T.R.
BOLU ABANT İZZET BAYSAL UNIVERSITY

INSTITUTE OF GRADUATE STUDIES
Department of Chemistry

1,3-DIPOLAR CYCLOADDITION REACTIONS OF IMIDAZOLIUM N-YLIDE WITH ELECTRON DEFICIENT ALKENES CARRYING 1,2,4-OXADIAZOLE MOEITY

MASTER OF SCIENCE

VEYSİ İNAN

ACADEMIC SUPERVISOR
Assoc.Prof.Dr. AKIN SAĞIRLI

BOLU, HAZİRAN - 2023

APPROVAL OF THE THESIS

1,3-DIPOLAR CYCLOADDITION REACTIONS OF IMIDAZOLIUM N-YLIDE WITH ELECTRON DEFICIENT ALKENES CARRYING 1,2,4-OXADIAZOLE MOEITY submitted by **Veysi İNAN** and defended before the Examining Committe Members listed below in partial fulfillment of the requirements for the degree of **Master of Science** in **Department of Chemistry, Institute of Graduate Studies of Bolu Abant Izzet Baysal University in 19.06.2023** by

Examining Committee Members	**Signature**
Supervisor Assoc. Prof. Dr. Akın SAĞIRLI Abant İzzet Baysal University	.....
Member Prof. Dr. Cevher ALTUĞ Abant İzzet Baysal University	.....
Member Assoc. Prof. Dr. Ersin ORHAN Düzce University	.....

Prof. Dr. İbrahim KÜRTÜL

Director of Instıtute of Graduate Studies

ETHICAL DECLARATION

In this thesis dissertation that was properly prepared according to the Thesis Writing Rules of Bolu Abant İzzet Baysal University of the Institute of Graduates Studies, I hereby declare that;

- All data, information, and documents presented in the thesis were obtained in accordance with the academic and ethical rules,
- All data, documents, assessments, and results were presented in accordance with the scientific ethical and moral rules,
- All works that were benefitted in the thesis were appropriately cited,
- No alteration was made in the data used,
- Study presented in this thesis is original,

Otherwise, I declare that I accept the loss of all my rights in case any contradiction that may arise against me.

Based on the plagiarism report that was generated on the date of 11/07/2023 by using predetermined filtrations set by Directorate of Institute of Graduate Studies of the Turnitin programme, a plagiarism detection sofware, the similarity index detected was 22%.

_____

Veysi İNAN

ABSTRACT

1,3-DIPOLAR CYCLOADDITION REACTIONS OF IMIDAZOLIUM N-YLIDE WITH ELECTRON DEFICIENT ALKENES CARRYING 1,2,4-OXADIAZOLE MOEITY
MSC THESIS
VEYSİ İNAN
BOLU ABANT IZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY
(SUPERVISOR: ASSOC. PROF. DR. AKIN SAĞIRLI)

BOLU, JUNE 2023
XV + 74

The 1,3-dipolar cycloaddition is one of the most utilized reactions between dipoles and dipolarophiles for the formation of five-membered heterocycles. There have been various examples of these heterocycles in the literature; however, nitrogen-containing ones are of great interest. In consideration of nitrogen-based heterocycles, pyrrole [1,2-*a*] imidazoles have drawn our attention due to not only their diverse biological activity but also being a part of many naturally occurring products. On the other hand, 1,2,4-oxadiazoles are of great importance among the five-membered heterocycles bearing an N-O atom. They have many applications, especially in the field of pharmacology, exhibiting remarkable biological activity. Therefore, in order to construct new pyrrole [1,2-*a*] imidazoles containing a 1,2,4-oxadiazole ring, 1,3-dipolar cycloaddition of imidazolinium N-ylide with p-substituted phenyl vinyl oxadiazoles has been investigated throughout this MSc dissertation study.

The outcomes of the study were discussed in three parts. In the first part, imidazolium N-ylide was synthesized via the reaction of 2-bromoacetophenone and 1-vinylimidazole in one step without any purification and characterized. Secondly, as a dipolarophilic reagent, 3-substituted phenyl-5-vinyl-1,2,4-oxadiazoles were obtained by reacting p-substituted benzamidoxime with acryloyl chloride according to a reliable literature method.

In the last part, the 1,3-dipolar cycloaddition reaction of imidazolium *N*-ylide with *p*-substituted phenyl-5-vinyl-1,2,4-oxadiazole derivatives unexpectedly gave rise to 7 new pyrrole[1,2-*a*] imidazole by the extrusion of ethene gas. The plausible mechanism was proposed for the formation of cycloaddition products. The structure of the products was identified based on data obtained from IR, ^{1}H NMR, ^{13}C NMR, and LC-MS measurements.

KEYWORDS: 1,3-Dipolar cycloaddition, *N*-vinyl imidazolium y, 1,2,4-oxadiazole

ÖZET

1,2,4 OKSADİAZOL PARÇASI TAŞIYAN ELEKTRONCA YOKSUN ALKENLERLE İMİDAZOLYUM N-İLİD' İN 1,3 DİPOLAR SİKLO KATILMA REAKSİYONLARI
YÜKSEK LİSANS TEZİ
VEYSİ İNAN
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ
KİMYA ANABİLİM DALI
ORGANİK KİMYA BİLİM DALI
(TEZ DANIŞMANI: DOÇ. DR. AKIN SAĞIRLI)

BOLU, HAZİRAN – 2023
XV+ 74

1,3-dipolar siklokatılma, beş üyeli heterosikllerin oluşumu için dipoller ve dipolarofiller arasında en çok kullanılan reaksiyonlardan biridir. Literatürde bu heterosikllerin çeşitli örnekleri bulunmaktadır; ancak azot içerenler büyük ilgi görmektedir. Azot bazlı heterosikller göz önüne alındığında, pirol[1,2-a]imidazoller hem çeşitli biyolojik aktiviteleri hem de doğal olarak oluşan birçok ürünün bir parçası olmaları nedeniyle dikkatimizi çekmiştir. Öte yandan, 1,2,4-oksadiazoller bir N-O atomu taşıyan beş üyeli heterosiklikler arasında büyük öneme sahiptir. Özellikle farmakoloji alanında dikkate değer biyolojik aktivite sergileyerek birçok uygulamaya sahiptirler. Bu nedenle, 1,2,4-oksadiazol halkası içeren yeni pirol[1,2-*a*]imidazoller oluşturmak amacıyla, bu yüksek lisans tez çalışması boyunca imidazolinyum *N*-ilid ile *p*-sübstitüe fenil vinil oksadiazollerin 1,3-dipolar siklokatılması araştırılmıştır.

Çalışmanın sonuçları üç bölümde tartışılmıştır. İlk bölümde, 2-bromoasetofenon ve 1-vinil imidazolün tek adımda gerçekleştirilen tepkimesiyle herhangi bir saflaştırma yapılmadan imidazolyum *N*-ilid sentezlenmiş ve karakterize edilmiştir. İkinci olarak, dipolarofilik bir reaktif olarak, 3-sübstitüe fenil-5-vinil-1,2,4-oksadiazoller, *p*-sübstitüe benzamidoksimin akriloil klorür ile güvenilir bir literatür yöntemine göre reaksiyona sokulmasıyla elde edilmiştir.

Son bölümde, imidazolyum *N*-ilid ile *p*-sübstitüe fenil-5-vinil-1,2,4-oksadiazol türevlerinin 1,3-dipolar siklokatılma reaksiyonu beklenmedik bir şekilde eten gazının ekstrüzyonu ile 7 yeni pirol[1,2-*a*]imidazole yol açmıştır. Siklokatılma ürünlerinin oluşumu için makul bir mekanizma önerilmiştir. Ürünlerin yapısı IR, ^{1}H NMR, ^{13}C NMR ve LC-MS ölçümlerinden elde edilen verilere dayanarak aydınlatılmıştır.

ANAHTAR KELİMELER: 1,3-Dipolar Siklo katılma, *N*-vinil imidazolyum , 1,2,4-oksadiazol

TABLE OF CONTENTS

Page

LIST OF FIGURES

Page

LIST OF TABLE

Page

LIST OF SCHEME

Page

LIST OF ABBREVIATIONS AND SYMBOLS

1,3-DC **:** 1,3-Dipolar

Ac **:** Acetyl

HOMO **:** Highest occupied molecular orbital

LUMO **:** Lowest unoccupied molecular orbital

R_f **:** Retention Factor

Mw **:** Microwave

NHCs **:** N-heterocyclic carbenes

TLC **:** Thin Layer Chromatography

NMR **:** Nuclear Magnetic Resonance

DCM **:** Dichloromethane

IR **:** Infrared

DBU : Diisobutylundecane

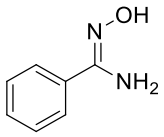
ACKNOWLEDGEMENTS

I owe a huge debt of gratitude to my supervisor, Assoc. Prof. Dr. Akn Sağırlı, for all of his advice, supervision, and suggestions over the course of this Msc study.

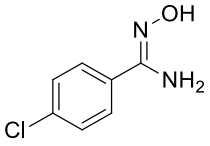
I also thank to and Prof. Dr. Cevher ALTUĞ for his supports, intimacy and his discussions throughout my Msc thesis.

I would like to convey my sincere gratitude to my wife, who just being in my life and offers me a great delight. Without her love and support, I would not have been able to complete my master thesis. A special gratitude goes out to my cute son Burak Asaf, who is the joy of my life. They have been my greatest supporters, teachers, and friends throughout my life, not only during this study but also in my life.

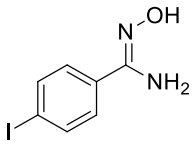
FORMULAE



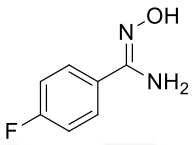
93a



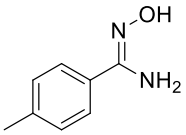
93b



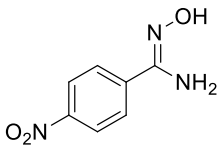
93c



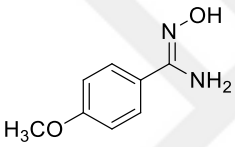
93d



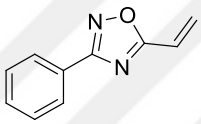
93e



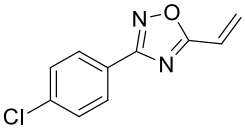
93f



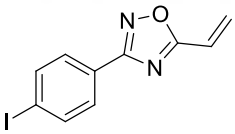
93g



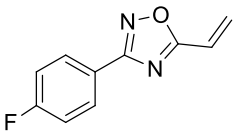
96a



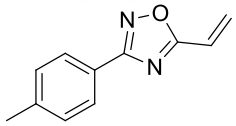
96b



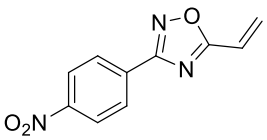
96c



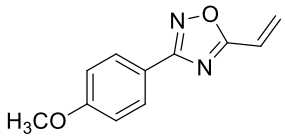
96d



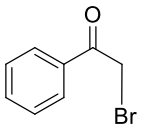
96e



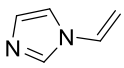
96f



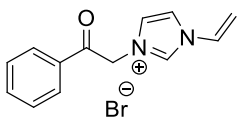
96g



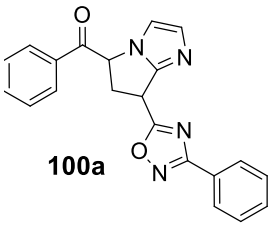
97



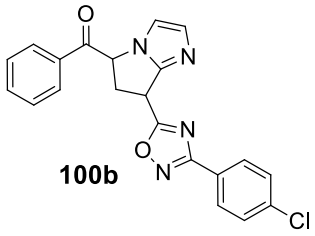
98



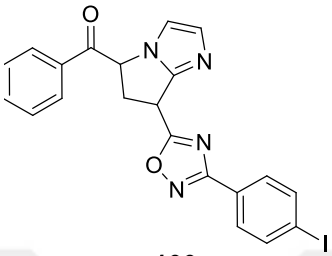
99



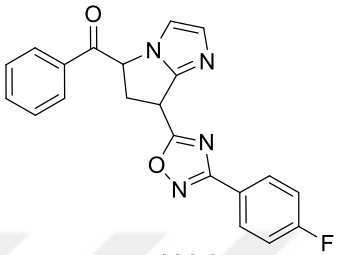
100a



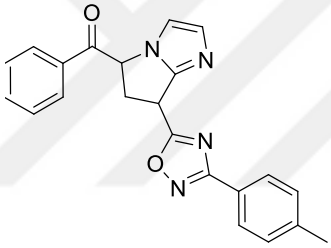
100b



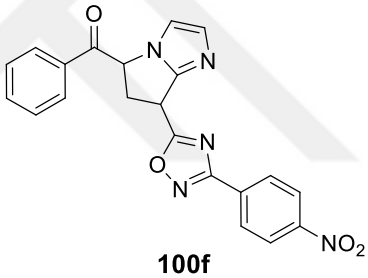
100c



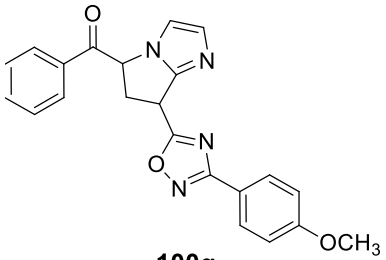
100d



100e



100f

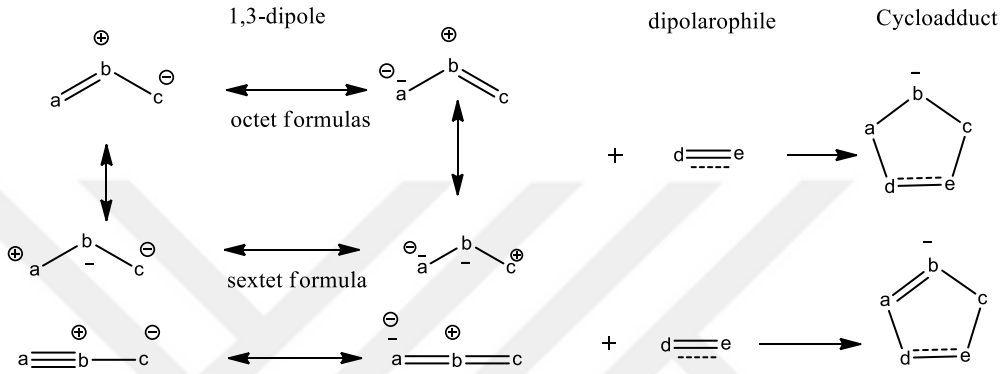


100g

1. INTRODUCTION

1.1 1,3-Dipolar Cycloaddition Reaction

1,3-Dipolar cycloaddition reactions have been widely utilized synthetic protocol to construct five-membered heterocyclic rings. The [3+2] cycloaddition reaction basically covers the raction of $4\pi e^-$ zwitterionic system (1,3-dipole), a-b-c, and $2\pi e^-$ neutral system (dipolarophile), d-e, leading to five-membered rings (Scheme 1.1) (Huisgen, 1963a; Huisgen, 1963b and Padwa, 1984).



Scheme 1.1. Cycloaddition of 1,3-dipoles "abc" and dipolarophiles "de" results in five-membered heterocyclic compounds.

1.1.1 1,3-Dipoles (Ylides)

The 1,3-dipole is a zwitterionic a-b-c system containing 4πe- in three parallel atomic p-orbitals. While the central atom b has a formal positive charge, negative charge distributed over the two atoms a and c. Huisgen and his colleagues subdivided into two comprehensive classes, the propargyl-allenyl type (linear) and the allyl-type (bent) (Figure 1.1) (Martin and Hans, 2020).

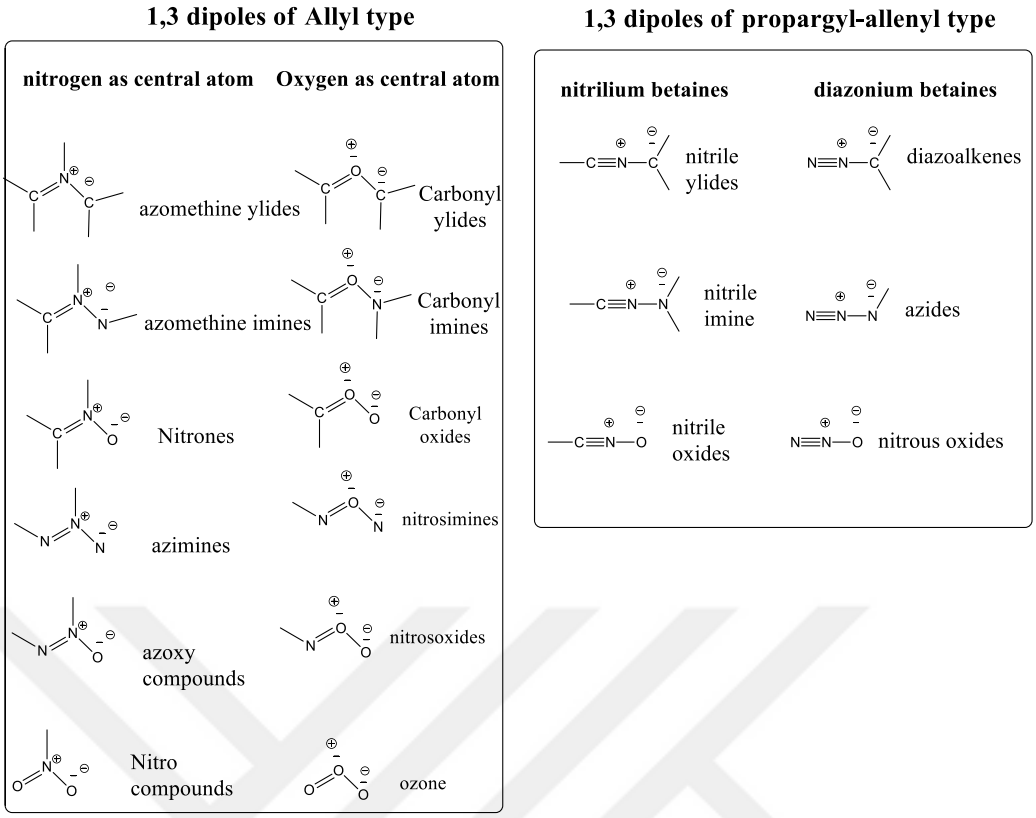


Figure 1.1. 1,3-dipole types.

1.1.2 Dipolarophiles

The term "dipolarophile" refers to any class of 2π-electrons that can react with a 1,3-dipole. Dipolarophiles are divided into three distinct categories: electron-rich, electron-poor, and conjugated. Alkenes, *α*-*β*-unsaturated aldehydes, ketones, esters, allylic alcohols, allylic halides, and vinylic ethers are dipolarophiles that readily react with various 1,3-dipoles (Figure 1.2) (Houk *et al.*, 1973).

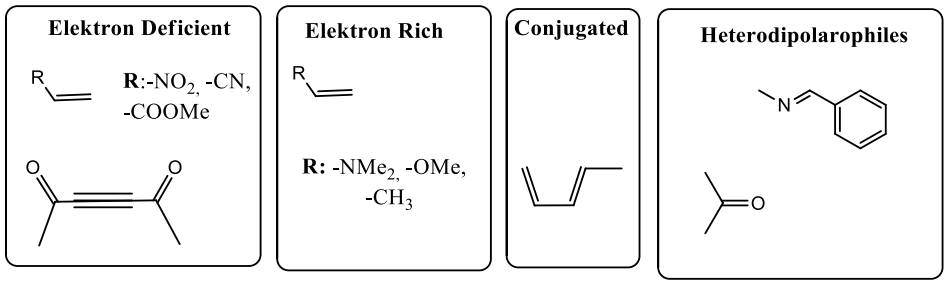
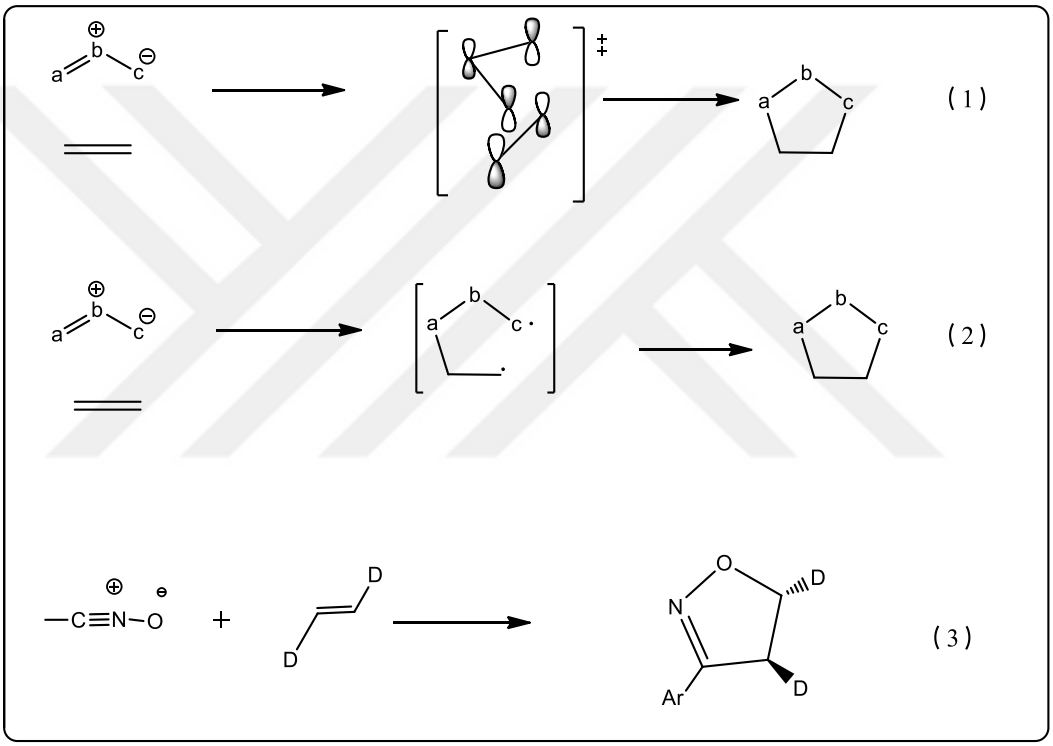


Figure 1.2. Examples for dipolarophiles.

1.1.3 1,3 Dipolar Cycloaddition Reaction Mechanism

Chemists have spent particular attention to the concept of 1,3-dipolar cycloaddition and its mechanism. Several reaction mechanisms have been put

forward for 1,3- dipolar cycloadditions (Huisgen, 1963b, Huisgen, 1968, Huisgen, 1976). According to the Woodward-Hoffmann rules, if the reaction of 1,3 dipoles with dipolarophiles proceeds via a concerted mechanism, the description [4s + 2s] is thermally allowed (Woodward and Hoffmann, 1969). For instance, Huisgen's primary mechanism proposes that all bonds are formed simultaneously. (Scheme1.2 eq 1). Firestone mentioned how the cycloadduct is formed via a singlet diradical intermediate (Scheme1.2 eq 2). The 180^{o} rotation of the terminal bond permitted by diradical intermediates resulted in a mixture of the cis and trans isomers of cycloadducts (Huisgen, 1963 and 1984).



Scheme 1.2. The 1,3-DC reactions (1) Concerted (2) single radical mechanism (3) benzonitrile oxide with transdideuterated ethylene produced exclusively transisoxazoline.

The transition state of the concerted 1,3-DC reactions is controlled by frontier molecular orbital (FMO) interaction. Sustmann has categorized 1,3-DC reactions into three types, Type I is the dipolarophiles with electron withdrawing groups; the $HOMO_{dipole}$ and $LUMO_{dipolarophile}$. Type II is given by the interaction between the $LUMO_{dipole}$ – $HOMO_{dipolarophile}$. The HOMO and LUMO energies of the dipole/dipolarophile pair is the Type III (Figure 1,3) (Sustmann,1974, Houk *et al.*, 1973).

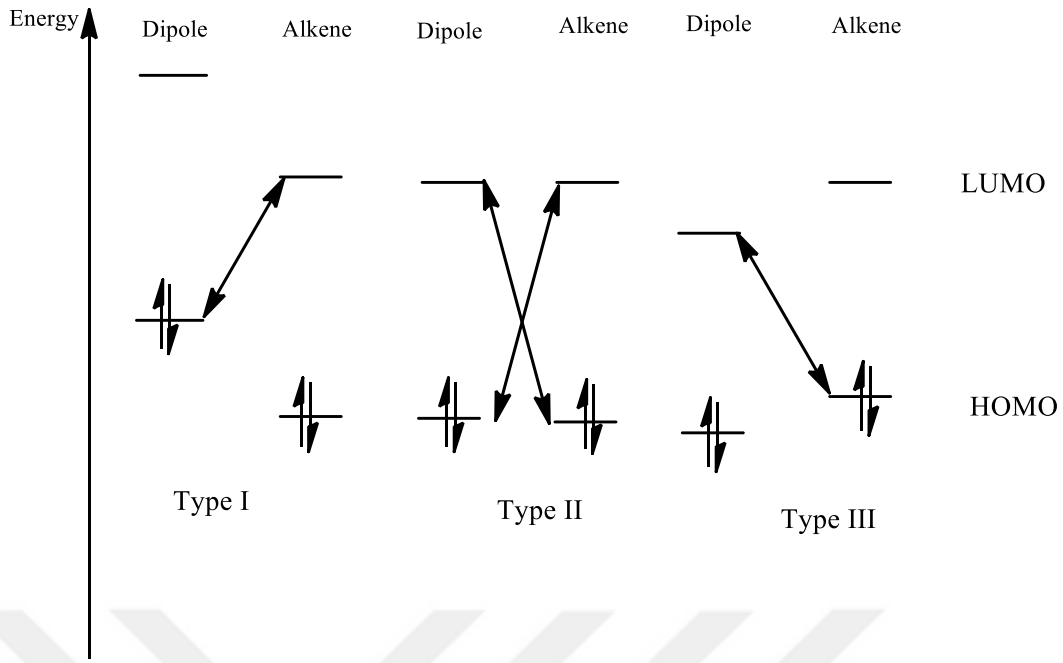


Figure 1.3. The classification of 1,3-DC reactions on the basis of the FMOs.

1.2 Introduction and Background of Ylide

Staudinger invented the expression "ylide" to describe a class of compounds in which a carbanion is immediately bonded to a heteroatom (typically phosphorus, sulfur, or nitrogen) carrying a positive charge (Figure 1.4) (Staudinger and Meyer, 1919, Petrovanu and Zugravescu, 1976 and Pidylpnyi *et al*. 2014).

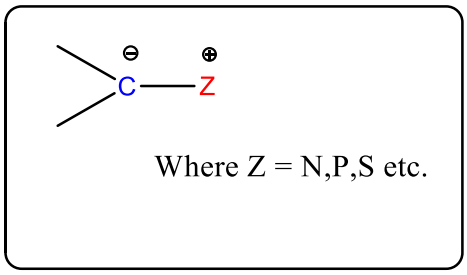


Figure 1.4. General representation of ylide.

There are numerous types of ylides that have been identified in the literature, but the most common are phosphorus ylides, sulfur ylides, and nitrogen ylides (Figure 1.5).

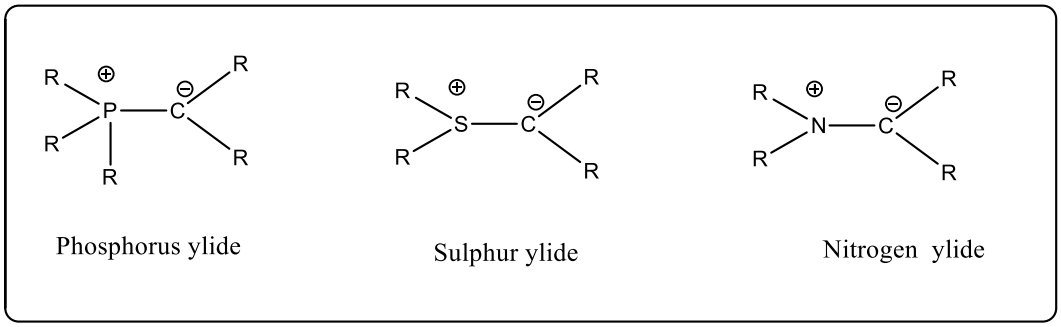


Figure 1.5. Common types of ylides.

These ylides are commonly studied in organic chemistry as reagents in the olefination, cyclization and rearrangement reactions or reactive intermediates in many transformations. Although sulfur and phosphorus ylides are commonly used intermediates in reactions, nitrogen based ylides has attracted considerable attention in point of no stabilization by d-orbital carbanion delocalization also the basicity trends. The generic structure of nitrogen based ylides **a**, **b** is exemplified in Figure 1.6 which play crucial role in 1,3 dipolar cycloaddition reaction as dipole (Philips and Ratts,1970, Jiyang and Chen,2014 and Pidylpnyi *et al*. 2014).

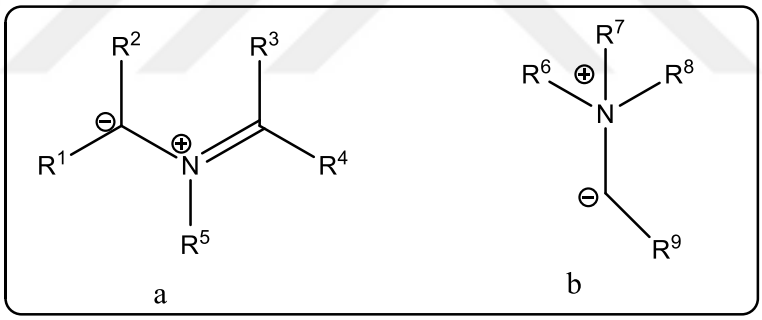


Figure 1.6. Structures of *N*-ylides a, b.

On the basis of our interest in *N*-type ylides, especially azomethine, we will provide an overview of the N(sp^2)-based ylides which are represented in Figure 1.7.

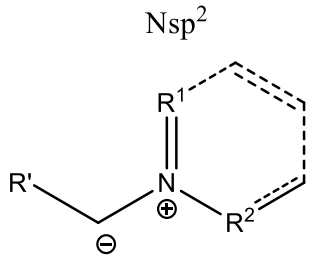


Figure 1.7. Nsp^2 type ylides.

1.2.1 Azomethine Ylide

Azomethine ylide has four electrons spread across a C-N-C unit, which can be represented by the two most common zwitterionic resonance forms, as shown in the figure 1.8. The represented structure of azomethine ylide is the one, negative charge spread over two carbon atoms and positive charge accomodated on the nitrogen. Furthermore, the representative 1,3-dipole and its resonance structures are shown in Figure 1.8 with the the positive and the negative charges. The most popular resonance model in these structure is the octet structure with the central N atom being positively charged and the two terminal carbon atoms receiving the negative charge (Huisgen,1984).

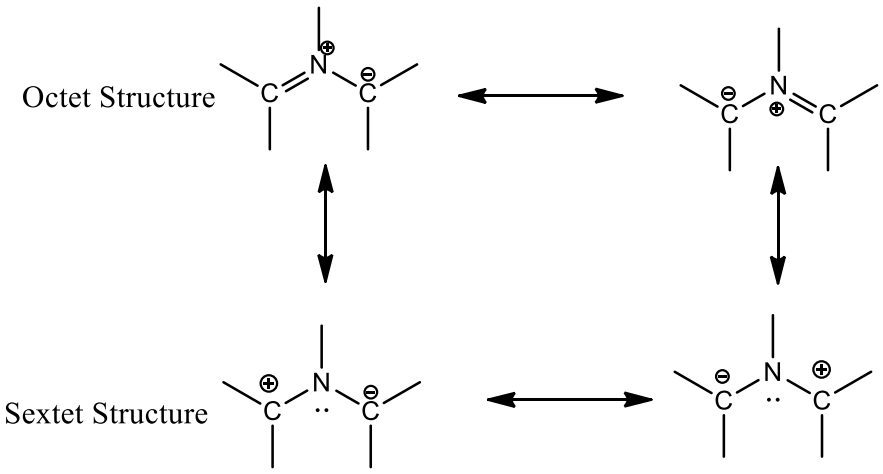
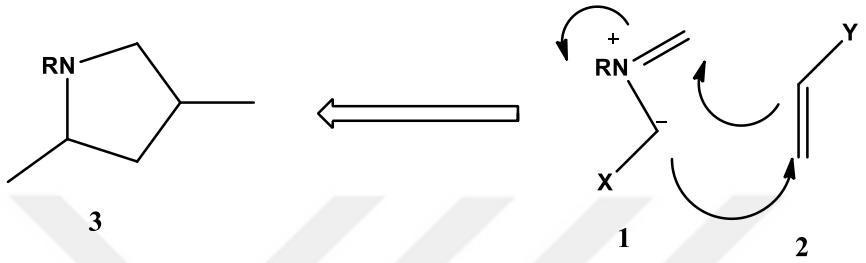


Figure 1.8. Four zwitterionic resonance forms.

