

**SYNTHESIS AND CYCLOADDITION
REACTIONS OF SOME NOVEL AZIDES
BEARING 1,2,4-OXADIAZOLE RING**

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JUNE 2010

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REACTIONS OF SOME NOVEL AZIDES
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**by
HAMZA KARAKUŞ**

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Approval of the Graduate School of Natural and Applied Science.

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

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ABSTRACT

SYNTHESIS AND CYCLOADDITION REACTIONS OF SOME NOVEL AZIDES BEARING 1,2,4-OXADIAZOLE RING

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In this work, in the first step, we aimed to obtain a number of 5-chloromethyl 1,2,4-oxadiazoles starting from *p*-substituted aromatic monoamidoximes. Then, 5-azidomethyl 3-aryl substituted 1,2,4-oxadiazoles were easily prepared from the reaction of chloromethyl 1,2,4-oxadiazoles and sodium azide in DMSO. To our best knowledge of literature survey, both a great number of chloromethyl oxadiazoles and all the azidomethyl oxadiazoles are novel heterocyclic compounds not known yet. As the major part of this work, 1,3-dipolar cycloaddition reactions of these novel 3-aryl substituted 5-azidomethyl 1,2,4-oxadiazoles with the dipolarophiles like *N*-phenyl maleimide, phenyl vinyl sulfone and some bicyclic olefinic dipolarophiles which were easily synthesized from furan-maleic anhydride and furan-*N*-phenyl maleimide reactions were performed to afford bicyclic and tricyclic

cycloaddition products which might be expected to exhibit biological activity. These cycloadducts are the members of substituted 1,6-dihydropyrrolo-[1,2,3] triazoles, substituted-4-phenylsulfonyl-4,5-dihydro-[1,2,3] triazoles and 8,8a-hexahydro-4,8-epoxyfuro-[1,2,3] triazoles. The structures of all the cycloadducts were elucidated by means of IR, NMR (^1H , ^{13}C), MASS spectra and physical characteristics (melting points and R_f values).

Key words: amidoxime, oxadiazole, azide, triazole, pyrrole, spectroscopy

ÖZET

1,2,4-OKSADİAZOL HALKASI İÇEREN BAZI YENİ AZİDLERİN SENTEZİ VE HALKA KATILMA TEPKİMLERİ

Karakuş, Hamza
Yüksek Lisans Tezi, Kimya Bölümü
Tez Danışmanı: Prof. Dr. Yaşar Dürüst

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Bu çalışmada, birinci adımda p-substitue aromatic monoamidoksimlerden başlayarak bir seri 3-aril substitute 5-klorometil 1,2,4-oksadiazol elde etmeyi hedefledik. Daha sonra 5-azidometil 3-aril substitute 1,2,4-oksadiazoller klorometil 1,2,4-oksadiazoller ve DMSO içinde sodyum azidden kolayca sentez edildiler. Literatür bilgimiz dahilinde, hem klorometil oksadiazollerin büyük çoğunluğu hem de tüm azidometil oksadiazoller henüz bilinmeyen heterohalkalı bileşiklerdir. Bu çalışmanın esas kısmı olarak, bu yeni 3-aril substitute 5-azidometil 1,2,4-oksadiazollerin *N*-fenil maleimid, fenil vinil sulfon gibi dipolarsevenler ve furan-maleik anhidrid and furan-*N*-fenil maleimid tepkimelerinden kolayca elde edilen bazı bisiklik olefinik dipolar dipolar sevenler ile 1,3-dipolar halkalı katılma tepkimelerinin gerçekleştirilmesi ve

biyolojik aktiflik göstermeleri beklenen bisiklik ve trisiklik katılma ürünlerinin elde edilmesidir. Bu katılma ürünleri substitue 1,6-dihidropirrol-1,2,3 triazol, substitue-4-fenilsulfonil-4,5-dihidro-1,2,3 triazol and 8,8a-hekzahidro-4,8-epoksifuro-1,2,3 triazol bileşik sınıfı üyeleridir. Tüm katılma ürünlerin yapıları IR, NMR (^1H , ^{13}C), kütle spektrumları ve fiziksel sabitler (erime noktası, R_f değerleri) ile aydınlatılmıştır.

Anahtar Kelimeler: amidoksim, oksadiazol, azid, triazol, spektroskopi

to my family

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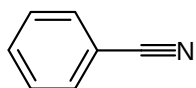
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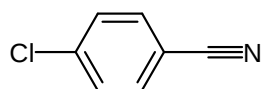
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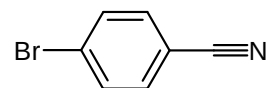
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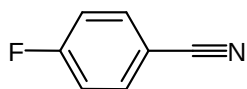
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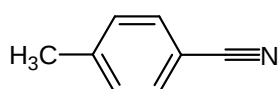
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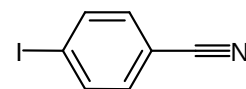
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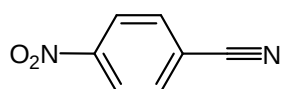
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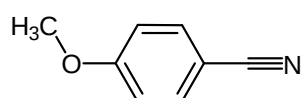
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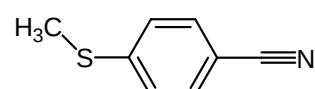
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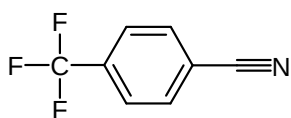
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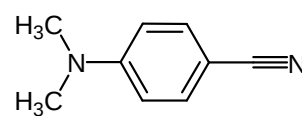
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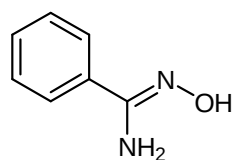
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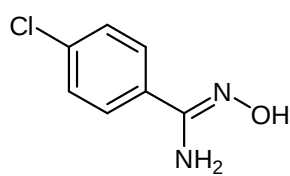
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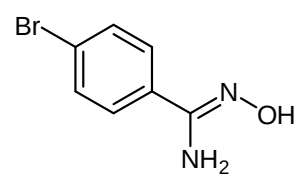
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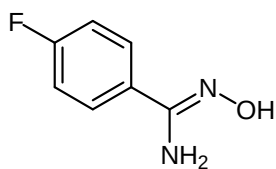
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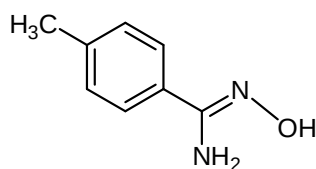
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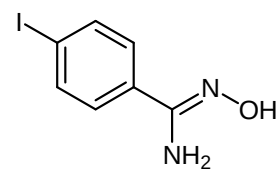
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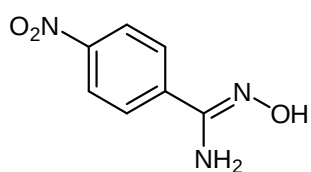
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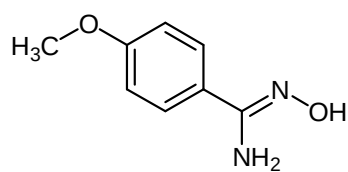
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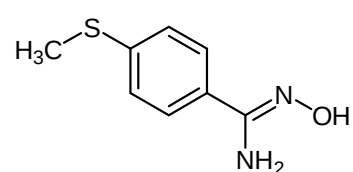
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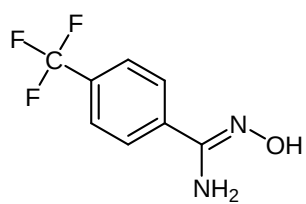
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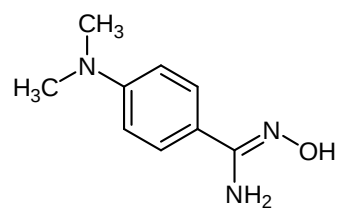
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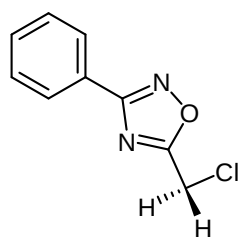
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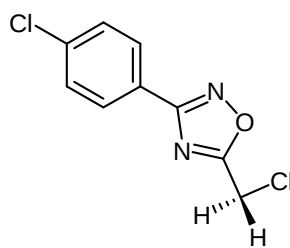
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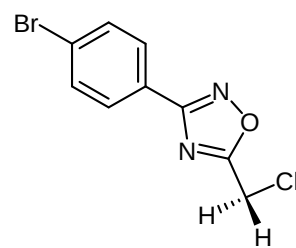
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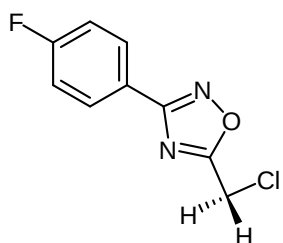
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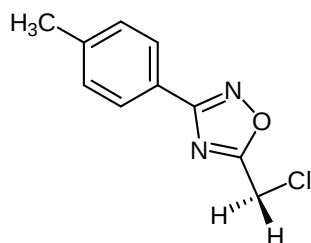
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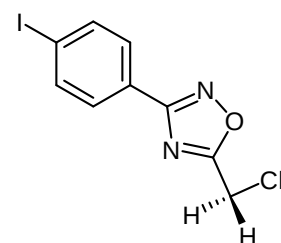
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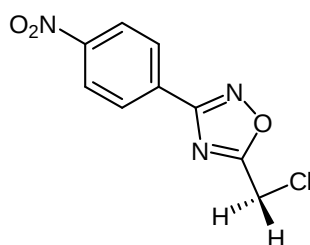
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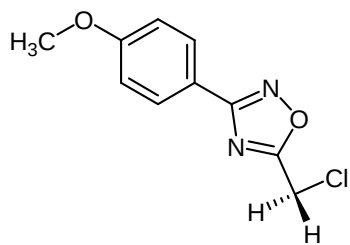
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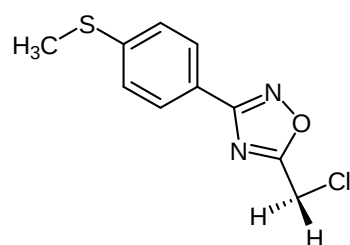
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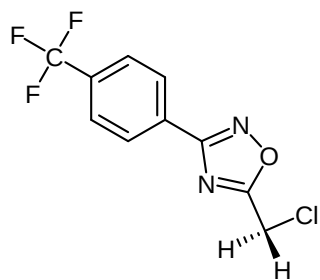
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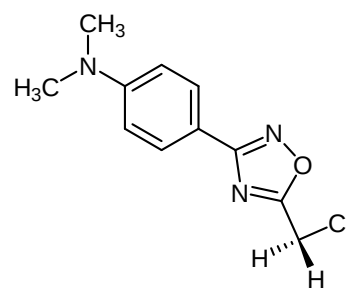
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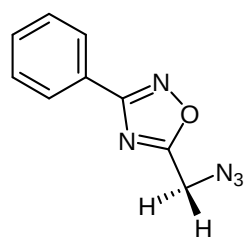
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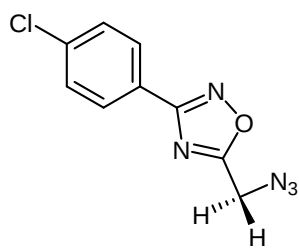
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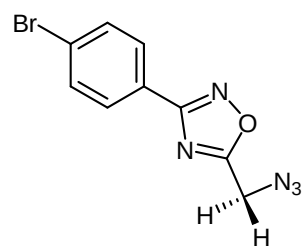
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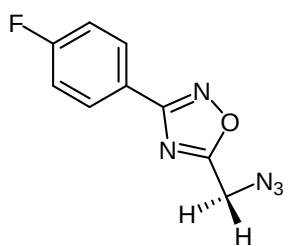
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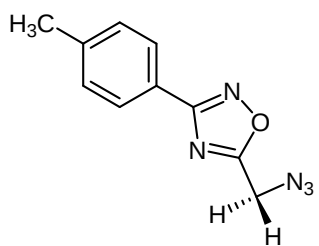
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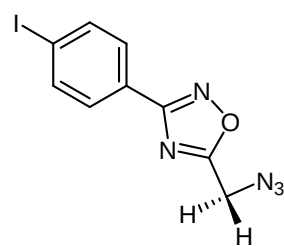
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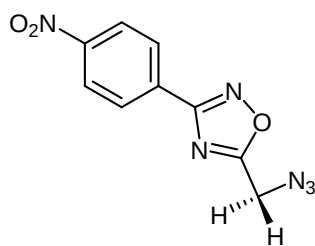
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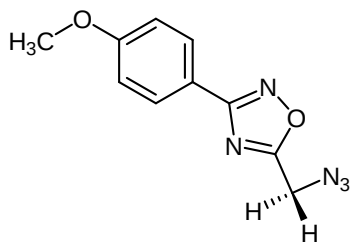
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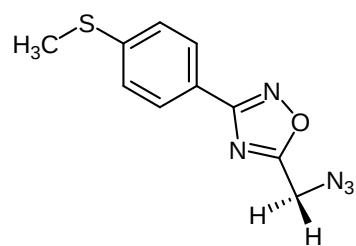
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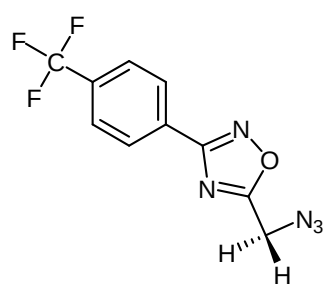
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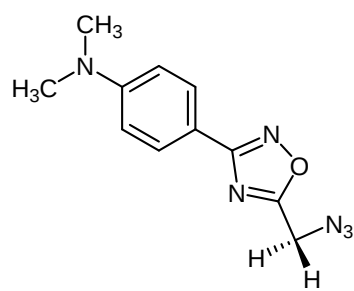
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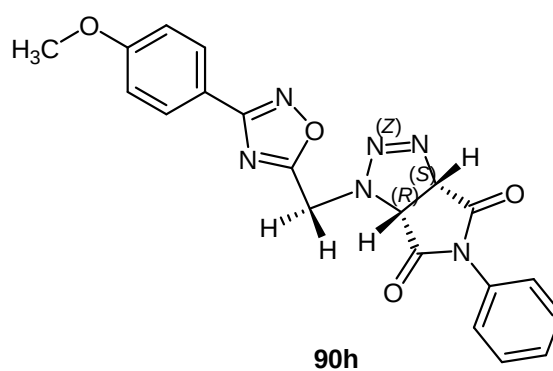
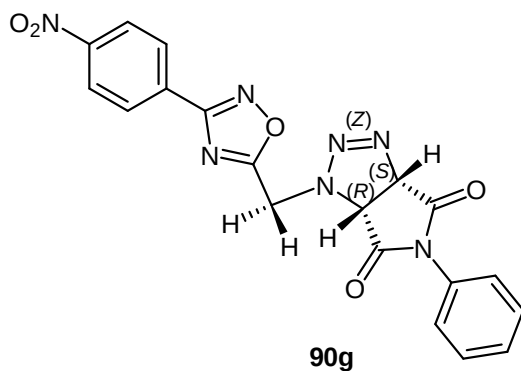
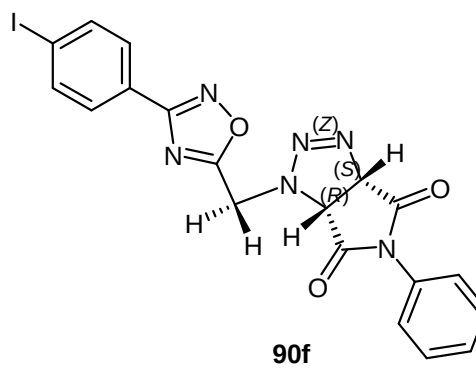
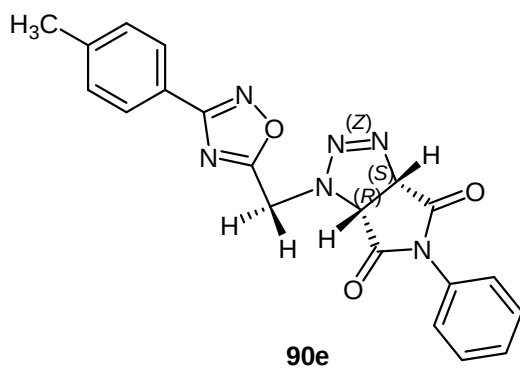
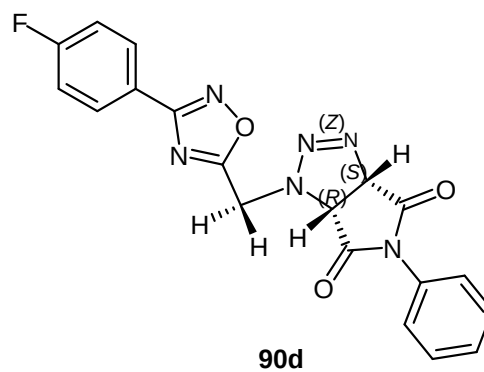
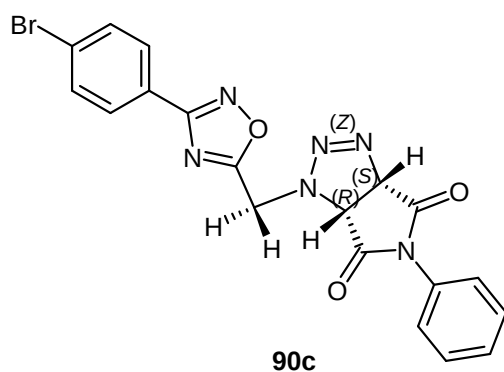
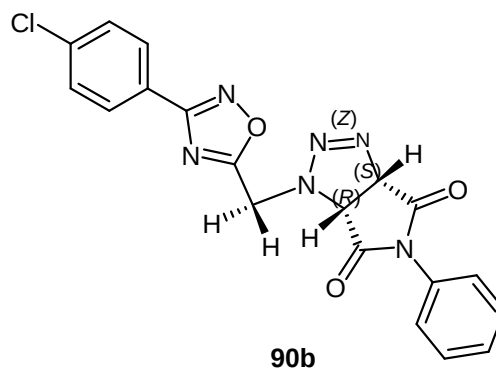
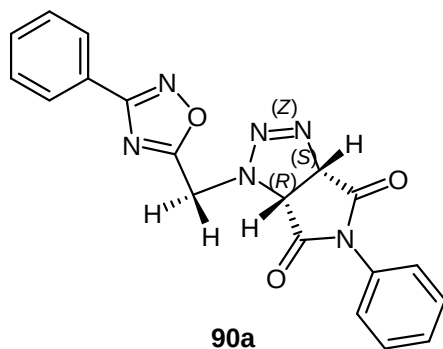
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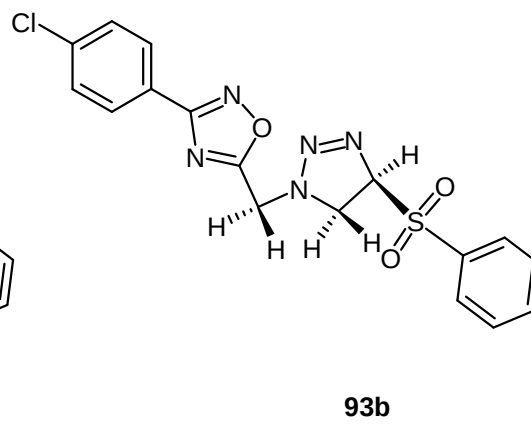
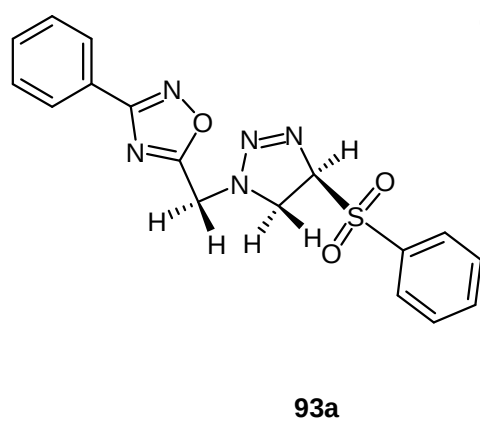
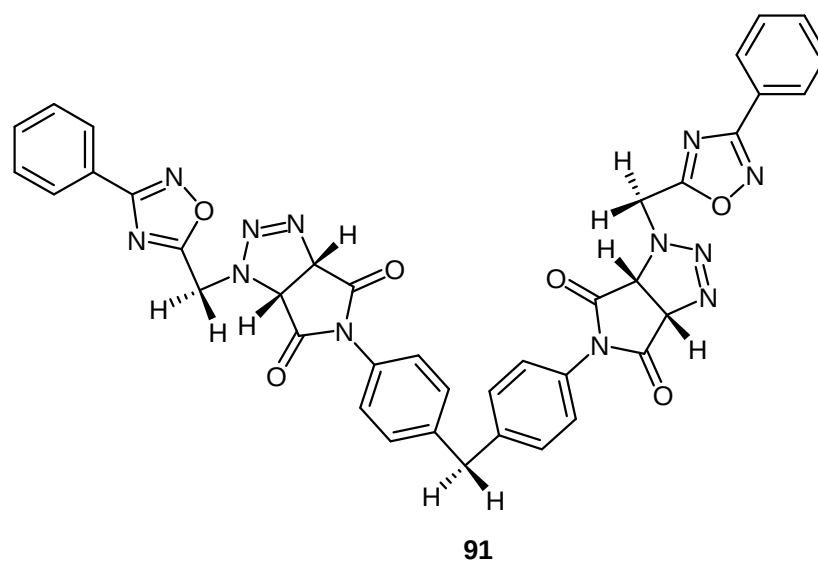
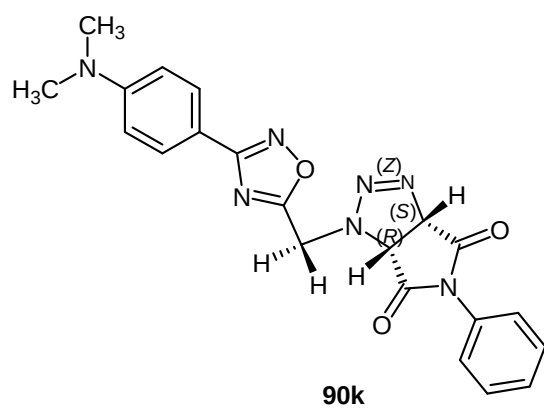
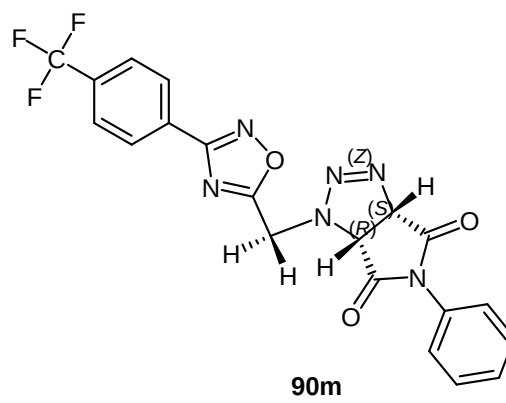
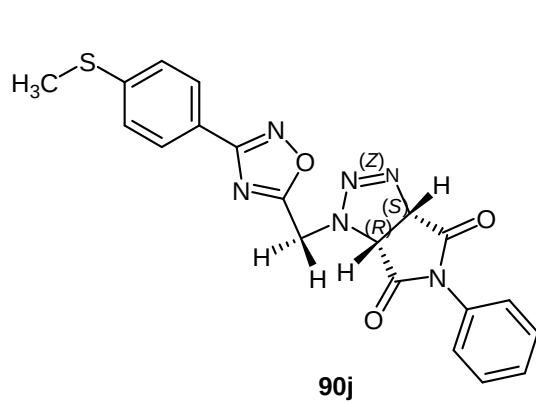


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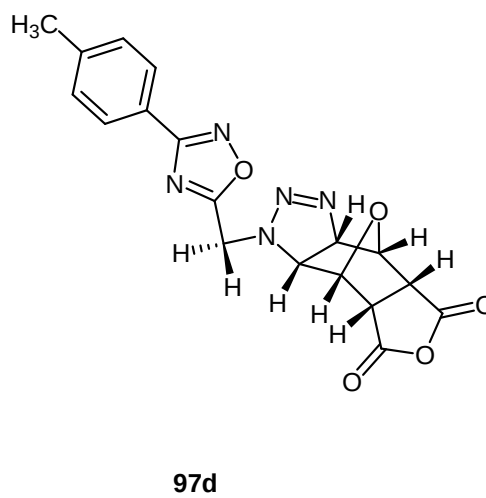
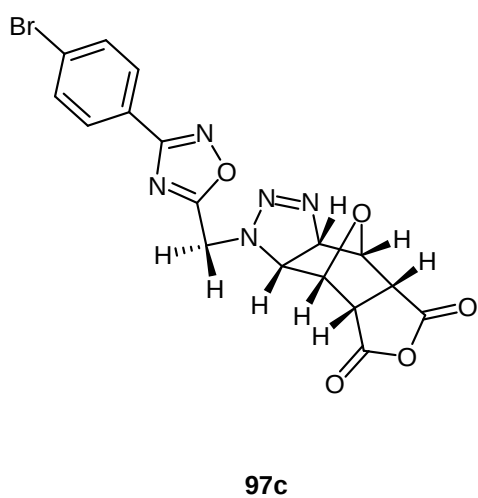
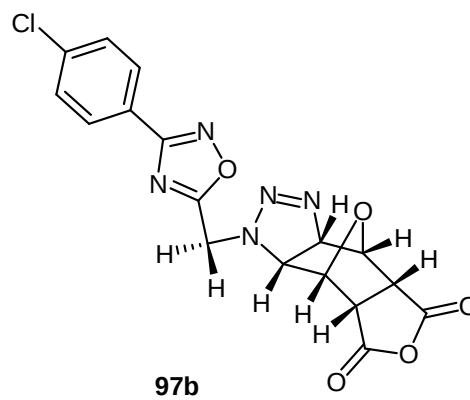
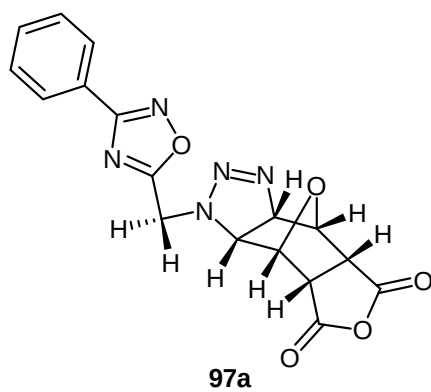
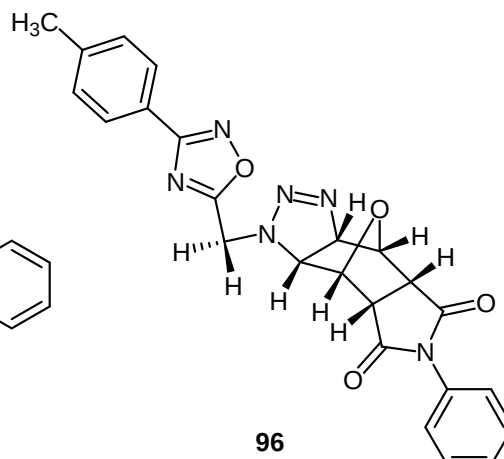
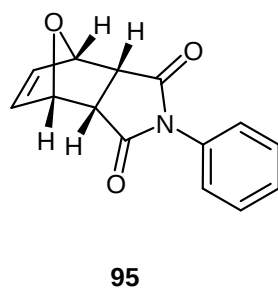
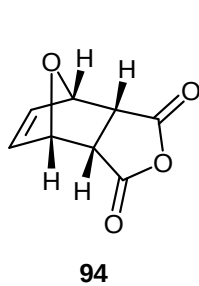
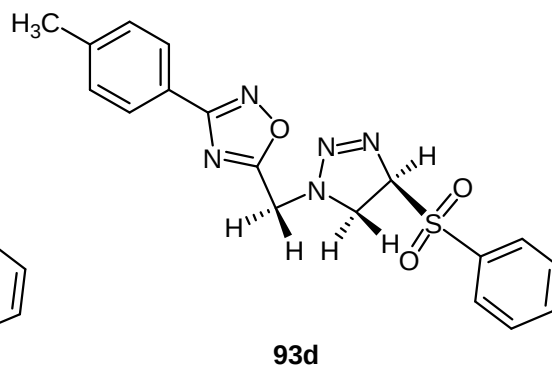
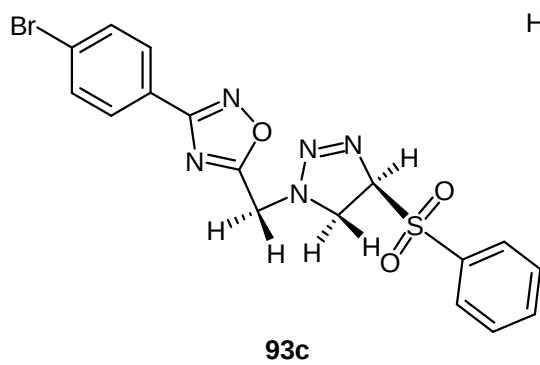


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ABBREVIATIONS

a.q.	Aqueous
cm	Centimetre
DCC	Dicyclohexylcarbodiimide
dd	Doublet of doublets (NMR)
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
Et ₃ N	Triethylamine
EtOAc	Ethyl acetate
FMO	Frontier molecular orbital
Hz	Hertz
IR	Infrared spectroscopy
J	Coupling constant (NMR)
KBr	Potassium bromide
LC-MS	Liquid Chromatography-Mass Spectroscopy
min	Minutes
m.p.	Melting point
MS	Mass
MW	Microwave
NMR	Nuclear magnetic resonance
ppm	Parts per million (NMR)
R _f	Retention Factor

r.t.	Room temperature
TLC	Thin Layer Chromatography
TOF	Time of Flight Instrument

CHAPTER 1

INTRODUCTION

1.1. AMIDOXIMES

Amidoximes are the class of compounds bearing both hydroxyimino and an amino function at the same carbon atom and have been used for the synthesis of a variety of valuable compounds.

In 1873, Lossen and Schifferdecher [1] prepared the first amidoxime **1** by reacting hydrogen cyanide with hydroxylamine. The compound is called as “isuretin” as shown below (Figure 1.1).

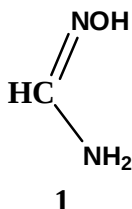
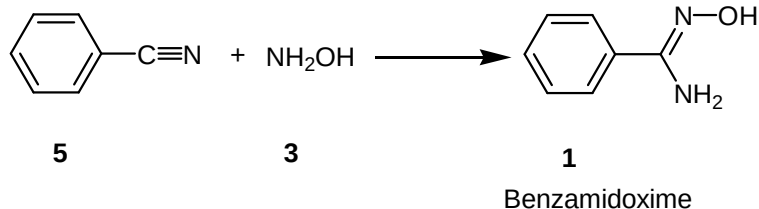


Figure 1. 1 Structure of isuretin

The name “amidoxime” was first used by Tiemann [2] who prepared two related compounds mandelamidoxime **4** and benzamidoxime **6** in 1884 by reacting hydroxylamine with benzaldehyde and benzonitrile respectively (Scheme 1.1).



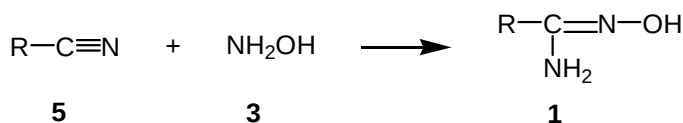
Scheme 1. 1 Mandelamidoxime and benzamidoxime

During the last years more amidoximes have been tested for pharmacological properties and have been found to be bactericidal and fungicidal [3], local anaesthetics and fibrinogen receptor antagonists [4].

1.1.1. Synthesis of Amidoximes

1.1.1.1. Action of Hydroxylamine on Nitriles

The preparation of amidoximes from nitriles **5** by the action of hydroxylamine **3** was first studied by Tiemann and Krüger (Scheme 1.2) [2].

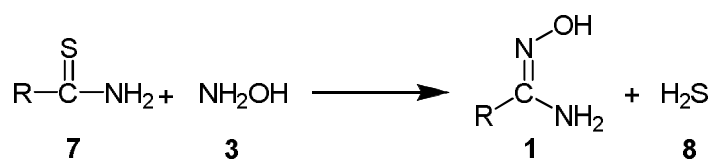


Scheme 1. 2 Action of hydroxylamine on nitriles

Addition of the equivalent amount of nitrile in ethanol to hydroxylamine whose hydrochloride part was liberated by sodium carbonate yields amidoximes at 60-80°C during a few hours. Amidoximes with highest yields were obtained when a 15% excess of a solution of hydroxylamine in butanol was used [5].

1.1.1.2. Action of Hydroxylamine on Amides and Thioamides

The procedure for the synthesis of amidoximes from amides and thioamides **7** is same as from nitriles. By this method some aromatic amidoximes have been prepared (Scheme 1.3) [6,7,8,9].

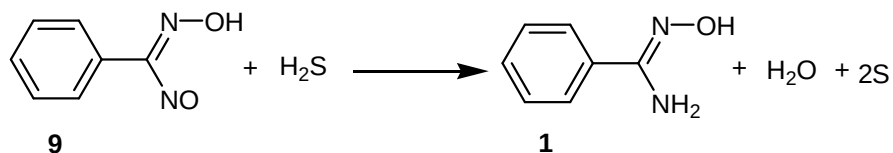


Scheme 1. 3 Action of hydroxylamine on thioamides

The preparation of amidoximes from amides and hydroxylamine has only been reported by Schiff [10] and Durio and Dugone [11].

1.1.1.3. Reduction of Nitrosolic Acids

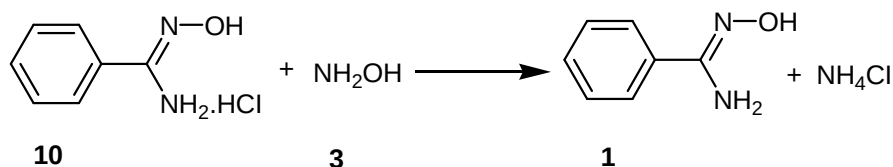
The reduction of nitrosolic and nitrolic acids **9** with hydrogen sulfide and hydrogen gases respectively gives amidoximes. Wieland and Bauer [12] prepared benzamidoxime by reducing benzonitrosolic acid with hydrogen sulphide (Scheme 1.4).



Scheme 1. 4 Reduction of Nitrosolic Acids by Hydrogen Sulfide

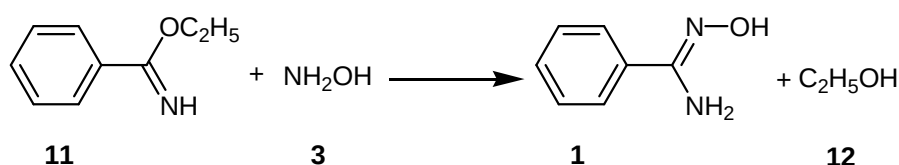
1.1.1.4. Action of Hydroxylamine on Amidine Hydrochlorides and Iminoethers

Action of hydroxylamine on amidine hydrochlorides and iminoethers was first studied by Pinner [13] who synthesized benzamidoxime by treating benzamidine hydrochloride **10** with hydroxylamine **3** (Scheme 1.5).



Scheme 1. 5 Synthesis of Benzamidoxime

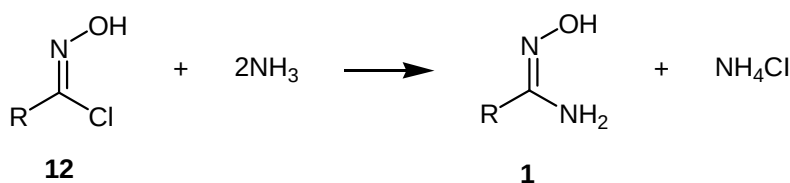
Benzamidoxime was also prepared by the action of hydroxylamine **3** on ethyl iminobenzoate **11** by Pinner [13] and Lossen [14] (Scheme 1.6).



Scheme 1. 6 Synthesis of Benzamidoxime

1.1.1.5. Action of Ammonia on Hydroximic Acid Chlorides

Chloroximes are formed by direct chlorination of aldoximes. The reactions of these chlorides with ammonia yield amidoximes. This procedure was firstly used by Werner (Scheme 1.7) [15,16].



Scheme 1. 7 Action of Ammonia on Chloroxime

1.1.2. Physical Properties of Amidoximes

The amidoximes are colorless crystalline compounds which can be decomposed by heating over their melting points. Aryl amidoximes which are insoluble in water and soluble in alcohols and some organic solvents are more stable than aliphatic amidoximes. The first member of aliphatic series is soluble in water but their solubilities decrease with increasing molecular weight. The amidoximes are O-H acids, not N-H acids as is brought out by the appreciably higher pK_{HA} of *O*-methyl derivative of benzamidoxime whose pK_{HA} value is 26.0. The pK_{HA} value of benzamidoxime is 23.0 [17]. Tautomerism, conformation, and configuration are important characteristics associated with amidoximes. Considerable work has been done since 1960 in determining these properties for simple amidoximes such as benzamidoximes, formamidoxime, and *N,N*-dimethylacetamidoxime. These studies indicate that there is a major configurational difference between unsubstituted amidoximes (**I**) or their *N*-alkyl analogues (**II**) and the *N,N*-dialkyl derivatives (**III**) (Figure 1.2).

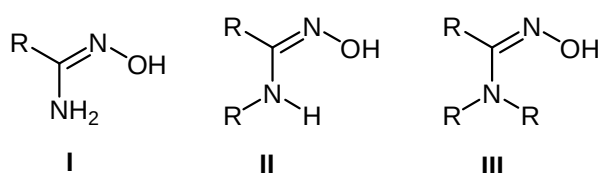


Figure 1. 2 Amidoximes

Infrared and nuclear magnetic resonance spectroscopy established that amidoximes and their *O*-acyl derivatives exist in solutions in the amino oxime form [18]. The infrared spectra of amidoximes shows two well defined absorption bands: the first is a doublet at $3484\text{--}3412\text{ cm}^{-1}$ and $3378\text{--}3300\text{ cm}^{-1}$, assigned to the two NH_2 stretching modes; the second between 1680 and

1644 cm^{-1} to the C=N stretching. The OH stretching band of the NOH group is very broad and has its maximum at approximately 3125 cm^{-1} .

Tiemann recognized that the amidoximes may be present in two tautomeric forms (Figure 1.3).

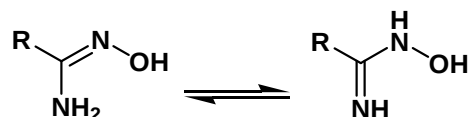


Figure 1. 3 Tautomeric forms of amidoximes

1.2. OXADIAZOLE

Nitrogen-oxygen heterocycles are of synthetic interest because they constitute an important class of natural and non-natural products, many of which exhibit useful biological activities. It is well known that oxadiazole is a heterocyclic nucleus has attracted a wide attention of the chemist in search for the new therapeutic molecules [19].

Oxadiazole is considered to be derived from furan by replacement of two methane (-CH=) group by two pyridine type nitrogen (-N=). There are four possible isomers of oxadiazole (I,II,III,IV) depending on the position of nitrogen atom in the ring and are numbered as shown in (Figure 1.4) [20].

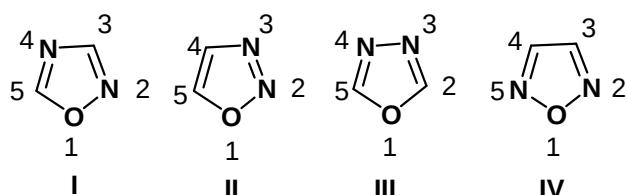


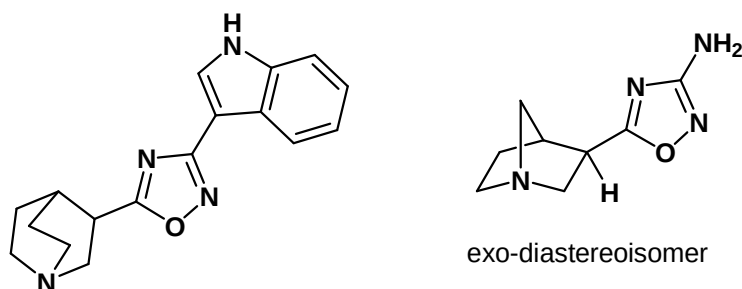
Figure 1. 4 Isomers of oxadiazole

Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom [21]. The replacement of two -CH= groups in furan by two

pyridine type nitrogen (-N=) reduces aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character of conjugated diene. The electrophilic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However the attack of electrophiles occurs at nitrogen, if oxadiazole ring is substituted with electron-releasing groups. Oxadiazole ring is generally resistant to nucleophilic attack. Halogen-substituted oxadiazole, however, undergo nucleophilic substitution with replacement of halogen atom by nucleophiles. Oxadiazole undergo nucleophilic substitution similarly as occurring at an aliphatic sp^2 carbon atom [22].

1.2.1. 1,2,4-Oxadiazole

1,2,4-Oxadiazoles are an important class of ring systems containing one O and two N atoms [23]. Furthermore, 1,2,4-oxadiazoles are well-known nitrogen compounds and sizeable work has been done in this area since their first preparation in 1884 [24]. 1,2,4-Oxadiazoles have often been used as bioisosteres of esters and amides [25] and as dipeptide mimetics [26] in a number of pharmacologically important molecules, because of its electronic properties. Its derivatives can be found in a vast number of compounds exerting biological activity such as ligands of benzodiazepine receptors, [27,28] anti-inflammatory agents, [29,30,31] antiviral agents, [32] inhibitors of protein tyrosine phosphatases, [33] agonists of muscarinic receptors, [34,35] antagonists of histamine HT_3 - receptors, [36] (Figure 1.5).



1. Potent 5-HT₃ antagonist 2. Highly efficacious muscarinic agonist

Figure 1. 5 Examples of biologically active 1,2,4-oxadiazoles

The basicity of the 1,2,4-oxadiazole ring, a fundamental property that governs many aspects of its chemical reactivity and is an essential factor influencing practical use of compounds. 1,2,4-oxadiazoles are as weak organic bases. Thus, the ability of these heterocycles to form azolium ('quaternized') salts has been examined and it has been suggested that the 'quaternization' of 5-phenyl-1,2,4-oxadiazoles takes place at N(2) predominantly because of steric reasons [37]. Tautomerism of some functionally substituted 1,2,4-oxadiazoles involving the ring N-atoms in ground and excited states has also been reported [38]. An attempt to determine pK_{BH}^+ values for 3-methyl- and 3,5-dimethyl-1,2,4-oxadiazoles has been undertaken by Brown and Ghosh back in 1969 [39]. However, this effort has failed because in both cases protonation of the heterocycle produced too little spectral change. In the present work, pK_{BH}^+ values of representative 3,5-disubstituted 1,2,4-oxadiazoles (**1** – **4**) (Scheme 2.1) have been determined experimentally in aqueous H₂SO₄ using ¹H-NMR and UV spectroscopy. Using substituent additivity increments, the basicity constant has been estimated for the unsubstituted parent heterocycle (**5**). The 1,2,4-oxadiazole ring features three potential protonation sites: the O-atom and two pyridine-like N-

atoms, N(2) and N(4). Protonation at the O-atom is unfavorable because of the low stability of the resulting OH^+ cation [40,41,42]. In contrast, neither of the two non-equivalent ring N-atoms can be *a priori* ruled out as a protonation site. Thus, protonation of neutral 1,2,4-oxadiazoles (**1** – **5**) could lead to the formation of two isomeric species, azolium cations (**1a** – **5a**) and (**1b** – **5b**), respectively (Figure 1.6).

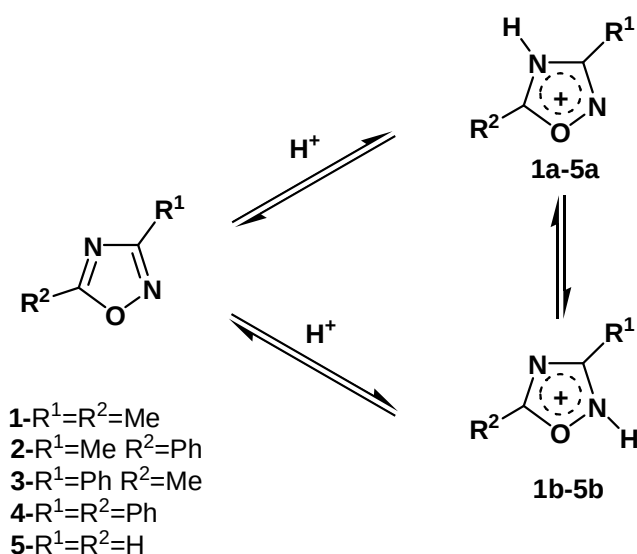


Figure 1. 6 Protonation of 1,2,4-Oxadiazoles

N(2) has a less-favorable protonation site than the distal N(4) because of being proximal to the electronegative O-atom. This inference is supported by published ^{15}N -NMR data [43] and by the fact that isoxazole (**6**), a model for protonation at N(2), is a substantially weaker base than oxazole (**7**), a model for protonation at N(4). The difference in basicity between these two heterocycles amounts to more than 3.5 units in solution (pK_{BH}^+ values of -2.97 and 0.80, respectively) (Figure 1.7).

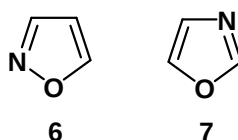


Figure 1. 7 Structure of isoxazole and oxazole

Basicity constants of a series of 1,2,4-oxadiazoles which has determined experimentally has positioned these compounds as weak bases. Protonation of the 1,2,4-oxadiazole ring occurs predominantly at N(4). Ring substituents can have a pronounced effect not only on the basicity constant but also on the regioselectivity of protonation [44].

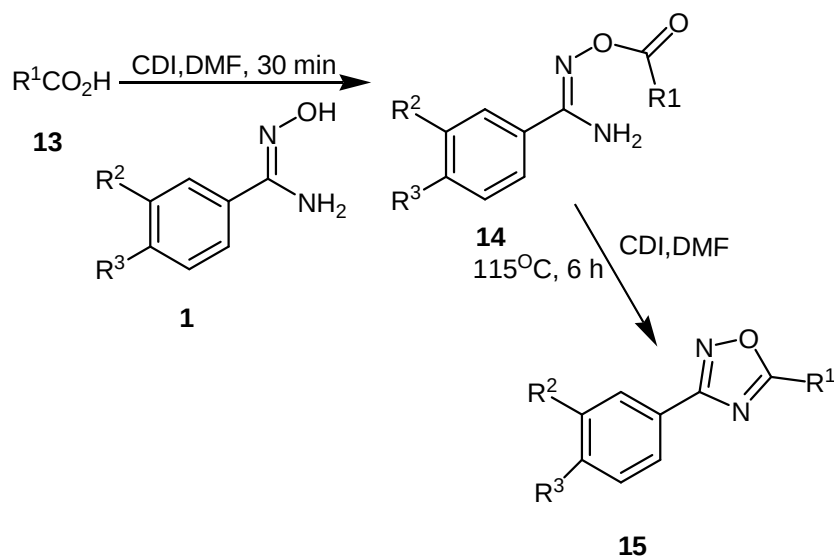
1.2.2. Synthesis of 1,2,4-Oxadiazoles

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

The well-known reactions of amidoximes, which have been thoroughly studied since 1920–1930 are those involving their acylation. The majority of publications devoted to the chemistry of amidoximes refer to the synthesis of O-acylated amidoximes and 1,2,4-oxadiazoles, which are among the most readily accessible heterocycles in recent years. The most common method for synthesizing 1,2,4-oxadiazoles involves O-acylation of amidoximes followed by cyclodehydration. Acyl chlorides, anhydrides, esters, fluorides, and trichloroalkanes are commonly used as acylating agents [45]. Carboxylic acids in the presence of coupling reagents like dicyclohexylcarbodiimide (DCC), 1,1'-carbonyldiimidazole (CDI), or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) are also employed to achieve the same procedure [46].

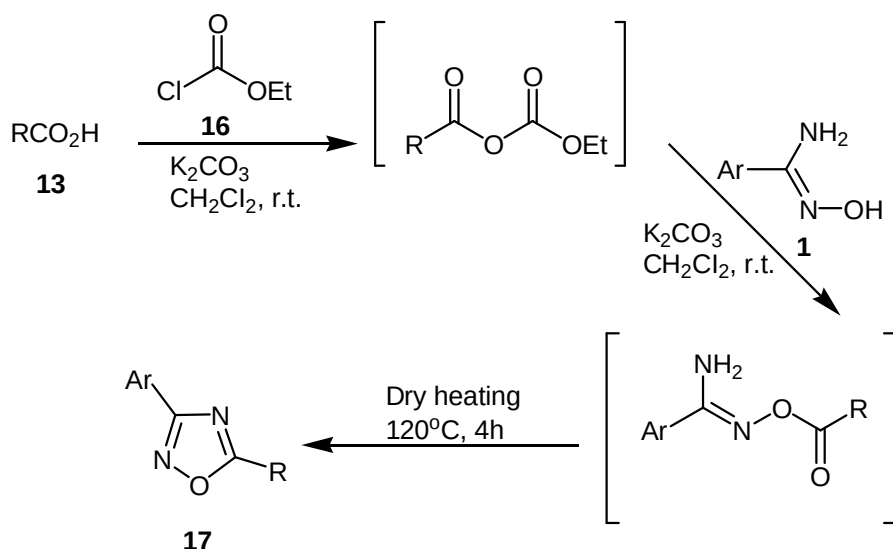
The general approach to parallel solution-phase synthesis of 1,2,4-oxadiazoles is provided in (Scheme 2.2). Carboxylic acids **13** were

activated with CDI in DMF at room temperature and treated with readily available benzamidoximes **1** in DMF (Scheme 1.8) [47].



Scheme 1. 8 Parallel Synthesis of 1,2,4-Oxadiazole using CDI Activation

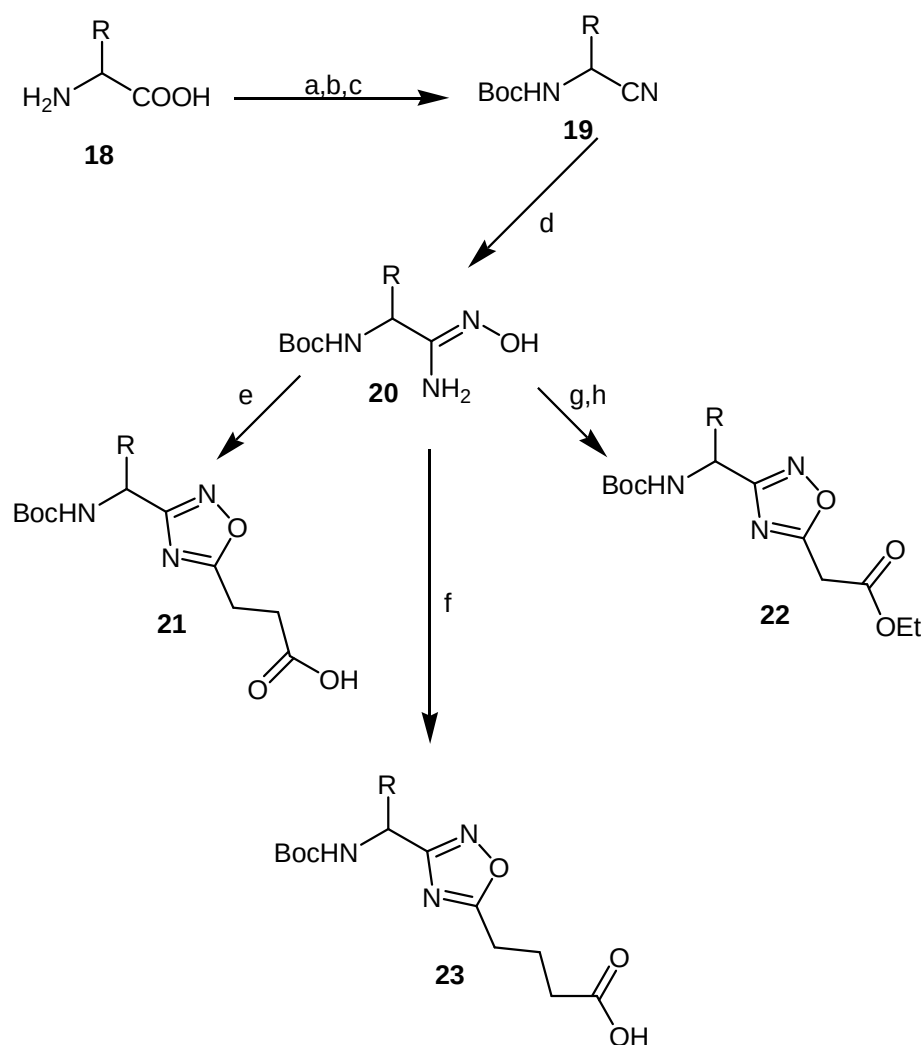
Synthesis of some 1,2,4-oxadiazoles from carboxylic acids **13** and arylamidoximes **1** in the presence of ethyl chloroformate **16** as a coupling agent (Scheme 1.9) [48].



Scheme 1. 9 Synthesis of 1,2,4-Oxadiazole using Acyl chloride

1,2,4-oxadiazole compounds which contain a protected amine and a carboxyl or an ester group have been synthesized. The synthetic route is simple and

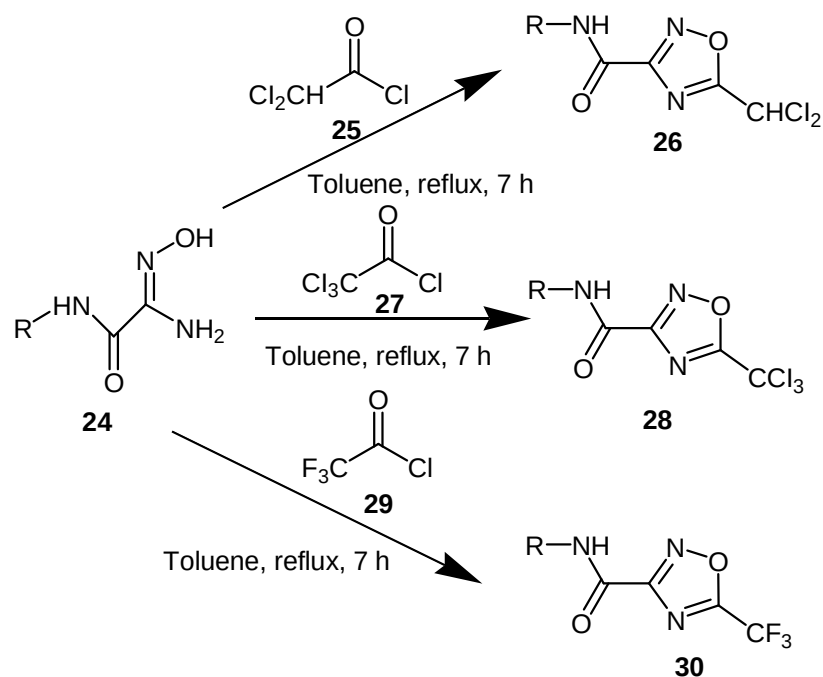
mild conditions are used so that the chirality of the starting amino acids is retained (Scheme 1.10) [49].



Reagents and conditions: (a) (Boc)₂O, NaOH, dioxane/water, 0°C; (b) ethyl chloroformate, Et₃N, CH₂Cl₂, -10°C, NH₃(g); (c) cyanuric chloride, DMF, rt; (d) NH₂OH x HCl, Et₃N, EtOH, reflux, 20 h; (e) succinic acid anhydride, DMF, pyridine, 110°C, 4 h; (f) glutaric acid anhydride, DMF, pyridine, 4 h; (g) ethyl malonyl chloride, Et₃N, CH₂Cl₂, 0°C; (h) toluene, 120°C, 72 h.

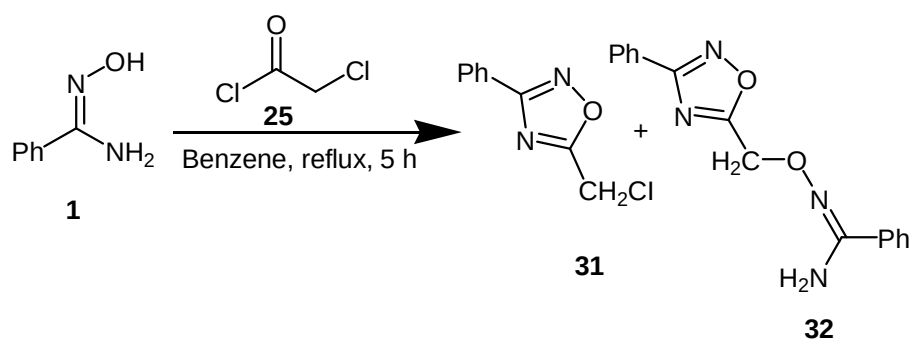
Scheme 1. 10 Different routes to synthesis of 1,2,4-Oxadiazole

Yarovenko et al. isolated 1,2,4-Oxadiazoles as the only products of reactions between carbamoylamidoximes **24** and chloroanhydrides and anhydrides of halogenoacetic acids (Scheme 1.11) [50].



Scheme 1. 11 Synhtesis of 1,2,4-Oxadiazole from Anhydride of halogenoacetic acid

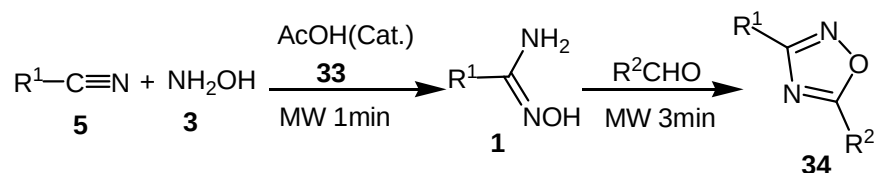
Dürüst *et al.* reported that the reaction of benzamidoxime **1** with chloroacetyl chloride **25** on boiling in benzene led to the formation of 1,2,4-oxadiazole **31** and 3-methyl-4H-1,2,4-oxadiazin-5(6H)-one **32** (Scheme 1.12) [51].



Scheme 1. 12 Synthesis of 1,2,4-oxadiazole from chloroacetyl chloride

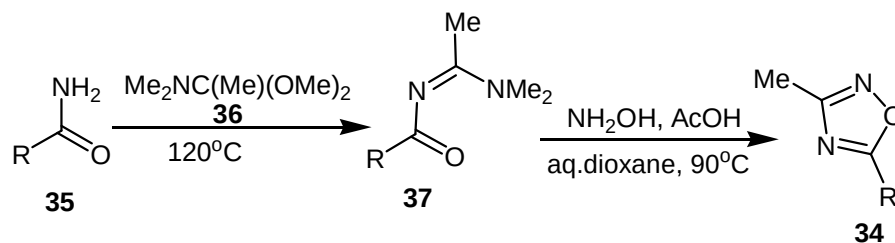
1.2.2.2. Other Methods for Preparation of 1,2,4-Oxadiazole

Adib et al. was developed a novel microwave-assisted one-pot, three-component reaction for the preparation of 1,2,4-Oxadiazole. Using aldehydes **33** instead of carboxylic acid derivatives (Scheme 1.13) [52].



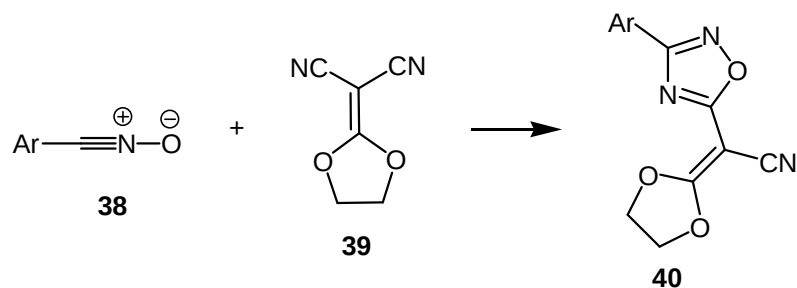
Scheme 1. 13 Synthesis of 1,2,4-Oxadiazole using Aldehyde

Lin and coworkers prepared 1,2,4-oxadiazole from amides *via* acylamidines **37** (Scheme 1.14) [53].



Scheme 1. 14 Producing 1,2,4-Oxadiazole from Amides

Another method was also developed by Neidlein et al., which is producing 1,2,4-oxadiazole *via* the cycloaddition of nitrile oxides **38** to nitriles **39** (Scheme 1.15) [54].



Scheme 1. 15 Formation of 1,2,4-oxadiazole from nitriles

1.3. AZIDES

Azide is the anion with the formula N_3^- . It is the conjugate base of hydrazoic acid which is a compound of nitrogen and hydrogen, HN_3 . It was first isolated in 1890 by Theodor Curtius. It is used primarily for preservation of stock solutions, and as a reagent. Azides are also bifunctional in organic chemistry, RN_3 . Azides are energy-rich and very reactive molecules with many applications. Because, reacting with electron-deficient compounds (electrophiles) at N(1) and with electron-rich compounds (nucleophiles) at N(3) (Figure 1.8) [55].

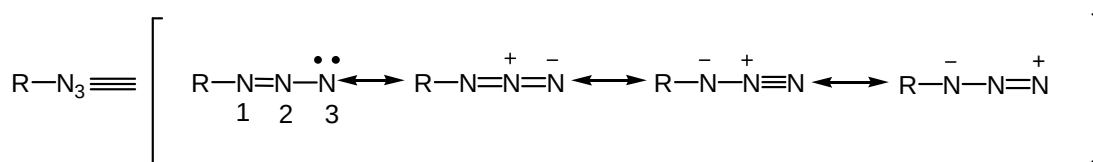


Figure 1. 8 Resonance forms of azides

Azides are very important precursors for the preparation and synthesis of heterocyclic aromatic compounds. Organic azides are capable of a great diversity of organic reactions and are the important components in Click chemistry. First organic azide, phenyl azide, was prepared by Peter Griess in 1864 [56]. The organic azides received considerable attention in the 1950s and 1960s with new applications in the chemistry of the acyl, aryl, and alkyl azides [57-58]. Azides are considered to be important for both industrial and biological applications. Azide derivatives have been used in rubber, polymers, dyes and plastics technology, as well as in pharmaceuticals, pesticides and herbicides developments [59]. Some azides have shown

mutagenic activities. For example, Azidothymidine which is azidonucleosides uses treatment of AIDS (Figure 1.9) [60].

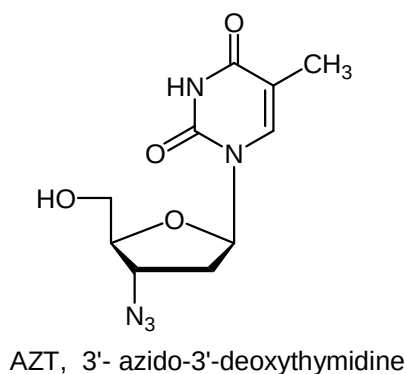


Figure 1. 9 Structure of azidothymidine using treatment of AIDS

Furthermore, other azides such as azapride, azidamfenicol, azidomorphine, and Ro15-4513 have used in pharmaceuticals (Figure 1.10).

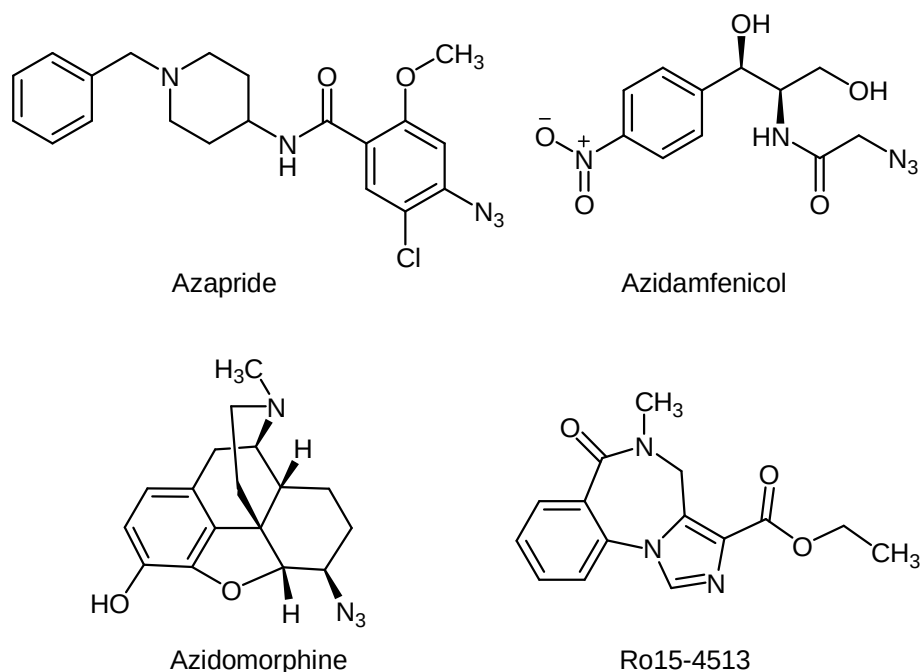
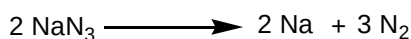


Figure 1. 10 Some of the biologically important azides

Sodium azide, NaN_3 , which is the inorganic azide is used for preparation of most inorganic and organic azides. Sodium azide is found in automobile air bags. It decomposes on heating to give dinitrogen gas which is used to quickly expand the air bag. Sodium azide is also used in airplane escape

chutes [61] (Scheme 2.10). Like sodium azide other inorganic azides such as ammonium azide (NH_4N_3), copper(II) azide ($\text{Cu}(\text{N}_3)_2$), diphenylphosphoryl azide (DPPA), lead(II) azide ($\text{Pb}(\text{N}_3)_2$), silver azide (AgN_3), trimethylsilyl azide ($(\text{CH}_3)_3\text{SiN}_3$) are used as reagent for preparation of organic azides (Scheme 1.16).



Scheme 1. 16 Decompose of sodium azide

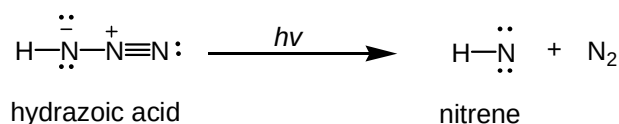
Azides are also used in the synthesis of 1,2,3-triazoles via 1,3-dipolar cycloaddition reactions.

1.3.1. Physical Properties of Azides

The azides which form by metals, fall into two main groups, according to their stabilities; explosive and nonexplosive. The explosive group may be subclassified broadly into the covalent and heavy metal (silver, lead) azides. The nonexplosive group contains the alkali and some of the alkali earth azides, which are all ionic. The ionic azides NaN_3 , KN_3 , etc., are colorless crystalline salts and contain a symmetrical linear N_3^- group. The heavy metal azides are less ionic and have more complex structures [62]. The bond angles $\text{R}-\text{N}^1-\text{N}^2-\text{N}^3$ and $\text{R}-\text{N}^1-\text{N}^2-\text{N}^3$ are approximately 115.2° and 172.5° , respectively (calculated for methyl azide, $\text{R} = \text{CH}_3$). The bond lengths in methyl azide were determined as $d(\text{R}-\text{N}^1) = 1.472$, $d(\text{N}^1-\text{N}^2) = 1.244$, $d(\text{N}^2-\text{N}^3) = 1.162 \text{ \AA}$ [63]. The infrared spectra of azides shows strong absorption at $2100\text{--}2270 \text{ cm}^{-1}$. The N_3 stretching band of the organic azides is very sharp and has its maximum at approximately 2100 cm^{-1} . Phenyl azide itself absorbs

at 250 nm with characteristic shoulders of an aryl azide which absorbs at 216-287 nm.

Azide anion is a good nucleophile. Many azide reactions proceed *via* formation of an active intermediate, nitrene, analogous to carbene. This results from the photolysis of hydrazoic acid (Scheme 1.17).



Scheme 1. 17 Photolysis of hydrazoic acid

1.3.2. Synthesis of Azides

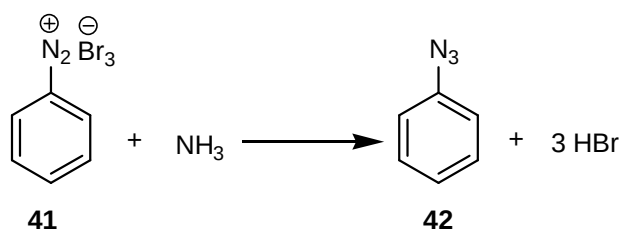
In principle, organic azides may be prepared through five different methods;

a) insertion of the N₃ group (substitution or addition), b) insertion of an N₂ group (diazo transfer), c) insertion of a nitrogen atom (diazotization), d) cleavage of triazines and analogous compounds, and e) rearrangement of azides.

1.3.2.1. Preparation of Aryl Azides

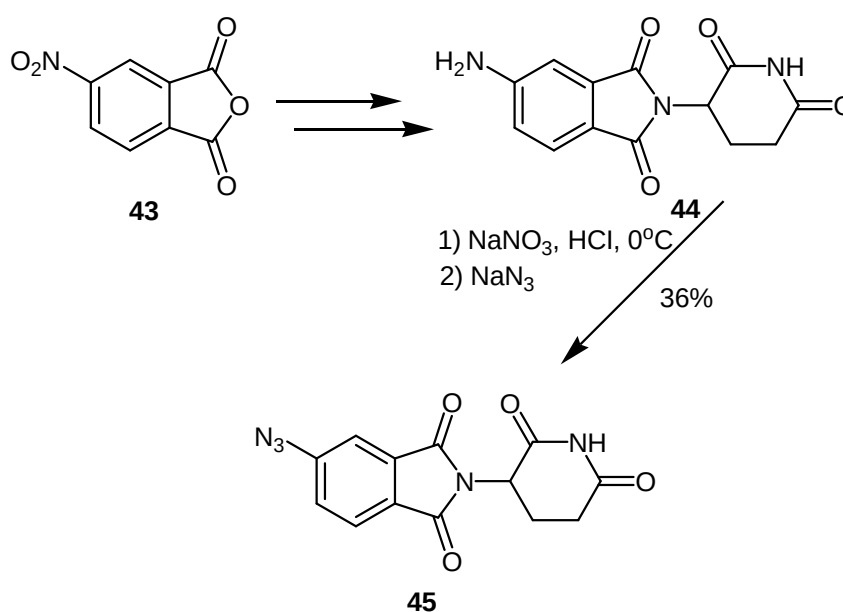
1.3.2.1.1. Preparation of Aryl Azides from Diazonium Compounds

The older preparative methods for aryl azides are based on the reaction of diazonium salts. The first organic azide, phenyl azide **42**, which is aryl azide, was synthesized by Peter Griess from benzenediazonium perbromide **41** and ammonia (Scheme 1.18) [56].



Scheme 1. 18 Synthesis of phenyl azide

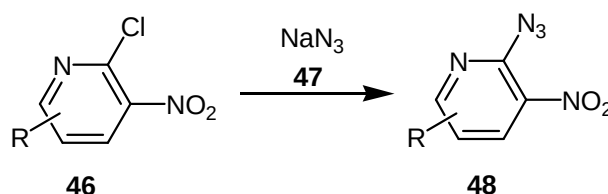
A more recent example of the decomposition of diazonium salts into the corresponding aryl azides is illustrated by synthesis of azidothalidomide **45** (Scheme 1.19) [64].



Scheme 1. 19 Synthesis of azidothalidomide

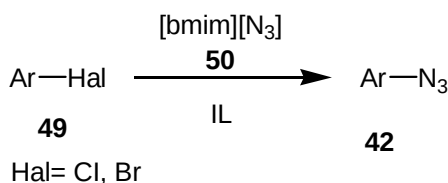
1.3.2.1.2. Nucleophilic Aromatic Substitution of Aryl Azides: $\text{S}_{\text{N}}\text{Ar}$ Reactions

Activated aryl or heteroaryl halides and a few heteroaromatic systems can undergo nucleophilic substitution by azide ions. They are generally sufficiently nucleophilic to produce aryl azides in good yields (Scheme 1.20) [65].



Scheme 1. 20 Aromatic substitution to give aryl azides

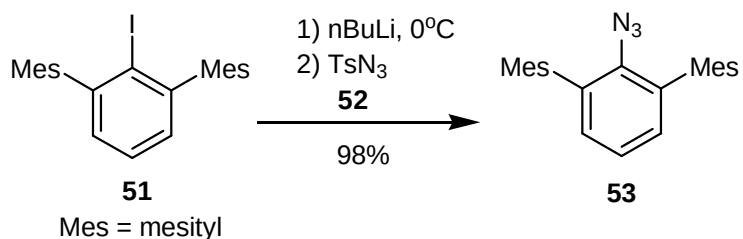
Anna et al. prepared some aryl azides in the presence of [bmim][N₃] **50**, which was used as the nucleophile, in IL solution (Scheme 1.21) [66].



Scheme 1. 21 Synthesis of aryl azides by using [bmim][N₃]

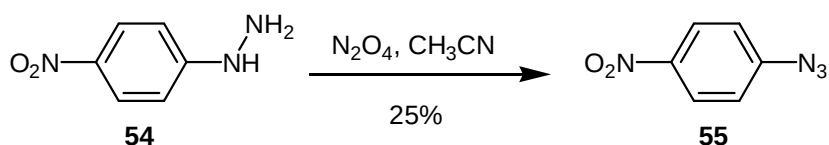
1.3.2.1.3. Other Methods for Preparation of Aryl Azides

Tilley and co-workers prepared aryl azides by using n-butyllithium and *p*-toluenesulfonyl azide **52** (Scheme 1.22) [67].



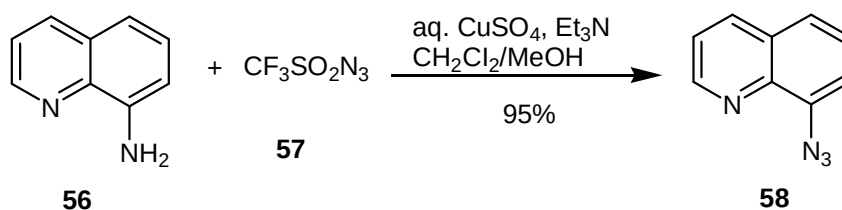
Scheme 1. 22 Preparation of aryl azide from n-butyllithium

Kim et al. treated hydrazones or hydrazines **54** derivatives with dinitrogen tetroxide to yield aryl azides (Scheme 1.23) [68].



Scheme 1. 23 Conversion of aromatic hydrazine into aryl azide

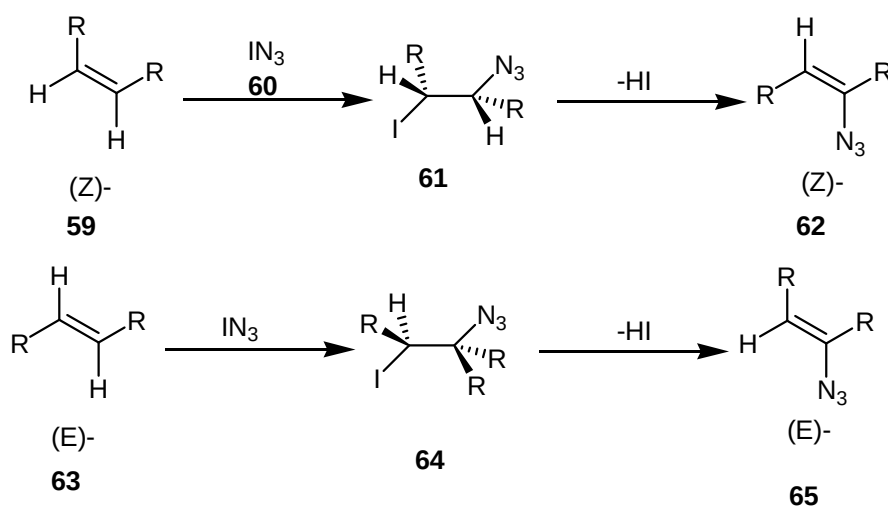
Tor and co-workers synthesized aryl azides from aromatic amines **56** was used triflyl azide **57** under mild conditions (Scheme 1.24) [69].



Scheme 1. 24 Preparation of aryl azides from aromatic amines

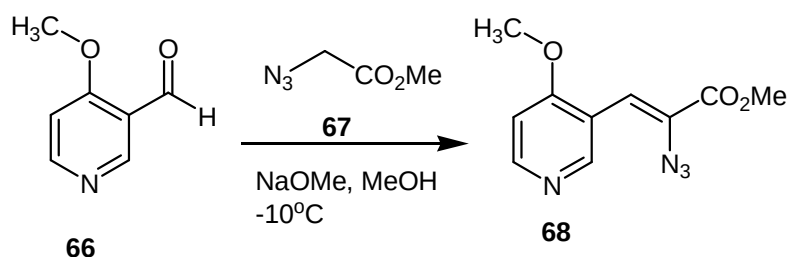
1.3.2.2. Preparation of Alkenyl Azides

A general synthetic route for synthesis of alkenyl azides was developed by Hassner and co-workers from the addition of iodine azides to the double bond and the subsequent elimination of hydrogen iodide (Scheme 1.25) [70].



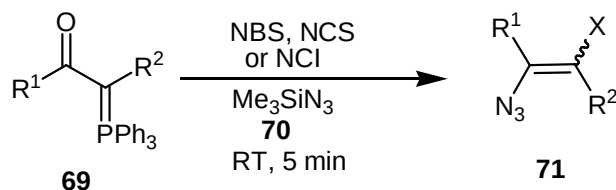
Scheme 1. 25 General synthesis of alkenyl azides

Interestingly, Hemetsberger and co-workers synthesized 3-aryl-2-azidopropenoates **68** from azidoacetate **67** and aldehydes **66**. This method is similar to the Knoevenagel condensation reaction (Scheme 1.26) [71].



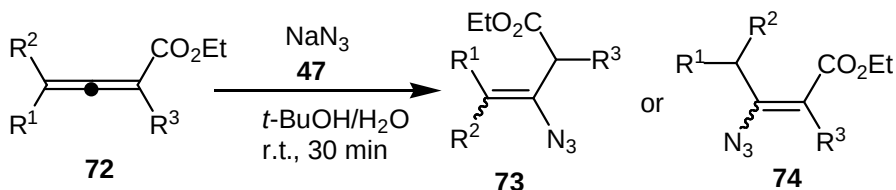
Scheme 1. 26 Synthesis of alkenyl azide from aldehyde

α -Oxophosphonium ylides **69** were reacted with N-chlorosuccinimide, N-bromosuccinimide and N-iodosuccinimide in the presence of trimethylsilyl azide **70** to yield alkenyl azides (Scheme 1.27) [72].



Scheme 1. 27 Preparation of alkenyl azides from ylides

Another method was also developed by Huang and co-workers which is producing alkenyl azides from 1, 2-Allenyl esters **72** and sodium azide **47** (Scheme 1.28) [73].

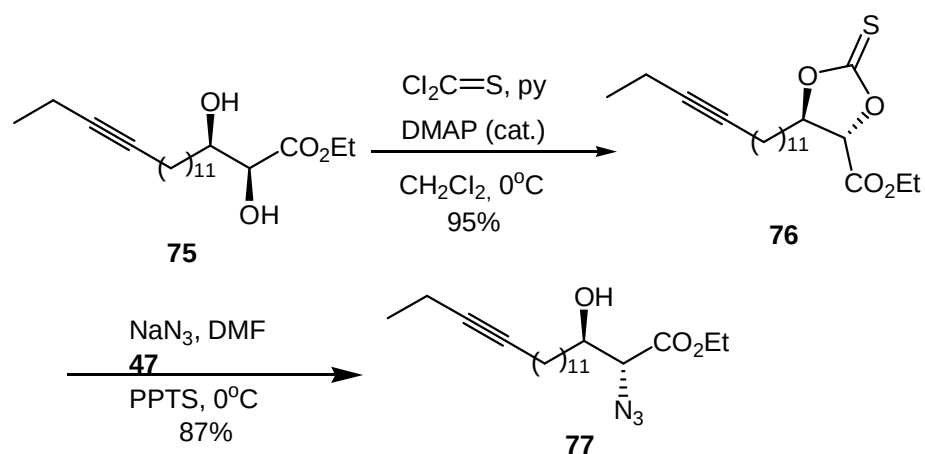


Scheme 1. 28 Preparation of alkenyl azides from 1, 2-allenyl esters

1.3.2.3. Preparation of Alkyl Azides

Alkyl azides are compounds readily accessible by nucleophilic substitution with the highly nucleophilic azide ion. Sodium azide is most commonly used as the azide source. Halides, carboxylates, and sulfonates are used as leaving groups.

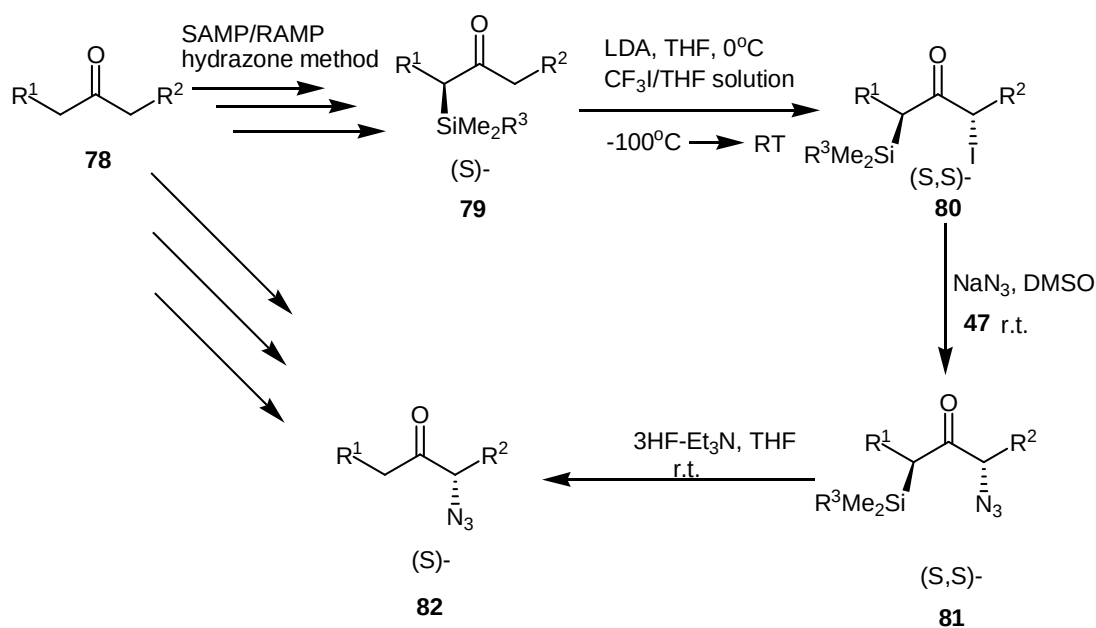
Bittman and co-workers were synthesized a regioselective alkyl azide from α,β -dihydroxy ester **75** via a cyclic thiocarbonate intermediate (Scheme 1.29) [74].



DMAP= 4-dimethylaminopyridine,
 PPTS= pyridinium *para*-toluenesulfonate

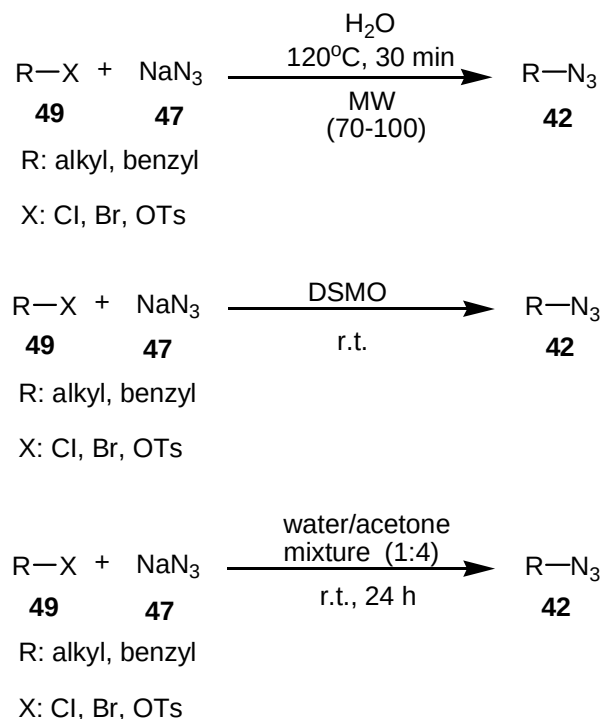
Scheme 1. 29 Synthesis of alkyl azide *via* cyclic thiocarbonate

The asymmetric synthesis of α -azidoketones **82** was described by Enders et al. A diastereoselective nucleophilic substitution of the iodine substituent with sodium azide **47** is the key step in this reaction (Scheme 1.30) [75].



Scheme 1. 30 Asymmetric synthesis of α -azidoketones

There are most routes to synthesis of alkyl azides which involve the classic nucleophilic substitution reaction from alkyl halides and inorganic azides (Scheme 1.31) [76-77-78].



Scheme 1. 31 Different routes to synthesis of alkyl azides

1.4. A Brief Introduction to 1,3-dipolar Cycloaddition Chemistry

Cycloaddition reactions are extremely vital in organic synthesis work. The 1,3-dipolar cycloaddition reaction is a reaction between a dipolarophile and a 1,3-dipole, combine to form a five-membered heterocycles. The 1,3-dipolar cycloaddition (1,3-DC) reactions are used for preparation of molecules of fundamental importance for both academia and industry (Figure 1.11) [79].

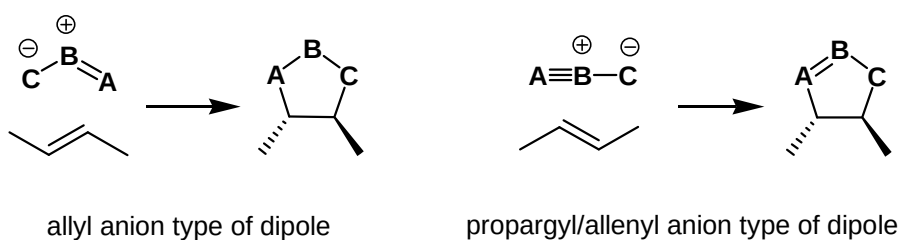


Figure 1. 11 Cycloaddition to 1,3-dipoles

1.4.1. The 1,3-dipole/ylide and dipolarophile

The 1,3-dipoles, which is a type of organic compound, consist of elements from main groups IV, V, VI. The parent 1,3-dipoles includes mainly second row and the central atom of dipole is limited to nitrogen, oxygen and carbon. A positive and a negative charges which are beared by the parent dipoles distributed over three atoms and has 4π electrons. The 1,3-dipoles divided into two different types, the allyl anion type which has a bent structure and the propargyl/allenyl anion type which has a linear structure (Figure 1.12) [80].

In this study, some novel organic azides bearing 1,2,4-Oxadiazole ring was used as dipoles for 1,3-cycloaddition reaction.

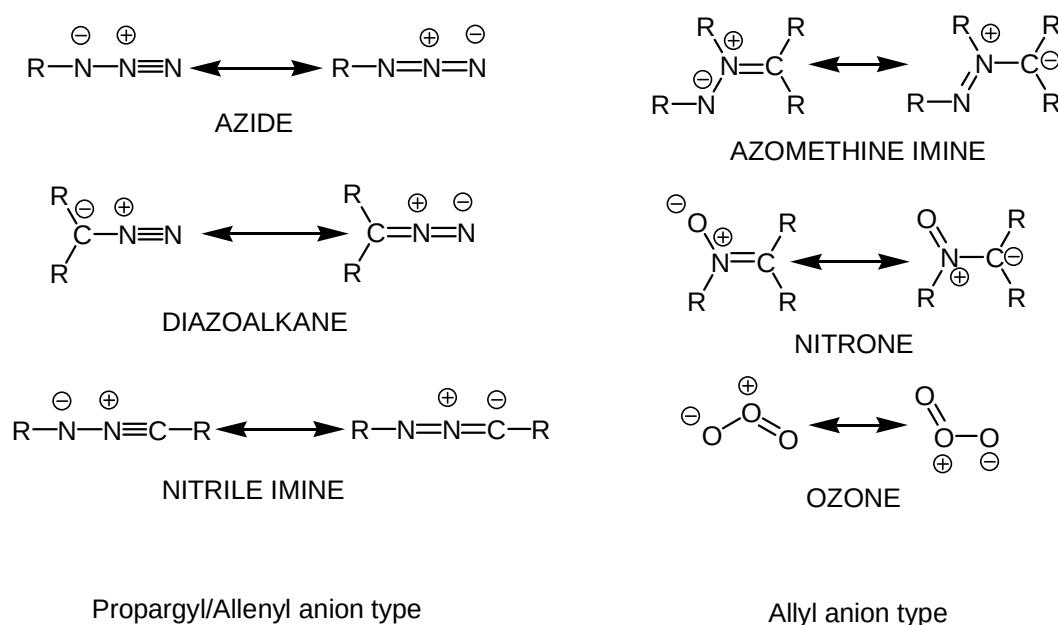


Figure 1. 12 Some types of 1,3-dipoles

The dipolarophile is a 2π electron specie that reacts with 1,3-dipoles in 1,3-dipolar cycloaddition reactions. Generally electron deficient dipolarophiles are

used for a model as dipolarophiles in 1,3-DC reactions. α , β -unsaturated aldehydes, ketones, allylic alcohols, allylic halides, imines, vinylic ethers and alkynes are examples of dipolarophiles (Figure 1.13) [81],

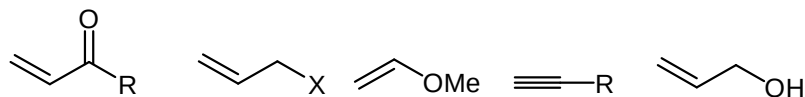
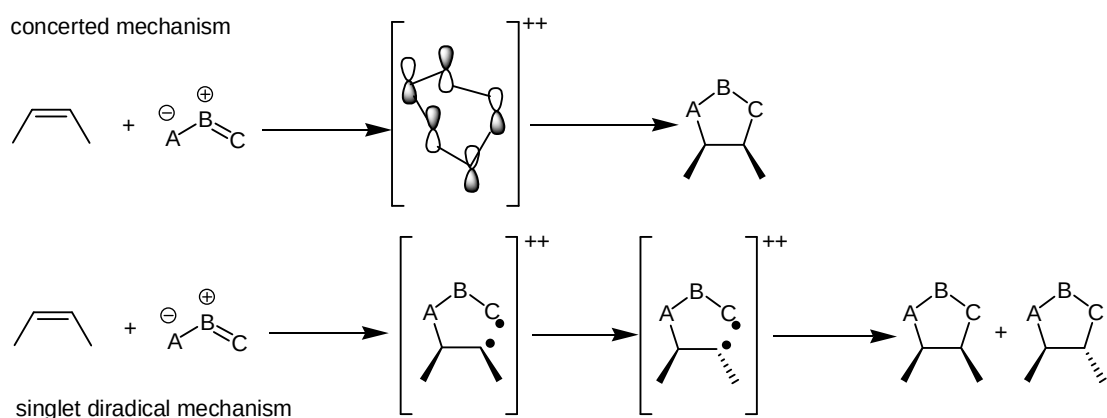


Figure 1. 13 Examples of some dipolarophiles

In this study, as dipolarophiles we used *N*-phenyl maleimide, phenyl vinyl sulfone and bicyclic dipolarophiles which were obtained from furan and maleic anhydride and furan and *N*-phenyl maleimide.

1.4.2. Mechanistic Aspects to 1,3-Dipolar Cycloaddition Reactions

In the 1960s, mechanism of the 1,3-dipolar cycloaddition reactions was studied by organic chemists. Huisgen claimed that, 1,3-dipolar cycloaddition reactions proceed through a concerted mechanism, which means that all the bonds were created simultaneously, but not necessarily to the same extent at a certain time [82]. Firestone et al. claimed that, 1,3-dipolar cycloaddition reactions proceed through a singlet diradical intermediate (Scheme 1.32).



Scheme 1. 32 Mechanism of 1,3-dipolar cycloaddition reaction

Rates of reaction between dipoles and dipolarophiles vary considerably. The interaction between molecular orbitals of the dipole and dipolarophile was explained by Frontier Molecular Orbital Theory (FMO). The most important interactions are those between the lowest occupied molecular orbital (LUMO) of one reactant and the highest occupied molecular orbital (HOMO) of the other reactant. Namely, these interactions occur HOMOdipole-LUMOdipolarophile and LUMOdipole-HOMOdipolarophile. Which interaction is dominant depends energy differences between the relevant pairs of orbitals. The closer in energy is presumed to play the dominant role (Figure 1.14) [82].

