

SYNTHESIS OF NOVEL AZAHETEROCYCLES
BY 1,3-DIPOLAR CYCLOADDITION REACTION OF
NITRILE OXIDES

by

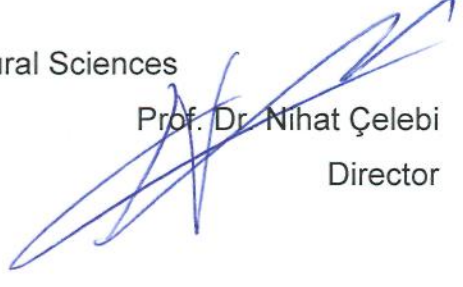
CEVHER ALTUĞ

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Approval of the Graduate School of Natural Sciences

Prof. Dr. Nihat Çelebi
Director



I certify that this thesis satisfies all the requirements as a thesis for the degree of Doctor of Philosophy.

Prof. Dr. Çetin Bozkurt
Head of Chemistry 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 Doctor of Philosophy.

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ABSTRACT

SYNTHESIS OF NOVEL AZAHETEROCYCLES BY 1,3-DIPOLAR CYCLOADDITION REACTION OF NITRILE OXIDES

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1,3-Dipolar cycloaddition reactions are among the most powerful and direct approaches for the synthesis of five membered organic molecules. During the past several decades, nitrile oxides are becoming increasingly important in providing intermediates for the synthesis of complex molecules, including natural products and bioactive compounds. Syntheses of novel azaheterocycles are the focus of this dissertation through 1,3-dipolar cycloaddition of nitrile oxides. The results and discussion sections of this thesis are divided into four parts:

Part 1 describes an efficient intermolecular 1,3-dipolar cycloaddition of a variety of nitrolic acids which are precursors of nitrile oxides with phenyl- and methyl vinylsulfone. This transformation produces stable 4,5-dihydroisoxazole-containing stereo- and regioselective cycloadducts.

Part 2 is mainly consisted of the investigation of a novel tricyclic oxadiazol-tetrahydropyrrolo-oxadiazole structure *via* a reaction of alkylidene-2-pyrrolidines with nitrolic acids. A plausible mechanism for this reaction is proposed, which suggests nitrosation of the enamine by the nitrous acid that is liberated from the nitrolic acid.

In part 3, a new method in order to synthesize isoxazole is improved by the reactions of alkylidenepyrrolidines with a range of α -chlorooximes; this reaction proceeds through, instead of 1,3-dipolar cycloaddition, the electrophilic addition of α -chlorooximes to alkylidenepyrrolidine then followed by ring isomerisation to give 3,4,5-trisubstituted isoxazoles.

Part 4 of this thesis is involved in the reaction of nitrile oxides generated *in situ* from α -chlorooximes, which underwent regio- and stereoselective cycloaddition with achiral and chiral phenylsulfonyl substituted alkylidene-2-pyrrolidines leading to novel heterocycles bearing bicyclic ring systems.

Key words: 1,3-dipolar cycloaddition, dipolarophile, dipole, nitrile oxide, nitrolic acid, alkylidene-2-pyrrolidine, α -chlorooxime

ÖZET

NİTRİL OKSİTLERİN 1,3-DİPOLAR HALKA KATILMA TEPKİMELERİ İLE YENİ AZAHETEROHALKALARIN SENTEZİ

Altuğ, Cevher

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Beş üyeli azaheterohalkalı organik moleküllerin sentezlenmesinde en önemli yöntemlerden biri de 1,3-dipolar halka katılma tepkimeleridir. Son yıllarda, nitril oksitlerin ara ürün olarak kullanımı doğal ve biyoaktif bileşikler gibi pek çok karmaşık molekülün sentezlenmesinde artan bir öneme sahiptir. Bu çalışmanın amacı nitril oksitlerin 1,3-dipolar halka katılma tepkimesi ile yeni aza-heterohalkalı bileşiklerin sentezi ve yapılarının aydınlatılmasıdır. Bu tezin sonuç ve tartışma kısımları dört bölümden oluşmaktadır.

Birinci kısım çeşitli nitril oksit öncülü olan nitrolik asitlerle fenil veya metil vinil sülfon molekülleri arasında etkin 1,3-dipolar halka katılma tepkimelerini tanımlamaktadır. Bu halka katılma dönüşümü sonucunda kararlı stereo- ve yerseçimli 4,5-dihidro izoksazol bileşikleri elde edilmiştir.

İkinci kısım, esas olarak alkiliden-2-pirrolidinle nitrolik asitlerin tepkimesi sonucunda oluşan yeni üç halkalı oksadiazol-tetrahidropirrol-oksadiazollerini içeren moleküllerin incelenmesinden oluşmaktadır. Bu tepkime için mantıklı bir mekanizma önerilmiştir. Bu mekanizma nitrolik asitin ısıtılması ile açığa çıkan nitroz asitin alkiliden pirrolidin tarafından tutulması esasına dayanır.

Üçüncü kısımda, isoksazollerin sentezi için yeni bir yöntem geliştirilmiştir. Bu yöntem, alkiliden-2-pirrolidin ile α -klorooksimlerin tepkimesi sonucu, 1,3-dipolar halka katılması yerine, alkilidenpirrolidine α -klorooksimin elektrofilik katılması, sonrasında da halka izomerleşmesi takip etmektedir.

Dördüncü kısımda, tepkime ortamında α -klorooksimlerden üretilen nitril oksitlerin akiral ve kiral fenilsülfonil sübstitue alkiliden pirrolidinlerle stereo ve yerseçimli tepkimesi sonucunda oluşan iki halkalı sistemler anlatılmıştır.

Anahtar kelimeler: 1,3-dipolar halka katılma, dipolarofil, dipol, nitril oksit, nitrolik asit, alkiliden-2-pirrolidin.

to my wife

ACKNOWLEDGEMENTS

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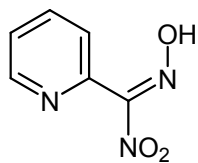
I am indebted to Dr Mark C. Elliott for his support and guidance during the course of my work in Cardiff University and also thanks to Dr. F. R. Fronzcek (Louisiana State University, LA, USA) for X-Ray Diffraction data.

I would also like to sincerely thank my coworkers throughout the years in Chemistry Dep. of AIBU. Specifically, I would like to thank Akın, Muhammet, Hamza, Elif Berna, Dilek.

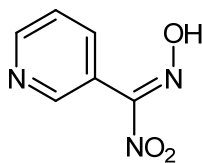
I would like to thank my parents, for their unconditional love and support throughout my entire education. Everything I have accomplished has been derived from the values they taught me.

Finally, I would like to thank my wife, Merve. The sacrifices she has made for me are more than I could ever ask for. I will always be grateful for the support and encouragement she has given me.

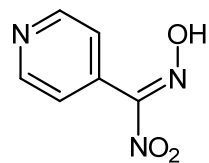
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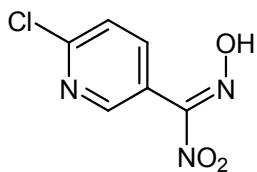
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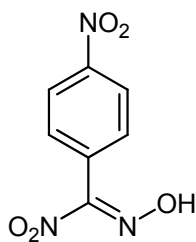
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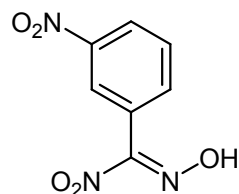
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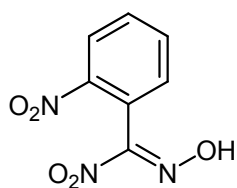
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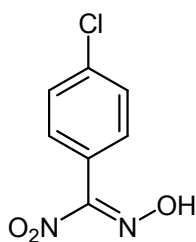
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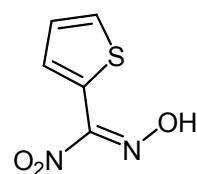
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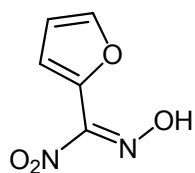
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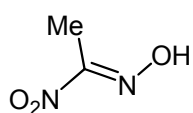
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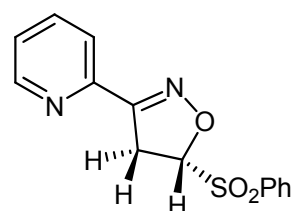
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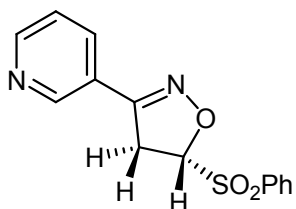
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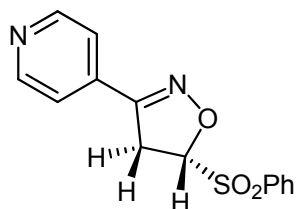
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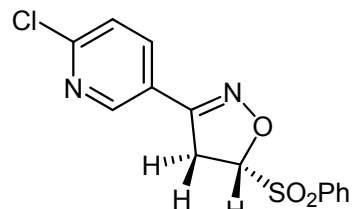
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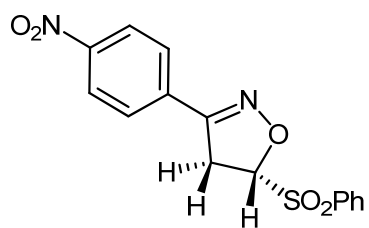
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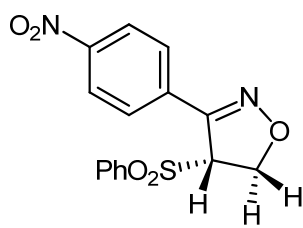
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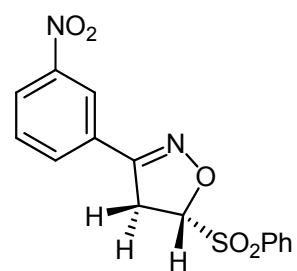
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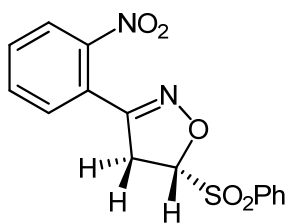
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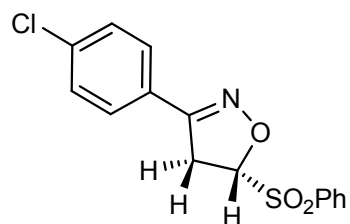
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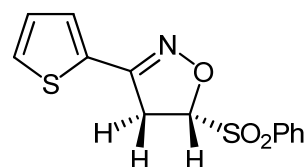
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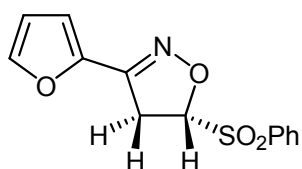
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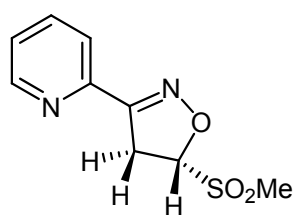
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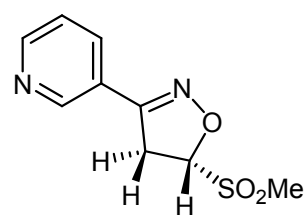
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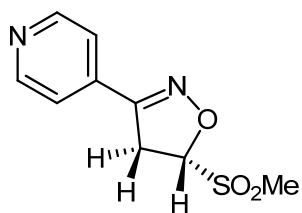
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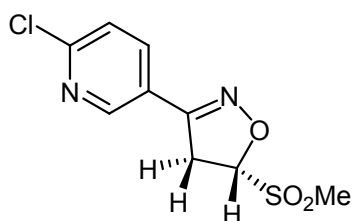
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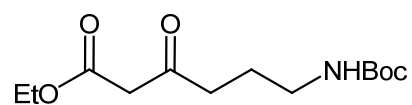
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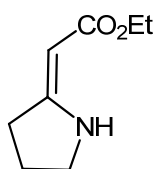
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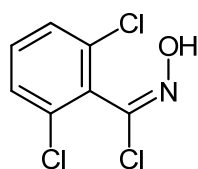
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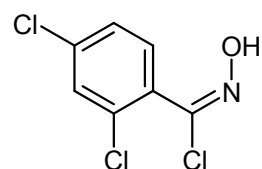
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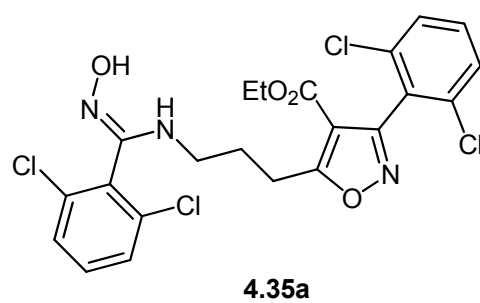
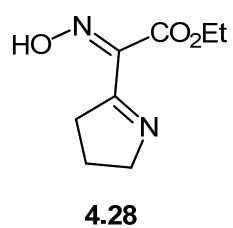
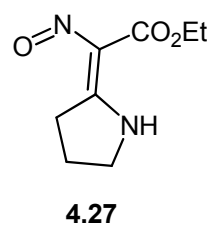
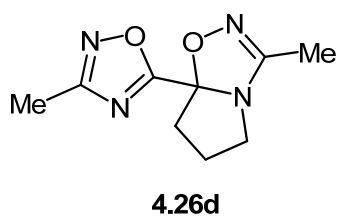
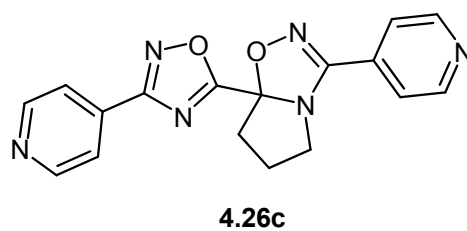
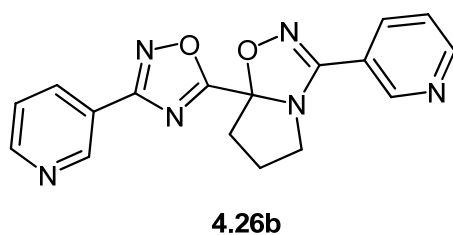
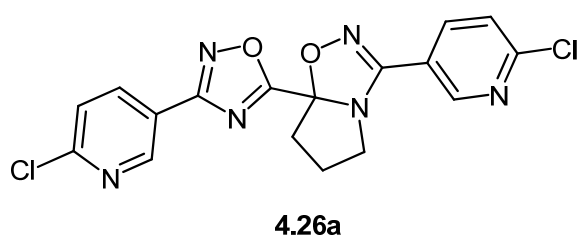
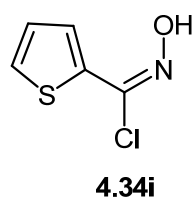
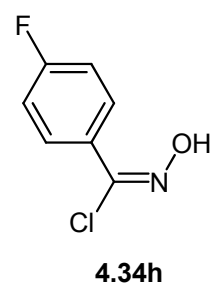
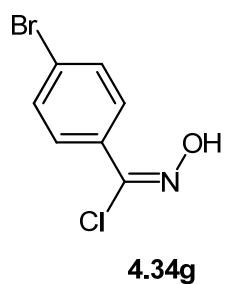
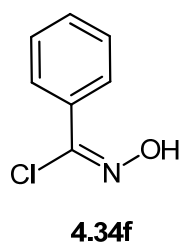
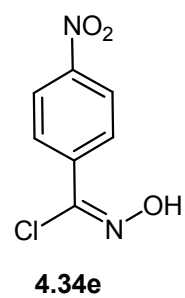
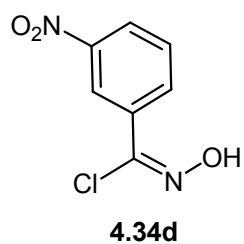
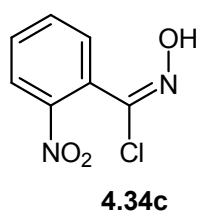
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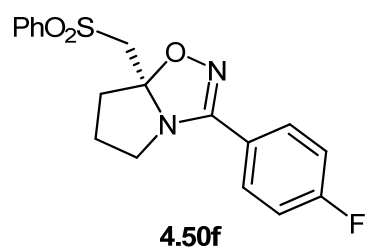
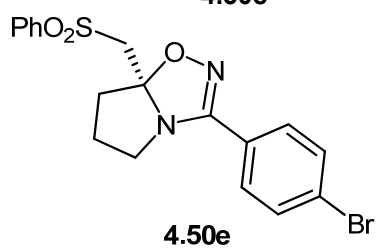
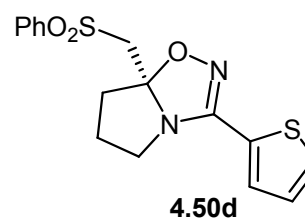
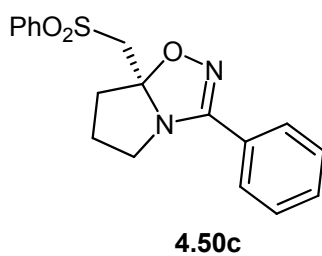
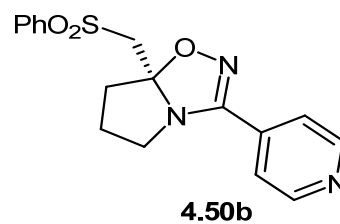
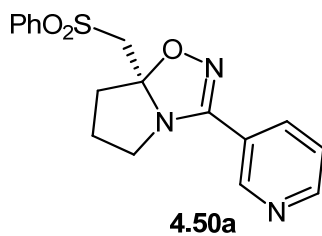
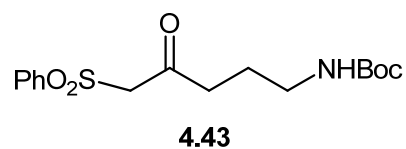
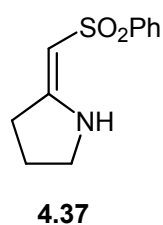
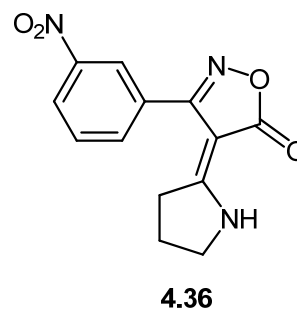
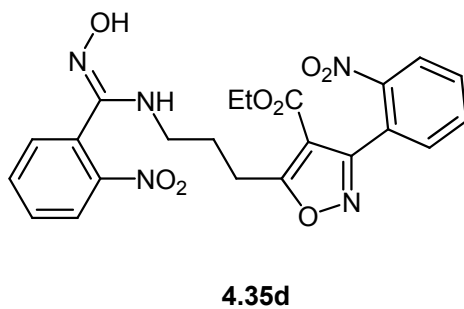
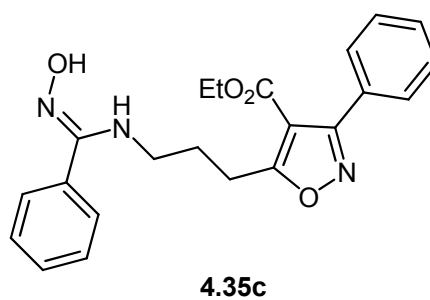
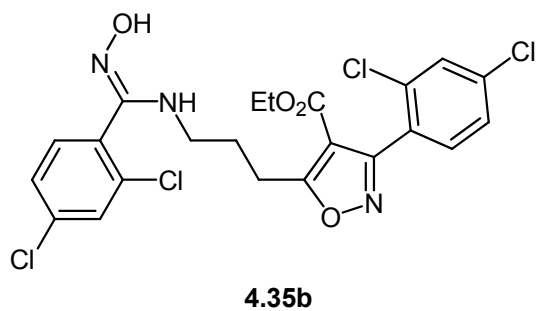


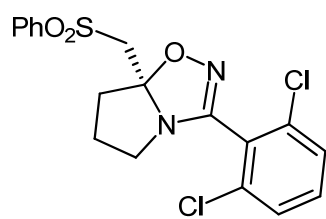
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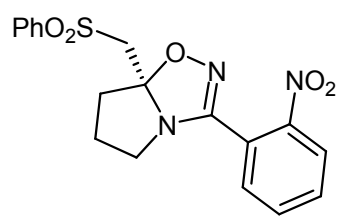
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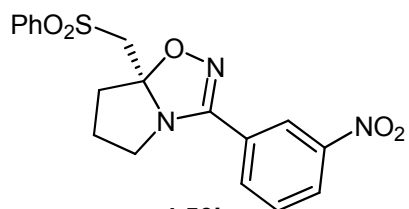




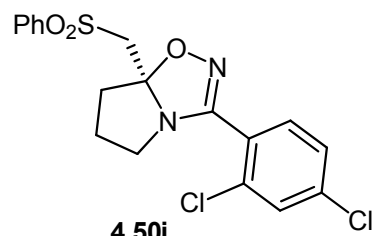
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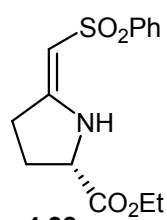
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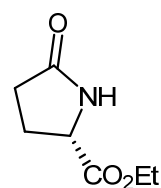
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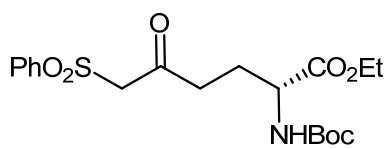
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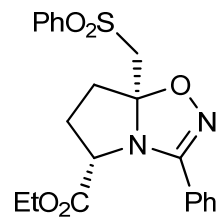
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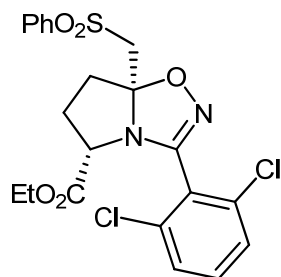
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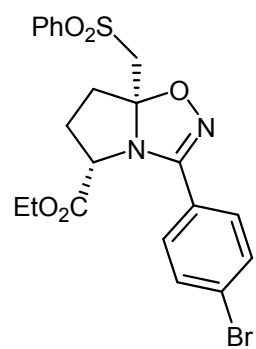
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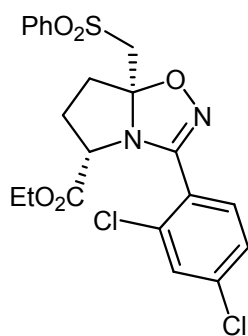
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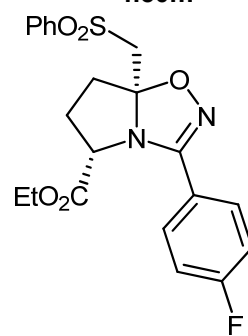
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4.50o

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ABBREVIATIONS

AcOH	Acetic acid
AP ⁺	Atmospheric pressure ionization
ArC	Aromatic carbon
ArCH	Aromatic methine
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
b.p.	Boiling point
bs	Broad singlet (NMR)
CDCl ₃	Deuterated chloroform
CHCl ₃	Chloroform
CI+ve	Chemical ionization (positive ion mode)
Chloramine-T	(<i>N</i> -chloro- <i>N</i> -sodio-4-methylbenzene sulfonamide
COSY	Correlation spectroscopy
d	Doublet (NMR)
δ	Chemical shift (NMR)
[1,3]-DC	[1,3]-Dipolar cycloaddition
DCM	Dichloromethane
dd	Doublet of doublets (NMR)
ddd	Doublet of doublet of doublets (NMR)
ddt	Doublet of doublet of triplets (NMR)
de	Diastereomeric excess
DEPT	Distortionless enhancement by polarization transfer
dm	Doublet of multiplets

DMAP	4-Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
DMSO	Dimethylsulfoxide
dq	Doublet of quartets (NMR)
dr	Diastereomer regioselectivity
dt	Doublet of triplets (NMR)
EI	Electron impact
eq.	Molar equivalents
ESI ⁺	Electrospray ionisation (positive)
ESI ⁻	Electrospray ionisation (negative)
Et ₂ O	Diethylether
EtOAc	Ethyl acetate
EtOH	Ethanol
FMO	Frontier molecular orbital
HMBC	Heteronuclear multiple bond correlation
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
<i>i</i>	<i>ipso</i>
IR	Infrared spectroscopy
<i>J</i>	Coupling constant (NMR)
LDA	Lithium diisopropylamide
lit.	Literature
m	Multiplet (NMR)
<i>m</i> -CBA	<i>meta</i> -Chlorobenzoic acid

MeCN	Acetonitrile
min	Minutes
m.p.	Melting point
MS	Mass spectrometry
Mtl	Metal
<i>n</i> -BuLi	<i>n</i> -Butyl lithium
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser enhancement spectroscopy
PE	Petroleum ether (b.p. 40-60°C)
Ph	Phenyl
ppm	Parts per million (NMR)
q	Quartet (NMR)
<i>R_f</i>	Retardation Factor
RT	Room temperature
s	Singlet (NMR)
t	Triplet (NMR)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
TOF	Time of Flight Instrument
tt	Triplet of triplets (NMR)

CHAPTER 1

1. INTRODUCTION TO 1,3-DIPOLAR CYCLOADDITION

Cycloadditions are of high practical use in the synthesis of heterocycles, due to their complete atom economy and high functional group compatibility [1,2]. 1,3-Dipolar cycloaddition reaction is a reaction in which two or more unsaturated molecules (or parts of the same molecule) combine with the formation of a cyclic adduct in which there is a net reduction of the bond multiplicity. (Figure 1.1).

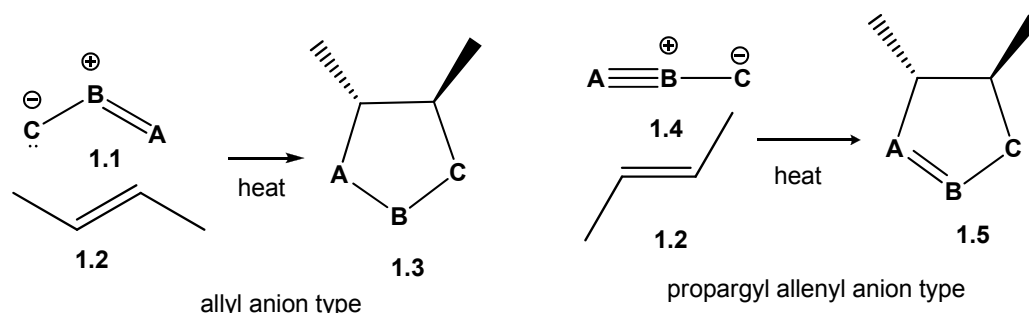


Figure 1. 1 Cycloaddition to 1,3-dipoles

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

The 1,3-dipoles consist of elements from main groups IV, V, and VI. The parent 1,3-dipoles includes mainly from the second row and the central atom of the dipole is limited to N or O and bears a positive and a negative charge distributed over three atoms and has 4π electrons. Thus, a limited number of structures can be formed by permutations of

N, C, and O. If higher row elements are excluded twelve allyl anion type and six allenyl anion type 1,3-dipoles (dipoles) can be obtained [3].

Since there is a considerable variety of dipoles Figure 1.2 shows small selection, but other types of dipoles also exist [2]. Dipoles divided into two groups, the allyl anion type which has a bent structure and the propargyl/allenyl anion type with a linear structure as shown in below.

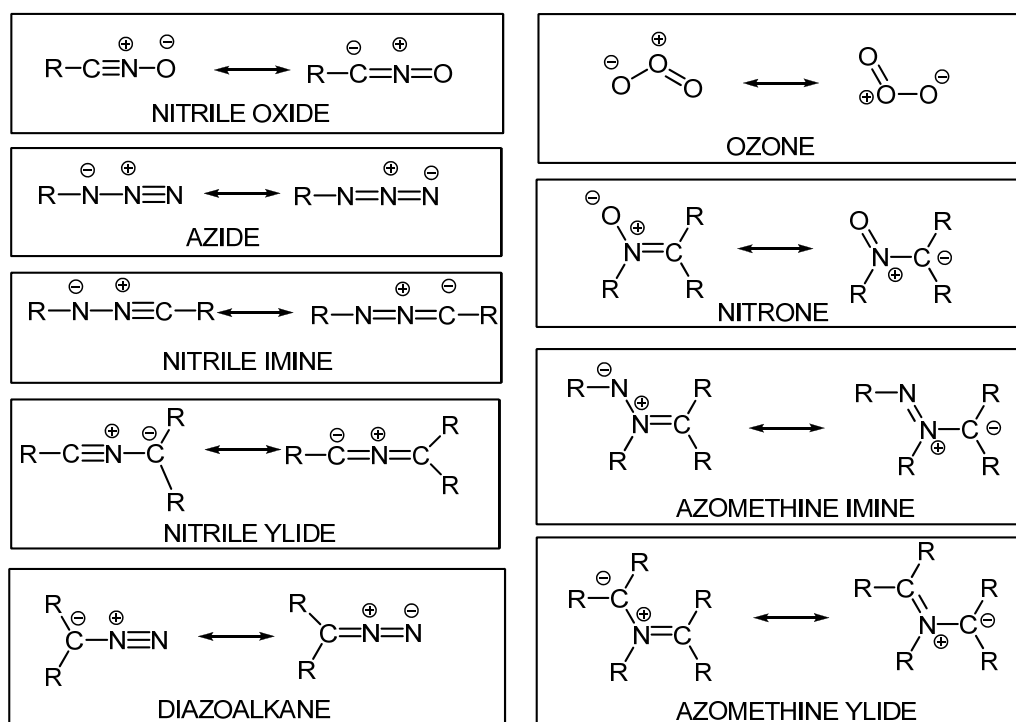


Figure 1. 2 Right column is propargyl/allenyl anion type dipoles and left column is allyl anion type dipoles

Dipoles vary in stability greatly. Some can be isolated and stored, others are relatively stable, but are usually made the same day as their use. Others are so unstable that are generated and reacted *in situ*. Nitrile imines and most of nitrile oxides and can be given an example for *in situ* type of dipoles.

The dipolarophile in a 1,3-dipolar cycloaddition is a reactive alkene moiety containing 2π electrons. It is possible to group dipolarophiles into three broad classes, electron-rich, electron-deficient, and conjugated dipolarophiles. Thus, depending on which dipole that is present, α,β -unsaturated aldehydes, ketones, esters, allylic alcohols, allylic halides, vinylic ethers and alkynes are examples of dipolarophiles that react readily (Figure 1.3). It must be noted, however, that other 2π -moieties such as carbonyls and imines also can undergo cycloaddition with dipoles [9].

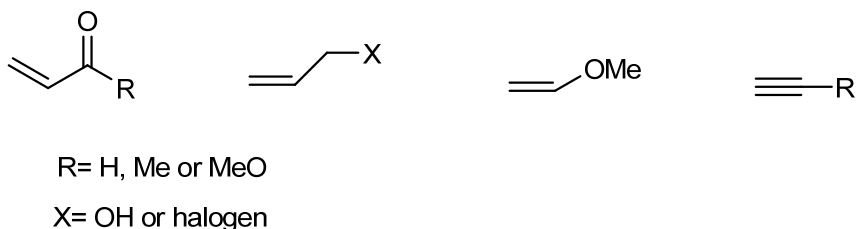
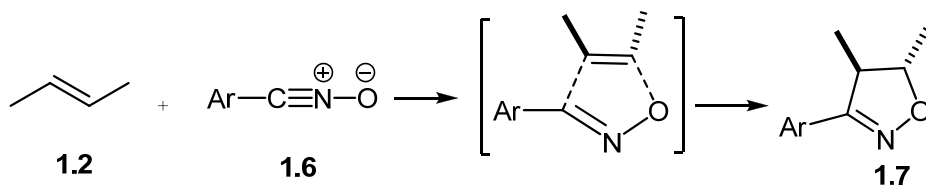


Figure 1. 3 Examples for dipolarophiles

1.2. Reaction Mechanism in 1,3-Dipolar Cycloaddition Reactions

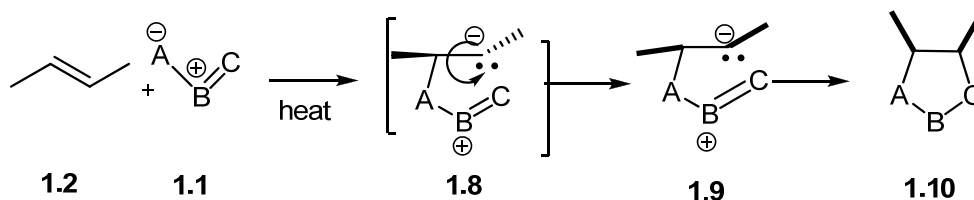
Since the 1960s, the regio- and stereochemistry as well as the overall mechanism of 1,3-dipolar cycloaddition reactions have intrigued organic chemists. The 1,3-dipolar cycloaddition reaction of a 1,3-dipole with a dipolarophile involves the 4π electrons of the dipole/ylide and the 2π electrons of the dipolarophile. The reaction mostly proceeds in a concerted manner, which means that all bonds are created simultaneously, but not necessarily to the same extent at a certain time. Consequently, the stereochemistry of the dipolarophile is conserved in the final product. This is exemplified in Scheme 1.1 where *trans*-2-butene

1.2 reacts with the hypothetical dipole **1.6** furnishing exclusively *trans*-product **1.7**. Starting from the *cis*-2-butene will thus yield the *cis* product [4].



Scheme 1. 1 1,3-Dipolar cycloaddition

If, on the other hand, the reaction proceeds *via* stepwise mechanism, the stereochemistry of the starting dipolarophile is not necessarily conserved throughout the whole reaction. This can be seen in Scheme 1.2, where *trans*-2-butene **1.2** reacts with the dipole **1.1** in a two step fashion furnishing the diastereomer *cis*-product **1.10** *via* isomerisation of the starting dipolarophile.



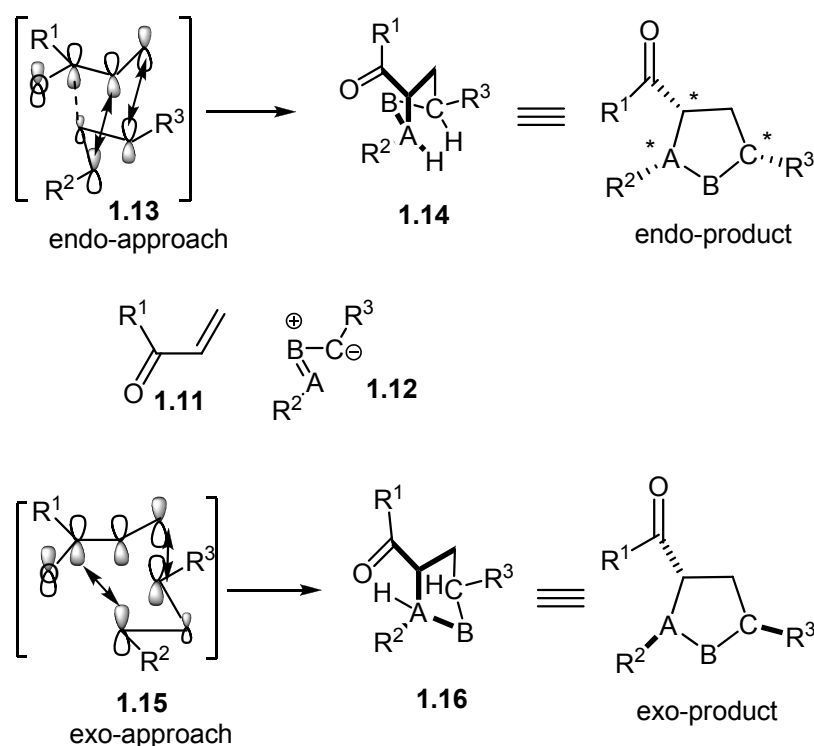
Scheme 1. 2 Isomerization of starting dipolarophiles

Several theoretical models have been advanced in recent years to rationalize the observed regio- and stereoselectivity of the 1,3-dipolar cycloadditions [5].

The way the substituents affect the rate of the reaction can be rationalised with the aid of the *Frontier Molecular Orbital (FMO) theory*. The FMO theory was developed during a study of the role of orbital symmetry in pericyclic reactions by Woodward and Hoffmann [6] and, independently, by Fukui [7]. The HOMO-LUMO values for dipolar

compounds and their orbital coefficients at the terminal atoms contributed significantly by Houk [8,9]. Depending on the nature of the dipole and the dipolarophile, orbital energy separation of the interactions [HOMO(1,3-dipole)/LUMO(dipolarophile) and LUMO(1,3-dipole)/HOMO(dipolarophile)] are compared. When these energy differences exhibit different values, the FMO interaction corresponding to the lower value is presumed to play the dominant role [10].

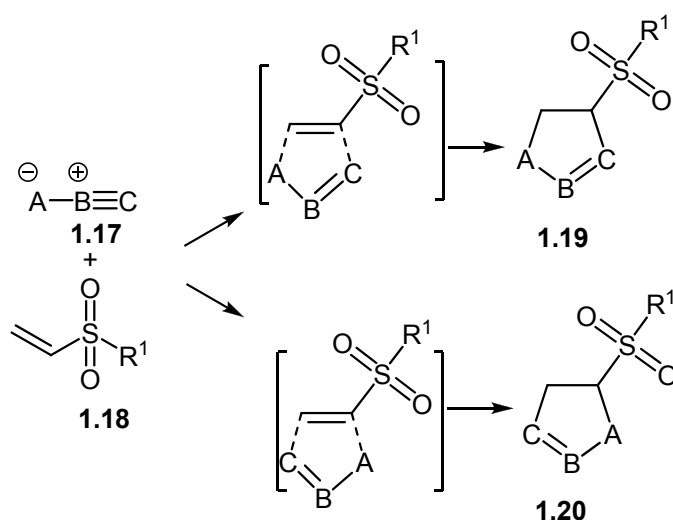
In the 1,3-dipolar cycloaddition reactions of especially allyl anion type 1,3-dipoles with alkenes the formation of diastereomers can occur in an *endo* or *exo* mode. The *endo* approach is electronically and *exo* approach is sterically favoured.



Scheme 1.3 The *endo/exo* interactions in 1,3-dipolar cycloaddition

Regiochemical orientation is then established by the rule of preferential facing where both the large and small coefficients of the terminal atoms of the 1,3-dipole and dipolarophile are involved. Which interaction is dominant depends on the difference in energies between the relevant pairs of orbital.

Thus, when both the ylide and the dipolarophile are nonsymmetric, regioisomeric adducts can be formed. This is exemplified in Scheme 1.4, where the hypothetical ylide reacts in two different modes with dipolarophile, giving rise to the regioisomeric cycloadducts. Nitrile oxides are examples of nonsymmetric ylides, which upon reaction with nonsymmetric dipolarophiles sometimes furnish two regioisomeric cycloadducts. Depending on electronic factors and the substitution pattern of the ylide and the dipolarophile, both modes of addition of the ylide to the dipolarophile can occur [11-12].



Scheme 1.4 Two alternative approaches of a hypothetical ylide to dipolarophile giving rise to regioisomers.

CHAPTER 2

2. INTRODUCTION AND BACKGROUND OF NITRILE OXIDES AND SYNTHESIS OF ISOXAZOL(IN)ES, OXADIAZOLINES

2.1. Generation of Nitrile Oxides

It is well known that nitrile oxides are useful and versatile building blocks for heterocyclic chemistry from synthetic and biological point of view. Huisgen categorized reactions of nitrile oxides with alkenes as being members of broad class of cycloaddition reactions [1-2].

Nitrile oxides, RNCO , can be named as *fulmido-substituted* parent molecules ($\text{R}=\text{H}$), but usually their names are derived from corresponding nitriles. Specific properties of nitrile oxides depend on the structure of the functional group, which have highly polarized C–N and N–O bonds (Figure 2.1).

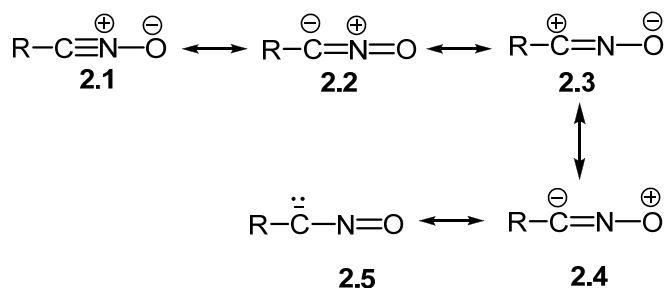


Figure 2. 1 Resonance forms of nitrile oxides

Most nitrile oxides are unstable and readily undergo dimerization to give the corresponding oxadiazole N-oxides which are called furoxans, isomerization to isocyanates, dimerizations to 1,2,4-oxadiazole 4-oxides

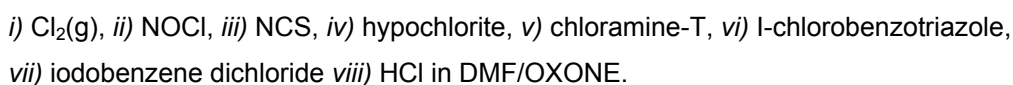
Chemical structures illustrating the resonance and tautomeric forms of diazo compounds and their derivatives:

- furoxans**: Rc1cc(R)[n+]([O-])oc1=O
- 1,2,4 oxadiazole 4-oxides**: Rc1cc(R)[n+]([O-])oc1=O
- 1,4,2,5-dioxadiazines**: Rc1cc(R)[n+]([O-])oc1=O
- isocyanates**: R-N=C=O

The central structure is a diazo compound: R-C#N+=[O-]. Arrows indicate resonance and tautomeric relationships between these structures.

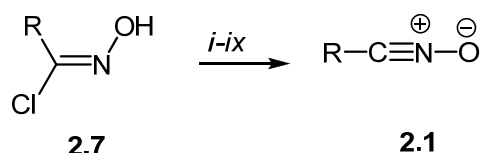
There are various methods for the formation of nitrile oxides which are dehydrohalogenation of hydroximoyl chlorides, dehydration of nitroalkanes, oxidation of aldoximes and thermolysis of furoxans. In this study, dehydrohalogenation of hydroximoyl chlorides and oxidation of aldoximes to produce nitrolic acids will be explained in details.

The most widely used nitrile oxide generation is in chlorination of aldoxime by using different chlorinating agents [13-18] (Scheme 2.1).



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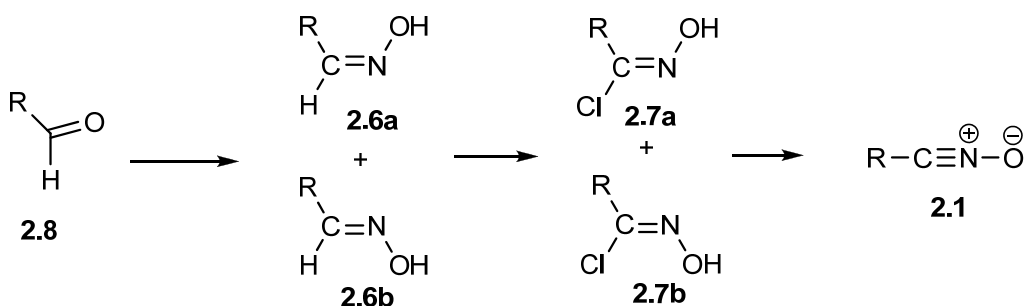
The transformation of aldoximes to nitrile oxides is essentially a dehydrogenation process. The process is carried out mainly as halogenation-dehydrohalogenation. There are numerous substances have been used for dehydrohalogenation process (Scheme 2.2) [19-27].



i) Et₃N, ii) Al₂O₃ iii) Florisil, iv) molecular sieves, v) hexabutylditin, vi) bis(tributyltin) oxide, vii) tetraphenyltin viii) tributyltin hydride, ix) alkali metal fluorides

Scheme 2. 2 Different routes to synthesis of nitrile oxides

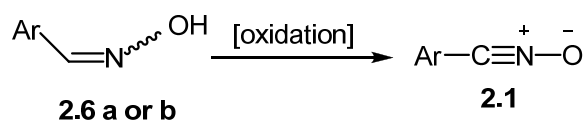
Hegarty et.al demonstrated that the critical dependence of the stability of hydroximoyl chlorides on oxime configuration; the loss of Cl⁻ from the *Z*-isomer **2.7b** occurs *ca.* 10⁷ times more rapidly than from the *E*-isomer **2.7a**. This has been attributed to the stereo-electronic effect of the anti-periplanar arrangement of the lone pair on the adjacent imino nitrogen and the leaving group in the reactive isomer **2.1** (Scheme 2.3) [26,27].



Scheme 2. 3 Stability of *E* and *Z* form of hydroximoyl chlorides

Additionally, one-pot synthesis of nitrile oxides by oxidation of oximes is succeeded by using dimethyldioxirane, ceric ammonium nitrate, and

hypervalent iodine compounds, such as iodobenzene dichloride, iodosylbenzene and diacetoxy iodobenzene were used as oxidants. Manganese (IV) oxide was also found to oxidize aldoximes to nitrile oxides, the best results being obtained with hydroximinoacetates as nitrile oxide precursors [28].

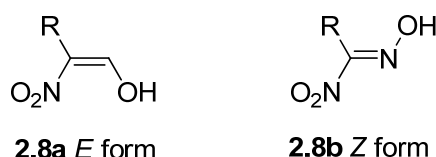


Scheme 2. 4 Oxidation of aldoximes to result nitrile oxide

2.3. Preparation of Nitrile Oxides from Nitrolic Acids

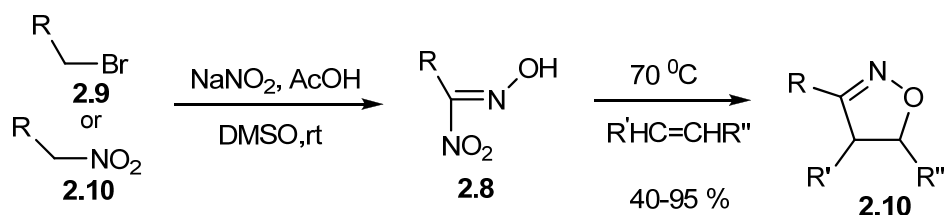
Victor Meyer reported nitrolic acids for the first time in 1875. After that time nitrolic acids has been forgotten class of chemical compounds. It was thought that these molecules were unstable at that time but nowadays it is proved that nitrolic acids are stable, easy to access and possible to keep in fridge over months.

Kinetic studies (*E*) **2.8a** and (*Z*) **2.8b** configuration of nitrolic acid isomers shows *Z*-acetonitrolic acid more rapidly loses NO_2^- to form unstable aryl nitrile oxide than *E*-configuration of aryl nitrolic acids ($X=p\text{-Cl}$, $m\text{-NO}_2$, $o\text{-NO}_2$), which could be detected by monitoring its subsequent reactions [29].



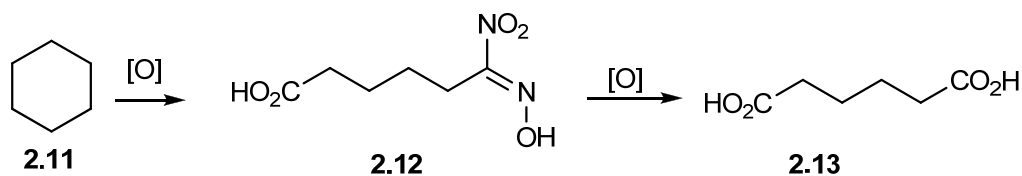
Scheme 2. 5 *E* and *Z* forms of nitrolic acids

Under neutral conditions, thermal fragmentation of nitrolic acids **2.8** which are easily prepared in moderately good yields from nitroalkanes or primary alkyl bromides and are readily converted into nitrile oxides **2.1** upon heating. Trapping of the resultant nitrile oxides **2.1** with alkenes generates the isoxazolidines **2.10** in 40–95% yields (Scheme 2.6) [30].



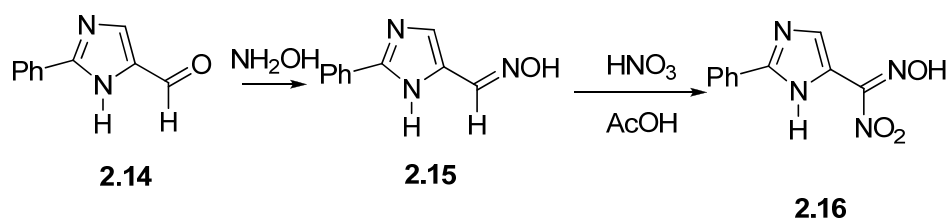
Scheme 2. 6 Synthesis of nitrolic acids from bromo- and nitro alkanes

The oxidation of cyclohexane in the presence of nitric acid and related oxidizing agents yields nitrolic acids as intermediates while synthesizing adipic acids **2.13** (Scheme 2.7) [31].



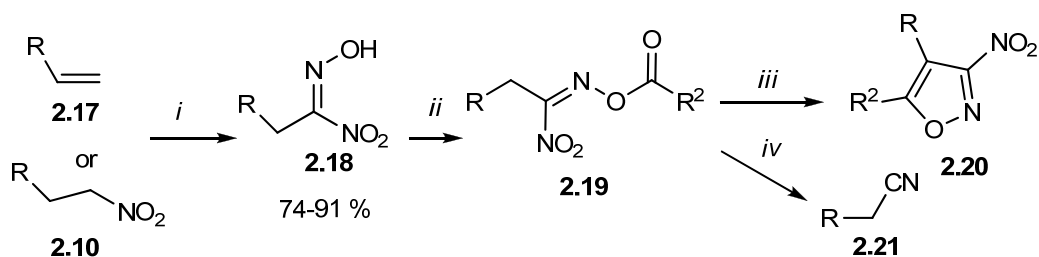
Scheme 2. 7 Oxidation of cyclohexane yields nitrolic acids as intermediates

Esterification reactions of imidazol-nitrolic acids and their ocular effects were investigated. These imidazole 2-nitrolic acids and imidazole 5-nitrolic acids were synthesized from oximes by treatment with a mixture of fuming nitric acid and acetic acid. The effects of these potential nitric oxide-donating compounds were subjected to some biological tests. (Scheme 2.8) [32,33].



Scheme 2. 8 Synthesis of imidazole nitrolic acids

Synthesis of nitrolic acids starting from alkenes and nitroalkanes was established by addition nitrosonium tetrafluoroborate (NOBF_4) subsequent additions yield nitriles and 3-nitroisoxazoles [34].

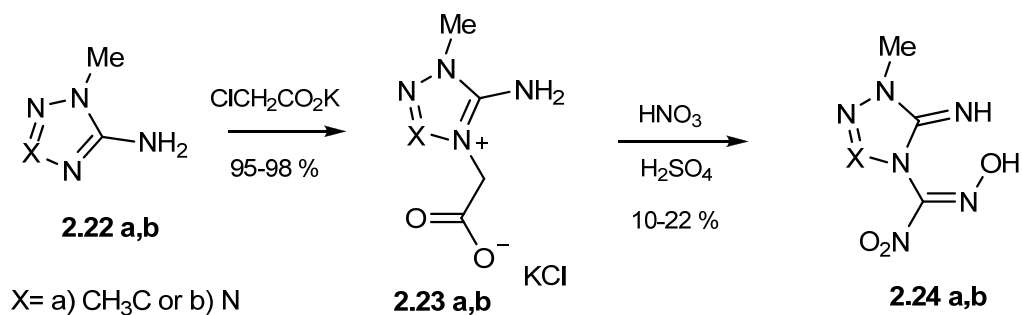


R= alkyl, aromatic; R^2 = biphenyl

Reagents and conditions: *i*, NOBF_4 , MeCN, rt; *ii*, 4-biphenylcarbonyl chloride, Et_3N , DCM; *iii*, Bu_3SnH , AIBN, PhH; *iv*, NaNO_2 , NaOH, MeOH, 0 °C.

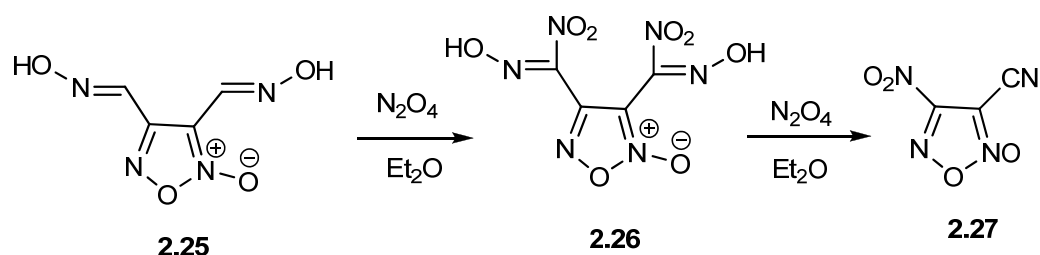
Scheme 2.9 Synthesis of alkyl nitriles *via* nitrolic acids

Katritzky *et al.* treated triazole (**2.22a**) and tetrazole (**2.22b**) derivatives with potassium chloroacetate salt subsequently with $\text{HNO}_3\text{--H}_2\text{SO}_4$ to yield nitrolic acids **2.24a** and **2.24b** (Scheme 2.10) [35].



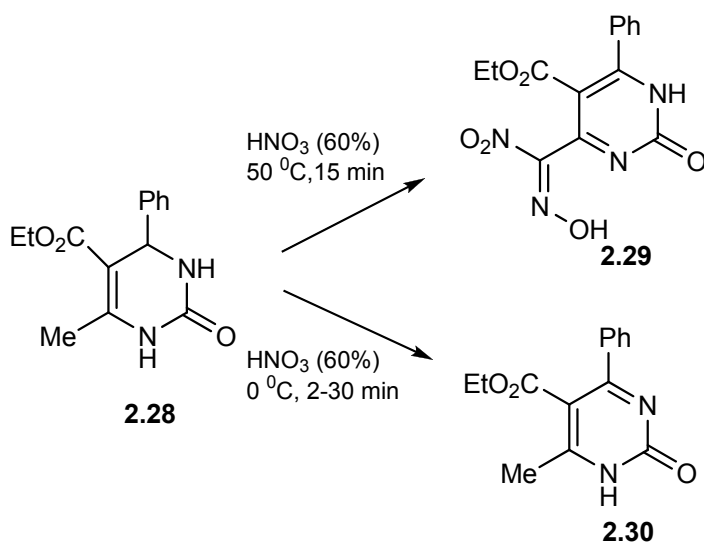
Scheme 2. 10 Synthesis of triazole and tetrazole substituted nitrolic acids

Investigation of the reaction of furoxanediazoxime with nitrogen tetroxide gave the corresponding precursor of nitrile oxides followed addition of nitrogen tetraoxide gas reduce and deoxygenate compound **2.26** to produce furoxancarbonitrile **2.27** [36].



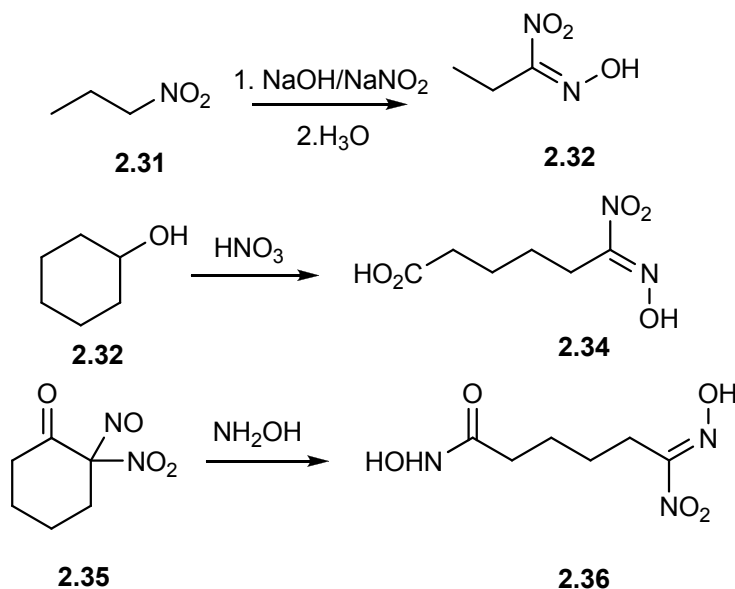
Scheme 2. 11 Treatment of bisnitrolic acids with $\text{N}_2\text{O}_4(\text{g})$ yield compound **2.28**

A series of substituted 3,4-dihydro-2-pyrimidones (DHPMs) **2.28** was reacted with nitric acid under different reaction conditions. Treatment of DHPMs with nitric acid at 0°C led to the formation of the corresponding dehydrogenated 2-pyrimidones. In contrast, reaction of one representative DHPM with nitric acid at 50°C led to an unusually stable nitrolic acid, involving a formal nitration, nitrosation, and dehydrogenation step [37].



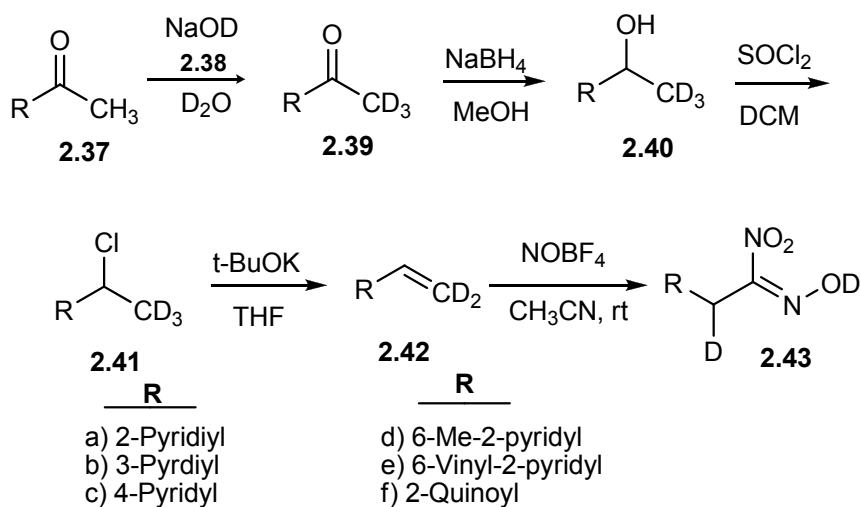
Scheme 2. 12 Unexpected nitrolic acids from pyrimidones

Rehse and coworkers prepared some nitrolic acids **2.32**, **2.34**, and **2.36** and tested antithrombotic and blood pressure lowering activities of these nitrolic acids (Scheme 2.13) [38].



Scheme 2.13 Synthetic routes to alkyl nitrolic acids

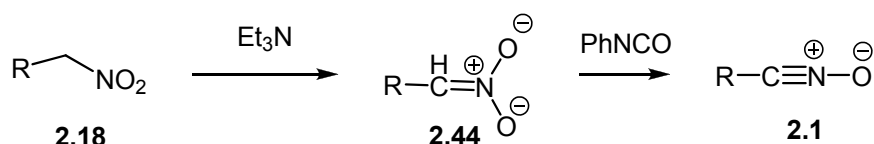
The reaction of nitrosonium tetrafluoroborate with ethenylpyridines and ethenylquinolines was studied systematically. The products thus obtained were acetonitrolic acids and nitroquinolineacetaldehyde oximes [39].



Scheme 2.14 Synthesis of various nitrolic acids from alkenes

2.4. Other Methods for Preparation of Nitrile Oxides

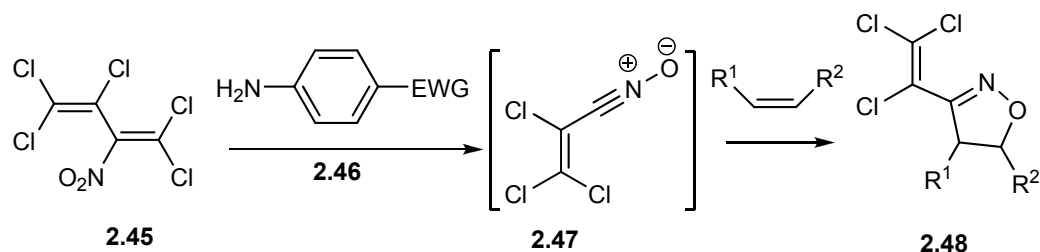
Generation of nitrile oxides by the Mukaiyama-Hoshino procedure, which is dehydration of primary nitroalkanes with an aryl isocyanate, usually in the presence of Et₃N as a base, is of high importance in nitrile oxide chemistry (Scheme 2.15) [40,41,42].



Scheme 2. 15 Producing nitrile oxides from nitro alkanes

There are other reagents than arylisocyanates, have been tested for the dehydration of nitroalkanes in the literature. POCl₃, AcCl, Ac₂O, BzCl, and MeSO₂Cl can be used instead of arylisocyanates [43].

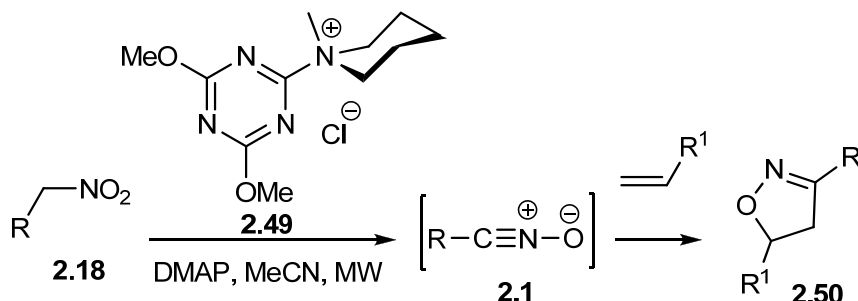
Zapolskii et al. has found a novel synthetic method which is fairly reaction of *gem*-dichloronitroalkenes in the presence of a base leads to the formation of chlorinated nitrile oxides, probably *via* a cyclic intermediate. These dipoles trapped with alkenes to give dihydroisoxazoles with a chlorinated side chain in 3-position [44].



Scheme 2. 16 Pentachloronitrobutadiene furnishes stable nitrile oxide

Another method was also developed by Giacomelli *et al.*, which is producing nitrile oxides *in situ* from nitroalkanes using very mild reagents

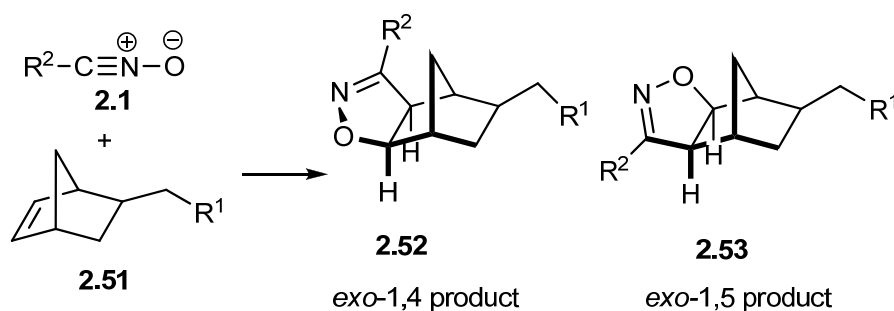
like 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride **2.49**, in the presence of a catalytic amount of 4-(dimethylamino)pyridine with microwave activation [45].



Scheme 2.17 Formation of compound **2.50** under MW conditions

2.5. Recent Applications of Nitrile Oxides in Click Chemistry

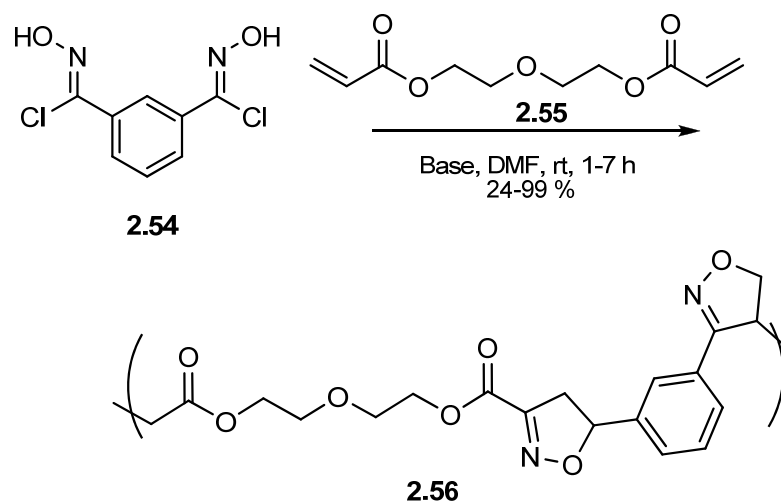
“Click Chemistry” has been described recently by the Sharpless group, the most studied reaction in the field is the azide-alkyne cycloaddition to form 1,2,3-triazoles. Applications of nitrile oxide click reaction are getting importance in this field from day-to-day, norbornene-modified DNA in copper-free click reaction with nitrile oxide was reported by Gutsmedl et al. [46].



Scheme 2. 18 Nitrile Oxide-Norbornene click reaction giving 1,4- and 1,5-*exo*-products

Click reaction between homo-ditopic hydroximoyl chlorides and bifunctional terminal olefinic and acetylenic monomers as dipolarophiles

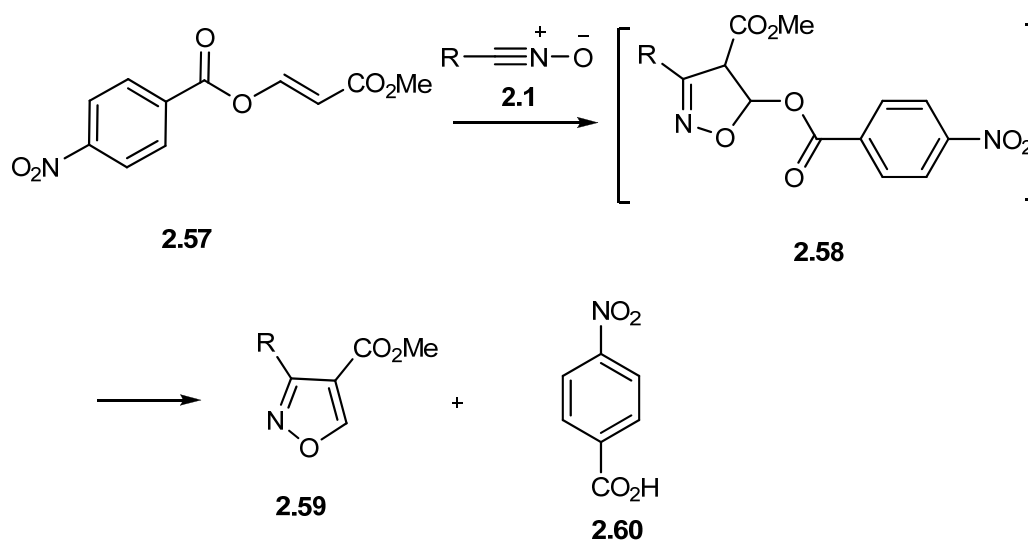
was demonstrated by Koyama and co-workers. Click polymerization proceeded *via* 1,3-dipolar polycycloaddition [47].



Scheme 2. 19 Click polymerization *via* nitrile oxides

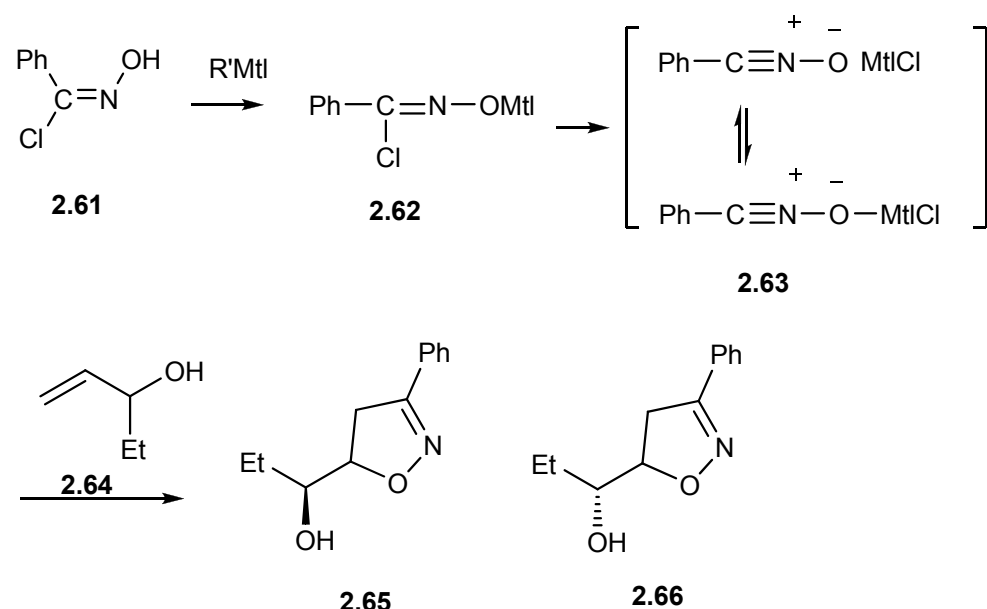
2.6. Regioselective reactions of Nitrile Oxides

Reactions of nitrile oxide with alkyne-esters results mainly 5-substituted cycloadduct despite this fact Zong et al. demonstrated using methyl 3-(4-nitrobenzoyloxy)acrylate reacted with corresponding nitrile oxides furnishes 4-substituted isoxazoles in 43–96% yields [48].



Scheme 2. 20 Regioselective synthesis of 3,4-disubstituted isoxazoles

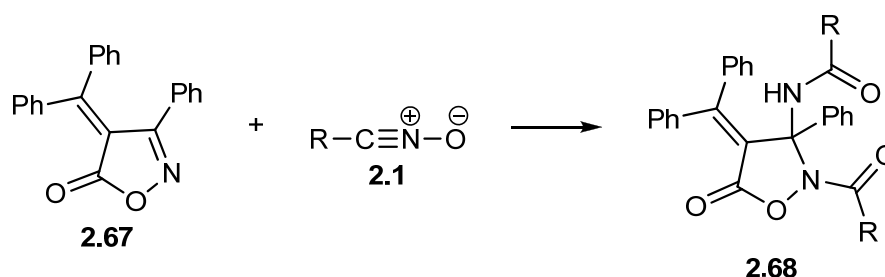
Kanemasa demonstrated that the first successful control of stereo- and regioselectivity in 1,3-dipolar cycloadditions by metal coordination is described. The liberated benzonitrile oxide forms a complex with the Lewis acidic metal salts. The presence of magnesium ions dramatically accelerates nitrile oxide dipolar cycloadditions to allylic alcohols, improving both the regio- and stereoselectivity of the reaction. These complexes then undergo high yielding 1,3-dipolar cycloadditions to the magnesium alkoxides of allylic alcohols with high *syn* selectivity [49].



Scheme 2. 21 Interaction of hydroximinoyl chlorides with organometallic compounds offers a new method to generate nitrileoxides

2.7. Nucleophilic Addition of Nitrile Oxides

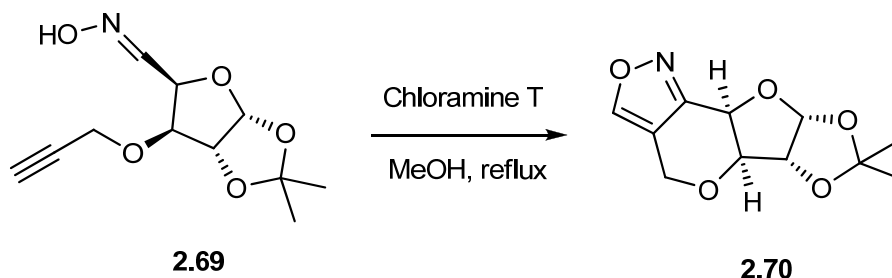
The reaction between nitrile oxides **2.1** and 4-diphenylmethylen-3-phenylisoxazol-5-one **2.89** does not proceed *via* a cyclisation but gives instead an unprecedented rearrangement to yield 4-diphenylmethylen-2,3,3-trisubstituted derivatives **2.90** in 15–16% yield (Scheme 2.22) [50].



Scheme 2. 22 Nucleophilic addition of nitrile oxide

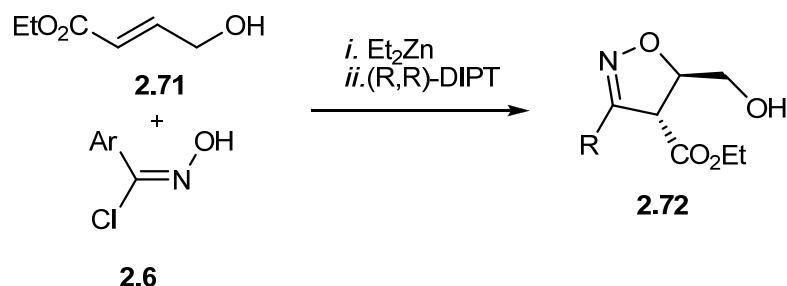
2.8. 4,5-Dihydro Isoxazole synthesis via 1,3-dipolar cycloaddition

Enantiomerically pure isoxazole **2.70** derivatives can be synthesized by intramolecular cycloaddition of 3-*O*-alkynyl carbohydrate nitrile oxides. Chloramine T was used to prepare nitrile oxide *in situ* by the action of on the oxime **2.69** with the subsequent cycloaddition proceeding in an 84% overall yield (Scheme 2.23) [51].



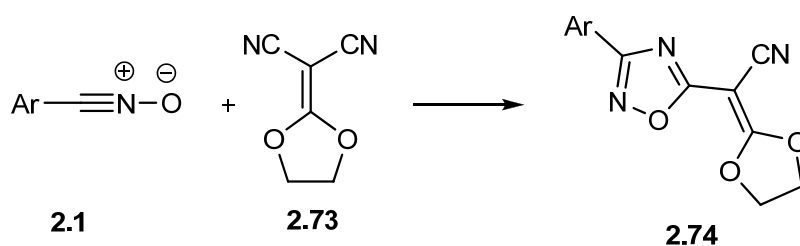
Scheme 2. 23 Synthesis of enantiomerically pure isoxazole

The asymmetric 1,3-dipolar cycloaddition of nitrile oxides, prepared from hydroximoyl chlorides, to γ -substituted allylic alcohols **2.71** has been demonstrated using the chiral additive diisopropyl (*R,R*)-tartrate to furnish 3,4,5-trisubstituted 1,2-isoxazolines **2.72** in high regio- and enantioselectivities (89–98 %ee) (Scheme 2.24) [52].



