ABANT IZZET BAYSAL UNIVERSITY

THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

1,3-DIPOLAR CYCLOADDITION REACTIONS OF SOME SYDNONE DERIVATIVES WITH ELECTRON DEFICIENT ALKENES AND ALKYNES

DOCTOR OF PHILOSOPHY

AKIN SAĞIRLI

BOLU, JUNE 2015

ABANT IZZET BAYSAL UNIVERSITY

THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

DEPARTMENT OF CHEMISTRY

1,3-DIPOLAR CYCLOADDITION REACTIONS OF SOME SYDNONE DERIVATIVES WITH ELECTRON DEFICIENT ALKENES AND ALKYNES

DOCTOR OF PHILOSOPHY

AKIN SAĞIRLI

BOLU, JUNE 2015

APPROVAL OF THE THESIS

1,3-DIPOLAR CYCLOADDITION REACTIONS OF SOME SYDNONE DERIVATIVES WITH ELECTRON DEFICIENT ALKENES AND ALKYNES submitted by **AKIN SAĞIRLI** in partial fulfillment of the requirements for the degree of Doctor of Philosophyin **Department of Chemistry, Abant Izzet Baysal University** by,

Examining Committee Members	**Signature**
Supervisor Prof. Dr. Yaşar DÜRÜST Abant İzzet Baysal University	
Prof. Dr. İzzet MORKAN Abant İzzet Baysal University	
Prof. Dr. Mustafa ARSLAN Sakarya University	
Prof. Dr. Canan ÜNALEROĞLU Hacettepe University	
Prof. Dr. Özdemir DOĞAN Middle East Technical University	

June 17, 2015

Prof. Dr. Duran KARAKAŞ……..

Director, **Graduate School of Natural and Applied Sciences**

To my wife and lovely son,

DECLARATION

I hereby declare that all information in this document has been obtained and presented in accordance with academic rules and ethical conduct. I also declare that, as required by these rules and conduct, I have fully cited and referenced all material and results that are not original to this work.

Akın SAĞIRLI

_____

ABSTRACT

1,3-DIPOLAR CYCLOADDITION REACTIONS OF SOME SYDNONE DERIVATIVES WITH ELECTRON DEFICIENT ALKENES AND ALKYNES
PHD THESIS
AKIN SAĞIRLI
ABANT IZZET BAYSAL UNIVERSITY GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF CHEMISTRY
(SUPERVISOR:PROF. DR. YAŞAR DÜRÜST)

BOLU, JUNE 2015

One of the most versatile method for the construction of five membered heterocyles is 1,3-dipolar cycloaddition reactions. Sydnones, a well-defined class of mesoionic compounds that can provide an easy access to a variety of heterocyclic systems containing especially pyrazole and pyrazoline ring, They are generally found in the core structure of many drugs and alkaloids. In order to construct new pyrazole (or pyrazoline)-based heterocyles, various electron deficient dipolarophiles have been attempted in the cycloaddition reaction of sydnones throughout this Ph.D. dissertation study. The outcomes of the study were disscussed in four parts;

In the first part, *N*-aryl sydnone derivatives as the precursor of azomethine imine were succesfully synthesized according to reliable literature method and characterized. Then, reactivity of acetylenic dipolarophile, 1-(prop-2-ynyl)-1*H*-indole, with *N*-aryl sydnones was investigated and reaction proceeded to give cycloadducts with lack of regioselectivity that is resulted from the nature of electon-withdrawing or donating substituents on the aromatic ring of sydnone.

The second section covers the synthesis of new cyclopropyl-(1-substituted phenyl)-(1*H*-pyrazol-3-yl)methanols as the result of the complete regioselective cycloaddition reaction of acetylenic alcohol, namely 1-cyclopropylprop-2-yn-1-ol with *N*-aryl sydnone derivatives.

The third part of this study involves the synthesis of new fused tricyclic cycloadducts bearing pyrazoline ring, namely, 2-(4-substituted phenyl)-3,3a-dihydro-2*H*-[1]benzothieno[3,2-*c*]pyrazole 4,4-dioxides via reaction of benzo[*b*]thiophene 1,1-dioxide with *N*-aryl sydnones in moderate yields. The synthesis of corresponding cycloadducts took place in completely regioselective manner.

In the last part of the present work, treatment of secondary heterocyclic enamine, 2-nitromethylenethiazolidine, with *N*-aryl sydnones gave rise to unusual decomposition of sydnone ring by the possible release of acetolactone in intermediate step and underwent diazocoupling reaction instead of 1,3-dipolar cycloaddition. To the best of our knowledge, there is no reported study comprising such kind of decomposition of sydnones leading diazocoupling

products.

KEYWORDS: Sydnone, Ylide, 1,3-Dipolar Cyloaddition, 2-Nitromethylenethiazolidine, Alkynol, Benzo[*b*]thiophene 1,1-dioxide, Propargyl indole

ÖZET

BAZI SIDNON TÜREVLERININ ELEKTRONCA YOKSUN ALKEN VE ALKINLERLE 1,3-DIPOLAR HALKA KATILMA REAKSIYONLARI
DOKTORA TEZI
AKIN SAĞIRLI
ABANT İZZET BAYSAL ÜNİVERSİTESİ FEN BİLİMLERİ ENSTİTÜSÜ
KIMYA ANABILIM DALI
(TEZ DANIŞMANI:PROF. DR. YAŞAR DÜRÜST)

BOLU, HAZİRAN - 2015

Beş üyeli heterohalka oluşturmak için en önemli yöntemlerden birisi 1,3-dipolar heterohalkasal katılma tepkimeleridir. Özellikle pirol ve pirolidin halkalarını içeren heterohalka sistemlerinin kolayca oluşumuna olanak sağlayan sidnonlar, mezoiyonik bileşiklerin en iyi bilinen sınıflarındandır. Pirol ve pirolidin cekirdek yapıları genellikle birçok ilaç ve alkaloidin yapısında bulunur. Yeni pirol veya pirolidin temelli heterohalkalı bileşikleri oluşturmak için bu doktora tezi çalışması boyunca sidnon türevlerinin çeşitli elektronca yoksun dipolarofillerle heterohalkasal katılma tepkimesi denendi. Bu çalışmanın sonucları dört kısımda tartışıldı;

Birinci bölümde, azomethine imine başlangıcı olan *N*-aril sidnon türevleri uygun literatür yöntemi izlenerek başarıyla sentezlendi ve karakterize edildi. Sonrasında asetilenik dipolarofil, 1-(propil-2-ynil)-1*H*-indol ün *N*-aril sidnon türevleriyle olan reaktivitesi incelendi ve sidnonun aromatik halkası üzerindeki elektron salıcı ya da çekici grupların doğasından kaynaklı tepkime sonunda yerseçicilikten yoksun halkalı katılma ürünleri elde edildi.

İkinci kısım, *N*-aril sidnon türevleri ile asetilenik alkol olan 1-siklopropilil-2-in-1-ol un tam yerseçicilikle gerçekleşen halkalı katılma tepkimesi sonucu oluşan yeni siklopropilil-(1-substitue fenil)-(1*H*-pirazol-3-il)metanollerin sentezini içermektedir.

Çalışmanın üçüncü kısmı, benzo[*b*]tiyofen-1,1-dioksit ve *N*-aril sidnonların tepkimesi ile 2-(4-substitue fenil)-3,3a-dihidro-2*H*-[1]benzotiyeno[3,2-c] pirazol 4,4-diokside ler olarak adlandırılan, pirazolin halkasını içeren yeni yapışık üç halkalı katılma ürünlerinin orta derecede verimli sentezini içerir. Bahsi geçen halka katılma ürünlerinin sentezi tam yerseçicilikle gerçekleşmiştir.

Mevcut çalışmanın son kısmında, ikincil halkasal enamin, 2-nitrometilentiyazolidin ile *N*-aril sidnonların etkileşimi, sidnon halkasının ara basamakta olası asetolakton salınımıyla alışılagelmedik şekilde bozunmasına yol açmıştır ve 1,3-dipolar halka katılması tepkimesi yerine diazo birleşme tepkimesi vermiştir. Bildiğimiz kadarıyla sidnonların bu şekilde bozunmasını içererek diazo birleşme ürünleri oluşmasına yol açan başka bir çalışma rapor edilmemiştir.

ANAHTAR KELİMELER: Sidnon, İlid, 1,3-Dipolar halka katılma, 2-Nitrometilentiyazolidin, Alkinol, Benzo[*b*]tiyofen-1,1-dioksit, Propargil indol

TABLE OF CONTENTS

Page

LIST OF FIGURES

Page

LIST OF SCHEMES

Page

LIST OF TABLES

Page

LIST OF ABBREVIATIONS AND SYMBOLS

1,3-DC	**:** 1,3-Dipolar cycloadditions
Ac	**:** Acetyl
DMAD	**:** Dimethyl acetylenedicarboxylate
E	**:** Conformation
ER	**:** Electron releasing
HMBC	**:** Heteronuclear multiple bond correlation
HOMO	**:** Highest occupied molecular orbital
IAN	**:** Isoamyl nitrite
Rf	**:** Retardation factor

ACKNOWLEDGEMENTS

I am deeply greatful to my supervisor Prof. Dr. Yaşar DÜRÜST for her guidance, endless encouragement, supervision, and suggestion in every phase in this study.

I also thank to Assist.Prof.Dr.Muhammet YILDIRIM and Assoc.Prof.Dr.Cevher ALTUĞ for their supports, intimacy and long discussions throughout my PhD thesis.

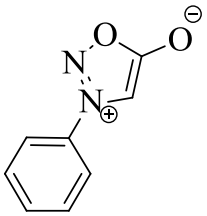
My gratitude is also extended to Prof. Dr. David W. KNIGHT for his academic support during six month period in Cardiff University and many thanks to Assoc.Prof.Dr. Yunus ZORLU and Dr. Benson M. KARIUKI for the X-ray data.

Special thanks to my group members and colleagues Dr. Hamza KARAKUŞ, Muhammet BÜYÜKBAYRAM, Lange Yakubu SALEH and Besra ÖZER for their help, encouragement and friendship.

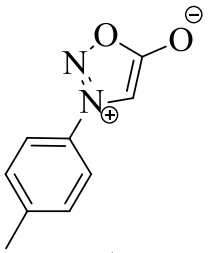
I would like to express my deepest appreciation to my family for their endless support, understanding and patience not only during this study but also throughout my life.

Finally, I would like to thank my dear wife also my colleague Eda SAĞIRLI who brings immeasurable joy to my life by simply being a part of it. I couldn't finished this Ph.D. thesis work without her support and love, and also greatest thanks goes to my cute boy Toprak Mete for being light of my life.

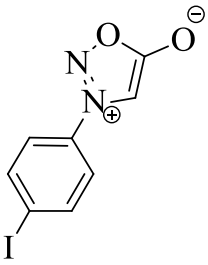
FORMULAE



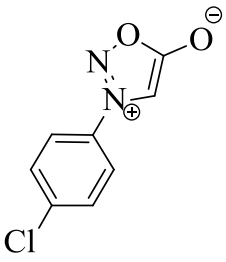
51a



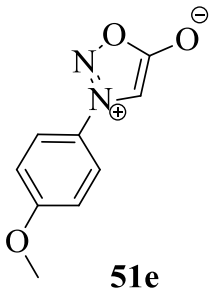
51b



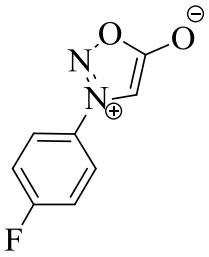
51c



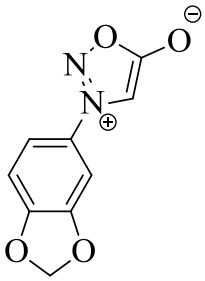
51d



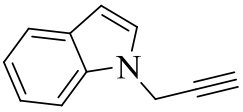
51e



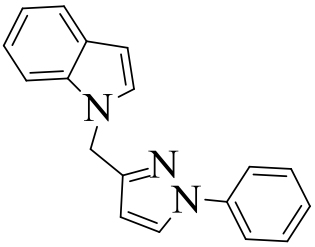
51f



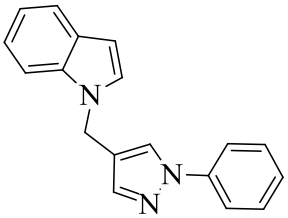
51g



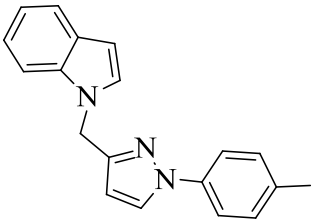
195



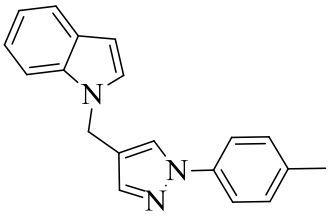
242 a



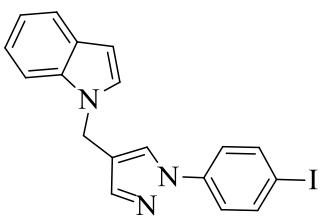
243 a



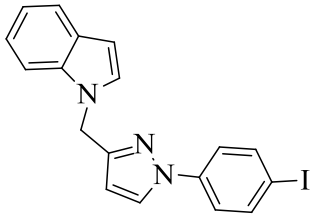
242 b



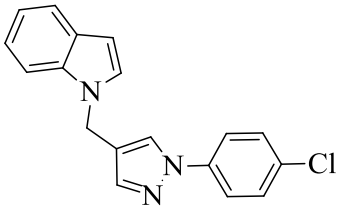
243 b



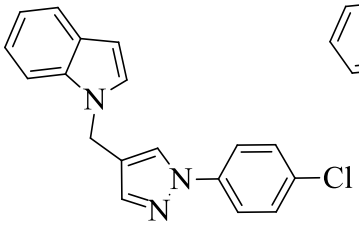
242 c



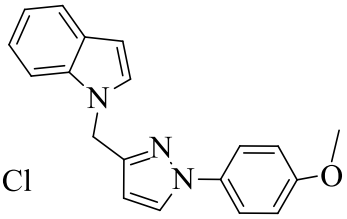
243 c



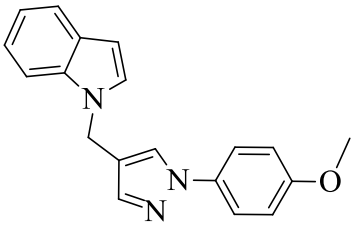
242 d



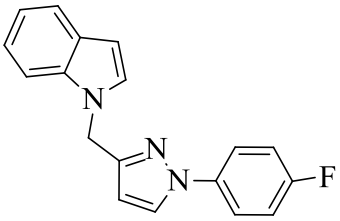
243 d



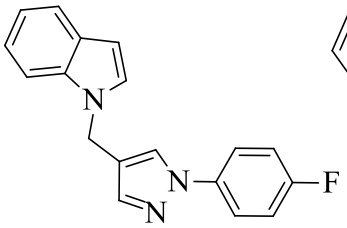
242 e



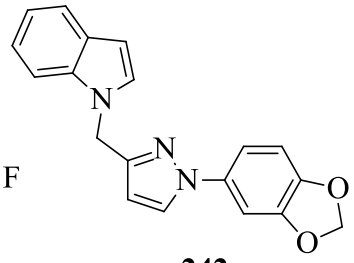
243 e



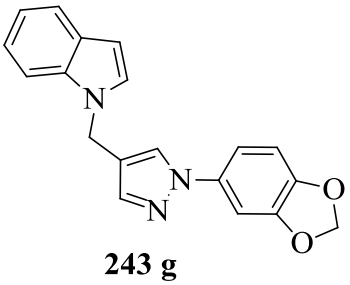
242 f



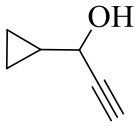
243 f



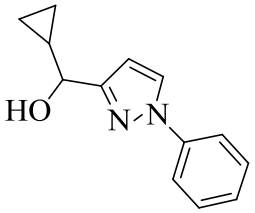
242 g



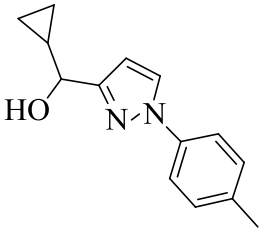
243 g



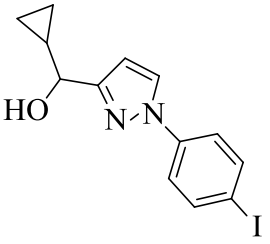
207



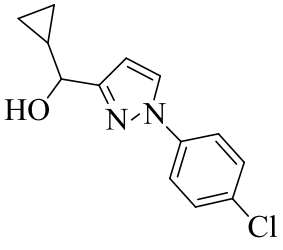
244 a



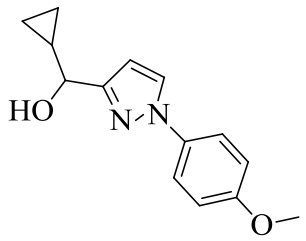
244 b



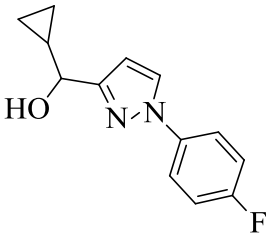
244 c



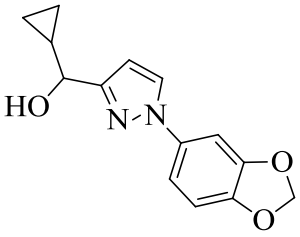
244 d



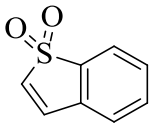
244 e



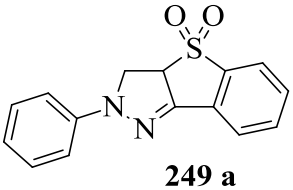
244 f



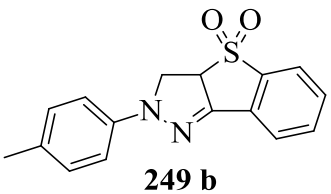
244 g



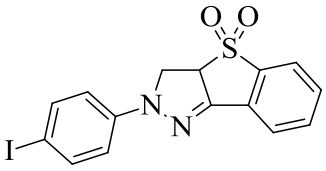
217



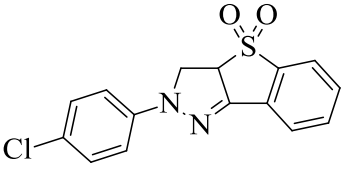
249 a



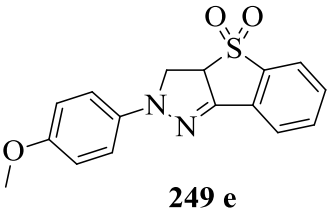
249 b



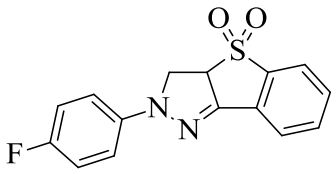
249 c



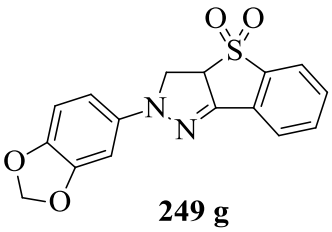
249 d



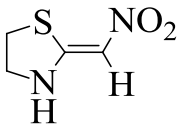
249 e



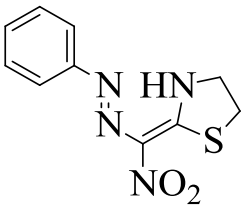
249 f



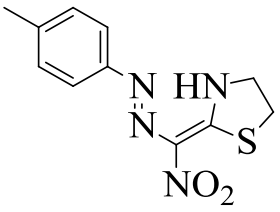
249 g



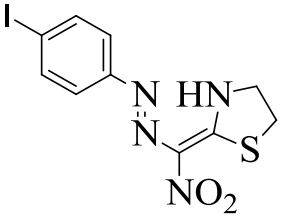
231



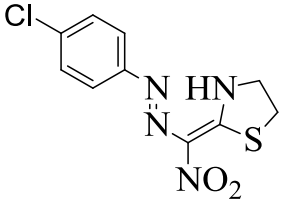
262 a



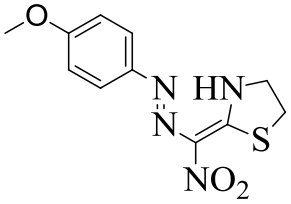
262 b



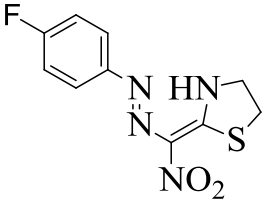
262 c



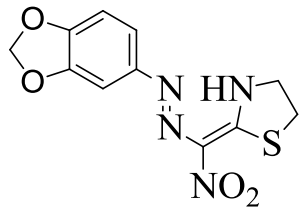
262 d



262 e



262 f



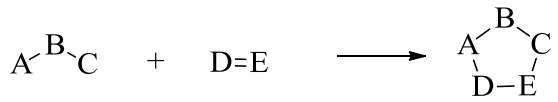
262 g

1. INTRODUCTION

1.1 CHAPTER 1

1.1.1 1,3-Dipolar Cycloaddition Reaction

1,3-Dipolar cycloaddition reactions are one of the most convenient technique for construction of five membered heterocyclic ring that is resulted from the reaction of a 4πe- zwitterionic system (1,3-dipole) with a 2πe- neutral system (dipolarophile) (Huisgen, 1963a; Huisgen, 1963b; Padwa, 1984).



1,3-dipole dipolarophile

Figure 1.1 Classical 1,3-dipolar cycloaddition reaction.

1,3-DC reactions have been investigated by many scientists. Curtius discovered diazoacetic ester in 1883 (Curtius, 1883). A couple of years later Buchner (1888) performed the reaction between diazoacetic ester with *α*-*β*-unsaturated esters as a first example of 1,3-DC reaction. In 1960s Huisgen and coworkers were studied on the nature of 1,3-dipoles and their applications (Huisgen, 1963). At the same time the concept of "conservation of orbital symmetry" was developed by Woodward and Hoffman (1970). Followed ability of understanding reactivity and regioselectivity of 1,3-DC reactions was explained by Houk *et al*.(1973a, 1973b).

1.1.2 1,3-Dipoles (ylides)

A 1,3-dipole is a a-b-c zwitterionic system containing 4πe- in three parallel atomic p-orbitals, in which the center atom b has a formal positive charge that compensates for the negative charge distributed over the two atoms a and c. These

systems can be classified into two categories: the propargyl-allenyl type (linear) and the allyl-type (bent) are shown in below (Gothelf and Jorgensen, 1998).

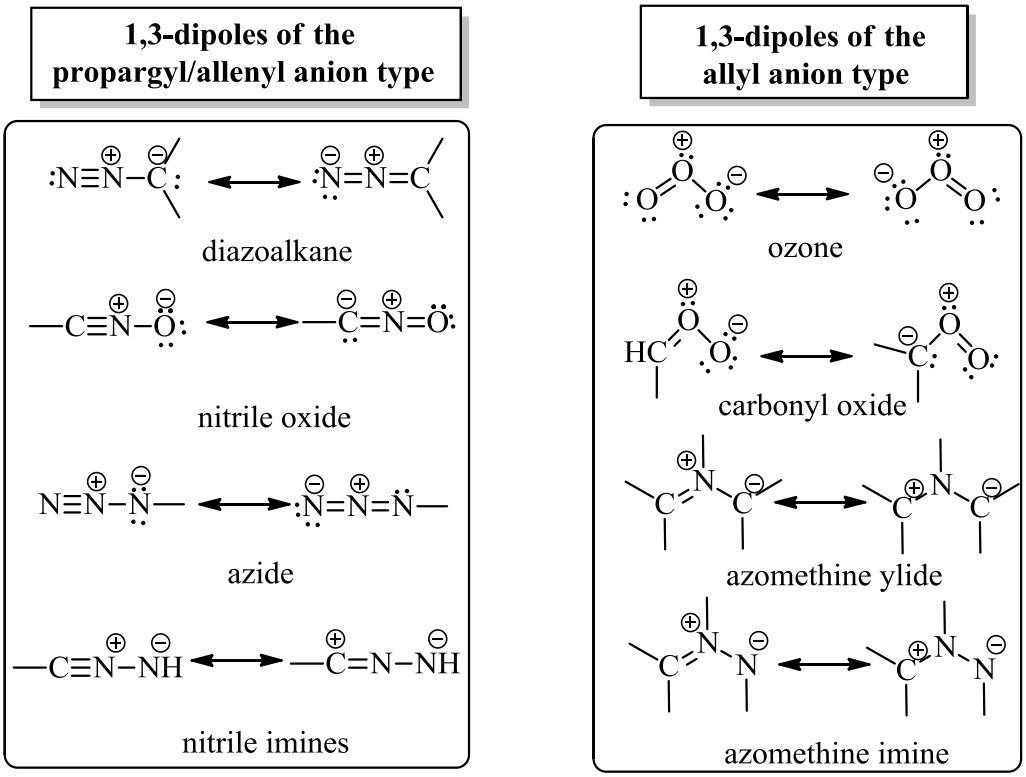


Figure 1.2 Some examples of propargyl-allenyl type and allyl type of dipoles.

1.1.3 Dipolarophiles

The term 'dipolarophile' is any group containing 2π-electrons that can react with a 1,3-dipolar group. They are generally classified into three groups; electron rich, electron poor and conjugated dipolarophiles. Alkenes, *α-β*-unsaturated aldehydes, ketones, esters, allylic alcohols, allylic halides, vinylic ethers are the examples of dipolarophiles that can react readily with various 1,3-dipoles depending on their nature. Heterodipolarophiles also are able to undergo 1,3-dipolar cycloaddition reaction but mostly reactivity of heterodipolarophiles are less than the corresponding C-C dipolaropiles (Houk *et al*., 1973).

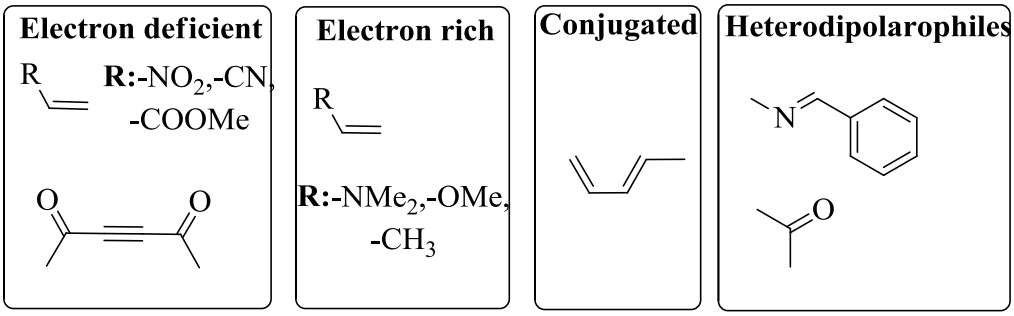
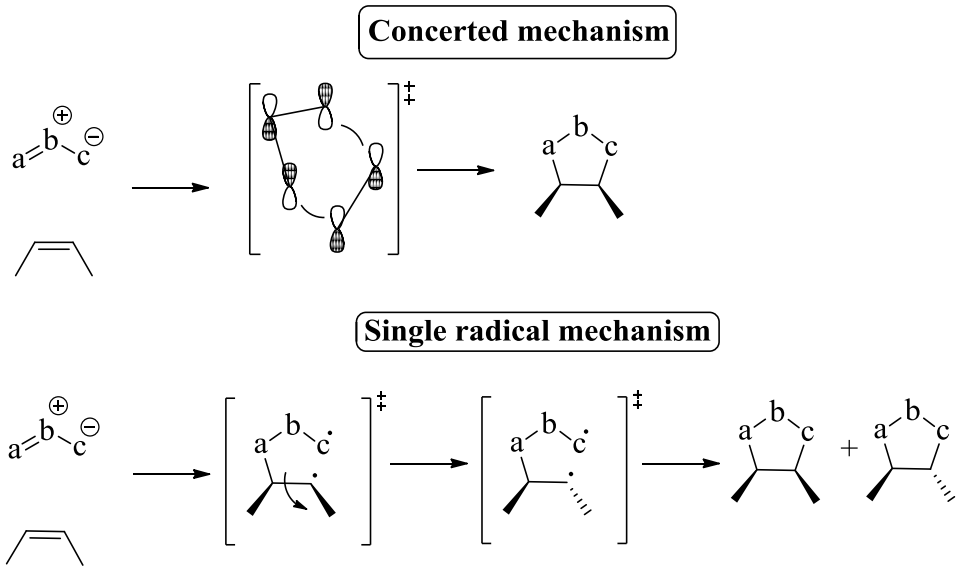


Figure 1.3 Examples of dipolarophiles

1.1.4 Reaction Mechanisms of 1,3 dipolar Cycloaddition Reactions

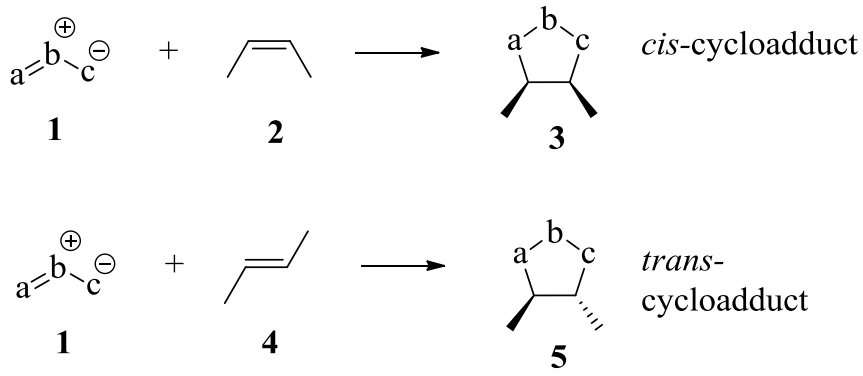
Since 1960s the reaction mechanism of 1,3-DC reaction has a great importance for organic chemists. From the mechanistic point of the view, two types of 1,3-DC reactions have been introduced; concerted and singlet diradical mechanism that were studied by the Huisgen *et al.* and Firestone *et al.* respectively. Huisgen *et al* claimed that 1,3-DC reactions proceed through a concerted mechanism which means that all the bonds are created simultaneously, but not necessarily to the same extent at a certain time. Firestone *et al.* discussed the formation of *cis* and *trans* isomer of cycloadducts that is resulted from the 180^{o} rotation of C-C bond in diradical intermediate (Huisgen, 1963, 1984).



Scheme 1.1 Concerted versus single radical mechanism of 1,3-DC reactions.

The Huisgen mechanism, in aggrement with Woodward-Hoffmann rules, combination of three p_z electrons of the 1,3-dipole/ylide and the two p_z electrons of the dipolarophile takes place suprafacially (Woodward and Hoffman, 1965, 1970).

The stereochemistry 1,3-DC reaction is a stereospecific which depends on the stereochemistry of dipolarophile that is used. When *cis*-configurated dipolarophile is used in 1,3-DC reaction, *cis*-isomer of final product will yield at the end of the reaction. For example, addition of *cis*- and *trans*-2-butene to the hypothetical 1,3 dipole **1** gives compound **3** and **5** respectively.



Scheme 1.2 Retaining the stereochemistry of dipolarophile during a concerted 1,3-DC reaction.

The stereoselectivity of 1,3-DC reaction can be interpreted in terms of interaction between FMO of 1,3-dipole and dipolarophile. Depending on the nature of the 1,3-dipole and dipolarophile, the 1,3-DC reaction is controlled either by a $LUMO_{dipolarophile} - HOMO_{dipole}$ or $LUMO_{dipole} - HOMO_{dipolarophile}$ interaction but in some cases a combination of both interactions is involved (Rispens *et al*., 1994; Sustmann, 1971, 1974; Houk *et al*., 1973). Usually, for dipolarophiles with electron withdrawing groups; the $HOMO_{dipole}$ and $LUMO_{dipolarophile}$ interaction is dominant. The reverse is true for dipolarophiles with electron releasing groups. According to the basis of the relative FMO energies between the dipole and the dipolarophile interactions, 1,3-DC reactions have been categorized by Sustman into three types (Sustmann, 1971; Sustmann, 1974).

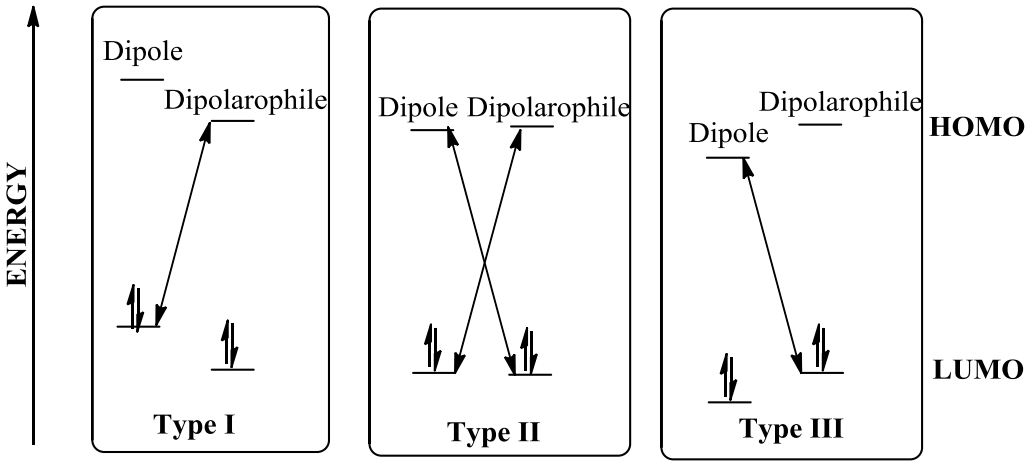
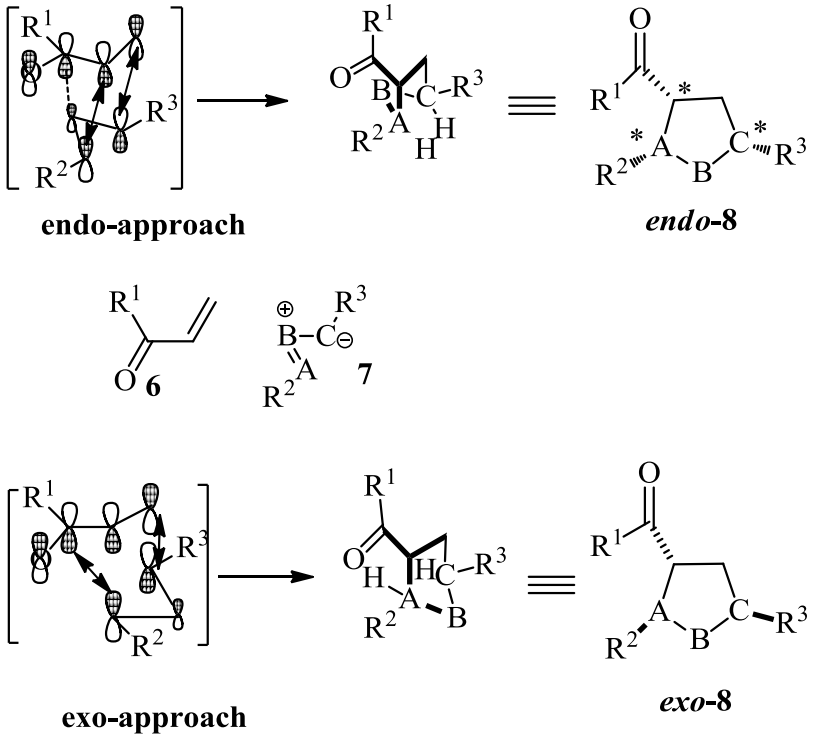


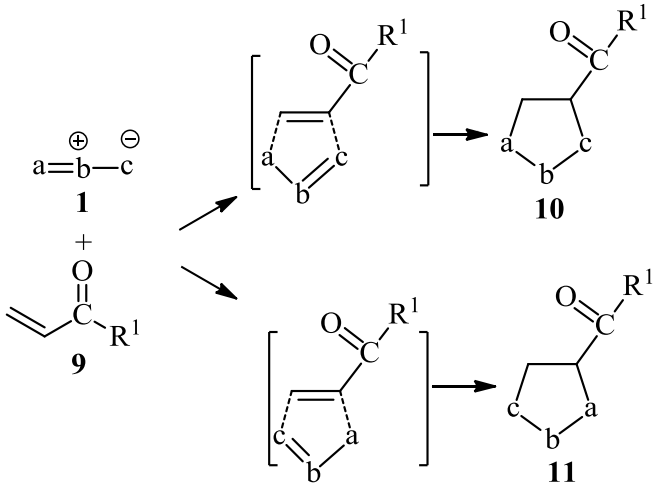
Figure 1.4 The classification of 1,3-DC reactions on the basis of the FMOs

In 1,3-DC concerted reaction, FMO energies of dipole and dipolarophile are very similar, a combination of both modes of interaction can occur, and referred as either *endo* or *exo*. Especially the reaction of allyl anion type of 1,3-dipole and dipolarophile give rise to two diastereomeric *endo/exo* cycloadducts, *endo* 8 and *exo* 8, resulting from the approaching of 1,3 dipole to dipolarophile in an *endo* or *exo* mode.



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

In addition to diastereoselectivity of 1,3-DC reactions that mentioned above, regioselectivity related ones can also arise. The regioselectivity outcome of cycloaddition reaction is dependent on the geometries of the 1,3-dipoles as well as dipolarophiles, electronic factors and the substitution pattern of the ylide and the dipolarophile. When non-symmetric 1,3-dipole and dipolarophile react to form cycloadduct, regioisomeric adducts can be formed. For example hypothetical 1,3-dipole **1** and dipolarophile **9** react each other in two different modes that can give rise to the regioisomeric cycloadducts **10** and **11**(Tufariello, 1984;Silva and Goodman, 2002;Magnuson and Pranata, 1998; DeShong *et al*., 1988).



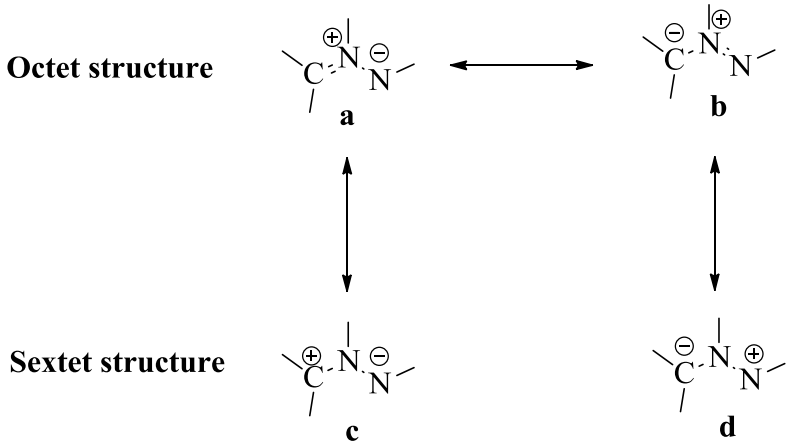
Scheme 1.4 Two alternative approaches of a hypothetical ylide to dipolarophile giving rise to regioisomers

1.2 CHAPTER 2

1.2.1 Introduction and Background of Azomethine Imines

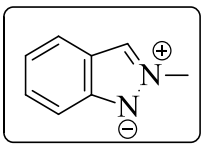
1.2.1.1 Structural Characteristic of Azomethine Imines

Azomethine imines, occasionally described as *N*-aminides, are 1,3-dipoles belonging to the class of allyl anion type 1,3-dipoles (Cordoba *et al*., 2008; Huisgen, 1976). In Scheme 1.5, **a** and **b** refers octet stabilized structures whereas **c** and **d** refers the sextet stabilized structures. Canonical form **a** is expected to be more important as a result of the higher electronegativity of nitrogen compared to carbon.



Scheme 1.5 Generel representation of azomethine imines.

2-Methylindazole **12**, which was prepared by Schad in 1893 can be considered as the first azomethine imine prepared, even though, he had not recognized it as a 1,3-dipole (Schad, 1893). Approximately 100 years later, Huisgen proposed the structure of 2-methylindazole **12** as an azomethine imine (Figure 1.5), while studying the reaction of 2-methylindazole with maleic anhydride (Huisgen, 1963).



12

Figure 1.5 Structure of 2-methylindazole **12**

1.2.1.2 Formation and Reactivity of Azomethine Imines

The reactivity and applicability of azomethine imines in organic synthesis remains largely unexplored. They can be used as a 1,3-dipole with corresponding dipolarophiles (alkene, alkyne and nucleophile) to form five and six membered heterocyclic rings (mostly; pyrazoles and pyrazolidines) (Schantl, 2008).

According to their different structural characteristics and reactivity, azomethine imines can be classified into four groups such as; *N,N'*-cyclic, *C,N'*-cyclic, *C,N,N'*-cyclic, and acyclic azomethine imines. They are shown in Figure 1.6.

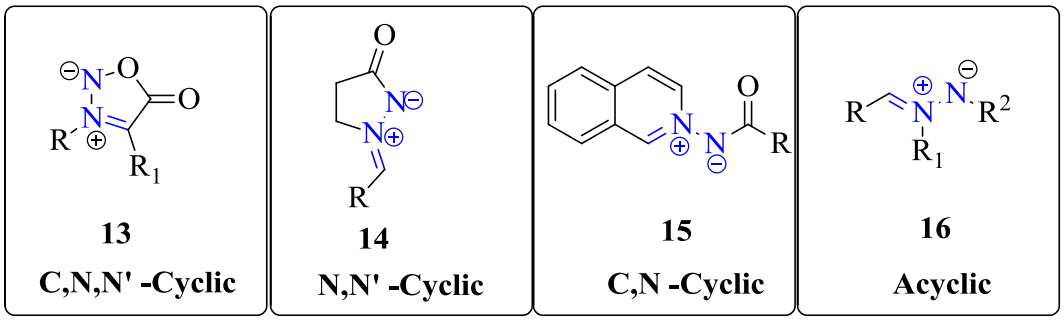
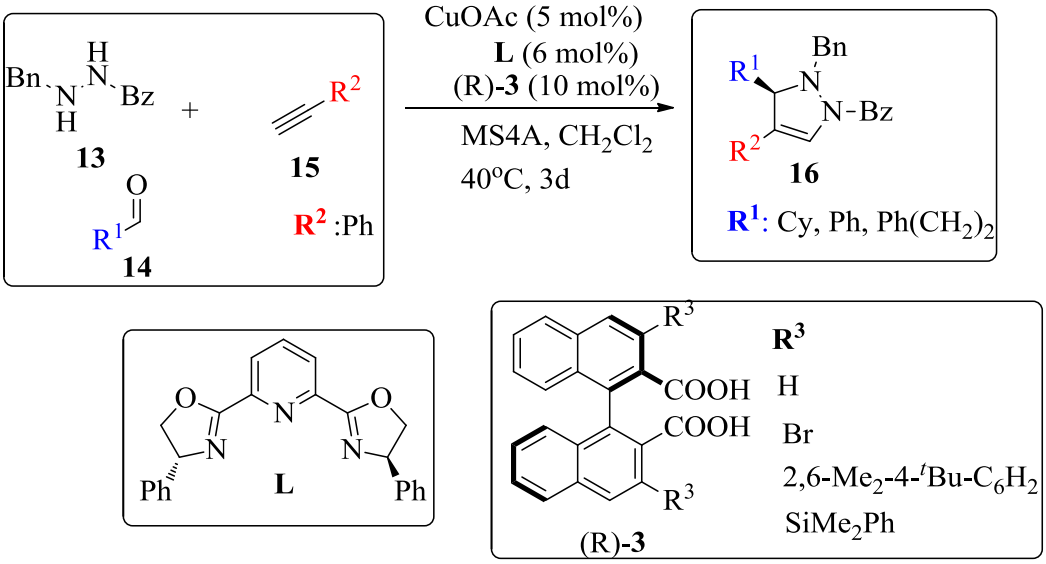


Figure 1.6 Classification of azomethine imines

1.2.1.2.1 Acyclic Azomethine Imines

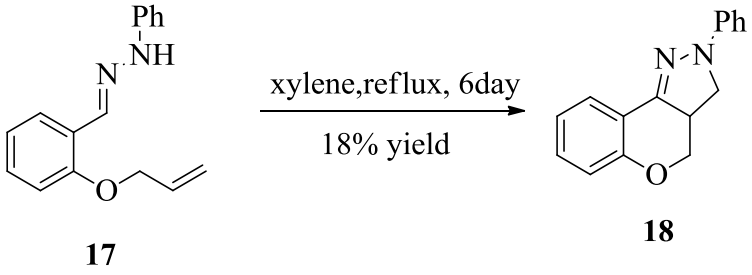
With a few exceptions, acyclic azomethine imines can not be isolated. They are generated *in situ* intermediates that are intercepted by the dipolarophile in 1,3-DC reaction to furnish cycloadducts. For example, Hashimoto *et al.*, claimed that 1,3 dipolar cycloaddition of acyclic azomethine imine derived from hydrazine **13** and corresponding aldehyde **14** with terminal alkyne **15** in the presence of Cu(I)/ pybox

and axially chiral dicarboxylic acid cocatalysts gave variety of 3,4- disubstituted pyrazolines **16** with high enantioselectivities (Hashimoto *et al*., 2013).



Scheme 1.6 Synthesis of 3,4-disubstituted pyrazolines

In addition, Grigg and coworkers reported an intramolecular acyclic azomethine imine cycloaddition reaction. Starting compound **17** that have both hydrazone and dipolarophile unit was heated to afford pyrazole derivatives **18** in low yield (Grigg *et al*., 1987).

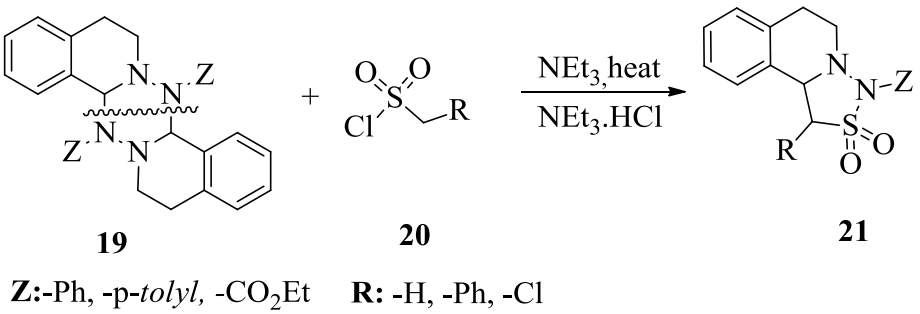


Scheme 1.7 Formation of fused tricyclic compound **18**

1.2.1.2.2 *C,N*-Cyclic Azomethine Imines

C,N-cyclic azomethine imines that bears carbon atoms and a nitrogen atom in a ring is the second group of azomethine imines. There are few studies concerning generation methods and synthetic applications of this type of azomethine imines. One of the convenient and effective method for the preparation of *in situ* generated

C,N-cyclic azomethine imines is the thermal dissociation of dimers of the hexahydrotetrazine derivatives **19.** As it exemplified in Scheme 1.8, *in situ* generated *C,N*-cyclic azomethine imines derived from hexahydrotetrazine derivatives **19** reacted with substituted sulfenes **20** in the presence of triethylamine leading cycloadducts in moderate to good yield **(**Truce and Allison, 1975).

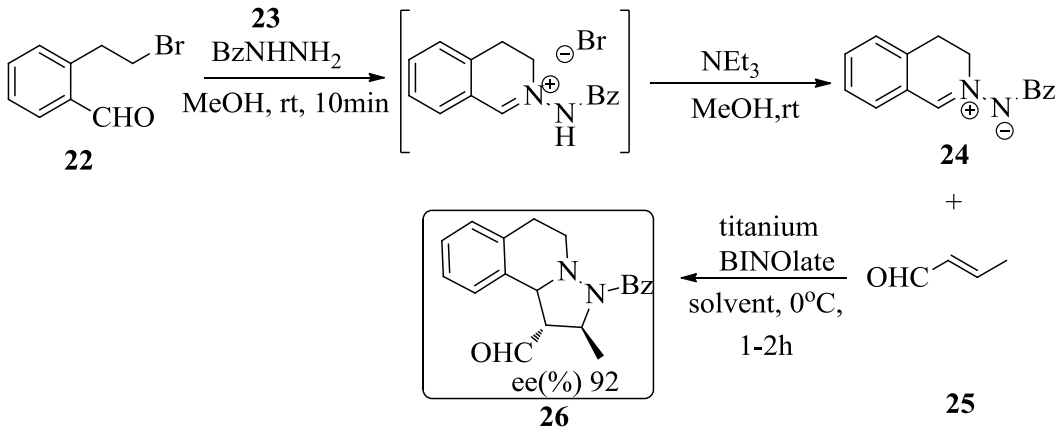


19 **20** **21**

Z:-Ph, -p-*tolyl,* -CO_2Et **R:** -H, -Ph, -Cl

Scheme 1.8 1,3-DC reaction of substituted sulfenes with hexahydrotetrazine derivatives

Another example of alternative generation method was suggested by Hashimoto *et al*. They reported the synthesis of metastable *C,N*-cyclic azomethine imine (*N*-Benzoylimino-3,4-dihydroisoquinolinium betaine **24**) that could be obtained by the reaction of corresponding 2-(2-bromoethyl)benzaldehyde **22** with benzoylhydrazine **23** in basic medium. Afterwards, *N*-Benzoylimino-3,4-dihydroisoquinolinium betaine **24** was treated with crotonaldehyde **25** in the presence of titanium-BINOLate complexes as a catalyst gave the cycloadduct **26** in 94% yield with excellent enantio- and diastereoselectivity (Hashimoto *et al*., 2010).

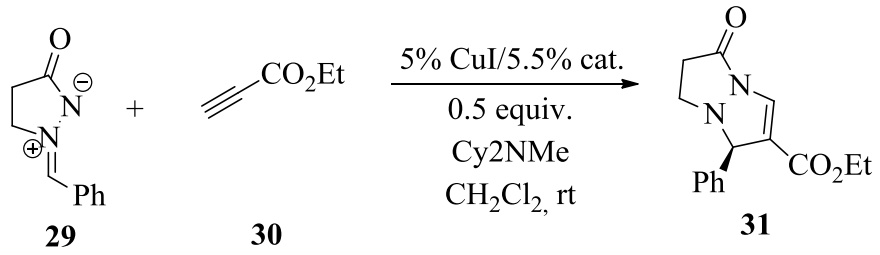


22 **24** **25** **26**

Scheme 1.9 Reaction of metastable *C,N*-cyclic azomethine imine with crotonaldehyde

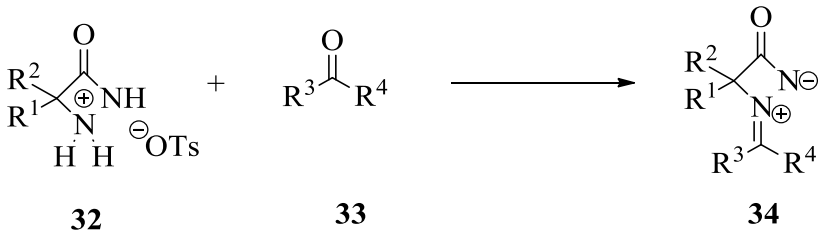
1.2.1.2.3 *N,N*-Cyclic Azomethine Imines

N,N-Cyclic azomethine imines are the third group of azomethine imines that comprise both nitrogen atoms in a ring. In 1968, Dorn and Otto established the preparation of room temperature stable 3-oxopyrazolidin-1-ium-2-ides **29** derived from the reaction of pyrazolidin-3-one with an aldehyde (Dorn and Otto, 1968a;Dorn and Otto, 1968b).Shintani and Fu (2003) studied the reaction of 3-oxopyrazolidin-1-ium-2-ides **29** with ethyl propiolate **30** which takes place at room temperature in the absence of copper catalyst, apparently none of the expected cycloadduct was produced. In contrast, desired 1,3-dipolar cycloaddition reaction proceeded by using 5% CuI succesfully, affording the title cycloadduct as a single regioisomer **31**.



Scheme 1.10 Copper catalyst [3+2] cycloaddition of 3-oxopyrazolidin-1-ium-2-ides **29** with ethyl propiolate **30**

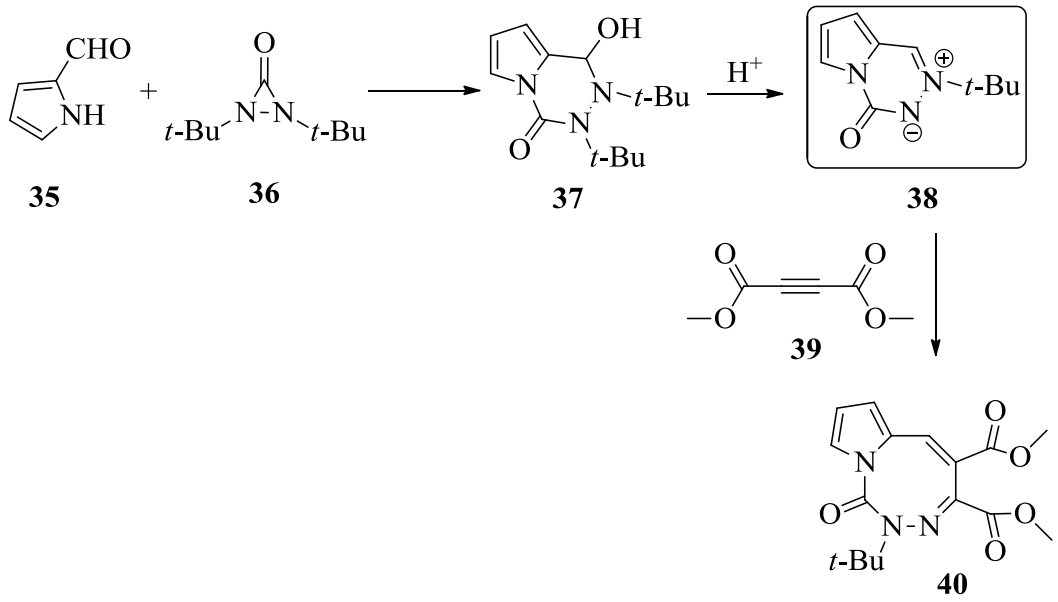
In addition to the study mentioned above, generation of *N,N*-cyclic azomethine imine bearing both two nitrogen in a four membered ring was discussed by Taylor and co-workers (1983). They have attempted the synthesis of 3-oxo-l,2-diazetidinium ylides **34** that are available through condensation of carbonyl compounds with 3-oxo-1,2-diazetidinium tosylates **32**.



Scheme 1.11 Formation of 3-oxo-l,2-diazetidinium ylides **34**

1.2.1.2.4 *C,N,N*-Cyclic Azomethine Imines

There are few examples of azomethine imines with all three atoms incorporated in the ring, such as 2-tert-buthylpyrrolo[1,2-*d*][1,2,4] triazinium-4-olate **38** which is an example of this type of azomethine imine, synthesized by the thermolysis of a ring expansion of a diaziridinone **36** with 2-pyrrolecarboxyaldehyde **35**. Followed its cycloaddition reaction carried out with an electron deficient alkyne (DMAD **39**) yielding a fused ring-enlarged compound, a triazochinone derivative **40** (Scheme 1.12) (Komatsu *et al.*, 1993).



Scheme 1.12 Synthesis and cycloaddition of 2-tert-buthylpyrrolo[1,2-*d*] [1,2,4] triazinium-4-olate

The most substantial example of this type of azomethine imine is sydnones (Figure 1.7). Detailed information about sydnones will be given in next chapter.

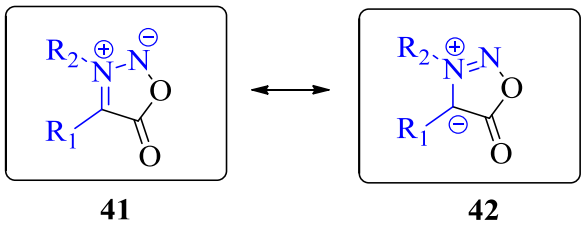


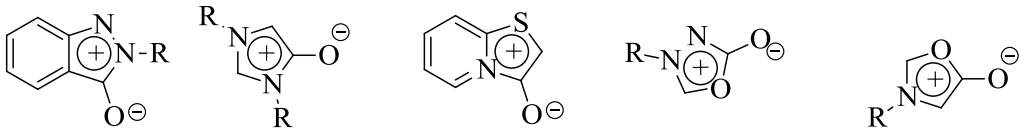
Figure 1.7 The structure of sydnones **41** and **42**.

1.3 CHAPTER 3

1.3.1 Introduction and Background of Sydnones and Synthesis of Pyrazoles, Pyrazolines

1.3.1.1 Introduction and History of Sydnones

Sydnone are unique, dipolar, heteroaromatic member of the general class of mesoionic compound. A number of five membered ionic heterocycles, with unusual structural features, have been recognised as members of a vast family of nonbenzenoid heterocycles, known as the mesoionic compounds. According to the original definition, the term mesoionic was defined as: "*A five or six-membered heterocycle which cannot be represented satisfactorily by any one covalent or polar structure and possesses a sextet of electrons in association with the atoms comprising heterocyclic ring*" (Baker *et al*., 1949, p.309). These heterocycles enclose two or more heteroatoms with an exocyclic heteroatom (sulfur, oxygen, nitrogen). The core of these heterocycles are generally related with the naturally occuring heterocyclic rings such as pyrazole, imidazole, thiazole, oxazole, oxadiazole.



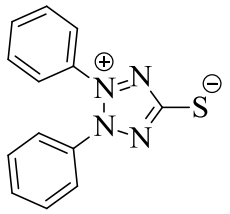
pyrazole **imidazole** **thiazole** **oxadiazole** **oxazole**

43 **44** **45** **46** **47**

Figure 1.8 Examples of some mesoionic compounds

But the term mesoionic has been restricted to the five-membered heterocycles and the definition of mesoionic heterocycle has been modified as: "*A five-membered heterocycle which cannot be represented satisfactorily by any one covalent or polar structure and possesses a sextet of electrons in association with the five atoms comprising the ring*."(Baker *et al*., 1949, p.309).

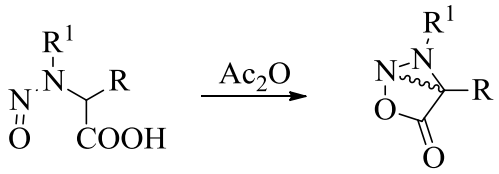
Mesoionic heterocycles have been known for more than 100 years, since the first mesoionic compound, tetrazoliumthiolate **48**, was unknowingly prepared by Fischer as early as 1882 (Figure 1.9) (Fischer and Besthorn, 1882; Busch, 1895; Busch and Best, 1899; Busch, 1905; Busch and Mehrtens, 1905).



48

Figure 1.9 First synthesized mesoionic compound **48**

Approximately 50 years later from the discovery of first mesoionic heterocycle, sydnones were synthesized by Earl and Mackney in Sydney, Australia in 1935. They proposed the fused ring structure **50** by treating *N*-nitroso-*N*-phenyl glycine **49** with acetic anhydride at room temperature (Earl and Mackney, 1935).



49 **50**

Scheme 1.13 Synthesis of sydnone **50**

The name of sydnone, 1,2,3-oxadiazole-5-one, comes from the combination of terms "**Sydn**ey"which refers the University of Sydney, where the sydnone was discovered for the first time and"Lact**one**".

In 1949, Baker *et al*. claimed that the proposed fused structure **50** for sydnones was incorrrect. Actually, the structure of sydnones must be monocyclic mesoionic heterocycle which has a resonance hybrid of a number of dipolar and tetrapolar ionic structures (Baker *et al*., 1946). Then, Simpson suggested the term, mesoionic, (mesomeric + ionic) and the representative symbol "±" for the first time in order to designate these type of heterocycles (Simpson, 1946). In this respect, representative sydnone derivative carrying "±" designation is shown in Figure 1.10

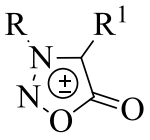


Figure 1.10 Designation of sydnone derivative

In 1950s, mesoionic compounds have undergone extensive changes and modifications due to the fact that many alternate representations of sydnone structures were proposed by many scientist such as Baker (1946; 1950), Earl (1935), Bieber (1958), Katritzky (1955) are depicted in Figure 1.11.

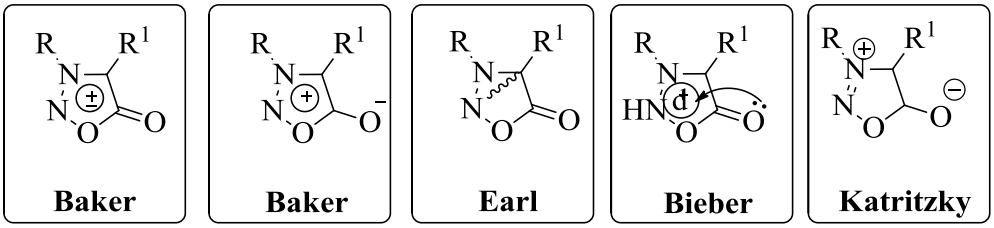


Figure 1.11 Alternate representations of sydnone structures

It is not possible to write a covalent structure for sydnones without separating the positive and negative charges. The resonance in sydnone can be figured out by structures as in Figure 1.12 (Badami, 2006).

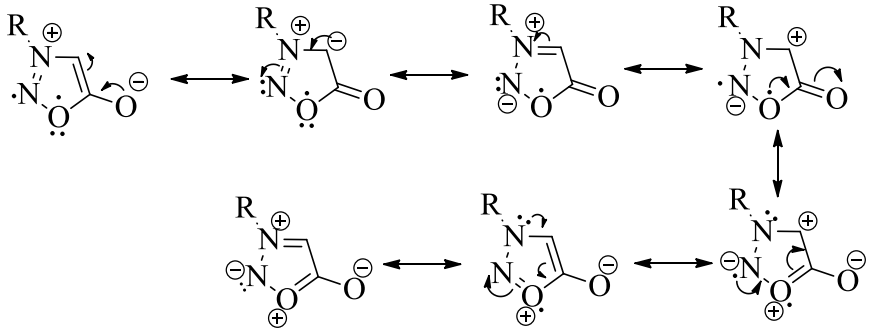


Figure 1.12 Resonance in sydnone

The aromaticity of the sydnone ring is explained by the classical sextet theory. Total of seven $2p_z$ electrons are contributed by the five atoms of the ring with one $2p_z$ electron on the exocyclic atom. A sextet of electrons will be obtained when one of the seven $2p_z$ electrons is paired with the single electron on the exocyclic atom. The circle indicates the delocalization of six electrons which is detected as ring current by ^{1}H-NMR spectroscopy. This polarization of charges is evidenced by large

dipole moments (4-6 D) for the mesoionic rings. The ring will be positively charged, balanced by the negative charge present on the exocyclic atom.

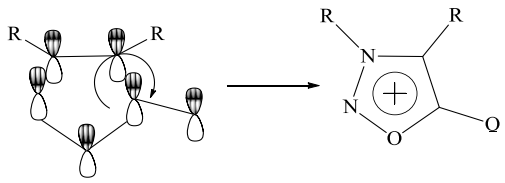
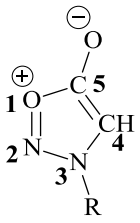


Figure 1.13 Overlap of p-orbitals in sydnone ring.

Numbering of the atoms in sydnone ring is important to discuss the reactivity of sydnones. General representative structure for sydnone numbering is shown in Figure 1.14.



51

Figure 1.14 General representative structure for sydnone numbering

Calculations and theoretical studies on sydnone reactivity showed that C-4 position of the ring has both nucleophilic and acidic character. The pKa value of C-4 hydrogen is approximately 18-20. Moreover N-3 position of the ring is comperatively electron poor and attachment of aromatic ring on N-3 reduces the participating in electrophilic substitution reaction (Tin-Lok *et al*., 1964; Fan *et al*., 1993).

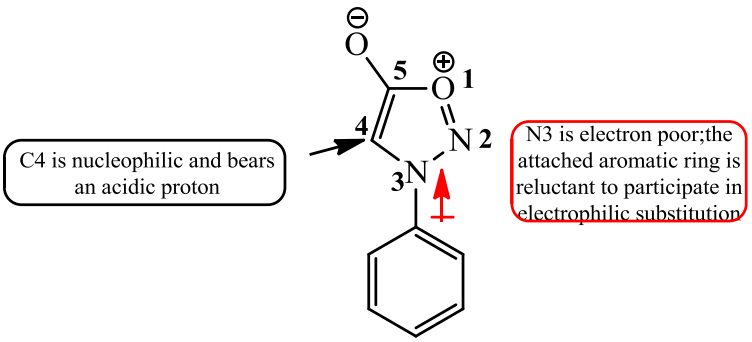
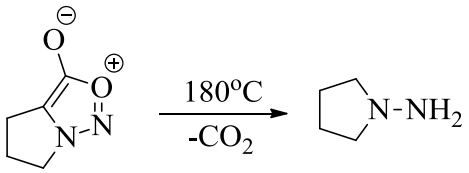


Figure 1.15 General reactivity profile of sydnone

Sydnones having aryl substituent on the ring are generally stable compounds and can be isolated as solids which usually have low melting points. Although they can be easily dissolved in polar solvents, solubility is too low in nonpolar solvents such as hexane and ether. In water they are generally insoluble but their solubility is enhanced when a polar functional group is present within the molecule. Sydnones can be stored at room temperature but the effect of heat, acid and light may cause the degredation of sydnones in some cases.

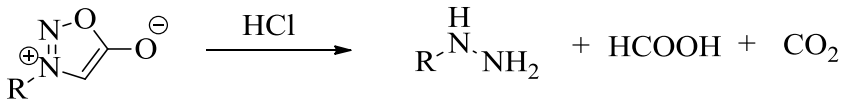
Nikitenko *et al*. (2006) studied the analysis of decomposition reaction for fused sydnone **52** into the formation of pyrrolidinehydrazine **53** at high temperatures (180 ^{o}C).



52 **53**

Scheme 1.14 Heat degredation of sydnone

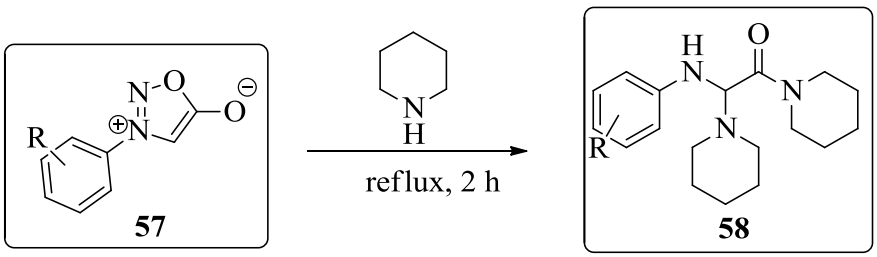
A concentrated HCl also cause degredation of sydnones. Staley and co-worker (1964) reported the hydrolysis of 3-arylsydnones **51** in the presence of concentrated HCl acid to yield the hydrazine drivatives **54** with the loss of CO_2.



51 **54** **55** **56**

Scheme 1.15 Acid hydrolysis of 3-arylsydnones

Another sydnone degredation was discovered by Puranick and Suschitzky (1967). A variety of *N*-substituted C-4 bromosydnones were treated with piperidine to afford corresponding glycyl amides in moderate to good yields.

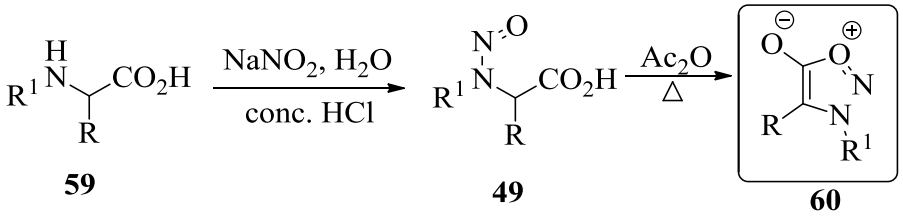


8 examples, 33 - 75%
R= MeO, NO_2, pyridyl, quinolyl

Scheme 1.16 Degredation of sydnones with piperidine.

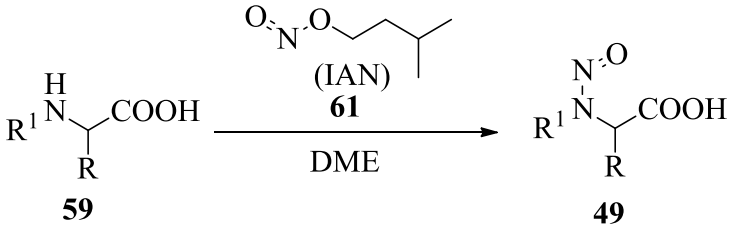
1.3.1.2 Generation of Sydnones

Classic method for preparation of sydnones have accomplished by Earl and Mackney (1935). The method covers the nitrosation reaction of *N*-substituted amino acids **59** followed by cyclodehydration reaction to give mesoionic products **60** in good to excellent yields.



Scheme 1.17 Classic method for sydnone preparation

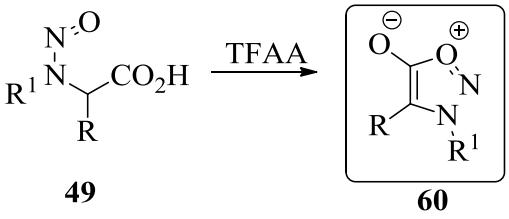
Applegate and Turnbull (1988) suggested a new method for the nitrosation of acid sensitive amino acids **59** by using IAN **61**.



Scheme 1.18 Alternate nitrosation of substituted aminoacids.

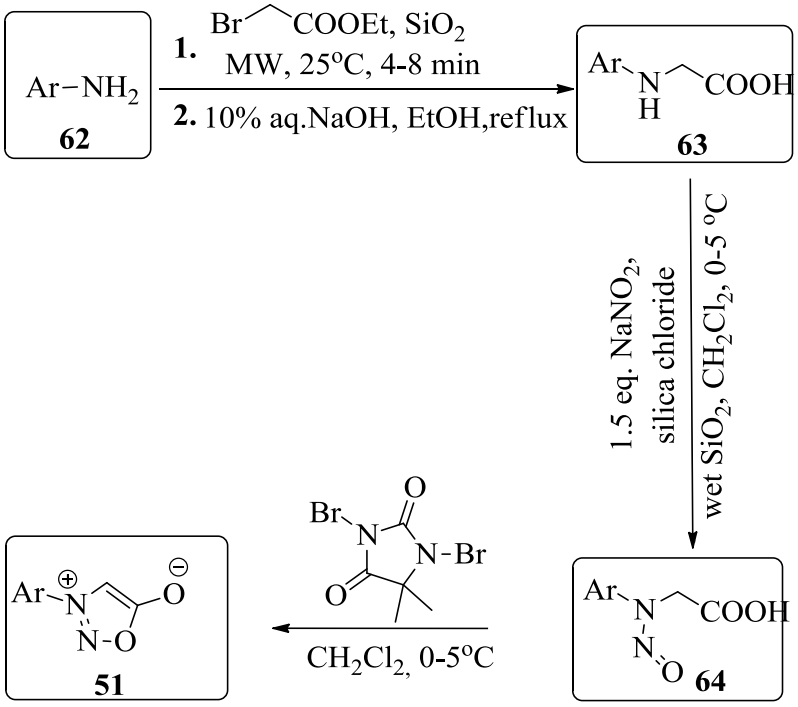
There are also various methods to synthesize sydnones such as the usage of trifluoroacetic acid, treatment with phosphorus pentoxide and heating in acetic

anhydride. Among them, the cyclization of *N*-nitroso glycines with trifluoroacetic acid is the more efficient and widely used one for the preparation of sydnone derivatives (Baker *et al*., 1950).



Scheme 1.19 Effective method for preparation of sydnones

A new synthetic route for the preperation of 3-arylsydnone derivatives has been suggested by Azarifar *at el*. The method covers the microwave assisted synthesis of aryl substituted aminoacids **63**, followed nitrosation reaction in the presence of SiO_2 as a catalyst then treatment nitrosoamino acid derivative **64** with dibromodimethyl hydantoin to get title aryl sydnones **51**. The proposed reaction mechanism involving formation of aryl sydnones by using dibromodimethyl hydantoin is shown in Figure 1.16 (Azarifar *et al*., 2006).



Scheme 1.20 A new methodology for generation of 3-arylsydnone derivatives

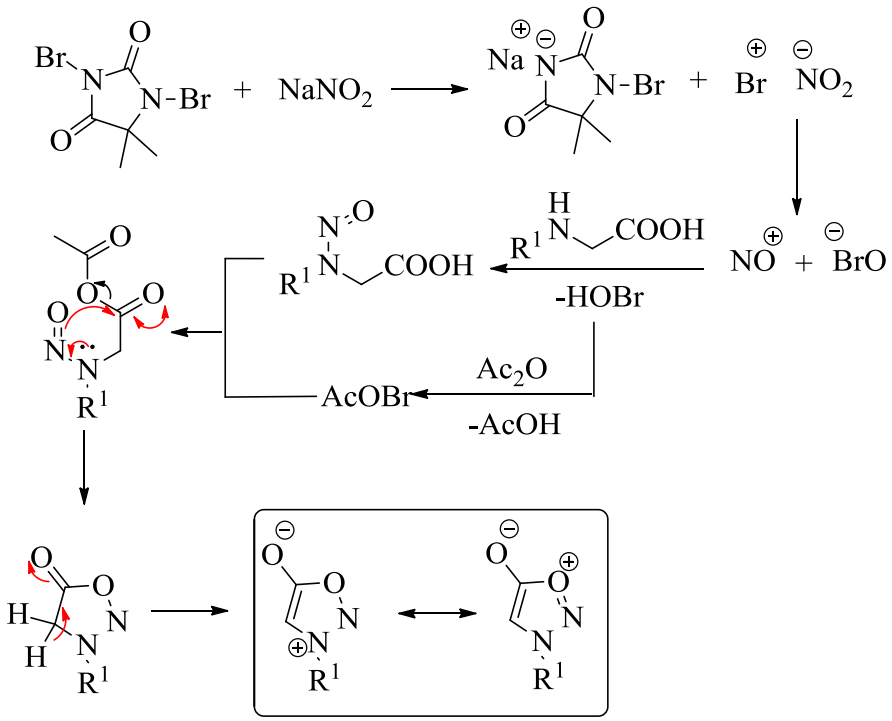


Figure 1.16 Proposed reaction mechanism for preperation of aryl sydnones with dibromodimethyl hydantoin

1.3.1.3 Reactions of Sydnones

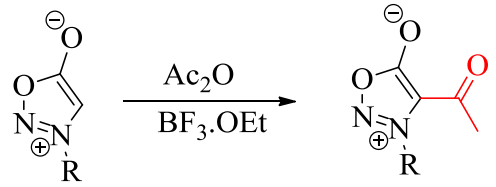
Sydnones have both aromatic and dipolar part in their nature. The ability of sydnone to undergo electrophilic substitution reaction and 1,3-DC reactions (cyclic *C*,*N*,*N*-azomethine imine) shows its aromatic and dipolar nature respectively.

1.3.1.3.1 Electrophilic Aromatic Substitution Reactions.

Nucleophilic character of C-4 position of the sydnone ring give rise to variety of electrophilic aromatic substitution reactions such as acylation, halogenation, nitration and sulfonation.

1.3.1.3.1.1 Acylation

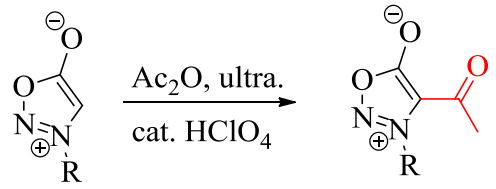
Acylation reaction of C-4 position of sydnone ring was performed firstly by Yashunskii *et al*. (1959) who reported the treatment of 3-substitutedsydnone with acetic anhydride in the presence of boron trifluoride etherate gave 4-acetyl derivative of sydnones **65**.



51 **65**

Scheme 1.21 Acylation of sydnones

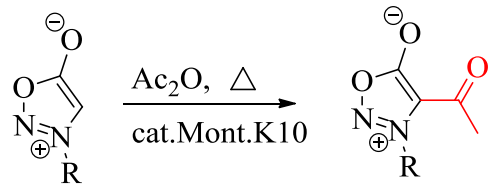
Later, alternative methods have been developed for acylation of 3-substituted sydnones. Tien and co-workers succeed the acylation of sydnones in ultrasonic medium by using acetic anhydride and catalytic amount of perchloric acid. Ultrasonification usage in this method brings some advantages such as lowering the equivalent of perchloric acid in the reaction medium and also providing safe environment for the reaction (Tien *et al*., 1992).



51 **65**

Scheme 1.22 Acylation of sydnones in ultrasonic medium

Another method for acylation of 3-substituted sydnones has been carried out by Turnbull and George (1996). In this method, acylated sydnones **65** were obtained via the reaction of 3-substituted sydnones with acetic anhydride in the presence of Montmorillonite K10 as a catalyst at elevated temperatures.



51 **65**

Scheme 1.23 Acylation of sydnones by using Montmorillonite K10 as a catalyst

1.3.1.3.1.2 Halogenation

A range of halogenation methods have been developed for the introduction of halogens into C-4 position of a sydnone. Methods of halogenation reactions are shown in Figure 1.17. 4-chloro substituted sydnone species **66** has been achieved by treatment chlorine with sydnone derivative (Nakahara and Ohta, 1956; Greco and Mehta, 1979), using potassium chlorate in dilute HCl (Earl, 1956), dichloroiodobenzene with triethylamine (Ito and Turnbull, 1996) and *N*-chlorosuccimide in DMF (Tien *et al*., 1985). Also, in order to get C-4 brominated *N*-aryl sydnones **67**, various methods have been used such as potassium bromate in HBr, bromine and *N*-bromosuccinamate (Azarifar and Ghasemnejad-Borsa, 2006; Turnbull, 1985; Kato and Ohta, 1962; Turnbull and Krein, 1997). There have been relatively few studies on the synthesis of iodosubstituted sydnones. Dumitrascu *et al*. reported the direct iodination of C-4 position of aryl sydnones using iodomonochloride in the presence of acetic acid and sodium acetate (Dumitrascu *et al.*, 2002; 1997).

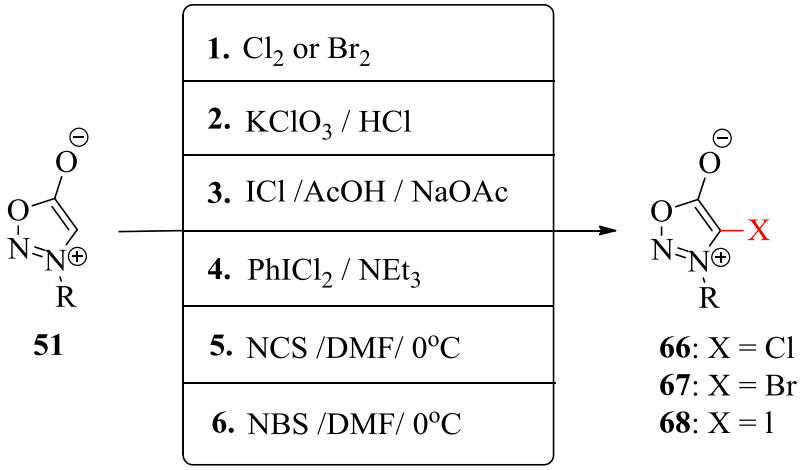
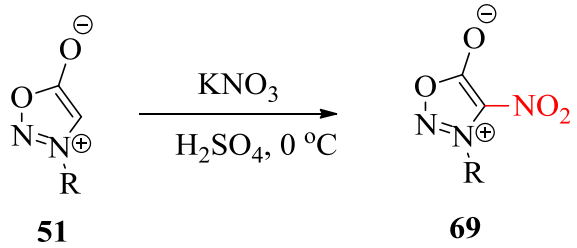


Figure 1.17 Various halogenation methods on C-4 position of 3-aryl sydnones

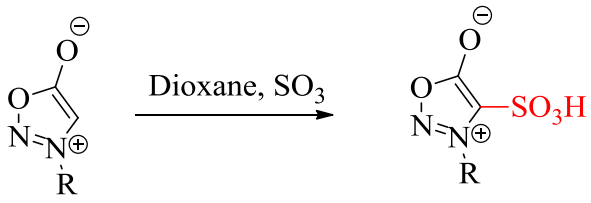
1.3.1.3.1.3 Nitration and Sulfonation

Synthesis of 4-nitro-3-aryl sydnones has been achieved by treating 3-aryl sydnones with potassium nitrate in the presence of concentrated sulfuric acid at 0 °C (Weintraub and Bambury, 1969).



Scheme 1.24 Nitration of 3-aryl sydnones

In 1959, Yashunskii and co-workers sulfonated the C-4 position of 3-aryl sydnones succesfully as a result of using dioxane-sulfur trioxide complex (SO_3) in CH_2Cl_2 at 20°C to 40°C (Yashunskii *et al*., 1959).



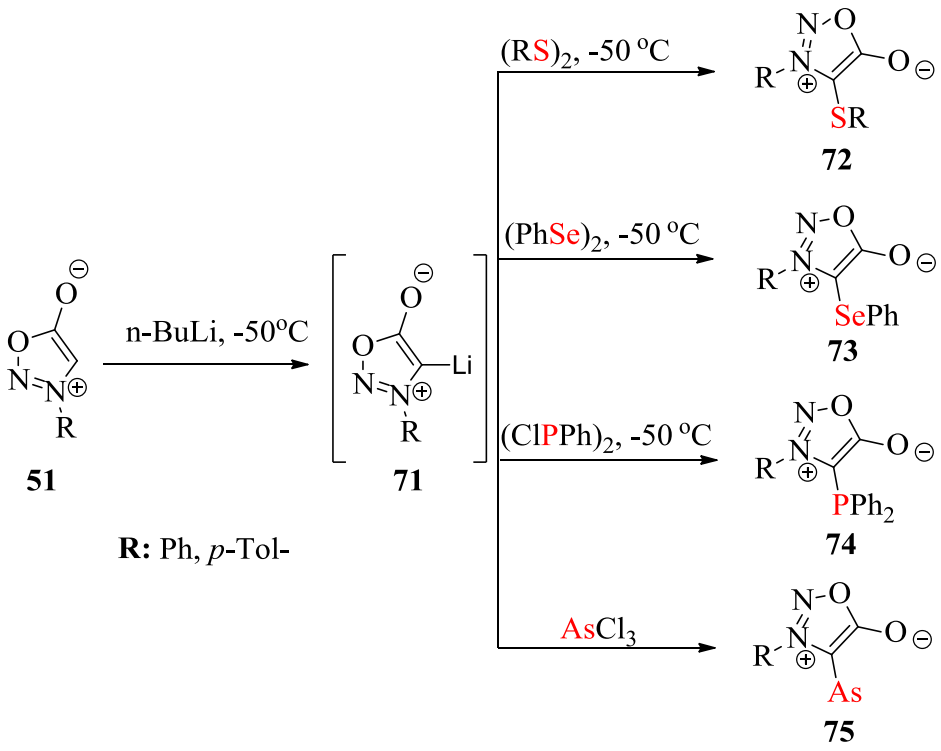
51 **70**

R: 4-OMe, 4-OEt-C_6H_4-

Scheme 1.25 Sulfonation of 3-aryl sydnones

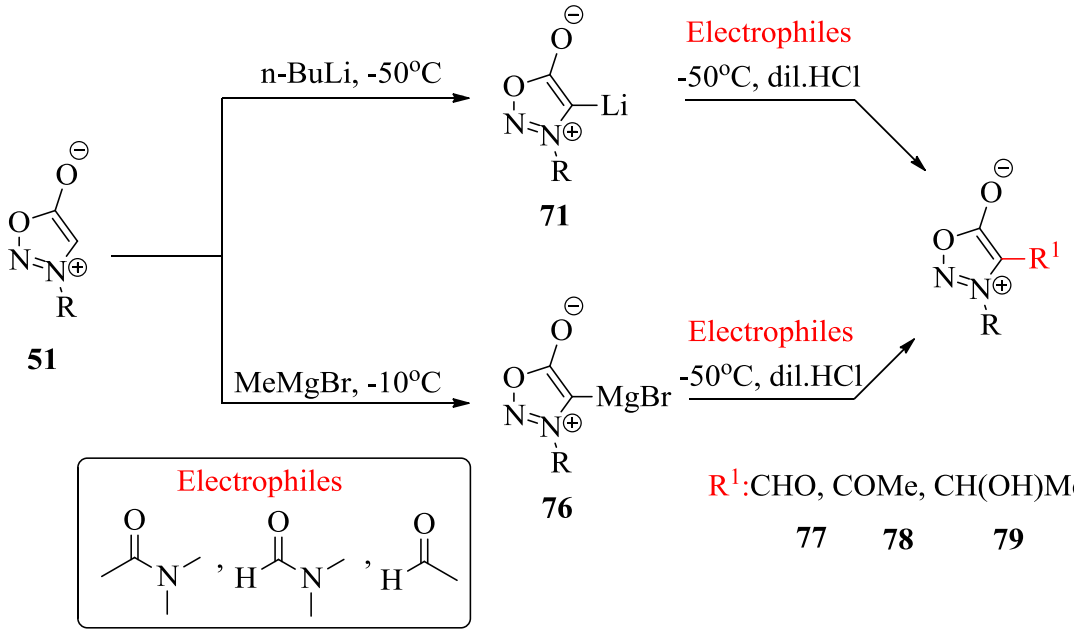
1.3.1.3.1.4 Metallation of Sydnones

Metallation at the C-4 position of sydnone derivatives and its substitution reactions have vital importance on sydnone chemistry. Many metal complexes have been prepared containing 4-lithio, 4-cupro, 4-chloromercurio, 4-seleno, 4-arseno and 4-palladium (0) derivatives in a same manner. Deprotonation of C-4 hydrogen with n-BuLi afforded compound **71**, followed by the addition of corresponding metal complexes gave the metalated sydnone derivatives. However the metalation reaction trial was not succesful with tin, antimony and tellurium metals (Kalinin *et al*., 1989; 1990).



Scheme 1.26 Metallation of sydnone derivatives

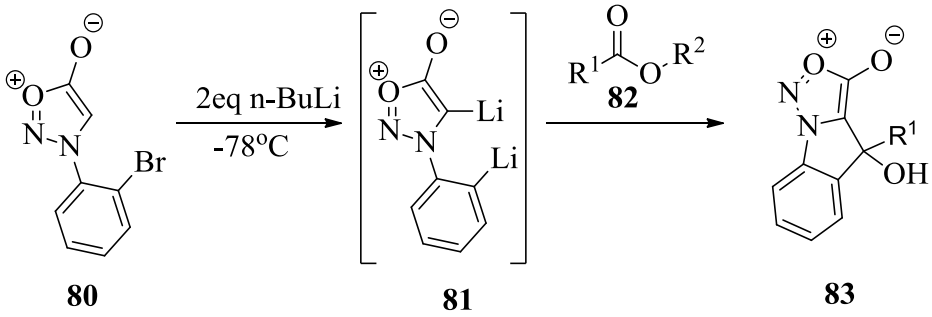
Tien *et al*. (1992) reported a similar protocol that differs only introduction of carboxy groups at the C-4 position of sydnones instead of metal species. In the same study, they also mentioned about the generation of negatively charge intermediate sydnones **76** by using methyl magnesium bromide.



Scheme 1.27 Carboxylation of C-4 position of sydnone

In continuation of lithiation chemistry of sydnones, treatment of double lithiated 3-(2-bromophenyl)sydnone **81** with subsequent ester derivatives yield fused tricyclic sydnones **83** in good yields (Turnbull and Krein, 1997).

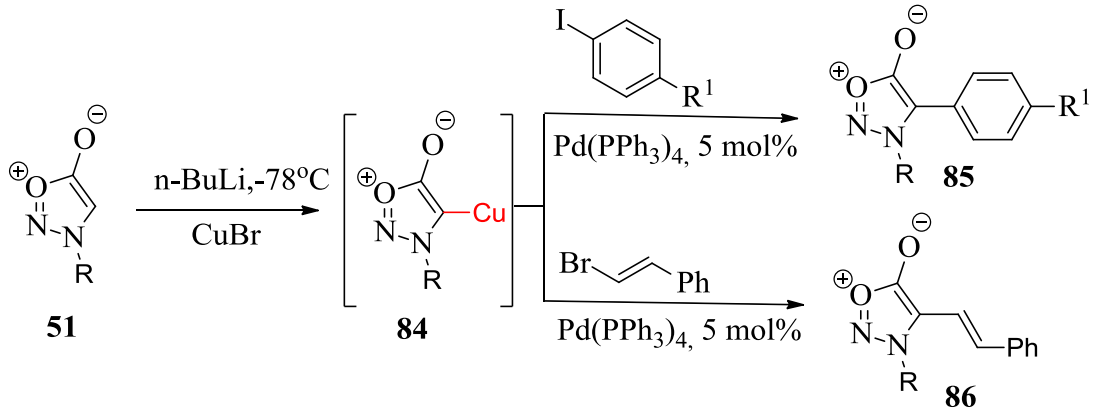
Table 1.1 Synthetic methodology of fused tricyclic sydnones



80 **81** **83**

R^1	R^2	Yield(%)	R^1	R^2	Yield(%)
H	Et	0	^{t}Bu	Me	95
Me	Et	71	Bn	Et	80
Et	Et	76	Ph	Et	86
^{i}Pr	Me	93			

Kalinin and Min (1988) described the transmetalation of lithiated sydnone to the corresponding organocopper reagents. The intermediate sydnonylcopper **84** was then shown to efficiently undergo palladium-mediated coupling processes with aryl and alkenyl halides in good yields.



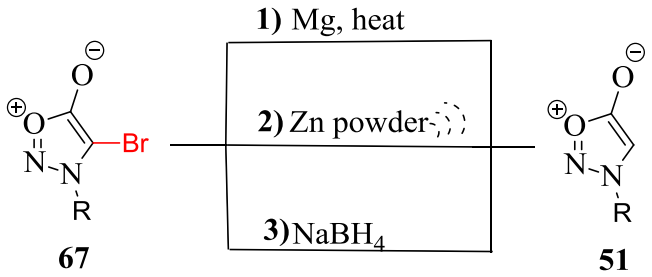
51 **84** **85** **86**

Scheme 1.28 Palladium mediated coupling reaction of sydnone with aryl and alkyl halides

1.3.1.3.2 Modification of Sydnones at C-4 position

1.3.1.3.2.1 Modification of C-4 halogenated Sydnones

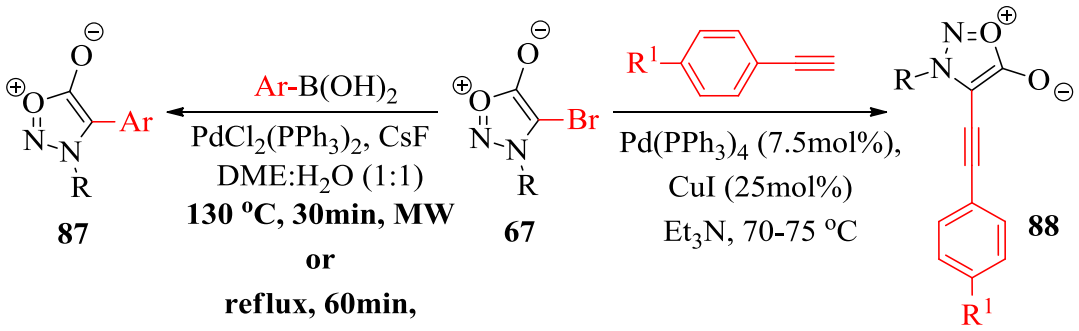
Various methods have been found for the removal of the halogen atom on the C-4 position of 3-aryl sydnone. Debromination from C-4 position takes place in many ways such as heating bromonated *N*-aryl sydnones in the presence of magnesium metal, treatment with sodium borohydride and zinc mediated ultrasonification process. All these methods give rise to unsubstituted parent sydnone (Tien *et al*., 1992; Kato and Ohta, 1962; Turnbull, 1986).



67 51

Scheme 1.29 Debromination of *N*-arylsydnones

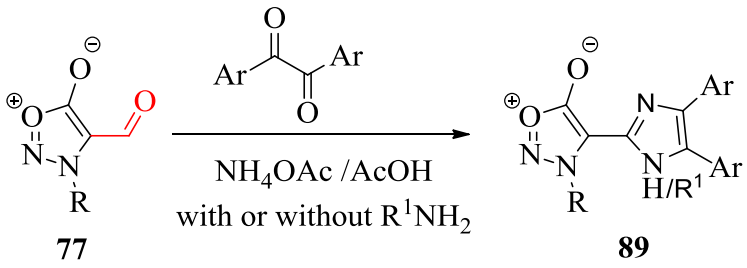
C-4-bromo-*N*-phenylsydnones **67** allows the Sonogashira and Suzuki-Miyaura cross coupling reaction that furnish alknyl and aryl substituted *N*-arylsydnones respectively. In the first method, palladium catalyzed Sonogashira coupling of bromo sydnones afforded title alkyne substituted *N*-phenylsydnones **88** (Turnbull *et al*., 2003). In the second one, the variety of boron containing substrates coupled with C-4-bromo-*N*-phenylsydnones **67** in the presence of palladium complex as a catalyst yielding aryl substituted *N*-arylsydnones under microwave or classical method (Browne *et al*., 2009).



