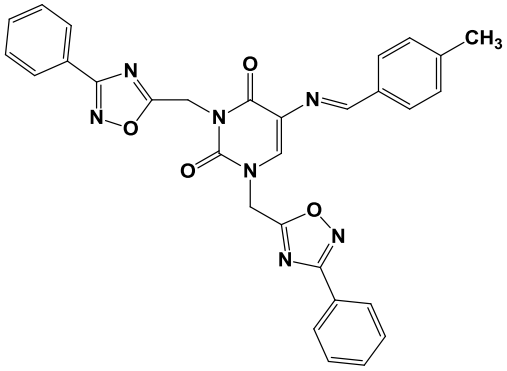
5-aminouracil **55** (1 eq, 0,381g,3 mmol) was dissolved in water with heating until the complete dissolution of the parent substance.Then the mixture which was containing 15mL Ethanol and benzaldehyde **(43g)** (1 eq, 0.318 g, 3 mmol) started to added in the mixture of 5-aminouracil by dropwise adding.White precipitate started to occur . After 5 min. later put it under reflux at about 1h. Then reaction mixture was left overnight. The light yellow precipitate was filtered off and washed with warm water and Ethanol to give (**56g)** as a white solid.

(200mg %31). Mp**:**334-337˚C .Rf :0.393 (Eluant: Ethyl acetate). IR (KBr, v:cm^{-1}): 3215, 3165(N-H), 3068, 3022(Ar.C-H), 2956, 2902, 2868 (Aliph.C-H stretching), 1712(C=O), 1678(C=N), 1573, 1485, 1143, 1070, 831, 748, 653 LC-MS: (80 eV): (*m/z*, %) 216(100) $[M+H]^+$.

PART 6

Synthesis of aryl substituted 5-(benzylideneamino)pyrimidine-2,4dione on N-substituted chloromethyloxadiazole.**(63a-e)**

(*E*)-5-((4-Methylbenzylidene)amino)-1,3-bis((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)pyrimidine-2,4(*1H,3H*)-dione (63a)

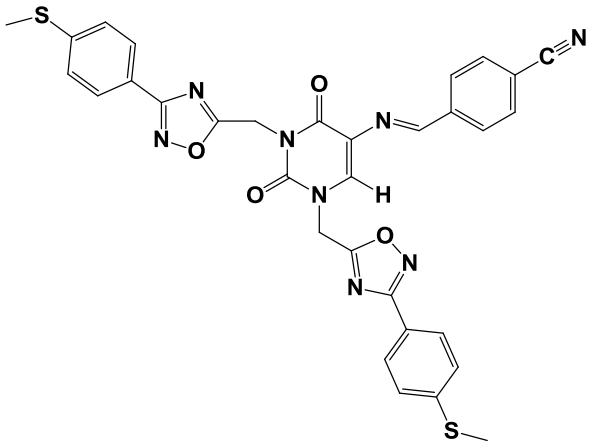


A mixture of (*E*)-5-((4-methylbenzylidene)amino)pyrimidine-2,4(*1H,3H*)-dione **(56a) (**1 eq, 0,132g, 0.57 mmol) and K_2CO_3 (1.1 eq, 0.97 g, 0.70 mmol) was mixed in DMF (5mL) at room temperature for 3h till a change of color observed and 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole **(36a)** (1.2 eq, 0.150 g, 0.73 mmol) was added in one portion and stirring was continued overnight and monitored by TLC the reaction was extracted with (DCM:H_2O;1:1)x3 The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo.*When added small amount of MeOH white precipitate **(63a)** occur then filter off the precipitate and it was checked with TLC .

(96 mg %31). Mp**:**168-16˚C. Rf : 0.750 (Eluant: Ethyl acetate:Hex;1:1) IR(KBr, v:cm^{-1}): 3173, 3066(Ar.C-H), 2920, 2856, 2820(Aliph.C-H stretching), 1716 (C=O), 1662, 1645, 1597, 1527(C=N), 1477, 1390, 1105, 1010, 781, 719. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6)*:* 9.30(d, *J*=16.4Hz, 1H), 8.36(s,1H), 8.00-7.95(m,3H), 7.77-7.50(m, 8H), 7.30(q,*J*=21Hz,2H), 5,57(s,2H), 5.50(s , 2 H), 2.36(d, J=4Hz,3H). ^{13}C NMR ($\delta_{C,}$ 400 MHz, DMSO-d_6):176.3,

176.0(C=O), 168.5, 168.4(C=O),162.2(C=N), 161.1(C=N),159.9(C=N),126.4, 126.3(C=C), 123.6(C=C), 158.7, 151.1, 150.2, 142.2, 141.3, 140.3, 138.9, 134.5, 132.5, 132.4, 130.2, 130.0, 129.9, 128.8, 128.5, 127.8, 127.7, 126.4, 45.7(CH_2), 37.9(CH_2), 21.8, 21.7(CH_3). LC-MS: (80 eV) :(*m/z*, %) 546(100) $[M+H]^+$.

(*E*)-4-(((1,3-Bis((3-(4-(methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)imino)methyl)benzonitrile (63b)

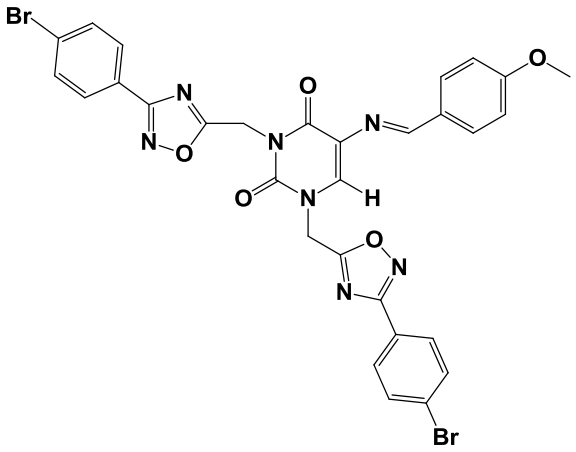


A mixture of (*E*)-4-((2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl) imino) methyl) benzonitrile **(56b)** (1 eq, 0.125 g, 0.52 mmol) and K_2CO_3 (1.1 eq, 0.79 g, 0.57 mmol) was mixed in DMF (5mL) at room temperature for 3h till a change of color observed and 5-(chloromethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole **(36i)** (1.2 eq, 0.150 g, 0.62 mmol) was added in one portion and stirring was continued overnight and monitored by TLC the reaction was extracted with (DCM:H_2O;1:1)x3 The organic layer was dried with Na_2SO_4.

Reaction mixture was concentrared *in vacuo.*When added small amount of MeOH white precipitate **(63b)** occur then filter off the precipitate and it was checked with TLC .

(80mg %24) .Mp**:** 208-209˚C. Rf : (Eluant: Ethyl acetate:Hex;1:1). IR(KBr, v:cm^{-1}): 3080, 3178(Ar.C-H), 2999, 2924, 2831 (Aliph.C-H stretching), 2222(C≡N), 1712(C=O), 1672, 1593, (C=N), 1410, 1346, 1220, 1114, 1089, 833, 744, 555. ^{1}H NMR (δ_H, 400MHz, DMSO-d_6): 9.54(s,1H),8.52(s,1H), 8.04-7.84(m, 8H), 7.36(td, *J*=6, 5.6Hz 4H), 5.58(s, 2H), 5.48(s,2H), 2.51(m, 6H). ^{13}C NMR ($\delta_{C,}$ 400MHz, DMSO-d_6): 176.0, 175.8(C=O), 168.1, 168.0(C=O), 159.6(C=N), 159.9(C=N), 158.8(C=N), 126.4, 126.3(C≡N), 122.4, 122.3 (C=C), 119.3(C=C),150.1, 144.0, 143.9,143.4,141.2, 133.5, 133.3, 129.2, 128.1, 128.0, 45.8(CH_2), 37.9(CH_2), 14.7(CH_3). LC-MS :(80 eV): (*m/z*, %) 649(34) $[M+H]^+$ 559(13).

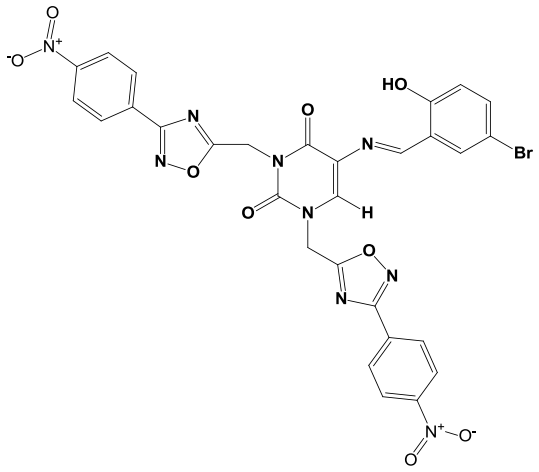
(*E*)-1,3-Bis((3-(4-bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-((4-methoxybenzylidene)amino)pyrimidine-2,4(*1H,3H*)-dione (63c)



A mixture of (*E*)-5-((4-methoxybenzylidene)amino)pyrimidine-2,4(*1H,3H*)-dione **(56d) (**0.9 eq, 0.101 g, 0.41 mmol) and K_2CO_3 (1.1 eq, 0.70 g, 0.50 mmol) was mixed in DMF (5mL) at room temperature for 3h till a change of color observed and 5-(chloromethyl)-3-(4-bromophenyl)-1,2,4-oxadiazole **(36f)** (1.2 eq, 0.150 g, 0.55 mmol) was added in one portion and stirring was continued overnight and monitored by TLC the reaction was extracted with (DCM:H_2O;1:1)x3 The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo.*When added small amount of MeOH white precipitate **(63c)** occur then filter off the precipitate and it was checked with TLC .

(67mg %23). Mp**:** 221-222˚C. Rf: (Eluant: Ethyl acetate:Hex;1:1). IR(KBr, v: cm^{-1}): 3076, 3010(Ar.C-H), 2916, 2839 (Aliph.C-H stretching), 1763, 1712 (C=O), 1658, 1595, 1573 (C=N), 1442, 1342, 1246,(-C-O) 1170, 1112, 904, 835, 744(C-Br). ^{1}H NMR (δ_H, 400MHz, DMSO-*d_6*): 9.17(s,1H), 8.24(s,1H), 7.88-7.77(m, 5H), 7.69(td, *J*=6,8,6.4Hz, 3H), 7.02(d, *J*=8.4Hz, 2H), 5.48(d, *J*=46Hz, 4H), 2.47(q, *J*=5.6Hz, 3H). ^{13}C NMR ($\delta_{C,}$ 100MHz, DMSO-*d_6*): 176.5, 176.3(C=O), 167.8, 167.7(C=O), 162.6(C=N), 160.8(C=N), 159.9(C=N), 124.0(C=C), 115.0(C=C), 150.2, 139.2, 133.1, 133.0, 130.7, 129.8, 129.7, 129.7, 126.1, 125.9, 125.6, 125.5, 56.1(OCH_3), 45.6(CH_2), 37.9(CH_2). LC-MS: (80 eV): (*m/z*, %) 719(64) $[M+H]^+$.

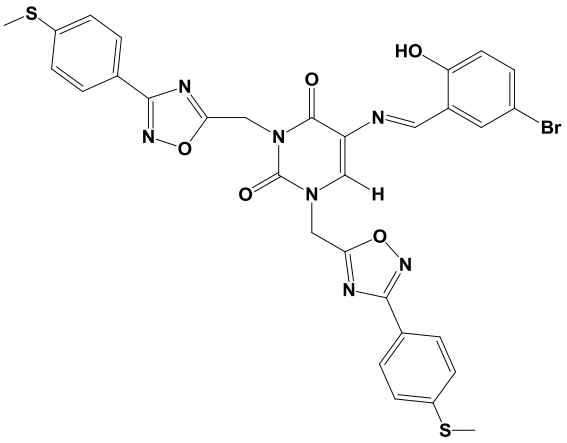
***(E)*-5-((5-Bromo-2-hydroxybenzylidene)amino)-1,3-bis((3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrimidine-2,4 (*1H,3H*)-dione(63d)**



A mixture of (*E)*-5-((5-bromo-2-hydroxybenzylidene)amino)pyrimidine-2,4(*1H,3H*)-dione **(56c)** (0.9 eq, 0.138 g, 0.47 mmol) and K_2CO_3 (1.1 eq, 0.79 g, 0.58 mmol) was mixed in DMF (5mL) at room temperature for 3h till a change of color observed and 5-(chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole **(36g)** (1.2 eq, 0.150 g, 0.63 mmol) was added in one portion and stirring was continued overnight and monitored by TLC the reaction was extracted with (DCM:H_2O;1:1)x3 The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo.*When added small amount of MeOH white precipitate **(63d)** occur then filter off the precipitate and it was checked with TLC .

Mp**:**190-195˚C. Rf :0.500 (Eluant: Ethyl acetate:Hex;1:1). IR (KBr, v:cm^{-1}): 3446(C-OH), 3068(Ar.C-H), 2914, 2860, 2804(Aliph.C-Hstretching), 1716(C=O), 1672, 1612(C=N), 1529, 1437, 1236, 1107, 854, 626(C-Br)

(*E*)-5-((5-Bromo-2-hydroxybenzylidene)amino)-1,3-bis((3-(4-(methylthio) phenyl)-1,2,4-oxadiazol-5-yl)methyl)pyrimidine-2,4(*1H,3H*)-dione (63e)



A mixture of *(E)*-5-((5-bromo-2-hydroxybenzylidene)amino)pyrimidine 2,4(*1H,3H*)-dione **(56c) (**0.8 eq, 0.122 g, 0.42 mmol) and K_2CO_3 (1.1 eq, 0.79 g, 0.57 mmol) was mixed in DMF (5mL) at room temperature for 3h till a change of color observed 5-(chloromethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole **(36i)** (1.2 eq, 0.150 g, 0.63 mmol) was added in one portion and stirring was continued overnight and monitored by TLC the reaction was extracted with (DCM:H_2O;1:1)x3 The organic layer was dried with Na_2SO_4. Reaction mixture was concentrared *in vacuo.*When added small amount of MeOH white precipitate **(63e)** occur then filter off the precipitate and it was checked with TLC .

Mp**:**181-184˚C. Rf: 0.600 (Eluant: Ethyl acetate:Hex;1:1). IR (KBr, v:cm^{-1}): 3443(C-OH), 3192, 3072(Ar.C-H), 2920, 2866 (Aliph.C-Hstretching), 1712 (C=O), 1664, 1591(C=N), 1469, 1408, 1346, 1274, 1230, 1014, 1116, 962, 746(C-Br).

