SYNTHESIS AND CYCLOADDITION REACTIONS OF SOME NEW SYDNONES CARRYING 1,2,4-OXADIAZOLYLMETHYL GROUP

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SYNTHESIS AND CYCLOADDITION REACTIONS OF SOME NEW SYDNONES CARRYING 1,2,4-OXADIAZOLYLMETHYL GROUP

by

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IN

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Approval of the Graduate School of Natural and Applied Sciences.

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Director

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

Prof.Dr.Nedime DÜRÜST

Head of Department

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

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ABSTRACT

SYNTHESIS AND CYCLOADDITION REACTIONS OF SOME NEW SYDNONES CARRYING 1,2,4-OXADIAZOLYL METHYL GROUP

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In this work, the synthesis of 5-(chloromethyl)-1,2,4-oxadiazole substituted sydnones is firstly described. Then, 5-(azidomethyl)-1,2,4-oxadiazole substituted sydnones were easily synthesized from the reaction between 5-(chloromethyl)-1,2,4-oxadiazole substituted sydnones and sodium azide in acetone/water. To best our knowledge of literature, both 5-(chloromethyl)-1,2,4-oxadiazole and 5-(azidomethyl)-1,2,4-oxadiazole substituted sydnones are novel heterocyclic compounds not known yet. Also, the 1,3-dipolar cycloaddition reactions of these 5-(azidomethyl)-1,2,4-oxadiazole substituted sydnones with dipolarophiles such as N-phenylmaleimide, phenyl vinyl sulfone and phenyl propiolic acid were performed to afford products which might be expected to exhibit biological acitivity. The structures of these novel

products were elucidated by means of IR, NMR (^{1}H, ^{13}C), Mass spectra, X-ray diffraction spectra and physical characteristics (melting points and R_f values).

Keywords: sydnone, oxadiazole, azide, triazole, pyrrole, 1,3-dipolar cycloaddition, spectroscopy

ÖZET

1,2,4-OKSADİAZOLİLMETİL GRUBU TAŞIYAN BAZI YENİ SİDNONLARIN SENTEZİ VE HALKALI KATILMA TEPKİMELERİ

Yıldız,Elif

Yüksek Lisans Tezi, Kimya Bölümü

Tez Danışmanı: Prof. Dr. Yaşar Dürüst

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Bu çalışmada, ilk olarak 5-klorometil-1,2,4-oksadiazol substitute sidnonların sentezi açıklanmıştır. Daha sonra, 5-azidometil-1,2,4-oksadiazol substitute sidnonlar 5-klorometil-1,2,4-oksadiazol substitute sidnonların ve aseton/su içinde sodyum azidin arasındaki reaksiyondan kolayca sentezlendiler. Literatür bilgimiz dahilinde, hem 5-klorometil-1,2,4-oksadiazol hem de 5-azidometil-1,2,4-oksadiazol substitute sidnonlar henüz literatürde bilinmeyen yeni heterohalkalı bileşiklerdir. Ayrıca, bu yeni 5-azidometil-1,2,4-oksadiazol substitute sidnonların N-fenil maleimid, fenil vinil sulfon ve fenil propiyolik asit gibi dipolar sevenler ile 1,3-dipolar halkalı katılma tepkimeleri biyolojik aktiflik göstermeleri beklenen yeni ürünler elde edilmesi için gerçekleştirilmiştir. Bu yeni ürünlerin yapıları IR, NMR (^{1}H, ^{13}C), kütle spektrumları,

X-ışını kırılımı spektrumları ve fiziksel sabitler(erime noktaları ve R_f değerleri) ile aydınlatılmıştır.

Anahtar Kelimeler: sidnon, oksadiazol, azid, triazol, pirol, 1,3-dipolar halkalı katılma, spektroskopi.

To my family

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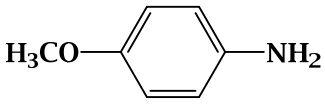
FORMULAE



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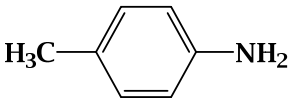

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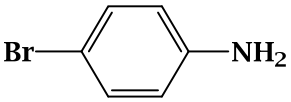

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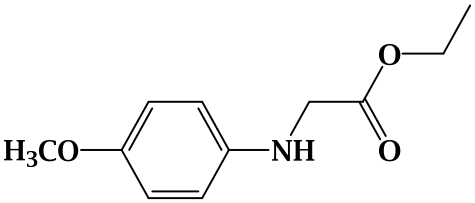

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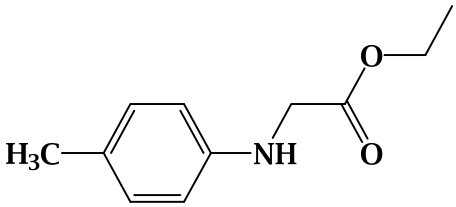

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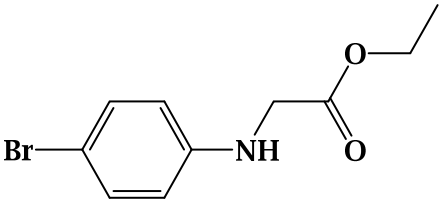

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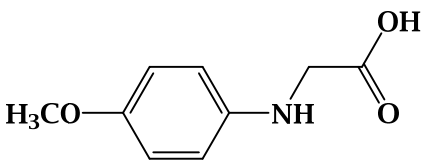

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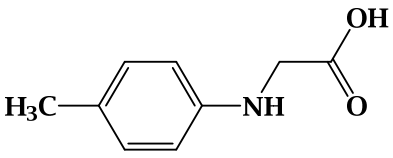

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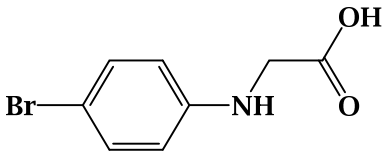

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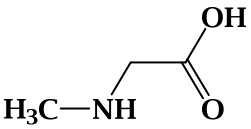

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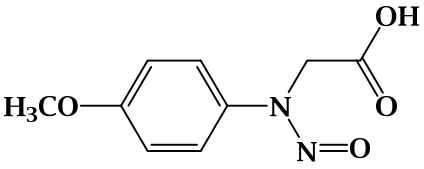

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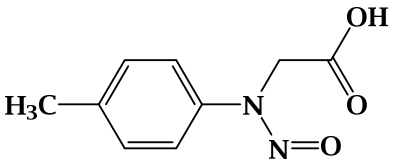

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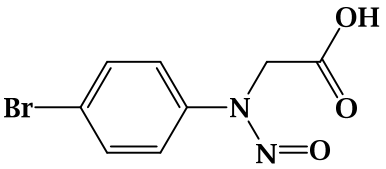

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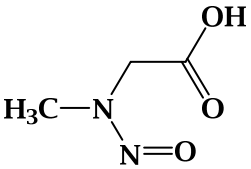

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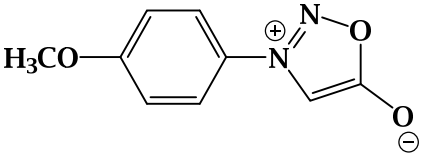

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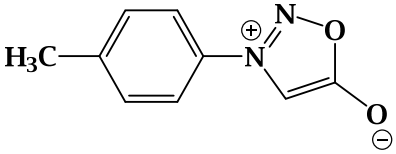

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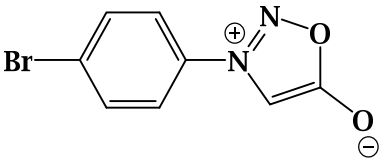

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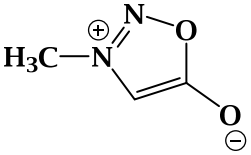

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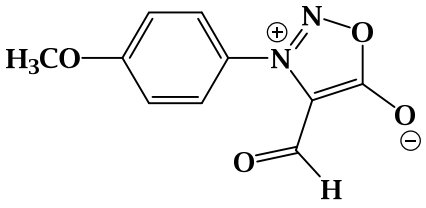

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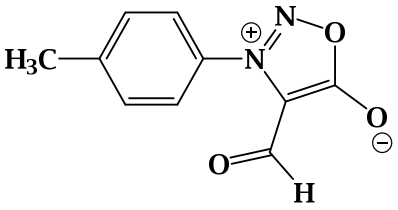

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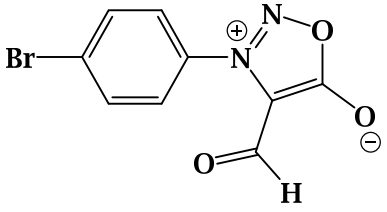

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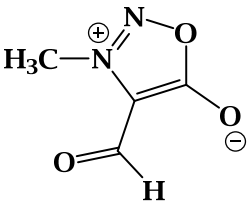

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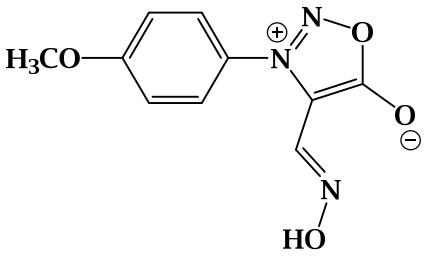

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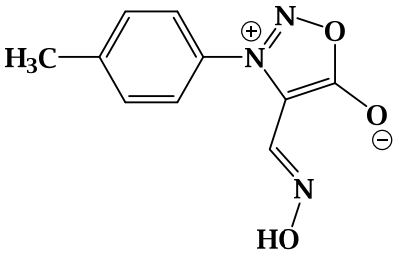

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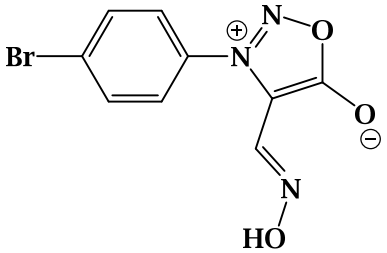

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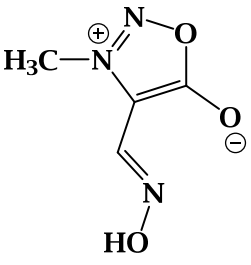

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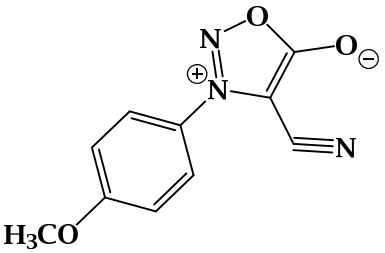

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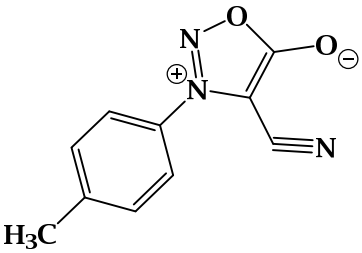

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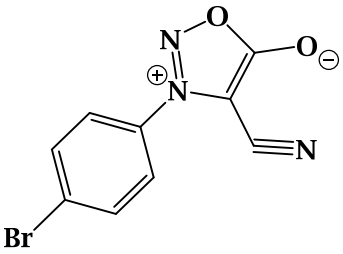

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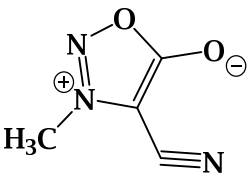

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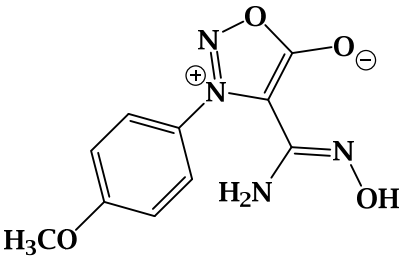

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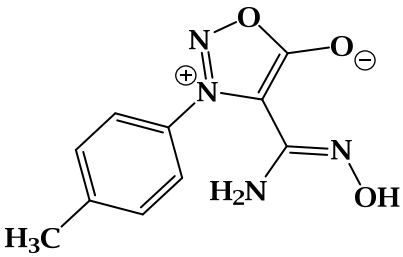

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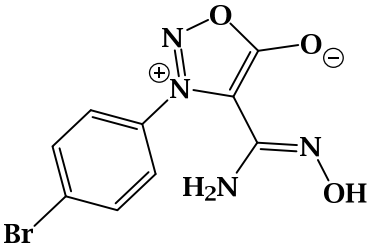

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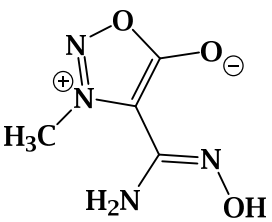

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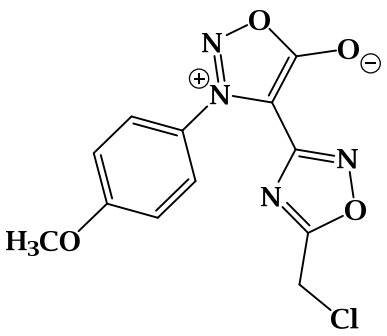

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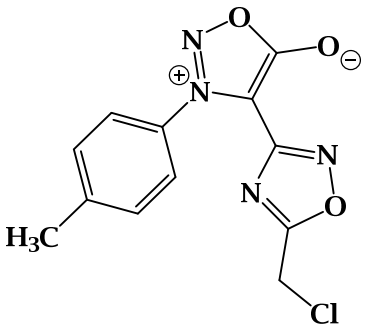

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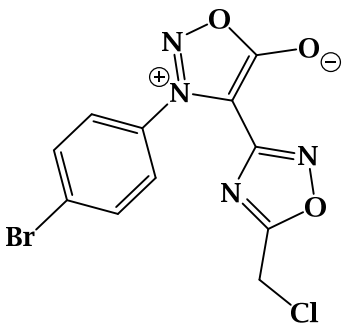

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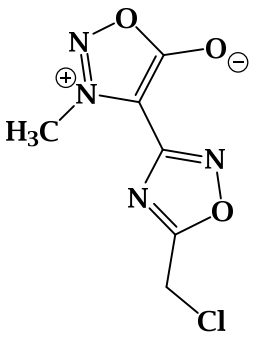

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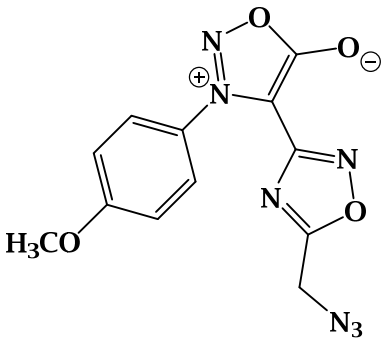

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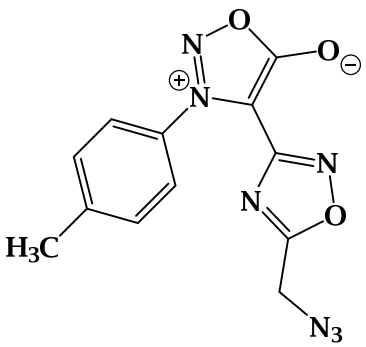

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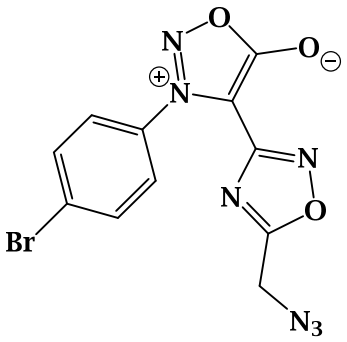

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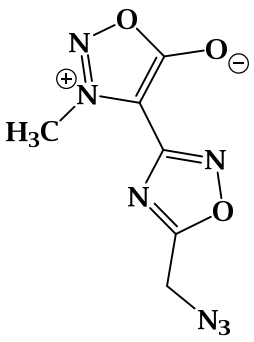

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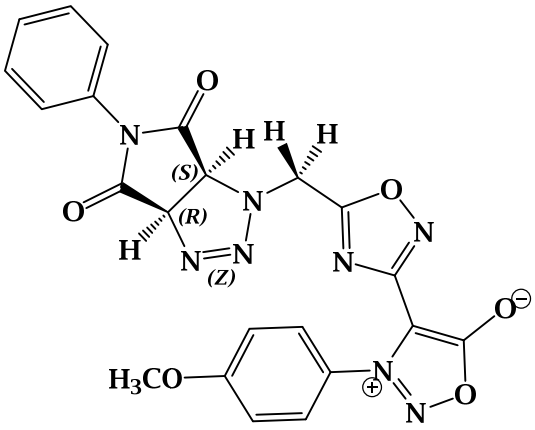

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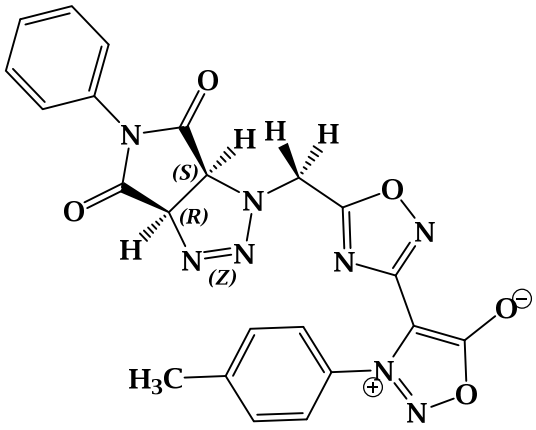

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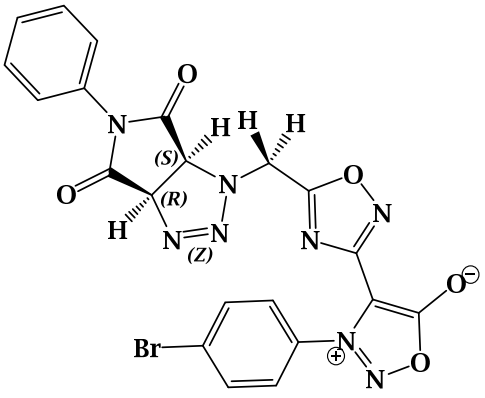

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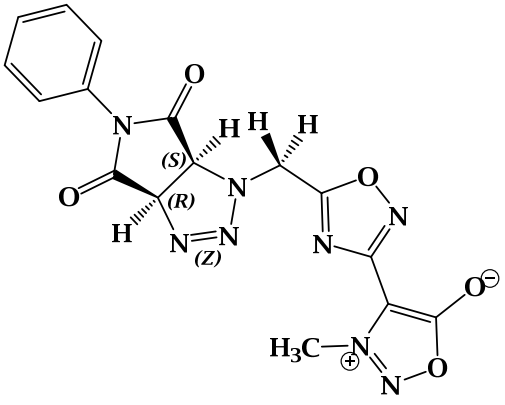

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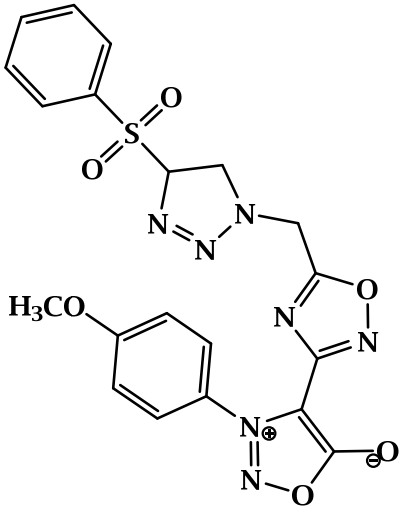

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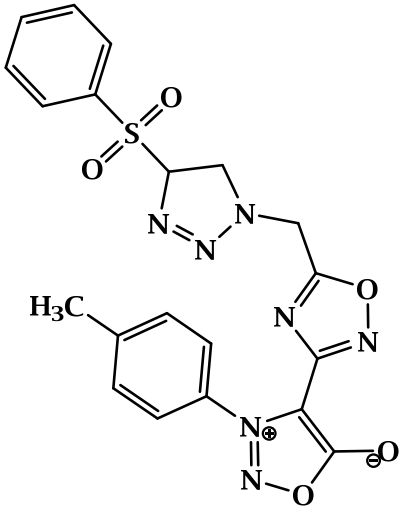

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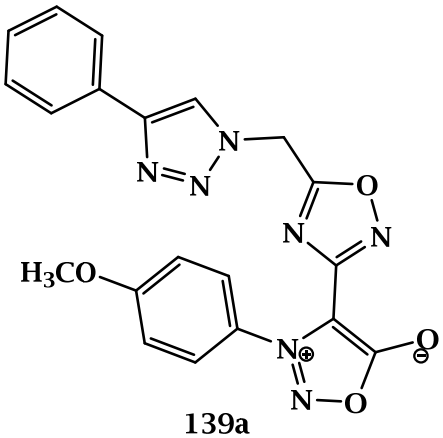

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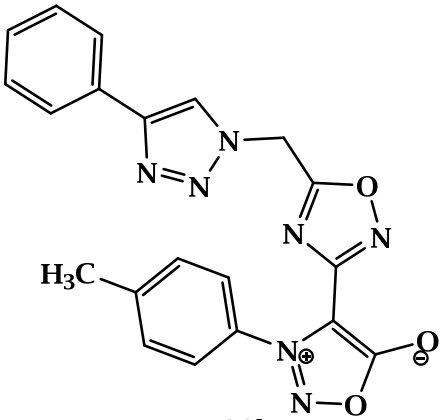

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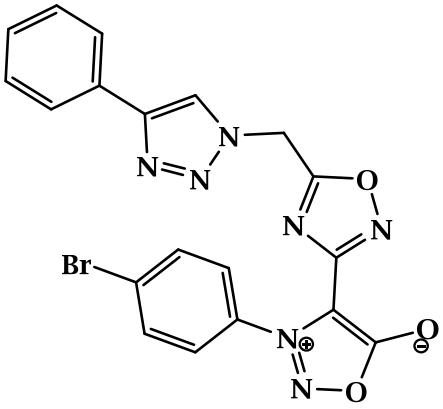

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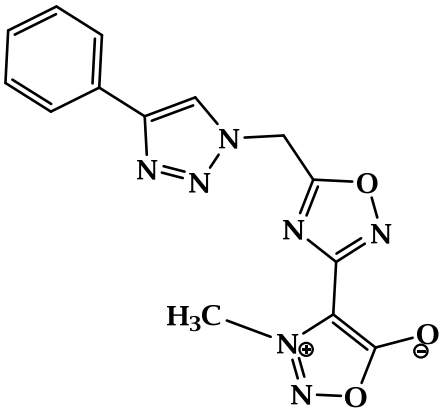

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ABBREVIATIONS

Bn- Benzyl

Ph- Phenyl

Me- Methyl

Et- Ethyl

Bu- Butyl

MeO- Methoxy

EtO- Ethoxy

p-tol- p-tolyl

Ar Aryl

Ac_2O Acetic anhydride

TFAA Trifluoroacetic anhydride

IAN Isoamylnitrite

DME Dimethoxyethane

NBS N-Bromosuccinimide

NCS N-Chlorosuccinimide

DMF N,N-Dimethylformamide

NMF N-Methylformanilide

PTSA p-Toluenesulfonic acid

LDA Lithium diisopropylamide

DMAP 4-Dimethylaminopyridine

PPTS Pyridinium p-toluenesulfonate

SAMP (S)-1-Amino-2-methoxymmethylpyrrolidine

RAMP (R)-1-Amino-2-methoxymmethylpyrrolidine

Conc. HCl Concentrated hydrochloric acid

HCl dil. Diluted hydrochloric acid

MeCN Acetonitrile

DMSO Dimethylsulfoxide

$CDCl_3$ Deuterated chloroform

CuAAC Cu(I) catalyzed azide-alkyne cycloaddition

Cat. Catalyst

r.t. Room temperature

d day

h hour

IR	Infrared Spctroscopy
UV	Ultraviolet
NMR	Nuclear Magnetic Resonance
MS	Mass
LC-MS	Liquid chromatography-mass spectroscopy
HRMS	High-resolution mass spectroscopy
R_f	Retention factor
Hz	Hertz
cm	centimetre
ppm	parts per million
J	coupling constant

CHAPTER I

INTRODUCTION

1.1. SYDNONES

Heterocyclic compounds are organic compounds containing at least one atom of carbon and at least one element other than carbon, such as sulfur, oxygen, or nitrogen within a ring structure [1].

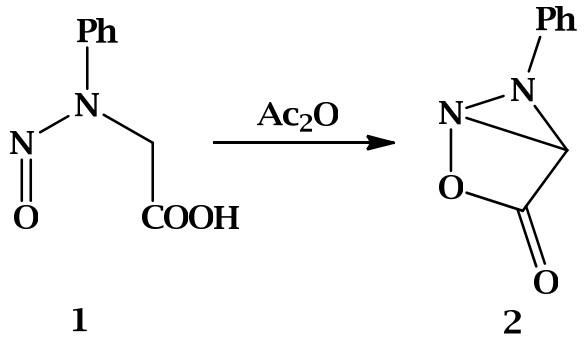
The chemistry of heterocyclic compounds is as logical at that aliphatic or aromatic in character, depending on their electronic constitution. Heterocyclic compounds are very widely distributed in nature and are essential to life in various ways. Compounds such as alkaloids, antibiotics, essential aminoacids, vitamins, hemoglobin, hormones, and a large number of synthetic drugs and dyes contain heterocyclic ring systems.

Heterocyclic compounds have a great applicability as drugs because;

i. They have specific chemical reactivity.
ii. They provide convenient building blocks to which biologically active substitutients can be attached.

Mesoionic compounds are five or six membered heterocyclic compounds in which both negative and positive are delocalized, for which a totally covalent structure cannot be written, and which cannot be represented satisfactorily by any one polar structure. The most important member of the mesoionic category of compounds is the sydnone ring system. Sydnones are mesoionic componds having the 1,2,3-oxadiazole skeleton bearing an oxgen atom attached to the 5 position [2].

Sydnones were first synthesized in 1935 by Earl and Mackney in Sydney, Australia. Earl and Mackney reported that treatment of N-nitroso-N-phenylglycine with acetic anhydride afford a light tan solid, which they named a sydnone **(Scheme 1.1)** [3].



Scheme 1.1. Synthesis of sydnones.

However, the assigned bicyclic structure **2** was met with skepticisim and was later disputed following solid arguments put forwards by Baker, Ollis and Poole [4,5]. For instance, the cyclization of the N-nitroso-N-arylgycine **1** with

acetic anhydride and the subsequent hydrolysis of the sydnones under basic conditions returned the starting N-nitroso species, a result which could not be attributed to the five-membered proposed bicyclic structure. The strained stereochemistry of the latter was also in sharp contradiction to its formation from acetic anhydride at low temperatures. The structure proposed by the three authors that later became accepted, was a monocyclic, resonance stabilized dipolar oxadiazolone derivative hybrid with many canonical forms **3a-h (Figure 1.1)** [6].

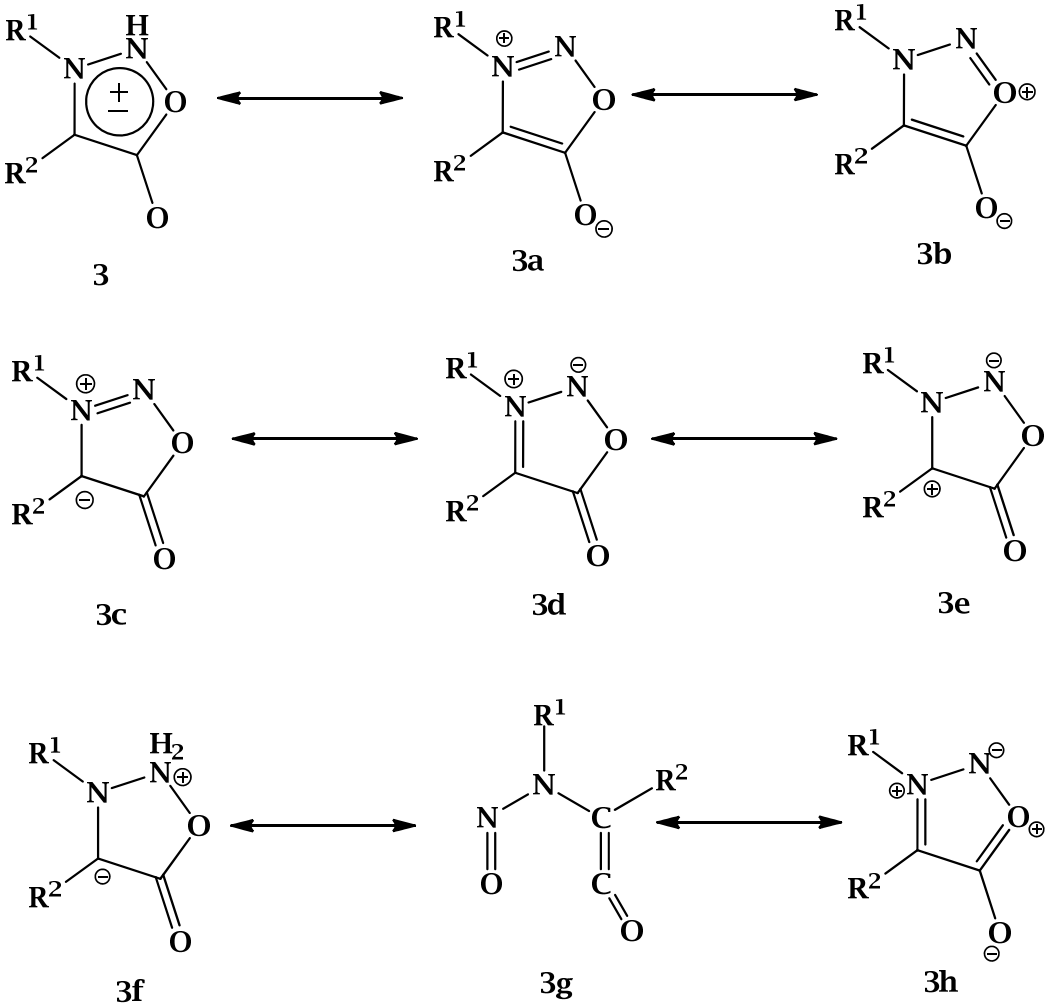


Figure 1.1. Resonance forms of sydnones.

Baker, Ollis, and Poole coined the term mesoionic (from mesomeric and ionic) to characterize the unique sydnone ring system, and since their use of the term, many more ring structure have been added to this class. In 1953, they listed general criteria for a compound to be considered mesoionic. The qualifications for a mesoionic compound are:

1. Contain fully delocalized positive and negative charges;
2. Be a planar, 5-membered heterocyclic ring with an exocyclic atom or functional group capable of bearing a considerable negative charge; and
3. Possess a considerable resonance energy [7].

The aromaticity of the sydnone ring is explained by the classical sextet theory. Total of seven $2p_z$ electrons are contributed by the five atoms of the ring with one $2p_z$ electron on the exocyclic atom **(Figure 1.2)**. The circle indicates the delocalization of six electrons which is detected as ring current by ^{1}H-NMR spectroscopy. This polarization of charges is evidenced by large dipole moments (4-6 D) for the mesoionic rings. The ring will be positively charged, balanced by the negatively charge present on the exocyclic atom [8].

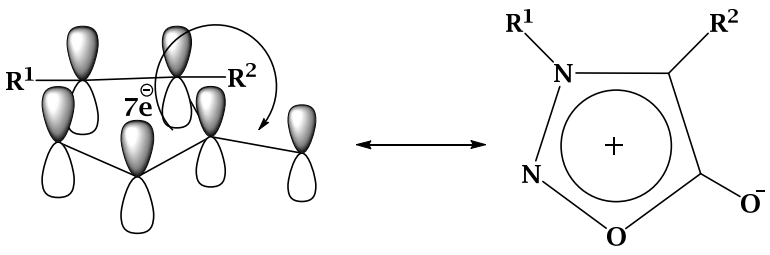


Figure 1.2. Overlap of p-orbitals in sydnone ring.

1.1.1. Physicochemical Properties and Electronic Structure of Sydnones

Sydnones are stable compounds of considerable polarity. Arylsydnones are generally solid crystals whereas alkylsydnones are usually either low melting point solids or liquids can be distilled in vacuo without appreciable decomposition. They readily dissolve in polar organic solvents but are insoluble in nonpolar solvents like hexane and ether. In water, they are generally insoluble but their solubility is enhanced when a polar functional group is presented within the molecule [6].

The infrared spectra of sydnones include two very prominent features: a strong carbonyl stretch at ~1730-1760 cm^{-1} and a stretch of medium intensity at ~ 3150 cm^{-1} for the C-H absorption of the C-4 ring proton (when present) [9-11]. Moreover, the latter is different from what would be expected for an alkyl or aryl substituent or from an epoxide with comparable ring strain, which absorb around 2900-3050 cm^{-1}, and therefore is particularly useful in determining if the C-4 position is substitued in sydnones of unresolved structure. With regard to the carbonyl stretch, a single, strong band is usually observed. However, due to Fermi resonance splitting, in some cases multiple bands have been seen. Furthermore, as stated above, the sydnone carbonyl typcially appears at ~ 1730-1760 cm^{-1} but, in comparison with congeneric carbonyl containing species such as δ-lactone **4** (which absorbs at 1770 cm^{-1}) and tropone **5** (which absorbs at 1638 cm^{-1}), one might conclude that the

exocyclic C=O bond at the sydnone C-5 position is clear in length to that of a double bond than a single bond **(Figure 1.3)** [12].

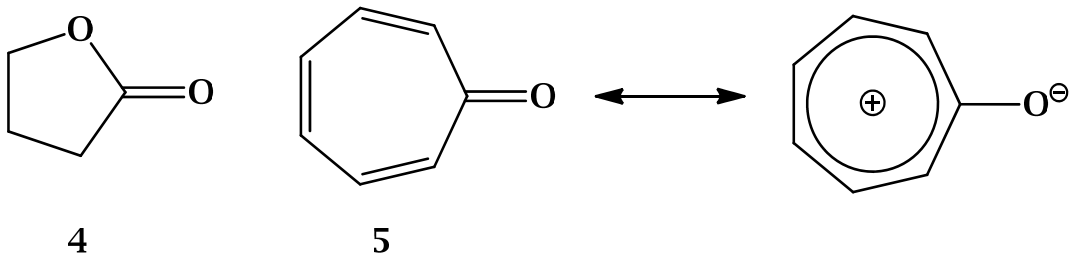


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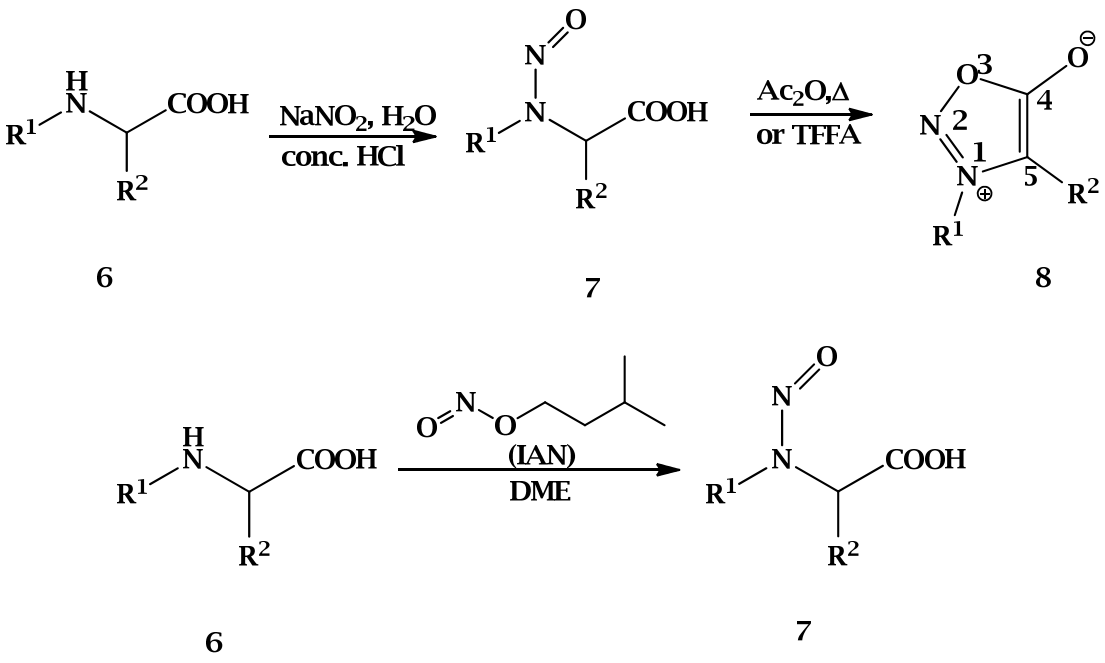
Figure 1.3. Structures of δ-lactone and tropene.

In the NMR spectra, the proton at the C-4 position, when present, is deshielded from where a typical proton would be found, appearing at 6.8 ppm. The sydnone has two distinctive peaks appearing in the carbon NMR at 165 ppm for the C-5 carbon and at about 95 ppm for the unsubstituted C-4 carbon [13].

1.1.2. Synthesis of Sydnones

Classically, sydnones are synthesized in just two steps from *N*-substituted amino acids **6**. *N*-nitrosation followed by cyclodehydration generally furnishes the mesoionic products in good-to-excellent yields. Whilst this is the most common method, several improvements or alternatives have been introduced. Of particular note, the employment of trifluoroacetic anhydride(TFFA) has superseded the use of acetic anhydride, largely due to an increased rate of cyclisation [14]. Turnbull et al. have described nitrosation

using isoamyl nitrite (IAN) for acid sensitive starting materials **(Scheme 1.2)** [15].



Scheme 1.2. Synthesis of sydnones.

1.1.3. Chemical and Biological Behavior of Sydnones

Given the interesting structural characteristics of the sydnone system, a focused effort has been made to illustrate the fact that the sydnone ring exhibits a distinct aromatic nature and dichotomy in electronic effects. A fundamental property of any aromatic system is to undergo electrophilic aromatic substitutions. It has been shown that sydnones do undergo electrophilic substitution at the C-4 position of the ring (with e.g **8,** R^2=H) [16]. Such reactions include halogenation, nitration, acylation, and sulfonation. The unexpectedly high regioselectivity of these reactions (even when an aryl

group is attached to the N-3 position) is a result of two major contributing factors:

1. the considerable partial negative charge that resides at the C-4 position appears to activate this position; and
2. the considerable partial positive charge that resides at the N-3 position seems to deactivate the attached aryl ring. However, in the case where activating groups are attached to the aryl ring, the aryl ring moiety can compete successfully for the electrophile, a premise observed for both halogenation and nitration [17].

Sydnones are also useful precursors to hydrazines [3], and can be utilized as 1,3-dipoles in cycloaddition reactions [18,19]. They can be used as electrolytic solvents for non-aqeous batteries [20] and facilitate micelle production in molecular aggregation [21]. However, even though sydnones have many potential applications, most researchers have been motivated by their potential biological applications. These include their potential use as antifungal, anti-inflammatory [22], analgesic, antibacterial, and anti-tumor prodrugs [23]. In addition; sydnones have liquid crystal properties [24], have been incorporated into azodyestuffs [25] and have been experimentally tested for use as lithium battery electrolytes.

1.1.4. Reactions of Sydnones

A majority of the reactions performed on the sydnone ring take place at the C-4 position. The hydrogen at the C-4 position is acidic with a pK_a at about 18-20. The C-4 position is also considered to be nucleophilic. This allows two main reactions to take place at the C-4 position:

1. electrophilic aromatic substitution or

2. deprotonation followed by electrophilic addition. Further, other major transformations that can take place with the sydnone ring are treatment with acid to form a hydrazine and 1,3-dipolar cycloaddition [25].

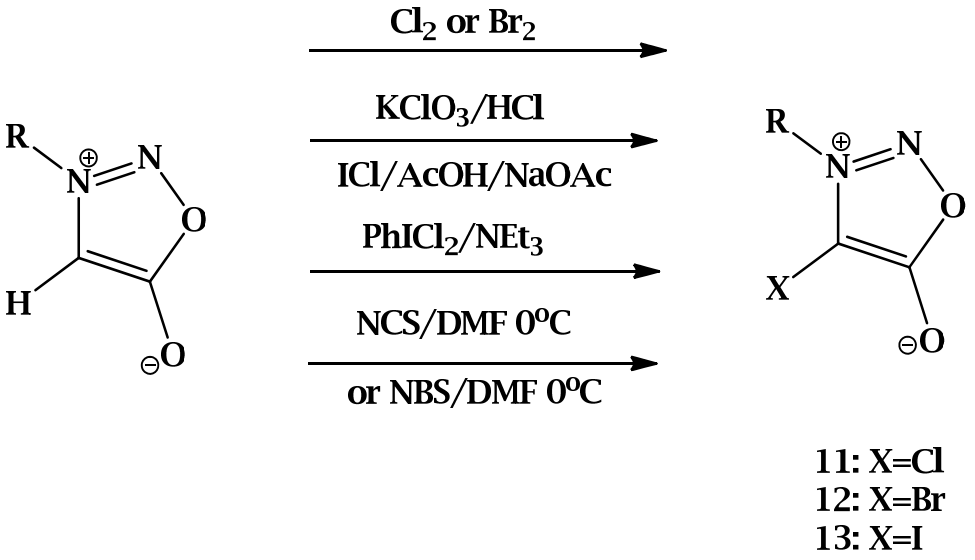
1.1.4.1. Electrophilic Aromatic Substitution

Sydnones can undergo electrophilic aromatic substitution at the C-4 position when there is a proton at this position (**8**, R^2=H). The electrophiles typcially used for aromatic substitution can also be employed with the sydnones due to the considerable negative charge density at the C-4 position [12]. Halogenation, nitration, acylation, carboxamidation, sulfonation, and formylation will be discussed in the following pages.

1.1.4.1.1. Halogenation of Sydnones

Sydnones **10** undergo halogenation at the C-4 position by a variety of different methods. Chlorination of sydnones to form the corresponding 4-

chloro species **11** has been performed by treatment **10** with chlorine [26-28], potassium chlorate in moderately concentrated HCl [29], dichloroiodobenzene with triethylamine[30], or N-chlorosuccinimide (NCS) [31]. Bromination at the C-4 position to form the corresponding 4-bromo species **12** has been achieved by treatment of **10** with bromine[26-28], potassium bromate in HBr, or N-bromosuccinimide (NBS) [31]. Iodination of **10** to form the corresponding 4-iodo species **13** is much less common but can be achieved by using iodine monochloride in acetic acid at room temperature **(Scheme 1.3)** [32].



Scheme 1.3. Halogenation of sydnones.

It has been shown that debromination at the C-4 position can be achieved by the use fo sodium borohydride or sodium dithionite in methanol [33] or activated zinc under ultrasonification [34]. However, several drawbacks associated with debromination by these methods including (1) the reactivity of sodium borohydride with pendent functional groups (e.g. carbonyl

compounds); (2) the effects of steric factors with the use of sodium dithionite; and (3) the in efficiency of the ultrasonification method when strong electron-withdrawing groups are present. The use of sodium sulfite is the preferred method for the bromination at the C-4 position, as it exhibits none of the drawbacks previously listed [35]. Due to the ease with which the sydnone ring can be brominated and debrominated, it has postulated that having the bromine at the C-4 position can serve as a protecting group for the sydnone ring [36].

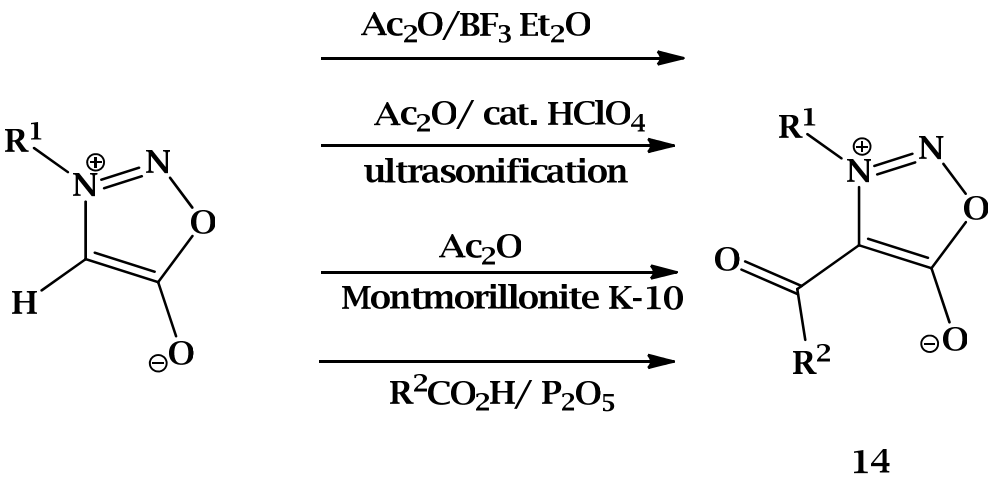
1.1.4.1.2. Nitration of Sydnones

Very little research has been done on the nitration of sydnones owing to the strongly acidic conditions required for this reaction. However, 3-phenylsydnone (**8**; R^1= Ph, R^2= H) reacts with potassium nitrate in the presence of sulfuric acid at -5^oC to yield a relatively unstable 4-nitro derivative **8** (R^1=Ph, R^2=NO_2) in modest yield [37, 6].

1.1.4.1.3. Acylation Of Sydnones

Yashunskii[38] was the first to acylate at the C-4 position of the sydnone ring to obtain 4-acetyl derivative **14** (R^1=Ph, R^2=Me) by the reaction of 3-phenylsydnone with acetic anhydride and boron trifluoride etherate[39]. Acetic anhydride and $HClO_4$ or H_3PO_4 were shown by Tien and co-workers to effect acetylation to form various substituted sydnones[40]. Using a different approach, Greco and co-workers were able to obtain the desired acylated

sydnones **14** by heating various substitued sydnones with an alkyl or aralkyl carboxylic acid in the presence of P_2O_5 **(Scheme 1.4)** [41].

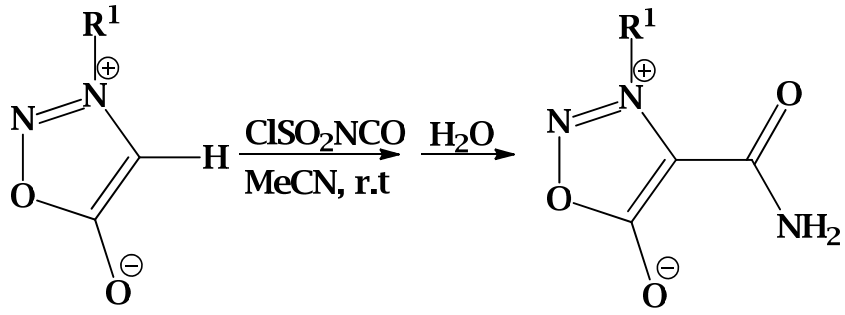


Scheme 1.4. Acylation of sydnones.

More recently, two improved routes to the 4-acyl derivatives heve been developed by Tien and co-workers [42] and Turnbull and co-workers [43]. First, in the presence of acetic anhydride and a catalytic amount of perchloric acid, ultrasonification of a 3-substituted sydnone led to the 4-acetyl derivative **14**. The use of ultrasonification improves safety by lowering the amount of perchloric acid needed. In the second method, 4- acetyl derivetives of 3-substitued sydnones **14** were obtained via the use of acetic anhydride and a catalytic amount of Montmorillonite K-10 at elevated temperatures [43]. This method is preferred due to the easy removal and disposal of the catalyst. However, with compounds containing electron-withdrawing groups ortho to the sydnone ring, this method proved to be sluggish or unsuccessful [44].

1.1.4.1.4. Carboxamidation of Sydnones

In the past, 4-carboxamido sydnone species **15** have been made by a multiple step process involving abstracting the sydnone ring proton with butyllithium, treatment with carbondioxide and subsequent conversion to the acid chloride followed by reaction with ammonia. In recent years, a new method of carboxamidation at the C-4 position has been developed. By use of chlorosulfonyl isocyanate in acetonitrile at room temperature, Turnbull, Gross and Hall prepared 4-carboxamido sydnones **15** in good yields, directly from a variety of 3-substituted sydnones **(Scheme 1.5)** [45].



15

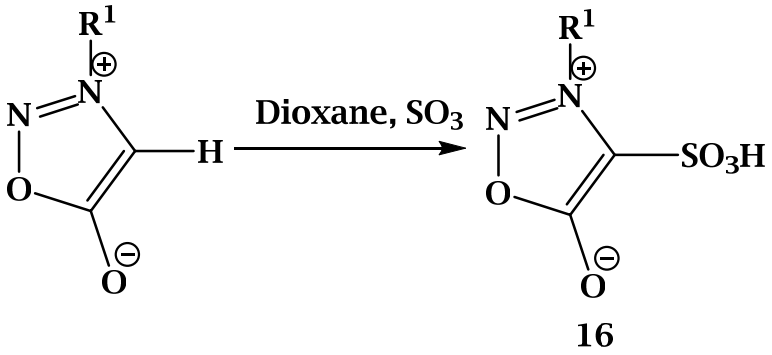
R^1= Ph, 3-$MeOC_6H_4$, 4-ClC_6H_4, 2,3-$Me_2C_6H_3$

Scheme 1.5. Carboxamidation of sydnones.

1.1.4.1.5. Sulfonation of Sydnones

In 1959, Yashunskii and co-workers showed that treatment of sydnones with dioxane-sulfur trioxide complex (SO_3) in CH_2Cl_2 at 20°C to 40°C, generated the sulfonated derivatives **16** (R^1= 4-MeO, or 4-$EtOC_6H_4$) **(Scheme 1.6)** [46]. Since all attempts to prepare these compounds as free sulfonic acids were

unsuccessful, these sulfonated derivatives were characterized as the barium or S-benzylthiuronium salts.



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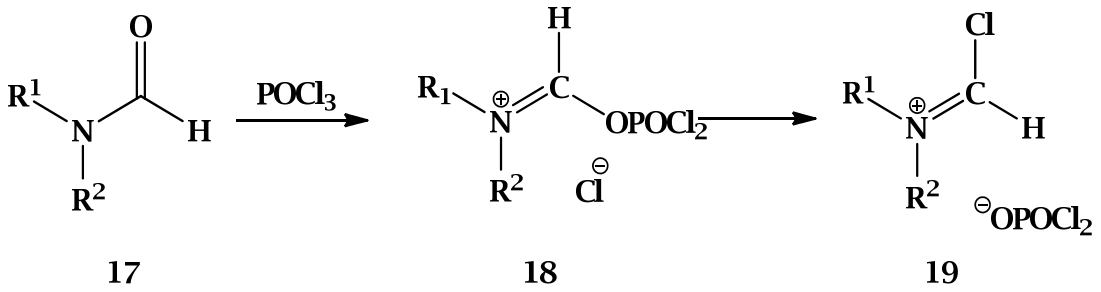
Scheme 1.6. Sulfonation of sydnones.

1.1.4.1.6. Formylation of Sydnones

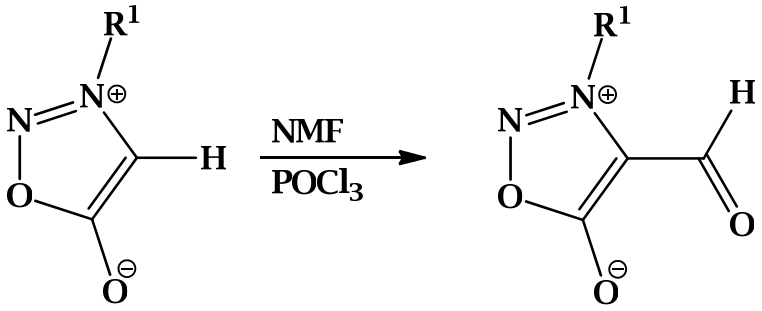
In 1927, Vilsmeier and Haack observed that *N*-methylforrmanilide can formylate aniline derivatives in the presence of $POCl_3$ [47]. Later, the reaction was extended using simple formamide derivatives like *N,N*-dimethylformamide, *N*-formylpiperidine, *N*-formylmorpholine etc. To formylate electron rich aromatic and aliphatic substrates, and these types of reactions are known as Vilsmeier-Haack reactions [48]. A Vilsmeier-Haack reagent **19** is produced when a disubstituted formamide or amide, typically *N,N*-dimethylformamide is treated with an acid halide, frequently phosphorous oxychloride, though to a lesser extent, oxalyl chloride **(Scheme 1.7)** [49].



17 18 19

Scheme 1.7. Vilsmeier-Haack reagent.

Thoman and co-workers synthesized 4-formyl-3-substituted sydnones **20** from direct formylation of 3-substituted sydnones by the Vilsmeier-Haack reaction **(Scheme 1.8)** [49].



20

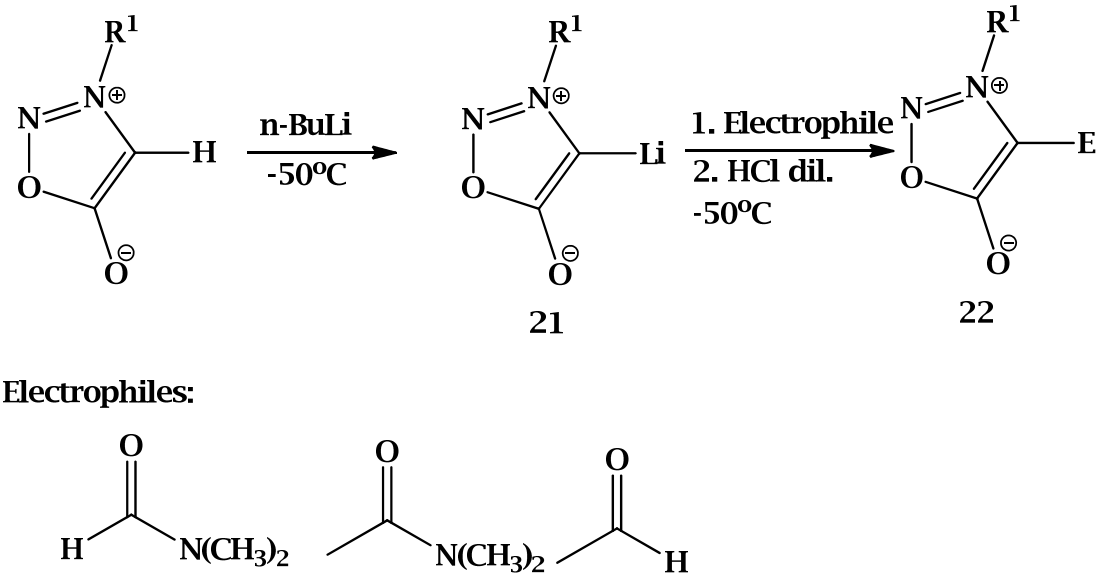
R^1= Ph, Bn

Scheme 1.8. Formylation of sydnones.

1.1.4.2. Lithiation Reactions

Lithiation reactions are favorable for the addition of functional groups by either deprotonation followed by quenching with an electrophile or lithiation followed transmetallation. Sydnone lithiations can be performed readily at the

C-4 position with n-butyllithium and using this method, selenide, phosphide, and arsenide analogues were synthesized while tin, antimony, and tellerium were unsuccessful [50]. Tien et al introduced carbonyl compounds to the C-4 position via a lithiation approach **(Scheme 1.9)** [34].

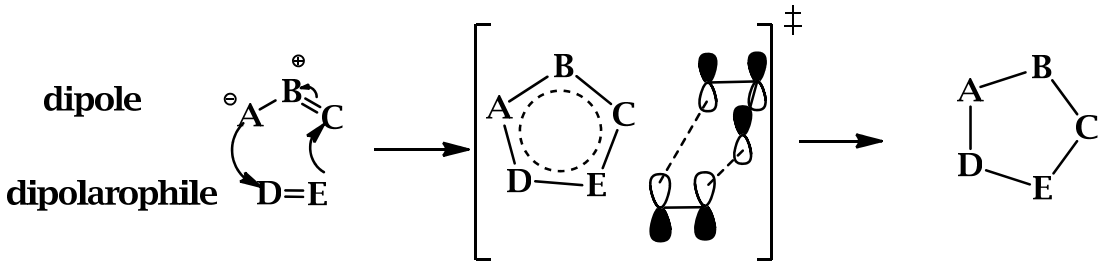


Scheme 1.9. Lithiation reactions of sydnones.

1.1.4.3. 1,3-Dipolar Cycloaddition Reactions

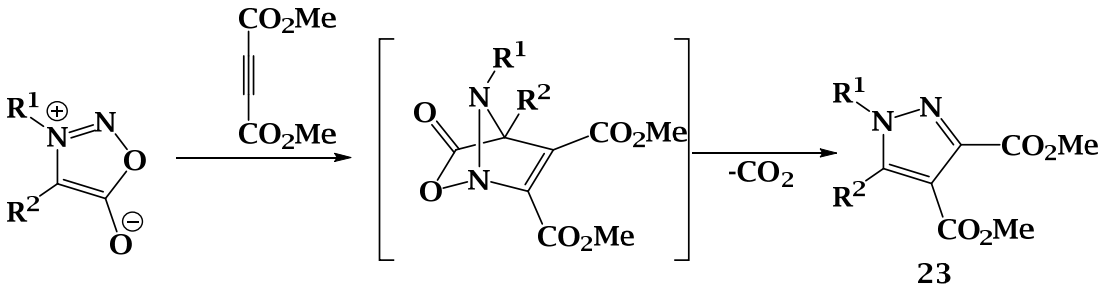
The 1,3-dipolar cycloaddition, also known as Huisgen cycloaddition, is a classic reaction in organic chemistry consisting of the reaction of a dipolarophile with a 1,3-dipolar compound that allows the production of various five membered heterocycles **(Scheme 1.10)**. Most of dipolaraphiles are alkenes, alkynes, and molecules possessing related heteroatom functional groups (such as carbonyls and nitriles). The 1,3-dipoles can be basically divided into two different types: the allyl anion type such as nitrones,

azomethine ylides, nitro compounds, bearing a nitrogen atom in the middle of dipole, carbonyl ylides, or carbonyl imines, bearing an oxygen atom in the middle of the dipole and the linear propargyl/allenyl anion type such as nitrile oxides, nitrilimines, nitrile ylides, diazoalkanes, or azides [51].



Scheme 1.10. 1,3-dipolar cycloaddition reaction.

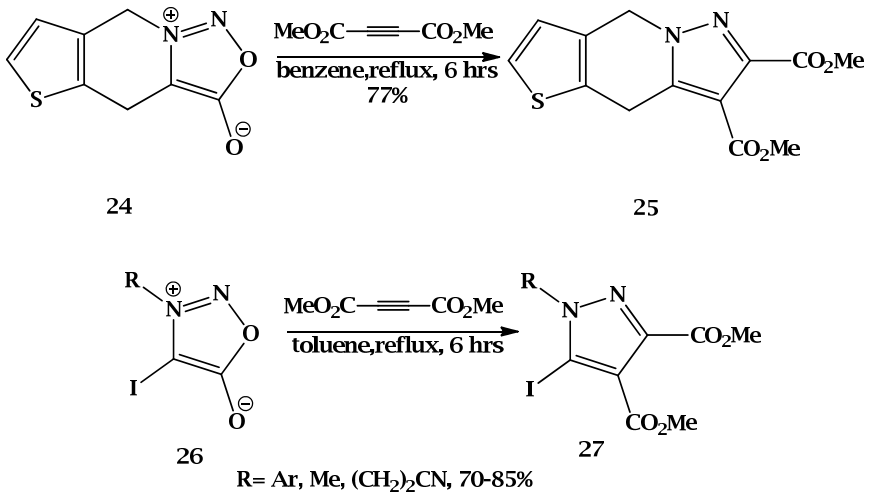
Sydnone rings possess not only a mesoionic character but also a labile nature. The charge distribution on the ring can be varied according to their resonance form depending on their aryl substituents at the position N-3 and C-4. In general, N-3 behaves as an electron-withdrawing substituent and C-4 shows as an electron-donating character to form the so-called duality effect for the ring. Sydnones can be converted to dihydropyrazoles by reacting with cyclopentadiene. Dehydrogenation of dihydropyrazole to form a pyrazole is strongly dependent on the nature of aryl substituents [52]. Sydnones undergo smooth cycloaddition with acetylenes to give pyrazoles in high yield. The reaction involves a 1,3-dipolar cycloaddition of the sydnones, behaving like a cyclic azomethine imine, to the corressponding acetylene followed by carbondioxide evolution and aromatization **(Scheme 1.11)** [53].



Scheme 1.11. 1,3-dipolar cycloaddition reactions of sydnones.

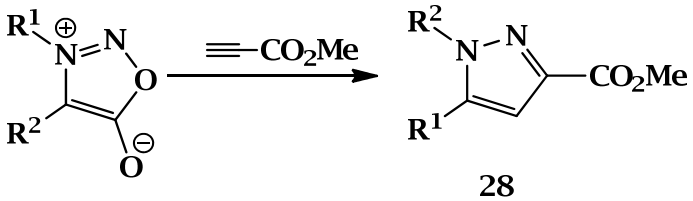
1.1.4.3.1. Alkyne Cycloadditions

Arguably, the most important synthetic application of sydnones is their cycloaddition reaction with alkynes. Cycloaddition reactions of sydnones are most commonly carried out with electron-deficient alkynes. For example, the reactive dienophile, dimetyl acetylenedicarboxylate, reacts readily with C-4 substituted sydnones, and this chemistry has been exploited to generate functionalised pyrazole products [25,32,54] **(Scheme 1.12)**.



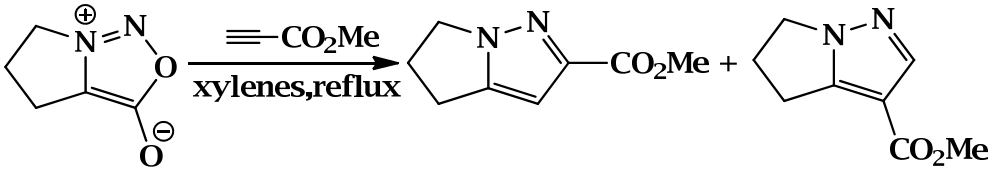
Scheme 1.12. Cycloaddition reaction of sydnone rings with dimetyl acetylenedicarboxylate.

Unsymmetrical alkynyl esters are potentially more synthetically useful, as they provide a simple opportunity for orthogonal functionalisation of the pyrazole products. In addition, these substrates offer a chance to study the regioselectivity of sydnone cycloadditions. Padwa et al. carried out an investigation into the regioselectivity of cycloadditions of methyl propiolate with various C-4 substituted sydnones [55]. As outlined in the **Scheme 16**, the reactions were found to proceed in moderate yield and with low levels of regiocontrol. Nonetheless, the 3,5-disubstituted isomer was favoured in all cases. Notably, the N-alkyl sydnone substrates were found to be unstable and were therefore generated in situ. Ranganathan extended this chemistry to the proline-derived sydnone **29.** The reaction was found to proceed in high yield, but exhibited essentially no regiocontrol **(Scheme 1.13)** [56].



28

R^1=Me, R^2=Bn; 62% (7:2)
R^1=Ph, R^2=Me; 42% (3:2)
R^1=Bn, R^2=Me; 44% (9:2)

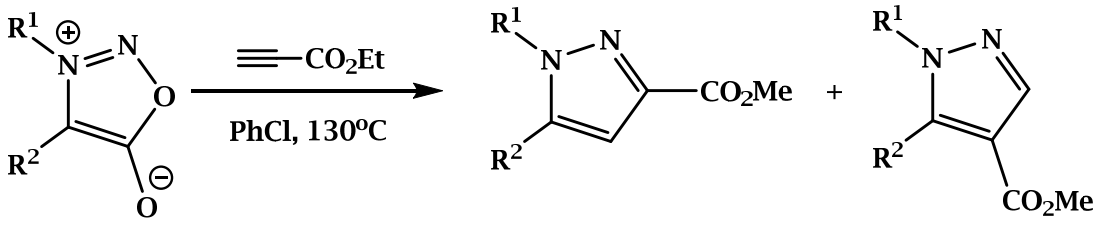


29 40% 30 35% 31

R= Ar, Me, $(CH_2)_2CN$, 70-85%

Scheme 1.13. Cycloaddition reactions of sydnone rings with methyl propiolate.

In an effort to address the limitations associated with the poor levels of regiocontrol observed in propiolate cycloadditions. Wong and Yeh undertook a systematic study of the potential for each reaction partner to affect cycloaddition selectivity [57]. Initialy, they studied a series of 4-substituted sydnones and found these to provide the corresponding pyrazoles with only very modest selectivity for the 3,5-disubstituted isomer **(Table 1.1)**.



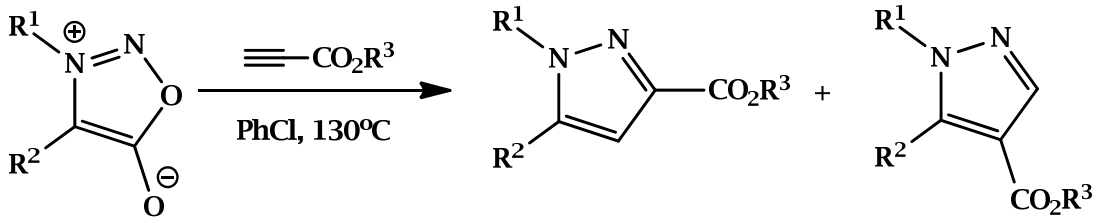
32 33

R^1= 4-OEtC_6H_4

R^2	Yield (32:33) (%)
H	90 (76:24)
I	81 (56:44)
CN	80 (58:42)
CH_2OH	71 (63:37)
SPh	71 (52:48)

Table 1.1. Efficiency and regioselectivity of different substituted sydnone cycloadditions with ethyl propiolate.

Subsequently, the size of ester substituent was varied in an effort to improve regiochemical control. As outlined in **Table 1.2**, this concept proved to be succesfull and excellent levels of regiocontrol were observed when diphenylmethyl propiolate was employed [58].



34 35

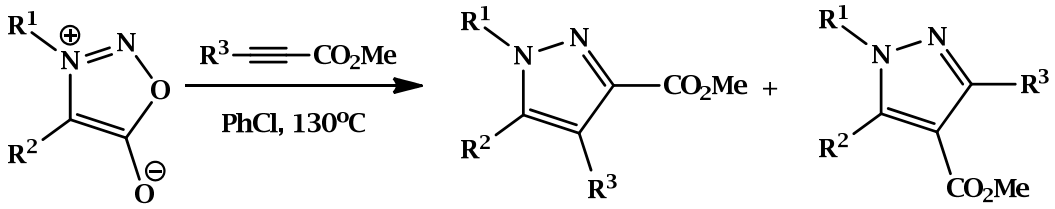
R^1= 4-OEtC$_6$H$_4$, R^2= CN

R^3	Yield (34:35) (%)
Et	80 (58:42)
Bn	76 (57:43)
t-Bu	79 (78:22)
$CHPh_2$	85 (100:0)

Table 1.2. Efficiency and regioselectivity of sydnone cycloadditions with different substitued propiolates.

The efficiency and regioselectivity of sydnone cycloadditions with substitued alkynyl esters have been investigated by Farina and co-workers [59]. Specifically, they noted a dramatic switch in selectivity of cycloaddition of propiolates bearing acetal, aldehyde and carbinol substituents. Interestingly,

alkynes bearing an acetal moiety showed o complementary regiochemical insertion pattern to the corresponding aldehydes **(Table 1.3)**.



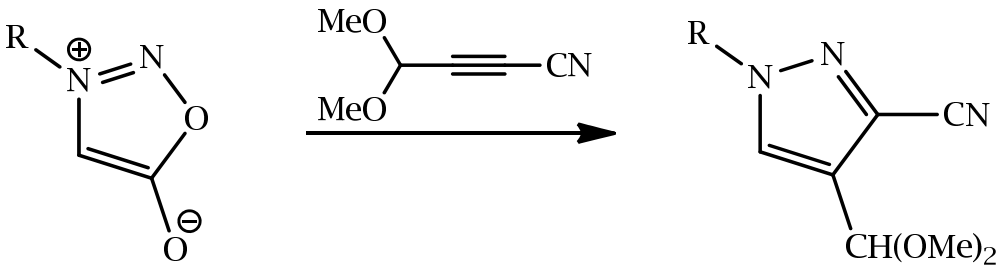
36 37

R^2= H

R^1	R^3	Time (h)	Yield (36:37) (%)
Bn	$CH(OMe)_2$	72	80 (81:19)
Ph	$CH(OMe)_2$	60	84 (79:21)
Bn	CHO	18	90 (28:72)
Ph	CHO	18	93 (34:66)
Bn	CH_2OH	72	75 (50:50)
Ph	CH_2OH	48	79 (40:60)

Table 1.3. Efficiency and regioselectivity of sydnone cycloadditions with different substituted alkynyl esters.

These authors extended their studies to include acetal-substituted propionitriles [59a] and showed that the selectivities could be enhanced still further **(Scheme 1.14)**. Notably, an analogous regiochemical insertion pattern to that of the corresponding propiolates was observed.

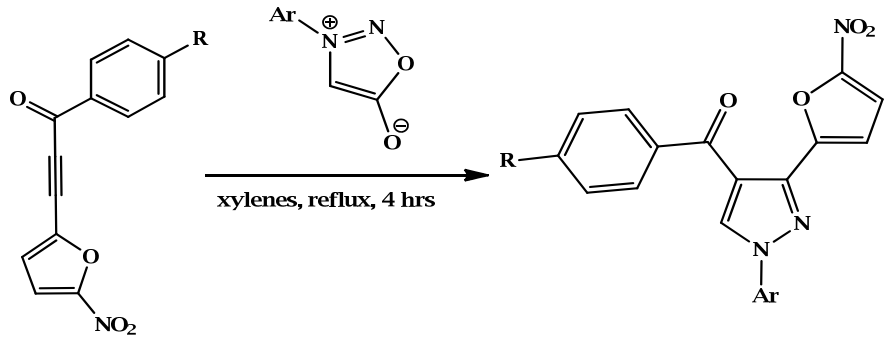


R= Ph, 84% (9:1)
R= Bn, 89% (9:1)

38

Scheme 1.14. Cycloadditions reactions of sydnone with acetal-substituted propionitriles.

An interesting and highly functionalised class of α,β-acetylenic ketones has been employed in sydnone cycloadditions by Hegde et al. and was found to generate the corresponding pyrazoles in excellent yield and as single regioisomers **(Scheme 1.15)** [60]. The authors also demonstrated that replacing the furan with a 5-nitrothiophene provided similar results. These compounds were further tested for their antibacterial and antifungal activities [61].

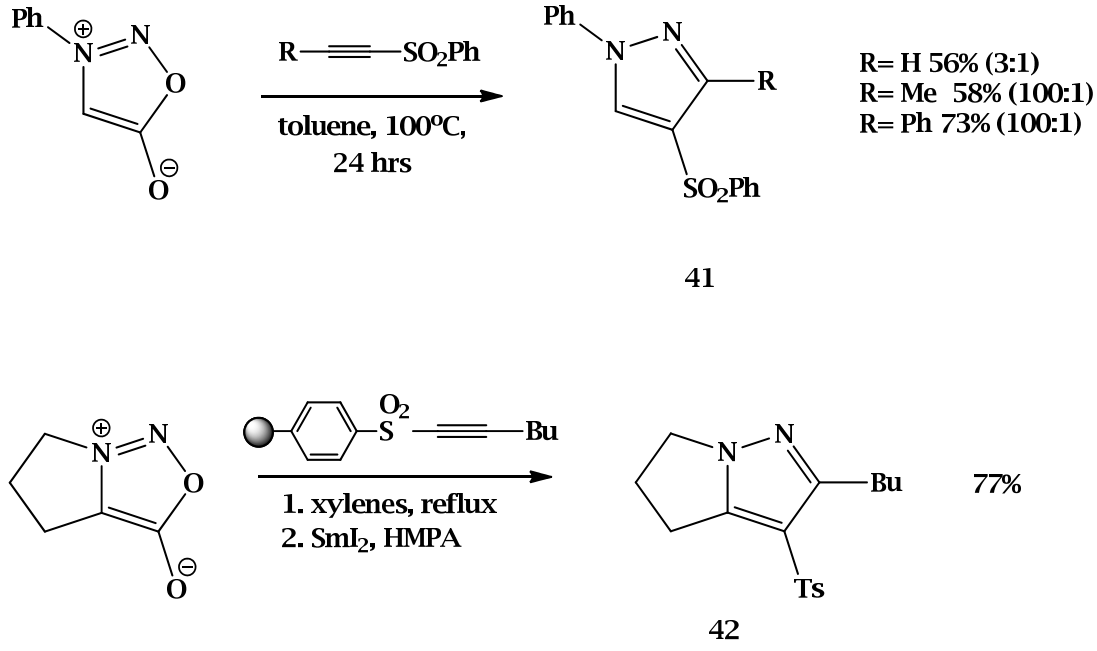


R= H, Me, Cl
Ar= Ph, p-tol, p-MeOPh
72-83%

39 **40**

Scheme 1.15. Cycloadditions reactions of sydnone with α,β-acetylenic ketones.

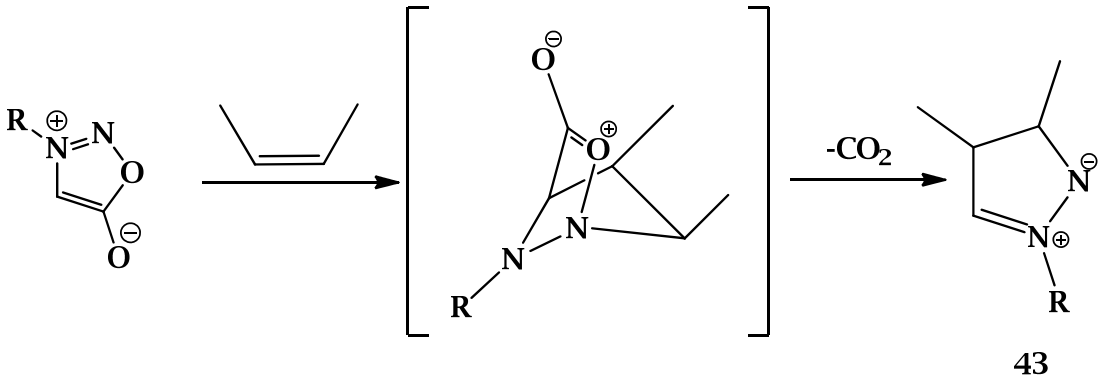
The employment of alkynylsulfones has been documented by Zecchi and co-workers [62]. By analogy to the cycloaddition of propiolates, the terminal alkyne provided the corresponding pyrazole with modest levels of regiocontrol. However, substitued alkynylsulfones have the potential to furnish 1,3,4-trisubstituted pyrazoles in good yield with excellent regioselectivity. This work recently extended by Back [63] to include solid supported alkynylsulfones that provided the corresponding bicyclic pyrazoles in good yield as single regioisomers after cleavage from Merrifield resin **(Scheme 1.16)**.



Scheme 1.16. Cycloaddition reactions of sydnone with alkynylsulfones.

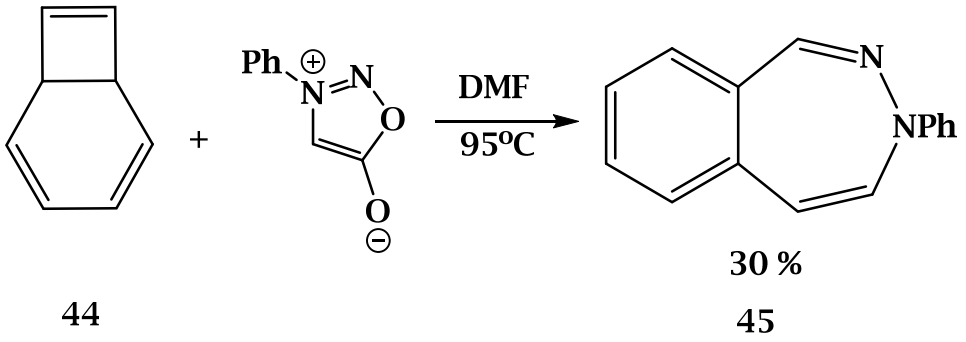
1.1.4.3.2. Alkene Cycloadditions

The dipolar cycloaddition of sydnones to alkenes could give rise to Δ^2-pyrazolines, and that the addition of an oxidant to this mixture allowed the corresponding pyrazoles to be isolated. The general reaction pathway involves a cycloaddition/cycloreversion process with evolution of CO_2. In the case of alkene dienophiles, this gives rise to an azomethine imine and it is the subsequent chemistry of this intermediate that determines the ultimate product distribution **(Scheme 1.17)**.



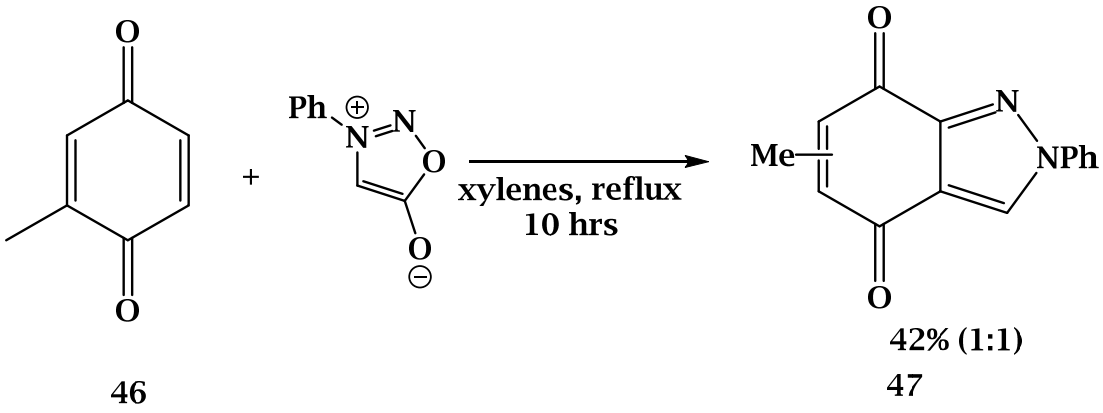
Scheme 1.17. Cycloaddition reaction of sydnone with alkene dienophile.

Kato confirmed the potential of sydnones to react with cyclobutenes to furnish ring-expanded products. Specifically, heating benzocyclobutene with sydnone provided the corresponding benzodiazepine, albeit in low yield **(Scheme 1.18)** [64].



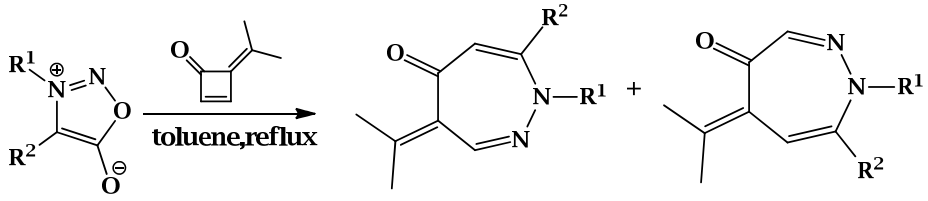
Scheme 1.18. Cycloaddition reaction of sydnone with cyclobutene.

Quinones are an alternative class of activated dienophiles/ dipolaraphiles and the group of Nan'ya has demonstrated that these can participitate in sydnone cycloadditions to produce indazole-4,7-diones **(Scheme 1.19)** [65].



Scheme 1.19. Cycloaddition reaction of sydnone with quinone.

Martin has shown that diazepinones can be prepared from alkylidenecyclobutenones, presumably via [3+2] cycloaddition followed by in situ ring opening initiated by azomethine imine intermediate **(Table 1.4)** [66].



48 49

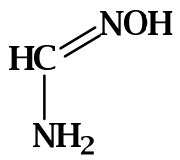
R^1	R^2	Yield(48:49)%
Ph	Me	56 (100:0)
Ph	H	93 (100:0)
Ph	Cl	84 (100:0)
Me	H	65 (4:3)
Bn	H	58 (4:3)
Me	Me	75 (100:0)
$(CH_2)_4$		57 (100:0)
$(CH_2)_3$		43 (100:0)

Table 1.4. Cycloaddition reactions of sydnone with alkylidenecyclobutenones.

1.2. 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.