Scheme 1.30 Coupling reactions of C-4-bromo-*N*-phenylsydnones **67**

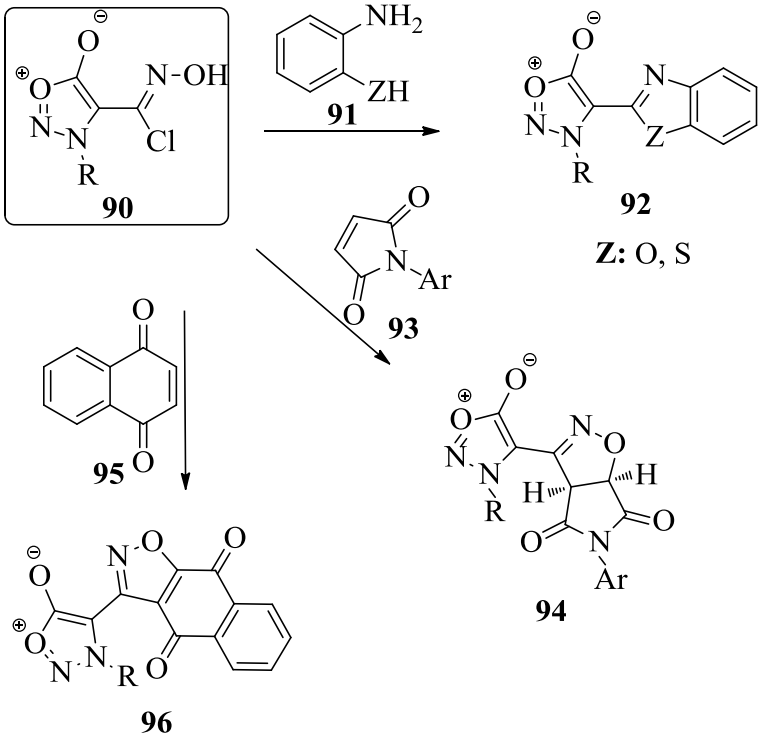
1.3.1.3.2.2 Modification of C-4 carbonyl sydnones

Shih (2002) reported the synthesis of imidazolyl-substituted sydnones by treating the 4-formyl sydnones with aromatic glyoxals in the presence of sodium acetate and acetic acid.



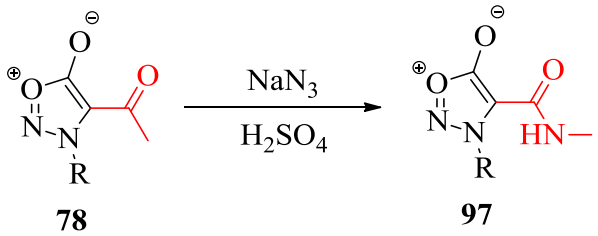
Scheme 1.31 Synthesis of imidazoyl substituted sydnones

The same group has also succeeded the conversion of the C-4 aldehyde into a chloroxime which can be used as a precursor of nitrile oxide to undergo cycloaddition and nucleophilic substitution reaction respectively (Shih, 2002).



Scheme 1.32 1,3-DC and nucleophilic substitution reactions of chloro oxime substituted sydnones

An application of Schmidt reaction on C-4 acetylated sydnones has been studied by Yeh *et al*. (1983). The treatment of sodium azide and sulfuric acid with the range of sydnones afforded variety of sydnonyl- methylamides.

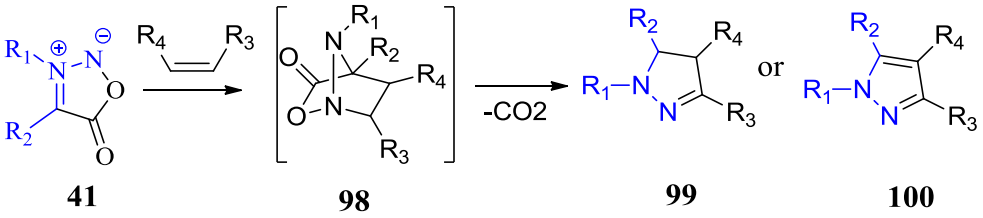


Scheme 1.33 Example of application of Schmidt reaction on C-4 acetylated sydnones

1.3.1.3.3 Sydnone Cycloaddition

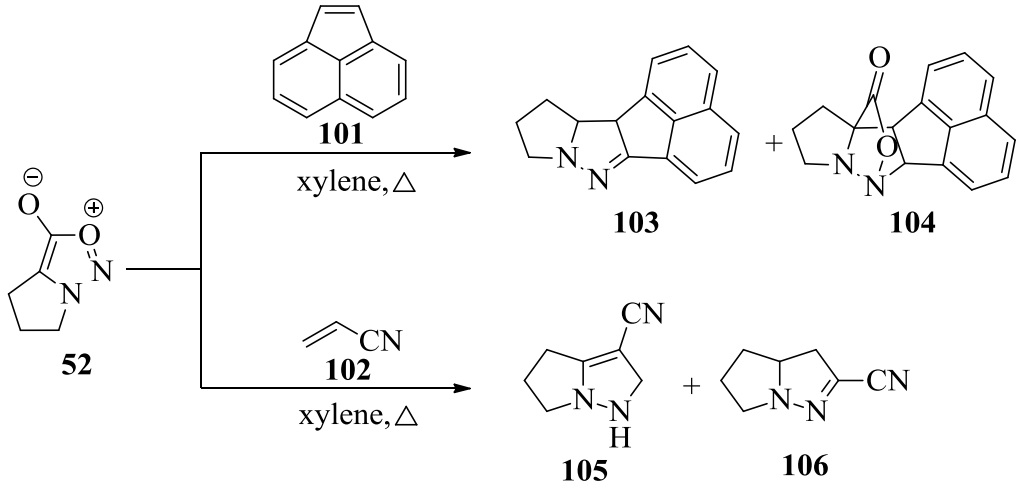
1.3.1.3.3.1 Alkene Cycloaddition

The 1,3-DC reaction of sydnones to alkenes has been known for over 40 years. Huisgen (1962) reported such cycloaddition reactions with alkenes to get corresponding pyrazole and pyrazoline derivatives. After these early findings about sydnone cycloaddition chemistry, modification of these reactions have been widen by many scientists. The general cycloaddition reaction process for sydnones involves generation of dipole (azomethine imine) by the evolution of CO_2 through alkene or alkyne to construct pyrazoline **99** and pyrazole **100** containing heterocycles. Representative cycloaddition reaction of sydnone with alkene is exemplified in Scheme 1.34.



Scheme 1.34 Representation of sydnone cycloaddition with alkenes

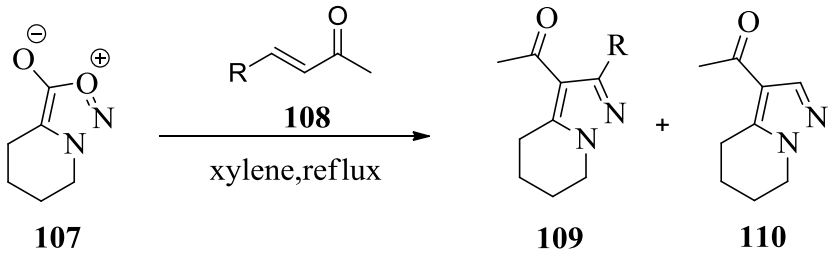
Ranganathan carried out the cycloaddition reaction of acenaphthylene **101** with the bicyclic sydnone **52** yielded the expected polycyclic pyrazoline **103** and cycloadduct **104** that fail to undergo evolution of CO_2. Followed, second dipolarophile, acrylonitrile **102** was used as an extension of this study that undergoes cycloaddition reaction with the same bicyclic sydnone **52** to provide corresponding pyrazolines **105** and **106** with the loss of regiocontrol (Ranganathan and Bamezai, 1983).



Scheme 1.35 Cyloaddition reaction of bicylic sydnone **52** and acenaphthylene **101** and acrylonitrile **102**

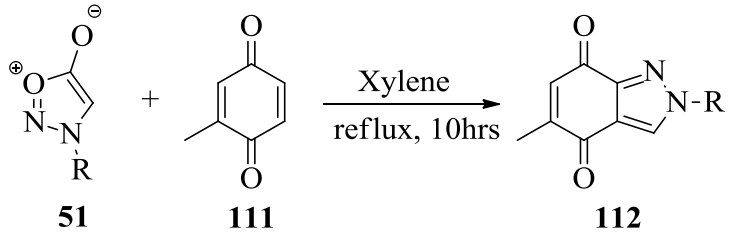
Further investigation regarding cycloaddition of bicyclic sydnones **107** and *β*-substituted enones **108** has been reported by Larsen. Expected pyrazole **109** and dealkylated pyrazole **110** were obtained at the end of the cycloaddition process. Enones bearing only alkyl groups favoured the dealkylated pyrazole however existence of aryl group on enones gave no expected cycloadduct (Larsen and Martinborough, 1989).

Table 1.2 Cycloaddition reaction of bicyclic sydnone **107** with *β*-substituted enones



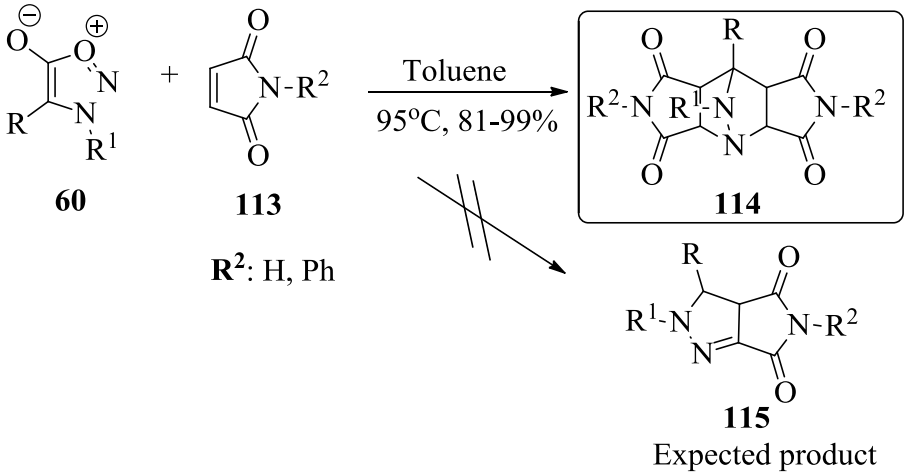
R	Yield **109** %	Yield **110** %
Me	61	7
Pr^n	20	55
Pr^i	7	72
Bn	12	58
Ph	67	0

Nan'ya *et al*. (1987), has demonstrated the cycloaddition reaction of *p*-toluquinone **111** with sydnone derivative **51**. Although *p*-toluquinone has two reactive sides to give cycloaddition reaction, sydnone prefered the less hindered side of olefin. And single regioisomeric product (indazole-4,7-diones **112**) was achieved at the end of the reaction.



Scheme 1.36 Regioselective cycloaddition of olefin with sydnone derivatives

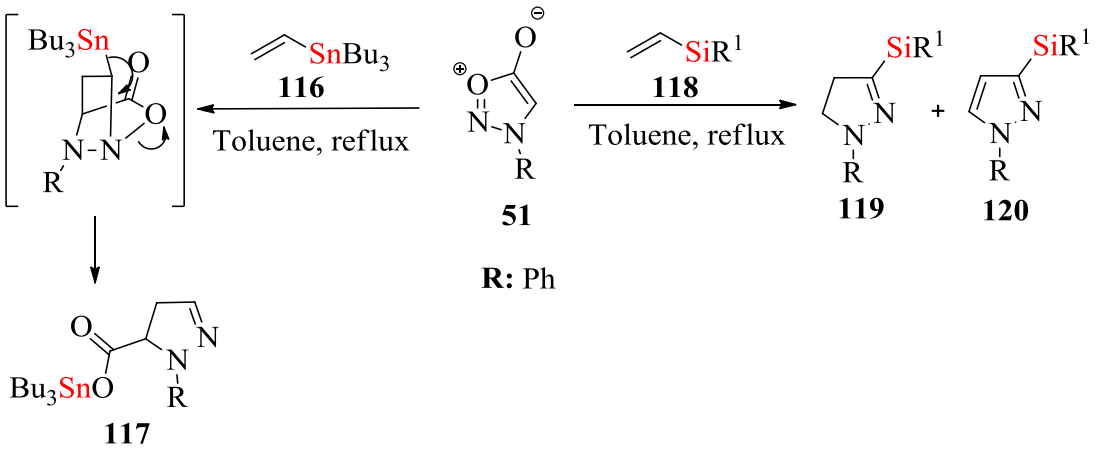
Sun (1986) has investigated the reactivity of sydnone derivatives on maleimides considering cycloaddition reaction. Normally substituted pyrrolo pyrazole-dione **115** can be considered only product as a result of cycloaddition reaction but in this case, attempted reaction between substituted sydnone derivatives **60** and maleimides **113** gave unexpectedly bis-imides **114** even the reaction was carried out in the presence of large excess of the sydnone derivatives.



Scheme 1.37 Unexpected formation of bis-imides as a result of reaction between substituted sydnones and maleimides

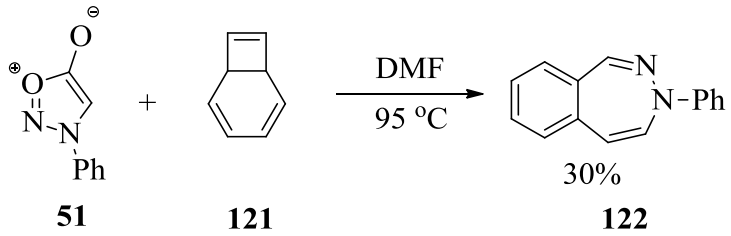
Gonzalez-Nogal *et al.* (2007) reported the cycloaddition reaction covering *N*-phenylsydnones with vinyl stannate **116** and –silanes **118.** The treatment of vinyl stannate with *N*-phenylsydnone favoured the stannyl ester **117** via the elimination of carboxylate from the intermediate. Due to the steric hindrance, vinyl silanes **118**

seem to be relatively unreactive toward cycloaddition. Nonetheless cycloaddition reaction trial furnished regioisomeric mixture containing sillyl pyrazolines **119** and pyrazoles **120**.



Scheme 1.38 Cycloaddition reaction of *N*-phenylsydnones with vinyl stannate **116** and –silanes **118**

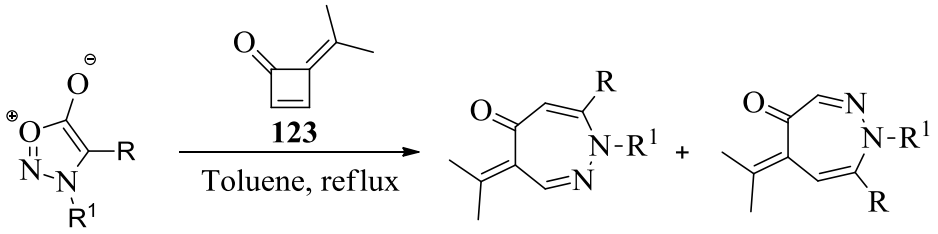
Surprisingly, attempted cycloaddition reaction of *N*-phenylsydnones **51** with cyclobutenes **121** yielded corresponding benzodiazepine **122** as a result of ring expansion through cycloaddition reaction (Kato *et al*., 1993).



Scheme 1.39 Synthesis of benzodiazepine **122**

Also, the reaction of substituted sydnone derivatives with alkylidenecyclobutenones gave unexpectedly regioisomeric products **124** and **125** with excellent regiocontrol depicted in Table 1.3 (Mais *et al*., 1987).

Table 1.3 Formation of diazepinones in an excellent regiocontrol

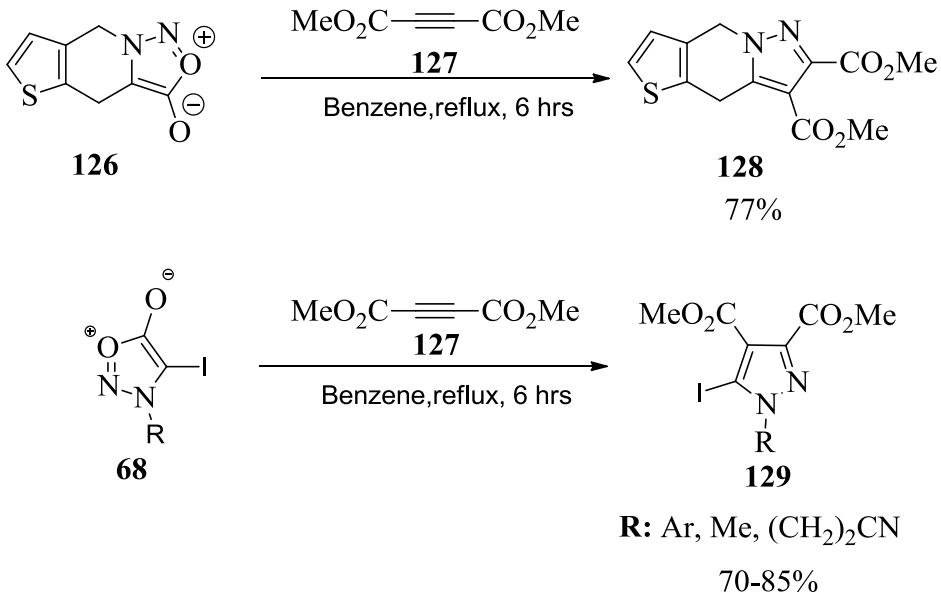


60 **124** **125**

R	**R^1**	Yield (**124:125**) (%)
Me	Ph	56 (100:0)
H	Ph	93 (100:0)
Cl	Ph	84 (100:0)
H	Me	65 (4:3)
H	Bn	58 (4:3)
Me	Me	75 (100:0)
	$(CH_2)_4$	57 (100:0)
	$(CH_2)_3$	43 (100:0)

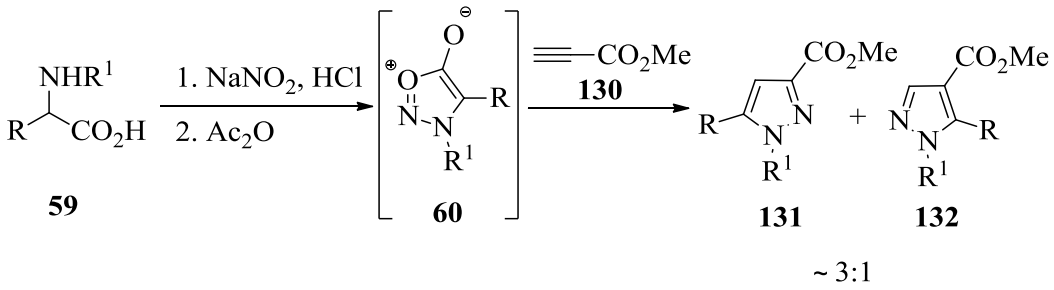
1.3.1.3.3.2 Alkyne cycloaddition

The cycloaddition reaction of sydnones with alkynes to construct pyrazole containing heterocycles is the most important part of sydnone chemistry. This process mainly covers [4+2] cycloaddition- retrocycloaddition with the releasing of CO_2. The alkyne cycloaddition reaction with sydnones was first reported by Huisgen (1962). Generally, electron deficient alkynes have been used in sydnone cycloaddition reactions. For example functionalized pyrazole products were obtained by reacting DMAD with various sydnone derivatives (Dumitrascu *et al*., 1997; Maffrand, 1981).



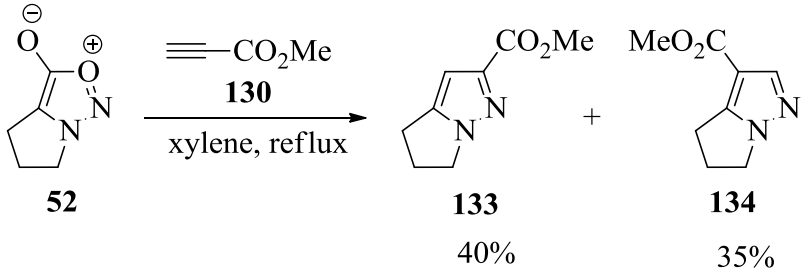
Scheme 1.40 Cycloaddition of DMAD with various sydnone derivatives.

In situ generated C-4 substituted aryl sydnones **60** were treated with methyl propiolate **130** afforded regiosomeric cycloadducts **131** and **132**. Surprisingly, compound **131** was obtained as major regioisomer in all cases (Padwa *et al*., 1982).



Scheme 1.41 Regioisomeric mixture of pyrazole derivative derived from in situ generated sydnone derivatives and methyl propiolate

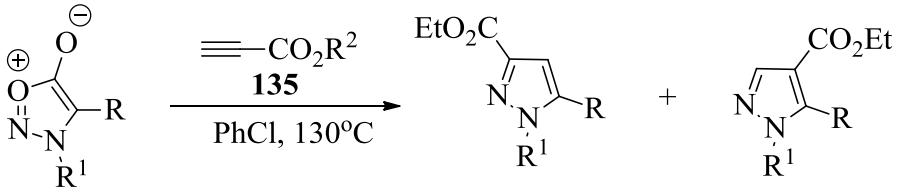
In addition to study mentioned above, bicyclic sydnone **52** derived from L-proline underwent cycloaddition with methyl propiolate **130** with the loss of regiocontrol in high yield (Ranganathan and Bamezai, 1983).



Scheme 1.42 Formation of fused pyrazole derivatives

Another efford for investigation of propiolate cycloaddition reaction was described by Chang who studied the selectivity of cycloaddition reaction of C-4 substituted aryl sydnones **60** with substituted propiolate **135** that provide corresponding pyrazoles with very poor selectivety in one exception (Chang *et al*., 2006a). When diphenylmethyl propiolate was conducted to reaction, excellent levels of regiocontrol were observed and single regioisomer **136** was obtained at the end of the reaction (Chang *et al*., 2006b).

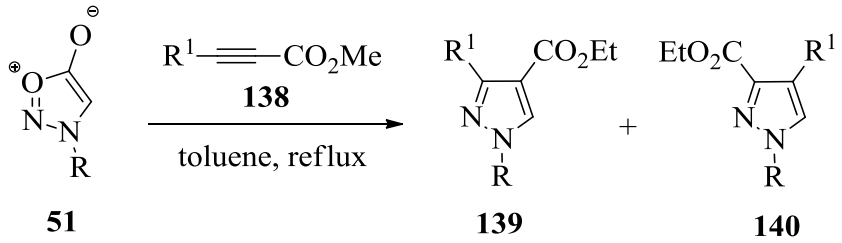
Table 1.4 Investigation of selectivity of propiolate cycloaddition with C-4 substituted aryl sydnones



60 **136** **137**

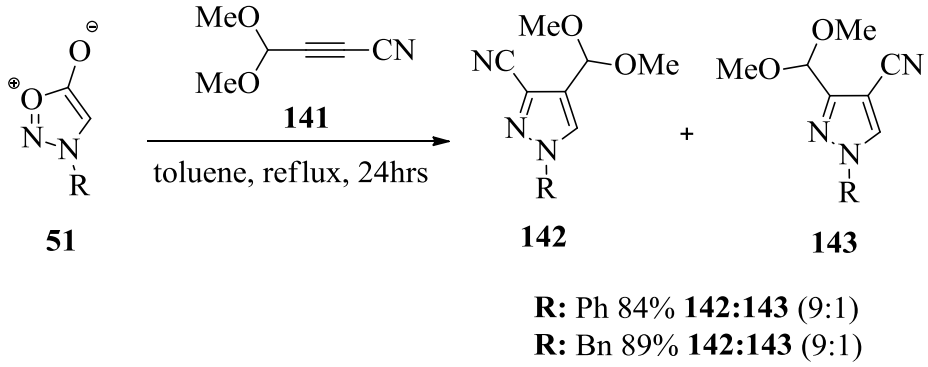
R	**R^1**	**R^2**	Yield (**136:137**) (%)
H	C_6H_4OEt-*p*	Et	90 (76:24)
I	C_6H_4OEt-*p*	Et	81 (56:44)
CN	C_6H_4OEt-*p*	Et	80 (58:42)
CH_2OH	C_6H_4OEt-*p*	Et	71 (63:37)
SPh	C_6H_4OEt-*p*	Et	71 (52:48)
CN	C_6H_4OEt-*p*	$CHPh_2$	85 (100:0)

The reactivity and regioselectivity of non terminal alknyl esters were examined in this case by Farina and coworkers. They used alknyl esters bearing acetal, aldehyde and carbinol substituents **138** to undergo cycloaddition reaction with aryl substituted sydnones **51** yielded corresponding regioisomeric mixture of pyrazoles **139** and **140** (Farina *et al*., 1989).



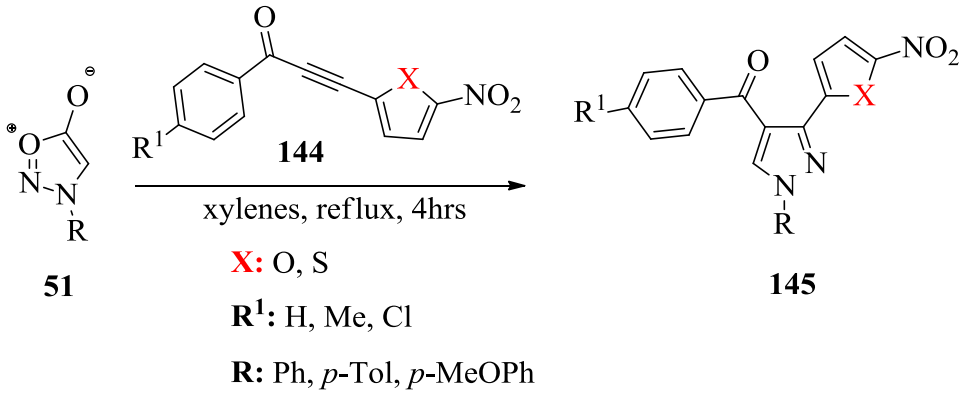
Scheme 1.43 Cycloaddition reacction of alknyl esters and sydnone derivatives

In addition, same authors carried out the reaction by using the acetal substituted propionitriles **141** instead alknyl esters. In this case corresponding pyrazoles **142** and **143** were afforded in a regioselective manner (Farina *et al.*, 1983).



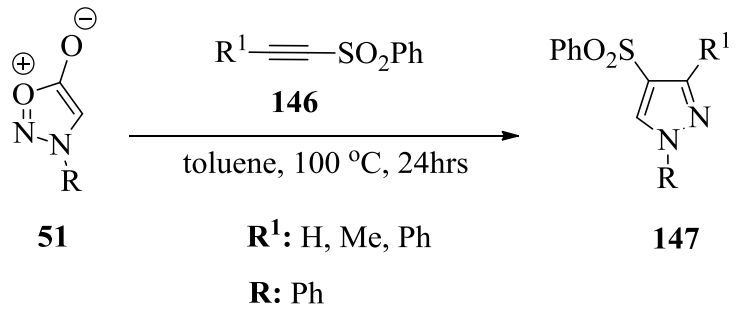
Scheme 1.44 Synthesis of cyano acetal subtituted pyrazoles in a regioselective manner

Hegde *et al.* (2006) demonstrated that *α,β*-acetylenic ketones were adapted to cycloaddition reaction with *N*-aryl sydnones to generate highly functionalized single regioisomers **145**.



Scheme 1.45 Highly functionalized pyrazole synthesis

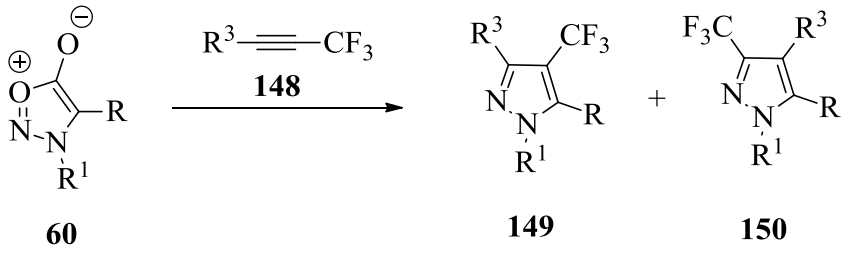
Mostly, terminal alkynes provided lowest regiocontrol on cycloaddition product. Due to the fact that substituted alknylsulfones **146** have potential to obtain corresponding pyrazoles **147** with excellent regioselectivity (Croce *et al*., 1985).



Scheme 1.46 Regioselective cycloaddition reaction of *N*-aryl sydnones with substituted alkynylsulfones

Meazza and co-workers (1993) reported the cycloaddition of C-4 substituted arylsydnone **60** with non terminal alkyne bearing aryl and trifluoromethyl substituent **148** yielded corresponding pyrazoles **149** and **150**. Interestingly, introduction of substituents C-4 position of sydnone decreases the selectivity of the reaction.

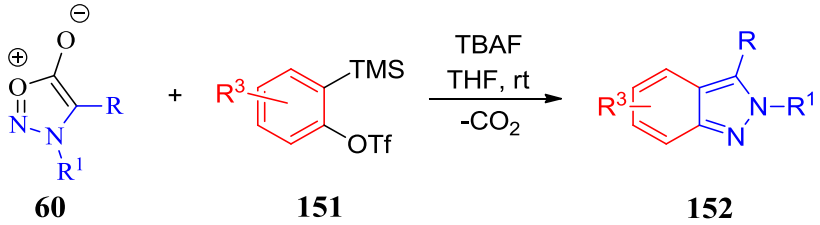
Table 1.5 Regioselective studies on formation of compound **149** and **150**



R	**R^1**	**R^3**	Yield (**149:150**) (%)
H	Ph	4-$MeOC_6H_4$	56 (93:7)
H	Ph	4-$NO_2C_6H_4$	93 (93:7)
H	4-$MeOC_6H_4$	4-ClC_6H_4	84 (93:7)
H	Bn	4-ClC_6H_4	65 (91:9)
H	Bu^t	4-ClC_6H_4	58 (93:7)
Me	Ph	4-ClC_6H_4	75 (84:16)
4-ClC_6H_4	Ph	4-ClC_6H_4	57 (60:40)
Br	Ph	4-ClC_6H_4	43 (71:29)
MeS	Ph	4-ClC_6H_4	62 (43:57)

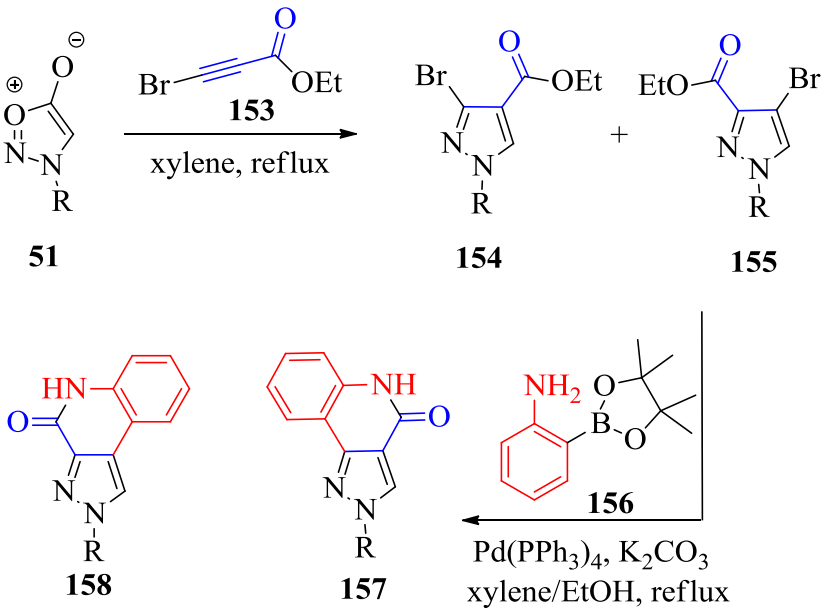
1.3.1.3.4 Recent Applications of Sydnone Chemistry

Last decades, sydnone chemistry especially cycloaddition reactions have been developed by many researchers. For example, Fang and co-workers (2011) succeed to synthesize the 2*H*-indazoles by the cycloaddition reaction of C-4 substituted *N*-aryl sydnones **60** with arynes **151** in good to excellent yields. The authors also performed the Pd-catalyzed coupling reactions to derive the C-4 substituted *N*-aryl sydnones.



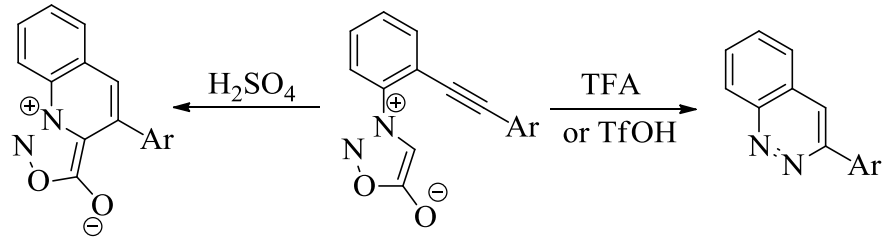
Scheme 1.47 Synthesis of 2*H*-indazoles **152**

On the other hand, Chang *et al.* (2012) demonstrated that one pot synthesis of 2-arylpyrazoloquinolinone derivatives by using three step methodology including in 1,3-DC, Suzuki coupling and intramolecular cyclization reaction. Cycloaddition reaction performed with lack of selectivity and provided corresponding pyrazoles **154** and **155**.



Scheme 1.48 Multistep synthesis of 2-arylpyrazoloquinolinone derivatives

Another interesting cyclization process bearing *o*-alknyl sydnones **159** and various acids have been performed by Turnbull *et al.* Intramolecular cyclization reaction of *o*-alknyl sydnones **159** with conc. H_2SO_4 afforded the novel fused ring sydnones **160**. However, when using of both TFA and TfOH seperately instead of conc. H_2SO_4 provided the hydrolysis of corresponding sydnone to hydrazine that easily underwent acid catalyzed cyclization reaction with alkyne to obtain 3-arylcinnolines **161** in good yield (Weisner and Turnbull, 2014).

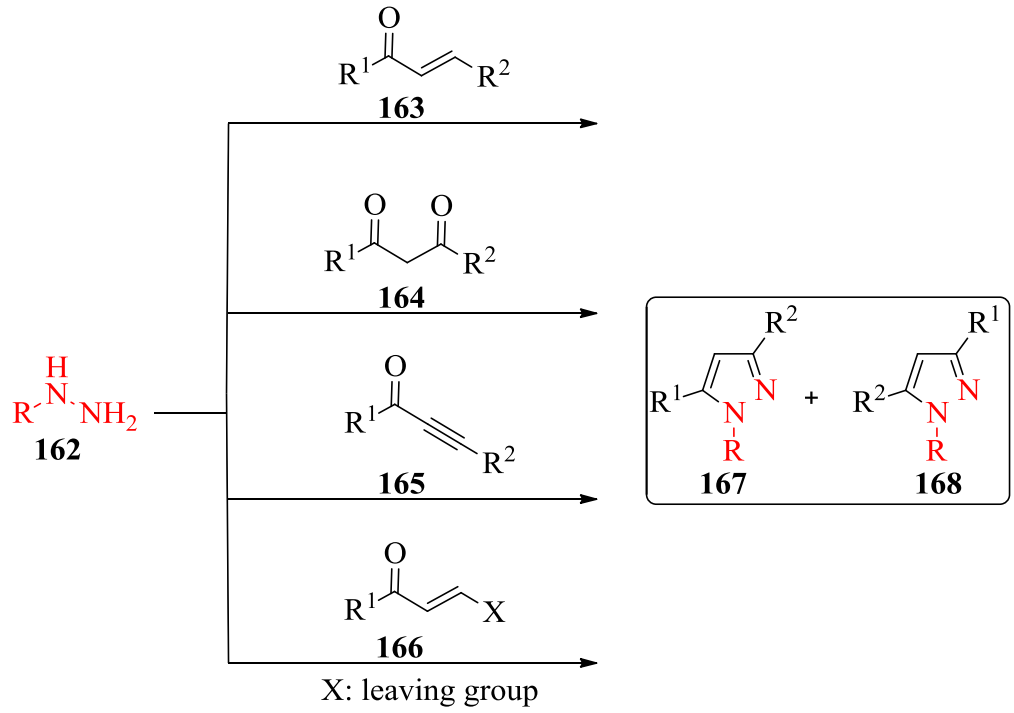


Scheme 1.49 Cylization reaction of *o*-alknyl sydnones **159** with various acids

1.3.1.4 Methods for Preparation of Pyrazoline and Pyrazole Derivatives

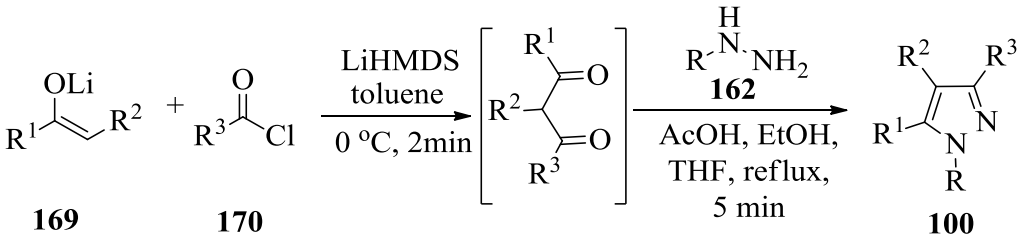
1.3.1.4.1 Cyclocondensation of Carbonyl Compounds with Hydrazines

Substituted phenyl hydrazine **162** has vital importance on the construction of pyrazole derivatives. For the preperation of corresponding pyrazoles **167** and **168**, phenyl hydrazines having two nucleophilic part can undergo cyclocondensation reaction with various substrates such as *α,β*-unsaturated carbonyl compounds **163**, 1,3-dicarbonyl **164**, *β*-enaminones or related compounds **165** and **166** (Fustero *et al*., 2011).



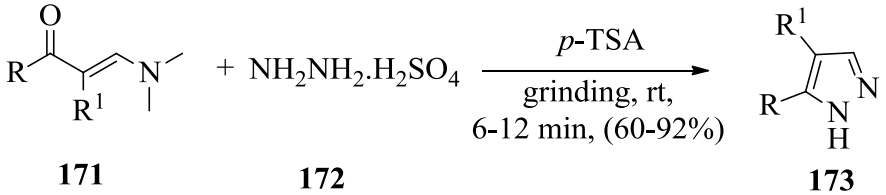
Scheme 1.50 Formation of pyrazoles **167** and **168**

Heller and Natarajan (2006) reported that *in situ* generated 1,3-diketones resulted from the reaction of enolizable ketones **169** and acid chlorides **170** converted into highly substituted pyrazoles **100** by the addition of appropriate hydrazines **162**.



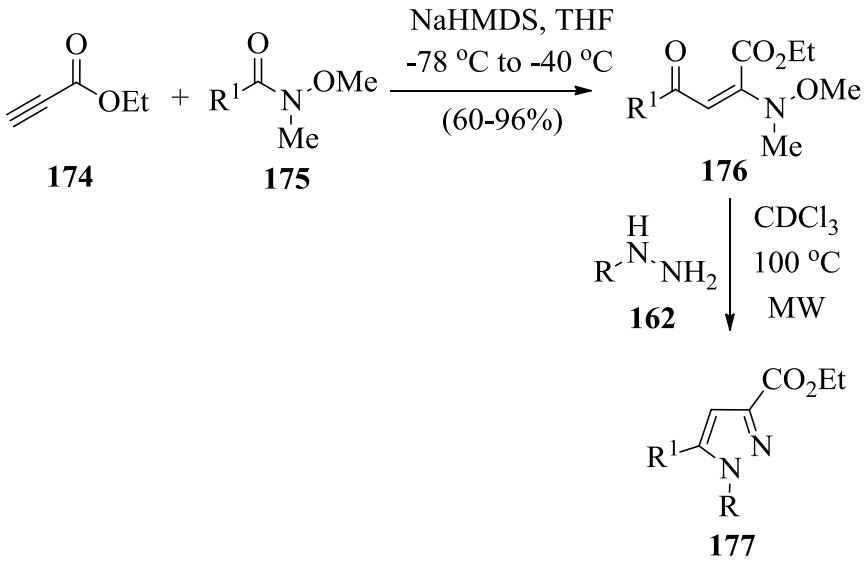
Scheme 1.51 Pyrazole synthesis by using 1,3-diketones

Solvent free protocol was reported for the preperation of NH-pyrazoles **173** by grinding reaction of *β*-dimethylaminovinylketones **171** with hydrazine hydrosulfate **172** in the presence of catalytic amount of *p*-TSA (Longhi *et al*., 2010).



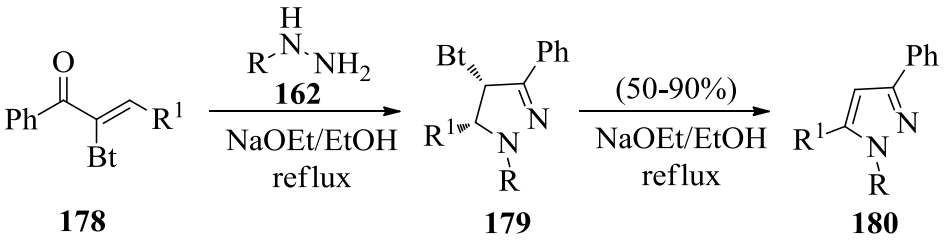
Scheme 1.52 Solvent free protocol for the preperation of NH-pyrazoles **173**

Persson and Nielsen (2006) studied that Weinreb amides **175** and ethyl propionate **174** converted into intermediate *α,β*-unsaturated compound **176** in the first place, than underwent cyclocondensation reaction with substituted phenyl hydrazine **162** to give title pyrazole compounds **177** in a regioselective manner.



Scheme 1.53 Synthesis of pyrazole-3-carboxylates

The reaction of *α,β*-unsaturated carbonyl compound **178** bearing a leaving group with phenyl hydrazine derivatives **162** resulted the highly substituted pyrazolines **179** that were easily converted into corresponding pyrazoles via the elimination of leaving group in a mild basic medium (Katritzky *et al*., 2001).



Scheme 1.54 Preperation of pyrazoles from *α,β*- unsaturated carbonyl compound.

1.3.1.4.2 1,3-DC Reaction Methods

1,3-DC reaction is one of the most powerful synthetic method to provide substituted pyrazoles and pyrazolines. Three main classes of 1,3-dipoles can be used

for this purpose such as diazoalkanes, nitrilimines and azomethine imines that are illustrated in Figure 1.18.

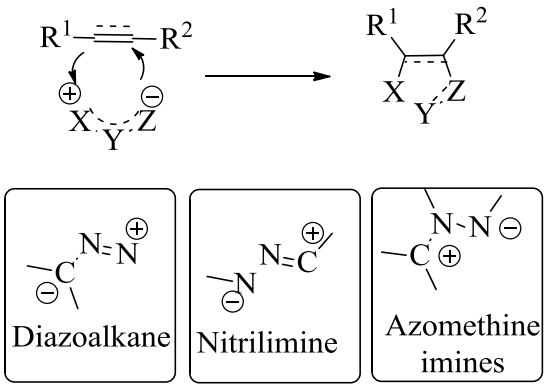
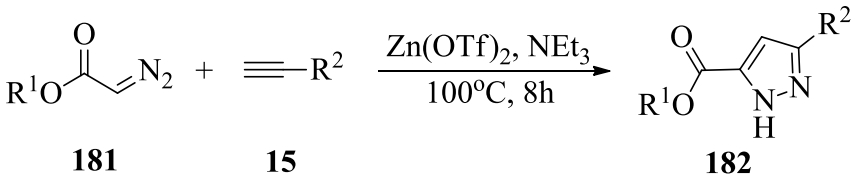


Figure 1.18 Representative 1,3-DC reaction of diazoalkane, nitrilimines and azomethine imine type dipoles into an alkene or alkyne

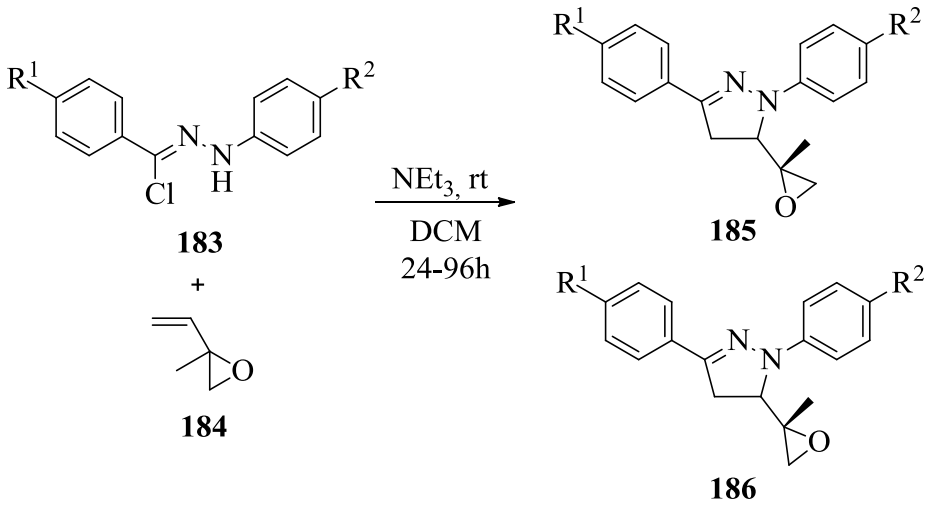
Diazocarboyl compounds **181** reacted with substituted alkynes **15** to give a variety of 3,5-disubstituted pyrazoles **182** in the presence of zinc triflate as a catalyst (Qi, 2007).



181 **15** **182**

Scheme 1.55 Synthesis of 3,5-disubstituted pyrazoles by means of diazoalkane cycloaddition

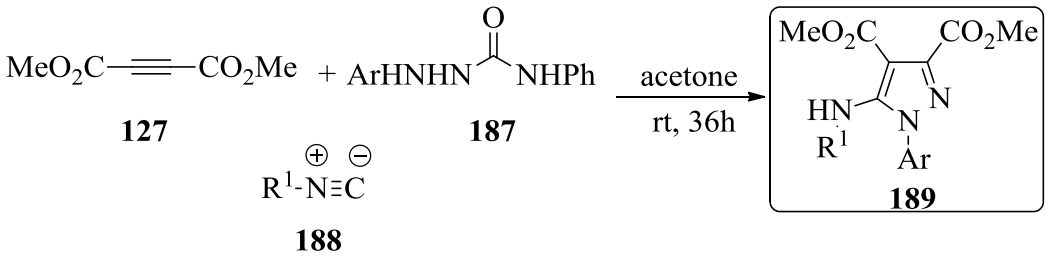
Yıldırım *et al.*(2011) performed the nitrilimine cycloaddition reaction by using *in situ* generated nitrile imines which was obtained from the treatment of NEt_3 with hydrazonyl chlorides **183** and isoprene monoxide **184** afforded to substituted 4,5-dihydro-1H-pyrazoles **185** and **186** in a regioselective manner.



Scheme 1.56 Regioselective cycloaddition reaction of nitrile imines with isoprene monoxide

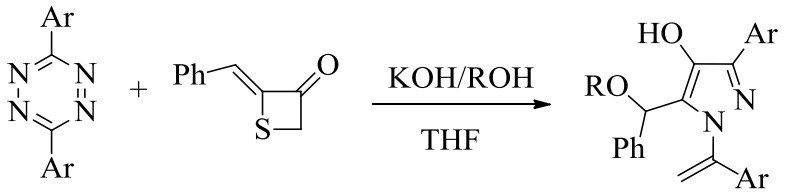
1.3.1.4.3 Other Methods for Creating the Pyrazole and Pyrazoline Ring

Isocyanide based multicomponent reactions are relevant for the construction of pyrazoles and pyrazolines. As an example of MCRs, Adip *et al.* showed the synthesis of highly substituted pyrazoles **189** that were resulted from the slow addition of isocyanide **188** into the solution containing dimethylacetylene dicarboxylate **127** and hydrazine carboxamide **187** in the same solvent (Dömling, 2006).



Scheme 1.57 Isocyanide based MCRs for construction of substituted pyrazoles **189**

Surprisingly, a new methodology was suggested by Suen and co-workers (2005) to get pyrazole derivatives. The reaction of 3,6-diaryl-1,2,4,5-tetrazines with thioethanones under basic condition furnished the fully substituted pyrazol-4-ols **192**.



190 **191** **192**

Scheme 1.58 Unexpected formation of fully substituted pyrazol-4-ols **192**.

1.3.1.5 Biological importance of pyrazole and pyrazolines

Pyrazole and pyrazoline derivatives, which are both important building blocks in organic synthesis and, which have numerous applications as pharmaceuticals and agrochemicals, can be sourced from many synthetic methods discussed above. Amongst the latter group of compounds, poly(hetero)aromatic-substituted pyrazoles are particularly important showing a broad spectrum of useful biological effects, including kinase inhibition (Adams *et al*., 1998), oestrogen receptor binding (Fink *et al*., 1999), anti-inflammatory (Tsuji *et al*., 1997) and herbicidal activities (Kudo *et al*., 1999). Although many pyrazole containing drugs and alkaloids exist in literature some important of them such as celebrex, betazole, antizole, benzydamine, epirizole and pyrazofurin are illustrated in Figure 1.19.

Celebrex, an anti inflammatory drug, is mainly named as celecoxib having pyrazole core used in the treatment of osteoarthritis, rheumatoid arthritis,ankylosing spondylitis, acute painin adults, painful menstruation, and juvenile rheumatoid arthritis in patients two years or older (Penning *et al*., 1997).

Betazole is a histamine H_2 receptor agonist that is mainly used as its salt form. Betazole hydrochloride has been used as a gastric stimulant to test for maximal production of gastric secretion activity (Wruble *et al*., 1967).

Antizole is the simplest pyrazole based drug which has been used as an antidote for methanol and ethylene glycol poisoning (Blomstrand *et al*., 1980).

Benzydamine, has been found as hydrochloride form having local anesthetic analgesic properties for pain relief and inflammatory treatment for the painful inflammatory conditions of the mouth and throat (Turnbull *et al*., 1995).

Epirizole,4-Methoxy-2-(5-methoxy-3-methylpyrazol-1-yl)-6-methylpyrimidine, is a nonsteroidal anti-inflammatory drug whaic has pyrimidinyl pyrazole core having antipyretic, analgesic, and anti-inflammatory activity.Pyrazofurin is naturally occuring alkaloid C-nucleoside antibiotics that acts also antiviral effect on selected RNA viruses (Moyer and Handschumacher, 1979).

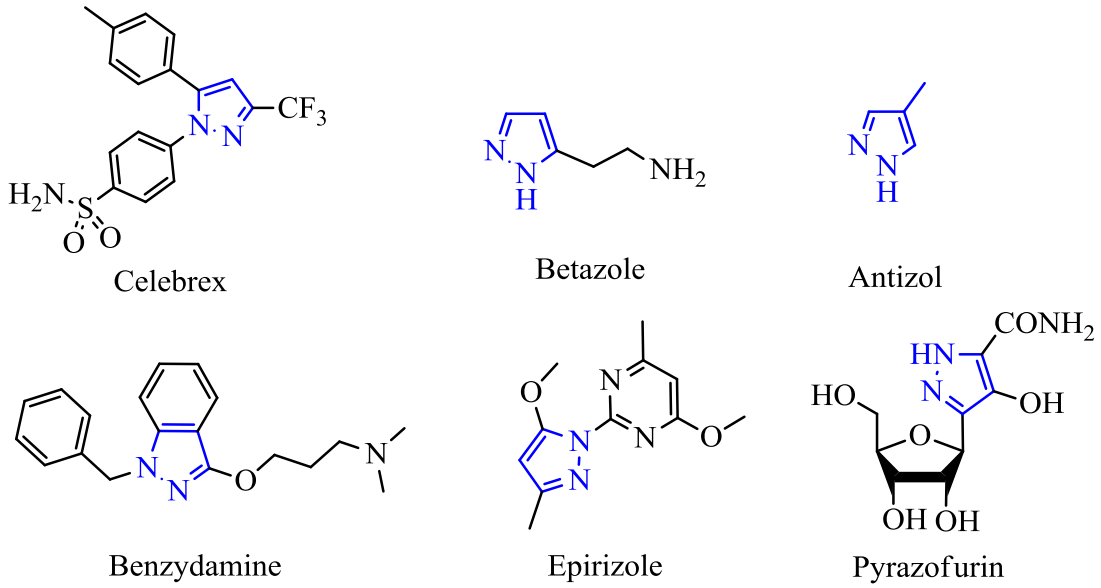
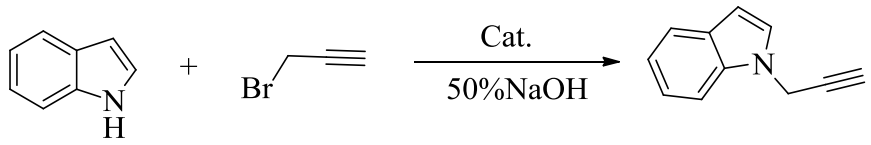


Figure 1.19 Pyrazole containing drugs and some alkaloids.

1.4 CHAPTER 4

1.4.1 Synthesis and Reactions of 1-(prop-2-ynyl)-1*H*-indole

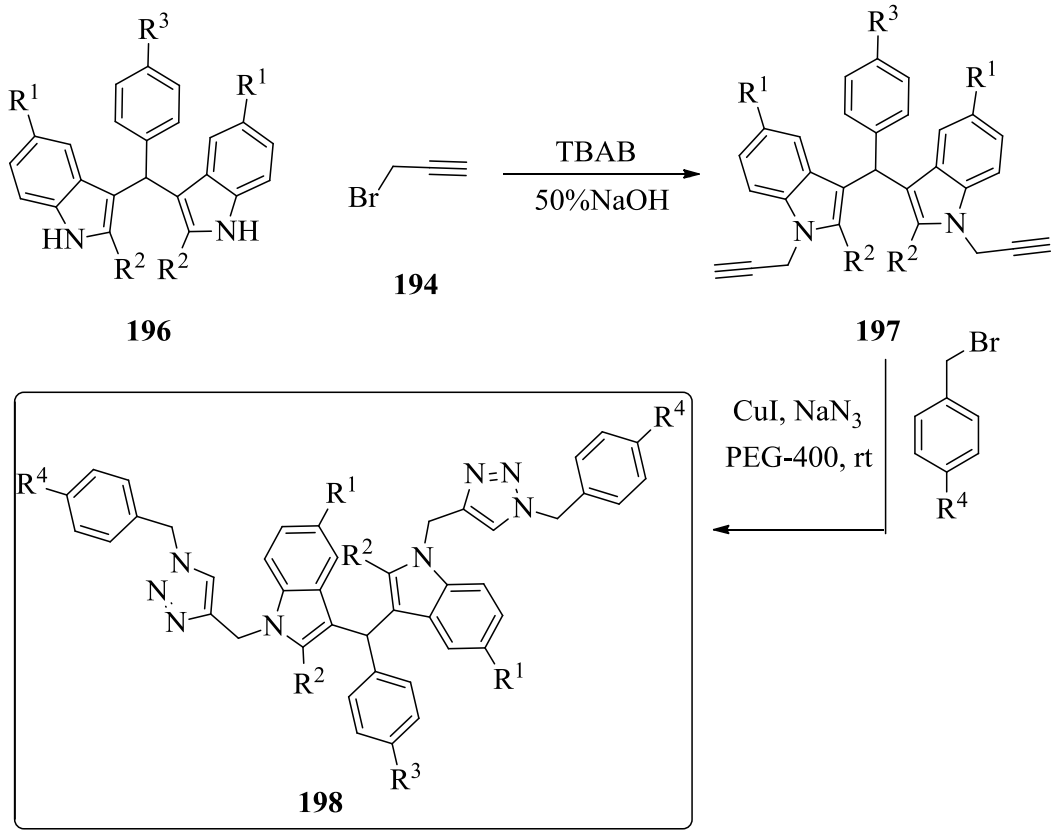
The synthesis of propargnyl indole derivatives has been reported firstly by Samsoniya *et al.* (1991). The authors have succesfully performed the synthesis of title 1-(prop-2-ynyl)-1*H*-indole **195** by reacting propargyl bromide **194** with indole **193** in the presence of interphase catalysis.



193 **194** **195**

Scheme 1.59 Synthesis of 1-(prop-2-ynyl)-1*H*-indole **195**

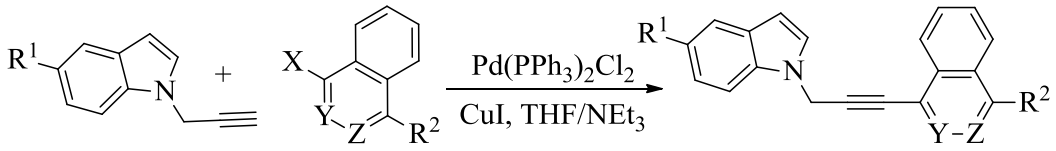
Damodiran and co-workers (2009) have also suggested similar preparation method for propargyl indole derivatives **197** that covers the introduction of propargyl bromide **194** with indole derivatives **196** by using tetrabuthylammonium bromide as a catalyst. Followed, regioselective [3+2] cycloaddition reaction carried out between corresponding propargnyl indoles **197** with sodium azide to form bis(indolyl)methane derivatized 1,4-disubstituted 1,2,3-bistriazoles **198**.



196 194 197 198

Scheme 1.60 The preparation and cycloaddition of propargnyl indoles **197**

Haider *et al*. (2007) performed the Sonogashira cross coupling reaction of an appropriate propargyl substituted indole **199** with substituted hetarene **200** provided the coupling products **201** in the presence of Pd-complex and CuI as catalysts.



199 200 201

R1 = H, OCH_3, Br, CO_2CH_3

R2 = H, CH_3, Ph

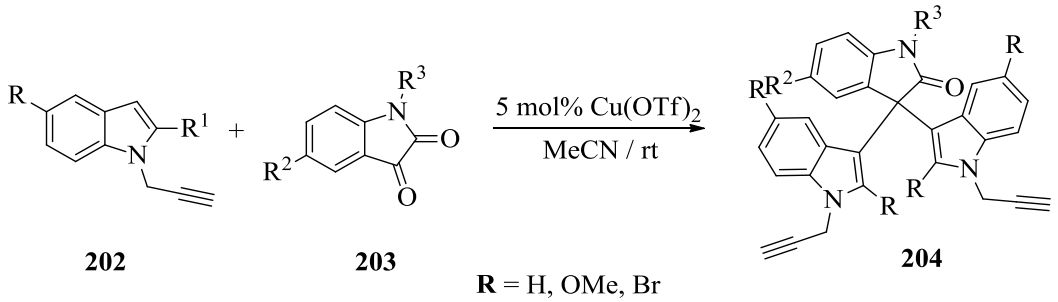
X = I, Br

Y = N, CH

Z = N, CH

Scheme 1.61 Sonogashira cross coupling reaction between propargyl substituted indole **199** and substituted hetarene **200**

In this case, $Cu(OTf)_2$ catalyzed bis addition of *N*-propargyl indoles **202** to isatin **203** gave di(indolyl)indolin-2-ones **204** in excellent yields without any purification technique (Praveen *et al*., 2011).



202 **203** **204**

R = H, OMe, Br

R^1 = H, Me

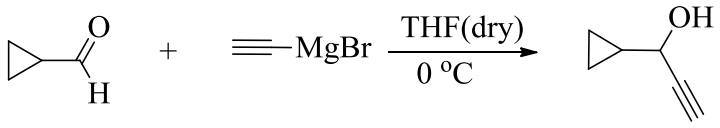
R^2 = H, Cl, Br, NO_2

R^3 = H, propargyl, benzyl, CH_2COOEt

Scheme 1.62 Bis-addition of *N*-propargyl indoles to isatin

1.4.2 Synthesis and Reactions of 1-cyclopropyl-2-yn-1-ols

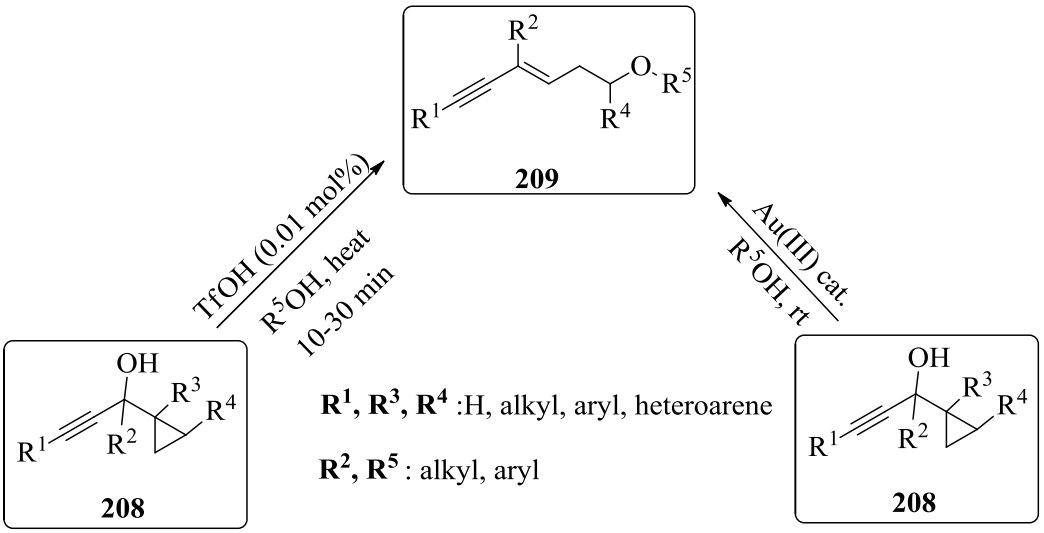
Classically, 1-cyclopropyl-2-yn-1-ol **207** was generated by successive addition of ethynylmagnesium bromide **206** into the solution of cyclopropylcarboxaldehyde **205** in dry THF at 0 ^oC (Mothe and Chan, 2009).



205 **206** **207**

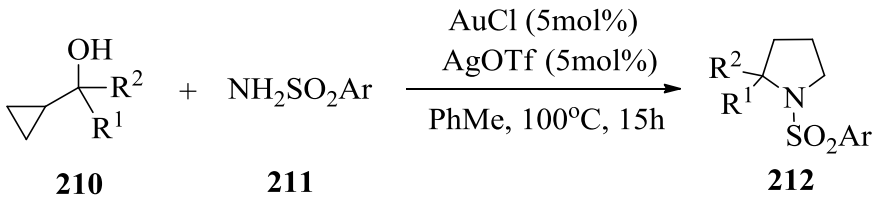
Scheme 1.63 Synthesis of 1-cyclopropyl-2-yn-1-ol **207**.

Although there are few examples regarding cycloaddition reaction of 1-cyclopropyl-2-yn-1-ols **207**, generally ring expansion and ring opening reaction have been found in the literature. For example acid catalyzed and Au(III) catalyzed ring opening of highly substituted1-cyclopropyl-2-yn-1-ols **208** were resulted in the formation of conjugated enynes **209** bearing alkoxy moiety (Mothe and Chan, 2009; Xiao *et al*., 2007).



Scheme 1.64 Ring opening reactions of highly substituted 1-cyclopropyl-2-yn-1-ols **208**

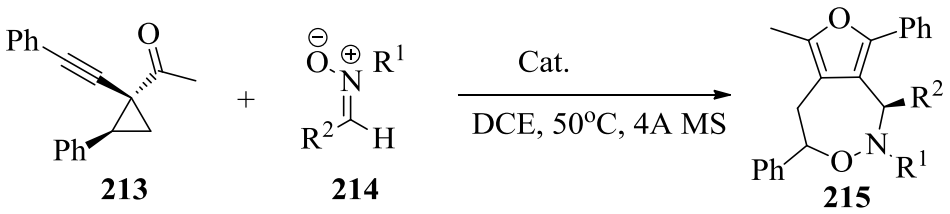
Gold and silver catalyzed ring expansion of cyclopropyl methanols **210** with sulfonamides **211** have been carried out via intramolecular aminocyclization reaction (Rao and Chan, 2008).



Scheme 1.65 Gold- and silver-catalyzed tandem amination/ring expansion of cyclopropyl methanols with sulfonamides

[4+3] cycloaddition reaction of 1-(1-Alkynyl) cyclopropyl ketones **213** with various nitrones **214** enclosed the many succesfull catalyst trial containing gold or copper mostly for the highly diastereoselective construction of 1,2,4,5-tetrahydrofuro [3,4-*d*][1,2]oxazepines **215** (Bai *et al*., 2009).

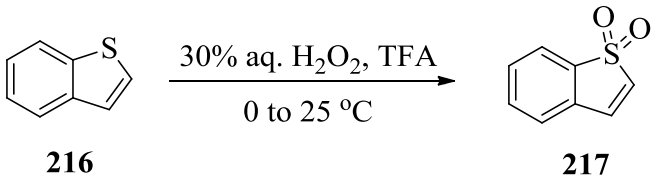
Table 1.6 Reaction conditions for the [4+3] cycloaddition reaction of 1-(1-Alkynyl) cyclopropyl ketones and nitrones



Entry	Catalyst	Time [h]	Yield [%]
1	None	7	0
2	$Sc(OTf)_3$	7	40
3	$Yb(OTf)_3$	7	34
4	$Ni(ClO_4)_2$	7.5	17
5	$Bi(OTf)_3$	7	32
6	$AuCl_3$	7	74
7	AgOTf	7	19
8	$Zn(OTf)_2$	8	0
9	CuOTf	8	67
10	CuBr	7	0
11	CuI	8	0
12	$Cu(OTf)_2$	7	83

1.4.3 Synthesis and Reactions of Benzo[b]thiophene 1,1-dioxide

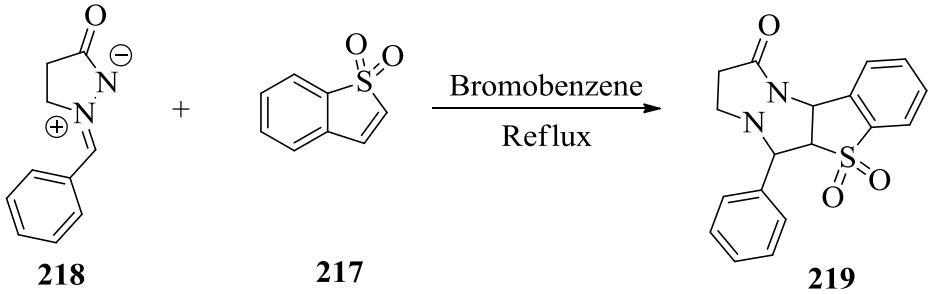
Benzothiophene itself is not very reactive with dipoles and also benzothiophene oxide is useless dipolarophile that is stable only dilute solutions (Pouzet *et al*., 1995). That's why, benzo[*b*]thiophene 1,1-dioxide is attractive dipolarophile due to its stability and electron deficiency with respect to its analogous. Synthetic pathway is illustrated in Scheme 1.66 (Iniesta *et al*., 2008).



Scheme 1.66 Synthesis of benzo[*b*]thiophene 1,1-dioxide

Benzo[*b*]thiophene 1,1-dioxide that easily undergo cycloaddition reactions with itself and many dipoles such as nitrile oxide, nitrone, azomethine ylide and azomethine imine.

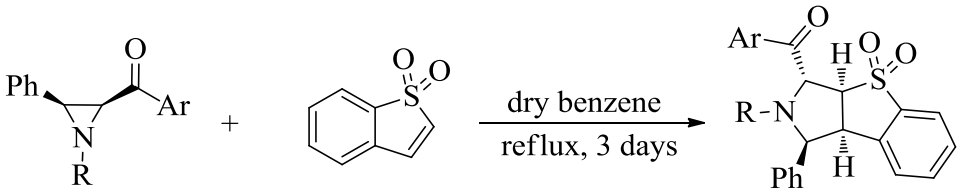
Dipolar addition of cyclic azomethine imine **218** to benzo[*b*]thiophene 1,1-dioxide **217** gave rise to tetracycle **219** in a regioselective manner (Wong *et al*., 2013).



218 **217** **219**

Scheme 1.67 Dipolar addition of cyclic azomethine imine **218** to benzo[*b*]thiophene 1,1-dioxide **217**

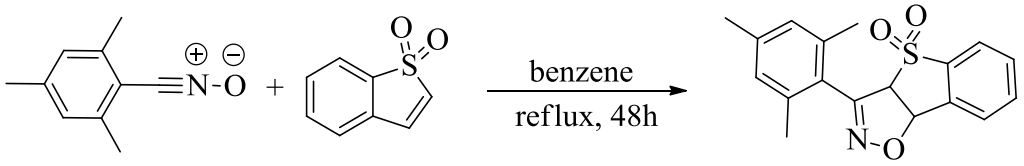
Azomethine ylide cycloaddition with benzo[*b*]thiophene 1,1-dioxide **217** has been performed succcesfully. The cycloadducts **221** were obtained stereoselectively by the reaction of benzo[*b*]thiophene 1,1-dioxide **217** with *in situ* generated dipoles that is resulted from thermal ring opening of aziridines **220** (Malatesti *et al*., 2006)**.**



220 **217** **R:** Alkyl, aryl **221**

Scheme 1.68 1,3-Dipolar cycloaddition reactions of **217** and azomethine ylides generated from aziridines **220**, affording only one cycloadduct **221**

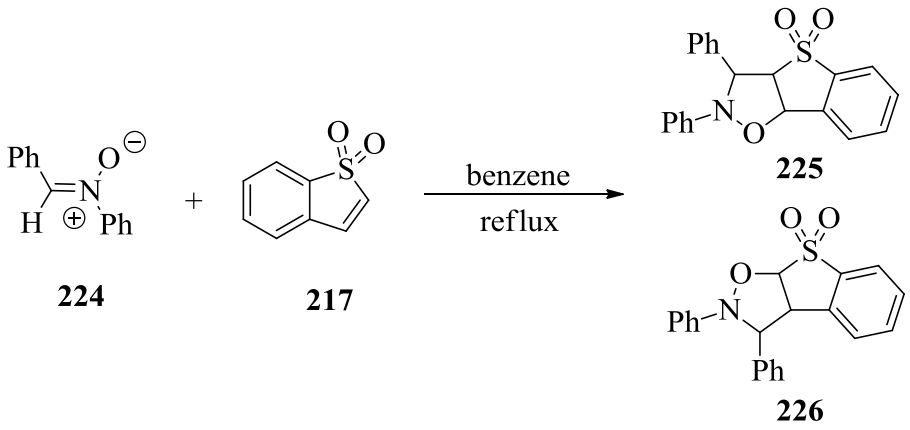
Regioselective nitrile oxide cycloaddition between mesitonitrile oxide **222** with benzo[*b*]thiophene 1,1-dioxide **217** has been accomplished to afford tricyclic cycloadduct **223** bearing isoxazoline ring (Bened *et al*., 1982).



222 **217** **223**

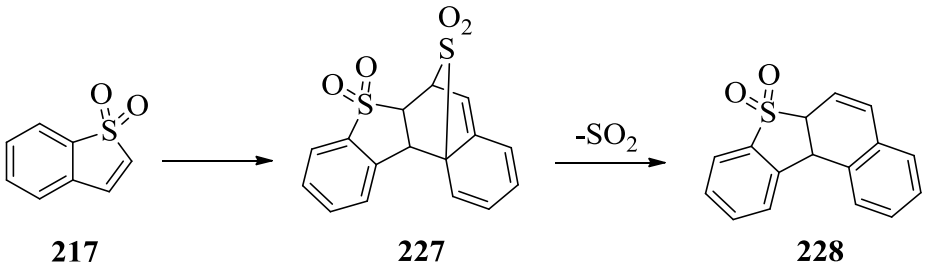
Scheme 1.69 Nitrile oxide cycloaddition reaction to benzo[*b*]thiophene 1,1-dioxide **217**

The regioisomeric mixture of adducts **225** and **226** were formed by 1,3-DC reaction of diphenyl nitrone **224** with benzo[*b*]thiophene 1,1-dioxide **217**(Bened *et al*., 1984).



Scheme 1.70 1,3-DC reaction of diphenyl nitrone **224** with benzo[*b*]thiophene 1,1-dioxide **217**

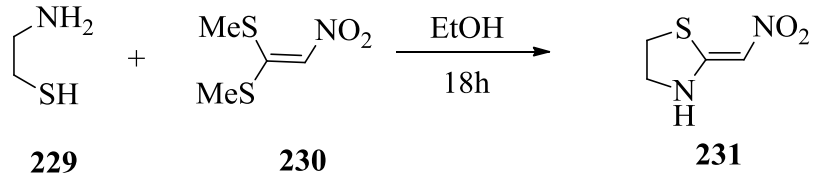
The diels alder condensation of benzo[*b*]thiophene 1,1-dioxide **217** with itself gave tetracyclic adduct **228** as a result of releasing SO_2 from the intermediate diels alder product **227** (Taylor and Wallace, 1968).



Scheme 1.71 Diels-Alder reaction of benzo[*b*]thiophene 1,1-dioxide **217** with itself

1.4.4 2-Nitromethylenethiazolidine

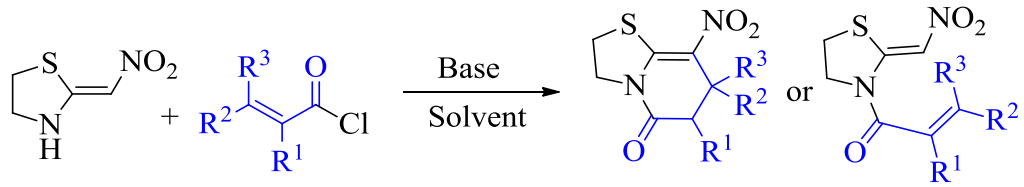
Heterocyclic enamines are the important class of functional groups that have been extensively studied for the synthesis of many functionalized heterocyclic systems. 2-nitromethylenethiazolidine **231** bearing electron withdrawing group belongs the heterocyclic enamine class that having two reactive sides. The synthesis of 2-nitromethylenethiazolidine **231** is probable by reacting 1,1-bis (methylmercapto)-2-nitroethylene **230** with cysteamine **229** in EtOH (Rajappa and Advani, 1982).



229 **230** **231**

Scheme 1.72 Synthesis of 2-nitromethylenethiazolidine **231**

Generally, intermolecular cyclization reactions have been studied over the 2-nitromethylenethiazolidine. For example Yıldırım *et al.* (2014a) reported that the cyclocondensation reaction between 2-nitromethylenethiazolidine **231** and acryloyl or cinnamoyl chlorides **232** leading cyclization products **233** in modarate to good yields.

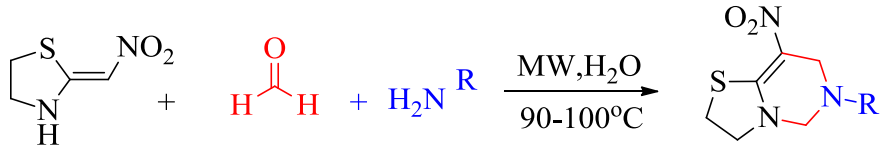


231 **232** **233** **234**

R[1],R[2],R[3] : Alkyl, aryl

Scheme 1.73 General method for the preparation of thiazolo(imidazolo)pyridinones **233** and **234**

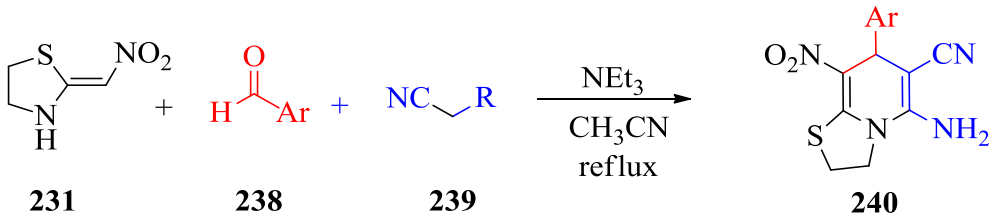
Cyclization chemistry of 2-nitromethylenethiazolidine **231** has been extended by the same authors.They have suggested the microwave assisted multicomponent cyclization reaction by using 2-nitromethylenethiazolidine **231**, formaldehyde **235** and various aliphatic or aramatic amines **236**. Several thiazolo[3,2-*c*]pyrimidines **237** having alkyl or aryl groups were obtained as a result of microwave or conventinal heating (Yıldırım *et al.*, 2014b).



231 **235** **236** **237**

Scheme 1.74 Synthesis of thiazolo[3,2-c]pyrimidines

Furthermore, Altuğ *et al.*(2011) succeed the synthesis of thiazolo[3,2-a]pyridines by means of successful one pot multicomponent reaction between 2-nitromethylenethiazolidine **231**, aromatic aldehydes **238** and nitriles bearing active metylene group **239** in the presence of NEt_3.



231 **238** **239** **240**

Scheme 1.75 One pot multicomponent reaction for the formation of thiazolo[3,2-*a*]pyridines **240**

2. AIM AND SCOPE OF THE STUDY

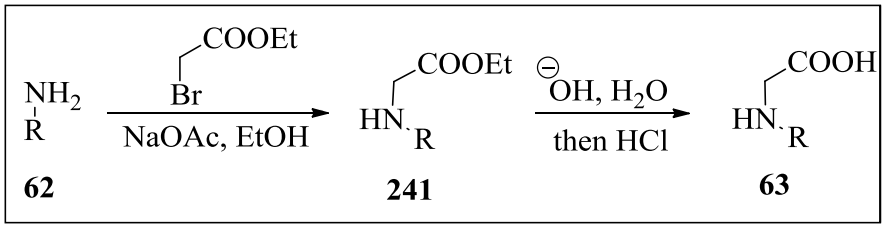
Since their discovery, sydnones have received increasing interest for the synthesis of a variety of valuable 5-membered heterocylic compounds. Two probable products (pyrazole and pyrazoline derivatives) can be obtained as a result of the cycloaddition reactions of sydnones with variety of dipolarophiles. It is known that pyrazole and pyrazoline derivatives, which are both important building blocks in organic synthesis and, which have numerous applications as pharmaceuticals and agrochemicals. Amongst the latter group of compounds, poly(hetero)aromatic-substituted pyrazoles are particularly important showing a broad spectrum of useful biological effects, including protein-kinase inhibition (Adams *et al*., 1998), oestrogen receptor binding (Fink *et al*., 1999), anti-inflammatory (Tsuji *et al*., 1997) and herbicidal activities (Kudo *et al*., 1999). Hovewer, biological and agricultural effect of these heterocycles have encouraged us to synthesize new cycloadducts bearing pyrazole and pyrazoline core on the skeleton.

Taking into account of these considerations, together with our continuing interest in the 1,3-dipolar cycloaddition chemistry of various ylides leading to pyrazoles, triazoles and spiropyrroles (Yıldırım and Dürüst, 2011; Dürüst *et al*., 2011; Dürüst *et al*., 2012), we focused in this Ph.D. study on the synthesis of various pyrazole and pyrazoline containing heterocycle via the reaction of *N*-aryl sydnones as a 1,3-dipole with four representative dipolarophiles such as; 1-(prop-2-ynyl)- 1*H*-indole, benzo[b]thiophene 1,1-dioxide, 1-cyclopropylprop-2-yn-1-ol and 2-nitromethylenethiazolidine. To the best of our knowledge, attempted cycloaddition reactions that cover the treatment of *N*-aryl sydnones with corresponding dipolarophiles were incorporated first time in this Ph.D. dissertation study.

3. MATERIALS AND METHODS

Microwave reactions were carried out in the CEM DISCOVER microwave reactor. Melting points were determined on a Meltemp apparatus and are uncorrected. Infrared spectra as KBr pellet or neat were recorded on Shimadzu 8400-S spectrophotometers. Mass spectra were recorded on Waters 2695 Alliance Micromass ZQ LC/MS instrument. HRMS measurements were performed on a Waters Synapt spectrometer. NMR spectra were recorded on Jeol and Varian spectrometers operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C, at 25 ºC. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Routine TLC analyses were carried out on precoated silica gel plates with fluorescent indicator. Flash column chromatography was performed on silica gel (230-400 Mesh ASTM). The stain solutions of potassium permanganate and iodine were used for visualization of the TLC spots.

Experimental

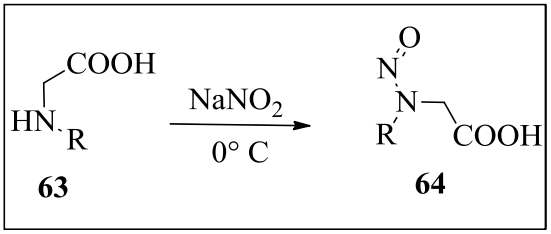


62 **241** **63**

General procedure for preparation of *N*-substituted glycine derivatives (63a-g).

A mixture of substituted aniline (50 mmol), ethyl bromoacetate (9.96 g 60 mmol) and anhydrous sodium acetate (5.0 g, 60 mmol) in 60 mL of ethanol was refluxed in an oil bath (120-125 ^{o}C) for 6 h. The reaction mixture was left overnight at room temperature and poured into crushed ice. The precipitate formed was collected by filtration and dried. The dried product, ethyl ester of *N*-substituted glycine without further purification was used for the next step. To ethyl ester of *N*-substituted glycine (40.0 mmol), sodium hydroxide (1.80 g, 45.0 mmol) in 80 mL of water was added and refluxed for 0.5 h. After cooling, the reaction mixture was

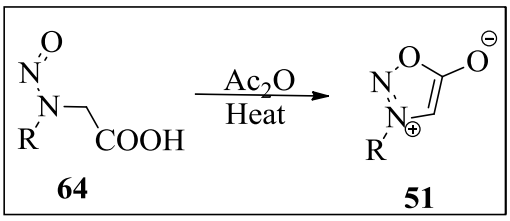
acidified to pH = 2 using hydrochloric acid. The precipitated *N*-substituted glycine **63 a-g** was filtered and washed thoroughly with cold water.



63 **64**

General procedure for preparation of *N*-nitroso-*N*-substituted glycine derivatives (64a-g)

To a stirred suspension of *N*-substituted glycine **63** (10.0 mmol) in water at (40 mL) at 0 °C, a solution of sodium nitrite (0.69 g, 10.0 mmol) in water (10 mL) was added dropwise during 30 min. The reaction mixture was practically clear after 2 h. It was filtered and acidified with concentrated hydrochloric acid. The precipitated product was filtered, washed with cold water and dried in air. The nitrosoglycines **64** prepared by the above method were recrystallised from aqueous ethanol.

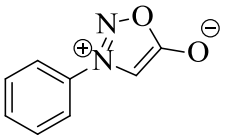


64 **51**

General procedure for preparation of *N*-aryl sydnone derivatives (51a-g)

N-Nitroso-*N*-substituted glycine **64** (5 mmol) was heated with acetic anhydride (0.236 mL, 2.5 mmol) on a water bath for 2-4 h. The reaction mixture was kept aside at room temperature for overnight. Then it was poured into ice-cold water, precipitate was filtered to give corresponding *N*-aryl sydnones. Followed it was washed with water and dried under high vacuum for several hours.

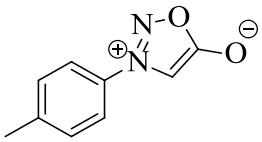
3-Phenyl-1,2,3-oxadiazol-3-ium-5-olate (51a)



Yield: 648 mg (80%); yellow solid. M.p.: 130-132 ^{o}C; R_f= 0.31 (*n*-hexane-EtOAc, 1:1).IR (KBr): 3126, 1759 (C=O), 1471, 1438, 1359,1290, 1226, 1087, 947, 758, 725

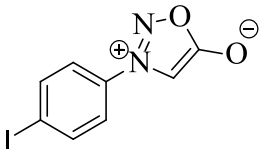
cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.2 Hz, 2H), 7.64 – 7.54 (m, 3H), 6.69 (s, 1H).

3-(*p*-Tolyl)-1,2,3-oxadiazol-3-ium-5-olate (51b)



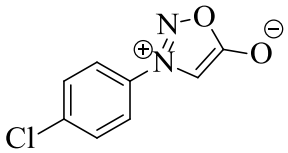
Yield: 686 mg (78%); orange solid. M.p.: 140-142 ^oC; R_f= 0.35 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3140, 1751 (C=O), 1508, 1446, 1350, 1292, 1226, 1172, 1080, 945, 817cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.62 (s, 1H), 2.41 (s, 3H).

3-(4-Iodophenyl)-1,2,3-oxadiazol-3-ium-5-olate (51c)



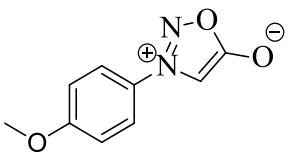
Yield: 1008 mg (70%); brown solid. M.p.: 138-140 ^oC; R_f= 0.46 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3128, 1745 (C=O), 1579, 1440, 1232,1058, 1003, 947, 854, 819, 727cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.9 Hz, 2H), 7.40 (d, *J* = 8.9 Hz, 2H), 6.66 (s, 1H).

3-(4-Chlorophenyl)-1,2,3-oxadiazol-3-ium-5-olate (51d)



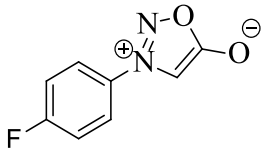
Yield: 735 mg (75%); brown solid. M.p.: 107-109 ^oC;R_f= 0.42 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3132, 1743 (C=O), 1492, 1442, 1234, 1095, 1010, 949, 856, 833, 729 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 2H), 6.65 (s, 1H).

3-(4-Methoxyphenyl)-1,2,3-oxadiazol-3-ium-5-olate (51e)



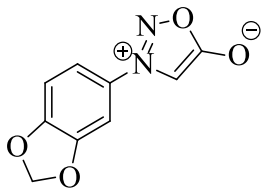
Yield: 720 mg (75%); brown solid. M.p.: 123-125 ^{o}C;R_f= 0.20 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3147, 1739 (C=O), 1604, 1512, 1454, 1257, 1165, 1006, 945, 833, 725cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 9.1 Hz, 2H), 7.01 (d, *J* = 9.1 Hz, 2H), 6.58 (s, 1H), 3.84 (s, 3H).

3-(4-Fluorophenyl)-1,2,3-oxadiazol-3-ium-5-olate (51f)



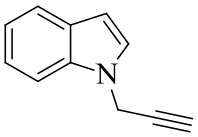
Yield: 720 mg (80%); yellow solid. M.p.: 152-154 ^{o}C;R_f= 0.35 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3111, 1737 (C=O), 1510, 1452, 1350,1240, 1178, 1022, 950, 840, 732 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.64 (m, 2H), 7.31–7.24 (m, 2H), 6.64 (s, 1H).

3-(Benzo[d][1,3]dioxol-5-yl)-1,2,3-oxadiazol-3-ium-5-olate (51g)



Yield: 700 mg (68%); brown solid. M.p.: 158-160 ^{o}C;R_f= 0.28 (*n*-hexane-EtOAc, 1:1). IR (KBr): 3124, 1753 (C=O), 1498, 1442, 1267,1074, 1037, 958, 929, 810, 731 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.16 (m, 2H), 6.95 (d, *J* = 8.3 Hz, 1H), 6.66 (s, 1H), 6.13 (s, 2H).

General procedure for the preparation of 1-(prop-2-ynyl)-1H-indole (195)



A procedure which was used in the literature for a similar compound (Munoz et al., 2012) has been followed. Thus, indole **193** (1.170 g, 10 mmol) in dry DMF (2 mL) was added dropwise to a suspension of NaH (0.40 g, 10 mmol) in dry DMF (5 mL) maintained at 0 °C and then the reaction mixture was stirred at room temperature for 8 h, followed by the addition of propargyl bromide **194** (1.190 g, 10 mmol) in dry DMF (1 mL). After completion of reaction (monitored by TLC), the

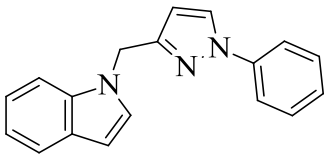
mixture was poured into cold water (30 mL) and the organic products extracted with dichloromethane (3×20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and the dichloromethane evaporated. The crude oily product was purified by column chromatography on silica gel using *n*-hexane/EtOAc (8:1) to give corresponding product.

Yield: 1160 mg (75%); yellow solid.Mp: 65–69 °C; R_f = 0.67 (*n*-hexane-EtOAc,1:1).IR (KBr): 3292, 3055, 2123, 1612, 1514, 1483, 1464, 1396, 1336, 1315, 1259, 1186, 1012, 931, 883, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$):δ=7.55 (dd, *J*=7.8, 0.9 Hz, 1H), 7.29 (dd, *J*=8.2, 0.7 Hz, 1H), 7.15 (ddd, *J*=8.2, 7.1, 1.1 Hz, 1H), 7.11–7.01 (m, 2H), 6.44 (dd, *J*=3.2, 0.8 Hz, 1H), 4.73 (d, *J*=2.6 Hz, 2H), 2.27 (t, *J*=2.6 Hz, 1H).

Preparation of pyrazolyl-*1H*-indoles 242 and 243

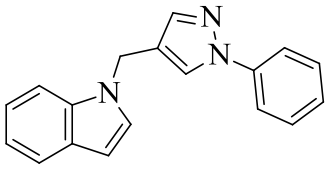
A solution of 1-(prop-2-ynyl)-1*H*-indole **193** (76 mg, 0.5 mmol) and a 4-aryl sydnone **51** (0.5 mmol) was refluxed in toluene (10 mL) for 12 h. After completion of the reaction, as indicated by TLC monitoring (*n*-hexane/EtOAc, 1:1), the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 230–400 Mesh ASTM) to give, separately, regioisomers **242**, which were eluted first as less polar fractions and **243** as second, more polar fractions.

((1-Phenyl-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (242a)



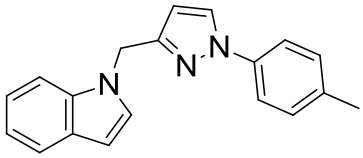
Yield: 25 mg (18%); white powder. Mp: 110–112 °C; R_f=0.58 (*n*-hexane/EtOAc, 1:1).IR (KBr): 3442, 1641, 1530, 1485, 1463, 1390, 1330, 1315, 1259, 1188, 1153, 1074, 1045, 754, 742 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ=7.67 (d, *J*=2.4 Hz, 1H), 7.62–7.50 (m, 3H), 7.44–7.30 (m, 3H), 7.26–7.17 (m, 1H), 7.17–7.09 (m, 2H), 7.09–6.99 (m, 1H), 6.45 (dd, *J*=3.1, 0.7 Hz, 1H), 6.02 (d, *J*=2.4 Hz, 1H), 5.32 (s, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ=151.2, 140.4, 136.6, 129.9, 129.1, 128.4 (2C; coincident), 126.9, 122.0, 121.3, 119.9, 119.5, 110.1, 106.8, 102.1, 44.7. HRMS: (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{16}N_3$: 274.1344. Found: 274.1349.

1-((1-Phenyl-1*H*-pyrazol-4-yl)methyl)-1*H*-indole (243a)



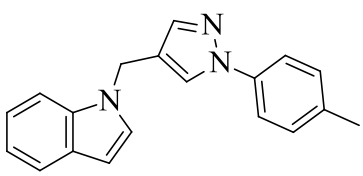
Yield: 49 mg (36%); light yellow solid. Mp: 105–107 °C; R_f=0.44 (*n*-hexane/EtOAc, 1:1).IR (KBr): 3442, 1642, 1600, 1567, 1504, 1460, 1396, 1333, 1313, 1265, 1217, 1186, 1109, 1042, 1012, 958, 902, 854, 798 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.61–7.55 (m, 3H), 7.54 (m, 1H), 7.50 (dd, *J*=9.2, 1.6 Hz, 1H), 7.32 (t, *J*=7.6 Hz, 2H), 7.20–7.09 (m, 3H), 7.07–7.02 (m, 2H), 6.45 (dd, *J*=2.8, 0.4 Hz, 1H), 5.18 (s, 2H).^{13}C NMR (101 MHz, $CDCl_3$): δ=140.4, 140.2, 136.3, 129.8, 129.2, 127.9, 127.0, 125.8, 122.1, 121.5, 120.4, 120.0, 119.5, 109.8, 102.1, 41.2.HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{16}N$: 274.1344. Found: 274.1354.

1-((1-*p*-Tolyl-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (242b)



Yield: 40 mg (28%); yellow solid. Mp: 95–97 °C; R_f=0.57 (*n*-hexane/EtOAc, 1:1).IR (KBr): 3435, 1638, 1527, 1511, 1441, 1383, 1354, 1297, 1238, 1198, 1058, 1004, 950, 810, 736 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.65 (d, *J*=2.4 Hz, 1H), 7.57 (d, *J*=8.0 Hz, 1H), 7.45 (d, *J*=8.4 Hz, 2H), 7.39 (d, *J*=8.0 Hz, 1H), 7.18–7.10 (m, 4H), 7.03 (t, *J*=8.0 Hz, 1H), 6.46 (d, *J*=3.2 Hz, 1H), 6.02 (d, *J*=2.4 Hz, 1H), 5.33 (s, 2H), 2.31 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ=150.9, 139.4, 136.8, 135.9, 133.1, 132.5, 130.3, 128.4, 122.0, 121.4, 119.9, 119.5, 110.1, 106.5, 102.0, 44.7, 21.3.HRMS: (ESI-TOF, $[M+H]^+$) calcd for $C_{19}H_{18}N_3$: 288.1501. Found: 288.1501.

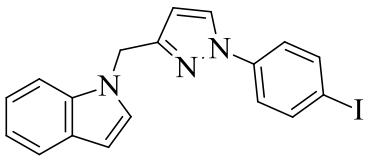
1-((1-*p*-Tolyl-1*H*-pyrazol-4-yl)methyl)-1*H*-indole (243b)



Yield: 61 mg (42%); dark yellow solid. Mp: 75–77 °C; R_f=0.40 (*n*-hexane/EtOAc, 1:1).IR (KBr): 3449, 1612, 1569, 1518, 1485, 1464, 1402, 1315, 1257, 1122, 1083,

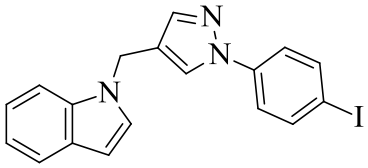
1037, 1012, 957, 883, 813, 738 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.62–7.51 (m, 3H), 7.37 (d, *J*=8.0 Hz, 2H), 7.30 (d, *J*=8.8 Hz, 1H), 7.16–7.01 (m, 5H), 6.45 (dd, *J*=3.2, 0.8 Hz, 1H), 5.17 (s, 2H), 2.27 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ=140.2, 138.1, 136.9, 136.3, 130.3, 129.1, 127.9, 125.8, 122.1, 121.5, 120.1, 120.0, 119.4, 109.8, 102.1, 41.2, 21.3.HRMS: *m*/*z*(ESI-TOF, $[M+H]^+$) calcd for $C_{19}H_{18}N_3$: 288.1501. Found: 288.1491.