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APPENDICES

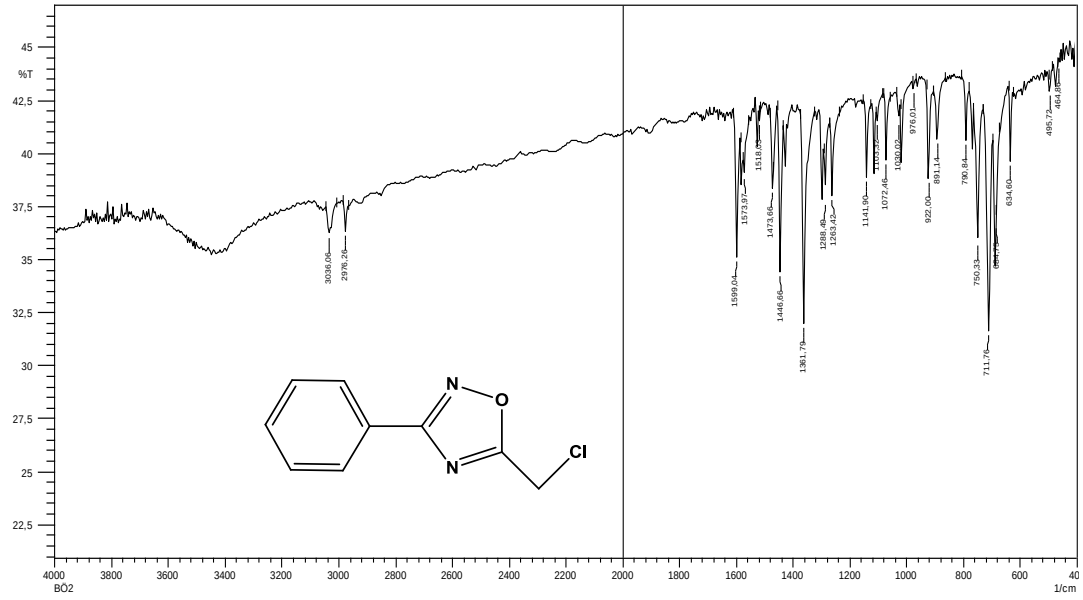

Figure 4.1. IR spectrum of compound **36a.**

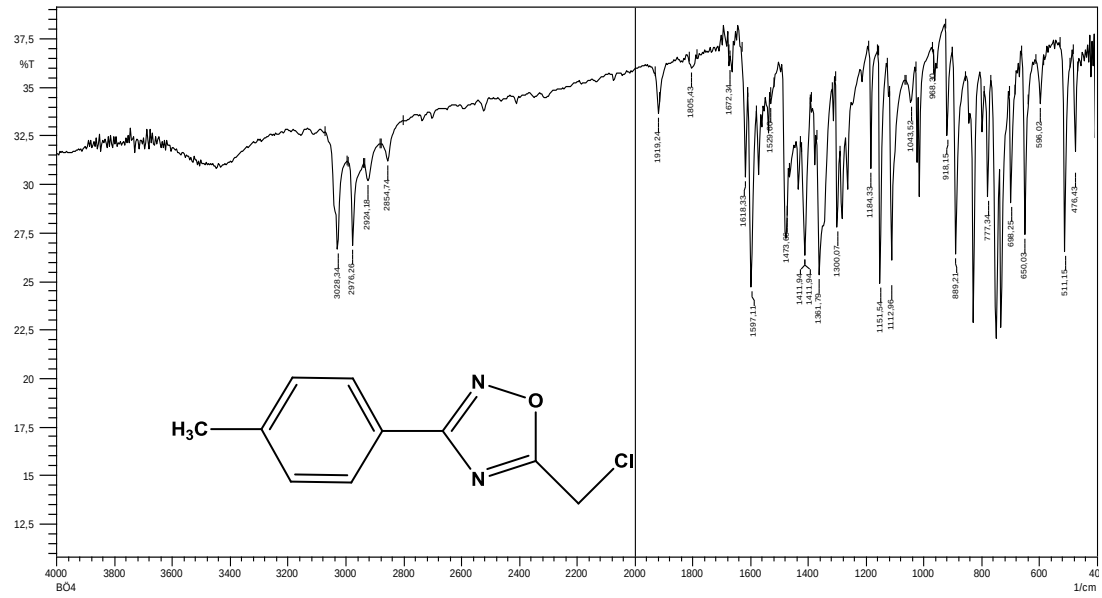

Figure 4.2. IR spectrum of compound **36b.**

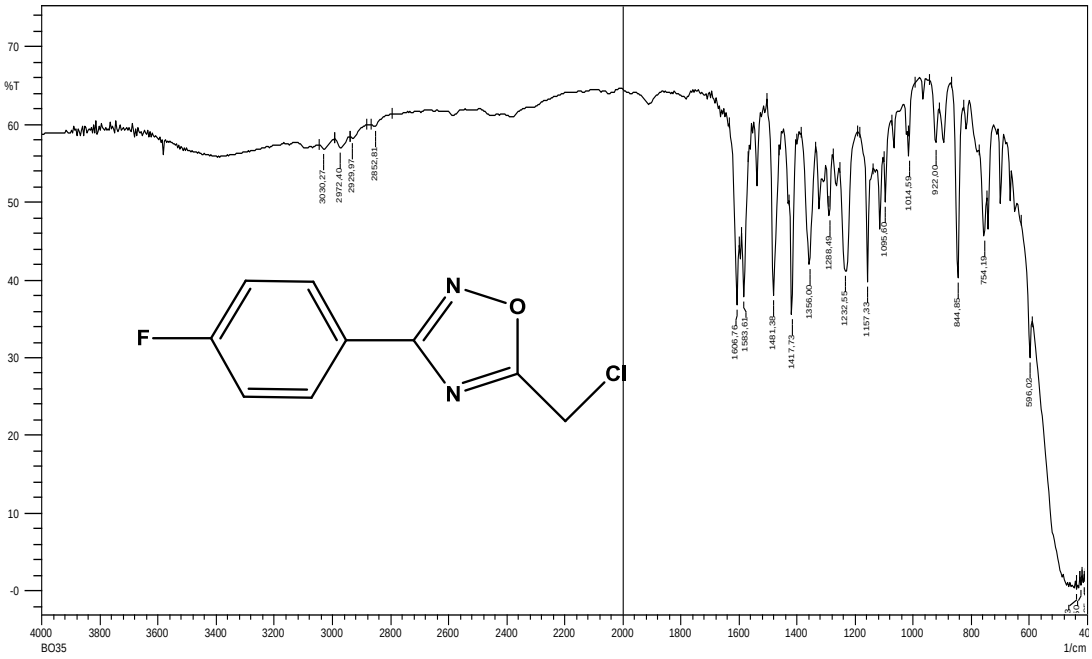

Figure 4.3. IR spectrum of compound **36c.**

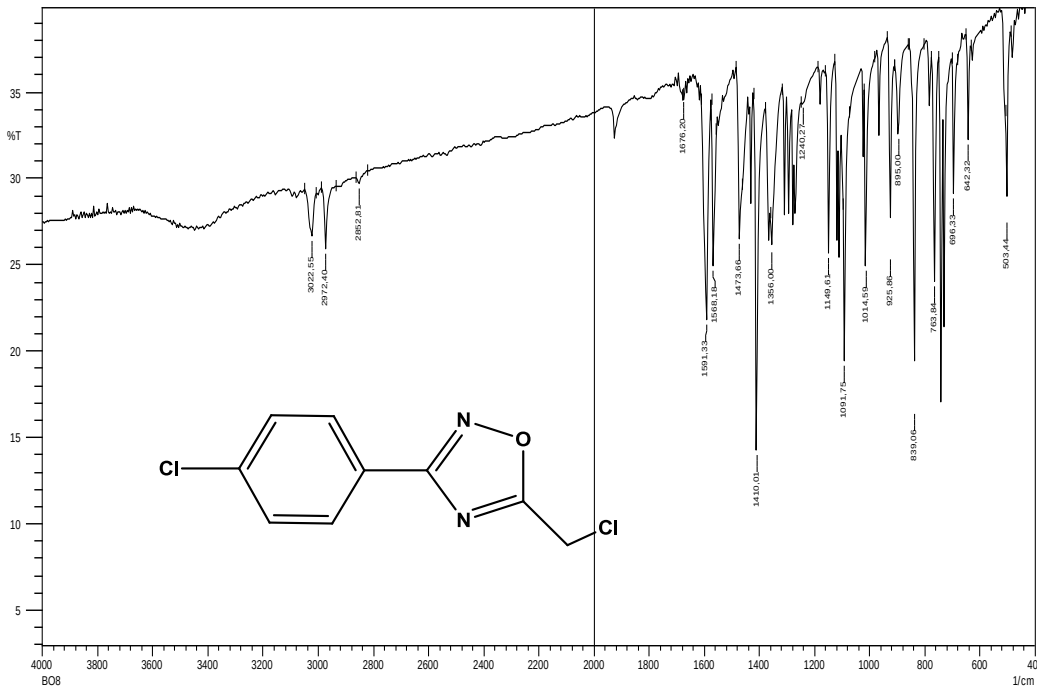

Figure 4.4. IR spectrum of compound **36d.**

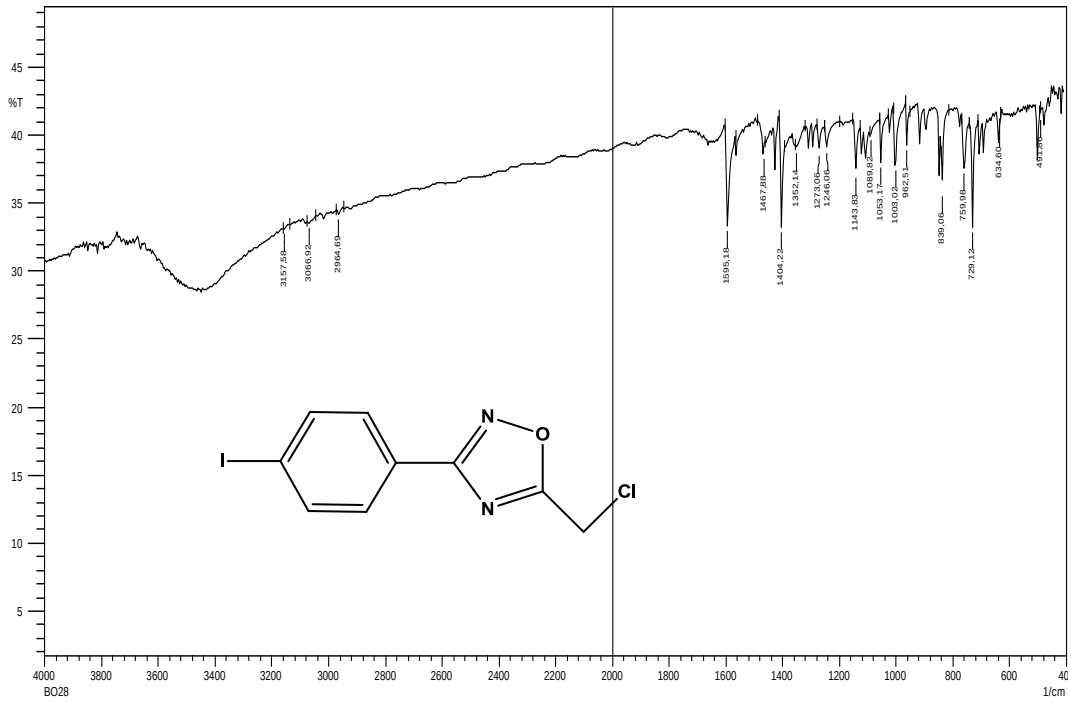

Figure 4.5. IR spectrum of compound **36e.**

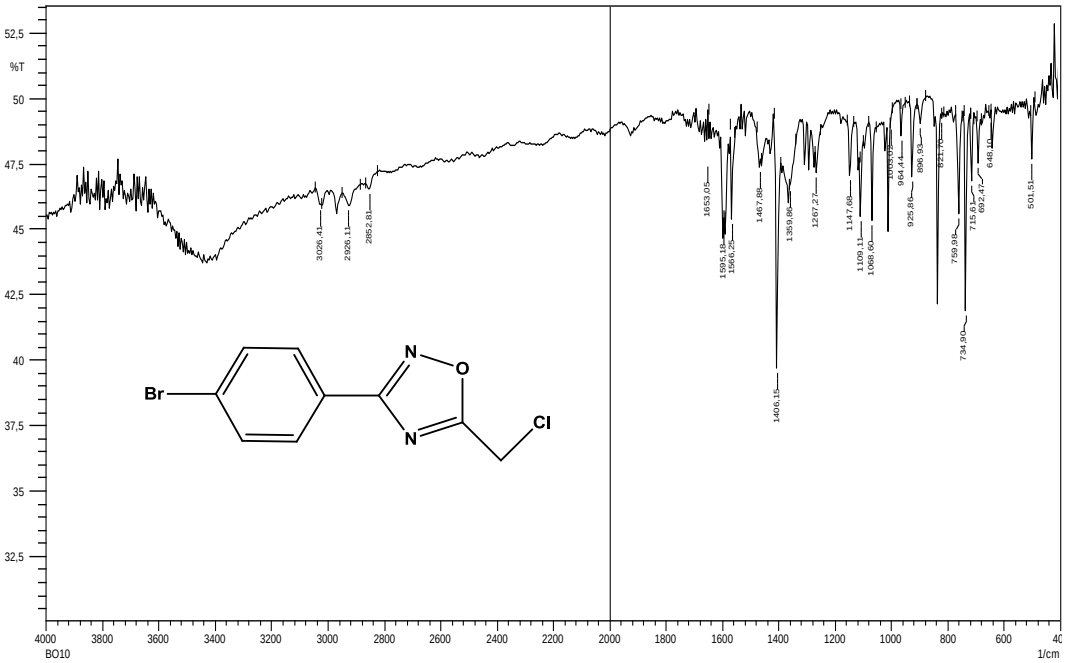

Figure 4.6. IR spectrum of compound **36f.**

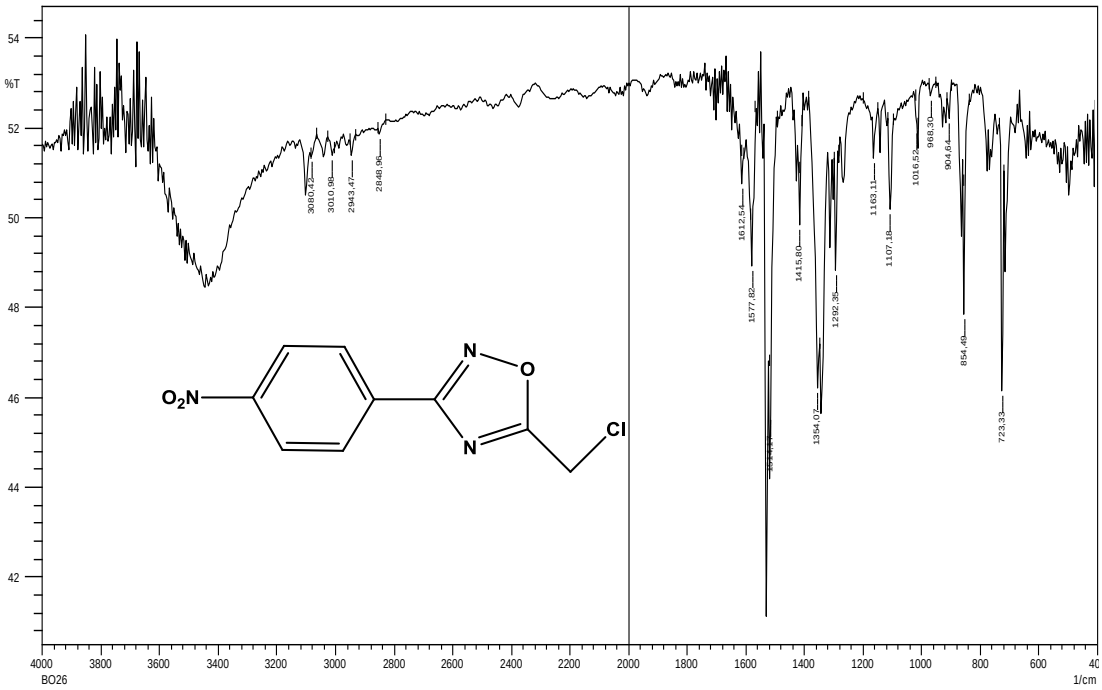

Figure 4.7. IR spectrum of compound **36g.**

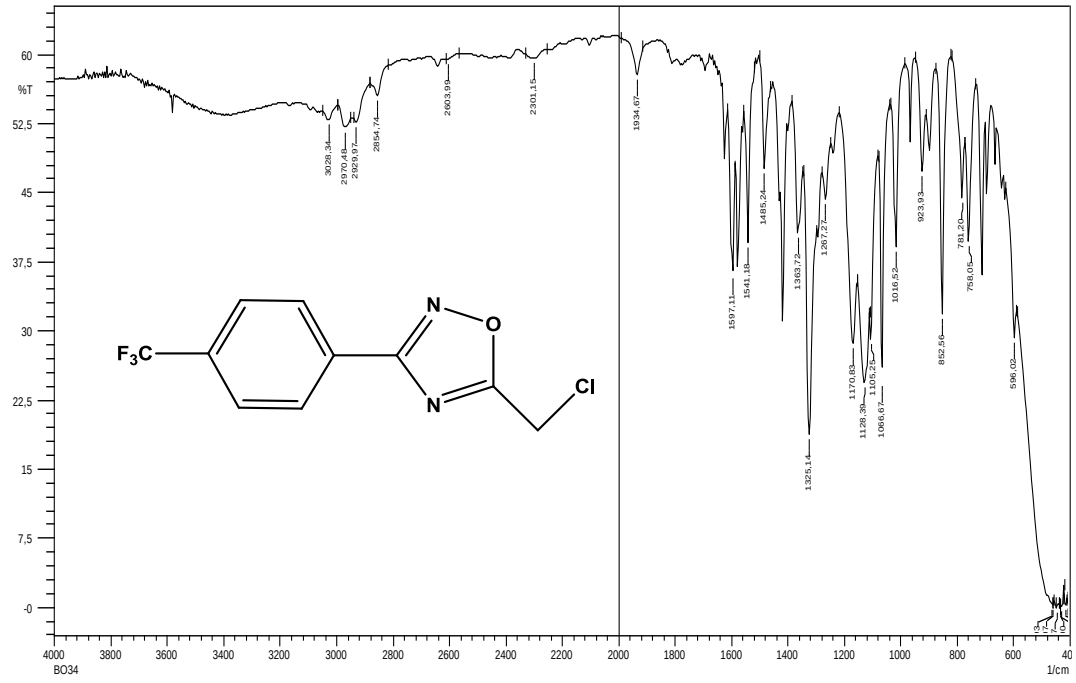

Figure 4.8. IR spectrum of compound **36h.**

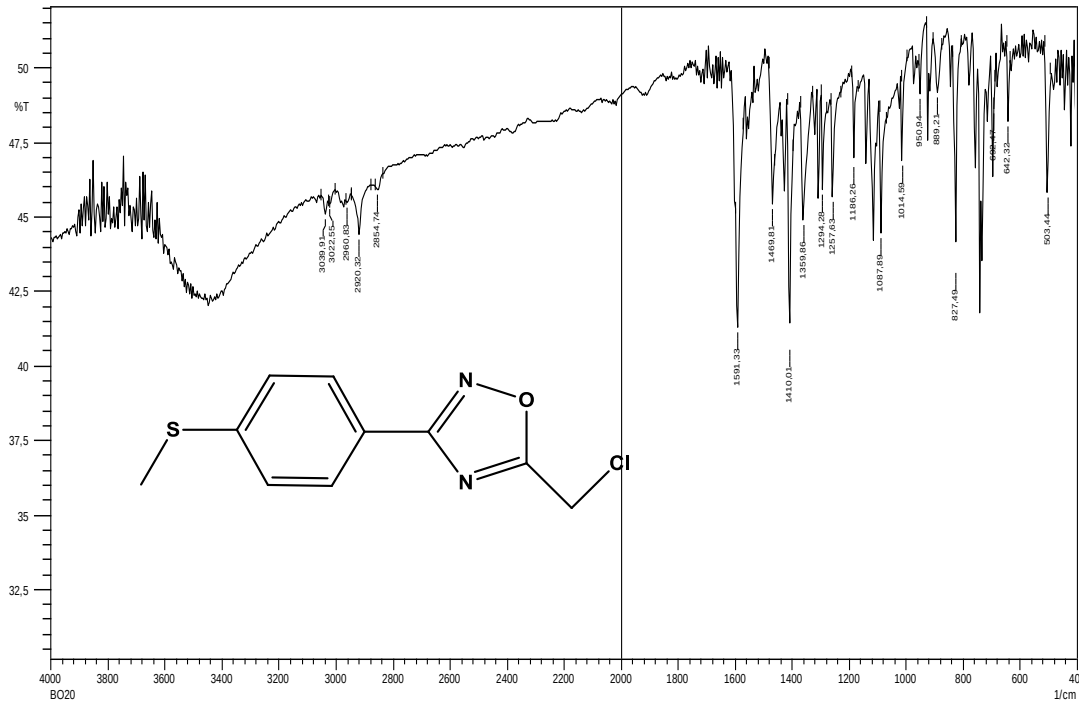

Figure 4.9. IR spectrum of compound **36i.**

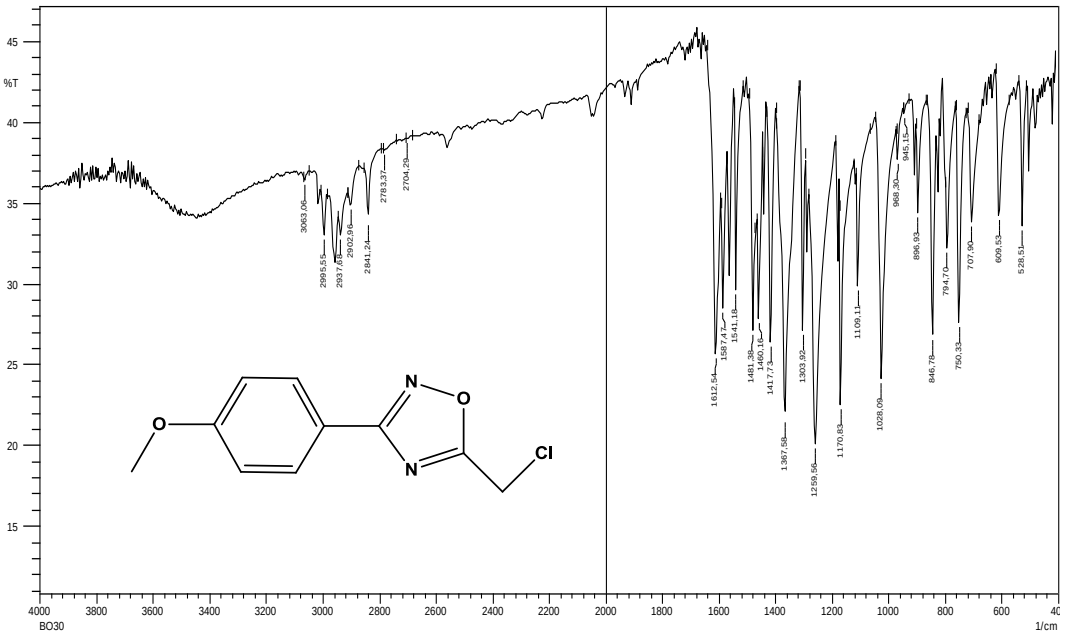

Figure 4.10. IR spectrum of compound **36j.**

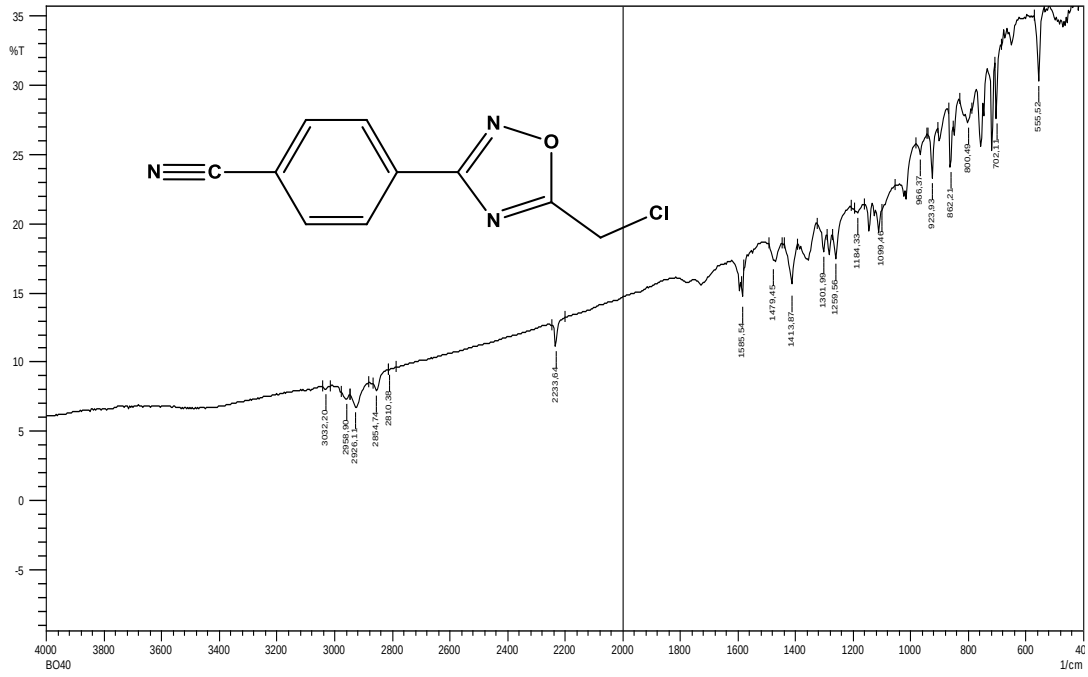

Figure 4.11. IR spectrum of compound **36k.**

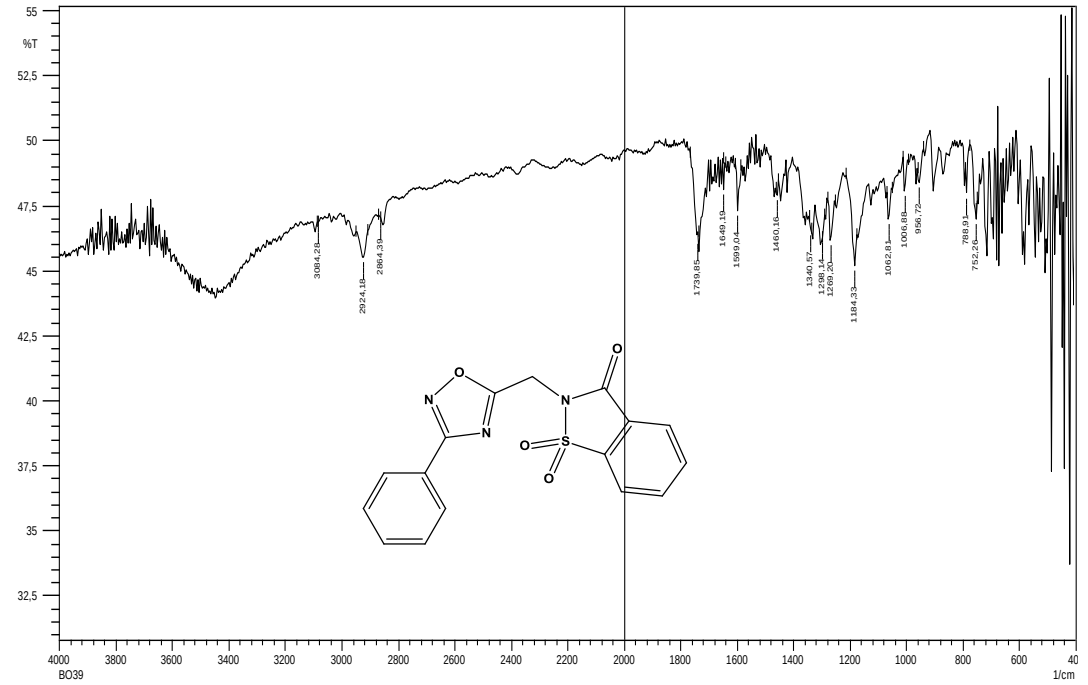

Figure 4.12. IR spectrum of compound **59a.**

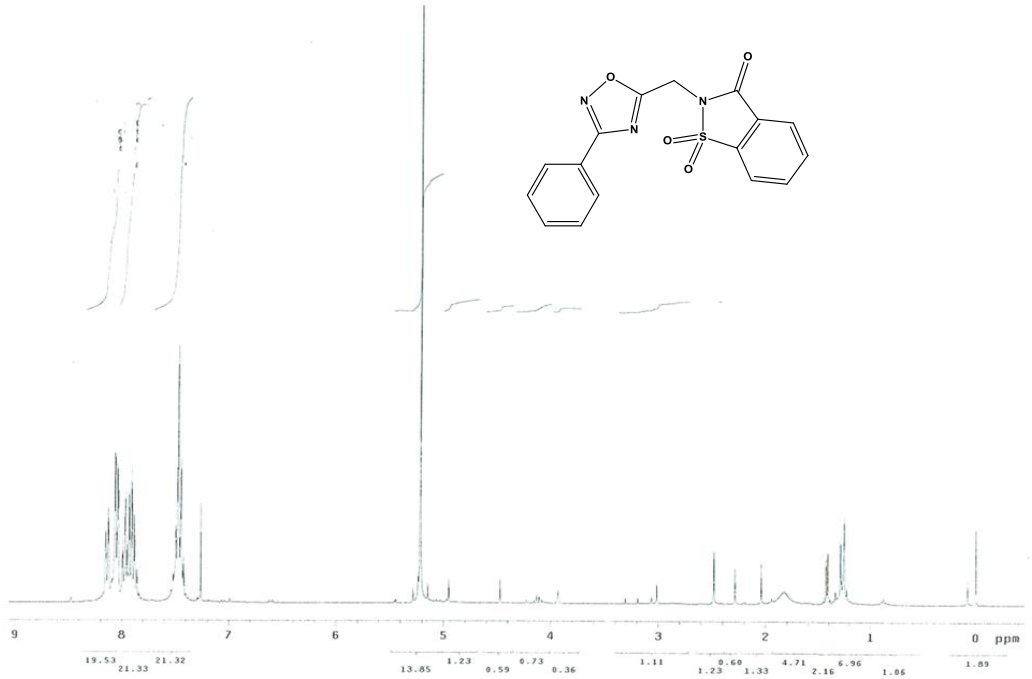

Figure 4.13. ^{1}H NMR spectrum of compound **59a.**

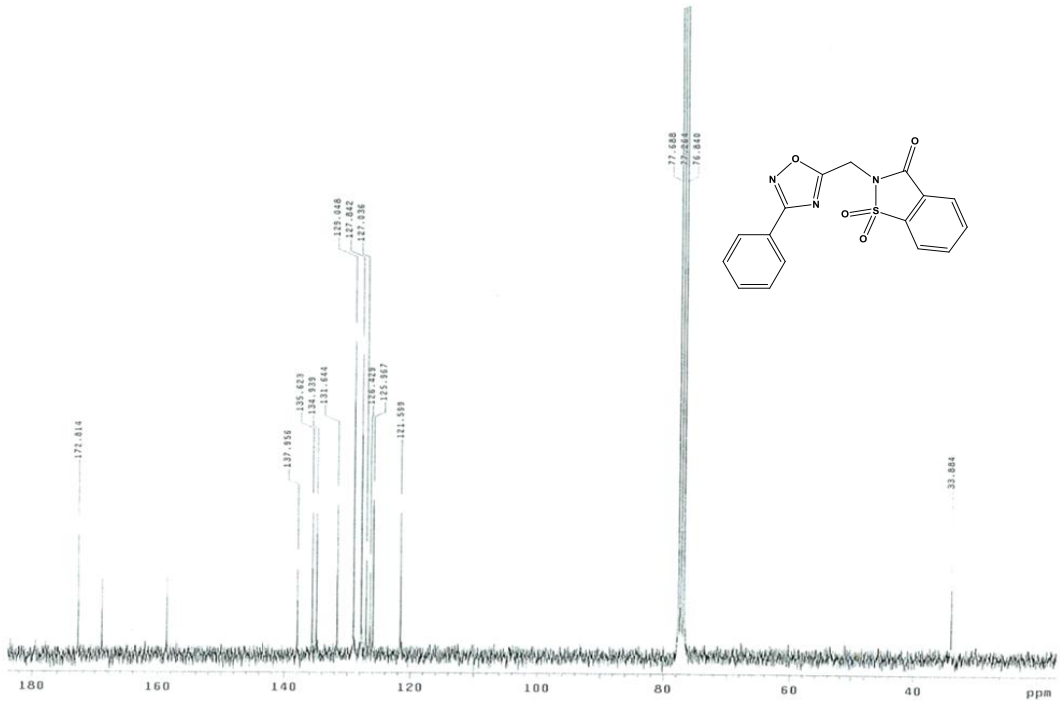

Figure 4.14. ^{13}C NMR spectrum of compound **59a.**

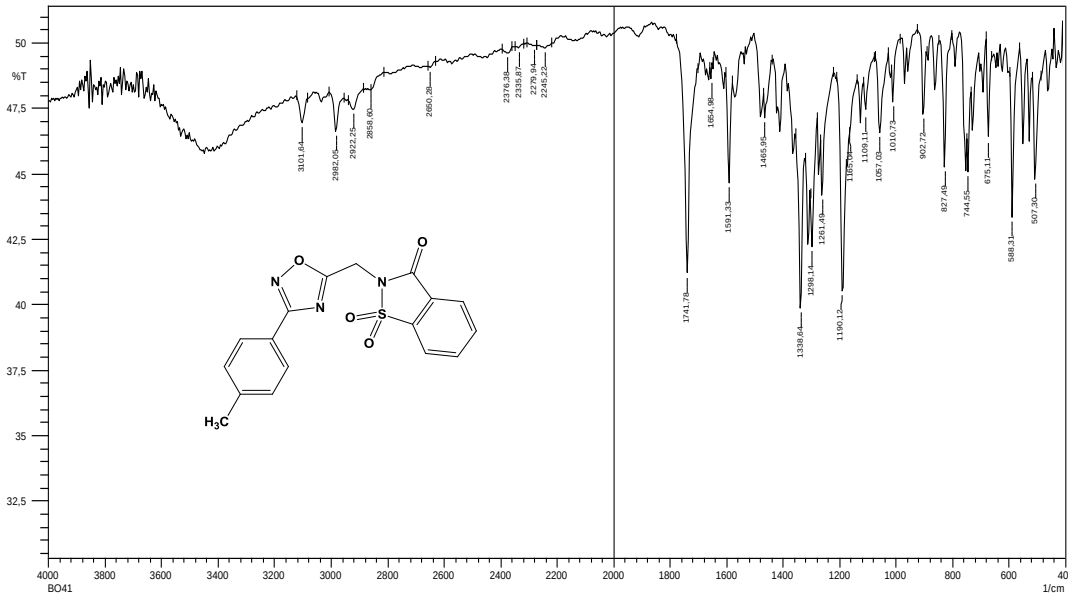

Figure 4.15. IR spectrum of compound **59b.**

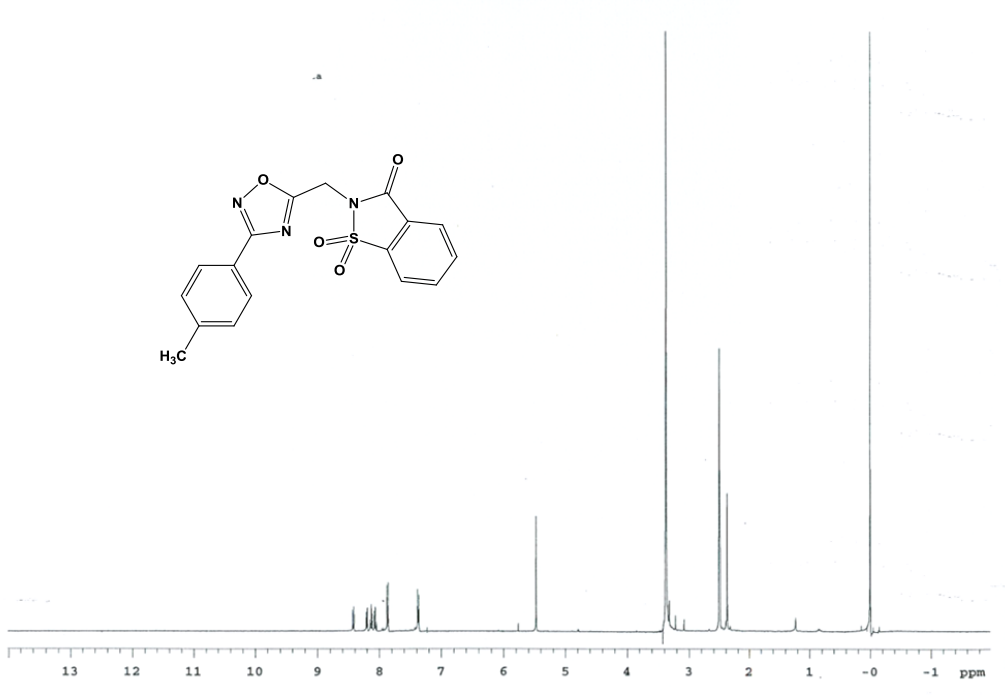

Figure 4.16. ^{1}H NMR spectrum of compound **59b.**

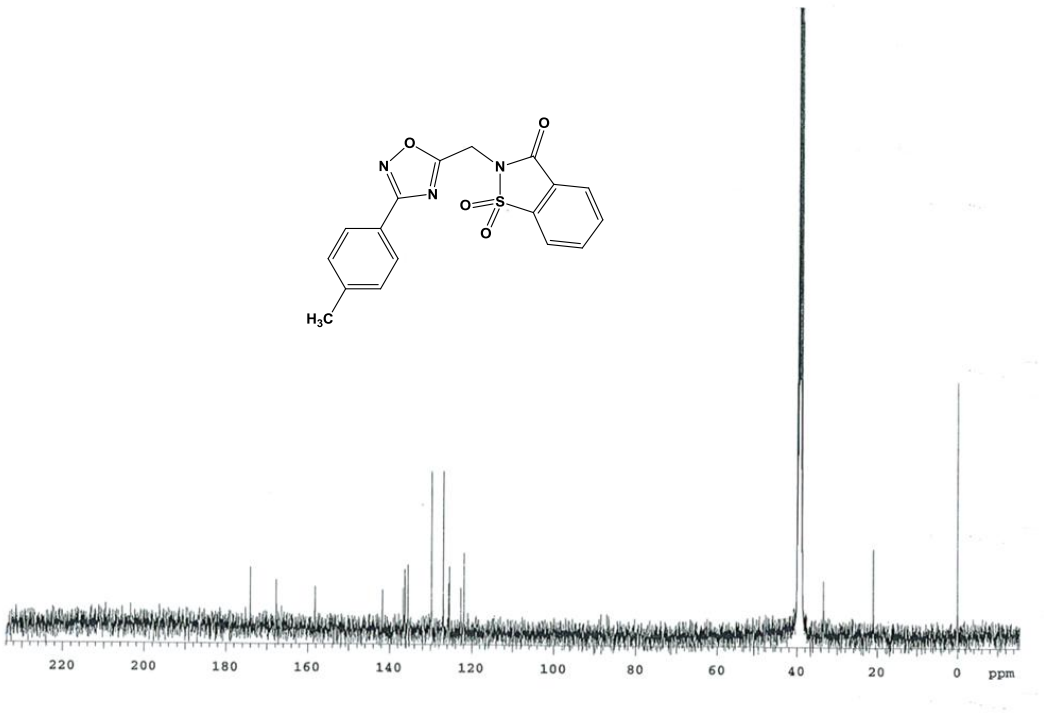

Figure 4.17. ^{13}C NMR spectrum of compound **59b.**

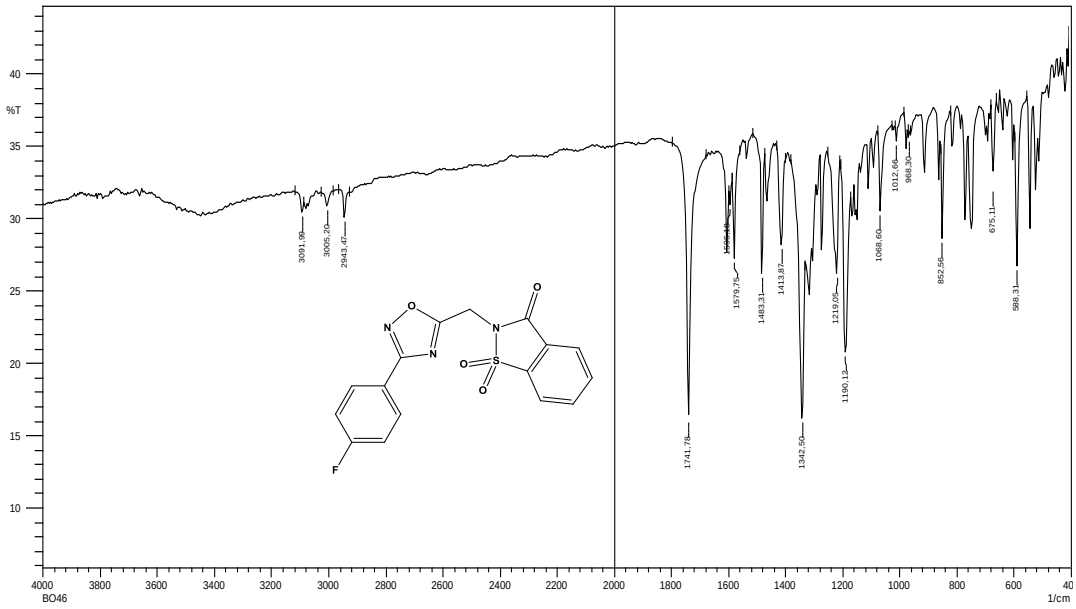

Figure 4.18. IR spectrum of compound **59c.**

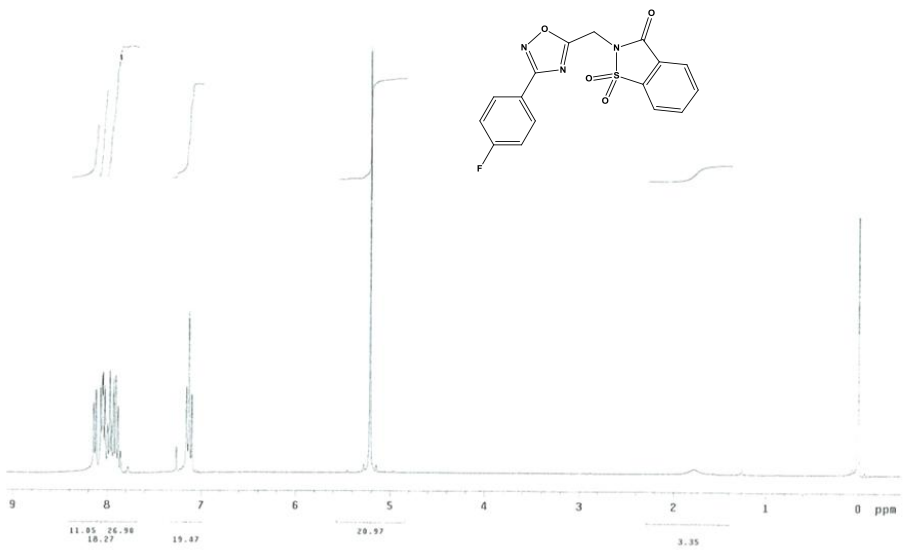

Figure 4.19. ^{1}H NMR spectrum of compound **59c.**

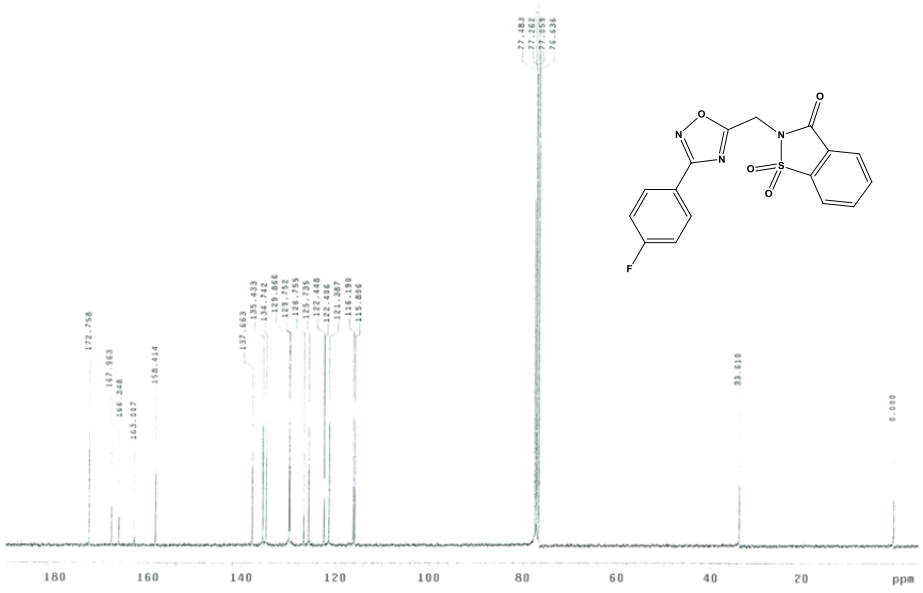

Figure 4.20. ^{13}C NMR spectrum of compound **59c.**

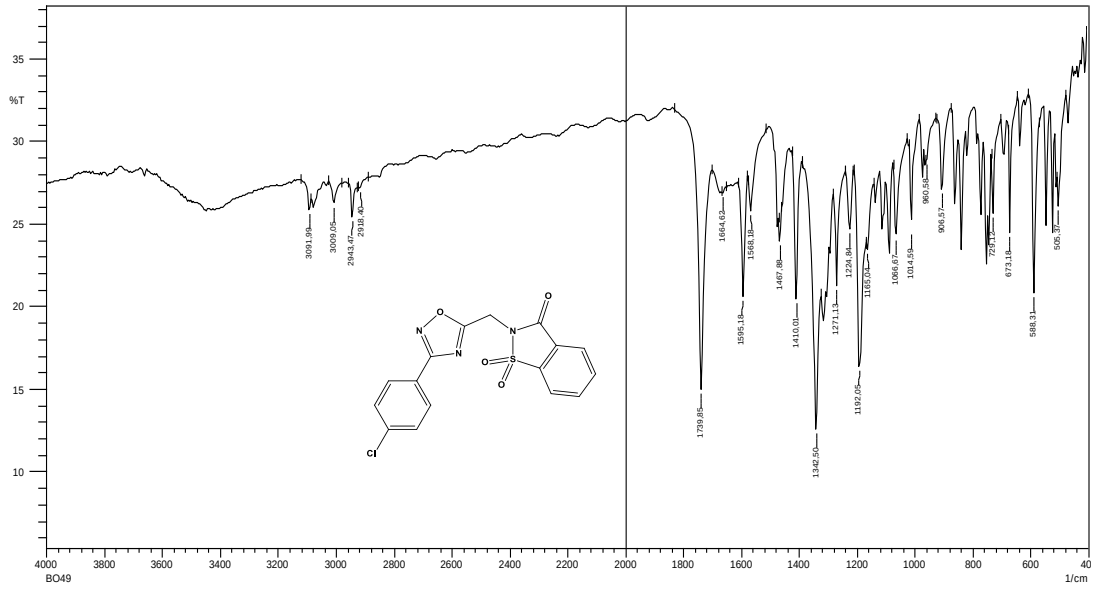

Figure 4.21. IR spectrum of compound **59d.**

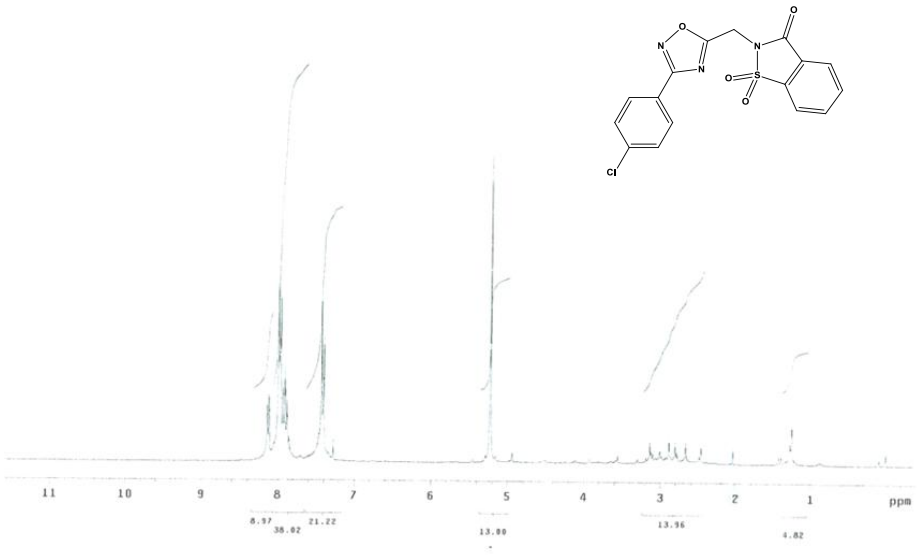

Figure 4.22. ^{1}H NMR spectrum of compound **59d.**

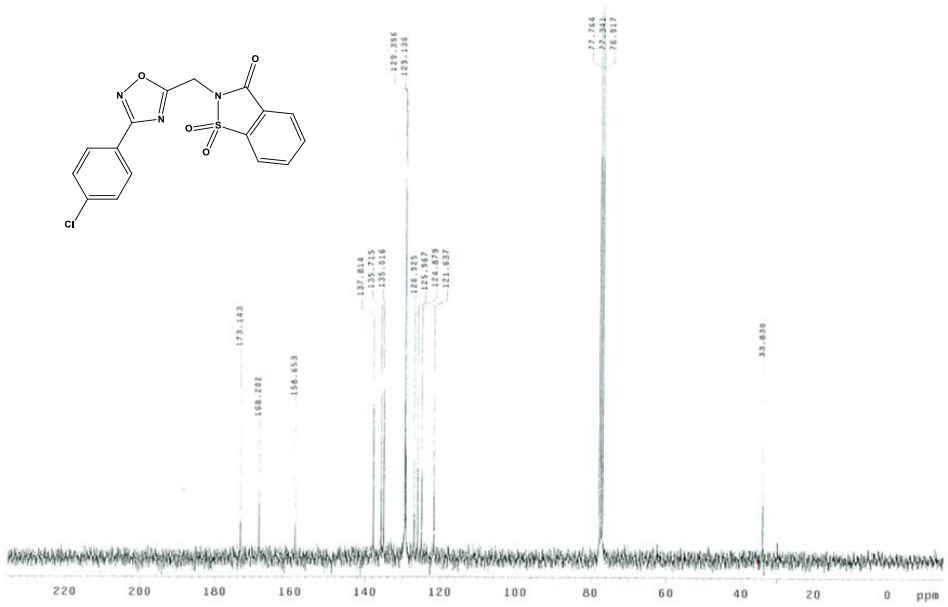

Figure 4.23. ^{13}C NMR spectrum of compound **59d.**

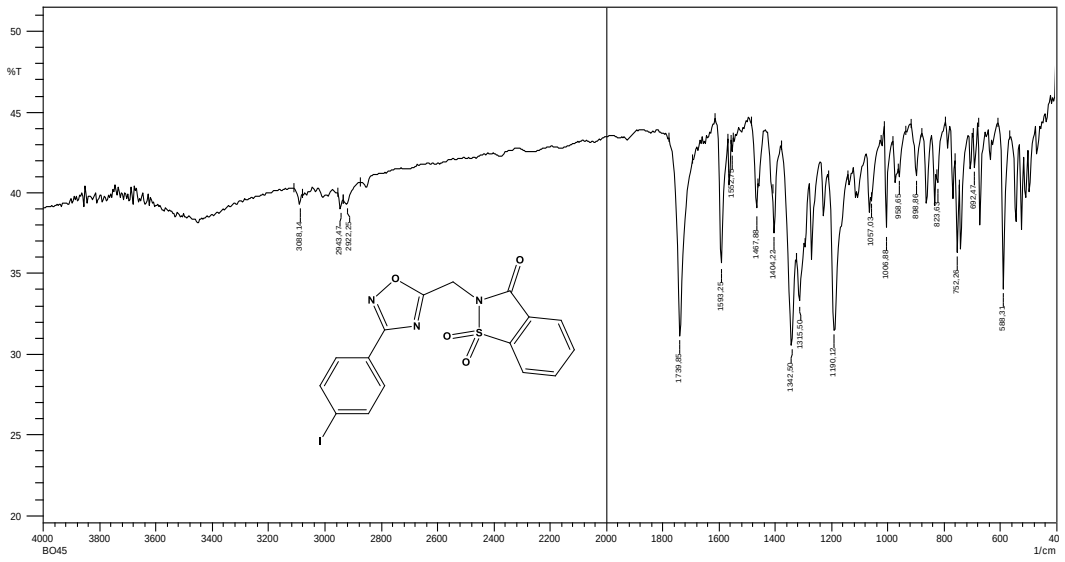

Figure 4.24. IR spectrum of compound **59e.**

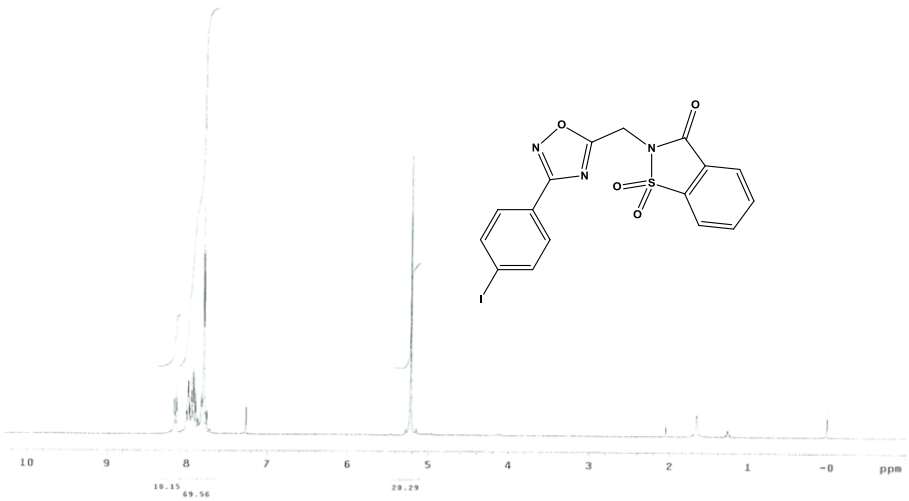

Figure 4.25. ^{1}H NMR spectrum of compound **59e.**