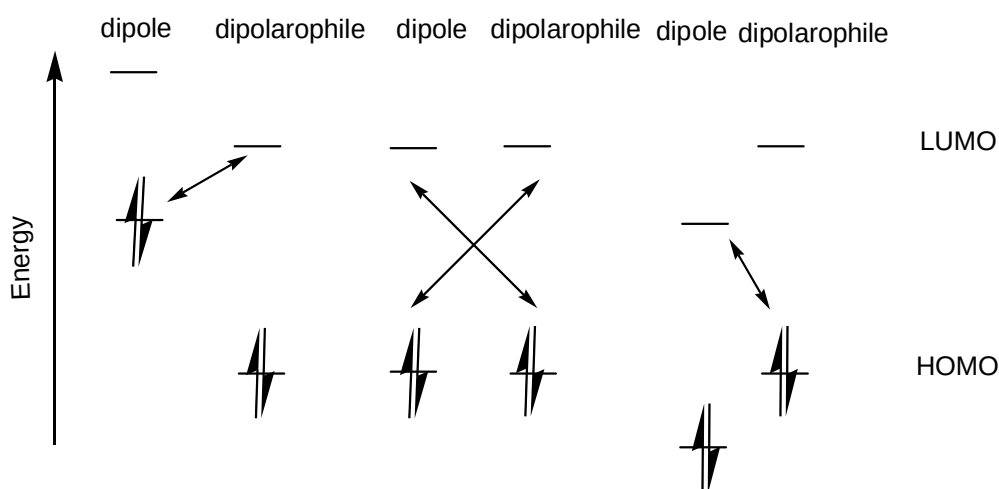


Figure 1. 14 The classification of 1,3-DC reactions on the basis of FMOs

1.5. TRIAZOLE

Triazoles are a specific type of heterocycle containing three nitrogen atoms; heterocycles being generally cyclic compounds in which the ring contains at least one non-carbon atom. In the case of triazoles, this non-carbon atom is nitrogen. Triazole compounds are aromatic heterocycles and includes either one of a pair of isomeric chemical compounds. They are five-membered ring

structures containing two carbon atoms and three nitrogen atoms. They follow the general molecular formula $C_2H_3N_3$ and are named based upon where the nitrogen atoms are located in the ring (Figure 1.15) [83].

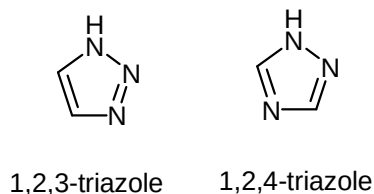
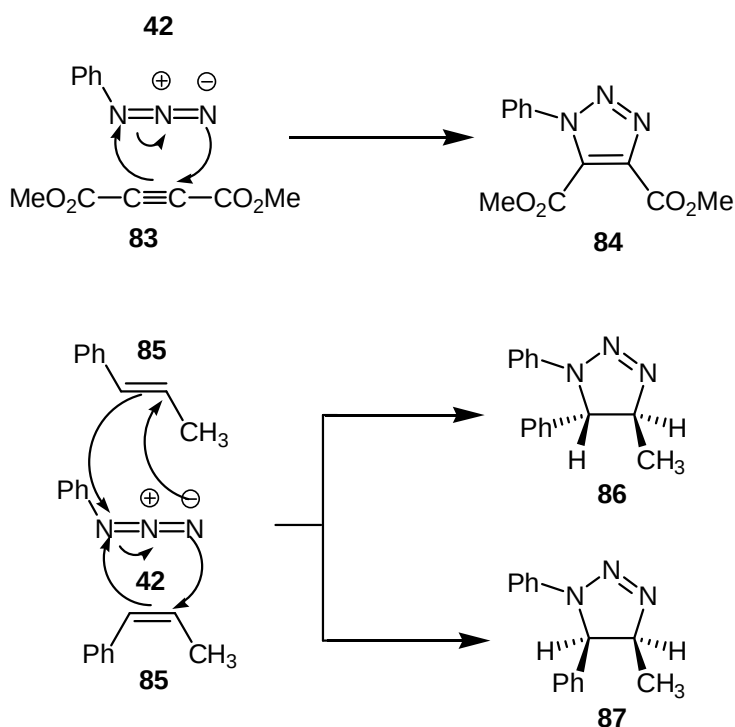


Figure 1. 15 Isomers of triazole

Traditionally, a 1,2,3-triazole can be synthesized through a dipolar cycloaddition reaction between an azide, an alkene and and alkyne (Huisgen cycloaddition) (Scheme 1.33).



Scheme 1. 33 Synthesis of 1,2,3-triazoles

CHAPTER 2

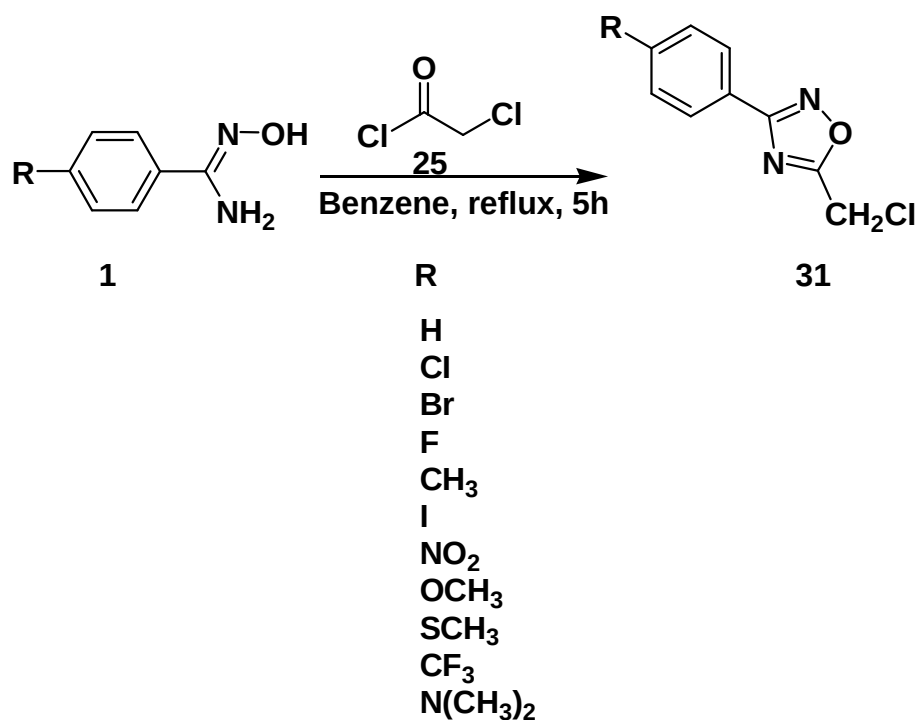
2.1. RESULTS and DISCUSSION

The 1,3-dipolar cycloaddition reactions of substituted azides with *N*-phenyl maleimide, phenyl vinyl sulfone and bicyclic molecules give substitute-[1,2,3] triazoles. To our best knowledge of literature survey, there are many examples of cycloaddition reactions of organic azides with alkenes, but, azides (**31a-m**) bearing 1,2,4-oxadiazole ring are not studied and registered as far as we searched the literature (WEB OF SCIENCE and SCIENCE FINDER SCHOLAR electronic databases). For this reason, we are focused, in this work, to obtain [1,2,3] triazoles heterocycles starting from amidoximes. The present research work is basically consisted of four parts.

- 1) Synthesis of substituted aryl amidoximes,
- 2) Synthesis of aryl substituted 5-(chloromethyl)-1,2,4-oxadiazoles,
- 3) Synthesis of aryl substituted 5-(azidomethyl)-1,2,4-oxadiazoles,
- 4) Synthesis of cycloadducts by the reaction between aryl substituted 5-(azidomethyl)-1,2,4-oxadiazoles and with four different dipolarophiles.

In the first part of the study, aryl substituted amidoximes were synthesized according to literature procedures [85-86].

In the second part, the pure monoamidoximes **1** were reacted with chloroacetyl chloride **25** at the reflux temperature of benzene to give 5-(chloromethyl)-1,2,4-oxadiazoles **31** (Scheme 2.1) [51].



Scheme2. 1 The synthesis and structures of 5-(chloromethyl)-1,2,4-oxadiazoles **31**

The 5-(chloromethyl)-1,2,4-oxadiazoles **31** were identified by IR, NMR, m.p., and R_f characteristics. The very basic proof for the generation of the 5-(chloromethyl)-1,2,4-oxadiazole ring is the disappearance of the NH and NOH absorptions of the corresponding amidoximes in the IR spectrum. In addition, the chemical shift positions of methylene protons appeared between 4.0-5.0 ppm in the ^1H NMR spectra (Figure 2.1).

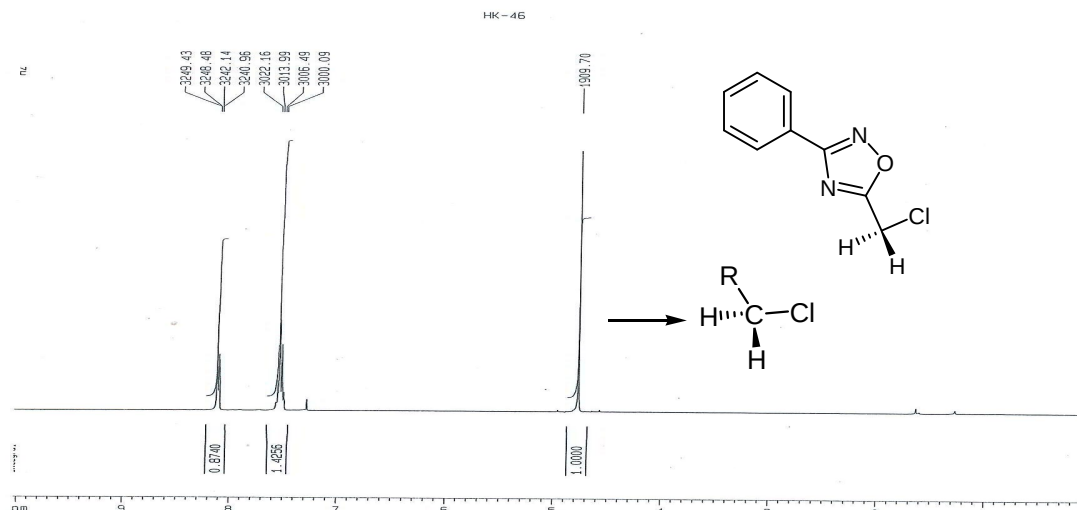


Figure 2. 1 ^1H NMR spectra of **31a**

In addition to the synthesis and identification of the chloromethyl oxadiazoles, a linear Hammett correlation has been established between the carbon chemical shifts of the number three carbon and Hammett σ_p substituent constants (Figure 2.2).

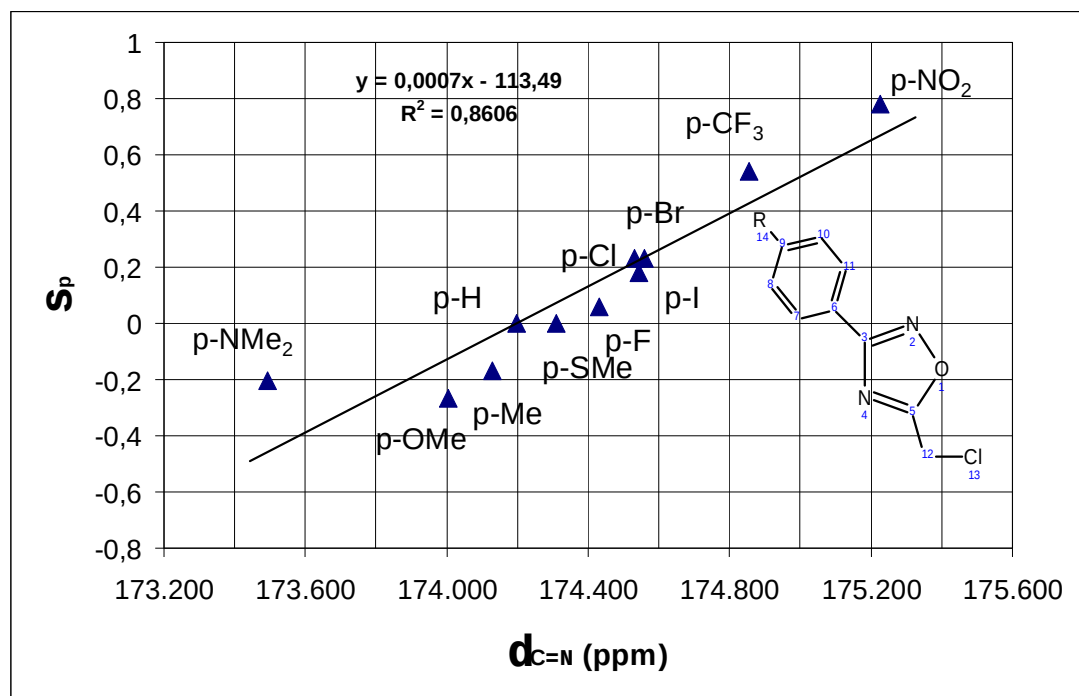
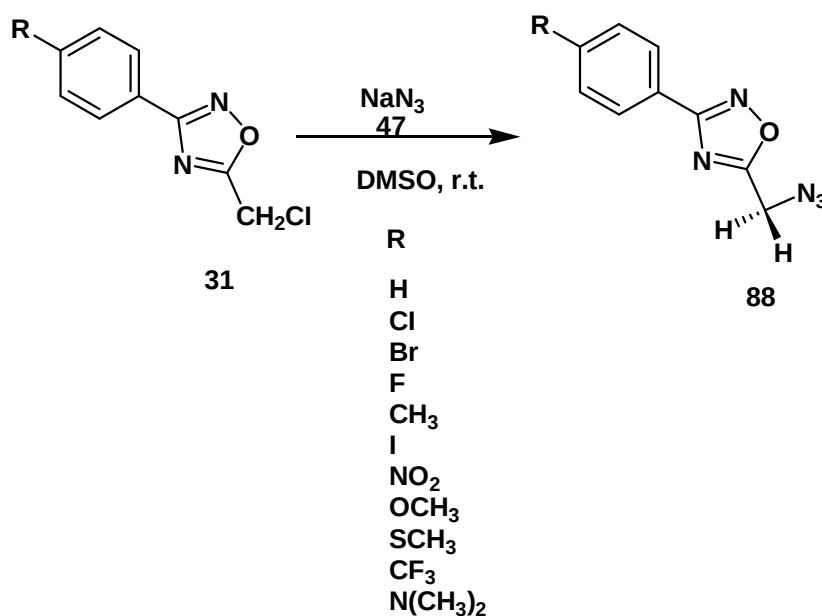


Figure 2. 2 Hammett correlation of carbon chemical shifts of chlormethyl 1,2,4-oxadiazoles and σ_p substituent constants

On the graph, electron-withdrawing substituents, CF_3 and NO_2 lie farthest right away while the electron-donating substituents, namely, OMe , NMe_2 and Me lie left closer to the origin of the plot. Electron-withdrawing groups cause to shift the carbon chemical shifts to the more deshielded region while electron-releasing groups cause to shift somewhat shielded positions. As it can be expected, the effect of halogens due to the both inductive and mesomeric effects appear as not much deshielding or shielding but it can be considered as quite deshielding in comparison with the electron-donating groups.

In the third part, the pure 5-(chloromethyl)-1,2,4-oxadiazoles **31** were reacted with sodium azide **47** at the room temperature in DMSO to give 5-(azidomethyl)-1,2,4-oxadiazoles **88** (Scheme 2.2) [77].



Scheme2. 2 The synthesis and structures of 5-(azidomethyl)-1,2,4-oxadiazoles **88**

The 5-(azidomethyl)-1,2,4-oxadiazoles **91** were identified by IR, NMR, Mass, m.p., and R_f characteristics. The primary indicative proof for the generation of

the 5-(azidomethyl)-1,2,4-oxadiazole is the appearance of the N=N=N absorption between 2100-2270 cm^{-1} in the IR spectrum. The mass spectrum is the another evidence of the 5-azidomethyl-1,2,4-oxadiazoles. Because, mass spectra showed that the most abundant ions are the molecular ions. Also, molecular ions (M^+) are base peaks (Figure 2.3). The mass spectral fragmentations of the compounds **88a-m** is shown below (Scheme 2.3).

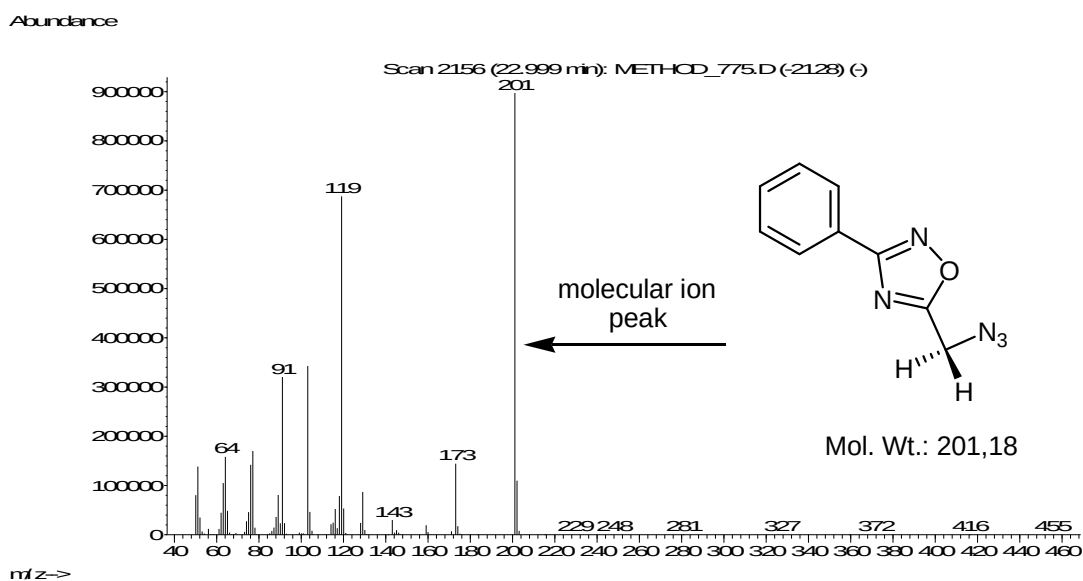
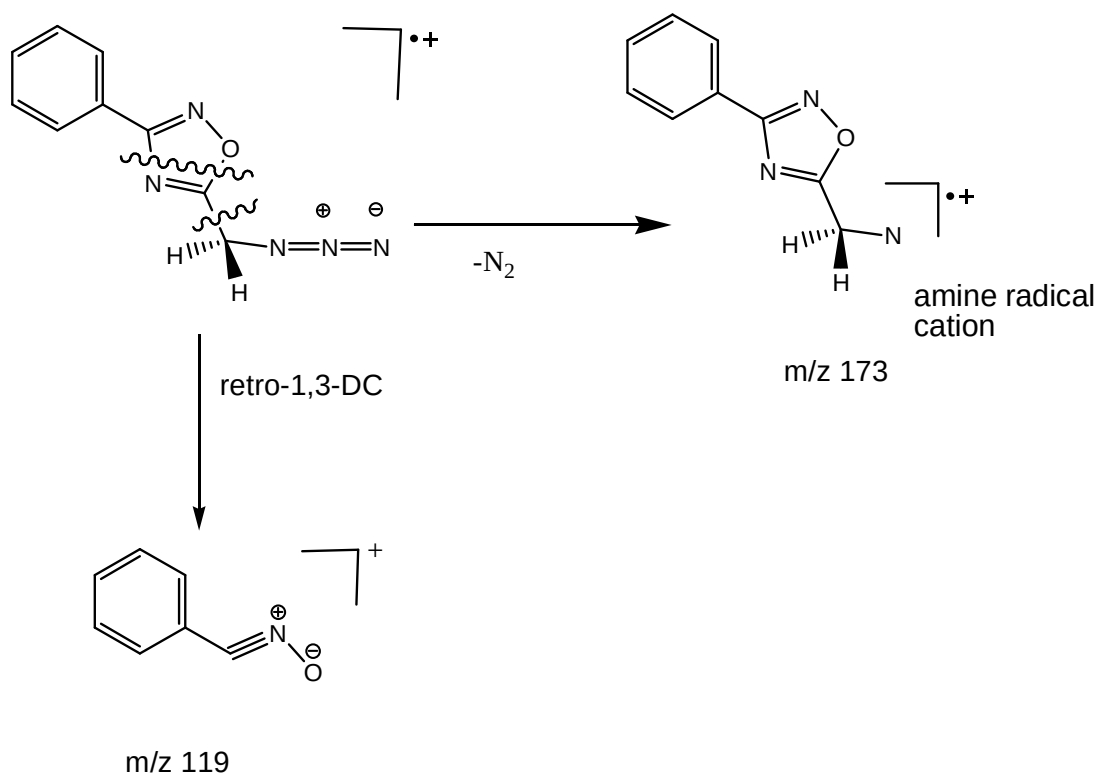


Figure 2. 3 Mass spectra of **88a**

The intense peak around m/z 119 can be accounted for the retro-1,3-dipolarcycloaddition to afford nitrile oxide moiety.



Scheme2. 3 The mass spectral fragmentations of the compounds **88a-m**

In addition to the synthesis of azidomethyl-1,2,4-oxadiazoles we wanted to make a linear correlation between the Hammett σ_p substituent constants and carbon chemical shifts of the number three carbon of the oxadiazole ring and it was clearly observed that there is a linear correlation between these values (Figure 2.4). On the graph, electron-withdrawing substituents, CF_3 and NO_2 lie farthest right away while the electron-donating substituents; OMe , NMe_2 and Me lie left closer to the origin. Electron-withdrawing groups cause to shift the carbon chemical shifts to the more deshielded region while electron-releasing groups cause to shift somewhat shielded positions. As it can be expected, the effect of halogens due to the both inductive and mesomeric effects appear as not much deshielding or shielding but it can be considered as quite deshielding in comparison with the electron-donating groups.

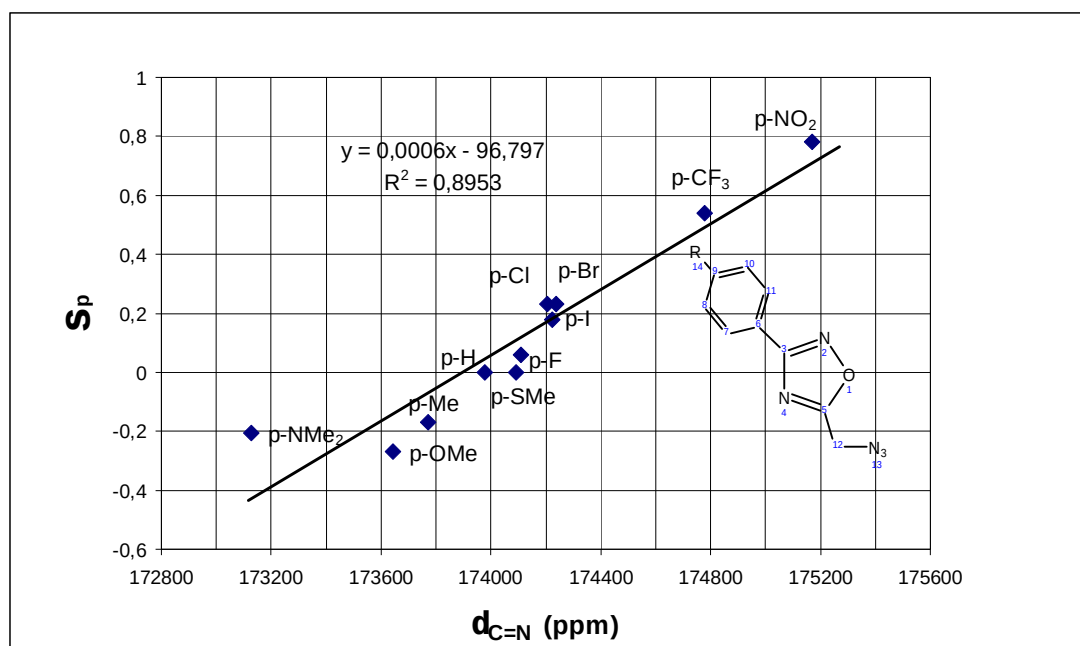
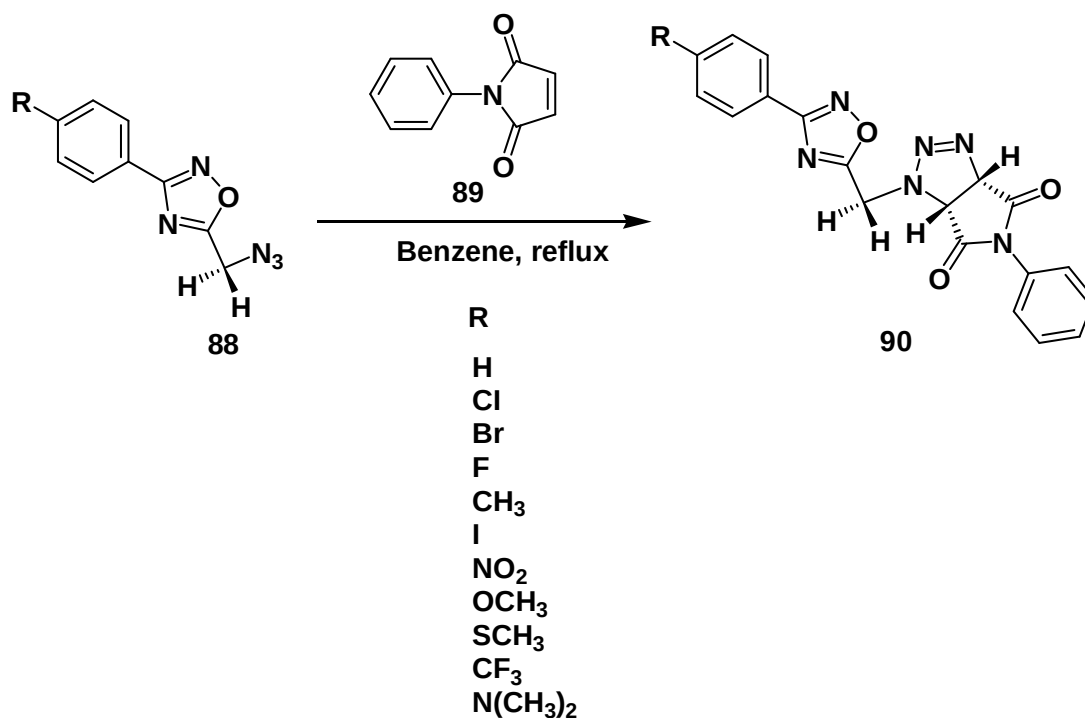


Figure 2. 4 Hammett correlation between Hammett σ_p substituent constants and carbon chemical shifts of the 1,2,4-oxadiazole ring

The fourth part of this work includes 1,3-dipolar cycloaddition reactions of 5-(azidomethyl)-1,2,4-oxadiazoles with four different dipolarophiles to give 1,2,4-oxadiazolo [1,2,3] triazoles.

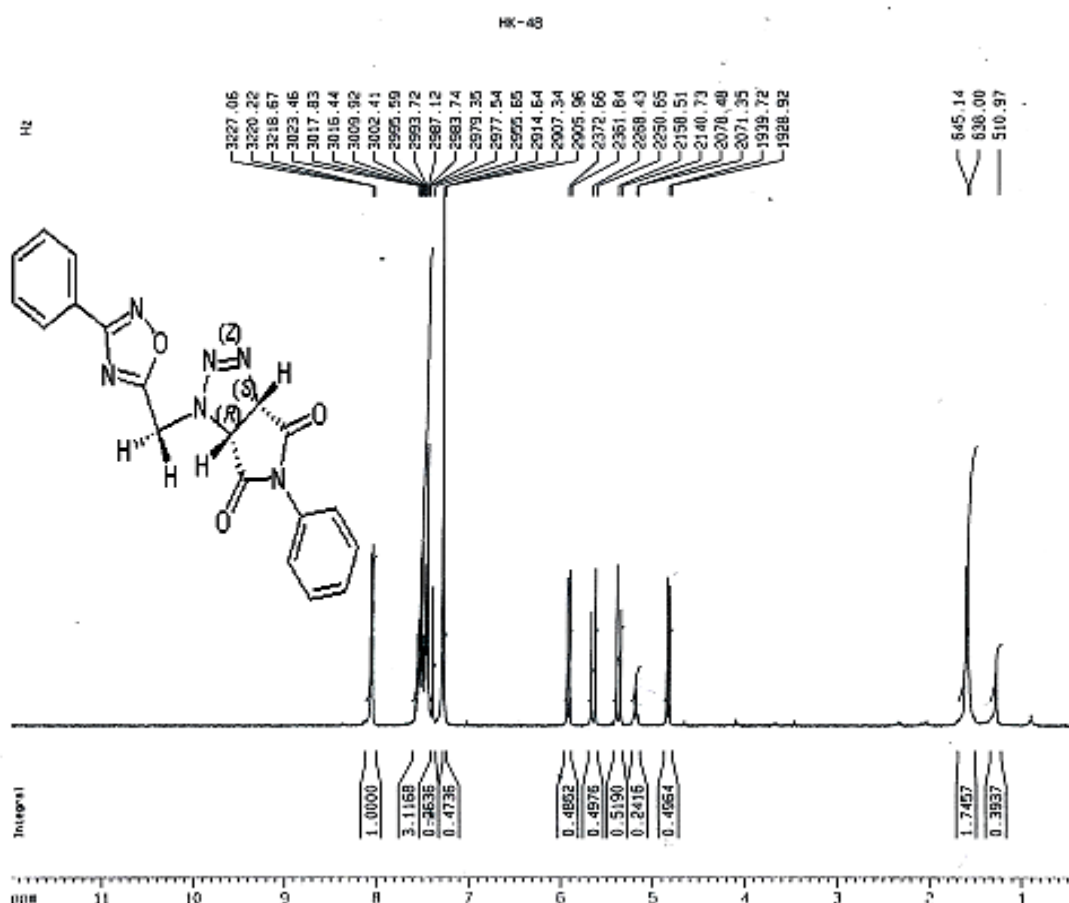
Firstly, the pure 5-(azidomethyl)-1,2,4-oxadiazoles **88** were reacted with N-phenyl maleimide **89** at the reflux temperature of benzene to give 11 novel 1,2,4-oxadiazolo-1,6a-dihydropyrrolo[1,2,3]triazole-(3,5)-diones **90** (Scheme 2.4).



Scheme2. 4 The synthesis and structures of cycloaddition products **90a-m** with *N*-phenyl maleimide

1,6a-dihydropyrrolo[1,2,3]triazole-(3,5)-diones **90** were identified by IR, NMR, Mass, m.p., and R_f characteristics. The primary indication for the generation of the 1,6a-dihydropyrrolo[1,2,3]triazole-(3,5)-dione is the disappearance of the $\text{N}=\text{N}=\text{N}$ absorption of the corresponding azides and the appearance of the $\text{C}=\text{O}$ absorption between $1725\text{-}1705\text{ cm}^{-1}$ in the IR spectrum. The another proof of the cycloadduct structure; 1,6a-dihydropyrrolo[1,2,3]triazole-(3,5)-dione is carbon chemical shifts in the ^{13}C NMR spectra which exhibited four different carbons between 160-180 ppm. Two of them are assigned to two carbonyl between 180-170 ppm at this spectra. The other two carbon signals were assigned to the iminic carbons; $\text{C}=\text{N}$ at the oxadiazole ring, at which the one closer to the oxygen resonates at lower field region in comparison to the carbon of azomethine attached to the phenyl ring, ca 170 ppm. In addition, at the ^1H NMR spectra, the H_a and H_b which must be one doublet signal, indicating that two doublet signals and chemical shifts of this

protons appear at around 6.0-4.0 ppm. Because of N=N of the [1,2,3] triazole ring, H_a is the more deshielded than H_b. Therefore, H_a chemical shift appears at approximately 6.0 ppm and H_b chemical shift appears at approximately 4.0 ppm at the ¹H NMR spectra. The methylene protons of 5-(chloromethyl)-1,2,4-oxadiazole and 5-(azidomethyl)-1,2,4-oxadiazole appear as a singlet signal, but the methylene protons of cycloadducts appear as doublets or quartets depending on solvent used for running NMR spectra. In CDCl₃+DMSO-d₆, methylene protons appear one doublet of doublet (dd) signal whereas methylene protons appear two doublet (d) signals in the CDCl₃ (Figure 2.5).



Assignment of these chemical shifts and patterns are in accord with the literature values given for a similar cycloaddition product at which a different azide derivative is used to react with *N*-phenyl maleimide [84].

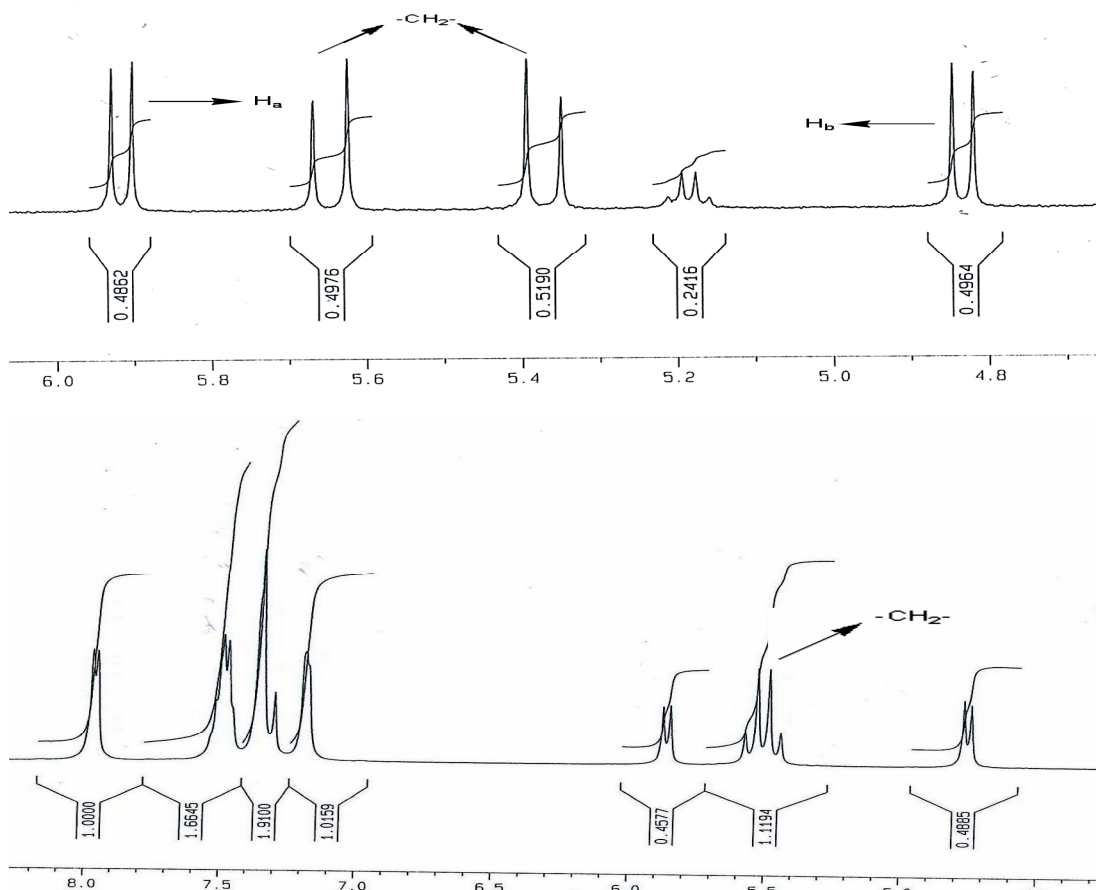
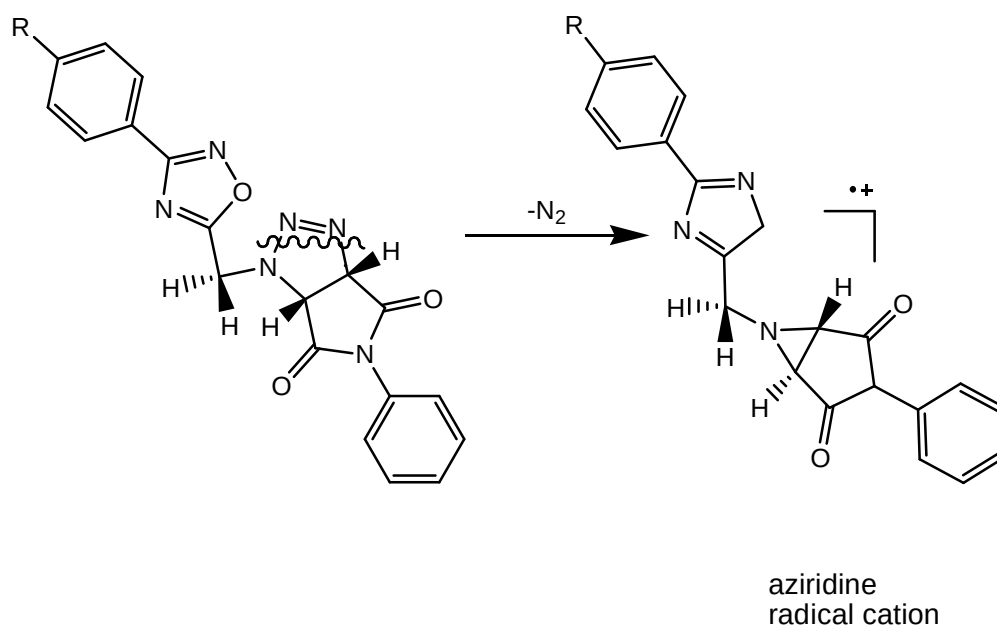


Figure 2. 5 ^1H NMR and expanded ^1H NMR spectrum of compound **90a**

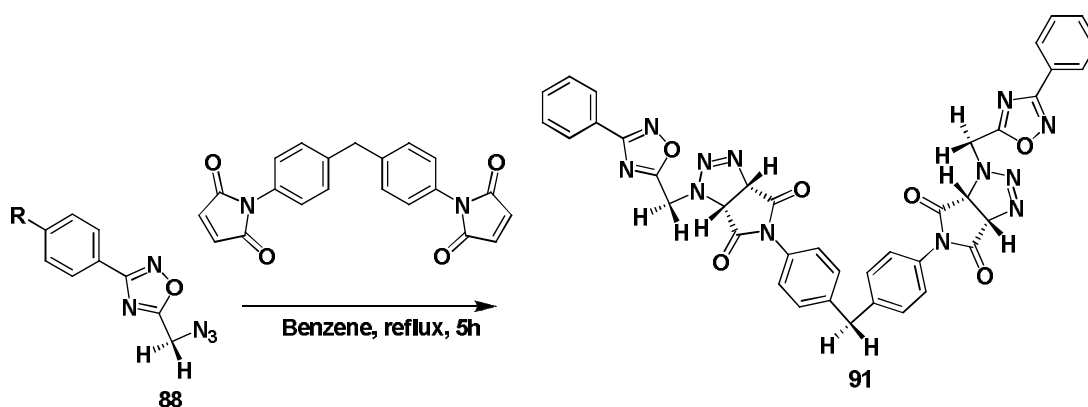
Upon investigation of the mass spectra of these novel heterocycles showed some interesting features. Peaks related to the molecular ions (M^+) of the cycloadducts were not observed in the mass spectra. But, instead, we have found major peaks at m/z : $\text{M}-\text{N}_2$ which can easily be predicted that loss of N_2 from the molecules, and depending on the running conditions there are also the peaks related to the clusters of $\text{M}+\text{K}^+$, and $\text{M}+\text{MeCNH}^+$ in the TOF AP^+ and TOF ES^+ mass spectrums (Scheme 2.5).



Scheme2. 5 The mass spectral fragmentations of the compounds **90a-m**

All experimental data show us, the reaction between 5-(azidomethyl)-1,2,4-oxadiazole and *N*-phenyl maleimide yields only endo products.

Also, the pure 5-(azidomethyl)-1,2,4-oxadiazole **88** were reacted with 4,4-methylenebis(*N*-phenyl maleimide) at the reflux temperature of benzene to give cycloadduct of **91** (Scheme 2.6).

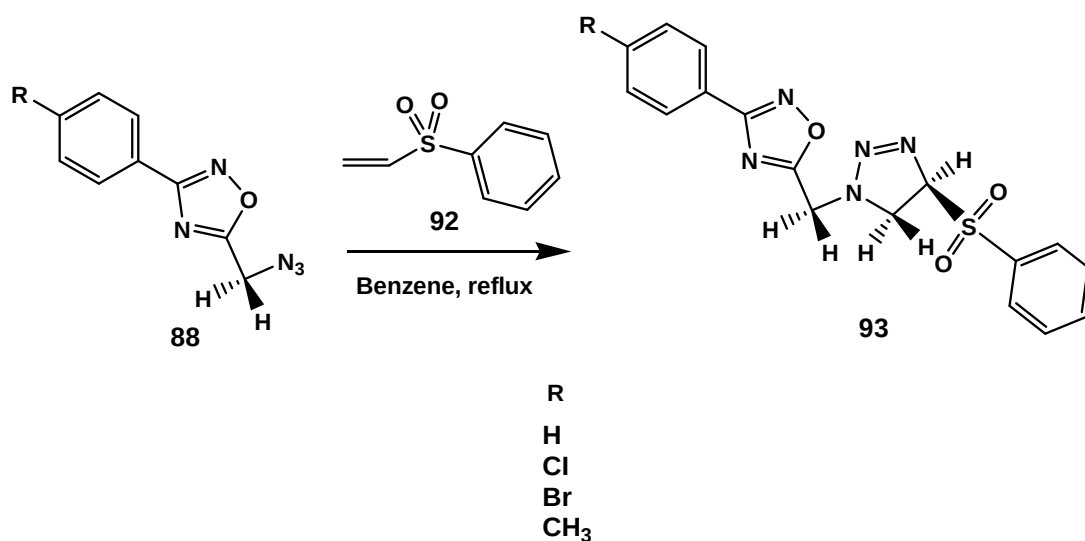


Scheme2. 6 The synthesis and structures of cycloaddition products **91**

Cycloadduct **91** was identified by IR, NMR, m.p., and R_f characteristics. The IR spectra seemed to be quite similar to those of the cycloadducts of **90a-m**,

but the C=O double bond absorption which is 1718 cm^{-1} and somewhat different. ^1H and ^{13}C NMR spectra are the another evidence for the generation of cycloadduct **91**.

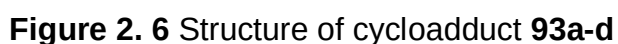
Secondly, the pure 5-(azidomethyl)-1,2,4-oxadiazoles **88** were reacted with phenyl vinyl sulfone at the reflux temperature of benzene to give 4-(phenylsulfonyl-4,5-dihydro-[1,2,3]triazole (Scheme 2.7).



Scheme2. 7 The synthesis and structures of cycloadducts with phenyl vinyl sulfone

The exact structures of these 4 novel cycloadducts were identified by IR, NMR, Mass, m.p., and R_f characteristics. In the IR spectra, the disappearance of the N=N=N absorption of the corresponding azides and the appearance of the sulfone S=O symmetric ($1160\text{-}1120\text{ cm}^{-1}$) and asymmetric ($1300\text{-}1350\text{ cm}^{-1}$) stretching absorptions are the evidences for the generation of the 4-(phenylsulfonyl-4,5-dihydro-[1,2,3]triazoles **93**.

In the proton NMR spectra of these compounds, the protons H_a , H_b , H_c , H_d , H_e have exhibited different splitting patterns at different chemical shift values (Figure 2.6).



Chemical Structure:

c1ccc(cc1)S(=O)(=O)[C@H]2[C@@H](c3nc(NC4=C(C(=O)N4)c5ccccc5)n3)[C@H](Cc6ccccc6)N2

¹H NMR Spectrum Data:

Chemical Shift (ppm)	Multiplicity	Integration
~8.0	m	1.0000
~7.6-7.8	m	0.9219
~7.2	t	0.2851
~6.8	t	0.5766
~5.5	dd	2.9932
~5.2	dd	0.4734
~4.5	dd	0.5106
~4.2	dd	0.5143
~3.8	dd	0.5550
~3.5	dd	0.5534
~3.2	dd	0.5538
~3.0	dd	-
~2.8	dd	-
~2.6	dd	-
~2.4	dd	-
~2.2	dd	-
~2.0	dd	-
~1.8	dd	-
~1.6	dd	-
~1.4	dd	-
~1.2	dd	-
~1.0	dd	-
~0.8	dd	-
~0.6	dd	-
~0.4	dd	-
~0.2	dd	-

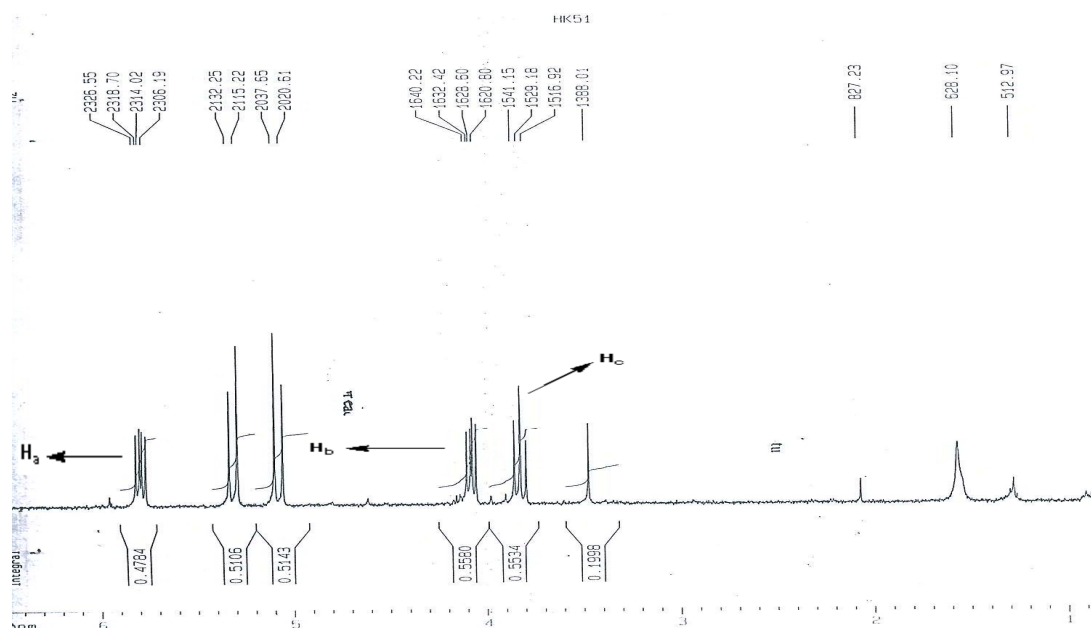
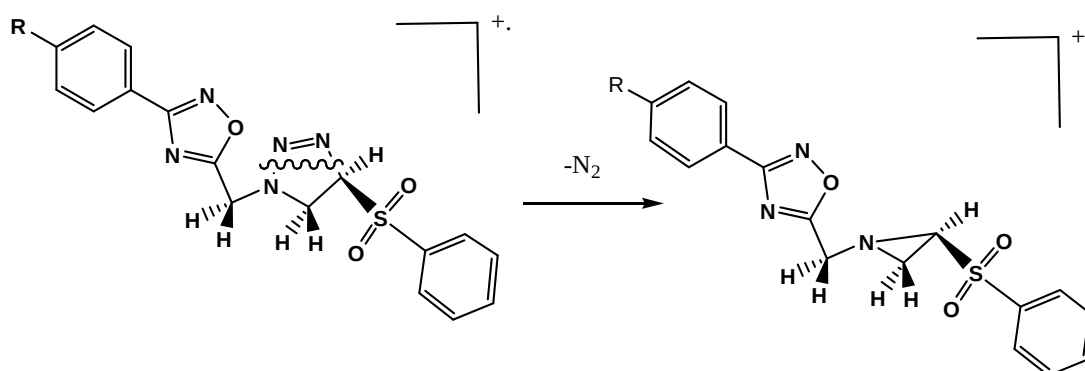


Figure 2. 7 Full-scale and expanded ^1H NMR spectra of compound **93a**

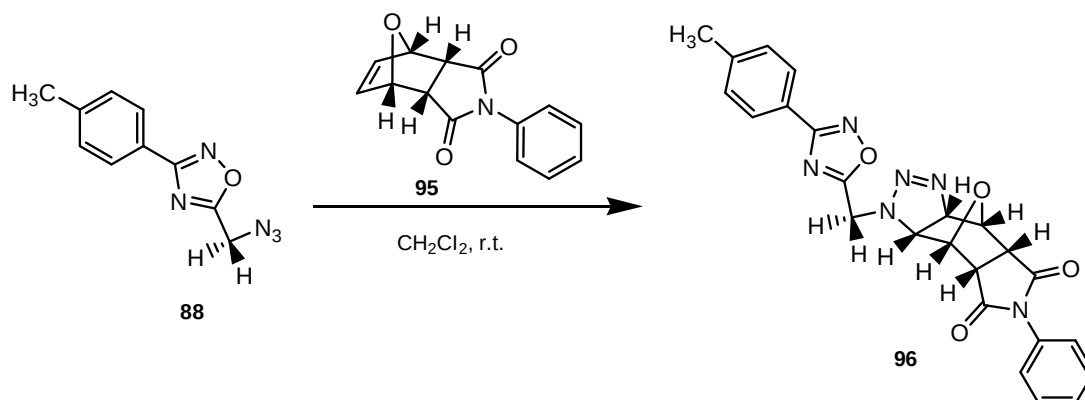
The mass spectral study of heterocycles **93a-d** showed the same interesting features as compounds of **88a-m**. Molecular ions (M^+) of cycloadducts were not detected in the mass spectra. In the LC-MS spectra, the main peaks of these cycloadducts appeared as; m/z : $\text{M}-\text{N}_2$ which can easily be predicted that loss of N_2 from the molecules leading to the cationic aziridine formation as shown below (Scheme 2.8).



Scheme2. 8 The mass spectral fragmentations of the compounds **93a-d**

Third reaction of the pure 5-(azidomethyl)-1,2,4-oxadiazole **88** was performed with the dipolarophile 7-oxabicyclo [2.2.1] hept-5-ene-2,3-

dicarboxy-N-phenylimide **95** which was easily obtained from the reaction of furan and N-phenyl maleimide, at the room temperature of CH_2Cl_2 to afford 1,6-dihydropyrrolo[1,2,3]triazole-(3,5)-dione **96** (Scheme 2.9).



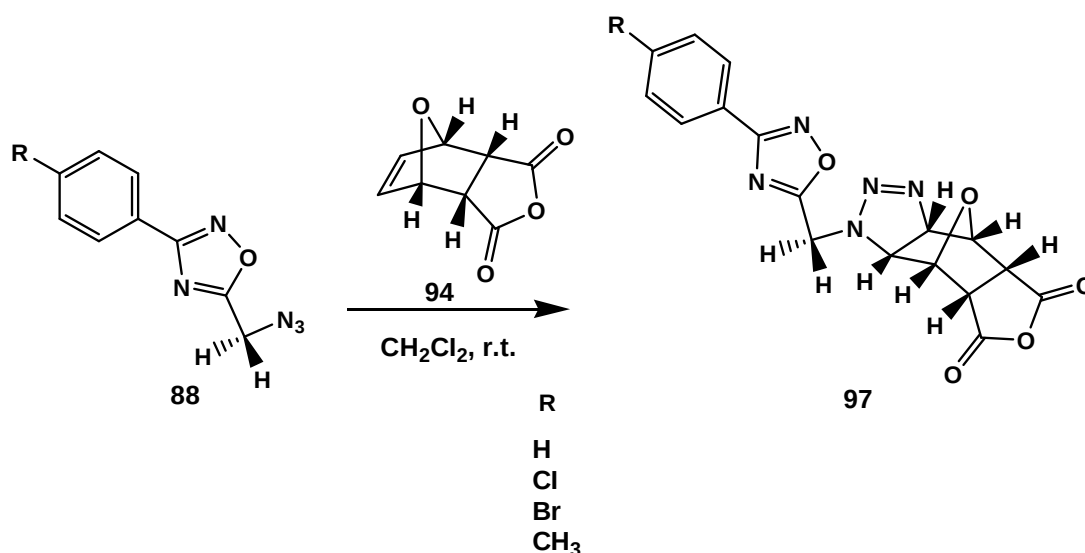
Scheme2. 9 Synthesis of cycloadducts **96** with bicyclic molecules

This cycloadducts **98** was identified by IR, NMR, Mass, m.p., and R_f characteristics. The IR spectra seemed to be quite similar to those of the cycloadducts of **90a-m**, but the $\text{C}=\text{O}$ double bond absorption which is 1778 cm^{-1} and somewhat different.

Molecular ions (M^+) of cycloadducts **96** were not observed in the mass spectra. The major peak of these cycloadducts appear as; m/z : $\text{M}-\text{N}_2$ which can easily be predicted that loss of N_2 from the molecules with the difference of cycloadducts of **90a-m**, in the LC-MS spectra. The molecular ions (M^+) and loss of N_2 ($\text{M}-\text{N}_2$)⁺ peaks of cycloadducts **90a-m** did not appear in the LC-MS, but the loss of N_2 ($\text{M}-\text{N}_2$)⁺ peak of cycloadduct **96a** appeared from LC-MS spectra. This indicates that change of dipolarophile for the 1,3-dipolar cycloaddition reactions effects the fragmentations of cycloadducts at the mass spectrums.

Finally, the pure 5-(azidomethyl)-1,2,4-oxadiazoles **88** were reacted with 7-oxabicyclo [2.2.1] hept-5-ene-cis-2,3-dicarboxylic anhydride **94** which was

easily prepared from the reaction furan and maleic anhydride, at the room temperature of CH_2Cl_2 to give hexahydro-4,8-epoxyfuro[1,2,3] benzotriazole-5,7-dione **97** (Scheme 2.10). The cycloaddition products were identified by spectral measurements (IR, NMR) and physical constants (m.p, and R_f values). The C=O double bond absorption ($\cong 1780\text{ cm}^{-1}$) appeared in the IR spectra. Also, the generation of these cycloadducts was assigned by ^1H NMR and ^{13}C NMR spectrums. Molecular ions (M^+) and the main peak of these cycloadduct appear as; m/z : $\text{M}-\text{N}_2$ which can easily be predicted that loss of N_2 from the molecules were not detected by the LC-MS spectra.



Scheme2. 10 Synthesis of compounds **97**

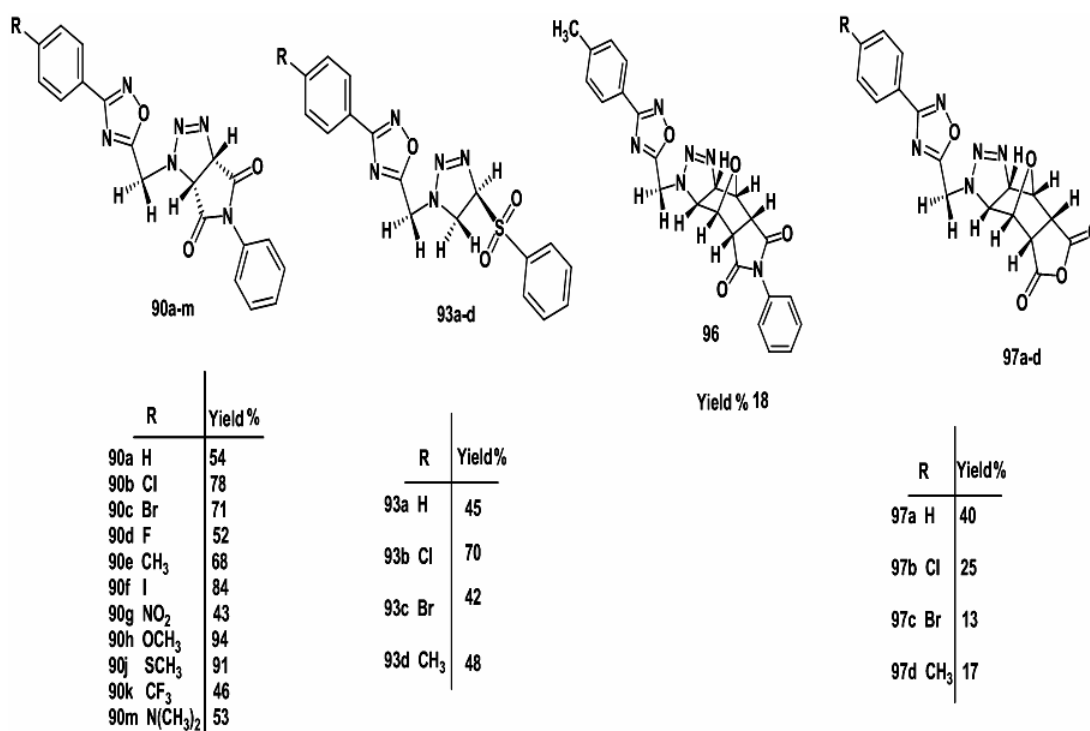


Figure 2. 8 Yields of cycloadducts

The yield of cycloadducts derived from monocyclic alkenes is of more high yield than the cycloadducts obtained from bicyclic alkenes. The steric bulk of this azide does not appear to play a significant role in the course of the reaction. However, the reactivity of the alkene was diminished significantly in cycloadducts.

The 1,2,3-triazole is a very widely used heterocyclic system present in many synthetic substances and commercial pharmaceutical compounds. In fact, 1,2,3-triazoles show several applications in many areas especially as medicines against many diseases like cancer, AIDS, Parkinson and Alzheimer.

2.2. CONCLUSION

In summary, firstly, we have synthesized of 11 chloromethyl 1,2,4-oxadiazoles some of which are novel, 11 novel azides bearing 1,2,4-oxadiazole ring. Secondly, from the reaction between azides and *N*-phenyl maleimide, 11 novel pyrrolo triazoles were obtained. In the third part of this study; 1,2,4-oxadiazolo azides were reacted with phenyl vinyl sulfone and 4 novel benzenesulfonyl substituted triazolo oxadiazoles were prepared and their structure and stereochemistry were established. Finally, it was attempted to synthesize cycloaddition products from the reaction of oxadiazolo azides and bicyclic alkenes prepared from maleic anhydride and furan; *N*-phenyl maleimide and furan, respectively. 5 novel compounds were obtained in this way. The structure of these novel cycloadducts were identified by the IR, ^1H NMR, ^{13}C NMR and MASS spectra.

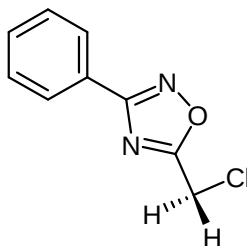
CHAPTER 3

EXPERIMENTAL

^1H and ^{13}C NMR spectra were recorded on BRUKER spectrometer (400 MHz for ^1H ; 100 MHz for ^{13}C and). IR spectra were recorded on a SHIMADZU FTIR 8400-S instrument (KBr pellet). Mass spectra were run on Agilent GC 6890 instrument with MS 5975 mass detector. 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 using precoated plates with fluorescent indicator (Merck 5735). The stain solutions of permanganate and iodine were used for visualization of the TLC spots. Amidoximes **1a-n** were synthesized according to the methods described in the literature [85-86].

Synthesis of Oxadiazoles 3a-m

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



To a solution of chloroacetylchloride (0.813 g, 7.2 mmol) in benzene (10 mL) was added dropwise to a solution of benzamidoxime (**1a**) (2.448 g, 18.0

mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 2:1) to give **(31a)** as a white solid (1.245 g, 89 %). M.p.: 39-40 °C.

R_f: 0.95 (Eluant: n-Hexane:Ethyl acetate; 1:1)

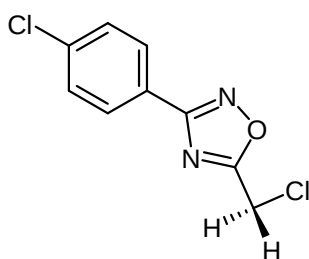
IR (KBr, ν : cm⁻¹): 3034 (Arom. C-H), 1599, 1573 (C=N), 1473, 1444, 1361, 1300, 922, 711 (C-Cl).

¹H NMR (δ _H, 400 MHz, CDCl₃): 8.11 (d, J=6.4 Hz, 2H), 7.52 (m, 3H), 4.77 (s, 2H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): 174.3 (C=N), 168.9 (C=N), 131.6, 129.0, 127.5, 126.2 (-CH), 33.4 (-CH₂-).

MS (m/z , %)= 194 (M⁺, 64), 119 (100), 77 (12).

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



To a solution of chloroacetylchloride (0.813 g, 7.2 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-chlorobenzamidoxime **(1b)** (3.070 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

concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 2:1) to give **(31b)** as a white solid (1.448 g, 88 %). M.p.:61-63 °C.

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

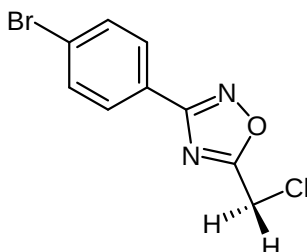
IR (KBr, ν : cm⁻¹): 3022 (Arom. C-H), 1593, 1566 (C=N), 1473, 1410, 1354, 1091, 839, 740 (C-Cl).

¹H NMR (δ _H, 400 MHz, CDCl₃): 8.04 (d, J=8.4 Hz, 2H), 7.49 (d, J=8.7 Hz, 2H), 4.77 (s, 2H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): 174.5 (C=N), 168.1 (C=N), 137.8, 129.3, 128.8, 124.6 (-CH), 33.3 (-CH₂-).

MS (*m/z*, %)= 228 (M⁺, 96), 153 (100), 125 (18), 90 (25), 50 (8).

5-(Chloromethyl)-3-(4-bromophenyl)-1,2,4-oxadiazole (**31c**)



To a solution of chloroacetylchloride (0.542 g, 4.79 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-bromobenzamidoxime (**1c**) (2.579 g, 11.99 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give **(31c)** as a white solid (1.309 g, 100 %). M.p.:61-62 °C.

R_f: 0.90 (Eluant: n-Hexane:Ethyl acetate; 1:1)

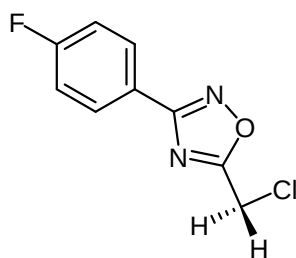
IR (KBr, ν : cm^{-1}): 3020 (Arom. C-H), 1600, 1558 (C=N), 1469, 1406, 1352, 1109, 835, 736 (C-Cl).

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 7.98 (dt, $J=2.1, 8.5$ Hz, 2H), 7.66 (dt, $J=2.1, 8.5$ Hz, 2H), 4.77 (s, 2H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): 174.6 (C=N), 168.2 (C=N), 132.3, 129.0, 126.2, 125.1 (-CH), 33.3 (-CH₂-).

MS (m/z , %)= 274 (M^+ , 96), 197 (61), 90 (44), 50 (12).

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



To a solution of chloroacetylchloride (0.438 g, 3.88 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-fluorobenzamidoxime (**1d**) (1.500 g, 9.73 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give (**31d**) as a yellow oil (0.786 g, 95 %).

R_f: 0.69 (Eluant: n-Hexane:Ethyl acetate; 1:1)

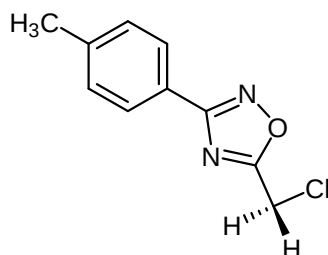
IR (KBr, ν : cm^{-1}): 3032 (Arom. C-H), 1610, 1583 (C=N), 1481, 1417, 1356, 1234, 1157, 844, 754 (C-Cl).

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 8.12 (m, 2H), 7.21 (t, $J=6.6$ Hz, 2H), 4.77 (s, 2H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): 174.4 (C=N), 168.1 (C=N), 166.2(-CF-), 128.9, 116.3, 116.1, (-CH), 33.3 (-CH₂-).

MS (m/z , %)= 212 (M^+ , 69), 137 (100), 107 (9), 75 (16).

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



To a solution of chloroacetylchloride (0.407 g, 3.60 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-tolylbenzamidoxime (**1e**) (1.350 g, 9.00 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 2:1) to give (**31e**) as a white solid (0.712 g, 95 %). M.p.:46-47 °C

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

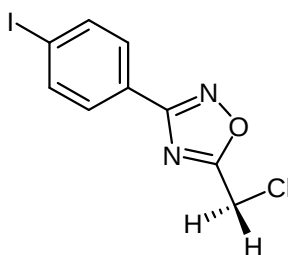
IR (KBr, ν : cm^{-1}): 3028 (Arom. C-H), 1618, 1597 (C=N), 1479, 1411, 1361, 1284, 1151, 827, 750 (C-Cl).

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 7.99 (d, $J=8.2$ Hz, 2H), 7.32 (d, $J=7.9$ Hz, 2H), 4.76 (s, 2H), 2.44 (s, 3H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): 174.1 (C=N), 168.9 (C=N), 142.0, 129.7, 127.4, 123.3 (-CH), 33.4 (-CH₂-), 21.6 (-CH₃).

MS (m/z , %)= 208 (M^+ , 100), 133 (100), 91 (26), 51 (13).

5-(Chloromethyl)-3-(4-iodophenyl)-1,2,4-oxadiazole (31f)



To a solution of chloroacetylchloride (0.449 g, 3.98 mmol) in benzene (10 ml) was added dropwise to a solution of *p*-iodobenzamidoxime (**1f**) (2.287 g, 9.97 mmol) in benzene (100 ml) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 2:1) to give (**31f**) as a yellow solid (0.926 g, 73 %). M.p.:70-72 °C

R_f : 0.94 (Eluant: n-Hexane:Ethyl acetate; 1:1)

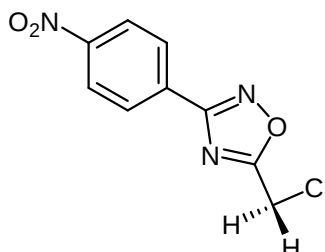
IR (KBr, ν : cm^{-1}): 3068 (Arom. C-H), 1695, 1562 (C=N), 1467, 1404, 1350, 1273, 1141, 846, 729 (C-Cl).

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 7.87 (d, $J=8.7$ Hz, 2H), 7.83 (d, $J=8.7$ Hz, 2H), 4.77 (s, 2H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): 174.5 (C=N), 168.4 (C=N), 138.2, 129.0, 125.6, 98.4, (-CH), 33.4 (-CH₂-).

MS (m/z , %)= 320 (M^+ , 100), 245 (48), 90 (22), 50 (8).

5-(Chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (**31g**)



To a solution of chloroacetylchloride (1.370 g, 12.13 mmol) in benzene (10 ml) was added dropwise to a solution of *p*-nitrobenzamidoxime (**1g**) (5.500 g, 30.36 mmol) in benzene (100 ml) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give (**31g**) as a white solid (1.321 g, 45 %). M.p.:88-89 °C

R_f: 0.90 (Eluant: n-Hexane:Ethyl acetate; 1:1)

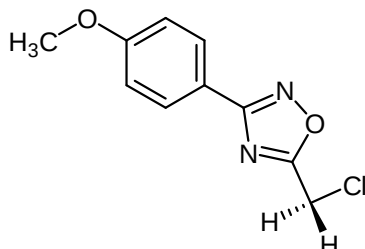
IR (KBr, ν : cm^{-1}): 3101 (Arom. C-H), 1612, 1573 (C=N), 1529 (N=O), 1415, 1356, 1294, 1107, 868, 721 (C-Cl).

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 8.25 (dd, $J=8.71, 19.52$ Hz, 4H), 4.72 (s, 2H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): $\delta=187.6$ (C=N), 175.2 (C=N), 149.7, 132.0, 128.5, 124.2, (-CH), 33.2 (-CH₂-),

MS (m/z , %)= 239 (M^+ , 100), 209 (80), 164 (44), 134 (34), 88 (44), 51 (30).

5-(Chloromethyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (31h)



To a solution of chloroacetylchloride (0.595 g, 5.27 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-methoxybenzamidoxime (**1h**) (2.189 g, 13.17 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 4:1) to give (**31h**) as a light yellow solid (1.183 g, 100 %). M.p.:39-40 °C

R_f: 0.75 (Eluant: n-Hexane:Ethyl acetate; 1:1)

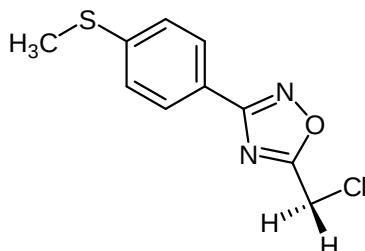
IR (KBr, ν : cm⁻¹): 3003 (Arom. C-H), 1612, 1597 (C=N), 1483, 1423, 1292, 1253, 1181, 842, 754 (C-Cl).

¹H NMR (δ _H, 400 MHz, CDCl₃): 8.04 (d, *J*=8.9 Hz, 2H), 7.01 (d, *J*=8.9 Hz, 2H), 4.75 (s, 2H), 3.73 (s, 3H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): δ =174.4 (C=N), 168.6 (C=N), 162.2(-C-), 129.1, 118.6, 114.4 (-CH), 55.4 (-CH₃-), 33.4 (-CH₂-).

MS (*m/z*, %)= 224 (M⁺, 100), 149 (43), 106 (29), 76 (11).

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



To a solution of chloroacetylchloride (0.261 g, 2.31 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-methylthiobenzamidoxime (**1j**) (1.056 g, 5.79 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give (**31j**) as a white solid (0.556 g, 100 %). M.p.:58-60 °C

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

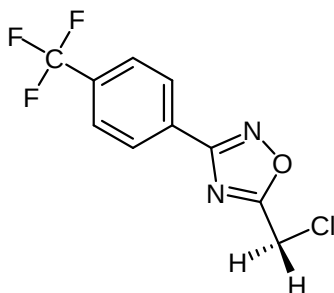
IR (KBr, ν : cm⁻¹): 3020 (Arom. C-H), 1664, 1595 (C=N), 1467, 1408, 1361, 1294, 1118, 825, 740 (C-Cl).

¹H NMR (δ _H, 400 MHz, CDCl₃): 7.91 (d, *J*=8.6 Hz, 2H), 7.24 (d, *J*=8.6 Hz, 2H), 4.67 (s, 2H), 2.44 (s, 3H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): δ =174.2 (C=N), 168.6 (C=N), 143.5, 127.7, 125.7, 122.4 (-CH), 33.4 (-CH₂-), 15.0 (-CH₃).

MS (*m/z*, %)= 240 (M⁺, 100), 149 (15), 106 (9), 63 (9).

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



To a solution of chloroacetylchloride (0.528 g, 4.68 mmol) in benzene (10 mL) was added dropwise to a solution of *p*-trifluoromethylbenzamidoxime (**1k**) (2.395 g, 11.73 mmol) in benzene (100 mL) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give **(31k)** as a yellow oil (1.229 g, 95 %).

R_f: 0.83 (Eluant: n-Hexane:Ethyl acetate; 1:1)

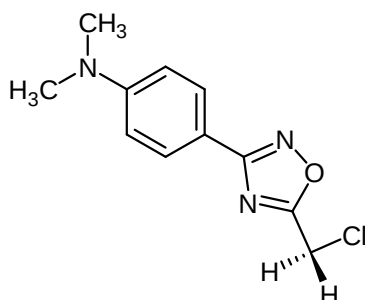
IR (KBr, ν : cm⁻¹): 3030 (Arom. C-H), 1656, 1597 (C=N), 1577, 1541, 1419, 1319, 1018, 854, 713 (C-Cl).

¹H NMR (δ _H, 400 MHz, CDCl₃): 8.24 (d, *J*=8.1 Hz, 2H), 7.79 (d, *J*=8.2 Hz, 2H), 4.79 (s, 2H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): δ =174.9 (C=N), 167.9 (C=N), 129.6, 128.0, 126.0, 126.0 (-CH-), 125.9 (-CF₃-) 33.3 (-CH₂-).

MS (*m/z*, %)= 262 (M⁺, 66), 187 (100), 139 (14), 109 (8), 75 (9).

5-(Chloromethyl)-3-(4-(*N,N*-dimethylamino)phenyl)-1,2,4-oxadiazole (31m)



To a solution of chloroacetylchloride (0.327 g, 2.89 mmol) in benzene (10 ml) was added dropwise to a solution of *p*-*N,N*-dimethylaminobenzamidoxime (**1m**) (1.300 g, 7.25 mmol) in benzene (100 ml) and the mixture was heated under reflux for 10h. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give (**31m**) as a white solid (0.387 g, 57 %). M.p.:81-83 °C

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

IR (KBr, ν : cm⁻¹): 3022 (Arom. C-H), 1653, 1647 (C=N), 1597, 1489, 1361, 1226, 1188, 817, 746 (C-Cl).

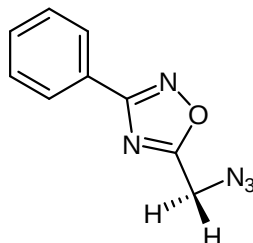
¹H NMR (δ _H, 400 MHz, CDCl₃): 7.95 (d, *J*=9.1 Hz, 2H), 6.76 (d, *J*=9.0 Hz, 2H), 4.73 (s, 2H), 3.06 (s, 6H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): δ =183.2 (C=N), 173.5 (C=N), 169.0 (-C-), 128.7, 121.1, 113.2 (-CH), 45.3 (-CH₂-), 39.9 (-CH₃-).

MS (*m/z*, %)= 237 (M⁺, 100), 145 (42), 102 (8), 63 (5).

Synthesis of Azides 88a-m

5-(Azidomethyl)-3-phenyl-1,2,4-oxadiazole (88a)



A stock solution of 0,5 M NaN₃ in DMSO was prepared by stirring the solution for 24 hours at 25°C. To a solution of 0,5 M NaN₃ (0,442 g, 6.80 mmol) in DMSO (15.0 mL) was added to a solution of 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (**31a**) (1,200 g, 6.18 mmol), and the mixture was stirred at room temperature for 1-3 day. The reaction was monitored by TLC. The reaction was quenched with water (50 mL) (slightly exothermic) and stirred until it cooled to room temperature. The reaction was extracted with diethyl ether (3×30 mL). The diethyl ether extracts were washed with water (2×50 mL) and brine solution (50 mL). The organic layer was dried with Na₂SO₄. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give (**88a**) as a yellow oil (0.685 g, 55 %).

R_f: 0.92 (Eluant: n-Hexane:Ethyl acetate; 1:1)

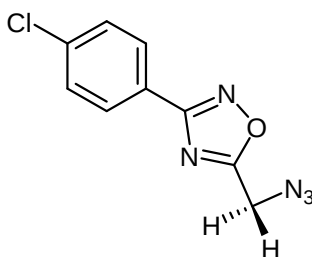
IR (KBr, ν: cm⁻¹): 3068 (Arom. C-H), 2108 (N=N=N), 1597, 1560 (C=N), 1475, 1446, 1346, 1288, 1114, 896, 714.

¹H NMR (δ_H, 400 MHz, CDCl₃): 8.13 (d, J=1.5 Hz, 1H), 8.12 (d, J=2.0 Hz, 1H), 7.56 (m, 2H), 7.51 (m, 1H), 4.65 (s, 2H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): δ =174.0 (C=N), 168.7 (C=N), 131.6, 129.0, 127.6, 126.5 (-CH), 45.1 (-CH₂-).

MS (m/z , %)= 207 (M^+ , 100), 173 (16), 119 (76), 91 (36), 64 (17).

5-(Azidomethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (**88b**)



A stock solution of 0,5 M NaN_3 in DMSO was prepared by stirring the solution for 24 hours at 25°C. To a solution of 0,5 M NaN_3 (0,442 g, 6.25 mmol) in DMSO (12.5 mL) was added to a solution of 5-(chloromethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (**31b**) (1,300 g, 5.68 mmol), and the mixture was stirred at room temperature for 1-3 day. The reaction was monitored by TLC. The reaction was quenched with water (50 mL) (slightly exothermic) and stirred until it cooled to room temperature. The reaction was extracted with diethyl ether (3×30 mL). The diethyl ether extracts were washed with water (2×50 mL) and brine solution (50 mL). The organic layer was dried with Na_2SO_4 . The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give (**88b**) as a yellow solid (0.453 g, 34 %). M.p.:40-41 °C
 R_f : 0.88 (Eluant: n-Hexane:Ethyl acetate; 1:1)

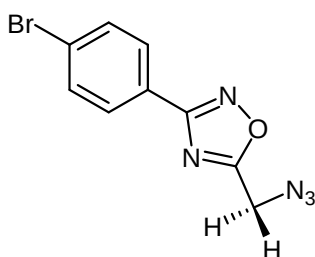
IR (KBr, ν : cm^{-1}): 3080 (Arom. C-H), 2110 (N=N=N), 1587, 1562 (C=N), 1471, 1410, 1365, 1282, 1095, 900, 837, 744.

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 8.06 (d, $J=8.6$ Hz, 2H), 7.50 (d, $J=8.6$ Hz, 2H), 4.64 (s, 2H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): $\delta=174.2$ (C=N), 168.0 (C=N), 137.8, 129.3, 128.9, 124.7 (-CH), 45.1 (-CH₂-).

MS (m/z , %)= 235 (M^+ , 81), 153 (100), 123 (12), 90 (54), 50 (23).

5-(Azidomethyl)-3-(4-bromophenyl)-1,2,4-oxadiazole (**88c**)



A stock solution of 0,5 M NaN_3 in DMSO was prepared by stirring the solution for 24 hours at 25°C. To a solution of 0,5 M NaN_3 (0,243 g, 3.74 mmol) in DMSO (7.0 mL) was added to a solution of 5-(chloromethyl)-3-(4-bromophenyl)-1,2,4-oxadiazole (**31c**) (0,930 g, 3.40 mmol), and the mixture was stirred at room temperature for 1-3 day. The reaction was monitored by TLC. The reaction was quenched with water (50 mL) (slightly exothermic) and stirred until it cooled to room temperature. The reaction was extracted with diethyl ether (3×30 mL). The diethyl ether extracts were washed with water (2×50 mL) and brine solution (50 mL). The organic layer was dried with Na_2SO_4 . The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 8:1) to give (**88c**) as a yellow solid (0.235 g, 25 %). M.p.:41-42 °C
 R_f : 0.88 (Eluant: n-Hexane:Ethyl acetate; 1:1)

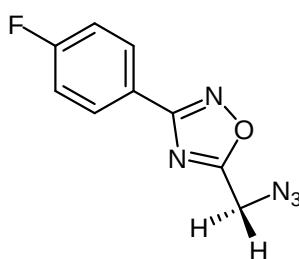
IR (KBr, ν : cm^{-1}): 3084 (Arom. C-H), 2110 (N=N=N), 1653, 1558 (C=N), 1467, 1406, 1361, 1276, 1070, 902, 829, 744.

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 7.99 (d, $J=8.6$ Hz, 2H), 7.66 (d, $J=8.6$ Hz, 2H), 4.65 (s, 2H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): δ =174.2 (C=N), 168.1 (C=N), 132.3, 129.0, 126.2, 125.1 (-CH), 45.1 (-CH₂-).

MS (m/z , %)= 281 (M^+ , 94), 251 (30), 197 (76), 169 (12), 114 (16), 90 (100), 50 (28).

5-(Azidomethyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (88d)



A stock solution of 0,5 M NaN_3 in DMSO was prepared by stirring the solution for 24 hours at 25°C. To a solution of 0,5 M NaN_3 (0,202 g, 3.10 mmol) in DMSO (6.0 mL) was added to a solution of 5-(chloromethyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole (**31d**) (0,600 g, 2.82 mmol), and the mixture was stirred at room temperature for 1-3 day. The reaction was monitored by TLC. The reaction was quenched with water (50 mL) (slightly exothermic) and stirred until it cooled to room temperature. The reaction was extracted with diethyl ether (3×30 mL). The diethyl ether extracts were washed with water (2×50 mL) and brine solution (50 mL). The organic layer was dried with Na_2SO_4 . The reaction mixture was concentrated *in vacuo*, and the crude

residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give **(88d)** as a yellow oil (0.290 g, 47 %).

R_f: 0.90 (Eluant: n-Hexane:Ethyl acetate; 1:1)

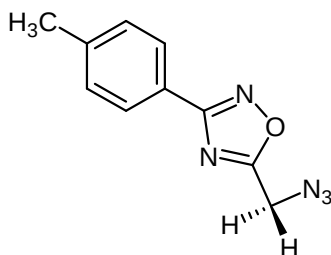
IR (KBr, ν : cm^{-1}): 3084 (Arom. C-H), 2104 (N=N=N), 1608, 1581 (C=N), 1483, 1419, 1367, 1234, 1157, 898, 846, 748.

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 8.12 (m, 2H), 7.21 (m, 2H), 4.64 (s, 2H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): δ =174.1 (C=N), 167.9 (C=N), 129.8, 122.4, 116.3, 116.0 (-CH), 45.1 (-CH₂-).

MS (m/z , %)= 219 (M^+ , 100), 191 (18), 137 (84), 109 (85), 75 (24), 57 (17).

5-(Azidomethyl)-3-p-tolyl-1,2,4-oxadiazole (**88e**)



A stock solution of 0,5 M NaN_3 in DMSO was prepared by stirring the solution for 24 hours at 25°C. To a solution of 0,5 M NaN_3 (0,206 g, 3.17 mmol) in DMSO (6.5 mL) was added to a solution of 5-(chloromethyl)-3-p-tolyl-1,2,4-oxadiazole (**31e**) (0,600 g, 2.88 mmol), and the mixture was stirred at room temperature for 1-3 day. The reaction was monitored by TLC. The reaction was quenched with water (50 mL) (slightly exothermic) and stirred until it cooled to room temperature. The reaction was extracted with diethyl ether (3×30 mL). The diethyl ether extracts were washed with water (2×50 mL) and brine solution (50 mL). The organic layer was dried with Na_2SO_4 . The reaction mixture was concentrated *in vacuo*, and the crude residue was

purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give **(88e)** as a yellow oil (0.253 g, 41 %).

R_f: 0.89 (Eluant: n-Hexane:Ethyl acetate; 1:1)

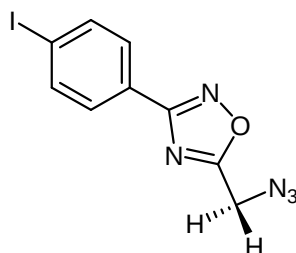
IR (KBr, ν : cm^{-1}): 3034 (Arom. C-H), 2104 (N=N=N), 1653, 1595 (C=N), 1481, 1413, 1340, 1286, 1112, 895, 829, 740.

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 8.01 (d, $J=8.2$ Hz, 2H), 7.32 (d, $J=8.0$ Hz, 2H), 4.64 (s, 2H), 2.45 (s, 3H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): δ =173.8 (C=N), 168.7 (C=N), 142.0, 129.7, 127.5, 123.3 (-CH), 45.1 (-CH₂-), 21.6 (-CH₃).

MS (m/z , %)= 215 (M^+ , 100), 187 (10), 133 (70), 91 (25), 63 (10).

5-(Azidomethyl)-3-(4-iodophenyl)-1,2,4-oxadiazole (**88f**)



A stock solution of 0,5 M NaN_3 in DMSO was prepared by stirring the solution for 24 hours at 25°C. To a solution of 0,5 M NaN_3 (0,179 g, 2.75 mmol) in DMSO (5.0 mL) was added to a solution of 5-(chloromethyl)-3-(4-iodophenyl)-1,2,4-oxadiazole (**31f**) (0,791 g, 2.50 mmol), and the mixture was stirred at room temperature for 1-3 day. The reaction was monitored by TLC. The reaction was quenched with water (50 mL) (slightly exothermic) and stirred until it cooled to room temperature. The reaction was extracted with diethyl ether (3×30 mL). The diethyl ether extracts were washed with water

(2×50 mL) and brine solution (50 mL). The organic layer was dried with Na₂SO₄. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give **(88f)** as a yellow solid (0.095 g, 12 %). M.p.: 50-51 °C, R_f: 0.96 (Eluant: n-Hexane:Ethyl acetate; 1:1)

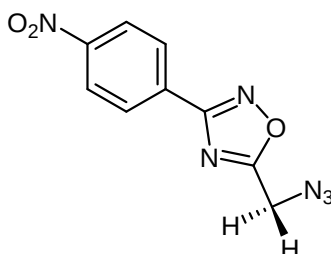
IR (KBr, ν : cm⁻¹): 3081 (Arom. C-H), 2119 (N=N=N), 1591, 1557 (C=N), 1467, 1402, 1317, 1109, 1008, 833, 738.

¹H NMR (δ _H, 400 MHz, CDCl₃): 7.86 (m, 4H), 4.65 (s, 2H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): δ =174.2 (C=N), 168.2 (C=N), 144.2, 138.5, 135.2, 129.0 (-CH), 45.1 (-CH₂-).

MS (m/z , %)= 327 (M⁺, 100), 299 (57), 245 (54), 90 (44), 50 (16).

5-(Azidomethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (**88g**)



A stock solution of 0,5 M NaN₃ in DMSO was prepared by stirring the solution for 24 hours at 25°C. To a solution of 0,5 M NaN₃ (0,391 g, 6.02 mmol) in DMSO (13.0 mL) was added to a solution of 5-(Chloromethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (**31g**) (1,310 g, 5.47 mmol), and the mixture was stirred at room temperature for 1-3 day. The reaction was monitored by TLC. The reaction was quenched with water (50 mL) (slightly exothermic) and stirred until it cooled to room temperature. The reaction was extracted

with diethyl ether (3×30 mL). The diethyl ether extracts were washed with water (2×50 mL) and brine solution (50 mL). The organic layer was dried with Na₂SO₄. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give **(88g)** as a yellow solid (0.350g, 26 %). M.p.:89-90 °C, R_f: 0.84 (Eluant: n-Hexane:Ethyl acetate; 1:1)

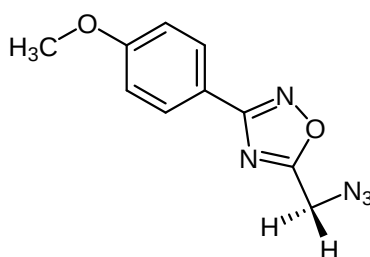
IR (KBr, v: cm⁻¹): 3107 (Arom. C-H), 2106 (N=N=N), 1610, 1577 (C=N), 1417, 1340, 1290, 1103, 860, 723.

¹H NMR (δ_H, 300 MHz, CDCl₃): 8.34 (m, 4H), 4.87 (s, 2H).

¹³C NMR (δ_C, 75 MHz, CDCl₃): δ=175.2 (C=N), 167.4 (C=N), 150.0, 133.8, 128.8, 124.5 (-CH), 45.3 (-CH₂-).

MS (*m/z*, %)= 246 (M⁺, 100), 241 (9), 187 (100), 168 (18), 139 (22), 109 (13), 75 (14).

5-(Azidomethyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (**88h**)



A stock solution of 0,5 M NaN₃ in DMSO was prepared by stirring the solution for 24 hours at 25°C. To a solution of 0,5 M NaN₃ (0,318 g, 4.90 mmol) in DMSO (9.0 mL) was added to a solution of 5-(chloromethyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (**31h**) (1,000 g, 4.45 mmol), and the

mixture was stirred at room temperature for 1-3 day. The reaction was monitored by TLC. The reaction was quenched with water (50 mL) (slightly exothermic) and stirred until it cooled to room temperature. The reaction was extracted with diethyl ether (3×30 mL). The diethyl ether extracts were washed with water (2×50 mL) and brine solution (50 mL). The organic layer was dried with Na₂SO₄. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give **(88h)** as a yellow oil (0.445 g, 43 %).

R_f: 0.83 (Eluant: n-Hexane:Ethyl acetate; 1:1)

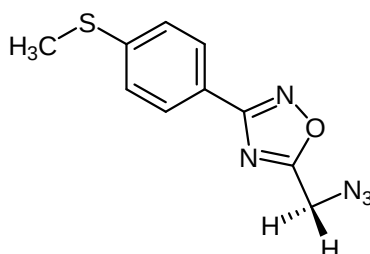
IR (KBr, ν : cm⁻¹): 3009 (Arom. C-H), 2108 (N=N=N), 1614, 1571 (C=N), 1483, 1425, 1342, 1174, 1008, 839, 752.

¹H NMR (δ _H, 400 MHz, CDCl₃): 8.05 (d, *J*=8.5 Hz, 2H), 7.02 (d, *J*=8.6 Hz, 2H), 4.62 (s, 2H), 3.88 (s, 3H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): δ =173.6 (C=N), 168.4 (C=N), 162.2, 129.2, 118.6, 114.4 (-CH), 55.4 (-CH₂-), 45.1 (-CH₃).

MS (*m/z*, %)= 231 (M⁺, 83), 203 (97), 133 (100), 90 (46), 50 (22).

5-(Azidomethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole (88j)



A stock solution of 0,5 M NaN₃ in DMSO was prepared by stirring the solution for 24 hours at 25°C. To a solution of 0,5 M NaN₃ (0,118 g, 1.82 mmol) in

DMSO (3.3 mL) was added to a solution of 5-(chloromethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole (**31j**) (0.398 g, 1.65 mmol), and the mixture was stirred at room temperature for 1-3 day. The reaction was monitored by TLC. The reaction was quenched with water (50 mL) (slightly exothermic) and stirred until it cooled to room temperature. The reaction was extracted with diethyl ether (3×30 mL). The diethyl ether extracts were washed with water (2×50 mL) and brine solution (50 mL). The organic layer was dried with Na₂SO₄. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 6:1) to give (**88j**) as a yellow oil (0.213 g, 52 %).

R_f: 0.86 (Eluant: n-Hexane:Ethyl acetate; 1:1)

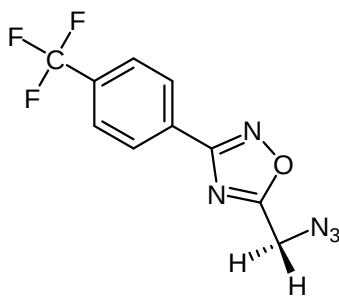
IR (KBr, ν : cm⁻¹): 2989 (Arom. C-H), 2108 (N=N=N), 1593, 1558 (C=N), 1471, 1408, 1340, 1162, 1089, 831, 746.

¹H NMR (δ _H, 300 MHz, CDCl₃): 8.00 (d, *J*=10.8 Hz, 2H), 7.30 (m, 2H), 4.62 (s, 2H), 2.52 (s, 3H).

¹³C NMR (δ _C, 75 MHz, CDCl₃): δ =174.1 (C=N), 168.6 (C=N), 143.7, 128.0, 126.0, 122.5 (-CH), 45.3 (-CH₂-), 15.2 (-CH₃).

MS (*m/z*, %)= 247 (M⁺, 100), 219 (67), 165 (62), 149 (88), 106 (17), 90 (12), 69 (12).

5-(Azidomethyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (**88k**)



A stock solution of 0,5 M NaN₃ in DMSO was prepared by stirring the solution for 24 hours at 25°C. To a solution of 0,5 M NaN₃ (0,128 g, 1.97 mmol) in DMSO (3.6 mL) was added to a solution of 5-(chloromethyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (**31k**) (0,470 g, 1.79 mmol), and the mixture was stirred at room temperature for 1-3 day. The reaction was monitored by TLC. The reaction was quenched with water (50 mL) (slightly exothermic) and stirred until it cooled to room temperature. The reaction was extracted with diethyl ether (3×30 mL). The diethyl ether extracts were washed with water (2×50 mL) and brine solution (50 mL). The organic layer was dried with Na₂SO₄. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 7:1) to give (**88k**) as a yellow oil (0.307 g, 64 %).

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

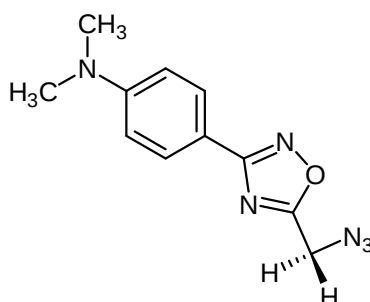
IR (KBr, ν: cm⁻¹): 2933 (Arom. C-H), 2100 (N=N=N), 1597, 1573 (C=N), 1485, 1419, 1329, 1174, 1066, 854, 759.

¹H NMR (δ_H, 400 MHz, CDCl₃): 8.24 (d, *J*=8.8 Hz, 2H), 7.77 (d, *J*=8.8 Hz, 2H), 4.66 (s, 2H).

¹³C NMR (δ_C, 100 MHz, CDCl₃): δ=174.8 (C=N), 168.0 (C=N), 133.7, 129.7, 128.2, 126.3 (-CF₃-), 45.3 (-CH₂-).

MS (m/z , %)= 269 (M^+ , 100), 241 (9), 187 (100), 168 (18), 139 (22) 109 (13), 75 (14).