1-((1-(4-Iodophenyl)-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (242c)



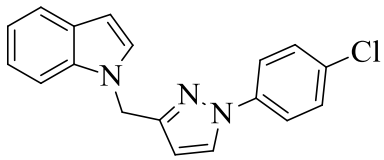
Yield: 40 mg (20%); light yellow solid. Mp: 136–138 °C; R_f=0.61 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3435, 1637, 1587, 1383, 1298, 1240, 1197, 1059, 1004, 946, 815, 765, 750, 665 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.66 (d, *J*=9.2 Hz, 2H), 7.63 (d, *J*=2.4 Hz, 1H), 7.56 (d, *J*=7.6 Hz, 1H), 7.36 (dd, *J*=8.0, 0.8 Hz, 1H), 7.33 (d, *J*=8.8 Hz, 2H), 7.13 (td, *J*=10.0, 7.2, 1.2 Hz, 2H), 7.04 (td, *J*=8.8, 8.0, 1.2 Hz, 1H), 6.46 (dd,*J*=3.2, 0.8 Hz, 1H), 6.03 (d, *J*=2.4 Hz, 1H), 5.31 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=151.6, 140.0, 138.8, 136.6, 129.1, 128.4, 128.2, 122.2, 121.2, 121.1, 119.9, 110.1, 107.2, 102.2, 91.0, 44.6. HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{15}IN_3$: 400.0311. Found: 400.0317.

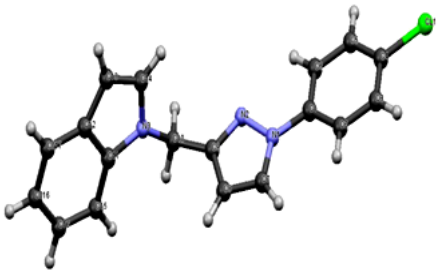
1-((1-(4-Iodophenyl)-1*H*-pyrazol-4-yl)methyl)-1*H*-indole (243c)



Yield: 10 mg (5%); yellow solid. Mp: 125–127 °C; R_f=0.55 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3428, 1647, 1492, 1460, 1394, 1332, 1311, 1257, 1195, 1168, 1082, 1041, 1011, 952, 860, 812, 738 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.63 (d, *J*=8.8 Hz, 2H), 7.59–7.55 (m, 2H), 7.28 (t, *J*=10.8 Hz, 3H), 7.20–7.01 (m, 4H), 6.46 (d, *J*=2.8 Hz, 1H), 5.18 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=140.7, 139.9, 138.8, 136.3, 129.1, 127.9, 125.5, 122.2, 121.5, 121.1, 121.0, 120.1, 109.7, 102.3, 91.1 (C–I), 41.2. HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{15}IN_3$: 400.0311. Found: 400.0311.

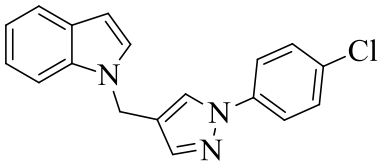
1-((1-(4-Chlorophenyl)-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (242d)

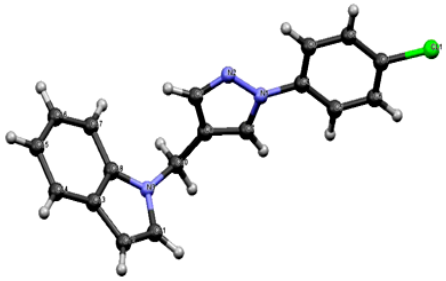




Yield: 54 mg (35%); yellow solid. Mp: 105–107 °C; R_f=0.64 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3422, 1615, 1597, 1530, 1498, 1464, 1383, 1309, 1256, 1174, 1093, 1051, 1010, 948, 830, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=7.63 (d, *J*=2.4 Hz, 1H), 7.56 (d, *J*=7.6 Hz, 1H), 7.52 (d, *J*=8.8 Hz, 2H), 7.36 (d,*J*=8.8 Hz, 1H), 7.32 (d, *J*=9.2 Hz, 2H), 7.17–7.10 (m, 2H), 7.03 (td, *J*=7.9, 0.9 Hz, 1H), 6.46 (d, *J*=4.0 Hz, 1H), 6.03 (d, *J*=2.4 Hz, 1H), 5.31 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ=151.5, 138.9, 136.6, 132.3, 129.9, 129.1, 128.4, 128.3, 122.1, 121.4, 120.6, 119.9, 110.1, 107.2, 102.2, 44.6. HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{15}ClN_3$: 308.0955. Found: 308.0948.

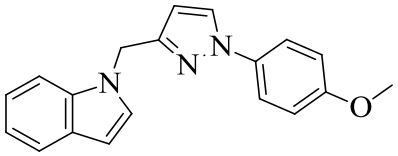
1-((1-(4-Chlorophenyl)-1*H*-pyrazol-4-yl)methyl)-1*H*-indole (243d)





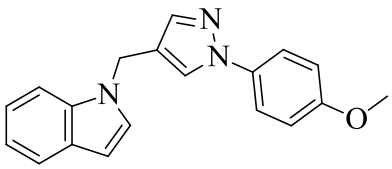
Yield: 11 mg (7%); yellow solid. Mp: 108–110 °C; R_f=0.55 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3435, 1639, 1500, 1471, 1408, 1309, 1215, 1122, 1092, 1037, 1012, 952 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ=7.59 (s, 1H), 7.57 (d, *J*=4.0 Hz, 2H), 7.45 (dt, *J*=10.0, 5.2, 3.2 Hz, 2H), 7.31–7.26 (m, 2H), 7.14 (td, *J*=8.4, 7.2, 1.2 Hz, 2H), 7.09–7.02 (m, 2H), 6.46 (dd, *J*=3.2, 0.8 Hz, 1H), 5.18 (s, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ=140.6, 138.7, 136.3, 132.5, 129.9, 129.1, 127.9, 125.7, 122.2, 121.5, 120.9, 120.6, 120.0, 109.7, 102.3, 41.2. HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{15}ClN_3$: 308.0955. Found: 308.0945.

1-((1-(4-Methoxyphenyl)-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (242e)



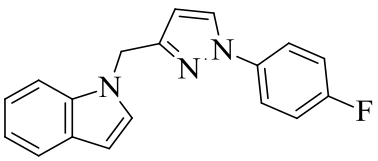
Yield: 15 mg (10%); light yellow solid. Mp: 93–96 °C; R_f=0.44 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3442, 1637, 1597, 1533, 1514, 1464, 1446, 1390, 1359, 1301, 1247, 1190, 1112, 1051, 1033, 962, 837, 768 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.59 (d, *J*=2.4 Hz, 1H), 7.56 (d, *J*=7.6 Hz, 1H), 7.47 (d, *J*=9.2 Hz, 2H), 7.39 (d,*J*=8.0 Hz, 1H), 7.17–7.09 (m, 2H), 7.04 (t, *J*=7.6 Hz, 1H), 6.89 (d, *J*=9.2 Hz, 2H), 6.46 (d, *J*=3.2 Hz, 1H), 6.02 (d, *J*=2.4 Hz, 1H), 5.32 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=158.7, 150.7, 136.6, 134.2, 129.1, 128.5, 128.4, 122.0, 121.3, 119.8, 114.9, 110.1, 106.3, 102.0, 56.0 (OCH_3), 44.7 (one quaternary coincident). HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{19}H_{18}N_3O$: 304.1450. Found: 304.1442.

1-((1-(4-Methoxyphenyl)-1*H*-pyrazol-4-yl)methyl)-1*H*-indole (243e)



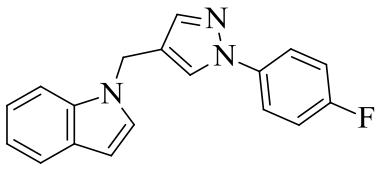
Yield: 61 mg (40%); light yellow solid. Mp: 106–108 °C; R_f=0.28 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3435, 1646, 1566, 1518, 1464, 1452, 1402, 1292, 1247, 1203, 1174, 1109, 1087, 1047, 1024, 958, 868, 836, 788, 741 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.58 (d, *J*=8.0 Hz, 1H), 7.53 (s, 2H), 7.40 (dt, *J*=12.4, 10.0, 3.2 Hz, 2H), 7.32 (d, *J*=8.8 Hz, 1H), 7.17–7.01 (m, 3H), 6.84 (dt, *J*=12.4, 8.0, 3.2 Hz, 2H), 6.46 (dd, *J*=3.2, 0.4 Hz, 1H), 5.18 (s, 2H), 3.74 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ=158.7 (C–OCH_3), 140.0, 136.3, 134.0, 129.1, 127.9, 125.9, 122.1, 121.4, 121.1, 119.9, 114.8, 109.8, 102.1, 55.9 (OCH_3), 41.2 (one quaternary coincident). HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{19}H_{18}N_3O$: 304.1450; found: 304.1451.

1-((1-(4-Fluorophenyl)-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (242f)



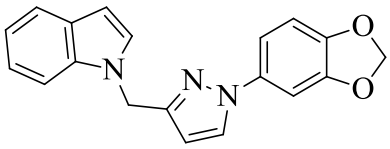
Yield: 26 mg (20%); light yellow solid. Mp: 94–96 °C; R_f=0.63 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3442, 1647, 1533, 1510, 1464, 1429, 1392, 1330, 1315, 1238, 1188, 1097, 1051, 1043, 1009, 952, 838, 755 cm^{-1}.^{1}H NMR (250 MHz, $CDCl_3$): δ=7.60 (d, *J*=2.5 Hz, 1H), 7.57–7.48 (m, 3H), 7.37 (d, *J*=8.7 Hz, 1H), 7.15–7.00 (m, 5H), 6.46 (dd, *J*=3.2, 0.7 Hz, 1H), 6.03 (d, *J*=2.2 Hz, 1H), 5.31 (s, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ=161.1 (d, *J*=246.3 Hz, C–F), 150.9, 136.4, 136.3, 136.2, 128.7, 128.1, 128.0, 121.6, 121.0, 120.9, 119.5, 116.3, 116.2, 109.7, 106.5, 101.7, 44.2 (one quaternary coincident). HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{15}FN_3$: 292.1250. Found: 292.1249.

1-((1-(4-Fluorophenyl)-1*H*-pyrazol-4-yl)methyl)-1*H*-indole (243f)



Yield: 14 mg (10%); yellow oil. R_f=0.44 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3442, 1642, 1516, 1485, 1462, 1400, 1313, 1264, 1228, 1153, 1097, 1035, 1010, 954, 835, 815, 738 cm^{-1}.^{1}H NMR (250 MHz, $CDCl_3$):δ=7.59 (t, *J*=1.0 Hz, 1H), 7.53 (d, *J*=3.0 Hz, 2H), 7.50–7.40 (m, 2H), 7.30 (d, *J*=8.2 Hz, 1H), 7.17–7.11 (td,*J*=8.2, 7.0, 2.2 Hz, 2H), 7.09–6.96 (m, 3H), 6.46 (dd, *J*=3.0, 0.7 Hz, 1H), 5.18 (s, 2H).^{13}C NMR (125 MHz, $CDCl_3$): δ=161.1 (d, *J*=244.6 Hz, C–F), 140.0, 136.2, 135.9, 127.5, 125.5, 121.8, 121.1, 120.9, 120.8, 119.6, 116.2, 116.1, 109.4, 101.8, 40.8. HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{18}H_{15}FN_3$: 292.1250. Found: 292.1248.

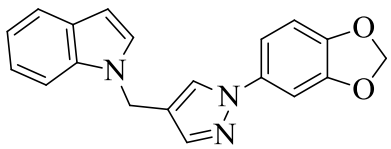
1-((1-(Benzo[d][1,3]dioxol-5-yl)-1*H*-pyrazol-3-yl)methyl)-1*H*-indole (242g)



Yield: 32 mg (20%); white solid. Mp: 121–123 °C; R_f=0.58 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3431, 1631, 1529, 1504, 1462, 1384, 1334, 1313, 1265, 1249, 1109, 1037, 934, 875, 739 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.56 (d, *J*=8.0 Hz, 1H), 7.53 (d, *J*=2.4 Hz, 1H), 7.37 (d, *J*=8.4 Hz, 1H), 7.15–7.09 (m, 3H), 7.02 (t,*J*=8.0 Hz, 1H), 6.96 (dd, *J*=8.4, 2.0 Hz, 1H), 6.76 (d, *J*=8.4 Hz, 1H), 6.45 (d, *J*=3.2 Hz, 1H), 5.99

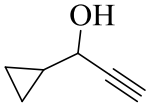
(d,*J*=2.4 Hz, 1H), 5.92 (s, 2H, OCH_2O), 5.29 (s, 2H).^{13}C NMR (100 MHz, $CDCl_3$): *δ*=150.8, 148.8, 146.7, 136.6, 135.3, 129.1, 128.6, 128.4, 122.0, 121.3, 119.9, 112.9, 110.1, 108.7, 106.5, 102.3, 102.2, 102.1, 44.6. HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{19}H_{16}N_3O_2$: 318.1243. Found: 318.1242.

1-((1-(Benzo[d][1,3]dioxol-5-yl)-1*H*-pyrazol-4-yl)methyl)-1*H*-indole (243g)



Yield: 16 mg (10%); brown oil. R_f=0.45 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3442, 1642, 1508, 1464, 1396, 1334, 1311, 1265, 1247, 1201, 1105, 1037, 966, 935, 881, 802, 738 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$):*δ*=7.57 (d, *J*=8.0 Hz, 1H), 7.51 (d, *J*=8.4 Hz, 2H), 7.31 (d, *J*=8.4 Hz, 1H), 7.17–7.02 (m, 4H), 6.90 (dd,*J*=8.4, 2.4 Hz, 1H), 6.71 (d, *J*=8.4 Hz, 1H), 6.46 (dd, *J*=3.2, 0.7 Hz, 1H), 5.92 (s, 2H), 5.18 (s, 2H).^{13}C NMR (100 MHz, $CDCl_3$): *δ*=148.7, 146.7, 140.0, 136.3, 135.2, 129.1, 127.9, 126.1, 122.1, 121.5, 120.1, 120.0, 112.9, 109.8, 108.6, 102.2, 102.1, 101.9, 41.2. HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{19}H_{16}N_3O_2$: 318.1243; found: 318.1238.

Preparation of 1-Cyclopropylprop-2-yn-1-ol (207)



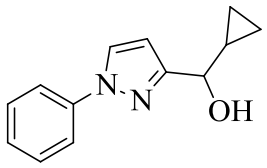
Cyclopropylcarboxaldehyde **205** (700 mg, 10 mmol) was added dropwise into a solution of ethynylmagnesium bromide **206** (22 mL of a 0.5 M solution in THF, 11 mmol) in dry THF at 0 °C. The reaction mixture was left to warm up to room temperature. After completion of the reaction, as indicated by TLC (*n*-hexane/EtOAc, 1:1), saturated aqueous ammonium chloride was added to the reaction mixture, which was then extracted with ethyl acetate (3×20 mL). The combined organic solutions were dried over Na_2SO_4 and the solvents evaporated. The crude oily product was then purified by column chromatography on silica gel using *n*-hexane/EtOAc (4:1) to give compound **207** (Mothe and Chan, 2009).

Yield: 768 mg (80%); bromn oil. R_f=0.67 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3373, 2966, 2110, 1712, 1452, 1438, 1381, 1317, 1207, 1078, 997, 945 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$):δ=4.13 (d, *J*=5.8 Hz, 1H), 2.38 (d, *J*=2.2 Hz 1H), 2.37 (s, 1H, OH), 1.23-1.15 (m, 1H), 0.62–0.31 (m, 4H).

Preparation of Cyclopropyl(1-substituted-1*H*-pyrazol-3-yl) methanols (244 a-g)

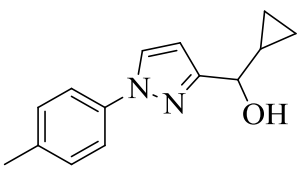
A mixture of 1-cyclopropylprop-2-yn-1-ol **207** (48 mg, 0.5 mmol) and a substituted sydnone **51** (0.5 mmol) was refluxed in toluene for 12 h. After completion of the reaction, as monitored by TLC (*n*-hexane/EtOAc, 1:1), the solvent was removed under reduced pressure. The crude product was purified by column chromatography to give regioisomers **244a-g** as the only isolable products.

Cyclopropyl(1-phenyl-1*H*-pyrazol-3-yl)methanol (244a)



Yield: 36 mg (33%); yellow oil. R_f=0.32 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3385, 1600, 1525, 1502, 1390, 1251, 1228, 1035, 754, 680 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.81 (d, *J*=2.4 Hz, 1H), 7.61–7.59 (m, 2H), 7.40–7.34 (m, 2H), 7.24–7.18 (m, 1H), 6.42 (d, *J*=2.4 Hz, 1H), 4.16 (d, *J*=8.3 Hz, 1H), 2.55 (br s, 1H, OH), 1.30–1.13 (m, 1H), 0.62–0.32 (m, 4H).^{13}C NMR (125 MHz, $CDCl_3$): δ=154.4 (C$=$N), 137.8, 127.1, 125.4, 124.1, 116.9, 102.6, 70.7 (C–OH), 15.3, 0.9. LC–MS (ES^+): *m*/*z* (%) 215 (M+H, 25), 197 (M−H_2O, 100). HRMS: (ESI-TOF, M+Na) calcd for $C_{13}H_{14}N_2ONa$: 237.1005. Found: 237.1004.

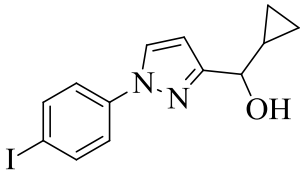
Cyclopropyl(1-*p*-tolyl-1*H*-pyrazol-3-yl)methanol (244b)



Yield: 36 mg (35%); yellow oil. R_f=0.34 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3408, 2922, 1739, 1612,1533, 1514, 1388, 1259,1035, 817 cm^{-1}. ^{1}H NMR (400 MHz,

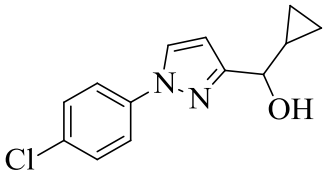
$CDCl_3$): δ=7.77 (d, J=2.3 Hz, 1H), 7.48 (d, J=8.3 Hz, 2H), 7.15 (d, J=8.3 Hz, 2H), 6.40 (d, J=2.3 Hz, 1H), 4.15 (d, J=8.3 Hz, 1H), 2.51 (br s, 1H, OH), 2.31 (s, 3H), 1.30–1.17 (m, 1H), 0.63–0.34 (m, 4H).^{13}C NMR (100 MHz, $CDCl_3$): δ=156.3 (C=N), 136.6, 130.3, 128.1, 119.5, 104.9, 73.5 (C–OH), 21.3, 18.0, 3.6, 2.6.LC–MS (ES^+): m/z (%) 229 (M+H, 78), 211 (M−H_2O, 100). HRMS: (ESI-TOF, M+Na) calcd for $C_{14}H_{16}N_2ONa$: 229.1341. Found: 229.1346.

Cyclopropyl(1-(4-iodophenyl)-1*H*-pyrazol-3-yl)methanol (244c)



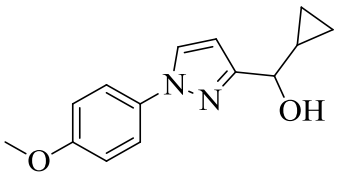
Yield: 64 mg (40%); light yellow oil. R_f=0.32 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3408, 2924, 1589, 1529, 1491,1383, 1251, 1033, 1004, 943, 823 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.79 (d, J=2.5 Hz, 1H), 7.65 (d, J=6.8 Hz, 2H), 7.38 (d, J=6.8 Hz, 2H), 6.43 (d, J=2.5 Hz, 1H), 4.13 (d, J=8.4 Hz, 1H), 2.51 (br s, 1H, OH), 1.31–1.08 (m, 1H), 0.66–0.32 (m, 4H).^{13}C NMR (125 MHz, $CDCl_3$): δ=154.7 (C=N), 136.1, 125.2, 118.4, 103.1, 88.0 (C–I), 70.6 (C–OH), 15.3, 0.9, 0.0.LC–MS (ES^+): m/z (%): 341 (M+H, 53), 323 (M−H_2O, 100). HRMS: (ESI-TOF, M+Na) calcd for $C_{13}H_{13}IN_2ONa$: 341.0151. Found: 341.0138.

Cyclopropyl(1-(4-chlorophenyl)-1*H*-pyrazol-3-yl)methanol (244d)



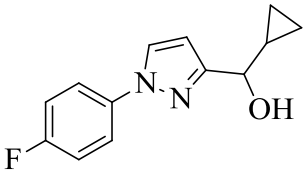
Yield: 53 mg (43%); brown oil. R_f=0.32 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3381, 1597, 1533, 1498, 1386, 1096, 1033, 1010, 947, 829, 738 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.77 (d, J=2.4 Hz, 1H), 7.54 (dt,J=9.6, 2.8 Hz, 2H), 7.33 (dt, J=9.6, 2.8 Hz, 2H), 6.43 (d, J=2.4 Hz, 1H), 4.13 (d, J=8.3 Hz, 1H), 2.58 (br s, 1H, OH), 1.33–1.10 (m, 1H), 0.68–0.30 (m, 4H).^{13}C NMR (125 MHz, $CDCl_3$): δ=154.7 (C=N), 136.3, 129.5, 127.2, 125.3, 117.9, 103.0, 70.6 (C–OH), 15.3, 0.9. LC–MS (ES^+): m/z (%) 249 (M+H, 18), 231 (M−H_2O, 100). HRMS: (ESI-TOF, M+Na) calcd for $C_{13}H_{13}ClN_2ONa$: 271.0614. Found 271.0627.

Cyclopropyl(1-(4-methoxyphenyl)-1*H*-pyrazol-3-yl)methanol (244e)



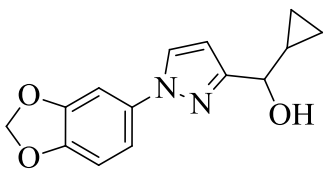
Yield: 40 mg (33%); yellow oil. R_f=0.23 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3385, 1658, 1525, 1514, 1249, 1031, 829, 798 cm^{-1}.^{1}H NMR (500 MHz, $CDCl_3$): δ=7.71 (d, *J*=2.4 Hz, 1H), 7.50 (d, *J*=6.8 Hz, 2H), 6.87 (d,*J*=6.8 Hz, 2H), 6.39 (d, *J*=2.4 Hz, 1H), 4.14 (d, *J*=8.3 Hz, 1H), 3.77 (s, 3H), 2.54 (br s, 1H, OH), 1.35–1.13 (m, 1H), 0.67–0.31 (m, 4H).^{13}C NMR (125 MHz, $CDCl_3$): δ=156.0 (C═N), 153.9 (C–OCH_3), 131.7, 125.5, 122.4, 118.6, 112.2, 102.1, 70.7 (C–OH), 53.3 (OCH_3), 15.3, 0.9. LC–MS (ES^+): *m*/*z* (%) 245 (M+H, 27), 227 (M−H_2O, 100).HRMS: (ESI-TOF, M+Na) calcd for $C_{14}H_{16}ClN_2O_2$: 267.1109. Found: 267.1112.

Cyclopropyl(1-(4-fluorophenyl)-1*H*-pyrazol-3-yl)methanol (244f)



Yield: 44 mg (38%); yellow oil. R_f=0.30 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3381, 1533, 1512, 1388, 1232, 1035, 835, 752 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.74 (d, *J*=2.4 Hz, 1H), 7.56 (dd, *J*=12.0, 4.5 Hz, 2H), 7.07 (t, *J*=8.0 Hz, 2H), 6.42 (d, *J*=2.4 Hz, 1H), 4.14 (d, *J*=8.4 Hz, 1H), 2.49 (br s, 1H, OH), 1.31–1.10 (m, 1H), 0.66–0.33 (m, 4H).^{13}C NMR (100 MHz, $CDCl_3$): δ=161.4 (C–F) (d, *J*=247.0 Hz), 157.0 (C═N), 128.2, 121.3, 116.7, 116.4, 105.4, 73.4 (C–OH), 18.0, 3.6, 2.7.LC–MS (ES^+): *m*/*z* (%) 233 (M+H, 48), 215 (M−H_2O, 100). HRMS: *m*/*z* (ESI-TOF, M+Na) calcd for $C_{13}H_{13}FN_2O$: 255.0910. Found: 255.0915.

(1-(Benzo[d][1,3]dioxol-5-yl)-1*H*-pyrazol-3-yl)(cyclopropyl)methanol (244g)

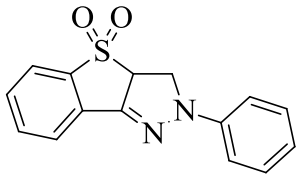


Yield: 39 mg (30%); brown oil. R_f=0.27 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3431, 1527, 1512, 1467, 1247, 1228, 1037, 933, 810 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.68 (d, *J*=2.4 Hz, 1H), 7.13 (d, *J*=2.2 Hz, 1H), 7.01 (dd, *J*=8.3, 2.2 Hz, 1H), 6.77 (d, *J*=8.3 Hz, 1H), 6.39 (d, *J*=2.4 Hz, 1H), 5.95 (s, 2H), 4.13 (d, *J*=8.3 Hz, 1H), 2.48 (br s, 1H, OH), 1.30–1.10 (m, 1H), 0.66–0.32 (m, 4H).^{13}C NMR (125 MHz, $CDCl_3$): δ=154.3 (C═N), 146.2, 144.0, 125.6, 110.3, 106.0, 102.3 (OCH_2O), 99.6, 99.4, 70.7 (C–OH), 27.4, 15.3, 0.9, 0.0.LC–MS (ES^+): *m*/*z* (%) 259 (M+H, 50), 241 (M−H_2O, 100). HRMS: *m*/*z* (ESI-TOF, M+Na) calcd for $C_{14}H_{14}N_2O_3Na$: 281.0902. Found: 281.0906.

Preparation of 2-(4-Substituted phenyl)-3,3a-dihydro-2*H*-[1]benzothieno[3,2-*c*]pyrazole 4,4-dioxides 249a-g

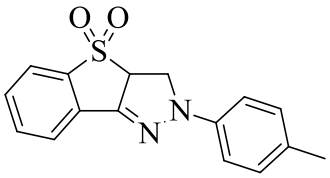
A mixture of benzo[*b*]thiophene 1,1-dioxide **217** (83 mg, 0.5 mmol) and a substituted sydnone **51 a-g** (0.5 mmol) was refluxed in toluene (10 mL) for 12 h. After completion of the reaction, as monitored by TLC (*n*-hexane/EtOAc, 1:1), the solvent was removed under reduced pressure. The crude product was then purified by column chromatography to give compounds **249 a-g.**

2-Phenyl-3,3a-dihydro-2*H*-[1]benzothieno[3,2-*c*]pyrazole 4,4-dioxide (249a)



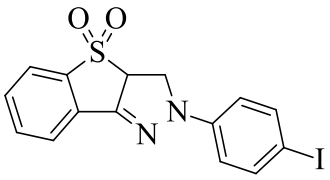
Yield: 50 mg (35%); yellow powder. Mp: 135–137 °C; R_f=0.49 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3061, 2924, 1653, 1597, 1500, 1465, 1375, 1296 (SO_2 asym), 1145 (SO_2 sym), 1062, 1001, 752 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.83–7.79 (m, 2H), 7.67 (t, *J*=7.6 Hz, 1H), 7.55 (t, *J*=7.6 Hz, 1H), 7.35 (t, *J*=8.4 Hz, 2H), 7.14 (d, *J*=8.0 Hz, 2H), 6.98 (t, *J*=7.2 Hz, 1H), 5.04 (dd, *J*=13.6, 10.4 Hz, 1H), 4.50 (t, *J*=10.4 Hz, 1H), 4.14 (dd, *J*=13.6, 10.4 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ=145.9, 145.1, 143.5, 134.3, 131.2, 130.1, 129.6, 123.2, 122.9, 121.7, 114.0, 66.8(C–SO_2), 50.3. HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{15}H_{13}N_2O_2S$: 285.0698. Found: 285.0701.

2-(4-Methylphenyl)-3,3a-dihydro-2*H*-[1]benzothieno[3,2-*c*]pyrazole 4,4-dioxide (249b)



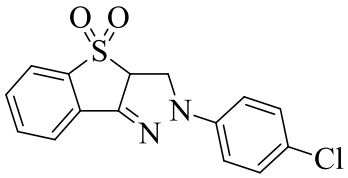
Yield: 49 mg (33%); yellow oil. R_f =0.50 (*n*-hexane/EtOAc, 1:1). IR (KBr): 2928, 1653, 1516, 1460, 1379, 1307 (SO_2 asym), 1168 (SO_2 sym), 1112, 954, 817 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ=7.84–7.78 (m, 2H), 7.66 (t, *J*=7.6 Hz, 1H), 7.54 (t, *J*=7.2 Hz, 1H), 7.14 (d, *J*=8.6 Hz, 2H), 7.04 (d, *J*=8.6 Hz, 2H), 5.03 (dd,*J*=13.6, 10.4 Hz, 1H), 4.48 (t, *J*=10.4 Hz, 1H), 4.10 (dd, *J*=13.6, 10.4 Hz, 1H), 2.31 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ=145.6, 142.8, 142.7, 134.0, 131.0, 130.8, 129.9, 129.8, 122.9, 122.6, 113.9, 66.6(C–SO_2), 50.4, 20.6 (CH_3). HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{16}H_{15}N_2O_2S$: 299.0854. Found: 299.0852.

2-(4-Iodophenyl)-3,3a-dihydro-2*H*-[1]benzothieno[3,2-*c*]pyrazole 4,4-dioxide (249c)



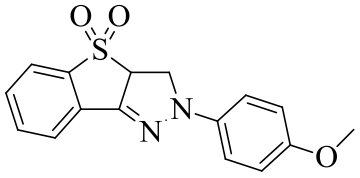
Yield: 78 mg (38%); yellow oil. R_f=0.47 (*n*-hexane/EtOAc, 1:1). IR (KBr): 2924, 1683, 1586, 1490,1381, 1305 (SO_2 asym), 1265, 1166 (SO_2 sym), 1146, 1070, 825, 833 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ=7.81 (t, *J*=6.7 Hz, 2H), 7.65 (td, *J*=7.6, 3.2 Hz, 1H), 7.62–7.55 (m, 2H), 6.89 (dt, *J*=9.7, 4.7 Hz, 2H), 5.04 (dd,*J*=13.6, 10.7 Hz, 1H), 4.47 (app. t, *J*=10.7 Hz, 1H), 4.10 (dd, *J*=13.6, 10.7 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ=146.0, 144.7, 144.2, 138.2, 134.3, 131.5, 129.8, 123.3, 122.9, 116.0, 83.8 (C–I), 66.9 (C–SO_2), 50.1. HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{15}H_{12}IN_2O_2S$: 410.9664. Found: 410.9664.

2-(4-Chlorophenyl)-3,3a-dihydro-2*H*-[1]benzothieno[3,2-*c*]pyrazole 4,4-dioxide (249d)



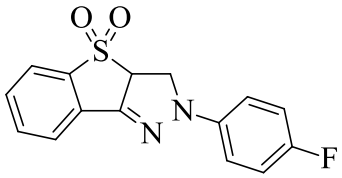
Yield: 64 mg (40%); orange solid. Mp: 163–165 °C; R_f=0.45 (*n*-hexane/EtOAc, 1:1). IR (KBr): 2926, 1683, 1653, 1593, 1492, 1465, 1379, 1303 (SO_2 asym), 1165 (SO_2 sym), 1145, 1124, 825, 767 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ=7.82 (t, *J*=7.0 Hz, 2H), 7.71 (t, *J*=6.7 Hz, 1H), 7.60 (t, *J*=6.7 Hz, 1H), 7.25 (d,*J*=8.7 Hz, 2H), 7.11–7.04 (m, 2H), 5.06 (dd, *J*=13.7, 10.5 Hz, 1H), 4.49 (t, *J*=10.5 Hz, 1H), 4.12 (dd, *J*=13.7, 10.5 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$): δ=146.0, 144.1, 143.7, 134.3, 131.4, 129.8, 129.5, 126.7, 123.3, 122.9, 115.2, 66.9 (C–SO_2), 50.4. HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{15}H_{12}ClN_2O_2S$: 319.0308. Found: 319.0308.

2-(4-Methoxyphenyl)-3,3a-dihydro-2*H*-[1]benzothieno[3,2-*c*]pyrazole 4,4-dioxide (249e)



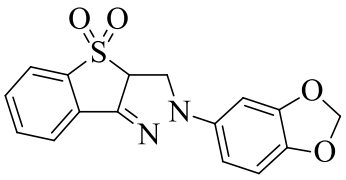
Yield: 55 mg (35%); yellow oil. R_f=0.46 (*n*-hexane/EtOAc, 1:1). IR (KBr): 3450, 1653, 1510, 1460, 1303 (SO_2 asym), 1244, 1145 (SO_2 sym), 1124, 1070, 1035, 827, 763 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ=7.81 (t, *J*=7.6 Hz, 2H), 7.73–7.20 (m, 2H), 7.11 (d, *J*=8.7 Hz, 2H), 6.89–6.82 (m, 2H), 5.04 (dd, *J*=14.0, 10.8 Hz, 1H), 4.48 (t, *J*=10.5 Hz, 1H), 4.08 (dd, *J*=14.0, 10.5 Hz, 1H), 3.80 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$):δ=155.1, 145.8, 139.4, 134.2, 133.8, 132.5, 131.0, 123.1, 122.8, 115.7, 114.9, 66.9 (C–SO_2), 55.8 (OCH_3), 51.4. HRMS: *m*/*z* (ESI-TOF, $[M+H]^+$) calcd for $C_{16}H_{15}N_2O_3S$: 315.0803. Found: 315.0808.

2-(4-Fluorophenyl)-3,3a-dihydro-2*H*-[1]benzothieno[3,2-*c*]pyrazole 4,4-dioxide (249f)



Yield: 68 mg (45%); yellow powder. Mp: 170–172 °C; R_f=0.45 (*n*-hexane/EtOAc, 1:1). IR (KBr): 2928, 1653, 1508, 1375, 1303 (SO_2 asym), 1224, 1145 (SO_2 sym), 1070, 825, 748 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$):δ=7.82 (t, *J*=7.0 Hz, 1H), 7.69 (t, *J*=7.6 Hz, 1H), 7.58 (t, *J*=7.6 Hz, 1H), 7.12–7.01 (m, 5H), 5.05 (dd, *J*=13.7, 10.5 Hz, 1H), 4.49 (t, *J*=10.5 Hz, 1H), 4.10 (dd, *J*=13.7, 10.5 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$): δ=159.3 (*J*=245.2 Hz, C–F), 145.9, 143.9, 141.7, 134.3, 131.3, 129.9, 123.4, 123.2, 116.0, 115.3, 67.0 (C–SO_2), 51.0. HRMS: (ESI-TOF, $[M+H]^+$) calcd for $C_{15}H_{12}FN_2O_2S$: 303.0604. Found: 303.0602.

2-(1,3-Benzodioxol-5-yl)-3,3a-dihydro-2*H*-[1]benzothieno[3,2-*c*]pyrazole 4,4-dioxide(249g)

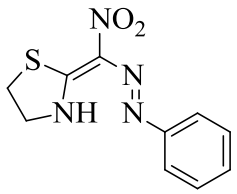


Yield: 49 mg (30%); orange solid. Mp: 155–157 °C; R_f=0.46 (*n*-hexane/EtOAc, 1:1). IR (KBr): 2924, 1683, 1587, 1506, 1489, 1303 (SO_2 asym), 1234, 1213, 1145 (SO_2 sym), 1037, 935, 812, 736 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$): δ=7.83–7.78 (m, 2H), 7.69 (t, *J*=6.7 Hz, 1H), 7.58 (t, *J*=6.7 Hz, 1H), 6.89 (dd, *J*=4.6, 2.6 Hz, 1H), 6.77 (d, *J*=8.2 Hz, 1H), 6.42 (dd, *J*=8.4, 2.3 Hz, 1H), 5.95 (s, 2H), 5.06 (dd, *J*=13.7, 10.5 Hz, 1H), 4.42 (t, *J*=10.5 Hz, 1H), 4.06 (dd, *J*=13.7, 10.5 Hz, 1H).^{13}C NMR (75 MHz, $CDCl_3$): δ=148.7, 145.9, 143.2, 142.9, 140.8, 134.2, 131.1, 130.0, 123.1, 122.8, 108.5, 106.0, 101.4, 97.6, 66.9 (C–SO_2), 51.3. HRMS: (ESI-TOF, $[M+H]^+$) calcd for $C_{16}H_{13}N_2O_4S$: 329.0596. Found: 329.0591.

Synthesis of (*Z*)-2-(nitro((*E*)-*p*-substitutedphenyldiazenyl)methylene) thiazolidines 261a-g

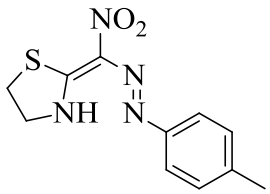
A mixture of *p*-substitutedphenyl sydnone **51a-g** (0.5 mmol) and 2-nitromethylenethiazolidine **231** (0.5 mmol, 73 mg) in xylene (5 mL) was irradiated by microwave (CEM Discover) at 125 ^{o}C, which was measured by internal probe, for 15 min. The reaction was monitored by TLC (*n*-hexane/EtOAc,1:1). After the completion of the reaction, the solvent was removed under the reduced pressure and crude product was chromatographed to give **261a-g**.

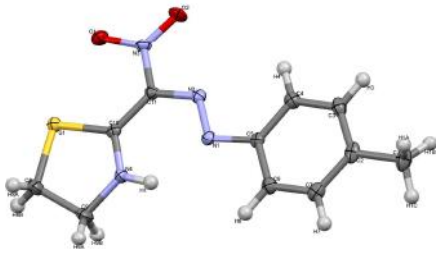
(*Z*)-2-(Nitro((*E*)-phenyldiazenyl)methylene)thiazolidine (261a)



Yield: 28.7 mg(%52); Yellow oil. R_f= 0.38 (EtOAc:*n*-hexane, 1:1). IR (KBr, cm^{-1}): 3419 (NH),2926, 1631, 1554, 1263, 1049, 794. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.56 (s, 1H, NH), 7.51 (dd,*J* = 7.6, 1.2 Hz, 2H), 7.41 (t, *J* = 8.2 Hz, 2H), 7.25–7.21 (m, 1H), 4.46 (t, *J* = 8.6 Hz, 2H, NCH_2), 3.24 (t, *J* = 8.8 Hz, 2H, SCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.6(C=**C**-NO_2), 142.6, 129.8,126.8, 117.7, 61.5 (NCH_2), 29.8 (SCH_2). LC-MS (AP-ESI) m/z (%): 251.7 [M^+ + H]. HRMS:*m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{10}H_{11}N_4O_2S$: 251.0603; found: 251.0589.

(*Z*)-2-(Nitro((*E*)-*p*-tolyldiazenyl)methylene)thiazolidine (261b)

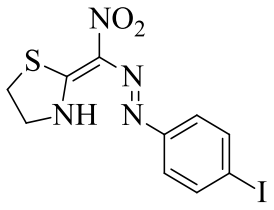




Yield: 26.4 mg (20%);Light yellow needles (dichloromethane:*n*-hexane). Mp: 135^{O}C (decomposed);R_f= 0.38 (EtOAc:*n*-hexane, 1:1). IR (KBr, cm^{-1}): 3356 (NH), 2920, 1653, 1548,1421, 1276, 1053, 817, 734. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.55 (s, 1H, NH), 7.42 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 4.42 (t, *J* = 8.6 Hz, 2H, NCH_2), 3.21 (t, *J* = 8.4 Hz, 2H,SCH_2), 2.35 (s, 3H). ^{1}H NMR (400 MHz, DMSO-*d6*)

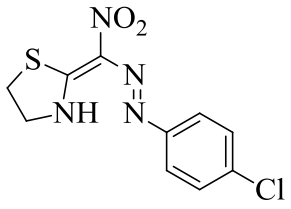
δ 12.44 (brs, 1H, NH), 7.63 (d, *J* = 8.0 Hz,2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.16 (t, *J* = 8.6 Hz, 2H, NCH2), 3.25 (t, *J* = 8.4 Hz, 2H, SCH_2),2.30 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (C=**C**-NO_2), 140.6, 137.0, 130.2, 117.8, 60.8 (NCH_2), 30.5 (SCH_2), 21.2 (CH_3). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 162.7 (C=**C**-NO_2), 148.1(**C**=C-NO_2), 138.7, 135.8, 130.3, 121.1, 53.9 (NCH_2), 29.2 (SCH_2), 21.3 (CH_3).LC-MS (APESI) m/z (%): 265.7 $[M+H]^+$. HRMS: *m/z* (ESI-TOF, $[M^+$+H]) calcd for $C_{11}H_{13}N_4O_2S$:265.0759; found: 265.0750.

(*Z*)-2-(((*E*)-(4-Iodophenyl)diazenyl)(nitro)methylene)thiazolidine (261c)



Yield: 50.6 mg(27%);Yellow oil. R_f= 0.36 (EtOAc:*n*-hexane, 1:1). IR (KBr, cm^{-1}): 3323 (NH),2924, 1663, 1546, 1485, 1267, 1051, 1003, 823, 738. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.39 (s,1H, NH), 7.72 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 10.0 Hz, 2H), 4.43 (t, *J* = 8.6 Hz, 2H, NCH_2),3.25 (t, *J* = 8.6 Hz, 2H, SCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8(C=**C**-NO_2), 143.0, 138.6, 119.6, 90.9 (C-I), 60.4 (NCH_2), 30.6 (SCH_2). ^{13}C NMR (100 MHz, DMSO-*d6*) δ 163.0 (C=**C**-NO_2), 150.2, 138.6, 136.1, 123.2, 94.9 (C-I), 53.7 (NCH_2), 29.9 (SCH_2). LC-MS (AP-ESI) m/z (%): 377.0 $[M^+$+H]. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{10}H_{10}N_4O_2SI$: 376.9569; found: 376.9570.

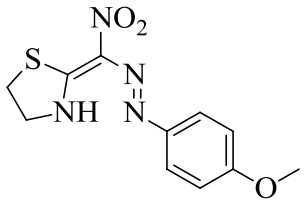
(*Z*)-2-(((*E*)-(4-Chlorophenyl)diazenyl)(nitro)methylene)thiazolidine (261d)



Yield: 38.3 mg(27%);Yellow oil.R_f= 0.35 (EtOAc:*n*-hexane, 1:1). IR (KBr, cm^{-1}): 3419 (NH),2916, 1629, 1548, 1483, 1419, 1267, 835, 732. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.34 (s, 1H,NH), 7.47 (d, *J* = 9.2 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 4.43 (t, *J* = 8.8 Hz, 2H, NCH_2), 3.25 (t, *J* = 8.4 Hz, 2H, SCH_2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.7 (C=C-NO_2), 142.1, 132.1, 129.7,119.1, 60.3 (NCH_2), 30.6 (SCH_2).

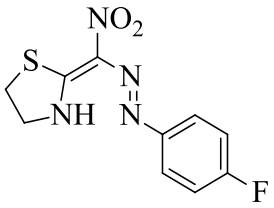
LC-MS (AP-ESI) m/z (%): 285.1 [M^++H]. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{10}H_{10}N_4O_2SCl$: 285.0213; found: 285.0200.

(*Z*)-2-(((*E*)-(4-Methoxyphenyl)diazenyl)(nitro)methylene)thiazolidine (261e)



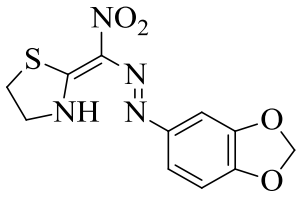
Yield: 32.2 mg(23%);Orange oil. R_f=0.36 (EtOAc:*n*-hexane, 1:1). IR (KBr, cm^{-1}): 3423 (NH),2916, 1664, 1514, 1467, 1379, 1263, 738. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.24 (s, 1H, NH), 7.52 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 4.38 (t, *J* = 8.6 Hz, 2H, NCH_2), 3.84 (s, 3H,OCH_3), 3.23 (t, *J* = 8.6 Hz, 2H, SCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7 (C=C-NO_2), 159.2(C-OCH_3), 138.6, 135.2, 120.2, 114.8, 58.5 (NCH_2), 55.6 (OCH_3), 30.1 (SCH_2). LC-MS (AP-ESI) m/z (%): 281 $[M^+H]^+$. HRMS: *m/z* (ESI-TOF, [M^++H]) calcd for $C_{11}H_{13}N_4O_3S$:281.0708;found: 281.0701.

(*Z*)-2-(((*E*)-(4-Fluorophenyl)diazenyl)(nitro)methylene)thiazolidine (261f)



Yield: 26.8 mg(20%);Orange oil.R_f= 0.35 (EtOAc:*n*-hexane, 1:1). IR (KBr, cm^{-1}): 3437 (NH),2916, 1637, 1548, 1483, 1427, 1267, 839, 734. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.24 (s, 1H, NH),7.55-7.52 (m, 2H), 7.12 (t, *J* = 8.6 Hz, 2H), 4.41 (t, *J* = 8.8 Hz, 2H), 3.25 (t, *J* = 8.6 Hz, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 163.0 (C=C-NO_2), 161.6 (C-F, d, *J* = 245.8 Hz), 140.7, 134.8,120.1, 116.8, 59.5 (NCH_2), 30.5 (SCH_2). LC-MS (AP-ESI) m/z (%): 269 [M^+ + H]. HRMS: *m/z* (ESI-TOF, $[M+H]^+$) calcd for $C_{10}H_{10}N_4O_2FS$: 269.0509; found: 269.0497.

(*Z*)-2-(((*E*)-Benzo[*d*][1,3]dioxol-5-yldiazenyl)(nitro)methylene)thiazolidine (261g)



Yield: 32.3 mg(22%);Brown oil.R_f= 0.32 (EtOAc:*n*-hexane, 1:1). IR (KBr, cm^{-1}): 3319 (NH),2924, 1689, 1546, 1491, 1253, 1035, 929, 810, 742. ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.02 (s, 1H,NH), 7.29 (d, *J* = 8.8 Hz, 1H), 7.01 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.99 (dd, *J* = 8.0, 2.0 Hz, 1H),6.04 (s, 2H, OCH_2O), 4.37 (t, *J* = 8.4 Hz, 2H, NCH_2), 3.26 (t, *J* = 8.4 Hz, 2H, SCH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (C=C-NO_2), 149.1, 147.4, 140.9, 114.5, 108.3, 101.9, 98.9 (OCH_2O), 57.8 (NCH_2), 30.0 (SCH_2). LC-MS (AP-ESI) m/z (%): 295 [M+H]. HRMS: *m/z*(ESI-TOF, $[M+H]^+$) calcd for $C_{11}H_{11}N_4O_4S$: 295.0501; found: 295.0490.

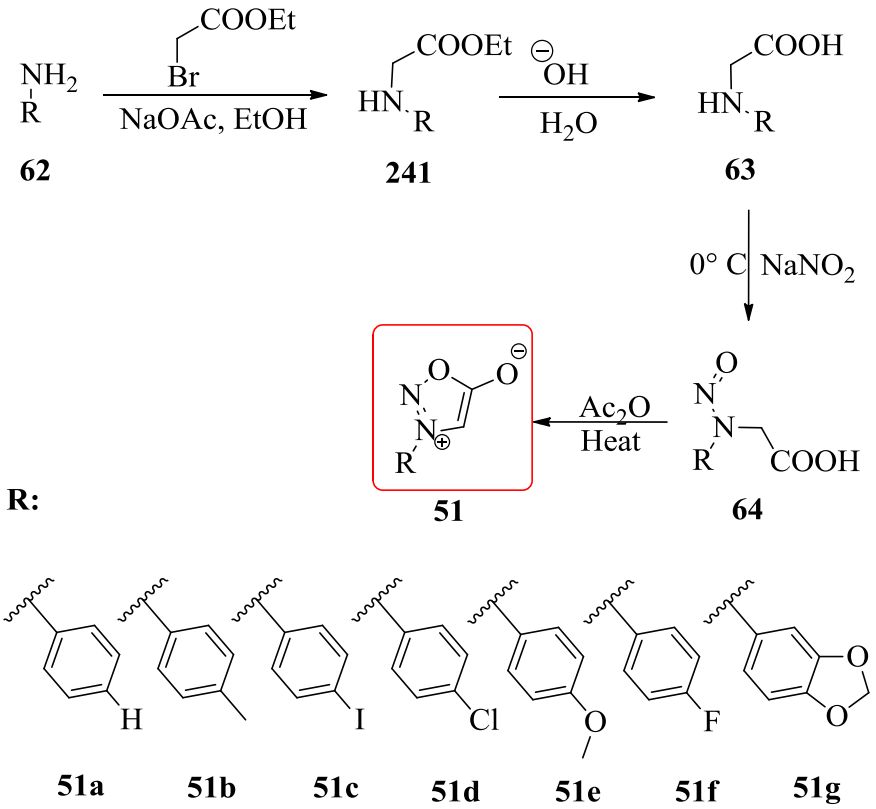
4. RESULTS AND DISCUSSION

CHAPTER 1

4.1 Cycloaddition Reactions of Aryl Sydnones with 1-(prop-2-ynyl)-1*H*-indole

4.1.1 Synthesis and Characterization of *N*-aryl Sydnone Derivatives

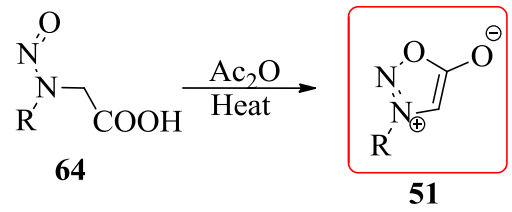
Sydnones have been known as a well-defined member of mesoionic compounds that generally used as azomethine precursors in cycloaddition reactions. In the first part of our work, our aim is to synthesize seven *N*-aryl sydnone derivatives **51a-g** by using convenient literature method that covers four sequential steps starting from aniline derivatives **62** to *N*-substituted aminoacids **63** followed nitrosation of *N*-substituted aminoacids **64** and cyclocondensation generally furnishes desired *N*-aryl sydnone derivatives **51a-g**. Synthetic methodology of *N*-aryl sydnones are shown in Scheme 4.1 (Satheesha *et al*., 2008).



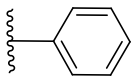
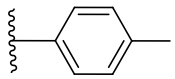
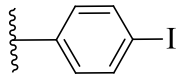
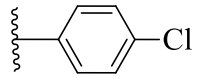
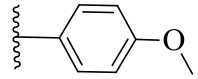
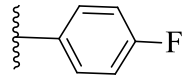
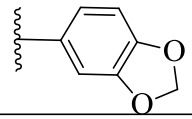
Scheme 4.1 Synthesis of *N*-aryl sydnone derivatives

N-aryl sydnone derivatives were prepared succesfully in moderate to good yield without any intermediate purification. Synthesized *N*-aryl sydnones can be regarded as air stable compounds therefore they were stored at room temperature for being used throughout this study. The structure elucidation of *N*-aryl sydnones were performed by means of spectroscopic methods IR and ^{1}H NMR. Physical and spectroscopic data of *N*-aryl sydnones are figured in Table 4.1

Table 4.1 Physical constants, IR data, ^{1}H NMR shifts of C-4-H protons of the compounds **51a-g**.



64 **51**

Compound	R	Melting point	$V_{(C=O)(cm-1)}$	δ_{C4H}	Yield
51 a		130-132 °C	1759	6.69 (s)	80
51 b		140-142 °C	1751	6.62 (s)	78
51 c		138-140 °C	1745	6.66 (s)	70
51 d		107-109 °C	1743	6.65 (s)	75
51 e		123-125 °C	1739	6.58 (s)	75
51 f		152-154 °C	1737	6.64 (s)	80
51 g		158-160 °C	1753	6.67 (s)	65

In the IR spectra of *N*-aryl sydnones **51a-g,** the carbonyl streching vibrations appeared between 1737-1759 cm^{-1} and chemical shifts of hydrogen which is bonded to C-4 position of sydnone ring appeared between 6.62-6.69 ppm as singlet. Also melting points of corresponding sydnones were found to be close enough to literature value (Hedge *et al*., 2006).

4.1.2 Synthesis and Characterization of Pyrazolyl-*1H*-indoles

The variability of indole nucleus in biological systems and biologically active naturally occurring alkaloids including the essential amino acid tryptophan, the neurotransmitter seratonine, the mammalian hormone melatonine and 5-HT3 receptor antagonists ondansetron (Corey *et al*., 2007; de Sa Alves *et al*., 2009; Eid *et*

al., 2002) has prompted us to synthesize 1-(prop-2-yn-1-yl)-1H-indole as an acetylenic dipolarophile.

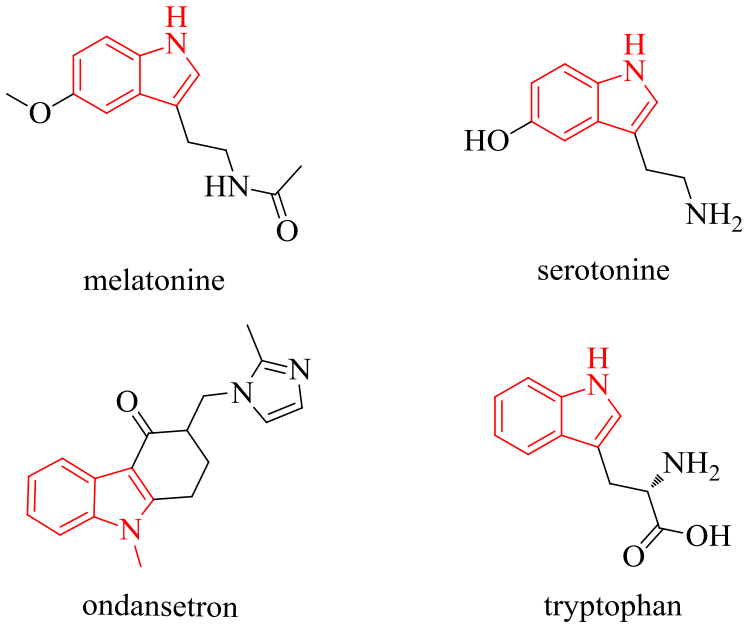
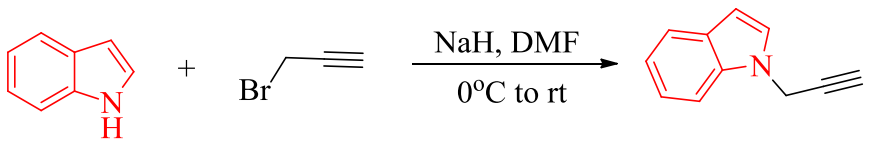


Figure 4.1 Biologically important molecules containing indole nucleus

Typical literature procedure for the preparation of 1-(prop-2-yn-1-yl)-1*H*-indole **195** is the treatment of indole **193** with propargyl bromide **194** in the presence of interphase catalysis affording the title compound in low yield (Samsoniya *et al*., 1991). For this reason, an efficient procedure has been utilized for the preparation of 1-(prop-2-yn-1-yl)-1*H*-indole, by a slight modification of the literature procedure used for a similar compound. The method involves the addition of NaH into a suspension of indole **193** then treatment of the mixture with propargyl bromide **194** without using any catalyst gave the pure 1-(prop-2-yn-1-yl)-1*H*-indole **195** by column chromatographic separation in relatively high yield (Munoz *et al*., 2012).



Scheme 4.2 Synthesis of 1-(prop-2-yn-1-yl)-1H-indole **195**

Synthesized 1-(prop-2-yn-1-yl)-1*H*-indole **195** was identified by the means of IR, ^{1}H NMR and physical properties such as M.p. and R_f value. Characteristic IR-streching vibrations of corresponding acetylenic dipolarophile appeared around 2123

cm^{-1}. In addition, methylenic proton signals H_b and acetylenic proton H_a of the 1-(prop-2-yn-1-yl)-1*H*-indole **195** were observed at 4.73 ppm, 2.27 ppm respectively in ^1H NMR spectra**.**

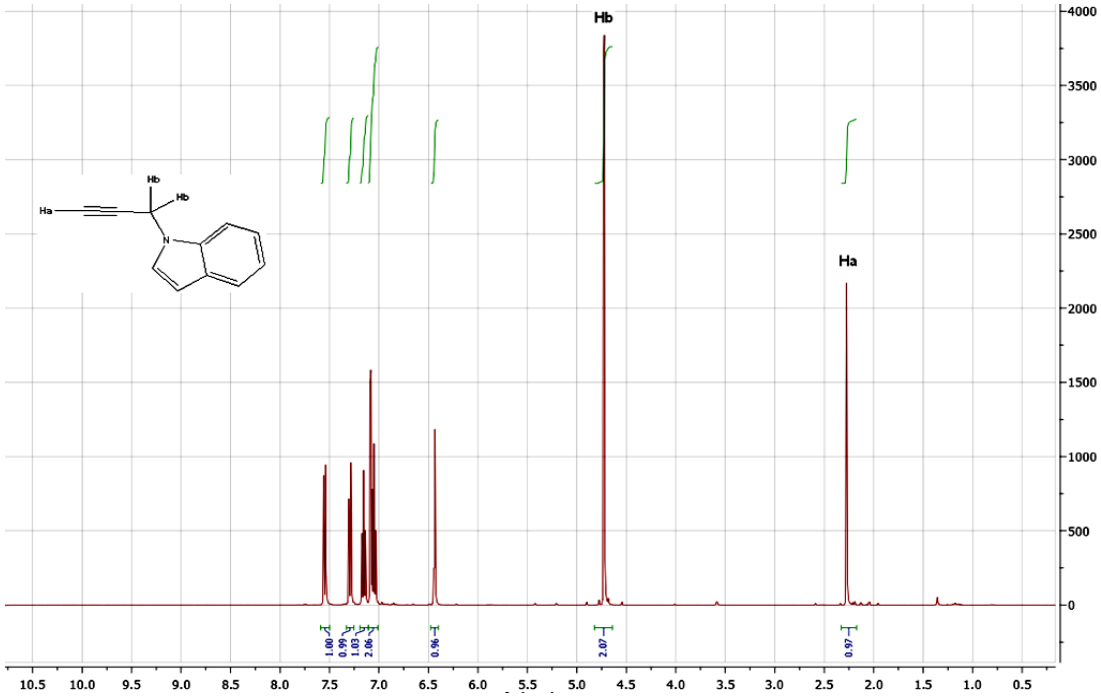
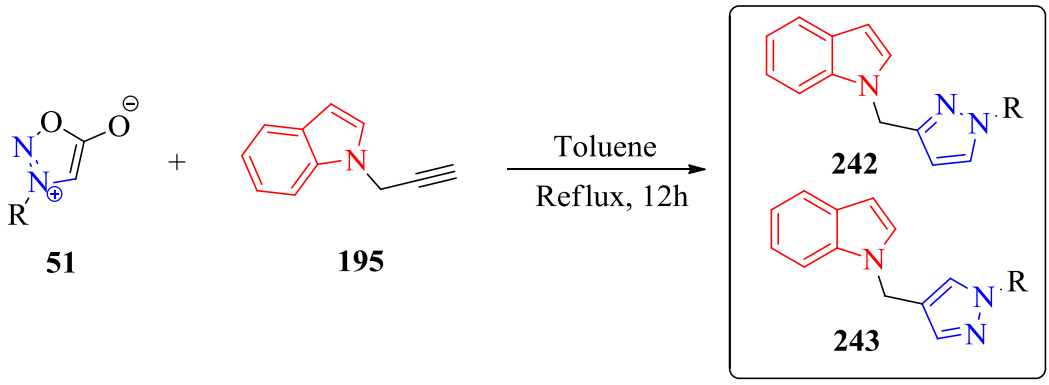


Figure 4.2 ^1H NMR spectrum of 1-(prop-2-yn-1-yl)-1*H*-indole **195**

1,3-Dipolar cycloaddition reactions of *in situ* generated azomethine imines, obtained via CO_2 release from *N*-aryl substituted sydnones, with 1-(prop-2-yn-1-yl)-1*H*-indole **195** in toluene at reflux temperature yielded regioisomeric products **242** and **243** in the ratios shown below (Table 4.2) Fortunately, the regioisomers (**242** and **243**) are reasonably easy to separate by column chromatography using hexanes-ethyl acetate mixtures.



Scheme 4.3 Synthesis of pyrazolyl-1H-indoles **242** and **243**

Table 4.2 Regioisomeric ratios and yields of the cycloadducts **242:243**

Entry	R	Reaction time (h)	Yield (**242**)(%)	Yield (**243**)(%)	Ratio (**242:243**)
1	C_6H_5	12	18	36	1:2
2	4-CH_3-C_6H_4	12	28	42	2:3
3	4-I-C_6H_4	12	20	5	4:1
4	4-Cl-C_6H_4	12	35	7	5:1
5	4-OCH_3-C_6H_4	12	10	40	1:4
6	4-F-C_6H_4	12	20	10	2:1
7	3,4-(OCH_2O)C_6H_4	12	20	10	2:1

In order to optimize the reaction yields and establish the regiochemistry of the products, different conditions have been assayed such as performing reaction in microwave reactor by using various solvents and refluxing in the presence of CuI as a catalyst. However, when the reaction was carried out in microwave reactor, no product was isolated at the end of the reaction. Interestingly, the presence of CuI showed no remarkable affect on the reaction yields and regioselectivity of dipoles. Cycloaddition reaction was attempted between *N*-aryl sydnones **51a-g** and1-(prop-2-yn-1-yl)-1*H*-indole **195** by using CuI as a catalyst, but present results were obtained in each case.

Table 4.3 Optimization of reaction conditions to yield compound **242** and **243**

Comp.1	**Comp.2**	**Reaction condition**		**Solvent**	**Ratio (242:243)**	**Total yield%**
51 a	195	MW, 300W	110-140°C, 1h	Toluene	-----	-----
51 b	195	MW, 300W	110-140°C, 1h	Toluene	-----	-----
51 c	195	MW, 300W	110-140°C, 1h	Toluene	-----	-----
51 a	195	MW, 300W	110-170°C, 1h	Xylene	-----	-----
51 b	195	MW, 300W	110-170°C, 1h	Xylene	-----	-----
51 c	195	MW, 300W	110-170°C, 1h	Xylene	-----	-----
51 a	195	MW, 300W	80-100°C, 1h	1,2-DME	-----	-----
51 b	195	MW, 300W	80-100°C, 1h	1,2-DME	-----	-----
51 c	195	MW, 300W	80-100°C, 1h	1,2-DME	-----	-----
51 a	195	5%(eq.) CuI	110 °C, 12h	Toluene	1:2	54
51 b	195	5%(eq.) CuI	110 °C, 12h	Toluene	2:3	70
51 c	195	5%(eq.) CuI	110 °C, 12h	Toluene	4:1	25

All of the new regioisomers were identified by means of spectroscopic and physical data including IR, NMR, HRMS and X-ray diffraction. Mainly, the stereochemistry of cycloadducts can be explained by interpreting coupling constants of hydrogens attached on pyrazole ring. While the related hydrogens comprising regioisomers **242** resonated at around 6.45-6.02 ppm as two doublets mostly, the one of the hydrogens on pyrazole ring belongs to regioisomers **243** resonated at around 6.45 as doublet of doublets. (Table 4.4) However, this data did not seem to provide a sufficiently reliable basis for structural assignment, particularly due to analysis of the proton data was incomplete owing to many overlapping resonances.

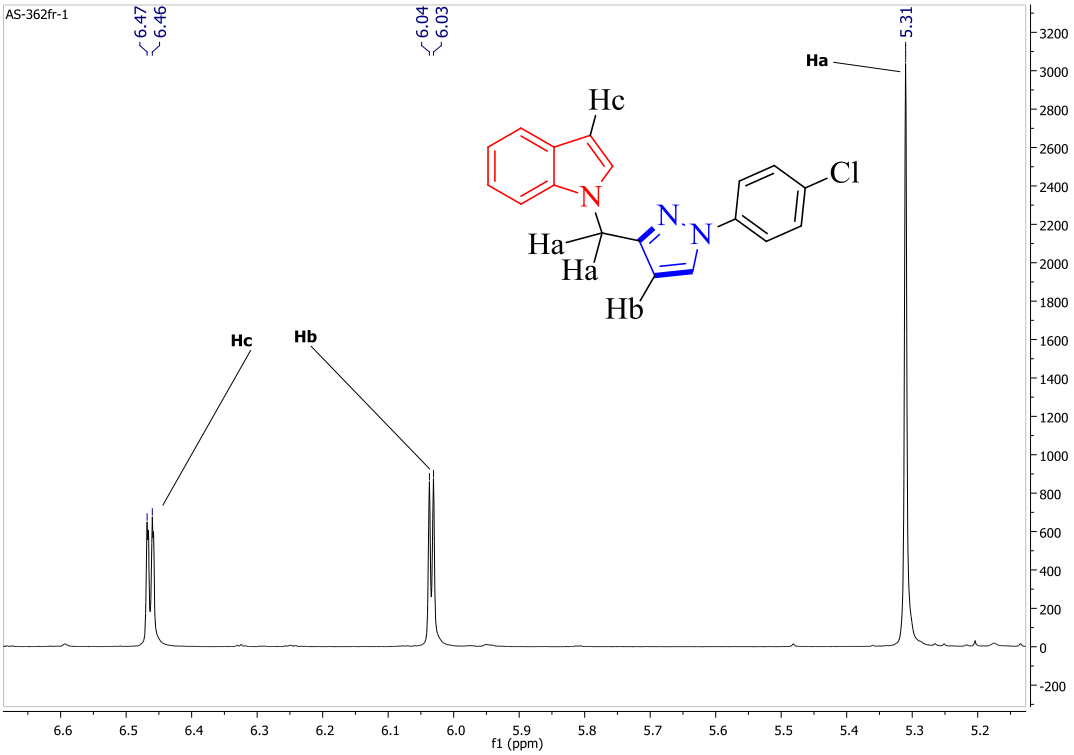


Figure 4.3 Representative expanded ^{1}H NMR spectrum of compound **242d**

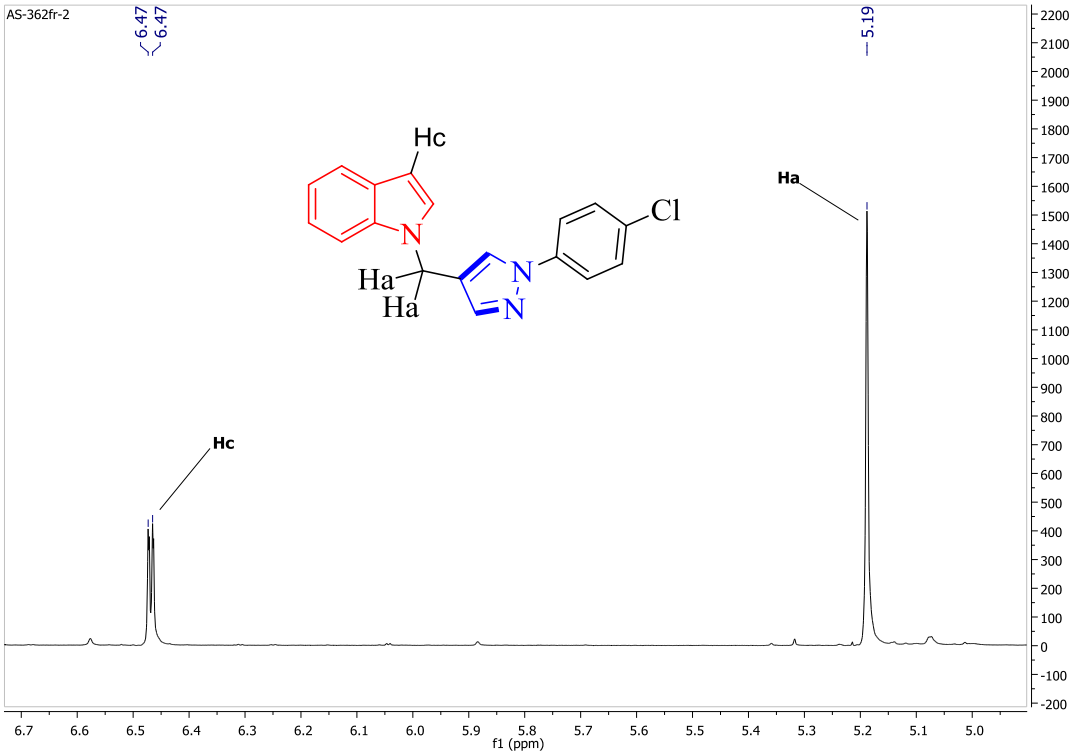


Figure 4.4 Representative expanded ^{1}H NMR spectrum of compound **243d**

Although NMR results were consistent with the regioisomers **242** and **243**, some peaks in the aliphatic region that are not related to the structures were observed both in ^{1}H and ^{13}C NMR spectra. These peaks most probably may be originated from the impurities in $CDCl_3$.

Table 4.4 ^{1}H NMR shifts and coupling constants for H_a, H_b and H_c protons of compound **242a-g** and **243a-g** in $CDCl_3$

Comp.	**Ha** (ppm)	**Hb** (ppm)	***J*** (Hz)	**Hc** (ppm)	***J*** (Hz)
242 a	5.32, s	6.02, d	2.4	6.45, dd	3.1, 0.7
243 a	5.18, s			6.45, dd	2.8, 0.4
242 b	5.33, s	6.02, d	2.4	6.46, d	3.2
243 b	5.17, s			6.45, dd	3.2, 0.8
242 c	5.31, s	6.03, d	2.4	6.46, dd	3.2, 0.8
243 c	5.18, s			6.46, d	2.8
242 d	5.31, s	6.03, d	2.4	6.46, d	4.0
243 d	5.18, s			6.46, dd	3.2, 0.8
242 e	5.32, s	6.02, d	2.4	6.46, d	3.2
243 e	5.18, s			6.46, dd	3.2, 0.4
242 f	5.31, s	6.03, d	2.2	6.46, dd	3.2, 0.7
243 f	5.18, s			6.46, dd	3.0, 0.7
242 g	5.29, s	5.99, d	2.4	6.45, d	3.2
243 g	5.18, s			6.46, dd	3.2, 0.7

Fortunately, many of the products were crystalline and we were able to resort to X-ray crystallographic analysis, specifically of products **242d** and **243d**. Exact structures of the regioisomers were established by the X-ray ORTEP views of the single crystals. In this manner, the NMR results of regioisomers (**242-243**) were supported by single X-ray diffraction measurements. Neither ORTEP diagram revealed any unusual features in these structures. Comparative NMR data then allowed structural assignments to be made to all the remaining products with certainty and good accordance.

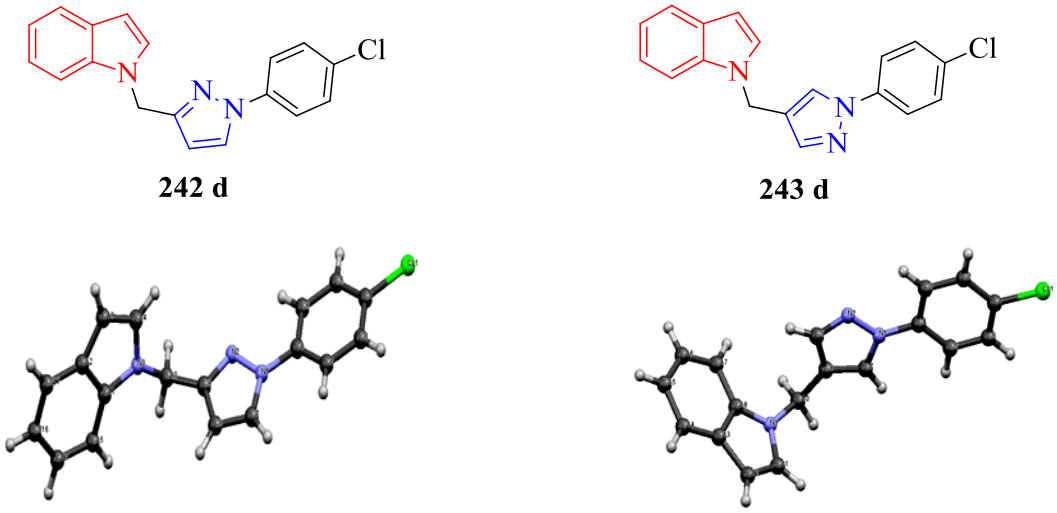
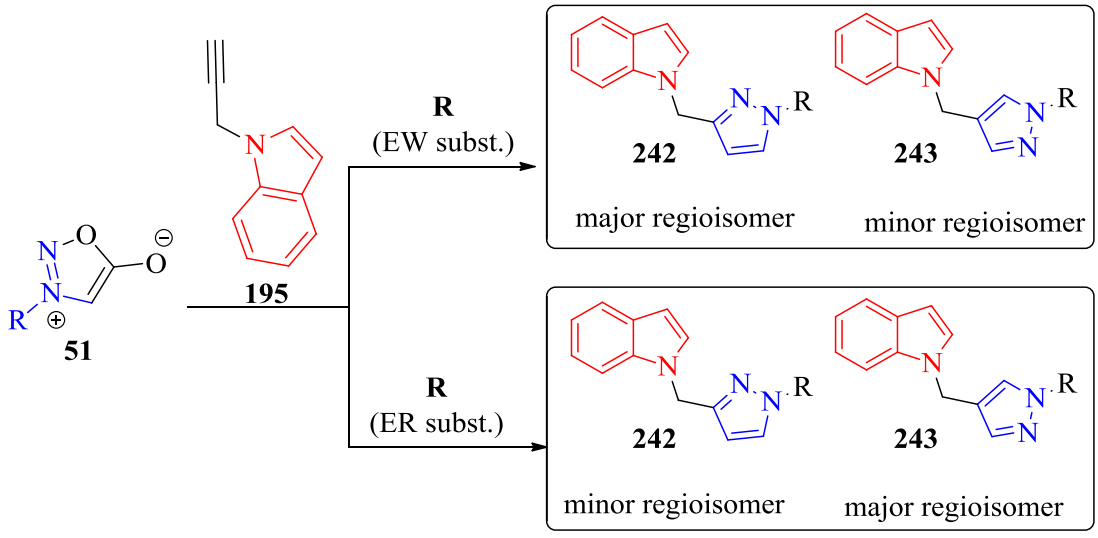


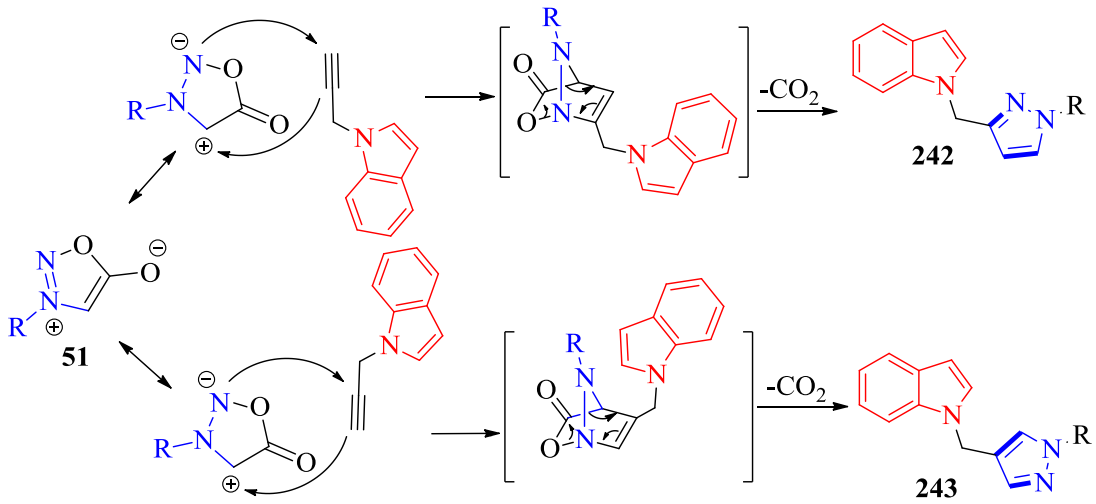
Figure 4.5 Structures of regioisomers **242d** and **243d** with X-ray views

By examining the ratio of the regioisomers based on the reaction yields (Table 4.2), it is seen that, in the case of electron donating groups present on the sydnone *N*-aryl substituent, the regioisomers **243** are the major products while regioisomers **242** are minor products. The reverse is true when there is an electron-withdrawing halogen atom at the 4-position of the phenyl group and the regioisomers **242** are the major products and the regioisomers **243** the minor.



Scheme 4.4 Effect of the substituents on the formation of regioisomeric pyrazolyl methyl indoles (**242**/**243**)

Plausible reaction mechanism for formation of regioisomers **242** and **243** are shown below (Scheme 4.5). N-aryl sydnones reacts in two different modes with 1-(prop-2-yn-1-yl)-1*H*-indole **195** giving rise to the regioisomers **242** and **243**.

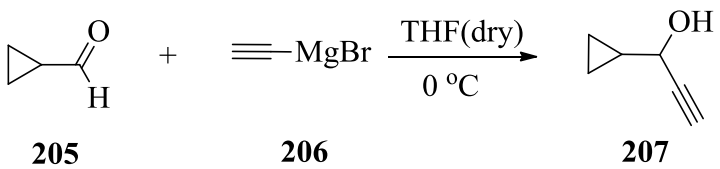


Scheme 4.5 Proposed mechanism for the formation of the cycloadducts **242** and **243**

CHAPTER 2

4.2 Cycloaddition Reactions of Aryl Sydnones with 1-cyclopropylprop-2-yn-1-ol

In continuation of our interest for the construction of pyrazole containing heterocycles, we conducted the cycloaddition of *N*-aryl sydnones with acetylenic dipolarophile, 1-cyclopropylprop-2-yn-1-ol, which was obtained from ethynylmagnesium bromide and cyclopropane carboxaldehyde (Scheme 4.6) (Mothe and Chan, 2009). To our best knowledge there was no report regarding the cycloaddition of 1-cyclopropylprop-2-yn-1-ol with azomethine imines, hereby we have introduced the first example of cycloaddition reaction between *N*-aryl sydnones and 1-cyclopropylprop-2-yn-1-ol **207**.



205 **206** **207**

Scheme 4.6 Synthesis of 1-cyclopropylprop-2-yn-1-ol **207**.

The structure of compound **207** can be identified by interpreting the IR and NMR data. In IR data, broad -OH, aliphatic -CH and alkyne stretching vibrations frequency were observed approximately 3373, 2965 and 2110 respectively. In Figure 4.6 expanded ^{1}H-NMR spectra revealed that H_a proton that attached carbon atom bearing hydroxy and alkyne group resonated at 4.13 ppm as doublets. H_b proton that belongs to terminal alkyne appeared at 2.38 ppm as doublet and -OH proton resonated at 2.37 ppm as singlet.

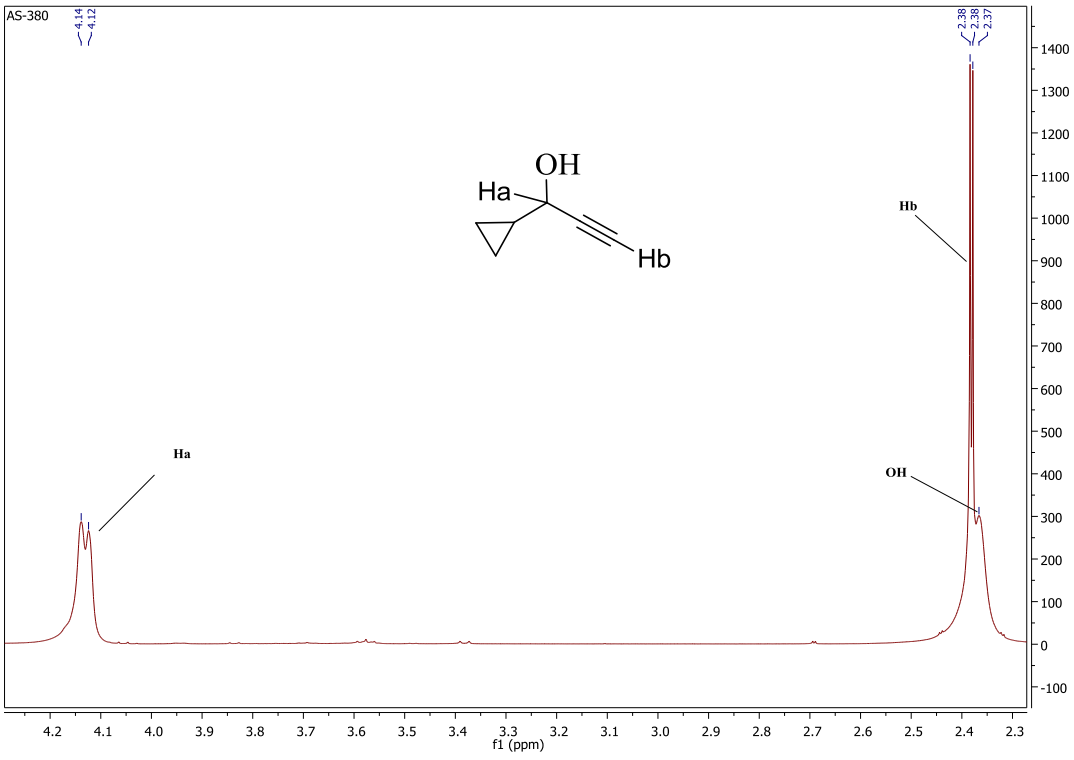
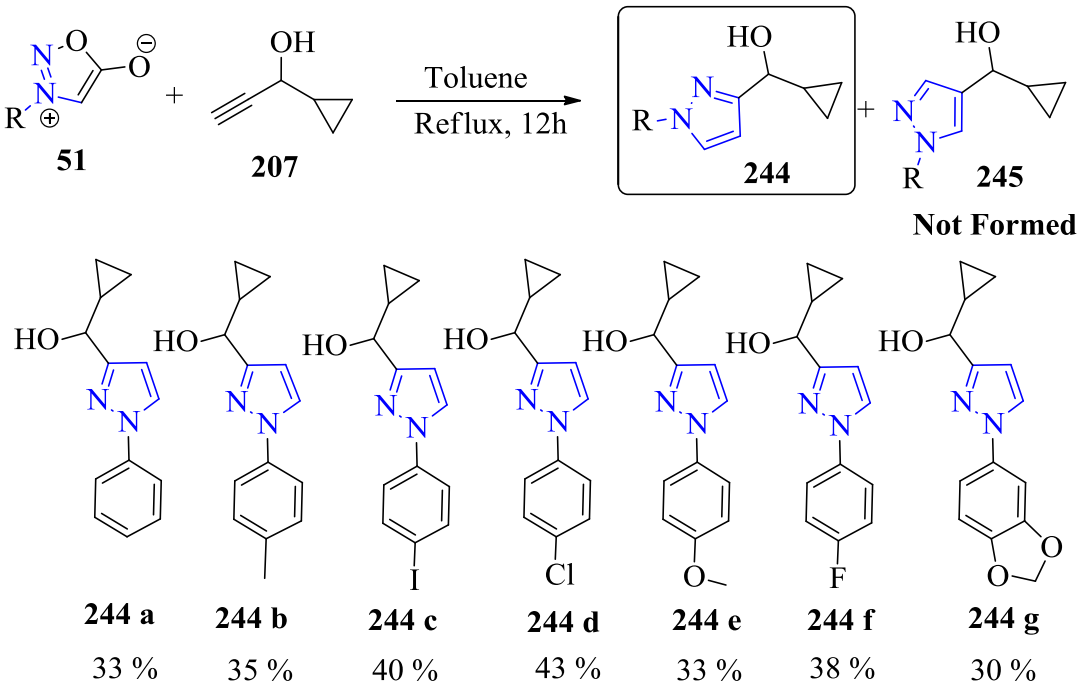


Figure 4.6 Representative expanded ^{1}H NMR spectrum of 1-Cyclopropylprop-2-yn-1-ol **207**

1,3-Dipolar cycloadditions of *N*-aryl sydnones **51a-g** to 1-Cyclopropylprop-2-yn-1-ol **207** in toluene, under reflux, proceeded slowly but smoothly and were also highly regioselective, yielding the regioisomers **244a-g** as the only isolable products.



Scheme 4.7 Formation of single regioisomers **244a-g** as a result of reaction between sydnones **51a-g** and 1-alkynol **207**

All the cycloadducts **244a-g** were obtained as oil. Thus, we were not able to crystallize corresponding cycloadducts to visualize the better view of relative configuration. Assignment of structures of cycloadducts **244a-g** was performed based on the data obtained from IR, ^{1}H NMR, ^{13}C NMR, LCMS and HRMS measurements. In the IR spectra of these cycloadducts -OH stretching absorption appeared at around 3381-3408 cm^{-1} and as for the proton NMR spectra, -OH proton resonates at around 2.50 ppm as a broad singlet, the chemical shift of the -CH proton attached to the -OH is found at around 4.20 ppm as a doublet. Pyrazole ring protons appeared at 6.40 ppm and 7.75 ppm (the one closer to nitrogen) as doublets. The expanded ^{1}H-NMR spectrum of compound **244a** indicating splitting patterns of protons discussed above is illustrated in Figure 4.7.

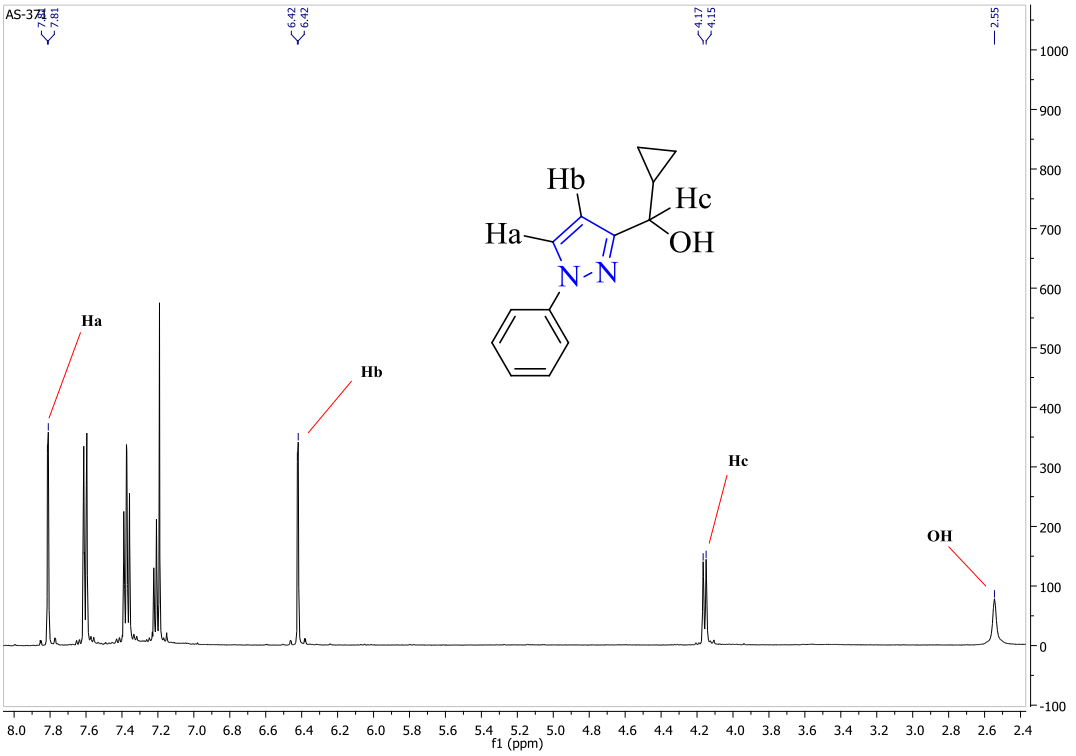


Figure 4.7 The expanded ^{1}H NMR spectrum of compound **244 a**

It was evident that single regioisomers **244a-g** had been formed from the ^{1}H NMR data which showed a pair of doublets resonating at 6.42 and 7.81 ppm (*J*=2.4 Hz) in adduct **244a**, assigned to the vicinal methines of the pyrazole ring; similar resonances were found in the remaining adducts **244b-g.**(Table 4.5)

Table 4.5 ^{1}H NMR chemical shifts and coupling constants for H_a, H_b and H_c protons of cycloadducts **244a-g**

Comp.	**Ha** (ppm)	***J*** (Hz)	**Hb** (ppm)	***J*** (Hz)	**Hc** (ppm)	***J*** (Hz)
244 a	7.81, d	2.4	6.42, d	2.4	4.16, d	8.3
244 b	7.77, d	2.3	6.40, d	2.3	4.15, d	8.3
244 c	7.79, d	2.5	6.43, d	2.5	4.13, d	8.4
244 d	7.77, d	2.4	6.43, d	2.4	4.13, d	8.3
244 e	7.71, d	2.4	6.39, d	2.4	4.14, d	8.3
244 f	7.74, d	2.4	6.42, d	2.4	4.14, d	8.4
244 g	7.68, d	2.4	6.39, d	2.4	4.13, d	8.3

This structural assignment is in agreement with earlier reports on the structural elucidation of isomeric 1-aryl-5-substituted pyrazoles **246** and 1-aryl-3-substituted pyrazoles **247**, both in terms of chemical shifts and coupling constant values, the latter being in the range *J*= 2.4-2.9 Hz (Cristau *et al*., 2004).

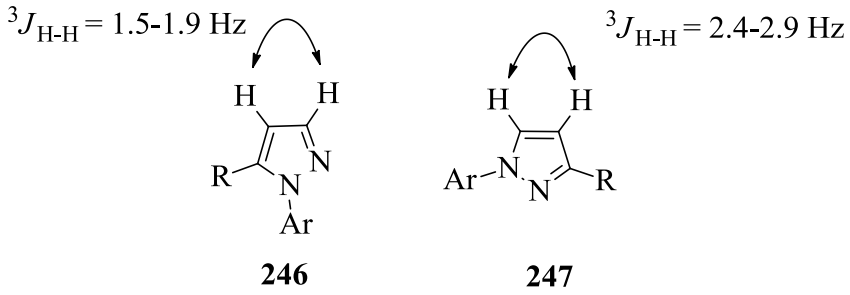


Figure 4.8 ^{1}H NMR $^3J_{H-H}$ coupling constants in ring substituted 1-arylpyrazoles

As for carbon chemical shifts of the cycloadducts, the carbon attached to hydroxyl group resonated at around 72.0 ppm, pyrazole iminic carbon at around 158-160 ppm and most shielded aliphatic carbons are cyclopropyl ring carbons.

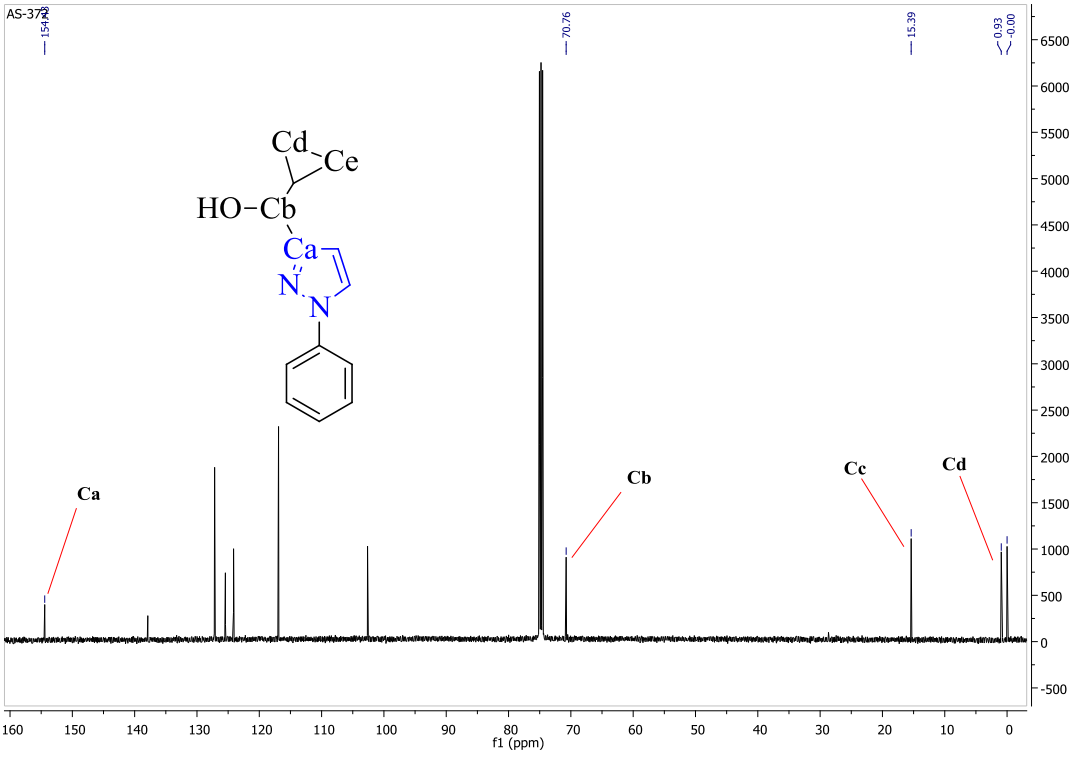
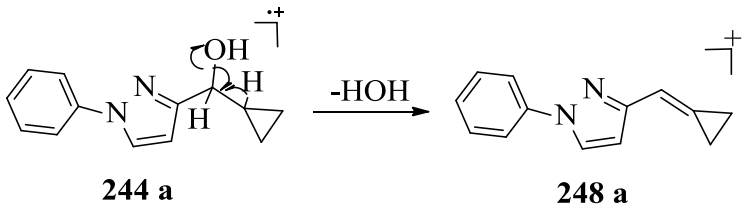


Figure 4.9 Representative ^{13}C NMR spectrum of compound **244a** indicating aliphatic carbons and iminic carbon.