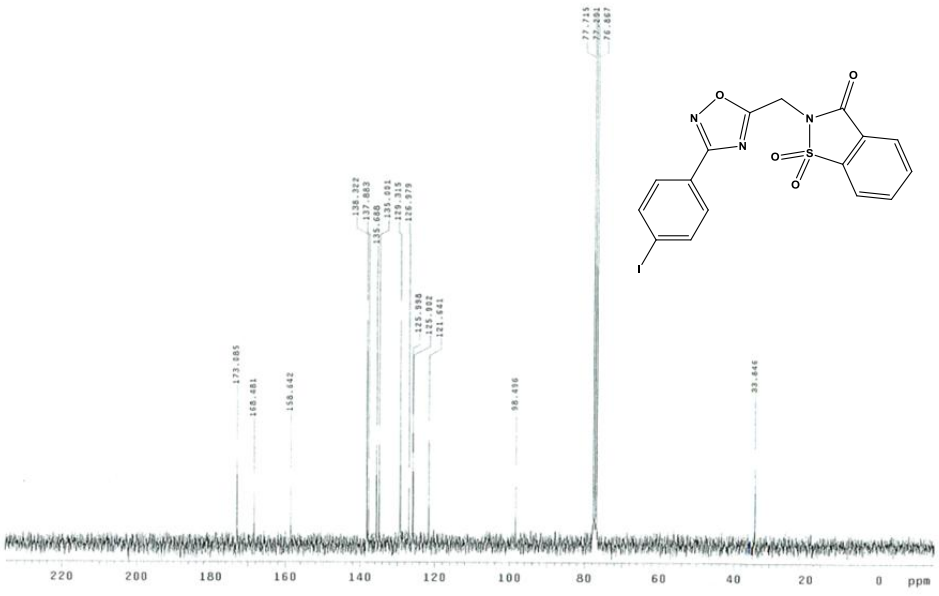

Figure 4.26. ^{13}C NMR spectrum of compound **59e.**

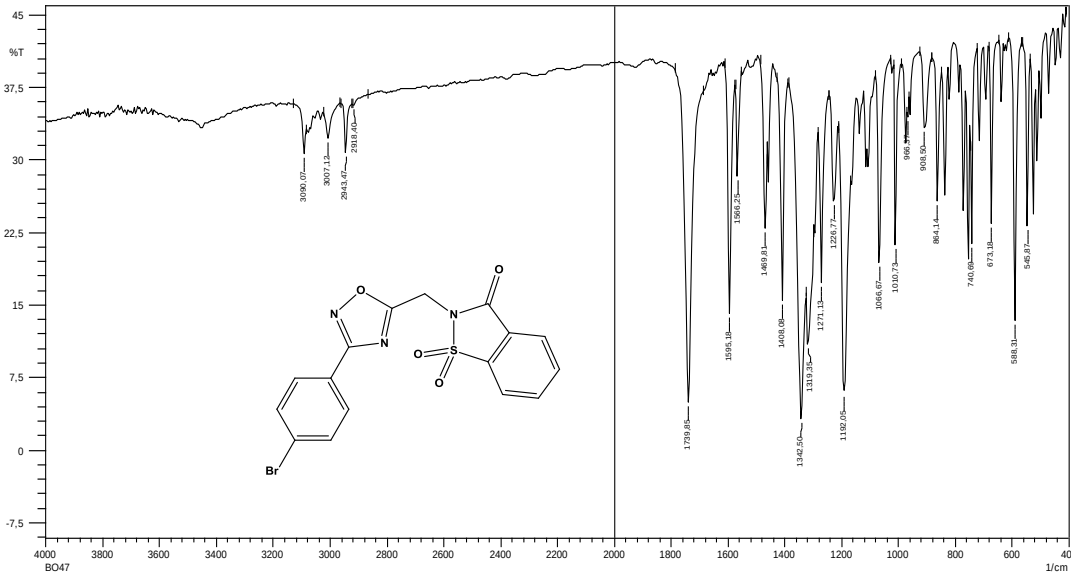

Figure 4.27. IR spectrum of compound **59f.**

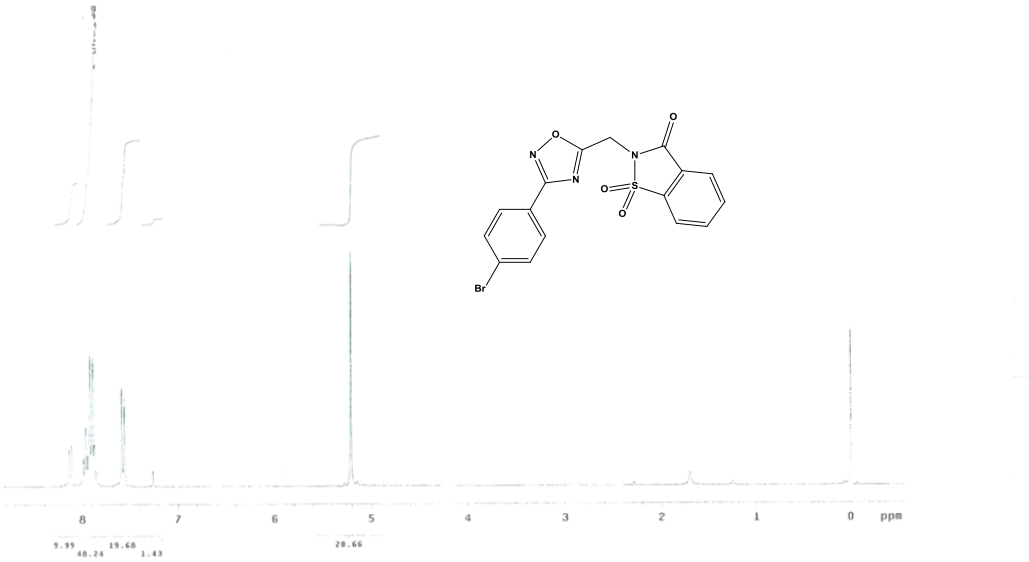

Figure 4.28. ^{1}H NMR spectrum of compound **59f.**

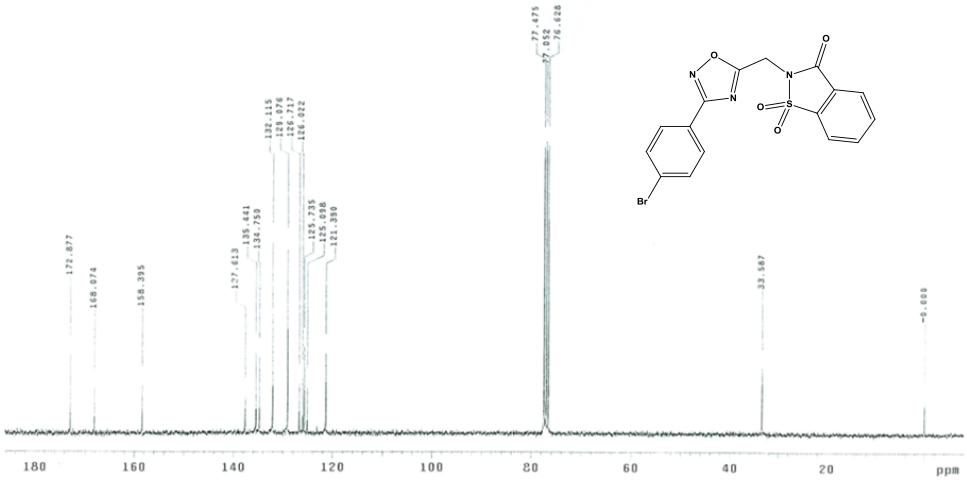

Figure 4.29. ^{13}C NMR spectrum of compound **59f.**

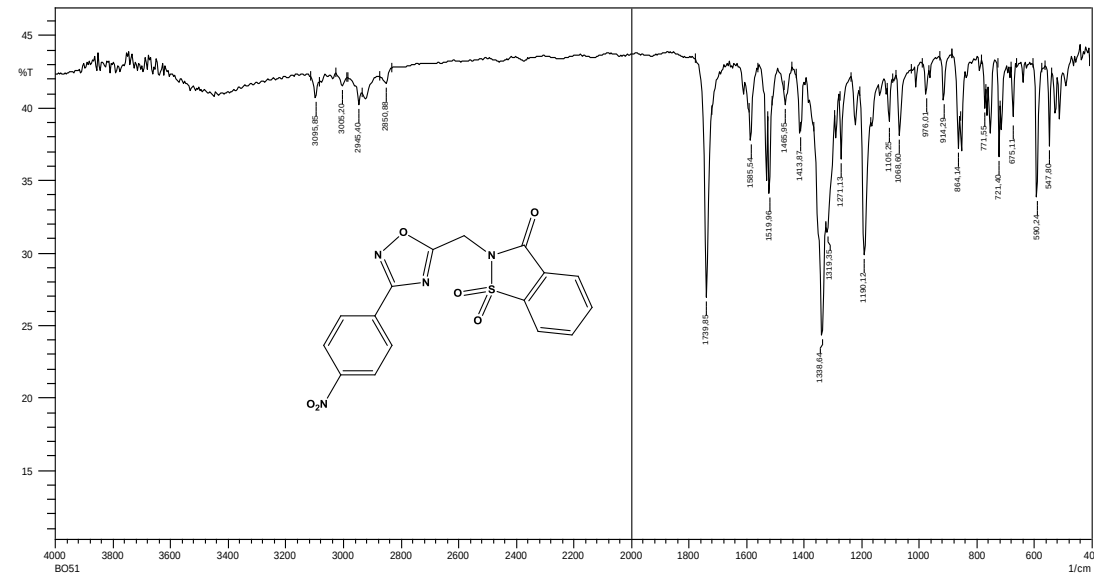

Figure 4.30. IR spectrum of compound **59g.**

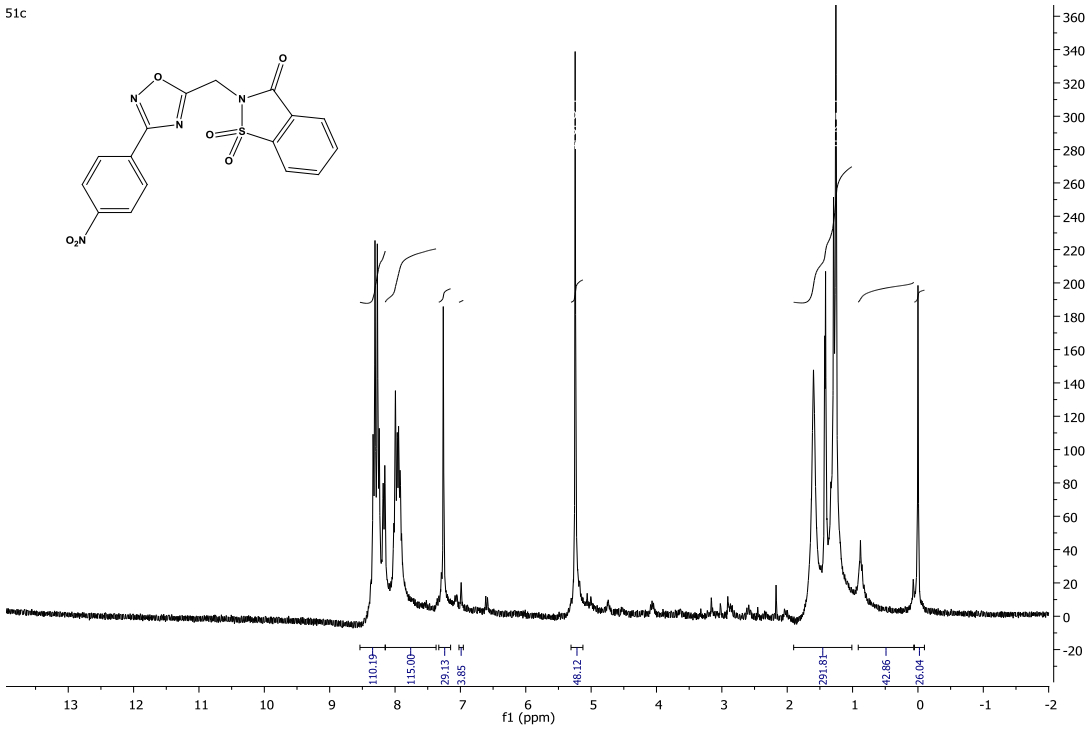

Figure 4.31. ^{1}H NMR spectrum of compound **59g.**

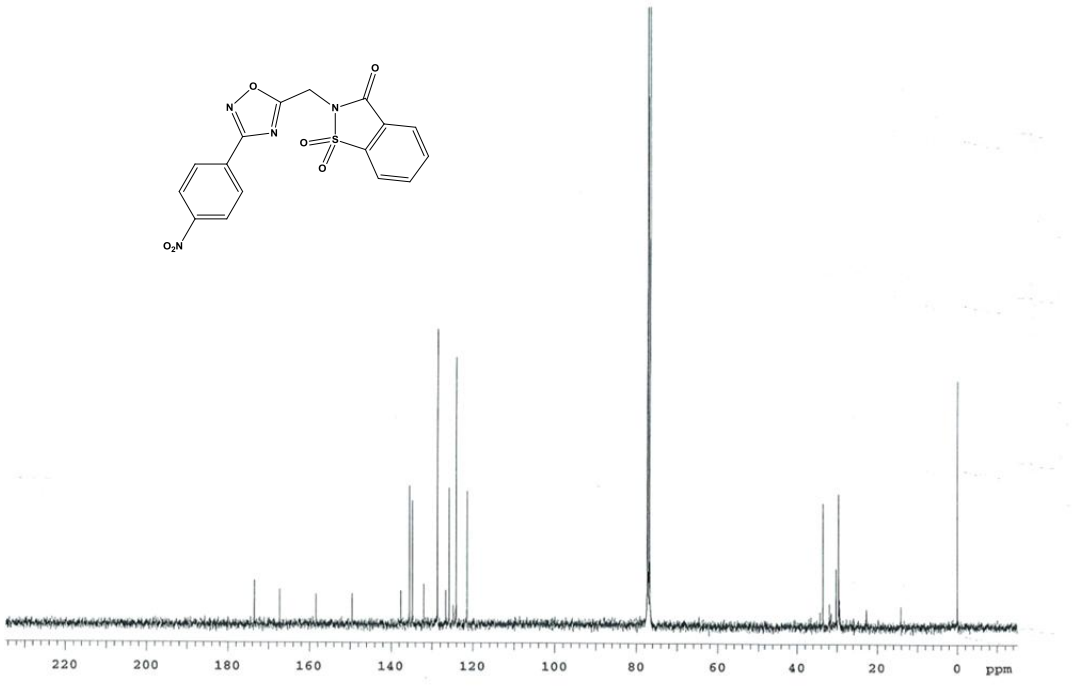

Figure 4.32. ^{13}C NMR spectrum of compound **59g.**

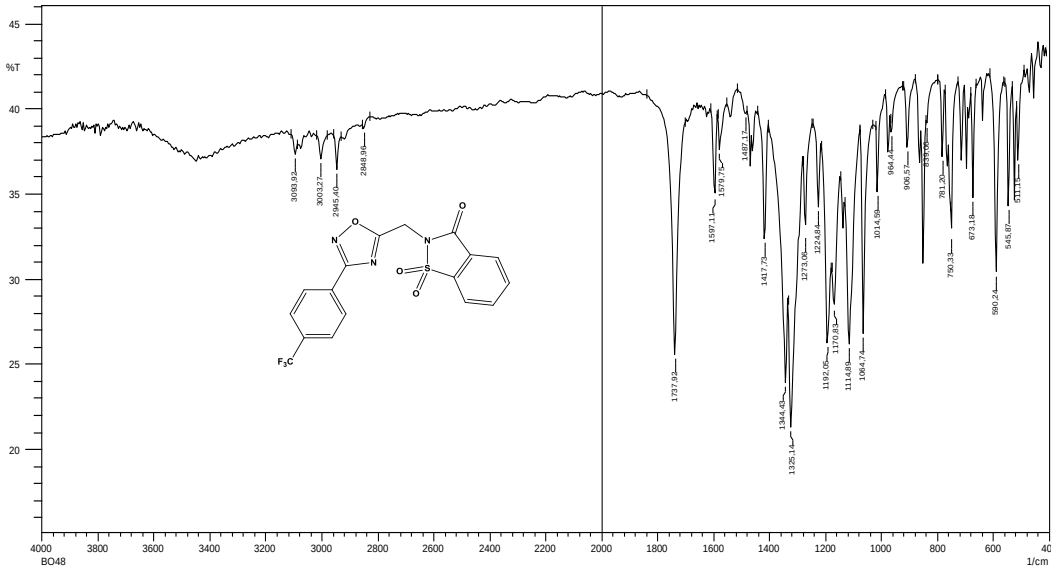

Figure 4.33. IR spectrum of compound **59h.**

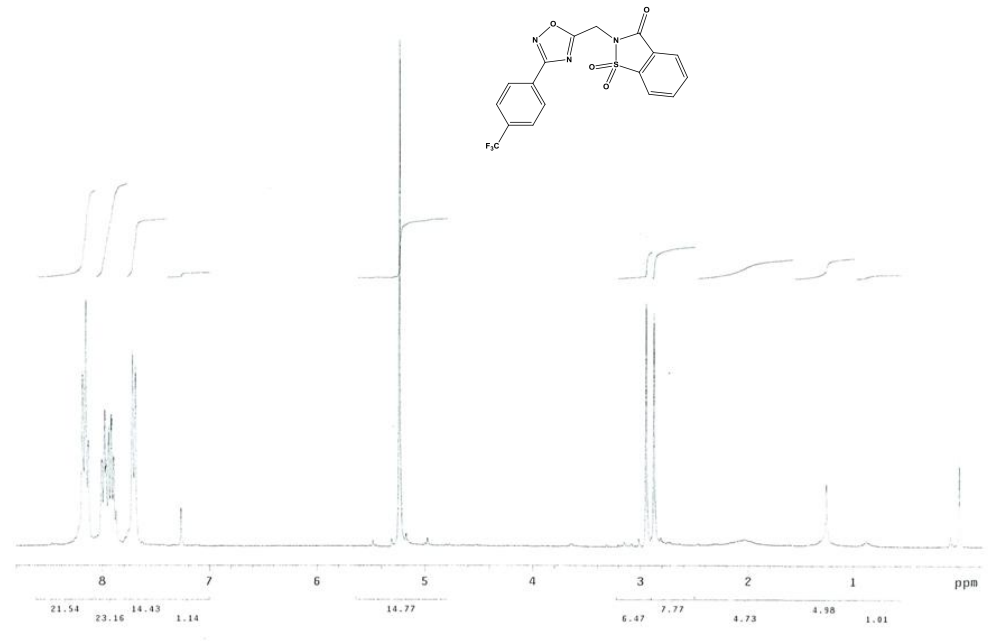

Figure 4.34. ^{1}H NMR spectrum of compound **59h.**

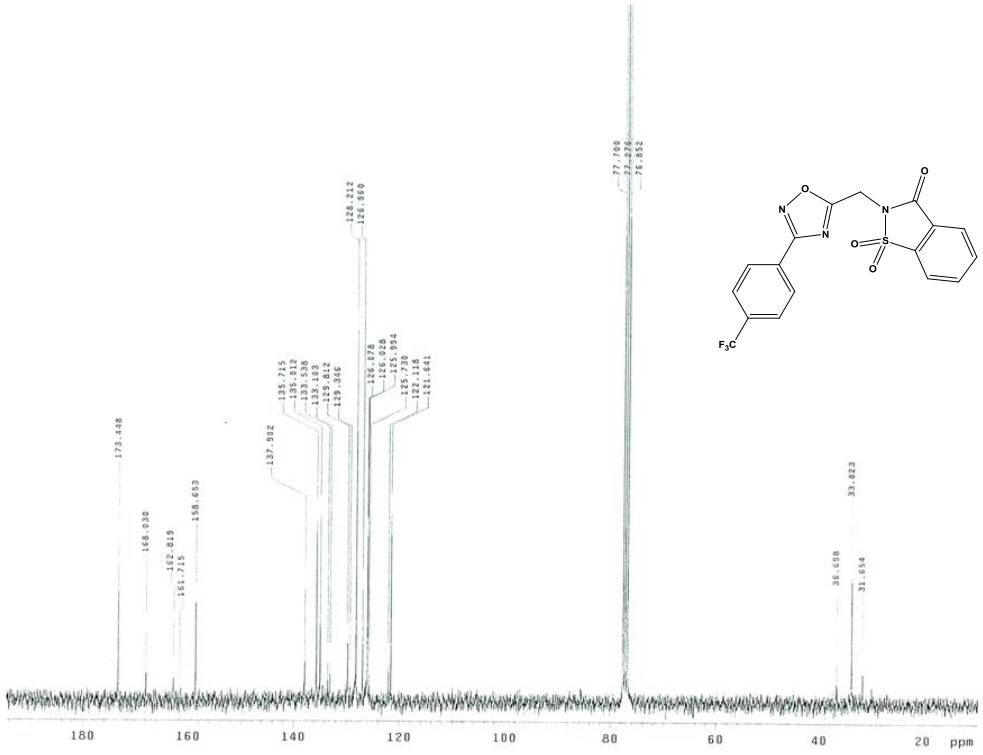

Figure 4.35. ^{13}C NMR spectrum of compound **59h.**

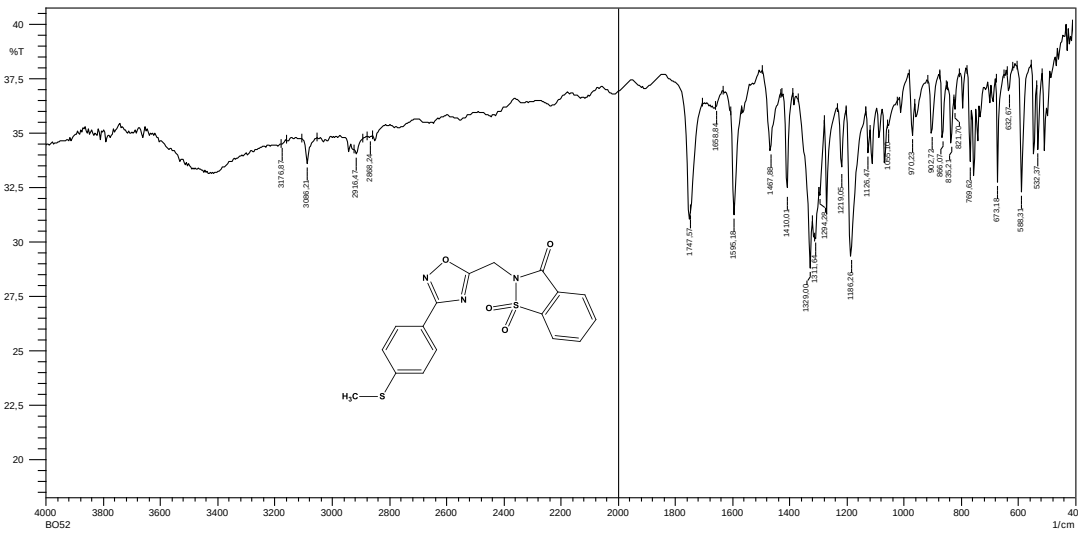

Figure 4.36. IR spectrum of compound **59i.**

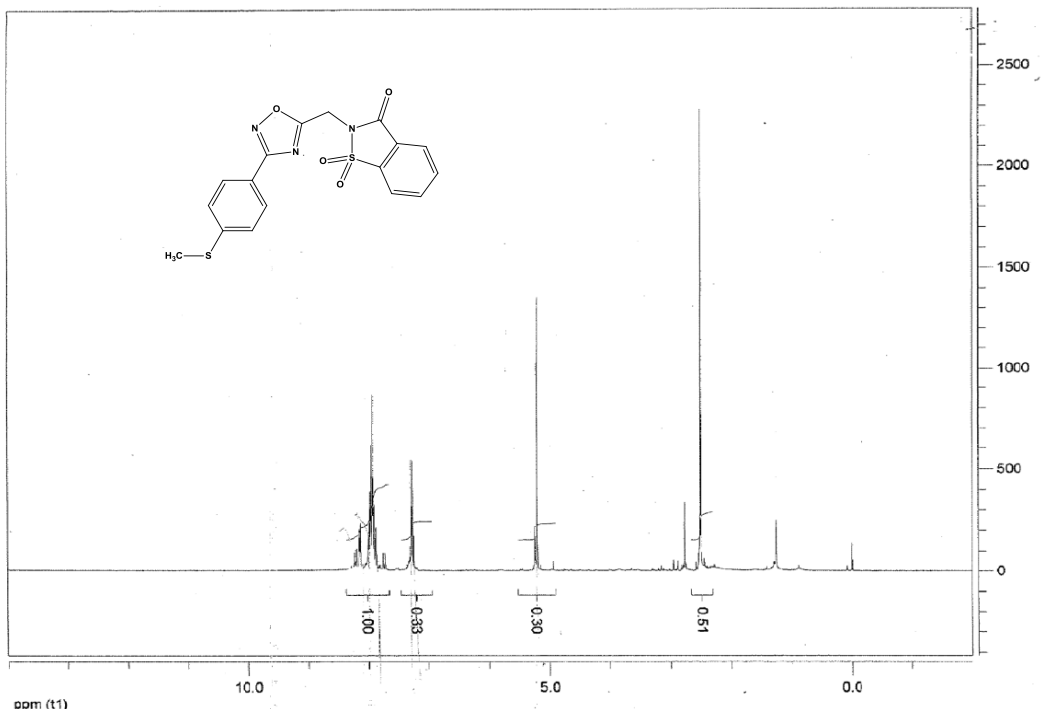

Figure 4.37. ^{1}H NMR spectrum of compound **59i.**

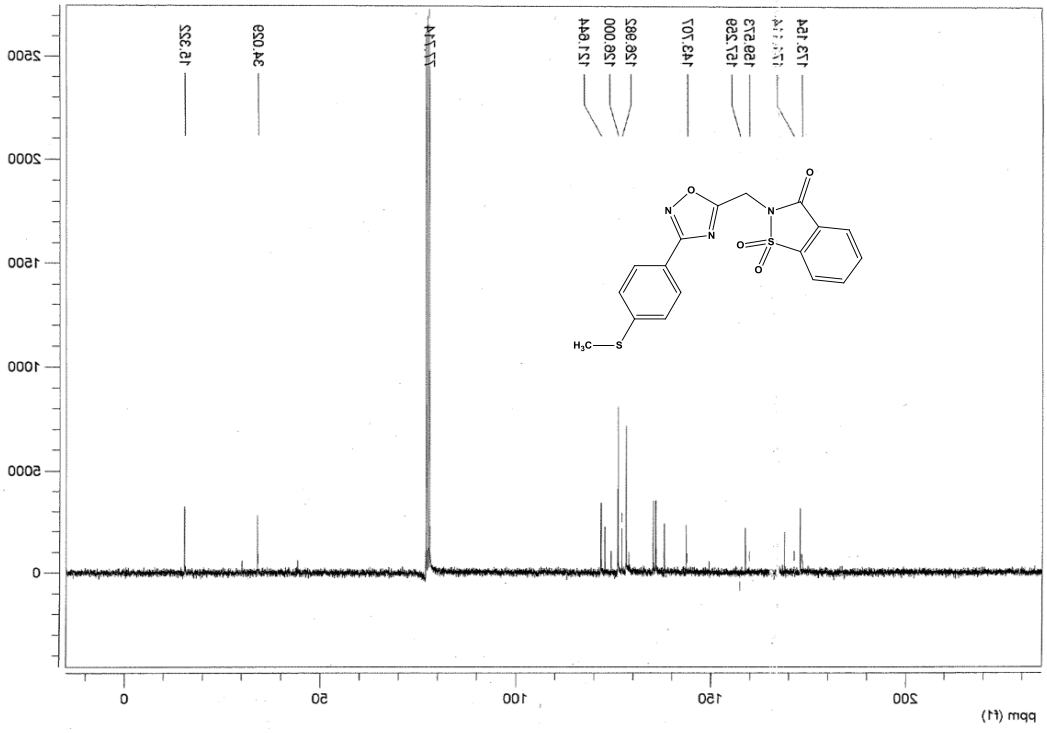

Figure 4.38. ^{13}C NMR spectrum of compound **59i.**

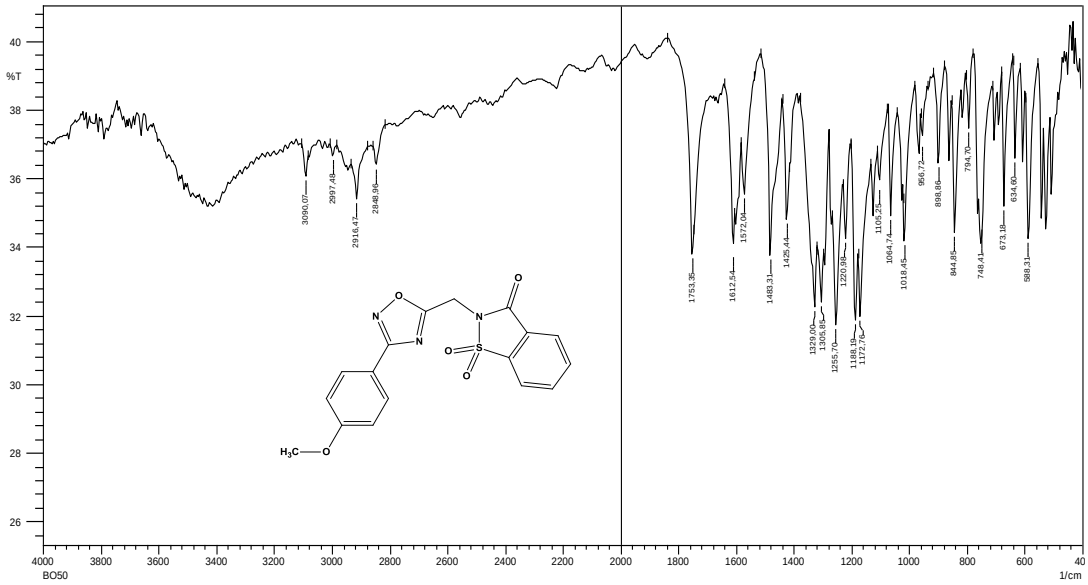

Figure 4.39. IR spectrum of compound **59j.**

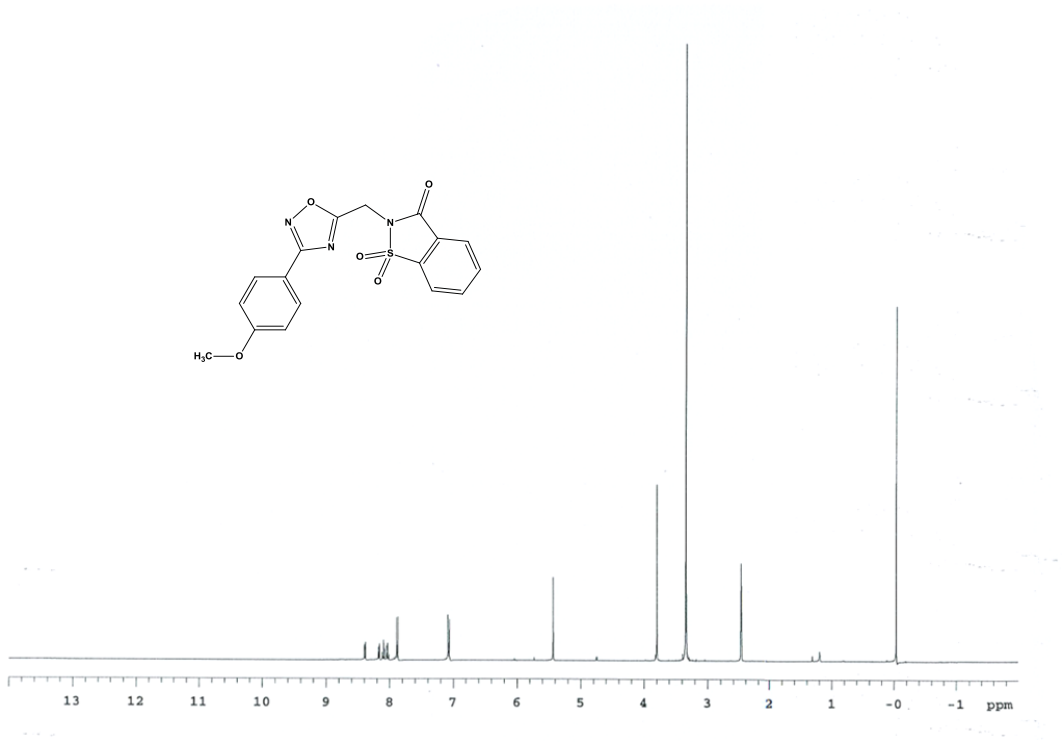

Figure 4.40. ^{1}H NMR spectrum of compound **59j.**

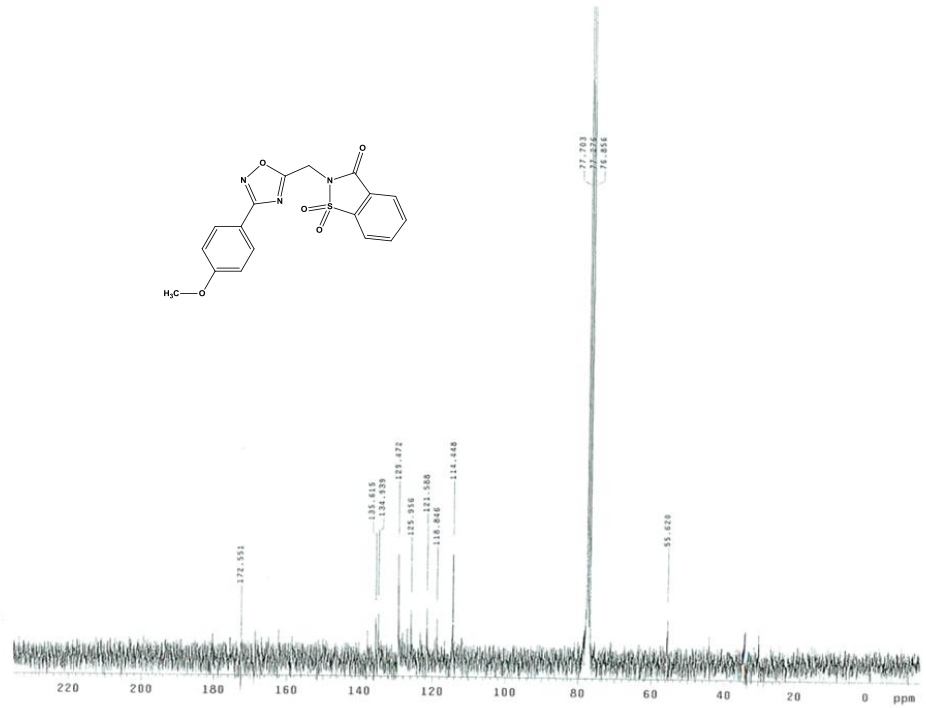

Figure 4.41. ^{13}C NMR spectrum of compound **59j.**

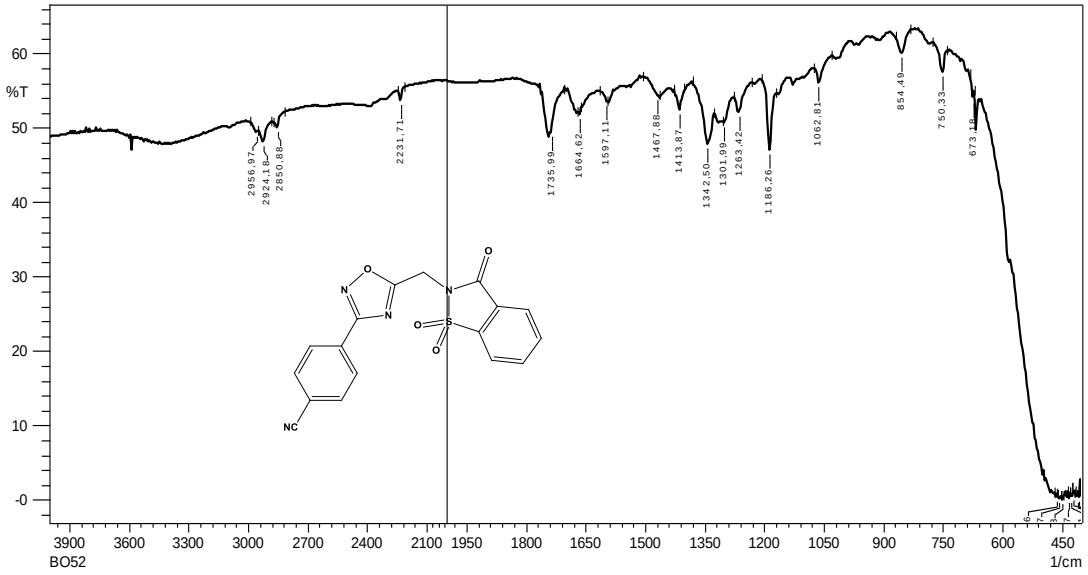

Figure 4.42. IR spectrum of compound **59k.**

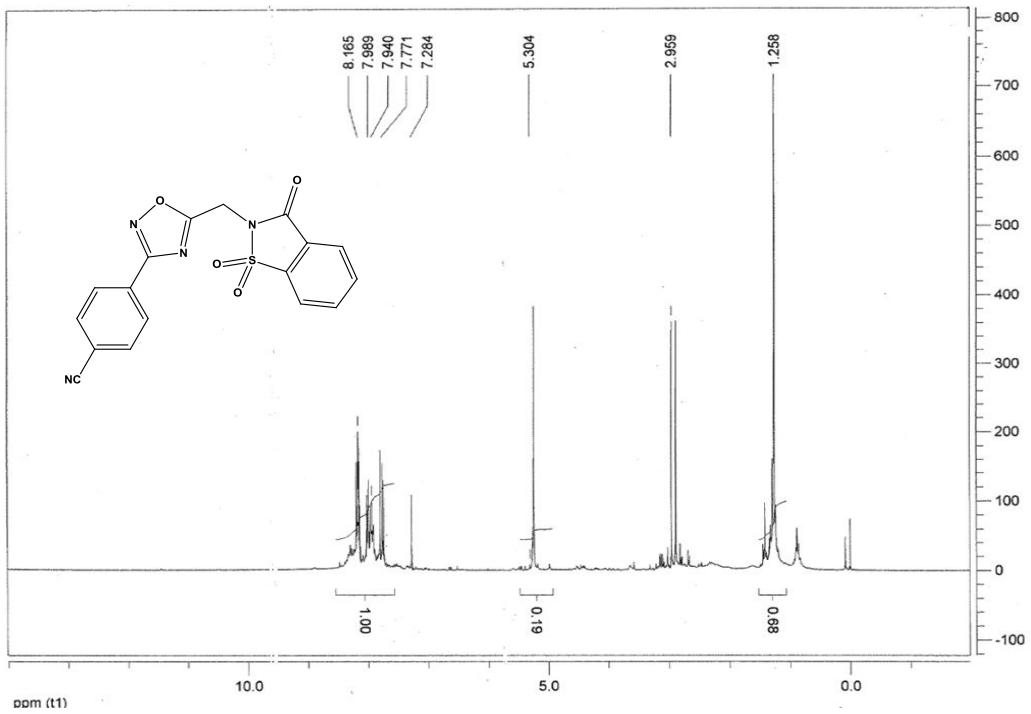

Figure 4.43. ^{1}H NMR spectrum of compound **59k.**

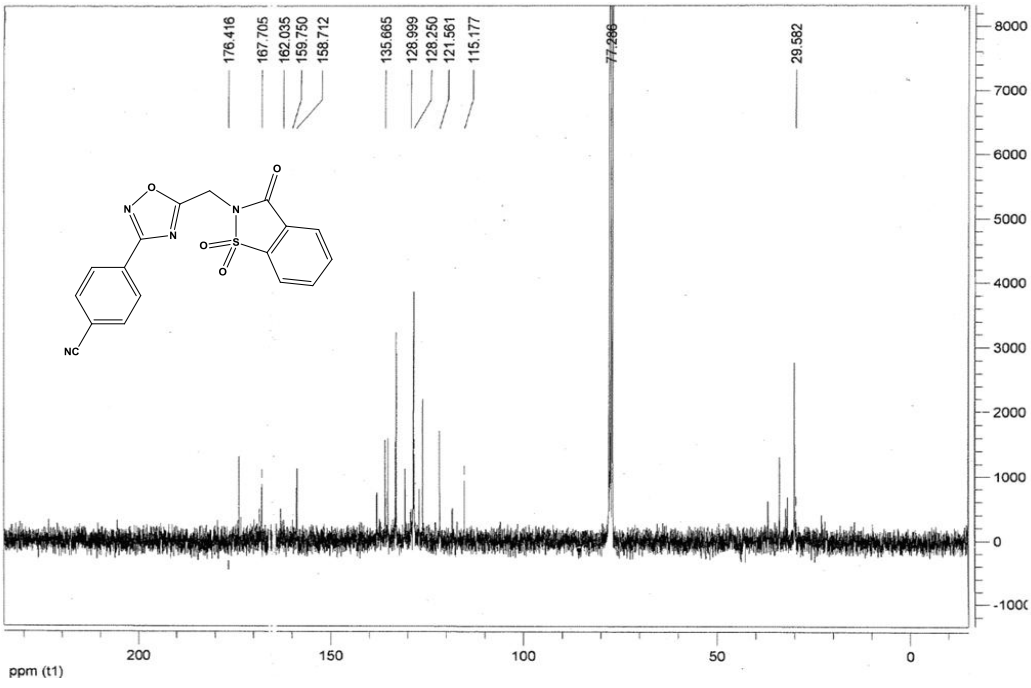

Figure 4.44. ^{13}C NMR spectrum of compound **59k.**

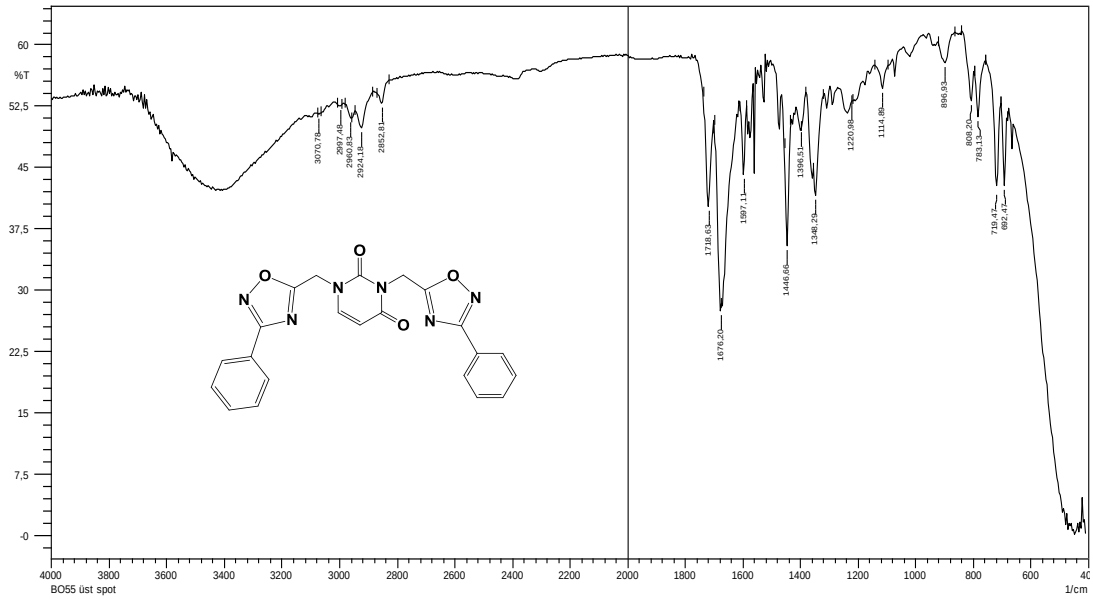

Figure 4.45. IR spectrum of compound **60a.**

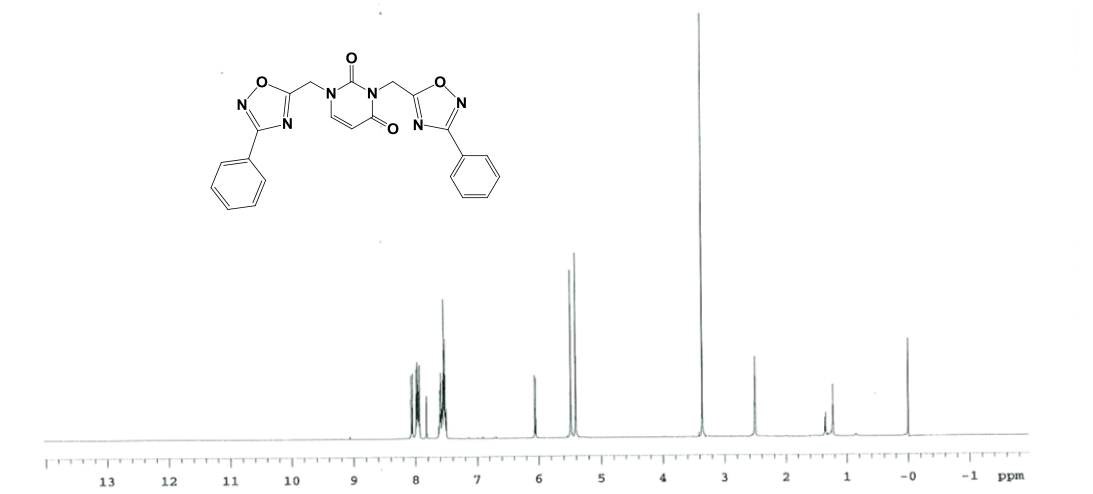

Figure 4.46. ^{1}H NMR spectrum of compound **60a.**

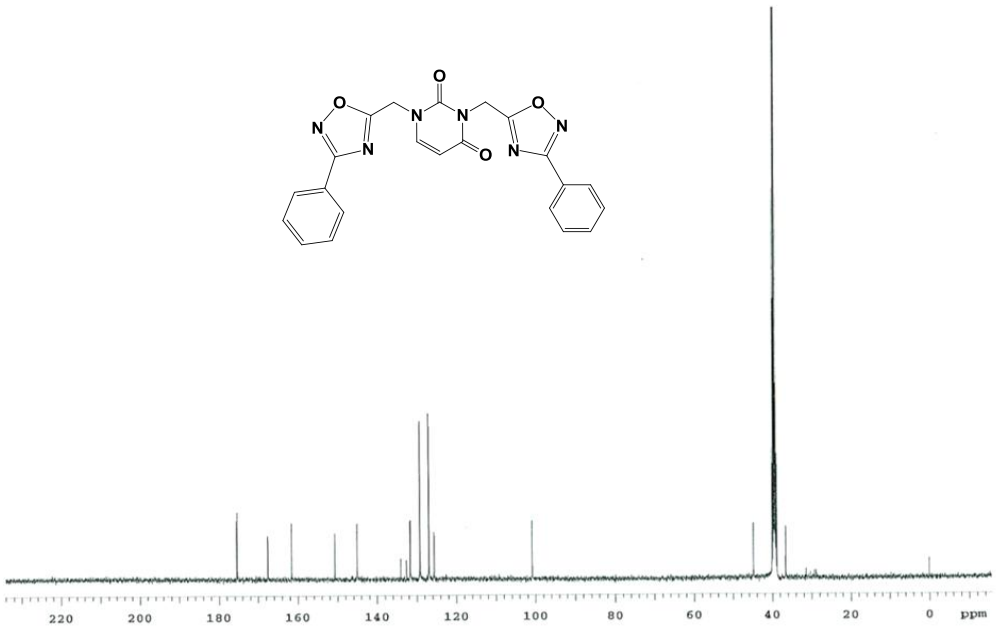

Figure 4.47. ^{13}C NMR spectrum of compound **60a.**

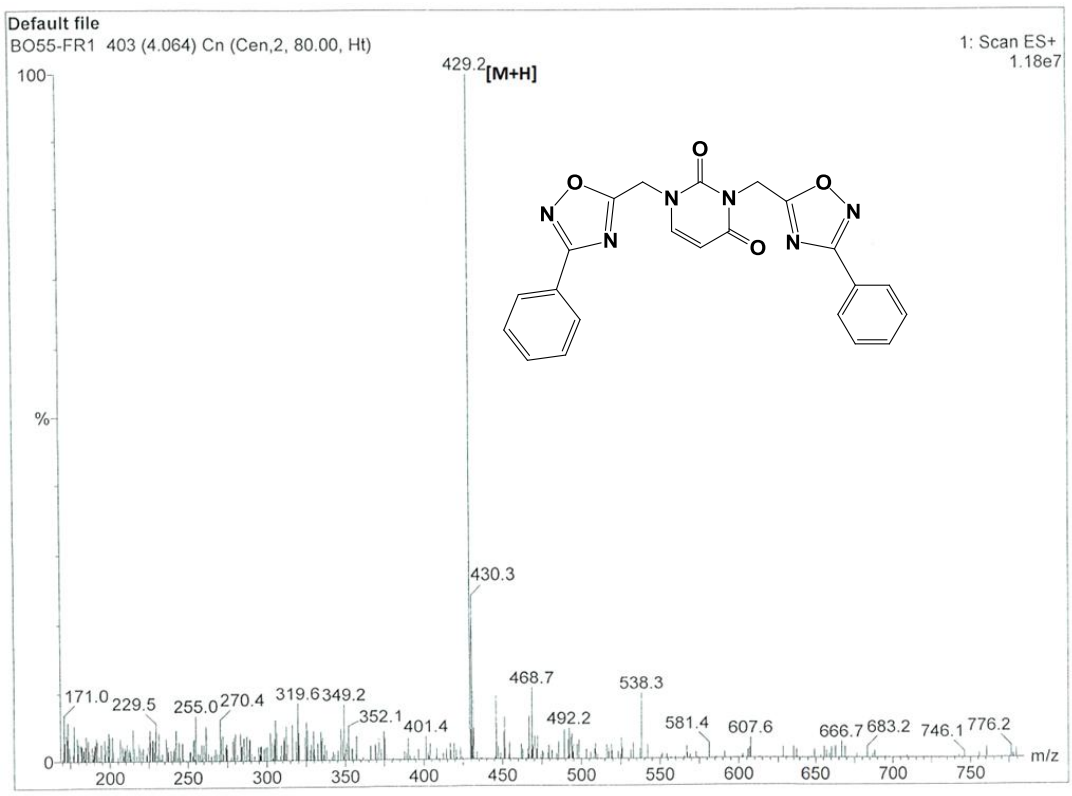

Figure 4.48. LC-MS spectrum of compound **60a.**

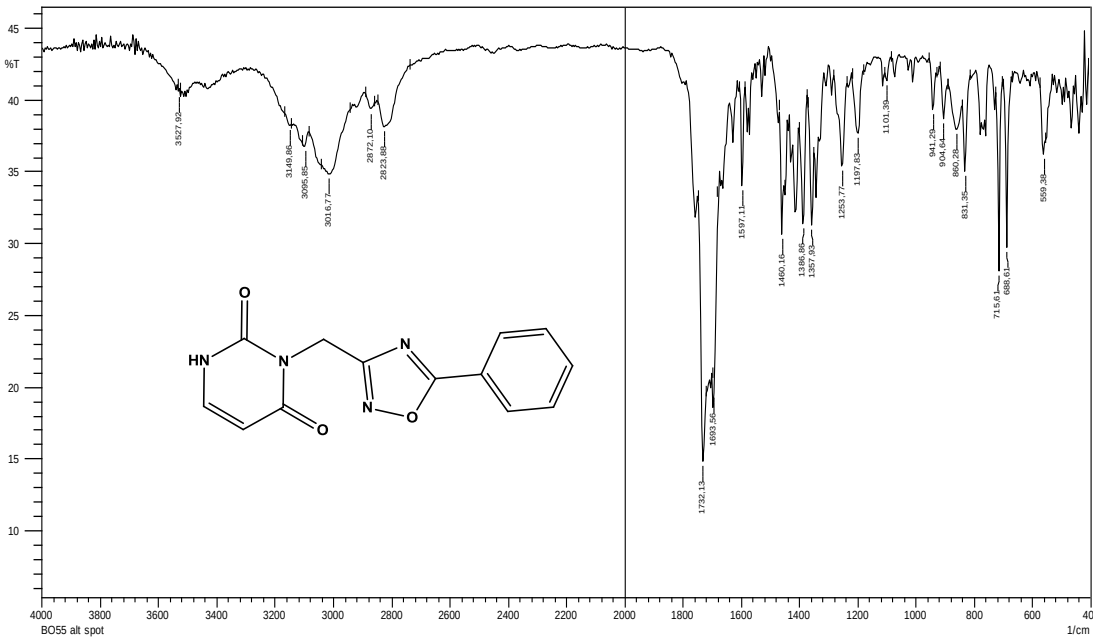

Figure 4.49. IR spectrum of compound **61a.**

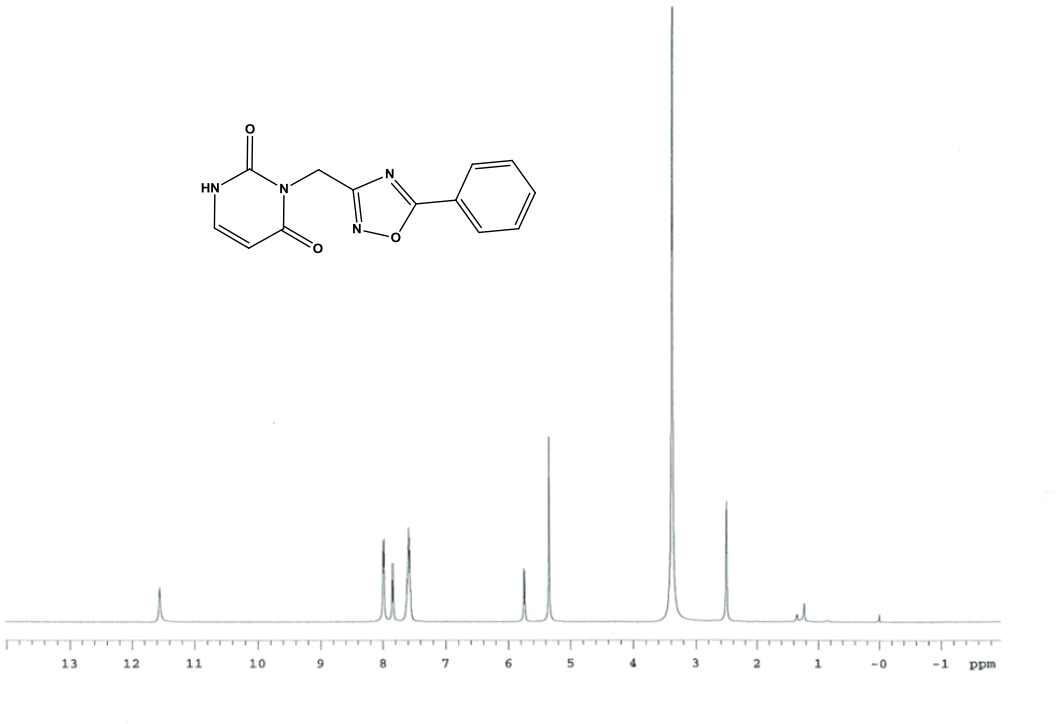

Figure 4.50. ^{1}H NMR spectrum of compound **61a.**

