BOLU ABANT IZZET BAYSAL UNIVERSITY

THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

DEPARTMENT OF CHEMISTRY

MW-ASSISTED SYNTHESIS OF NEW POLYSUBSTITUTED TETRAHYDROPYRIMIDINES

MASTER OF SCIENCE

CANSU GÜLBENEK

BOLU , MARCH 2019

APPROVAL OF THE THESIS

MW-ASSISTED SYNTHESIS OF NEW POLYSUBSTITUTED TETRAHYDROPYRIMIDINES submitted by **Cansu GÜLBENEK** in partial fulfillment of the requirements for the degree of **Master of Science** in **Department of Chemistry, The Graduate School of Natural and Applied Sciences of BOLU ABANT IZZET BAYSAL UNIVERSITY** in **11/03/2019** by

Examining Committee Members	**Signature**
Supervisor Assoc. Prof. Dr. Muhammet YILDIRIM Abant İzzet Baysal University	.....
Member Prof. Dr. Yaşar DÜRÜST Abant İzzet Baysal University	.....
Member Assoc.Prof. Dr. Ersin ORHAN Düzce University	.....

Graduation Date :

Doç. Dr. Ömer ÖZYURT ..

Director of Graduate School of Natural and Applied Sciences

To my family

DECLARATION

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

Cansu GÜLBENEK

ABSTRACT

MW-ASSISTED SYNTHESIS OF NEW POLYSUBSTITUTED TETRAHYDROPYRIMIDINES
MSC THESIS
CANSU GÜLBENEK
BOLU ABANT IZZET BAYSAL UNIVERSITY GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF CHEMISTRY
(SUPERVISOR: ASSOC.PROF.DR.MUHAMMET YILDIRIM

BOLU, MARCH 2019

Pyrimidines are important in the area of bioorganic and medicinal chemistry since they showed a variety of biological activities such as anticonvulsant, antidepressant, antioxidant, anti-inflammatory, antiviral, anti-HIV, antimicrobial and antitumor and also, the vital biomolecules DNA is composed of the pyrimidine bases. A fused heterocyclic analog of pyrimidines, the thiazolo[3,2-*c*]pyrimidines with their biological activities were reported by our group in 2014, 2015 and 2018.

In order to elaborate the chemistry and biology of pyrimidine compounds, synthesis of new polysubstituted nitropyridimines were aimed in the current study. To achieve this goal, first of all, aryl substituted β-nitroenamines as suitable precursors were prepared by the reaction of anilines with α-nitroketones and characterized by IR, NMR and HRMS analyses.

In the second part of the study, nitrotetrahydropyrimidines were efficiently synthesized through Mannich cyclizations of nitroenamines with formaldehyde and aniline derivatives under microwave heating in 30-40 minutes. The structures of all the nitropyrimidine products were fully characterized by IR, NMR and HRMS analyses.

In the last part of the study, an antioxidant study was conducted for nitropyrimidine products using DPPH radical scavenging activity assay. Two of the nitropyrimidine products exhibited moderate percentage inhibition effect and three of the derivatives exhibitied moderate-low percentage inhibition effects in DPPH radical solution. Also, a preliminary antibacterial activity study was performed for five of the nitropyrimidine derivatives against *S.Epidermidis* and *S.Aureus* bacterial strains using disc diffusion method. It was observed that only one nitropyrimidine derivative exhibited moderate antibacterial activity against *S.Epidermidis* bacteria.

KEYWORDS:
Nitroenamine, Mannich, tetrahydropyrimidine, cyclization, antioxidant, antibacterial.

ÖZET

YENİ POLİSÜBSTITÜE TETRAHİDROPİRİMİDİNLERİN MİKRODALGA DESTEKLİ SENTEZİ
YÜKSEK LİSANS TEZİ
CANSU GÜLBENEK
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ
KİMYA ANABİLİM DALI
(TEZ DANIŞMANI: DOÇ. DR. MUHAMMET YILDIRIM)

BOLU, MART - 2019

Pirimidinler, antikonvülsan, antidepresan, antioksidan, antiiflamatuar, antiviral, anti-HIV, antimikrobiyal ve antitümör gibi çok çeşitli aktiviteler gösterdiklerinden dolayı biyoorganik ve tıbbi kimya alanında önemlidirler, ayrıca hayat molekülü olan DNA pirimidin bazlarından oluşmaktadır. Pirimidinlerin bir bitişik heterohalkalı eşdeğeri, tiyazolo[3,2-*c*]pirimidinler biyoaktiviteleriyle birlikte grubumuz tarafından 2014, 2015 ve 2018 yıllarında rapor edilmiştir.

Pirimidin bileşiklerinin kimya ve biyolojisini daha da detaylandırmak için, bu çalışmamızda yeni polisübstitüe nitropirimidinlerin sentezi amaçlanmıştır. Bu amaca ulaşmak için, öncelikle uygun başlangıç maddeleri olarak aril sübstitüe β-nitroenaminler, anilinlerin α-nitroketonlarla reaksiyonu sonucu hazırlanmış ve IR, NMR ve HRMS analizleriyle karakterize edilmiştir.

Çalışmamızın ikinci kısmında ise nitrotetrahidropirimidinler, nitroenaminlerin formaldehit ve anilin türevleriyle Mannich halkalaşmaları yoluyla mikrodalga ısıtması altında 30-40 dakika içinde etkili bir şekilde sentezlenmiştir. Bütün nitropirimidin ürünlerinin yapıları, IR, NMR ve HRMS analizleriyle tam olarak karakterize edilmiştir.

Çalışmanın son aşamasında ise, DPPH radikal sönümleme yöntemi kullanılarak nitropirimidin ürünleri için bir antioksidan aktivite çalışması gerçekleştirilmiştir. Nitropirimidin ürünlerinin ikisi, DPPH çözeltisi içinde orta seviyede yüzde inhibisyon ve 3 türev ise orta-düşük seviyede yüzde inhibisyon etkisi göstermiştir. Ayrıca, 5 nitropirimidin türevi için *S.Epidermidis* ve *S.Aureus* bakteri zincirlerine karşı disk difüzyon yöntemi kullanılarak bir ön antibakteriyel aktivite çalışması da yapılmıştır. Sadece bir nitropirimidin türevinin *S.Epidermidis* bakterisine karşı orta seviyede antibakteriyel etki gösterdiği gözlemlenmiştir.

ANAHTAR KELİMELER:
Nitroenamin, Mannich, tetrahidropirimidin, halkalaşma, antioksidan, antibakteriyel.

TABLE OF CONTENTS

Page

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

Page

LIST OF ABBREVIATIONS AND SYMBOLS

^{13}C	**:** Carbon-13
^{1}H	**:** Proton
AcOH	**:** Acetic acid
$AlCl_3$	**:** Aluminium (III) chloride
APCI	**:** Atmospheric pressure chemical ionization
Ar	**:** Aryl
$BaMnO_4$	**:** Barium manganate
BINAP	**:** (*R*)-(+)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
CC	**:** Column chromatography
$CDCl_3$	**:** Deuterated chloroform
$CH(OEt)_3$	**:** Triethyl orthoformate
CH_3CN	**:** Acetonitrile
CNTs	**:** Carbon nanotubes
conc.	**:** Concentration
Conv.	**:** Conventional
CrO_3	**:** Chromium (VI) oxide
$Cu(OAc)_2$	**:** Copper (II) acetate
DBU	**:** 1,8-Diazabicyclo[5.4.0]undec-7-ene
DIPEA	**:** Diisopropylethylamine
DMAD	**:** Dimethylacetylene dicarboxylate
DMF	**:** Dimethyl formamide
DMSO-d_6	**:** Deuterated dimethylsulfoxide
DNA	**:** Deoxyribonucleic acid
ED	**:** Electron-donating
eq.	**:** Equivalent
equiv.	**:** Equivalent
ESI	**:** Electrospray ionization
Et	**:** Ethyl
Et_3N	**:** Triethylamine
EtOAc	**:** Ethyl acetate

EtOH : Ethanol

EW : Electron-withdrawing

FTIR : Fourier-transform infra-red

g : Gram

h : Hour

HIV : Human immunodeficiency virus

HRMS : High-resolution mass spectrometry

Hz : Hertz

IR : Infra-red

J : Coupling constant

KBr : Potassium bromide

m.p. : Melting point

m/z : Mass to charge ratio

M^+ : Molecular ion

MAOS : Microwave-assisted Organic Synthesis

MCR : Multi-component Reaction

Me : Methyl

MeO : Methoxy

MeOH : Methanol

Mes : Mestyl

mg : Miligram

MHz : Megahertz

min : Minute

mL : Mililiter

mmol : Milimole

MW : Microwave

$NaBH_4$: Sodium borohydride

NaOH : Sodium hydroxide

NaOR : Sodium alkoxide

NaOt-Bu : Sodium tertiary butoxide

neat : Solventless

NH_4OAc : Ammonium acetate

NMR : Nuclear magnetic resonance

NO_2 : Nitro

OAc : Acetate

OTf : Triflate

$Pd(OAc)_2$: Palladium acetate

Ph : Phenyl

PhMe : Toluene

PMP : p-methoxyphenyl

$POCl_3$: Phosphorus oxychloride

R : Radical group

R_f : Retention factor

RNA : Ribonucleic acid

RT : Room temperature

t-BuOK : Potassium tertiary-butoxide

t-Bu : Tertiary butyl

TEMPO : 2,2,6,6-Tetramethyl-1-piperidinyloxy

THF : Tetrahydrofuran

$TiCl_4$: Titanium (IV) tetrachloride

TMS : Tetramethylsilane

TOF : Time of flight

UV : Ultra-violet

v/v : Volume per volume

$ZnCl_2$: Zinc chloride

δ : Chemical shift

Δ : Heat

υ : Wavenumber

ACKNOWLEDGEMENTS

Firstly, I would like to express my deepest and sincere gratitude to my supervisor Assoc. Prof. Dr. Muhammet YILDIRIM for his valuable support, encouragements, advice and immense knowledge. His guidance helped me at all stages of researching and writing of this thesis and he allowed reach me whenever I needed and directed me right throughout my master studies.

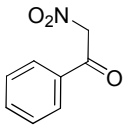
I extremely would like to thank to Assist. Prof. Dr. Arzu YILDIRIM for her helps and supports in antibacterial and antioxidant activity studies.

I would also like to express my special thanks to Dr. Akın SAĞIRLI for his friendships, supports and valuable comments.

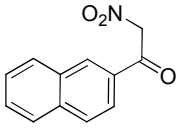
My sincere thanks to most precious person in my life, Ahmet GÜNBÜR, for being with me throughout my undergrauate and graduate life, his love, continuous support and understanding. I wish to thank to my housemate Aylin ALTINTAŞ for her lovely friendships and support, to my colleague Kübra UYSAL for her support and help in the laboratory.

Finally, I must express my sincere gratitude to my father Sinan GÜLBENEK, my mother Serap TEPEDELEN for their love, great support, endless patience and allowance; to my brother Cihan GÜLBENEK for his love and encouragement; to my paternal aunt Gönül GÜLBENEK for inspiration, support and encouragement throughout the long period of my study. Without their support, it was not possible for me to finish my education seamlessly.