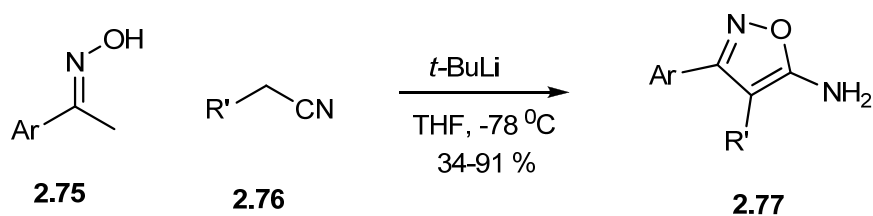
Scheme 2. 24 Formation of compound **2.72**

Arenecarbonitrile oxides add to the dicyanoketene ethylene acetal to yield 1,2,4-oxadiazoles **2.74** (Scheme 2.25) [53].



Scheme 2. 25 Synthesis of compound **2.74**

Nucleophilic addition of lithiated alkyl nitriles to α -chlorooximes yield 5-aminoisoxazoles **2.77** with moderate to high yields [54].



R' = H, Me, Ph, Bn, i-Pr, cyclopropyl

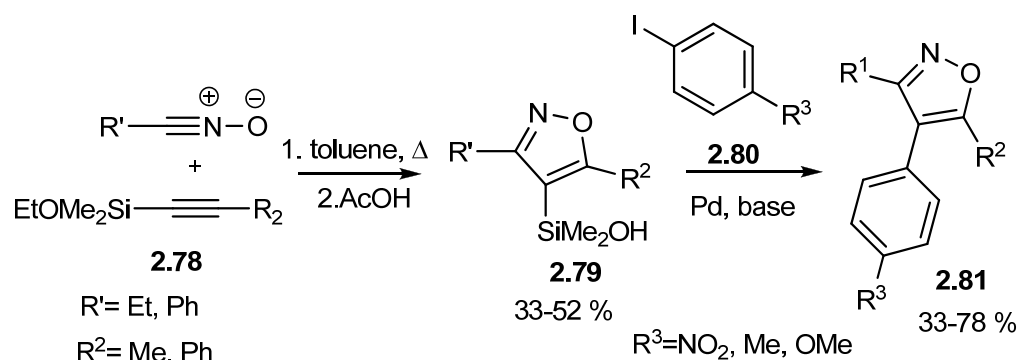
Scheme 2. 26 Synthesis of 5-amino isoxazole

2.9. Reaction of Nitrile Oxides to Yield 3,4,5-Trisubstitued Isoxazoles

Substituted isoxazoles are of interest because they are versatile building blocks in organic synthesis and evince valuable pharmacological properties. 3,4,5-Trisubstitued isoxazoles are usually synthesized using

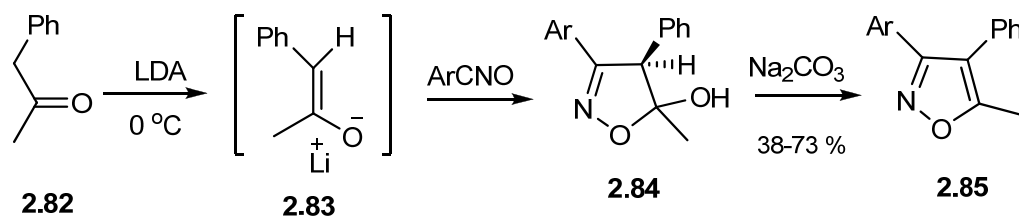
disubstituted alkynes but just using alkenes are also exist to produce 3,4,5-tri substituted isoxazoles.

Analogously, sequential [3+2] cycloaddition/silicon-based cross-coupling reactions allowed for the synthesis of 3,4,5-trisubstituted isoxazoles **2.81**. Regioselective 1,3-DC reactions between alkynyldimethylsilyl ethers **2.78** and aryl nitrile oxides, generated *in situ* from *N*-hydroxybenzene carboximidoyl chloride, gave as predominant products after hydrolysis isoxazol-4-ylsilanols **2.79**, converted into 4-arylisoxazoles **2.81** by treatment with a variety of aryl iodides **2.80** (Scheme 2.27) [55].



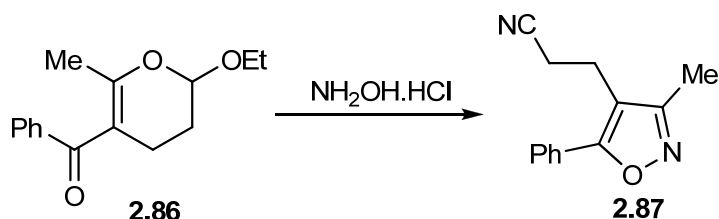
Scheme 2. 27 Silicon based cross coupling cycloaddition

When an alkene is used as a dipolarophile, isoxazoles are usually prepared in two step Nunna et al. has prepared stable lithium enolate of phenylacetone by using lithium diisopropylamide *in situ* at 0 °C, reacted with aryl nitrile oxides giving 5-hydroxy-2-isoxazolines **2.84**. The adduct were dehydrated under basic conditions to afford 3-aryl-5-methyl-4-phenylisoxazoles **2.85** [56].



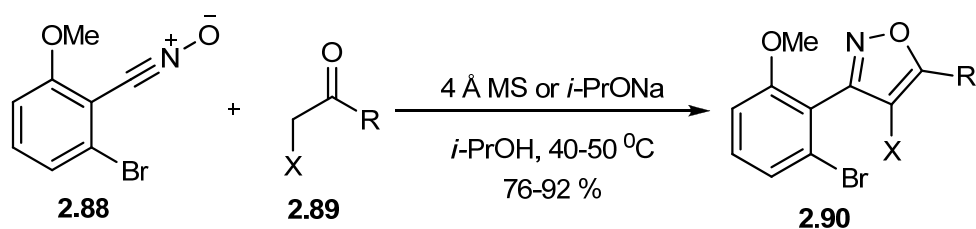
Scheme 2. 28 Reaction of nitrile oxides with metal mediated dipolarophiles

Hydroxylaminehydrochloride transforms ethoxydihydropyrans into (cyanoethyl)isoxazoles [57].



Scheme 2. 29 Interesting ring isomeration to yield isoxazole

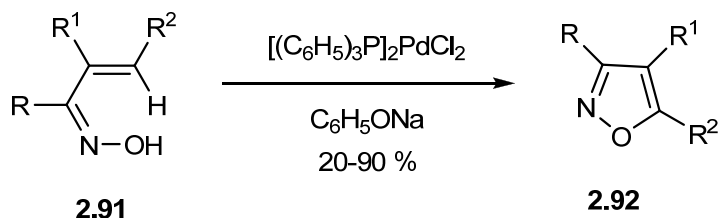
Stable *ortho*-disubstituted nitrile oxides, such as compound **2.88**, were also involved in base-promoted cyclocondensation with various active methylene compounds **2.89** providing a concise route to highly functionalized isoxazole derivatives **2.90** [58].



R = Me, Ph
X = CN, CO₂Et, SO₂Me

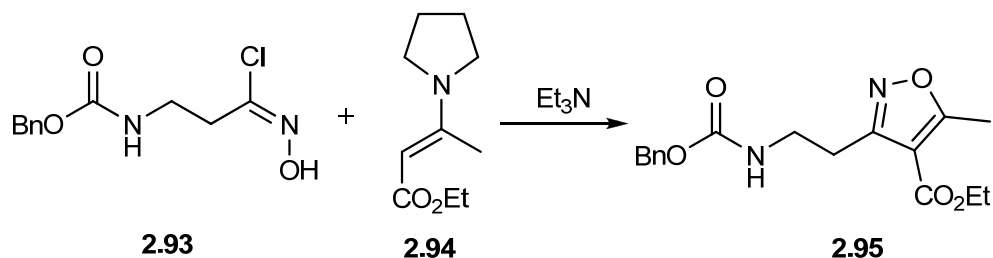
Scheme 2. 30 Stable nitrile oxides react with electron-poor carbonyl compounds

3,4,5-trifunctionalised isoxazoles were also synthesized intramolecular oxidatively cyclization of α,β -unsaturated ketoximes in the presence of Pd catalysis [59].



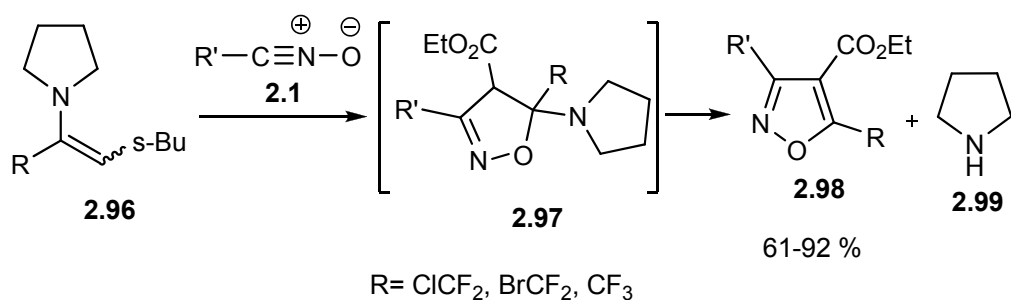
Scheme 2. 31 Pd catalyzed formation of isoxazole

A β -aminonitrile oxide, formed from an oxime derivative of β -alanine **2.93**, has been treated with an enamine of a β -ketoester **2.94** to afford the 3-(2-aminoalkyl)isoxazole-4-carboxylic ester **2.95** in 69% yield (Scheme 2.32) [60].



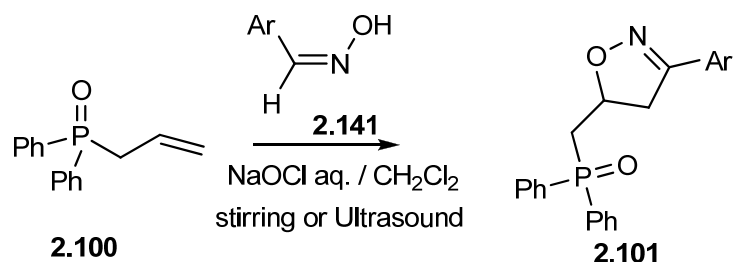
Scheme 2. 32 Synthesis of 3-(2-aminoalkyl)isoxazole-4-carboxylic ester

Perfluoroalkyl pyrrolidino acrylates **2.96** reacted with nitrile oxides **2.1** generated *via* dehydration of nitroalkanes to synthesize isoxazolines. Reaction underwent spontaneous elimination of pyrrolidine to deliver isoxazoles **2.98** in high yield [61].



Scheme 2. 33 Elimination of pyrrolidine give isoxazole

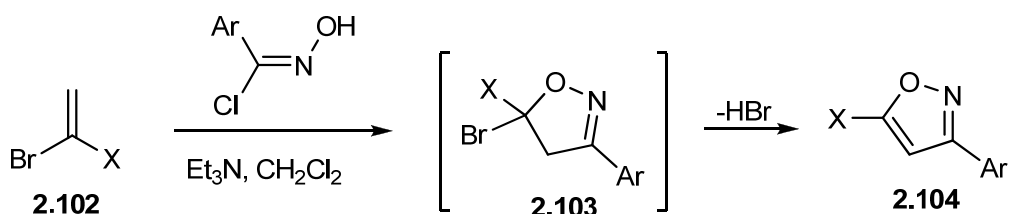
Bougrin and coworkers published the ultrasound assisted cycloaddition reactions and compared with “classical” stirring under the same conditions the yields are enhanced under ultrasound irradiation [62].



Scheme 2.34 Synthesis of isoxazoles under ultrasound conditions

2.10. Reactions of Nitrile Oxides to Yield One-Pot Synthesis of Isoxazoles

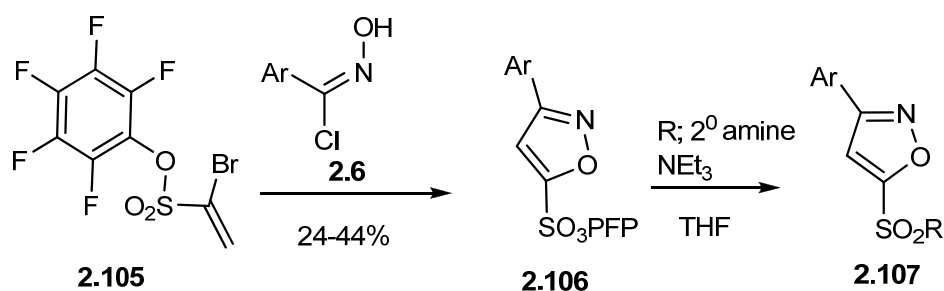
The regioselective synthesis of 3,5-disubstituted isoxazoles was achieved through the 1,3-dipolar cycloaddition of nitrile oxides with 1,1-disubstituted bromoalkenes. The substituted bromoalkenes function as alkyne synthons which were used to construct 5,5-disubstituted bromoisoxazoline intermediates that aromatize to the analogous isoxazoles through the loss of HBr [63].



X = CO₂CH₃, C(O)CH₃, SO₂Ph, S(O)Ph

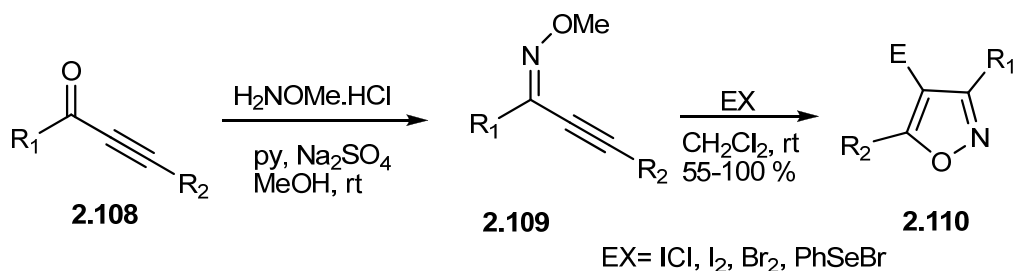
Scheme 2. 35 Isoxazole synthesis from 1,1-disubstituted bromoalkene

Similar example for one pot synthesis of isoxazoles was reported by Caddick et al. with 1,3-dipolar cycloaddition of α -bromo-pentafluoro phenyl vinylsulfonate with nitrile oxides was used to rapidly access a range of 3,5-isoxazoles which could be converted directly to their corresponding sulfonamides [64].



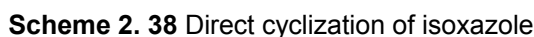
Scheme 2. 36 Synthesis of isoxazoles from α -bromo PFP vinylsulfonates

Cyclocondensations of hydroxylamine with 1,3-bielectrophiles such as conjugated alkynyl-carbonyl compounds **2.108**, electrophilic cyclization allowed a facile access to a variety of 3,5-disubstituted-4-halo(or seleno)isoxazoles **2.109** in high yields under mild reaction conditions, by treatment of O-methyl oximes **2.110** with ICl, I₂, Br₂, or PhSeBr [65].

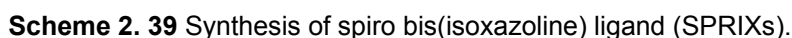


Scheme 2. 37 Synthesis of halo (or seleno) substituted isoxazoles

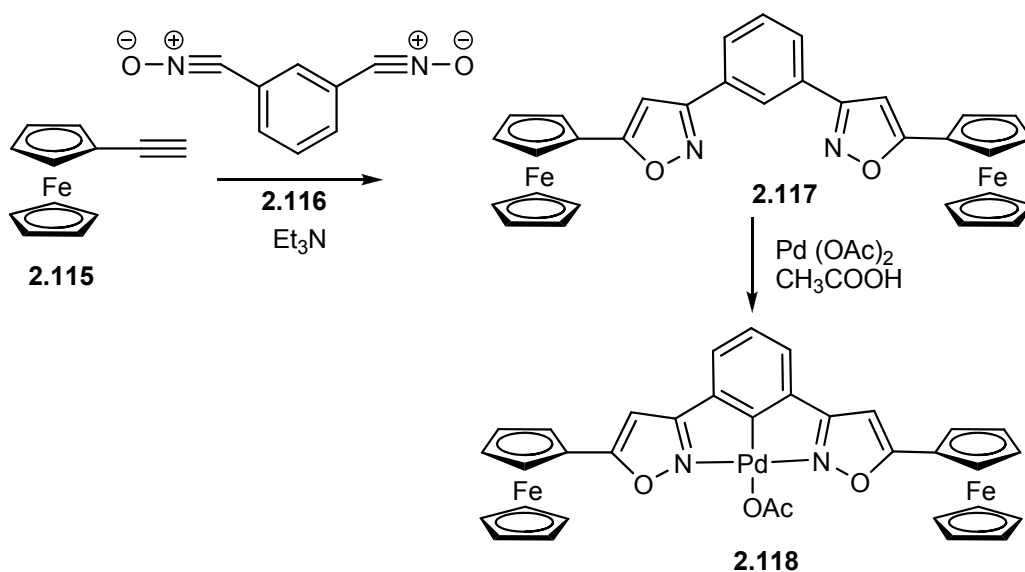
Interestingly, direct addition of hydroxylamine to cyanoethylthio-ethenylpyrroles **2.111** selectively furnished 5-amino-3-(pyrrol-2-yl)isoxazoles **2.112**. When carbamoyl derivatives ($R^3 = \text{CONH}_2$) were used minor amounts of regioisomers were also isolated [66].



The first isoxazoline ligands to be used in asymmetric synthesis have been constructed by double intramolecular addition of nitrile oxides produced from hydroximoylchlorides **2.113**. Spirobis(isoxazolines) **2.114** were formed and pure enantiomers were separated by chiral stationary phase chromatography and were used as ligands for copper(II) [67].



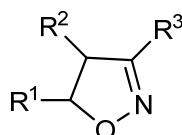
26



Scheme 2. 40 Synthesis of 1,3-bis-(5-ferrocenylisoxazole-3-yl) benzene-derived palladium(II) acetate complex **2.118**

2.12. Biologically importance of Isoxazol(in)es

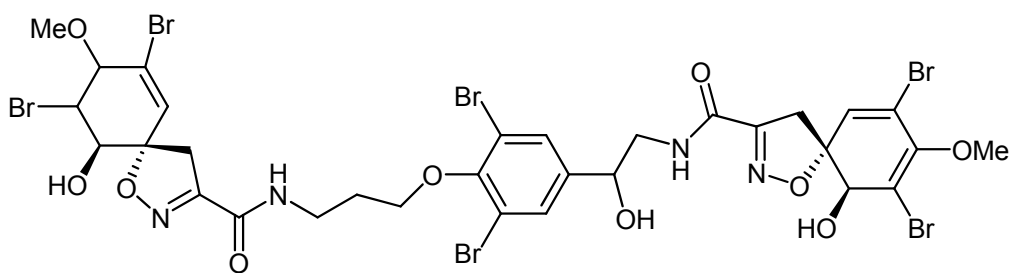
Many synthesized and naturally occurring spiroisoxazolines exhibit biological activity against a variety of disease states, microorganisms, and enzymes. 4,5-dihydroisoxazoles **2.119** are one of the key O- and N-containing five-membered ring heterocycles which possess significant synthetic and biological applications [69,70]. Besides being precursors to many multi-functional synthetic intermediates such as β -hydroxyketones and nitriles, α , β -unsaturated ketones and oximes, γ -amino alcohols etc. [71], isoxazolines **1** are excellent substrates for the synthesis of β -amino acids [72], amino sugars and novel azaheterocycles [73].



2.119

Figure 2. 3 Depending on R groups isoxazoles show various biological properties

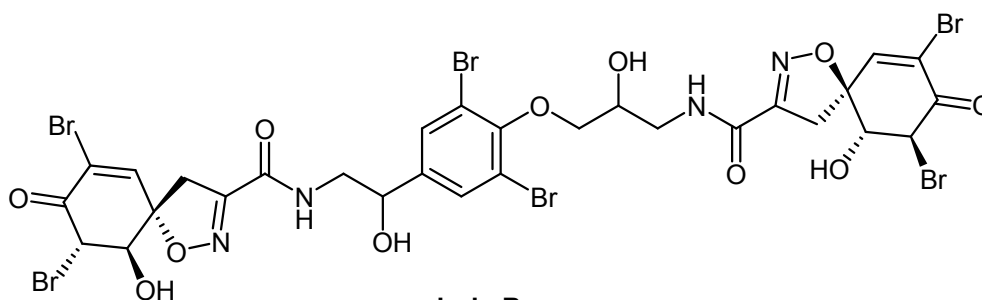
The spiroisoxazolines 11-deoxyfistularin-3 and purealidin Q have been shown to be cytotoxic against mcf-7 breast cancer tissue.



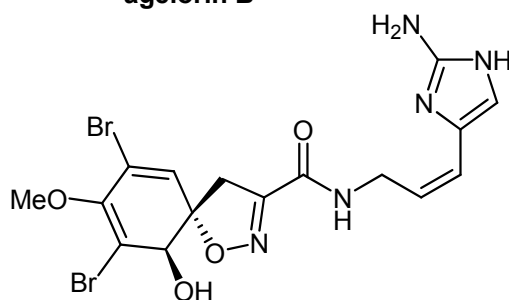
11-deoxyfistularin-3

Figure 2. 4 Spiroisoxazolines show cytotoxic properties against breast cancer

Furthermore, other spiroisoxazolines such as aerothionin, aplysinamisines I–III, and agelorin display antifungal, antibiotic, or antimycobacterial activity (Figure 2.5) [74].



agelorin B



aplysinamisine I

Figure 2. 5 Some of the biologically important spiroisoxazolines

Isoxazolines exhibit interesting and diverse biological properties and represent a unique class of pharmacophores that is present in many therapeutic agents. Phosphonate-containing isoxazolines enhance the accumulation of indole alkaloids in periwinkle cell cultures [75].

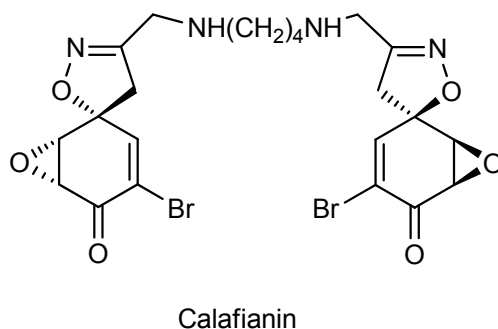


Figure 2. 6 Structure of Calafianin

The therapeutic potential of isoxazoline derivatives is further evident from their antimicrobial, anti inflammatory, fibrinogen receptor antagonistic, anticancer, antiHIV and antidepressant properties [76].

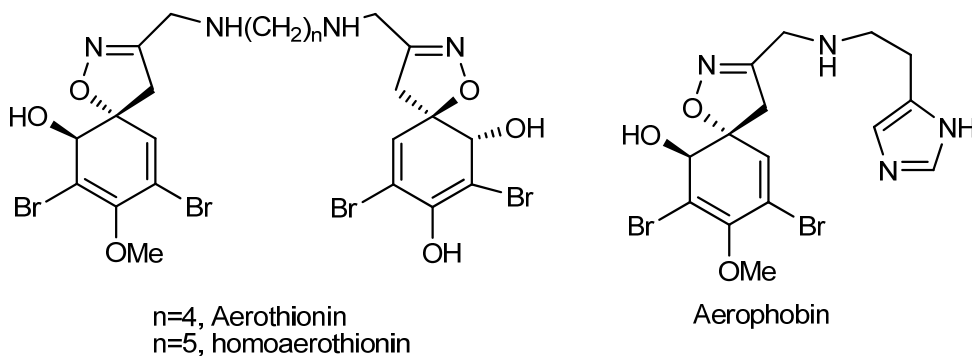


Figure 2. 7 Structure of aerotionins and aerophobin

An efficient synthesis of the cholinergic channel activator ABT–418 **2.120**, which contains isoxazole moiety is being evaluated for the treatment of Alzheimer's disease, from *N*-methylproline methyl ester has been described [77].

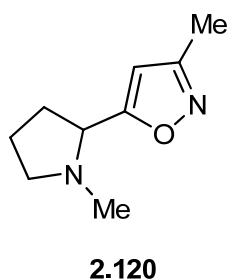
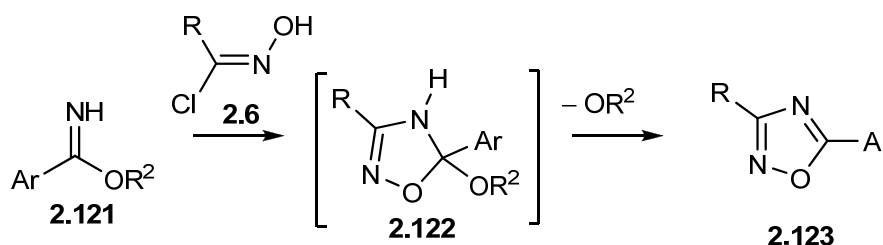


Figure 2. 8 Structure of compound **2.120**

Since these and other spiroisoxazoline containing natural products express such a wide array of bioactivities, the synthesis and derivatization of this family of compounds continue to be of interest.

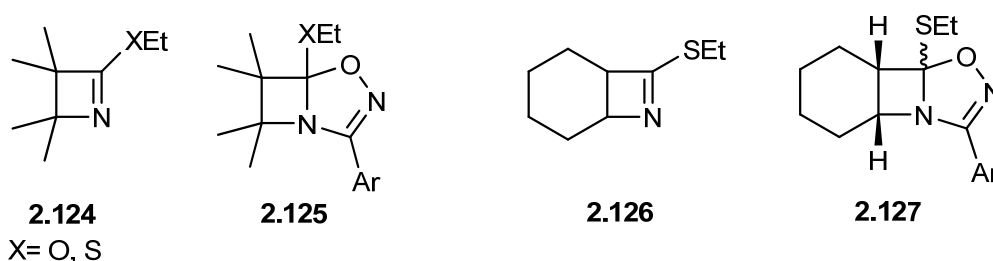
2.13. Addition of Nitrile Oxides to C=N bond

Nitrile oxides undergo facile cycloaddition to the C=N bond of azomethines. Eloy and Lanaers firstly reported that 1,2,4-oxadiazoles **2.123** could be made by the condensation of hydroximoyl chloride **2.6** with two moles of imidic esters **2.121** [78].



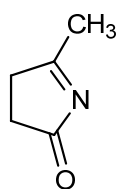
Scheme 2. 41 Reaction of nitrileoxides with imidic esters

The first example of 1,3-dipolar cycloaddition products **2.125**, **2.127** of 1-azetines **2.124** and **2.126** with nitrile oxides were reported in moderate to good yields [79].

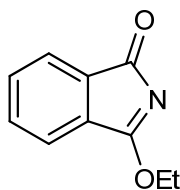


Scheme 2. 42 Cycloaddition reactions of azetines with nitrile oxides

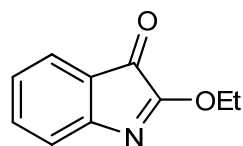
Miller and coworkers investigated cycloaddition reactions of nitrile oxides with various cyclic imidate esters **2.128**, **2.129** and **2.130** to furnish expected 1,2,4-oxadiazoline bicycles [80].



2.128



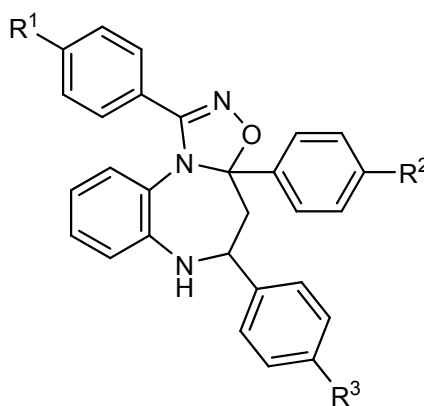
2.129



2.130

Scheme 2. 43 Imidate esters as dipolarophiles

Reaction of 1,5-benzodiazepine with nitrile oxide furnishes readily 3a,4,5,6-tetrahydro-[1,2,4]oxadiazolo[4,5-a][1,5]benzodiazepine derivatives **2.131** [81].

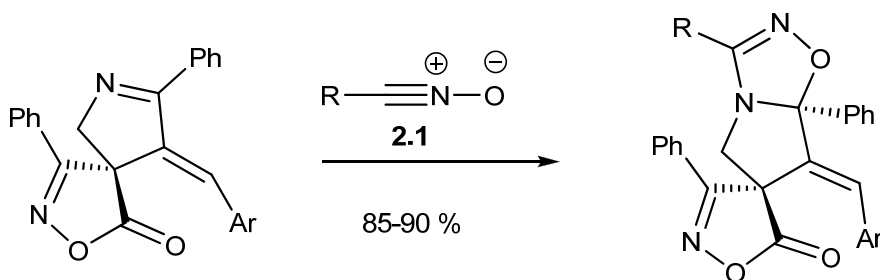


2.131

R¹= H, Br R²= H, OMe R³= H, OMe

Scheme 2. 44 Cycloaddition of 1,5-benzodiazepine with nitrile oxides

Surprisingly, cycloaddition reactions between spiro compounds **2.132** and nitrile oxides show that the reactivity of the C=N moiety of these dipolarophiles is greater than that of *exocyclic* C=C bond to furnish regiospecific cycloadduct 1,2,4-oxadiazoline derivative [82].



2.132

2.133

Scheme 2. 45 Unexpected cycloaddition reaction

When phosphorylnitrile oxide was used with azomethines, PhCH=NR , phosphorylated 1,2,4-oxadiazolines **2.134** were observed [83].

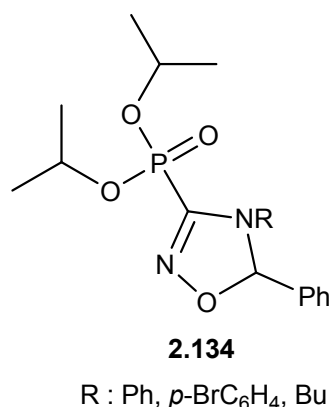
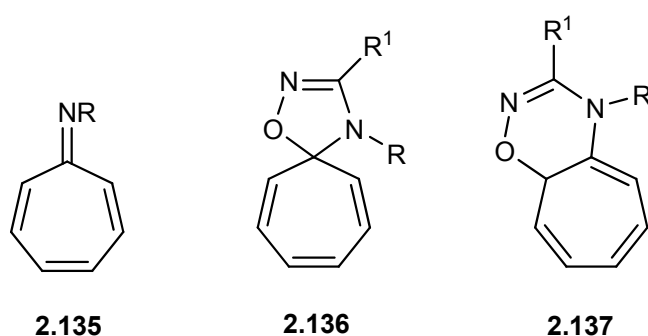


Figure 2. 9 Phosphorylated 1,2,4-oxadiazolines

1,2,4-oxadiazaspiro[4.6]undeca-6,8,10-trienes, is described for cycloaddition of *p*-substituted benzonitrile oxides with azaheptafulvenes **2.135**. The reaction show that give, as a rule, only adducts **2.136**. However, the adducts consist of a mixture of rapidly equilibrating spiro and fused isomer, that is, **2.137** [84].



Scheme 2. 46 Structure of compounds **2.135**, **2.136** and **2.137**

A complete review of the uses of nitrile oxides in synthetic organic chemistry is beyond the scope of this work however, the above examples are presented to give the reader a small insight into the uses of nitrile oxides as a easily accessible 1,3-dipole in modern synthetic chemistry.

CHAPTER 3

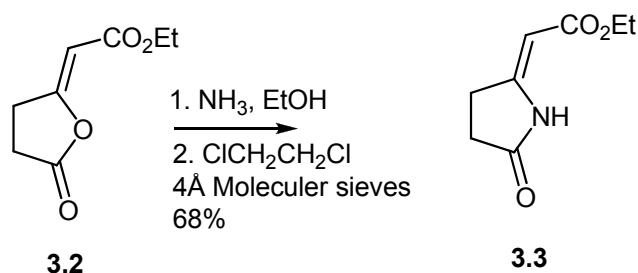
3.1. Alkylidene Pyrrolidine Synthesis

Alkylidenepyrrolidines **3.1** also known as exo-cyclic secondary enamines, frequently observed structural unit in various alkaloid type natural products, pharmaceutical molecules, etc., is of current interest [85]. Among the various pyrrolidine-containing structures, condensed and transannular ring skeletons are important structural subunits present in many alkaloids and are common scaffolds in biologically active and pharmaceutically significant compounds [86]. Most methods for the formation of alkylidenepyrrolidines start from the readily available pyrrolutamic acid **3.2** derivatives. As the γ -lactam carbonyl is relatively unreactive, various methods are used to enhance the reactivity of this key functional group [87].



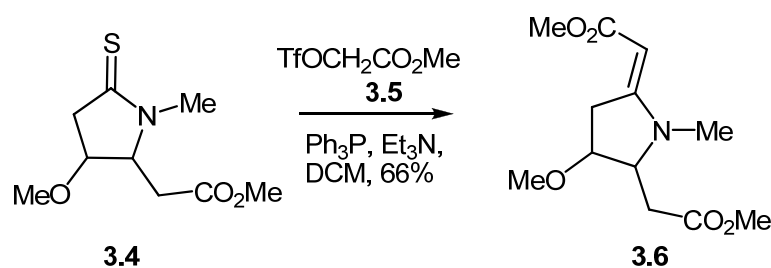
Figure 3. 1 Structure of alkylidene pyrrolidine **3.1** and pyrrolutamic acid **3.2**

Alkylidenepyrrolidine lactams **3.3** are relatively straightforward to prepare from the corresponding lactones **3.2** by simple ammonolysis (Scheme 3.1) [47].



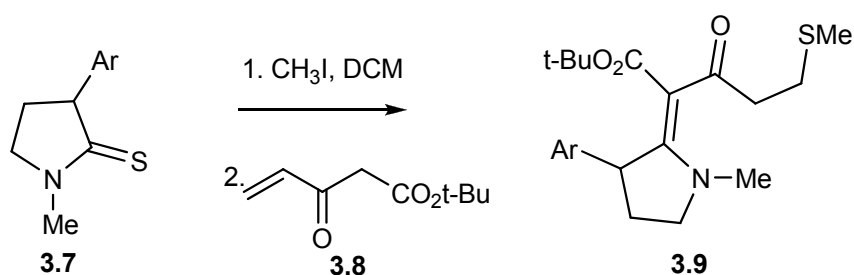
Scheme 3. 1 Synthesis of alkylidenepyrrolidine lactam

The halocarbonyl compounds are most commonly used as the alkylating agent for the synthesis of alkylidenepyrrolidines. However, other leaving groups have been used. In the synthesis of carbapenems, Koskinen *et al.* utilised the triflate leaving group **3.5** [88].



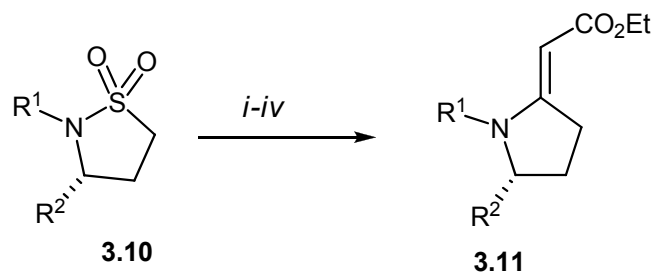
Scheme 3. 2 Transformation of thione to alkylidene

A further modification to the reaction by Micheal *et al.* showed that alkylating agent does not need leaving group adjacent to the carbonyl. In this example the methanethiolate is displaced in a Knoevenagel-type reaction (Scheme 3.3) [89].



Scheme 3. 3 Knoevenagel-type reaction to synthesis alkylidenepyrrolidines

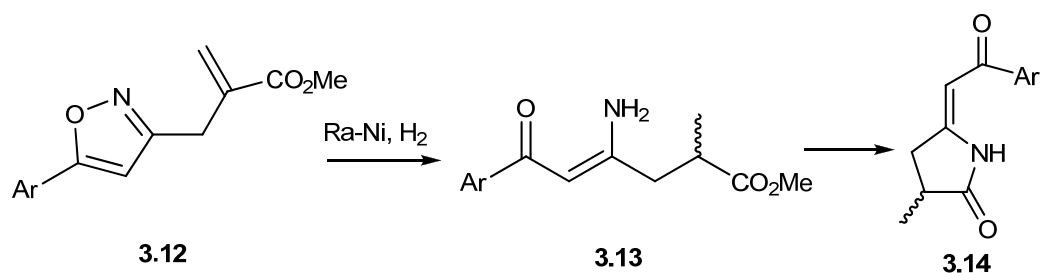
Dienolates of keto esters are generated by successive treatment with NaH and BuLi. Reaction with five- or six-membered sulfamidates affords N-sulfate intermediates which undergo an acid-promoted hydrolysis/cyclization to form the pyrrolidines **3.11** [90].



i: 1 eq. NaH, THF
ii: BuLi, hexanes
iii: addition of cyclic sulfamidate
iv: HCl (aq)

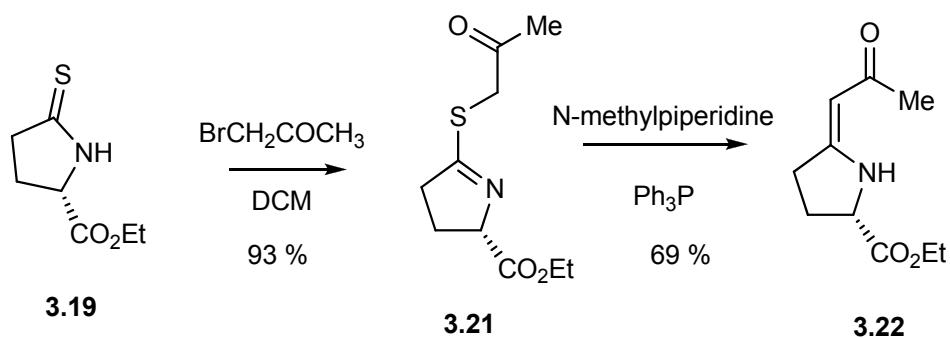
Scheme 3. 4 Subsequent reactions of sulfamidates yield alkylidene pyrrolidine

Hydrogenolysis in the presence of Raney-Ni of derivatives, coming from Baylis-Hillman adducts of 3-isoxazole carbaldehydes that underwent ring-closure reactions to afford substituted 5-alkylidenepyrrolidin-2-one. [91].



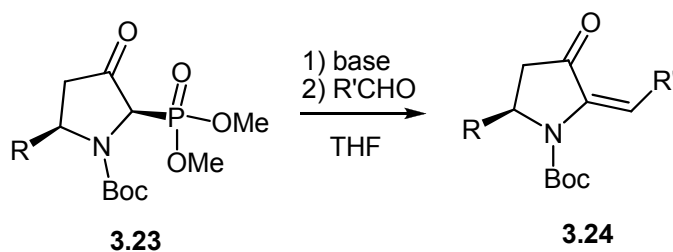
Scheme 3. 5 Hydrogenation of isoxazole finally results alkylidene pyrrolidine

The general reaction in Scheme 3.6 indicates the chemical pathway for alkylidenepyrrolidine synthesis. It starts with the alkylation of the thiolactam **3.19** with α -halocarbonyl. This intermediate **3.21**, was followed with a base such as *N*-methylpiperidine gives the alkylidenepyrrolidine **3.22**.



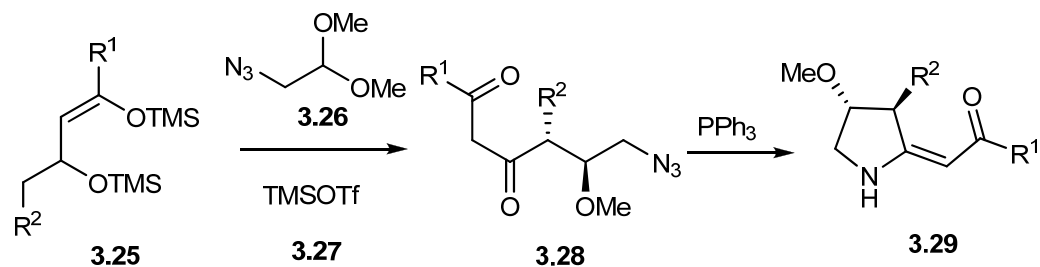
Scheme 3. 6 Synthesis of alkylidene pyrrolidine starting from thiolactam

The Horner-Wadsworth-Emmons reaction of aldehydes with sulfinimine-derived 3-oxo pyrrolidine phosphonates represents a new method for the asymmetric synthesis of ring-functionalized *cis*-2,5-disubstituted 3-oxo pyrrolidines [92].



Scheme 3. 7 Synthesis of 3-oxopyrrolidines

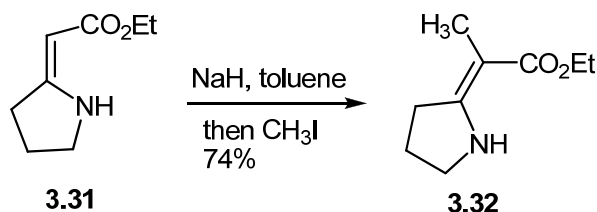
Treatment of azidoketones **3.28** with triphenylphosphine led to the formation of pyrrolidine **3.29** via a Staudiner-aza-Wittig reductive cyclization. [93].



Scheme 3. 8 Staudiner-aza-Wittig cyclization

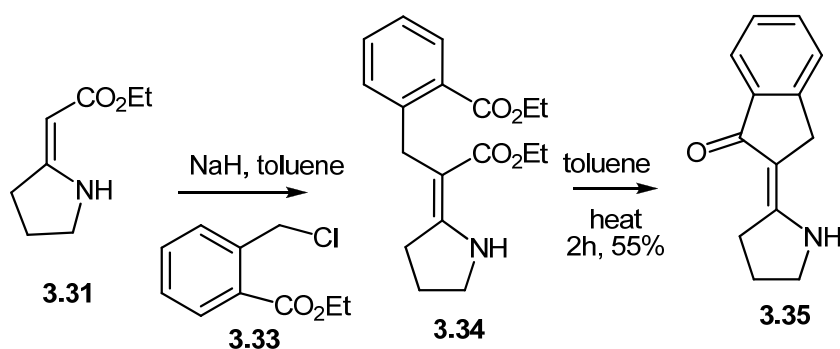
3.2. Various reactions of Alkylidene-2-pyrrolidines

Reaction of iodomethane with alkylidenepyrrolidine which bears ethylacetyl as electron-pulling group results substitution reaction on exocyclic double bond [71].



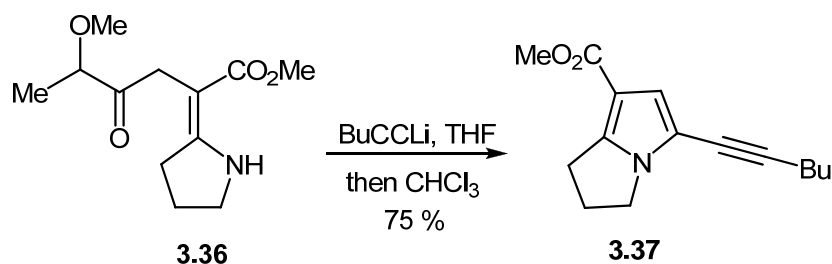
Scheme 3. 9 Substitution of methyl group

This kind of reactions has been used for annulation reactions. For example, alkylation of compound **3.31** on carbon to give adduct **3.34** was followed by an intramolecular C-acylation and subsequent decarboxylation to provide new alkylidenepyrrolidine **3.35** (Scheme 3.10) [94].



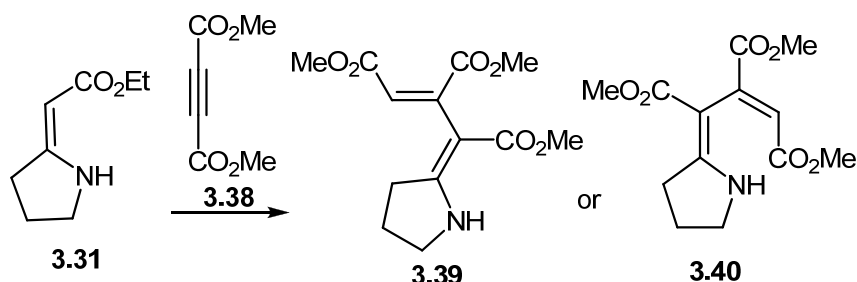
Scheme 3. 10 Annulation of alkylidenepyrrolidine

Alkylidenepyrrolidine **3.36**, prepared by a similar alkylation reaction with an α -bromo Weinreb amide, undergoes attack by a range of organometallic nucleophiles followed by facile cyclisation to prepare pyrrolizidines such as **3.37** (Scheme 3.11) [95].



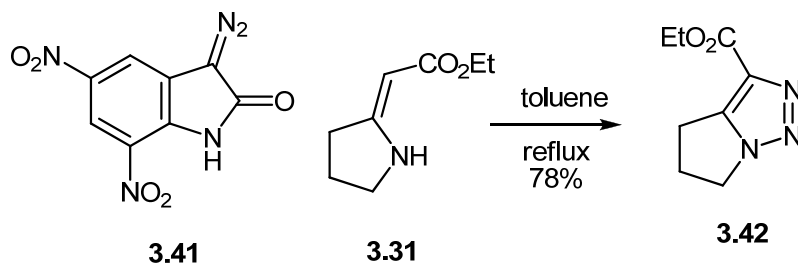
Scheme 3. 11 Formation of compound **3.37**

In reactions with doubly-substituted alkyne esters, the double-bond geometry formed depends upon the reaction conditions. For example, in the reaction of alkylidenepyrrolidine **3.31** with diester **3.38** at room temperature in benzene, the (*Z,Z*) isomer **3.39** is formed preferentially (92% isolated yield after 24 h), while at reflux the (*E,E*) isomer **3.40** is the major product (Scheme 3.12) [96].



Scheme 3. 12 Addition of DMAD to alkylidenepyrrolidine

A relatively unusual diazo-transfer reaction occurs between alkylidenepyrrolidine **3.31** and diazoindolone **3.41**, giving the triazole **3.42** (Scheme 3.13). This reaction is in fact relatively general, and works with many vinylogous carbamates and amides [97].



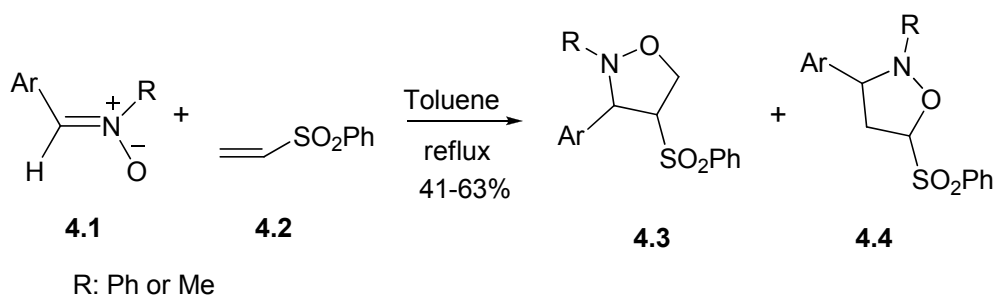
Scheme 3. 13 Diazotransfer to alkylidene pyrrolidine

CHAPTER 4

4.1. RESULTS and DISCUSSION

Part 1: Synthesis of 4,5-dihydroisoxazoles

Applications of *N,O*-heterocycles as key building blocks in the total synthesis of several natural and unnatural compounds have found increasing interest over decades. We have recently reported the synthesis and mass spectral study of novel phenyl sulfonyl substituted isoxazolines *via* 1,3-dipolar cycloaddition reaction of nitrones with phenyl vinyl sulphone. This reaction produced 4-phenylsulfonyl substituted isoxazolines **4.3** regioselectively [98].

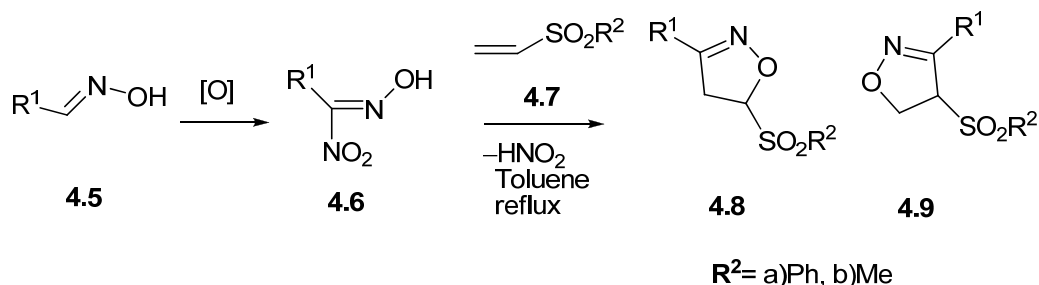


Scheme 4. 1 1,3-DC of nitrones with phenyl vinylsulfone

In continuation of our cycloaddition chemistry, we have been focused on the 1,3-dipolar cycloaddition reaction of nitrile oxides, which are *in situ* generated from nitrolic acids **4.6** and thus they were reacted regioselectively with phenyl or methyl vinyl sulfones to afford 3,5-disubstituted-4,5-dihydroisoxazoles **4.8** and **4.9**.

Vinyl sulfones are useful intermediates in organic chemistry. They can act both Michael acceptor and 2π partners in cycloaddition reactions [99,100]. Nitrolic acids are well-known to undergo 1,3-dipolar cycloadditions, however, to our best knowledge, synthetic applications of

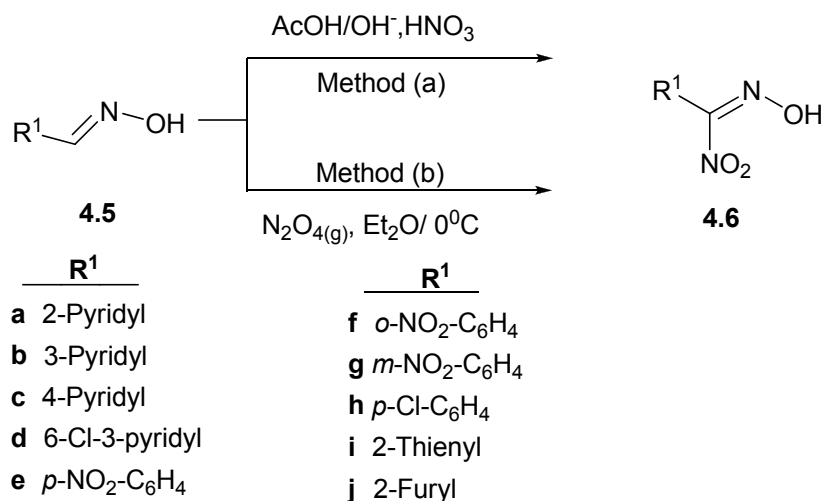
this process are rarely found in the literature in contrast to the functionally equivalent cycloadditions of nitrile oxides (Scheme 4.2 and Scheme 4.3).



Scheme 4. 2 1,3-DC of nitrolic acids with vinyl sulfones

All nitrolic acids were prepared by nitration of corresponding aromatic aldehyde oximes which can easily be obtained from the corresponding aromatic aldehyde and hydroxyl amine [20].

Reaction of nitrolic acid with a dipolarophile to yield cycloadduct is under neutral condition can be regarded as one of the main advantages of using nitrolic acids in comparison to the other nitrile oxide precursors. Pyridine substituted nitrolic acids **4.6 a-d** were prepared from reaction of aldoximes with fuming nitric acid in acetic acid. Other aryl substituted nitrolic acids **4.6 e-h** were prepared from reaction of aryl aldoximes with dinitrogen tetroxide gas in diethyl ether (Scheme 4.3). All nitrolic acids were obtained as single isomer and kept in refrigerator without decomposition over months.



Scheme 4. 3 Synthesis of nitrolic acids

In the literature, there are numerous examples of pyridine containing hetero-aromatic aldoximes undergoing a reaction with fuming nitric acid to produce nitrolic acids but it is not clear why benzaldoxime derivatives do not yield nitrolic acids with fuming nitric acid. Pyridine ring might reduce the π -electron density on the C=N group allowing HNO₃ to react with **4.5a-d**.

The structure elucidations of the new cycloadducts, namely, isoxazolines, were performed by means of spectroscopic methods, especially by ¹H NMR, ¹³C NMR, MS and X-Ray diffraction. Depending on the substituent existing in dipolarophiles and dipoles, 1,3-dipolar cycloaddition reaction can be supposed to generate either 4- or 5-regioisomers.

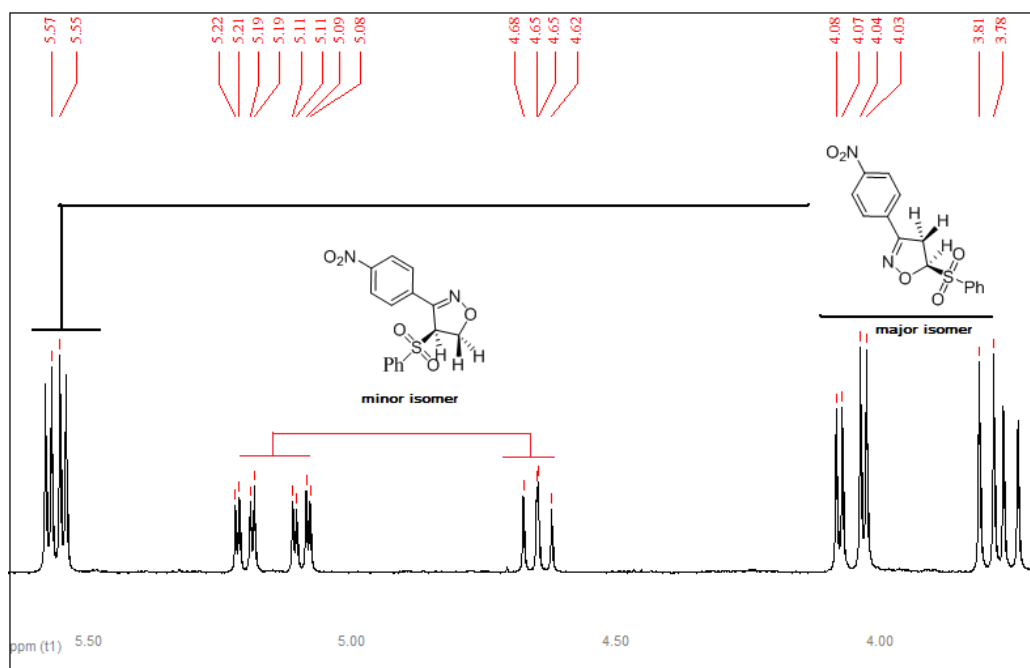


Figure 4. 1 Partial ^1H NMR Spectrum of compounds **4.8e** and **4.8e'**

Based on the relative positions of the peaks and coupling constants of the relevant protons in the ^1H NMR for the regioisomers **4.8e** and **4.8e'** revealed that the major isomers are 5-regioisomers which are observed in all cases, only in the case of *p*-nitro phenyl substitution (Figure 4.1), we assigned two regioisomers as 5:4 in 3.46 ratio calculated from the ^1H NMR spectrum of the crude reaction mixture.

The regioselectivity and absolute configurations of the stereocenters for the compounds **4.8a** and **4.8b** (Figure 4.2) were also established by single crystal X-ray diffraction.

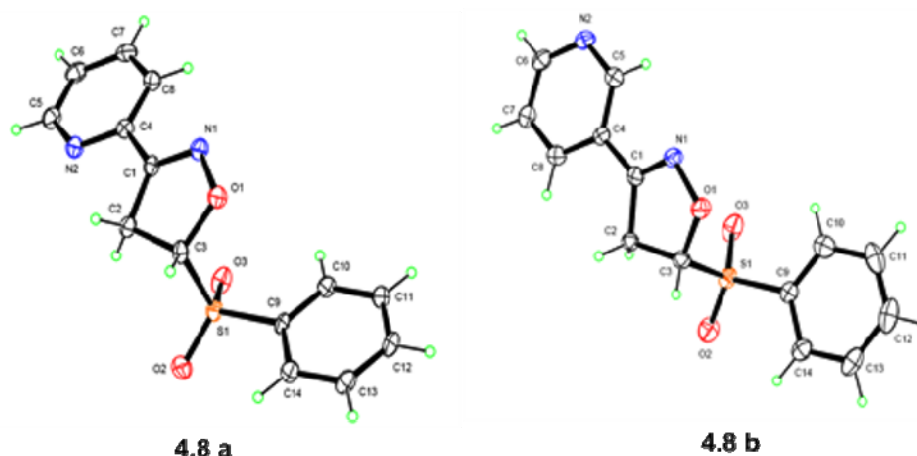


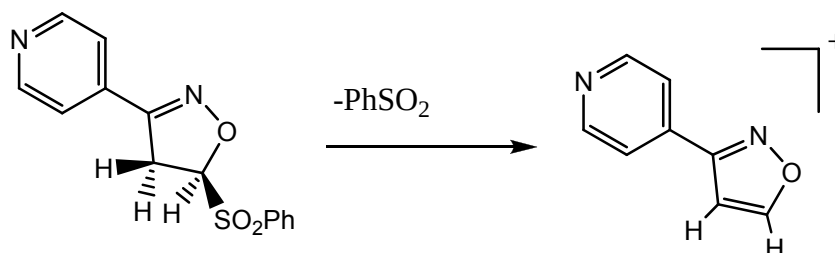
Figure 4. 2 X-Ray crystal structures of compounds **4.8a** and **4.8b**.

The cycloaddition products, isoxazoles are highly stable and easy to handle. In the IR spectra of these heterocycles, the C=N stretching vibration arises around at $1602\text{--}1541\text{ cm}^{-1}$ and stretching vibration for SO_2 group is found between $1155\text{--}1126\text{ cm}^{-1}$ indicating asymmetric and symmetric stretching of sulfonyl group, respectively. Synthesis of methyl sulphonyl substituted isoxazoles required less severe reaction conditions than phenyl sulphonyl substituted ones and yields are also found to be relatively higher than phenyl sulphonyl substitution which may be attributed to the electron releasing nature of methyl group (Table 1).

Compound	R ¹	R ²	Yield %	Solvent	Time	$\nu_{\text{C=N}}$ cm ⁻¹	ν_{SO_2} cm ⁻¹
4.8a	2-Pyridyl	Ph	65	toluene	2 h	1580	1150
4.8b	3-Pyridyl	Ph	71	toluene	2 h	1580	1155
4.8c	4-Pyridyl	Ph	59	toluene	2 h	1600	1144
4.8d	6-Cl-3-pyridyl	Ph	72	toluene	2 h	1602	1139
4.8e	<i>p</i> -NO ₂ -C ₆ H ₄	Ph	70	toluene	2 h	1600	1151
4.8f	<i>o</i> -NO ₂ -C ₆ H ₄	Ph	69	toluene	2 h	1599	1143
4.8g	<i>m</i> -NO ₂ -C ₆ H ₄	Ph	65	toluene	2 h	1531	1149
4.8h	<i>p</i> -Cl-C ₆ H ₄	Ph	77	toluene	2 h	1591	1151
4.8i	2-Thienyl	Ph	55	toluene	2 h	1480	1151
4.8j	2-Furyl	Ph	58	toluene	2 h	1583	1151
4.8k	2-Pyridyl	Me	88	THF	30 min	1581	1126
4.8l	3-Pyridyl	Me	80	THF	30 min	1541	1130
4.8m	4-Pyridyl	Me	82	THF	30 min	1600	1137
4.8n	6-Cl-3-pyridyl	Me	92	THF	30 min	1602	1139

Table 4. 1 Experimental conditions for compounds **4.8 a-n** and IR Spectra

Upon examination of the electron impact mass spectra of the isoxazolines, the base peaks were found to be ionic species; m/z : M-PhSO₂ which can easily be predicted that extrusion of PhSO₂ from the molecule produces this, an aromatic species, isoxazole (Scheme 4.5).

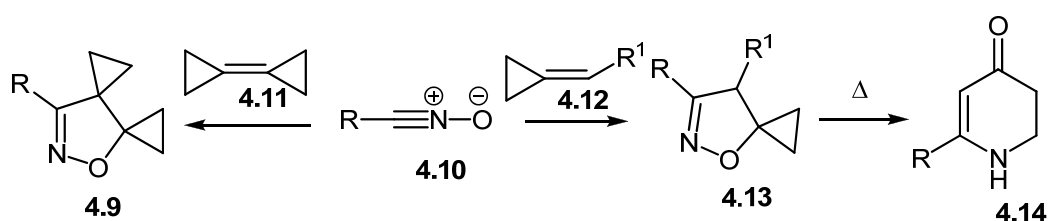


Scheme 4. 4 EI Mass fragmentation of compound **4.8c**

In addition to synthesis of isoxazolines, some bioactivity assays will be underway in the near future.

Part 2: Tandem nitrosation/cycloaddition of heterocyclic enamines using nitrolic acids

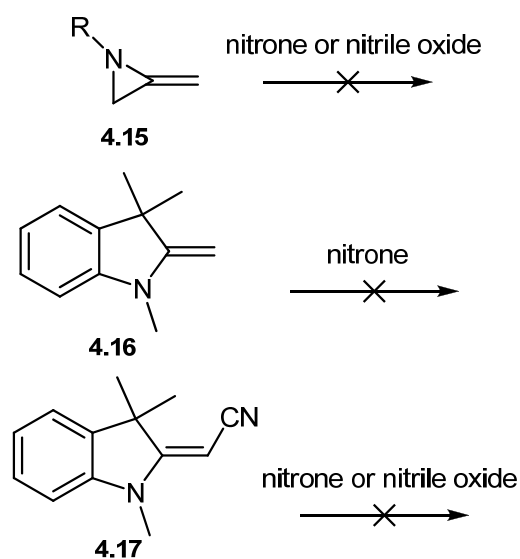
As mentioned in the introduction (Chapter 2), the spiroisoxazoline moiety is found in many natural products. Nitrile oxide cycloadditions to methylenecyclopropanes, alkylidenecyclopropanes **4.12** and bicyclopropylidenes **4.11** have widely been utilized for the highly regio and stereoselective synthesis of spiroisoxazolines **4.13** and **4.9**, respectively (Scheme 4.5) [101].



Scheme 4. 5 Nitrile oxides-alkylidene cyclopropanes cycloaddition

In this perspective, we have tried many reaction between 1,3-dipoles, (nitrile oxides, nitrones) and various alkenes which possess exocyclic double bond. As it was mentioned in progress report 1, we couldn't get satisfactory results from the reactions of abovementioned dipoles with *N*-substituted 2-methylene aziridines **4.15**, 1,3,3-trimethyl-2-methylene indoline **4.16** and 2-(1,3,3-trimethylindolin-2-ylidene)acetonitrile **4.17** (Scheme 4.6) [102]. It is difficult to rationalize the relative (un)reactivity of the methyleneaziridines with nitrile oxides and nitrones, since computational studies show that there is no favourable interaction between the lone pair of electrons and the π -electrons of the double bond, i.e. the nitrogen is pyramidal, directing the lone pair away from the exocyclic π -bond [103].

The electron withdrawing of cyano- group on methyleneindoline **4.17**, might have an effect to increase reactivity of this dipolarophile but we also did not obtain expected product from this reaction even though different conditions and solvents were tried, so a possible explanation could be that the cyano group sterically hinder alkene moiety and it decreases essentially the reactivity of this compound **4.17**.



Scheme 4. 6 Attempted reactions of dipoles (nitrones and nitrile oxides) with dipolarophiles

In second progress report, we have have been involved in 1,3-dipolar cycloaddition reactions of nitrile oxides and nitrones with novel electron rich iminic dipolarophiles **4.18** and **4.19**. But, unfortunately, the reaction did not produce desired products in both cases [104].

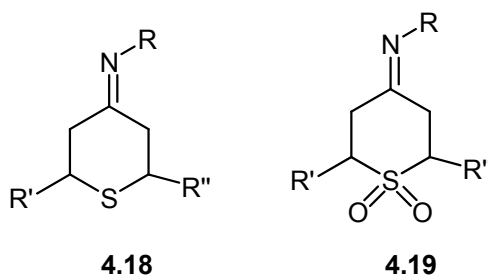
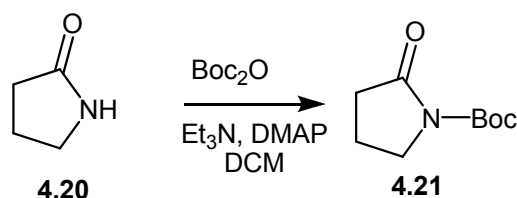


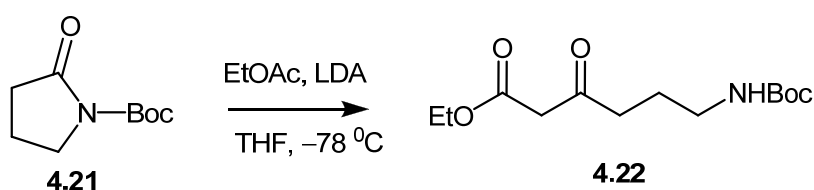
Figure 4. 3 Some of electron rich iminic dipolarophiles

Due to the failure of above trials, then we have been directed into the cycloaddition reactions of nitrile oxides and nitrones with alkylidene pyrrolidines. The first efforts focused on the conversion of the ethyl 2-(pyrrolidin-2-ylidene)acetate **4.23** prepared from the initial addition of di-*tert*-butyl dicarbonate to pyrrolidin-2-one in the presence of Et₃N and catalytic amount of *p*-*N,N*-dimethylaminopyridine in DCM at room temperature as a Boc protection group to lactam in order to prevent strong base attack to amide (Scheme 4.7) [105].



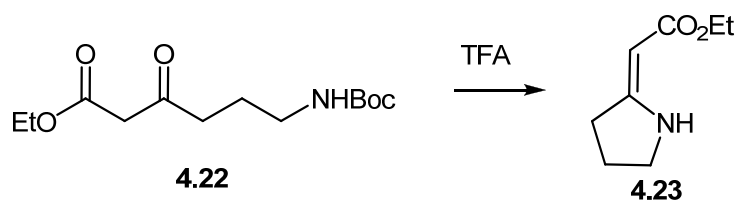
Scheme 4. 7 Synthesis of Boc protected 2-pyrrolidinone

Next step is deprotonation of ethylacetate by adding lithium diisopropylamide which is prepared *in situ* using diisopropylamine and buthyl lithium at -78°C . Then attack of nucleophile to Boc protected lactam results 1,3-diketone **4.22** (Scheme 4.8).



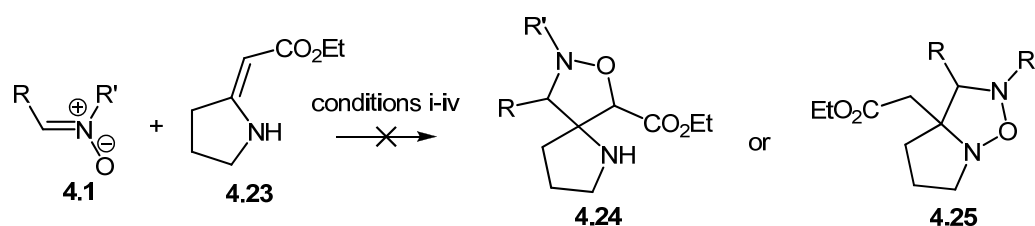
Scheme 4. 8 Ring opening reaction of *N*-Boc-2-Pyrrolidinone

Cyclisation precursor, 1,3-diketone, treated with trifluoroacetic acid without using any solvent yields ethyl 2-(pyrrolidin-2-ylidene)acetate **4.23** (Scheme 4.9).



Scheme 4. 9 Ring-closing with trifluoroacetic acid

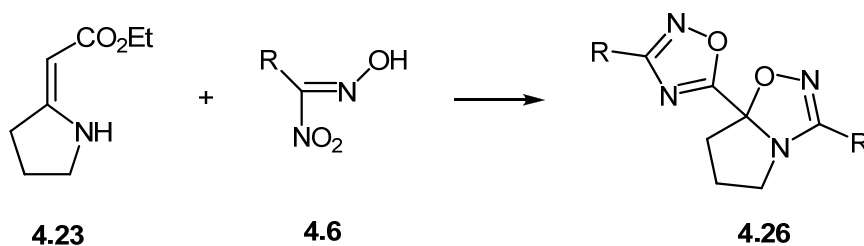
Reactions of nitrones with alkylidene pyrrolidine were unsuccessful to give the expected cycloadducts. Even we tried different solvents and conditions but none of the conditions were successful (Scheme 4.10).



Conditions : *i.* DCM, reflux, 18h, *ii.* Zn, DCM, reflux, 18 h, *iii.* Toluene, reflux
iv. MW, 100 W, 110 °C, 30 min, 240 Psi

Scheme 4. 10 Conditions for nitron-alkylidene pyrrolidine reactions

Although alkylidene pyrrolidines seem to show dipolarophile character at double bond, they did not behave as dipolarophile to give desired spiro compounds. Instead of spiro compounds, the reaction between nitrolic acids and alkylidenepyrrolidines result in unexpected tricyclic compounds **4.26** [106].



Scheme 4. 11 Tandem cycloaddition of nitrolic acid

The assignment of the signals from the tricyclic ring which contains oxadiazole-oxadiazoline moiety was fairly difficult. Although aliphatic and

aromatic protons and carbons were assigned by ^1H and ^{13}C NMR spectra and in addition, exact mass measurement supported molecular weight, we were still away from ruling out the exact structure due to decarboxylation of ethylacetate moiety was not easy and spectral data were not enough for this explanation but recrystallization of compound **4.26a** from CDCl_3 gave single fine crystals and structure of the compound eventually could be elucidated by single crystal X-Ray diffraction (Figure 4.4).

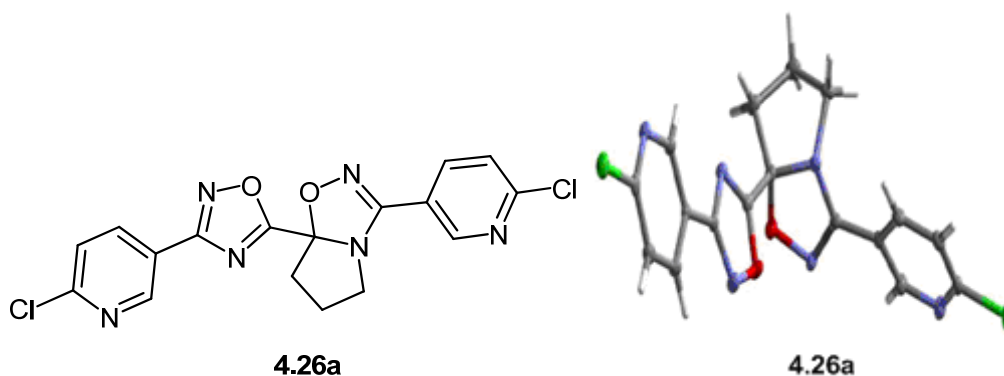
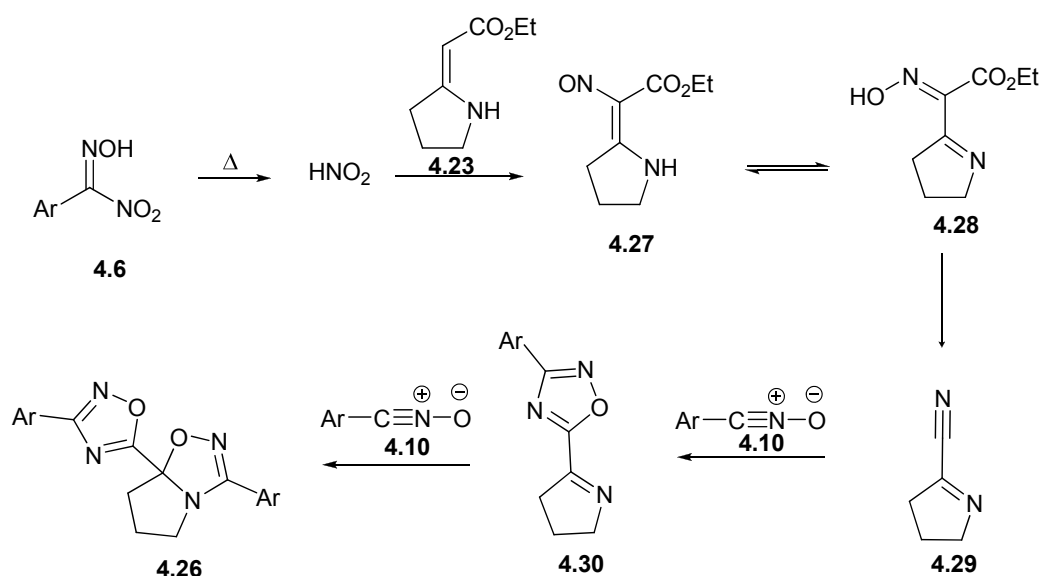


Figure 4. 4 X-Ray diffraction for compound **4.26a**

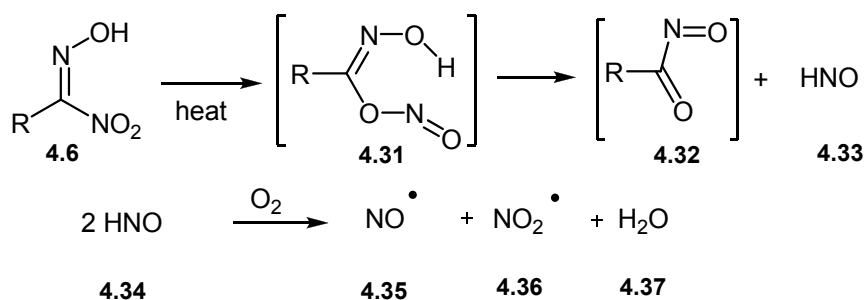
The transformation to tricyclic compound **4.26** starting from corresponding nitrolic acid and alkylidene pyrrolidine is extremely intriguing. The alkylidenepyrrolidine ester appears to have undergone hydrolysis/decarboxylation, which is unusual under such mild conditions. Two equivalents of the nitrolic acid have been incorporated, with one of them appearing to retain the nitrogen of the nitro group. Although we are unable to give a definitive mechanism, the following (Scheme 4.12) is plausible, and is supported by some experimental data.