5-(Azidomethyl)-3-(4-(*N,N*-dimethylamino)phenyl)-1,2,4-oxadiazole (88m)



A stock solution of 0,5 M NaN₃ in DMSO was prepared by stirring the solution for 24 hours at 25°C. To a solution of 0,5 M NaN₃ (0,090 g, 1.39 mmol) in DMSO (2.5 mL) was added to a solution of 5-(chloromethyl)-3-(4-(*N,N*-dimethylamino)phenyl)-1,2,4-oxadiazole (**31m**) (0,300 g, 1.29 mmol), and the mixture was stirred at room temperature for 1-3 day. The reaction was monitored by TLC. The reaction was quenched with water (50 mL) (slightly exothermic) and stirred until it cooled to room temperature. The reaction was extracted with diethyl ether (3×30ml). The diethyl ether extracts were washed with water (2×50 mL) and brine solution (50 mL). The organic layer was dried with Na₂SO₄. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 7:1) to give (**88m**) as a yellow solid (0.169 g, 55 %). M.p.:61-62 °C. R_f: 0.83 (Eluant: n-Hexane:Ethyl acetate; 1:1)

IR (KBr, ν : cm^{-1}): 2914 (Arom. C-H), 2098 (N=N=N), 1614, 1587 (C=N), 1491, 1435, 1375, 1276, 1197, 821, 756.

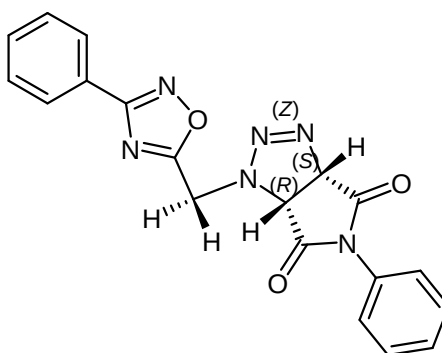
^1H NMR (δ_{H} , 400 MHz, CDCl_3): 7.96 (d, $J=9.1$ Hz, 2H), 6.76 (d, $J=9.1$ Hz, 2H), 4.60 (s, 2H), 3.06 (s, 6H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): δ =173.1 (C=N), 168.8 (C=N), 152.4, 133.4, 128.8, 111.7 (-CH), 45.1 (-CH₂-), 40.1 (-NCH₃).

MS (m/z , %)= 244 (M^+ , 59), 215 (65), 145 (100), 102 (13).

Synthesis of Dihydropyrrolo Triazoles 90 a-m and 93 a-d

(3a*S*,6a*R*)-5-Phenyl-1-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-1,6a-dihydropyrrolo[3,4-*d*][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (90a)



A mixture of *N*-phenyl maleimide (0.044 g, 0.252 mmol) and 5-(azidomethyl)-3-phenyl-1,2,4-oxadiazole (**88a**) (0.050 g, 0.240 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with hexane to give (**90a**) as a white solid (0.048 g, 54 %). M.p.:162-164 °C

R_f : 0.74 (Eluant: n-Hexane:Ethyl acetate; 1:1)

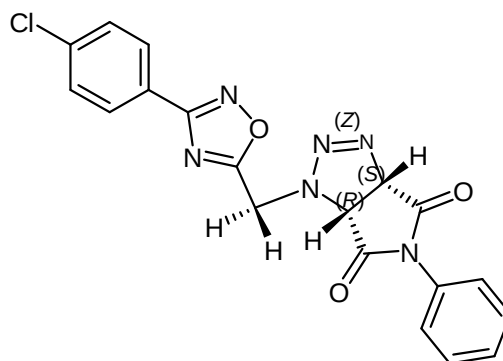
IR (KBr, ν : cm^{-1}): 3068 (Arom. C-H), 1716 (C=O), 1597, 1500 (C=N), 1475, 1444, 1384, 1348, 1188, 933, 717.

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 8.06 (d, $J=6.8$ Hz, 2H), 7.73 (m, 7H), 7.26 (m, 1H), 5.92 (d, $J=10.8$ Hz, 1H), 5.65 (d, $J=17.8$ Hz, 1H), 5.37 (d, $J=17.8$ Hz, 1H), 4.83 (d, $J=10.8$ Hz, 1H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): 175.4 (C=O), 171.6 (C=O), 170.1 (C=N), 168.2 (C=N), 131.7, 129.2, 129.1, 129.0, 128.5, 127.5, 126.8, 100.0 (-CH), 83.8 (-CH), 58.2(-CH), 44.5 (-CH₂-).

TOF AP⁺ (m/z , %)= 416 ($\text{M}+\text{MeCNH}^+$, 3), 375 ($\text{M}+\text{H}^+$, 7), 117 (8), 100 (100).

(3a*S*,6a*R*)-1-((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-phenyl-1,6a-dihydropyrrolo[3,4-*d*][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (90b)



A mixture of *N*-phenyl maleimide (0.039 g, 0.222 mmol) and 5-(azidomethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (**88b**) (0.050 g, 0.212 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in*

vacuo, and the crude residue was washed with hexane to give **(90b)** as a white solid (0.068 g, 78 %). M.p.:164-165 °C

R_f: 0.50 (Eluant: n-Hexane:Ethyl acetate; 1:1)

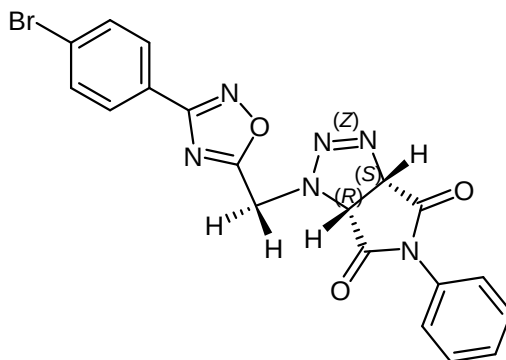
IR (KBr, ν : cm⁻¹): 3074 (Arom. C-H), 1720 (C=O), 1653, 1593 (C=N), 1494, 1471, 1388, 1340, 1089, 850, 740.

¹H NMR (δ _H, 400 MHz, CDCl₃): 7.91 (d, *J*=8.6 Hz, 2H), 7.37 (m, 6H), 7. (dd, *J*=2.8, 9.8 Hz, 2H), 5.84 (d, *J*=10.8 Hz, 1H), 5.51 (d, *J*=17.8 Hz, 1H), 5.35 (d, *J*=17.8 Hz, 1H), 4.73 (d, *J*=10.8 Hz, 1H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): 175.4 (C=O), 171.1 (C=O), 169.4 (C=N), 167.6 (C=N), 137.5, 131.2, 129.2, 129.2, 129.0, 128.9, 126.3, 124.7 (-CH), 83.5 (-CH), 58.3(-CH), 44.3 (-CH₂-).

TOF AP⁺ (*m/z*, %)= 450 (M+MeCNH⁺, 9), 409 (M+H⁺, 8), 117 (23), 100 (100).

(3a*S*,6a*R*)-1-((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-phenyl-1,6a-dihydropyrrolo[3,4-*d*][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (90c)



A mixture of *N*-phenyl maleimide (0.045 g, 0.261 mmol) and 5-(azidomethyl)-3-(4-bromophenyl)-1,2,4-oxadiazole **(88c)** (0.070 g, 0.249 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in*

vacuo, and the crude residue was washed with hexane to give **(90c)** as a white solid (0.080 g, 71 %). M.p.:156-157 °C

R_f: 0.62 (Eluant: n-Hexane:Ethyl acetate; 1:1)

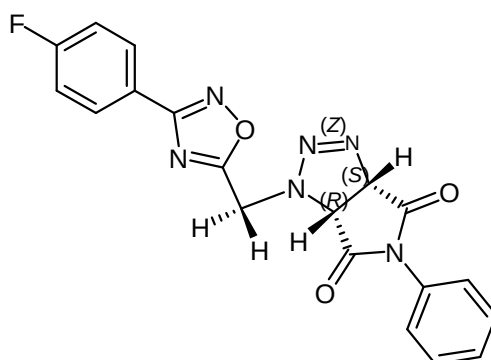
IR (KBr, ν : cm⁻¹): 3059 (Arom. C-H), 1722 (C=O), 1595, 1566 (C=N), 1498, 1471, 1383, 1342, 1190, 835, 742.

¹H NMR (δ _H, 400 MHz, CDCl₃): 7.91 (d, *J*=8.7 Hz, 2H), 7.62 (d, *J*=8.5 Hz, 2H), 7.44 (d, *J*=7.5 Hz, 3H), 7.25 (t, *J*=7.7 Hz, 2H), 5.83 (d, *J*=10.7 Hz, 1H), 5.52 (d, *J*=17.6 Hz, 1H), 5.37 (d, *J*=17.7 Hz, 1H), 4.72 (d, *J*=10.8 Hz, 1H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): 179.9 (C=O), 176.3 (C=O), 174.4 (C=N), 172.5 (C=N), 137.0, 136.9, 133.8, 131.3, 130.7, 130.0, 88.9 (-CH), 62.7 (-CH), 48.4 (-CH₂-).

TOF AP⁺ (*m/z*, %)= 453 (M⁺, 3), 117 (21), 100 (100).

(3a*S*,6a*R*)-1-((3-(4-Fluorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-phenyl-1,6a-dihydropyrrolo[3,4-*d*][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (90d)



A mixture of *N*-phenyl maleimide (0.060 g, 0.345 mmol) and 5-(azidomethyl)-3-(4-fluorophenyl)-1,2,4-oxadiazole **(88d)** (0.072 g, 0.329 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The

reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with hexane to give **(90d)** as a white solid (0.067 g, 52 %). M.p.:155-157 °C

R_f: 0.52 (Eluant: n-Hexane:Ethyl acetate; 1:1)

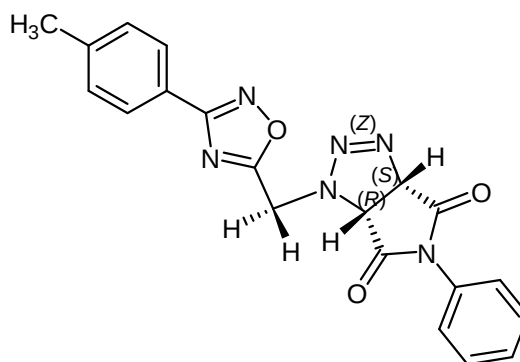
IR (KBr, ν : cm⁻¹): 3059 (Arom. C-H), 1724 (C=O), 1606, 1581 (C=N), 1479, 1417, 1383, 1342, 1190, 852, 740.

¹H NMR (δ _H, 300 MHz, CDCl₃): 8.04 (m, 2H), 7.45 (m, 3H), 7.30 (m, 4H), 5.93 (d, *J*=10.8 Hz, 1H), 5.59 (d, *J*=17.6 Hz, 1H), 5.40 (d, *J*=17.9 Hz, 1H), 4.82 (d, *J*=10.8 Hz, 1H).

¹³C NMR (δ _C, 75 MHz, CDCl₃): 174.5 (C=O), 171.2 (C=O), 169.4 (C=N), 167.6 (C=N), 130.9, 129.9, 129.3, 129.2, 126.3, 123.4, 122.4, 116.4 (-CH), 83.4 (-CH), 57.6 (-CH), 44.4 (-CH₂-).

TOF AP⁺ (*m/z*, %)= 434 (M+MeCNH⁺, 33), 393 (M+H⁺, 38), 117 (55), 100 (100).

(3a*S*,6a*R*)-5-Phenyl-1-((3-*p*-tolyl-1,2,4-oxadiazol-5-yl)methyl)-1,6a-dihydropyrrolo[3,4-*d*][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (90e)



A mixture of *N*-phenyl maleimide (0.042 g, 0.242 mmol) and 5-(azidomethyl)-3-*p*-tolyl-1,2,4-oxadiazole **(88e)** (0.050 g, 0.230 mmol) were stirred in

benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with hexane to give **(90e)** as a white solid (0.060 g, 68 %). M.p.:138-140 °C

R_f: 0.43 (Eluant: n-Hexane:Ethyl acetate; 1:1)

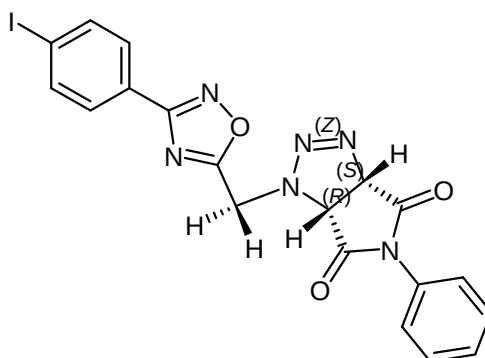
IR (KBr, ν : cm⁻¹): 3049 (Arom. C-H), 1720 (C=O), 1597, 1572 (C=N), 1483, 1383, 1342, 1107, 740.

¹H NMR (δ _H, 400 MHz, CDCl₃): 7.93 (d, *J*=8.2 Hz, 2H), 7.45 (m, 3H), 7.28 (m, 4H), 5.88 (d, *J*=10.8 Hz, 1H), 5.60 (d, *J*=17.8 Hz, 1H), 5.32 (d, *J*=17.8 Hz, 1H), 4.80 (d, *J*=10.8 Hz, 1H), 2.44 (s, 3H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): 173.4 (C=O), 170.7 (C=O), 168.7 (C=N), 168.5 (C=N), 130.6, 129.7, 129.4, 129.3, 128.4, 127.5, 126.2, 123.1 (-CH), 83.0 (-CH), 57.2(-CH), 44.4 (-CH₂-), 21.6 (-CH₃-).

TOF ES⁺ (*m/z*, %)= 427 (M+K⁺, 5), 359 (M-N₂⁺, 6), 274 (100), 146 (90), 129 (19), 105 (33).

(3a*S*,6a*R*)-1-((3-(4-Iodophenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-phenyl-1,6a-dihydropyrrolo[3,4-*d*][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (90f)



A mixture of *N*-phenyl maleimide (0.028 g, 0.160 mmol) and 5-(azidomethyl)-3-(4-iodophenyl)-1,2,4-oxadiazole (**88f**) (0.050 g, 0.153 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with hexane to give (**90f**) as a white solid (0.064 g, 84 %). M.p.:161-163 °C.

R_f: 0.61 (Eluant: n-Hexane:Ethyl acetate; 1:1)

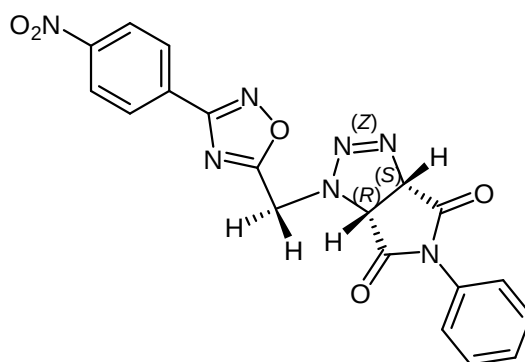
IR (KBr, ν : cm⁻¹): 3053 (Arom. C-H), 1716 (C=O), 1689, 1558 (C=N), 1498, 1402, 1384, 1334, 1195, 837, 742.

¹H NMR (δ _H, 300 MHz, CDCl₃): 7.80 (m, 5H), 7.38 (m, 4H), 5.93 (d, *J*=10.8 Hz, 1H), 5.60 (d, *J*=17.6 Hz, 1H), 5.41 (d, *J*=17.9 Hz, 1H), 4.81 (d, *J*=10.8 Hz, 1H).

¹³C NMR (δ _C, 75 MHz, CDCl₃): 174.7 (C=O), 171.2 (C=O), 169.4 (C=N), 167.9 (C=N), 138.2, 130.9, 129.3, 129.2, 129.1, 126.4, 125.6, 98.5 (-CH), 83.5 (-CH), 57.6 (-CH), 44.4 (-CH₂-).

TOF ES⁺ (*m/z*, %)= 541 (M+MeCNH⁺, 22), 521 (100), 478 (9), 391 (39).

(3a*S*,6a*R*)-1-((3-(4-Nitrophenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-phenyl-1,6a-dihydropyrrolo[3,4-*d*][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (90g)



A mixture of *N*-phenyl maleimide (0.044 g, 0.255 mmol) and 5-(azidomethyl)-3-(4-nitrophenyl)-1,2,4-oxadiazole (**88g**) (0.060 g, 0.244 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with hexane to give (**90g**) as a white solid (0.044 g, 43 %). M.p.:184-186 °C.

R_f: 0.54 (Eluant: n-Hexane:Ethyl acetate; 1:1)

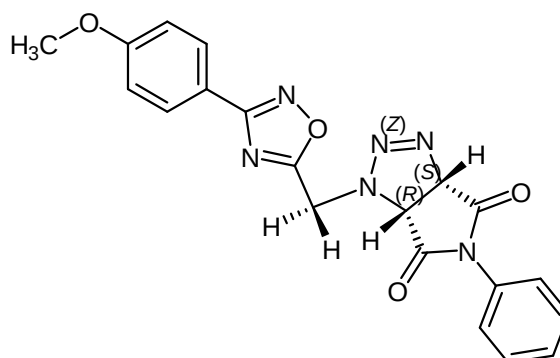
IR (KBr, ν : cm⁻¹): 3144 (Arom. C-H), 1720 (C=O), 1573, 1538 (C=N), 1385, 1334, 1190, 834, 744.

¹H NMR (δ _H, 300 MHz, CDCl₃): 8.30 (dd, *J*=8.3, 19.3 Hz, 4H), 7.42 (m, 5H), 5.94 (d, *J*=10.8 Hz, 1H), 5.64 (d, *J*=17.6 Hz, 1H), 5.48 (d, *J*=17.6 Hz, 1H), 4.82 (d, *J*=10.5 Hz, 1H).

¹³C NMR (δ _C, 75 MHz, CDCl₃): 176.6 (C=O), 172.0 (C=O), 170.4 (C=N), 167.0 (C=N), 149.8, 132.3, 131.9, 129.4, 129.3, 129.0, 127.1, 124.8 (-CH), 84.1 (-CH), 58.6 (-CH), 44.8 (-CH₂-).

TOF AP⁺ (*m/z*, %) = 461 (M+MeCNH⁺, 1), 391 (M-N₂⁺, 3), 165 (7), 117 (42), 100 (100).

(3a*S*,6a*R*)-1-((3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-phenyl-1,6a-dihydropyrrolo[3,4-*d*][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (90h)



A mixture of *N*-phenyl maleimide (0.055 g, 0.318 mmol) and 5-(azidomethyl)-3-(4-methoxyphenyl)-1,2,4-oxadiazole (**88h**) (0.070 g, 0.303 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with hexane to give (**90h**) as a white solid (0.116 g, 94 %). M.p.:141-143 °C.

R_f: 0.46 (Eluant: n-Hexane:Ethyl acetate; 1:1)

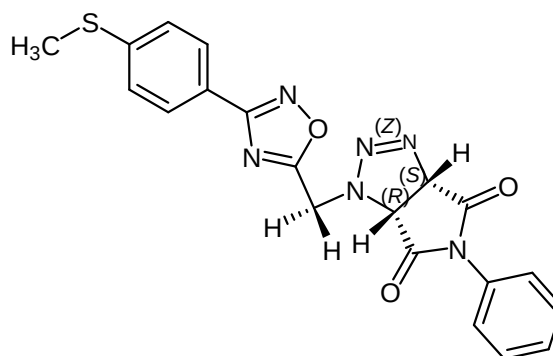
IR (KBr, ν : cm⁻¹): 3061 (Arom. C-H), 1720 (C=O), 1610, 1595 (C=N), 1481, 1425, 1377, 1257, 1178, 844, 748.

¹H NMR (δ _H, 400 MHz, CDCl₃): 7.90 (d, *J*=8.6 Hz, 2H), 7.38 (m, 4H), 6.99 (d, *J*=14.7 Hz, 3H) 5.86 (d, *J*=10.8 Hz, 1H), 5.53 (d, *J*=17.5 Hz, 1H), 5.42 (d, *J*=17.5 Hz, 1H), 4.75 (d, *J*=10.8 Hz, 1H), 3.82 (s, 3H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): 174.9 (C=O), 171.6 (C=O), 170.0 (C=N), 169.4 (C=N), 162.2, 131.6, 129.1, 129.1, 129.0, 126.8, 119.0, 114.6 (-CH), 83.8 (-CH), 58.2 (-CH), 55.6 (-CH₂-), 44.5 (-CH₃-).

TOF AP⁺ (*m/z*, %)= 446 (M+MeCNH⁺, 1), 377 (M-N₂⁺, 3), 117 (38), 100 (100).

(3aS,6aR)-1-((3-(4-(Methylthio)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-phenyl-1,6a-dihydropyrrolo[3,4-d][1,2,3]triazole-4,6(3aH,5H)-dione (90j)



A mixture of *N*-phenyl maleimide (0.056 g, 0.321 mmol) and 5-(azidomethyl)-3-(4-(methylthio)phenyl)-1,2,4-oxadiazole (**88j**) (0.076 g, 0.307 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with hexane to give (**90j**) as a white solid (0.117 g, 91 %). M.p.:156-158 °C.

R_f: 0.67 (Eluant: n-Hexane:Ethyl acetate; 1:1)

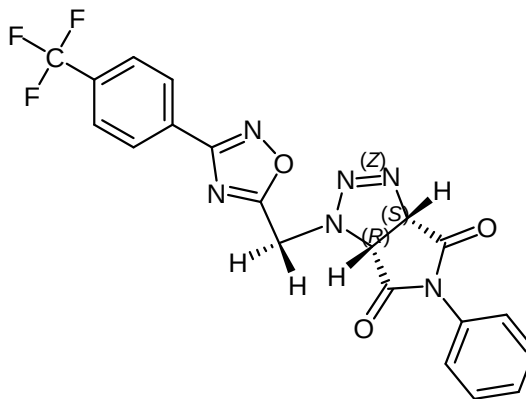
IR (KBr, ν : cm⁻¹): 3061 (Arom. C-H), 1720 (C=O), 1593, 1556 (C=N), 1498, 1469, 1383, 1186, 1114, 829, 742.

¹H NMR (δ _H, 300 MHz, CDCl₃): 7.92 (d, *J*=8.5 Hz, 2H), 7.42 (m, 3H), 7.27 (m, 4H), 5.92 (d, *J*=10.5 Hz, 1H), 5.58 (d, *J*=17.6 Hz, 1H), 5.38 (d, *J*=17.9 Hz, 1H), 4.81 (d, *J*=10.8 Hz, 1H), 2.89 (s, 3H).

¹³C NMR (δ _C, 75 MHz, CDCl₃): 174.3 (C=O), 171.2 (C=O), 169.4 (C=N), 168.1 (C=N), 143.6, 131.0, 129.3, 129.2, 127.8, 126.4, 125.7, 122.2 (-CH), 83.5 (-CH), 57.6 (-CH), 44.4 (-CH₂-), 15.0 (-CH₃).

TOF AP⁺ (*m/z*, %)= 462 (M+MeCNH⁺, 2), 421 (M+H⁺, 4), 392 (M-N₂⁺, 10), 391 (40), 248 (16), 117 (76), 100 (100).

(3a*S*,6a*R*)-5-Phenyl-1-((3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-1,6a-dihydropyrrolo[3,4-*d*][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (90k)



A mixture of *N*-phenyl maleimide (0.051 g, 0.292 mmol) and 5-(azidomethyl)-3-(4-(trifluoromethyl)phenyl)-1,2,4-oxadiazole (**88k**) (0.075 g, 0.279 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with hexane to give (**90k**) as a white solid (0.056 g, 46 %). M.p.:170-172 °C.

R_f: 0.39 (Eluant: n-Hexane:Ethyl acetate; 1:1)

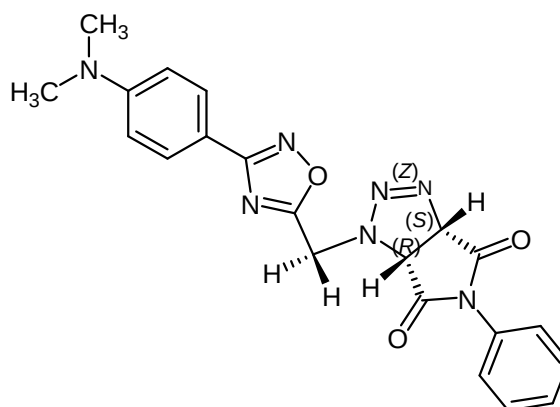
IR (KBr, ν : cm⁻¹): 3061 (Arom. C-H), 1718 (C=O), 1595, 1573 (C=N), 1500, 1419, 1323, 1197, 1064, 862, 746.

¹H NMR (δ _H, 300 MHz, CDCl₃): 8.19 (d, *J*=8.2 Hz, 2H), 7.75 (m, 2H), 7.34 (m, 5H), 5.92 (d, *J*=10.8 Hz, 1H), 5.62 (d, *J*=17.6 Hz, 1H), 5.48 (d, *J*=17.9 Hz, 1H), 4.81 (d, *J*=10.5 Hz, 1H).

¹³C NMR (δ _C, 75 MHz, CDCl₃): 175.2 (C=O), 171.2 (C=O), 169.5 (C=N), 167.2 (C=N), 132.8, 132.4, 131.0, 129.6, 129.0, 128.2, 127.9, 126.3, 125.8 (-CH), 83.5 (-CH), 57.7 (-CH), 44.3 (-CH₂-).

TOF AP⁺ (*m/z*, %)= 484 (M+MeCNH⁺, 45), 443 (M+H⁺, 36), 392 (36), 391 (100), 117 (19), 100 (73).

(3a*S*, 6a*R*)-1-((3-(4-(Dimethylamino)phenyl)-1,2,4-oxadiazol-5-yl)methyl)-5-phenyl-1,6a-dihydropyrrolo[3,4-*d*][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (90m)



A mixture of *N*-phenyl maleimide (0.045 g, 0.258 mmol) and 5-(azidomethyl)-3-(4-(*N,N*-dimethylamino)phenyl)-1,2,4-oxadiazole (**88m**) (0.060 g, 0.246 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with hexane to give (**90m**) as a white solid (0.099 g, 53 %). M.p.:152-154 °C.

R_f: 0.53 (Eluant: n-Hexane:Ethyl acetate; 1:1)

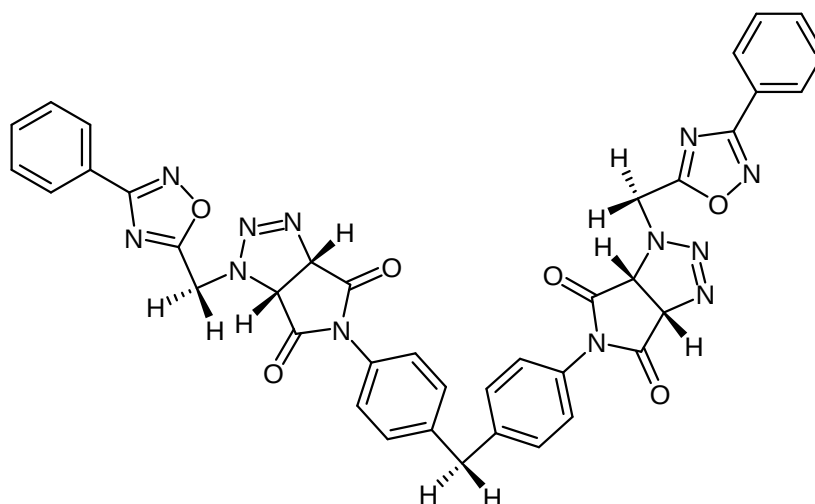
IR (KBr, ν: cm⁻¹): 3074 (Arom. C-H), 1720 (C=O), 1612, 1593 (C=N), 1492, 1431, 1348, 1193, 823, 742.

¹H NMR (δ_H, 300 MHz, CDCl₃): 7.89 (d, *J*=8.2 Hz, 2H), 7.36 (m, 5H), 6.75 (d, *J*=7.6 Hz, 2H), 5.90 (d, *J*=10.8 Hz, 1H), 5.57 (d, *J*=17.9 Hz, 1H), 5.29 (d, *J*=17.9 Hz, 1H), 4.81 (d, *J*=10.8 Hz, 1H), 3.05 (s, 6H).

^{13}C NMR (δ_{C} , 75 MHz, CDCl_3): 173.3 (C=O) 171.6 (C=O), 170.0 (C=N), 169.4 (C=N), 162.2, 130.8, 129.5, 128.9, 126.4, 111.7, 110.0, (-CH), 83.8 (-CH), 44.6 (-CH), 40.6 (-CH₂-), 40.0 (-CH₃-).

TOF ES⁺ (m/z , %)= 481 (M+MeCNa⁺, 35), 459 (M+MeCNH⁺, 36), 418 (M+H⁺, 9), 389 (M-N₂⁺, 10), 169 (14), 146 (100), 105 (31).

(3a*S*,6a*R*)-5-(4-((9*S*,10*R*)-4-((3a*S*,6a*R*)-4,6-Dioxo-1-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-3a,4,6,6a-tetrahydropyrrolo[3,4-*d*][1,2,3]triazol-5(1*H*)-yl)benzyl)phenyl)-1-((3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-1,6a-dihydropyrrolo[3,4-*d*][1,2,3]triazole-4,6(3a*H*,5*H*)-dione (91)



A mixture of 4,4-methylene bis(*N*-phenyl maleimide) (0.090 g, 0.250 mmol) and 5-(azidomethyl)-3-phenyl-1,2,4-oxadiazole (**88a**) (0.100 g, 0.500 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with hexane to give (**91**) as a white solid (0.095 g, 50 %). M.p. 172-174 °C.

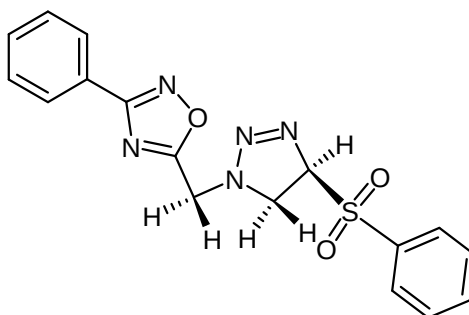
R_f: 0.63 (Eluant: n-Hexane:Ethyl acetate; 1:1)

IR (KBr, ν : cm^{-1}): 3074 (Arom. C-H), 1718 (C=O), 1595, 1572 (C=N), 1348, 1192, 719.

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 7.94 (s, 4H), 7.44 (m, 6H), 7.13 (d, $J=10.1$ Hz, 8H), 5.85 (d, $J=10.5$ Hz, 2H), 5.50 (dd, $J=17.4, 33.0$ Hz, 4H), 4.74 (d, $J=10.5$ Hz, 2H), 3.94 (s, 2H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): 175.3 (C=O), 171.3 (C=O), 170.0 (C=N), 168.2 (C=N), 141.3, 131.7, 129.8, 129.5, 129.2, 127.4, 126.8, 126.2 (-CH), 83.8 (-CH), 58.1 (-CH), 44.5 ($-\text{CH}_2-$), 29.5 ($-\text{CH}_2-$).

1-((3-Phenyl-1,2,4-oxadiazol-5-yl)methyl)-4-(phenylsulfonyl)-4,5-dihydro-1H-1,2,3-triazole (93a)



A mixture of phenyl vinyl sulfone (0.087 g, 0.504 mmol) and 5-(azidomethyl)-3-phenyl-1,2,4-oxadiazole (**88a**) (0.100 g, 0.500 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated in vacuo, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 2:1) to give (**93a**) as a white solid (0.083 g, 45 %). M.p.:120-122 °C.

R_f : 0.52 (Eluant: n-Hexane:Ethyl acetate; 1:1)

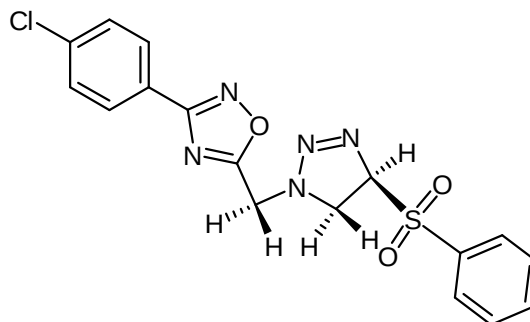
IR (KBr, ν : cm^{-1}): 3064 (Arom. C-H), 1597, 1573 (C=N), 1477, 1446, 1309, 1153, 742.

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 8.09 (d, $J=9.5$ Hz, 2H), 8.00 (d, $J=8.0$ Hz, 2H), 7.56 (m, 6H), 5.79 (dd, $J=7.9, 12.5$ Hz, 1H), 5.31 (d, $J=17.0$ Hz, 1H), 5.07 (d, $J=17.0$ Hz, 1H), 4.08 (dd, $J=7.8, 11.6$ Hz, 1H), 3.82 (t, $J=12.0$ Hz, 1H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): 172.8 (C=N) 168.2 (C=N), 135.5, 134.3, 131.1, 129.1, 128.8, 128.5, 127.0, 125.5, 94.7, (-CS-), 44.8, 44.3 (- CH_2 -).

LC-MS (70 eV) (m/z , %)= 342 ($\text{M}^+ - \text{N}_2$, 100), 278 (32), 200 (15), 172 (53), 121 (27).

1-((3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-(phenyl sulfonyl)-4,5-dihydro-1H-1,2,3-triazole (93b)



A mixture of phenyl vinyl sulfone (0.085 g, 0.504 mmol) and 5-(azidomethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (**88b**) (0.118 g, 0.500 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography

(n-hexane:ethyl acetate; 2:1) to give **(93b)** as a white solid (0.141 g, 70 %).

M.p.:125-126 °C.

R_f: 0.53 (Eluant: n-Hexane:Ethyl acetate; 1:1)

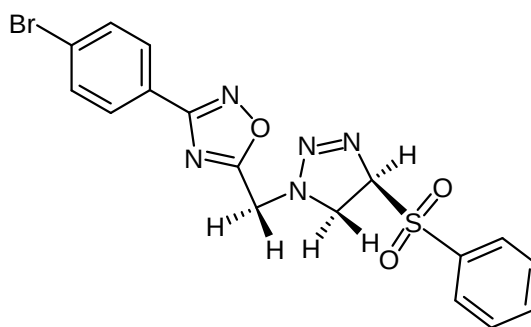
IR (KBr, ν : cm⁻¹): 3061 (Arom. C-H), 1597, 1566 (C=N), 1416, 1410, 1309, 1153, 742.

¹H NMR (δ _H, 400 MHz, CDCl₃): 8.01 (t, *J*=9.0 Hz, 4H), 7.60 (t, *J*=7.8 Hz, 2H), 7.49 (d, *J*=8.5 Hz, 3H), 5.78 (dd, *J*=7.9, 12.5 Hz, 1H), 5.29 (d, *J*=17.1 Hz, 1H), 5.08 (d, *J*=17.1 Hz, 1H), 4.10 (dd, *J*=10.1, 16.8 Hz, 1H), 3.80 (t, *J*=12.1 Hz, 1H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): 173.6 (C=N) 167.9 (C=N), 137.9, 136.1, 134.8, 129.6, 129.3, 129.2, 128.8, 124.5, 95.2, (-CS-), 45.3, 44.7 (-CH₂-).

LC-MS (70 eV) (*m/z*, %)= 375 (M⁺-N₂, 65), 312 (53), 206 (100), 171 (11).

1-((3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl)methyl)-4-(phenyl sulfonyl)-4,5-dihydro-1H-1,2,3-triazole (93c)



A mixture of phenyl vinyl sulfone (0.061 g, 0.360 mmol) and 5-(azidomethyl)-3-(4-bromophenyl)-1,2,4-oxadiazole **(88c)** (0.100 g, 0.357 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in*

vacuo, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 2:1) to give **(93c)** as a light yellow solid (0.067 g, 42 %). M.p.:158-160 °C.

R_f: 0.49 (Eluant: n-Hexane:Ethyl acetate; 1:1)

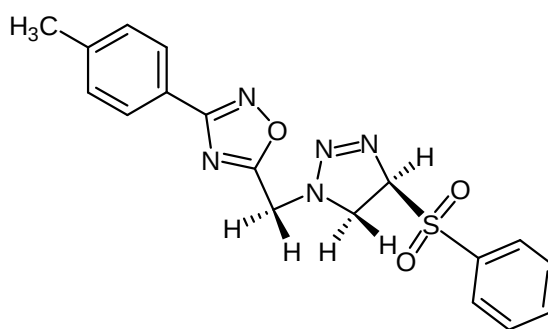
IR (KBr, ν : cm⁻¹): 2955 (Arom. C-H), 1595, 1566 (C=N), 1446, 1408, 1346, 1155, 840, 738.

¹H NMR (δ _H, 400 MHz, CDCl₃): 8.02 (d, *J*=6.3 Hz, 2H), 7.96 (m, *J*=7.9 Hz, 2H), 7.63 (m, 5H), 5.75 (dd, *J*=7.9, 12.5 Hz, 1H), 5.30 (d, *J*=17.1 Hz, 1H), 5.07 (d, *J*=17.1 Hz, 1H), 4.07 (dd, *J*=7.9, 11.6 Hz, 1H), 3.80 (t, *J*=12.2 Hz, 1H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): 174.0 (C=N) 168.0 (C=N), 135.1, 134.8, 132.5, 129.8, 129.5, 129.0, 126.2, 125.0, 95.2, (-CS-), 45.0, 44.0 (-CH₂-).

LC-MS (70 eV) (*m/z*, %)= 451 (M⁺, 100), 417 (11), 282 (10), 226 (13).

4-(Phenylsulfonyl)-1-((3-p-tolyl-1,2,4-oxadiazol-5-yl)methyl)-4,5-dihydro-1H-1,2,3-triazole (93d)



A mixture of phenyl vinyl sulfone (0.085 g, 0.504 mmol) and 5-(azidomethyl)-3-p-tolyl-1,2,4-oxadiazole **(88e)** (0.104 g, 0.500 mmol) were stirred in benzene (25 mL) and the mixture was heated under reflux for 2-4 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in*

vacuo, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 2:1) to give **(93d)** as a light yellow solid (0.093 g, 48 %). M.p.:152-154 °C.

R_f: 0.48 (Eluant: n-Hexane:Ethyl acetate; 1:1)

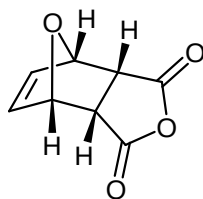
IR (KBr, ν : cm⁻¹): 2980 (Arom. C-H), 1593, 1570 (C=N), 1448, 1343, 1153, 829, 742.

¹H NMR (δ _H, 400 MHz, CDCl₃): 7.98 (m, 3H), 7.82 (m, 1H), 7.71 (m, 1H), 7.59 (m, 1H), 7.31 (t, *J*=8.3 Hz, 3H), 5.79 (dd, *J*=7.8 Hz, 12.6, 1H), 5.28 (d, *J*=17.0 Hz, 1H), 5.05 (d, *J*=17.0 Hz, 1H), 4.06 (dd, *J*=7.8 Hz, 11.7 1H), 3.81 (t, *J*=12.1 Hz, 1H), 2.45 (s, 3H).

¹³C NMR (δ _C, 100 MHz, CDCl₃): 173.1 (C=N) 168.6 (C=N), 142.1, 135.9, 134.8, 129.7, 129.6, 128.3, 127.5, 123.2, 95.2, (-CS-), 45.3, 44.8 (-CH₂-), 21.6 (-CH₃).

LC-MS (70 eV) (*m/z*, %)= 356 (M⁺-N₂, 100), 242 (22), 214 (16), 186 (8).

7-Oxabicyclo [2.2.1] hept-5-ene-cis-2,3-dicarboxylic anhydride (**94**)



A mixture of furan (10 mL, 137.5 mmol) and maleic anhydride (2.500 g, 25.5 mmol) were mixed in ether (10 mL) and the mixture was stirred at room temperature for 48 h. The reaction was monitored by TLC. The white precipitated was collected by suction filtered (3.679 g, 87 %). M.p.:110-111 °C.

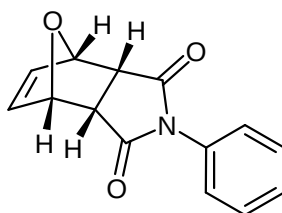
R_f: 0.63 (Eluant: n-Hexane:Ethyl acetate; 1:1)

IR (KBr, ν : cm^{-1}): 3001 (Arom. C-H), 1788 (C=O), 1282, 1244, 1213, 1085, 1022, 954, 881.

^1H NMR (δ_{H} , 300 MHz, CDCl_3): 6.59 (s, 2H), 4.60 (s, 2H), 3.19 (s, 2H).

^{13}C NMR (δ_{C} , 75 MHz, CDCl_3): 170.1 (C=O), 137.2, 82.5, 49.0 (-CH-).

7-Oxabicyclo [2.2.1] hept-5-ene-2,3-dicarboxy-*N*-phenylimide (95)



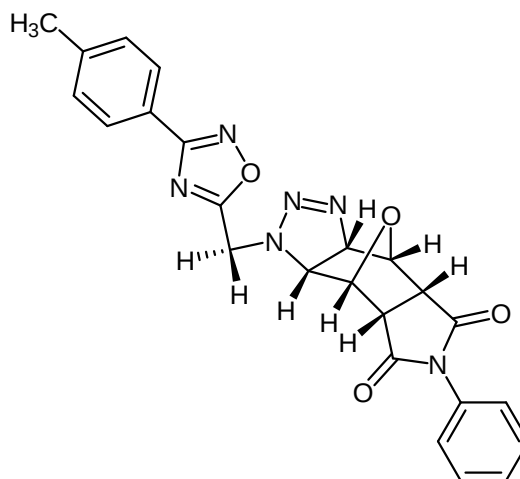
A mixture of furan (2.0 mL, 27.5 mmol) and *N*-phenyl maleimide (0.882 g, 5.1 mmol) were mixed in ether (10 mL) and the mixture was stirred at room temperature for 48 h. The reaction was monitored by TLC. The white precipitated was collected by suction filtered (0.506 g, 41 %). M.p.:123-124 °C.

R_f: 0.63 (Eluant: n-Hexane:Ethyl acetate; 1:1)

IR (KBr, ν : cm^{-1}): 3012 (Arom. C-H), 1708 (C=O), 1496, 1381, 1325, 1184, 923, 875.

Synthesis of Triazoles 96a and 97a-d

1-[3-(4-Methylphenyl)-1,2,4-oxadiazol-5-yl]methyl-6-phenyl-3a, 4,4a,7a,8,8a-hexahydro-4,8-epoxy[1,2,3]triazolo[4,5-]isoindole-5,7(1H)-dione (96a)



A mixture of 7-oxabicyclo [2.2.1] hept-5-ene-2,3-dicarboxy-N-phenylimide (**94b**) (0.092 g, 0.380 mmol) and 5-(azidomethyl)-3-p-tolyl-1,2,4-oxadiazole (**88e**) (0.075 g, 0.360 mmol) were stirred in CH_2Cl_2 (5 mL) the mixture was stirred at room temperature for 5 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with ethyl acetate to give (**96a**) as a white solid (0.030 g, 18 %).

M.p.: 210-212 °C.

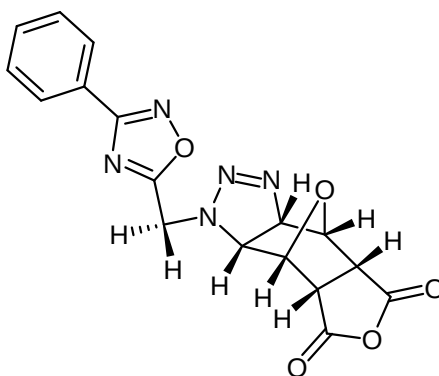
R_f : 0.39 (Eluant: n-Hexane:Ethyl acetate; 1:1)

IR (KBr, ν : cm^{-1}): 2995 (Arom. C-H), 1716 (C=O), 1595, 1500 (C=N), 1390, 1347, 1193, 887, 719.

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 7.98 (d, $J=8.1$ Hz, 2H), 7.47 (m, 3H), 7.30 (dd, $J=7.8, 20.3$ Hz, 6H), 5.43 (t, $J = 23.6$ Hz, 2H), 5.16 (d, $J=8.4$ Hz, 2H), 3.62 (d, $J=7.1$ Hz, 1H), 3.17 (d, $J = 7.1$ Hz, 1H), 2.45 (s, 3H).

LC-MS (70 eV) (m/z , %)= 429 ($\text{M}^+ - \text{N}_2$, 100).

(3a*S*,4*S*,4a*R*,7a*S*,8*R*,8a*R*)-1-([3-Phenyl]-1,2,4-oxadiazol-5-yl)methyl)-3a,4,4a,7a,8,8a-hexahydro-1H-4,8-epoxyfuro[3,4-][1,2,3]benzotriazole-5,7-dione (97a)



A mixture of 7-oxabicyclo [2.2.1] hept-5-ene-cis-2,3-dicarboxylic anhydride (**94a**) (0.122 g, 0.743 mmol) and 5-(azidomethyl)-3-phenyl-1,2,4-oxadiazole (**88a**) (0.144 g, 0.716 mmol) were stirred in CH_2Cl_2 (5 mL) the mixture was stirred at room temperature for 5 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with ethyl acetate to give (**97a**) as a light yellow solid (0.105 g, 40 %). M.p.:154-156 °C.

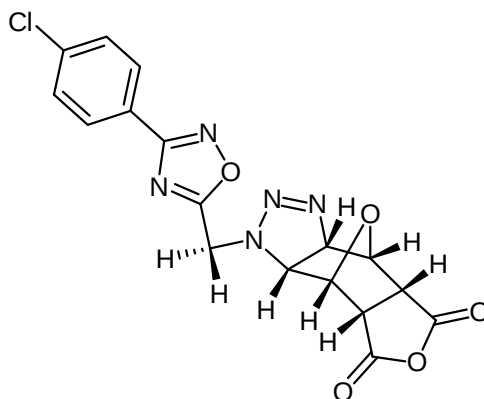
R_f : 0.39 (Eluant: n-Hexane:Ethyl acetate; 1:1)

IR (KBr, ν : cm^{-1}): 2989 (Arom. C-H), 1778 (C=O), 1600, 1529 (C=N), 1477, 1352, 1095, 933, 825.

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 8.02 (m, 2H), 7.60 (m, 3H), 5.51 (d, $J=17.7$ Hz, 1H), 5.35 (d, $J=17.7$ Hz, 1H), 5.23 (d, $J=9.4$ Hz, 1H), 5.12 (d, $J=5.1$ Hz, 1H), 4.12 (d, $J=9.4$ Hz, 1H), 4.12 (d, $J=9.4$ Hz, 1H), 3.68 (d, $J=7.3$ Hz, 1H), 3.53 (d, $J=7.3$ Hz, 1H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): 176.9 (C=O), 172.4 (C=O), 172.2 (C=N), 168.1 (C=N), 132.2, 129.8, 127.5, 126.4, 88.0, 83.0, 61.0, 49.0 (-CH), 48.0 (-CH), 44.0 (-CH).

(3a*S*,4*S*,4a*R*,7a*S*,8*R*,8a*R*)-1-([3-(4-Chlorophenyl)-1,2,4-oxadiazol-5-yl]methyl)-3a,4,4a,7a,8,8a-hexahydro-1*H*-4,8-epoxyfuro[3,4-][1,2,3]benzotriazole-5,7-dione (97b)



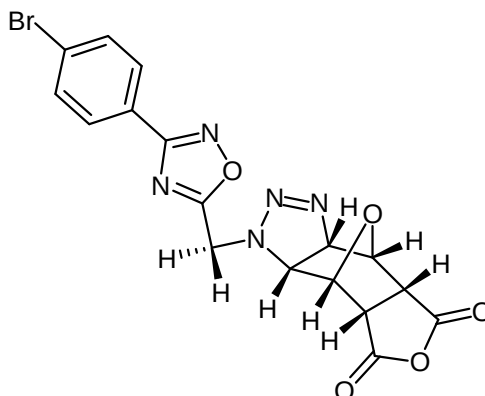
A mixture of 7-oxabicyclo [2.2.1] hept-5-ene-cis-2,3-dicarboxylic anhydride (**94a**) (0.043 g, 0.262 mmol) and 5-(azidomethyl)-3-(4-chlorophenyl)-1,2,4-oxadiazole (**88b**) (0.059 g, 0.250 mmol) were stirred in CH₂Cl₂ (5 mL) the mixture was stirred at room temperature for 5 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with ethyl acetate to give (**97b**) as a white solid (0.025 g, 25 %). M.p.:158-160 °C.

R_f: 0.42 (Eluant: n-Hexane:Ethyl acetate; 1:1)

IR (KBr, ν : cm⁻¹): 2987 (Arom. C-H), 1797 (C=O), 1597, 1566 (C=N), 1410, 1346, 1087, 947, 746.

¹H NMR (δ _H, 400 MHz, CDCl₃): 8.02 (d, *J*=8.6 Hz, 2H), 7.51 (d, *J*=8.6 Hz, 2H), 5.41 (d, *J*=5.1 Hz, 1H), 5.13 (t, *J*=7.8 Hz, 2H), 3.98 (d, *J*=9.0 Hz, 1H), 3.42 (d, *J*=7.5 Hz, 1H), 3.31 (d, *J*=7.5 Hz, 1H).

(3a*S*,4*S*,4a*R*,7a*S*,8*R*,8a*R*)-1-{[3-(4-Bromophenyl)-1,2,4-oxadiazol-5-yl]methyl}-3a,4,4a,7a,8,8a-hexahydro-1*H*-4,8-epoxyfuro[3,4-][1,2,3]benzotriazole-5,7-dione (97c)



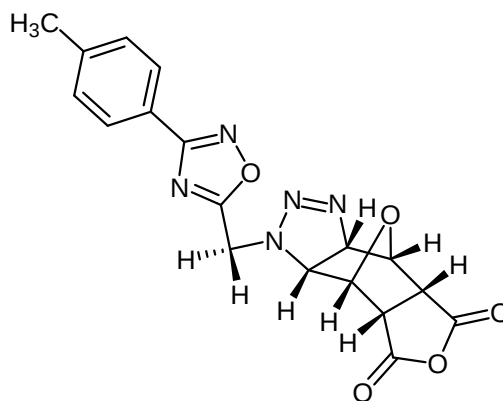
A mixture of 7-oxabicyclo [2.2.1] hept-5-ene-cis-2,3-dicarboxylic anhydride (**94a**) (0.046 g, 0.281 mmol) and 5-(azidomethyl)-3-(4-bromophenyl)-1,2,4-oxadiazole (**88c**) (0.075 g, 0.268 mmol) were stirred in CH₂Cl₂ (5 mL) the mixture was stirred at room temperature for 5 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with ethyl acetate to give (**97c**) as a white solid (0.015 g, 13 %). M.p.:156-158 °C.

R_f: 0.45 (Eluant: n-Hexane:Ethyl acetate; 1:1)

IR (KBr, ν: cm⁻¹): 2985 (Arom. C-H), 1795 (C=O), 1595, 1560 (C=N), 1408, 1344, 1085, 940, 740.

¹H NMR (δ_H, 400 MHz, CDCl₃): 7.95 (d, *J*=8.6 Hz, 2H), 7.67 (d, *J*=8.6 Hz, 2H), 5.13 (t, *J*=7.8 Hz, 2H), 3.98 (d, *J*=9.0 Hz, 2H), 3.42 (d, *J*=7.5 Hz, 2H), 3.31 (d, *J*=7.4 Hz, 2H).

(3a*S*,4*S*,4a*R*,7a*S*,8*R*,8a*R*)-1-([3-(4-Methylphenyl)-1,2,4-oxadiazol-5-yl]methyl)-3a,4,4a,7a,8,8a-hexahydro-1*H*-4,8-epoxyfuro[3,4-][1,2,3]benzotriazole-5,7-dione (97d)



A mixture of 7-oxabicyclo [2.2.1] hept-5-ene-cis-2,3-dicarboxylic anhydride (**94a**) (0.092 g, 0.560 mmol) and 5-(azidomethyl)-3-p-tolyl-1,2,4-oxadiazole (**88e**) (0.121 g, 0.540 mmol) were stirred in CH_2Cl_2 (5 mL) the mixture was stirred at room temperature for 5 day. The reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo*, and the crude residue was washed with ethyl acetate to give (**97d**) as a white solid (0.035 g, 17 %).

M.p.:162-164 °C.

R_f : 0.36 (Eluant: n-Hexane:Ethyl acetate; 1:1)

IR (KBr, ν : cm^{-1}): 2999 (Arom. C-H), 1728 (C=O), 1593, 1572 (C=N), 1413, 1344, 1102, 742.

^1H NMR (δ_{H} , 400 MHz, CDCl_3): 7.86 (d, $J=8.0$ Hz, 2H), 7.22 (d, $J=8.0$ Hz, 2H), 4.70 (m, 2H), 4.06 (m, 1H), 3.07 (m, 2H), 2.43 (s, 3H).

^{13}C NMR (δ_{C} , 100 MHz, CDCl_3): 176.0 (C=O), 172.0 (C=O), 168.0 (C=N), 141.5 (C=N), 129.5, 127.3, 123.0, 60.5, 51.0, (-CH), 21.3 (-CH), 14.0 (-CH₃).

REFERENCES

[1] Lossen, W. and Schifferdecker, P., 1873, Ueber Isuretin, eine dem Harnstoff isomere Base, *Ann. Chem.*, 166, 295.

[2] Tiemann, F., *Ber.*, Ueber die Einwirkung von Hydroxylamin auf Nitrile, 17, 126-129.

[3] Bandiera, T., Albini, F. M., Albini, E., 1987, Synthesis and antifungal activity of some allylamine derivatives, *J.Heterocyclic Chem.*, 24, 1597-1598.

[4] Sindelar, K., Sedivy, Z., Hrubantova, M., Valchar, M., Metysava, J., and Protiva, M., 1988, *Collect. Czech. Commun.*, 53, 381.

[5] Lenaers, R., Eloy, F., and Moussebois, C., 1962, Synthèse du dérivé diméthylé et de quelques dérivés monosubstitués de l'oxadiazole-1,2,4, *Helv. Chim. Acta*, 45, 437-441.

[6] Goldbeck, O., 1891, Zur Kenntniss der stickstoffhaltigen Abkömmlinge der *p*-Homosalicylsäure, *Ber.*, 24, 3658-3667.

[7] Hurd, R. N. and De La Mater, G., 1961, The preparation and chemical properties of thionamides, *Chem. Revs.*, 61, 45-86.

[8] Spilker, A., 1889, Ueber neue stickstoffhaltige Abkömmlinge der Salicylsäure, *Ber.*, 22, 2767-2789.

[9] Tiemann, F., Ueber eine neue Bildungsweise der Amidoxime, 1886, *Ber.*, 19, 1668.

[10] Schiff, H., 1902, Ueber einige Reactionen der Amidoxime, *Ann.*, 321, 357-371.

- [11] Durio, E., and Dugone, S., 1936, *Gazz. Chim. Ital.*, 66, 139.
- [12] Wieland, H., and Bauer, H., 1906, Ueber Benznitrosolsäure, *Ber.*, 39, 1480-1488.
- [13] Pinner, A., 1884, Einwirkung von Hydroxylamin auf die Imidoäther und die Amidine. Acidoxime, *Ber.*, 17, 184-186.
- [14] Lossen, W., 1884, Ueber die Struktur der Hydroxylaminderivate, *Ber.*, 17, 1587-1589.
- [15] Werner, A. and Bloch, C., 1899, Ueber o-Chlorbenzhydroximsäurechlorid und Umwandlungsproducte desselben, *Ber.*, 32, 1975-1985.
- [16] Werner, A. and Buss, H., 1894, Ueber Benzhydroximsäurechlorid, *Ber.*, 27, 2193-2201.
- [17] Bordwell, G. F. and Ji G. Z., 1992, Equilibrium acidities and homolytic bond dissociation energies of the H-O bonds in oximes and amidoximes, *J. Org. Chem.*, 57, 3019-3025.
- [18] Bauer, L., Nambury, C.N.V. and Bell, C.L., 1964, Studies in the chemistry of 3- and 5- isoxazolones, *Tetrahedron*, 20, 165-171.
- [19] Swinbourne, J. F., Hunt, H. J., Klinkert, G., 1979, Advances in Indolizine Chemistry, *Adv. Heterocycl. Chem.*, 23, 103-170.
- [20] Gupta, R. R., Kumar, M., Gupta, V., 2005, Heterocyclic Chemistry: Five membered Heterocycles, 1st ed., Springer, India, 422.
- [21] Jole, J. A., Mills, K., 2004, Heterocyclic Chemistry. 4th ed., Blackwell, Oxford, 648.
- [22] Katritzky, A. R., Charles, W. R., 1984, Comprehensive Heterocyclic Chemistry II, 1st, Pergamon press, New York, 736.

[23] a) Jochims, J. C., 1996, in *Comprehensive Heterocyclic Chemistry II*, Elsevier, Oxford, 906. Chem. b) Hemming, K., 2001. Recent developments in the synthesis, chemistry, and applications of the fully unsaturated 1,2,4-oxadiazoles, *J. Chem. Res.*, 209-216.

[24] Tiemann, F., Krüger, P., 1884, Ueber Amidoxime und Azoxime, *Ber. Dtsch. Chem. Ges.*, 17, 1685-1698.

[25] Diana, G. D., Volkots, D. L., Nitz, T. J., Baily, T. R., Long, M. A., Vescio, N., Aldous, S., Pevear, D. C., Dutko, F., 1994, Oxadiazoles as Ester Bioisosteric Replacements in Compounds Related to Disoxaril. Antirhinovirus Activity *J. Med. Chem.*, 37, 2421–2436.

[26] Borg, S. Vollinga, R. C. Labarre, M. Payza, K. Terenius, L. Luthman, K., 1999, Design, Synthesis, and Evaluation of Phe-Gly Mimetics: Heterocyclic Building Blocks for Pseudopeptides, *J. Med. Chem.*, 42, 4331–4342.

[27] Ahn, J. M., Boyle, N. A., MacDonald, M. T., Janda, K. D., 2002, Peptidomimetics and Peptide Backbone Modifications, *Mini Rev. Med. Chem.*, 2, 463–473.

[28] Watjen, F., Baker, R., Engelstoff, M., Herbert, R., MacLeod, A., Knight, A., Merchant, K., Moseley, J., Saunders, J., Swain, C. J., Wong, E., Springer, J. P., 1989, Novel benzodiazepine receptor partial agonists: oxadiazolylimidazobenzodiazepines, *J. Med. Chem.*, 32, 2282–2291.

[29] Leite, A. C. L., Vieira, R. F., de Faria, A. R., Wanderley, A. G., Afiatpour, P., Ximenes, E. C. P. A., Srivastava, R. M., De Oliveira, C. F., Medeiros, M. V., Antunes, E., Brondani, D. J., 2000, Synthesis, anti-inflammatory and antimicrobial activities of new 1,2,4-oxadiazoles peptidomimetics, *Il Farmaco*, 55, 719–724.

[30] Bezerra, N. M. M., De Oliveira, S. P., Srivastava, R. M., Da Silva, J. R., 2005, Synthesis of 3-aryl-5-decapentyl-1,2,4-oxadiazoles possessing antiinflammatory and antitumor properties, *Il Farmaco*, 60, 955–960.

[31] Nicolaidis, D. N., Fylaktakidou, K. C., Litinas, K. E., Hadjipavlou-Litina, D. Eur., 1998, Synthesis and biological evaluation of several coumarin-4-carboxamidoxime and 3-(coumarin-4-yl)-1,2,4-oxadiazole derivatives, *Eup. J. Med. Chem.*, 33, 715– 724.

[32] Diana, G. D., Volkots, D. L., Nitz, T. J., Bailey, T. R., Long, M. A., Vescio, N., Aldous, S., Pevear, D. C., Dutko, F. J., 1994, Oxadiazoles as Ester Bioisosteric Replacements in Compounds Related to Disoxaril. Antirhinovirus Activity, *J. Med. Chem.*, 37, 2421–2436.

[33] Amarasinghe, K. K. D., Evidokimov, A. G., Xu, K., Clark, C. M., Maier, M. B., Srivastava, A., Colson, A.-O., Gerwe, G. S., Stake, G. E., Howard, B. W., Pokross, M. E., Gray, J. L., Peters, K. G., 2006, Design and synthesis of potent, non-peptidic inhibitors of HTP β , *Bioorg. Med. Chem. Lett.*, 16, 4252–4256.

[34] Orlek, B. S., Blaney, F. E., Brown, F., Clark, M. S. G., Hadley, M. S., Hatcher, J., Riley, G. J., Rosenberg, H. E., Wadsworth, H. J., Wyman, P., Comparison of azabicyclic esters and oxadiazoles as ligands for the muscarinic receptor, *J. Med. Chem.*, 34, 2726–2735.

[35] Street, L. J., Baker, R., Book, T., Kneen, C. O., MacLeod, A. M., Merchant, K. J., Showell, G. A., Saunders, J., Herbert, R. H., Freedman, S. B., Harley, E. A., 1990, Synthesis and biological activity of 1,2,4-oxadiazole derivatives: highly potent and efficacious agonists for cortical muscarinic receptors, *J. Med. Chem.*, 33, 2690–2697.

[36] Clitherow, J. W., Beswick, P., Irving, W. J., Scopes, D. I. C., Barnes, J. C., Clapham, J., Brown, J. D., Evans, D. J., Hayes, A. G., 1996, Novel 1, 2, 4-oxadiazoles as potent and selective histamine H₃ receptor antagonists, *Bioorg. Med. Chem. Lett.*, 6, 833–838.

[37] Zoltewicz, J. A., Deady, L. W., 1978, Quaternization of Heteroaromatic Compounds: Quantitative Aspects, *Adv. Heterocycl. Chem.*, 22, 71–121.

[38] a) Brinn, I. M., C. Carvalho, E. M., Heisel, F., Miehe, J. A., 1991, Excited-state acidity of bifunctional molecules. 2. Picosecond emission of 5-(2-hydroxyphenyl)-3-phenyl-1,2,4-oxadiazole, *J. Phys. Chem.*, 95, 6540–6544. b) Carvalho, C., Brinn, I., Baumann, W., Reis, H., Nagy, Z., 1997, Excited-state acidity of bifunctional compounds Part 5 5-(2-Hydroxyphenyl)-3-phenyl-1,2,4-oxadiazole and 3-(2-hydroxyphenyl)-5-phenyl-1,2,4-oxadiazole, *J. Chem. Soc., Faraday Trans.*, 93, 3325. c) Ra, D. Y., Cho, N. S., Kang, S. K., Choi, E. S., Suh, I. H., 1999, Synthetic and tautomeric studies of 5-amino-2,3-dihydro-1,2,4-oxadiazol-3-one, *J. Chem. Soc., Perkin Trans. 2*, 81.

[39] Brown, P. J., Ghosh, P. B., 1969, The spectra, ionization, and deuteration of oxazoles and related compounds, *J. Chem. Soc. B*, 270.

[40] Meot-Ner, M., Liebman, J. F., Del Bene, J. E., 1986, Proton affinities of azoles: experimental and theoretical studies, *J. Org. Chem.*, 51, 1105-1110.

[41] Rauk, A., Hunt, I. R., Keay, B. A., 1994, Lewis Acidity and Basicity: An Ab Initio Study of Proton and BF₃ Affinities of Oxygen-Containing Organic Compounds, *J. Org. Chem.*, 59, 6808-6816.

[42] Matyus, P., Fuji, K., Tanaka, K., 1994, Density functional calculations on heterocyclic compounds. : Part 1. Studies of protonations of 5- and 6-membered nitrogen heterocyclics, *Tetrahedron*, 50, 2405-2414.

[43] Stefaniak, L., Roberts, J. D., Witanowski, M. G., Webb, A., 1984, A ¹⁵N NMR study of some azoles, *Org. Magn. Reson.*, 22, 215-220.

[44] Trifonov, R. E., Volovodenko, A. P., Vergizov, S. N., Shirinbekov, N. I., Gindin, V. A., Koren, A. O., and Ostrovskii, V. A., 2005, Basicity of Phenyl- and Methyl-Substituted 1,2,4-Oxadiazoles, *Helvetica Chimica Acta*, 85, 1790-1797.

[45] a) Kaboudin, B., Saadati, F., 2005, Novel method for the synthesis of 1,2,4-oxadiazoles using alumina supported ammonium fluoride under solvent-free condition, *J. Heterocycl. Chem.*, 42, 699-701. b) Srivastava, R. M., Seabra, G. M., 1997, Preparation and Reactions of 3-[3(Aryl)-1,2,4-Oxadiazol-5-yl] Propionic Acids, *J. Braz. Chem. Soc.*, 8, 397. d) de Freitas, J. J. R., de Freitas, J. C. R., da Silva, L. P., de Freitas Filho, J. R., Kimura, G. Y. V., Srivastava, R. M., 2007, Microwave-induced one-pot synthesis of 4-[3-(aryl)-1,2,4-oxadiazol-5-yl]-butan-2-ones under solvent free conditions, *Tetrahedron Lett.*, 48, 6195-6198. e) Belen'kii, L. I., Brokhovetskii, D. B., Krayushkin, M. M., 1990, Synthesis of 3,5-diaryl-1,2,4-oxadiazoles from trichloromethylarenes and areneamidoximes, *Tetrahedron*, 46, 1659-1668. f) Denney, D. B., Feig, G., 1959, The Reactions of N,N'-Dicyclohexyl-

carbodiimide with Benzoyl Peroxide and t-Butyl Perbenzoate, *J. Am. Chem. Soc.*, 81, 225-228.

[46] a) Katritzky, A. R., Shestopalov, A. A., Suzuki, K., 2005, A convenient synthesis of chiral 1,2,4-oxadiazoles from N-protected (α -aminoacyl)benzotriazoles, *ARKIVOC*, 7, 36. b) Braga, V. M. L., Melo, S. J., Srivastava, R. M., Falcão, E. P. S., 2004, Synthesis of New 1,2,4-Oxadiazole Carrying (1'S,2'S)-*t*-Butyloxycarbonyl-1-amino-2-methyl-1-butyl and (1'S)-*t*-Butyloxycarbonyl-1'-amino-1'-ethyl Groups at C-5, *J. Braz.Chem. Soc.*, 15, 603. c) Melo, S. J., Sobral, A. D., Lopes, H. L., Srivastava, R. M., 1998, Synthesis of Some 3-aryl-1,2,4-oxadiazoles Carrying a Protected L-alanine Side Chain, *J. Braz.Chem. Soc.*, 9, 465.

[47] Deegan, T. L., Nitz, T. J., Cebzanov, D., Pufko, D. E., and Porco Jr., J. A., 1999, Parallel synthesis of 1,2,4-oxadiazoles using CDI activation, *Bioorg. & Med. Chem. Lett.*, 9, 209-212.

[48] Filho, R. A. W., Bezerra, N. N. M., Guedes, M. J., and Srivastava, R. M., 2009, An Easy Synthesis of 3,5-Disubstituted 1,2,4-Oxadiazoles from Carboxylic Acids and Arylamidoximes Mediated by Ethyl Chloroformate, *J.Braz. Chem.Soc.*, 00, 1-5.

[49] Jakopin, Z., Roskar, R., Dolenc, M.S., 2007, Synthesis of 3,5-disubstituted 1,2,4-oxadiazoles as peptidomimetic building blocks, *Tetrahedron Letters*, 48, 1465-1468.

[50] Yarovenko, V. N., Kosarev, S. A., Zavarzin, I. V., and Krayushkin, M. M., 2002, Synthesis of 3-carbamoyl-1,2,4-Oxadiazoles, *Russ.Chem.Bull., Int.Ed.*, 51, 1857-1861.

[51] Ağırbaş, H., Sümengen, D., Dürüst, Y., Dürüst, N., 1992, The reaction of amidoximes with chloroacetyl chloride, *Synthetic Communications*, 22, 209-217.

[52] Adib, M., Jahromi, A. H., Tavoosi, N., Mahdavi, M., and Bijanzadeh, H. R., 2006, Microwave-assisted efficient, one-pot, three-component synthesis of

3,5-disubstituted 1,2,4-oxadiazole under solvent-free conditions, *Tetrahedron Lettres*, 47, 2965-2967.

[53] Lin, Y., Lang, S. A., Lovell, M. F., and Perkinson, N. A., 1979, New Synthesis of 1,2,4-Triazoles and 1,2,4-Oxadiazoles, *J. Org. Chem.*, 44, 4160.

[54] Neidlein, R. and Li, S., 1995, The syntheses of heterocyclic compounds with 1,2,4-oxadiazole as well as 1,2-Pyrazole-Rings, *Synth. Commun.*, 25, 16, 2379.

[55] Brase, S., Knepper, K., Gil G., Zimmermann, V., 2005, Organic Azides: An Exploding Diversity of a Unique Class of Compounds, *Angew. Chem. Int. Ed.*, 44, 5188-5240.

[56] a) Griess, P., 1864, On a New Class of Compounds in Which Nitrogen Is Substituted for Hydrogen, *Philos. Trans. R. Soc. London*, 13, 375-384. b) Griess, P., 1865, *Justus Liebigs Ann. Chem.*, 135, 131.

[57] Smith, P. A. S., 1946, The Curtius Reaction, *Org. React.*, 3, 337-349.

[58] Boyer, J. H., Canter, F. C., 1954, Alkyl and Aryl Azides, *Chem. Rev.*, 54, 1-57.

[59] Scriven, E. F. V., 1984, Azides and Nitrenes: Reactivity and Utility, Orlando, Fla., 1297.

[60] Lin, T. S., Prusoff, W. H., 1978, A novel synthesis and biological activity of several 5-halo-5'-amino analogs of deoxyribopyrimidine nucleosides, *J. Med. Chem.*, 21, 106-109.

[61] Betterton, E. A., 2003, Environmental Fate of Sodium Azide Derived from Automobile Airbags. *Critical Reviews in Environmental Science and Technology*, 33, 423-458.

[62] Bayley, H., 1983, Photogenerated reagents in biochemistry and molecular biology, Elsevier science publishers B.V., Netherlands, 187.

[63] Nguyen, M. T., Sengupta, D., Ha T. K., 1996, Another Look at the Decomposition of Methyl Azide and Methanimine: How Is HCN Formed?, *J. Phys. Chem.*, 100, 6499-6503.

[64] Capitosti, S.M., Hansen, T. P., Brown, M. L., 2003, Facile Synthesis of an Azido-Labeled Thalidomide Analogue, *Org. Lett.*, 5, 2865-2867.

[65] a) Lowe-Ma, C. K., Nissan, A., Wilson, W. S., 1990, Tetrazolo[1,5-a]pyridines and furazano[4,5-b]pyridine 1-oxides, *J. Org. Chem.*, 55, 3755-3761. b) Stadlbauer, W., Fischer, M., Hojas, G., 2000, Thermal Cyclization of 4-azido-3-nitropyridines to Furoxanes, *J. Heterocycl. Chem.*, 37, 1253-1256.

[66] Anna, F.D., Marullo, S., Noto, R., 2008, Ionic Liquids/[bmim][N₃] Mixtures: Promising Media for the Synthesis of Aryl Azides by S_NAr, *J. Org. Chem.*, 73, 6224-6228.

[67] Tilley, T. D., Gavenonis, J., 2002, Tantalum Alkyl and Silyl Complexes of the Bulky (Terphenyl)imido Ligand [2,6-(2,4,6-Me₃C₆H₂)₂C₆H₃N=]²⁻ ([Ar*N=]²⁻). Generation and Reactivity of [(Ar*N=)(Ar*NH)Ta(H)(OSO₂CF₃)], Which Reversibly Transfers Hydride to an Aromatic Ring of the Arylamide Ligand, *Organometallics*, 21, 5549 -5563.

[68] Kim, Y.H., Kim, K., Shim, S. B., 1986, Facile synthesis of azides: Conversion of hydrazines using dinitrogen tetroxide, *Tetrahedron Lett.*, 27, 4749-4752.

[69] Tor, Y., Liu, Q., 2003, Simple Conversion of Aromatic Amines into Azides, *Org. Lett.*, 5, 2571-2572.

[70] Hassner, A., and Fowler, F. W., 1968, A General Synthesis of Vinyl Azides from Olefins. Stereochemistry of Elimination from β -Iodo Azides, *J. Org. Chem.*, 33, 2686-2691.

[71] Hemetsberger, H. and Knittel, D., 1972, Synthese und Thermolyse von α -Azidoacrylestern, *Monatsh. Chem.*, 103, 194-204.

[72] Pinho e Melo, T. M. V. D., Lopes, Cardoso, C. S. J., and Gonsalves, A. L., Rocha, A. M. A., 2001, Synthesis of 2-halo-2H-aziridines, *Tetrahedron*, 57, 6203-6208.

[73] Huang, X., Shen, R., Zhang, T., 2007, Reaction of allenyl esters with sodium azide: An efficient synthesis of E- Vinyl azides and polysubstituted pyrroles, *J. Org. Chem.*, 72, 1534-1537.

[74] He, L., Byun, H. S., and Bittman, R., 2000, Stereoselective preparation of ceramide and its skeleton backbone modified analogues *via* cyclic thionocarbonate intermediates derived by catalytic asymmetric dihydroxylation of α,β -unsaturated ester precursors, *J. Org. Chem.*, 65, 7627-7633.

[75] Enders, D., Klein, D., 1999, A Novel enantioselective synthesis of α -azido ketones, *Synlett.*, 719-720.

[76] Ju, Y., Kumar, D., and Varma, R. S., 2006, Revisiting nucleophilic substitution reactions: Microwave-assisted synthesis of azides, thiocyanates, and sulfones in an aqueous medium, *J. Org. Chem.*, 71, 6697-6700,

[77] Park, S. H., 2003, Synthesis of azides from alkyl halides in DMSO, *Bull. Korean Chem.*, 24, 253-255.

[78] Campbell, L. V., Elsinga, P. H., Mirfeizi, L., Dierckx, R. A., Feringa, B. L., 2008, Copper free click: 1,3-dipolar cycloaddition of azides and arynes, *Org. Biomol. Chem.*, 6, 3461-3463.

[79] Huisgen, R., 1963, 1,3-Dipolar Cycloadditions. Past and Future, *Angew. Chem., Int. Ed. Engl.*, 2, 565-598.

[80] Huisgen, R., 1963, 1,3-Dipolar Cycloadditions. Kinetic and Mechanism, *Angew. Chem., Int. Ed. Engl.*, 2, 633-645.

[81] (a) Padwa, A., Weingarten, M. D., 1996, Cascade Processes of Metallo Carbenoids, *Chem. Rev.*, 96, 223-269. (b) Mehta G., Muthusamy S., 2002, Tandem cyclization–cycloaddition reactions of rhodium generated carbenoids from α -diazo carbonyl compounds *Tetrahedron*, 58, 9477-9504.

[82] Huisgen, R., 1984, in 1,3-Dipolar Cycloaddition Chemistry, Vol. 1, A. Padwa, ed., *Wiley-Interscience*, New York, Chapter 1, p. 1.

[83] Brown, W. H., Foote, C. S., 2002, Fundamental derivatives of carboxylic acids, *Organic Chemistry*, 3rd Edition, Emily Barrosse, Orlando, FL, 646.

[84] Sincilar, A. J., del Amo, V, P. D., 2009, Structure-reactivity relationships in a recognition mediated [3+2] dipolar cycloaddition reaction, *Org. Biomol. Chem.*, 7, 330 - 3318.

[85] İvgen H., 2008, The synthesis of five and six-membered heterocycles containing oxygen, nitrogen and phosphorus, MSc Thesis, Department of Chemistry, Abant İzzet Baysal University, Bolu, p.177.

[86] Akcan M., 2007, The ring closure reactions of amidoximes with phenylboronic acid, MSc Thesis, Department of Chemistry, Abant İzzet Baysal University, Bolu, p.176.

Chemical structure: ClC[C@@H]1N=NC(=O)N1c2ccccc2

IR Spectrum (cm⁻¹):

- 3400.00 (broad, O-H stretch)
- 3000.00 (C-H stretch)
- 2900.00 (C-H stretch)
- 1600.00 (aromatic ring vibration)
- 1500.00 (aromatic ring vibration)
- 1450.00 (aromatic ring vibration)
- 1380.00 (aromatic ring vibration)
- 1300.00 (aromatic ring vibration)
- 1250.00 (aromatic ring vibration)
- 1150.00 (aromatic ring vibration)
- 1100.00 (aromatic ring vibration)
- 1050.00 (aromatic ring vibration)
- 1000.00 (aromatic ring vibration)
- 950.00 (aromatic ring vibration)
- 900.00 (aromatic ring vibration)
- 850.00 (aromatic ring vibration)
- 800.00 (aromatic ring vibration)
- 750.00 (aromatic ring vibration)
- 700.00 (aromatic ring vibration)
- 650.00 (aromatic ring vibration)
- 600.00 (C-Cl stretch)
- 550.00 (C-Cl stretch)
- 500.00 (C-Cl stretch)
- 450.00 (C-Cl stretch)
- 400.00 (C-Cl stretch)

Chemical structure of 2-chloro-4-phenyl-1,2,4-oxadiazole (SMILES: c1ccccc1c2nc(C(Cl)H)no2) is shown above the spectrum.

The spectrum displays the following chemical shifts (ppm) and integrations:

Chemical Shift (ppm)	Integration
3249.43, 3248.48, 3242.14, 3240.96, 3022.16, 3013.99, 3006.49, 3000.09	0.8740, 1.4256
199.70	1.0000