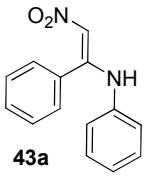
FORMULAE



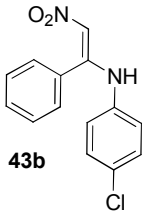
60a



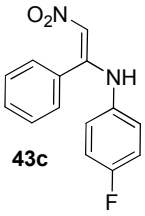
60b



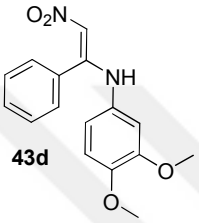
43a



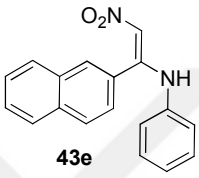
43b



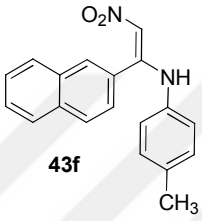
43c



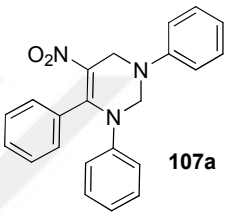
43d



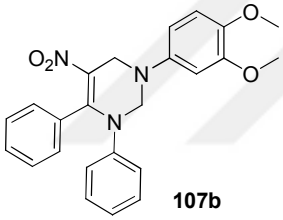
43e



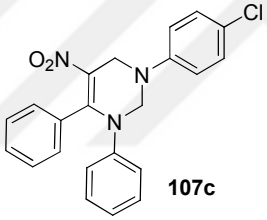
43f



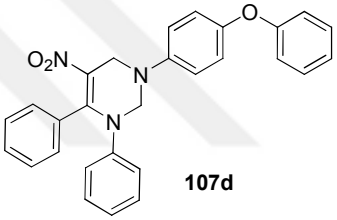
107a



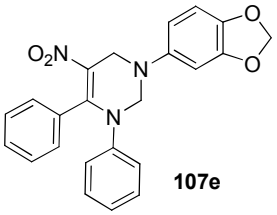
107b



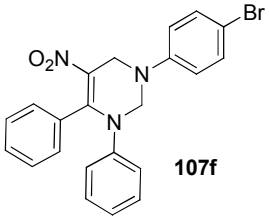
107c



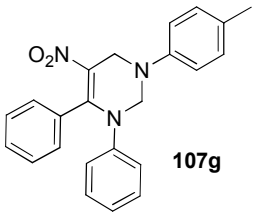
107d



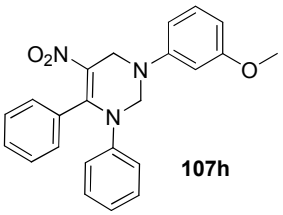
107e



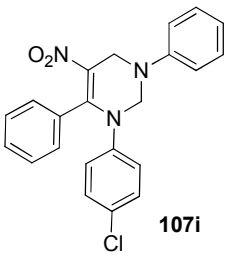
107f



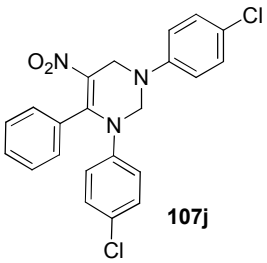
107g



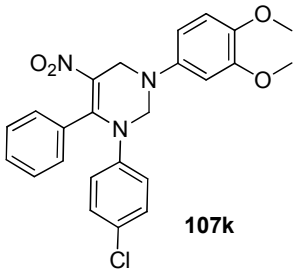
107h



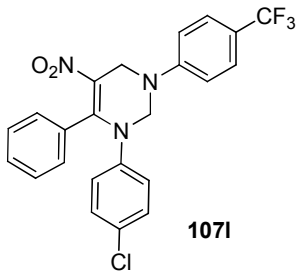
107i



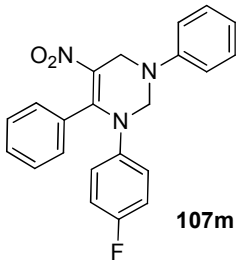
107j



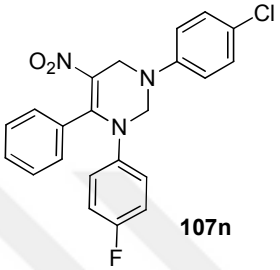
107k



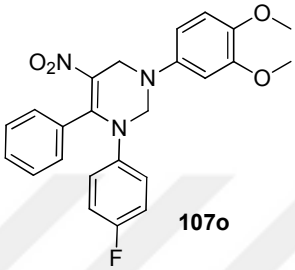
107l



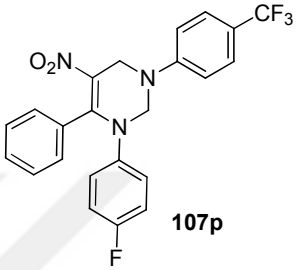
107m



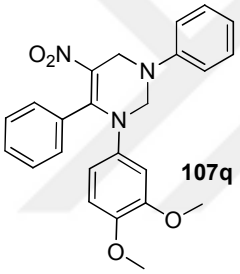
107n



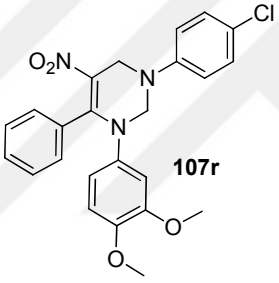
107o



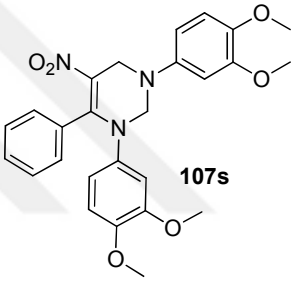
107p



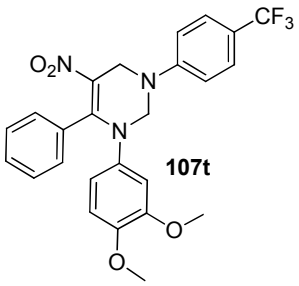
107q



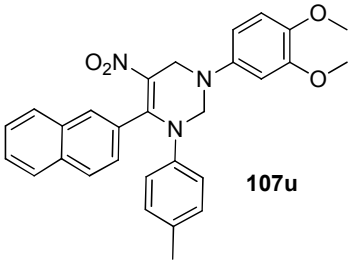
107r



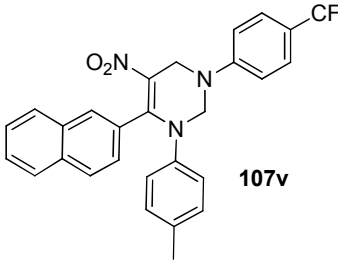
107s



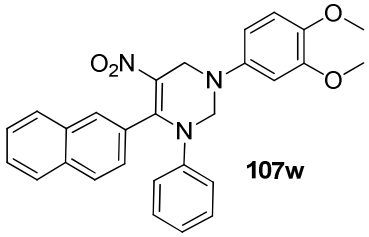
107t



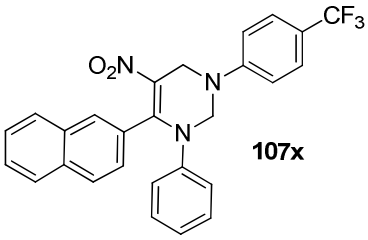
107u



107v



107w



107x

1. INTRODUCTION

1.1 MULTICOMPONENT REACTIONS

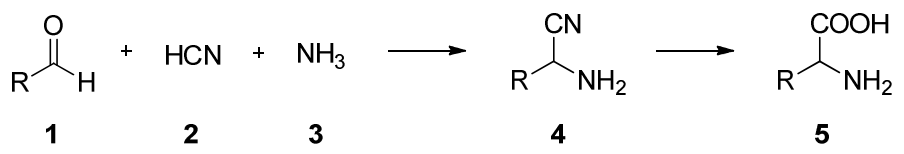
Generally the chemical reactions involve one or two starting materials, while synthesis can be carried out with three or more different precursors. In this way, one-pot reactions with more than two reactants are called MCRs. Although the reactants can be different individual compounds, it is also possible that the same reactant has different functional groups (Ugi et al., 1994).

MCRs that occur as one-pot reactions are single-step transformations in practice and are easier to execute than step by step synthesis. If the synthesis of a product can be accomplished with MCR, this procedure offers a number of advantages and thus can be referred to as "ideal synthesis" for MCRs. (Dömling & Ugi, 2000).

1.1.1 Types of Multicomponent Reactions

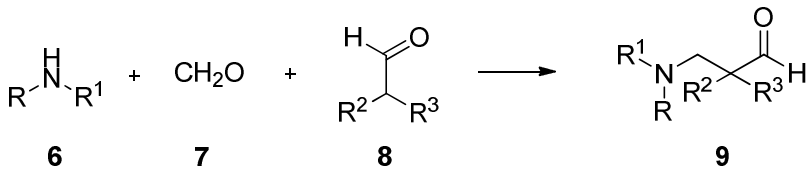
There are three different types of MCRs exist. In type I that all subreactions are the equilibrating reactions, including all intermediate reactions from the starting material to the final product. Generally this type MCRs are three component reactions (Ugi et al., 2003).

Strecker (1850) synthesis which is accepted to be the first MCR of type I in the literature and it was reported as α-amino acid **5,** via α-aminonitrile **4** (Scheme 1.1).



Scheme 1.1. Synthesis of α-amino acid from α-aminonitrile

Another example of MCRs for type I is the Mannich reaction which is one of the most important and widely used MCRs was presented by Mannich and Krosche (1912) (Scheme 1.2). They introduced formation of aminomethylated product **9** from a primary or secondary amine **6,** formaldehyde **7** and a carbonyl compound containing at least one α-hydrogen **8**.

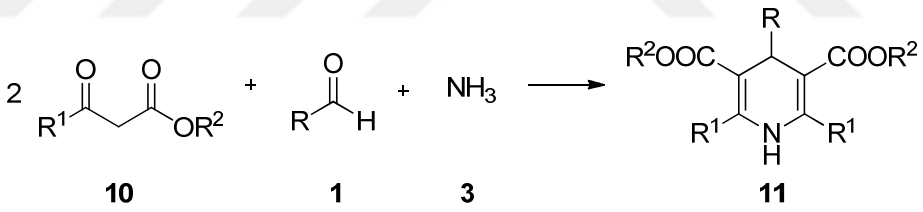


6 **7** **8** **9**

Scheme 1.2. Mannich reaction

In type II, principle reactions that between products and intermediates are in equilibrium but the final reaction step is irreversible (Ugi et al., 2003). The mainly examples for type II are as follows;

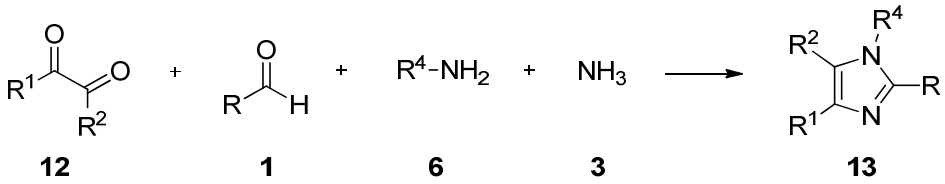
Hantzsch (1882) reported of dihydropyridine derivatives of an aldehyde **1,** with two equivalents of a β-ketoester **10,** in the presence of ammonia **3** (Scheme 1.3).



10 **1** **3** **11**

Scheme 1.3. Hantzsch synthesis of dihydropyridines

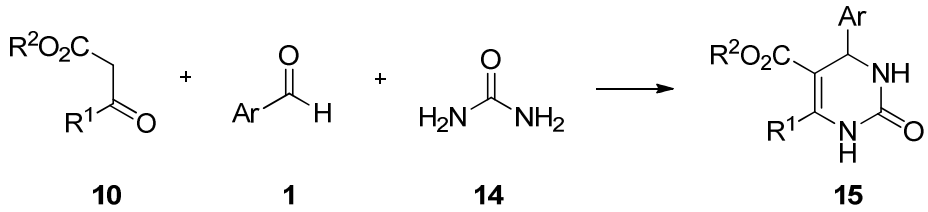
Radziszewski (1882) introduced synthesis of imidazole derivative **13,** from an α-dicarbonyl **12,** an aldehyde **1** and two equivalents ammonia or an ammonia **3** and a substituted ammonia **6** (Scheme 1.4).



12 **1** **6** **3** **13**

Scheme 1.4. Radziszewski synthesis of imidazole

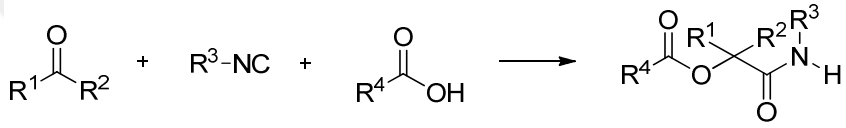
Biginelli (1891) reported three-component reaction for the synthesis of substituted dihydropyrimidine derivatives **15** from β-ketoesters **10,** an aromatic aldehyde **1** and urea **14** (Scheme 1.5).



10 **1** **14** **15**

Scheme 1.5. Biginelli synthesis of dihydropyrimidines

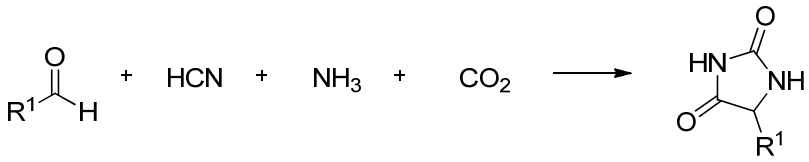
Passerini (1921) discovered one of the most important first MCR of the isocyanides and published formation of α-acyloxy carboxamides **19** from a carbonyl compound **16,** an isocyanide **17** and a carboxylic acid **18** (Scheme 1.6).



16 **17** **18** **19**

Scheme 1.6. Passerini synthesis of α-acyloxycarboxamides

Bucherer and Bergs (1934) that were the first to describe a four-component reaction, discovered a hydantoin **21** synthesis from hydrogen cyanide **2,** aldehyde **1,** ammonia **3** and carbon dioxide **20** (Scheme 1.7).