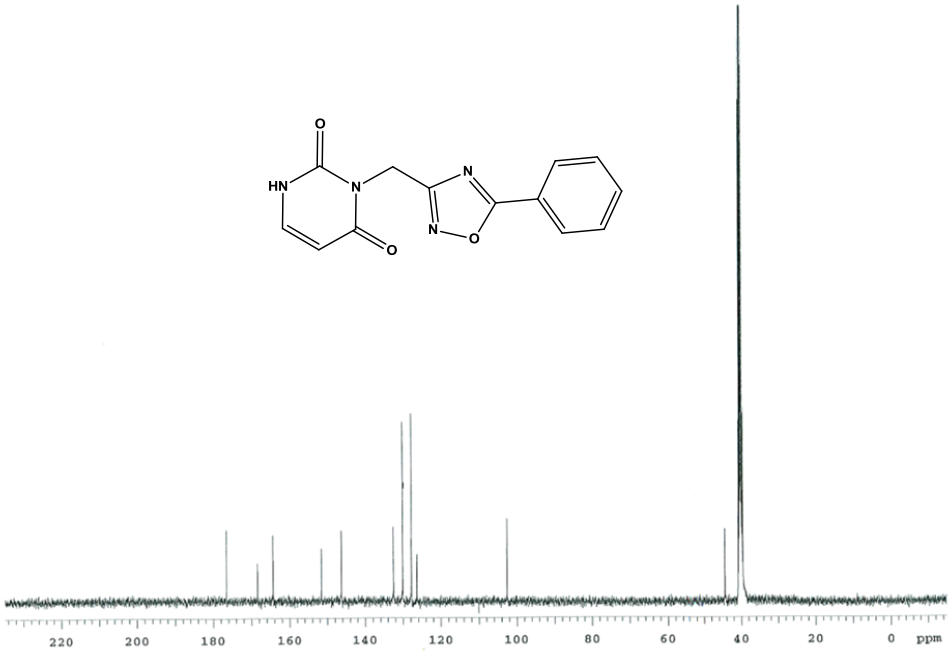

Figure 4.51. ^{13}C NMR spectrum of compound **61a.**

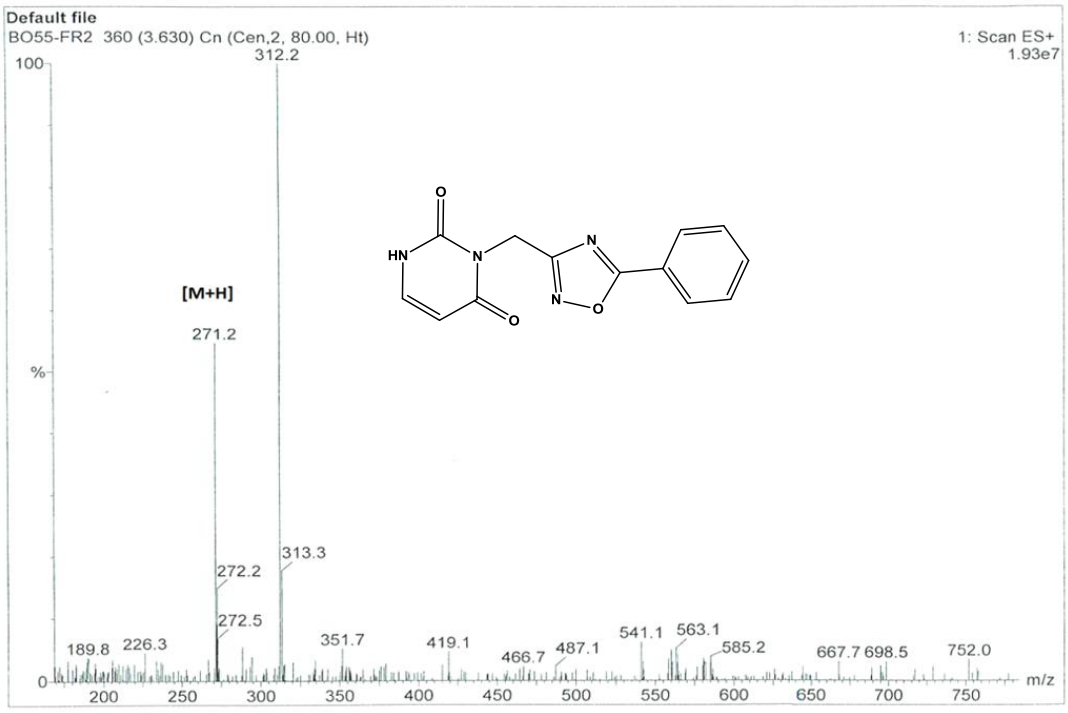

Figure 4.52. LC-MS spectrum of compound **61a.**

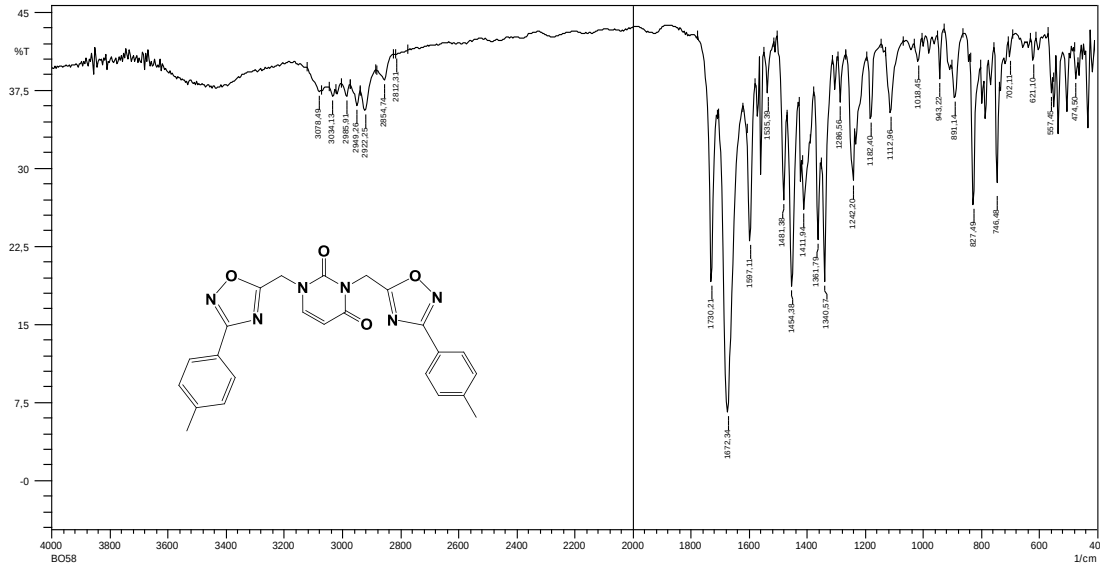

Figure 4.53. IR spectrum of compound **60b.**

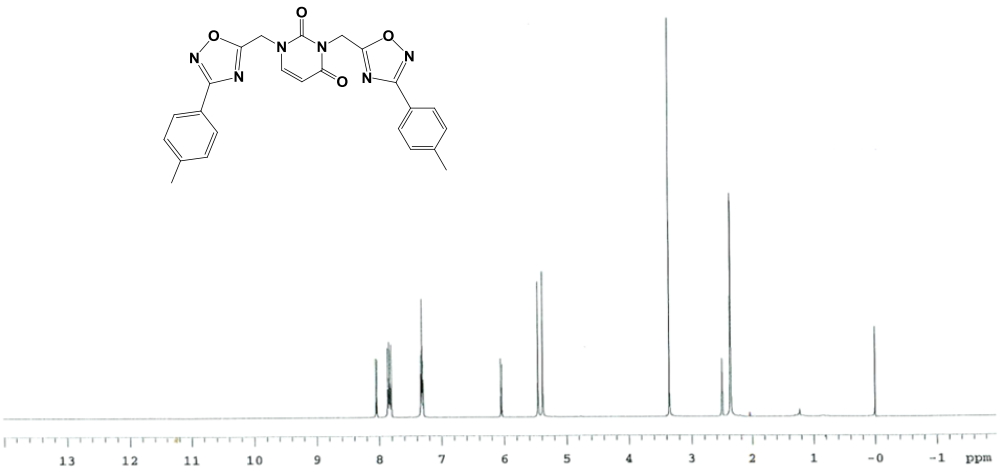

Figure 4.54. ^{1}H NMR spectrum of compound **60b.**

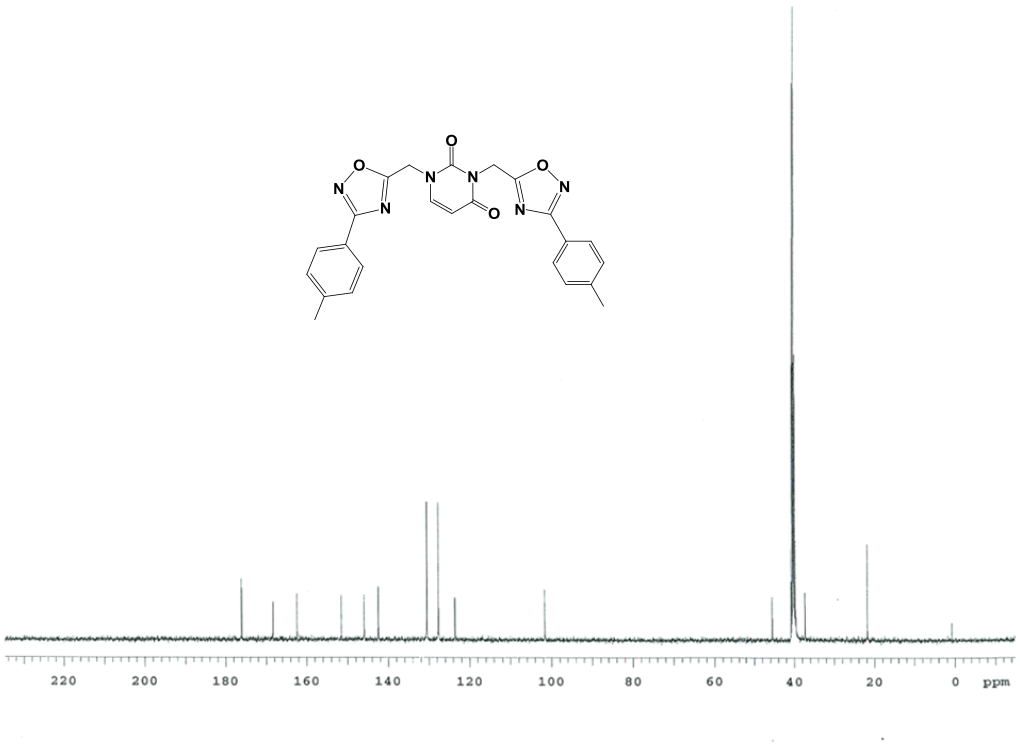

Figure 4.55. ^{13}C NMR spectrum of compound **60b.**

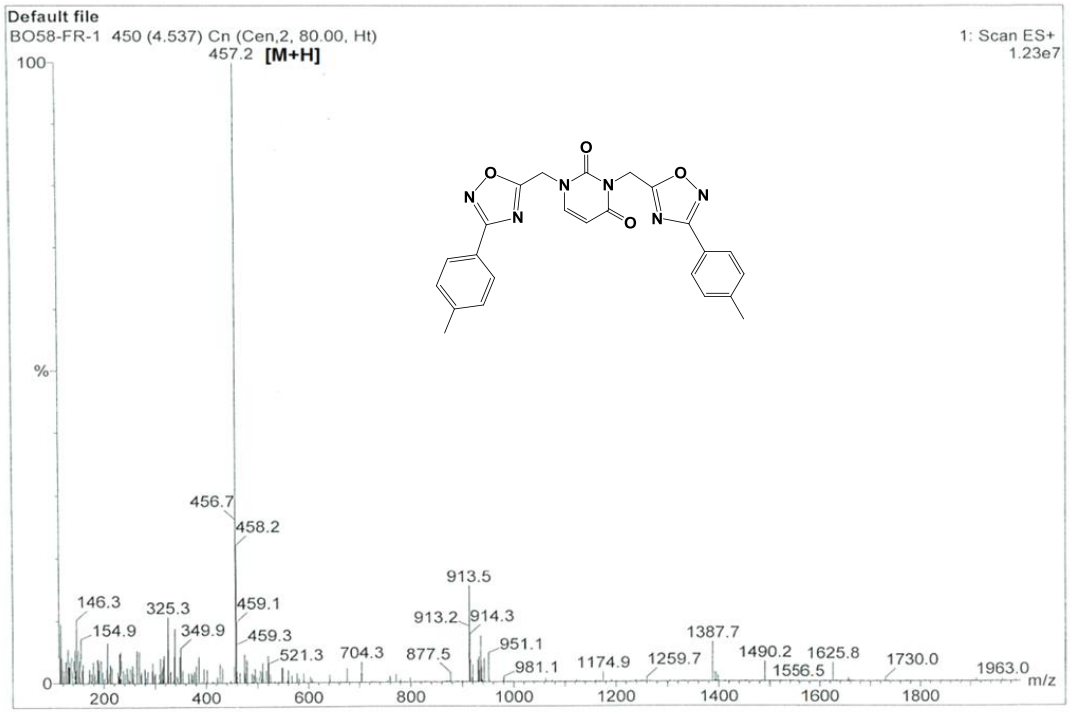

Figure 4.56. LC-MS spectrum of compound **60b.**

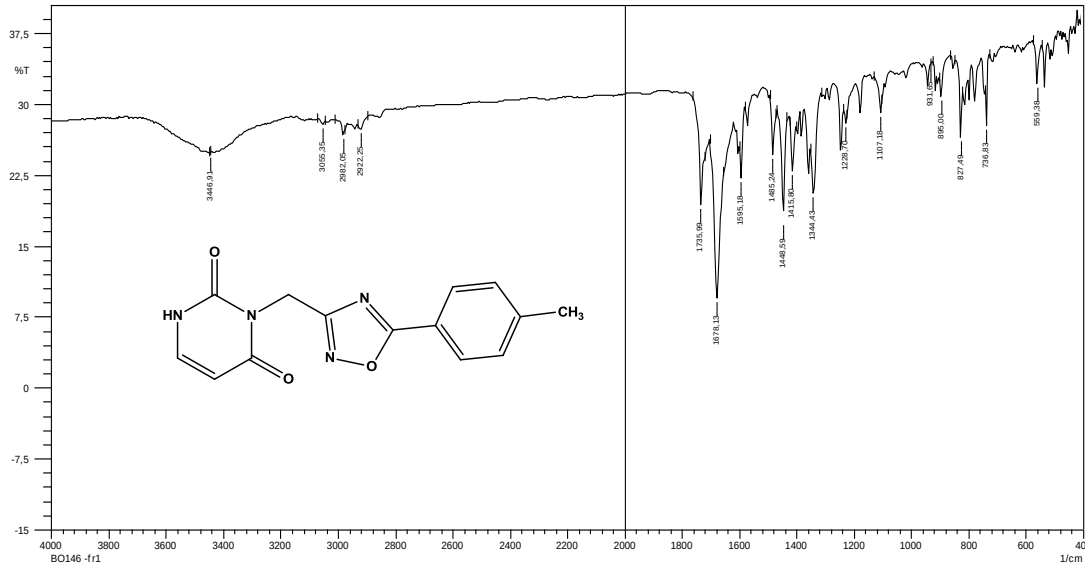

Figure 4.57. IR spectrum of compound **61b.**

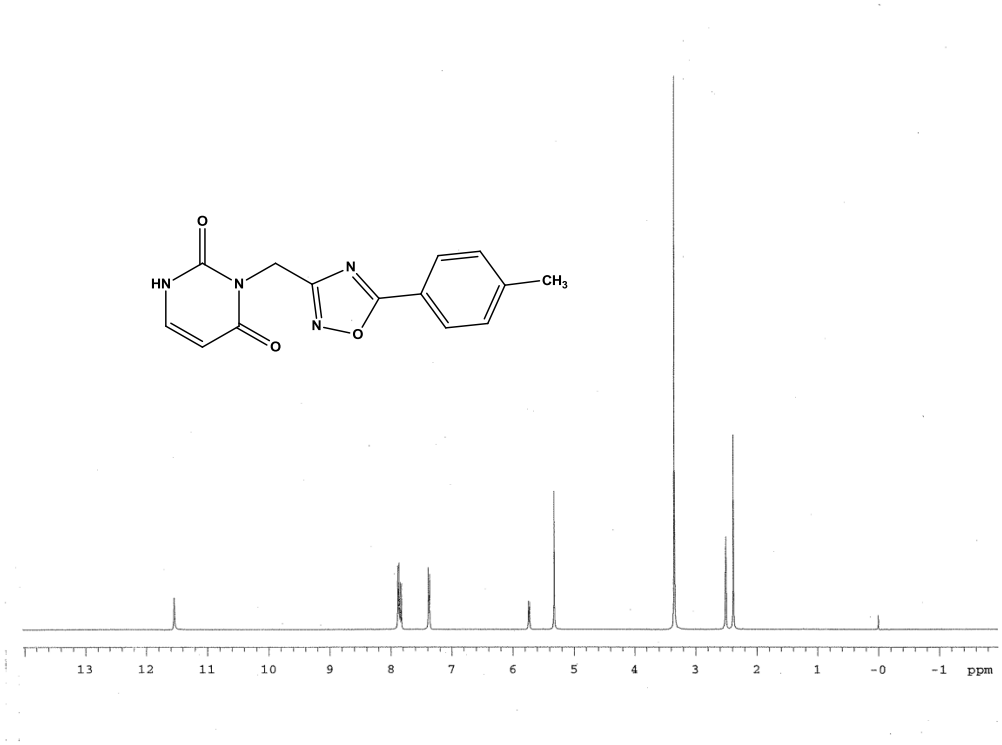

Figure 4.58. ^{1}H NMR spectrum of compound **61b.**

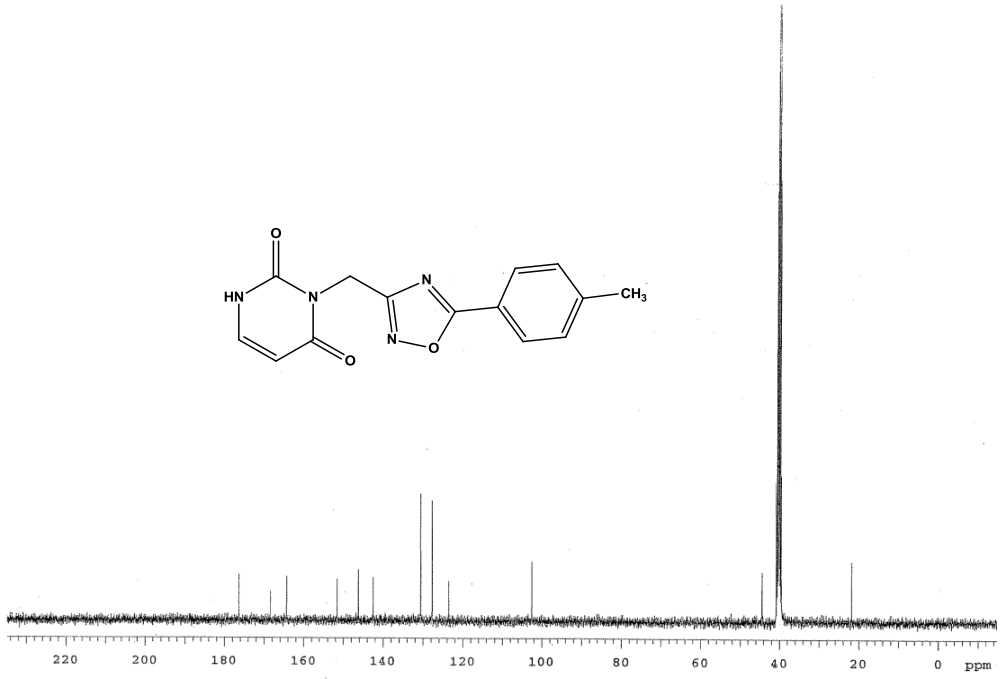

Figure 4.59. ^{13}C NMR spectrum of compound **61b.**

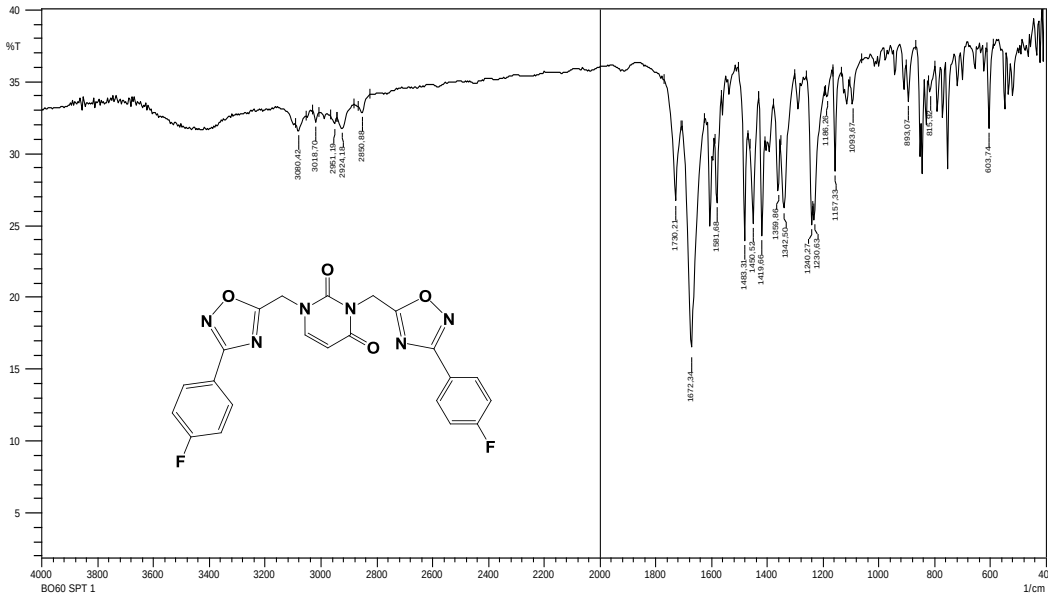

Figure 4.60. IR spectrum of compound **60c.**

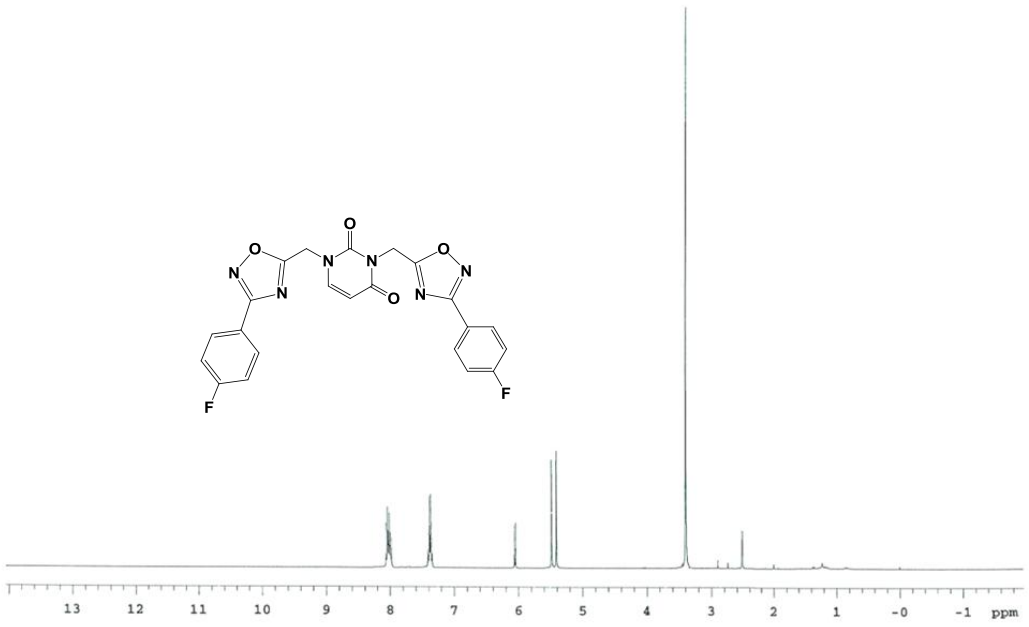

Figure 4.61. ^{1}H NMR spectrum of compound **60c.**

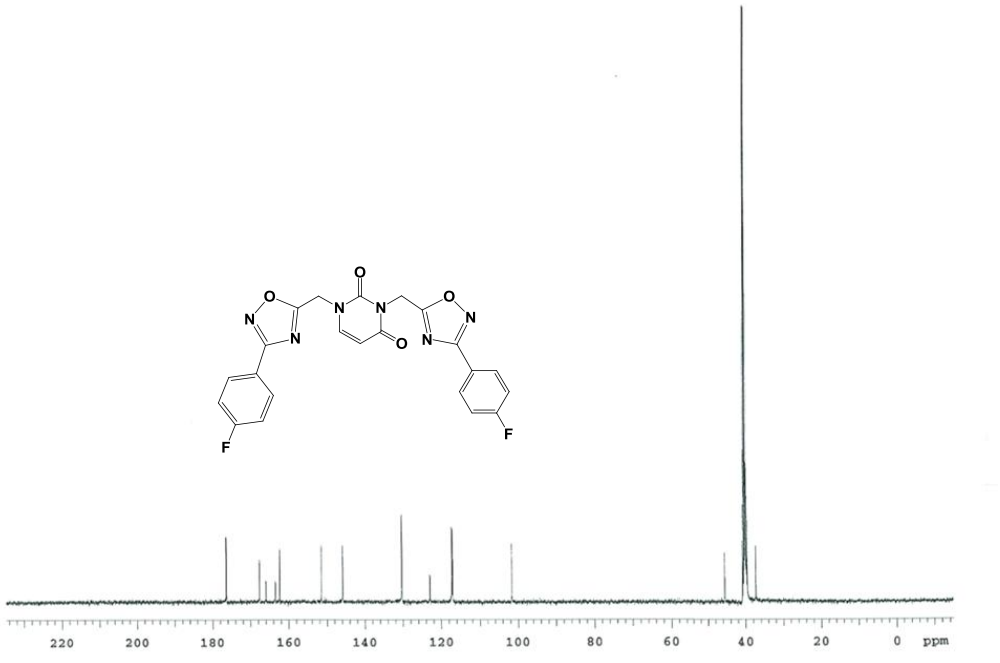

Figure 4.62.^{13}C NMR spectrum of compound **60c.**

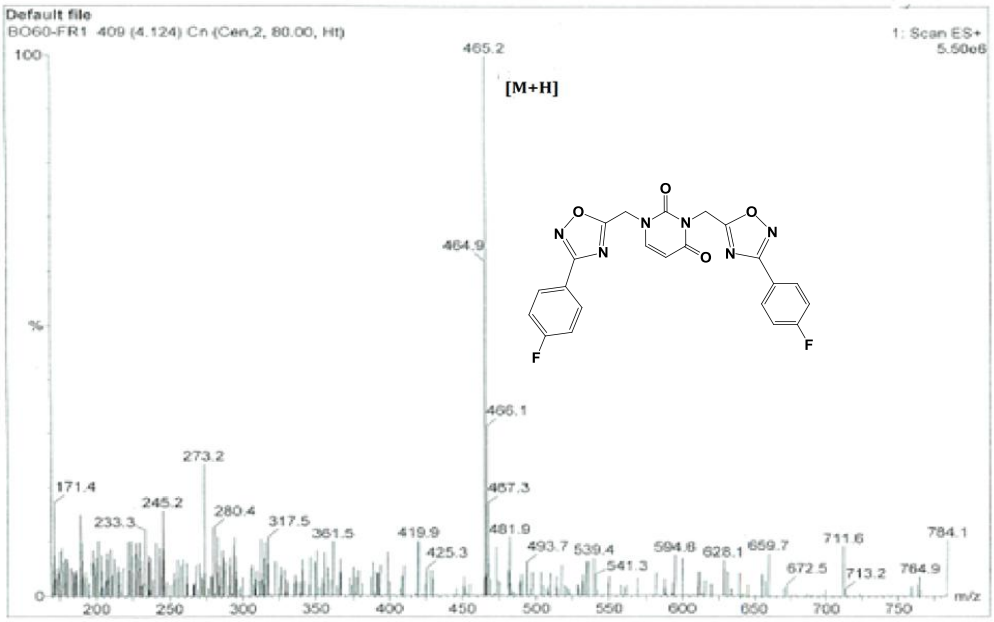

Figure 4.63. LC-MS spectrum of compound **60c.**

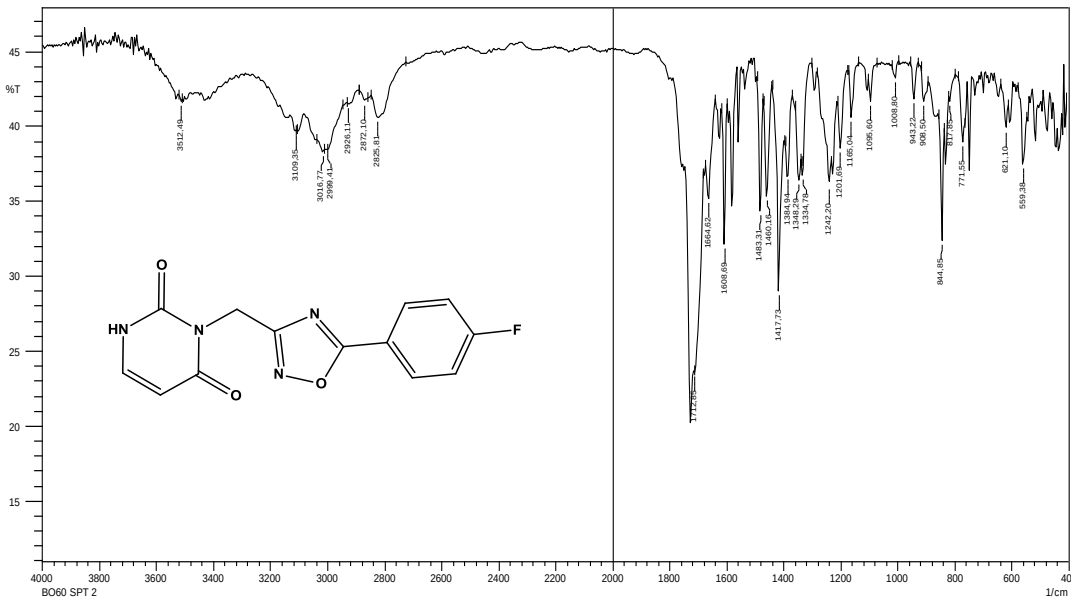

Figure 4.64. IR spectrum of compound **61c.**

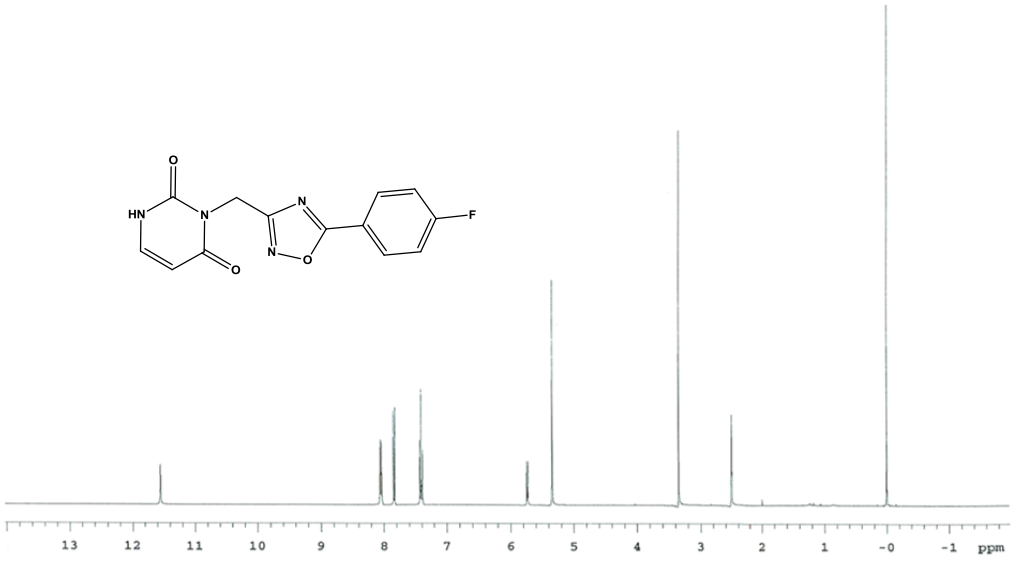

Figure 4.65. ^{1}H NMR spectrum of compound **61c.**

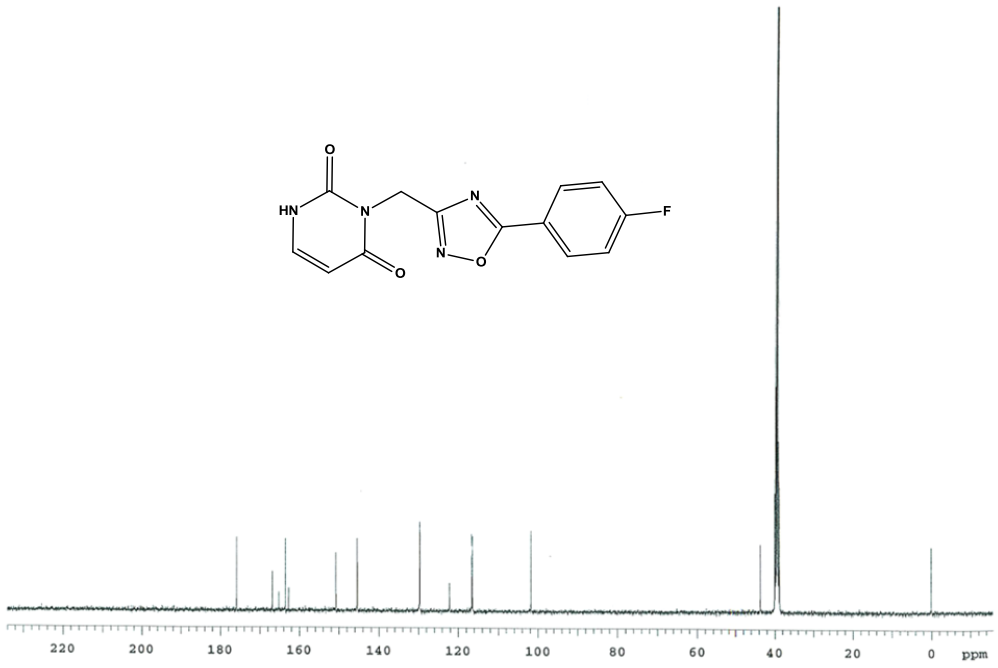

Figure 4.66. ^{13}C NMR spectrum of compound **61c.**

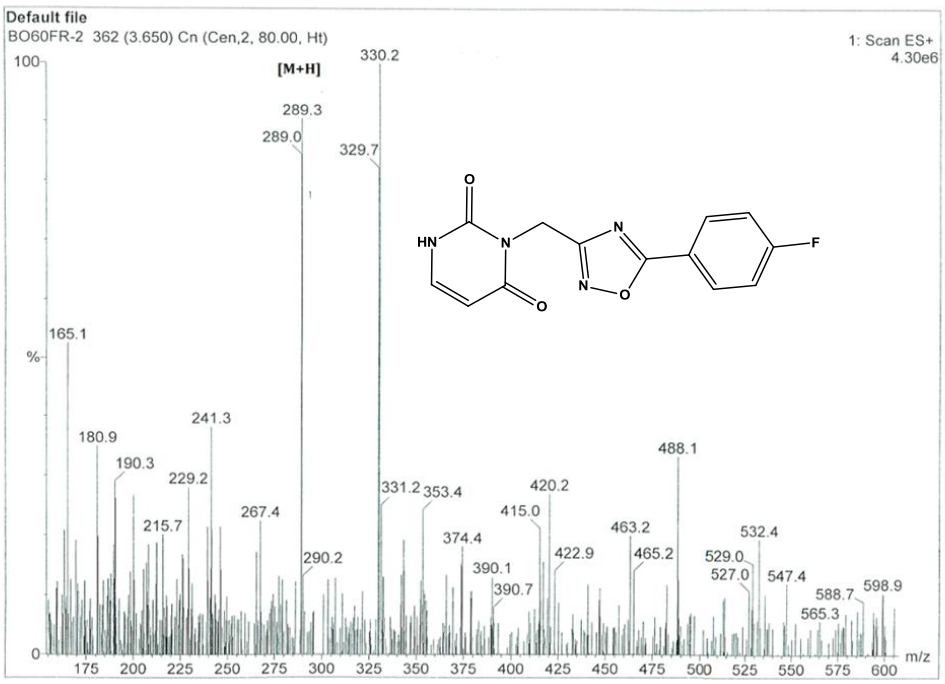

Figure 4.67. LC-MS spectrum of compound **61c.**

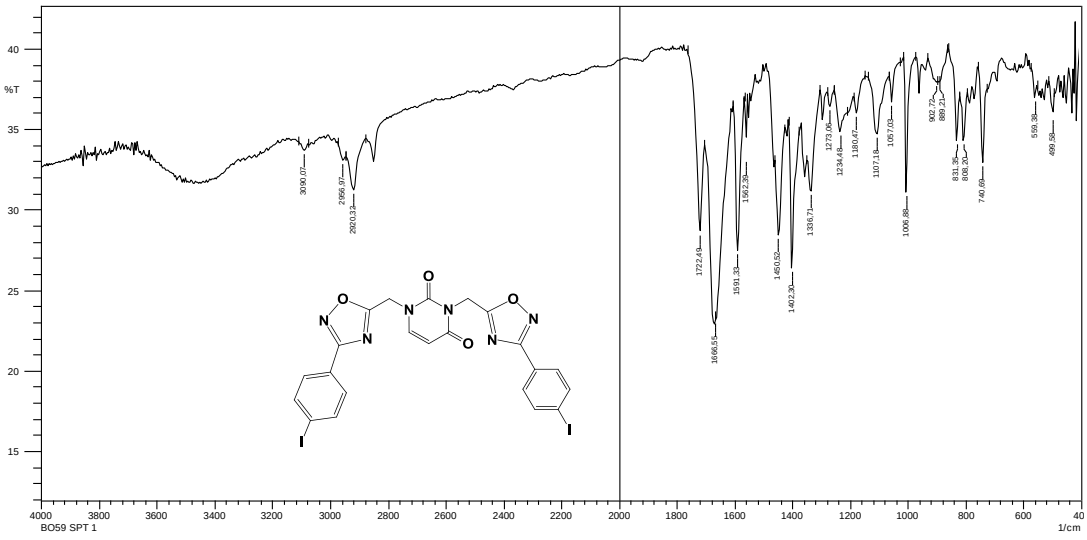

Figure 4.68. IR spectrum of compound **60d.**

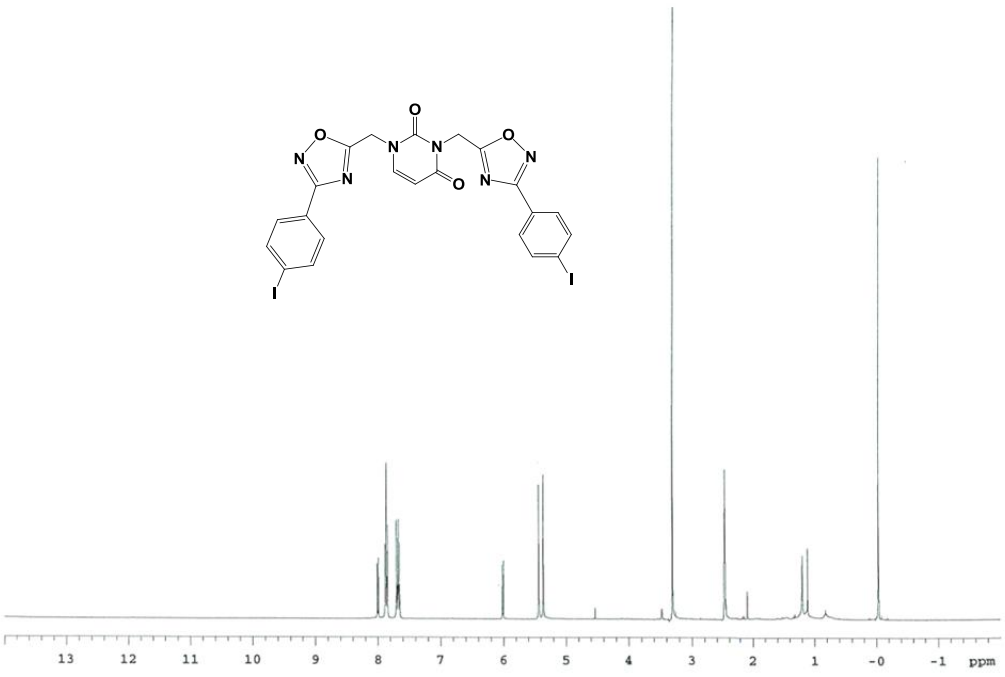

Figure 4.69. ^{1}H NMR spectrum of compound **60d.**

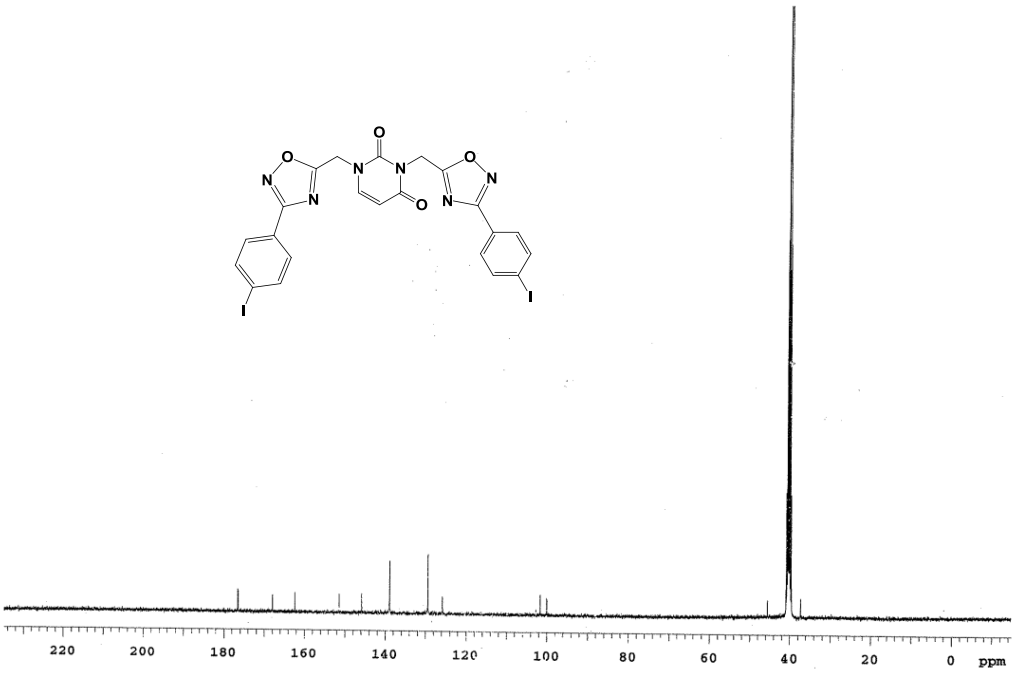

Figure 4.70. ^{13}C NMR spectrum of compound **60d.**

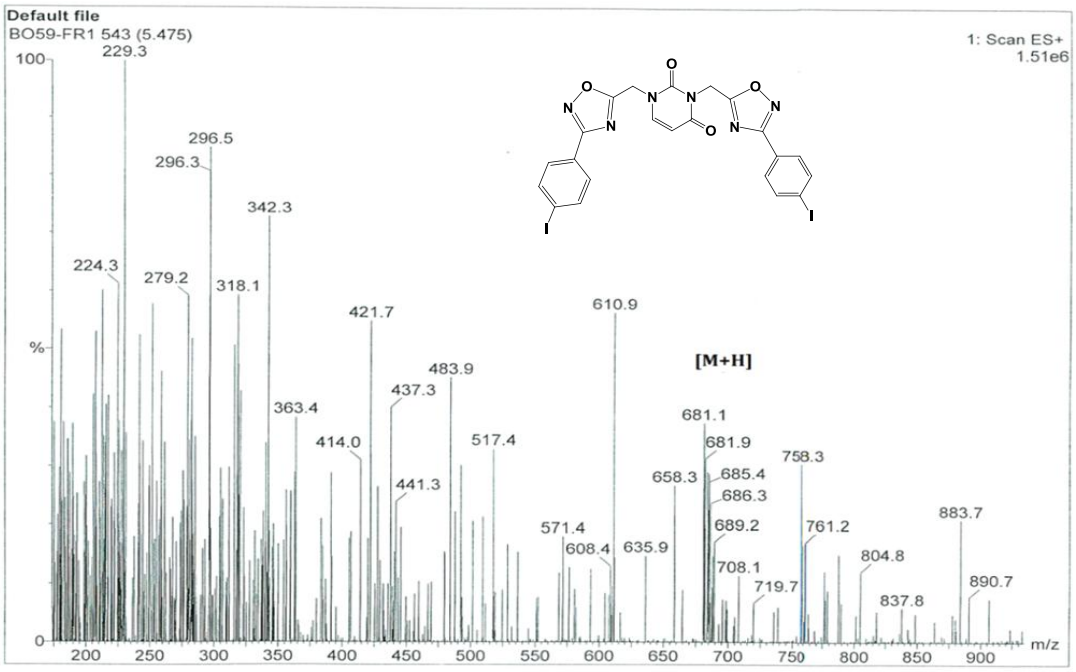

Figure 4.71. LC-MS spectrum of compound **60d.**

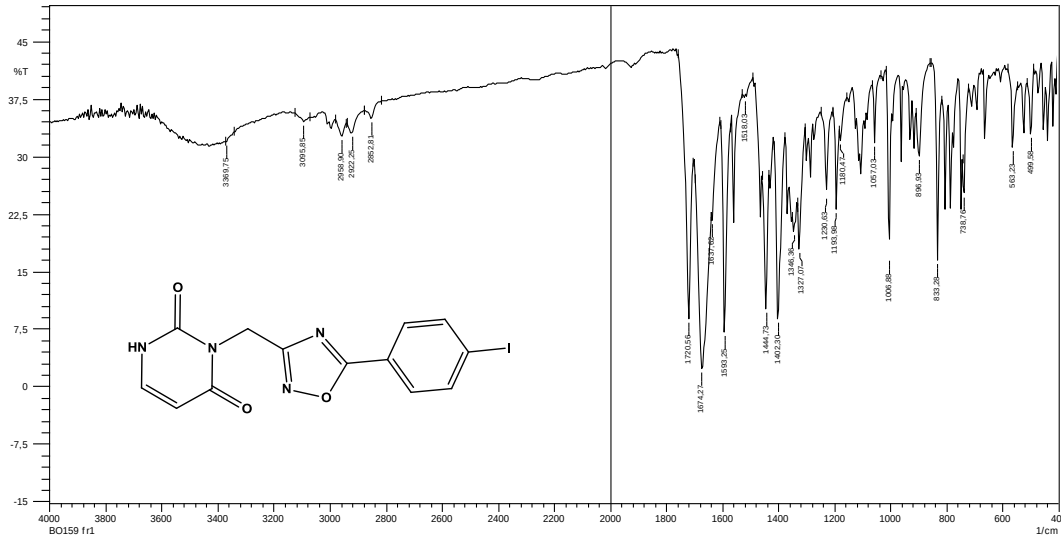

Figure 4.72. IR spectrum of compound **61d.**

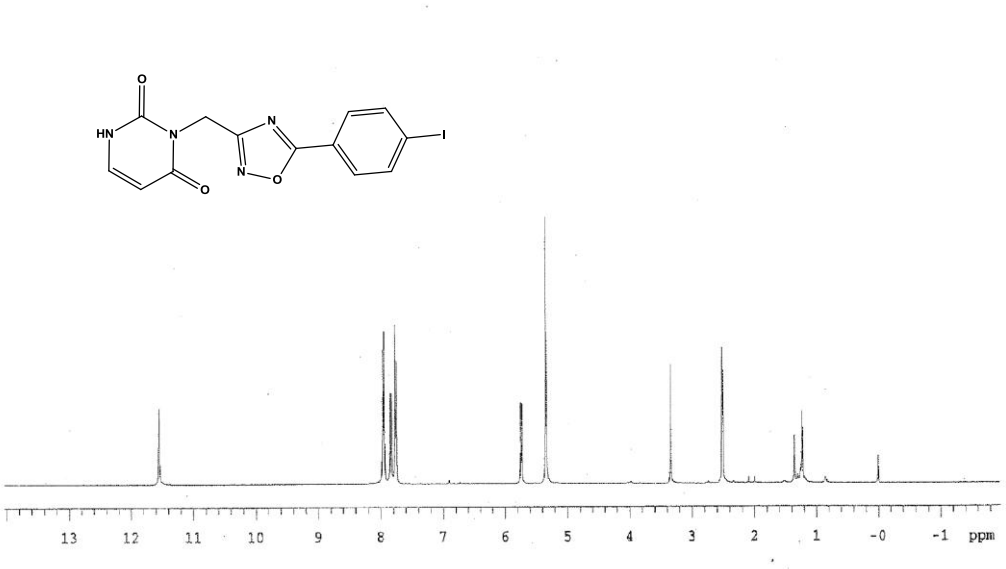

Figure 4.73. ^{1}H NMR spectrum of compound **61d.**

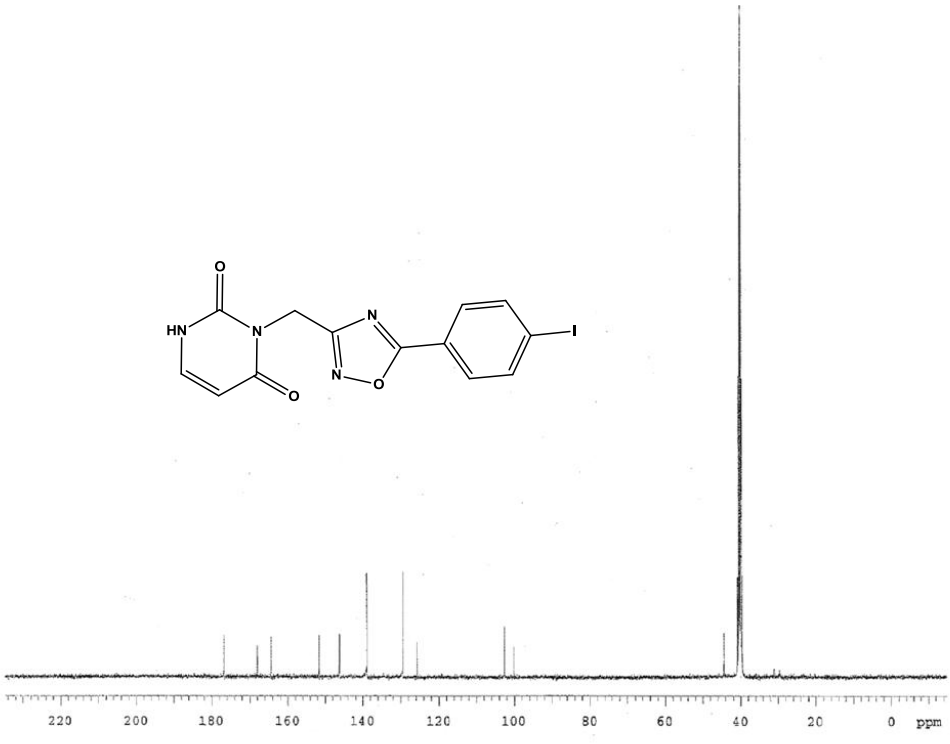

Figure 4.74. ^{13}C NMR spectrum of compound **61d.**

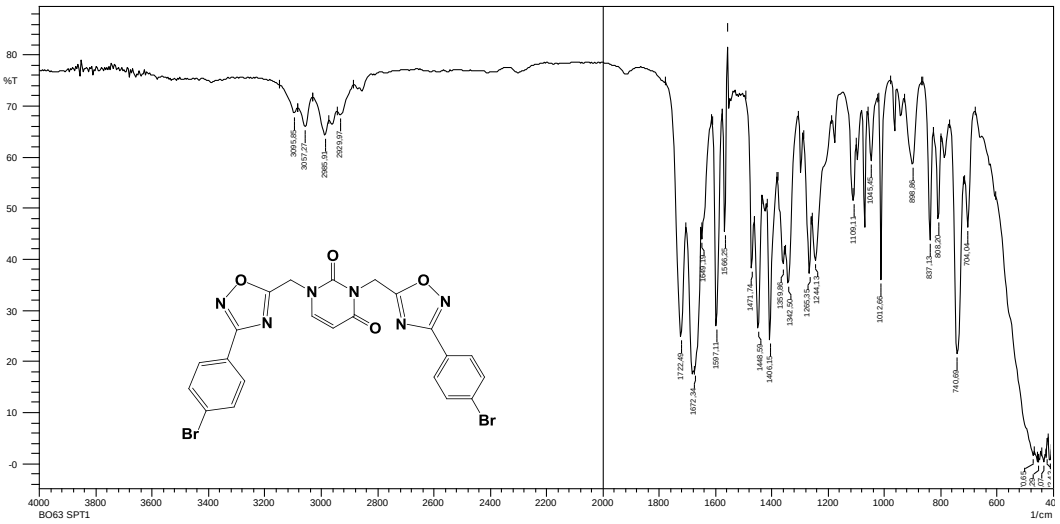

Figure 4.75. IR spectrum of compound **60e.**