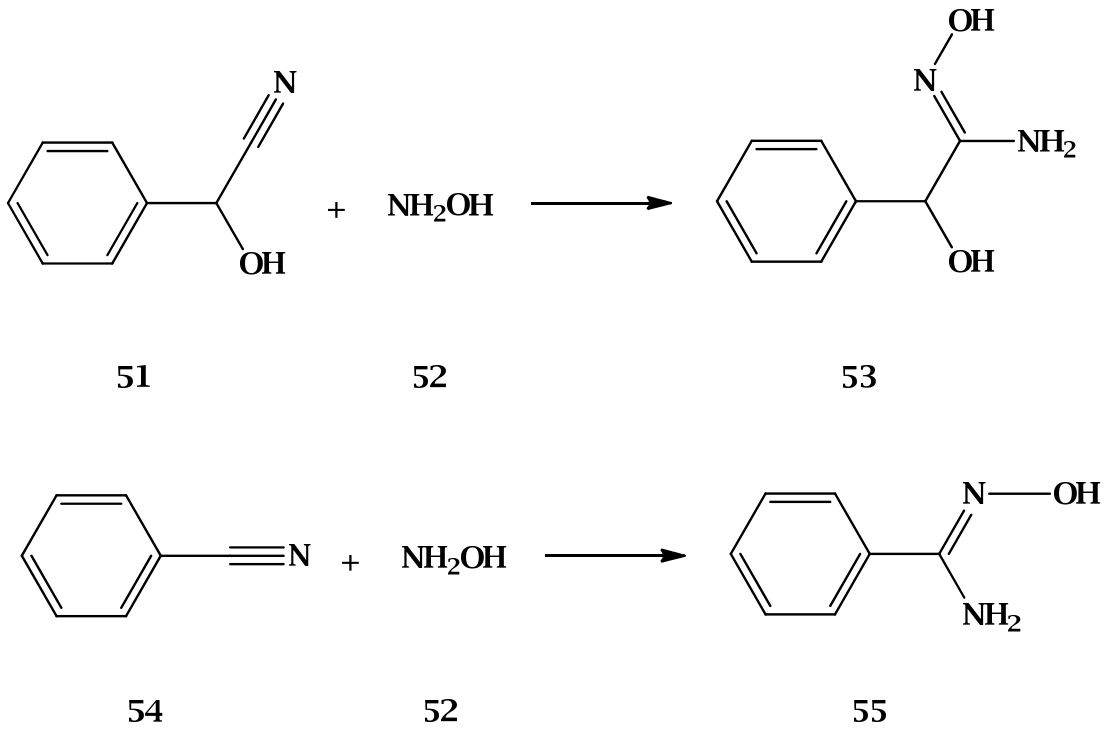
In 1873, Lossen and Schifferdecherprepared the first amidoxime **50** by reacting hydrogen cyanide with hydroxylamine. The compound is called as '**isuretin' (Figure 1.4)** [67].



50

Figure 1.4. Structure of isuretin.

The name of amidoxime was first used by Tiemann who prepared two related compounds mandelamidoxime **53** and benzamidoxime **55** in 1884 by reacting hyrdoxylamine **52** with benzaldehyde and benzonitrile respectively **(Scheme 1.20)** [68].

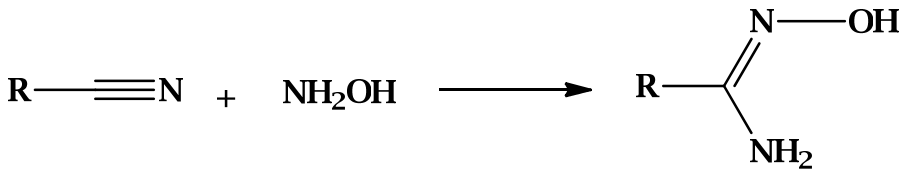


Scheme 1.20. Mandelamidoxime and benzamidoxime.

1.2.1. Synthesis of Amidoximes

1.2.1.1. By Action of Hydroxylamine on Nitriles

The preparation of amidoximes **57** from nitriles **56** by the action of hydroxylamine **52** was first studied by Tiemann and Krüger **(Scheme 1.21)** [68].



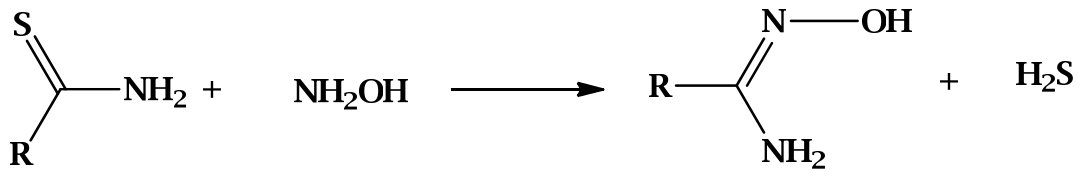
56 52 57

Scheme 1.21. 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^{o}C during a few hours. Amidoximes with highest yields were obtained when a 15% excess of a solution of hydroxylamine in butanol was used [69].

1.2.1.2. By Action of Hydroxylamine on Amides and Thioamides

The procedure for synthesis of amidoximes **57** from amides and thioamides **58** is same as from nitriles. By this method, some aromatic amidoximes have been prepared **(Scheme 1.22)** [70-75].

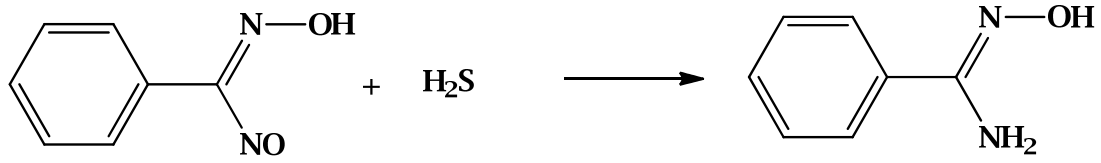


58 52 57 59

Scheme 1.22. Action of hydroxylamine on thioamides.

1.2.1.3. By Reduction of Nitrosolic Acids and Nitrolic Acids

The reduction of nitrosolic acids and nitrolic acids with hydrogen sulfide and hydrogen gases respectively gives amidoximes. Wieland and Bauer[76] prepared benzamidoxime **55** by reducing benzonitrosolic acid **60** with hydrogen sulfide **59 (Scheme 1.23)**.

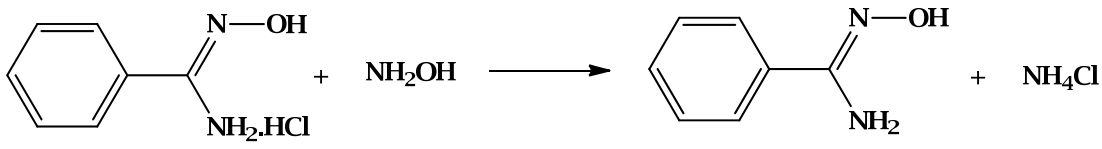


60 59 55

Scheme 1.23. Reduction of nitrosolic acids by hydrogen sulfide.

1.2.1.4. By Action of Hydroxylamine on Amidine Hydrochlorides and Iminoethers

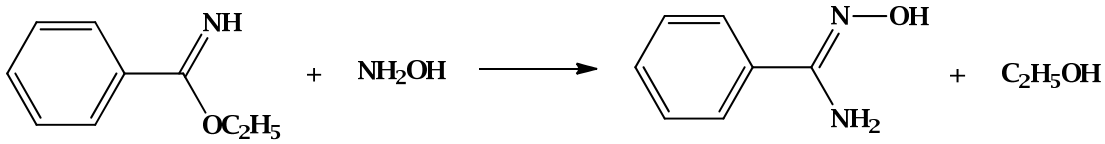
Action of hydroxylamine on amidine hydrochlorides and iminoethers was first synthesized by Pinner[77] who synthesized benzamidoxime **55** by treating benzamidine hydrochloride **61** with hydroxylamine **52 (Scheme 1.24)**.



61 52 55 62

Scheme 1.24. Synthesis of benzamidoxime from benzamidine hydrochloride.

Benzamidoxime **55** was also prepared by the action of hydroxylamine **52** on ethyl iminobenzoate **63** by Pinner [77] and Lossen [78] **(Scheme 1.25)**.

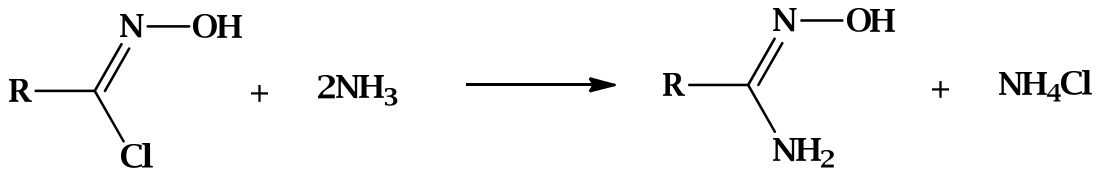


63 52 55 64

Scheme 1.25. Synthesis of benzamidoxime from ethyl iminobenzoate.

1.2.1.5. By Action of Ammonia on Hydroximic Acid Chlorides

Chloroximes are formed by direct chlorination of oximes. The reactions of these chlorides **65** with ammonia **66** yields amidoximes **57**. This procedure was firstly used by Werner **(Scheme 1.26)** [79,80].

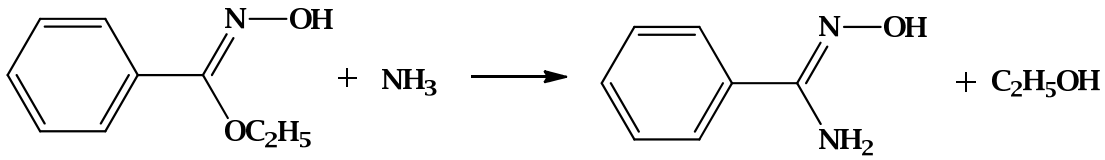


65 66 57 62

Scheme 1.26. Action of ammoniaon hyrdoximic acid chlorides.

1.2.1.6. By Action of Ammonia on Oximinoethers

Ethyl benzohydroxamic acid **67** and an alcoholic solution of ammonia **66** are heated in pressure bottle for 8 hrs. at 175°C to yields benzamidoximes **55 (Scheme 1.27)** [81]. These reactions are not found in general applications.



67 66 55 64

Scheme 1.27. Action of ammonia on oxoiminoethers.

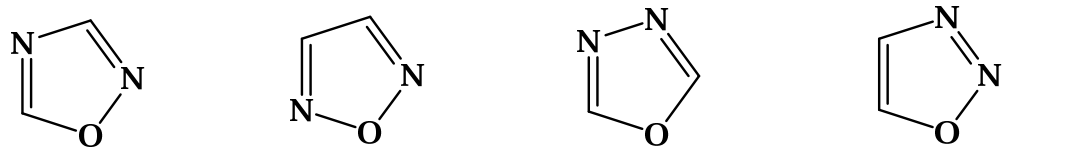
1.2.2. Physical Properties of Amidoximes

The amidoximes are colorless, crystalline compounds. Aryl amidoximes, which are soluble in alcohols and some organic solvents and insoluble in water, are more stable than aliphatic amidoximes.The solubility of aliphatics in water decrease with increasing molecular weight, but the first series are soluble [82].

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

1.3. OXADIAZOLES

Oxadiazoles and their derivatives are considered as simple five membered heterocycles possessing one oxygen and two nitrogen atoms. Oxadiazole exist in different isomeric forms such as 1,2,4-, 1,2,5-, 1,3,4-, and 1,2,3-oxadiazole **68a-d (Figure 1.5)**. Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom. The replacement of two –CH= groups 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.



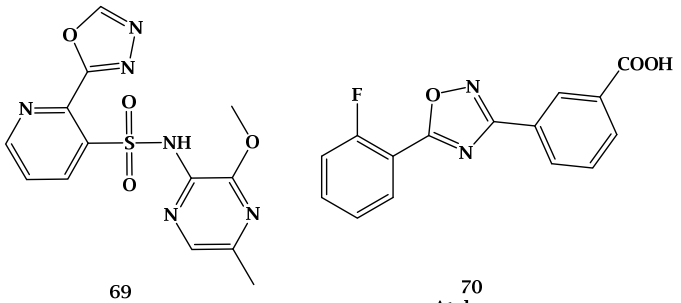
1,2,4-oxadiazole a | 1,2,5-oxadiazole b | 1,3,4-oxadiazole c | 1,2,3-oxadiazole d

(68a-d)

Figure 1.5. Different isomeric forms of oxadiazoles.

Nitrogen-oxygen containing heterocycles are of synthetic interest because they constitute an important class of natural and synthetic products, many of which exhibit useful biological activities [83].

In drug discovery and development, a number of compounds containing an oxadiazole moiety are in late stage clinical trials, including Zibotentan **69** as an anticancer agent [84] an Ataluren **70** for the treatment of cystic fibrois[85]. So far, one oxadiazole contanining compound, Raltegravir **71**[86], an antiretroviral drug for the treatment of HIV infection, has been launched onto the marketplace **(Figure 1.6)**. It is clear that oxadiazoles are having a large impact on multiple drug discovery programs across a variety of disease areas, including diabetes, obesity[87], inflammation[88], cancer[89], and infection [90].



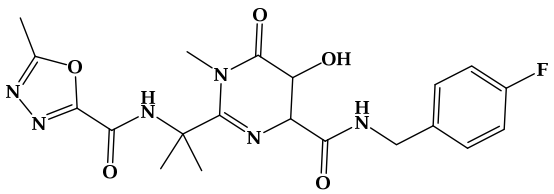


Figure 1.6. Structures of Zibontentan **69**, Ataluren **70**, and Raltegravir **71**.

1.3.1. Chemistry of Oxadiazoles

Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom [91]. The replacement of two -CH= groups in furan by two

pyridine type nitrogen (-N=) reduces the aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character of conjugated diene. The electrophilic substitutions in the 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 occuring at an aliphatic sp^2 carbon atom [92].

1.3.2. 1,2,4-Oxadiazoles

1,2,4-oxadiazole, an important heterocycle with five members, is usually found in marine organisms, *Phdiana militaris* [93], or can be synthesized via many methods [94]. The derivatives of this oxadiazole possess various biological activities such as antidiabetic, anti-inflammatory [95], immunosuppressive [96], anti-microbial [97,98] and anti-tumor [99,100,101]. Especially, 1,2,4-oxadiazole derivatives are benefical for interacting with DNA[102] and inhibiting bacterial [103]. This phenomenon gives us an important information that 1,2,4-oxadiazole may be a powerful core to construct functional groups in the drug design.

1.3.2.1. Synthesis of 1,2,4-oxadiazoles

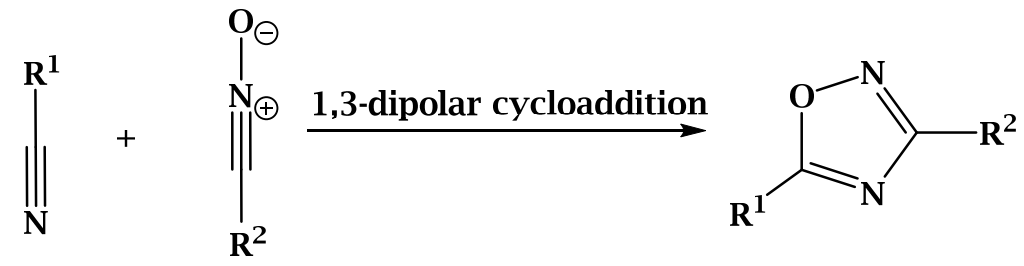
1,2,4-oxadiazoles are generally prepared by

(i) 1,3-dipolar cycloaddition of nitrile oxides with nitriles and

(ii) cyclocondensation of amidoximes with carbonyl-containing reactants; such as activated acids, acid chlorides and flourides, acid anhydrides, esters and β-ketoesters [104].

1.3.2.1.1. Synthesis of 1,2,4-oxadiazoles via 1,3-dipolar cycloaddition of nitrile oxides with nitrile

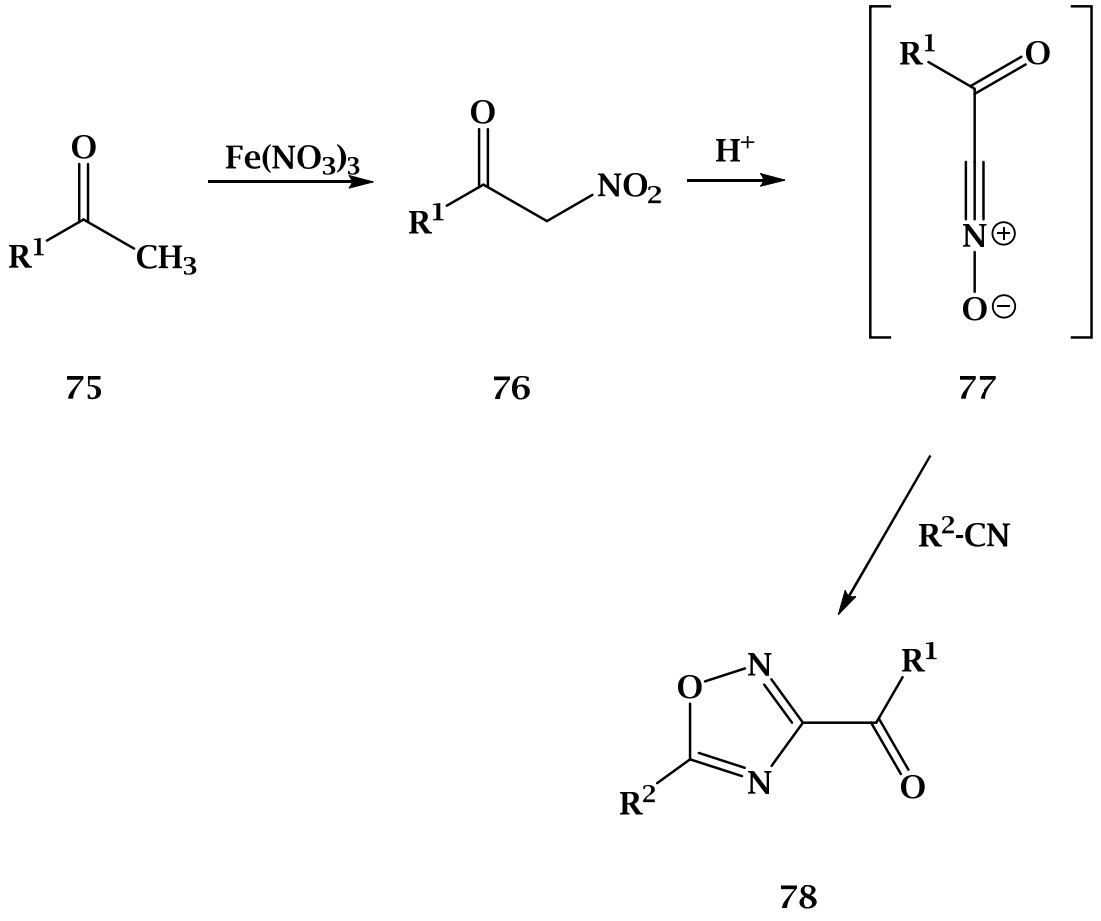
1,3-dipolar cycloaddition reactions are one of the most common methods for the synthesis of heterocyclic compounds. 1,2,4-oxadiazoles are also prepared by the cycloaddition betweeen nitrile oxides and nitriles, and 3,5-disubstituted-1,2,4-oxadiazoles are isolated as illustrated in **Scheme 1.28** [105].



72 73 74

Scheme 1.28. Synthesis of 1,2,4-oxadiazoles via 1,3-dipolar cycloaddition of nitrile oxides and nitriles.

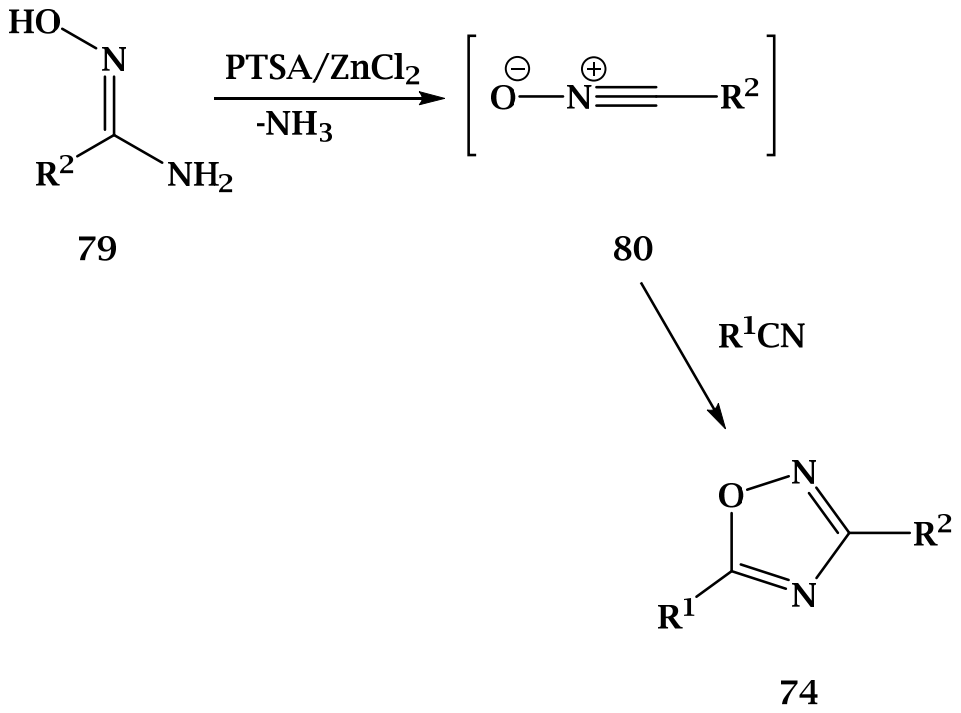
Synthesis of 3-acyl-1,2,4-oxadiazoles **78** is important for the further functionalization of 1,2,4-oxadiazoles [106]. Itoh reported a rare example for the synthesis of such 1,2,4-oxadiazoles by using iron-catalyzed cycloaddition reaction with nitriles and carbonyl compounds. For this purpose, α-nitroketones **76** were first synthesized from methyl ketones **75** [107]. Subsequent elimination of water gave in situ nitrile oxides. Finally, 1,3-dipolar cycloaddition of nitrile oxides **77** with appropriate nitriles produced the desired 3-acyl-1,2,4-oxadiazoles **78 (Scheme 1.29)** [108].



75 76 77 78

Scheme 1.29. Synthesis of 3-acyl-1,2,4-oxadiazoles.

Augustine developed one-pot synthesis of 1,2,4-oxadiazoles from amidoximes and nitriles in the presencce of PTSA/$ZnCl_2$ catalyst system as depicted in **Scheme 1.30** [109]. Interestingly, amidoximes **61** were used as a nitrile oxides precursor in this methodology.

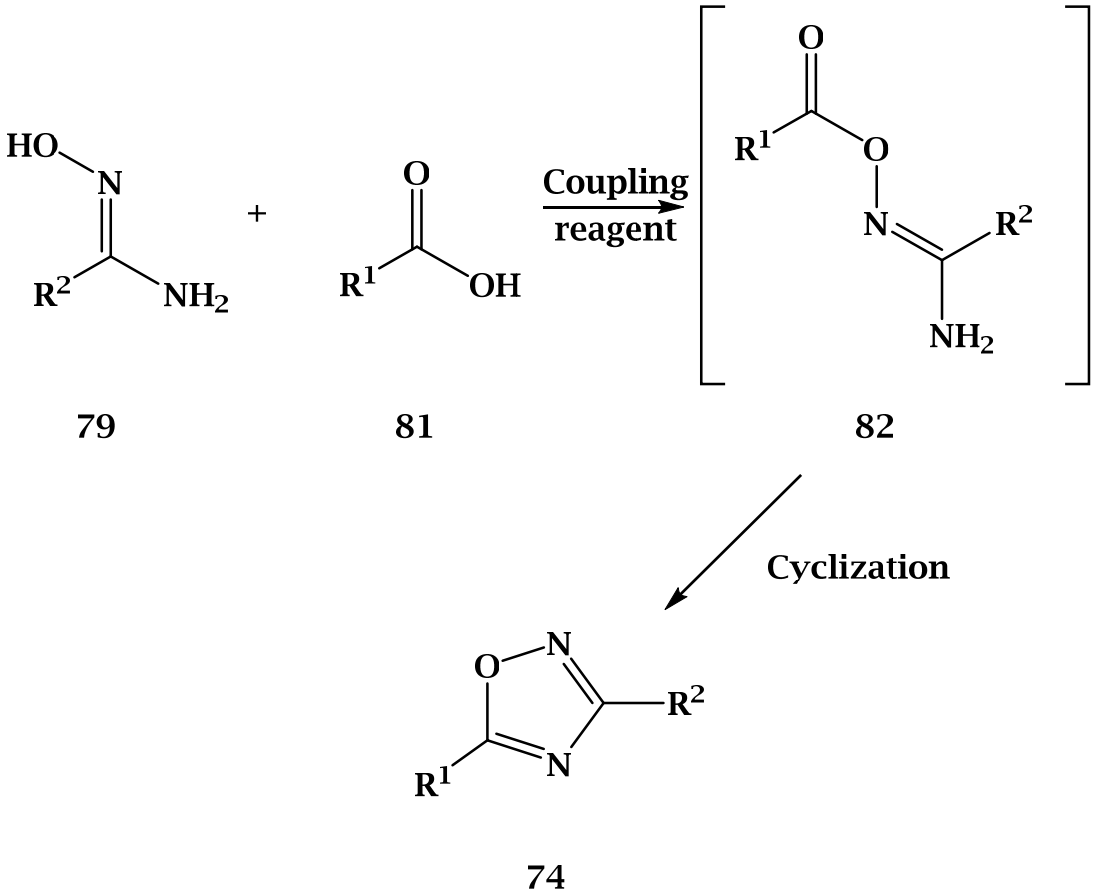


Scheme 1.30. Synthesis of 1,2,4-oxadiazoles from amidoximes and nitriles.

1.3.2.1.2. Synthesis of 1,2,4-oxadiazoles by cyclocondensation of amidoximes with carboxylic acid derivatives

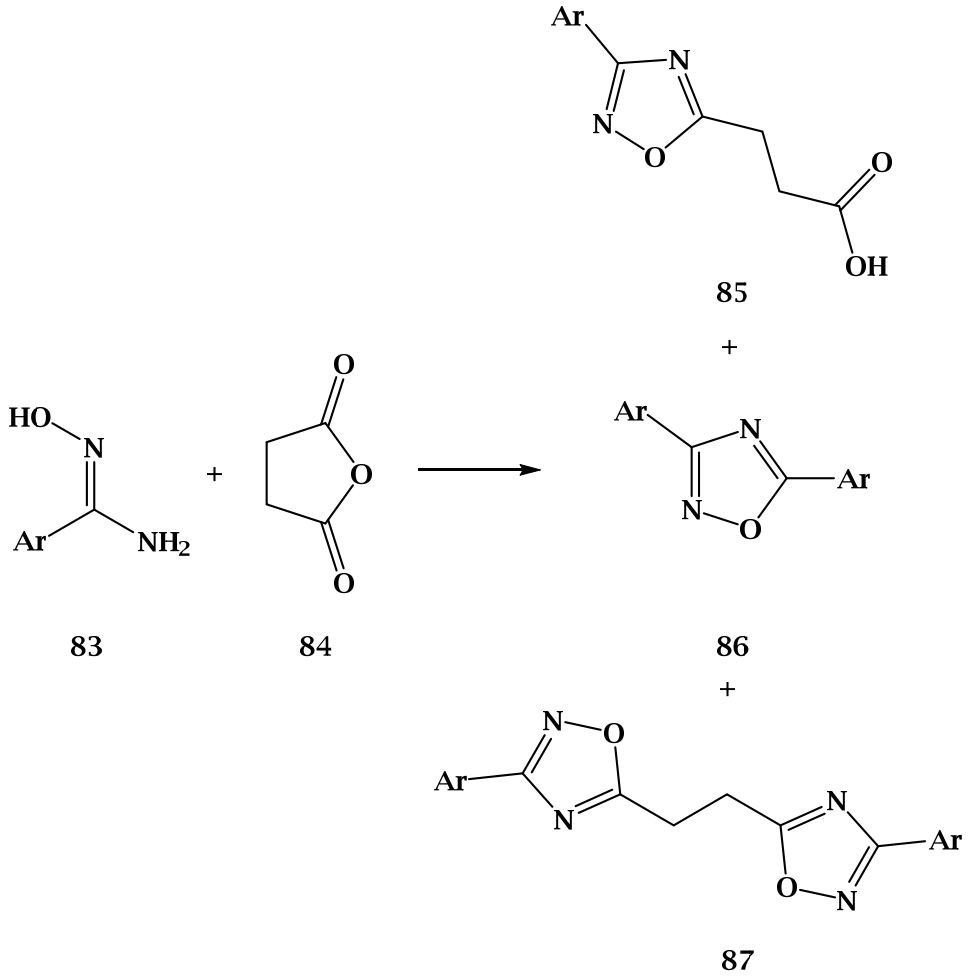
Cyclocondensation of amidoximes with carboxylic acids in the presence of a coupling reagent is most common method for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles **74** [110]. The reaction consists of two steps; coupling and cyclization. Amidoximes **79** are often either commercially available or easily prepared by the reaction of nitriles with

hydroxylamine[111]. Activated carboxylic acid derivatives, such as acid chlorides and flourides, esters and anhydrides, are also used for the formation of *O*-acylated amidoxime intermediates. *N,N*-Carbonyl-diimidazole (CDI) [112], acyl-palladium complex [113], *N,N*-dicyclohexylcarbodiimide (DCC) [114], (*N,N*-dimethylamino)isopropyl chloride (DIC) [115], 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (EDC) [116], and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU) are commonly used as coupling (activating) agents for carboxylic acids [117].



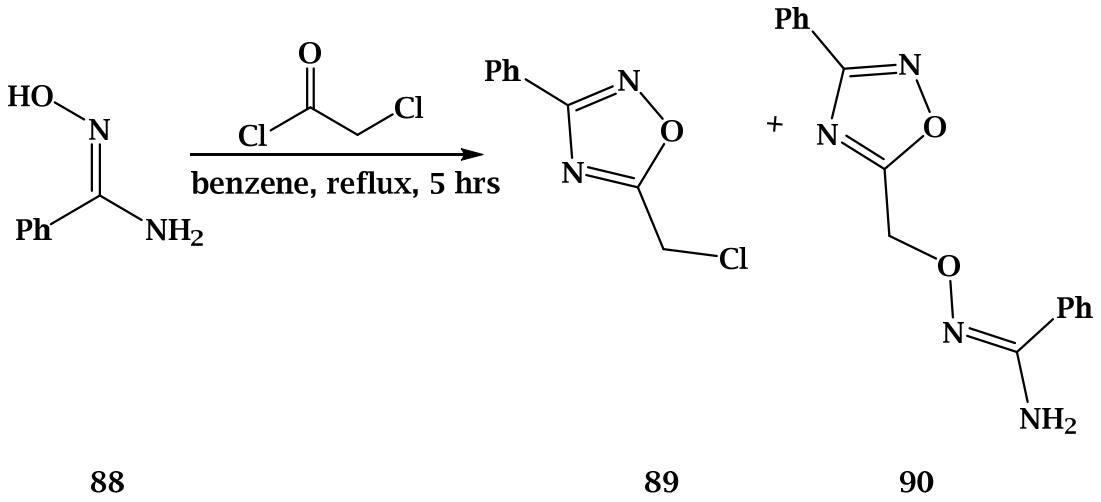
Scheme 1.31. Synthesis of 1,2,4-oxadiazoles from amidoximes and carboxylic acids.

The reaction of aryl amidoximes **83** with succinic anhydride **65** in high boiling solvents or under microwave irradiation produced a mixture of 1,2,4-oxadiazole derivatives **85**, **86** and **87**, the former being the major product of the reaction [118]. Oxadiazole derivatives **86** and **87** were obtained as minor products. Derivatives containing propionic acid units, such as **85**, are important building blocks for the synthesis of pharmaceuticals such as cannabinoid receptor 2 (CB2) [119] and niacin receptor agonists [120]. For this purpose, elaborated anti-inflammatory and anti-microbial derivatives of 1,2,4-oxadiazole peptidomimetics were prepared **(Scheme 1.32)** [121].



Scheme 1.32. Synthesis of 1,2,4-oxadiazoles from amidoximes and succinic anhydride.

Dürüst *et. al.* reported that the reaction of benzamide oxime with chloroacetyl chloride on boiling in benzene led to the formation of 1,2,4-oxadiazole **89** and 3-methyl-4*H*-1,2,4-oxadiazin-5(6*H*)-one **90 (Scheme 1.33)** [122].

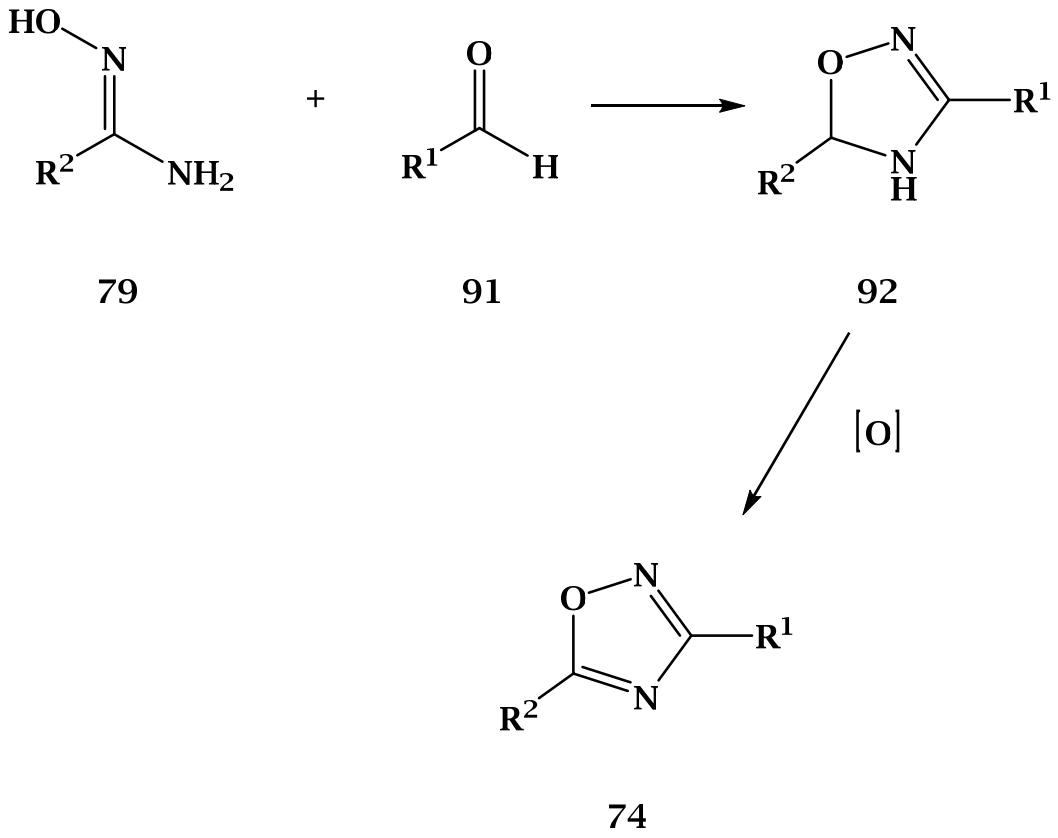


88 89 90

Scheme 1.33. Synthesis of 1,2,4-oxadiazole from chloroacetyl chloride.

1.3.2.1.3. Other methods for the synthesis of 1,2,4-oxadiazoles

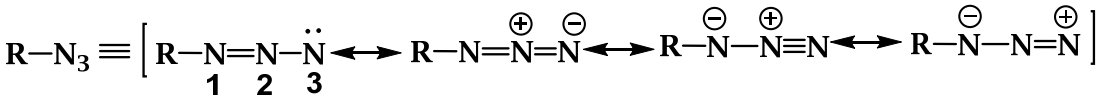
Reactions of amidoximes with aldehydes gave 4,5-dihydro-1,2,4-oxadiazoles **73** instead of 1,2,4-oxadiazoles **56** [97]. Then, oxidation of dihydrooxadiazoles by using potassium permanganate, MnO_2 or sodium hypochlorite furnished 1,2,4-oxadiazoles **56**. Recently, Okimoto electrochemically oxidized dihydrooxadiazoles **73** to oxadiazoles **56** in good yields [123].



Scheme 1.34. Synthesis of 1,2,4-oxadiazoles via oxidation of 4,5-dihydro-1,2,4-oxadiazoles.

1.4. 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 shock solutions and as a reagent. Azides are energy-rich and very reactive molecules with many applications. Since, reacting with electron-deficient compounds (electrophiles) at N-1 and with electron-rich compounds (nucleophiles) at N-3 [124].



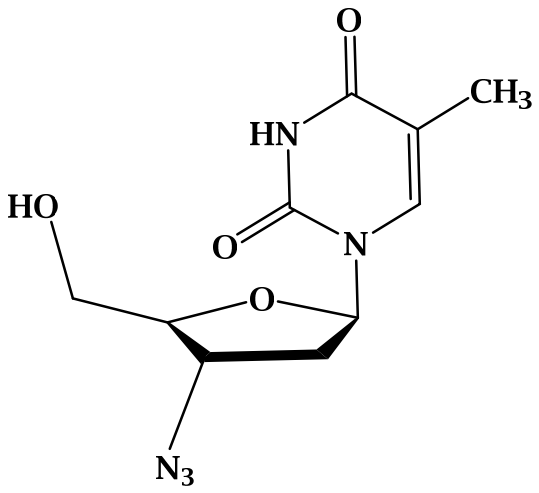
93 93a 93b 93c 93d

Figure 1.7. Resonance forms of azides.

Azides are very important precursors for the preparation and synthesis of heterocyclic aromatic compounds. Organic azides are capable of 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 [125]. The organic azides received considerable attention in the 1950s and 1960s with new applications in the chemistry of the acyl, aryl and alkyl azides [126,127]. Azides are considered to be important for both industrial and biological applications. 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 [128].

Organic azides are used for the synthesis of heterocycles (triazoles, tetrazoles, aziridines), as blowing agents, and functional groups in pharmaceuticals e.g. azidonucleoside for the treatment of AIDS (azidothymidine) **(Figure 1.8)** [129].



AZT, 3'-azido-3'-deoxythymidine

Figure 1.8. Structure of azothymidine.

1.4.1. Physicochemical Properties of Azides

The structural determination of azides originates from the initial postulation of Curtius and Hantzsch, who had suggested a cyclic 1*H*-triazirine structure, that was, however, rapidly revised in favor of the linear structure.

A basis for the chemical diversity of azides comes from the physicochemical properties of azides. Some of the physicochemical properties of the organic azides can be explained by a consideration of polar mesomeric structures [130]. Aromatic azides are stabilized by conjugation with aromatic ring system. The dipolar structures of type **93c,d (Figure 1.7)** also compellingly explained the facile decomposition into the corresponding nitrene and dinitrogen as well as the reactivity as a 1,3-dipole. The regioselectivity of their reactions with electrophiles and nucleophiles is explained on the basis of the mesomeric structure **93d** (attack on N-3 by nucleophiles, whereas electrophiles are attacked by N-1.)

The angles R-N^1-N^2-N^3 and RN^1-N^2-N^3 are approximately 115.2^o and 172.5^o, respectively (calculated for methyl azide, R=CH_3[131]). The bond lengths in methyl azide were determined as *d*(R-N^1)= 1.472, *d*(N^1-N^2)= 1.244, and *d*(N^2-N^3)= 1.162 Å; slightly shorter N^2-N^3 bond lengths are observed with aromatic azides [124].

The polar resonance structures **93b,c** explained the strong IR absorption at ≈2114 cm^{-1} (for phenyl azide), the UV absorption (287 nm and 216 nm for alkyl azides), the weak dipole moment (1.44D for phenyl azide), the acidity of aliphatic azides [132] .

1.4.2. Synthesis of Azides

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

i) insertion of the N_3 group (substitution or addition),

ii) insertion of N_2 group (diazo group),

iii) insertion of a nitrogen atom (diazotization),

iv) cleavage of triazines and analogous compounds,

v) rearrangements of azides.

1.4.2.1. Synthesis of Aryl Azides

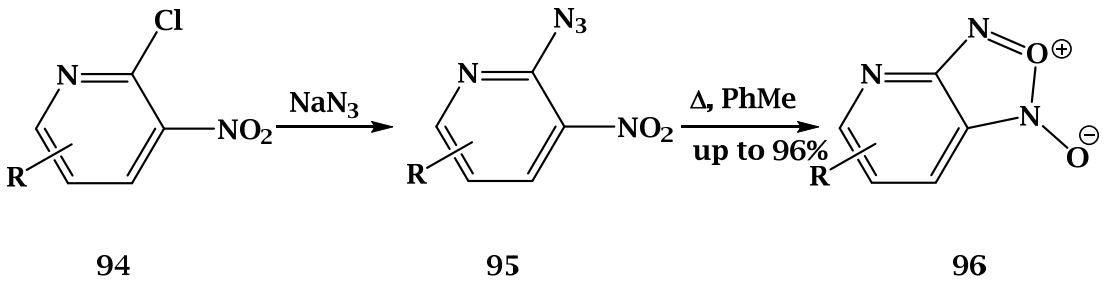
1.4.2.1.1. Aryl Azides from Diazonium Compounds

The older preparative methods for aryl azides are based on the reaction of diazonium salts with hydrazine [133] or *O*-benzylhydroxylamine hydrochloride [134]. The reaction of arene diazonium perbromides with ammonia also leads to aryl azides and is the oldest method for the preparation of azides [114-115].

In meantime, however, more convenient conversions of diazonium salts into aryl azides are known. Thus, aryl diazonium salts react directly with azide ions without catalysts directly to the corresponding aryl azides [136]. Alkali azides or trimethylsilyl azide act as source [137]. The latter compound is especially suitable because of its solubility in organic solvents.

1.4.2.1.2. Nucleophilic Aromatic Substitution: S_NAr Reactions

Activated aromatic ring systems such as fluoro- and chloronitro arenes [138a] and a few aromatic heteroaromatic systems [138b] can undergo nucleophilic substitution by azide ions. They are generally sufficiently nucleophilic to produce aryl azides in good yields. The ortho-nitroazidoarenes formed react further at elevated temperatures with loss of nitrogen and formation of benzofurozane derivatives. Analogous reactivity is exhibited by the corresponding azidonitropyridine **95**, which can be prepared from chloronitropyridine **94** and sodium azide **(Scheme 1.35)** [139].

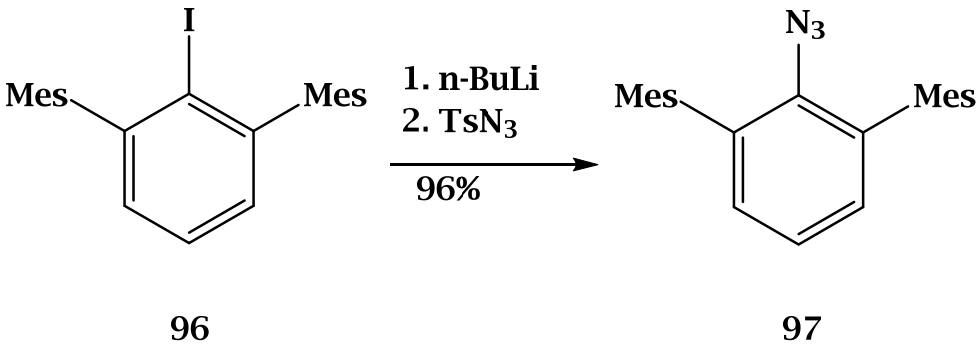


94 95 96

Scheme 1.35. Aromatic substitution to give aryl azides.

1.4.2.1.3. Aryl Azides from Organometallic Reagents

Over the last decades, numerous methods for the preparation of aryl azides with organometallic reagents have been developed. For example, tosyl azide reacts with Grignard or lithium reagents- depending on the corresponding aryl halide- to form novel aryl azides [140]. One example is the preparation of aryl azide **97 (Scheme 1.36)** [141].



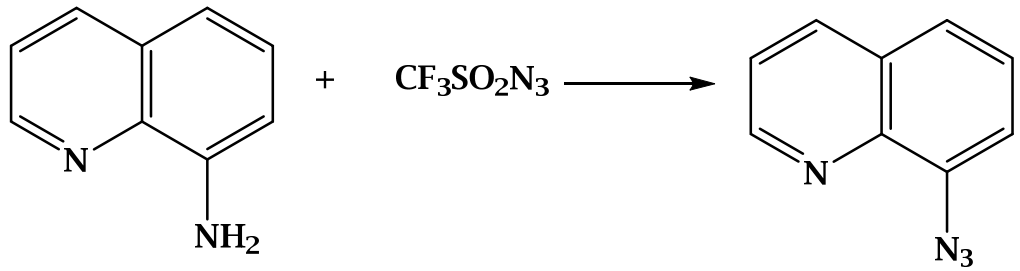
96 97

Scheme 1.36. Aryl azides according to Tilley and co-workers. (Mes=mesityl, Ts=paratoluenesulfonyl)

1.4.2.1.4. Aryl Azides by Diazo Transfer

In analogy to aliphatic amines, aryl azides and heteroaryl azides may be prepared by the reaction of anilines with triflyl azide [142]. The mild reaction condiitons and very high yields make these transformations the method of choice for the preparation of numerous aromatic azides. In the typcial reaction freshly prepared **99** is treated with 8-aminoquinoline **98** at room temperature in a mixture of dichloromethane and methanol in the presence of

triethylamine and copper sulfate. The reaction produces 8-azidoquinoline **100** in almost quantitative yield **(Scheme 1.37)**.



98 **99** **100**

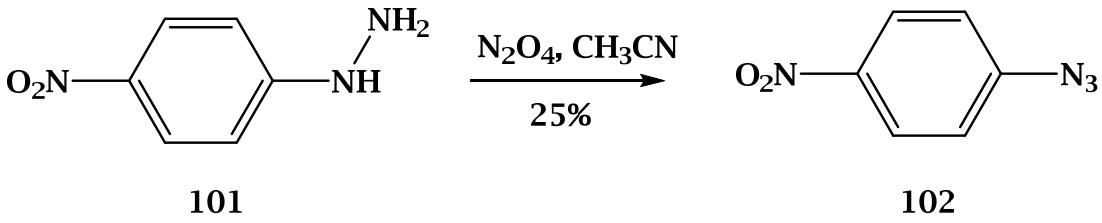
Scheme 1.37. Conversion of aromatic amines **98** into aryl azides **100** according to Tor and co-workers.

1.4.2.1.5. Aryl Azides from Nitrosoarenes

The reaction of nitrosoarenes with hydrogen azide leads to aryl azides in good yields [143]. However, the diazonium ions must first be formed and then treated with azide ions as the second step: Thus, 2 equivalents of the explosive acid are required.

1.4.2.1.6. Diazotization of Hydrazines

A well-established procedure that is equally suitable for the preparetion of different classes of compounds such as aromatic and aliphatic azides, acyl azides, and sulfonyl azides is the reaction of hydrazines with nitrosyl ions or their precursors **(Scheme 1.38)** [144,145].

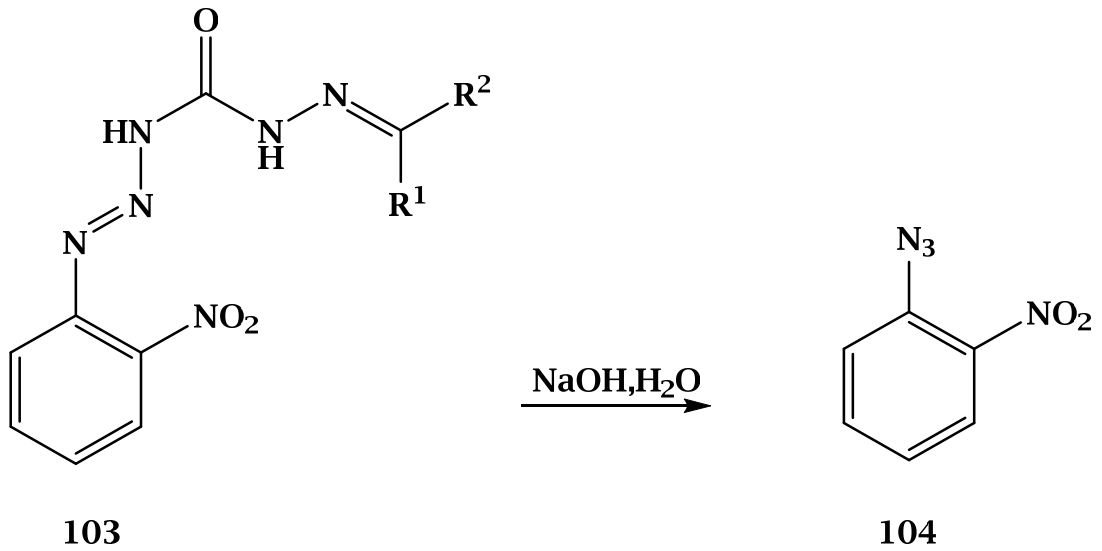


101 102

Scheme 1.38. Conversion of the aromatic hydrazine **101** into aryl azide **102** according to Kim and co-workers.

1.4.2.1.7. Modifications of Triazenes and Related Compounds

An older method for the preparation of azides is based on the rearrangement of triazenes into azides [146]. In particular, the base-induced cleavage of semicarbazones **103** can be used for the preparation of azides **104 (Scheme 1.39)** [146a].

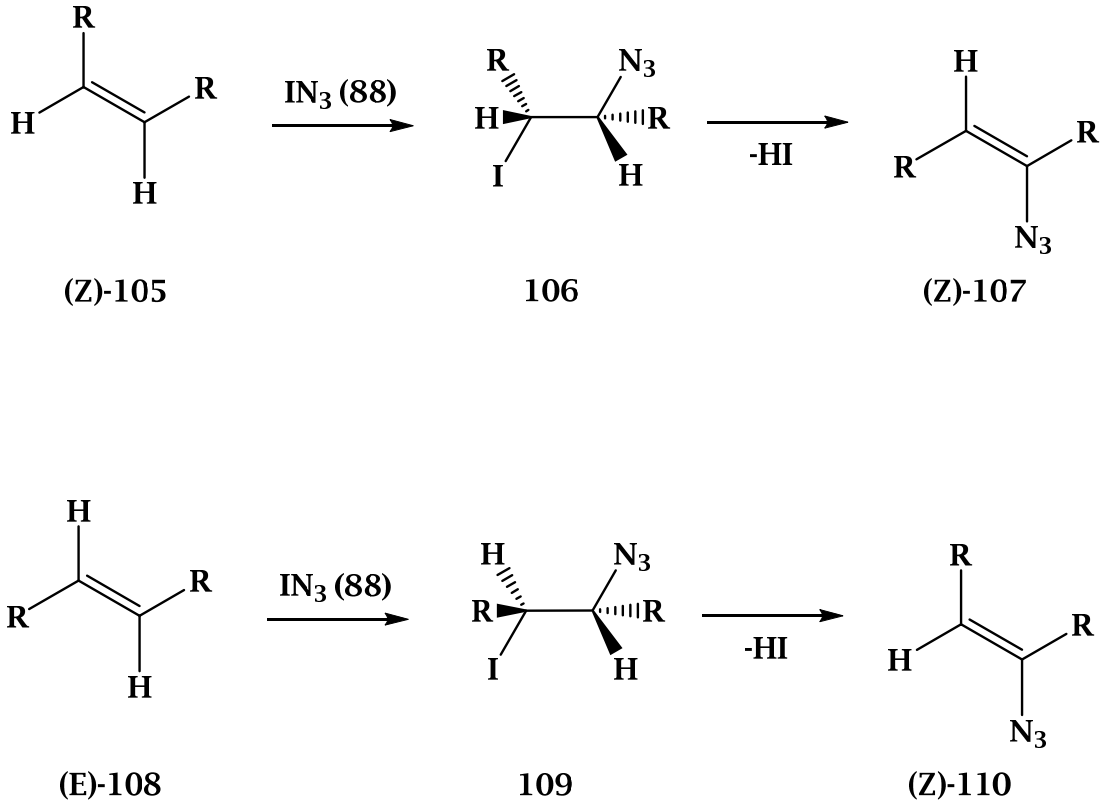


103 104

Scheme 1.39. Synthesis of the aryl azide **104** from the semicarbazone **103**.

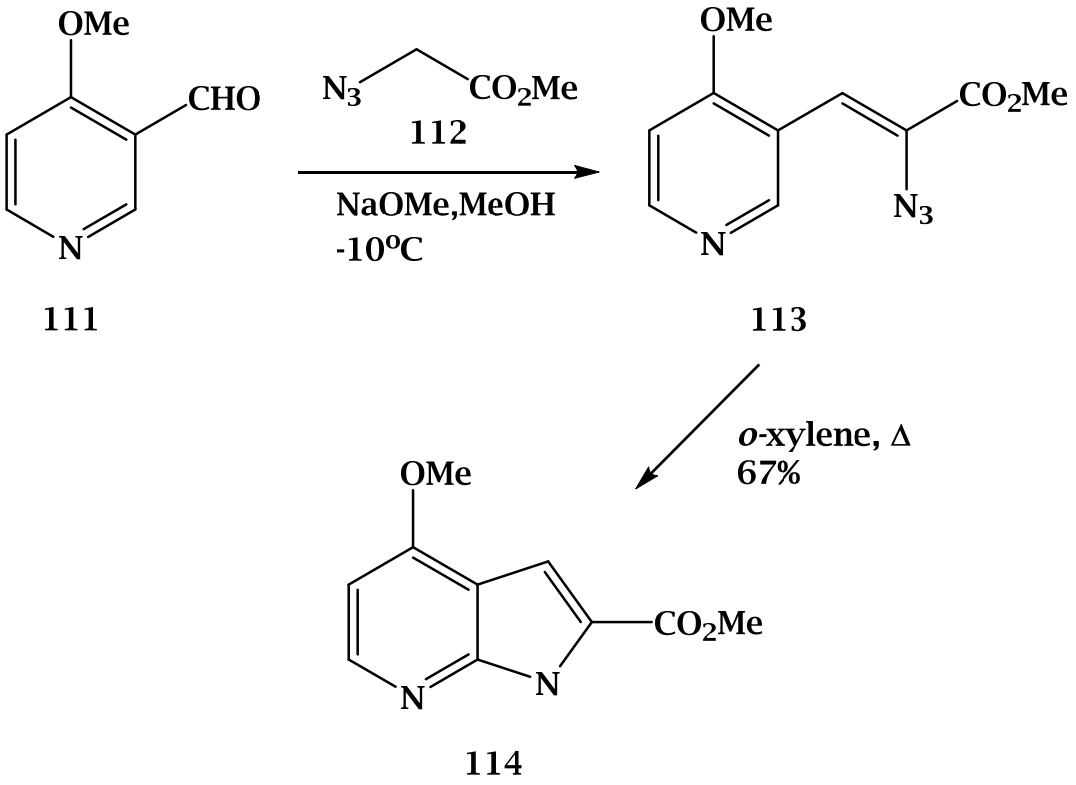
1.4.2.2. Synthesis of Alkenyl Azides

A general synthetic route for alkenyl azides was developed by Hassner and co-workers [147]. In this method, the addition of iodine azide to the double bond and the subsequent elimination of hydrogen iodide (base induced) occurs with a high degree of stereospecificity **(Scheme 1.40)**.



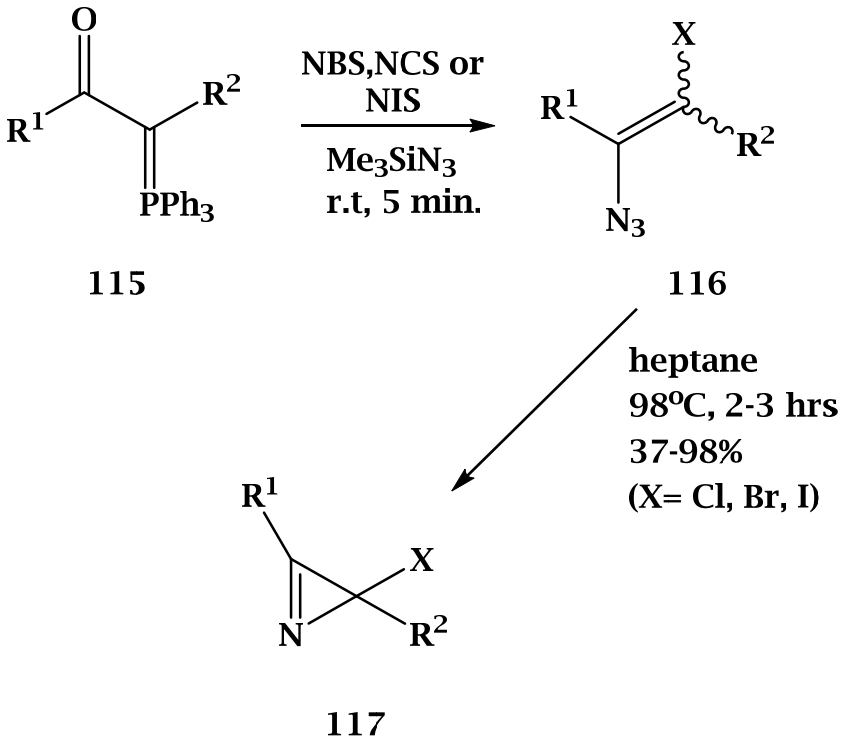
Scheme 1.40. General synthesis of alkenyl azides.

An interesting access to 3-aryl-2-azidopropenoates is provided by Knoevenagel reaction of aldehydes (e.g. **111**) and azidoacetate (e.g. **113**) **(Scheme 1.41)** [148]. The subsequent thermolysis then gives the corresponding indoles or pyrazoles. This reaction sequence was first described by Hemetsberger and co-workers [149].



Scheme 1.41. Synthesis steps in the synthesis of the alkaloid varioline **114** and its analogues.

Halogenated alkenyl azides can be formed from, among others, α-oxophosphonium ylides by the reaction with N-halosuccinimides and trimethylsilyl azide. These haloalkenyl azides can be transformed into the corresponding 2-halo-2*H*-azirines by heating to 98°C **(Scheme 1.42)** [150].

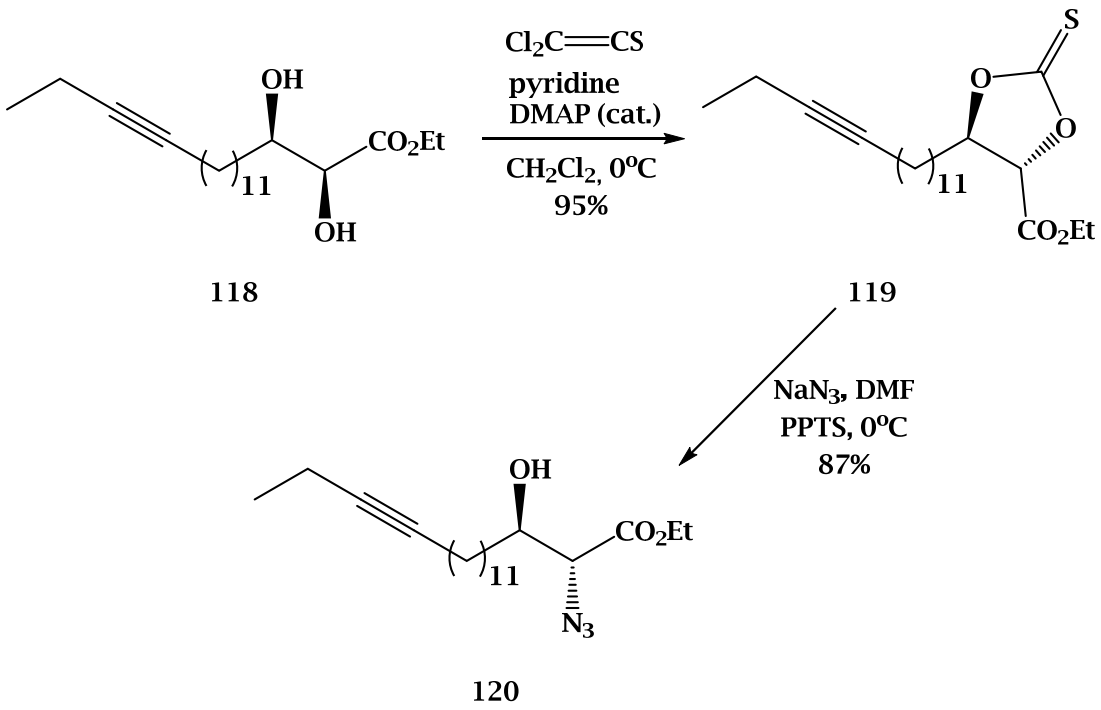


Scheme 1.42. Synthesis of 2-halo-2*H*-azirines **117** via haloalkenyl azides **116**.

1.4.2.3. Synthesis of Alkyl Azides

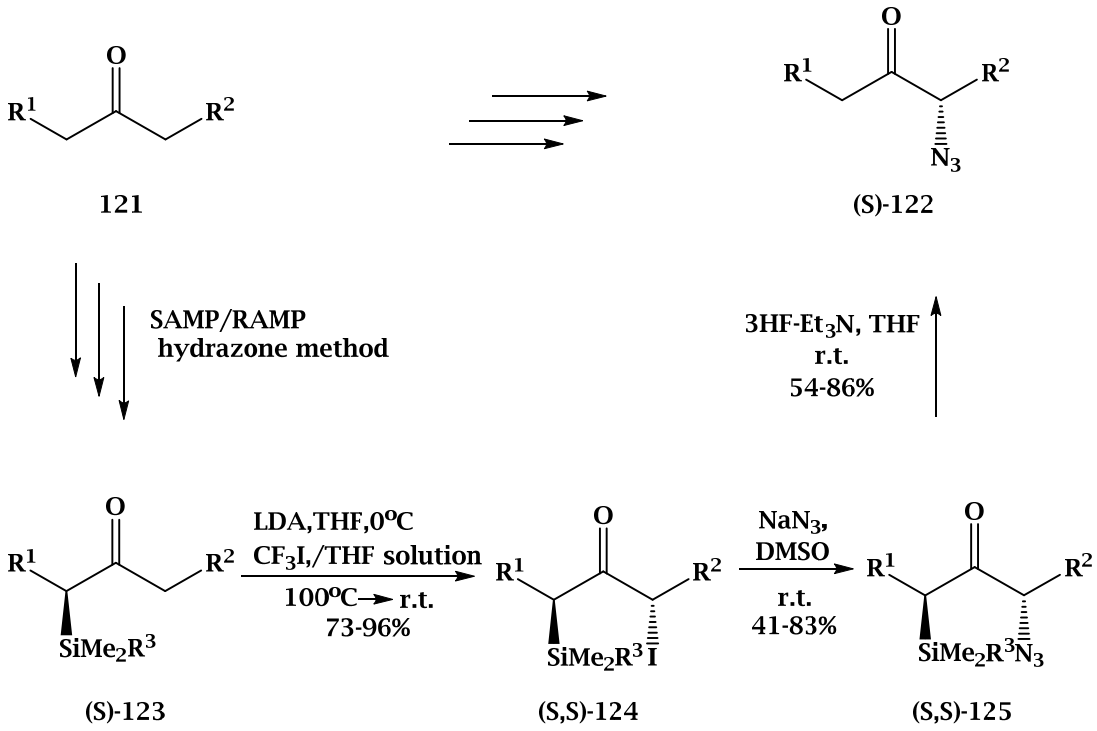
Alkyl azides are compounds readily accessible by nucleophilic substitution with the highly nucleophilic azide ion. Sodium azide is most commonly used as the azide source. Halides, carboxylates, and sulfones are used as leaving groups.

Bittman and co-workers were synthesized a regioselective alkyl azide **120** from α,β-dihydroxy ester **118** via a cyclic thiocarbonate intermediate **119** **(Scheme 1.43)** [151].



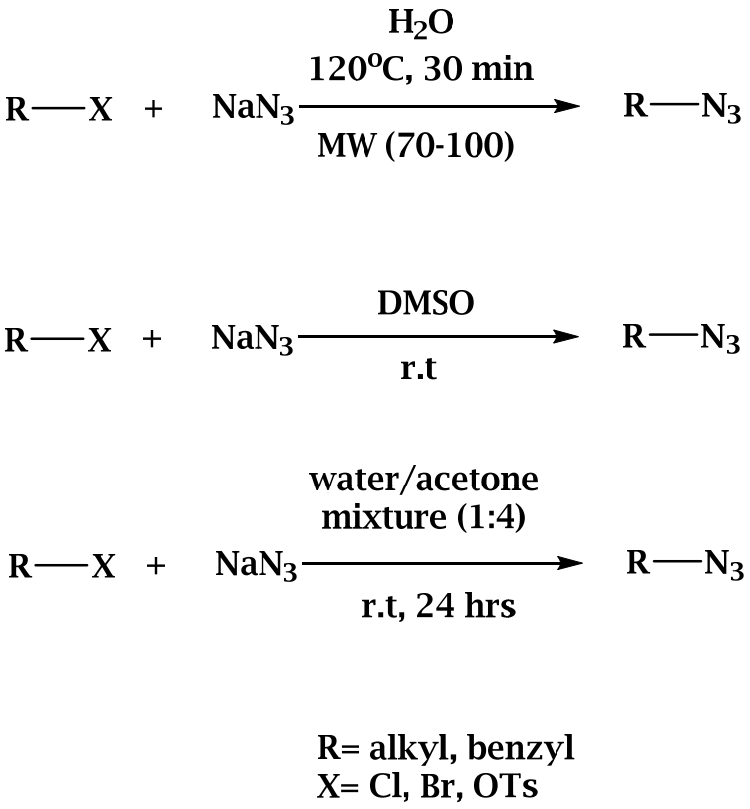
Scheme 1.43. Synthesis alkyl azide via cyclic thiocarbonate.

The asymmetric synthesis of α-azidoketones was described by Enders et al. A diastereoselective nucleophilic substitution of the iodine substituent with sodium azide is the key step in this reaction **(Scheme 1.44)** [152].



Scheme 1.44. 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 1.45)** [153-155].



Scheme 1.45. Different routes to synthesis of alkyl azides.

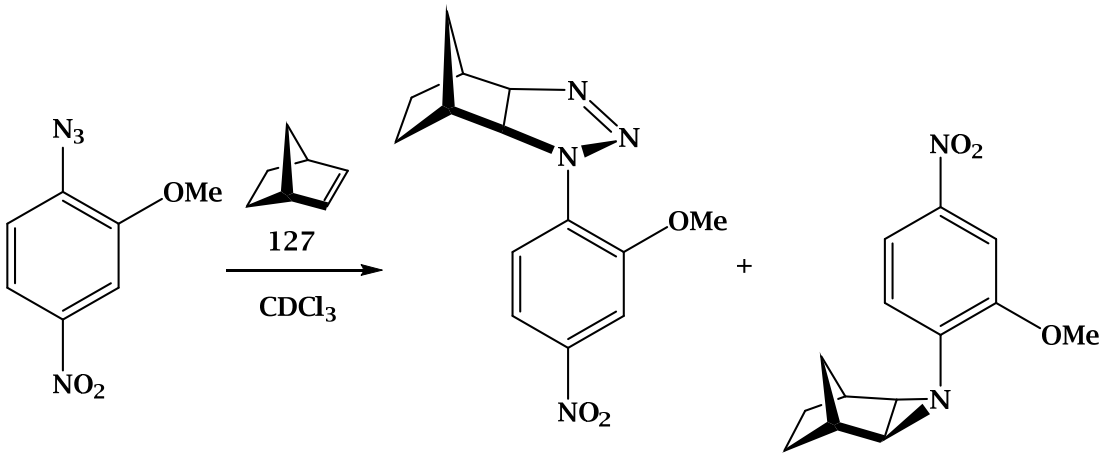
1.4.3. 1,3-Dipolar Cycloaddition Reactions of Azides

The Huisgen reaction- the cycloaddition of dipoles to dipolarophiles- also succeeds with azides as dipoles, and selected dipolarophiles can be used.

The uncatalyzed thermal cycloaddition of organic azides to alkynes and olefins allows the synthesis of 1*H*-triazoles and Δ^2-1,2,3-triazolines [156,157]. The addition takes place at different rates depending on the dipolarophile. Whereas strained olefins or alkynes such as norbornene and cyclooctyne [158] react readily, terminal alkenes react extremely slowly [157b]. In

principle, suitable dipolarophiles include both electron-deficient and electron-rich alkenes (enol ethers such as glycans [156f], and enamines [159]) as well as magnesium acetylides [156e]. Many olefins are so unreactive, however, that intramolecular reaction control or the use of microwaves is necessary [160].

The reaction of organoazides with alkenes is illustrated with a number of examples [161,162]. The aryl azide **126** reacted with norbornene **127** at 40^{o}C within 18 hours and a conversion of ≈75% with the formation of the Δ^2-1,2,3-triazoline **128** can react further to furnish the aziridine derivative **129** in a ratio 6:1 [163]. This ratio is temperature-dependent as the primarily formed Δ^2-1,2,3-triazoline **111** can react further to furnish the aziridine derivative **129** **(Scheme 1.46)**.

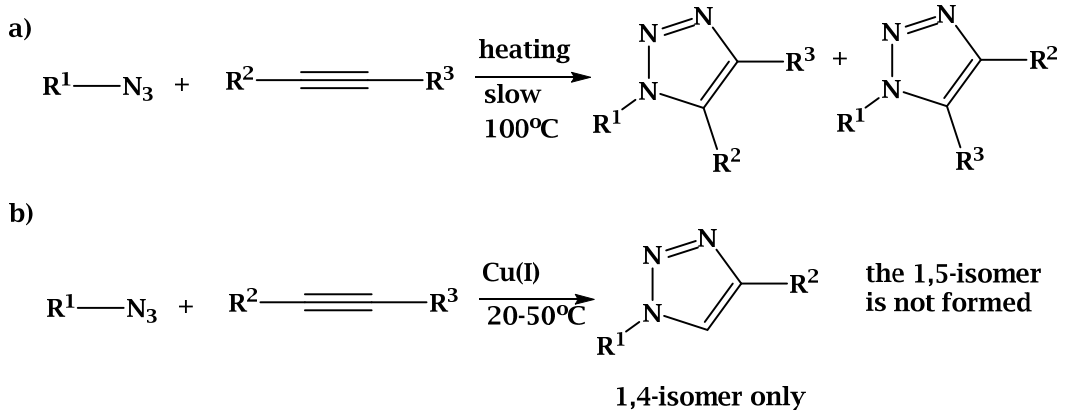


126 128 129

6 : 1

Scheme 1.46. Cycloaddition of aryl azide **109** to norbornene.

In 2001, Kolb, Finn and Sharpless defined the very useful and 'green' concept of a 'click' reaction, with the aim of binding two molecular building blocks together in a facile, selective, high-yield reaction under mild water-tolerant conditions with little or no by-products [164]. The most used click reaction that can fulfill these conditions is by far the Cu(I)-catalyzed azide-alkyne cycloaadition (CuAAC). In 2002, the research groups of Fokin and Sharpless [165] and of Meldal et al. [166] have independently reported the efficient Cu(I) catalysis of the azide/alkyne cycloaddition. The non-catalyzed azide-alkyne reaction has been known since 1893 when A. Micheal reported the first synthesis of 1,2,3-triazoles from diethyl acetylenedicarboxylate and phenyl azide. It is known as the Huisgen reaction following Huisgen's studies of the family of 1,3-dipolar cycloaddition reaction in the middle of the 20th century [160]. The Huisgen reaction produces a mixture of 1,4- and 1,5-disubstitution products; whereas, the CuAAC reaction of terminal alkynes is completely selective in the formation of the 1,4-disubstituted triazoles with a variety of Cu(I)catalysts or precursors of Cu(I) catalysts **(Scheme 1.47)** [165,166].



Scheme 1.47. Azide-alkyne cycloaddition **a)** Huisgen reaction, **b)** CuAAC reaction.

A large variety of copper catalysts can be used for the CuAAC reaction provided that some Cu^{I} species is generated [165,166,168-171]. It is essential to keep the Cu^{I} concentration at its maximum in order to facilitate the reaction. The pre-catalyst can be a Cu^{II} salt (usually $CuSO_4$) together with a reducing agent (usually sodium ascorbate), a Cu^{I} compound (preferably CuBr or CuOAc), together with a base or amine ligand and a reducing agent (sodium ascorbate) in order to inhibit aerobic oxidation to Cu^{II}, or a Cu^{0} compound (wire, turnings, powder or nanoparticles), the surface of which forms the required Cu^{I} species [172,173].

1.5. TRIAZOLES

Triazoles are a specific type of heterocycle containing three nitrogen atoms; heterocyles 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 [174].

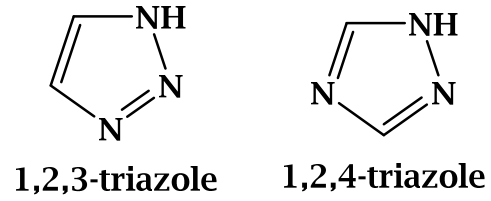


Figure 1.9. Isomers of triazole.

1,2,3-triazoles have been widely used especially in biomedical applications including treatments of tumors [175,176], HIV [177], allergy [178], fungal infection [179,180], and microbial diseases [181-185].

One of the synthetic methods to assemble 1,2,3-triazoles is the Huisgen 1,3-dipolar cycloaddition of azides and alkynes **(Section 1.4.3)**.

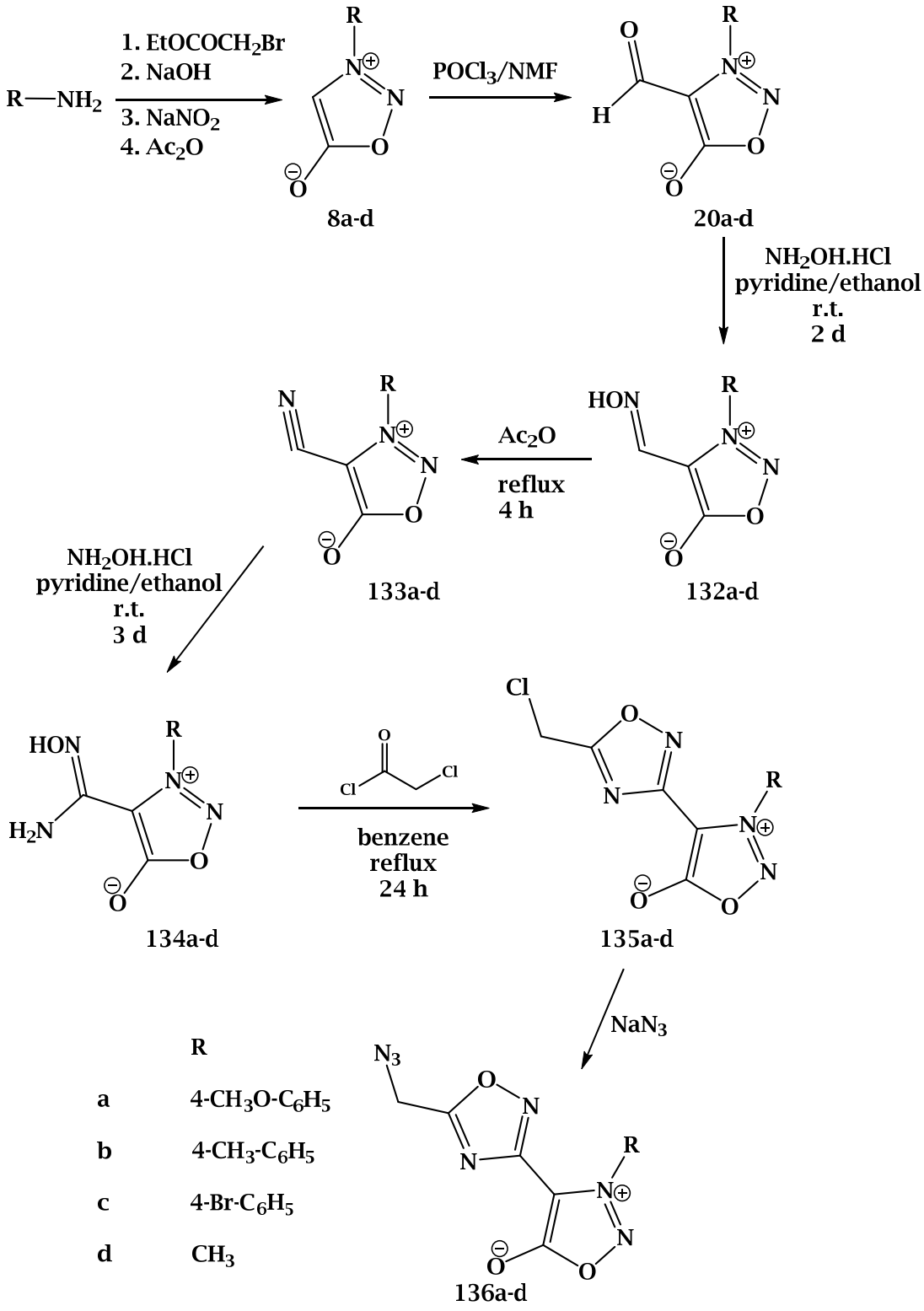
CHAPTER II

2.1. RESULTS and DISCUSSION

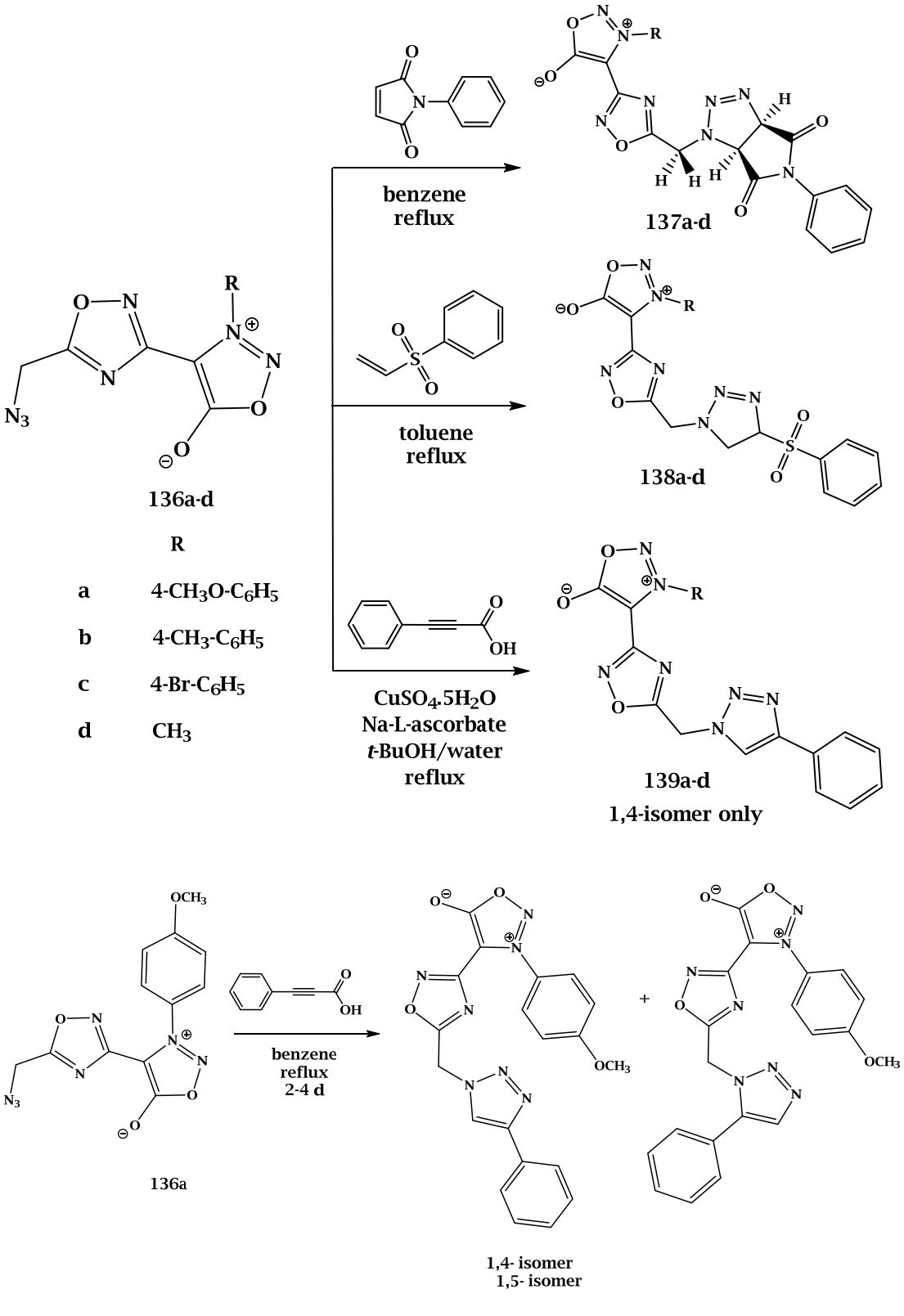
In this study, the synthesis of a series of chloromethyl-1,2,4-oxadiazole substituted sydnones and azidomethyl-1,2,4-oxadiazole substituted sydnones, respectively, have been introduced. Also, the 1,3-dipolar cycloaddition reactions of these novel substituted sydnone azides, which is the major purpose of this work, with *N*-phenylmaleimide, phenyl vinyl sulfone and phenylpropiolic acid give rise to a series of substituted 1,2,3-triazoles carrying oxadiazole, pyrrolidine, phenyl sulfonyl groups. To our best knowledge of literature, there are many examples of cycloaddition reactions of organic azides with alkenes and alkynes, but azides **134a-d,** bearing sydnone mesoionic system, which are substituted with a 1,2,4-oxadiazole ring, are not reported and registered as far as we searched the literature (SCIENCE FINDER and WEB OF KNOWLEDGE electronic databases). On the other hand, heterocyclic compounds carrying sydnone, oxadiazole and triazole moieties seemed to have a reputation and attract a continuous interest because of their varied pharmacological activities. For these reasons, we have focused, in this work, on the synthesis of these triazolo oxadiazole substituted sydnones starting from simple sydnones.