In the mass spectra, while significant molecular ions were observed for all cycloadducts **244a-g**, the base peaks, 3-(cyclopropylidenemethyl)-1-phenyl-1*H*-pyrazoles, can be attributed to loss of a molecule of water from the corresponding cycloadducts.



244 a **248 a**

Scheme 4.8 Mass spectral fragmentation of **244a** leading to the base peak at m/z 197

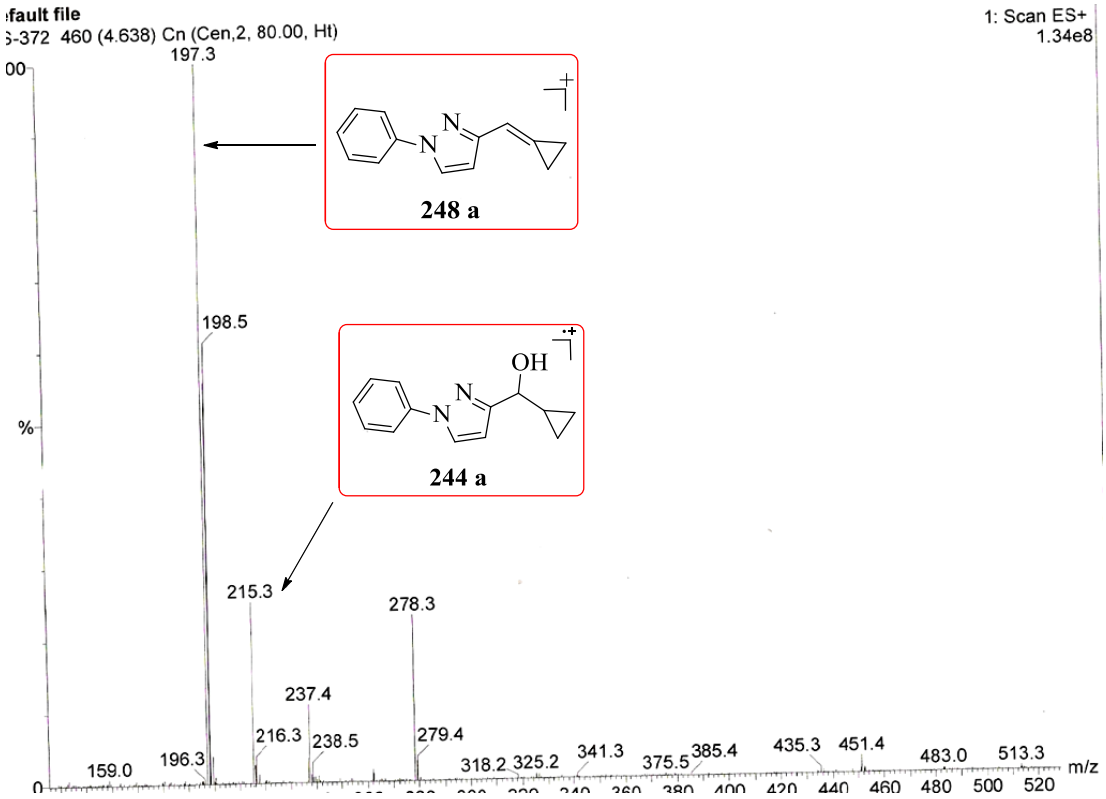


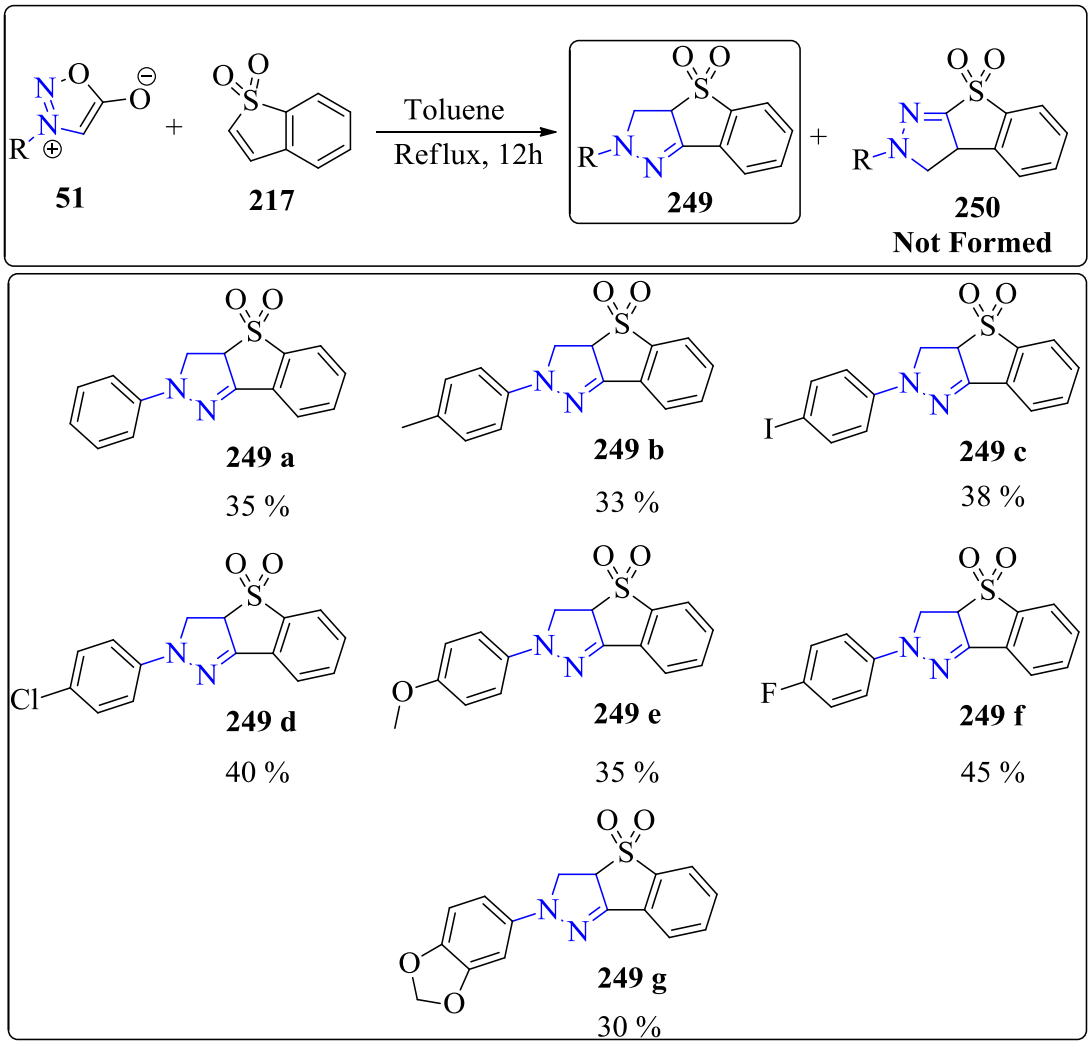
Figure 4.10 LCMS spectrum of compound **244a**

CHAPTER 3

4.3 Cycloaddition Reactions of *N*-Aryl Sydnones with Benzo[*b*]thiophene 1,1-dioxide

Heterocyclic compounds with a benzo[*b*]thiophene 1,1-dioxide structural frame have been used for the synthesis of pharmaceutically important molecules

showing bioactivities including hepatitis C virus NS5B polymerase inhibition and various cytotoxic properties (Kim *et al.*, 2008; Villar *et al.*, 2004). In order to construct these heterocycles there are various synthetic routes, among them 1,3-DC reaction can be counted as the most versatile leading to benzo[*b*]thiophene 1,1-dioxide fused heterocycles. Some of related cycloaddition studies have been detailed in the chapter 3. Taking account of the above considerations, we have focused herein on the synthesis of 2-substituted phenyl-3,3a-dihydro-2*H*-benzo[4,5]thieno[3,2-c]pyrazole 4,4-dioxide that have been derived by reacting *N*-aryl sydnones **51 a-g** with benzo[*b*]thiophene 1,1-dioxide **217.** The reaction has proceeded smoothly to afford regioisomers **249 a-g** in moderate yields as the only isolable products.



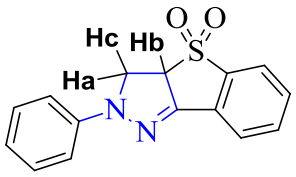
Scheme 4.9 Cycloaddition of sydnones **51** to benzo[*b*]thiophene 1,1-dioxide **217** yielding regioisomers **249a-g**

All cycloadducts were obtained as solid compound thus many attempts have been performed to get a fine crystal to evaluate the relative configuration of

cycloadducts **249a-g** but they failed each time**.** In this regard, the structure elucidation of regioisomers **249a-g** was performed by the means of ^{1}H and^{13}C NMR, IR and HRMS measurements.

Typical characteristics of these cycloadducts in their IR spectra are the symmetric and asymmetric stretching vibrations of SO_2 moiety at around 1150 and 1300 cm^{-1}, respectively. Aliphatic ring protons of these compounds resonate in the range of 4-5 ppm as two double doublets and one triplet, which correspond to the three hydrogens of the pyrazoline portion in the cycloadduct; the chemical shifts observed strongly support the structural assignment as being the regioisomers **249a-g**. The proton at the bridge position was split into a doublet of doublets (which usually appeared as an apparent triplet) and usually appeared between the AB double doublet resonances due to the methylene group adjacent to nitrogen.

Table 4.6 IR data and ^{1}H NMR chemical shifts and coupling constants of three hydrogens of the pyrazoline portion in the cycloadducts **249a-g**



Comp.	**Ha** (ppm)	***J*** (Hz)	**Hb** (ppm)	***J*** (Hz)	**Hc** (ppm)	***J*** (Hz)	$\upsilon_{C=N}$	$\upsilon_{SO2(sym)}$
249 a	4.14, dd	13.6, 10.4	4.50, t	10.4	5.04, dd	13.6, 10.4	1653	1145
249 b	4.10, dd	13.6, 10.4	4.48, t	10.4	5.03, dd	13.6, 10.4	1653	1168
249 c	4.10, dd	13.6, 10.7	4.47, t	10.7	5.04, dd	13.6, 10.7	1683	1166
249 d	4.12, dd	13.7, 10.5	4.49, t	10.5	5.06, dd	13.7, 10.5	1683	1165
249 e	4.08, dd	14.0, 10.5	4.48, t	10.5	5.04, dd	14.0, 10.8	1653	1145
249 f	4.10, dd	13.7, 10.5	4.49, t	10.5	5.05, dd	13.7, 10.5	1653	1145
249 g	4.06, dd	13.7, 10.5	4.42, t	10.5	5.06, dd	13.7, 10.5	1683	1145

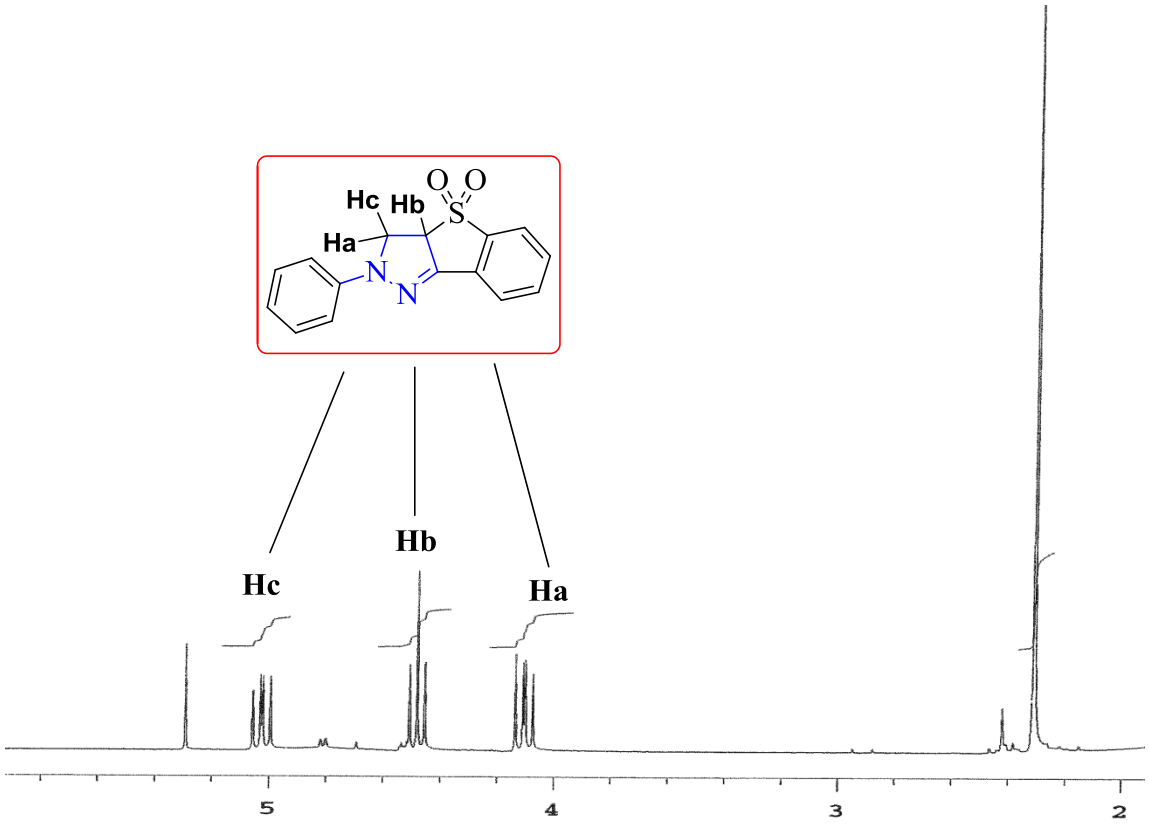


Figure 4.11 Expanded ^{1}H NMR spectrum of **249b** indicating H_a, H_b and H_c protons

In addition to above results, ^{13}C NMR data also supported the structural assignment that iminic carbons and the methylene carbons of the pyrazole ring resonating at around 146 ppm and 51 ppm respectively while the bridge methine adjacent to the sulfone resonates at around 63 ppm.

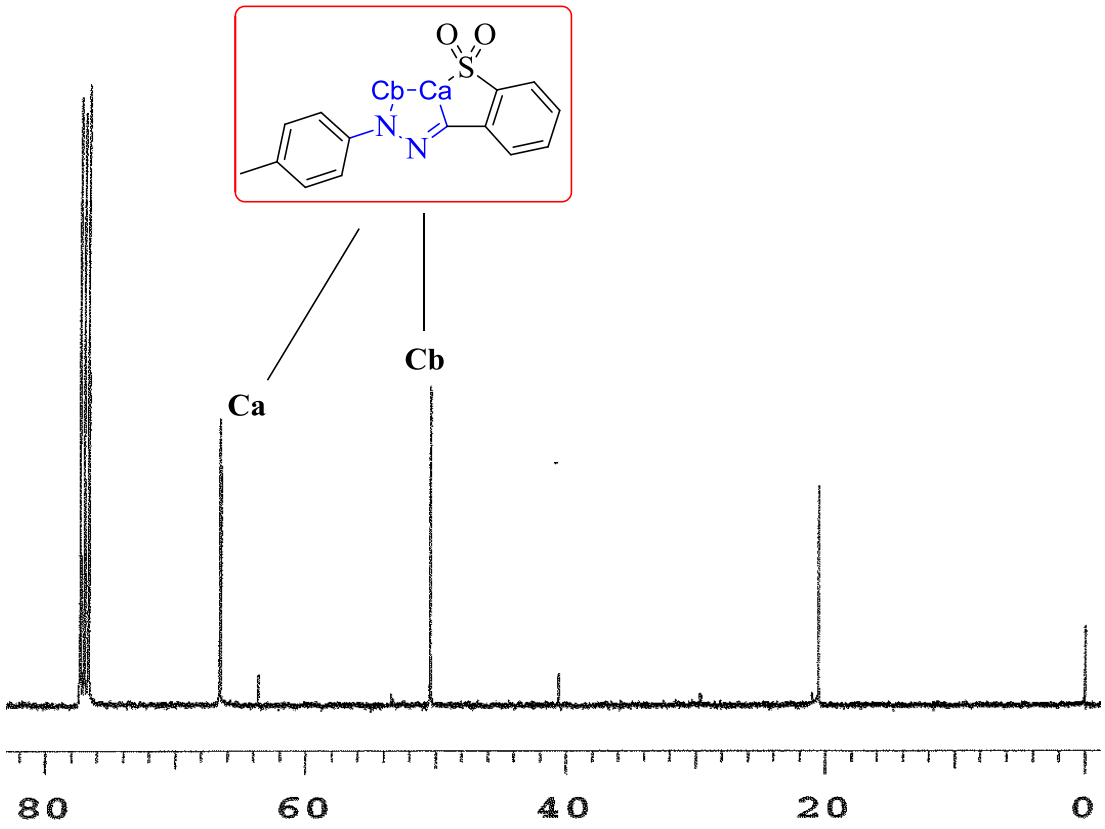
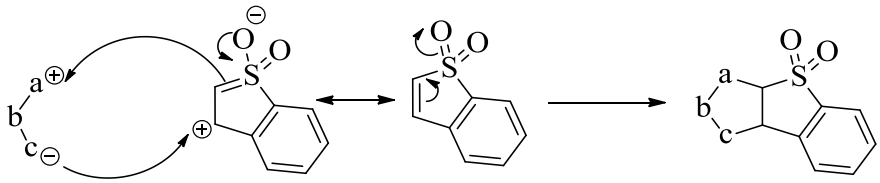


Figure 4.12 Expanded ^{13}C NMR spectrum of **249b** comprising aliphatic carbons of pyrazole portion of cycloadduct.

The regioselectivity of this cycloaddition reaction also corresponds to previous observations that have been discussed in chapter 3 containing cycloaddition reaction of various dipoles such as nitrile oxide, nitrone and azomethine imine with benzo[*b*]thiophene 1,1-dioxide afforded the cycloadducts with the same regioselectivity. This behaviour can be explained by the addition of the electron-rich end of the dipole to the more electron deficient end of the dipolarophiles, the 3-position of the benzo[*b*]thiophene 1,1-dioxide.

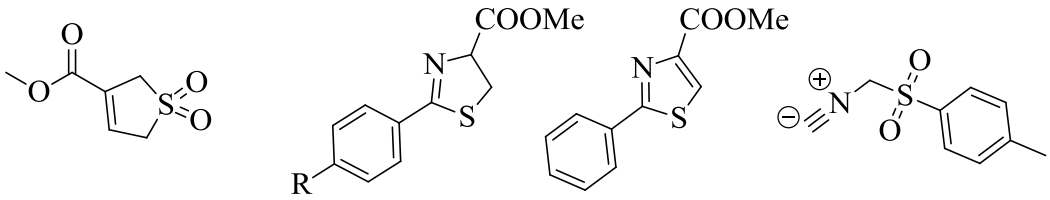


Scheme 4.10 Representative cycloaddition reaction of hypothetical 1,3-dipole and benzothiophene-1,1-dioxide.

CHAPTER 4

4.4 Attempted Cycloaddition Reactions of *N*-Aryl Sydnones to Various Electron Deficient Dipolarophiles

As a connection of our interest in the synthesis of heterocyclic systems carrying pyrazole and pyrazoline ring, various electron deficient dipolarophiles such as 2,5-dihydrothiophene-3-carboxylate 1,1-dioxide **251,** *p*-substituted thioimidates **252**, methyl 2-phenylthiazole-4-carboxylate **253** and toluenesulphonylmethyl isocyanide **254** have been utilized in the cycloaddition reaction with *N*-aryl sydnones. The attempted cycloaddition reactions of *N*-arylsydnones with those mentioned dipolarophiles did not give anticipated products even if a number of trials of different reaction conditions have been experienced.



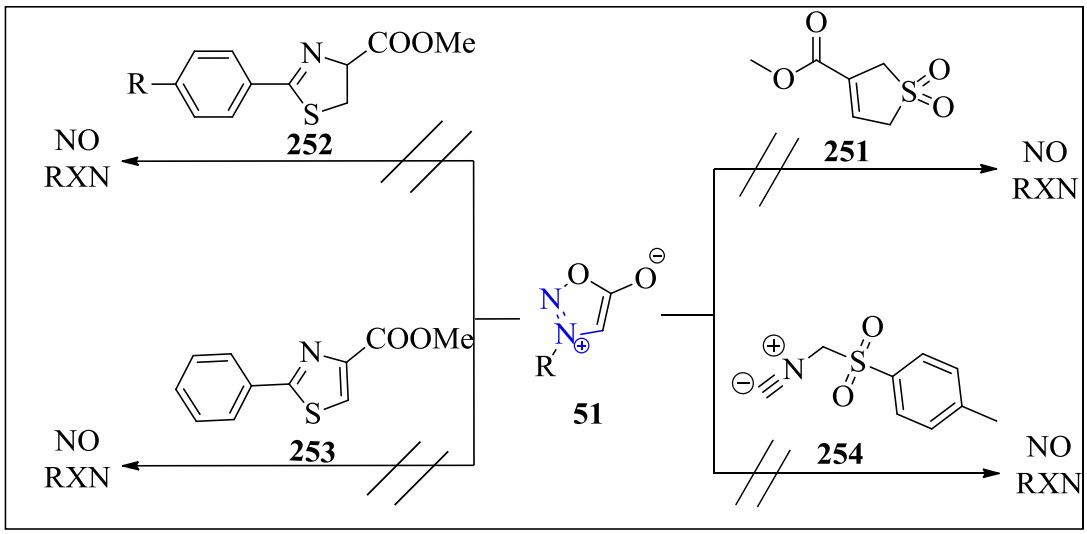
251 **252** **253** **254**

R: H, OMe, NO_2

Figure 4.13 Various dipolarophiles for *N*-aryl sydnone cycloadditions in attempted assays

Those trials have been performed using both microwave and conventional method in protic and aprotic solvents depicted in Table 4.7. The reactions were monitored by thin layer chromatography but there was no product obtained in each case. Failure of attempted cycloaddition reactions can be explained by the nature of heterodipolarophiles **252**, **253** and **254**. Generally, reactivity of those dipolarophiles is less than equivalent of alkenes and alkynes (Houk *et al*., 1973)..

Table 4.7 Reaction conditions for the attempted cycloadditon reactions of *N*-aryl sydnones with dipolarophiles

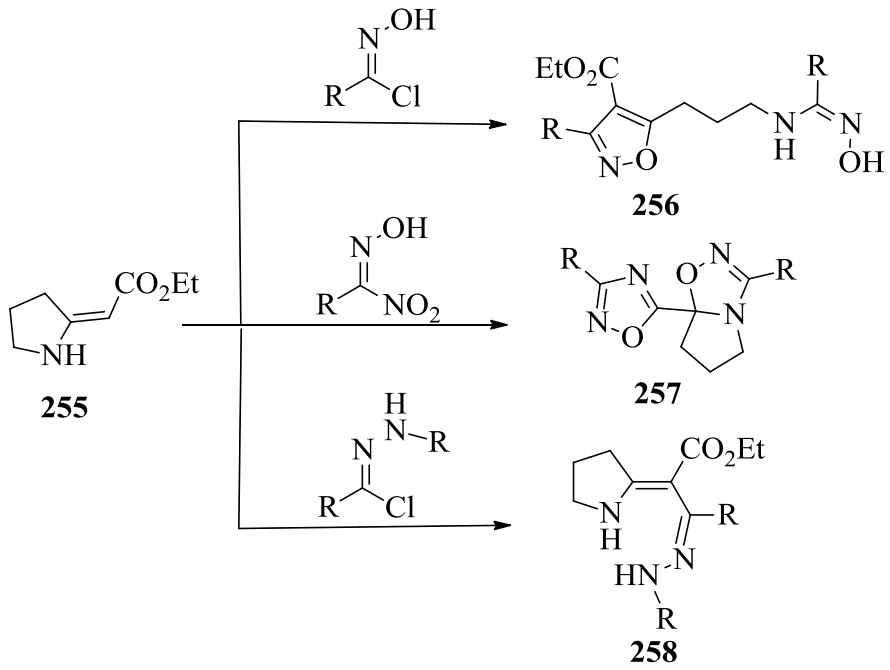


Comp.1	Comp.2	Reaction condition		Solvent	Base	Product
51 a	**251**	MW, 300W	110-170°C, 30min	Xylene	—	—
51 a	**252**	MW, 300W	110-170°C, 30min	Xylene	—	—
51 a	**253**	MW, 300W	110-170°C, 30min	Xylene	—	—
51 a	**254**	MW, 300W	110-170°C, 30min	Xylene	—	—
51 a	**254**	MW, 300W	110-170°C, 30min	Xylene	K_2CO_3	—
51 a	**251**	MW, 300W	80-110°C, 1h	EtOH	—	—
51 a	**252**	MW, 300W	80-110°C, 1h	EtOH	—	—
51 a	**253**	MW, 300W	80-100°C, 1h	EtOH	—	—
51 a	**254**	MW, 300W	80-100°C, 1h	EtOH	K_2CO_3	—
51 a	**251**	Reflux	12h	Xylene	—	—
51 a	**252**	Reflux	12h	Xylene	—	—
51 a	**253**	Reflux	12h	Xylene	—	—
51 a	**254**	Reflux	12h	DMF	K_2CO_3	—

4.5 Attempted Cycloaddition Reactions of *N*-Aryl Sydnones to 2-nitromethylenethiazolidine

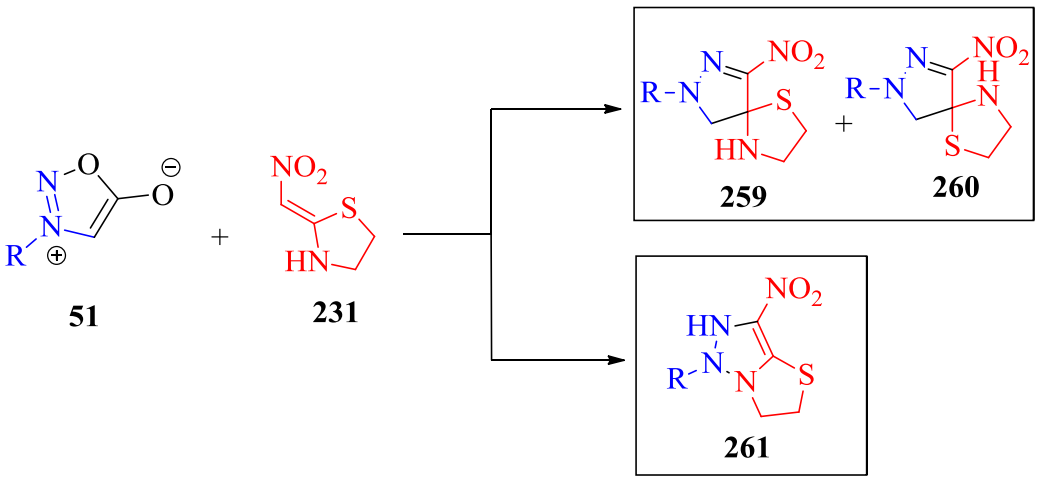
2-Nitromethylenethiazolidine is an attractive reagent due to its nucleophilic and electrophilic nature. In last decades it has been used for the synthesis of many

heterocyclic systems containing thiazolidine ring (Yıldırım *et al*., 2014a; 2014b; Altuğ *et al*., 2011). On the other hand, thiazolidine substituted heterocyclic scaffolds have been reported as insecticide agent against Lepidoptera species (Shiokawa *et al*., 1992; Nishida *et al*., Liu *et al*., 2012). Taking account of above considerations, our efforts in present study is to use 2-nitromethylenethiazolidine as dipolarophilic reagent. Because similar heterocyclic enamine, alkylidene pyrrolidine **255**, that bears electron withdrawing group was used in cycloaddition reaction trial with various dipoles afforded the surprising products in each case (Altuğ *et al*., 2009). This unexpected behaviour of heterocyclic enamine encouraged us to use 2-nitromethylenethiazolidine in cycloaddition trial process.



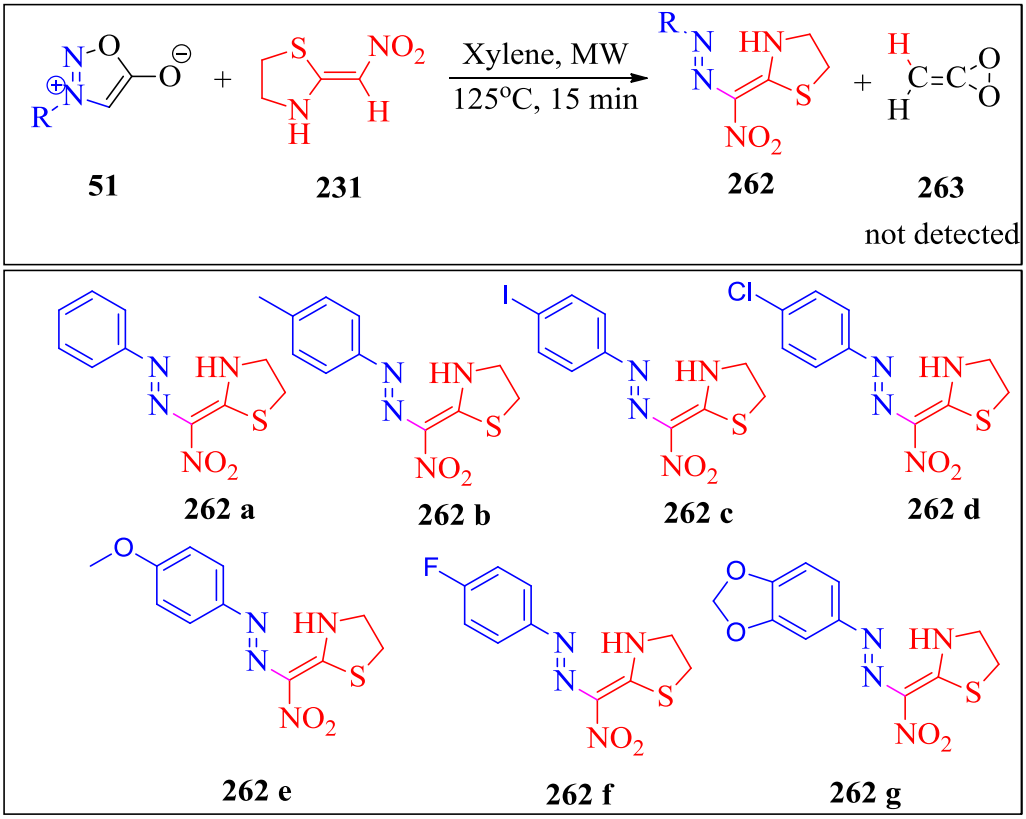
Scheme 4.11 Reaction of alkylidene pyrrolidine with various dipoles

Our initial expectation was to perform cycloaddition reaction between *N*-aryl sydnones **51a-g** with 2-nitromethylenethiazolidine **231** throughout this study. In this respect, the reaction was carried out by using both conventional heating and microwave irradiation. Hovewer, isolable products were only obtained under microwave irradiation in low yields. Upon an initial examination of the structures of the reaction products, basically, based on NMR, IR and HRMS data, despite the expected spiro structures **259** and **260** we concluded that fused cyclic compounds **261** might be formed.

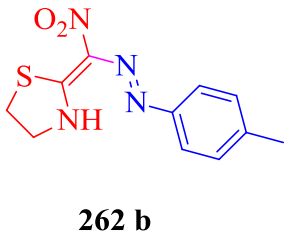


Scheme 4.12 Anticipated reaction products of sydnone-2 nitromethylenethiazolidine 1,3-dipolar cycloaddition leading to fused heterocycles **261** and spiro heterocycles **259** and **260**

In order to elucidate the exact structures of the products, we decided to crystallize the reaction products. Although all products were obtained as an oil after purification by column chromatography, we were able to obtain a fine crystal of the compound **262b**. X-ray diffraction ORTEP view revealed the structures assigned as depicted in Figure 4.14. As a result of X-ray diffraction data of compound **262b** we concluded that mesoionic sydnones **51a-g** underwent, unexpectedly, a coupling reaction with the electron deficient dipolarophile; 2-nitromethylene thiazolidine **231,** under microwave irradiation instead of 1,3-dipolar cycloaddition and afforded 7 novel (*Z*)-2-(nitro((*E*) *p*-substitutedphenyldiazenyl)methylene)thiazolidines **262a-g.**



Scheme 4.13 Reaction between *N*-aryl sydnones **51** with 2-nitromethylenethiazolidine **231** afforded unexpected diazenyl thiazolidines **262a-g**



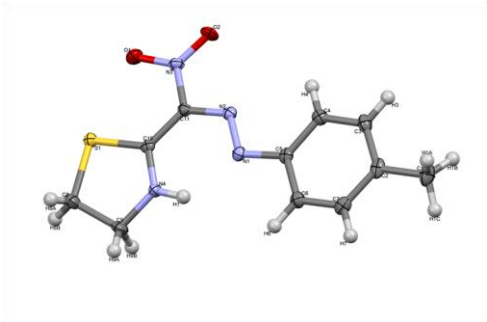


Figure 4.14 Single crystal ORTEP view of compound **262b**

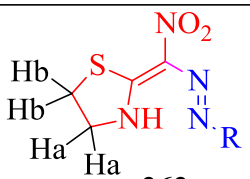
However, reactions with dipolarophile **231** gave unexpected products **262a-g** but in very low yields, even many attempts to increase and optimize the reaction yields have been conducted, they did not result in better yields (Table 4.8).

Table 4.8 Reaction yields and optimization studies

Comp.1	Comp.2	Reaction condition		Solvent	Product	Total yield%
51 a	231	MW, 300W	125°C, 15min	Xylene	262 a	23
51 b	231	MW, 300W	125°C, 15min	Xylene	262 b	20
51 c	231	MW, 300W	125°C, 15min	Xylene	262 c	27
51 d	231	MW, 300W	125°C, 15min	Xylene	262 d	27
51 e	231	MW, 300W	125°C, 15min	Xylene	262 e	23
51 f	231	MW, 300W	125°C, 15min	Xylene	262 f	20
51 g	231	MW, 300W	125°C, 15min	Xylene	262 g	22
51 a	231	MW, 300W	125°C, 1h-3h	Xylene	262 a	23
51 a	231	MW, 300W	125-170°C, 15min	Xylene	262 a	23
51 a	231	Conventional	125°C, 12h	Xylene	262 a	-
51 a	231	Reflux	12h	Xylene	262 a	-

The structural assignments of corresponding products were also confirmed by the means of IR, ^{1}H NMR, ^{13}C NMR, 2D NMR (COSY, HMBC and NOESY), LCMS, HRMS and physical characteristics. These measurements indicated two triplets of the methylene protons which are originated from the 2-nitromethylenethiazolidine. In addition, NH proton which is located adjacent to nitro group might arise quite much deshielded at around 14.5 ppm in the proton NMR spectra and exhibits a strong absorption at around 3300-3400 cm^{-1} in the IR spectra (Table 4.9). Also, LC-MS spectra and HRMS measurements reveal that M+H values exactly coincides with the molecular formulas of the structures.

Table 4.9 IR data and chemical shifts and coupling constants indicating aliphatic protons and NH proton of products **262a-g**



262

Comp.	**Ha** (ppm)	***J*** (Hz)	**Hb** (ppm)	***J*** (Hz)	**NH** (ppm)	υ_{NH}	$\upsilon_{N=N(sym)}$
262 a	4.46, t	8.6	3.24, t	8.8	14.56, s	3419	1554
262 b	4.42, t	8.6	3.21, t	8.4	14.55, s	3356	1548
262 c	4.43, t	8.6	3.25, t	8.6	14.39, s	3323	1546
262 d	4.43, t	8.8	3.25, t	8.4	14.34, s	3414	1548
262 e	4.38, t	8.6	3.23, t	8.6	14.24, s	3423	1514
262 f	4.41, t	8.8	3.25, t	8.6	14.24, s	3437	1548
262 g	4.37, t	8.4	3.26, t	8.4	14.02, s	3319	1491

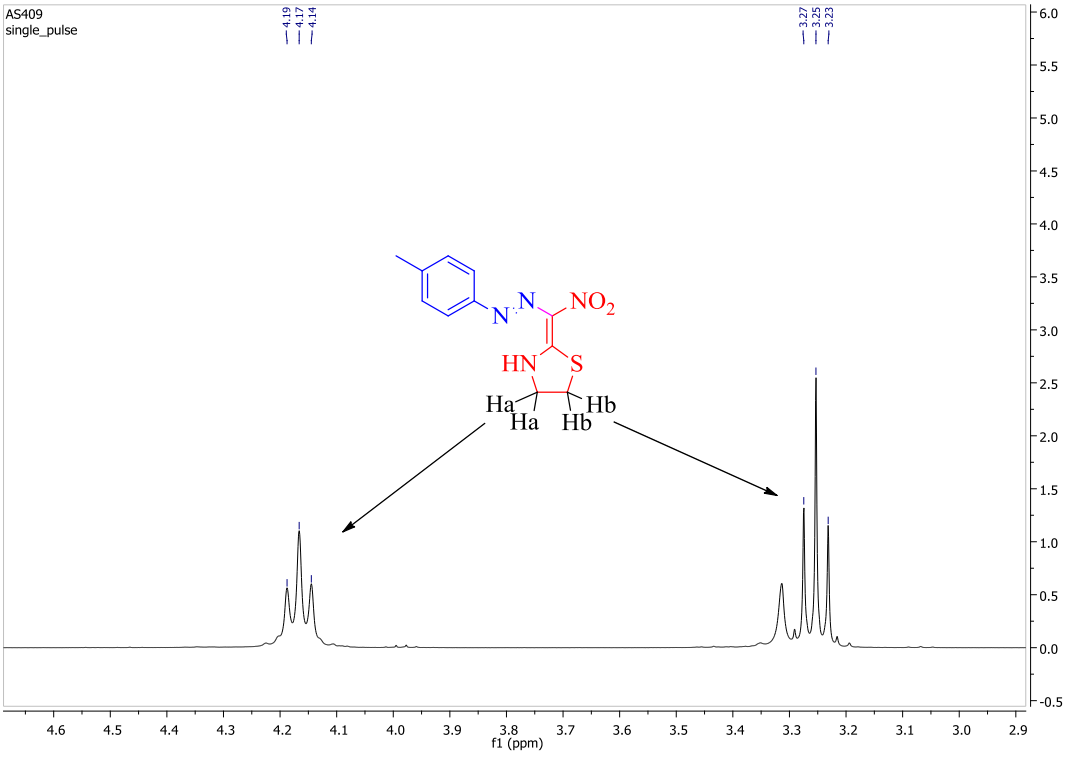
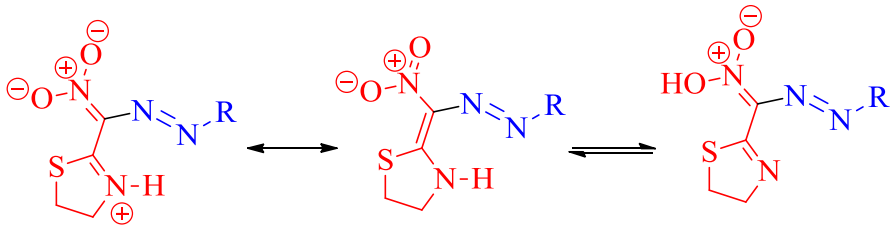


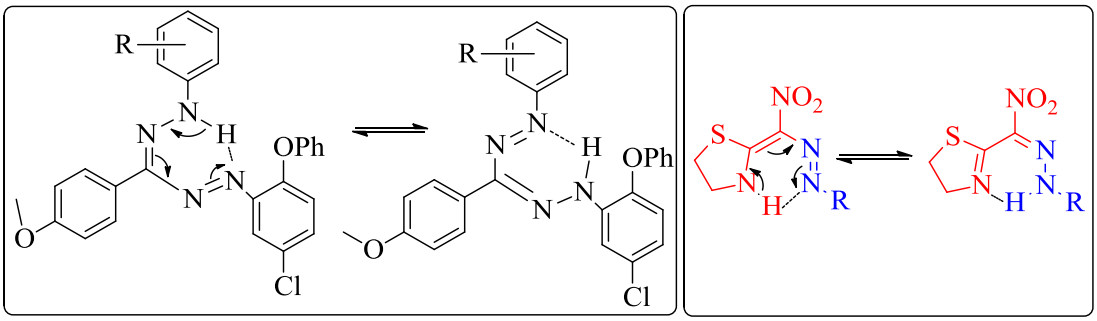
Figure 4.15 Expanded ^{1}H NMR spectrum of **262b** indicating aliphatic protons

Surprisingly, NH proton shifted up to 14.5 ppm was not frequently encountered. Therefore, we may think about a tautomeric equilibriation in NMR solvent ($CDCl_3$) or a resonance form as depicted in Scheme 4.14. In this way, due to being closer to quite electron deficient nitrogens via a complete electron delocalization, we can consider that OH proton arises at around 14.5 ppm which shifts to 12.7 in DMSO-d_6. Another supporting evidence might be our failed attempts of trying D_2O exchange of NH proton, caused by this fast equilibrium.



Scheme 4.14 Nitro-aci-nitrolic acid type tautomerization and resonance form of (*Z*)-2-(Nitro((*E*)-*p*-substitutedphenyldiazenyl)methylene) thiazolidines

In addition to above consideration, due to the tautomeric equilibriation and intramolecular hydrogen bonding in formazan structures, NH proton was detected as singlet between 14.8 and 15.3 ppm. Similar tautomeric equilibration can be possible for diazocoupling products **262 a-g** and also can explain the NH proton shifting to 14.5 ppm (Berber *et al*., 2015).



Scheme 4.15 Tautomerization of formazan structures and diazocoupling products

As for ^{13}C NMR signals, the carbon resonance of the one attached to nitro group appeared at around 162 ppm, and the other exocyclic double bond carbon did at around 150 ppm (in DMSO-d_6). We have noticed that one carbon resonance is missing for some samples recorded in $CDCl_3$. For this reason, we decided to record ^{13}C NMR spectra in dimethylsulfoxide-d_6 instead of $CDCl_3$ for those samples. In this regard, we observed 8 carbon signals for compound **262c** and 9 carbons for **262b**.

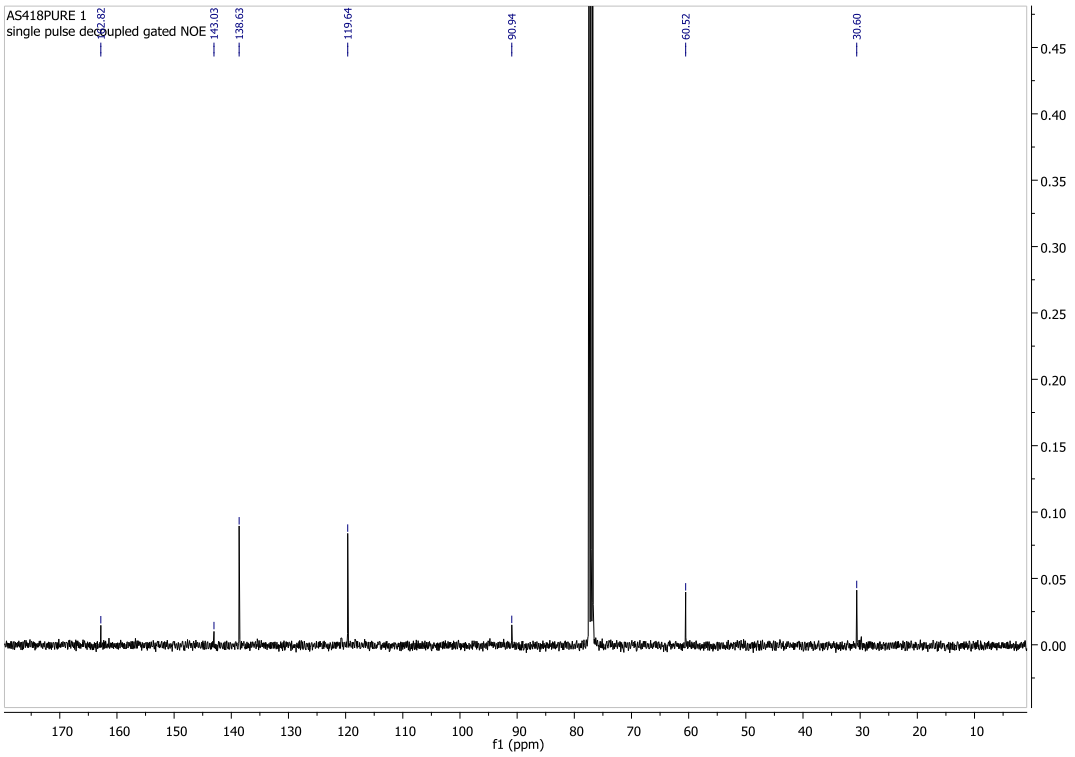


Figure 4.16^{13}CNMR spectra of compound **262 c** recorded in $CDCl_3$

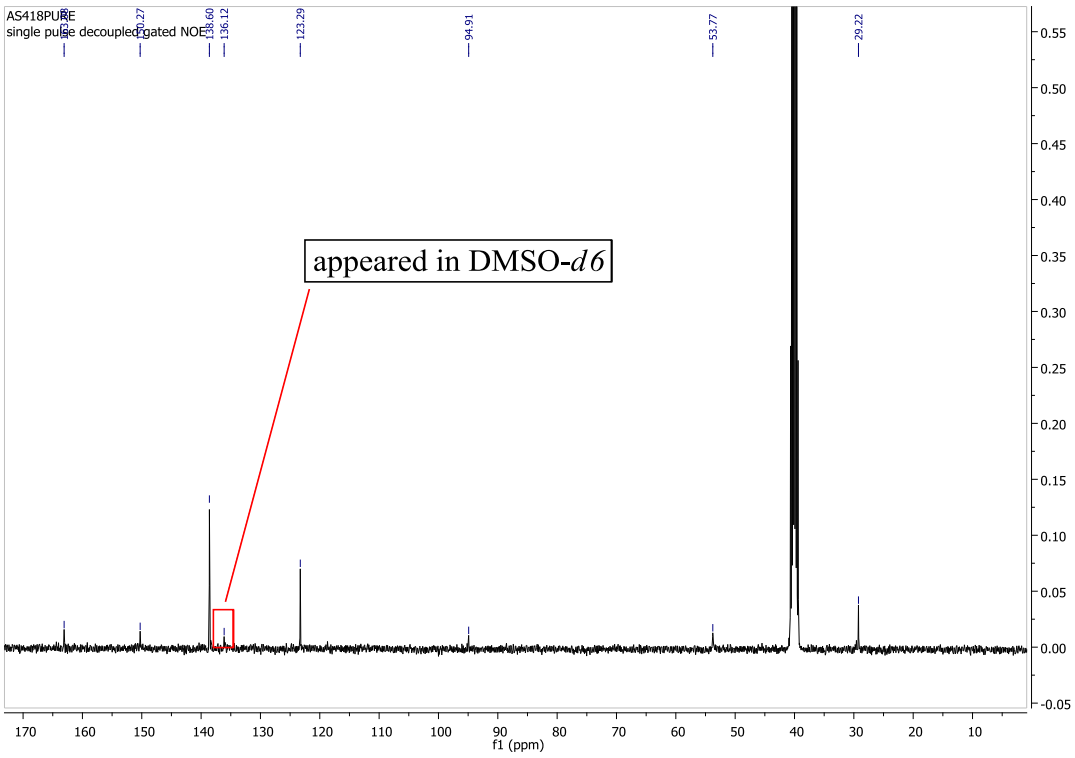
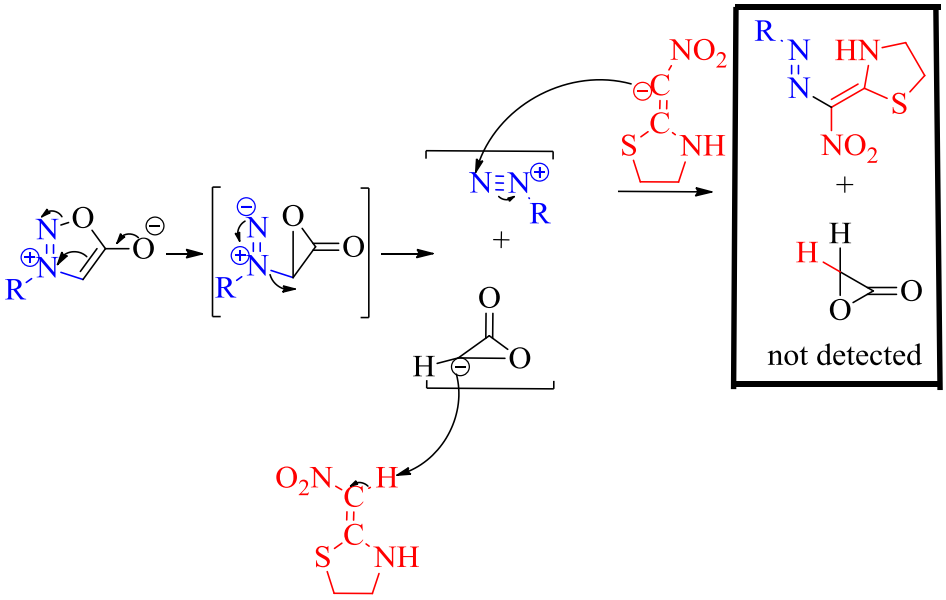


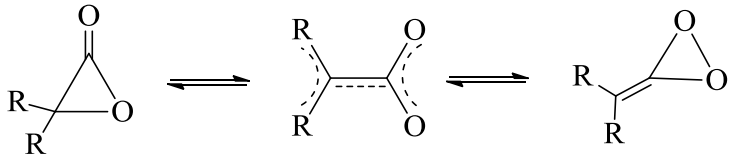
Figure 4.17 ^{13}C NMR spectra of compound **262c** recorded in DMSO-d_6

The formation of **262a-g** can be probable by the unusual decomposition of mesoionic sydnone. A possible reaction mechanism for this transformation was proposed below (Scheme 4.16). It seems to be most likely that a structure resembling

acetolactone or methylenedioxirane (Liebman and Greenberg, 1974; Ruggiero and Williams, 2001; Rodriquez and Williams, 1997; Chung, 1976) is released during the reaction but not isolated (Scheme 4.17). It was reported that only in the case of trifluoromethyl substitution, these structures are stable and can be isolated. In addition, in a recent study it was reported that during the nitrosation of aminoacids, lactones have been formed as alkylating agents (Garcia-Santos *et al*., 2001).



Scheme 4.16 Proposed mechanism for the generation of **262a-g**



Scheme 4.17 Resonance forms of acetolactone (oxiranone) structure

5. CONCLUSION

In summary, throughout this thesis work, in the first part, *N*-aryl sydnone derivatives were succesfully synthesized and characterized as a precursor of azomethine imine type dipole. Followed as a dipolarophilic reagent, proparyl indole was prepared and it underwent cycloaddition reaction with *N*-aryl sydnones leading 14 new regioisomeric pyrazolyl-1-*H*-indoles in moderate yields. The structure and stereochemistry of regioisomeric mixtures were identified by means of IR, ^{1}H,^{13}C NMR spectra and single cystal X-ray diffraction measurements.

In the second part of the thesis, other electron deficient acetylenic dipolarophile which is namely, alknylcyclopropyl methanol, was treated with *N*-aryl sydnones give rise to the formation of 7 new cyclopropyl-(1-substituted phenyl)-(1*H*-pyrazol-3-yl)methanols as a single product in a regioselective manner. The structures and relative stereochemistries of regioisomers were established by IR, ^{1}H,^{13}C NMR spectra and the results were supported by HRMS measurement.

In the third part of our work, treatment of benzo[b]thiophene 1,1-dioxide with *N*-aryl sydnones leaded to the formation of 7 new (4-substituted phenyl)-3,3a-dihydro-2*H*-[1]benzothieno[3,2-c] pyrazole 4,4-dioxides regioselectively. The newly synthesized structures were identified based on the data obtained from IR, ^{1}H NMR, ^{13}C NMR and HRMS data.

In the fourth part of the thesis, to the best of our knowledge since no reaction between *N*-aryl sydnones and 2-nitromethylenethiazolidine was reported, we have incorporated *N*-aryl sydnone-2-nitromethylenethiazolidine reaction which occurred as diazo coupling reaction via the possible liberation of an acetolactone (oxiranone) or methylenedioxirane intermediate. 7 Novel diazocoupling products bearing thiazolidine ring were isolated in low yields and their structural assignments were established by IR, ^{1}H, ^{13}C, COSY, NOESY and HMBC NMR spectra and single cystal X-ray diffraction measurements.

All newly synthesized products carrying pyrazole, indole, pyrazoline and thiazolidine groups may be considered as potential bioactive heterocycles. For this reason, investigation of biological activity of these heterocycles will be assayed in the near future.

REFERENCES

Adams JL, Gallagher T, Osifo IK (1998) Novel pyrazole and pyrazoline substituted compounds: PCT Int. Appl WO9856377.

Altuğ C, Burnett AK, Caner E, Dürüst Y, Elliott MC, Glanville RPJ,Guy C, Westwell AD (2011) "An efficient one-pot multicomponent approach to 5-amino-7-aryl-8-nitrothiazolo[3,2-a]pyridines", Tetrahedron, 67: 9522-9528.

Altuğ C, Dürüst Y, Elliott MC, Kariuki BM (2009) "Tandem nitrosation/cycloaddition of heterocyclic enamines using nitrolic acids", Tetrahedron Lett., 39: 4919-492.

Applegate J and Turnbull K (1988) "The Efficient Synthesis of 3-Arylsydnones Under Neutral Conditions", Synthesis, (12): 1011-1012.

Azarifar D, Bosra HG, Zolfigol MA, Tajbaksh M (2006) "Microwave-Assisted Synthesis of N-Arylglycines: Improvement of Sydnone Synthesis", Heterocycles, 68: 175-181.

Azarifar D and Ghasemnejad BH (2006) "Catalytic Activity of 1,3-Dibromo-5,5-dimethylhydantoin (DBH) in the One-Pot Transformation of N-Arylglycines to N-Arylsydnones in the Presence of $NaNO_2$/Ac_2O under Neutral Conditions: Subsequent Bromination of these Sydnones to their 4-Bromo Derivatives", Synthesis, (7): 1123-1126.

Badami B (2006) "Mesoionic Compounds - An Unconventional Class of Aromatic Heterocycles", Resonance, 11: 40-48.

Bai Y, Fang J, Ren J, Wang Z (2009) "Highly Diastereoselective Gold- or Copper-Catalyzed Formal [4+3] Cycloaddition of 1-(1-Alkynyl) Cyclopropyl Ketones and Nitrones", Chem. Eur. J., 15: 8975–8978.

Baker W, Ollis WD, Poole VD (1946) "Structure of the 'Sydnones", Nature, 158: 703-704.

Baker W, Ollis WD, Poole VD (1949) "Cyclic meso-ionic compounds. Part I. The structure of the sydnones and related compounds", J. Chem. Soc., 307-314.

Baker W, Ollis WD, Poole VD (1950) "Cyclic meso-ionic compounds. Part III. Further properties of the sydnones and the mechanism of their formation", J. Chem. Soc., 1542-1551.

Bened A, Durand R, Pioch D, Geneste P, Declercq JP, Germain G, Rambaud J, Reques R, Guimon C, Guillouzo GP (1982) "Isoxazolines by Cycloadditions of Mesitonitrile Oxide with Theoretical Explanations, and Kinetics Benzo[b]thiophene S-Oxide and S,S-Dioxide. Structural Studies", J. Org. Chem., 47: 2461-2465.

Bened A, Durand R, Pioch D, Geneste P, Guimon C, Guillouzo GP, Declercq JP, Germain G, Briard P, Rambaud J, Roques R (1984) "Isoxazolidines by Cycloadditions of N,a-Diphenyl Nitrone in the Benzo[b]thiophene S-Oxide and SS-Dioxide Series", J. Chem. Soc., Perkin Trans. 2: 1-6.

Berber H, Turkoğlu G, Kani I (2015) "Synthesis, crystal structure, optical and electrochemical properties of novel diphenylether-based formazan derivatives", New J.Chem., 39: 2728-2740.

Bieber TI (1958) "Representation of Polycyclic Aromatic Compounds", J.Chem. Educ., 35: 235-237.

Blomstrand R, Ellin A, Lof A, Ostlingwintzell H (1980) "Biological effects and metabolic interactions after chronic and acute administration of 4- methylpyrazole and ethanol to rats", Arch. Biochem. Biophys., 199 (2): 591-605.

Browne DL and Taylor JB, Plant A, Harrity JPA (2009) "Cross Coupling of Bromo Sydnones: Development of a Flexible Route toward Functionalized Pyrazoles", J. Org. Chem., 74: 396-400.

Buchner E (1888) "Einwirkung von Diazoessigäther auf die Aether ungesättigter Säuren", Ber. Dtsch. Chem. Ges., 21: 2637-2647.

Busch M (1895) "Synthese von Biazolinderivaten", Ber. Deutsch. Chem. Ges., 28: 2635-2647.

Busch M (1905) "Ueber Endimino-triazole", Ber.Deutsch. Chem. Ges., 38: 856-860.

Busch M and Best F (1899) "Untersuchungen in der Biazolreihe (Schluss). 11. Ueber o-Anisyl-, α-und β-Naphtyldithiocarbazinsäure und Derivate derselben", J. Prakt. Chem., 60: 225-232.

Busch M and Mehrtens G (1905) "Ueber Endiminotriazole. II", Ber. Deutsch. Chem. Ges., 38: 4049-4068.

Chang EC, Wen YL, Chang CH, Shen YH , Wen SB, Yeh MY, Wong FF (2012) "A novel one-pot synthesis of 2-arylpyrazoloquinolinone derivatives", Tetrahedron 68: 5920-5924.

Chang EM, Chen EH, Wong FF, Chang EC, Yeh MY (2006) "Convenient and Efficient Synthesis of Pyrazole-Based DHODase Inhibitors from 3-Aryl-4-cyanosydnone", Synlett, (6): 901-905.

Chang EM, Wong FF, Chen TH, Chiang KC, Yeh MY (2006) "Regioselectivity in 1,3-Dipolar Cycloaddition of 3-(4-Ethoxyphenyl)-4-cyanosydnone with Propargylic Esters", Heterocycles, 68: 1007-1015.

Chung CSC (1976) "α-Lactones: a semi-empirical scf mo study", J. Mol. Struct., 30: 189-191.

Cordoba MM, Izquierdo ML, Alvarez-Builla J (2008) "New approaches to the synthesis of pyridinium N-heteroarylaminides", Tetrahedron, 64: 7914-7919.

Corey EJ, Czako B, Kurti L (2007) Molecules and medicine, Wiley, Hoboken, NJ.

Cristau HJ, Cellier PP, Spindler JF, Taillefer M (2004) "Mild Conditions for Copper-Catalysed N-Arylation of Pyrazoles", Eur. J. Org. Chem., (4): 695-709.

Croce PD, La Rosa C, Zecchi G (1985) "1,3-Dipolar cycloadditions with alkynyl phenyl sulphones", J. Chem. Soc., Perkin Trans. 1, 2621-2624.

Curtius T (1883) "Ueber die Einwirkung von salpetriger Säure auf salzsauren Glycocoläther", Ber. Dtsch. Chem. Ges., 16: 2230-2231.

Damodiran M, Muralidharan D, Perumal PT (2009) "Regioselective synthesis and biological evaluation of bis(indolyl)methane derivatized 1,4-disubstituted 1,2,3-bistriazoles as anti-infective agents", Bioorg. Med. Chem. Lett., 19: 3611–3614.

De Sa Alves FR, Barreiro EJ, Fraga CAM (2009) "From Nature to Drug Discovery: The Indole Scaffold as a Privileged Structure", Mini Rev. Med. Chem., 9: 782-793.

DeShong PJr, Lander SW, Leginus JM, Dicken CM (1988) In Advances in Cycloaddition, 1, JAI Press, London.

Dömling A (2006) "Recent Developments in Isocyanide Based Multicomponent Reactions in Applied Chemistry", Chem. Rev., 106: 17-89.

Dorn H, Otto A (1968) "Syntheses by Means of 1-Alkylidene- and 1-(Arylalkylidene)-3-pyrazolidone *N*,*N*-Betaines, a New Type of Stable Azomethine Imine", Angew. Chem., Int. Ed. Engl., 7: 214-215.

Dorn H, Otto A (1968) "Über die Reaktion von Pyrazolidon-(3) mit Carbonylverbindungen", Chem. Ber., 101: 3287-3301.

Dumitrascu F, Draghici C, Dumitrescu D, Tarko L, Raileanu D (1997) "Direct Iodination of Sydnones and Their Cycloadditions to Form 5-Iodopyrazoles", Leibigs Ann. /Recueil, 12: 2613-2616.

Dumitrascu F, Mitan CI, Dumitrescu D, Draghici MT, Caproiu MT (2002) "Steric effects on the sydnones reactivity. New sydnones and pyrazoles", Arkivoc, 2: 80-86.

Dürüst Y, Sağırlı A, Fronczek FR (2011) "Regioselective 1,3-dipolar cycloaddition of phenanthrolinium *N*-ylides to substituted arylidene oxazolones", Mol. Divers., 15: 799-808.

Dürüst Y, Yıldırım M, Fronczek CF, Fronczek FR (2012) "Synthesis and stereochemistry of some novel dihydropyrrolo[3,4-***c***]pyrazoles",Monatsh. Chem., 143: 127-138.

Earl JC (1956) "Chemistry of sydnones", Rec. Trav. Chim., 75: 1080-1082.

Earl J and Mackney A (1935) "The action of acetic anhydride on N-nitrosophenylglycine and some of its derivatives", J. Chem. Soc., 899-900.

Eid CNJr, Wu YJ, Kenny G (2002) Burger's medicinal chemistry & drug discovery, 6, Wiley, New York.

Fan JM, Wang Y, Ueng CH (1993) "Electrostatic properties of sydnone derivatives", J. Phys. Chem., 97: 8193-8199.

Fang Y, Wu C, Larock RC, Shi F (2011) “Synthesis of 2H-Indazoles by the [3+2] Dipolar Cycloaddition of Sydnones with Arynes”, J. Org. Chem., 76: 8840−8851.

Farina F, Fernandez P, Teresa Fraile M, Victoria Martin M (1989) “1,3-Dipolar Cycloadditions with Methyl 4-Oxo- and 4-Hydroxy-2-butynoates. Synthesis of Functionalized Pyrazoles and Triazoles”, Heterocycles, 29: 967-974.

Farina F, Fernandez P, Rosario Martin M, Victoria Martin M, Sanchez F (1983) “Cicloadiciones 1,3-dipolares a derivados del ácido 4,4-dimetoxi-2-butinoico: Síntesis de pirazoles y triazoles sustituidos.”, An. Quim., 79(3): 323-339.

Fink BE, Mortensen DS, Stauffer SR, Aron ZD, Katzenellenbogen JA (1999) “Novel structural templates for estrogen-receptor ligands and prospects for combinatorial synthesis of estrogens”, Chem. Biol., 6: 205-219.

Fischer E, Besthorn E (1882) “Ueber die Hydrazinverbindungen”, Liebigs Ann. Chem., 212: 316-339.

Fustero S, Sanchez-Rosell M, Barrio P, Simon-Fuentes (2011) “AFrom 2000 to Mid-2010: A Fruitful Decade for the Synthesis of Pyrazoles”, Chem. Rev., 111: 6984–7034.

Garcia-Santos MDP, Calle E, Casado J (2001) “Amino Acid Nitrosation Products as Alkylating Agents”, J. Am. Chem. Soc., 123: 7506-7510.

Gonzalez-Nogal AM, Calle M, Cuadrado P, Valero R (2007) “1,3-Dipolar cycloadditions of silicon and tin alkynes and alkenes. Regiospecific synthesis of silyl and stannylpyrazoles and pyrazolines”, Tetrahedron, 63: 224-231.

Gothelf K, Jorgensen K (1998) “Asymmetric 1,3 Dipolar Cycloaddition Reactions”, Chem. Rev., 98: 863-909.

Greco CV, Mehta JR (1979) “Meso-ionic compounds. XI, photochromic 4-halogeno-3-(3-pyridyl)sydnones”, J. Heterocycl. Chem., 16: 1059-1060.

Grigg R, Dowling M, Jordan MW, Sridharan V, Thianpatanagul S (1987) “X=Y-ZH Systems as potential 1,3-dipoles : Part 131. Prototropic generation of azomethine imines from hydrazones”, Tetrahedron, 43: 5873-5886.

Haider N, Kabicher T, Käferböck J, Plenk A (2007) “A Synthesis and In-vitro Antitumor Activity of 1-[3-(Indol-1-yl)prop-1-yn-1-yl]phthalazines and Related Compounds”, Molecules, 12: 1900-1909.

Hashimoto T, Maeda Y, Omote M, Nakatsu H, Maruoka K (2010) “Catalytic Enantioselective 1,3-Dipolar Cycloaddition of C,N-Cyclic Azomethine Imines with α,β-Unsaturated Aldehydes”, J. Am. Chem. Soc., 12: 4076–4077.

Hashimoto T, Takiguchi Y, Maruoka K (2013) “Catalytic Asymmetric Three-Component 1,3-Dipolar Cycloaddition of Aldehydes, Hydrazides, and Alkynes”, J. Am. Chem. Soc., 135: 11473−11476.

Hegde JC, Rai G, Puranik VG, Kalluraya B (2006) “Exclusive Formation of 1-Aryl-3-(5-nitro-2-furyl)-4-aroylpyrazoles via Regiospecific 1,3-Dipolar

Cycloaddition of 3-Arylsydnones with α,β-Acetylenic Ketones",Synth. Commun., 36: 1285-1290.

Heller ST and Natarajan SR (2006) "1,3-Diketones from Acid Chlorides and Ketones: A Rapid and General One-Pot Synthesis of Pyrazoles", Org. Lett., 8: 2675-2678.

Houk KN, Sims J, Duke RE, Strozier RWJr, George JK (1973) "Frontier molecular orbitals of 1,3 dipoles and dipolarophiles", J. Am. Chem. Soc., 95: 7287-7301.

Houk KN, Sims J, Watts CR, Luskus LJ (1973) "Origin of reactivity, regioselectivity, and periselectivity in 1,3-dipolar cycloadditions", J. Am. Chem. Soc., 95: 7301-7315.

Houk KN, Sims J, Watts CR, Luskus LJ (1973) "Origin of reactivity, regioselectivity, and periselectivity in 1,3-dipolar cycloadditions", J. Am. Chem. Soc., 95: 7301-7315.

Huisgen R (1963) "1,3-Dipolar cycloaddition: Kinetic and mechanism", Angew. Chem., Int. Ed. Engl., 2: 633–645.

Huisgen R (1963) "1,3-Dipolar Cycloadditions. Past and Future", Angew. Chem., Int. Ed. Engl., 2: 565–598.

Huisgen R (1976) "1,3-Dipolar cycloadditions. 76. Concerted nature of 1,3-dipolar cycloadditions and the question of diradical intermediates", J. Org. Chem., 41: 403-419.

Huisgen R (1984) In 1,3-Dipolar Cycloaddition Chemistry, 1, Wiley, New York.

Huisgen R, Gotthardt H, Grashley R (1962) "Reactions of Sydnones with Alkenes", Angew. Chem., Int. Ed. Engl., 1: 49-50.

Huisgen R, Grashley R, Gotthardt H, Schmidt R (1962) "1,3-Dipolar Additions of Sydnones to Alkynes. A New Route into the Pyrazole Series", Angew. Chem., Int. Ed. Engl., 1: 48-49.

Iniesta J, Matsumoto T, Thiemann T (2008) "Cycloaddition of benzo[b]thiophene- S , S -dioxide – a route to substituted dibenzothiophenes and dibenzothiophene S , S – dioxides", J. Chem. Res., 2: 109-114.

Ito S, Turnbull K (1996) "Chlorination of 3-Substituted Sydnones with Dichloroiodobenzene", Synth. Commun., 26: 1441-1446.

Kalinin VN, Min SF (1988) "Synthesis of aryl- and vinyl-sydnones. Crosscoupling of 4-copper-3-phenylsydnone with aryl and vinyl halides catalyzed by palladium(0) complexes", J. Organomet. Chem., 352: 34–36.

Kalinin VN, Minh SP, Petrovskii PV (1989) "Synthesis of sydnone complexes with C • Pd and C • Pt σ-bonds. Application of palladium salts for the preparation of 4-alkenylsydnones", J. Organomet. Chem., 379: 195-199.

Kalinin VN, Minh SP, Petrovskii PV (1990) "Nickel σ-sydnonyl complexes, stabilized by tertiary phosphines", J. Organomet. Chem., 381: 281-284.

Kato H, Kobayashi T, Horie K, Oguri K, Moriwaki M (1993) “Heterocycles by cycloaddition. Part 10. Cycloaddition–extrusion–ring expansion of mesoionic compounds with benzocyclobutene. Approaches to seven- and eight-membered fully conjugated systems”, J. Chem. Soc., Perkin Trans. 1: 1055-1059.

Kato H and Ohta M (1962) “Decomposition of the Sydnone Ring”, Bull. Chem. Soc. Jpn., 35: 1418-1419.

Katritzky A R, (1955) “The Representation of the So-called Mesoionic Compounds” Chem. Ind., 521-522.

Katritzky AR, Wang M, Zhang S, Voronkov MV (2001) “Regioselective Synthesis of Polysubstituted Pyrazoles and Isoxazoles”, J. Org. Chem., 66: 6787-6791.

Kim SH, Tran MT, Ruebsam F, Xiang AX, Ayida B, McGuire H, Ellis D, Blazel J, Tran CV, Murphy DE, Webber SE, Zhou YF, Shah AM, Tsan M, Showalter RE, Patel R, Gobbi A, LeBrun LA, Bartkowski DM, Nolan TG, Norris DA, Sergeeva MV, Kirkovsky L, Zhao Q, Han Q, Kissinger CR (2008) “Structure-based design, synthesis, and biological evaluation of 1,1-dioxoisothiazole and benzo[b]thiophene-1,1-dioxide derivatives as novel inhibitors of hepatitis C virus NS5B polymerase”, Bioorg. Med. Chem. Lett., 18: 4181-4185.

Komatsu M, Kobayashi M, Itoh S, Ohshiro Y (1993) “Ring enlargement of diaziridinone with 2-substituted pyrrole leading to bicyclic triazine and its transformation to novel mesomeric betaine”, J. Org. Chem., 58: 6620-6624.

Kudo N, Furuta S, Tanigushi M, Endo T, Sato K (1999) “Synthesis and Herbicidal Activity of 1, 5-Diarylpyrazole Derivatives”, Chem. Pharm. Bull., 47: 857-868.

Larsen SD and Martinborough E (1989) “Cycloaddition of β-substituted enones to a bicyclic sydnone: Observation of an unexpectedly facile hydrocarbon elimination”, Tetrahedron Lett., 30: 4625-4628.

Liebman JF and Greenberg A (1974) “Estimation by bond-additivity schemes of the relative thermodynamic stabilities of three-membered-ring systems and their open dipolar forms”, J. Org. Chem., 39: 123-130.

Liu K, Rao W, Parikh H, Li QB, Guo TL, Grant S, Kellogg GE, Zhang SJ (2012) “3,5-Disubstituted-thiazolidine-2,4-dione analogs as anticancer agents: Design, synthesis and biological characterization”, Eur. J. Med. Chem., 47: 125-137.

Longhi K, Moreira DN, Marzari MRB, Floss VM, Bonacorso HG, Zanatta N, Martins MAP (2010) “An efficient solvent-free synthesis of NH-pyrazoles from β-dimethylaminovinylketones and hydrazine on grinding”, Tetrahedron Lett., 51: 3193-3196.

Maffrand JP (1981) “1,3-Dipolar Cycloaddition Reactions of Munchnone and Sydnone Derivatives Obtained from 4,5,6,7-Tetrahydrothieno[3,2-c]pyridine-4 and -6-carboxylic Acids”, Heterocycles, 16: 35-37.

Magnuson EC and Pranata J (1998) “Theoretical study of 1,3-dipolar cycloadditions of nitrone and fulminic acid with substituted ethylenes”, J. Comput. Chem., 19: 1795-1804.

Mais FJ, Dickopp H, Middelhauve B, Martin HD, Mootz D, Steigel A (1987) "Diazepinones from Syndnones and Isopropylidenecyclobutenone. Extension of the Frontier Molecular Orbital Model for Sydnone Cycloadditions", Chem. Ber., 120: 275-283.

Malatesti N, Boa AN, Clark S, Westwood R (2006) "1,3-Dipolar cycloaddition reactions of benzo[b]thiophene 1,1-dioxide with azomethine ylides", Tetrahedron Lett., 47: 5139–5142.

Meazza G, Zanardi G, Piccardi P (1993) "A convenient and versatile synthesis of 4-trifluoromethyl-substituted pyrazoles", J. Heterocycl. Chem., 30: 365-371.

Mothe SR and Chan PWH (2009) "Highly Efficient Synthesis of Tri- and Tetrasubstituted Conjugated Enynes from Brønsted Acid Catalyzed Alkoxylation of 1-Cyclopropylprop-2-yn-1-ols with Alcohols", J. Org. Chem., 74: 5887–5893.

Moyer JD and Handschumacher RE (1979) "Selective inhibition of pyrimidine synthesis and depletion of nucleotide pools by N- (phosphonacetyl)-L-aspartate", Cancer Res., 39: 3089.

Munoz MP, Maria C, Sierra MA (2012) "Platinum-Catalysed Bisindolylation of Allenes: A Complementary Alternative to Gold Catalysis", Chem.Eur. J., 18: 4499-4504.

Nakahara K and Ohta M (1956) "Studies on Mesoionic Compounds. I. Bromination of 3-Phenylsydnone", Nippon Kagaku Zasshi, 77: 1304-1306.

Nan'ya S, Katsuraya K, Maekawa E, Kondo K, Eguchi S (1987) "Synthesis of 2H-indazole-4,7-dione derivatives from 3-phenylsydnone and p-toluquinone. The crystal and molecular structure of 6-bromo-5-methyl-2-phenyl-2H-indazole-4,7-dione", J. Heterocycl. Chem., 24: 971-975.

Nikitenko AA, Winkley MW, Zeldis J, Kremer K, Chan AWY, Strong H, Jennings M, Jirkovsky I, Blum D, Khafizova G, Grosu GT, Venkatesan AM (2006) "Selective Hydrolysis of Ethyl 5,6-Dihydro-4H-pyrrolo[1,2-b]pyrazole-2-carboxylate and Ethyl 5,6-Dihydro-4H-pyrrolo[1,2-b]pyrazole-3-carboxylate as a Key Step in the Large-Scale Synthesis of Bicyclic Heteroaryl Carboxyaldehydes", Org. Process Res. Dev., 10: 712-716.

Nishida S, Maruoka H, Yoshimura Y, Goto T, Tomita R, Masumoto E, Okabe F, Yamagata K, Fujioka T (2012) "Synthesis and biological activities of some new thiazolidine derivatives containing pyrazole ring system", J. Heterocycl. Chem., 49: 303-309.

Padwa A, Burgess EM, Gingrich HL, Roush DM (1982) "On the Problem of Regioselectivity in the 1,3-Dipolar Cycloaddition Reaction of Munchnones and Sydnones with Acetylenic Dipolarophiles", J. Org. Chem., 47: 786-791.

Padwa A (1984) 1,3-Dipolar Cycloadditions, John Wiley, New York.

Penning TD, Talley JJ, Bertenshaw SR, Carter JS, Collins PW, Docter S, Graneto MJ, Lee LF, Malecha JW, Miyashiro JM, Rogers RS, Rogier DJ, Yu SS, Anderson GD, Burton EG, Cogburn JN, Gregory SA, Koboldt CM, Perkins WE, Seibert K, Veenhuizen AW, Zhang YY, Isakson PC (1997) "Synthesis and Biological

Evaluation of the 1,5-Diarylpyrazole Class of Cyclooxygenase-2 Inhibitors: Identification of 4-91 [5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzene sulfonamide", J. Med. Chem., 40: 1347.

Persson T and Nielsen J (2006) "Synthesis of N-Methoxy-N-methyl-β-enaminoketoesters: New Synthetic Precursors for the Regioselective Synthesis of Heterocyclic Compounds", Org. Lett., 8: 3219-3222.

Pouzet P, Erdelmeier I, Ginderow D, Mornon JP, Dansette P, Mansuy D (1995) "Thiophene S-oxides: convenient preparation, first complete structural characterization and unexpected dimerization of one of them, 2,5-diphenylthiophene-1-oxide", J. Chem. Soc., Chem. Commun., (4): 473–474.

Praveen C, Ayyanar A, Perumal PT (2011) "Practical synthesis, anticonvulsant, and antimicrobial activity of *N*-allyl and *N*-propargyl di(indolyl)indolin-2-ones", Bioorg. Med. Chem. Lett., 21: 4072–4077.

Puranik GS, Suschitzky H (1967) "Syntheses of heterocyclic compounds. Part XVIII. Aminolysis of 3-aryl-4-bromosydnones, and acid hydrolysis of 3-arylsydnoneimines", J. Chem. Soc. C, 1006-1008.

Qi X (2007) "Ready, Copper-Promoted Cycloaddition of Diazocarbonyl Compounds and Acetylides", Angew. Chem., Int. Ed. Engl., 46: 3242-3244.

Rajappa S and Advani BG (1982) "The enaminic reactivity of 2-nitromethylenethiazolidine", Proc. Ind. Acad. Sci. Chem. Sci., 91: 463-466.

Ranganathan D and Bamezai S (1983) "A novel proline derived meso-ionic synthon", Tetrahedron Lett., 24: 1067-1070.

Rao W and Chan PWH (2008) "Gold- and Silver-Catalyzed Tandem Amination/Ring Expansion of Cyclopropyl Methanols with Sulfonamides as an Expedient Route to Pyrrolidines", Chem. Eur. J., 14: 10486–10495.

Rispens MT, Keller E, Lange B, Zijlstra RWJ, Feringa BL (1994) "Asymmetric 1,3-dipolar cycloadditions to 5-(R)-menthyloxy-2(5H)-furanone", Tetrahedron Asymmetry, 5: 607-624.

Rodriquez CF, Williams IH (1997) "Ring strain energy and enthalpy of formation of oxiranone: an ab initio theoretical determination", J. Chem. Soc., Perkin Trans. 2: 953-958.

Ruggiero GD, Williams IH (2001) "Oxiranones: α-lactones or zwitterions? Insights from calculated electron density distribution analysis", J. Chem. Soc., Perkin Trans. 2: 733-737.

Samsoniya SA, Esakiya NA, Suvorov NN (1991) "Synthesis of some derivatives of indole and indoloindoles under conditions of interphase catalysis", Chem. Heterocycl. Compd., 27: 366-369.

Satheesha RN, Balakrishna K, Lingappa B, Shaliny S, Vedavati GP (2008) "Convenient access to 1,3,4-trisubstituted pyrazoles carrying 5-nitrothiophene moiety via 1,3-dipolar cycloaddition of sydnones with acetylenic ketones and their antimicrobial evaluation", Eur. J. Med. Chem., 43: 1715-1720.

Schad P (1893) “Synthese ringförmiger Verbindungen aus Benzolderivaten mit offenen Seitenketten”, Ber. Dtsch. Chem. Ges., 26: 216-224.

Schantl JG (2008) In Science of Synthesis, 27, Thieme, New York.

Shih MH (2002) “Studies on the syntheses of heterocycles from 3-arylsydnone-4-carbohydroximic acid chlorides with N-arylmaleimides, [1,4] naphthoquinone and aromatic amines”,Tetrahedron, 58: 10437-10445.

Shintani R, Fu GC (2003) “A New Copper-Catalyzed [3 + 2] Cycloaddition: Enantioselective Coupling of Terminal Alkynes with Azomethine Imines To Generate Five-Membered Nitrogen Heterocycles”, J. Am. Chem. Soc., 36: 10778–10779.

Shiokawa K, Moriya K, Shibuya K, Hattori Y, Tsuboi S, Kagabu S (1992) “3-(6-Chloronicotinyl)-2-nitromethylene-thiazolidine as a New Class of Insecticide Acting against Lepidoptera Species”, Biosci. Biotech. Biochem., 56: 1364-1365.

Silva MA, Goodman JM (2002) “Nitrone cyclisations: the development of a semi-quantitative model from ab initio calculations”, Tetrahedron, 58: 3667-3671.

Simpson J (1946) “6-Aminoacetoveratrone and 5:6-dimethoxy-3-methylanthranil”, J. Chem. Soc., 94-97.

Staley J, Clarke D (1964) “Acid hydrolysis of 3-phenylsydnone-2-N”, J. Org. Chem., 29: 2483-2484.

Suen YF, Hope H, Nantz MH, Haddadin MJ, Kurth MJA (2005) “Novel Route to Fully Substituted 1*H*-Pyrazoles”, J. Org. Chem., 70: 8468-8471.

Sun KK (1986) “Cycloaddition reaction of sydnone and maleimide”, Tetrahedron Lett., 27: 317-320.

Sustmann R (1971) “A simple model for substituent effects in cycloaddition reactions I. 1,3-dipolar cycloadditions”, Tetrahedron Lett., 12(29): 2717-2720.

Sustmann R (1974) “Orbital energy control of cycloaddition reactivity”, Pure Appl. Chem., 40: 569-593.

Taylor EC, Clemens RJ, Davies HML (1983) “Synthesis of Cyclic Azomethine Imines from Aza β-Lactams. Conversion of 3-0xo-1,2-diazetidinium Tosylates into 1-Substituted 3-0xo-l,2-diazetidinium Inner Salts”, J. Org. Chem., 48: 4567-4571.

Taylor WF and Wallace TJ (1968) “Kinetics of the self condensation of benzo[b]thiophene 1,1-dioxide”, Tetrahedron, 24: 5081-5087.

Tien HJ, Fang GM, Lin ST, Tien LL (1992) “A Facile One-Pot Synthesis of 4-Acyl and 4-(1-Hydroxyethyl)Sydnones”, J. Chin. Chem. Soc., 39: 107-110.

Tien HJ, Yeh JC, Wu SJ (1992) “Acetylation and Debromination of Sydnones Accelerated by Ultrasound”, J. Chin. Chem. Soc., 39: 443-447.

Tien HJ, Yeh MY, Huang CY (1985) “A Study of the Sydnone Compounds: Bromination and Chlorination”, J. Chin. Chem. Soc., 32: 461-465.

Tin-Lok C, Miller J, Stansfield F (1964) “The SN mechanism in aromatic compounds. Part XXX. The sydnone ring”, J. Chem. Soc., 1213-1216.

Truce WE and Allison JR (1975) “1,3-Dipolar cycloadditions of azomethine imines and sulfenes”, J. Org. Chem., 40: 2260-2261.

Tsuji K, Nakamura K, Konishi N, Tojo T, Ochi T, Senoh H, Matsuo M (1997) “Studies on Anti-inflammatory Agents. IV. Synthesis and Pharmacological Properties of 1, 5-Diarylpyrazoles and Related Derivatives”, Chem. Pharm. Bull., 45: 987-995.

Tufariello JJ (1984) In 1,3-Dipolar Cycloaddition Chemistry, 2, Wiley, New York.

Turnbull K (1985) “Bromination of sydnones.I. Reaction with 3-arylsydnones containing electron-donors on the aryl ring” J. Hetereocycl. Chem., 22: 965-968.

Turnbull K (1986) “Debromination of 3-Aryl-4-bromosydnones with Sodium Borohydride”, Synthesis, (4): 334-336.

Turnbull K, Krein DM (1997) “The sydnone ring as an ortho-director of lithiation. Dilithiation of 3-phenylsydnone and trapping by electrophiles”, Tetrahedron Lett., 38: 1165-1168.

Turnbull K, Krein DM, Tullis SA (2003) “Alkynylation of 4-Bromo-3-phenylsydnone with Aryl Acetylenes”, Synth.Commun., 33: 2209-2214.

Turnbull RS (1995) “Benzydamine Hydrochloride (Tantum) in the management of oral inflammatory conditions”, J. Can. Dent. Assoc., 61(2): 127-134.

Villar R, Encio I, Migliaccio M, Gil MJ, Martinez-Merino V (2004) “Synthesis and cytotoxic activity of lipophilic sulphonamide derivatives of the benzo[b]thiophene 1,1-dioxide”, Bioorg. Med. Chem., 12: 963-968.

Weintraub PM, Bambury RE (1969) “Heterocycles. II. Nitration of 3-arylsydnones”, Tetrahedron Lett., 10(7): 579-581.

Weisner AJ and Turnbull K (2014) “Treatment of o-alkynylphenylsydnones with acids: a new route to 3-arylcinnolines”, Arkivoc, (4): 164-169.

Wong SSY, Brant MG, Barr C, Oliver AG, Wulff JE (2013) “Dipolar addition to cyclic vinyl sulfones leading to dual conformation tricycles”, Beilstein J. Org. Chem., 9: 1419–1425.

Woodward RB and Hoffmann R (1965) “Stereochemistry of Electrocyclic Reactions”, J. Am. Chem. Soc., 87: 395-397.

Woodward RB and Hoffmann R (1970) The Conservation of Orbital Symmetry, Academic Press, New York.

Wruble LD, Cummins AJ, Goldenberg J, Schapiro H (1967) “The effect of intravenous histalog on gastric secretion in man”, Digest. Dis. Sci., 12: 1087-1090.

Xiao H, Shu X, Ji K, Qi C, Liang Y (2007) “Au(III)-catalyzed ring opening reaction of 1-cyclopropyl-2-yn-1-ols with nucleophiles: highly efficient approach to (*Z*)-conjugated enynes”, New J. Chem., 31: 2041–2043.

Yashunskii VG, Vasil'eva VF, Skender YN (1959) Zh. Obshch. Khim., 29:2712.

Yeh MY, Tien HJ, Nonaka T (1983) "Sydnone compounds. 18. Schmidt reaction of 4-acetyl-3-arylsydnones", J. Org. Chem., 48: 1382-1384.

Yıldırım M and Dürüst Y (2011) "Regioselective 1,3-dipolar cycloaddition of nitrilimines to 2-methyl-2-vinyl oxirane", Tetrahedron, 67: 3209-3215.

Yıldırım M, Celikel D, Evis N, DürüstY, Knight DW, Kariuki BM (2014) "A rapid and efficient protocol for the synthesis of novel nitrothiazolo [3,2-c]pyrimidines via microwave-mediated Mannich cyclisation", Tetrahedron, 70: 2122-2128.

Yıldırım M, Celikel D, Evis N, Knight DW, Kariuki BM (2014) "Base-promoted new C-C bond formation: an expedient route for the preparation of thiazolo- and imidazolo-pyridinones via Michael addition", Tetrahedron, 70: 5674-5681.