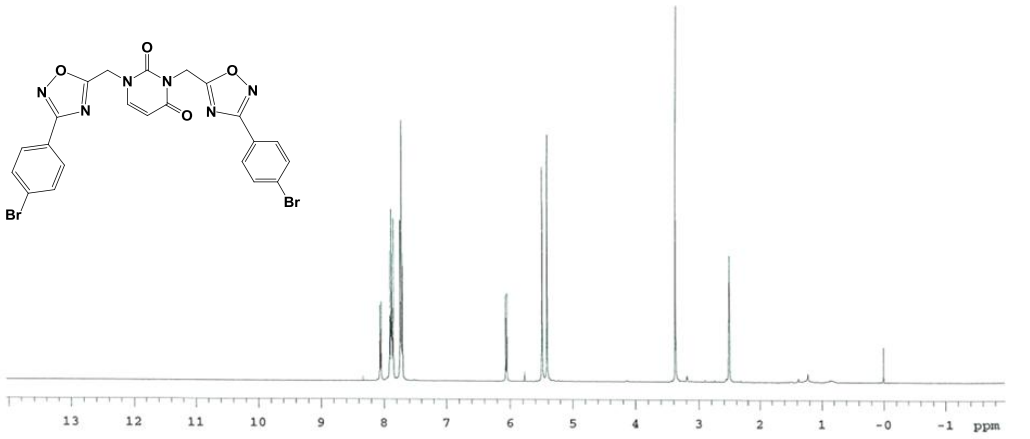

Figure 4.76. ^{1}H NMR spectrum of compound **60e.**

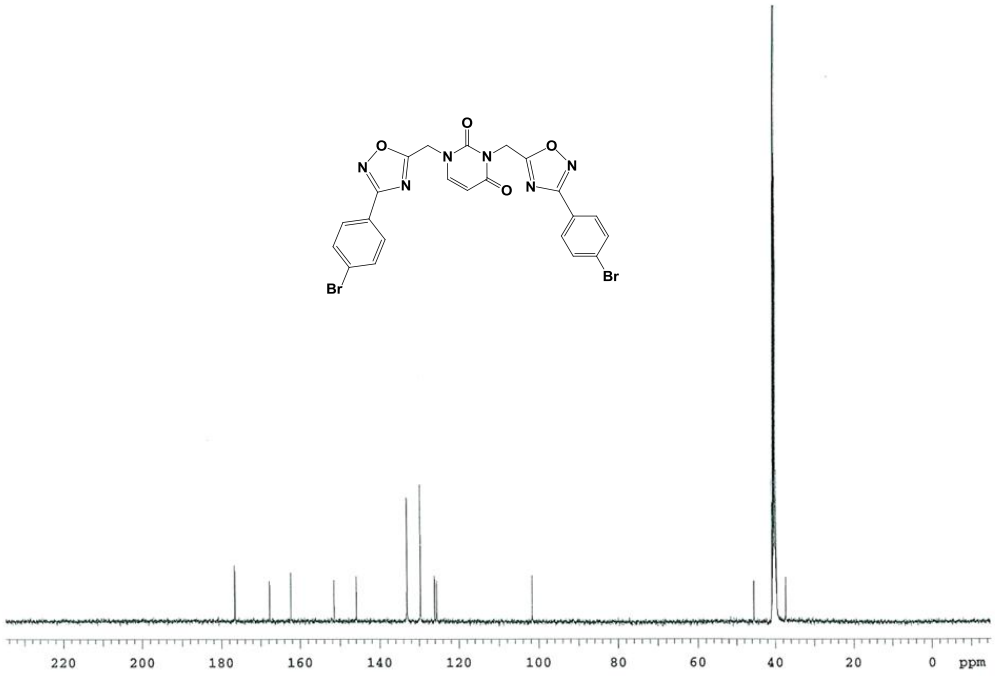

Figure 4.77. ^{13}C NMR spectrum of compound **60e.**

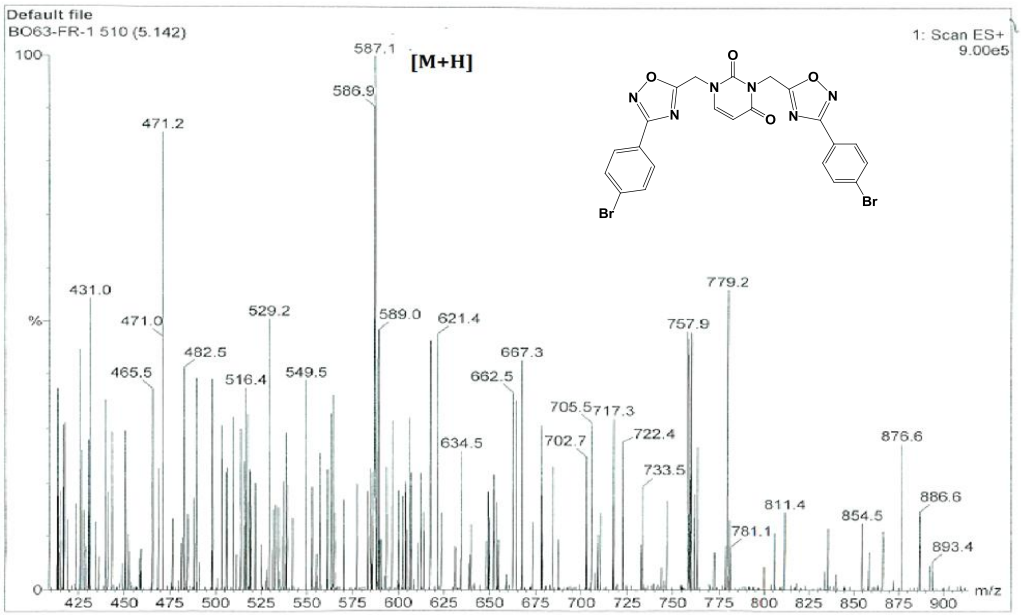

Figure 4.78. LC-MS spectrum of compound **60e.**

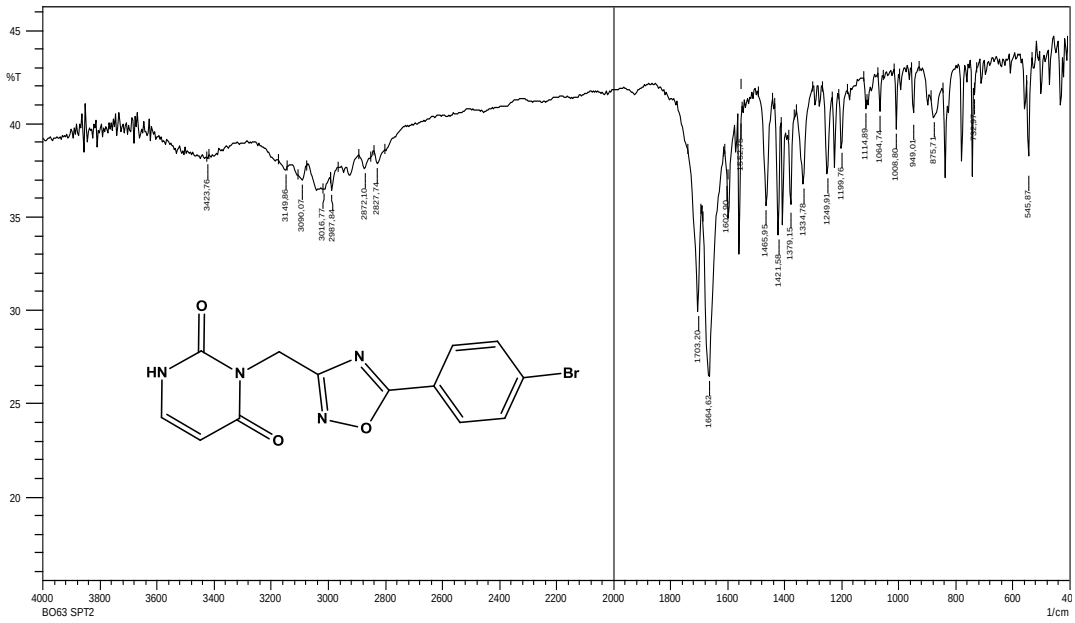

Figure 4.79. IR spectrum of compound **61e.**

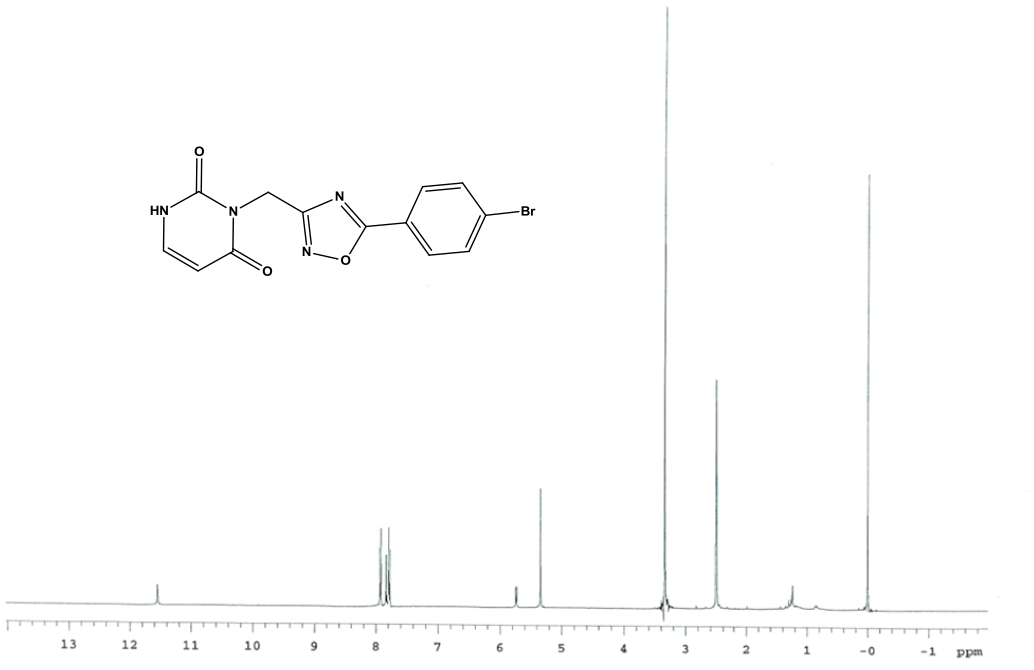

Figure 4.80. ^{1}H NMR spectrum of compound **61e.**

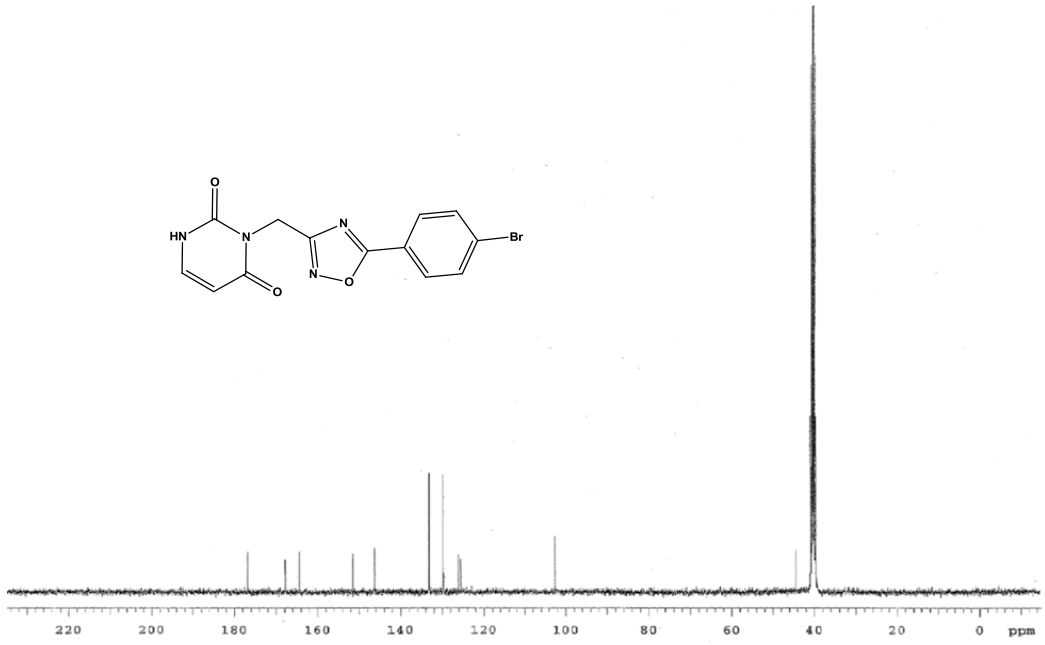

Figure 4.81. ^{13}C NMR spectrum of compound **61e.**

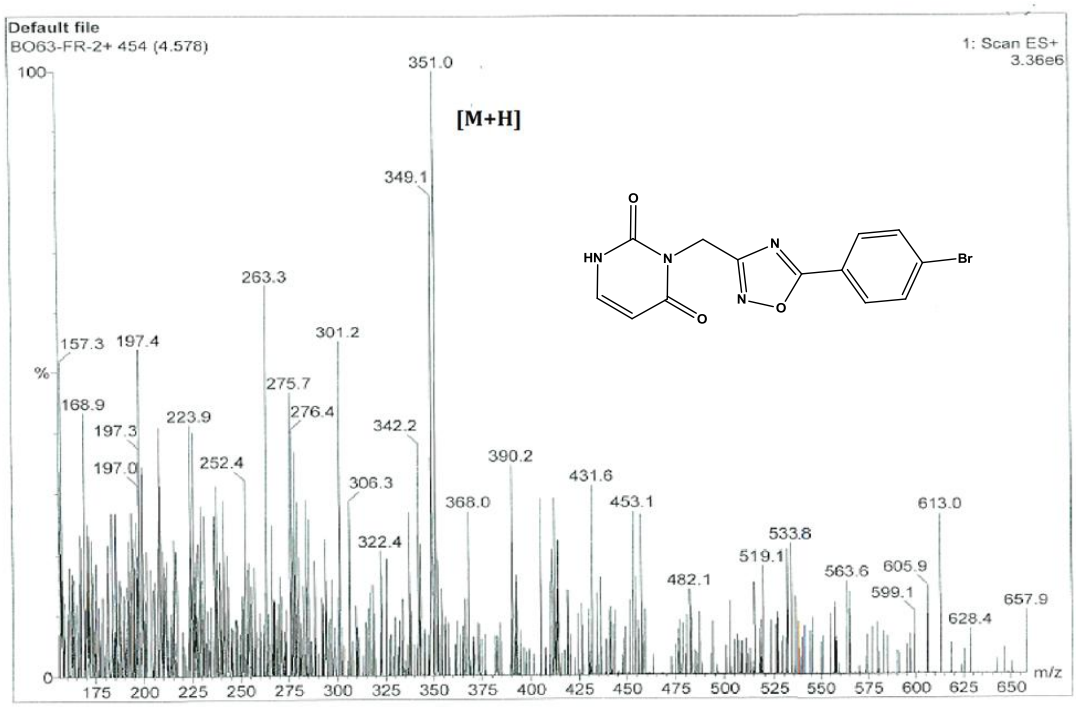

Figure 4.82. LC-MS spectrum of compound **61e.**

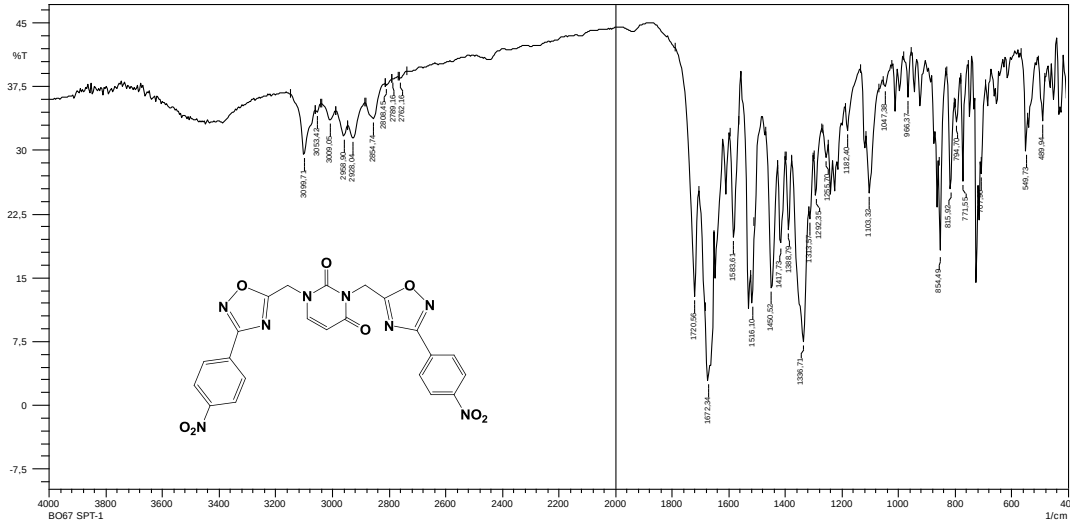

Figure 4.83. IR spectrum of compound **60f.**

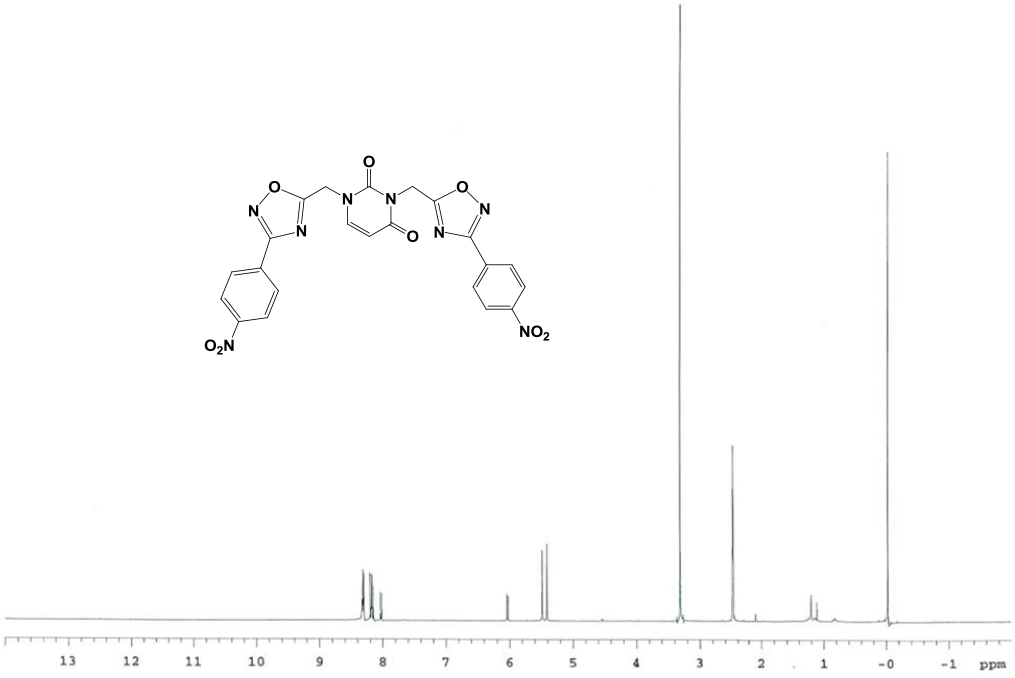

Figure 4.84. ^{1}H NMR spectrum of compound **60f.**

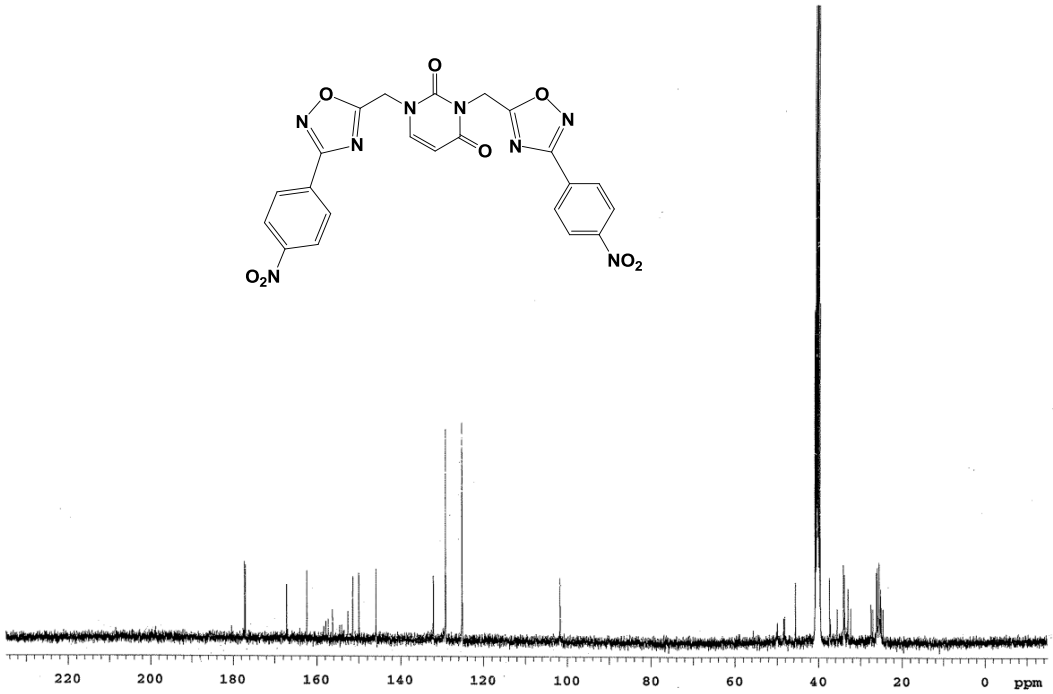

Figure 4.85. ^{13}C NMR spectrum of compound **60f.**

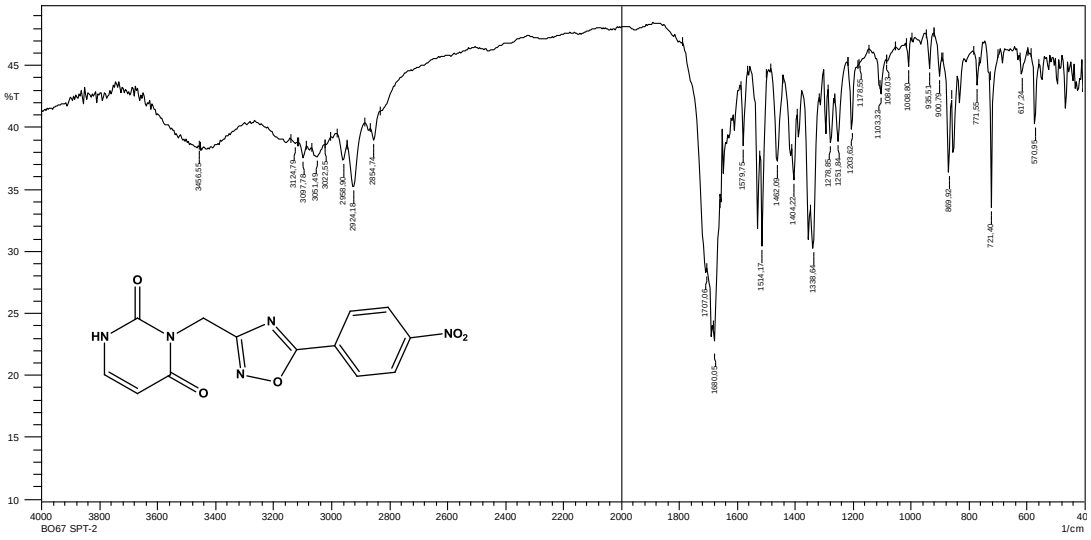

Figure 4.86. IR spectrum of compound **61f.**

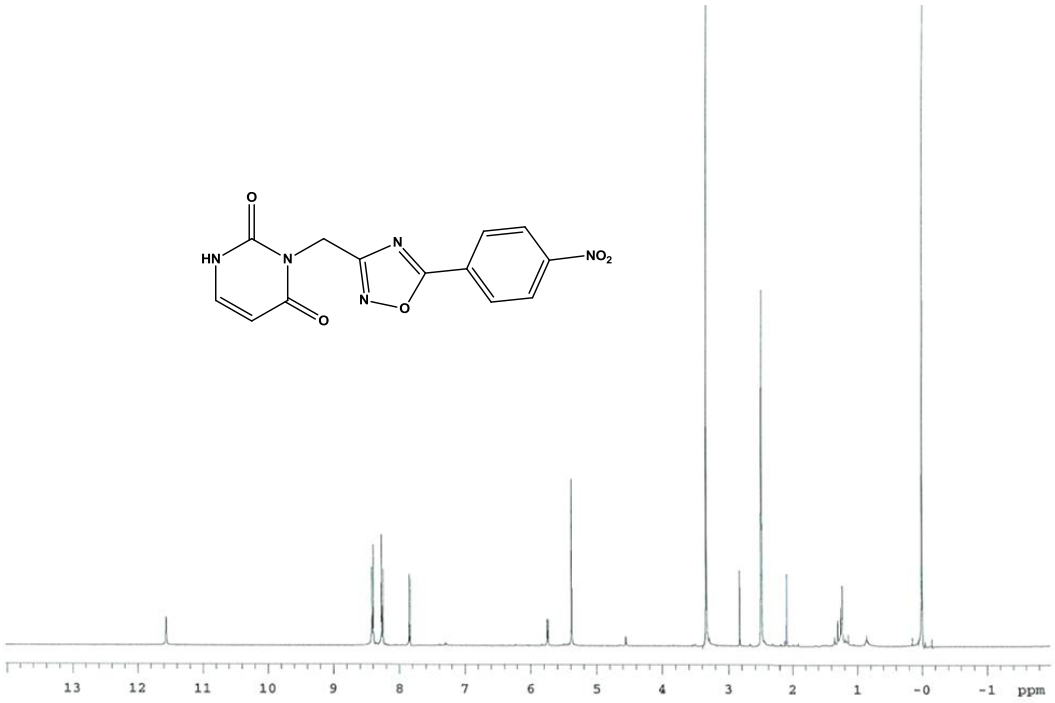

Figure 4.87. ^{1}H NMR spectrum of compound **61f.**

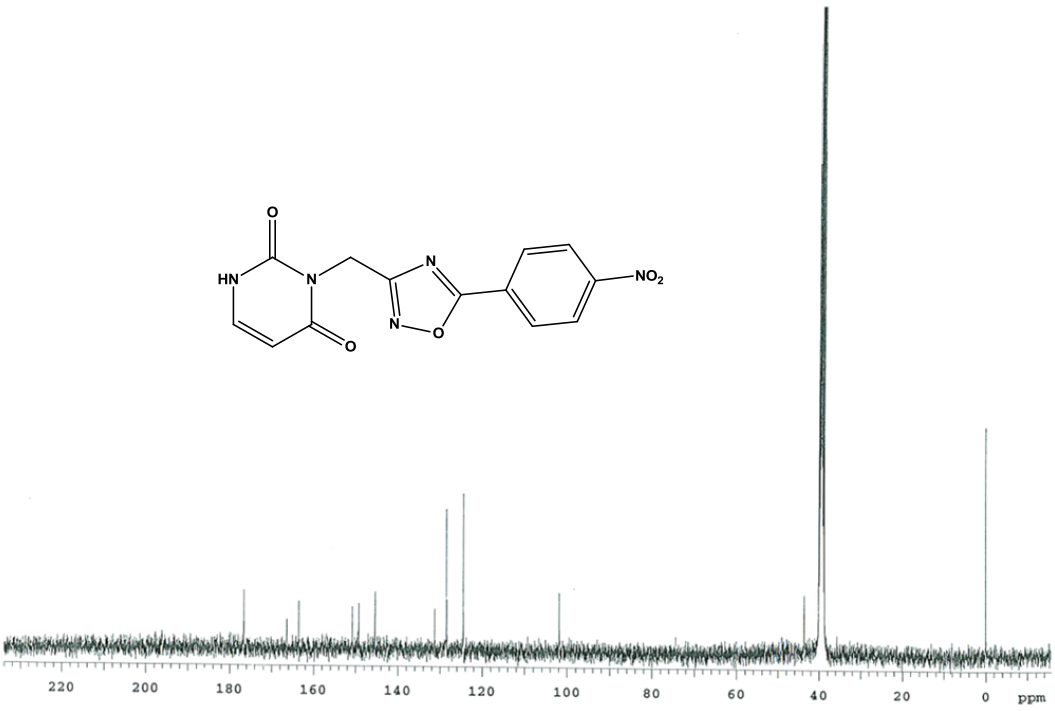

Figure 4.88. ^{13}C NMR spectrum of compound **61f.**

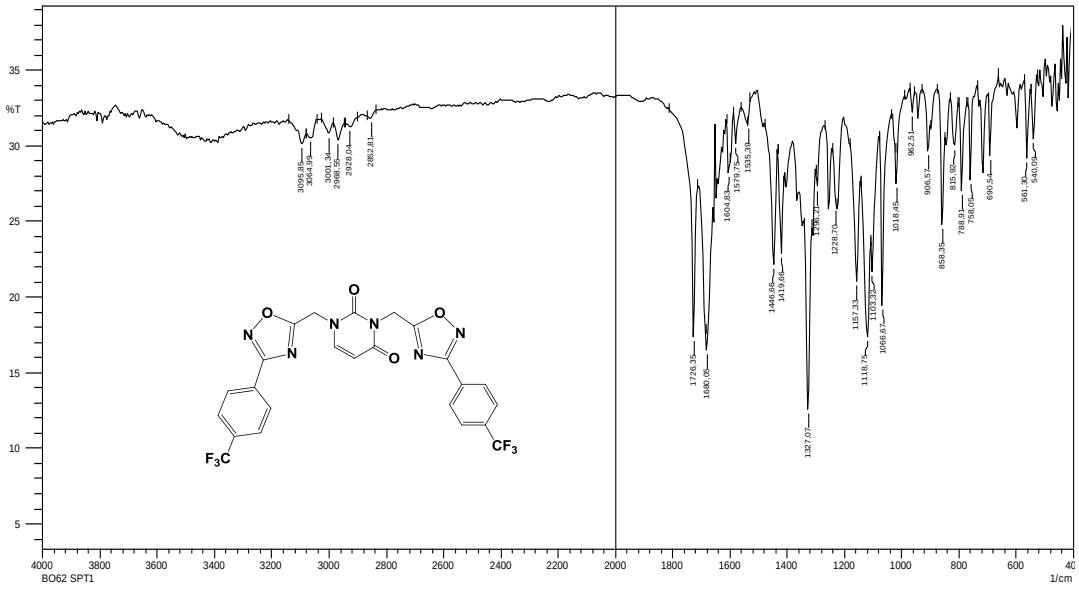

Figure 4.89. IR spectrum of compound **60g.**

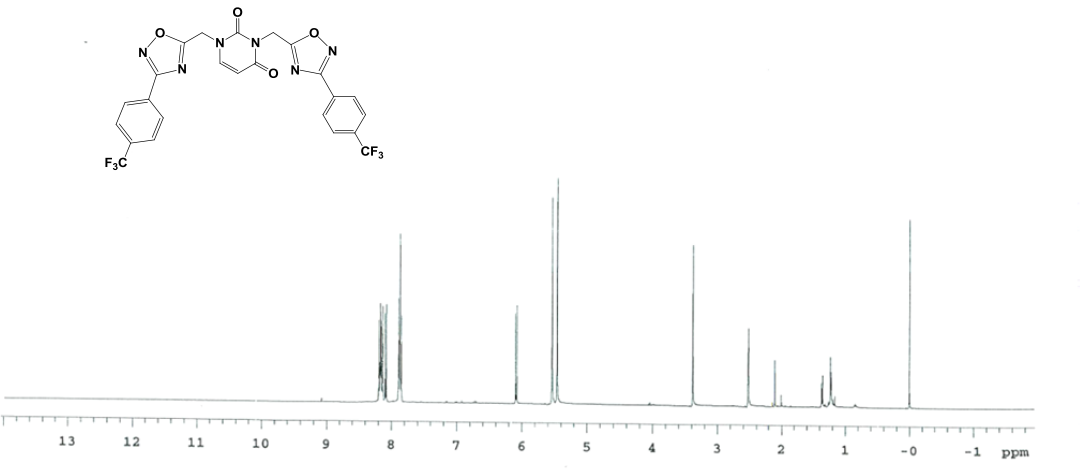

Figure 4.90.[1]H NMR spectrum of compound **60g.**

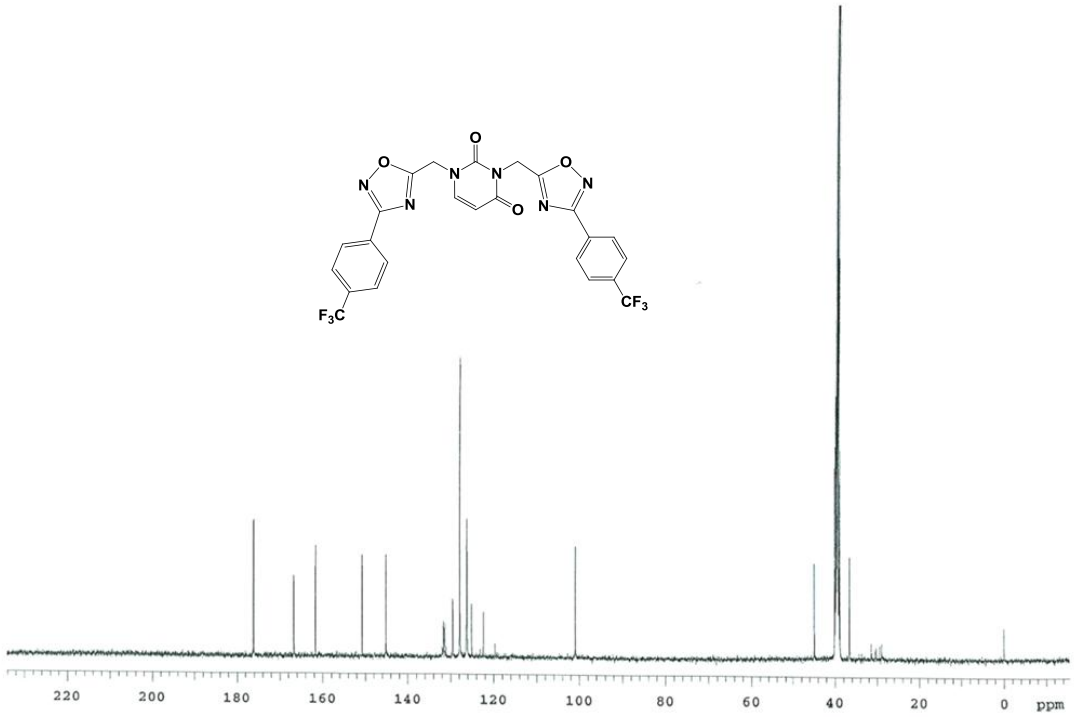

Figure 4.91. ^{13}C NMR spectrum of compound **60g.**

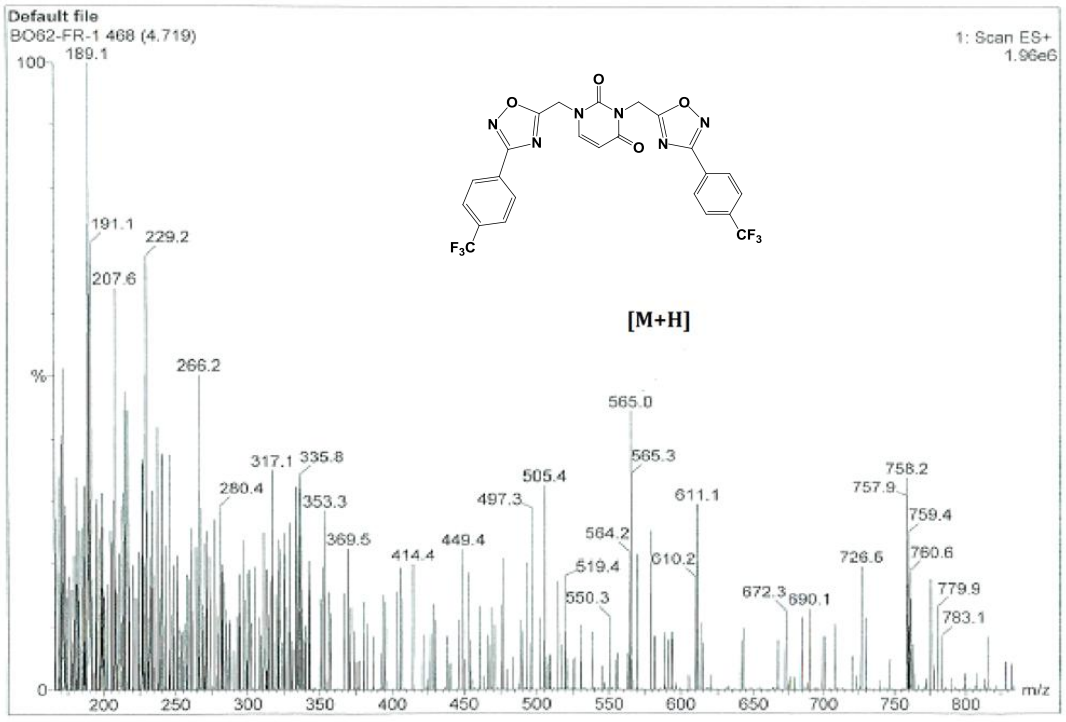

Figure 4.92. LC-MS spectrum of compound **60g.**

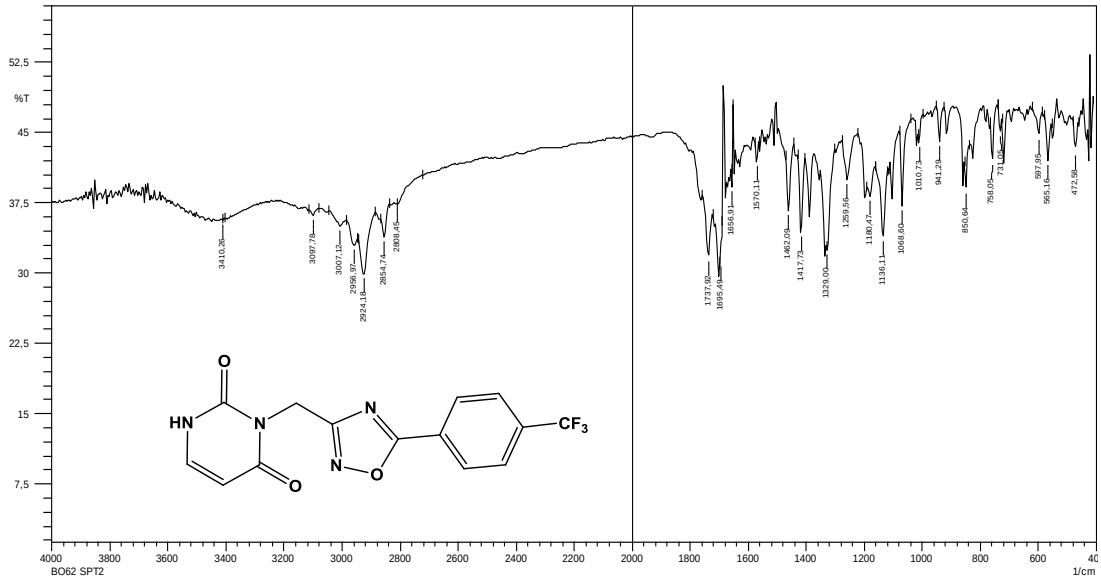

Figure 4.93. IR spectrum of compound **61g.**

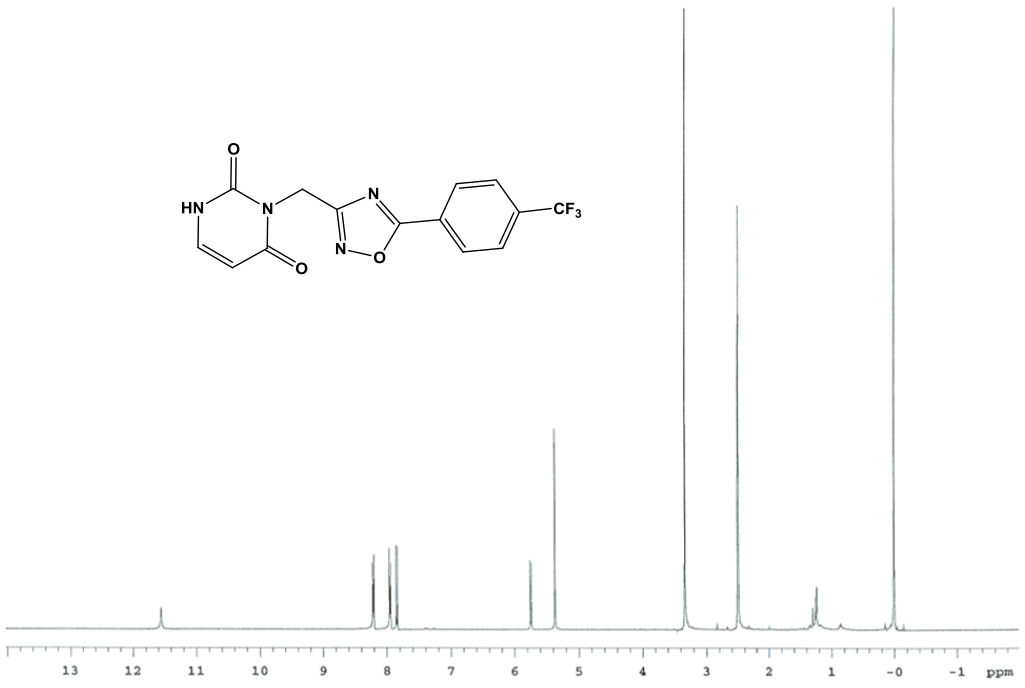

Figure 4.94. ^{1}H NMR spectrum of compound **61g.**

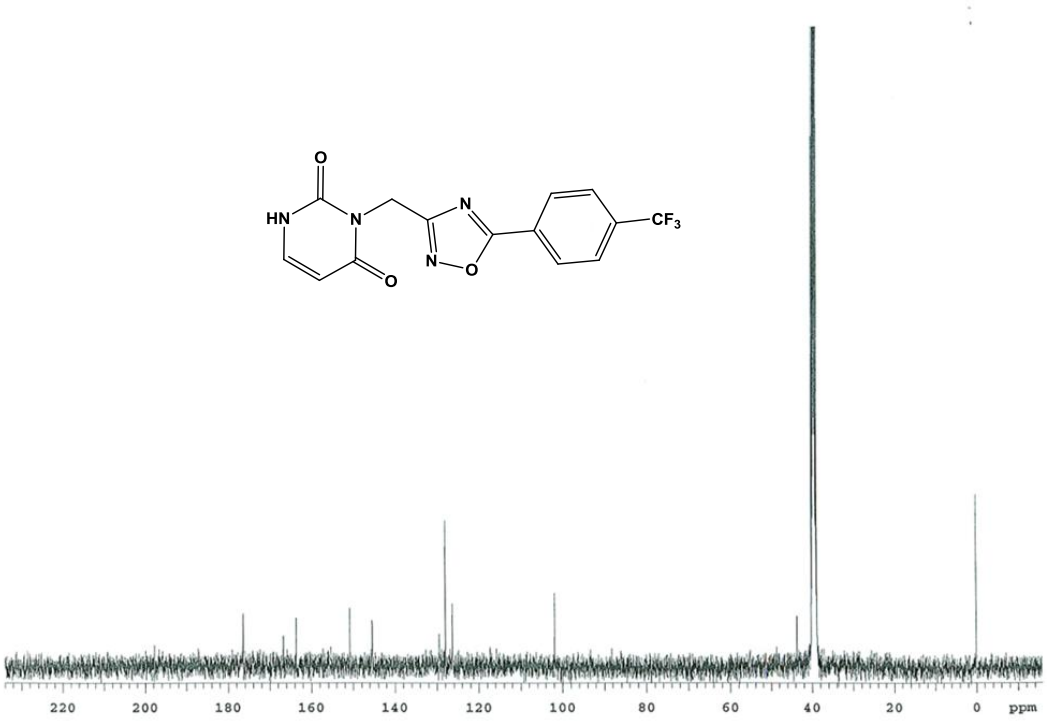

Figure 4.95. ^{13}C NMR spectrum of compound **61g.**

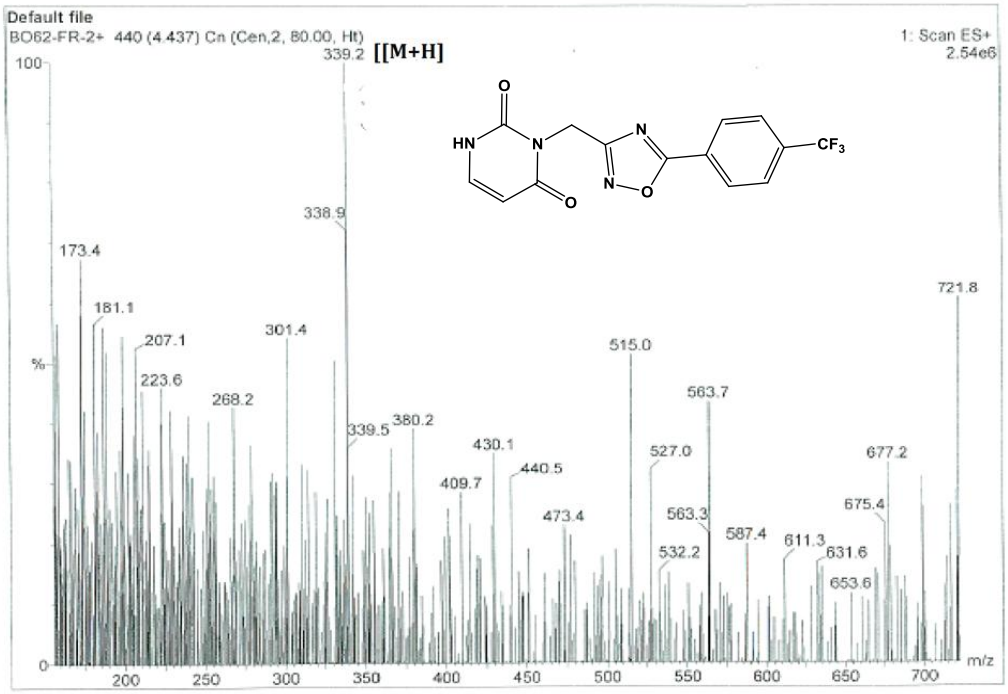

Figure 4.96. LC-MS spectrum of compound **61g.**

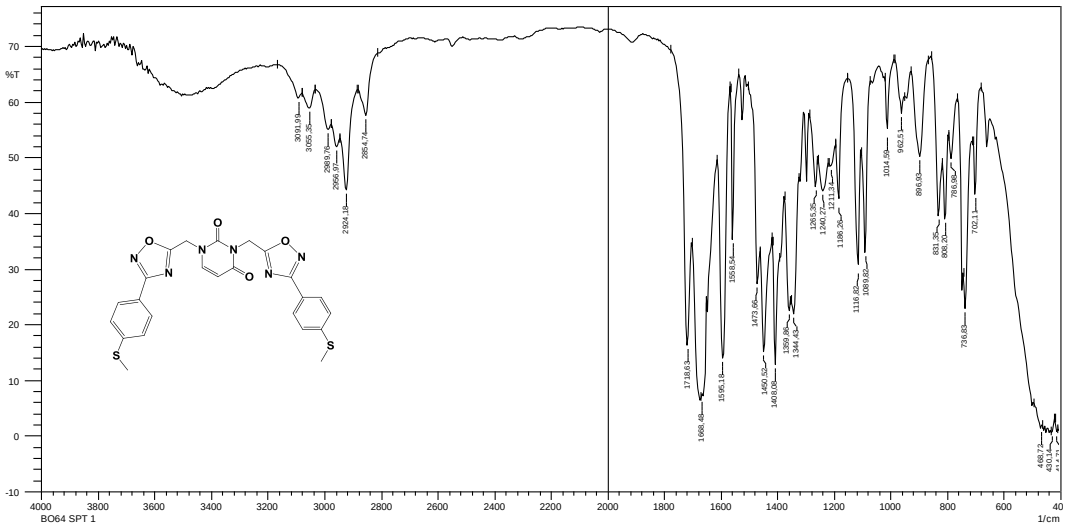

Figure 4.97. IR spectrum of compound **60h.**

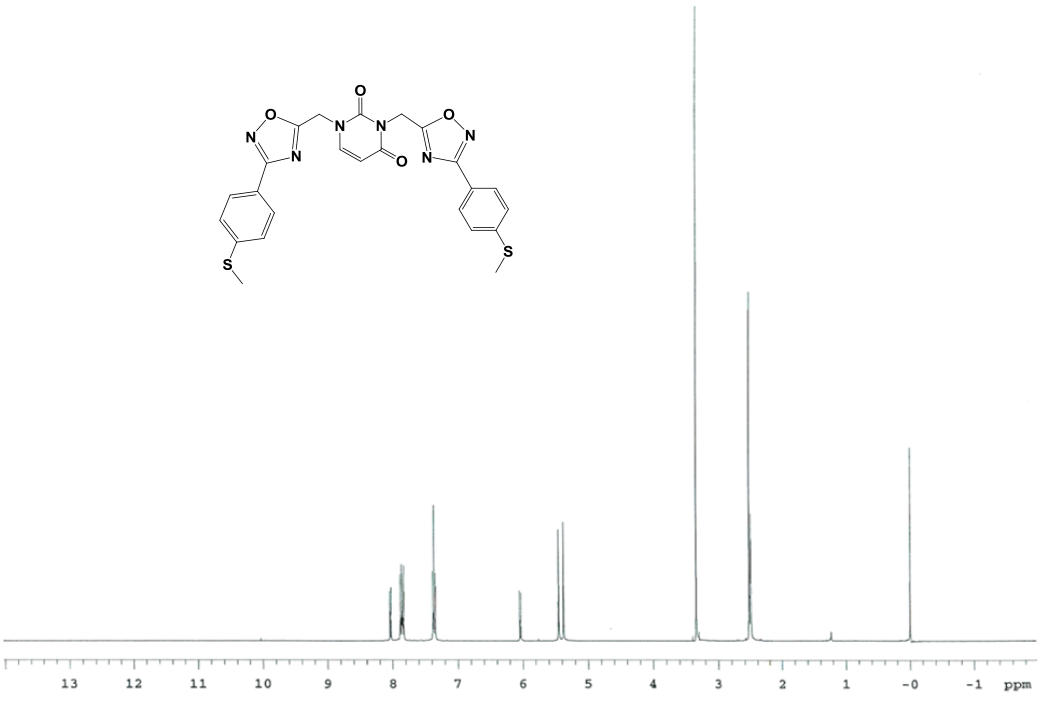

Figure 4.98. ^{1}H NMR spectrum of compound **60h.**

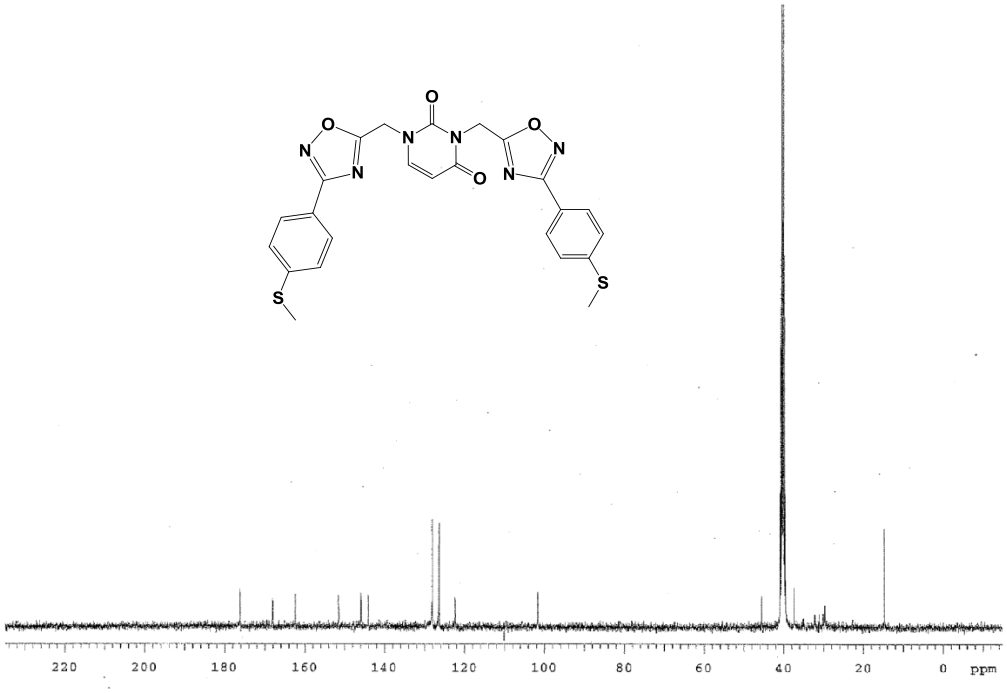

Figure 4.99. ^{13}C NMR spectrum of compound **60h.**

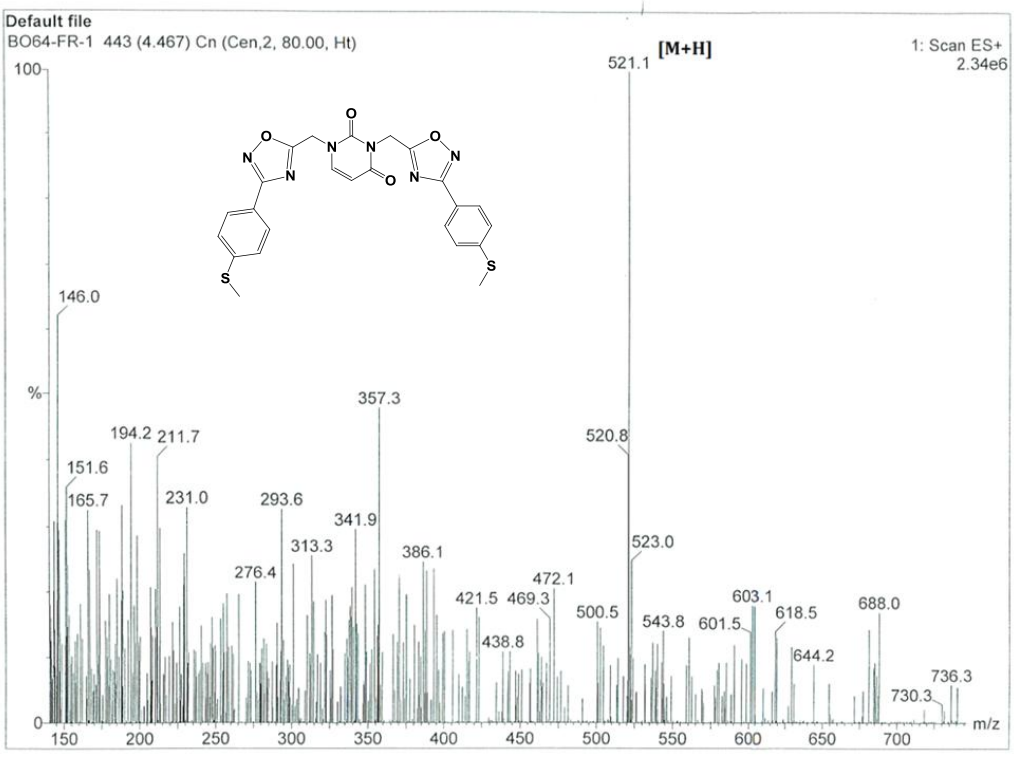

Figure 4.100. LC-MS spectrum of compound **60h.**