Scheme 4. 12 Plausible mechanism for synthesis of compound **4.26**

The most probable driving force for the formation of **4.30** is the creation of a stable aromatic 1,2,4-oxadiazole system through the decarboxylation of ethylacetate. Alternatively, since the reaction conditions are acidic (evaluation of nitrous acid), it is quite possible for alkylidenepyrrolidine, **4.23**, to decompose to the corresponding nitrile before reacting with the nitrile oxide. The experimental data point to the formation of **4.28** followed by decarboxylation then two equivalents of nitrile oxide results corresponding cycloadduct **4.26**.

Nitrosyl formation mechanism might also be possible *via* nitrosyl radical which can be given by following transformation (Scheme 4.13).



Scheme 4. 13 Formation mechanism of nitrosyl radical

During the optimization studies, the reaction was carried out in different solvent systems. It was observed that though benzene and toluene gave similar cyclization derivatives, the best yields were achieved when the reaction was performed in benzene. The reaction failed to occur in DMSO (Table 4.2). In order to evaluate the generality of this reaction several analogues of novel 3,7a-disubstituted (1,2,4-oxadiazol-5-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4] oxadiazoles **4.26 a-d** were synthesized.

R	Product	Solvent	Time	Equivalent 4.6
6-Chloro-3-pyridyl	4.26	Benzene	2h, reflux	1 eq.
3-Pyridyl	No product	Benzene	2h, rt	1.5eq
3-Pyridyl	4.26	toluene	18 h, reflux	1 eq
4-Pyridyl	No product	THF	2h, reflux	2 eq
4-Pyridyl	4.27	Benzene	18 h, rt	1 eq.
4-Pyridyl	No product	DMSO	18 h at 80 ⁰	2 eq.
Ph	4.27	Benzene	2h, reflux	1 eq

Table 4. 2 Optimization reactions for compound **4.26**

Three other nitrolic acids were used in the above reaction. In all cases, the reactions were more sluggish, but could be accelerated by microwave heating to provide similar products in good yields (Table 4.3). In all cases, complete consumption of the alkylidenepyrrolidine reagent **4.23** was observed.

Compound	R	Conditions	Yield/%
4.26 a	6-Chloro-3-pyridyl	Benzene, reflux, 2 h	76
4.26 b	3-Pyridyl	110 °C, 100 W, 10 min	66
4.26 c	4-Pyridyl	110 °C, 100 W, 10 min	58
4.26 d	Me	Toluene, reflux, 2 h	65

Table 4. 3 Reaction conditions for compound **4.26 a-d**

Variable amounts of a by-product were observed in the ^1H NMR data of the crude reaction mixtures. Under milder conditions that used in Table 4.2, this became a significant side-product, and appeared to be consistent with either structure **4.27** or **4.28**. Upon chromatography, compound **4.28** was obtained (^1H NMR, ^{13}C NMR, IR, MS). This was similar but not identical to the compound that we had observed in the crude reaction mixtures, which we would therefore attribute to the compound **4.28** (Figure 4.5).

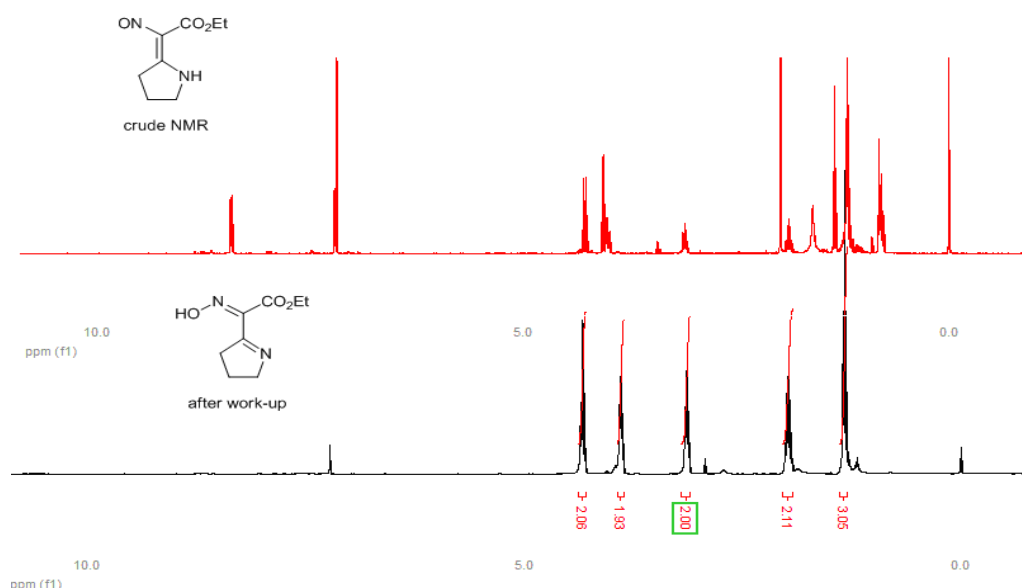


Figure 4. 5 Comparing ^1H NMR of crude and after work-up **4.27** and **4.28**.

In particular, iminic carbon of the oxime in compound **4.28** resonates at 143.2 ppm, whereas the corresponding carbon in alkylidenepyrrolidine

4.23 resonates at 76.5 ppm. Nitrosation of the alkene, as in compound **4.27**, is unlikely to lead to such a dramatic increase, whereas related α -oximinoesters show almost identical chemical shifts [107].

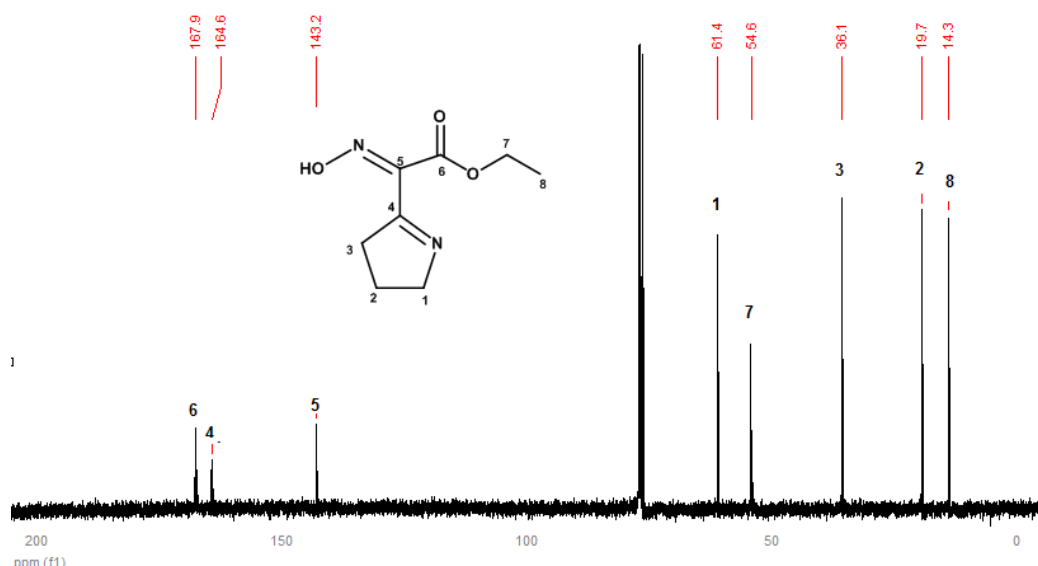


Figure 4. 6 ^{13}C NMR spectra of compound **4.28**

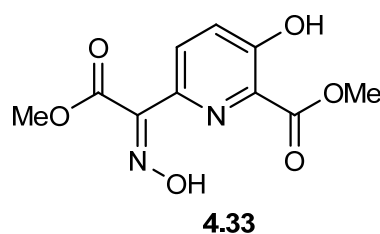
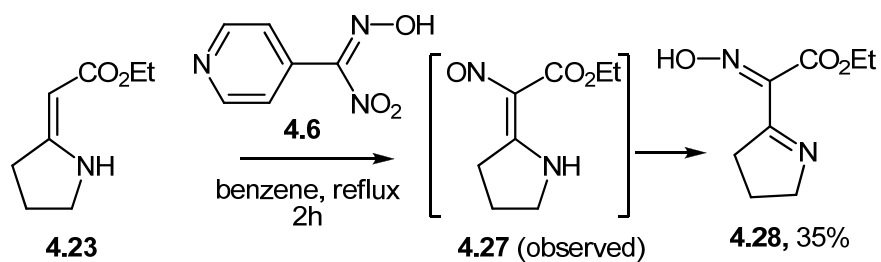


Figure 4. 7 Chemical shift for α -oximinoesters

Reaction of phenylnitrolic acid only gave compounds **4.27/28**, with compound **4.26** not observed even under forcing conditions.

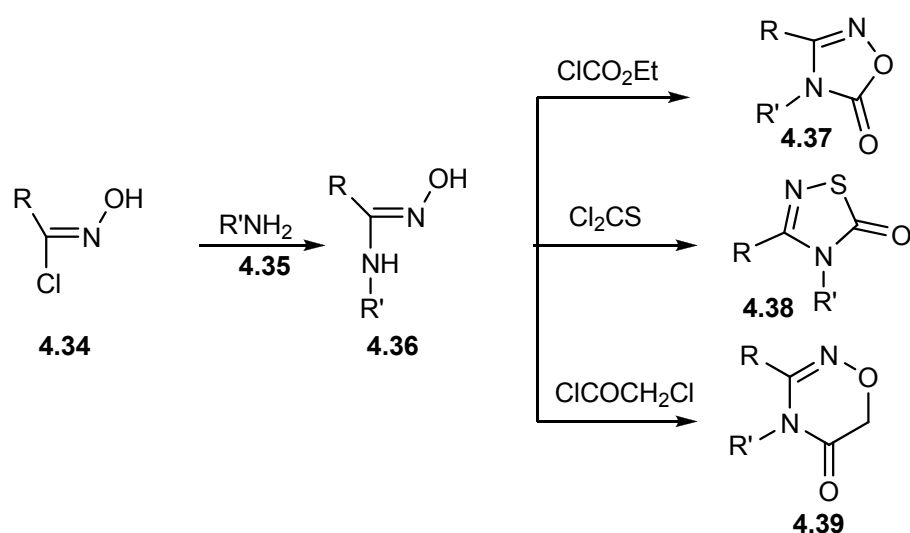


Scheme 4. 14 Formation of compound **4.28**

Part 3: Reactions of Alkylidenepyrrolidines with α -chlorooximes

α -Chlorooximes are widely used mainly as precursors of nitrile oxide for use in cycloaddition chemistry. However, they can also be considered as highly functionalised electrophiles due to the chlorine.

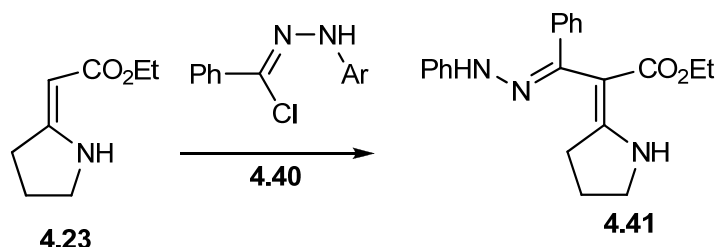
We have previously used α -chlorooximes in the synthesis of *N*-substituted amidoximes which subsequently then were converted to 1,2,4-oxadiazol-5(4H)-ones **4.37**, 1,2,4-oxadiazol-5(4H)-thiones **4.38** and 1,2,4-oxadiazin-5(6H)-ones **4.39** (Scheme 4.15) [108].



Scheme 4. 15 Reaction of α -chlorooximes

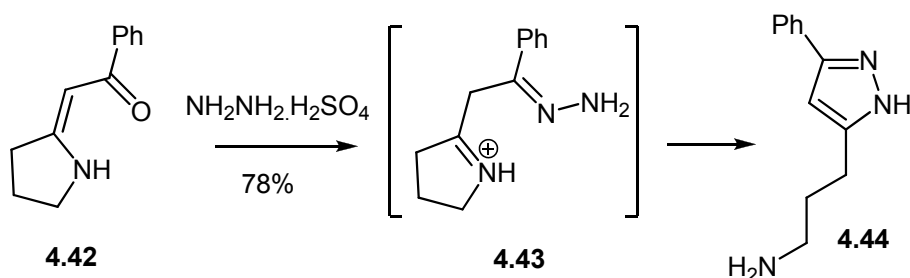
At the first part of the present work, nitrolic acids were used as nitrile oxide precursors, while the addition of the dipolarophile to nitrile oxide generated from nitrolic acid is expected, due to having nitro group, nitrolic acid exhibited also as nitrosyl source and thus the reaction went to completion in an unexpected way. Two sequential cycloaddition reactions then took place to give the observed products.

The reaction of alkylidenepyrrolidines such as **4.23** with α -chlorohydrazones **4.40** has been reported to give products **4.41**, by simple acylation of the alkylidenepyrrolidine double-bond (**Scheme 4.18**) [109].



Scheme 4. 16 Substitution of nitrilimine to alkylidenepyrrolidine

This preference for C-acylation is unsurprising. The possibility that the product **4.44** could isomerise to give the corresponding pyrazoles was mentioned by the authors, although it was not observed in this instance.



Scheme 4. 17 Ring isomerization to pyrrolole

If at least one substituent at the nitrogen is hydrogen, the enamines show tautomeric proton exchange to the corresponding imines **4.43**, which are generally thermodynamically the more favoured isomers. Due to the n,π -conjugation of the amino group with the $C=C$ double bond, the electron density is increased at the β -carbon atom as shown below by the mesomeric formula **4.42**. As a consequence, enamines may be attacked by electrophiles under mild conditions at the electron-rich β -

carbon (as indicated by the mesomeric formula 4.43) leading to iminium compounds [110].

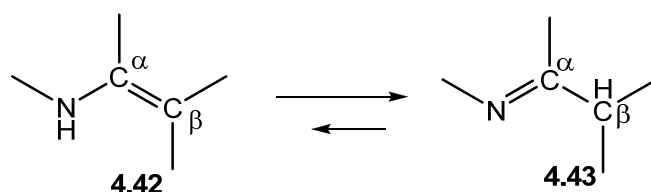
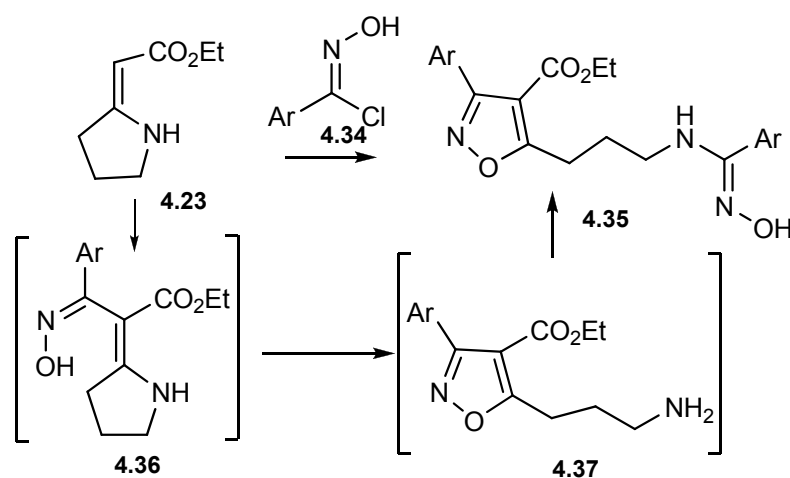


Figure 4. 8 Tautomerization of enamines

Reaction of alkylidene pyrrolidine **4.23** with α -chlorooxime **4.34** occurs presumably through by an initial acylation to give compound **4.36** followed by isomerisation to give **4.37** and a rapid second acylation to give the observed products. Use of a single equivalent of the α -chlorooxime gave the same products, but in lower yield and with some alkylidenepyrrolidine left unreacted.



Scheme 4. 18 Reaction mechanism for isoxazole transformation

Isoxazoles have been reported to possess a range of useful biological activity. In particular, a wide range of the compounds closely related to the structure **4.38** are ghrelin receptor modulators, having potential for the treatment of a range of eating disorders [111].

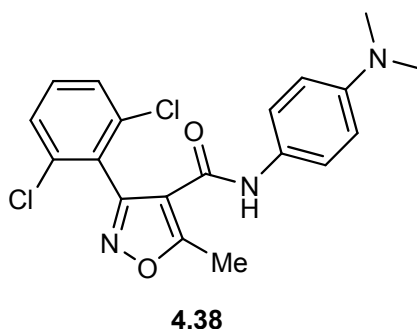
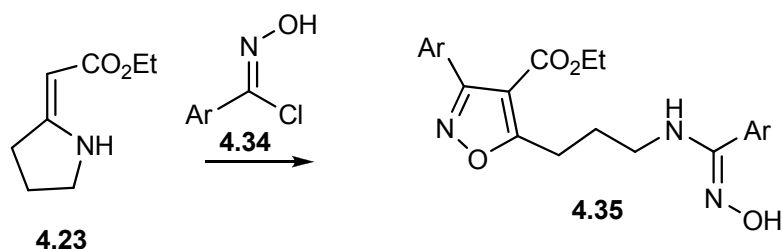


Figure 4. 9 Compound **4.38** shows biological activity against eating disorders

Therefore a new method for the formation of such compounds from readily-available starting materials is noteworthy. The reverse of the ring transformation in **Scheme 4.19** is known, leading to the formation of aromatic pyrrole compounds from suitably-substituted isoxazoles [112].

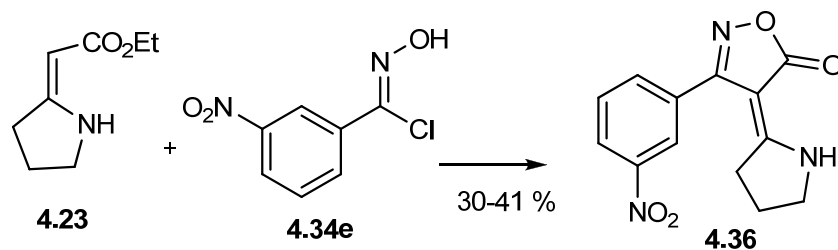


Scheme 4. 19 Reaction of alkylidenepyrrolidine with hydroximoylchlorides

Compound	Ar	Yield/%
4.35a	2,6-Dichlorophenyl	69
4.35b	2,4-Dichlorophenyl	67
4.35c	Phenyl	68
4.35d	2-Nitrophenyl	56

Table 4. 4 Formation of adducts **4.35a-d**

Surprisingly, when the 3-nitrophenyl α -chlorooxime **4.34e** was used, compound **4.36** was obtained as the sole product (Scheme 4.22). This result is entirely reproducible, although it is not clear why the oxime cyclises onto the ester in this case, but onto the alkylidenepyrrolidine ring in other cases.



Scheme 4. 20 Formation of compound **4.36**

However, from the reaction ketones with hydroxylamine and subsequently oximes generated in this way with alkylidenepyrrolidine leading to isoxazoles have been reported [113]. NMR data for these compounds are similar to those reported by Dannhardt et al. for analogues lacking the ester and side-chain acylation, although as would be expected, the chemical shifts of the methylene groups adjacent to nitrogen and to the isoxazole ring are slightly higher in compounds.

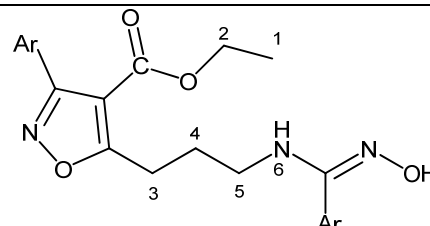
 4.35				
	4.35a	4.35b	4.35c	4.35d
H-1	0.90, t	1.01, t	1.05, t	0.95
<i>J</i>	7.1	7.1	7.1	-
H-2	4.01 q	4.07 q	4.09 q	4.04 q
<i>J</i>	7.1	7.1	7.1	7.1
H-3	3.13 t	3.09 t	3.09-2.94 m	3.10 t
<i>J</i>	7.4	7.4	-	7.4
H-4	1.88 app. q	1.87 app. q	1.79 app. q	1.89 app. q
<i>J</i>	7	7.2	7.2	7.1
H-5	2.88 app. q	2.93 app. q	3.09-2.94 m	2.95 app. q
<i>J</i>	5.1	6.5	-	6.4
H-6	5.57 br s	5.52 br t	5.45 br s	5.53 br s
<i>J</i>	-	5.7	-	-

Table 4. 5 The proton chemical shifts in ppm and coupling constants for stereochemically essential aliphatic protons in Hz) for compounds **4.35a-d** in CDCl₃ at 298 K referenced internally to TMS (0.00 ppm).

Part 4. Reaction of Phenyl Sulfonyl Substituted Alkylidene Pyrrolidines with Nitrile Oxides

As part of the research on the investigation of the reactions of alkylidene pyrrolidines with nitrile oxides at this stage we turned our attention to the synthesis of achiral and chiral 2-phenylsulfonylmethylene substituted pyrrolidines **4.37** and **4.38**, respectively. 2-Phenylsulfonylmethylene substituted achiral alkylidene pyrrolidines were synthesized by Elliot et al. in high yields [114]. Chiral phenyl sulfonyl substituted alkylidene pyrrolidine **4.38** is firstly synthesized and characterised by means of IR, ^1H , ^{13}C NMR and MASS spectrum.

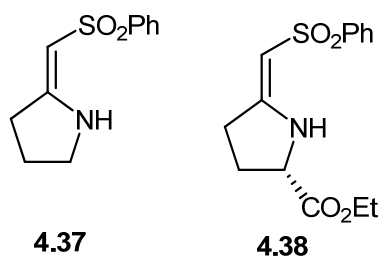
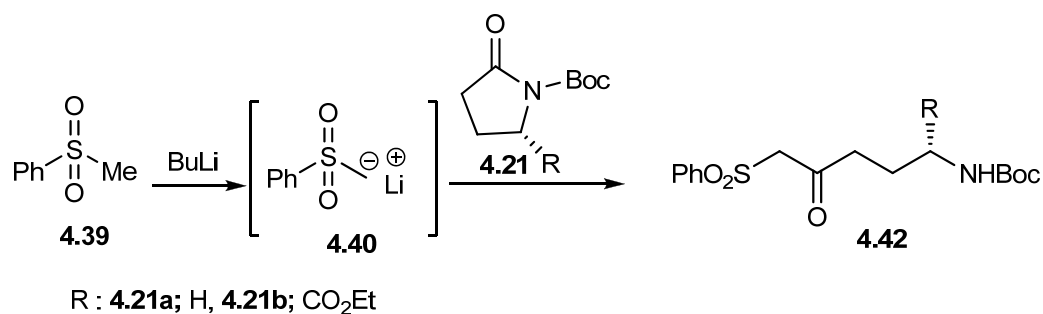


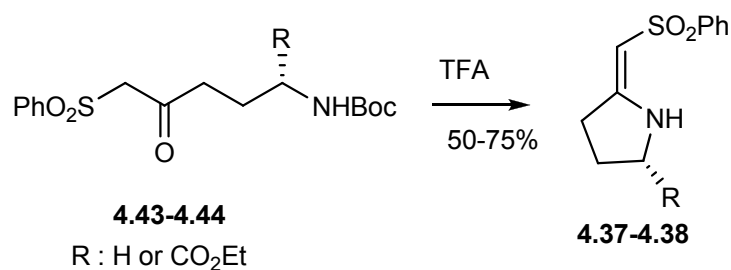
Figure 4. 10 Phenylsulfonyl substituted achiral and chiral alkylidene pyrrolidines **4.37** and **4.38**

Corresponding alkylidene pyrrolidines were prepared from lithiation of phenyl methyl sulfone with *n*-butyllithium in THF at $-78\text{ }^{\circ}\text{C}$ and formed lithium anions treated with *N*-carbo-*tert*-butoxy-2-pyrrolidinone or (*R*)-1-*tert*-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate at $-78\text{ }^{\circ}\text{C}$ to give desired cyclisation precursors respectively **4.37** and **4.38**. Product was used without purification in the latter case.



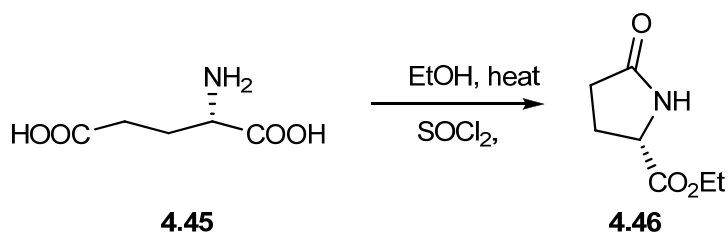
Scheme 4. 21 Formation of compound **4.42**

The protected ω -amino keto sulfones **4.42a** and **4.42b** were converted into the enamines **4.37** and **4.38** by trifluoroacetic acid. The substrate for the key step, **4.42**, was prepared as shown in **Scheme 4.24**, albeit in relatively low yield in chiral one. In both cases the resulting products **4.37** and **4.38** were isolated 50-75% overall yield after basic workup and column chromatography with hexane/ethyl acetate as waxy oils.



Scheme 4. 22 Synthesis of compounds **4.37** and **4.38**

Chiral phenylsulfonyl substituted alkylidene pyrrolidine **4.38** was also prepared in same way like achiral one but instead of 2-pyrrolidinone as a starting material, *L*-glutamic acid was used to synthesize the corresponding chiral pyrrolidin-2-one [115].



Scheme 4. 23 Formation of compound **4.46**

Reactions of *N*-substituted alkenes with various substances which are electron-deficient olefins to give [2 + 2] cycloadducts [116], with ketenes [117] or with dipoles to yield cycloadducts has been investigated [118]. The yield of products depends critically on the kind of substitution on nitrogen or β -carbon atom.

The $^1\text{H-NMR}$ studies for phenyl sulfonyl substituted alkylidene pyrrolidines, enamines are in a dynamic equilibrium with the imine tautomers **4.48** showed that enamine **4.37** was formed in a 5:1 ratio together with imine **4.48** which was identified by its absorption at 4.20 ppm corresponding to the exocyclic methylene protons [119].

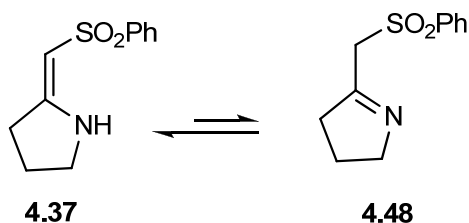
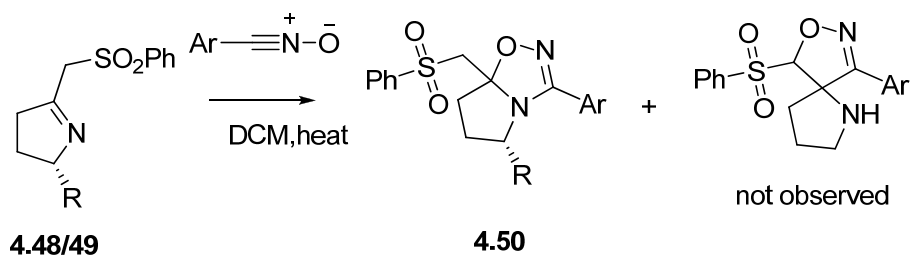


Figure 4. 11 Tautomerization of compounds **4.37** and **4.48**

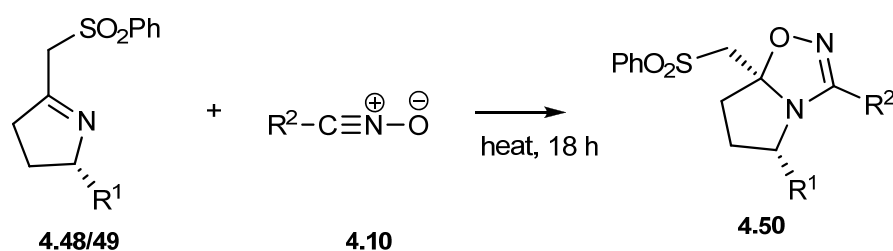
Instead of spiro adduct **4.45** we have observed cycloaddition of nitrile oxides to iminic part **4.48/49**.



Scheme 4. 24 1,3-Dipolarcycloaddition of nitrile oxides to Phenylsulfonyl substituted alkylidene pyrrolidine

The very basic proof of the generation of the aryloxime is the disappearance of the carbonyl absorption of the corresponding aldehyde in the IR spectrum of the crude product during the course of reaction. On the other hand, the polar structure of the α -chlorooxime in comparison with the oxime prevents it ascending much higher point on thin layer chromatography plates.

Nitrile oxides **4.10** were almost always generated in situ in order to avoid dimerization. The chiral phenylsulfonyl substituted alkylidene pyrrolidine react with equimolar of nitrile oxide to yield isoxazole **4.50** with complete diastereocontrol in moderate to high yields (Scheme 4.25). From literature precedent and theoretical considerations, it was reasonable to predict that we would achieve the 1,2,4-oxadiazolin regioisomer as the major product.



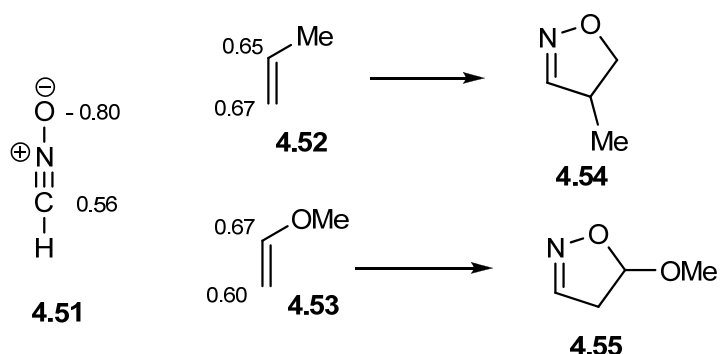
Scheme 4. 25 Synthesis of compound **4.50**

Product	R ¹	R ²	Yield %
4.50a	H	3-Pyridyl	58
4.50b	H	4-Pyridyl	68
4.50c	H	Ph	69
4.50d	H	2-Thienyl	78
4.50e	H	4-Br-C ₆ H ₄	66
4.50f	H	4-F-C ₆ H ₄	73
4.50g	H	2,6-DiClC ₆ H ₃	75
4.50h	H	2-NO ₂ C ₆ H ₄	71

Product	R ¹	R ²	Yield %
4.50i	H	3-NO ₂ C ₆ H ₄	76
4.50j	H	2,4-DiClC ₆ H ₃	44
4.50k	CO ₂ Et	Ph	46
4.50l	CO ₂ Et	2,6-DiClC ₆ H ₃	51
4.50m	CO ₂ Et	4-Br-C ₆ H ₄	29
4.50n	CO ₂ Et	2,4-DiClC ₆ H ₃	65
4.50o	CO ₂ Et	4-F-C ₆ H ₄	56

Table 4. 6 Substituents and reaction yields

FMO orbital theory predicts that nitrile oxides should react faster with electron rich alkenes (vinyl ethers, enamines, or simple alkenes. The orbital coefficients suggest that propene reacts with **4.52** (HOMO dipole-LUMO_{dipolarophile}) to give **4.54**. This obviously depends on the substrate, but substituents that are adjacent to the carbon that possesses an electron releasing group (such as methyl vinyl ether to give **4.53**) or electron withdrawing group are preferred. The reversal in selectivity may be due to the alkyl group on the nitrile oxide [120].



Scheme 4. 26 HOMO-LUMO interaction for electron-rich and electron-poor dipolarophiles

	4.50a	4.50b	4.50c	4.50d	4.50e
H-4	3.68 app. s	3.69 d	3.69 d	3.69 d	3.66 app. s
<i>J</i>		14.8	14.8	14.9	
H-4'	3.68 app. s	3.64 d	3.67 d	3.63 d	3.66 app. s
<i>J</i>		–	–	–	–
H-1	3.13 app. dd	3.20 – 3.10 m	3.21 – 3.01 m	3.34 – 3.26 m	3.09 app. dd
<i>J</i>	10.4, 4.3	–	–	–	9.7, 4.0
H-1'	3.13 app. dd	3.20 – 3.10 m	3.21 – 3.01 m	3.12 app. dt	3.09 dd
<i>J</i>	10.4, 4.3	–	–	11.2, 5.7	9.7, 4.0
H-3	2.77 ddd	2.75 ddd	2.73 ddd	2.72 ddd	2.74 ddd
<i>J</i>	14.2, 11.8, 6.9	14.2, 11.7, 6.9	14.1, 11.7, 7.0	14.2, 11.6, 7.0	14.2, 11.7, 7.0
H-3'	2.41 ddd	2.42 ddd	2.38 ddd	2.39 br dd,	2.38 ddd,
<i>J</i>	14.2, 7.1, 1.7	14.2, 7.3, 1.7	14.1, 7.1, 1.0	14.2, 6.9	14.2, 7.0, 1.6
H-2	1.95 – 1.86 m	1.95 – 1.86 m	1.89 – 1.79 m	1.90 – 1.71 m	1.91 – 1.82 m
H-2'	1.84 – 1.70 m	1.82 – 1.68 m	1.78 – 1.67 m	1.90 – 1.71 m	1.81 – 1.71 m

Table 4. 7 The proton chemical shifts in ppm and coupling constants for stereochemically essential aliphatic protons in Hz for compounds **4.50 a-e** in CDCl₃ at 298 K referenced internally to TMS (0.00 ppm).

	4.50f	4.50g	4.50h	4.50i	4.50j
H-4	3.66 app. s	3.88 d	3.75 d	3.69 app. s	3.71 d
<i>J</i>	–	14.6	14.7		14.7
H-4'	3.66 app. s	3.56 d	3.61 d	3.69 app. s	3.64 d
<i>J</i>	–	–	–	–	–
H-1	3.13 – 3.07 m	3.24 – 3.17 m	3.15 – 3.08 m	3.19 – 3.07 m	3.03 – 2.99m
<i>J</i>	–	–	–	–	–
H-1'	3.13 – 3.07 m	2.92 – 2.84 m	2.94 app. td	3.19 – 3.07 m	3.03 – 2.99m
<i>J</i>	–	–	11.1, 6.2	–	–
H-3	2.73 ddd	2.68 ddd	2.61 ddd	2.78 ddd	2.68 ddd
<i>J</i>	14.1, 11.7, 7.0	14.4, 10.7, 8.0	14.2, 11.0, 7.6	14.2, 11.8, 6.9	14.2, 11.5, 7.0
H-3'	2.38 ddd	2.56 – 2.49 m	2.50 – 2.43 m	2.41 ddd	2.68 ddd
<i>J</i>	14.1, 7.2, 1.6			14.2, 7.3, 1.2	14.2, 11.5, 7.0
H-2	1.89 – 1.82 m	1.97 – 1.88 m	1.98 – 1.85 m	1.95 – 1.86 m	2.41, ddd
<i>J</i>	–	–	–	–	14.2, 7.3, 2.1
H-2'	1.80 – 1.70 m	1.97 – 1.88 m	1.98 – 1.85 m	1.82 – 1.71 m	1.92 – 1.70m

Table 4. 8 The proton chemical shifts in ppm and coupling constants for stereochemically essential aliphatic protons in Hz) for compounds **4.50 f-j** in CDCl₃ at 298 K referenced internally to TMS (0.00 ppm).

For the compound **4.50i** one C_q is missing from ¹³C NMR and this must be due to overlap of peaks since spectrum is excellent and for the another compound **4.50l** in ¹³C NMR spectrum one C_q is missing and there is a broad peak that might be due to hindered rotation.

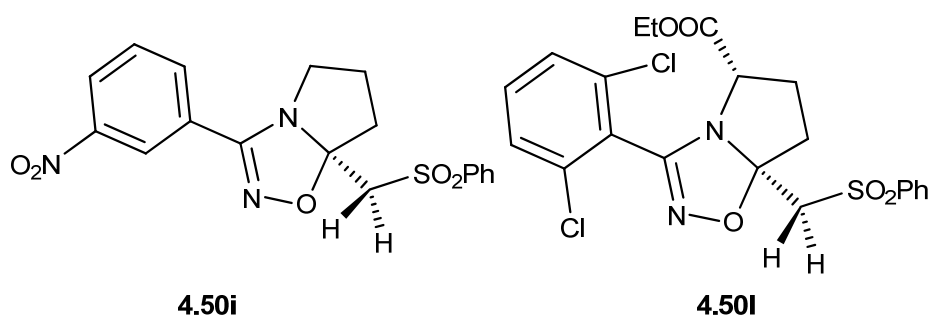
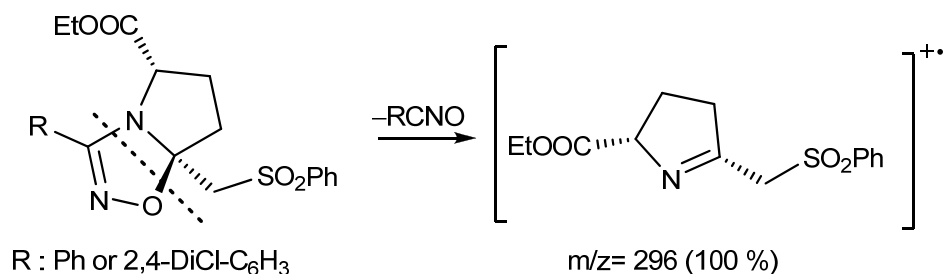


Figure 4. 12 Compound **4.50i** and **4.50l**

Electron ionization mass spectra of the compounds **4.50k** and **4.50n** were considered to show retro-cycloaddition mainly the following fragmentation pathways depicted in Scheme 4.30.



Scheme 4. 27 EI Mass spectra for compounds **4.50k** and **4.50n**

The stereochemistry of the bicyclic products has been established by standard ¹H, ¹³C NMR, the values of the coupling constants and the NOESY experiments being particularly diagnostic. Table 4.9 shows the most important proton chemical shifts and coupling constants data for compounds **4.50 k-o**.

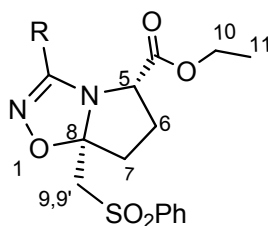


Figure 4. 13 General representation of compounds 4.50 k-o

	4.50k	4.50l	4.50m	4.50n	4.50o
H-5	3.98 dd	3.95 dd	3.92 dd	3.81 dd	3.94 dd
<i>J</i>	7.2, 2.2	7.6, 2.1	8.0, 1.4	5.3, 4.2	7.9, 1.5
H-6	2.15 – 2.04 m	2.34 – 2.09 m	2.18 – 2.03 m	2.12 – 2.04 m	2.18 – 2.04 m
H-7	2.65 – 2.60 m	2.79 – 2.56 m	2.65 – 2.59 m	2.69 – 2.54 m	2.64 – 2.59 m
H-9	3.88 d	4.04 d	3.85 d	3.92 d	3.86 d
<i>J</i>	14.7	14.8	14.7	14.8	14.3
H-9'	3.62 d	3.70 d	3.60 d	3.74 d	3.60 d
<i>J</i>	14.7	14.8	14.7	14.8	14.3
H-10	4.18 q	4.09 m	4.18 q	4.11 q	4.18 dq
<i>J</i>	7.1	–	7.1	–	7.1, 0.8
H-11	1.25	1.15	1.25	1.21	1.25
<i>J</i>	7.1	7.1	7.1	7.1	7.1

Table 4. 9 The proton chemical shifts in ppm and coupling constants particularly for aliphatic region protons in Hz for compounds 4.50 k-o in CDCl₃ at 298 K referenced internally to TMS (0.00 ppm).

The 1,3-dipolar cycloaddition (DC) reaction can furnish very complex heterocycles, containing multiple stereogenic centres. Therefore this reaction is often used as a key step in the syntheses of many natural products and pharmaceuticals. Reactions of enamines with nitrile oxides proceeded readily to give 1,2,4-oxadiazolines independently of the nature of substituents both in dipole and dipolarophile molecules.

4.2. Conclusion Remarks

In summary, in the first part of the thesis, we have demonstrated the synthesis of 14 new cycloaddition products from the reaction between nitrolic acids and Me or Ph sulfonyl substituted alkenes. The structure and regiochemistry of the cycloadducts were identified by means of ^1H NMR, ^{13}C NMR, COSY, NOESY, MASS and IR spectra.

In the second part, the first example of the chemical trapping of nitrous acid liberated from a nitrolic acid was performed, although there are reports of biological studies in which nitrolic acids are used as NO_2/NO sources [121]. Four novel heterocyclic compounds were synthesized in this way. The electron-rich double-bond of the alkylidenepyrrolidine clearly renders this a “special case”, although we would anticipate many other instances in which the nitrous acid would be trapped. This may therefore limit the applicability of nitrolic acids as nitrile oxide precursors.

In the third part, since the reaction of alkylidenepyrrolidine **4.23** with α -chlorooximes **4.34** has not been reported in the literature, to our best knowledge (Web of Science, SciFinder Scholar), we therefore reacted alkylidenepyrrolidine **4.23** with a range of α -chlorooximes **4.34 a-d**. Novel heterocyclic compounds **4.35 a-d** were obtained in good yields.

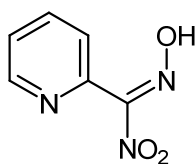
In the last part, 15 new cycloaddition products and a new chiral phenylsulfonyl substituted 2-alkylidene pyrrolidine were synthesized and characterized by the reaction of 5-(phenylsulfonylmethyl)-3,4-dihydro-2H-

pyrrole **4.37** and (S)-ethyl 5-(phenylsulfonylmethyl)-3,4-dihydro-2H-pyrrole-2-carboxylate **4.38** with nitrile oxides. The structures of these cycloadducts were elucidated by means of IR, ^1H -, ^{13}C -, COSY, NOESY-NMR and HRMS analyses.

EXPERIMENTAL

Microwave reactions were carried out in the CEM explorer instrument. Melting points were determined on a Gallenkamp and Electro Thermal melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 and Shimadzu FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^1H and at 100 MHz for ^{13}C at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (J) are reported in Hz. Multiplicity in ^1H -NMR is reported as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double triple doublet (dtd), double quartet (dq), triplet (t), and multiplet (m).

Pyridine-2-nitrolic acid (4.6a) [122]



A solution of the pyridin-2-carbaldehyde oxime (2.44 g, 20 mmol) in glacial acetic acid (16 mL) was cooled in an ice bath. Fuming nitric acid was added dropwise to this solution. Immediate precipitate was observed. The ice bath was removed, and the mixture was stirred at ambient temperature for 30 minutes. Then the reaction mixture was poured into ice and NaOH (2 M) was added dropwise until the pH was

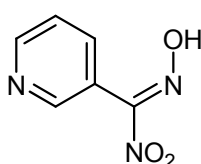
about 3-4. The precipitate was filtered and washed with cold water to give the *title compound* (1.60 g, yield 48%) as a pale yellow solid.

M.p. : 96-100 °C.

$\nu_{\max}$. (KBr) 1658, 1598, 1541, 1336, 1039, 1010, and 817 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 8.77 (d, J = 2.67 Hz, 1H), 8.35 (d, J = 1.58 Hz, 1H), 8.29 (s, 1H), 8.10 (d, J = 1.63 Hz, 1H), 7.81 (s, 1H).

Pyridine-3-nitrolic acid (4.6b)

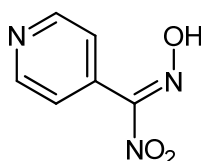


A solution of the pyridine-3-carbaldehyde oxime (2.44 g, 20 mmol) in glacial acetic acid (16 mL) was cooled in an ice bath. Fuming nitric acid was added dropwise to this solution. Immediate precipitate was observed. The ice bath was removed, and the mixture was stirred at ambient temperature for 30 minutes. Then the reaction mixture was poured into ice and NaOH (2 M) was added dropwise until the pH was about 3-4. The precipitate was filtered and washed with cold water to give the *title compound* (1.98 g, yield 48%) as a pale yellow solid.

M.p. : 98 decomp.

$\nu_{\max}$. (KBr) 1596, 1541, 1384, 1334, 1236, 1194, 1074 and 695 cm^{-1} .

Pyridine-4-nitrolic acid (4.6c)



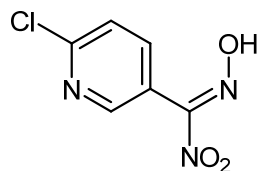
A solution of the pyridine-4-carbaldehyde oxime (2.44 g, 20 mmol) in glacial acetic acid (16 mL) was cooled in an ice bath. Fuming nitric acid was added dropwise to this solution. Immediate precipitate was observed. The ice bath was removed, and the mixture was stirred at ambient temperature for 30 minutes. Then the reaction mixture was poured into ice and NaOH (2 M) was added dropwise until the pH was about 3-4. The precipitate was filtered and washed with cold water to give the title compound (1.84 g, yield 55%) as a pale yellow solid.

M.p. 98 °C decomposed

ν_{max} . (KBr) 1604, 1546, 1419, 1280, 1222, 1055, 987 and 822 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 8.78 (d, $J = 0.7$ Hz, 1H), 7.81 (d, $J = 3.9$ Hz, 1H), 1.91 (s, 1H).

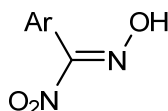
6-Chloropyridine-3-nitrolic acid (4.6d)



A solution of the 6-chloronicotinaldehyde oxime (3.12 g, 20 mmol) in glacial acetic acid (16 mL) was cooled in an ice bath. Fuming nitric acid was added dropwise to this solution. The ice bath was removed, and the mixture was stirred at ambient temperature for 30 minutes. Then the reaction mixture was poured into ice and NaOH (2 M) was added dropwise until the pH was about 3-4. The precipitate was filtered and washed with cold water to give the title compound (1.25 g, yield 62%) as a white solid.

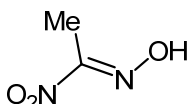
δ_{H} (400 MHz; CDCl_3) : 8.64 (d, J = 2.6 Hz, 1H), 8.03 (dd, J = 8.5, 2.6 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 3.37 (s, 1H)

General procedure for the synthesis of aryl nitrolic acids (4.6 e–j) [20]



A solution of corresponding aromatic aldehyde oxime (10 mmol) in dry ether (50 cm^3) was cooled to 0°C and excess dinitrogen tetraoxide^{123,124} (ca. 1.00 g) was added during 15 min. After 1 h at 20 °C the precipitate was removed by filtration. The filtrate was diluted with hexane (75 cm^3) washed with water and filtered again. The filtrate was evaporated at 0°C to give the nitrolic acid, residual water was removed in *vacuo* without heating. The crude product was used without further purification.

Ethyl nitrolic acid (4.6k) [125]



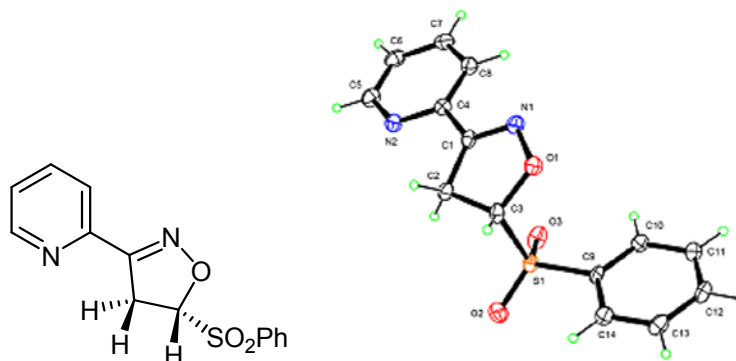
Sodium nitrite (8.9 g) was added to a solution of nitroethane (8 mL) in aqueous sodium hydroxide (4.3 g in 100 mL) at 0 °C. At the same time 5M sulphuric acid was added to maintain acidic pH in the reaction mixture. The aqueous solution was extracted with diethyl ether (3 x 50 mL) and dried over sodium sulphate, stored at 0 °C and used without further purification.

M.p. 82–83 °C (Lit. 80 °C) [126]

δ_{H} (400 MHz; CDCl_3) : 6.38 (s, 1H, OH), 1.58 (s, 3H, CH_3).

SYNTHESIS OF DIHYDROISOXAZOLES

(*R*)-5-Phenylsulfonyl-3-pyridin-2-yl-4,5-dihydroisoxazole (4.8a)



Pyridine-2-nitrolic acid (**4.6a**) (167 mg, 1.0 mmol) was added to phenyl vinyl sulphone (**4.7a**) (168 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 2 hours. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent petroleum ether:ethyl acetate 2:1) to give the title compound (187 mg, 65%) as a pale yellow solid which was recrystallized from ethylacetate/hexane to afford crystals suitable for single crystal X-ray diffraction.

M.p. 127-129°C.

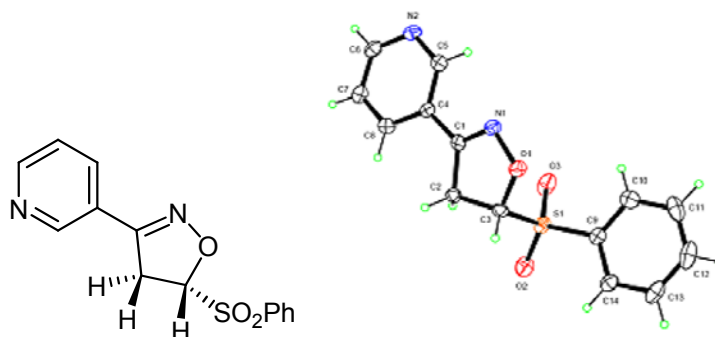
ν_{max} (KBr) 1580, 1444, 1364, 1306, 1150, 859, 783, 735 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 8.55 (d, $J=4.6$ Hz, 1H), 7.93 (d, $J=7.4$ Hz, 2H), 7.83 (d, $J=8.0$ Hz, 1H), 7.69-7.58 (m, 2H), 7.48 (t, 2H), 7.28 (m, 1H), 5.50 (dd, $J=11.0, 4.8$ Hz, 1H), 4.20 (dd, $J=9.3, 4.8$ Hz, 1H), 3.90 (dd, $J=9.2, 4.8$ Hz, 1H).

δ_{C} (100 MHz; CDCl_3) : 158.7 (C=N), 149.4, 147.2, 136.6, 135.4, 134.5, 129.7, 129.2, 125.1, 122.1, 93.7, 36.8.

Crystal Data : C₁₄H₁₂N₂O₃S, Mr = 288.32, Monoclinic, P2₁/n *a* = 5.3810 (10) Å *b* = 8.2117 (7) Å *c* = 29.564 (7) Å, β = 92.742 (9)° *V* = 1304.9 (5) Å³, *Z* = 4, *D*_x = 1.468 Mg m⁻³, *D*_m not measured, Mo K_α radiation, λ = 0.71073 Å, Cell parameters from 3214 reflections, θ = 2.5– 28.3°, μ = 0.257 mm⁻¹, *T* = 90 K, Needle, Colorless, 0.37 × 0.07 × 0.03 mm.

(*R*)-5-Phenylsulfonyl-3-pyridin-3-yl-4,5-dihydroisoxazole (4.8b)



Pyridine-3-nitrolic acid (**4.6b**) (167 mg, 1.0 mmol) was added to phenyl vinyl sulphone (**4.7a**) (168 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 2 hours. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent petroleum ether:ethyl acetate 2:1) to give the title compound (205 mg, 71%) as a colorless solid which was recrystallized from ethylacetate/hexan to afford crystals suitable for single crystal X-ray diffraction.

M.p. 154-155°C.

ν_{max}. (KBr) 1580, 1451, 1311, 1306, 1155, 851, 770, 735 cm⁻¹.

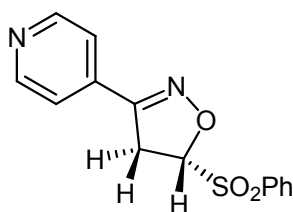
δ_{H} (400 MHz; CDCl_3) : 8.75 (s, 1H), 8.60 (s, 1H), 7.91 (t, 3H), 7.61 (t, 1H), 7.50 (t, 2H), 7.30 (m, 1H), 5.56 (dd, $J=10.9, 4.6$ Hz, 1H), 4.00 (dd, $J=8.3, 4.5$ Hz, 1H), 3.75 (q, 1H).

δ_{C} (100 MHz; CDCl_3) : 154.7 (C=N), 151.8, 147.8, 135.1, 134.7, 134.2, 129.7, 129.3, 128.3, 123.7, 93.5, 36.3.

MS (m/e, %): M- PhSO_2 , 146 (100), 78 (46), 51 (25).

Crystal Data : $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$, Mr = 288.32, Orthorhombic, $\text{P2}_1\text{2}_1\text{2}_1$, $a = 5.2052$ (10) Å, $b = 9.894$ (2) Å, $c = 25.166$ (7) Å, $V = 1296.1$ (5) Å³, $Z = 4$, $D_x = 1.478$ Mg m⁻³, D_m not measured, Mo K_α radiation, $\lambda = 0.71073$ Å, Cell parameters from 1779 reflections, $\theta = 2.5\text{--}28.7^\circ$, $\mu = 0.258$ mm⁻¹, $T = 90$ K, Plate, Colorless, $0.37 \times 0.22 \times 0.03$ mm.

(R)-5-Phenylsulfonyl-3-pyridin-4-yl-4,5-dihydroisoxazole (4.8c)



Pyridine-4-nitrolic acid (**4.6c**) (167 mg, 1.0 mmol) was added to phenyl vinyl sulphone (**4.7a**) (168 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 2 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent petroleum ether:ethyl acetate 2:1) to give the *title compound* (170 mg, 49%) as a yellow solid.

M.p. 151-152°C.

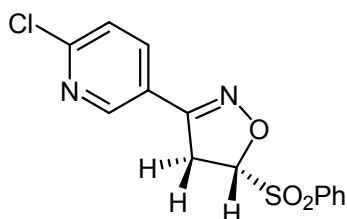
ν_{max} . (KBr) 1595, 1444, 1408, 1363, 1309, 1146, 862, 824, 735 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 8.72 (d, $J=5.8$ Hz, 2H), 8.02 (d, $J=7.6$ Hz, 2H), 7.73 (t, 1H), 7.61 (t, 1H), 7.50 (d, $J=5.9$ Hz, 2H), 5.56 (dd, $J=10.9, 4.6$ Hz, 1H), 4.10 (dd, $J=8.3, 4.6$ Hz, 1H), 3.80 (q, 1H).

δ_{C} (100 MHz; CDCl_3) : 155.5 (C=N), 150.3, 137.2, 135.0, 134.8, 129.7, 129.4, 120.9, 93.6, 35.9.

MS (m/e, %): M- PhSO_2 , 146 (100), 78 (44), 51 (28).

(R)-3-(6-Chloropyridin-3-yl)-5-phenylsulfonyl-4,5-dihydroisoxazole (4.8d)



6-Chloro-pyridine-3-nitrolic acid (**4.6d**) (201 mg, 1.0 mmol) was added to phenyl vinyl sulphone (**4.7a**) (168 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 2 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent; petroleum ether:ethyl acetate 2:1) to give the title compound (268 mg, 72%) as a yellow solid.

M.p. 142-144°C.

ν_{max} . (KBr) 1584, 1480, 1408, 1369, 1308, 1151, 1110, 859, 765 and 729 cm^{-1} .

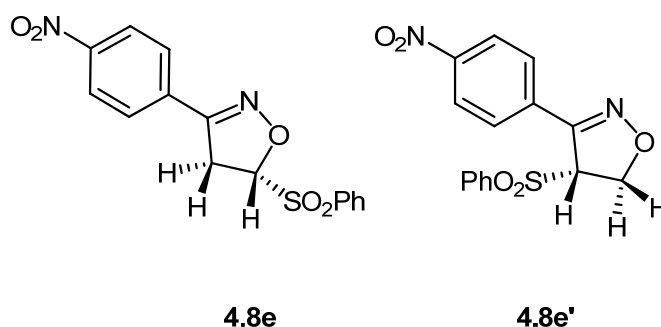
δ_{H} (400 MHz; CDCl_3) : 8.56 (d, $J=2.0$ Hz, 1H), 7.98 (m, 3H), 7.70 (m, 1H), 7.58 (t, 3H), 7.37 (d, $J=5.9$ Hz, 2H), 5.60 (dd, $J=10.9, 4.5$ Hz, 1H), 4.10 (dd, $J=18.3, 4.5$ Hz, 1H), 3.80 (q, 1H).

δ_{C} (100 MHz; CDCl_3) : 153.9 (C=N), 148.5, 136.6, 135.1, 129.7, 129.4, 124.7, 122.7, 93.3, 36.1. MS (m/e , %): M- PhSO_2 , 180 (100), 152 (19), 112 (28), 76 (44), 50 (28).

(*R*)-3-(4-Nitrophenyl)-5-phenylsulfonyl-4,5-dihydroisoxazole (4.8e)

(*R*)-3-(4-Nitrophenyl)-4-phenylsulfonyl-4,5-dihydroisoxazole (4.8e')

(It was deduced from ^1H NMR spectra that ratio between 5-regioisomer and 4-regioisomer is 3.46)



4-Nitrobenzonitrolic acid (**4.6 e**) (211 mg, 1.0 mmol) was added to phenyl vinyl sulphone (**4.7a**) (168 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 2 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (petroleum ether:ethyl acetate 2:1) to give the title compound (232 mg, 70%) as a yellow solid.

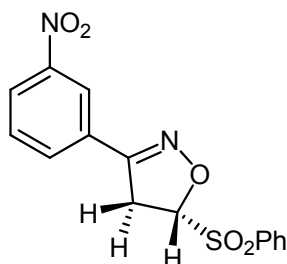
M.p. 143-145°C.

ν_{max} . (KBr) 1600, 1585, 1521, 1446, 1348, 1151, 848, 732 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 8.20 (m, 4H), 7.98-7.40 (m, 5H), 5.55 (dd, $J=10.9$, 4.6 Hz, 1H), 5.20 (dd, $J=11.2$, 2.9 Hz, 1H, 4-regioisomer), 5.10 (dd, $J=10.1$, 2.9 Hz, 4-regioisomer), 1H), 4.60 (t, 1H, 4-regioisomer), 4.05 (dd, $J=18.3$, 4.6 Hz, 1H, 5-regioisomer), 3.75 (q, 1H, 5-regioisomer).

δ_{C} (100 MHz; CDCl_3) : 155.5 (C=N), 149.1, 135.1, 135.0, 134.8, 133.3, 129.7, 129.4, 129.2, 129.1, 128.5, 127.9, 124.1, 123.9, 93.6 (C-5 of 5-regioisomer), 73.5, 72.2 (C-5 of 4-regioisomer, DEPT), 36.2 (C-5 of 5-regioisomer, DEPT), 29.7 (C-4 of 4-regioisomer). MS (m/e , %): M-PhSO_2 , 180 (100), 152 (19), 112 (28), 76 (44), 50 (28).

(R)-3-2-Nitrophenyl-5-phenylsulfonyl-4,5-dihydroisoxazole (4.8f)



2-Nitrobenzonitrolic acid (**4.6f**) (166 mg, 0.78 mmol) was added to phenyl vinyl sulphone (**4.7a**) (110 mg, 0.65 mmol) in dry THF (10 mL) and the mixture was heated to reflux for 2 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent; petroleum ether:ethyl acetate 2:1) to give the title compound (179 mg, 69%) as a yellow solid.

M.p. 159-160°C.

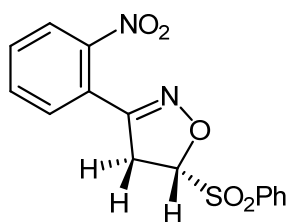
ν_{max} . (KBr) 1599, 1579, 1512, 1348, 1317, 1143, 1085, 846, 729 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 8.30 (d, $J=2.0$ Hz, 2H), 8.00 (d, 2H), 7.85 (d, 2H), 7.70-7.60 (m, 4H), 5.60 (dd, $J=10.9, 4.5$ Hz, 1H), 4.15 (dd, $J=18.3, 4.5$ Hz, 1H), 3.80 (q, 1H).

δ_{C} (100 MHz; CDCl_3) : 153.9 (C=N), 148.5, 136.6, 135.1, 129.7, 129.4, 124.7, 122.7, 93.3, 36.1.

MS MALDI TOF HRMS calculated for $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_5\text{S}$ 350.0811 found: 350.0817.

(R)-3-3-Nitrophenyl-5-phenylsulfonyl-4,5-dihydroisoxazole (4.8g)



3-Nitrobenzonitrolic acid (**4.6g**) (211 mg, 1.0 mmol) was added to phenyl vinyl sulphone (**4.7a**) (168 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 2 hours. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent; petroleum ether:ethyl acetate 2:1) to give the title compound (216 mg, 65%) as a yellow solid.

M.p. 162-163°C.

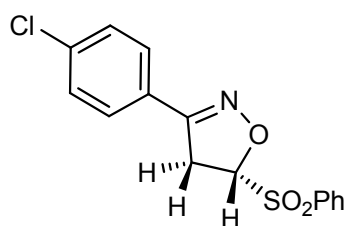
ν_{max} . (KBr) 1531, 1352, 1311, 1149, 720 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 8.50 (s, 1H), 8.35 (dd, $J=8.2, 1.2$ Hz, 1H), 8.03 (t, 2H), 7.75 (t, 1H), 7.70-7.60 (m, 5H), 5.65 (dd, $J=11.5, 4.4$ Hz, 1H), 4.15 (dd, $J=18.3, 4.5$ Hz, 1H), 3.80 (q, 1H).

δ_C (100 MHz; $CDCl_3$) : 156.9 (C=N), 148.4, 135.5, 135.2, 133.7, 131.1, 129.9, 129.8, 129.2, 125.9, 121.9, 93.7, 36.8.

MS (m/e, %): M- $PhSO_2$, 189 (100), 143 (20), 116 (21), 89 (74), 76 (44), 50 (29).

(R)-3-4-Chlorophenyl-5-phenylsulfonyl-4,5-dihydroisoxazole (4.8h)



4-Chlorobenzonitrolic acid (**4.6h**) (200 mg, 1.0 mmol) was added to phenyl vinyl sulphone (**4.7a**) (168 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 2 hours. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent; petroleum ether : ethyl acetate 2:1) to give the title compound (247 mg, 60%) as a yellow solid.

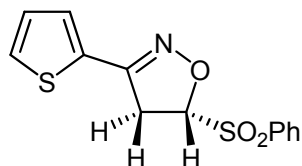
M.p. 136-138 °C.

ν_{max} . (KBr) 1591, 1477, 1446, 1321, 1151, 1084, 852, 759, 732 cm^{-1} .

δ_H (400 MHz; $CDCl_3$) : 8.05 (d, $J=7.4$ Hz, 1H), 7.72 (t, 1H), 7.60 (m, 2H), 7.46-7.25 (m, 5H), 5.63 (t, 1H), 4.10 (d, $J=18.4$ Hz, 2H).

δ_C (100 MHz; $CDCl_3$) : 156.9 (C=N), 135.2, 134.5, 132.8, 131.7, 130.8, 130.6, 129.9, 129.2, 128.9, 128.7, 127.0, 93.9, 39.1. MS (m/e, %): M- $PhSO_2$, 178 (100), 150 (19), 111 (28), 89 (32), 75 (44), 50 (28).

(R)-5-Phenylsulfonyl-3-thiophen-2-yl-4,5-dihydroisoxazole (4.8i)



Thiophene-2-nitrolic acid (**4.6i**) (172 mg, 1.0 mmol) was added to phenyl vinyl sulphone (**4.7a**) (168 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 2 hours. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent; petroleum ether: ethyl acetate 2:1) to give the title compound (176 mg, 60%) as a waxy oil.

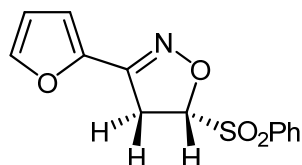
ν_{max} . (KBr) 1480, 1408, 1369, 1308, 1151, 1110, 859, 765, 729 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 7.90 (dd, $J=7.2, 5.3$ Hz, 2H), 7.60 (t, 1H), 7.50 (t, 3H), 7.35 (t, 1H), 7.20 (m, 3H), 7.08 (m, 1H), 5.45 (dd, $J=10.7, 4.4$ Hz, 1H), 4.00 (dd, $J=18.0, 4.4$ Hz, 1H), 3.70 (q, 1H).

δ_{C} (100 MHz; CDCl_3) : 154.9 (C=N), 148.5, 134.6, 129.9, 129.8, 129.2, 127.5, 93.1, 37.6.

MS MALDI TOF HRMS : Calculated for $\text{C}_{13}\text{H}_{11}\text{NO}_3\text{S}_2$ 294.0259 found: 294.0260.

(R)-3-Furan-2-yl-5-phenylsulfonyl-4,5-dihydroisoxazole (4.8j)



Furanyl-2-nitrolic acid (**4.6j**) (156 mg, 1.0 mmol) was added to phenyl vinyl sulphone (**4.7a**) (168 mg, 1 mmol) in dry toluene (10 mL) and the

mixture was heated to reflux for 2 hours. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent petroleum ether: ethyl acetate 2:1) to give the title compound (161 mg, 58%) as a yellow oil.

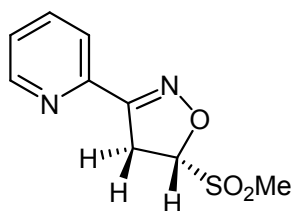
ν_{max} . (neat) 1583, 1483, 1446, 1319, 1309, 1151, 1085, 840, 783 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 7.90 (t, 2H), 7.60 (t, 1H), 7.45 (m, 4H), 6.70 (d, $J=4.0$ Hz, 1H), 6.40 (dd, $J=3.4, 1.7$ Hz, 1H), 5.45 (dd, $J=10.8, 4.4$ Hz, 1H), 4.00 (dd, $J=18.3, 4.4$ Hz, 1H), 3.70 (q, 1H).

δ_{C} (100 MHz; CDCl_3) : 159.0 (C=N), 149.4, 147.0, 136.6, 135.4, 134.5, 129.7, 125.1, 122.1, 93.7, 36.8.

MS MALDI TOF HRMS calculated for $\text{C}_{13}\text{H}_{11}\text{NO}_4\text{S}$ 278.0442 found: 278.0489.

(R)-5-Methylsulfonyl-3-pyridin-2-yl-4,5-dihydroisoxazole (4.8j)



Pyridine-2-nitrolic acid (**4.6a**) (167 mg, 1.0 mmol) was added to methyl vinyl sulphone (**4.7b**) (106 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 30 minutes. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent petroleum ether: ethyl acetate 2:1) to give the title compound (199 mg, 88 %) as a yellow solid.

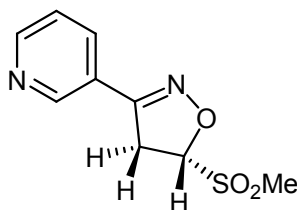
M.p. 140°C (decomposed).

$\nu_{\max}$. (KBr) 1581, 1469, 1444, 1367, 1305, 1126, 945, 862, 786 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 8.55 (d, $J=4.0$ Hz, 1H), 7.90 (d, $J=7.9$ Hz, 1H), 7.65 (t, 1H), 7.30 (t, 1H), 5.50 (dd, $J=11.0, 4.8$ Hz, 1H), 4.15 (dd, $J=19.2, 4.9$ Hz, 1H), 3.85 (q, 1H), 2.90 (s, 3H).

δ_{C} (100 MHz; CDCl_3) : 156.9 (C=N), 135.2, 134.5, 132.8, 131.7, 130.8, 130.6, 129.9, 129.2, 128.9, 128.7, 127.0, 93.9, 39.1. MS MALDI TOF HRMS calculated for $\text{C}_9\text{H}_{11}\text{N}_2\text{O}_3\text{S}$ 227.0490 found: 227.0480.

(R)-5-Methylsulfonyl-3-pyridin-2-yl-4,5-dihydroisoxazole (4.8k)



Pyridine-3-nitrolic acid (**4.6b**) (167 mg, 1.0 mmol) was added to methyl vinyl sulphone (**4.7b**) (106 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 30 minutes. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent; petroleum ether: ethyl acetate 2:1) to give the title compound (182 mg, 80%) as a orange colored solid.

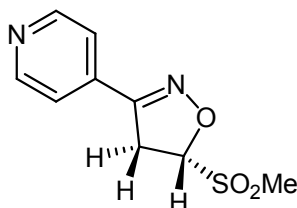
M.p. 144-146°C.

$\nu_{\max}$. (KBr) 1411, 1365, 1305, 1263, 1130, 1028, 979, 939, 858, 804, 773 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 8.90 (d, $J= 1.7$ Hz, 1H), 8.70 (t, 1H), 8.05 (d, $J=8.1$ Hz, 1H), 7.40 (t, 1H), 5.60 (dd, $J=10.8, 4.7$ Hz, 1H), 4.05 (dd, $J=18.2, 4.7$ Hz, 1H), 3.80 (q, 1H) .

δ_C (100 MHz; $CDCl_3$) : 156.9 (C=N), 135.2, 134.5, 132.8, 131.7, 130.8, 130.6, 129.9, 129.2, 128.9, 128.7, 127.0, 93.9, 39.1. MS MALDI TOF HRMS calculated for $C_9H_{11}N_2O_3S$ 227.0490 found:227.0484.

(R)-5-Methylsulfonyl-4-pyridin-2-yl-4,5-dihydroisoxazole (4.8l)



Pyridine-4-nitrolic acid (**4.6c**) (167 mg, 1.0 mmol) was added to methyl vinyl sulphone (**4.7b**) (106 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 30 minutes. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent; petroleum ether: ethyl acetate 2:1) to give the title compound (185 mg, 82%) as a white solid.

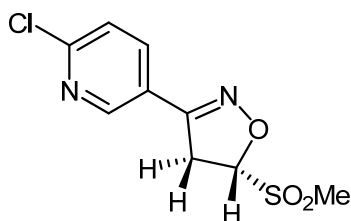
M.p. 138-140°C.

ν_{max} . (KBr) 1600, 1419, 1365, 1305, 1271, 1037, 947, 857, 765 cm^{-1} .

δ_H (400 MHz; $CDCl_3$) : 8.90 (d, J = 1.7 Hz, 1H), 8.70 (t, 1H), 8.05 (d, J =8.1 Hz, 1H), 7.40 (t, 1H), 5.60 (dd, J =10.8, 4.7 Hz, 1H), 4.05 (dd, J =18.2, 4.7 Hz, 1H), 3.80 (q, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ =156.9 (C=N), 135.2, 134.5, 132.8, 131.7, 130.8, 130.6, 129.9, 129.2, 128.9, 128.7, 127.0, 93.9, 39.1.

(R)-3-(6-chloropyridin-3-yl)-5-(methylsulfonyl)-4,5-dihydroisoxazole
(4.8m)



6-Chloro-pyridine-4-nitrolic acid (**4.6e**) (201 mg, 1.0 mmol) was added to methyl vinyl sulphone (**4.7b**) (106 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated to reflux for 30 minutes. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent; petroleum ether: ethyl acetate 2:1) to give the title compound (239 mg, 92%) as a white solid.

M.p. 159-160°C.

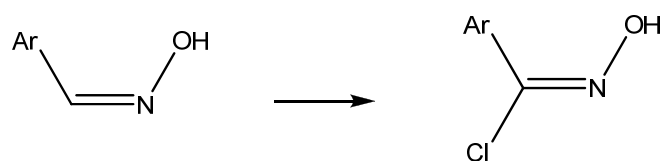
$\nu_{\max}$. (KBr) 1602, 1552, 1433, 1379, 1305, 1139, 1109, 1010, 933, 864, 765 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 8.55 (d, $J=2.4$ Hz, 1H), 7.95 (dd, $J=8.4$, 2.4 Hz, 1H), 7.35 (d, $J=8.3$ Hz, 1H), 5.50 (dd, $J=10.8$, 4.7 Hz, 1H), 3.90 (dd, $J=18.2$, 4.9 Hz, 1H), 3.70 (q, 1H) .

MS MALDI TOF HRMS calculated for $\text{C}_9\text{H}_{10}\text{N}_2\text{O}_3\text{SCl}$ 261.0101 found: 261.0095.

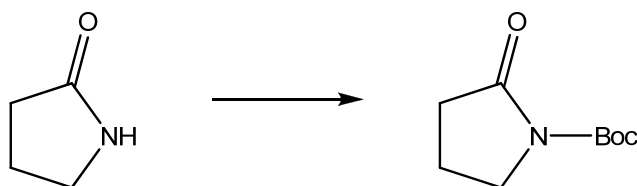
General Procedure for the Synthesis of α -Chlorooxime (4.34 a-

i)



To a stirred solution of aromatic aldehyde oxime **4.5** (2 mmol) in *N,N*-dimethyl formamide (5 mL) at ambient temperature was added *N*-chlorosuccinimide (3mmol) in portions over 15 min. The reaction mixture was stirred at room temperature for 2 hours until the disappearance of the starting materials, as evidenced by TLC. After the reaction was complete, the solution was poured into ice water (60 mL) and extracted with diethyl ether (3 x 50 mL), washed with brine (2 x 15 mL) and dried over anhydrous sodium sulphate and finally evaporated under reduced pressure to give the desired compound **4.34 a-i**. The product was used immediately without further purification.