APPENDICES

6. APPENDICES

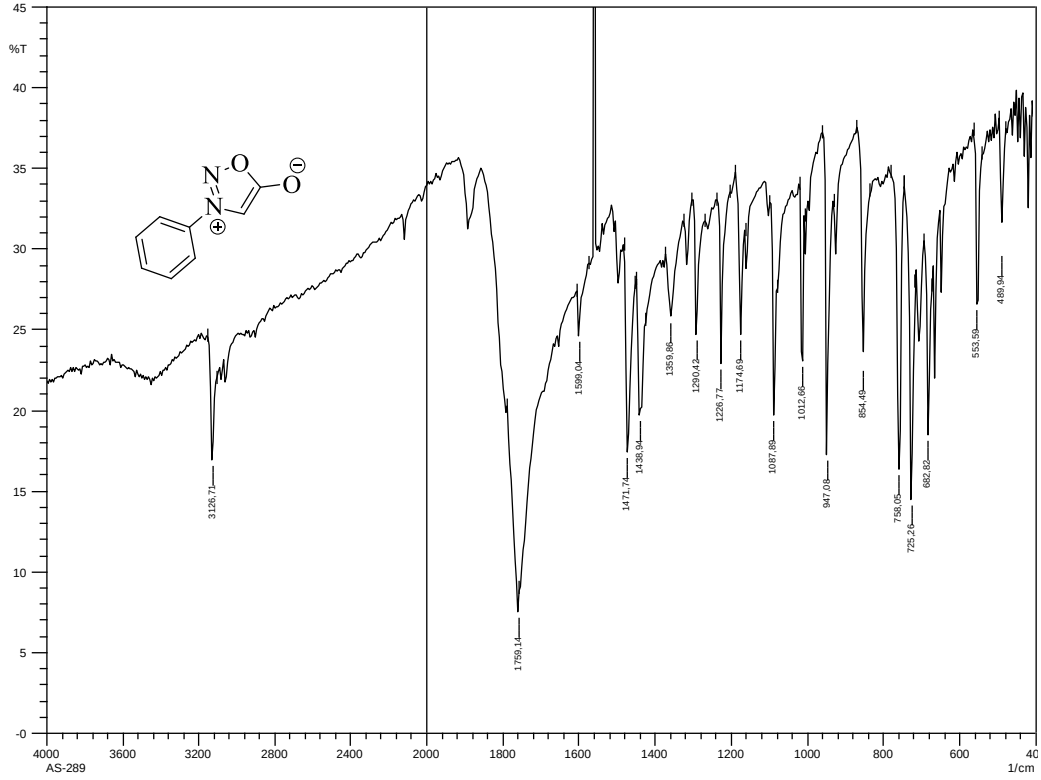


Figure 6.1 IR spectrum of compound **51a**

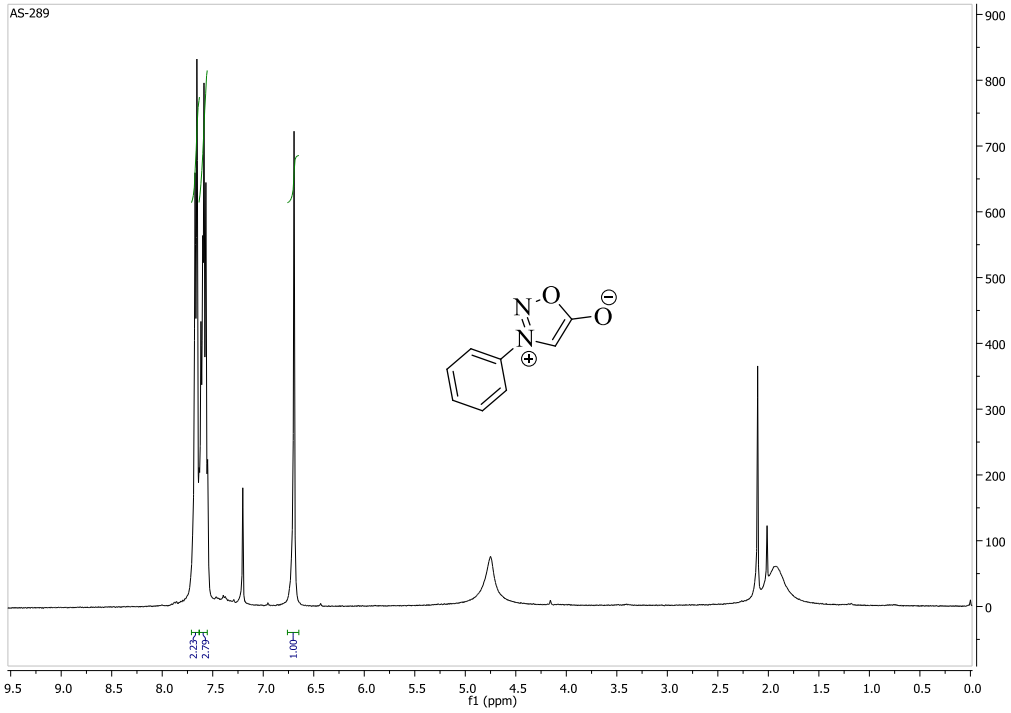


Figure 6.2 ^{1}H NMR spectrum of compound **51a**

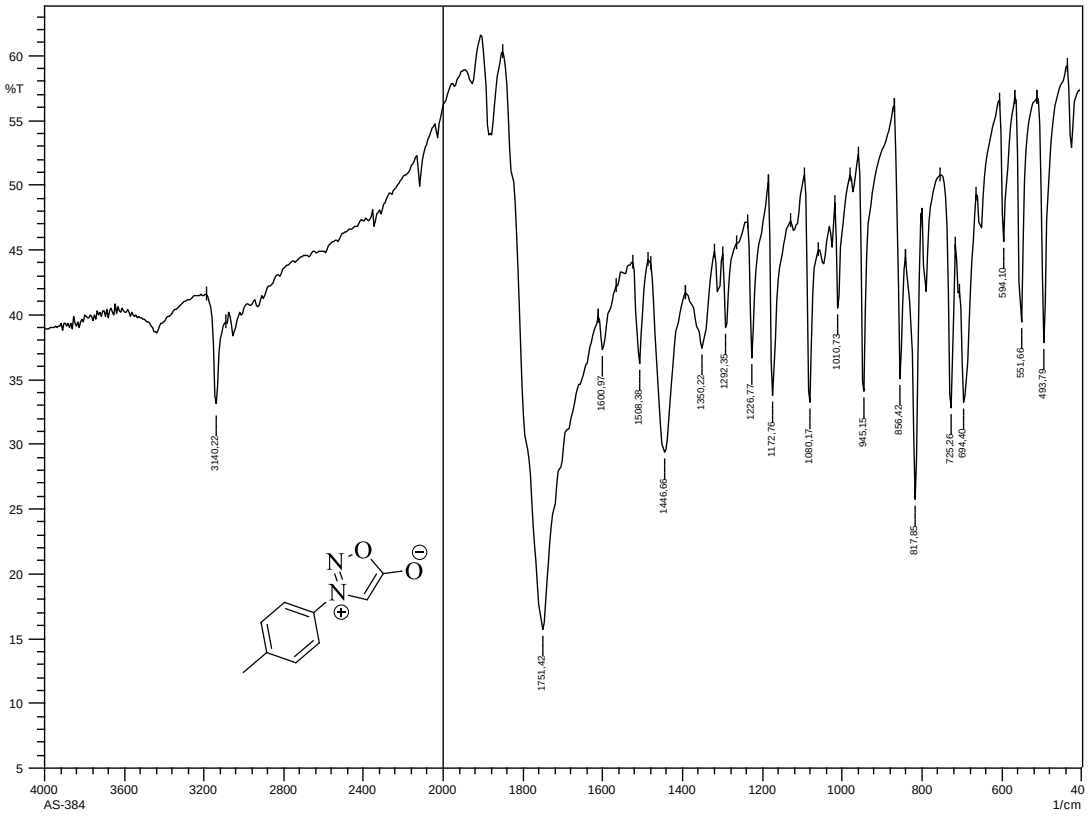


Figure 6.3 IR spectrum of compound **51b**

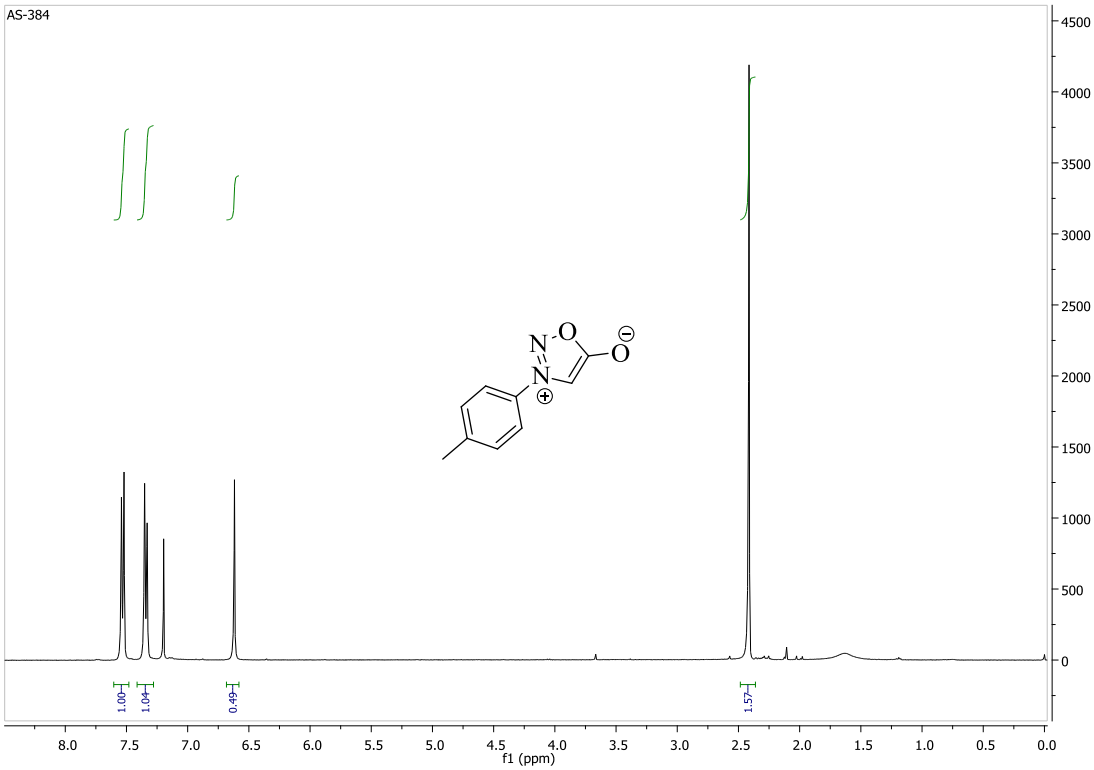


Figure 6.4 ^{1}H NMR spectrum of compound **51b**

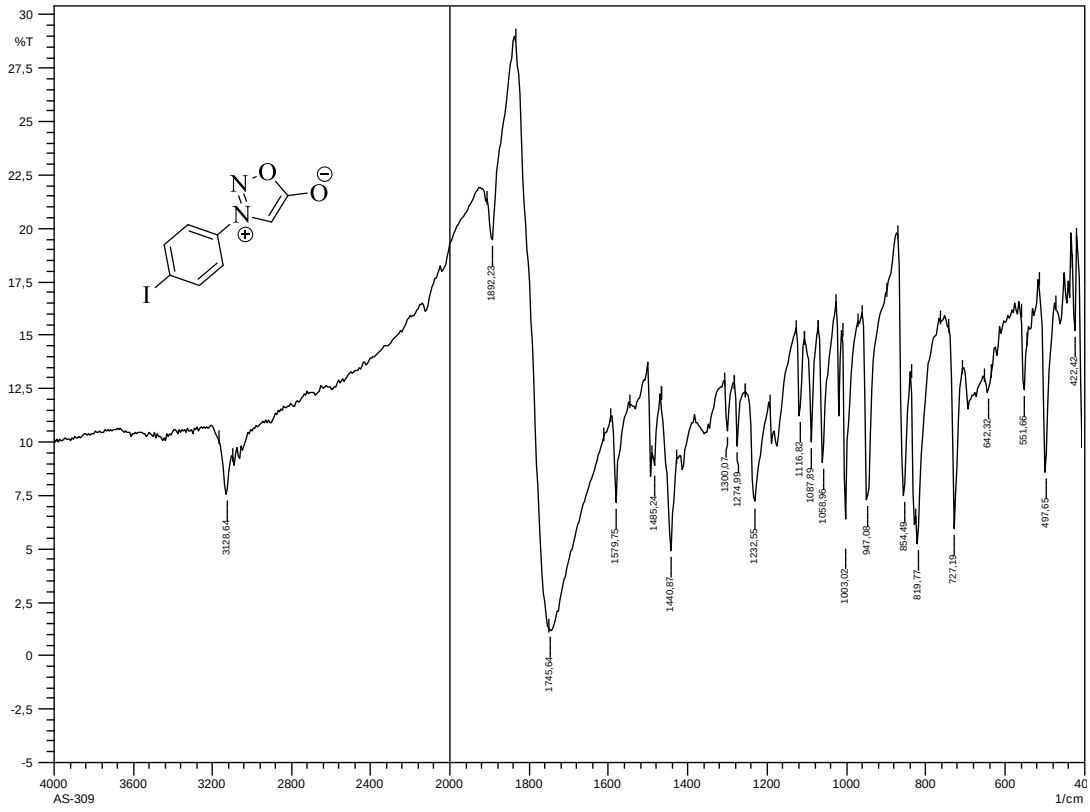


Figure 6.5 IR spectrum of compound **51c**

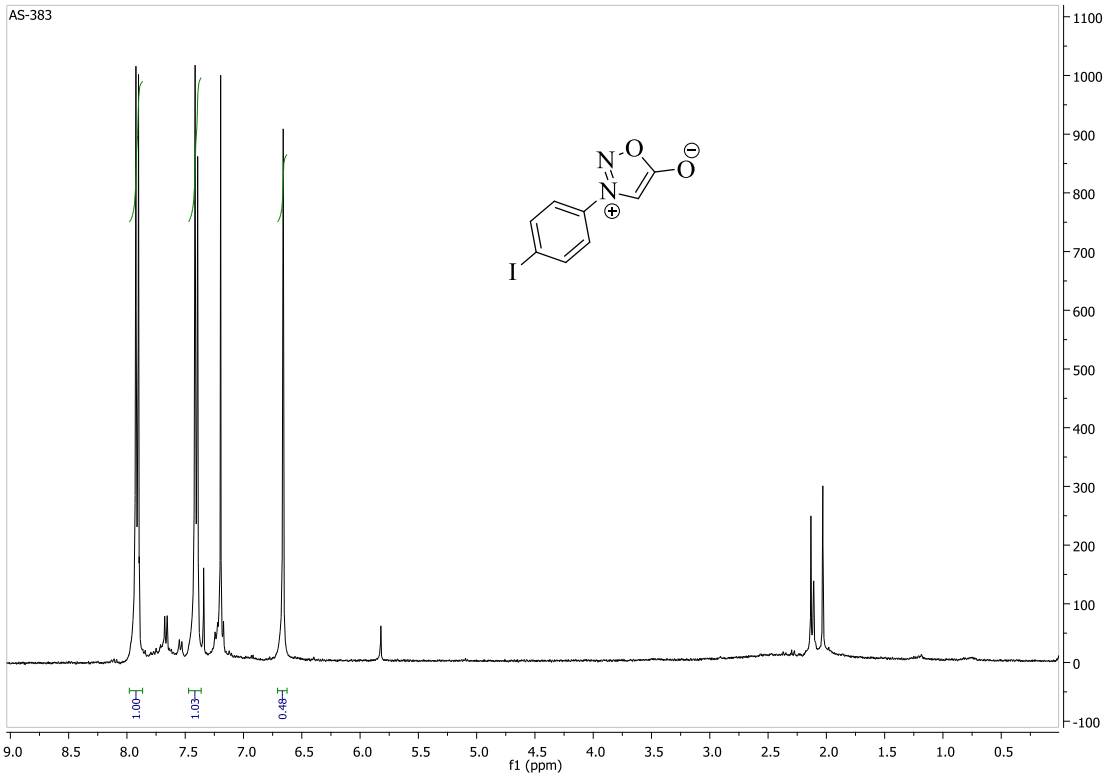


Figure 6.6 ^{1}H NMR spectrum of compound **51c**

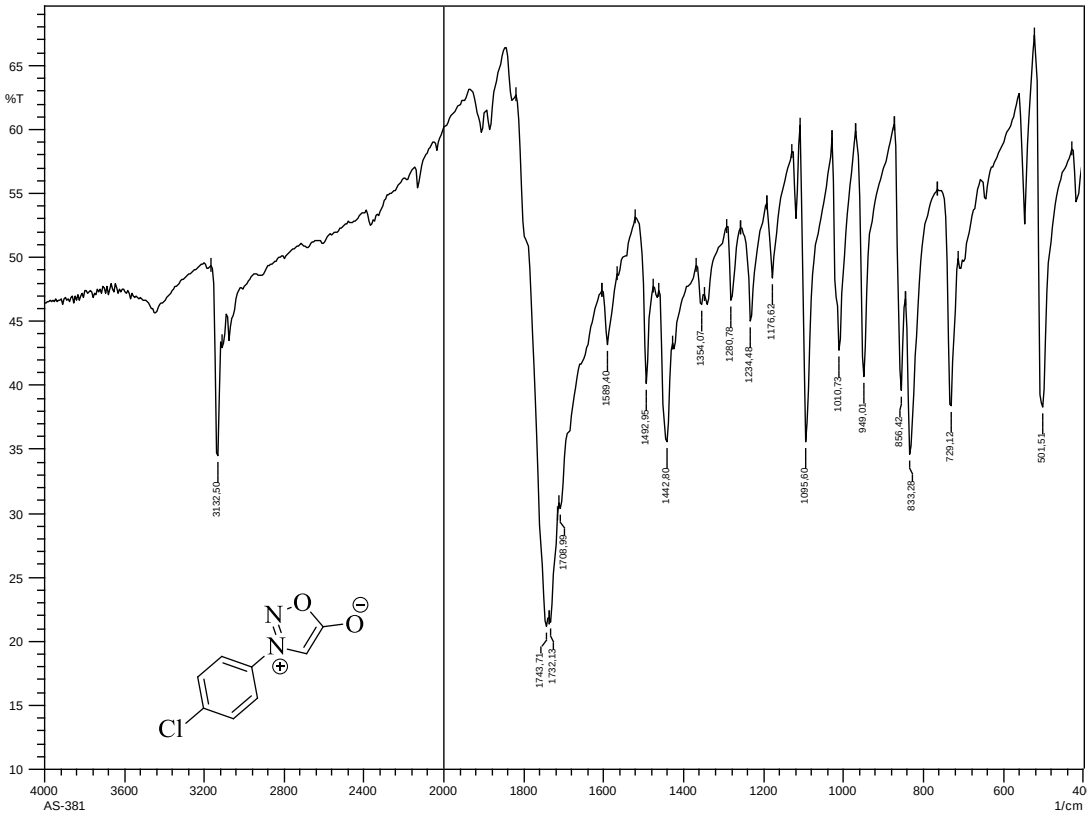


Figure 6.7 IR spectrum of compound **51d**

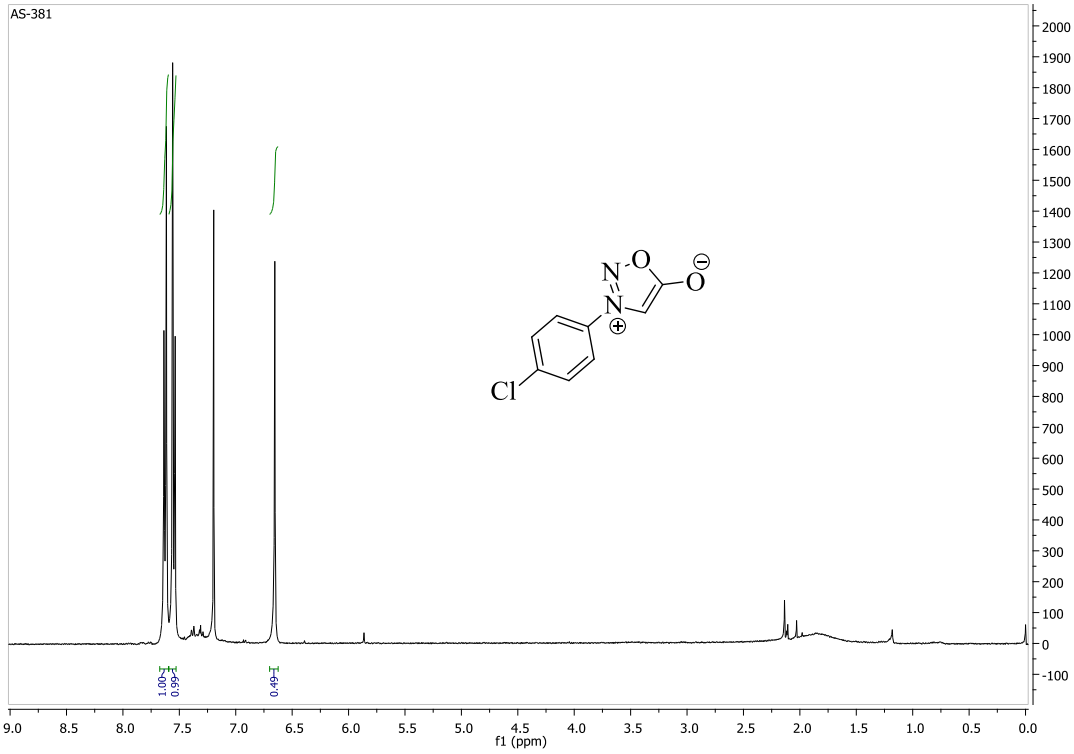


Figure 6.8 ^{1}H NMR spectrum of compound **51d**

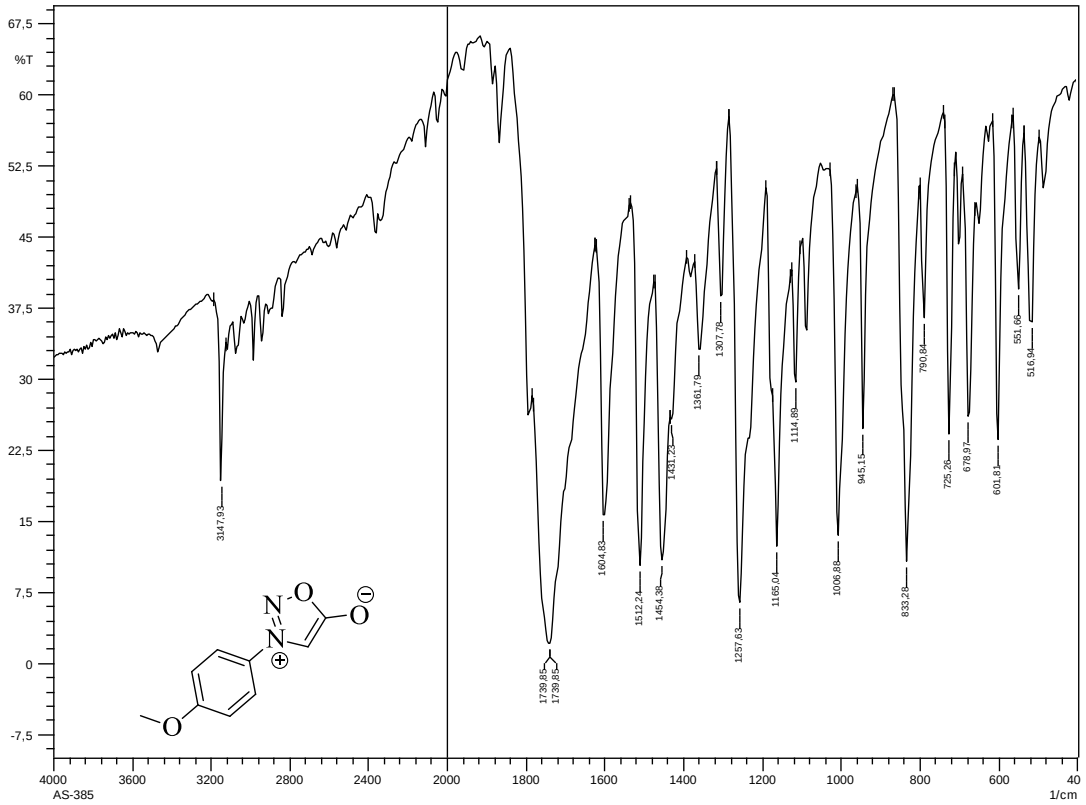


Figure 6.9 IR spectrum of compound **51e**

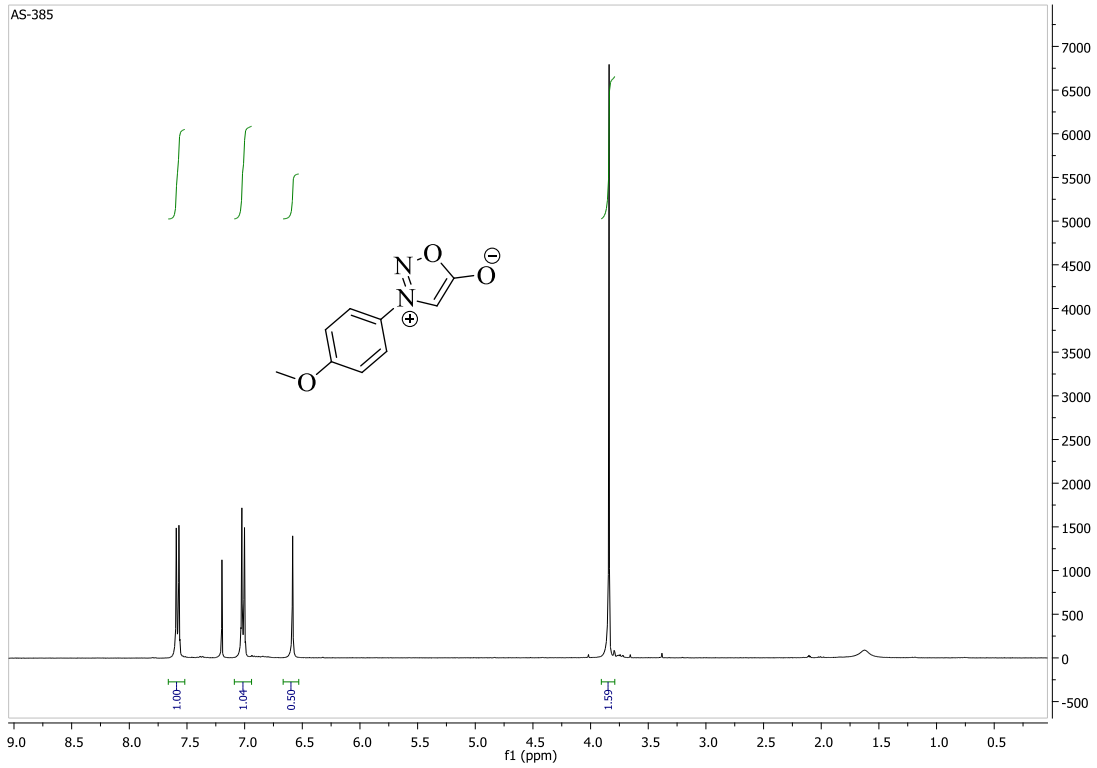


Figure 6.10 ^{1}H NMR spectrum of compound **51e**

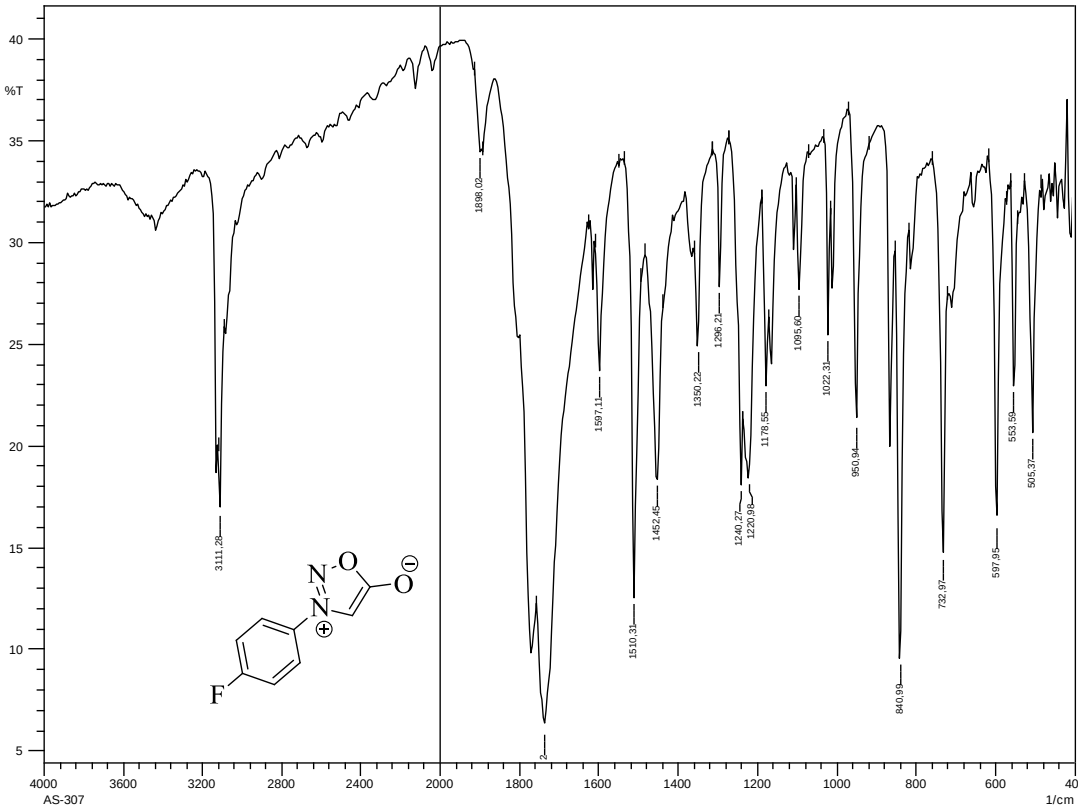


Figure 6.11 IR spectrum of compound **51f**

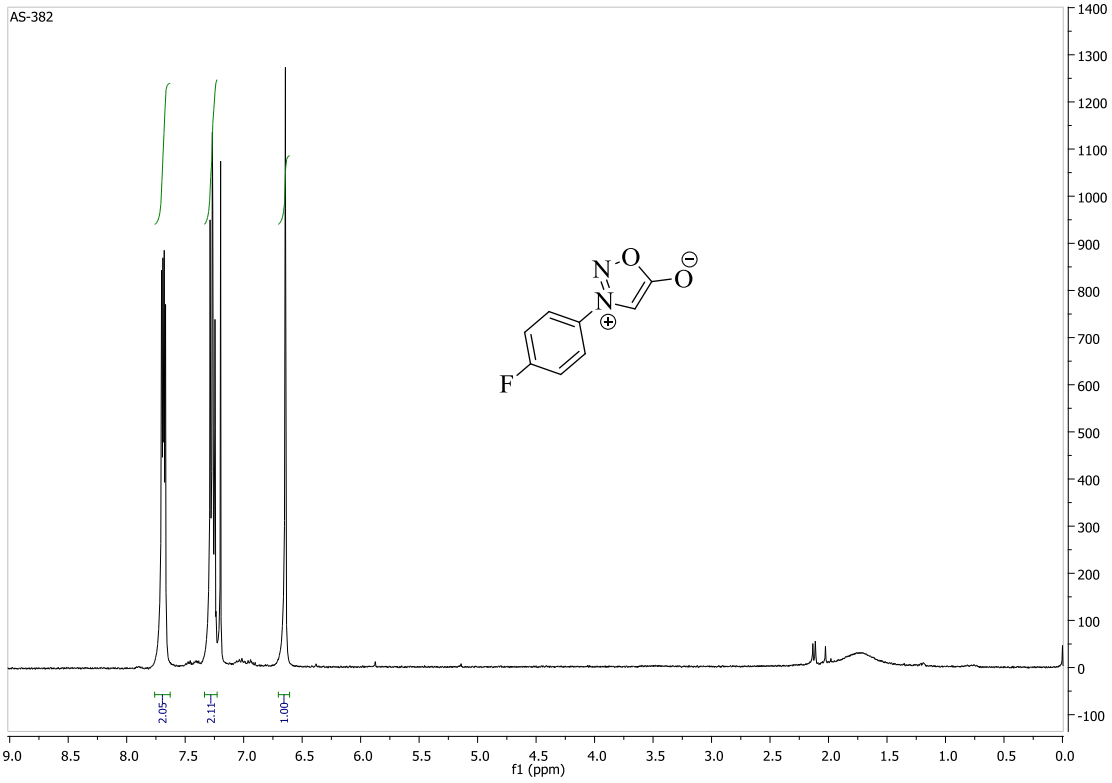


Figure 6.12 ^{1}H NMR spectrum of compound **51f**

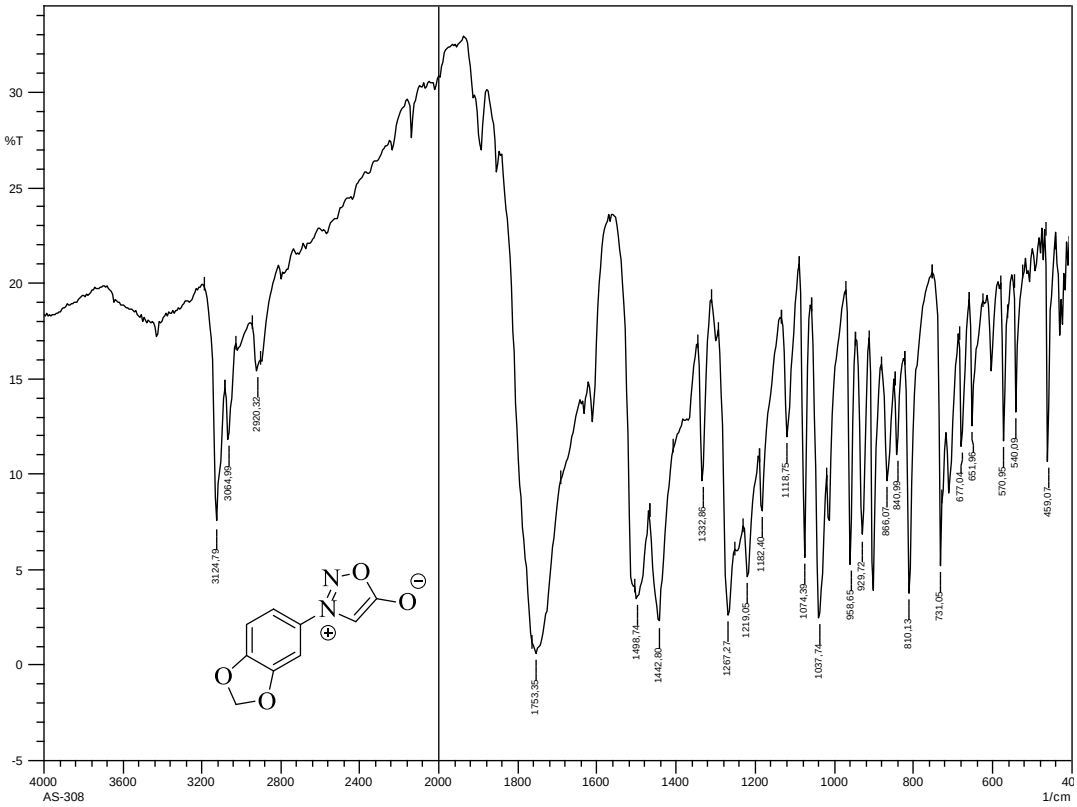


Figure 6.13 IR spectrum of compound **51g**

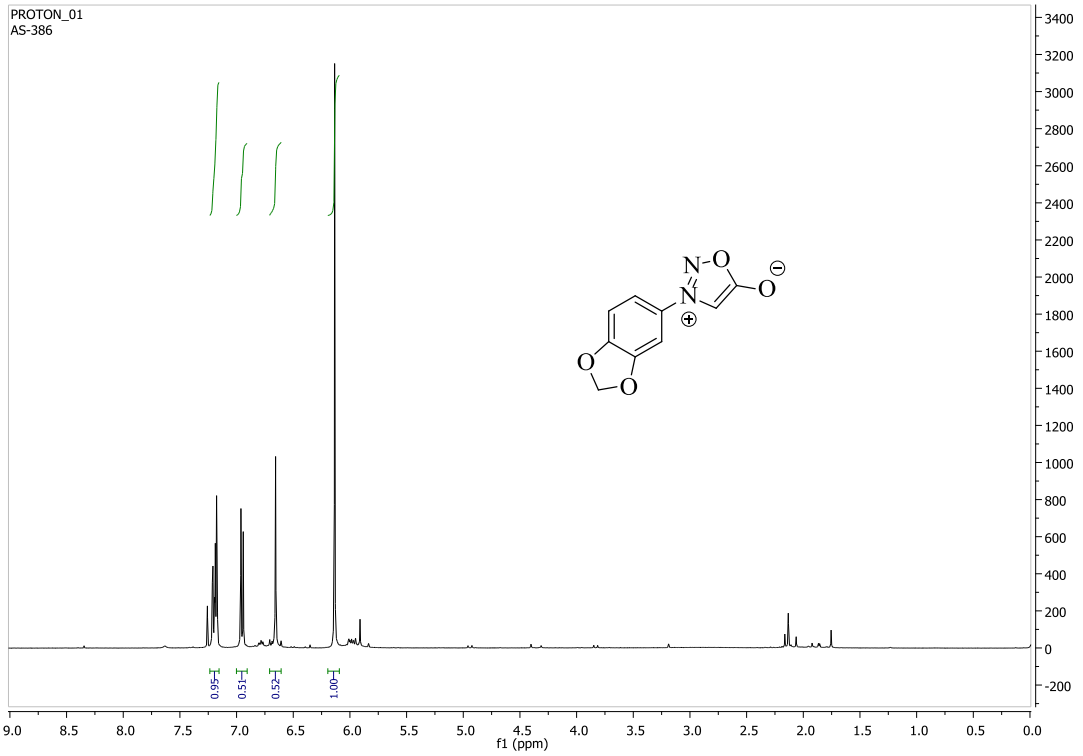


Figure 6.14 ^{1}H NMR spectrum of compound **51g**

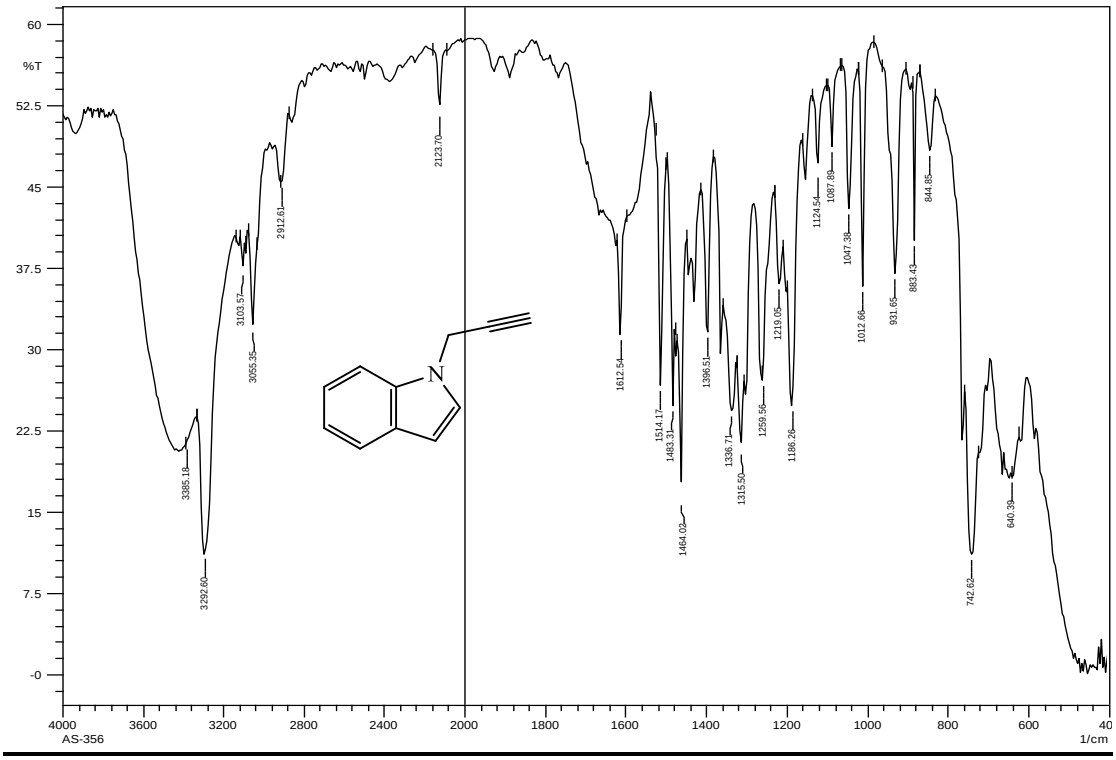


Figure 6.15 IR spectrum of compound **195**

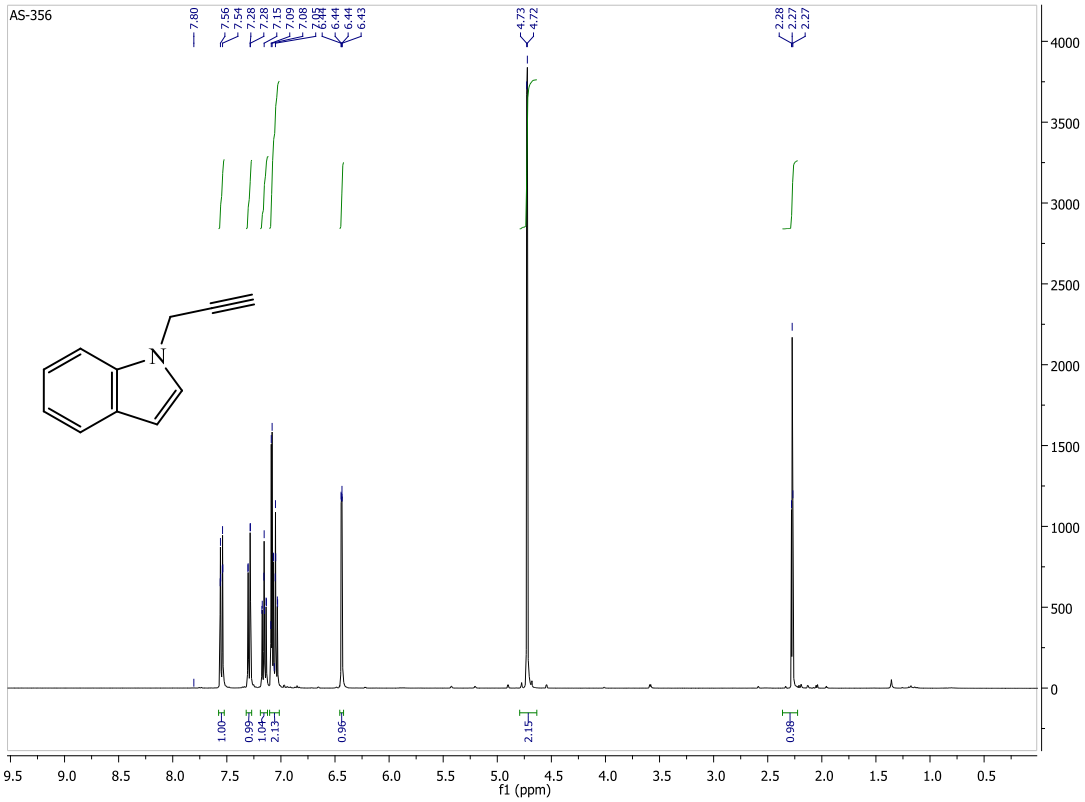


Figure 6.16 ^{1}H NMR spectrum of compound **195**

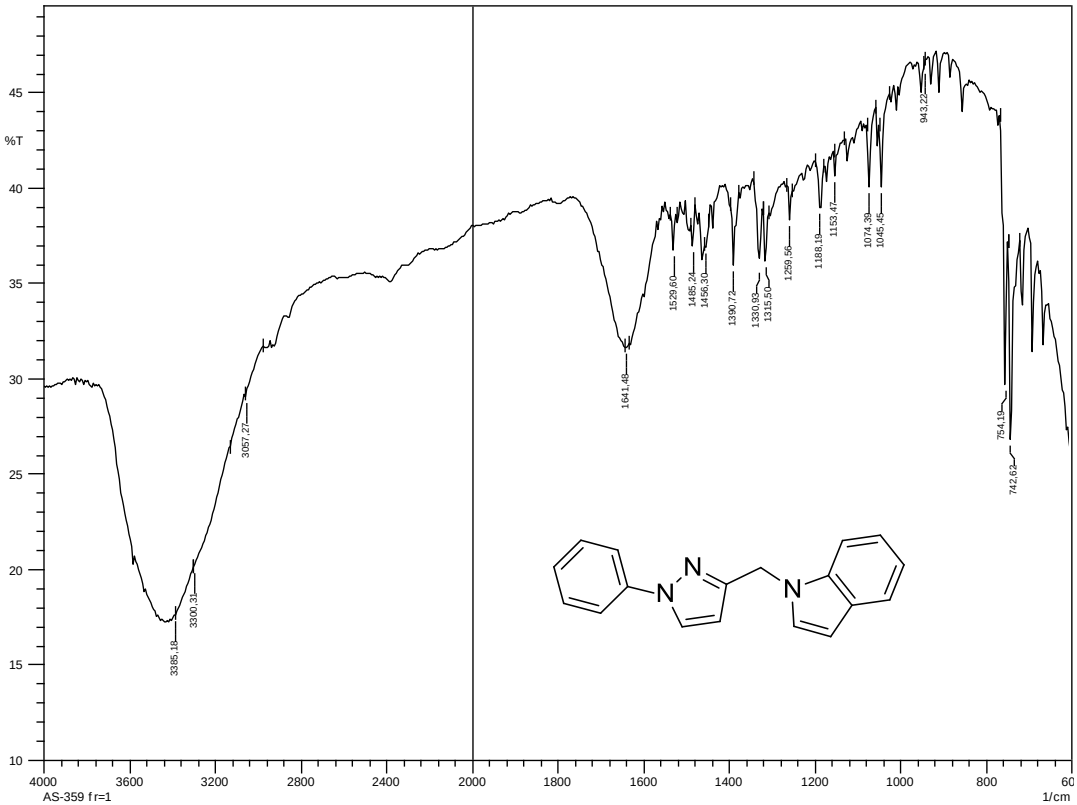


Figure 6.17 IR spectrum of compound **242a**

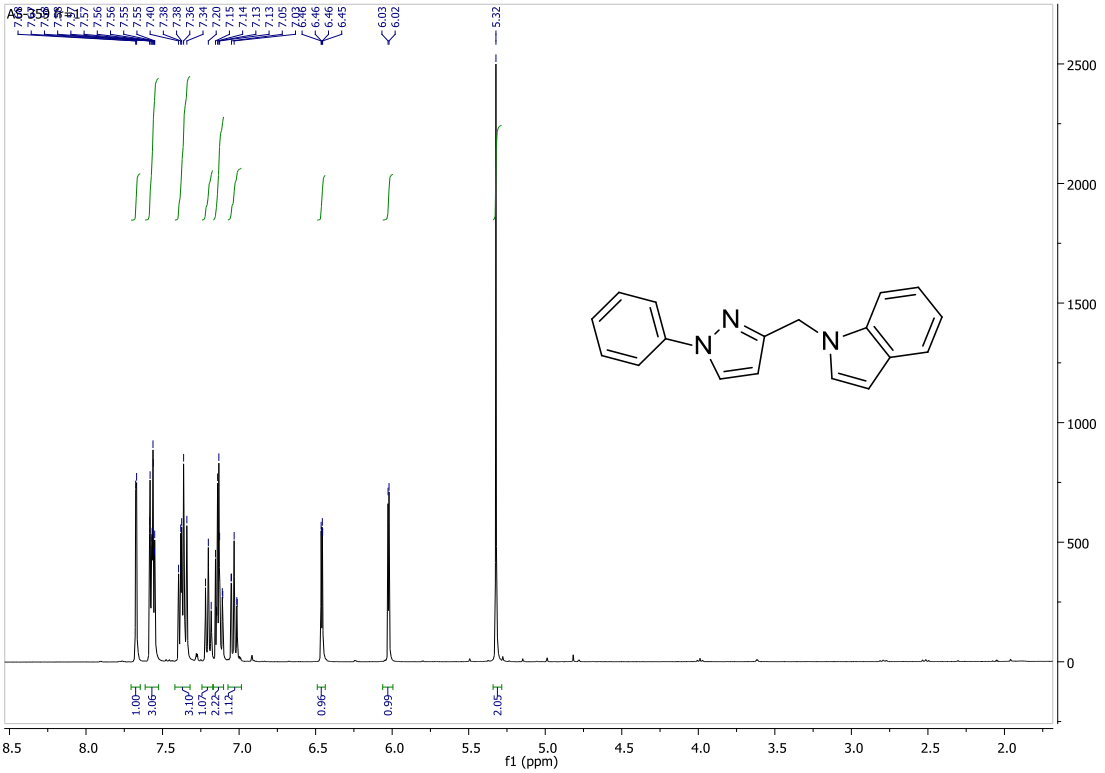


Figure 6.18 ^{1}H NMR spectrum of compound **242a**

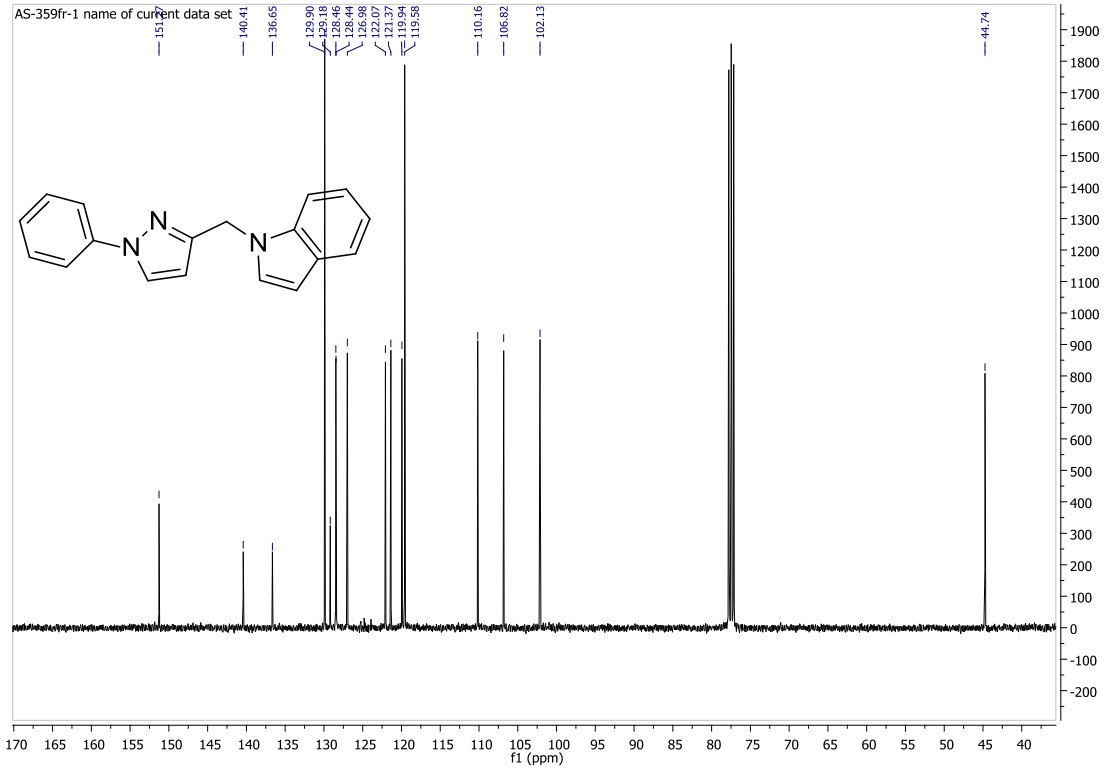


Figure 6.19 ^{13}C NMR spectrum of compound **242a**

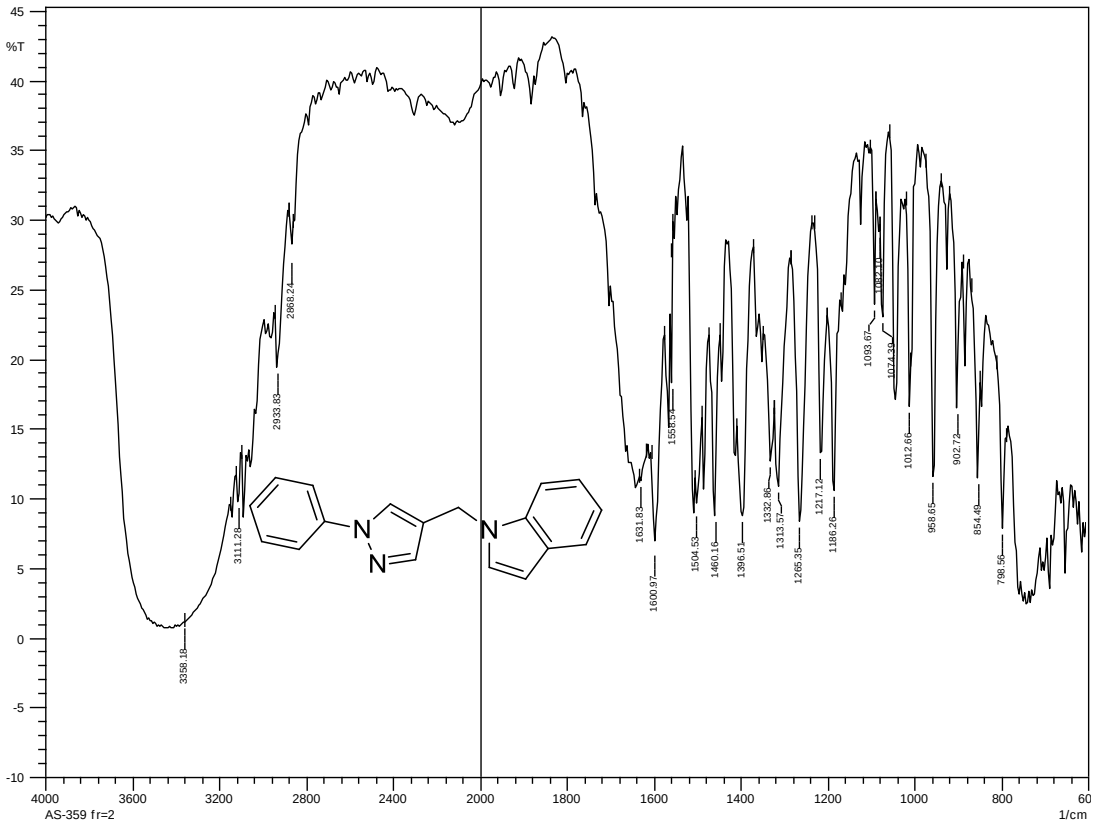


Figure 6.20 IR spectrum of compound **243a**

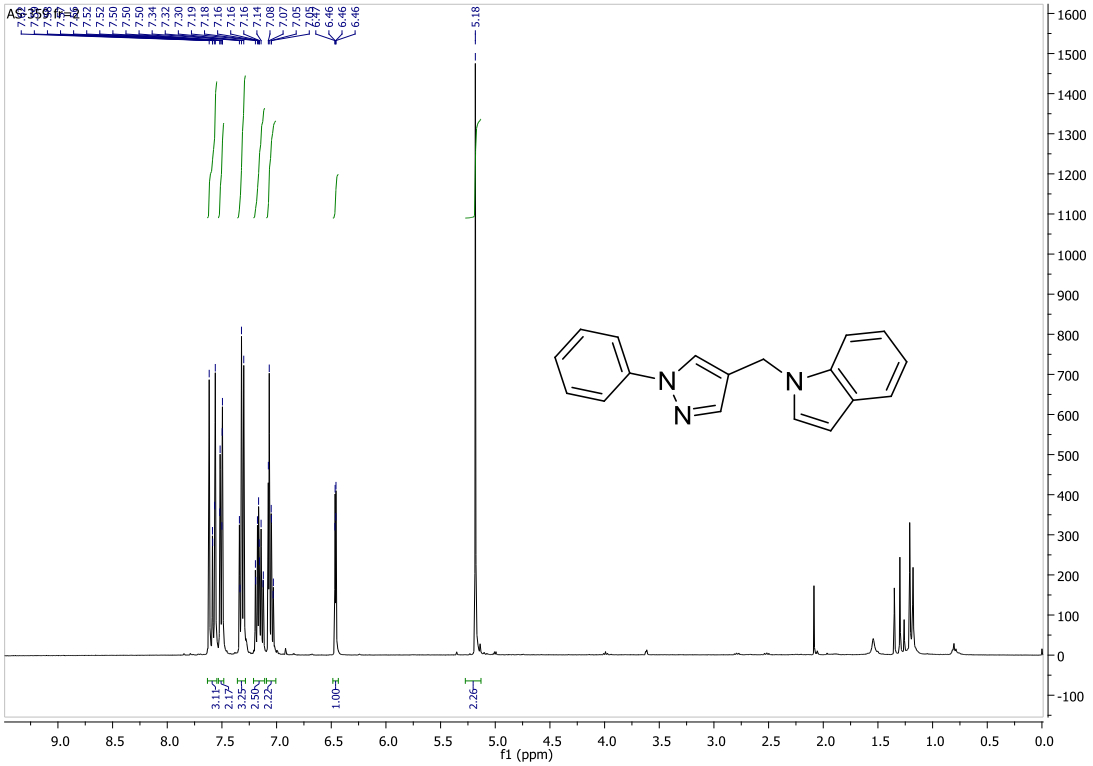


Figure 6.21 ^{1}H NMR spectrum of compound **243a**

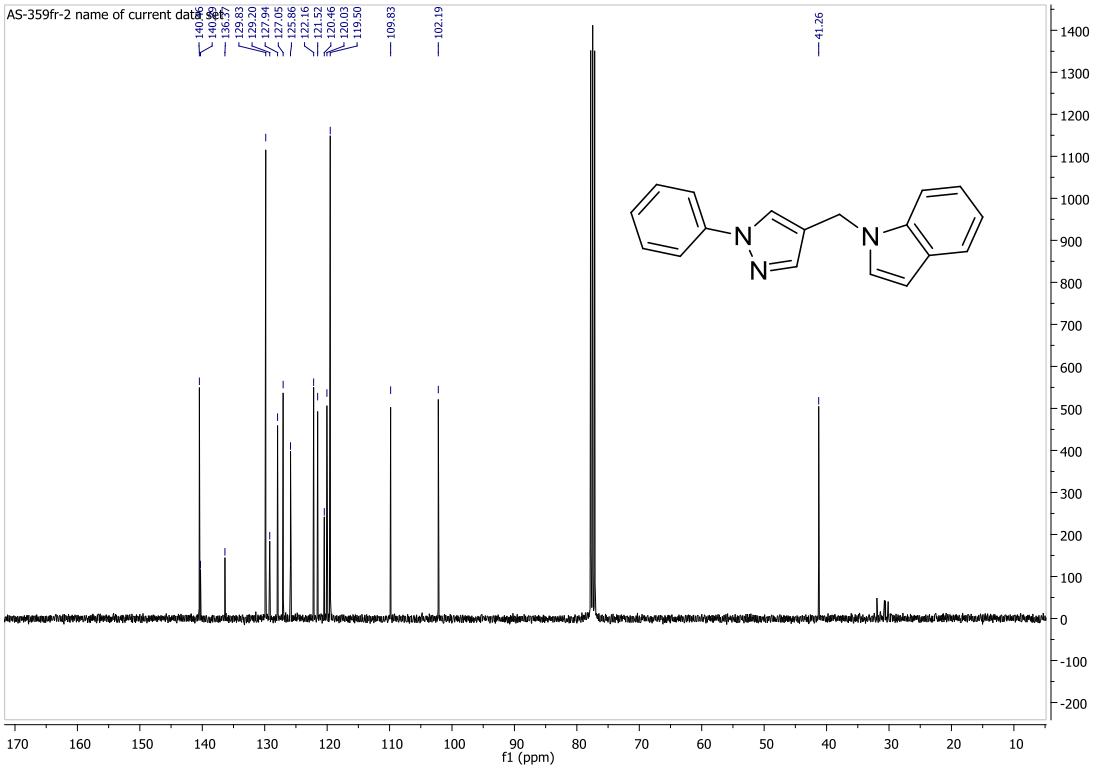


Figure 6.22 ^{13}C NMR spectrum of compound **243a**

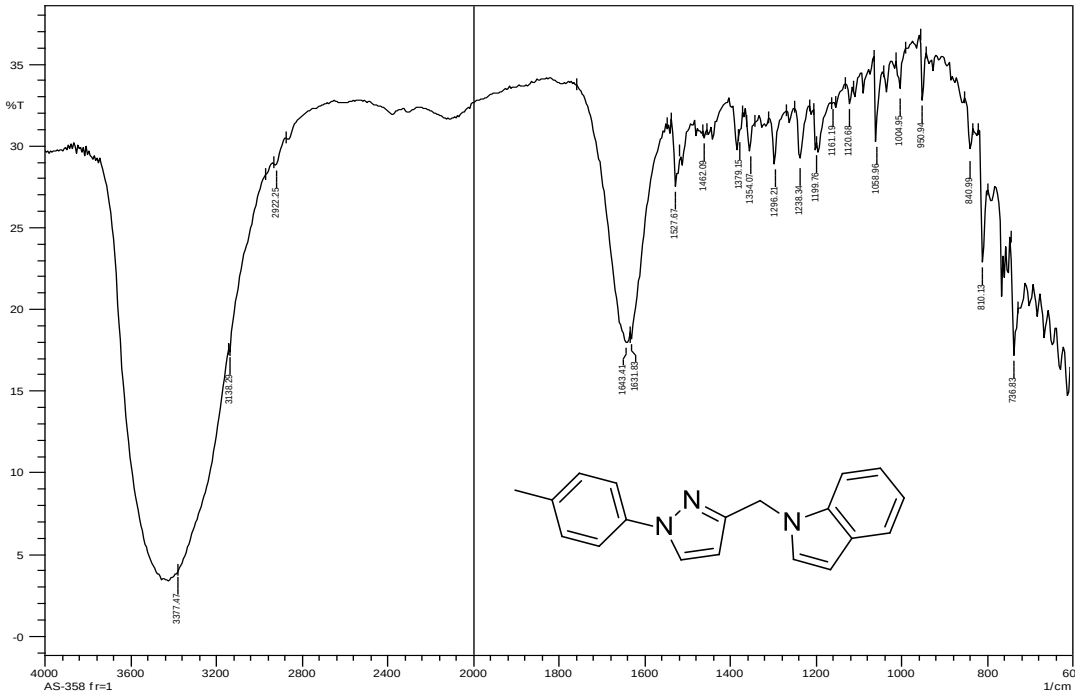


Figure 6.23 IR spectrum of compound **242b**

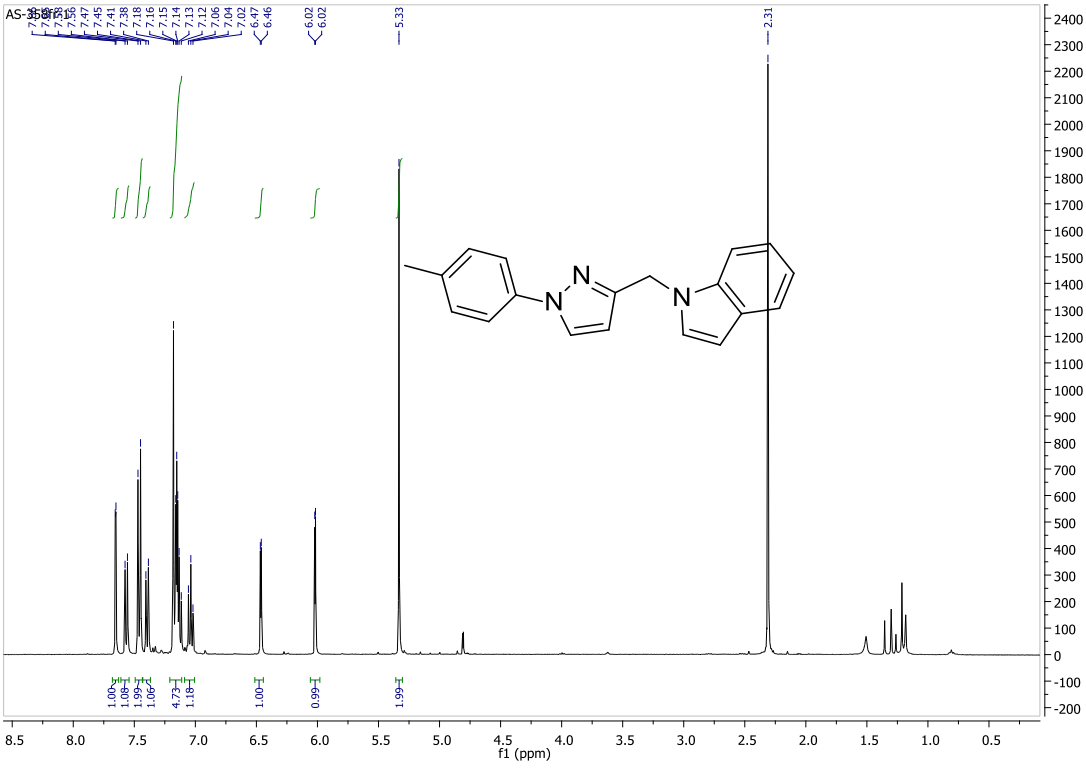


Figure 6.24 ^{1}H NMR spectrum of compound **242b**

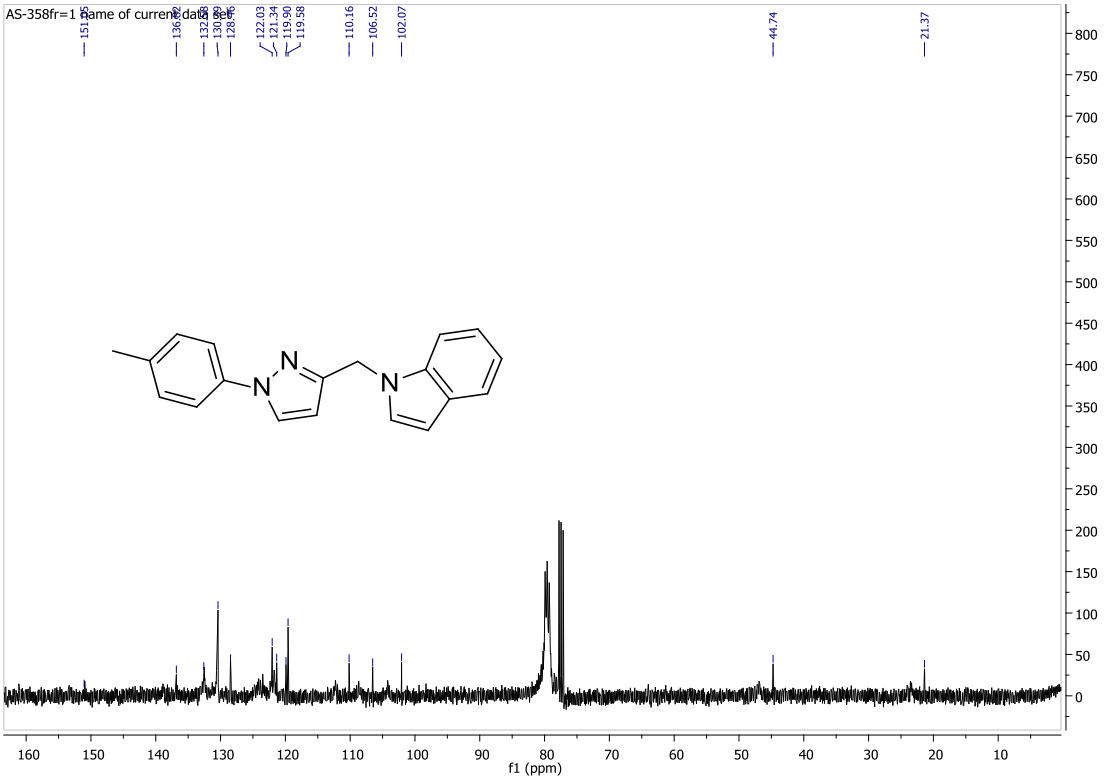


Figure 6.25 ^{13}C NMR spectrum of compound **242b**

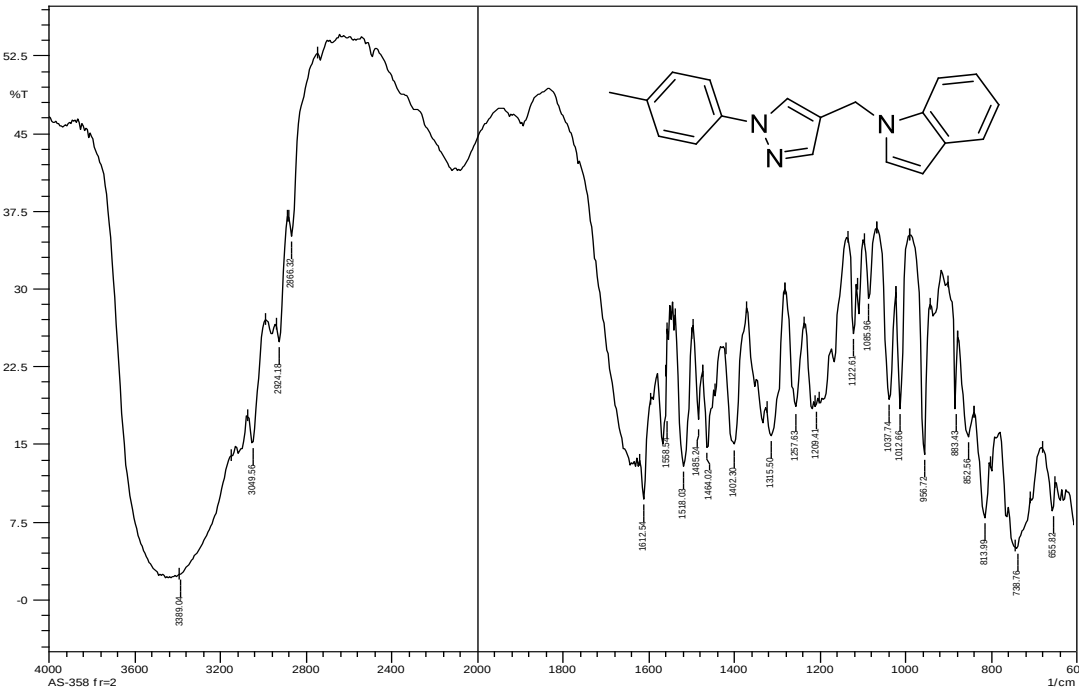


Figure 6.26 IR spectrum of compound **243b**

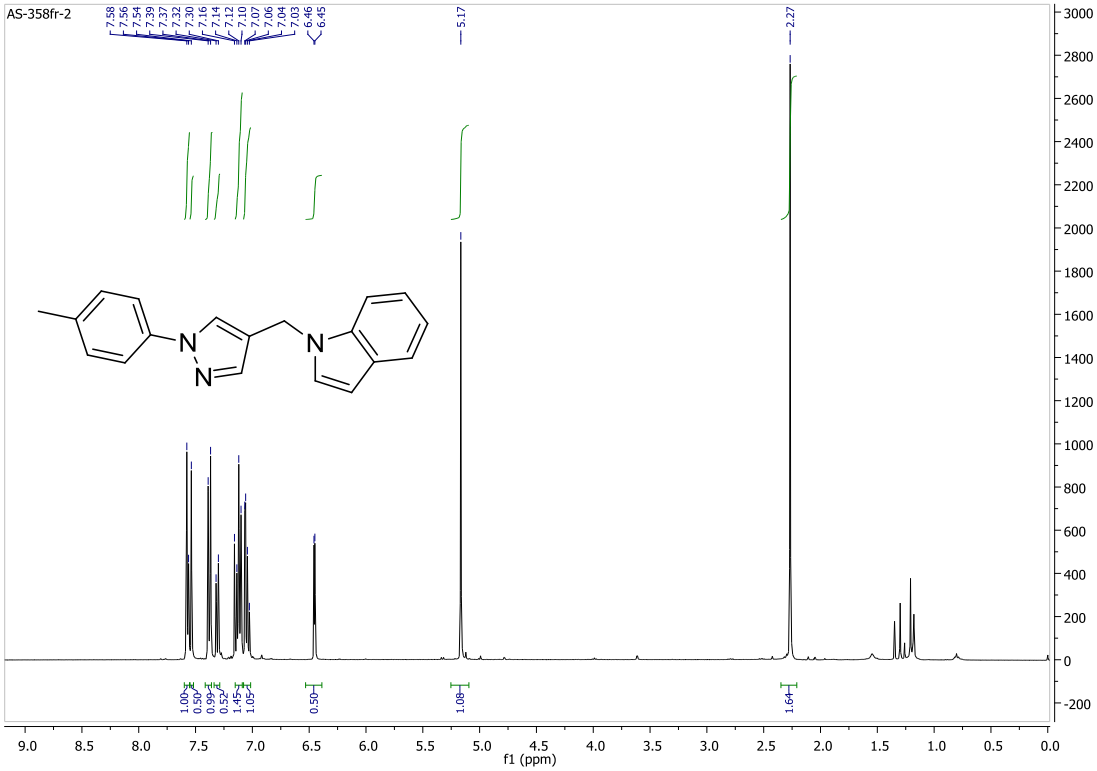


Figure 6.27 ^{1}H NMR spectrum of compound **243b**

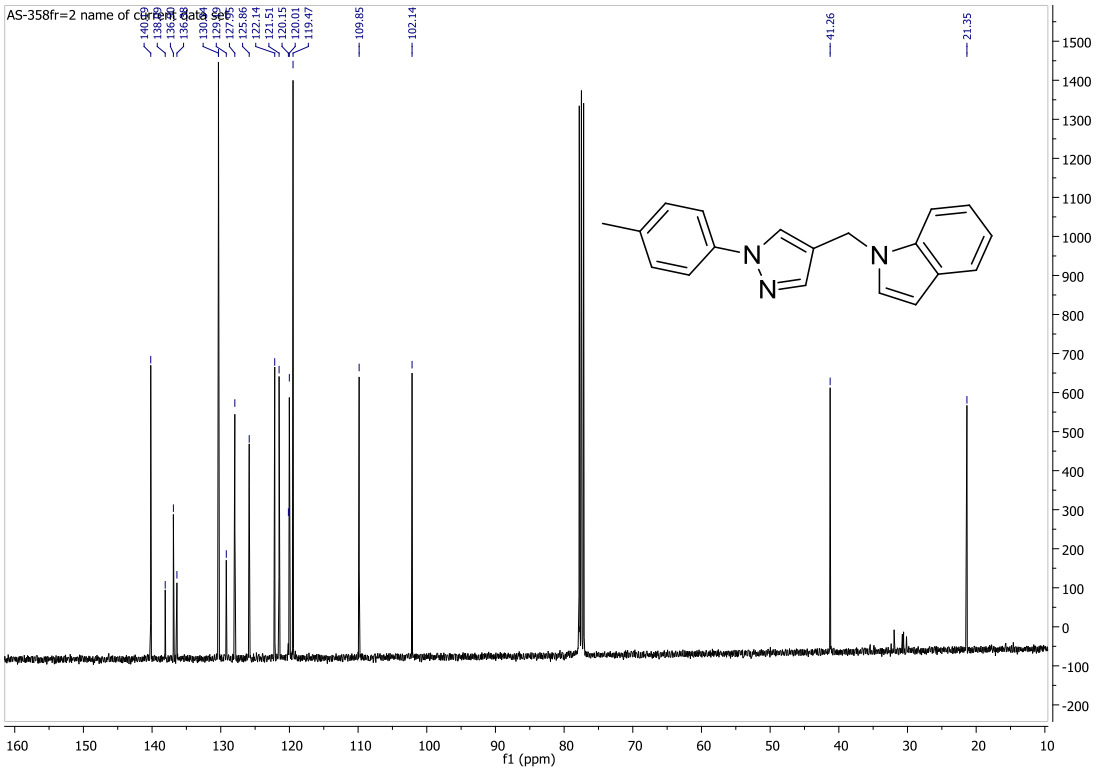


Figure 6.28 ^{13}C NMR spectrum of compound **243b**

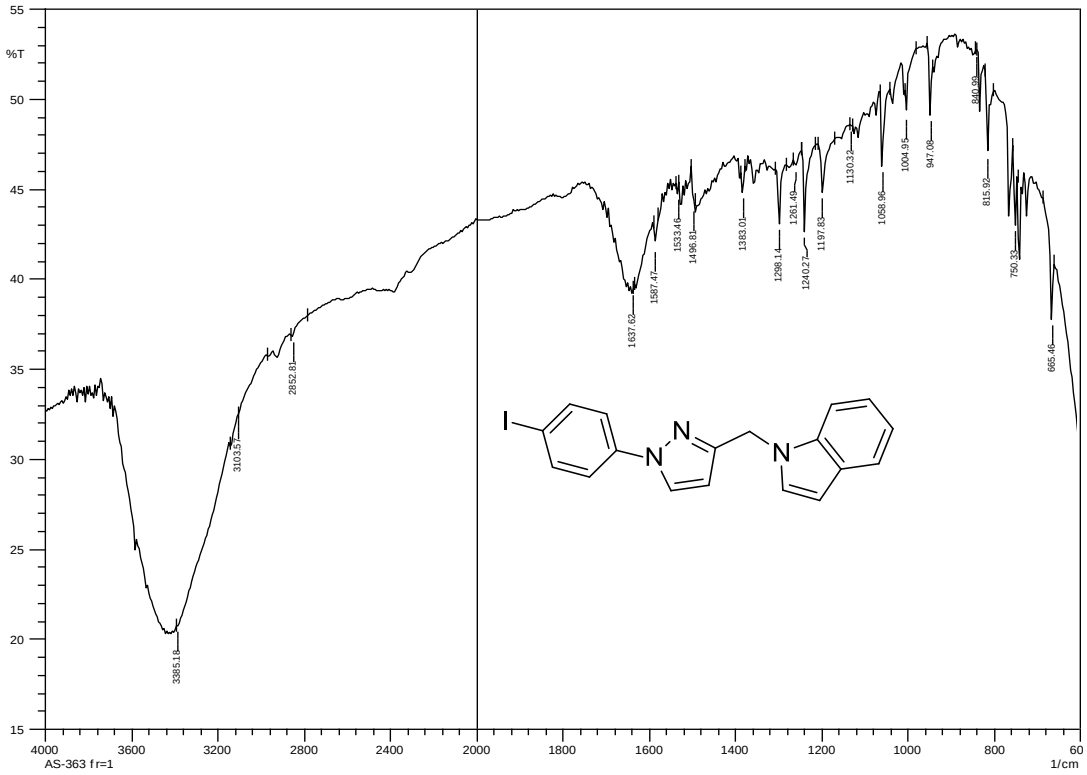


Figure 6.29 IR spectrum of compound **242c**

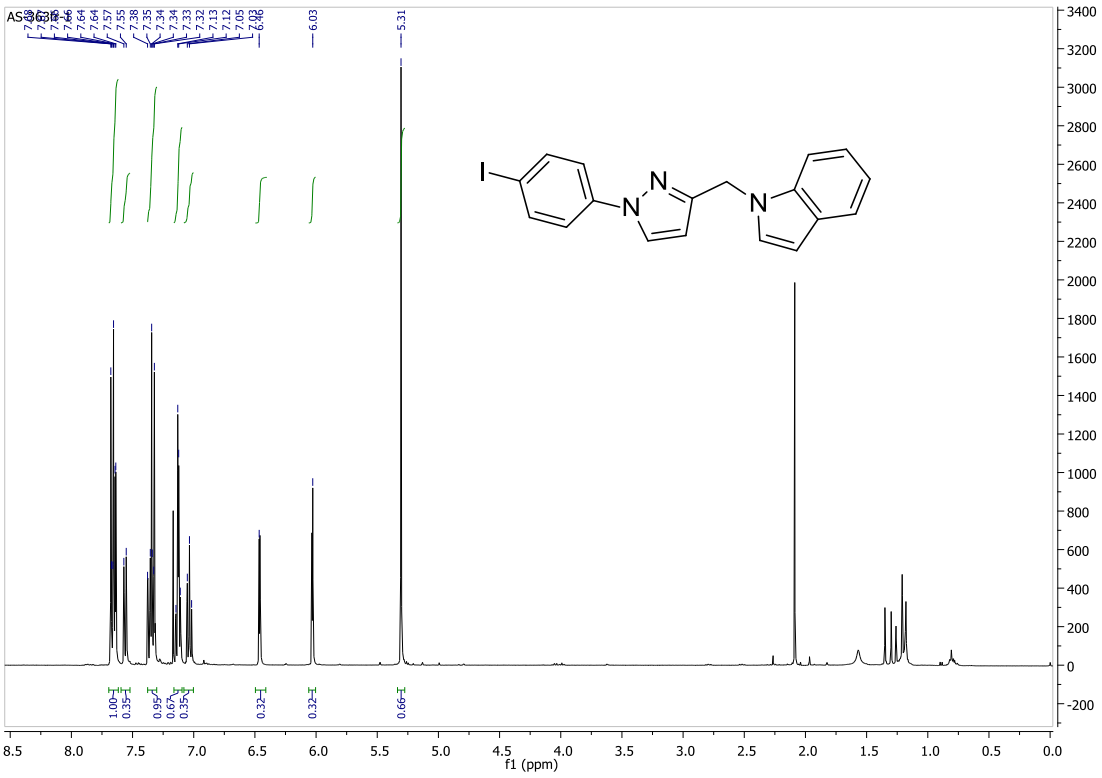


Figure 6.30 ^{1}H NMR spectrum of compound **242c**

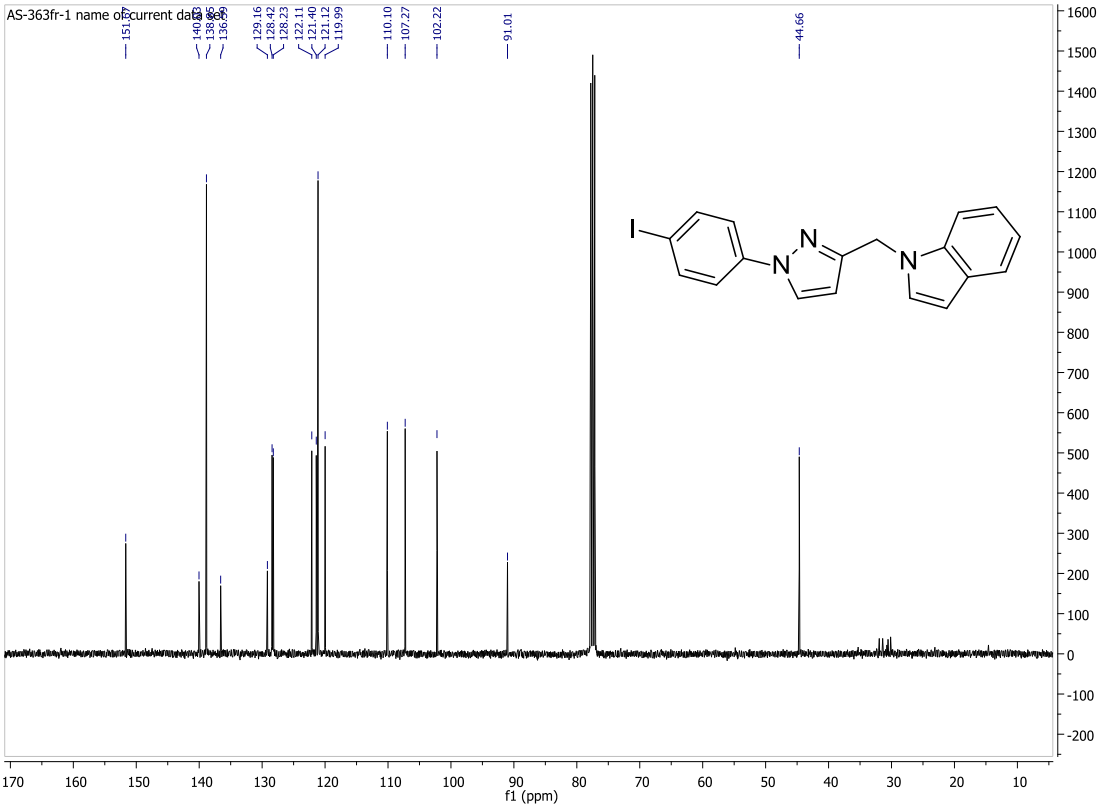


Figure 6.31 ^{13}C NMR spectrum of compound **242c**

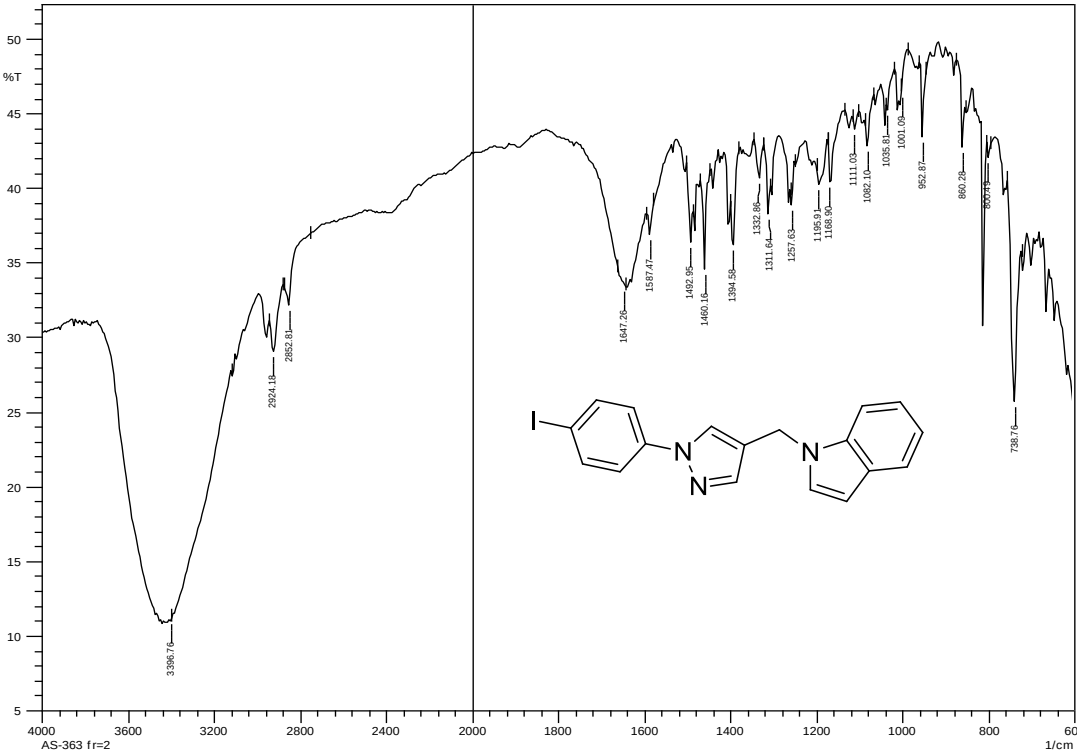


Figure 6.32 IR spectrum of compound **243c**

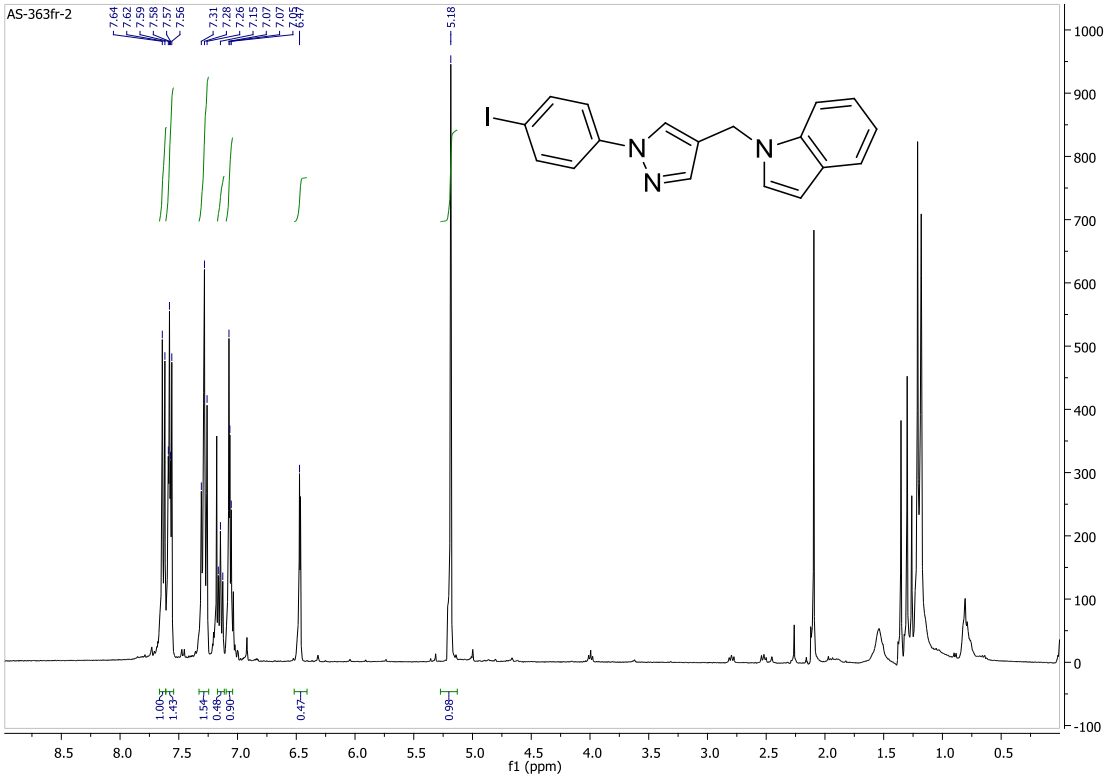


Figure 6.33 ^{1}H NMR spectrum of compound **243c**

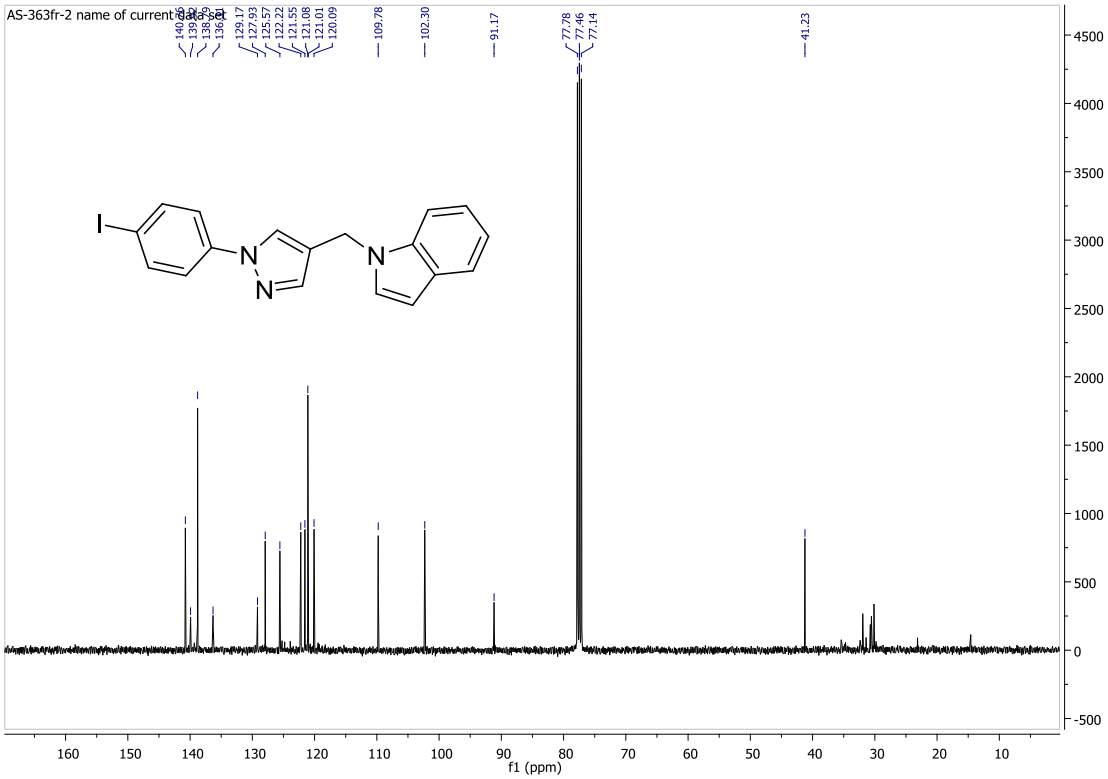


Figure 6.34 ^{13}C NMR spectrum of compound **243c**

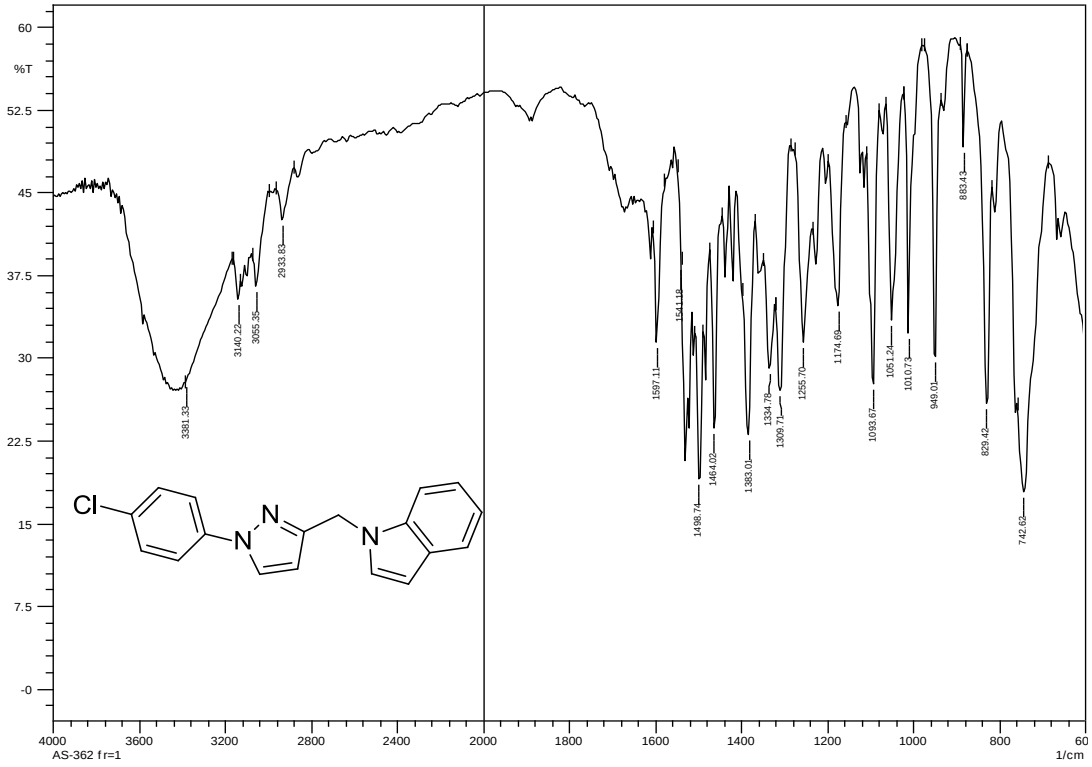


Figure 6.35 IR spectrum of compound **242d**

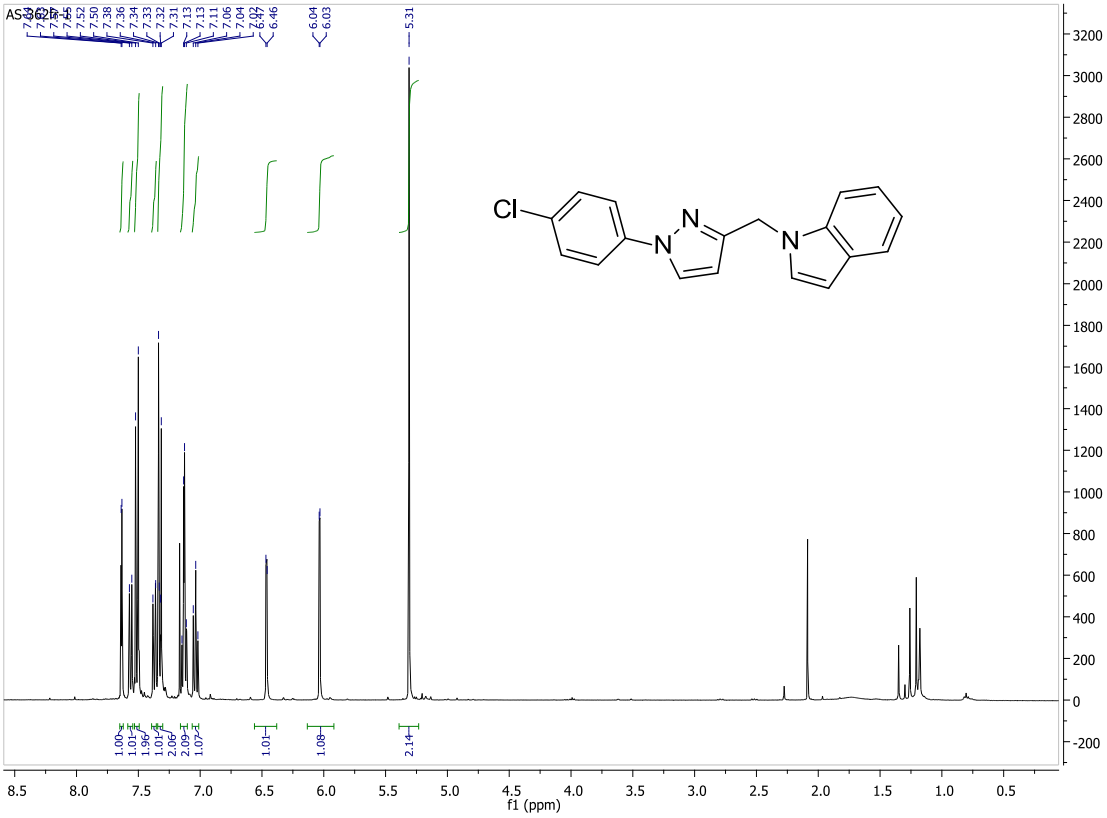


Figure 6.36 ^{1}H NMR spectrum of compound **242d**

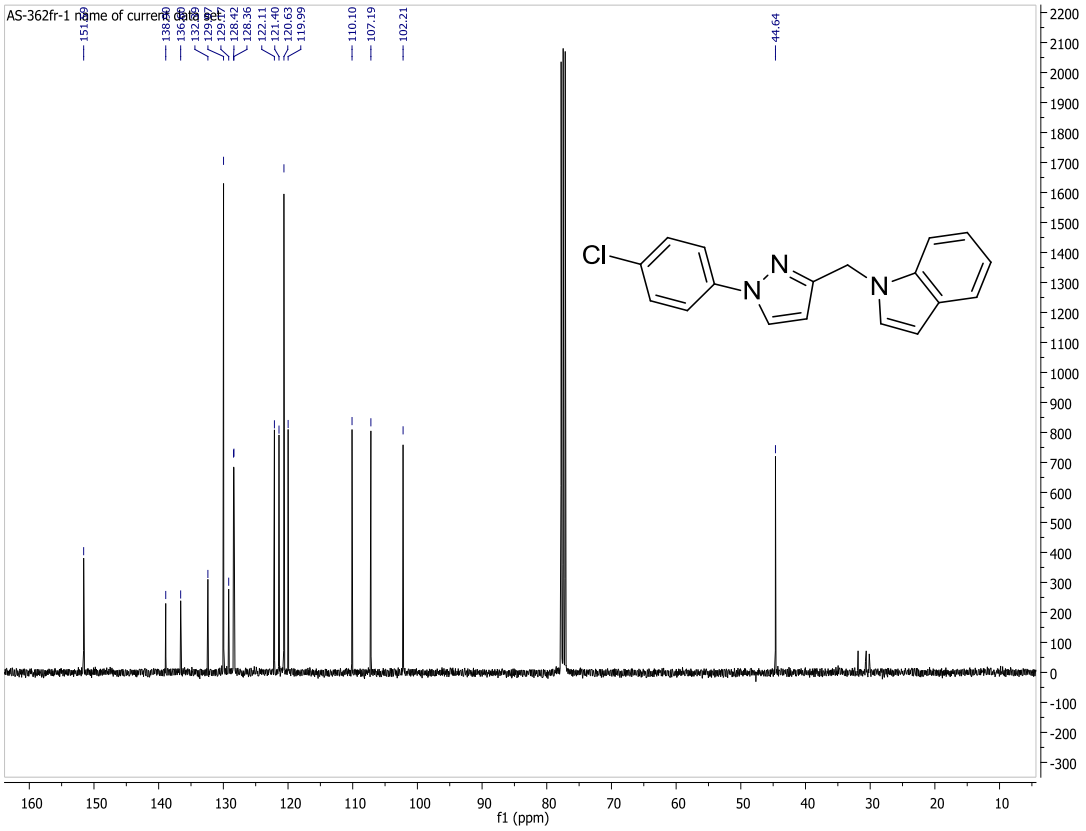


Figure 6.37 ^{13}C NMR spectrum of compound **242d**

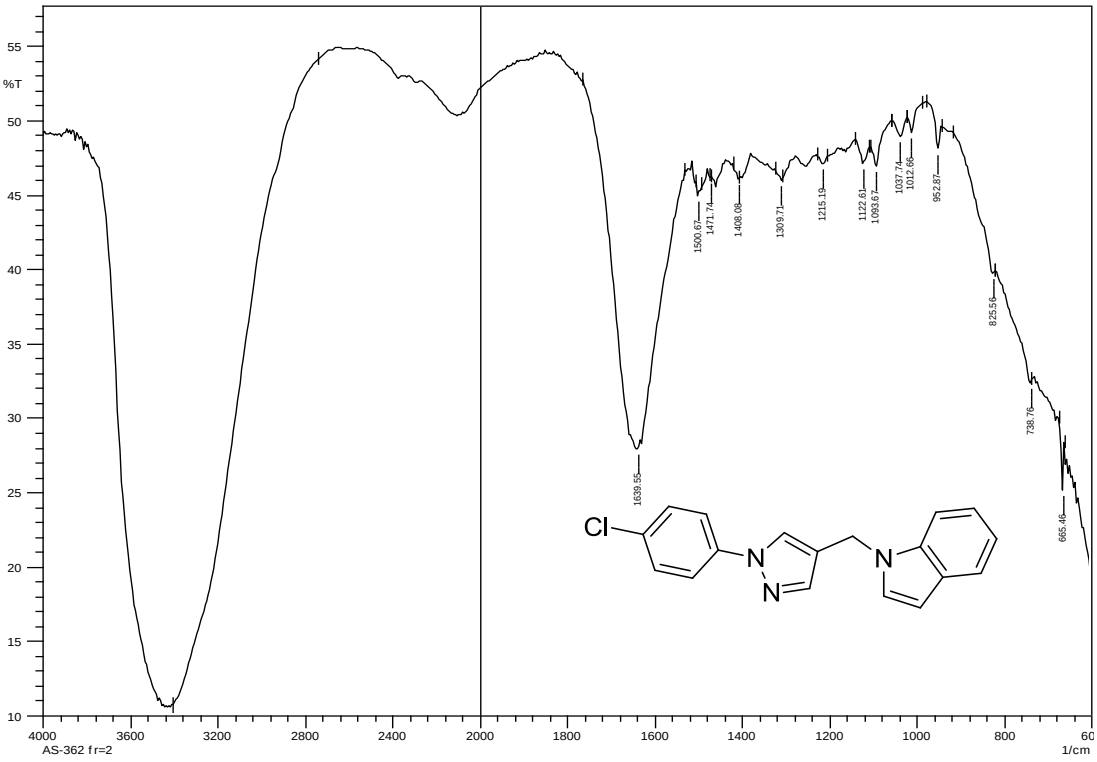


Figure 6.38 IR spectrum of compound **243d**