1 **2** **3** **20** **21**

Scheme 1.7. Bucherer-Bergs synthesis of hydantoins

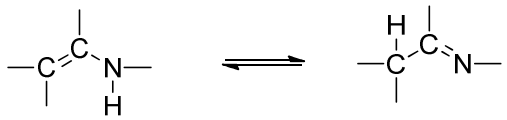
MCRs of type III are sequences of irreversible all subreactions. Biochemical MCRs are in this group and are usually rare compared to other types (Ugi et al., 2003).

1.2 MICROWAVE ENERGY

The purpose of using microwave energy was to heating the foods in the 1940s. It has been applied in many different fields for a long time, however, its using in organic synthesis has only been in the mid-1980s (Kappe et al., 2012). Gedye et al. (1986) and Giguere et al. (1986) were first published that many organic reactions can be carried out very rapidly using microwave heating. In these years, the initial improvement of the microwave technology was comparatively slow due to many reasons, for example, safety anxieties, reproducibility, temprature and pressure control. Some reactions have resulted in explosions until safe technological microwave instuments have been developed in all respects (Bose et al., 1991; Shaikh, 2017). The number of publications related to MW-assisted organic synthesis has increased since the late 1990s. In recent years, the number of those reactions (MAOS) have increased exponentially because of the many important advantages which are dramatically reduced reaction times, obtained higher product yields and purities by reducing side reactions compared to conventional heating conditions (Dallinger & Kappe, 2007).

1.3 ENAMINES

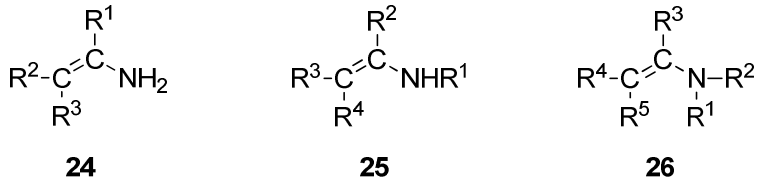
Enamines are the α,β-unsaturated amines which include an amino group in α-position and as a consequence in conjugation with an olefinic carbon-carbon double bond (Häfelinger and Mack, 1994). The term ‘‘enamine’’ was described that structurally related to the nitrogen analogs of enols by Wittig and Blumenthal (1927). If one of the nitrogen substituents is a hydrogen atom, the enamine **22** is tautomeric form of an imine **23** by exchanging a hydrogen atom between nitrogen and β-carbon atom (Scheme 1.8).



22 **23**

Scheme 1.8. Enamine – imine tautomerism

Enamines are classified as primary **24**, secondary **25** and tertiary **26** according to the variety of substitution on nitrogen (Figure 1.1).

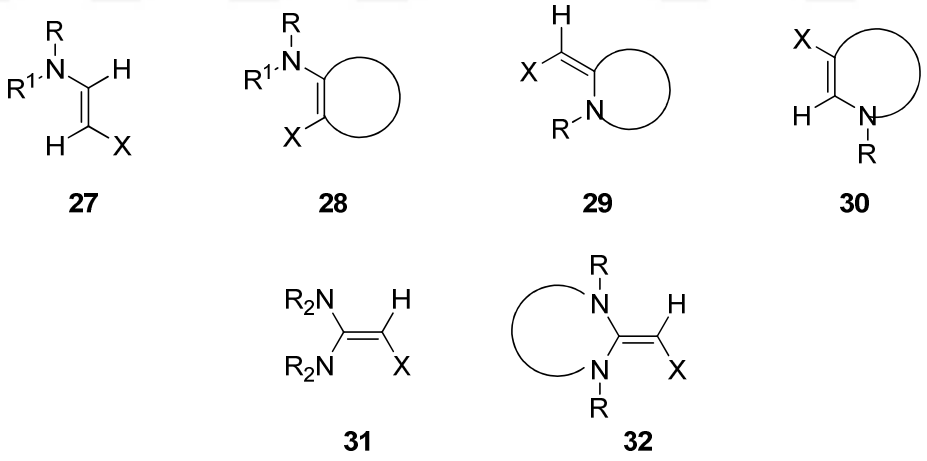


24 **25** **26**

Figure 1.1. Classification of enamines

Generally, tertiary enamines defined as containing non-hydrogen substituent on nitrogen are the most stable one which are easily prepared by mixing of an aldehyde or ketone with a secondary amine (Häfelinger & Mack, 1994).

Another classification is related to the double bond of enamines, which are acyclic enamines **27**, endocyclic enamines **28**, exocyclic enamines **29** and heterocyclic enamines **30**. If the amino group is substituted instead of the α-hydrogen of acyclic enamine, these enamines are called ketene aminals **31** and **32** (Figure 1.2) (Shawali & Edrees, 2006).



27 **28** **29** **30**

31 **32**

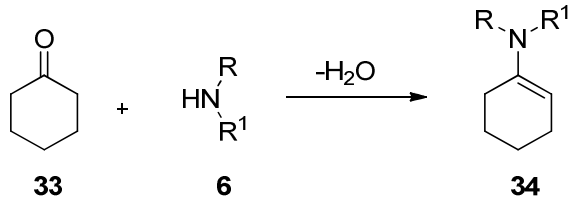
R=R^1= Me, Et R-R'= -(CH$_2$)$_n$- (n=4,5,6) X= CN, ArCO, ROCO

Figure 1.2. Main types of enamines

Moreover, enamine derivatives have many advantages and important role as asymmetric catalysts for alkylations and also used as blocking groups and intermediates in organic synthesis (West, 1963; Friary et al., 1973).

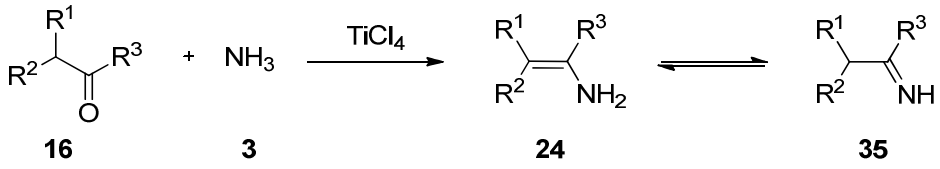
1.3.1 Synthesis of Enamines

Mannich and Davidson (1936) introduced the pioneering enamine **34** preparation procedures which was readily prepared starting from an aldehyde or ketone **33** with a secondary amine **6** in the presence of a dehydrating agent (Scheme 1.9) (Mannich et al., 1936; Stork et al., 1963).



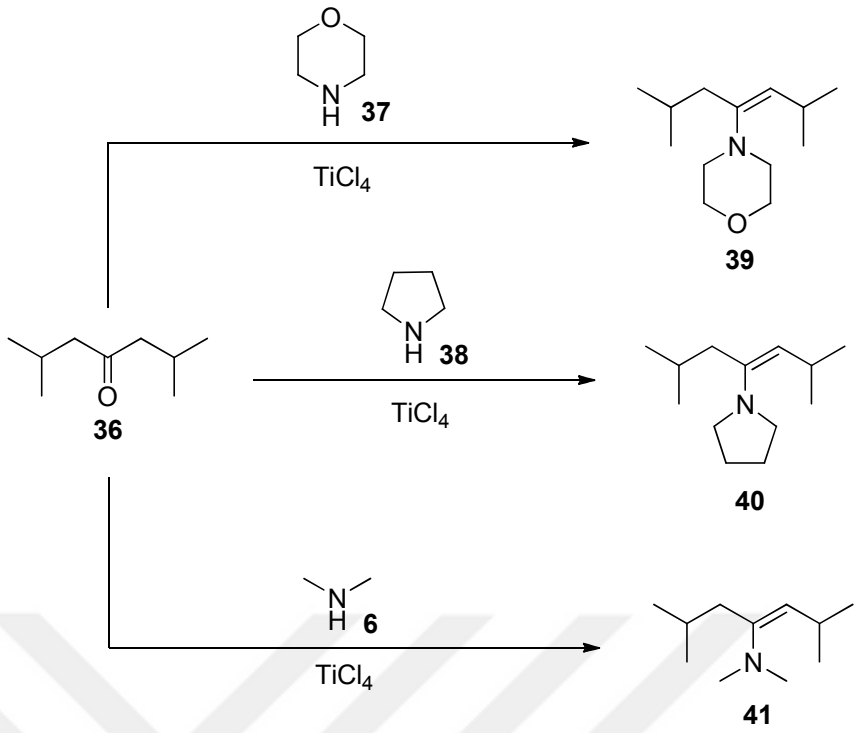
Scheme 1.9. General method of preparation of enamine

Ahlbrecht et al. (1973) prepared various sequence of primary enamine and their ketimine tautomers systems **24** and **35** by reacting carbonyl compounds **16** with ammonia **3** containing the titanium tetrachloride catalyst as Lewis-acid (Scheme 1.10). They investigated the effect of solvent and substituents on the primary enamine-imine tautomeric equilibrium, as a result of which increase of solvent polarity strongly stabilized the enamine component in equilibrium conditions and that equilibrium ratio highly depends on the substituents at the carbon-carbon double bond of primary enamine (Erker et al., 1993).



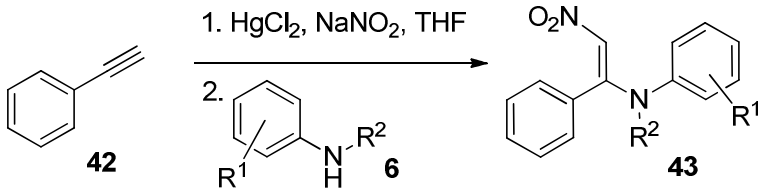
Scheme 1.10. Synthesis of primary enamine-ketimine tautomerization

Carlson et al. (1983) developed a modified procedure for a series of enamine synthesis from acyclic ketones **36** with various secondary amines which are morpholine **37**, pyrrolidine **38** and dimethylamine **6** using titanium tetrachloride as a catalyst leading to the formation of morpholine enamine **39**, pyrrolidine enamine **40** and dimethylamine enamine **41** respectively under optimum conditions (Scheme 1.11).

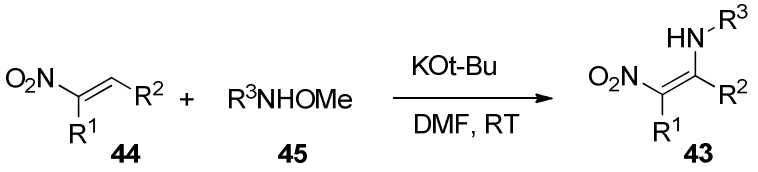


Scheme 1.11. Modified procedure for enamine synthesis

Firstly, Barluenga et al. (1983) reported the synthesis of β-nitro diaryl substituted enamines **43** by the reaction of phenylacetylene **42** and secondary amines **6** with mercuric chloride and sodium nitrite (Scheme 1.12). Then, Seko & Komoto (1998) prepared β-nitroenamines **43** by the amination of nitroolefines **44** using methoxylamine derivatives **45** in moderate yields (Scheme 1.13).

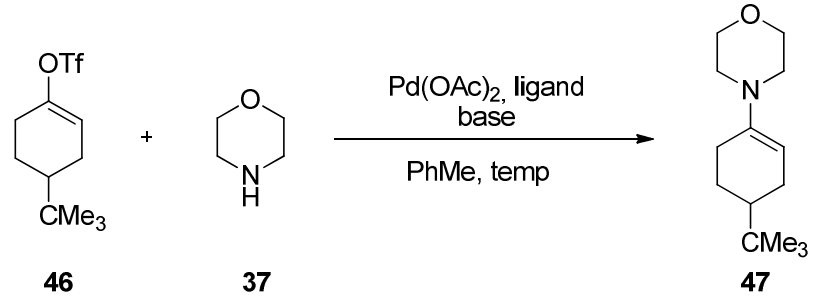


Scheme 1.12. Synthesis of β-nitroenmines from phenylacetylene



Scheme 1.13. Synthesis of β-nitroenmines using methoxylamines

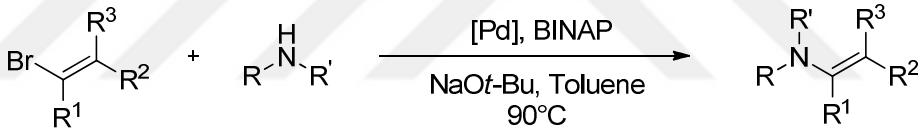
Willis et al. (2002) reported that synthesis of enamines **47** from 4-(*t*-butyl) cyclohexanone derived triflate **46** with morpholine **37** by using $Pd(OAc)_2$ as a catalyst and variety of ligand and bases (Scheme 1.14).