The present research work is basically consisted of eight parts:

1. Synthesis of 3-substituted sydnones **8a-d** from anilines or glycine.
2. Synthesis of 4-formyl-3-substituted sydnones **20a-d** from 3-substituted sydnones **8a-d**.
3. Synthesis of 3-substituted-4-formylsydnone oximes **132a-d** from 4-formyl-3-substituted sydnones **20a-d**.
4. Synthesis of 4-cyano-3-substituted sydnones **133a-d** from 3-substituted-4-formylsydnone oximes **132a-d**.
5. Synthesis of 3-substituted sydnone-4-carboxamidoximes **134a-d** from 4-cyano-3-substituted sydnones **133a-d**.
6. Synthesis of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-3-substituted sydnones **135a-d** from 3-substituted-4-carboxamidoximes **134a-d**.
7. Synthesis of 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-substituted sydnones **136a-d** from of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-3-substituted sydnones **135a-d**.
8. Synthesis of cycloadducts by the reaction between 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-substituted sydnones **136a-d** and with three different dipolarophiles.



Scheme 2.1. Synthetic pathways leading to the formation of 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-substituted sydnones **136a-d**.

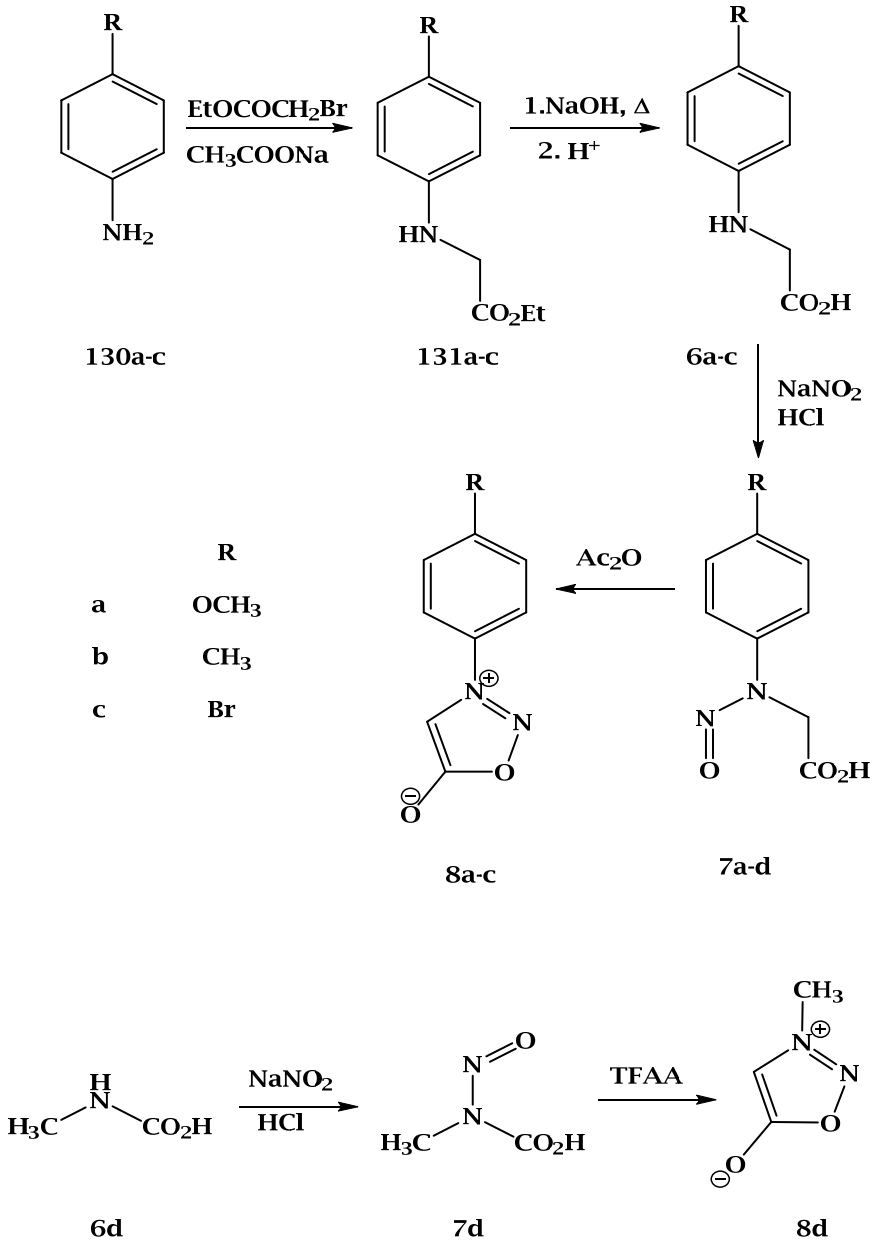


Scheme 2.2. Synthesis of cycloadducts by the reaction between 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-substituted sydnones **136a-d** and with *N*-phenylmaleimide, phenyl vinyl sulfone, and phenylpropiolic acid.

In the first part of the study, 3-aryl substituted sydnones **8a-c** were synthesized using a four-step approach with little purification until the last step, where the desired sydnone was purified by recrystallisation [186]. The stepwise approach involved:

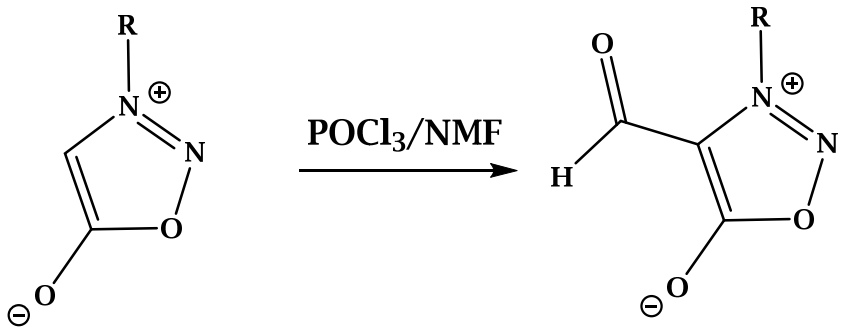
i. Alkylation of the aniline with ethyl bromoacetate and sodium acetate in ethanol to yield glycine ester.
ii. Hydrolysis of ester with sodium hydroxide to reveal the *N*-arylglycine.
iii. Nitrosation of *N*-arylglycine with sodium nitrite in hydrochloric acid and water to provide the nitroso compound.
iv. Cyclization of the nitrosated glycine to the sydnone with acetic anhydride.

However, 3-methylsydnone **8d** was synthesized from sarcosine in two steps according to literature procedure [187]. The first step was nitrosation of sarcosine with sodium nitrite in hydrochloric acid and water. The last step was cyclisation of nitroso compound with trifluoroacetic anhydride in dry ether **(Scheme 2.3)**.



Scheme 2.3. Synthesis of 3-(*p*-substitutedphenyl) and methyl substituted sydnones **8a-d**.

In the second part, 3-aryl and methyl substituted sydnones **8a-d** were reacted with phosphoryl chloride and *N*-methylformanilide, via Vilsmeier-Haack reaction, to give 4-formyl-3-aryl and methyl substituted sydnones **20a-d (Scheme 2.4)** [49].

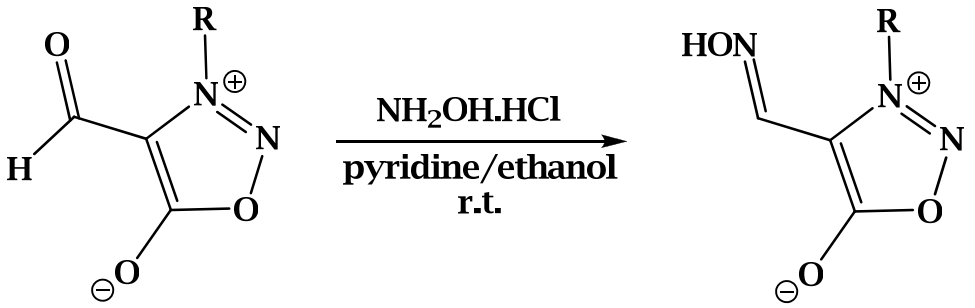


5	R	20
a	4-CH_3O-C_6H_5	
b	4-CH_3-C_6H_5	
c	4-Br-C_6H_5	
d	CH_3	

Scheme 2.4. Synthesis of 4-formyl-3-aryl and methyl substituted sydnones **20a-d**.

The structures of 4-formyl sydnones **20a-d** were confirmed on the basis of IR, LC-MS, ^{1}H NMR and R_f values reported in literature. The very basic proof for the generation of formyl group is the carbonyl absorption bands in the IR spectra of compounds at around 1770-1790 cm^{-1} which came out from sydnone and at around 1643-1680 cm^{-1} which came out from formyl group. In addition, the chemical shift position of aldehydic formyl protons appear between 9-10 ppm in the ^{1}H NMR spectra.

In the third part, 4-formyl-3-aryl and methyl substituted sydnones **20a-d** were reacted with hydroxylamine hydrochloride at room temperature in pyridine to give 3-aryl and methyl substituted-4-formylsydnone oximes **132a-d (Scheme 2.5)** [188]**.**



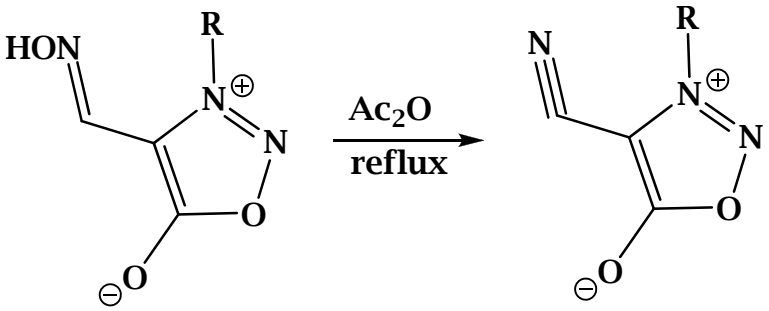
20 **132**

	R
a	4-CH_3O-C_6H_5
b	4-CH_3-C_6H_5
c	4-Br-C_6H_5
d	CH_3

Scheme 2.5. Synthesis of 3-aryl and methyl substituted-4-formylsydnone oximes **132a-d** from 4-formyl-3-aryl and methyl substituted sydnones **20a-d**.

The structures of the sydnone aldoximes were identified by IR, ^{1}H NMR, LC-MS and R_f characteristics. The primary indicative evidence of this series is the appearance of NOH absorption bands at around 3260-3320 cm^{-1} in the IR spectra of compounds. In addition, ^{1}H NMR spectra further exhibited the aldoxime protons at around 8-12 ppm.

In the fourth part, 3-aryl and methyl substituted-4-formylsydnone oximes **130a-d** were reacted with excess acetic anhydride to give 4-cyano-3-aryl and methyl substituted sydnones **131a-d (Scheme 2.6)** [188].



132 **133**

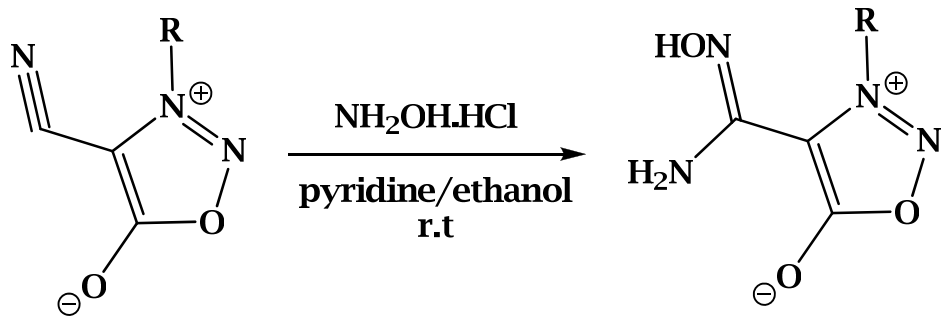
	R
a	**4-CH_3O-C_6H_5**
b	**4-CH_3-C_6H_5**
c	**4-Br-C_6H_5**
d	**CH_3**

Scheme 2.6. Synthesis of 4-cyano-3-aryl and methyl substituted sydnones **133a-d** from 3-aryl and methyl substituted-4-formylsydnone oximes **132a-d**.

The structures of 4-cyano-3-aryl and methyl substituted sydnones **133a-d** were confirmed on the basis of IR, LC-MS, ^{1}H NMR and R_f values. In the IR spectra, the C≡N absorption bands appearing at around 2220-2230 cm^{-1} is major descriptive indication of the formation of cyano derivatives.

In the fifth part of this study, 3-aryl and methyl substituted sydnone-4-carboxamidoximes **134a-d** were synthesized from 4-cyano-3-aryl and methyl

substituted sydnones **133a-d** using hydroxylamine hydrochloride in pyridine/ethanol mixture at room temperature **(Scheme 2.7)** [189].



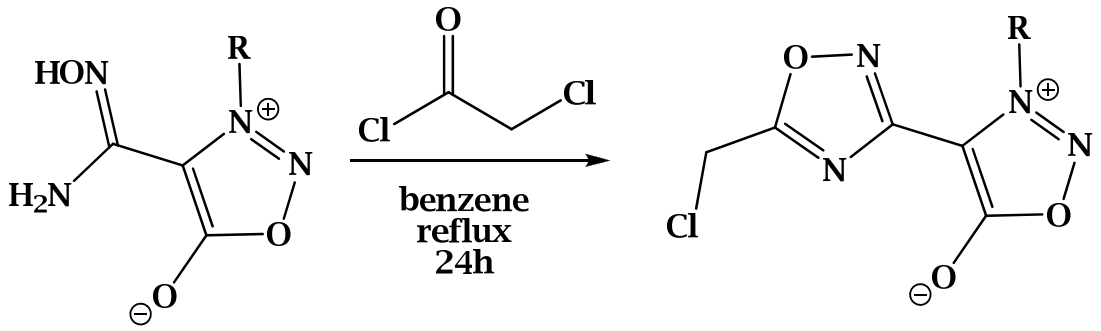
133 **134**

	R
a	4-CH_3O-C_6H_5
b	4-CH_3-C_6H_5
c	4-Br-C_6H_5
d	CH_3

Scheme 2.7. Synthesis of 3-aryl and methyl substituted sydnone-4-carboxamidoximes **134a-d** from 4-cyano-3-aryl and methyl substituted sydnones **133a-d**.

The structures of the sydnone carboxamidoximes **134a-d** were identified by LC-MS, ^{1}H NMR, LC-MS and R_f characteristics. The primary indicative evidence of this series is the disapperance of C≡N absorption bands and the apperance of NH_2 absorption bands and NOH absorption bands at around 3100-3500 cm^{-1} in the IR spectra of the compounds. In addition, NH_2 protons are appeared at around 5 ppm in the ^{1}H NMR spectra.

In the sixth part, 3-aryl and methyl substituted sydnone-4-carboxamidoximes **134a-d** were treated with chloroacetyl chloride at the reflux temperature of benzene to give 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-3-aryl and methyl substituted sydnones **135a-d (Scheme 2.8)**.



134 **135**

	R
a	4-CH_3O-C_6H_5
b	4-CH_3-C_6H_5
c	4-Br-C_6H_5
d	CH_3

Scheme 2.8. Synthesis of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-3-aryl and methyl substituted sydnones **135a-d** from 3-aryl and methyl substituted sydnone-4-carboxamidoximes **134a-d**.

The structures of the novel chloromethyl oxadiazolyl substituted sydnones were determined by their physical (melting point and R_f values) and spectral data, namely, IR, NMR (^1H, ^{13}C), LC-MS and HRMS measurements. In the IR spectra, the disappearance of the NH_2 and NOH absorptions of the corresponding amidoximes is major descriptive indication of the formation of

5-(chloromethyl)-1,2,4-oxadiazole ring. In addition, the chemical shift positions of methylene protons appears between 4.0-5.0 ppm in the ^{1}H NMR spectra **(Figure 2.1)**.

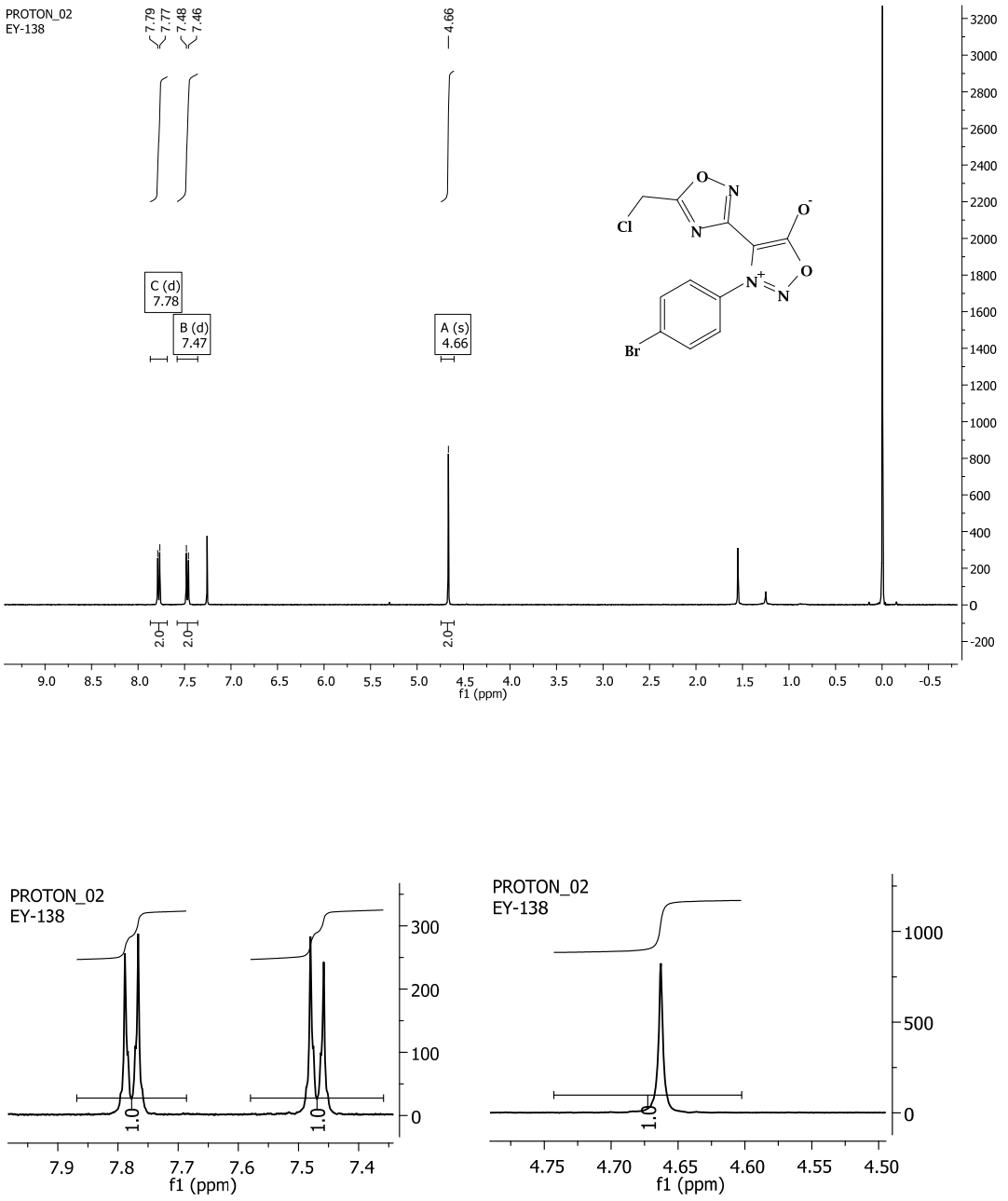


Figure 2.1. The full-scale and expanded ^{1}H NMR spectrum of **135c**.

In the ^{13}C NMR spectra of these compounds, three different carbon signals are appeared between 180-160 ppm **(Figure 2.2)**. One of them is assigned sydnone carbonyl at ~174 ppm. The other two carbon signals at ~ 164 ppm and ~158 ppm are assigned the iminic carbons, C=N, which came out from 1,2,4-oxadiazole ring. The C-3 on oxadiazole ring (~164 ppm) is the more deshielded than the C-5 on oxadiazole ring (~158 ppm).

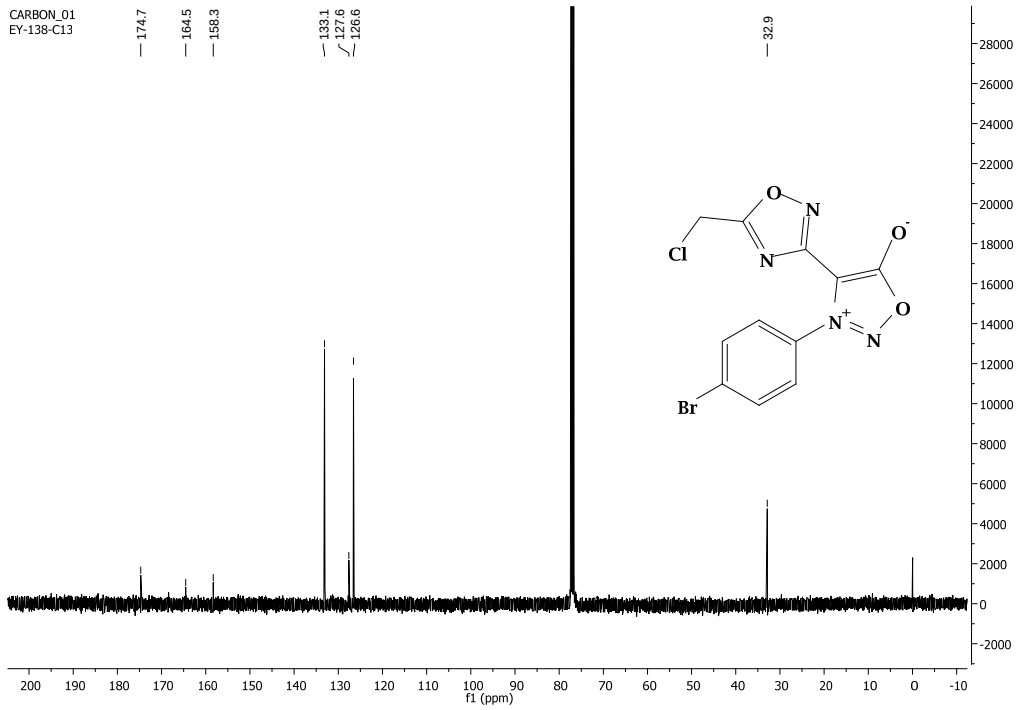


Figure 2.2. The ^{13}C NMR spectrum of **135c**.

The recrystallization of **135c** from ethyl acetate/hexane gave crystals and the structure of compounds were elucidated by X-ray diffraction.

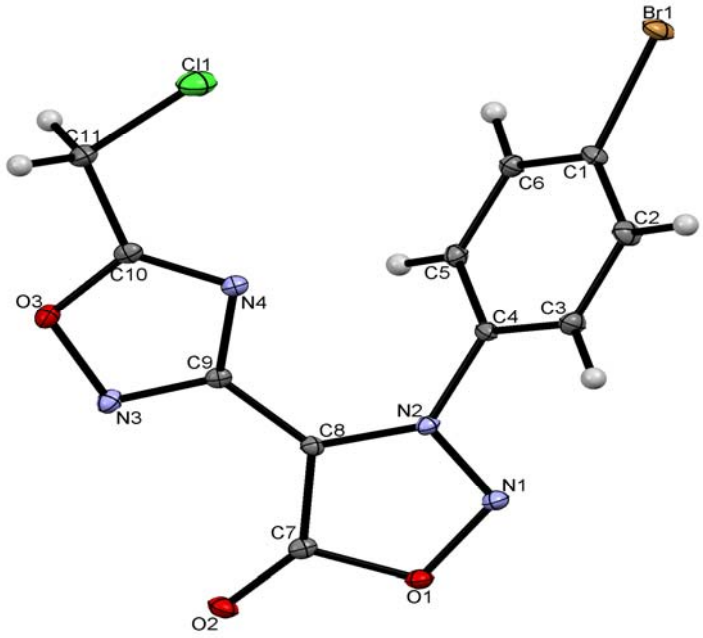
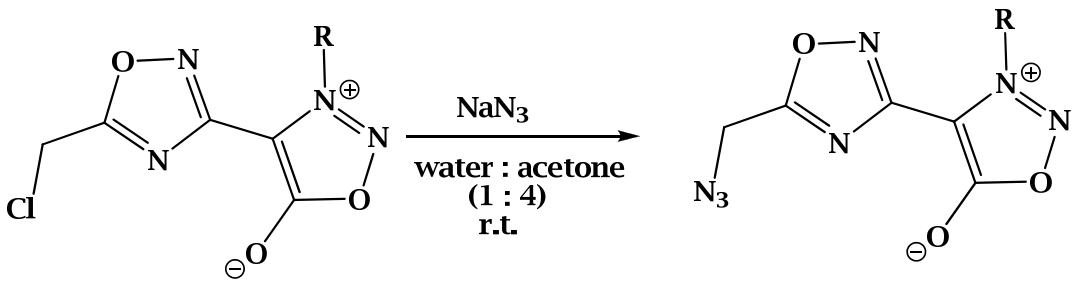


Figure 2.3. X-Ray ORTEP view of **135c**.

In the next part of the study, the pure 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-3-aryl and methyl substituted sydnones **135a-d** were reacted with sodium azide at room temperature in water/acetone mixture to give 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-aryl and methyl substituted sydnones **136a-d** **(Scheme2.9).**



135 **136**

	R
a	4-CH_3O-C_6H_5
b	4-CH_3-C_6H_5
c	4-Br-C_6H_5
d	CH_3

Scheme 2.9. Synthesis of 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-aryl and methyl substituted sydnones **136a-d** from 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-3-aryl and methyl substituted sydnones **135a-d**.

The 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-aryl and methyl substituted sydnones **136a-d** were identified by IR, NMR (^1H, ^{13}C),, LC-MS, HRMS, melting point and R_f characteristics. The very basic proof for the generation of the 5-(azidomethyl)-1,2,4-oxadiazole group is the appearance of the N=N=N absorption band between 2090-2200 cm^{-1} in the IR spectra of these compounds **(Figure 2.4)**.

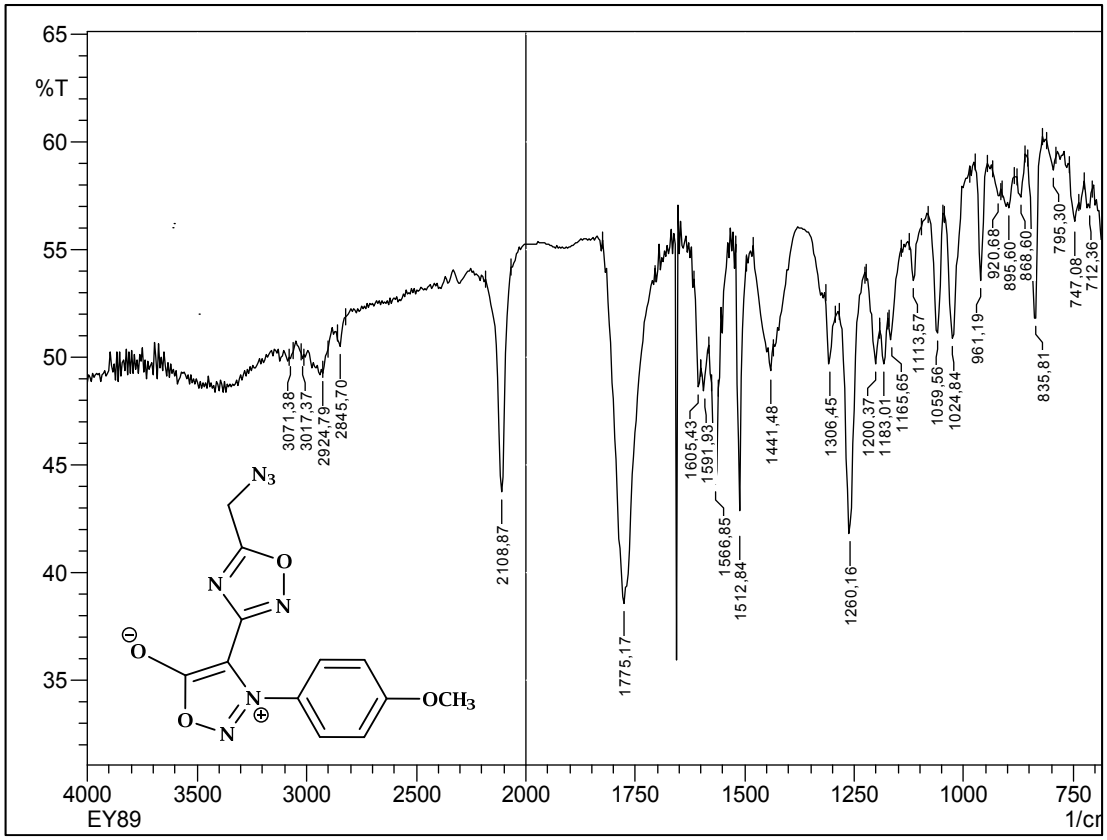


Figure 2.4. The IR spectrum of **136a**.

The mass spectra are the another evidence of the 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-aryl and methyl substitued sydnones **136a-d (Figure 2.5)**. Since, mass specta shows that the base peaks are the $[M+H]^+$ ions.

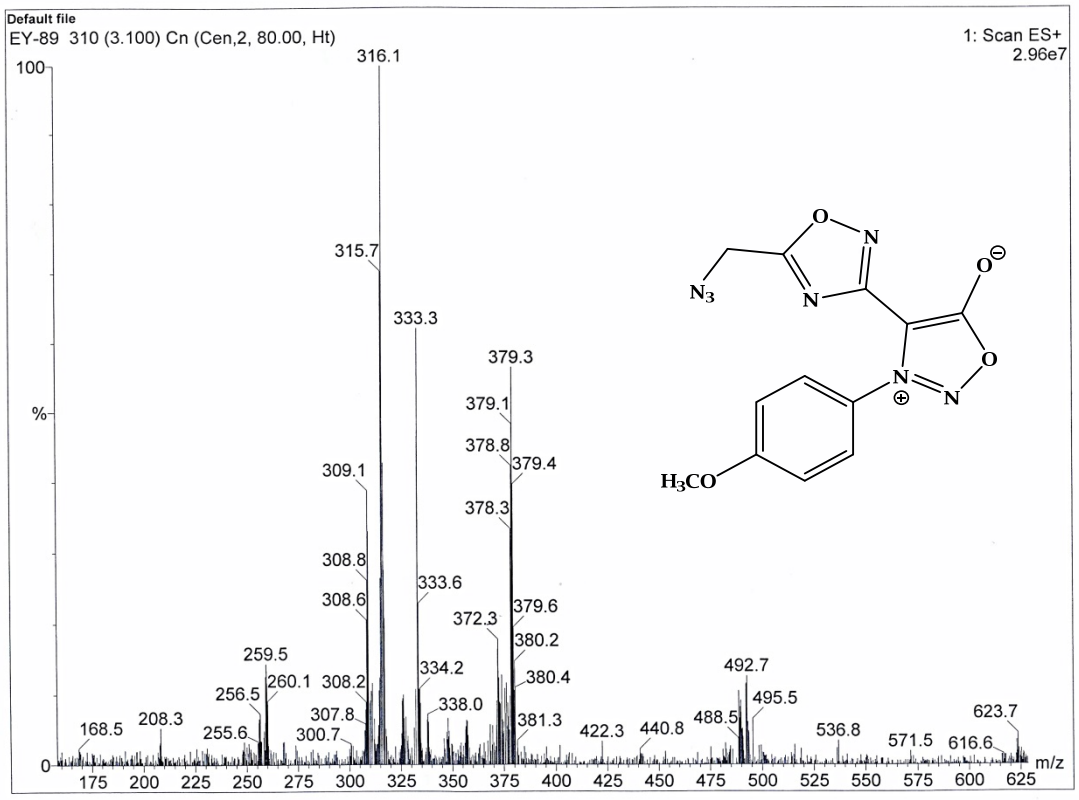
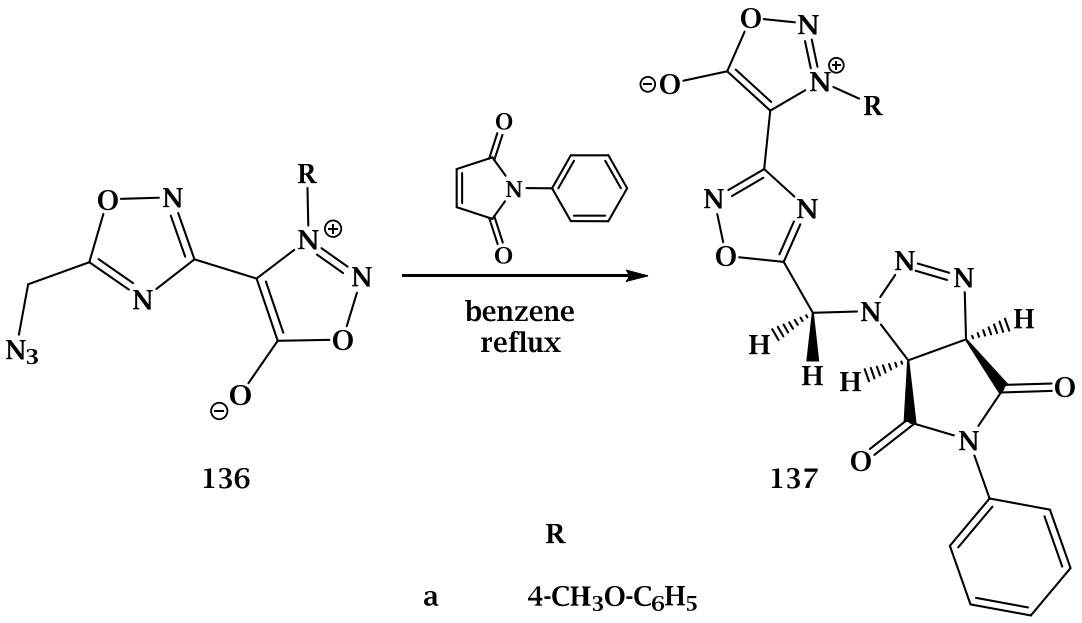


Figure 2.5. The LC-MS spectrum of **136a**.

The last part of this study includes 1,3-dipolar cycloaddition reactions of 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-aryl and methyl substituted sydnones **136a-d** with three different dipolarophiles to give pyrrolo oxadiazole substituted sydnones.

Firstly, 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-aryl and methyl substituted sydnones **136a-d** were reacted with *N*-phenylmaleimide at the reflux temperature of benzene to give four novel 4-(5-(((3a*R*,6a*S*)-4,6-dioxo-5-phenyl-4,5,6,6a-tetrahydropyrrolo[3,4-*d*][1,2,3]triazol-1(3a*H*)-yl)methyl)-1,2,4-

oxadiazol-3-yl)-3-aryl and methyl substituted sydnones **137a-d (Scheme 2.10)**.



136 137

	R
a	4-CH_3O-C_6H_5
b	4-CH_3-C_6H_5
c	4-Br-C_6H_5
d	CH_3

Scheme 2.10. Synthesis of 4-(5-(((3a*R*,6a*S*)-4,6-dioxo-5-phenyl-4,5,6,6a-tetrahydropyrrolo[3,4-*d*][1,2,3]triazol-1(3a*H*)-yl)methyl)-1,2,4-oxadiazol-3-yl)-3-aryl and methyl substituted sydnones **137a-d**.

These novel cycloadducts **137a-d** were identified by IR, NMR (^1H, ^{13}C), LC-MS, HRMS, melting point and R_f characteristics. In the IR spectra, the disappearance of N=N=N absorption band of the corresponding azides and the appearance of C=O absorption band between 1725-1720 cm^{-1} in addition to sydnone C=O absorption band between 1750-1775 cm^{-1} are the primary indications for the generation of these novel compounds **(Figure 2.6)**.

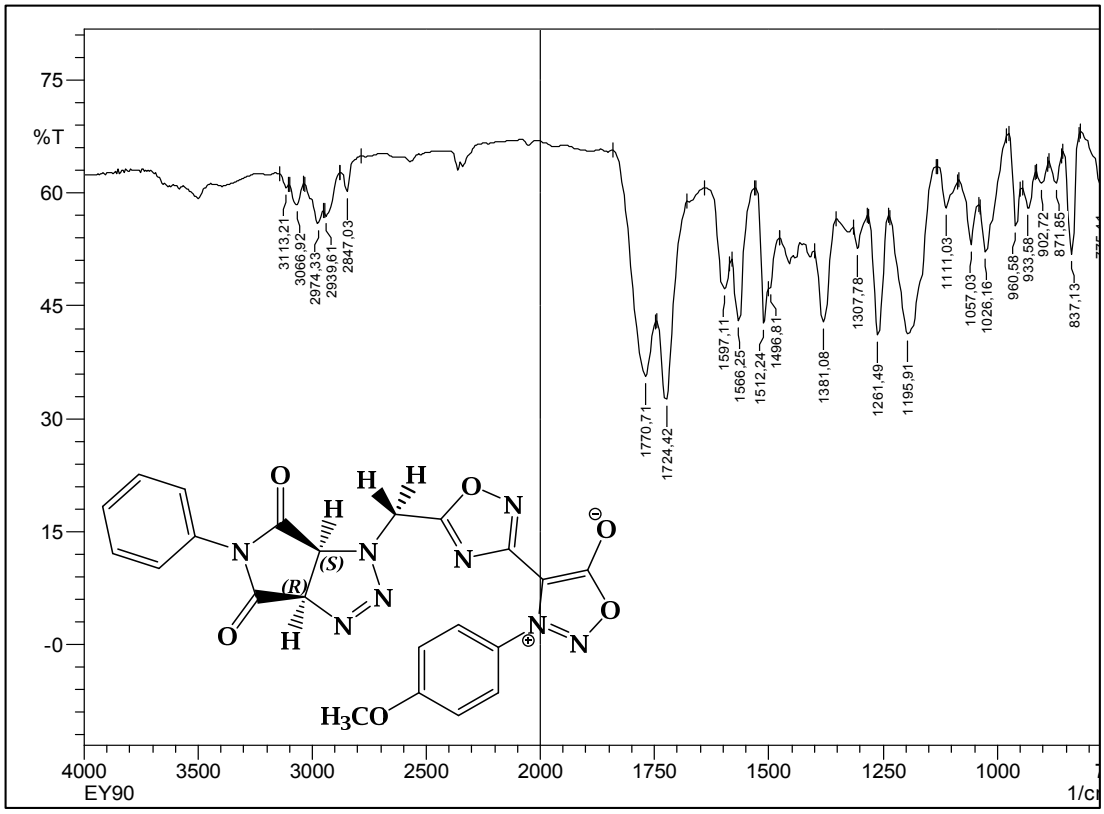


Figure 2.6. The IR spectrum of **137a**.

The another proof regarding the structure of the cycloadduct **137a** is carbon chemical shift positions in the ^{13}C NMR spectrum which exhibits six different carbons between 158-180 ppm **(Figure 2.7)**. One of them is assigned to sydnone carbonyl at ~174 ppm. Two of these carbon signals are assigned to two carbonyl of maleimide group at ~170 ppm and ~168 ppm. The signal at ~162 ppm is assigned to methoxy attached carbon. The other two carbon signals are assigned to the iminic carbons, C=N, at ~164 ppm and ~158 ppm.

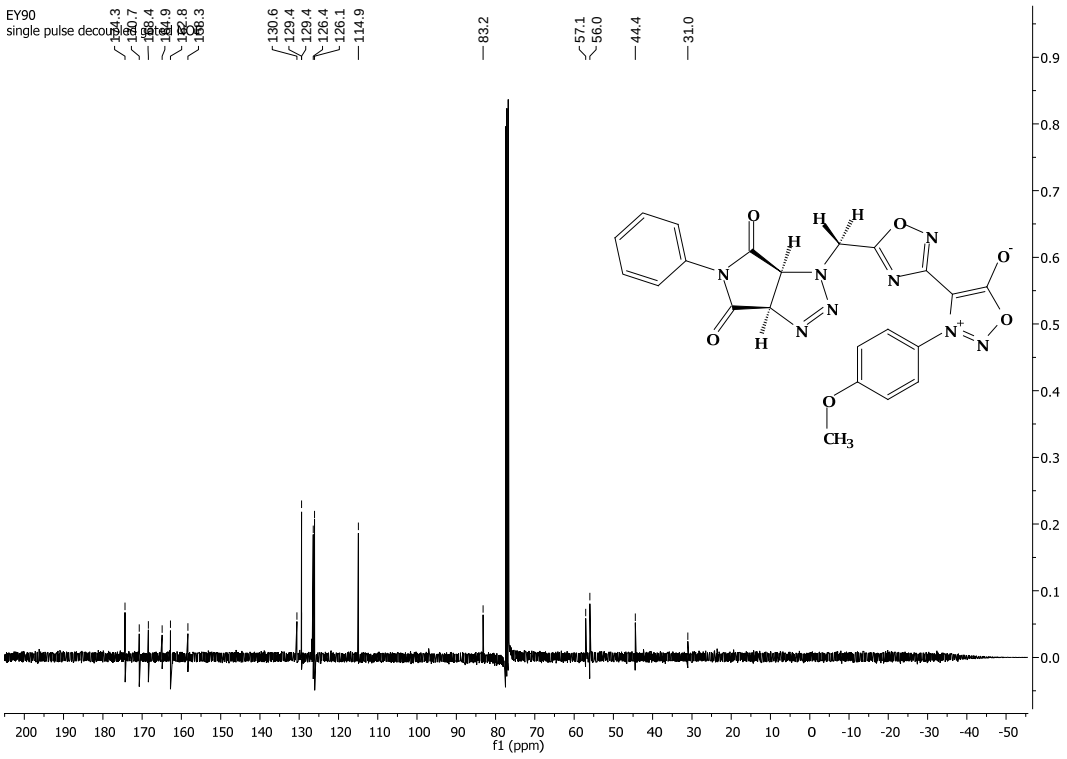


Figure 2.7. The ^{13}C NMR spectrum of **137a**.

In addition, in ^{1}H NMR spectra, the H_a and H_b must be one doublet signal, but they shows two doublet signals between 4.0-6.0 ppm **(Figure 2.8)**. H_b (~5.6 ppm) is more deshielded than H_a (~4.5 ppm) because of N=N of the 1,2,3-triazole group. The metylene protons must appear as a singlet signal, but they appear two doublet signals between 6.0-5.0 ppm in $CDCl_3$.

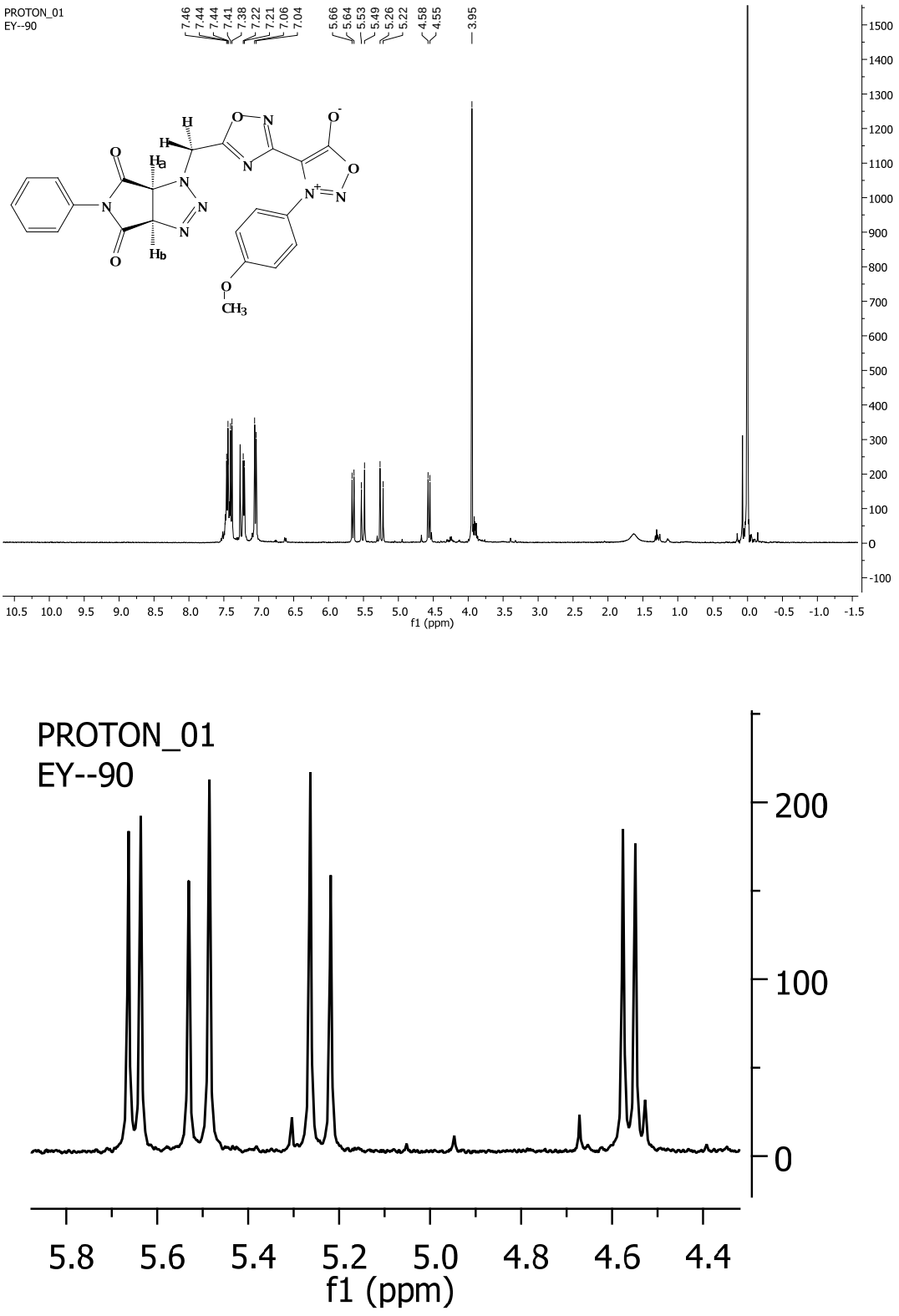


Figure 2.8. The full-scale and expanded ^{1}H NMR spectrum of **137a**.

Moreover, the recrystallization of **137a** from ethyl acetate/hexane gave fine crystals and the exact structure of compound was elucidated by X-ray diffraction **(Figure 2.9)**.

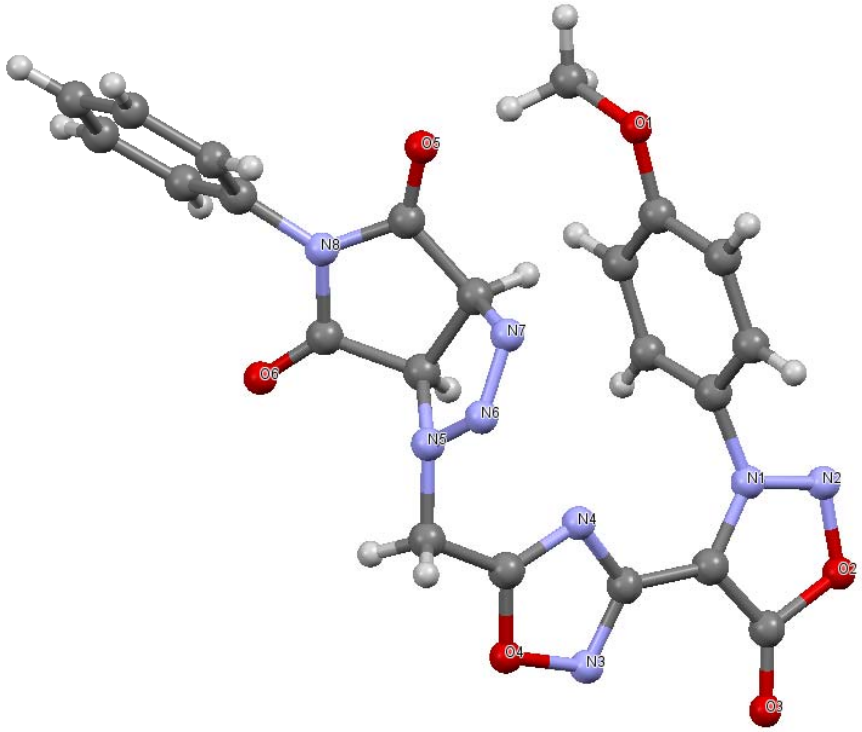
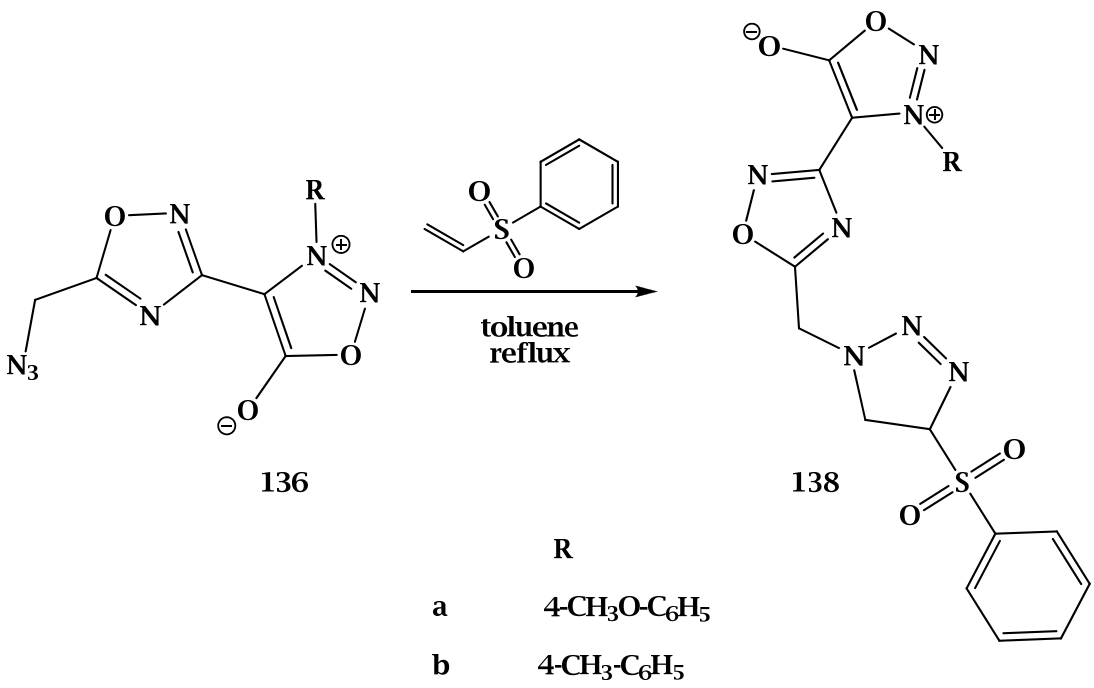


Figure 2.9. The ORTEP view of **137a**.

Secondly, 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-substituted sydnones **136a-b** were reacted with electron deficient alkene; phenyl vinyl sulfone at the reflux temperature of toluene to afford 3-aryl substituted-4-(5-((5-(phenylsulfonyl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazol-3-yl)sydnones **138a-b (Scheme 2.11)**.



136 138

R	
a	4-CH_3O-C_6H_5
b	4-CH_3-C_6H_5

Scheme 2.11. Synthesis of 3-aryl substituted-4-(5-((5-(phenylsulfonyl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazol-3-yl)sydnones **138a-b**.

These two novel cycloadducts were identified by means of IR, NMR (^{1}H, ^{13}C), LC-MS, HRMS, melting point and R_f characteristics. The primary indication for the generation of this compounds are the disappearance of N=N=N absorption band of the corresponding azides and the appearance of the sulfone (SO_2) symmetric (1140-1150 cm^{-1}) and asymmetric (1300-1330 cm^{-1}) stretching absorptions in their IR spectra **(Figure 2.10)**.

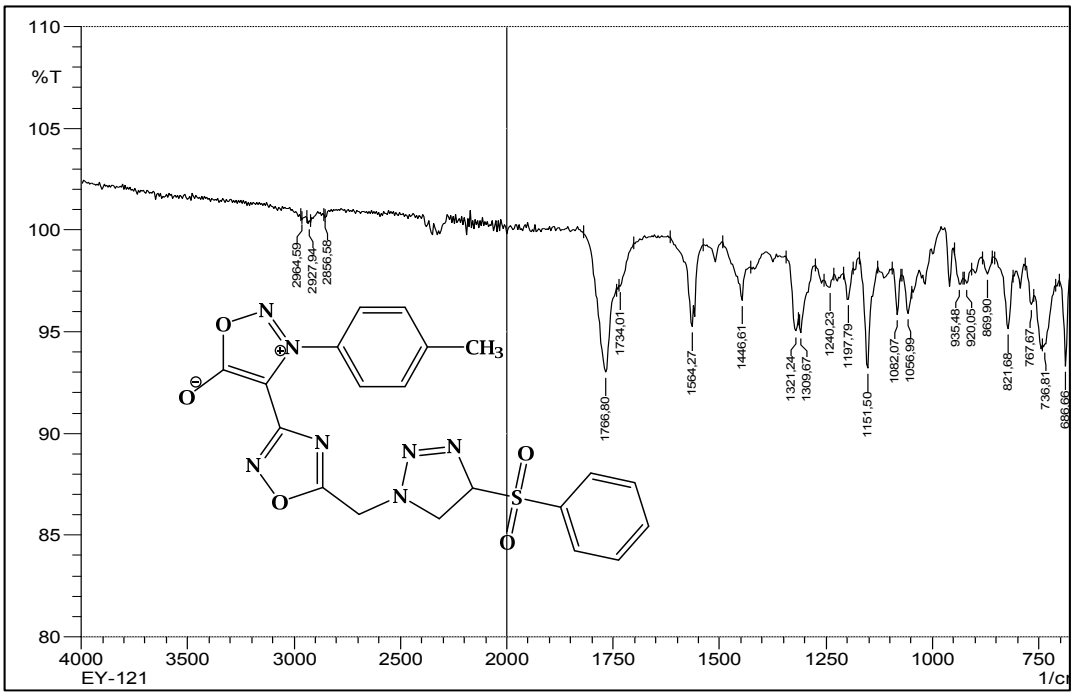
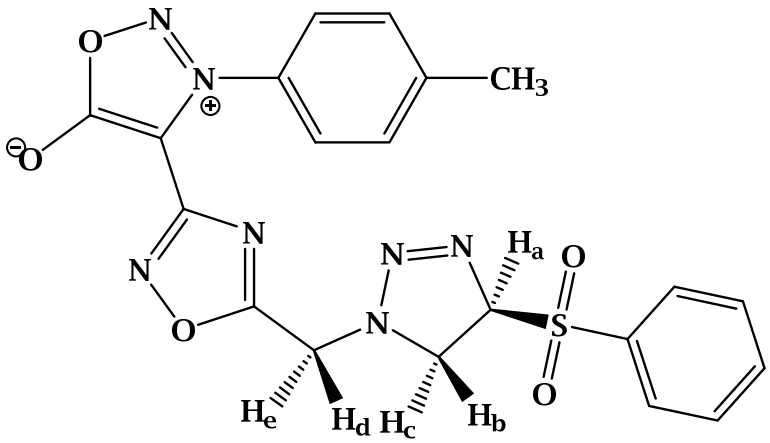


Figure 2.10. The IR spectrum of **138b**.

In the ^{1}H NMR spectra of these compounds, the protons H_a, H_b, H_c, H_d, H_e exhibits different splitting patterns at different chemical shift values **(Figure 2.11)**.



138b

Figure 2.11. The structure of **138b**.

The H_a proton is the most deshielded due to the phenylsulfonyl group. This proton appears as doublet of doublet at ~5.5 ppm. Two doublets at ~5.2 ppm and ~4.9 ppm indicate the geminal H_b and H_c protons. Geminal protons H_d and H_e appear as one doublet of doublet and a triplet which may be attributed to long range coupling with H_b and H_c protons.

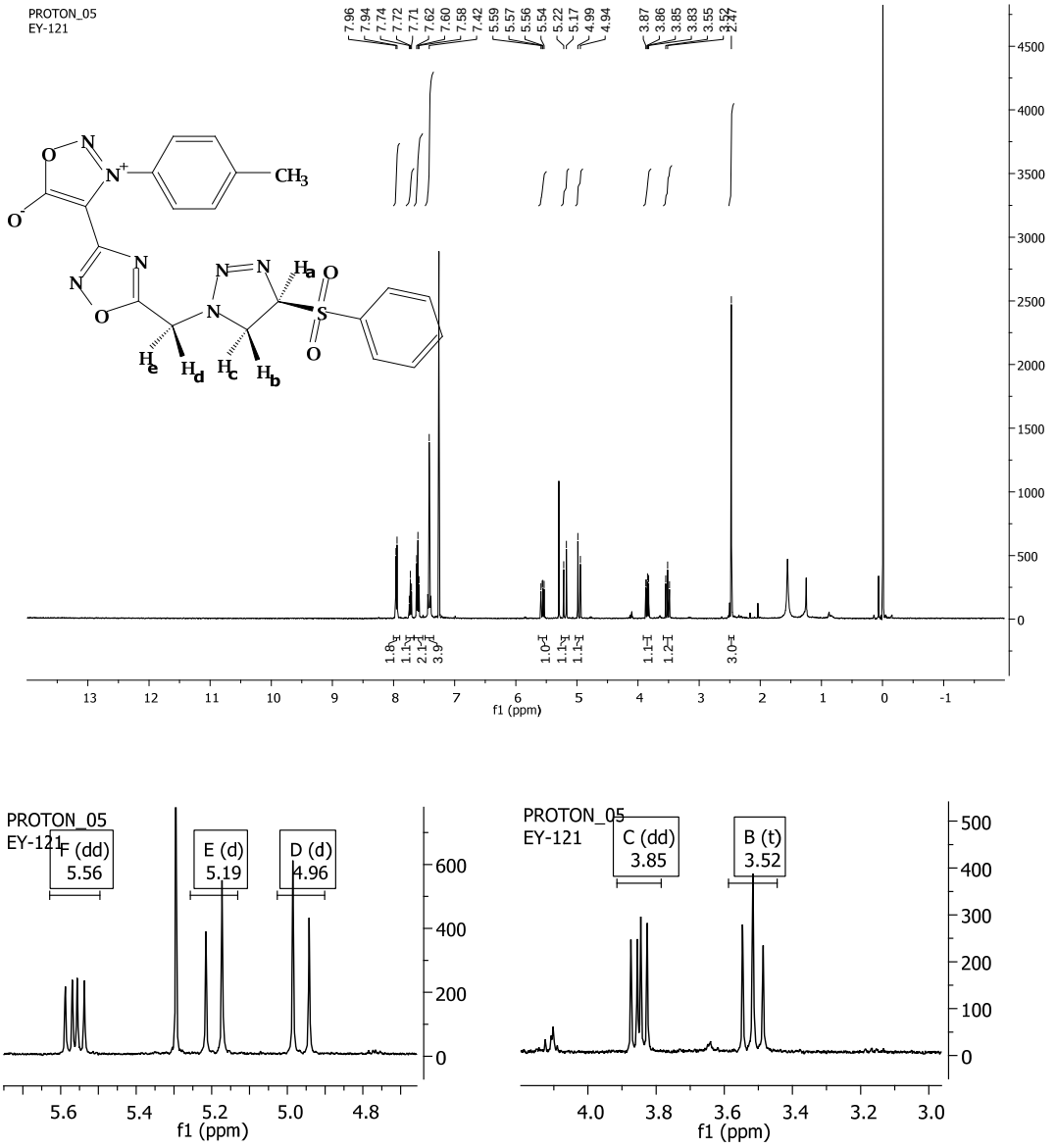
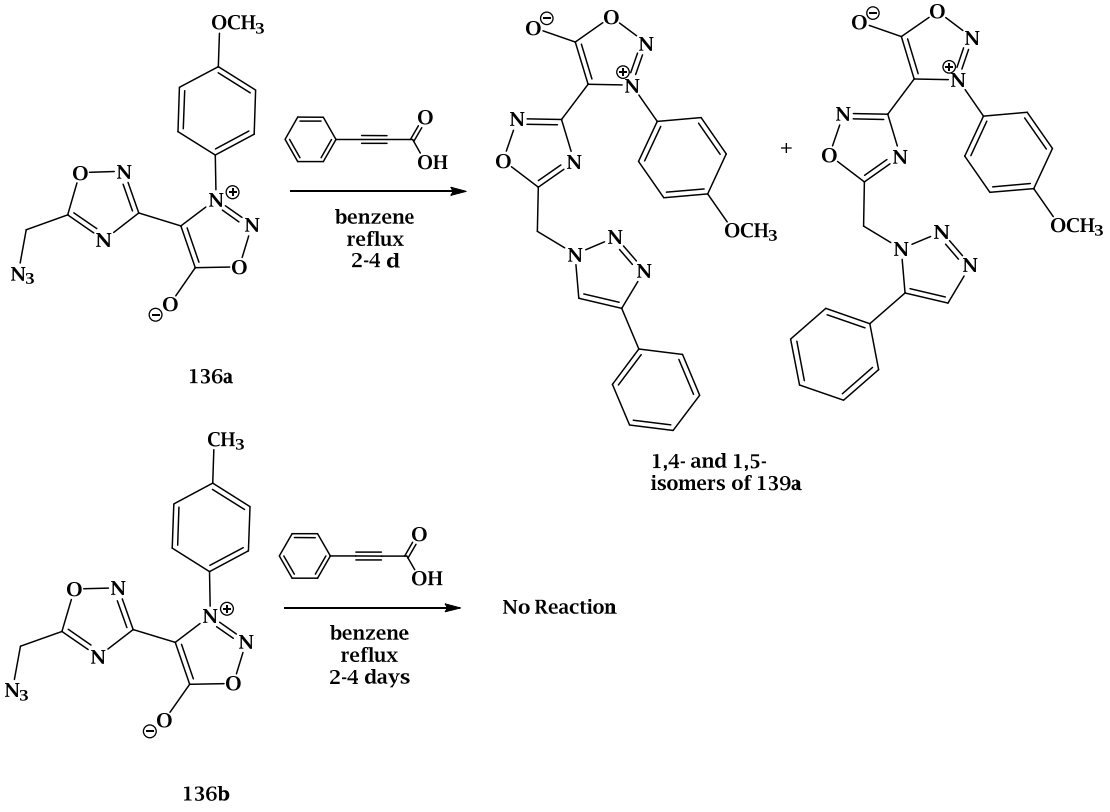


Figure 2.12. The full-scale and expanded ^{1}H NMR spectrum of **138a**.

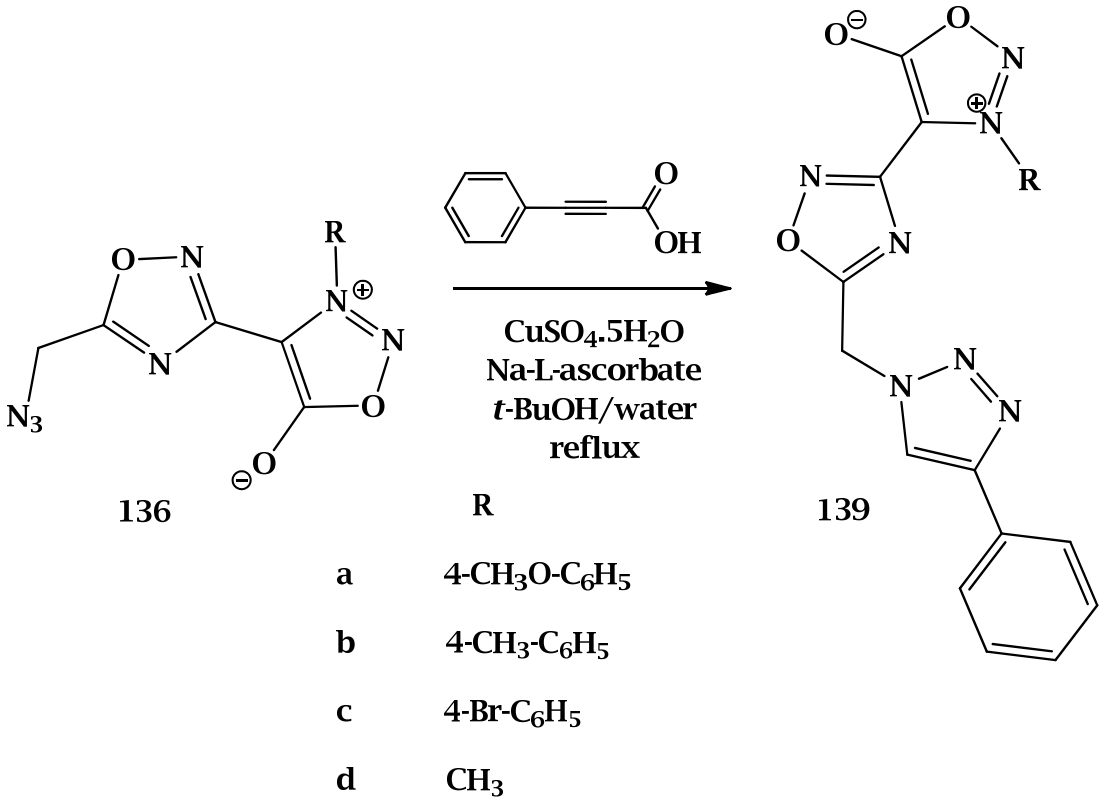
In the last reaction of 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-substituted sydnones **136a-b;** they were reacted with phenylpropiolic acid to give 3-substituted-4-(5-((5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazol-3-yl)sydnones **139a-d**.

In order to carry out the reactions of azides **136a** and **136b,** two methods have been assayed; without catalyst and under Cu(I) catalyst conditions. The azide **136a** gave reaction with phenylpropiolic acid to give cycloaddition without catalyst, but the azide **136b** did not undergo any reaction **(Scheme 2.12)**.



Scheme 2.12. The cycloaddition reactions of **136a** and **136b** with phenylpropiolic acid without catalyst.

The azides **136a-d** were reacted with phenylpropiolic acid using Cu(I) catalyst **(Scheme 2.13)**.



136

R	
a	4-CH_3O-C_6H_5
b	4-CH_3-C_6H_5
c	4-Br-C_6H_5
d	CH_3

139

Scheme 2.13. The Cu(I) catalyzed azide-alkyne cycloaddition reaction and cycloadducts **139a-d**.

These four novel compounds were identified by IR, NMR (^1H, ^{13}C), LC-MS, HRMS, melting point and R_f characteristics. In the IR spectra, the disappearance of N=N=N absorption band of corresponding azide is the primary proof for the generation of this compounds. Moreover, the C=O and –OH absorption bands which come out from phenylpropiolic acid are not observed. Therefore, reaction proceeded via a decarboxylative route. **(Figure 2.13)**.

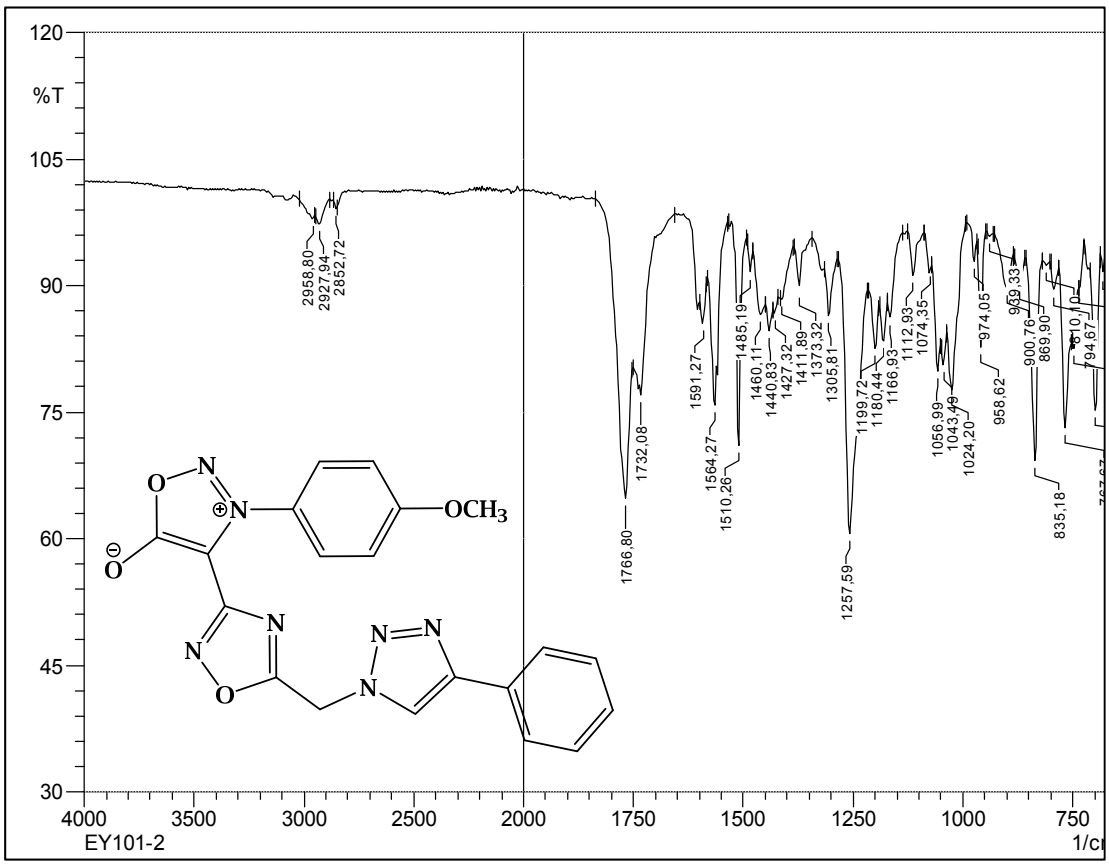


Figure 2.13. The IR spectrum of **139a**.

In the ^{1}H NMR spectrum of **139a** produced from the reaction under catalyst-free conditions, two singlet peaks have been observed at ~5.7 and ~5.8 ppm **(Figure 2.14)**. These peaks are assigned two methylene groups. Also, two singlet peaks which are assigned two methyl groups appears at ~3.8 ppm. Therefore, we concluded that this reaction yields a mixture of 4- and 5-regioisomers of **139a**.

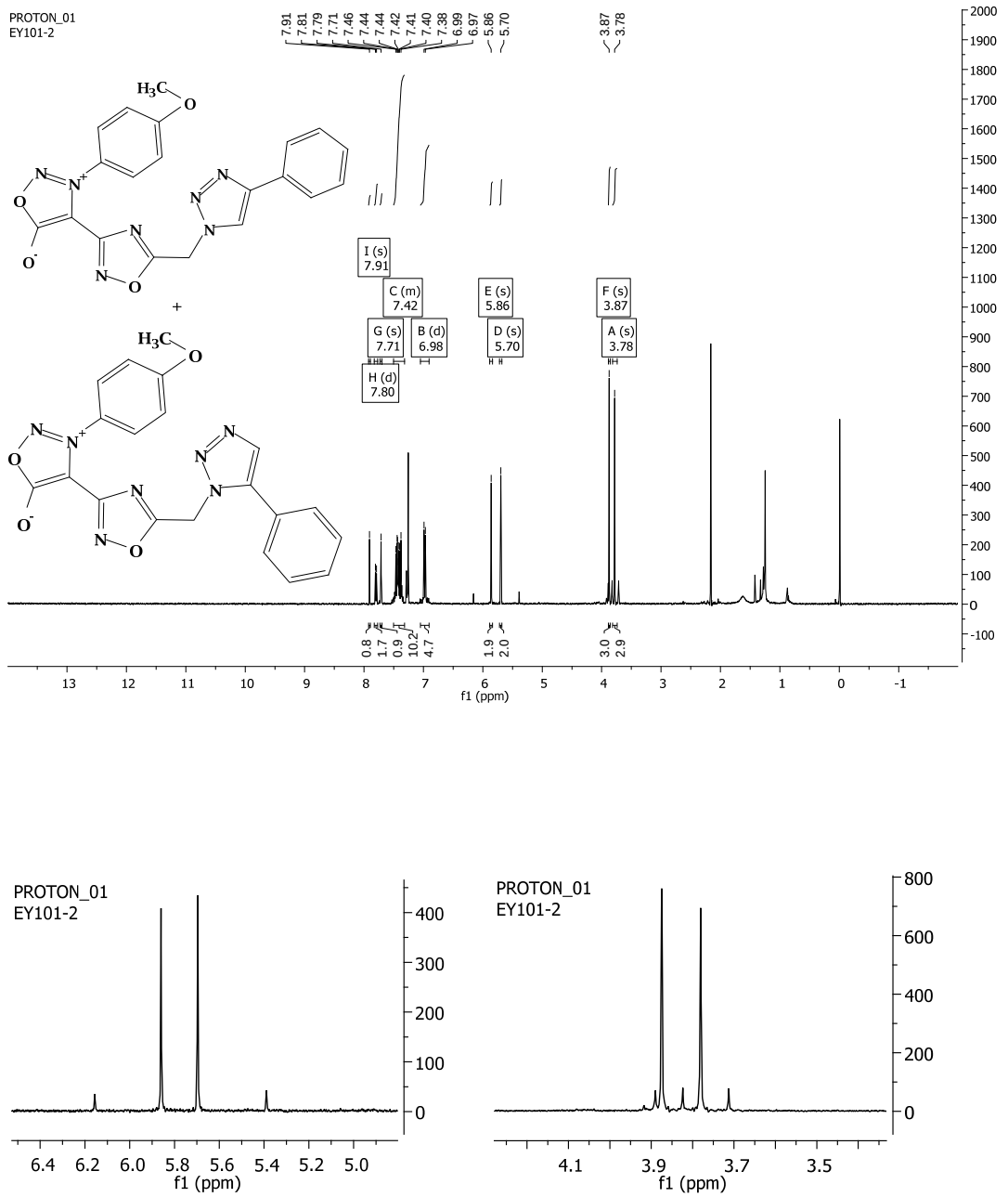
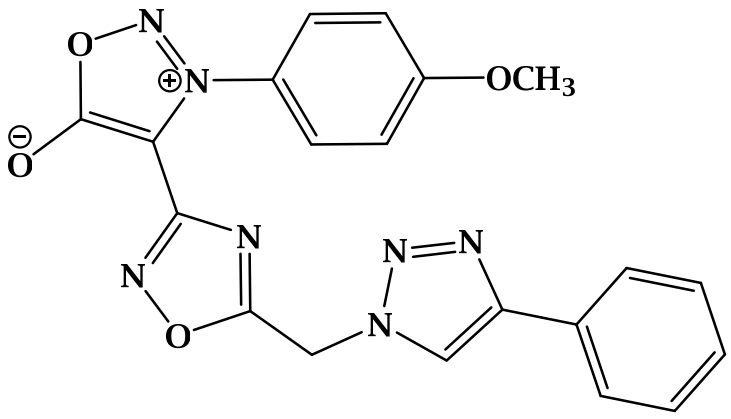


Figure 2.14. The full-scale and expanded ^{1}H NMR spectrum of **139a** produced under no catalyst conditions.

In the ^{1}H NMR spectra of **139a-d** produced from Cu(I) catalyzed cycloaddition reaction, only one singlet peak appears between 5.5-6.5 ppm **(Figure 2.15)**. This peak is assigned methylene protons. Therefore, we can conclude that only 4-regioisomer of **139a** is observed when Cu(I) is utilized **(Figure 2.15)**.



139a

Figure 2.15. The structure of **139a** from Cu(I) catalyzed azide-alkyne cycloaddition reaction.

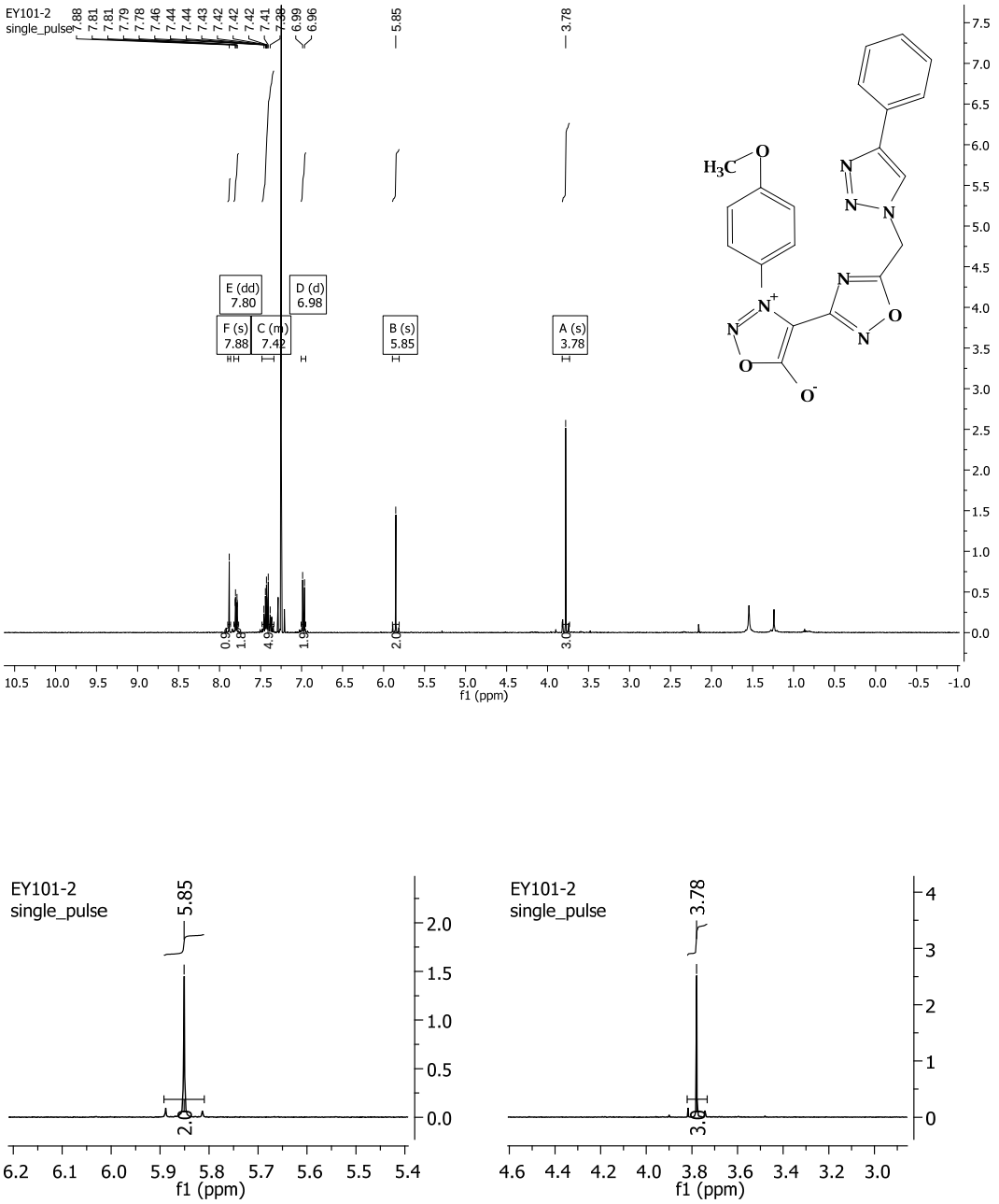


Figure 2.16. The full-scale and expanded ^{1}H NMR spectrum of **139a** produced from Cu(I) catalyzed azide-alkyne cycloaddition reaction.

In addition, the recrystallization of 4-regioisomer of **139a** from ethylacetate/hexane gave fine crystals and the structure of this compound was elucidated by means of X-Ray diffraction data **(Figure 2.17)**.