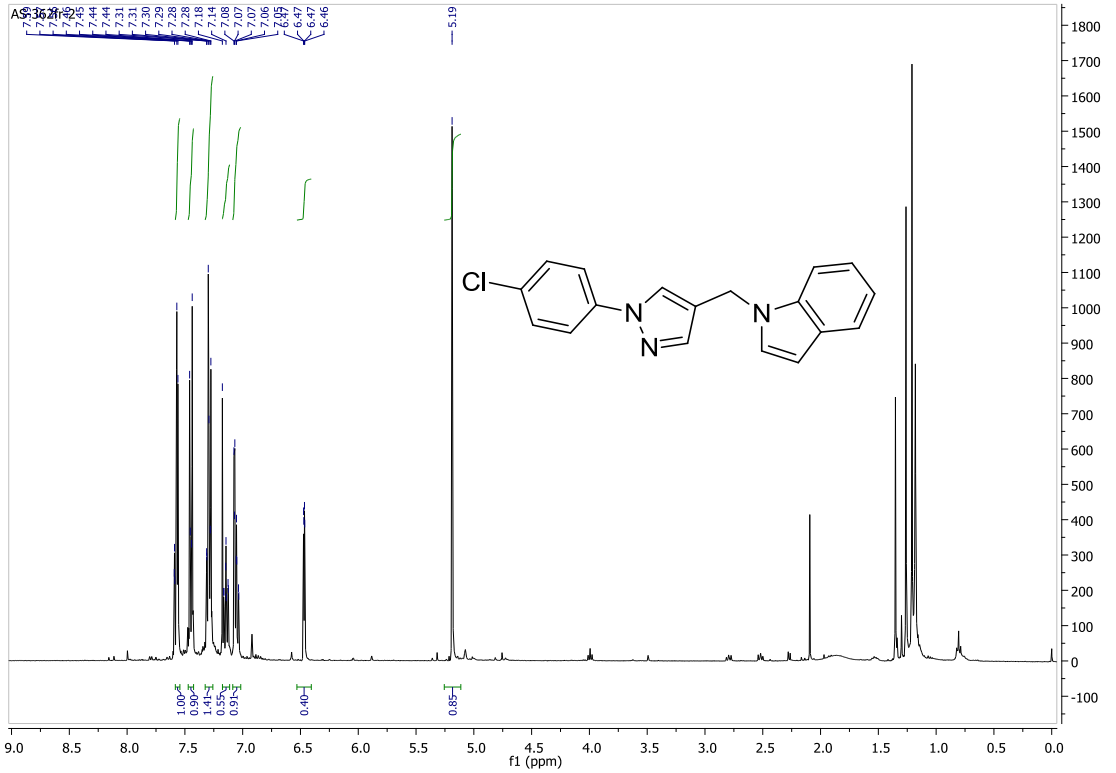


Figure 6.39 ^{1}H NMR spectrum of compound **243d**

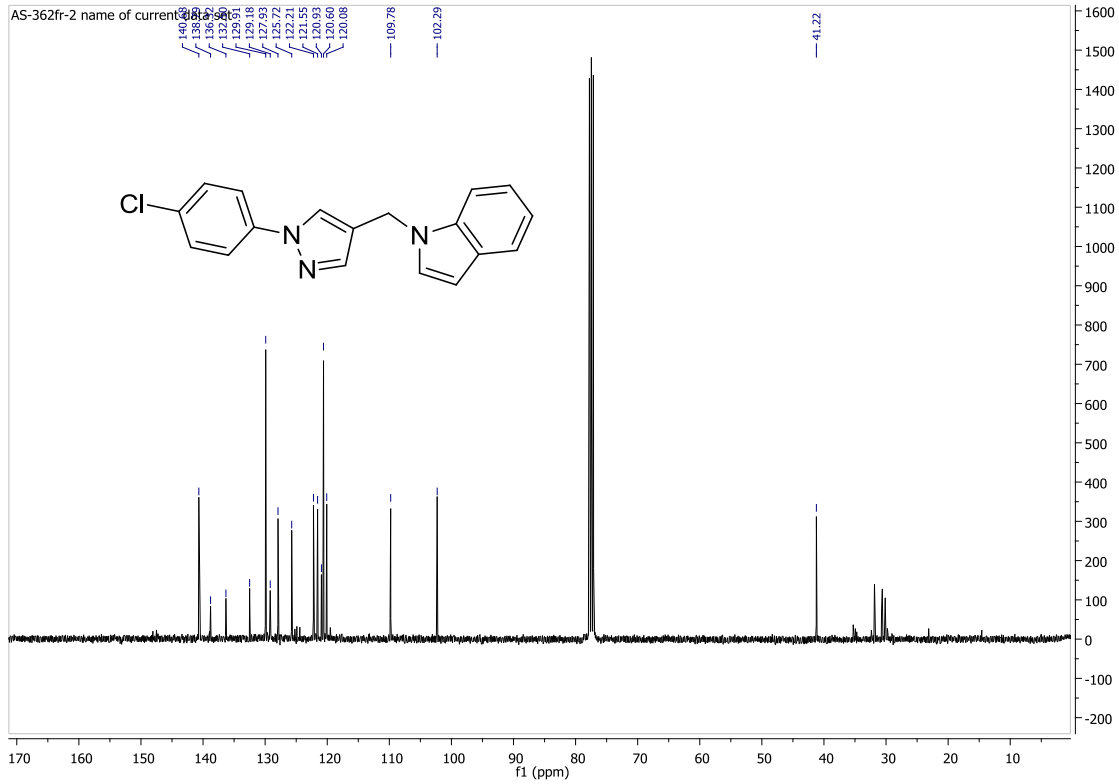


Figure 6.40 ^{13}C NMR spectrum of compound **243d**

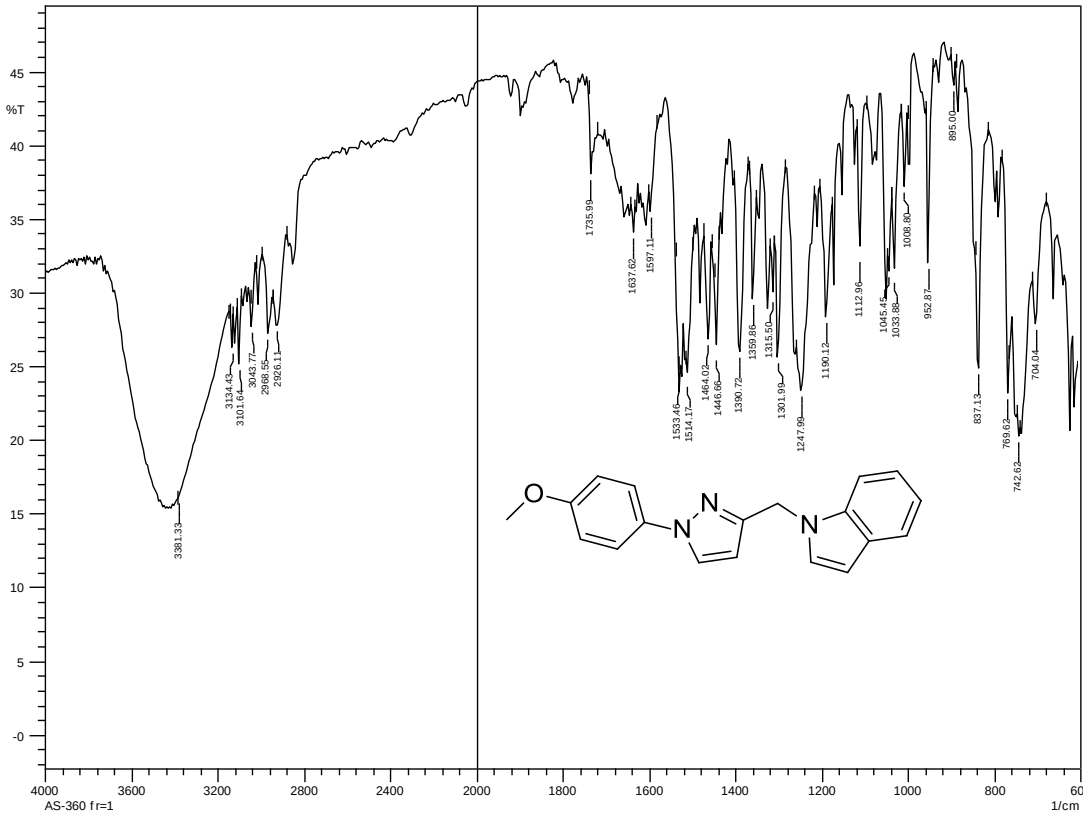


Figure 6.41 IR spectrum of compound **242e**

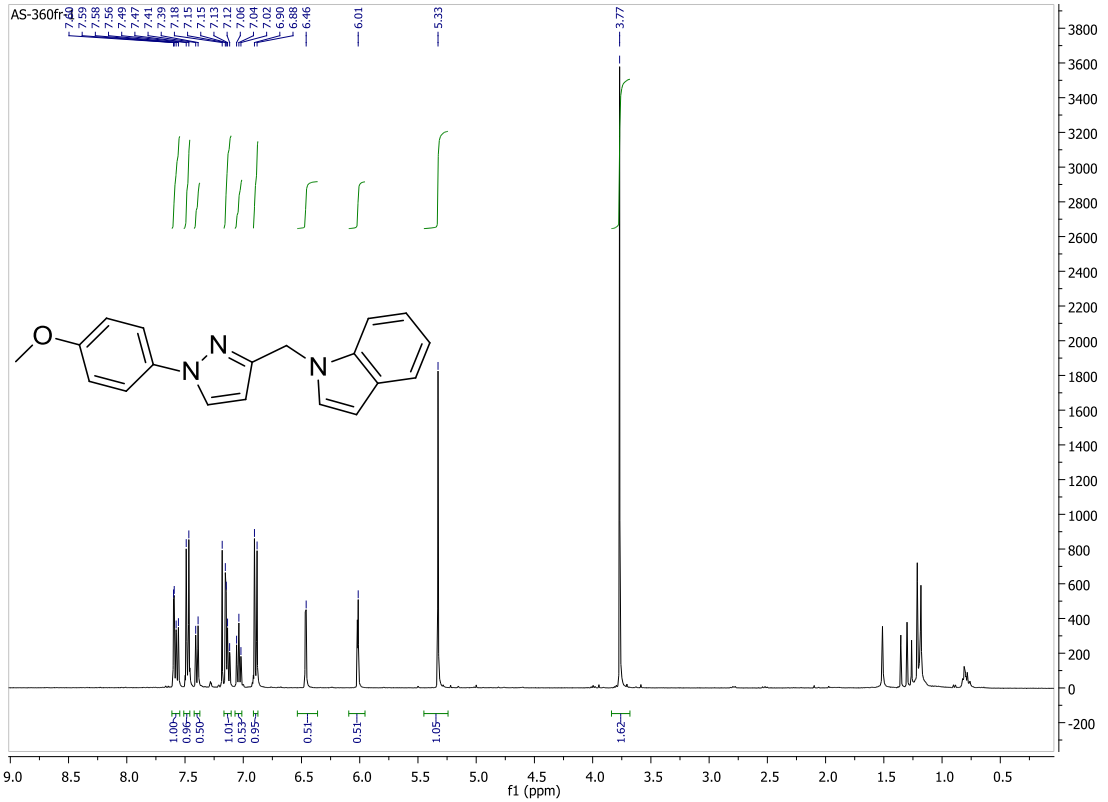


Figure 6.42 ^{1}H NMR spectrum of compound **242e**

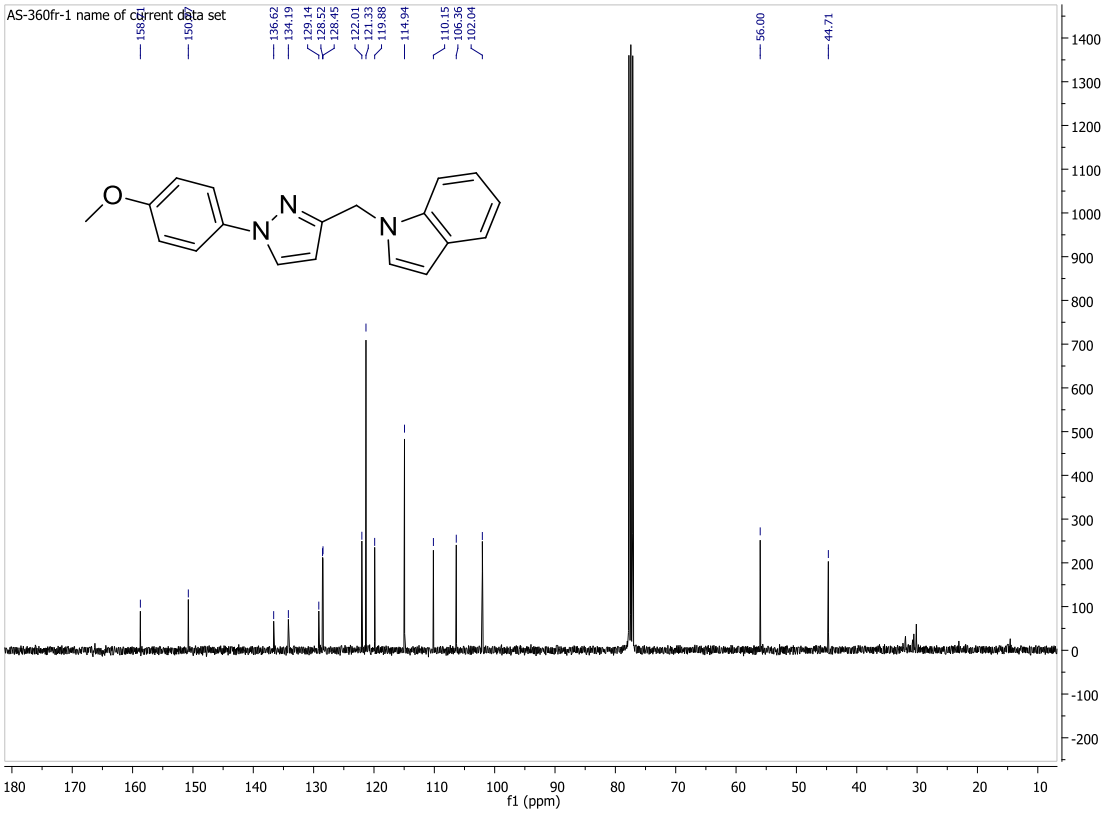


Figure 6.43 ^{13}C NMR spectrum of compound **242e**

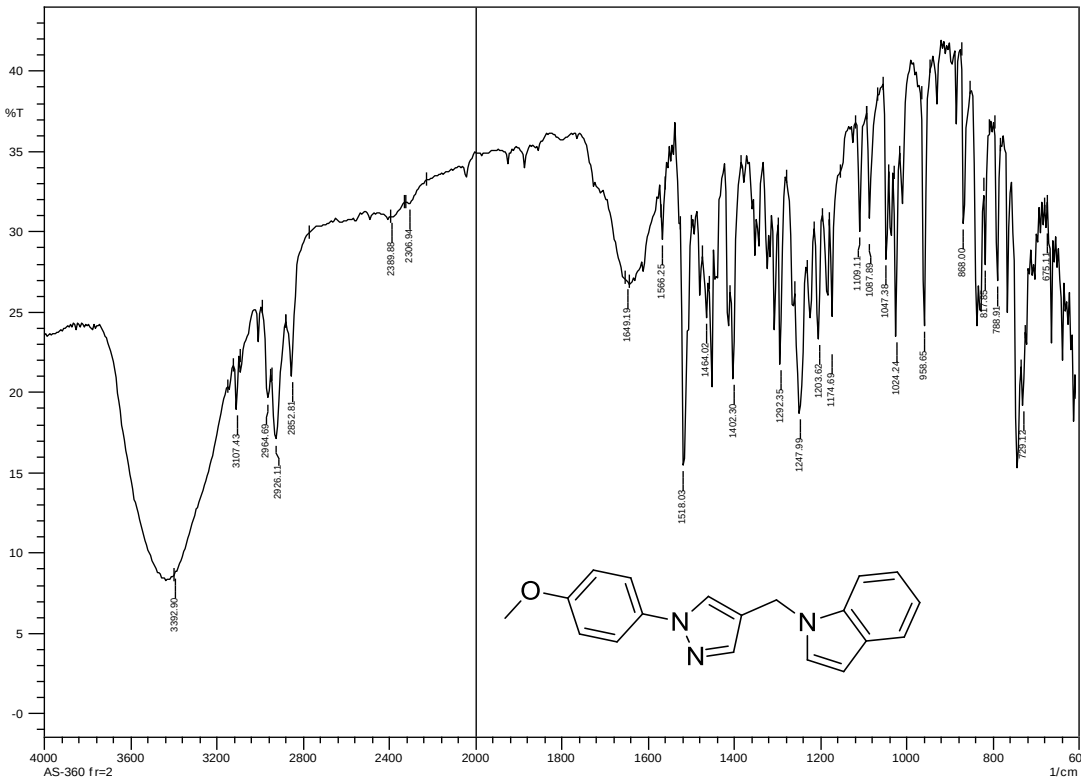


Figure 6.44 IR spectrum of compound **243e**

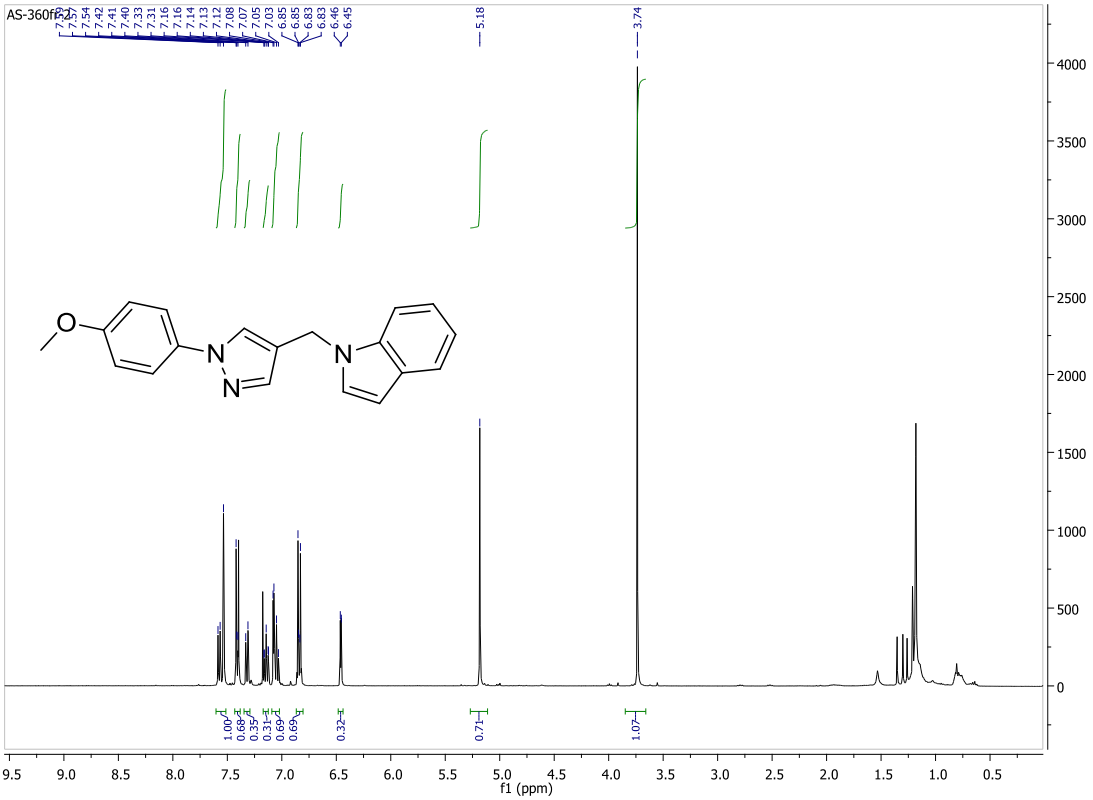


Figure 6.45 ^{1}H NMR spectrum of compound **243e**

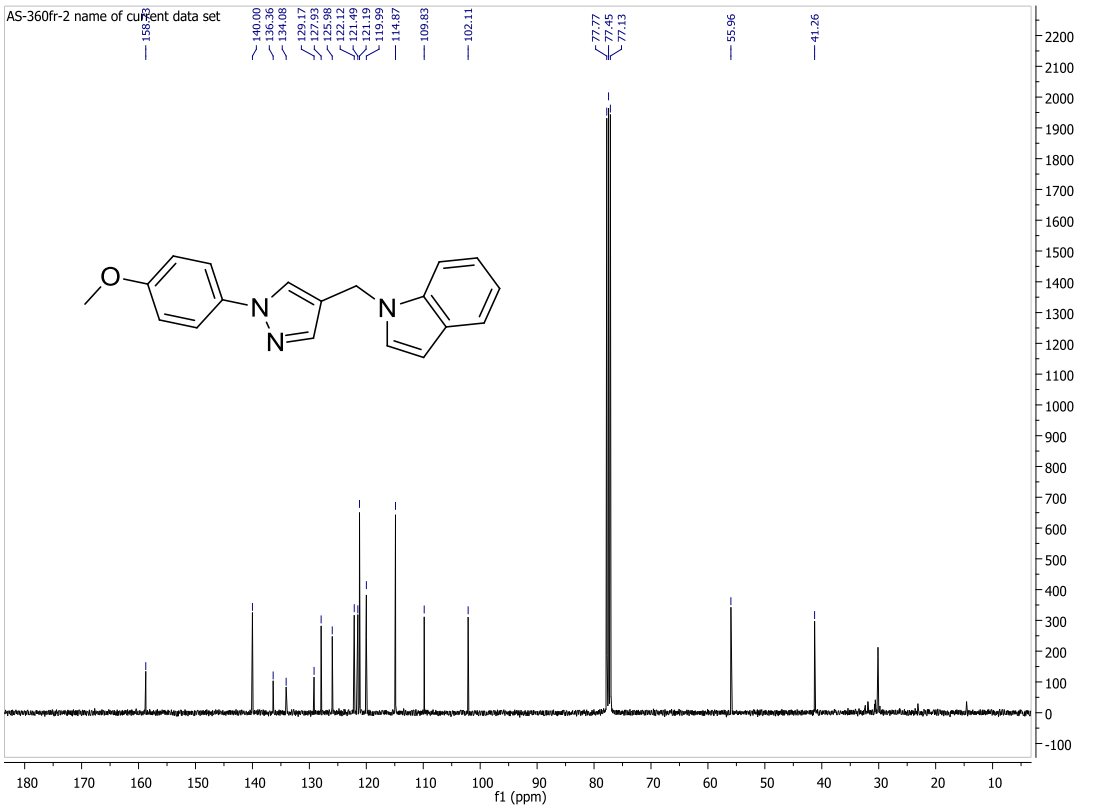


Figure 6.46 ^{13}C NMR spectrum of compound **243e**

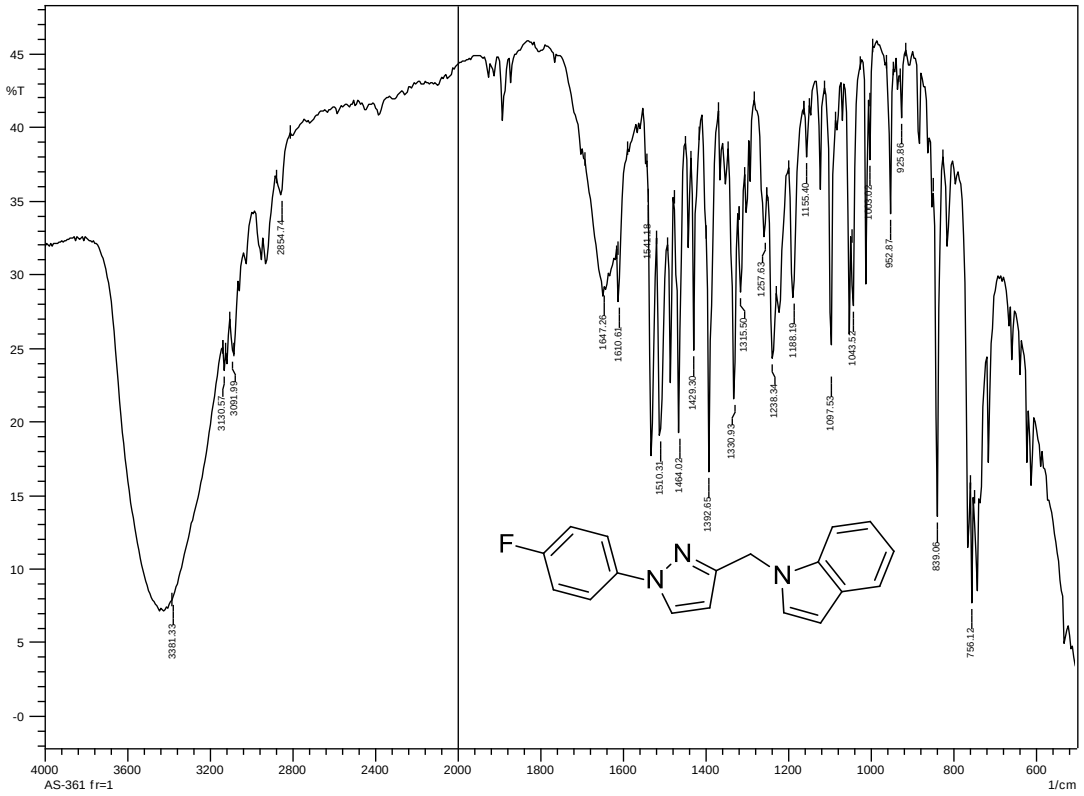


Figure 6.47 IR spectrum of compound **242f**

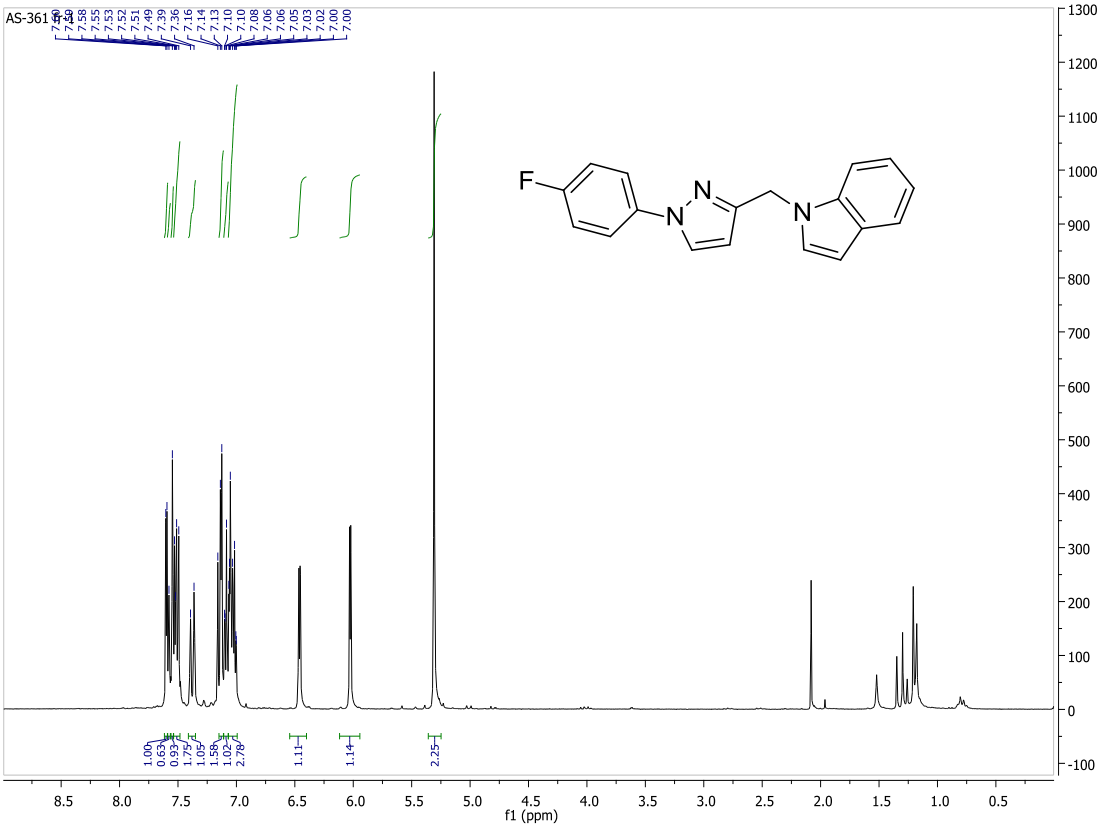


Figure 6.48 ^{1}H NMR spectrum of compound **242f**

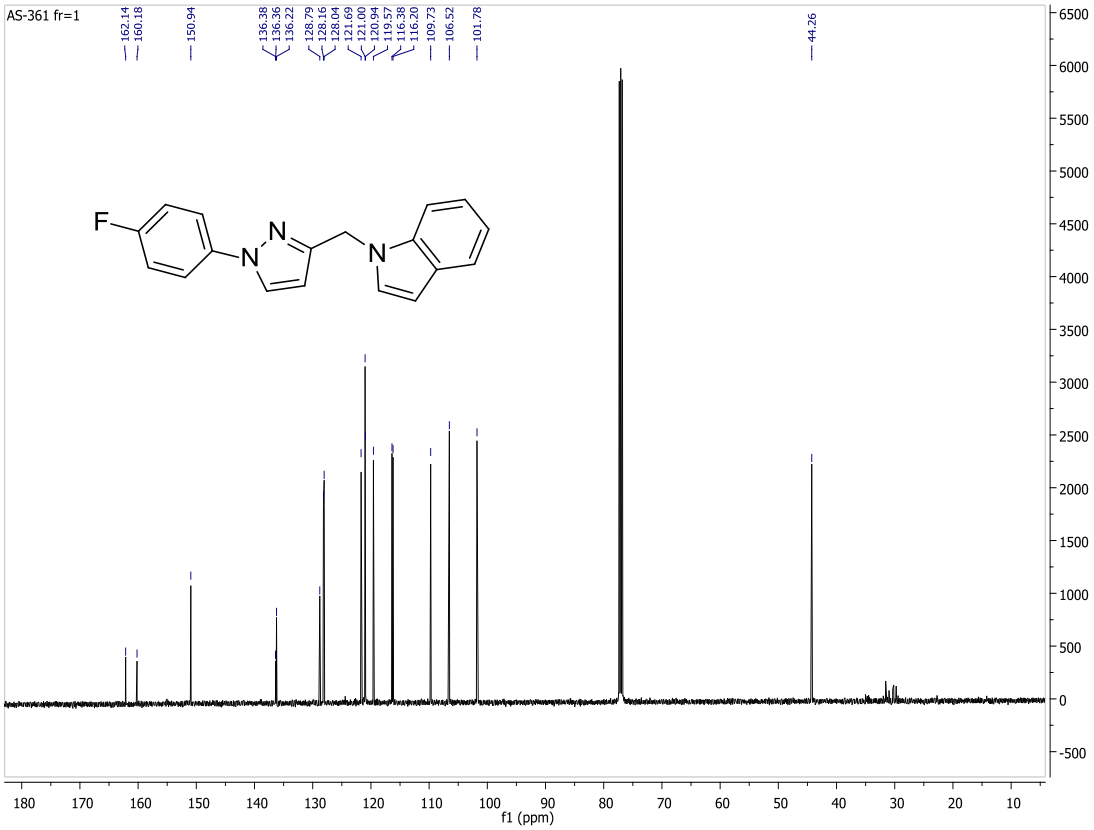


Figure 6.49 ^{13}C NMR spectrum of compound **242f**

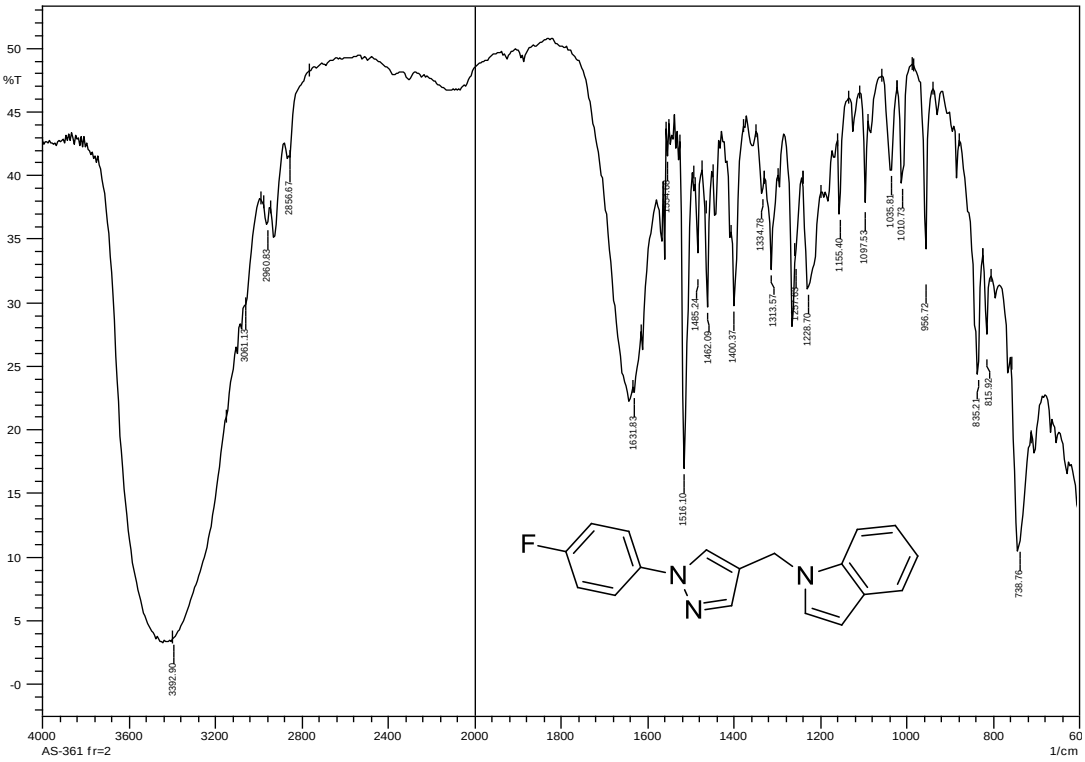


Figure 6.50 IR spectrum of compound **243f**

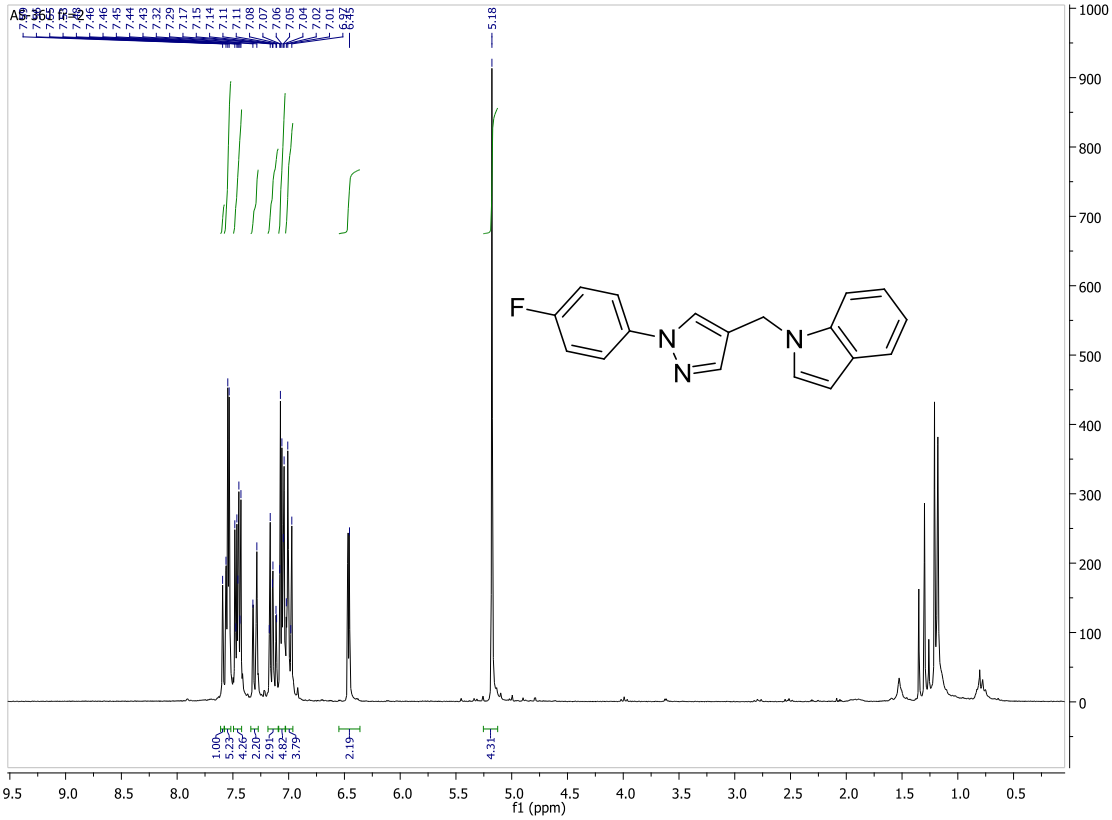


Figure 6.51 ^{1}H NMR spectrum of compound **243f**

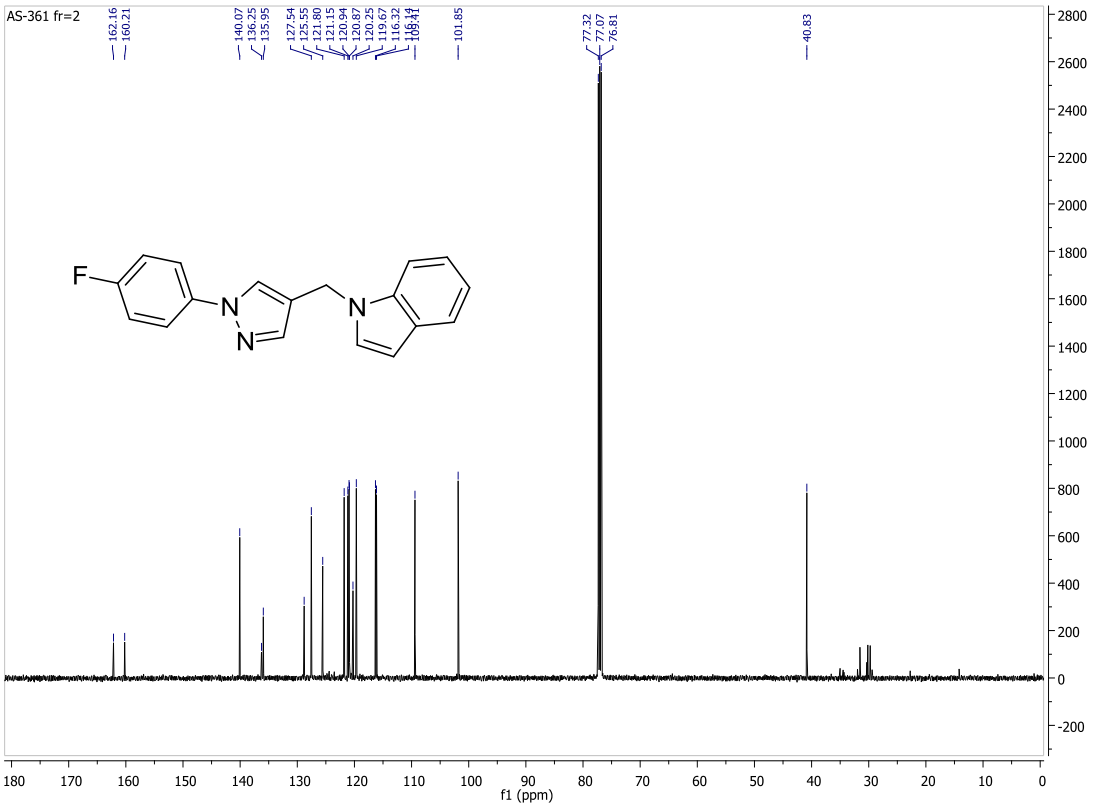


Figure 6.52 ^{13}C NMR spectrum of compound **243f**

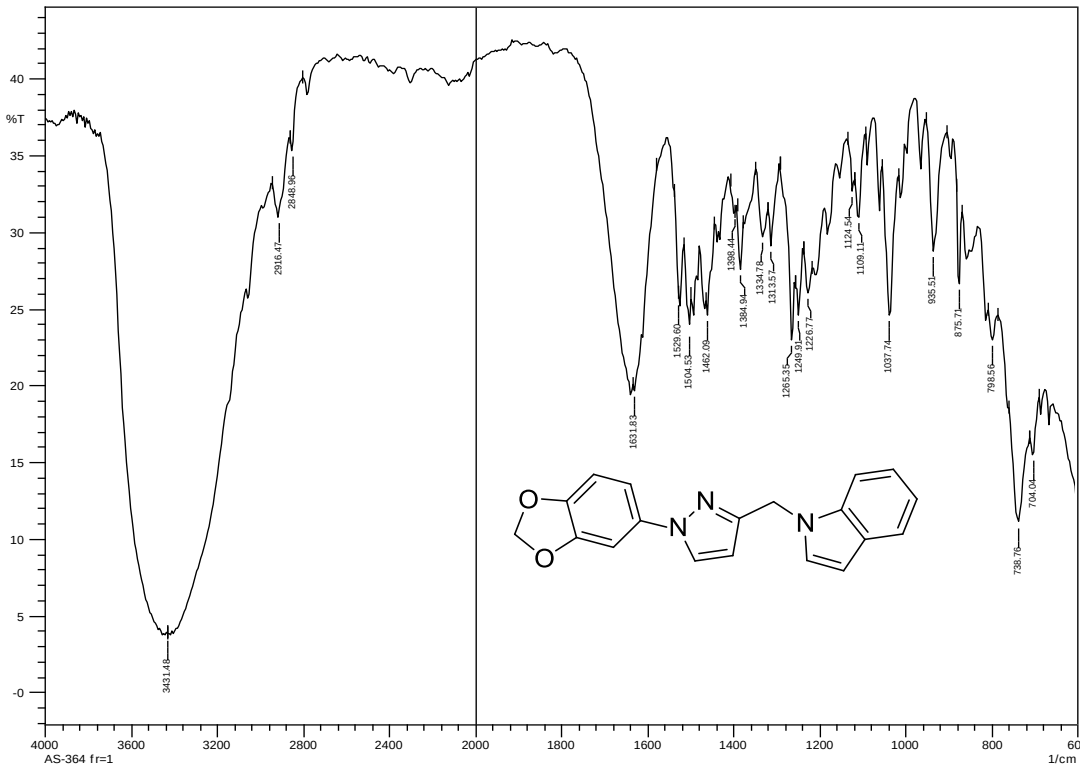


Figure 6.53 IR spectrum of compound **242g**

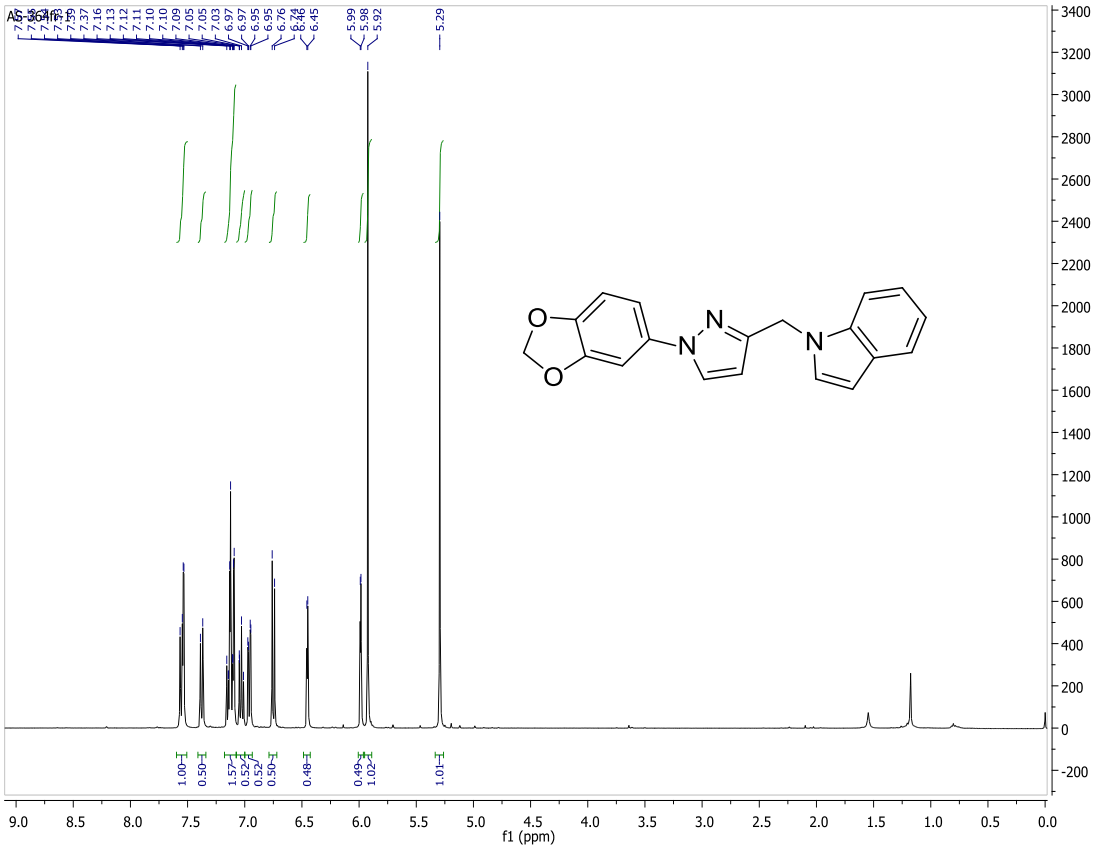


Figure 6.54 ^{1}H NMR spectrum of compound **242g**

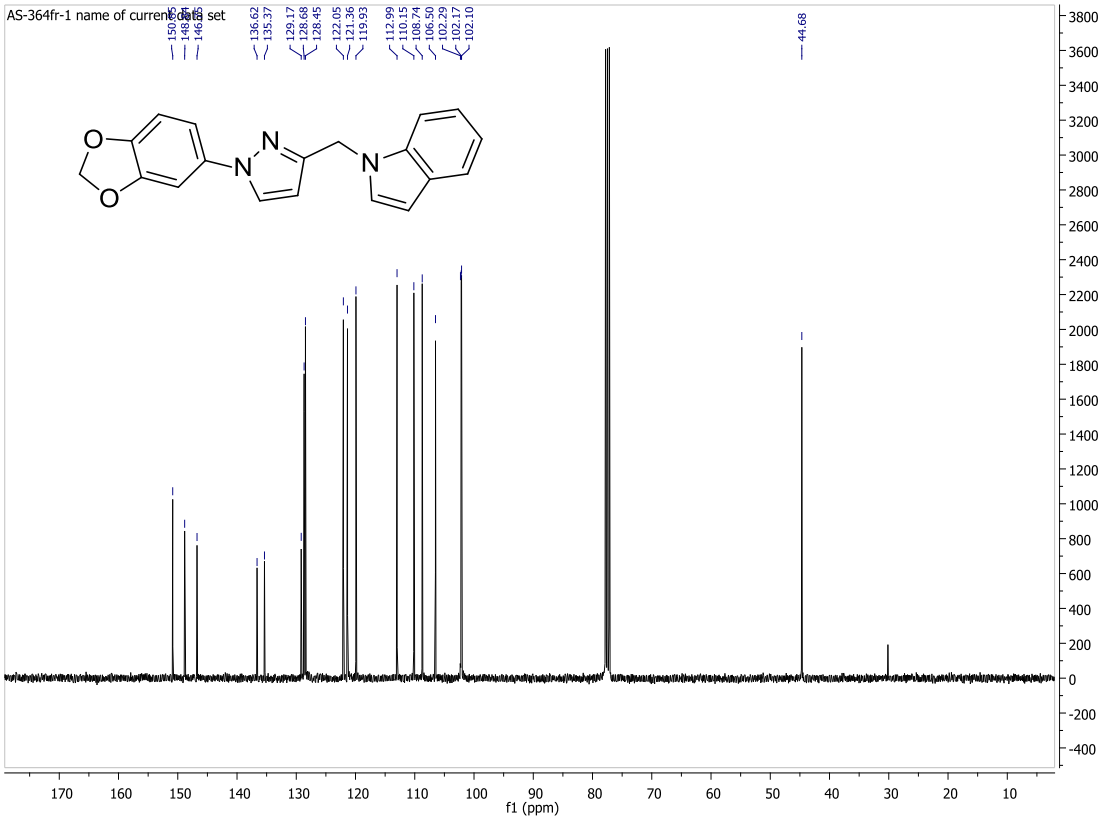


Figure 6.55 ^{13}C NMR spectrum of compound **242g**

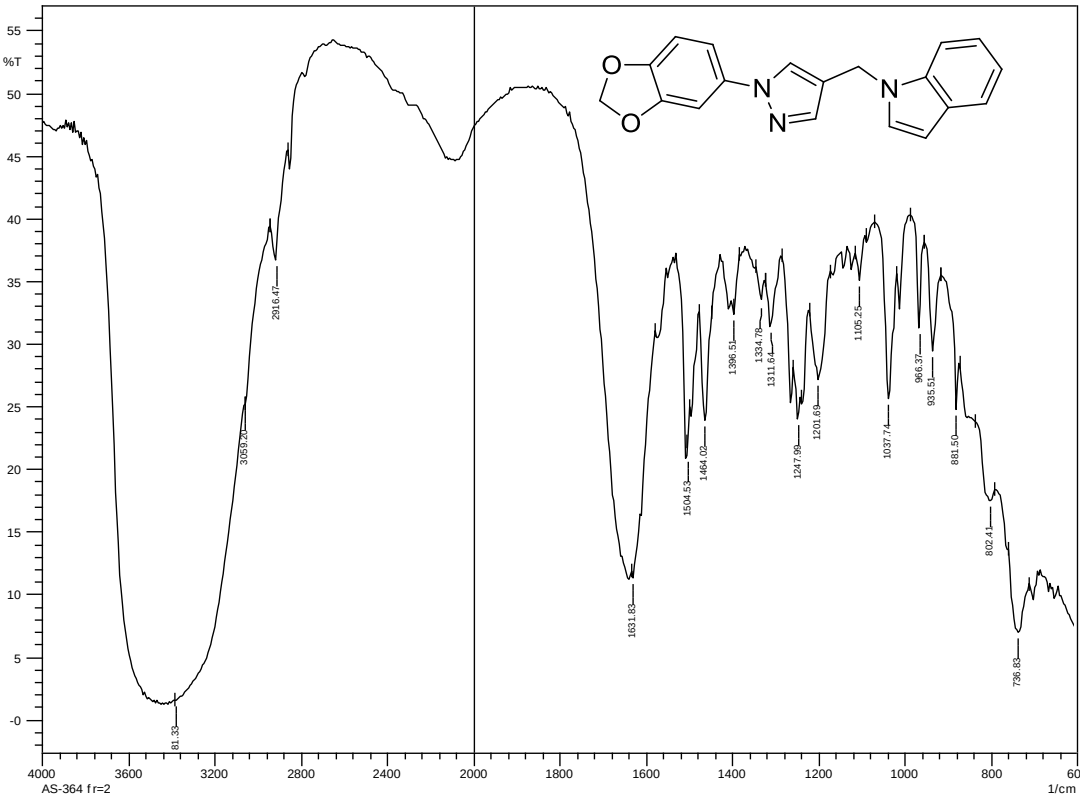


Figure 6.56 IR spectrum of compound **243g**

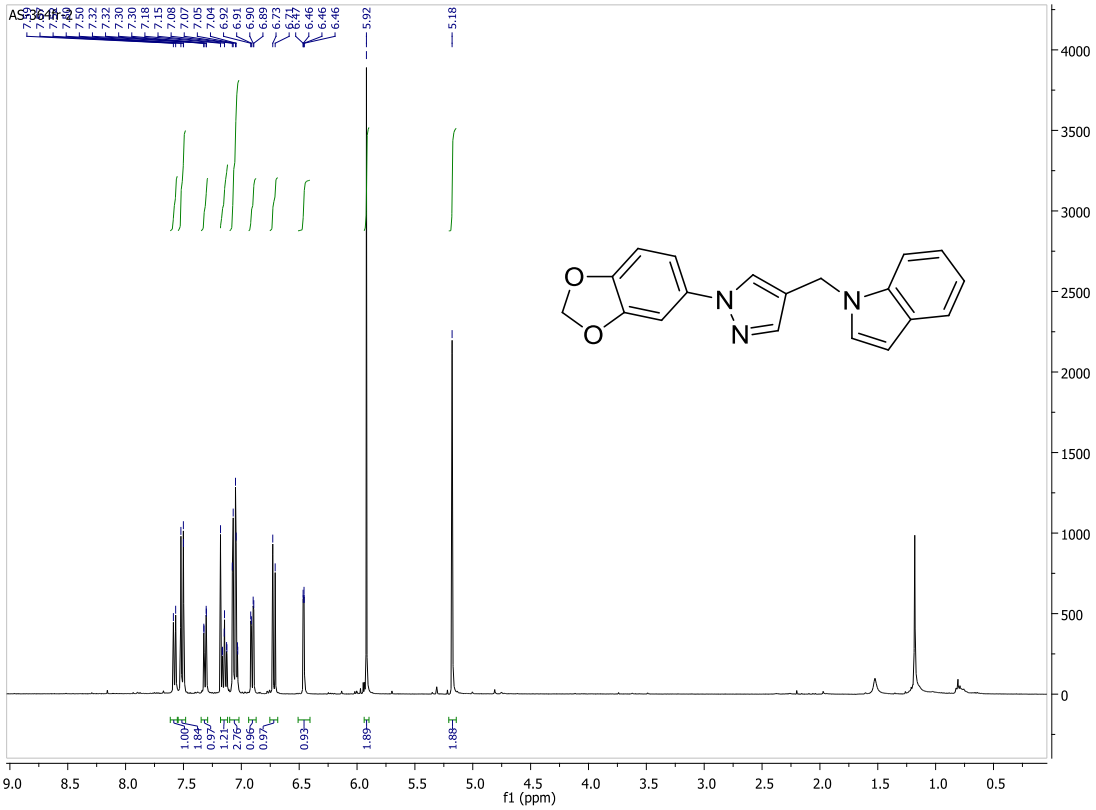


Figure 6.57 ^{1}H NMR spectrum of compound **243g**

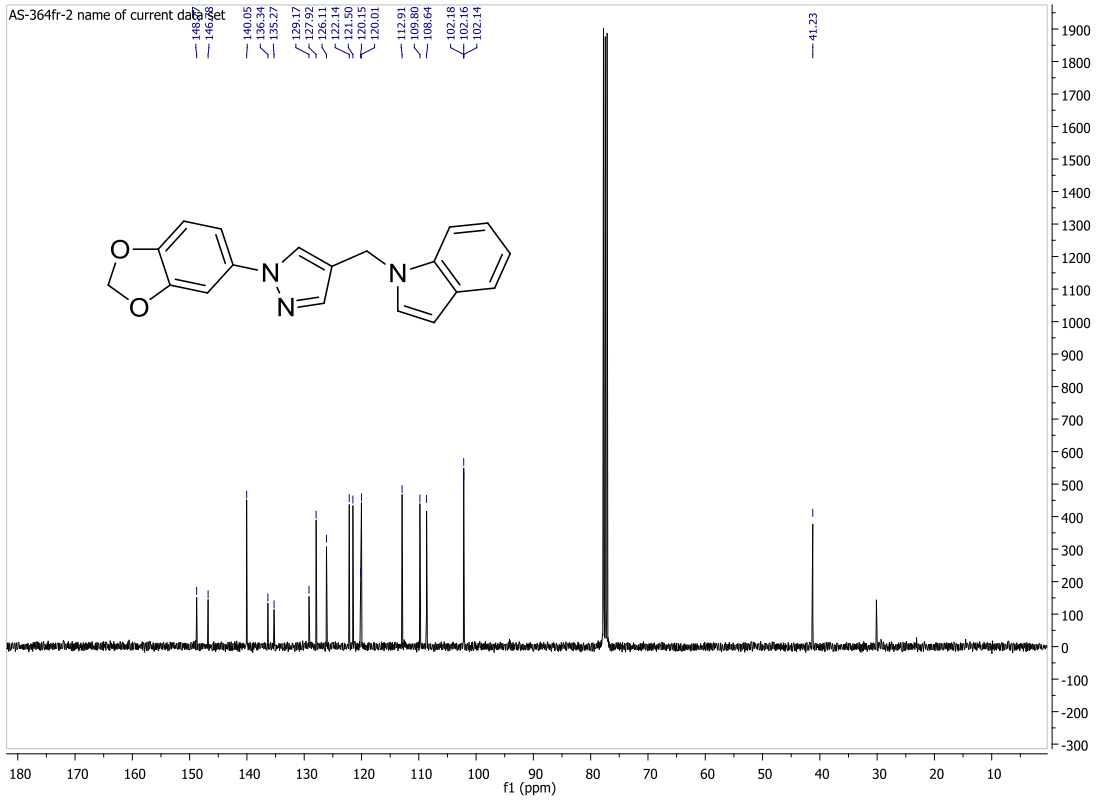


Figure 6.58 ^{13}C NMR spectrum of compound **243g**

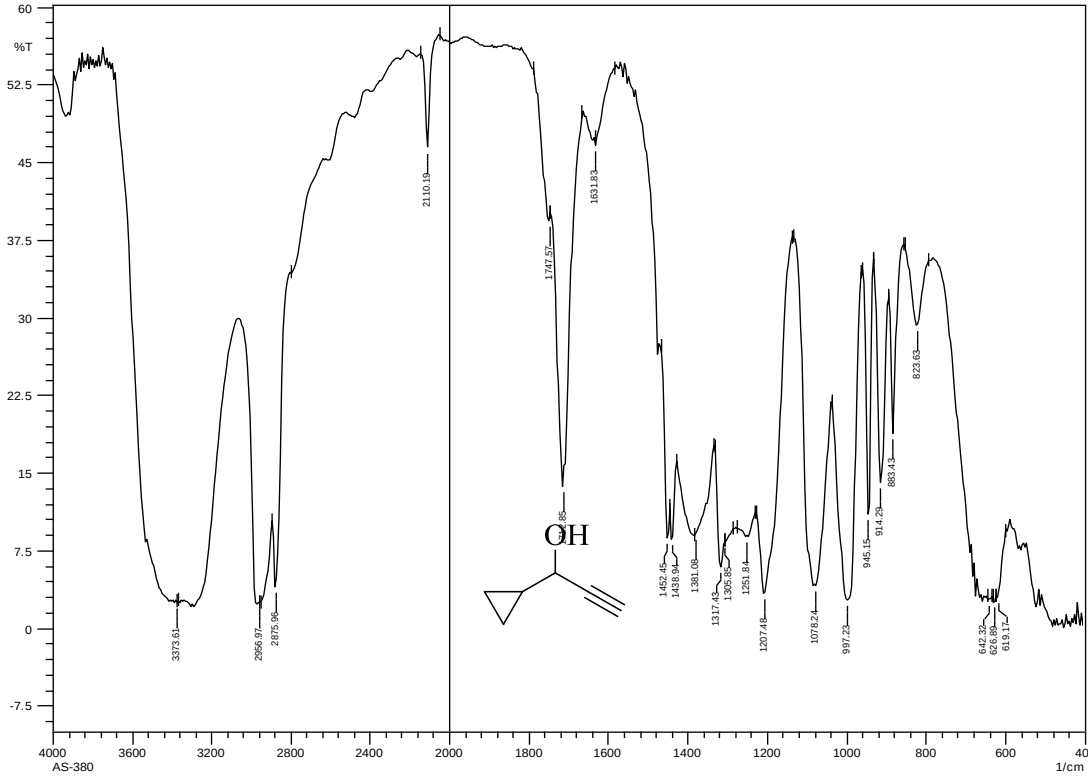


Figure 6.59 IR spectrum of compound **207**

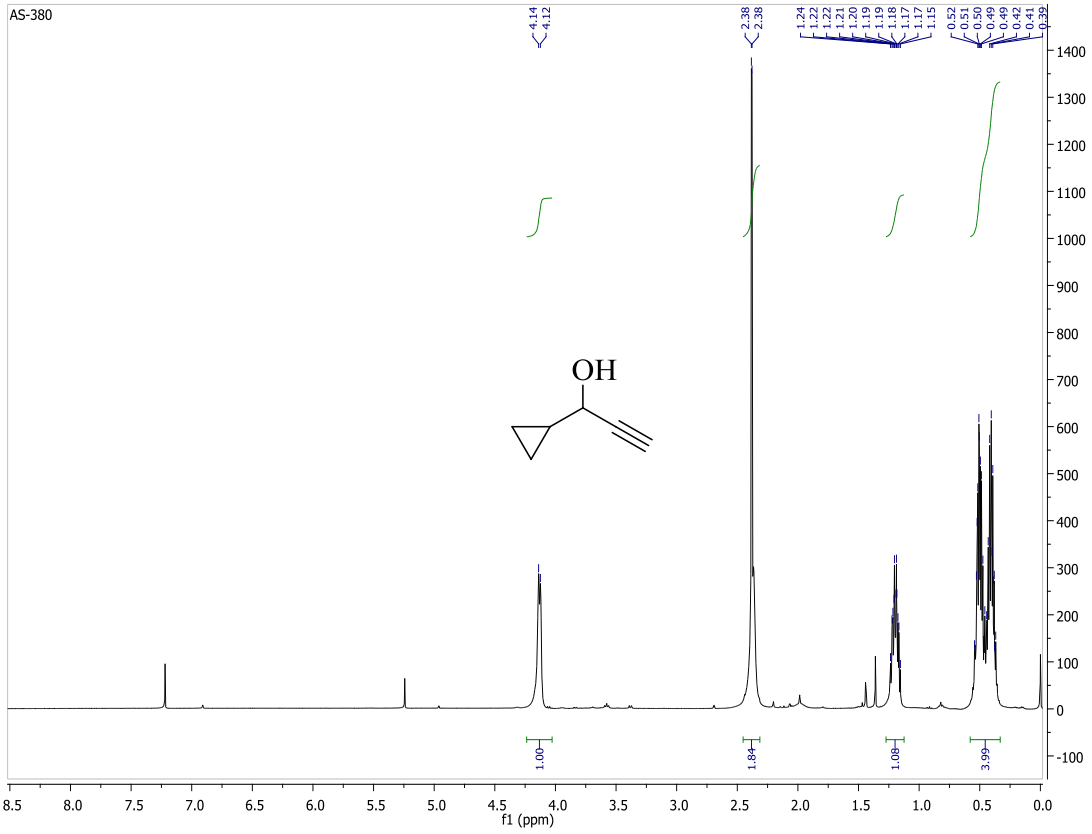


Figure 6.60 ^{1}H NMR spectrum of compound **207**

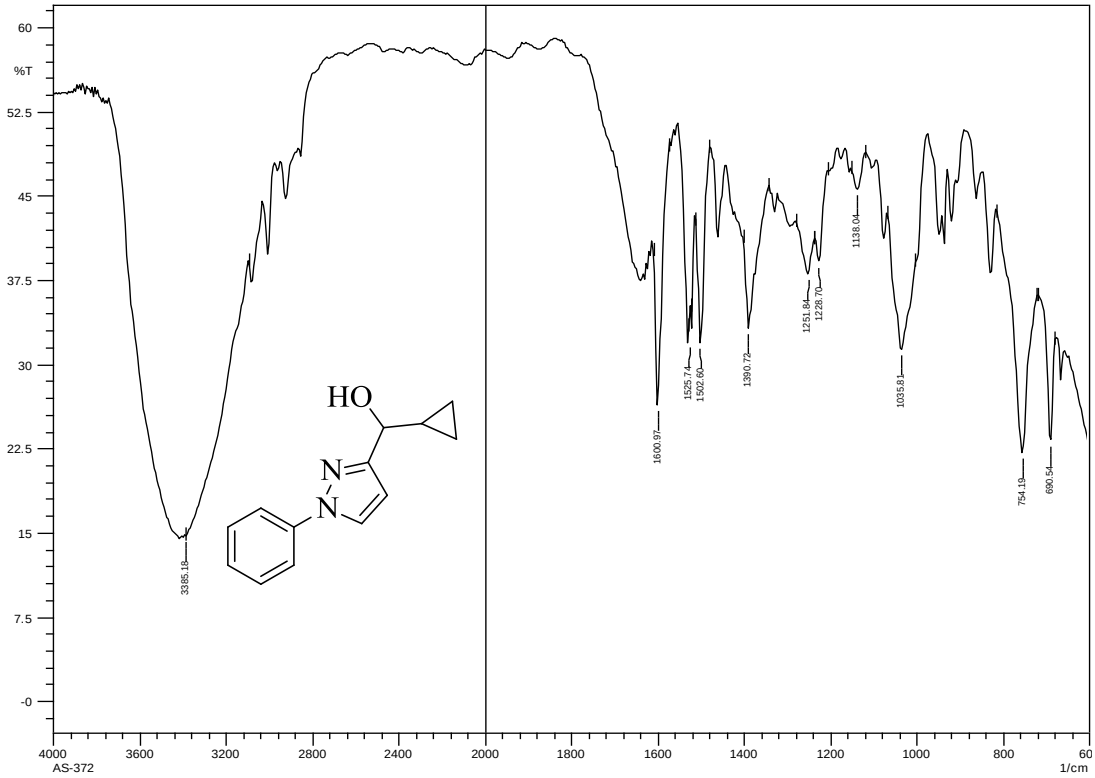


Figure 6.61 IR spectrum of compound **244a**

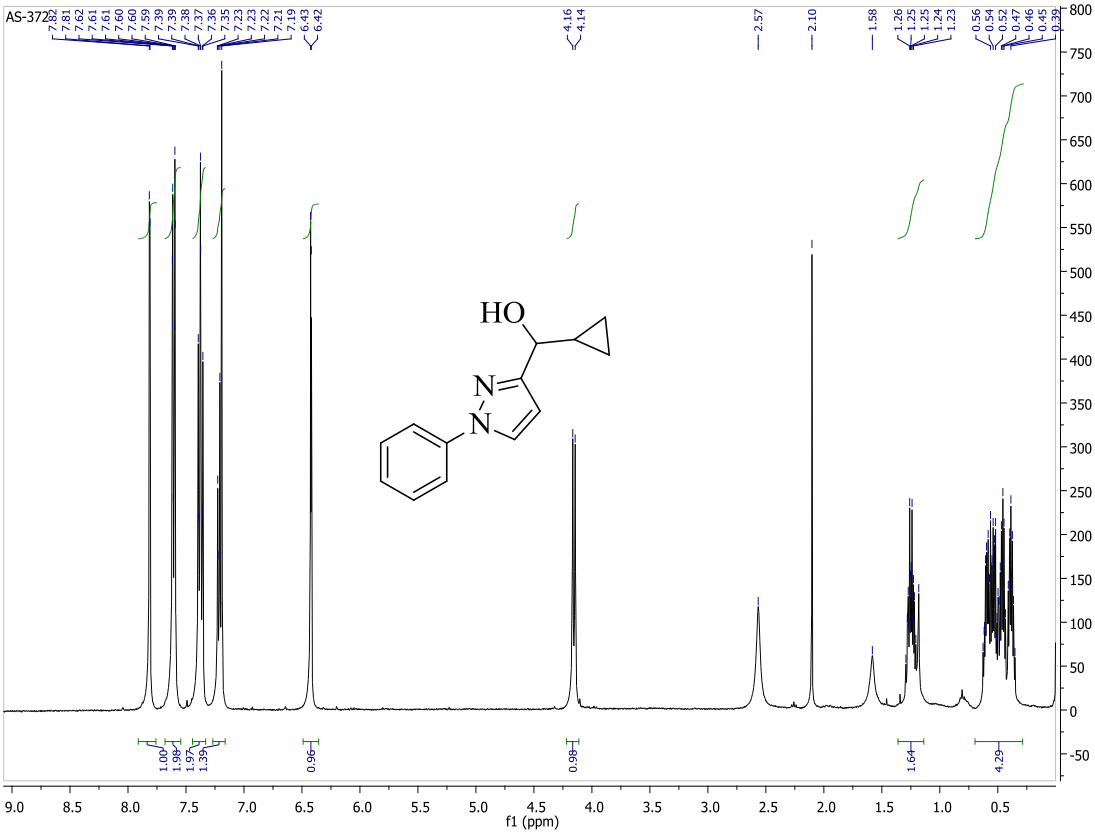


Figure 6.62 ^{1}H NMR spectrum of compound **244a**

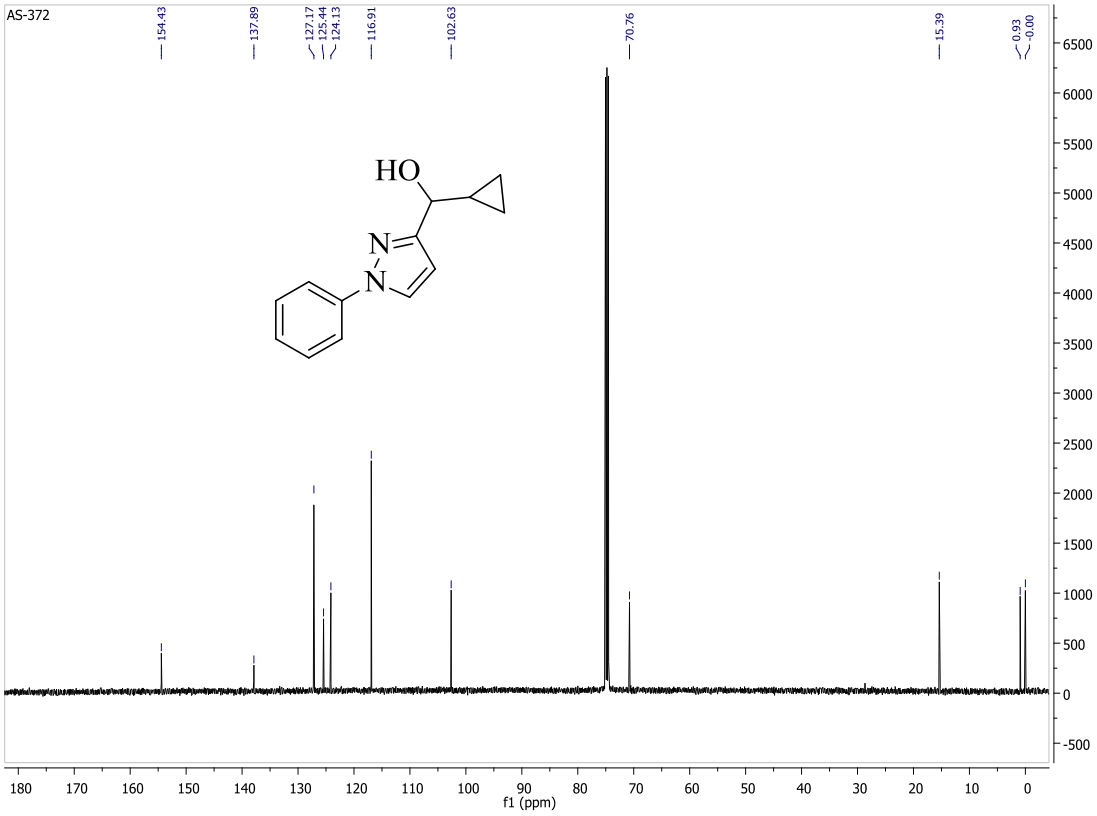


Figure 6.63 ^{13}C NMR spectrum of compound **244a**

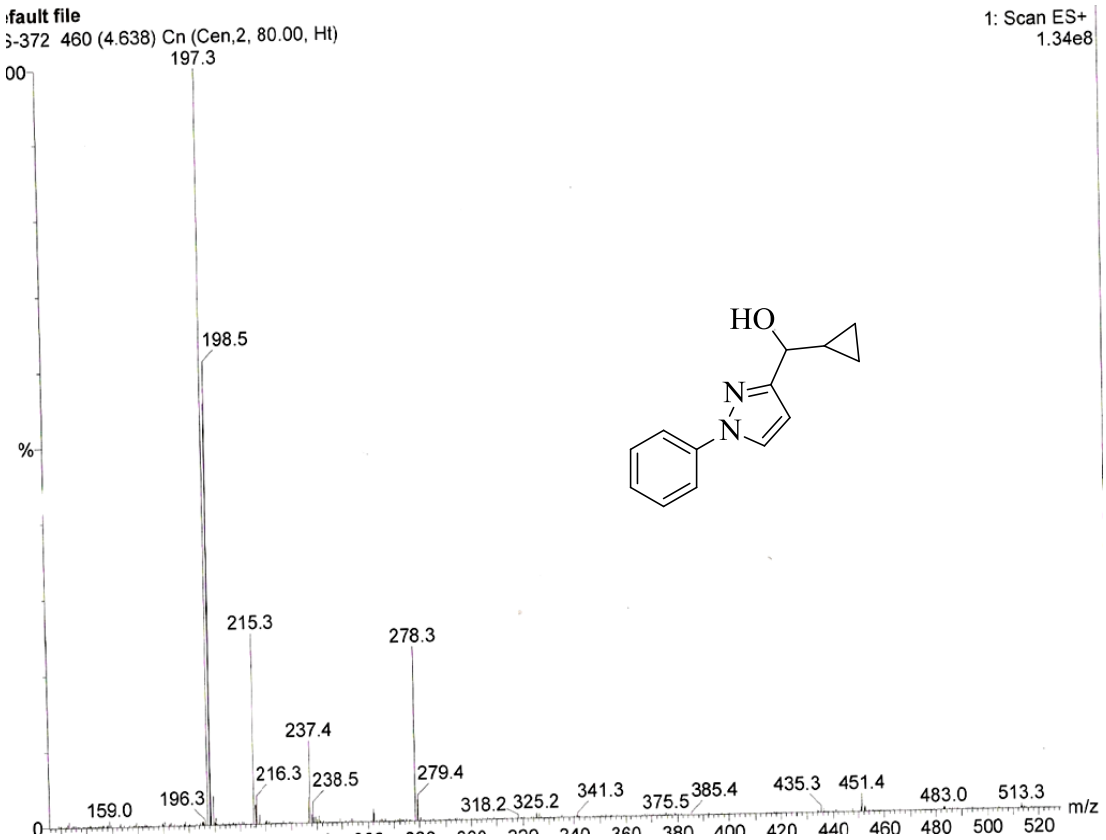


Figure 6.64 LC-MS spectrum of compound **244a**

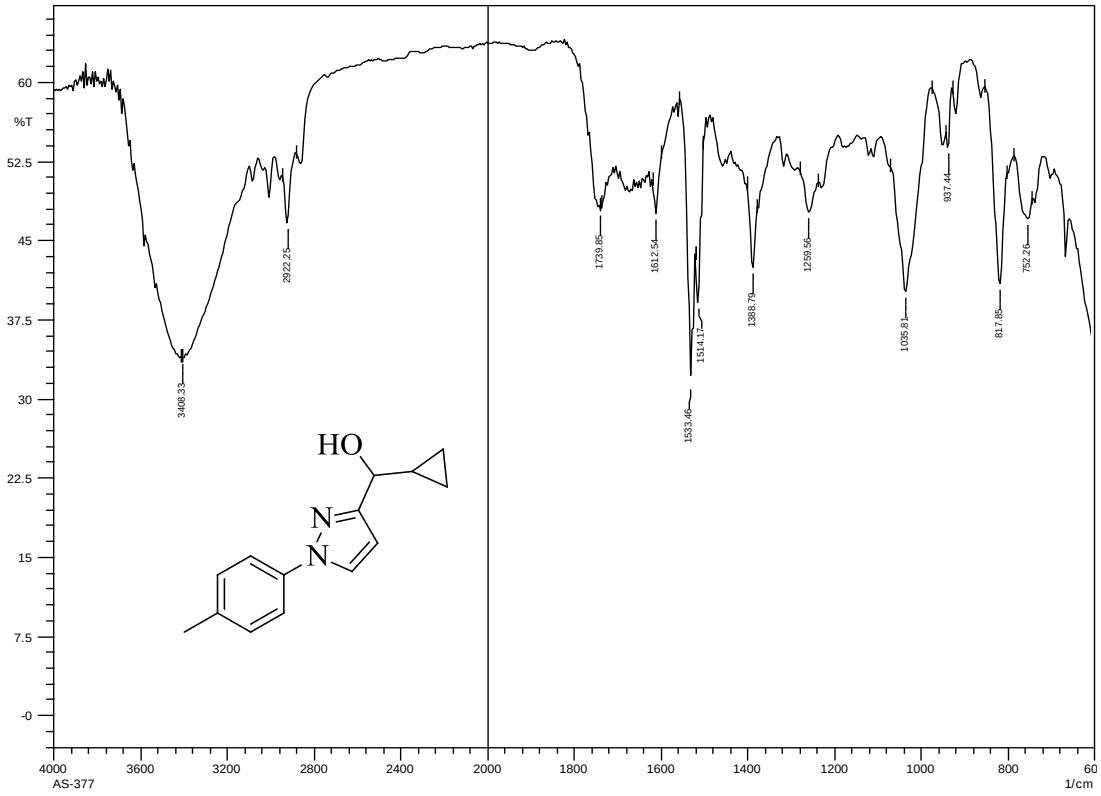


Figure 6.65 IR spectrum of compound **244b**

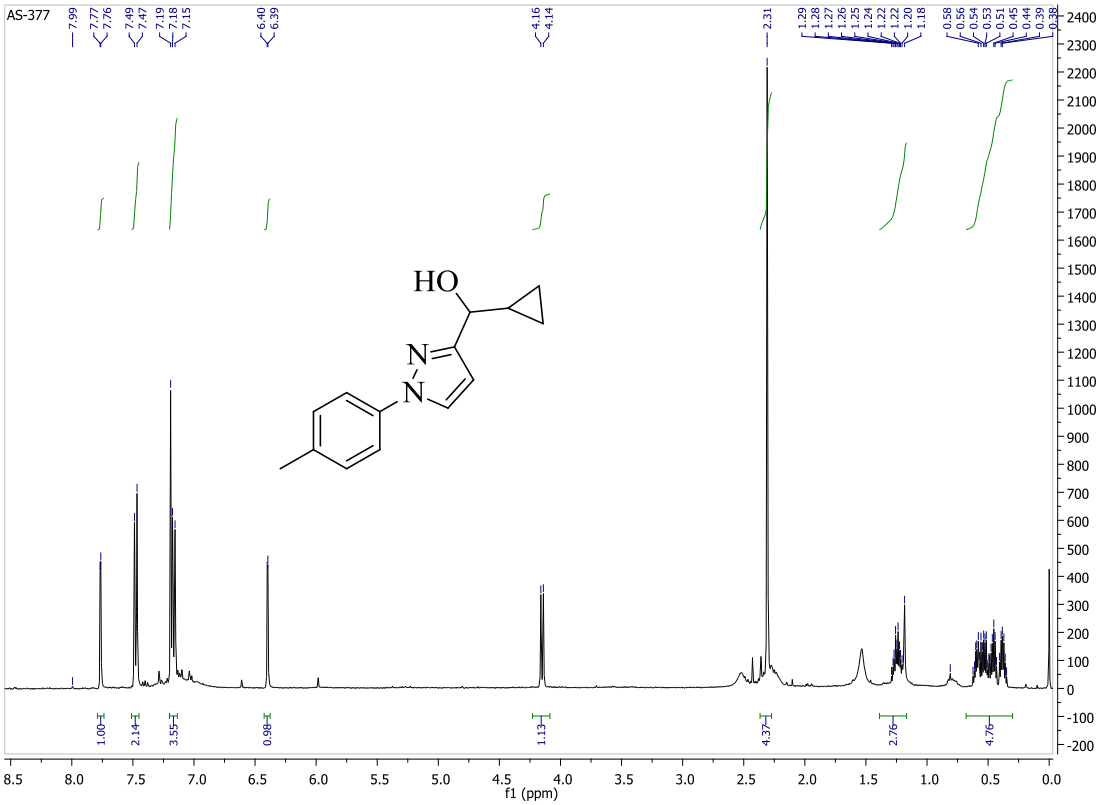


Figure 6.66 ^{1}H NMR spectrum of compound **244b**

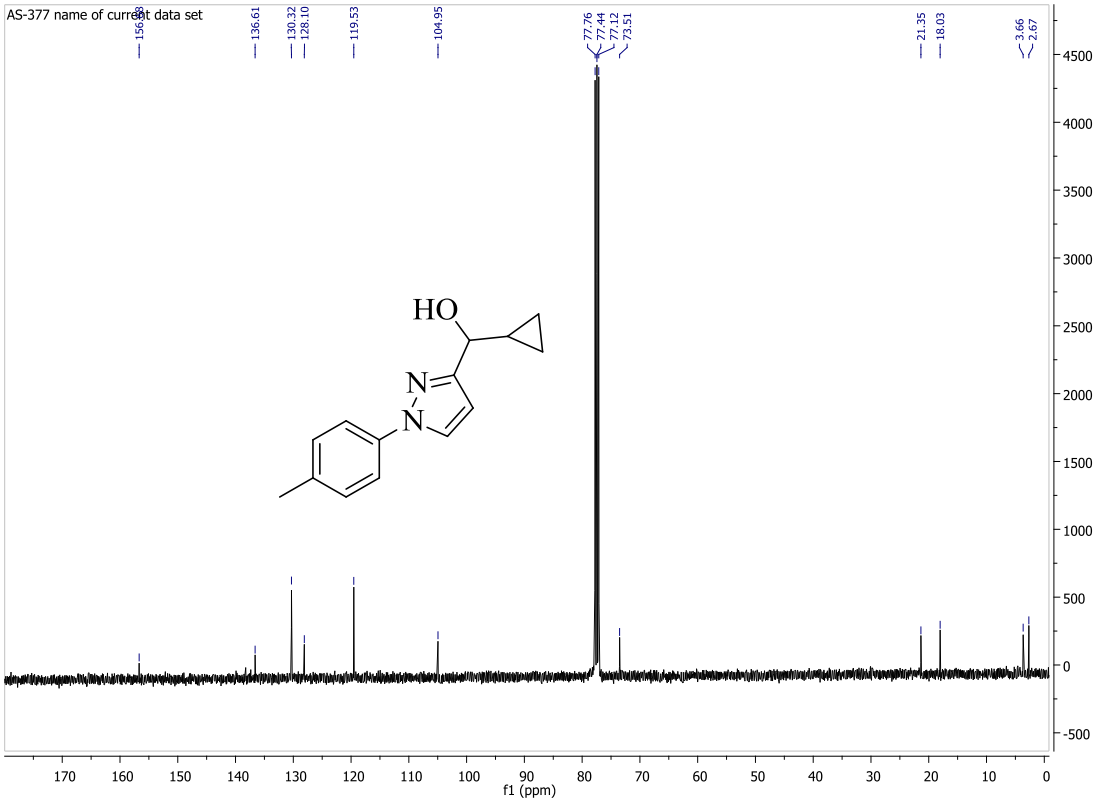


Figure 6.67 ^{13}C NMR spectrum of compound **244b**

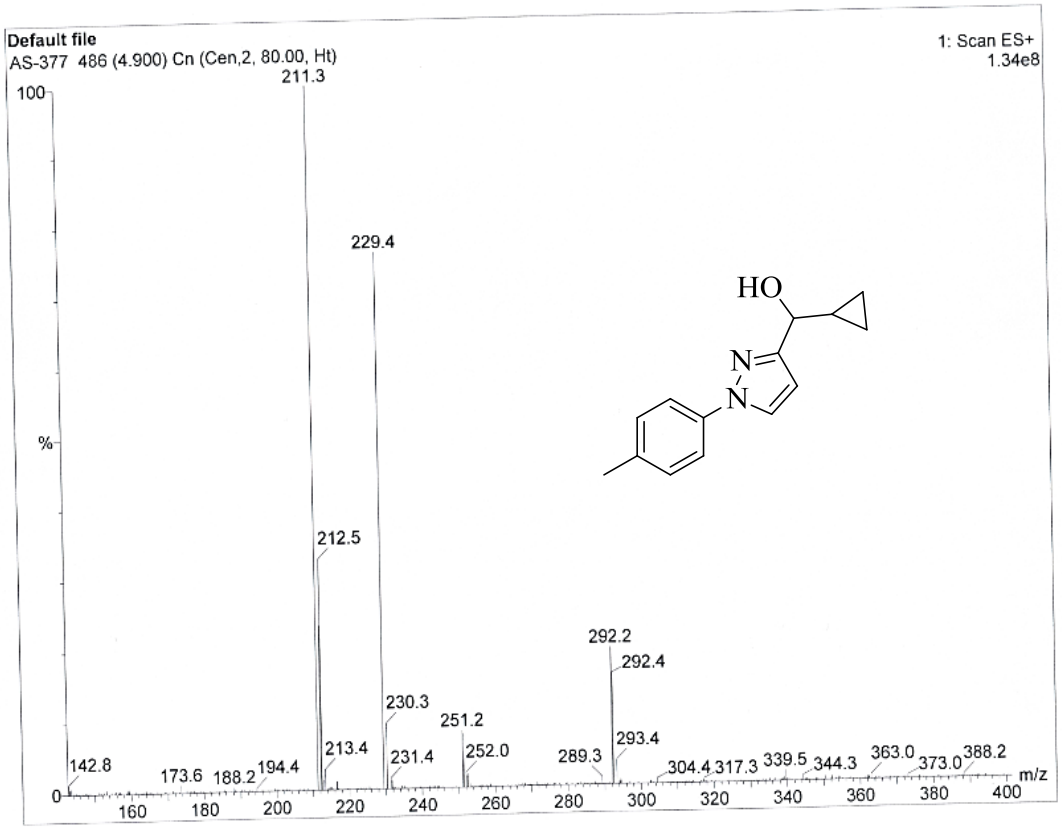


Figure 6.68 LC-MS spectrum of compound **244b**

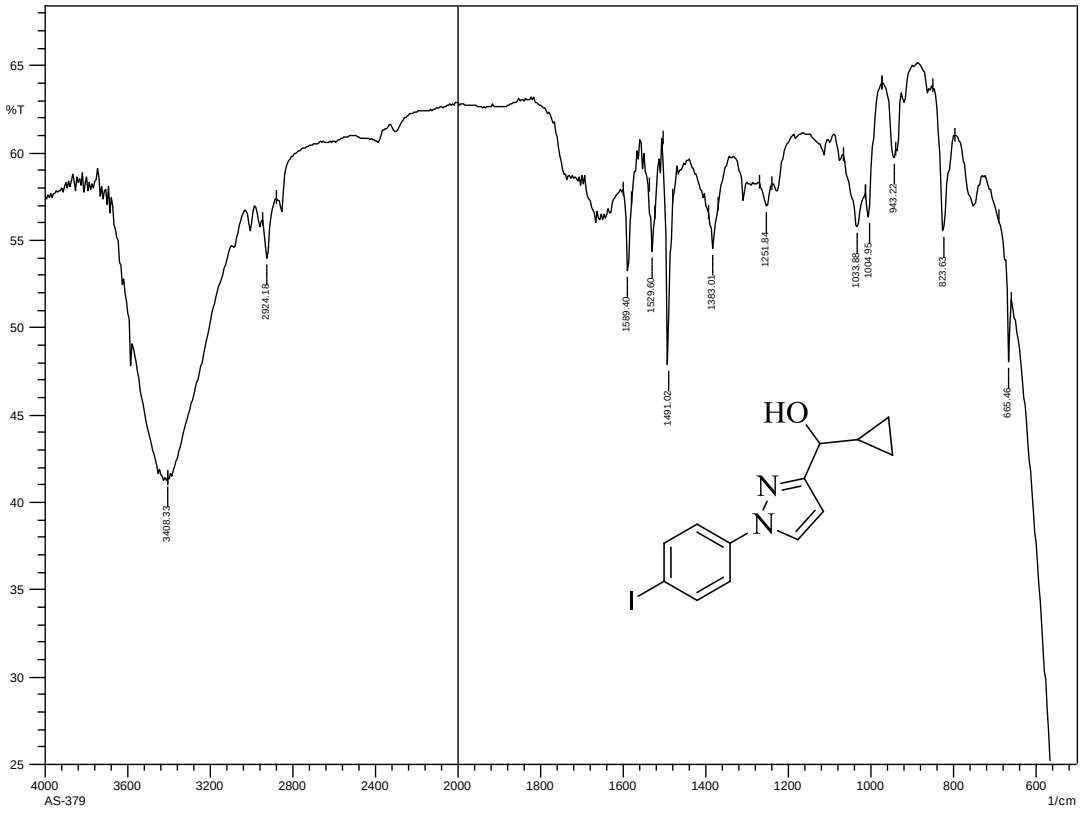


Figure 6.69 IR spectrum of compound **244c**

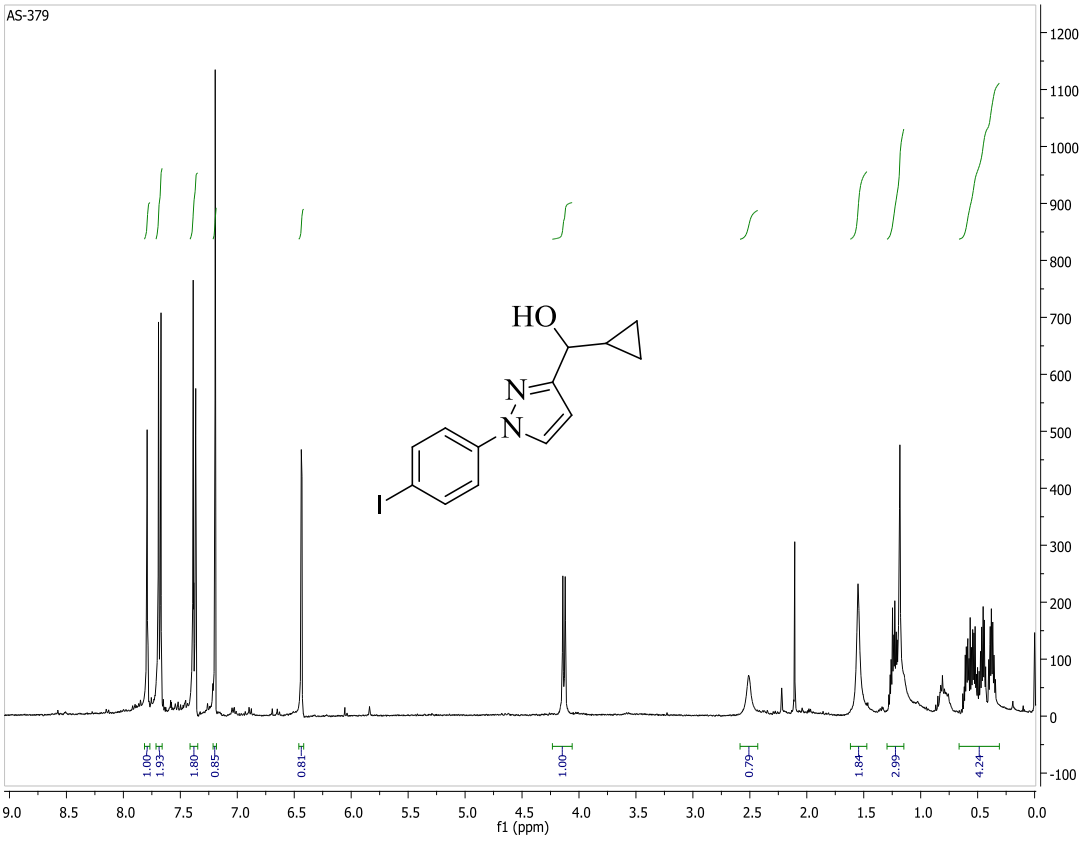


Figure 6.70 ^{1}H NMR spectrum of compound **244c**

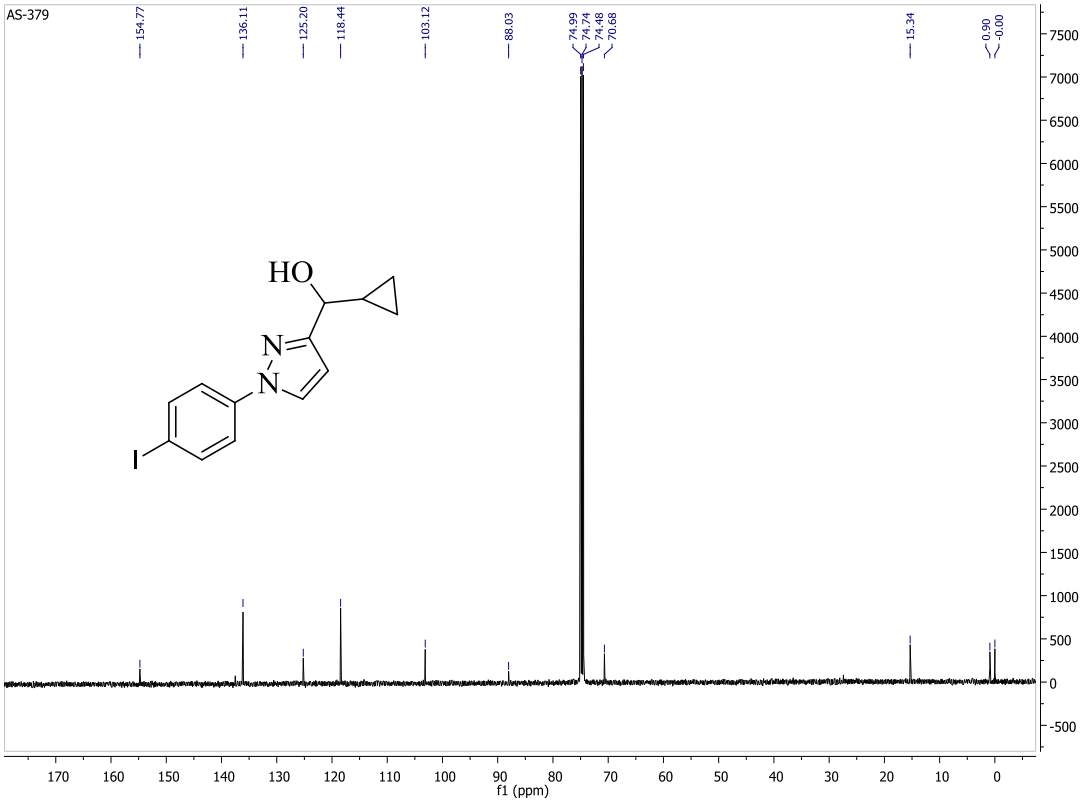


Figure 6.71 ^{13}C NMR spectrum of compound **244c**

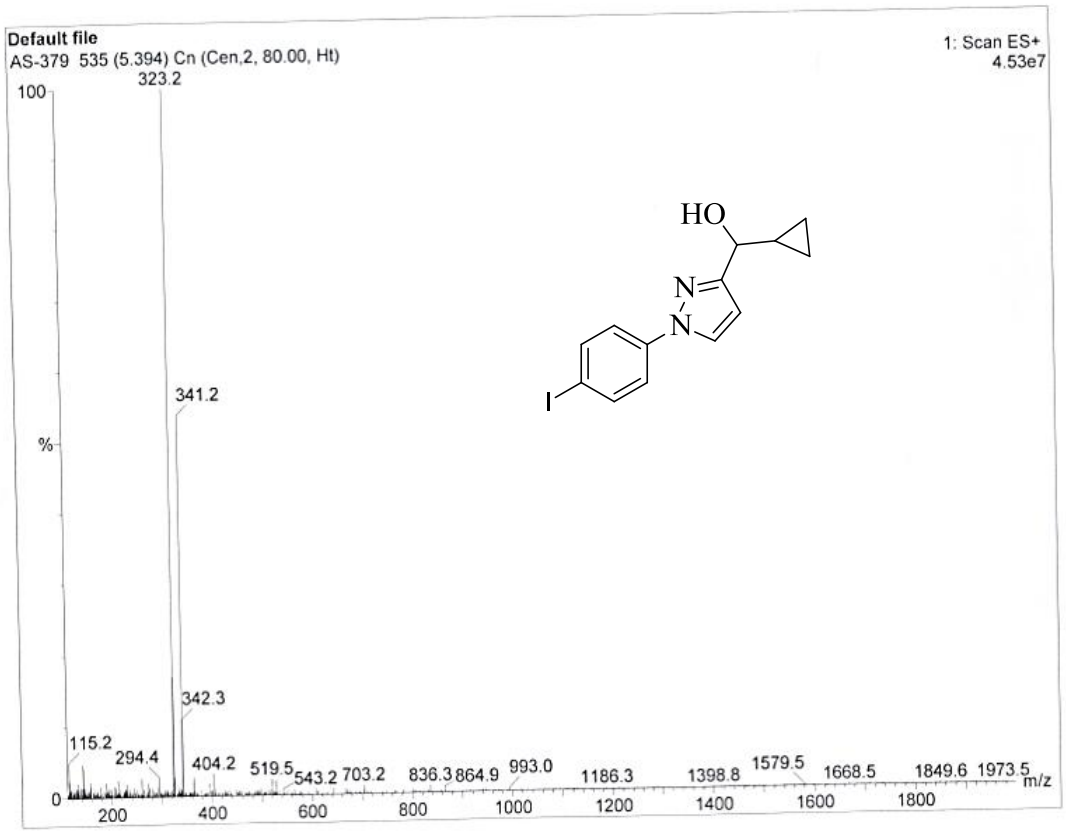


Figure 6.72 LC-MS spectrum of compound **244c**

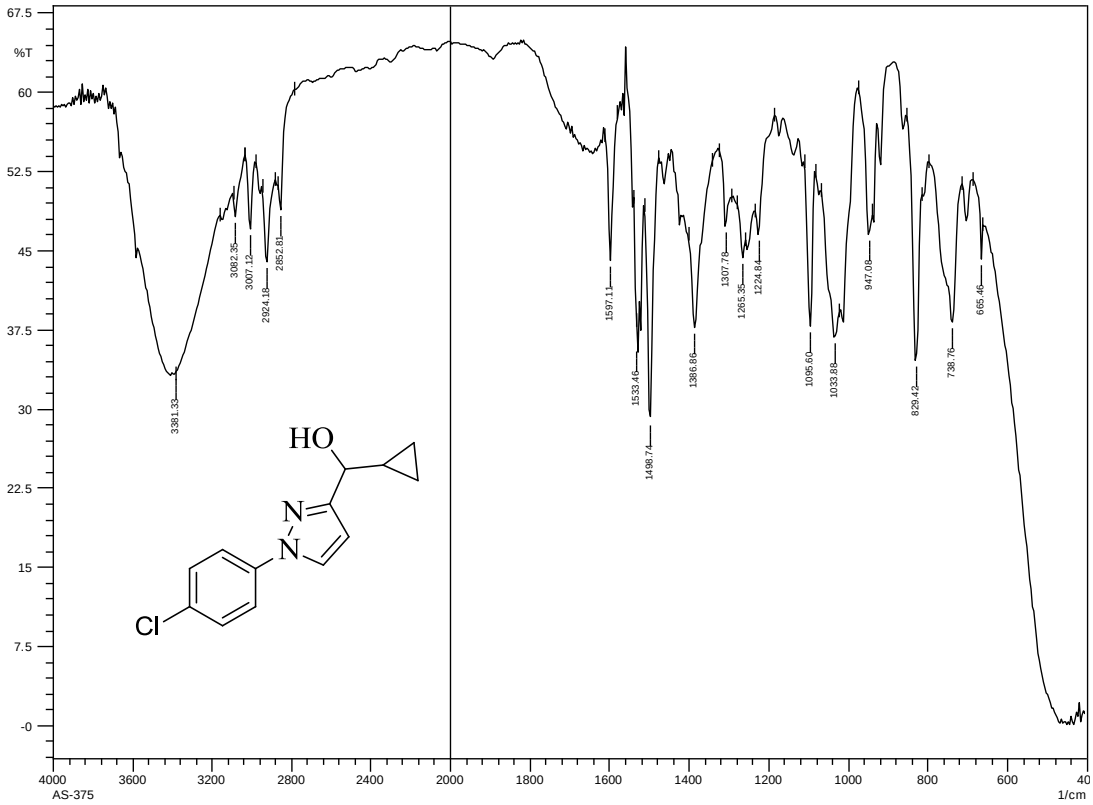


Figure 6.73 IR spectrum of compound **244d**

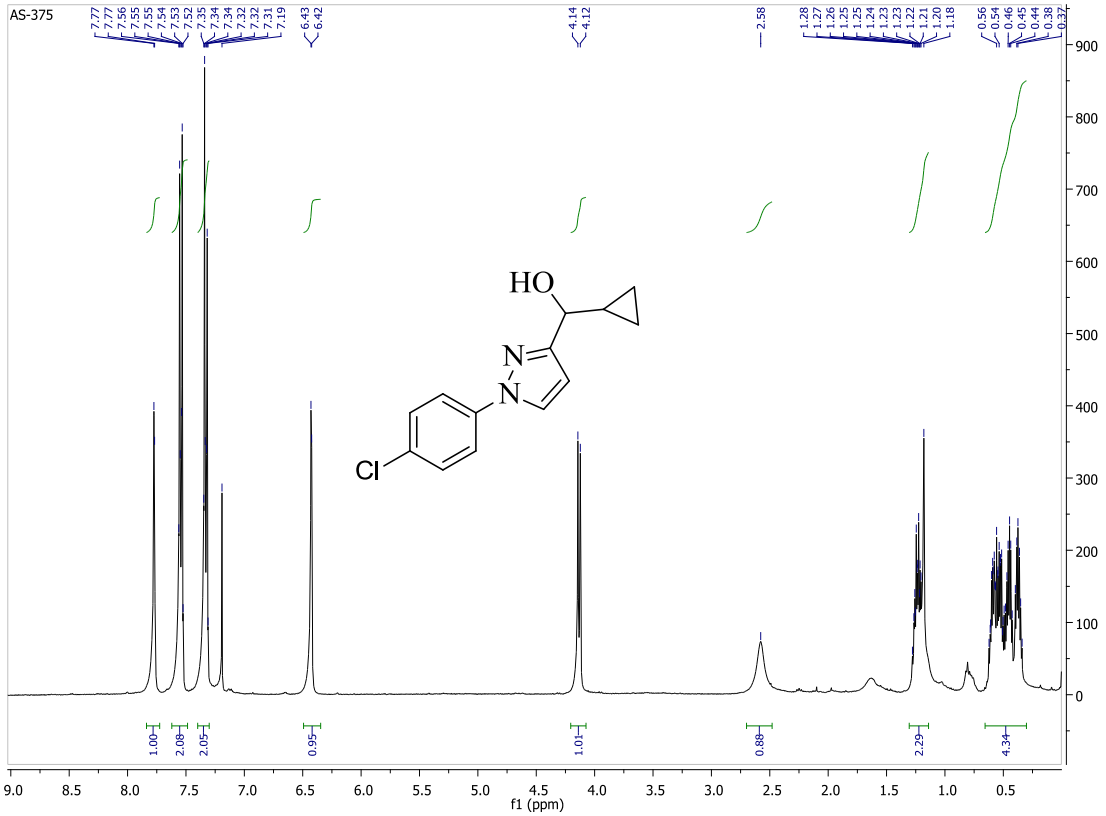


Figure 6.74 ^{1}H NMR spectrum of compound **244d**

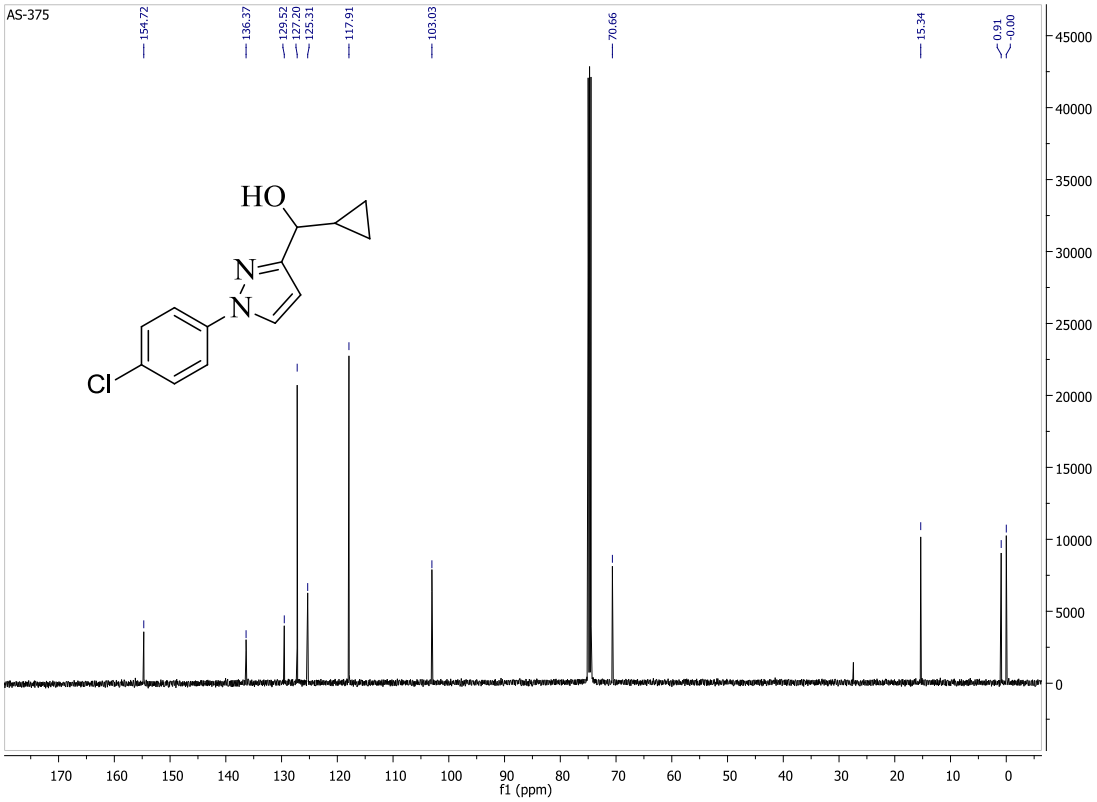


Figure 6.75 ^{13}C NMR spectrum of compound **244d**

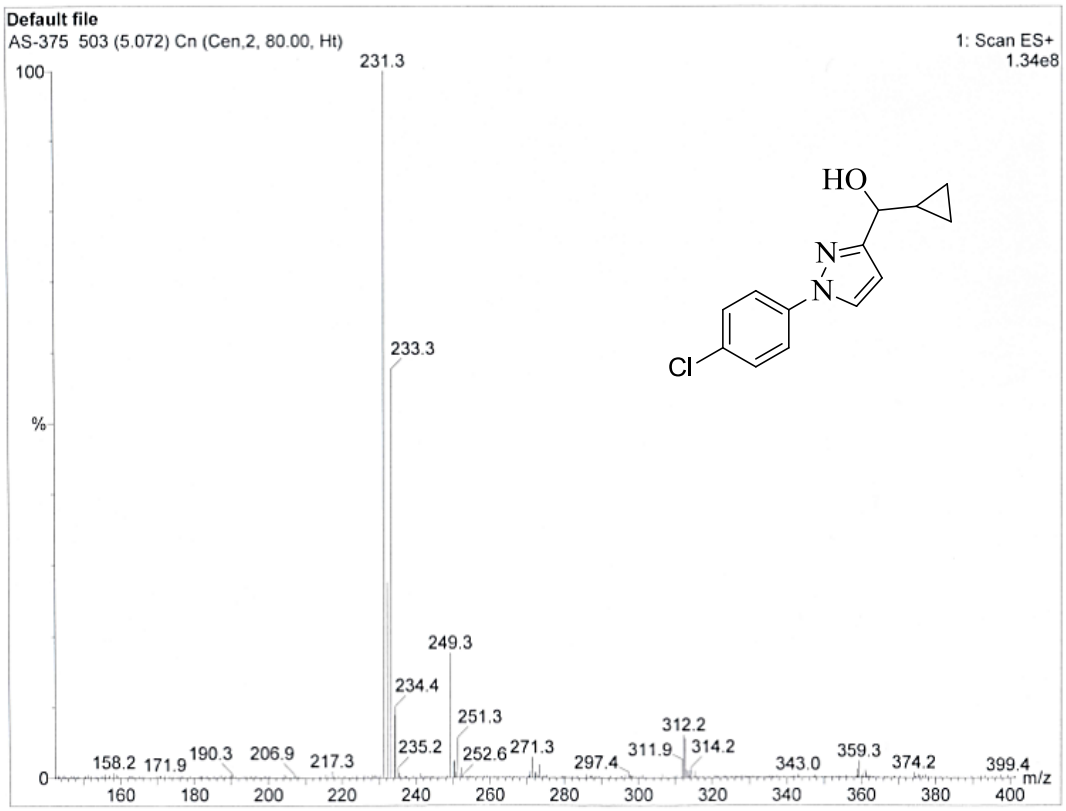