104

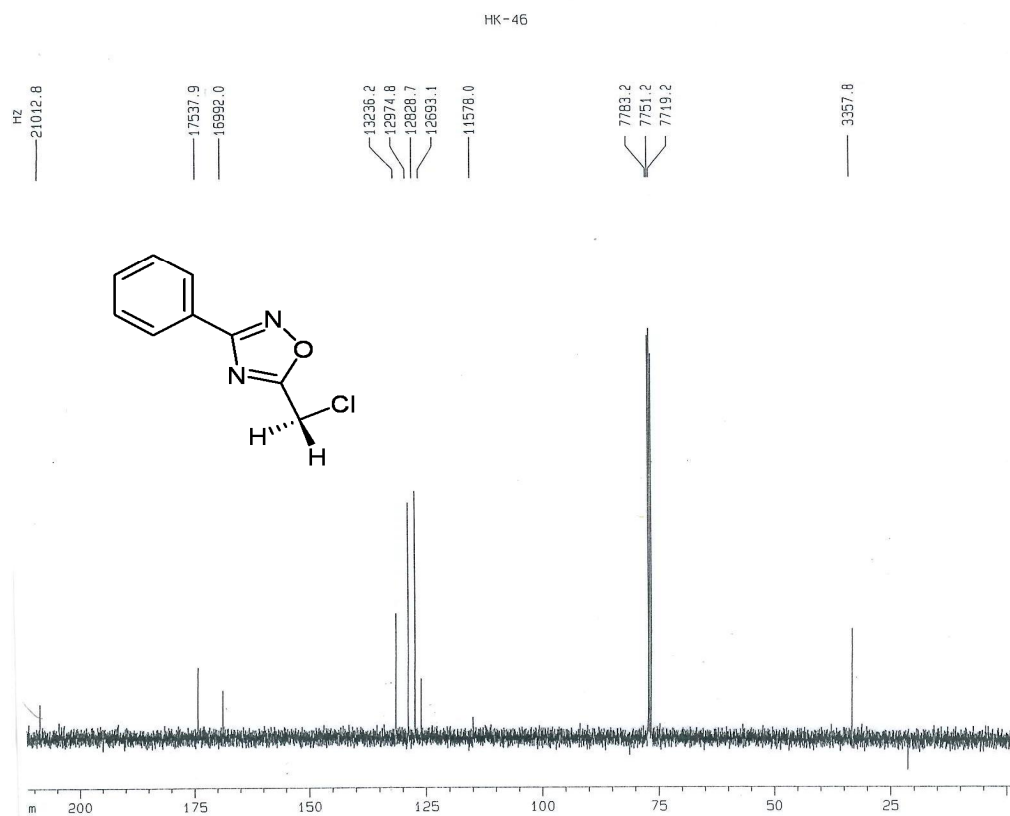


Figure 4. 3 ¹³C NMR Spectrum of compound **31a**

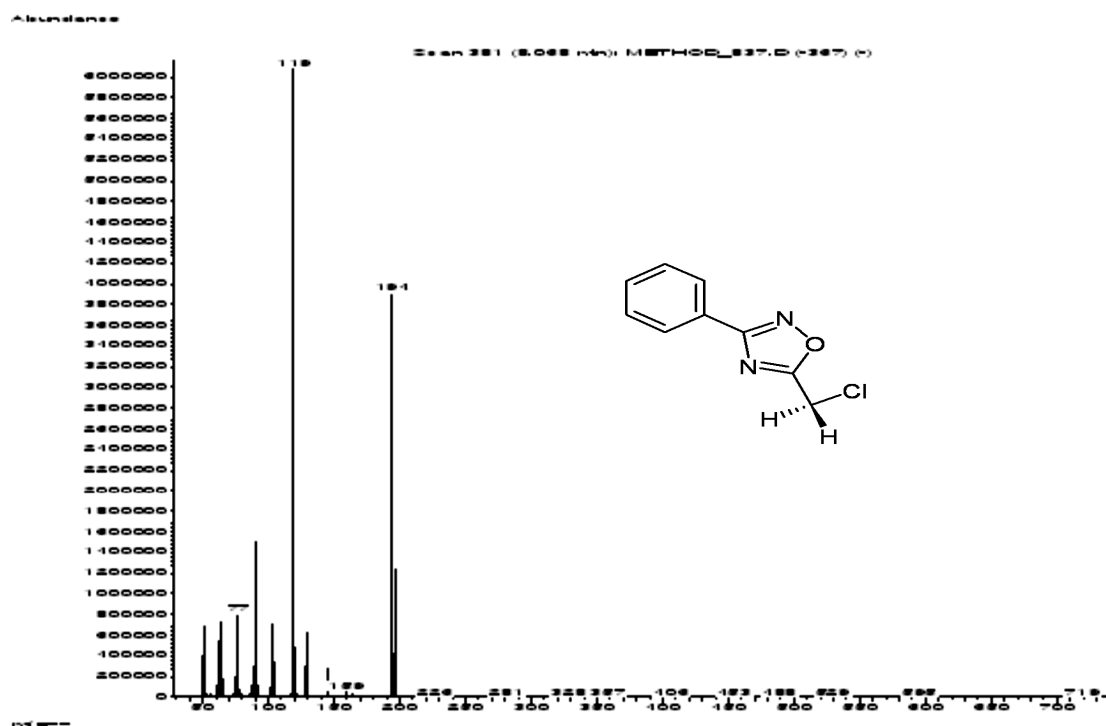


Figure 4. 4 Mass spectra of compound **31a**

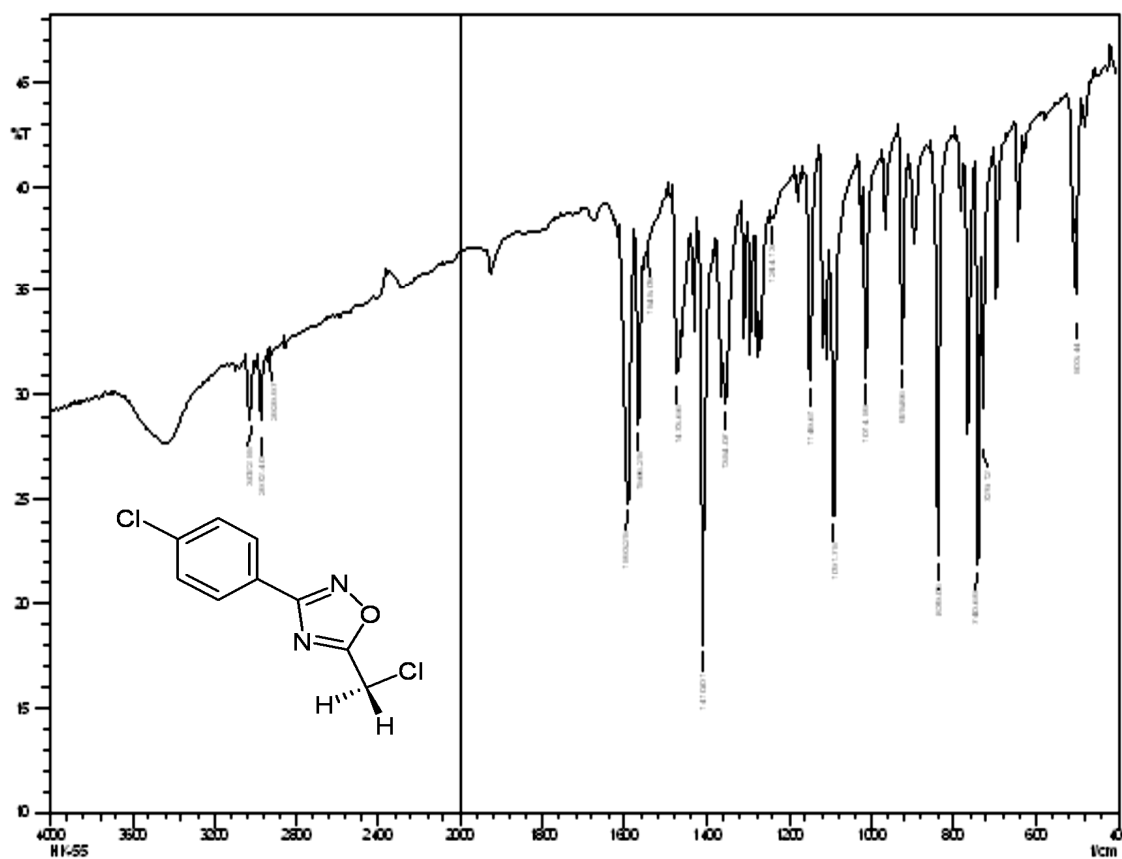


Figure 4. 5 IR spectrum of compound **31b**

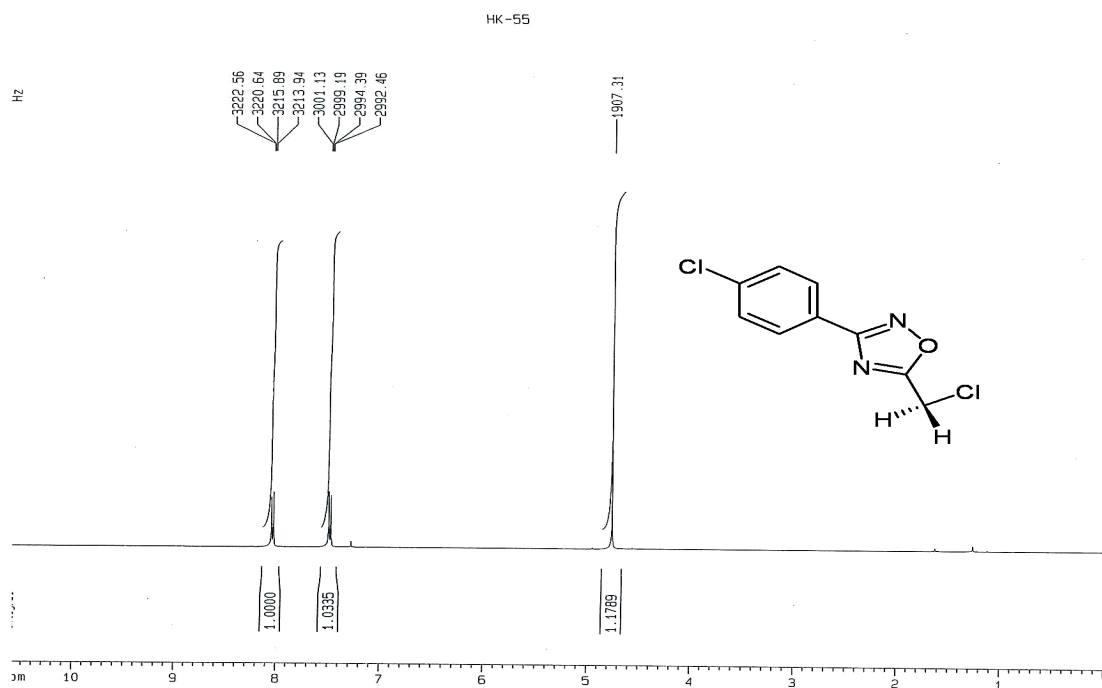


Figure 4. 6 ¹H NMR Spectrum of compound **31b**

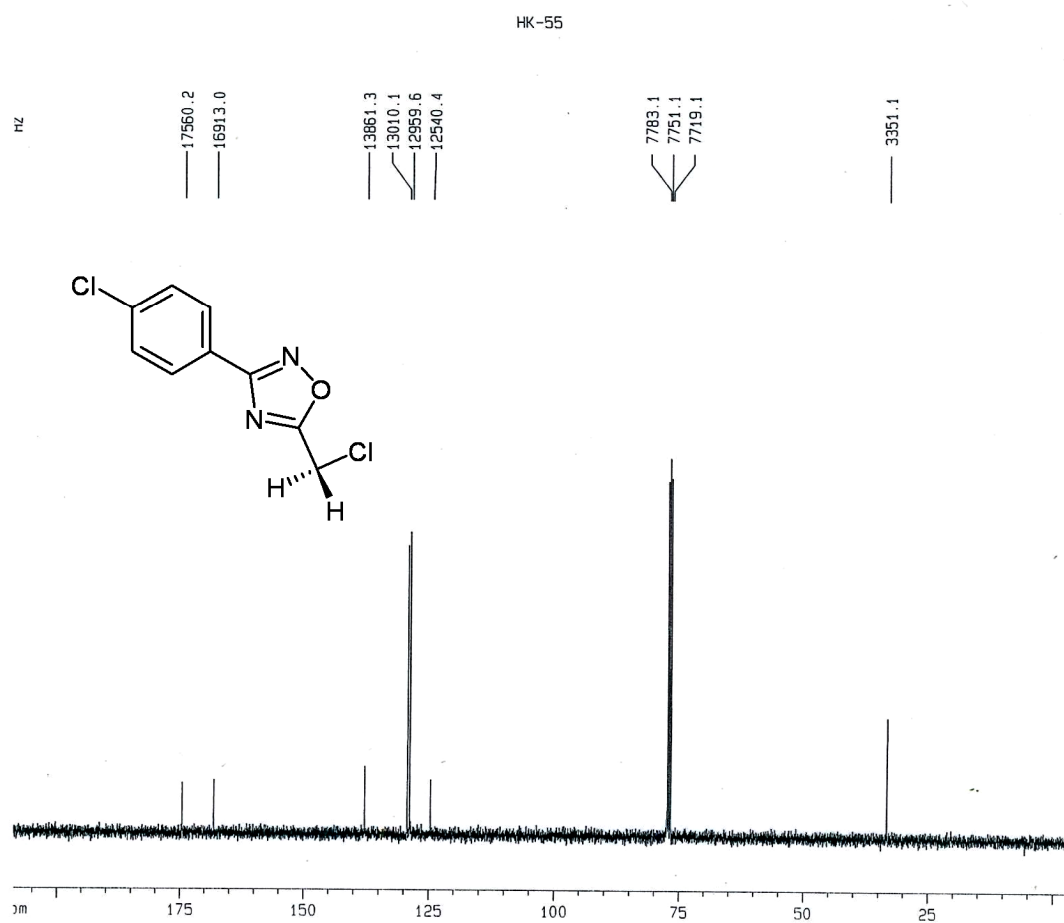


Figure 4. 7 ¹³C NMR Spectrum of compound 3b

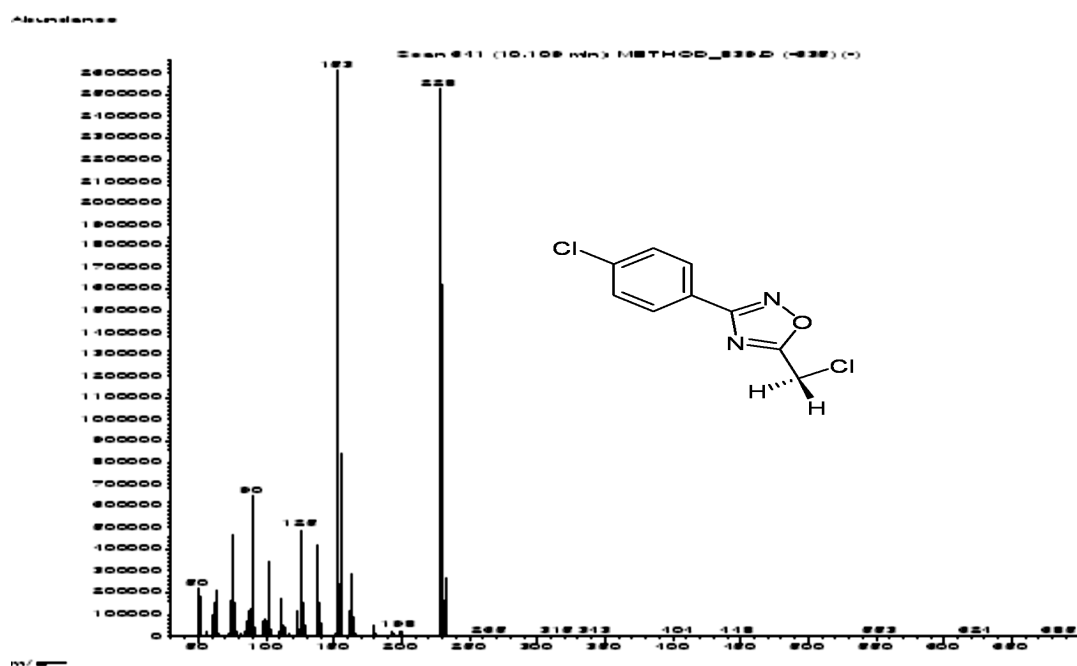


Figure 4. 8 Mass spectra of compound 31b

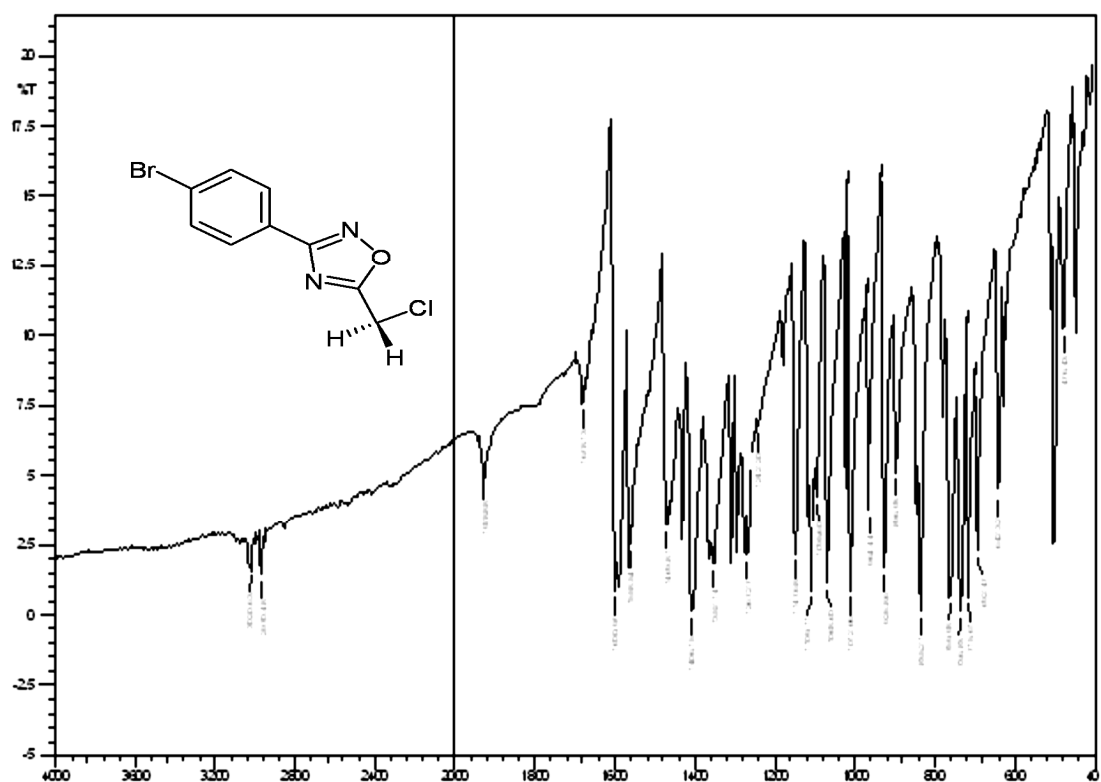


Figure 4. 9 IR spectrum of compound **31c**

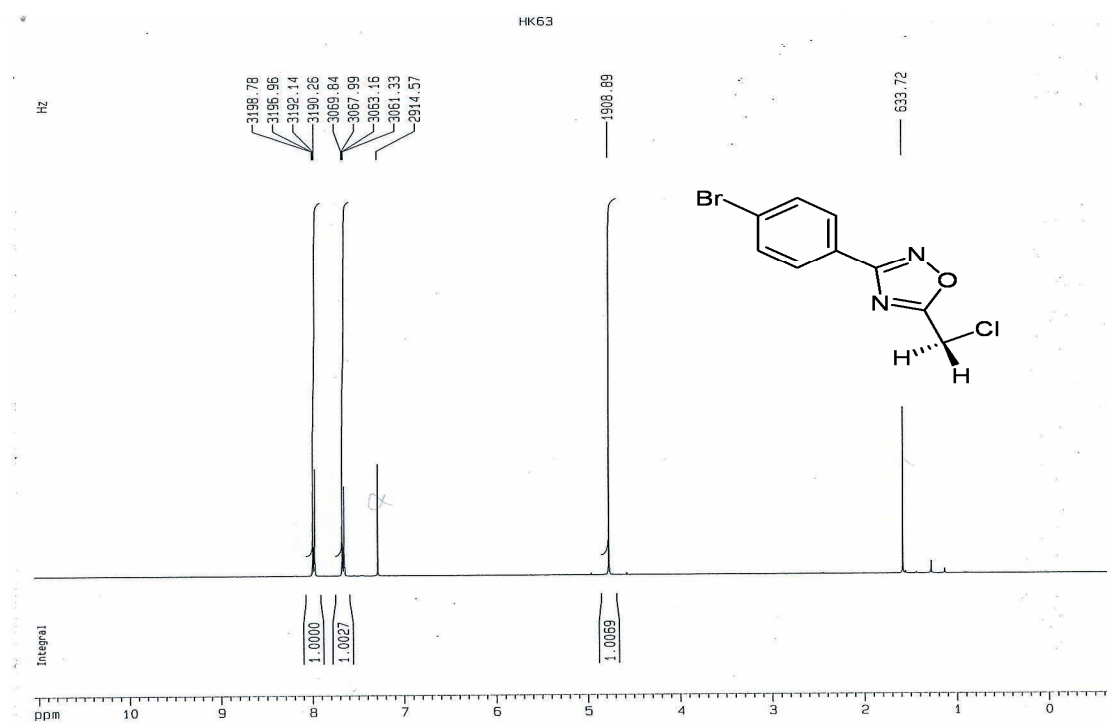


Figure 4. 10 ¹H NMR Spectrum of compound **31c**

HK63

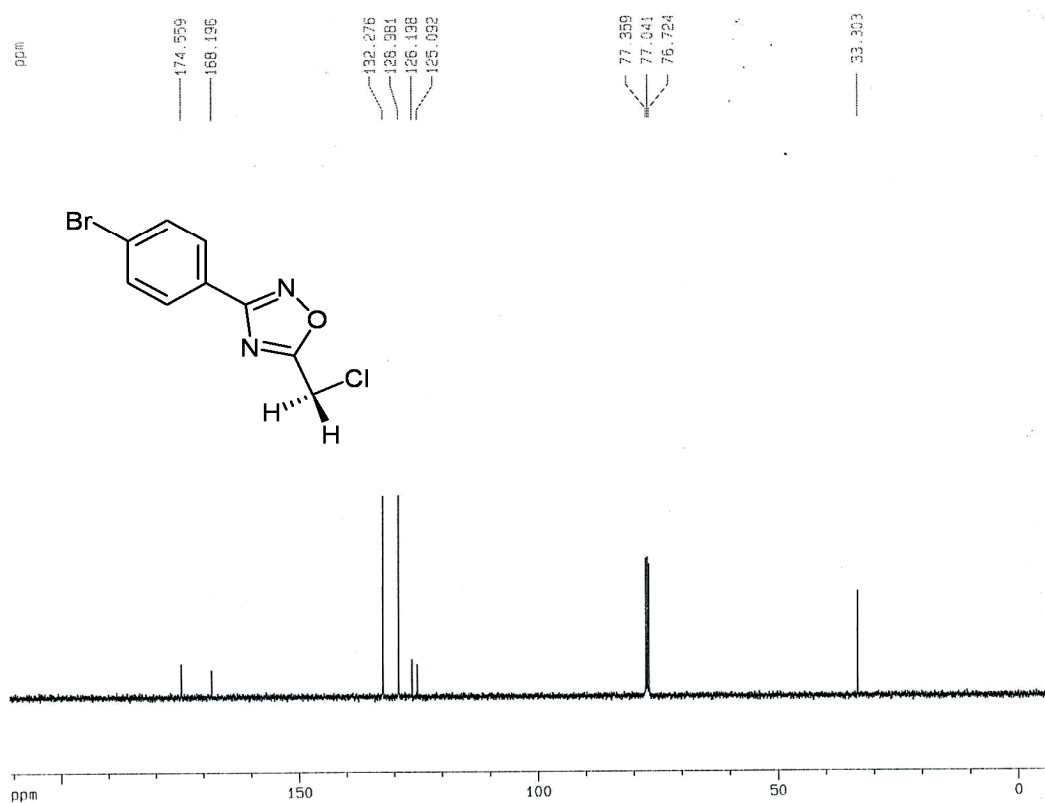


Figure 4. 11 ¹³C NMR Spectrum of compound 31c

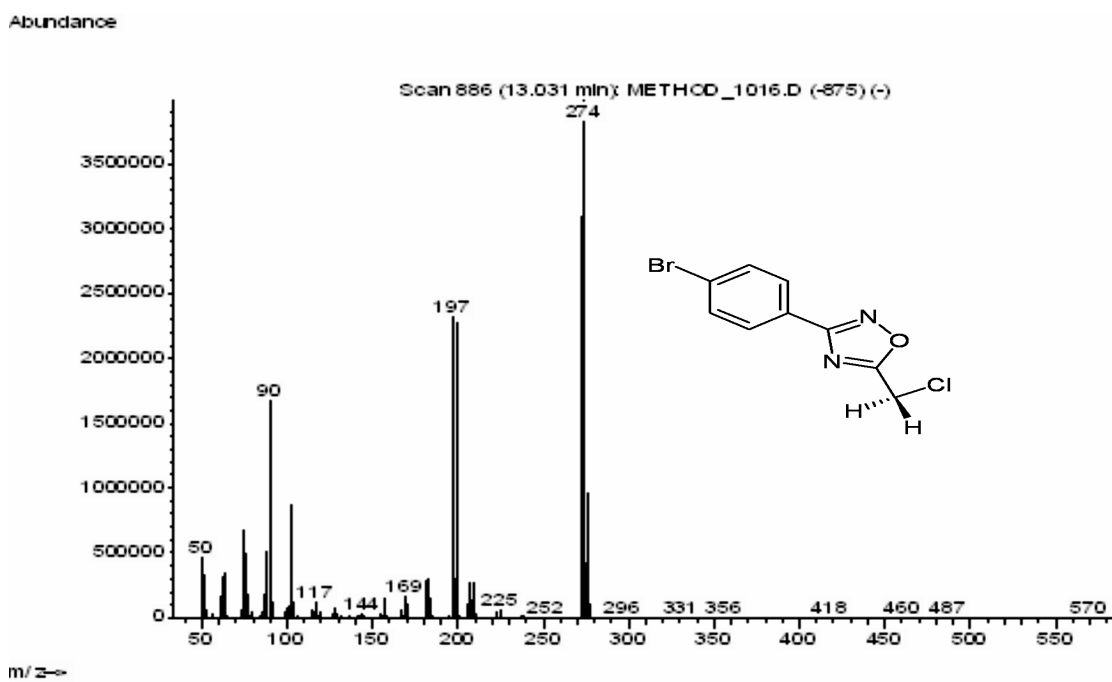
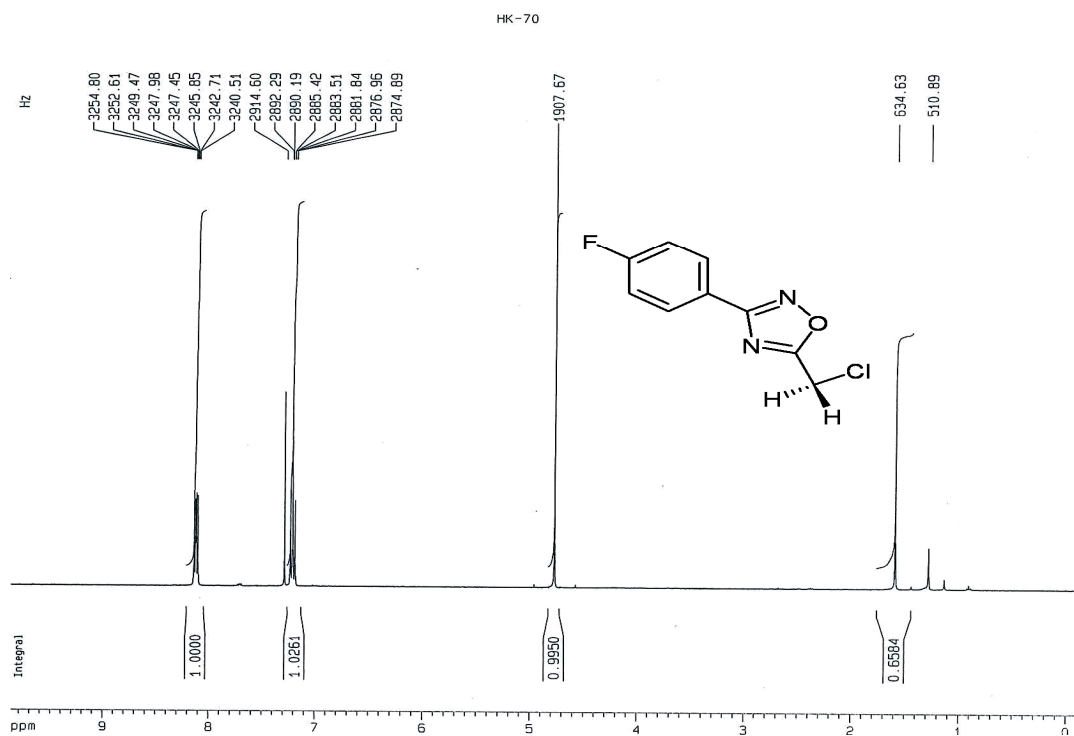
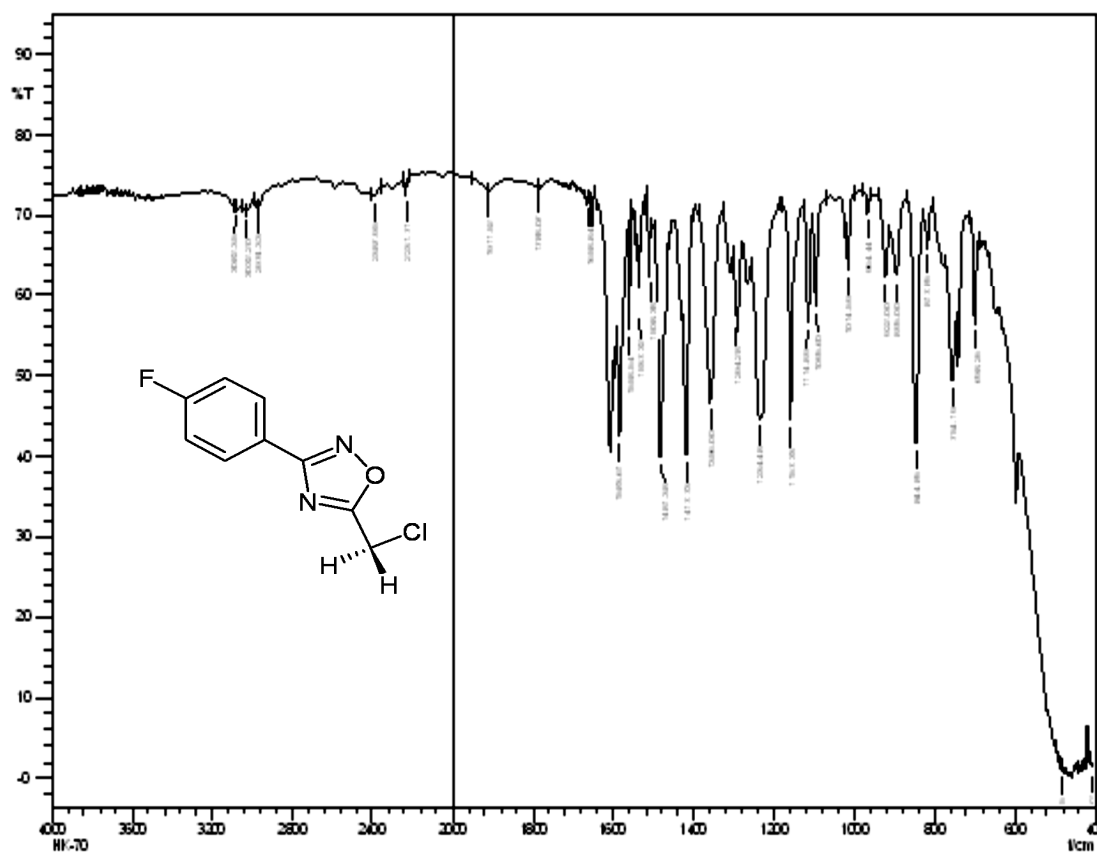