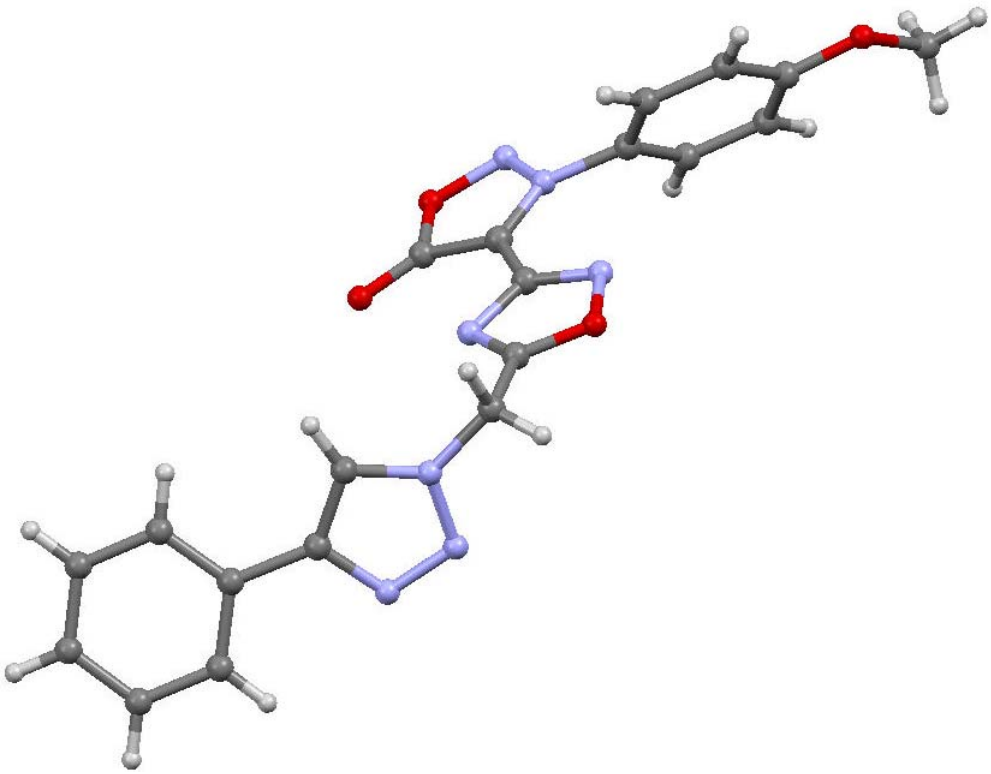


Figure 2.17. X-Ray ORTEP view of **139a**.

2.2. CONCLUSION

In summary, we have firstly demonstrated a practical method for the synthesis of 4 novel azidomethyl-1,2,4-oxadiazole substituted sydnones through chloromethyl-1,2,4-oxadiazole substituted sydnones. Secondly, from 1,3-dipolar cycloaddition reaction between azido sydnones and *N*-phenylmaleimide, 4 novel pyrrolo triazole substituted sydnones have been synthesized. In addition, 2 azidosydnones were reacted with phenyl vinyl sulfone to afford 2 novel 5-(phenylsulfonyl)1,2,3-triazolo oxadiazole substituted sydnones. Finally, the azidosydnones underwent 1,3-dipolar cycloaddition with phenylpropiolic acid by two methods, without catalyst and Cu(I) catalyzed azide-alkyne click reaction to give rise to 4 triazole ring carrying sydnones. The structure of these novel compounds were identified by the IR, ^{1}H NMR, ^{13}C NMR, LC-MS, HRMS and X-ray diffraction spectra.

CHAPTER III

EXPERIMENTAL

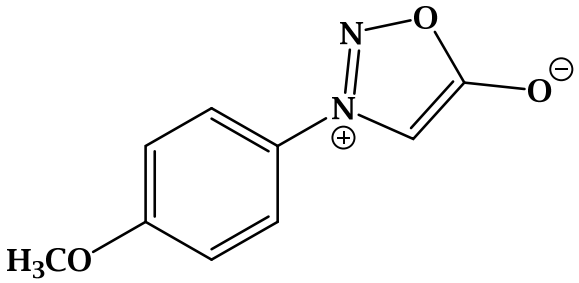
^{1}H and ^{13}C NMR spectra were recorded on JEOL ECS and VARIAN spectrometers (400 MHz for ^{1}H; 100 MHz for ^{13}C). IR spectra were recorded on a SHIMADZU FTIR 8400-S instrument (KBr pellet). LC-MS spectra were run on Waters 2695 Alliance Micromass ZQ. HRMS measurements were performed on a Waters Synapt instrument. Melting points were determined on a MELTEMP apparatus and uncorrected. Flash column chromatography was performed on Silica Gel (Merck, 230-400 Mesh ASTM). TLC was done by using precoated plates with fluorescent indicator (Merck 5735). The stain solutions of permanganate and 2,4-dinitrophenylhydrazine were used for visualization of the TLC spots.

PART 1

In this part, sydnones **8a-c** were synthesized according to the method described in the literature [186]. 3-Methyl sydnone **8d** were synthesized from sarcosine according to the method described in the literature [187].

Synthesis of Sydnones (8a-d):

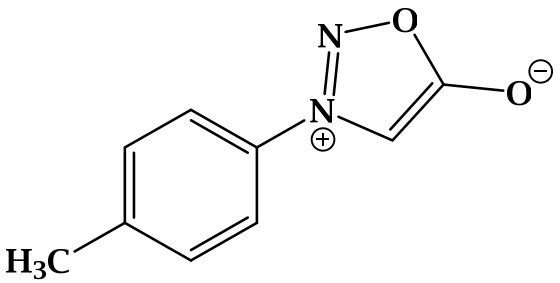
3-(4-Methoxyphenyl)sydnone (8a):



A mixture of p-anisidine (24.630 g, 0.20 mol), ethyl bromoacetate (22.1 mL, 0.20 mol) and anhydrous sodium acetate (32.812 g, 0.40 mol) in 50 mL ethanol was refluxed in an oil bath for 6 h. The reaction mixture was left overnight at room temperature and poured into crushed ice. The precipitate formed was collected by filtration and dried. The dried product, ethyl ester of *N*-(4-methoxyphenyl)glycine without further purification was used for the next step. To ethyl ester of *N*-(4-methoxyphenyl)glycine (41.850 g, 0.20 mol),sodium hydroxide (12.000 g, 0.30 mol) in water:ethanol (96mL:24mL) was added and refluxed for 0.5 h. After cooling, the reaction mixture was acidified to pH=2 using hydrochloric acid. The precipitated N-(4-methoxyphenyl)glycine was filtered and washed thoroughly with cold water. Further purification was done by recrystallisation from ethanol. To a well stirred mixture of N-(4-methoxyphenyl)glycine (30.000 g, 0.166 mol) in 10% HCl solution (166 mL) at 0-5^{o}C, a solution of sodium nitrite (11.453 g, 0.166 mol) in 166 mL water was added dropwise during 30 min. Stirring was continued for 2 h. The precipitated N-nitroso-N-(4-methoxyphenyl)glycine

was collected by filtation, washed with cold water and dried in air. N-nitroso-N-(4-methoxyphenyl)glycine (31.500g, 0.15 mol) was heated with acetic anhydride (70 mL, 0.75mL) on a water bath for 3 h. The reaction solution was kept aside at room temperature for overnight. Then, it was poured into ice-cold water, filtered and washed with water. The solid was dried and recrystallised from ethanol. (4.05 g, 0.021 mol). IR(KBr, v: cm^{-1}): 3149 (arom. C-H), 2985, 2941 (aliph. C-H), 1741 (syd. C=O), 1597, 1512, 1259, 1165, 833.

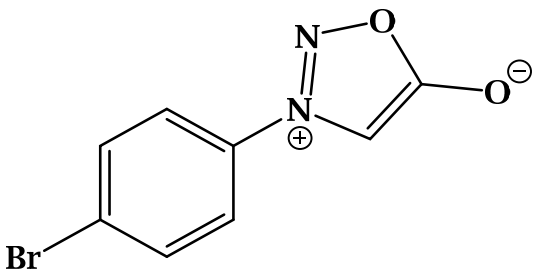
3-(4-Methylphenyl)sydnone (8b):



A mixture of p-toluidine (26.788 g, 0.25 mol), ethyl bromoacetate (27.6 mL, 0.25 mol) and anhydrous sodium acetate (41.015 g, 0.50 mol) in 50 mL ethanol was refluxed in an oil bath for 6 h. The reaction mixture was left overnight at room temperature and poured into crushed ice. The precipitate formed was collected by filtration and dried. The dried product, ethyl ester of *N*-(4-methylphenyl)glycine without further purification was used for the next step. To ethyl ester of N-(4-methylphenyl)glycine (34.785 g, 0.18 mol),sodium hydroxide (10.800 g, 0.27 mol) in water:ethanol (88mL:22mL) was added and

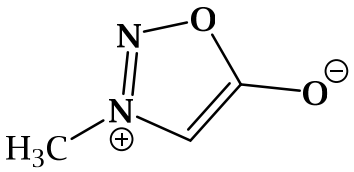
refluxed for 0.5 h. After cooling, the reaction mixture was acidified to pH=2 using hydrochloric acid. The precipitated *N*-(4-methylphenyl)glycine was filtered and washed thoroughly with cold water. Further purification was done by recrystallisation from ethanol. To a well stirred mixture of N-(4-methylphenyl)glycine (24.779 g, 0.15 mol) in 10% HCl solution (150 mL) at 0-5^{o}C, a solution of sodium nitrite (10.350 g, 0.15 mol) in 150 mL water was added dropwise during 30 min. Stirring was continued for 2 h. The precipitated N-nitroso-N-(4-methoxyphenyl)glycine was collected by filtation, washed with cold water and dried in air. N-nitroso-N-(4-methylphenyl)glycine (14.564 g, 0.075 mol) was heated with acetic anhydride (35 mL, 0.375mL) on a water bath for 3 h. The reaction solution was kept aside at room temperature for overnight. Then, it was poured into ice-cold water, filtered and washed with water. The solid was dried and recrystallised from ethanol. (3.520 g, 0.020 mol). IR(KBr, v:cm^{-1}): 3138 (arom. C-H), 2964 (aliph. C-H), 1753 (syd. C=O), 1664, 1604, 1442, 1285, 1174, 817.

3-(4-Bromophenyl)sydnone (8c):



A mixture of p-anisidine (34.404 g, 0.20 mol), ethyl bromoacetate (22.1 mL, 0.20 mol) and anhydrous sodium acetate (32.812 g, 0.40 mol) in 50 mL ethanol was refluxed in an oil bath for 6 h. The reaction mixture was left overnight at room temperature and poured into crushed ice. The precipitate formed was collected by filtration and dried. The dried product, ethyl ester of N-(4-bromophenyl)glycine without further purification was used for the next step. To ethyl ester of N-(4-bromophenyl)glycine (50.000 g, 0.19 mol),sodium hydroxide (11.400 g, 0.285 mol) in water:ethanol (96mL:24mL) was added and refluxed for 0.5 h. After cooling, the reaction mixture was acidified to pH=2 using hydrochloric acid. The precipitated N-(4-bromophenyl)glycine was filtered and washed thoroughly with cold water. Further purification was done by recrystallisation from ethanol. To a well stirred mixture of N-(4-bromophenyl)glycine (34.500 g, 0.15 mol) in 10% HCl solution (150 mL) at 0-5^{o}C, a solution of sodium nitrite (10.350 g, 0.150 mol) in 150 mL water was added dropwise during 30 min. Stirring was continued for 2 h. The precipitated N-nitroso-N-(4-bromophenyl)glycine was collected by filtation, washed with cold water and dried in air. N-nitroso-N-(4-bromophenyl)glycine (25.906 g, 0.10 mol) was heated with acetic anhydride (47 mL, 0.5 mol) on a water bath for 3 h. The reaction solution was kept aside at room temperature for overnight. Then, it was poured into ice-cold water, filtered and washed with water. The solid was dried and recrystallised from ethanol. (3.620 g, 0.015 mol)

3-Methylsydnone (8d):



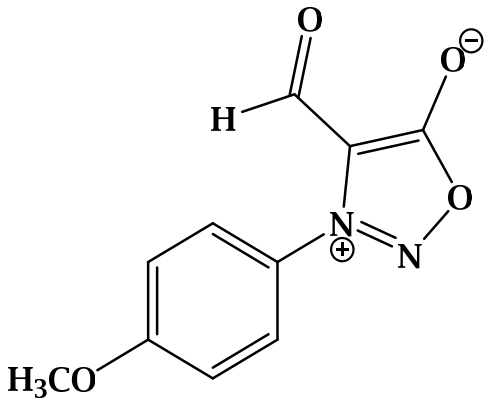
To an ice-cold solution of concentrated hydrochloric acid (33.5 mL) and sarcosine (17.818 g, 0.20 mol) in 50 mL of water, was added a saturated solution of sodium nitrite (27.598 g, 0.40 mol) in water. The mixture was stirred at 0^{o}C for 1 h and then extracted with ethyl acetate three times. The combined organic layers were concentrated under vacuum to obtain N-nitroso-N-methylglycines as a yellow oil. The resulting oil (9.800g, 0.083 mol) was dissolved in 50 mL of dry ether and charged dropwise with ~500 µL of trifluoroacetic anhydride (21.2 mL, 0.15 mol) at 0^{o}C. The reaction was stirred at 0^{o}C for a few minutes and gradually warmed to room temperature and stirred for another 1 h. The solvents were evaporated and the residue was dissolved in ethyl acetate. Solid sodium bicarbonate was added to neutralize the excess acid and was removed by filtration. The ethyl acetate was evaporated to obtain yellow oil. (7.000g, 0.07 mol). IR(KBr, v:cm^{-1}): 3437, 3163, 2989, 2947, 1890, 1724 (syd. C=O), 1678, 1423, 1276, 1199, 1045, 952, 840, 802, 725.

PART 2

This part include synthesis of 4-formylsydnone derivatives **20a-d** from sydnones **8a-d** according to the method described in the literature [49].

Synthesis of 4-Formylsydnone Derivatives (20a-d):

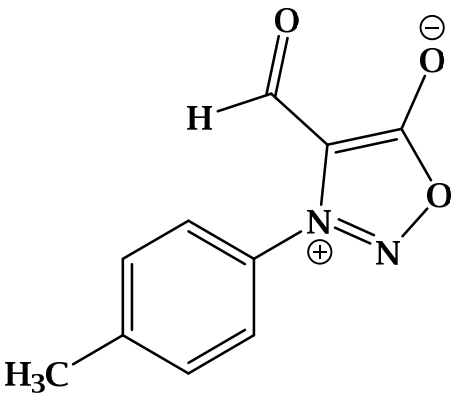
4-Formyl-3-(4-methoxyphenyl)sydnone (20a):



N-Methylformanilide (3.0 mL, 0.024 mol) and phosphoryl chloride (2.1 mL, 0.023 mL) were mixed, and after 0.5 h, 3-(4-methoxyphenyl)sydnone **8a** (4.050 g, 0.021 mol) was added portionwise with swirling and cooling as needed to keep the temperature below 45°C. Hydrogen chloride was evolved vigorously. After standing overnight, the viscous dark-brown mixture was dissolved in 17 mL of acetone and poured (stirring) into 85 mL of ice water. The solid obtained was filtered and washed with cold water. The 4-formyl-3-(4-methoxyphenyl)sydnone was purified by column chromatography (n-hexane: ethyl acetate 7:1) to give a pale yellow plates. (2.282 g, 10.36 mol). Yield: 49%. R_f : 0.61 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3111, 3036 (arom. C-H), 2980, 2937 (aliph.C-H), 2847 (aldehyde C-H), 1778 (sydnone C=O), 1643 (aldehyde C=O), 1597, 1508, 1460, 1257, 1074, 1018, 846, 759. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 9.56 (s, 1H), 7.56 (d, *J*=9.2 Hz, 2H), 7.08 (d, *J*=9.2 Hz, 2H), 3.91 (s, 3H). ^{13}C NMR (δ_C,101 MHz, $CDCl_3$):

174.9 (ald. C=O), 166.7 (syd. C=O), 163.2 (C-OCH_3), 126.1 , 114.9, 105.0, 56.0 (-CH_3).

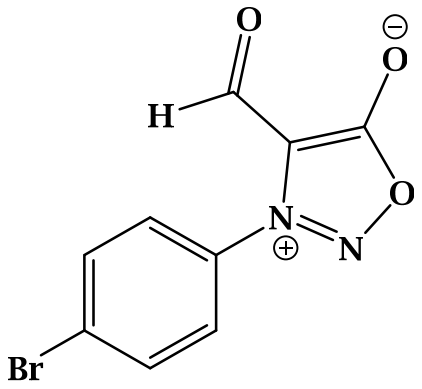
4-Formyl-3-(4-methylphenyl)sydnone (20b):



N-Methylformanilide (2.8 mL, 0.023 mol) and phosphoryl chloride (2.1 mL, 0.022 mL) were mixed, and after 0.5 h, 3-(4-methylphenyl)sydnone **8b** (4.010 g, 0.020 mol) was added portionwise with swirling and cooling as needed to keep the temperature below 45^{o}C. Hydrogen chloride was evolved vigorously. After standing overnight, the viscous dark-brown mixture was dissolved in 16 mL of acetone and poured (stirring) into 81 mL of ice water. The solid obtained was filtered and washed with cold water. The 4-formyl-3-(4-methylphenyl)sydnone was purified by column chromatography (n-hexane: ethyl acetate 7:1) to give a pale orange plates. (1.367 g, 6.69 mmol). Yield: 33%. R_f : 0.59 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3103, 3084, 3064, 3043 (arom. C-H), 2856 (aldehyde C-H), 1778 (sydnone C=O), 1647 (aldehyde C=O), 1600, 1506, 1452, 1317, 1080, 1024, 827, 763. ^{1}H

NMR (δ_H ,400 MHz, $CDCl_3$): 9.58 (s, 1H) , 7.50 (d, *J*=8.8 Hz, 2H), 7.43 (d, *J*=8.4 Hz, 2H), 2.50 (s, 3H). LC-MS (80eV) (*m/z*) (%): 346 (100), 268 ($[M+CH_3CN+Na]^+$, 95), 204 (M^+, 25).

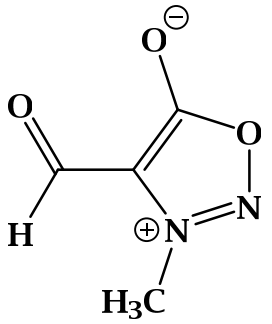
4-Formyl-3-(4-bromophenyl)sydnone (20c):



N-Methylformanilide (2.1 mL, 0.0169 mol) and phosphoryl chloride (1.5 mL, 0.0165 mL) were mixed, and after 0.5 h, 3-(4-bromophenyl)sydnone **8c** (3.620 g, 0.015 mol) was added portionwise with swirling and cooling as needed to keep the temperature below 45^oC. Hydrogen chloride was evolved vigorously. After standing overnight, the viscous dark-brown mixture was dissolved in 16 mL of acetone and poured (stirring) into 81 mL of ice water. The solid obtained was filtered and washed with cold water. The 4-formyl-3-(4-bromophenyl)sydnone was purified by column chromatography (n-hexane: ethyl acetate 8:1) to give a pale orange plates. (1.300 g, 4.83 mmol). Yield: 32%. R_f : 0.72 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3101, 3086 (arom. C-H), 2974 (aliph.C-H), 1786 (sydnone C=O), 1681, 1658 (aldehyde C=O), 1577, 1485, 1438, 1400, 1068, 1018, 895, 775, 597 (C-Br).

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 9.57 (s, 1H), 7.77 (d, *J*=8.0 Hz, 2H), 7.50 (d, *J*=8.0 Hz, 2H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 174.7 (C=O), 133.2, 128.1, 126.0. LC-MS (80 eV) (*m/z*) (%): 444 (47), 332 ($[M+CH_3CN+Na]^+$,25), 330 (38%), 236 (100%), 208 (49%).

4-Formyl-3-methylsydnone (20d):



N-Methylformanilide (9.8 mL, 0.079 mol) and phosphoryl chloride (7.2 mL, 0.077 mL) were mixed, and after 0.5 h, 3-methylsydnone **8d** (7.000 g, 0.070 mol) was added portionwise with swirling and cooling as needed to keep the temperature below 45^{o}C. Hydrogen chloride was evolved vigorously. After standing overnight, the viscous dark-brown mixture was dissolved in 56 mL of acetone and poured (stirring) into 282 mL of ice water. The solid obtained was filtered and washed with cold water. The 4-formyl-3-(4-bromophenyl)sydnone was purified by column chromatography (n-hexane: ethyl acetate 6:1) to give a pale orange plates. (1.300 g, 10.15 mmol). Yield: 15%. R_f : 0.40 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 2968, 2928 (aliph.C-H), 2858 (aldehyde C-H), 1782 (sydnone C=O), 1664

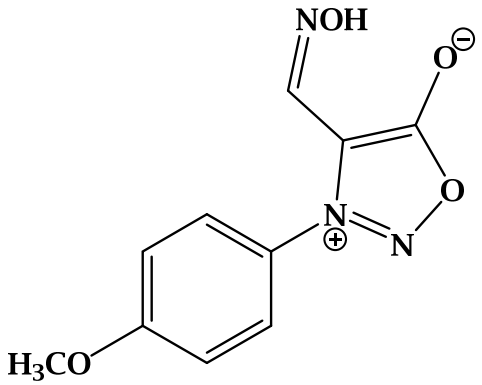
(aldehyde C=O), 1599, 1496, 1442, 1323, 1151, 1028, 916, 734. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 9.56 (s, 1H), 4.39 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 176.5 (C=O), 41.5 ($-CH_3$).

PART 3

In this part, 4-formylsydnone oxime derivatives **132a-d** were synthesized according to the method described in the literature [188].

Synthesis of 4-formylsydnone oximes (132a-d):

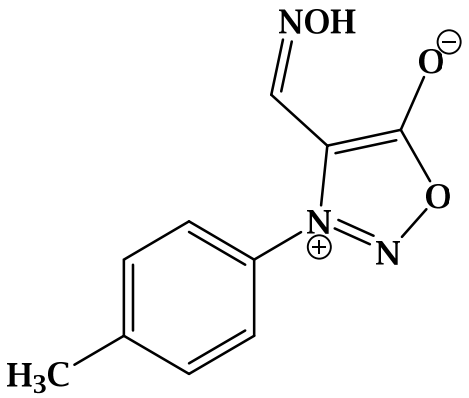
3-(4-Methoxyphenyl)-4-formylsydnone oxime (132a):



2.282 g (10.36 mmol) of 4-formyl-3-(4-methoxyphenyl)sydnone **20a** was suspended in 15 mL of 95% ethanol and 1.5 mL of pyridine. To the solution, 1.090 g (15.69 mmol) of hydroxylamine hydrochloride, dissolved in 3 mL of

water, was added and stirred at room temperature for 2 days. The precipitate was collected by filtration and washed with water and then with cold ethanol to afford pale yellow solid. (2.440 g, 10.36 mmol). Yield: 100%. R_f : 0.30 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3304 (broad, ald. N-OH), 3064 (arom. C-H), 2964 (aliph.C-H), 1745 (sydnone C=O), 1502, 1381, 1255, 1170, 1028, 977, 829. ^{1}H NMR (δ_H, 400 MHz, DMSO-d_6): 11.70 (s, 1H), 7.69 (s, 1H), 7.71 (d, *J*=10.0 Hz, 2H), 7,54 (s, 1H), 7.19 (d, *J*=9.2 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, DMSO-d_6): 165.0 (syd. C=O), 162.4 (C-OCH_3), 135.6 (C=N) , 131.9, 127.5, 126.5, 115.6, 114.3, 104.8, 56.4 (-CH_3).

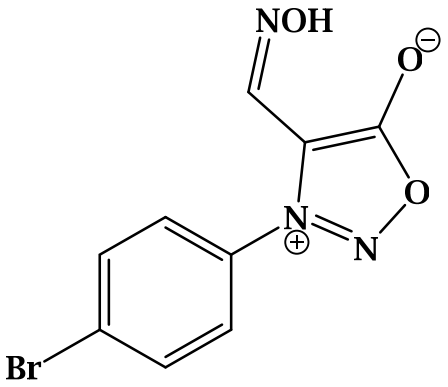
3-(4-Methylphenyl)-4-formylsydnone oxime (132b):



1.367 g (6.69 mmol) of 4-formyl-3-(4-methylphenyl)sydnone **20b** was suspended in 10 mL of 95% ethanol and 1.0 mL of pyridine. To the solution, 0.704 g (10.13 mmol) of hydroxylamine hydrochloride, dissolved in 2 mL of water, was added and stirred at room temperature for 2 days. The precipitate

was collected by filtration and washed with water and then with cold ethanol to afford pale yellow solid. (1.100 g, 5.02 mmol). Yield: 75%. R_f : 0.29 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3311 (broad, ald. N-OH), 3082, 3066, 3035 (arom. C-H), 1743 (sydnone C=O), 1514, 1379, 1278, 1271, 1255, 1186, 1010, 975, 819, 732. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 9.74 (s, 1H), 7.82 (s, 1H), 7.44 (s, 4H) 2.50 (s, 3H). LC-MS (80 eV) (*m/z*) (%): 461 (100), 369 (48), 324 ([M+2CH_3CN+Na]$^+$, 14), 283 ([M+CH_3CN+Na]$^+$, 85), 261 ([M+H+CH_3CN]$^+$, 81), 220 ([M+H]$^+$, 29).

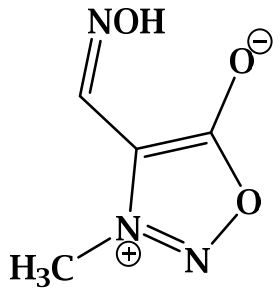
3-(4-Bromophenyl)-4-formylsydnone oxime (132c):



1.300 g (4.83 mmol) of 4-formyl-3-(4-bromophenyl)sydnone **20c** was suspended in 7 mL of 95% ethanol and 0.7 mL of pyridine. To the solution, 0.508 g (7.31 mmol) of hydroxylamine hydrochloride, dissolved in 1.5 mL of water, was added and stirred at room temperature for 2 days. The precipitate was collected by filtration and washed with water and then with cold ethanol to afford pale yellow solid. (0.675 g, 2.38 mmol). Yield: 49%. R_f : 0.46 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3279 (broad, ald. N-

OH), 3101, 3078 (arom. C-H), 1716 (sydnone C=O), 1658, 1485, 1419, 1288, 1261, 1068, 964, 902, 817, 713, 513 (C-Br). ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 8.09 (s, 1H), 7.84 (s, 1H), 7.80 (d, *J*=8.8 Hz, 2H), 7.46 (d, *J*=8.8 Hz, 2H). LC-MS (80 eV) (*m/z*) (%): 284 ([M-H]$^-$ (^{81}Br), 98), 282 ([M-H]$^-$ (^{79}Br), 100).

3-Methyl-4-formylsydnone oxime (132d):



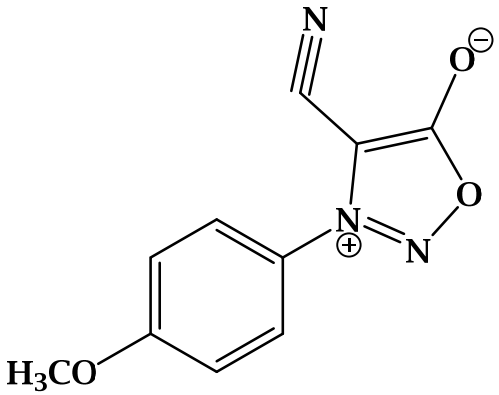
1.300 g (10.15 mmol) of 4-formyl-3-methylsydnone **20d** was suspended in 15 mL of 95% ethanol and 1.5 mL of pyridine. To the solution, 1.068 g (15.37 mmol) of hydroxylamine hydrochloride, dissolved in 3 mL of water, was added and stirred at room temperature for 2 days. The precipitate was collected by filtration and washed with water and then with cold ethanol to afford pale yellow solid. (1.080 g, 7.55 mmol). Yield: 74%. R_f : 0.40 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3319(broad, ald. N-OH), 2964, 2924 (alip. C-H), 1741 (sydnone C=O), 1535, 1444, 1371, 1301, 1261, 1058, 977, 813. ^{1}H NMR (δ_H, 400 MHz, DMSO-d_6): 11.67 (s, 1H), 7.89 (s, 1H), 4.15 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, DMSO-d_6): 165.7 (syd. C=O), 136.1 (C=N), 103.1, 40.3 (-CH_3).

PART 4

This part include synthesis of 4-cyanosydnone derivatives **133a-d** according to the method described in the literature [188].

Synthesis of 4-cyanosydnone derivatives (133a-d):

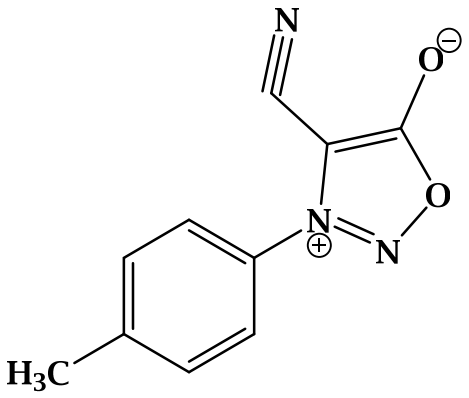
4-Cyano-3-(4-methoxyphenyl)sydnone (133a):



2.444 g (10.36 mmol) of 3-(4-methoxyphenyl)-4-formylsydnone oxime **132a** was added into 10 mL of acetic anhydride, and the reaction mixture was refluxed in an oil bath for 4 h. After cooling to room temperature, the reaction mixture was poured into crushed ice. The precipitate was filtered and dried. The product was purified by column chromatography (n-hexane: ethyl acetate 6:1) to afford pale yellow solid. (1.900 g, 8.75 mmol). Yield: 84%. R_f : 0.70 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3115, 3080 (arom. C-H), 2982 (alip. C-H), 2229 (C≡N), 1786 (sydnone C=O), 1604,

1510, 1464, 1263, 1182, 1074, 1020, 839, 723. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.74 (d, *J*=8.0 Hz, 2H), 7.16 (d, *J*=12.0 Hz, 2H), 3.94 (s, 3H). LC-MS (80 eV) (*m/z*) (%): 495 (58), 407 (73), 386 (82), 341 (100), 284 (98), 262 (88), 259 ($[M+CH_3CNH]^+$, 38), 218 ($[M+H]^+$, 56).

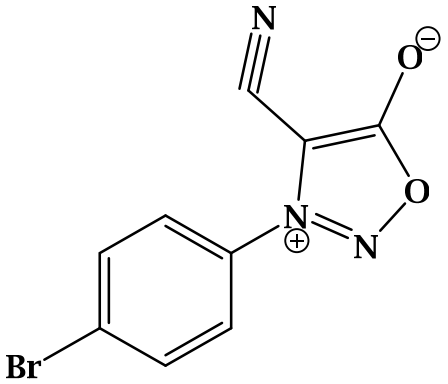
4-Cyano-3-(4-methylphenyl)sydnone (133b):



1.100 g (5.02 mmol) of 3-(4-methoxyphenyl)-4-formylsydnone oxime **132b** was added into 5 mL of acetic anhydride, and the reaction mixture was refluxed in an oil bath for 4 h. After cooling to room temperature, the reaction mixture was poured into crushed ice. The precipitate was filtered and dried. The product was purified by column chromatography (n-hexane: ethyl acetate 6:1) to afford white solid. (0.468 g, 2.33 mmol). Yield: 47%. R_f : 0.72 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3078, 3003 (arom. C-H), 2970, 2924 (alip. C-H), 2227 (C≡N), 1809, 1782 (sydnone C=O), 1732, 1602, 1506, 1313, 1294, 1230, 1066, 1022, 873, 823, 725. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.67 (d, *J*=8.8 Hz, 2H), 7.49 (d, *J*=8.0 Hz, 2H), 2.52 (s, 3H).

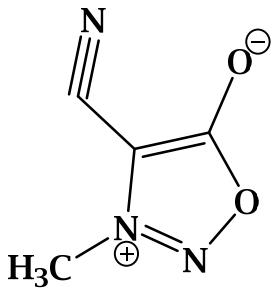
LC-MS (80 eV) (*m/z*) (%): 463 (66), 383 (84), 306 ([M+2CH_3CN+Na]$^+$, 42), 303 (100), 265 ([M+CH_3CN+Na]$^+$, 22), 223 (27), 208 (30).

4-Cyano-3-(4-bromophenyl)sydnone (133c):



0.675 g (2.38 mmol) of 3-(4-bromophenyl)-4-formylsydnone oxime **132c** was added into 2 mL of acetic anhydride, and the reaction mixture was refluxed in an oil bath for 4 h. After cooling to room temperature, the reaction mixture was poured into crushed ice. The precipitate was filtered and dried. The product was purified by column chromatography (n-hexane: ethyl acetate 6:1) to afford pale yellow solid. (0.630 g, 2.37 mmol). Yield: 99%. R_f : 0.87 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3093, 3063, 3043 (arom. C-H), 2222 (C≡N), 1832, 1809, 1790 (sydnone C=O), 1755, 1585, 1485, 1454, 1307, 1292, 1180, 1072, 1014, 887, 829, 721, 628 (C-Br). ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.87 (d, *J*=9.2 Hz, 2H), 7.69 (d, *J*=9.2 Hz, 2H). LC-MS (80 eV) (*m/z*) (%): 222 (100), 220 (95), 175 (32), 126 (38), 112 (71).

4-Cyano-3-methylsydnone (133d):



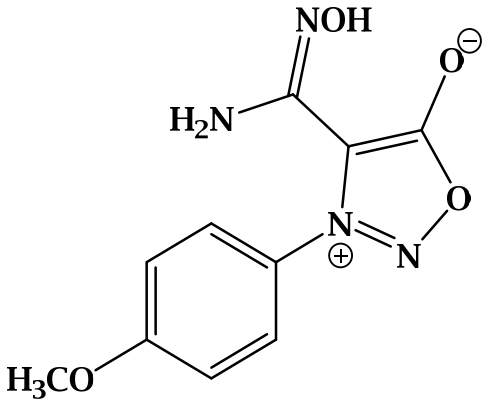
1.080 g (7.55 mmol) of 3-methyl-4-formylsydnone oxime **133d** was added into 7.5 mL of acetic anhydride, and the reaction mixture was refluxed in an oil bath for 4 h. After cooling to room temperature, the reaction mixture was poured into crushed ice. The precipitate was filtered and dried. The product was purified by column chromatography (n-hexane: ethyl acetate 6:1) to afford pale yellow solid. (0.254 g, 2.03 mmol). Yield: 27%. R_f : 0.51 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3034, 2962, 2862 (alip. C-H), 2229 (C≡N), 1871, 1788 (sydnone C=O), 1712, 1502, 1440, 1425, 1325, 1224, 1130, 1033, 908, 723.

PART 5

In this part, 4-carboxamidoxime derivatives **134a-d** were synthesized according to the method described in the literature [189].

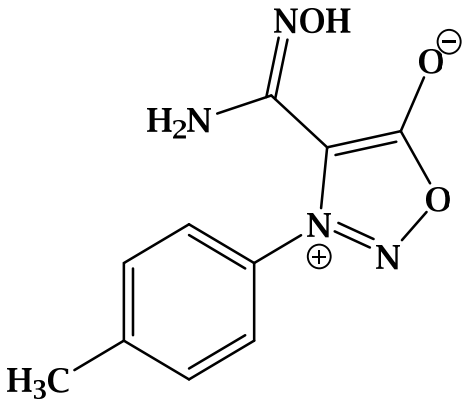
Synthesis of 4-carboxamidoxime derivatives (134a-d)

3-(4-Methoxyphenyl)sydnone-4-carboxamidoxime (134a):



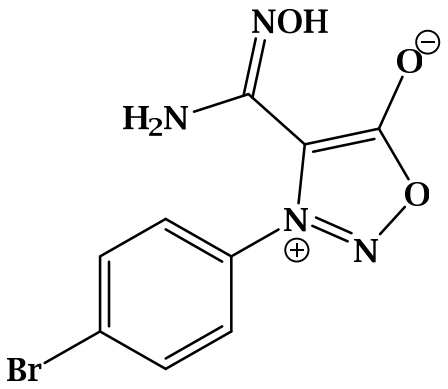
To a suspension of 4-cyano-3-(4-methoxyphenyl)sydnone **133a** (1.900 g, 8.75 mmol) in 95% ethanol (22 mL)-pyridine (2 mL), hydroxylamine hydrochloride (0.912 g, 13.12 mmol) in water (4 mL) was added with stirring. The stirring was continued for 3 d at room temperature. The resulting precipitate was collected by filtration. (1.000 g, 4.00 mmol). Yield: 46%. R_f : 0.30 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3497, 3379 (amid. -NH), 3254 (broad, amid. –OH), 3080 (arom. C-H), 2974, 2916, 2847 (alip. C-H), 1735 (sydnone C=O), 1635, 1558, 1508, 1425, 1267, 1220, 1168, 1022, 927, 840. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.47 (d, *J*=8.0 Hz, 2H), 7.03 (d, *J*=12.0 Hz, 2H), 5.49 (s, 2H), 3.90 (s, 3H).

3-(4-Methylphenyl)sydnone-4-carboxamidoxime (134b):



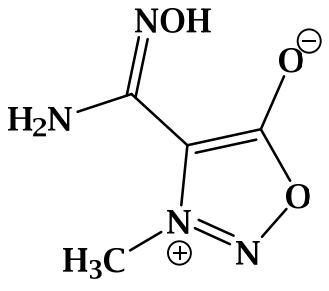
To a suspension of 4-cyano-3-(4-methylphenyl)sydnone **133b** (0.468 g, 2.33 mmol) in 95% ethanol (6 mL)-pyridine (0.6 mL), hyrdoxylamine hydrochloride (0.243 g, 3.50 mmol) in water (1 mL) was added with stirring. The stirring was continued for 3 d at room temperature. The resulting precipitate was collected by filtration. (0.360 g, 1.54 mmol). Yield: 66%. R_f : 0.48 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3431, 3304 (amide -NH), 3151 (broad, amide –OH), 3047 (arom. C-H), 2970, 2906 (alip. C-H), 1724 (sydnone C=O), 1631, 1506, 1417, 1323, 1217, 1053, 941, 904, 819. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.38 (dd, *J*=8.4, 8.4 Hz, 4H), 5.48 (s, 2H), 2.47 (s, 3H). LC-MS (80 eV) (*m/z*) (%): 276 ($[M+H+CH_3CN]^+$, 38), 236 ($[M+2H]^{2+}$, 21), 235($[M+H]^+$, 100).

3-(4-Bromophenyl)sydnone-4-carboxamidoxime (134c):



To a suspension of 4-cyano-3-(4-bromophenyl)sydnone **133b** (0.630 g, 2.37 mmol) in 95% ethanol (6 mL)-pyridine (0.6 mL), hyrdoxylamine hydrochloride (0.247 g, 3.56 mmol) in water (1 mL) was added with stirring. The stirring was continued for 3 d at room temperature. The resulting precipitate was collected by filtration. (0.350 g, 1.17 mmol). Yield: 49%. R_f : 0.51 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3487, 3414, 3371, 3236 (amid. –NH and -NOH), 3093 (arom. C-H), 2962, 2924, 2858 (alip. C-H), 1743 (sydnone C=O), 1631, 1570, 1523, 1485, 1438, 1384, 1327, 1226, 1068, 1018, 925, 891, 825, 617 (C-Br). ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.70 (d, *J*=8.8 Hz, 2H), 7.42 (d, *J*=8.8 Hz, 2H), 5.48 (s, 2H). LC-MS (80 eV) (*m/z*) (%): 340 ($[M+H+CH_3CN]^+$, 53), 299 ($[M+H]^+$, 100), 231.

3-Methylsydnone-4-carboxamidoxime (134d):

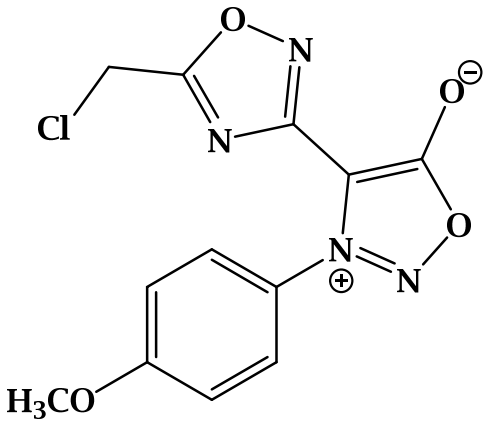


To a suspension of 4-cyano-3-methylsydnone **133d** (0.254 g, 2.03 mmol) in 95% ethanol (5 mL)-pyridine (0.5 mL), hyrdoxylamine hydrochloride (0.212 g, 3.05 mmol) in water (1 mL) was added with stirring. The stirring was continued for 3 d at room temperature. The resulting precipitate was collected by filtration. (0.210 g, 1.33 mmol). Yield: 66%. R_f : 0.31 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3448, 3340 (amid. -NH), 3132 (broad, amid. –OH), 2935 (alip. C-H), 1735 (sydnone C=O), 1643, 1581, 1543, 1411, 1361, 1234, 1030, 929, 798. ^{1}H NMR (δ_H, 400 MHz,DMSO-d_6): 9.96 (s, 1H), 5.79 (s, 2H), 4.15 (s, 3H).

PART 6

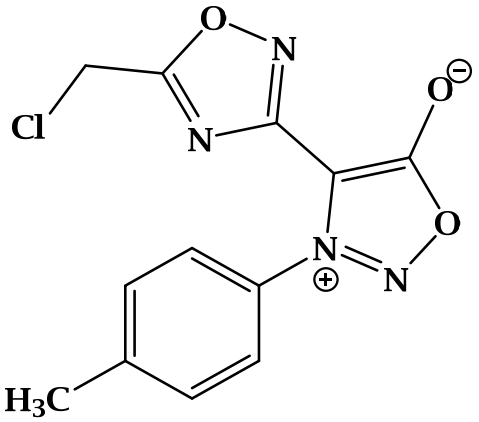
Synthesis of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)sydnone derivatives (135a-d):

4-(5-(Chloromethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methoxyphenyl) sydnone (135a):



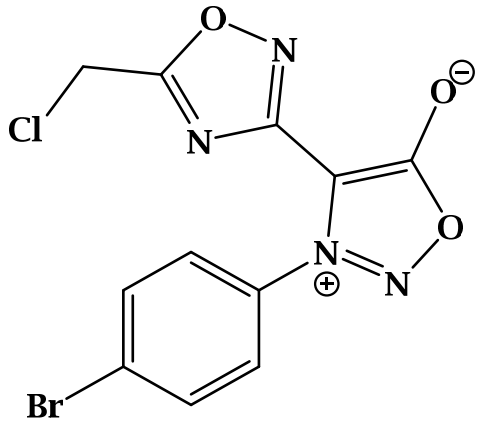
A solution of chloroacetylchloride (0.181 g, 1.60 mmol) in benzene (2 mL) was added dropwise to a solution of 3-(4-methoxyphenyl)sydnone-4-carboxamidoxime **134a** (1.000 g, 4.00 mmol) in benzene (20 mL) and the mixture was heated under reflux for 24 h. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane:ethyl acetate; 4:1) to give **135a** as a light yellow solid. (0.450 g, 1.48 mmol). Yield: 36%. Melting Point: 129-131^{o}C. R_f : 0.47 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3115, 3076, 3036 (arom. C-H), 2974, 2929, 2839 (alip. C-H), 1774 (sydnone C=O), 1602, 1595, 1570 (C=N), 1512, 1450, 1307, 1259, 1201, 1178, 1058, 1016, 956, 835, 758, 738 (C-Cl). ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.50 (d, *J* = 9.2 Hz, 2H), 7.09 (d, *J* = 9.2 Hz, 2H), 4.67 (s, 2H), 3.92 (s, 3H). LC-MS (AP-ESI) m/z (%): 309 $[M + H]^+$.

4-(5-(Chloromethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone (135b):



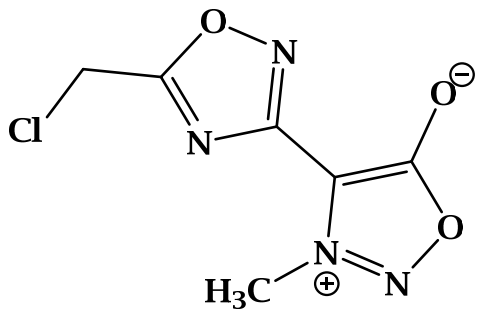
A solution of chloroacetylchloride (0.070 g, 0.62 mmol) in benzene (2 mL) was added dropwise to a solution of 3-(4-methoxyphenyl)sydnone-4-carboxamidoxime **134b** (0.360 g, 1.54 mmol) in benzene (20 mL) and the mixture was heated under reflux for 24 h. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (*n*-hexane:ethyl acetate; 4:1) to give **135b** as a white solid. (0.400 g, 1.37 mmol). Yield: 89%. Melting Point.:155-156^{o}C. R_f : 0.59 (Eluant: *n*-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3014 (arom. C-H), 2960 (alip. C-H), 1797, 1778 (sydnone C=O), 1568 (C=N), 1510, 1444, 1282, 1199, 1058, 1010, 954, 891, 779, 750 (C-Cl). ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.45 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 4.66 (s, 2H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 174.5 (syd. C=O), 143.8 (C-CH_3) , 130.3, 124.7, 32.9 (-CH_2), 21.6 (-CH_3). LC-MS (AP-ESI) m/z (%): 316 $[M + H]^+$.

4-(5-(Chloromethyl)-1,2,4-oxadiazol-3-yl)-3-(4-bromophenyl)sydnone (135c):



A solution of chloroacetylchloride (0.053 g, 0.47 mmol) in benzene (2 mL) was added dropwise to a solution of 3-(4-methoxyphenyl)sydnone-4-carboxamidoxime **134c** (0.350 g, 1.17 mmol) in benzene (20 mL) and the mixture was heated under reflux for 24 h. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 5:1) to give **135c** as a white solid. (0.382 g, 1.07 mmol). Yield: 91%. Melting Point: 195-197^{o}C. R_f : 0.66 (Eluant: *n*-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3093, 3063, (arom. C-H), 2989, 2947 (alip. C-H), 1770 (sydnone C=O), 1751, 1585, 1562 (C=N), 1481, 1419, 1188, 1057, 1014, 960, 910, 833, 794, 740 (C-Cl), 659 (C-Br). ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.78 (d, *J*=8.8 Hz, 2H), 7.47 (d, *J*=8.8 Hz, 2H), 4.66 (s, 2H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 174.7 (syd. C=O), 164.5 (C=N), 158.3 (C=N), 133.1, 127.6, 126.6, 32.9 (-CH_2-). LC-MS (80 eV) (*m/z*) (%): 357 ([M-H]$^-$ (^{81}Br), 100), 355 ([M-H]$^-$ (^{79}Br), 90).

4-(5-(Chloromethyl)-1,2,4-oxadiazol-3-yl)-3-methylsydnone (135d):

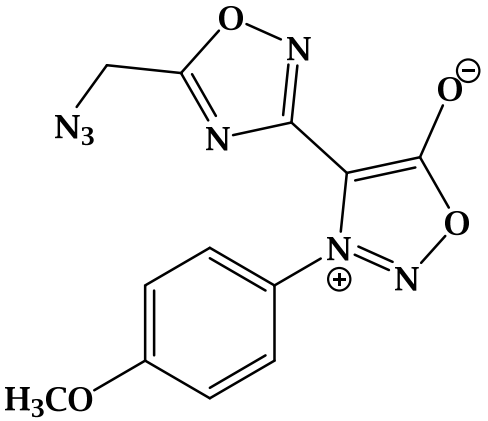


A solution of chloroacetylchloride (0.059 g, 0.52 mmol) in benzene (2 mL) was added dropwise to a solution of 3-(4-methoxyphenyl)sydnone-4-carboxamidoxime **134d** (0.210 g, 1.30 mmol) in benzene (20 mL) and the mixture was heated under reflux for 24h. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 3:1) to give **135d** as a yellow solid. (0.150 g, 0.69 mmol). Yield: 53%. Melting Point.: 100-101^{o}C. R_f : 0.36 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 2962, 2924 (alip. C-H), 1747 (sydnone C=O), 1681, 1577 (C=N), 1512, 1454, 1419, 1346, 1265, 1211, 1122, 1080, 1041, 1010, 968, 925, 898, 736 (C-Cl). ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 4.76 (s, 2H), 4.44 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 174.9 (syd. C=O), 164.5 (C=N), 158.5 (C=N), 41.6 (-CH_2-), 33.1 (-CH_3). LC-MS (80 eV) (*m/z*) (%): 280 ([M+CH_3CN+Na]$^{+}$, 100). HRMS-ES: Found: MH^{+}, 217.0111. $C_6H_6N_4O_3Cl$ requires M, 217.0128**.**

PART 7

Synthesis of 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)sydnone dervivatives (136a-d):

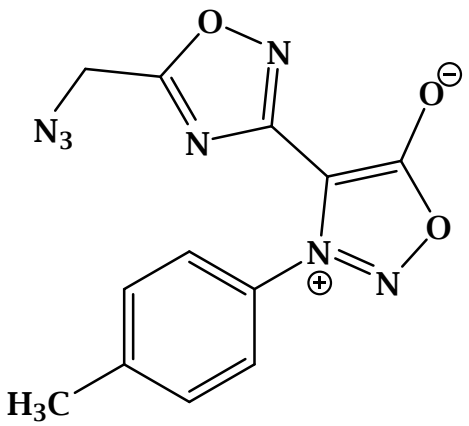
4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methoxyphenyl)sydnone (136a):



To a stirred solution of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methoxyphenyl)sydnone **135a** (0.450 g, 1.48 mmol) in a 10 mL water/acetone mixture (1:4) was added sodium azide (0.106 g, 1.63 mmol). The resulting suspension was stirred at room temperature for 24 h. Dichloromethane (DCM) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with 3x10 mL aliquots of DCM and the combined organic layers were dried over sodium sulfate. Solvent was removed under reduced pressure to give **136a** as a light orange solid.

(0.460 g, 1.46 mmol). Yield: 99%. M.p.: 105-108^{o}C. R_f : 0.44 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3082, 3016 (arom. C-H), 2939, 2845 (alip. C-H), 2108 (azide N=N=N), 1774 (sydnone C=O), 1604, 1591, 1566 (C=N), 1512, 1440, 1305, 1259, 1199, 1058, 1024, 835. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.49 (d, *J*=8.8 Hz, 2H), 7.06 (d, *J*=9.2 Hz, 2H), 4.51 (s, 2H), 3.90 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 174.4 (syd. C=O), 165.0 (C=N), 162.8 (C-OCH_3), 158.6 (C=N), 126.8, 126.5, 114.9, 55.9 (-CH_3), 44.8 (-CH_2-). LC-MS (80 eV) (*m/z*) (%): 379 ([M+CH_3CN+Na]$^+$, 58), 333 (62), 316 ([M+H]$^+$, 100). HRMS-ES: Found: MH$^+$,316.0783. $C_{12}H_{10}N_7O_4$ requires M, 316.0794.

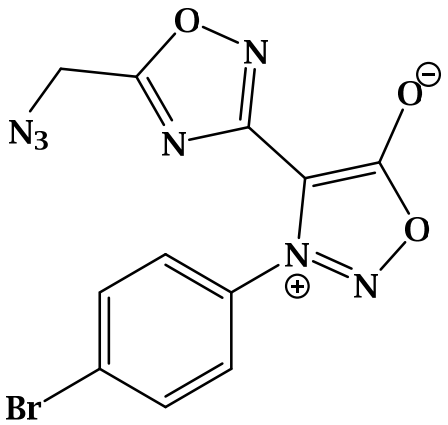
4-(5-(Azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone (136b):



To a stirred solution of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone **135b** (0.400 g, 1.37 mmol) in a 10 mL water/acetone mixture (1:4) was added sodium azide (0.098 g, 1.51 mmol). The resulting suspension was stirred at room temperature for 24 h. Dichloromethane

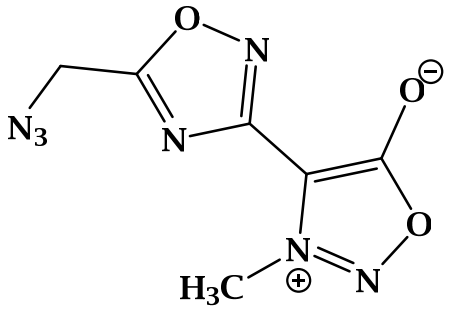
(DCM) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with 3x10 mL aliquots of DCM and the combined organic layers were dried over sodium sulfate. Solvent was removed under reduced pressure to give **136b** as a light yellow solid. (0.200 g, 0.67 mmol). Yield: 49%. Melting Point: 98-101^{o}C. R_f : 0.58 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3061 (arom. C-H), 2991, 2922 (alip. C-H), 2098 (azide N=N=N), 1759, 1743 (sydnone C=O), 1558 (C=N), 1508, 1435, 1319, 1273, 1197, 1056, 1016, 960, 817, 740. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.43 (q, 4H), 4.51 (s, 2H), 2.49 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 174.2 (syd. C=O), 164.9 (C=N), 158.4 (C=N), 143.7 (C-CH_3), 131.7, 130.3, 124.7, 44.7 (-CH_2-), 21.5 (-CH_3). LC-MS (80 eV) (*m/z*) (%): 468 (45), 363 ([M+CH_3CN+Na]$^+$, 94), 300 ([M+H]$^+$, 100). HRMS-ES : Found: MH$^+$,300.0834. $C_{12}H_{10}N_7O_3$ requires M, 300.08345.

4-(5-(Azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-bromophenyl)sydnone (136c):



To a stirred solution of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-3-(4-bromophenyl)sydnone **135c** (0.382 g, 1.07 mmol) in a 10 mL water/acetone mixture (1:4) was added sodium azide (0.077 g, 1.18 mmol). The resulting suspension was stirred at room temperature for 24 h. Dichloromethane (DCM) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with 3x10 mL aliquots of DCM and the combined organic layers were dried over sodium sulfate. Solvent was removed under reduced pressure to give **136c** as a light yellow solid. (0.200 g, 0.55 mmol). Yield: 51%. Melting Point: 177-179^{o}C. R_f : 0.63 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3093, 3063 (arom. C-H), 2989, 2920 (aliph. C-H), 2106 (azide N=N=N), 1763 (sydnone C=O), 1585, 1562 (C=N), 1423, 1276, 1199, 1057, 960, 833, 740, 659 (C-Br). ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.77 (d, *J*=8.8 Hz, 2H), 7.47 (d, *J*=8.8 Hz, 2H), 4.52 (s, 2H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 174.6 (syd. C=O), 162.2 (C=N), 158.4 (C=N), 133.2, 127.7, 126.7 (two peaks), 44.8 (-CH_2-). HRMS-ES : Found: MH^+,363.9777. $C_{11}H_7N_7O_3Br$ requires M, 363.9794.

4-(5-(Azidomethyl)-1,2,4-oxadiazol-3-yl)-3-methylsydnone (136d):

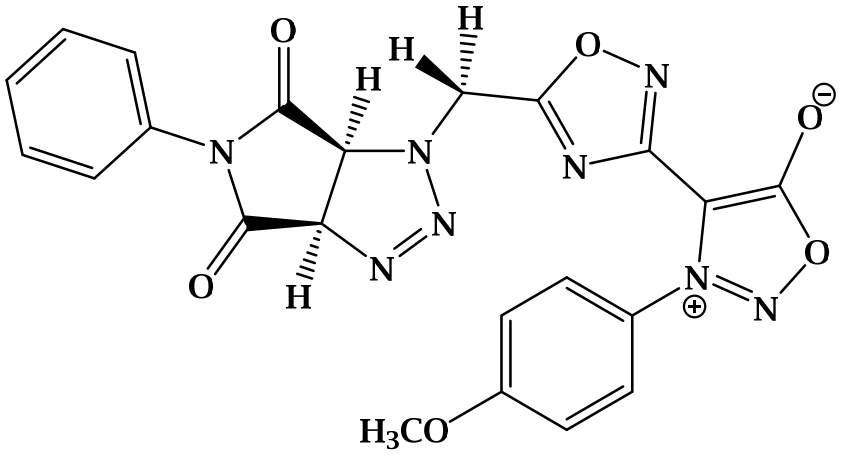


To a stirred solution of 4-(5-(chloromethyl)-1,2,4-oxadiazol-3-yl)-3-methylsydnone **135d** (0.150 g, 0.69 mmol) in a 10 mL water/acetone mixture (1:4) was added sodium azide (0.049 g, 0.76 mmol). The resulting suspension was stirred at room temperature for 24 h. Dichloromethane (DCM) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with 3x10 mL aliquots of DCM and the combined organic layers were dried over sodium sulfate. Solvent was removed under reduced pressure to give **136d** as a light yellow oil. (0.080 g, 0.36 mmol). Yield: 52%. R_f : 0.38 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3043, 2966, 2928 (aliph. C-H), 2106 (azide N=N=N), 1747 (sydnone C=O), 1681, 1573 (C=N), 1454, 1415, 1338, 1207, 1122, 1080, 1041, 968, 902. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 4.71 (d, 2H), 4.44 (m, 3H). HRMS-ES : 217.0053.

PART 8

1,3-Dipolar cycloaddition reactions of azido oxadiazolyl methyl sydnones:

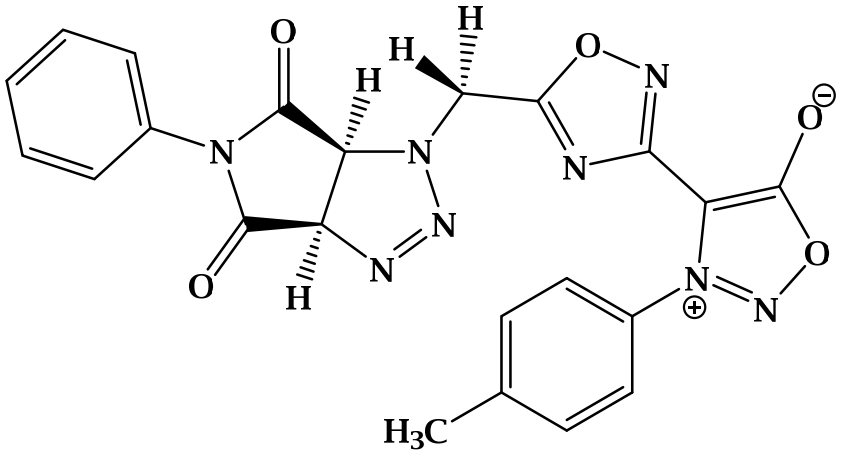
4-(5-(((3a*R*,6a*S*)-4,6-Dioxo-5-phenyl-4,5,6,6a-tetrahydropyrrolo[3,4-*d*][1,2,3]triazol-1(3a*H*)-yl)methyl)-1,2,4-oxadiazol-3-yl)-3-(4-methoxyphenyl)sydnone (137a):



A mixture of *N*-phenyl maleimide (0.017 g, 0.100 mmol) and 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methoxyphenyl)sydnone **136a** (0.030 g, 0.095 mmol) were stirred in 10 mL benzene and the mixture was heated under reflux for 2-4 d. Thereaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 1:2) to give **137a** as a light yellow solid. (0.030 g, 0.061 mmol). Yield: 65%. Melting Point.: 153-156^{o}C. R_f : 0.18 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3113, 3066 (arom. C-H), 2974, 2939, 2847 (alip. C-H), 1770 (sydnone C=O), 1724 (C=O), 1597, 1566 (C=N), 1498, 1381, 1261, 1195, 1057, 1026, 837, 740. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.43 (m, 5H), 7.21 (d, *J*=8.4 Hz, 2H), 7.05 (d, *J*=8.8 Hz, 2H), 5.65 (d, *J*=10.8 Hz, 1H), 5.51 (d, *J*=18.4 Hz, 1H), 5.24 (d, *J*=18.0 Hz, 1H), 4.56 (d, *J*=10.8 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 174.4 (syd. C=O), 170.8 (C=O), 168.4

(C=O), 164.9 (C=N), 162.8 (C-OCH_3), 158.3 (C=N), 130.6, 129.4, 126.7, 126.4, 126.1, 114.9, 83.2 (-CH), 57.1 (-CH), 56.0 (-CH_3), 44.4 (-CH_2-). LC-MS (80 eV) (*m/z*) (%): 543 (65), 538 ([M+CH_3CNa]$^+$, 100), 493 (60). HRMS-ES : 493.1543.

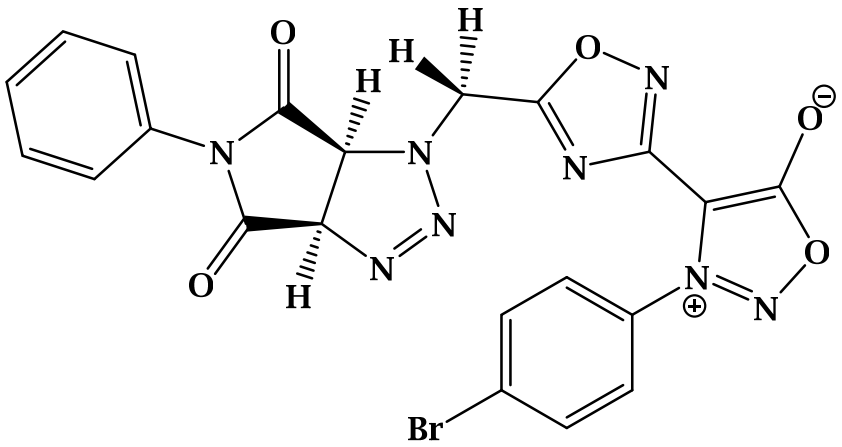
4-(5-(((3a*R*,6a*S*)-4,6-Dioxo-5-phenyl-4,5,6,6a-tetrahydropyrrolo[3,4-*d*][1,2,3]triazol-1(3a*H*)-yl)methyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone (137b):



A mixture of *N*-phenyl maleimide (0.030 g, 0.175 mmol) and 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone **136b** (0.050 g, 0.167 mmol) were stirred in 17 mL benzene and the mixture was heated under reflux for 2-4 d. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 1:2) to give **137b** as a light yellow solid. (0.020 g, 0.042 mmol). Yield: 25%. Melting Point.: 143-144^{o}C. R_f : 0.19 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 1766 (sydnone C=O), 1720 (C=O), 1564 (C=N), 1492, 1379, 1195, 1041, 817, 742.

^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.43 (m, 5H), 7.35 (d, 2H), 7.20 (dd, 2H), 5.61 (d, *J*=10.8 Hz, 1H), 5.48 (d, *J*=18.0 Hz, 1H), 5.22 (d, *J*=18.0 Hz, 1H), 4.56 (d, *J*=10.8 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 174.3 (syd. C=O), 170.7 (C=O), 168.3 (C=O), 164.8 (C=N), 158.2 (C=N), 143.7 (C-CH_3), 131.7, 130.3, 129.3, 126.8, 126.3, 126.0, 124.6, 83.2 (-CH), 57.0 (-CH), 44.4 (-CH_2-), 21.5 (-CH_3). HRMS-ES: 477.1466, 522.1790.

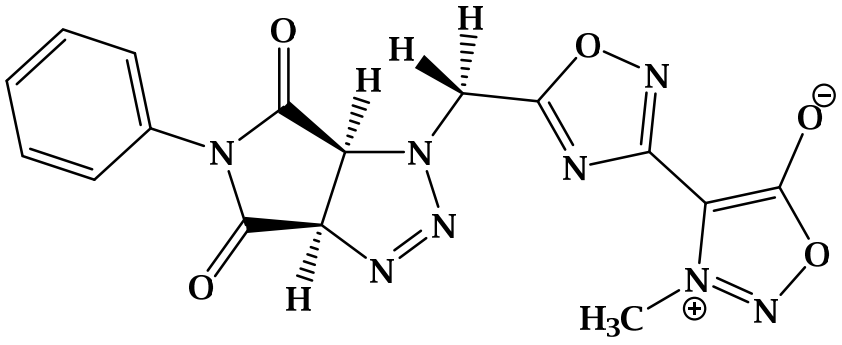
4-(5-(((3a*R*,6a*S*)-4,6-dioxo-5-phenyl-4,5,6,6a-tetrahydropyrrolo[3,4-*d*][1,2,3]triazol-1(3a*H*)-yl)methyl)-1,2,4-oxadiazol-3-yl)-3-(4-bromophenyl)sydnone (137c):



A mixture of *N*-phenyl maleimide (0.020 g, 0.116 mmol) and 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-bromophenyl)sydnone **136c** (0.040 g, 0.110 mmol) were stirred in benzene (11 mL) and the mixture was heated under reflux for 2-4 d. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 1:2) to give **137c** as a light yellow solid. (0.025 g, 0.047 mmol). Yield: 42%. Melting Point: 170-

172^{o}C. R_f : 0.21 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3097, 3066 (arom. C-H), 2982 (alip. C-H), 1774 (sydnone C=O), 1724 (C=O), 1651, 1566 (C=N), 1496, 1381, 1195, 1068, 833, 740, 694 (C-Br). ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.72 (d, 2H), 7.46 (m, 5H) 7.22 (dd, 2H), 5.73 (d, *J*=10.4 Hz, 1H), 5.49 (d, *J*=17.6 Hz, 1H), 5.28 (d, *J*=18.0 Hz, 1H), 4.53 (d, *J*=10.8 Hz, 1H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 174.4 (syd. C=O), 170.5 (C=O), 168.1 (C=O), 164.4 (C=N), 158.0 (C=N), 133.1, 133.0, 130.5, 129.4, 127.5, 126.6, 126.5, 126.0, 83.1 (-CH), 57.0 (-CH), 44.3 (-CH_2-).

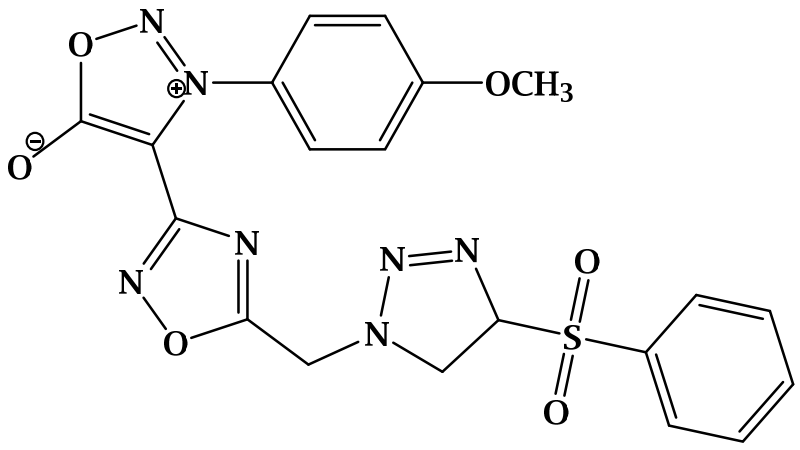
4-(5-(((3a*R*,6a*S*)-4,6-Dioxo-5-phenyl-4,5,6,6a-tetrahydropyrrolo[3,4-*d*][1,2,3]triazol-1(3a*H*)-yl)methyl)-1,2,4-oxadiazol-3-yl)-3-methylsydnone (137d):



A mixture of *N*-phenyl maleimide (0.029 g, 0.169 mmol) and 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-methylsydnone **136d** (0.036 g, 0.161 mmol) were stirred in 17 mL benzene and the mixture was heated under reflux for 2-4 d. Thereaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 1:2) to give **137d** as a pale

yellow solid. (0.017 g, 0.052 mmol). Yield: 31%. Melting Point.: 149-150^{o}C. R_f: 0.16 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 2989, 2928, 2854 (alip. C-H), 1751 (sydnone C=O), 1720 (C=O), 1647, 1577 (C=N), 1496, 1377, 1195, 1080, 895, 740. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.34 (m, 2H) 5.88 (d, *J*=10.8 Hz, 1H), 5.56 (d, *J*=17.6 Hz, 1H), 5.38 (d, *J*=17.6 Hz, 1H), 4.76 (d, *J*=10.8 Hz, 1H), 4.35 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 174.6 (syd. C=O), 170.8 (C=O), 168.6 (C=O), 164.7 (C=N), 158.7 (C=N), 130.6, 129.5, 129.4, 126.5, 126.2, 83.3 (-CH), 57.4 (-CH), 44.5 (-CH_2-), 41.6 (-CH_3). HRMS-ES : 446.1510.

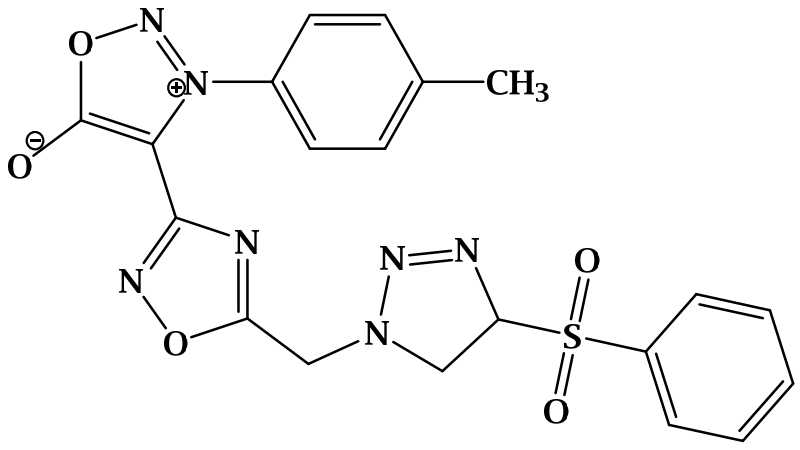
3-(4-Methoxyphenyl)-4-(5-((5-(phenylsulfonyl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazol-3-yl)sydnone (138a):



A mixture of phenyl vinyl sulfone (0.032 g, 0.192 mmol) and 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methoxyphenyl)sydnone **136a** (0.060 g, 0.190 mmol) were stirred in10 mL toluene and the mixture was heated under reflux for 5-6 d. The reaction was monitored by TLC. The

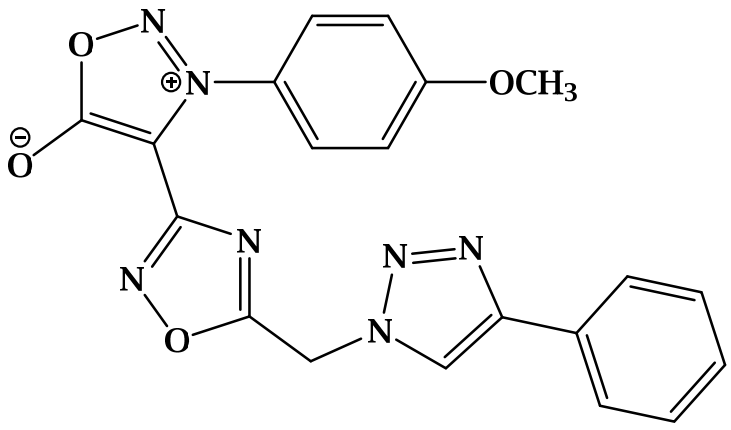
reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 1:2) to give **138a** as a brown solid. (0.009 g, 0.019 mmol). Yield: 10%. Melting Point.: 111-114^{o}C. R_f : 0.19 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3068 (arom. C-H), 2956, 2924, 2852 (alip. C-H), 1766 (sydnone C=O), 1747, 1604, 1566 (C=N), 1510, 1446, 1305 (S=O), 1257, 1149 (S=O), 1083, 1024, 835, 731. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.34 (m, 9H), 5.58 (dd, *J*=7.2, 7.2 Hz, 1H), 5.21 (d, *J*=17.2 Hz, 1H), 4.97 (d, *J*=17.2 Hz, 1H), 4.10 (dd, *J*=7.2, 7.6 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 173.7 (syd. C=O), 165.0 (C=N), 162.7 (C-OCH_3), 158.4 (C=N), 136.2, 134.9, 129.6, 129.4, 114.8, 95.0 (-CS-), 55.9, 53.5(-CH_3), 45.0, 44.3 (-CH_2-). LC-MS (80 eV) (*m/z*) (%): 506 ([M+Na]$^+$, 34), 478 (92), 456 ([M+H-N_2]$^+$, 23), 309 (55), 208 (100). HRMS-ES: 367.1043.

3-(4-Methylphenyl)-4-(5-((5-(phenylsulfonyl)-4,5-dihydro-1*H*-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazol-3-yl)sydnone (138b):



A mixture of phenyl vinyl sulfone (0.024 g, 0.135 mmol) and 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone **136b** (0.040 g, 0.134 mmol) were stirred in 7 mL toluene and the mixture was heated under reflux for 5-6 d. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 1:2) to give **138b** as a light yellow solid. (0.008 g, 0.017 mmol). Yield: 13%. Melting Point.: 84-86^{o}C. R_f : 0.20 (Eluant: n-hexane: ethyl acetate, 1:1). IR (KBr, v:cm^{-1}): 2958, 2927, 2852 (alip. C-H), 1770 (sydnone C=O), 1564 (C=N), 1446, 1321 (S=O), 1240, 1151 (S=O), 1082, 1056, 935, 821, 744. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.95 (d, 2H), 7.72 (t, 1H), 7.60 (t, 2H), 7.42 (m, 4H), 5.56 (dd, *J*=7.2, 7.6 Hz, 1H), 5.19 (d, *J*=17.6 Hz, 1H), 4.96 (d, *J*=17.2 Hz, 1H), 3.85 (dd, *J*=7.6, 7.6 Hz, 1H), 3.52 (t, 1H), 2.47 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 173.5 (syd. C=O), 164.8 (C=N), 158.3 (C=N), 143.7 (C-CH_3), 136.0, 134.8, 131.8, 130.3, 129.5, 129.3, 124.7, 95.1 (-CS-), 45.0, 44.2 (-CH_2-), 21.5 (-CH_3). LC-MS (80 eV) (*m/z*) (%): 490 ([M+Na]$^+$, 100), 468 ([M+H]$^+$, 19), 459 (60). ESI-MS (80 eV) (*m/z*) (%): 466 ([M-H]$^-$, 100). HRMS-ES : Found: MH^+,468.1081. $C_{20}H_{18}N_7O_5S$ requires M, 468.1081.

3-(4-Methoxyphenyl)-4-(5-((5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazol-3-yl)sydnone (139a):



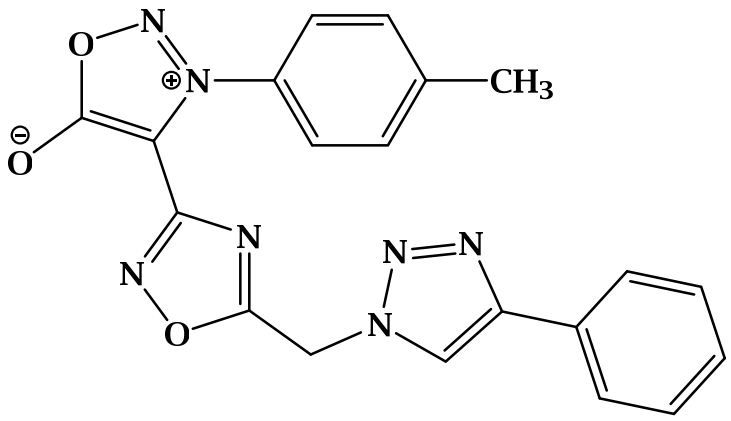
Method A

A mixture of phenylpropiolic acid (0.031 g, 0.21 mmol) and 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methoxyphenyl)sydnone **136a** (0.064 g, 0.20 mmol) were stirred in 20 mL benzene and the mixture was heated under reflux for 2-4 d. The reaction was monitored by TLC. The reaction mixture was concentrared *in vacuo*, and the crude residue was purified by flash column chromatography (n-hexane:ethyl acetate; 1:2) to givetwoisomers of **139a** as a white solid. (0.020 g, 0.048 mmol). Yield: 24%. Melting Point.: 163-166^{o}C. R_f : 0.26 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3074 (arom. C-H), 2920, 2850 (alip. C-H), 1770 (sydnone C=O), 1593, 1566 (C=N), 1508, 1438, 1261, 1199, 1060, 1026, 960, 837. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.91 (s, 1H), 7.80 (dd, 2H), 7.71 (s, 1H), 7.42 (m, 10H), 6.98 (d, 5H), 5.86 (s, 2H), 5.70 (s, 2H), 3.87 (s, 3H), 3.78 (s, 3H). LC-MS (80 eV) (*m/z*) (%): 459 ([M+CH_3CNH]$^{+}$, 100), 435 (28), 418 ([M+H]$^{+}$, 90).

Method B

A mixture of 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methoxyphenyl)sydnone **136a** (0.032 g, 0.102 mmol), catalytic amount of $CuSO_4.5H_2O$ (0.001 g, 0.005 mmol), Na-L-ascorbate (0.005 g, 0.026 mmol) and phenylpropiolic acid (0.016 g, 0.107 mmol) were stirred in 1 ml *t*-BuOH/water mixture (1:2) at room temperature for 2 d. Then, the reaction mixture was extracted with ethyl acetate three times. The combined organic layers were dried over sodium sulfate. The solvent was evaporated under reduced pressure to give one isomer of **139a** as a white solid. (0.040 g, 0.096 mmol). Yield: 95%. Melting Point: 163-166^oC. R_f : 0.26 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 2958, 2927, 2855 (aliph. C-H), 1766 (sydnone C=O), 1732, 1591, 1564 (C=N), 1510, 1460, 1440, 1427, 1257, 1199, 1180, 1056, 1056, 958, 835, 767. ^1H NMR (δ_H, 400 MHz, $CDCl_3$): 7.88 (s, 1H), 7.80 (dd, *J*=1.6, 1.2 Hz, 2H), 7.42 (m, 5H), 6.98 (d, *J*=9.2 Hz, 2H), 5.85 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 172.5 (syd. C=O), 162.9 (C=N), 129.0, 128.8, 126.5, 125.9, 120.3, 114.8, 55.8 (-CH_3), 45.1 (-CH_2-).

3-(4-methylphenyl)-4-(5-((5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazol-3-yl)sydnone (139b):



Method A

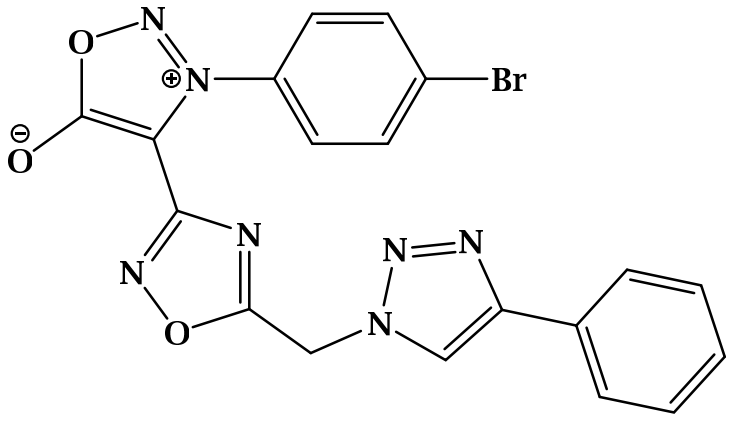
A mixture of phenylpropiolic acid (0.026 g, 0.175 mmol) and 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone **136b** (0.050 g, 0.167 mmol) were stirred in 17 mL benzene and the mixture was heated under reflux for 2-4 d. Thereaction was monitored by TLC. **No Reaction occurred.**

Method B

A mixture of 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-methylphenyl)sydnone **136b** (0.050 g, 0.167 mmol), catalytic amount of $CuSO_4.5H_2O$ (0.002 g, 0.008 mmol), Na-L-ascorbate (0.009 g, 0.043 mmol) and phenylpropiolic acid (0.026 g, 0.175 mmol) were stirred in 1 ml *t*-BuOH/water mixture (1:2) at room temperature for 2 d. Then, the reaction mixture was extracted with ethyl acetate three times. The combined organic layers were dried over sodium sulfate. The solvent was evaporated under

reduced pressure to give **139b** as a brown solid. (0.060 g, 0.149 mmol). Yield: 90%. Melting Point.: 129-131^{o}C. R_f : 0.21 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3047 (arom. C-H), 2935 (alip. C-H), 1780 (sydnone C=O), 1625, 1568 (C=N), 1450, 1338, 1232, 1068, 908, 815, 761. ^{1}H NMR (δ_H, 400 MHz, $CDCl_3$): 7.89 (s, 1H), 7.81 (d, *J*=8.4 Hz, 2H), 7.45 (t, 2H), 7.38 (m, 3H), 7.30 (d, *J*=8.4 Hz, 2H), 5.85 (s, 2H), 2.35 (s, 3H). ^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 173.4 (syd. C=O), 164.8 (C=N), 143.8 (C-CH_3), 131.5, 130.2, 129.8, 128.9, 128.7, 125.8, 124.7, 120.3, 45.0 (-CH_2-), 21.3 (-CH_3). LC-MS (80 eV) (*m/z*) (%): 424 ([M+Na]$^+$, 83), 402 ([M+H]$^+$, 100), 282 (93). ESI-MS (80 eV) (*m/z*) (%): 400 ([M-H]$^-$, 100). HRMS-ES : Found: MH$^+$,402.1296. $C_{20}H_{16}N_7O_3$ requires M, 402.1315.