Five-membered cyclic amines, such as pyrrolidines, dihydropyrroles, and pyrroles can be prepared by 1,3-dipolar cycloaddition of azomethine ylides with alkenes or alkynes has been widely studied (Grigg,1987, Tsuge, 1989,

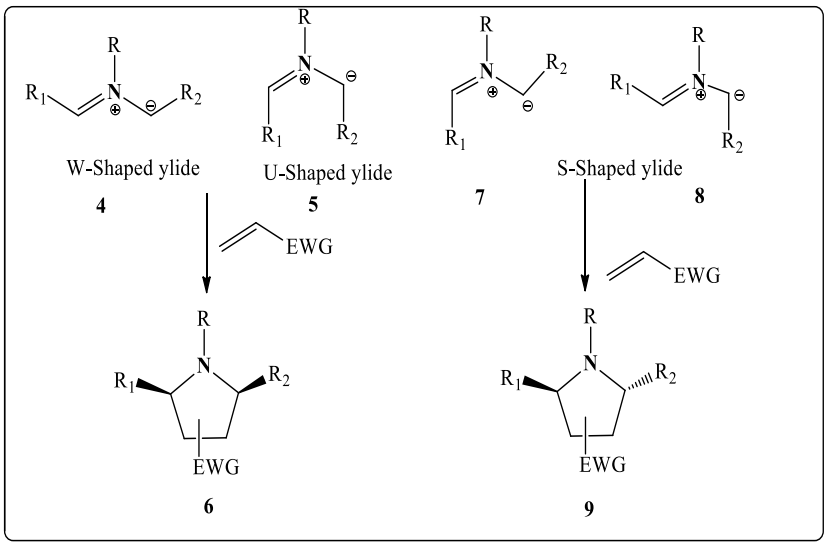
Kanemasaand Tsuge, 1993, Grigg and Siridharan, 1993 and Najera and Sansano 2003). 1,3 dipolar cycloaddition of azomethine ylide with dipolarophiles involves a total of six π electrons [π4s + π2s] according to the principles of the Woodward-Hoffmann (Woodward and Hoffmann, 1970, Houg and Yamaguchi, 1984). In this regard, the cycloaddition reaction of azomethine ylides **1** with alkenes **2** is a useful way for the formation of pyrrolidines **3** in one step (Pandey *et al*., 2006, Jones *et al*., 2011) (Scheme 1.3).



Scheme 1.3. Generation pyrrolidines via 1,3-Dipolar cycloaddition of azomethine ylides (X, Y usually electron-withdrawing).

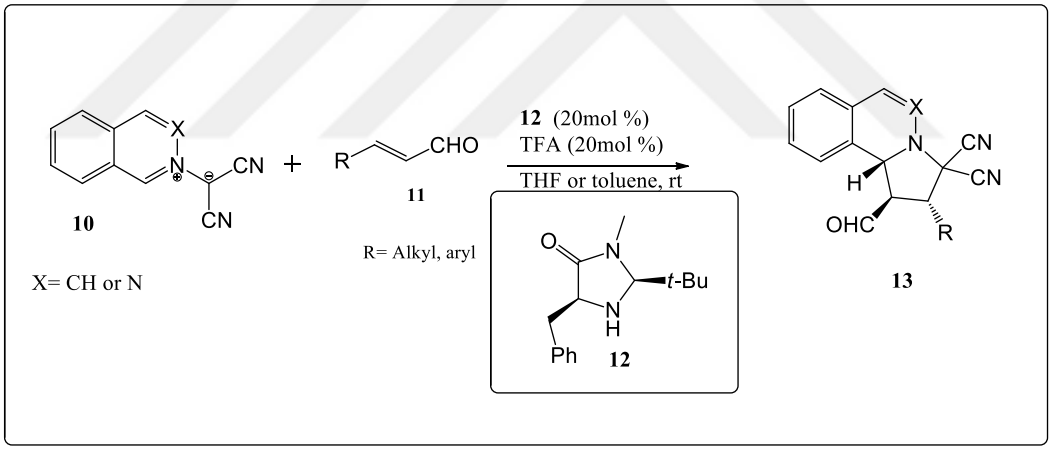
1.2.1.1 The Stereochemistry of Azomethine Ylide

A very effective approach for the synthesis of modified and stereoisomerically pure pyrrolidines which are crucial building block in the synthesis of many natural products and pharmaceuticals (Ibarra *et al*., 1997, Wait *et al*., 1996, Bianco *et al*.,1996) is the reaction between azomethine ylides and alkenes (Kanemasa and Tsuge, 1993, Pearson, and Stoys 2003). The geometry of the 1,3-dipoles and the dipolarophiles affects the stereochemistry of cycloaddition products. For example, While W-**4** and U-**5** shaped dipoles gives 2,5-cis-disubstituted pyrrolidine **6** product two potential S-shaped ylides **7**,**8** yield the 2,5-trans-disubstituted product **9** (Scheme 1.4) (Pandey *et al*., 2006).



Scheme 1.4. Stereoisomers of pyrolidines resulted from the reaction of different type of ylides (4,5,7,8) and dipolarphile.

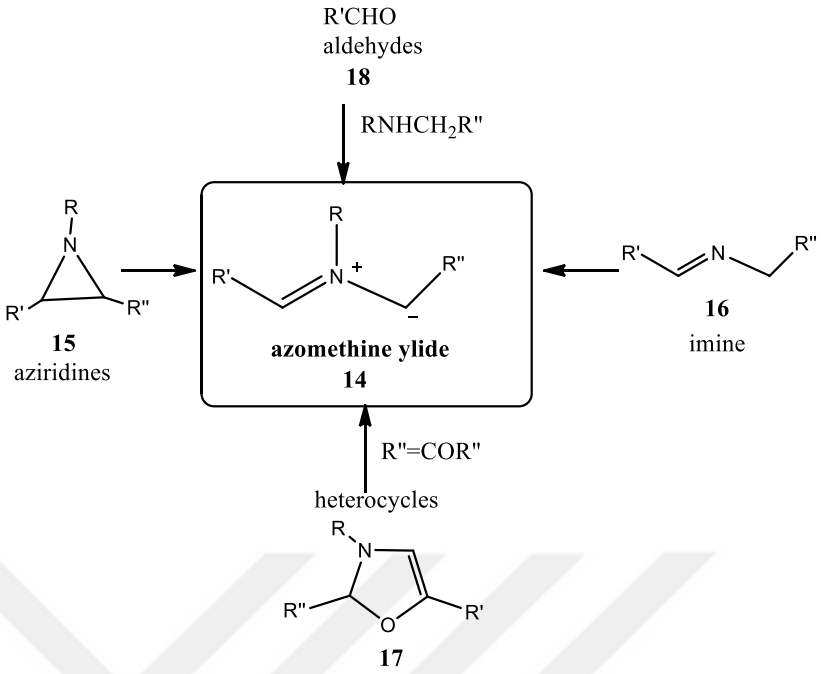
Jiyang and Chen reported that isoquinolinium type ylide **10** was treated with α, β-unsaturated aldehydes **11** in the presence of imidazolidinone **12** as a catalyst furnished pyrrolo[2,1-*a*] isoquinoline **13** stereoselectively.



Scheme 1.5. Stereoselective [3+2] cycloaddition of isoquinolinium type ylide **10** with α, β-unsaturated aldehydes **11**.

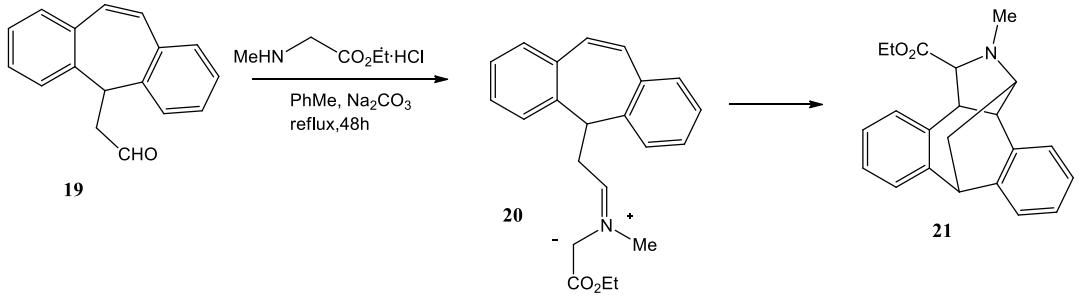
1.2.1.2 Generation of Azomethine Ylides

There have been number of synthetic protocol exist for the achievement of azomethine ylide **14**. The one of the simplest one is the condensation reaction of an amine with an aldehyde **18** to form imine that is precursor of azomethine ylide. The other method are the thermal ring-opening of aziridines **15** and oxazole **17**, respectively. Furthermore, azomethine ylide can be obtained by the deprotonation of the iminium ion or prototropic shift of the imine **16** (Scheme 1.5) (Coldham and Hufton, 2005, Gothelf and Jorgensen, 1998).



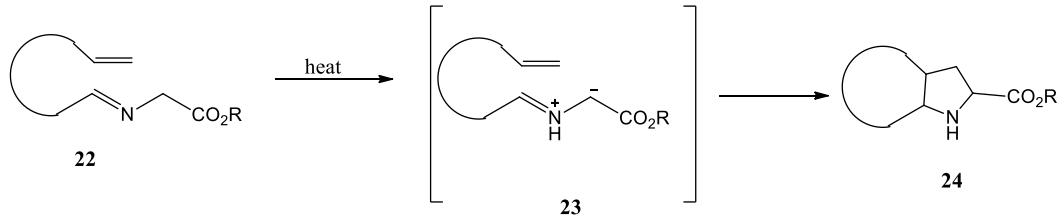
Scheme 1.6. Preperation of the azomethine ylide **14** via different methods.

Confalone and Huie studied that synthesis of the cycloadduct **21** via the intermediate azomethine ylide **20** by heating the aldehyde **19** with the hydrochloride salt of *N*-methyl-glycine ethyl ester (also known as sarcosine ethyl ester) in toluene in the presence of sodium carbonate (Confalone and Huie, 1983).



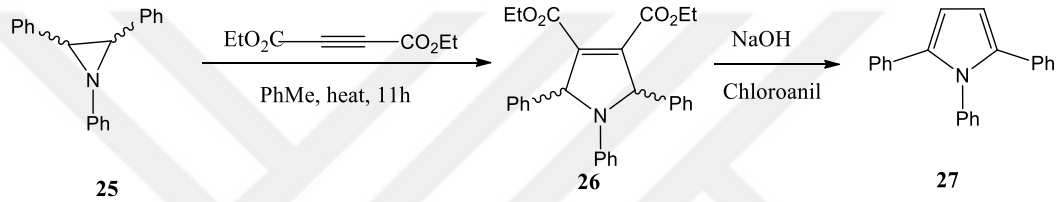
Scheme 1.7. Synthesis of the azomethine ylide **20** from aldehyde **19**.

Grigg and co-workers demonstrated that in situ azomethine ylide **23** are generated from imines **22** by migration of a proton from the α-carbon to the N atom and it is called 1,2-prototropic shift (Grigg, 1987).



Scheme 1.8. Synthesis of the azomethine ylide **23** and cycloadduct **24** by 1,2-prototropic shift.

Heine's team reported that reaction of the aziridine **25** with diethylacetylene dicarboxylate in toluene at reflux produced a solid product that was supposedly the pyrrolidine **26** and followed oxidation of this cycloaddition product gave substituted pyrrole **27** (Heine and Peavy, 1965).



Scheme 1.9. Heating the aziridine, proceed through azomethine ylide intermediates pyrrolidine.

1.2.2 Imidazolium Salts

Imidazolium salts **29** are the salts of imidazoles where one of the nitrogen atoms in the ring is in the cationic form. They can be formed by alkylation of both nitrogen atoms in the heterocycle of imidazole rings **28** (Scheme 1.10) (Riduan and Zhang, 2013, Wilkes *et al*.,1982 and Kim and Varma,2005).

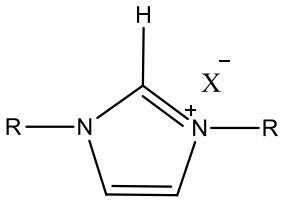
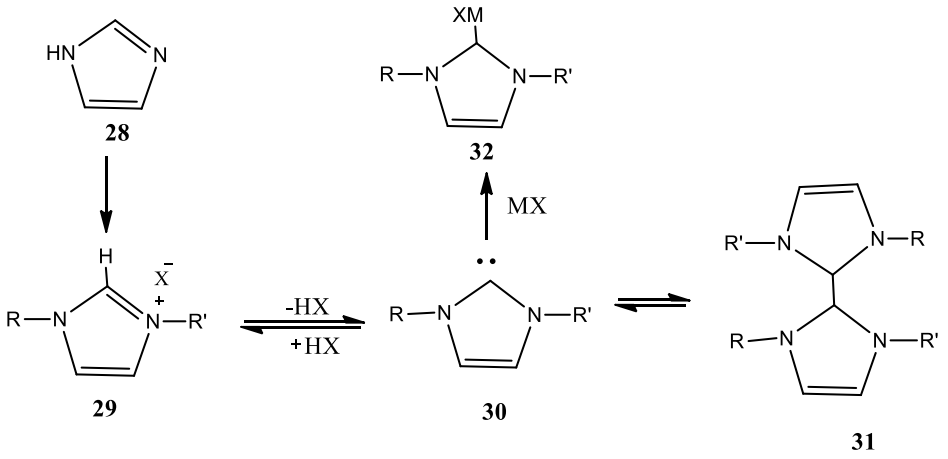


Figure 1.9. Structure of the imidazolium salt **28**.

Furthermore, they are used as pioneer of the *N*-heterocyclic carbenes (NHCs) with various resultant implementations in organic synthesis (Scheme 1.10) and ionic liquids too (Riduan and Zhang, 2013, Hu *et al.,* 2015, Jones *et al*. 2011, Sathiyamoorthi *et al.,* 2021, Ogura and Kikuchi, *1972,* Zhong *et al*.,2016).



Scheme1.10. Associations between imidazole **29**, imidazolium salt **28**, N-heterocyclic carbine **30**, bisimidazolidine **31** and the NHC–metal complex **32**.

The imidazolium cations **33**, **34**, **35**, **36**, **37**, **38** which are exhibit several interesting perspectives in area of synthesis are given below (Figure 1.10). Due to their great chemical stability and low vapor pressure, imidazolium salts (IMSs) are well known as an ionic liquid that can be employed as electrolytes or green solvents (Singh and Svoy,2020, Riduan and Zhang, 2013). In addition, they are used in a wide range of bioactive compounds (Riduan and Zhang, 2013), stable carbene precursors (Cazin, 2011) and their complexes (Zhang and Chan, 2010).

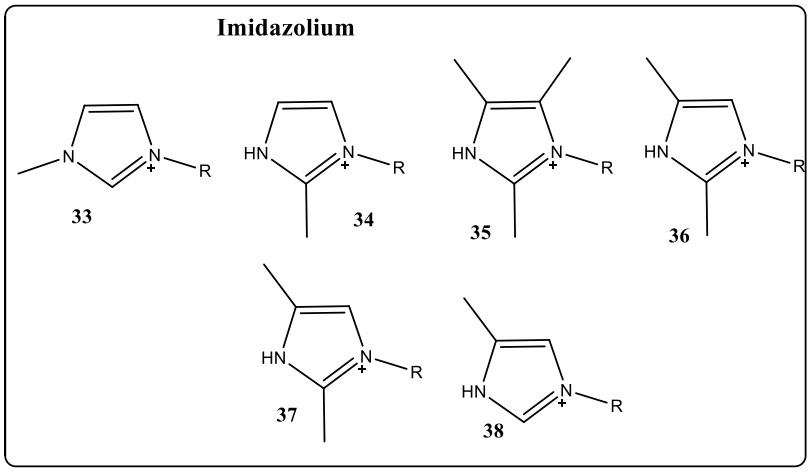
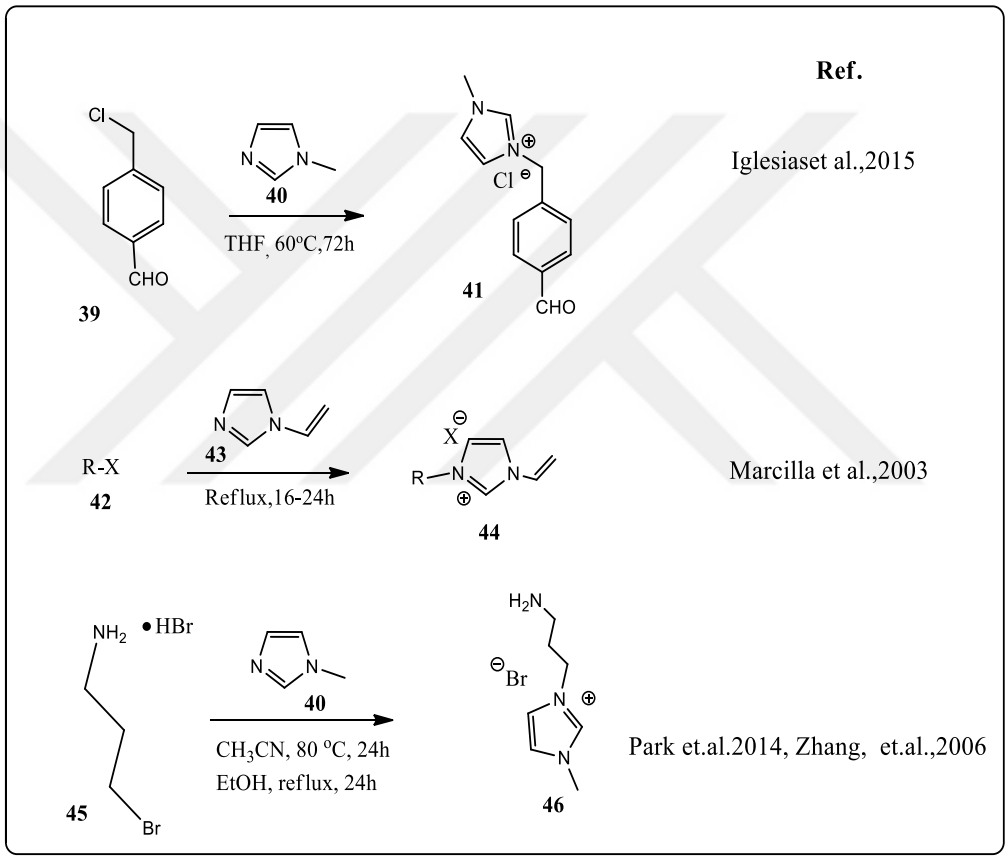


Figure 1.10. Commonly used imidazolium cations.

1.2.2.1 Synthesis of Imidazolium Salts

The one of the most commonly used synthetic protocol for the synthesis of imidazolium salt is the substitution reaction of alkyl halides with imidazole and generated the discrete cation and anion pair. Another method describe the synthesis asymmetrical imidazolium ylide (salts) via the deprotonation of imidazole with a

strong base and than reacted with a suitable alkyl, acyl or benzyl halide (Wilkes *et al*.,1982, Kim and Varma, 2005, Kitazume *et al*., 2000). Furthermore, the transformation of schiff bases into imidazolium salts is also known method (Arduengo *et al*., 1999). Herein some examples regarding imidazolium ylide formation by alkylation of imidazole derivatives are given in below. For example, Iglesiaset *et al*, Marcilla *et al*., and Park *et al*., have synthesized alkyl imidazolium ylides **41, 44 and 46** respectively by utilizing imidazole **40** and 1-vinyl imidazole **43** as a starting material (Scheme 1.11).



Scheme 1.11. Preparation of some imidazolium ylides.

1.2.2.2 Biological Activity of Some Imidazolium Salts

The structural units of the Imidazolium salts can be found in the natural products such as Lepidiline A **47** and Lepidiline B **48** which are isolated from the Lepidium meyenii (Figure 1.11) (Cui *et al*., 2003).

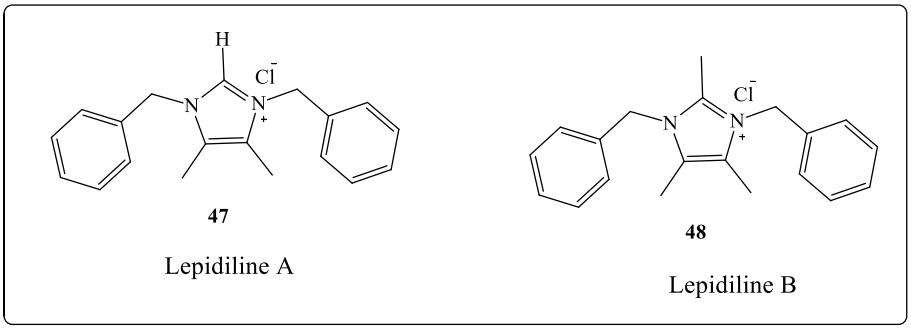


Figure 1.11. Imidazolium salts isolated from the Lepidium meyenii.

Furthermore, the imidazolinium salts with their versatile amphiphilic structures that are used to produce *N*-heterocyclic carbene have been attracted much attention due to playing crucial role in functions within the human body. (Riduan and Zhang, 2013, Zhang *et al*., 2014, Edwards *et.al*., 2011) For example, imidazolium salts bearing heteroaromatics with a vinylic bridge **49** (Figure 1.12) have been synthesized by Musumarra's group and their investigation showed that a diverse series of imidazolium ylides exhibited in vitro antitumour activity against the human mammary carcinoma (MCF7) and prostate carcinoma (LNCap) cell line (Mussummara *et al*.,2004 and 2008).

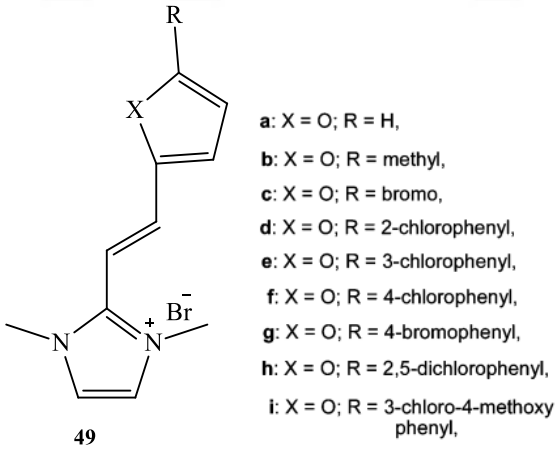
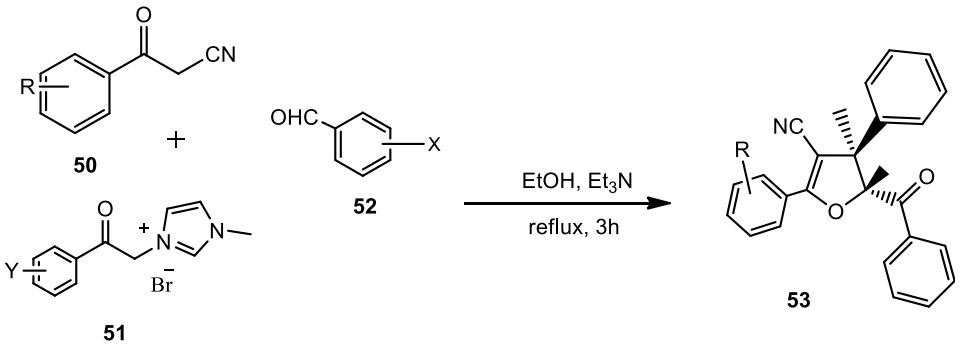


Figure 1.12. Imidazolium salts with a vinylic bridge **49**.

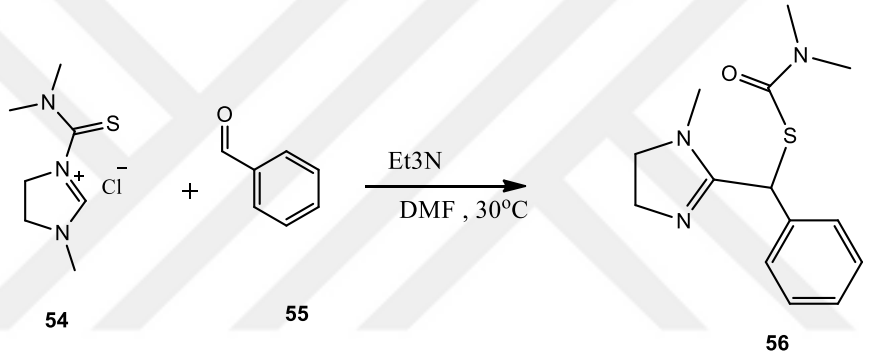
1.2.2.3 Reactions

Imidazolium ylide posses many reactions including multi component, cycloaddition, addition and carbene formation. For instance, Sathiyamoorthi and coworkers reported that treatment of aroyl acetonitriles, aromatic aldehydes **52** and imidazolium ylide **51** in the presence of Et_3N provided tetra-substituted dihydrofurans **53** in a one pot manner (Sathiyamoorthi, *et al*., 2020) (Scheme 1.12).



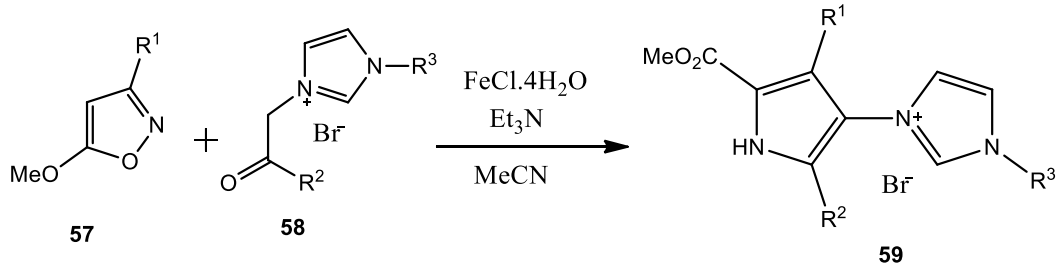
Scheme 1.12. Synthesis of tetra-substituted dihydrofurans **53**.

Zhao *et al*. demonstrated that N-thiocarbamate imidazolium ylide **54** was reacted with benzaldehyde **55** in the presence of Et_3N at 30 °C gave 2-imidazolium alkylcarbamothioate **56** in good yield (Zhao *et al*.,2012) (Scheme 1.13).



Scheme 1.13. Reaction of imidazolium ylide **54** with benzaldehyde **55**.

Galenko *et al*., describe the preparation of 5-alkoxycarbonylpyrrol-3-ylimidazolium bromides **59** by introducing isoxazole **57** with phenacylimidazolium salt **58** in basic medium resulted from $FeCl_2 \cdot 4H_2O$ and Et_3N (Scheme 1.14).



Scheme 1.14. The synthesis of 5-alkoxycarbonylpyrrol-3-ylimidazolium salts **59** by the domino reaction of 5-methoxyisoxazoles **57** and phenacylimidazolium bromides **58**.

1.3 Oxadiazoles

The usual formula for oxadiazole is $C_2H_2ON_2$. It is a five-membered heterocycle with two carbons, two nitrogens, one oxygen, and two double bonds. By substituting two of the methane (-CH=) groups with two of the nitrogen (-N=) groups of the pyridine type, oxadiazole is thought to be produced from furan. There are four possible isomers of oxadiazole depending on the position of nitrogen atom in the ring as shown in Figure 1.12 (Somani and Shirodkar, 2009).

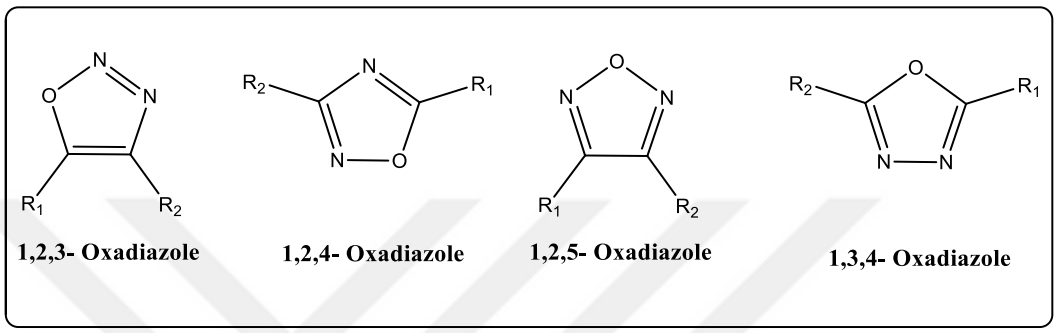


Figure 1.13. Four isomers of the Oxadiazole.

Their importance is highlighted by a wide range of applications in various scientific fields, such as the pharmaceutical industry, medicinal chemistry, scintillating materials, and dyestuff industry (Salahuddin, *et al*., 2017). In pharmaceutical aspect of view, the three isomers 1,2,4-oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole have a wide range of pharmaceutical applications; they appear in a variety of drugs including butalamine **60,** raltegravir **61**, oxolamine **62**, fasiplon **63**, and pleconaril **64** (Das and Banik,2020).

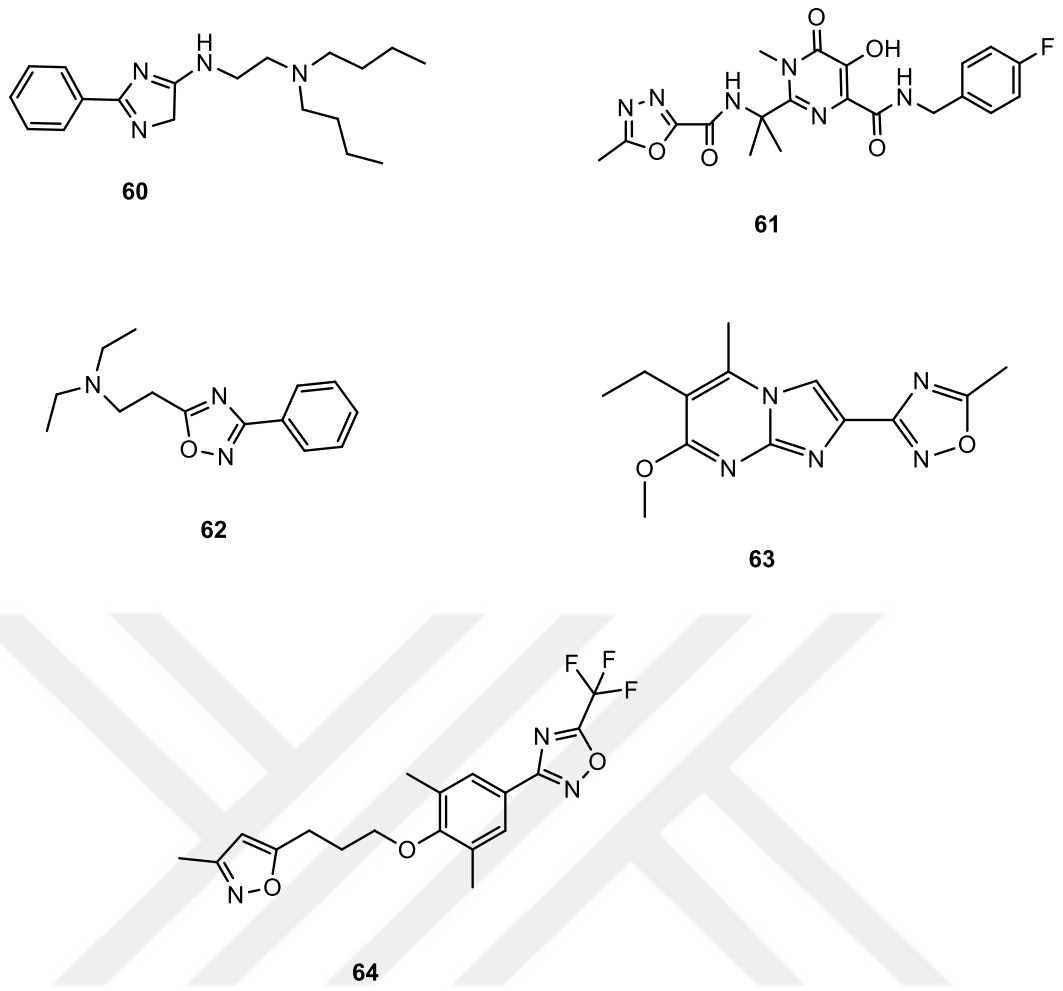


Figure 1.14. A variety of drugs including butalamine **60,** raltegravir **61**, oxolamine **62**, fasiplon **63**, and pleconaril **64**.

Apart from the other isomers, 1,2,4-oxadiazole has drawn an attention due to their diverse spectrum of medicinal and pharmaceutical properties (Kayukova, 2005, Rosa *et al*.,2015 and Benassi et al., 2020). On the other hand, 1,2,4-oxadiazole ring is the only one isomer found in the skeleton of naturally occuring products (Carbone *et al*., 2011). Also, 1,2,4-oxadiazole derivatives have been used as supramolecular liquid crystals (Wei, *et al*., 2015, Parra, *et al*., 2005, Yan, T.; Cheng and Yang 2019).