46 **37** **47**

Scheme 1.14. Palladium catalysed enamine synthesis

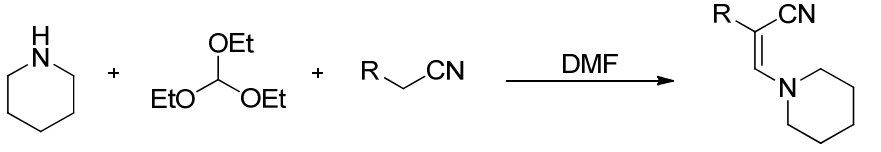
Barluenga et al. (2002) designed a novel palladium-catalyzed cross-coupling method for the synthesis of enamines **26** from secondary amines **6** and alkenyl bromide **48** in the presence of toluene using BINAP as the most effective ligand with a good yield (Scheme 1.15).



48 **6** **26**

Scheme 1.15. Palladium-catalyzed cross-coupling of alkenyl bromide with amines

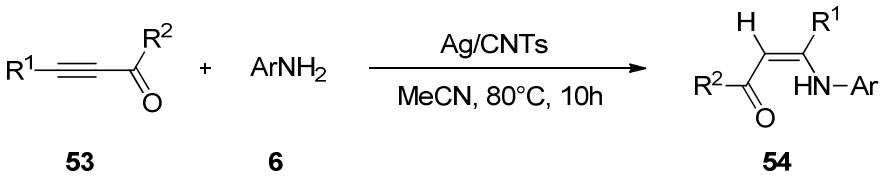
Darwish et al. (2011) described an efficient preparation of enamine derivatives **52a**-**b** from condensation of intermediate product consisting triethoxymethane **50** and piperidine **49** with ethyl cyanoacetate **51a** or benzylcyanide **51b** in DMF (Scheme 1.16).



49 **50** **51a**, R=COOEt
51b, R=Ph
52a, R=COOEt
52b, R=Ph

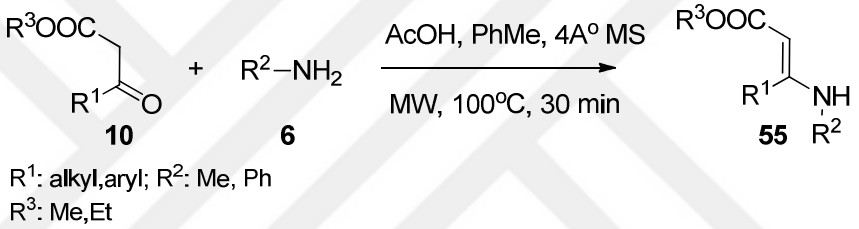
Scheme 1.16. Synthesis of piperidine enamine

Liu et al. (2013) published a reaction of non-terminal alkynes **53** with various substituted anilines **6** to formation of enamines **54** via an efficient Ag/CNT-catalyzed hydroamination process under optimal reaction conditions (Scheme 1.17)



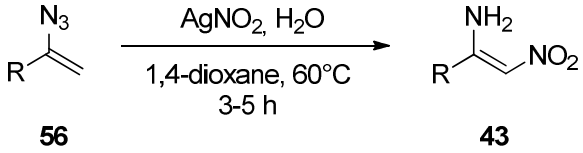
Scheme 1.17. Ag/CNT-catalyzed synthesis of enamines

Zhang et al. (2016) obtained β-enaminoesters **55** through an efficient MW-assisted condensation of β-ketoesters **10** with aryl or alkyl amines **6** in good yields for 30 minutes at 100°C.



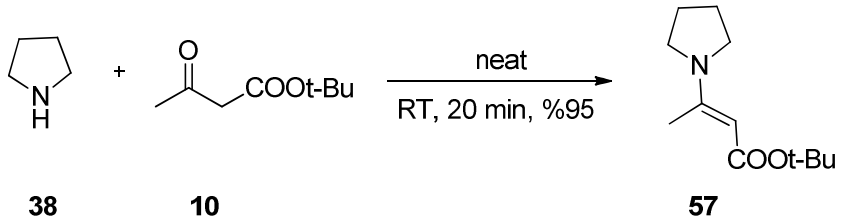
Scheme 1.18. MW-assisted synthesis of pyrroles from enamines

Ning et al. (2017) introduced a practical and efficient synthetic procedure for β-nitroenamines **43** from conversion of a wide variety of alkyl, alkenyl, aryl and heteroaryl vinyl azides **56** with $AgNO_2$ in high efficiency (Scheme 1.19).



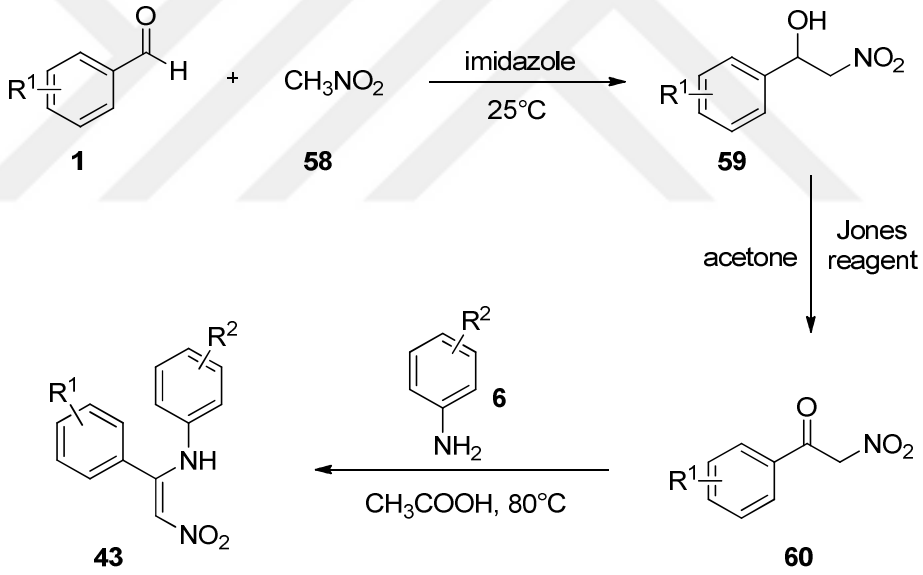
Scheme 1.19. Conversion of vinyl azides into β-nitroenamines

Bujok et al. (2017) synthesized t-butyl 3-(1-pyrrolidinyl)crotonate **57** from pyrrolidine **38** and *t*-butyl acetoacetate **10** in an excellent yield (Scheme 1.20).



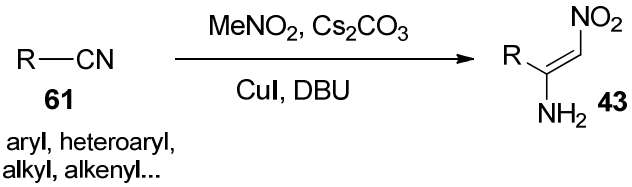
Scheme 1.20. Synthesis of tert-butyl 3-(1-pyrrolidinyl)crotonate

Borah et al. (2009) synthesized of 2-nitro-1-arylethanols **59** from substituted aromatic aldehyde **6** with nitromethane **58** via nitro-aldol reaction in the presence of a cost-effective, readily available and safe to handle imidazole catalyst. In the same year, Zhao et al. (2009) reported the synthesis of 2-nitro-1-arylethanones **60** from 2-nitro-1-arylethanols **59** by Jones oxidation and subsequent conversion of 2-nitro-1-arylethanones **60** into diaryl substituted nitroenamine derivatives **43** using various anilines **6** (Scheme 1.21).



Scheme 1.21. Synthesis of nitroenamines starting from aryl aldehydes

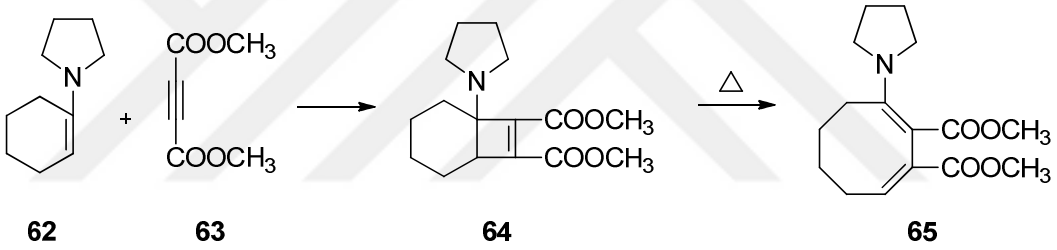
Very recently, Kuwabara et al. (2018) reported first CuI-mediated aza-Henry reactions of nitriles **61** with nitromethane **58** to afford β-nitroenamines **43** in good yields (Scheme 1.22).



Scheme 1.22. CuI-mediated synthesis of nitroenamines

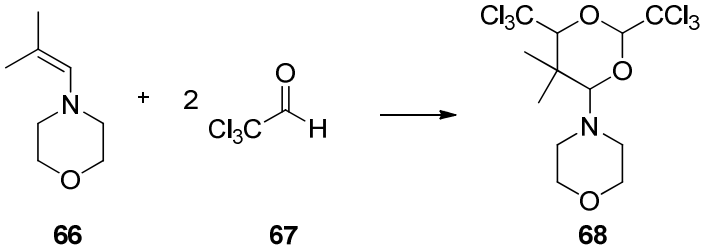
1.3.2 Reactions of Enamines

Brannock et al. (1963) published synthesis of a heat-sensitive dimethyl 1-(-pyrrolidinyl)bicyclo[4.2.0]oct-7-ene-7,8-dicarboxylate **64** from 1-(1-cyclohexenyl) pyrrolidine **62** and DMAD **63** in ether to hold the temperature at 25-35°C. This bicyclooctene compound was thermally unstable, so it was heated for 18 hours and the ring expansion product that dimethyl 3-(1-pyrrolidinyl)-2,8-cyclooctadiene-1,2-dicarboxylate **65** was obtained (Scheme 1.23).



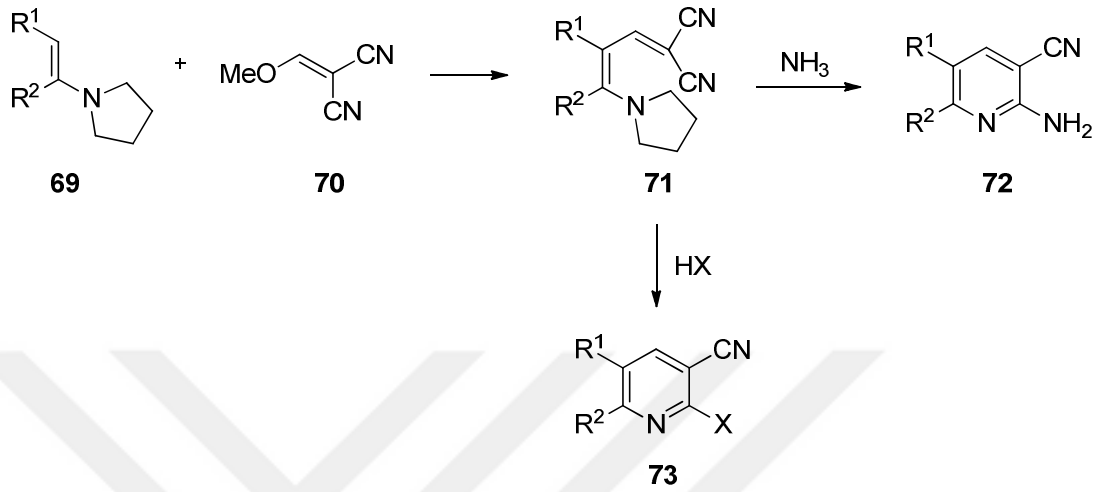
Scheme 1.23. Synthesis of dimethyl 3-(1-pyrrolidinyl)-2,8-cyclooctadiene-1,2-dicarboxylate

Brannock et al. (1964) synthesized of 4-(5,5-dimethyl-2,6-bis(trichloromethyl)-1,3-dioxan-4-yl)morpholine **68** from one equivalent of 4-isobutenylmorpholine **66** and two equivalent of chloral **67** in the presence of acetonitrile in good yield (Scheme 1.24).



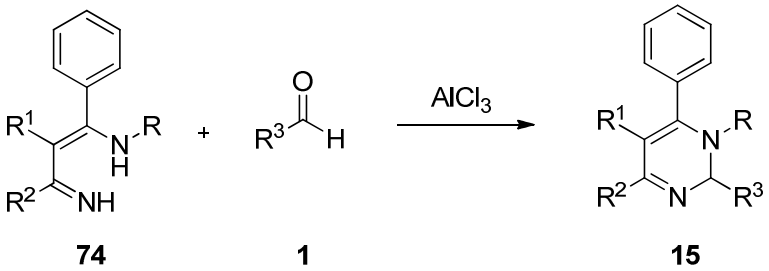
Scheme 1.24. Synthesis of 4-(5,5-dimethyl-2,6-bis(trichloromethyl)-1,3-dioxan-4-yl) morpholine

Kurihara & Mishima (1977) published the synthesis of 5- and/or 6-alkyl substituted-3-cyanopyridines **72**, **73** by the interaction of ammonia or acids with dienamine intermediate **71** which was produced the reaction of pyrrolidine enamines **69** with methoxymethylene malononitrile **70** at room temperature (Scheme 1.25).