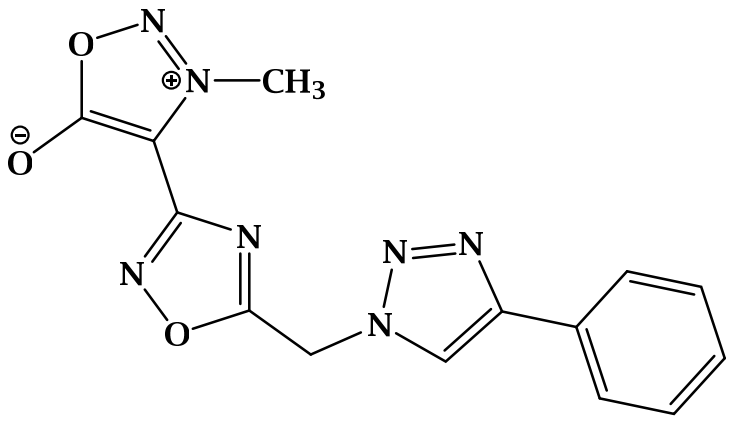
3-(4-Bromophenyl)-4-(5-((5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazol-3-yl)sydnone (139c):



Method B

A mixture of 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-(4-bromophenyl)sydnone **136c** (0.040 g, 0.110 mmol), catalytic amount of $CuSO_4.5H_2O$ (0.001 g, 0.005 mmol), Na-L-ascorbate (0.006 g, 0.028 mmol) and phenylpropiolic acid (0.017 g, 0.115 mmol) were stirred in 1 ml *t*-BuOH/water mixture (1:2) at room temperature for 2 d. Then, the reaction mixture was extracted with ethyl acetate three times. The combined organic layers were dried over sodium sulfate. The solvent was evaporated under reduced pressure to give **139c** as a white solid. (0.020 g, 0.043 mmol). Yield: 39%. Melting Point.: 221-223^oC. R_f : 0.30 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3140, 3093, 3063 (arom. C-H), 2924, 2850 (alip. C-H), 1774 (sydnone C=O), 1566 (C=N), 1438, 1415, 1199, 1068, 960, 829, 736, 690 (C-Br). ^1H NMR (δ_H, 400 MHz, $CDCl_3$): 7.90 (s, 1H), 7.82 (d, *J*=7.2 Hz, 2H), 7.70 (d, *J*=8.4 Hz, 2H), 7.42 (dq, 5H), 5.86 (s, 2H).^{13}C NMR (δ_C, 101 MHz, $CDCl_3$): 172.7 (syd. C=O), 158.4 (C=N), 133.1, 129.0, 128.7, 127.7, 126.5, 125.8, 120.1, 45.0 (-CH_2-). LC-MS (80 eV) (*m/z*) (%): 466 ([M-H]$^-$ (^{81}Br), 100), 464 ([M-H]$^-$ (^{79}Br), 95). HRMS-ES : Found: MH^+,466.0262. $C_{19}H_{13}N_7O_3Br$ requires M, 466.0263.

3-Methyl-4-(5-((5-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)-1,2,4-oxadiazol-3-yl)sydnone (139d):



Method B

A mixture of 4-(5-(azidomethyl)-1,2,4-oxadiazol-3-yl)-3-methylsydnone **136d** (0.038 g, 0.170 mmol), catalytic amount of $CuSO_4.5H_2O$ (0.002 g, 0.008 mmol), Na-L-ascorbate (0.008 g, 0.043 mmol) and phenylpropiolic acid (0.026 g, 0.178 mmol) were stirred in 1 ml *t*-BuOH/water mixture (1:2) at room temperature for 2 d. Then, the reaction mixture was extracted with ethyl acetate three times. The combined organic layers were dried over sodium sulfate. The solvent was evaporated under reduced pressure to give **139d** as a pale yellow solid. (0.017 g, 0.052 mmol). Yield: 31%. Melting Point.: 149-150^oC. R_f : 0.16 (Eluant: n-hexane: ethyl acetate, 1:1). IR(KBr, v:cm^{-1}): 3136, 3101, 3059 (arom. C-H), 2958, 2924, 2854 (alip. C-H), 1778 (sydnone C=O), 1755, 1573 (C=N), 1465, 1438, 1415, 1203, 1122, 968, 763. ^1H NMR (δ_H, 400 MHz,DMSO-d_6): 8.74 (s, 1H), 7.84 (d, 2H), 7.38 (m, 3H), 6.26 (s, 2H), 4.31 (s, 3H). ^{13}C NMR (δ_C, 101 MHz,DMSO-d_6): 174.5 (syd. C=O), 164.6 (C=N), 159.0 (C=N), 148.4, 147.3, 130.7, 129.5, 128.7, 125.8, 123.1, 45.4 (-

CH_2-), 42.3 (-CH_3). HRMS-ES : Found: MH^+, 326.0987. $C_{14}H_{12}N_7O_3$ requires M, 326.1002.

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APPENDICES

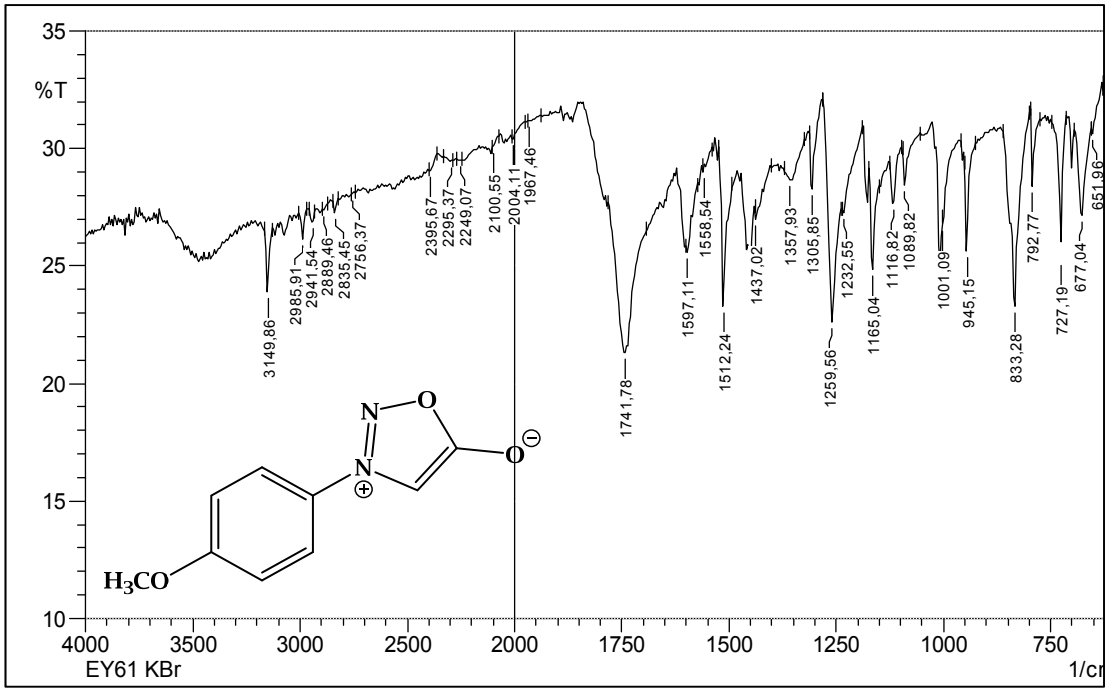


Figure 4.1. The IR spectrum of **8a**.

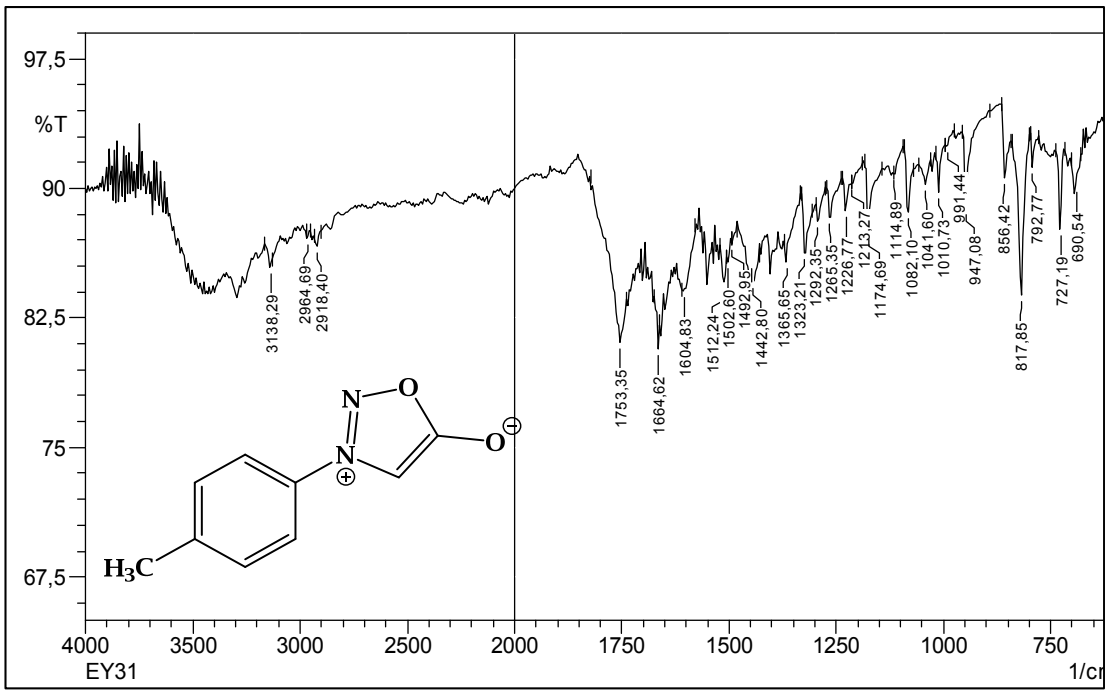


Figure 4.2. The IR spectrum of **8b**.

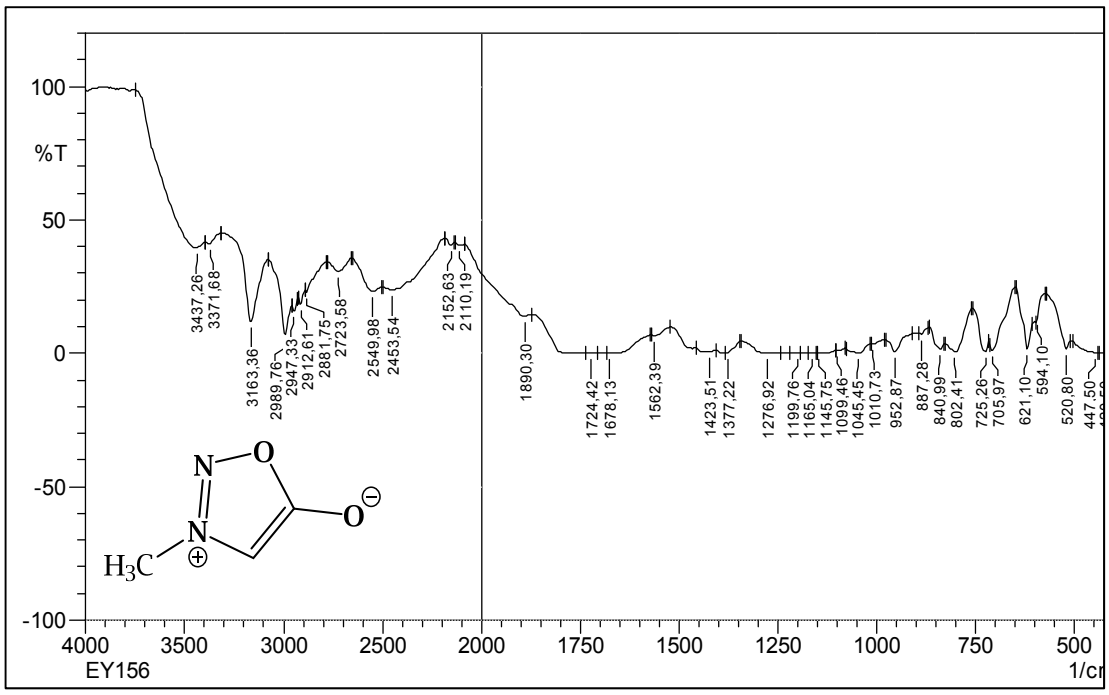


Figure 4.3. The IR spectrum of **8d**.

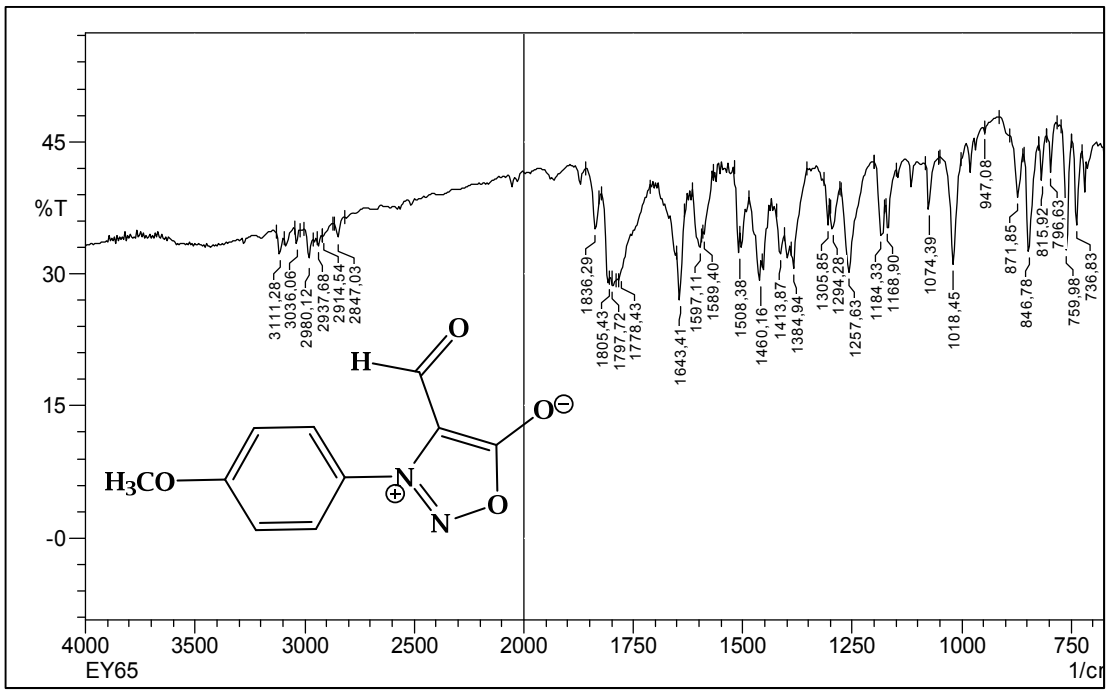


Figure 4.4. The IR spectrum of **20a**.

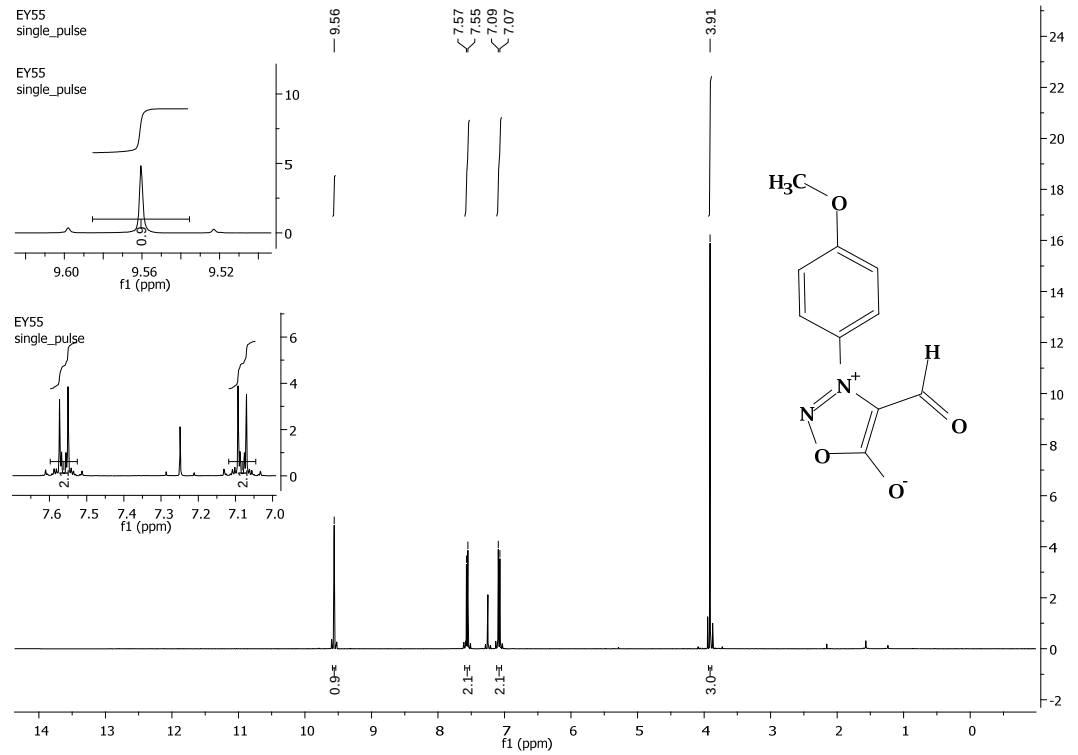


Figure 4.5. The ^{1}H NMR spectrum of **20a**.

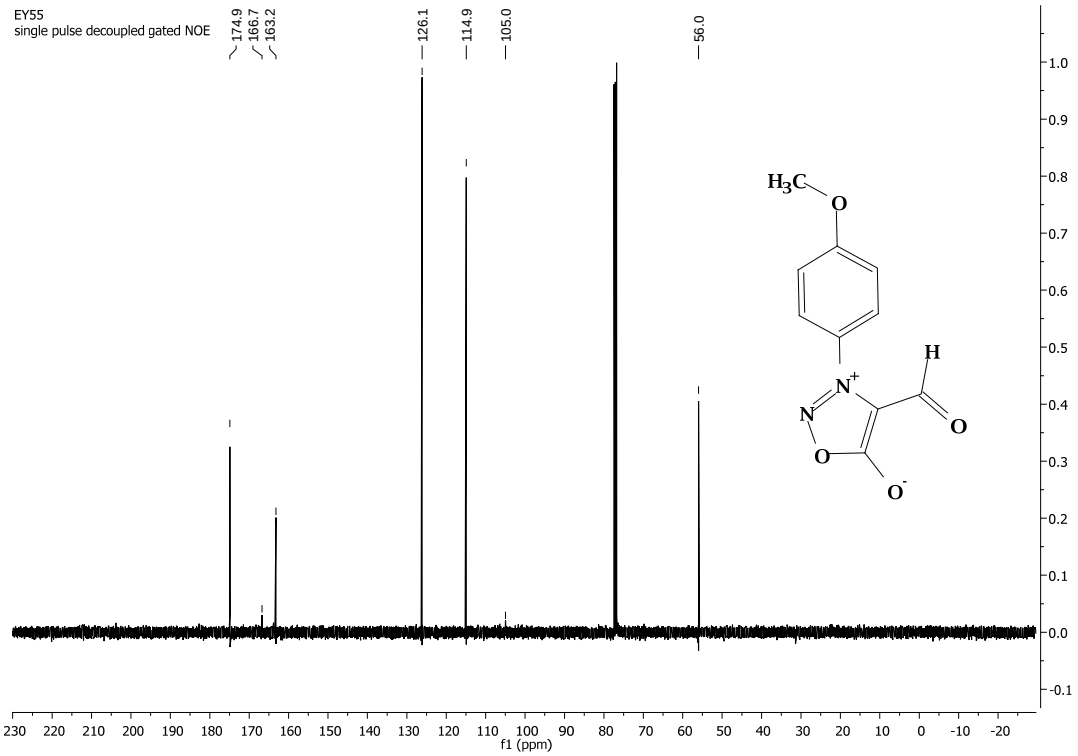


Figure 4.6. The ^{13}C NMR spectrum of **20a**.

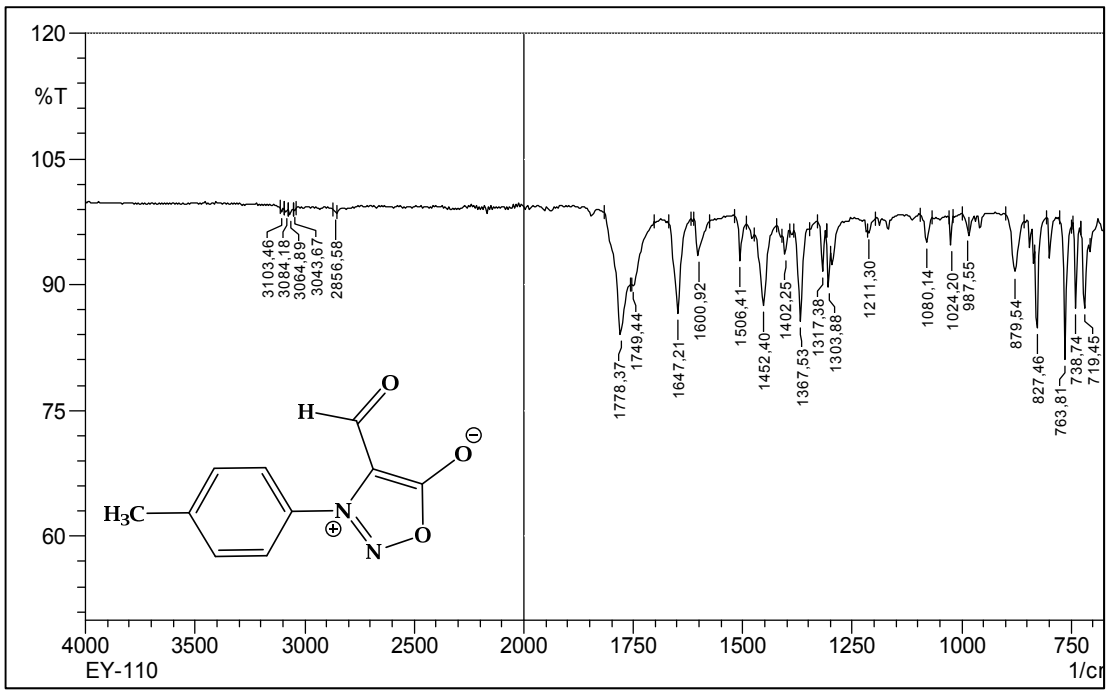


Figure 4.7. The IR spectrum of **20b**.

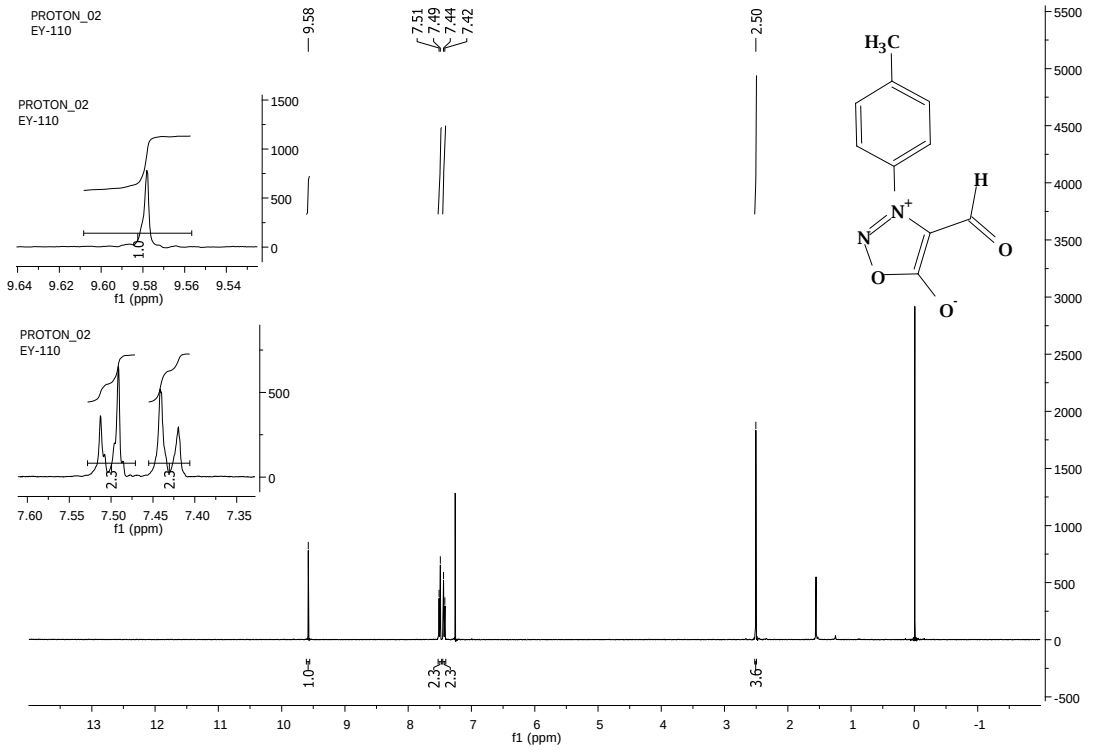


Figure 4.8. The ^{1}H NMR spectrum of **20b**.

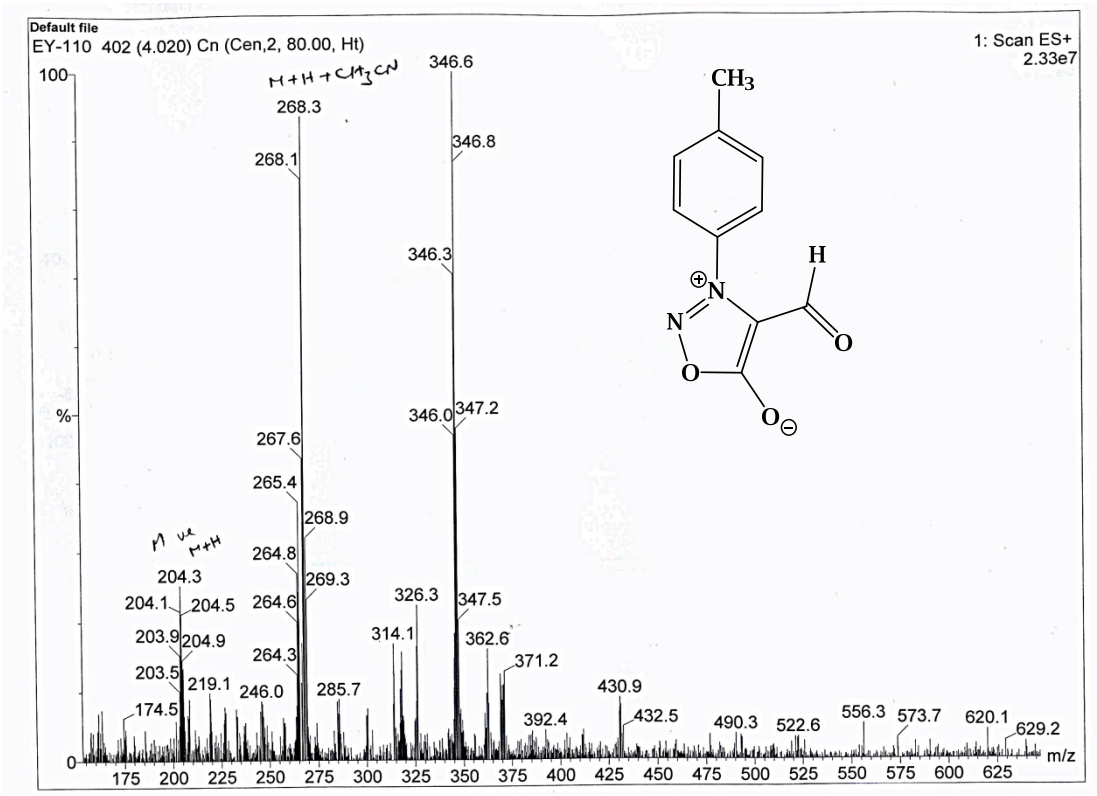


Figure 4.9. The LC-MS spectrum of **20b**.

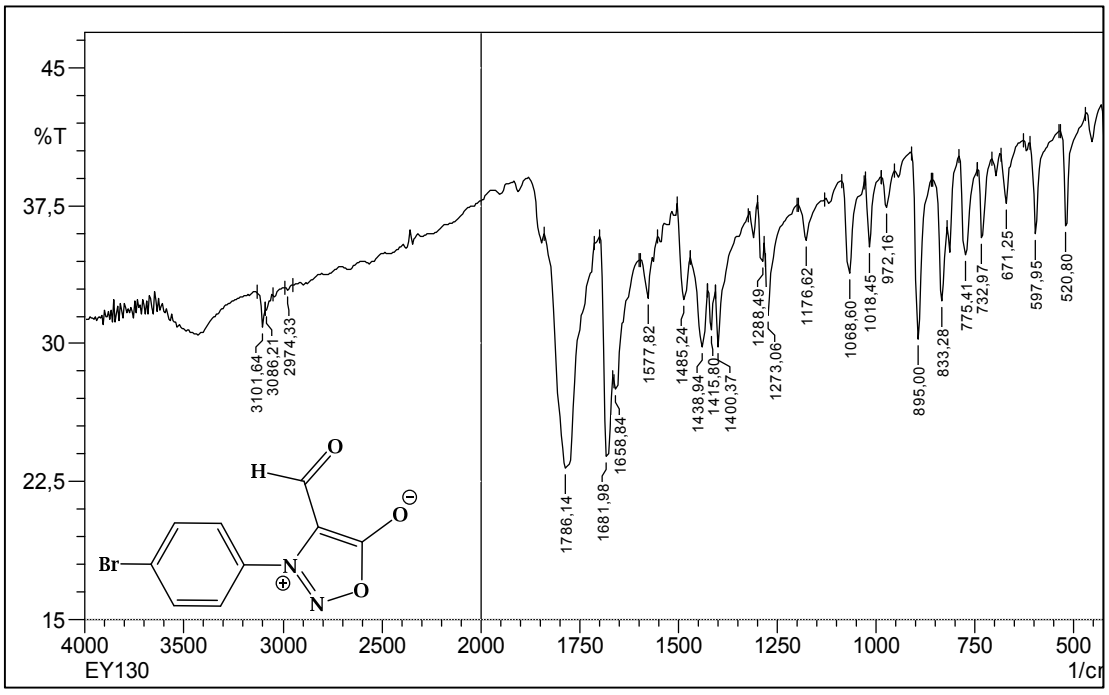


Figure 4.10. The IR spectrum of **20c**.

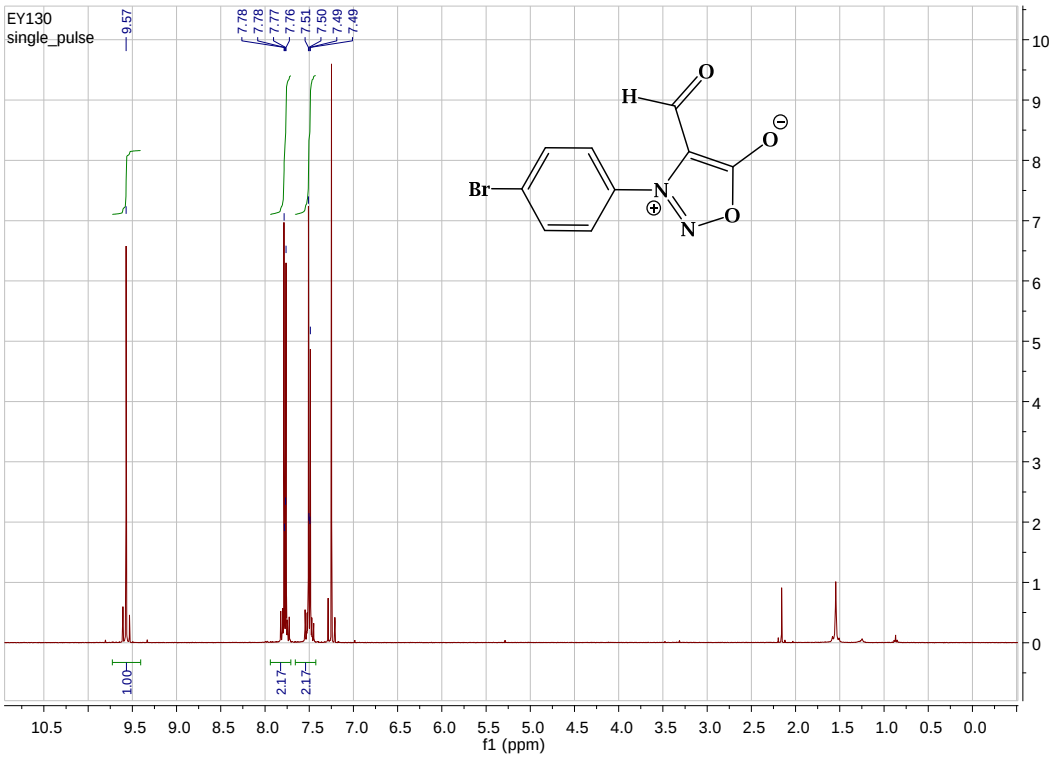


Figure 4.11. The ^{1}H NMR spectrum of **20**c.

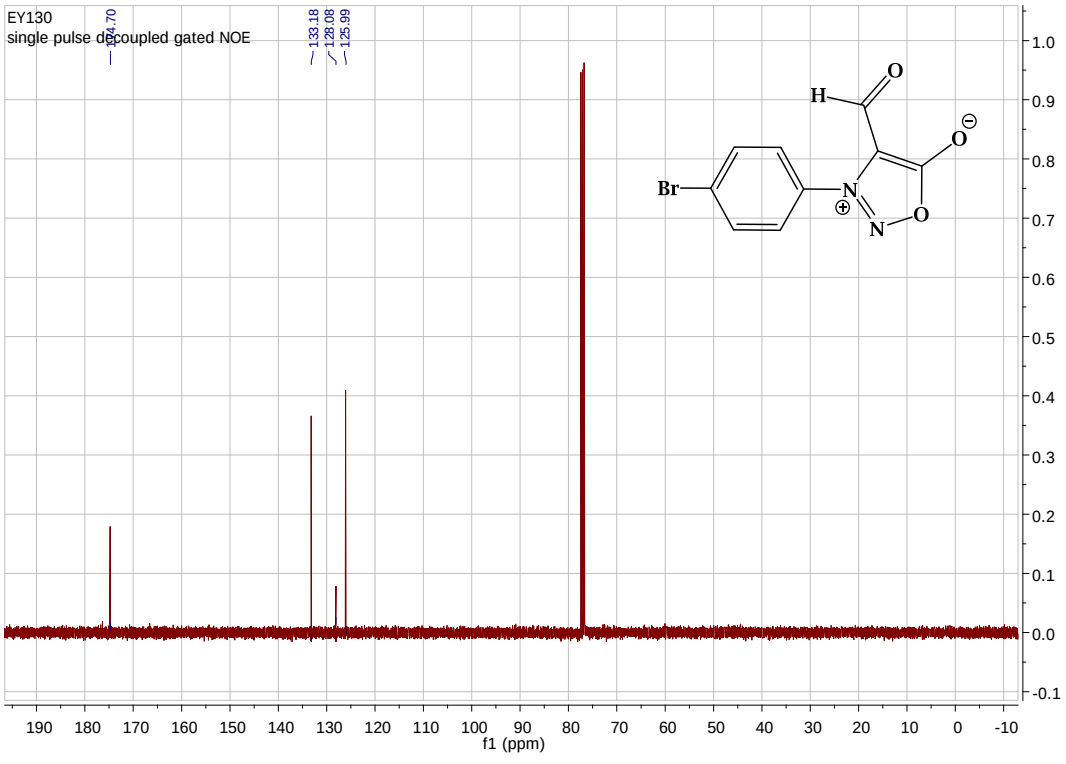


Figure 4.12. The ^{13}C NMR spectrum of **20c**.

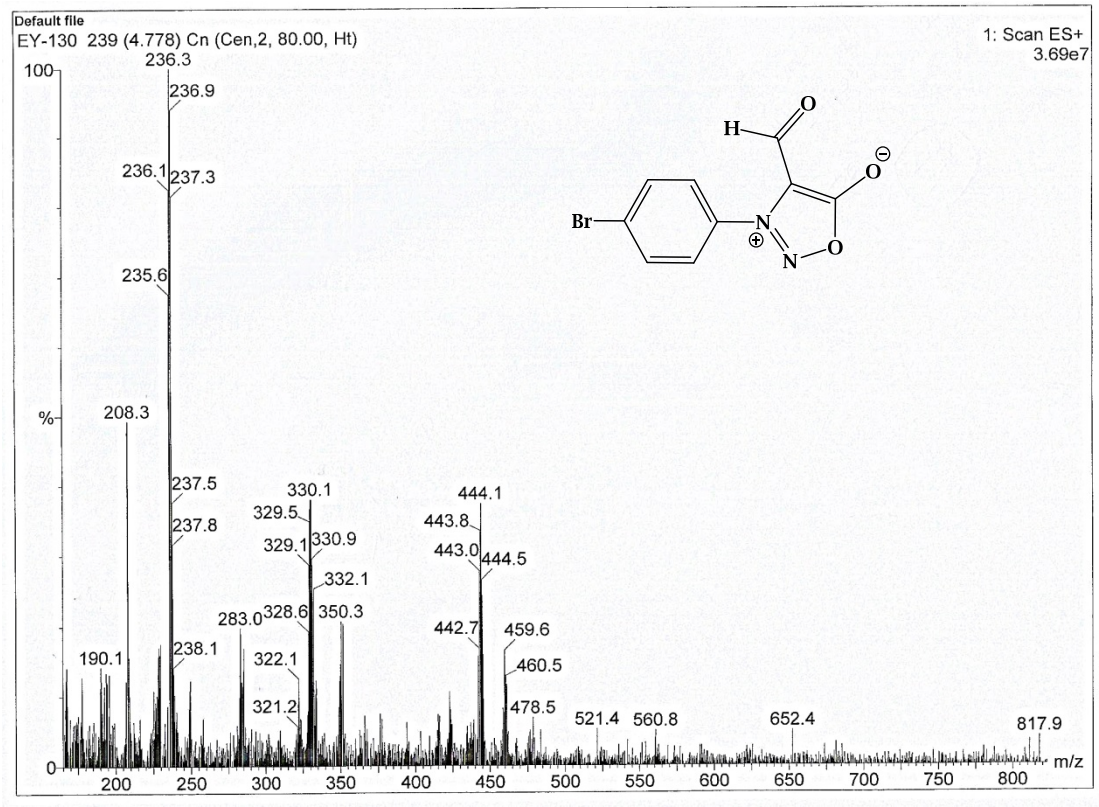


Figure 4.13. The LC-MS spectrum of **20**c.

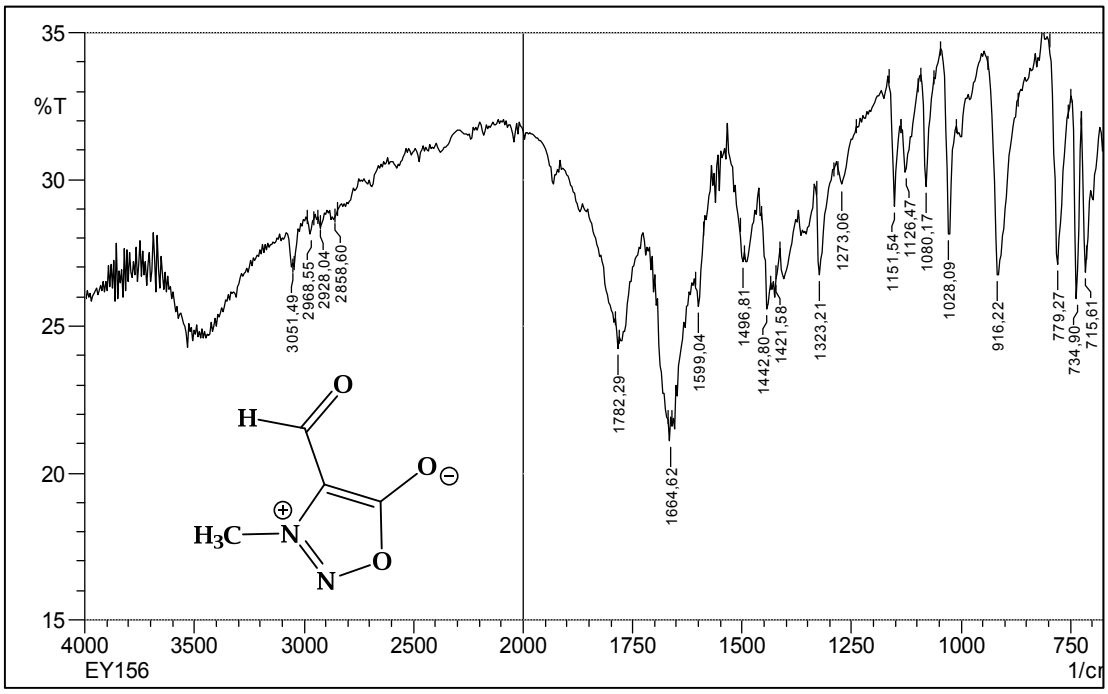


Figure 4.14. The IR spectrum of **20d**.

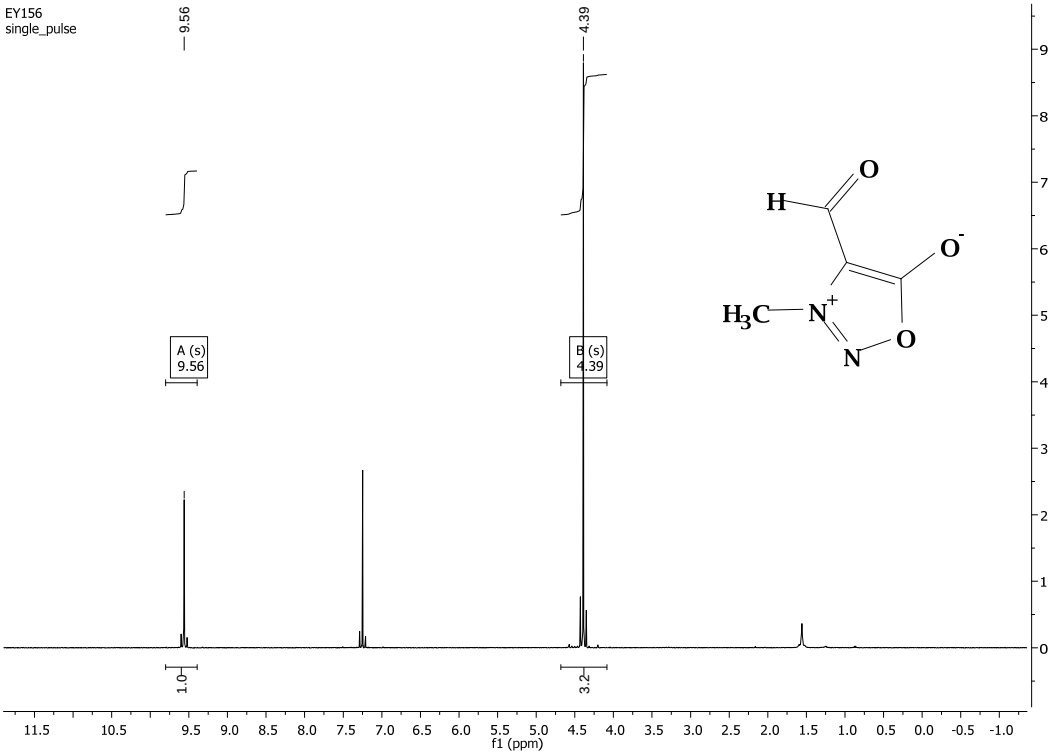


Figure 4.15. The ^{1}H NMR spectrum of **20d**.

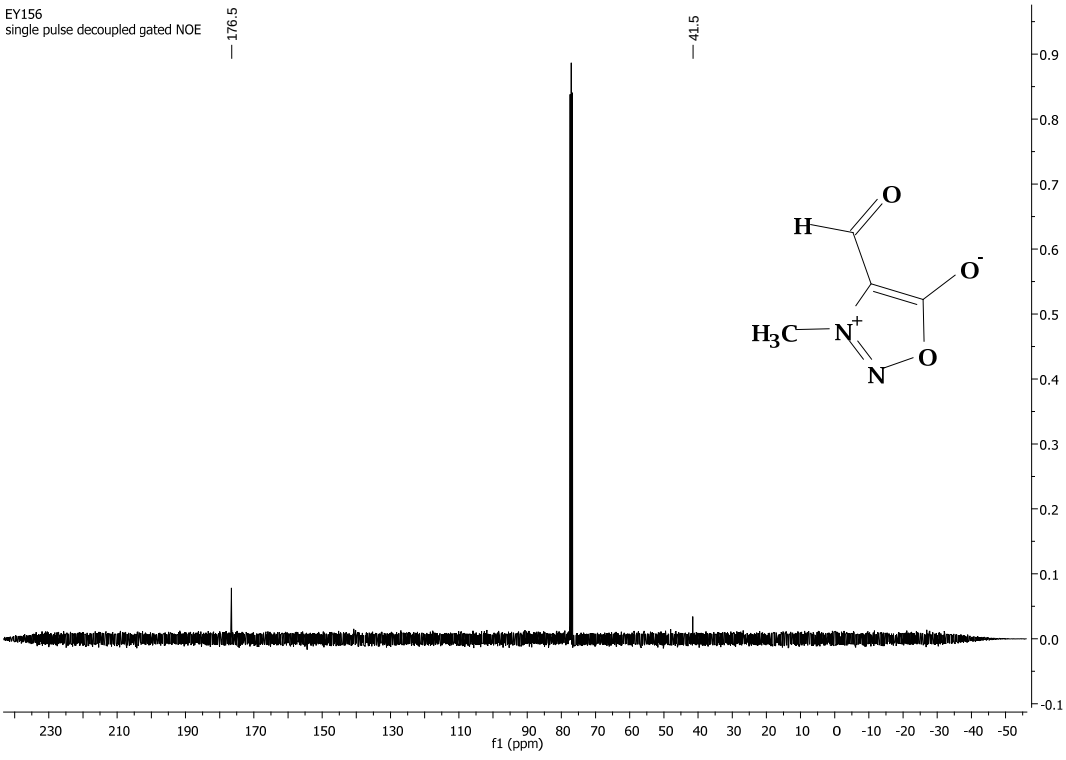


Figure 4.16. The ^{13}C NMR spectrum of **20d**.

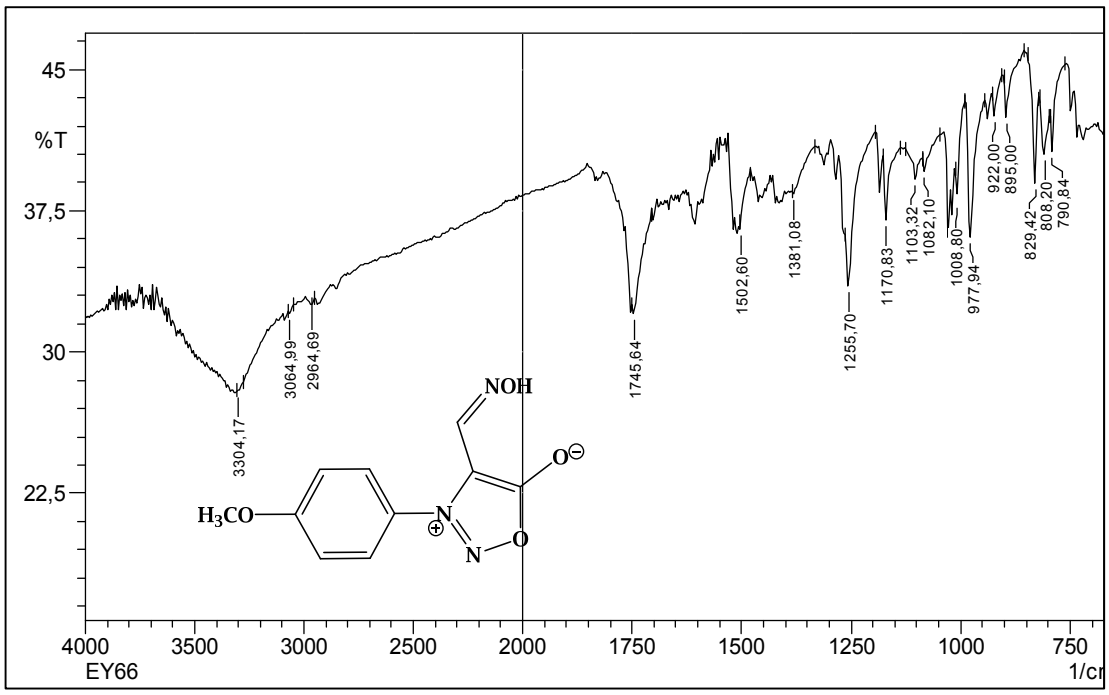


Figure 4.17. The IR spectrum of **132a**.

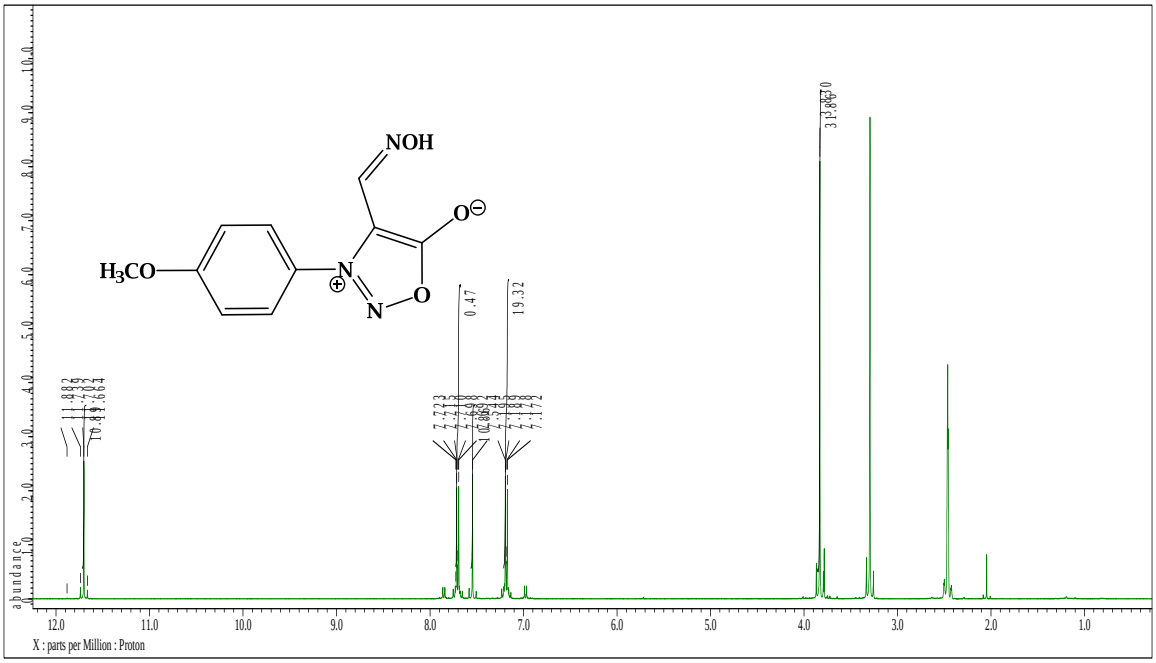


Figure 4.18. The ^{1}H NMR spectrum of **132a**.

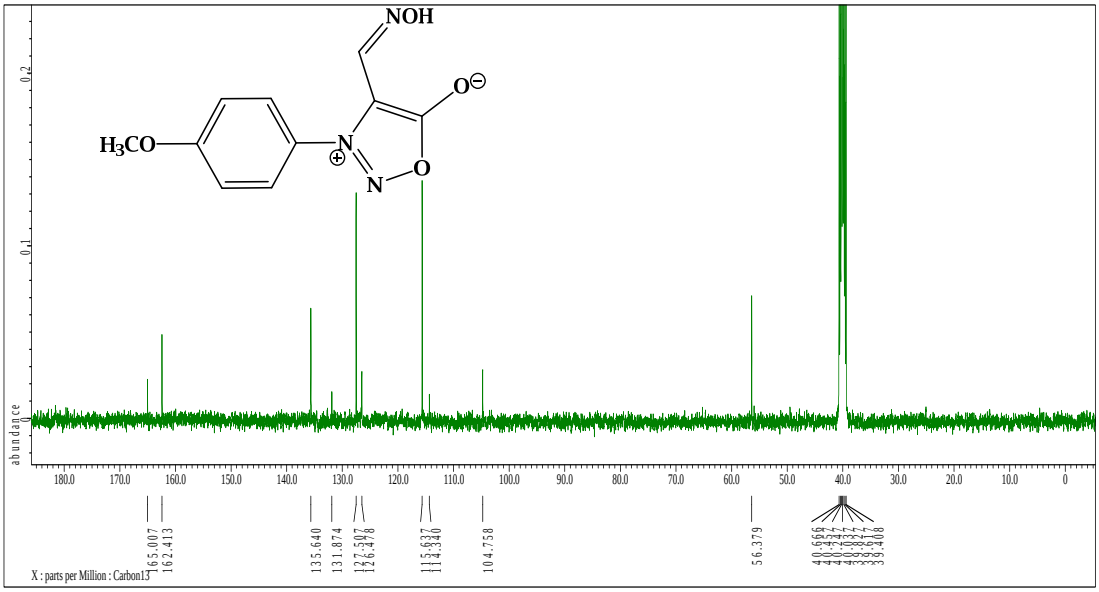


Figure 4.19. The ^{13}C NMR spectrum of **132a**.