Figure 4. 12 Mass spectra of compound 31c



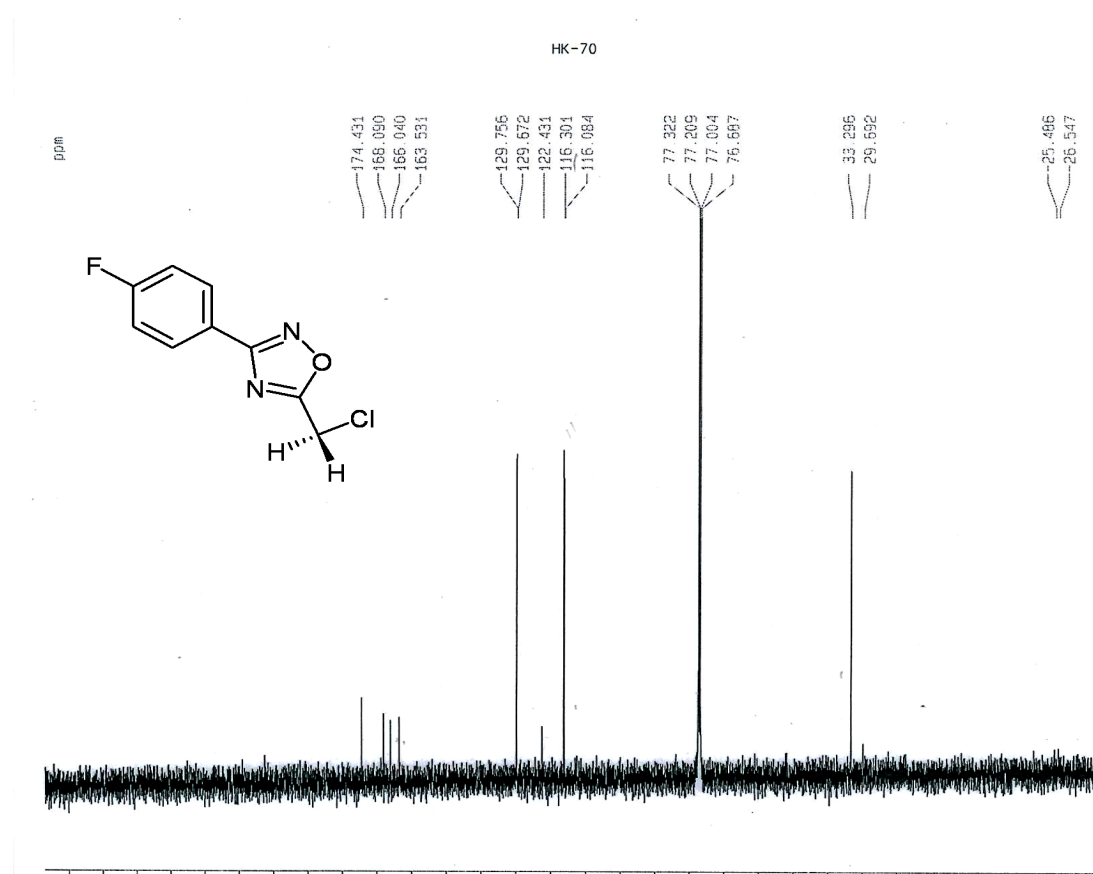


Figure 4. 15 ¹³C NMR Spectrum of compound 31d

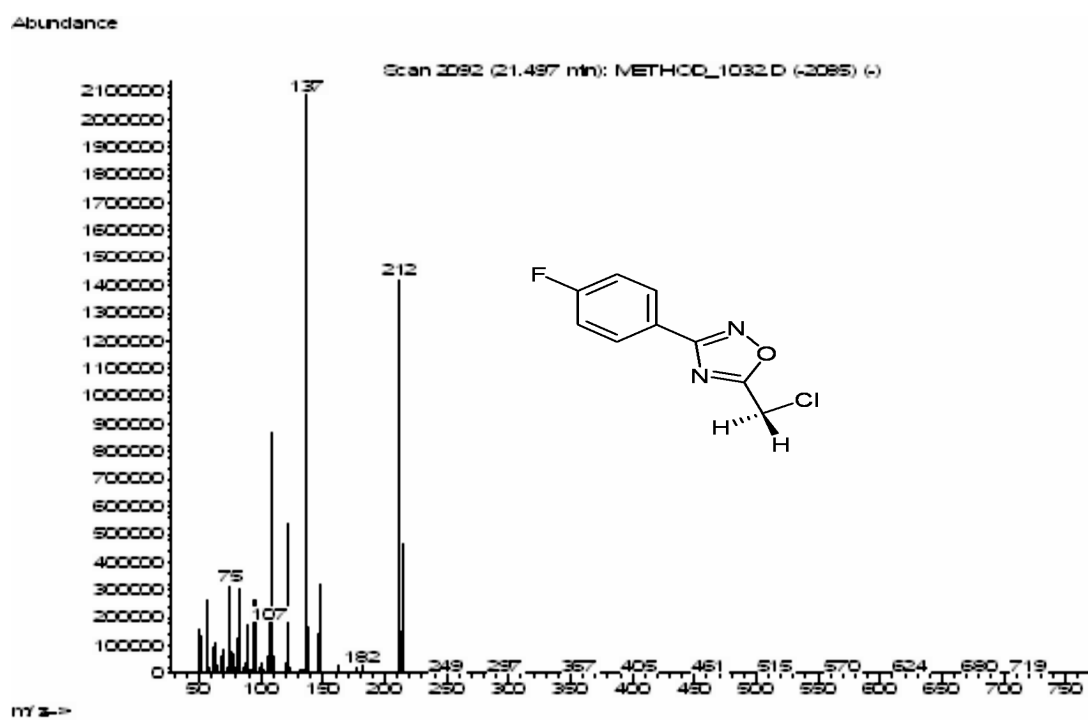


Figure 4. 16 Mass spectra of compound 31d

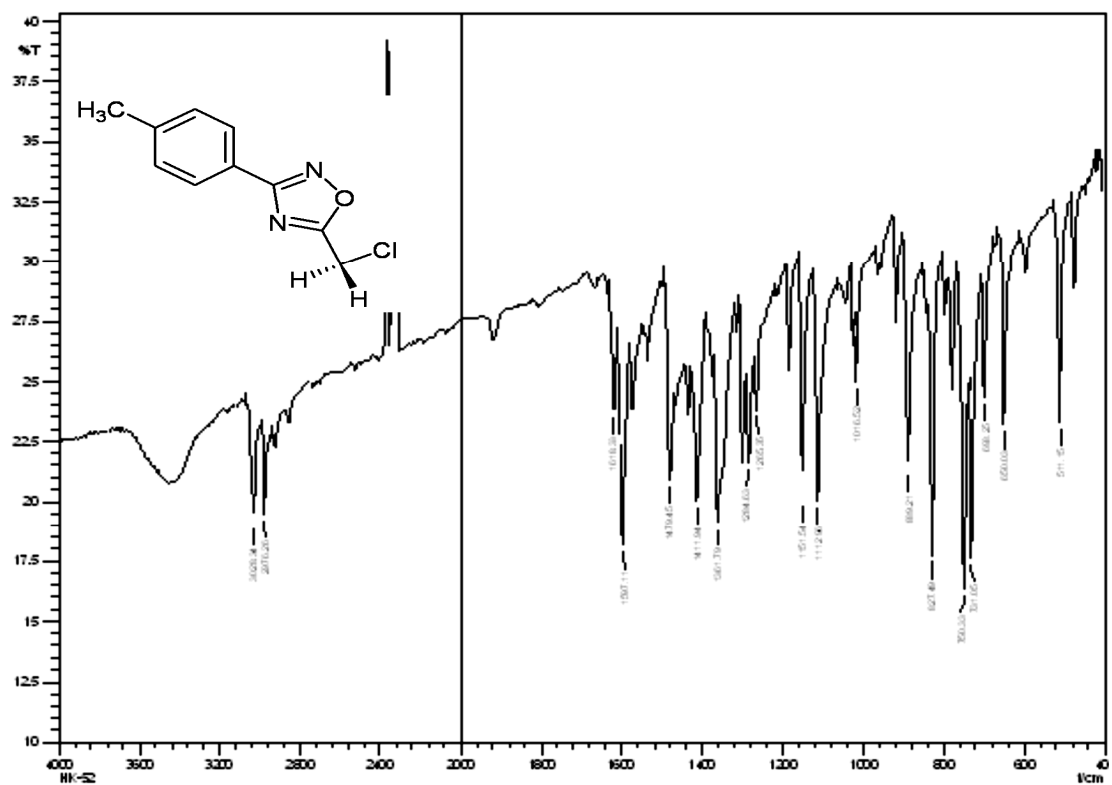


Figure 4. 17 IR spectrum of compound **31e**

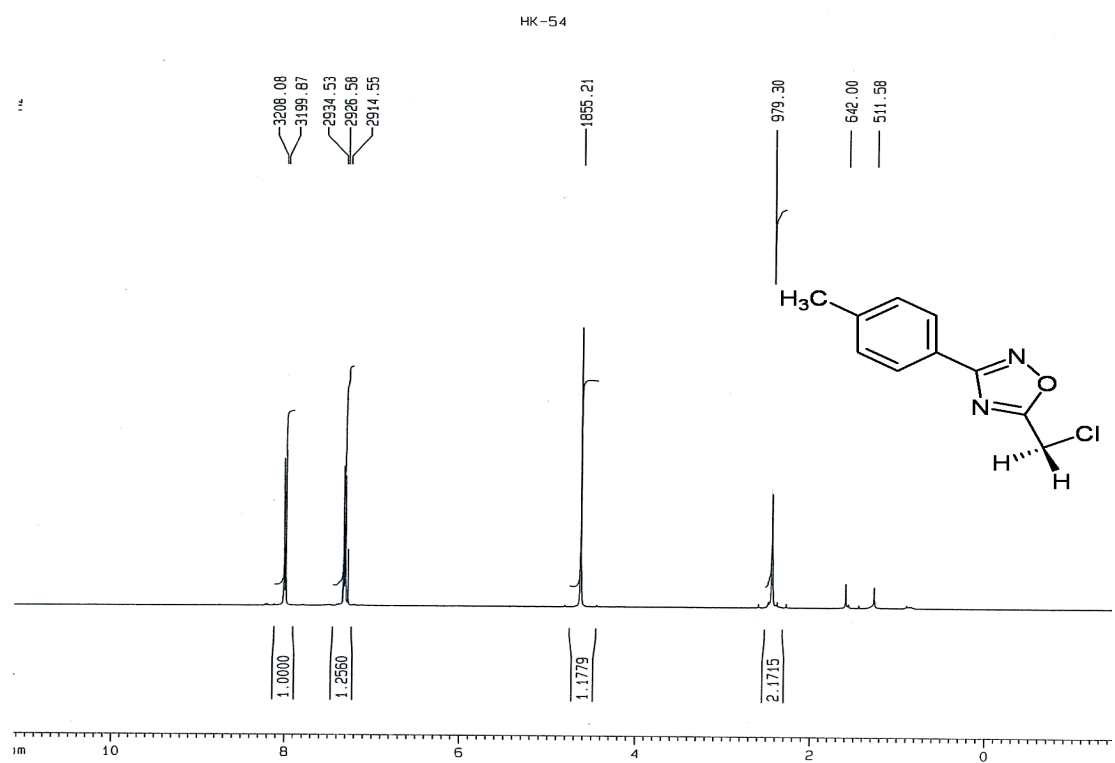


Figure 4. 18 ^1H NMR Spectrum of compound **31e**

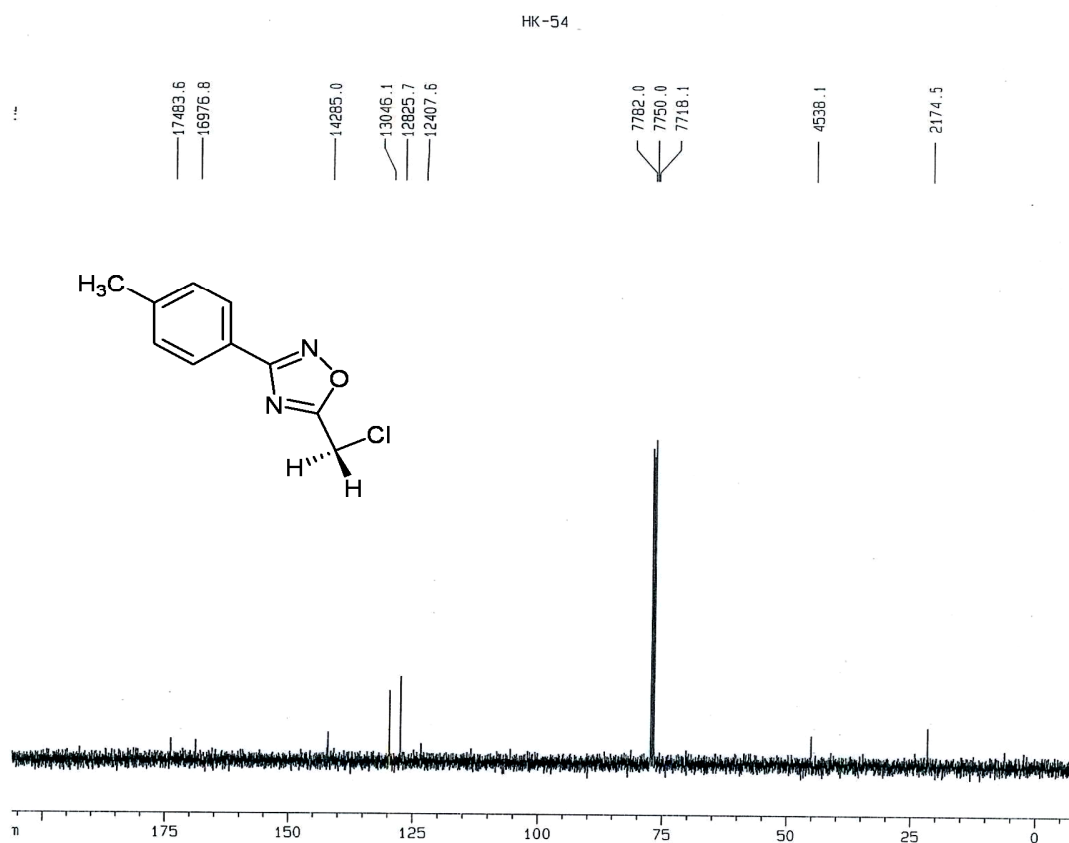


Figure 4. 19 ¹³C NMR Spectrum of compound **31e**

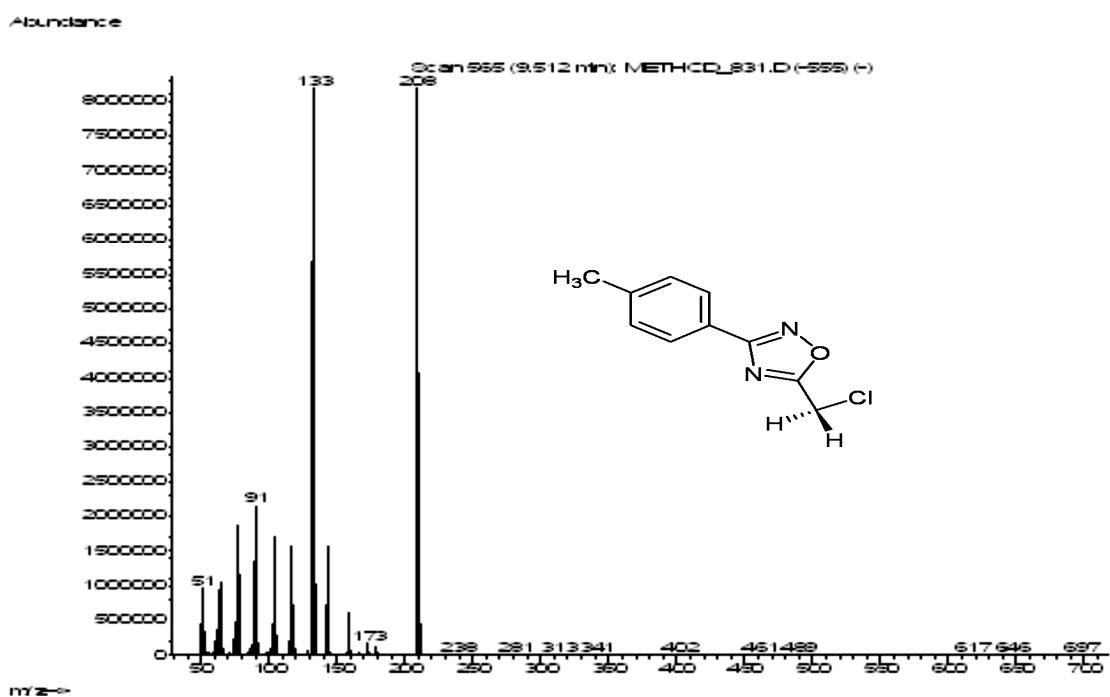


Figure 4. 20 Mass spectra of compound **31e**

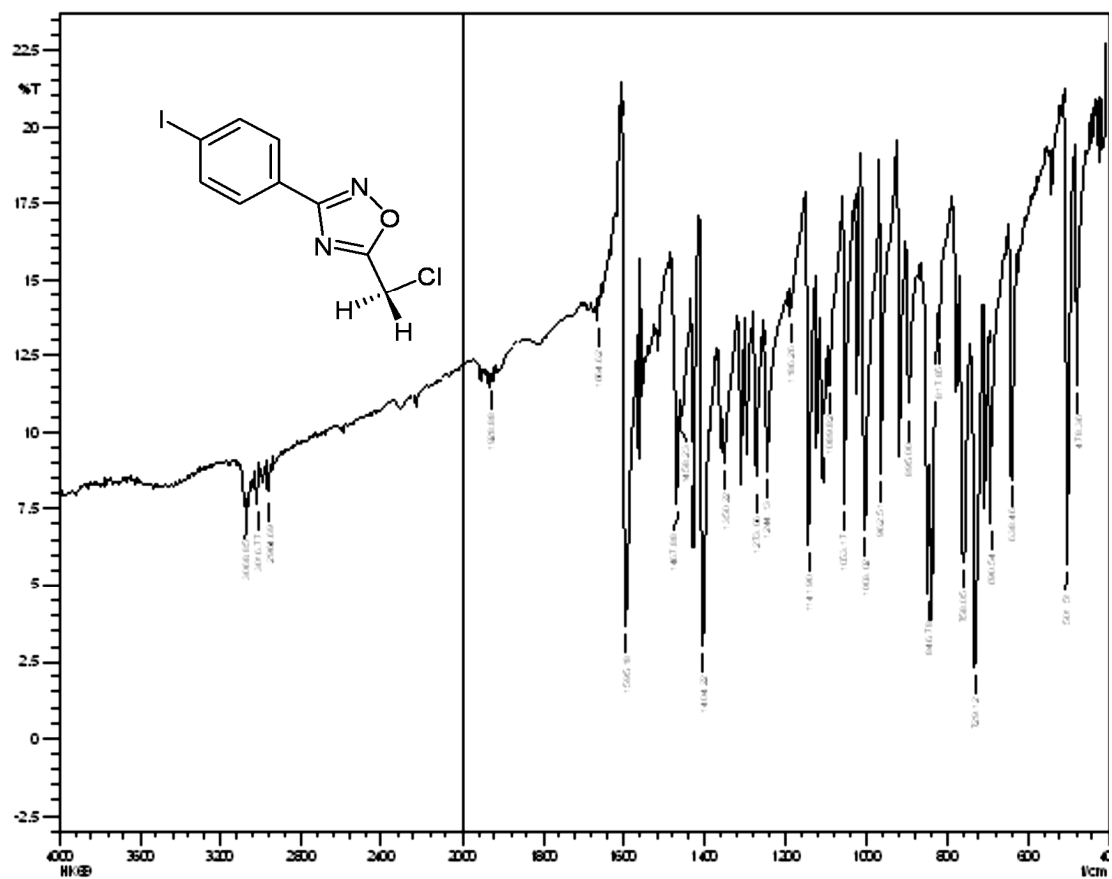


Figure 4. 21 IR spectrum of compound **31f**

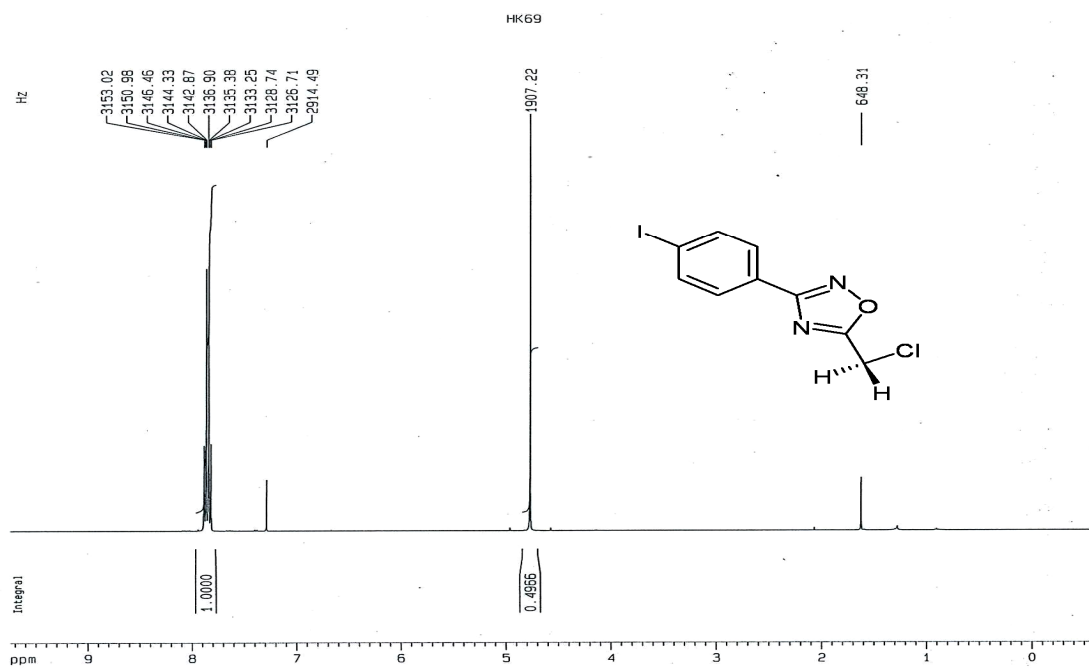


Figure 4. 22 ¹H NMR Spectrum of compound **31f**

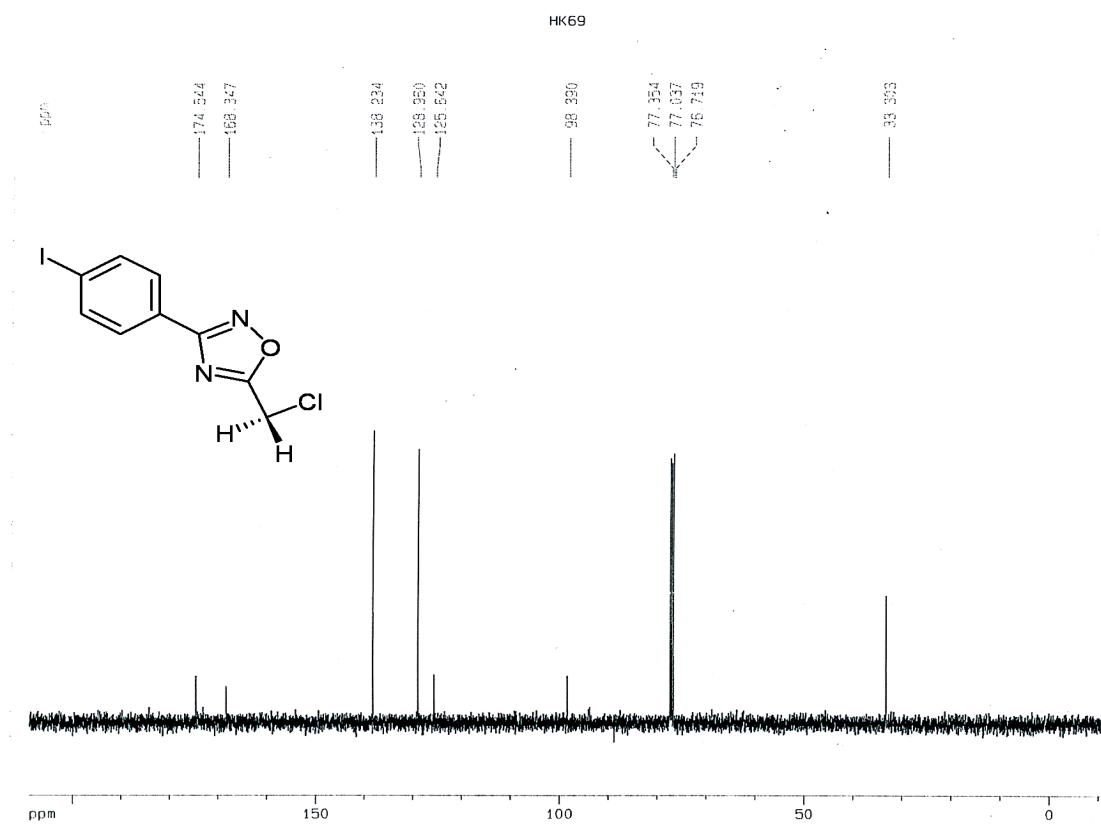


Figure 4. 23 ^{13}C NMR Spectrum of compound **31f**

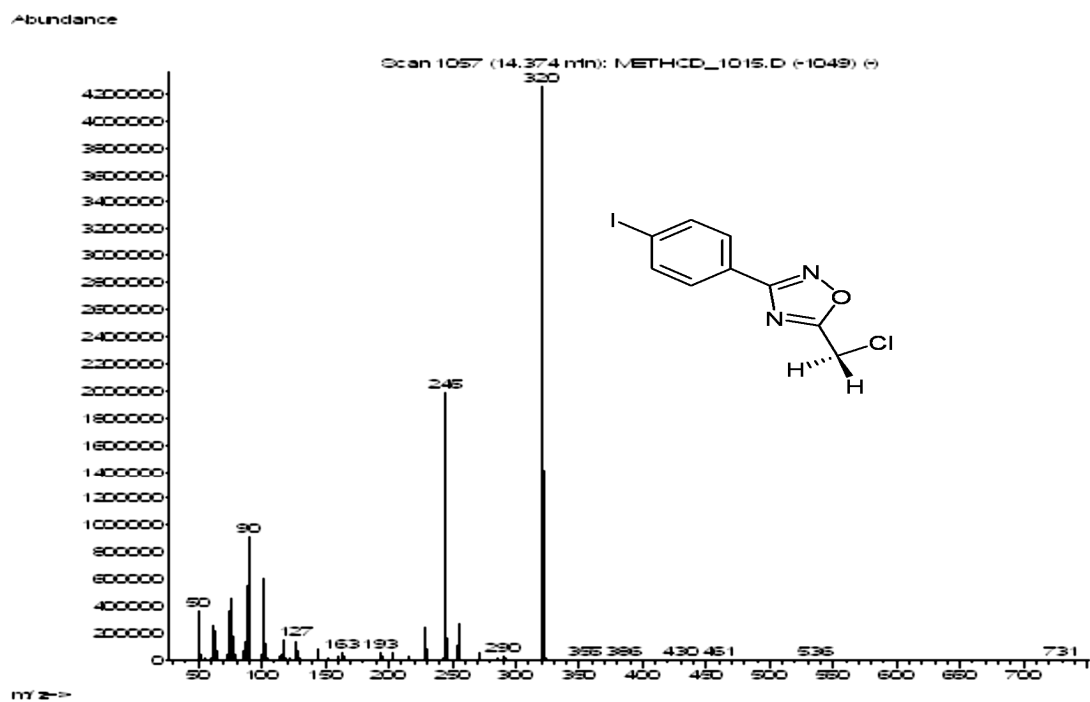


Figure 4. 24 Mass spectra of compound **31f**

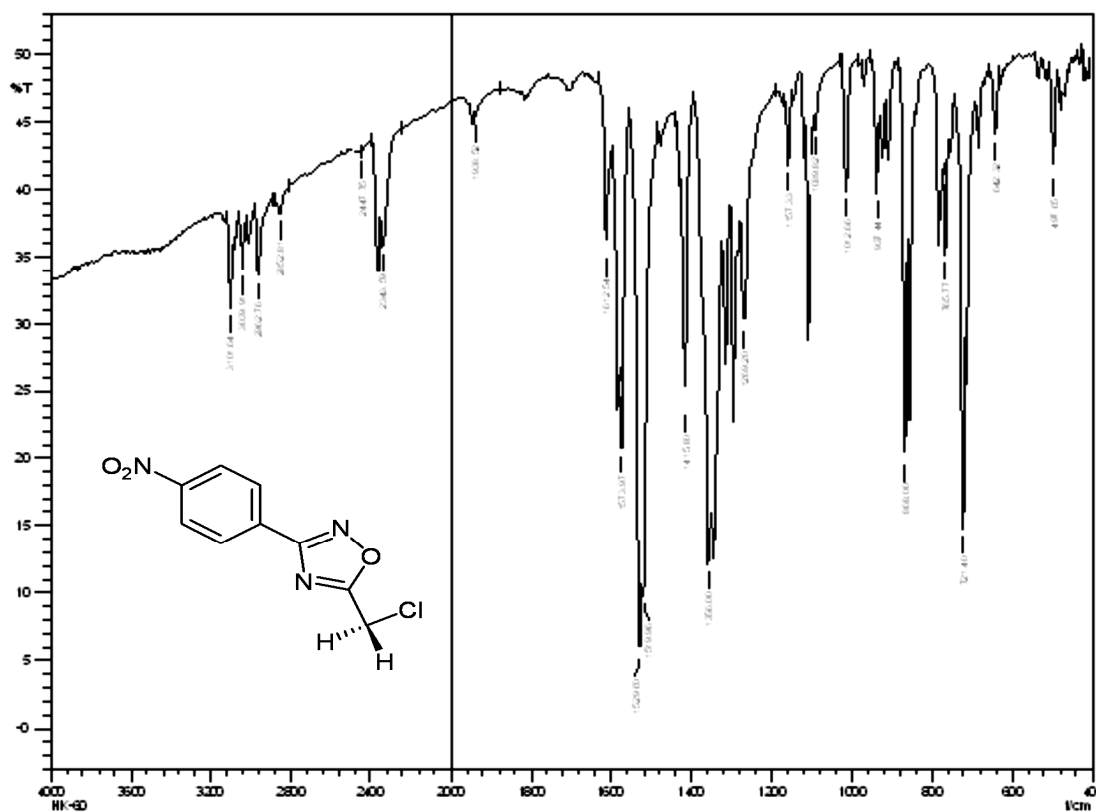


Figure 4. 25 IR spectrum of compound **31g**

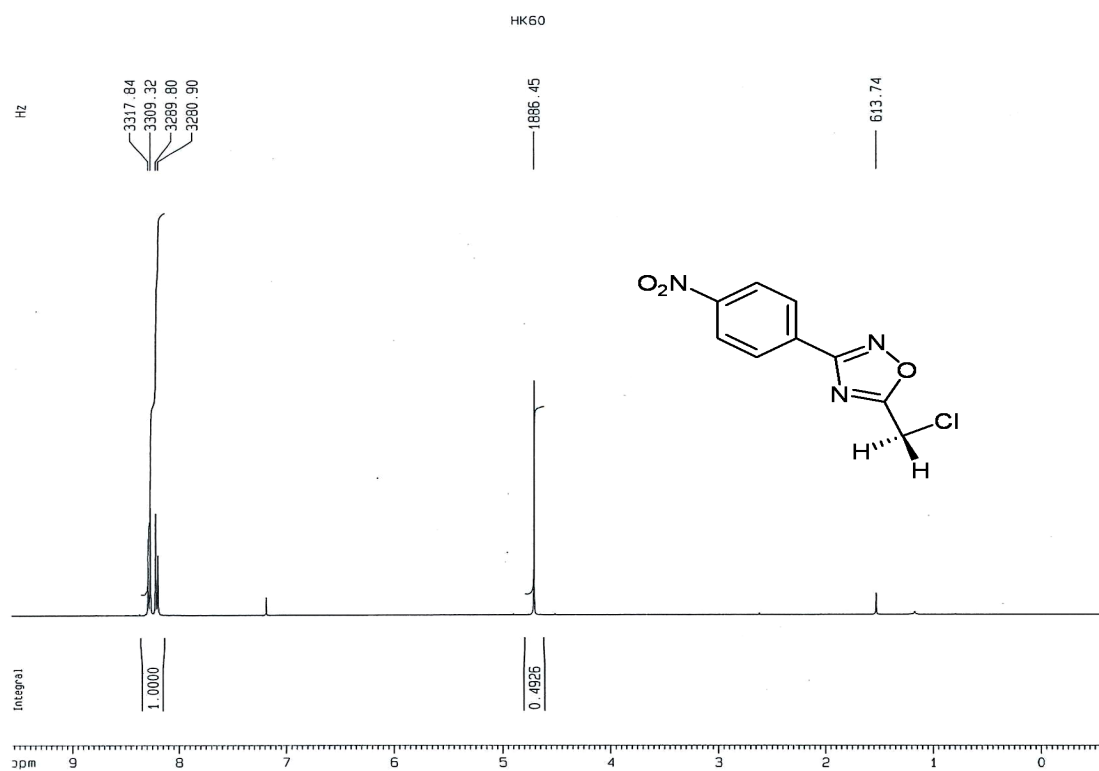


Figure 4. 26 ¹H NMR Spectrum of compound **31g**

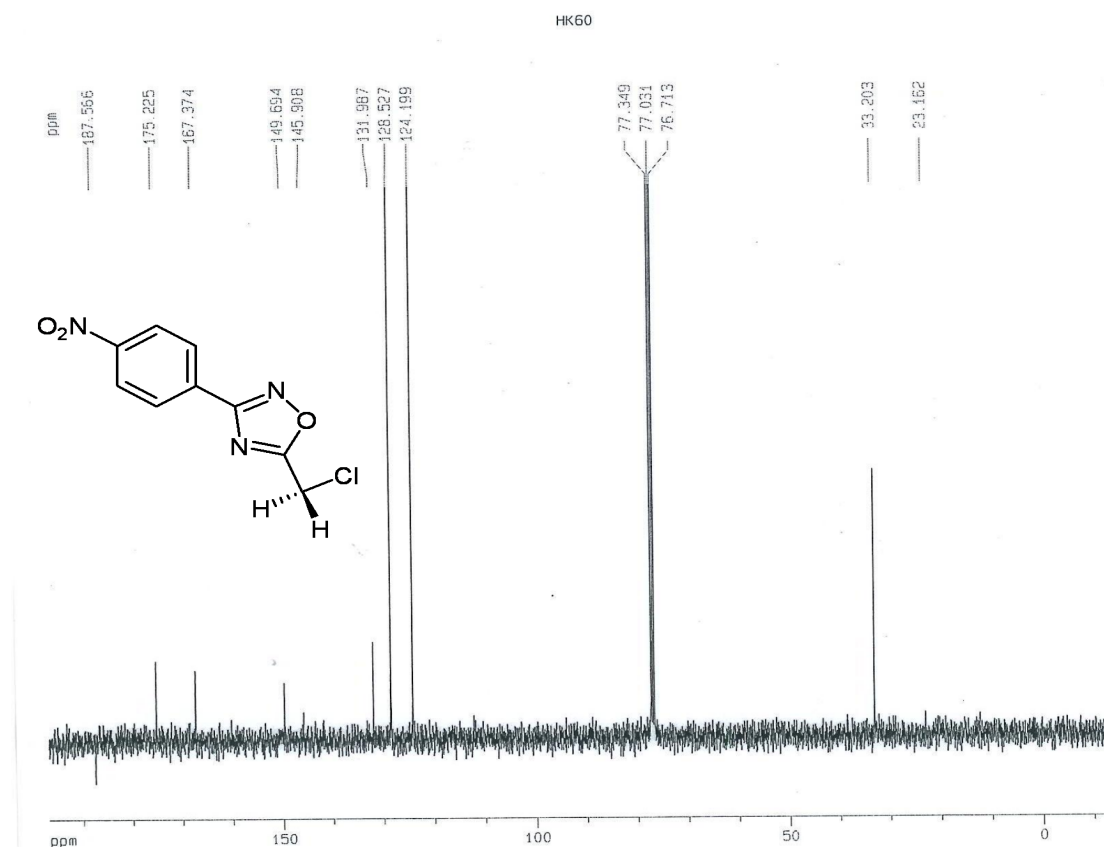


Figure 4. 27 ^{13}C NMR Spectrum of compound **31g**

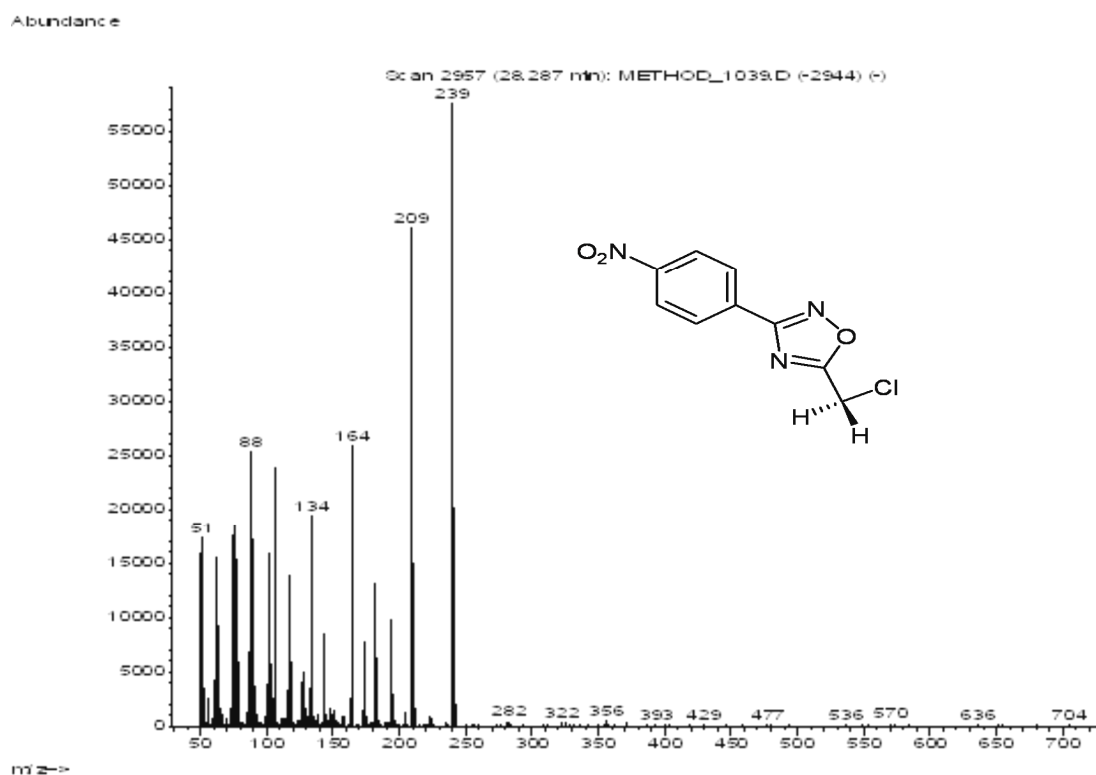


Figure 4. 28 Mass spectra of compound **31g**

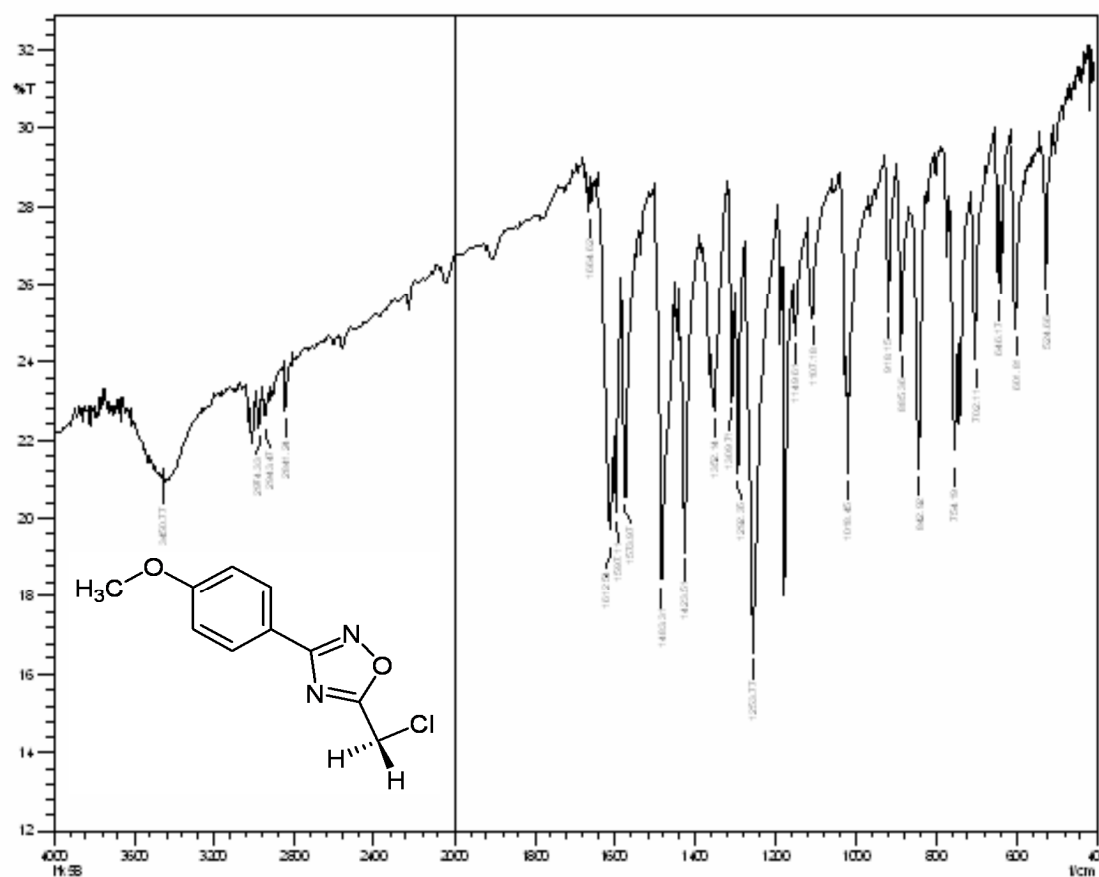


Figure 4. 29 IR spectrum of compound 31h

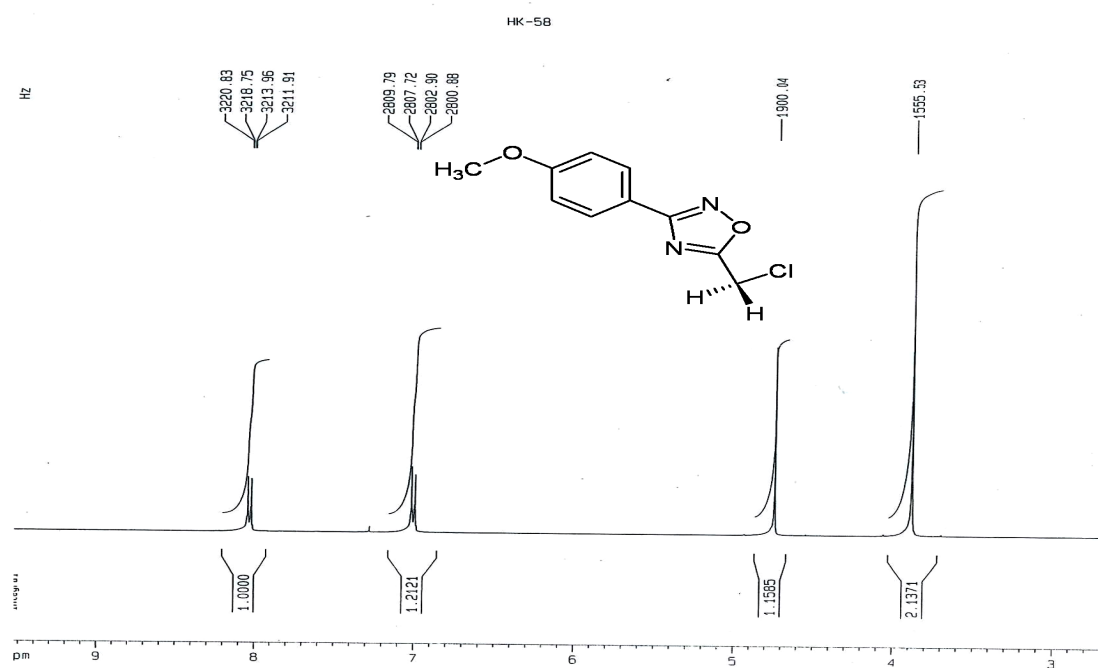


Figure 4. 30 ¹H NMR Spectrum of compound 31h

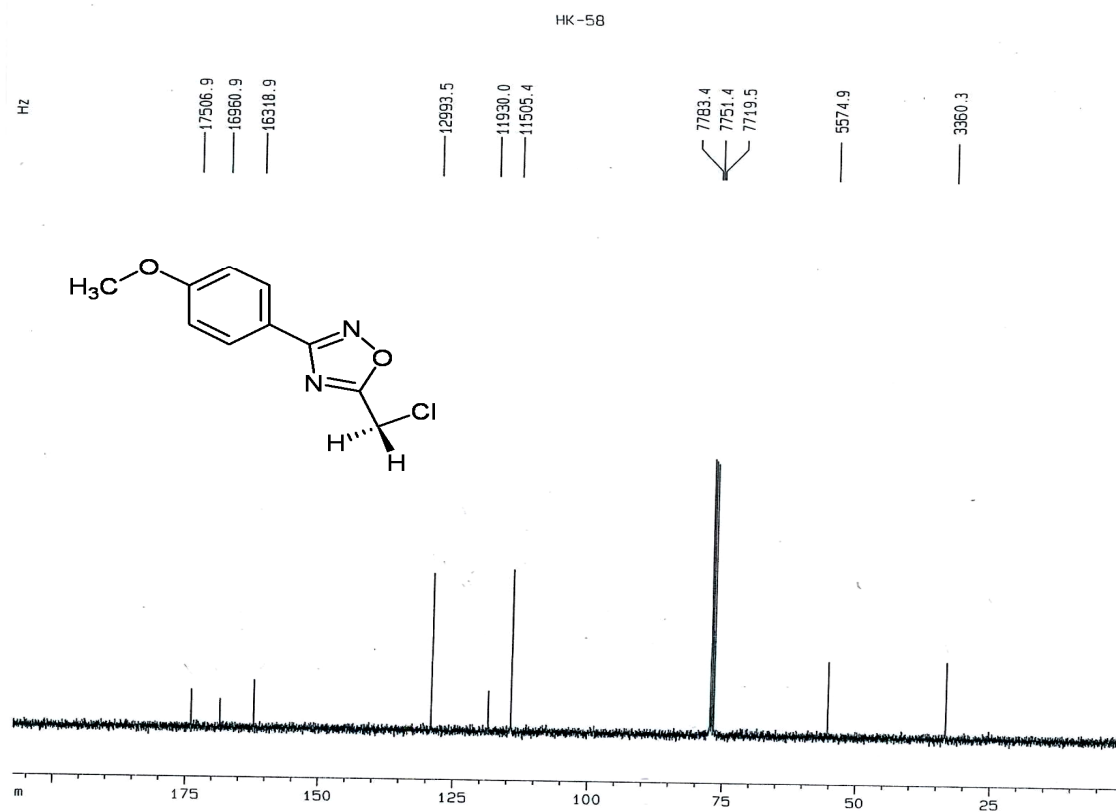


Figure 4. 31 ^{13}C NMR Spectrum of compound 31h

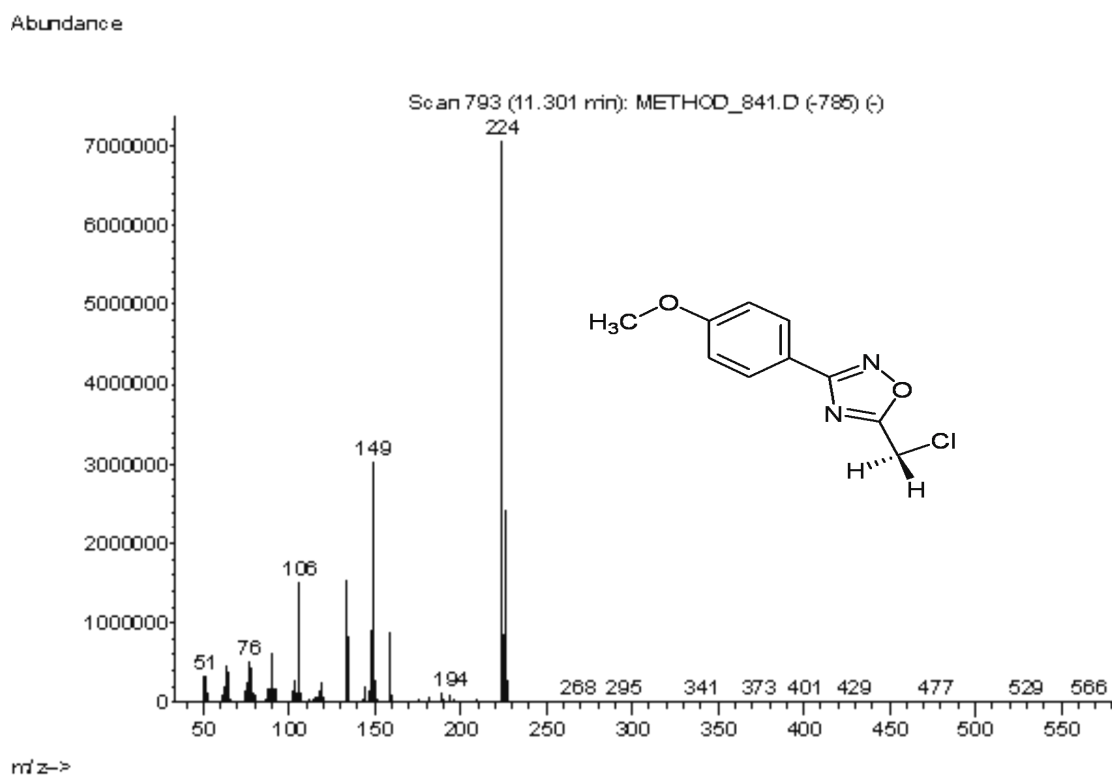


Figure 4. 32 Mass spectra of compound 31h

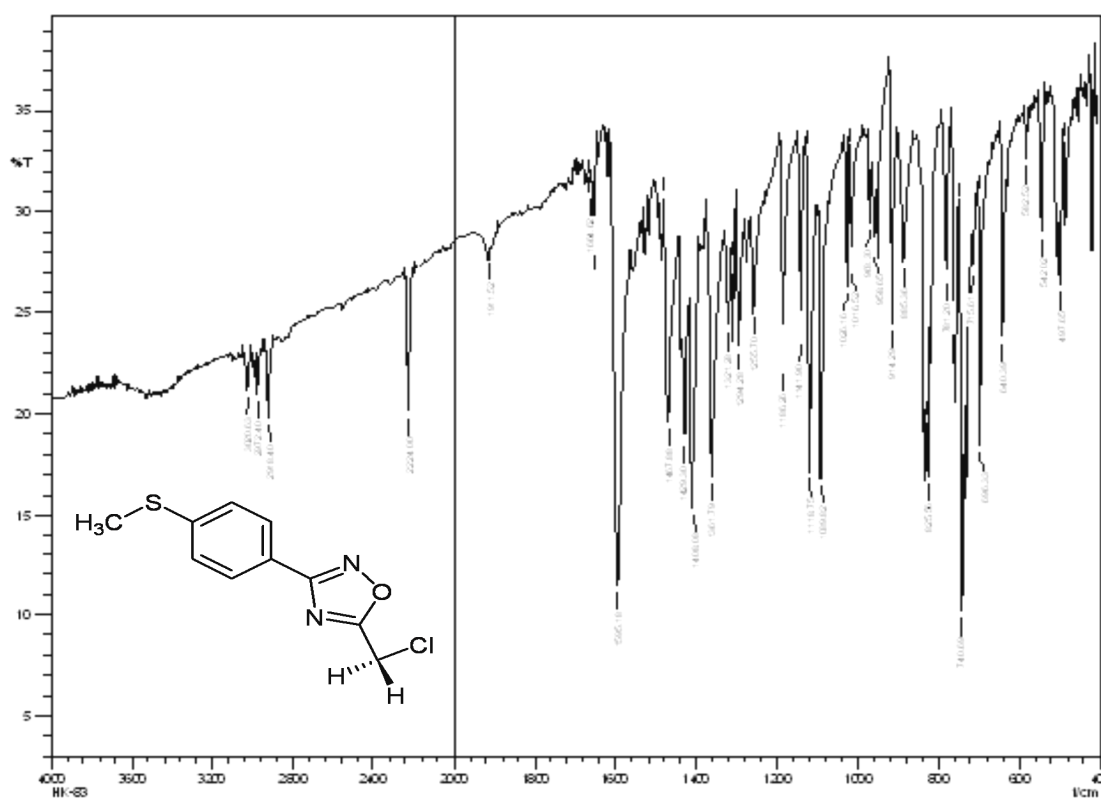


Figure 4. 33 IR spectrum of compound 31j

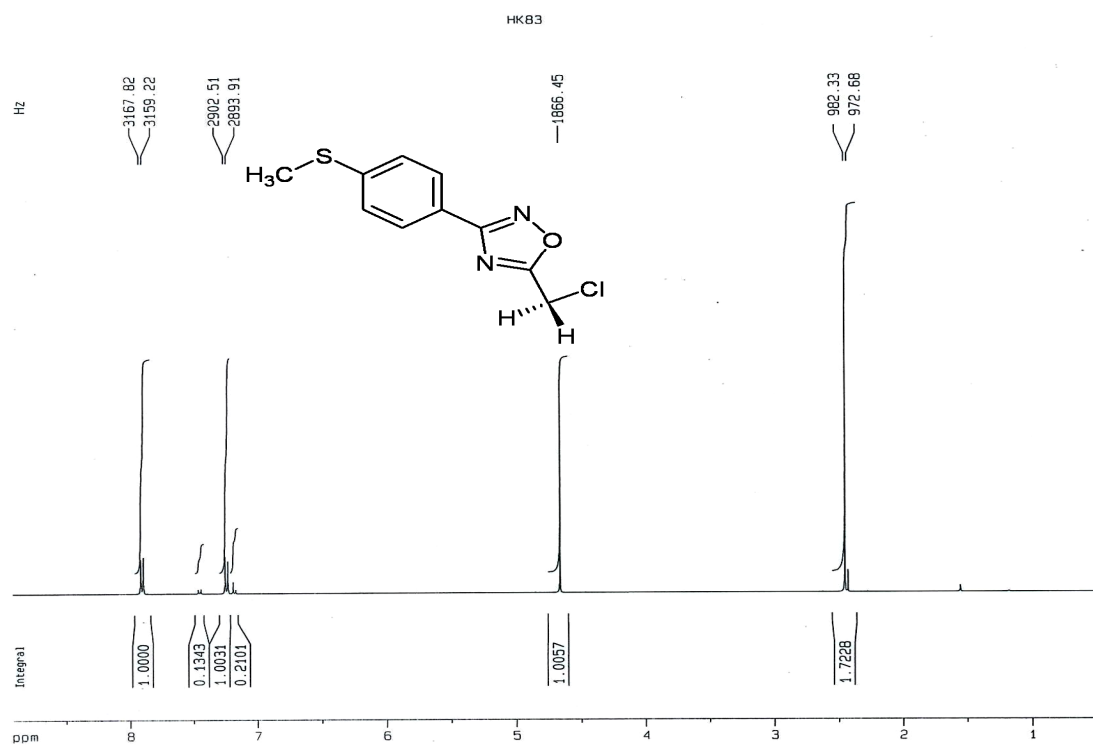


Figure 4. 34 ¹H NMR Spectrum of compound 31j

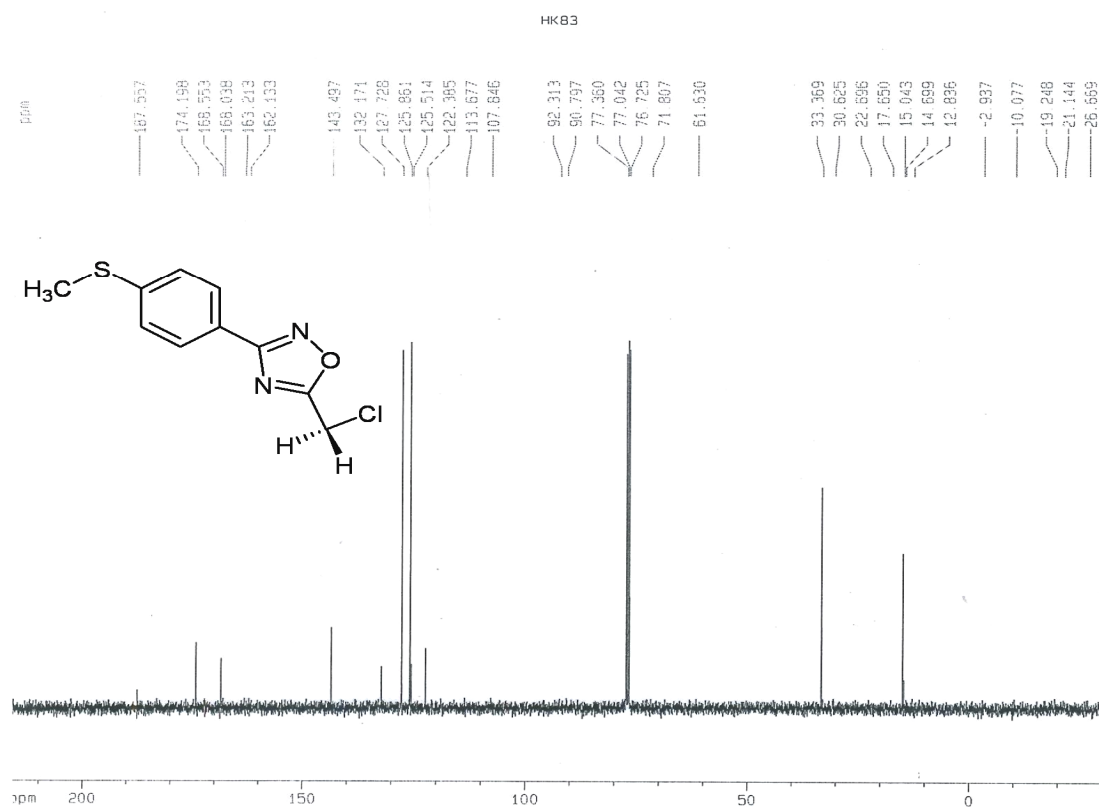


Figure 4. 35 ¹³C NMR Spectrum of compound **31j**

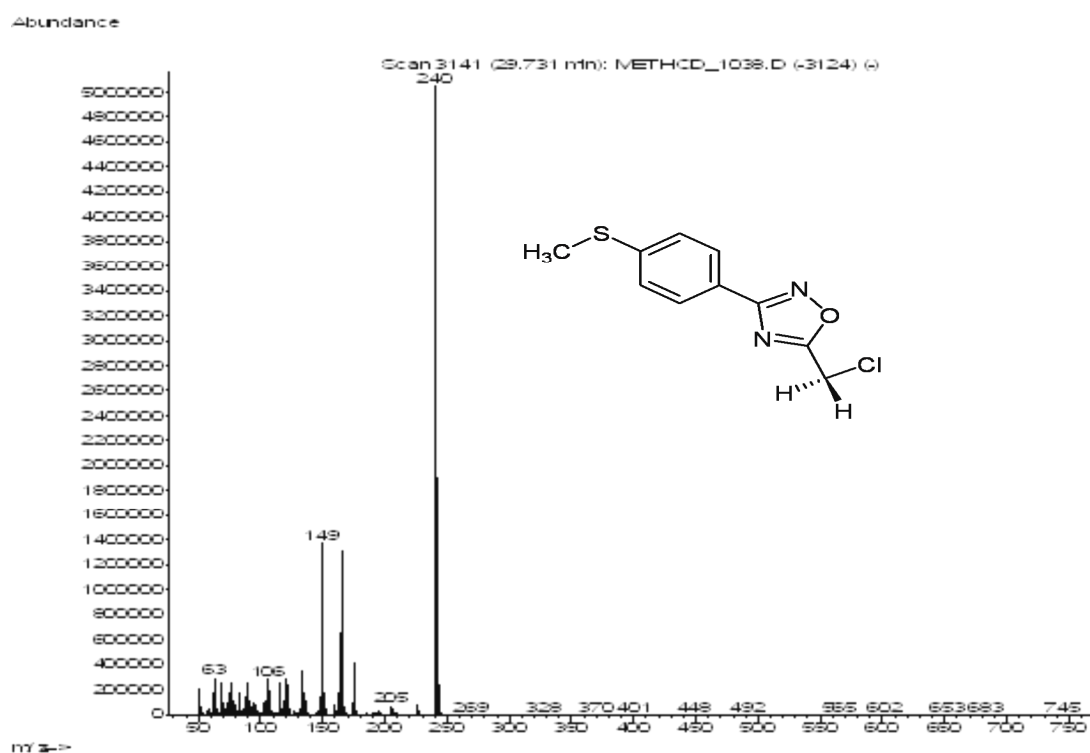


Figure 4. 36 Mass spectra of compound **31j**

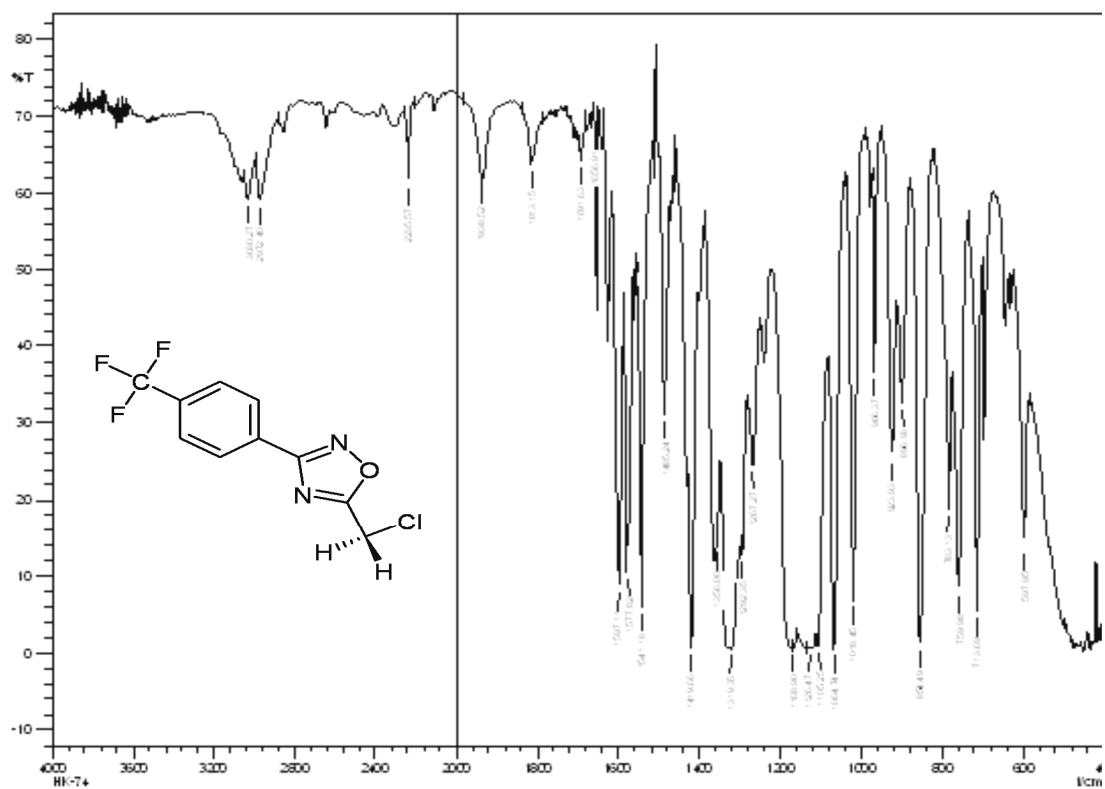


Figure 4. 37 IR spectrum of compound **31k**

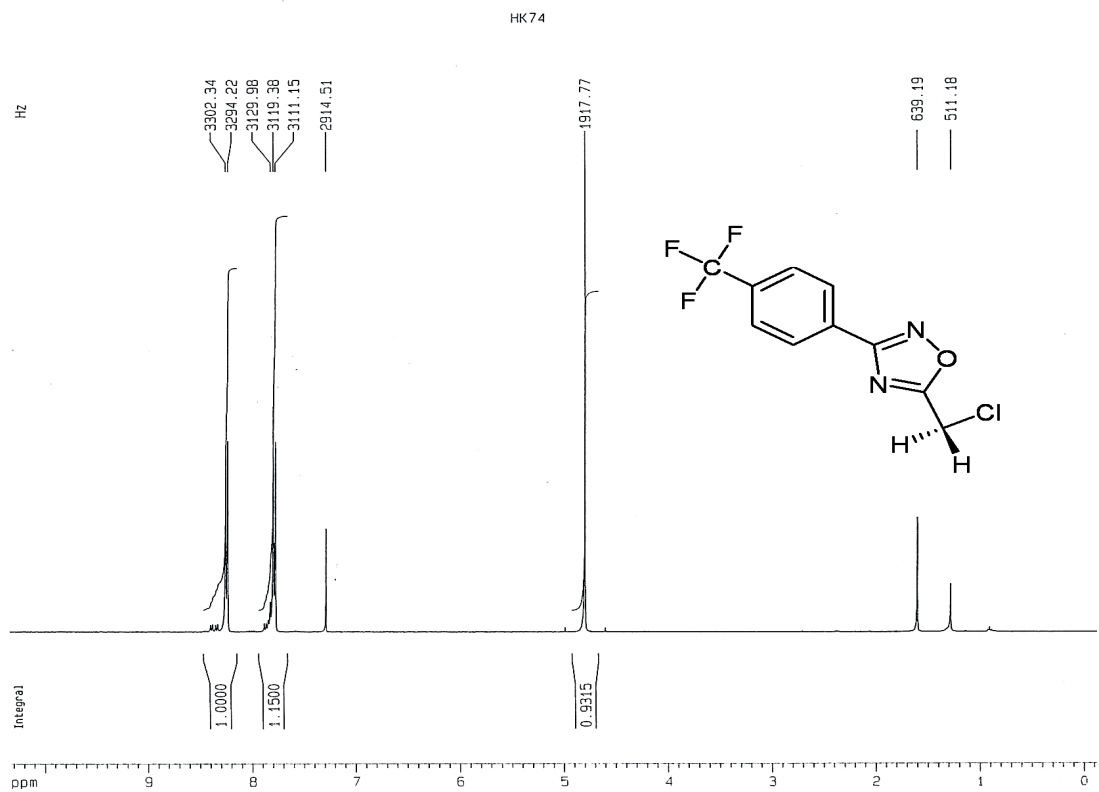


Figure 4. 38 ^1H NMR Spectrum of compound **31k**

HK74

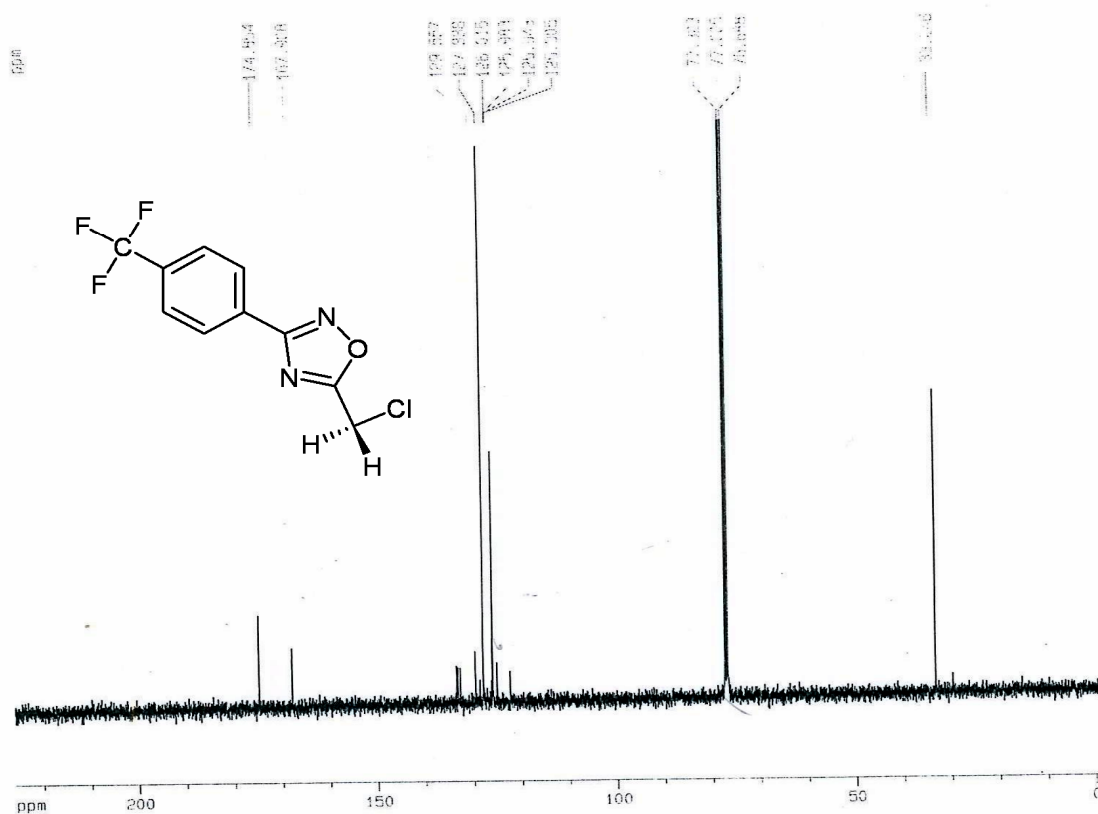


Figure 4. 39 ¹³C NMR Spectrum of compound 31k

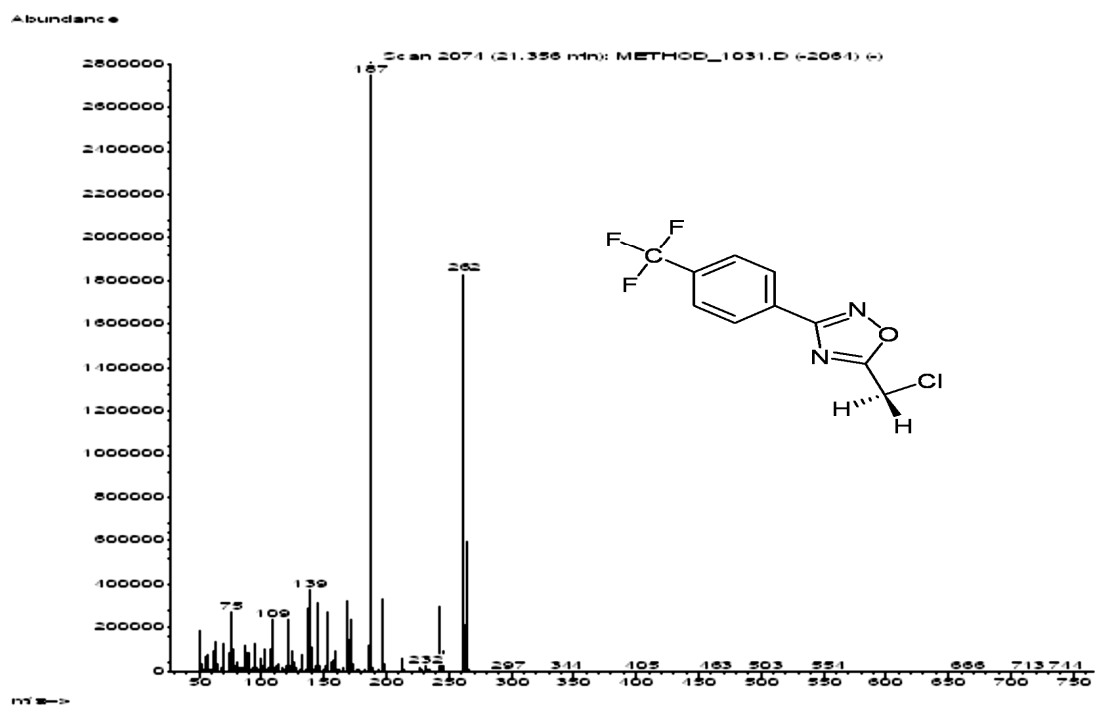


Figure 4. 40 Mass spectra of compound 31k

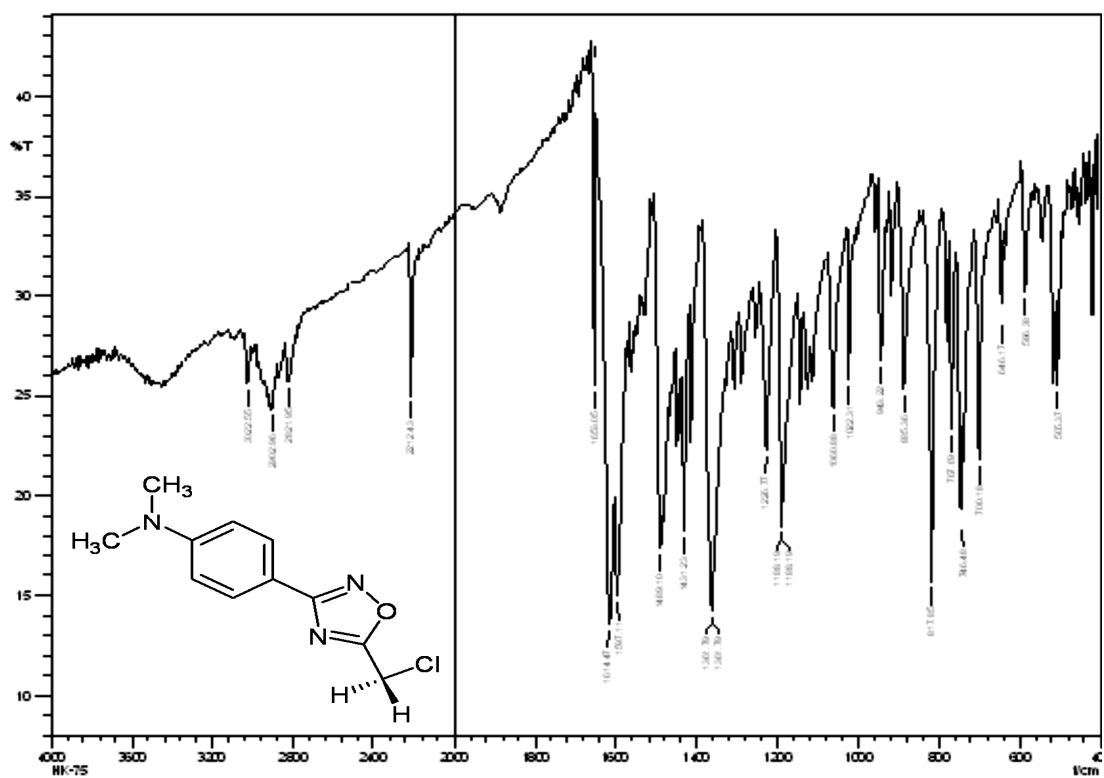


Figure 4. 41 IR spectrum of compound 31m

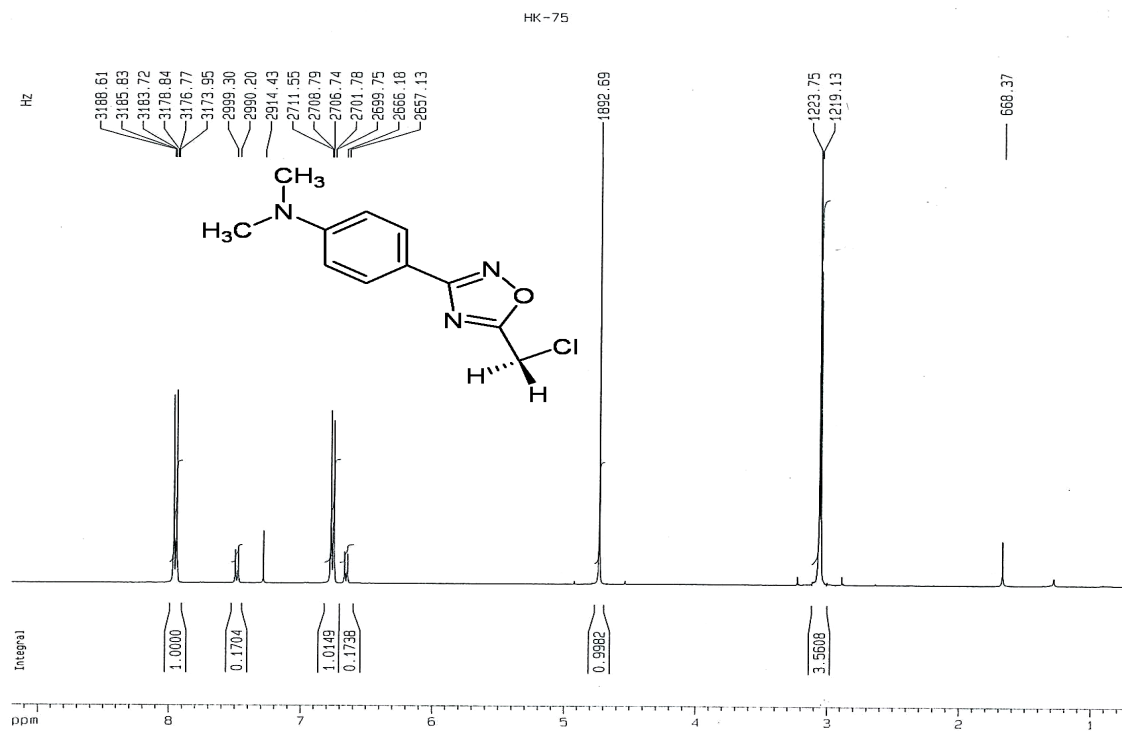


Figure 4. 42 ¹H NMR Spectrum of compound 31m

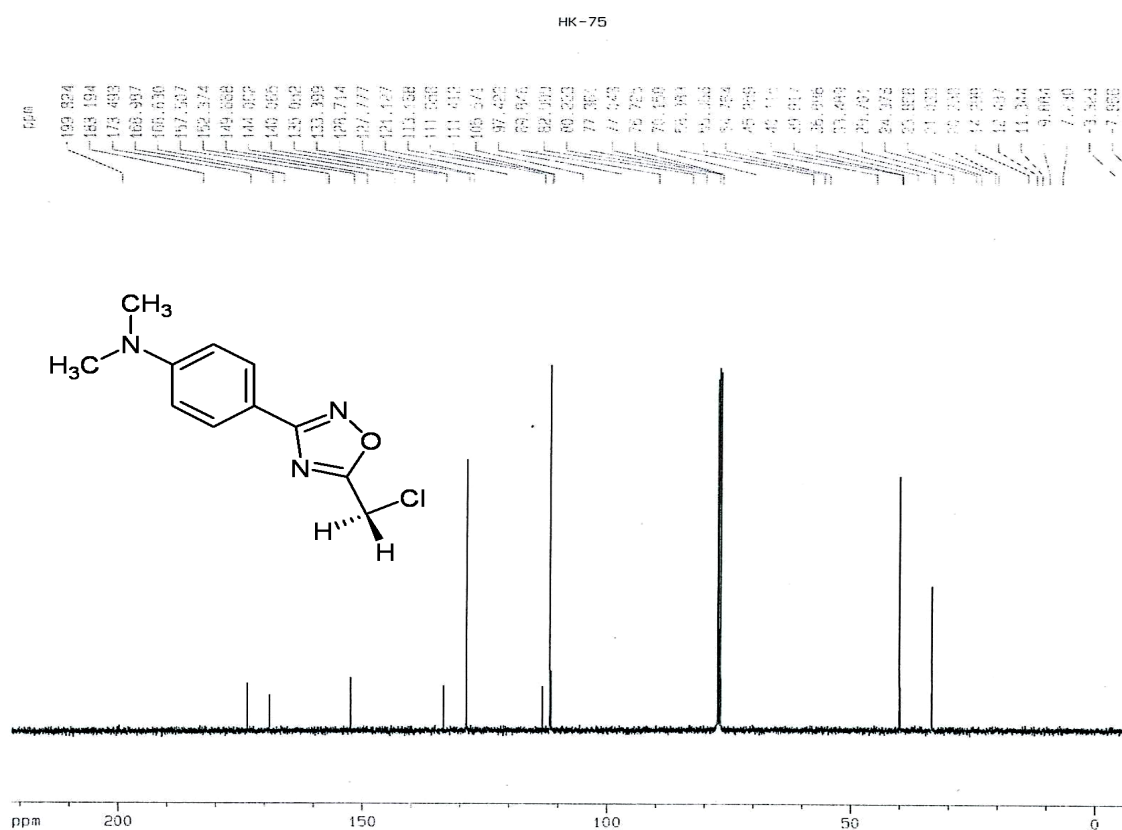


Figure 4. 43 ^{13}C NMR Spectrum of compound 31m

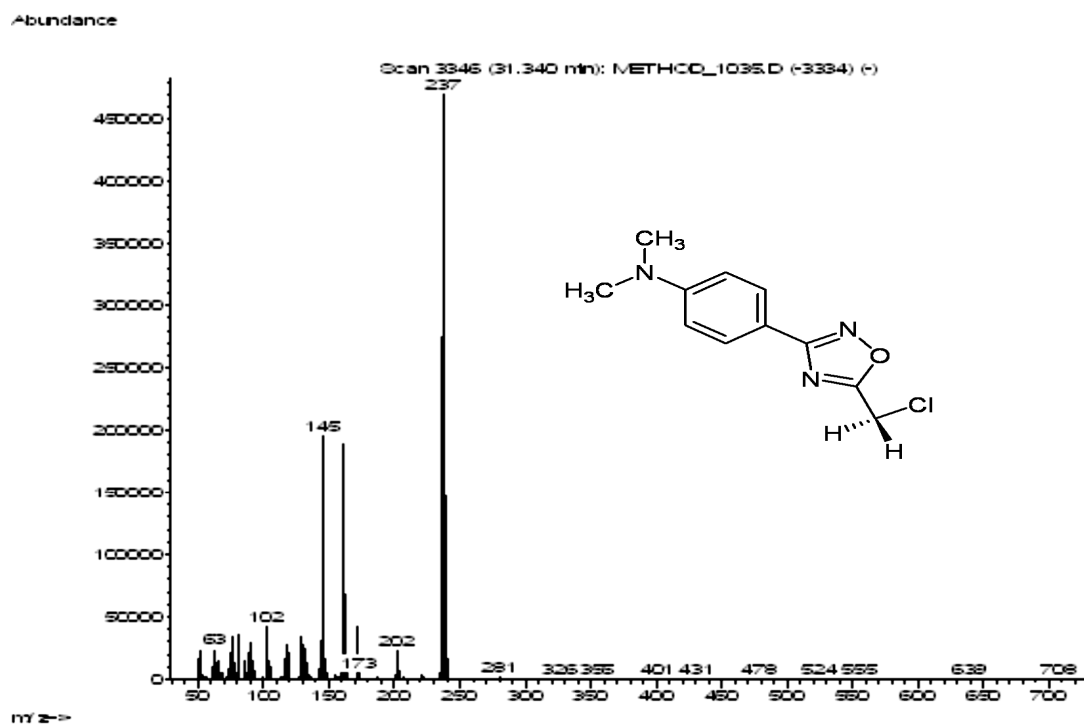


Figure 4. 44 Mass spectra of compound 31m

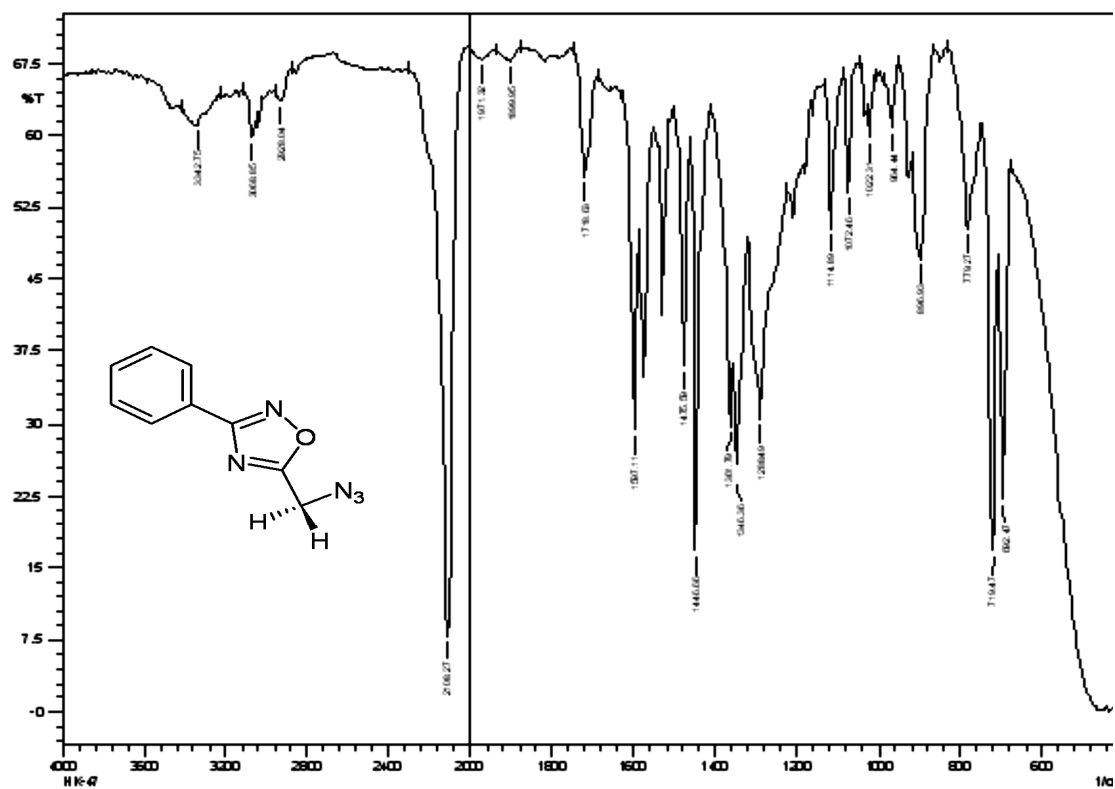


Figure 4. 45 IR spectrum of compound **88a**

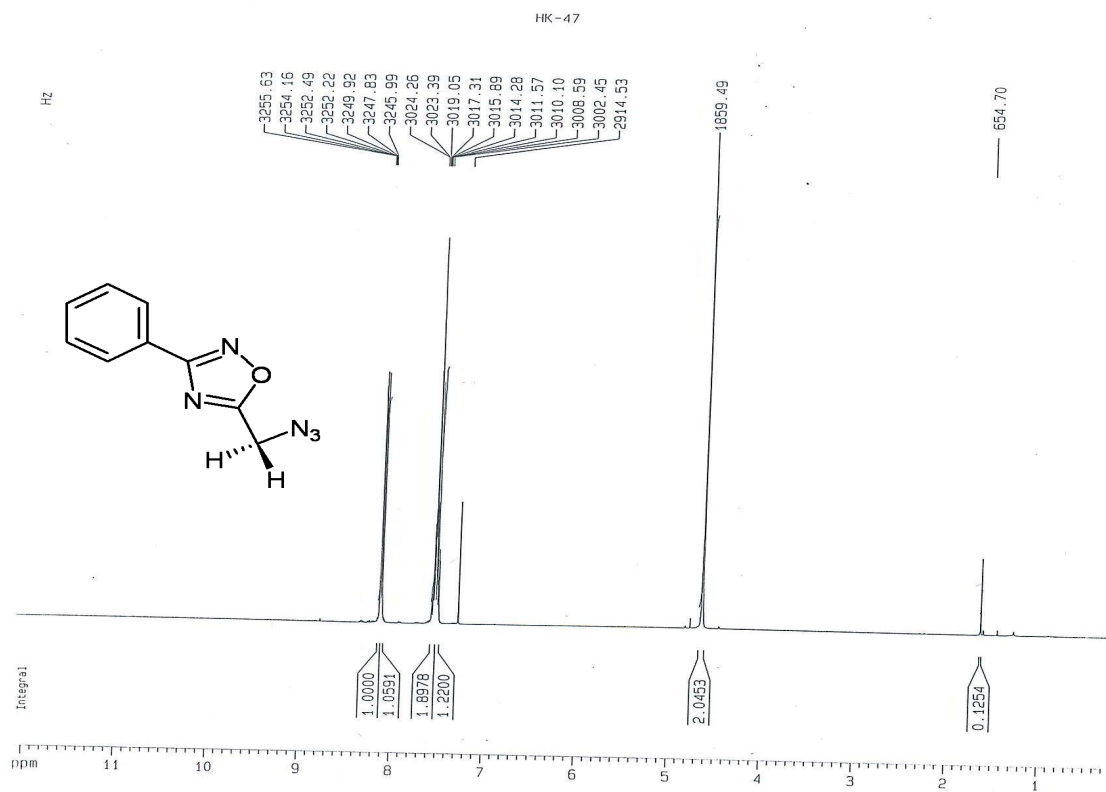


Figure 4. 46 1H NMR Spectrum of compound **88a**

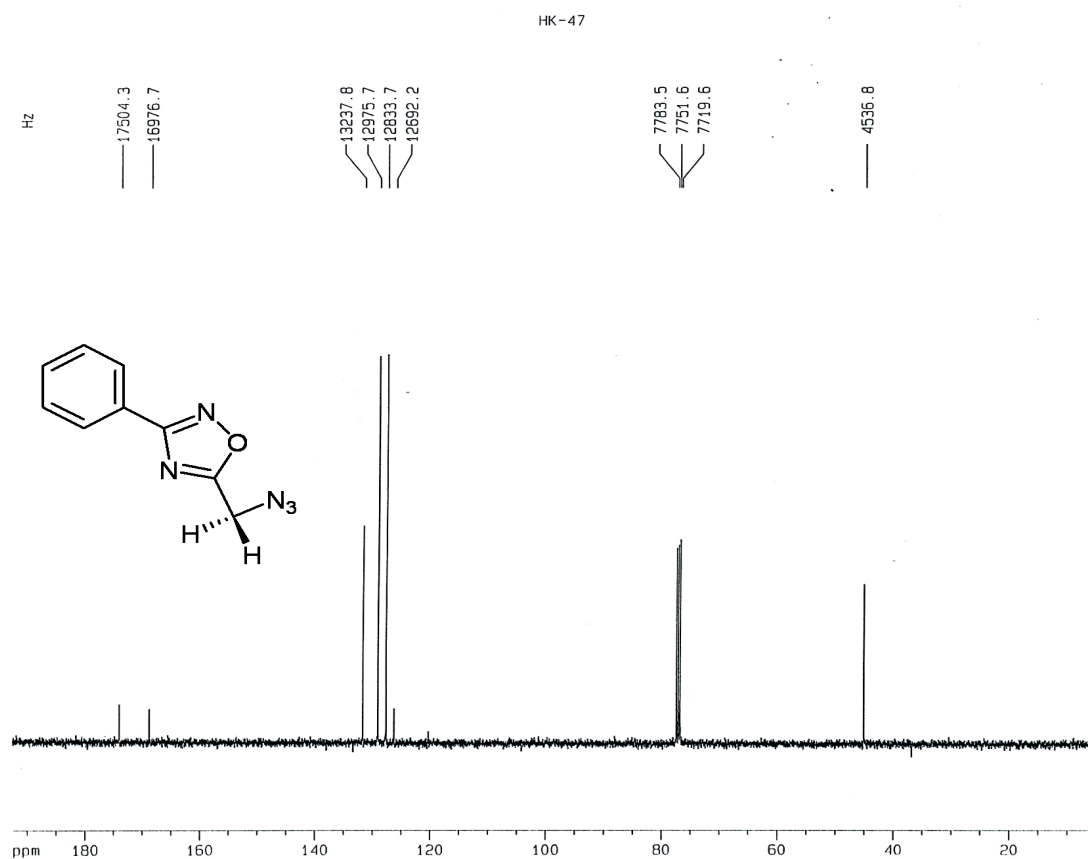


Figure 4. 47 ¹³C NMR Spectrum of compound **88a**

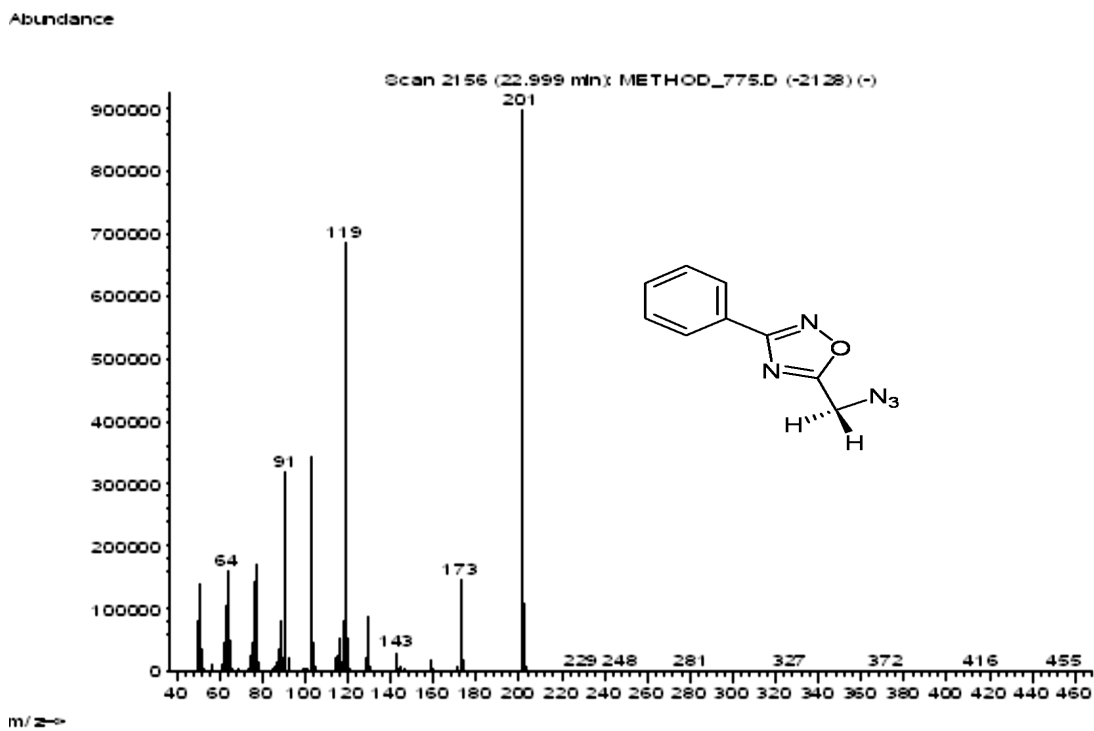


Figure 4. 48 Mass spectra of compound **88a**

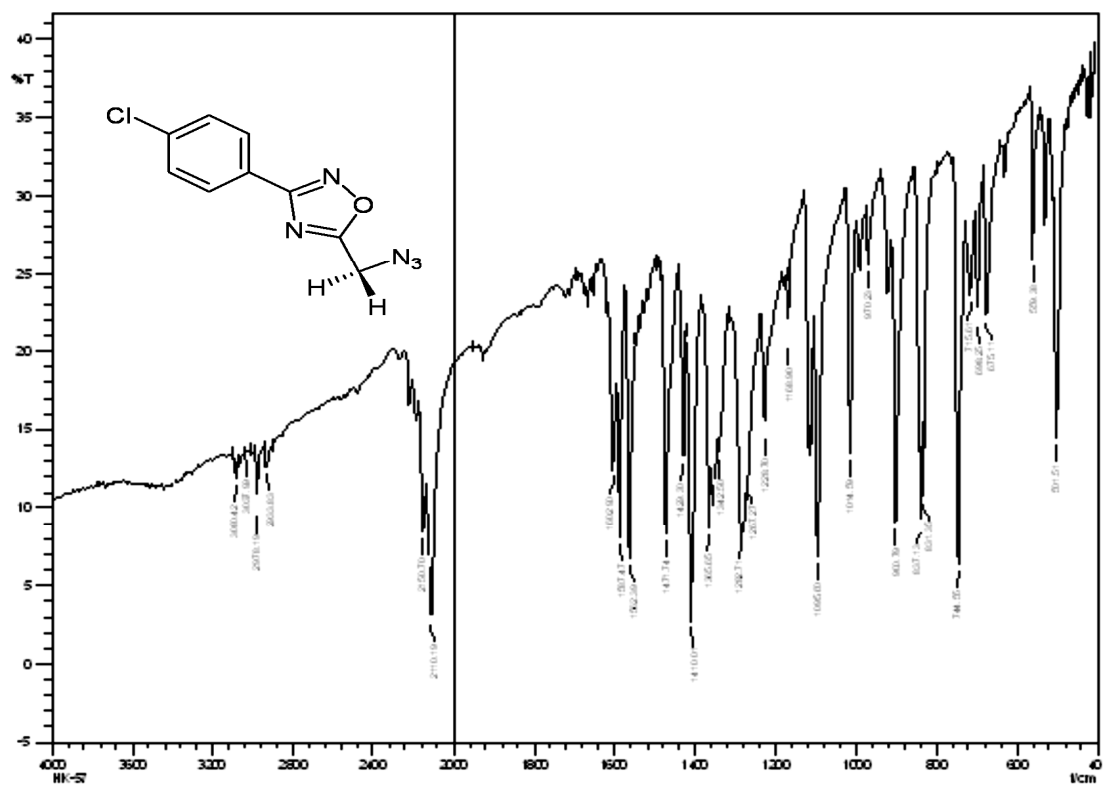


Figure 4. 49 IR spectrum of compound 88b

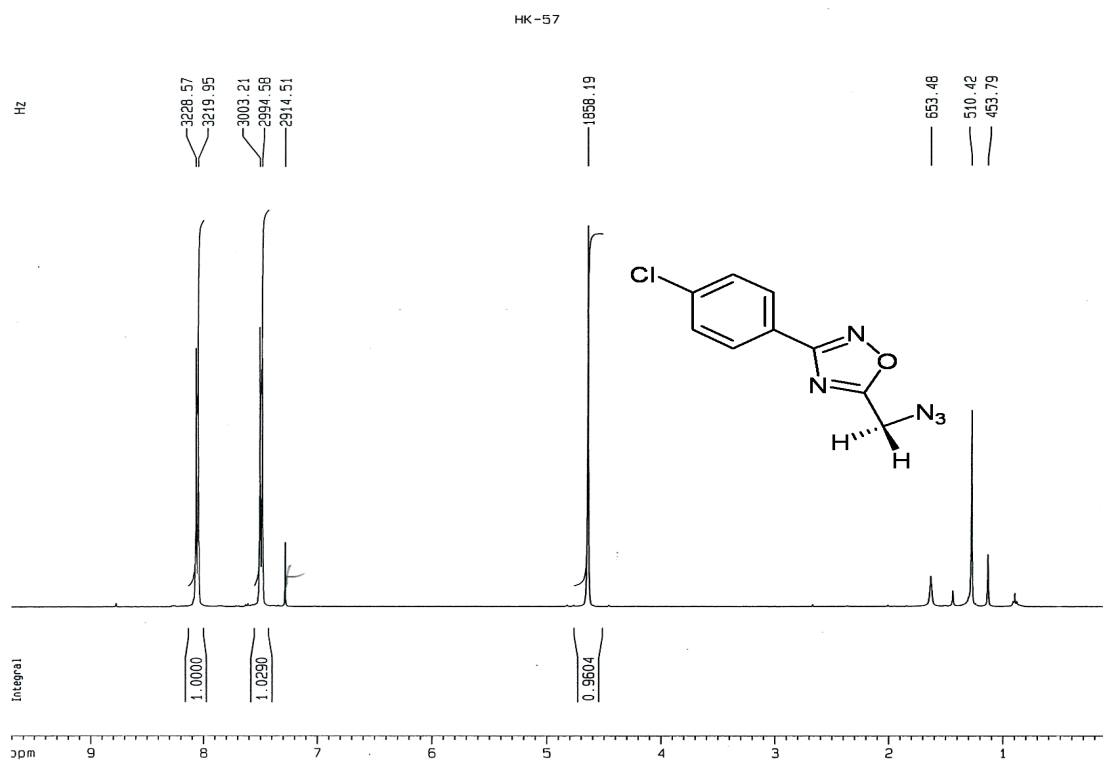


Figure 4. 50 ^1H NMR Spectrum of compound 88b

HK-57

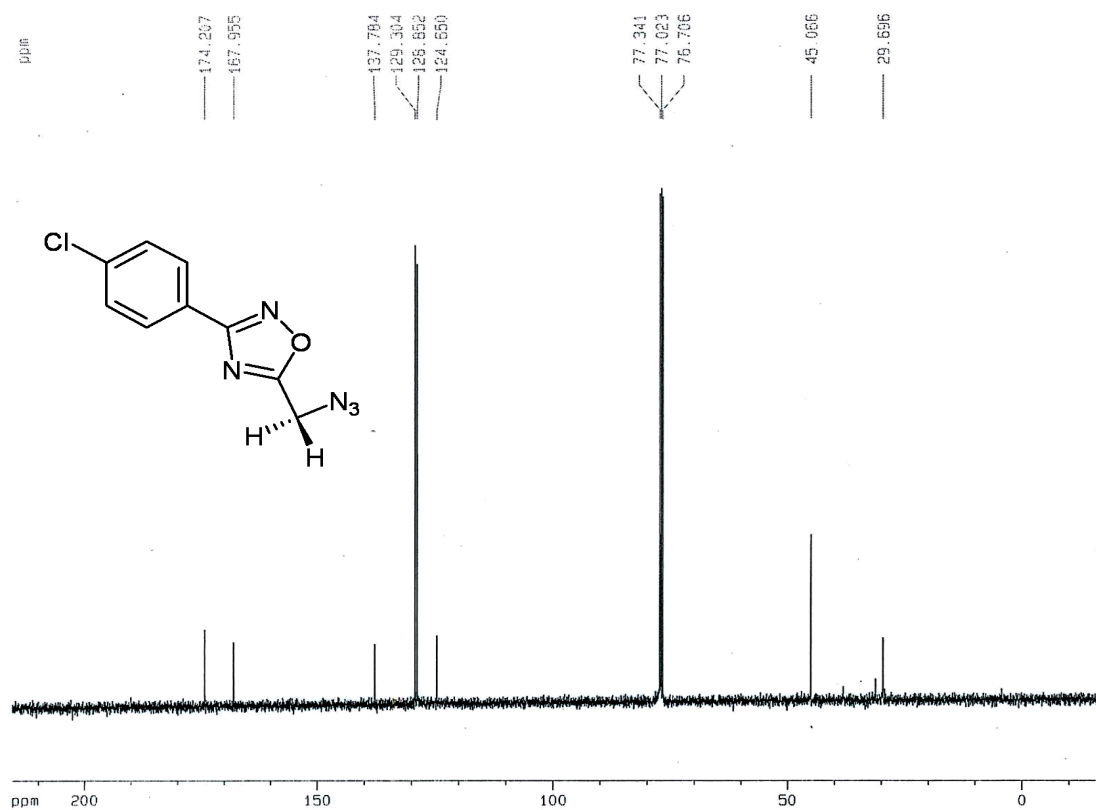


Figure 4. 51 ¹³C NMR Spectrum of compound 88b

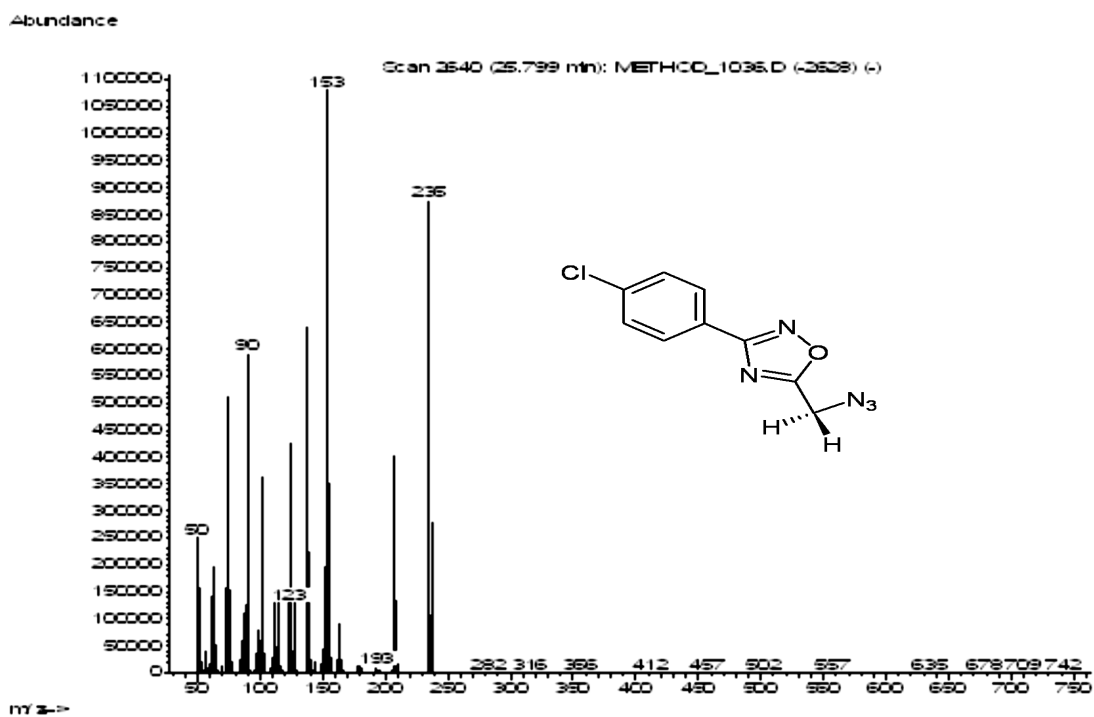


Figure 4. 52 Mass spectra of compound 88b

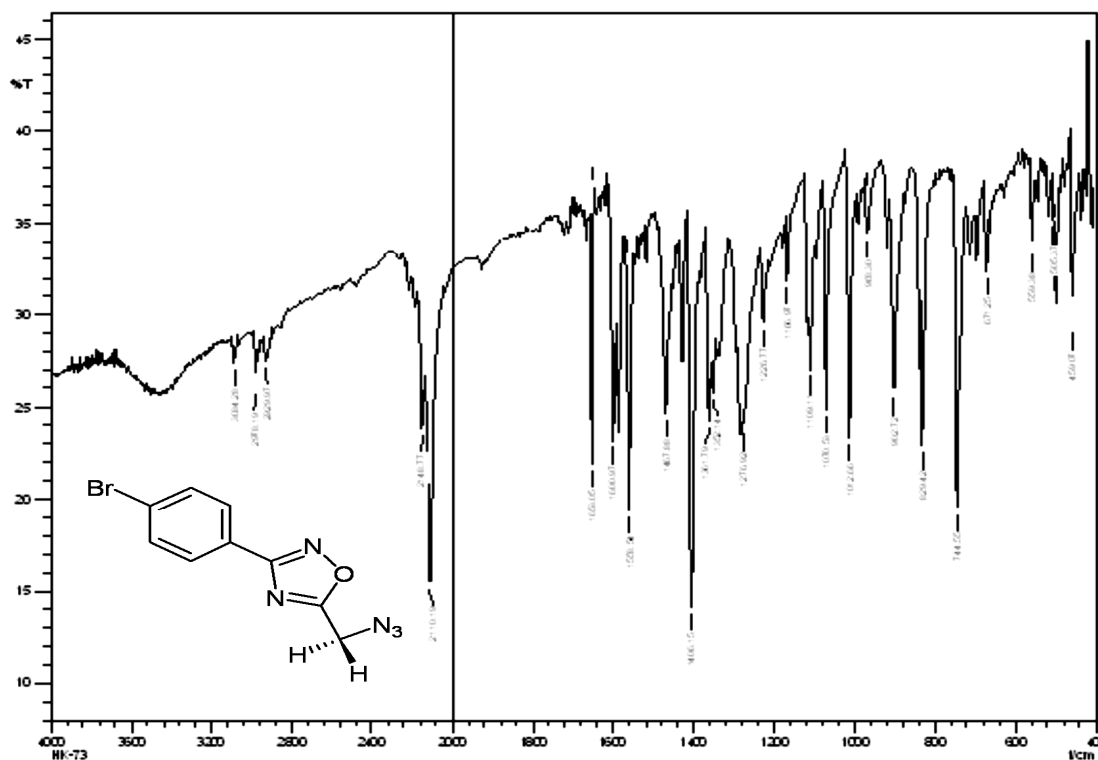


Figure 4. 53 IR spectrum of compound 88c

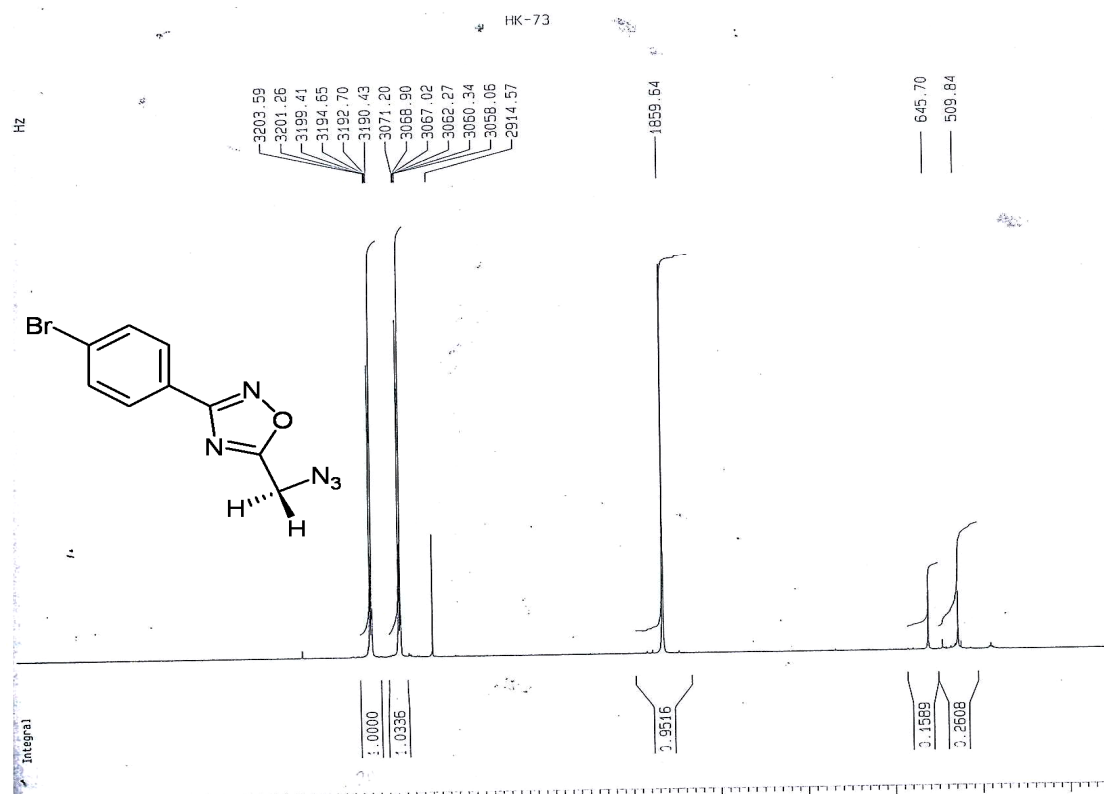


Figure 4. 54 ¹H NMR Spectrum of compound 88c

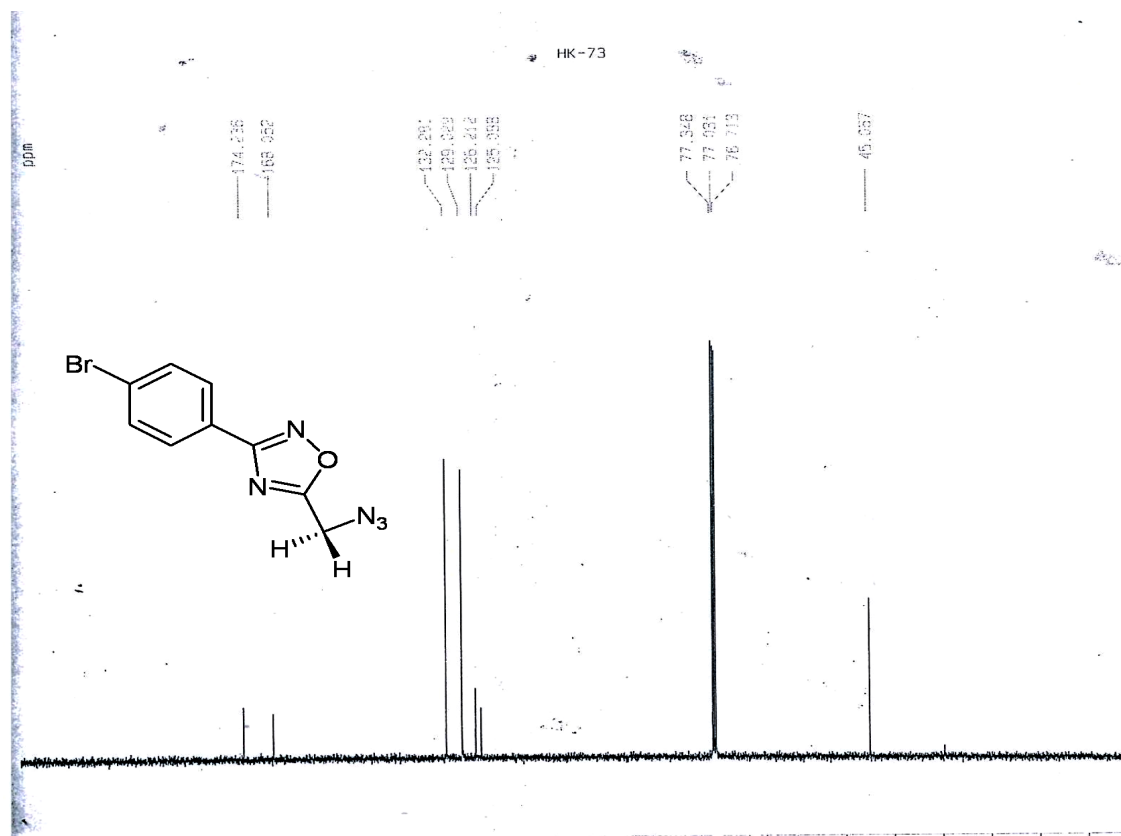


Figure 4. 55 ¹³C NMR Spectrum of compound 88c

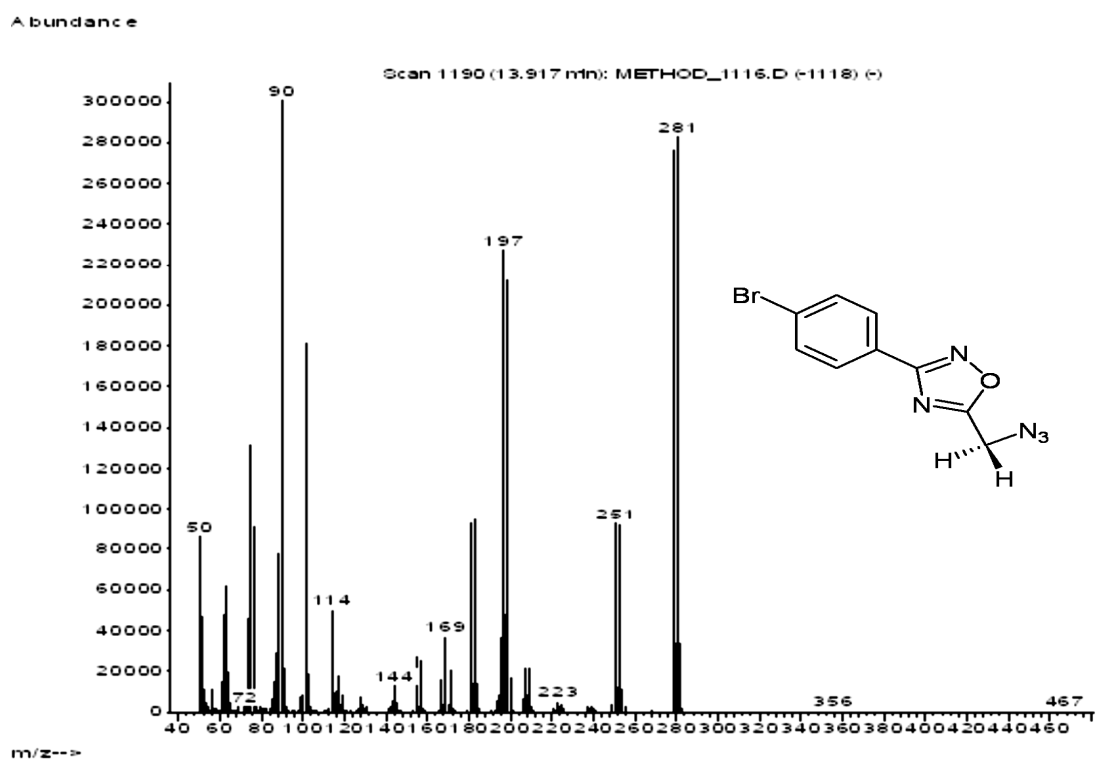


Figure 4. 56 Mass spectra of compound 88c

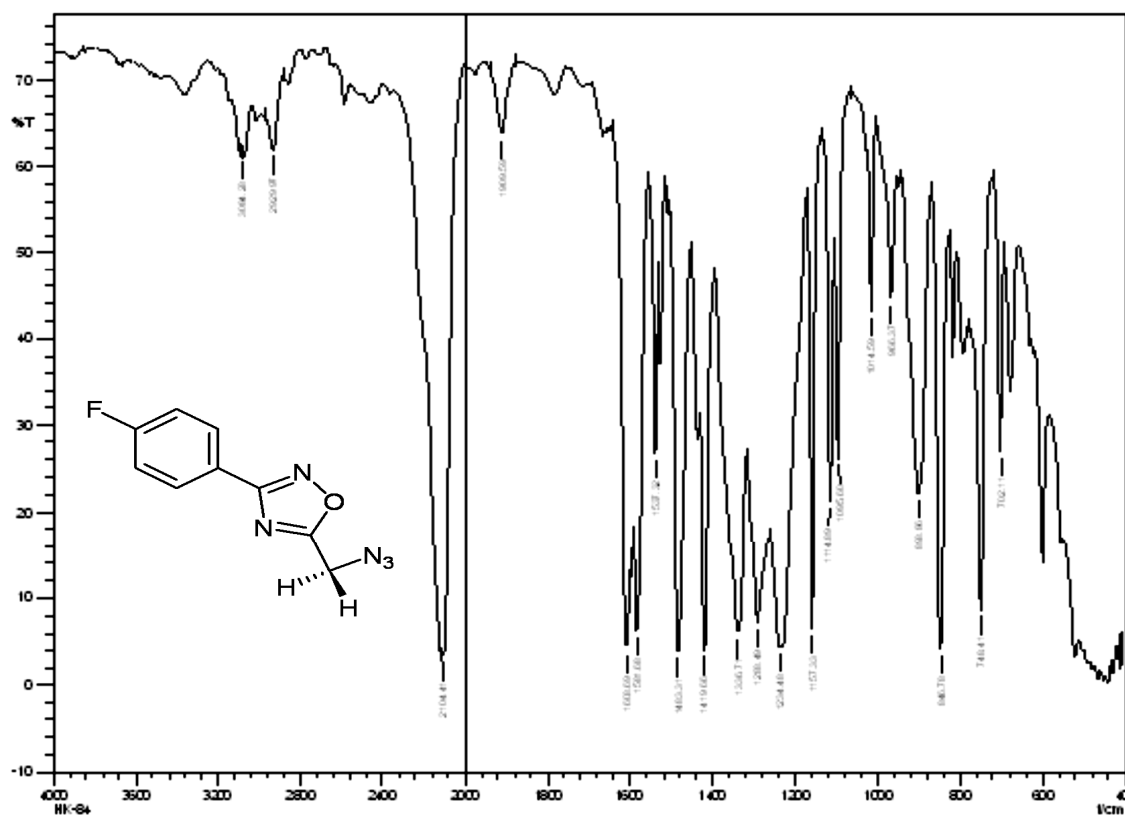


Figure 4. 57 IR spectrum of compound **88d**

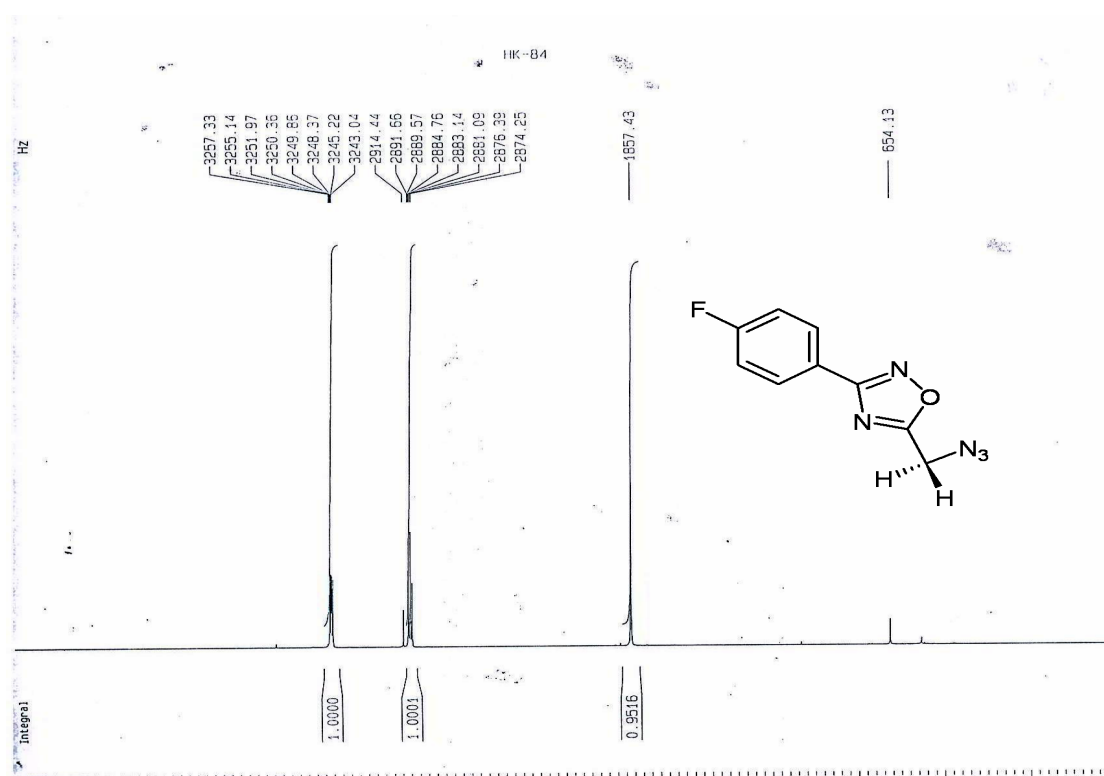


Figure 4. 58 ^1H NMR Spectrum of compound **88d**

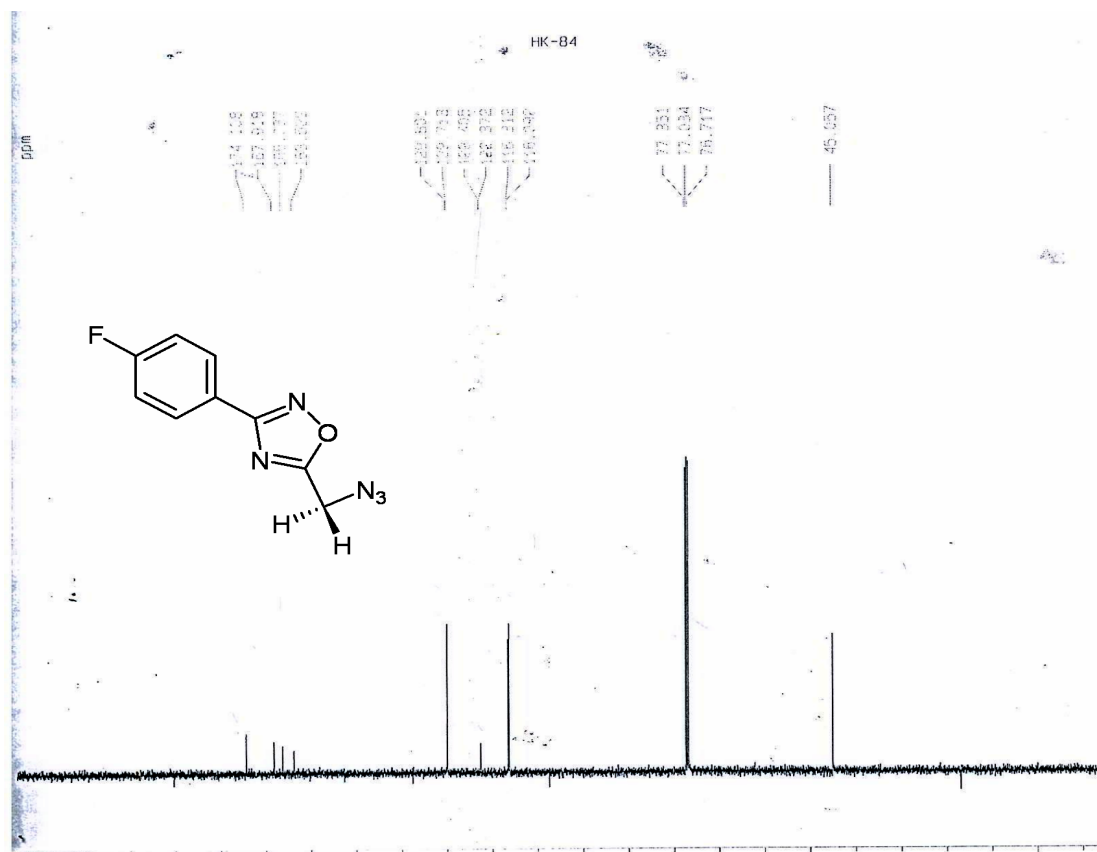


Figure 4. 59 ¹³C NMR Spectrum of compound 88d

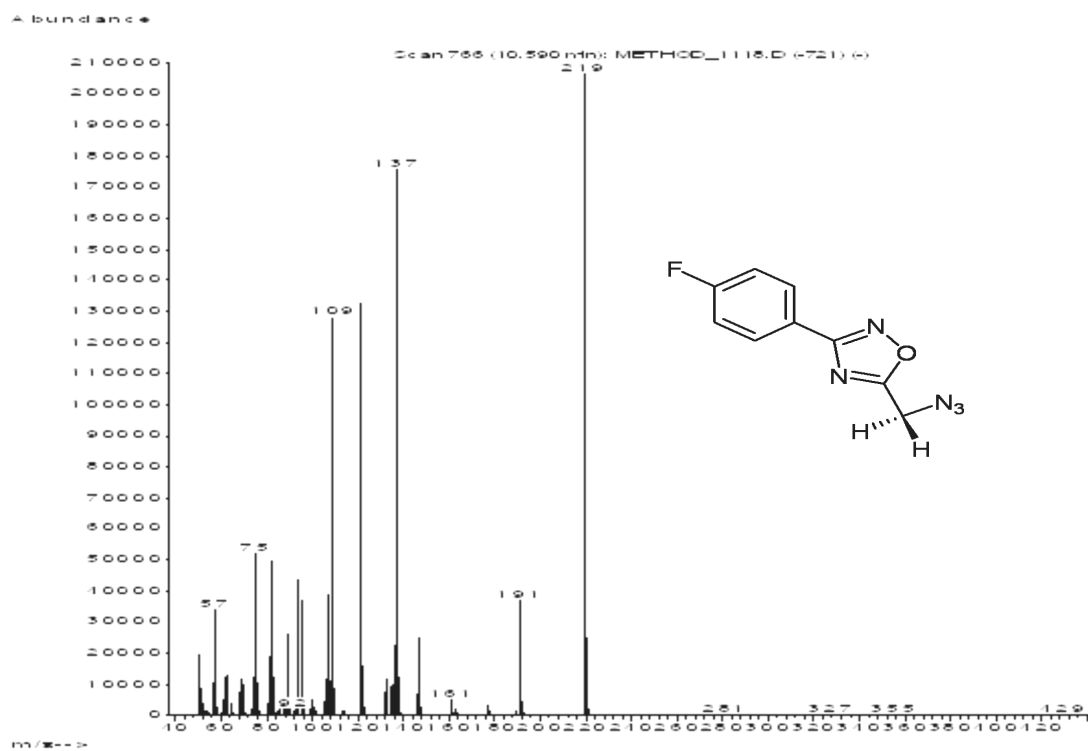


Figure 4. 60 Mass spectra of compound 88d

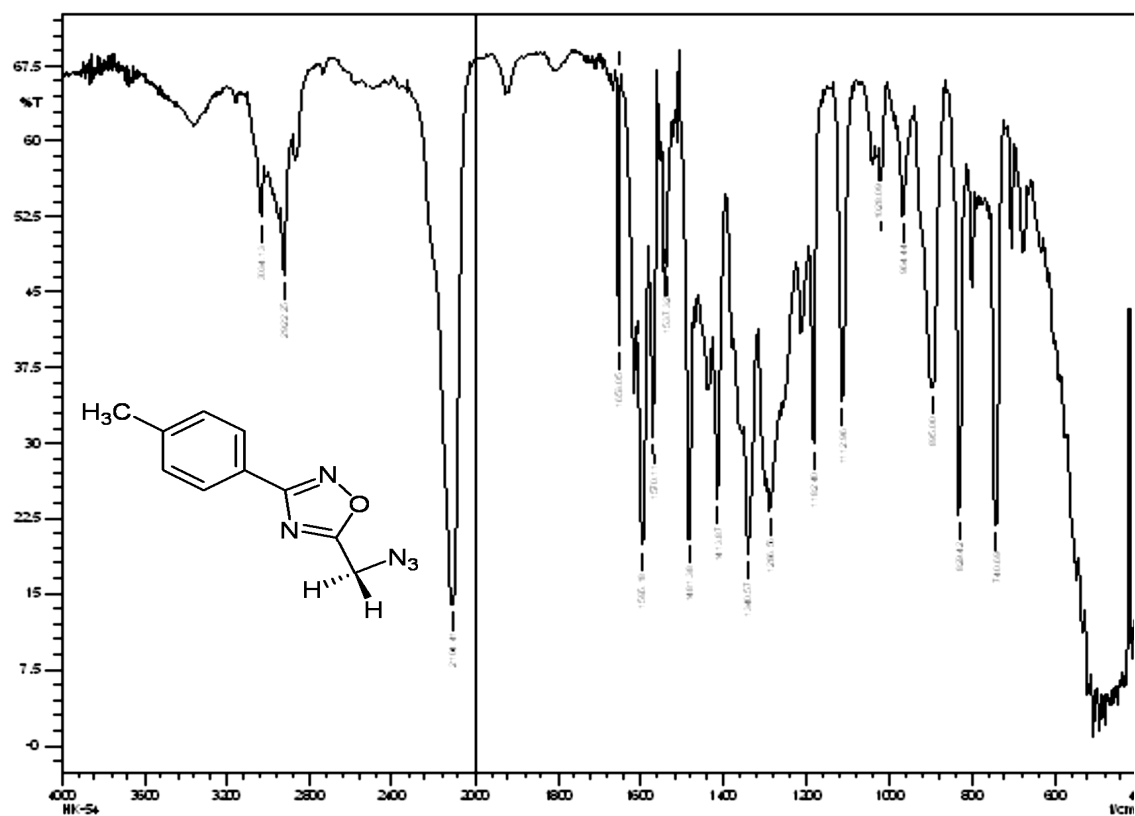


Figure 4. 61 IR spectrum of compound **88e**

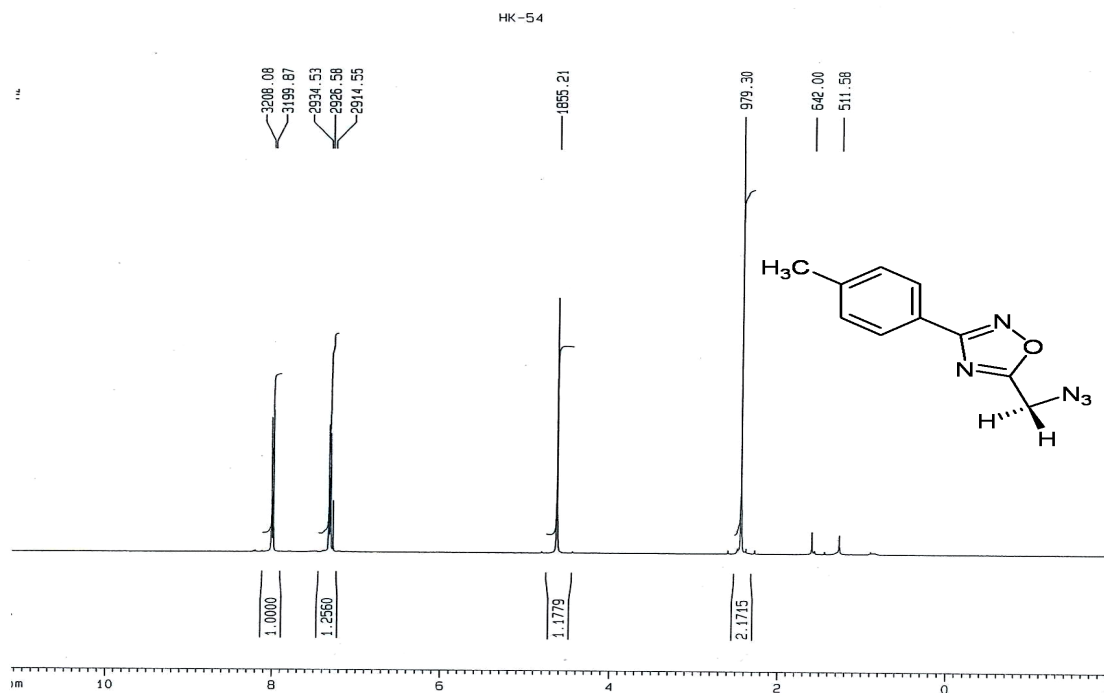


Figure 4. 62 ¹H NMR Spectrum of compound **88e**

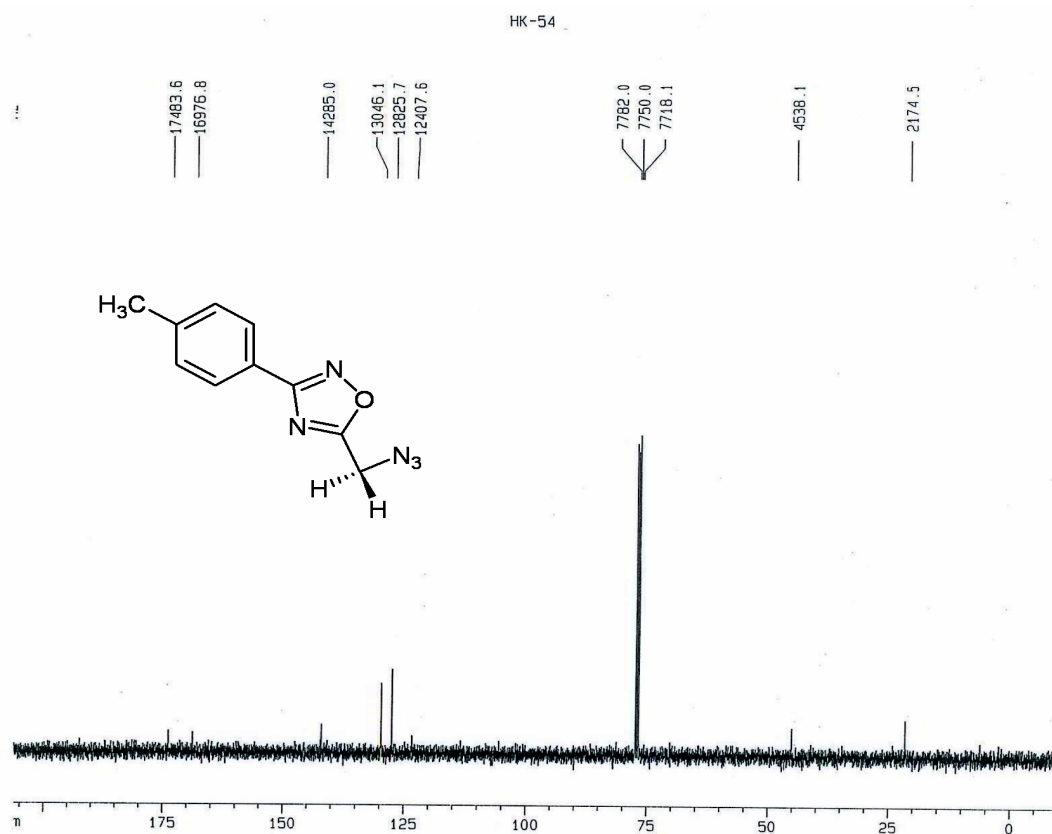


Figure 4. 63 ^{13}C NMR Spectrum of compound 88e

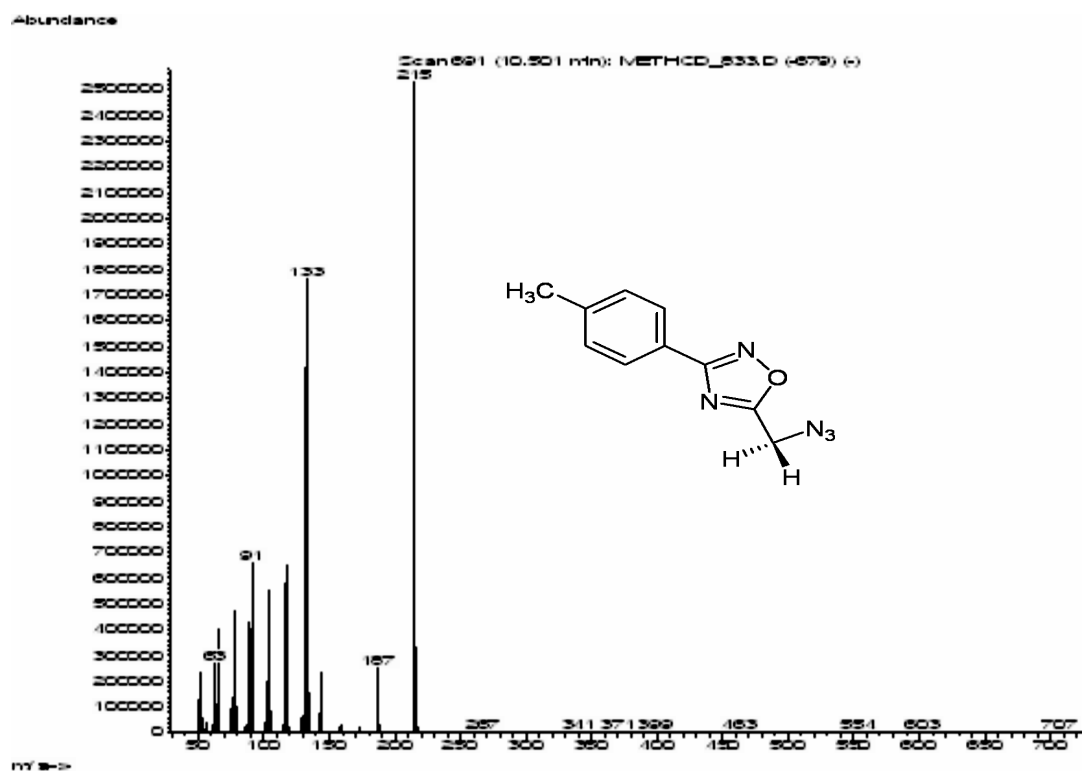


Figure 4. 64 Mass spectra of compound 88e

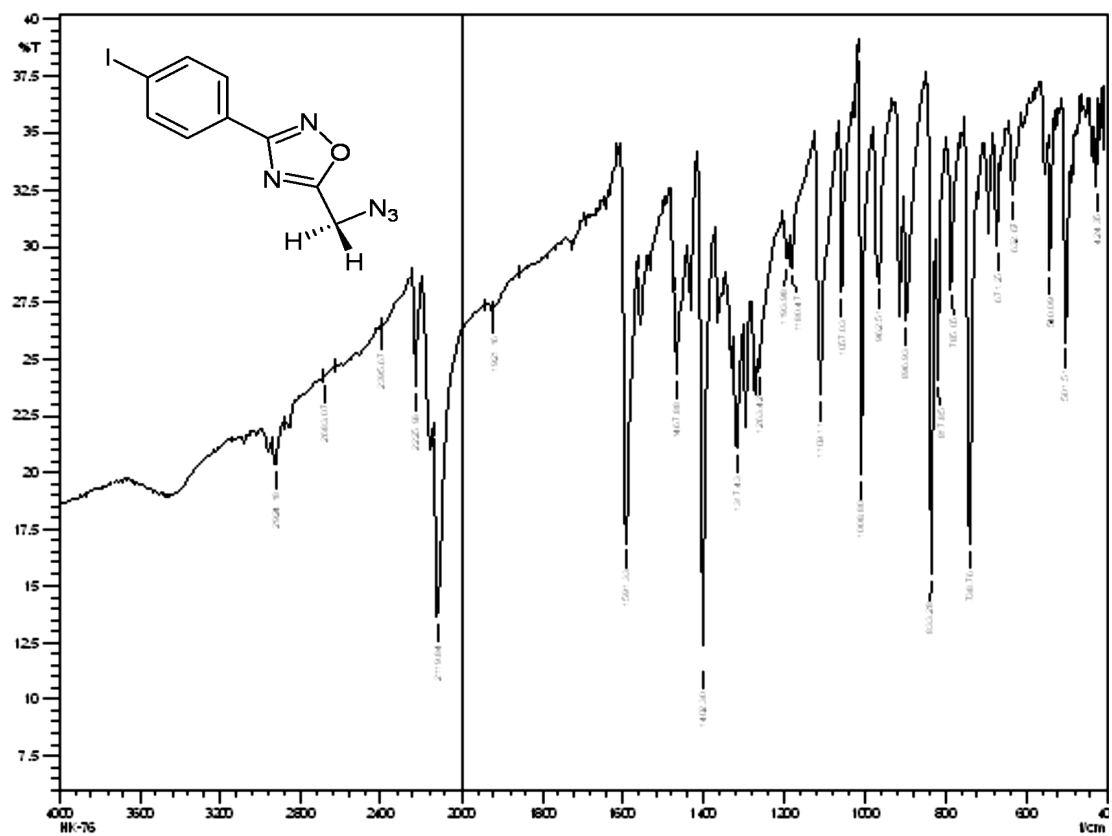


Figure 4. 65 IR spectrum of compound 88f

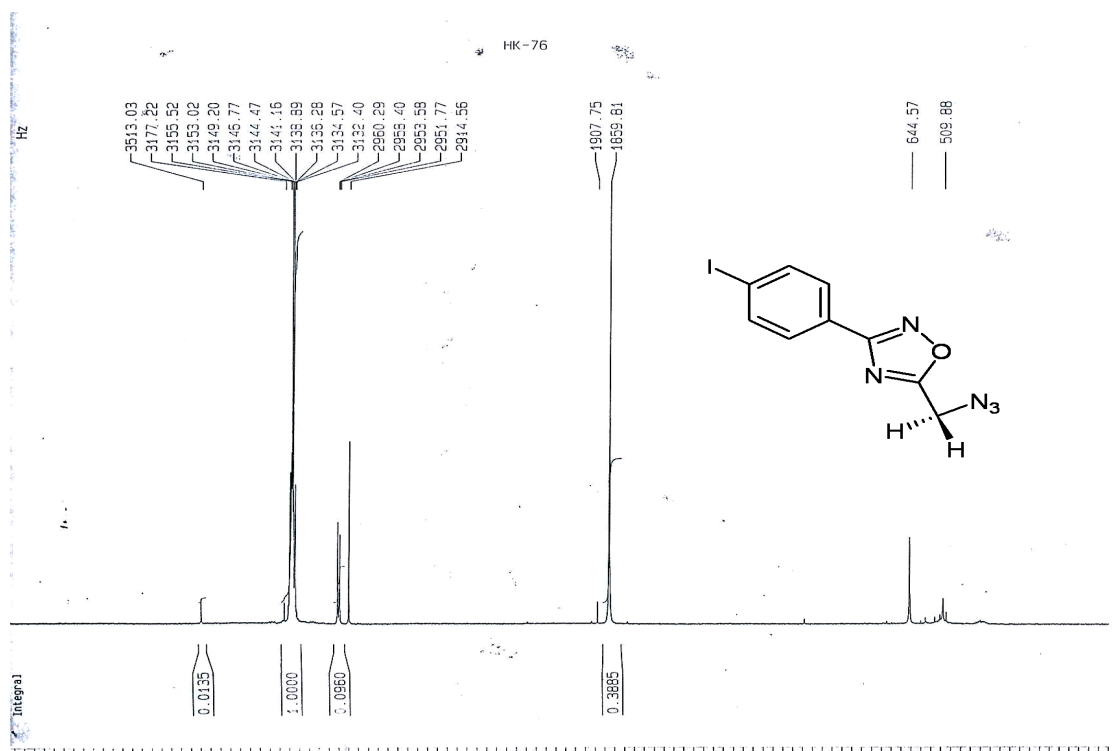


Figure 4. 66 ¹H NMR Spectrum of compound 88f

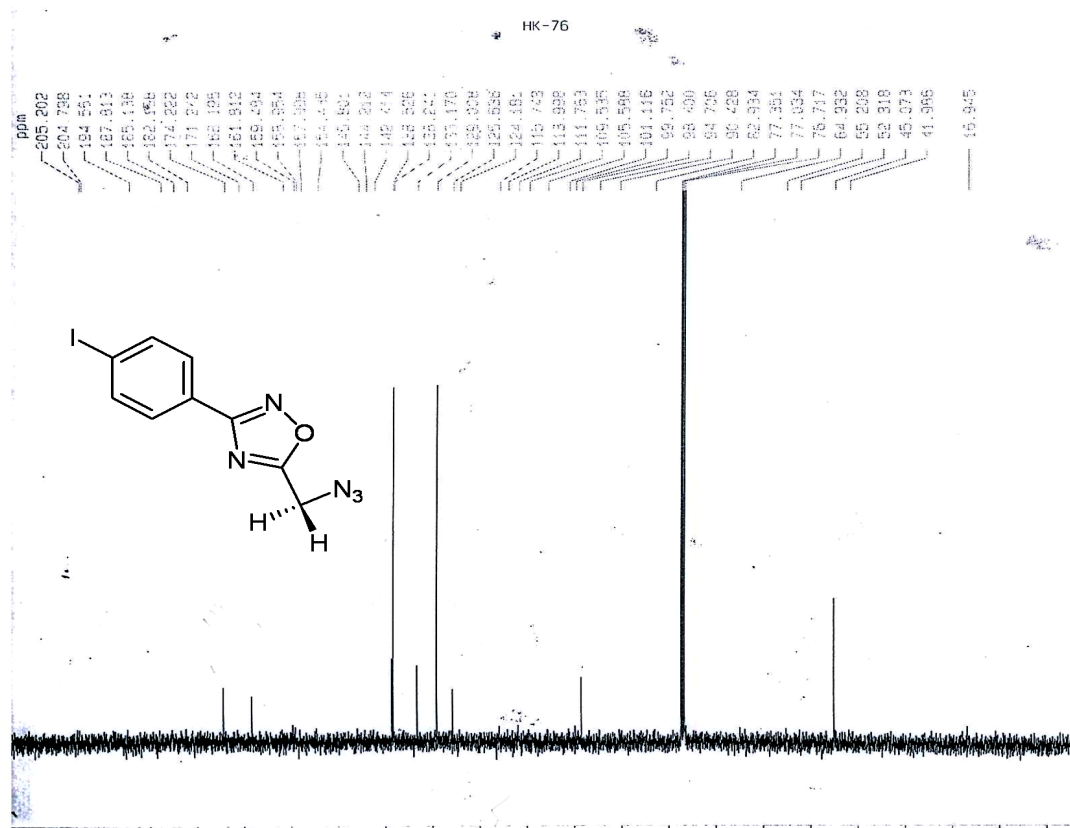


Figure 4. 67 ¹³C NMR Spectrum of compound 88f

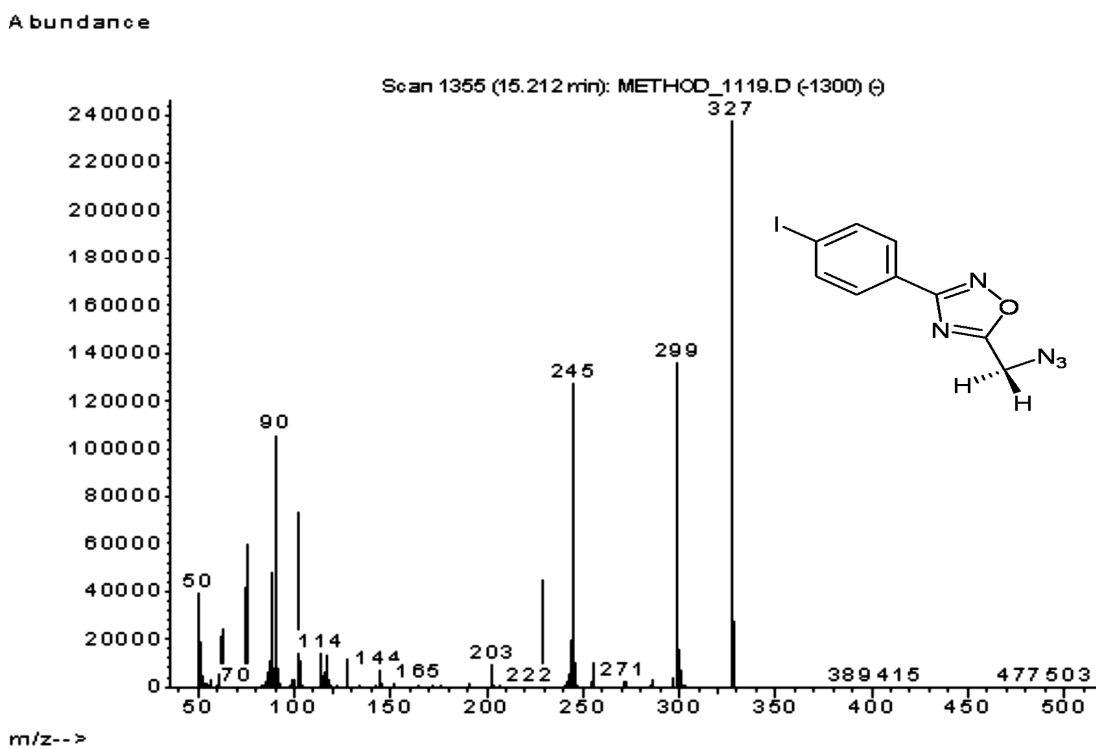


Figure 4. 68 Mass spectra of compound 88f

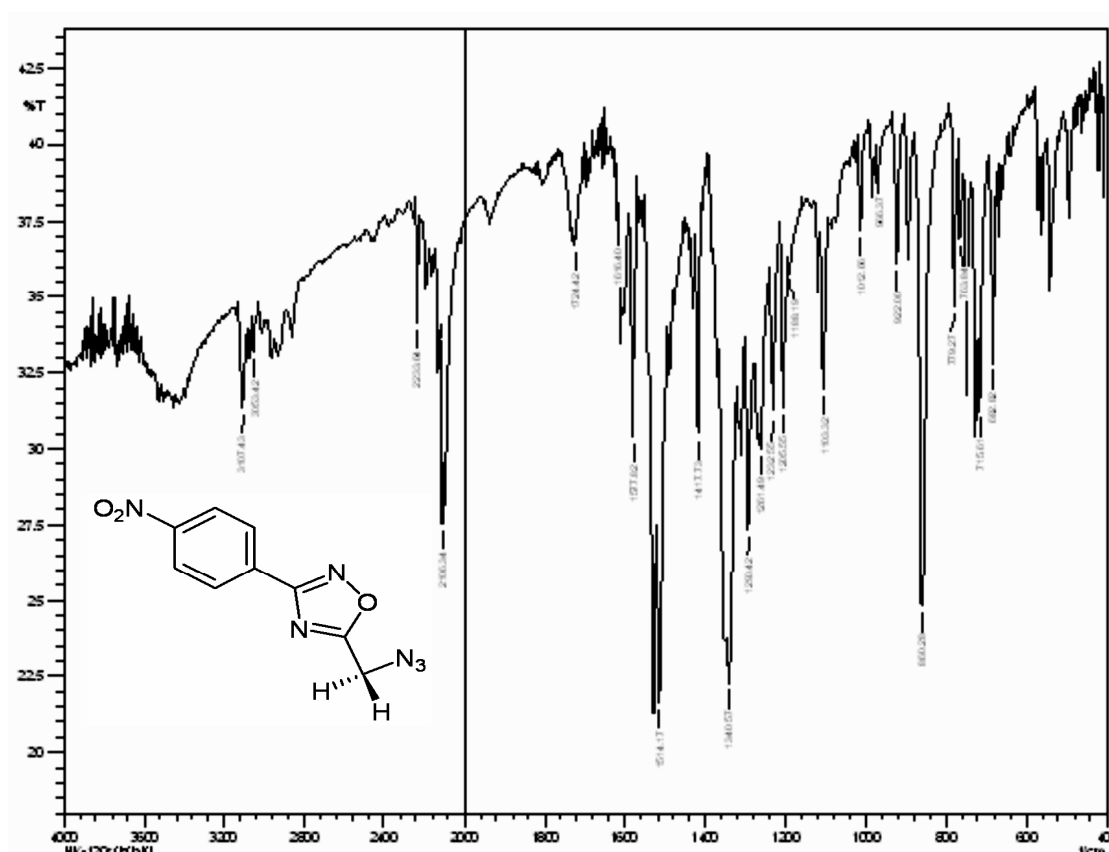


Figure 4. 69 IR spectrum of compound **88g**

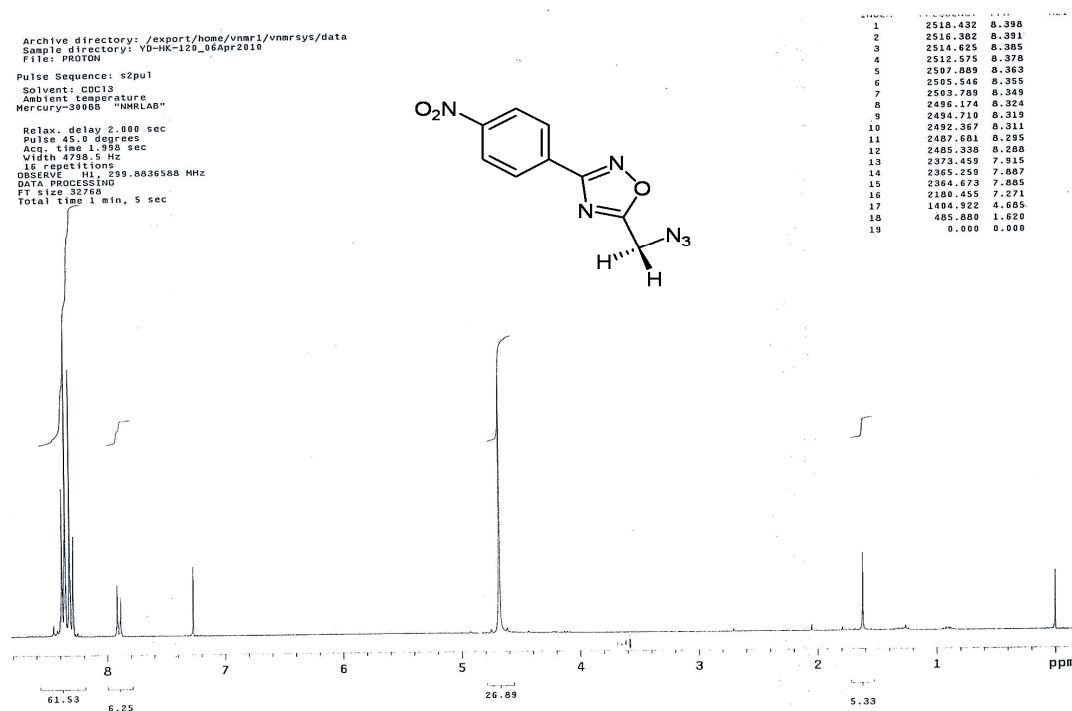


Figure 4. 70 ¹H NMR Spectrum of compound **88g**

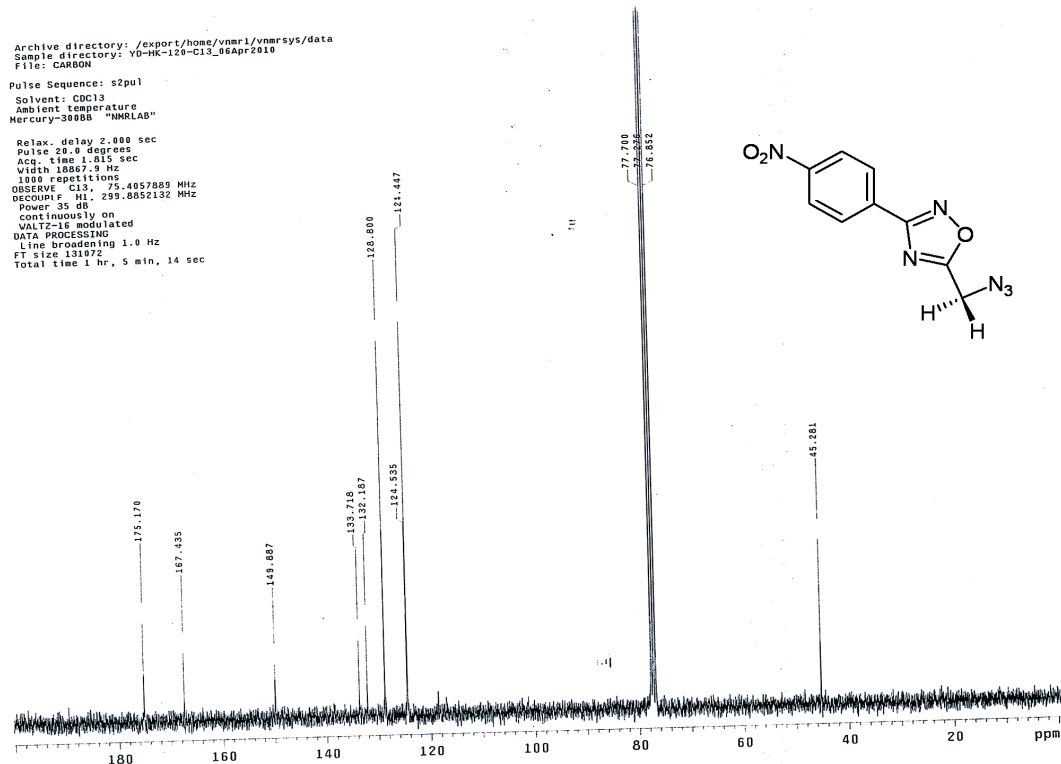
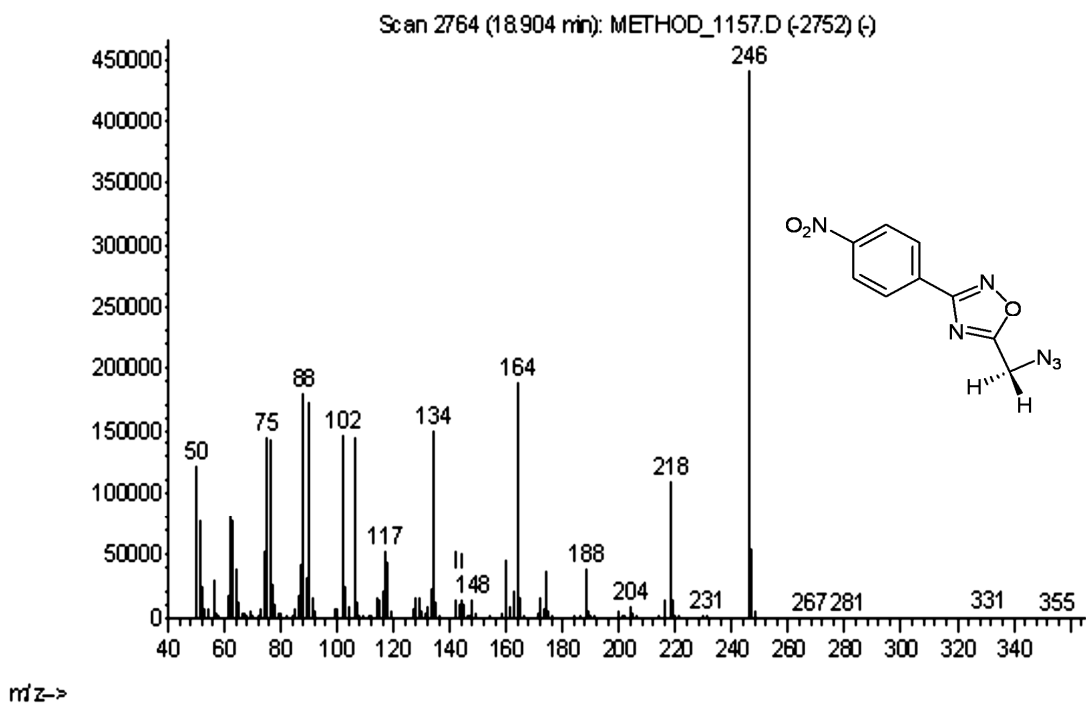