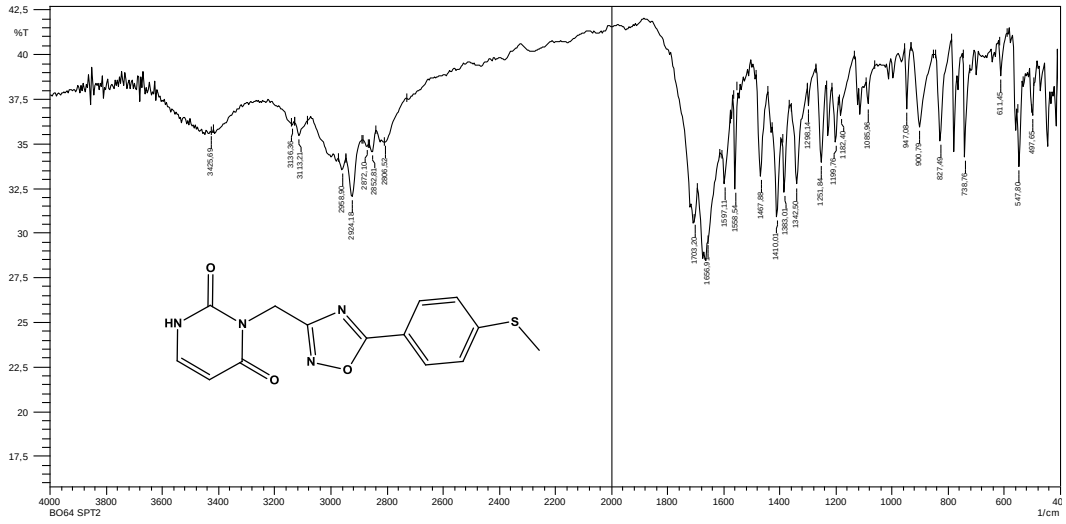

Figure 4.101. IR spectrum of compound **61h.**

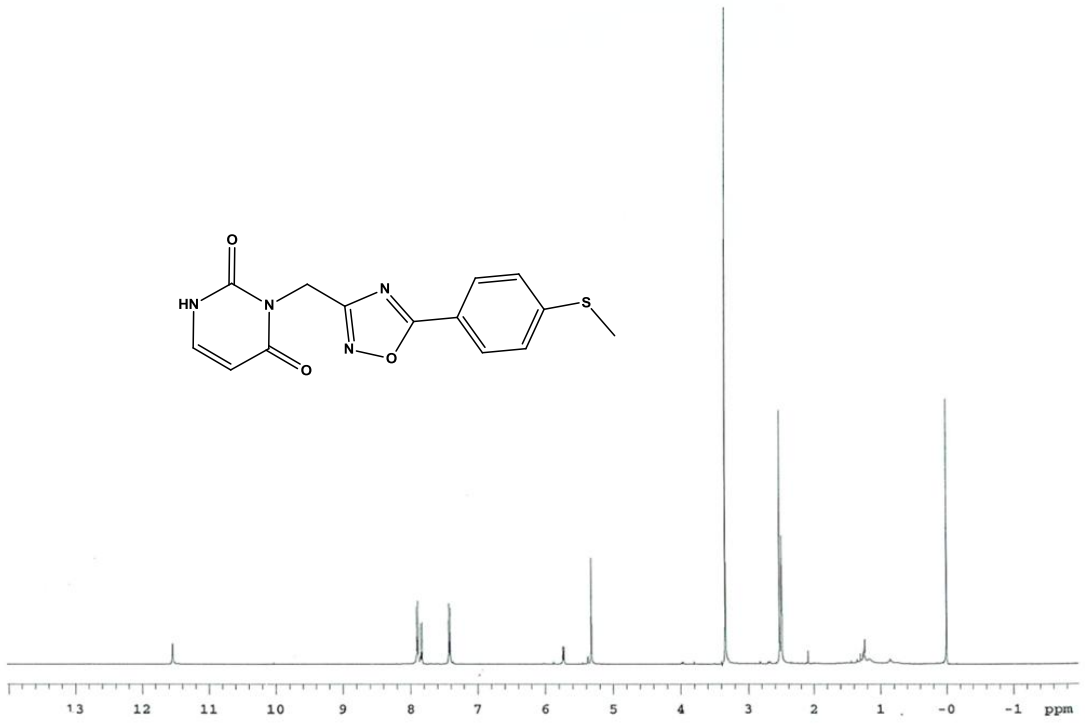

Figure 4.102. ^{1}H NMR spectrum of compound **61h.**

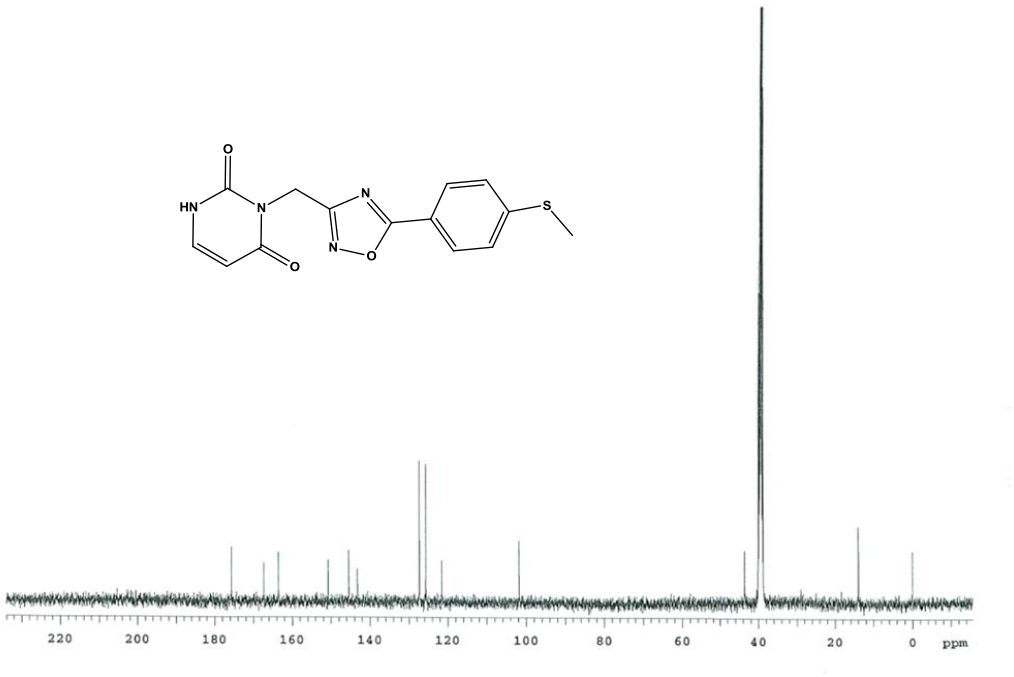

Figure 4.103. ^{13}C NMR spectrum of compound **61h.**

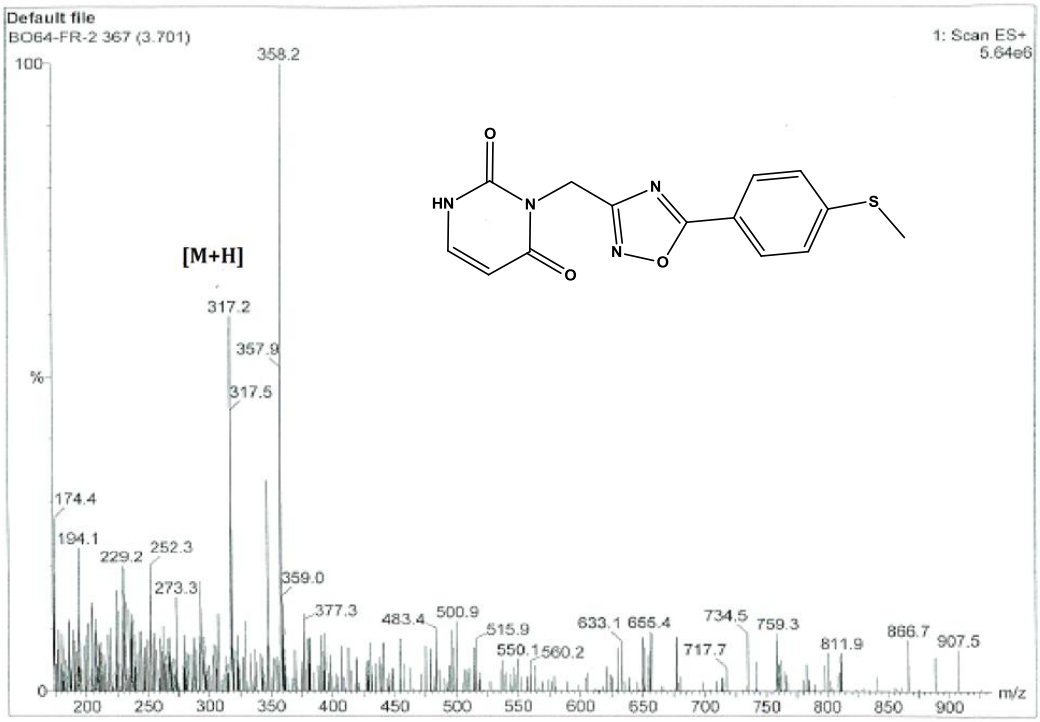

Figure 4.104. LC-MS spectrum of compound **61h.**

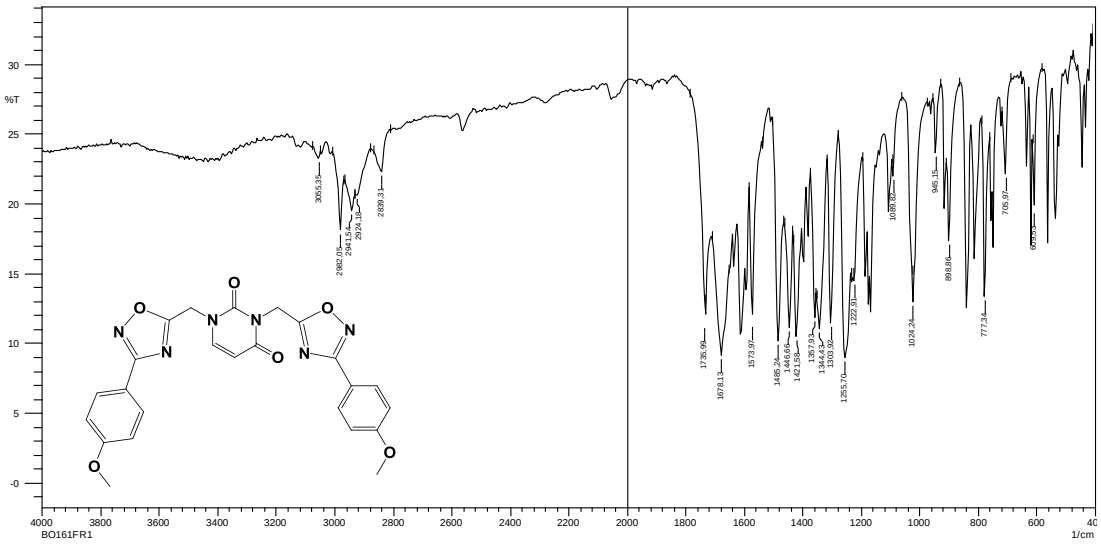

Figure 4.105. IR spectrum of compound **60i.**

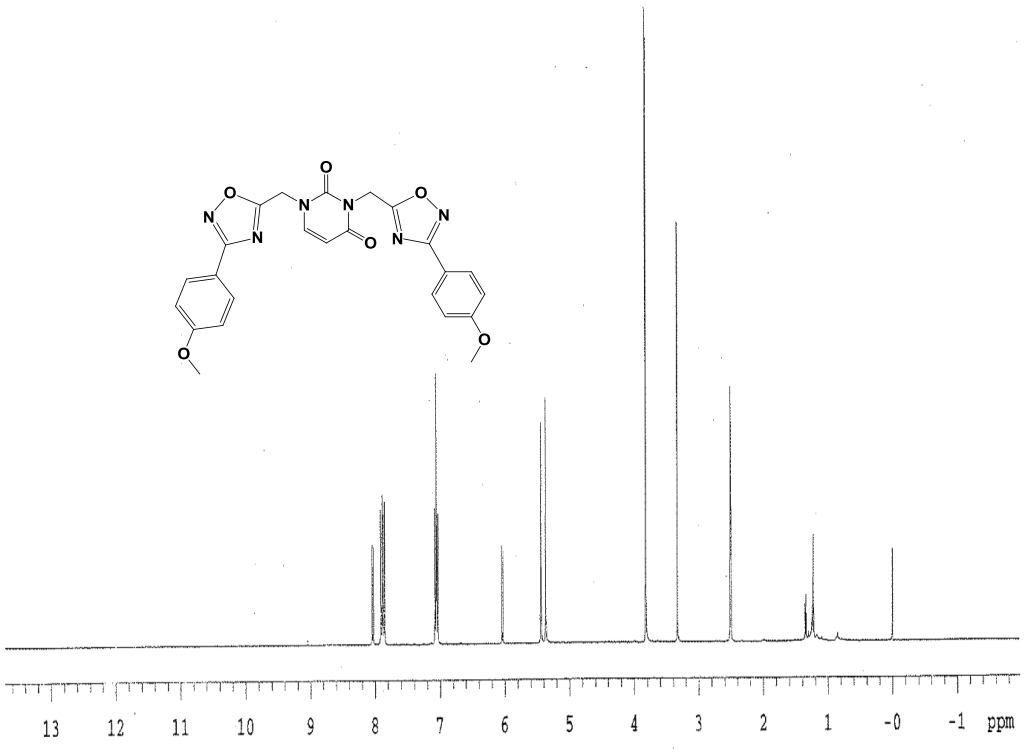

Figure 4.106. ^{1}H NMR spectrum of compound **60i.**

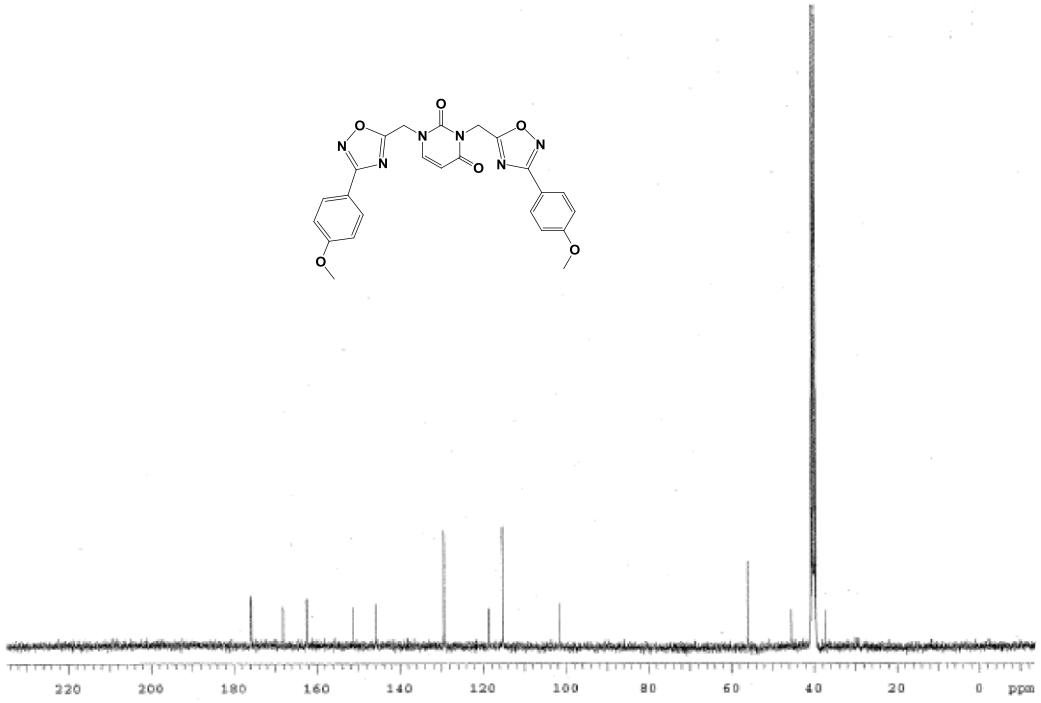

Figure 4.107. ^{13}C NMR spectrum of compound **60i.**

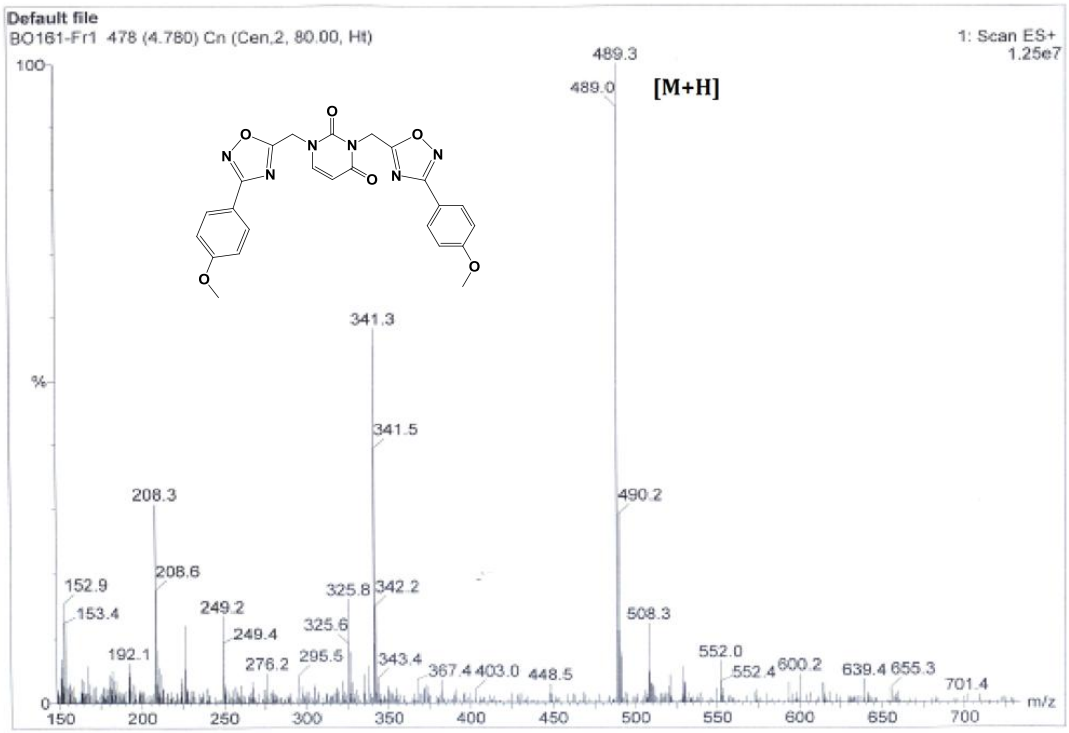

Figure 4.108. LC-MS spectrum of compound **60i.**

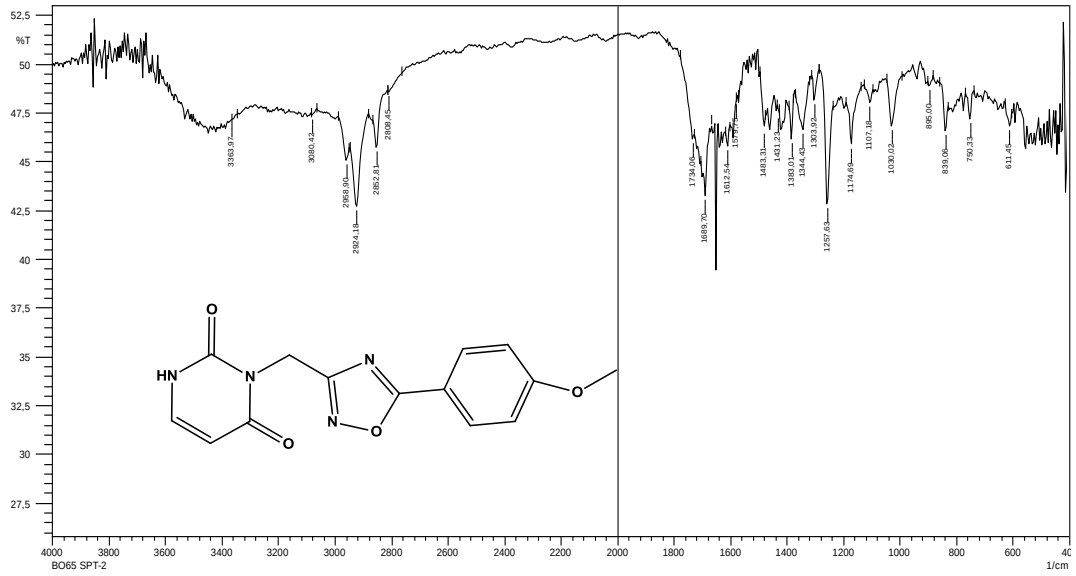

Figure 4.109. IR spectrum of compound **61i.**

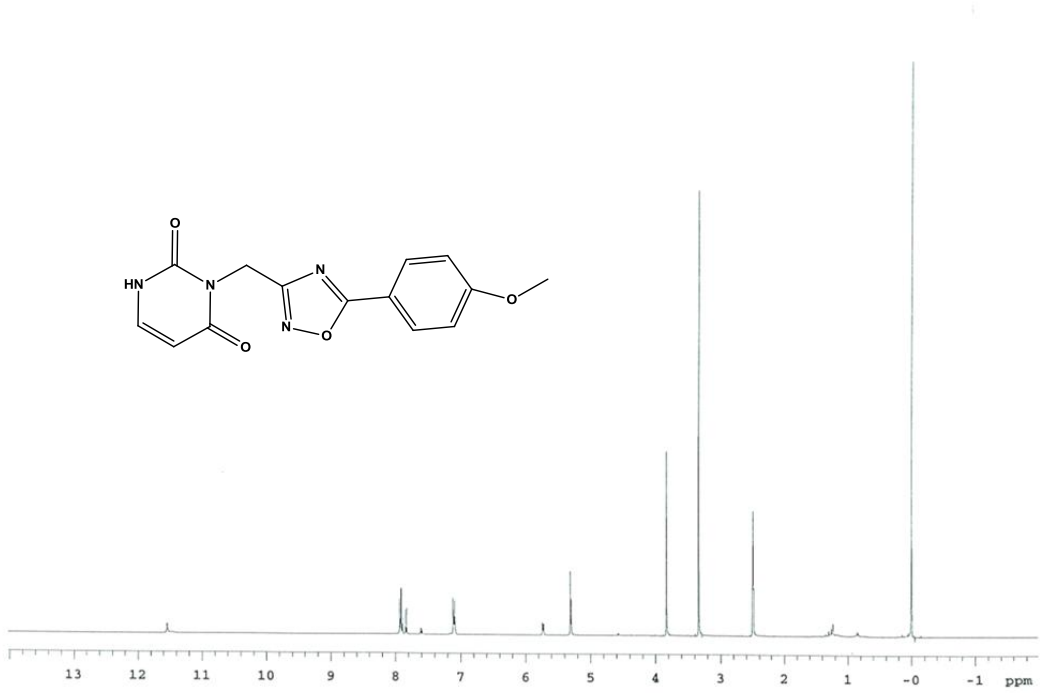

Figure 4.110. ^{1}H NMR spectrum of compound **61i.**

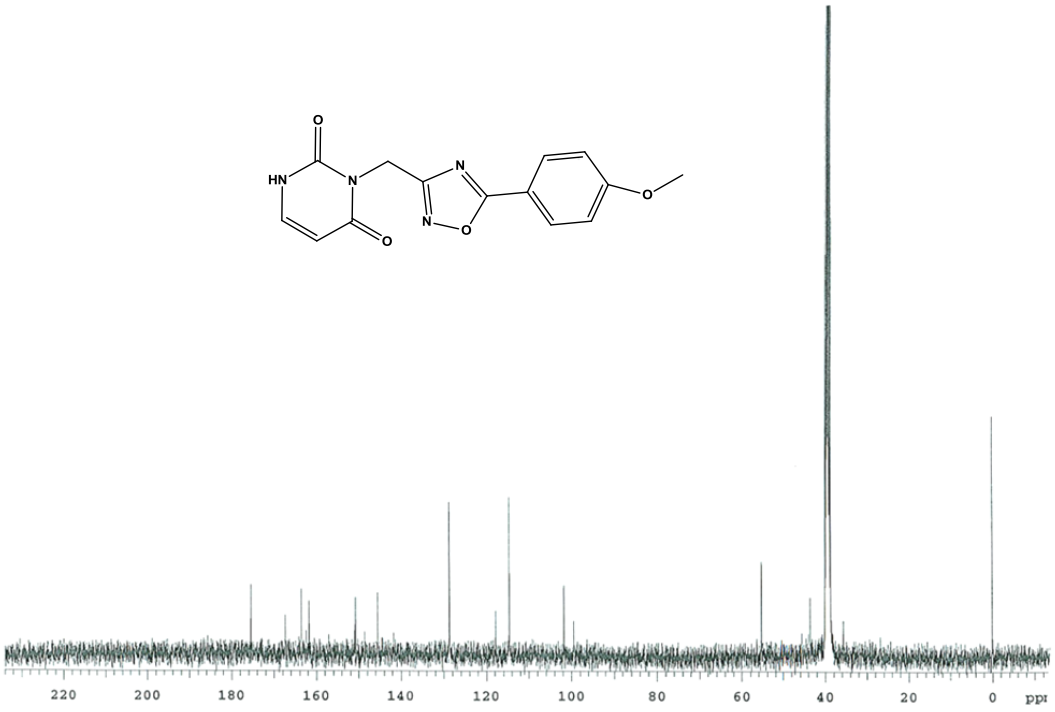

Figure 4.111. ^{13}C NMR spectrum of compound **61i.**

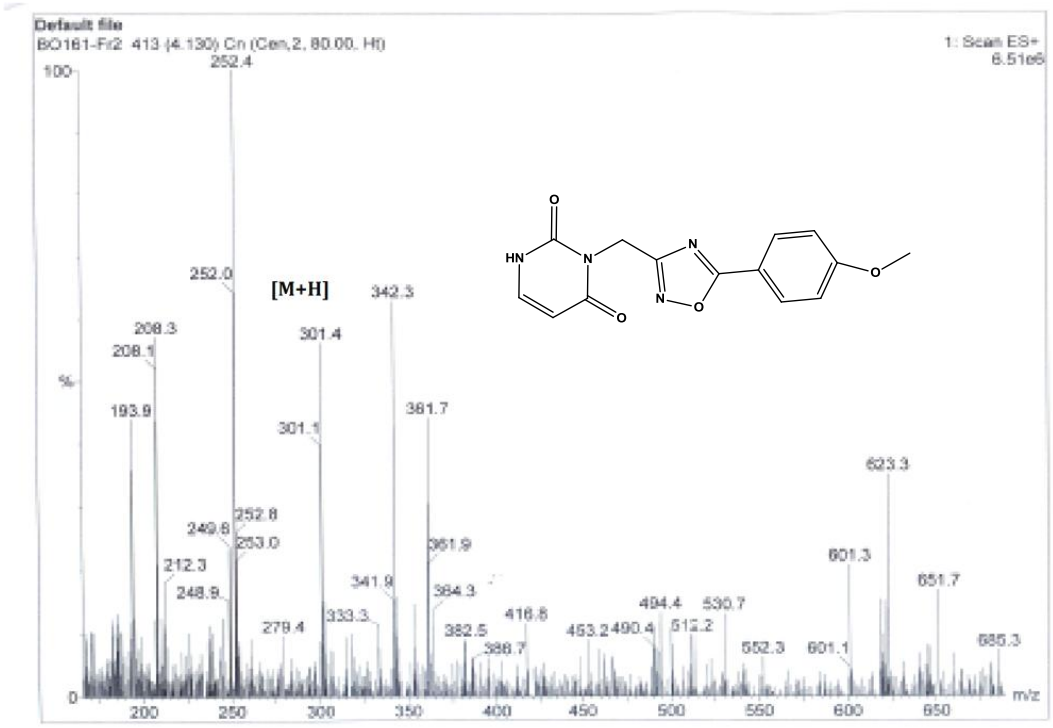

Figure 4.112. LC-MS spectrum of compound **61i.**

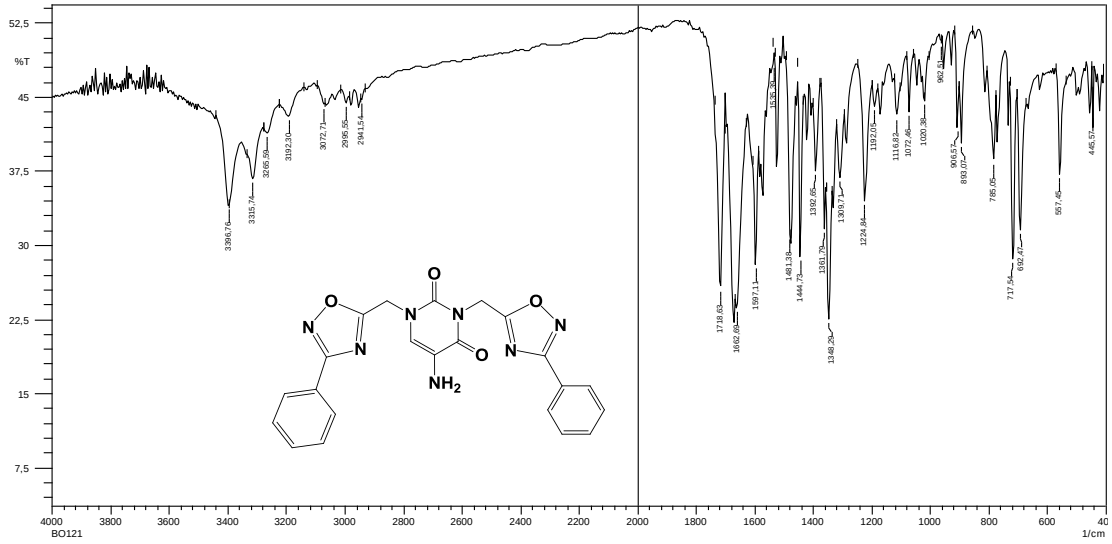

Figure 4.113. IR spectrum of compound **62a.**

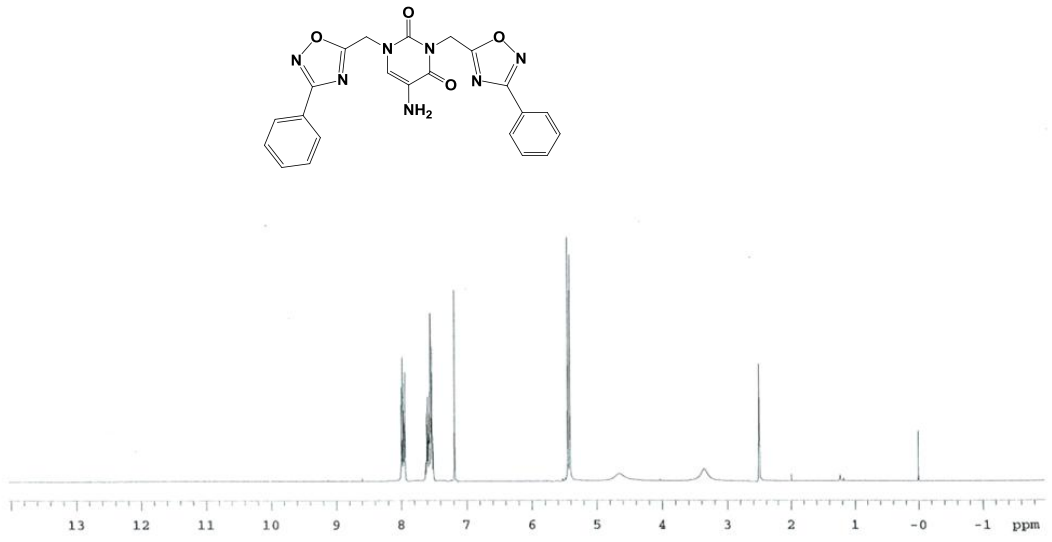

Figure 4.114. ^{1}H NMR spectrum of compound **62a.**

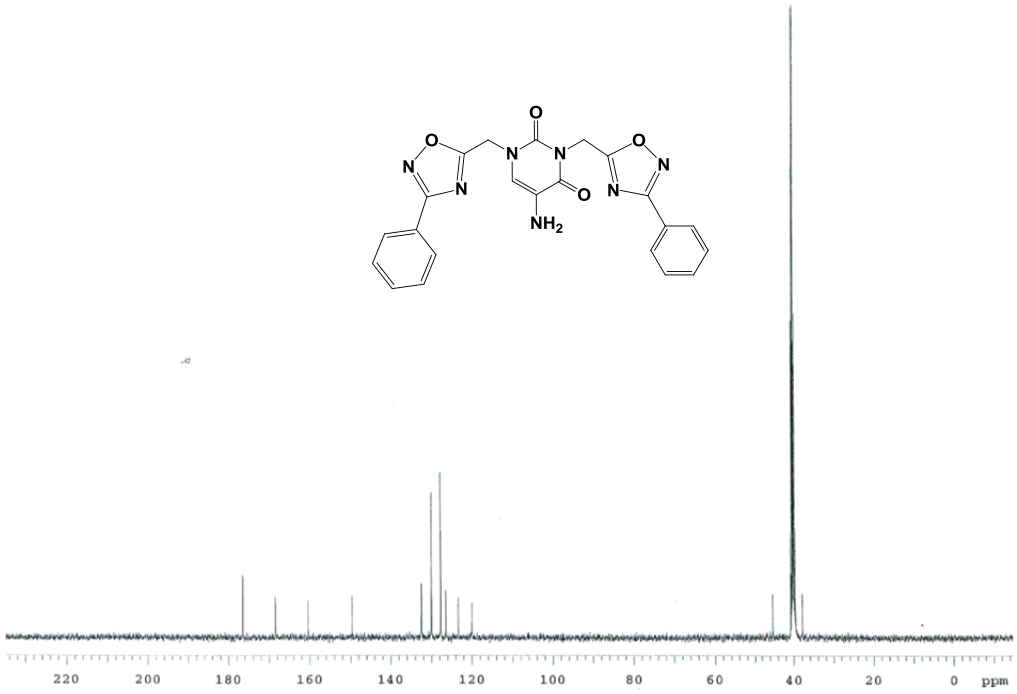

Figure 4.115. ^{13}C NMR spectrum of compound **62a.**

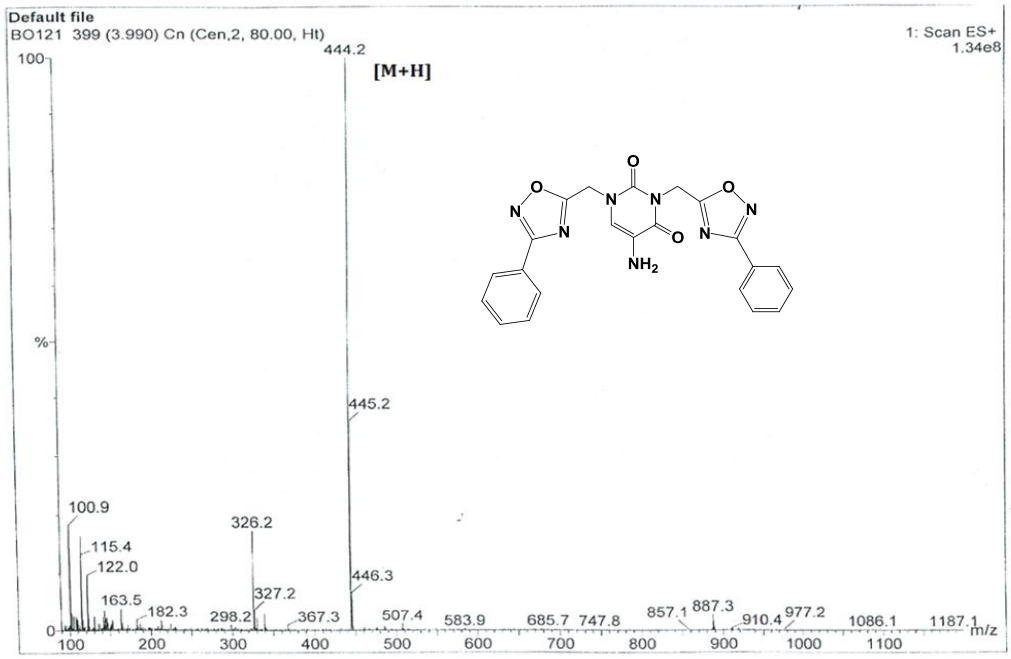

Figure 4.116. LC-MS spectrum of compound **62a.**

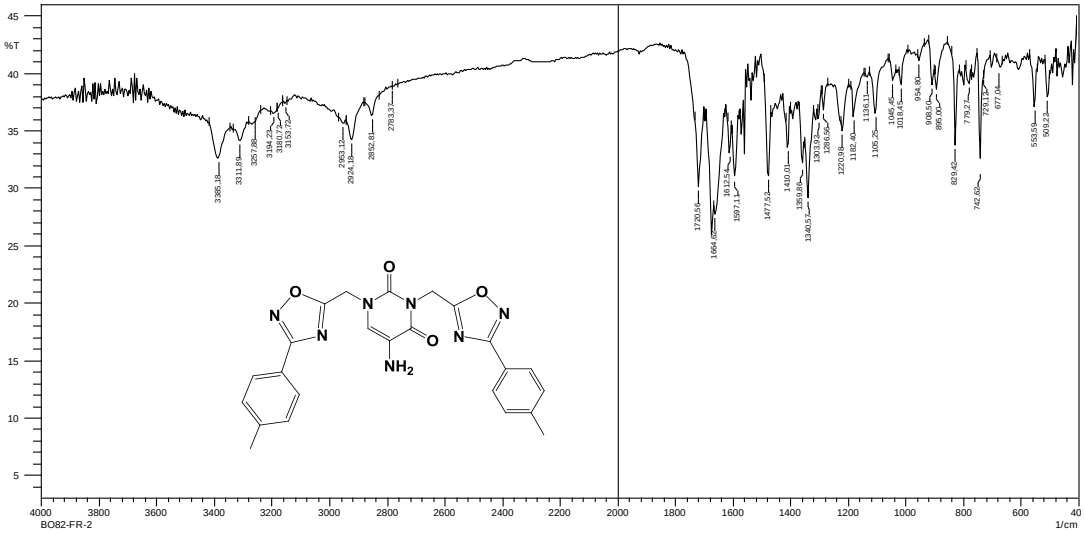

Figure 4.117. IR spectrum of compound **62b.**

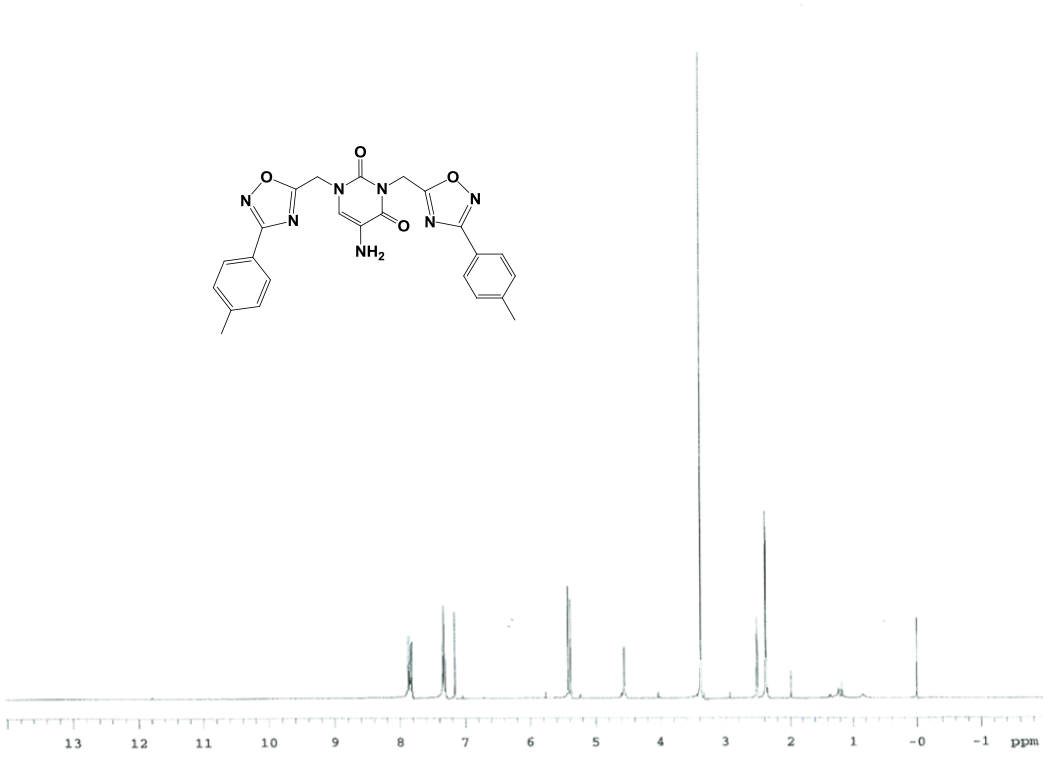

Figure 4.118. ^{1}H NMR spectrum of compound **62b.**

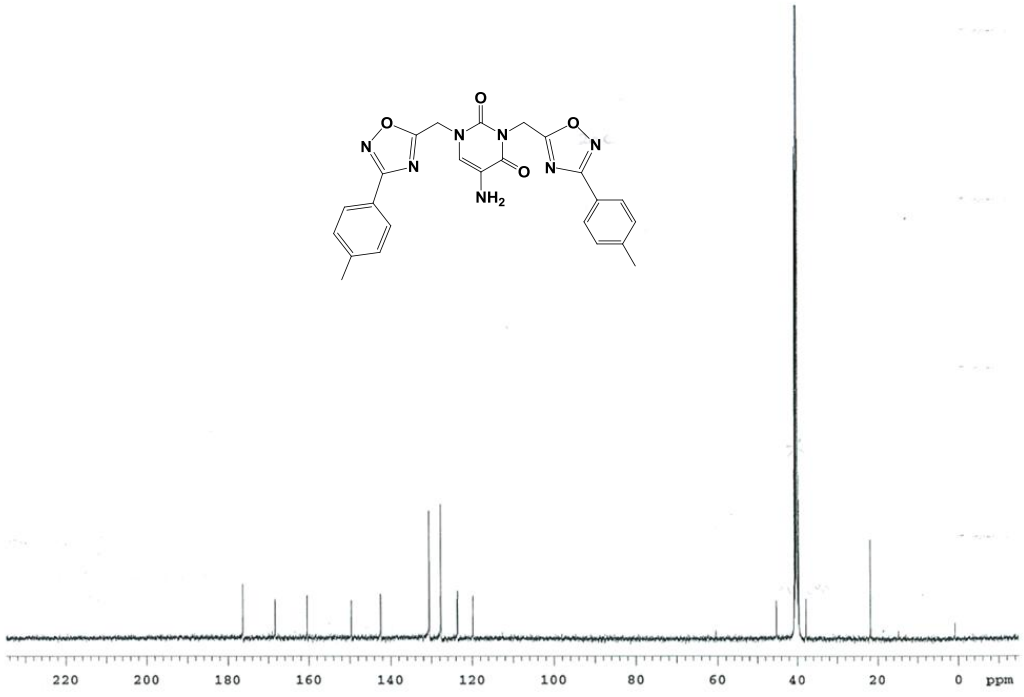

Figure 4.119. ^{13}C NMR spectrum of compound **62b.**

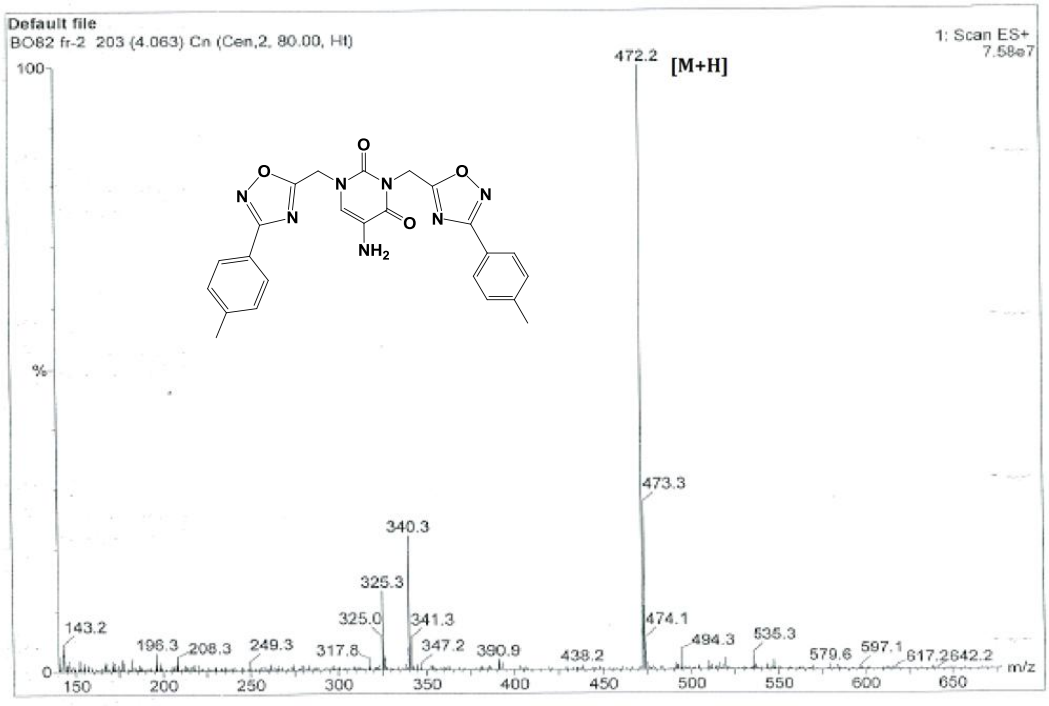

Figure 4.120. LC-MS spectrum of compound **62b.**

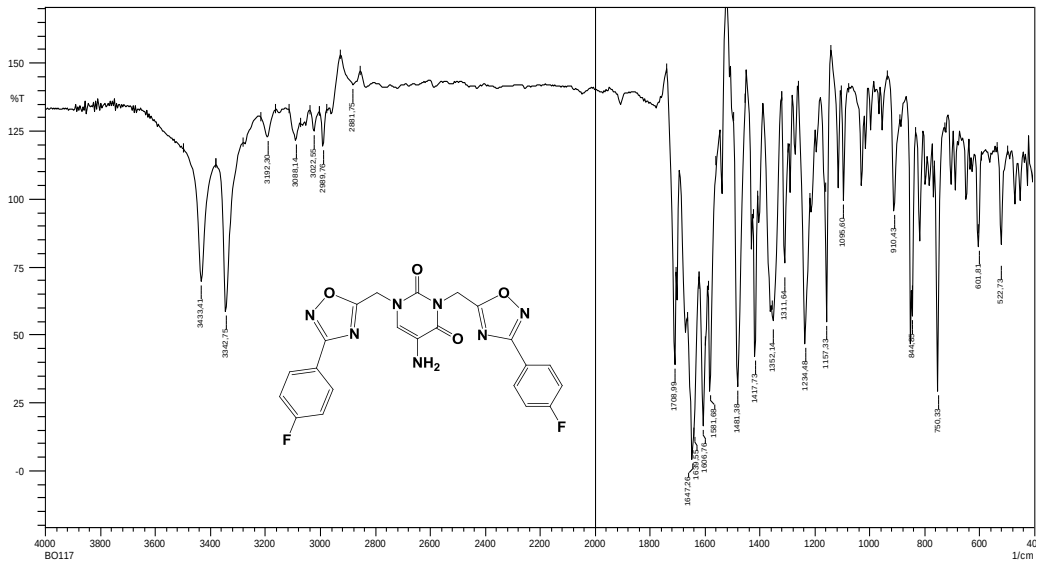

Figure 4.121. IR spectrum of compound **62c.**

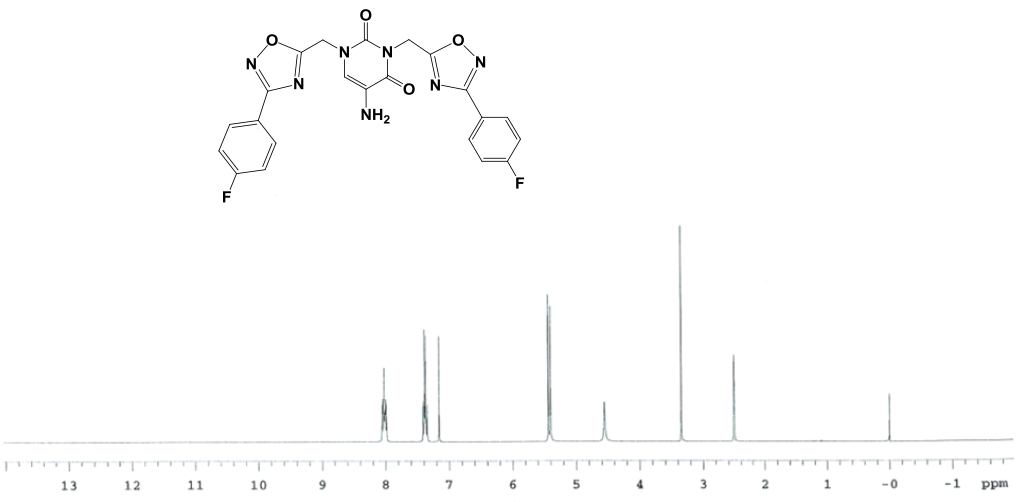

Figure 4.122. ^{1}H NMR spectrum of compound **62c.**

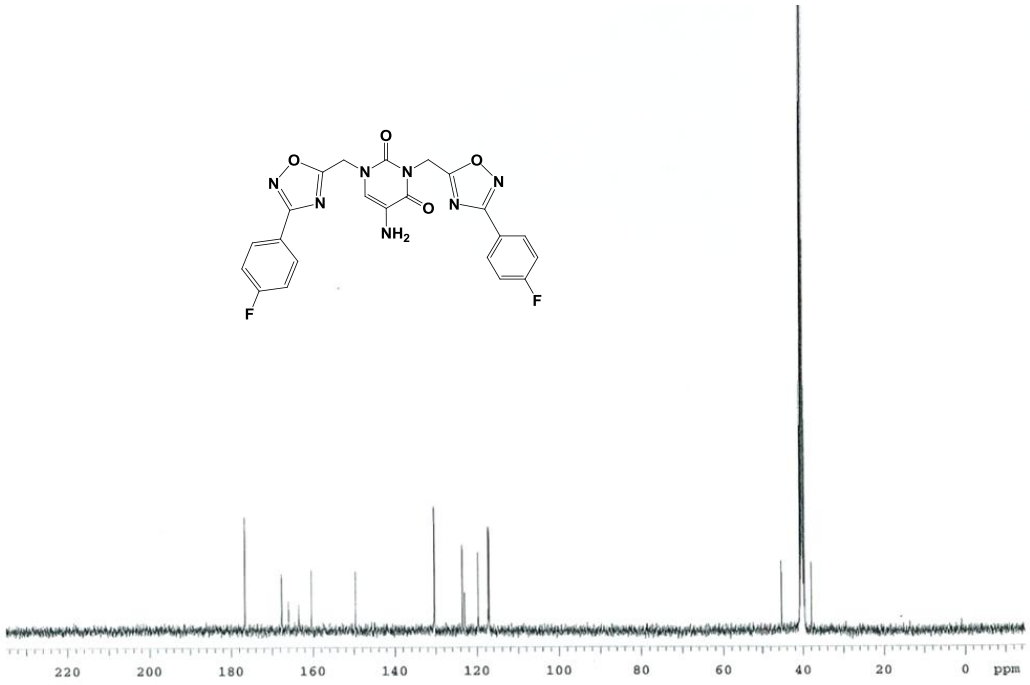

Figure 4.123. ^{13}C NMR spectrum of compound **62c.**

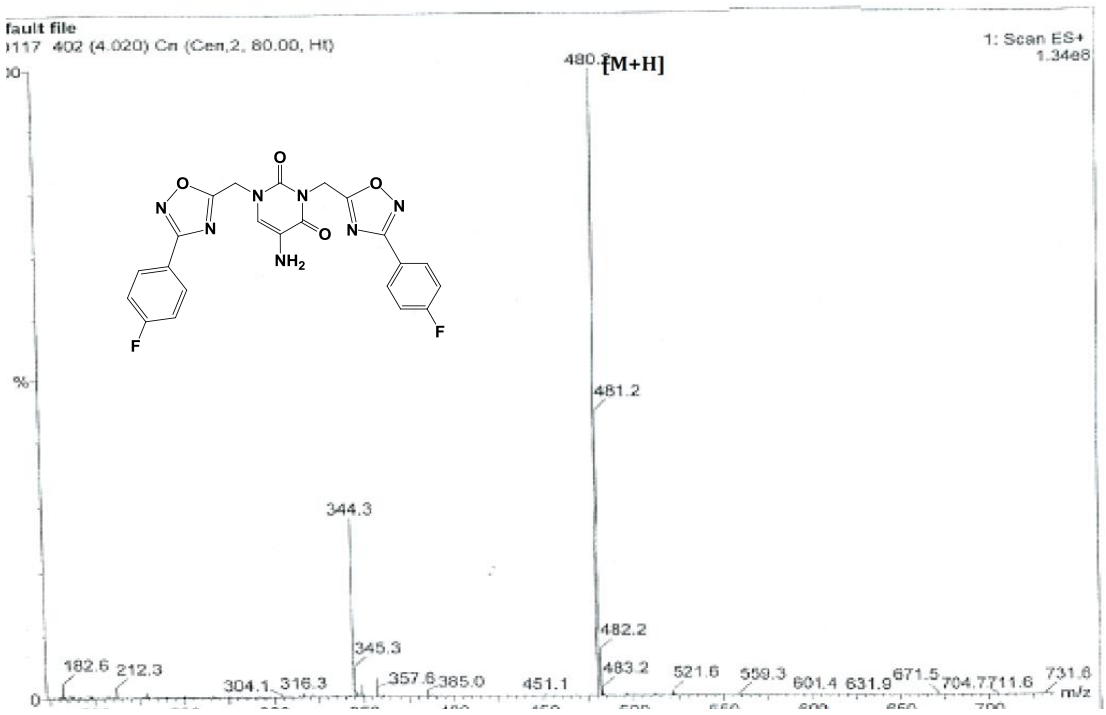

Figure 4.124. LC-MS spectrum of compound **62c.**

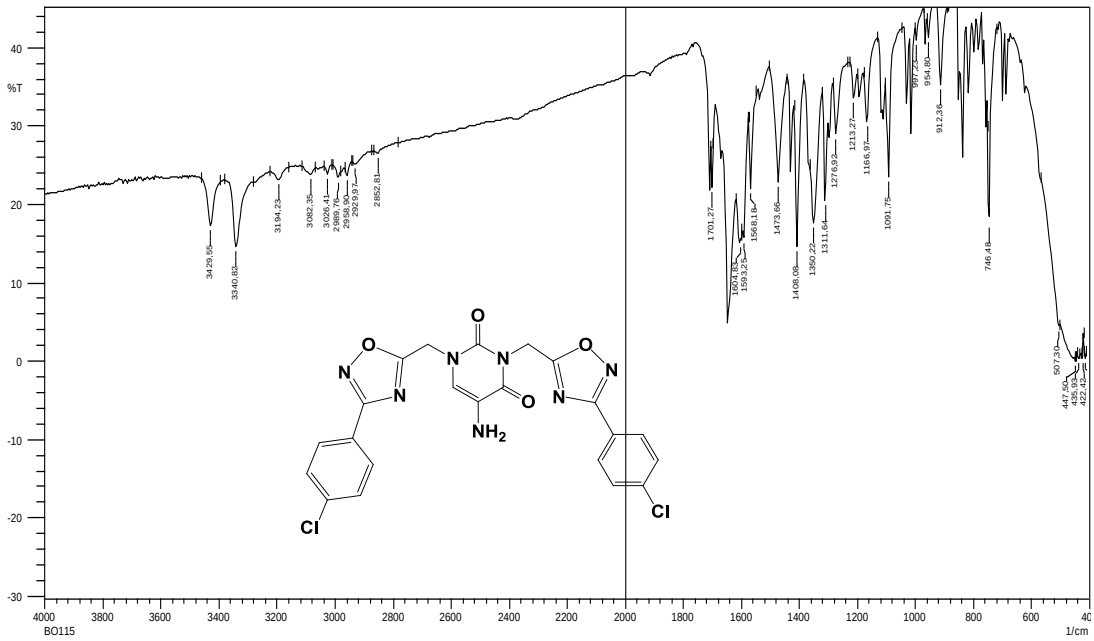

Figure 4.125. IR spectrum of compound **62d.**