Scheme 1.25. Synthesis of 5- and/or 6-alkyl substituted 3-cyanopyridine derivatives

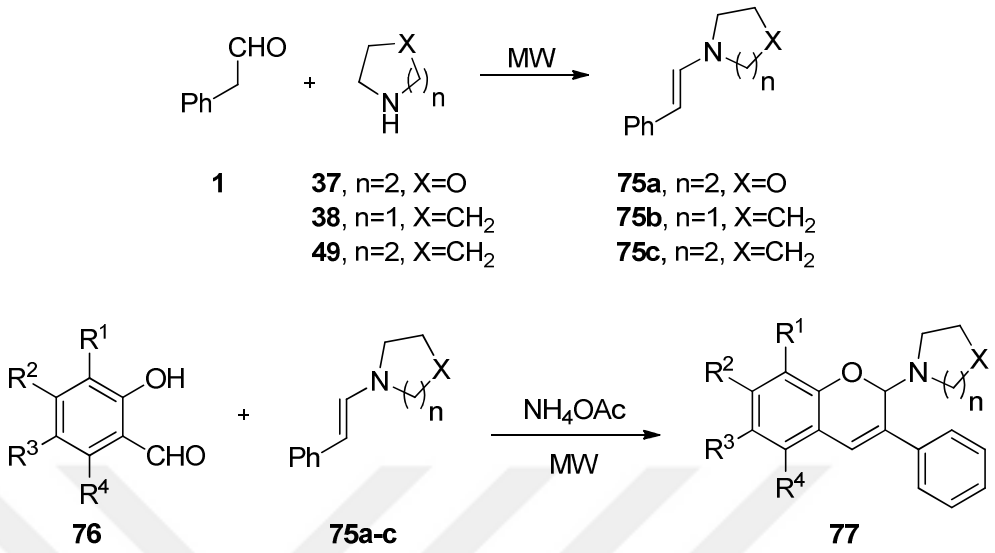
Barluenga et al. (1979) introduced the Friedel-Crafts reaction of enaminoimines **74** with aldehydes **1** in the presence of $AlCl_3$ as catalyst to formation of 1,2-dihydropyrimidines **15** in dioxane at 90°C (Scheme 1.26).



Scheme 1.26. Synthesis of dihydropyrimidines

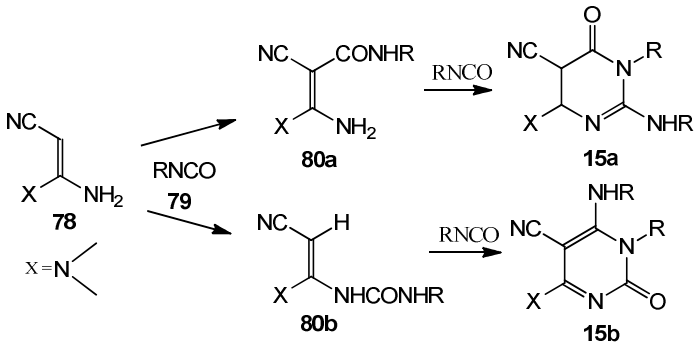
Varma et al. (1998) published the microwave-assisted one-pot reaction of 2-substituted isoflav-3-ene derivatives **77**. Firstly, the enamines *N*-styrylmorpholine **75a**, *N*-styrylpyrrolidine **75b** and *N*-styrylpiperidine **75c** were generated as intermediates from phenyl acetaldehyde **1** and respective cyclic amines **37**, **38** and **49** for 2 min then the subsequent reactions were performed with the adding of

salicylaldehydes **76** to the same reaction vessel in the present of NH_4OAc as a catalyst (Scheme 1.27).



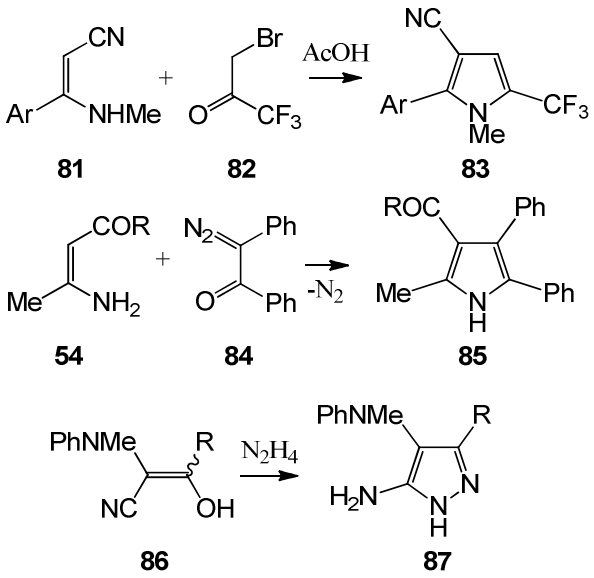
Scheme 1.27. One-pot solvent-free synthesis of isoflav-3-ene derivatives

Granik et al. (1998) reported the heterocyclization reactions of enamines **78, 80a-b** with isocyanates (benzyl isocyanate or phenyl isocyanate) **79** providing 4-pyrimidinone and 2-pyrimidinone derivatives (**15a-b**) (Scheme 1.28).



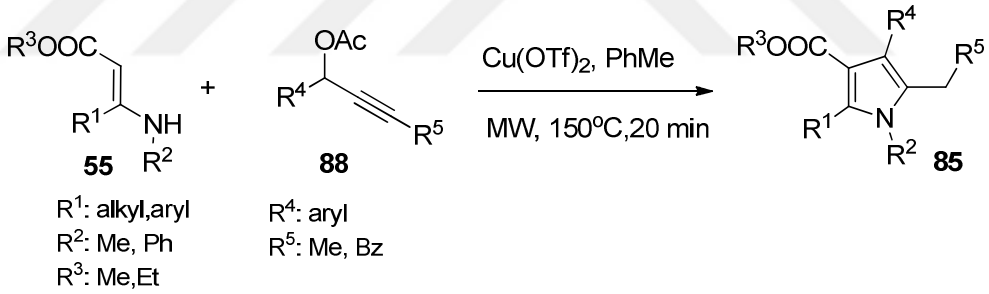
Scheme 1.28. The heterocyclizations affording pyrimidinone derivatives

Recently, Khan et al. (2010) carried out the synthesis of the *N*-methylpyrrole **83** by the reaction of secondary enamine **81** with 1-bromo-3,3,3-trifluoro-2-propanone **82** using acetic acid under reflux. Besides, the preparation of 1*H*-pyrroles **85** were achieved by the reaction of primary *β*-carbonylenamines **54** with diazodeoxybenzoin **84** and also, the pyrazoles **87** were synthesized over the reaction of enamines **86** with hydrazine (Scheme 1.29) (Boyd, 1994).



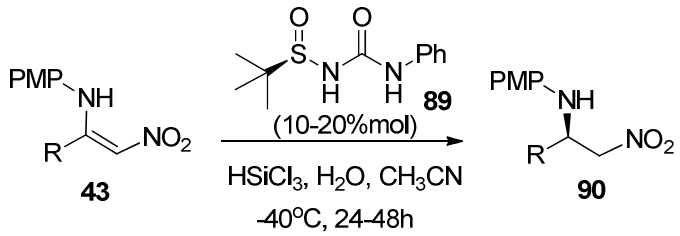
Scheme 1.29. The synthesis of pyrroles and pyrazoles from enamines

Besides, Zhang et al. (2016) reported the MW-assisted synthesis of polysubstituted pyrroles **85** in high yields through copper-catalyzed tandem azacyclization/isomerization reactions using *β*-enaminoesters **55** and propargyl acetates **88** (Scheme 1.30).



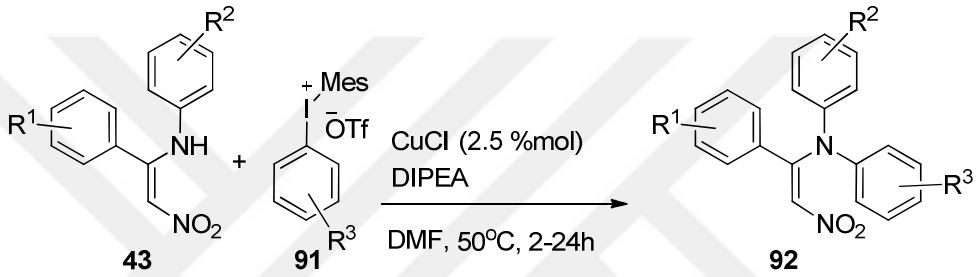
Scheme 1.30. MW-assisted synthesis of pyrroles from enamines

More recently, Ferraro et al. (2016) performed organocatalytic hydrogenation of β-acylamino- and β-tert-butyloxycarbonylamino-nitroolefins **43** using a thiourea catalyst **89** and an ester as hydrogen source to afford 2-amino-1-nitropropane derivatives **90** in good enantioselectivities (Scheme 1.31).



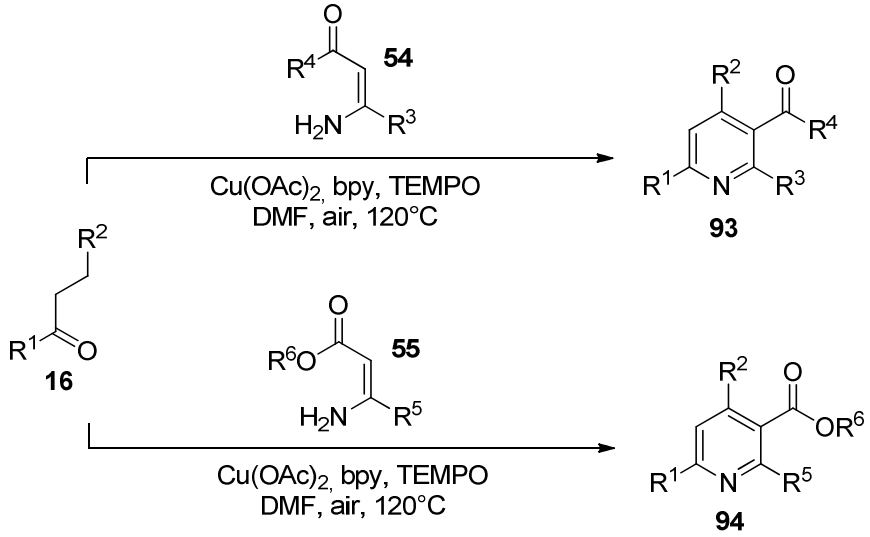
Scheme 1.31. The organocatalytic hydrogenation of nitroenamines

In another recent study, Aradi et al. (2017) reported *N*-arylation of nitroenamines **43** using diaryliodonium triflate salts **91** and CuCl catalyst under mild conditions in high yields (Scheme 1.32).



Scheme 1.32. Catalytic *N*-arylation of nitroenamines

Besides, Chen et al. (2017) introduced a new and efficient one-pot sequential process for the synthesis of 3-acylpyridines **93** and pyridine-3-carboxylates **94** from various inactivated saturated ketones **16** with β-enaminones **54** or β-enaminoesters **55** under an air atmosphere and optimum conditions (Scheme 1.33).



Scheme 1.33. Synthesis of functionalized pyridines

1.4 PYRIMIDINES

Pyrimidines **95** are six membered heterocyclic aromatic compounds containing two nitrogen atoms at 1,3-position (Sharma et al., 2014).

Pyrimidine and their derivatives are biologically very important heterocycles which are an integral part of nucleic acids i.e., RNA and DNA (Gore et al., 2013). Three types of nitrogenous organic bases in nucleic acids as pyrimidines which are thymine **96**, uracil **97** and cytosine **98**. Thymine is only present in DNA, uracil is only present in RNA and cytosine is present in both DNA and RNA (Dansena et al, 2015). The first pyrimidine derivative which is name alloxan **99** was isolated by Brugnatelli via oxidizing uric acid with nitric acid (Lagoja, 2005) (Figure 1.3).