Figure 4. 71 ^{13}C NMR Spectrum of compound **88g**

Abundance



m/z->

Figure 4. 72 Mass spectra of compound **88g**

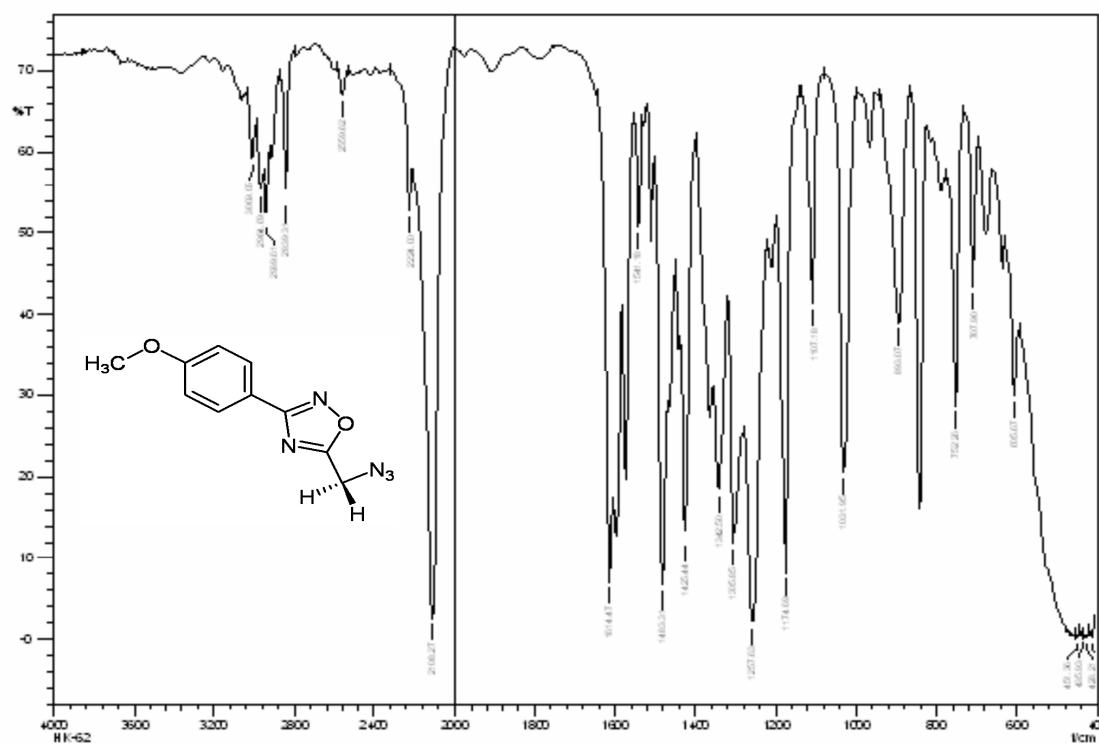


Figure 4. 73 IR spectrum of compound **88h**

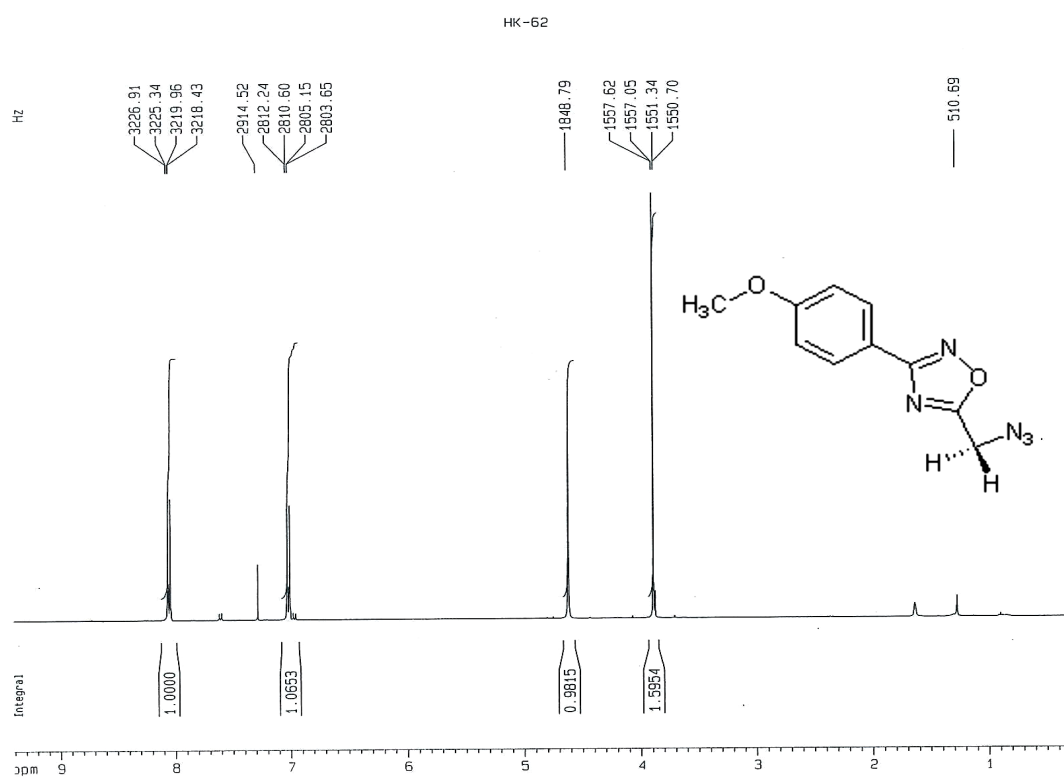


Figure 4. 74 ¹H NMR Spectrum of compound **88h**



Figure 4. 75 ¹³C NMR Spectrum of compound 88h

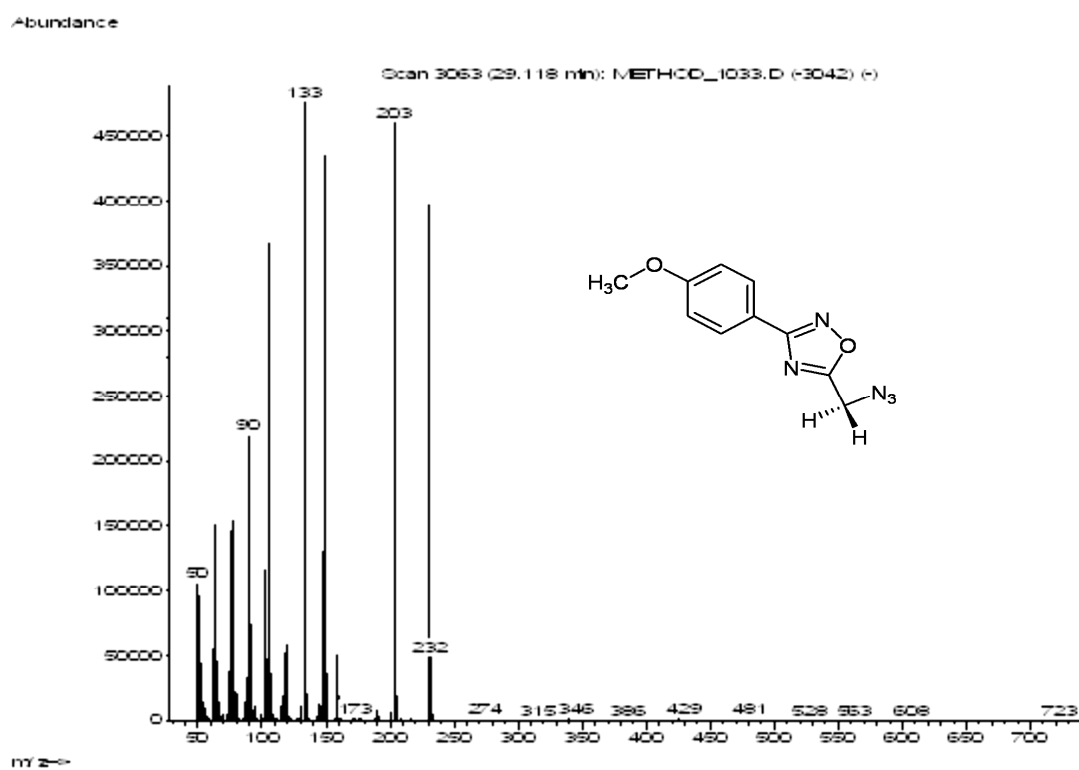


Figure 4. 76 Mass spectra of compound 88h

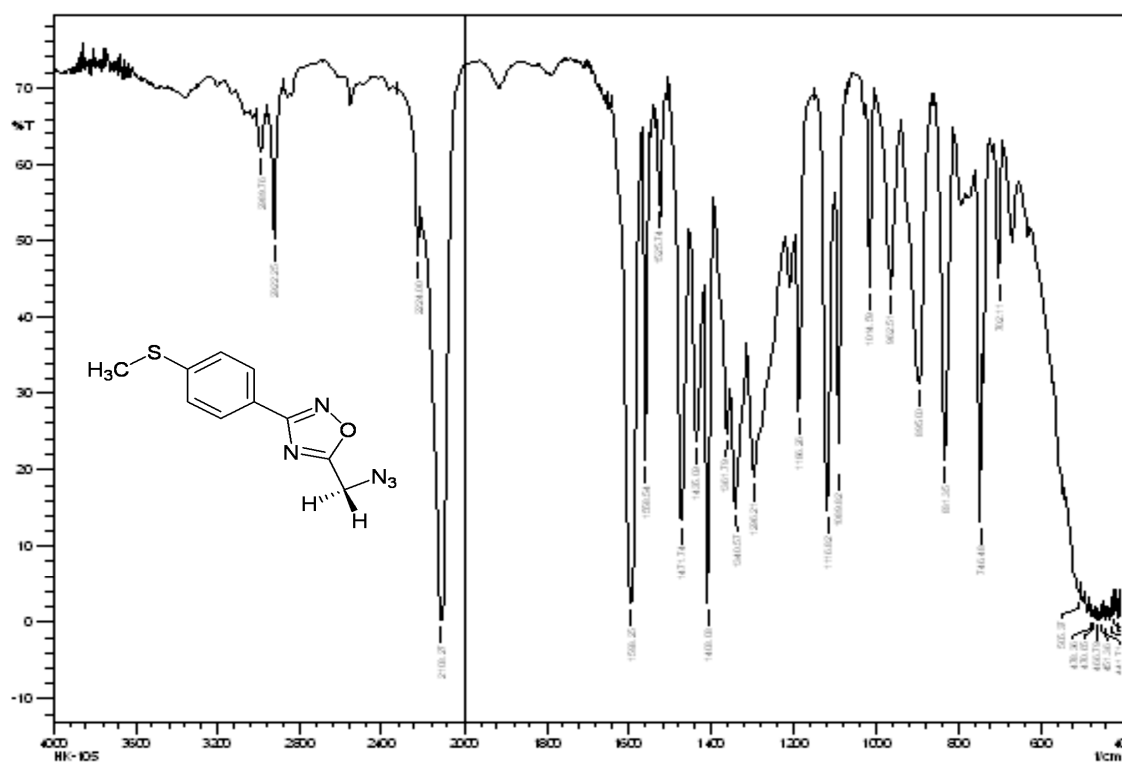


Figure 4. 77 IR spectrum of compound 88j

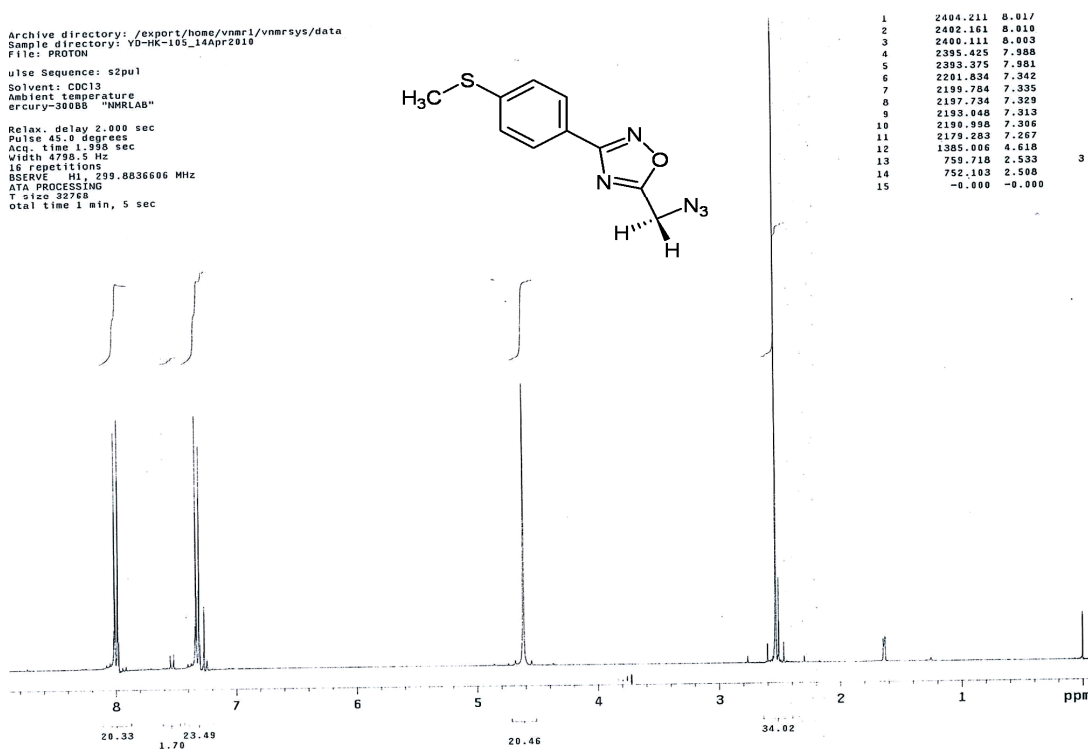


Figure 4. 78 ¹H NMR Spectrum of compound 88j

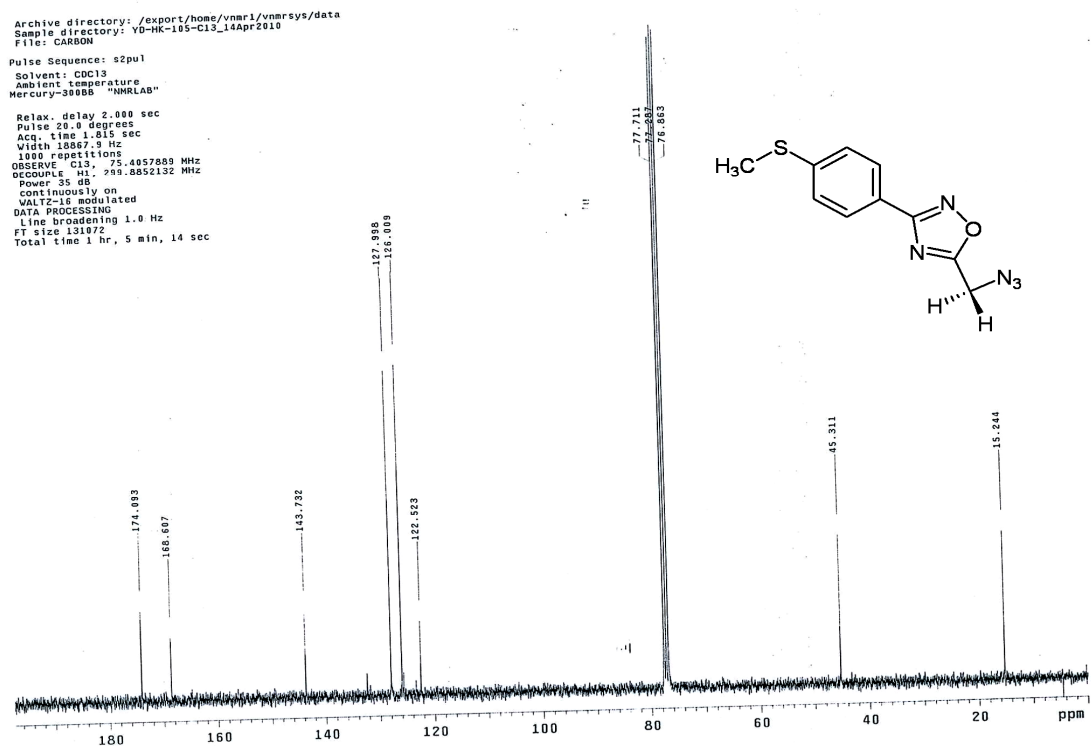


Figure 4. 79 ^{13}C NMR Spectrum of compound 88j

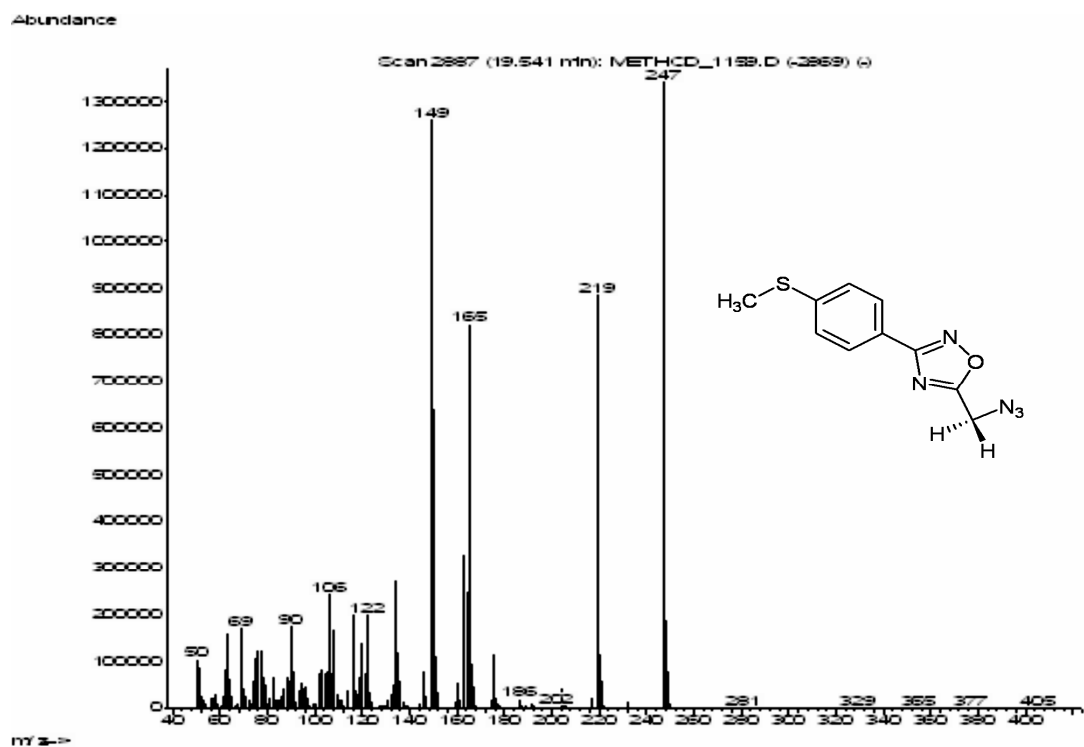


Figure 4. 80 Mass spectra of compound 88j

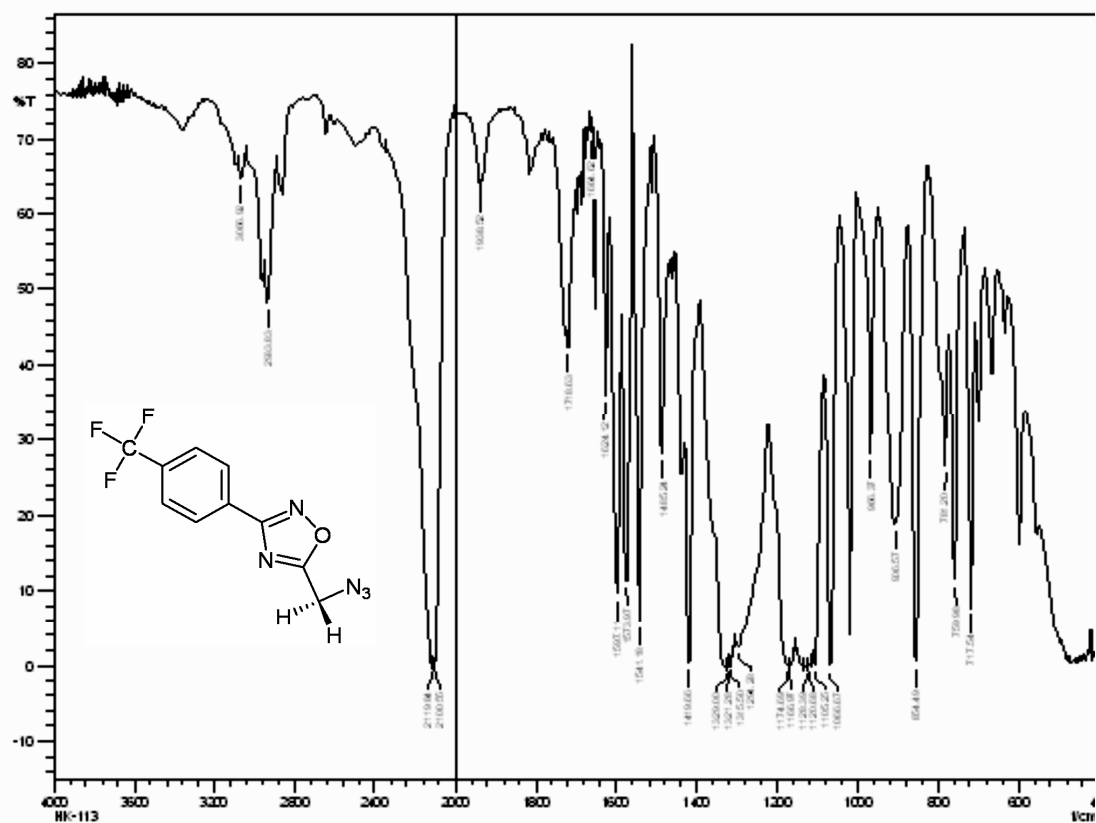


Figure 4. 81 IR spectrum of compound 88k

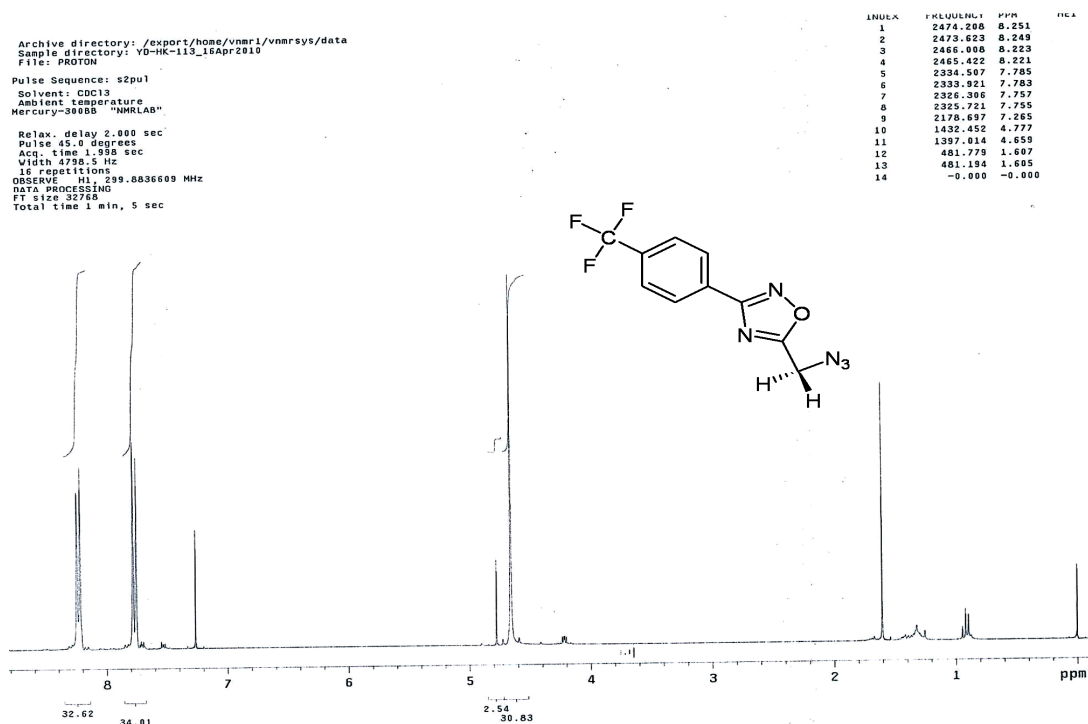


Figure 4. 82 ¹H NMR Spectrum of compound 88k

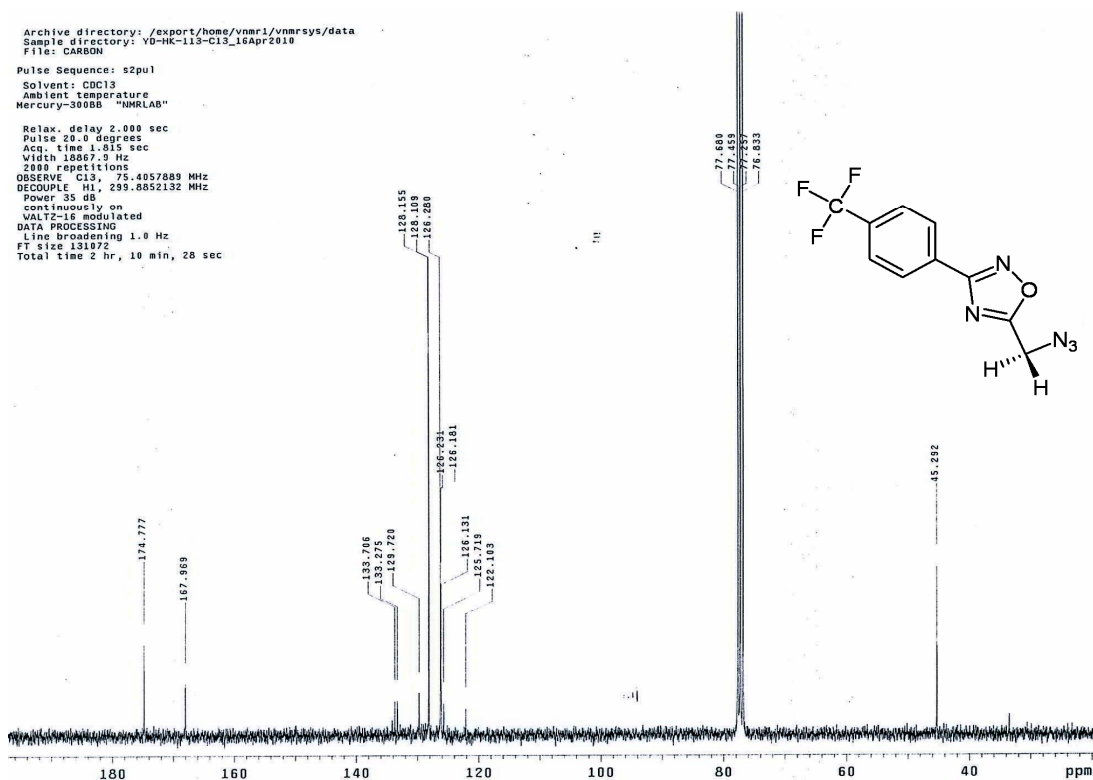


Figure 4. 83 ^{13}C NMR Spectrum of compound 88k

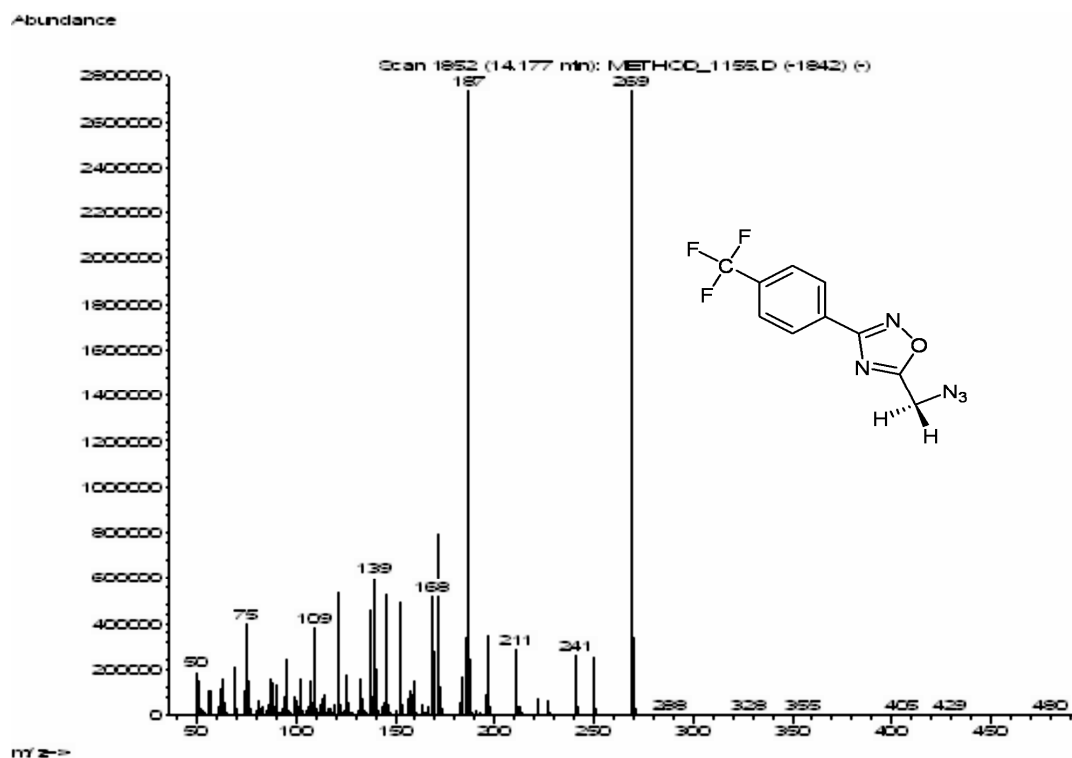


Figure 4. 84 Mass spectra of compound 88k

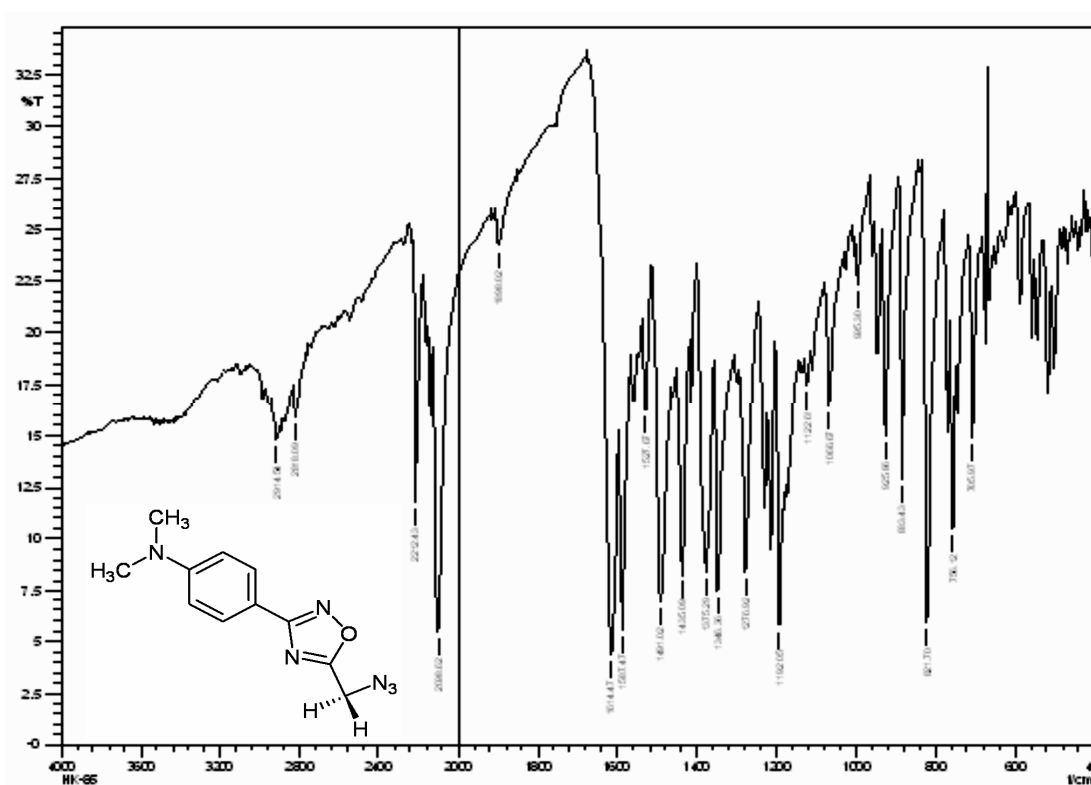


Figure 4. 85 IR spectrum of compound **88m**

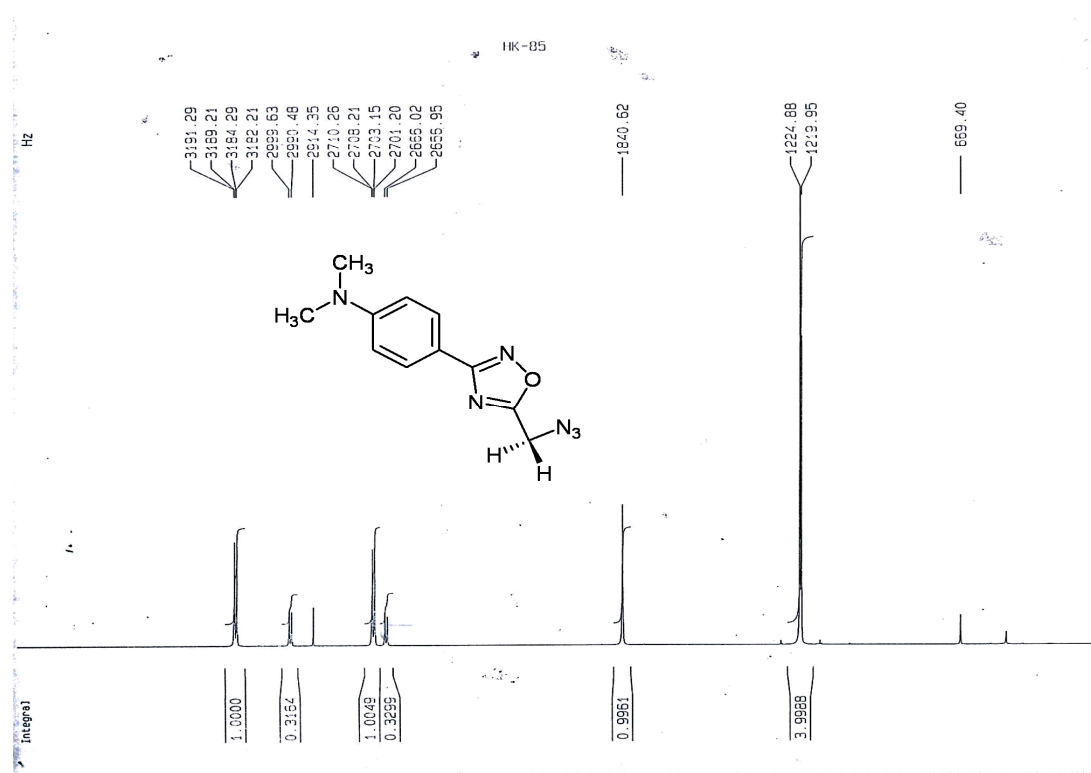


Figure 4. 86 ^1H NMR Spectrum of compound **88m**

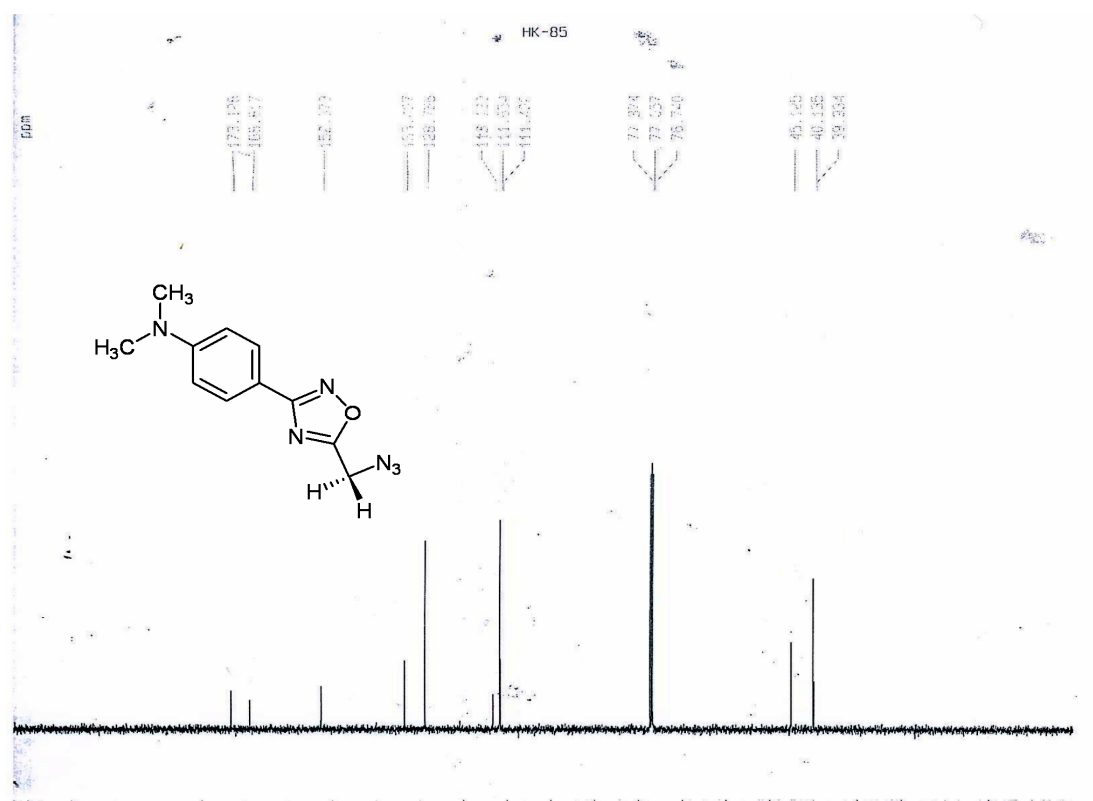


Figure 4. 87 ¹³C NMR Spectrum of compound 88m

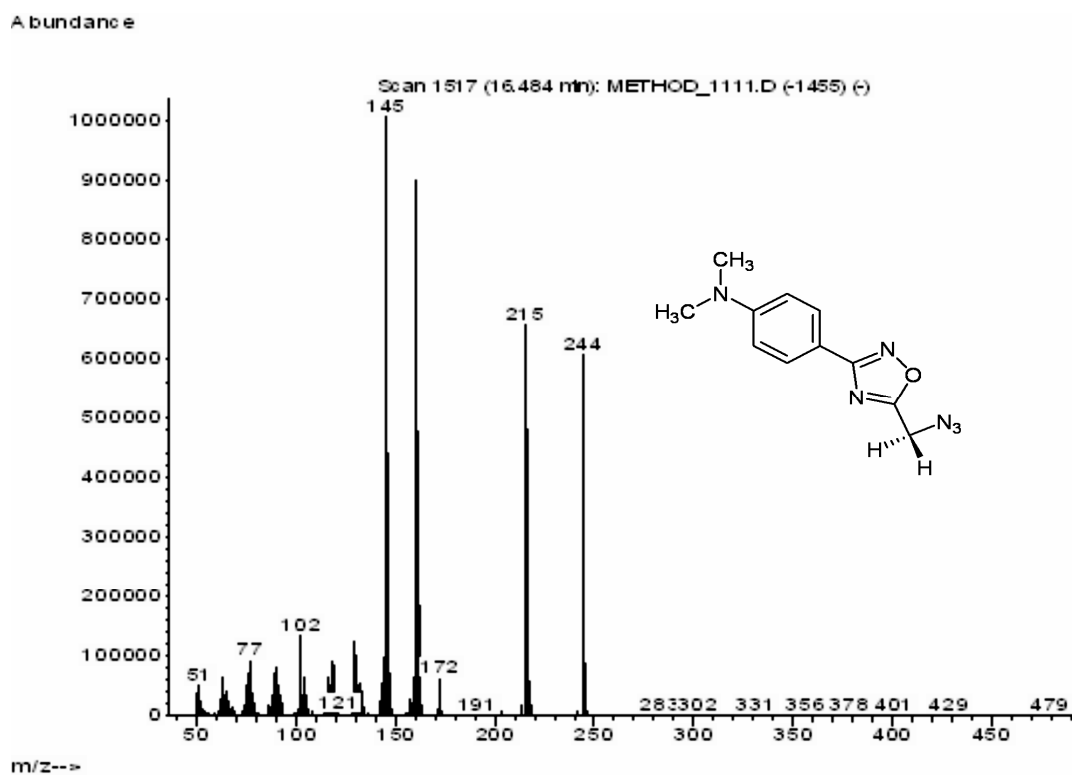


Figure 4. 88 Mass spectra of compound 88m

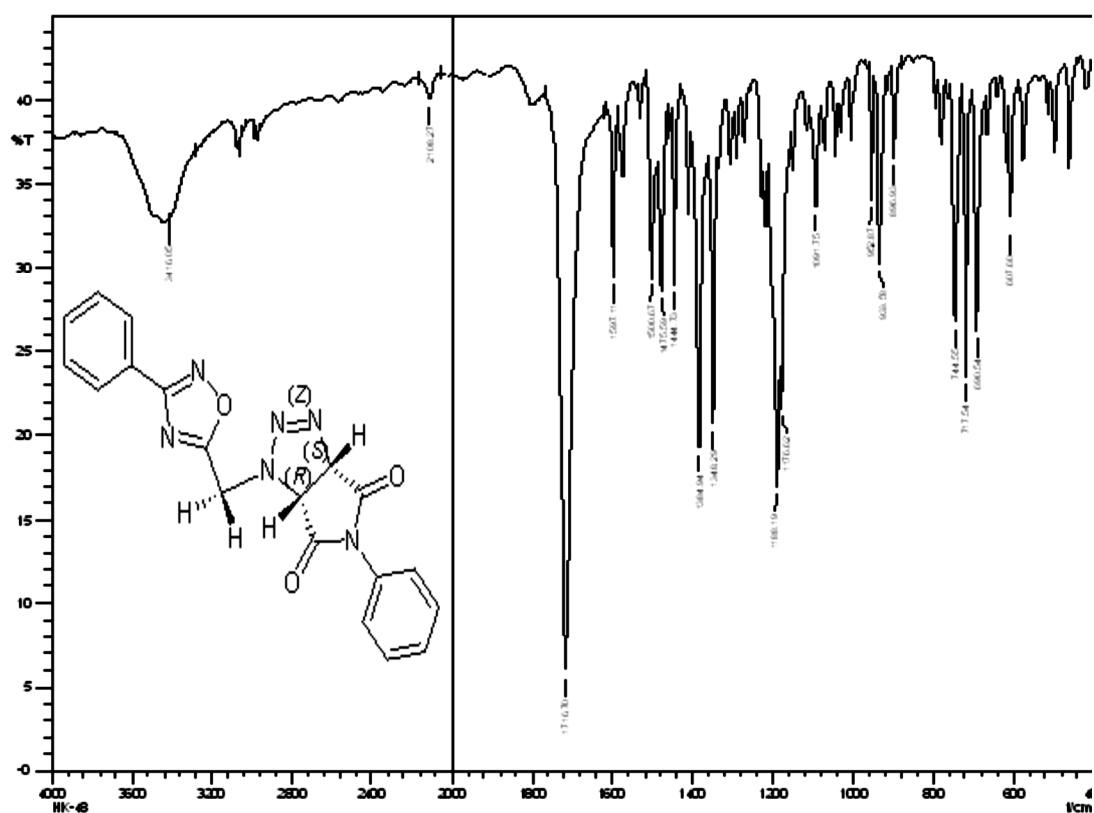


Figure 4. 89 IR spectrum of compound 90a

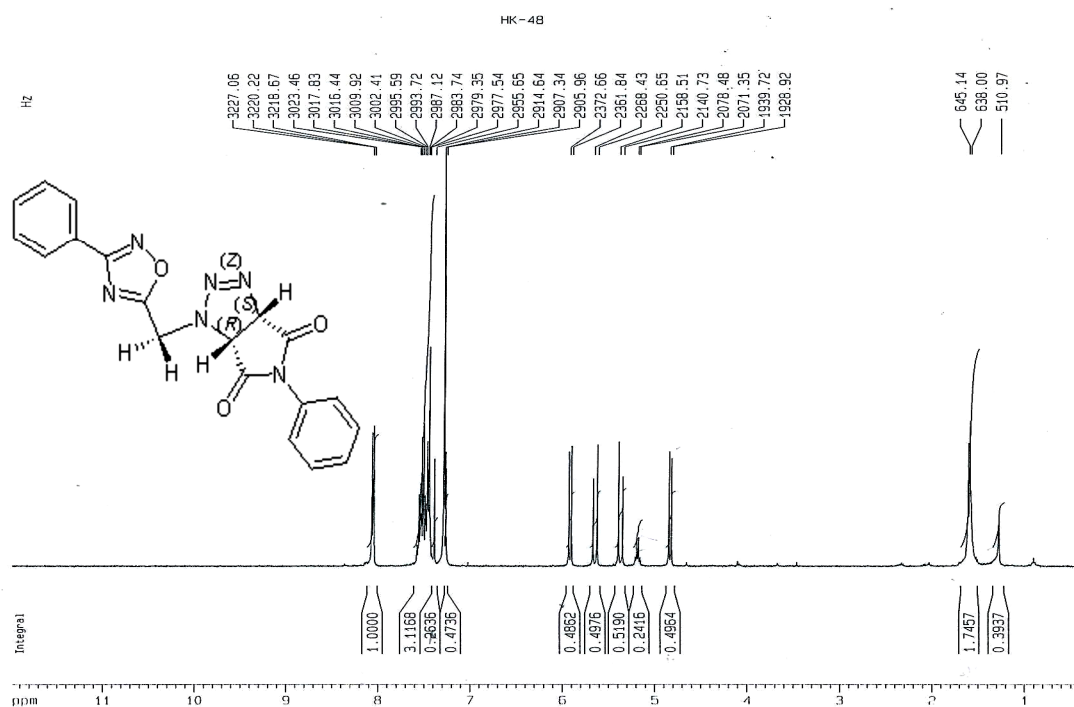


Figure 4. 90 ^1H NMR Spectrum of compound 90a

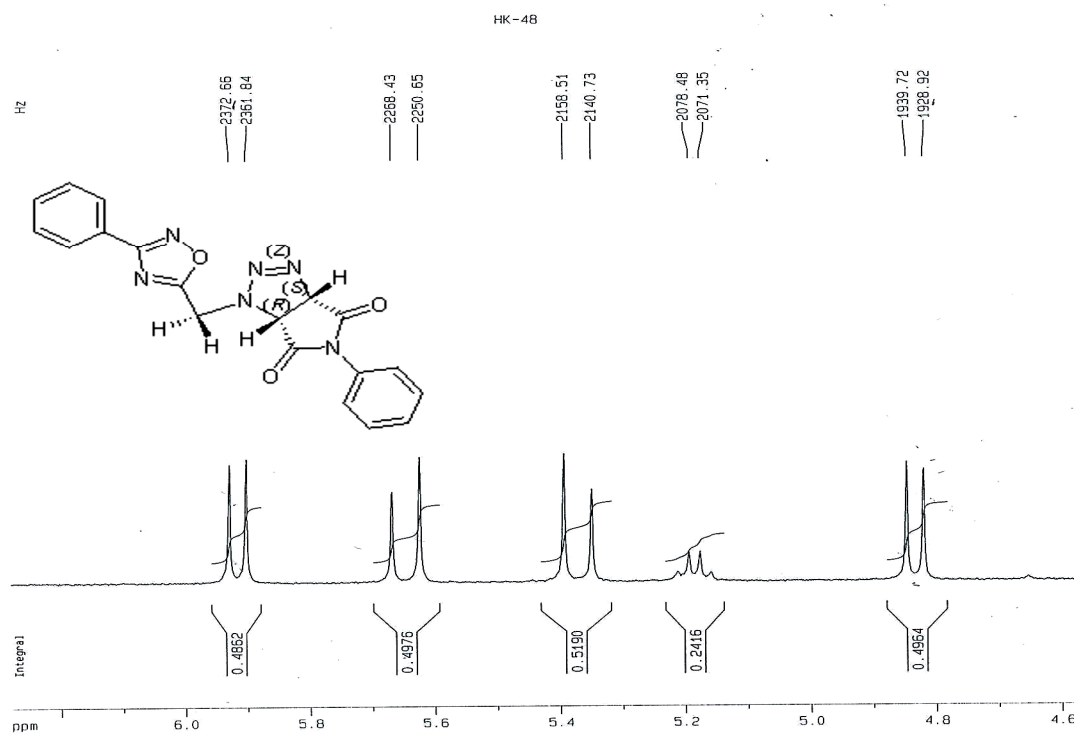


Figure 4. 91 Expanded ¹H NMR Spectrum of compound 90a

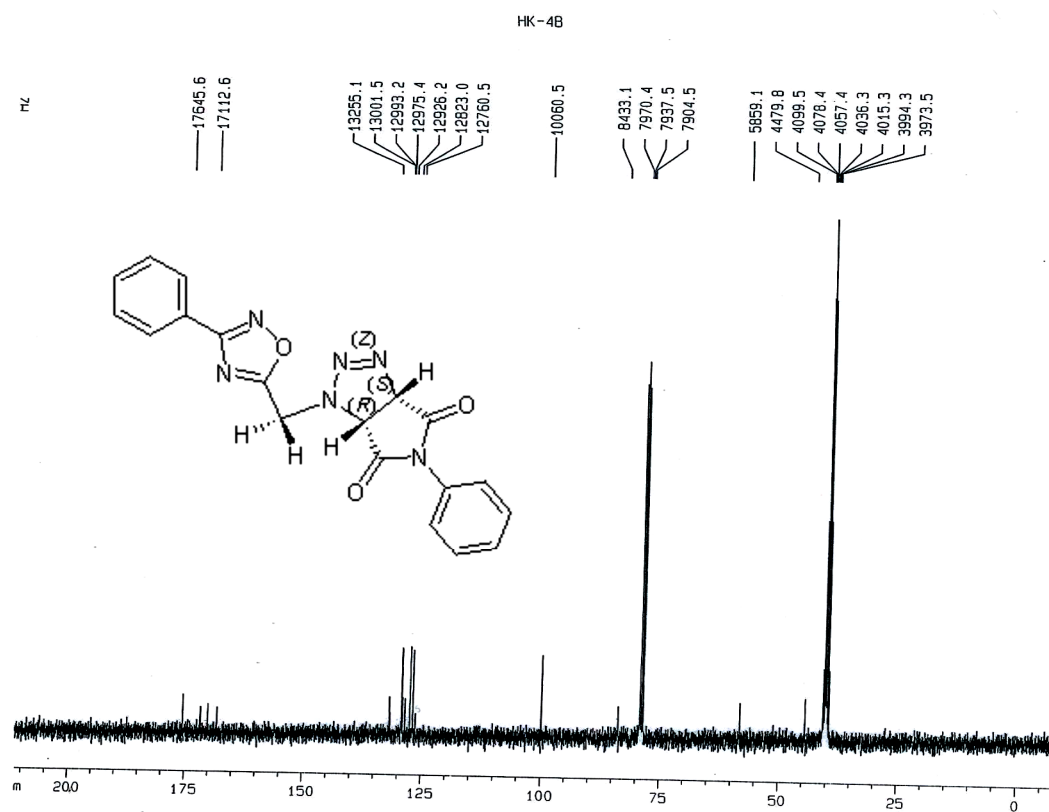


Figure 4. 92 ¹³C NMR Spectrum of compound 90a

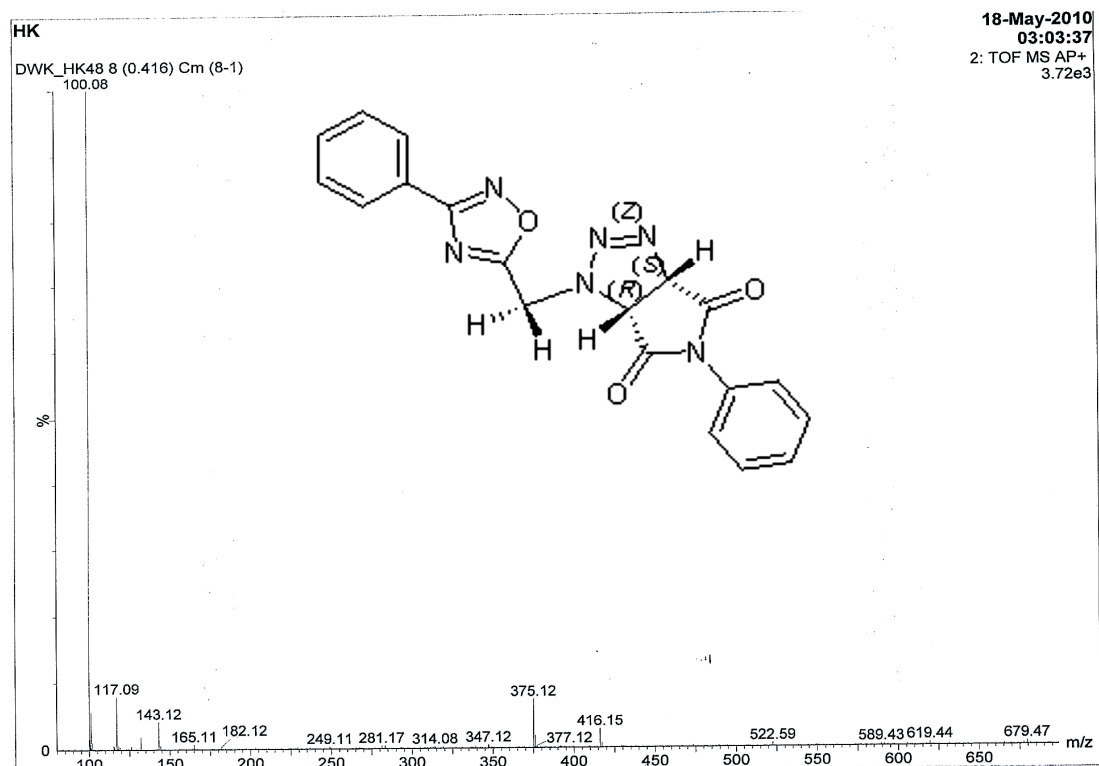


Figure 4. 93 Mass spectra of compound 90a

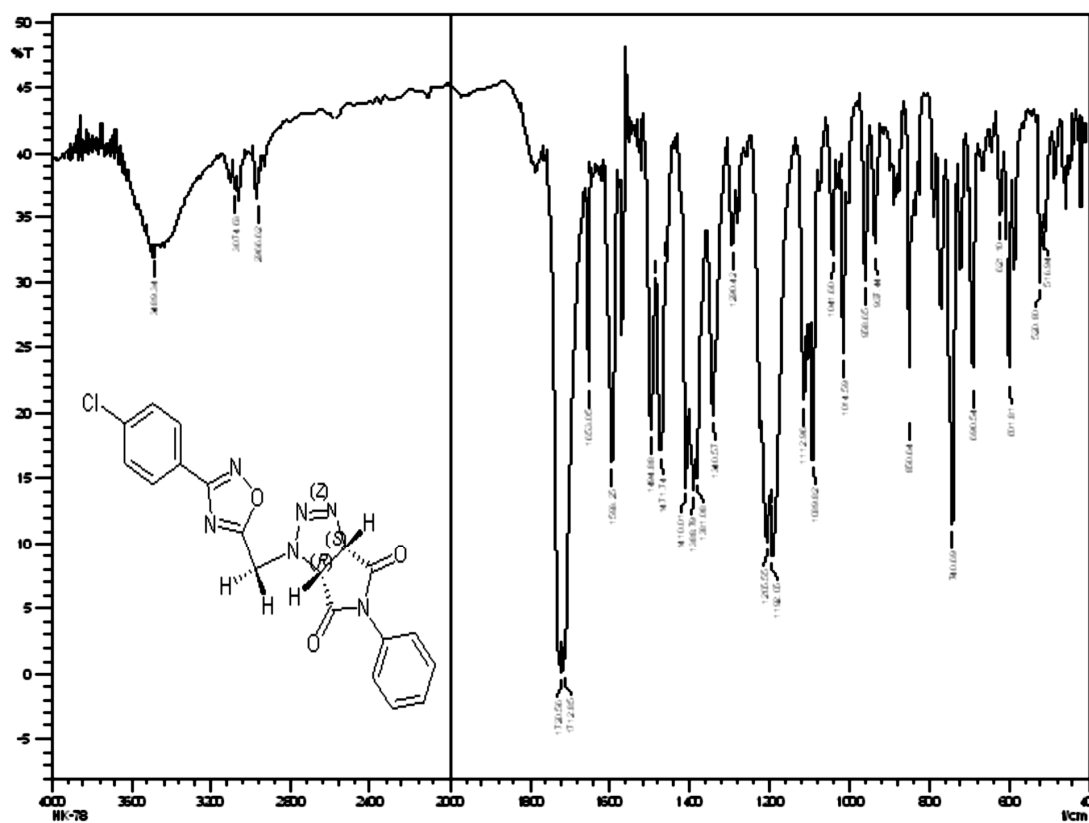


Figure 4. 94 IR spectrum of compound 90b

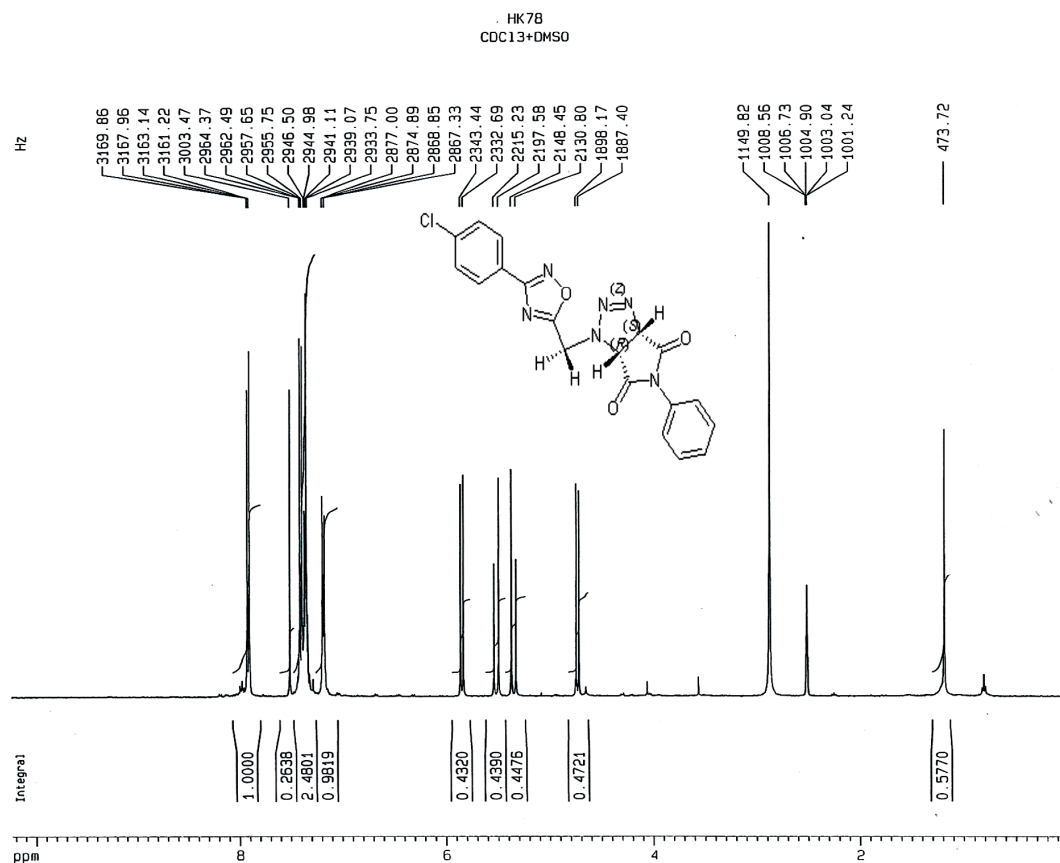


Figure 4. 95 ¹H NMR Spectrum of compound 90b

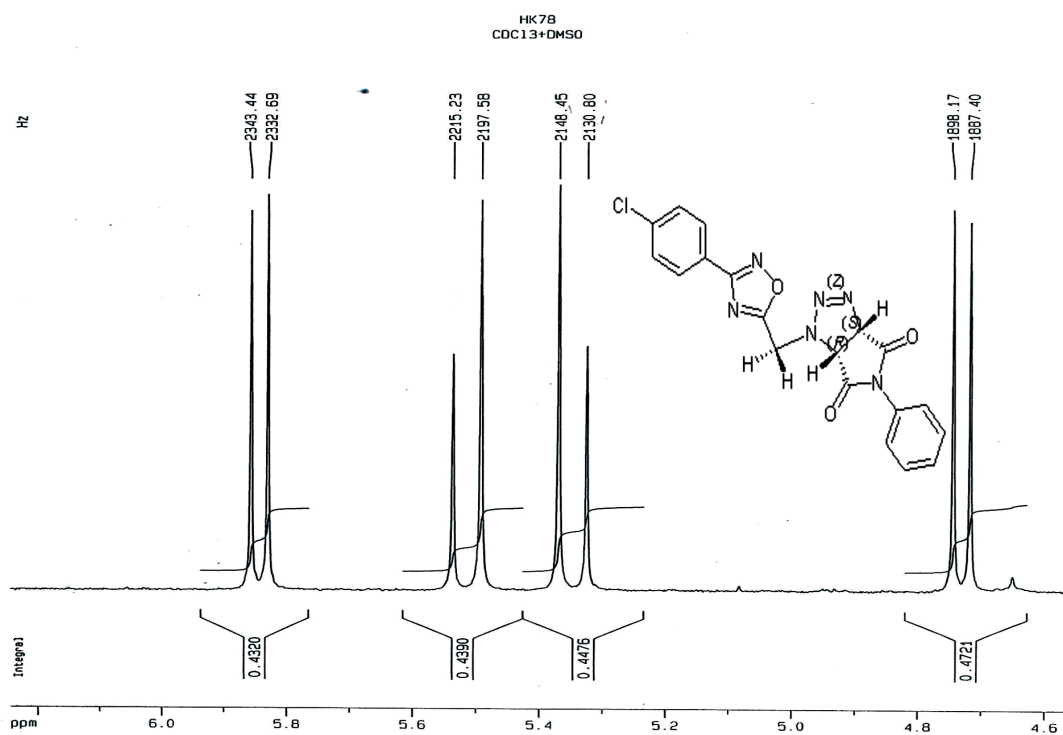


Figure 4. 96 Expanded ¹H NMR Spectrum of compound 90b

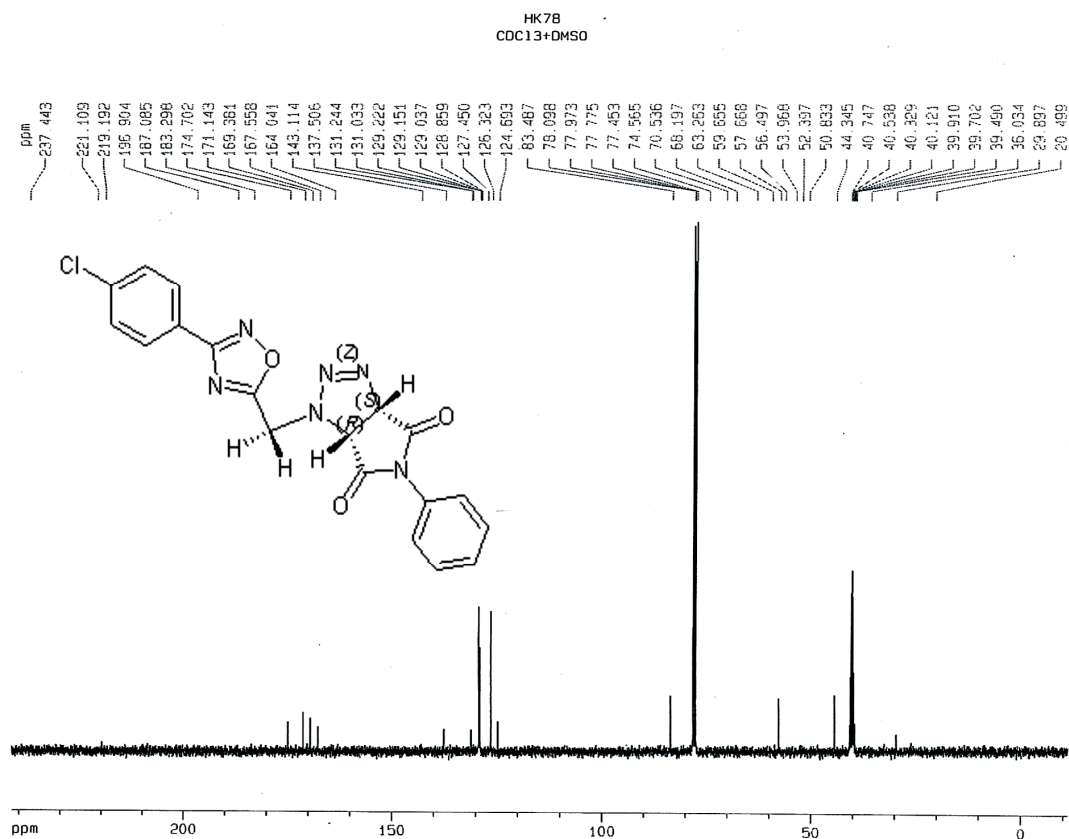


Figure 4. 97 ^{13}C NMR Spectrum of compound 90b

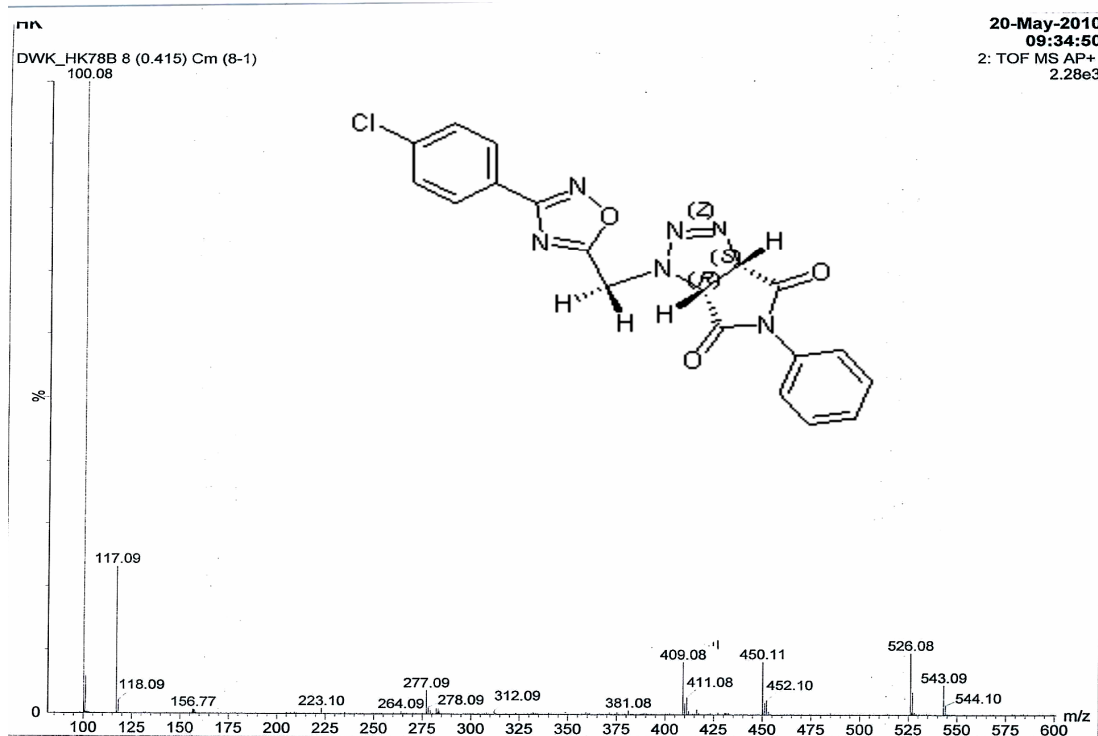


Figure 4. 98 Mass spectra of compound 90b

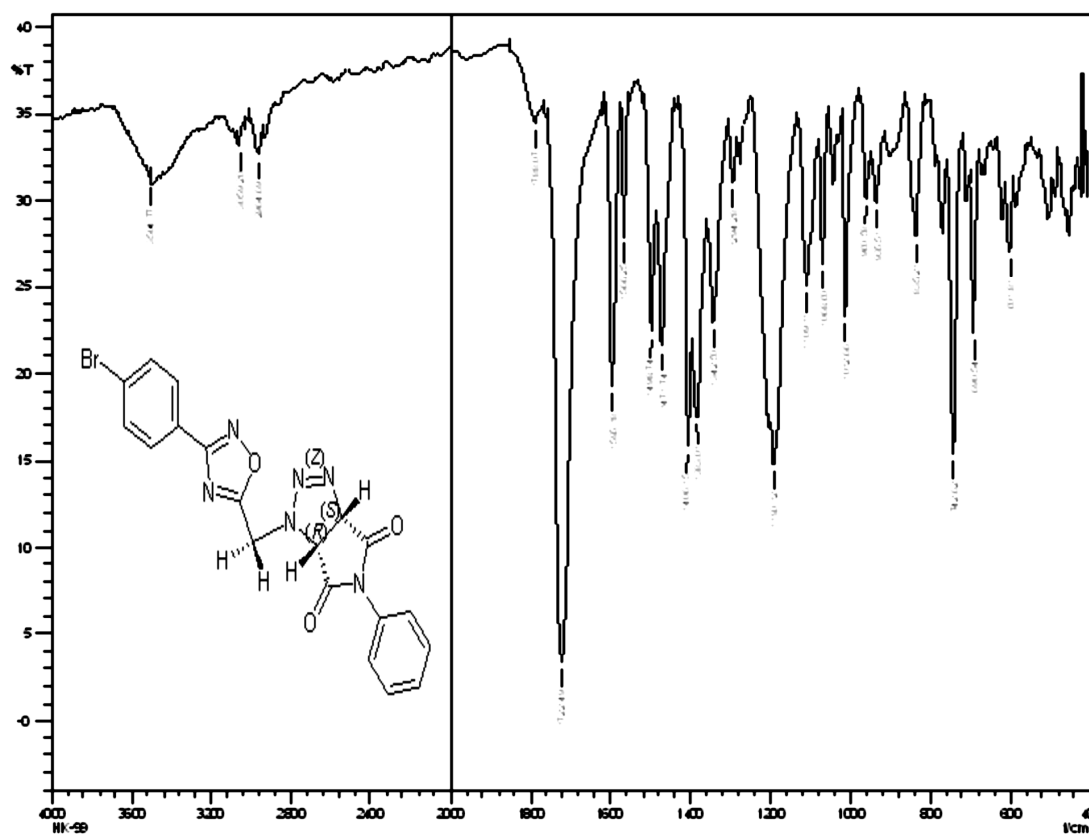


Figure 4. 99 IR spectrum of compound 90c

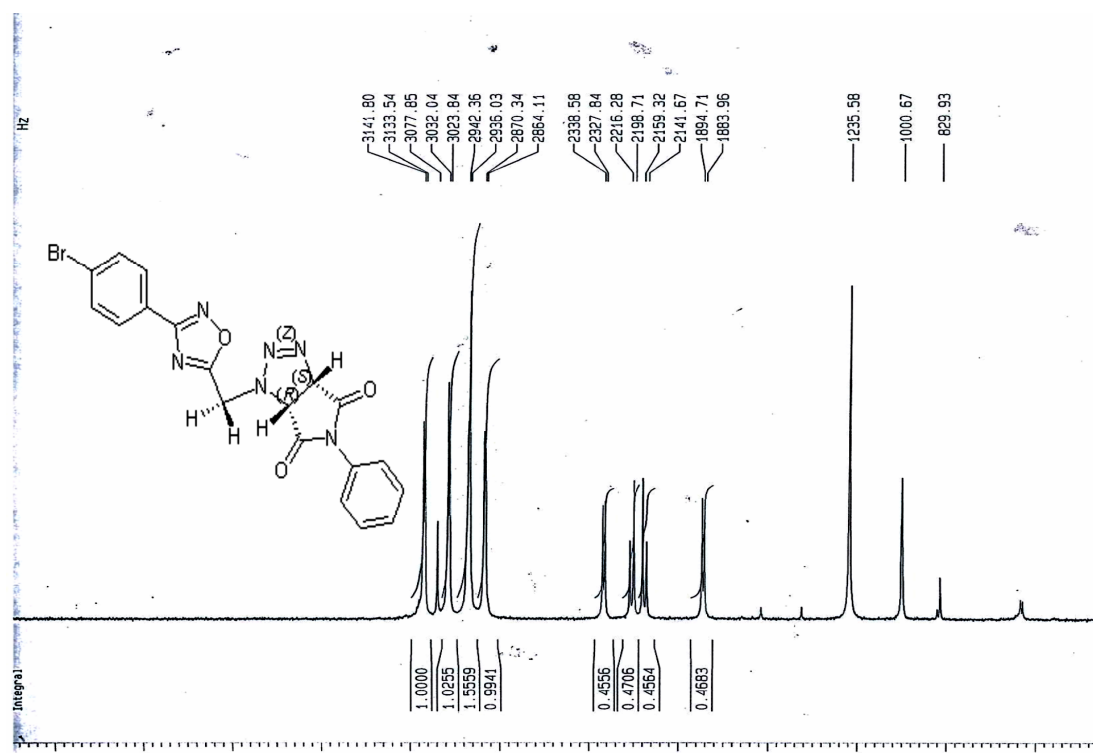


Figure 4. 100 ¹H NMR Spectrum of compound 90c

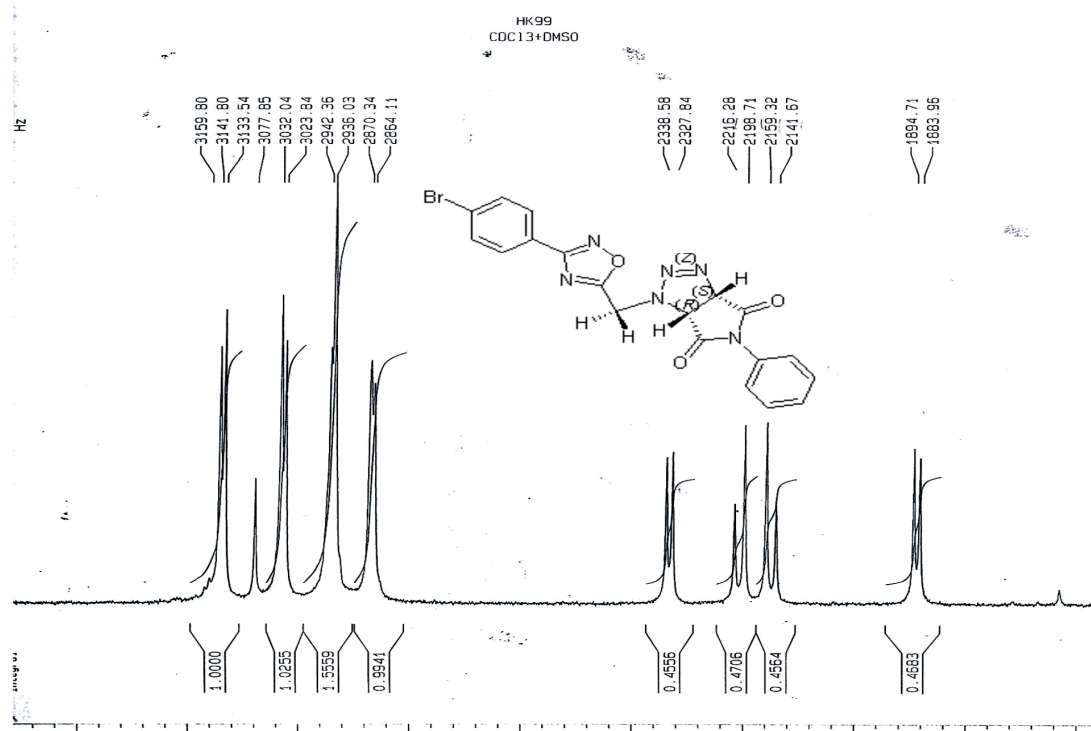


Figure 4. 101 Expanded ^1H NMR Spectrum of compound 90c

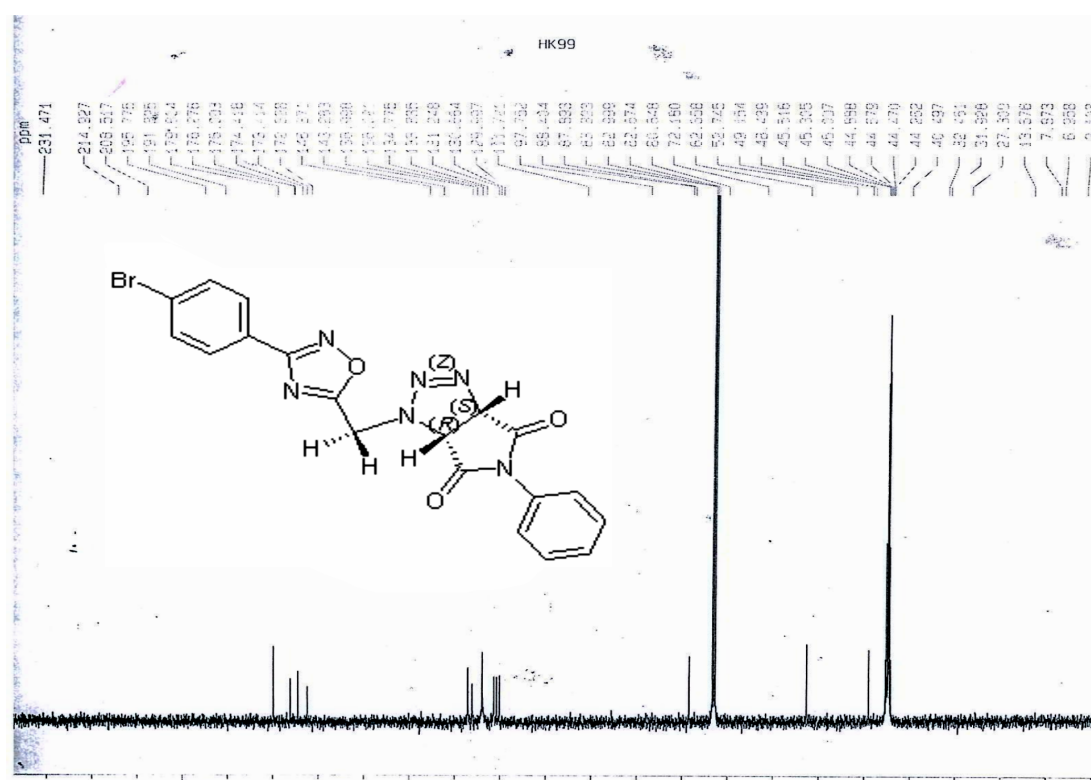


Figure 4. 102 ^{13}C NMR Spectrum of compound 90c

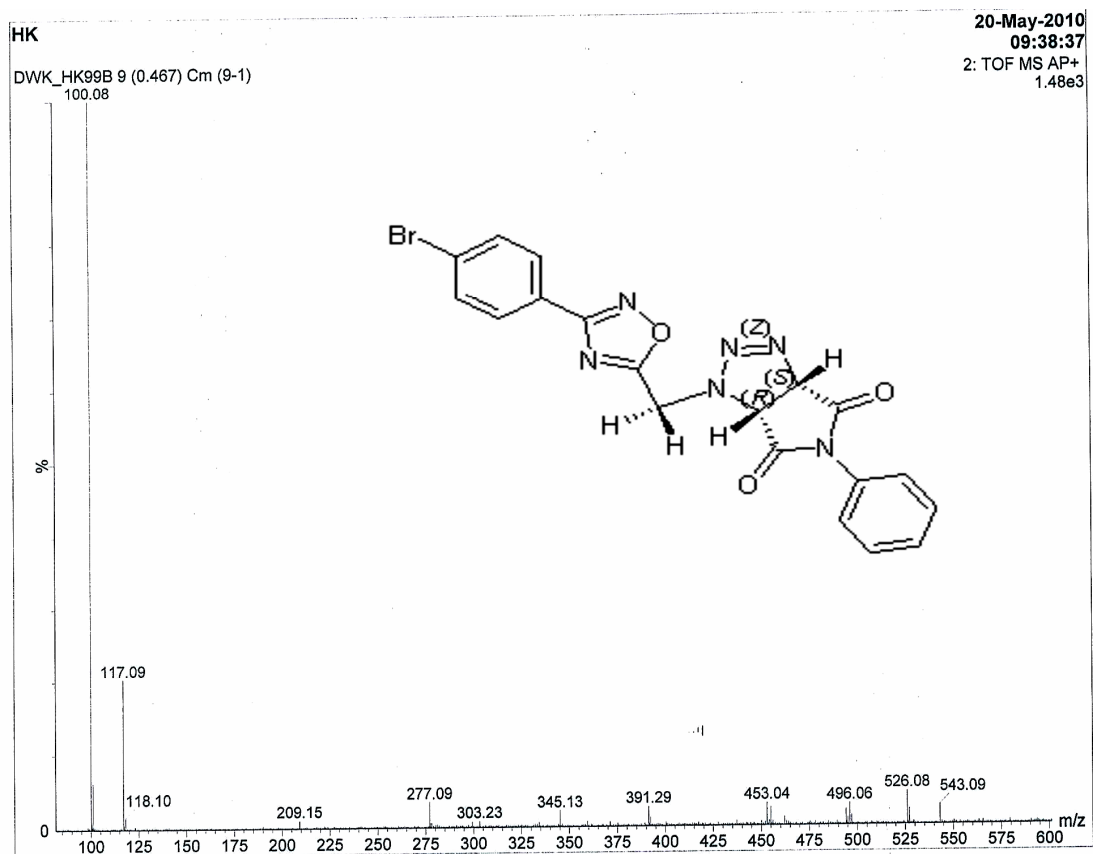


Figure 4. 103 Mass spectra of compound 90c

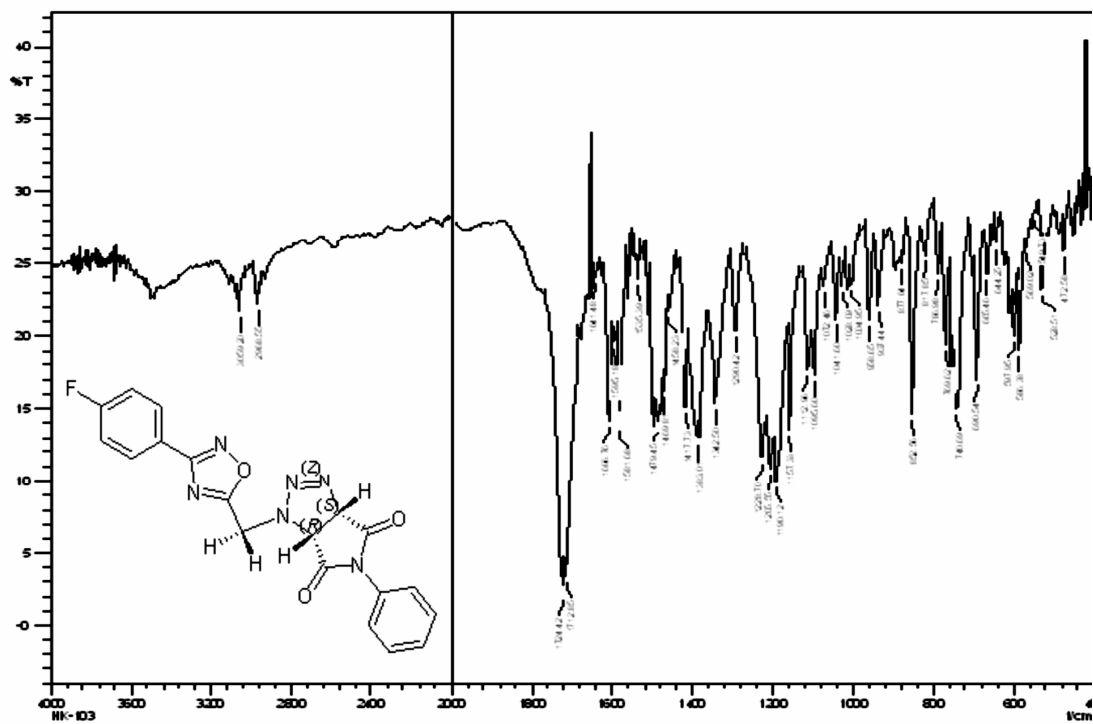


Figure 4. 104 IR spectrum of compound 90d

Archive directory: /export/home/vnmr1/vnmrsys/data
 Sample directory: YD-HK-103_13Apr2010-12:44:53
 File: PROTON

Pulse Sequence: s2pul1
 Solvent: CDCl3
 Ambient temperature
 Mercury-300BB "NMRLab"

Relax. delay 2.000 sec
 Pulse 45.0 degrees
 Acq. time 1.930 sec
 Width 4730.5 Hz
 16 repetitions
 OBSERVE H1, 299.8835932 MHz
 DATA PROCESSING
 FT size 32768
 Total time 1 min, 5 sec

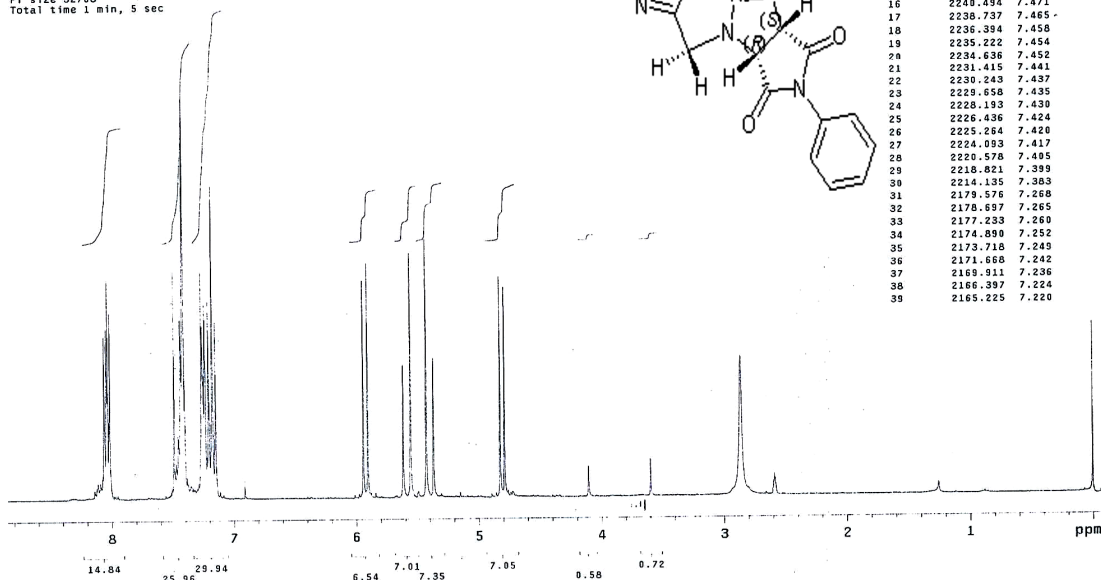


Figure 4. 105 ^1H NMR Spectrum of compound 90d

Archive directory: /export/home/vnmr1/vnmrsys/data
 Sample directory: YD-HK-103-Cl3_13Apr2010
 File: CARBON

Pulse Sequence: s2pul1
 Solvent: CDCl3
 Ambient temperature
 Mercury-300BB "NMRLab"

Relax. delay 2.000 sec
 Pulse 28.0 degrees
 Acq. time 1.815 sec
 Width 18867.9 Hz
 2800 repetitions
 OBSERVE C13, 75.4057889 MHz
 DECOUPLE H1, 299.8852132 MHz
 Power 35 dB
 continuously on
 VMLT2-16 modulated
 DATA PROCESSING
 Line broadening 1.0 Hz
 FT size 131072
 Total time 2 hr, 10 min, 20 sec