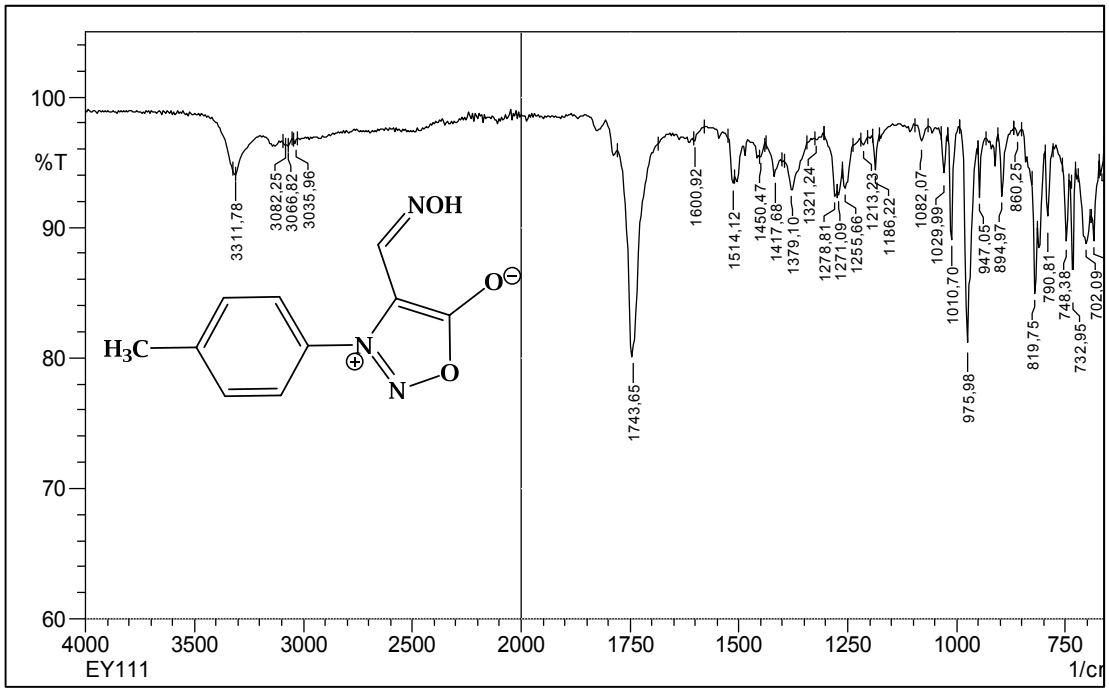


Figure 4.20. The IR spectrum of **132b.**

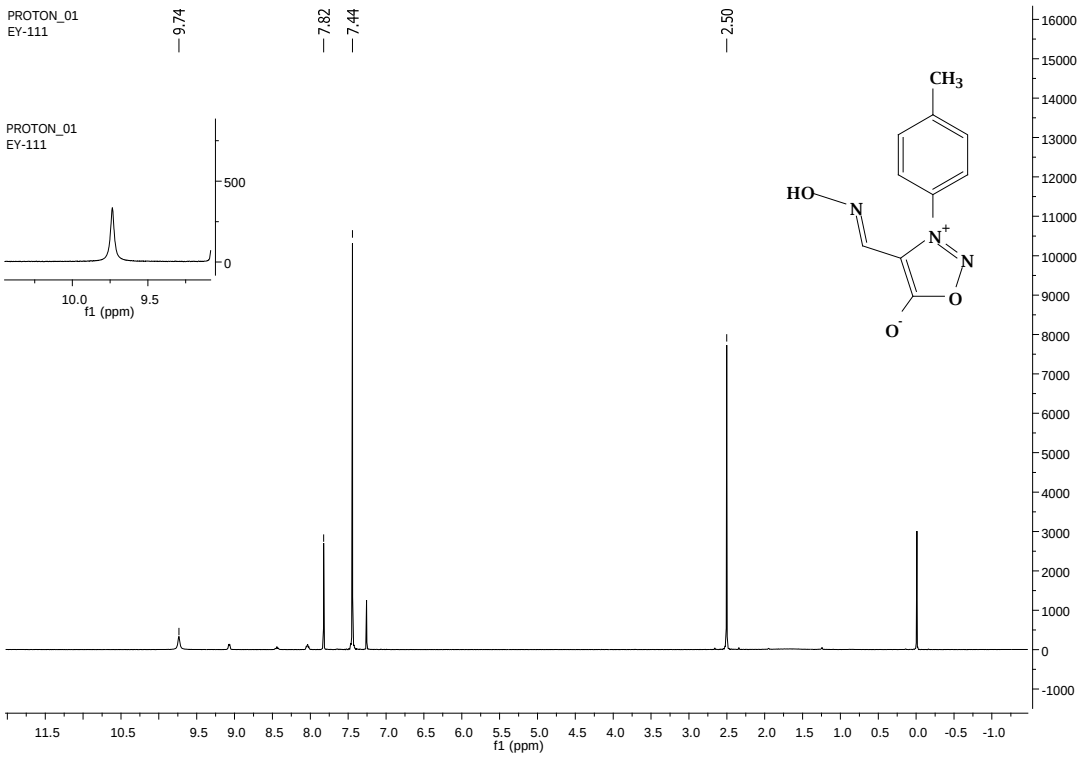


Figure 4.21. The ^{1}H NMR spectrum of **132b.**

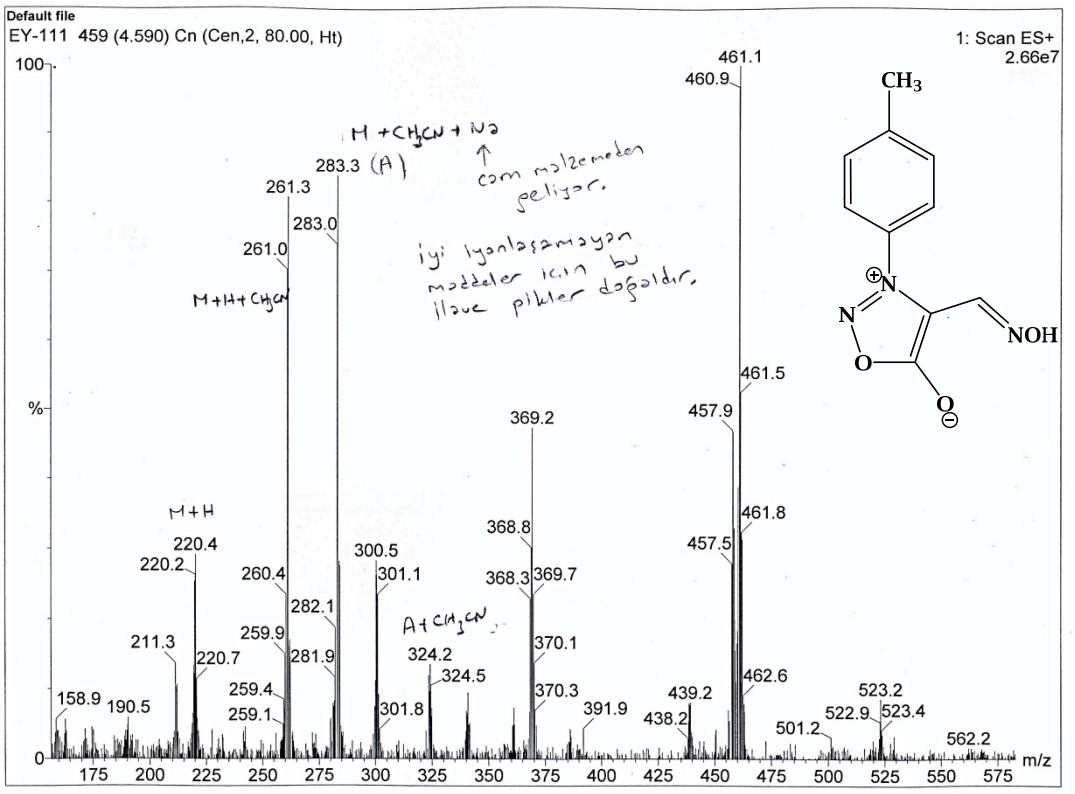


Figure 4.22. The LC-MS spectrum of **132b.**

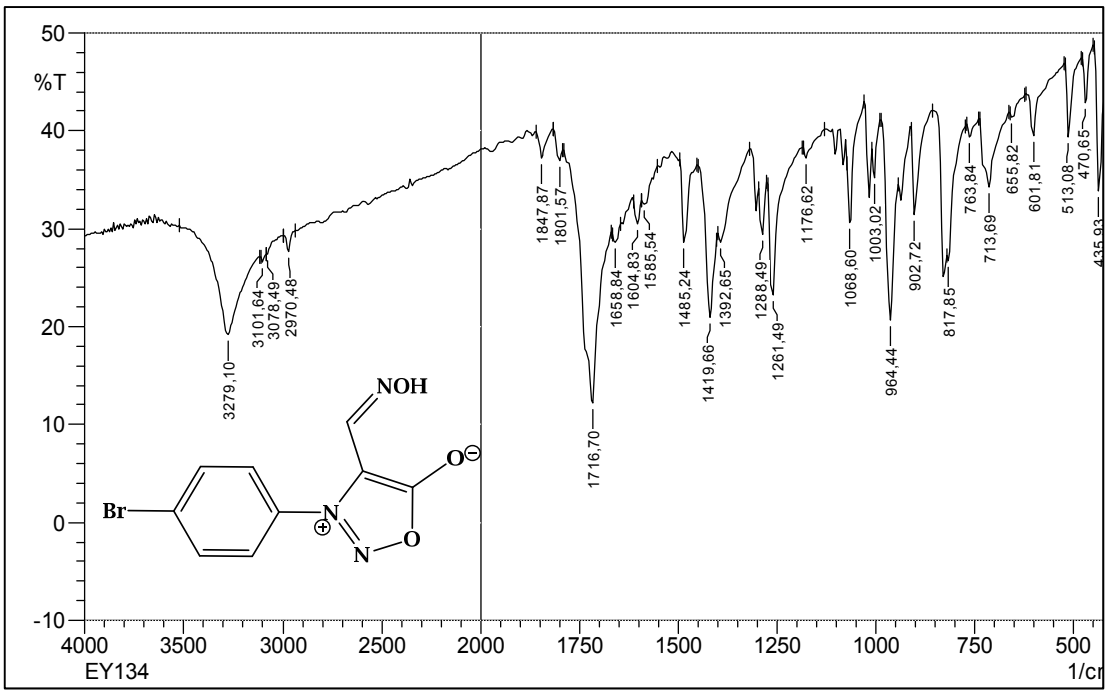


Figure 4.23. The IR spectrum of **132c.**

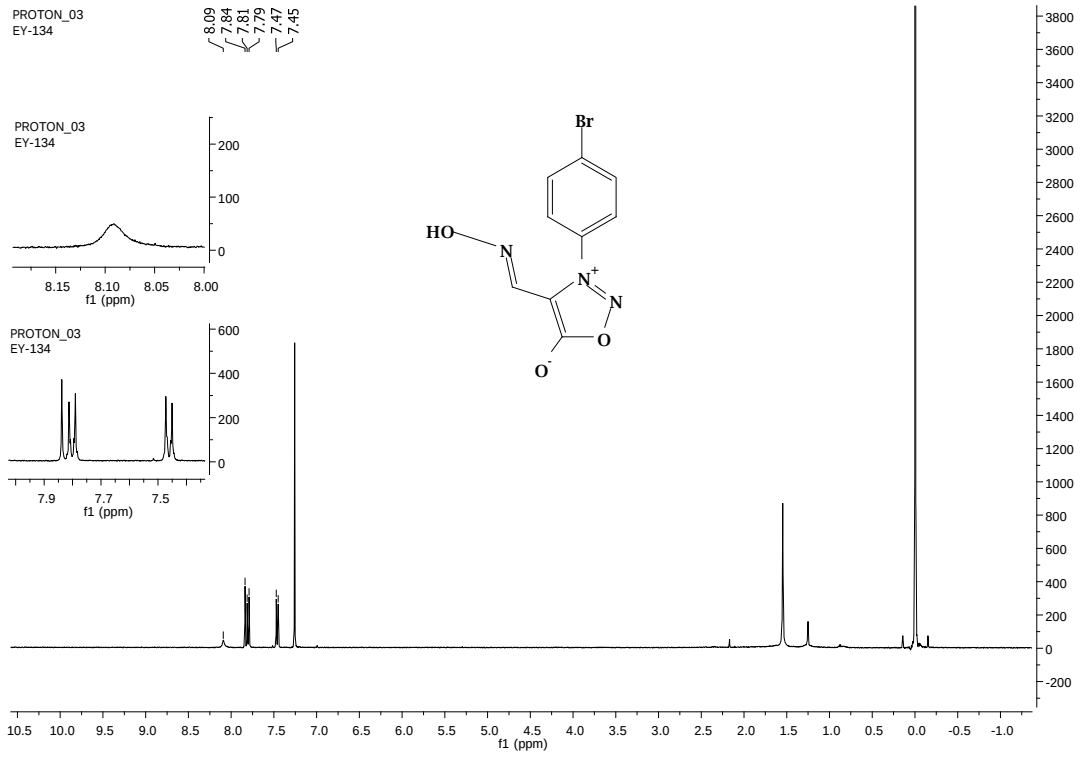


Figure 4.24. The ^{1}H NMR spectrum of **132c.**

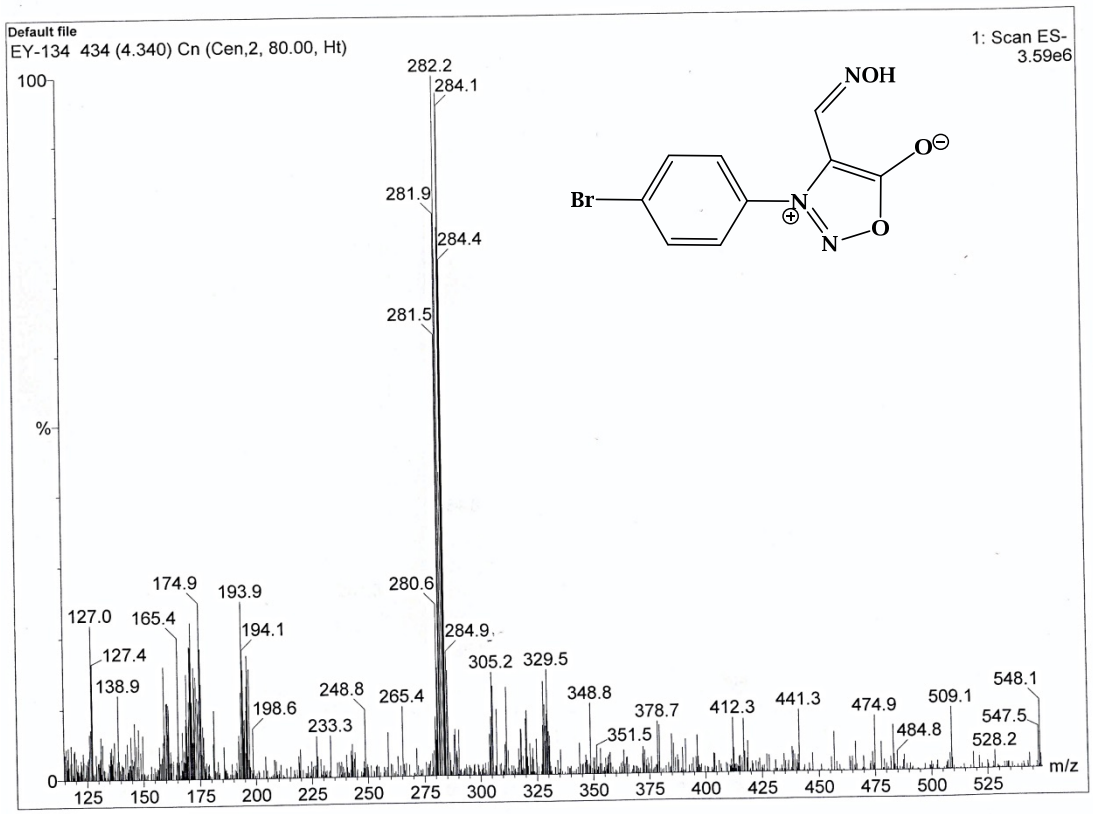


Figure 4.25. The LC-MS spectrum of **132c.**

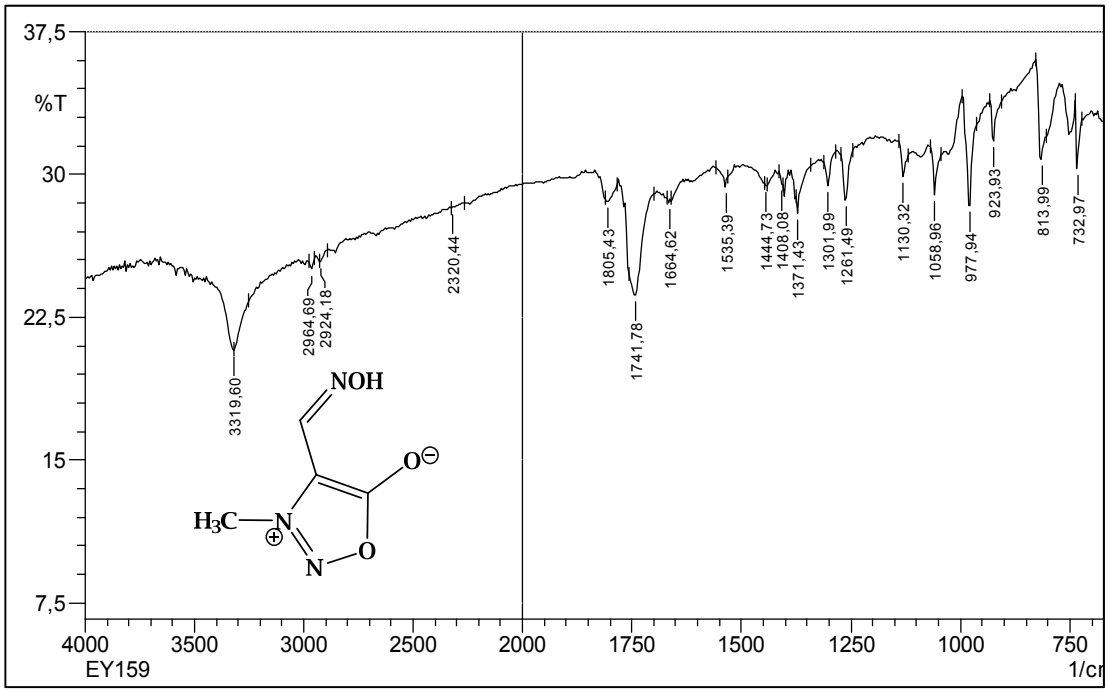


Figure 4.26. The IR spectrum of **132d.**

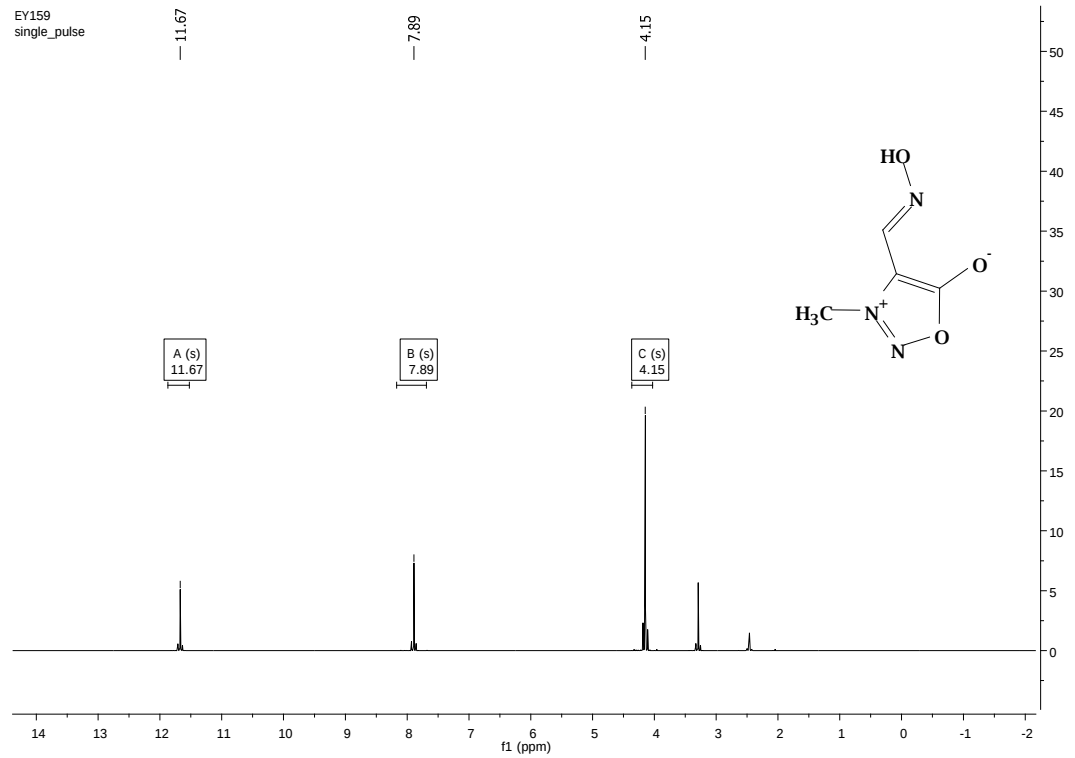


Figure 4.27. The ^{1}H NMR spectrum of **132d.**

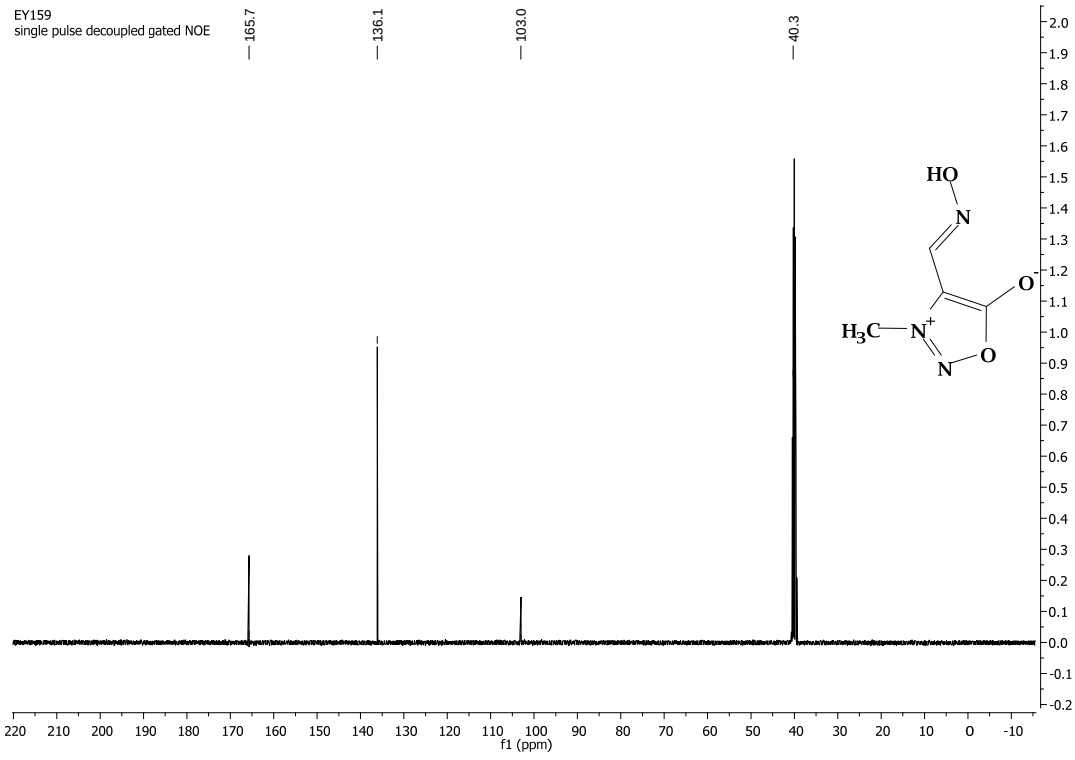


Figure 4.28. The ^{13}C NMR spectrum of **132d.**

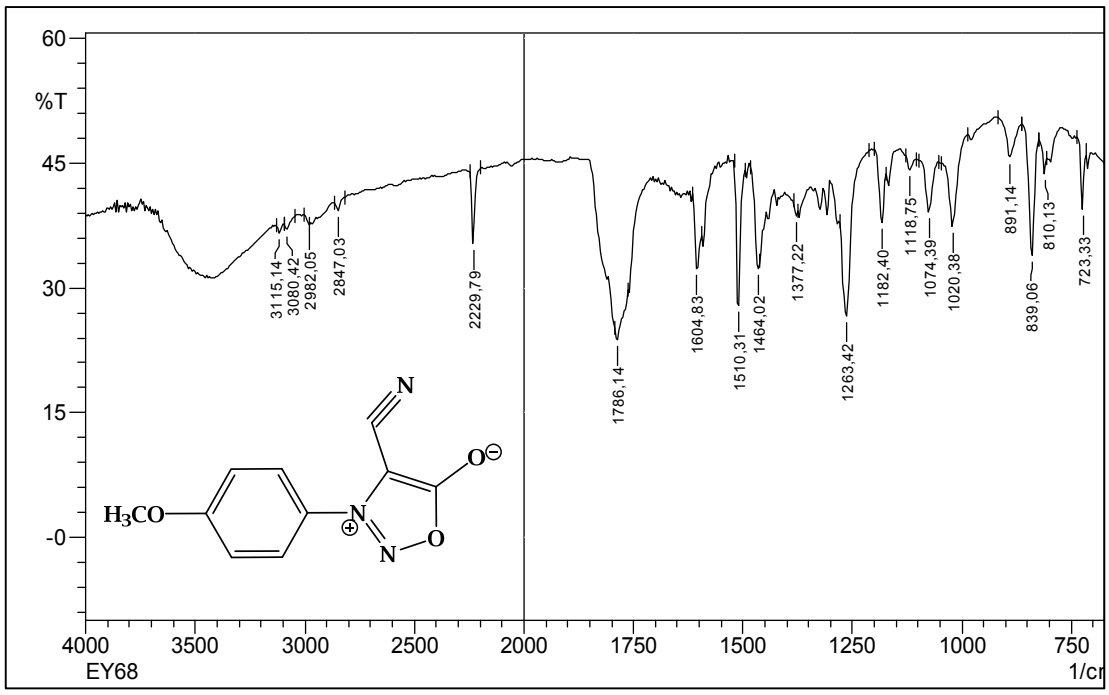


Figure 4.29. The IR spectrum of **133a.**

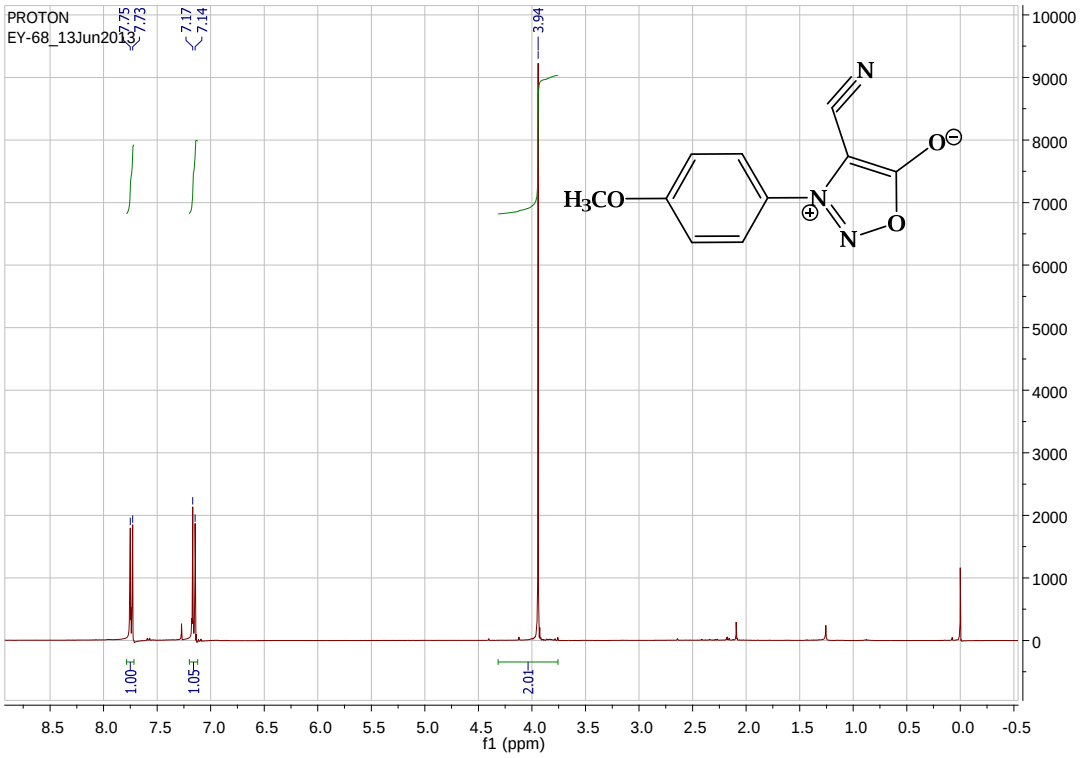


Figure 4.30. The ^{1}H NMR spectrum of **133a.**

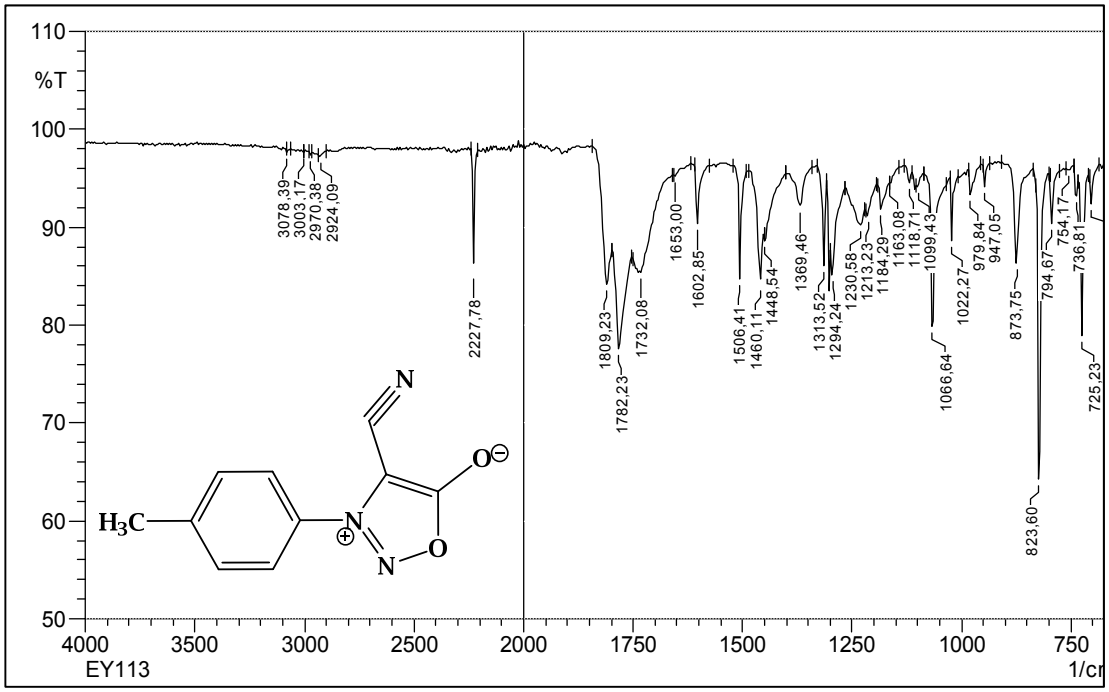


Figure 4.31. The IR spectrum of **133b.**

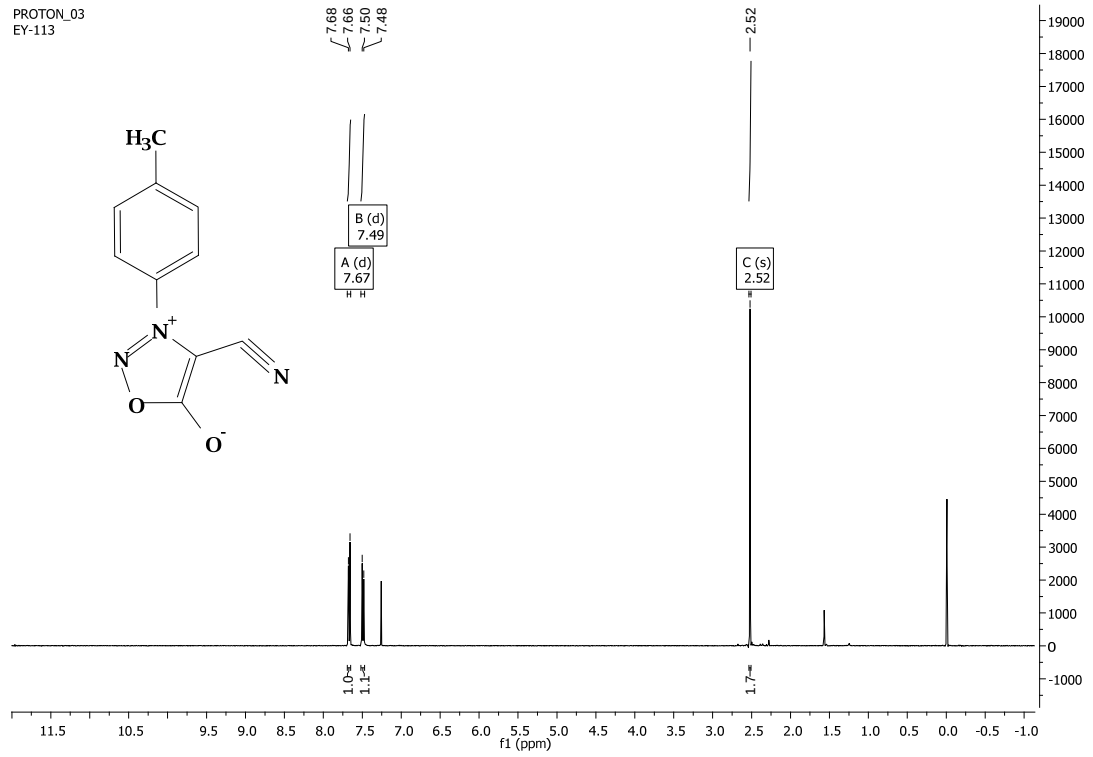


Figure 4.32. The ^{1}H NMR spectrum of **133b.**

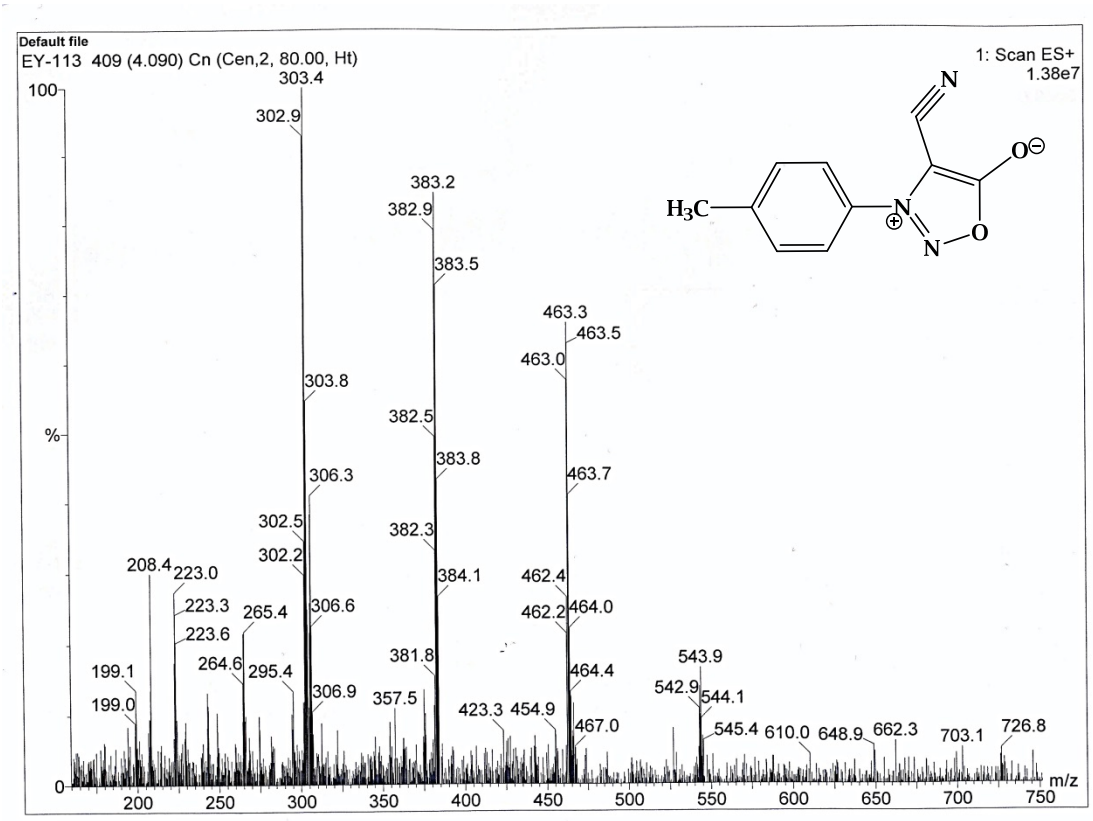


Figure 4.33. The LC-MS spectrum of **133b.**

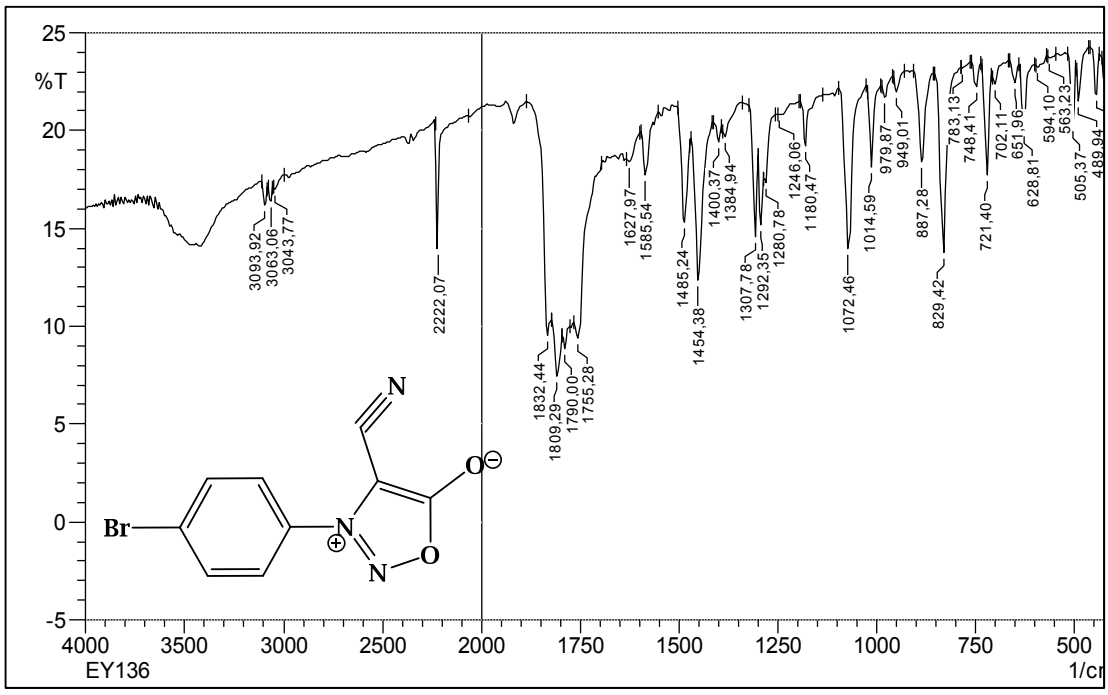


Figure 4.34. The IR spectrum of **133c.**

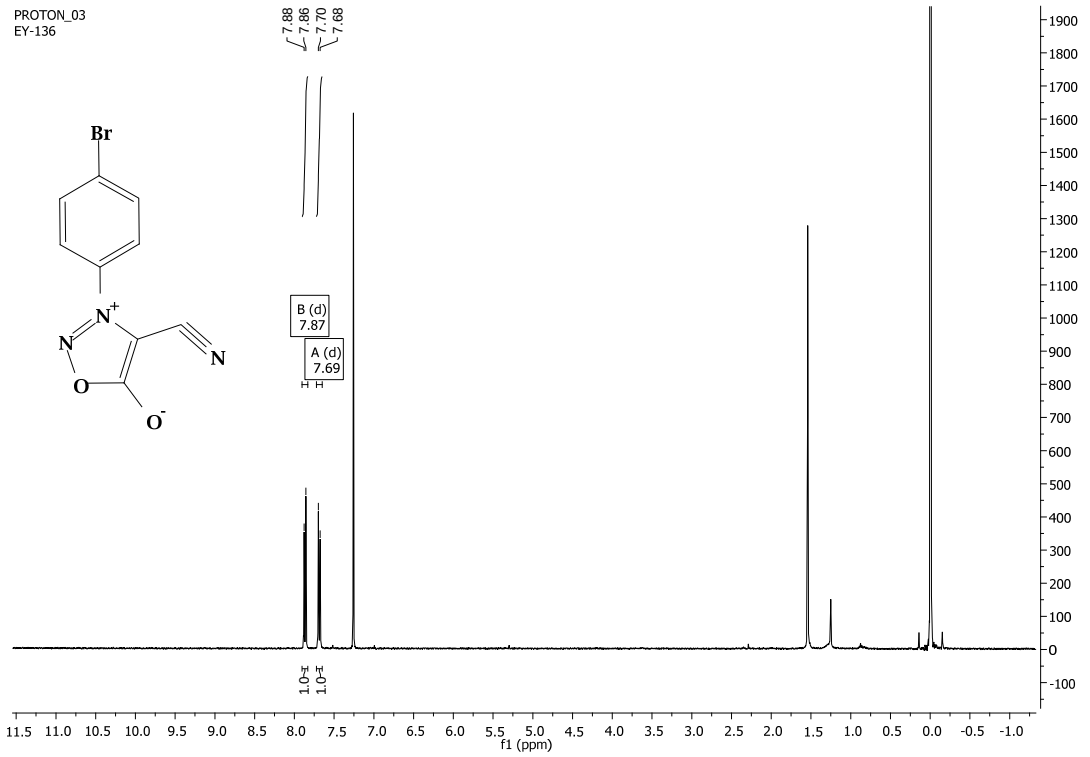


Figure 4.35. The ^{1}H NMR spectrum of **133c.**

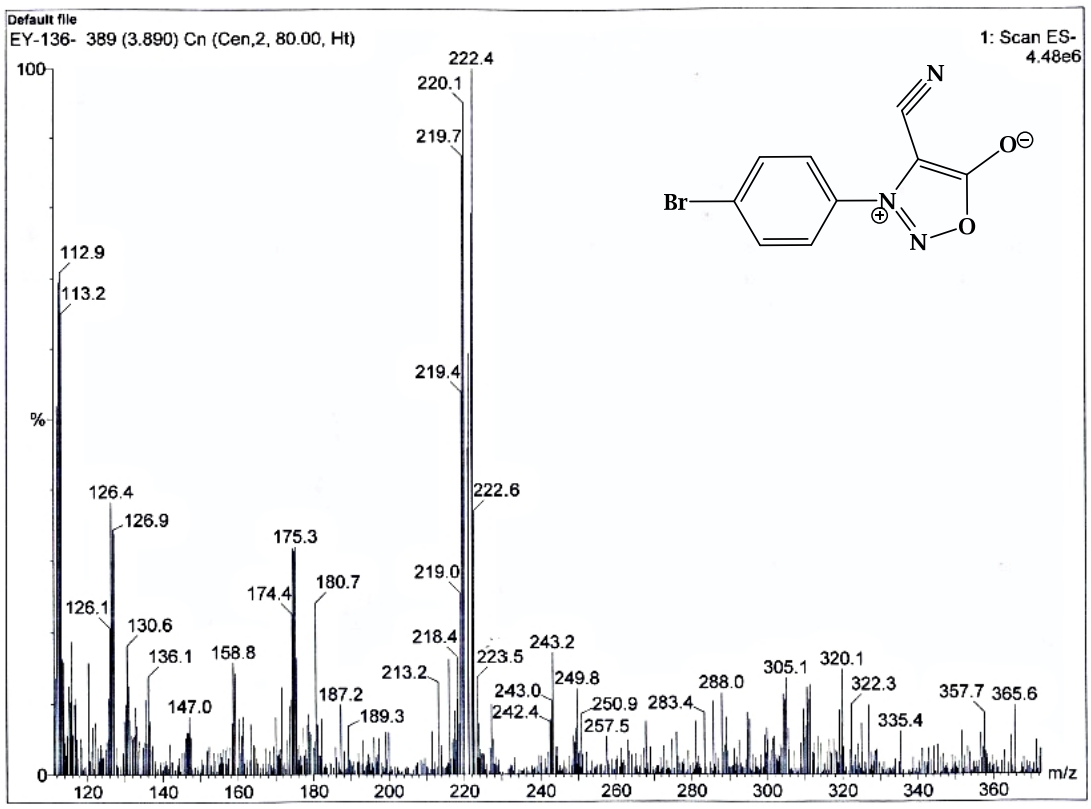


Figure 4.36. The LC-MS spectrum of **133c.**

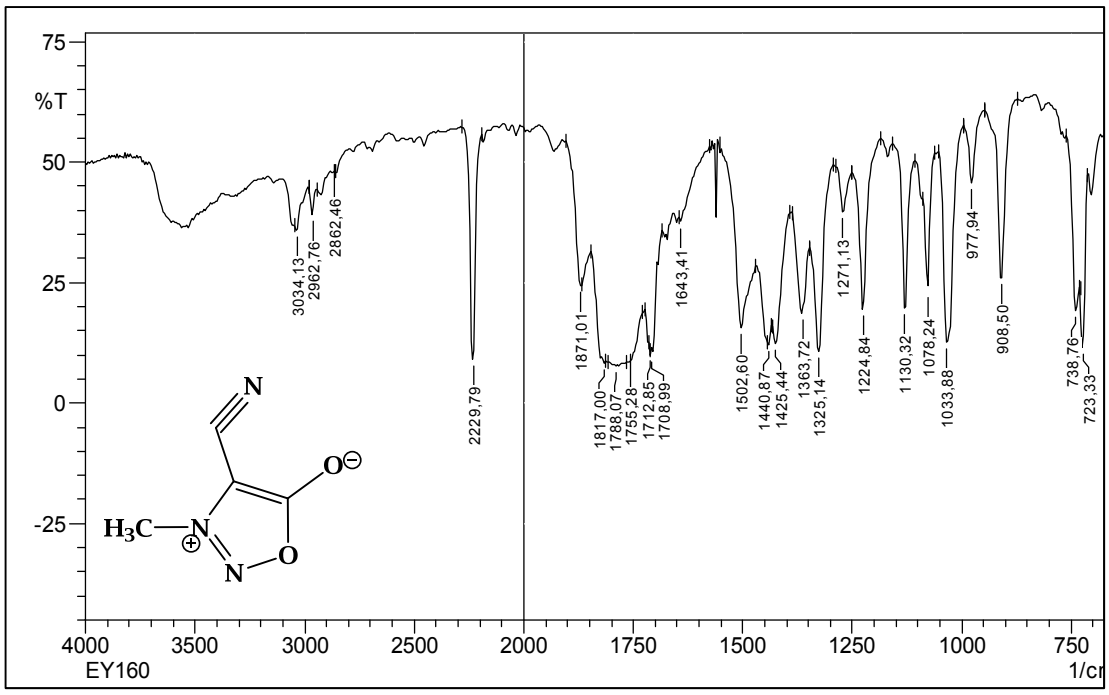


Figure 4.37. The IR spectrum of **133d.**

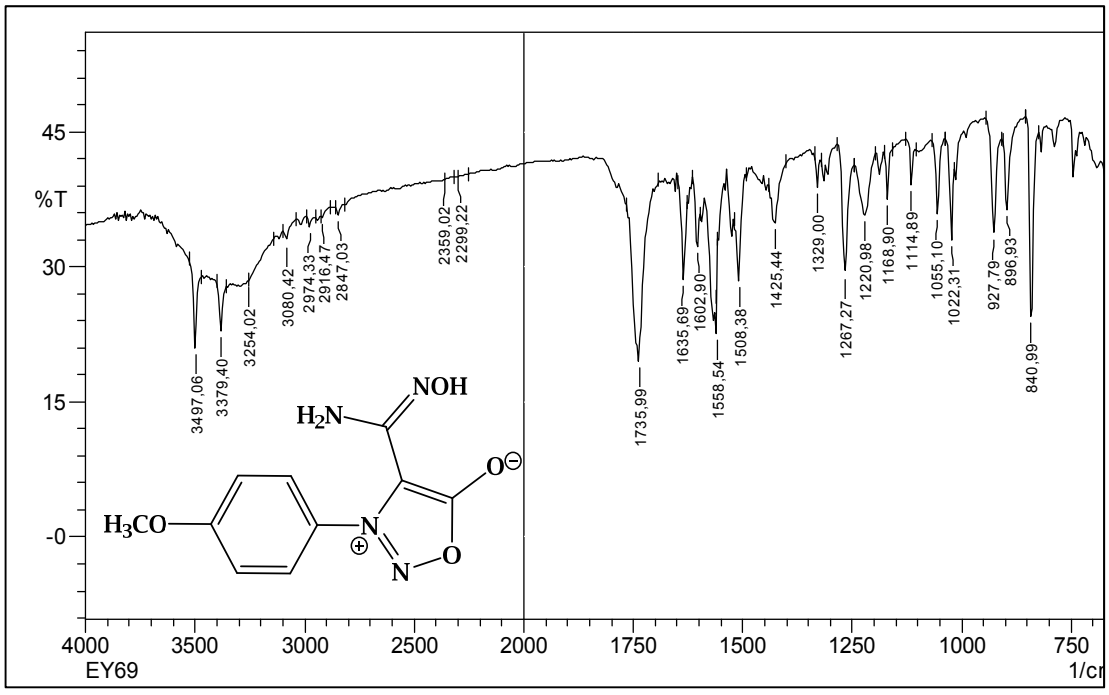


Figure 4.38. The IR spectrum of **134a.**

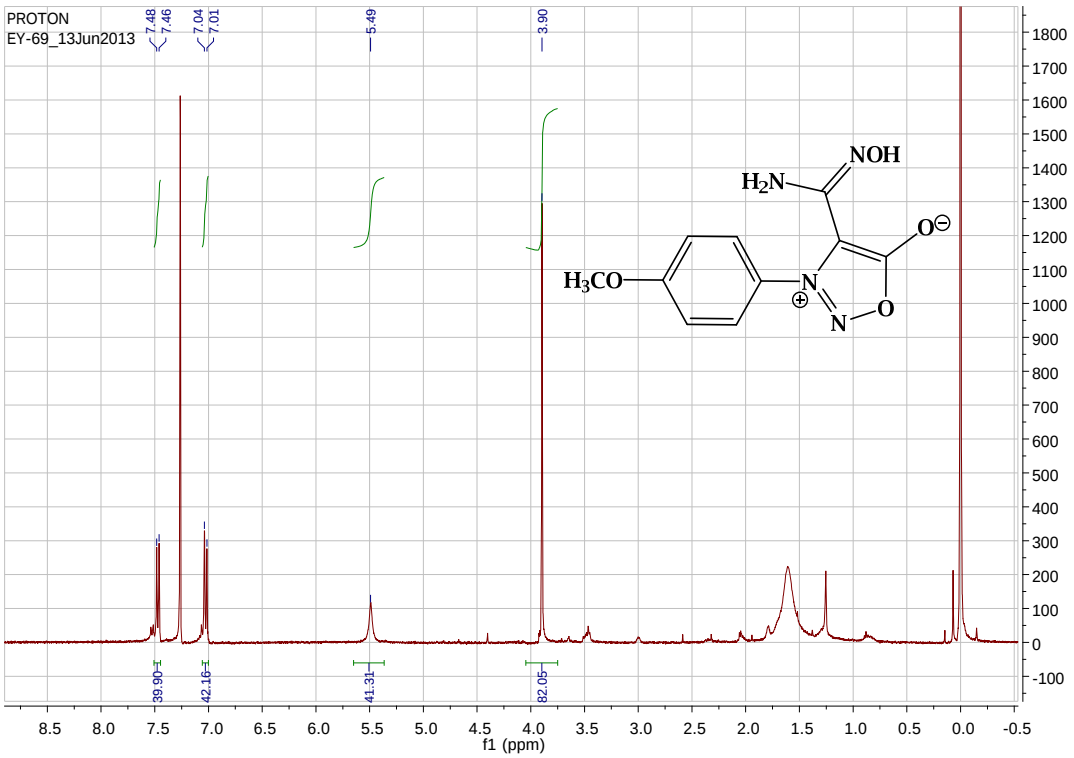


Figure 4.39. The ^{1}H NMR spectrum of **134a.**

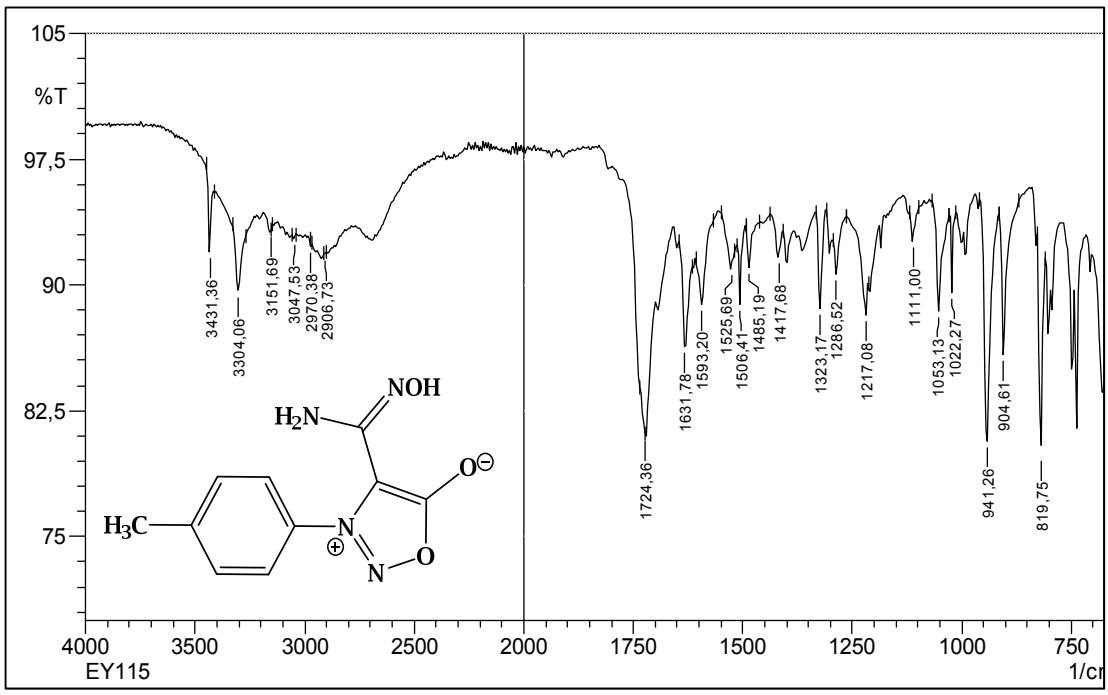


Figure 4.40. The IR spectrum of **134b.**

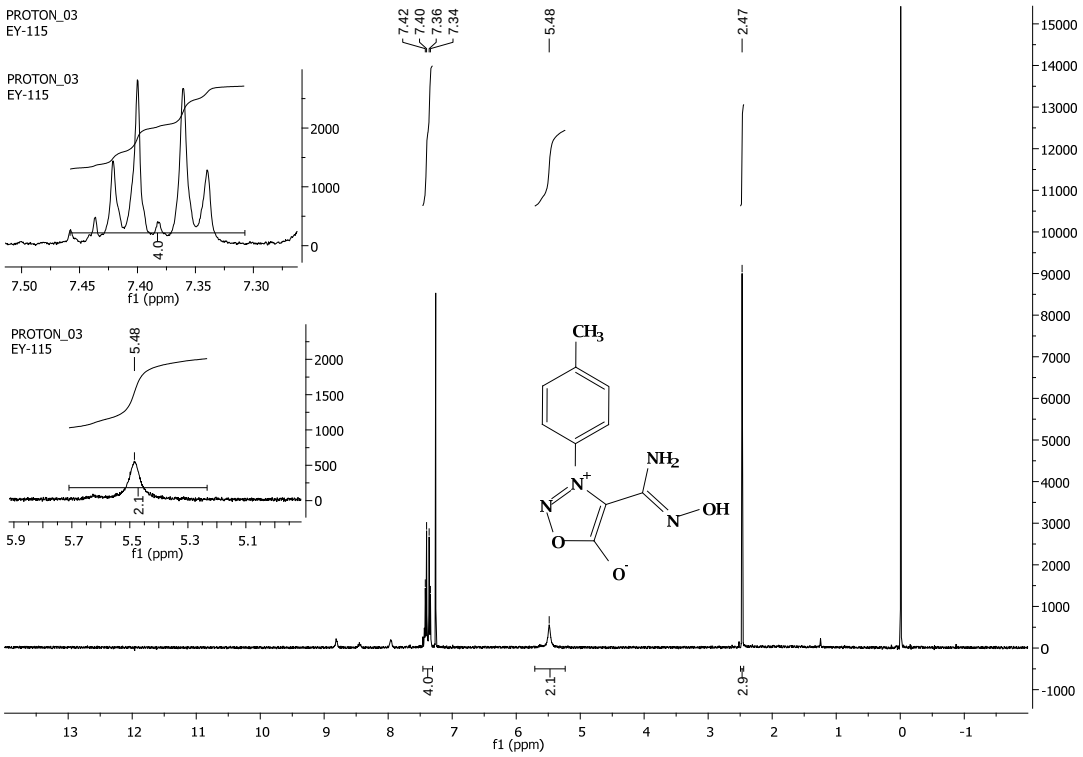


Figure 4.41. The ^{1}H NMR spectrum of **134b.**

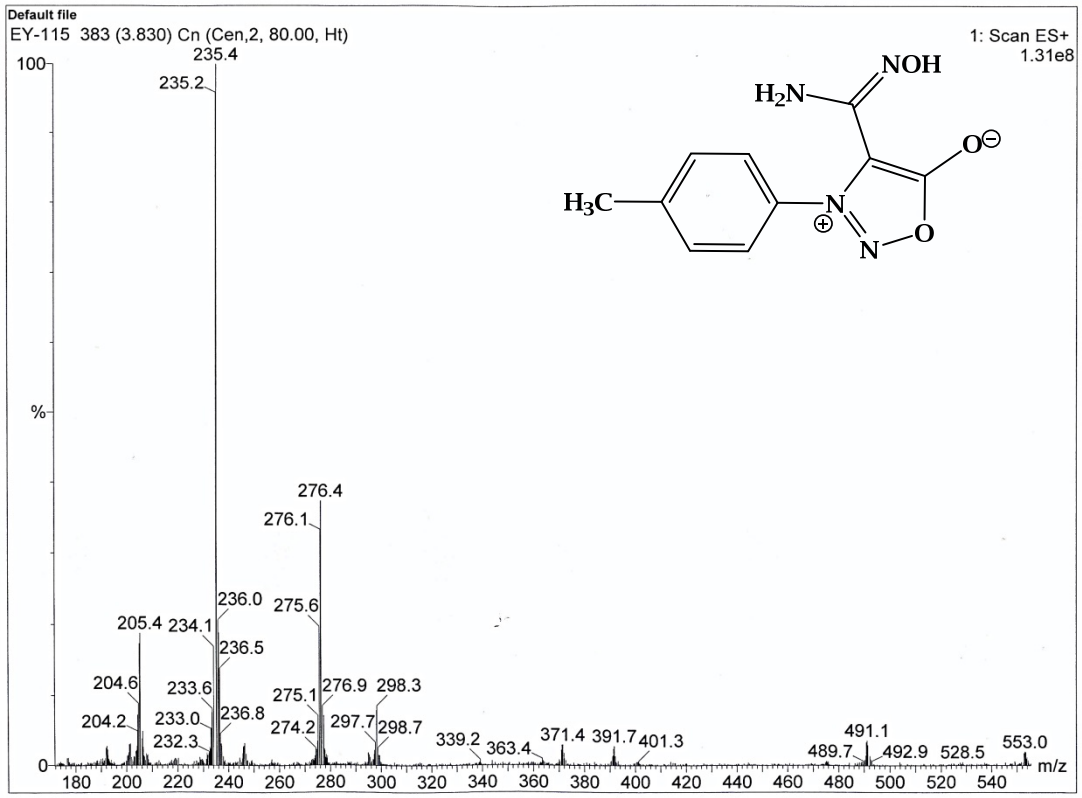


Figure 4.42. The LC-MS spectrum of **134b.**

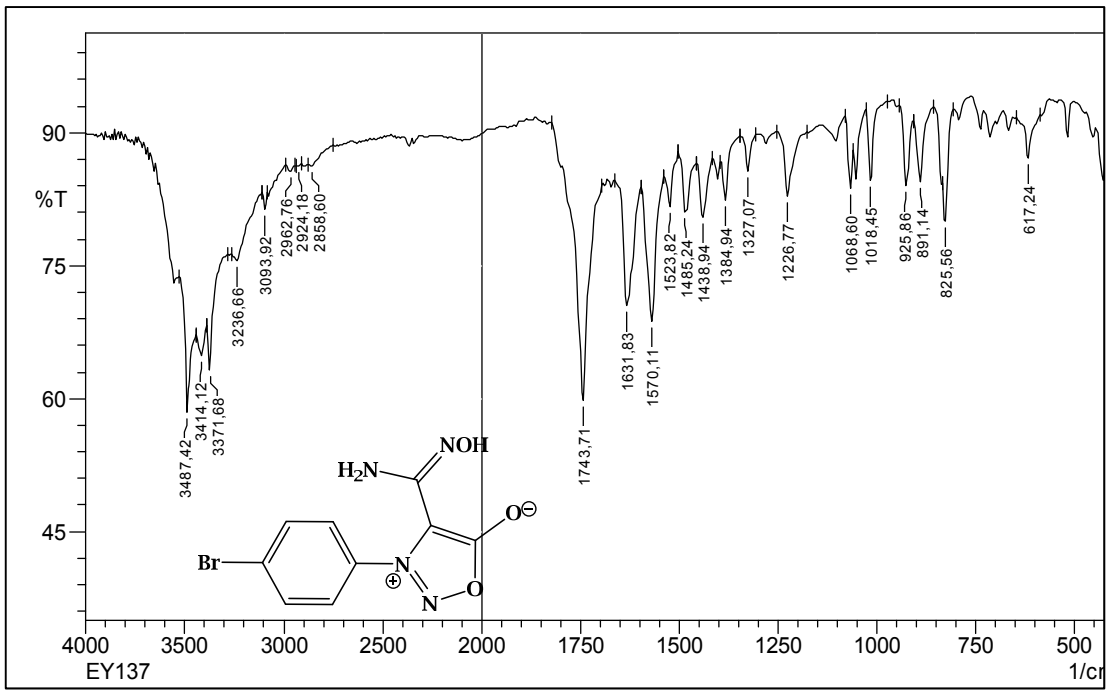


Figure 4.43. The IR spectrum of **134c.**

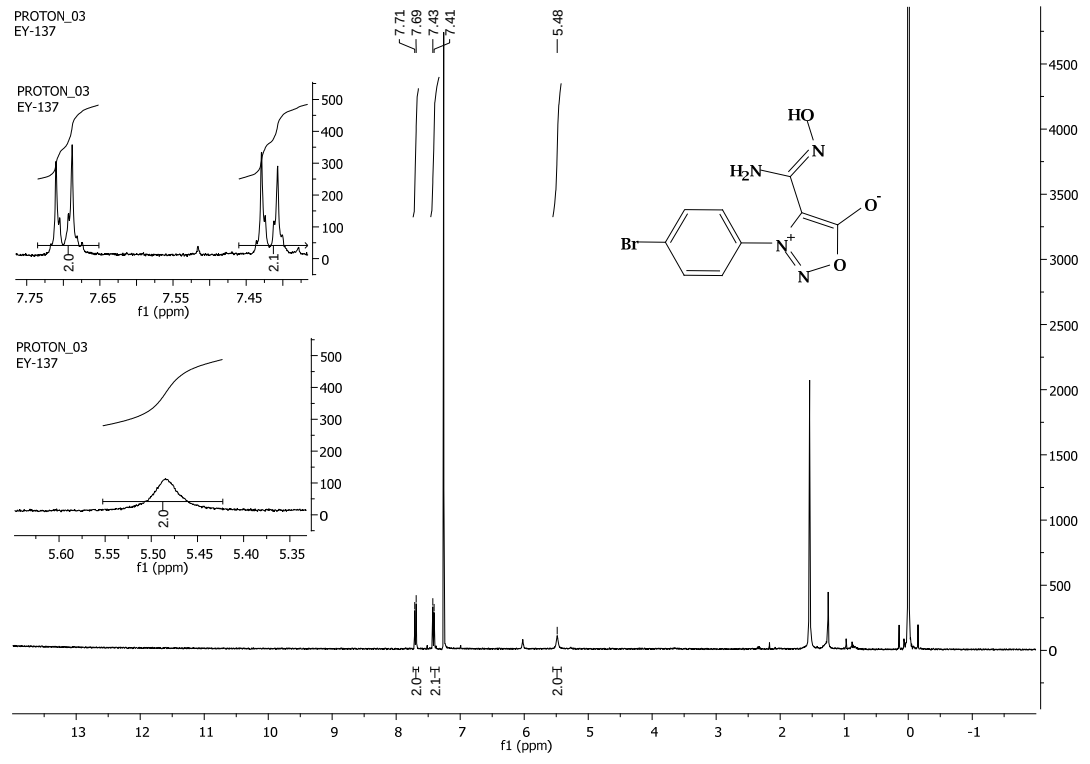


Figure 4.44. The ^{1}H NMR spectrum of **134c.**

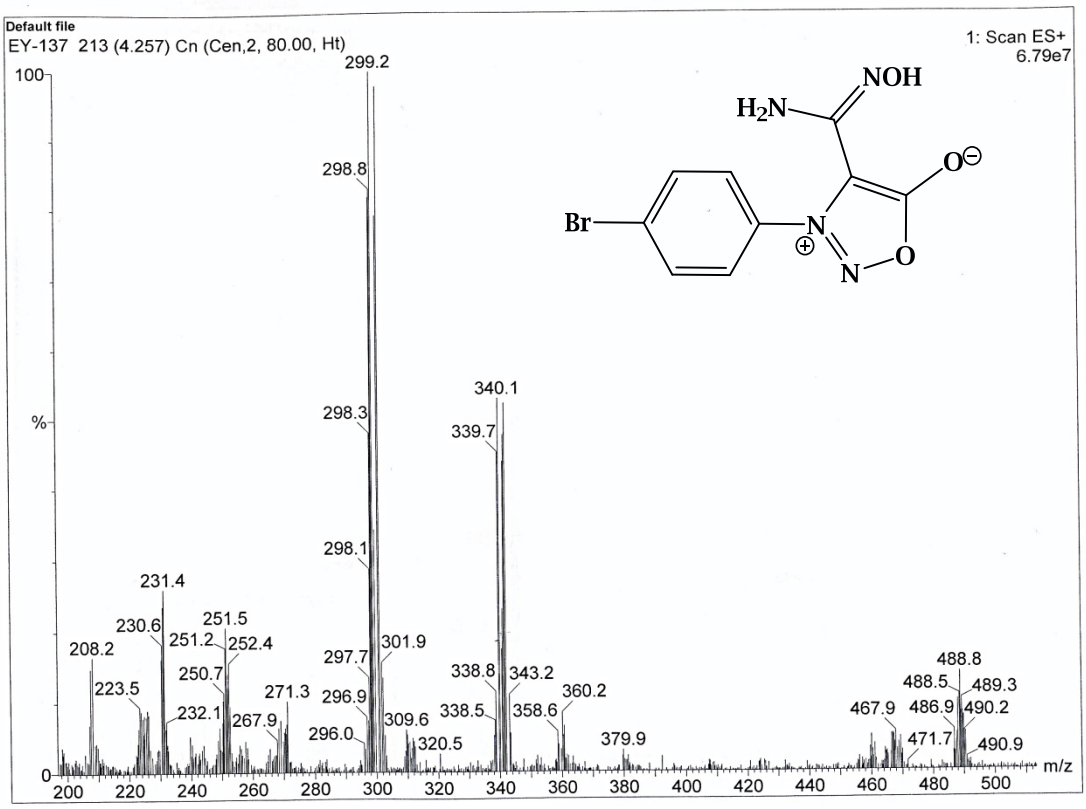


Figure 4.45. The LC-MS spectrum of **134c.**

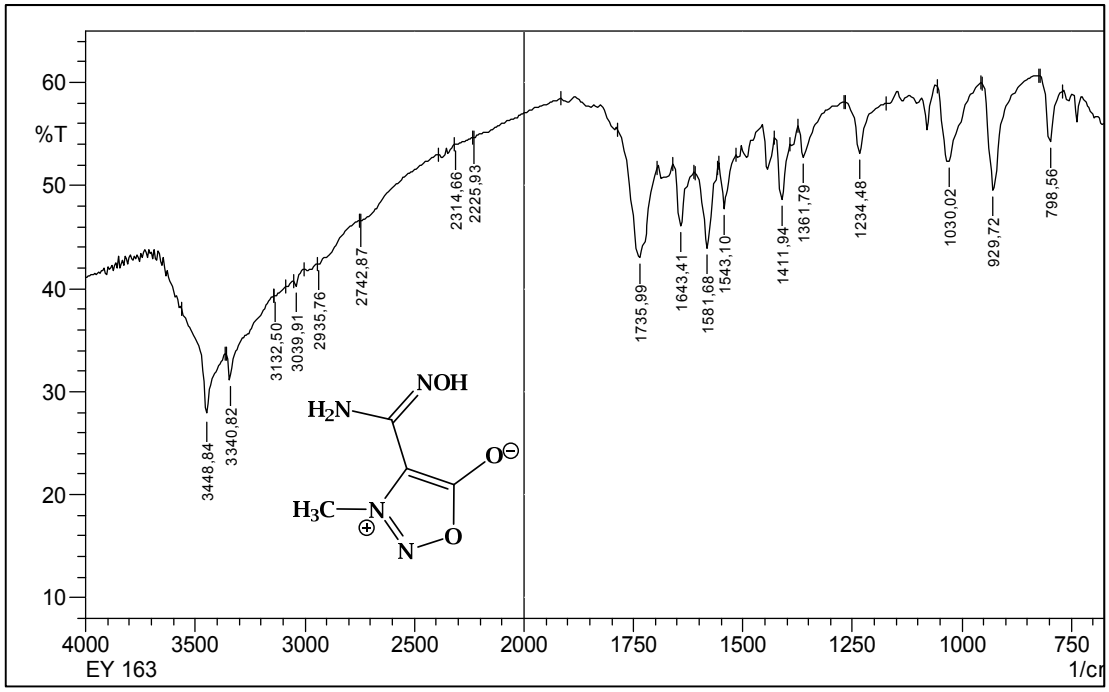


Figure 4.46. The IR spectrum of **134d.**

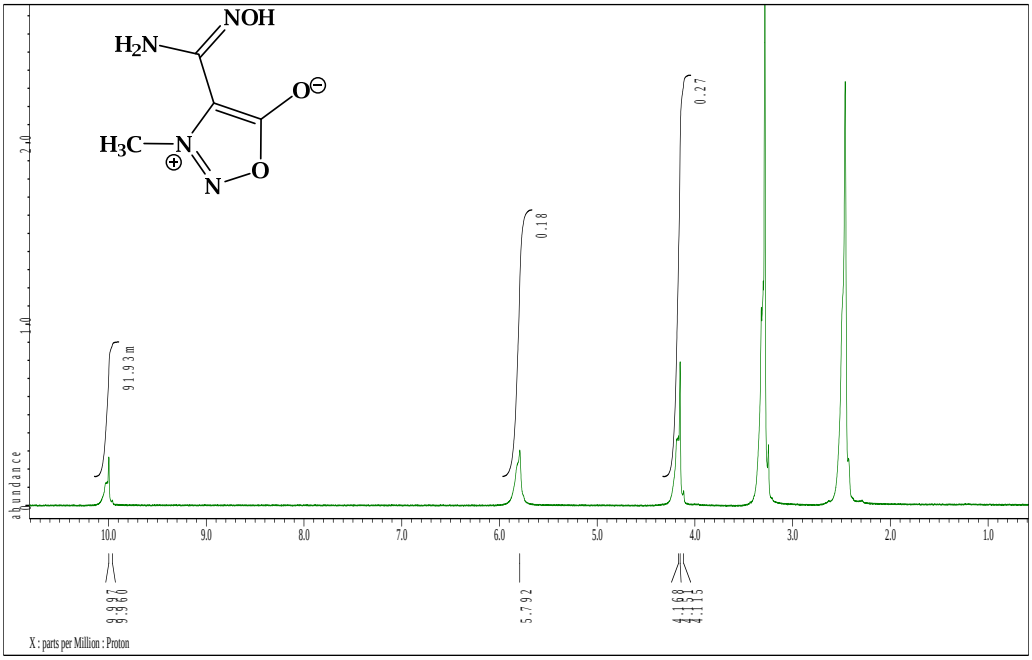


Figure 4.47. The ^{1}H NMR spectrum of **134d.**

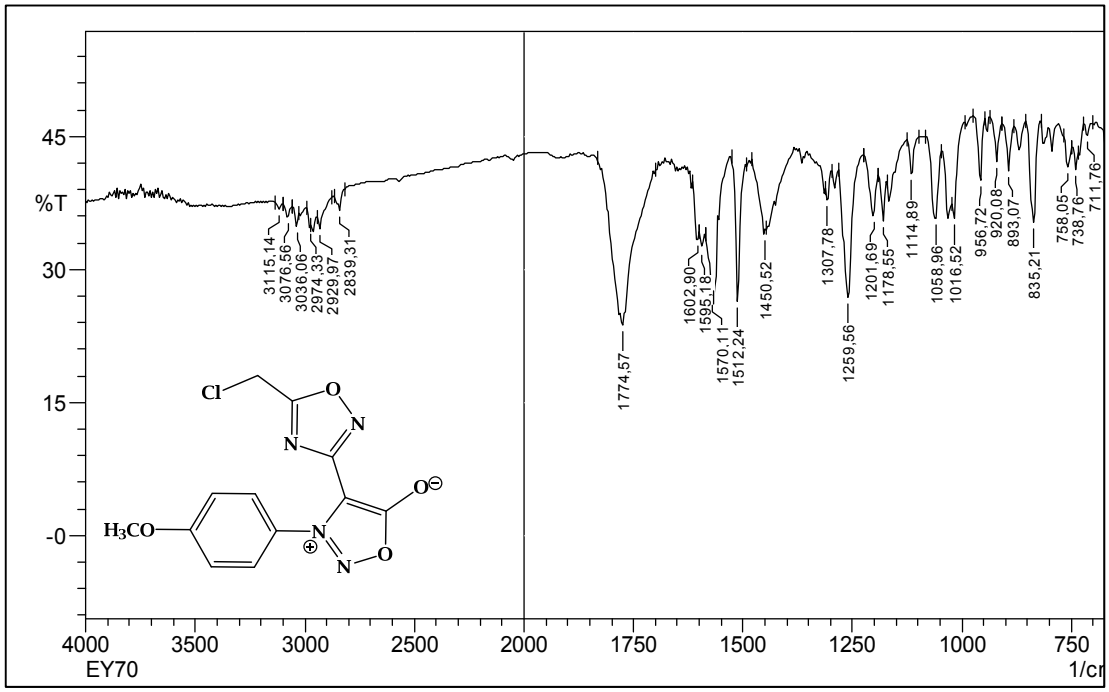


Figure 4.48. The IR spectrum of **135a.**

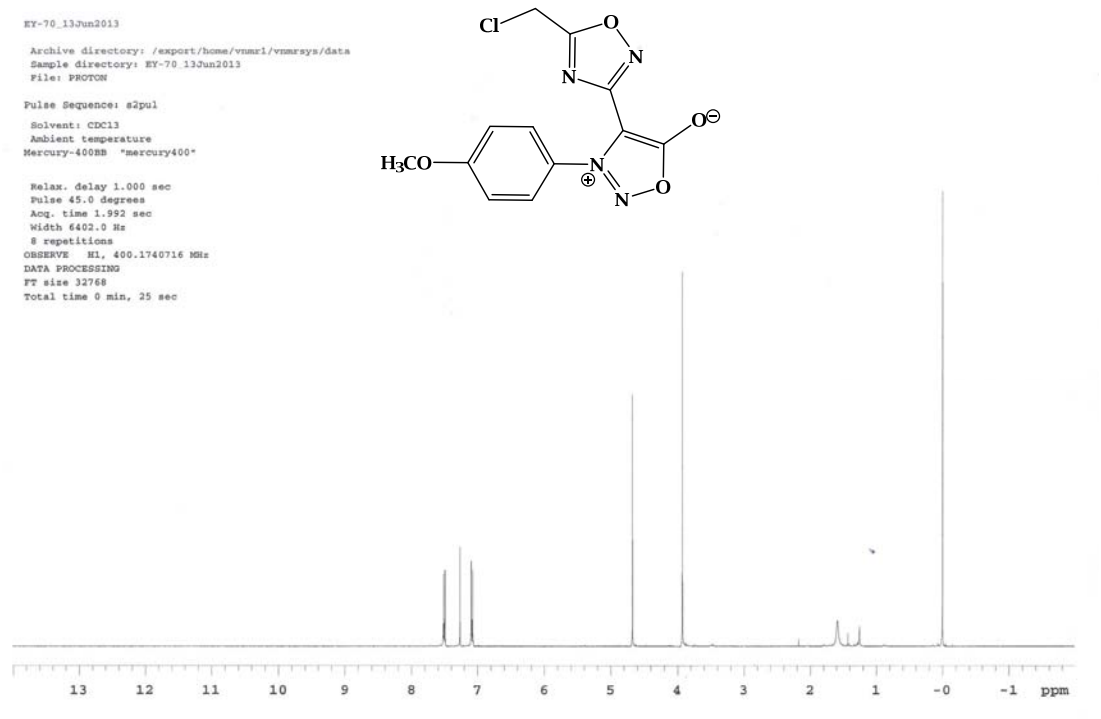


Figure 4.49. The ^{1}H NMR spectrum of **135a.**

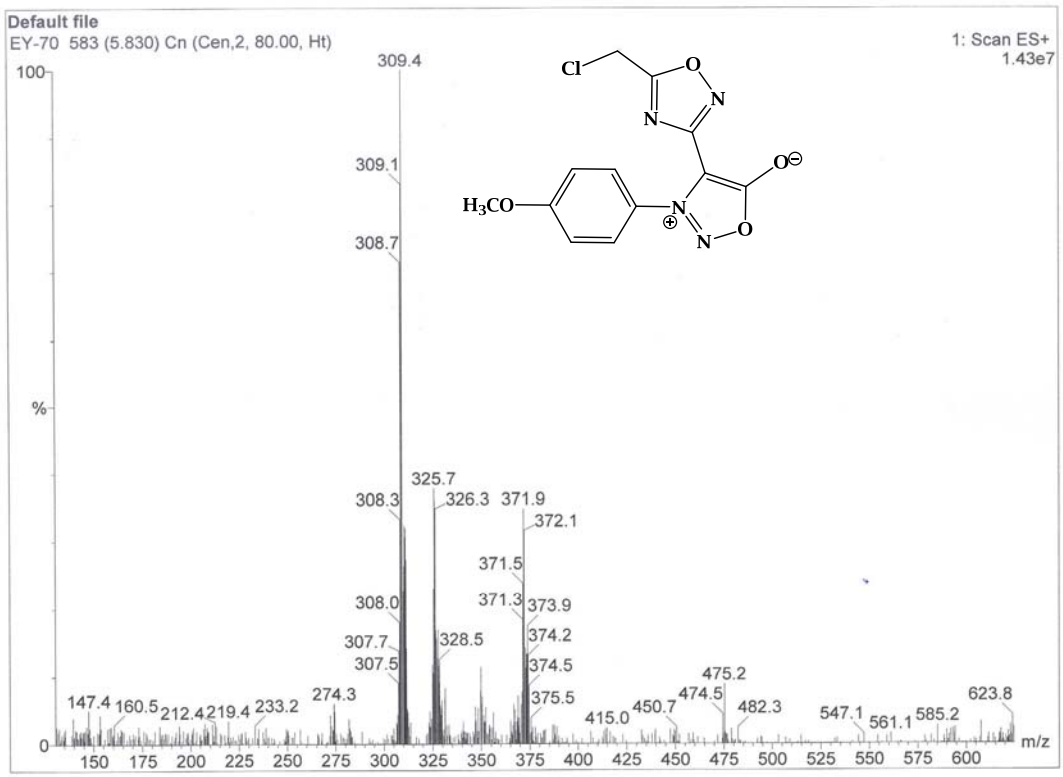


Figure 4.50. The LC-MS spectrum of **135a.**

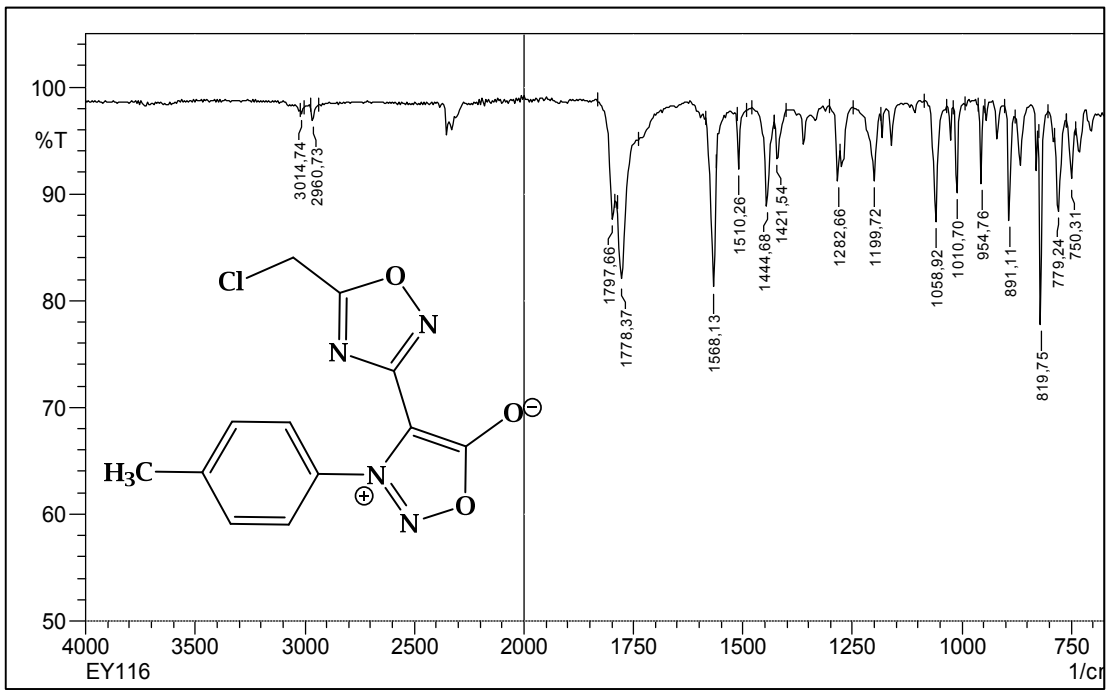


Figure 4.51. The IR spectrum of **135b.**

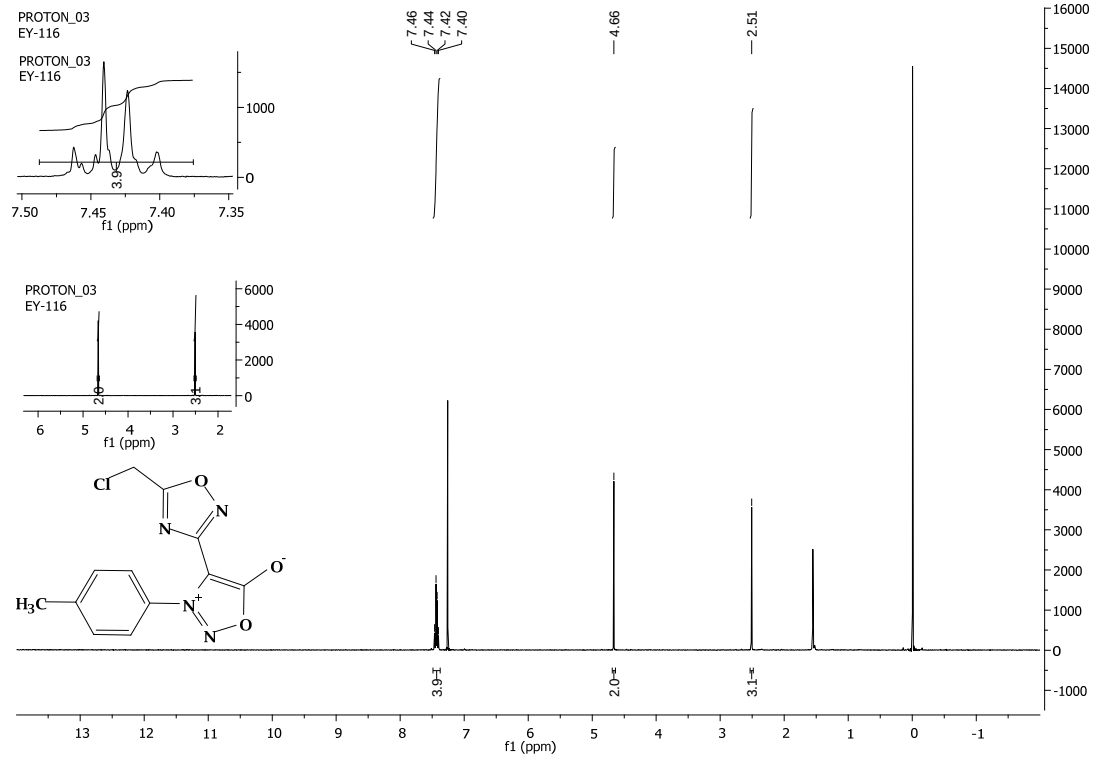