1.3.1 1,2,4-Oxadiazoles

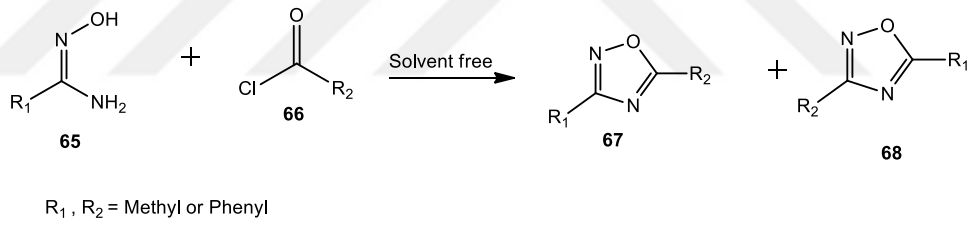
1,2,4-oxadiazoles are a class of highly valuable five-membered heterocycles that were first synthesized by Tiemann and Krüger in 1884 (Tiemann and Krüger, 1884). Initially classified as azoxime these heterocycles have garnered attention in various fields of chemistry, particularly in medicinal and biological research due to their therapeutic effects and biological importance (Macor *et al*., 1996, Burns *et al*.,

2010, Kumar *et al*., 2011, Hemming, 2008 and Diana *et al*., 1994). In addition, they have found applications in material science, polymer chemistry, and synthetic organic and heterocyclic chemistries (Pace *et al*., 2009 and 2015) (Ko, *et al*., 2015 and Agneeswari, *et al*., 2013) (Joule and Mills, 2013, Cicchi *et al*., 2007 and Piccionello*, et al*., 2011). As bioisosteres of esters and amides, 1,2,4 oxadiazoles have been widely used to design and synthesize biologically active compounds (Diana *et al*., 1994). Given their versatile properties, these heterocycles continue to attract significant interest in the scientific community.

1.3.2 Synthesis of 3,5-Disubstituted 1,2,4-Oxadiazoles

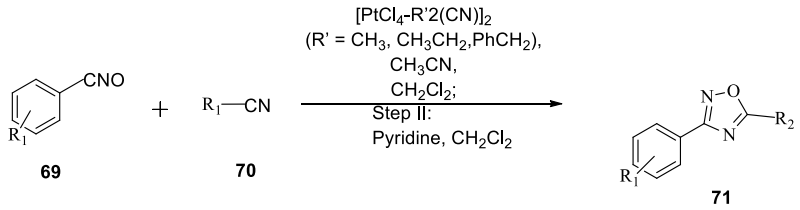
To date, numerous methods for producing 1,2,4-oxadiazole compounds have been developed. The methods used to synthesize 1,2,4-oxadiazoles can be summarized as follows:

Tiemann and Krüger's first method employs amidoximes **65** and acyl chlorides **66**, resulting in the formation of two products **67** and **68** (Scheme 1.15) (Tiemann and Krüger, 1884)



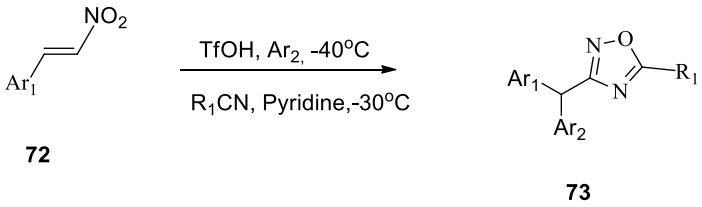
Scheme 1.15. Synthesis of the 1,2,4- oxadiazoles in solvent free condition.

One alternative approach for the synthesis of 1,2,4-oxadiazoles involves the 1,3-dipolar cycloaddition of nitrile oxides **69** and nitriles **70**. Bokach *et al*. conducted a study on the 1,3-dipolar cycloaddition of nitrile oxides **69** with nitriles **70** in the presence of a platinium(IV) catalyst. The reaction was found to generate 1,2,4-oxadiazoles under mild reaction conditions (Bokach*, et al*., 2003).



Scheme 1.16. 1,3-Dipolar cycloaddition of nitrile and nitrile oxide with nitrile derivatives.

Golushko and colleagues have recently proposed a novel synthetic approach for the preparation of 1,2,4-oxadiazole **73**. This method involves a tandem reaction, which includes the reaction of nitroalkenes **72** with arenes and nitriles in the presence of trifluoromethanesulfonic acid (TfOH) (Scheme 1.17) (Golushko *et al*.,2019).

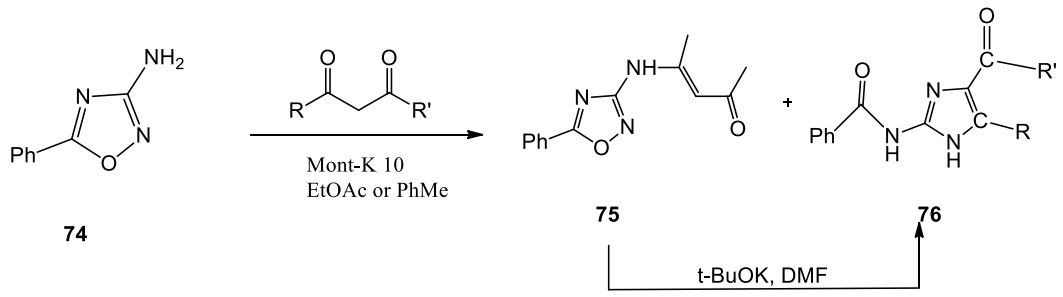


72 **73**

Scheme 1.17. Synthesis of the 1,2,4-oxadiazole via the tandem reaction of nitroalkenes with arenes and nitriles.

1.3.3 Reactions of The 3,5-Disubstituted 1,2,4-Oxadiazoles

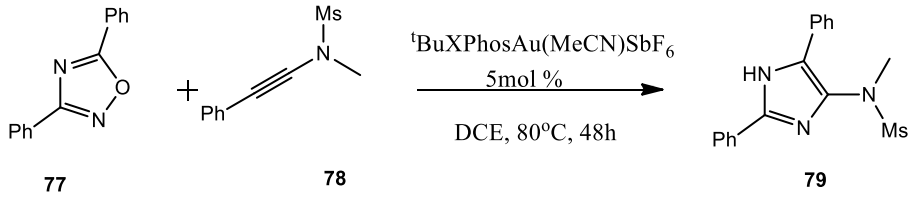
1,2,4-Oxadiazoles are versatile heterocyclic compounds that exhibit a range of chemical reactivity (Biernacki *et al*., 2020, Clapp, 1984, Piccionello, *et al*., 2017 and Pace, *et al*., 2015). The N(2) atom in 1,2,4-oxadiazoles exhibits nucleophilic character, while the carbon atoms are electrophilic. One of the most extensively studied transformations of 1,2,4-oxadiazoles is the thermal Boulton-Katritzky rearrangement (BKR) (Piccionello, *et al*., 2017). Additionally, the BKR reaction has been employed to synthesize imidazoles from 1,2,4-oxadiazoles possessing two different side-chain sequences (Scheme 1.18) (Piccionello, et al., 2018, Marzullo et al. 2020).



74 **75** **76**

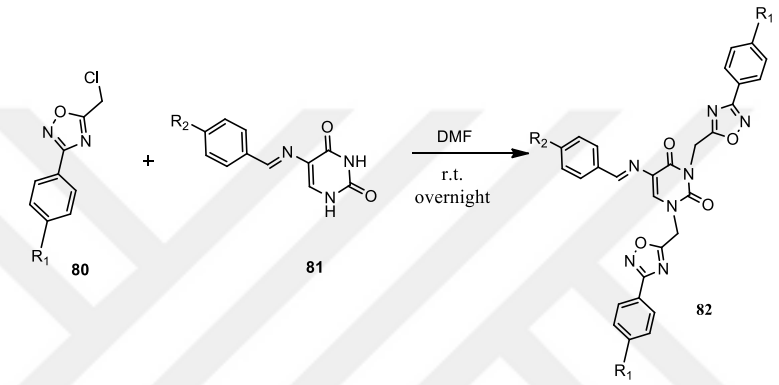
Scheme 1.18. Formation of fluorinated-imidazoles via oxadiazole.

Zeng *et al.* conducted a study on the synthesis of *N*-acylimidazoles **79** through the [3 + 2] cycloaddition reaction of 1,2,4-oxadiazoles **77** using Au(I) as a catalyst (Scheme 1.19) (Zeng, et al.,2017).



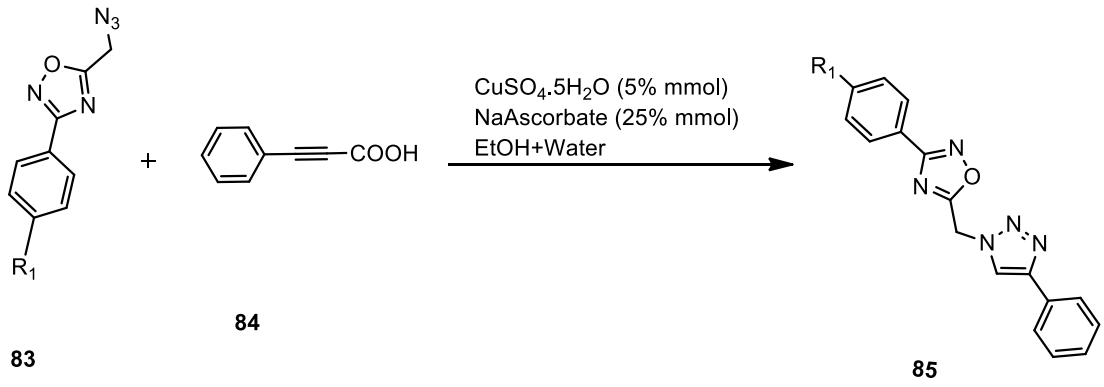
Scheme 1.19. Au(I)-catalyzed reaction of anthranil with ynamides.

Dürüst *et al*. utilized the substitution reaction of chloromethyl-1,2,4-oxadiazole compounds **80** with benzylideneamino pyrimidinediones **81**. (Scheme 1.20) (Dürüst *et al*., 2015).



Scheme 1.20. Synthesis of *N,N*-bisoxadiazolylmethyl-substituted benzylideneamino pyrimidinedione via substitution reaction of 1,2,4-oxadiazole.

Furthermore, Dürüst and his research team investigated the 1,3-dipolar cycloaddition of 1,2,4-oxadiazole derivatives **83** with electron-deficient alkyne **84** (Scheme 1.21) (Dürüst and Karakuş, 2017).



Scheme 1.21. 1,3 dipolar reaction of azidomethyl-1,2,4-oxadiazole with alkyne

1.3.4 Biological Activity

The 1,2,4-oxadiazole is a significant pharmacophore due to its heterocyclic scaffold that is of great interest in medicinal chemistry (Macor *et al*., 1996, Hu, *et al*., 2008 and Wang, *et al*., 2007). Notably, several noteworthy drug molecules such as Perebron **86**, Libexin **87**, serotonin agonist **88**, and L-690548 84, contain the 1,2,4-oxadiazole moiety (Figure 1.15) and are used in antitussive drugs, for the treatment of migraine, and Alzheimer's disease, respectively (Angelini, 1963, Ledniczky and Seres, 1999, Street *et al*., 1993, Saunders and Freedman 1989, Street *et al*., 1990).

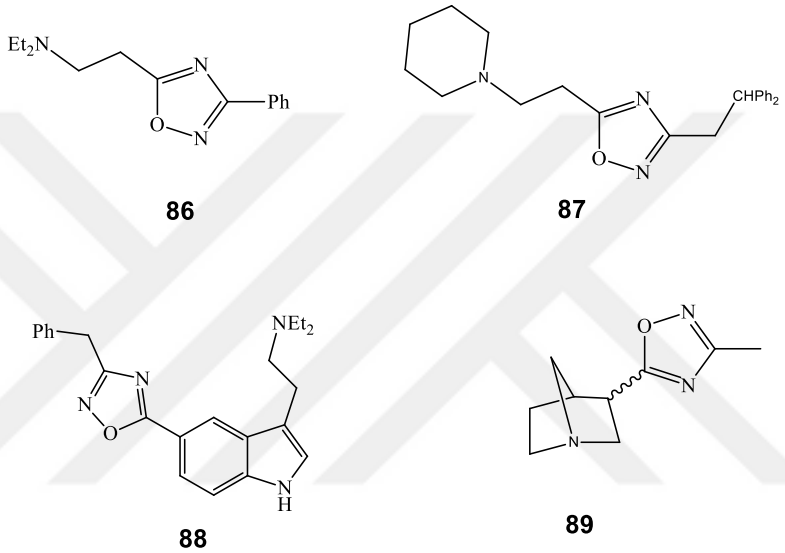
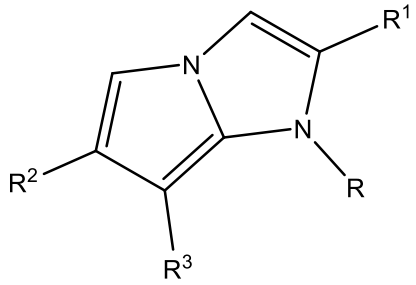


Figure 1.15. Bioactive compounds containing the 1,2,4-oxadiazole moiety.

Moreover, oxadiazoles serve as important bioisosteres, and their derivatives have been reported to exhibit various pharmacological activities. For instance, 1,2,4-oxadiazole derivatives have been identified as muscarinic agonists (Orlek *et al*., 1991), benzodiazepine receptor partial agonists (Watjen *et al*., 1989), dopamine transporter inhibitors (Carroll et al., 1993), antirhinovirals (Diana *et al*., 1994), growth hormone secretagogues (Ankersen *et al*., 1997), and 5-HT agonists (Chen *et al*., 1994).

1.4 Pyrrole[1,2-*a*] Imidazole

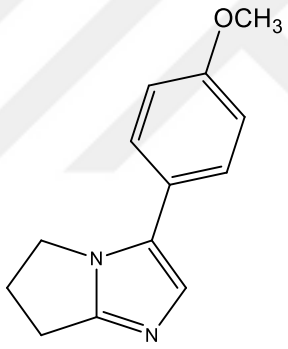
Pyrrole[1,2-*a*]imidazoles, depicted in Figure 1.16, represent a group of significant chemical compounds belonging to the class of imidazole derivatives. They are utilized as fundamental structural components in a wide range of natural and synthetic biological medicines (Wang *et al*., 2015, Kochergi *et al*., 1966, Schlingmann *et al*., 2007 and Clark et al., 2004).



90

Figure 1.16. Structure of the Pyrrole[1,2-*a*] imidazole

Moreover, a number of pyrrole[1,2-*a*]imidazole derivatives have demonstrated potent inhibition of kinases, making them valuable for the development of new kinase inhibitors. Additionally Demchenko et al., demonstrated the antifungal activity of derivatives of the structurally similar heterocycles, 3-aryl-6,7-dihydro-5H pyrrolo[1,2-a]imidazole such a derivative is shown in Figure 1.17 as compound **91** (Demchenko *et al.,* 1987, Wang *et al*., 2015, Graczyk *et al*., 2005, Brown *et al*., 2009 and Roberts *et al*., 2009).



91

Figure 1.17. 3-(4-methoxyphenyl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazole

2. AIM AND SCOPE OF THE STUDY

Pyrrole[1,2-*a*]imidazole is a significant heterocyclic scaffold that has gained considerable attention in recent years due to its versatile biological and pharmaceutical properties. Pyrrole[1,2-*a*]imidazoles have been identified as essential structural components of many biologically active compounds, including natural products and synthetic molecules used in medicinal chemistry. The potent kinase inhibitory activity of pyrrole[1,2-*a*]imidazole derivatives has been studied in the development of novel kinase inhibitors. Additionally, pyrrole[1,2-*a*]imidazoles exhibit anti-inflammatory and antiproliferative activities, making them potential candidates for the treatment of cancer and other diseases. Therefore, the synthesis and characterization of novel pyrrole[1,2-*a*]imidazole derivatives is of great interest in the field of medicinal chemistry and drug discovery.

1,2,4-oxadiazole is a class of heterocyclic compounds that has attracted considerable attention due to its diverse applications in different fields of chemistry, especially in medicinal chemistry. The 1,2,4-oxadiazole scaffold has been found to possess various biological activities, including antimicrobial, anti-inflammatory, anticonvulsant, antitumor, and antiviral activities. Furthermore, this ring system has been reported to exhibit high affinity towards various enzymes, receptors, and ion channels. Several research studies have focused on the synthesis of novel 1,2,4-oxadiazole derivatives to develop potent drugs for the treatment of various diseases. Moreover, this ring system has been used as a core structure for the development of various agrochemicals and materials science. Therefore, the significance of 1,2,4-oxadiazole is evident due to its versatile nature and potential applications in different fields.

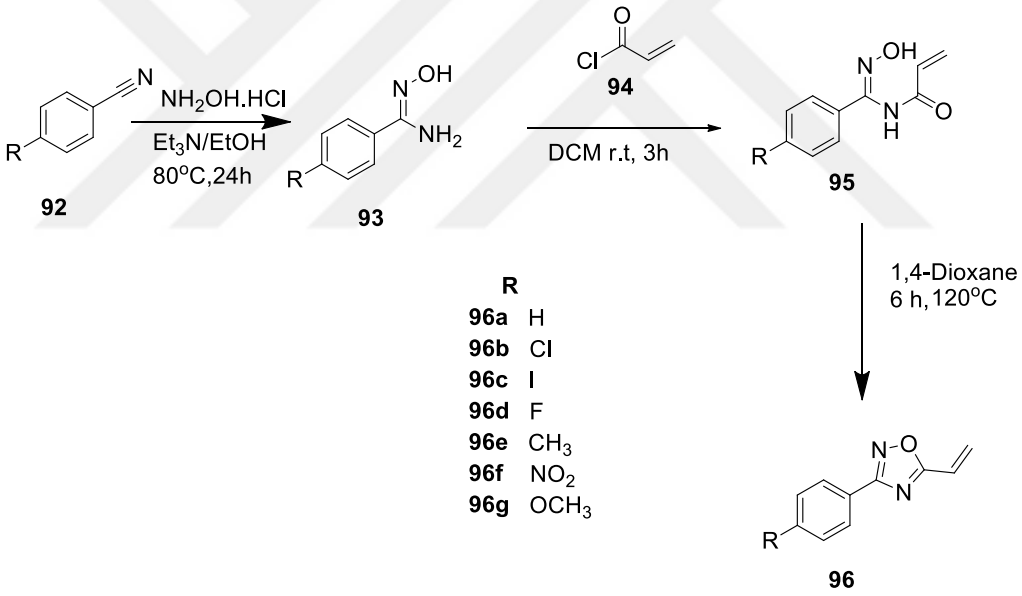
Taking into account the considerations mentioned above, the aim of this MSc study was to synthesize new derivatives of pyrrole[1,2-*a*] imidazole **100** containing a 1,2,4-oxadiazole ring by utilizing the 1,3-dipolar cycloaddition reaction of imidazolium *N*-ylide **99** with substituted phenyl vinyl 1,2,4-oxadiazole **96**.

3. MATERIALS AND METHODS

^{1}H and ^{13}C NMR spectra were recorded on BRUKER and VARIAN spectrometers (400 and 500MHz for proton and 100 and 125MHz for carbon). IR spectra were recorded on a SHIMADZU FTIR-8400S instrument (KBr pellet). Mass spectra were recorded on an Agilent 1200 series LC-MS instrument. Chromatotron^{TM} Centrifugal Thin-Layer Chromatography System was used for the isolation and purification of the reaction products. Melting points were determined on a MELTEMP apparatus and uncorrected. TLC was done by using precoated plates with fluorescent indicator (Merck 5735). The stain solutions of permanganate and iodine were used for visualization of the TLC spots.

Experimental

General Procedure for Preparation of 3-phenyl-5-vinyl-1,2,4-Oxadiazoles(96a-g)



General Method for Preparation of Amidoximes (93a-g)

Hydroxylamine hydrochloride (20.25 mmol) in round bottom flask is dissolved in ethanol (75 mL). Then, triethylamine (4.5 mL) is added to solution and corresponding substituted benzonitrile (13.5 mmol) is added into solution carefully and stirred at 80°C for overnight. After completion of the reaction, ethanol was rotaevaporated. Crude product is mixed with water and extracted with

ethyl acetate (3x30 mL). Then, organic layers are collected and dried over sodium sulfate or calcium chloride. The solution is filtered and the solvent is removed under vacuo to afford the solid product.

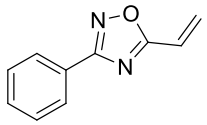
General Method for Preparation of Acrylamides 95

4-Substituted benzamidoxime (2.09 mmole) is placed in a round bottom flask and dichloromethane (20 mL) is added then 0.2 mL of acryloyl chloride is carefully added and resulting mixture is stirred for three hours at room temperature. After three hours, $NaHCO_3$ solution (2 mL) is added to reaction mixture and followed by addition of water. Resulting mixture is extracted with DCM three times and collected DCM extracts are dried over sodium sulfate, filtered and evaporated under vacuum to get the crude product.

General Method for Preparation of Vinyloxadiazoles (96a-g)

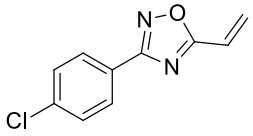
A solution of **95** (1 equiv.), 1,4-dioxane (5 mL) and K_2CO_3 (2 equiv.) was heated at 120 ˚C for 6 h. The mixture was allowed to cool before being filtered and concentrated to a residue which was purified by column chromatography eluting with 10% Et_2O/light petroleum to afford (**96a-g**) (Burns et al., 2010). Spectral/physical data of the compounds are given below.

3-phenyl-5-vinyl-1,2,4-oxadiazole 96a



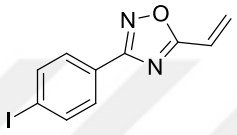
Clear colorless oil. Yield: 500.0 mg (65%). b. p (293.7 °C). Rf (25% EtOAc/hexane). IR (neat cm^{-1}): Vmax = 3070 (arom. CH), 2926, 1646 (C=N), 1543 (arom C=C), 1445, 1360, 956, 910, 770, 705

3-(4-chlorophenyl)-5-vinyl-1,2,4-oxadiazole 96b



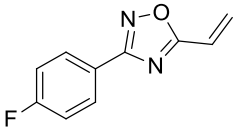
Ivory(cream) solid. Yield: (325 mg, 75.23%). M.p. 63-65 ºC. IR (ATR, cm^{-1}): 3120-3058 (=CH), 3014-2958 (arom. CH), 2858, 1920, 1645 (C=N), 1559, 1541 (C=C), 1488, 1408, 1349, 1289 (C-O), 1178, 1107, 1089 (C-O), 1013, 957, 904 (N-O), 836, 785, 757, 730. (Cl), 568, 519. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.6 Hz, 2H), 7.47 (d, *J* = 6.7 Hz, 2H), 6.75 (d, *J* = 11.0 Hz, 1H), 6.60 (d, *J* = 17.5 Hz, 1H), 6.02 (d, *J* = 11.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.76, 168.02, 137.48, 129.31, 129.18, 128.86, 125.39, 120.53.

3-(4-iodophenyl)-5-vinyl-1,2,4-oxadiazole 96c



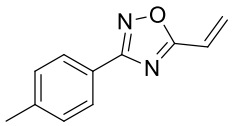
White(cream) solid. Yield: (315 mg, 50.64%). M.p. 82-84 ºC. IR (ATR, cm^{-1}): 3077(=CH), 3001 (arom. CH), 1908, 1642 (C=N), 1569, 1532(C=C), 1486, 1454, 1400, 1349, 1281 (C-O), 1117, 1107, 1054 (C-O), 989, 980, 951 (N-O), 838, 785, 729, 690. (I), 667, 501. ^{1}H NMR (400 MHz, cdcl3) δ 7.85 (d, *J* = 9.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 6.7 Hz, 1H), 6.60 (d, *J* = 17.6 Hz, 1H), 6.02 (d, *J* = 11.0 Hz, 1H). ^{13}C NMR (101 MHz, cdcl3) δ 174.76, 168.24, 38.22, 133.28, 129.05, 126.38, 120.51, 98.08.

3-(4-fluorophenyl)-5-vinyl-1,2,4-oxadiazole 96d



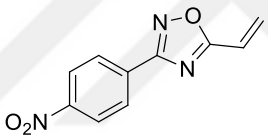
White solid. Yield: (261 mg, 65 %). M.p. 50-52 ºC. IR (ATR, cm^{-1}): 3062(=CH), 2924 (arom. CH), 1950, 1651 (C=N), 1606, 1564, 1544 (C=C), 1534, 1486, 1351, 1214 (C-O), 1161, 1128, 1098 (C-O), 989, 978, 913 (NO), 841, 778, 734, 713. (F), 601, 512 . ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, *J* =8.8, 5.4 Hz, 2H), 7.17 (t, *J* = 8.7 Hz, 2H), 6.76 (dd, *J* = 17.7, 11.0 Hz, 1H), 6.59 (d, *J* = 17.4 Hz, 1H), 6.01 (d, *J* = 11.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.99, 165.95, 163.45, 129.75, 129.66, 123.10, 120.56, 116.08.

3-(p-tolyl)-5-vinyl-1,2,4-oxadiazole 96e



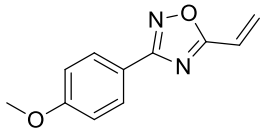
White solid. Yield: 430 mg (52%). m.p. 51-53°C. Rf (25% EtOAc/hexane) 0.89. IR (ATR, cm^{-1}): 3074, 3048, 3029 (arom. CH), 2919 (CH3), 1647, 1610 (C=N), 1581 (C=N), 1538 (arom C=C), 1477 (arom C=C), 1412, 1362, 1280 (C-O), 1181, 1114, 1018 (C-O), 991, 961, 909, 827 (N-O), 786, 731, 684, 606, 504, 426. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 6.77 (dd, J = 17.7, 11.0 Hz, 1H), 6.59 (d, J = 17.7 Hz, 1H), 6.00 (d, J = 11.0 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 168.7, 141.5, 129.6, 128.63, 127.3, 123.9, 120.6, 21.6.

3-(4-nitrophenyl)-5-vinyl-1,2,4-oxadiazole 96f



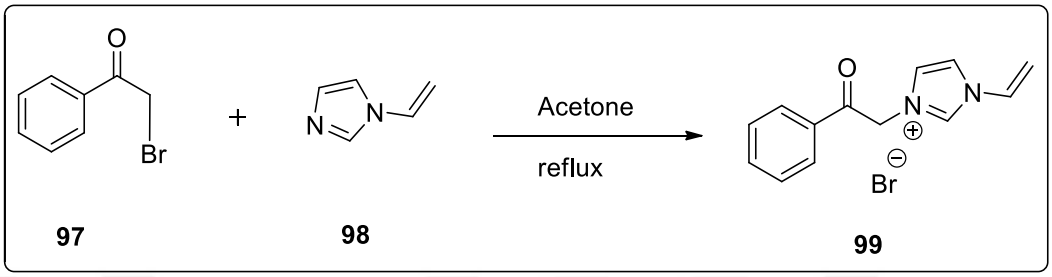
Ivory (cream) Crystal solid. Yield: (268 mg, 59%). M.p. 110-113. ºC. IR (ATR, cm−1): 3103(=CH), 3081 (arom. CH), 1924, 1643(C=N), 1607, 1543 (C=C), 1511 (NO2), 1418, 1340 (NO2) 1331, 1312, 1290 (C-O), 1104, 1017 (CO), 977, 956, 888, (N-O), 866, 788, 762, 710. ^{1}H NMR (400 MHz, cdcl3) δ 8.35 (d, *J* = 9.0 Hz, 2H), 8.30 (d, *J* = 9.0 Hz, 2H), 6.79 (dd, *J* = 17.7, 10.9 Hz, 1H), 6.65 (d, *J* = 17.5 Hz, 1H), 6.07 (d, *J* = 10.9 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 167.1, 149.4, 132.6, 129.6, 128.4, 124.1, 120.1.

3-(4-methoxyphenyl)-5-vinyl-1,2,4-oxadiazole(96g)



White solid. Yield: 630 mg (58%). m.p. 59-61°C. Rf (25% EtOAc/hexane): 0.72. IR (ATR, cm^{-1}): 3107(=CH), 3075-3002 (arom. CH), 2971, 2840 (CH_3), 1651,

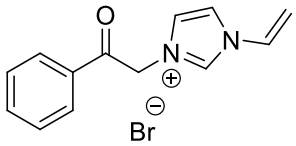
1611(C=N), 1585 (C=N), 1538 (arom C=C), 1480 (arom C=C), 1441, 1419, 1365, 1255 (C-O), 1177, 1107, 1027 (C-O), 994, 948, 904, 839 (N-O), 814, 787, 740, 685, 614, 518. ^{1}H NMR (400 MHz, CDCl3) δ 8.04 (d, J = 8.9 Hz, 2H), 6.99 (d, J = 8.9 Hz, 2H), 6.75 (dd, J = 17.7, 11.0 Hz, 1H), 6.57 (d, J = 18.3 Hz, 1H), 5.98 (d, J = 11.1 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 168.4, 161.9, 129.0, 128.6, 120.6, 119.2, 114.2, 55.4.



97 98 99

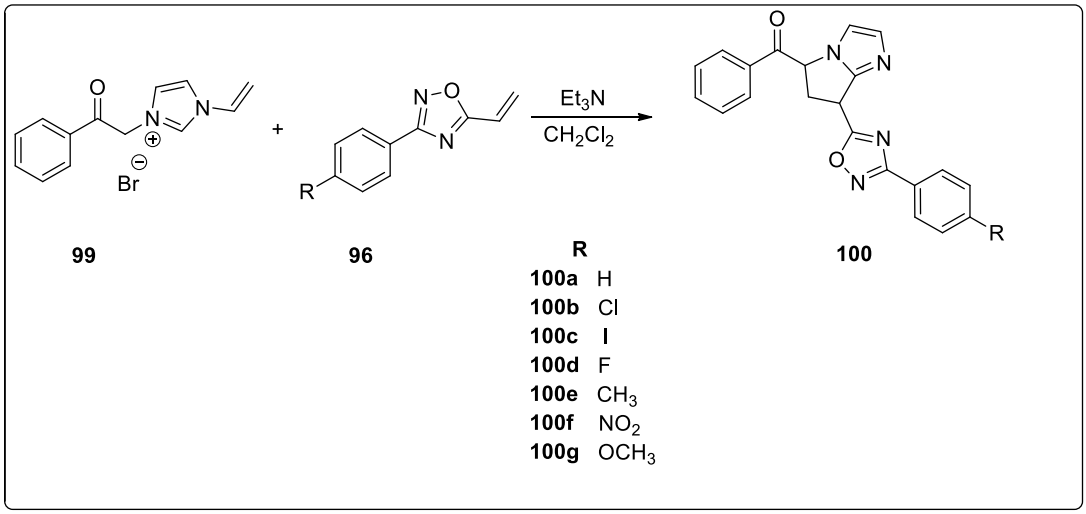
General Procedure for Preparation of 3-(2-oxo-2-phenylethyl)-1-vinyl-1H-imidazol-3-ium Bromide 99

A solution of 2-bromoacetophenone **97** (1.00 g, 5 mmol, 1 eq) and *N*-vinyl imidazole **98** (0.47 g, 5 mmol, 1 eq) were refluxed in 50 ml acetone (20 mL) for 24 h. The precipitate formed was collected by filtering under vacuo, washed thoroughly with acetone and dried to give a white solid **99**.



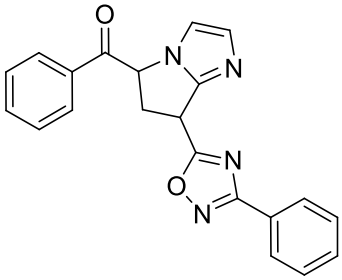
White solid. Yield: 1241 mg (85%). R_f (10% MeOH/EtOAc): 0.15. IR (ATR, cm^{-1}): 3130, 3103 (=CH), 3051 (arom. CH), 2921, 2843 (aliph. CH), 1701 (C=O), 1647 (C=N), 1572 (C=C), 1446, 1356, 1234, 1180, 991, 758, 690, 619, 569.

General Procedure for Cycloadducts (100a-g)



To the 3-(2-oxo-2-phenyletil)-1-vinyl-1H-imidazole-3-ium bromide **99** (1mmol, 292 mg) mixture dissolved in DCM (10 ml) was added to *p*-phenylsubstituted vinyl oxadiazole (**96a-g**). Then, triethylamine (1.2 mmol, 0.16 ml) was added slowly to the reaction mixture. The progress of the reaction was monitored by TLC (Thin Layer Chromatography). After completion of reaction, the mixture was extracted with water. The organic layer was dried over Na_2SO_4. Then, the dichloromethane was evaporated under reduced pressure. The remaining crude product was separated by column chromatography (EtOAc: Hexane (2:1)). Spectral/physical data of the compounds are given below.

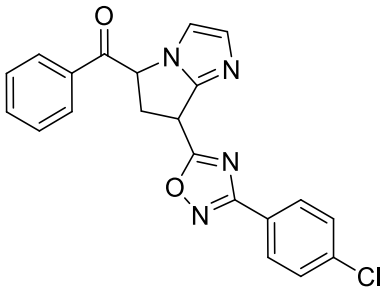
Phenyl(7-(3-phenyl-1,2,4-oxadiazol-5-yl)-6,7-dihydro-5H-pyrrolo[1,2 a]imidazol-5-yl)methanone 100a



Light yellow oily. (35%). IR (KBr): ν = 3363, 2928, 1693 (C=O), 1600, 1573, 1446, 1357, 1288, 1215, 1076, 906, 721 cm^{-1}.^{1}H NMR (400 MHz, CDCl3) δ 8.10 (dd, *J* = 7.9,1.9 Hz, 2H), 8.04 (d, J = 7.1 Hz, 2H), 7.69 (s, 1H), 7.62 (t, J = 7.4 Hz, 1H), 7.54-7.47 (m, 5H), 7.12 (s, 2H), 6.14 (dd, J = 6.4, 4.0 Hz, 1H), 3.04 – 2.97 (m, 1H), 2.82 – 2.72 (m, 2H),2.58 – 2.50 (m, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 193.99,

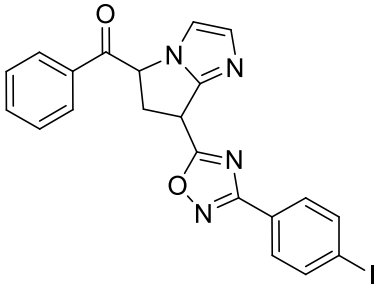
178.03, 168.31, 134.41, 134.13, 131.43, 130.20 ,129.13, 128.97, 128.67, 127.37, 126.49, 118.21, 68.14, 58.65, 29.59, 22.27. LC—MS (70 eV): (m/z, %)= 359.2 (100) $[M+H]^+$.