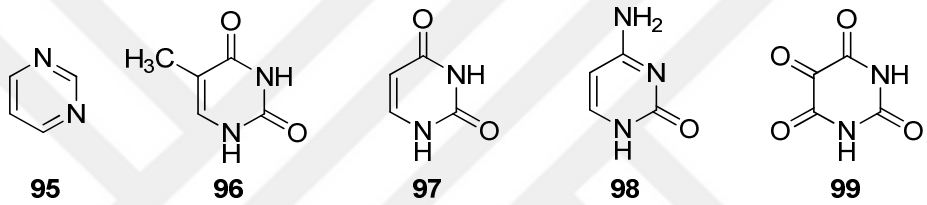
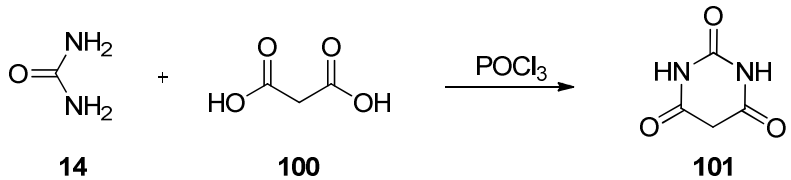


Figure 1.3. Pyrimidine and DNA bases

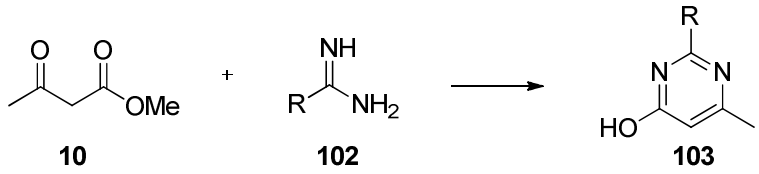
1.4.1 General Synthesis of Pyrimidines

Grimaux (1879) developed the first synthesis of barbituric acid **101** (pyrimidine trione) by the condensation of malonic acid **100** and urea **14** with the $POCl_3$ (Scheme 1.34).



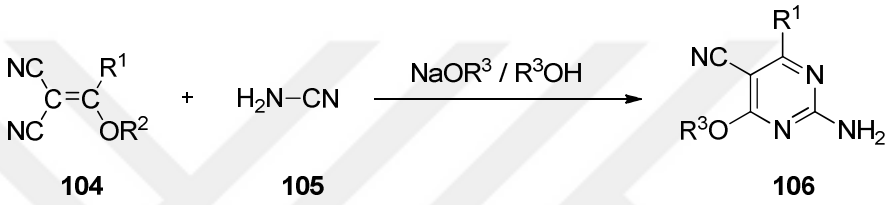
Scheme 1.34. Grimaux synthesis of barbituric acid

Pinner (1884) performed the synthesis of 2-substituted-6-hydroxy-4-methyl pyrimidine **103** generated from amidine derivative **102** and acetoacetic ester **10** (Scheme 1.26).



Scheme 1.35. Pinner synthesis of 2-substituted-6-hydroxy-4-methyl pyrimidine

Perez and Soto (1981) synthesized of 4-alkoxy-2-amino-5-cyanopyrimidines **106** by cyclization from 3-alkoxy-3-aryl(or alkyl)-2-cyanopropenenitriles **104** and cyanamide **105** in alcohols in the presence of sodium alkoxides (Scheme 1.36).

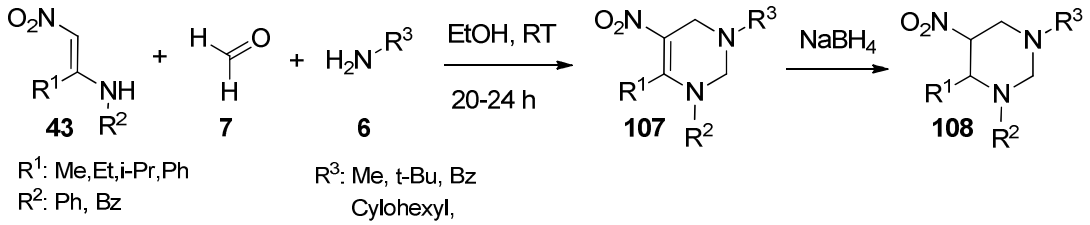


Scheme 1.36. Synthesis of 4-alkoxy-2-amino-5-cyanopyrimidines

1.4.2 Preparation of Pyrimidines via Multicomponent Reactions

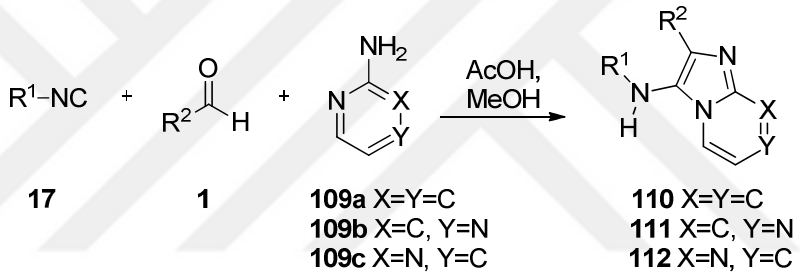
Combinatorial chemistry is particularly remarkable for modern drug research and involves highly effective synthetic methods. Syntheses by such methods ensures large and efficient compound in one-pot instead of step by step. MCRs are an attractive synthesis process for creating a various large number of product quickly and efficiently. In view of these method, examples of a wide variety of heterocyclic compounds are available in literature.

For instance, Sokolov et al. (1985) prepared derivatives of 5-nitro-tetrahydropyrimidines **107** in moderate yields by treating alkyl and aryl substituted nitroenamines **43** with formaldehyde **7** and alkylamines **6** in EtOH for 20-24 hour and successive reduction of tetrahydropyrimidines **107** with $NaBH_4$ afforded hexahydropyrimidines **108** in low yields (Scheme 1.37).



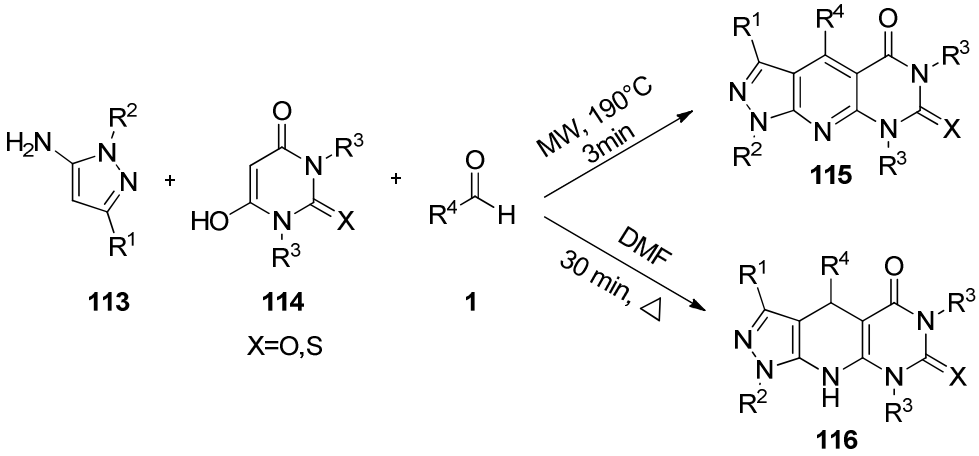
Scheme 1.37. Synthesis of tetra- and hexa-hydropyrimidines

Groebke et al. (1998) synthesized of 3-amino-imidazo[1,2-a]pyridines **110,** 3-amino-imidazo[1,2-a]pyrazines **111** and 3-amino-imidazo[1,2-a]pyrimidines **112** from aldehydes **1,** isonitriles **17** and 2-aminopyridine **109a,** 2-amino-pyrazine **109b** and 2-amino-pyrimidine **109c** via multicomponent one-pot condensation. They also stated that pyrimidines-fused heterocyclic products could be biologically active compounds such as antiinflammtory, antibacterial and antiacid (Scheme 1.38).



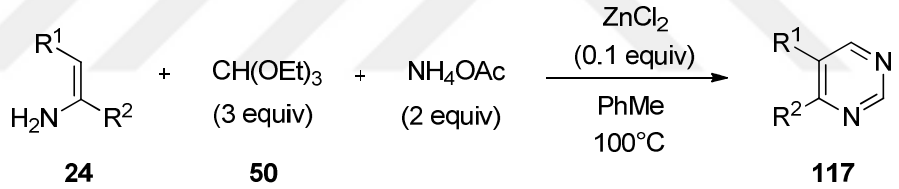
Scheme 1.38. Synthesis of imidazo[1,2-a] annulated pyridines, pyrazines and pyrimidines

Chebanov et al. (2008) described the multicomponent reaction of 5-aminopyrazoles **113,** barbituric acid derivatives **114** and aromatic aldehydes **1** under microwave irradiation, conventional heating or ultrosonic irradiation in two different manners. The reactions gave different results which were fused heterocyclic pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidines **115** or their dihydro compounds **116** depending on the nature of the starting material 5-aminopyrazoles (Scheme 1.39).



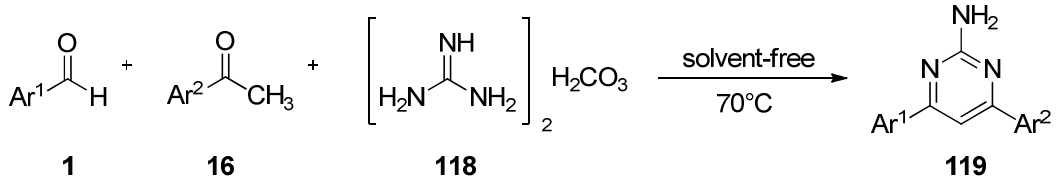
Scheme 1.39. Synthesis of pyrazolo[4',3':5,6]pyrido[2,3-d]pyrimidines and their dihydro derivatives

Sasada et al. (2009) reported effective synthesis of 4,5-disubstituted pyrimidine derivatives **117** from functionalized enamines **24**, $CH(OEt)_3$ **50** and ammonium acetate using $ZnCl_2$ catalyst via three-component coupling reaction in single step (Scheme 1.40).



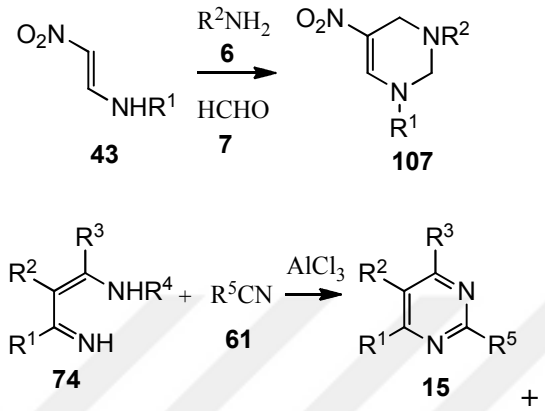
Scheme 1.40. Synthesis of 4,5-disubstituted pyrimidines

Zhuang et al. (2009) published an efficient and rapid multicomponent one-pot cyclocondensation reaction for the synthesis of various 2-amino-4,6-diarylpyrimidine **119** from aromatic aldehydes **1**, aromatic ketones **16** and guanidine carbonate **118** under enviromentally friendly solvent-free conditions with the advantages of high reaction rapidness and cleaner products (Scheme 1.41).



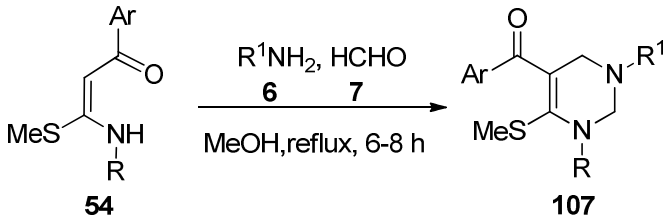
Scheme 1.41. Synthesis of 2-amino-4,6-diarylpyrimidines

Khan et al. (2010) achieved the preparation of 1,2,3,4-tetrahydropyrimidines **107** by the reaction of β-nitroenamines **43** with primary aliphatic amines **6** and formaldehyde **7**. Moreover, Boyd (1994) reported that the pyrimidines **15** can be synthesized over the reaction of azadienes **74** with aliphatic or aromatic nitriles **61** (Scheme 1.42).



Scheme 1.42. The synthesis of pyrimidines vs the general synthesis of pyrimidines

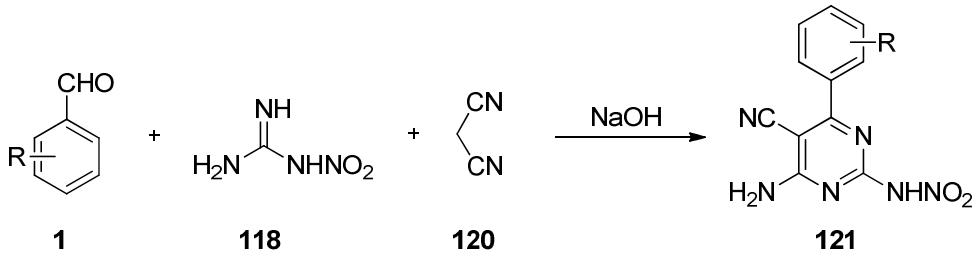
Devi et al. (2011) also synthesized novel tetrahydropyrimidines **107** as acetylcholine receptor (AchR) inhibitors via multicomponent Mannich cyclizations of enaminones **54** with primary amines **6** and formaldehyde **7** under reflux in very good yields (Scheme 1.43).