Tert-butyl 2-oxopyrrolidine-1-carboxylate (4.21)



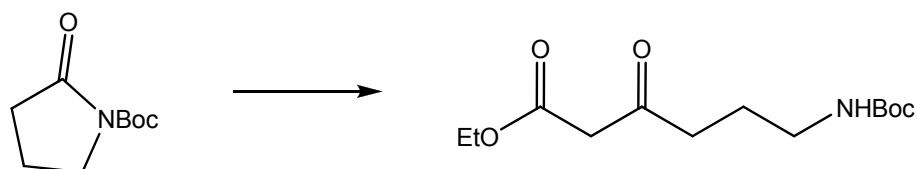
To a solution of pyrrolidin-2-one (6.10g, 71.7 mmol), DMAP (10 mg) and triethylamine (15 mL, 108 mmol) in dichloromethane (75 mL) was added di-*tert*-butyl dicarbonate (17.2 g, 78.8 mmol) in dichloromethane (25 mL) over 15 minutes at 0 °C. The resulting solution was mixed for 18 hours at 25 °C. The reaction was quenched with saturated aqueous ammonium

chloride solution (100 mL) and extracted into dichloromethane (3 x 100 mL). The combined dichloromethane layers washed with brine (2 x 150 mL) and dried over sodium sulphate. The solvent was removed *in vacuo*, to give a dark brown oil. Purification by flash column chromatography on silica gel (eluent; hexane: ethyl acetate 4:1) gave the title compound (11.88 g, 90%) as a pale yellow oil.

δ_{H} (400 MHz; CDCl_3) : 3.69 (t, J = 7.2 Hz, 2H, CH_2N), 2.45 (t, J = 8.1 Hz, 2H, CH_2CO), 1.94 (m, 2H, CH_2CH_2), and 1.46 (s, 9H, $(\text{CH}_3)_3\text{C}$).

δ_{C} (100 MHz; CDCl_3) : 174.4 (ester $\text{C}=\text{O}$), 150.3 (carbamate $\text{C}=\text{O}$), 82.8 ($(\text{CH}_3)_3\text{CO}$), 46.5 (CH_2N), 33.0 (CH_2CO), 28.1 ($(\text{CH}_3)_3\text{C}$), and 17.4 (CH_2CH_2).

Ethyl 6-(tert-butoxycarbonylamino)-3-oxohexanoate (4.22)



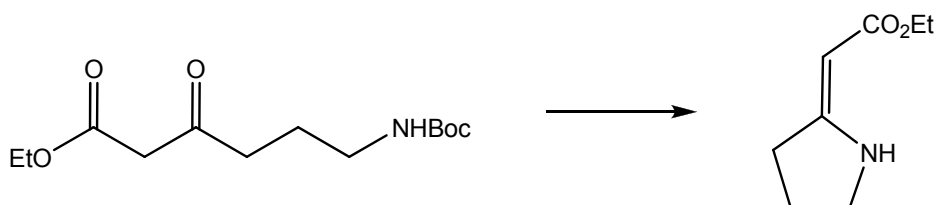
To a solution of diisopropylamine (48 mmol, 6.72 mL) in dry THF (40 mL) at -78°C is added a solution of *n*-butyllithium (2.5 M in hexanes, 19.2 mL) with stirring under N_2 . The solution is warmed to 0°C in 15 minutes to provide lithium diisopropylamide. To the above solution, ethyl acetate (32 mmol, 2.86 g) in dry THF was added dropwise over 30 minutes, and the solution allowed to stir for further 30 minutes. *N*-*t*-butoxycarbonyl

pyrrolidin-2-one (**4.21**) (32 mmol, 6 g) in 5 mL THF was added over 30 minutes at -78°C and the solution warmed to 25°C and left to stir 18 hours. Saturated aqueous ammonium chloride solution (100 mL) was added and the organic layer extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine (2 x 150 mL), dried over Na_2SO_4 and the solvent were removed *in vacuo*. Purification by flash column chromatography (eluent; hexane:ethyl acetate 2:1) gave the title compound (6.5 g, 78%) as a pale yellow oil.

δ_{H} (400 MHz; CDCl_3) : 4.72 (br s, 1 H, NH), 4.15 (q, J 7.1, 2 H, CH_2O), 3.42 (s, 2 H, COCH_2CO), 3.09 (app q, J 6.5, 2 H, CH_2NHBoc), 2.58 (t, J 7.1, 2 H, COCH_2), 1.74 (app quintet, J 6.9, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.50 [s, 9 H, $\text{C}(\text{CH}_3)_3$], 1.40 (t, J 7.1, 3 H, $\text{CH}_3\text{CH}_2\text{O}$).

δ_{C} (100 MHz; CDCl_3) : 203.7 (C=O), 168.3 (C=O), 157.0 (C=O), 79.7 ($\text{OC}(\text{CH}_3)_3$), 61.8 (OCH_2), 49.6 (NCH_2), 40.2 (COCH_2CO), 39.9 (COCH_2CH_2), 28.6 ($(\text{CH}_3)_3$), 24.0 ($\text{CH}_2\text{CH}_2\text{N}$), and 14.2 (OCH_2CH_3).

Pyrrolidin-(2Z)-ylidene-acetic acid ethyl ester (**4.23**)



Ethyl 6-(tert-butoxycarbonylamino)-3-oxohexanoate (**4.22**) (1.761 g, 6.3 mmol) was dissolved in TFA (1.5 mL, 19 mmol) and resulting solution stirred for 3 hours at 25°C . Saturated aqueous sodium bicarbonate was added until neutral to pH paper, and the organic materials were extracted

into dichloromethane (3 x 20 mL). The combined organic layers were dried over sodium sulphate and the solvent was removed *in vacuo*. The resulting yellow solid was purified by flash column chromatography (eluent; hexane:ethyl acetate 4:1) to give the title compound (650 mg, 67 %) as yellow solid.

Mp: 62–64 °C (Lit. 60–62 °C) [127].

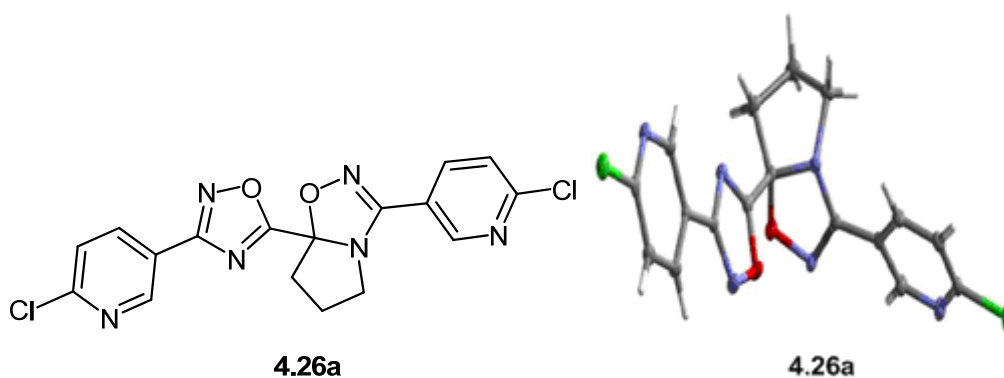
$\nu_{\max}$ (neat) 3360, 2983, 1652, 1590 and 1143 cm^{-1} .

δ_{H} (500 MHz; CDCl_3) : 7.92 (br s, 1 H, NH), 4.55 (br s, 1H, alkene CH), 4.13 (q, J 7.1, 2 H, CH_2O), 3.53 (t, J 6.9, 2 H, CH_2N), 2.60 (t, J 7.8, 2 H, CH_2CO), 1.99 (apparent quintet, J 7.3, 2 H $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.27 (q, J 7.1, 3 H, CH_3CH_2).

δ_{C} (125 MHz; CDCl_3) : 170.8 (C=O), 166.6 (alkene C), 76.5 (alkene CH), 58.4 (CH_2O), 47.1 (CH_2N), 32.2 (CH_2), 22.0 (CH_2), 14.7 (CH_3).

MS-ES: m/z (%) = 156 (MH^+ , 100), 128 (37).

3-(6-Chloropyridin-3-yl)-7a-[3-(6-chloropyridin-3-yl)-1,2,4-oxadiazol-5-yl]-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (4.26a)



6-Chloropyridine-3-nitrolic acid (**4.6a**) (2.0 eq., 201 mg, 1.0 mmol) was added to ethyl 2-pyrrolidin-2-ylidene acetate (**4.23**) (77.5 mg, 0.5 mmol) in dry benzene (10 mL) and the mixture was heated to reflux for 2 hours. The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent; petroleum ether/ethyl acetate;1:1) to give the title compound (154 mg, 76%) as a yellow solid.

m.p. 162 – 163 °C.

$\nu_{\max}$. (KBr) 3060, 2980, 1597, 1584, 1382, 1134, 1113 and 740 cm^{-1} .

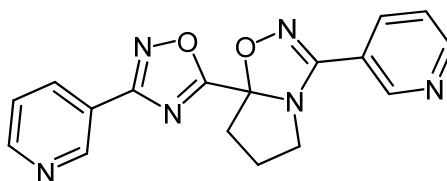
δ_{H} (400 MHz; CDCl_3) 9.03 (1 H, d, $J = 1.8$ Hz, pyridine 2-H), 8.71 (1 H, d, $J = 1.8$ Hz, pyridine 2-H), 8.27 (1 H, dd, $J = 8.3, 2.4$ Hz, pyridine 4-H), 8.02 (1 H, dd, $J = 8.4, 2.4$ Hz, pyridine 4-H), 7.41 – 7.36 (2 H, m, pyridine 5-H), 3.43 – 3.40 (2 H, m, CH_2N), 2.88 (1 H, ddd, $J = 14.2, 10.7, 6.9$ Hz, one of CH_2C), 2.72 (1 H, ddd, $J = 14.2, 7.1, 3.3$ Hz, one of CH_2C), 2.15 – 2.07 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$) and 2.05 – 1.98 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$).

δ_{C} (100 MHz; CDCl_3) : 178.2 (C), 166.3 (C), 156.8 (C), 154.7 (C), 154.5 (C), 149.3 (CH), 149.2 (CH), 138.3 (CH), 137.9 (CH), 125.2 (CH), 125.1 (CH), 122.0 (C), 121.1 (C), 104.4 (C), 54.1 (CH_2), 37.7 (CH_2) and 25.6 (CH_2); m/z (TOF ES^+) 446 ($\text{MH}^+ + \text{CH}_3\text{CN}$, 67%), 444 ($\text{MH}^+ + \text{CH}_3\text{CN}$, 100), 405 (M^+ , 16) and 403.0 (M^+ , 25).

Selected crystallographic data: $\text{C}_{17}\text{H}_{12}\text{Cl}_2\text{N}_6\text{O}_2$, FW =403.23, T = 150(2) K, $\lambda = 0.71073$ Å, Monoclinic, $P2_1/c$, $a = 6.8900(3)$ Å, $b = 13.7810(5)$ Å, $c = 18.1120(9)$, $\beta = 94.5030(10)^\circ$, $V = 1714.45(13)$ Å³, $Z = 4$, $\rho(\text{calc}) = 1.562$ Mg/m³, crystal size = 0.50 x 0.12 x 0.12 mm³, reflections collected

= 6624, independent reflections = 3885, $R(\text{int}) = 0.0569$, parameters = 244, $R_1 [I > 2\sigma(I)] = 0.085$, $wR_2 [I > 2\sigma(I)] = 0.19$, $R_1 (\text{all data}) = 0.12$, $wR_2 (\text{all data}) = 0.21$. Full crystallographic data for this compound have been deposited with the CCDC, reference number 731459.

3-(Pyridin-3-yl)-7a-[3-pyridin-3-yl]-1,2,4-oxadiazol-5-yl]-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (4.26b)



Pyridine-3-nitrolic acid (**4.6b**) (334 mg, 2 mmol) was added to ethyl (2-pyrrolidin-2-ylidene acetate (**4.23**) (155 mg, 1 mmol) in dry toluene (4 mL) and the mixture was heated in a CEM Discover microwave reactor for 10 minutes (100 W, 110 °C, 240 Psi). The reaction mixture was concentrated *in vacuo*, and the crude residue purified by flash column chromatography (eluent; petroleum ether/ethyl acetate/methanol; 20:20:1) to give the title compound (220 mg, 66%) as a yellow oil.

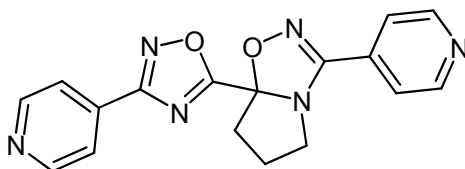
ν_{max} . (neat) 1591, 1558, 1371, 1260, 1097, 1026, 813 and 705 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) 9.26 (1 H, d, J 1.9, pyridine 2-H), 8.96 (1 H, d, J 2.0, pyridine 2-H), 8.70 (1 H, dd, J 4.9, 1.6, pyridine 6-H), 8.67 (1 H, dd, J 4.9, 1.6, pyridine 6-H), 8.32 (1 H, app. dt, J 8.0, 1.9, pyridine 4-H), 8.07 (1 H, app. dt, J 8.0, 1.9, pyridine 4-H), 7.39 – 7.30 (2 H, m), 3.47 – 3.38 (2 H, m, CH_2N), 2.90 (1 H, ddd, J 14.2, 10.7, 7.0, one of CH_2C), 2.72 (1 H, ddd, J 14.2, 7.1, 3.3, one of CH_2C) and 2.14 – 1.99 (2 H, m, $\text{CH}_2\text{CH}_2\text{N}$).

δ_{C} (100 MHz; CDCl_3) : 177.7 (C), 166.5 (C), 157.2 (C), 152.1 (CH), 152.0 (CH), 148.8 (CH), 148.6 (CH), 135.5 (CH), 135.1 (CH), 123.9 (CH), 123.8 (CH), 122.7 (C), 121.8 (C), 103.8 (C), 53.6 (CH_2), 37.4 (CH_2) and 25.1 (CH_2).

m/z (TOF AP^+) 376 ($\text{MH}^+ + \text{CH}_3\text{CN}$, 100%), 335 (MH^+ , 35).

3-(Pyridin-4-yl)-7a-(3-(pyridin-4-yl)-1,2,4-oxadiazol-5-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (4.26c)



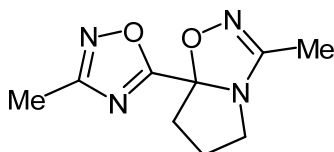
Pyridine-4-nitrolic acid (**4.6c**) (334 mg, 2 mmol) was added to ethyl 2-pyrrolidin-2-ylidene acetate (**4.23**) (155 mg, 1 mmol) in dry toluene (4 mL) and the mixture was heated in a CEM Discover microwave reactor for 10 minutes (100 W, 110 °C, 240 Psi). The reaction mixture was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent; petroleum ether/ethyl acetate/methanol ;20:20:1) to give the title compound (193 mg, 58%) as a pale oil.

ν_{max} . (neat) : 2924, 1679, 1599, 1375, 1257, 835 and 799 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 8.73 - 8.67 (4 H, m), 7.92 (2 H, app. broad d, J 6.1), 7.63 – 7.59 (2 H, m), 3.53 – 3.29 (2 H, m, CH_2N), 2.89 (1 H, ddd, J 14.2, 10.8, 6.9, one of CH_2C), 2.73 (1 H, ddd, J 14.2 7.1, 3.1, one of CH_2C), 2.15 – 2.06 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$) and 2.05 – 1.99 (1H, m, one of $\text{CH}_2\text{CH}_2\text{N}$).

δ_{C} (100 MHz; CDCl_3) : 177.8 (C), 167.0 (C), 157.7 (C), 150.6 (2 x CH), 150.5 (2 x CH), 133.8 (C), 132.8 (C), 121.7 (2 x CH), 121.4 (2 x CH), 104.3 (C), 53.8 (CH_2), 37.3 (CH_2) and 25.0 (CH_2); m/z (TOF AP^+) 376 ($\text{MH}^+ + \text{CH}_3\text{CN}$, 100%) and 335 (MH^+ , 45).

**3-Methyl-7a-(3-methyl-1,2,4-oxadiazol-5-yl)-5,6,7,7a-tetrahydro
pyrrolo[1,2-d][1,2,4]oxadiazole (4.26d)**



Acetonitrolic acid (**4.6d**) (208 mg, 2 mmol) was added to ethyl 2-pyrrolidin-2-ylidene acetate (**4.23**) (155 mg, 1 mmol) in dry toluene (10 mL) and the mixture was heated under reflux for 2 hours. The reaction mixture was concentrated in vacuo and the crude residue purified by flash column chromatography (eluent; petroleum ether/ethyl acetate;1:1) to give the title compound (135 mg, 65%) as a yellow oil.

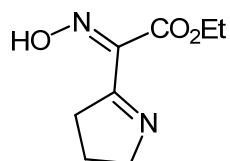
ν_{max} . (neat) 2982, 1622, 1561, 1436, 1396, 1302, 1105 and 853 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) 3.45 (1 H, ddd, J 11.3, 6.9, 3.5, one of CH_2N), 3.18 (1 H, ddd, J 11.3, 9.5, 6.1, one of CH_2N), 2.62 (1 H, ddd, J 14.0, 9.4, 7.1, one of CH_2C), 2.46 (1 H, ddd, J 14.0, 7.5, 4.4, one of CH_2C), 2.36 (3 H, s, CH_3), 2.08 – 1.84 (2 H, m, $\text{CH}_2\text{CH}_2\text{N}$) and 1.96 (3 H, s, CH_3).

δ_{C} (100 MHz; CDCl_3) 177.5 (C), 167.3 (C), 155.8 (C), 102.5 (C), 51.0 (CH_2), 37.4 (CH_2), 24.9 (CH_2), 11.7 (CH_3) and 10.3 (CH_3).

m/z (TOF EI^+) 208 (M^+ , 22%), 178 (100), 111 (38) and 85 (95).

Ethyl 2-(3,4-dihydro-2H-pyrrol-5-yl)-2-(hydroxyimino)acetate (4.28)



Pyridine-4-nitrolic acid (**4.6c**) (334 mg, 2 mmol) was added to ethyl 2-pyrrolidin-2-ylidene acetate (**4.23**) (155 mg, 1 mmol) in dry benzene (10 mL) and the mixture was heated to reflux for 2 h. The reaction was concentrated *in vacuo*, and the crude residue was purified by flash column chromatography (eluent; petroleum ether : ethyl acetate 2 : 1) to give the title compound (65 mg, 35%) as a yellow oil;

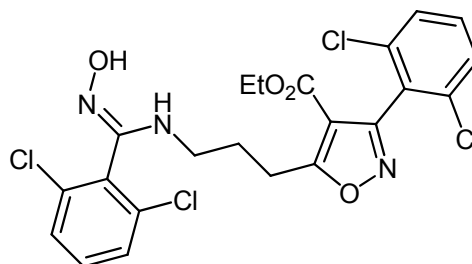
ν_{max} . (neat) 3546, 2988, 1739, 1608, 1291, 1205, 1029 and 946 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) 4.33 (2 H, q, J 7.1, OCH_2), 3.89 (2 H, t, J 7.7, NCH_2), 3.14 (2 H, t, J 8.1, CH_2), 1.97 (2 H, app. quintet, J 7.9, CH_2) and 1.33 (3 H, t, J 7.1, CH_3).

δ_{C} (100 MHz; CDCl_3) 167.9 (C), 164.7 (C), 143.2 (C), 61.4 (CH_2), 54.6 (CH_2), 36.1 (CH_2), 19.7 (CH_2) and 14.3 (CH_3).

m/z (TOF AP^+) 248 ($\text{MNa}^+ + \text{CH}_3\text{CN}$, 61%), 185 (MH^+ , 100) and 152 (38).

Ethyl 5-(3-(2,6-dichloro- N' -hydroxybenzimidamido)propyl)-3-(2,6-dichlorophenyl)isoxazole-4-carboxylate (4.35a)



The ethyl 2-pyrrolidin-2-ylidene acetate (**4.23**) (155 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added to a solution of 2,6-dichloro-*N*-hydroxybenzimidoyl chloride (**4.34a**) (448 mg, 2 mmol) in CH_2Cl_2 (5 mL). Triethylamine (250 mg, 2.5 mmol) was added dropwise in 2 minutes and reaction mixture stirred at ambient temperature for 18 hours. The crude reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated *in vacuo* and purified by flash column chromatography (eluent; petroleum ether:ethyl acetate; 2:1) to give the title compound (366 mg, 69%) as a colourless solid.

m.p. 122 – 123 °C

$\nu_{\text{max.}}$ (neat) : 3372, 2922, 1721, 1644, 1457, 1377, 1297, 910, 784 and 732 cm^{-1} .

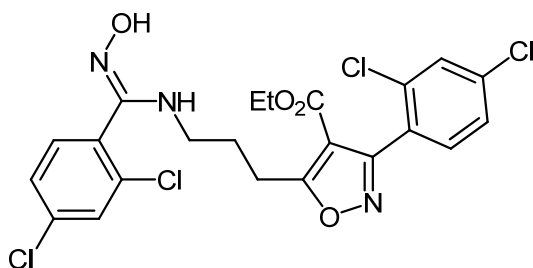
δ_{H} (400 MHz; CDCl_3) : 7.39 – 7.11 (6 H, m, aromatic CH), 5.57 (1 H, broad s, NH), 4.01 (2 H, q, J 7.1, OCH_2), 3.13 (2 H, t, J 7.4, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.88 (2 H, poorly resolved app. q, J 5.1, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.88 (2 H, app. quintet, J 7.0, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$) and 0.90 (3 H, t, J 7.1, CH_2CH_3).

δ_{C} (100 MHz; CDCl_3) : 178.1 (C), 170.0 (C), 158.6 (C), 150.4 (C), 136.0 (2 x C-Cl), 135.4 (2 x C-Cl), 131.3 (CH), 131.0 (CH), 129.5 (C), 128.3 (C), 128.1 (2 x CH), 127.7 (2 x CH), 109.3 (C), 60.8 (CH_2), 42.0 (CH_2), 28.0 (CH_2), 24.6 (CH_2) and 13.6 (CH_3).

HRMS-ES : Found: MH^+ , 530.0182. $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_4^{35}\text{Cl}_4$ requires M, 530.0208.

m/z (TOF ES^+) : 532 (MH^+ , 100%) (isotopic distribution consistent with 4 x Cl).

Ethyl 5-(3-(2,4-dichloro-N'-hydroxybenzimidamido)propyl)-3-(2,4-dichlorophenyl)isoxazole-4-carboxylate (4.35b)



The ethyl 2-pyrrolidin-2-ylidene acetate (**4.23**) (78 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added to a solution of 2,4-dichloro-*N*-hydroxybenzimidoyl chloride (**4.34b**) (224 mg, 1 mmol) in CH_2Cl_2 (5 mL). Triethylamine (150 mg, 1.5 mmol) was added dropwise in 2 minutes and reaction mixture stirred at ambient temperature for 18 hours. The crude reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated *in vacuo* and purified by flash column chromatography (eluent; petroleum ether:ethyl acetate; 2:1) to give the title compound (179 mg, 67%) as an orange oil.

ν_{max} . (neat) 3383, 3090, 2980, 1723, 1634, 1594, 1433, 1372, 1308, 1246, 1102 and 825 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 7.43 (1 H, d, J 1.3), 7.39 (1 H, d, J 1.8), 7.31 – 7.21 (4 H, m), 5.52 (1 H, app. broad t, J 5.7, NH), 4.07 (2 H, q, J 7.1, OCH_2), 3.09 (2 H, t, J 7.4, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.93 (2 H, app. q, J 6.5, CH_2N), 1.87 (2 H, app. quintet, J 7.2, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$) and 1.01 (3 H, t, J 7.1, CH_2CH_3).

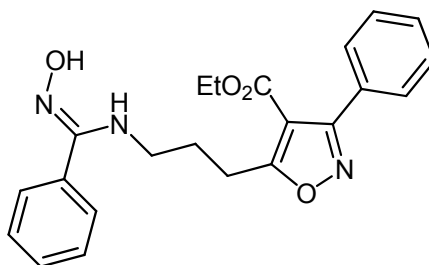
δ_{C} (100 MHz; CDCl_3) : 177.7 (C), 161.3 (C), 160.0 (C), 152.5 (C), 136.3 (C), 136.3 (C), 134.9 (C), 134.8 (C), 132.4 (CH), 131.8 (CH), 129.6 (CH),

129.3 (CH), 129.0 (C), 127.4 (CH), 127.2 (C), 127.0 (CH), 109.6 (C), 60.9 (CH₂), 42.1 (CH₂), 28.4 (CH₂), 24.3 (CH₂) and 13.7 (CH₃).

HRMS-ES: Found: MH⁺, 530.0205. C₂₂H₂₀N₃O₄³⁵Cl₄ requires M, 530.0208.

m/z (TOF ES⁺) : 532 (MH⁺, 100%) (isotopic distribution consistent with 4 x Cl).

Ethyl 5-(3-(N'-hydroxybenzimidamido)propyl)-3-phenylisoxazole-4-carboxylate (4.35c)



The ethyl 2-pyrrolidin-2-ylidene acetate (**4.23**) (155 mg, 1 mmol) in CH₂Cl₂ (5 mL) was added to a solution of *N*-hydroxybenzimidoyl chloride (**4.34f**) (310 mg, 2 mmol) in CH₂Cl₂ (5 mL). Triethylamine (150 mg, 1.5 mmol) was added dropwise in 2 minutes and reaction mixture stirred at ambient temperature for 18 hours. The crude reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated *in vacuo* and purified by flash column chromatography (eluent; petroleum ether:ethyl acetate; 2:1) to give the title compound (267 mg, 68%) as a yellow oil.

ν_{max} . (neat) 3372, 3063, 2980, 1722, 1627, 1447, 1306, 767 and 698 cm⁻¹.

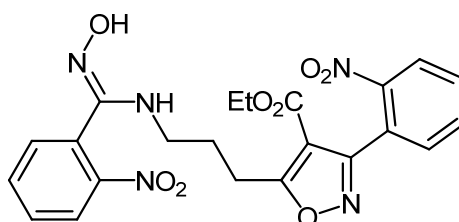
δ_{H} (400 MHz; CDCl_3) : 7.49 (2 H, dd, J 7.8, 1.7), 7.38 – 7.25 (8 H, m), 5.45 (1 H, broad s, NH), 4.09 (2 H, q, J 7.1, OCH_2), 3.09 – 2.94 (4 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.79 (2 H, app. quintet, J 7.2, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$) and 1.05 (3 H, t, J 7.1, OCH_2CH_3).

δ_{C} (100 MHz; CDCl_3) : 178.1 (C), 162.6 (C), 161.7 (C), 156.3 (C), 131.2 (C), 129.8 (CH), 129.7 (CH), 129.6 (CH), 129.4 (CH), 128.5 (CH), 128.4 (C), 127.9 (CH), 108.3 (C), 60.9 (CH_2), 42.7 (CH_2), 28.9 (CH_2), 24.5 (CH_2) and 13.9 (CH_3).

HRMS-ES : Found: M^+ , 393.1690. $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_4$ requires M , 393.1689.

m/z (TOF ES^+) 393 (M^+ , 3%), 245 (12), 144 (26) and 104 (100).

Ethyl 5-(3-(N' -hydroxy-2-nitrobenzimidamido)propyl)-3-(2-nitrophenyl) isoxazole-4-carboxylate (4.35d**)**



The ethyl 2-pyrrolidin-2-ylidene acetate (**4.23**) (78 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added to a solution of *N*-hydroxy-2-nitro benzimidoyl chloride (**4.34c**) (224 mg, 1 mmol) in dichloromethane (5 mL). Triethylamine (150 mg, 1.5 mmol) was added dropwise in 2 minutes and reaction mixture stirred at ambient temperature for 18 hours. The crude reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated *in vacuo* and purified by

flash column chromatography (eluent; petroleum ether:ethyl acetate; 2:1) to give the title compound (135 mg, 56%) as a yellow oil.

ν_{max} . (neat) 3382, 2980, 1718, 1637, 1529, 1348, 1315 and 855 cm^{-1} .

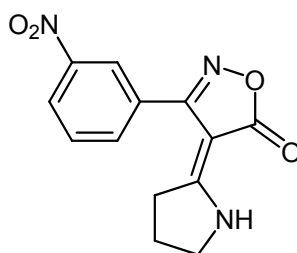
δ_{H} (400 MHz; CDCl_3): 8.16 (1 H, dd, J 8.0, 1.3), 7.96 (1 H, dd, J 8.1, 1.0), 7.66 (1 H, app. td, J 7.5, 1.5), 7.62 – 7.57 (2 H, m), 7.52 (1 H, app. td, J 7.7, 1.5), 7.47 (1 H, dd, J 7.5, 1.4), 7.44 (1 H, dd, J 7.5, 1.4), 5.53 (1 H, broad s, NH), 4.04 (2 H, q, J 7.1, OCH_2), 3.10 (2 H, t, J 7.4, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 2.95 (2 H, app. q, J 6.4, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$), 1.89 (2 H, app. quintet, J 7.1, $\text{CH}_2\text{CH}_2\text{CH}_2\text{N}$) and 0.95 (3 H, t, J 7.1, OCH_2CH_3).

δ_{C} (100 MHz; CDCl_3): 177.7 (C), 161.2 (C), 160.8 (C), 152.7 (C), 148.8 (C), 148.3 (C), 133.6 (CH), 133.4 (CH), 132.3 (CH), 131.9 (CH), 130.8 (CH), 130.7 (CH), 126.4 (C), 124.8 (C), 124.6 (CH), 124.5 (CH), 108.7 (C), 61.1 (CH_2), 42.6 (CH_2), 28.1 (CH_2), 24.4 (CH_2) and 13.6 (CH_3).

HRMS-ES: Found: MH^+ , 484.1479. $\text{C}_{22}\text{H}_{22}\text{N}_5\text{O}_8$ requires M, 484.1468.

m/z (TOF ES^+): 506 (MNa^+ , 46%) and 484 (MH^+ , 100).

3-(3-Nitrophenyl)-4-(pyrrolidin-2-ylidene)isoxazol-5(4H)-one (4.36)



The ethyl 2-pyrrolidin-2-ylidene acetate (**4.23**) (155 mg, 1 mmol) in dichloromethane (5 mL) was added to a solution of *N*-hydroxy-3-nitrobenzimidoyl chloride (**4.34d**) (400 mg, 2 mmol) in dichloromethane (5 mL). Triethylamine (250 mg, 2.5 mmol) was added dropwise and reaction mixture stirred at ambient temperature for 18 hours. The crude

reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated in vacuo and purified by flash column chromatography (eluent; petroleum ether/ethyl acetate;1:1) to give title compound (193 mg, 41%) as a yellow solid.

m.p.: 144 – 146 °C.

ν_{max} . (KBr) 3284, 2926, 1691, 1599 and 1351 cm^{-1} .

δ_{H} (400 MHz; DMSO) : 10.11 (1 H, broad s, NH), 8.38 (1 H, dd, J 8.2, 2.3), 8.31 (1 H, app. broad s), 8.00 (1 H, d, J 7.6), 7.80 (1 H, app. t, J 8.0), 3.62 (2 H, t, J 7.0, CH_2N), 2.53 – 2.47 (2 H, m, CH_2C) and 1.89 (2 H, app. quintet, J 7.2, $\text{CH}_2\text{CH}_2\text{N}$).

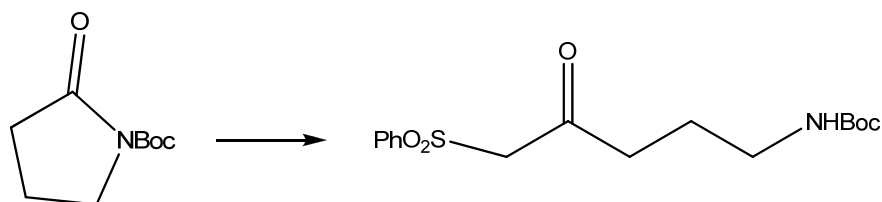
δ_{C} (100 MHz; DMSO) : 173.9 (C), 170.0 (C), 161.2 (C), 148.1 (C), 135.8 (CH), 132.6 (C), 130.7 (CH), 125.0 (C), 123.9 (CH), 85.2 (C), 49.6 (CH_2), 33.8 (CH_2) and 20.8 (CH_2).

HRMS-EI : Found: M^+ , 273.0750; $\text{C}_{13}\text{H}_{11}\text{N}_3\text{O}_4$ requires M, 273.0750.

m/z (TOF EI⁺) : 273 (M^+ , 58%), 230 (100), 200 (93) and 184 (73).

Achiral phenylsulfonylmethyl compounds

tert-Butyl-4-oxo-5-phenylsulphonyl-pentyl carbamate (4.47)

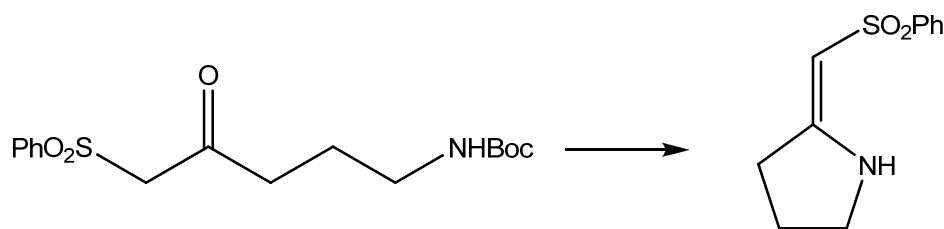


A solution of *n*-butyllithium (2 mL, 2.5 M in hexanes, 5 mmol) in THF (10 mL) was cooled to –78 °C. Methyl phenyl sulphone (0.77 g, 5 mmol) in

THF (3 mL) was added over 30 minutes, after which the solution was stirred for a further 30 min at $-78\text{ }^{\circ}\text{C}$. *N*-*tert*-Butoxycarbonylpyrrolidin-2-one (**4.21**) (0.92 g, 5 mmol) in THF (5 mL) was added over 30 minutes at $-78\text{ }^{\circ}\text{C}$, and the solution warmed to $25\text{ }^{\circ}\text{C}$ and left to stir for 18 hours. Saturated aqueous ammonium chloride (100 mL) was added and the solution was extracted with dichloromethane ($3 \times 100\text{ mL}$). The combined organic layers were washed with brine ($2 \times 150\text{ mL}$), dried over sodium sulphate and the solvent removed *in vacuo* to give the title compound (1.4 g, 75%) as an orange oil which solidified upon standing to give a waxy solid.

^1H NMR (400 MHz, CDCl_3): δ = 7.82 (d, J = 7.4 Hz, 2 H arom.), 7.62 (t, J = 7.5 Hz, 1 H arom.), 7.52 (apparent t, J = 7.7 Hz, 1 H arom.), 4.62 (br s, 1 H, NH), 4.15 (s, 2 H, OCCH_2CO), 3.05 (apparent q, J = 6.4 Hz, 2 H, CH_2NH), 2.70 (t, J = 6.8 Hz, 2 H, COCH_2), 1.69 (apparent quintet, J = 6.8 Hz, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.36 [s, 9 H, $\text{C}(\text{CH}_3)_3$].

2-Phenylsulphonylmethyl-(Z)-ylidenepyrrolidine (**4.37**)



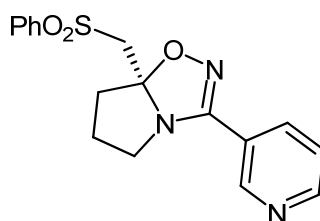
To a solution of *N*-*t*-butoxycarbonyl-4-oxo-5-phenylsulphonylpentylamine (**4.47**) (1.4 g, 4.1 mmol) in dichloromethane (5 mL) was added TFA (3.48 mL, 45 mmol) and the solution stirred for 18 hours at $25\text{ }^{\circ}\text{C}$. The volatiles were removed *in vacuo* and the resulting oil was dissolved in dichloromethane (5 mL). Saturated aqueous sodiumhydrogen

carbonate was added until neutral to pH paper, and the organic material was extracted into dichloromethane (3 × 50 mL). The combined organic layers were dried over sodium sulphate and the solvent removed *in vacuo*. The residual yellow oil was purified by flash column chromatography (eluent: hexane–EtOAc;4:1) to give the title compound (620 mg, 67%) as a yellow oil.

δ_{H} (400 MHz; CDCl_3) : 7.80 (d, J = 6.7 Hz, 2 H aromatic), 7.50–7.48 (m, 3 H aromatic), 7.22 (br s, 1 H, NH), 4.58 (s, 1 H, CCH), 3.38 (t, J = 6.9 Hz, 2 H, CH_2N), 2.48 (t, J = 7.8 Hz, 2 H, CH_2CO), 1.86 (apparent quintet, J = 7.3 Hz, 2 H, $\text{CH}_2\text{CH}_2\text{CH}_2$).

MS-ES: m/z = 344 (MH^+ , 100%).

7a-(Phenylsulfonylmethyl)-3-(pyridin-3-yl)-5,6,7,7a-tetrahydro pyrrolo[1,2-d][1,2,4]oxadiazole (4.50a)



A solution of the pyridine-3-nitrolic acid (**4.6b**) (42 mg, 0.25 mmol) and (Z)-2-(phenylsulfonylmethylene) pyrrolidine (**4.37**) (56 mg, 0.25 mmol) in dry toluene (5 mL) was heated under reflux for 2 h. The solvent was removed *in vacuo* and crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether:ethyl acetate; 2:1) to give the title compound (49 mg, 58%) as a pale yellow oil.

ν_{max} . (neat) : 2962, 2926, 1550, 1447, 1378, 1261, 1083, 1020, 800 and 687 cm^{-1} .

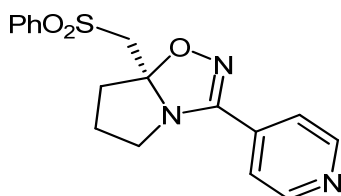
δ_{H} (400 MHz; CDCl_3) : 8.58 (1 H, d, J 3.8, pyridine 6-H), 8.47 (1 H, d, J 1.2, pyridine 2-H), 7.88 (2 H, d, J 7.2), 7.75 (1 H, app. dt, J 7.9, 1.6, pyridine 4-H), 7.61 (1 H, t, J 7.4), 7.51 (2 H, app. t, J 7.6), 7.23 (1 H, dd, J 7.9, 4.9, pyridine 5-H), 3.68 (2 H, app. s, CH_2SO_2), 3.13 (2 H, app. dd, J 10.4, 4.3, CH_2N), 2.77 (1 H, ddd, J 14.2, 11.8, 6.9, one of CH_2C), 2.41 (1 H, ddd, J 14.2, 7.1, 1.7, one of CH_2C), 1.95 – 1.86 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$) and 1.84 – 1.70 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$).

δ_{C} (100 MHz; CDCl_3) : 157.5 (C), 151.8 (CH), 148.7 (CH), 140.9 (C), 135.1 (CH), 133.8 (CH), 129.3 (2 x CH), 127.7 (2 x CH), 123.5 (CH), 122.0 (C), 106.2 (C), 60.9 (CH_2), 53.0 (CH_2), 36.6 (CH_2) and 25.0 (CH_2).

HRMS-EI : Found: M^+ , 343.0994. $\text{C}_{17}\text{H}_{17}\text{N}_3\text{SO}_3$ requires M , 343.0991.

m/z (TOF EI⁺) 343 (M^+ , 57%), 302 (47), 160 (100) and 105 (95).

**7a-(Phenylsulfonylmethyl)-3-(pyridin-4-yl)-5,6,7,7a-tetrahydro
pyrrolo[1,2-d][1,2,4]oxadiazole (4.50b)**



A solution of the pyridine-4-nitrolic acid (**4.6c**) (42 mg, 0.25 mmol) and (Z)-2-(phenylsulfonylmethylene) pyrrolidine (**4.37**) (56 mg, 0.25 mmol) in dry toluene (5 mL) was heated under reflux for 2 h. The solvent was removed *in vacuo* and the crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether:ethyl acetate; 2:1) to give the title compound (58 mg, 68%) as a pale yellow oil.

ν_{max} . (neat) : 3059, 1590, 1447, 1374, 1307 and 1143 cm^{-1} .

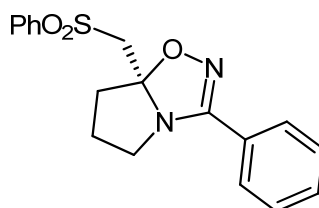
δ_{H} (400 MHz; CDCl_3) : 8.56 (2 H, d, J 6.0, pyridine 2-H and 6-H), 7.87 (2 H, broad app. d, J 7.3), 7.59 (1 H, app. tt, J 7.4, 1.9), 7.50 (2 H, app. t, J 7.6), 7.26 (2 H, d, J 6.0, pyridine 3-H and 5-H), 3.69 (1 H, d, J 14.8, one of CH_2SO_2), 3.64 (1 H, d, J 14.8, one of CH_2SO_2), 3.20 – 3.10 (2 H, m, CH_2N), 2.75 (1 H, ddd, J 14.2, 11.7, 6.9, one of CH_2C), 2.42 (1 H, ddd, J 14.2, 7.3, 1.7, one of CH_2C), 1.95 – 1.86 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$) and 1.82 – 1.68 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$).

δ_{C} (100 MHz; CDCl_3) : 157.8 (C), 150.3 (2 x CH), 140.8 (C), 133.7 (CH), 133.4 (C), 129.3 (2 x CH), 127.7 (2 x CH), 121.4 (2 x CH), 106.9 (C), 61.0 (CH_2), 53.1 (CH_2), 36.7 (CH_2) and 25.0 (CH_2).

HRMS-ES : Found: MH^+ , 343.1074. $\text{C}_{17}\text{H}_{18}\text{N}_3\text{SO}_3$ requires M, 344.1069.

m/z (TOF ES^+) : 385 ($\text{MH}^+ + \text{CH}_3\text{CN}$, 41%) and 344 (MH^+ , 100%).

3-Phenyl-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo [1,2-d][1,2,4]oxadiazole (4.50c)



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (Z)-2-(phenylsulfonylmethylene)pyrrolidine (**4.37**) (56 mg, 0.25 mmol) and *N*-hydroxybenzimidoyl chloride (**4.34f**) (39 mg, 0.25 mmol) in dry dichloromethane (5 mL). The reaction mixture was heated under reflux for 18 hours. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by flash column

chromatography on silica gel (eluent; petroleum ether:ethyl acetate; 3:1) to give the title compound (59 mg, 69%) as a yellow oil.

ν_{max} (neat) : 2974, 1593, 1562, 1447, 1371, 1308, 1143, 1082, 751 and 690 cm^{-1} .

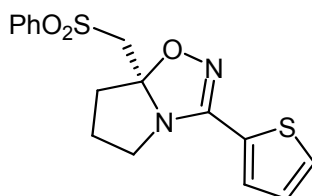
δ_{H} (400 MHz; CDCl_3) : 7.87 (2 H, d, J 7.1), 7.56 (1 H, app. tt, J 7.4, 2.1), 7.47 (2 H, app. t, J 7.6), 7.36 – 7.30 (3 H, m), 7.24 (2 H, app. broad tt, J 7.4, 1.3), 3.69 (1 H, d, J 14.8, one of CH_2SO_2), 3.67 (1 H, d, J 14.8, one of CH_2SO_2), 3.21 – 3.01 (2 H, m, CH_2N), 2.73 (1 H, ddd, J 14.1, 11.7, 7.0, one of CH_2C), 2.38 (1 H, ddd, J 14.1, 7.1, 1.0, one of CH_2C), 1.89 – 1.79 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$) and 1.78 – 1.67 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$).

δ_{C} (100 MHz; CDCl_3) : 159.5 (C), 140.9 (C), 133.6 (CH), 131.0 (CH), 129.2 (2 x CH), 128.7 (2 x CH), 127.9 (2 x CH), 127.8 (2 x CH), 125.6 (C), 105.7 (C), 61.1 (CH_2), 52.9 (CH_2), 36.7 (CH_2) and 25.0 (CH_2).

HRMS-ES : Found: MH^+ , 343.1121. $\text{C}_{18}\text{H}_{19}\text{N}_2\text{SO}_3$ requires M, 343.1116.

m/z (TOF ES^+) : 343 (MH^+ , 100%) and 224 (7).

7a-(Phenylsulfonylmethyl)-3-(thien-2-yl)-5,6,7,7a-tetrahydropyrrolo[1,2-d] [1,2,4] oxadiazole (4.50d)



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (Z)-2-(phenylsulfonylmethylene)pyrrolidine (**4.37**) (56 mg, 0.25 mmol) and *N*-hydroxythiophene-2-carbimidoyl chloride (**4.34i**) (40 mg, 0.25 mmol) in dry dichloromethane (5 mL). The reaction mixture was heated under

reflux for 18 hours. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent petroleum ether:ethyl acetate 3:1) to give the *title compound* (56 mg, 78%) as a yellow oil.

$\nu_{\text{max.}}$ (neat) : 2952, 1585, 1513, 1440, 1367, 1307, 1156 and 1082 cm^{-1} .

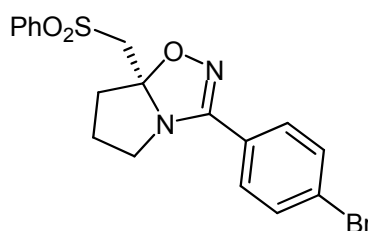
δ_{H} (400 MHz; CDCl_3) : 7.87 (2 H, app. broad d, J 7.1), 7.56 (1 H, app. tt, J 7.4, 1.3), 7.48 (2 H, app. tt, J 7.5, 1.7), 7.32 (1 H, dd, J 5.0, 1.2, thiophene 5-H), 7.06 (1 H, dd, J 3.7, 1.2, thiophene 3-H), 6.95 (1 H, dd, J 5.0, 3.7, thiophene 4-H), 3.69 (1 H, d, J 14.9, one of CH_2SO_2), 3.63 (1 H, d, J 14.9, one of CH_2SO_2), 3.34 – 3.26 (1 H, m, one of CH_2N), 3.12 (1 H, app. dt, J 11.2, 5.7, one of CH_2N), 2.72 (1 H, ddd, J 14.2, 11.6, 7.0, one of CH_2C), 2.39 (1 H, app. broad dd, J 14.2, 6.9, one of CH_2C) and 1.90 – 1.71 (2 H, m, $\text{CH}_2\text{CH}_2\text{N}$).

δ_{C} (100 MHz; CDCl_3) : 155.1 (C), 140.7 (C), 133.6 (CH), 129.5 (CH), 129.2 (CH), 129.1 (2 x CH), 127.8 (2 x CH), 127.5 (CH), 127.3 (C), 105.8 (C), 61.1 (CH_2), 53.2 (CH_2), 36.4 (CH_2) and 25.0 (CH_2).

HRMS-EI : Found: M^+ , 348.0590. $\text{C}_{16}\text{H}_{16}\text{N}_2\text{S}_2\text{O}_3$ requires M, 348.0602.

m/z (TOF EI⁺) 348 (M^+ , 8%), 193 (99), 158 (98), 108 (99) and 77 (100).

3-(4-Bromophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (4.50e)



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (Z)-2-(phenylsulfonylmethylene)pyrrolidine (**4.37**) (34 mg, 0.22 mmol) and 4-bromo-*N*-hydroxybenzimidoyl chloride (**4.34g**) (52 mg, 0.22 mmol) in dry dichloromethane (5 mL). The reaction mixture was heated under reflux for 18 hours. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether:ethyl acetate; 3:1) to give the title compound (61 mg, 66%) as a waxy oil.

ν_{max} (neat) 2976, 1604, 1510, 1308, 1157, 845 and 688 cm^{-1} .

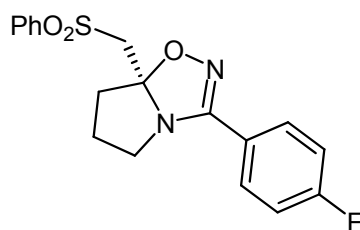
δ_{H} (400 MHz; CDCl_3) : 7.87 (2 H, app. broad d, J 7.2), 7.9 (1 H, app. tt, J 7.4, 1.2), 7.49 (2 H, app. broad t, J 7.7), 7.40 (2 H, d, J 8.5), 7.21 (2 H, d, J 8.5), 3.66 (2 H, app. s, CH_2SO_2), 3.09 (2 H, app. dd, J 9.7, 4.0, CH_2N), 2.74 (1 H, ddd, J 14.2, 11.7, 7.0, one of CH_2C), 2.38 (1 H, ddd, J 14.2, 7.0, 1.6, one of CH_2C), 1.91 – 1.82 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$) and 1.81 – 1.71 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$).

δ_{C} (100 MHz; CDCl_3) : 158.8 (C), 140.9 (C), 133.7 (CH), 132.0 (2 x CH), 129.3 (2 x CH), 129.3 (2 x CH), 127.7 (2 x CH), 125.5 (C), 124.7 (C), 106.0 (C), 60.9 (CH_2), 53.0 (CH_2), 36.6 (CH_2) and 25.0 (CH_2).

HRMS-ES : Found: MH^+ , 421.0242. $\text{C}_{18}\text{H}_{18}\text{N}_2\text{SO}_3^{79}\text{Br}$ requires M , 421.0222.

m/z (TOF ES^+) : 423 (MH^+ , 100%), 421 (MH^+ , 92).

3-(4-Fluorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (4.50f)



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (Z)-2-(phenylsulfonylmethylene)pyrrolidine (**4.37**) (45 mg, 0.29 mmol) and 4-fluoro-*N*-hydroxybenzimidoyl chloride (**4.34h**) (50 mg, 0.29 mmol) in dry dichloromethane (5 mL). The reaction mixture was heated under reflux for 18 hours. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether:ethyl acetate; 3:1) to give the title compound (76 mg, 73%) as a colourless solid.

m.p. : 134 – 136 °C.

ν_{max} . (Nujol) : 1587, 1447, 1373, 1306, 1143, 838 and 752 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 7.87 (2 H, app. broad d, J 7.1), 7.58 (1 H, app. tt, J 7.4, 1.3), 7.48 (2 H, app. broad t, J 7.6), 7.35 (2 H, app. dd, J 8.8, 5.4), 6.95 (2 H, app. t, J 8.8), 3.66 (2 H, app. s, CH_2SO_2), 3.13 – 3.07 (2 H, m, CH_2N), 2.73 (1 H, ddd, J 14.1, 11.7, 7.0, one of CH_2C), 2.38 (1 H, ddd, J 14.1, 7.2, 1.6, one of CH_2C), 1.89 – 1.82 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$) and 1.80 – 1.70 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$).

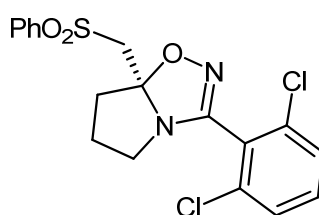
δ_{C} (100 MHz; CDCl_3) : 164.3 (C, $^1\text{J}_{\text{C-F}}$ 252), 158.7 (C), 140.9 (C), 133.6 (CH), 130.0 (2 x CH, $^3\text{J}_{\text{C-F}}$ 8.6), 129.2 (2 x CH), 127.7 (2 x CH), 121.9 (C,

$^4J_{C-F}$ 3.3), 116.0 (2 x CH, $^2J_{C-F}$ 22.0), 105.7 (C), 61.0 (CH₂), 52.9 (CH₂), 36.7 (CH₂) and 25.0 (CH₂).

HRMS-ES : Found: MH⁺, 361.1035. C₁₈H₁₈N₂SO₃F requires M, 361.1022.

m/z (TOF ES⁺) : 361 (MH⁺, 100%).

3-(2,6-Dichlorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (4.50g)



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (Z)-2-(phenylsulfonylmethylene)pyrrolidine (**4.37**) (56 mg, 0.25 mmol) and 2,6-dichloro-*N*-hydroxybenzimidoyl chloride (**4.34a**) (56 mg, 0.25 mmol) in dry dichloromethane (5 mL). The reaction mixture was heated under reflux for 18 hours. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether:ethyl acetate; 3:1) to give the title compound (76 mg, 75%) as a colourless oil.

$\nu_{\max}$ (neat) : 2975, 1606, 1574, 1431, 1351, 1307, 1156, 1083 and 747 cm⁻¹.

δ_H (400 MHz; CDCl₃) : 7.91 (2 H, app. broad d, J 7.1), 7.59 (1 H, app. tt, J 7.4, 1.3), 7.51 (2 H, app. broad t, J 7.5), 7.31 – 7.24 (3 H, m), 3.88 (1 H, d, J 14.6, one of CH₂SO₂), 3.56 (1 H, d, J 14.6, one of CH₂SO₂), 3.24

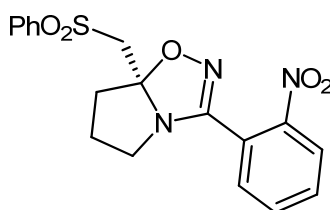
– 3.17 (1 H, m, one of CH₂N), 2.92 – 2.84 (1 H, m, one of CH₂N), 2.68 (1 H, d, J 14.4, 10.7, 8.0, one of CH₂C), 2.56 – 2.49 (1 H, m, one of CH₂C) and 1.97 – 1.88 (2 H, m, CH₂CH₂N).

δ_C (100 MHz; CDCl₃) : 153.9 (C), 140.5 (C), 136.4 (C), 133.8 (CH), 132.1 (CH), 129.1 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 125.0 (C), 106.1 (C), 62.5 (CH₂), 50.8 (CH₂), 36.8 (CH₂) and 25.5 (CH₂).

HRMS-ES : Found: M⁺, 410.0271. C₁₈H₁₆N₂SO₃³⁵Cl₂ requires M, 410.0259.

m/z (TOF ES⁺) : 410 (M⁺, 2%), 375 (8), 255 (36) and 173 (100) (isotopic distribution of peaks with m/z > 254 consistent with 2 x Cl).

3-(2-Nitrophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (4.50h)



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (Z)-2-(phenylsulfonylmethylene)pyrrolidine (**4.37**) (56 mg, 0.25 mmol) and *N*-hydroxy-2-nitrobenzimidoyl chloride (**4.34c**) (50 mg, 0.25 mmol) in dry dichloromethane (5 mL). The reaction mixture was heated under reflux for 18 hours. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether:ethyl acetate; 3:1) to give the title compound (69 mg, 71%) as a yellow oil.

$\nu_{\text{max.}}(\text{neat})$: 2925, 1534, 1447, 1369, 1308, 1157, 1083 and 687 cm^{-1} .

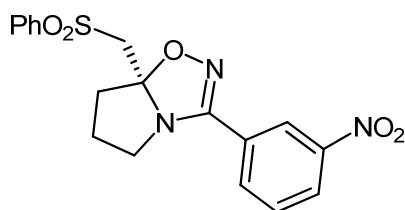
δ_{H} (400 MHz; CDCl_3) : 7.93 (2 H, app. broad d, J 7.3), 7.78 (1 H, app. dd, J 5.9, 3.4), 7.61 (1 H, app. tt, J 7.4, 1.2), 7.57 – 7.49 (4 H, m), 7.40 (1 H, app. dd, J 5.8, 3.3), 3.75 (1 H, d, J 14.7, one of CH_2SO_2), 3.61 (1 H, d, J 14.7, one of CH_2SO_2), 3.15 – 3.08 (1 H, m, one of CH_2N), 2.94 (1 H, app. td, J 11.1, 6.2, one of CH_2N), 2.61 (1 H, ddd, J 14.2, 11.0, 7.6, one of CH_2C), 2.50 – 2.43 (1 H, m, one of CH_2C) and 1.98 – 1.85 (2 H, m, $\text{CH}_2\text{CH}_2\text{N}$).

δ_{C} (100 MHz; CDCl_3) : 155.9 (C), 149.7 (C), 140.9 (C), 133.8 (CH), 132.7 (CH), 131.7 (CH), 131.7 (CH), 129.2 (2 x CH), 128.1 (2 x CH), 124.4 (CH), 120.7 (C), 106.3 (C), 61.9 (CH_2), 52.1 (CH_2), 37.1 (CH_2) and 24.9 (CH_2).

HRMS- EI : Found: M^+ , 387.0877. $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_5\text{S}$ requires M , 387.0889.

m/z (TOF EI^+) : 387 (M^+ , 5%), 232 (15), 141 (32), 118 (48), 94 (30) and 77 (100).

3-(3-Nitrophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (4.50i)



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (Z)-2-(phenylsulfonylmethylene)pyrrolidine (**4.37**) (56 mg, 0.25 mmol) and *N*-hydroxy-3-nitrobenzimidoyl chloride (**4.34d**) (50 mg, 0.25 mmol) in dry

dichloromethane (5 mL). The reaction mixture was heated under reflux for 18 hours. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether:ethyl acetate; 3:1) to give the title compound (74 mg, 76%) as a yellow oil.

ν_{max} . (neat) : 2974, 1593, 1531, 1350, 1308, 1142, 1084, 739 and 688 cm^{-1} .

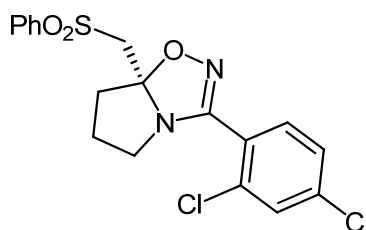
δ_{H} (400 MHz; CDCl_3) : 8.19 (1 H, ddd, J 8.2, 2.3, 1.0), 8.06 (1 H, t, J 1.9), 7.88 (2 H, app. broad d, J 7.1), 7.81 (1 H, app. dt, J 7.8, 1.3), 7.58 (1 H, app. tt, J 7.4, 1.3), 7.54 – 7.46 (3 H, m), 3.69 (2 H, app. s, CH_2SO_2), 3.19 – 3.07 (2 H, m, CH_2N), 2.78 (1 H, ddd, J 14.2, 11.8, 6.9, one of CH_2C), 2.41 (1 H, ddd, J 14.2, 7.3, 1.2, one of CH_2C), 1.95 – 1.86 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$) and 1.82 – 1.71 (1 H, m, one of $\text{CH}_2\text{CH}_2\text{N}$).

δ_{C} (100 MHz; CDCl_3) : 157.8 (C), 148.3 (C), 140.7 (C), 133.9 (CH), 133.4 (CH), 130.0 (CH), 129.4 (2 x CH), 127.7 (2 x CH), 125.5 (CH), 122.3 (CH), 106.8 (C), 60.8 (CH_2), 53.2 (CH_2), 36.7 (CH_2) and 25.0 (CH_2).

HRMS-EI : Found: M^+ , 387.0886. $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_5\text{S}$ requires M , 387.0889.

m/z (TOF EI⁺) 387 (M^+ , 7%), 346 (25), 232 (100), 185 (98) and 102 (99).

3-(2,4-Dichlorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole (4.50j)



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (Z)-2-(phenylsulfonylmethylene)pyrrolidine (**4.37**) (56 mg, 0.25 mmol) and 2,4-dichloro-*N*-hydroxybenzimidoyl chloride (**4.34b**) (56 mg, 0.25 mmol) in dry dichloromethane (5 mL). The reaction mixture was heated under reflux for 18 hours. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether:ethyl acetate; 3:1) to give the title compound (45 mg, 44%) as a colourless oil.

ν_{max} (neat) 2974, 1584, 1480, 1447, 1359, 1157, 1083 and 830 cm^{-1} .

δ_{H} (400 MHz; CDCl_3) : 7.89 (2 H, app. broad d), 7.60 (1 H, app. tt, J 7.4, 1.2), 7.51 (2 H, app. broad t, J 7.6), 7.39 (1 H, d, J 1.8), 7.16 (1 H, dd, J 8.4, 1.8), 7.13 (1 H, d, J 8.4), 3.71 (1 H, d, J 14.7, one of CH_2SO_2), 3.64 (1 H, d, J 14.7, one of CH_2SO_2), 3.03 – 2.99 (2 H, m, CH_2N), 2.68 (1 H, ddd, J 14.2, 11.5, 7.0, one of CH_2C), 2.41 (1 H, ddd, J 14.2, 7.3, 2.1, one of CH_2C) and 1.92 – 1.70 (2 H, m, $\text{CH}_2\text{CH}_2\text{N}$).

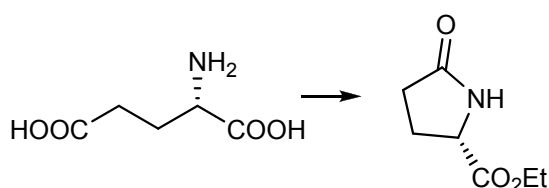
δ_{C} (100 MHz; CDCl_3) : 156.6 (C), 140.9 (C), 137.3 (C), 134.8 (C), 133.8 (CH), 132.6 (CH), 130.8 (CH), 129.3 (2 x CH), 128.0 (2 x CH), 127.3 (CH), 123.4 (C), 105.6 (C), 61.8 (CH_2), 52.1 (CH_2), 37.2 (CH_2) and 24.9 (CH_2).

HRMS-ES : Found: MH^+ , 411.0320. $\text{C}_{18}\text{H}_{16}\text{N}_2\text{SO}_3^{35}\text{Cl}_2$ requires M, 411.0337.

m/z (TOF ES^+) : 411 (MH^+ , 100%) (isotopic distribution consistent with 2 x Cl).

Chiral phenylsulfonylmethyl compounds

(S)-Ethyl 5-oxopyrrolidine-2-carboxylate (4.46) [128]



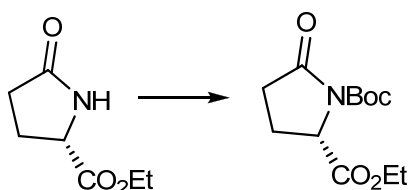
Thionyl chloride (32.3 g, 0.27 mmol) was added to a suspension of *L*-glutamic acid (20.0 g, 0.135 mmol) in ethanol (200 mL) dropwise at 0 °C. The resulting solution was slowly brought to reflux for 1 hour. The solvent was removed *in vacuo* to yield white crystals which, after heating at 145 °C at 1mm Hg for 8 hours gave the *title compound* (17.2 g, 81%) as a waxy solid.

Mp: 49-50 °C (lit: 50-51 °C).

δ_{H} (400 MHz; CDCl_3): 7.12 (s, 1 H, NH), 4.20 (dd, J = 8.2 and 5.1, 1H, CHN), 4.15 (q, J = 7.1, 2 H, CH_2CH_3), 2.45 – 2.25 (m, 3 H, CH_2O and one of CH_2CH_2), 2.18 – 2.09 (m, 1H, one of CH_2CH_2), 1.22 (t, J =7.1, 3 H, CH_3).

δ_{C} (100 MHz; CDCl_3): 178.2 (ester C=O), 172.1 (amide C=O), 61.6 (CH_2O), 55.5 (CHN), 29.3 (CH_2CO), 24.8 (CH_2CH_2), 14.1 (CH_3).

(S)-1-tert-Butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate (4.21b)



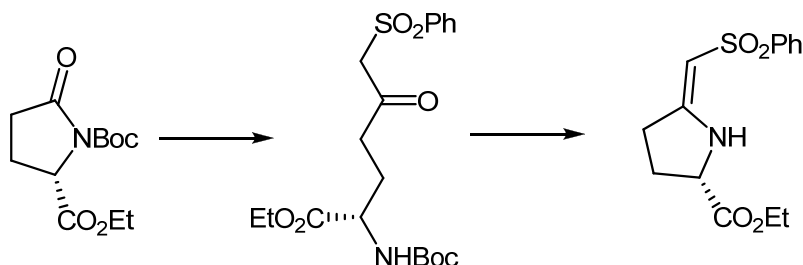
To a solution of di-*t*-butyl dicarbonate (10.6 g, 48.4 mmol) in dichloromethane (25 mL) was added to a solution of (S)-ethyl 5-oxopyrrolidine-2-carboxylate (**4.46**) (7.6 g, 48.4 mmol), DMAP (10 mg) and triethylamine (7.5 mL, 54 mmol) in dichloromethane (75 mL) over 10 minutes at 0 °C. The resulting solution was mixed for 18 hours at 25 °C. The reaction was quenched with saturated aqueous ammonium chloride solution (100 mL) and extracted into DCM (3 x 100 mL). The combined DCM layers washed with brine (2 x 150 mL) and dried (Na₂SO₄). The solvent was removed *in vacuo*, to give a dark brown oil. Purification by flash column chromatography on silica gel (eluent; hexane- ethyl acetate; 4:1) gave the title compound (10.63 g, 85 %) as a pale yellow oil.

δ_{H} (400 MHz; CDCl₃): 4.50 (dd, J = 9.5 and 2.9, 1 H, CHN), 4.15 (q, J = 7.1, 2 H, CH₂O), 2.56 (dt, J = 17.5 and 9.5, one of CH₂CO), 2.41 (ddd, J = 17.5, 9.5 and 3.5, 1 H, one of CH₂CO), 2.25 (ddd, J = 19.5, 13.3 and 3.8, one of CH₂CH₂), 1.96 (ddt, J = 13.3, 9.6 and 3.3, 1 H, one of CH₂CO), 1.39 (s, 9 H, (CH₃)₃), 1.25 (t, J = 7.1, 3 H, CH₃).

δ_{C} (100 MHz; CDCl₃): 173.4 (ester C=O), 171.2 (amide C=O), 149.0 (carbamate C=O), 83.1 (OC(CH₃)₃), 61.4 (CHN), 58.8 (CH₂O), 27.6 (CH₂CH₂), 21.3 ((CH₃)₃), 14.0 (CH₃).

(S,Z)-Ethyl 5-(phenylsulfonylmethylene)pyrrolidine-2-carboxylate

(4.38)



A solution of *n*-butyllithium (1.6 M in Hexanes, 3.8 mL, 6.1 mmol) in dry THF (10 mL) was cooled to -78°C . Methyl phenyl sulphone (0.94 g, 6.1 mmol) in THF (3 mL) was added over 30 minutes after which the solution was allowed to stir for further 30 minutes at -78°C . (2*S*)-1-*t*-butyl 2-ethyl 5-oxopyrrolidine-1,2-dicarboxylate (1.54 g, 6 mmol) in THF (5 mL) was added over 30 minutes and the solution allowed to warm to 25°C and stirred for 18 hours. Saturated aqueous ammonium chloride solution (25 mL) was added and the organic layer extracted with dichloromethane (3 x 25 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over sodium sulphate and the solvent was removed *in vacuo*. The resulting oil was dissolved in dichloromethane (5 mL) and trifluoroacetic acid (1.37 g, 12 mmol) added. The resulting solution was stirred for 18 h at 25°C before being concentrated *in vacuo*. Saturated aqueous sodium bicarbonate solution (20 mL) was added and the organic materials extracted into dichloromethane (3 x 25 mL). The combined organic extracts were washed with brine (2 x 50 mL), dried over magnesium sulphate and the solvent was removed *in vacuo*.

Purification by flash column chromatography (eluent; petroleum ether/ethyl acetate;2:1) gave the title compound (885 mg, 51 %) as a pale oil.

ν_{max} . (neat) : 3395, 2981, 1735, 1607, 1446, 1279, 1199, 1078, 847 and 717 cm^{-1} .

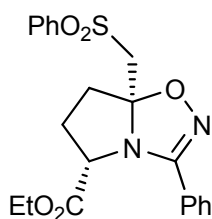
δ_{H} (400 MHz; CDCl_3) : 7.83 (2 H, broad d, J 7.0), 7.53 – 7.37 (3 H, m), 4.68 (1 H, s, alkene CH), 4.30 (1 H, dd, J 8.4, 4.8, CHN), 4.14 (2 H, q, J 7.1, OCH_2), 2.64 – 2.49 (2 H, m, CH_2C), 2.27 – 2.16 (1 H, m, one of CH_2CHN), 2.06 – 1.96 (1 H, m, one of CH_2CHN) and 1.22 (3 H, t, J 7.1, CH_3CH_2).

δ_{C} (100 MHz; CDCl_3) : 171.7 (C), 160.4 (C), 145.0 (C), 132.1 (CH), 129.0 (2 x CH), 125.6 (2 x CH), 85.5 (CH), 61.7 (CH_2), 60.6 (CH), 31.8 (CH_2), 25.8 (CH_2) and 14.2 (CH_3).

HRMS- AP : Found: MH^+ , 296.0945. $\text{C}_{14}\text{H}_{18}\text{NO}_4\text{S}$ requires M, 296.0957.

m/z (TOF MS AP^+) : 296 (MH^+ , 100%).

(5S,7aS)-Ethyl 3-phenyl-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole-5-carboxylate (4.50k)



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (S,Z)-Ethyl 5-(phenylsulfonylmethylene)pyrrolidine-2-carboxylate (**4.38**) (74 mg, 0.25 mmol) and *N*-hydroxybenzimidoyl chloride (**4.34f**) (39 mg, 0.25 mmol) in

dry CH_2Cl_2 (5 mL). The reaction mixture was heated under reflux for 18 h. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether/ethyl acetate;3:1) to give the title compound (48 mg, 46%) as a yellow oil.

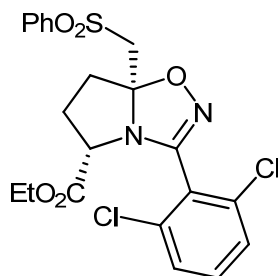
ν_{max} . (neat) : 2980, 1732, 1608, 1447, 1370, 1309, 1084, 750 and 688 cm^{-1} ;

δ_{H} (400 MHz; CDCl_3) : 7.91 (2 H, app. broad d, J 7.1), 7.60 – 7.54 (3 H, m), 7.48 (2 H, app. broad t, J 7.5), 7.38 (1 H, app. tt, J 7.4, 1.4), 7.31 (2 H, app. broad t, J 7.3), 4.18 (2 H, q, J 7.1, OCH_2), 3.98 (1 H, dd, J 7.2, 2.2, CHN), 3.88 (1 H, d, J 14.7, one of CH_2SO_2), 3.62 (1 H, d, J 14.7, one of CH_2SO_2), 2.65 – 2.60 (2 H, m, CH_2C), 2.15 – 2.04 (2 H, m, CH_2CHN) and 1.25 (3 H, t, J 7.1, CH_3CH_2).

δ_{C} (100 MHz; CDCl_3) : 171.1 (C), 158.2 (C), 140.4 (C), 133.8 (CH), 131.5 (CH), 129.1 (2 x CH), 129.0 (2 x CH), 128.3 (2 x CH), 128.0 (2 x CH), 125.1 (C), 106.2 (C), 64.5 (CH), 63.2 (CH_2), 61.7 (CH_2), 35.7 (CH_2), 29.1 (CH_2) and 14.2 (CH_3).

HRMS- ES : Found: MH^+ , 415.1338. $\text{C}_{21}\text{H}_{23}\text{N}_2\text{SO}_5$ requires M, 415.1328.
 m/z (TOF MS ES^+) : 415 (MH^+ , 64%) and 296 (100).

(5S,7aS)-Ethyl 3-(2,6-dichlorophenyl)-7a-(phenylsulfonyl methyl)-5,6,7,7a-tetrahydropyrrolo [1,2-d][1,2,4]oxadiazole-5-carboxylate (4.50I)



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (S,Z)-Ethyl 5-(phenylsulfonylmethylene)pyrrolidine-2-carboxylate (**4.38**) (74 mg, 0.25 mmol) and 2,6-dichloro-*N*-hydroxybenzimidoyl chloride (**4.34a**) (56 mg, 0.25 mmol) in dry CH₂Cl₂ (5 mL). The reaction mixture was heated under reflux for 18 h. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether/ethyl acetate;3:1) to give the title compound (62 mg, 51%) as a yellow oil.

ν_{max} . (neat) : 2980, 1740, 1434, 1322, 1157 and 790 cm⁻¹.

δ_{H} (250 MHz; CDCl₃) : 7.94 (2 H, app. dd, J 8.2, 1.5), 7.62 – 7.47 (3 H, m), 7.31 – 7.27 (3 H, m), 4.09 – 3.97 (2 H, m, OCH₂), 4.04 (1 H, d, J 14.8, one of CH₂SO₂), 3.95 (1 H, dd, J 7.6, 2.1, CHN), 3.70 (1 H, d, J 14.8, one of CH₂SO₂), 2.79 – 2.56 (2 H, m, CH₂C), 2.34 – 2.09 (2 H, m, CH₂CHN) and 1.15 (3 H, t, J 7.1, CH₃CH₂).

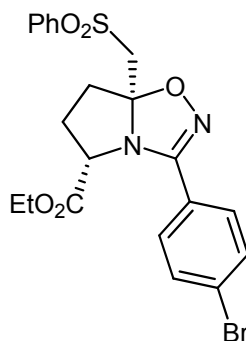
δ_{C} (62.5 MHz; CDCl₃) : 170.6 (C), 152.4 (C), 140.3 (C), 133.8 (CH), 132.4 (CH), 129.1 (2 x CH), 128.5 (CH), 128.3 (2 x CH), 124.2 (C) 106.6

(C), 63.3 (CH₂), 62.6 (CH₂), 61.6 (CH), 35.5 (CH₂), 29.7 (CH₂) and 14.0 (CH₃);

HRMS- AP : Found: MH⁺, 483.0534. C₂₁H₂₁N₂SO₅³⁵Cl₂ requires M, 483.0534.

m/z (TOF AP⁺) : 505 (MNa⁺, 100%) and 483 (MH⁺, 69) (isotopic distribution consistent with 2 x Cl).