(7-(3-(4-chlorophenyl)-1,2,4-oxadiazol-5-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-5-yl)(phenyl)methanone 100b



Yellow oily .(37%). IR (KBr): *v* = 3363, 3113, 2928, 1693 (C=O), 1566, 1408, 1342, 1230, 1091, 1014, 840, 744 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (t, *J* = 6.6 Hz, 4H), 7.67 (s, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50-7.47 (m,4H), 7.10 (d, *J* = 6.6 Hz, 2H), 6.07 (dd, *J* = 10.4, 4.2 Hz, 1H), 3.04 – 2.96 (m, 1H), 2.83 – 2.71 (m, 2H), 2.60 – 2.51 (m, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 193.83, 178.25, 167.54, 137.61, 136.96, 134.44, 134.12, 130.30, 129.30,129.13, 128.64, 124.96, 118.12, 58.63, 29.44, 22.33.LC—MS (70 eV): (m/z, %)= 393.1 (100) $[M+H]^+$.

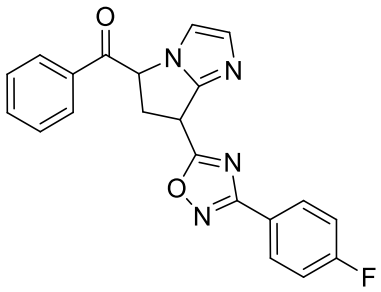
(7-(3-(4-iodophenyl)-1,2,4-oxadiazol-5-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-5-yl)(phenyl)methanone 100c



Yellow oily. (38%). IR (KBr): *v* = 3363, 3113, 2928, 1693 (C=O), 1566, 1408, 1342, 1230, 1091, 1014, 840, 744 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (t, *J* = 7.3 Hz, 2H), 7.82 (dd, *J* = 21.1, 8.5 Hz, 4H), 7.66 (s, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.10 (d, *J* = 3.9 Hz, 2H), 6.06 (dd, *J* = 10.0, 4.2 Hz, 1H), 3.02 – 2.95 (m, 1H), 2.82 – 2.70 (m, 2H), 2.59 – 2.49 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.85, 178.26, 167.76, 138.21, 134.44, 134.10, 130.29, 129.13, 128.82,

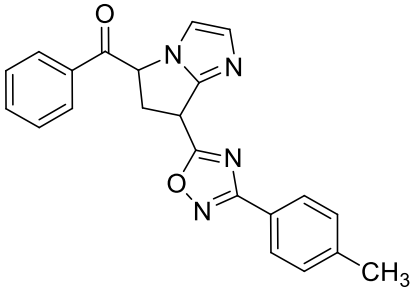
128.62, 125.96, 118.14, 98.16, 58.65, 29.43, 22.33.LC—MS (70 eV): (m/z, %)= 485.1 (100) $[M+H]^+$.

(7-(3-(4-fluorophenyl)-1,2,4-oxadiazol-5-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-5-yl)(phenyl)methanone 100d



Yellow oily. (34%). IR (KBr): *v* = 3363, 2928, 1693 (C=O), 1604, 1574, 1485, 1342, 1226, 1156, 1080, 846, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 6.9 Hz, 2H), 8.02 (d, *J* = 7.7 Hz, 2H), 7.68 (s, 1H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.19 (t, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 5.9 Hz, 2H), 6.08 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.03 – 2.96 (m, 1H), 2.83 – 2.71 (m, 2H), 2.60 – 2.50 (m, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 193.85, 178.13, 167.51, 136.97, 134.44, 134.12, 130.23, 129.54, 129.13, 128.63, 118.13, 116.29, 116.07, 58.65, 53.40, 29.46, 22.31. LC—MS (70 eV): (m/z, %)= 377.2 (100) $[M+H]^+$.

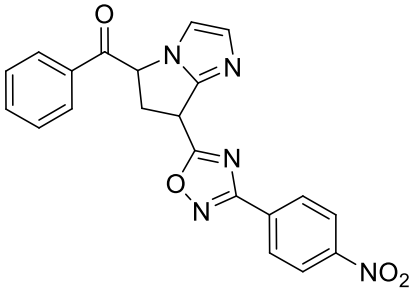
Phenyl(7-(3-(p-tolyl)-1,2,4-oxadiazol-5-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-5-yl)methanone 100e



Yellow oily. (32%). IR (KBr): *v* = 3363, 2928, 1693 (C=O), 1604, 1593, 1485, 1346, 1215, 1111, 1084, 910, 829 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.5 Hz, 2H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.67 (s, 1H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.11 (s,2H), 6.13 (dd, *J* = 10.6, 3.9 Hz, 1H), 3.02 – 2.95 (m, 1H), 2.81 – 2.71 (m, 2H), 2.59 – 2.48 (m, 1H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.03 (s), 177.83, 168.30, 141.83, 137.01, 134.39,

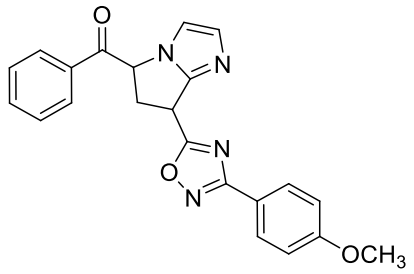
134.12, 130.16, 129.67, 129.12, 128.68, 127.29, 123.64, 118.22, 58.65, 29.51, 22.23, 21.58. LC—MS (70 eV): (m/z, %)= 373.0 (100) $[M+H]^+$.

(7-(3-(4-nitrophenyl)-1,2,4-oxadiazol-5-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-5-yl)(phenyl)methanone 100f



Yellow oily .(40%). IR (KBr): *v* = 3363, 3105, 1693 (C=O), 1577, 1527, 1414, 1346, 1107, 853, 729 cm^{-1}. 1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.6 Hz, 2H), 8.27 (d, *J* = 8.6 Hz, 2H), 7.99 (d, *J* = 7.5 Hz,2H), 7.68 (s, 1H), 7.63 (t, *J* = 7.4 Hz, 1H),7.49 (t, *J* = 7.7 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 6.02 (dd, *J* = 10.1, 4.7 Hz, 1H), 3.07 – 3.00 (m, 1H), 2.91 – 2.74 (m, 2H), 2.64 – 2.55 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.63, 178.93, 166.83, 149.56, 136.89, 134.51, 134.11, 132.32, 130.42, 129.16, 128.58, 128.36, 124.18, 118.03, 58.66, 29.36, 22.48. LC—MS (70 eV): (m/z, %)= 404.1 (100) $[M+H]^+$.

(7-(3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-5-yl)(phenyl)methanone 100g



Yellow oily. (32%). IR (KBr): *v* = 3363, 3113, 1693 (C=O), 1612, 1485, 1423, 1257, 1176, 1030, 840, 736 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.9 Hz, 4H), 7.67 (s, 1H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.10 (s,2H), 7.00 (d, *J* = 8.9 Hz, 2H),6.12 (dd, *J* = 10.5, 4.1 Hz, 1H), 3.87 (s, 3H), 3.00 – 2.93 (m, 1H), 2.79 – 2.70 (m, 2H), 2.56 – 2.48 (m, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ

194.03, 177.70, 168.00, 162.09, 137.01, 134.38, 134.12, 130.16, 129.11, 128.98, 128.67, 118.89, 118.21, 114.36, 58.66, 55.41, 29.52, 22.24.LC—MS (70 eV): (m/z, %)= 389.0 (100) $[M+H]^+$.

4. RESULTS AND DISCUSSION

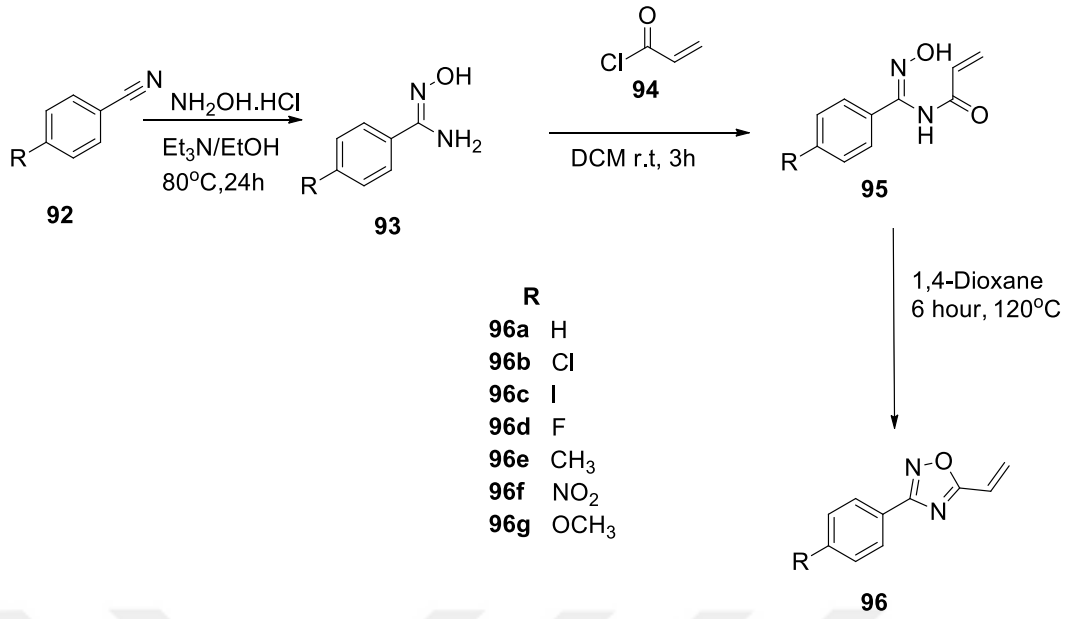
Pyroloimidazoles are a class of cycloadducts obtained through the annulation of azomethine ylides with alkenes that are a potential source of new drug candidates as they exhibit high affinity and selectivity towards various biological targets. Their synthetic accessibility, high stability, and biological activity make them an attractive scaffold for drug discovery and development. Besides, 1,2,4-oxadiazole and its derivatives possess several important pharmacological activities, such as antibacterial, antifungal, antitumor, and anti-inflammatory properties. Additionally, 1,2,4-oxadiazole derivatives are widely used in the development of organic semiconductors, fluorescent dyes, and as precursors for the synthesis of various complex organic molecules. The unique electronic and structural features of 1,2,4-oxadiazole make it an important molecule in modern chemistry and a promising target for designing new biologically active compounds. Therefore, the synthesis of pyrrole [1,2,-*a*]imidazoles bearing 1,2,4-oxadiazole ring is highly desirable and of interest. On the basis of above considerations, in this study, imidazolium *N*-ylide **99** was employed as a dipole towards *p*-substituted phenyl vinyl oxadiazoles **96** to synthesize seven new aryl-substituted phenyl(7-(3-phenyl-1,2,4-oxadiazol-5-yl)-6,7-dihydro-5H-pyrrolo[1,2-a]imidazol-5-yl)methanones **(100a-g)**.

The results of the study were disscussed in two parts;

- synthesis and characterization of starting materials
- synthesis and characterization of pyrrolo[1,2-*a*] imidazoles

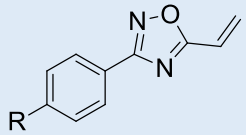
4.1 Synthesis and Characterization of Starting Materials

In the first part of this dissertation study involved the synthesis of vinyl-1,2,4-oxadiazoles (96 a-g) through a three-step conversion of benzonitriles 92a-g. The benzonitriles were first converted to 4-substituted benzamidoximes 93a-g, which were then transformed into the corresponding acrylamides 100 and subsequently into vinyl-1,2,4-oxadiazoles 96 (Scheme 4.1). All seven vinyl-1,2,4-oxadiazoles were synthesized using the current synthetic route and were obtained in moderate to good yields (50-75%) (Scheme 4.2, Table 4.2). The highest yield (75%) was achieved for the unsubstituted derivative 96b, while the lowest yield (50%) was obtained for the I-substituted vinyl-1,2,4-oxadiazole 96c.



Scheme 4.1. Synthesis of the *p*-substituted vinyl oxadiazoles **96a-g**.

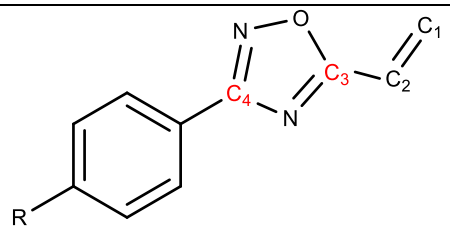
Table 4.1. Reaction optimizations for the synthesis of **96a-g**.



Entry	Product	R	Temp. (°C)	Time (h)	Yield (%)	m.p °C
1	**95a**	H	120	6	65	Oily
2	**95b**	Cl	120	6	75	63-65
3	**95c**	I	120	6	50	82-84
4	**95d**	F	120	6	65	50-52
5	**95e**	CH_3	120	6	52	51-53
6	**95f**	NO_2	120	6	59	110-113
7	**95g**	OCH_3	120	6	58	59-61

Column chromatography was utilized to purify the derivatives of **96**, which were primarily characterized through physical data such as melting points, as well as infrared (IR) spectroscopy (refer to Table 4.2 and 4.3). The IR spectra of 96a-g indicated peaks at approximately 3062-3107 cm^{-1}, 1538-1569 cm^{-1}, and 1585-1646 cm^{-1}, corresponding to =CH, C=C, and C=N functional groups, respectively (as depicted in Table 4.2). These IR results confirmed the formation of the expected products and agreed with previously reported literature values (77-82, 102, 103, 104, 109, 111).

Table 4.2. Indicative IR, proton and C-13 NMR data for the compounds **96a-g**.



	IR (νmax/cm)			^{1}H (δ, ppm)	^{13}C (δ, ppm)	
95						
A	3070	1646	1543	6.74, 6.58, 6.01	174.6	168.0
B	3058	1645	1559	6.75, 6.60, 6.02	174.6	168.0
C	3077	1642	1569	6.77, 6.60, 6.02	174.7	168.2
D	3062	1651	1564	6.76, 6.59, 6.01	167.9	165.9
E	3074	1610	1538	6.77, 6.59, 6.00	174.3	168.7
F	3103	1643	1543	6.79, 6.65, 6.07	175.2	167.1
G	3107	1585	1538	6.75, 6.57, 5.98	174.2	168.4

The ^{1}H NMR spectra revealed that the relevant vinylic protons, including =CH_2 and =CH, resonated within the range of 6.77-6.00 ppm. Furthermore, the ^{13}C NMR spectra exhibited signals for the C-4 and C-3 carbons at approximately 167-175 ppm and 165-168 ppm, respectively, which also supported the formation of the expected arylvinyl-1,2,4-oxadiazoles 96a-g (see Table 4.2). For example, figures 4.1, 4.2 provided the specific details of principal ^{1}H- and ^{13}C-NMR chemical shifts for compound 96g. All the vinyl-1,2,4-oxadiazoles (96a-g) were characterized based on their principal ^{1}H- and ^{13}C-NMR chemical shifts, which were provided in Table 4.2 and exemplified in figures 4.1 and 4.2.

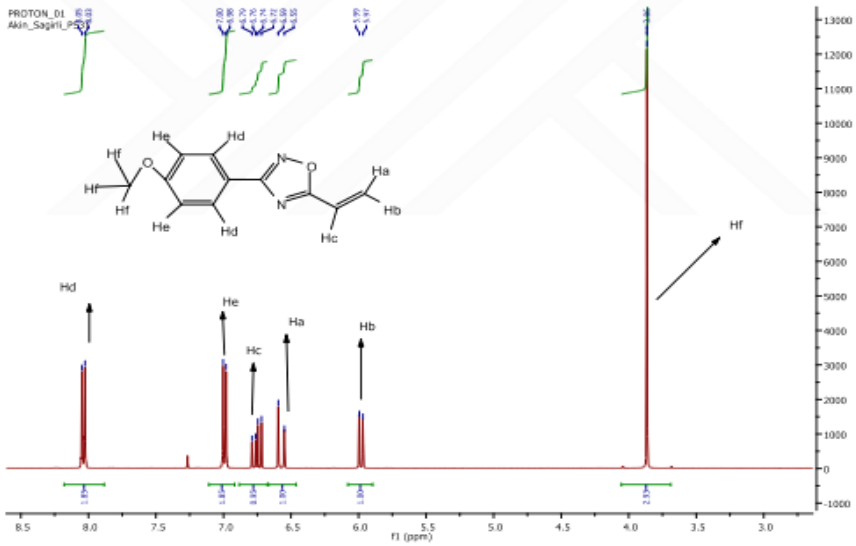


Figure 4.1. Expanded ^{1}H NMR spectrum of compound **96g**.

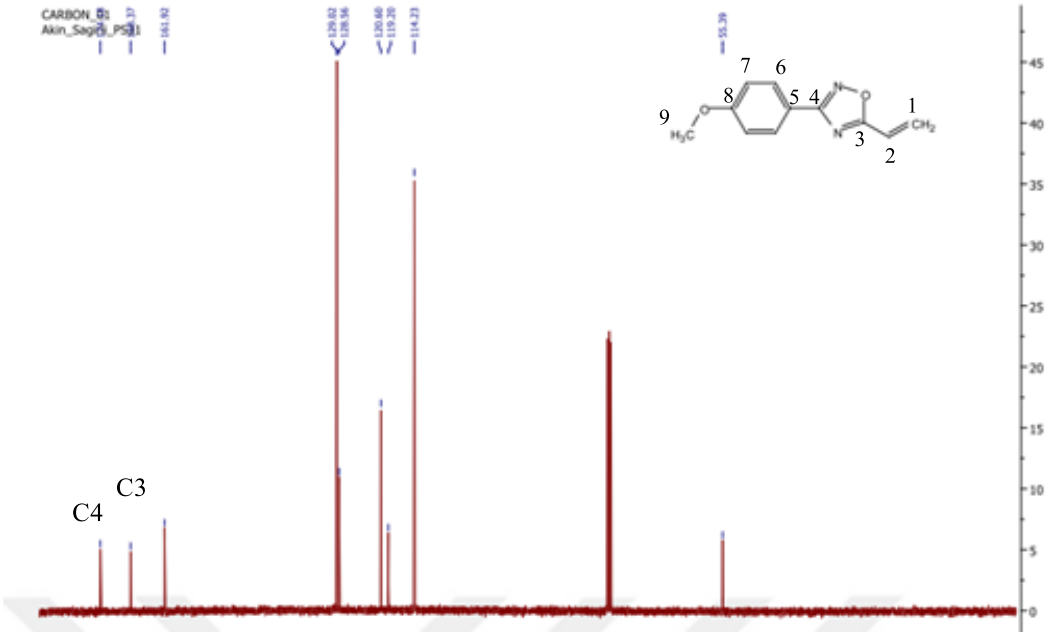
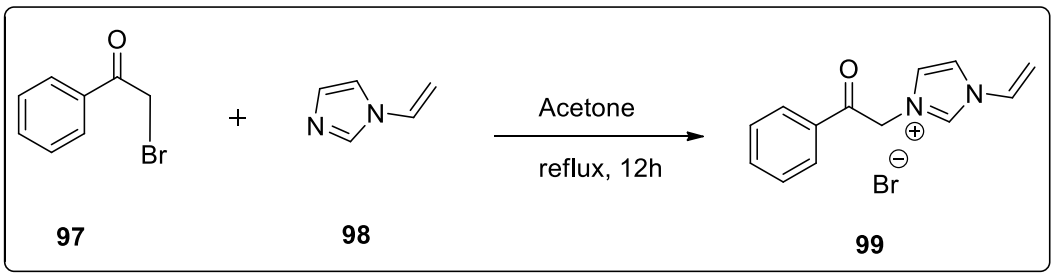


Figure 4.2. ^{13}**C** NMR spectrum of compound **96g**.

Besides, another precursor, *N*-vinyl imidazolium ylide **99**, was synthesized using readily available starting materials, namely 2-bromoacetophenone **97** and 1-vinylimidazole **98**. The procedure involved treating 2-bromoacetophenone **97** with 1-vinylimidazole **98** in acetone at reflux temperature, which led to the direct precipitation of the *N*-vinyl imidazolium ylide from the mother liquor Scheme 4.2.



Scheme 4.2. Preparation of 3-(2-oxo-2-phenylethyl)-1-vinyl-1H-imidazol-3-ium bromide **99**.

No further purification is needed for *N*-vinyl imidazolium ylide after precipitation in the reaction medium. Washing it with diethyl ether removes the unreacted starting material and provides the imidazolium ylide in a pure state. The structural characterization of compound **99** was elucidated by IR spectroscopy. The IR spectrum of **99** showed carbonyl stretching peak at around 1701 cm^{-1}, which is characteristic peaks for the formation of **99**.

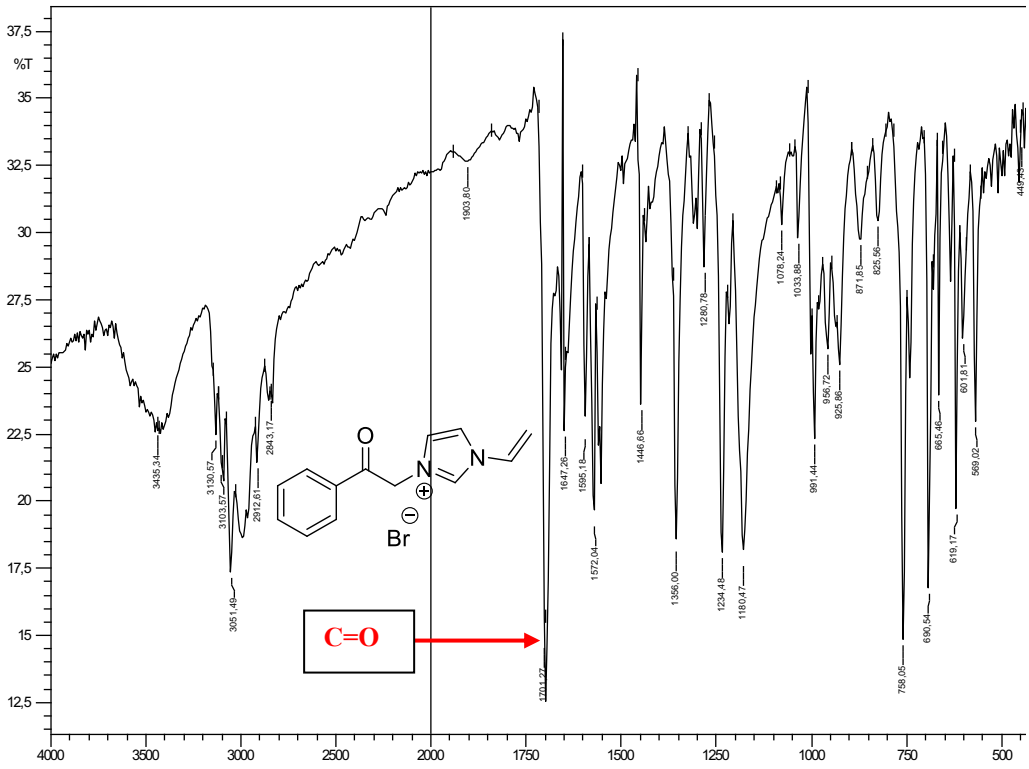
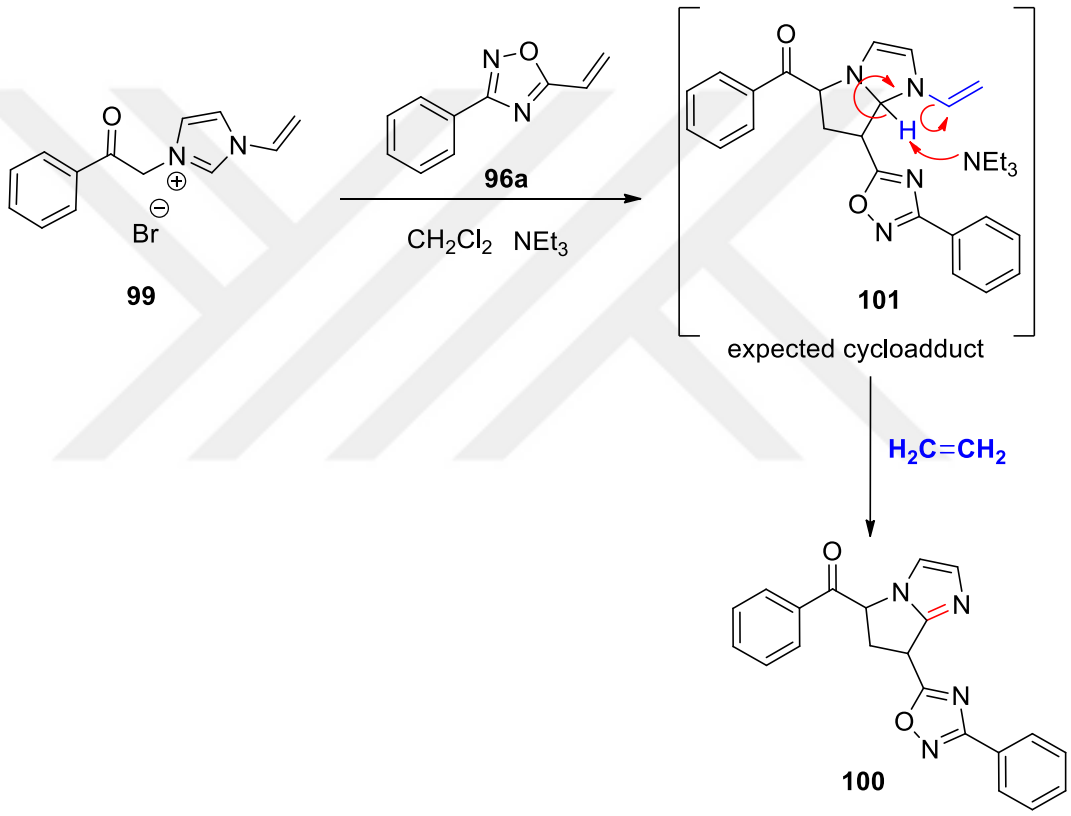


Figure 4.3. IR spectrum of compound **99.**

4.2 Synthesis and Characterization of Pyrrolo[1,2-*a*] Imidazoles

After synthesizing both precursors for the azomethine cycloaddition reaction, we proceeded with our thesis work by conducting 1,3-dipolar cycloaddition trials. Firstly, we carried out the 1,3-dipolar cycloaddition of imidazolium ylide **99** with

the 3-phenyl-5-vinyl-1,2,4-oxadiazole **96a** at room temperature in dichloromethane (DCM), in the presence of triethylamine as a base, to afford the new parent, vinyl-pyrrolo[1,2-*a*]imidazole **101** (Table 4.3, Entry 1). Unexpectedly, this model reaction resulted in the formation of fully conjugated imidazole **100** through the extrusion of ethene gas with the yield of 55%. We speculate that the reason behind this transformation is the acidity of the hydrogen located between the two nitrogens of the pyrrolo imidazole ring, which is easily removed by the action of NEt_3 as a base, leading to the release of ethene gas and the formation of cycloadduct **100** (Scheme 4.3.).

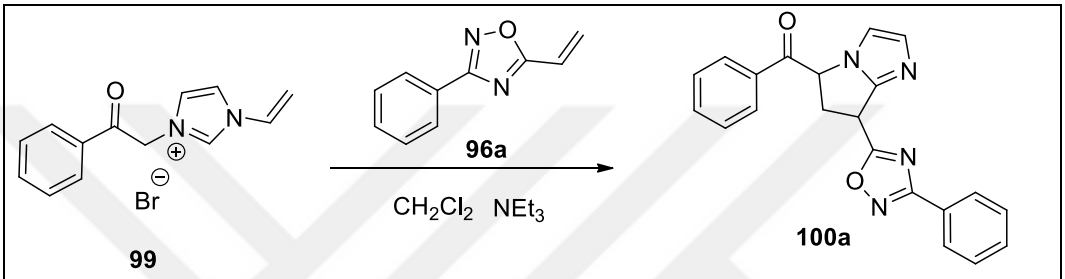


Scheme 4.3. 1,3-dipolar cycloaddition reaction between imidazolium *N*-ylide **99** and 3-phenyl-5-vinyl-1,2,4-oxadiazole **96a**.

This model reaction was optimized by utilizing a variety of bases with different strengths in the reaction instead of NEt_3. While no reaction product was obtained by using pyridine and DBU (diisobutylundecane) in DCM at room temperature (Table 4.3, Entry 3-4), K_2CO_3, KOtBu, and piperidine gave the cycloadduct **106** with the loss of ethene under the same reaction conditions (Table 4.3, Entry 5-7). However, NEt_3 was found to be proper base for this transformation in terms of reaction yields. After selecting the suitable base for this reaction, a

mixture of 1 eq imidazolium *N*-ylide **102**, 1 eq substituted vinyl 1,2,4-oxadiazoles, and 1.5 eq of NEt_3 in 10 mL DCM was used, but no increment of reaction product yield was observed in 12 hours (Table 4.3, Entry 8). In the last trial, changing the reaction solvent from DCM to acetonitrile showed no positive contribution to the reaction yield, even at higher temperatures (Table 4.3, Entry 9-10). Finally, the best protocol for the achievement of cycloadducts was the one using 1.0 eq of imidazolium *N*-ylide, 1.0 eq of vinyl 1,2,4-oxadiazoles, 1.2 eq of NEt_3 in 10 mL DCM at room temperature.

Table 4.3. Reaction optimizations for the synthesis of **100a**.

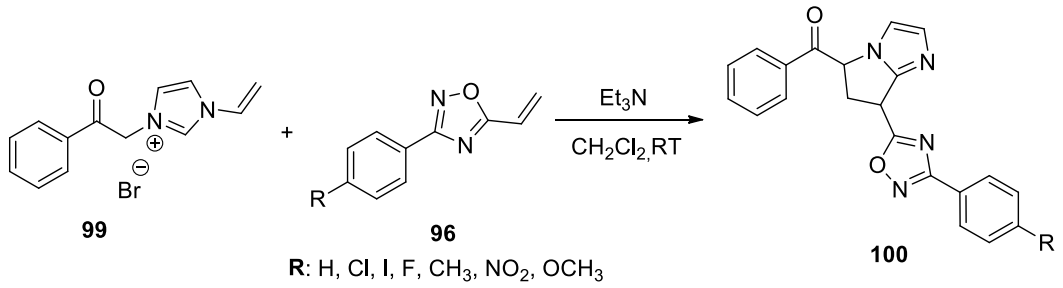


Entry	**96**(eq)	**100a**(eq)	Base	Solvent	Temp. °C	Yield%
1	**1.0**	**1.0**	**NEt_3[a]**	**DCM**	**25**	**55**
2	1.0	1.0	NEt_3[a]	DCM	40	55
3	1.0	1.0	Pyridine [a]	DCM	25	-
4	1.0	1.0	DBU [a]	DCM	25	-
5	1.0	1.0	K_2CO_3	DCM	25	26
6	1.0	1.0	KOtBu	DCM	25	42
7	1.0	1.0	piperidine	DCM	25	50
8	1.0	1.0	NEt_3[b]	DCM	25	55
9	1.0	1.0	NEt_3[a]	CH_3CN	25	48
10	1.0	1.0	NEt_3[a]	CH_3CN	60	48

a 1 eq. , **b** 1.5 eq.

Through the optimization of the cycloaddition reaction between the precursors **96** and **98**, we aimed to synthesize new derivatives of **100**. A mixture of p-substituted phenyl vinyl-1,2,4-oxadiazoles (1 eq.), imidazolium *N*-ylide (1 eq.), and NEt_3 (1.2 eq.) in DCM was stirred at RT for 12 hours, which afforded 7 new pyrrolo[1,2-*a*]imidazole derivatives in moderate to good yields (Table 4.4, Entry 1-7). The results showed that phenyl vinyl 1,2,4-oxadiazoles bearing electron-

withdrawing substituents gave comparatively higher reaction yields with respect to electron-donating ones. Probably, the presence of electron-withdrawing substituents on the intermediate cycloadduct makes the corresponding hydrogen more acidic, allowing the extrusion of ethene to be easier.



Scheme 4.4. Preperation of pyrrole[1,2-a]imidazole compounds.

Table 4.4. Reaction conditions for pyrido[1,2-*a*]imidazole compounds.