Scheme 1.43. The synthesis of tetrahydropyrimidines via Mannich cyclizations

Xia et al. (2012) described the multicomponent one-pot reaction for the synthesis of 4-amino-5-carbonitrile-2-nitroaminopyrimidine derivatives **121** from substituted aromatic aldehydes **1**, 1-nitroguanidine **118** and malononitrile **120** under ethanol. In these reactions, NaOH was preferred as the catalyst because of the

products were obtained with higher yields. Furthermore, other advantages of these procedure are mild reaction conditions and short reaction time (Scheme 1.44).

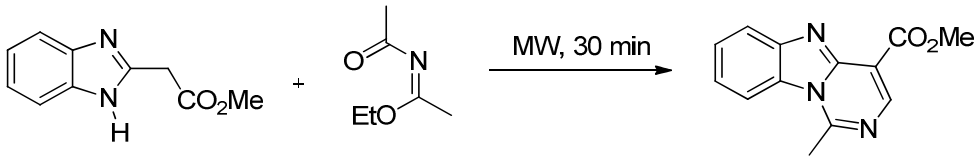


1 **118** **120** **121**

Scheme 1.44. Synthesis of 4-amino-5-carbonitrile-2-nitroaminopyrimidine derivatives

1.4.3 MW-Assisted Synthesis of Pyrimidines

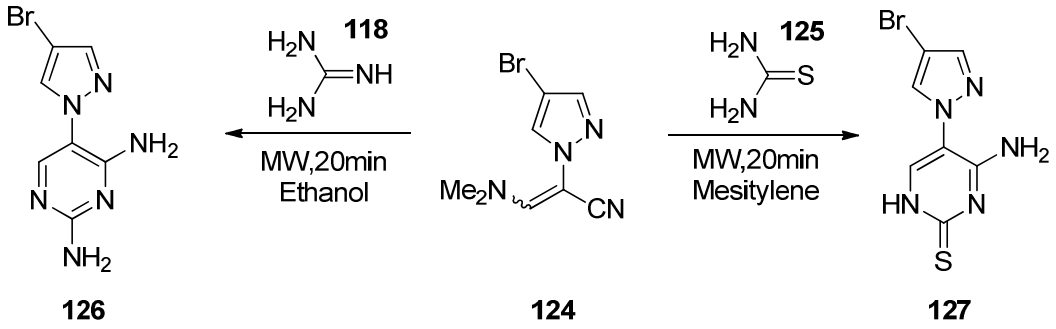
Caddick (1995) reported a microwave-assisted cyclocondensation reaction for the formation of pyrimido[1,6-a]benzimidazoles **111**. The product was carried out in an open-vessel via a condensation of neat benzimidazole **122** and n-acylimidate **123** with a good yield. An open-vessel was used to remove of the water and ethanol formed in the reaction (Scheme 1.45).



122 **123** **111**

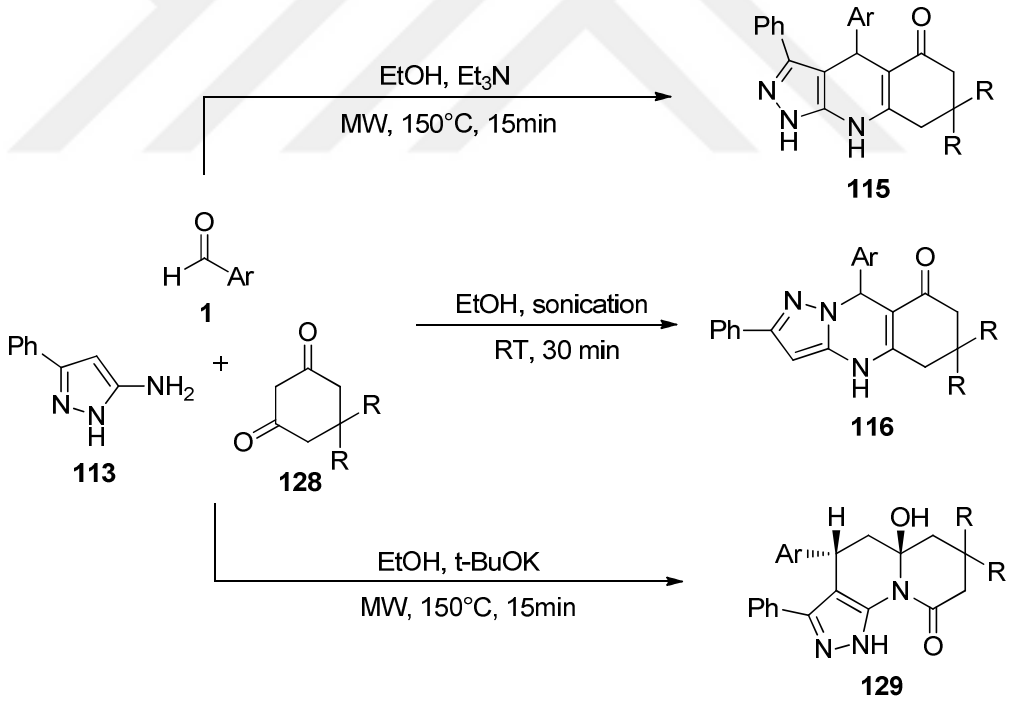
Scheme 1.45. Synthesis of pyrimido[1,6-a]benzimidazoles

Hoz et al. (2007) described a novel procedure for the preparation of 4-pyrazolylpyrimidines **126**, **127** under microwave irradiation by the reaction of 2-pyrazolyl-3-dimethylaminoacrylonitrile **124** with guanidine **118** and thiourea **125**, respectively (Scheme 1.46).



Scheme 1.46. Synthesis of 4-pyrazolylpyrimidines from dimethylamino acrylonitrile

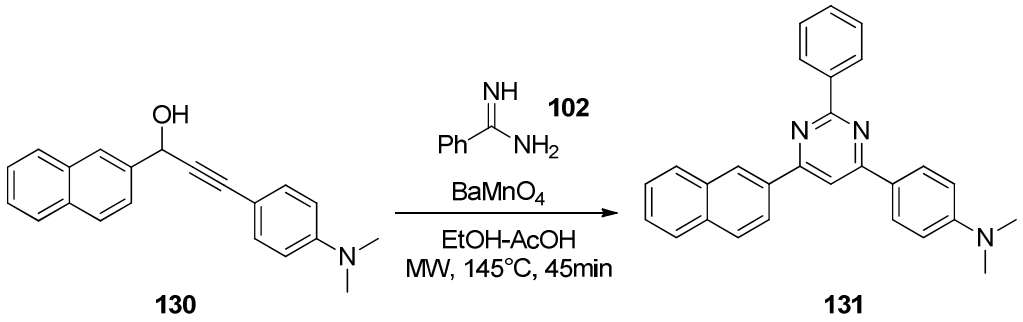
Chebanov et al. (2008) described several different three-component reaction pathways for the condensation of 5-amino-3-phenylpyrazole **113**, aromatic aldehydes **1** and cyclic 1,3-dicarbonyl compounds **128** leading to the formation of pyrazolo[3,4-b]quinolin-5-ones **115**, pyrazolo[5,1-b]quinazolin-8-ones **116** and pyrazolo[4,3-c]quinolizin-9-ones **129** by various reaction conditions (Scheme 1.47).



Scheme 1.47. Different MCR pathways for the condensation of aromatic aldehydes, 5-amino-3-phenylpyrazole and 1,3-dicarbonyl compounds

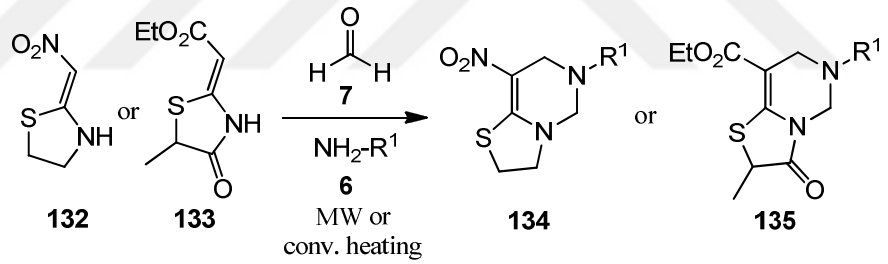
Bagley et al. (2009) published the synthesis of 2,4,6-triarylpyrimidines **131** from propargylic alcohols **130** and amidines **102** by MW-assisted tandem oxidation/

heterocyclocondensation using effectively $BaMnO_4$ at 145°C in 45 minutes (Scheme 1.48).



Scheme 1.48. MW-assisted synthesis of 2,4,6-triarylpyrimidine

Very recently, it was reported very efficient preparation of nitrothiazolo[3,2-c]pyrimidines **134** and oxothiazolo[3,2-c]pyrimidine carboxylates **135** via Mannich cyclisations of heterocyclic enamines (**132** or **133)** with primary amines **6** and formaldehyde **7** under reflux or MW conditions. (Yildirim et al., 2014a; Yildirim and Çelikel, 2015) (Scheme 1.49).



Scheme 1.49. Synthesis of thiazolo[3,2-c]pyrimidines via Mannich Cyclisations

1.4.4 Biological Importance of Pyrimidines

Pyrimidines are very important member of the nitrogen-containing heterocyclic family and they are physiologically and pharmaceutically active compounds. These aromatic heterocyclic organic compounds are a key component of the potential treatment of many diseases and have a wide range of pharmacological activities, such as inhibitory effects against serious diseases. So, these remarkable pyrimidine derivatives are found in the substructures of therapeutic natural products.

Chemists have performed a number of syntheses in this field using efficient methods and contributed to biologically active drugs (Bhat, 2017). They exhibit a wide range of biological properties, such as anticancer **136** (Ma et al, 2014), antidiabetic **137** (Koga et al., 2013), antihepatitis **138** (Shakya et al., 2012), antiinflammatory **139** (Keche et al., 2012), antimalarial **140** (Singh et al., 2013), antioxidant **141** (Attri et al., 2014), antileishmanial **142** (Suryawanshi et al., 2013), antithyroid **143** (Lacotte et al., 2013), antimicrobial **144** (Desai et al., 2015), anti-HIV **145** (Guo et al., 2012), antitubercular **146** (Chikhale et al., 2015) activities (Figure 1.4).