Figure 6.76 LC-MS spectrum of compound **244d**

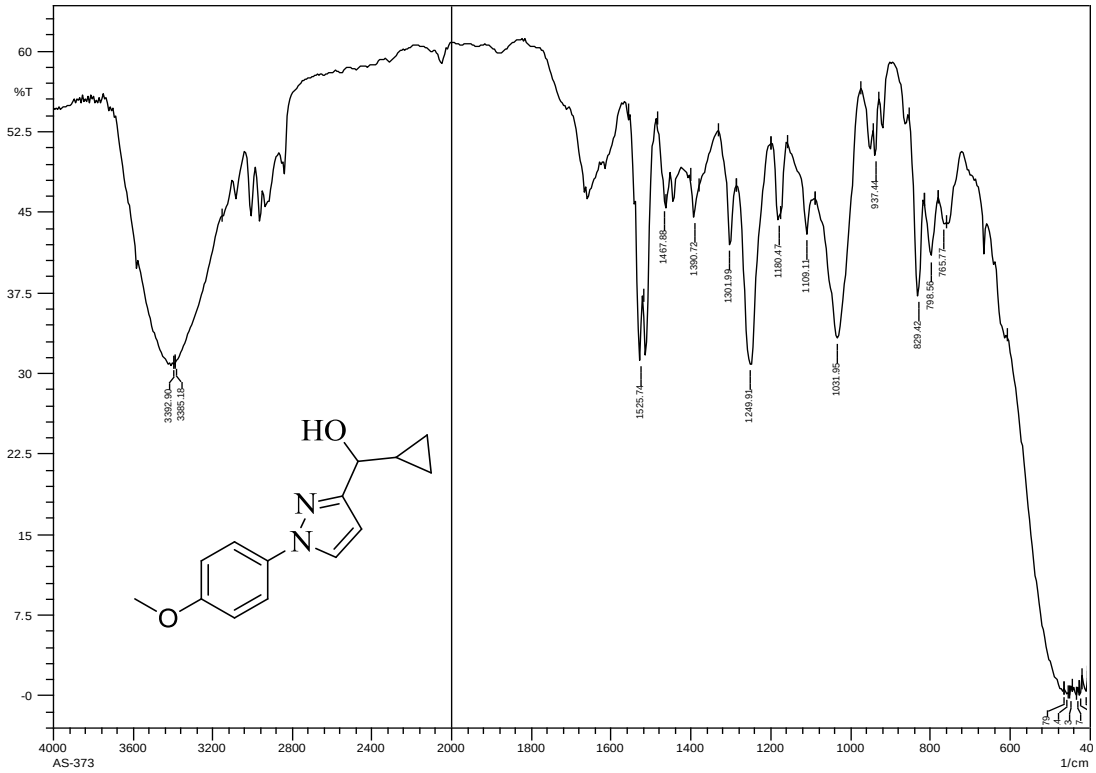


Figure 6.77 IR spectrum of compound **244e**

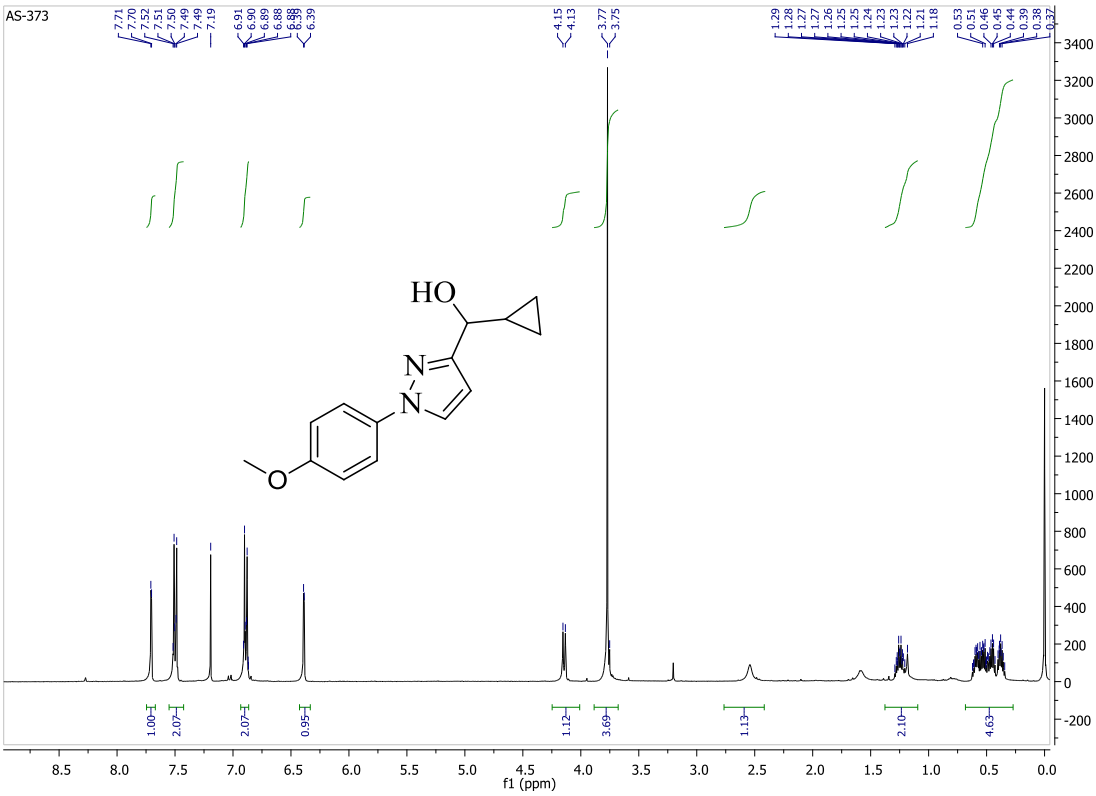


Figure 6.78 ^{1}H NMR spectrum of compound **244e**

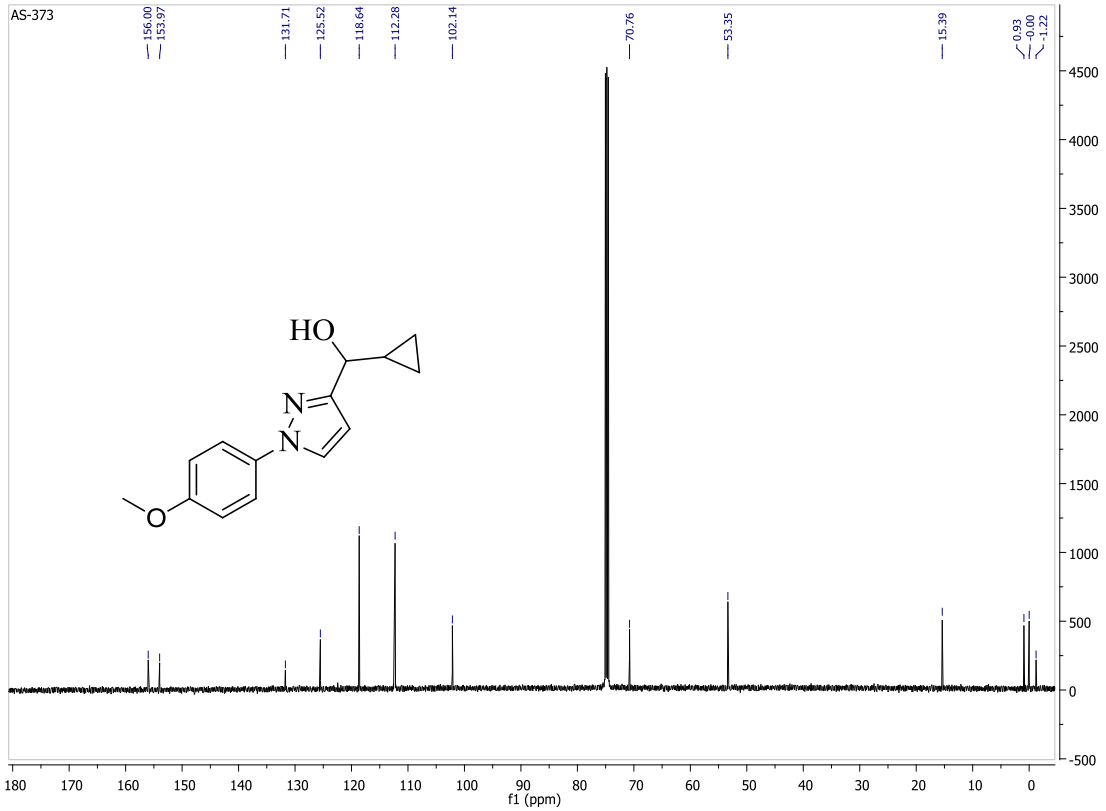


Figure 6.79 ^{13}C NMR spectrum of compound **244e**

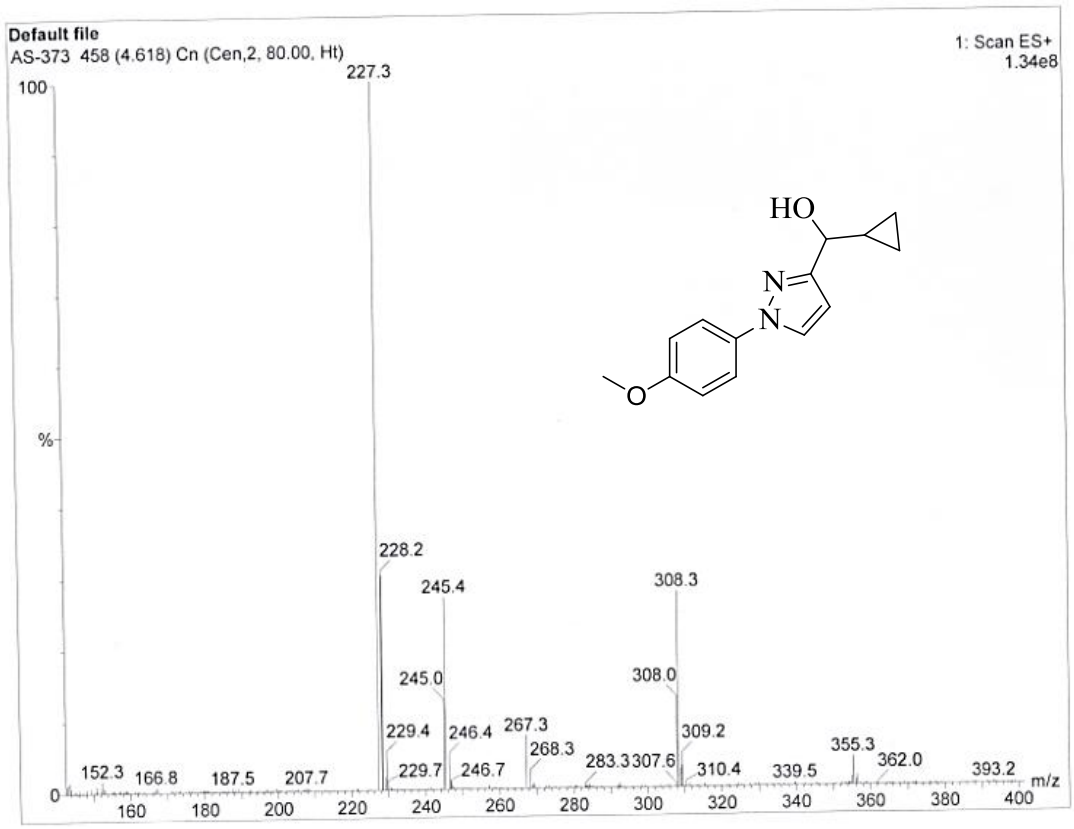


Figure 6.80 LC-MS spectrum of compound **244e**

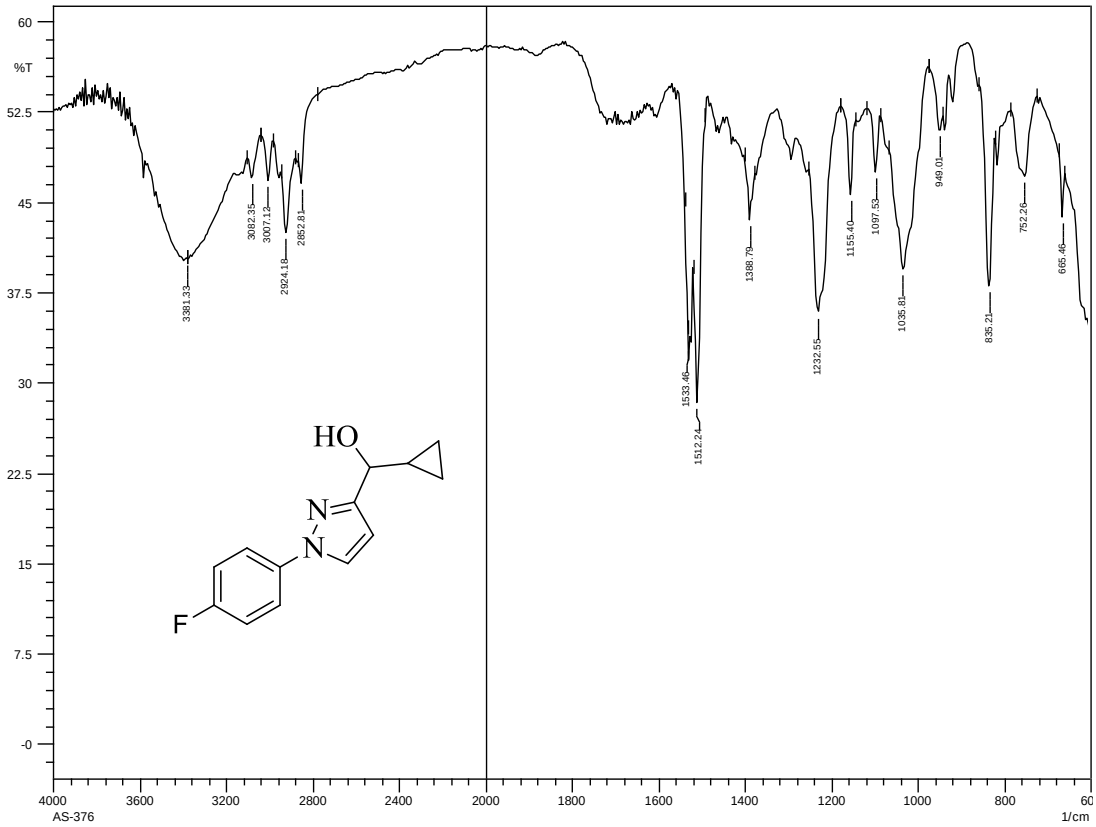


Figure 6.81 IR spectrum of compound **244f**

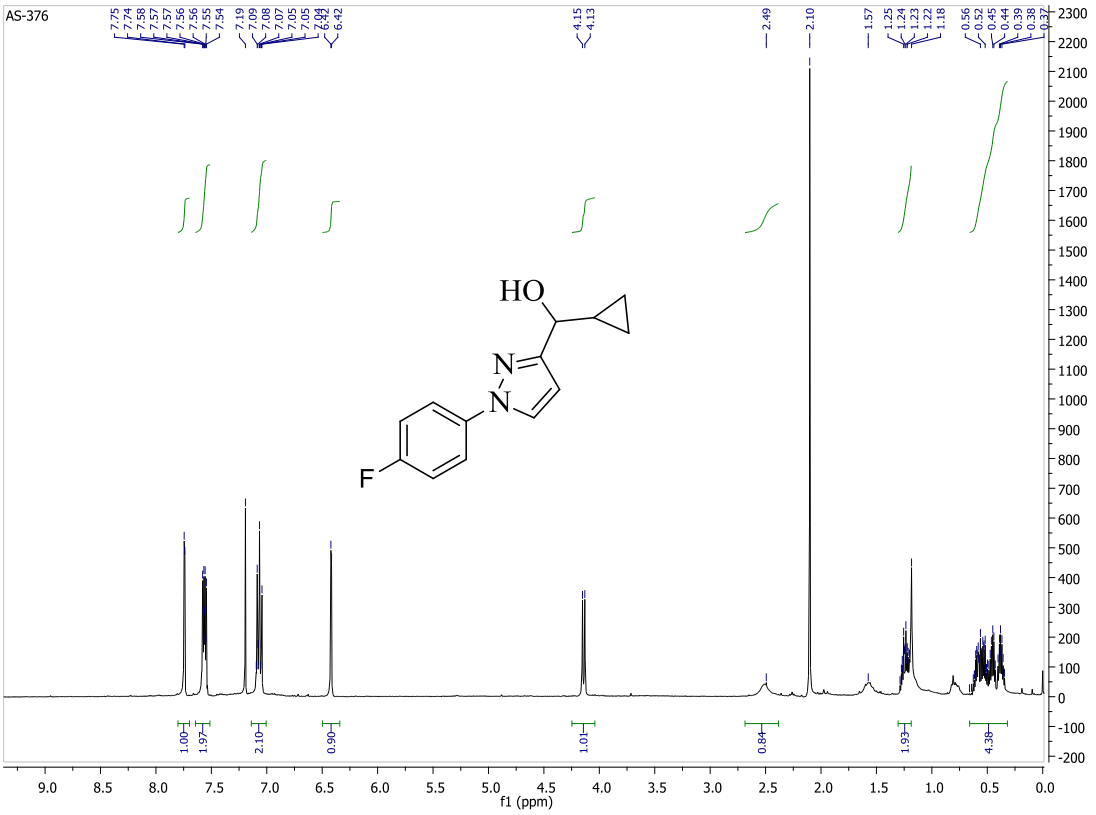


Figure 6.82 ^{1}H NMR spectrum of compound **244f**

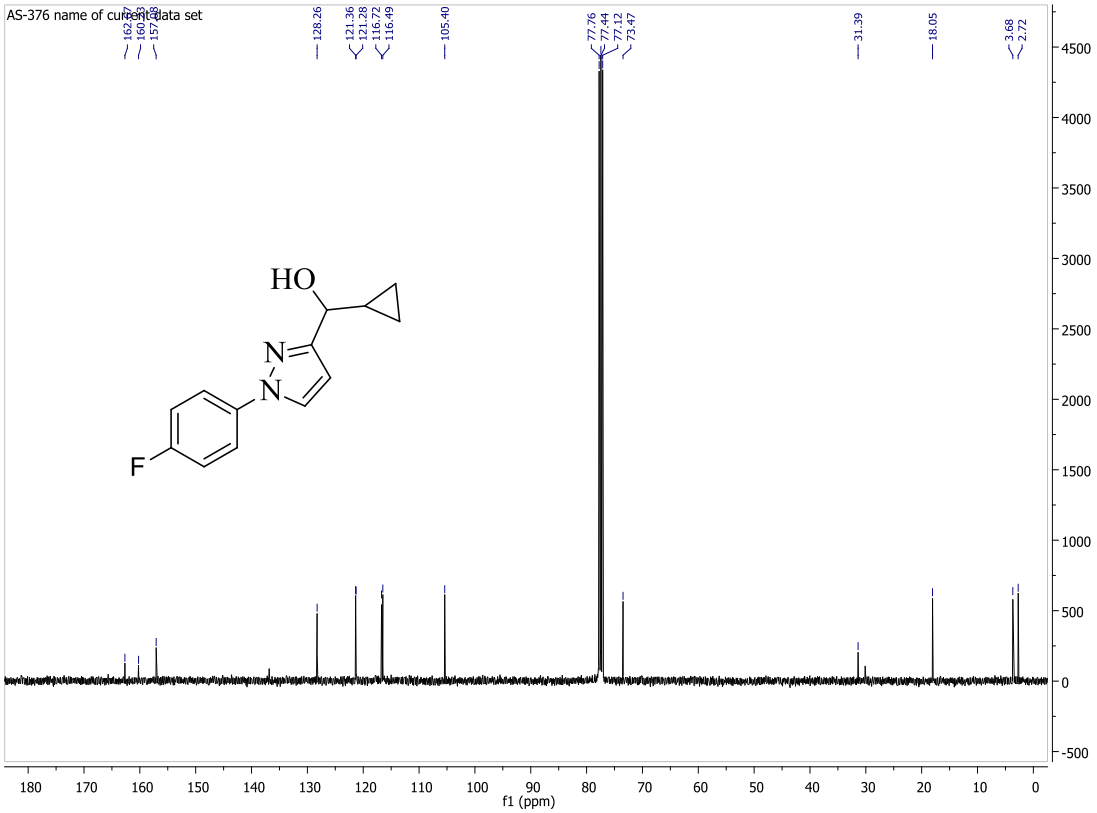


Figure 6.83 ^{13}C NMR spectrum of compound **244f**

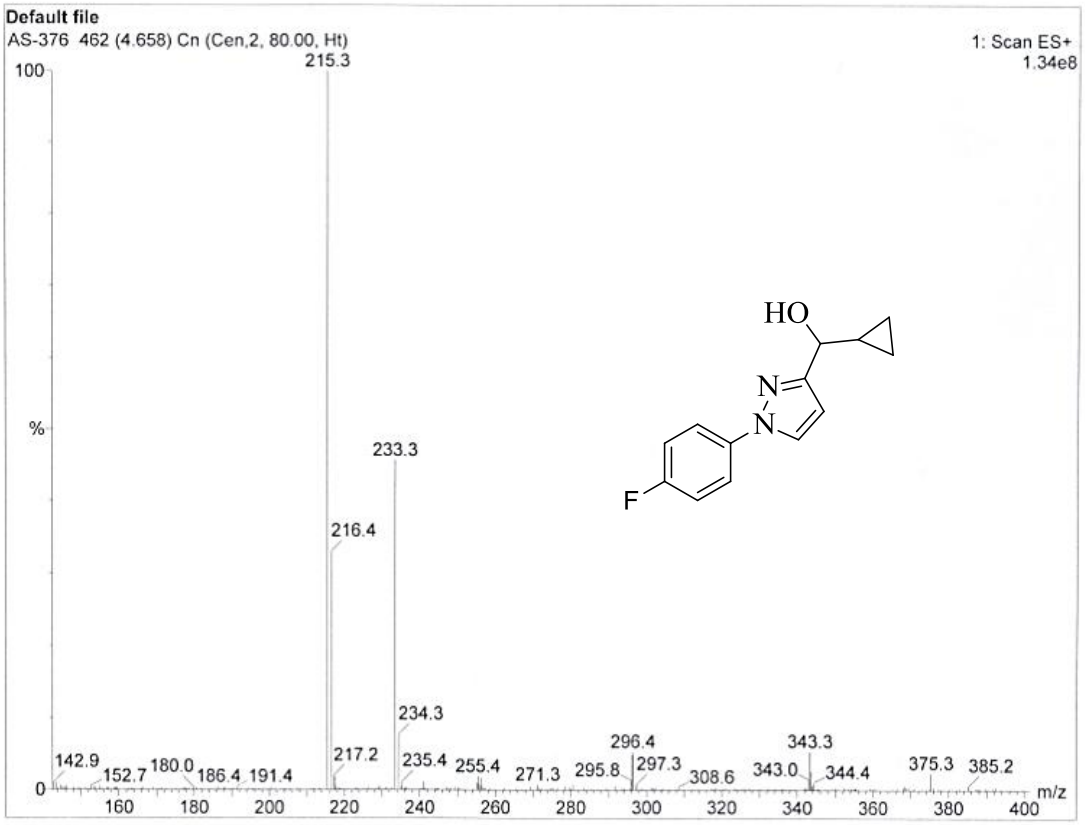


Figure 6.84 LC-MS spectrum of compound **244f**

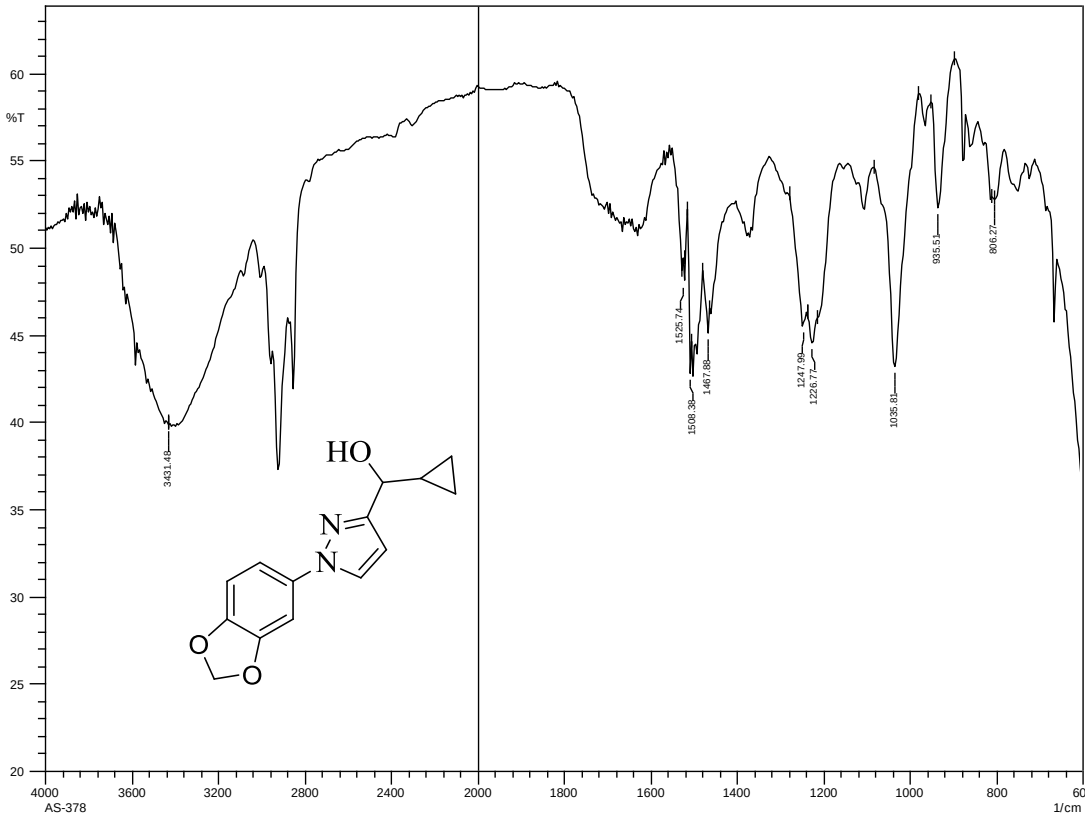


Figure 6.85 IR spectrum of compound **244g**

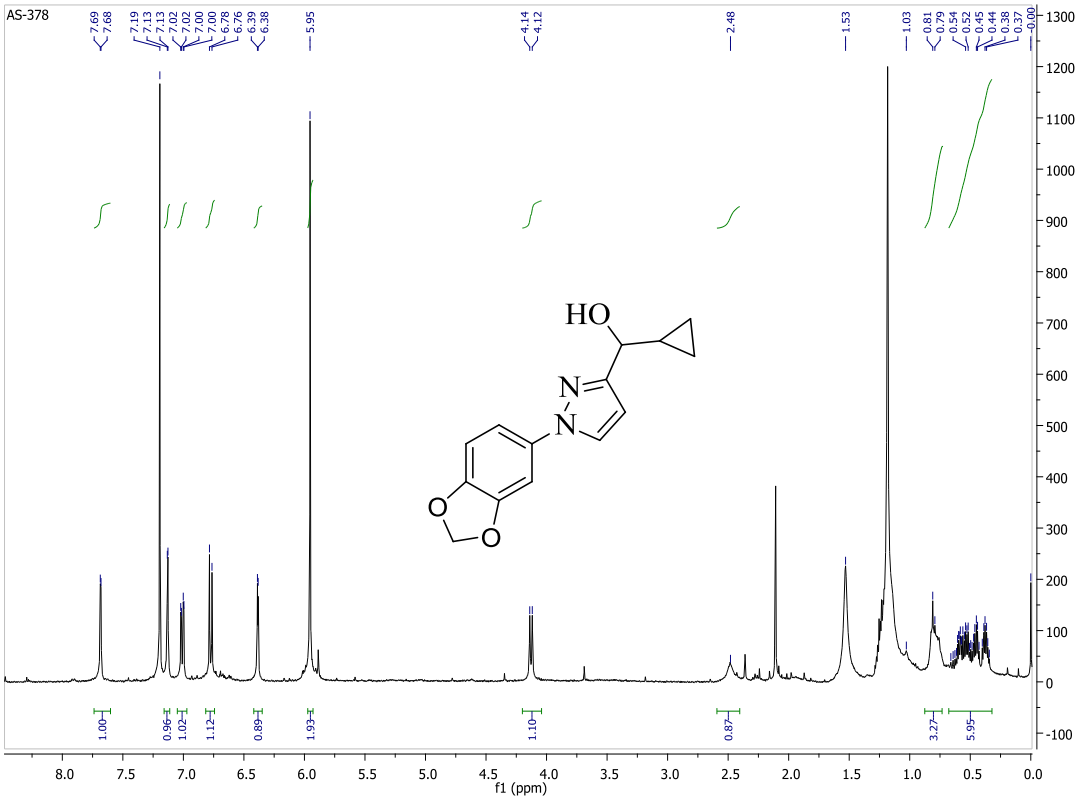


Figure 6.86 ^{1}H NMR spectrum of compound **244g**

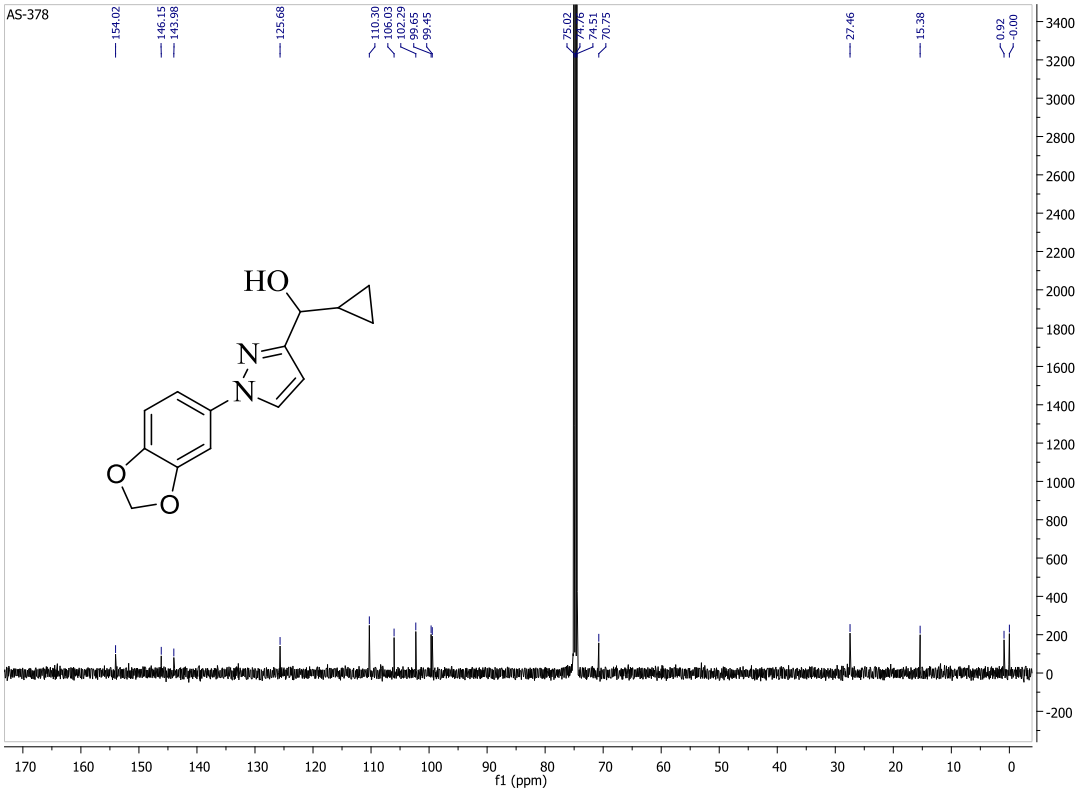


Figure 6.87 ^{13}C NMR spectrum of compound **244g**

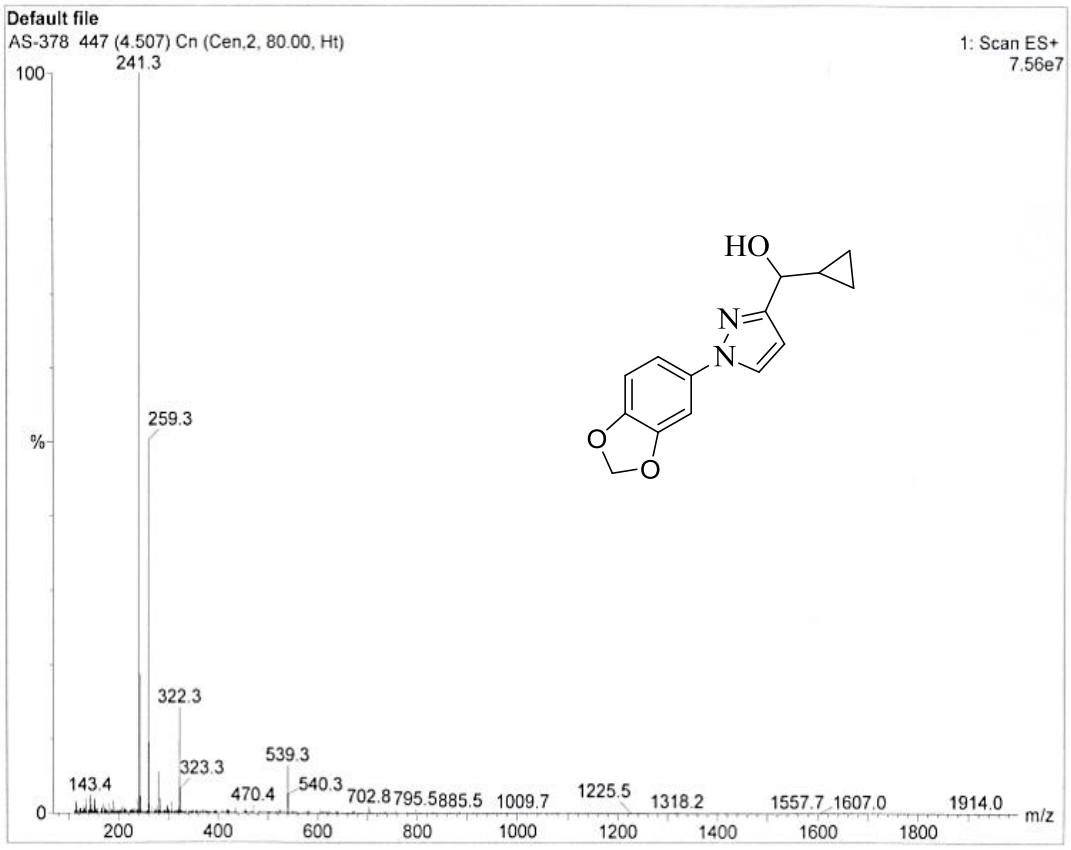


Figure 6.88 LC-MS spectrum of compound **244g**

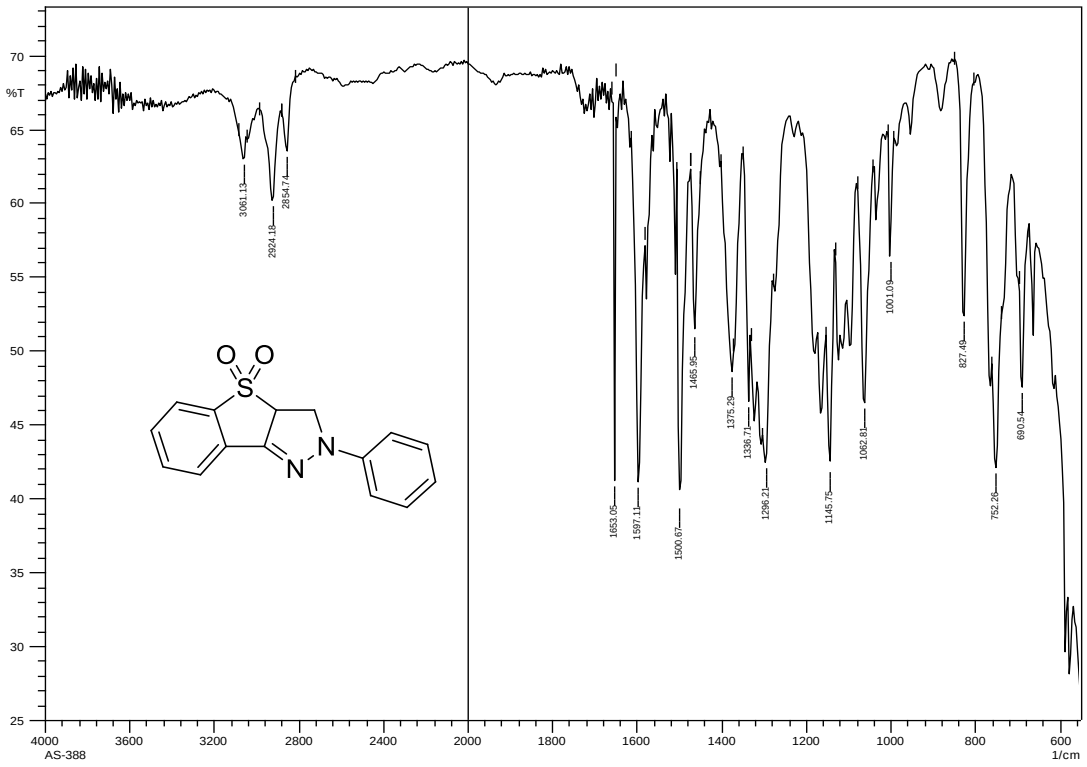


Figure 6.89 IR spectrum of compound **249a**

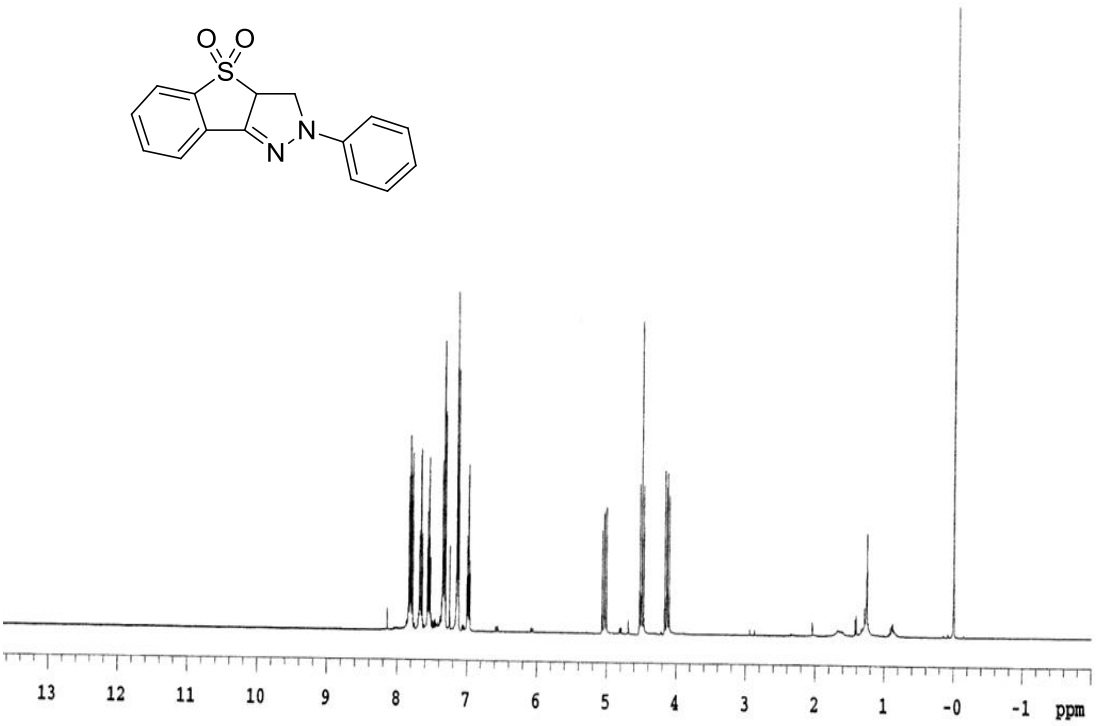


Figure 6.90 ^{1}H NMR spectrum of compound **249a**

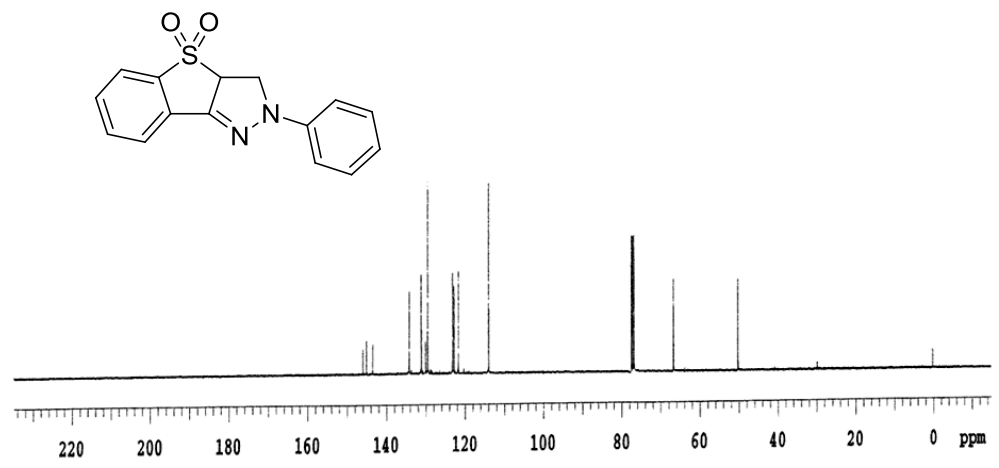


Figure 6.91^{13}C NMR spectrum of compound **249a**

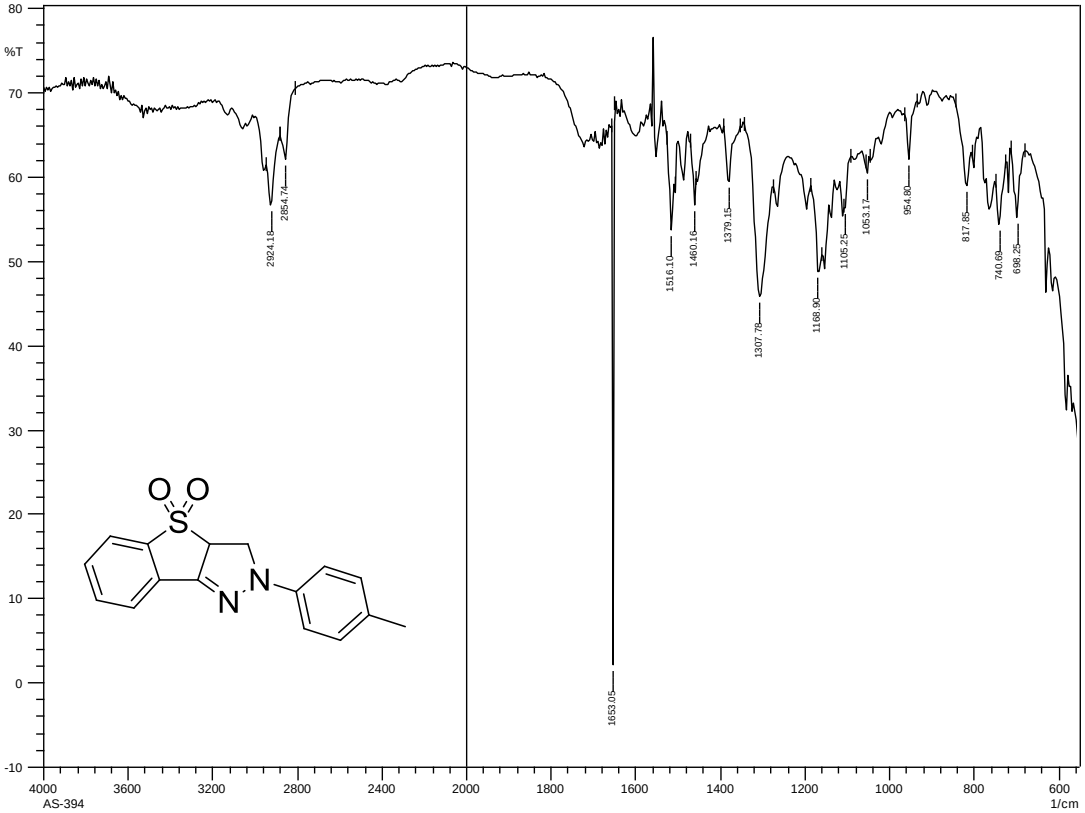


Figure 6.92 IR spectrum of compound **249b**

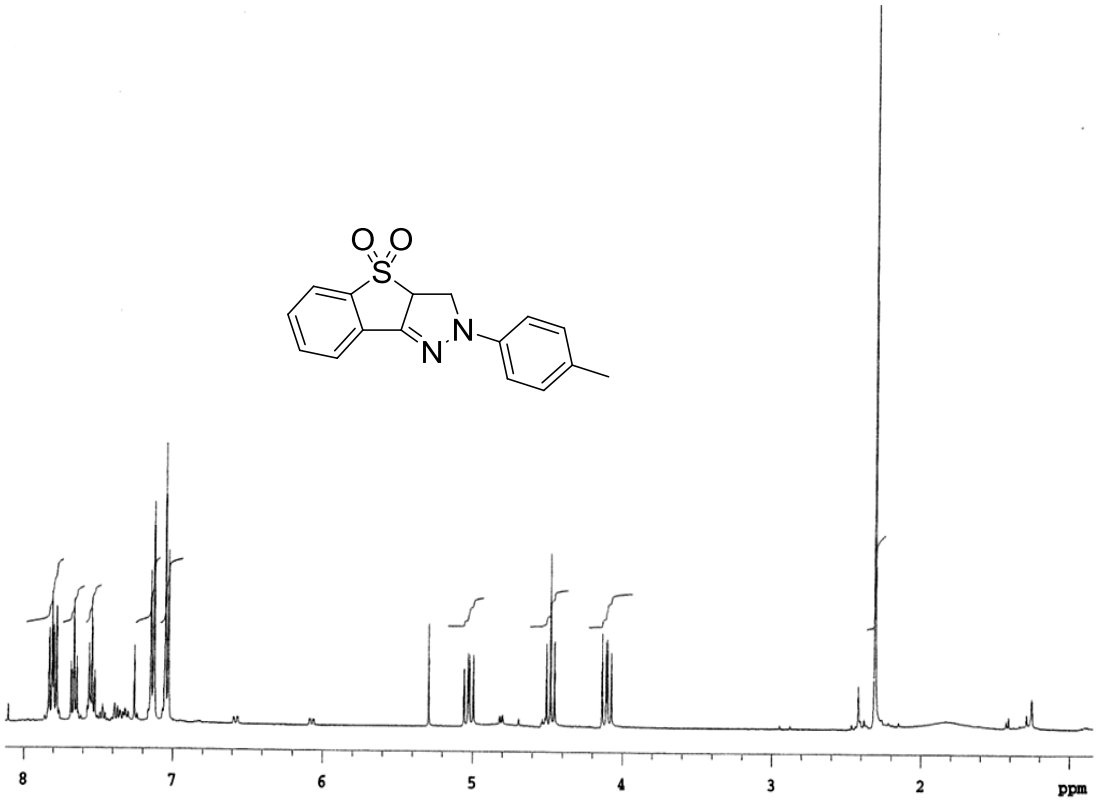


Figure 6.93 ^{1}H NMR spectrum of compound **249b**

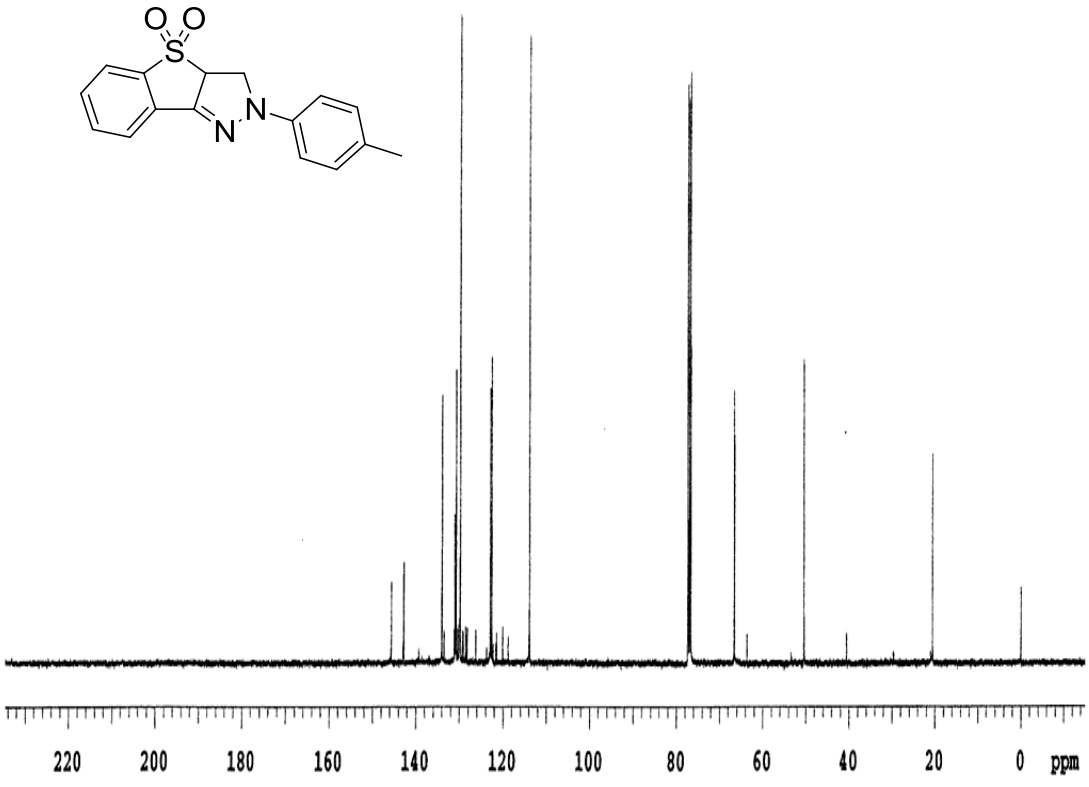


Figure 6.94 ^{13}C NMR spectrum of compound **249b**

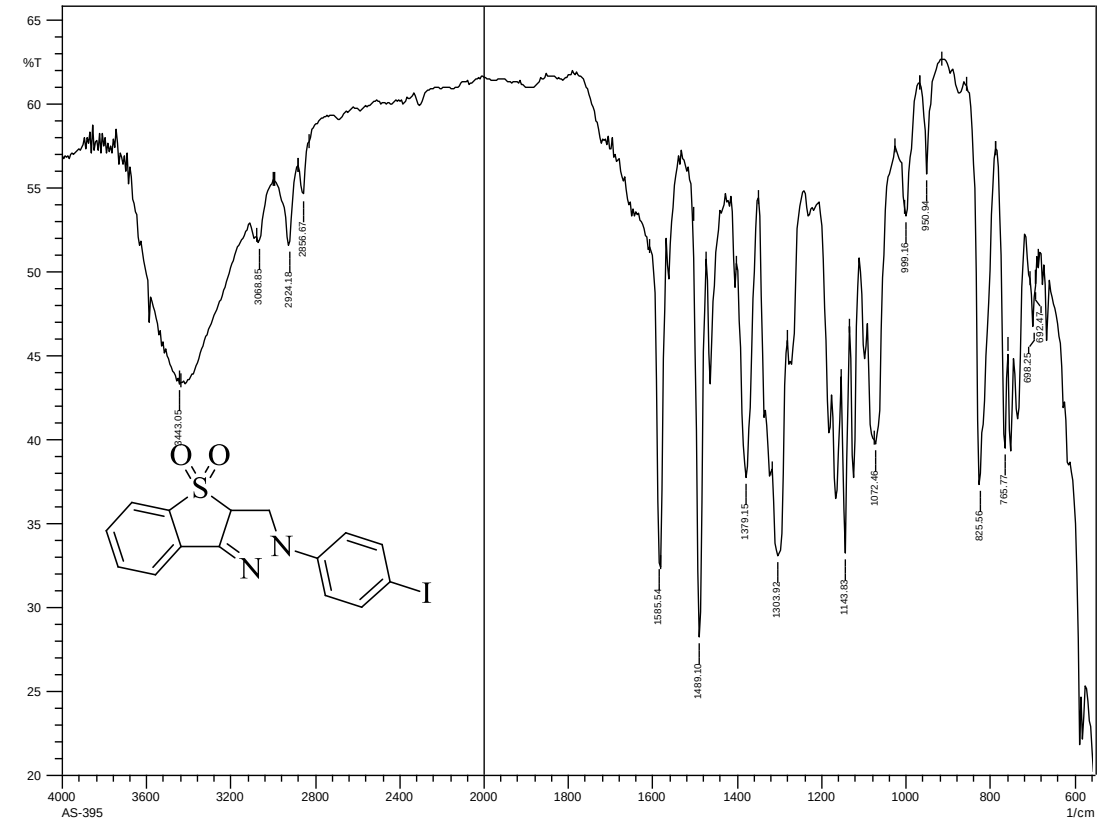


Figure 6.95 IR spectrum of compound **249c**

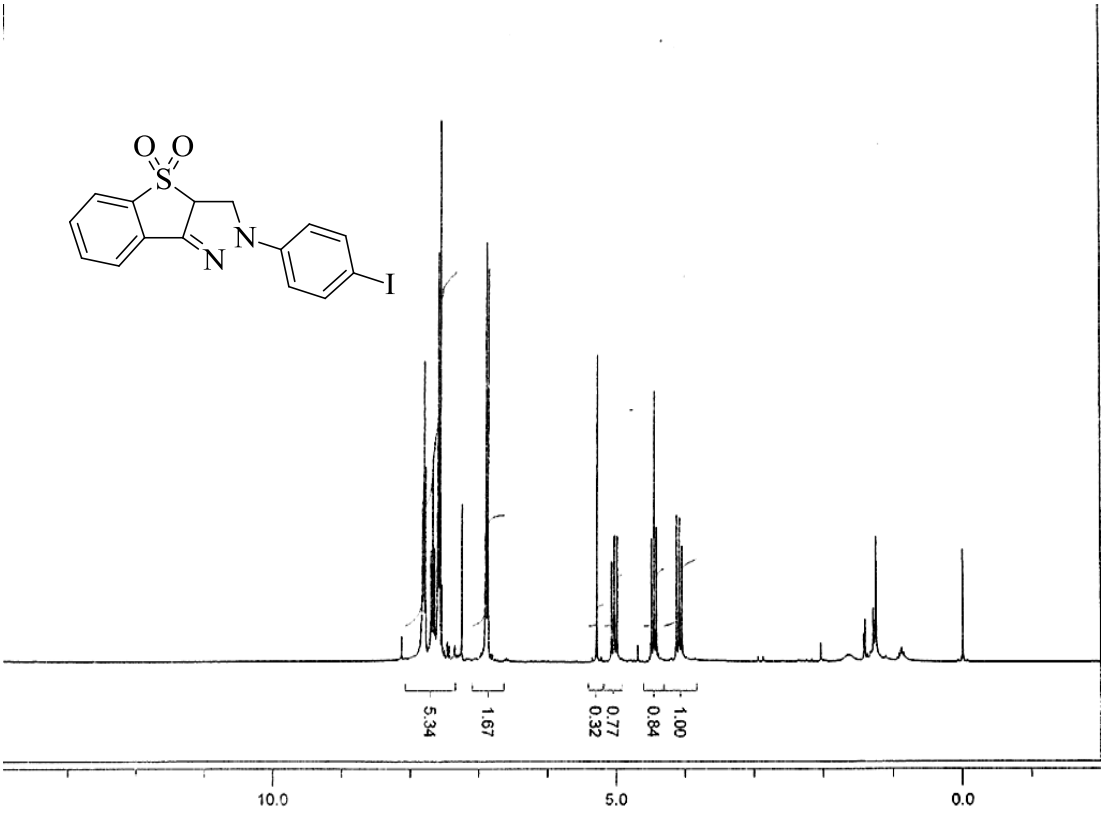


Figure 6.96 ^{1}H NMR spectrum of compound **249c**

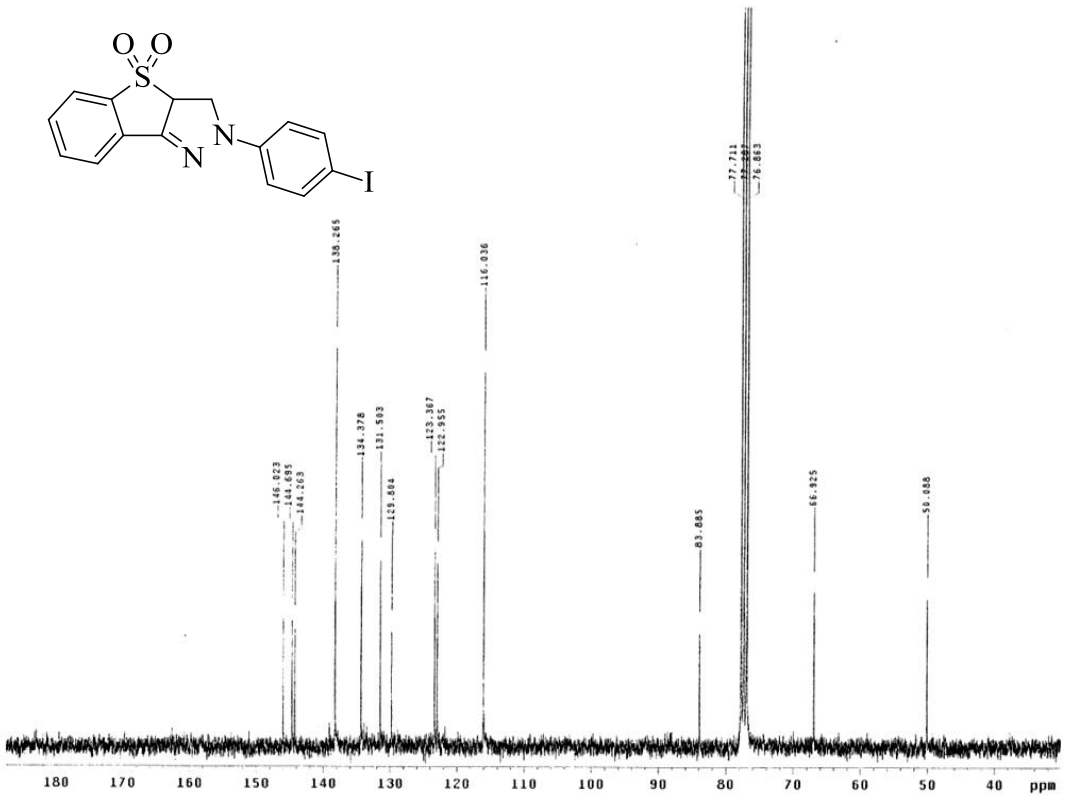


Figure 6.97 ^{13}C NMR spectrum of compound **249c**

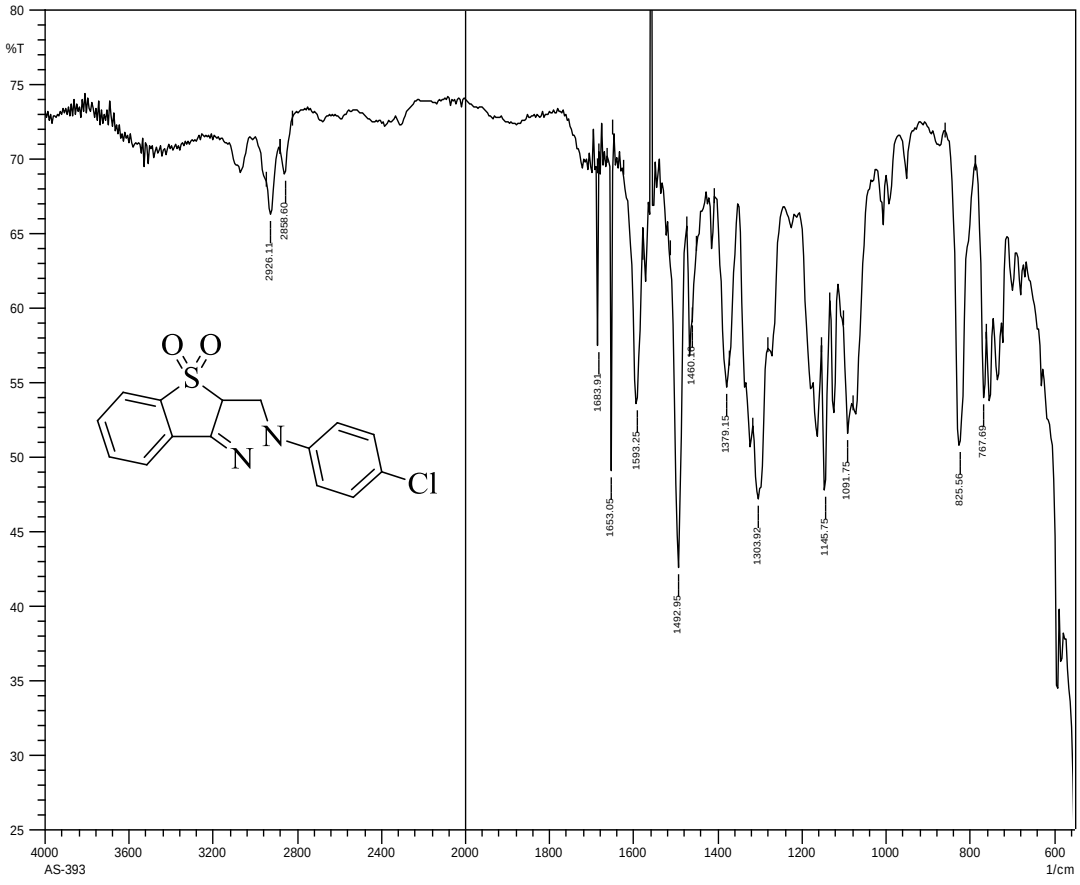


Figure 6.98 IR spectrum of compound **249d**

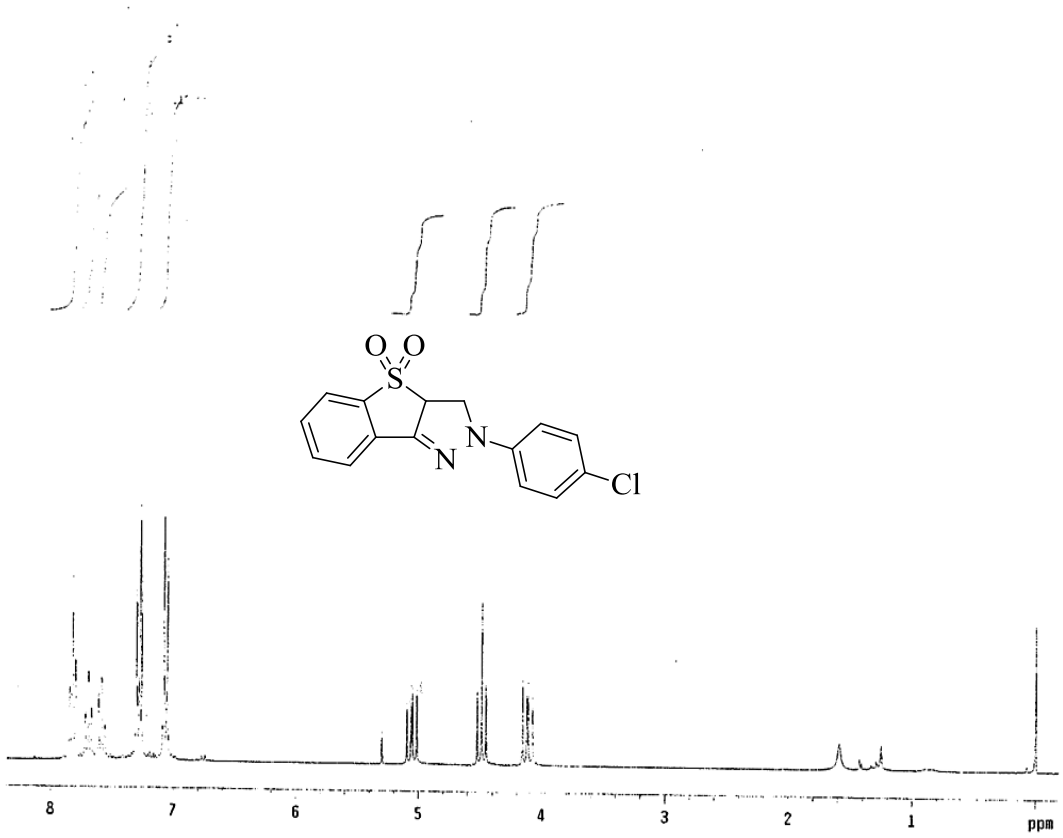


Figure 6.99 ^{1}H NMR spectrum of compound **249d**

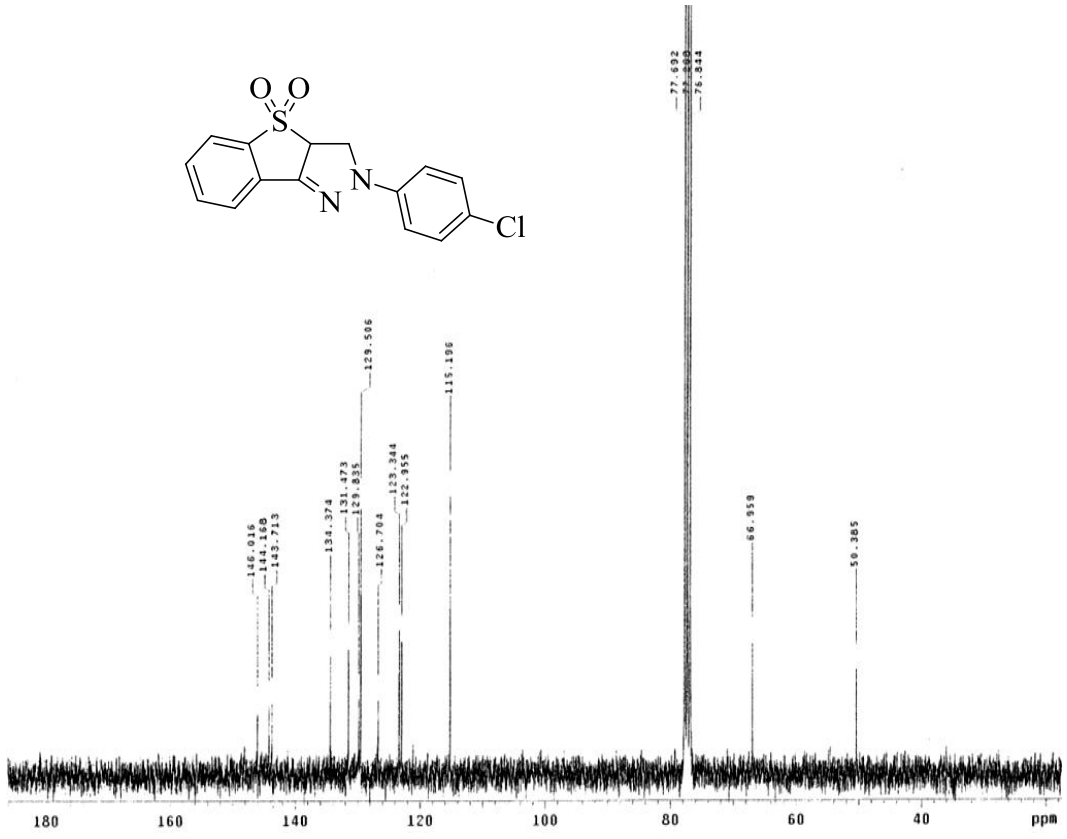


Figure 6.100 ^{13}C NMR spectrum of compound **249d**

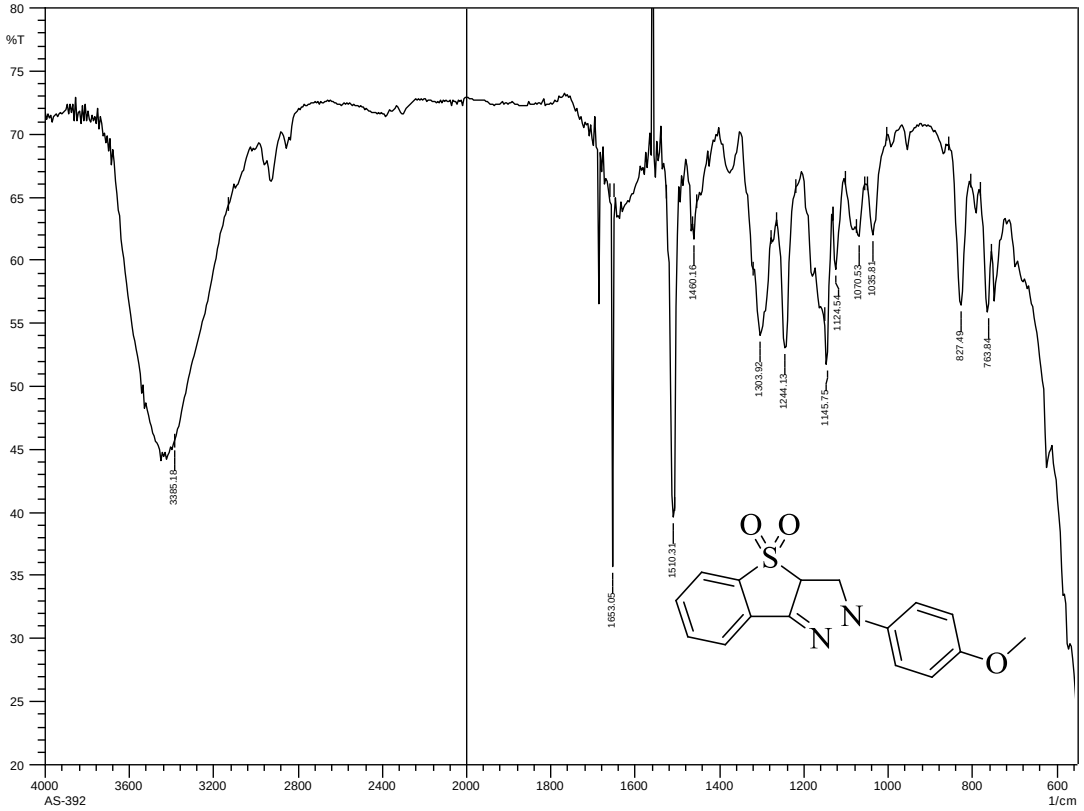


Figure 6.101 IR spectrum of compound **249e**

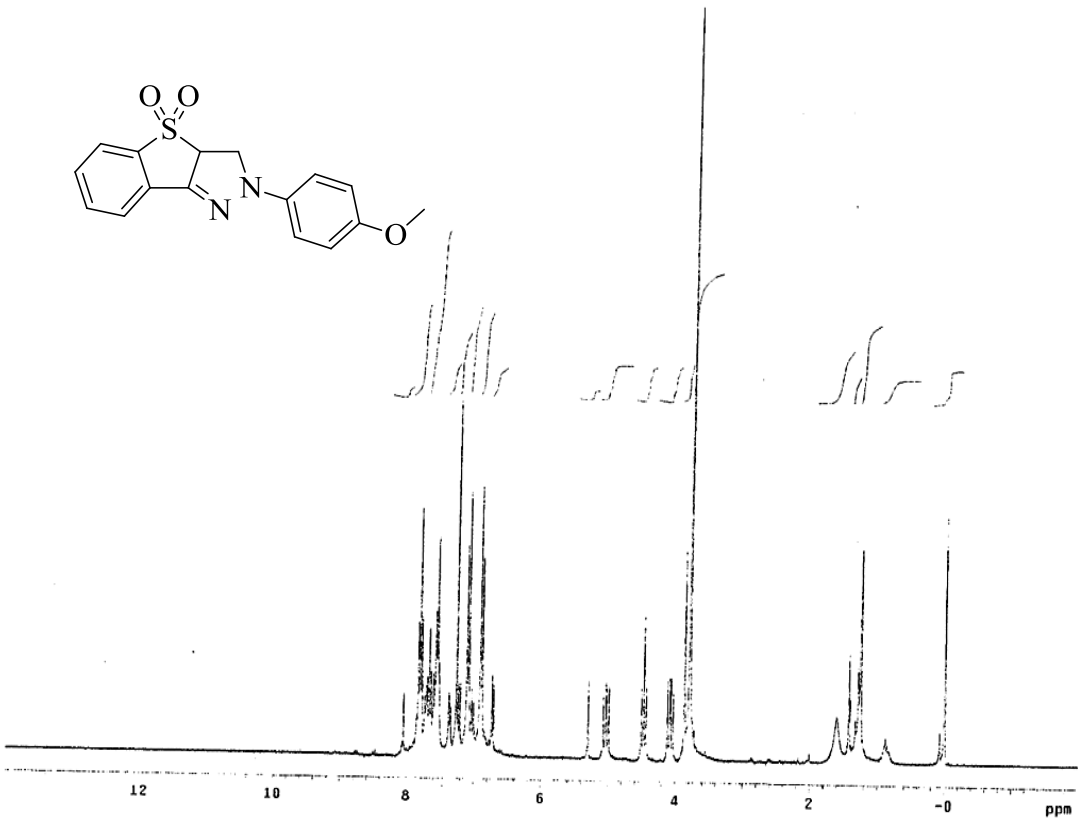


Figure 6.102 ^{1}H NMR spectrum of compound **249e**

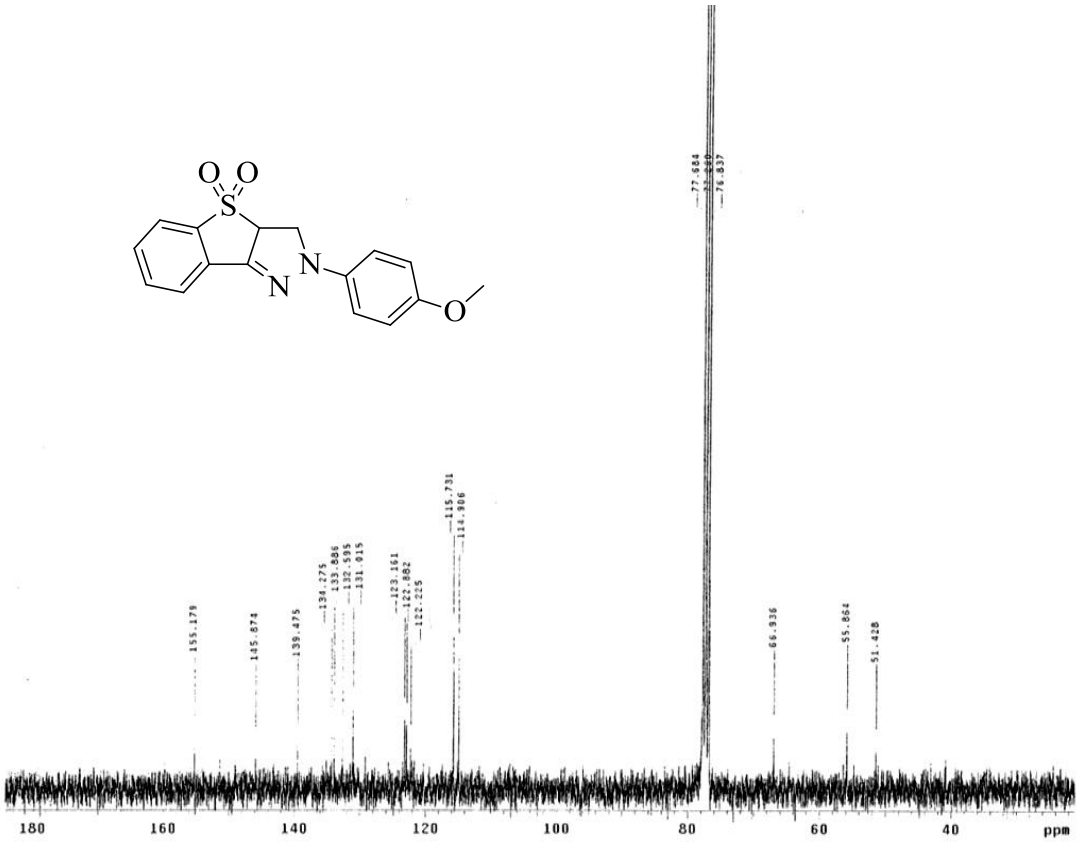


Figure 6.103 ^{13}C NMR spectrum of compound **249e**

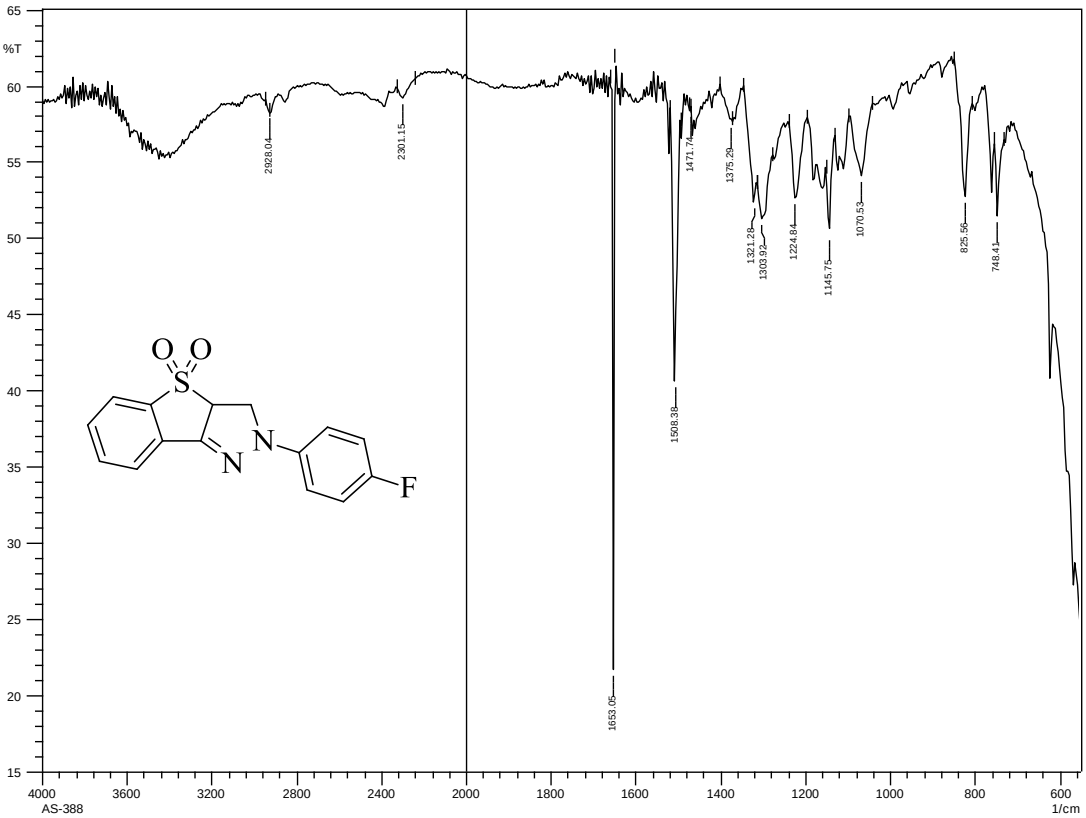


Figure 6.104 IR spectrum of compound **249f**

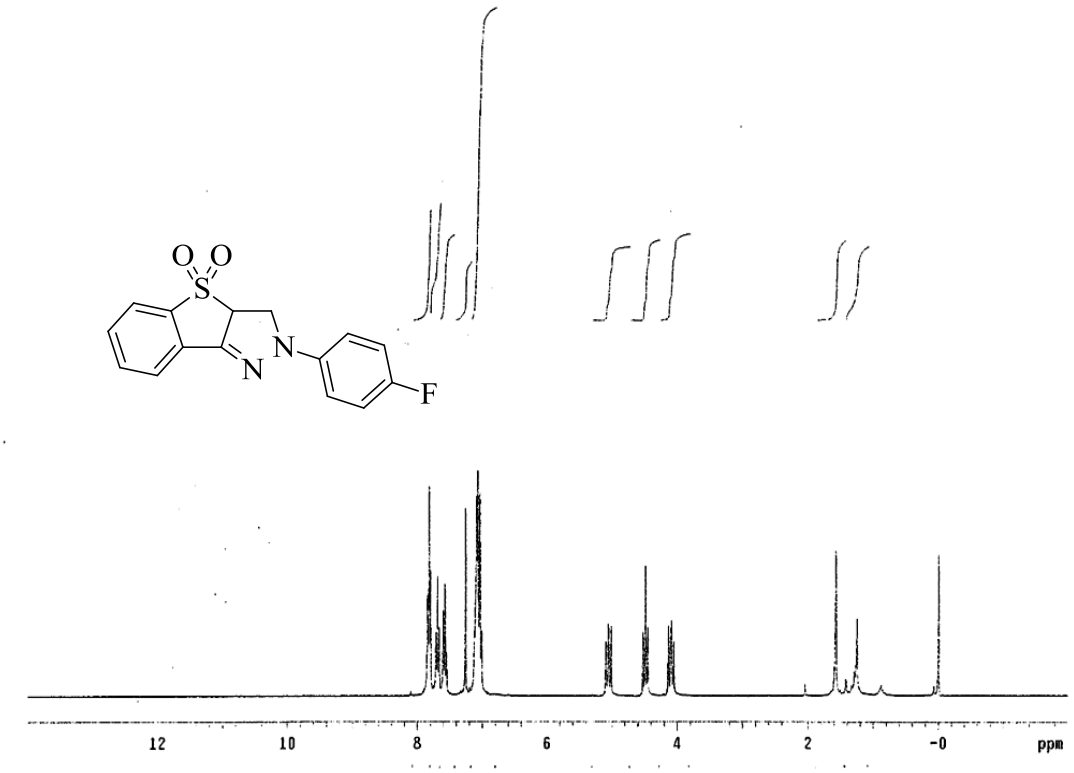


Figure 6.105 ^{1}H NMR spectrum of compound **249f**

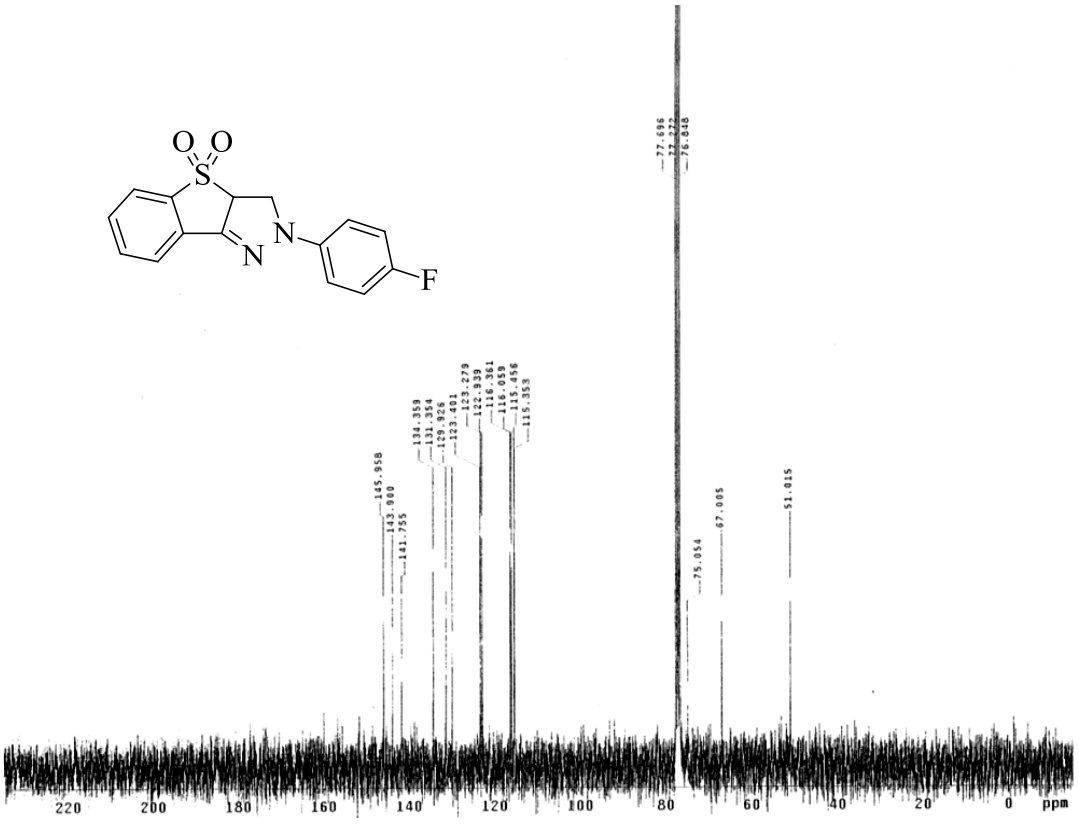


Figure 6.106 ^{13}C NMR spectrum of compound **249f**

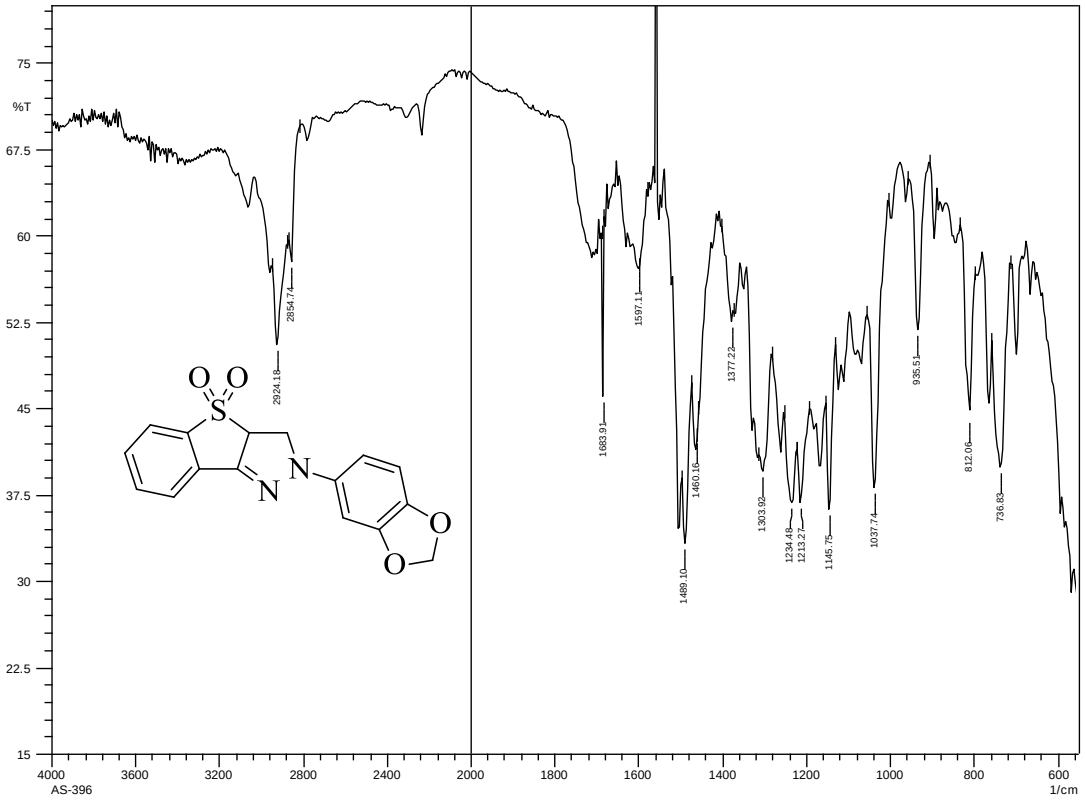


Figure 6.107 IR spectrum of compound **249g**

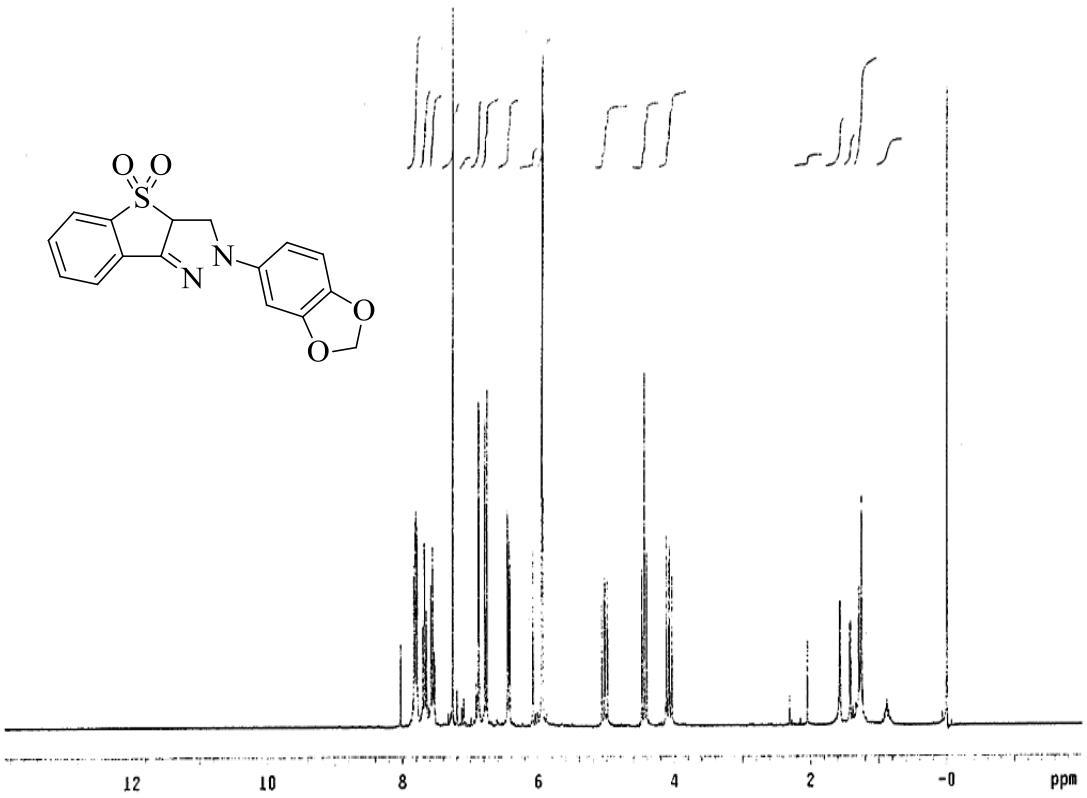


Figure 6.108 ^{1}H NMR spectrum of compound **249g**

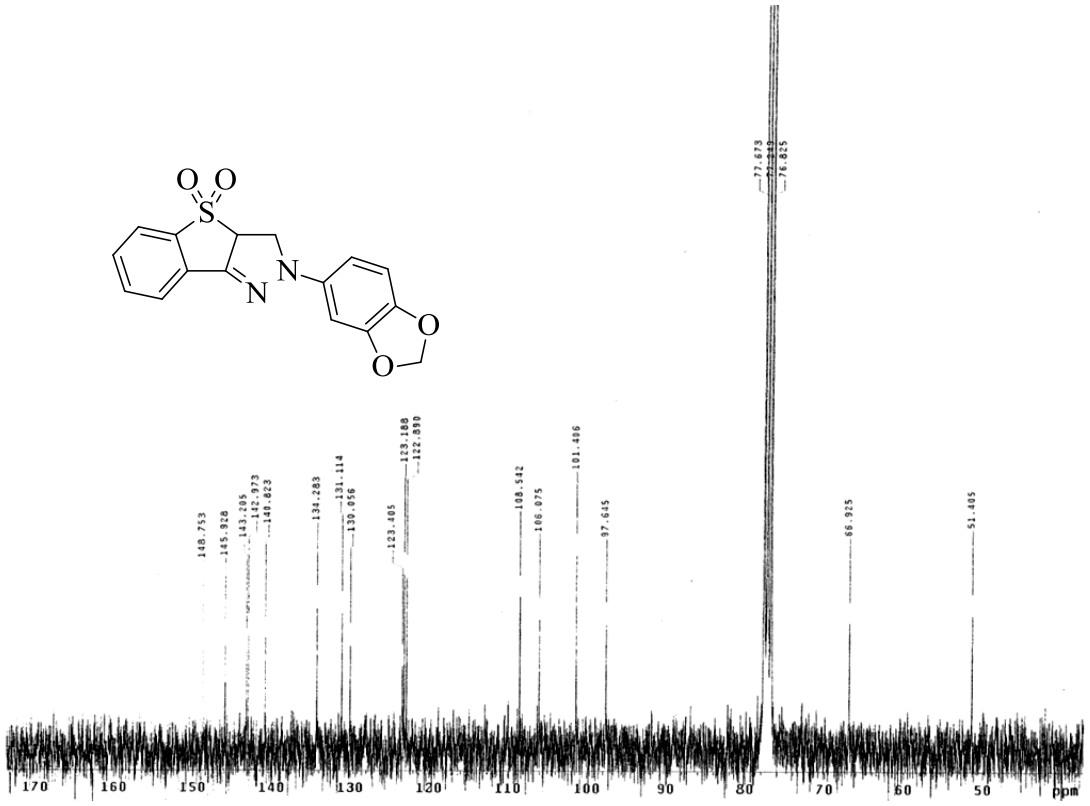


Figure 6.109 ^{13}C NMR spectrum of compound **249g**

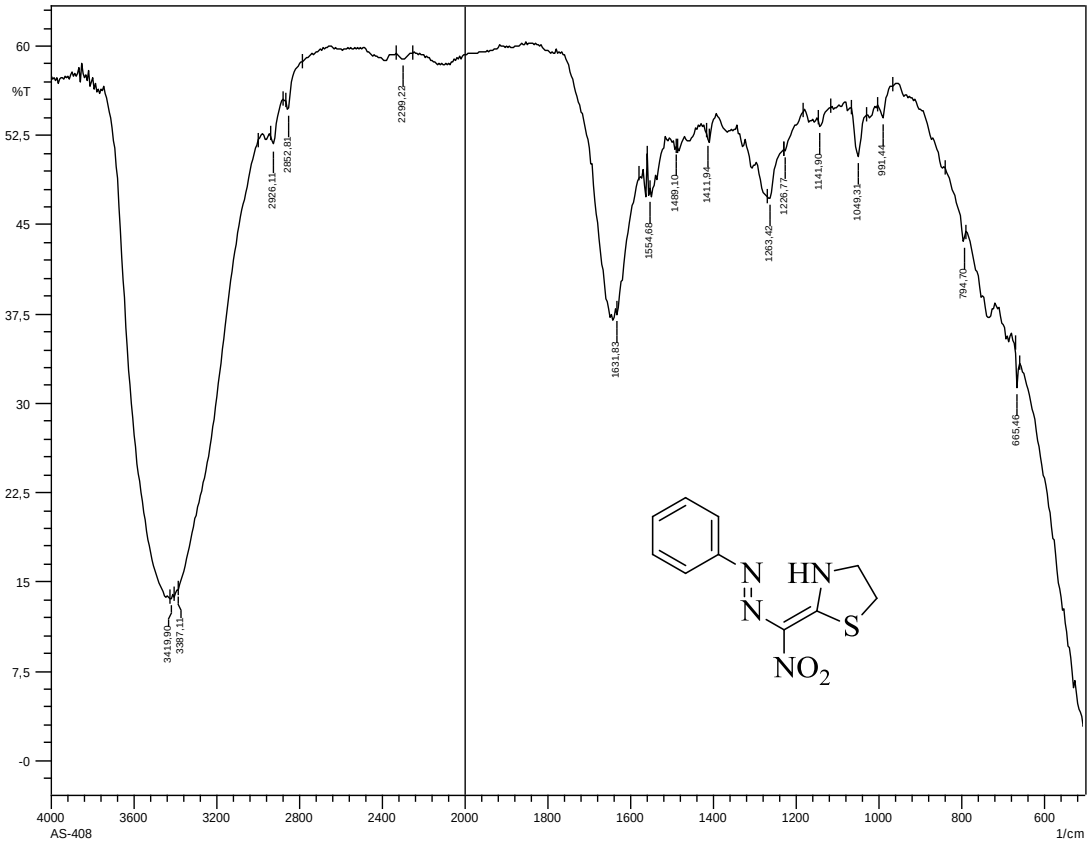


Figure 6.110 IR spectrum of compound **262a**

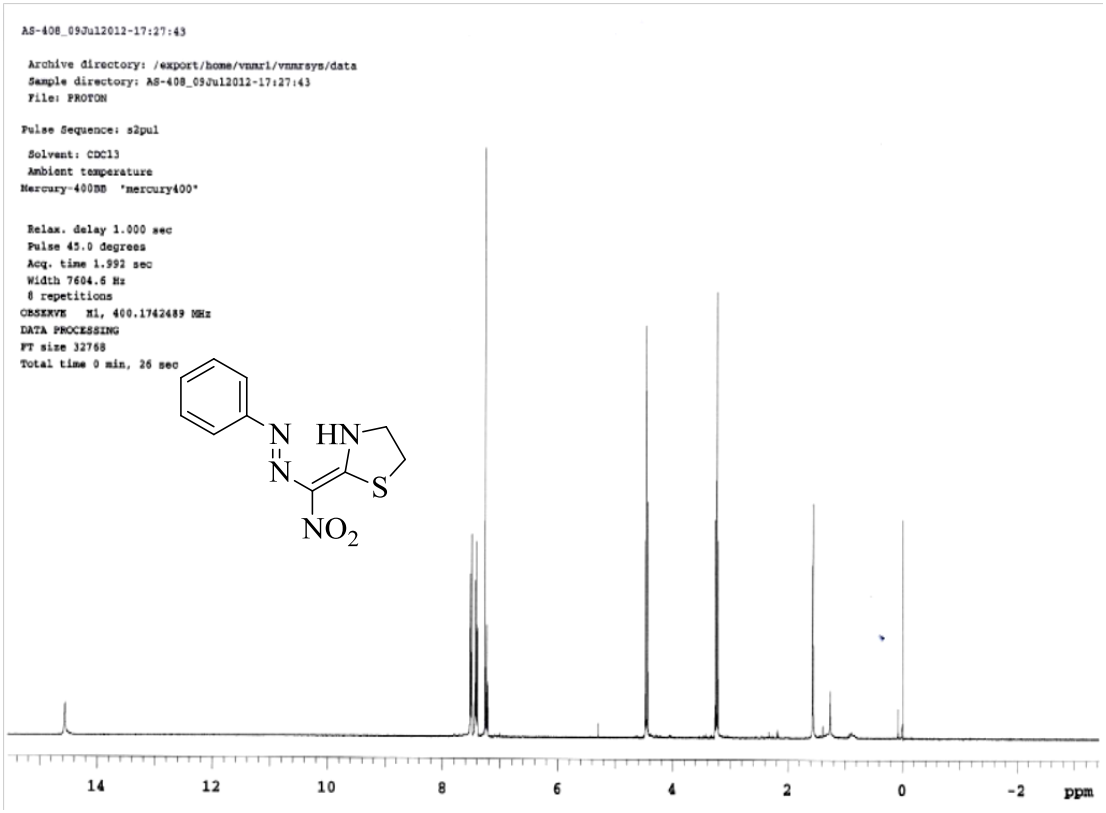


Figure 6.111 ^{1}H NMR spectrum of compound **262a**

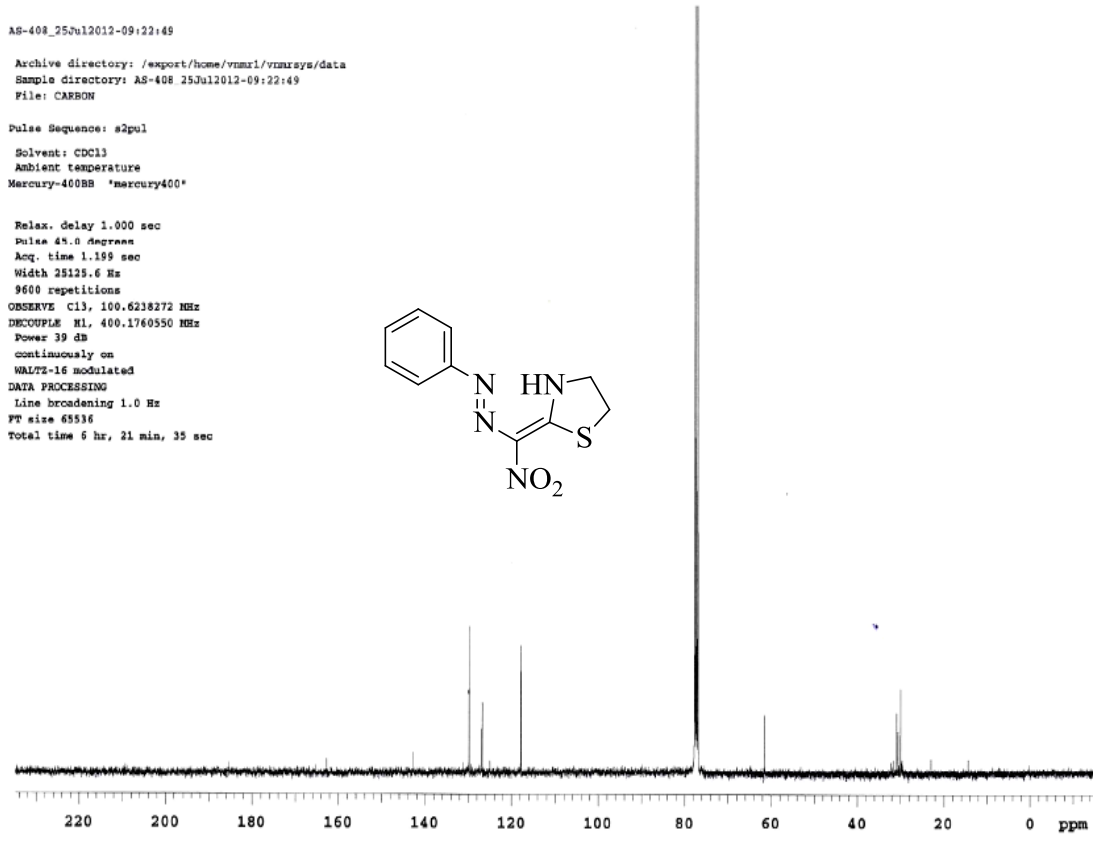


Figure 6.112 ^{13}C NMR spectrum of compound **262a**

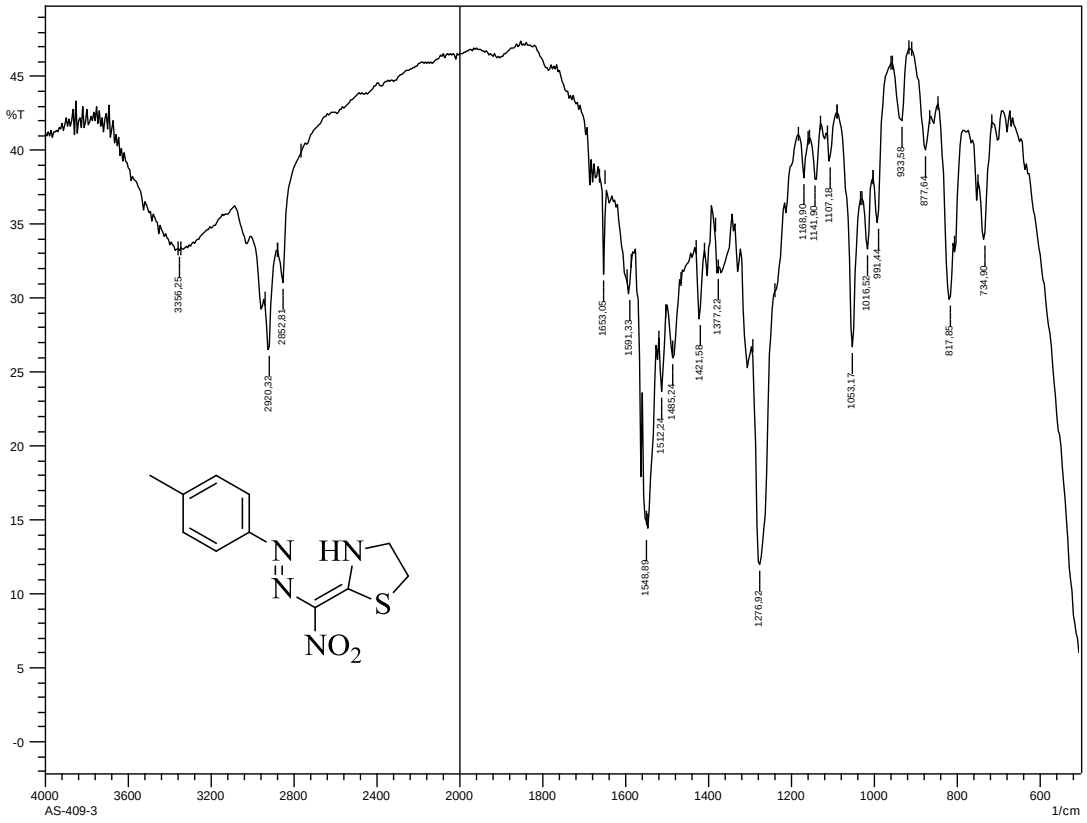


Figure 6.113 IR spectrum of compound **262b**