Entry	Product	Substituent	Time	Solvent	Temp. °C	Yield%
1	100a	H	12h	DCM	25	55
2	100b	Cl	12h	DCM	25	57
3	100c	I	12h	DCM	25	51
4	100d	F	12h	DCM	25	55
5	100e	Me	12h	DCM	25	48
6	100f	NO_2	12h	DCM	25	60
7	100g	OCH_3	12h	DCM	25	45

After purification of cycloadducts by column chromatography, the structural characterization was identified by the means of IR, NMR and LC-MS measurements. In the IR data of compound **100 a-g,** the characteristic peaks for the formation of pyrrole[1,2-*a*] imidazole are C=O and C=N bond stretchings appeared between 1693 cm^{-1} and 1566-1612 cm^{-1}, respectively. Additionally, the identification of regioisomers resulting from cycloaddition reactions, as well as the determination of the structures of novel target compounds (**100a-g**), have predominantly relied on their proton nuclear magnetic resonance (NMR) data. The ^{1}H NMR spectra of compounds **99a-g** exhibit two signals from the pyrrolo imidazole ring, appearing as a doublet of doublets and multiplets, ranging from 6.14-6.02 ppm and 3.07-3.00 ppm, respectively. Figure 4.4 provides a detailed

analysis of the ^{1}H NMR spectrum of **100b**, highlighting the proton signals of the pyrrolo imidazole rings.

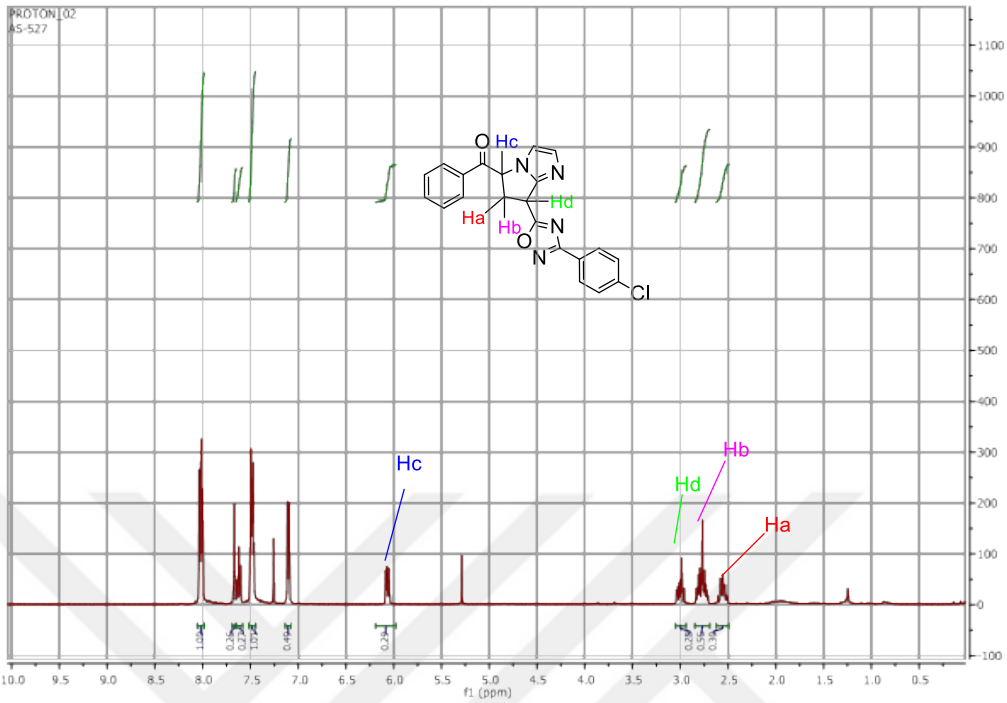


Figure 4.4 ^{1}H NMR spectrum of compound **100b**.

Regarding the carbon chemical shifts of the cycloadduct 100b, the primary signals of the carbonyl carbon C1 were observed in the range of 193 ppm. The iminic carbon C3 in the oxazadiazole ring adjacent to the phenyl ring was found to be around 178 ppm, and the methylenic carbon C2 in the pyrrole imidazole ring was observed at 22 ppm, as shown in Figure 4.5.

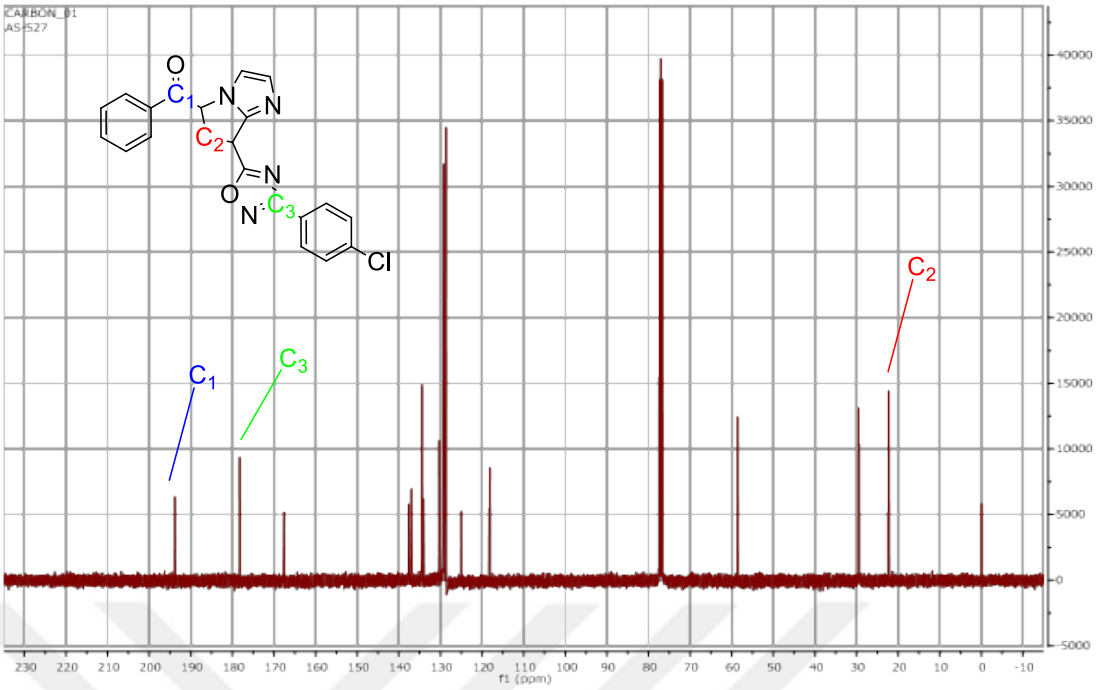


Figure 4.5. ^{13}C NMR spectrum of compound **100b**.

The structures of all new 1,2,4-oxadiazoyl pyrrole[1,2-*a*]imidazole products (100a-g) were characterized by their principal IR, ^{1}H-NMR, and ^{13}C-NMR data, as shown in the examples above. The main characterization data for the products were presented in Table 4.5, and their details were provided in the experimental section. Additionally, the supportive spectra for all target products 100a-g were placed in the appendices section of this dissertation study. Furthermore, supportive mass data (LC-MS) was provided for all target products in ESI (+) mode, and significant molecular ions were observed for all cycloadducts. Finally, HR-MS analyses for all target products are currently underway.

Table 4.5. Indicative IR, proton and C-13 NMR data for the compounds **100a-g**.

IR (νmax/cm)			^{1}H (δ, ppm)				^{13}C (δ, ppm)			LC-MS (m/z, %)
Comp.	**C=O**	**C=N**	**Ha**	**Hb**	**Hc**	**Hd**	**C1**	**C2**	**C3**	**[M+H]$^+$**
99										
A	1693,	1600	2.58,	3.04,	6.14,	2.82	193.9	22.2	178.0	359.2
B	1693,	1566	2.60,	3.04,	6.07,	2.82	193.8	22.2	178.2	393.1
C	1693,	1566	2.59,	3.02,	6.06,	2.82	193.8	22.3	178.2	485.1
D	1693,	1604	2.60,	3.03,	6.08,	2.83	193.8	22.3	178.1	377.2
E	1693,	1604	2.59,	3.02,	6.13,	2.81	194.0	22.2	177.1	373.0
F	1693,	1577	2.64,	3.07,	6.02,	2.91	193.6	22.4	178.9	404.1
G	1693,	1612	2.56,	3.00,	6.12,	2.79	194.0	22.2	177.7	389.0

5. CONCLUSIONS AND RECOMMENDATIONS

In summary, throughout this thesis work, we described a simple practical method for the preparation of new pyrrolo [1,2,-*a*] imidazoles bearing 1,2,4-oxadiazole ring through 1,3-dipolar cycloaddition reaction of imidazolium *N*-ylide and phenyl substituted vinyl 1,2,4-oxadiazoles in one pot. The structures of these seven new and unexpected cycloadducts were identified by means of IR, ^{1}H,^{13}C NMR and LC-MS spectra. All newly synthesized products carrying both pyrrole [1,2,-*a*] imidazole and 1,2,4-oxadiazole groups could be considered as potential bioactive heterocycles. For this reason, investigation of biological activity of these heterocycles will be assayed in the near future.

6. REFERENCES

''APA citation system was used in this thesis.''

Iglesias, D., Sabater, S., Azua, A., & Mata, J. A. (2015). Catalytic applications of Magnetic nanoparticles functionalized using iridium N-Heterocyclic carbene complexes. *New Journal of Chemistry, 39*, 6437-6444.

Agneeswari , R., Tamilavan , V., Song , M., Kang, J., Jin , S., & Hyun, M. (2013). Synthesis of Polymers Containing 1,2,4 Oxadiazole as an Electron-Acceptor Moiety in their Main Chain and Their Solar Cell Applications. *Journal of Polymer Science Chemistry, 51*, 2131-2141.

Alan, R., Katritzky, F. R., & Charles, W. (1996). *Comprehensive Heterocyclic Chemistry II.* Pergamon.

Alvarez, I., Csaky, A., Lüpez, I., & Quirroga, M. (1997). Diastereoselective Synthesis of α,α-Disubstituted γ-Carboxypyroglutamates via Sm(III)−Azomethine Ylide Cycloadditions. *Journal of Organic Chemistry, 62*, 479-484.

Ankersen, M., Peschke, B., Hansen, B. S., & Hansen, T. K. (1997). Investigation of bioisosters of the growth hormone secretagogue L-692,429. *Bioorganic Medicinal Chemistry Lettrers, 7*, 1293-1998.

Arduengo, A., Krafcyzk, R., Schmutzler, R., Craig, H., Goerlich, J., Marshall , W., & Unverzagt, M. (1999). Imidazolylidenes, imidazolinylidenes and imidazolidines. *Tetrahedron, 55*, 14523–14534.

Awal, H. M., Kinoshita, T., Yoshida, I., Doe, M., & Hirasawa, E. (1997). Aminoaldehyde Dehydrogenase of Pea Epicotyls. *Phytochemistry, 44*, 997-1000.

Bellina, F., & Rossi, R. (2006). Synthesis and biological activity of pyrrole, pyrroline and pyrrolidine derivatives with two aryl groups on adjacent positions. *Tetrahedron, 62*, 7217256.

Benassi, A., Doria, F., & Pirota, V. (2020). Groundbreaking Anticancer Activity of Highly Diversified Oxadiazole Scaffolds. *International Journal of Molecular Sciences, 21*, 8692.

Bhatia, G., Khan, A., Graczyk, P., Palmer, V., Medland, D., Numata, H., & Staddon, J. (2005). The neuroprotective action of JNK3 inhibitors based on the 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole scaffold. *Bioorganic Medicinal Chemistry Letters, 15*, 4666-4670.

Bianco , A., Maggini , M., Scorrano, G., Toniolo, C., Marconi, G., Villani, C., & Prato, M. (1996). Synthesis, chiroptical properties, and configurational assignment of fulleroproline derivatives and peptides. *Journal of American Chemical Society, 118*, 4072-4080.

Biernacki, K., Dasko, M., Ciupak, O., Kubinski, K., Rachon, J., & Demkowicz, S. (2020). Novel 1,2,4-Oxadiazole Derivatives in Drug Discovery. *Pharmaceuticals, 13*, 111.

Bokach, N. A., Khripoun, A. V., Kukushkin, V. Y., Haukka, M., & Pombeiro, A. J. (2003). A Route to 1,2,4-Oxadiazoles and Their Complexes via Platinum-Mediated 1,3-Dipolar Cycloaddition of Nitrile Oxides to Organonitriles. *Inorganic Chemistry, 42*, 896-903.

Breugst, M., & Reissing, H. U. (2020). The Huisgen Reaction: Milestones of the 1,3-Dipolar Cycloaddition. *Angewandte Chemie International Edition, 59*, 12293-12307.

Brown, J. A., De Candole, B. C., Morgan, T., & Patent, W. O. (2009). *Chemical Abstract*.

Brown, J., De Candole, B., & Morgan, T. (2009). *Patent No. WO2009071888.*

Burns, A. R., Kerr, J. H., Kerr, W. J., Passmore, J., Paterson, L. C., & Watson, A. J. (2010). Tuned methods for conjugate addition to a vinyl oxadiazole; synthesis of pharmaceutically important motifs. *Organic Biomolecular Chemistry, 8*, 2777-2783.

Carroll, F. I., Gray, J. L., Abrahm, P., Kuzemko, M. A., Lewin, A. H., Boja, J. W., & Kuhar, M. J. (1993). 3-Aryl-2-(3'-substituted-1',2',4'-oxadiazol-5'-yl)tropane analogs of cocaine: affinities at the cocaine binding site at the dopamine, serotonin, and norepinephrine transporters. *Journal of Medicinal Chemistry, 36*, 2886-2890.

Cazin, C. S. (2011). *N-Heterocyclic Carbenes in Transition Metal Catalysis Organocatalysis.* New York,London: Springer, Dordrecht.

Chen, C., Senanayake, C. H., Bill, T. J., Larsen, R. D., Verhoeven, T. R., & Reider, P. J. (1994). Chen, C., Senanayake, C. H., Bill, T. J., Larsen, R. D., Verhoeven, T. R., & Reider, P. J. (1994). Journal of Organic Chemistry, 59. *Journal of Organic Chemistry, 59*, 3738-3741.

Cicchi, S., Cordero F.M., & Giomi, D. (2007). *Progress in Heterocyclic Chemistry, 18*, 288-309.

Clapp, L. B., Potts, K. T., Katritzky, A. R., & Rees, C. W. (1984). *Comprehensive Heterocyclic Chemistry, 6*, 365-391.

Clark, M. P., Laughlin, S. K., Laufersweiler, M. J., Bookland, R. G., Brugel, T. A., Golebiowski, A., . . . Janusz, M. J. (2004). Development of orally bioavailable bicyclic pyrazolones as inhibitors of tumor necrosis factor-α production. *Journal of Medicinal Chemistry, 47*, 2724-2727.

Coldham, L., & Hufton, R. (2005). Intramolecular Dipolar Cycloaddition Reactions of Azomethine Ylides. *Chemical Reviews, 105*, 2765-2809.

Confalone, P. N., & Huie, E. M. (1983). Intramolecular [3 + 2] cycloaddition routes to carbon-bridged dibenzocycloheptanes and dibenzazepines. *Journal Organic Chemistry, 48*, 2994-2997.

Cui, B., Zheng, B. L., He, K., & Zheng, Q. Y. (2003). Imidazole Alkaloids from Lepidium meyenii. *Journal of Natural Products, 66*, 1101-1103.

Dürüst, Y., & Karakuş, H. (2017). Microwave-assisted synthesis and crystal structure of some novel 1,2,4-oxadiazol-5-ylmethyl-1,2,3-triazoles. *Synthetic Communications, 47*, 660-670.

Dürüst, Y., Özer, B., & Cariuki, B. (2015). Synthesis and crystal structure of new heterocyles derived from saccharin and uracil carrying 1,2,4-oxadiazolylmethyl group. *Molecular Diversity, 19*, 213-230.

Das, A., & Banik, B. K. (2020). 26- Dipole Moment in Medicinal Research: Green and Sustainable Approach. *Green Approaches in Medicinal Chemistry for Sustainable Drug Design*, 921-964.

Demchenko, A. M., Sinchenko, V. G., Prodanchuk, N. G., Kovtunenko, V. A., Patratii, V. K., Tyltin, A. K., & Babichev, F. S. (1987). Synthesis and antifungal activity of 3-aryl-6,7-dihydro-5h-pyrrolo[1,2-a]imidazoles. *21*, 789-791.

Diana, G. D., Volkots, D. L., Nitz, T. J., Bailey, T. R., Long, M. A., Vescio, N., & Dutko, F. J. (1994). Oxadiazoles as Ester Bioisosteric Replacements in Compounds Related to Disoxaril. Antirhinovirus Activity. *Journal of Medicinal Chemistry, 37*, 2421-2436.

Edwards, T. K., Koeller, K. J., Slomczynska, U., Fok, K., Helmus, M., Bashkin, J. K., & Fisher, C. (2011). HPV episome levels are potently decreased by pyrrole-imidazole polyamides. *Antiviral Research, 91*, 177-186.

Fortuna, C., Barresi, V., & Berellini, G. (2008). Design and synthesis of trans 2-(furan-2-yl)vinyl heteroaromatic iodides with antitumour activity. *Bioorganic Medicinal Chemistry, 16*, 4150-4159.

Golushko, A. A., Khoroshilova, O. V., & Vasilyev, A. V. (2019). Synthesis of 1,2,4-Oxadiazoles by Tandem Reaction of Nitroalkenes with Arenes and Nitriles in the Superacid TfOH. *Journal of Organic Chemistry, 84*, 7495-7500.

Gothelf, K. V., & Jorgensen, K. A. (1998). Asymmetric 1,3-Dipolar Cycloaddition Reactions. *Chemical Reviews, 98*, 863-909.

Graczyk, P. P., Khan, A., Bhatia, G. S., Palmer, V., Medland, D., Numata, H., & Staddon, J. M. (2005). The neuroprotective action of JNK3 inhibitors based on the 6,7-dihydro-5H-pyrrolo[1,2-a]imidazole scaffold. *Bioorganic Medicinal Chemistry Letters*, 4666-4670.

Grigg , R., & Siridharan, V. (1993). In Advances in Cycloaddition. In D. Curran. Greenwich: JAI Press.

Grigg, R. (1987). Prototropic routes to 1,3- and 1,5-dipoles, and 1,2-ylides: applications to the synthesis of heterocyclic compounds. *Chemical Society Reviews, 16*, 89-121.

Heine, H. W., & Peavy, R. (1965). Aziridines XI. Reaction of 1, 2, 3-triphenylaziridine with diethylacetylene dicarboxylate and maleic anhydride. *Tetrahedron Letters*, 3123-3126.

Hemming, K. (2008). *1,2,4-Oxadiazoles.* UK: University of Huddersfield.

Houk, K. N., Sims, J., Watts, C. R., & Luskus, L. J. (1973). The Origin of Reactivity, Regioselectivity, and Periselectivity in 1,3-Dipolar Cycloadditions. *Journal of the American Chemical Society, 95*, 7287-7301.

Houk, K., & Yamaguchi, K. (1984). *In 1,3 Dipolar Cycloaddition Chemistry* (Vol. 2). (P. A., Ed.) New York: Wiley.

Hu, Q.-S., Sheng, S.-R., Liu, F., Cai, H., & Cai, M.-Z. (2008). Facile Solid-Phase Organic Synthesis of 5-Vinyl-Substituted 1, 2, 4-Oxadiazoles from Polymer-Bound α-Selenopropionic Acid. *Journal of Chinese Chemical Society, 55*, 768-771.

Hu, W. Q., Cui, Y. S., Wu, Z. J., Zhang, C. B., Dou, P. H., Niu, S. Y., Fu, J.Y., Liu, Y. (2015). Construction of spirocycles containing highly substituted pyrroli-dine and 1-indanone motifs with spiro quaternary stereogenic centers via 1,3-dipolar cycloaddition of 2-alkylidene-1-indanone and azomethine ylides promoted by simple imidazolium salts. *Royal Society of Chemistry, 5*, 70910-70914.

Huisgen, R. (1963). 1,3-Dipolar Cycloadditions. *Angewandte Chemie International Edition, 2*, 565-632.

Huisgen, R. (1963). Kinetics and Mechanism of 1,3-Dipolar Cycloadditions. *Angewandte Chemie International Edition, 2*, 633-696.

Huisgen, R. (1968). On the Mechanism of 1,3-Dipolar Cycloadditions. A Reply. *The Journal of Organic Chemistry, 33*, 2291-2297.

Huisgen, R. (1976). The Concerted Nature of 1,3-Dipolar Cycloadditions and the Question of Diradical Intermediates. *The Journal of Organic Chemistry, 41*, 403-419.

Huisgen, R. (1984). *In 1,3-Dipolar Cycloaddition Chemistry* (Vol. 1). New York: Padwa A. Edition Wiley.

Jiang, K., & Chen, Y. C. (2014). Organocatalytic Reaction Involving Nitrogen-Ylides. *Tetrahedron Letters, 55*, 2049-2055.

Jochim, J. (1996). In Comprehensive Heterocyclic Chemistry II. In A. Katritzky, C. Rees, & E. Seriven. London: Pergamon Press .

Jones, R. C., Howard, K. J., & Snaith, J. S. (1996). Cycloaddition of Homochiral Imidazolinium Ylides: A Route to Optically Active Pyrroloimidazoles. *Tetrahedron Letters, 37*, 1707-1710.

Jones, R. C., Howard, K. J., Snaith, J. S., Blake, A. J., Li, W. S., & Steel, P. J. (2011). Cycloaddition of homochiral dihydroimidazoles: A 1,3-dipolar cycloaddition route to optically active pyrrolo[1,2-a]imidazoles. *Organic & Biomolecular Chemistry, 9*, 297-306.

Jones, R. C., Nichols, J. R., & Cox, M. T. (1990). Annulation of Imıdazolines: A 1,3-Dipolar Cycloaddition route to Pyrroloimidazoles, Pyrrolidines and Pyrroles. *Tetrahedron Letters, 31*, 2333-2336.

Joule, J., & Mills, K. (2013). *In Heterocyclic Chemistry.* New york: John-Wiley and Sons 5th Eddition.

Kayukova, L. A. (2005). Synthesis of 1,2,4-Oxadiazoles. *Pharmaceutical Chemistry Journal, 39*, 32-40.

Kim, Y. J., & Varma, R. S. (2005). Microwave-assisted preparation of imidazolium-based tetrachloroindate(III) and their application in the tetrahydropyranylation of alcohols. *Tetrahedron Letters, 46*, 1467-1469.

Kitazume, T., Zulfigar, F., & Tanaka, G. (2000). Molten salts as a reusable medium for the preparation of heterocyclic compounds. *Green Chemistry, 2*, 133-136.

Ko, D., Patel, H., & Yavuz , C. (2015). Synthesis of Nanoporous 1,2,4-Oxadiazole Networks with High CO2 Capture Capacity. *Chemical Communication, 51*, 2915-2917.

Kochergin, P. M., Druzhinina, A. A., & Palei, R. M. (1966). Synthesis of Pyrrolo [1,2-a] Imidazole and Pyrrolo [1,2-a] Benzimidazole Derivatives. *Khimiya Geterotsiklicheskikh Soedinenii, 2*, 149-150.

Kumar, D., Patel, G., Chavers, A. K., Chang, K. H., & Shah, K. (2011). Synthesis of novel 1,2,4-oxadiazoles and analogues as potential anticancer agents. *European Journal of Chemistry, 46*, 3085-3092.

Ledniczky, L., & Seres, I. (1999). (inverntors, & P. I. 199904822, Eds.) *In Chem. Abstr, 130*, 172993.

Macor, J. E., Ordway, T., Smith, R. L., Verhoest, P. R., & Mack, R. A. (1996). Synthesis and Use of 5-Vinyl-1,2,4-oxadiazoles as Michael Acceptors. A Rapid Synthesis of the Potent Muscarinic Agonist L-670,548. *Journal Organic Chemistry, 61*, 3228-3229.

Malatesti, N., Boa, A. N., Clark, S., & Westwood, R. (2006). 1,3-Dipolar cycloaddition reactions of benzo[b]thiophene 1,1-dioxide with azomethine ylides. *Tetrahedron Letters, 47*, 5139-5142.

Marcilla, R., Blazquez, J. A., Rodriguez, J., Pomposo, J. A., & Mecerreyes, D. (2004). Tuning the Solubility of Polymerized Ionic Liquids by Simple Anion-Exchange Reactions. *Journal of Polymer Science, 42*, 208-212.

Marzullo, P., Pace, A., Pibiri, I., Piccionello, A. P., & Buscemi, S. (2020). Recent Advances on 1,2,4-Oxadiazoles: From Synthesis to Reactivity and Pharmaceutical Applications. *Chemical and Pharmaceutical Sciences and Technologies*, 377-397.

Musumarra, G., Ballistreri, F., Barresi, V., Benedetti, P., Caltabinao, G., Fortruna , C., & Longo , M. (2004). Design, synthesis and in vitro antitumor activity of new trans 2-[2-(heteroaryl)vinyl]-1,3-dimethylimidazolium iodides. *Bioorganic Medicinal Chemistry*, 1689-1695.

Najera, C., & Sansano, J. (2003). *Current Organic Chemistry, 7*, 1105-.

Ogura, H., & Kikuchi, K. (1972). Studies on Heterocyclic Compounds. XI. 1,3-Dipolar Cycloaddition of Benzimidazoliurn Ylide with Acetylenic Compounds. *Journal Organic Chemistry, 37*, 2679-2682.

O'Hagan, D. (2000). Pyrrole, pyrrolidine, pyridine, piperidine and tropane alkaloids. *Natural Product Reports, 17*, 435-446.

Orlek, B. S., Blaney, F. E., Brown, F., Clark, M. S., Hadley, M. S., Hatcher, J., & Wyman, P. (1991). *Journal of Medicinal Chemistry, 34*.

Pace , A., Buscemi , S., Piccionello, A., & Pibirini, I. (2015). Recent Advances in the Chemistry of 1,2,4-Oxadiazole. *Advanced Hetrocyclic Chemistry, 116*, 85-136.

Pace, A., & Pierro , P. (2009). The new era of 1,2,4-Oxadiazole. *Organic Biomolecular Chemistry, 7*, 4337- 4348.

Pace, A., Buscemi, S., Palumbo, P. A., & Pibiri, I. (2015). *Advances in Heterocyclic Chemistry, 116*, 85-136.

Padwa, A. (1994). *1,3-Dipolar Cycloadditions.* New York: John Wiley.

Palumbo , P. A., Pace, A., Buscemi, S., Vivona, N., & Pani, M. (2008). Synthesis of trifluoromethylated 2-benzoyl-and 2-aminoimidazoles from ring rearrangement of 1, 2, 4-oxadiazole derivatives. *Tetrahedron, 64*, 4004-4010.

Palumbo, P. A., Pace, A., & Buscemi, S. (2017). Rearrangements of 1,2,4-Oxadiazole: "One Ring to Rule Them All". *Chemistry of Heterocyclic Compounds, 53*, 936-947.

Pandey, G., Banerjee, P., & Gadre, S. R. (2006). Construction of Enantiopure Pyrrolidine Ring System via Asymmetric [3+2]-Cycloaddition of Azomethine Ylides. *Chemical Revies, 106*, 4484-4517.

Park, J. H., Raza, F., Jeon, S. J., Kim, H. I., Kang, T. W., Yim, D. B., & Kim, J. H. (2014). Recyclable N-heterocyclik carbene/palladium catalyst on graphene oxide for the aqueous-phase Suzuki reaction. *Tetrahedron Letters, 55*, 3426-3430.

Parra, M., Hidalgo, P., & Alderete, J. (2005). New Supramolecular Liquid Crystals Induced by Hydrogen Bonding Between Pyridyl-1,2,4-Oxadiazole Derivatives and 2,5-Thiophene Dicarboxylic Acid. *Liquid Crystals, 32*, 449-455.

Pearson, W., & Stoys, P. (2003). 1, 3-Dipolar cycloaddition− decarboxylation reactions of an azomethine ylide with isatoic anhydrides: formation of novel benzodiazepinones. *Synlett*, 903.

Phillips, W., & Ratts, K. (1970). Basicity of N- Ylides. *Journal of Organic Chemistry, 35*, 3145-3147.

Piccionello, A., Pace , A., & Buscemi, S. (2011). Tandem Reactions of 1,2,4-Oxadiazoles with Allylamines. *Organic Letters, 13*, 4749-4751.

Pidlypnyi, N., Wolf, S., Liu, M., Rissanen, K., Nieger, M., & Schmidt, A. (2014). N-Heterocyclic carbenes from ylides of indolyl-imidazolium, azaindolyl-imidazolium, and indolyl-triazolium salts, and their borane adducts. *Tetrahedron, 70*, 8672-8680.

Riduan, S. N., & Zhang, Y. (2013). Imidazolium salts and their polymeric materials for biological applications. *Chemical Society Review, 42*, 9055-9071.

Roberts, L., Brennan, P., Fish, P., Storer, R., & Whitlock, G. (2009). 6, 7-Dihydro-5H-pyrrolo [1, 2-a] imidazoles as potent and selective α1A adrenoceptor partial agonists. *Bioorganic Medicinal Chemistry Letters, 19*, 3113-3117.

Rosa , M. F., Morcelli, A. C., & Lobo, V. S. (2015). 1,2,4-Oxadiazole: A Brief Review From The Literature About The Synthesis and Pharmacological Applications. *Visao Academica*, 130-157.

Salahuddin, Mazumder, A., Yar, M. S., Mazumder, R., Chakraborthy, G. S., Ahsan, M. J., & Rahman, M. U. (2017). Updates on Systhesis and Biological Activities of 1,3,4-Oxadiazole. *Synthetic Communications, 47*, 1805-1847.

Sathiyamoorthi, S., Almansour, A. I., Raju, S. K., Natarajan, A., & Kumar, R. R. (2020). Imidazolium ylide mediated Knoevenagel-Michael-O-cyclization sequence for the synthesis of multi-substituted 4,5-dihydrofurans. *Synthetic Communications*, 1-12.

Sathiyamoorthi, S., Almansour, A. I., Raju, S. K., Natarajan, A., & Kumar, R. R. (2021). Imidazolium ylide mediated tandem Knoevenagel–Michael–O-cyclization sequence for the synthesis of multi-substituted 4,5-dihydrofurans. *Synthetic Communications, 51*, 234-244.

Saunders, J., & Freedman, S. B. (1989). The design of full agonists for the cortical muscarinic receptor. *Trends in Pharmacological Sciences, 70*, 70-75.

Schlingmann, G., Taniguchi, T., He, H. Y., Bigelis, R., Yang, H. Y., Koehn, F. E., & Berova, N. (2007). Reassessing the Structure of Pyranonigrin. *Journal of Natural Products, 70*, 1180-1187.

Shen, Y. M., Lv, P. C., Zhang, M. Z., Xiao, H. Q., Deng, L. P., & Zhu, H. L. (2011). Synthesis and antiproliferative activity of multisubstituted N-fused heterocycles against the Hep-G2 cancer cell line. *Original Paper, 142*, 521-528.

Singh, S. K., & Savoy, A. W. (2020). Ionic liquids synthesis and applications: An overview. *Journal of Molecular Liquids, 297*, 1-23.

Somani, R. R., & Shirodkar, P. Y. (2009). Oxadiazole: A Biologically Important Heterocycle. *Der Pharma Chemica, 1*, 130-140.

Staudinger, H., & Meyer, J. (1919). Über neue organische phosphorverbindungen III. Phosphinmethylenderivate und phosphinimine. *Helvatica Chimia Acta, 2*, 635-646.

Street, L. J., Baker , R., Castro, J. L., Chambers, M. S., Guiblin, A. R., Hoobs, S. C., & Hargreaves, R. J. (1993). *Journal of Medicinal Chemistry, 36*.

Street, L. J., Baker, R., Book, T., Kneen, C. O., MacLeod, A. M., Merchant, K. J., & Harley, E. A. (1990). Novel quinuclidine-based ligands for the muscarinic cholinergic receptor. *Journal of Medicinal Chemistry, 33*, 1128-1138.

Sustmann, R. (1974). Orbital Energy Control of Cycloaddition Reactivity. *Physical Organic Chemistry-2*, 569-593.

Swain, C. J., Baker, R., Kneen, C., Moseley, J., Saunders, J., Seward, E. M., & Watling, K. (1991). Novel 5-HT3 Antagonists. Indole Oxadiazoles. *Journal of Medicinal Chemistry, 34*, 140-151.

Taher, A., Lee, K. C., Han, H. J., & Kim, D. W. (2017). Pyrene-Tagged Ionic Liquids: Separable Organic Catalysts for SN2 Fluorination. *Organic Letters*, A-D.

Tiemann, F., & Krüger, P. (1884). Ueber Amidoxime und Azoxime. *Berichte Der Deutschen Chemischen Gesellschaft, 17*, 1685-1698.

Wait , P., Flynn, G., Huber, E., & Sabol, J. (1996). Constrained amino acids. An approach to the synthesis of 3-substituted prolines. *Tetrahedron Letters, 37*, 4091-4094.

Wang, K. M., Ma, Y. L., Lin, X. R., Yan, S. J., & Lin, J. (2015). Regioselective Synthesis of Pyrrolo [1,2-a] Imidazoles and Imidazol[1,2-a] Pyridines. *The Royal Society of Chemistry*, 1-9.

Wang, Y.-G., Xu, W.-M., & Huang, X. (2007). Selenium-Based Safety-Catch Linker: Solid-Phase Synthesis of Vinyl-Substituted Oxadiazoles and Triazoles. *Journal of Combinatorial Chemistry, 9*, 513-519.

Watjen, F., Baker, R., Engelstoff, M., Herbert, R., MacLeod, A., Knight, A., & Springer, J. P. (1989). Novel benzodiazepine receptor partial agonists: oxadiazolylimidazobenzodiazepines. *Journal of Medicinal Chemistry, 32*, 2282-2291.