**(5S,7aS)-Ethyl 3-(4-bromophenyl)-7a-(phenylsulfonylmethyl)- -
5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole-5-carboxylate
(4.50m)**



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (S,Z)-Ethyl 5-(phenylsulfonylmethylene)pyrrolidine-2-carboxylate (**4.38**) (74 mg, 0.25 mmol) and 4-bromo-*N*-hydroxybenzimidoyl chloride (**4.34g**) (59 mg, 0.25 mmol) in dry CH₂Cl₂ (5 mL). The reaction mixture was heated under reflux for 18 h. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether/ethyl acetate;3:1) to give the title compound (24 mg, 29%) as a colourless oil.

ν_{max}. (neat) : 2977, 1739, 1589, 1447, 1321, 1156 and 1084 cm⁻¹.

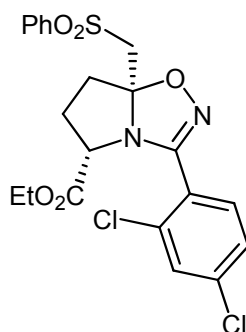
δ_{H} (400 MHz; CDCl_3) : 7.90 (2 H, app. broad d, J 7.2), 7.58 (1 H, app. tt, J 7.4, 1.2), 7.48 (2 H, app. broad t, J 7.9), 7.46 (4 H, app. s), 4.18 (2 H, q, J 7.1, OCH_2), 3.92 (1 H, dd, J 8.0, 1.4, CHN), 3.85 (1 H, d, J 14.7, one of CH_2SO_2), 3.60 (1 H, d, J 14.7, one of CH_2SO_2), 2.65 – 2.59 (2 H, m, CH_2C), 2.18 – 2.03 (2 H, m, CH_2CHN) and 1.25 (3 H, t, J 7.1, CH_3CH_2).

δ_{C} (100 MHz; CDCl_3) : 170.9 (C), 157.6 (C), 140.4 (C), 133.8 (CH), 132.3 (2 x CH), 129.4 (2 x CH), 129.1 (2 x CH), 128.2 (2 x CH), 126.0 (C), 124.1 (C), 106.6 (C), 64.6 (CH_2), 63.0 (CH), 61.9 (CH_2), 35.7 (CH_2), 29.0 (CH_2) and 14.2 (CH_3).

HRMS-ES : Found: MH^+ , 493.0438. $\text{C}_{21}\text{H}_{22}\text{N}_2\text{SO}_5^{79}\text{Br}_2$ requires M, 493.0433);

m/z (TOF ES^+) : 495 (MH^+ , 100%) and 493 (MH^+ , 98).

(5S,7aS)-Ethyl 3-(2,4-dichlorophenyl)-7a-(phenylsulfonylmethyl)-5,6,7,7a-tetrahydropyrrolo [1,2-d][1,2,4]oxadiazole-5-carboxylate (4.50n)



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (S,Z)-Ethyl 5-(phenylsulfonylmethylene)pyrrolidine-2-carboxylate (**4.38**) (74 mg, 0.25 mmol) and 2,4-dichloro-*N*-hydroxybenzimidoyl chloride (**4.34b**) (56 mg, 0.25 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was heated under

reflux for 18 h. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether/ethyl acetate;3:1) to give the title compound (78 mg, 65%) as a colourless oil.

ν_{max} . (neat) : 2926, 1739, 1584, 1447, 1308, 1153, 1085 and 687 cm^{-1} .

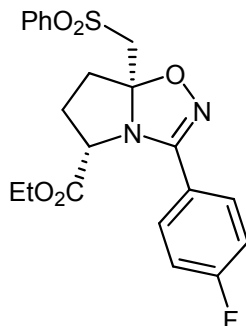
δ_{H} (400 MHz; CDCl_3) : 7.91 (2 H, broad d, J 7.2), 7.63 – 7.48 (4 H, m), 7.40 (1 H, d, J 2.0), 7.22 (1 H, dd, J 8.4, 2.0), 4.11 (2 H, q, J 7.1, OCH_2), 3.92 (1 H, d, J 14.8, one of CH_2SO_2), 3.81 (1 H, dd, J 5.3, 4.2, CHN), 3.74 (1 H, d, J 14.8, one of CH_2SO_2), 2.69 – 2.54 (2 H, m, CH_2C), 2.12 – 2.04 (2 H, m, CH_2CHN) and 1.21 (3 H, t, J 7.1, CH_3CH_2).

δ_{C} (100 MHz; CDCl_3) : 170.7 (C), 155.2 (C), 140.5 (C), 137.8 (C), 134.9 (C), 133.8 (CH), 132.8 (CH), 131.0 (CH), 129.1 (2 x CH), 128.3 (2 x CH), 122.7 (C), 106.4 (C), 63.9 (CH), 63.3 (CH_2), 61.7 (CH_2), 36.0 (CH_2), 29.0 (CH_2) and 14.1 (CH_3).

HRMS-AP : Found: MH^+ , 483.0528. $\text{C}_{21}\text{H}_{21}\text{N}_2\text{SO}_5^{35}\text{Cl}_2$ requires M, 483.0548.

m/z (TOF AP^+) : 485 (MH^+ , 52%), 483 (MH^+ , 67), 296 (100) and 198 (60) (isotopic distribution of MH^+ peaks consistent with 2 x Cl).

**(5S,7aS)-Ethyl 3-(4-fluorophenyl)-7a-(phenylsulfonylmethyl)- -
5,6,7,7a-tetrahydropyrrolo[1,2-d][1,2,4]oxadiazole-5-carboxylate
(4.50o)**



Triethylamine (30 mg, 0.3 mmol) was added to a solution of (S,Z)-Ethyl 5-(phenylsulfonylmethylene) pyrrolidine-2-carboxylate **(4.38)** (74 mg, 0.25 mmol) and 4-fluoro-*N*-hydroxybenzimidoyl chloride **(4.34h)** (43 mg, 0.25 mmol) in dry CH₂Cl₂ (5 mL). The reaction mixture was heated under reflux for 18 h. The solution was then washed with water (3 x 15 mL), dried over magnesium sulphate and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (eluent; petroleum ether/ethyl acetate;3:1) to give the title compound (108 mg, 56% from 0.45 mmol of 10) as a pale yellow oil.

ν_{max} . (neat) : 1737, 1604, 1510, 1447, 1369, 1309 and 1156 cm⁻¹.

δ_{H} (400 MHz; CDCl₃) : 7.90 (2 H, app. dd, J 7.2, 1.4), 7.62 – 7.54 (3 H, m), 7.49 (2 H, app. broad t, J 7.6), 7.01 (2 H, app. t, J 8.7), 4.18 (2 H, app. dq, J 7.1, 0.8, OCH₂), 3.94 (1 H, dd, J 7.9, 1.5, CHN), 3.86 (1 H, d, J 14.3, one of CH₂SO₂), 3.60 (1 H, d, J 14.3, one of CH₂SO₂), 2.64 – 2.59 (2 H, m, CH₂C), 2.18 – 2.04 (2 H, m, CH₂CHN) and 1.25 (3 H, t, J 7.1, CH₃CH₂).

δ_C (100 MHz; $CDCl_3$) : 171.0 (C), 157.4 (C), 140.4 (C), 133.8 (CH), 130.2 (2 x CH, $^3J_{C-F}$ 8.7), 129.1 (2 x CH), 128.2 (2 x CH), 121.4 (C, $^4J_{C-F}$ 3.3), 116.3 (2 x CH, $^2J_{C-F}$ 22.2), 106.3 (C), 64.6 (CH), 63.0 (CH_2), 61.8 (CH_2), 35.7 (CH_2), 29.0 (CH_2) and 14.2 (CH_3).

HRMS-AP: Found: MH^+ , 433.1216. $C_{21}H_{22}N_2SO_5F$ requires M, 433.1233.

m/z (TOF AP $^+$) : 433 (MH^+ , 100%).

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APPENDICES

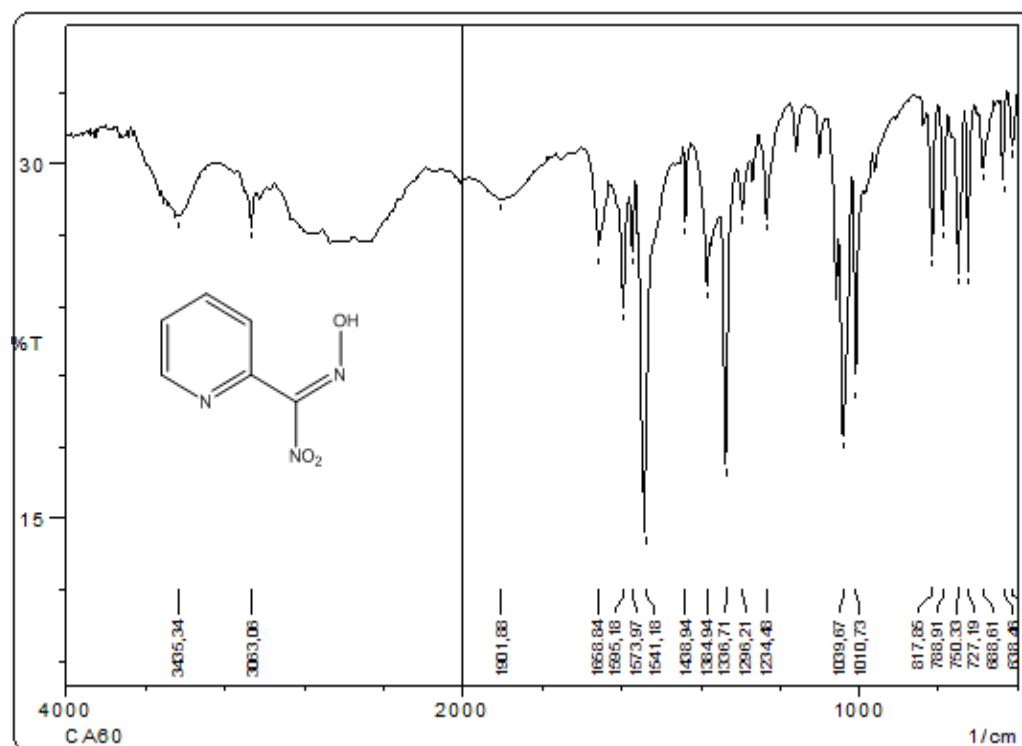


Figure 5. 1 IR Spectrum of compound 4.6a

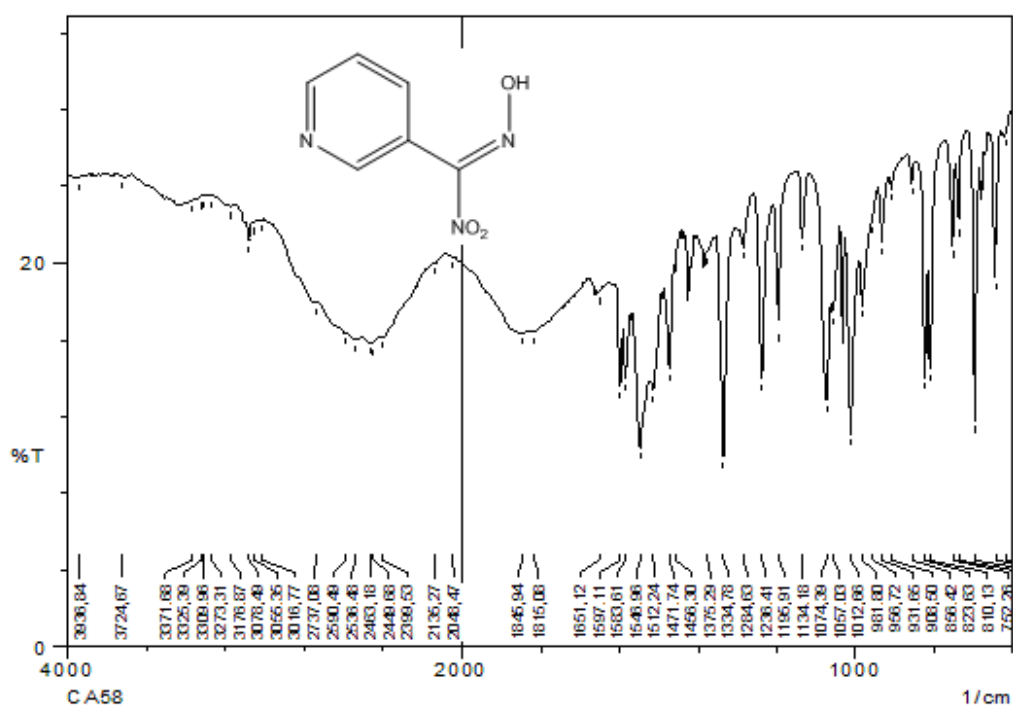


Figure 5. 2 IR Spectrum of compound 4.6b

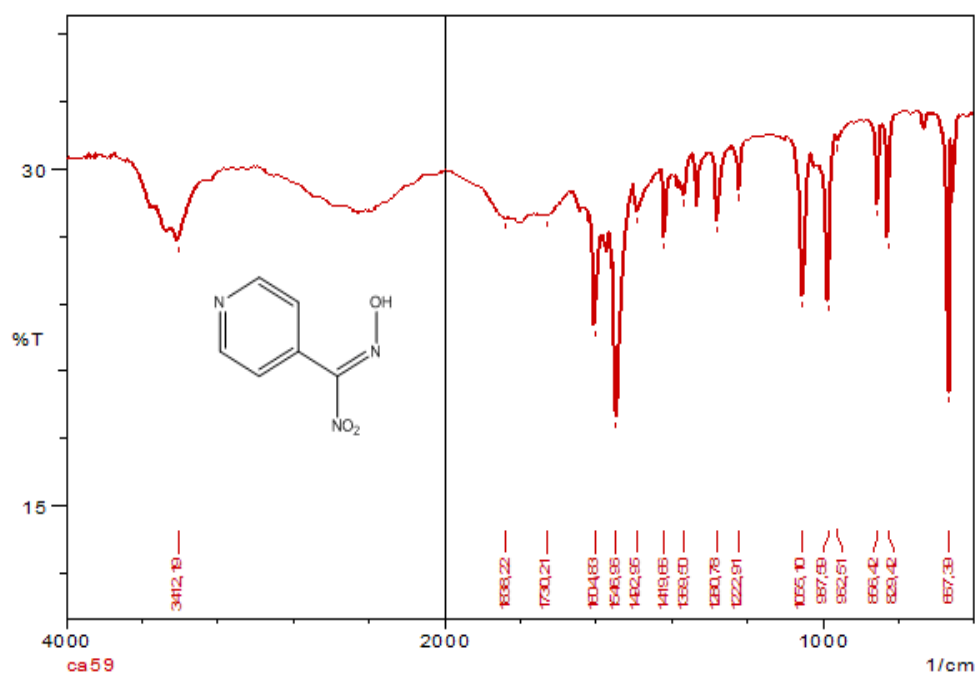


Figure 5. 3 IR Spectrum of compound 4.6c

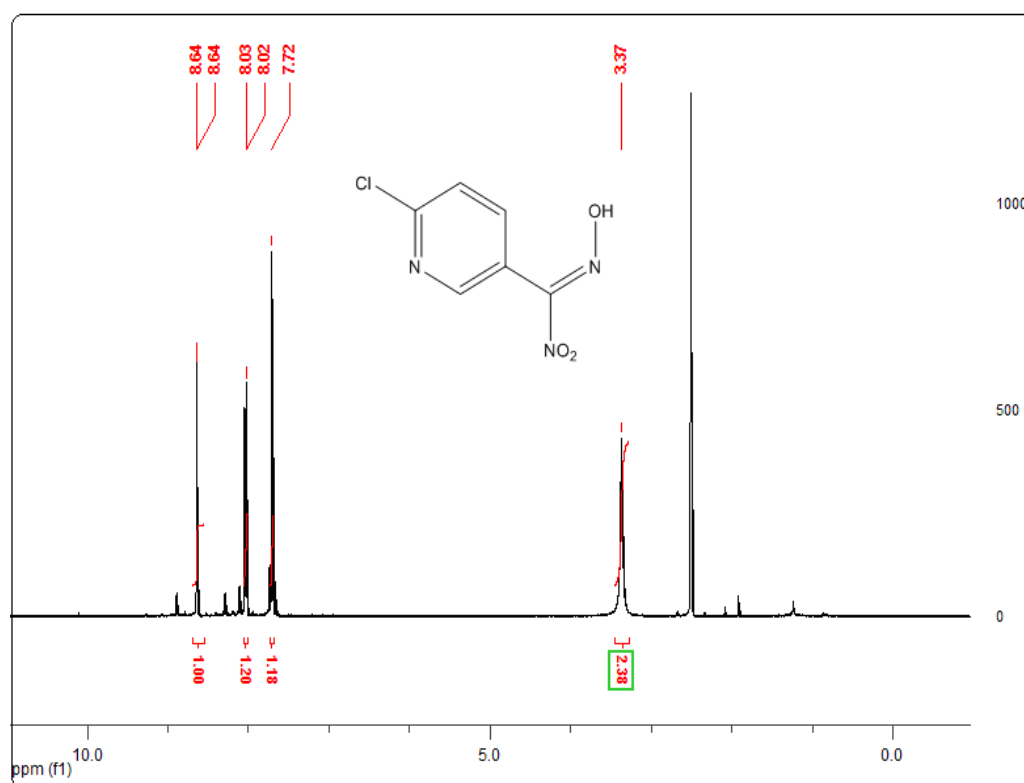


Figure 5. 4 ¹H NMR of compound 4.6d

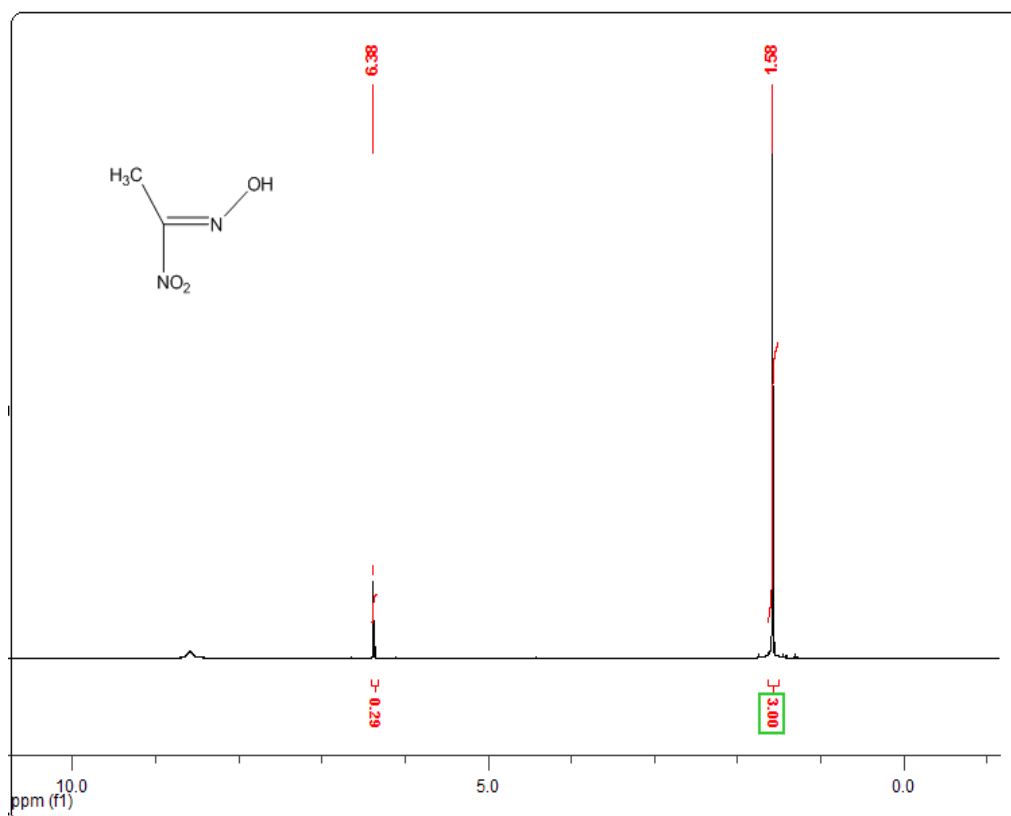


Figure 5. ¹H NMR of compound 4.6k

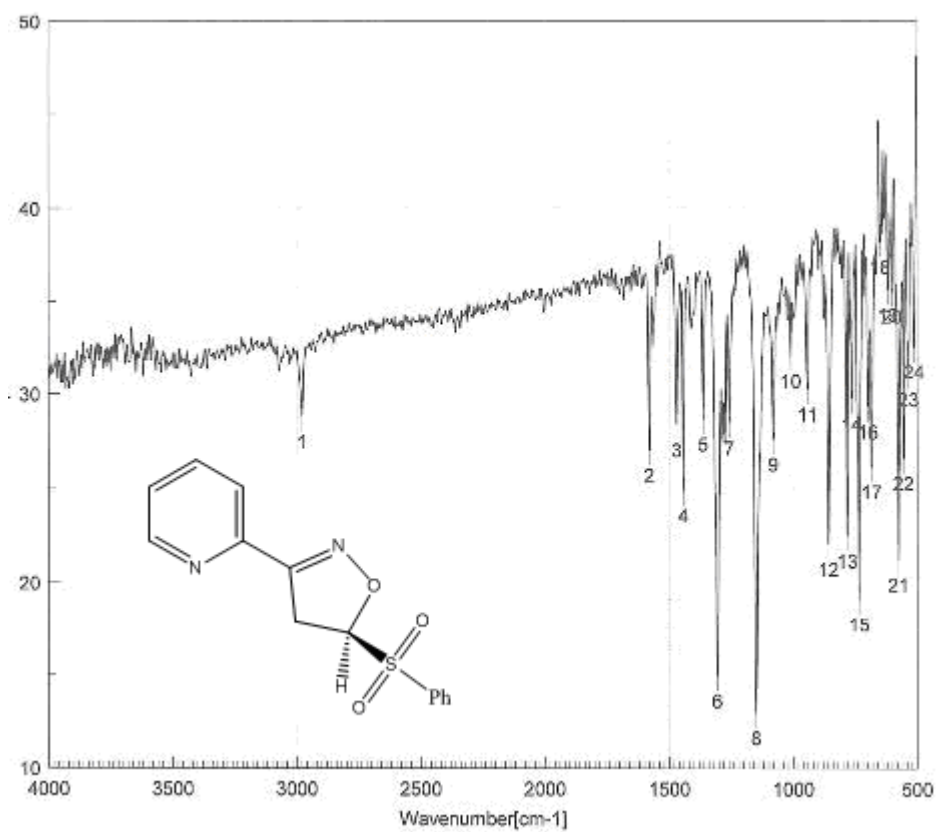


Figure 5. 6 IR Spectrum of compound 4.8a

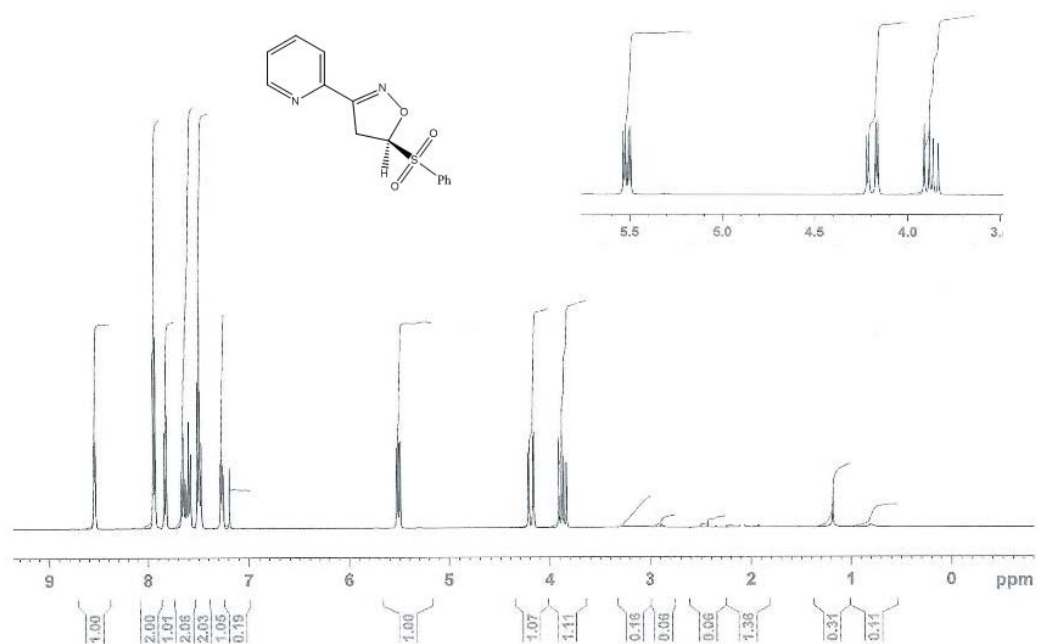


Figure 5. 7 ¹H NMR Spectrum of compound 4.8a

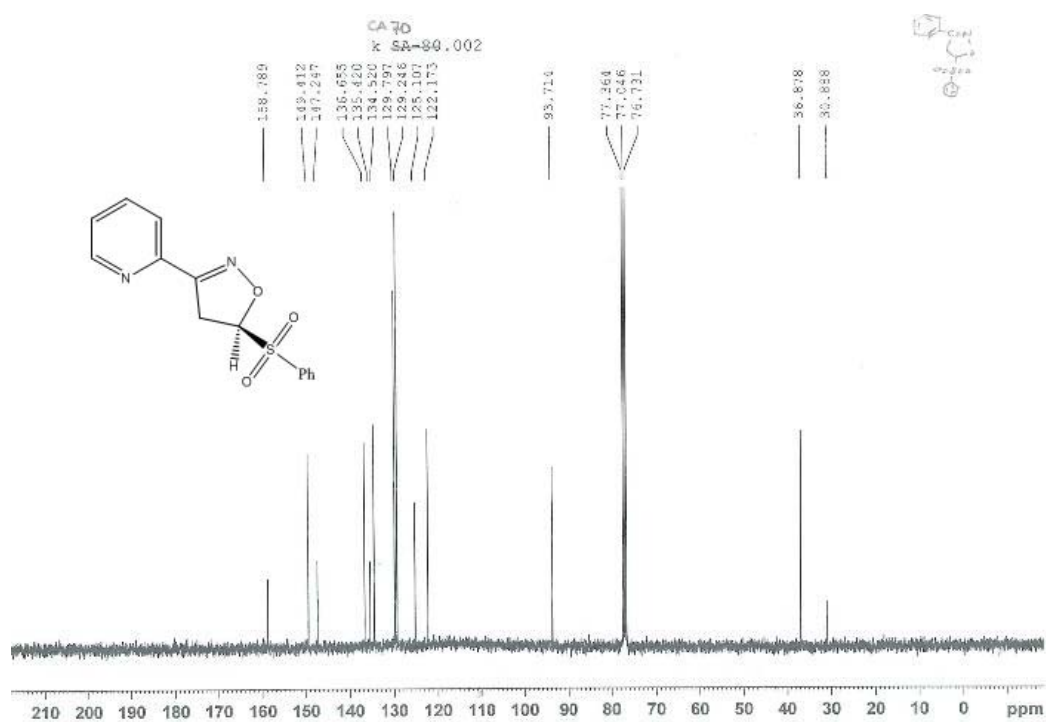


Figure 5. 8 ¹³C NMR Spectra of compound 4.8a

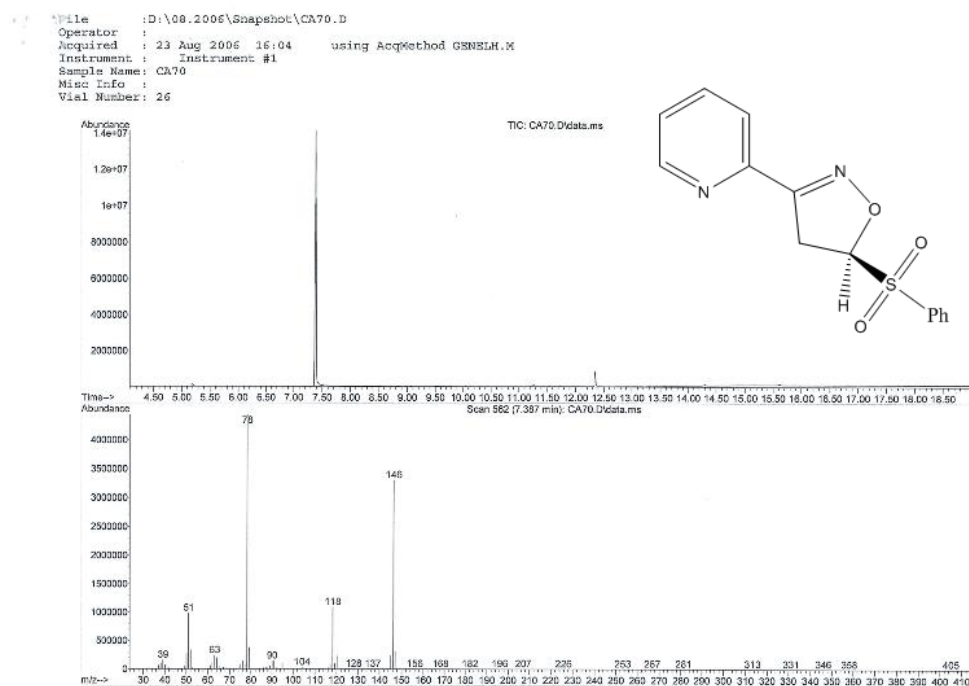


Figure 5. 9 MASS Spectra of compound 4.8a

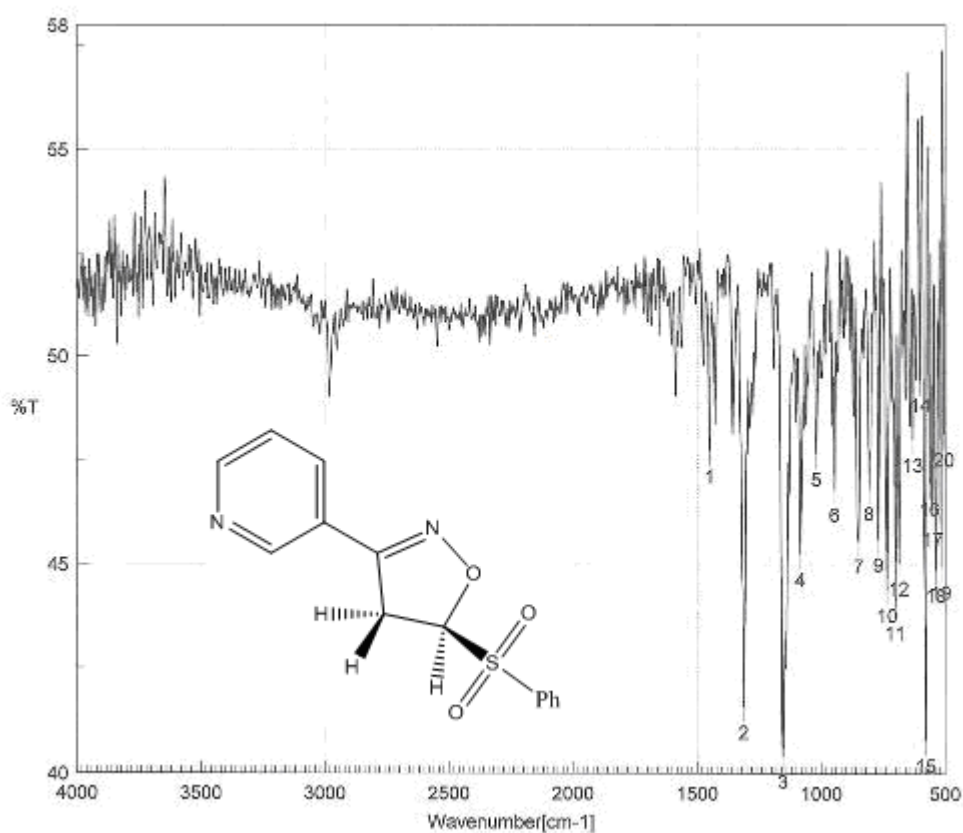


Figure 5. 10 IR Spectra of compound 4.8b

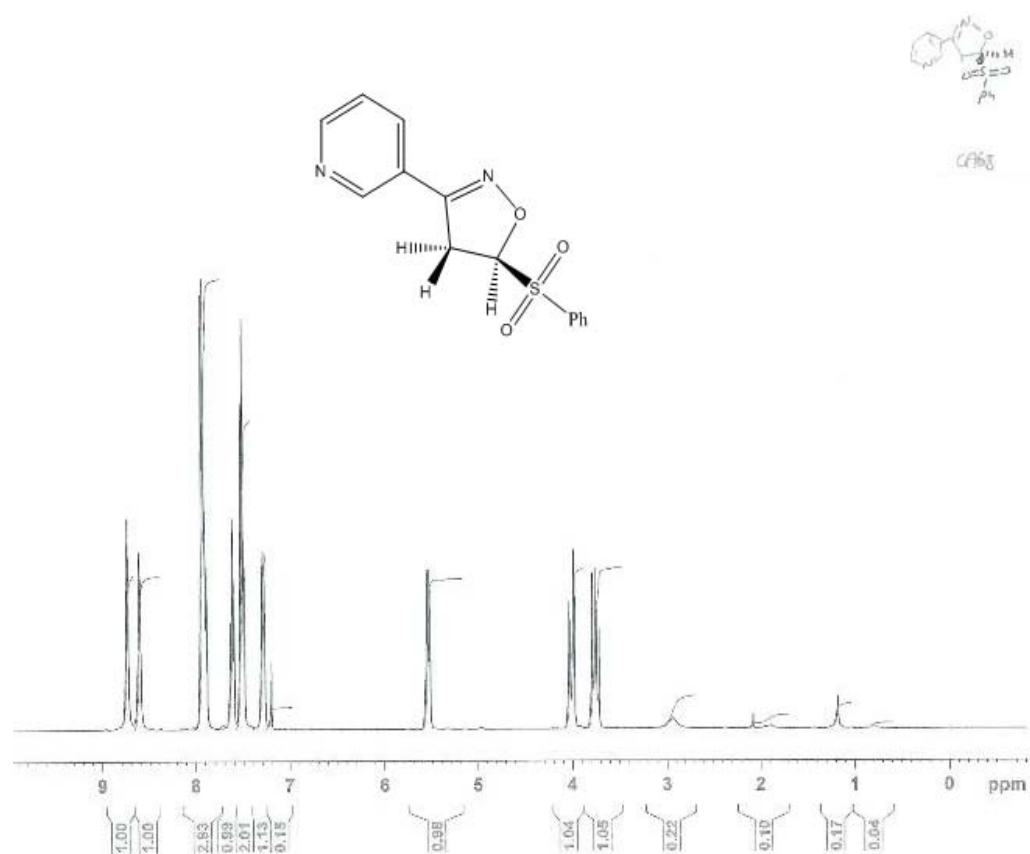


Figure 5.11 ¹H NMR Spectra of compound 4.8b

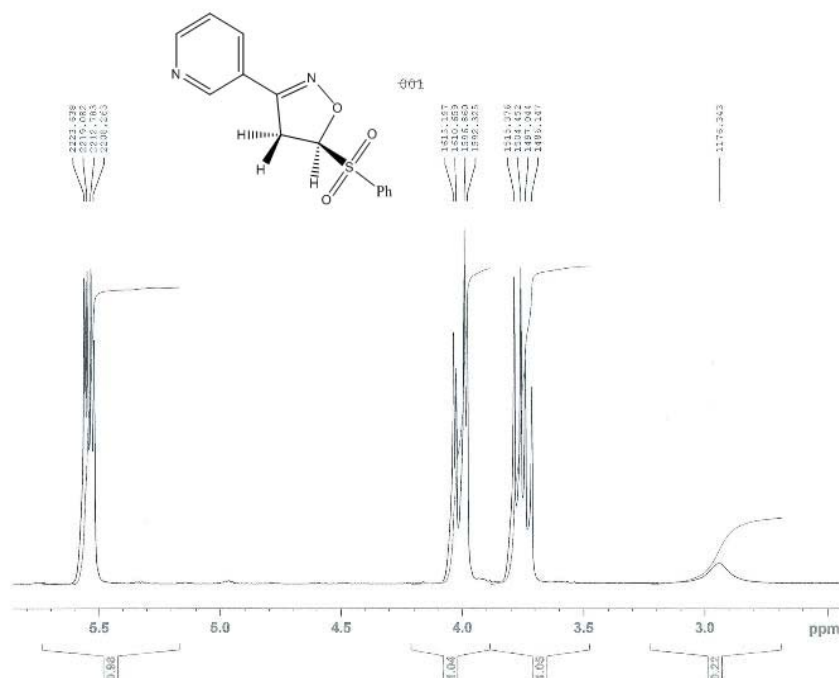


Figure 5.12 Expanded ¹H NMR Spectrum of compound 4.8b

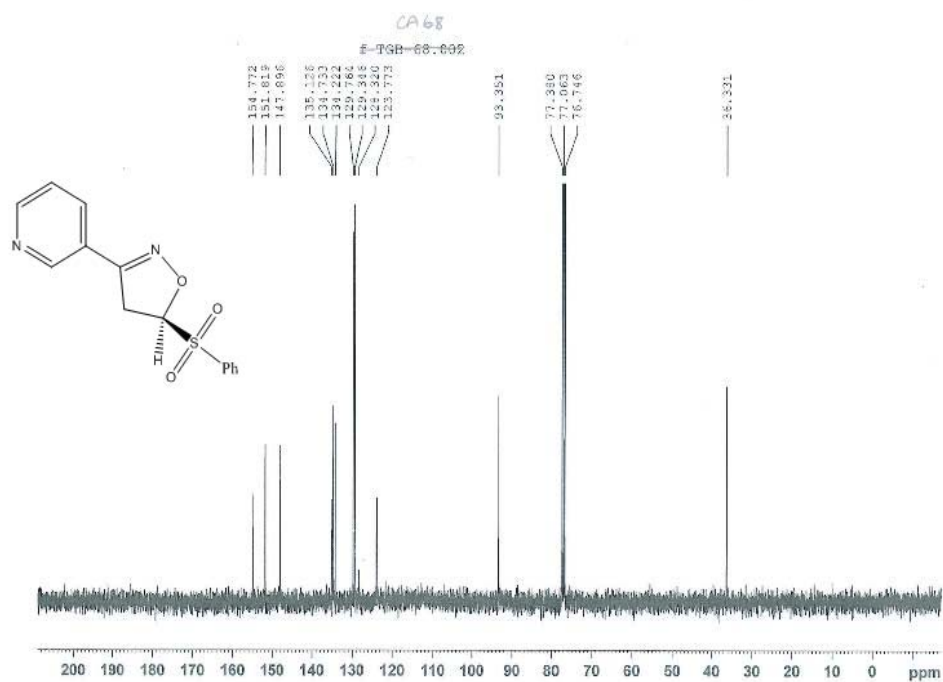


Figure 5. 13 ^{13}C NMR Spectrum of compound 4.8b

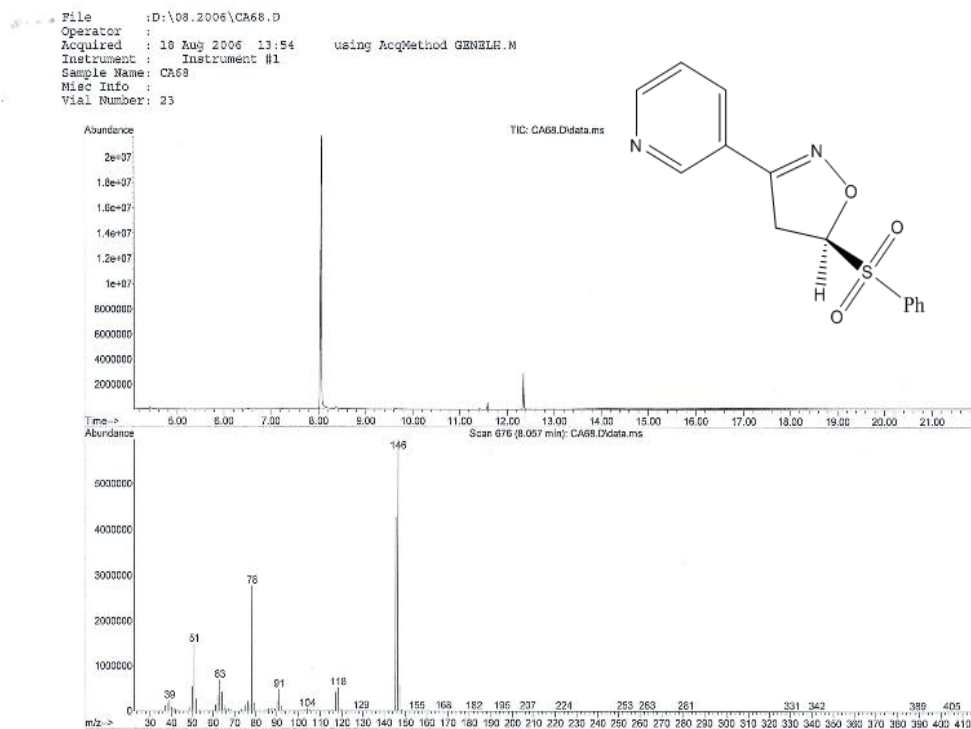


Figure 5. 14 Mass Spectrum of compound 4.8b

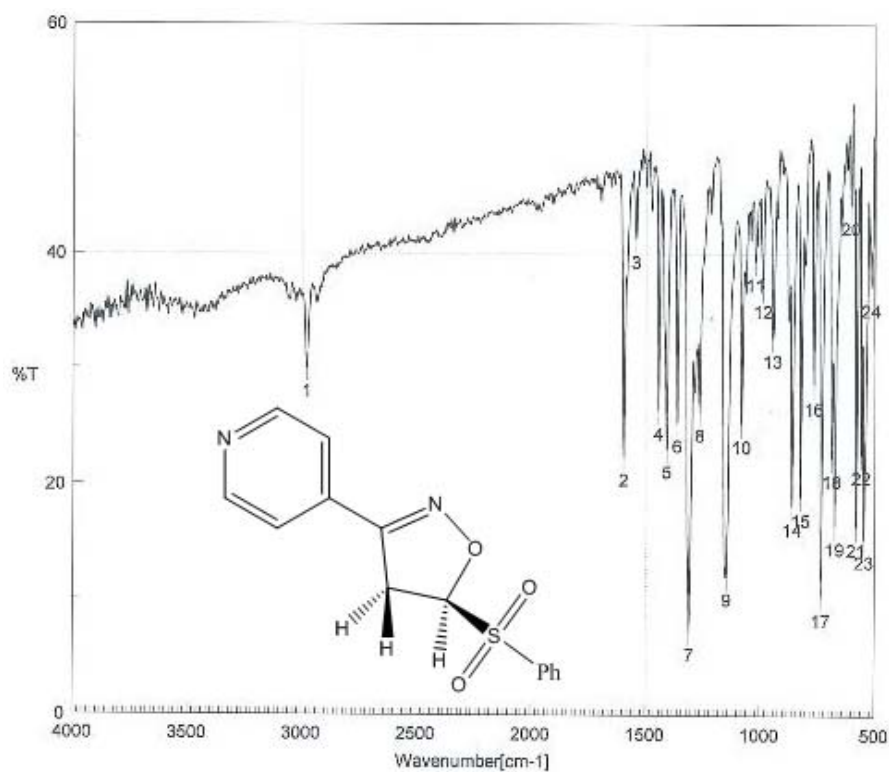


Figure 5. 15 IR Spectrum of compound 4.8c

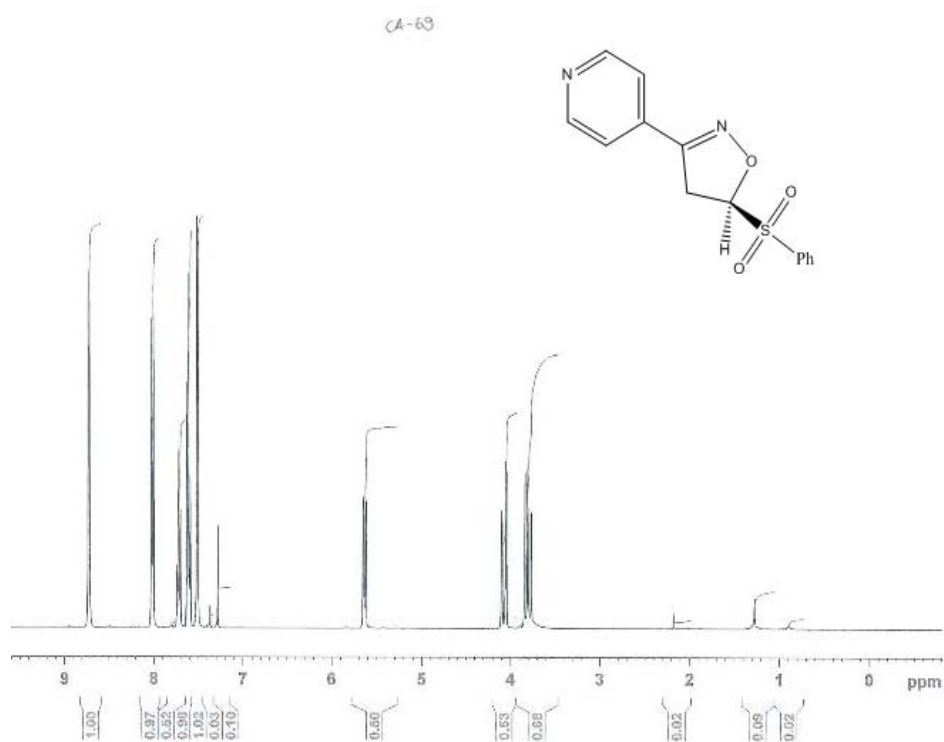


Figure 5. 16 ^1H NMR Spectra of compound 4.8c

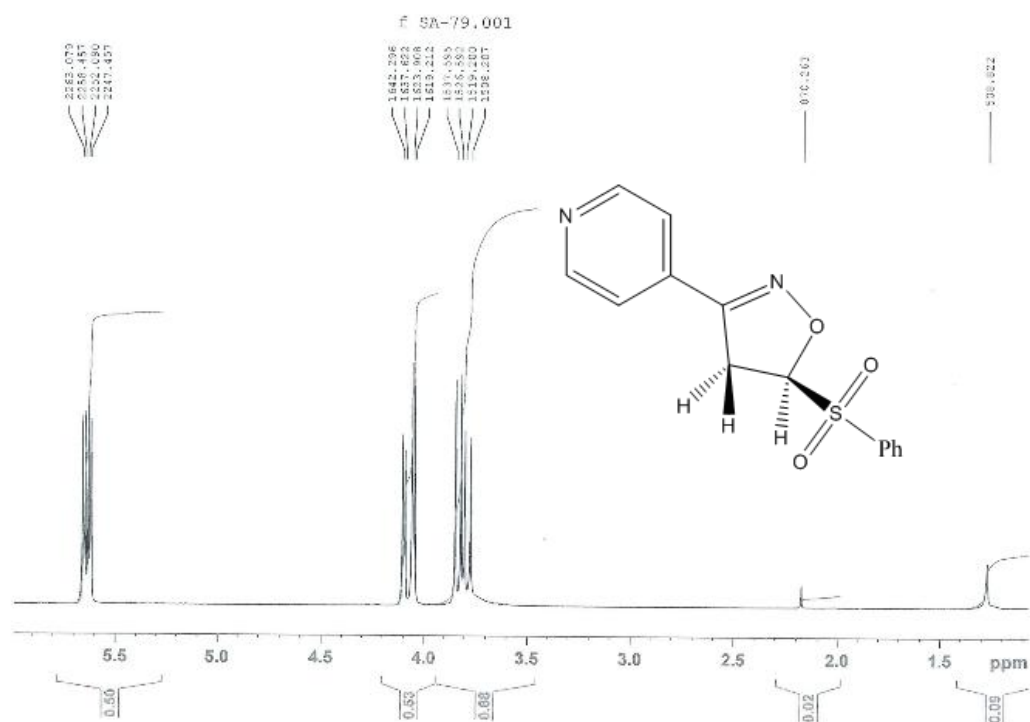


Figure 5. 17 Expanded ^1H NMR Spectra of compound 4.8c

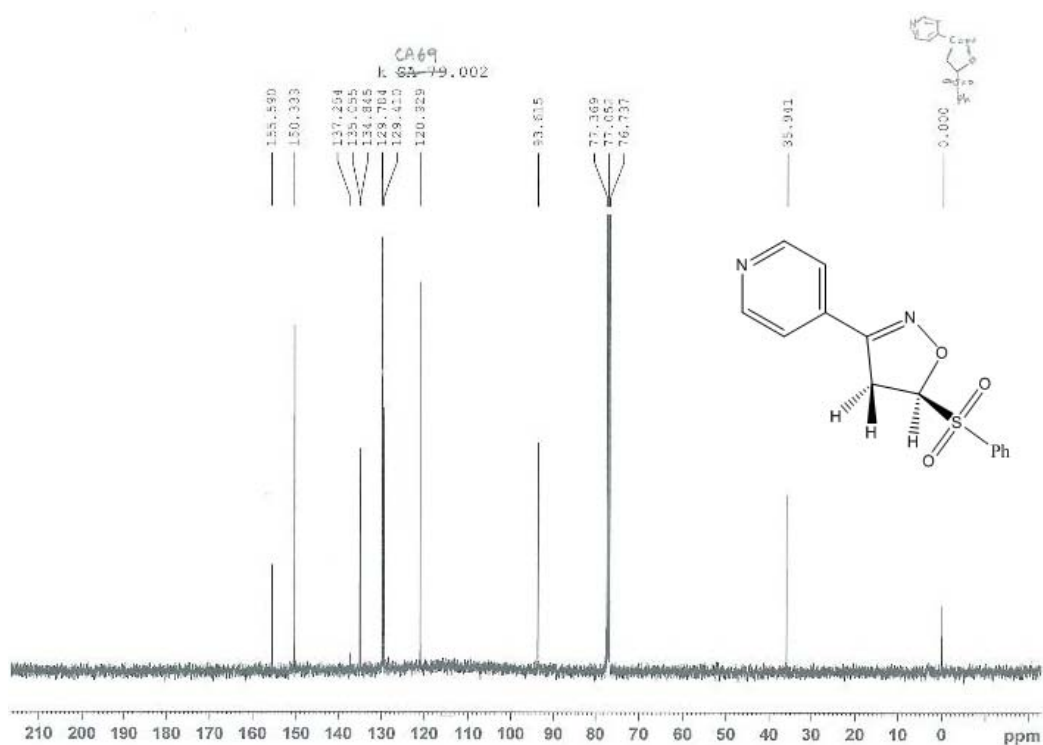


Figure 5. 18 ^{13}C NMR Spectrum of compound 4.8c

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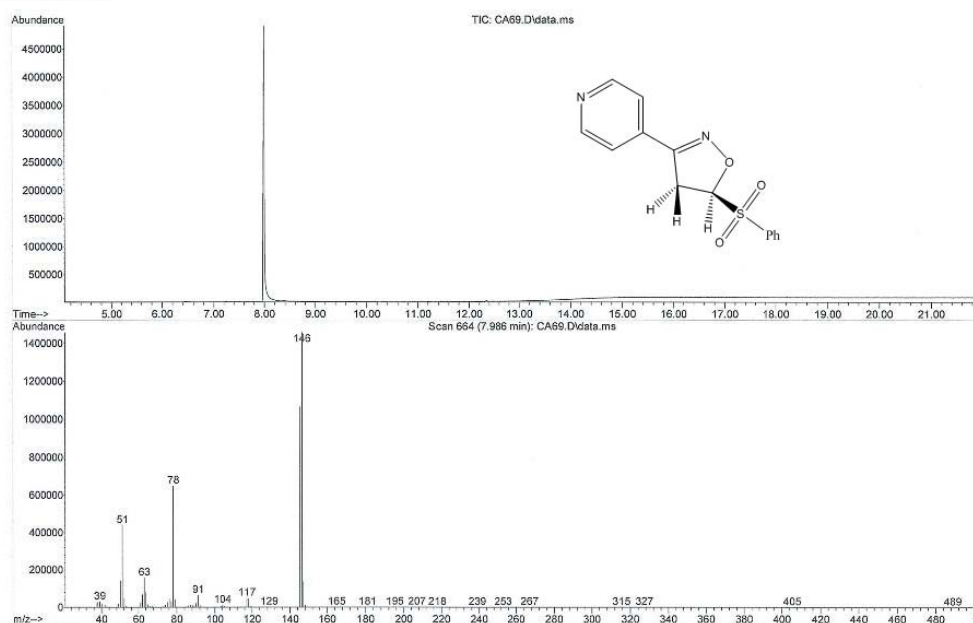


Figure 5. 19 Mass Spectrum of compound 4.8c

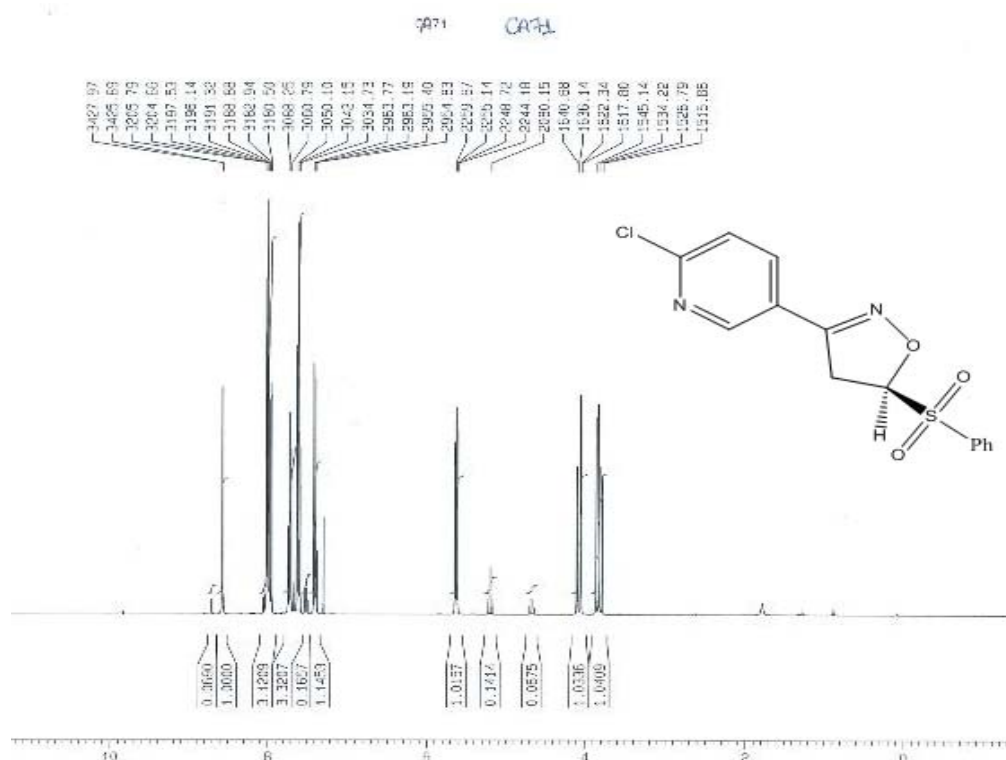


Figure 5. 20 ¹H NMR Spectrum of compound 4.8d

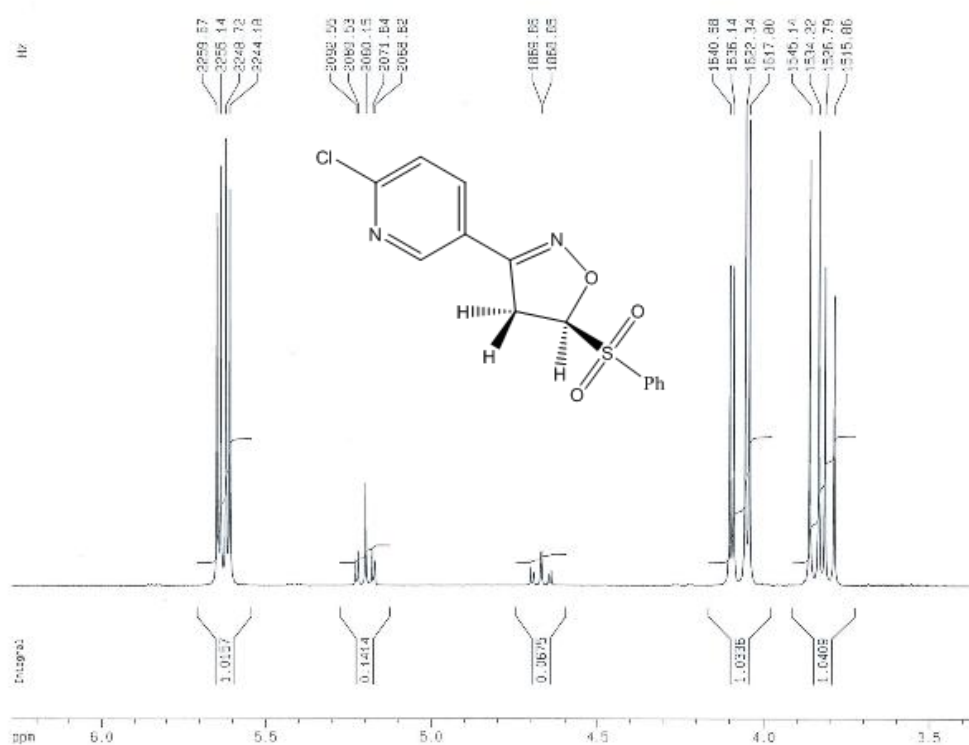
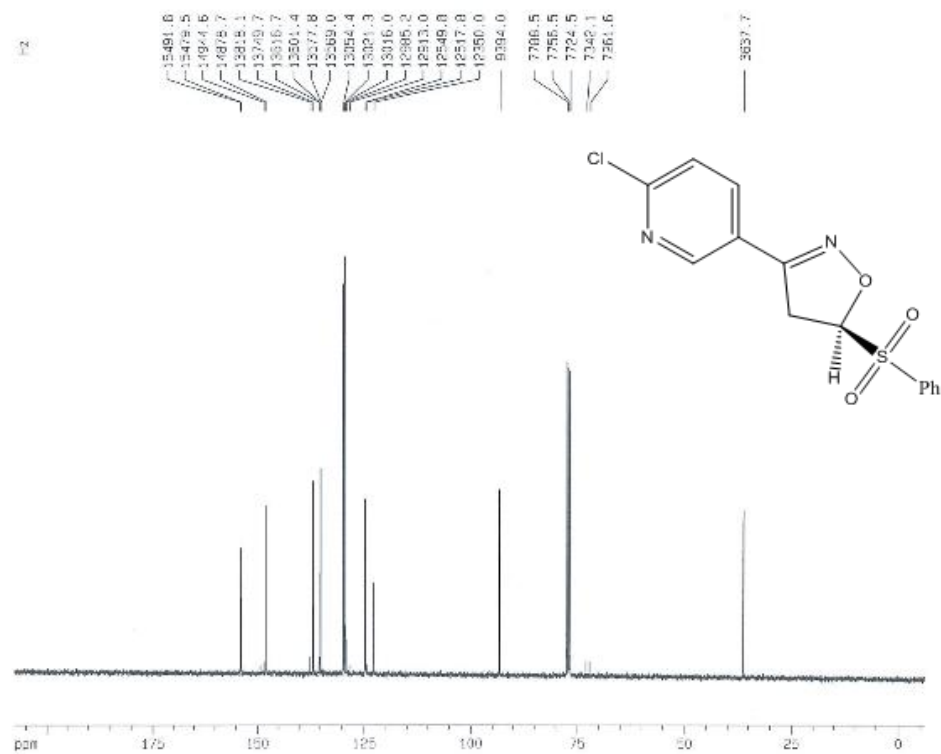


Figure 5. 21 Expanded ¹H NMR Spectrum of compound **4.8d**



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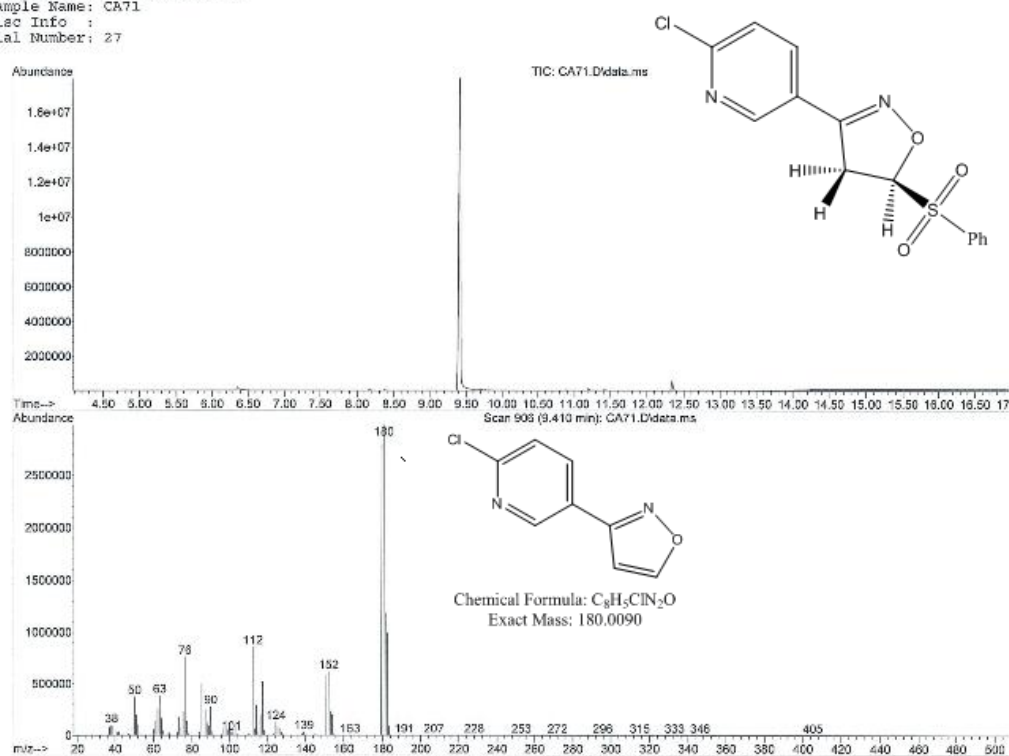


Figure 5. 23 Mass Spectrum of compound 4.8d

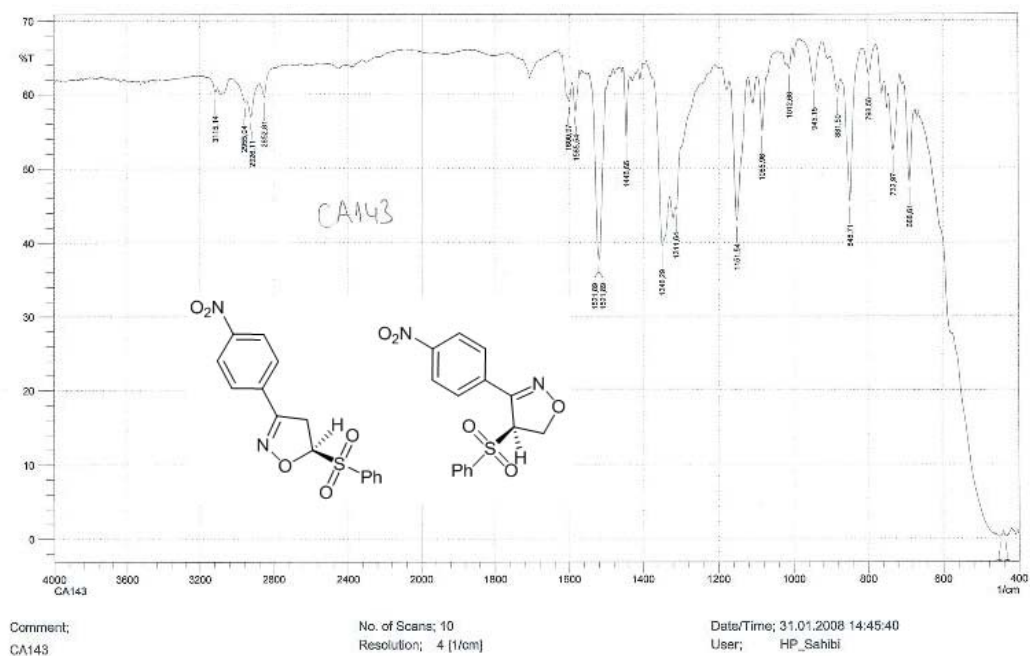


Figure 5. 24 IR Spectrum of regioisomers 4.8e and 4.8e'

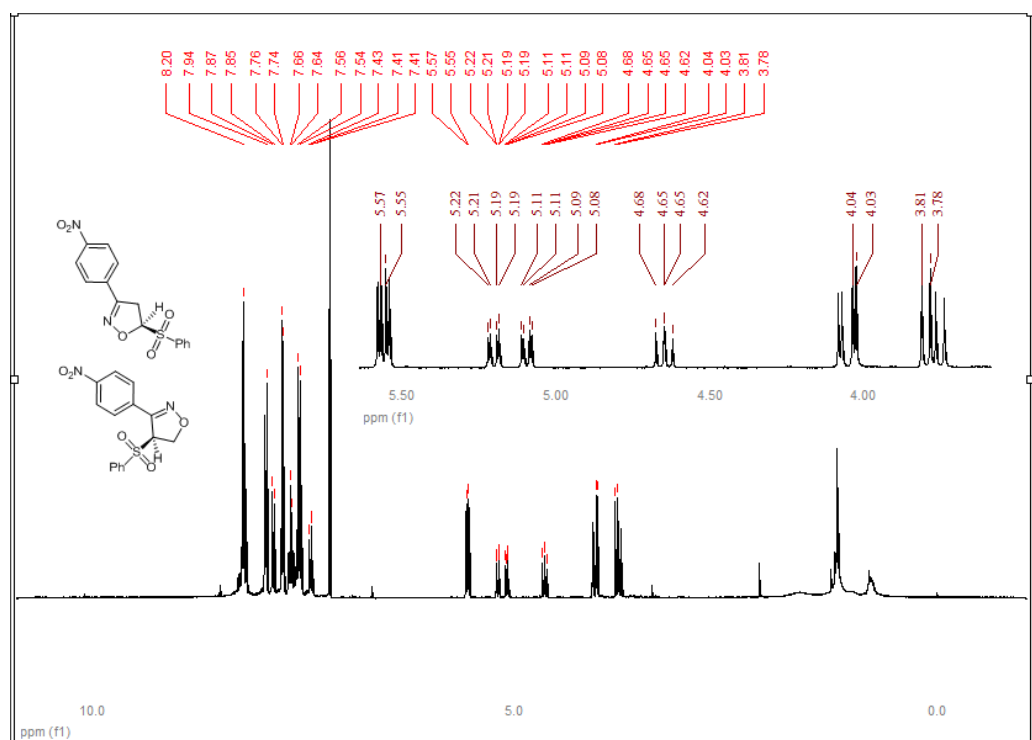


Figure 5. 25 ^1H NMR Spectrum of regioisomers 4.8e and 4.8e'

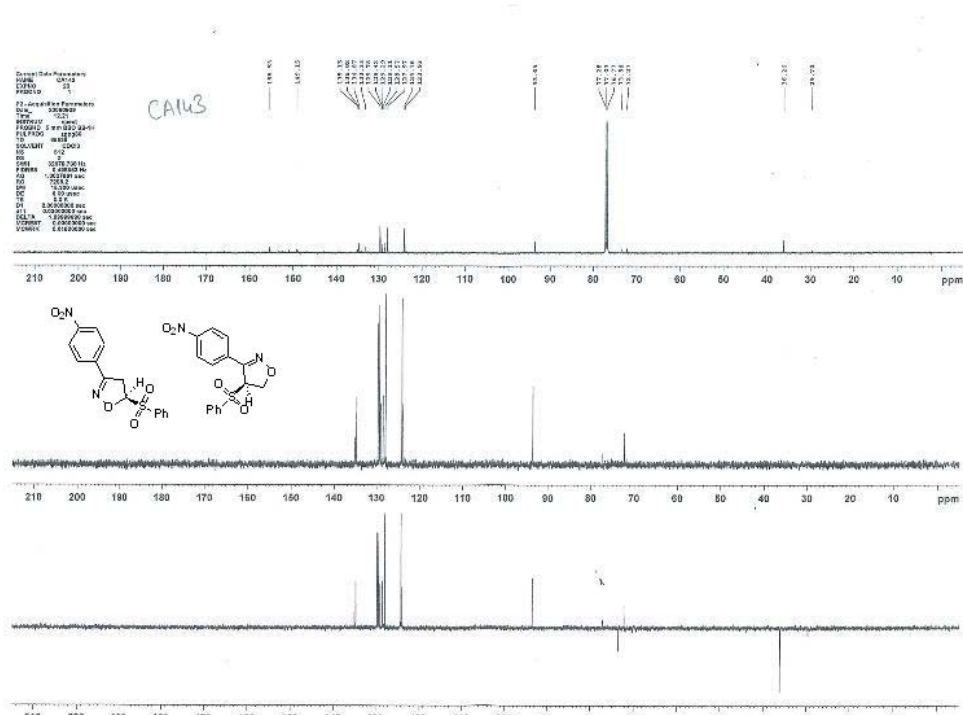


Figure 5. 26 ^{13}C NMR Spectrum of compound regioisomers 4.8e and 4.8e'