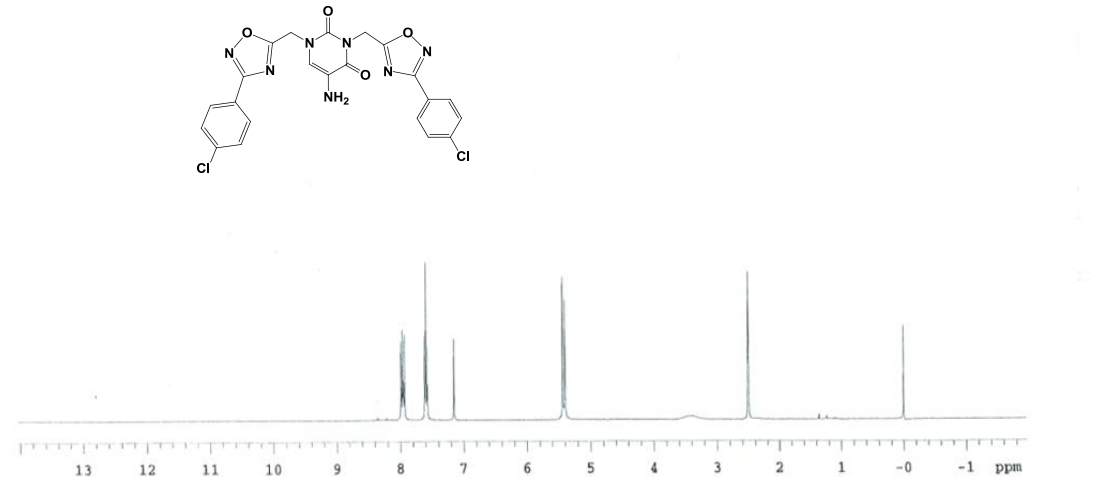

Figure 4.126. ^{1}H NMR spectrum of compound **62d.**

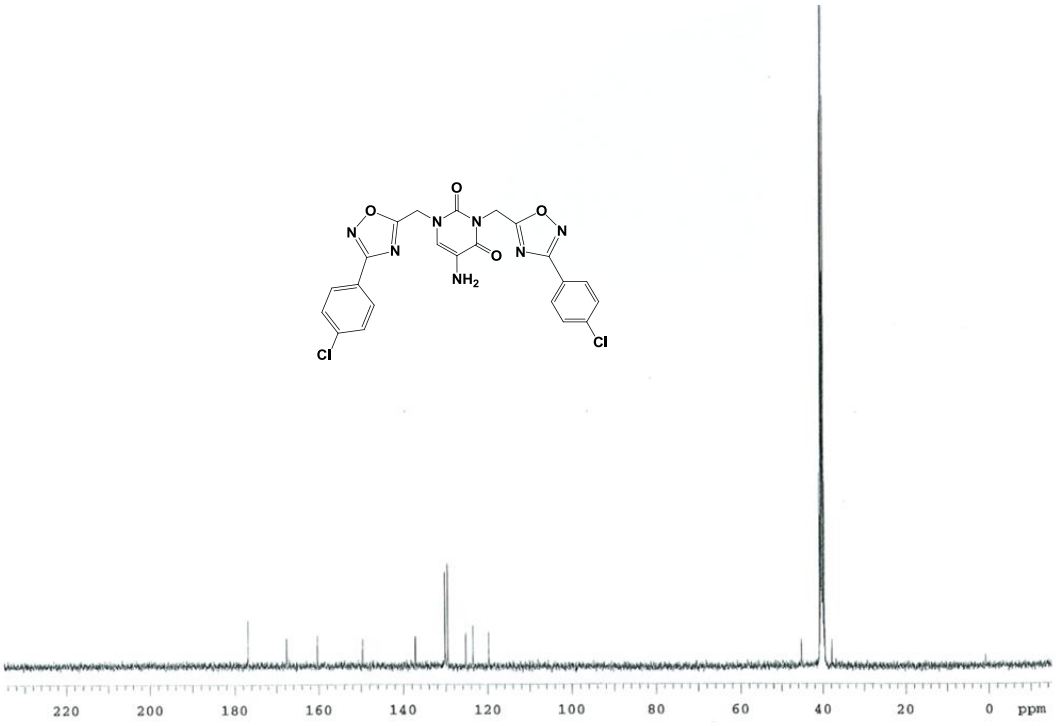

Figure 4.127. ^{13}C NMR spectrum of compound **62d.**

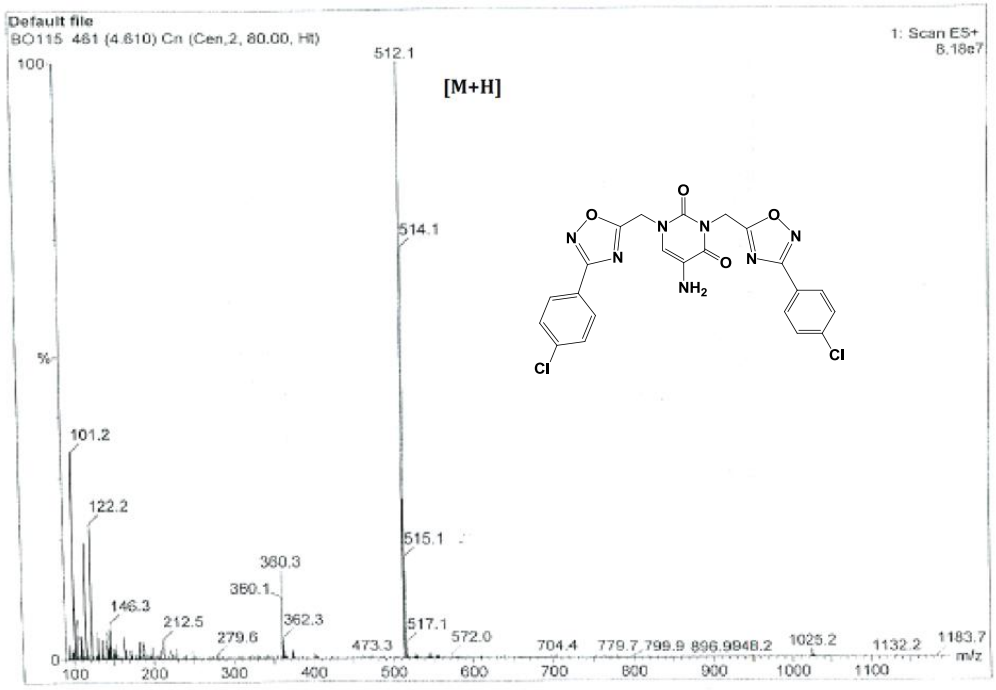

Figure 4.128. LC-MS spectrum of compound **62d.**

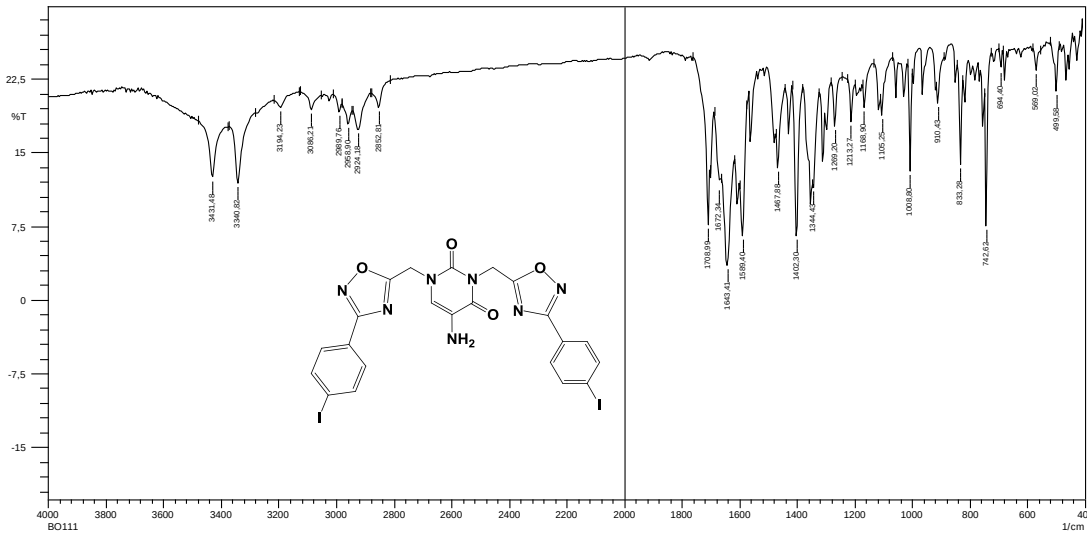

Figure 4.129. IR spectrum of compound **62e.**

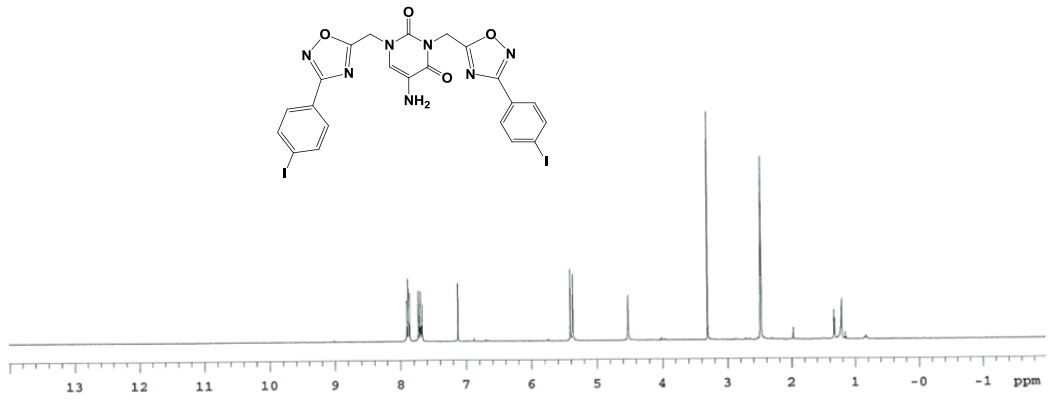

Figure 4.130. ^{1}H NMR spectrum of compound **62e.**

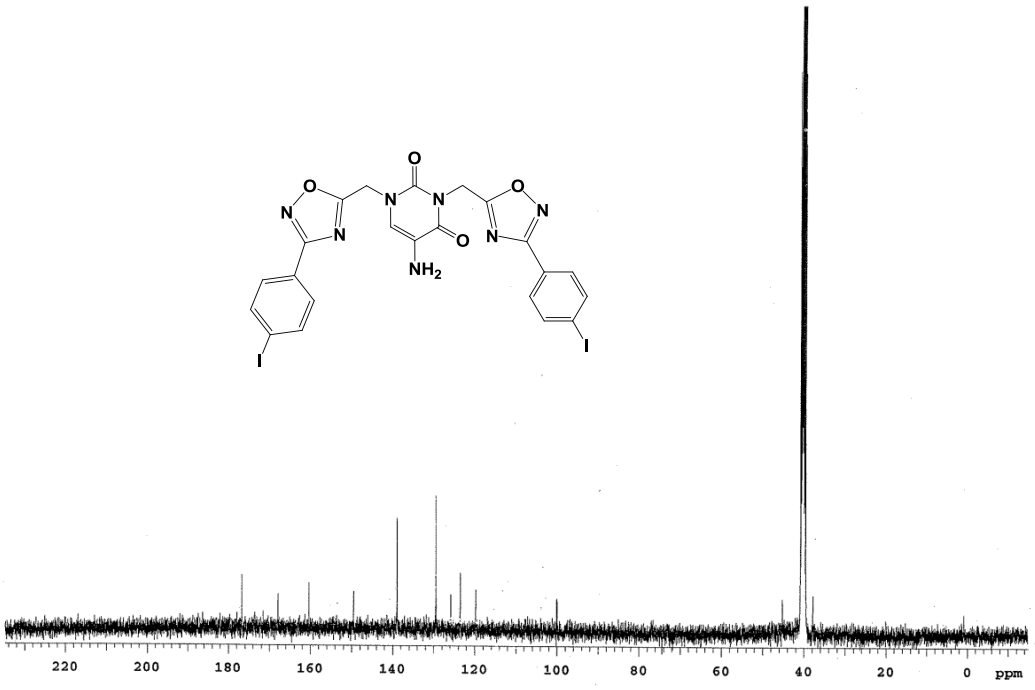

Figure 4.131. ^{13}C NMR spectrum of compound **62e.**

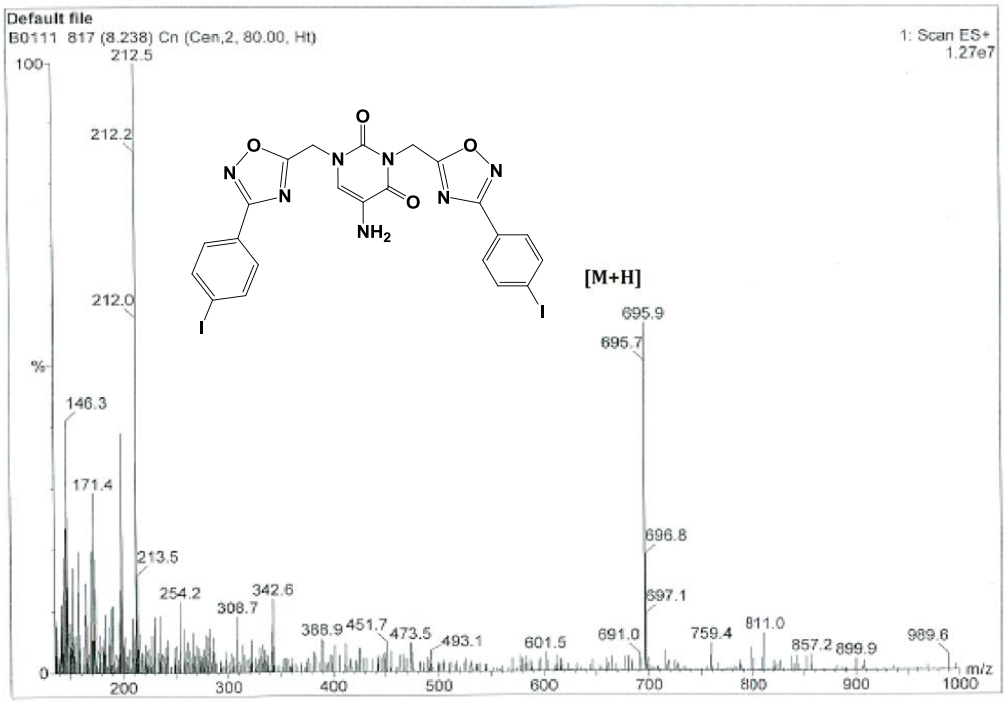

Figure 4.132. LC-MS spectrum of compound **62e.**

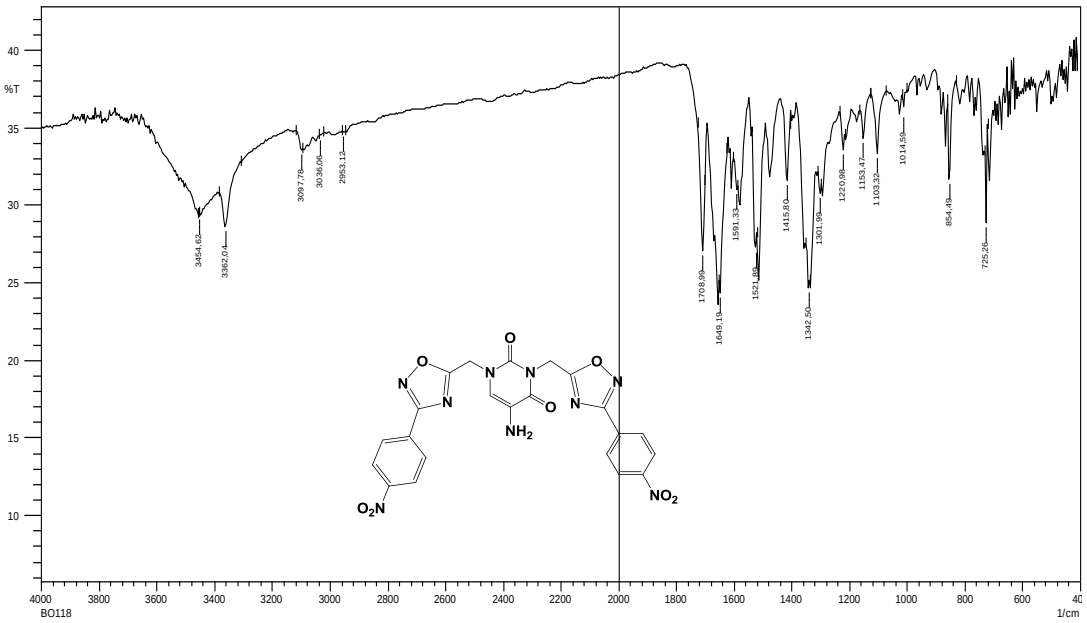

Figure 4.133. IR spectrum of compound **62f.**

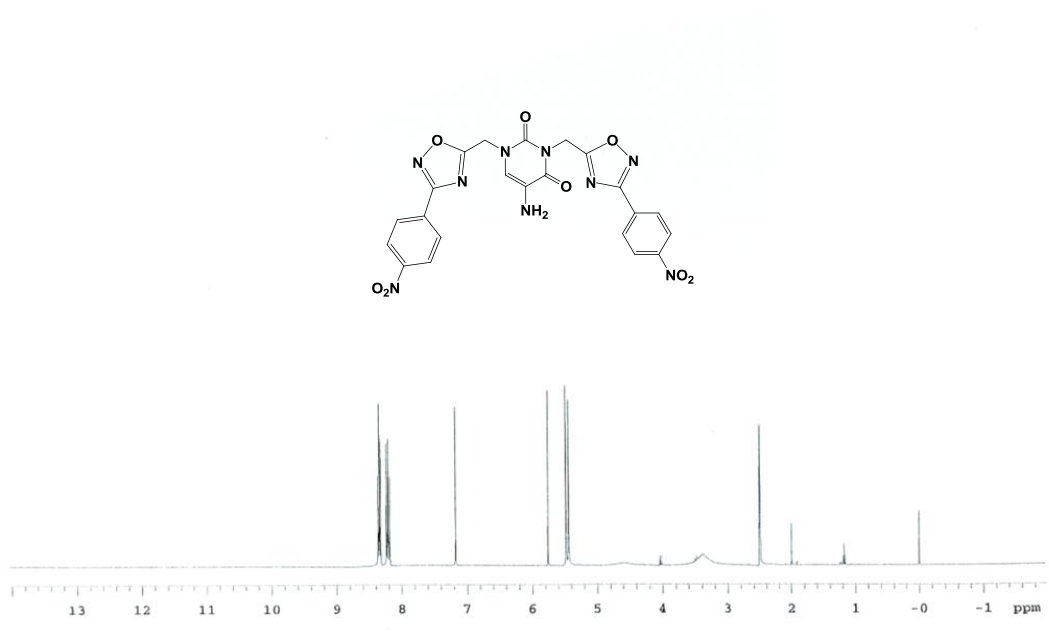

Figure 4.134. ^{1}H NMR spectrum of compound **62f.**

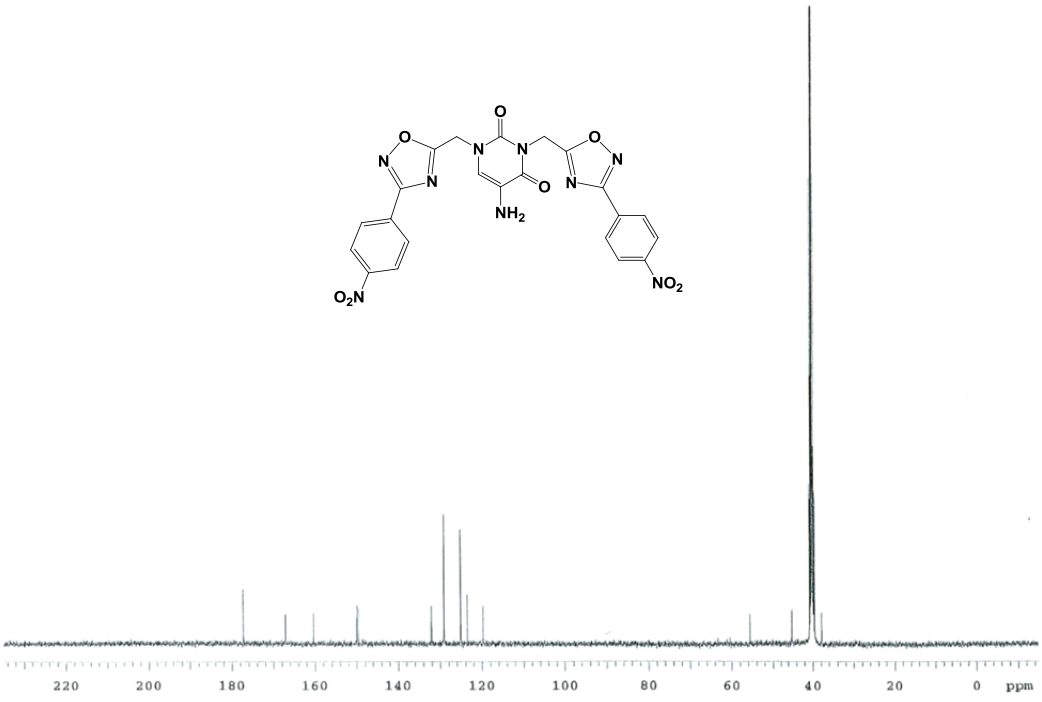

Figure 4.135. ^{13}C NMR spectrum of compound **62f.**

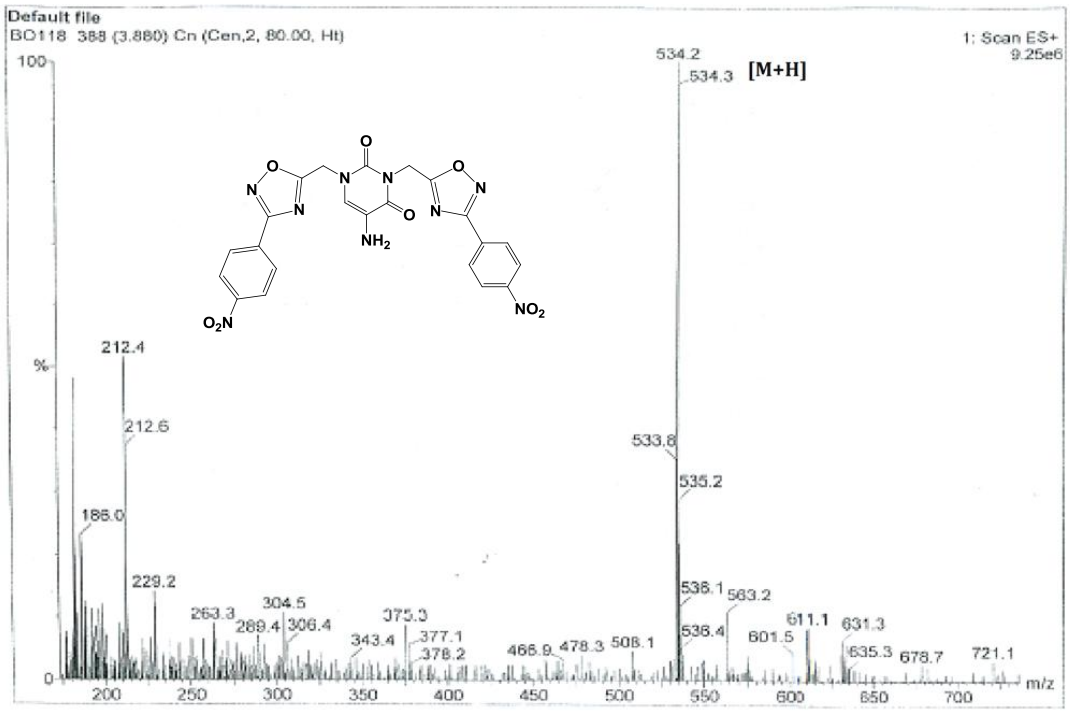

Figure 4.136. LC-MS spectrum of compound **62f.**

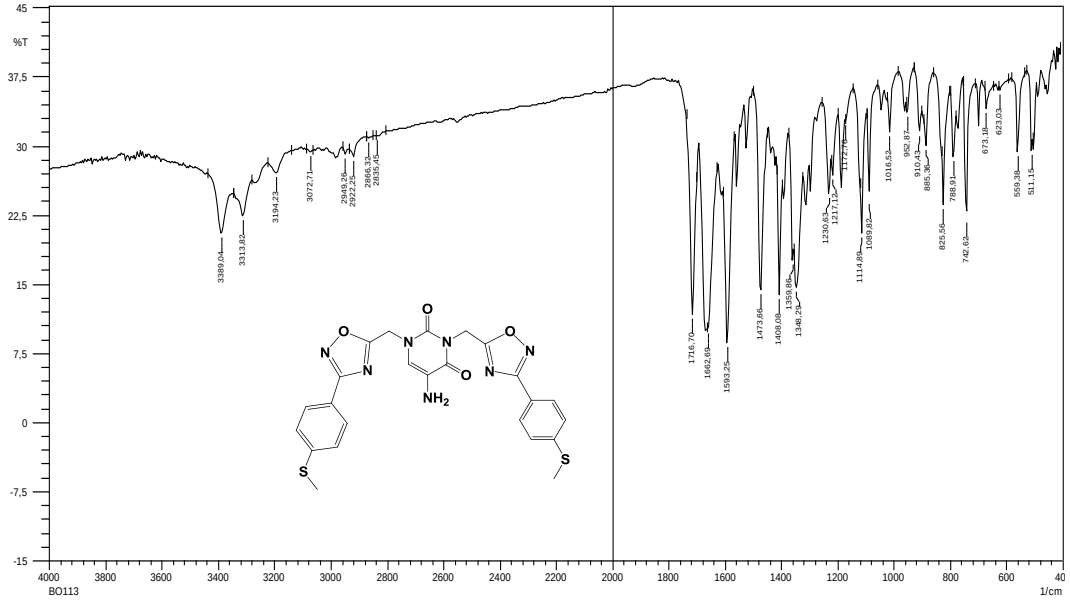

Figure 4.137. IR spectrum of compound **62g.**

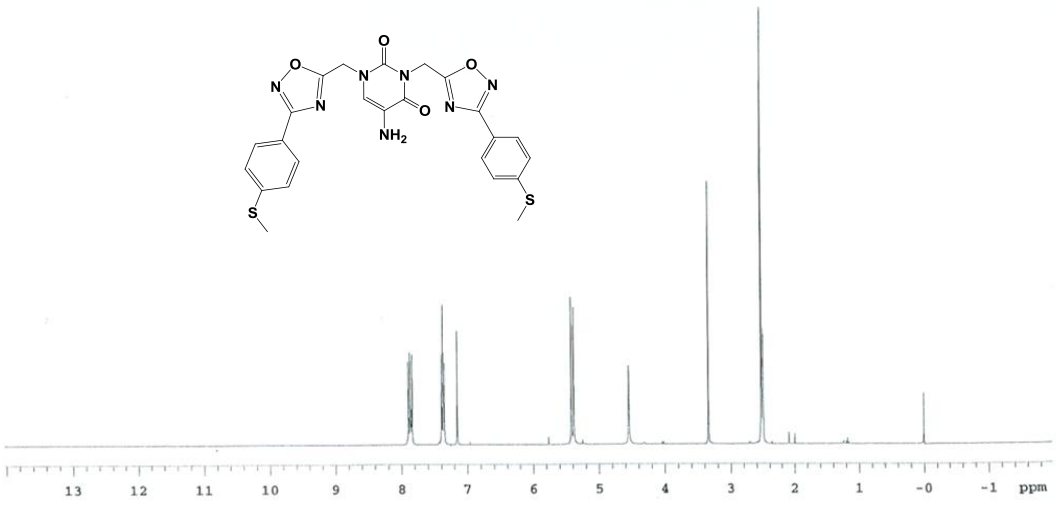

Figure 4.138. ^{1}H NMR spectrum of compound **62g.**

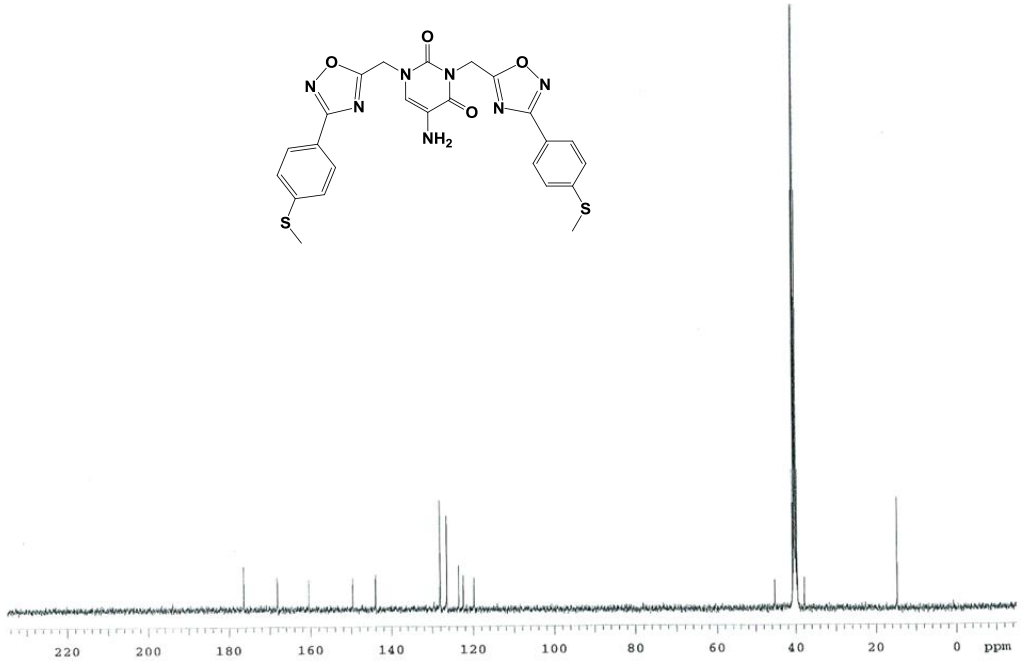

Figure 4.139. ^{13}C NMR spectrum of compound **62g.**

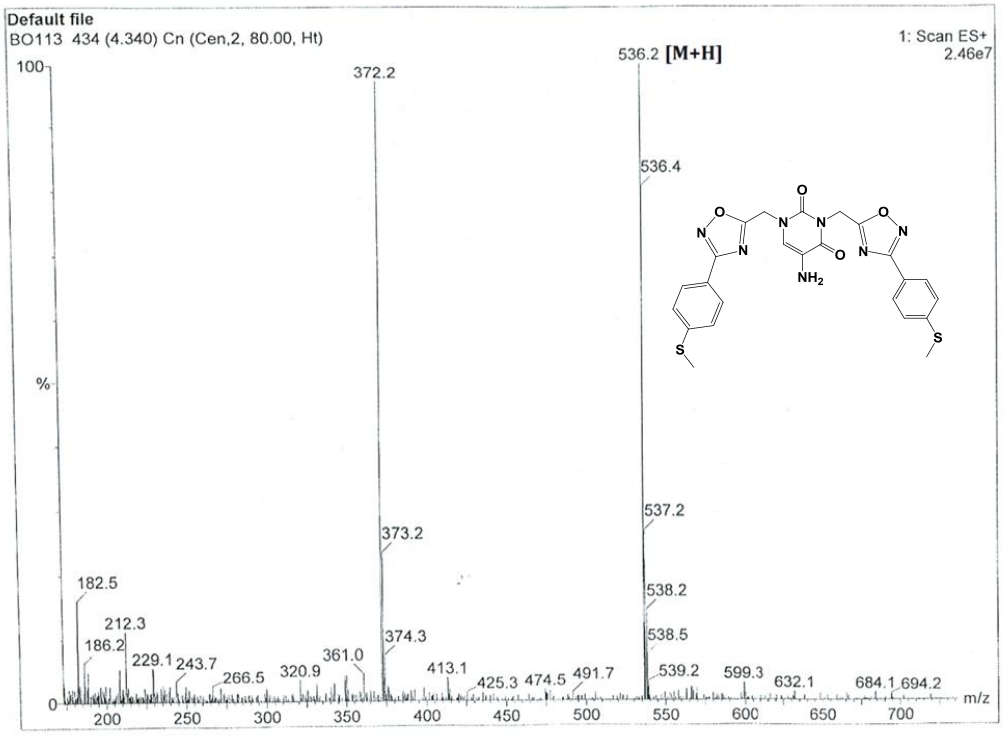

Figure 4.140. LC-MS spectrum of compound **62g.**

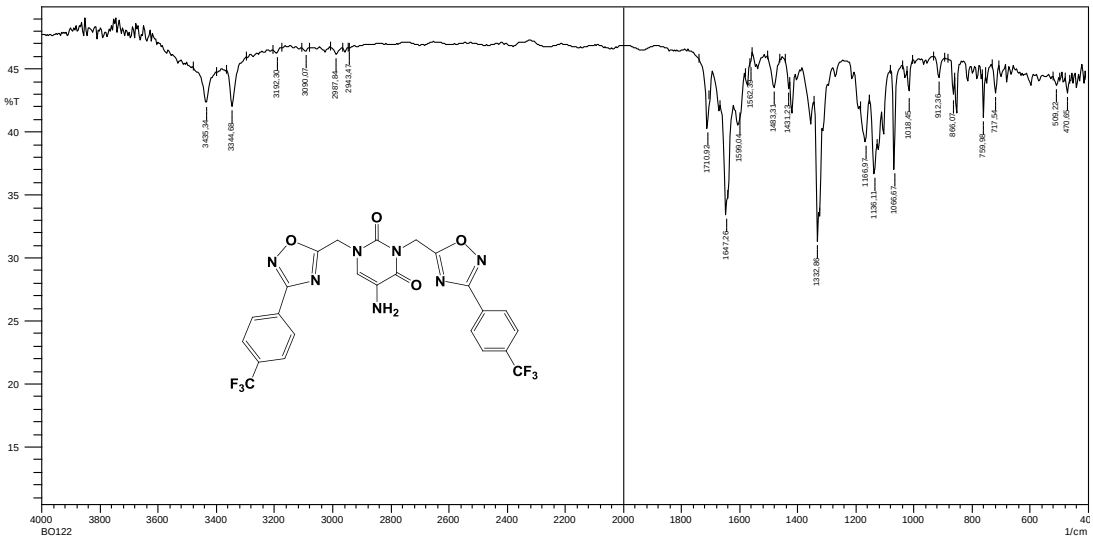

Figure 4.141. IR spectrum of compound **62h.**

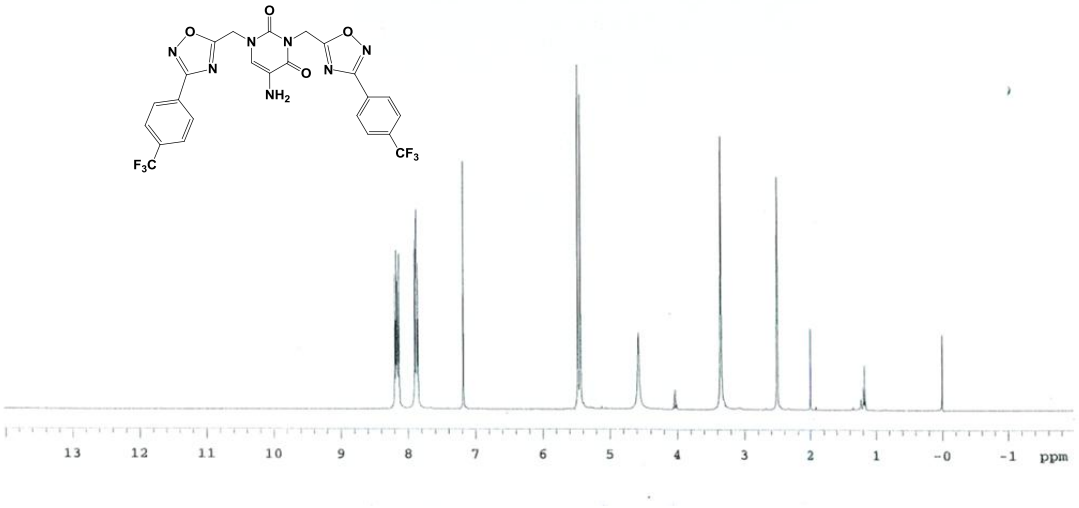

Figure 4.142. ^{1}H NMR spectrum of compound **62h.**

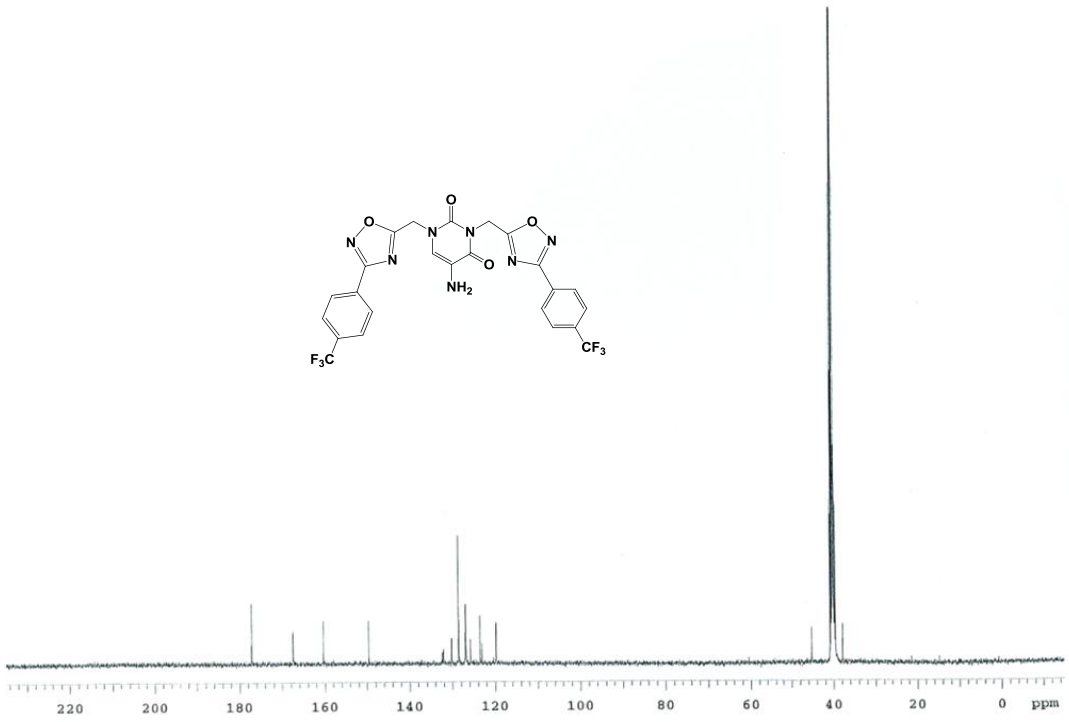

Figure 4.143. ^{13}C NMR spectrum of compound **62h**

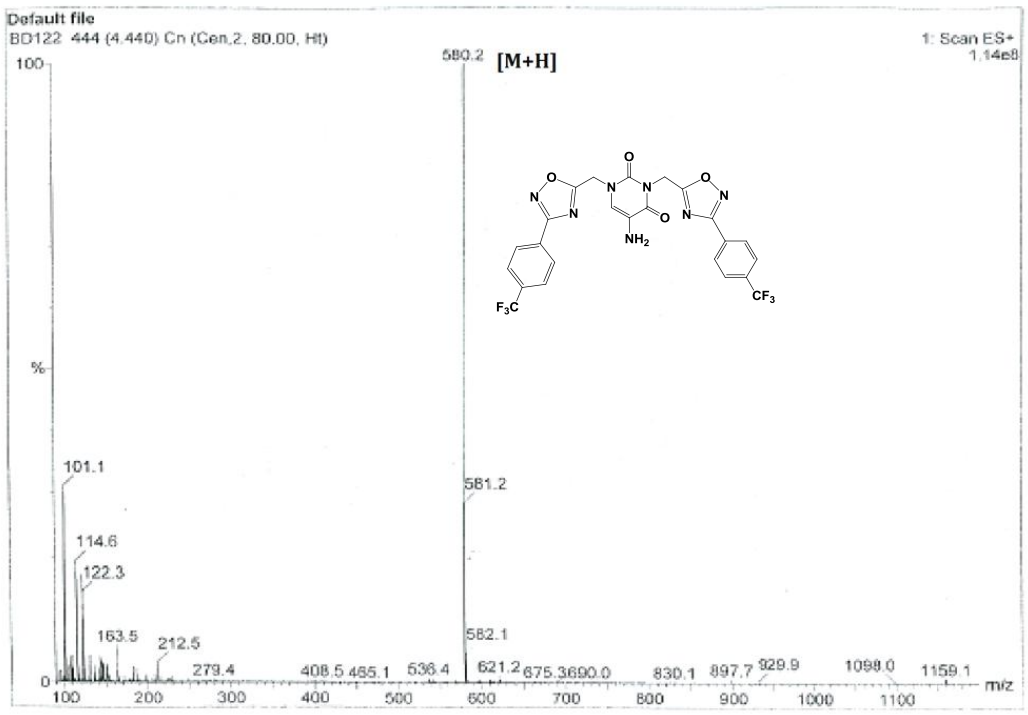

Figure 4.144 .LC-MS spectrum of compound **632h.**

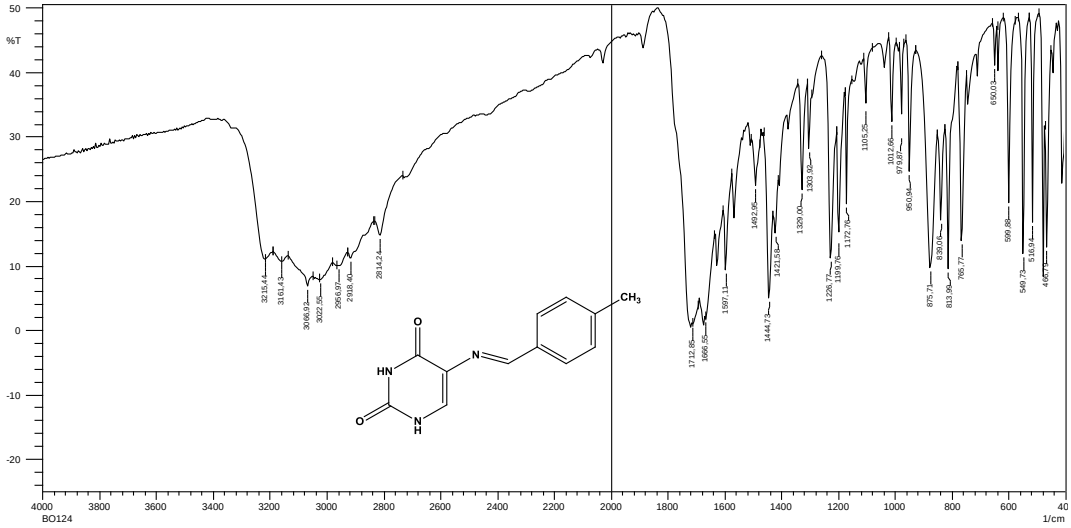

Figure 4.145. IR spectrum of compound **56a.**

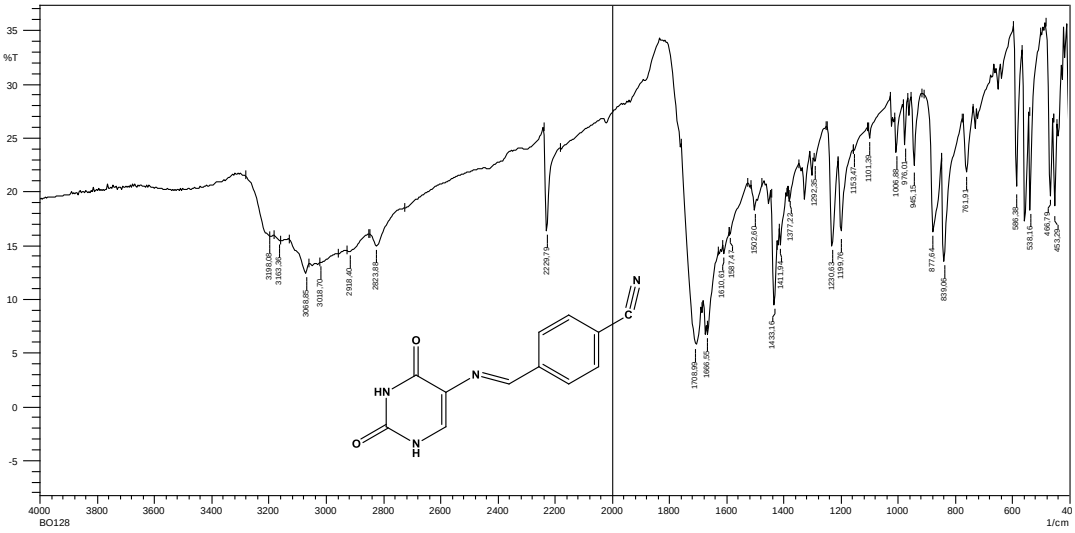

Figure 4.146. IR spectrum of compound **56b.**

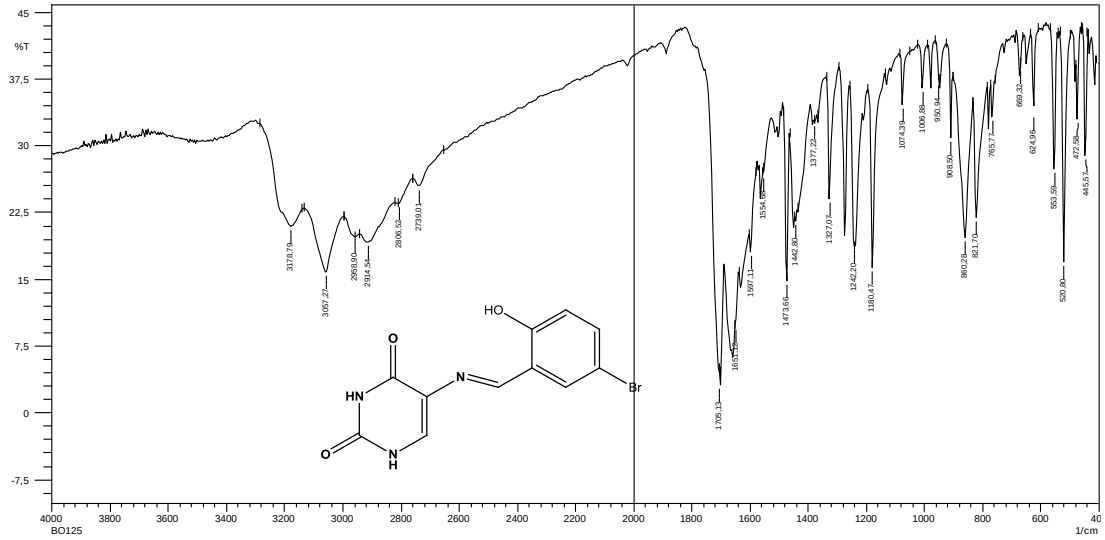

Figure 4.147. IR spectrum of compound **56c.**

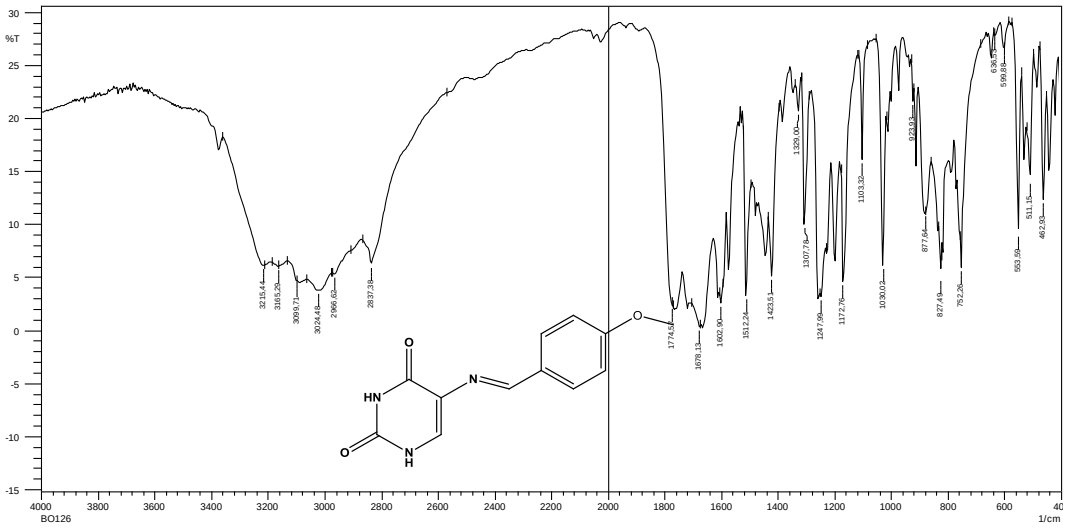

Figure 4.148. IR spectrum of compound **56d.**

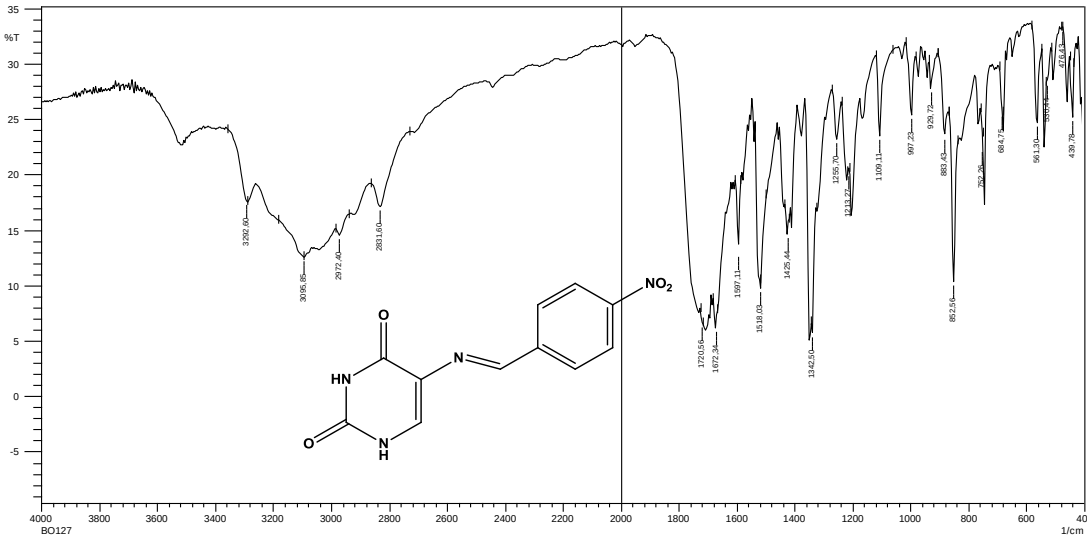

Figure 4.149. IR spectrum of compound **56e.**

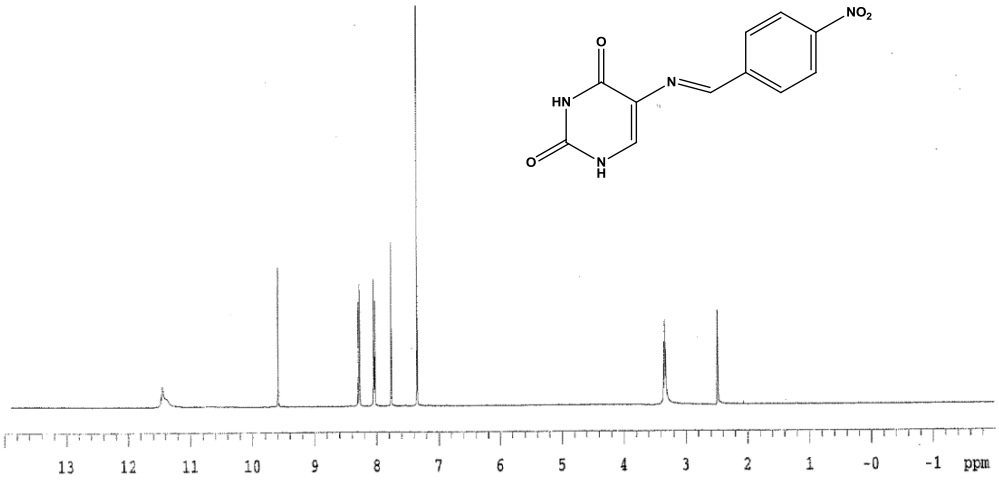

Figure 4.150. ^{1}H NMR spectrum of compound **56e.**