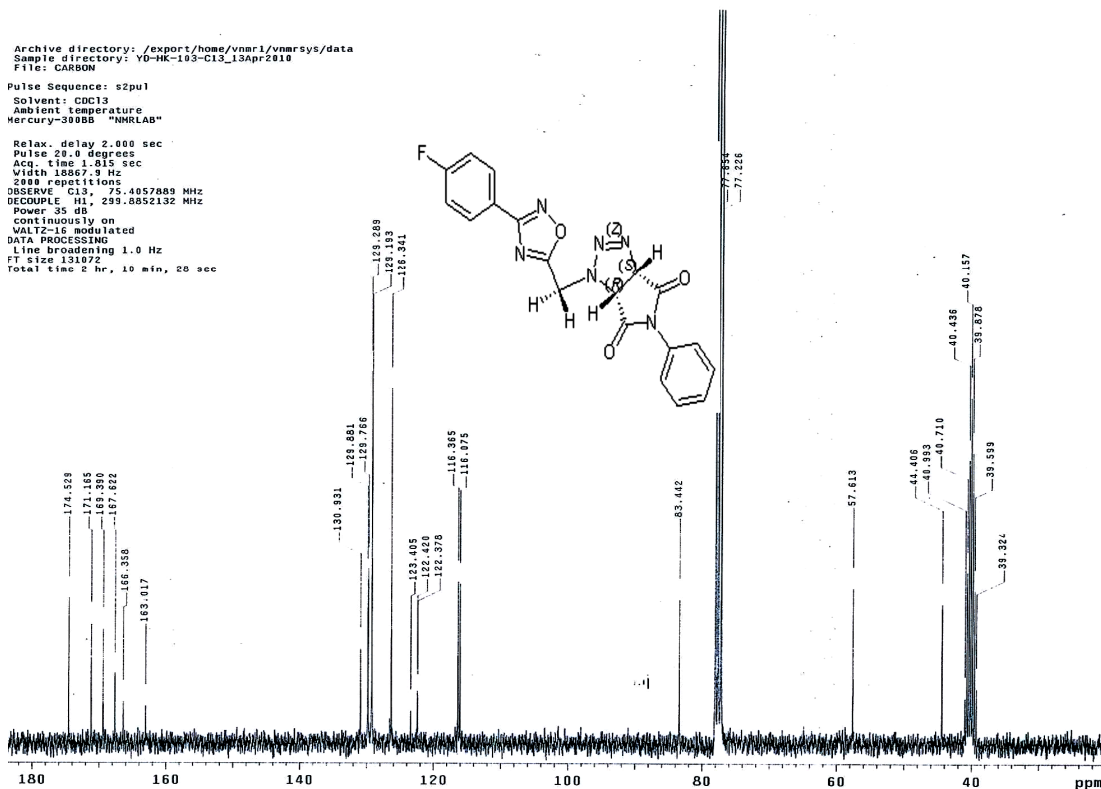


Figure 4. 106 ^{13}C NMR Spectrum of compound 90d

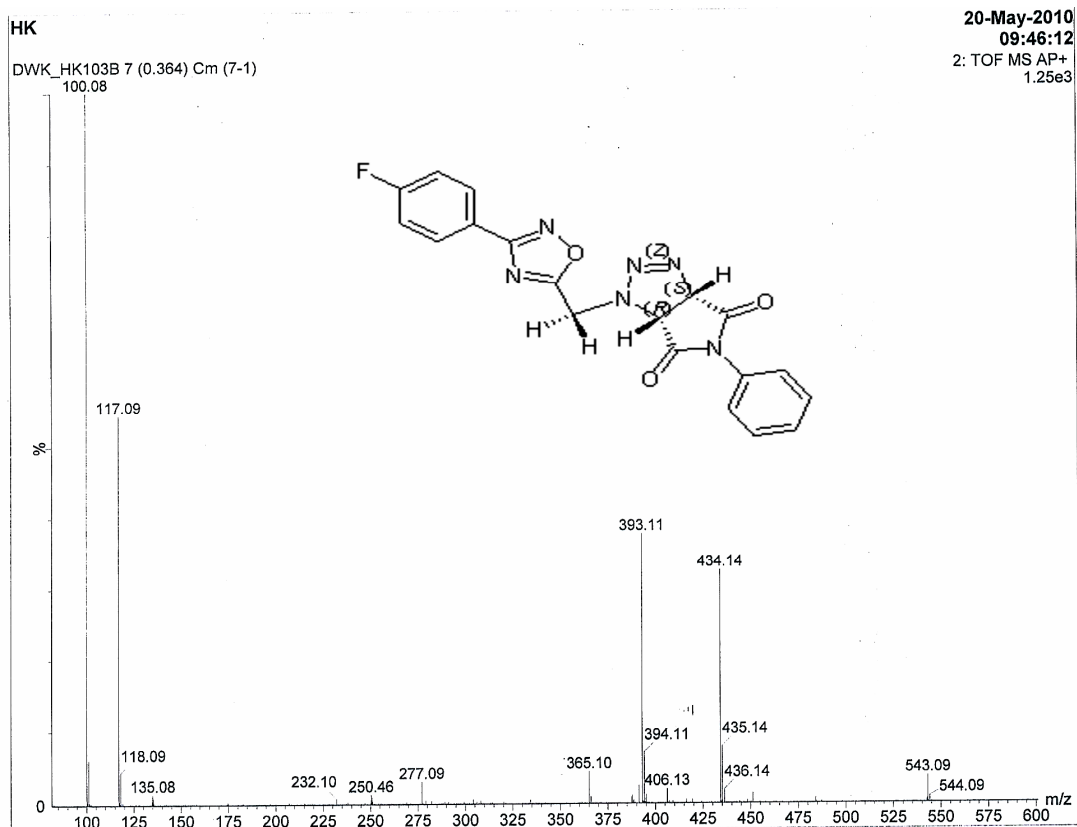


Figure 4. 107 Mass spectra of compound 90d

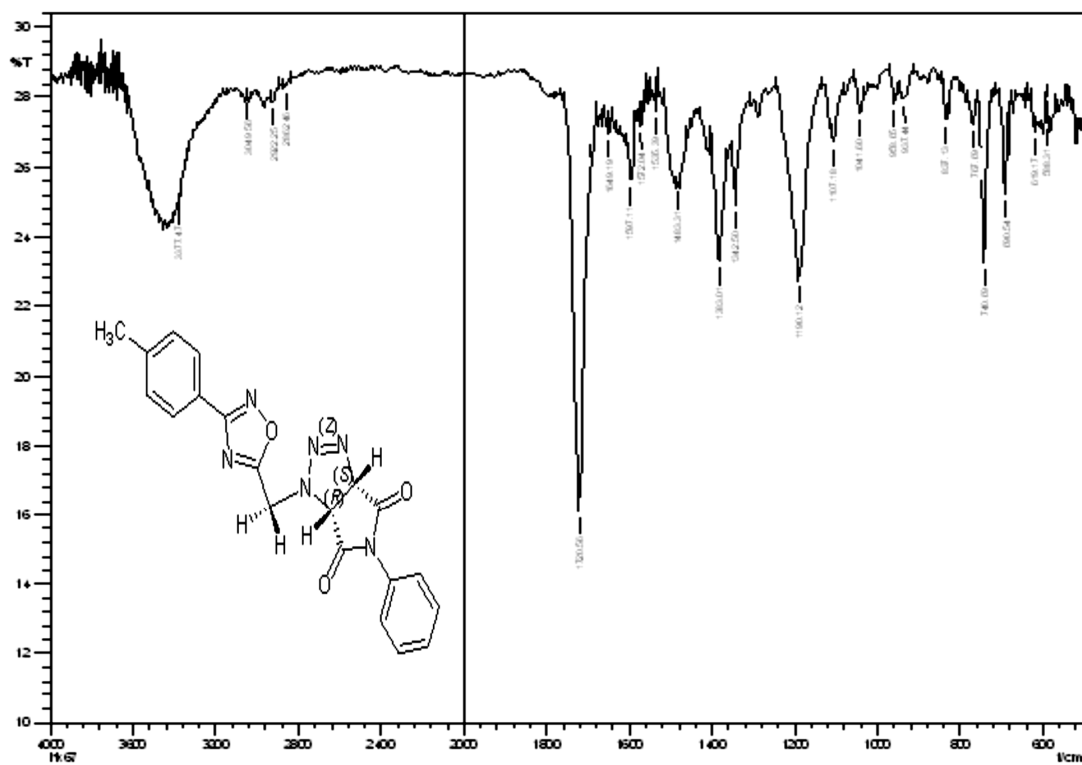


Figure 4. 108 IR spectrum of compound 90e

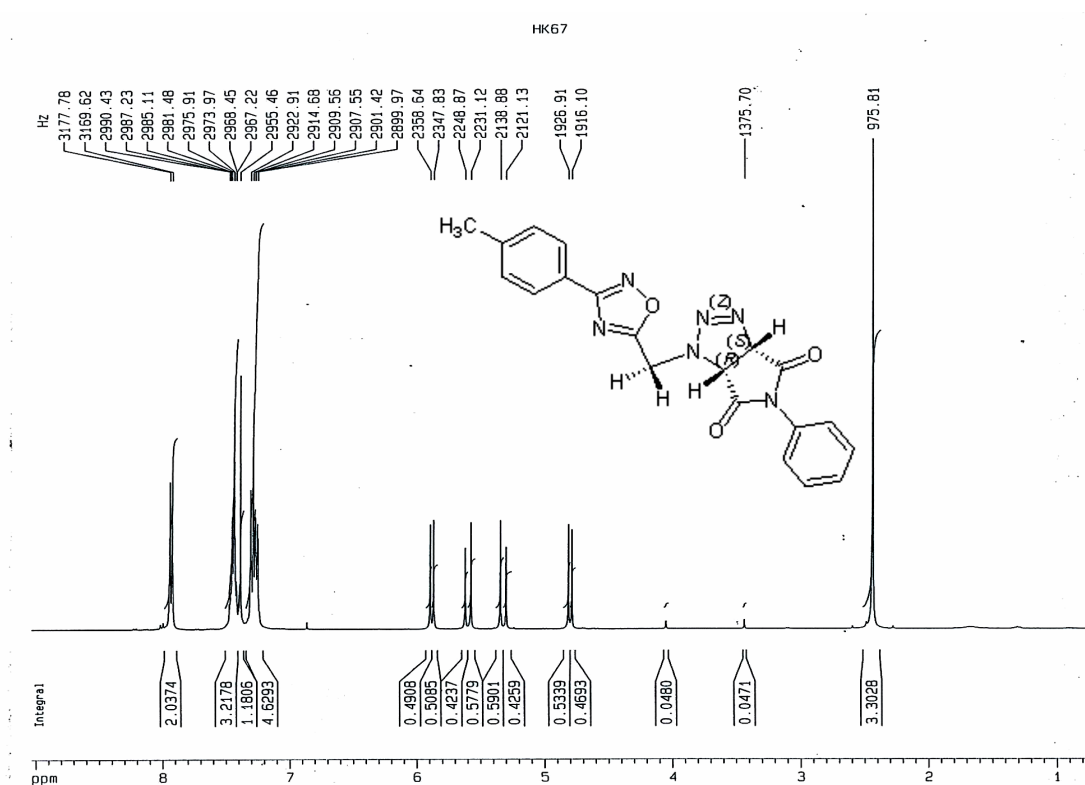


Figure 4. 109 ^1H NMR Spectrum of compound 90e

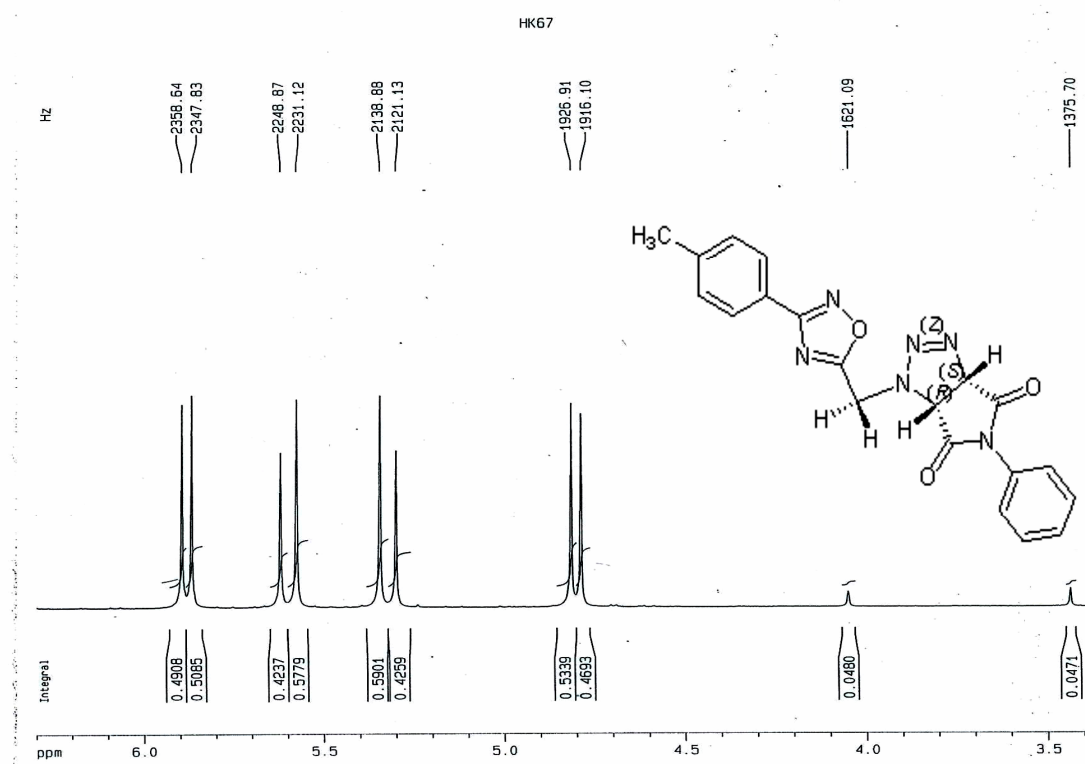


Figure 4. 110 Expanded ^1H NMR Spectrum of compound 90e

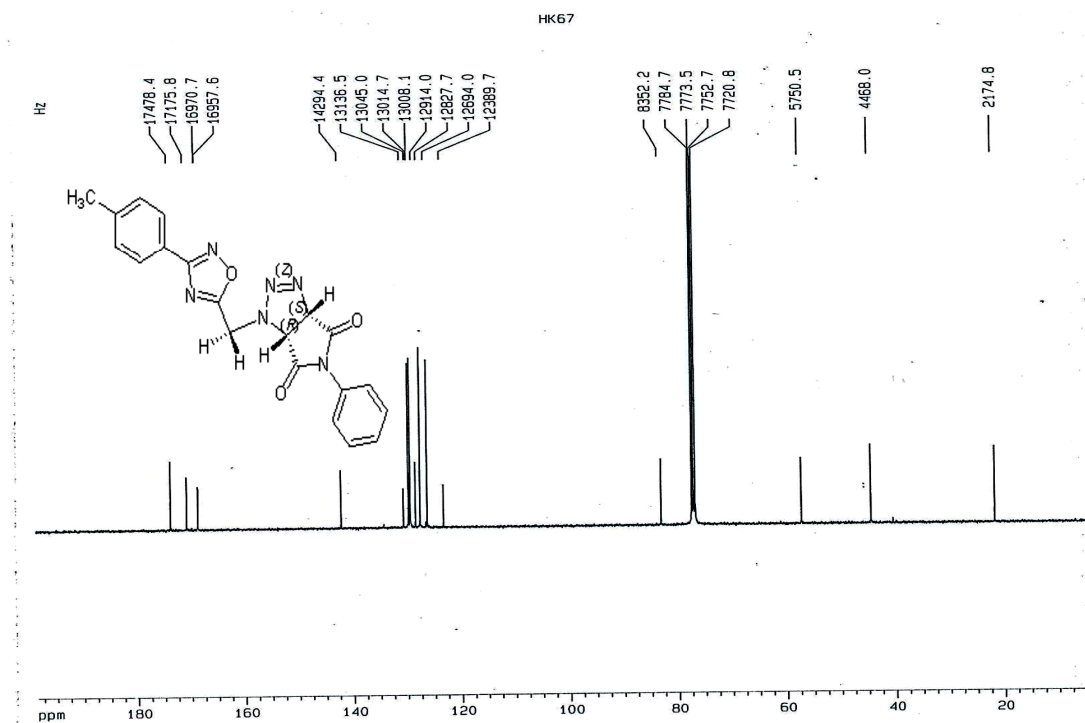


Figure 4. 111 ^{13}C NMR Spectrum of compound 90e

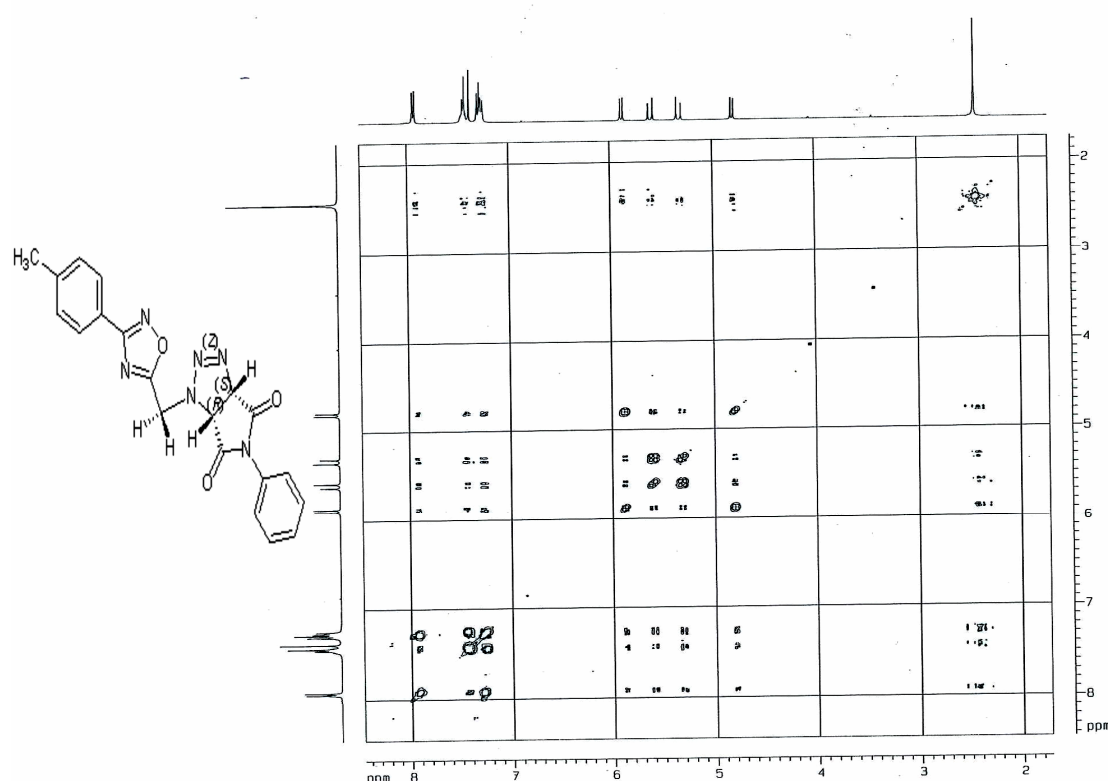


Figure 4. 112 COSY NMR Spectrum of compound 90e

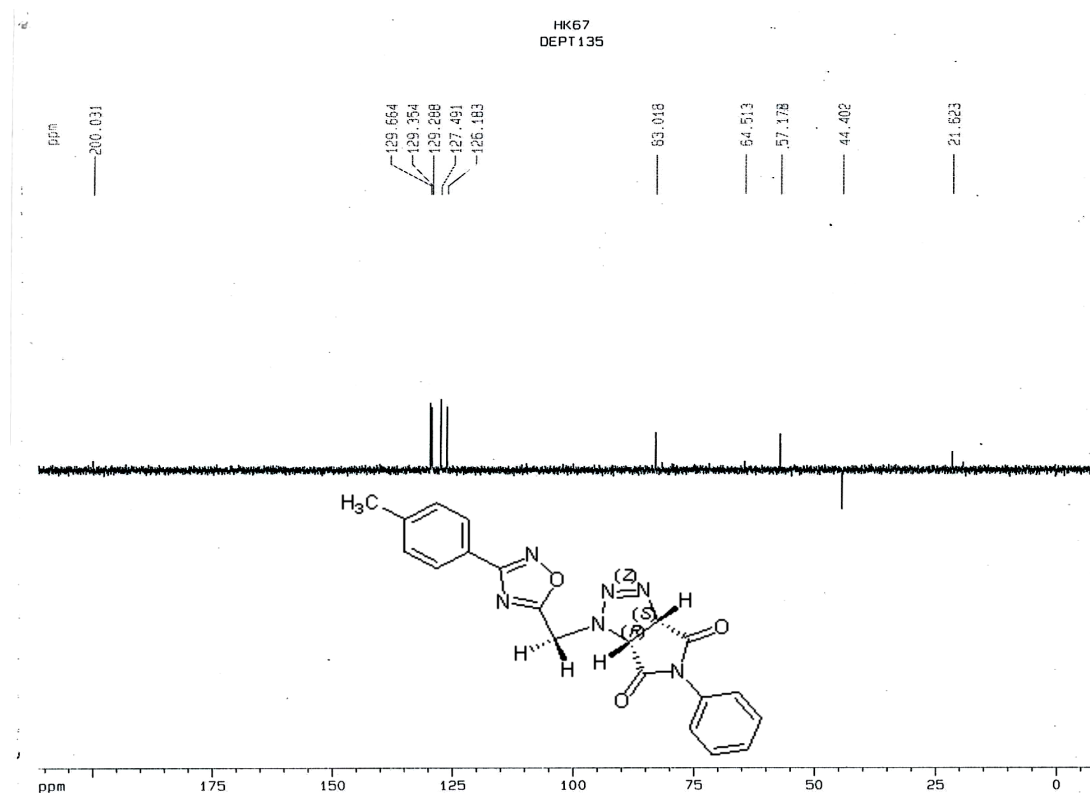


Figure 4. 113 DEPT NMR Spectrum of compound 90e

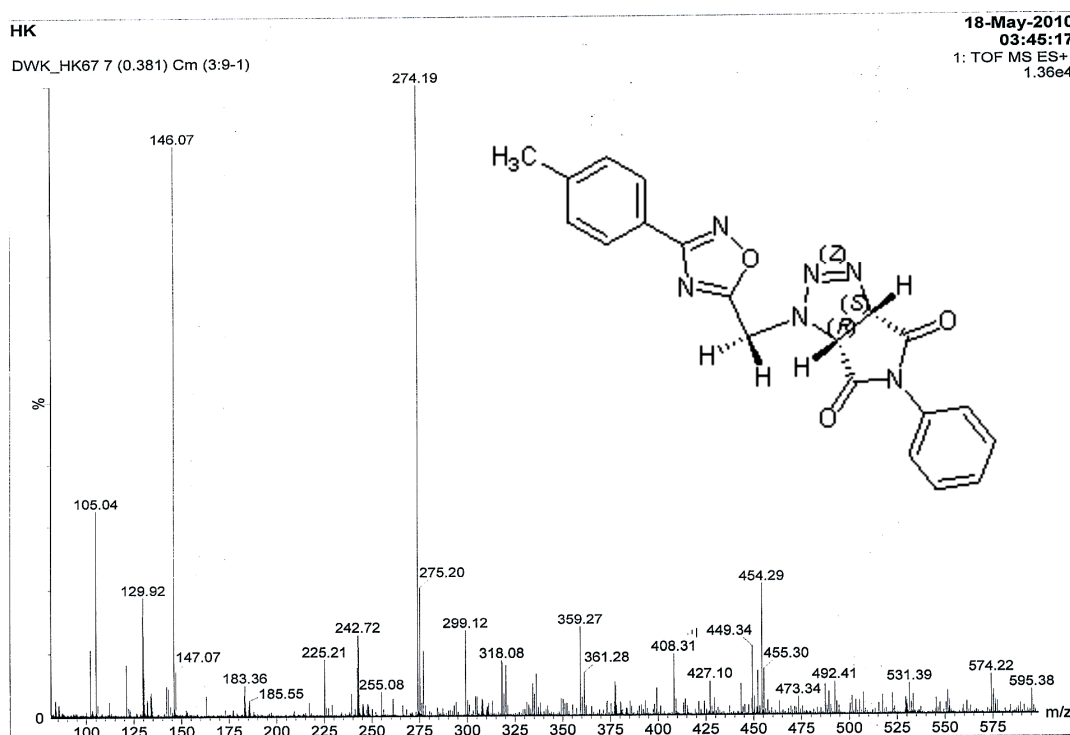


Figure 4. 114 Mass spectra of compound 90e

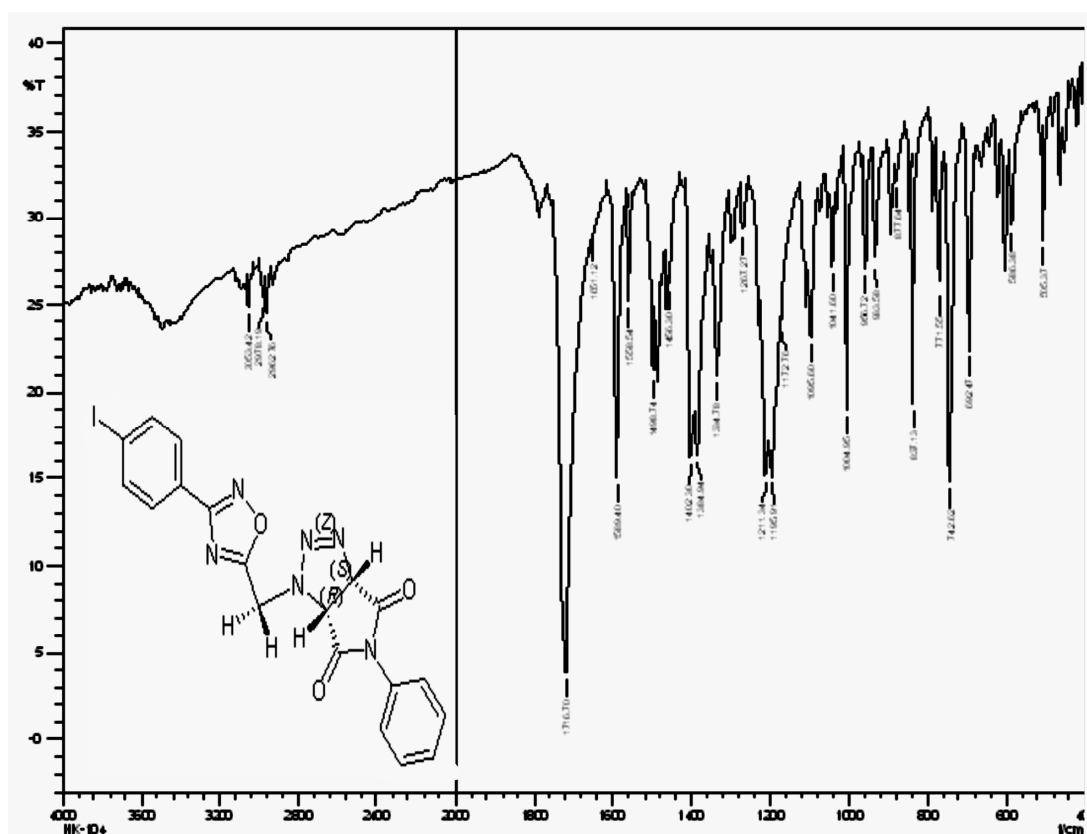


Figure 4.115 IR spectrum of compound 90f

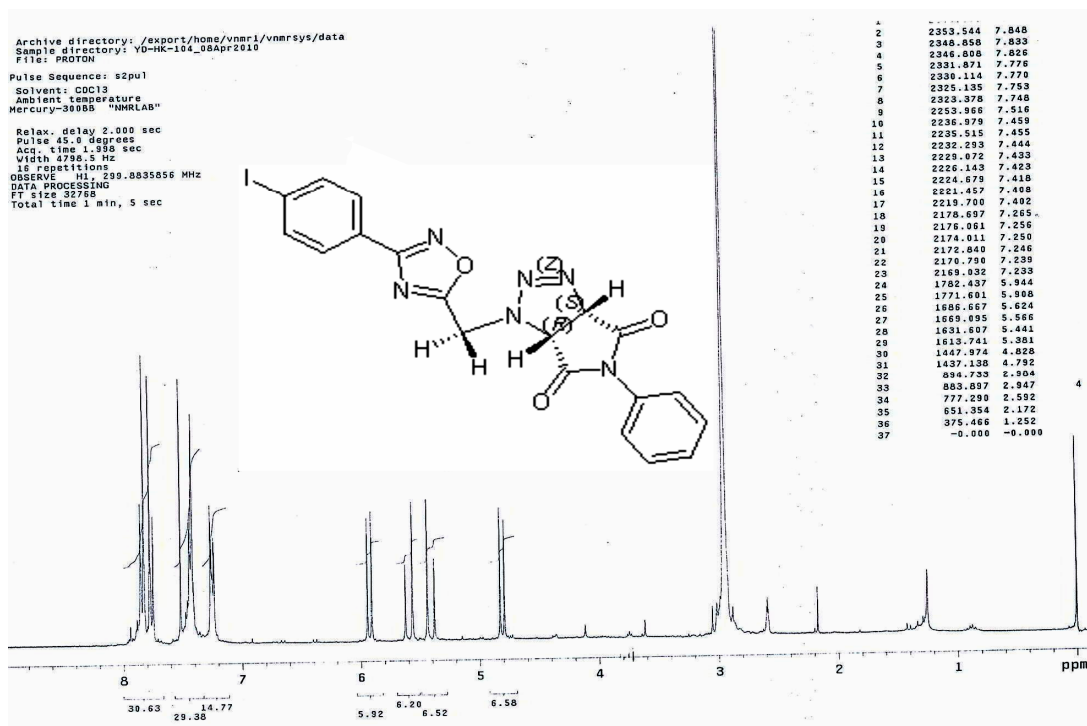
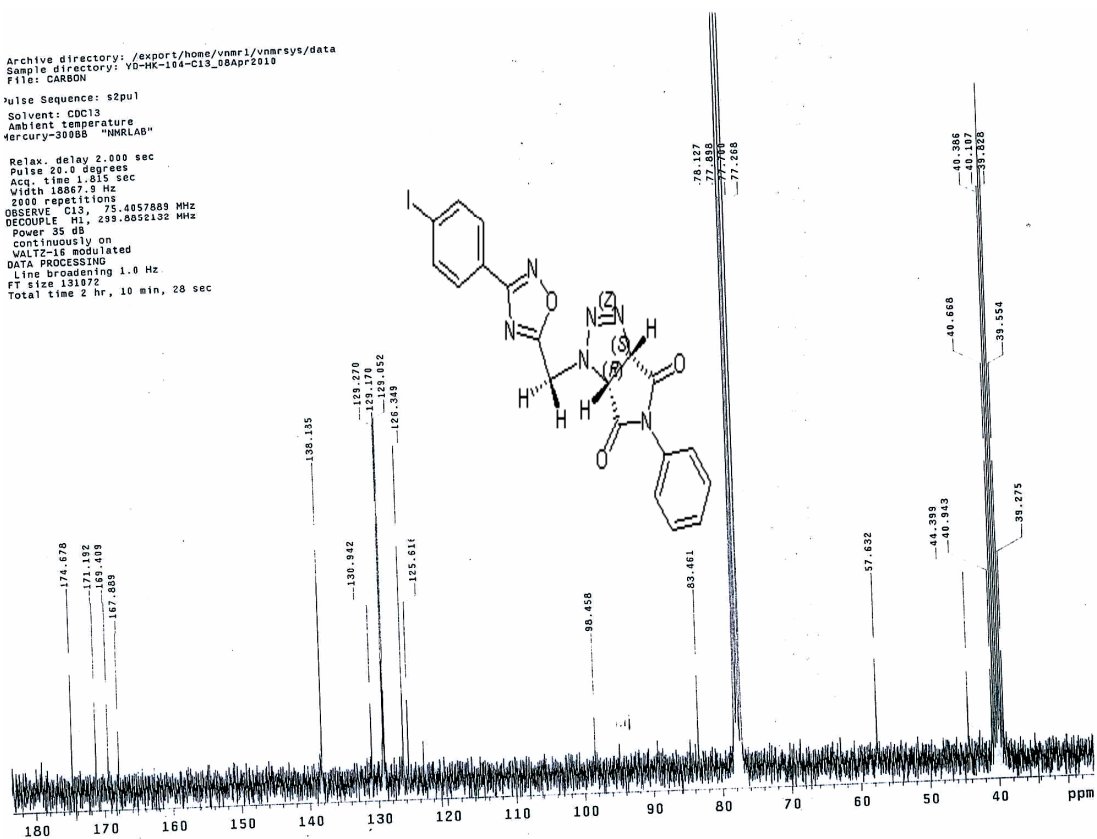


Figure 4.116 ¹H NMR Spectrum of compound 90f

Archive directory: /export/home/vnmr1/vnmrsys/data
 Sample directory: VD-HK-104-C13_08Apr2010
 File: CARBON

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 Mercury-300SB "NMRLAB"

Relax. delay 2.000 sec
 Pulse 20.0 degrees
 Acq. time 1.815 sec
 Width 16867.9 Hz
 2000 repetitions
 OBSERVE C13, 75.4057889 MHz
 DECOUPLE H1, 299.6052192 MHz
 Power 35 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 1.0 Hz
 FT size 131072
 Total time 2 hr, 10 min, 28 sec