Figure 4.52. The ^{1}H NMR spectrum of **135b.**

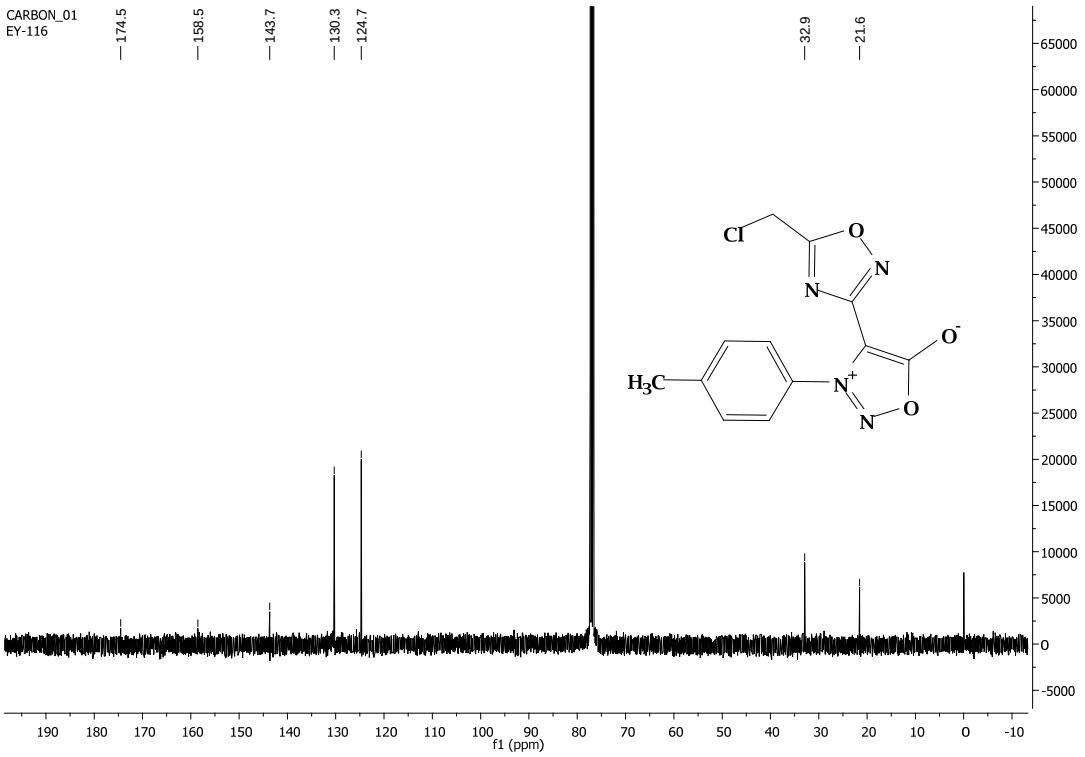


Figure 4.53. The ^{13}C NMR spectrum of **135b.**

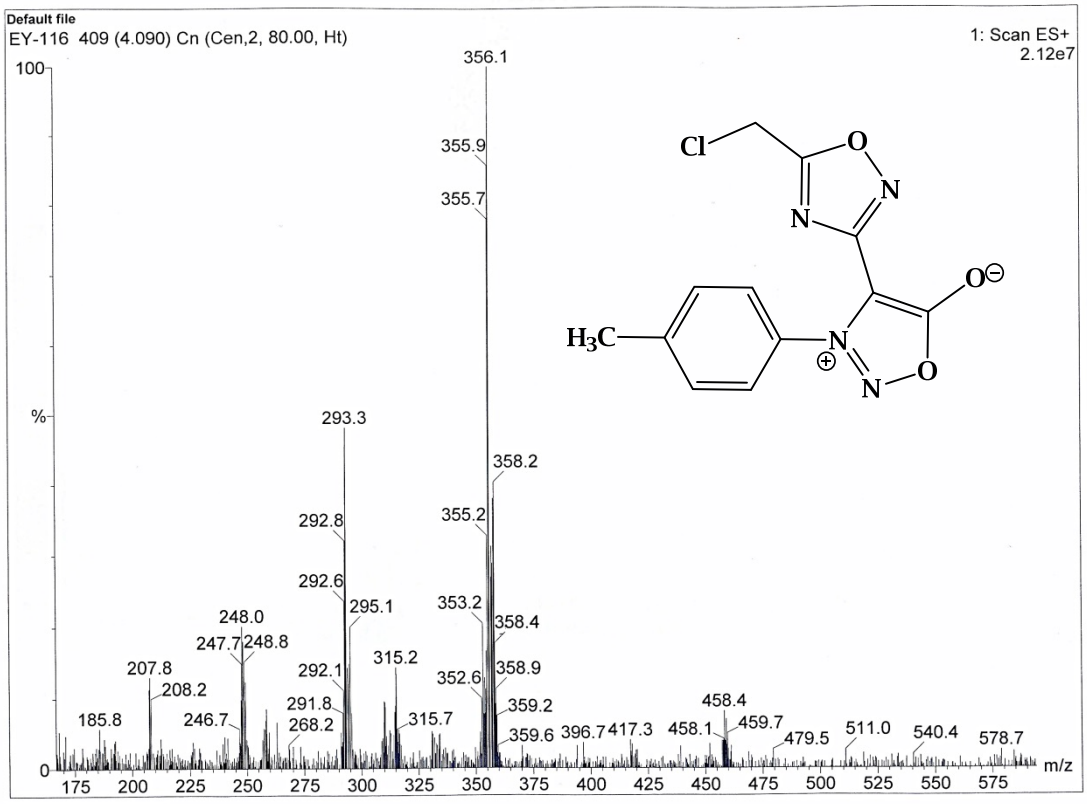


Figure 4.54. The LC-MS spectrum of **135b.**

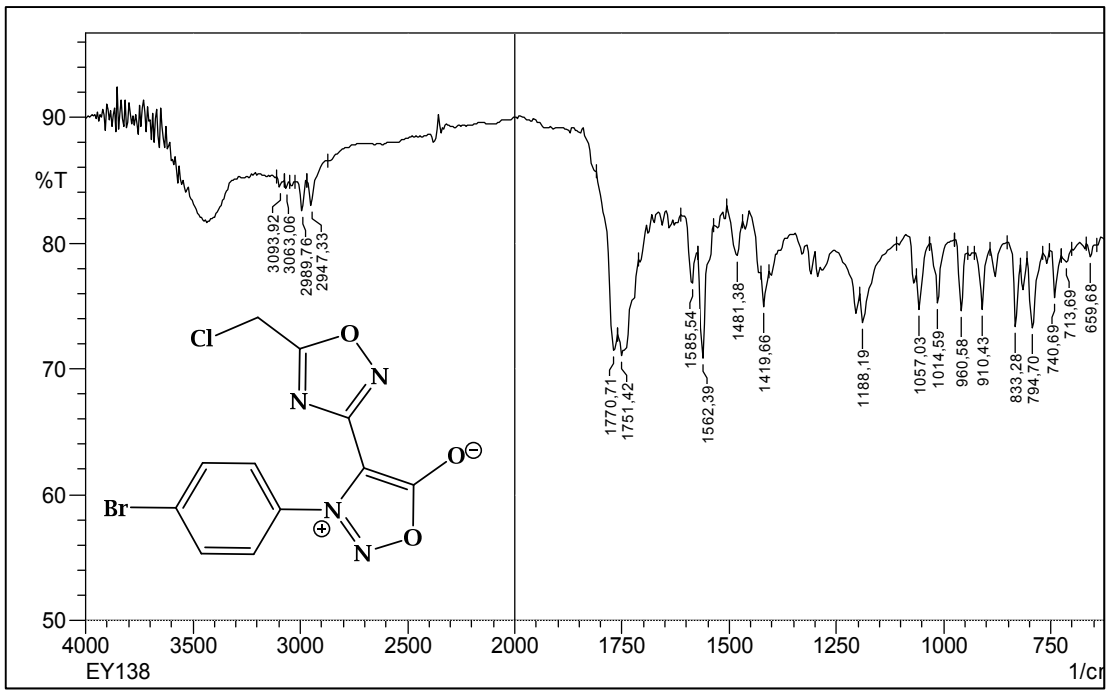


Figure 4.55. The IR spectrum of **135c.**

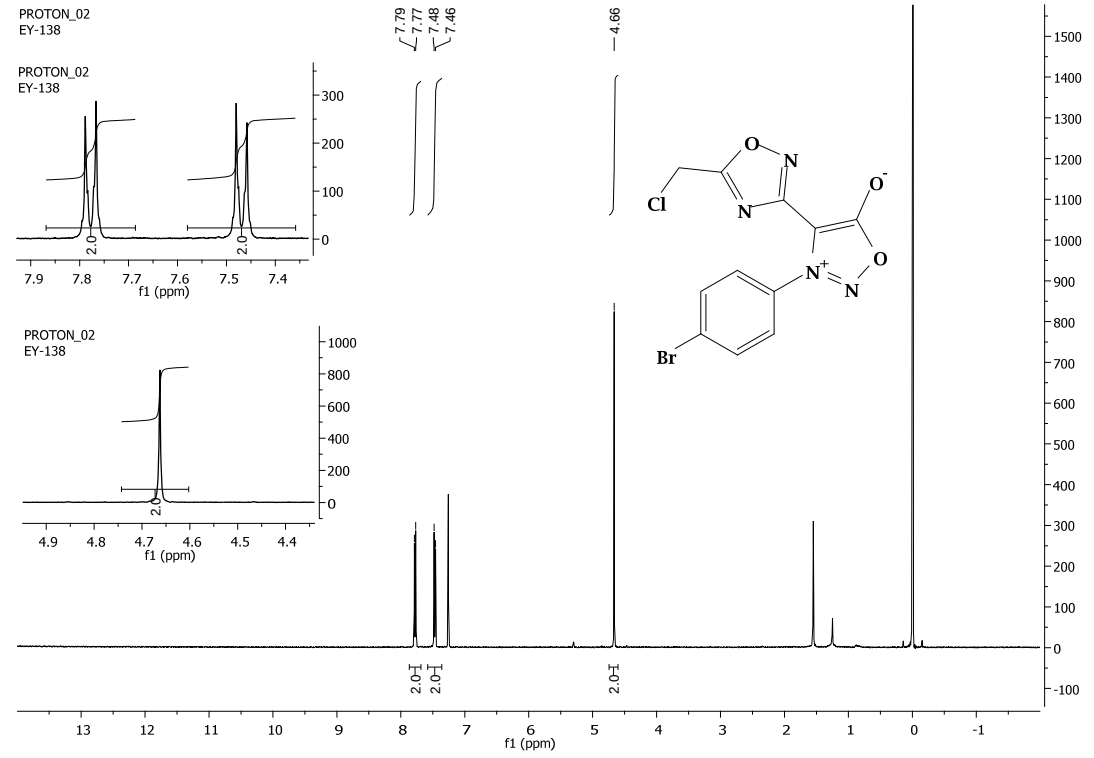


Figure 4.56. The ^{1}H NMR spectrum of **135c.**

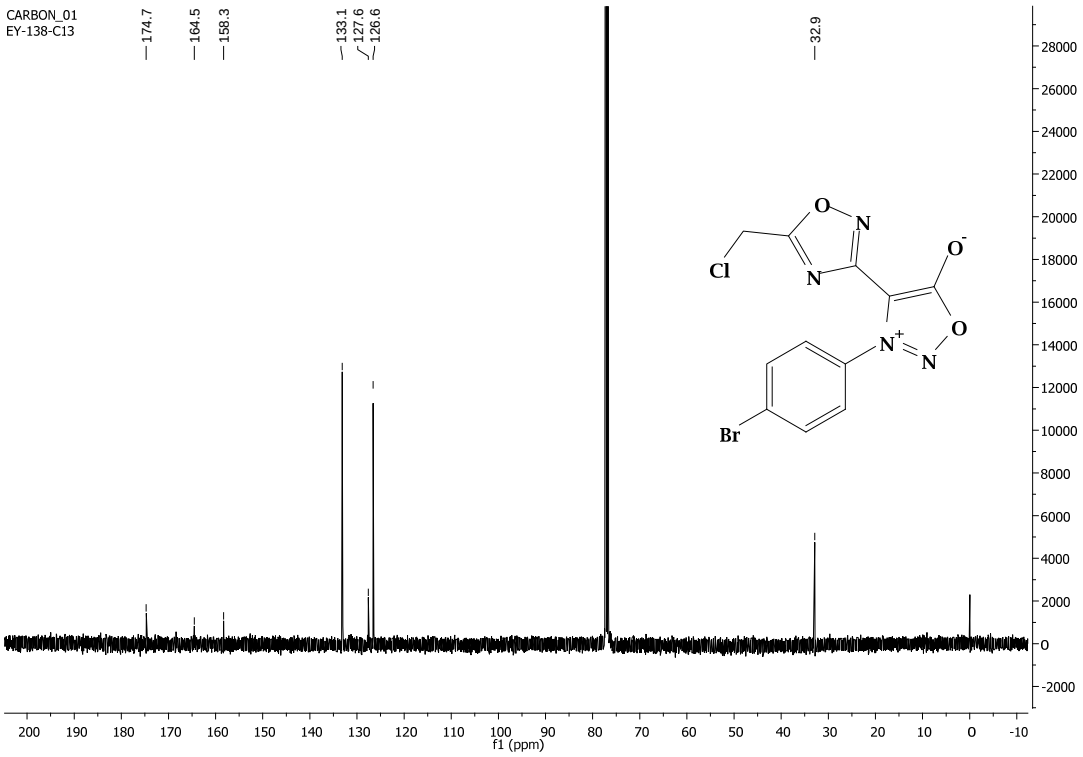


Figure 4.57. The ^{13}C NMR spectrum of **135c.**

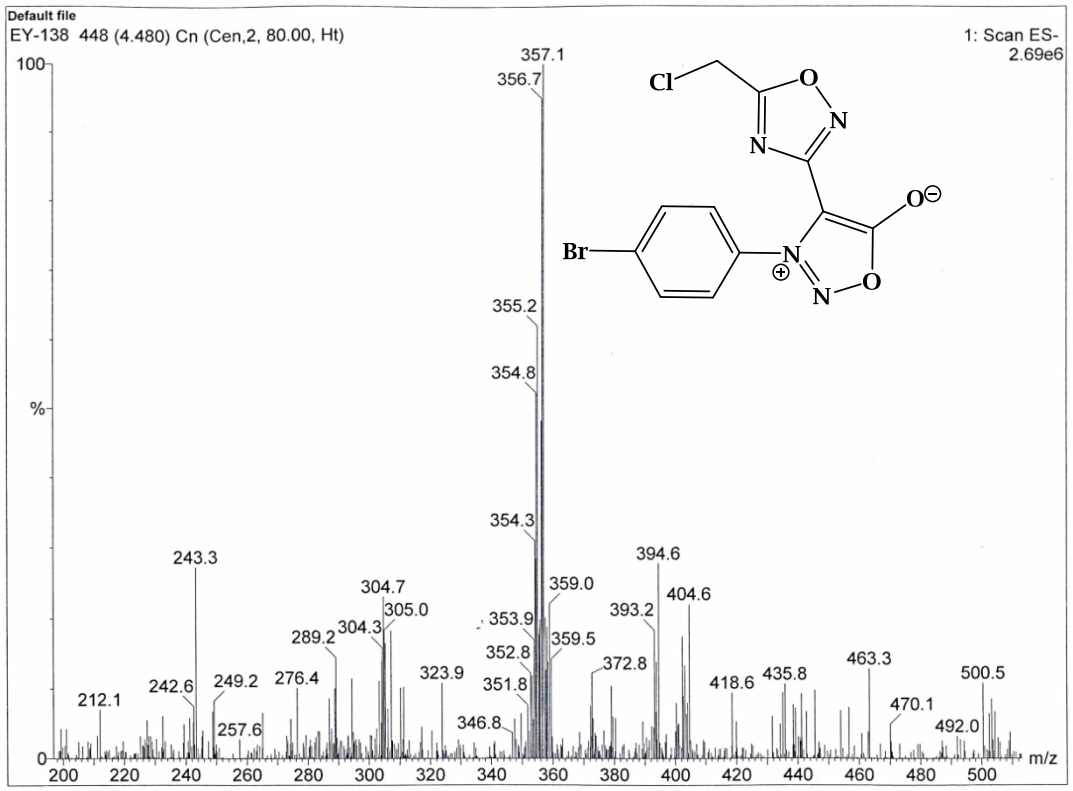


Figure 4.58. The LC-MS spectrum of **135c.**

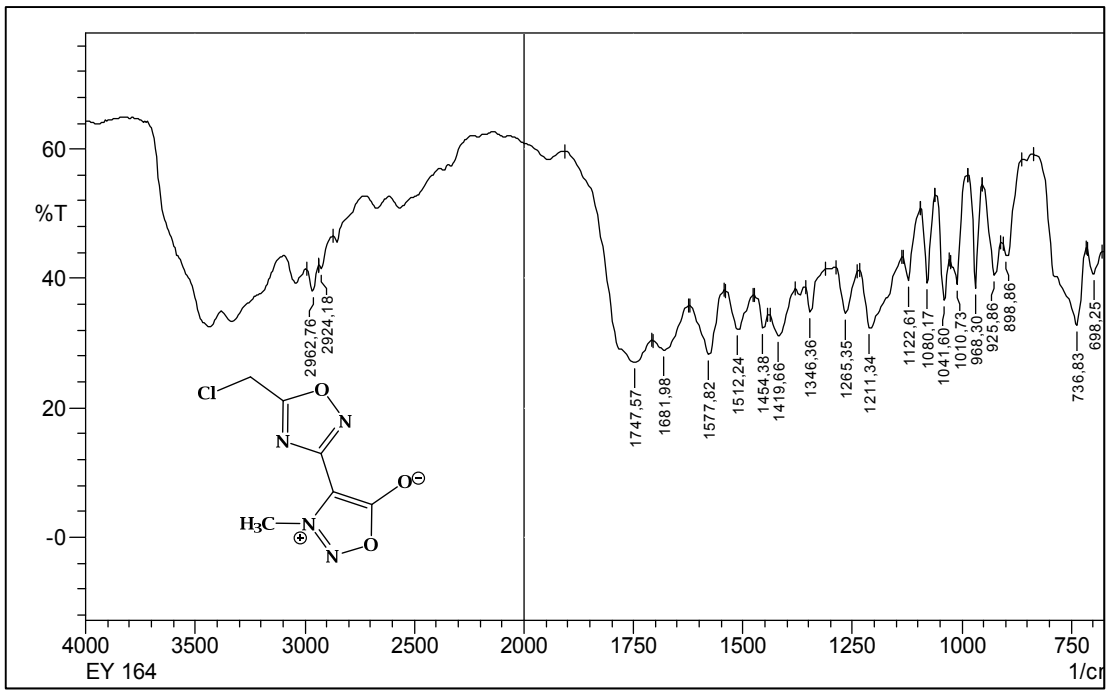


Figure 4.59. The IR spectrum of **135d.**

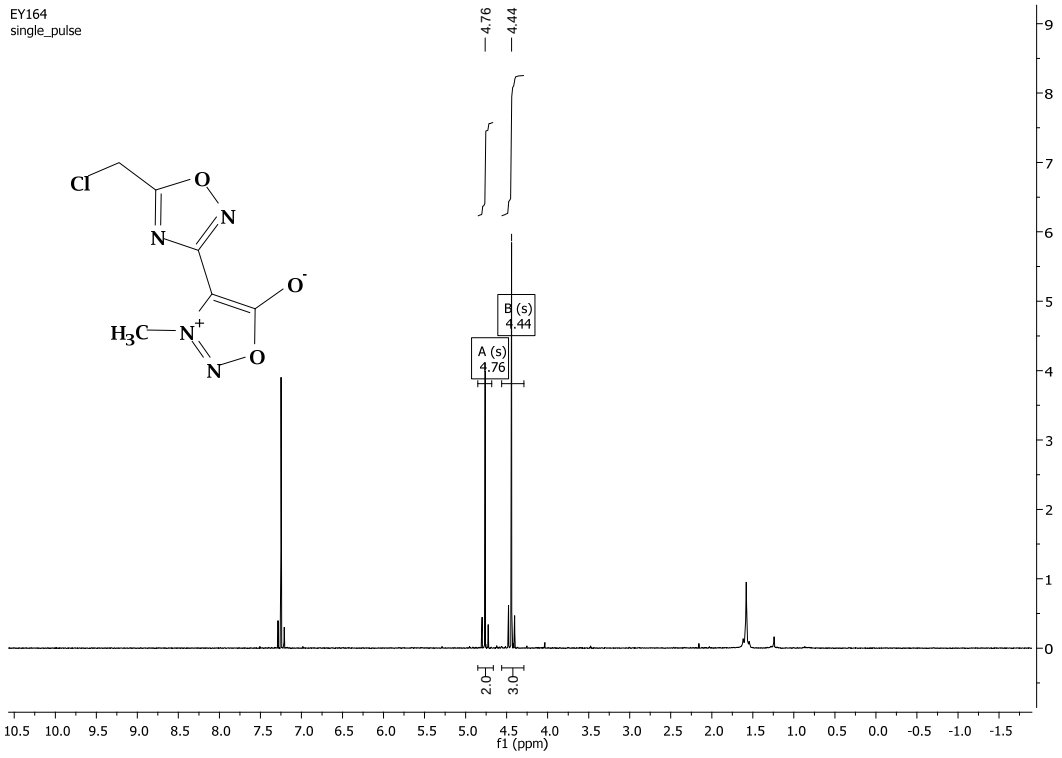


Figure 4.60. The ^{1}H NMR spectrum of **135d.**

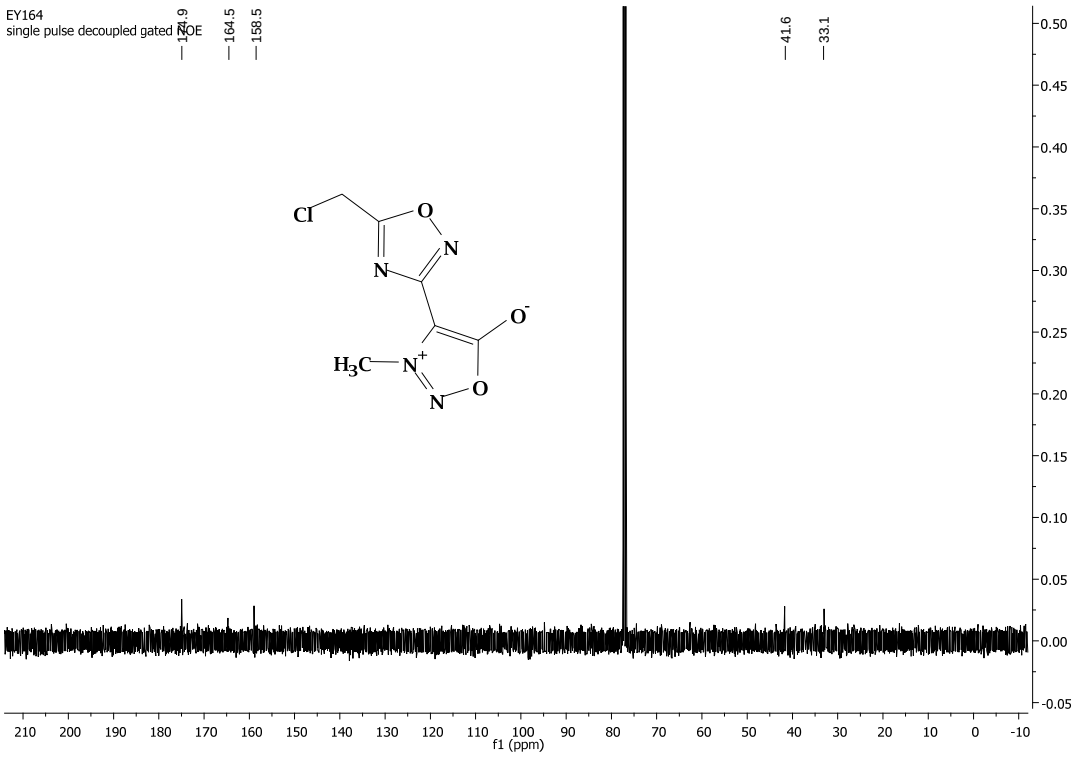


Figure 4.61. The ^{13}C NMR spectrum of **135d.**

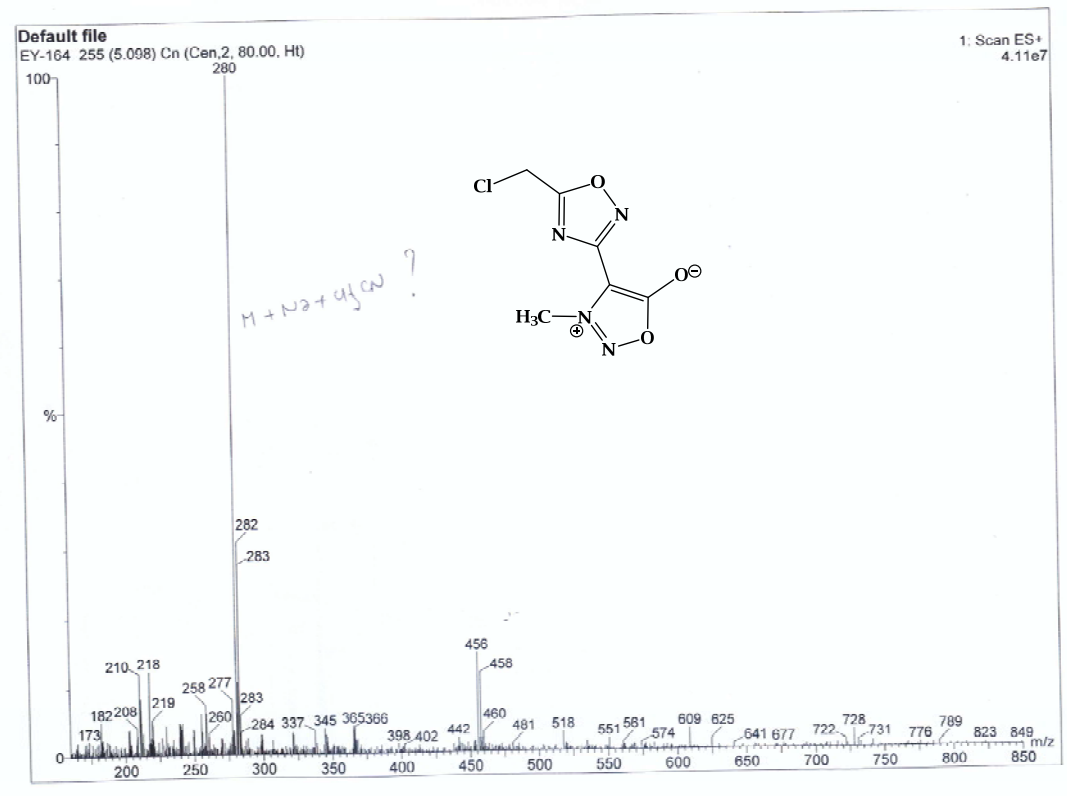


Figure 4.62. The LC-MS spectrum of **135d.**

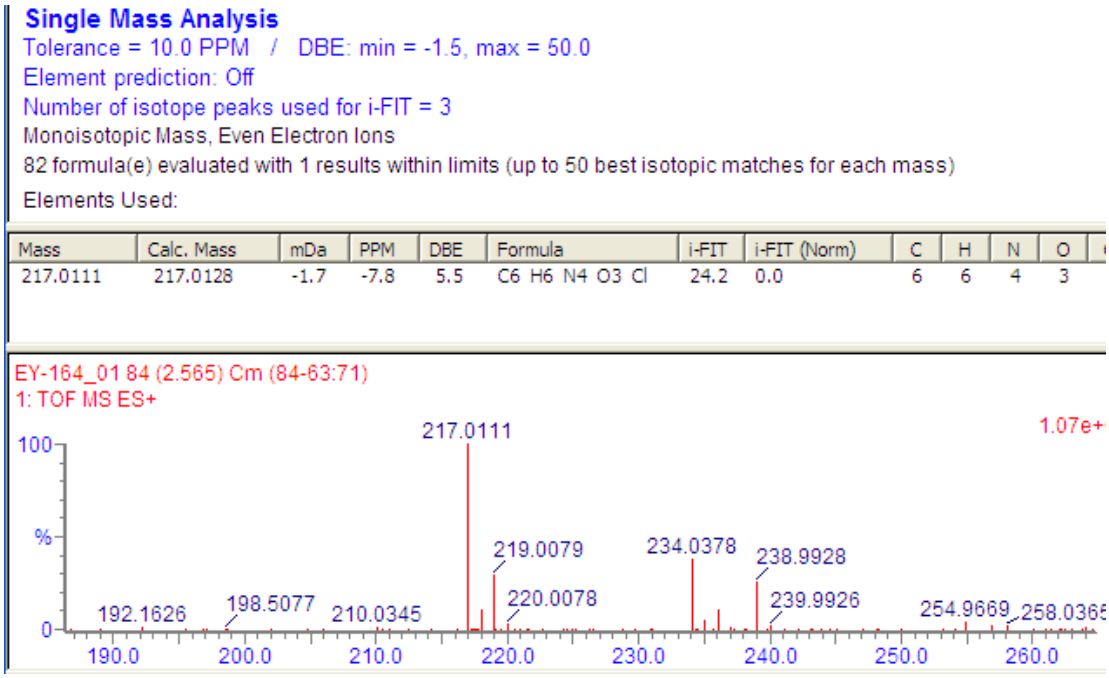


Figure 4.63. The HRMS spectrum of **135d.**

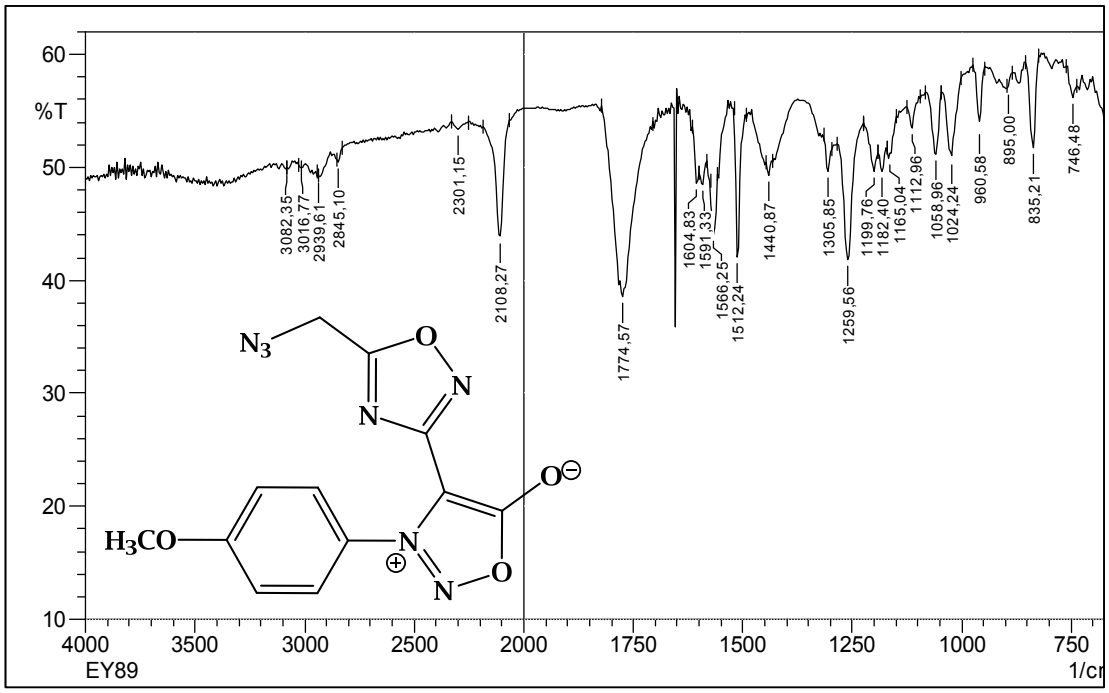


Figure 4.64. The IR spectrum of **136a.**

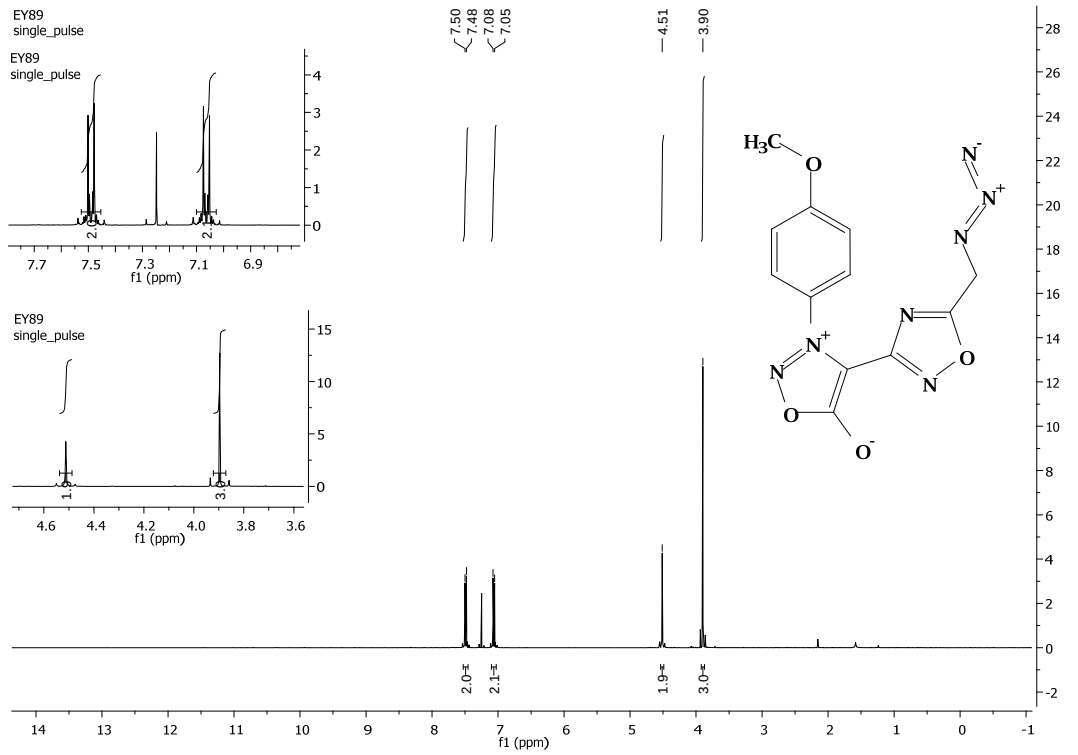


Figure 4.65. The ^{1}H NMR spectrum of **136a.**

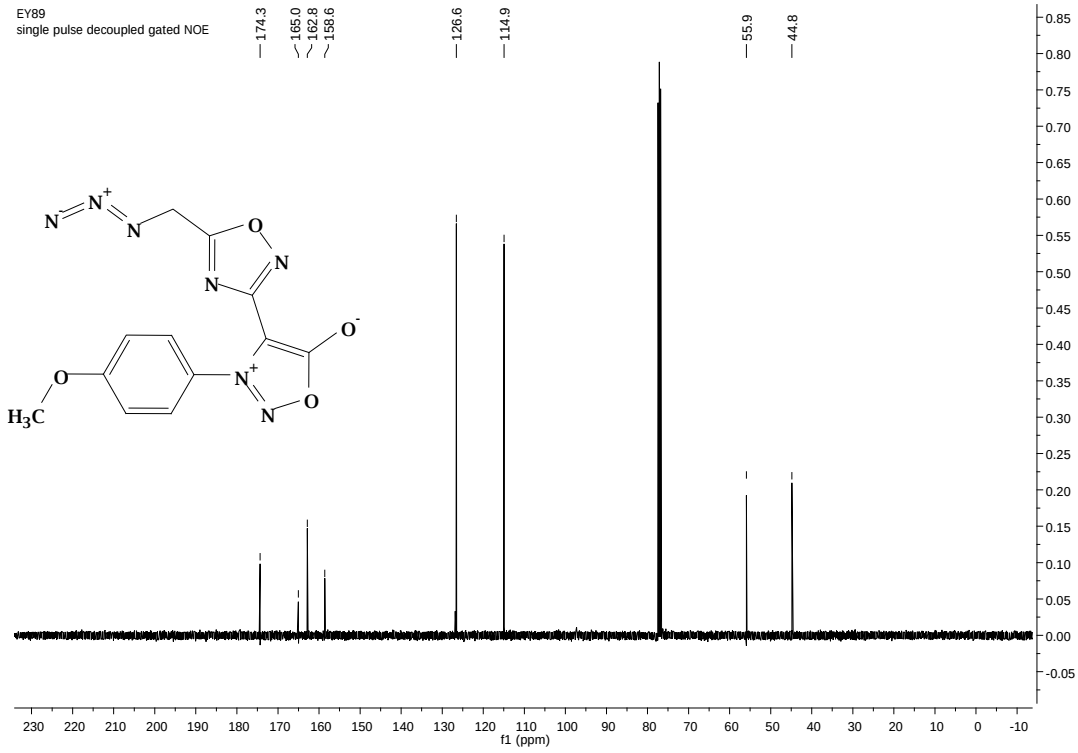


Figure 4.66. The ^{13}C NMR spectrum of **136a.**

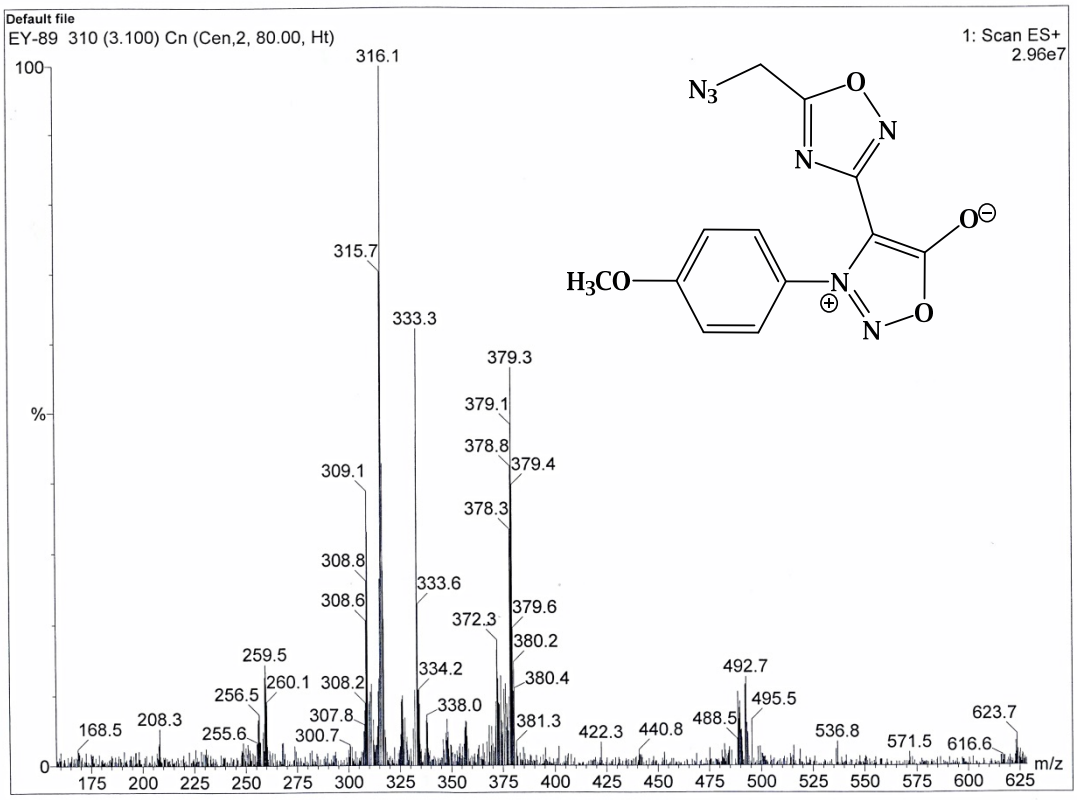


Figure 4.67. The LC-MS spectrum of **136a.**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
70 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT (Norm)	C	H	N
316.0783	316.0794	-1.1	-3.5	11.5	C12 H10 N7 O4	16.4	0.0	12	10	7

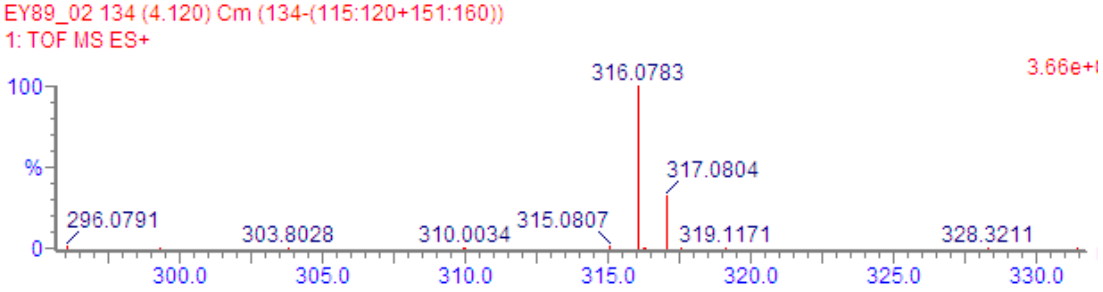


Figure 4.68. The HRMS spectrum of **136a.**

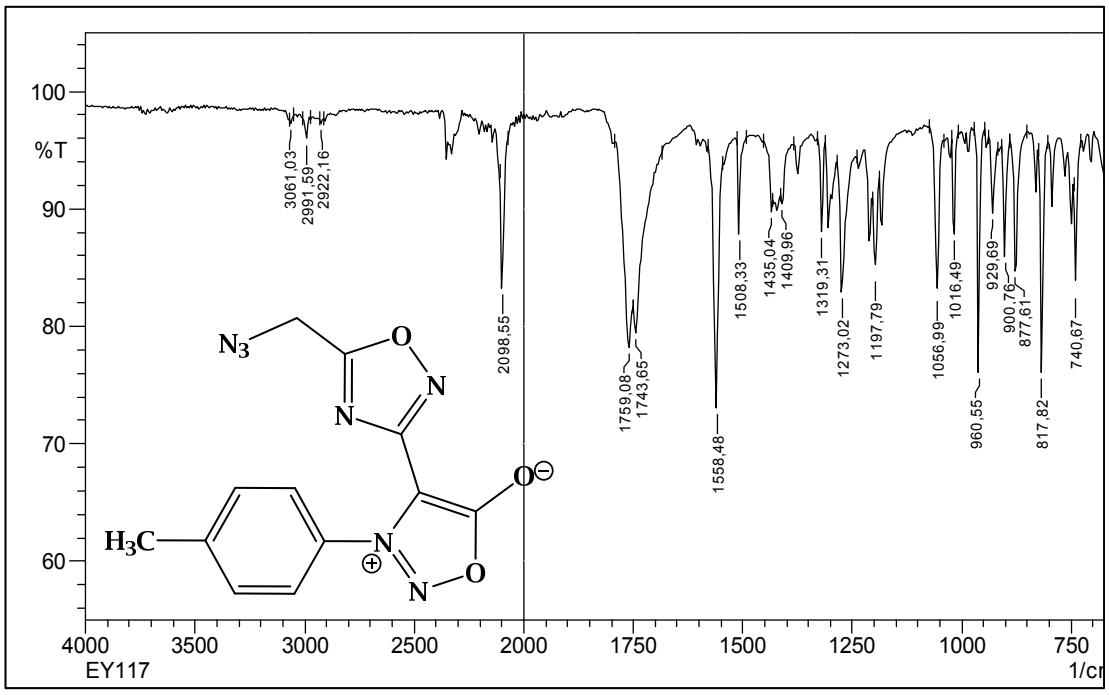


Figure 4.69. The IR spectrum of **136b.**

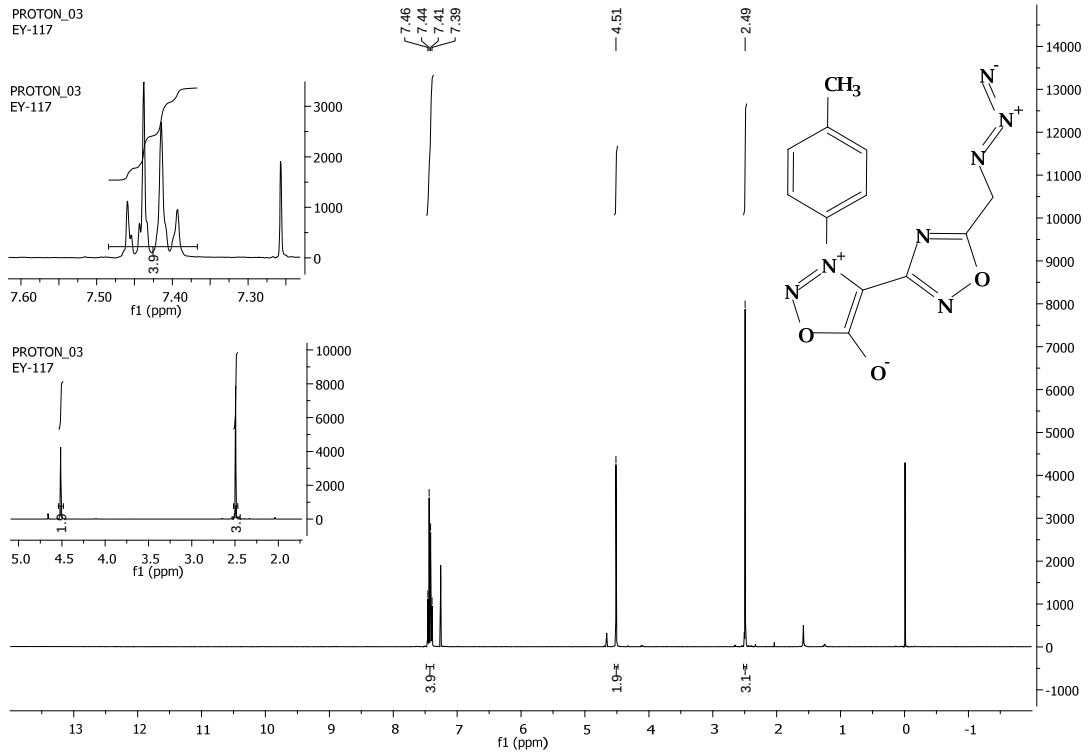


Figure 4.70. The ^{1}H NMR spectrum of **136b.**

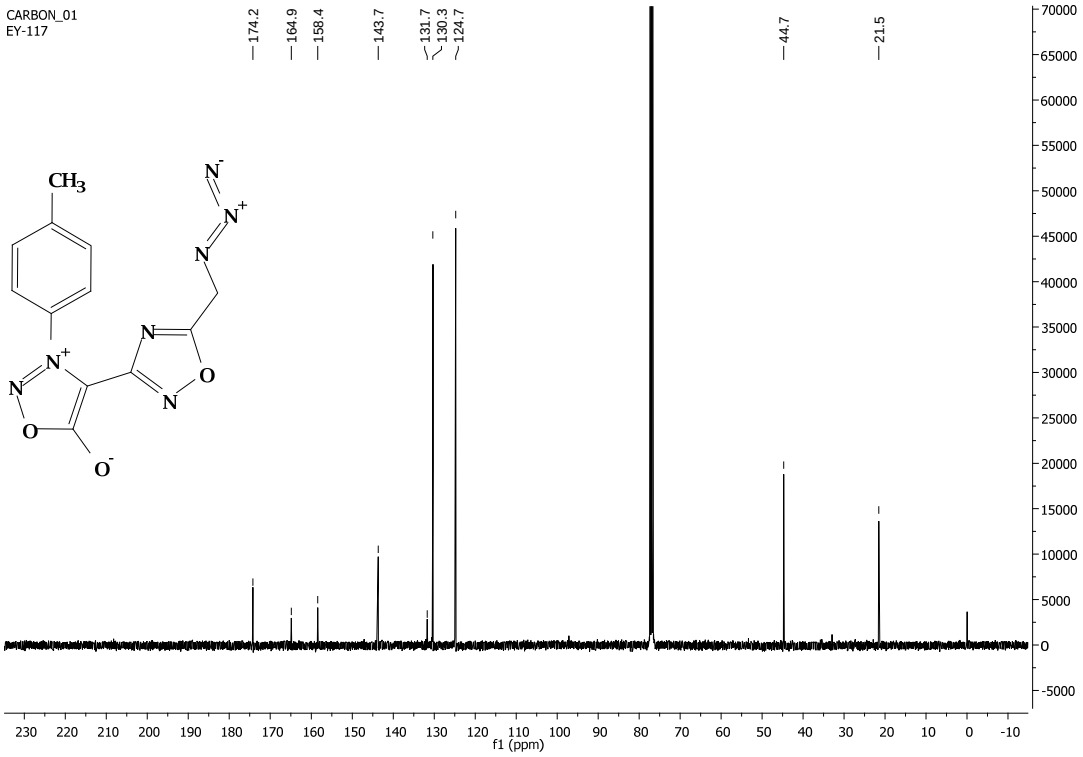


Figure 4.71. The ^{13}C NMR spectrum of **136b.**

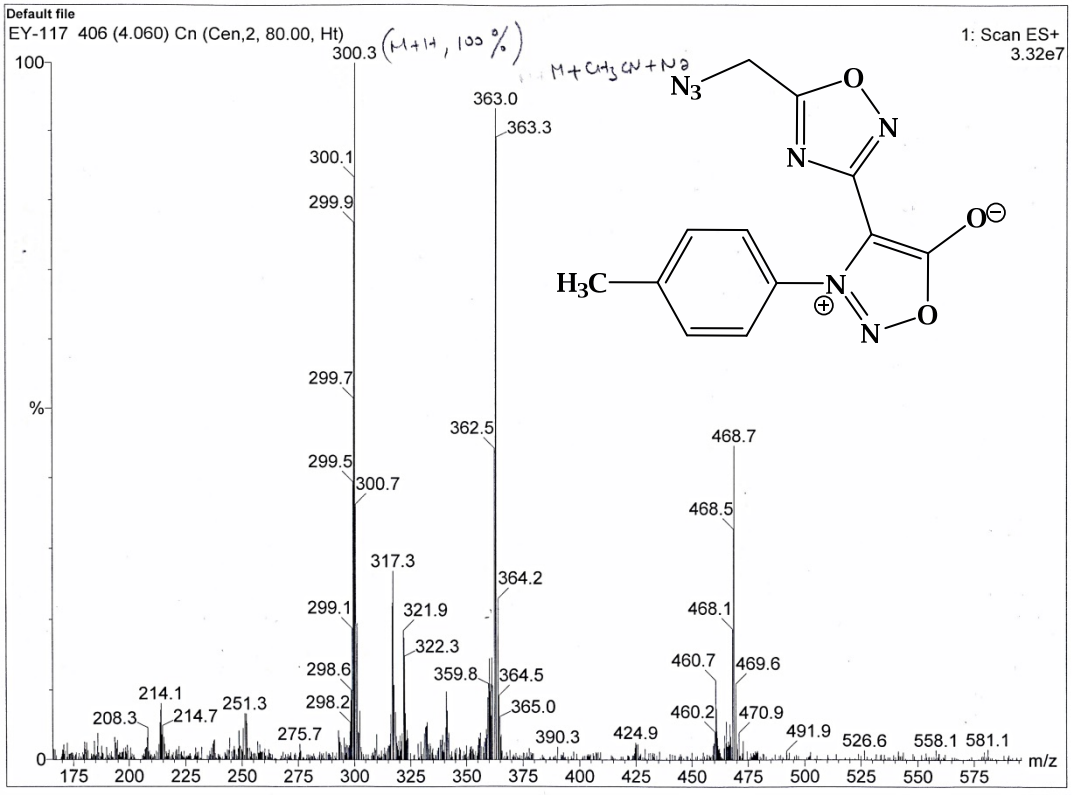


Figure 4.72. The LC-MS spectrum of **136b.**

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

32 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT (Norm)	C	H	N
300.0834	300.0845	-1.1	-3.7	11.5	C12 H10 N7 O3	26.6	0.0	12	10	7

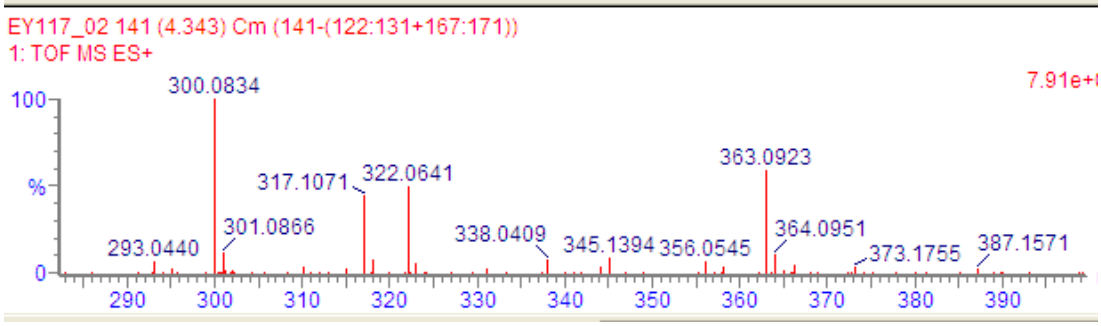


Figure 4.73. The HRMS spectrum of **136b.**

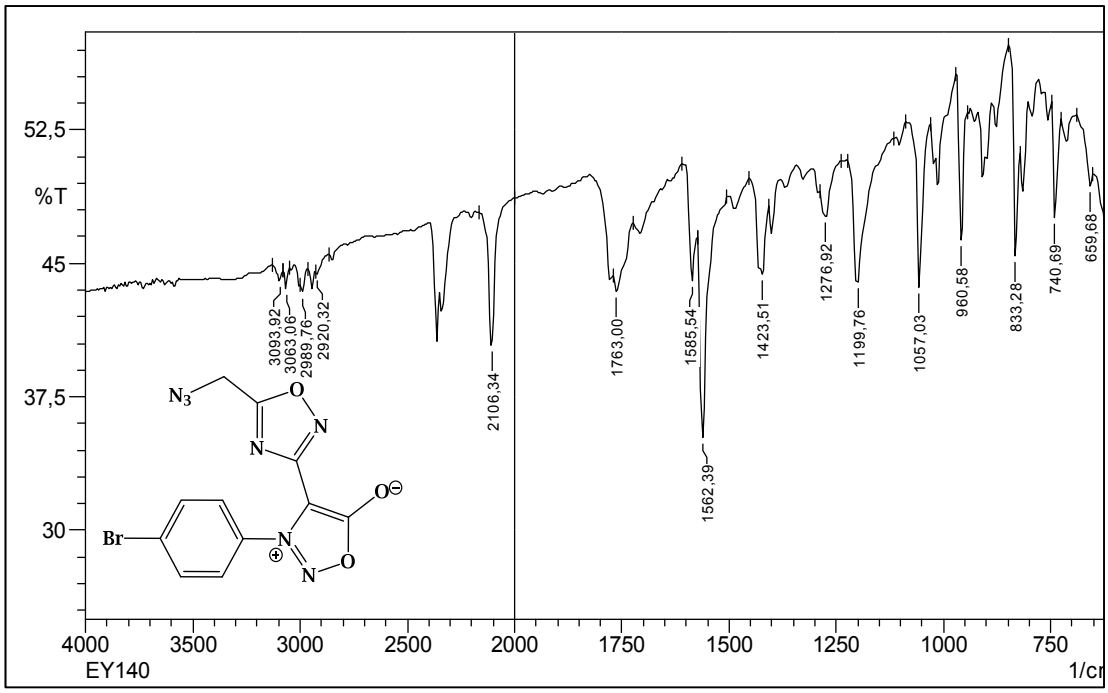


Figure 4.74. The IR spectrum of **136c.**

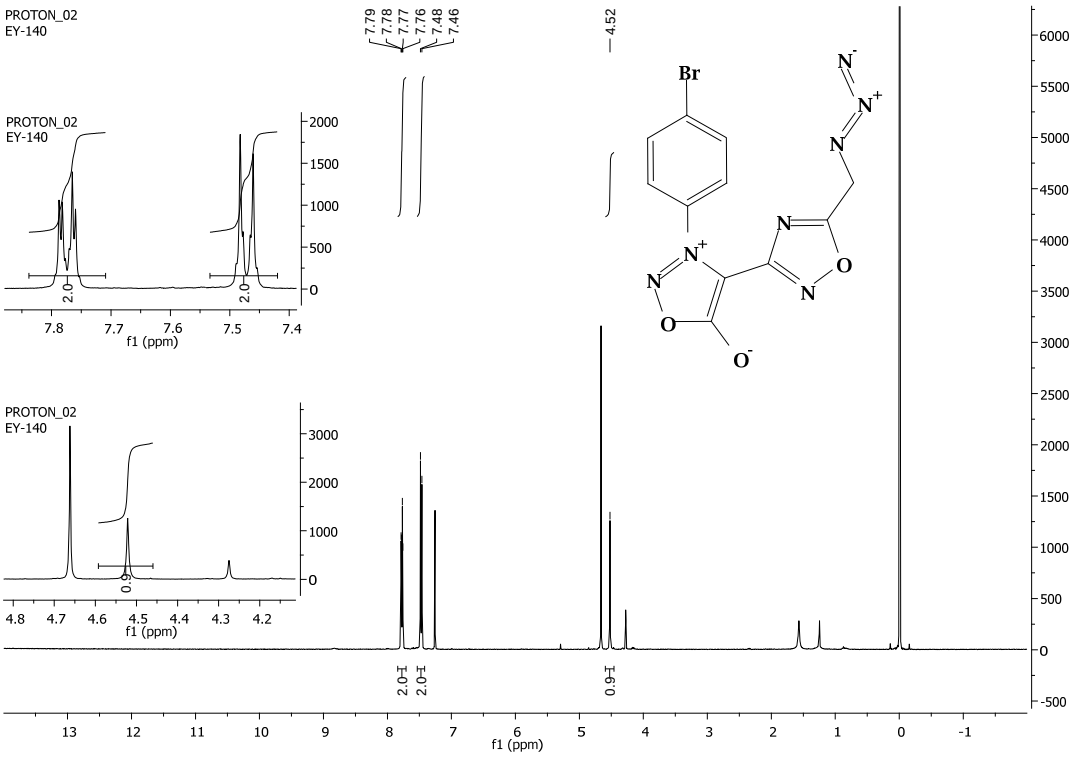


Figure 4.75. The ^{1}H NMR spectrum of **136c.**

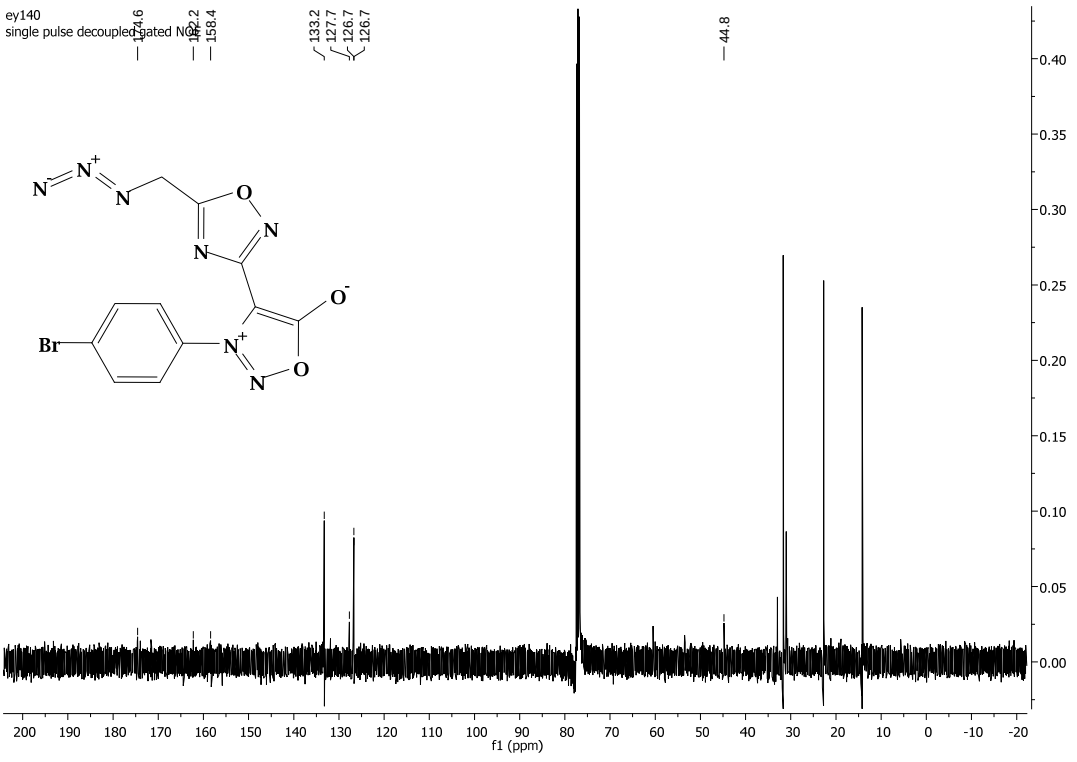


Figure 4.76. The ^{13}C NMR spectrum of **136c.**

Single Mass Analysis
Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
109 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)
Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT (Norm)	C	H	N	O	Br
363.9777	363.9794	-1.7	-4.7	11.5	C11 H7 N7 O3 Br	49.4	0.0	11	7	7	3	1