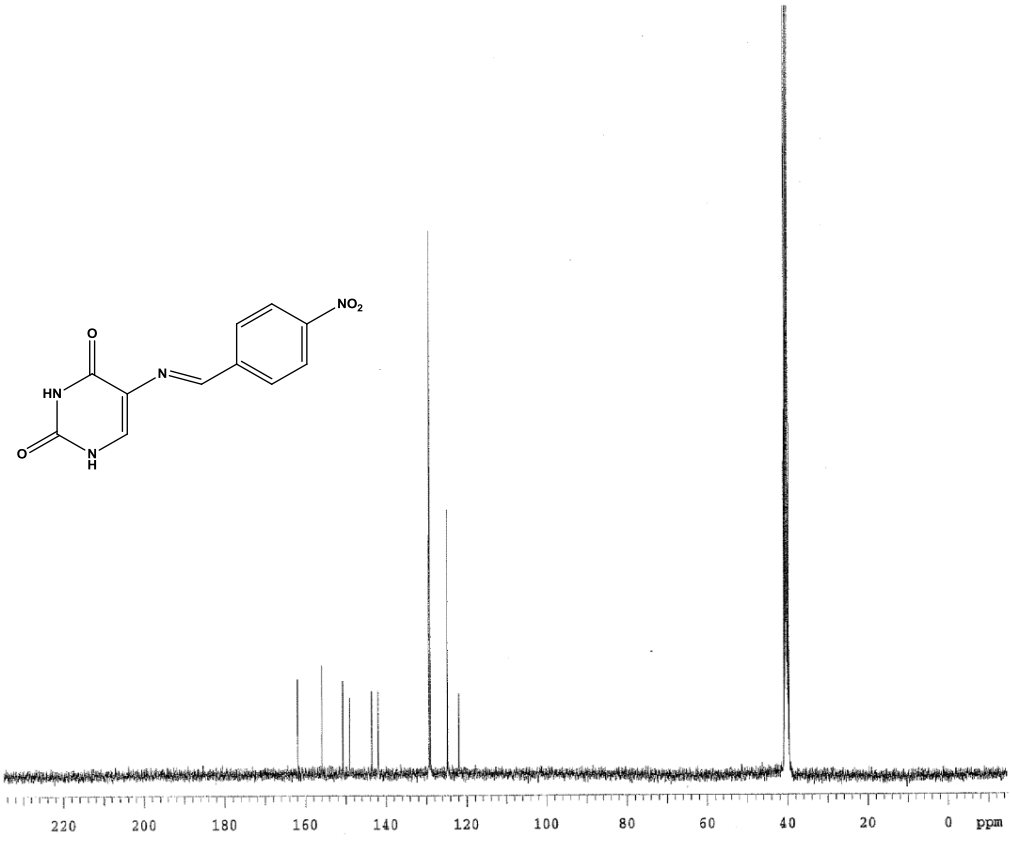

Figure 4.151. ^{13}C NMR spectrum of compound **56e.**

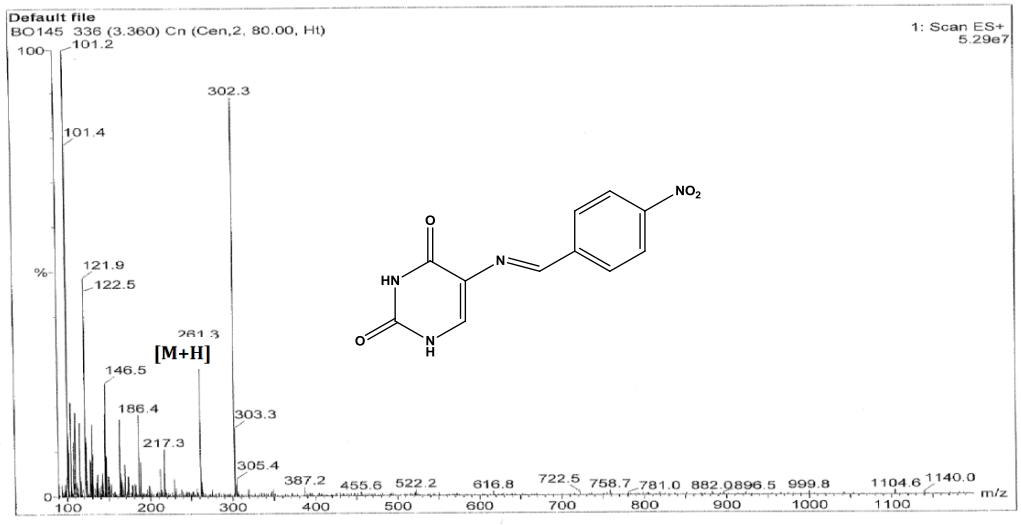

Figure 4.152. LC-MS spectrum of compound **56e.**

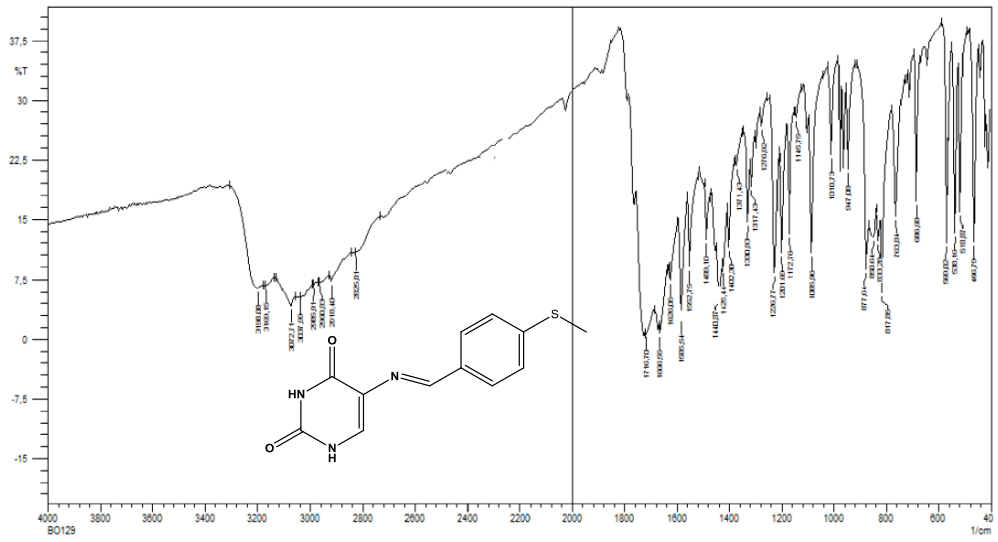

Figure 4.153. IR spectrum of compound **56f.**

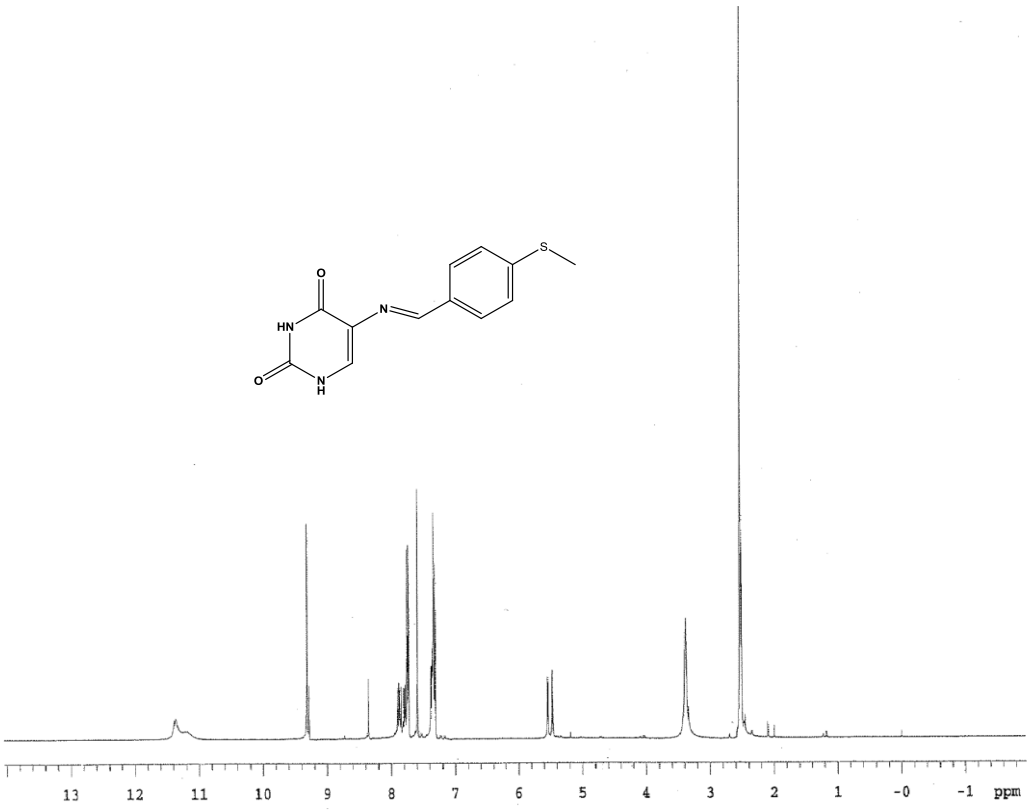

Figure 4.154. ^{1}H NMR spectrum of compound **56f.**

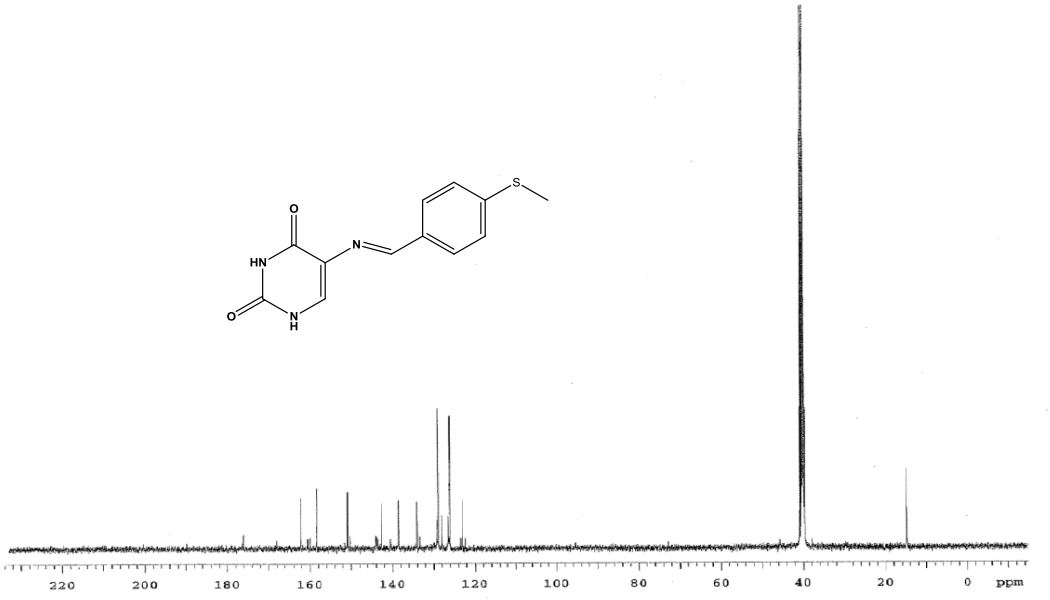

Figure 4.155. ^{13}C NMR spectrum of compound **56f.**

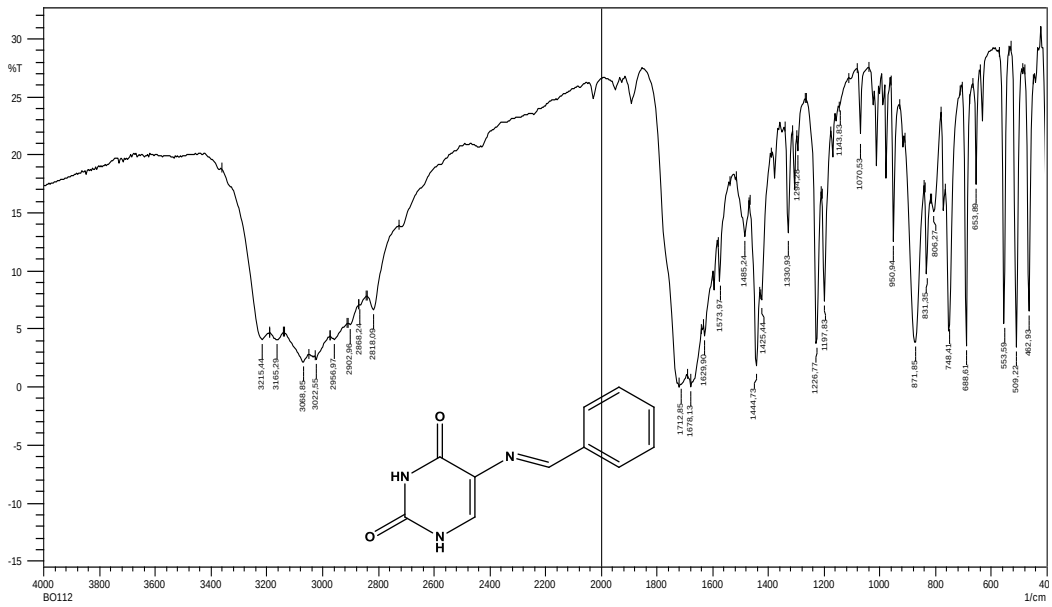

Figure 4.156. IR spectrum of compound **56g.**

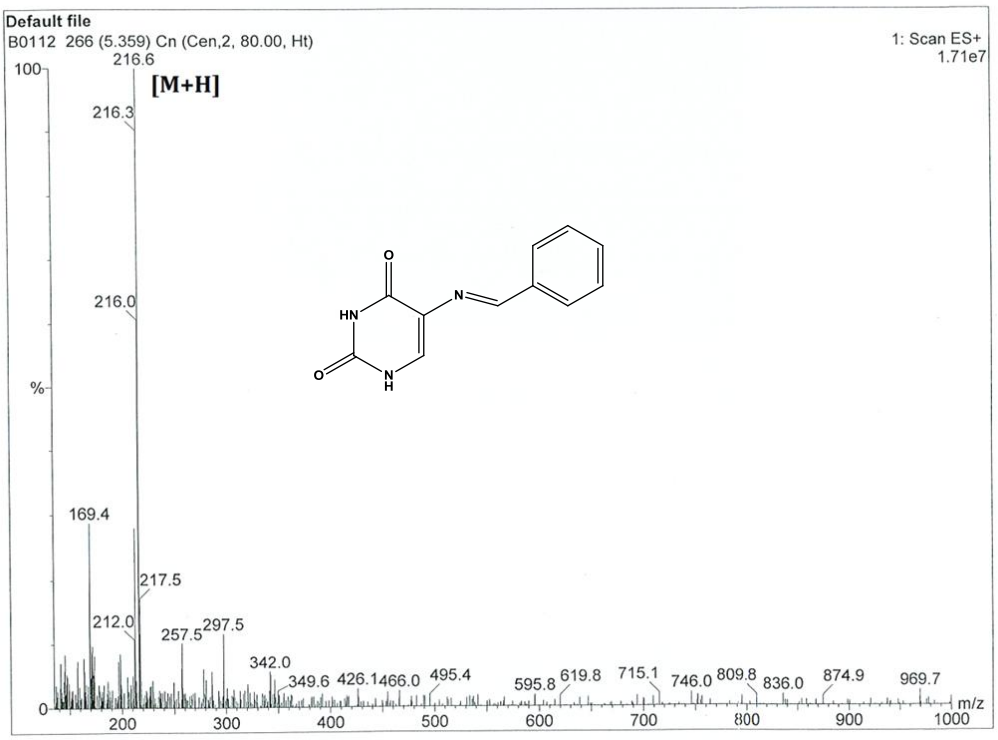

Figure 4.157. LC-MS spectrum of compound **56g.**

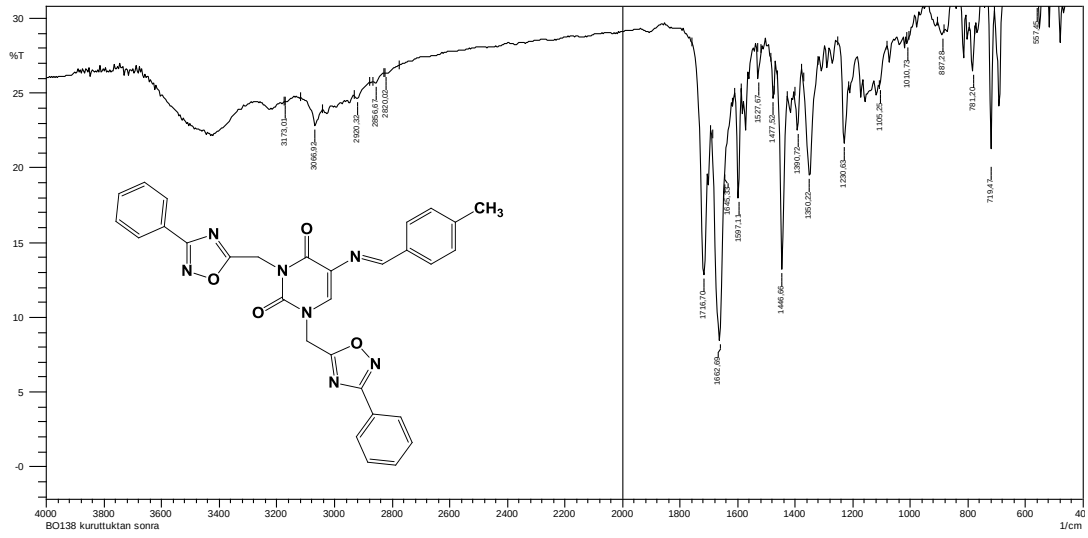

Figure 4.158. IR spectrum of compound **63a.**

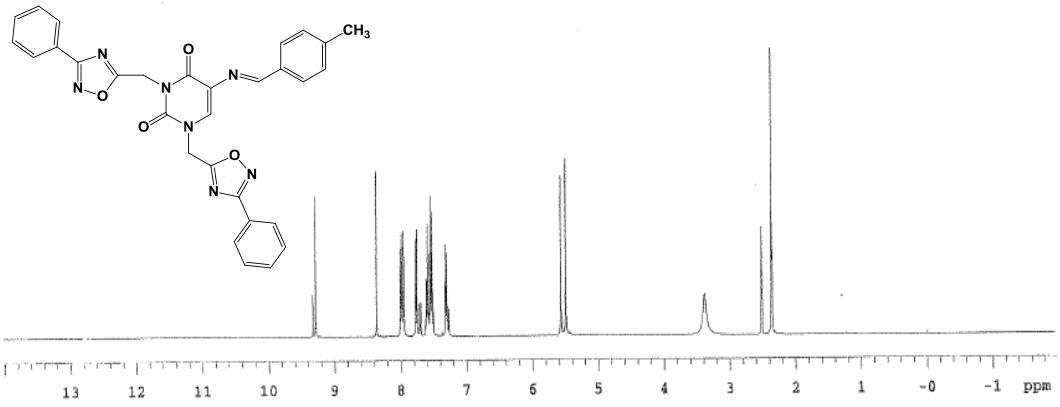

Figure 4.159. ^{1}H NMR spectrum of compound **63a.**

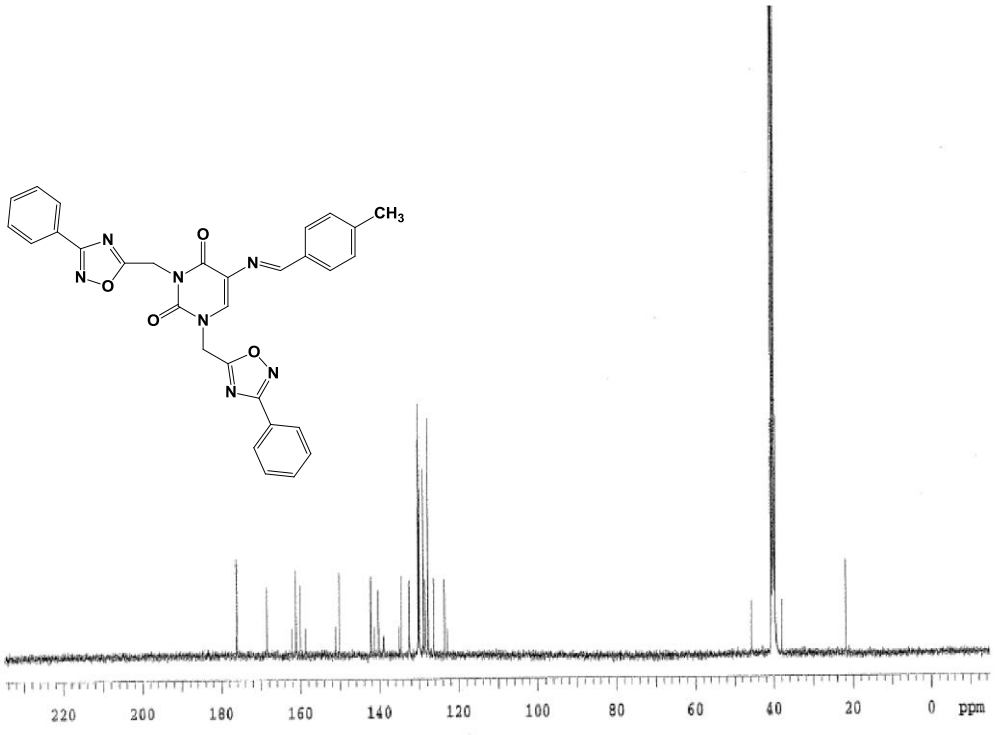

Figure 4.160. ^{13}C NMR spectrum of compound **63a.**

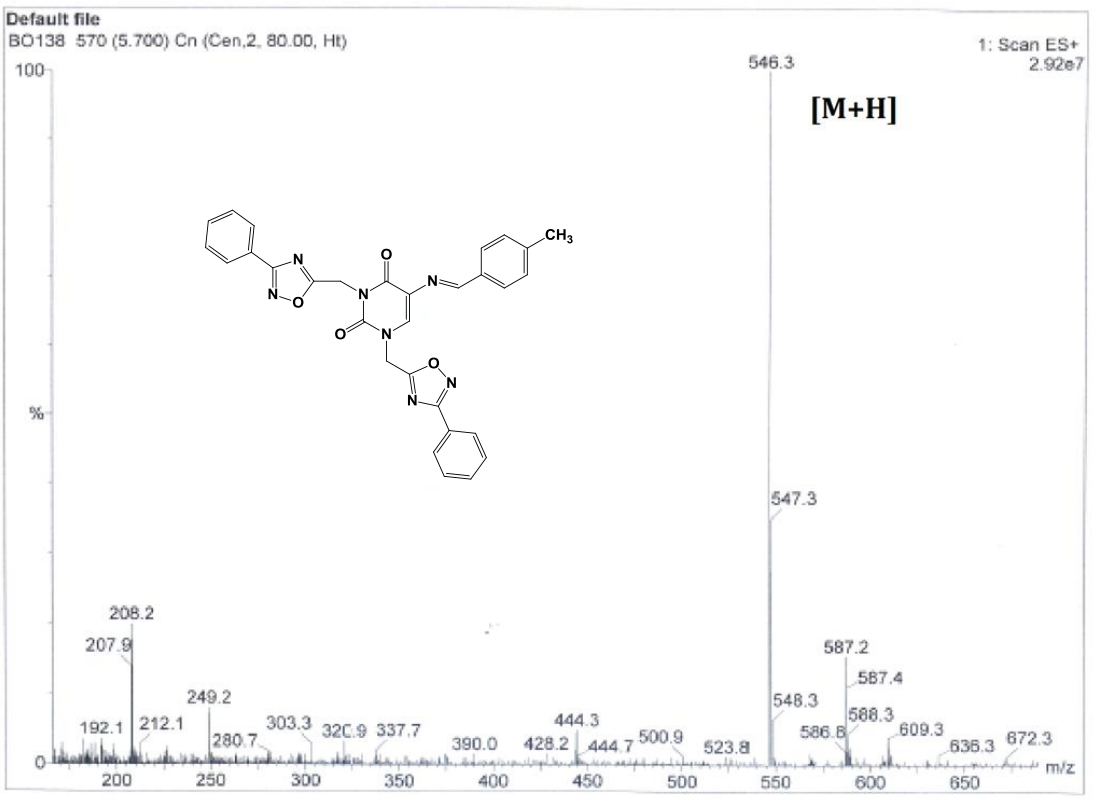

Figure 4.161. LC-MS spectrum of compound **63a**

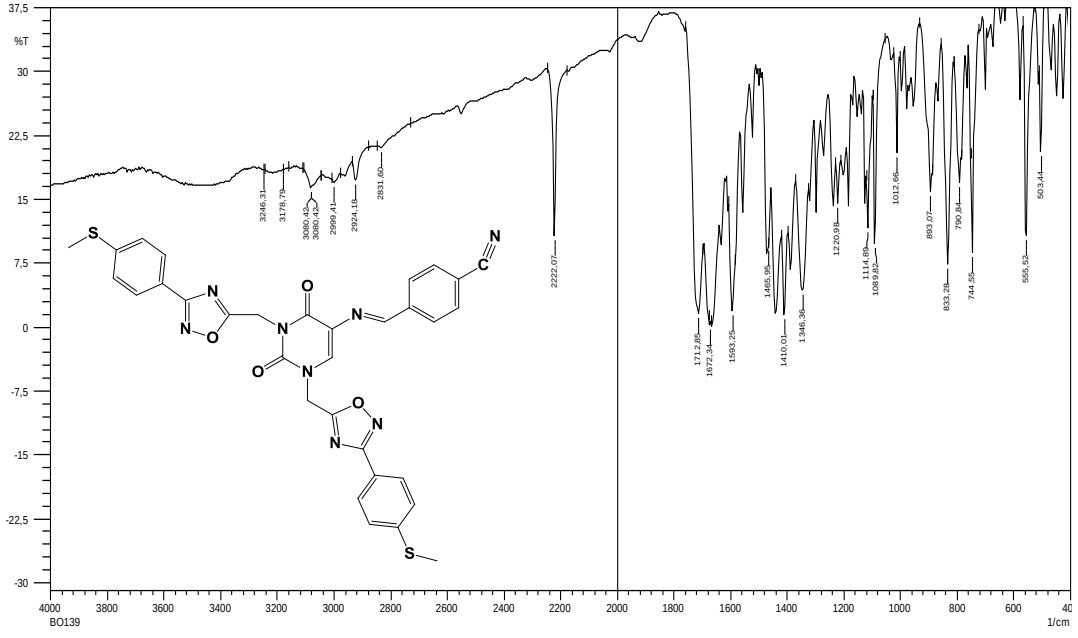

Figure 4.162. IR spectrum of compound **63b.**

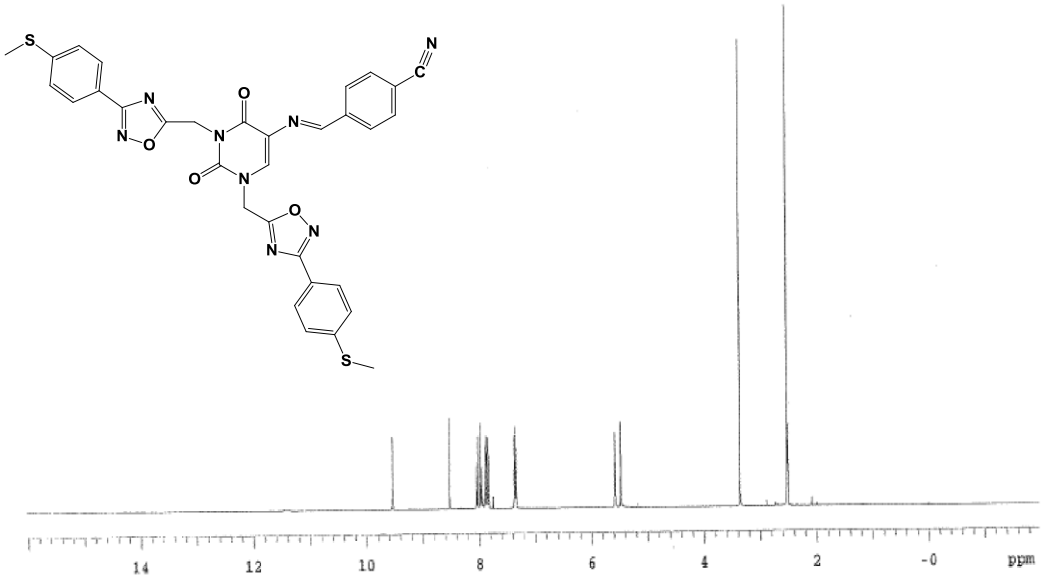

Figure 4.163. ^{1}H NMR spectrum of compound **63b**

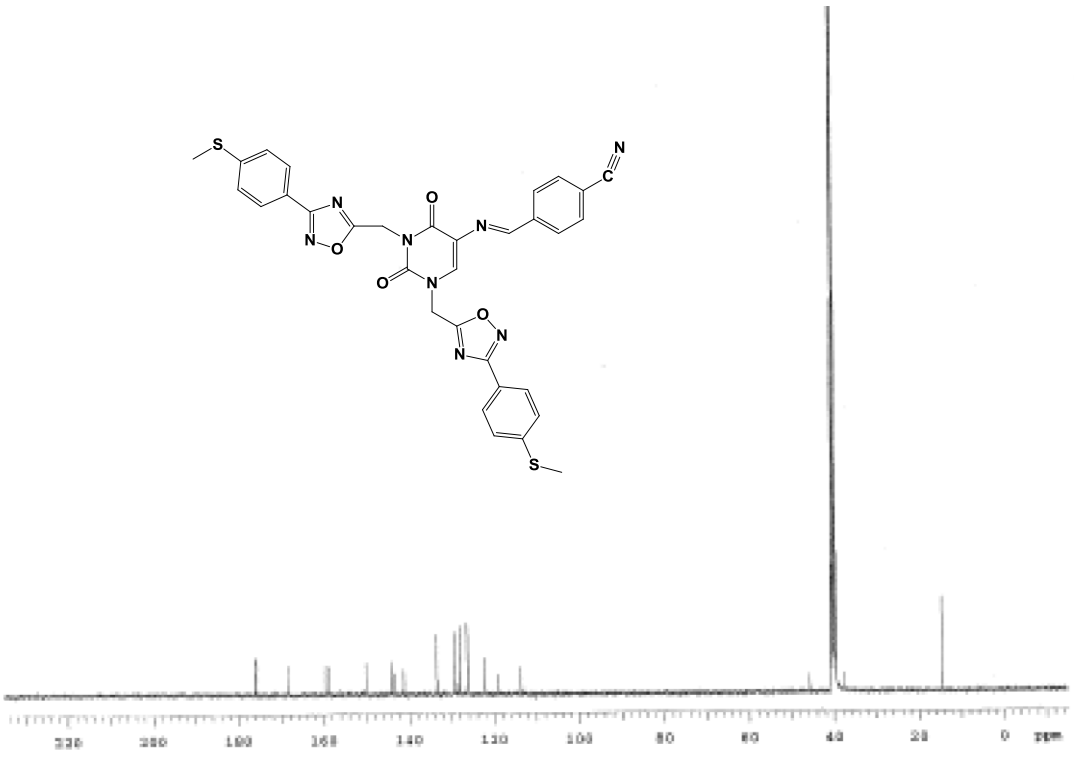

Figure 4.164. ^{13}C NMR spectrum of compound **63b.**

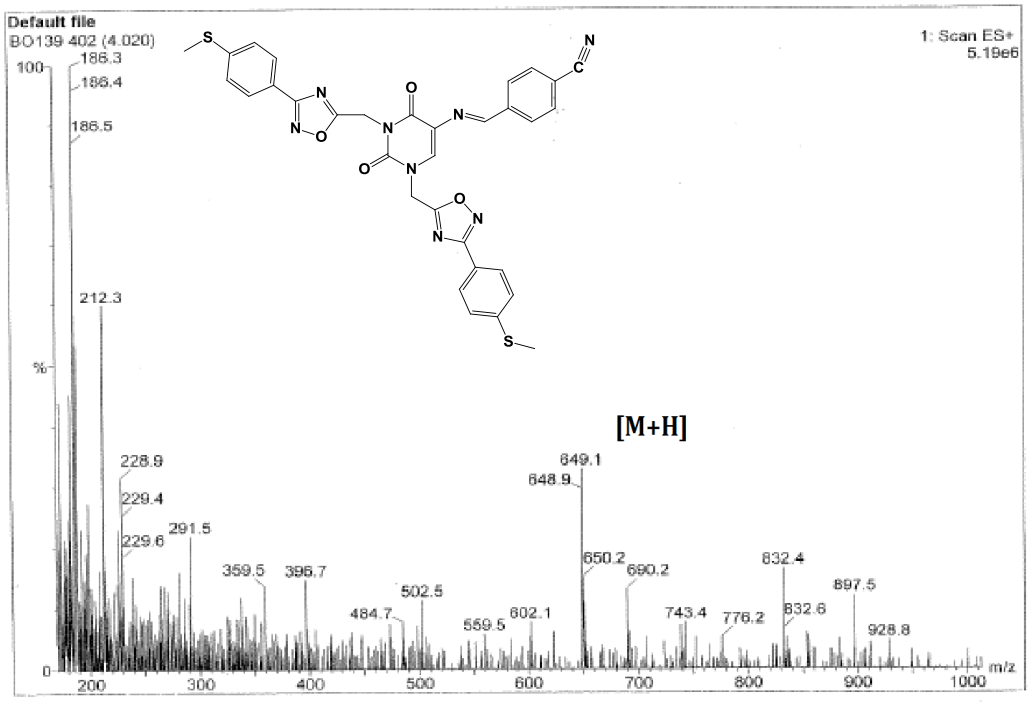

Figure 4.165. LC-MS spectrum of compound **63b.**

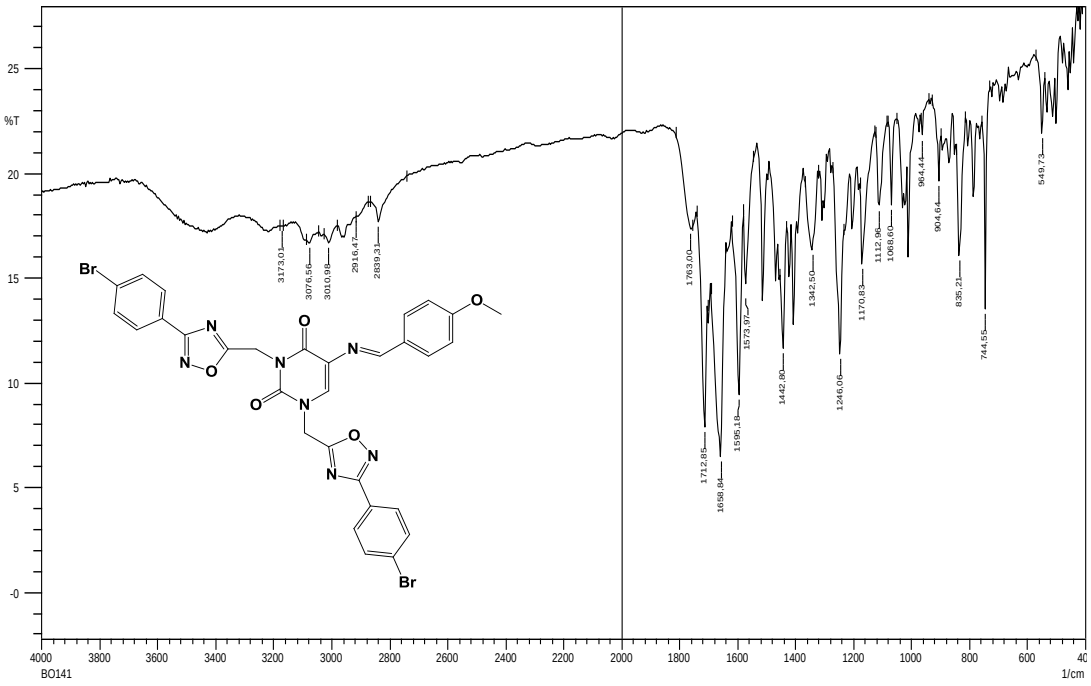

Figure 4.166. IR spectrum of compound **63c** .

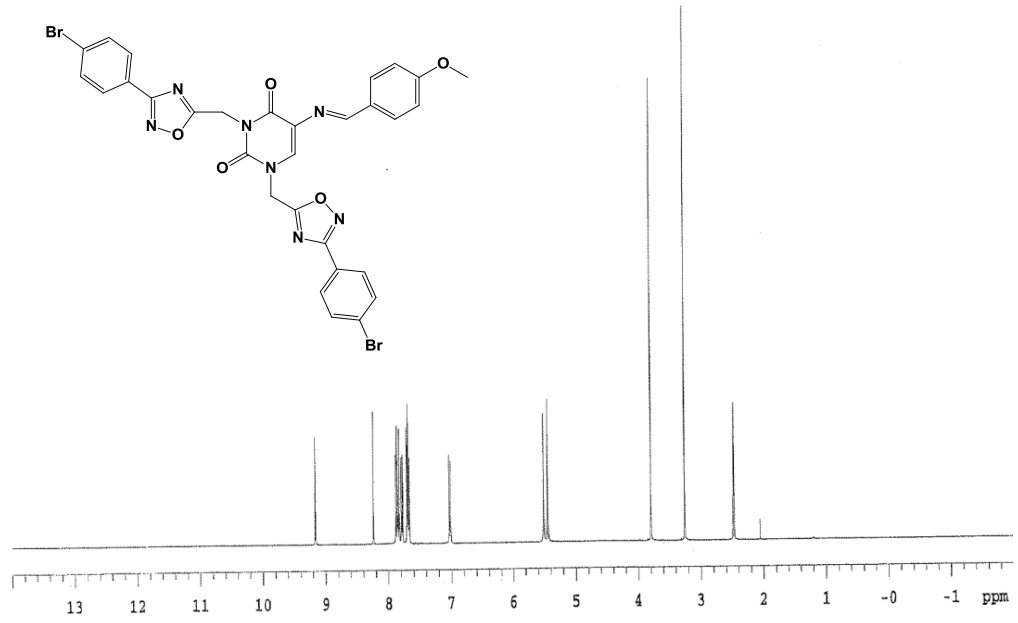

Figure 4.167. ^{1}H NMR spectrum of compound **63c.**

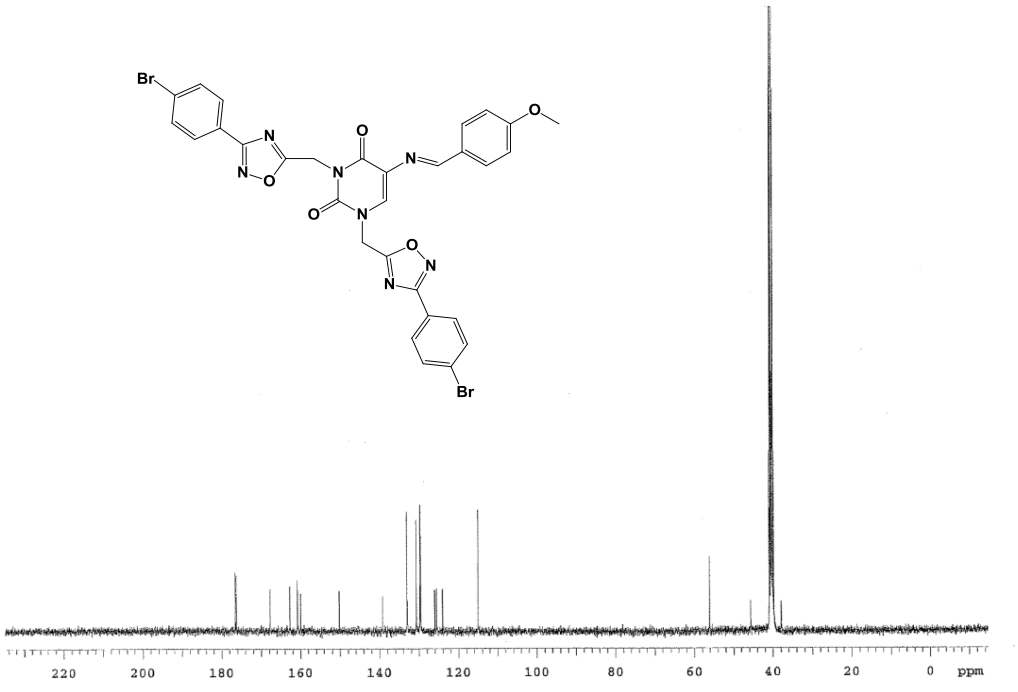

Figure 4.168. ^{13}C NMR spectrum of compound **63c.**

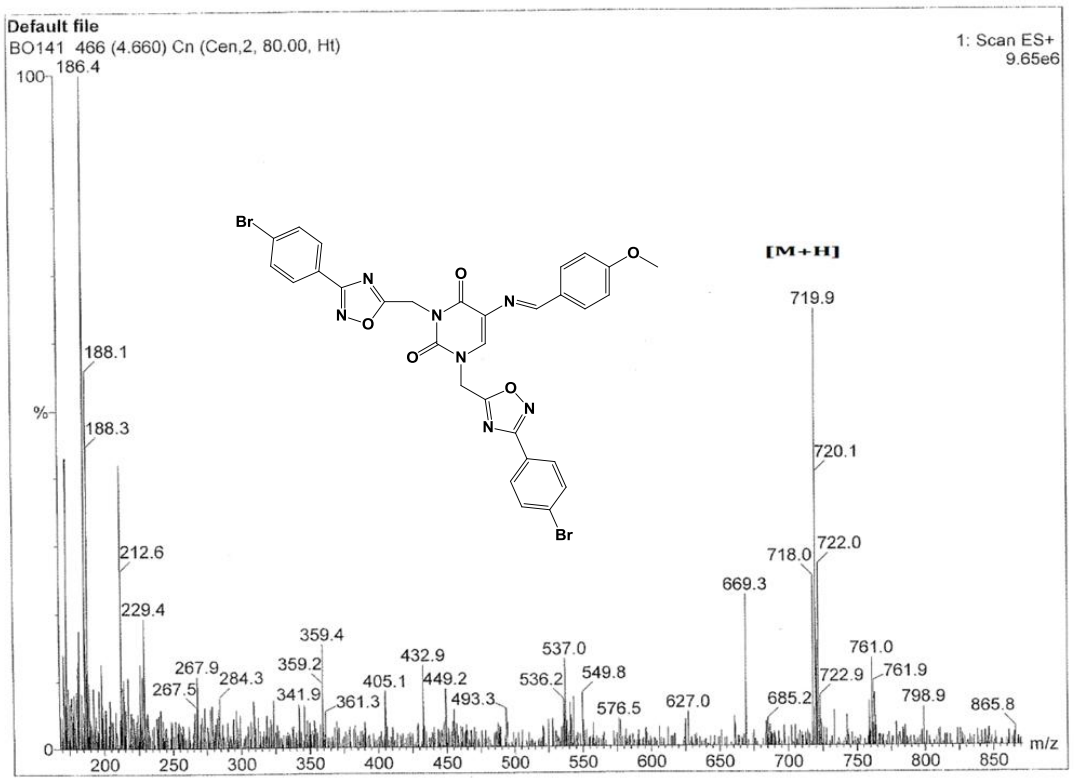

Figure 4.169. LC-MS spectrum of compound **63c.**

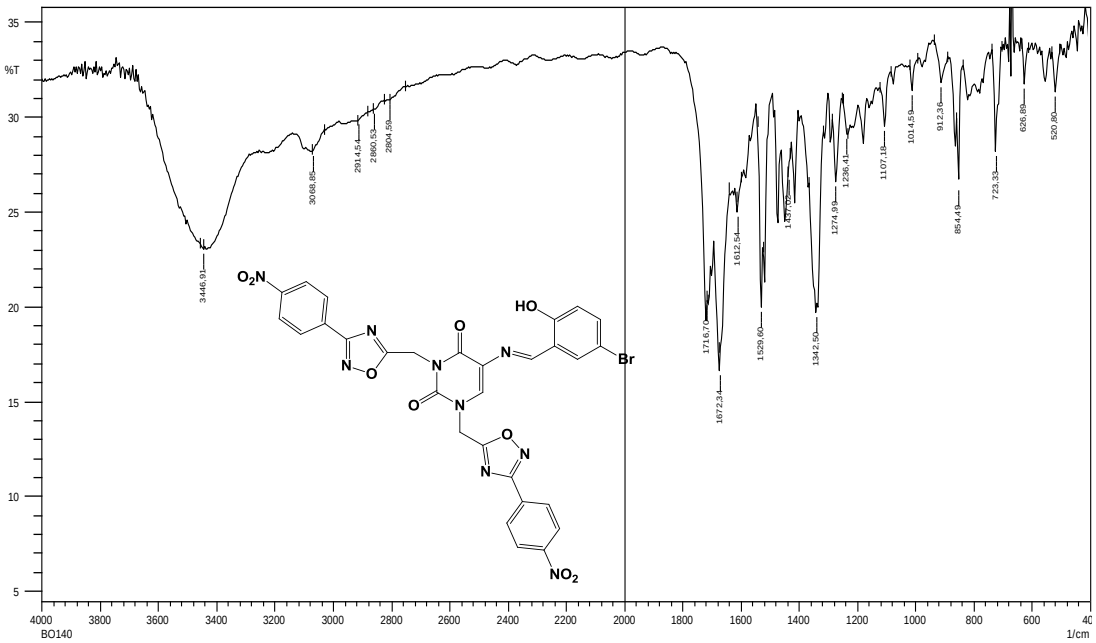

Figure 4.170. IR spectrum of compound **63d.**

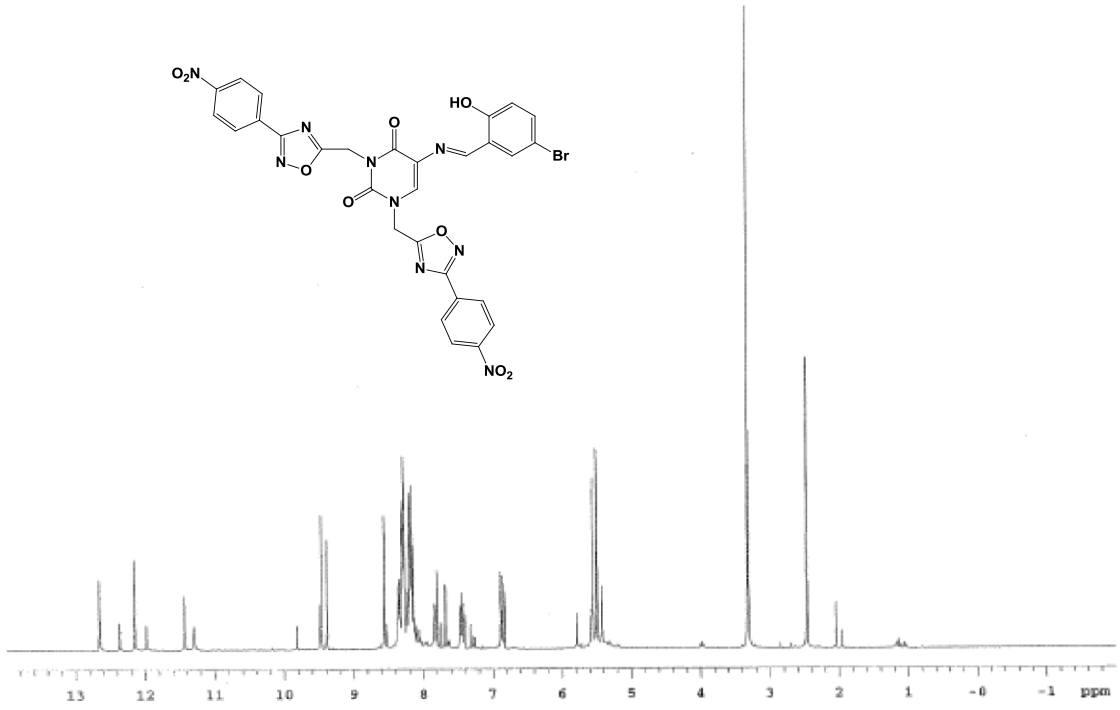

Figure 4.171. ^{1}H NMR spectrum of compound **63d.**

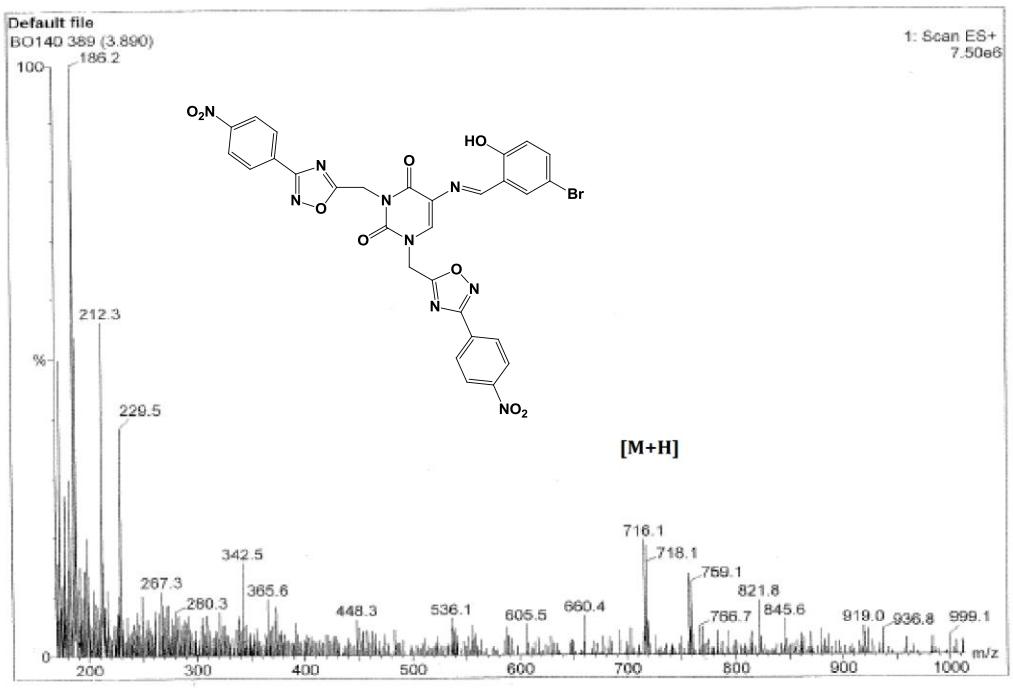

Figure 4.172. LC-MS spectrum of compound **63d.**

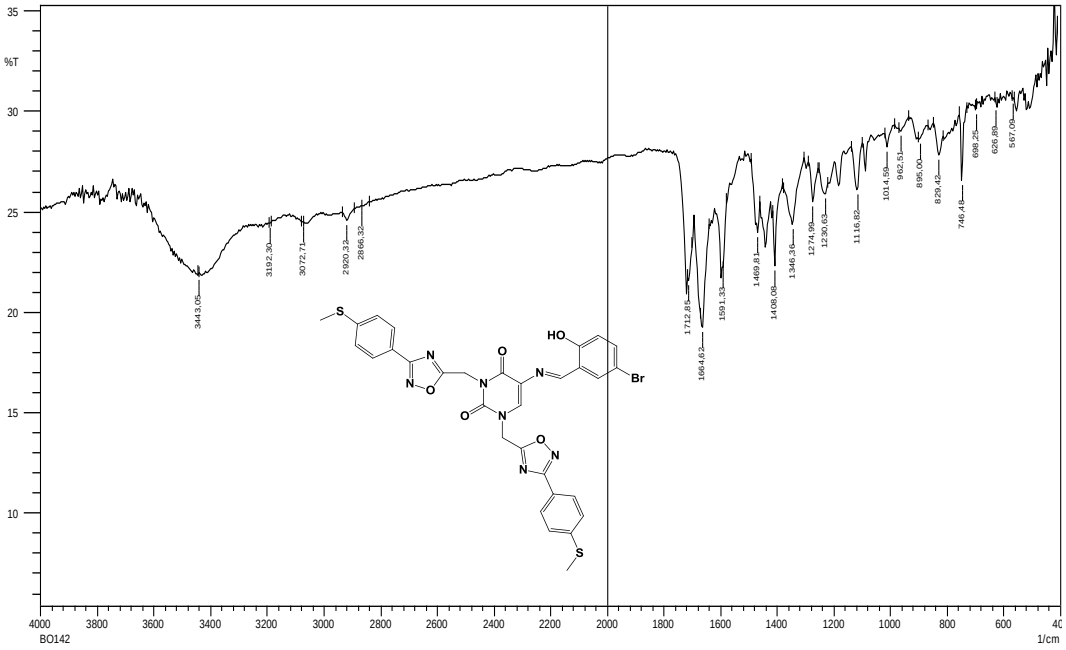

Figure 4.173. IR spectrum of compound **63e** .

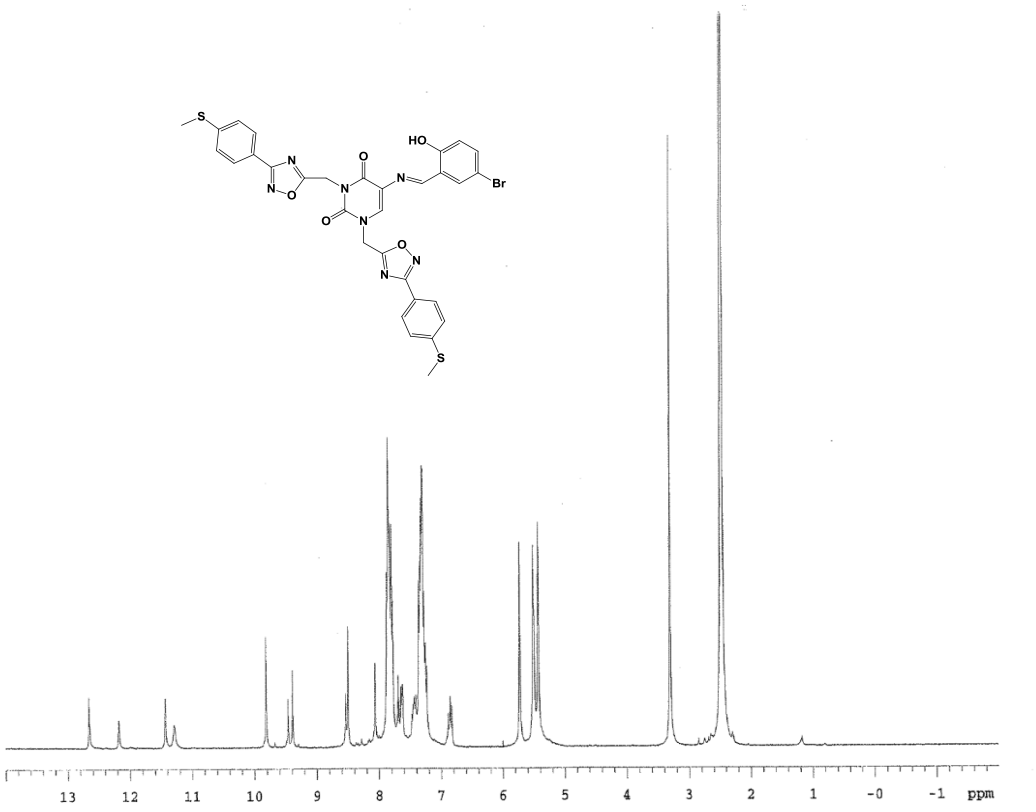

Figure 4.174.[1]H NMR spectrum of compound **63e.**

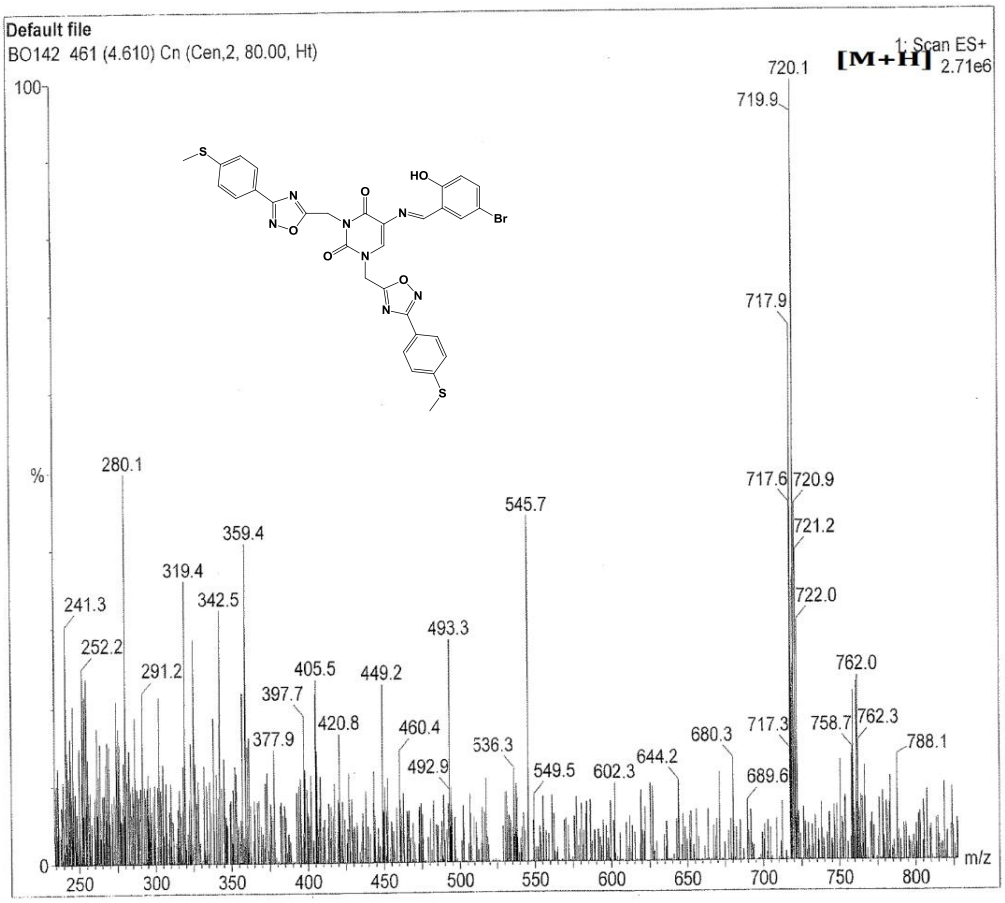

Figure 4.175. LC-MS spectrum of compound **63e.**