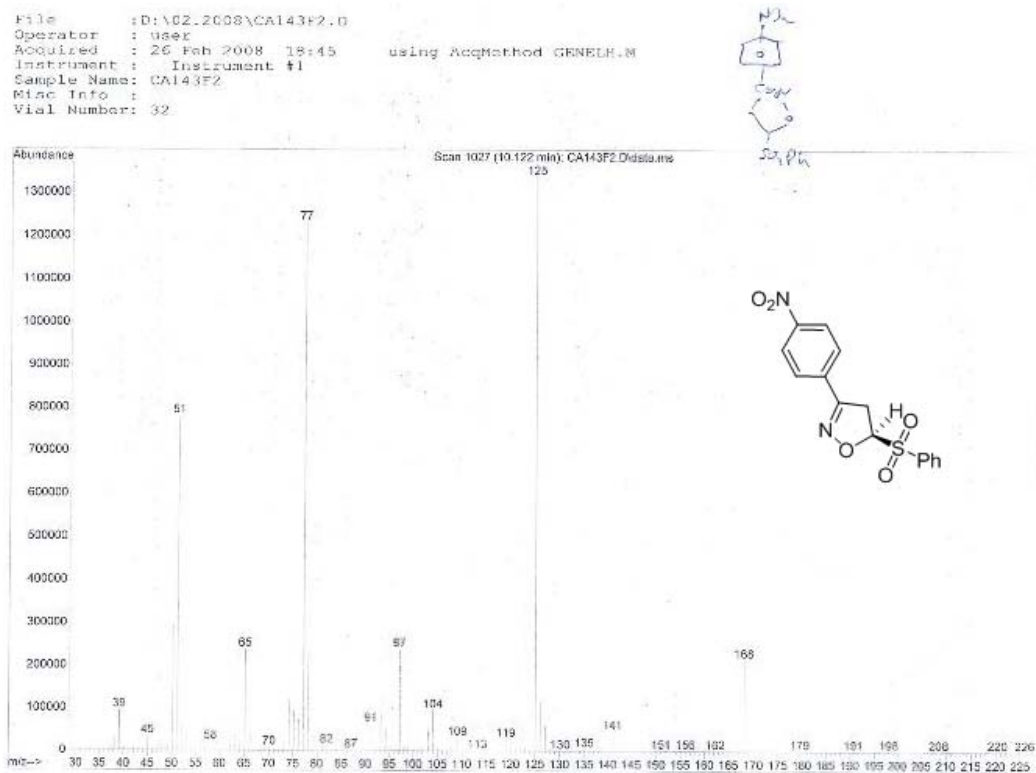


Figure 5. 27 Mass Spectrum of compound 4.8e

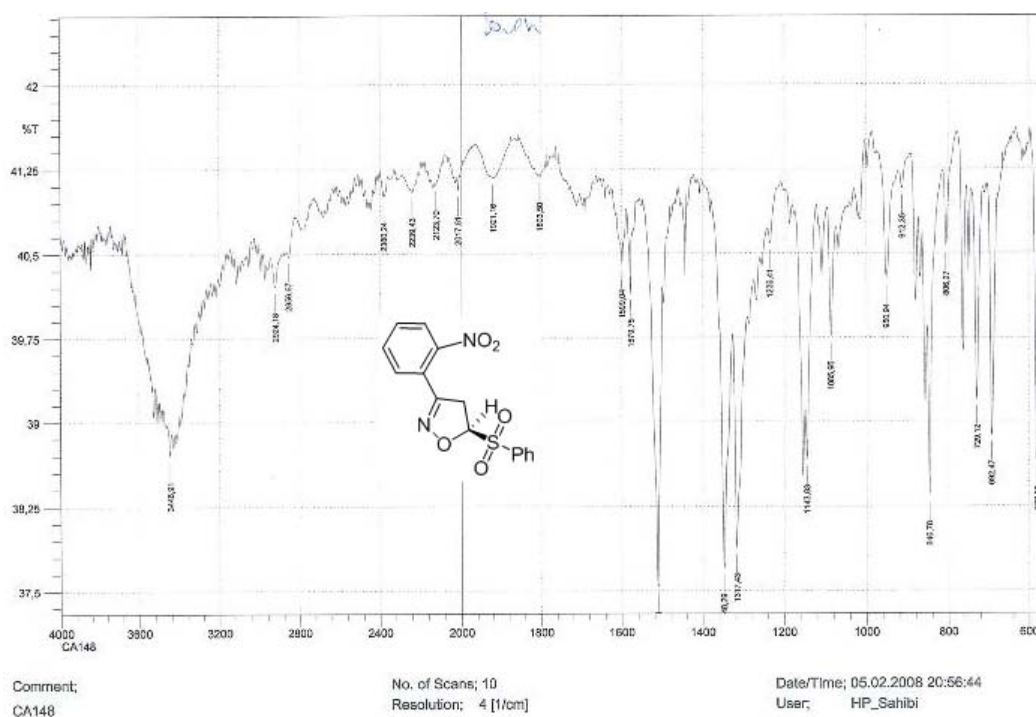


Figure 5. 28 IR Spectrum of compound 4.8f

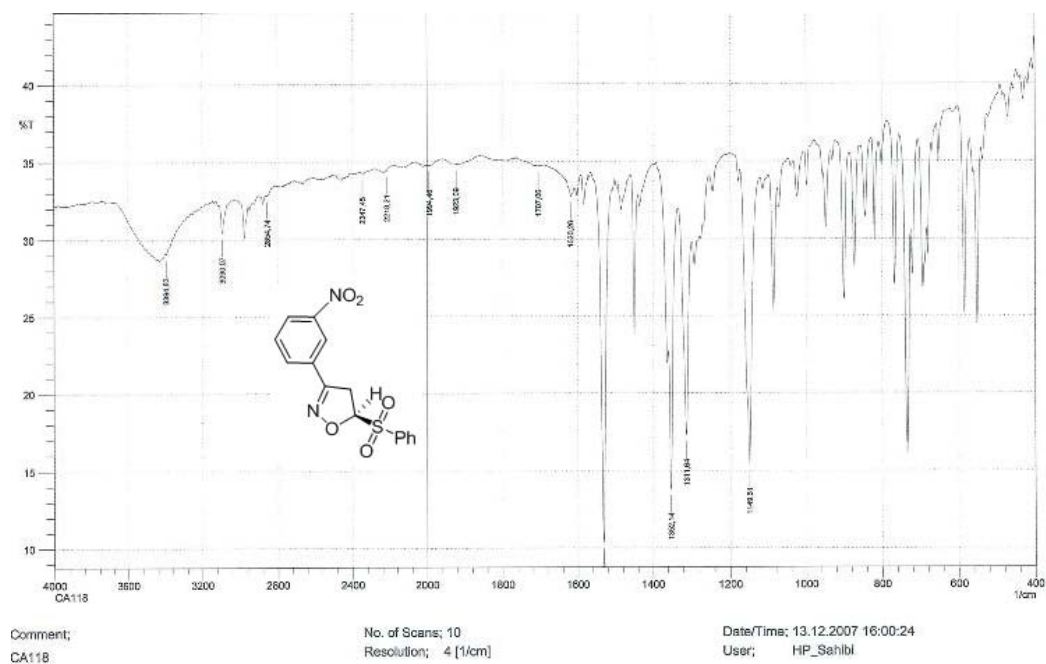


Figure 5. 29 IR Spectrum of compound 4.8g

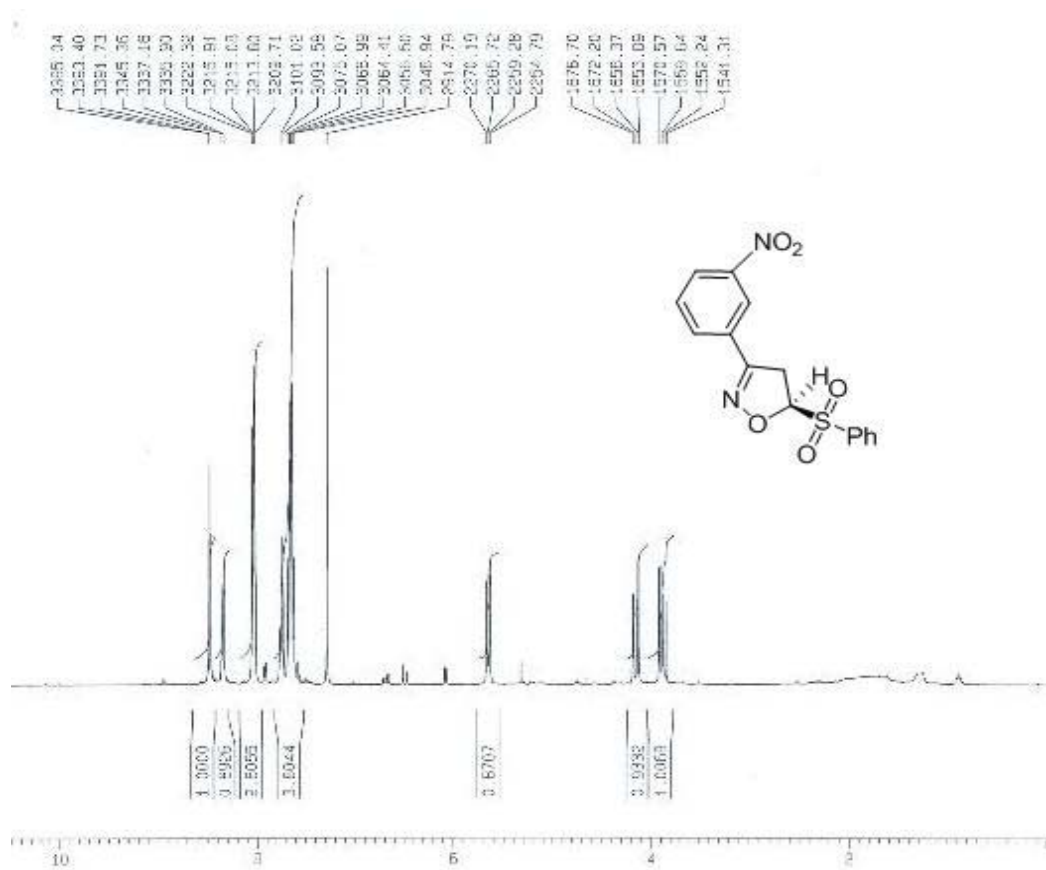


Figure 5. 30 ¹H NMR Spectrum of compound 4.8g

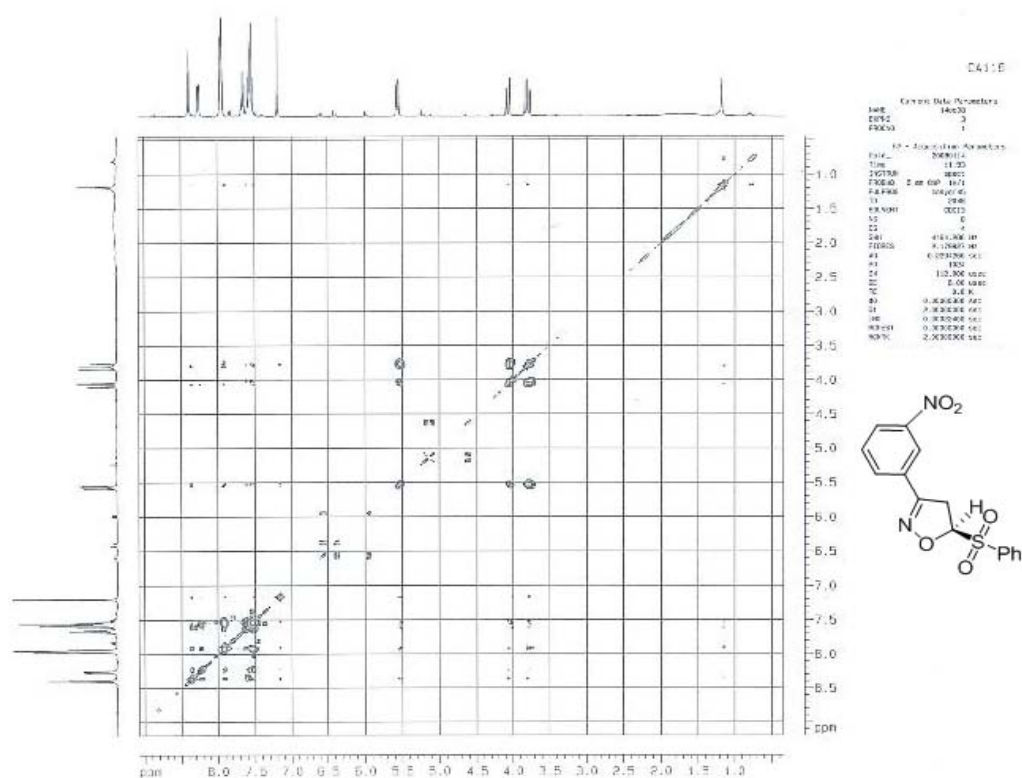


Figure 5. 31 COSY NMR Spectrum of compound 4.8g

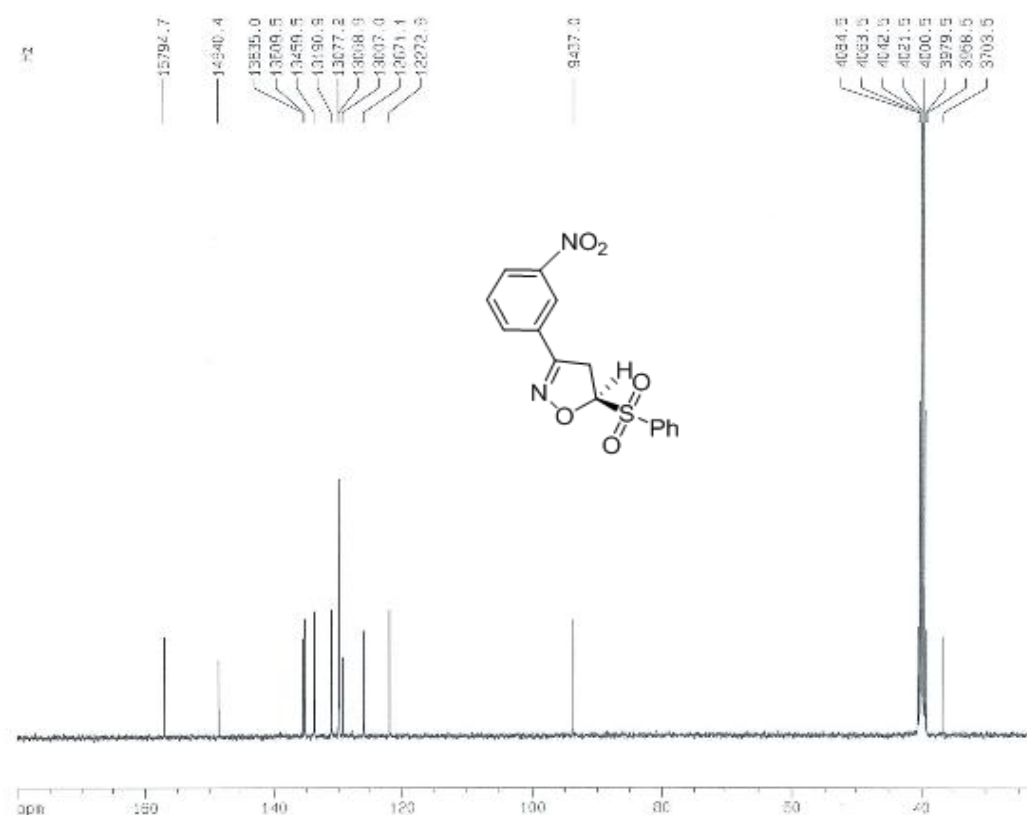


Figure 5. 32 ¹³C NMR Spectrum of compound 4.8g

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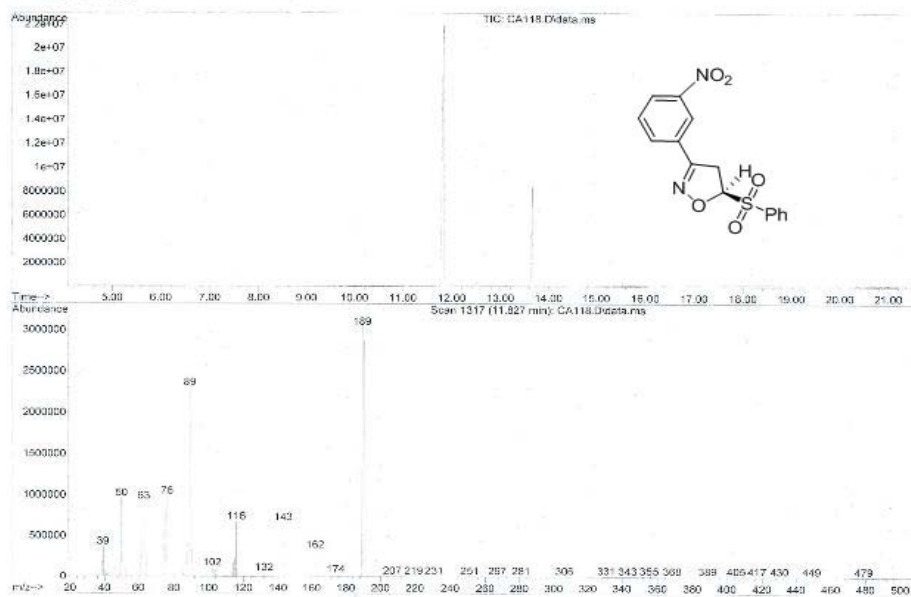