Wei, H., He, C., Zhang, J., & Shreeve, J. M. (2015). Combination of 1,2,5-Oxadiazole Moieties for the Generation of High-Performance Energetic Materials. *Angewandte Chemie International Edition, 127*, 9499-9503.

Wikes, J. S., Levisky, J. A., Wilson, R. A., & Hussey, C. L. (1982). Dialkylimidazolium Chloroaluminate Melts: A New Class of Room-Temperature Ionic Liquids for Electrochemistry, Spectroscopy, and Synthesis. *Inorganic Chemistry, 21*, 1263-1264.

Woodward, R., & Hoffmann, R. (1970). *The Conservation of Orbital Symmetry.* Weinheim Germany: Verlag Chemie .

Yan, T., Cheng, G., & Yang, H. (2019). 1,2,4-Oxadiazole-Bridge Polynitropyrazole Energetic Materials with Enhanced Thermal Stability and Low Sensitivity. *ChemPlusChem, 84*, 1567-1577.

Zeng, Z., Jin, H., Xie, J., Tian , B., Rudolph, M., & Rominger, A. S. (2017). Alfa-Imino Gold Carbenes from 1,2,4-Oxadiazoles: Atom -Economical Access to Full Substituted Aminoimidazoles. *Organic Letters, 19*, 1020-1023.

Zhang, L., Peng, X. M., Damu, G. L., Geng, R. X., & Zhou, C. H. (2014). Comprehensive Review in Current Developments of Imidazole-Based Medicinal Chemistry. *Medicinal Research Reviews, 34*, 340-437.

Zhang, Y., Shen, Y., Yuan, J., Han, D., Wang, Z., Zhang, Q., & Niu, L. (2006). Design and Synthesis of Multifunctional Materials Based on an Ionic-Liquid Backbone. *Angewandte Chemie, 118*, 5999-6002.

Zhao, Y., Lei, M., Yang, L., Han, F., Li, Z., & Xia, C. (2012). Oxygen- Sulfur Rearrangement in the Reaction of Thiocarbamate Imidazolium Ylide with Arylaldehyde. *Organic Biomolecular Chemistry, 10*, 8956-8959.

Zhong, R., Lindhorst, A. C., Groche, F. J., & Kühn, F. E. (2017). Immobilization of N-Heterocyclic Carbene Compounds: A Synthetic Perspective. *Chemical Reviews, 117*, 1970-2058.

Zugravecu, I., & Petrovanu, M. (1976). *N-Ylide Chemistry.* New York: McGraw Hill International .

Zugravescu, I., & Petrovanu, M. (1976). *N-Ylide Chemistry.* New York: McGraw Hill International Book.