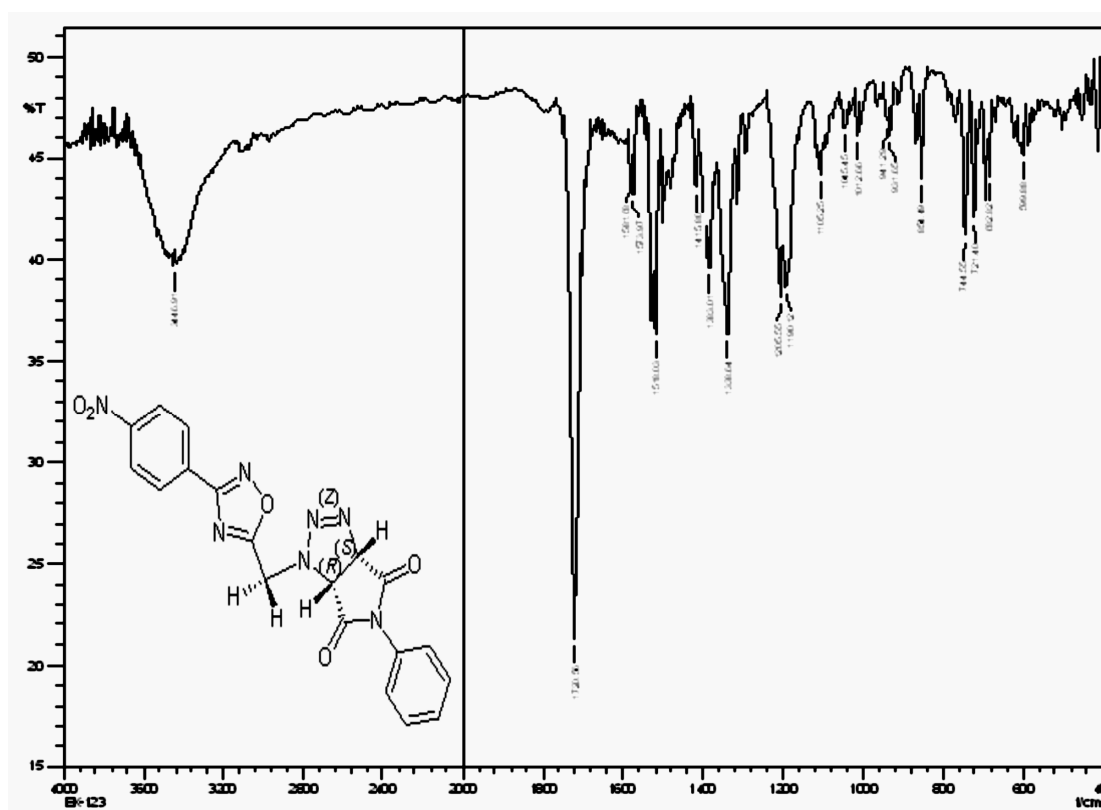


Figure 4. 119 IR spectrum of compound 90g

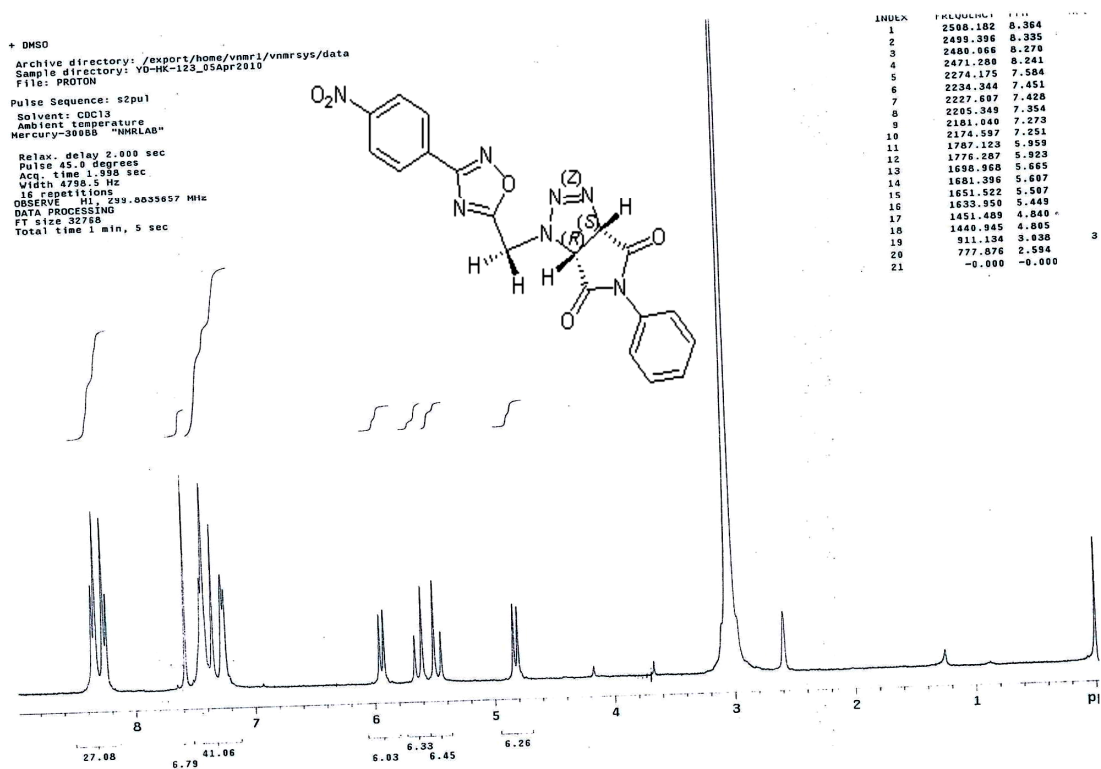


Figure 4. 120 ¹H NMR Spectrum of compound 90g

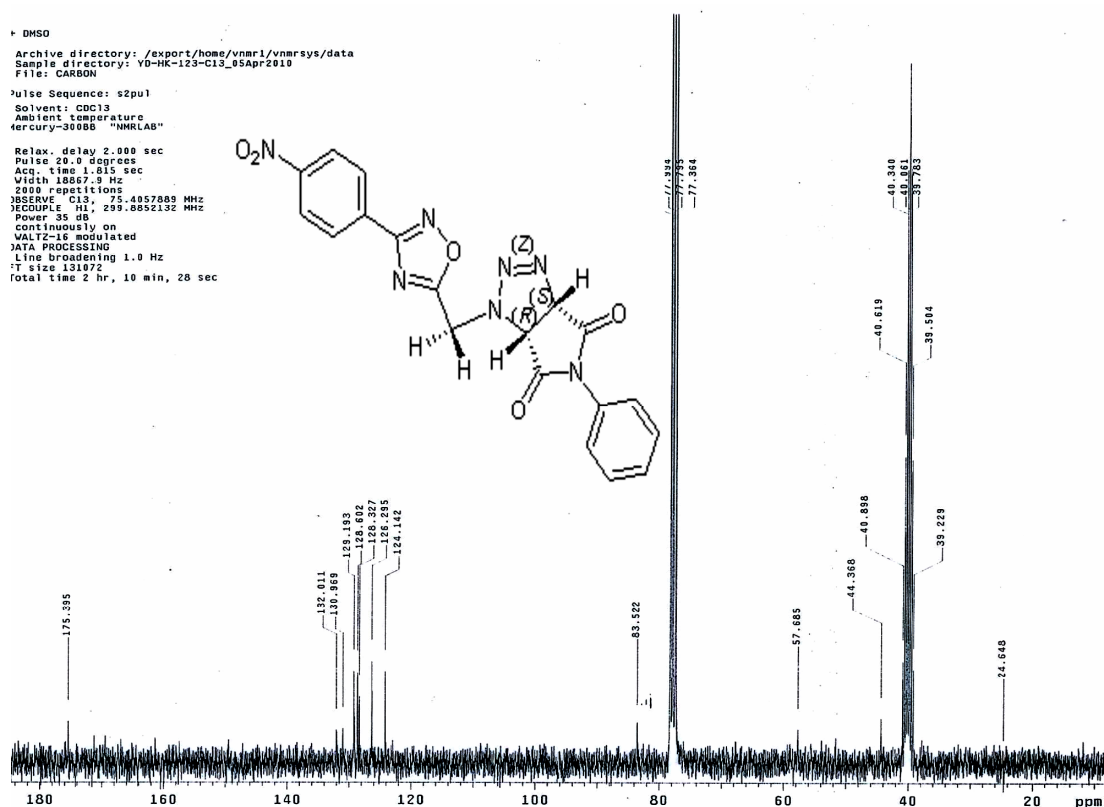


Figure 4. 121 ^{13}C NMR Spectrum of compound 90g

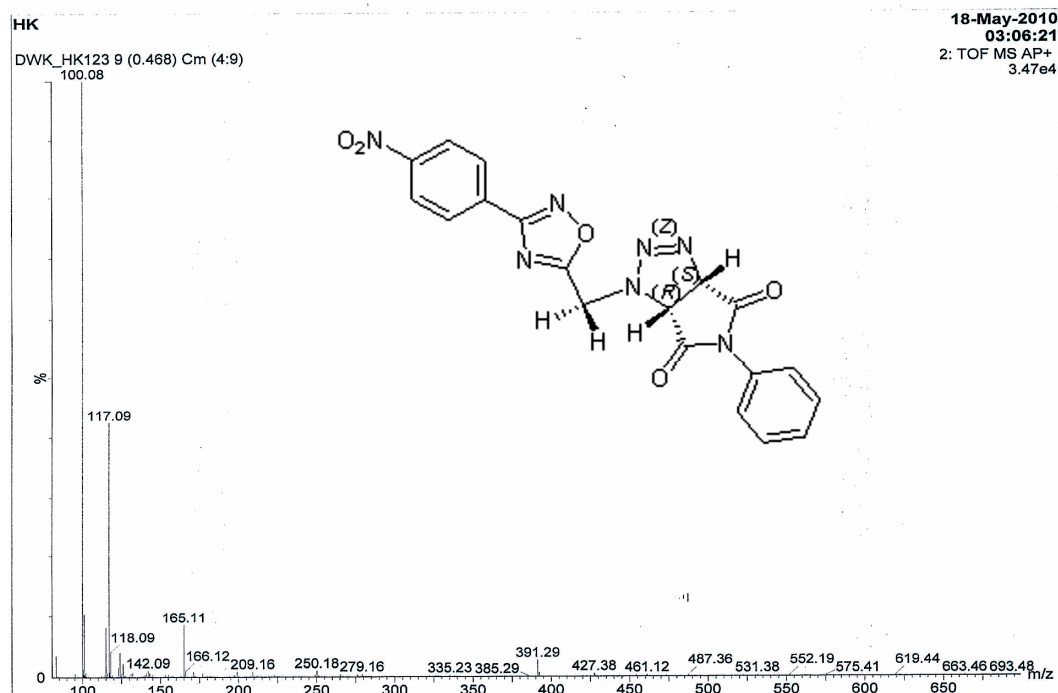


Figure 4. 122 Mass spectra of compound 90g

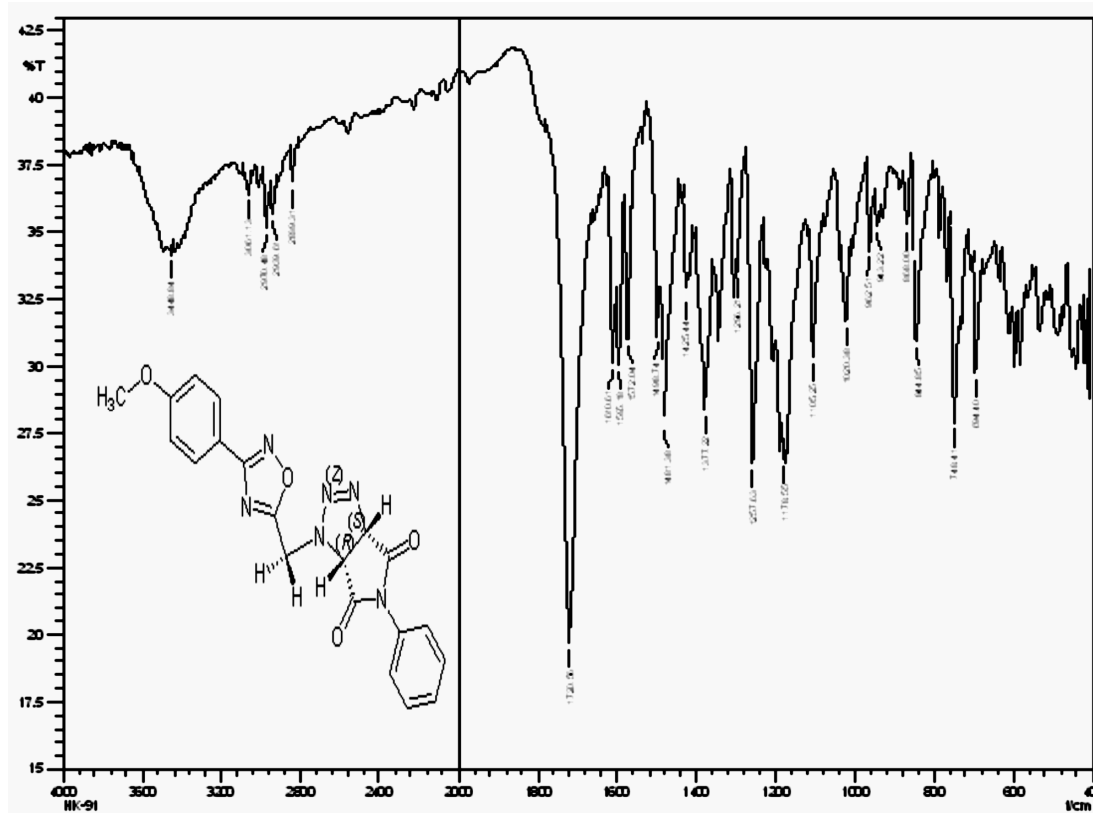


Figure 4. 123 IR spectrum of compound 90h

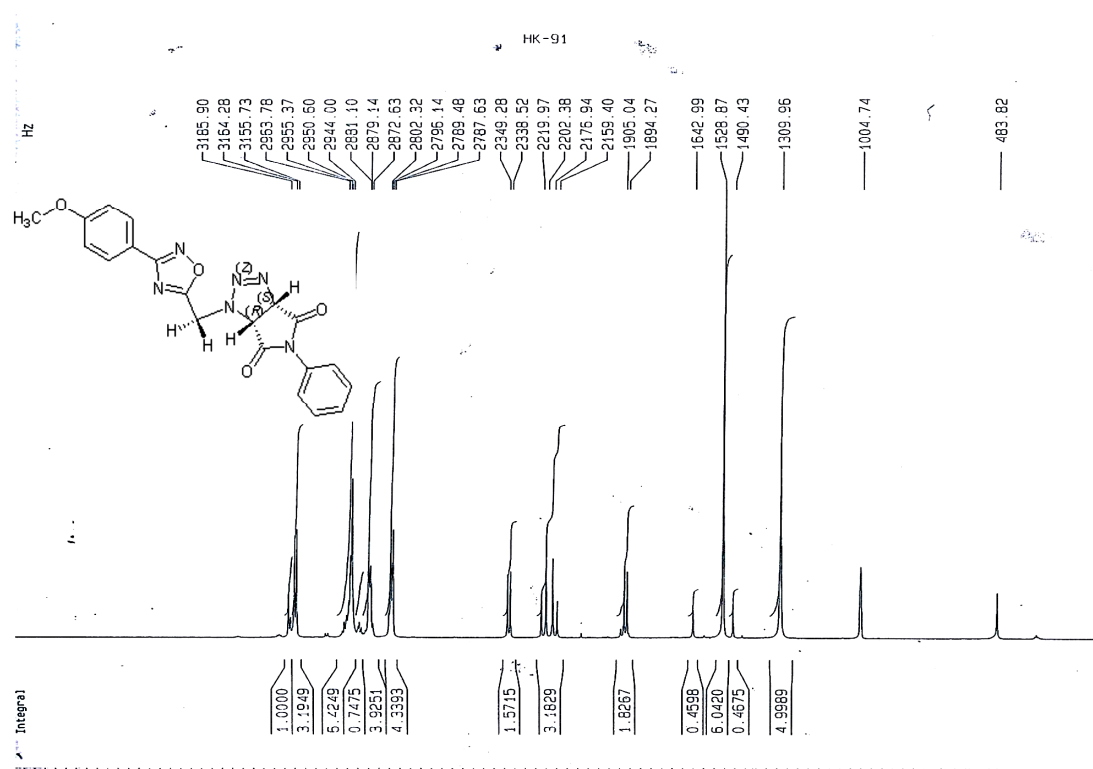


Figure 4. 124 ¹H NMR Spectrum of compound 90h

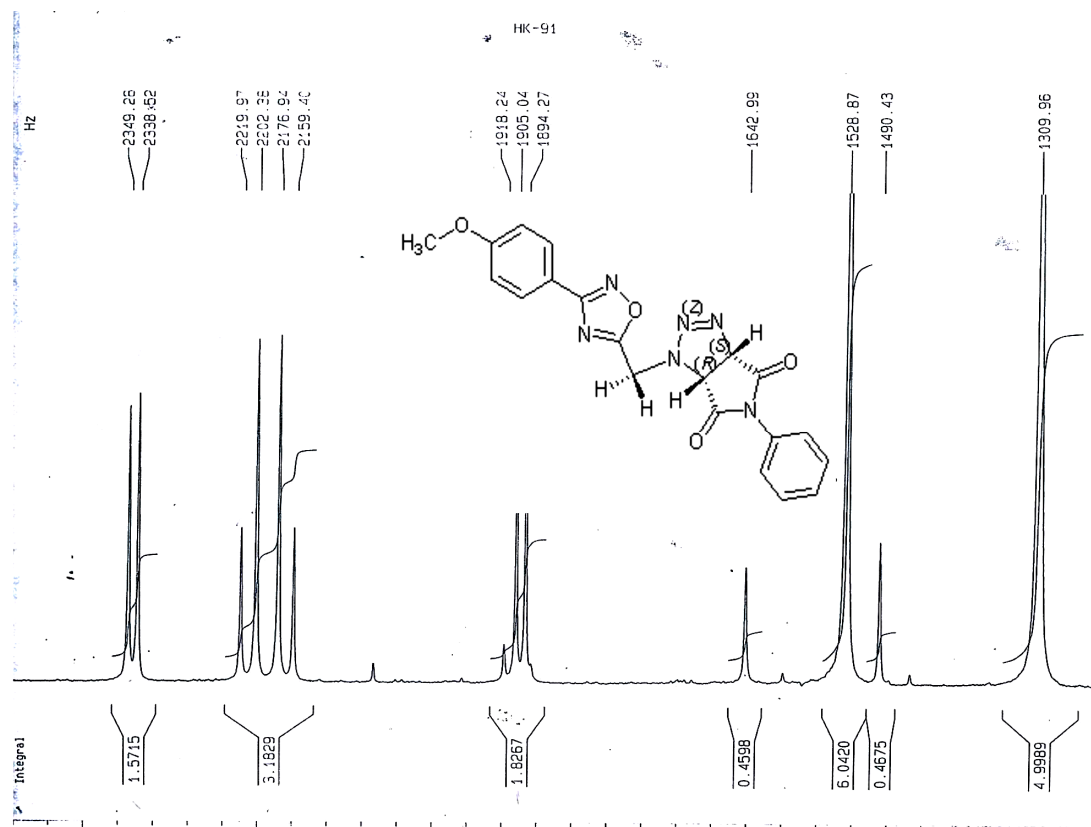


Figure 4.125 Expanded ^1H NMR Spectrum of compound 90h

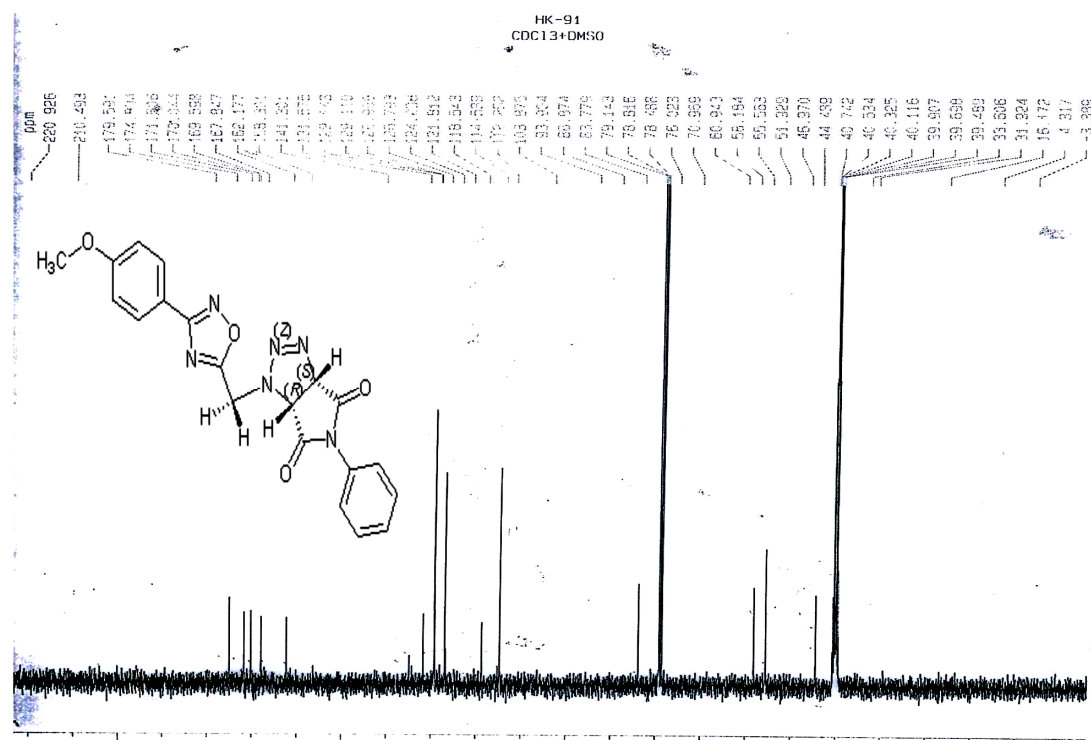


Figure 4.126 ^{13}C NMR Spectrum of compound 90h

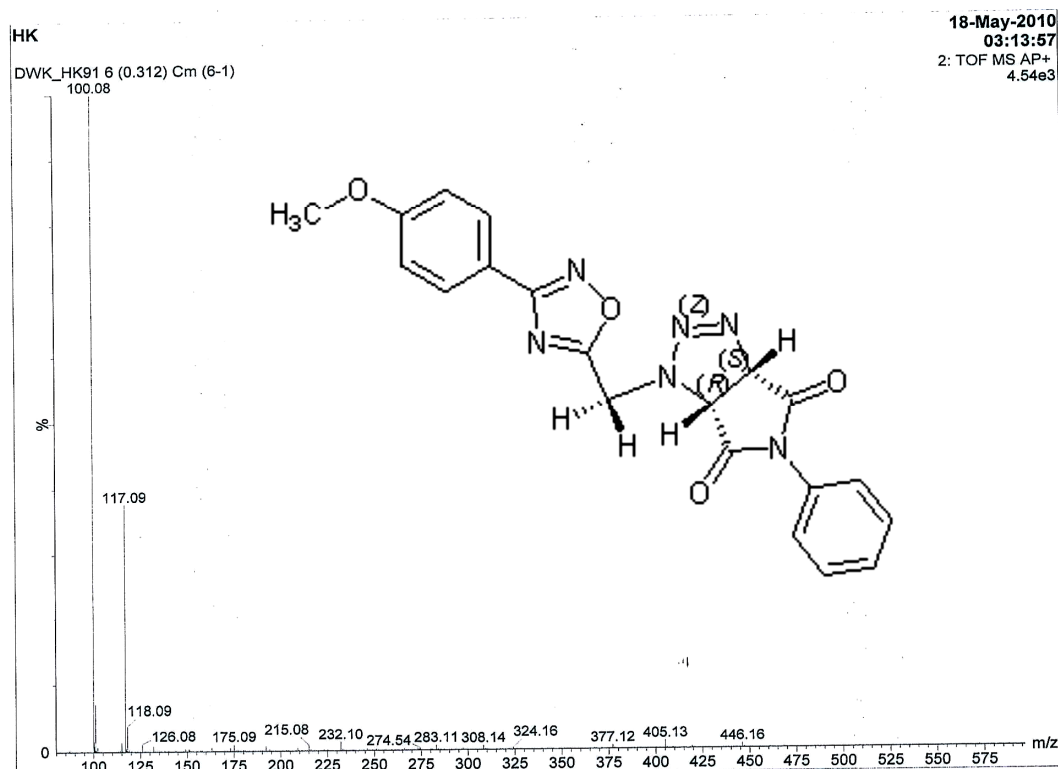


Figure 4. 127 Mass spectra of compound 90h

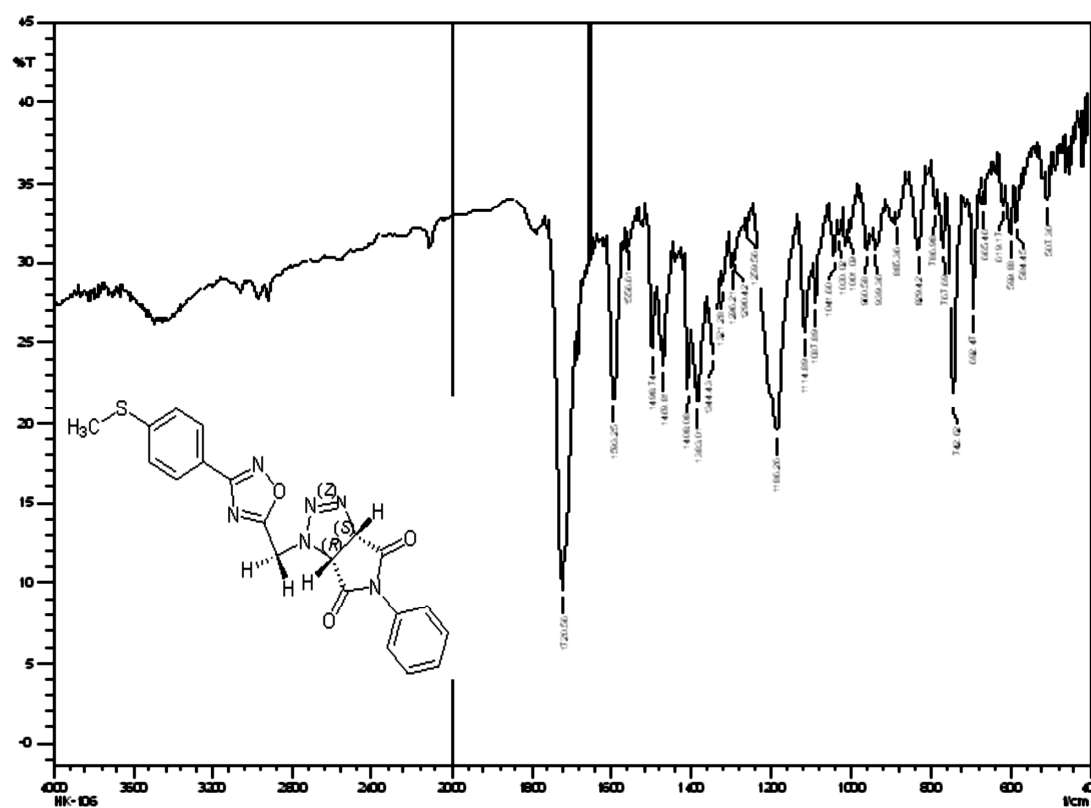


Figure 4. 128 IR spectrum of compound 90j

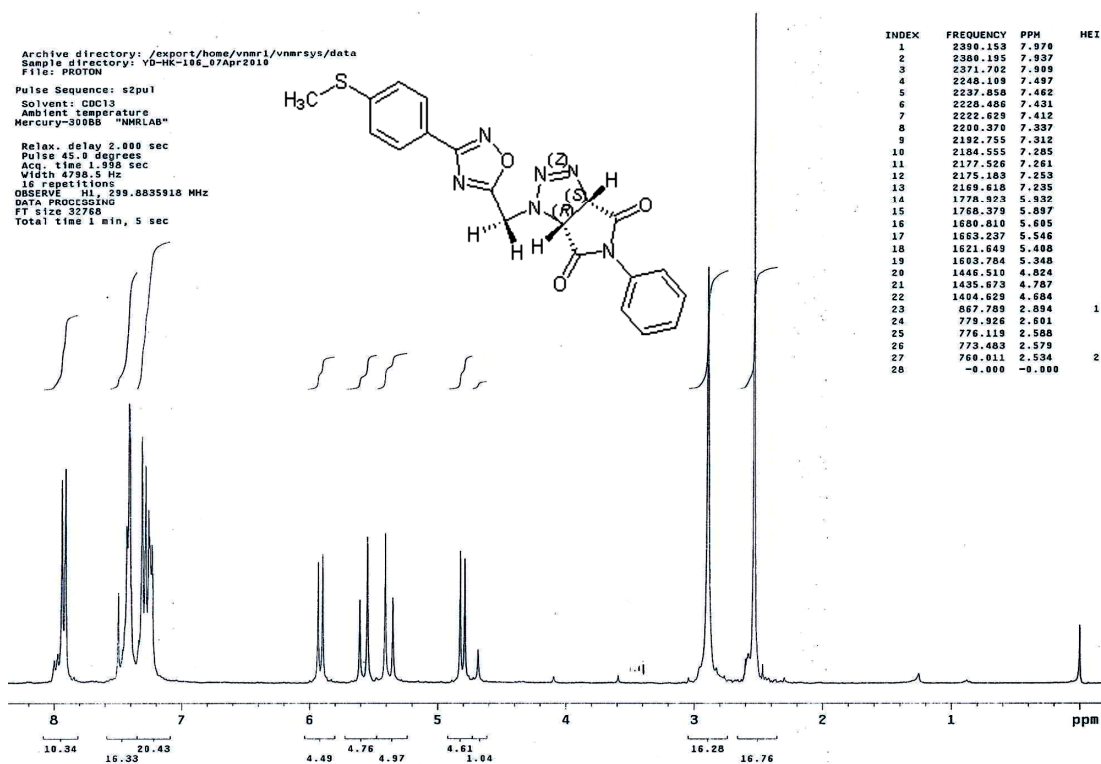


Figure 4. ^{129}H NMR Spectrum of compound 90j

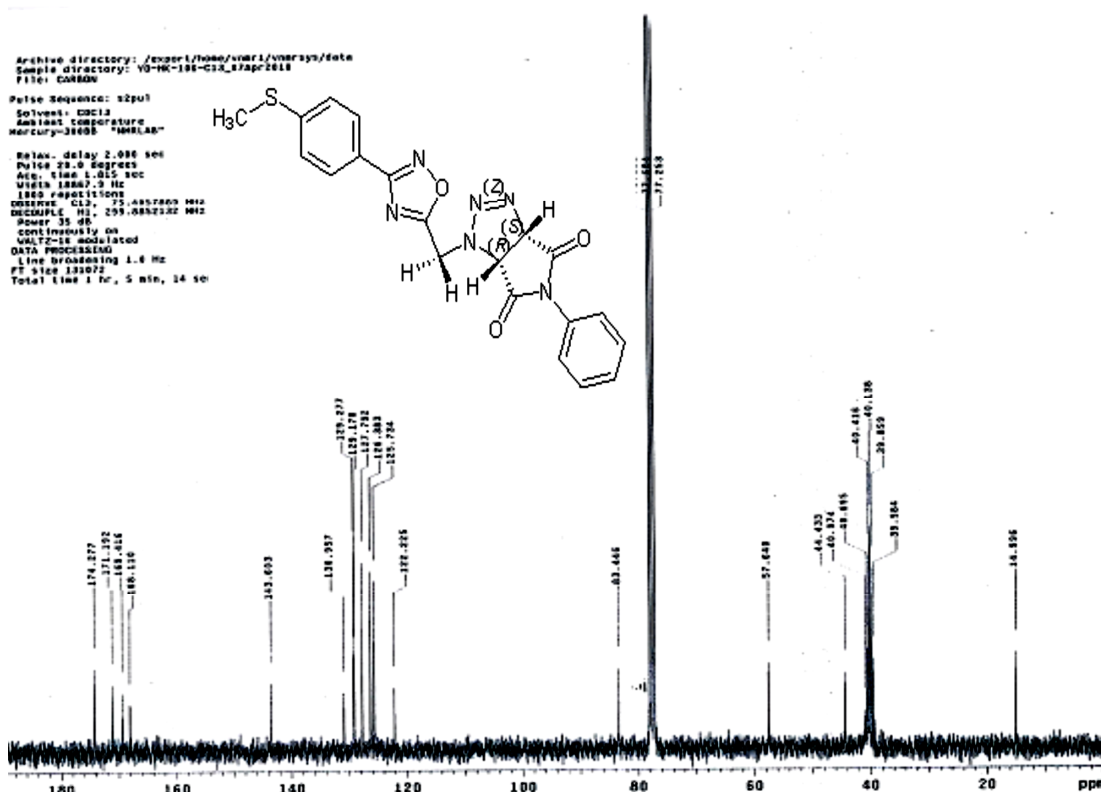


Figure 4. ^{130}C NMR Spectrum of compound 90j

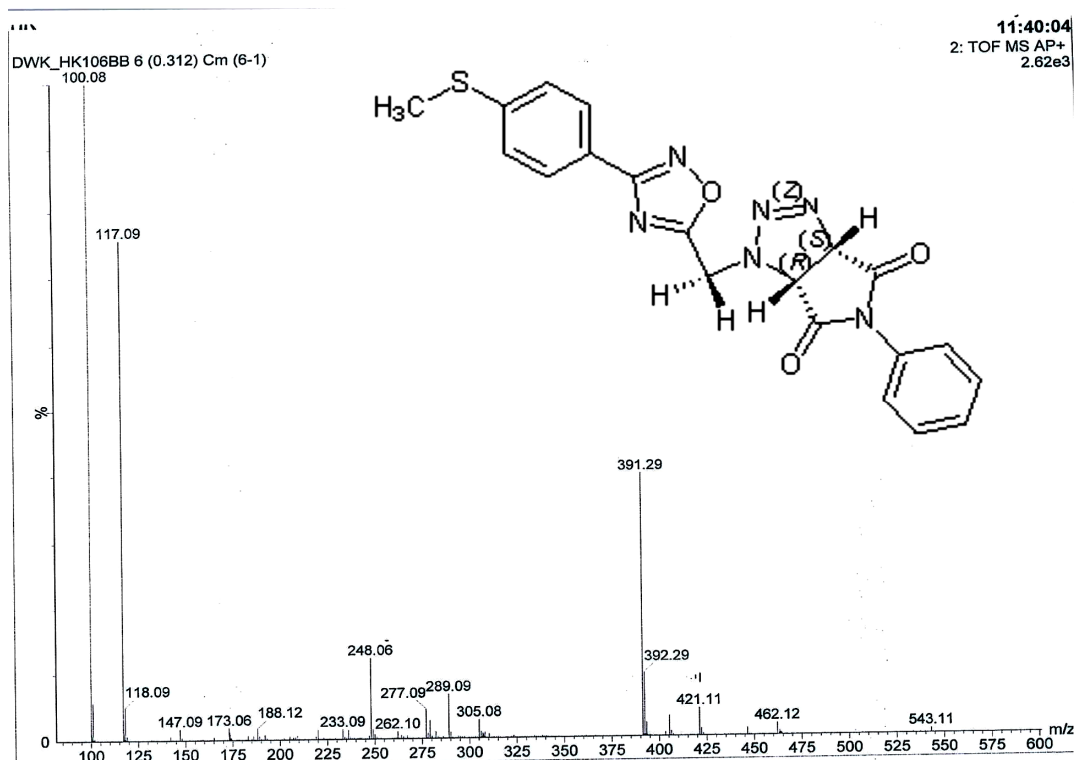


Figure 4. 131 Mass spectra of compound 90j

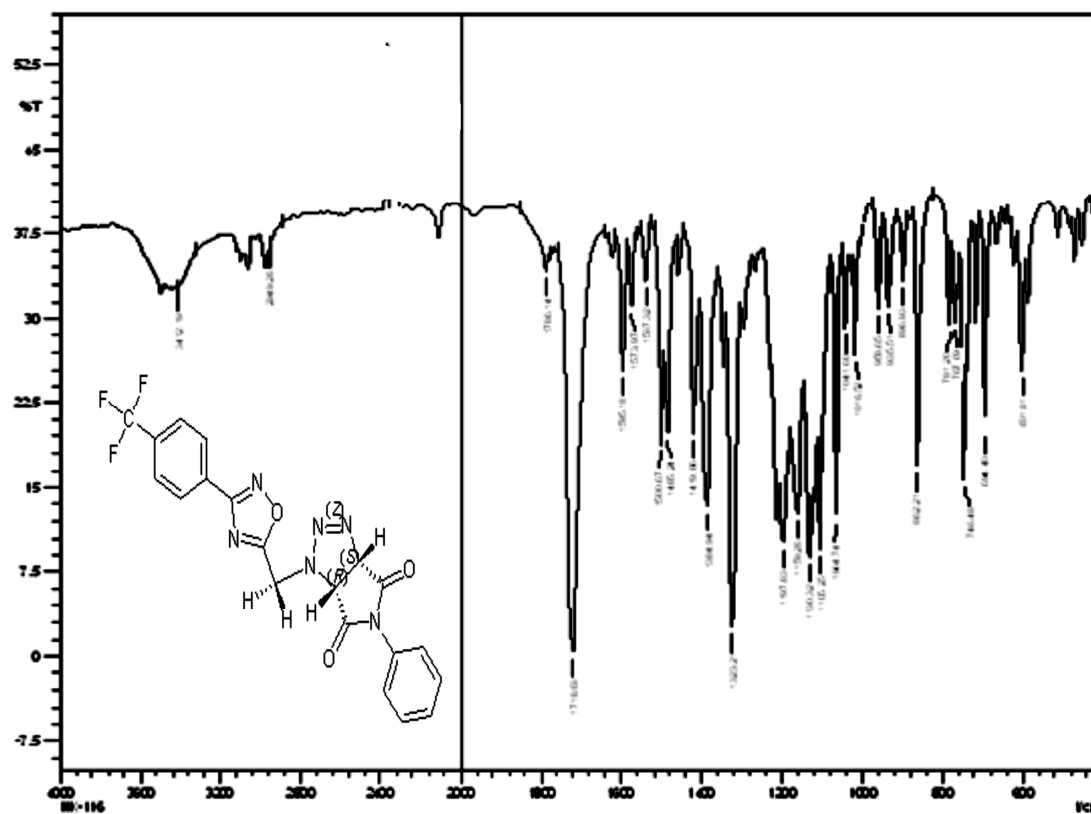


Figure 4. 132 IR spectrum of compound 90k

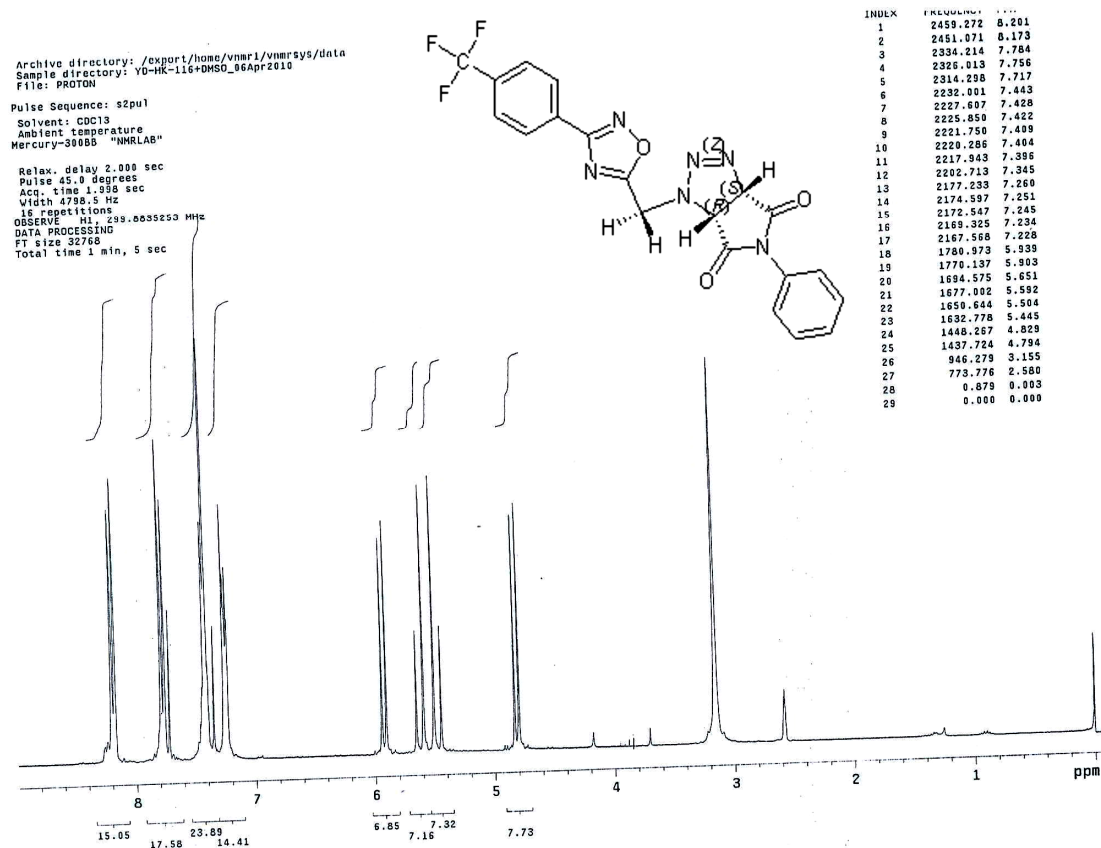


Figure 4. 133 ¹H NMR Spectrum of compound 90k

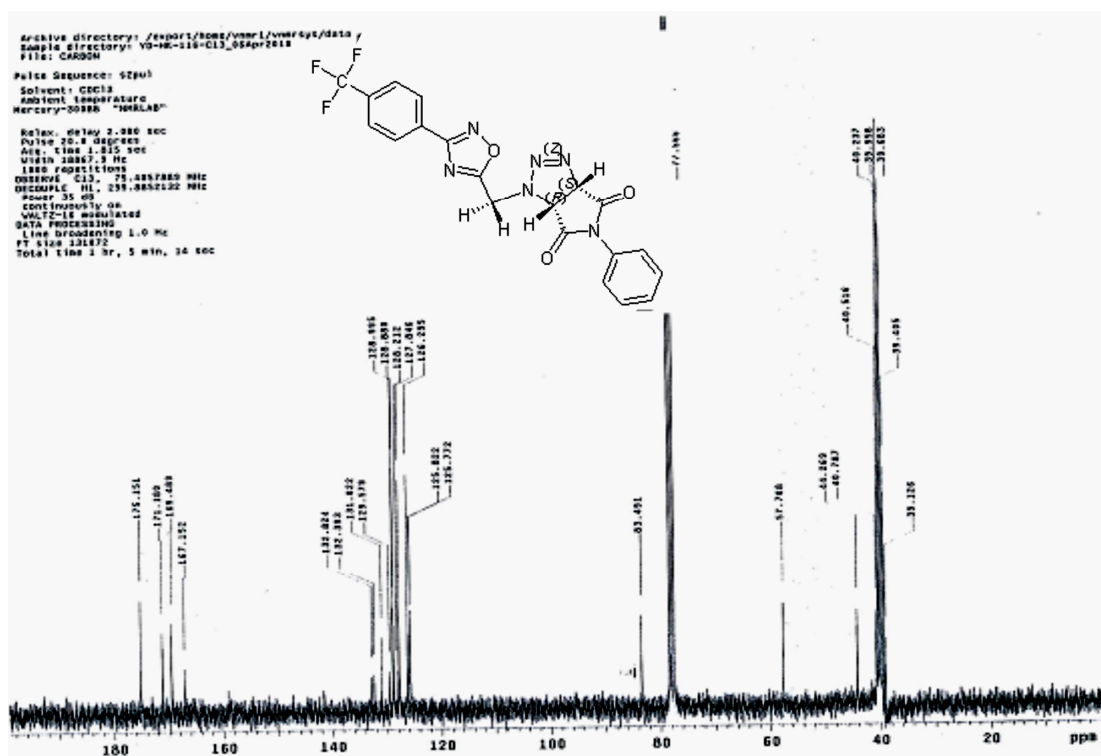


Figure 4. 134 ¹³C NMR Spectrum of compound 90k

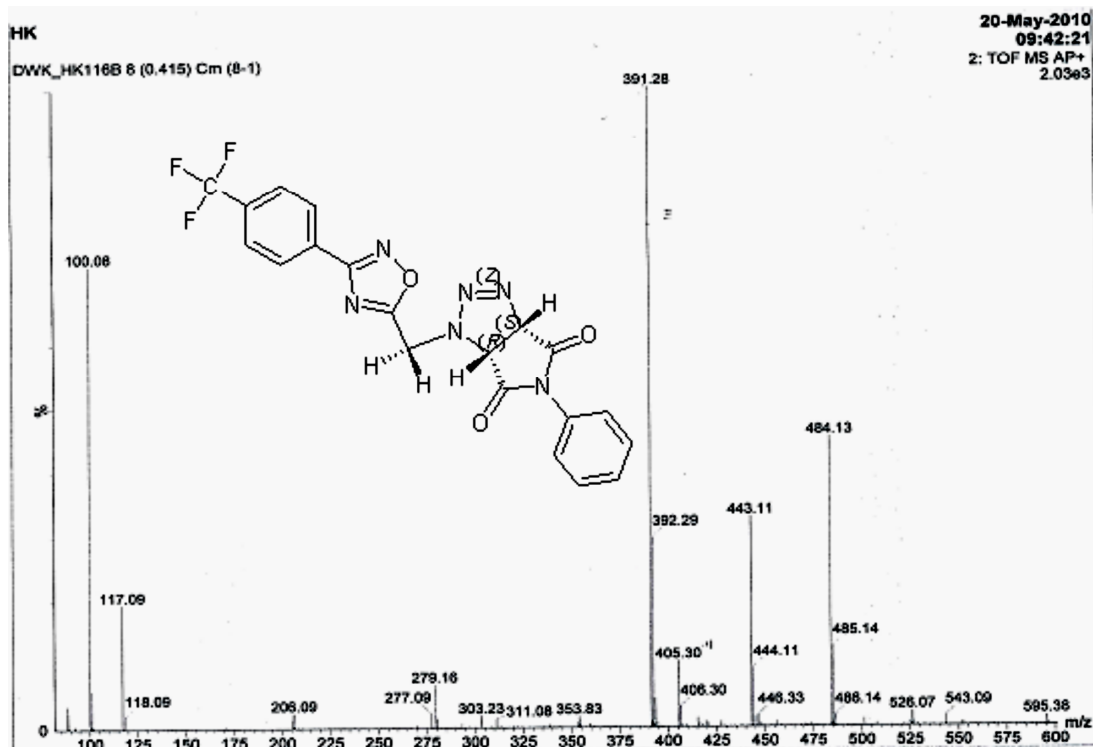


Figure 4. 135 Mass spectra of compound 90k

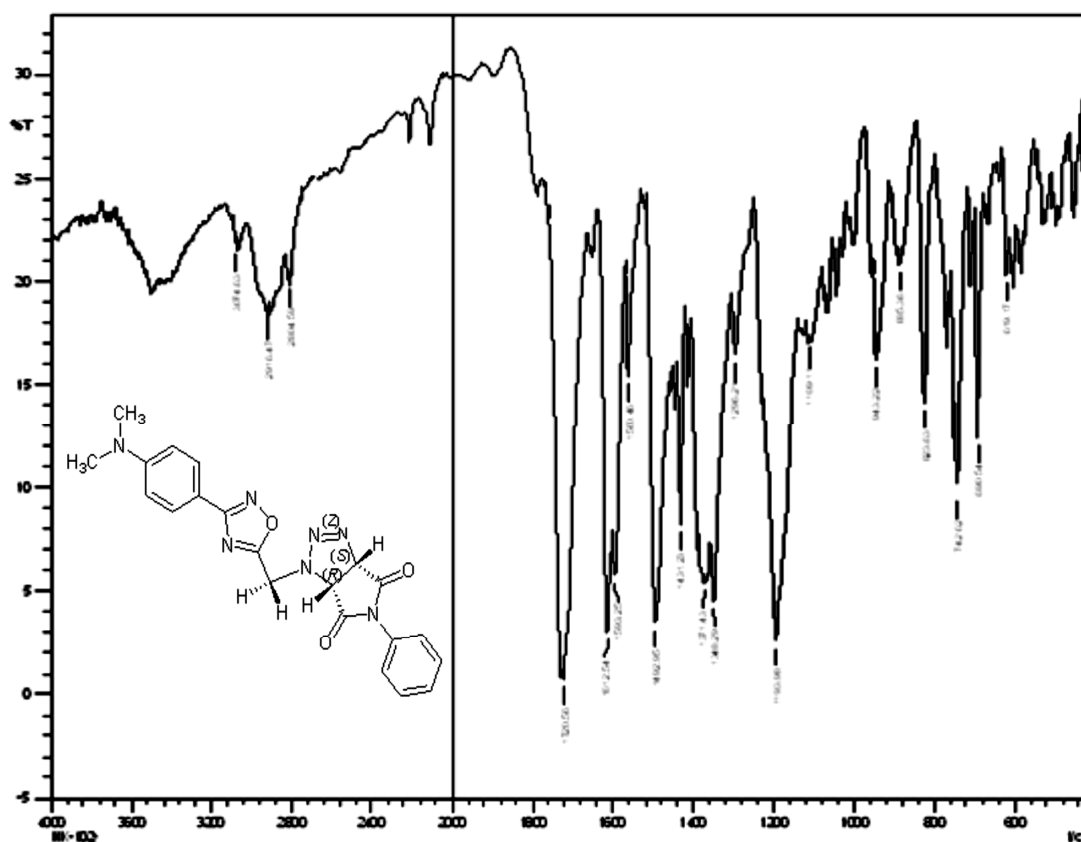


Figure 4. 136 IR spectrum of compound 90m

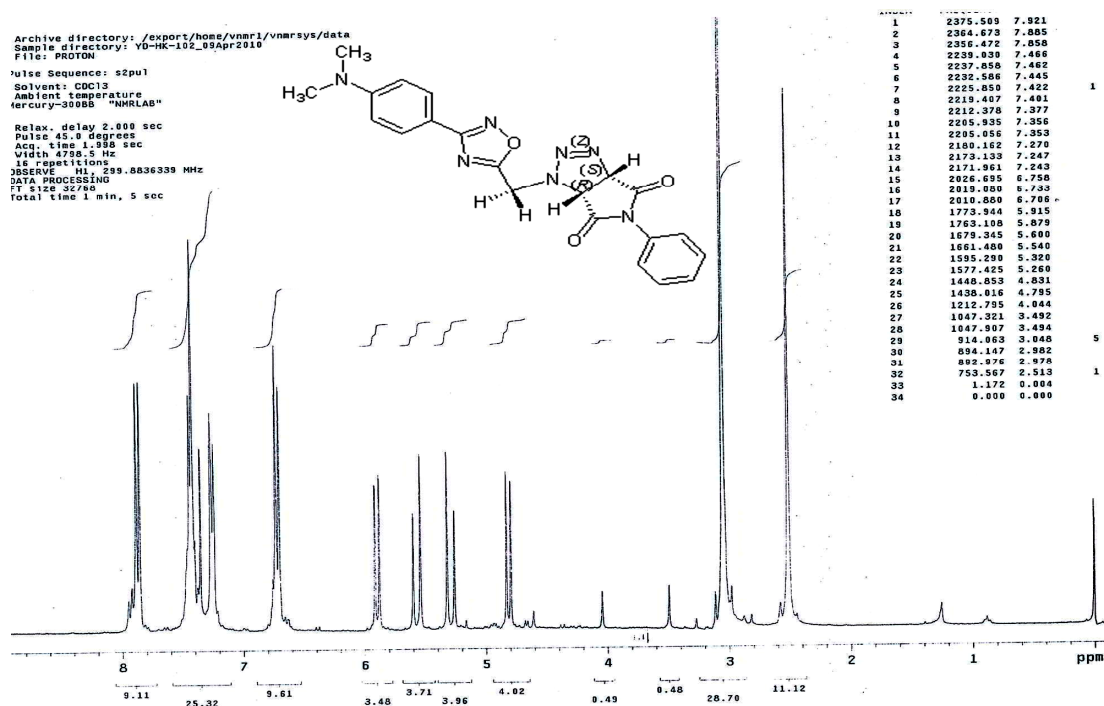


Figure 4. 137 ^1H NMR Spectrum of compound 90m

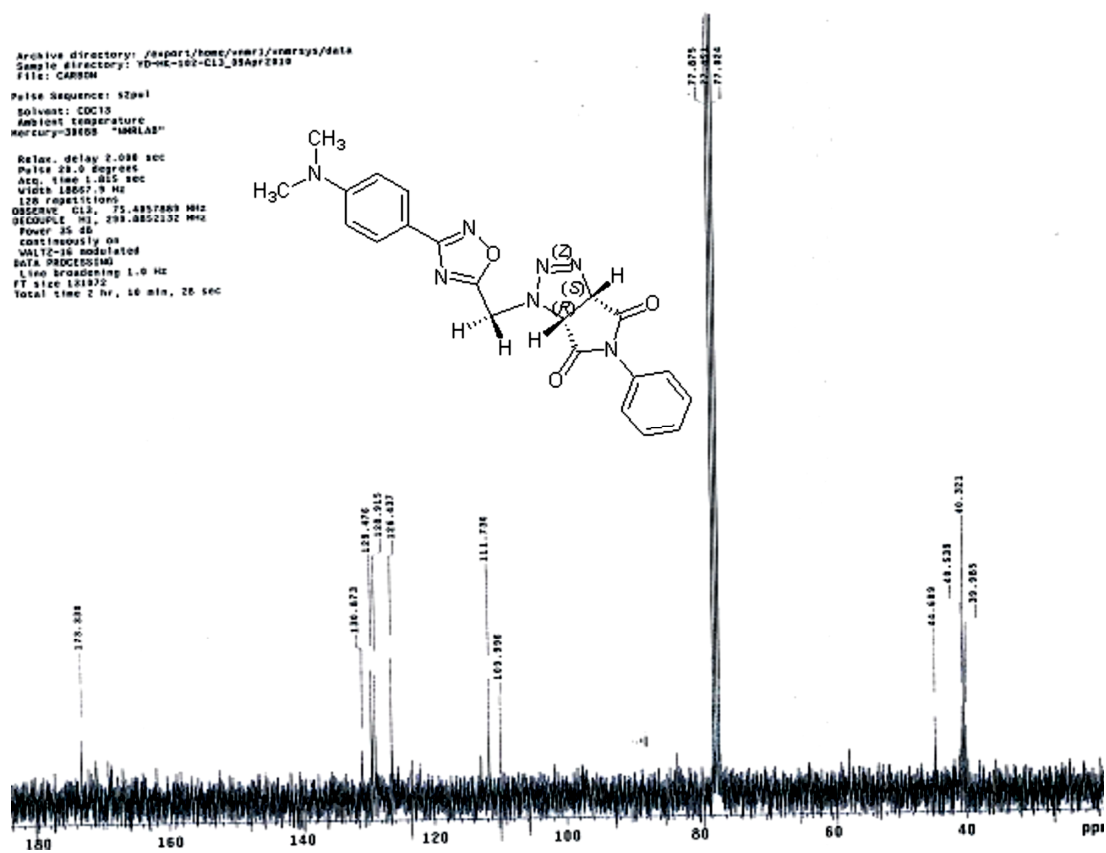


Figure 4. 138 ^{13}C NMR Spectrum of compound 90m

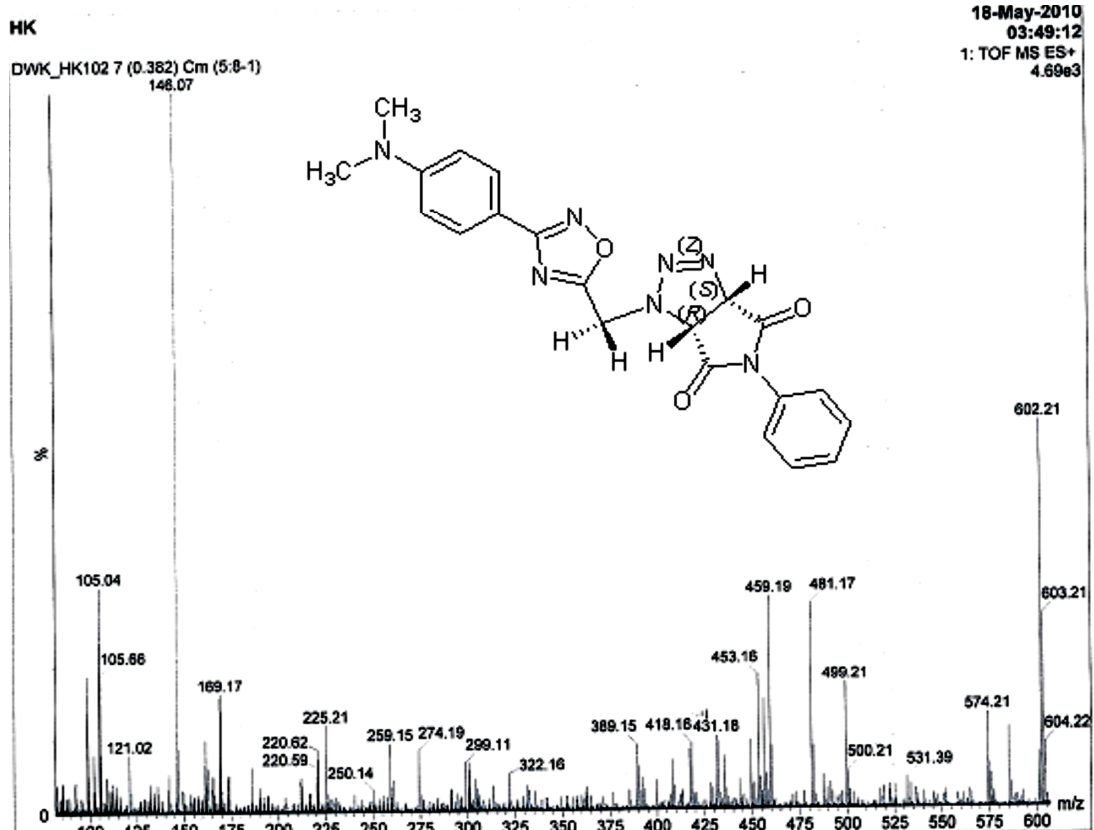


Figure 4. 139 Mass spectra of compound 90m

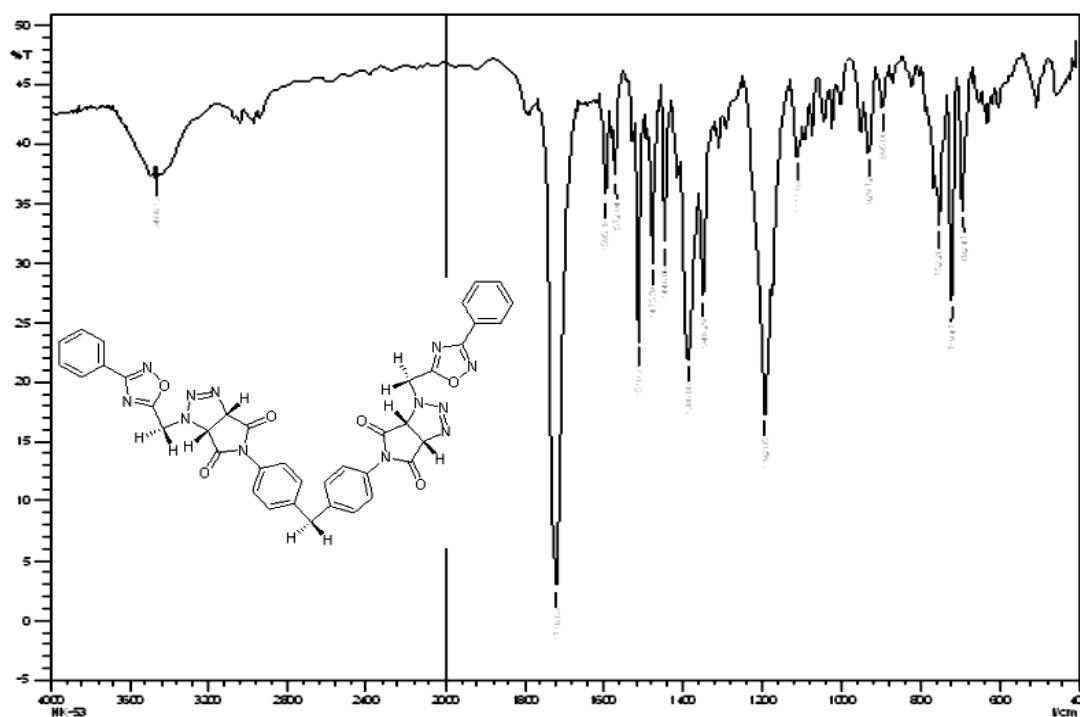


Figure 4. 140 IR spectrum of compound 91

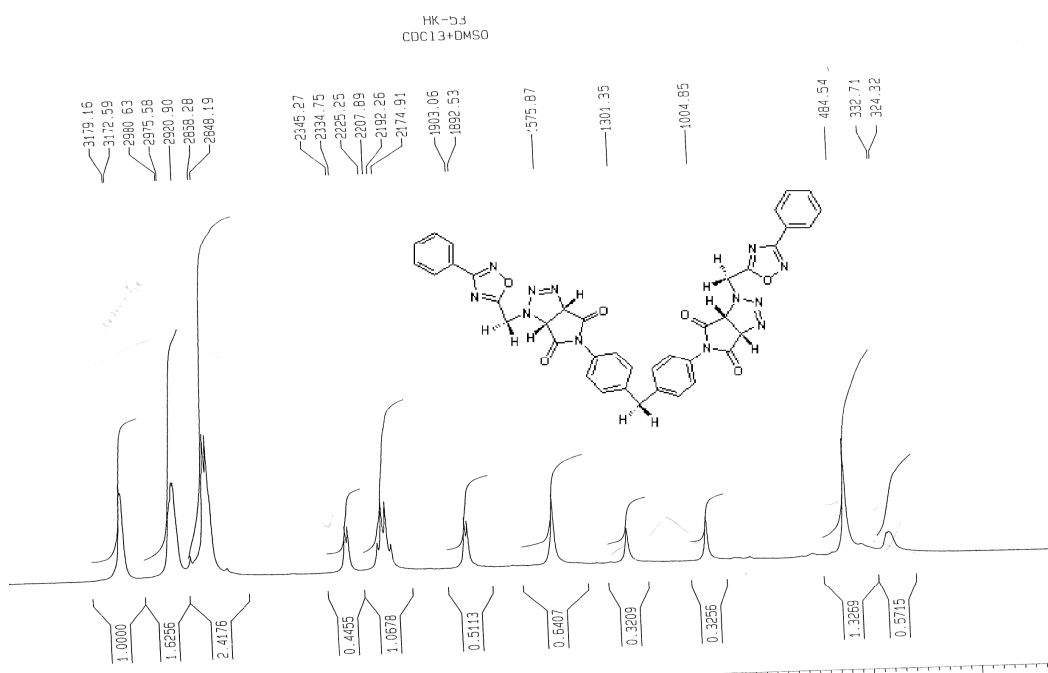


Figure 4. 141 ¹H NMR Spectrum of compound **91**

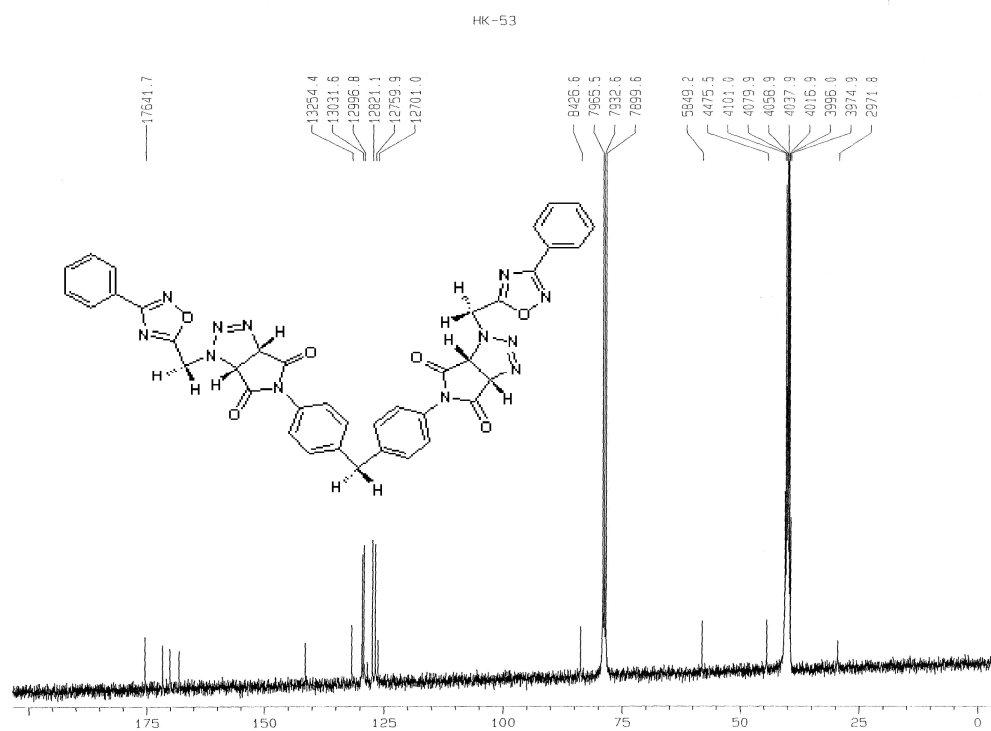


Figure 4. 142 ¹³C NMR Spectrum of compound **91**

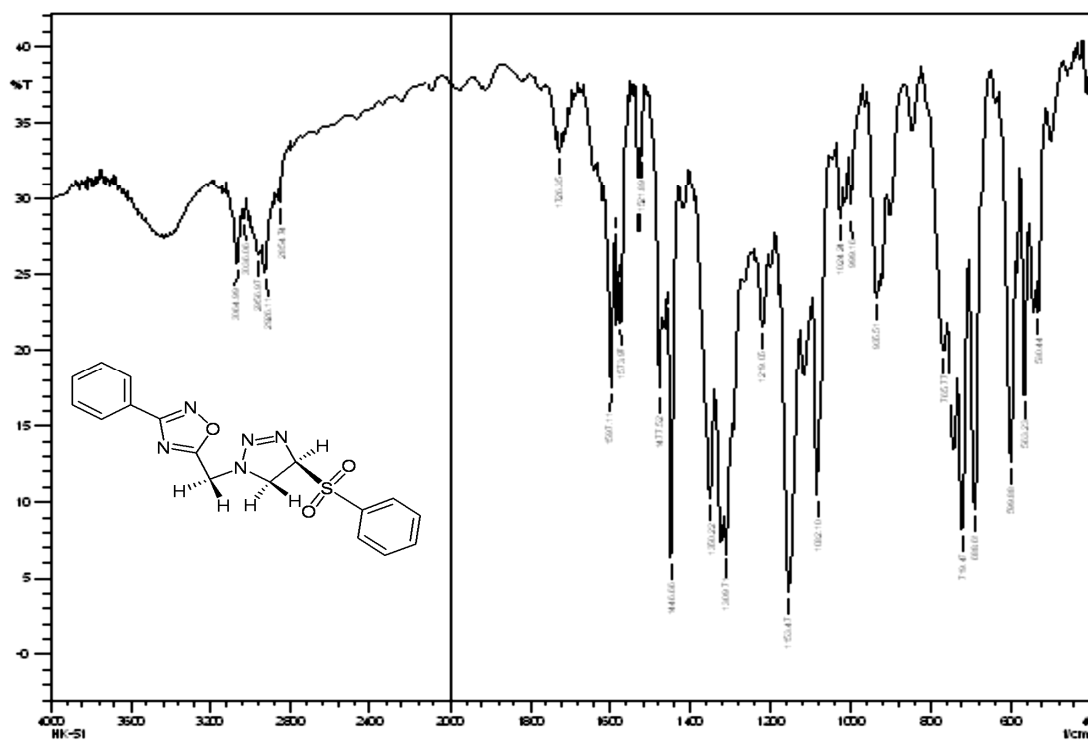


Figure 4. 143 IR spectrum of compound **93a**



Figure 4. 144 ¹H NMR Spectrum of compound **93a**

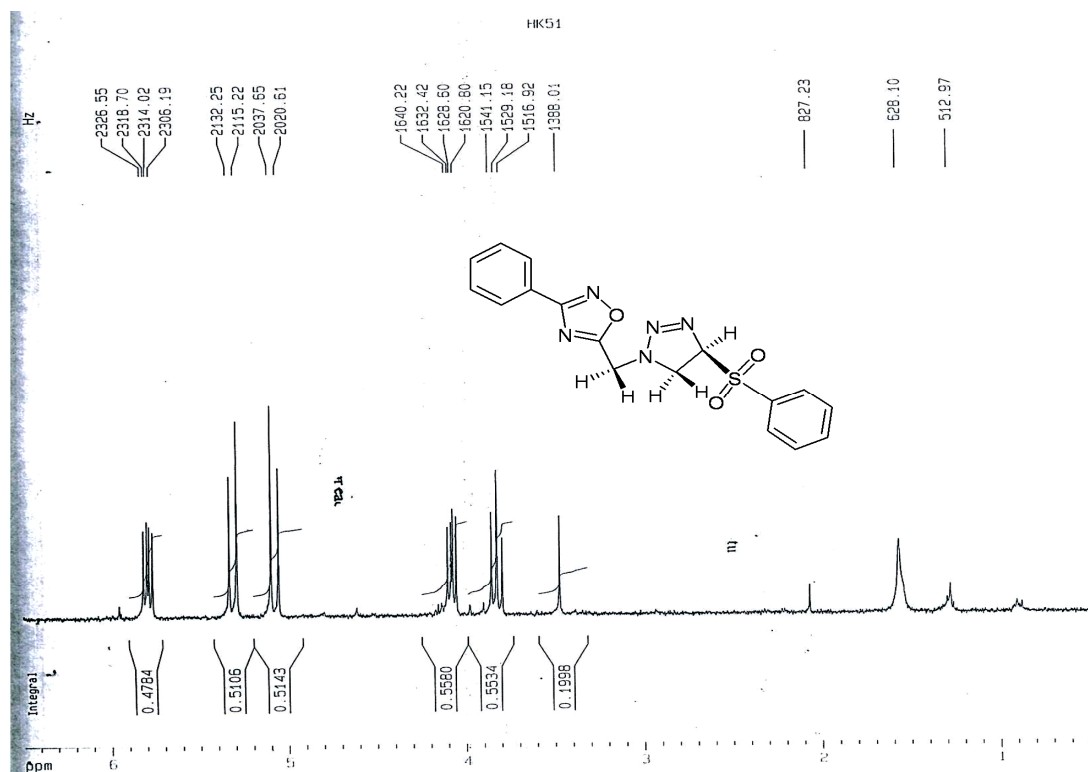


Figure 4. 145 Expanded ¹H NMR Spectrum of compound 93a

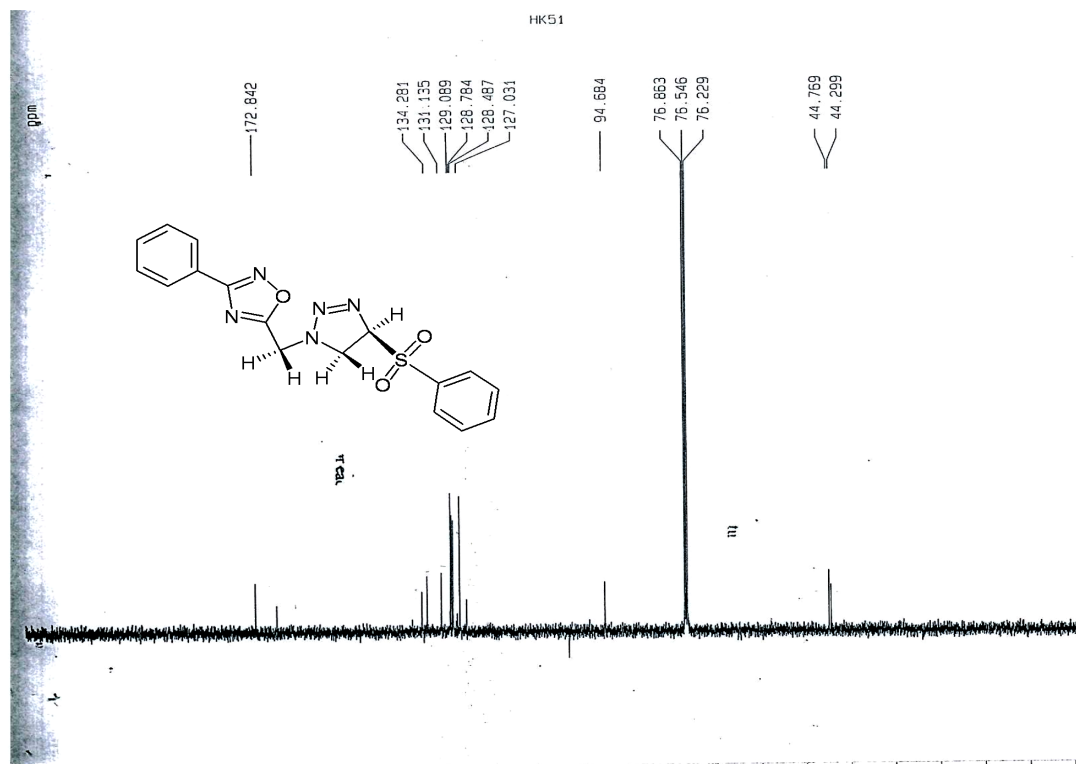


Figure 4. 146 ¹³C NMR Spectrum of compound 93a

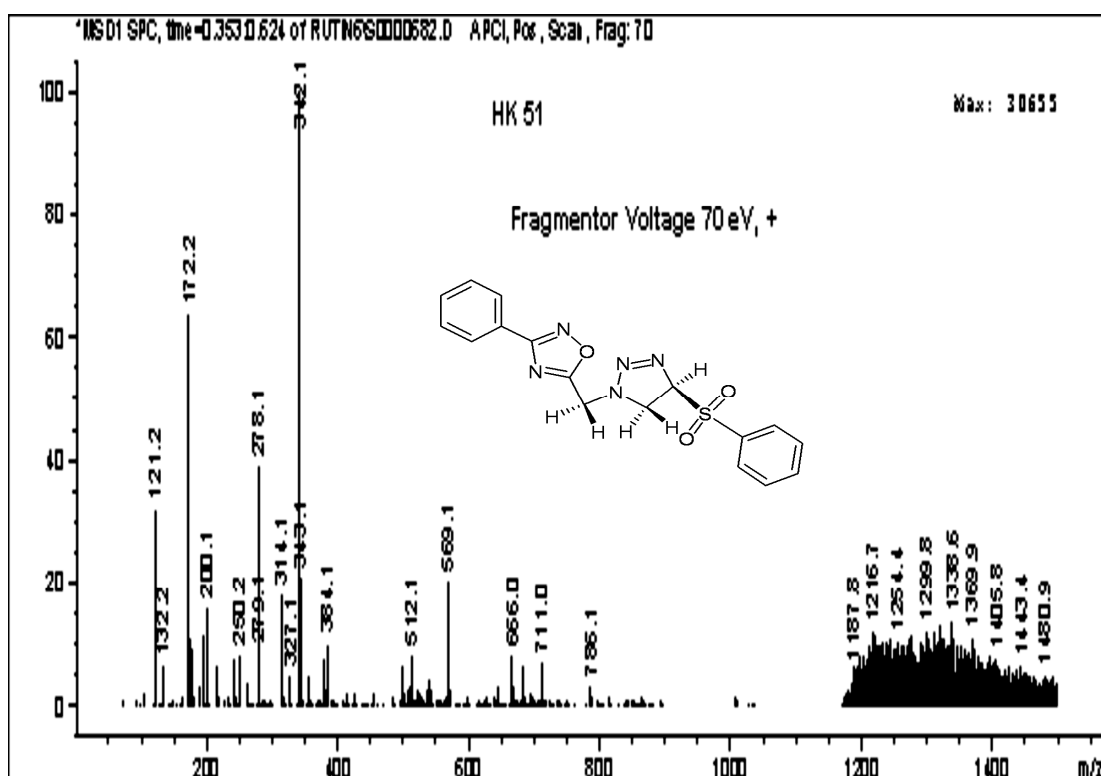


Figure 4. 147 Mass spectra of compound 93a

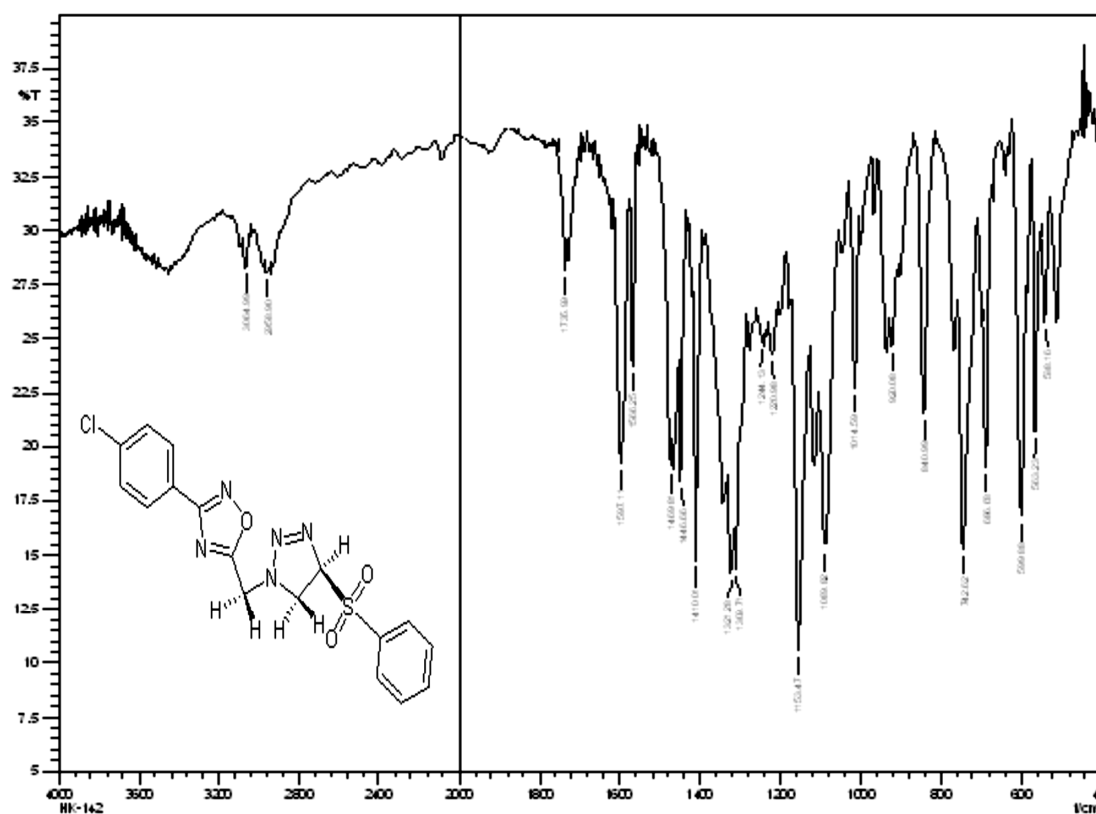


Figure 4. 148 IR spectrum of compound 93b

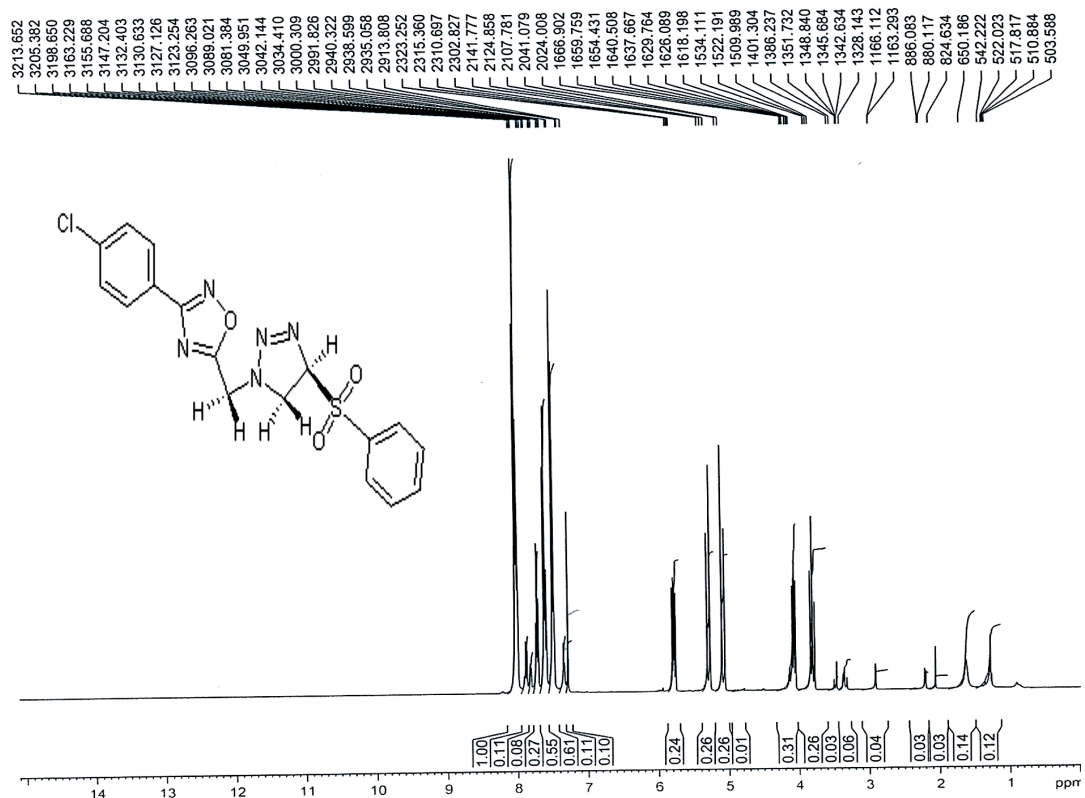


Figure 4. 149 ¹H NMR Spectrum of compound **93b**

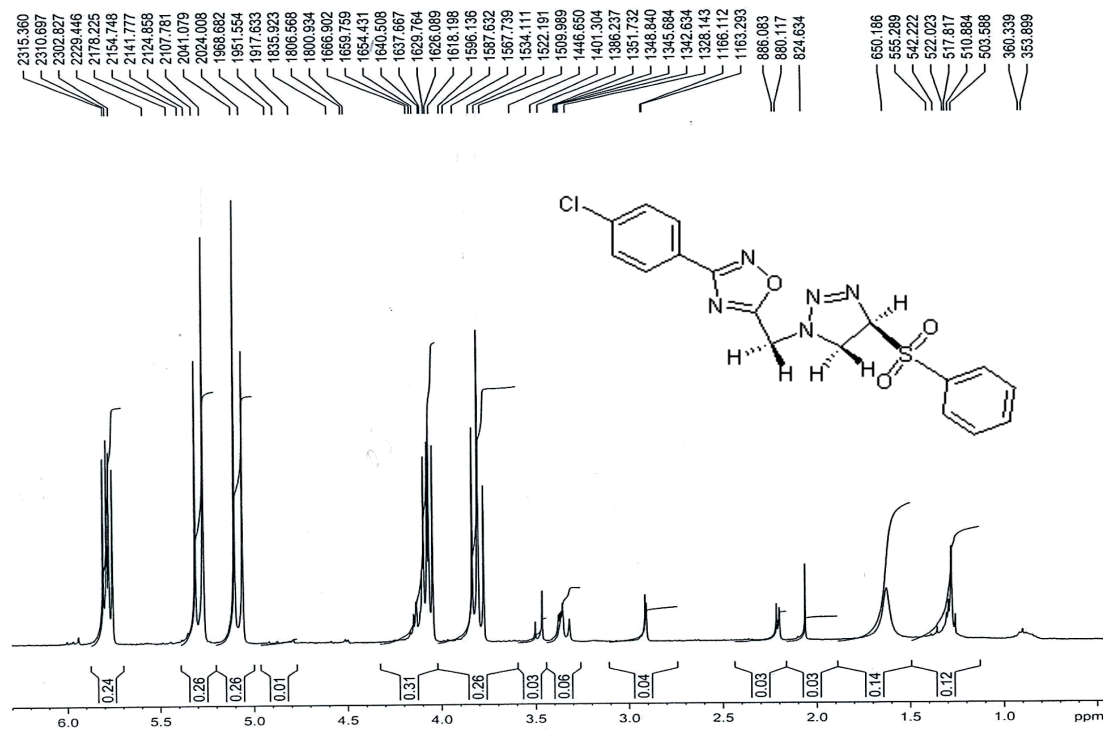


Figure 4. 150 Expanded ¹H NMR Spectrum of compound **93b**

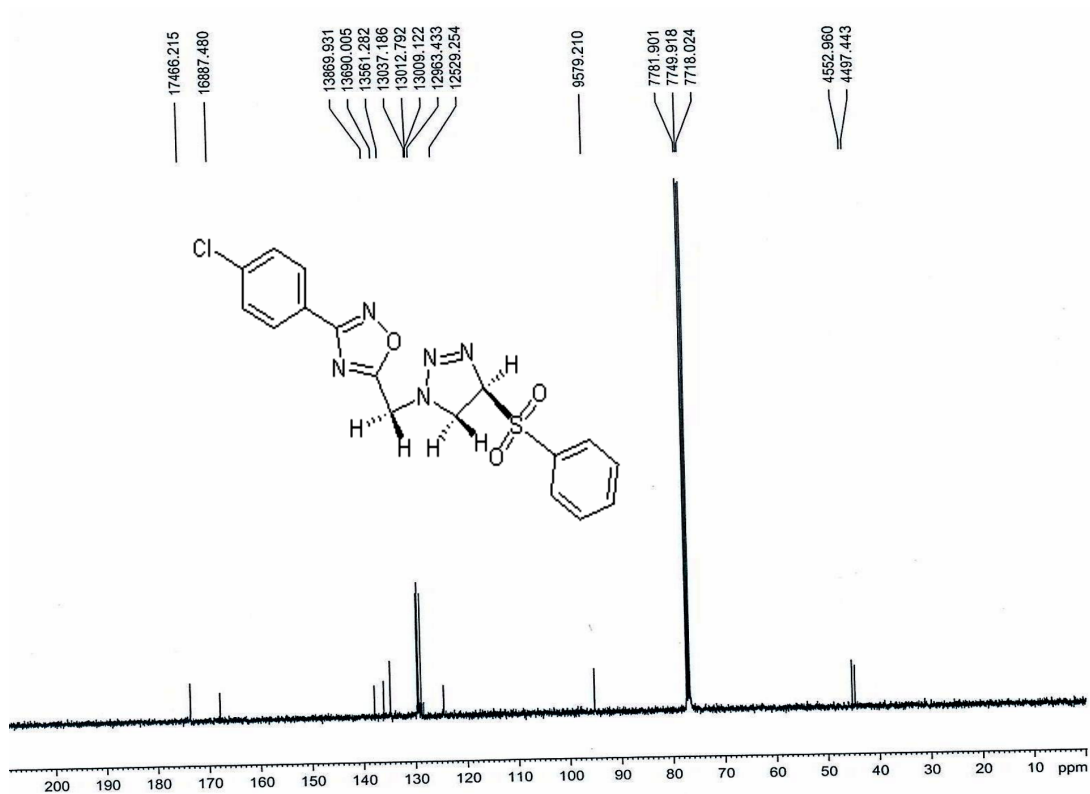


Figure 4. 151 ¹³C NMR Spectrum of compound 93b

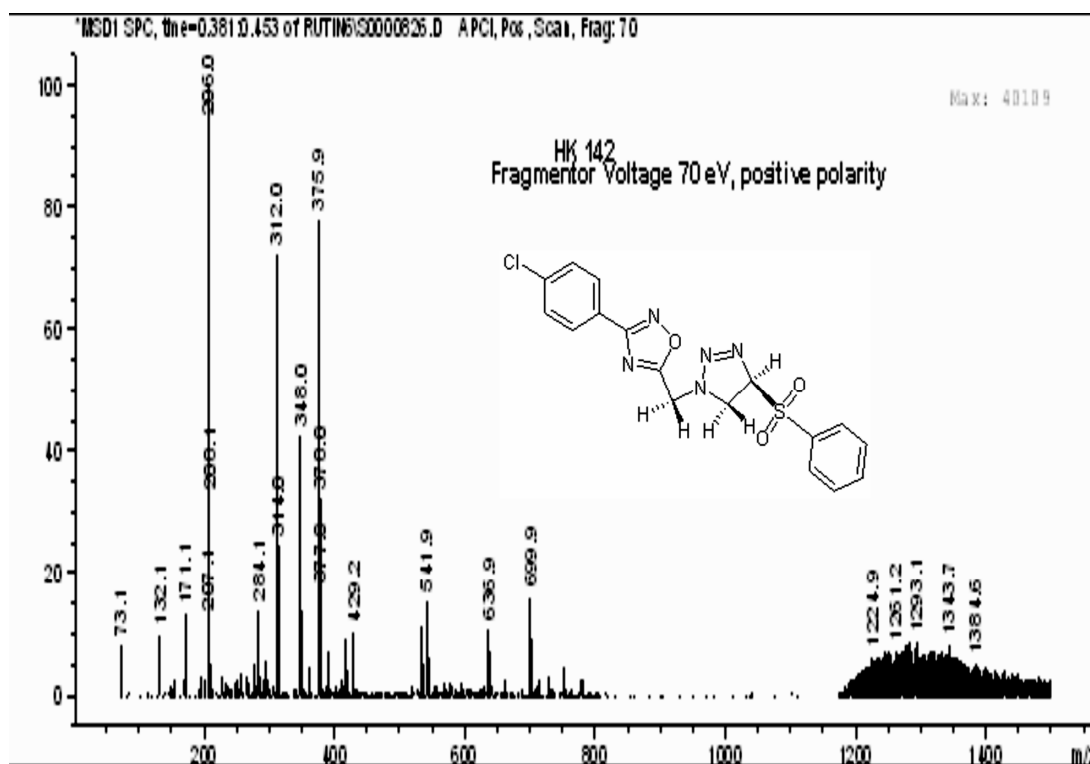


Figure 4. 152 Mass spectra of compound 93b

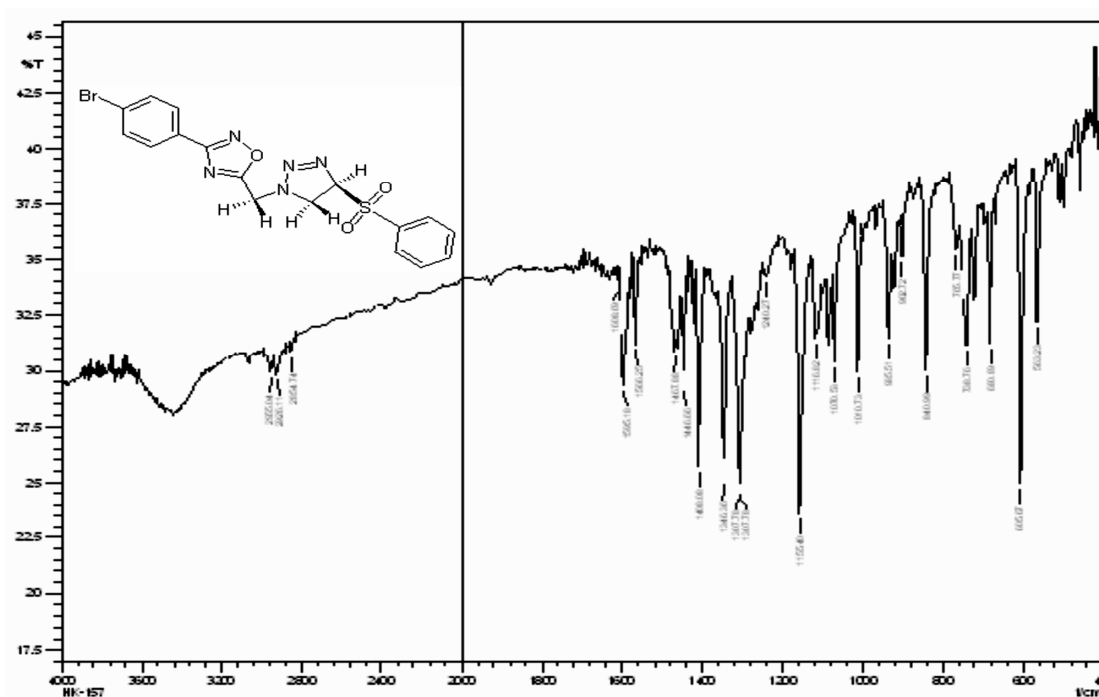


Figure 4. 153 IR spectrum of compound **93c**

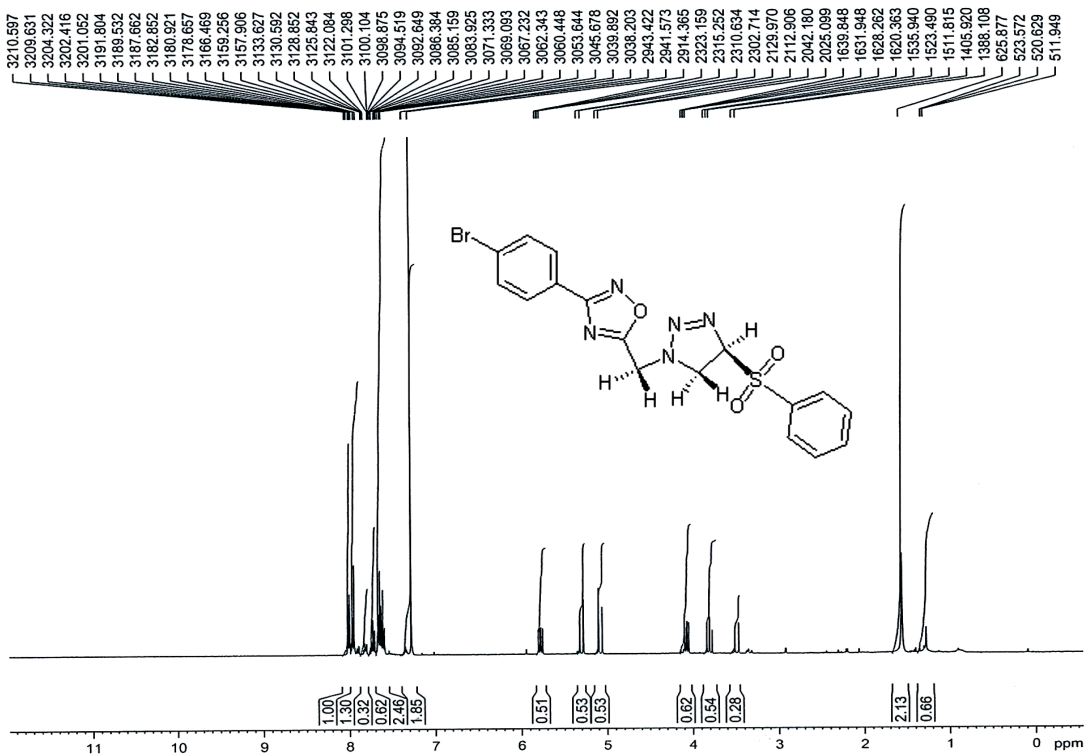


Figure 4. 154 ¹H NMR Spectrum of compound **93c**

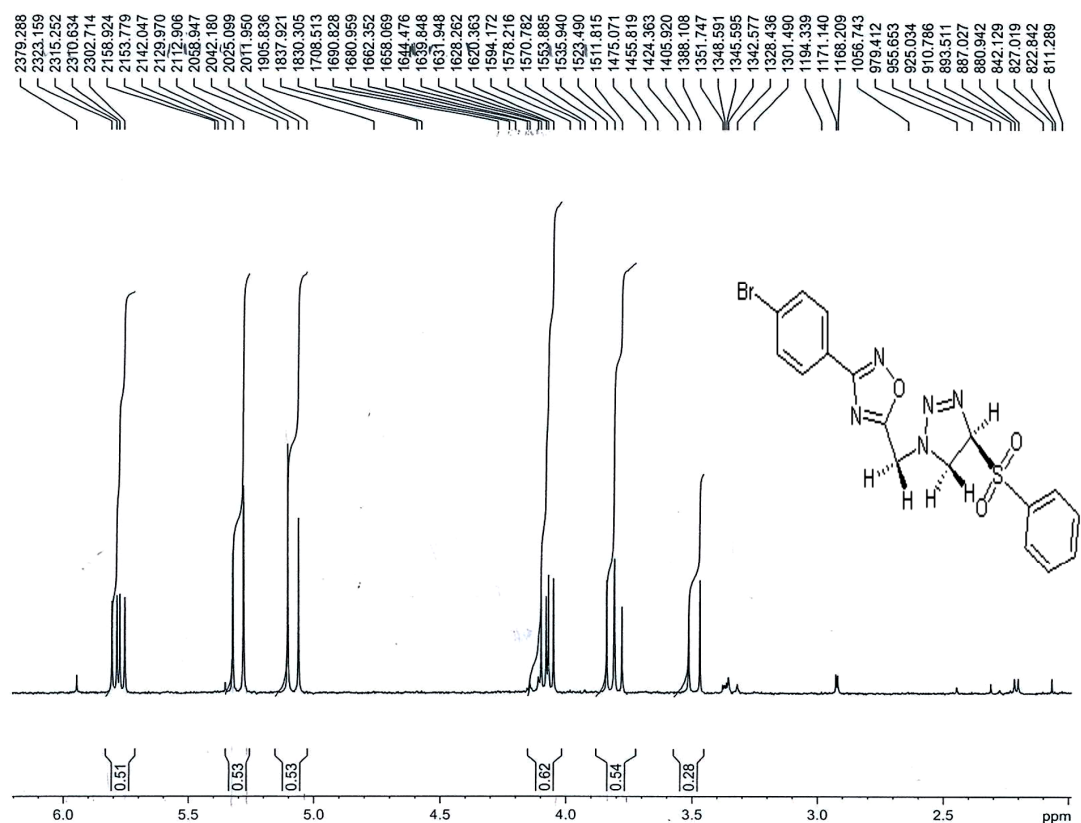


Figure 4. 155 Expanded ¹H NMR Spectrum of compound **93c**

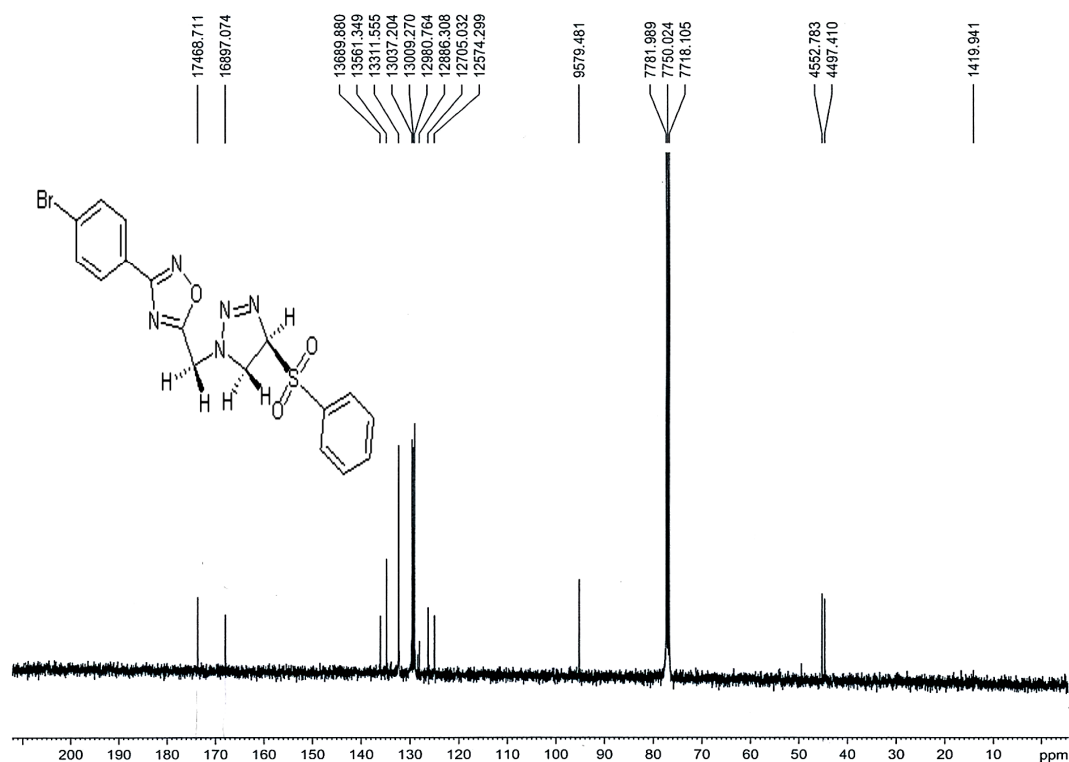


Figure 4. 156 ¹³C NMR Spectrum of compound **93c**

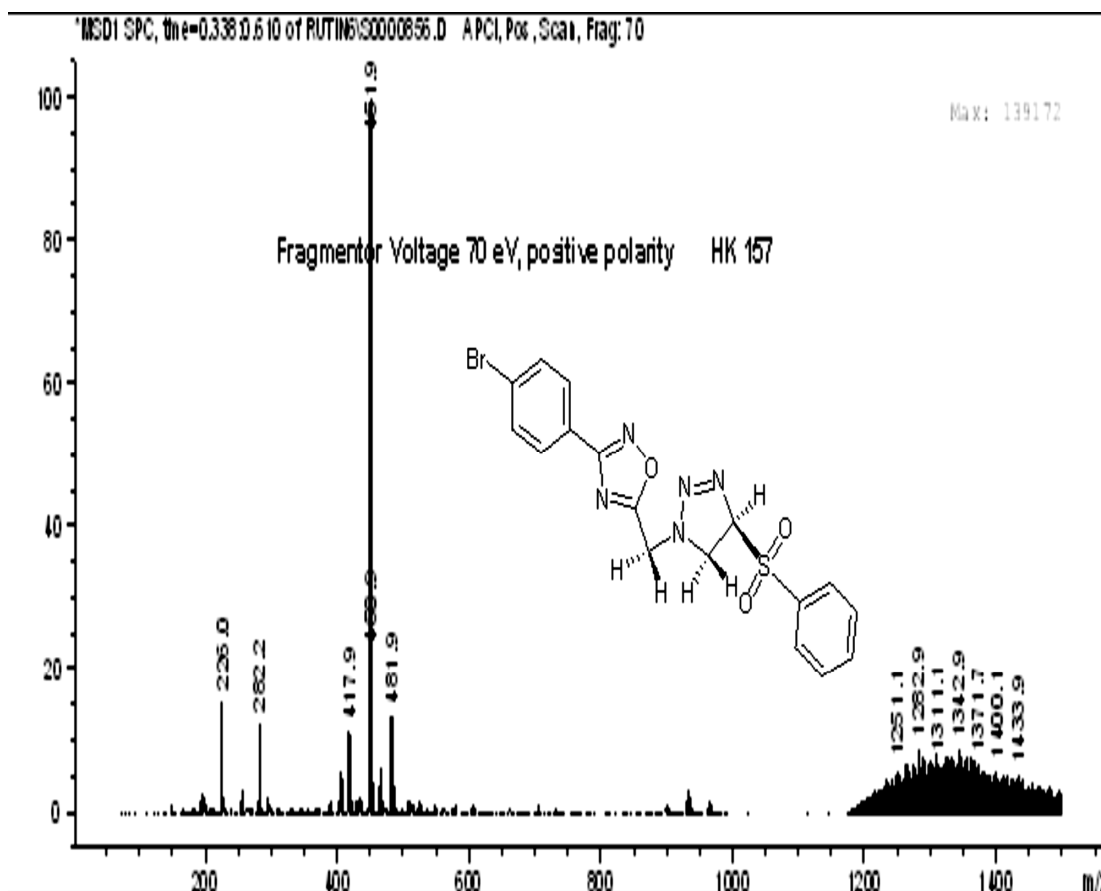


Figure 4. 157 Mass spectra of compound 93c

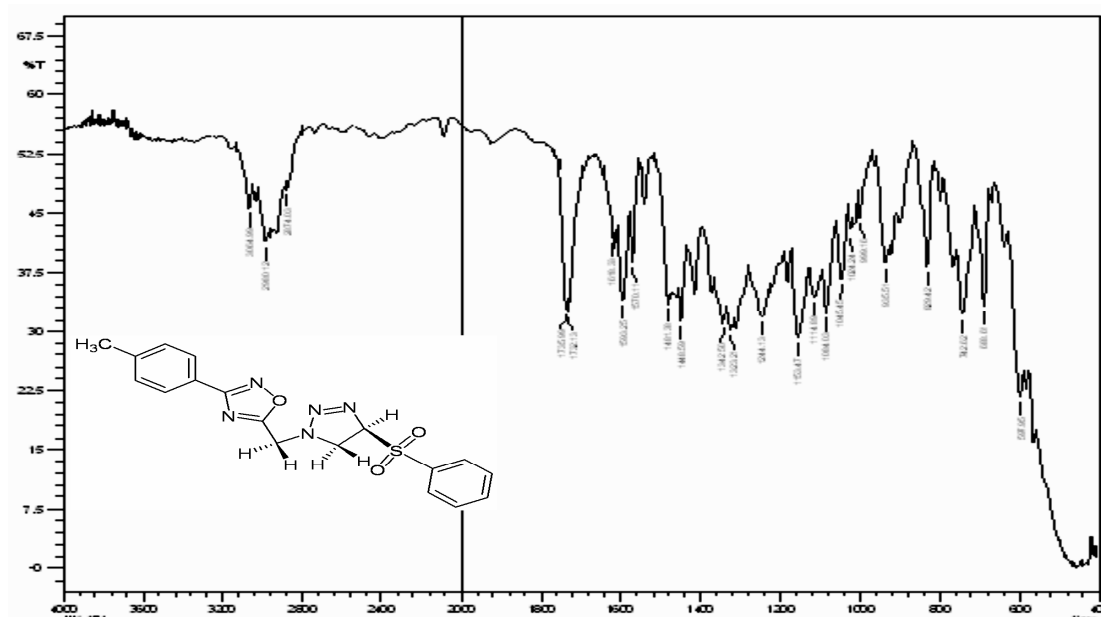


Figure 4. 158 IR spectrum of compound 93d

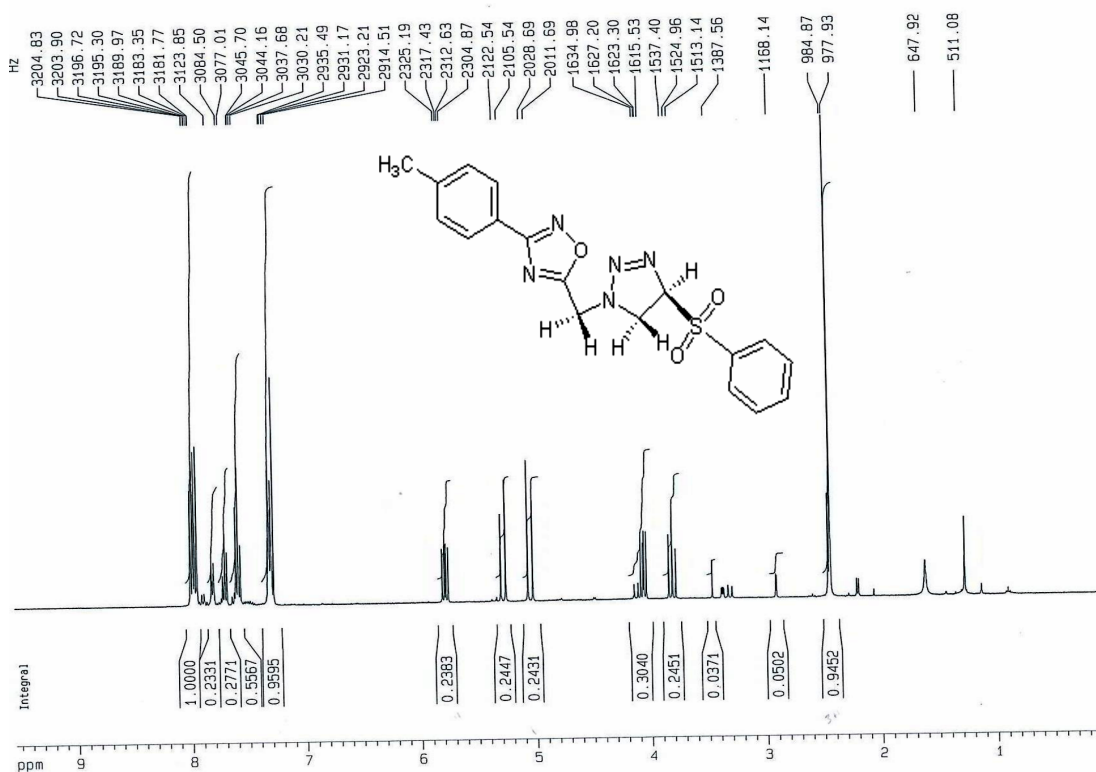


Figure 4. 159 ^1H NMR Spectrum of compound 93d

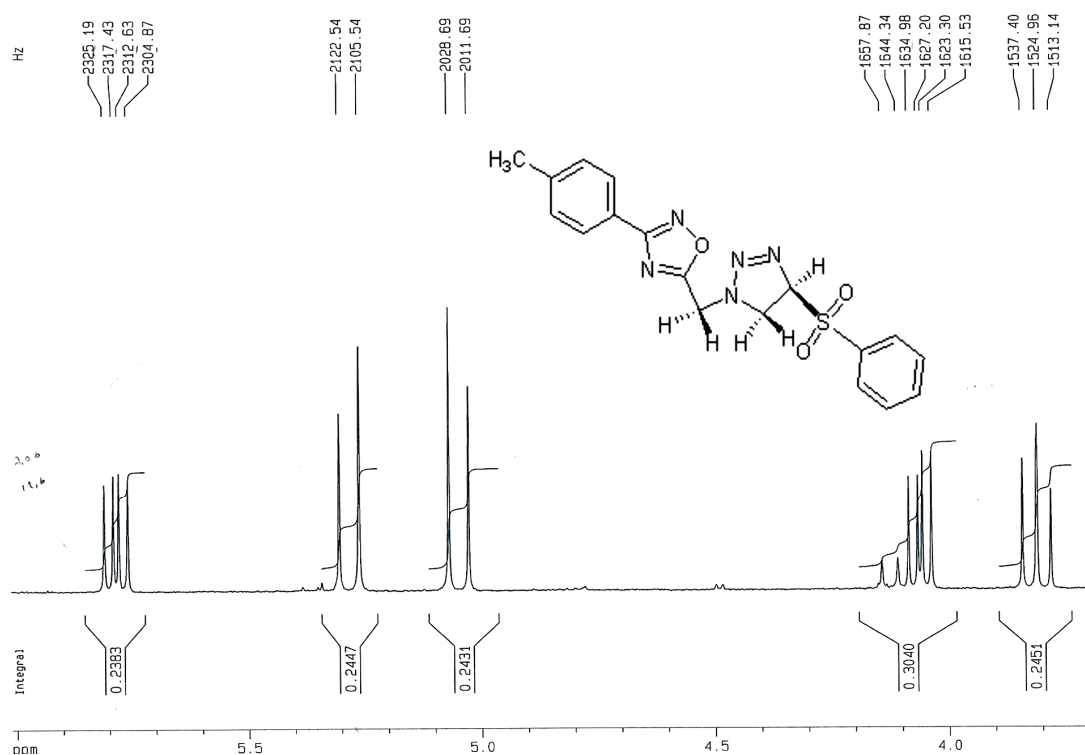


Figure 4. 160 Expanded ^1H NMR Spectrum of compound 93d

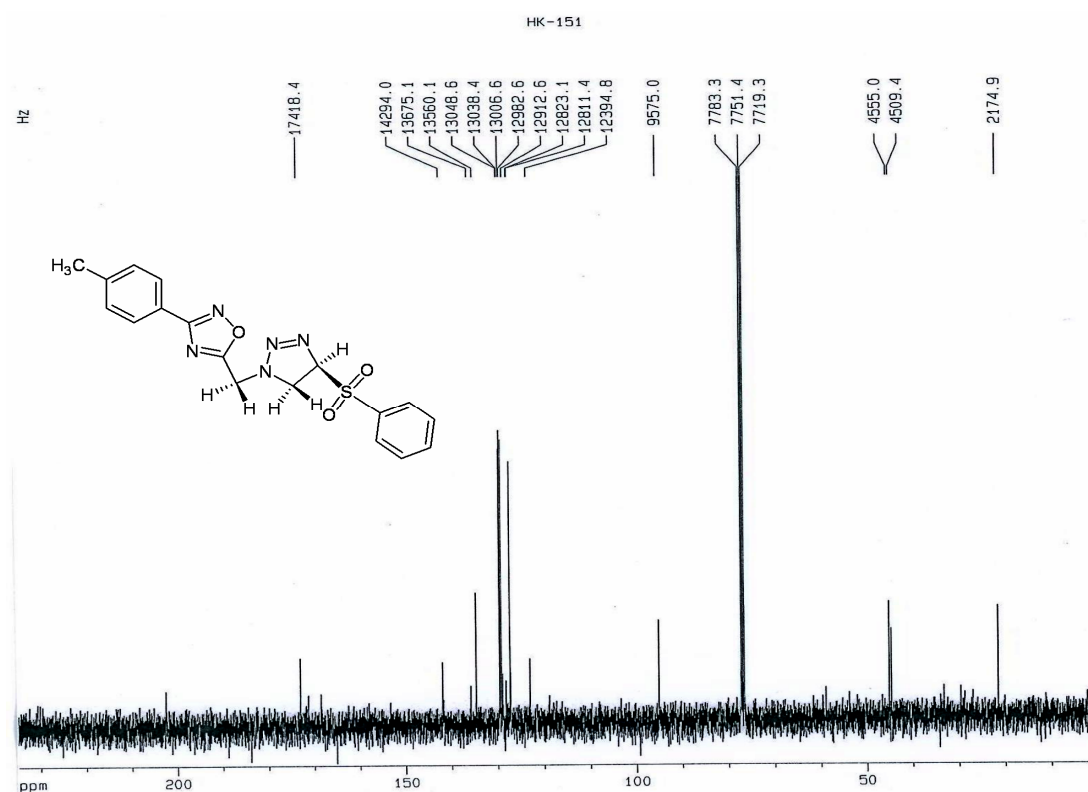


Figure 4. 161 ^{13}C NMR Spectrum of compound **93d**

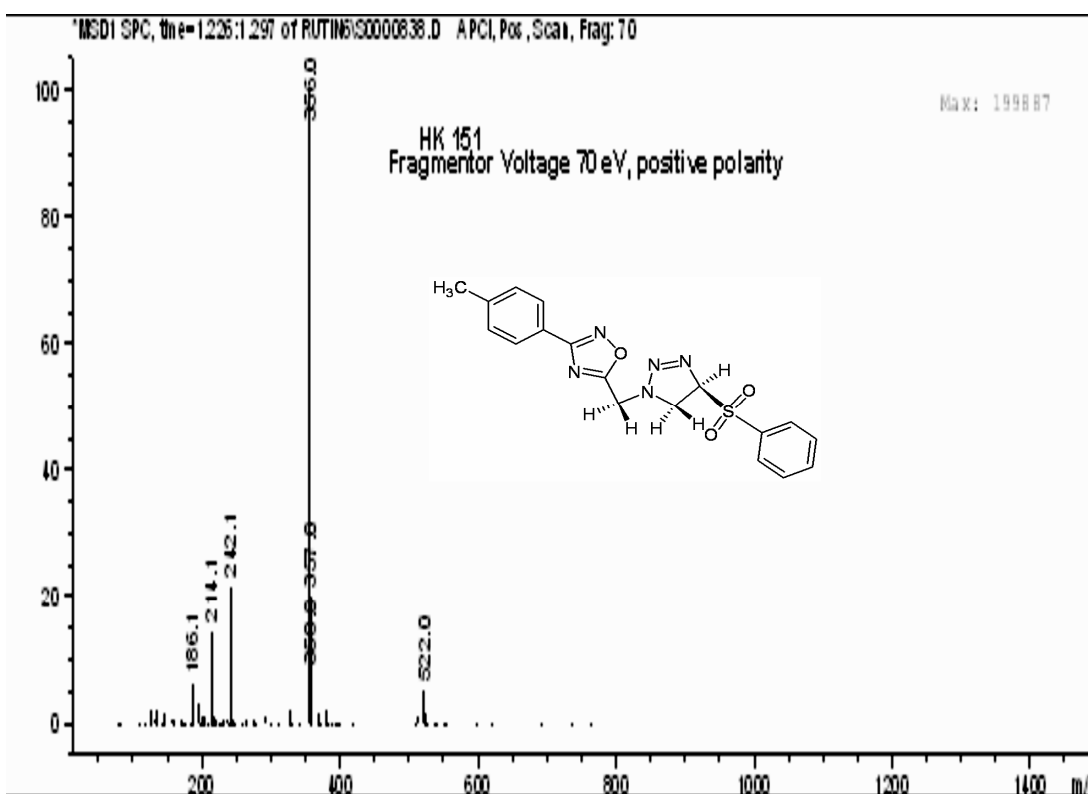


Figure 4. 162 Mass spectra of compound **93d**

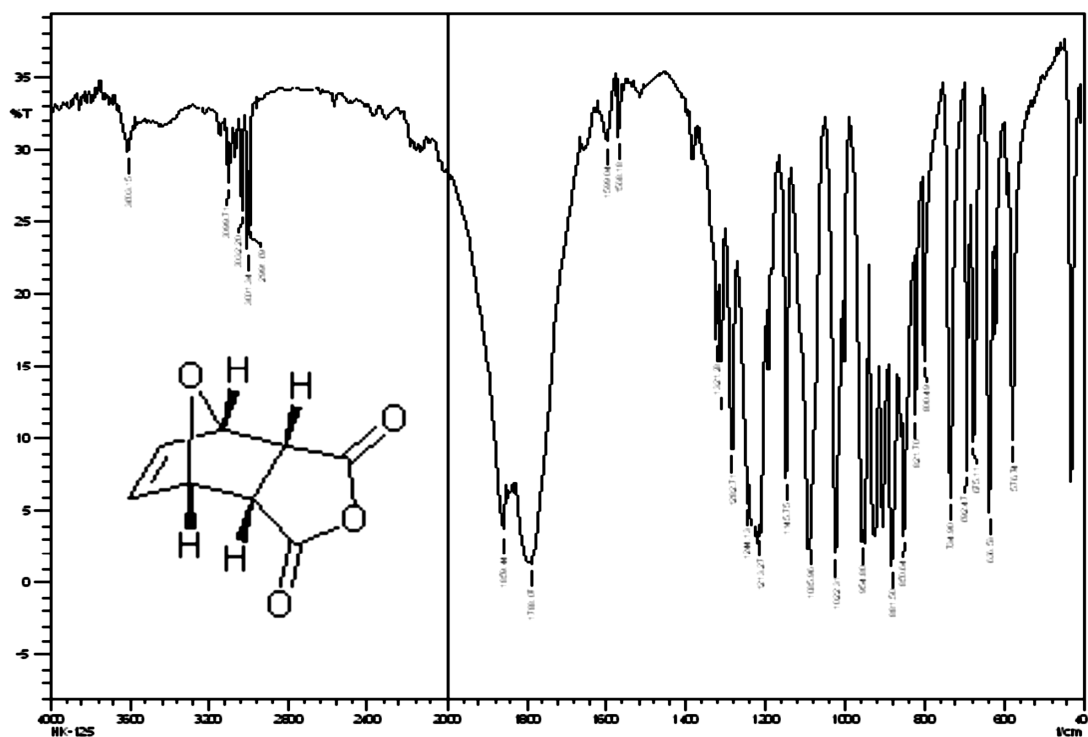


Figure 4. 163 IR spectrum of compound 94

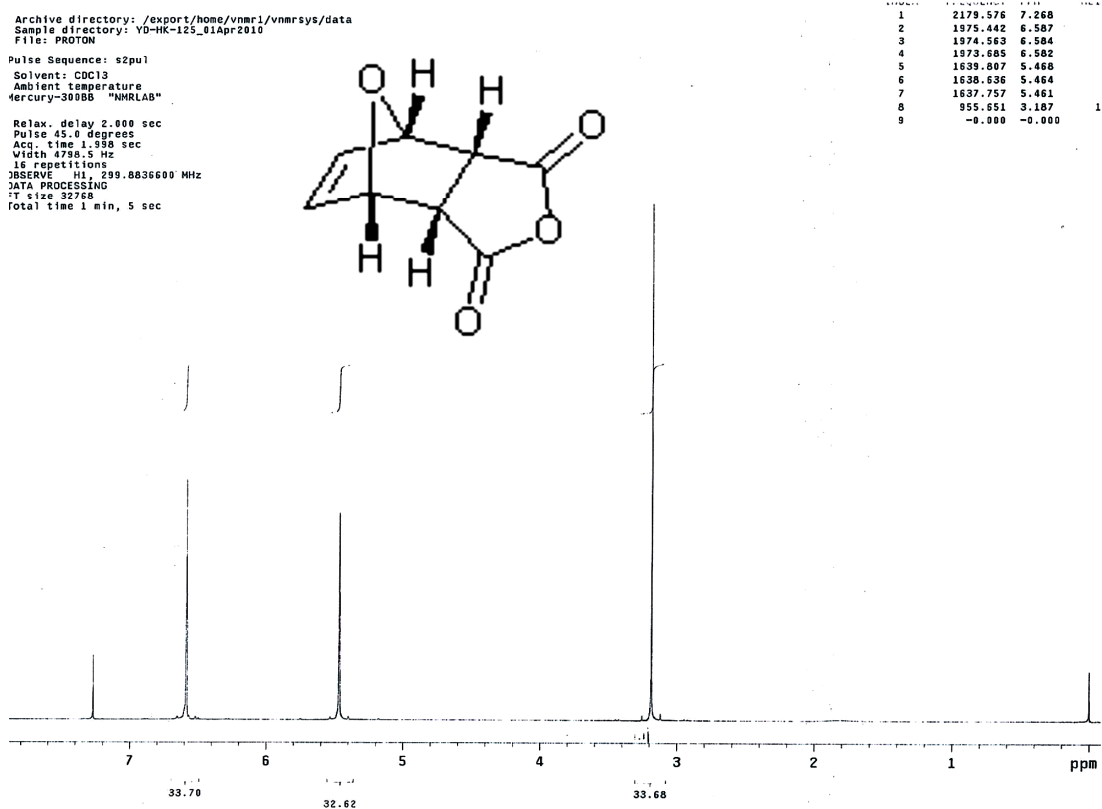


Figure 4. 164 ¹H NMR Spectrum of compound 94

Archive directory: /export/home/vnmr1/vnmrsys/data
 Sample directory: VD-HK-125-C13_91Apr2010
 File: CARBON

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
 Mercury-300MS "NMRLab"

Relax. delay 2.000 sec
 Pulse 20.0 degrees
 Acq. time 1.015 sec
 Width 18867.9 Hz
 1800 repetitions
 OBSERVE C13, 75.4057689 MHz
 DECOUPLE H1, 299.6052132 MHz
 Power 35 dB
 continuously on
 WALTZ-16 modulated
 DATA PROCESSING
 Line broadening 1.0 Hz
 T1 size 131072
 Total time 1 hr, 5 min, 14 sec

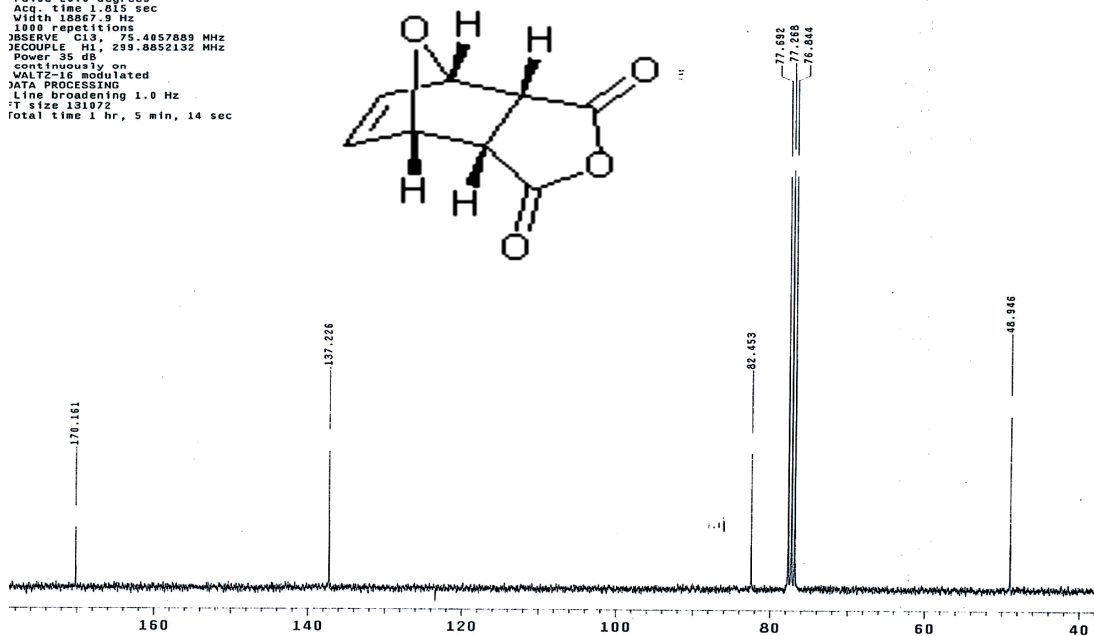


Figure 4. 165 ^{13}C NMR Spectrum of compound 94

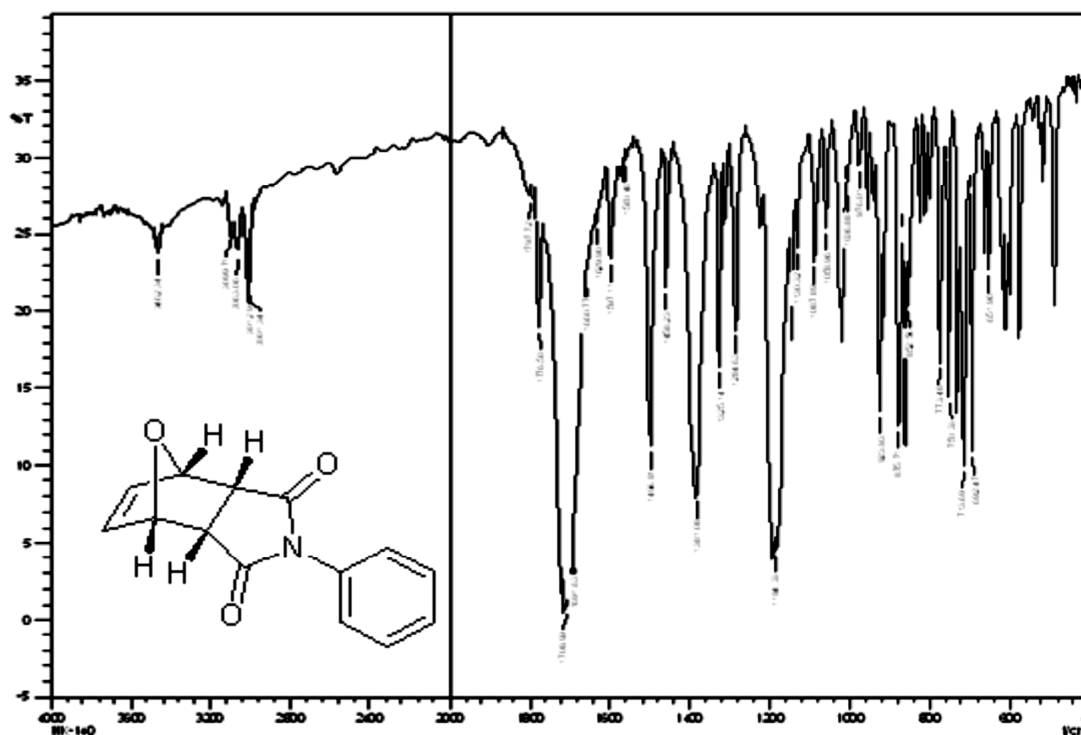


Figure 4. 166 IR spectrum of compound 95

187

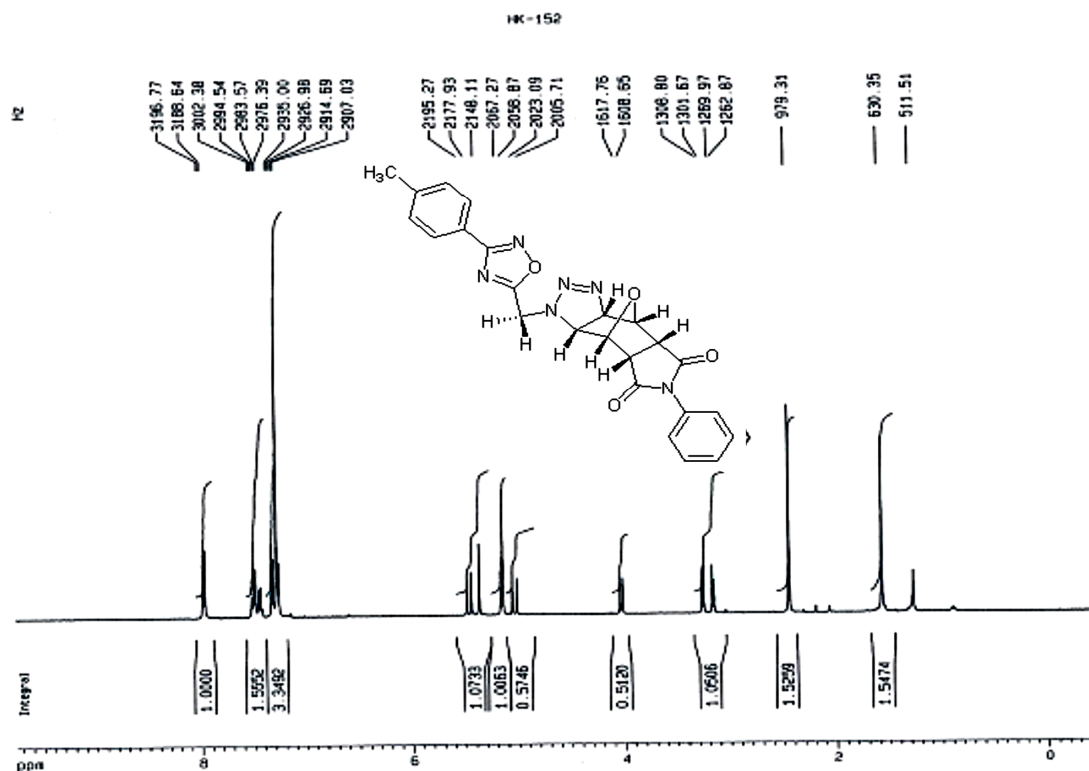


Figure 4. 169 ¹H NMR Spectrum of compound **96**

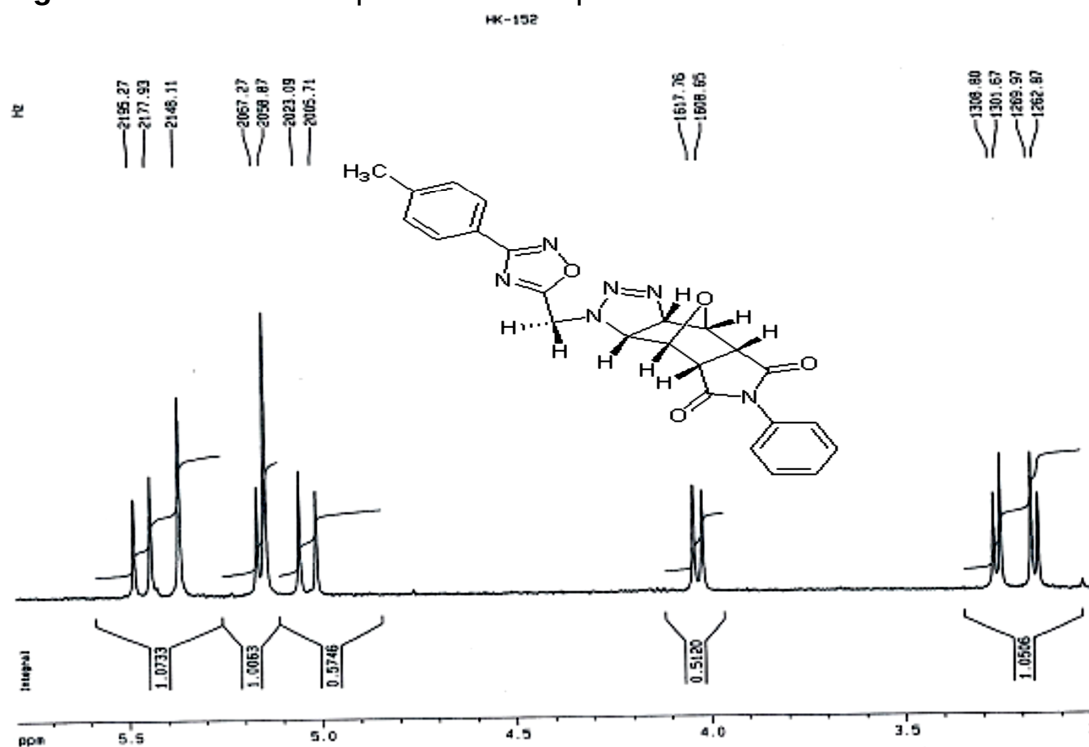


Figure 4. 170 Expanded ¹H NMR Spectrum of compound **96**

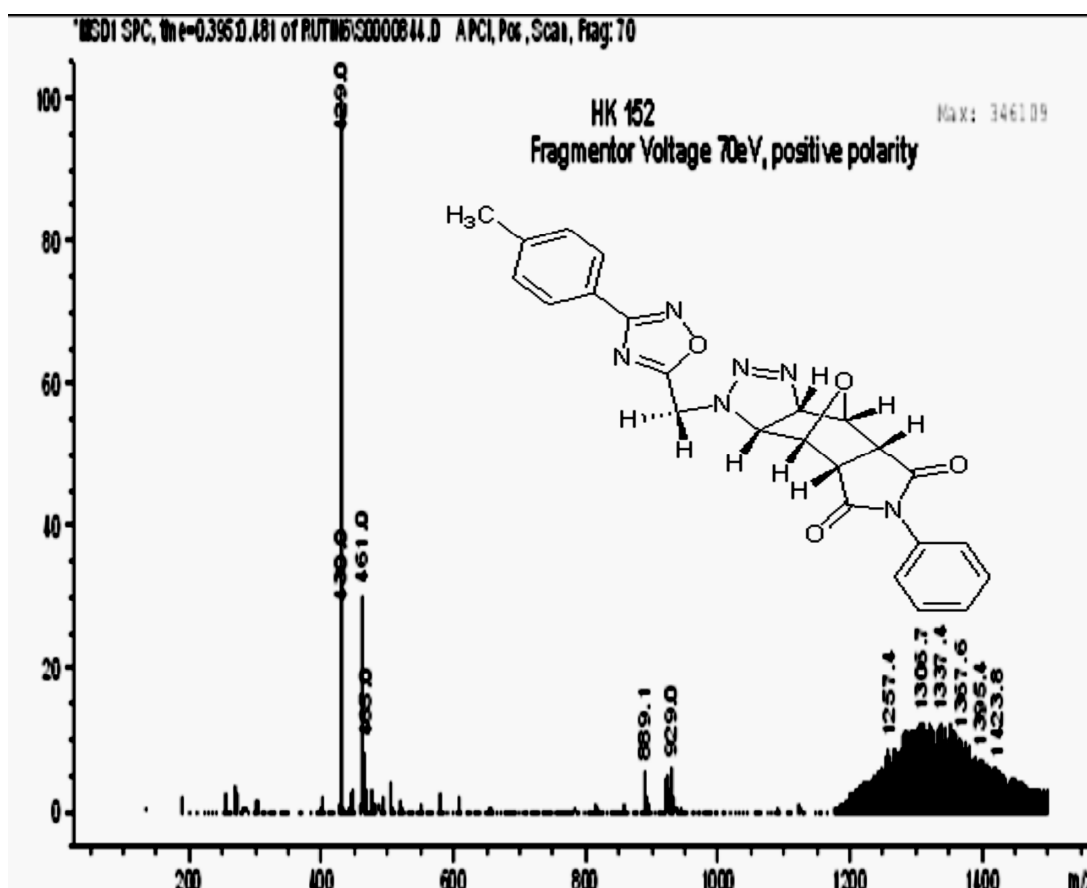


Figure 4. 171 Mass spectra of compound 96

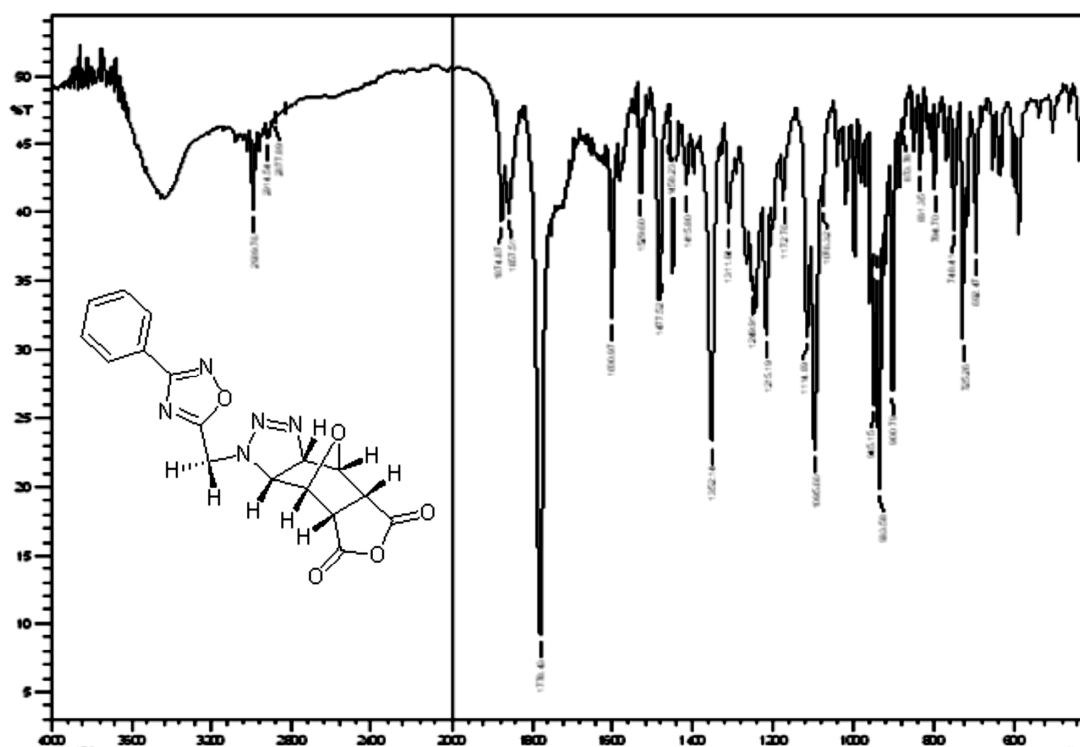


Figure 4. 172 IR spectrum of compound 97a

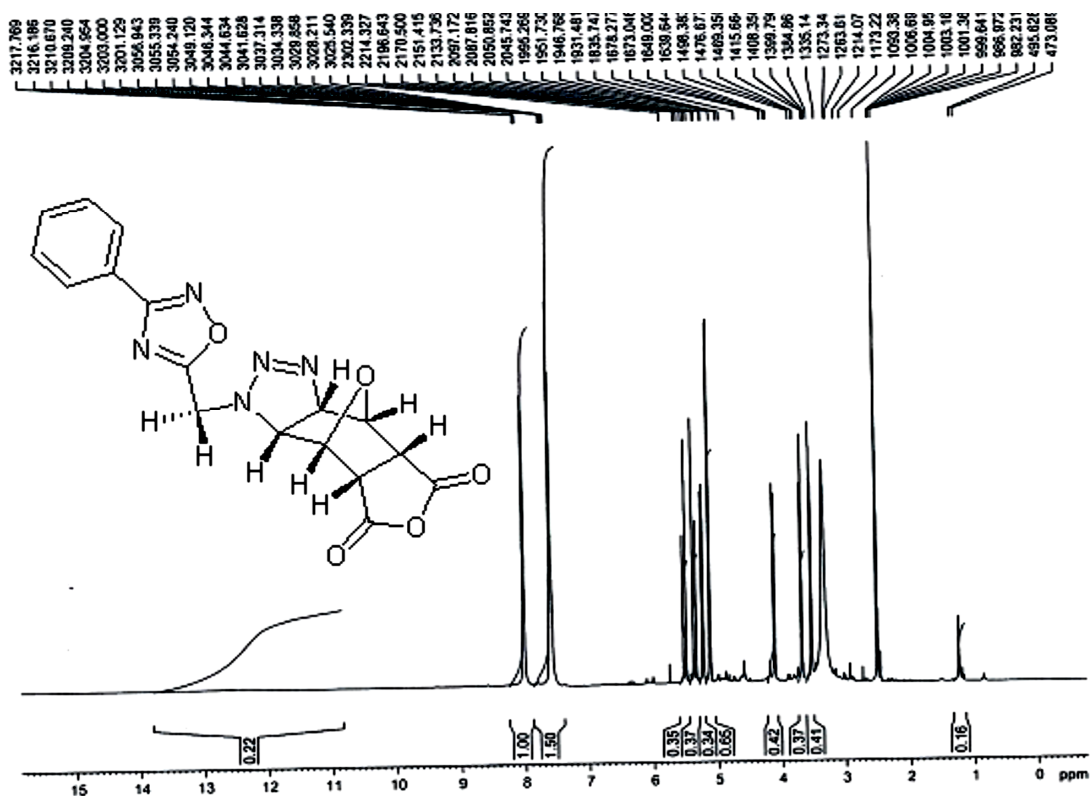


Figure 4.173 ^1H NMR Spectrum of compound **97a**

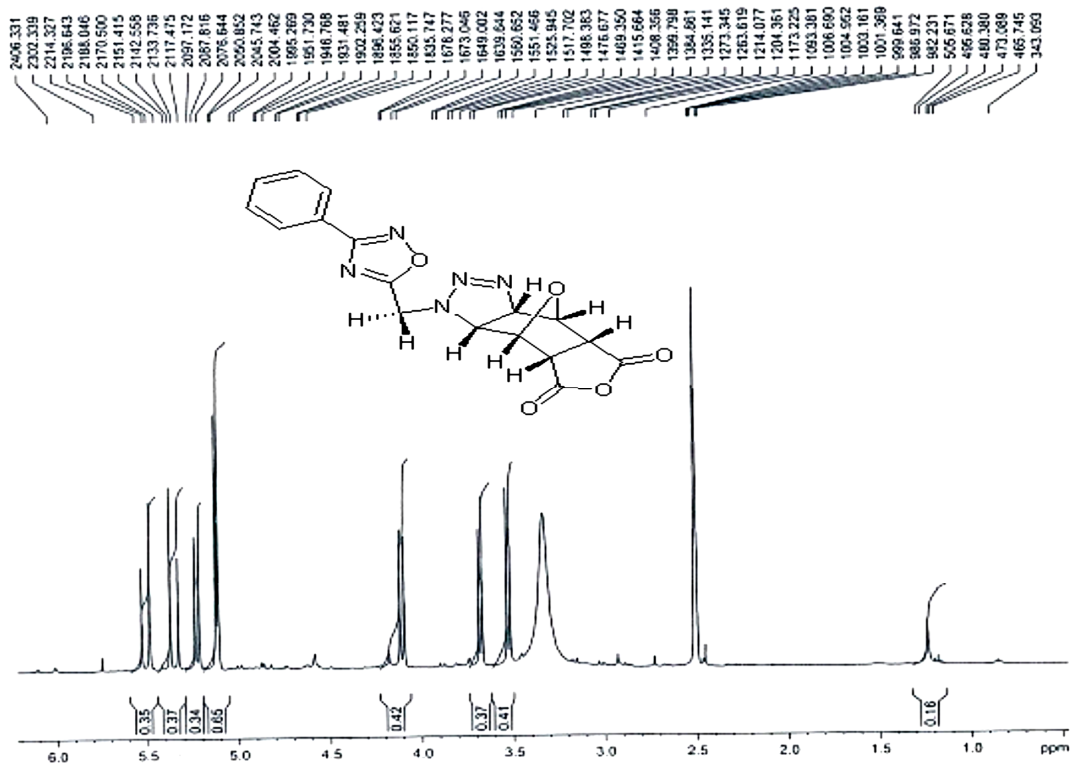


Figure 4.174 Expanded ^1H NMR Spectrum of compound **97a**

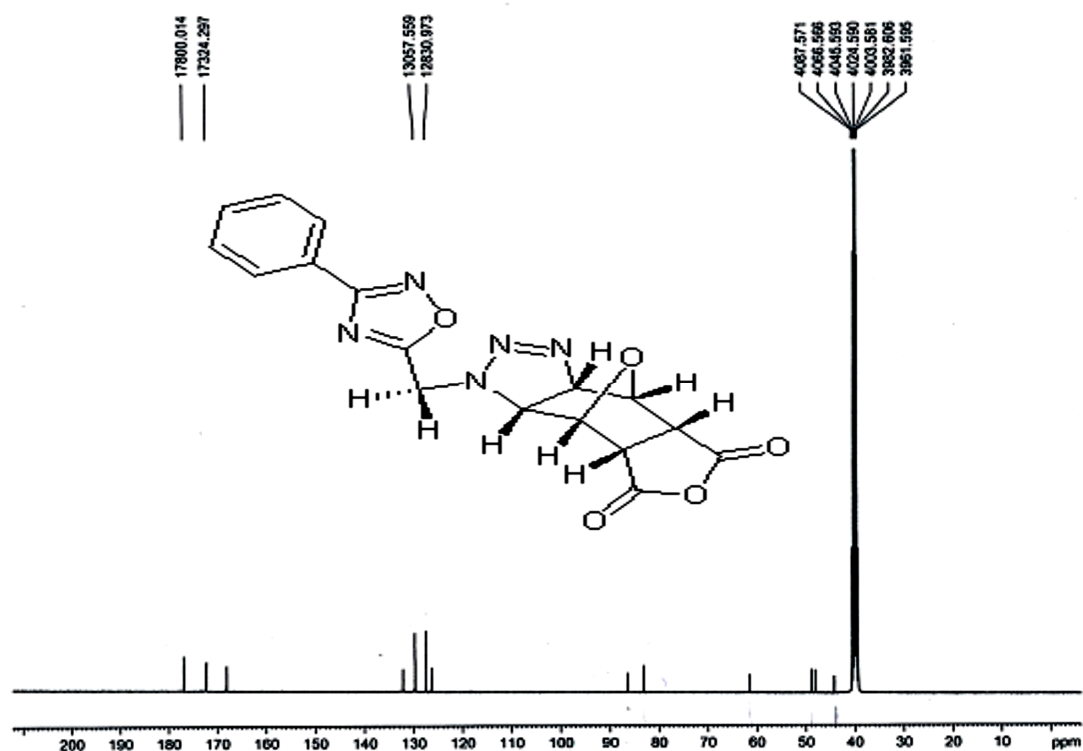


Figure 4. 175 ^{13}C NMR Spectrum of compound 97a

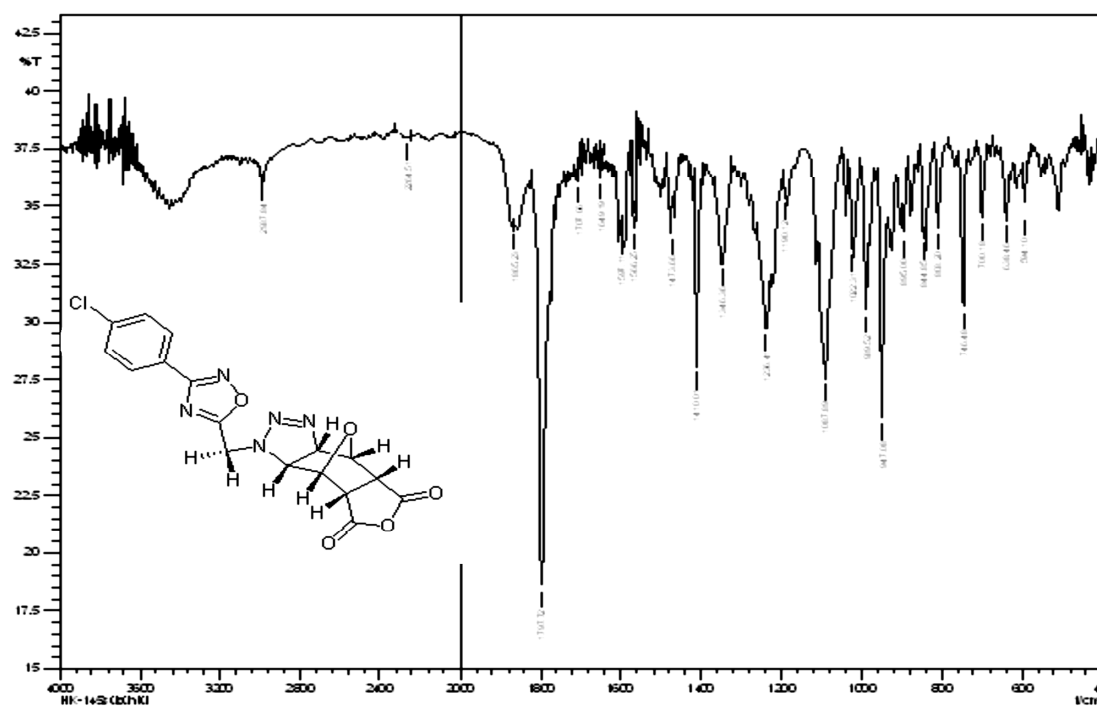
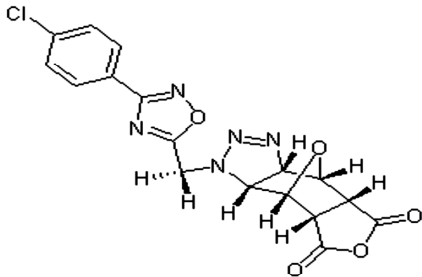


Figure 4. 176 IR spectrum of compound 97b



Chemical structure of compound 10b is shown as an inset. The structure is a complex bicyclic molecule featuring a bromophenyl group, a furan ring, and a fused bicyclic system with a carbonyl group and a hydroxyl group.

Figure 4. 178 IR spectrum of compound **97c**

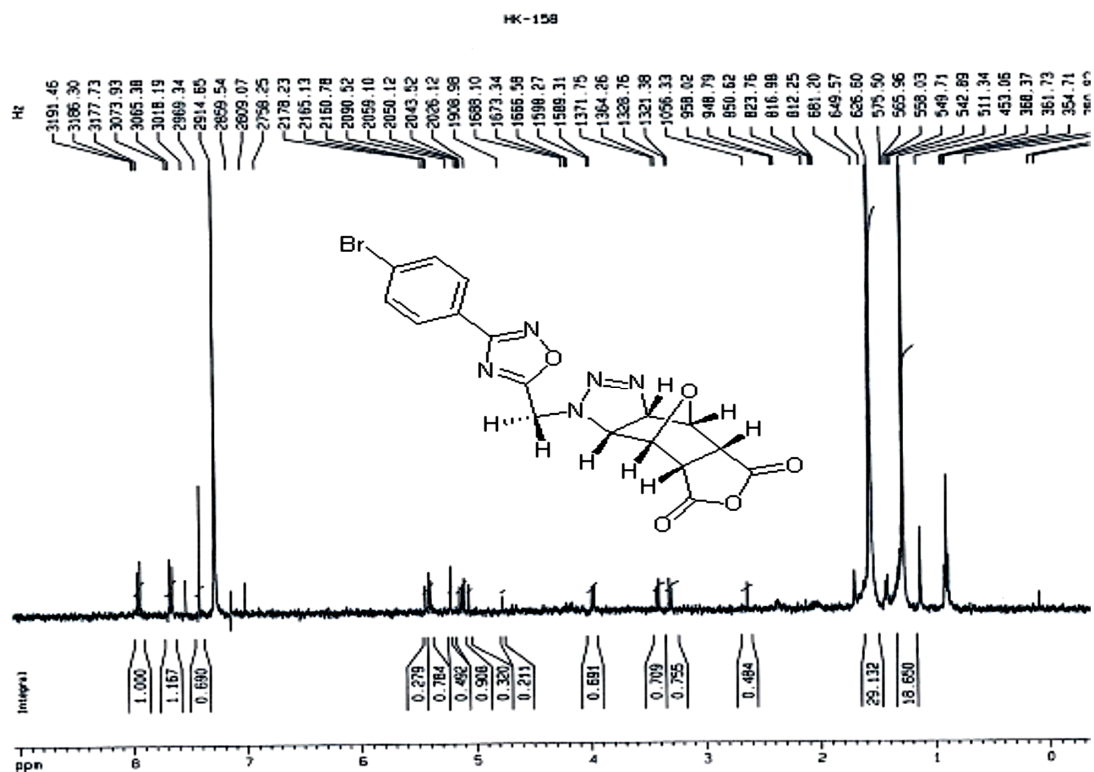


Figure 4. 179 ^1H NMR Spectrum of compound 97c

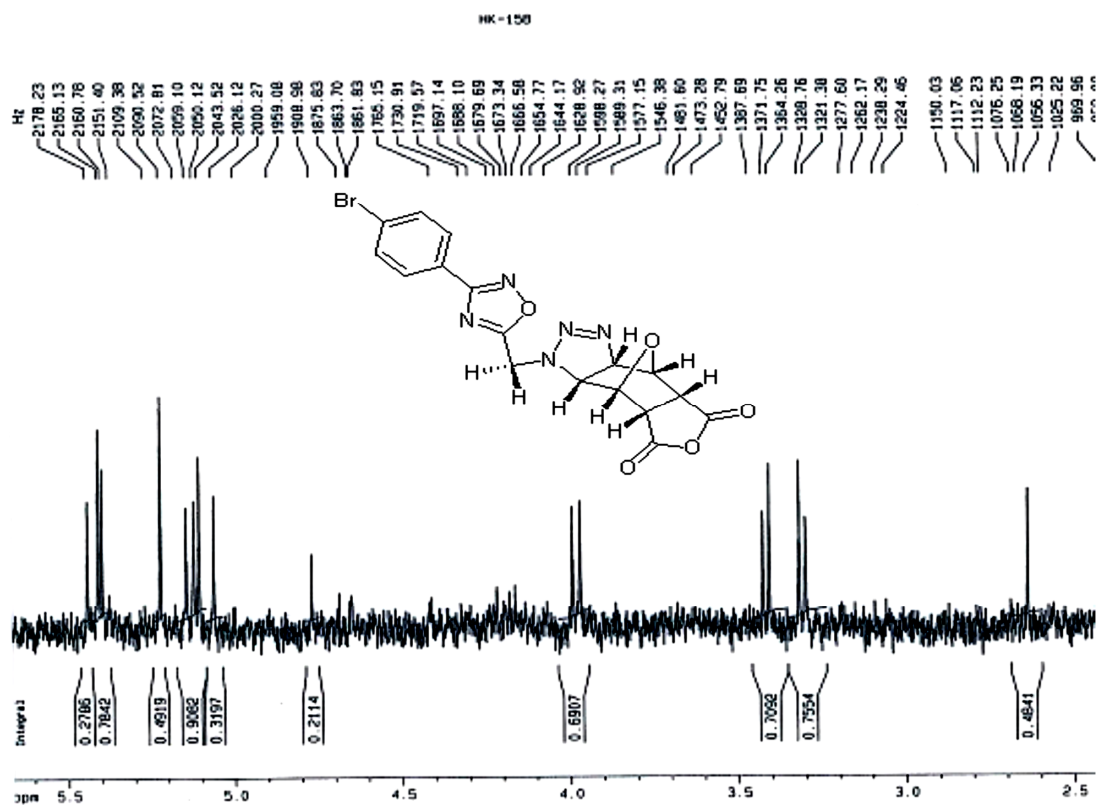


Figure 4. 180 Expanded ^1H NMR Spectrum of compound 97c

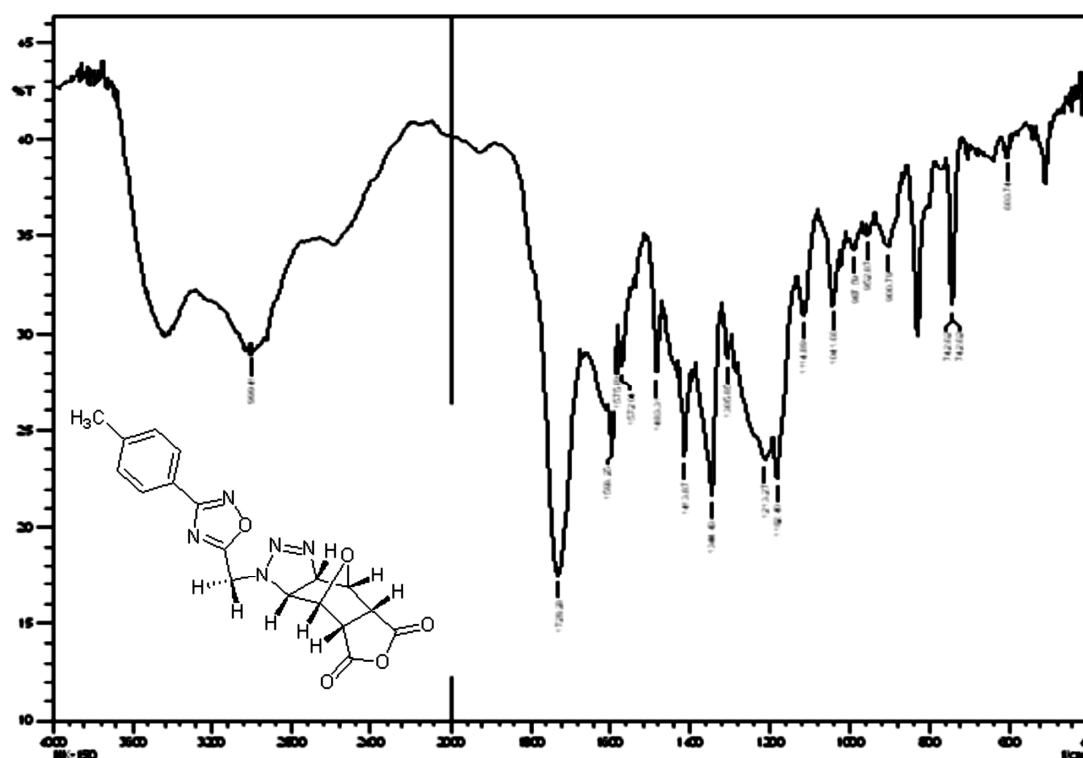


Figure 4.181 IR spectrum of compound 97d

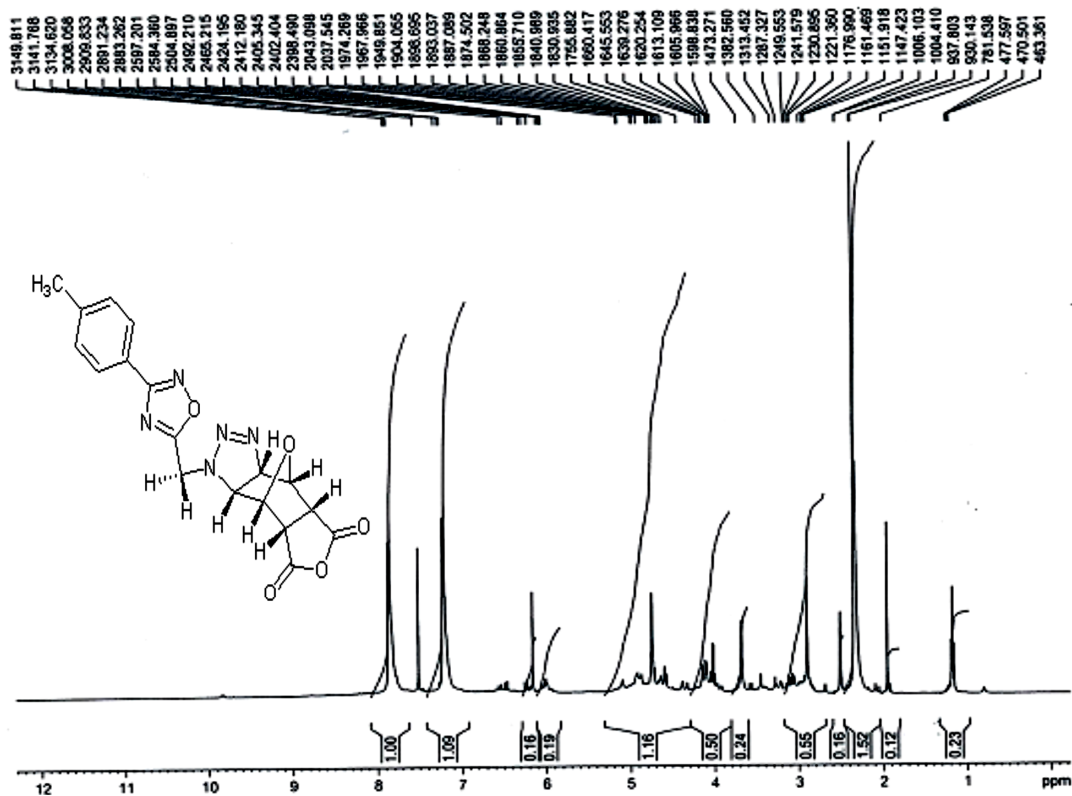


Figure 4.182 ¹H NMR Spectrum of compound 97d

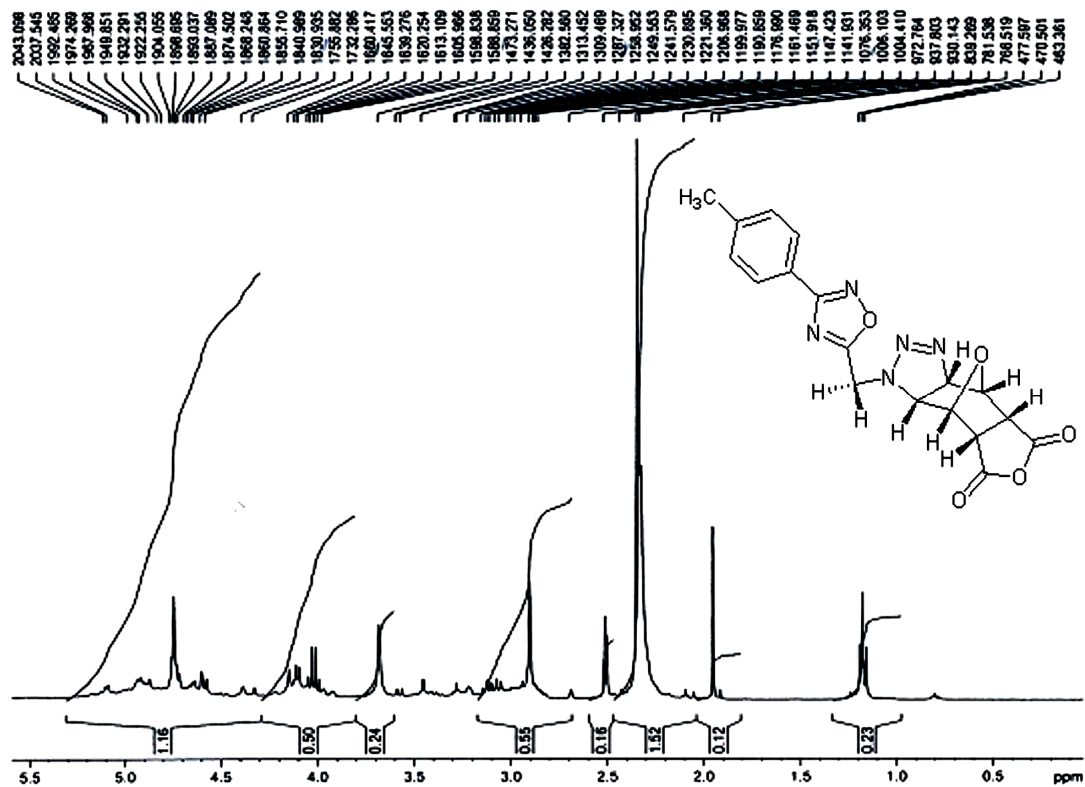


Figure 4. 183 Expanded ^1H NMR Spectrum of compound 97d