Figure 5. 33 Mass Spectrum of compound 4.8g

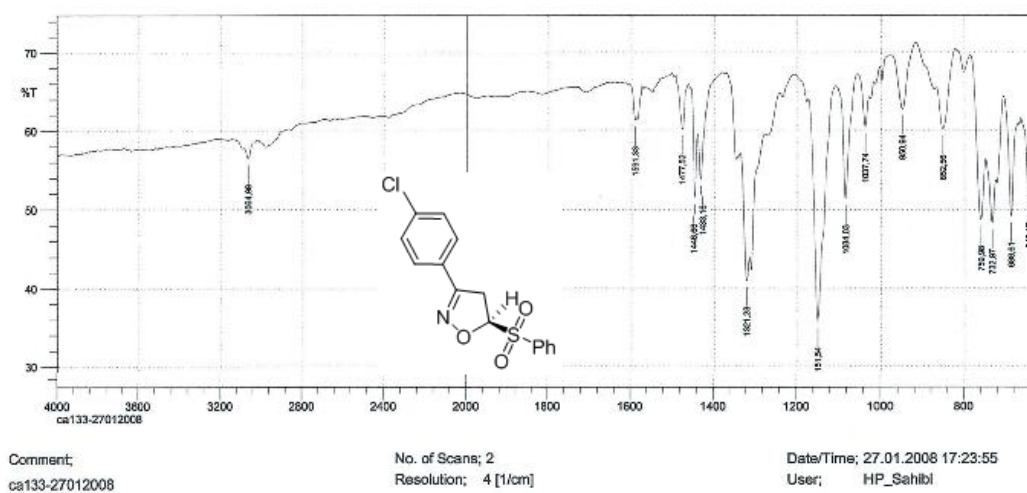


Figure 5. 34 IR Spectrum of compound 4.8h

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 Vial Number: 97

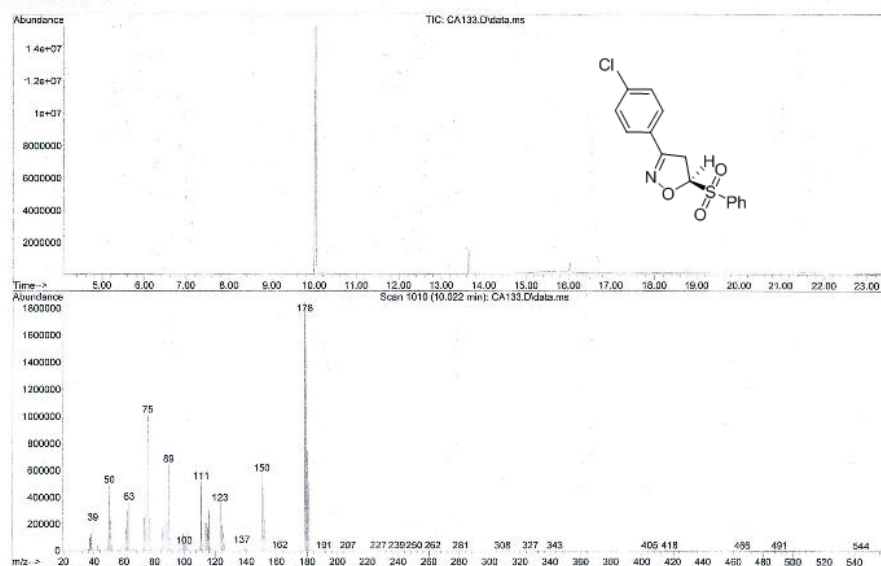


Figure 5. 35 Mass Spectrum of compound 4.8h

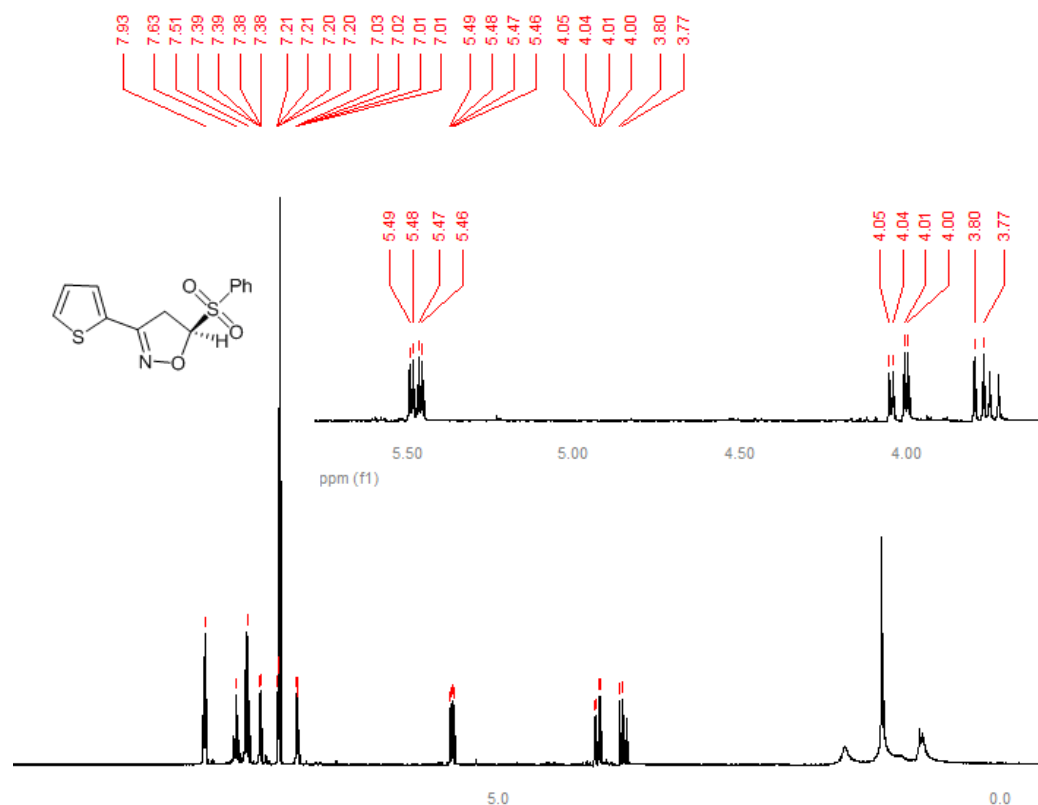


Figure 5. 36 ^1H NMR Spectrum of compound 4.8i

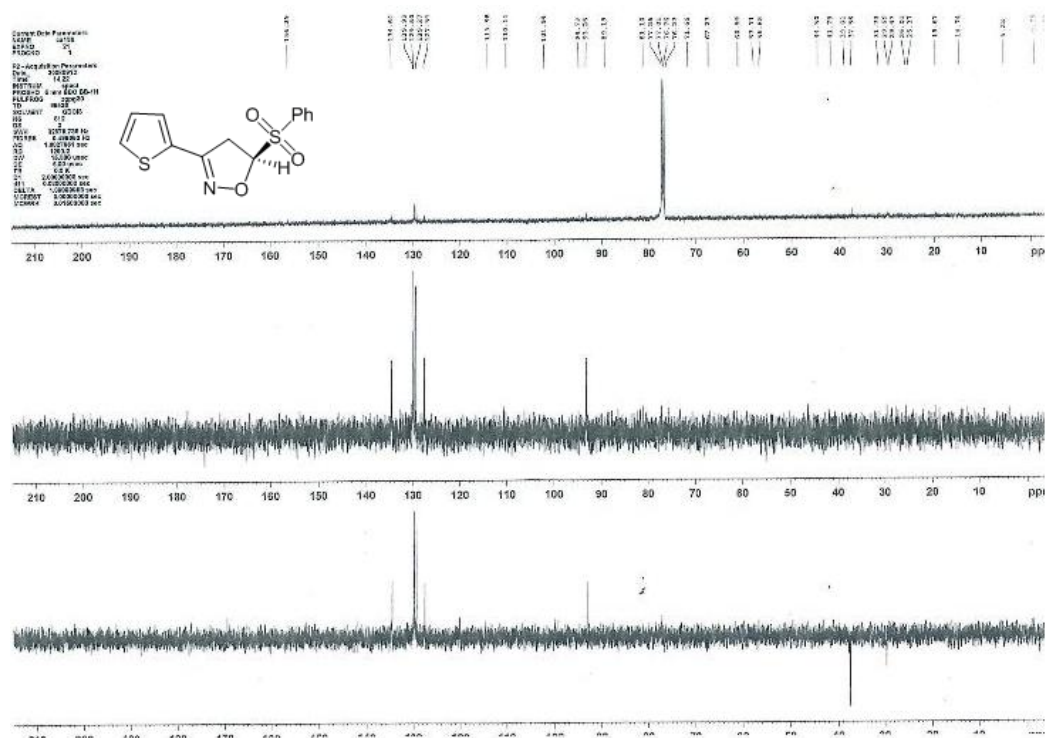


Figure 5. 37 ^{13}C NMR Spectrum of compound 4.8i

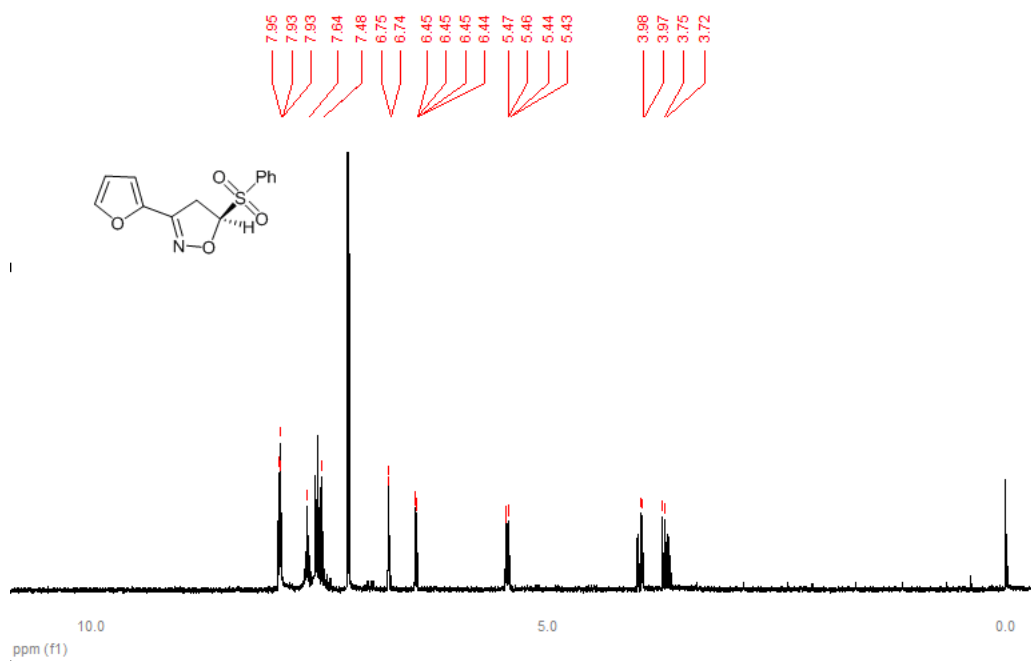


Figure 5. 38 ^1H NMR Spectrum of compound 4.8j

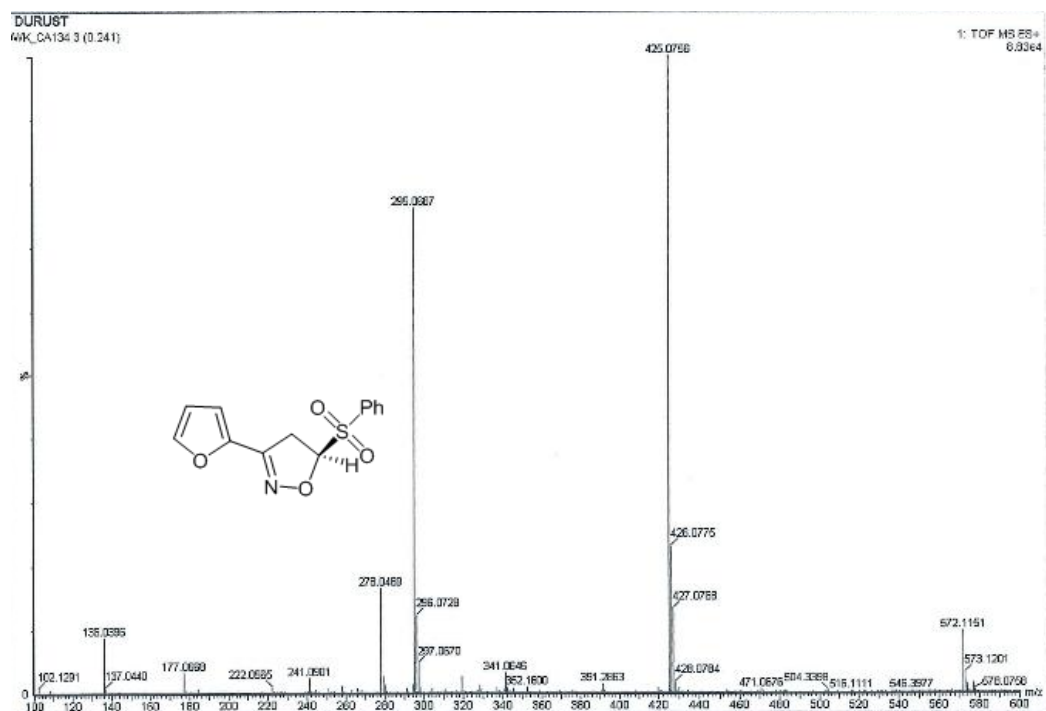


Figure 5. 39 Mass Spectrum of compound 4.8j

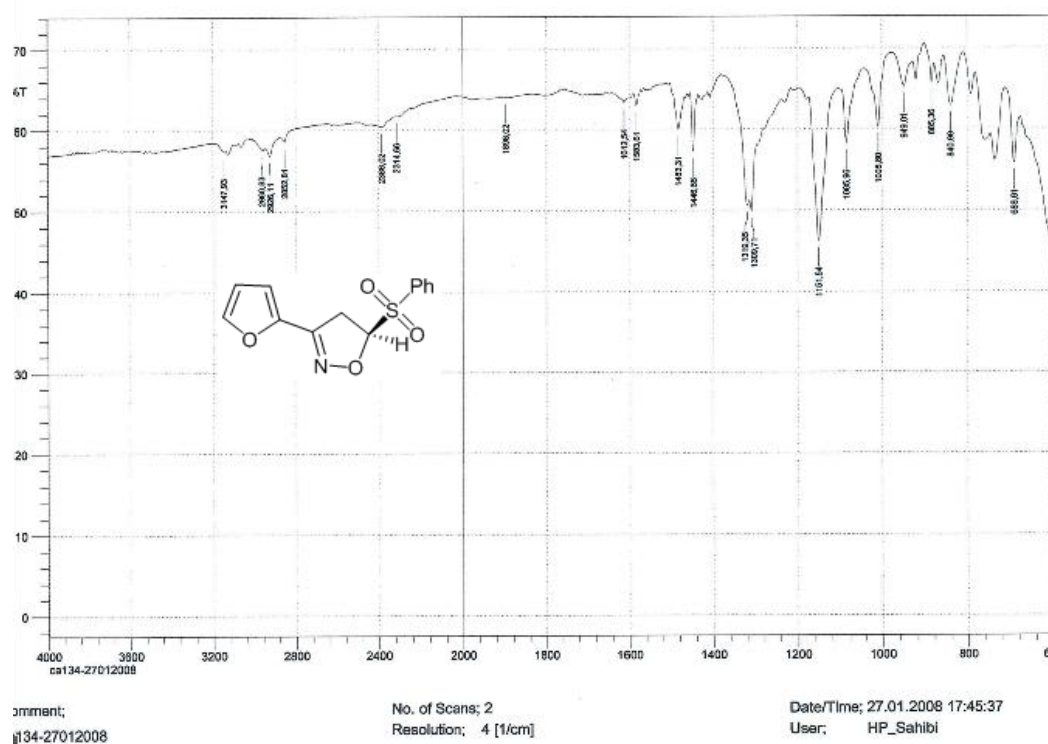


Figure 5. 40 IR Spectrum of compound 4.8j

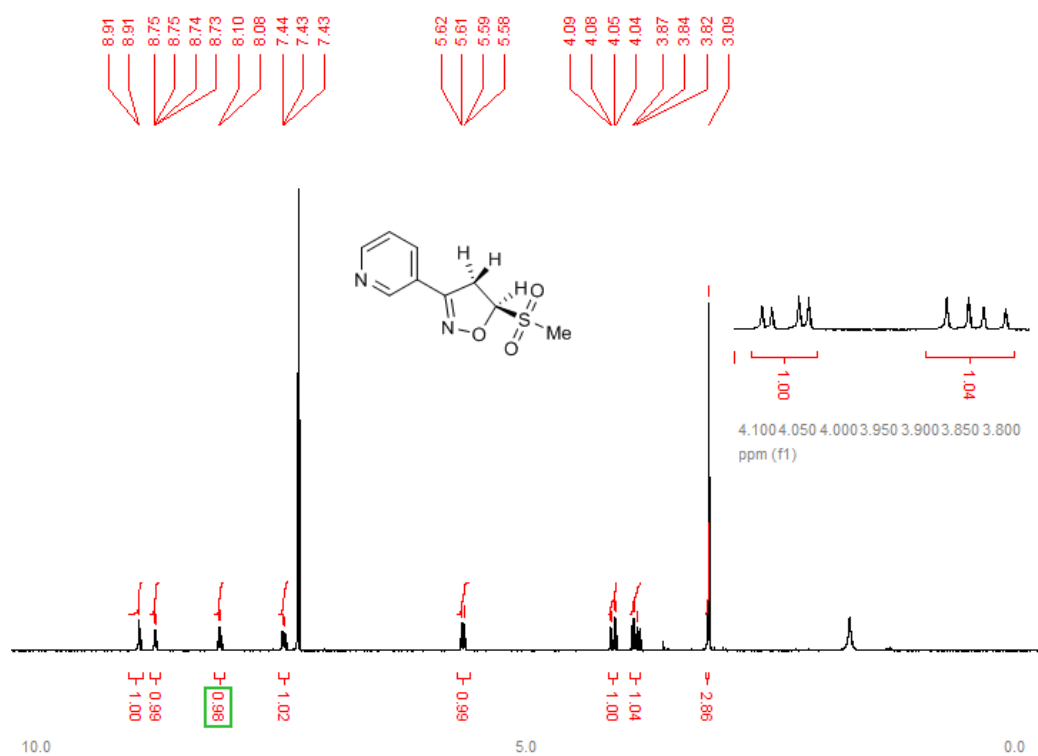


Figure 5. 43 ¹H NMR Spectrum of compound 4.8I

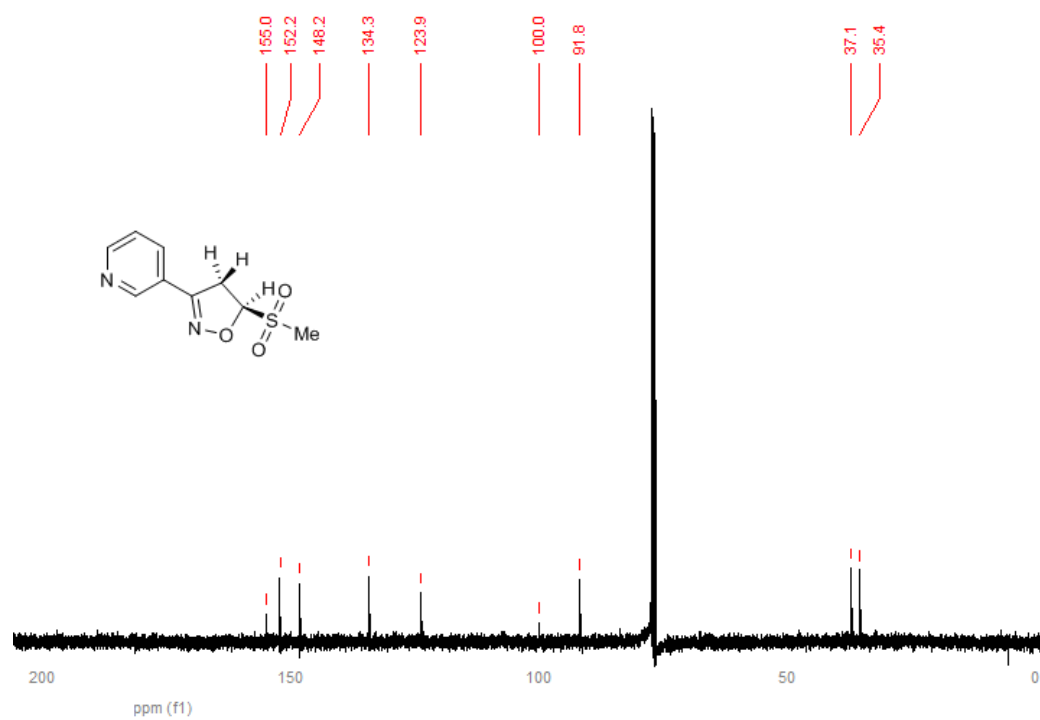


Figure 5. 44 ¹³C NMR Spectrum of compound 4.8I

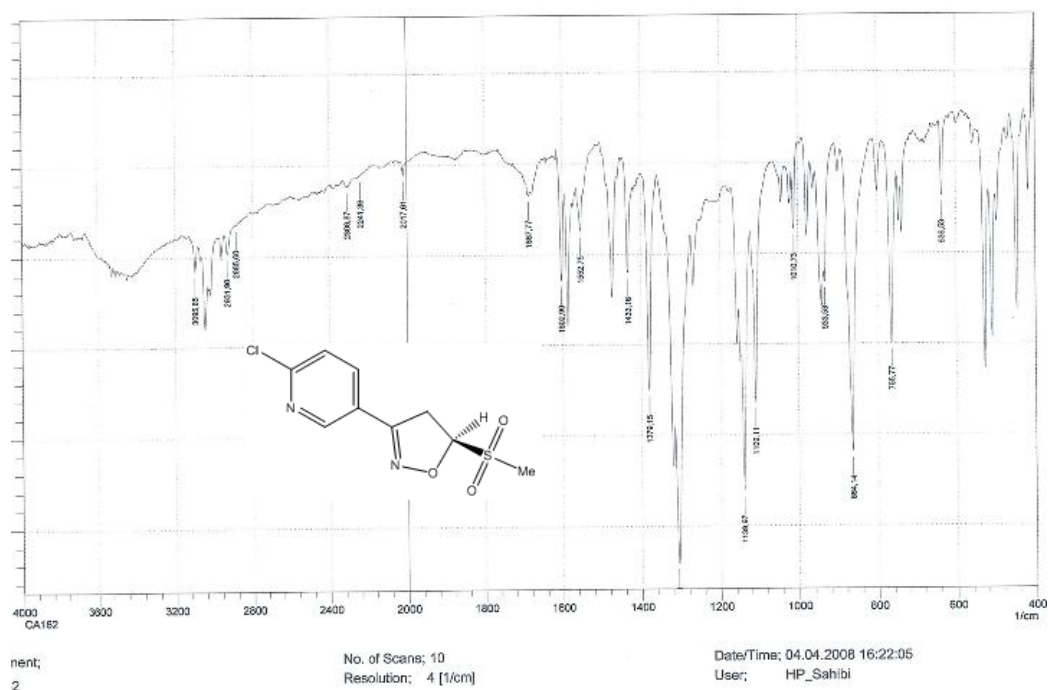


Figure 5. 47 IR Spectrum of compound 4.8m

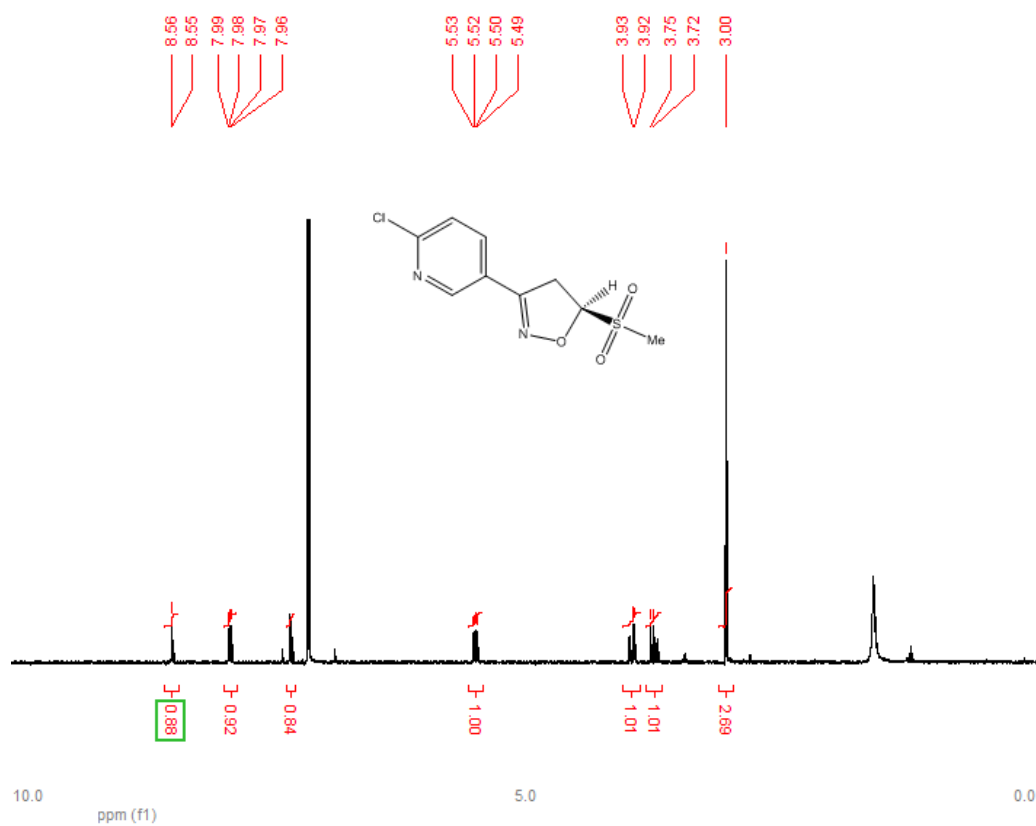


Figure 5. 48 ¹H NMR Spectrum of compound 4.8m

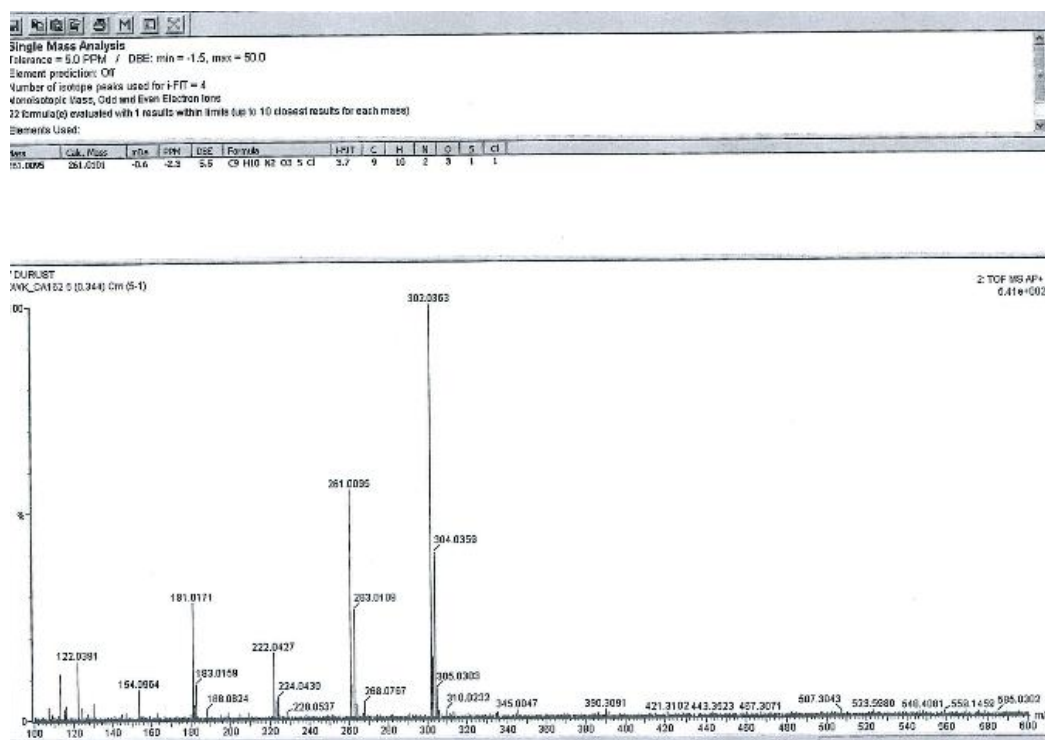


Figure 5. 49 Mass Spectrum of compound 4.8m

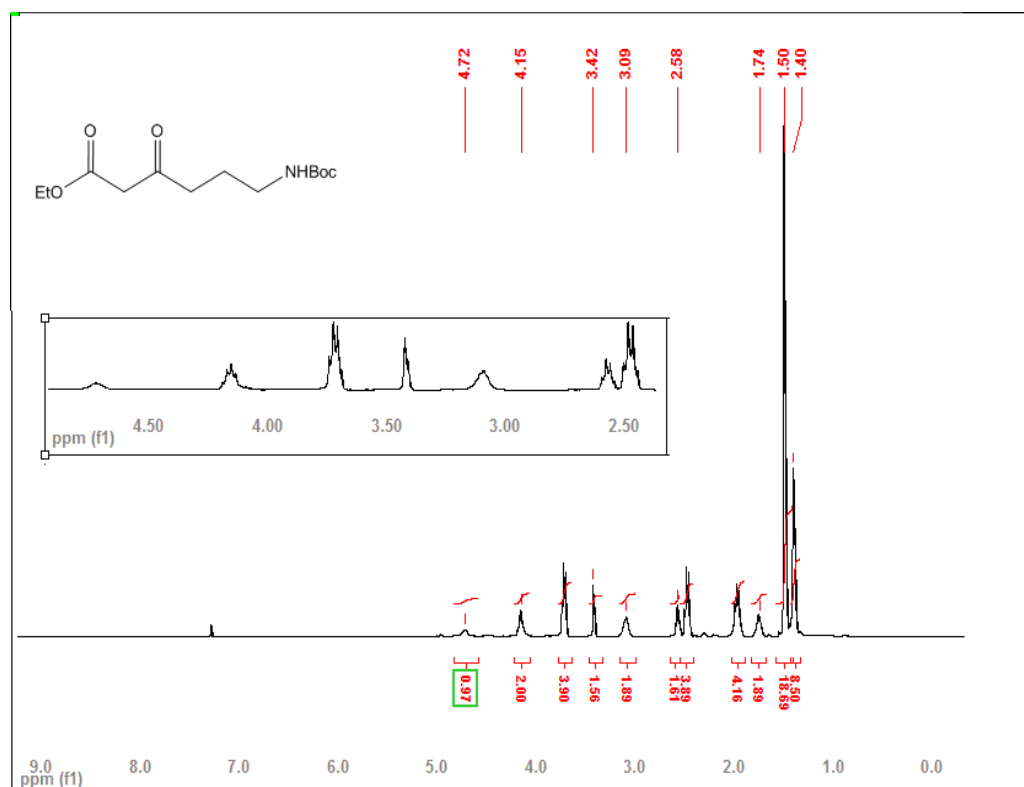


Figure 5. 50: ¹H NMR of compound 4.22

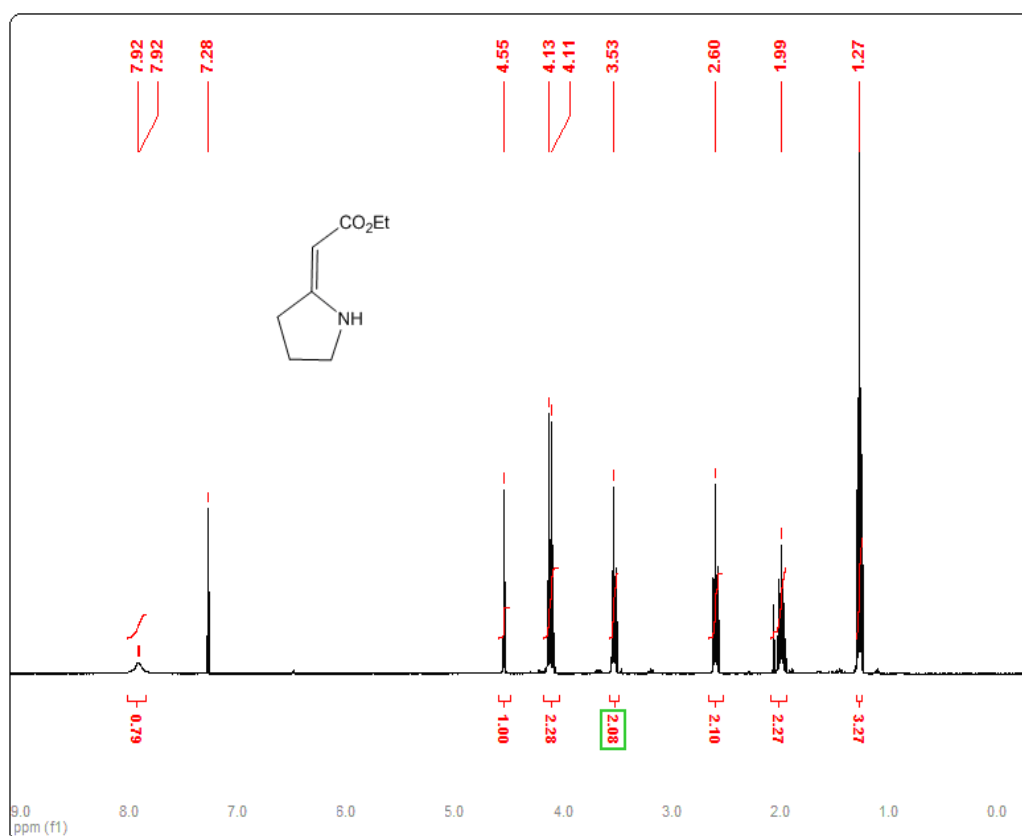


Figure 5. 51: ^1H NMR Spectrum of compound 4.23

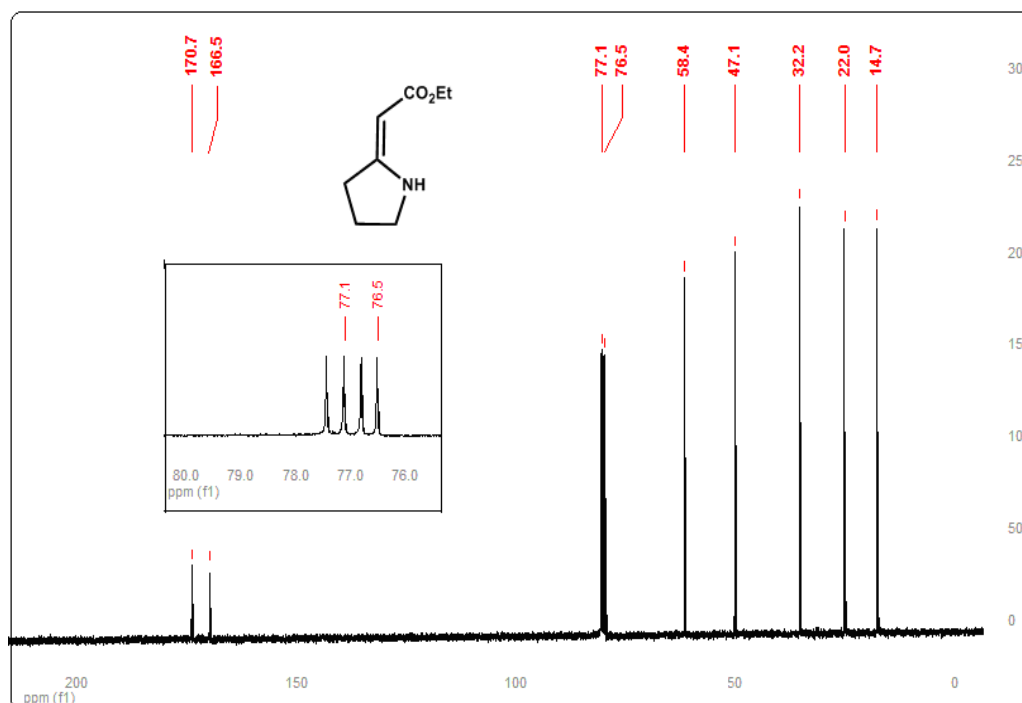


Figure 5. 52: ^{13}C NMR Spectrum of compound 4.24

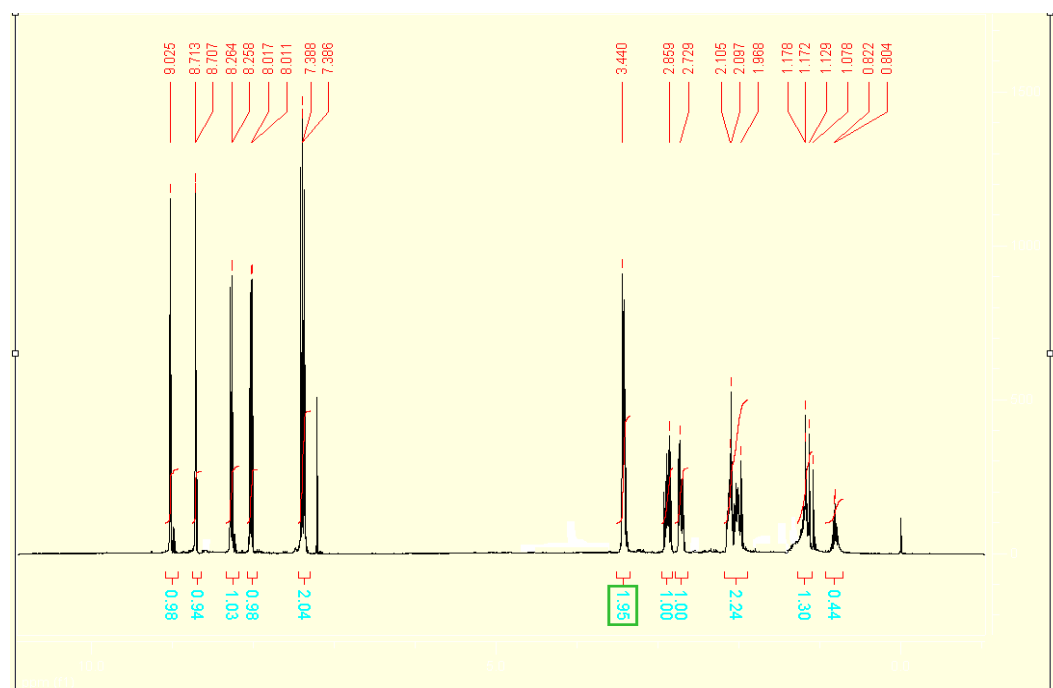


Figure 5. 53 ¹H NMR Spectrum of compound 4.26a

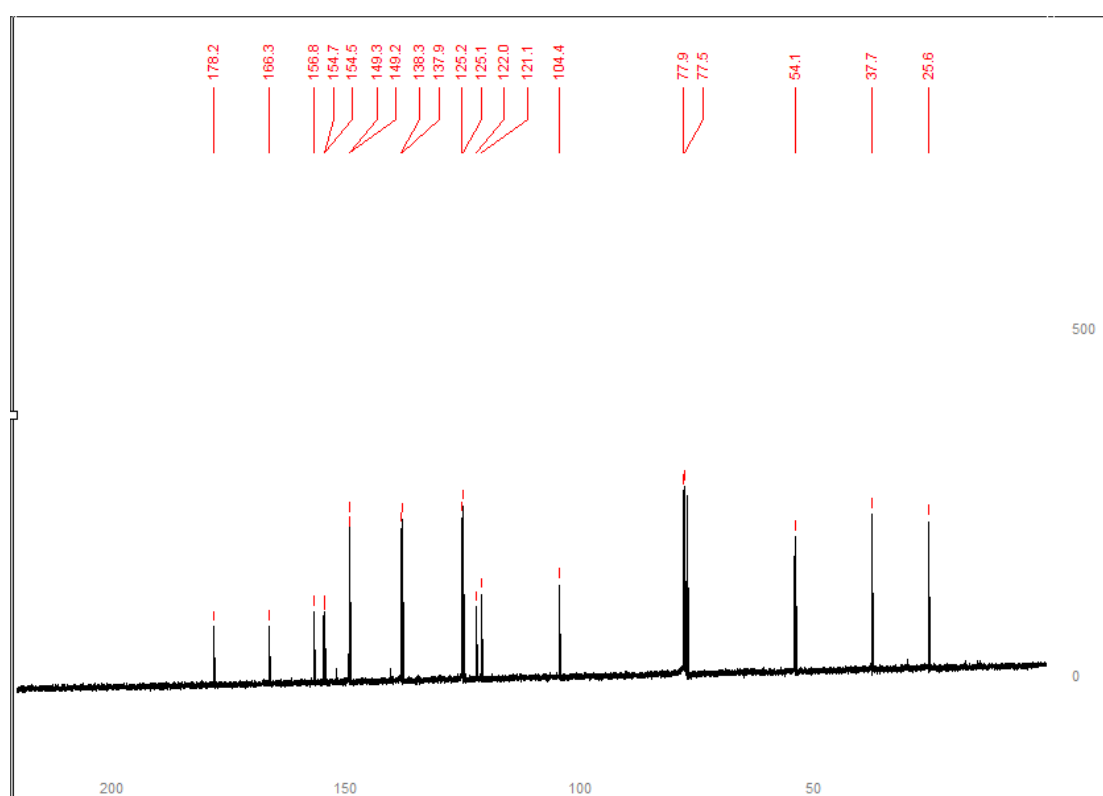


Figure 5. 54 ¹³C NMR Spectrum of compound 4.26a

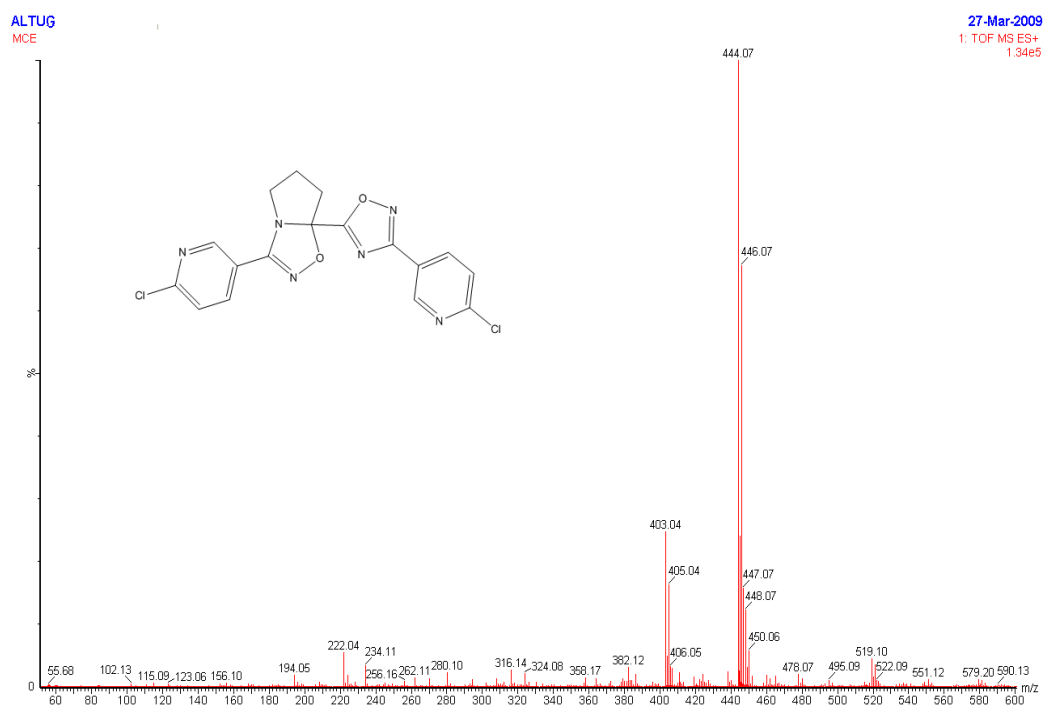


Figure 5. 55: MASS Spectrum of compound 4.26a

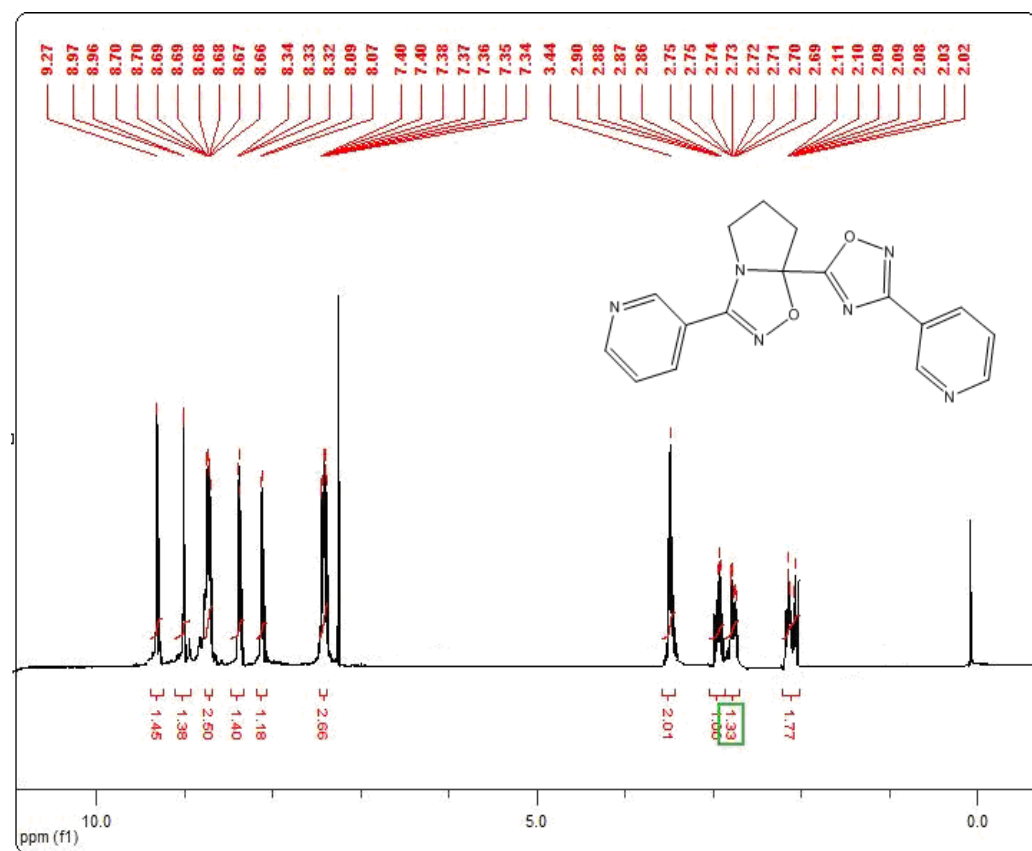


Figure 5. 56: ¹H NMR Spectrum of compound 4.26b

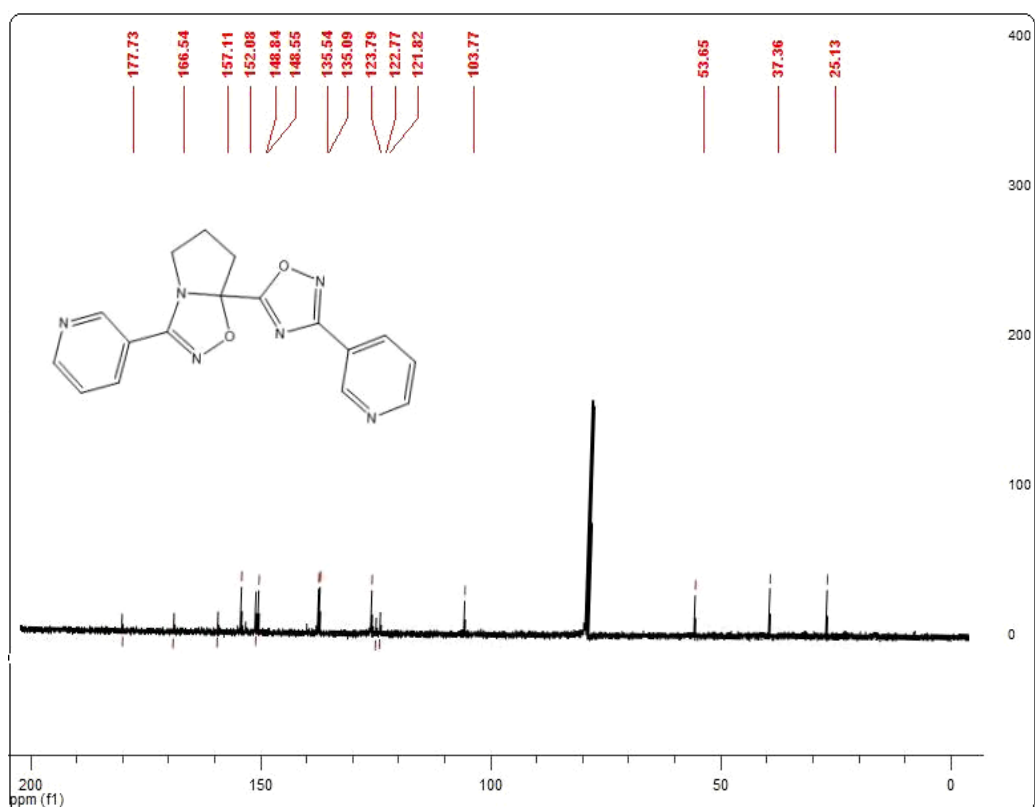


Figure 5. 57: ¹³C NMR Spectrum of compound 4.26b

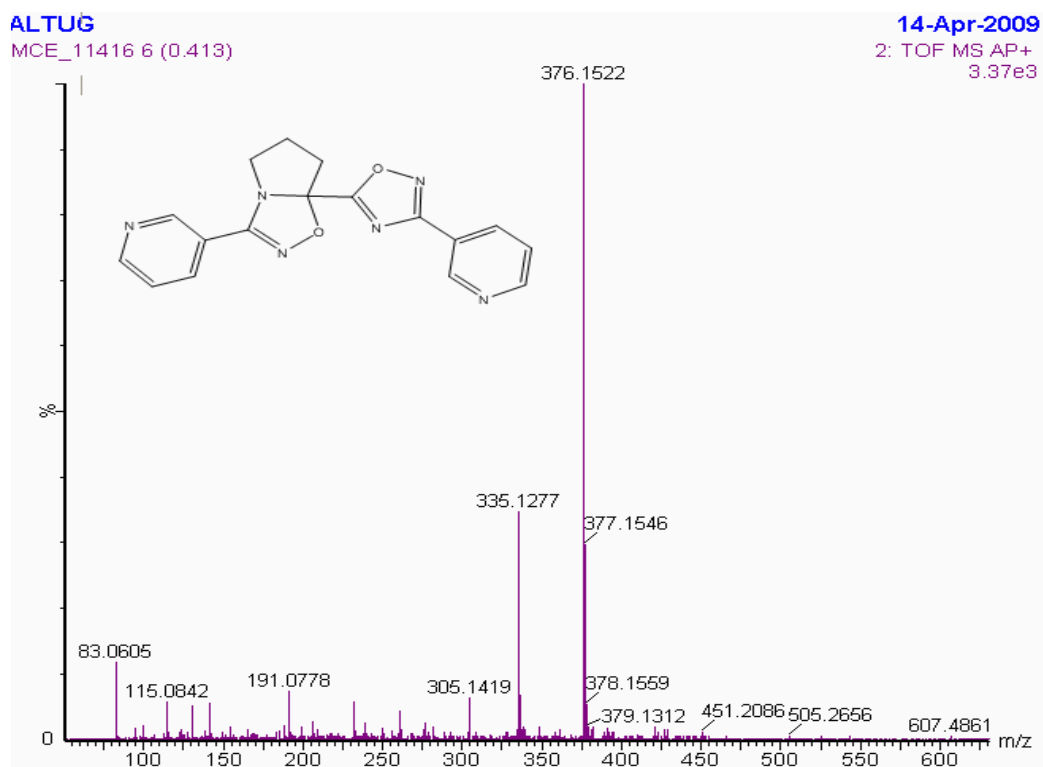


Figure 5. 58: MASS Spectrum of compound 4.26b

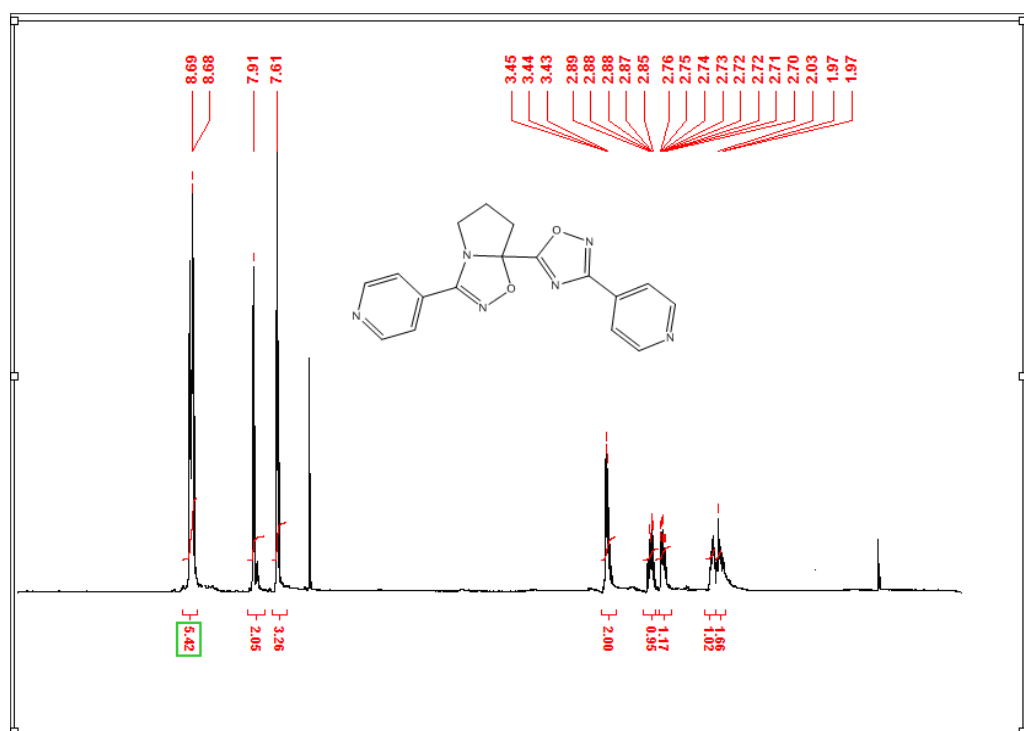


Figure 5. 59: ¹H NMR Spectrum of compound 4.26c

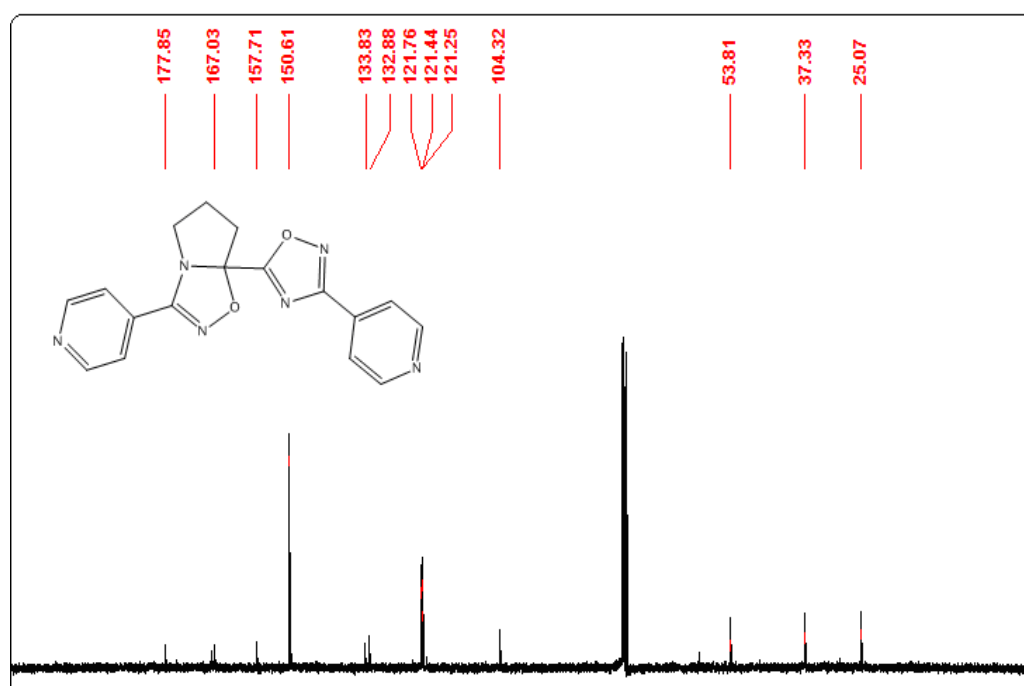


Figure 5. 60: ¹³C NMR Spectrum of compound 4.26c

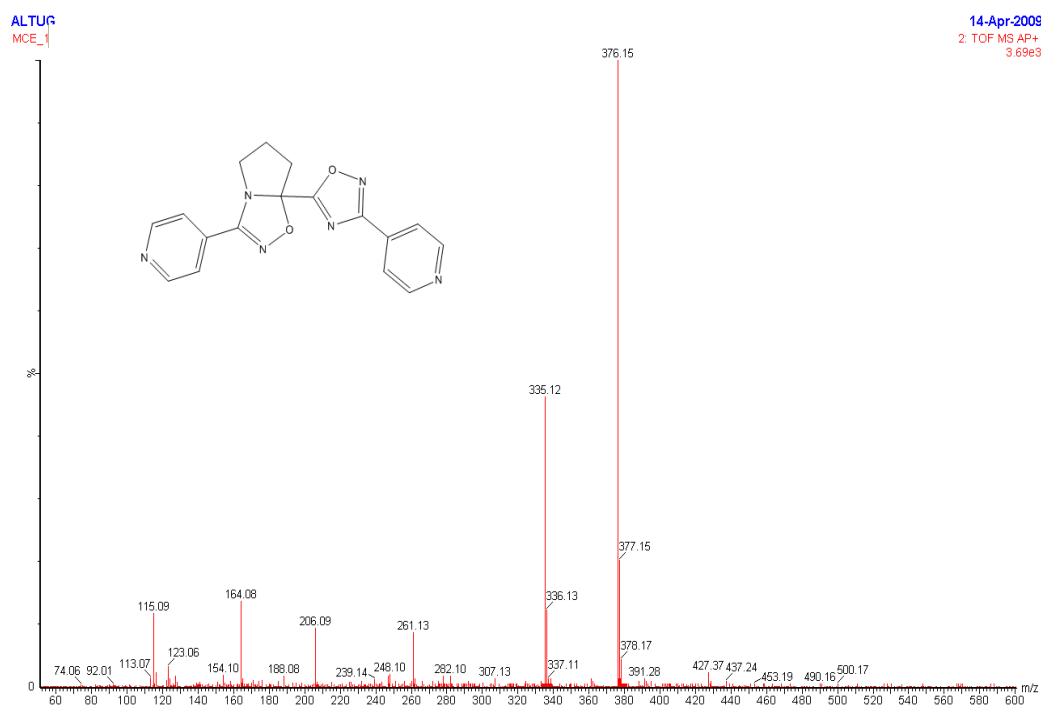


Figure 5. 61: MASS Spectrum of compound 4.26c

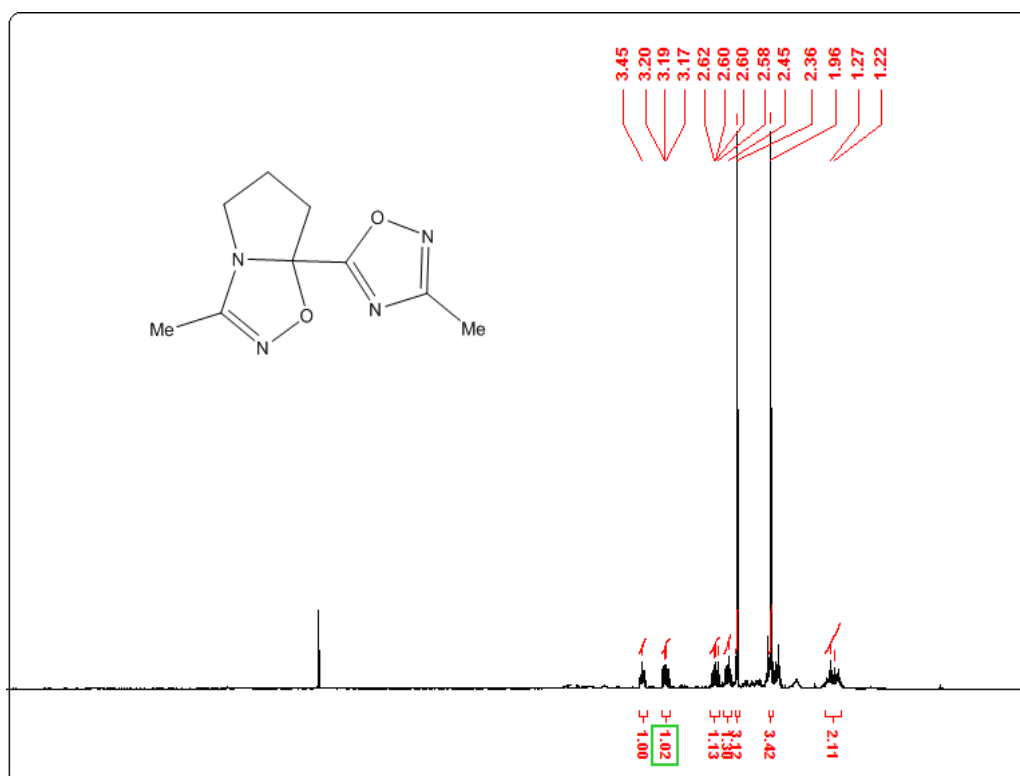


Figure 5. 62: ¹H NMR Spectrum of compound 4.26d

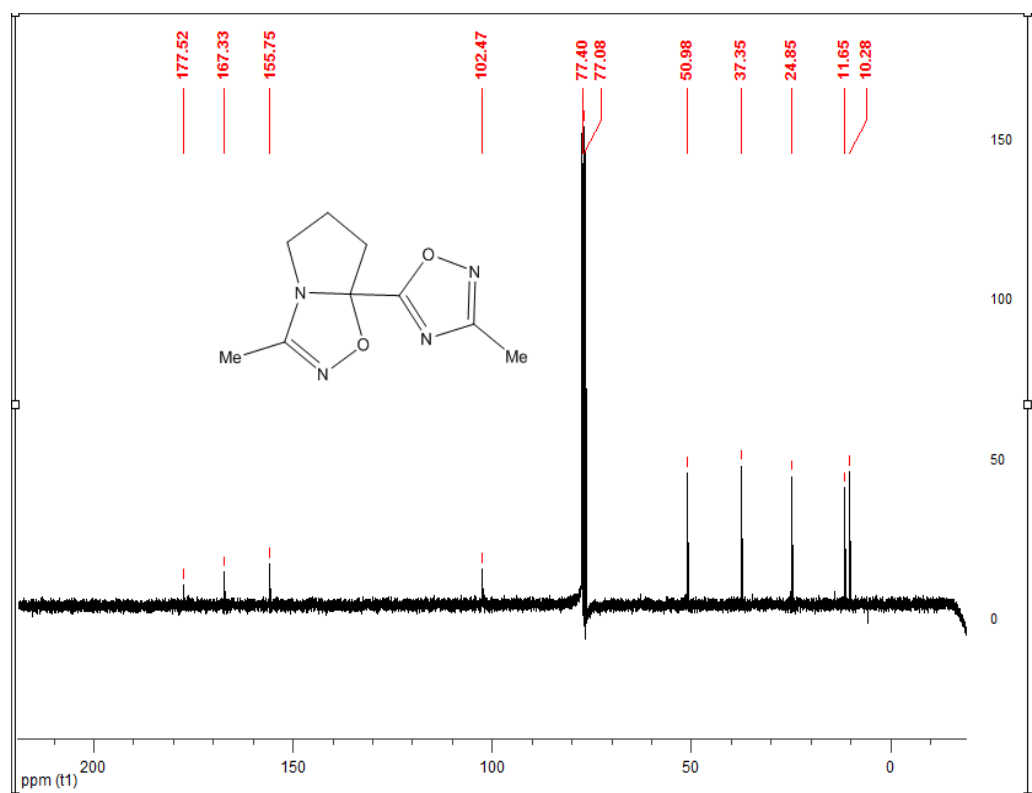


Figure 5. 63: ^{13}C NMR Spectrum of compound **4.26d**

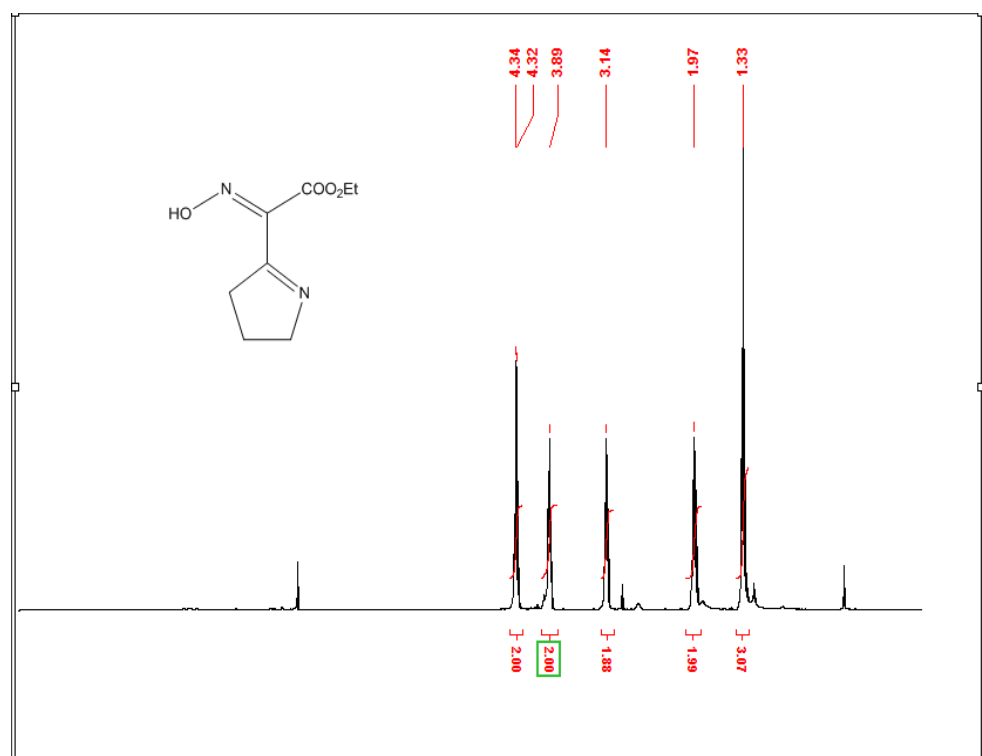


Figure 5. 64: ^1H NMR Spectrum of compound **4.28**

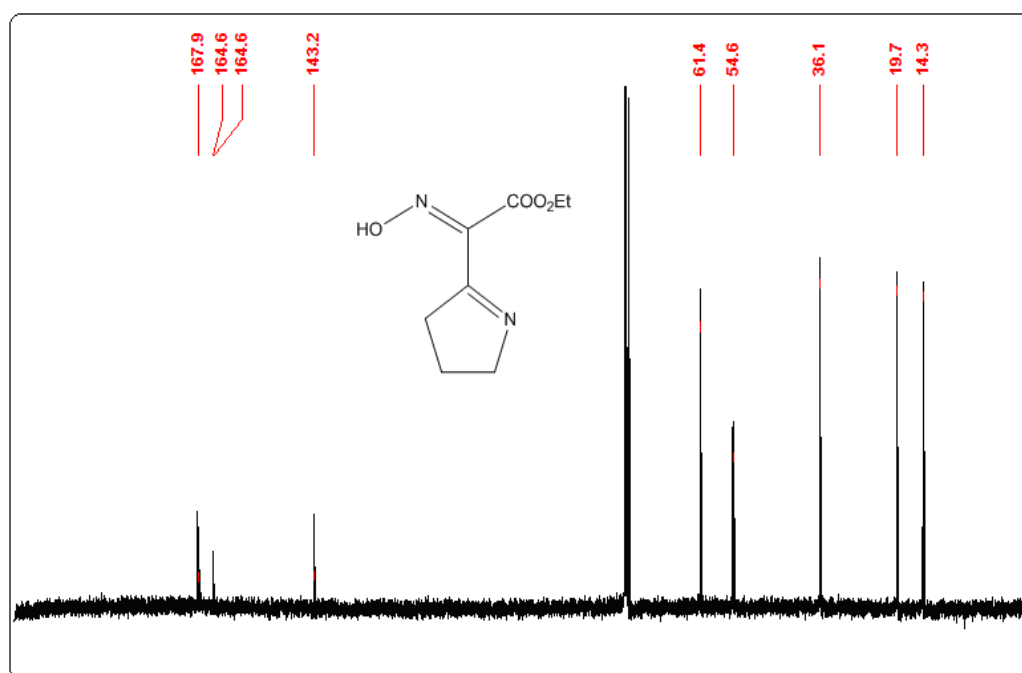


Figure 5. 65: ¹³C NMR Spectrum of compound 4.28

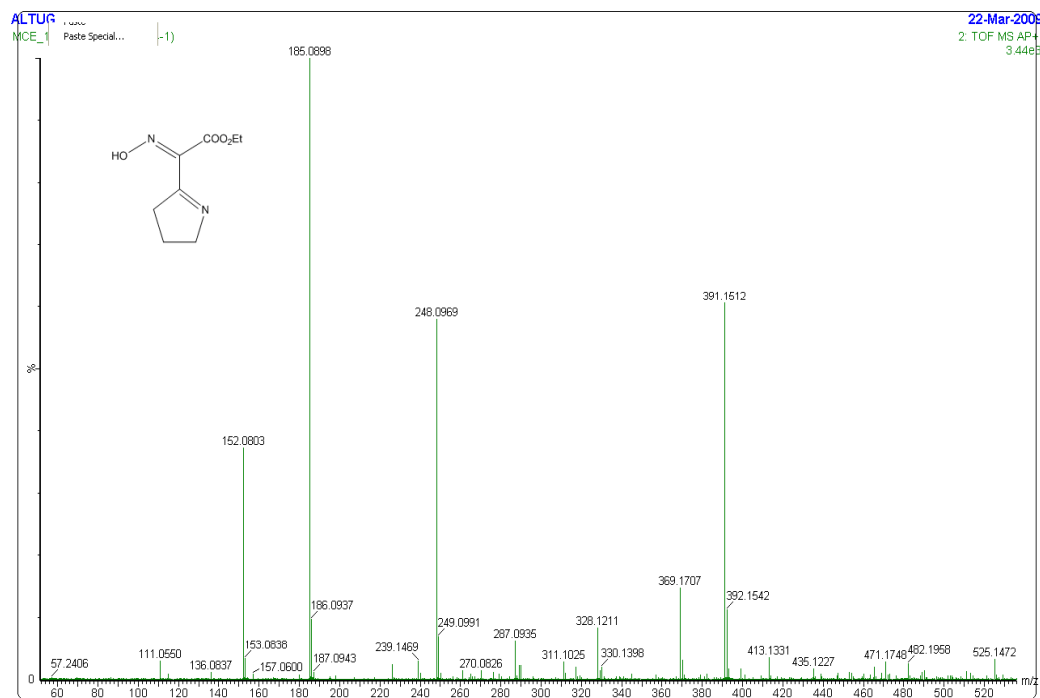


Figure 5. 66: MASS Spectrum of compound 4.28

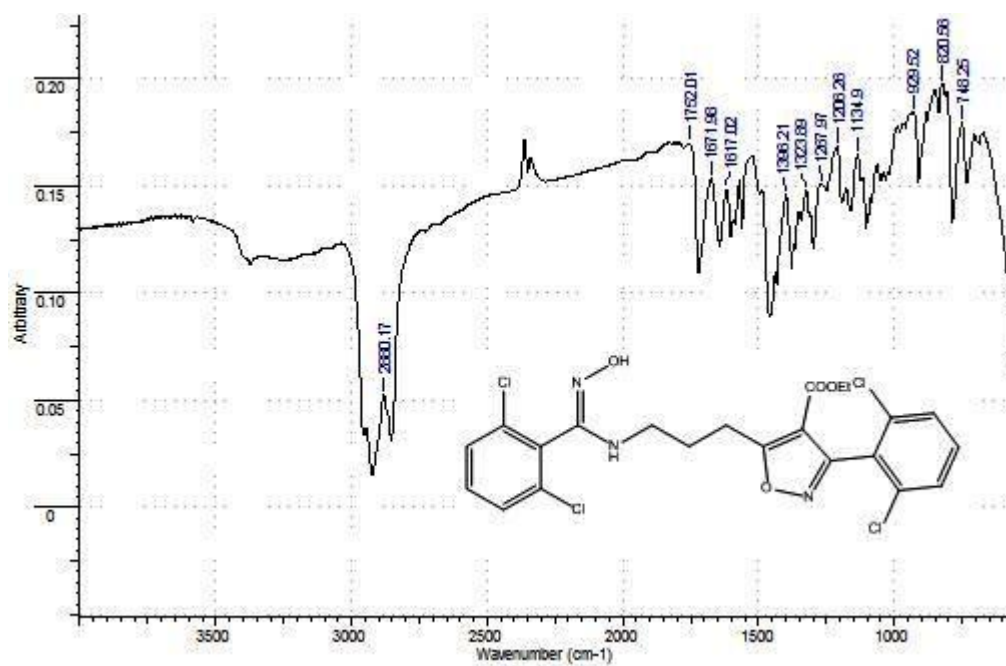


Figure 5. 67: IR spectrum of compound 4.35a

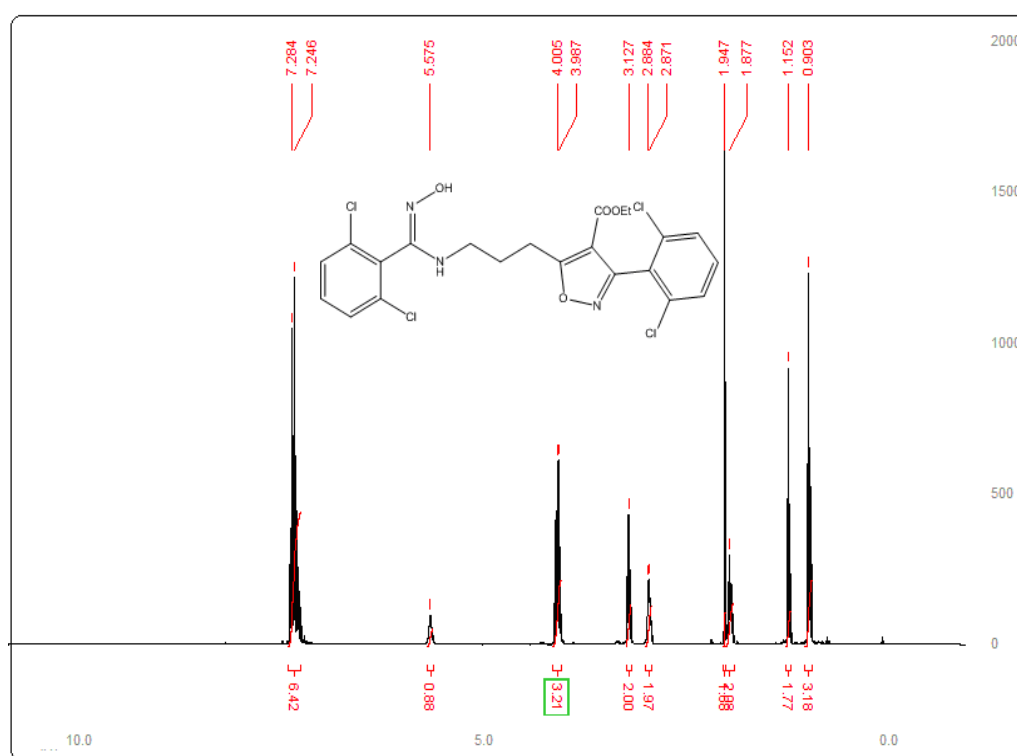


Figure 5. 68: ¹H NMR Spectrum of compound 4.35a

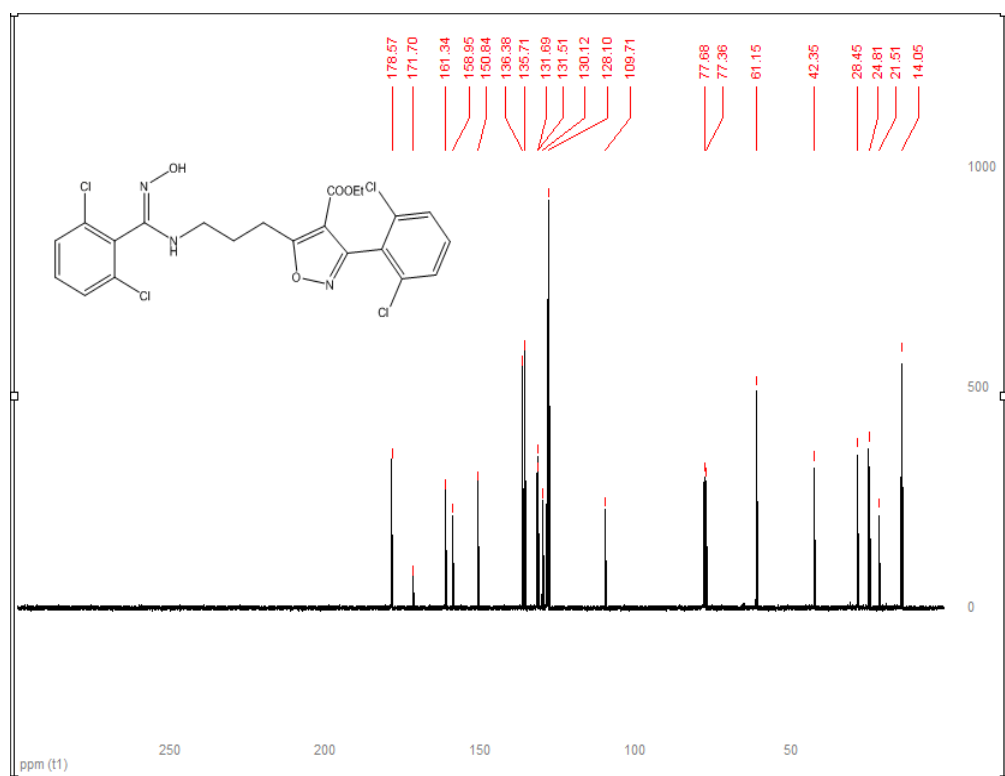


Figure 5. 69: ¹³C NMR Spectrum of compound 4.35a

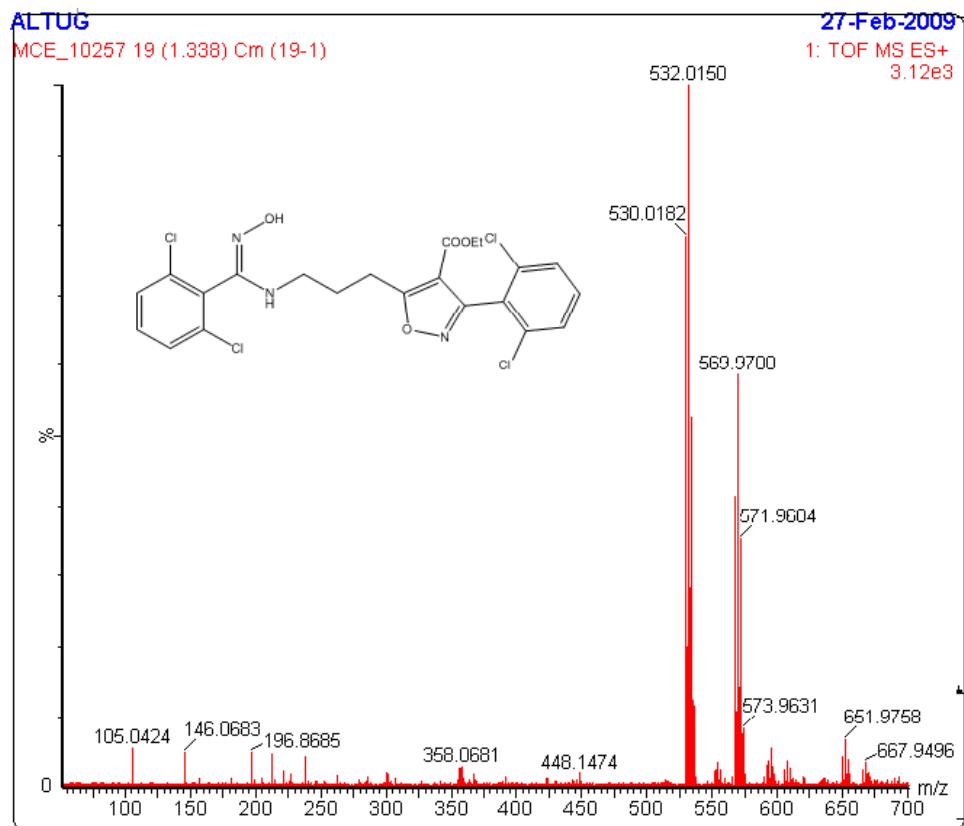


Figure 5. 70: MASS Spectrum of compound 4.35a

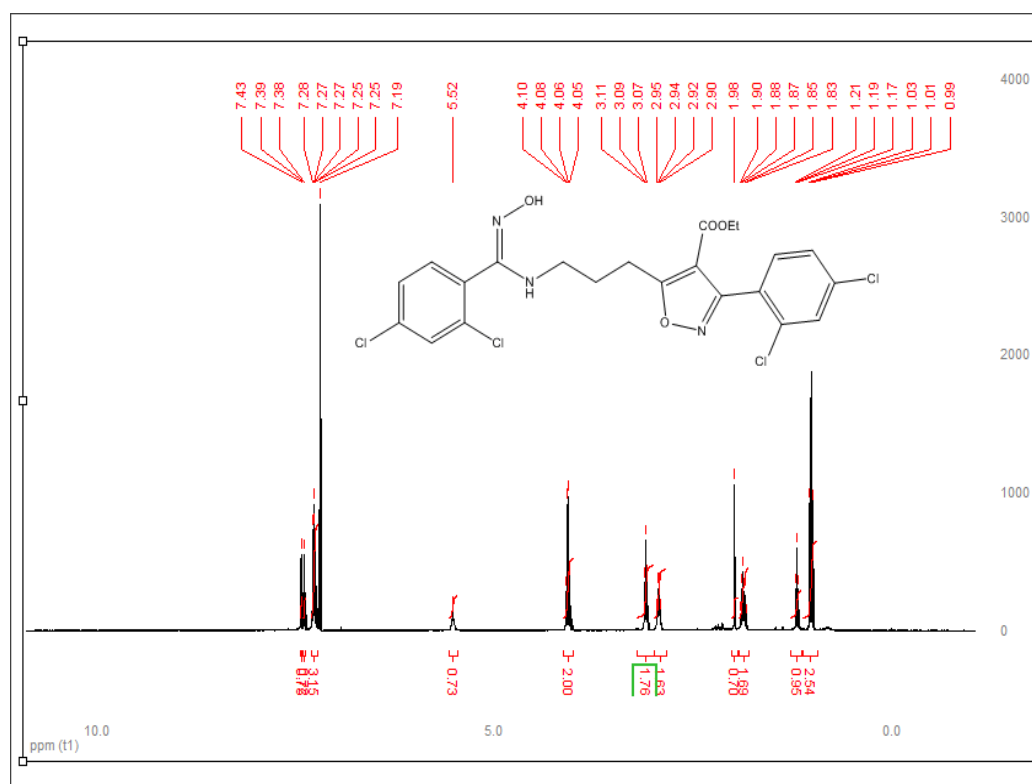


Figure 5. 71: ¹H NMR Spectrum of compound 4.35b

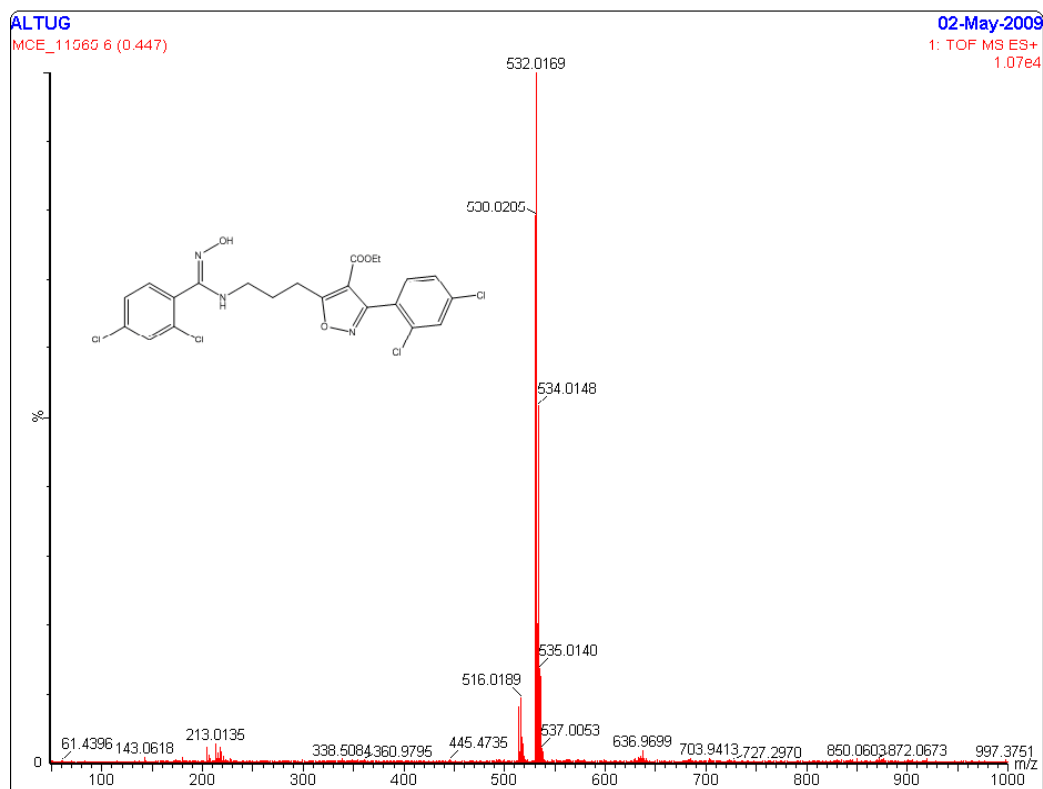


Figure 5. 72: MASS Spectrum of compound 4.35b

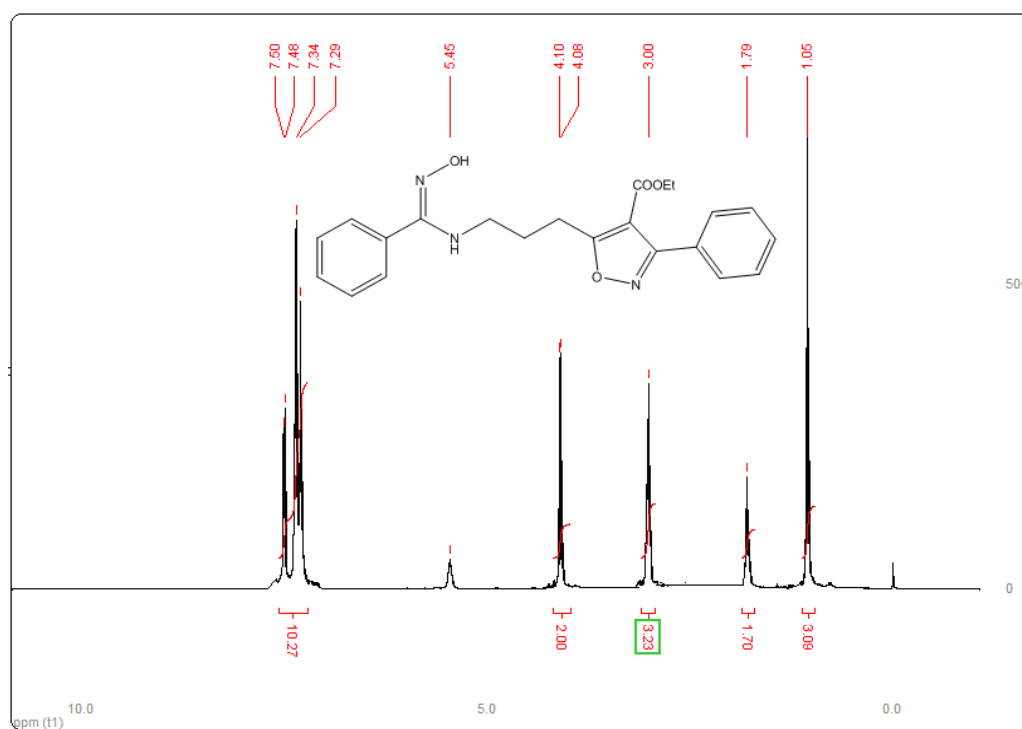


Figure 5. 73: ^1H NMR Spectrum of compound 4.35c

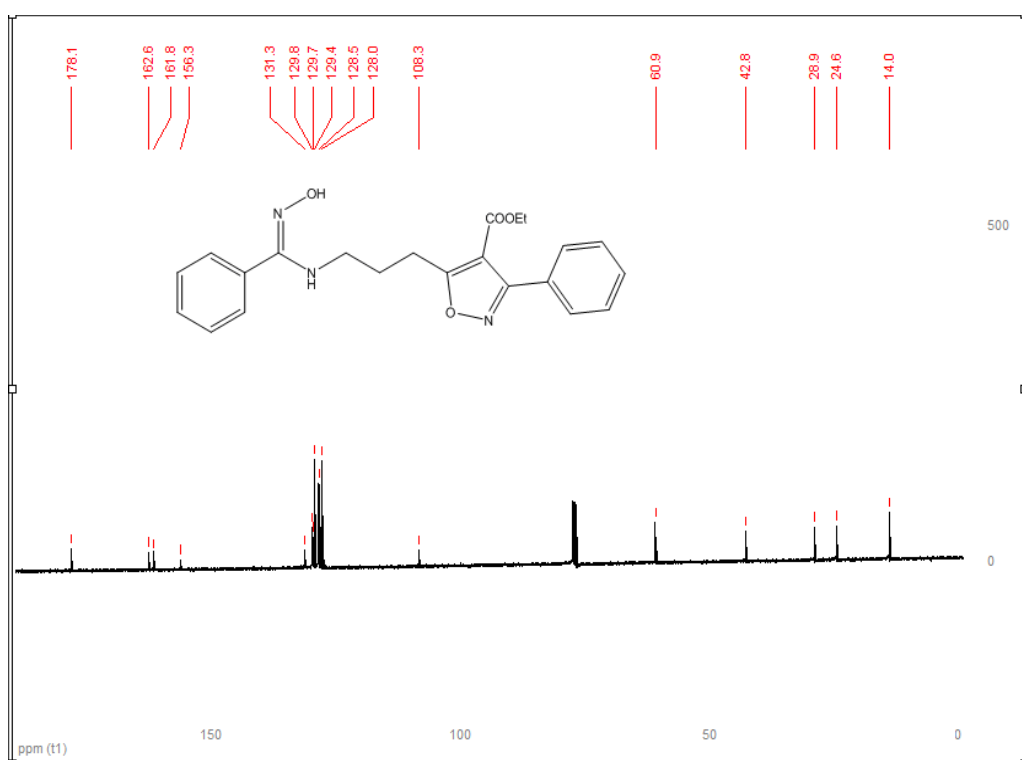
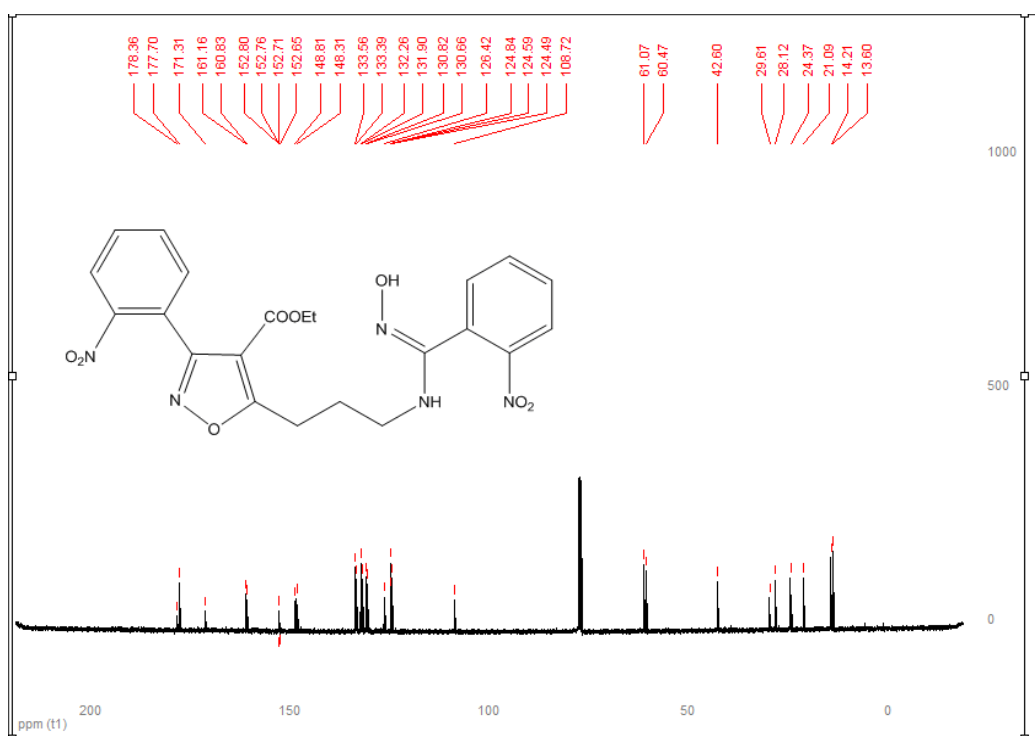
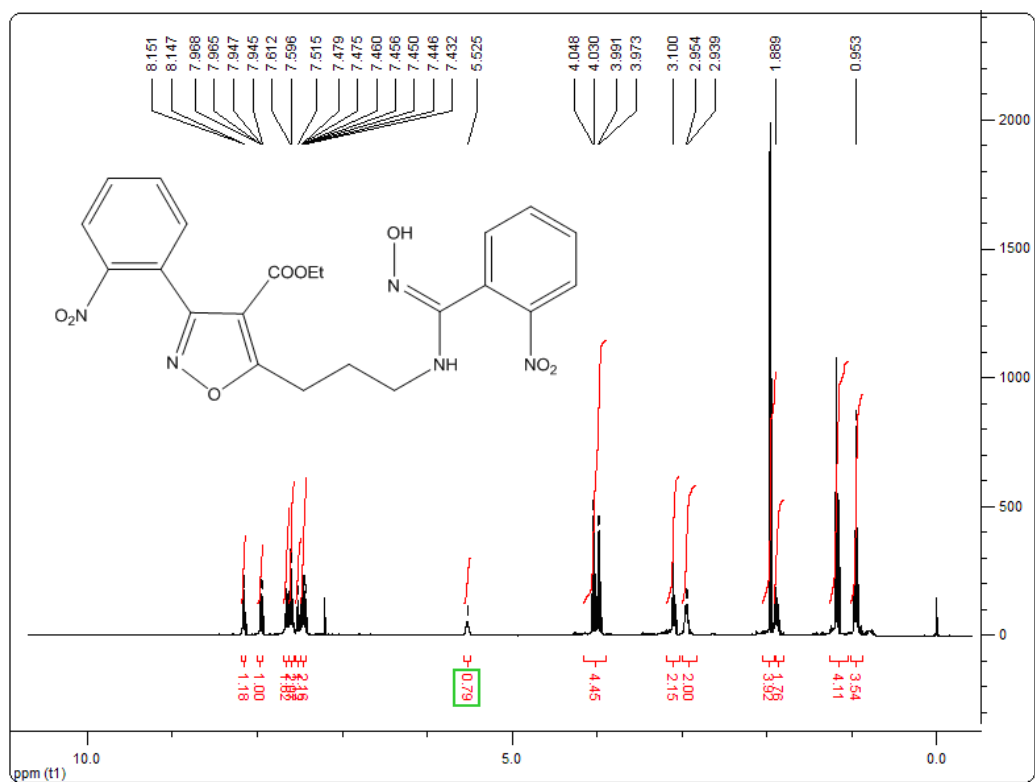