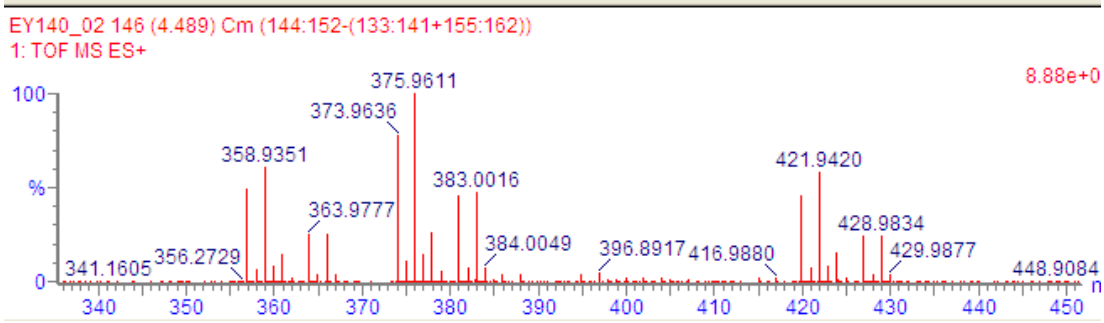


Figure 4.77. The HRMS spectrum of **136c.**

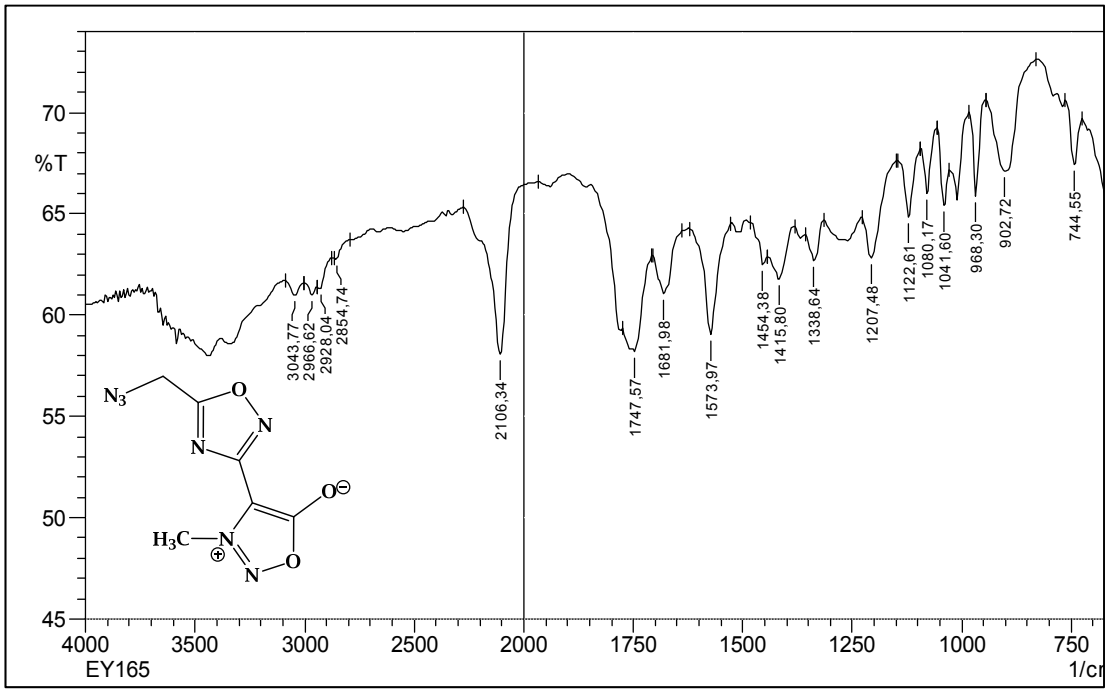


Figure 4.78. The IR spectrum of **136d**

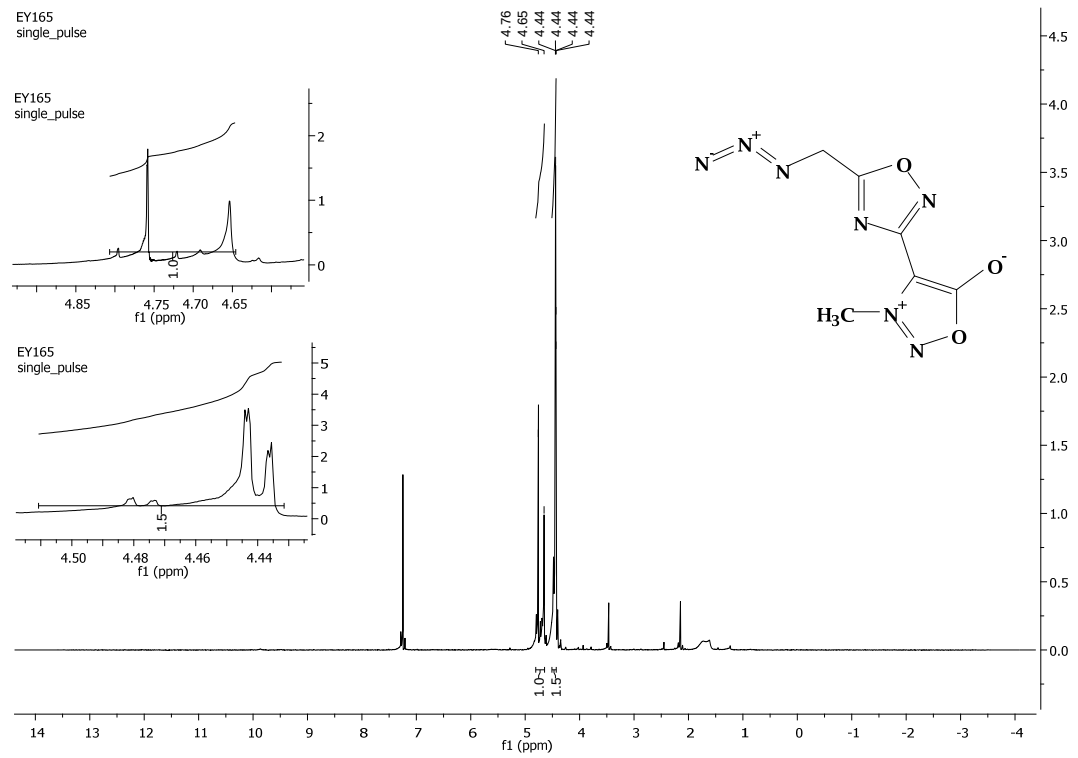


Figure 4.79. The ^{1}H NMR spectrum of **136d.**

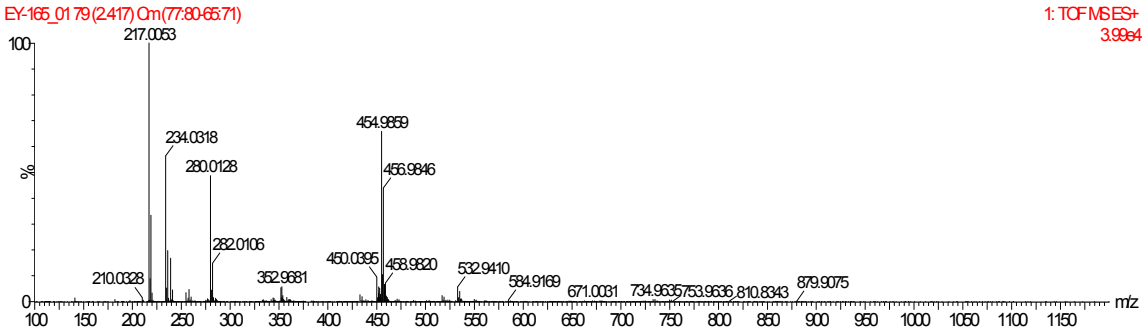


Figure 4.80. The HRMS spectrum of **136d.**

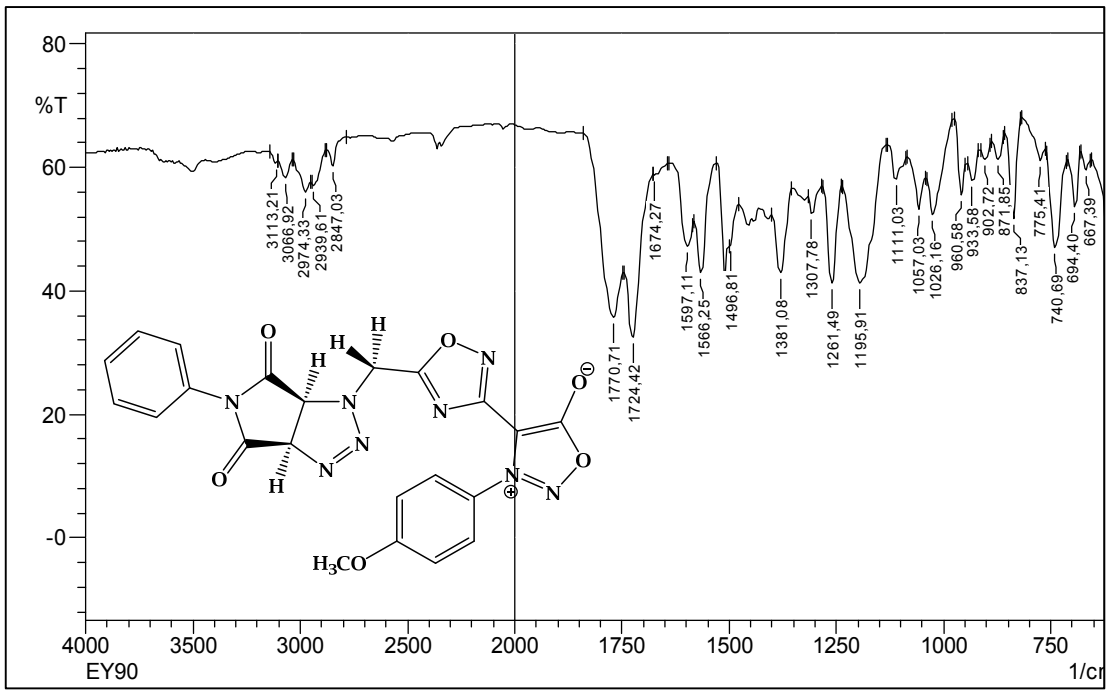


Figure 4.81. The IR spectrum of **137a.**

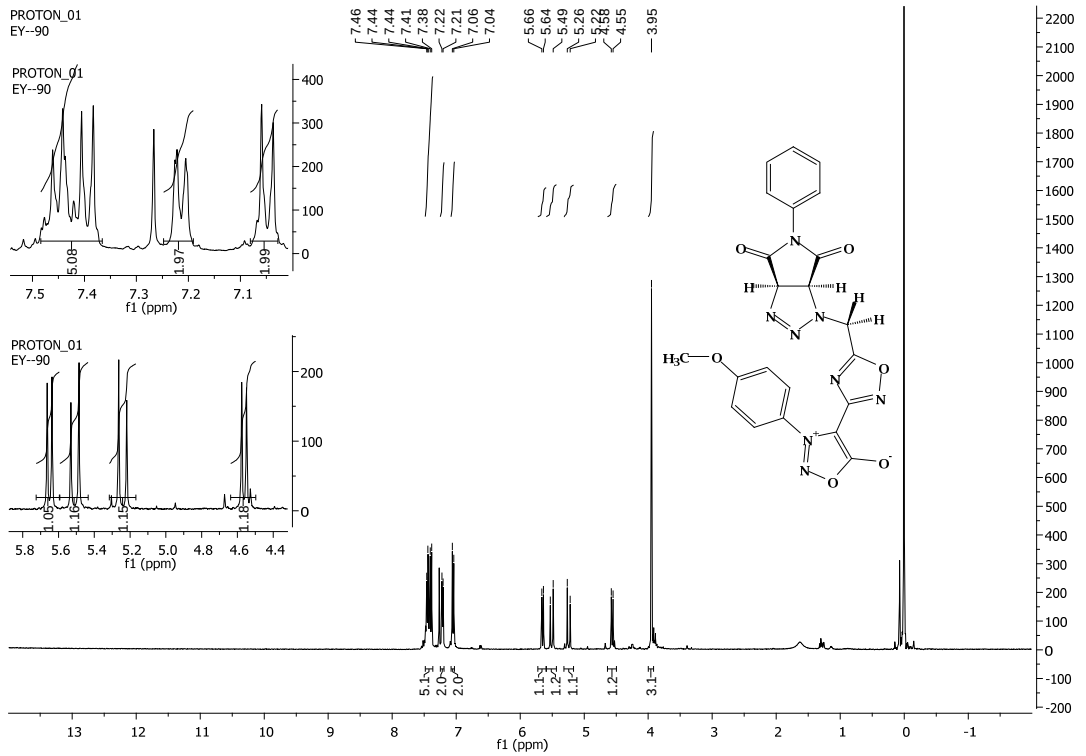


Figure 4.82. The ^{1}H NMR spectrum of **137a.**

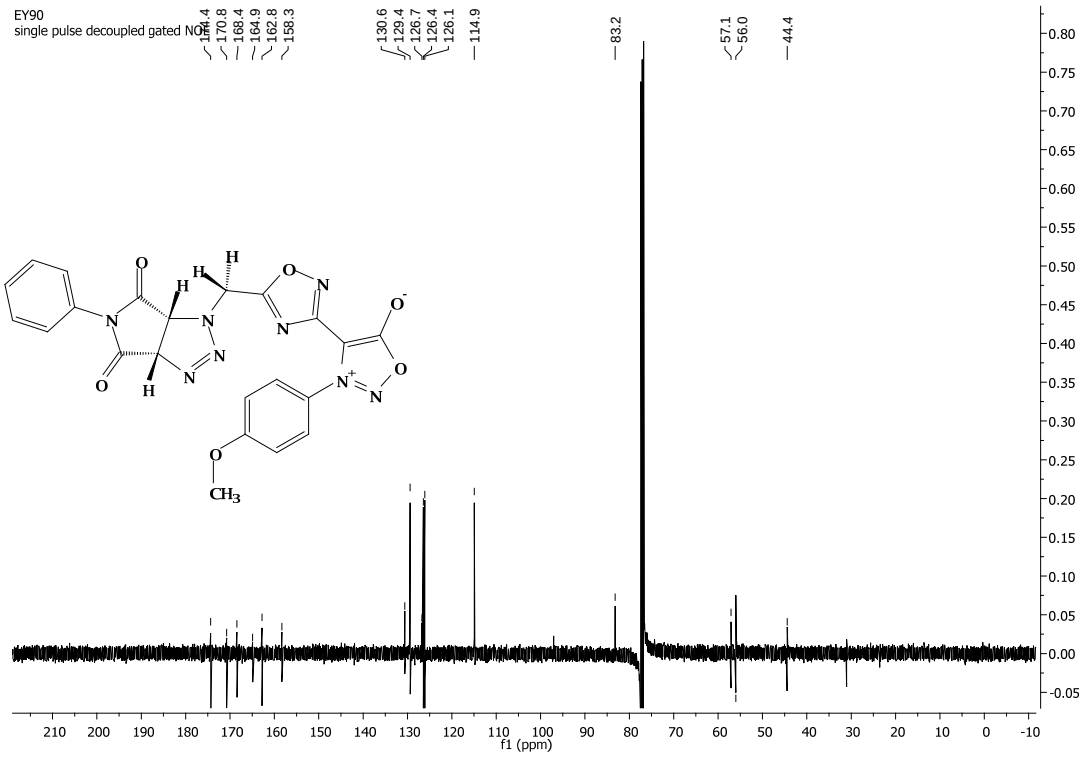


Figure 4.83. The ^{13}C NMR spectrum of **137a.**

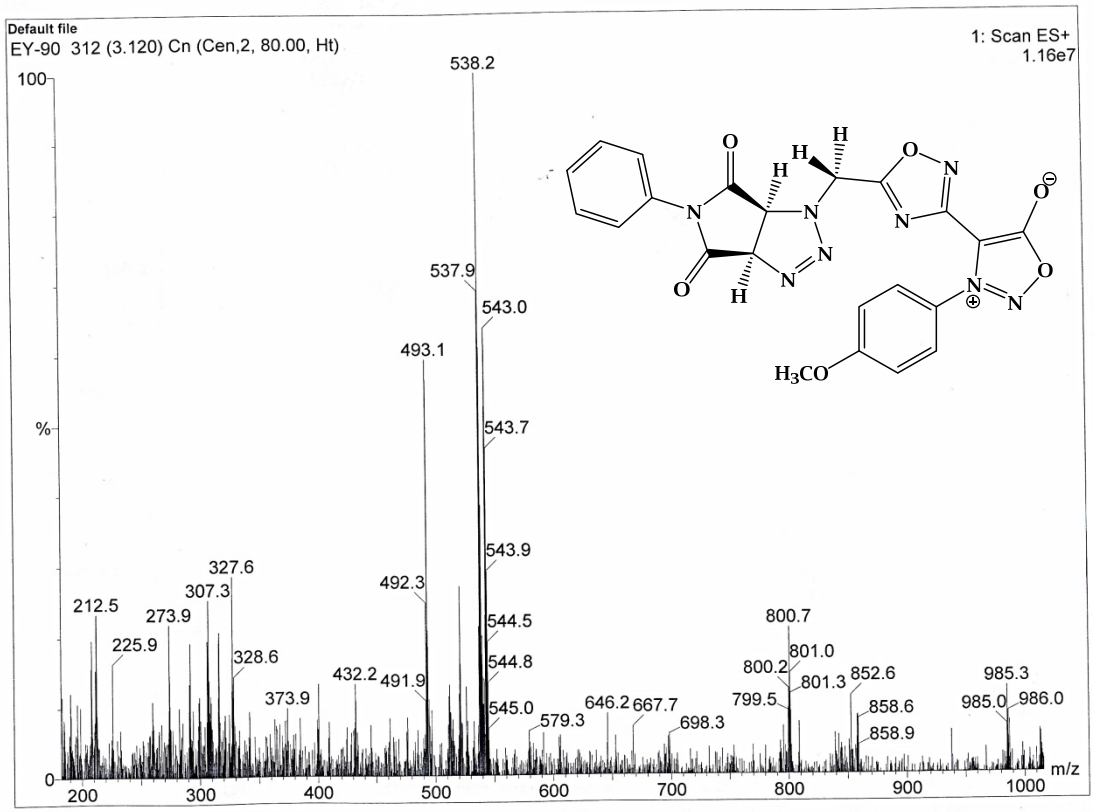


Figure 4.84. The LC-MS spectrum of **137a.**

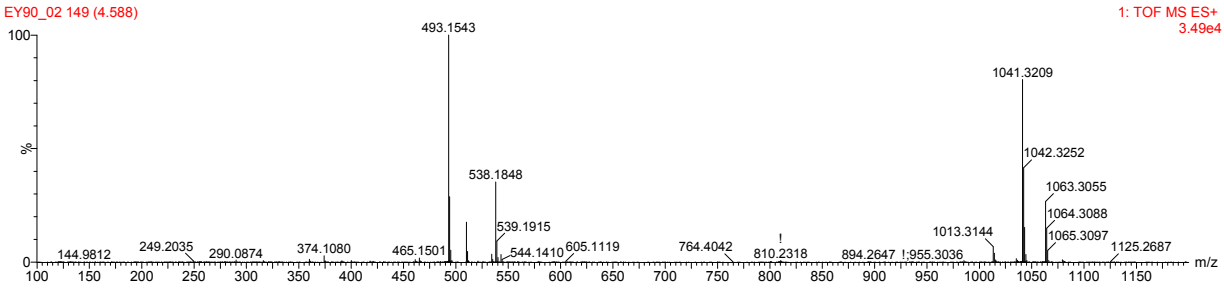


Figure 4.85. The HRMS spectrum of **137a.**

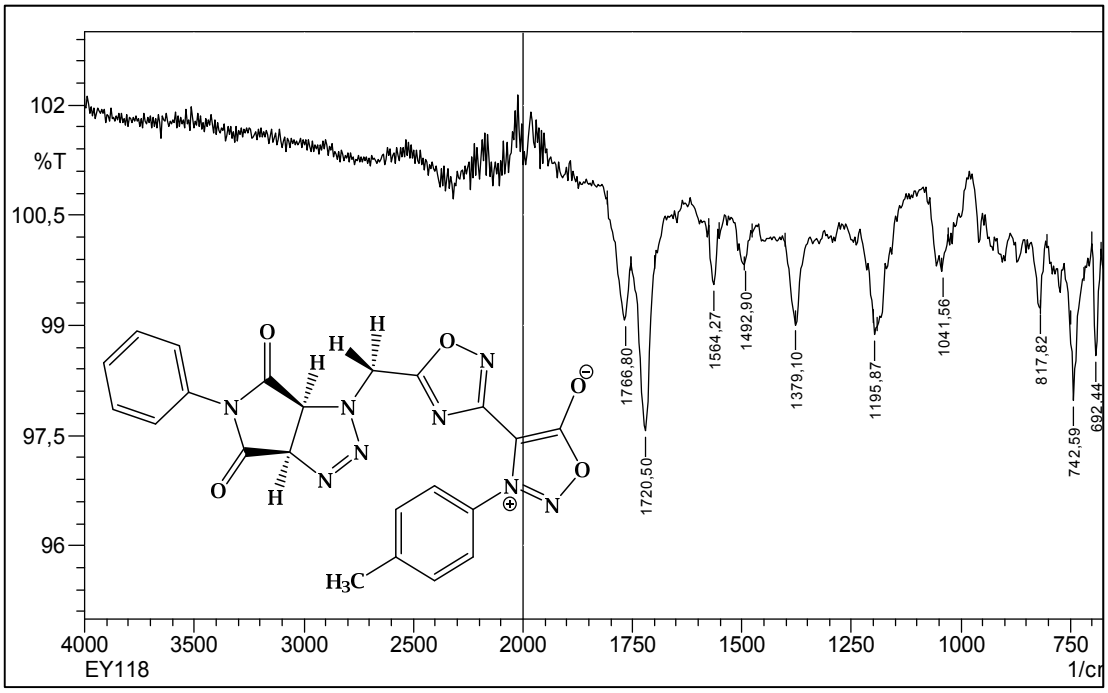


Figure 4.86. The IR spectrum of **137b.**

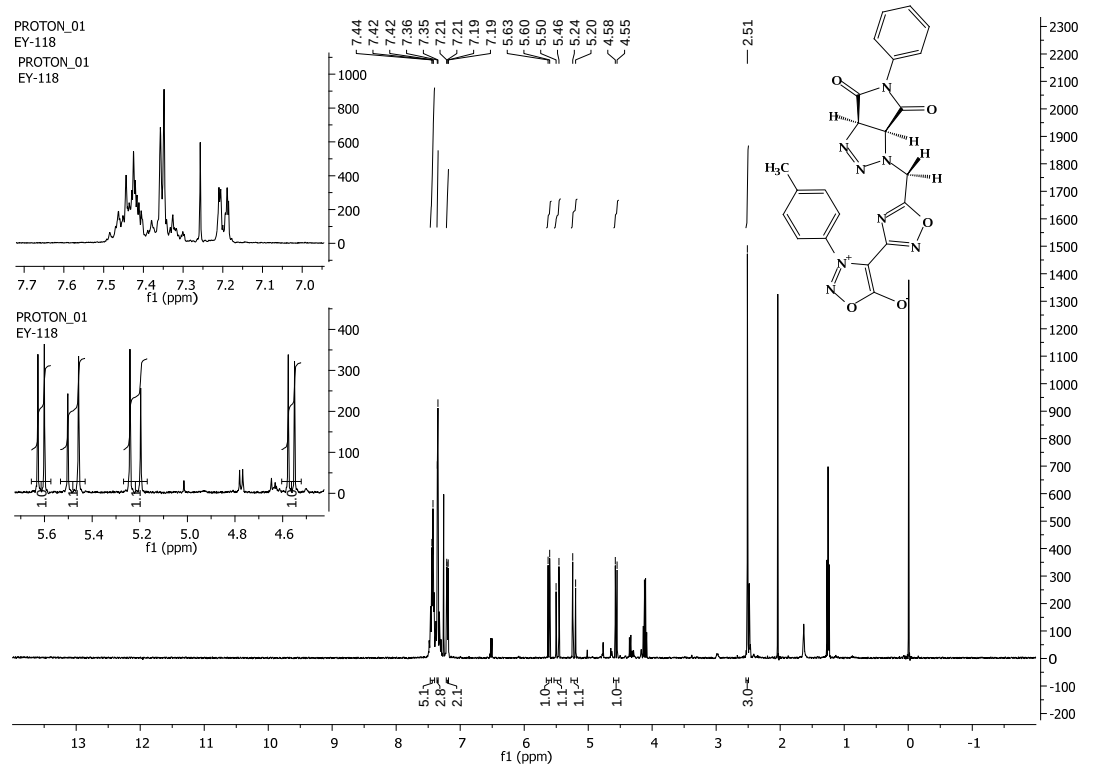


Figure 4.87. The ^{1}H NMR spectrum of **137b.**

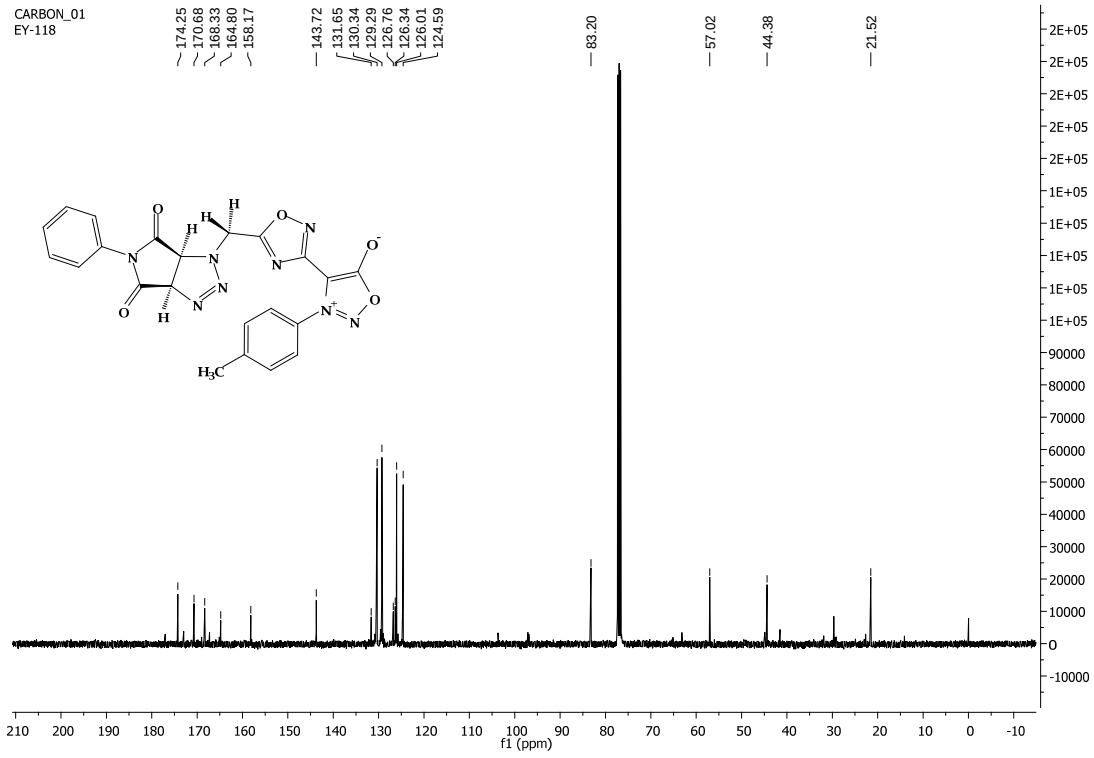


Figure 4.88. The ^{13}C NMR spectrum of **137b.**

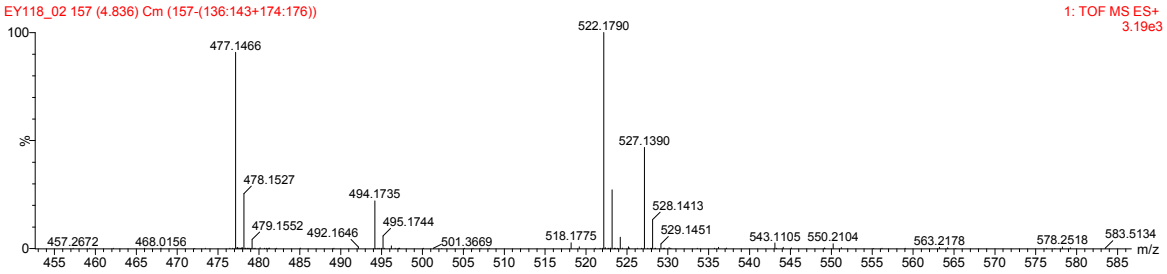


Figure 4.89. The HRMS spectrum of **137b.**

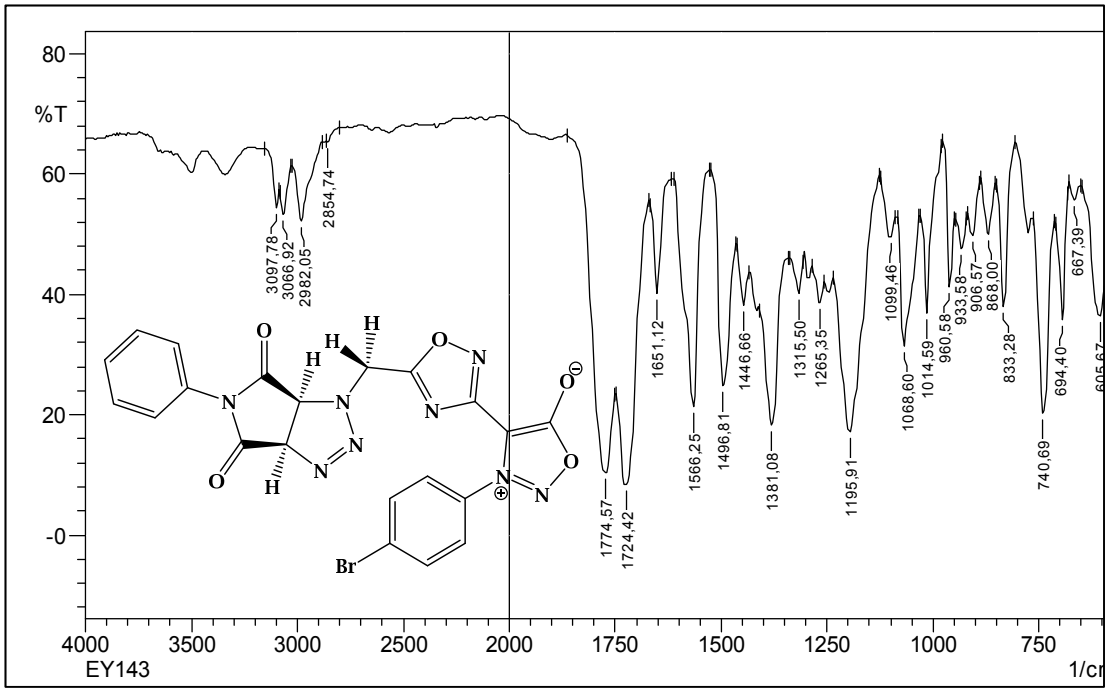


Figure 4.90. The IR spectrum of **137c.**

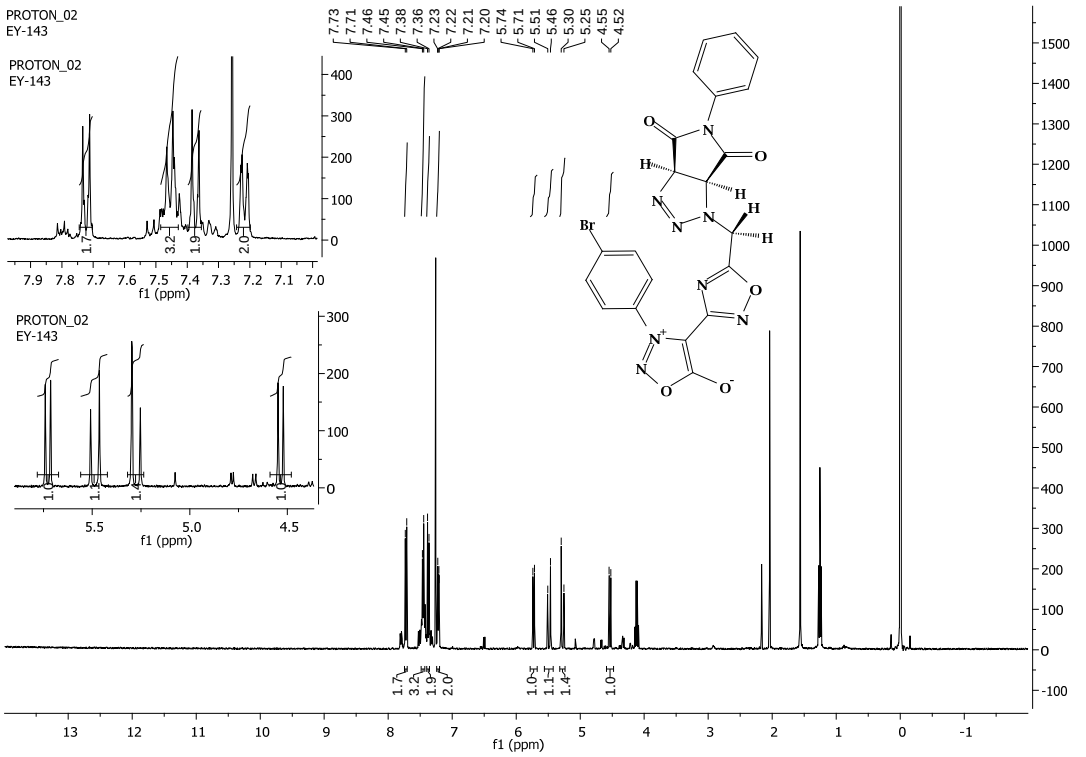


Figure 4.91. The ^{1}H NMR spectrum of **137c.**

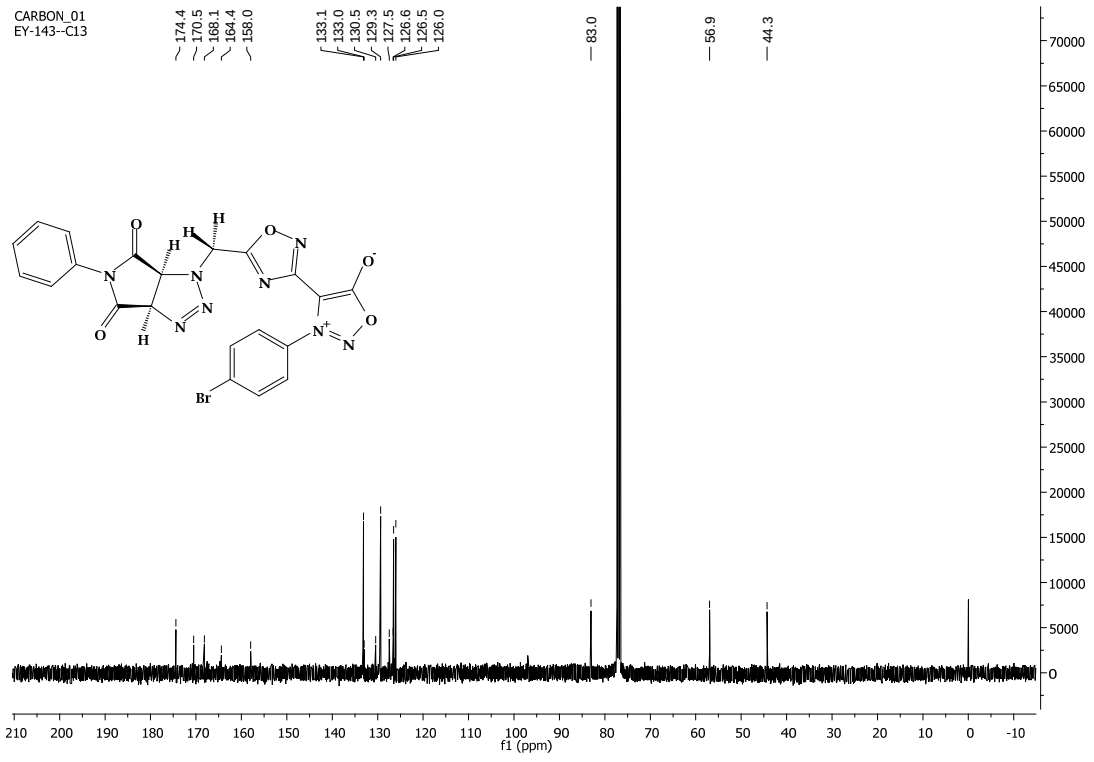


Figure 4.92. The ^{13}C NMR spectrum of **137c.**

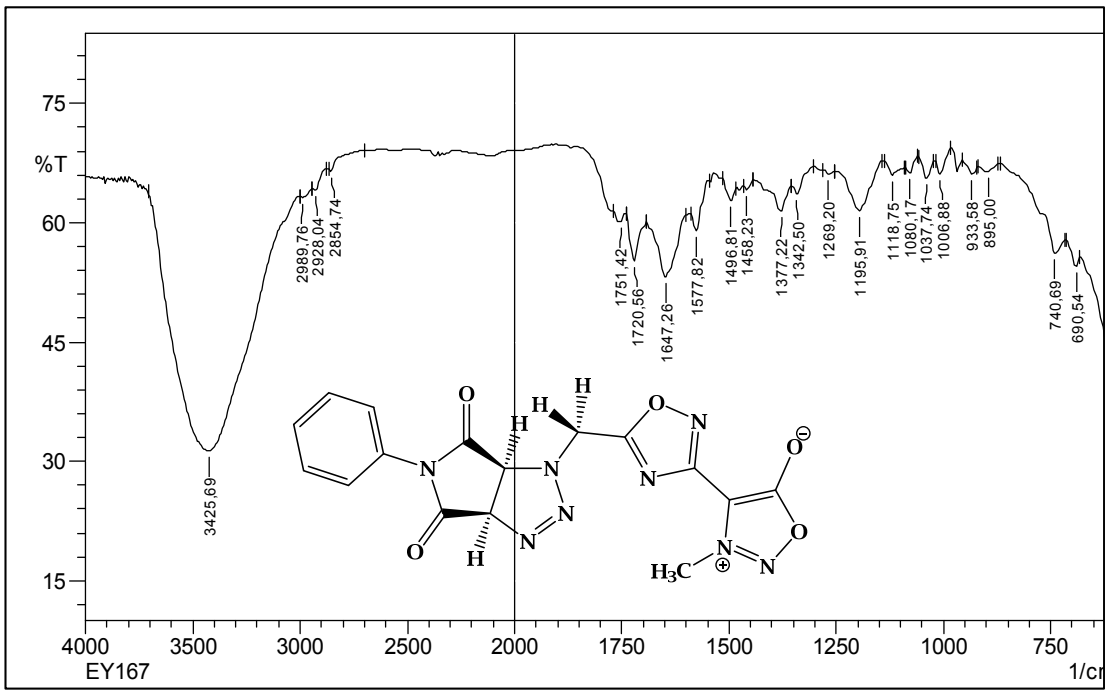


Figure 4.93. The IR spectrum of **137d.**

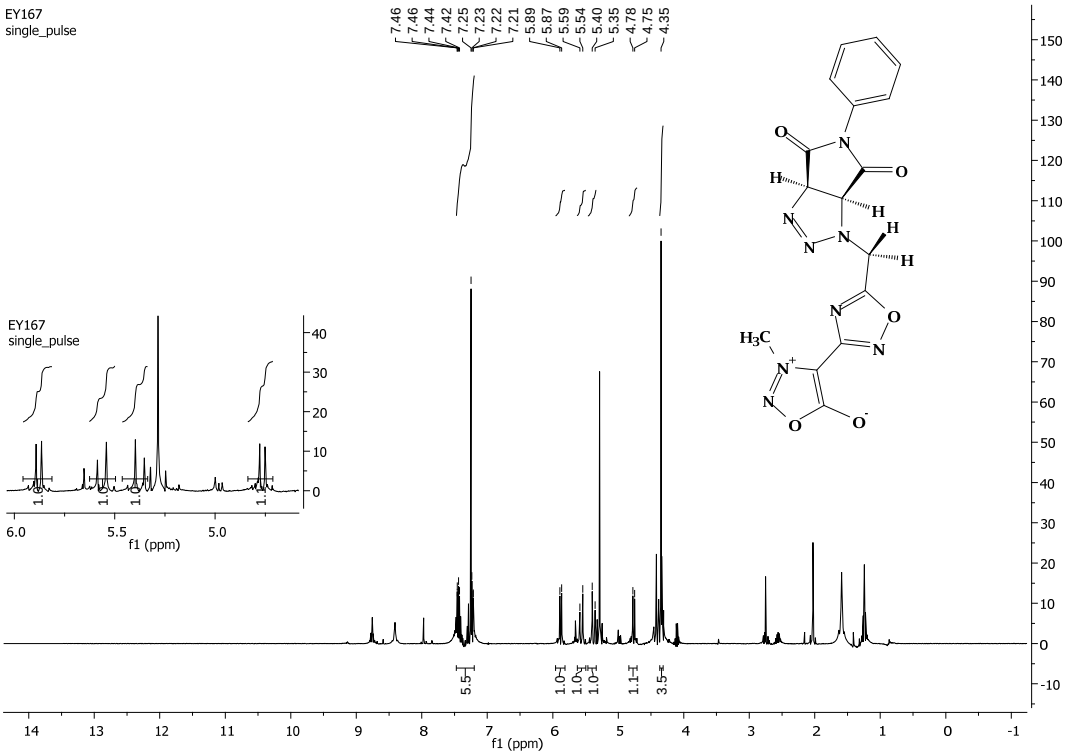


Figure 4.94. The ^{1}H NMR spectrum of **137d.**

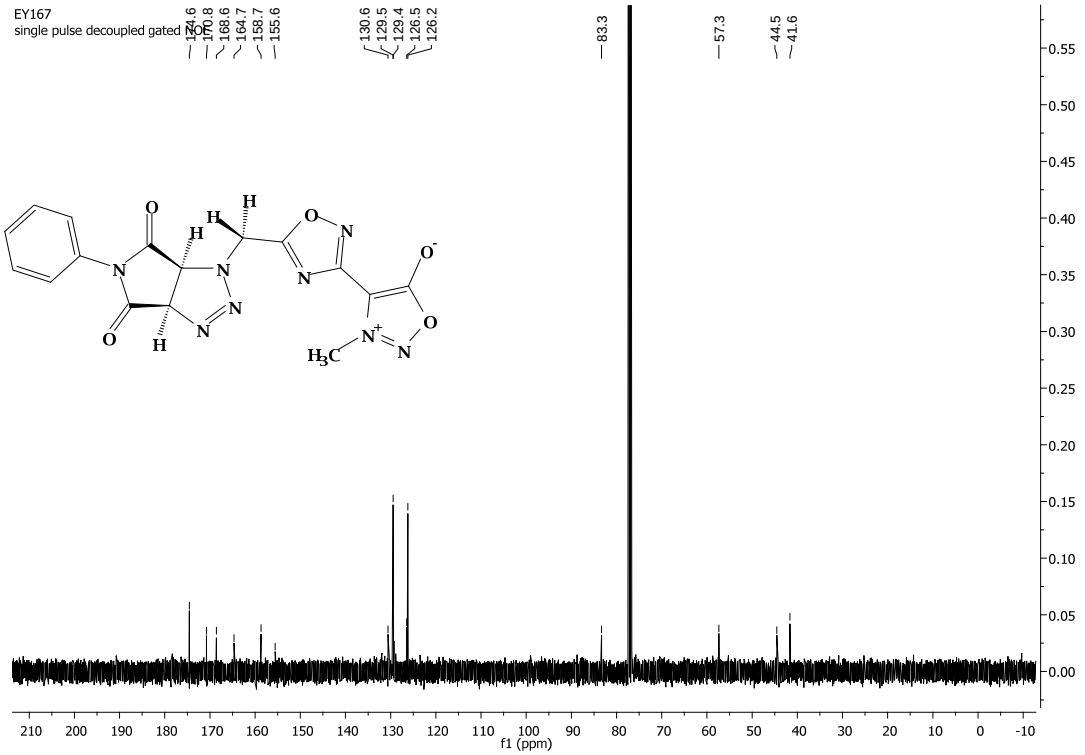


Figure 4.95. The ^{13}C NMR spectrum of **137d.**

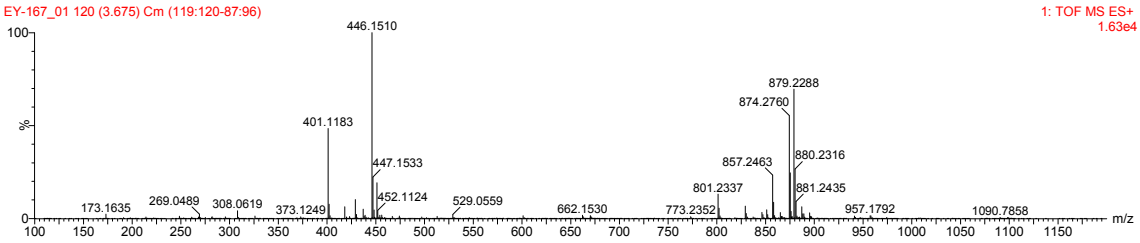


Figure 4.96. The HRMS spectrum of **137d.**

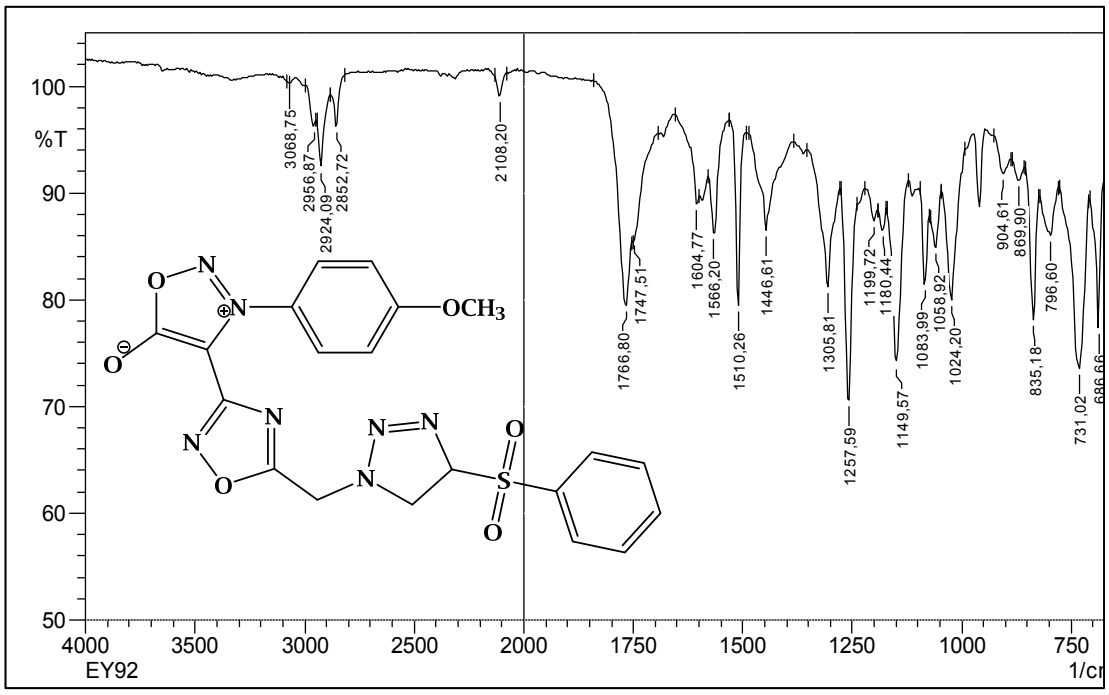


Figure 4.97. The IR spectrum of **138a.**

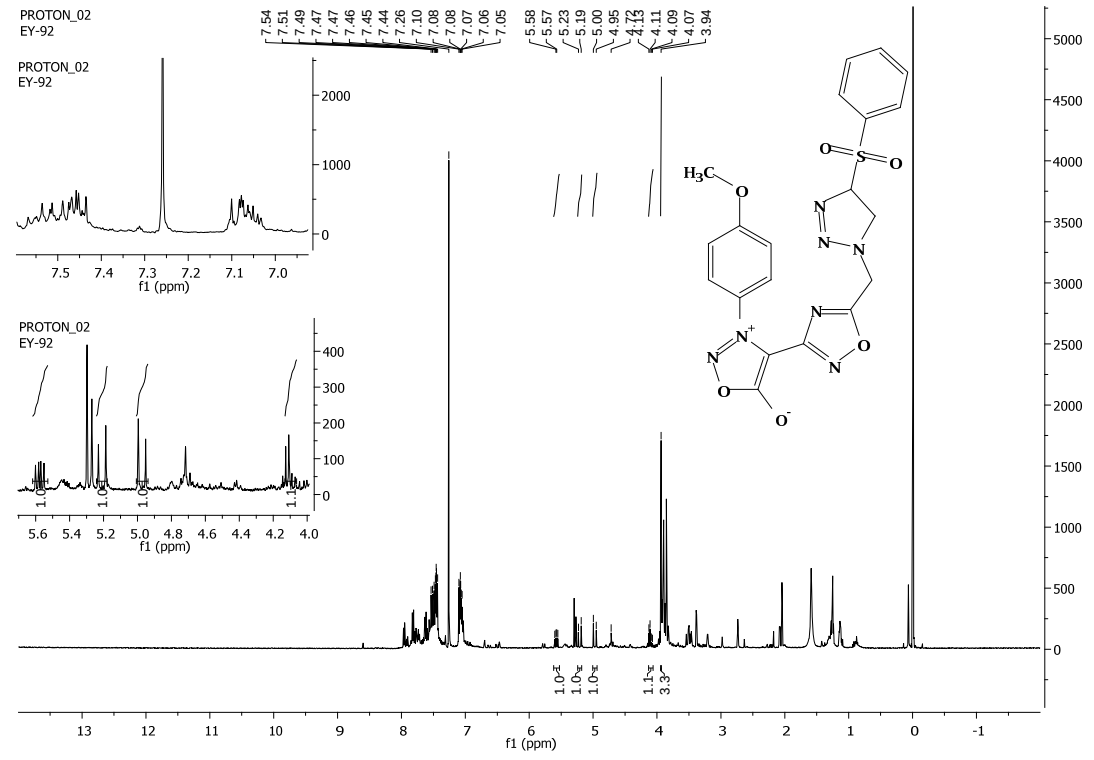


Figure 4.98. The ^{1}H NMR spectrum of **138a.**

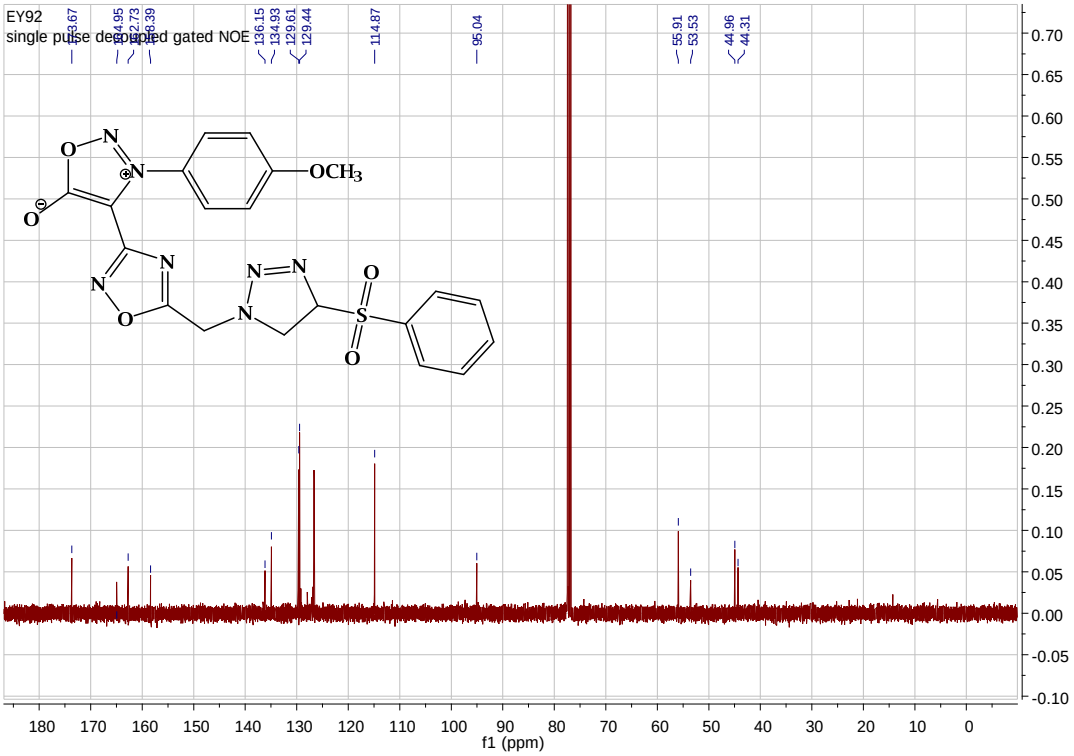


Figure 4.99. The ^{13}C NMR spectrum of **138a.**

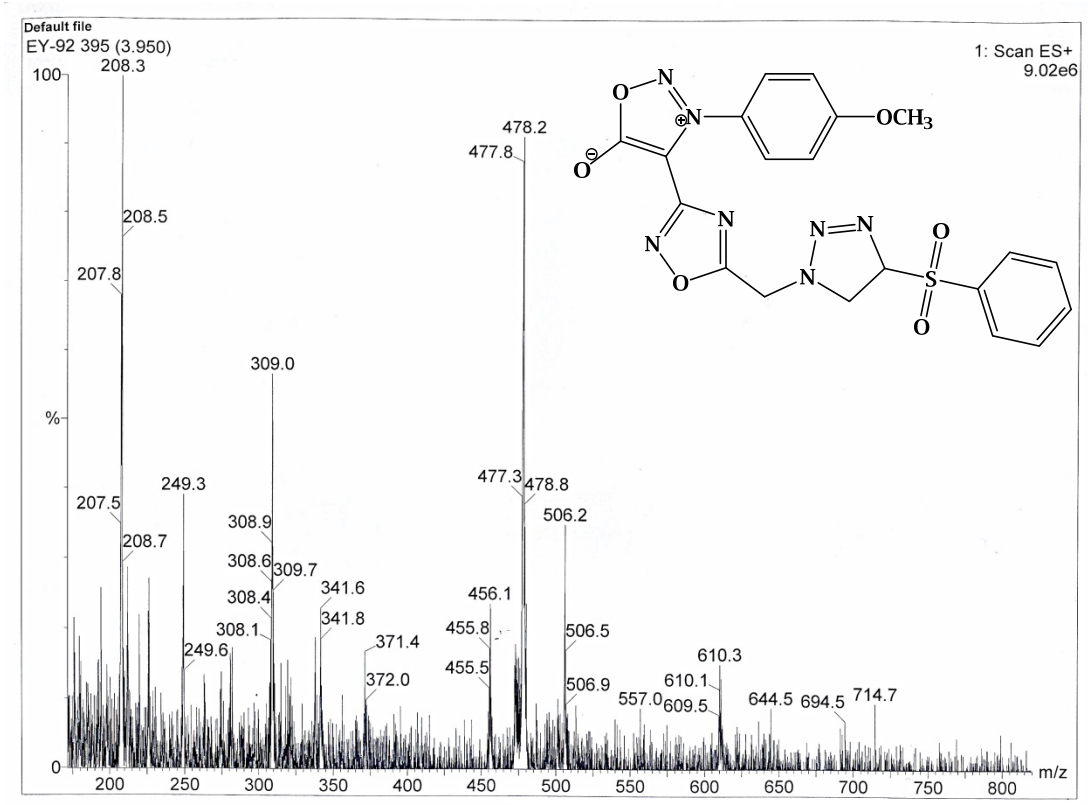


Figure 4.100. The LC-MS spectrum of **138a.**

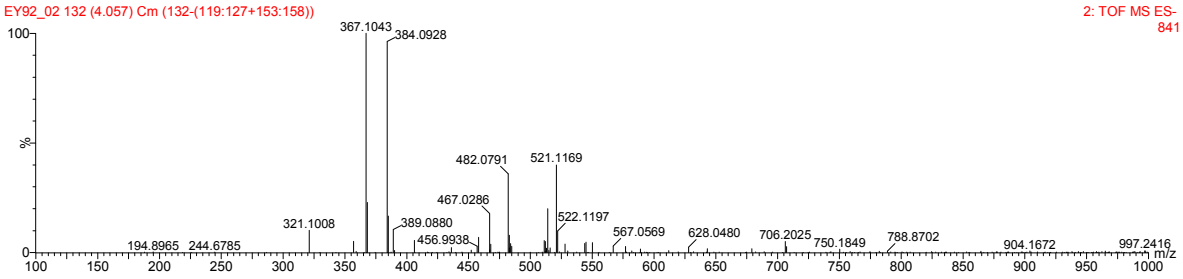


Figure 4.101. The HRMS spectrum of **138a.**

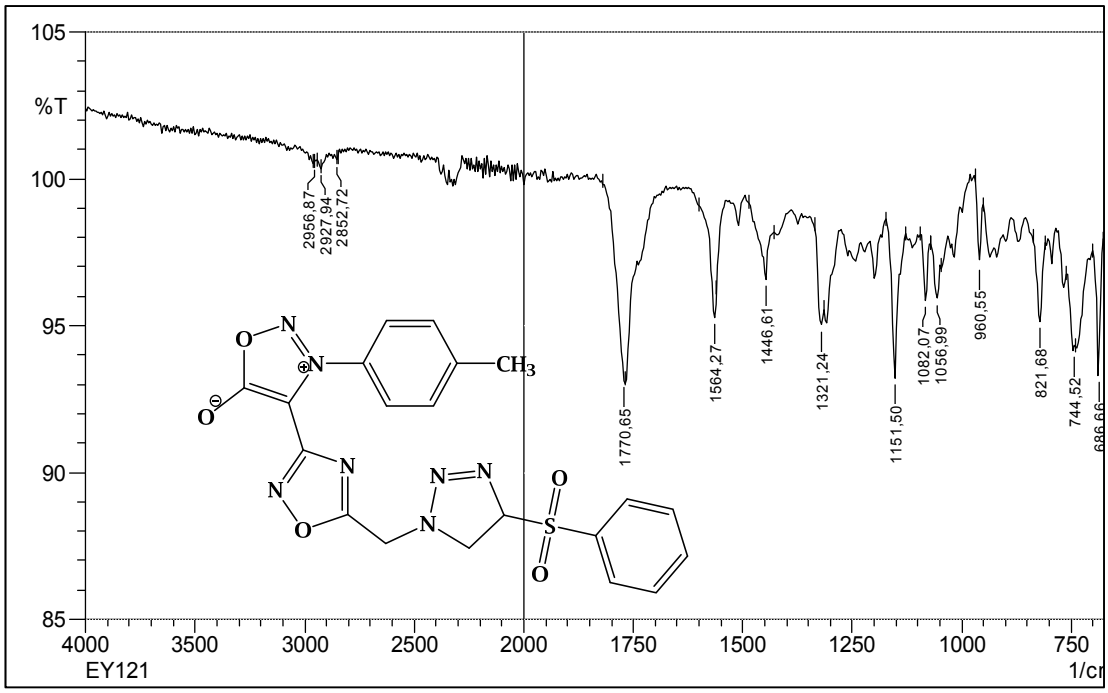


Figure 4.102. The IR spectrum of **138b.**

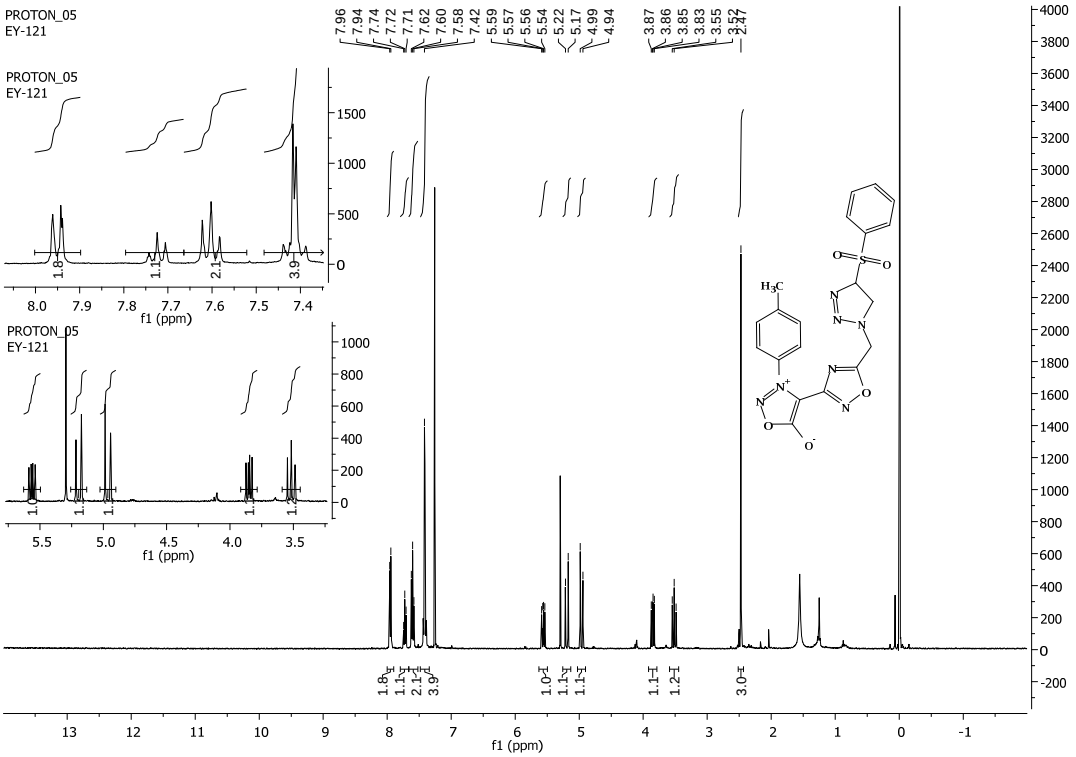


Figure 4.103. The ^{1}H NMR spectrum of **138b.**

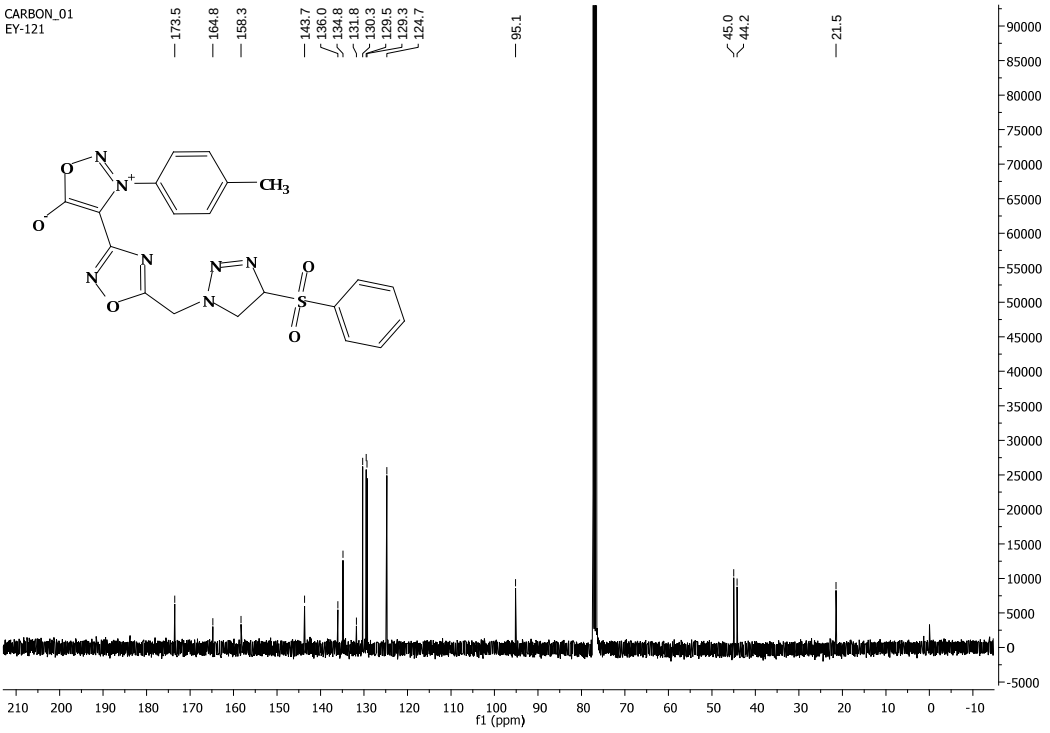


Figure 4.104. The ^{13}C NMR spectrum of **138b.**

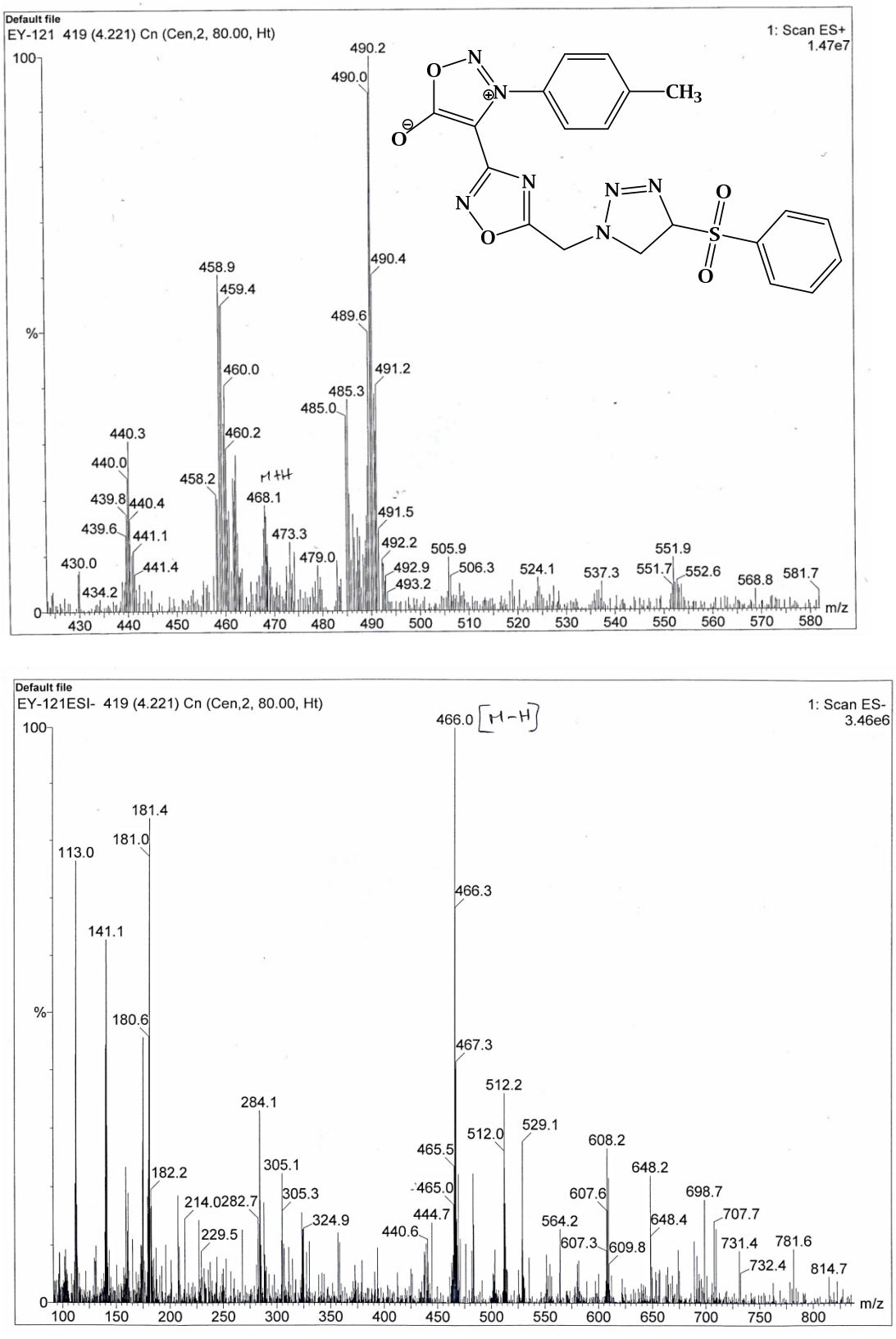


Figure 4.105. The LC-MS spectrum of **138b**(ES+ and ES- mode)**.**

Single Mass Analysis

Tolerance = 5.0 PPM / DBE: min = -1.5, max = 50.0

Element prediction: Off

Number of isotope peaks used for i-FIT = 3

Monoisotopic Mass, Even Electron Ions

70 formula(e) evaluated with 1 results within limits (up to 50 closest results for each mass)

Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT (Norm)	C	H	N	O
468.1081	468.1090	-0.9	-1.9	15.5	C20 H18 N7 O5 S	11.6	0.0	20	18	7	5

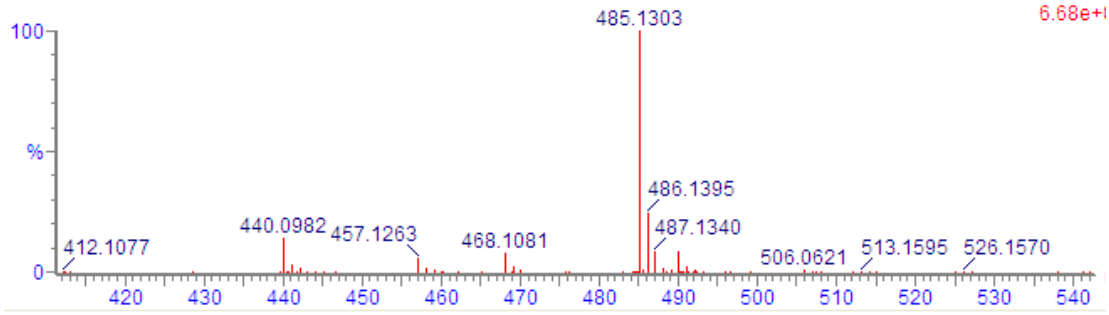


Figure 4.106. The HRMS spectrum of **138b.**

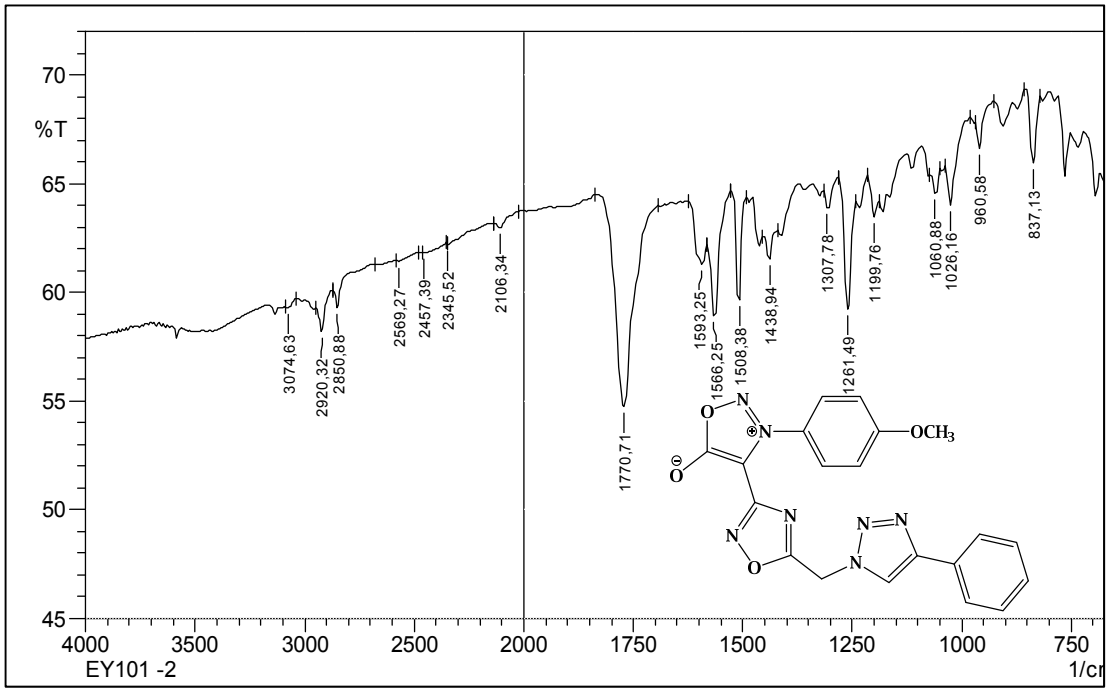


Figure 4.107. The IR spectrum of **139a.**

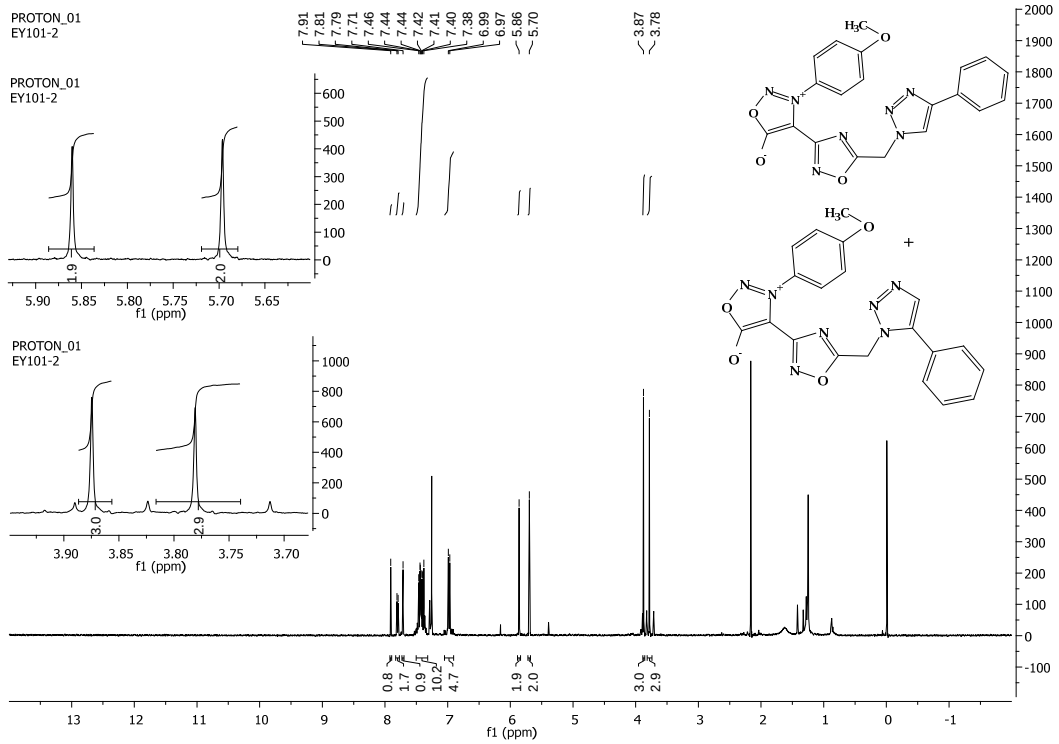


Figure 4.108. The ^{1}H NMR spectrum of **139a** obtained from cycloaddition reaction without catalyst.

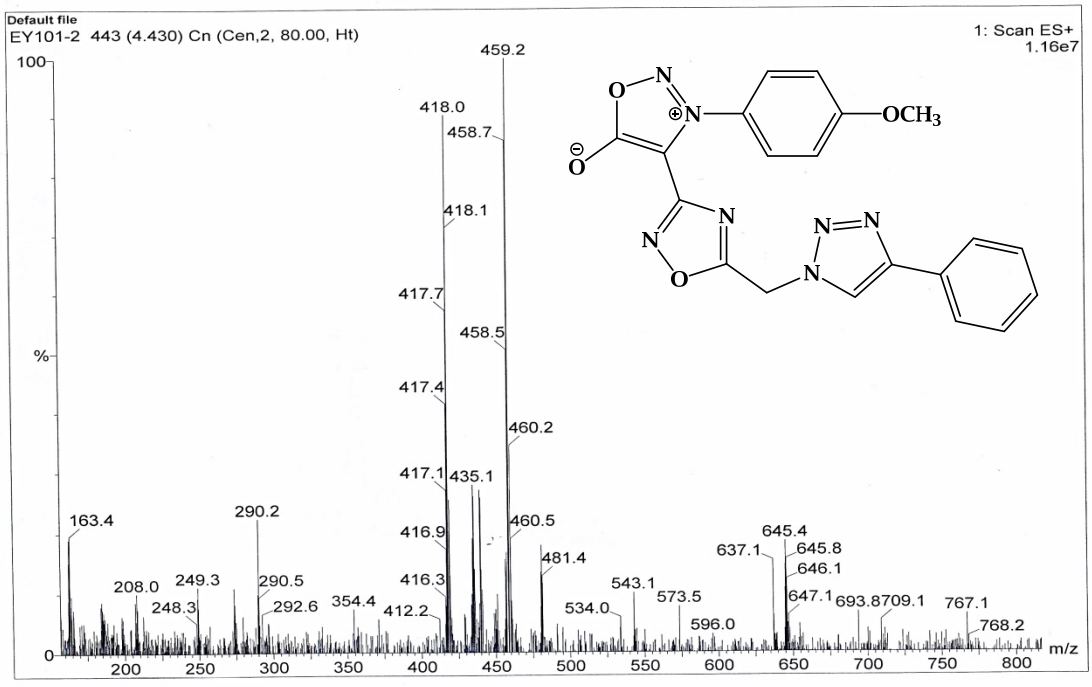


Figure 4.109. The LC-MS spectrum of **139a** produced from cycloaddition reaction without catalyst**.**

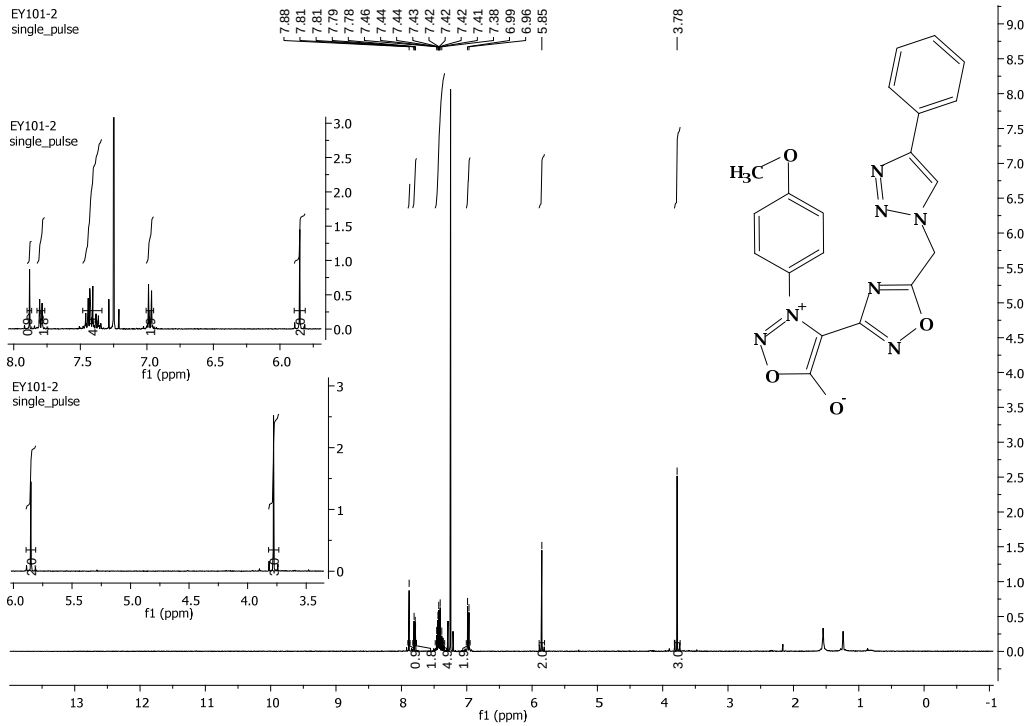


Figure 4.110. The ^{1}H NMR spectrum of **139a** produced from Cu(I) catalyzed azide-alkyne cycloaddition reaction.

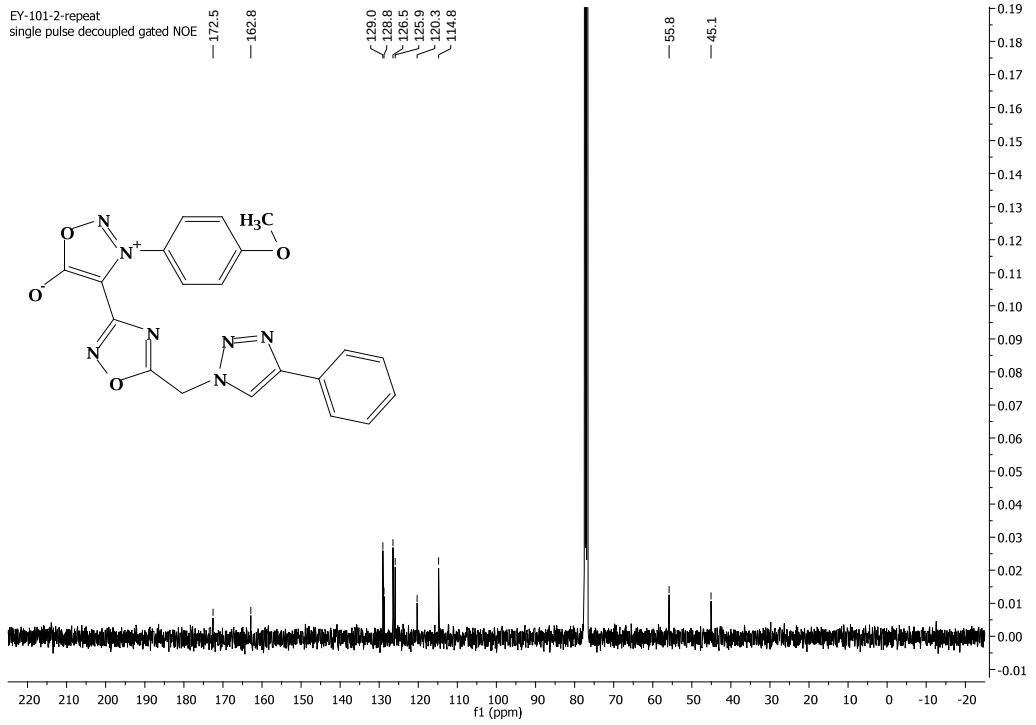


Figure 4.111. The ^{13}C NMR spectrum of **139a** produced from Cu(I) catalyzed azide-alkyne cycloaddition reaction.

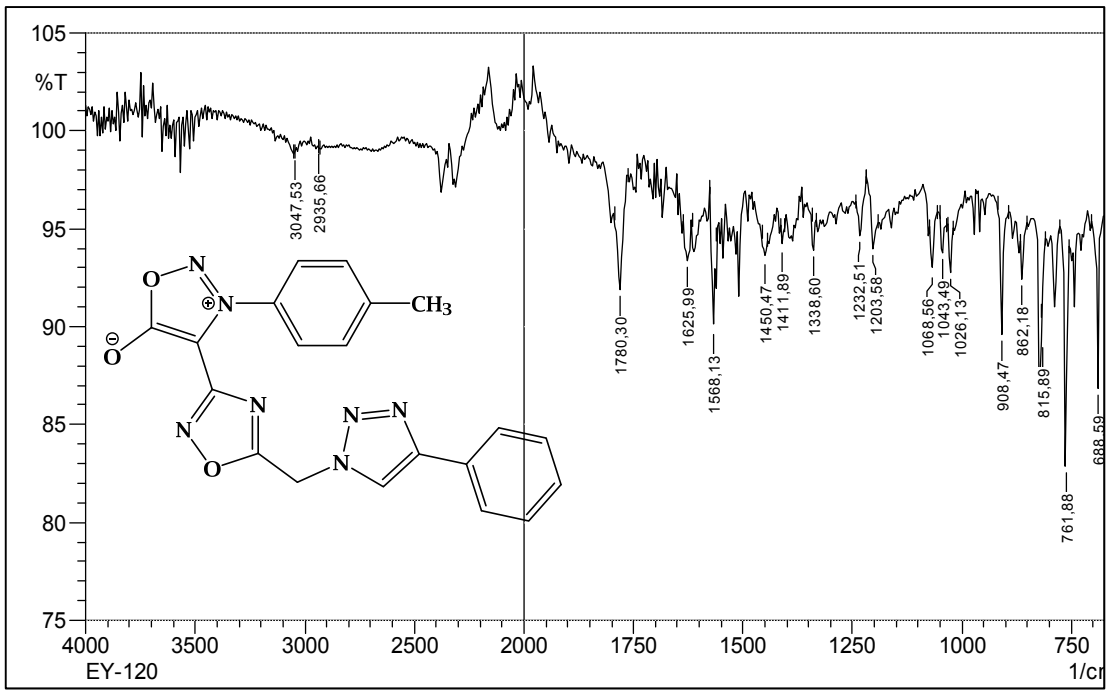


Figure 4.112. The IR spectrum of **139b.**

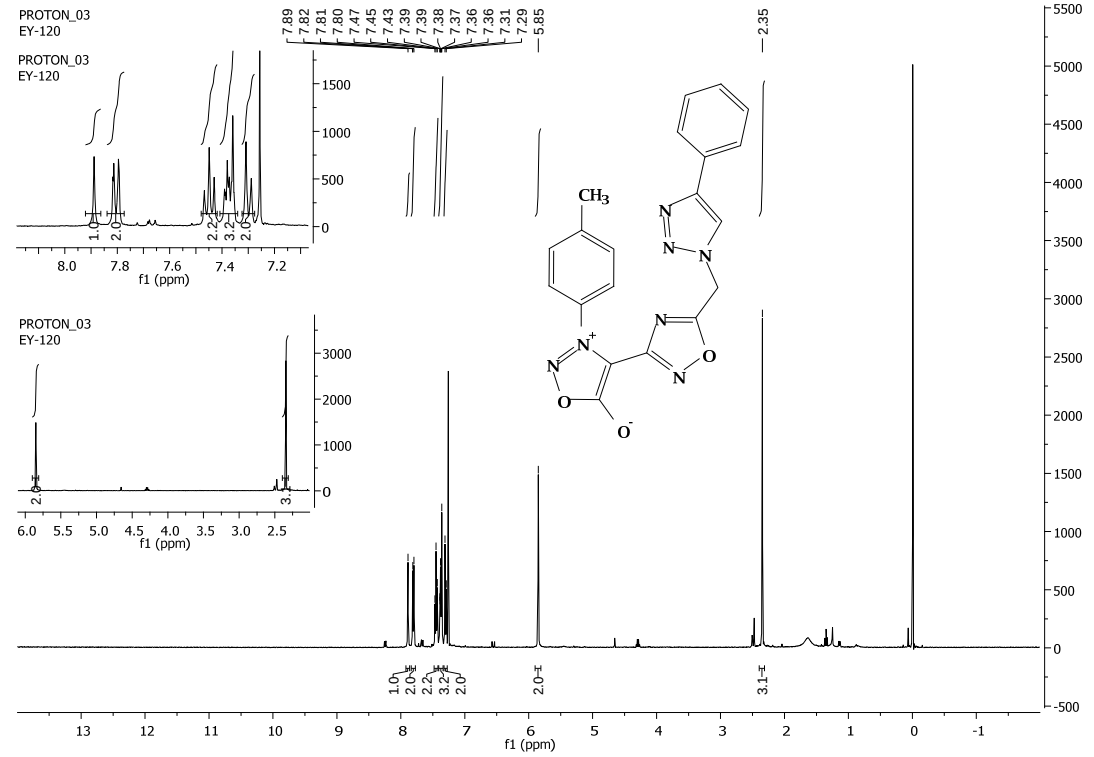


Figure 4.113. The ^{1}H NMR spectrum of **139b.**

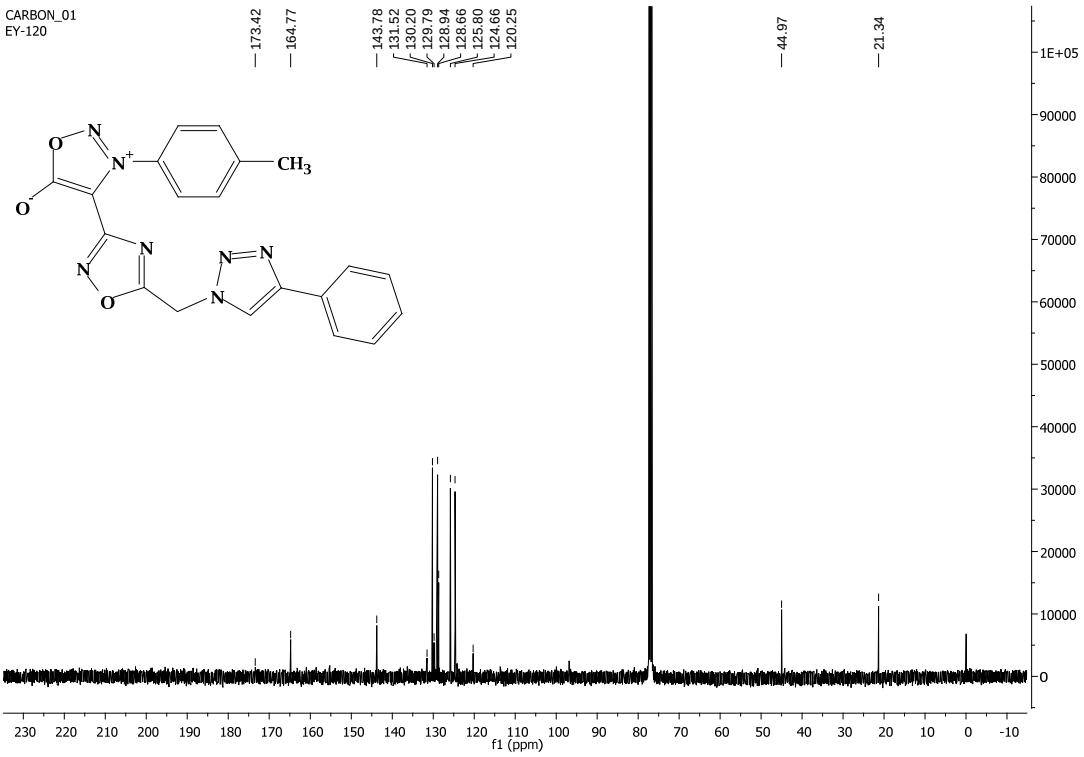
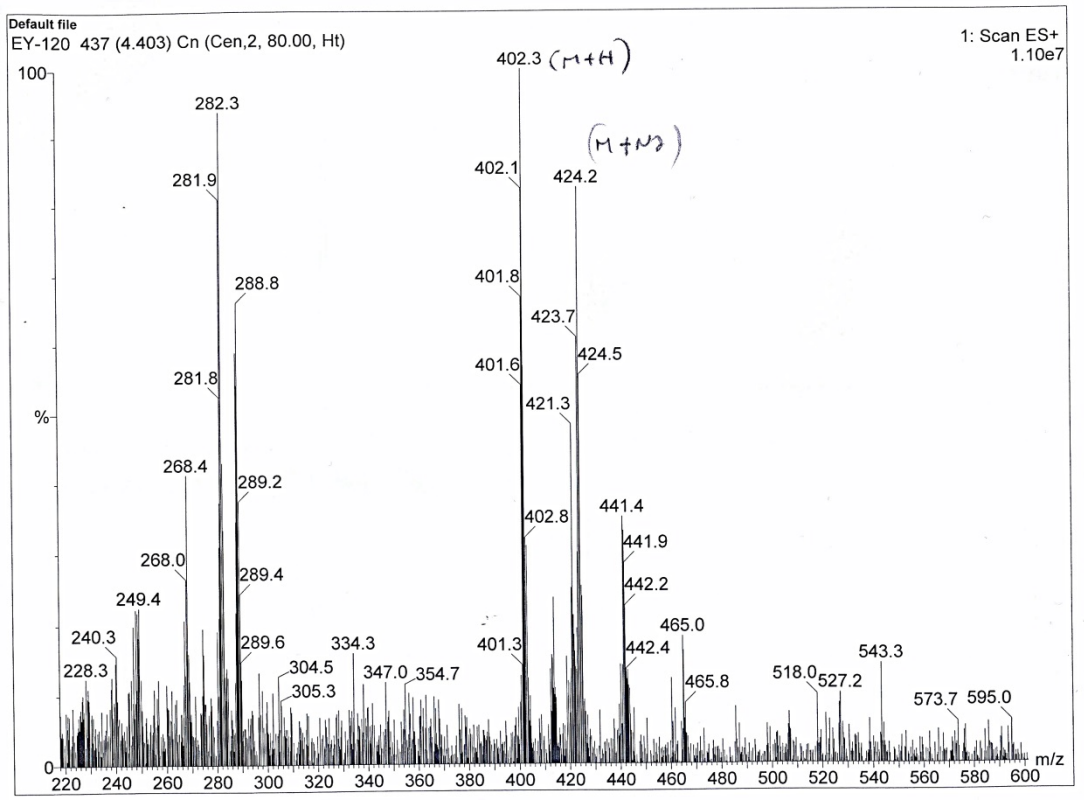


Figure 4.114. The ^{13}C NMR spectrum of **139b.**



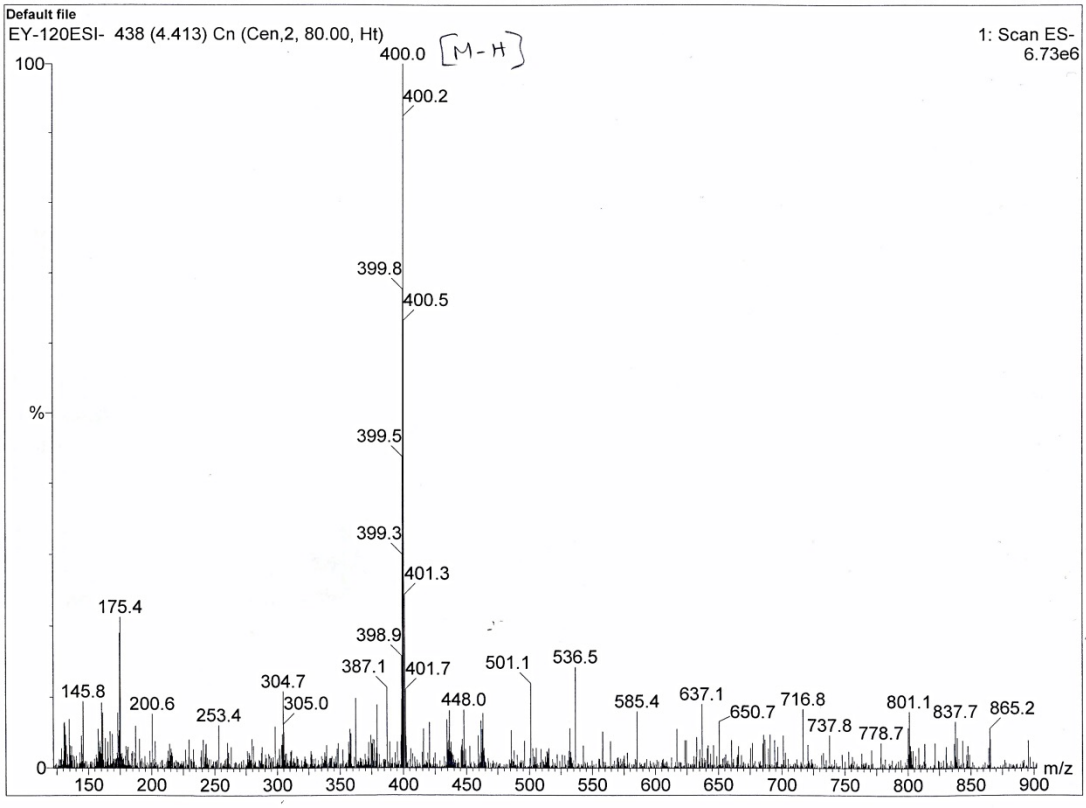


Figure 4.115. The LC-MS spectra of **139b**(ES+ and ES- mode).

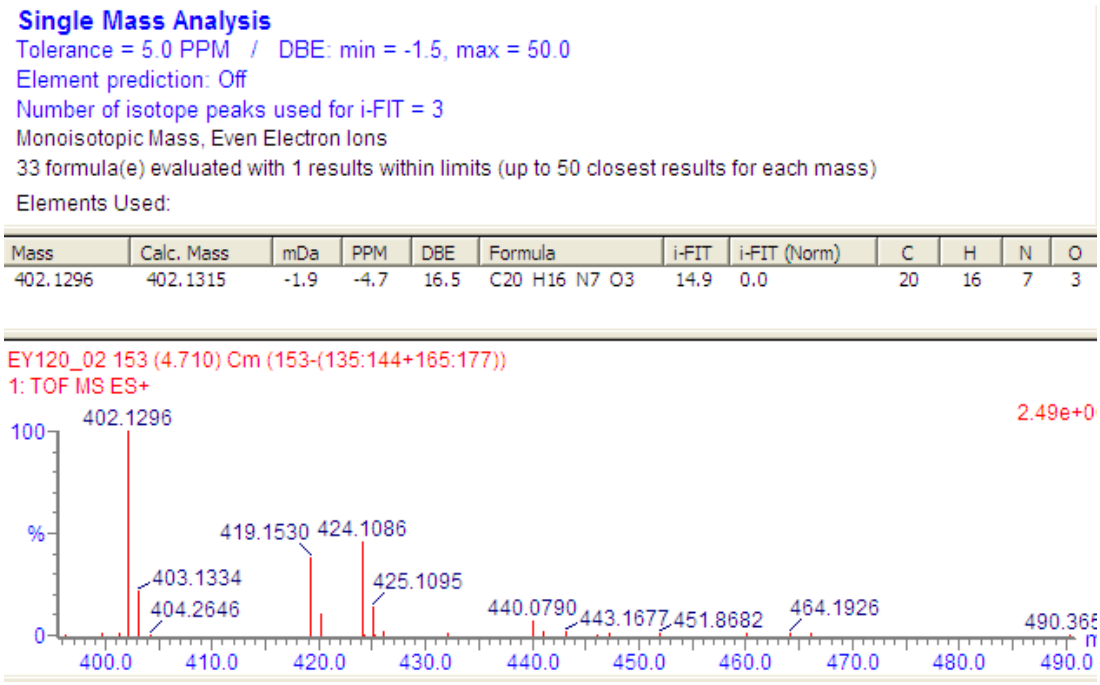


Figure 4.116. The HRMS spectrum of **139b.**

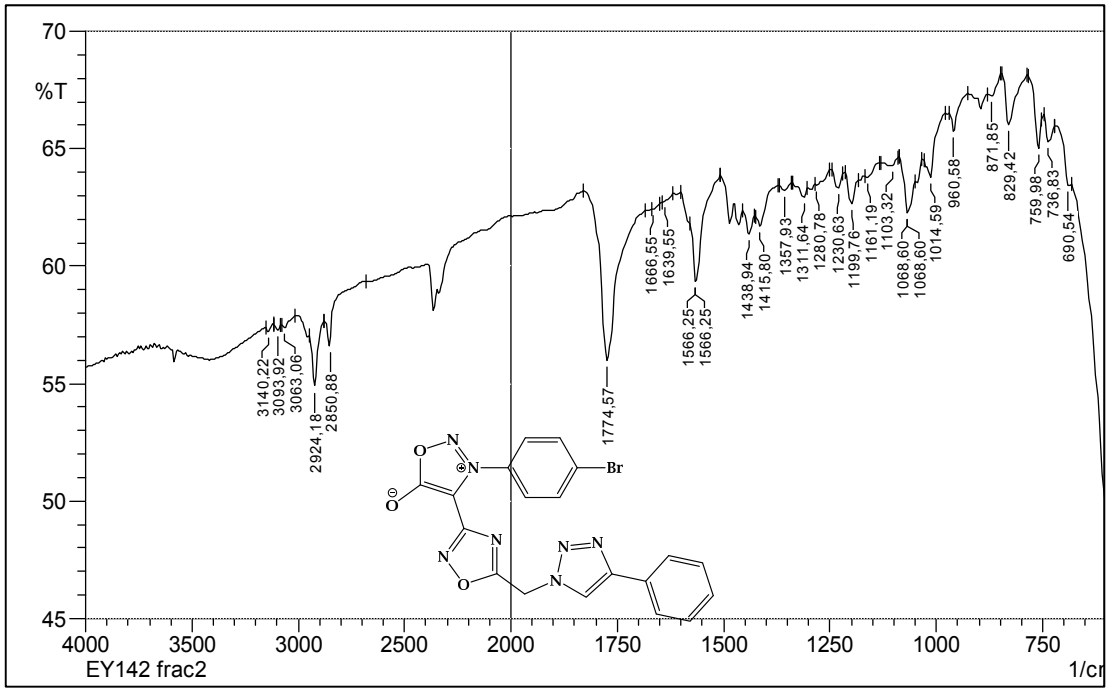


Figure 4.117. The IR spectrum of **139c.**

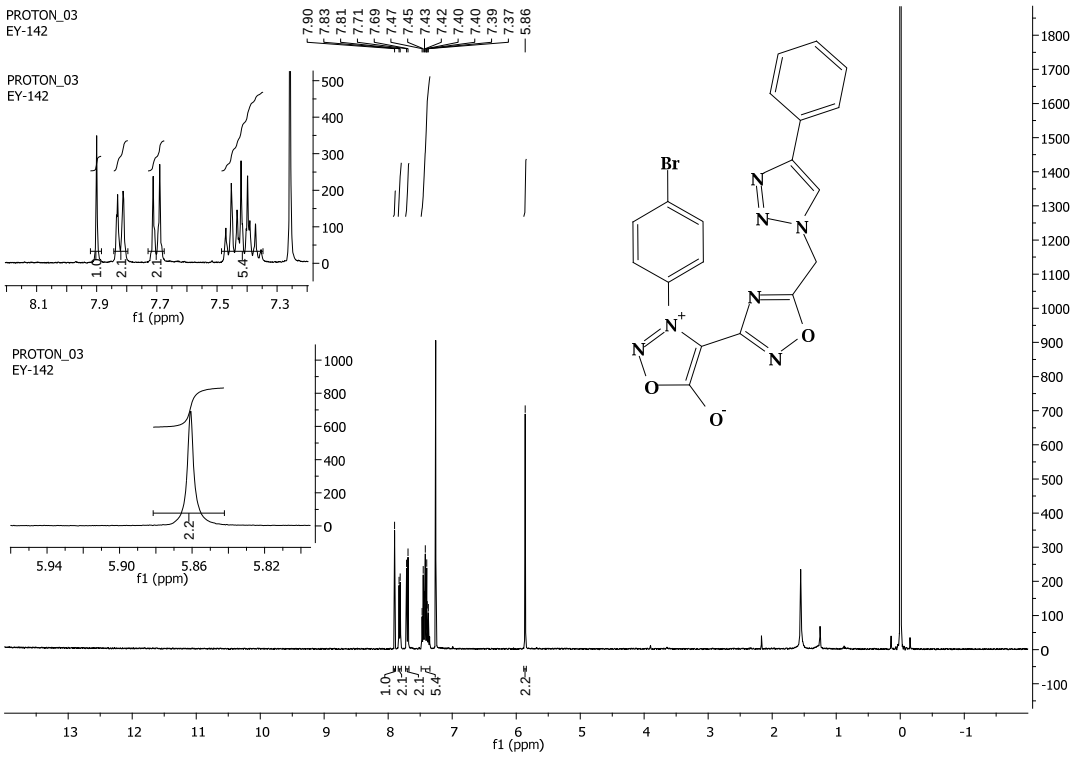


Figure 4.118. The ^{1}H NMR spectrum of **139c.**

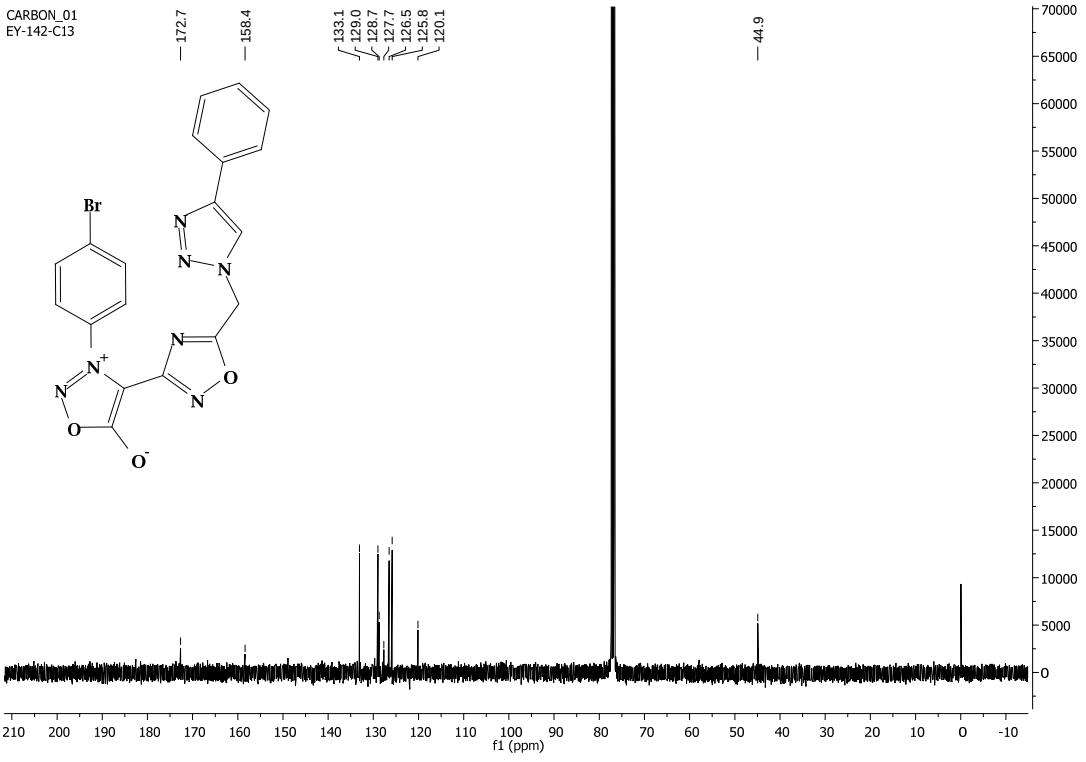


Figure 4.119. The ^{13}C NMR spectrum of **139c.**

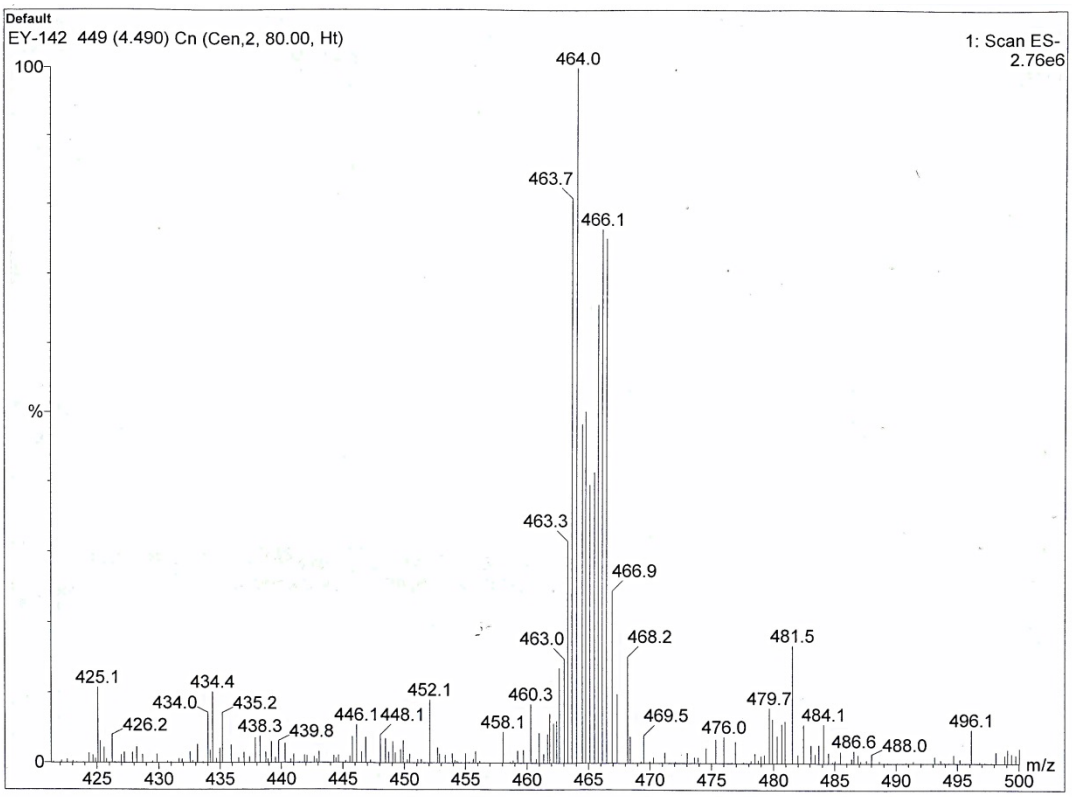


Figure 4.120. The LC-MS spectrum of **139c.**

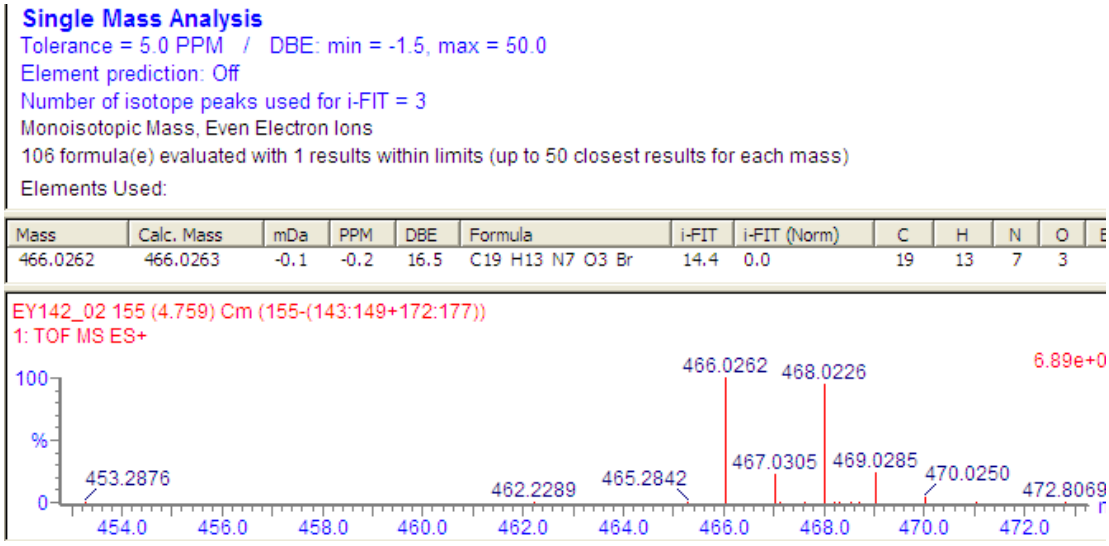


Figure 4.121. The HRMS spectrum of **139c.**

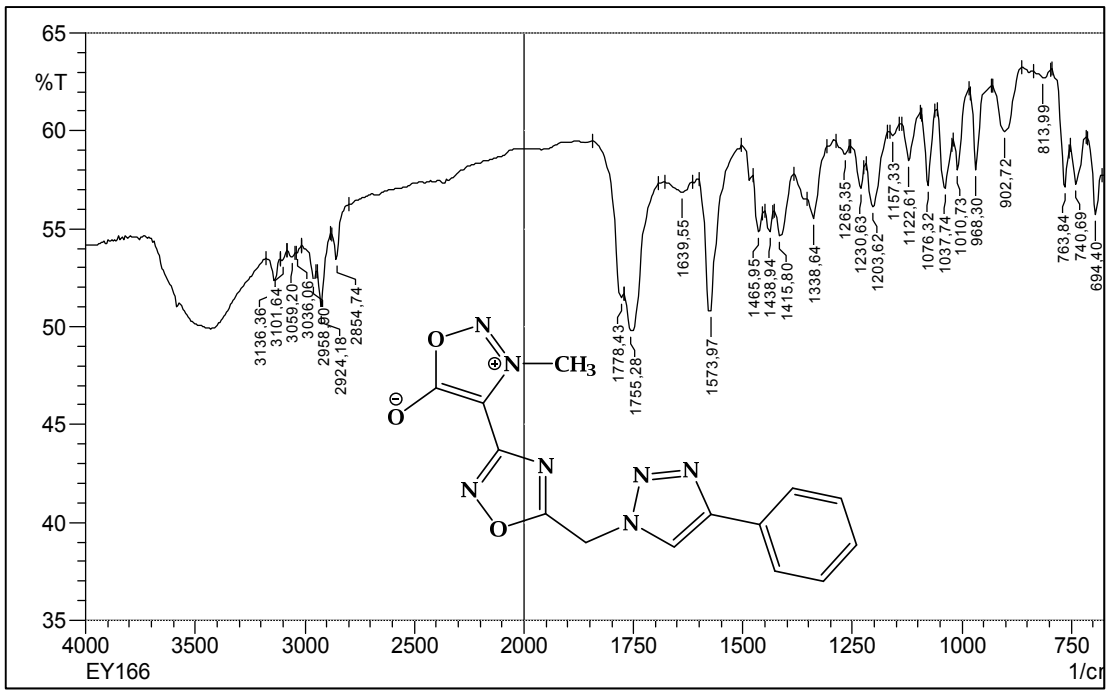


Figure 4.122. The IR spectrum of **139d.**

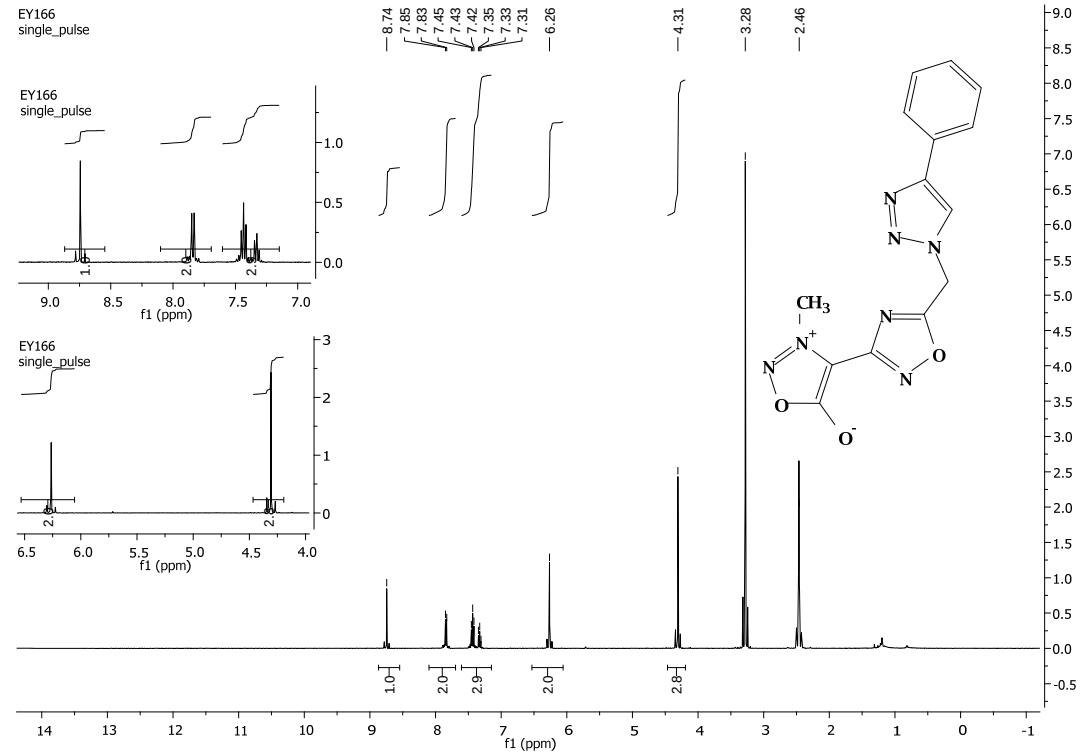


Figure 4.123. The ^{1}H NMR spectrum of **139d.**

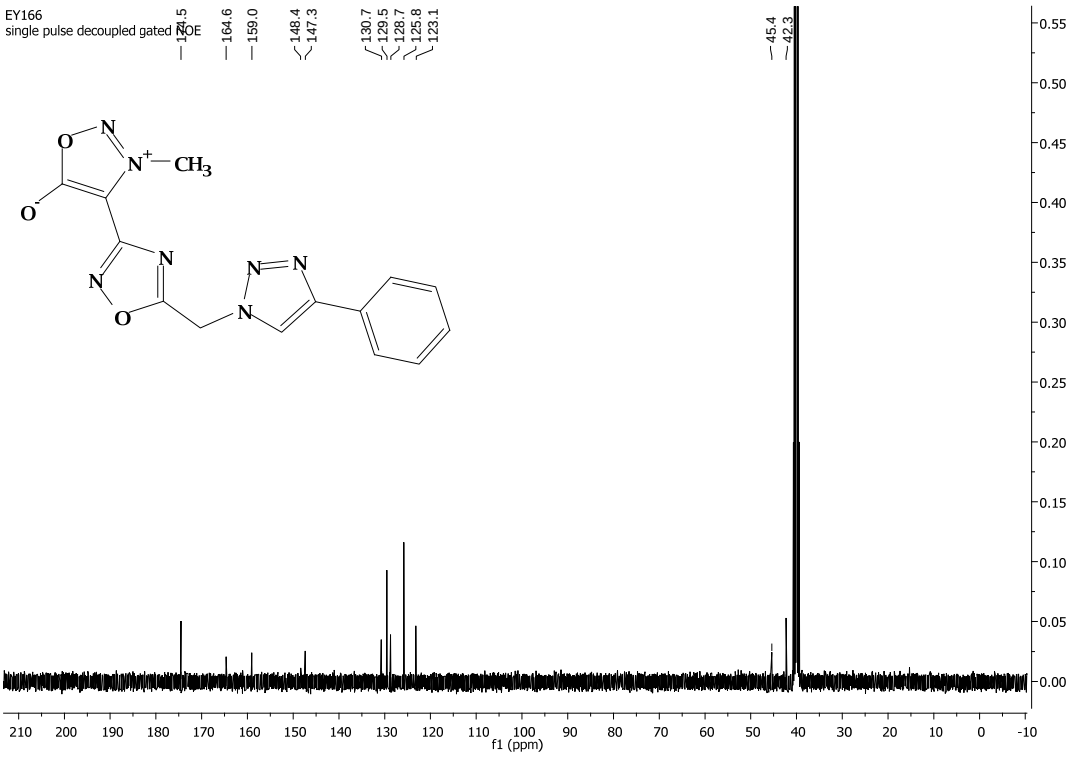


Figure 4.124. The ^{13}C NMR spectrum of **139d.**

Single Mass Analysis
Tolerance = 10.0 PPM / DBE: min = -1.5, max = 50.0
Element prediction: Off
Number of isotope peaks used for i-FIT = 3
Monoisotopic Mass, Even Electron Ions
59 formula(e) evaluated with 1 results within limits (up to 50 best isotopic matches for each mass)
Elements Used:

Mass	Calc. Mass	mDa	PPM	DBE	Formula	i-FIT	i-FIT (Norm)	C	H	N
326.0987	326.1002	-1.5	-4.6	12.5	C14 H12 N7 O3	17.7	0.0	14	12	7

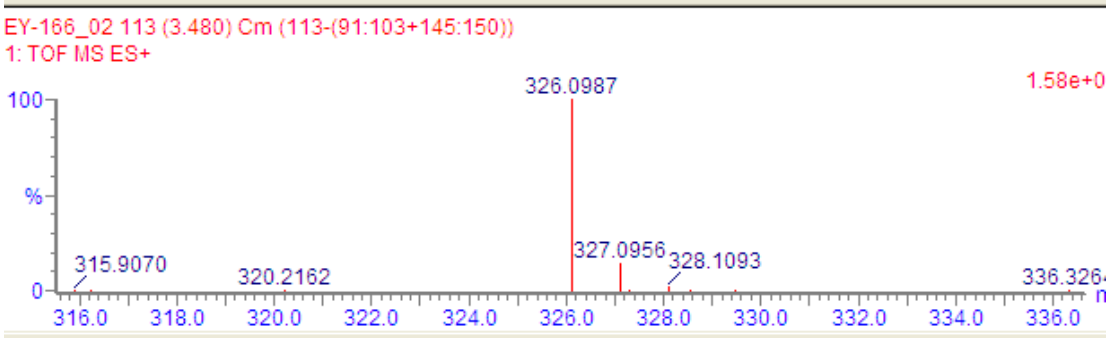


Figure 4.125. The HRMS spectrum of **139d.**