7. APPENDICES

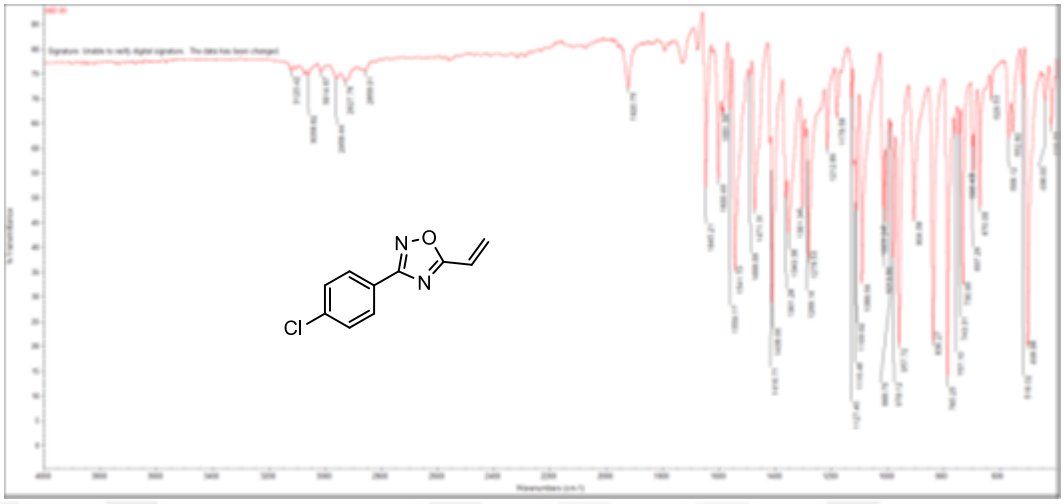


Figure 7.1. IR Spectrum of compound **96b.**

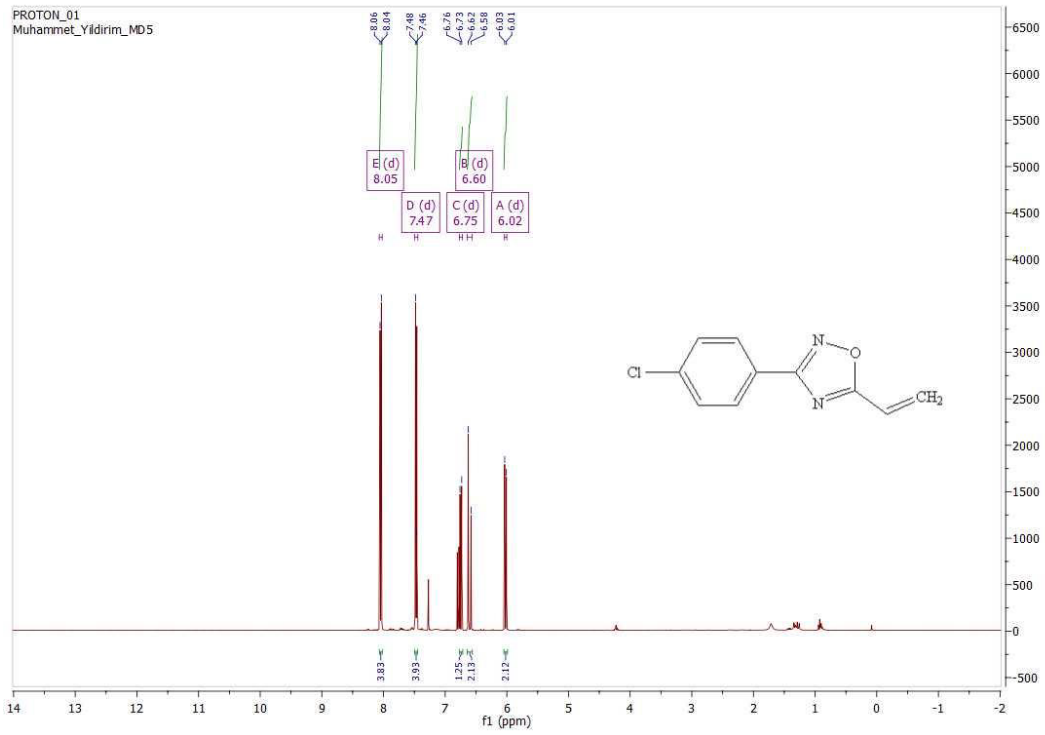


Figure 7.2. ^{1}H-NMR Spectrum of compound **96b.**

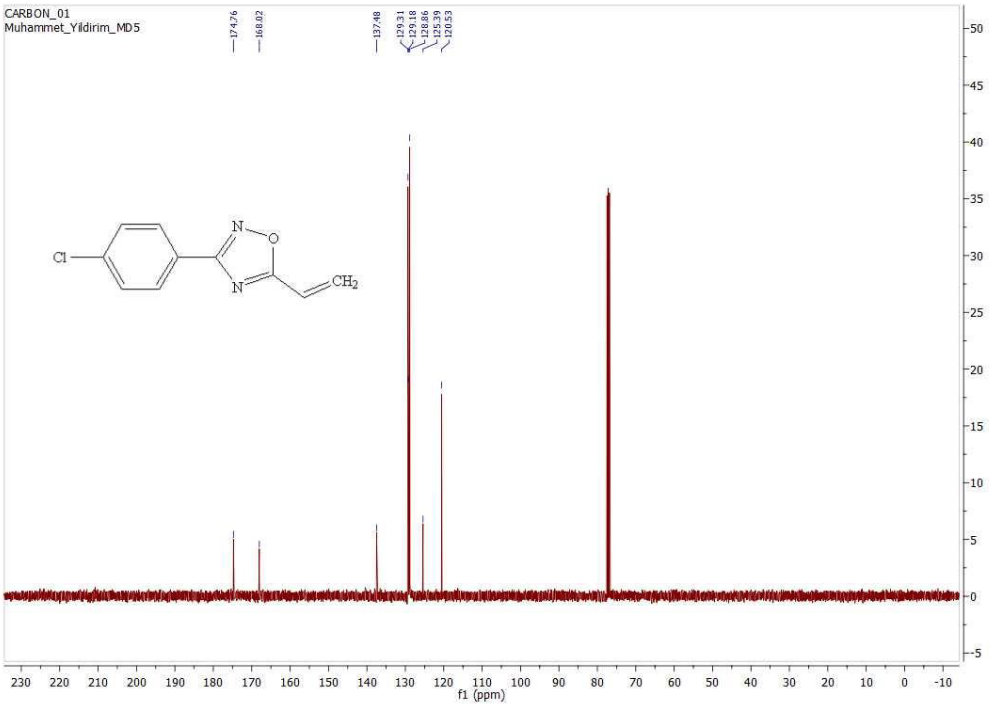


Figure 7.3. ^{13}C-NMR Spectrum of compound **96b.**

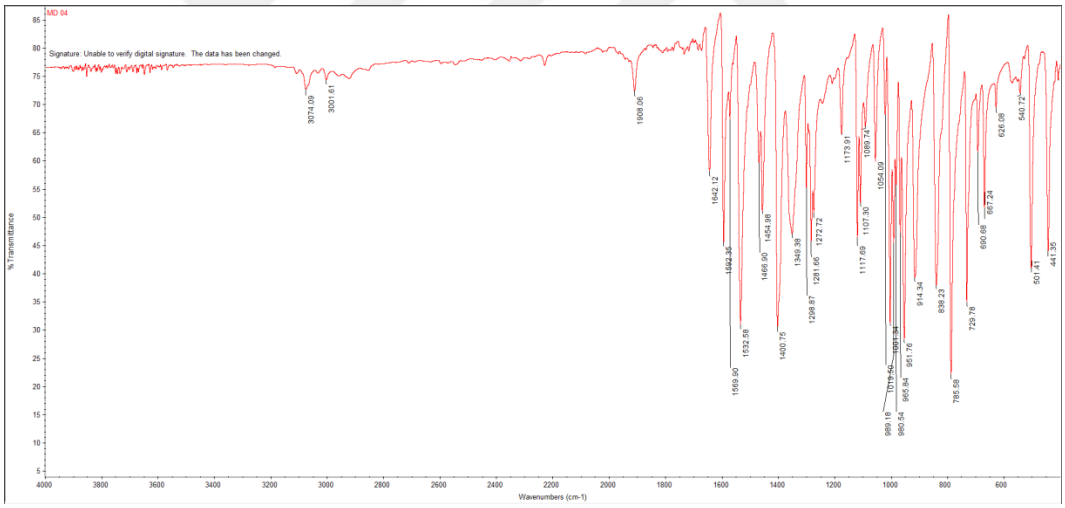


Figure 7.4. IR Spectrum of compound **96c.**

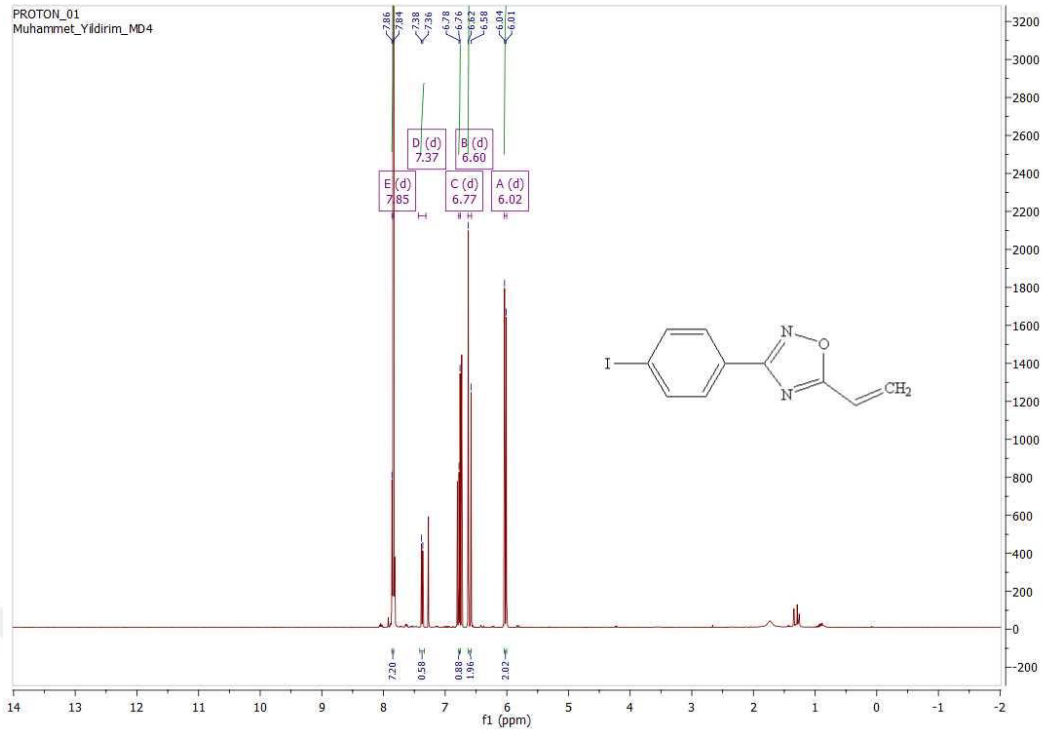


Figure 7.5. [1]H-NMR Spectrum of compound **96c.**

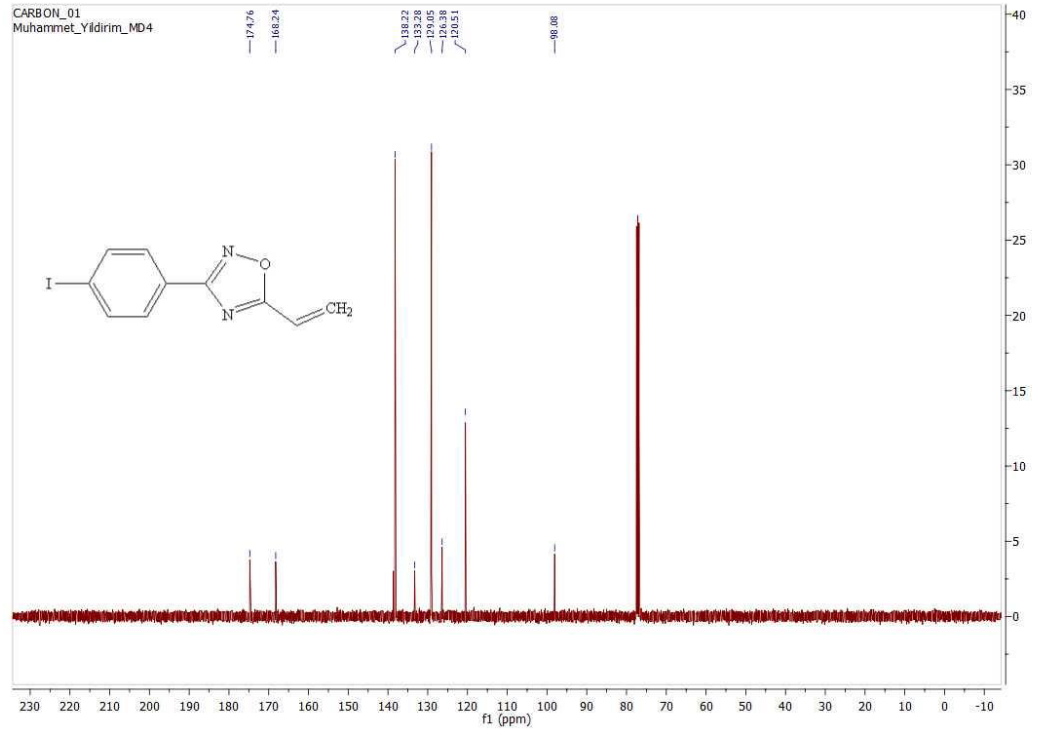


Figure 7.6. [13]**C**-NMR Spectrum of compound **96c.**

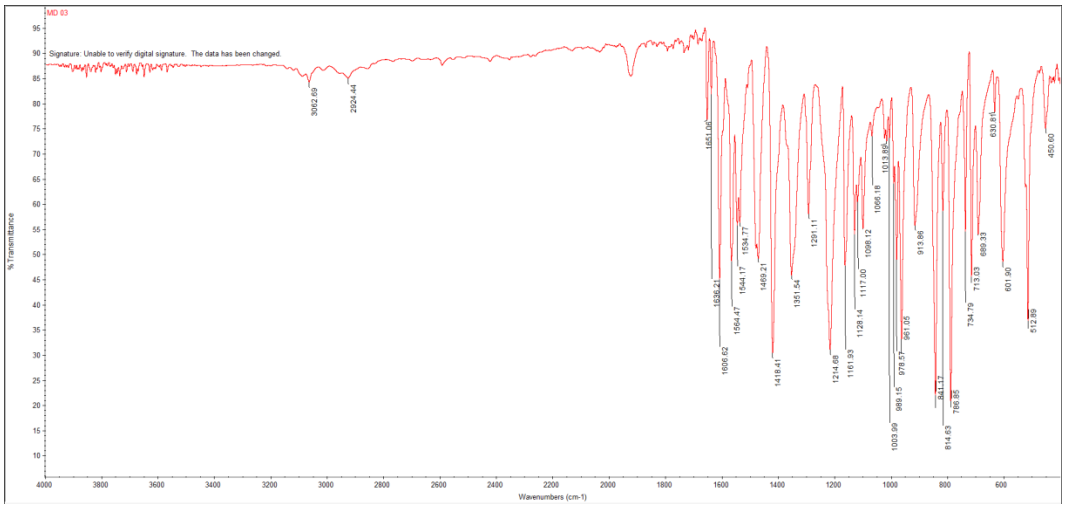


Figure 7.7. IR Spectrum of compound **96d.**

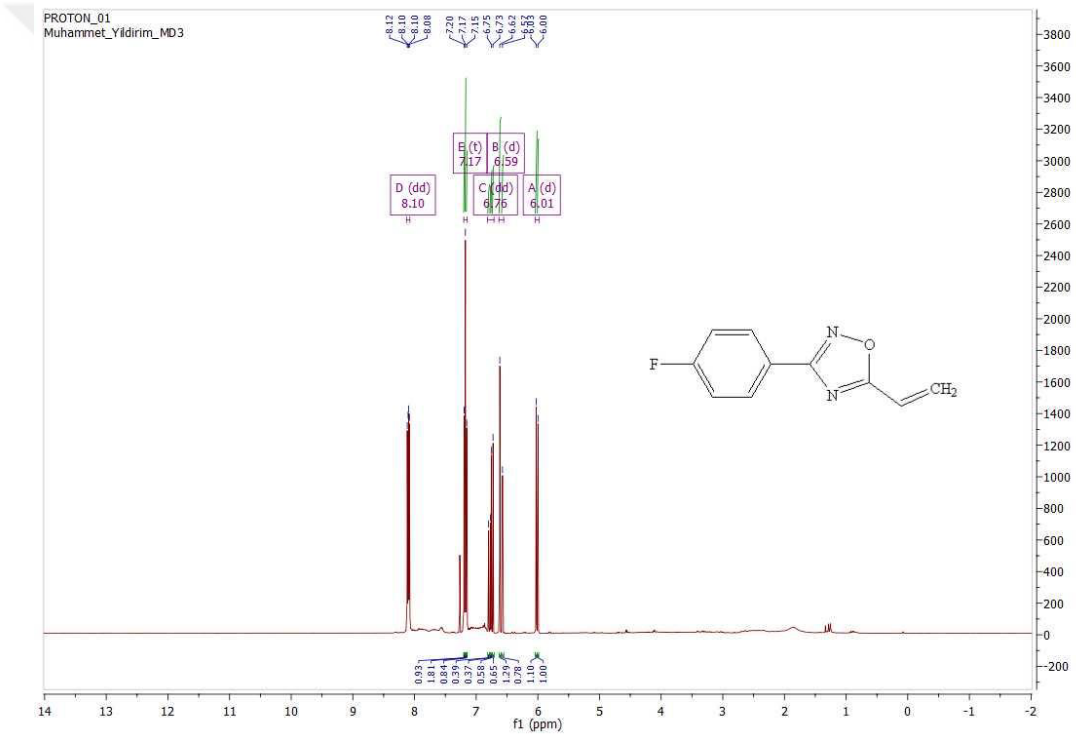


Figure 7.8. ^{1}H-NMR Spectrum of compound **96d.**

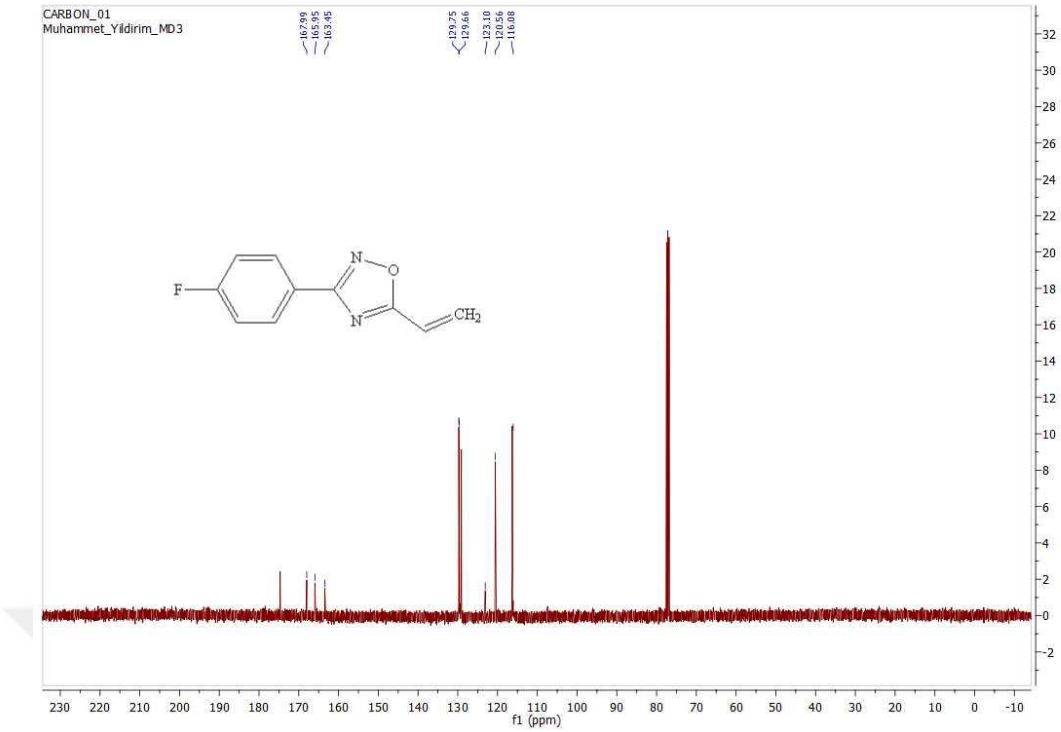


Figure 7.9. ^{13}C-NMR Spectrum of compound **96d.**

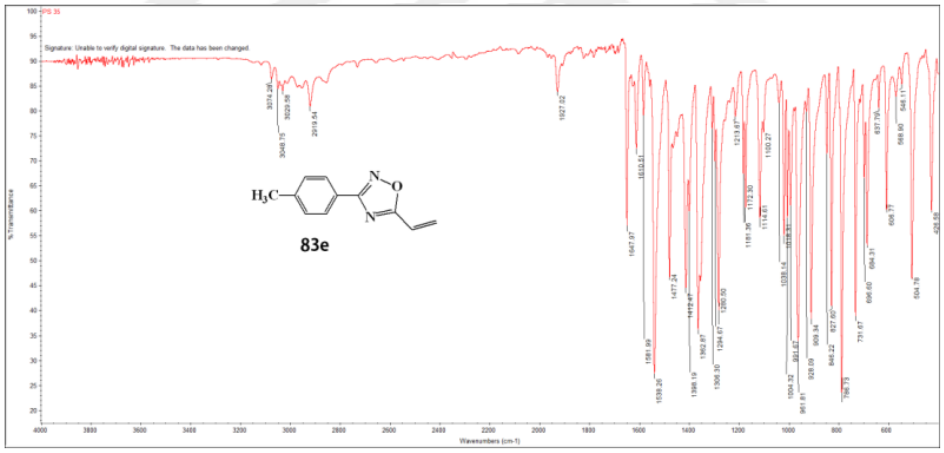


Figure 7.10. IR Spectrum of compound **96e.**

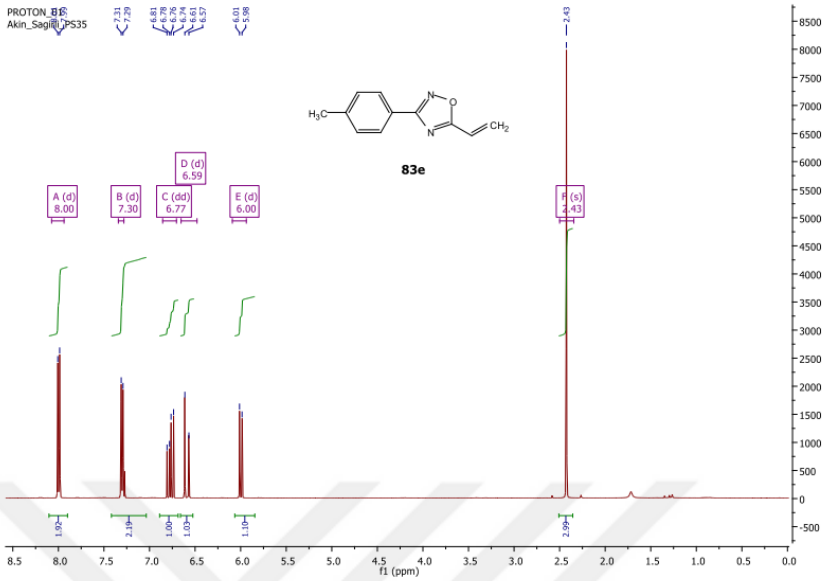


Figure 7.11. ^{1}H-NMR Spectrum of compound **96e.**

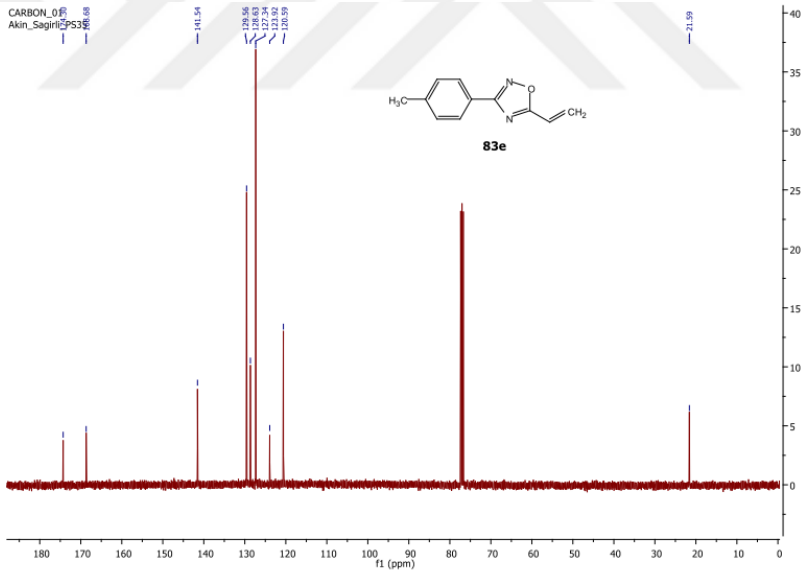


Figure 7.12. ^{13}C-NMR Spectrum of compound **96e.**

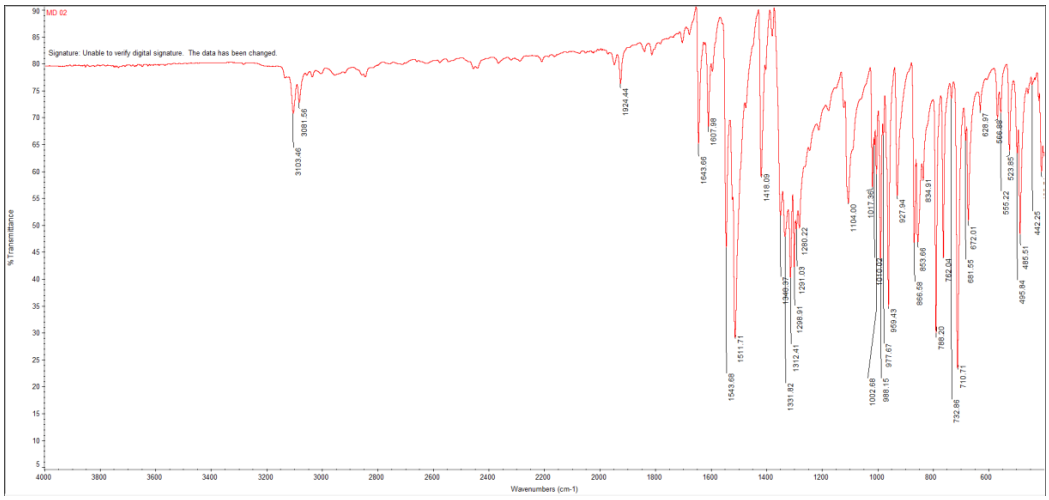


Figure 7.13. IR Spectrum of compound **96f.**

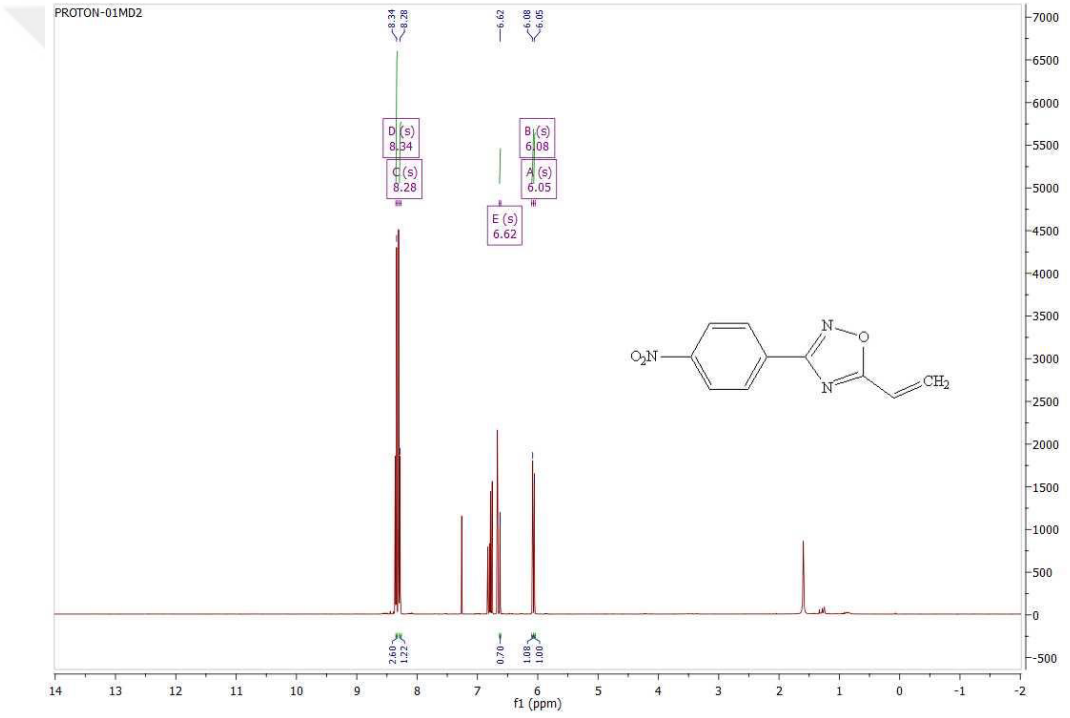


Figure 7.14. [1]H-NMR Spectrum of compound **96f.**

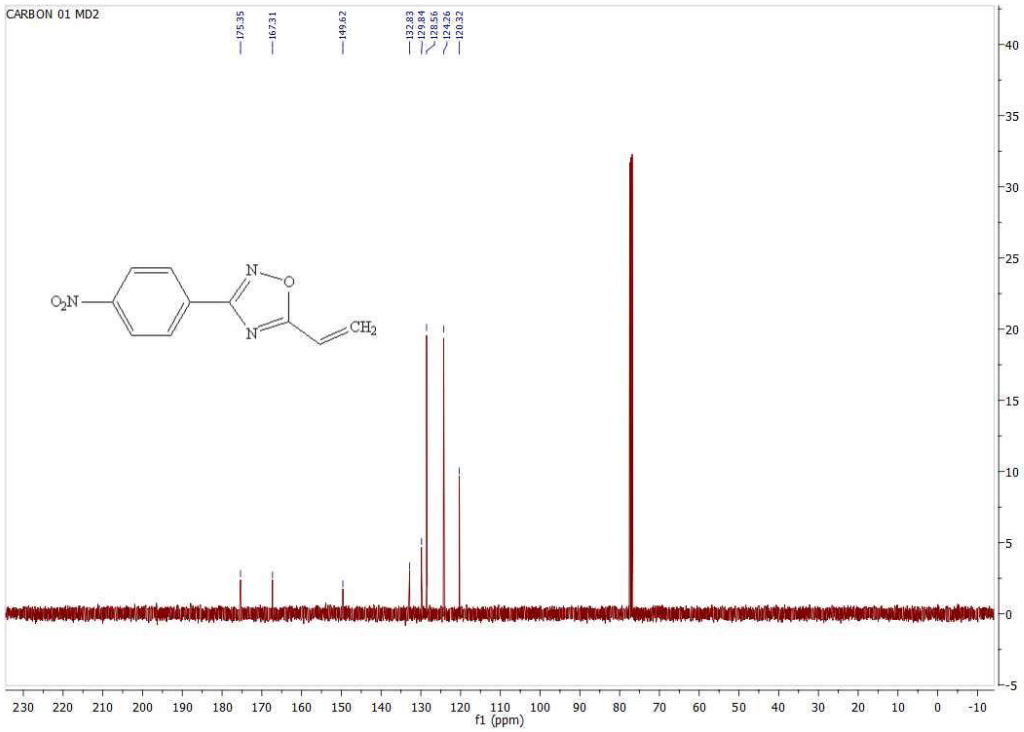


Figure 7.15. ^{13}C-NMR Spectrum of compound **96f.**

Figure 7.16. IR Spectrum of compound **96g.**

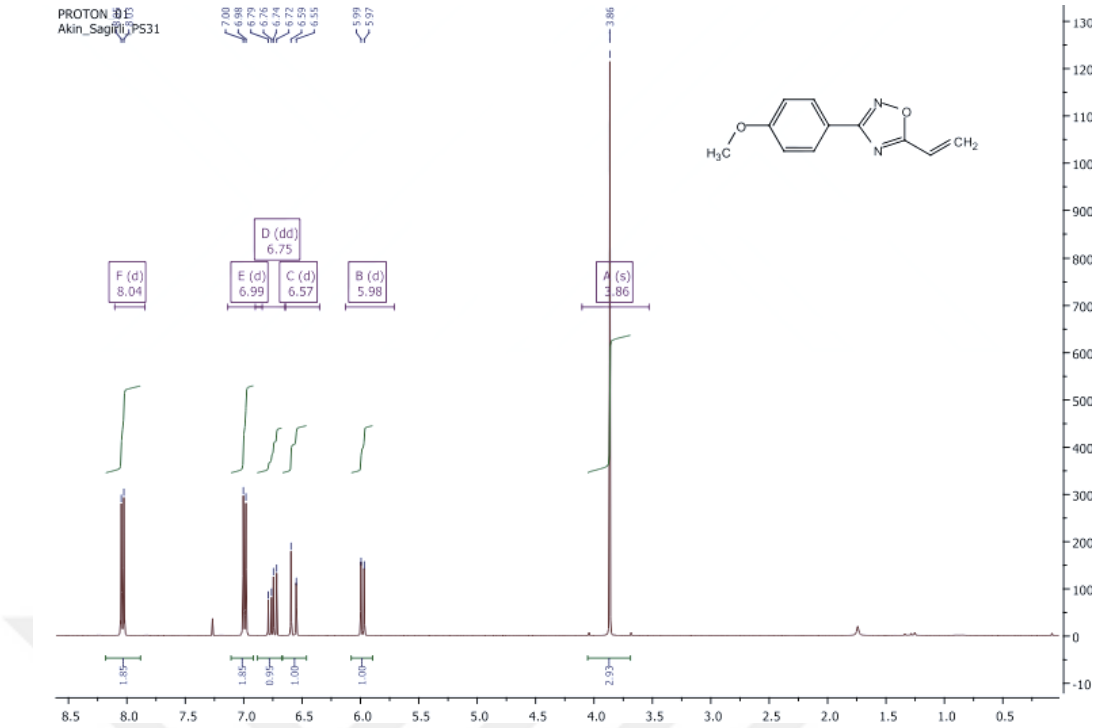


Figure 7.17. ^{1}H-NMR Spectrum of compound **96g.**

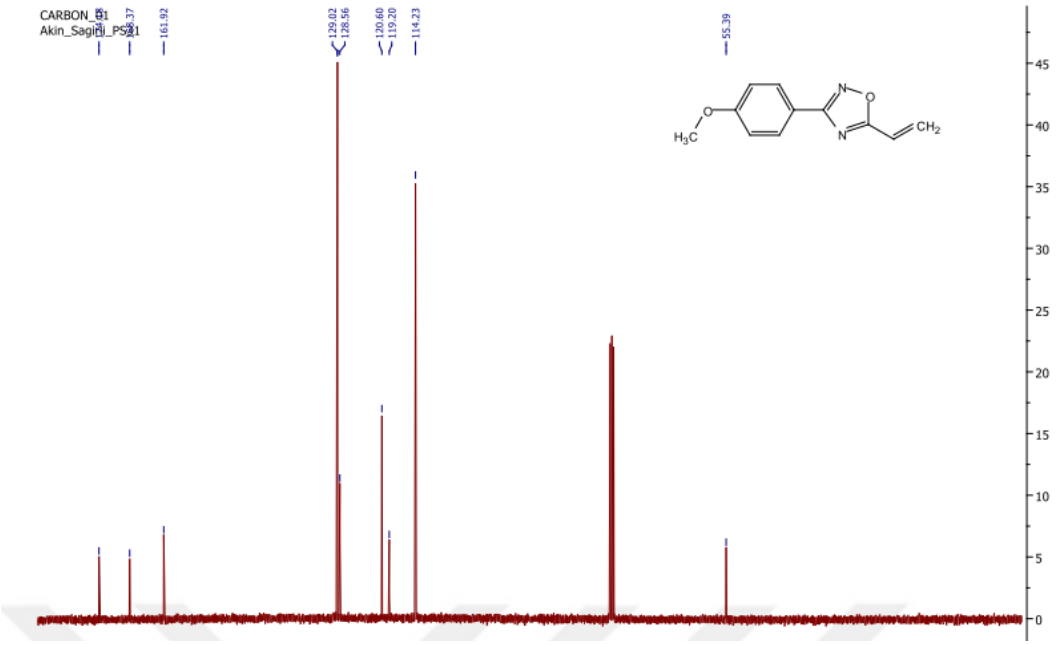


Figure 7.18. ^{13}C-NMR Spectrum of compound **96g.**

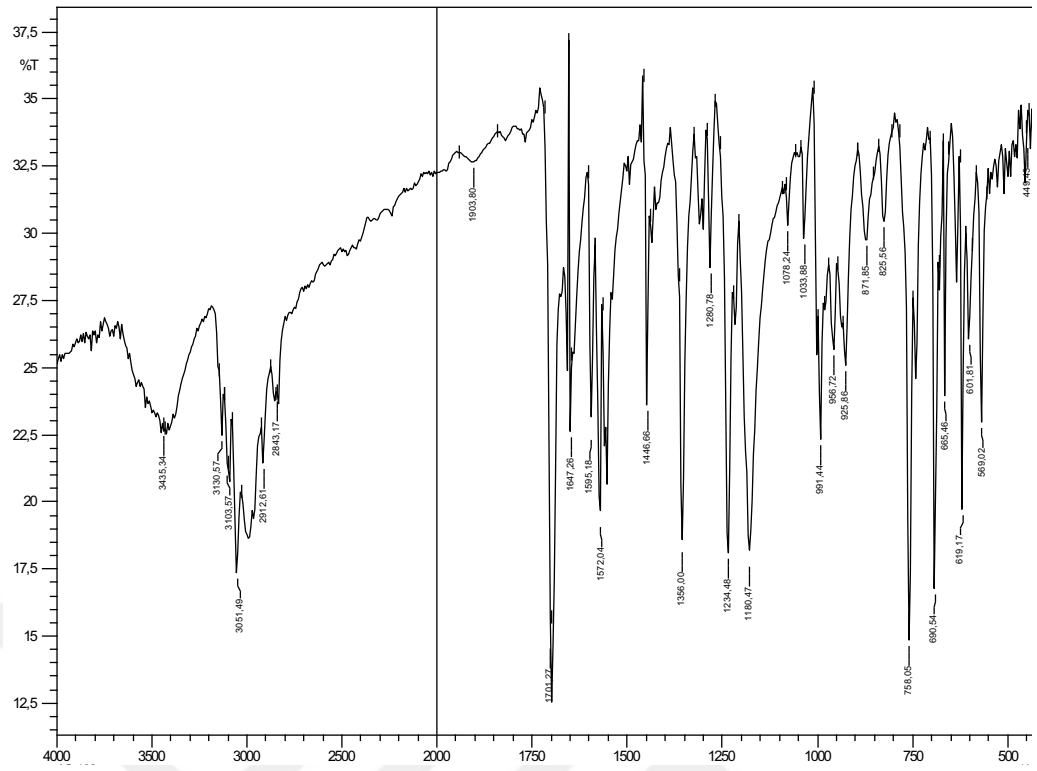


Figure 7.19. IR spectrum of compound **99.**

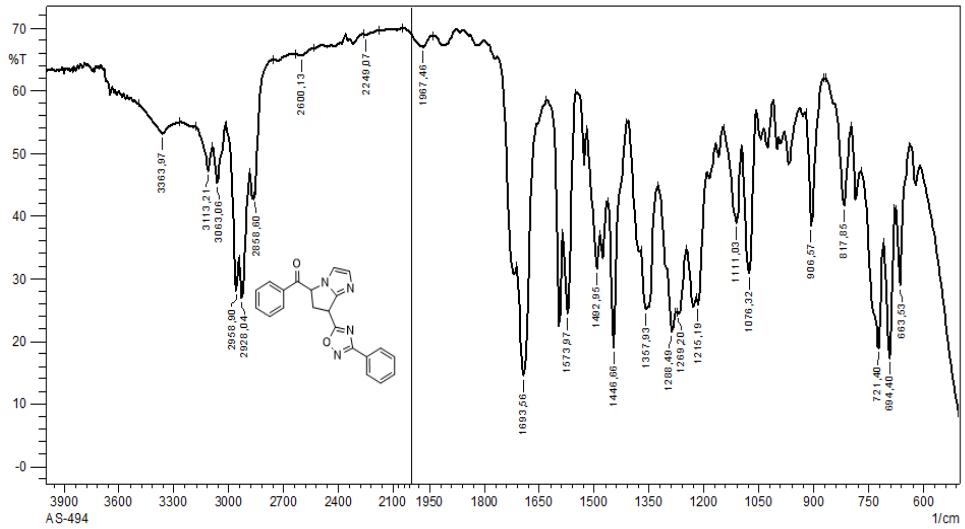


Figure 7.20. Hata! Başvuru kaynağı bulunamadı.IR spectrum of compound **100a.**

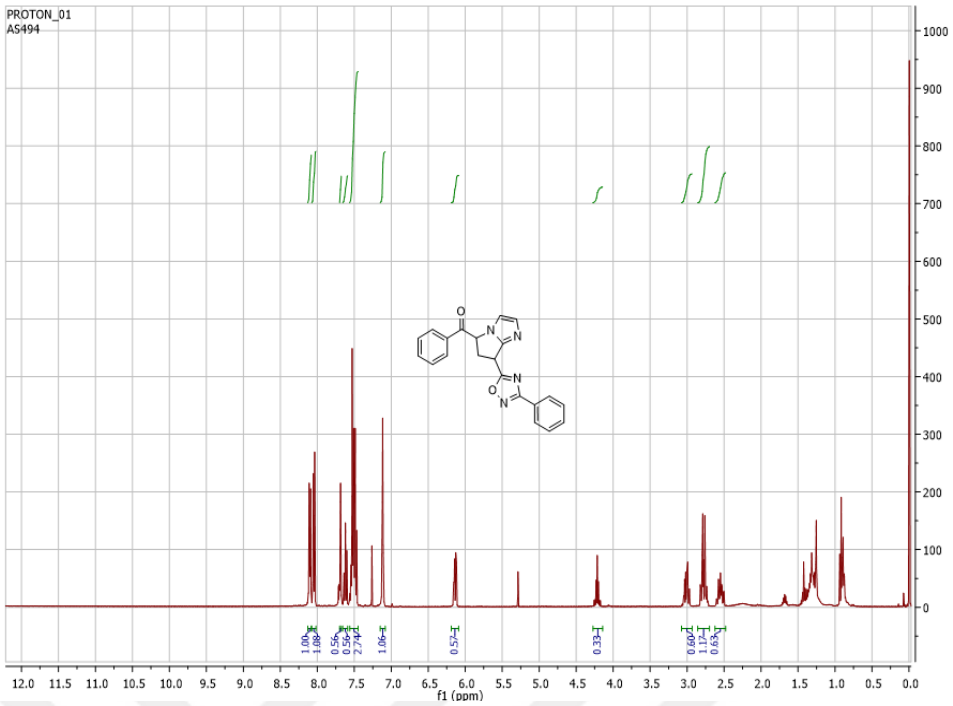


Figure 7.21. ^{1}H NMR spectrum of compound **100a.**

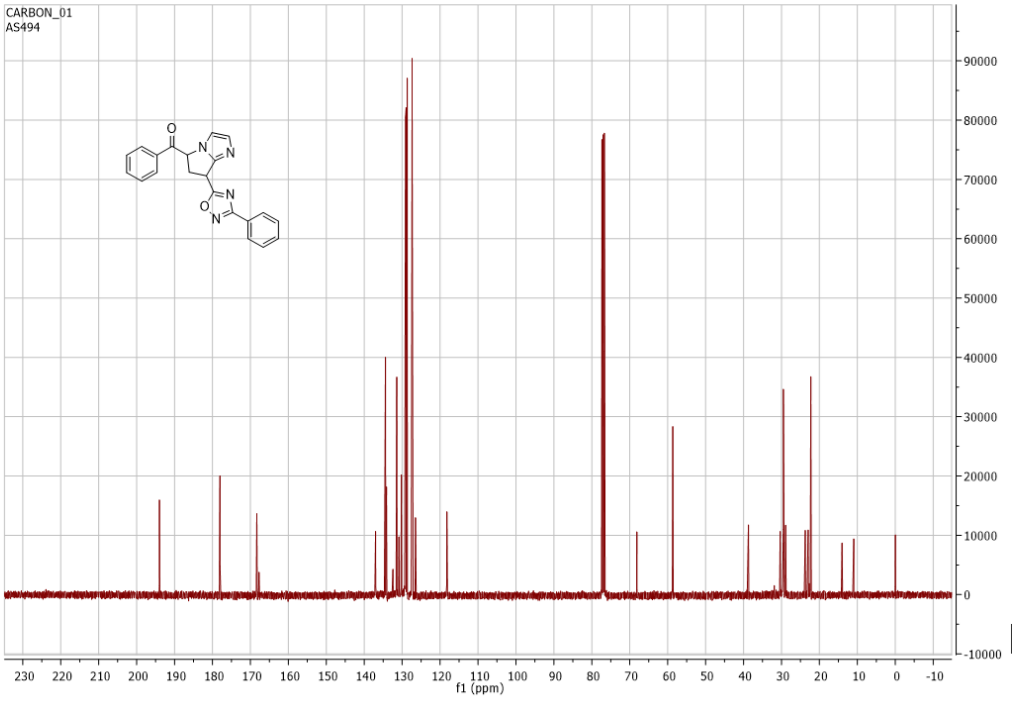


Figure 7.22. ^{13}C NMR spectrum of compound **100a.**

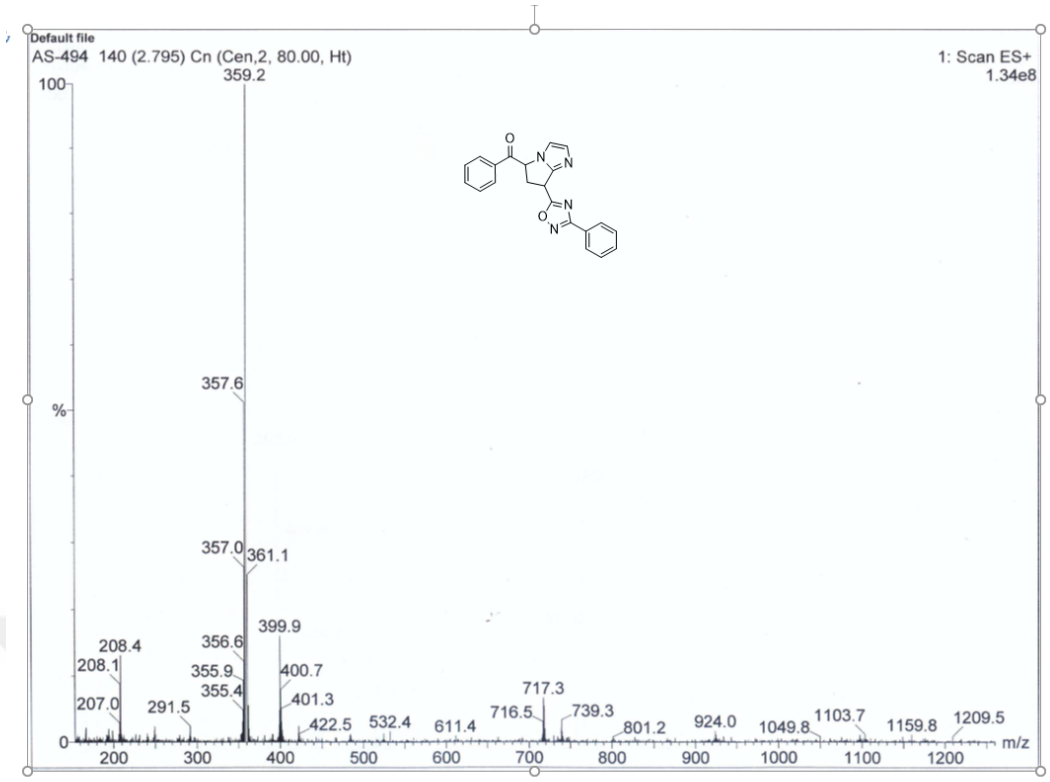


Figure 7.23. LC-MS spectrum of compound **100a.**