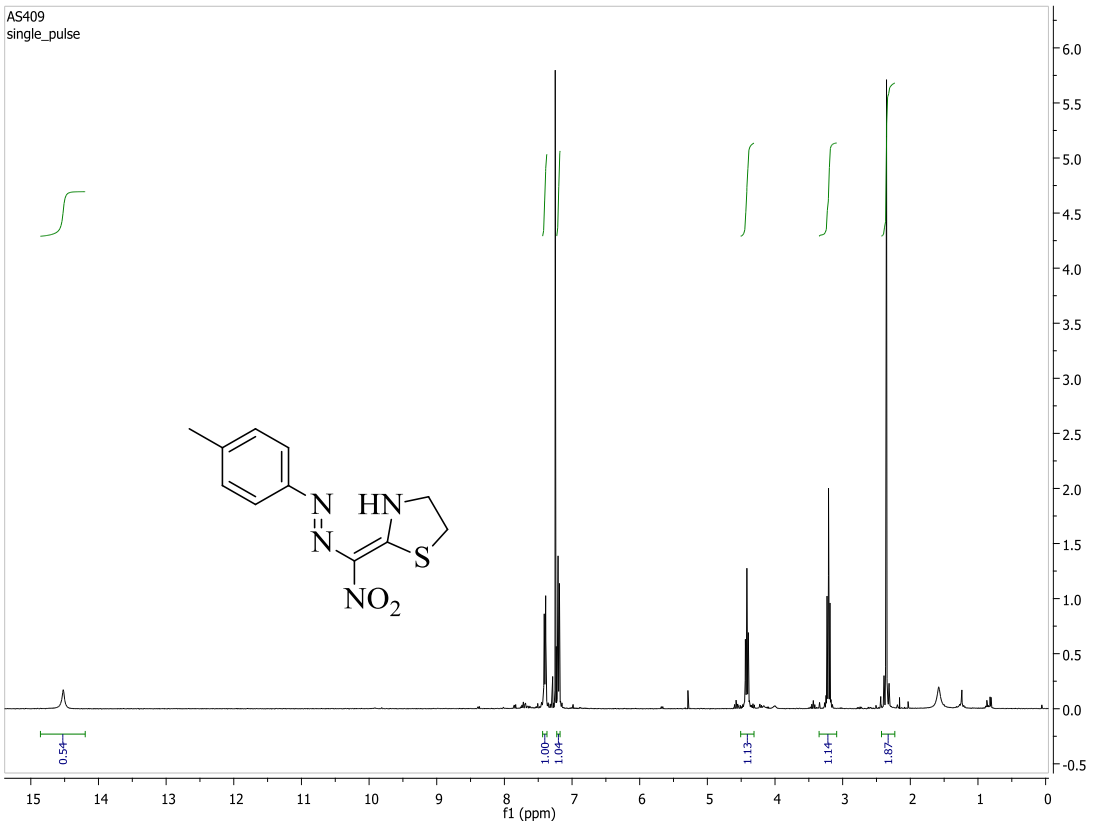


Figure 6.114 ^{1}H NMR spectrum of compound **262b** in $CDCl_3$

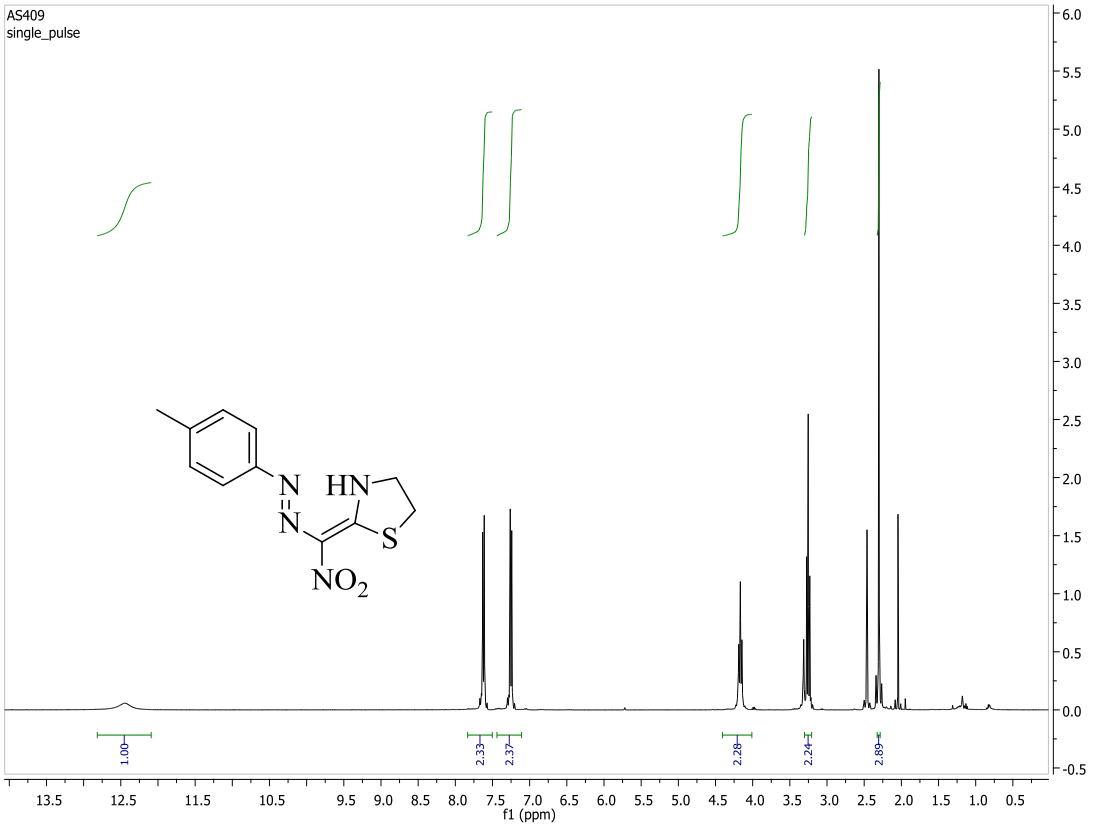


Figure 6.115 ^{1}H NMR spectrum of compound **262b** in *d6*-DMSO

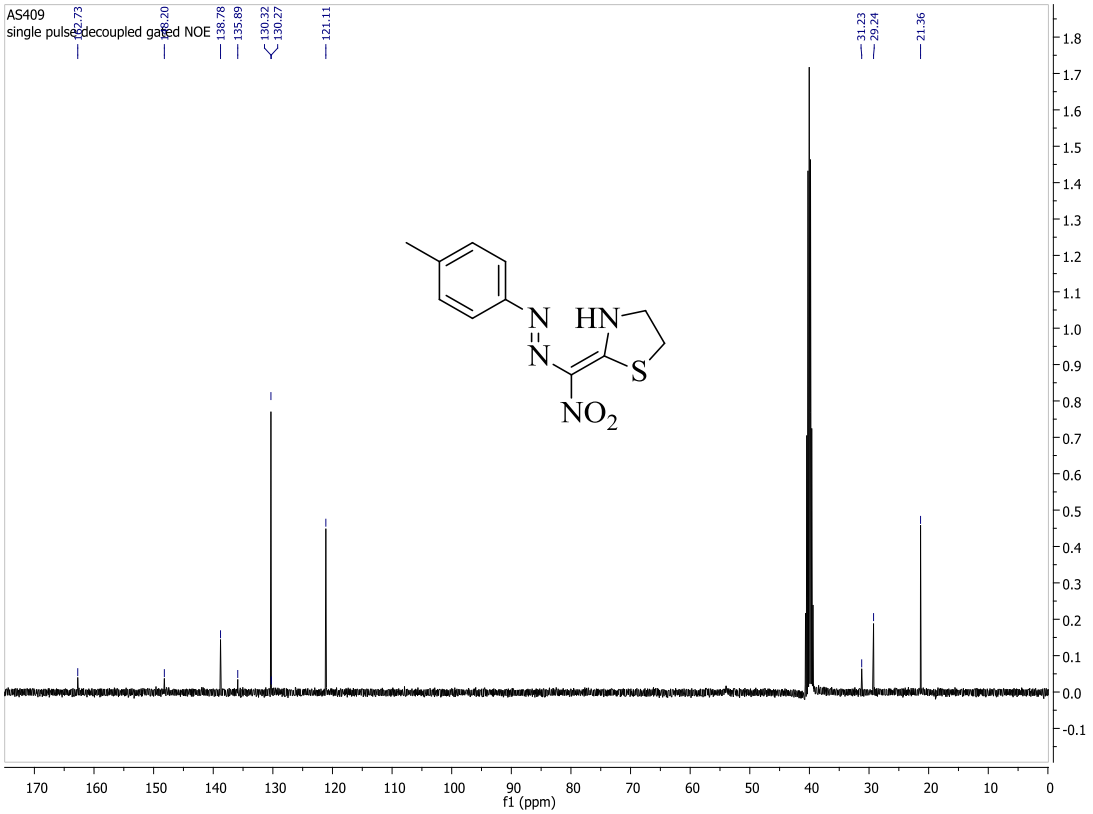


Figure 6.116 ^{13}C NMR spectrum of compound **262b** in *d6*-DMSO

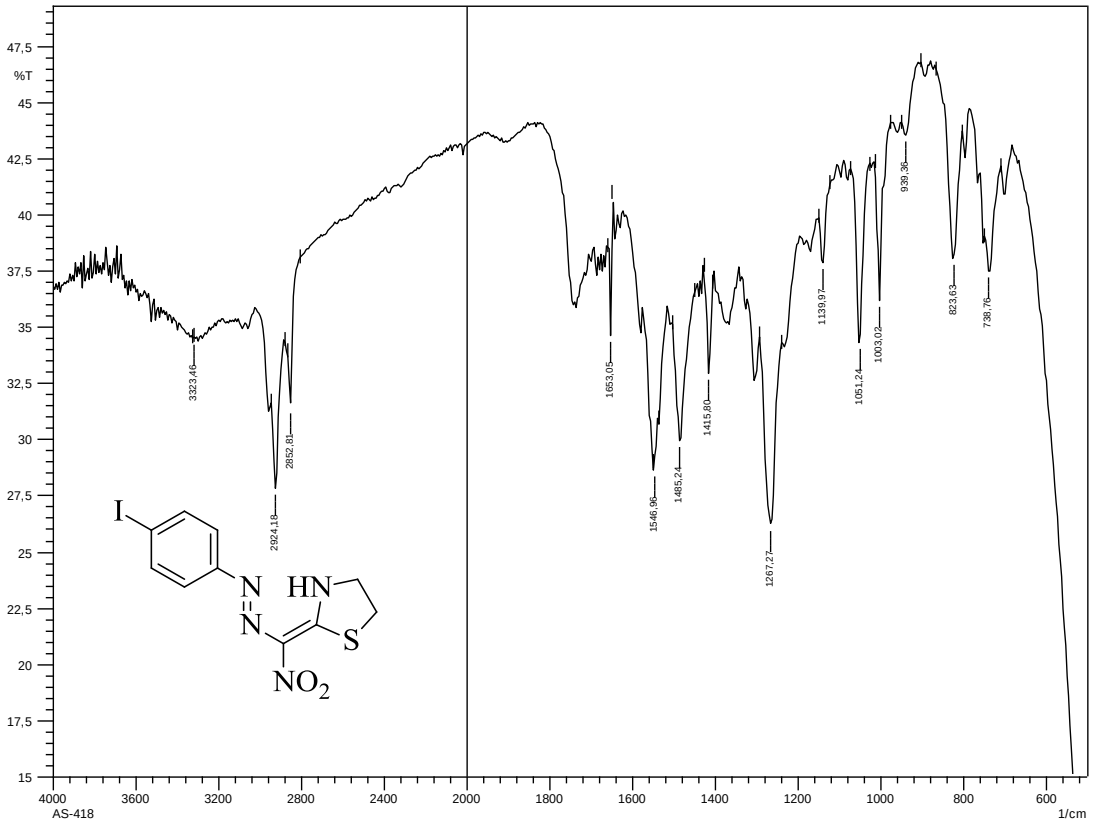


Figure 6.117 IR spectrum of compound **262c**

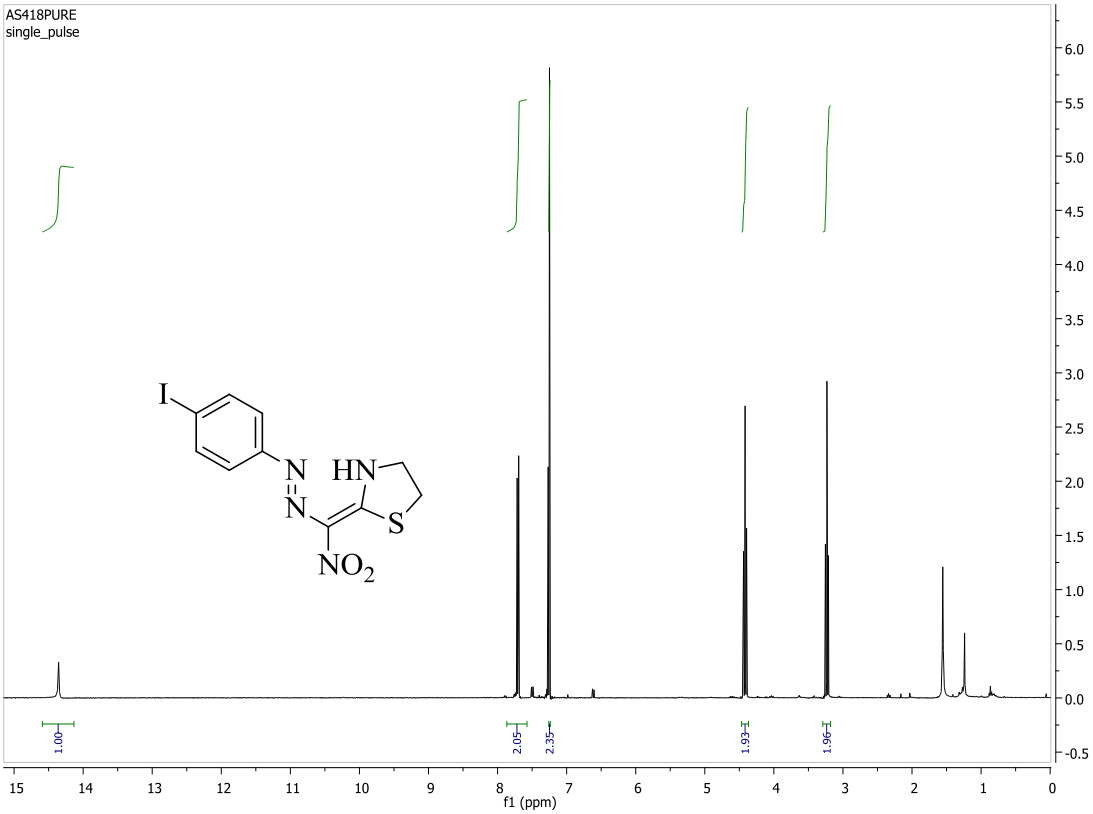


Figure 6.118 ^{1}H NMR spectrum of compound **262c** in $CDCl_3$

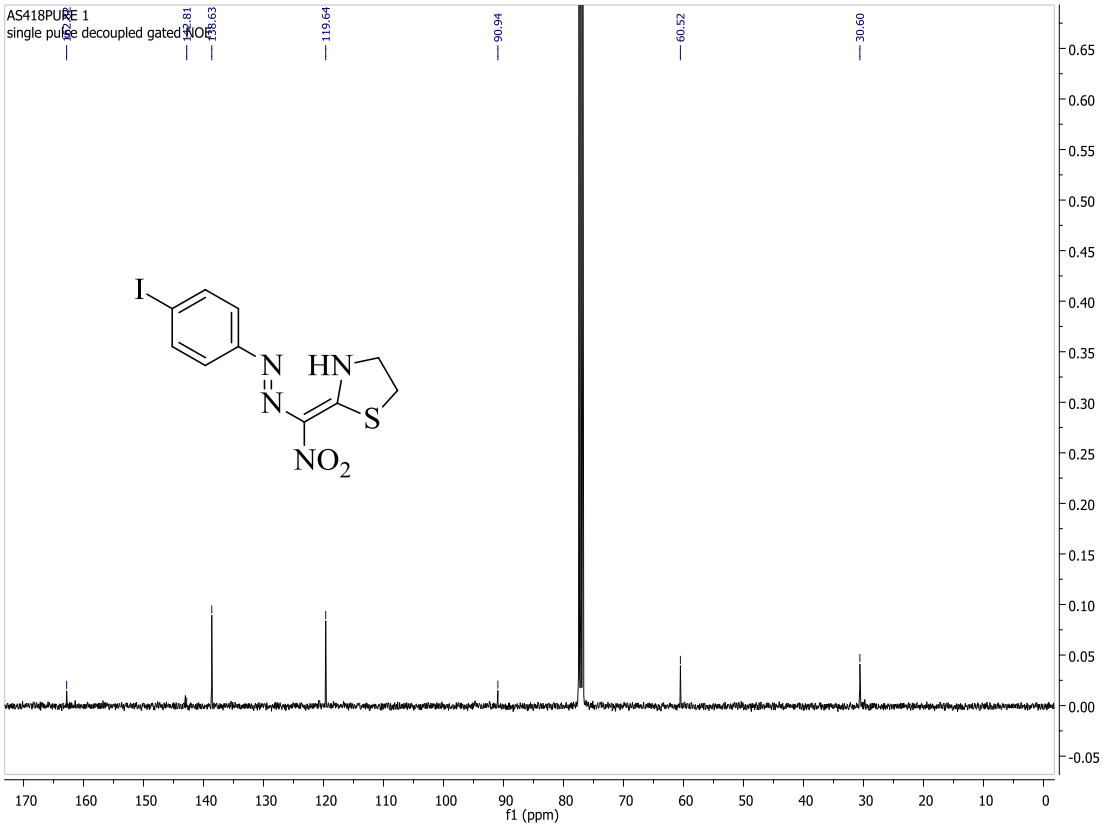


Figure 6.119 ^{13}C NMR spectrum of compound **262c** in $CDCl_3$

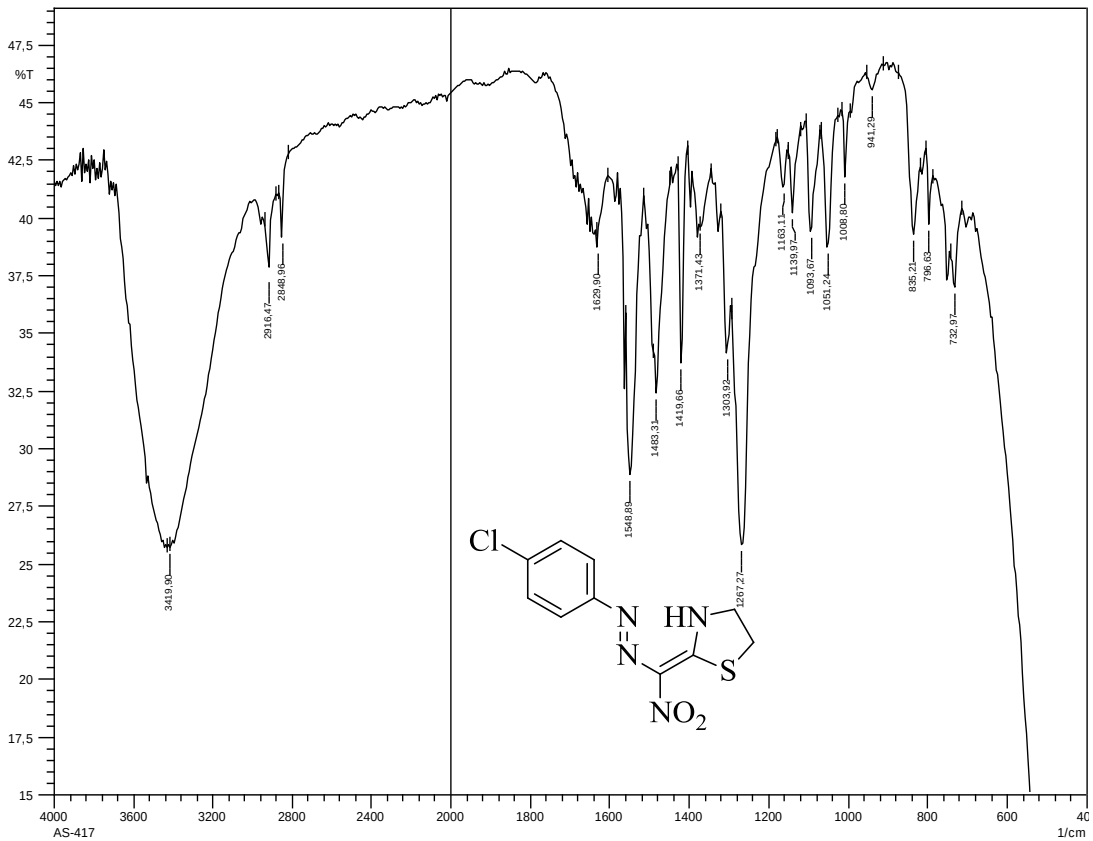


Figure 6.120 IR spectrum of compound **262d**

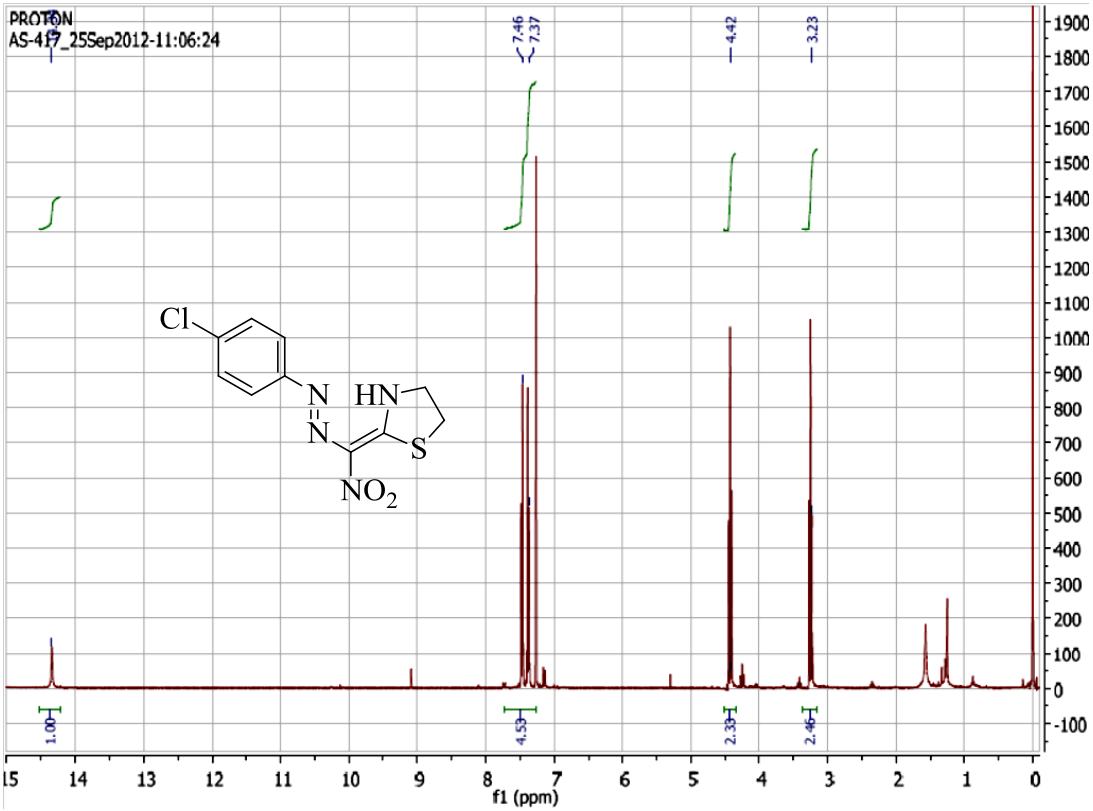


Figure 6.121 ^{1}H NMR spectrum of compound **262d** in $CDCl_3$

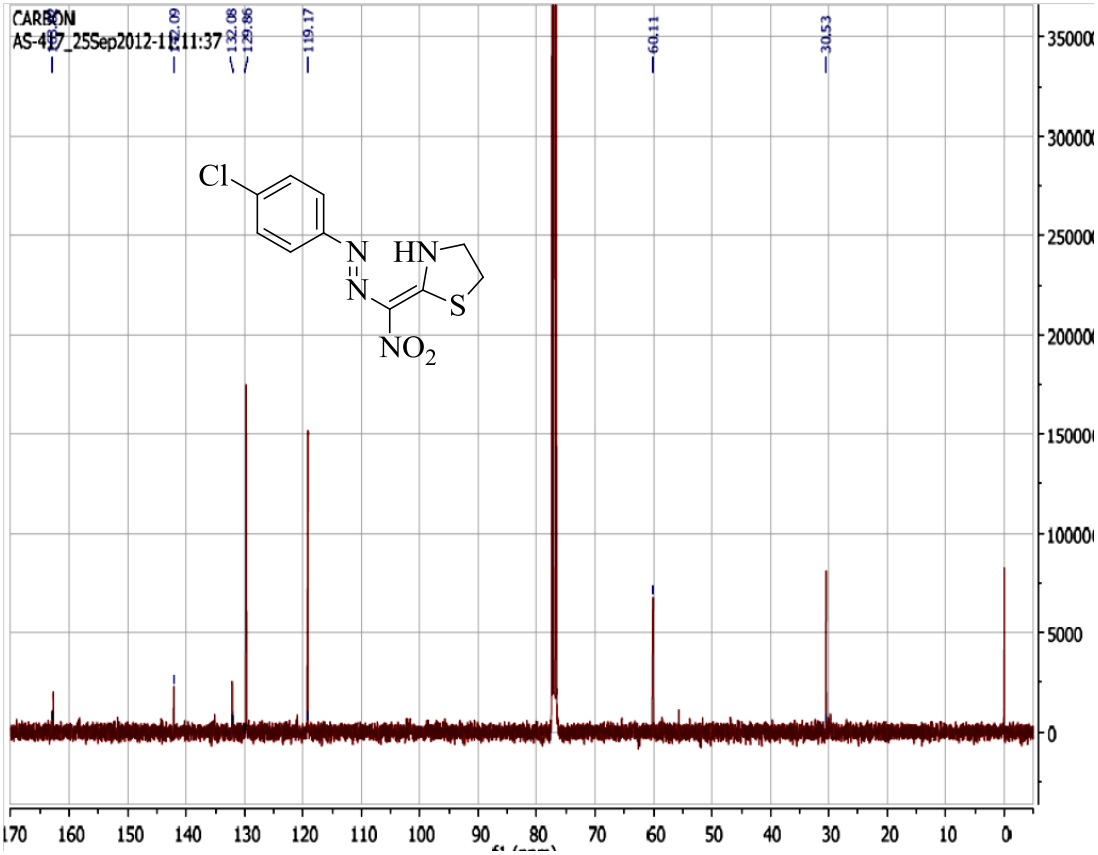


Figure 6.122 ^{13}C NMR spectrum of compound **262d** in $CDCl_3$

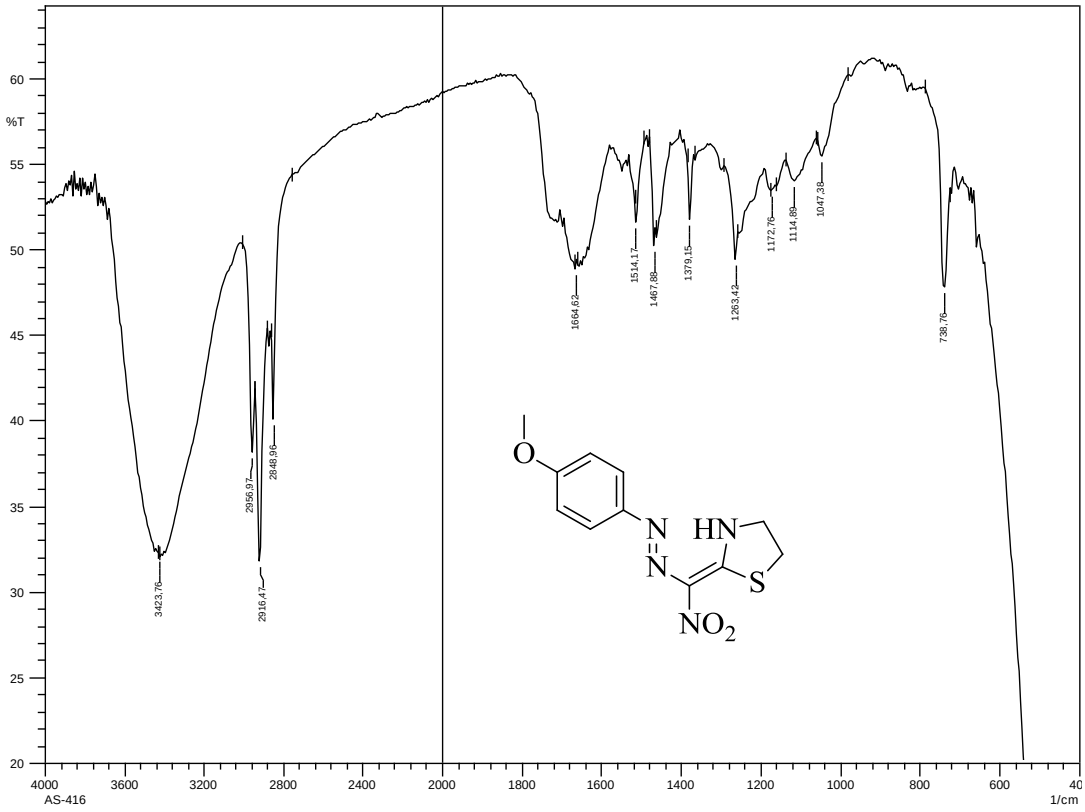


Figure 6.123 IR spectrum of compound **262e**

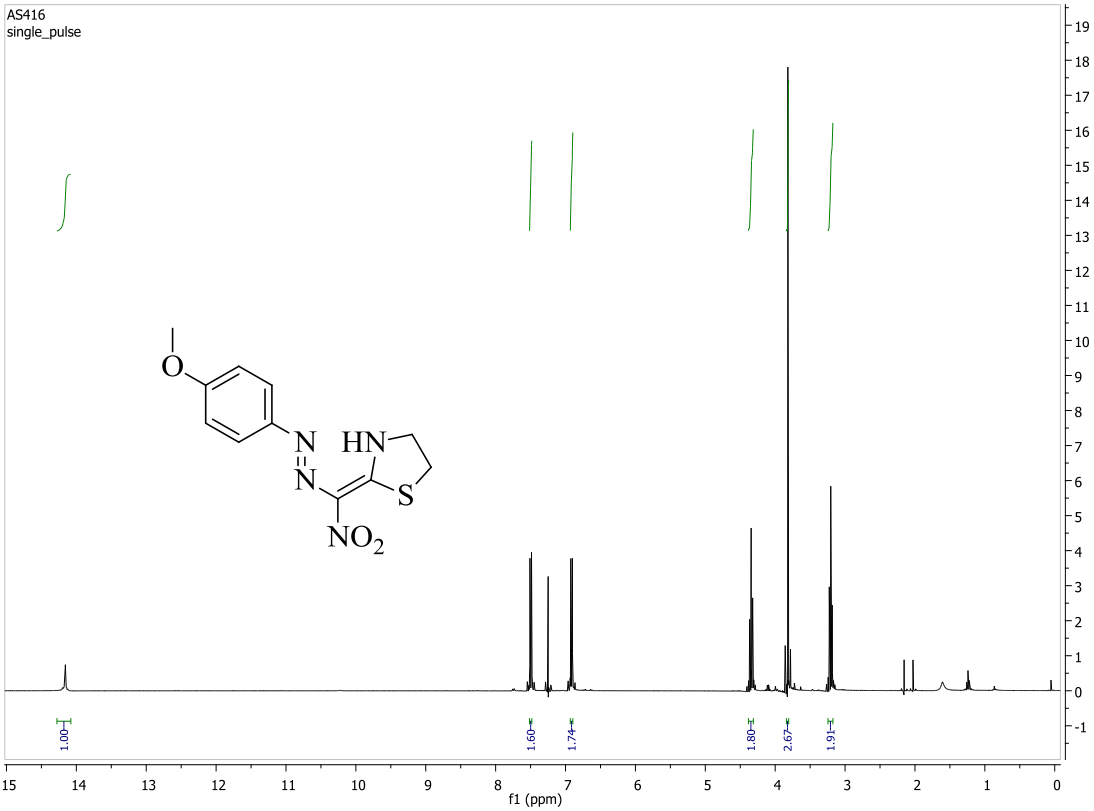


Figure 6.124 ^{1}H NMR spectrum of compound **262e** in $CDCl_3$

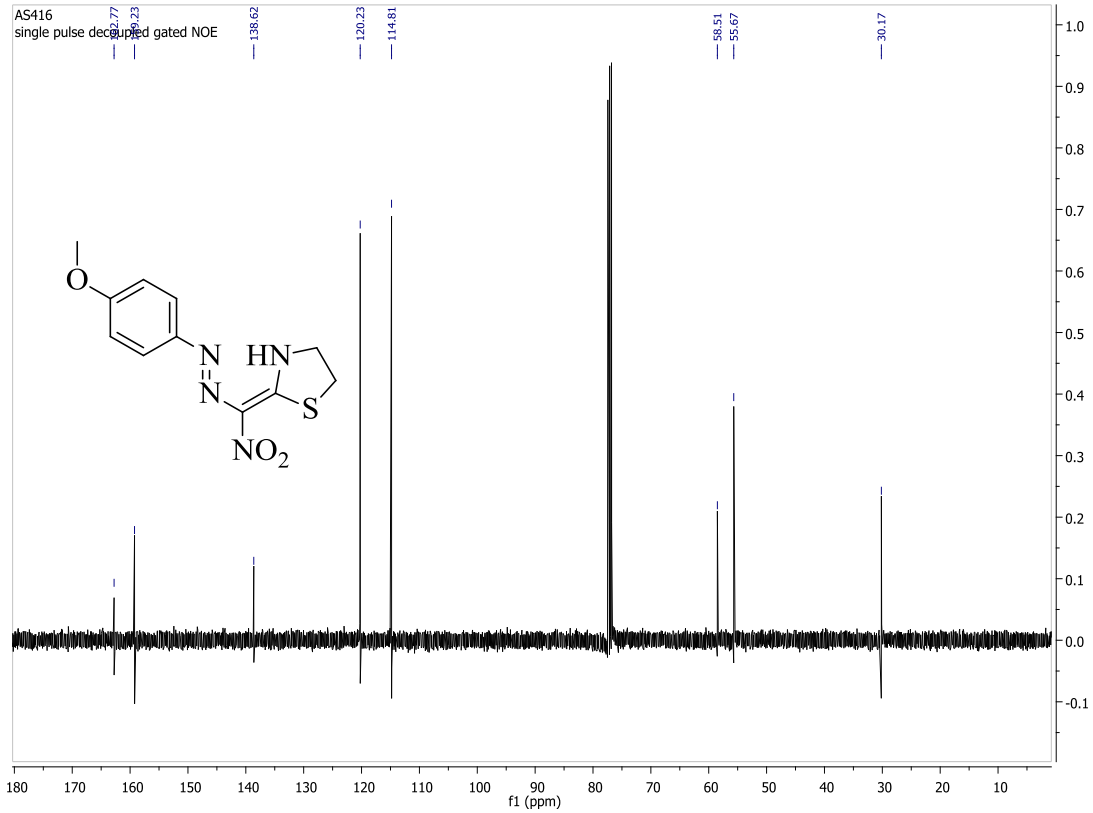


Figure 6.125 ^{13}C NMR spectrum of compound **262e** in $CDCl_3$

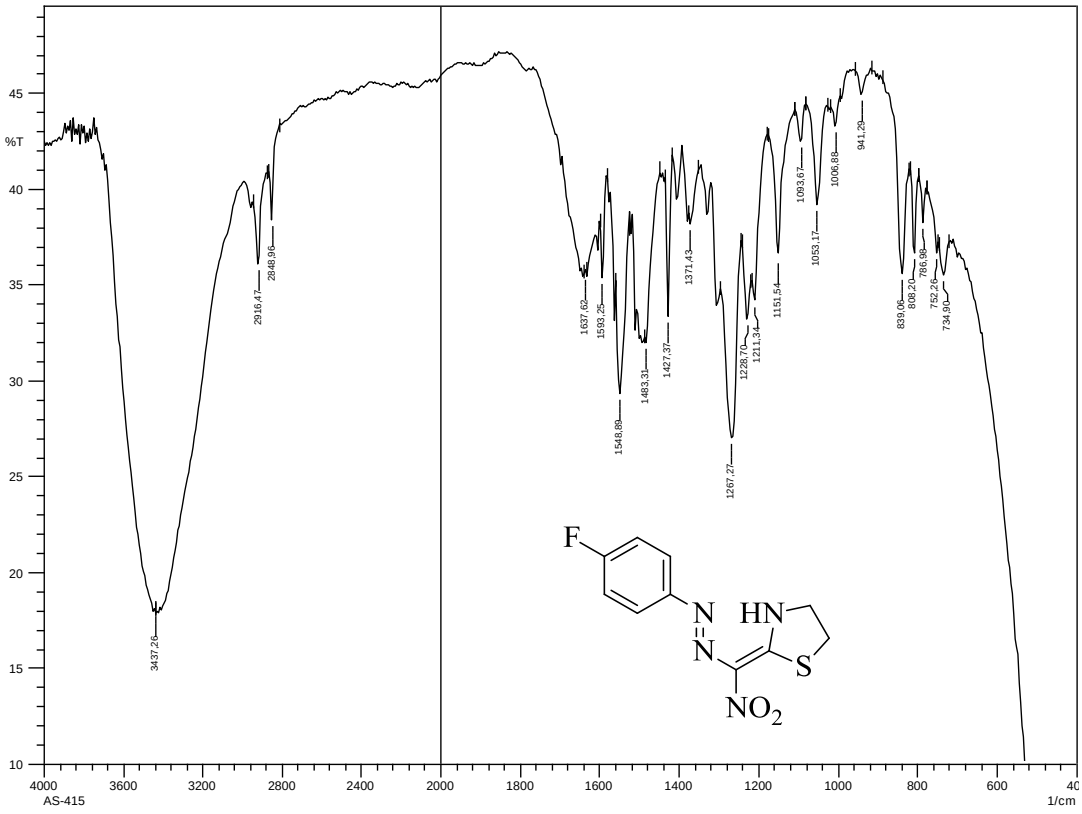


Figure 6.126 IR spectrum of compound **262f**

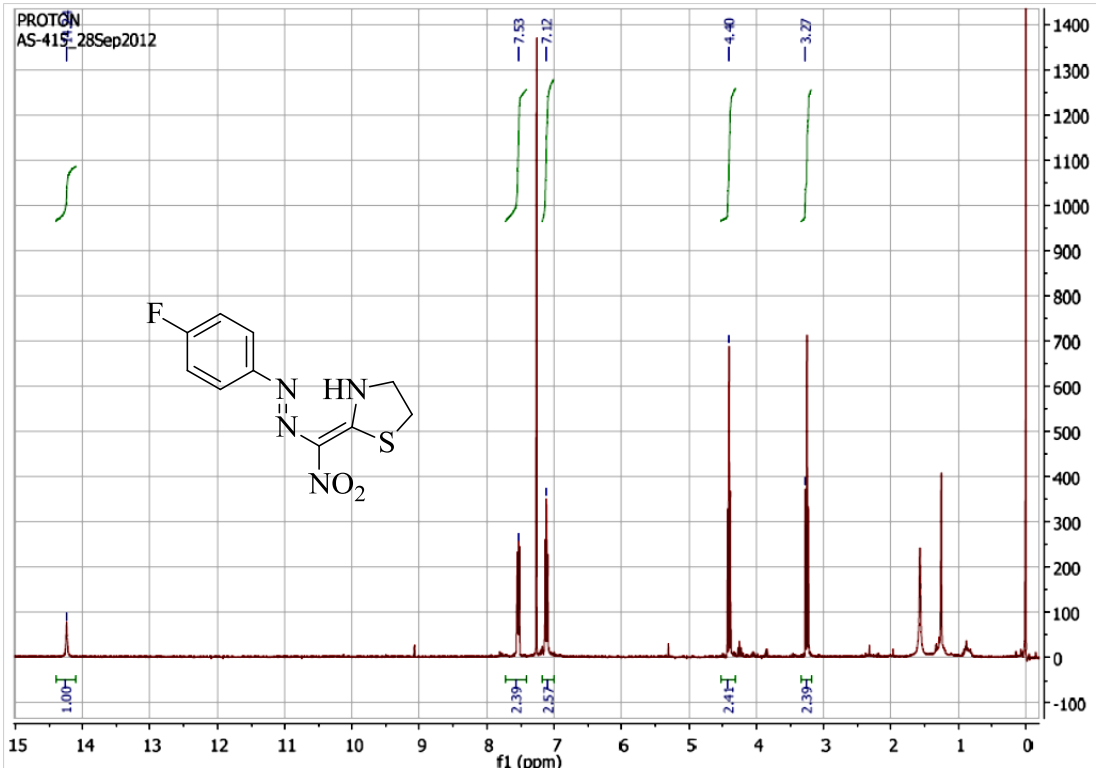


Figure 6.127 ^{1}H NMR spectrum of compound **262f** in $CDCl_3$

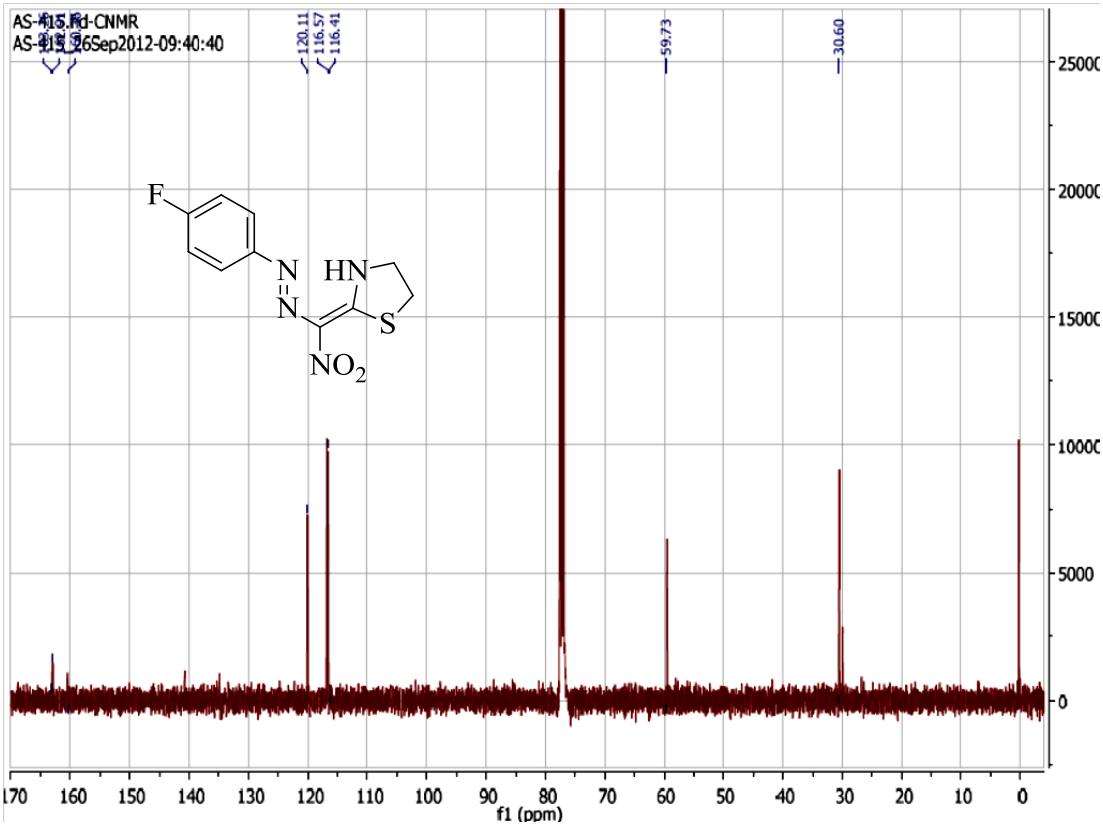


Figure 6.128 ^{13}C NMR spectrum of compound **262f** in $CDCl_3$

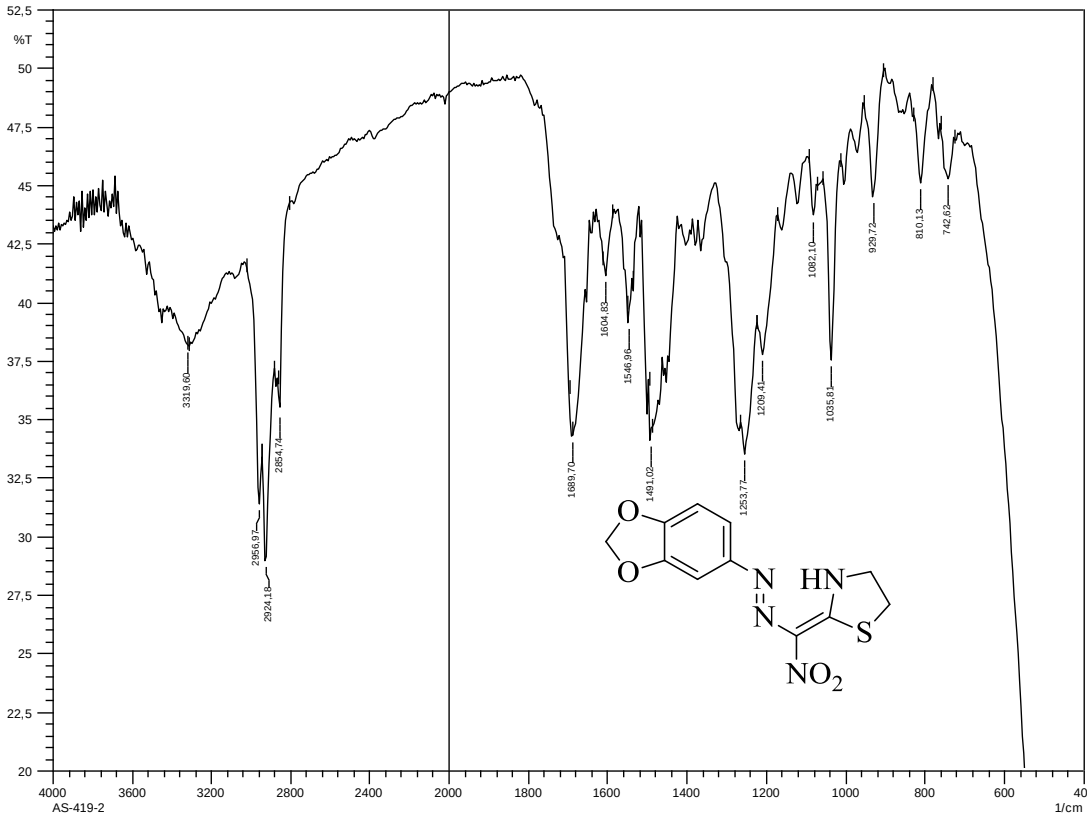


Figure 6.129 IR spectrum of compound **262g**

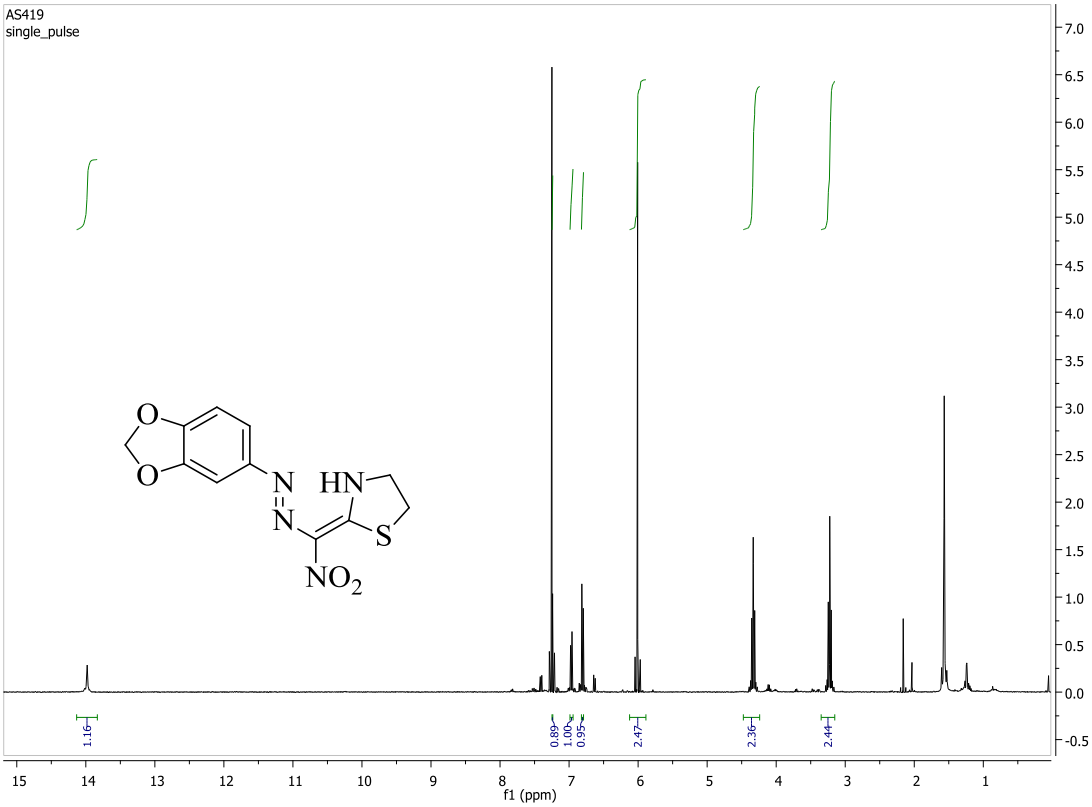


Figure 6.130 ^{1}H NMR spectrum of compound **262g** in $CDCl_3$

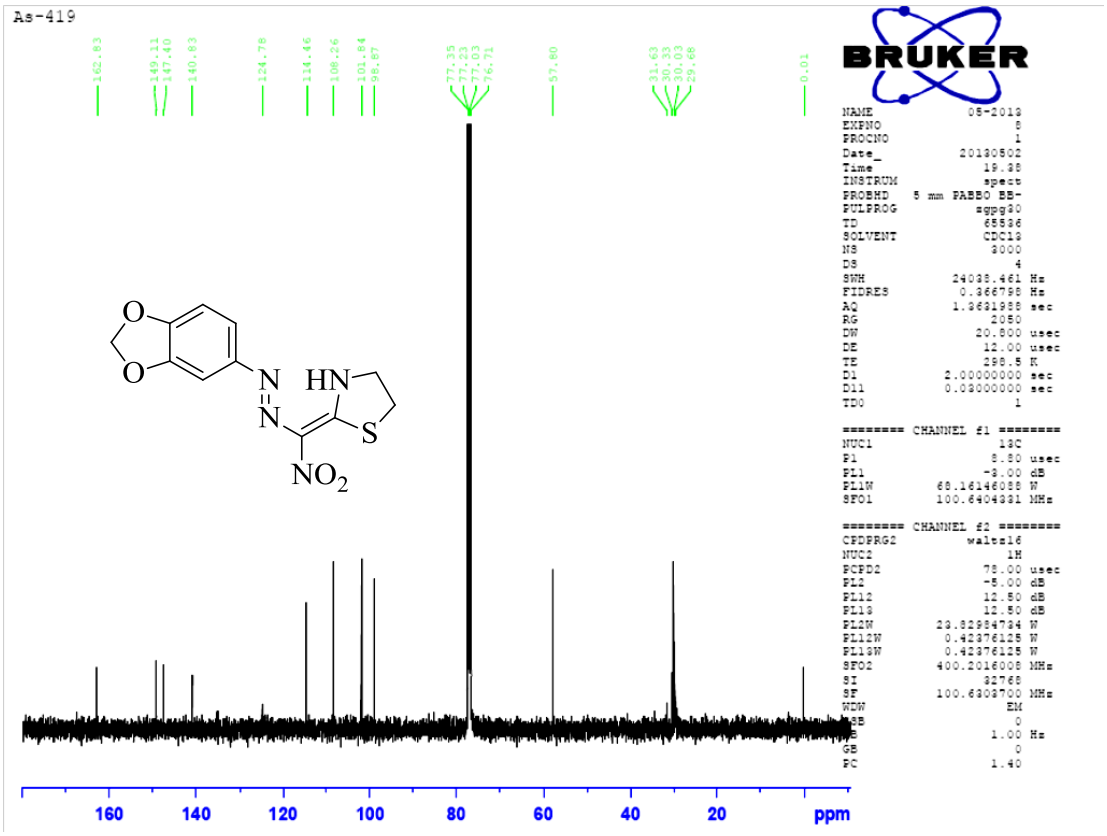


Figure 6.131 ^{13}C NMR spectrum of compound **262g** in $CDCl_3$

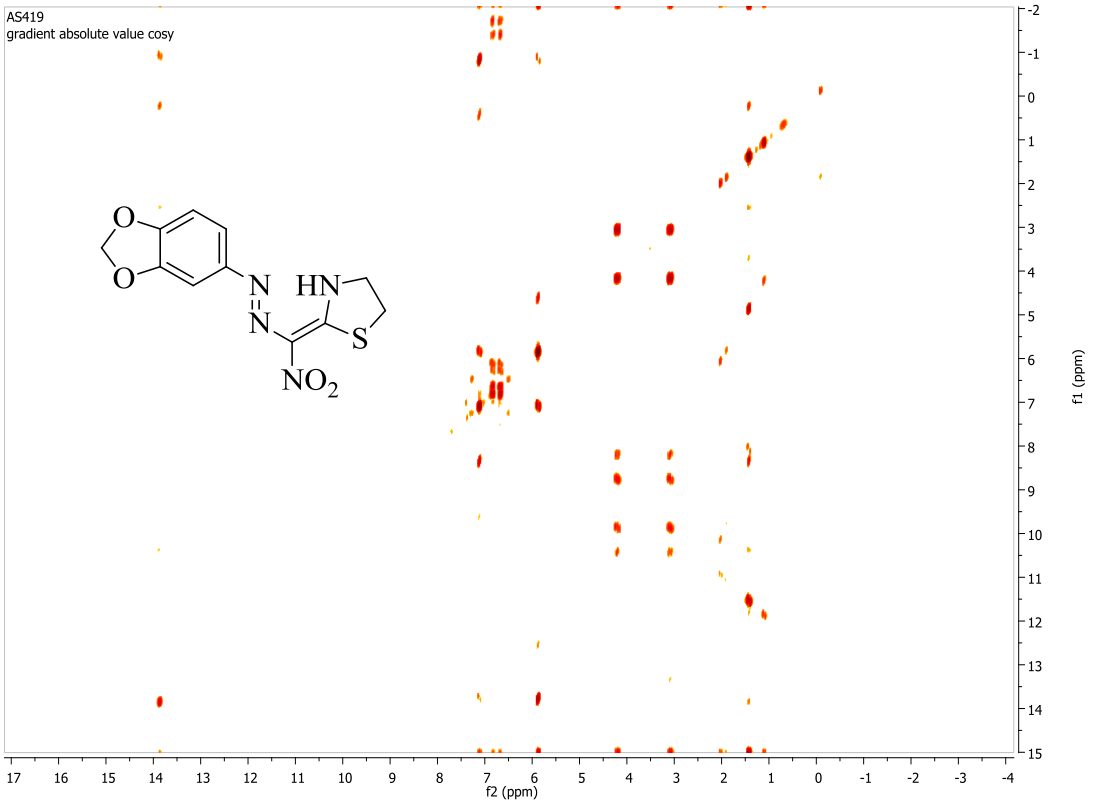


Figure 6.132 COSY spectrum of compound **262g** in $CDCl_3$

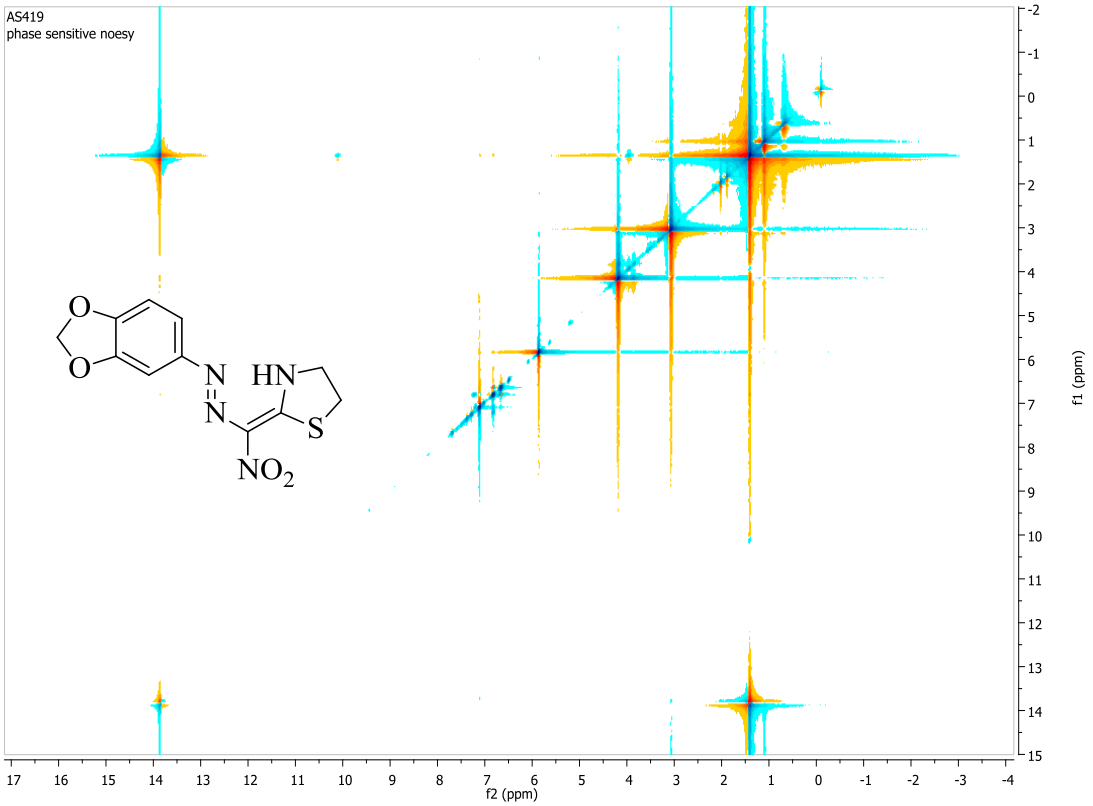


Figure 6.133 NOESY spectrum of compound **262g** in $CDCl_3$

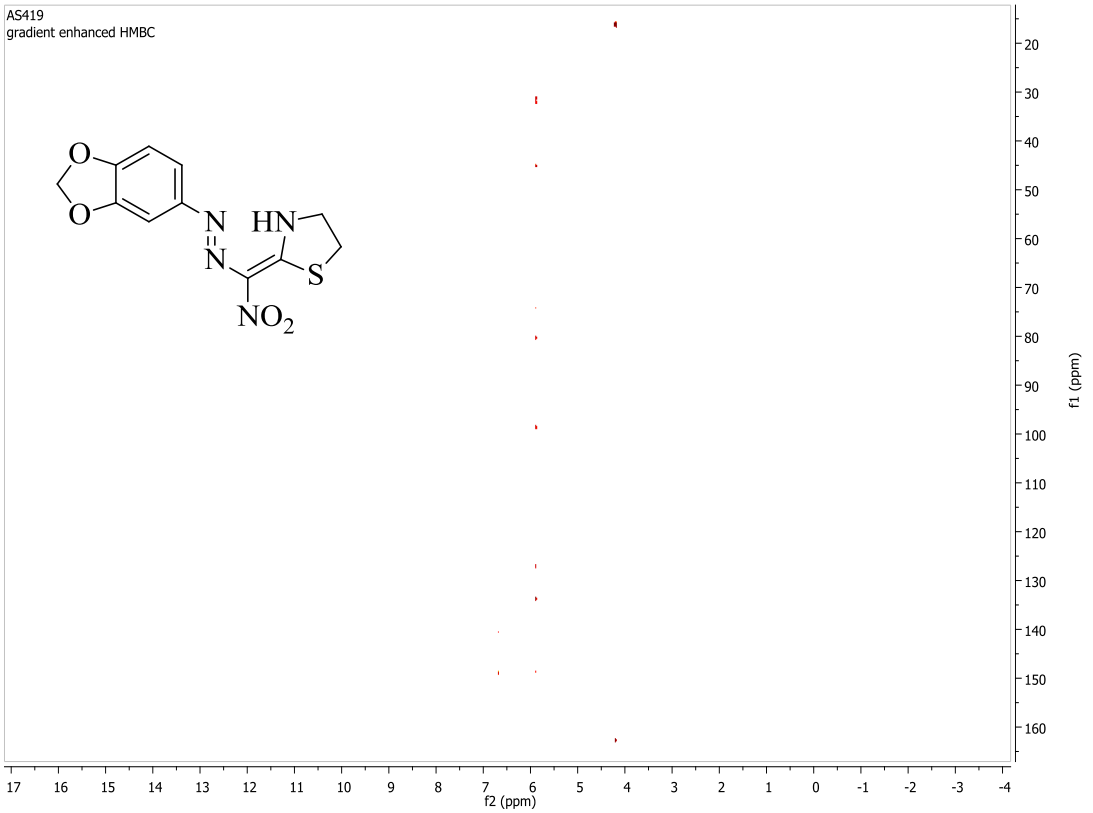


Figure 6.134 HMBC spectrum of compound **262g** in $CDCl_3$

7. CURRICULUM VITAE

Name SURNAME **:** Akın SAĞIRLI

Place and Date of Birth **:** ANKARA-07.07.1985

Universities

Bachelor's Degree **:** Abant İzzet Baysal University

MSc Degree (varsa) **:** Abant İzzet Baysal University

e-mail **:** akinsagirli@gmail.com

Address **:** Abant İzzet Baysal University

Science&Art Faculty

Gölköy Campus BOLU

List of Publications **:**

Dürüst Y, Sağırlı (2014) "A Microwave-Assisted Coupling Reaction of N-Aryl Sydnones with 2-Nitromethylenethiazolidine: Unexpected Formation of (Z)-2(Nitro((E)-p-substitutedphenyldiazenyl)methylene)thiazolidines", J.Org.Chem., 79: 6380-6384.

Dürüst Y, Sağırlı A, Kariuki BM, Knight DW (2014) "[1,3]-Dipolar cycloaddition of *N*-aryl sydnones to benzothiophene 1,1-dioxide, 1-cyclopropylprop-2-yn-1-ol and 1-(prop-2-ynyl)-1*H*-indole", Tetrahedron, 70: 6012-6019.

Dürüst Y, Sağırlı A, Kariuki BM, Knight DW (2013) "A practical isocyanide-based multicomponent synthesis of polysubstituted cyclopentenes", Tetrahedron, 69: 69-72.

DürüstY, SağırlıA, FronczekFR (2011) “Phenyl (3-(phenylsulfonyl)-1,2-dihydropyrrolo[1,2-*a*]quinoxalin-1-yl) methanone”, Acta Cryst. E., 67: 2859-2860.

Dürüst Y, Sağırlı A, Fronczek FR (2011) “Regioselective 1,3-Dipolar Cycloaddition of Phenanthrolinium *N*-Ylides to Substituted Arylidene Oxazolones”, Mol. Divers., 15: 799-808.