Figure 5. 74: ^{13}C NMR Spectrum of compound 4.35c



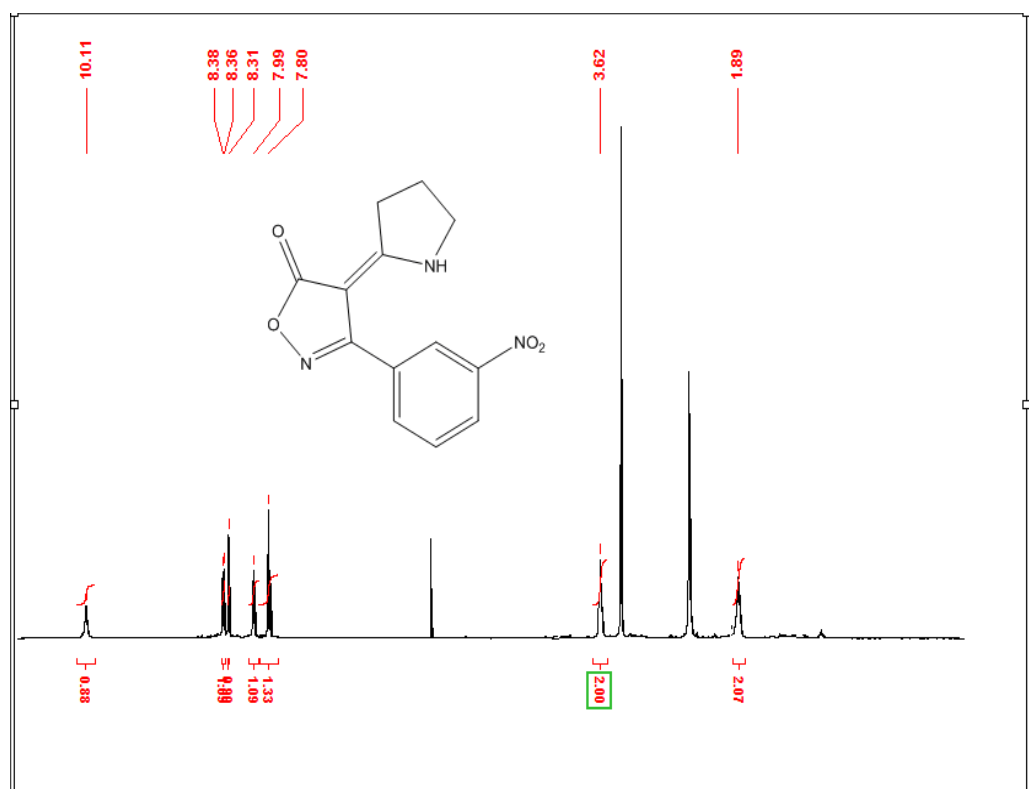


Figure 5. 77: ¹H NMR Spectrum of compound 4.36

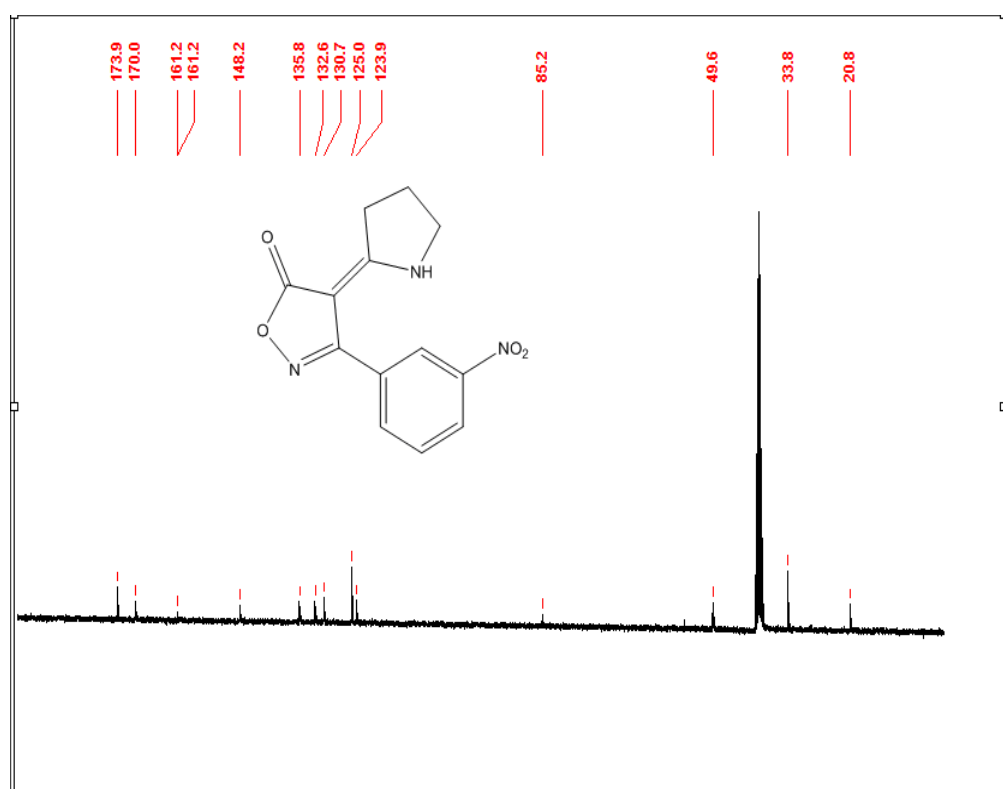


Figure 5. 78: ¹³C NMR Spectrum of compound 4.36

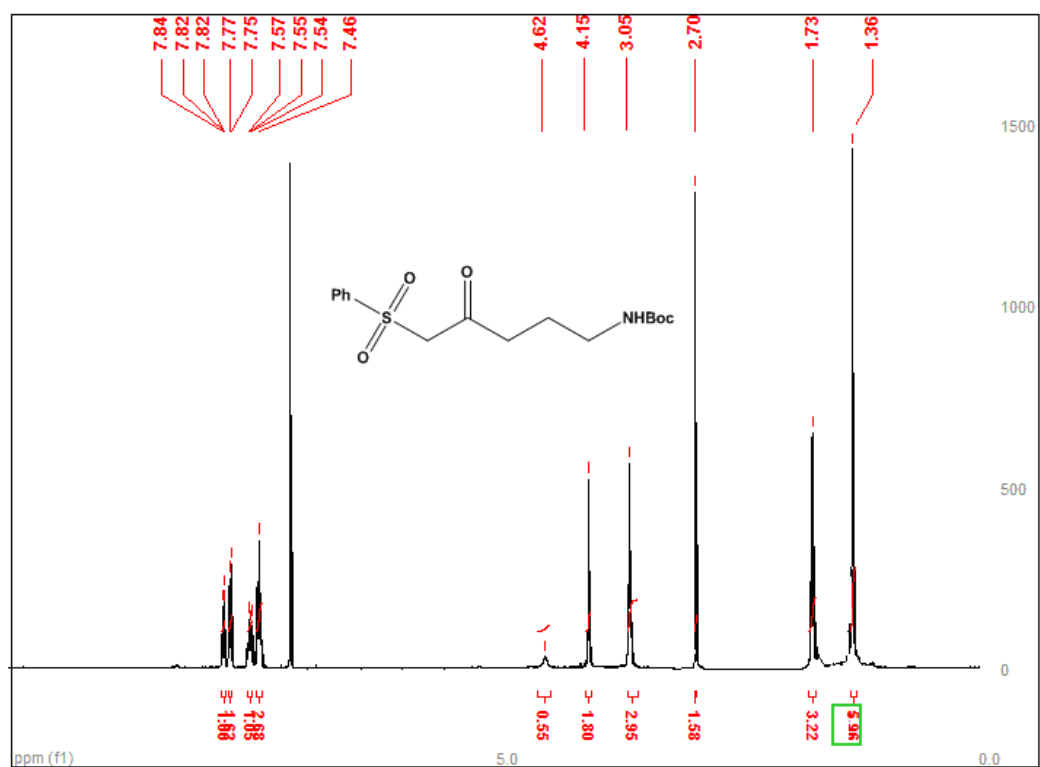


Figure 5. 79: ^1H NMR Spectrum of compound 4.43

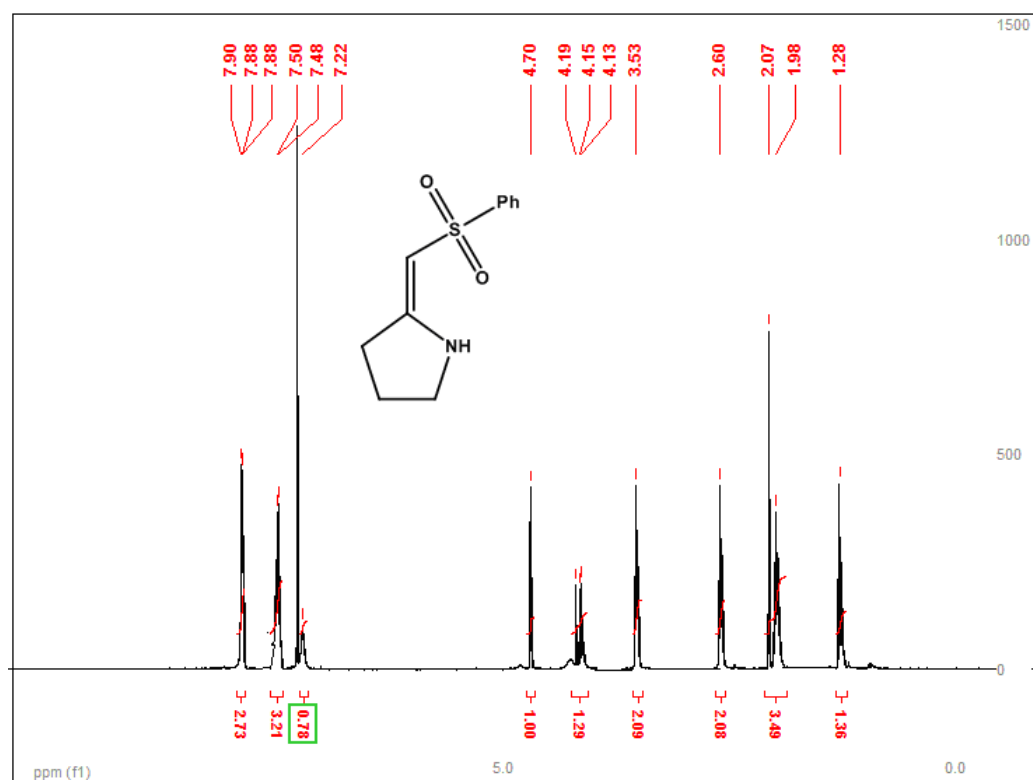


Figure 5. 80: ^1H NMR Spectrum of compound 4.37

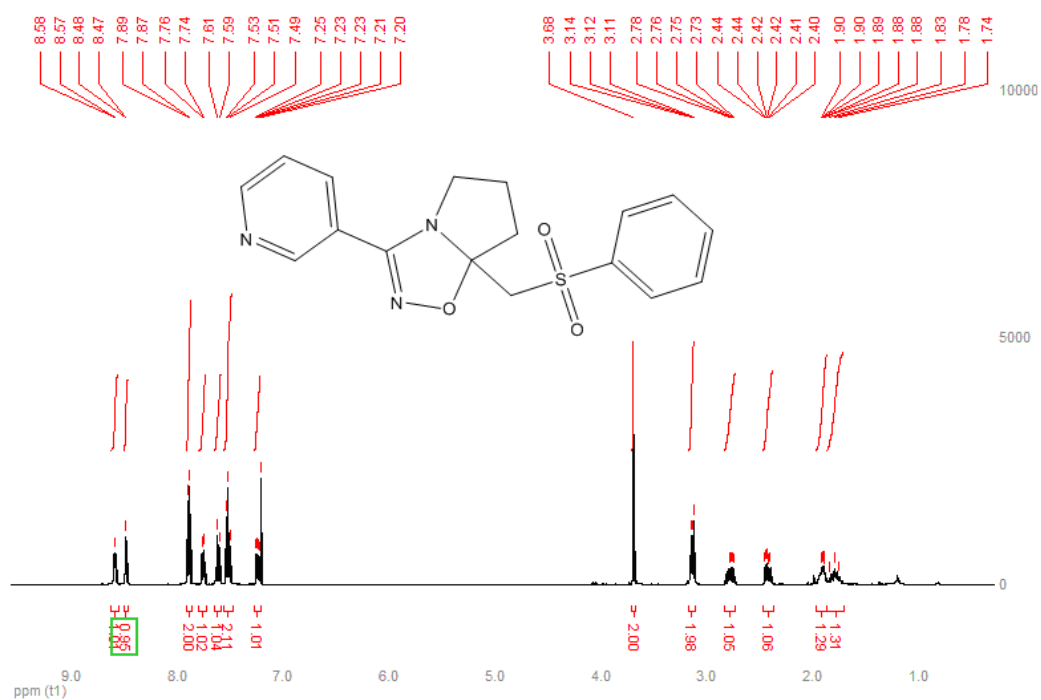


Figure 5. 81: ¹H NMR Spectrum of compound 4.50a

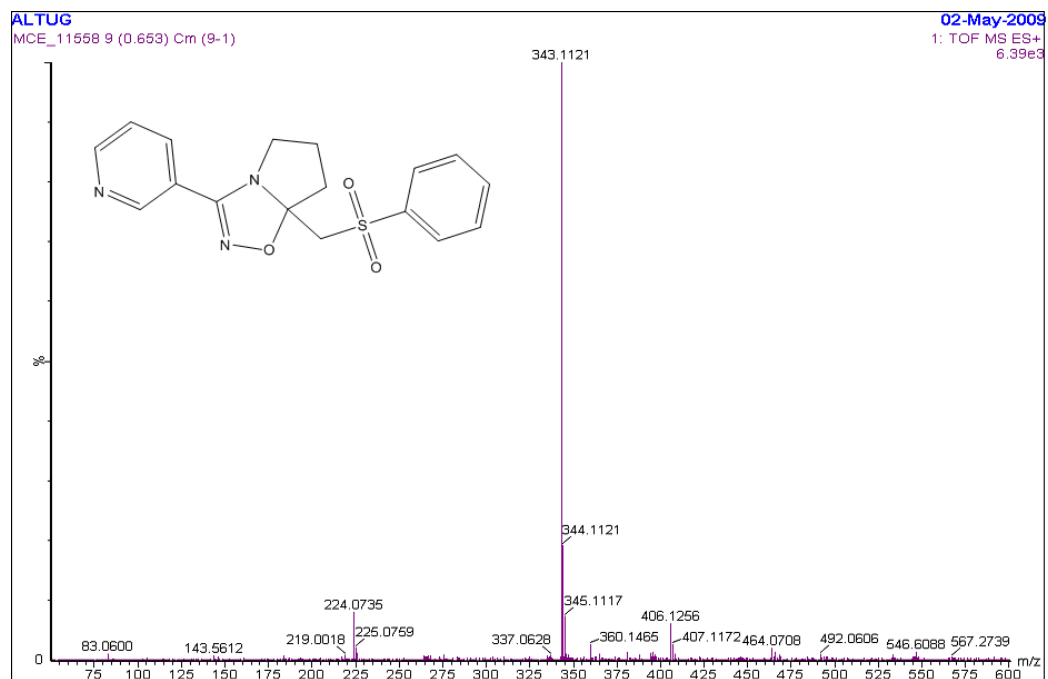


Figure 5. 82: MASS Spectrum of compound 4.50a

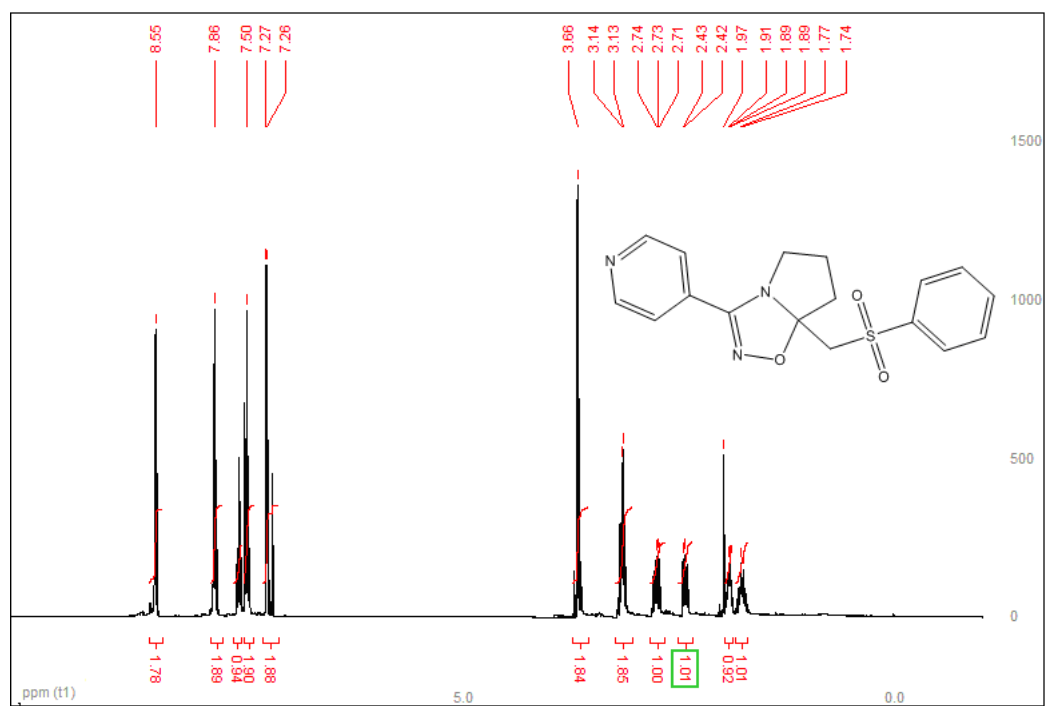


Figure 5. 83: ¹H NMR Spectrum of compound **4.50b**

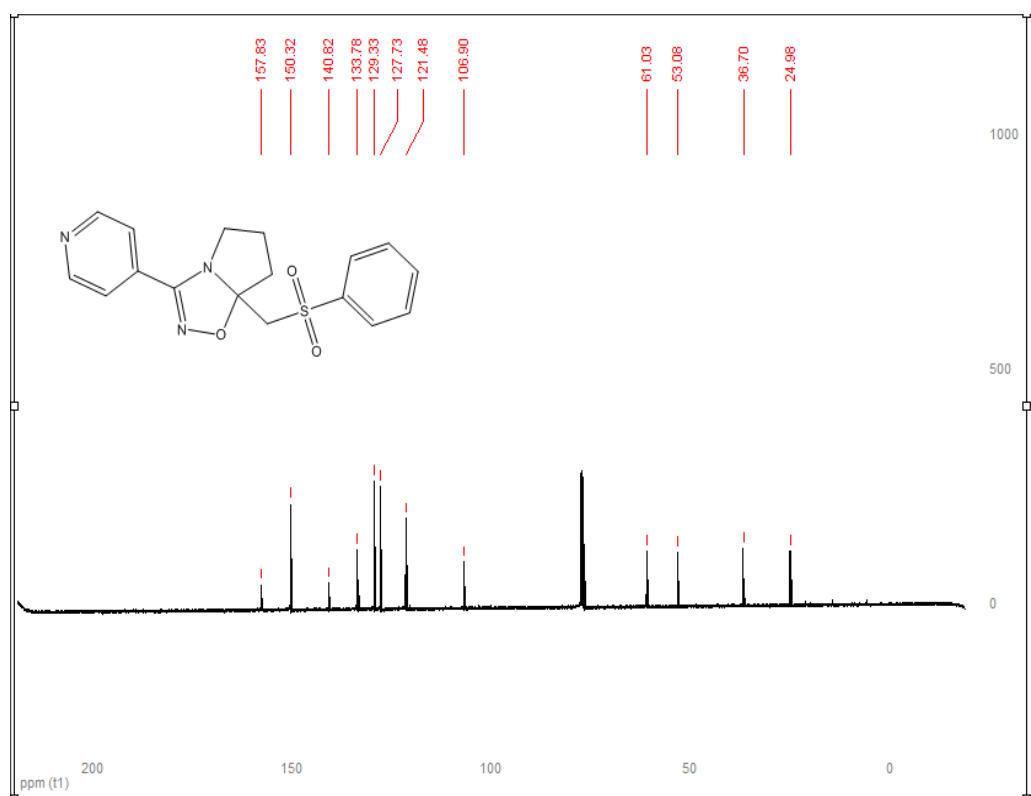


Figure 5. 84: ¹³C NMR Spectrum of compound **4.50b**

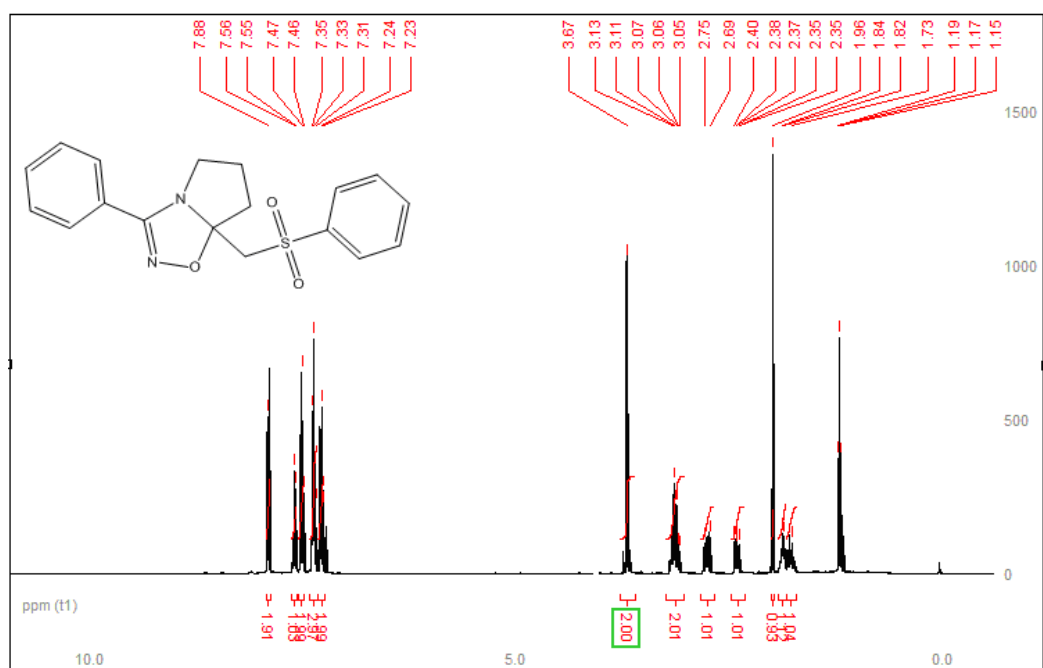


Figure 5. 85: ¹H NMR Spectrum of compound 4.50c

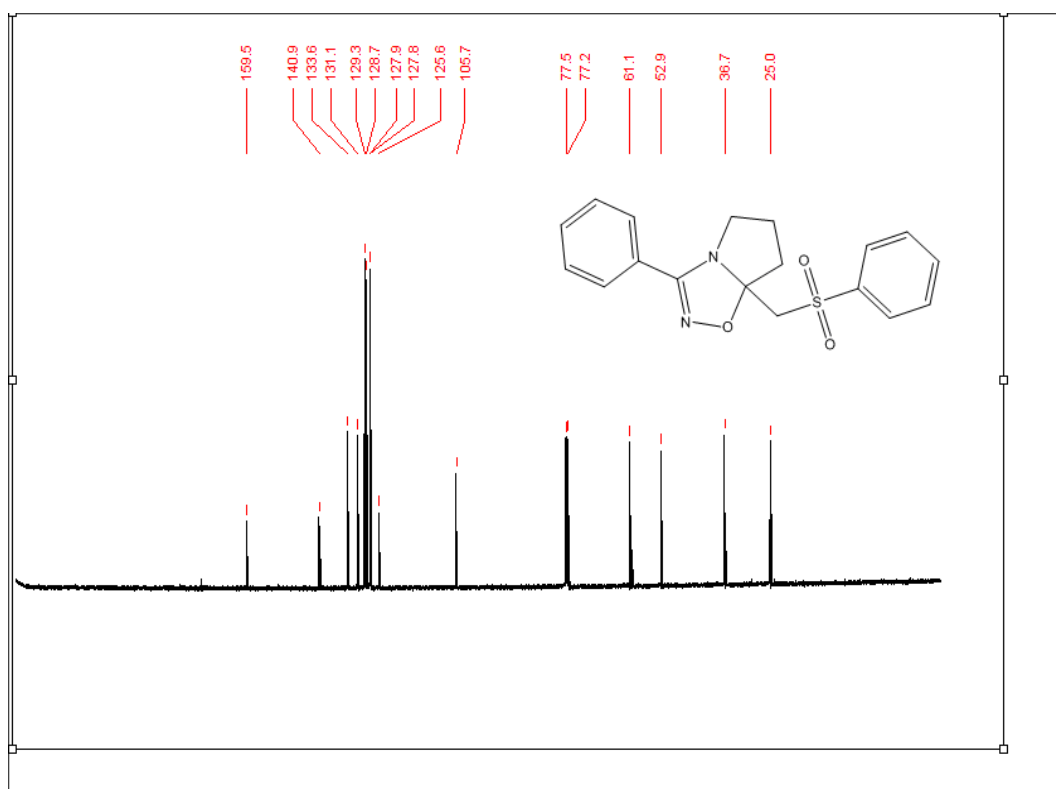


Figure 5. 86: ¹³C NMR Spectrum of compound 4.50c

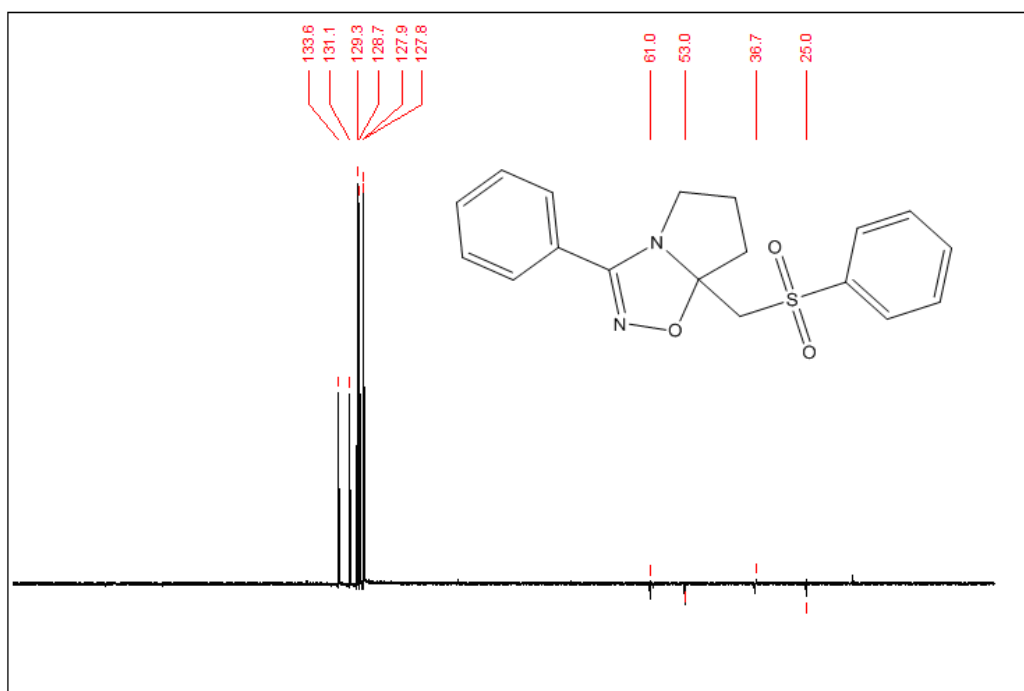


Figure 5. 87: DEPT Spectrum of compound 4.50c

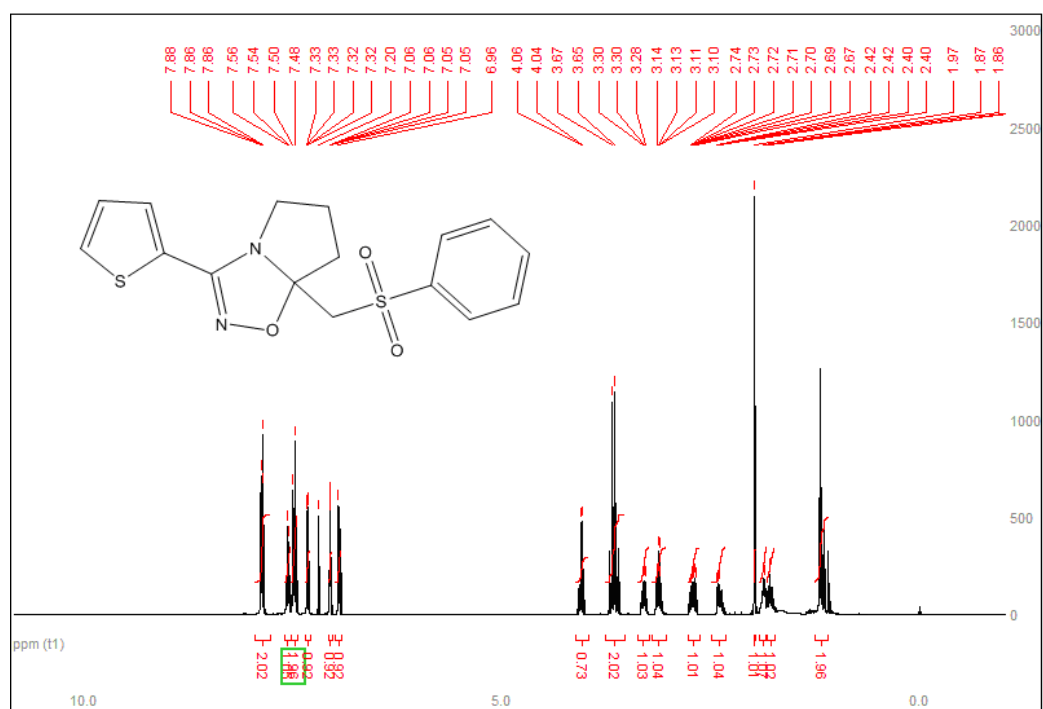


Figure 5. 88: ^1H NMR Spectrum of compound **4.50d**

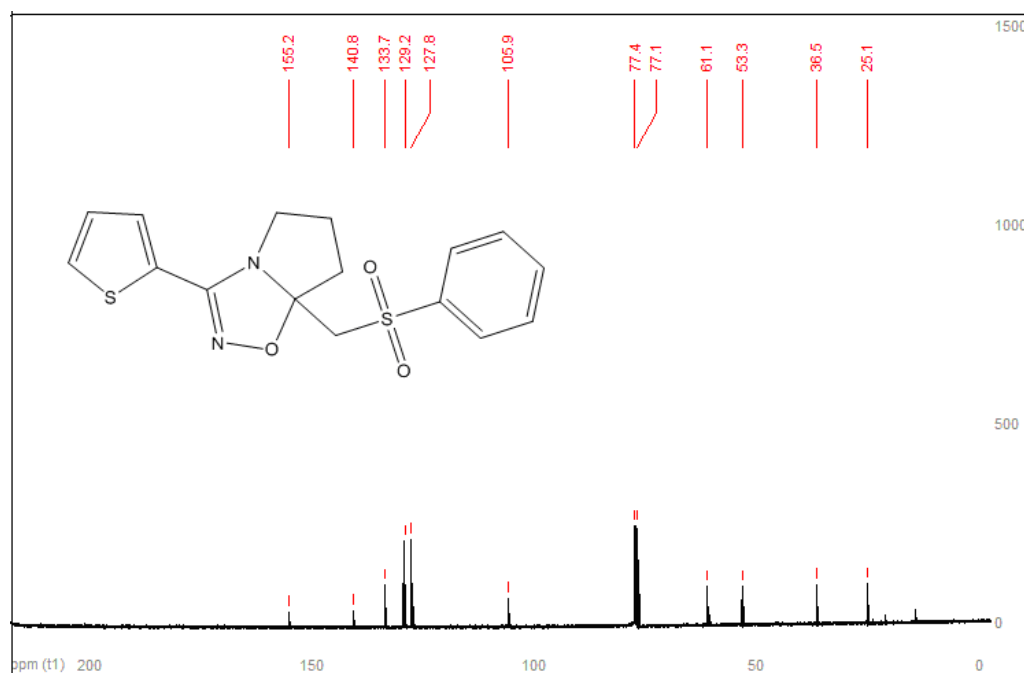


Figure 5. 89: ¹³C NMR Spectrum of compound 4.50d

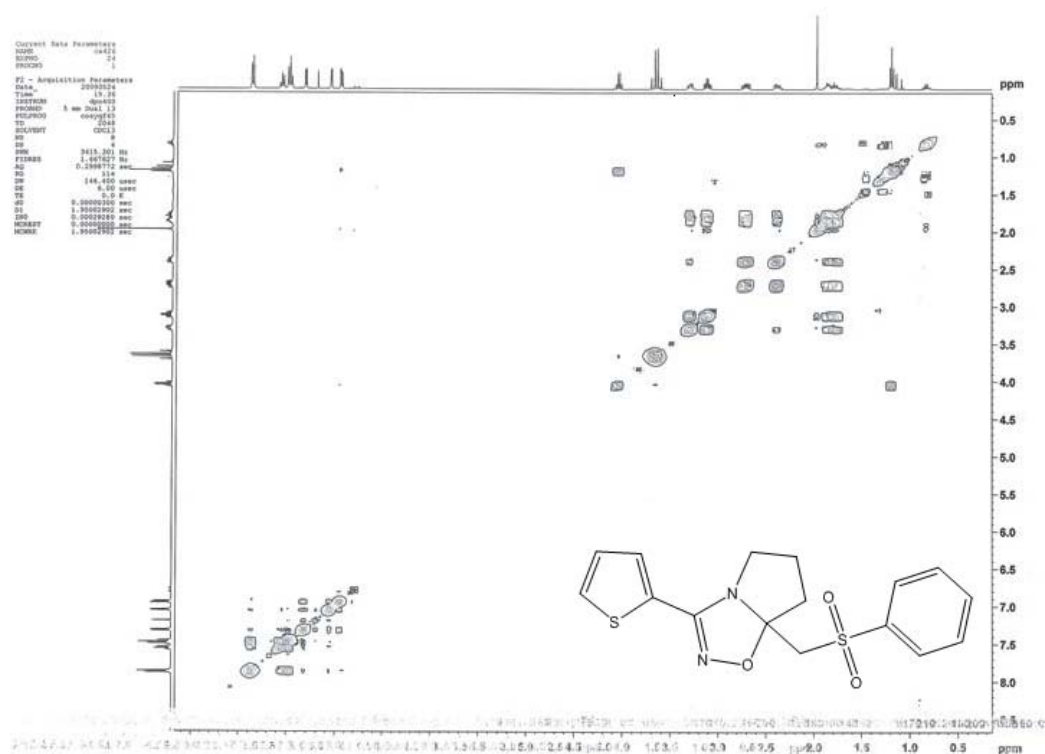


Figure 5.88. COSY NMR Spectrum of compound 4.50d

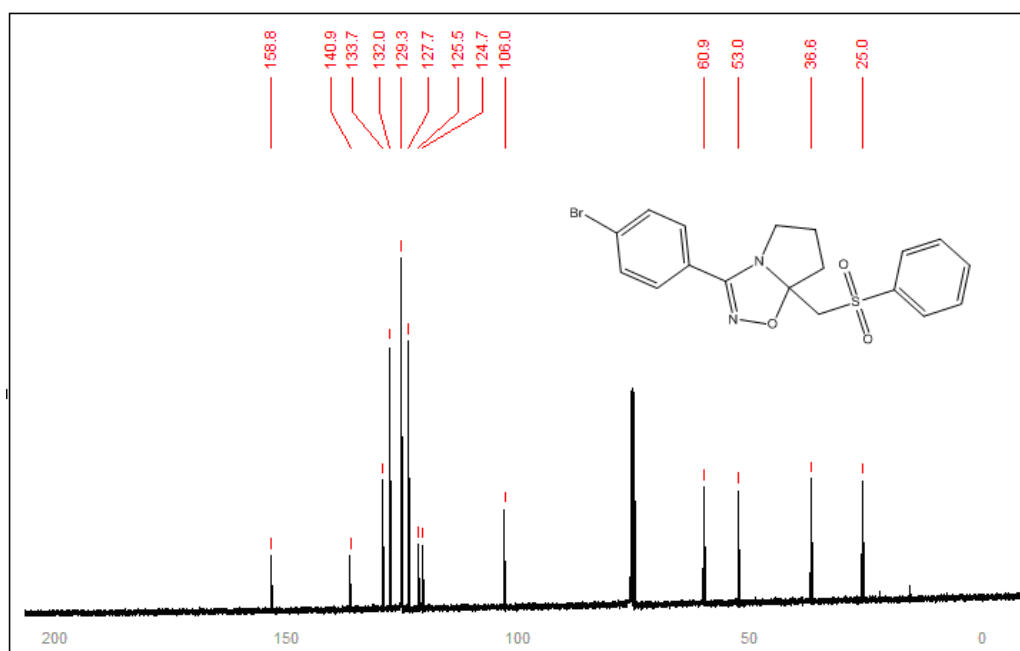


Figure 5. 91: ¹³C NMR Spectrum of compound 4.50e

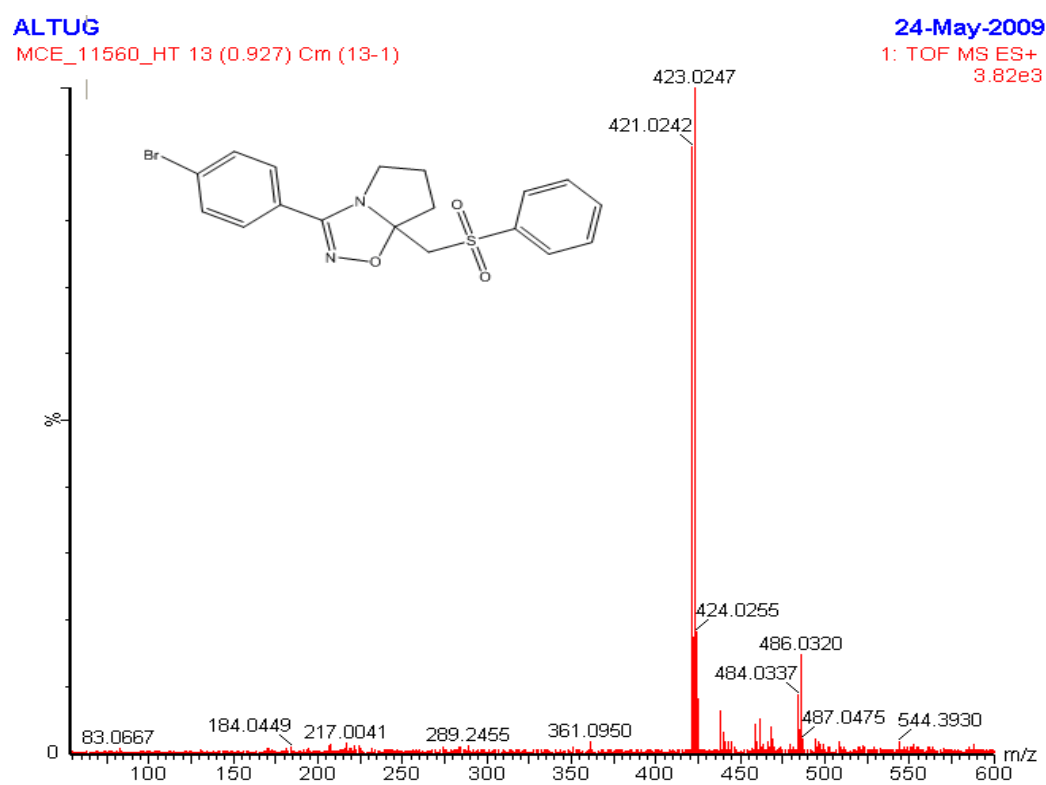


Figure 5. 92: MASS Spectrum of 4.50e

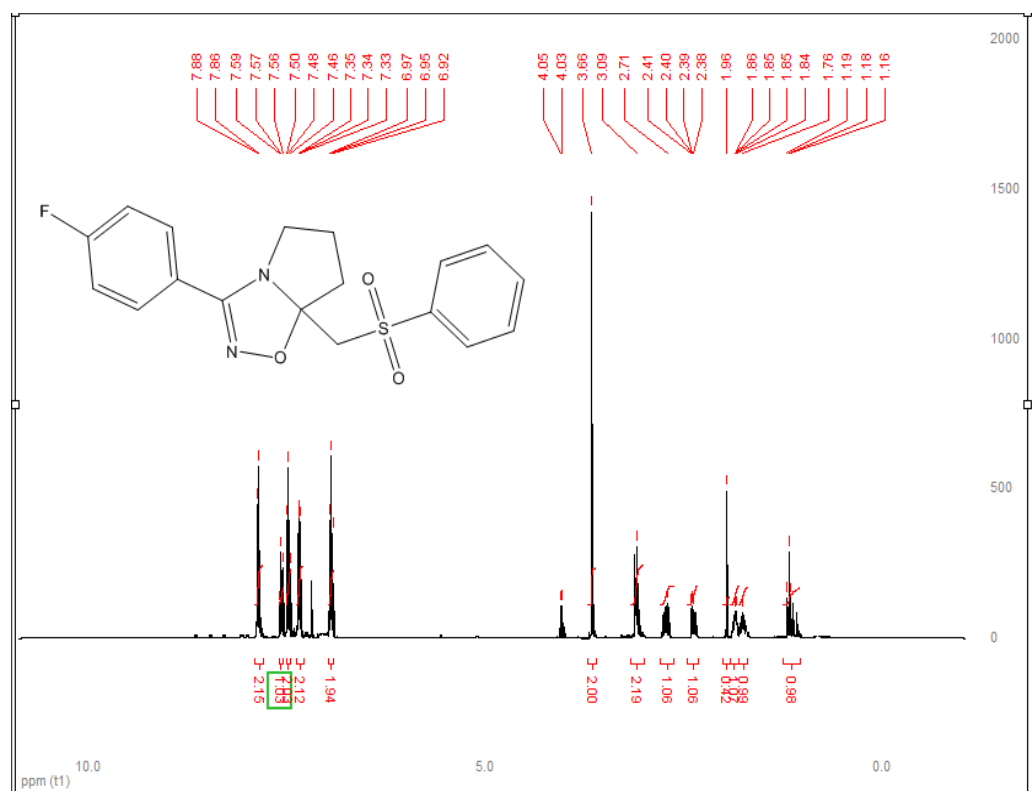


Figure 5. 93: ¹H NMR Spectrum of compound **4.50f**

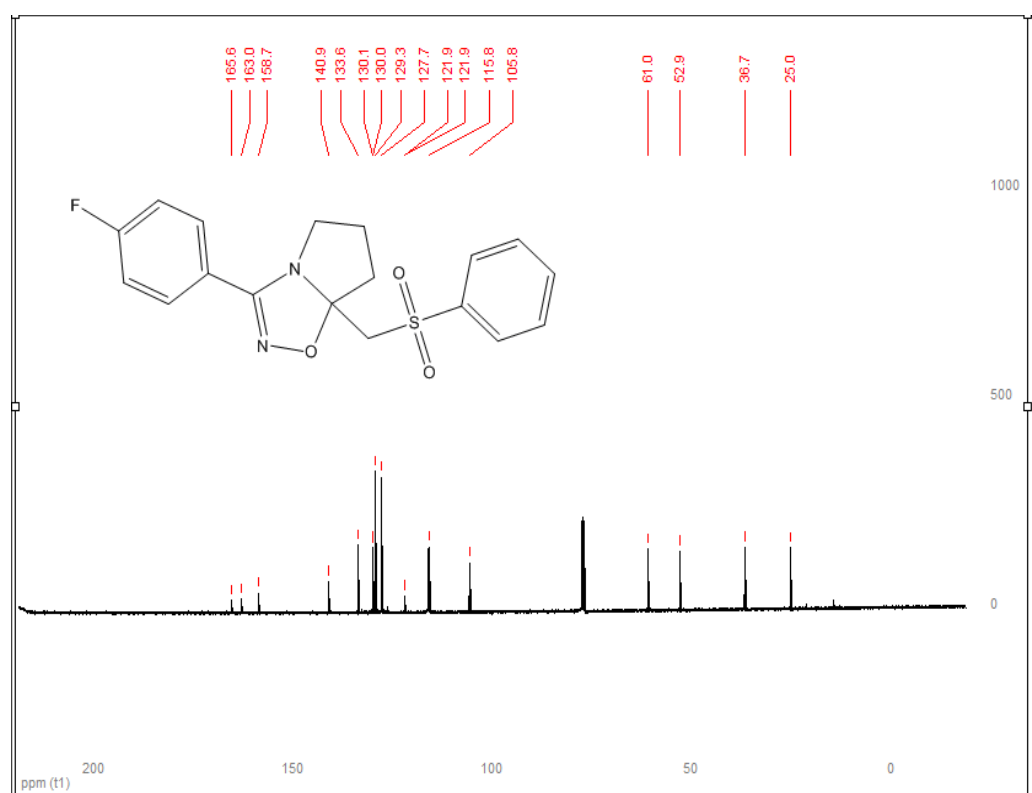


Figure 5. 94: ¹³C NMR Spectrum of compound **4.50f**

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4.89e4

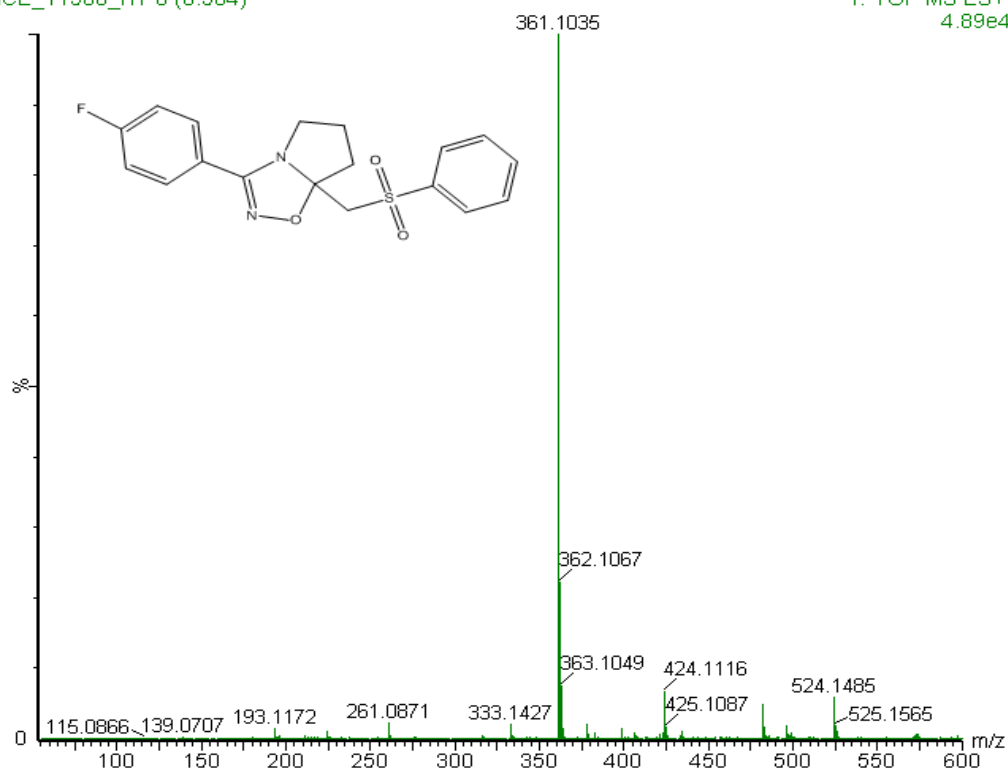


Figure 5. 95: MASS Spectrum of compound 4.50f

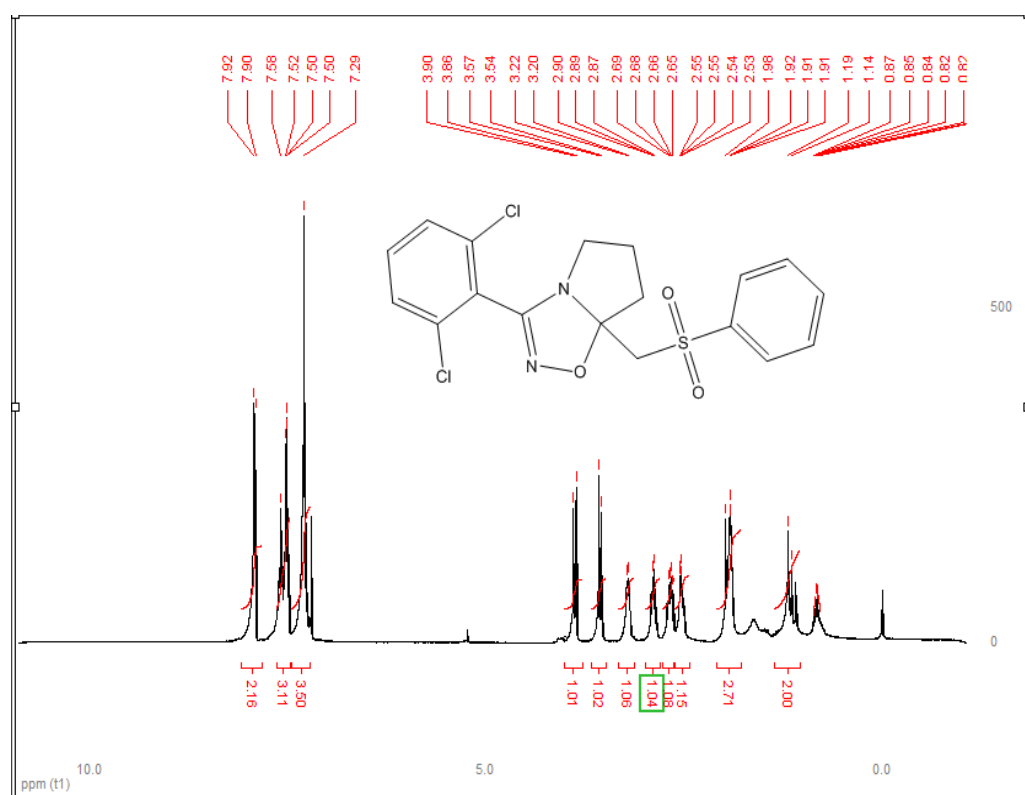
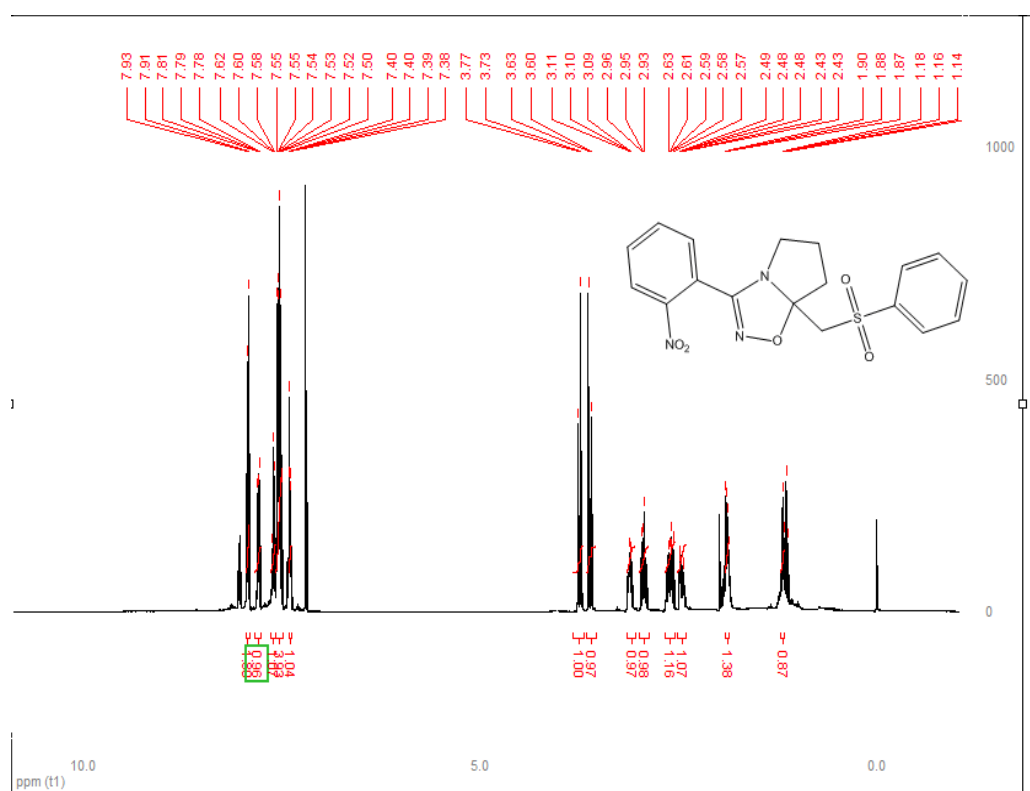
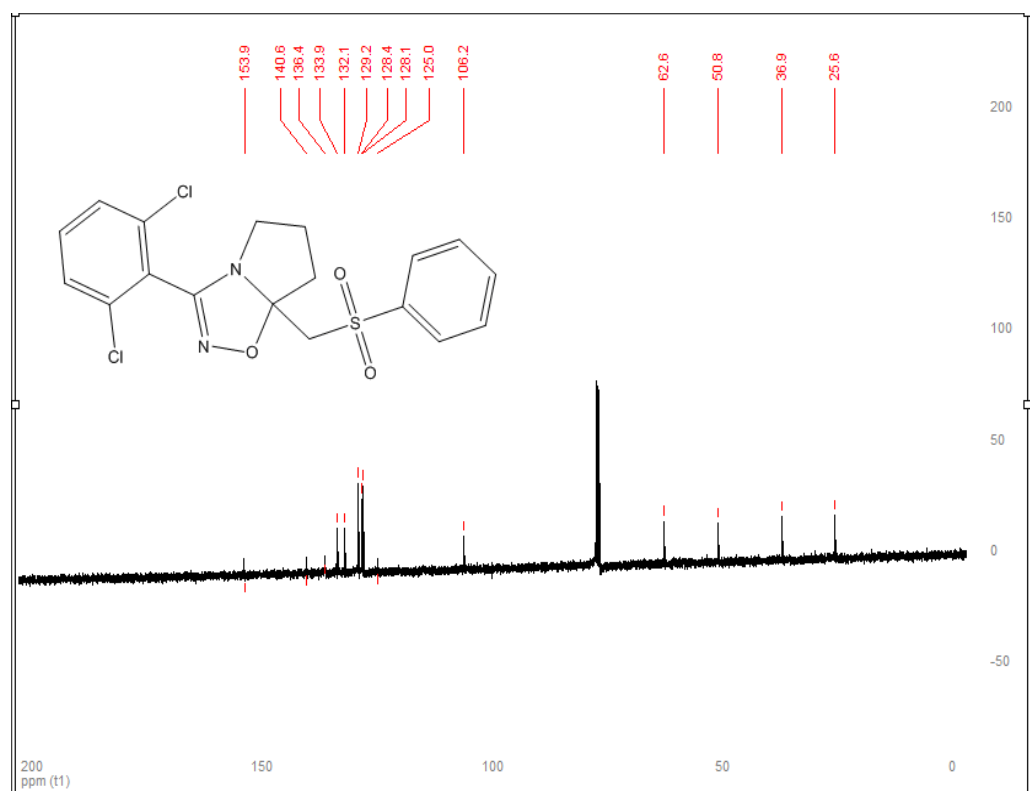
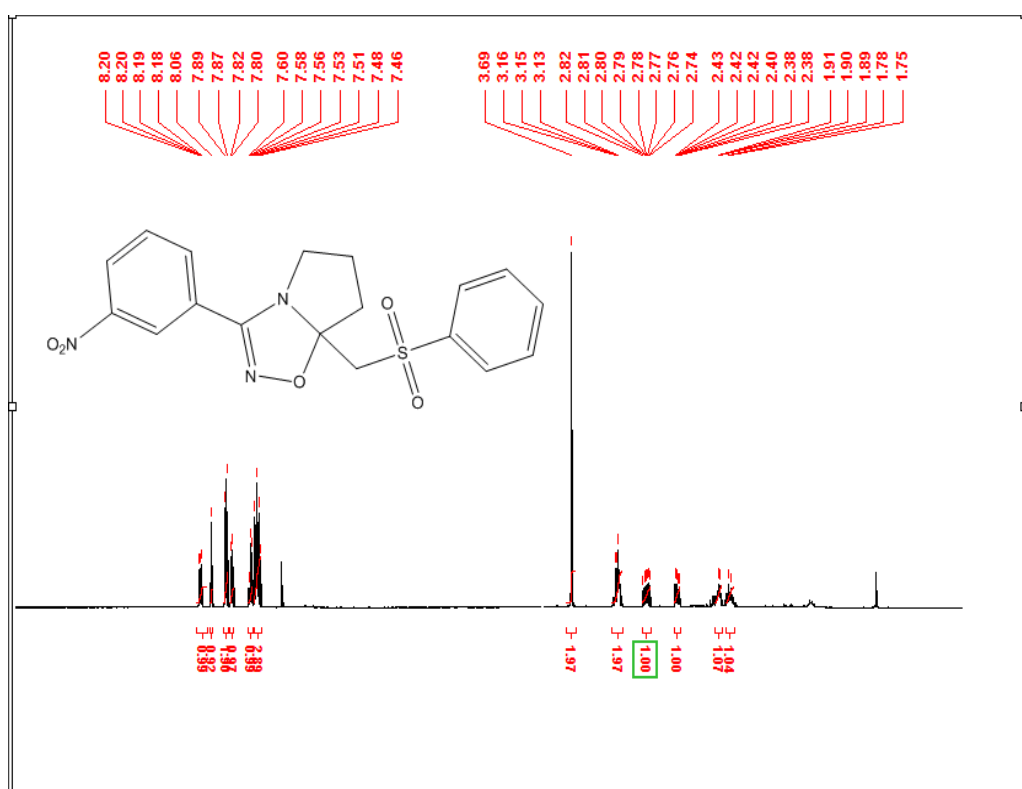
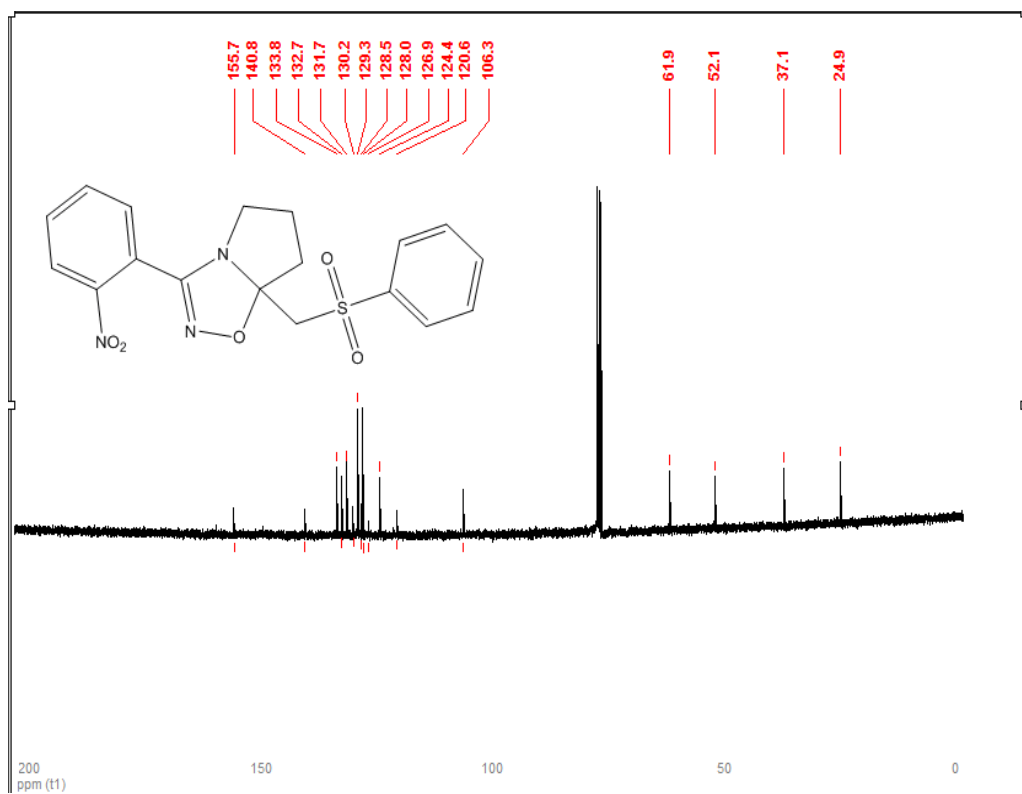


Figure 5. 96: ¹H NMR Spectrum of compound 4.50g





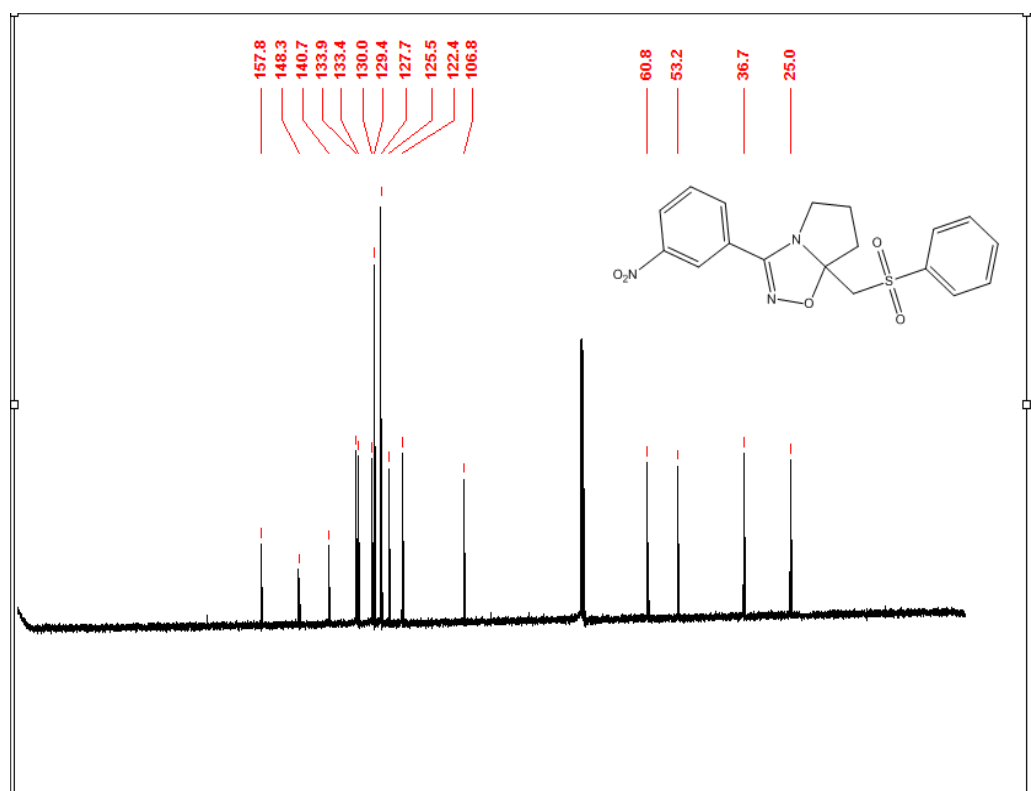


Figure 5. 101: ^{13}C NMR Spectrum of compound **4.50i**

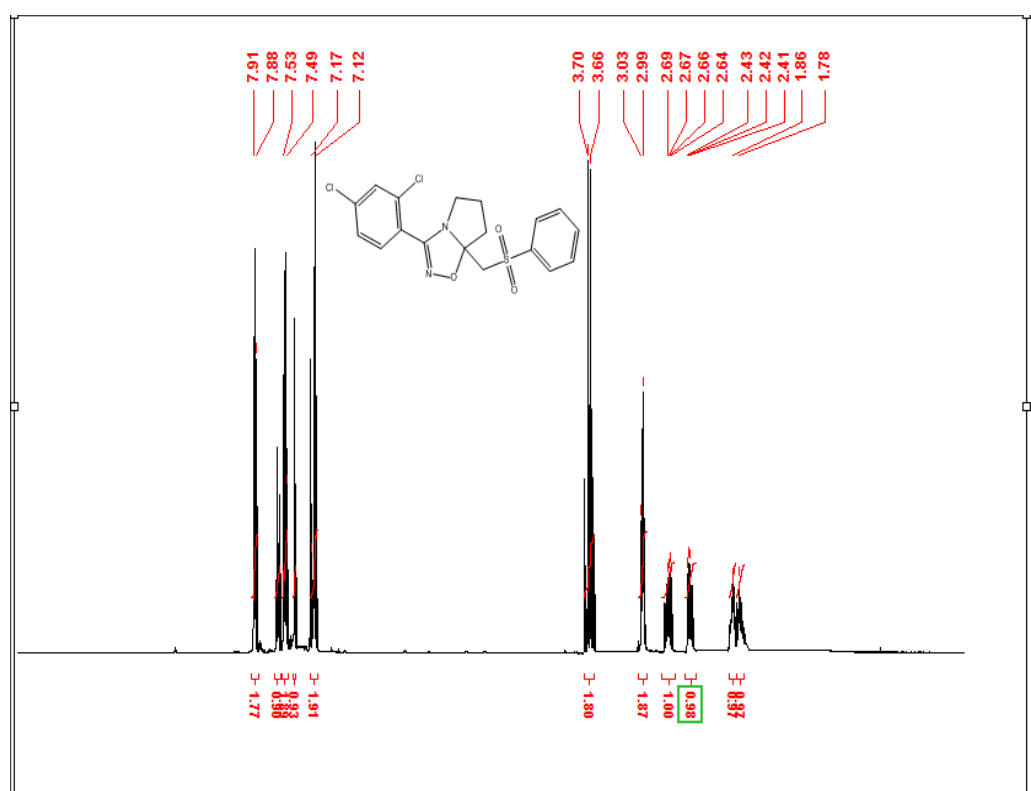


Figure 5. 102: ^1H NMR Spectrum of compound **4.50j**

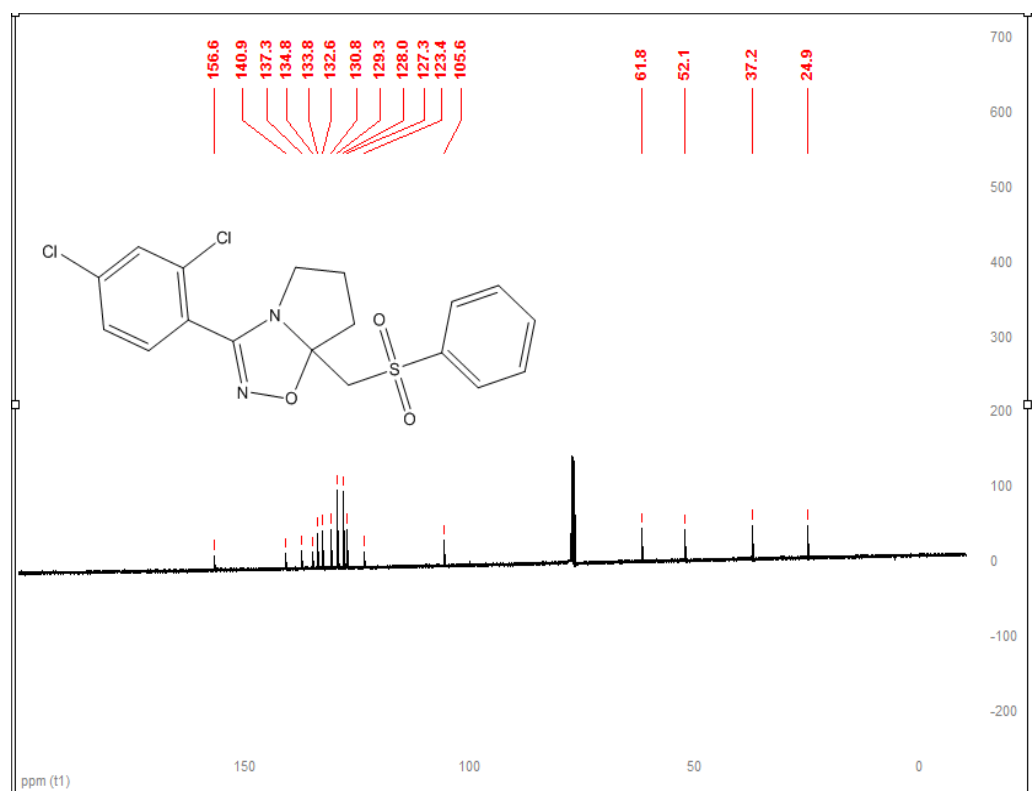


Figure 5. 103: ¹³C NMR Spectrum of compound 4.50j

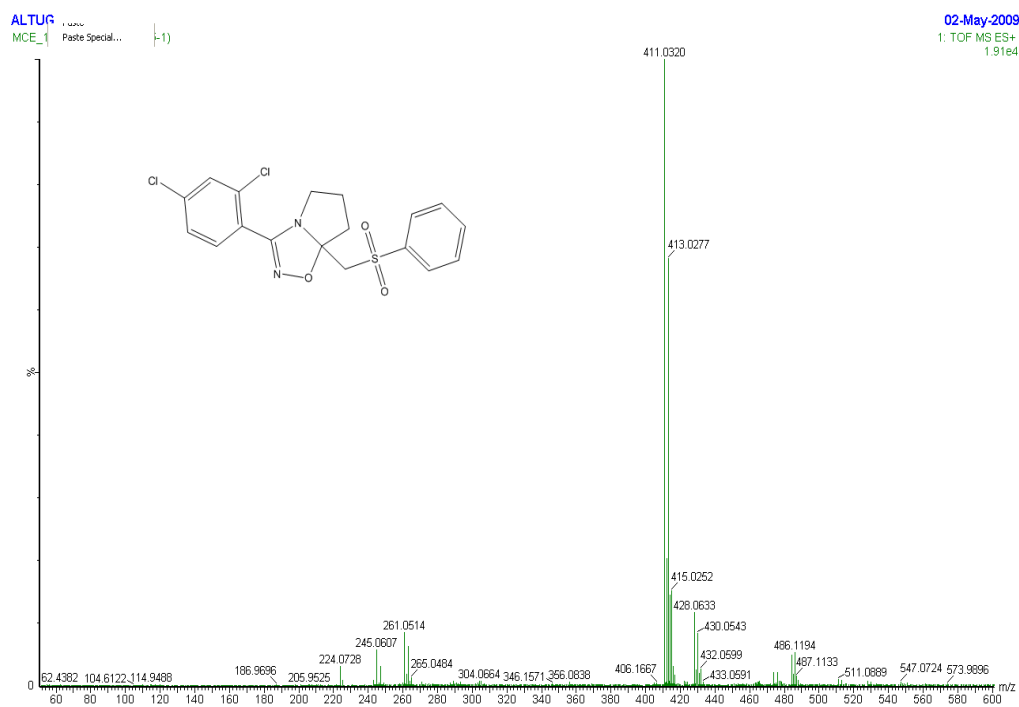


Figure 5. 104: MASS Spectrum of 4.50j

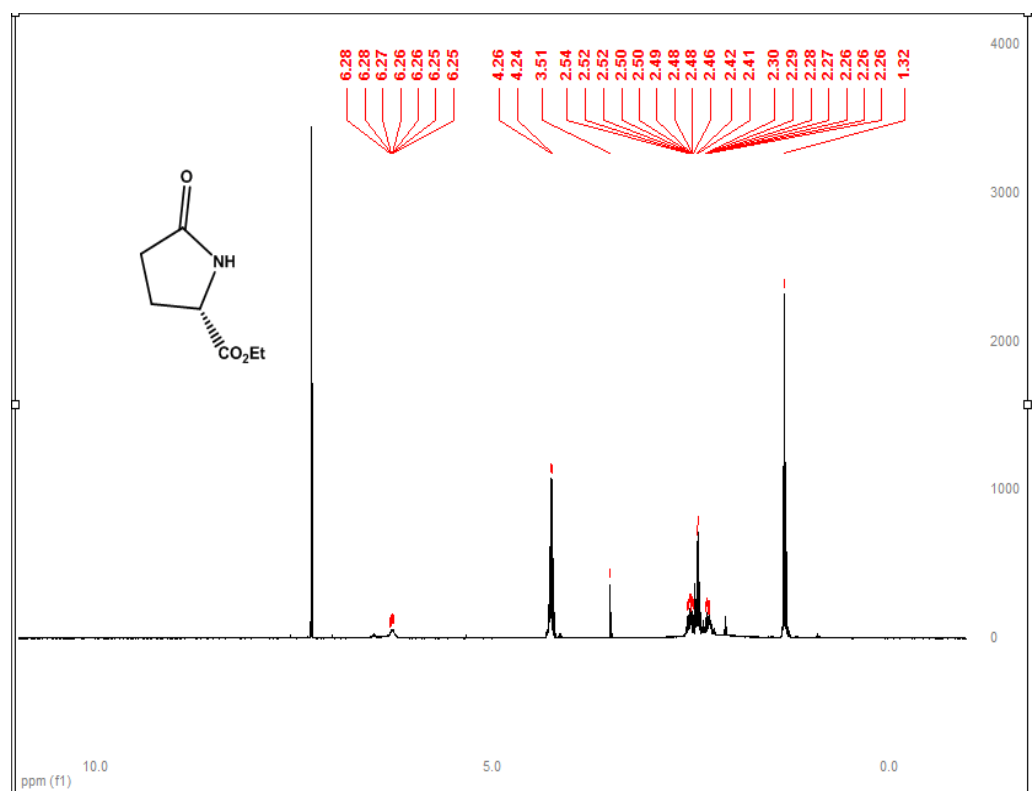


Figure 5. 105: ¹H NMR Spectrum of compound 4.46

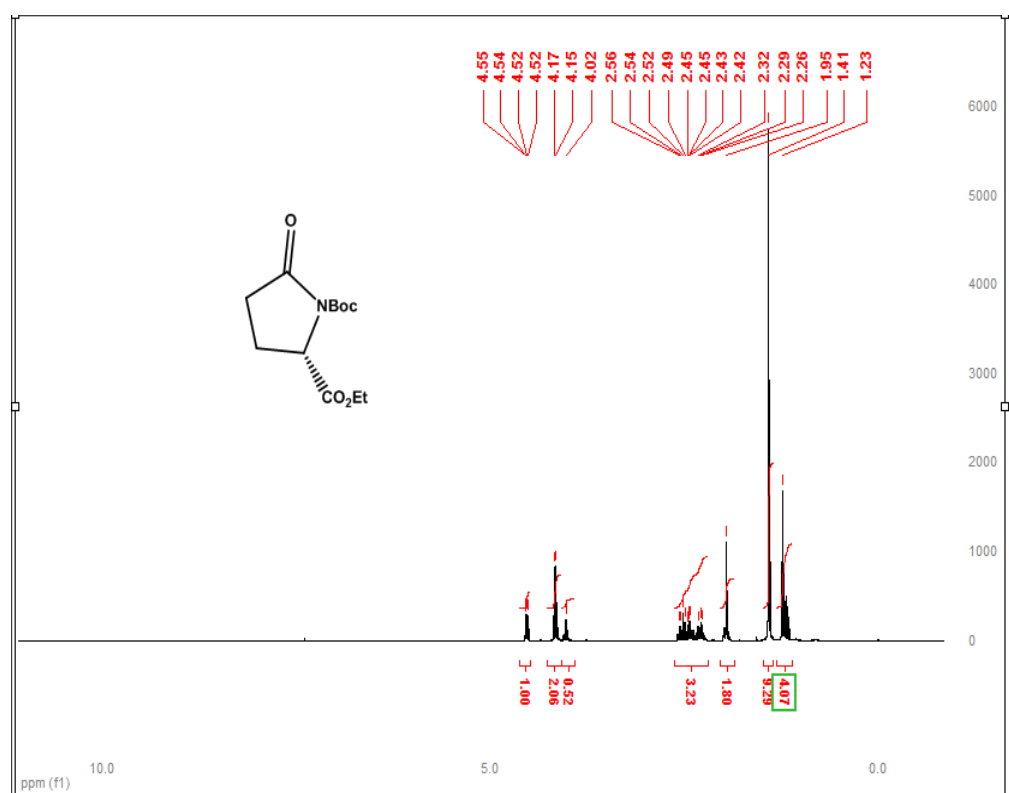


Figure 5. 106: ¹H NMR Spectrum of compound 4.47

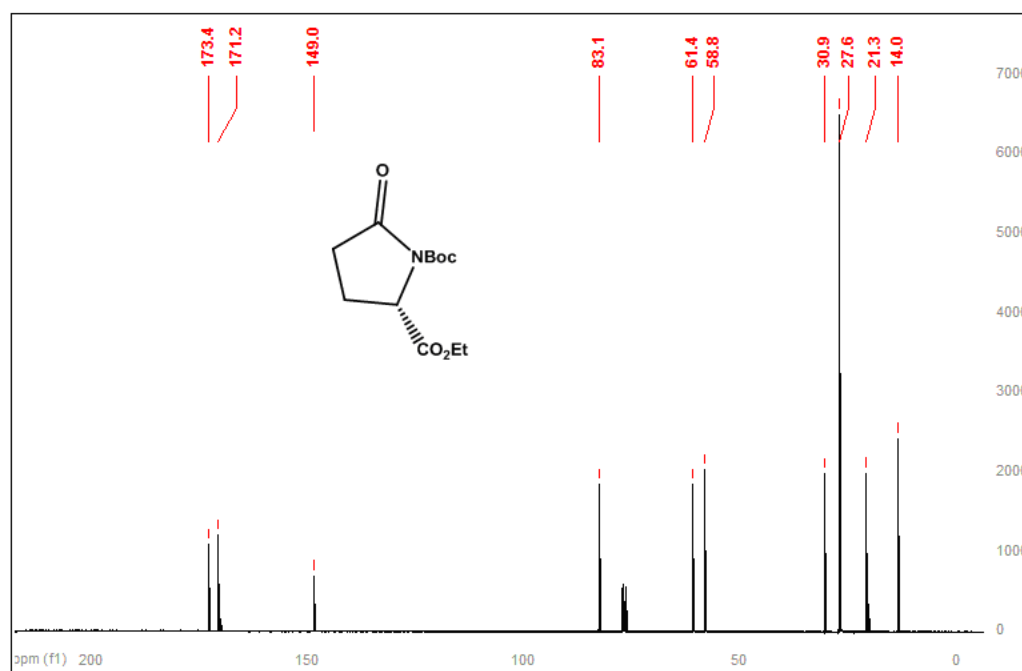


Figure 5. 107: ^{13}C NMR Spectrum of compound 4.47

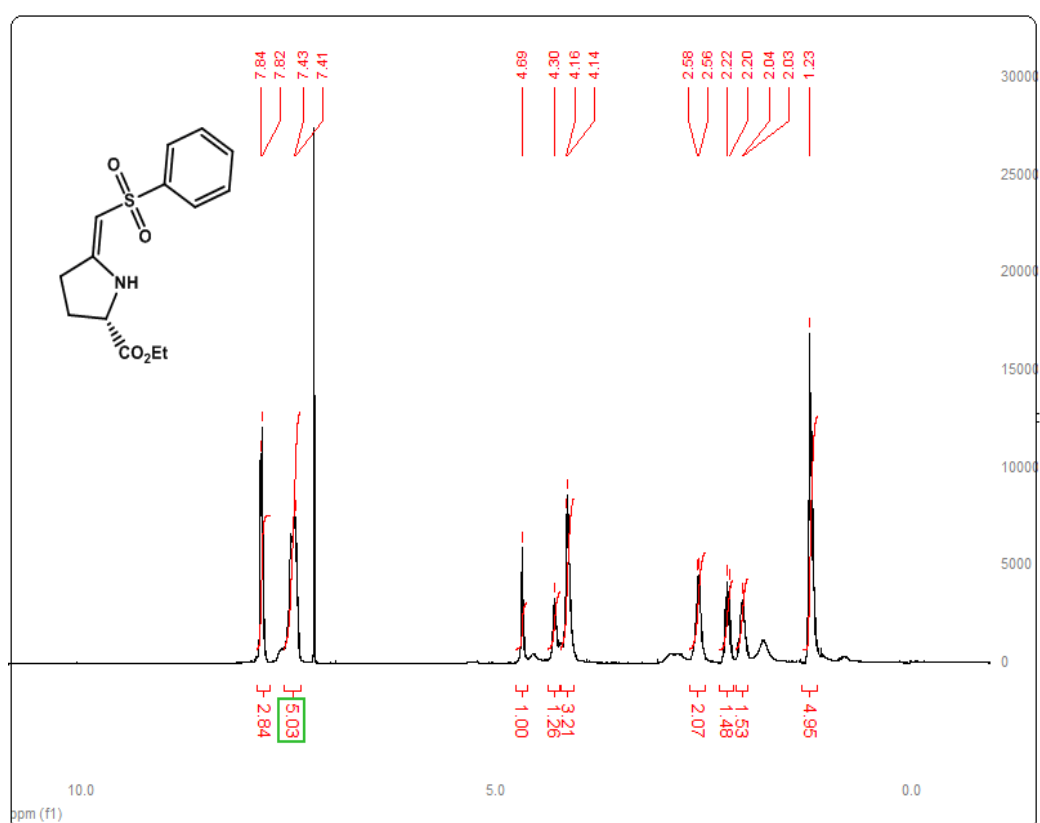


Figure 5. 108: ^1H NMR Spectrum of compound 4.38

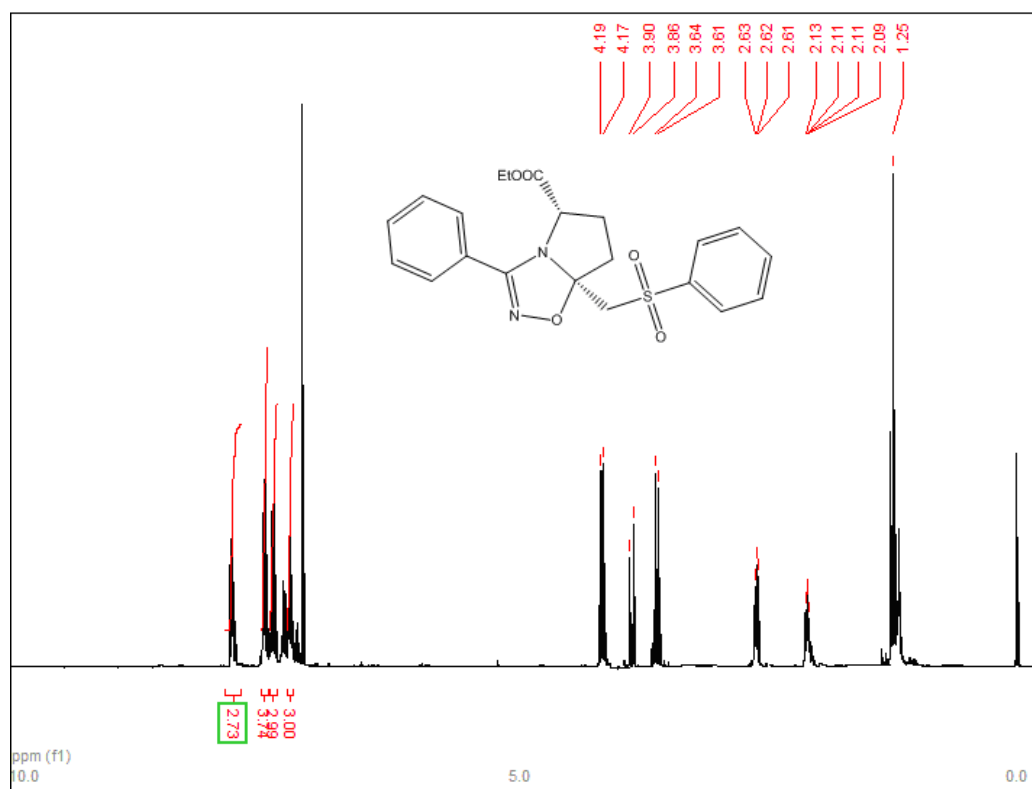


Figure 5. 109 ¹H NMR Spectrum of compound 4.50k

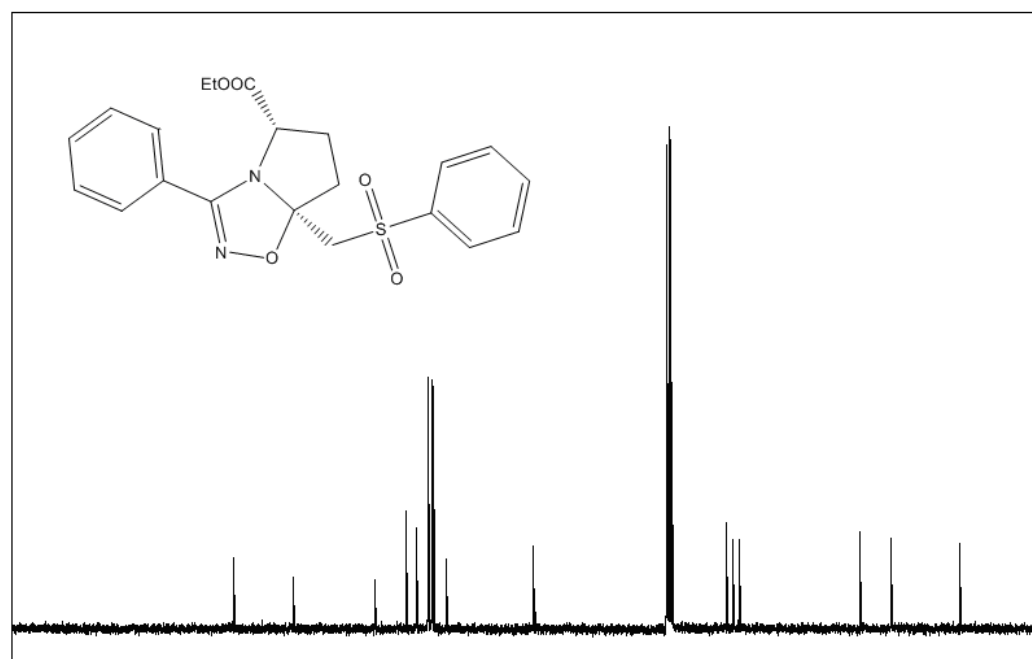


Figure 5. 110 ¹³C NMR Spectrum of compound 4.50k

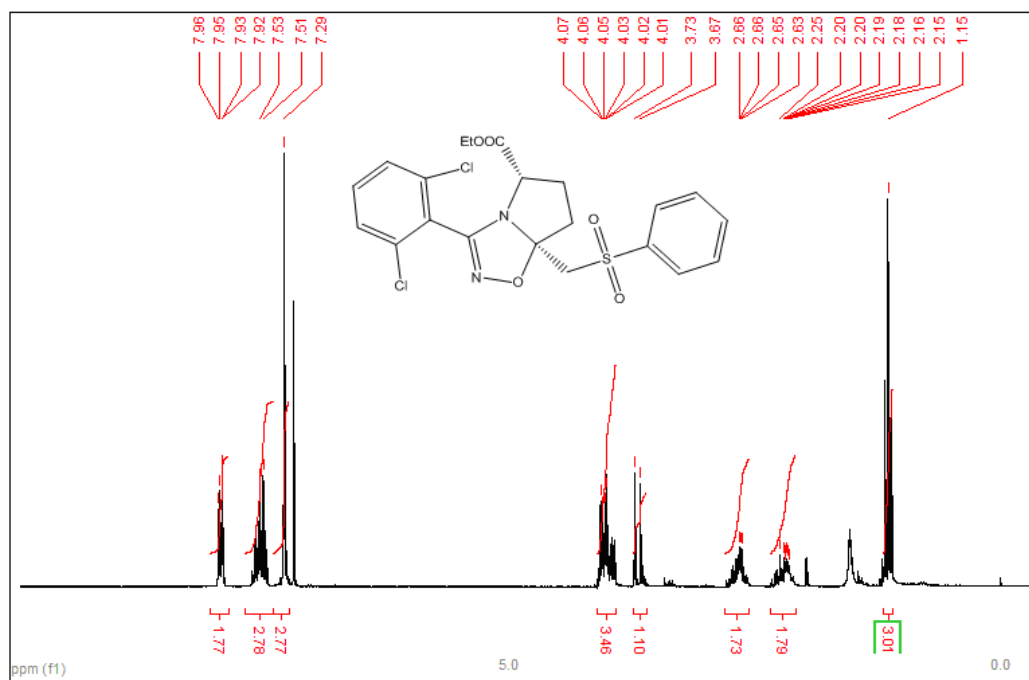


Figure 5. 111 ¹H NMR Spectrum of compound 4.50I

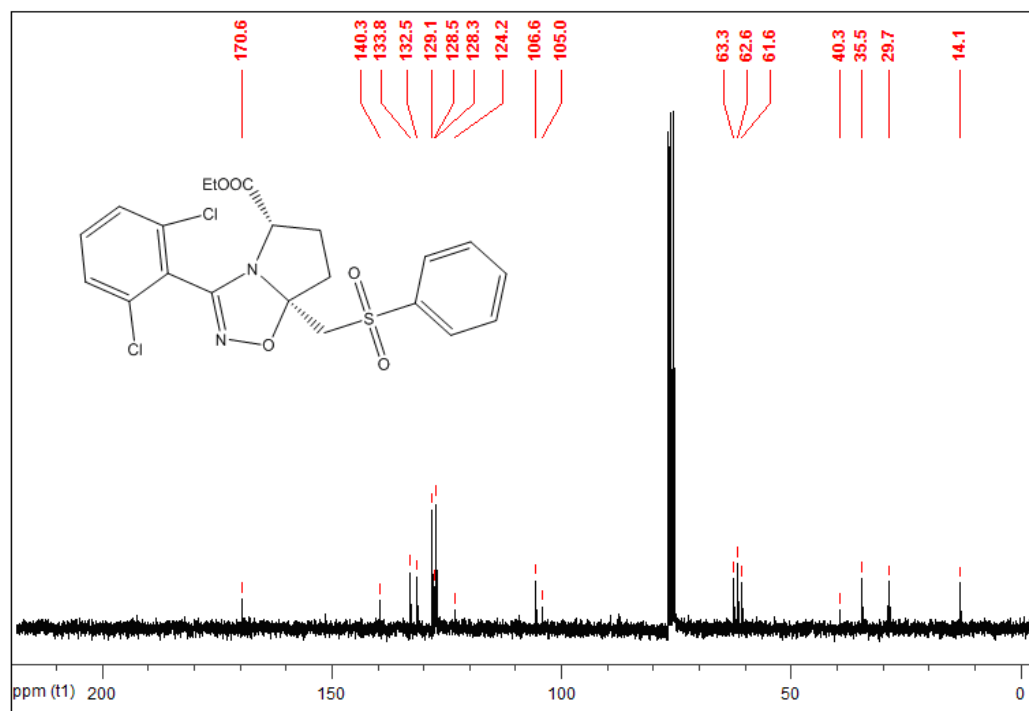


Figure 5. 112 ¹³C NMR Spectrum of compound 4.50I

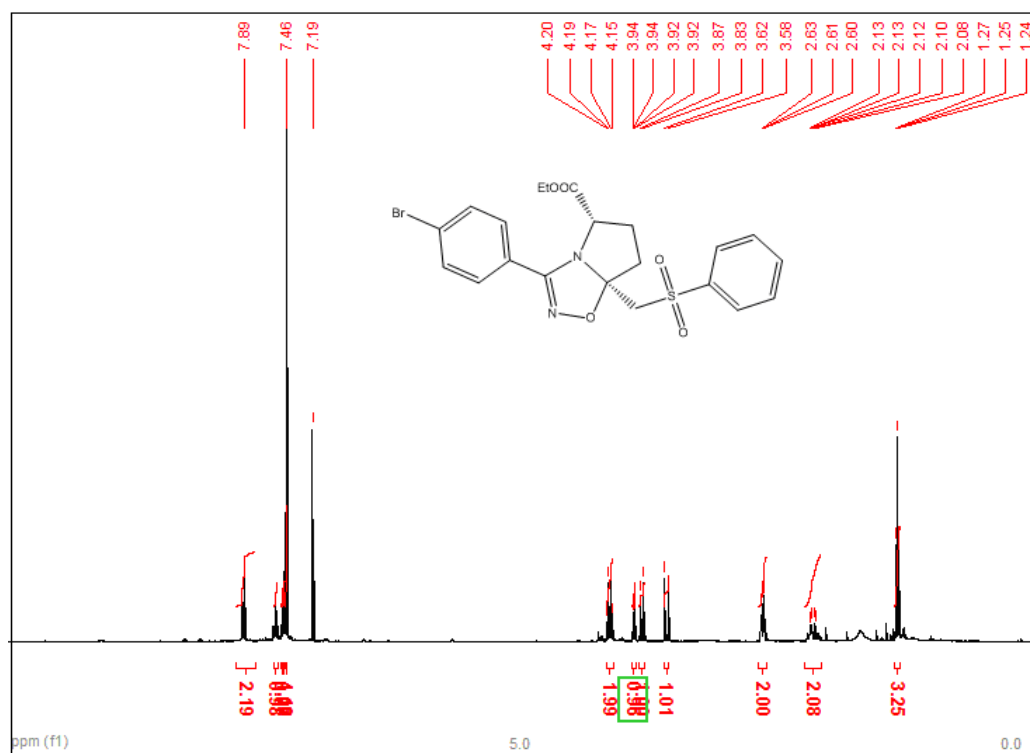


Figure 5. 113 ¹H NMR Spectrum of compound 4.50m

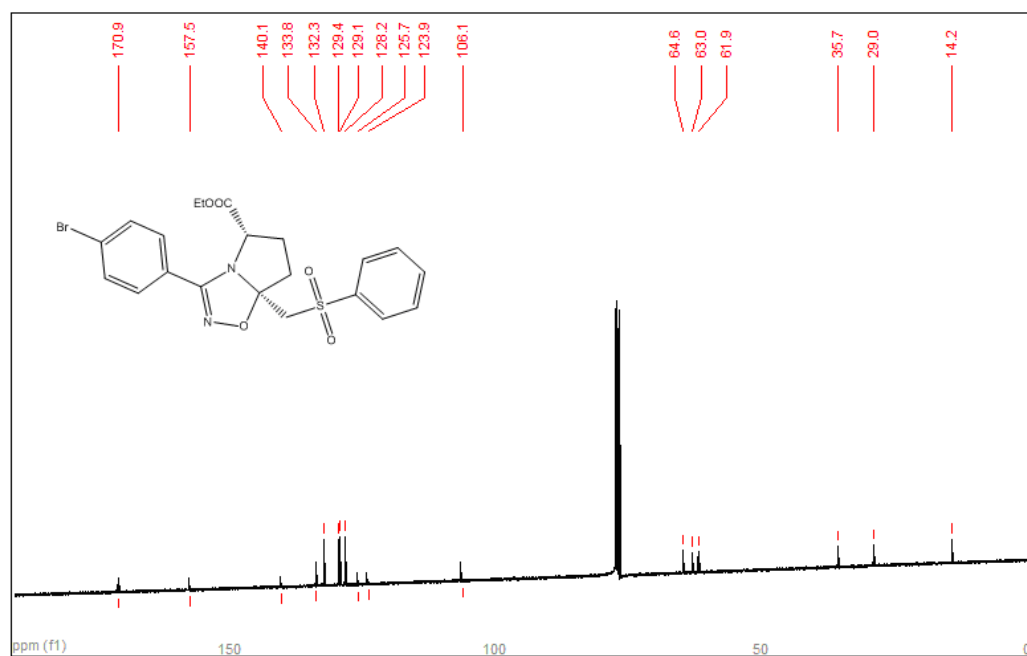
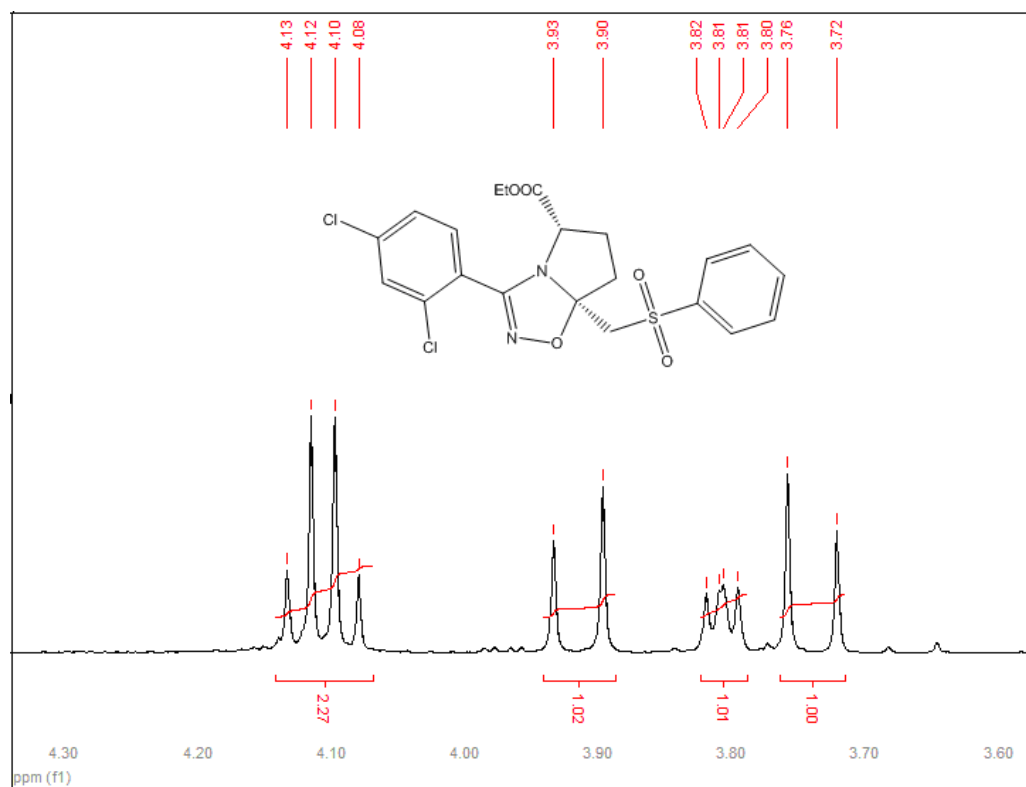
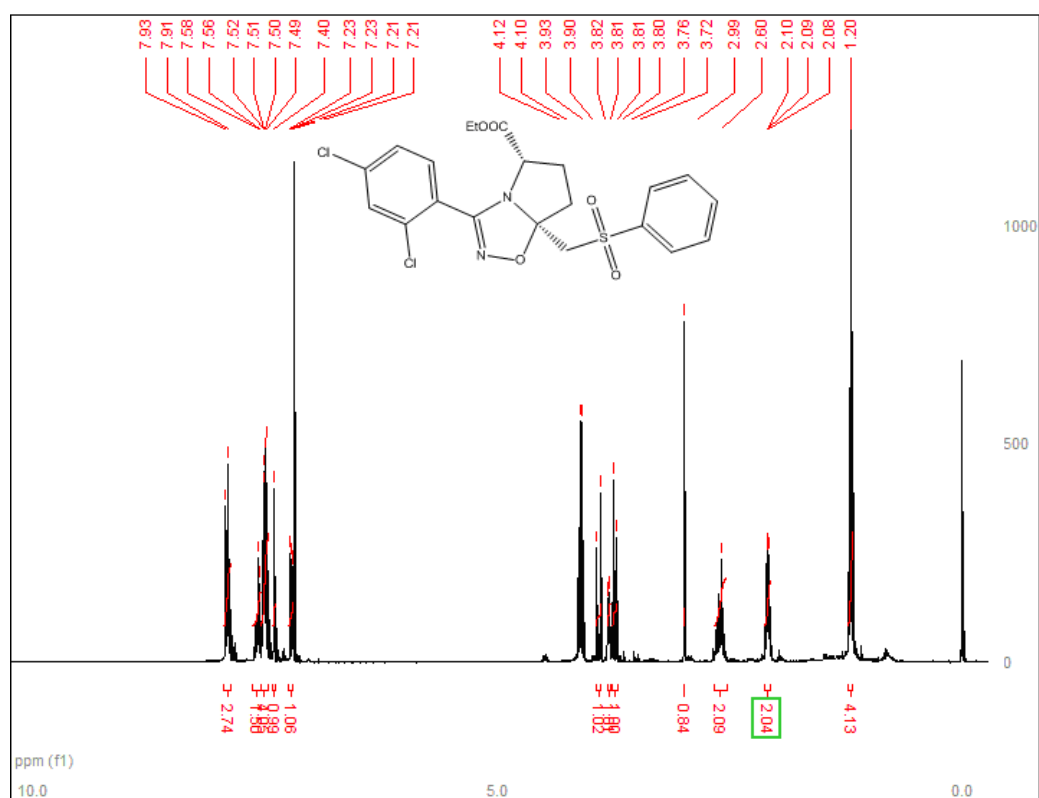


Figure 5. 114 ¹³C NMR Spectrum of compound 4.50m



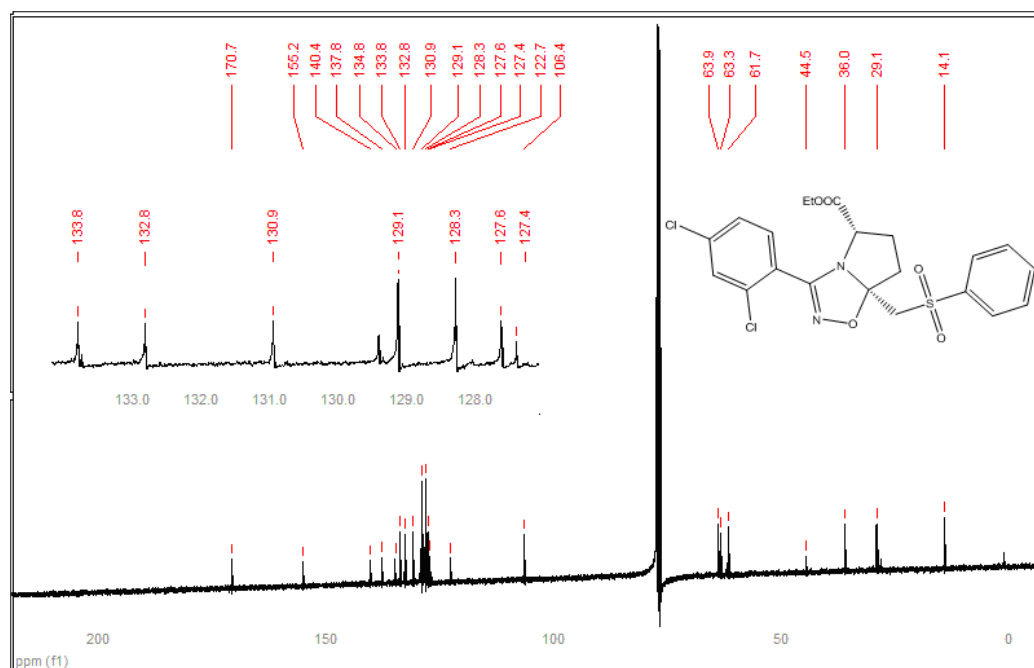


Figure 5. 117 ^{13}C NMR Spectrum of compound 4.50n

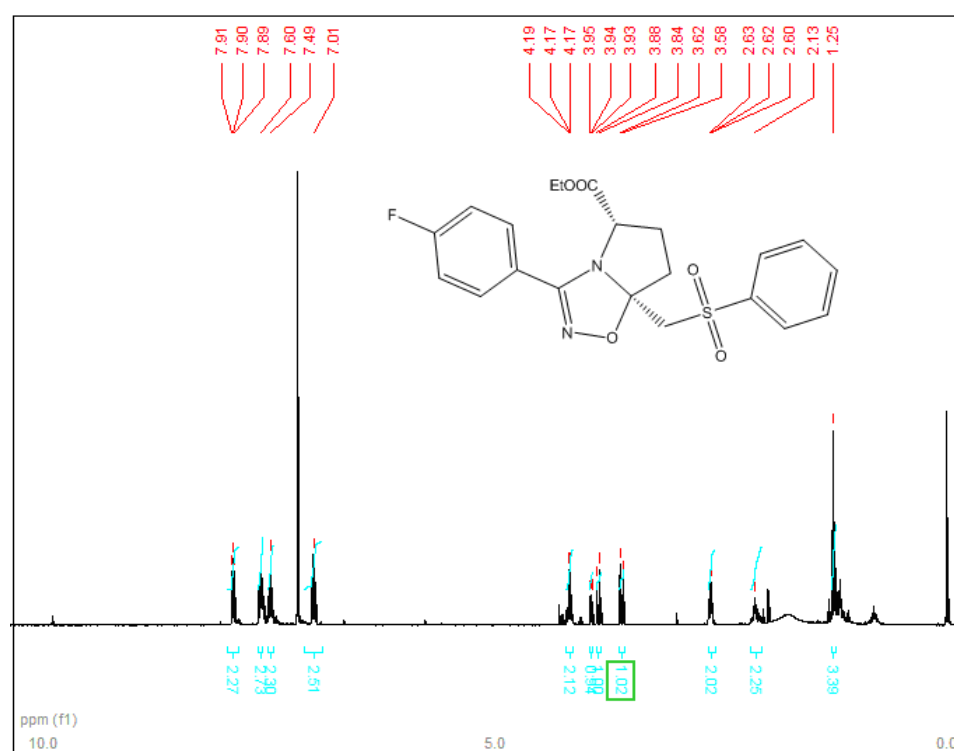


Figure 5. 118 ^1H NMR Spectrum of compound 4.50o

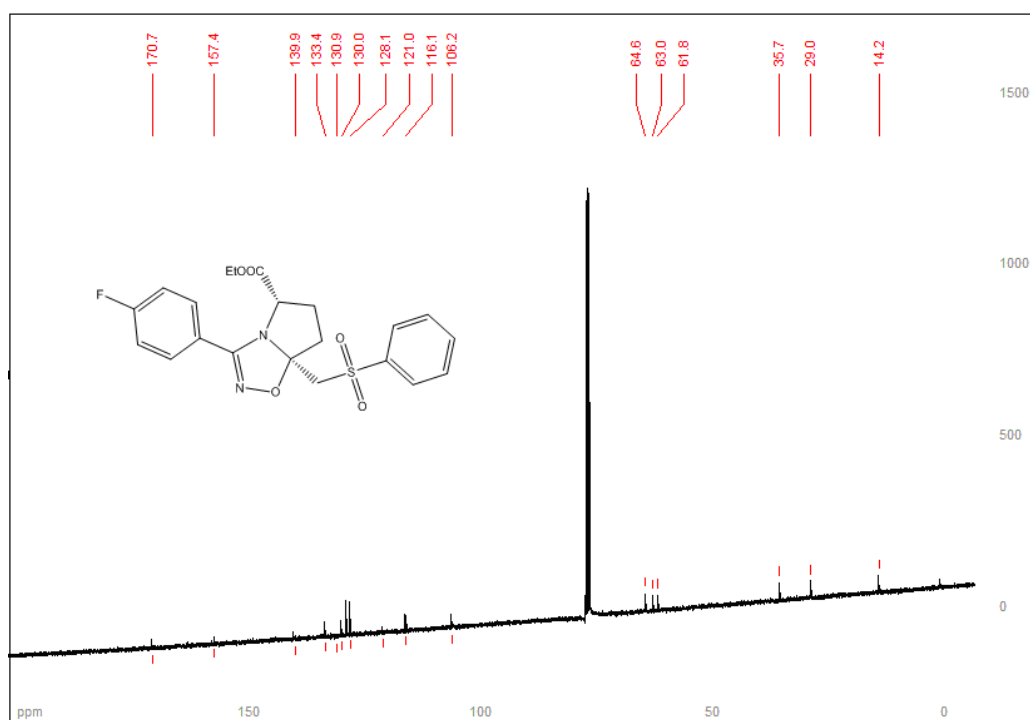


Figure 5. 119 ^{13}C NMR Spectrum of compound **4.50o**

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- Gülen Floor and Milling Factory – 2002-2003

Membership to the professional societies

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Research interests

- Synthesis and rearrangement of potential biologically active thiadiazoles, oxadiazoles, oxadiazins.
- Stereoselective reactions of pyrrolidine, oxazoline and thiazoline derivatives which provide access to a range of novel heterobicyclic systems.
- Cycloaddition of nitrones, nitrile oxides with various dipolarophiles,
- Chemistry of Polyhalogenated Nitrobutadienes.

Communications to scientific meetings

- C.Altuğ , Y.Durust . 1,3-Dipolar Cycloaddition of Nitron and Oxime Compounds. The 2003 Younger European Chemist' Conference-27 to 29 August 2003 Grenoble, FRANCE.
- C.Altuğ , Y.Durust, F.Kilic , Synthesis and rearrangement of thiadiazoles, oxadiazoles and oxadiazines. XX. National Chemistry Congress , 04-08 Sep. 2006, Kayseri, TURKEY.
- C.Altuğ , Y.Durust, A New Route For The Synthesis of Phenyl Sulfonyl Substituted Isoxazoles, International Conference on Organic Chemistry, 05-09 June 2007 , Erzurum, TURKEY.

Publications

- C. Altuğ, Y. Dürüst and M.C. Elliott
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Tetrahedron Letters, vol.50,52,7392-7394, 2009
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Bis(3-phenyl-1,2,4-thiadiazole-5-thiolato)mercury(II) *Acta Cryst. C*, vol.61,9,m442-m444,2005.