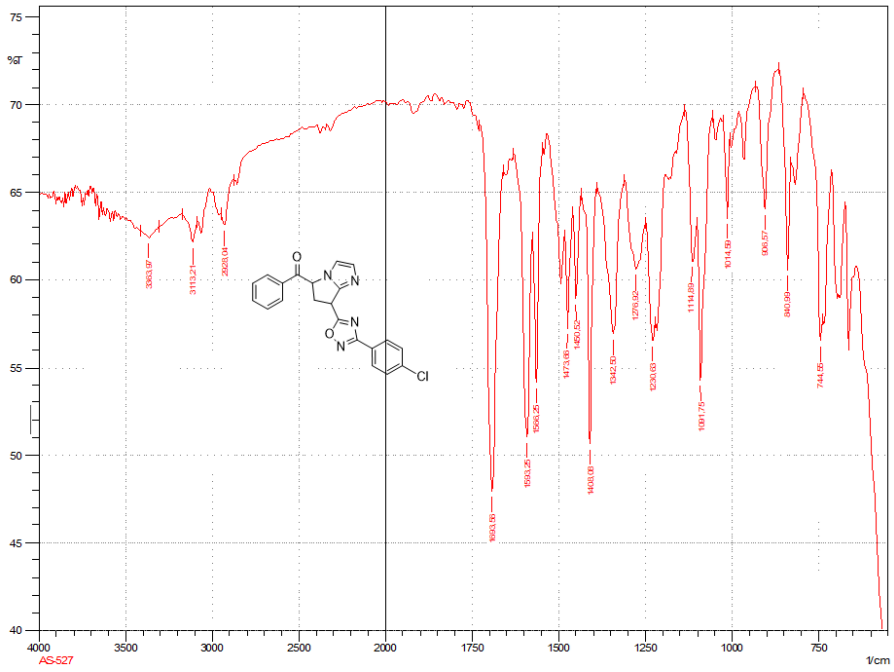


Figure 7.24. IR spectrum of compound **100b.**

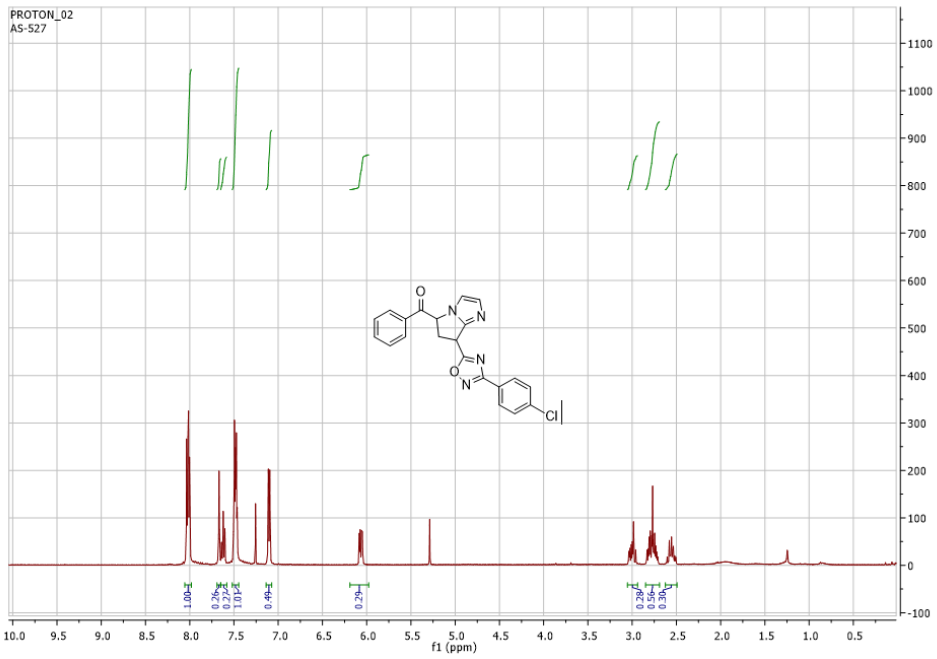


Figure 7.25. ^{1}H NMR spectrum of compound **100b.**

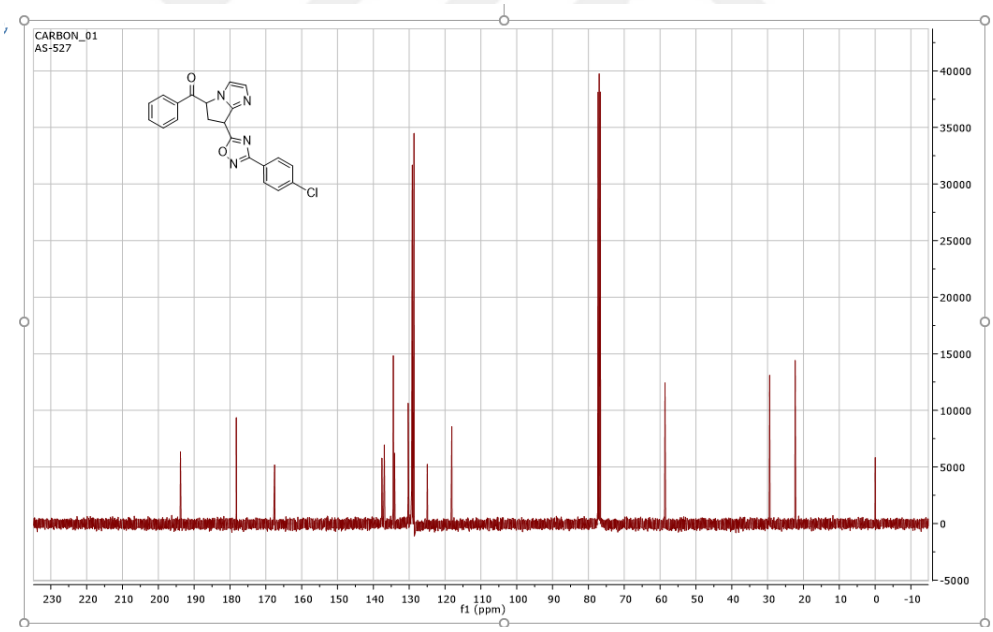


Figure 7.26. ^{13}**C** NMR spectrum of compound **100b.**

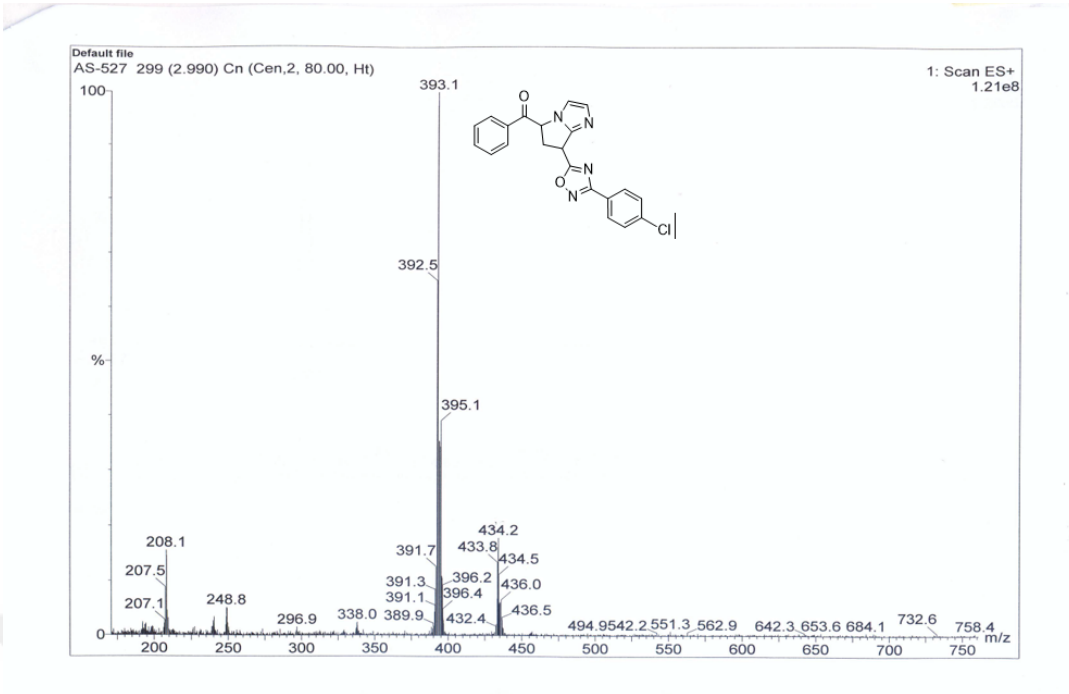


Figure 7.27. LC-MS spectrum of compound **100b.**

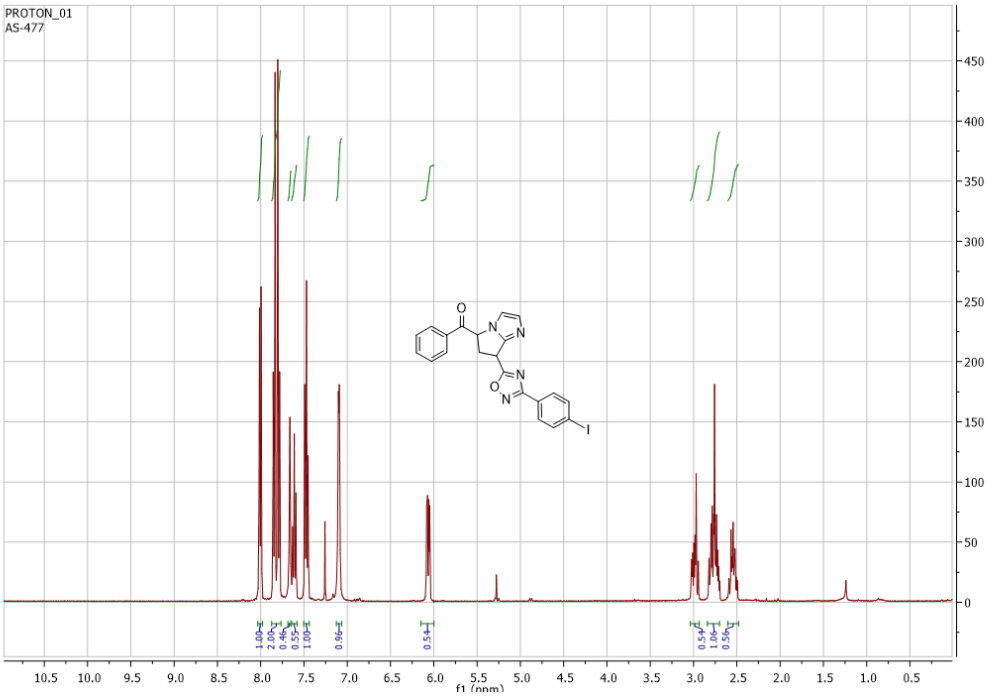


Figure 7.28. ^{1}H NMR spectrum of compound **100c.**

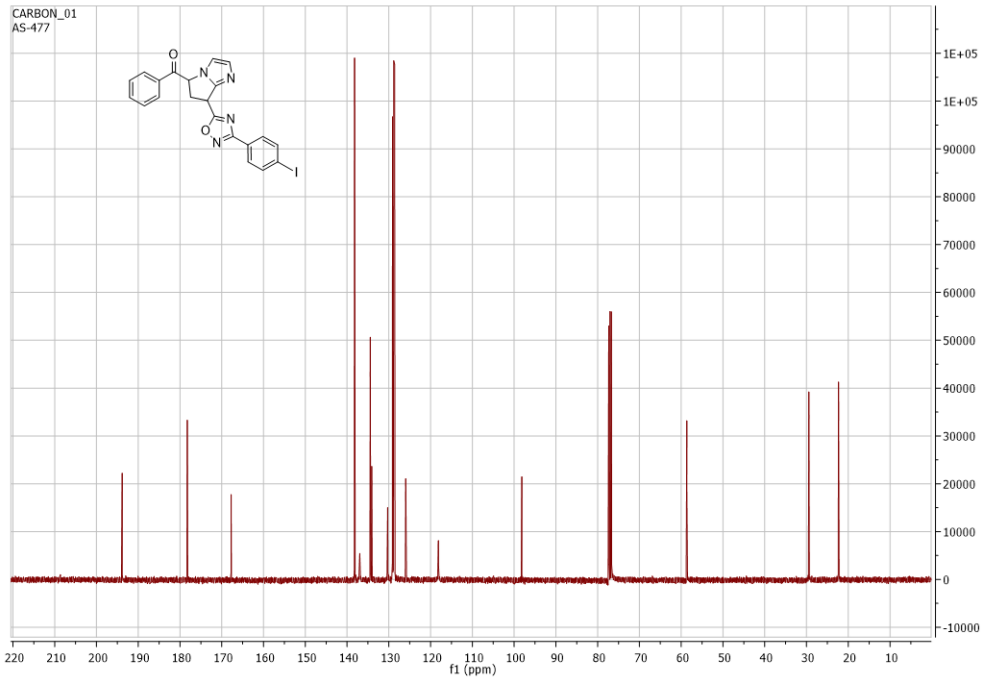


Figure 7.29. ^{13}C NMR spectrum of compound **100c.**

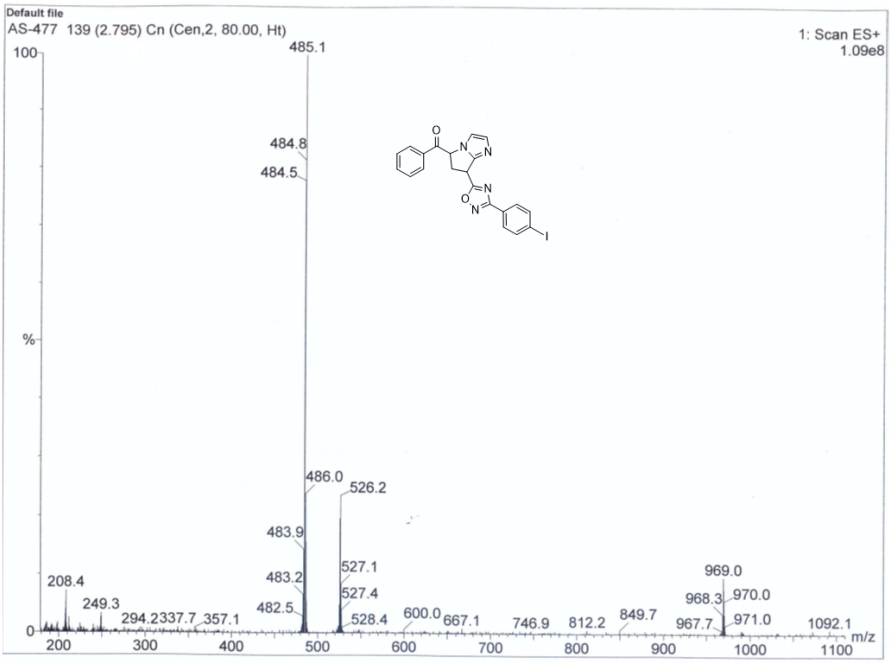


Figure 7.30. LC-MS spectrum of compound **100c.**

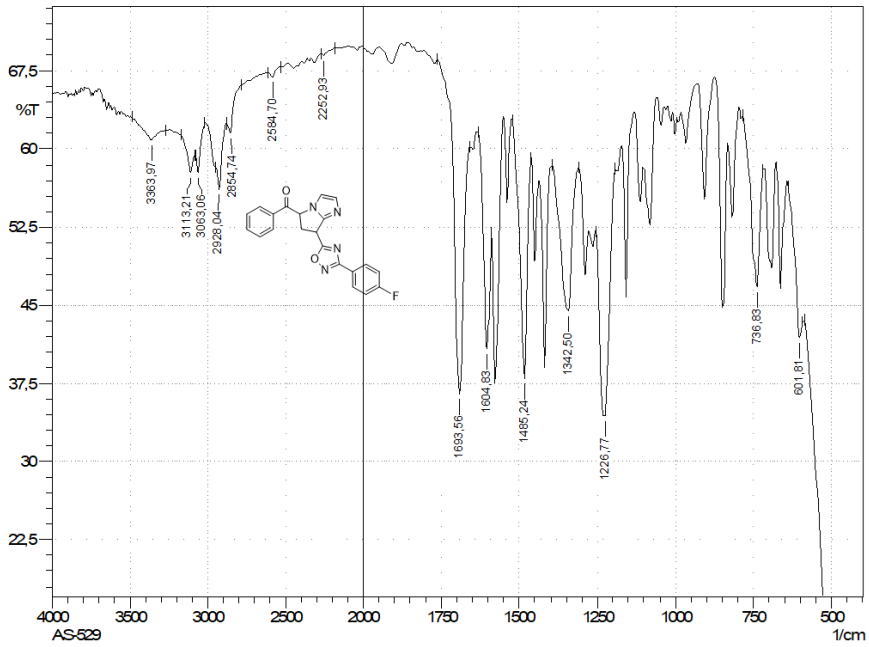


Figure 7.31. IR spectrum of compound **100d.**

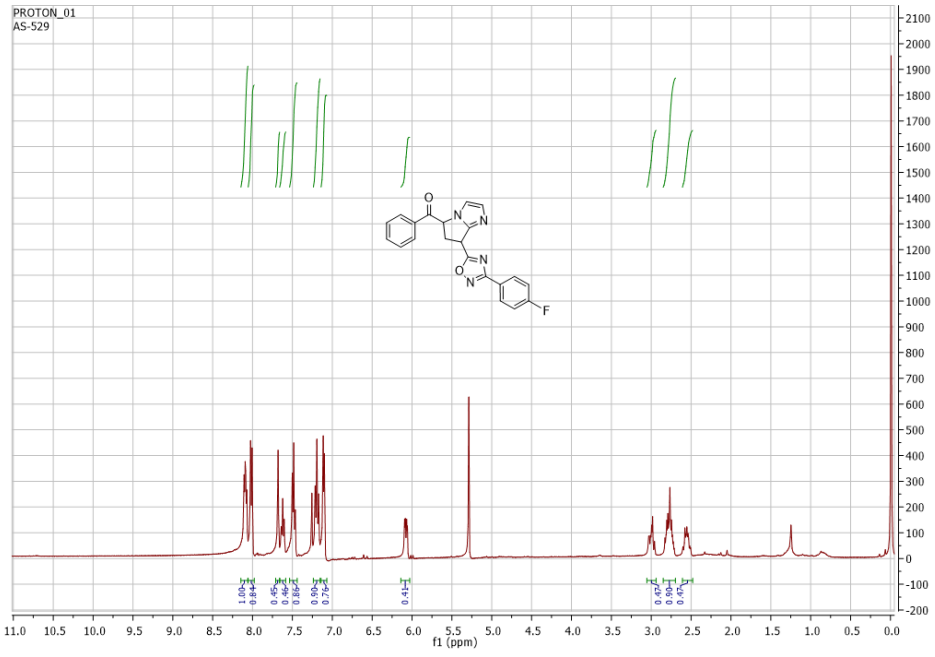


Figure 7.32. ^{1}H NMR spectrum of compound **100d.**

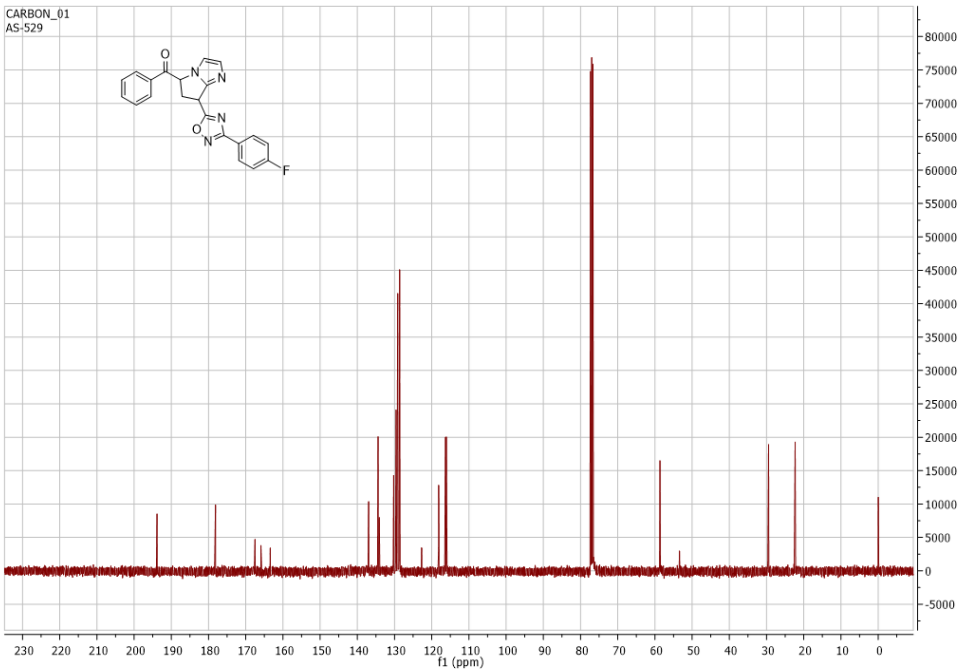


Figure 7.33. ^{13}C NMR spectrum of compound **100d.**

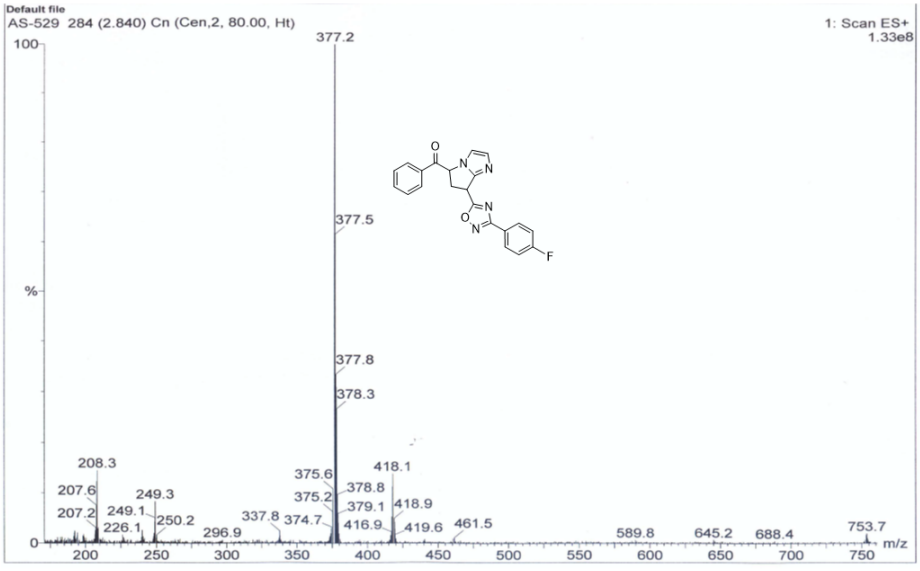


Figure 7.34. LC-MS spectrum of compound **100d.**

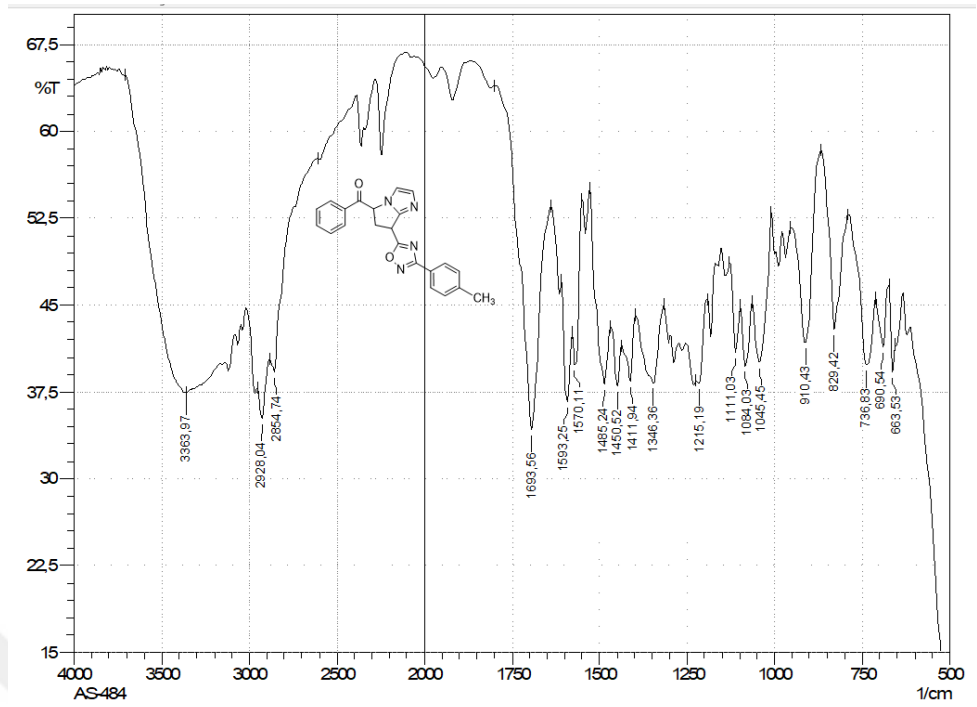


Figure 7.35. IR spectrum of compound **100e.**

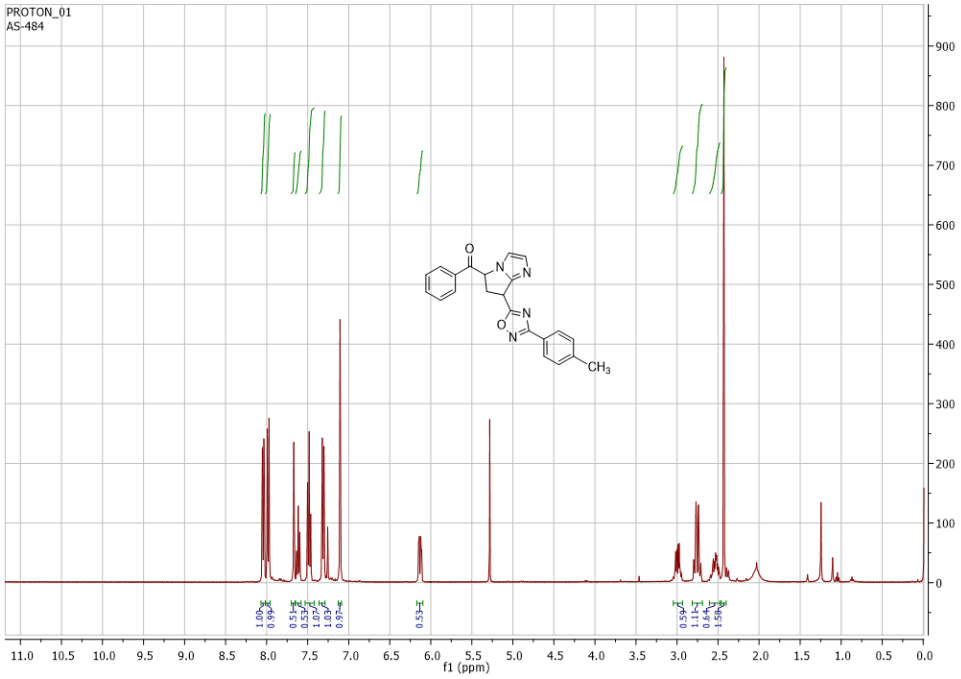


Figure 7.36. ^{1}H NMR spectrum of compound **100e.**

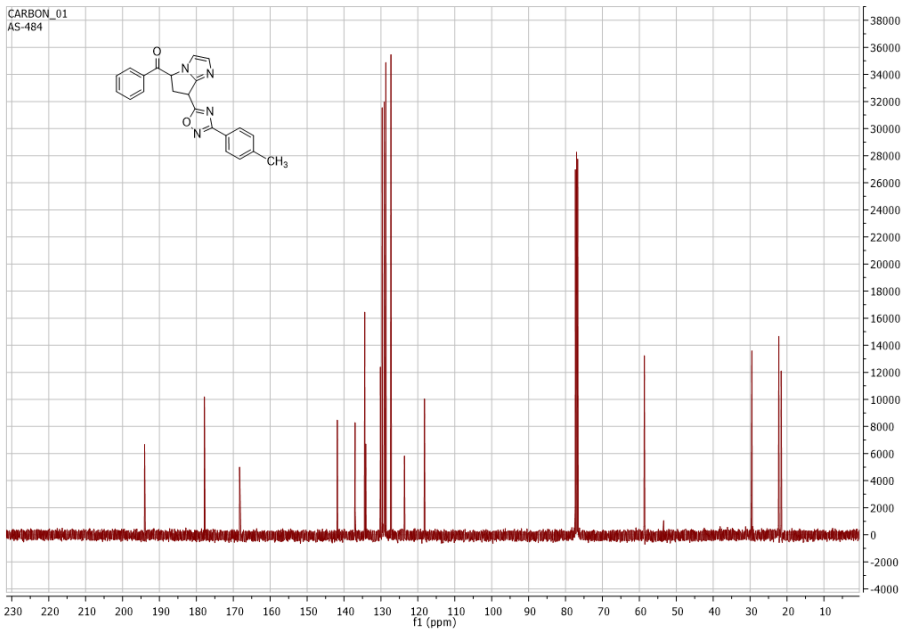


Figure 7.37. ^{13}**C** NMR spectrum of compound **100e.**

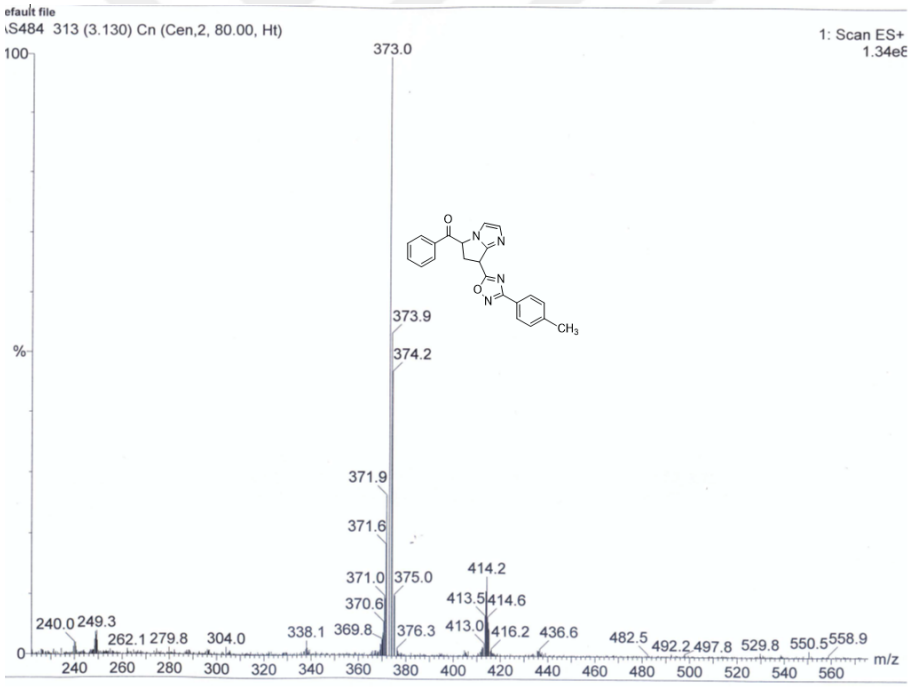


Figure 7.38. LC-MS spectrum of compound **100e.**

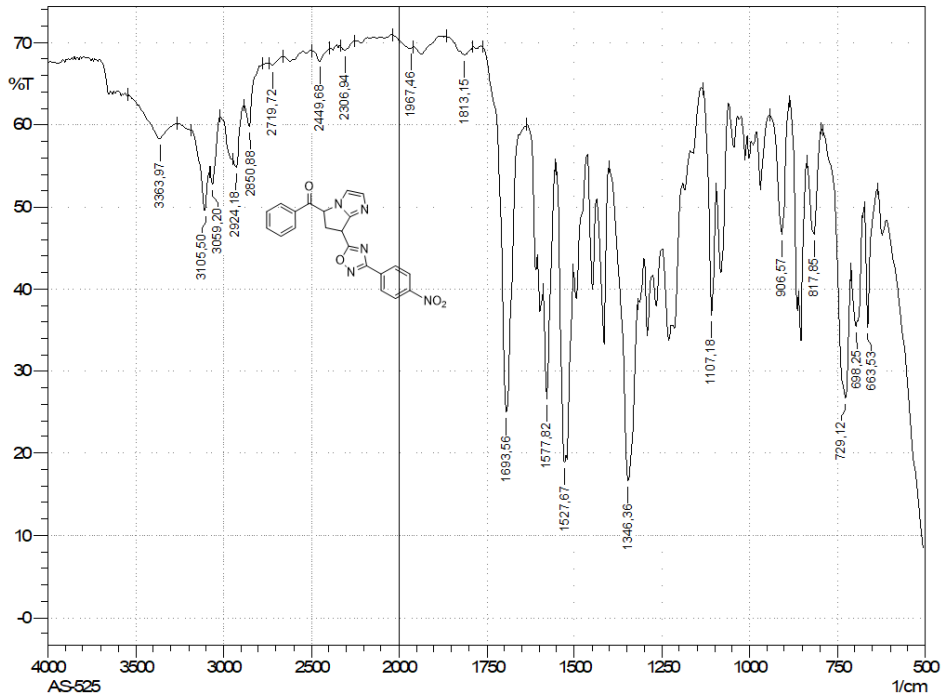


Figure 7.39. IR spectrum of compound **100f.**

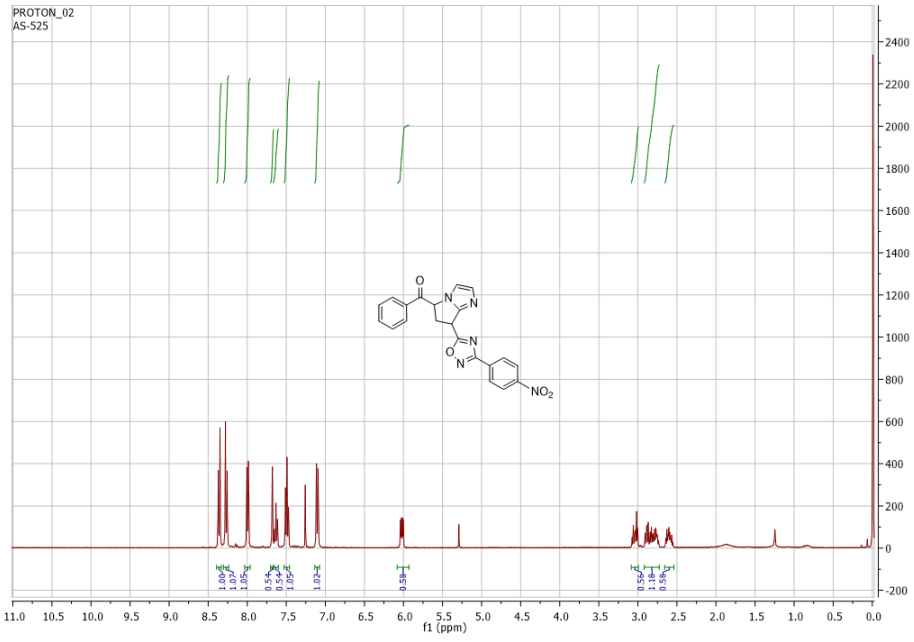


Figure 7.40. ^{1}H NMR spectrum of compound **100f.**

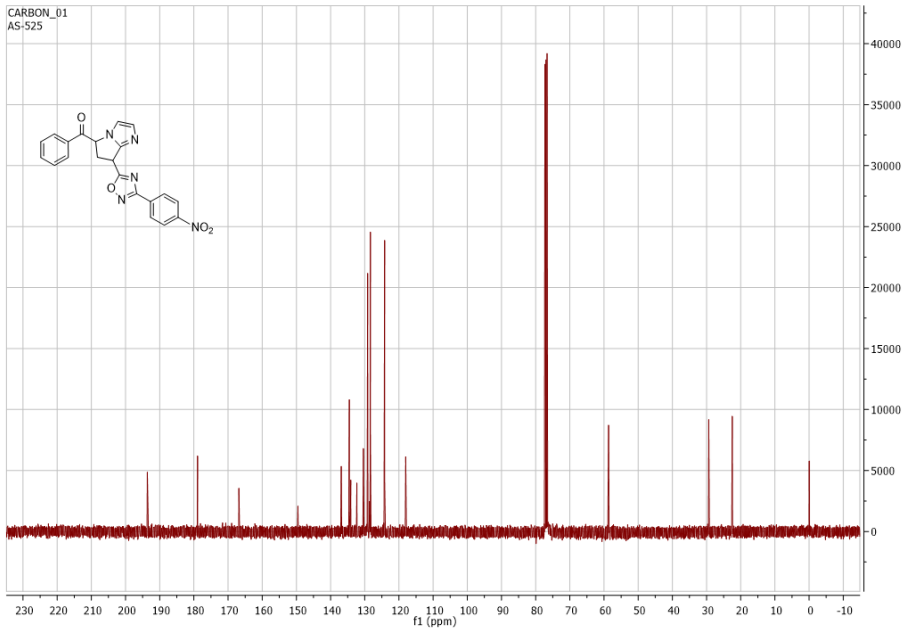


Figure 7.41. ^{13}C NMR spectrum of compound **100f.**

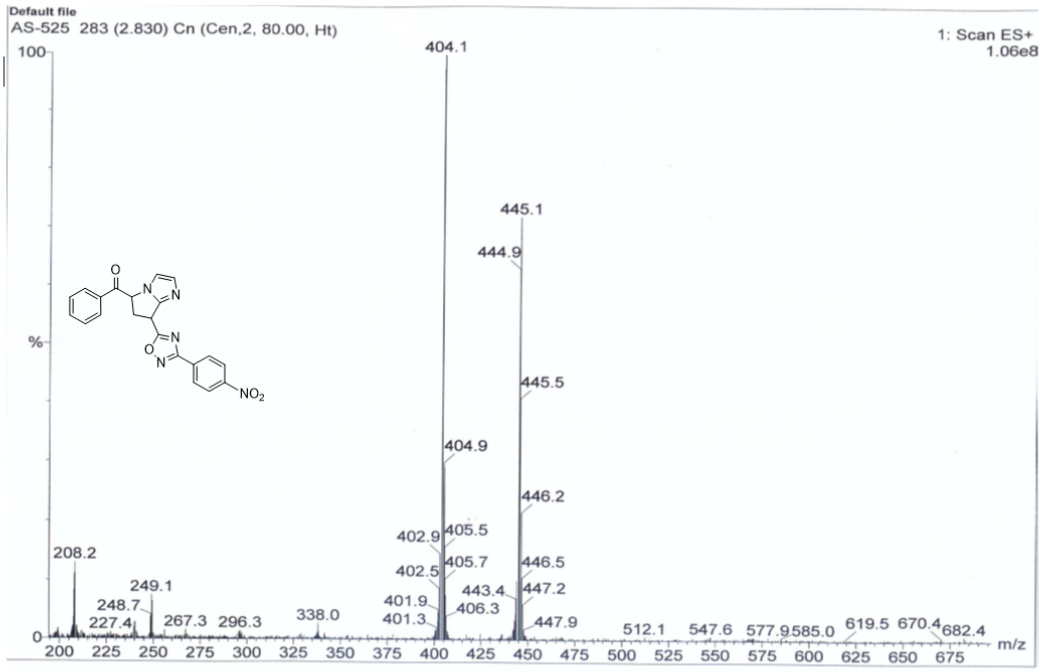


Figure 7.42. LC-MS spectrum of compound **100f.**

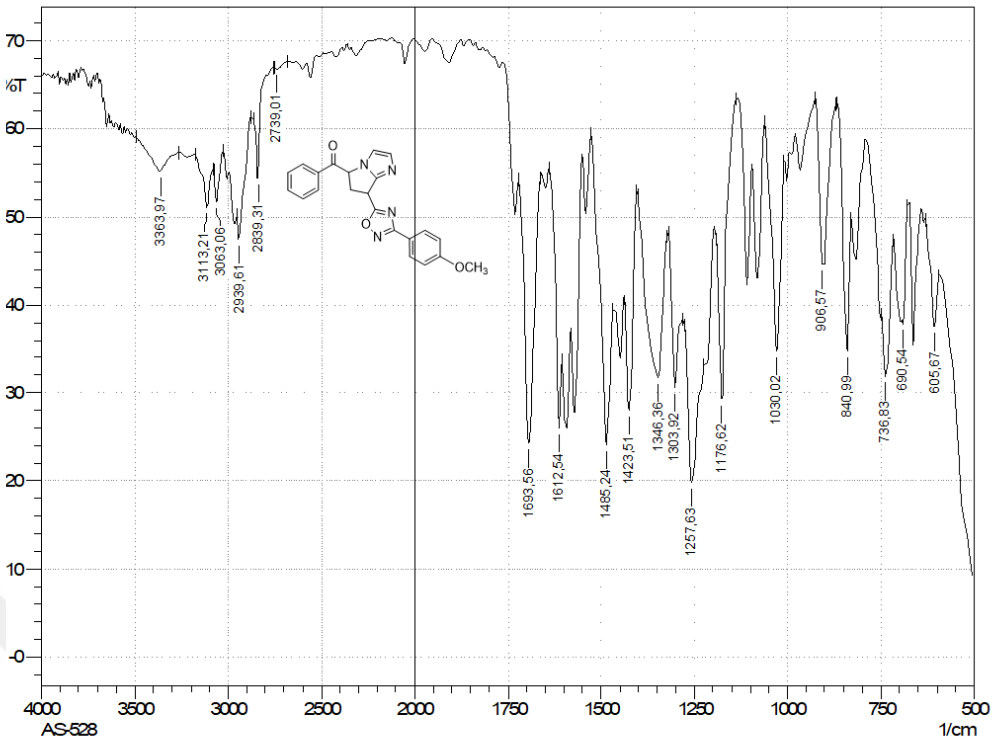


Figure 7.43. IR spectrum of compound **100g.**

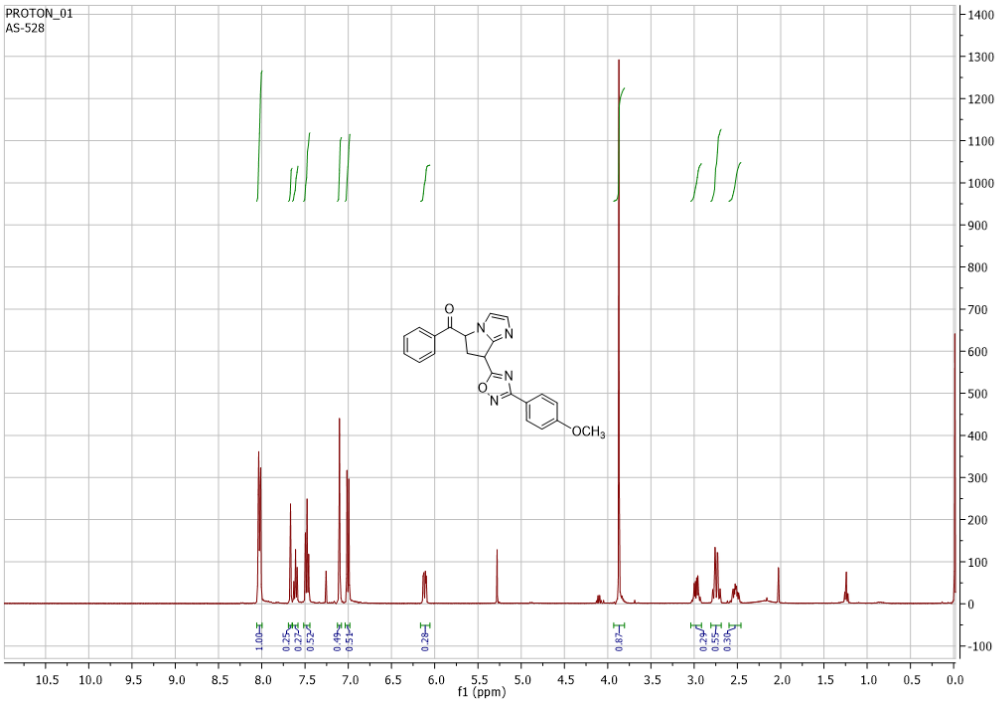


Figure 7.44. ^{1}H NMR spectrum of compound **100g.**

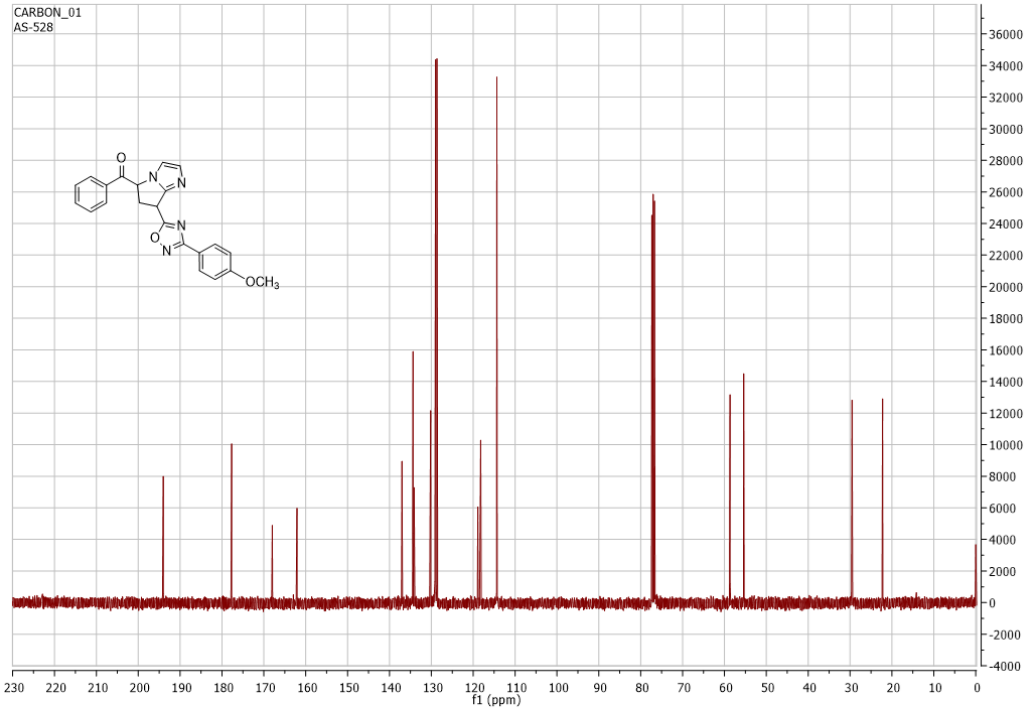


Figure 7.45. ^{13}C NMR spectrum of compound **100g.**

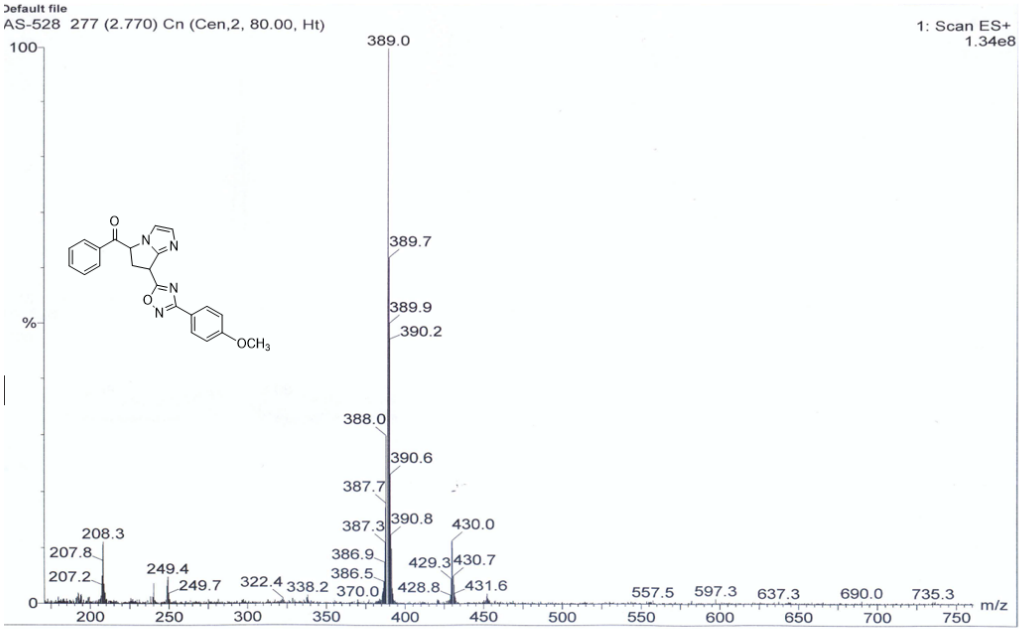


Figure 7.46. LC-MS spectrum of compound **100g.**