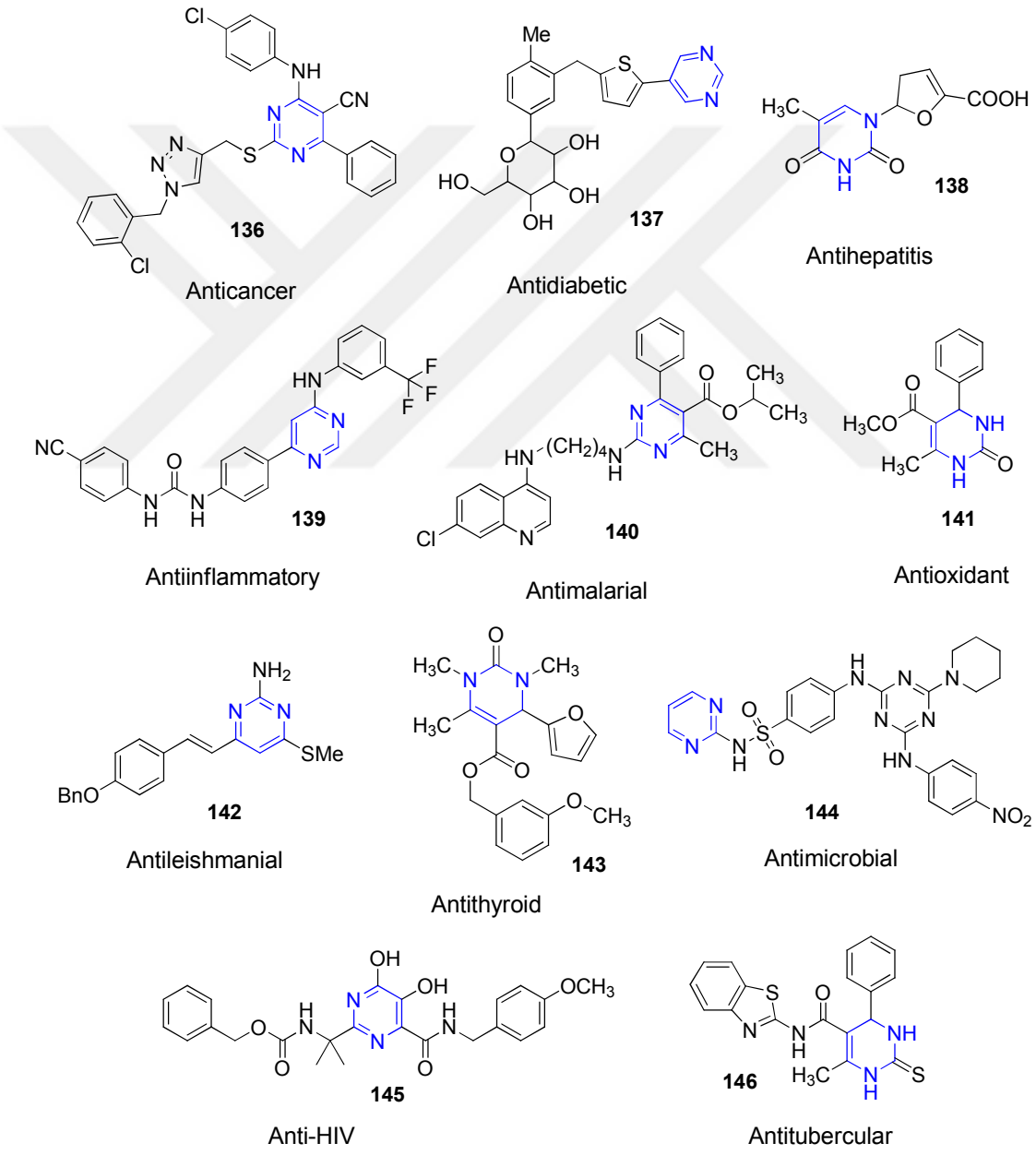


Figure 1.4. Biologically active pyrimidines-based molecules

1.5 ANTIOXIDANT ACTIVITY

Antioxidant agents are capable of slowing or inhibiting the oxidation of other molecules which could be damaged by free radicals. These molecules react with free radicals and avoid the oxidation process by deactivating free radicals (Moon & Shibamoto, 2009).

Reactive oxygen species (ROS) affects the biological molecules, leading to cell or tissue injury. They also cause oxidative damages on biomolecules (lipids, carbohydrates, proteins and nucleic acids) which can initiate a chain of events resulting variety of diseases such as aging, cancer (Aruoma, 1994). They are free radicals such as superoxide anion radicals (O_2 –), hydroxyl radicals (OH·), and non-free radical species such as hydrogen peroxide (H_2O_2) and singlet oxygen ($1O_2$) (Gülçin, 2006a).

Many naturally occurring antioxidant compounds have been identified as free radical or active oxygen scavengers such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate, and tert-butylhydroquinone. Antioxidant compounds can protect the human body from free radicals and reduce the risk of chronic diseases. Hence, the free radical scavenging activity studies using antioxidants have gained increasingly greater importance (Gulcin et al., 2003).

The antioxidant activity is usually determined by using DPPH assay. It is simple and accurate test, so, DPPH assay is the most commonly used technique to evaluate antioxidant potential of the synthesized or isolated compounds. During this assay, DPPH (2,2'-diphenylpicrylhydrazyl) in alcoholic solution is reduced by tested antioxidant compound to give the non-radical form of DPPH in the reaction (fig.1.5).

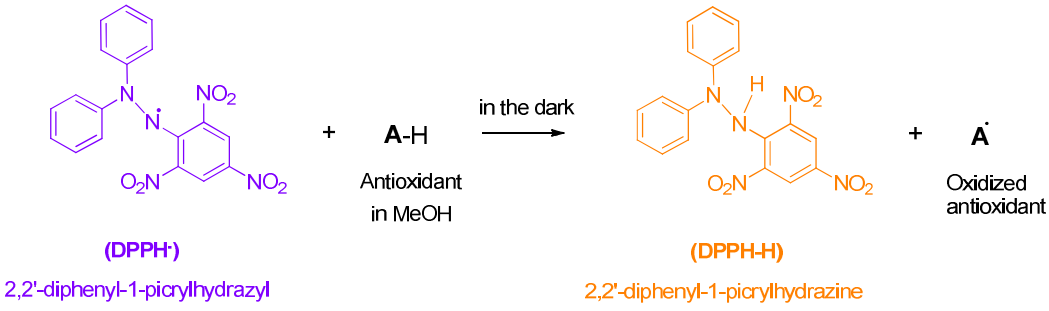


Figure 1.5. DPPH radical reaction with antioxidant compounds

1.6 ANTIBACTERIAL ACTIVITY

A convenient antibiotic susceptibility test (Kirby-Bauer Method) is used to screen for antimicrobial activity based on bacteriostatic/bacteriocidal properties (Atlas, 1988) and it was developed by Kirby and Bauer in 1960s (Prescott et.al., 1990). Reasonably accurate and precise results can be obtained with this assay in which all-procedural details are carefully standardized by the FDA and the NCCLS (Barry & Thornsberry, 1985).

In this disc-diffusion test, a pathogenic microorganism is inoculated onto a Mueller-Hinton agar plate. Filter paper discs containing known amounts of antimicrobial agents or antibiotics are placed in middle of the agar plates which are then incubated at 37°C for 18-24 h. The antimicrobial agents or antibiotics diffuse into the agar and cause an inhibition zone for the growth of the bacterial strain around the disc which corresponds to the susceptibility of the strains to the agents. At the end of the incubation period, a clear area depicting zone of inhibition around the disc is measured. The formed zones are compared to known values obtained with standard antibiotics (Prescott et.al., 1990). Standardized zones for each antibiotic disc have been established to determine whether the microorganism is sensitive (S), intermediately sensitive (IS), or resistant (R) to an antimicrobial agent or a particular antibiotic. This method is not applicable for filamentous fungi, anaerobes, or slowly-growing bacteria (Atlas, 1988).

2. AIM AND SCOPE OF THE STUDY

Pyrimidines have an important role in the medicinal chemistry area since they exhibited diverse biological activities such as analgesic, anticonvulsant, antidepressant, antipyretic, anti-inflammatory, antiviral, anti-HIV, antimicrobial and antitumor. Also, the vital biomolecules DNA and of critically important drugs (Fluorouracil **148**, Etravirine **150**, Risperidone **149**, Iclaprim **151** etc.) includes the pyrimidine core.

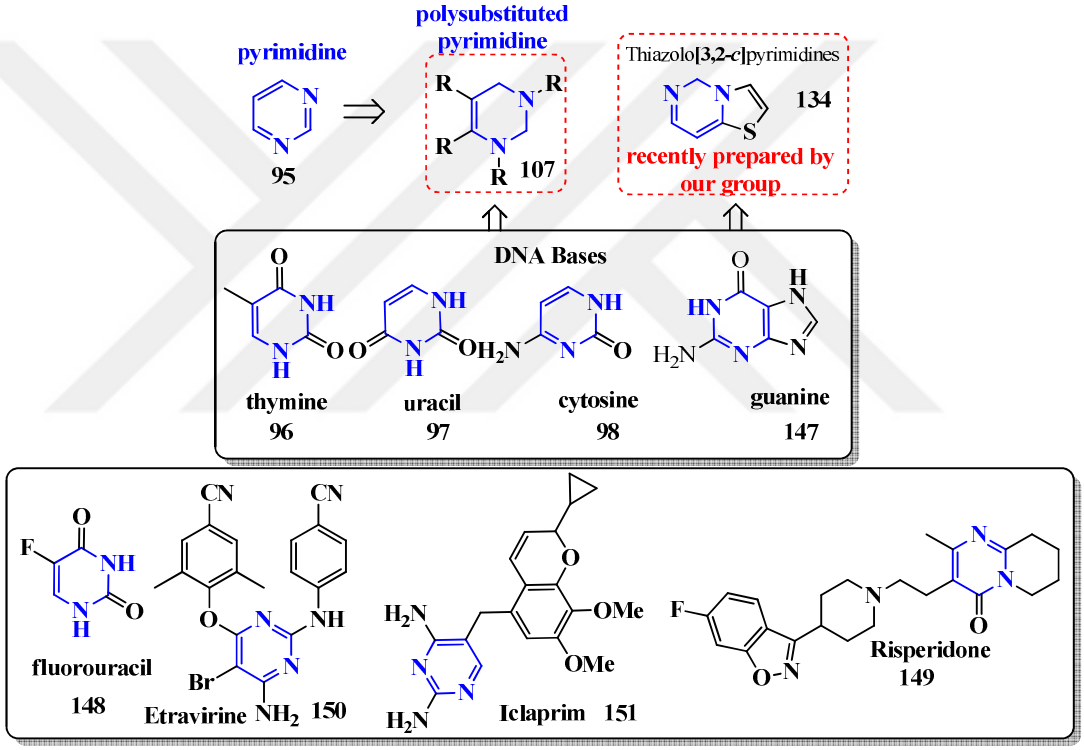


Figure 2.1. Various pyrimidine-based important molecules

Recently, first synthetic examples of some biologically active thiazolo[3,2-*c*]pyrimidines (S-analogs of guanidine) **134** were efficiently prepared and reported by our group. With our ongoing interest on the chemistry of pyrimidine-based molecules, new potentially bioactive polysubstituted nitropyridimines (**107**) are intented to synthesize using multicomponent reactions of diaryl substituted nitroenamines (**43**) with formaldehyde **7** and arylamines **6** in the present dissertation study. Secondly, biological activities of newly prepared polysubstituted

nitropyridimines (**107**) such as antioxidant or antibacterial etc. were planned to perform after purification and characterization steps.

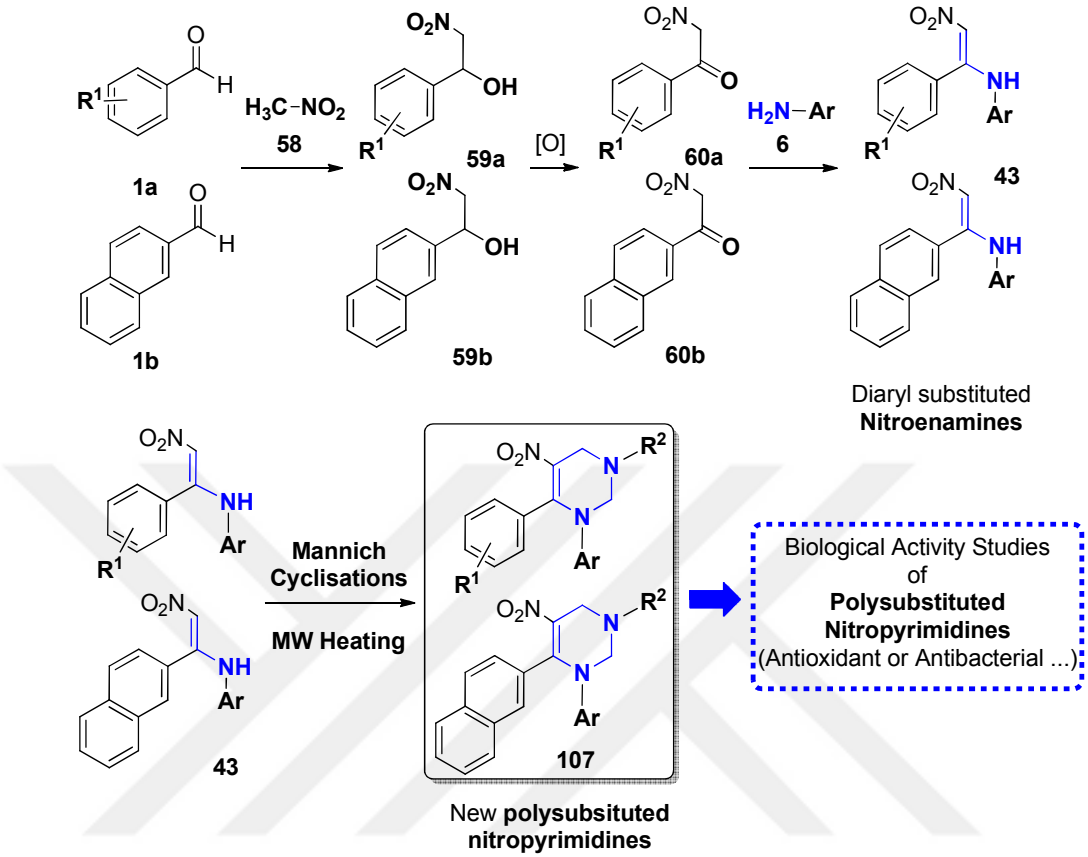


Figure 2.2. Synthetic route affording new polysubstituted nitropyrimidines (107)

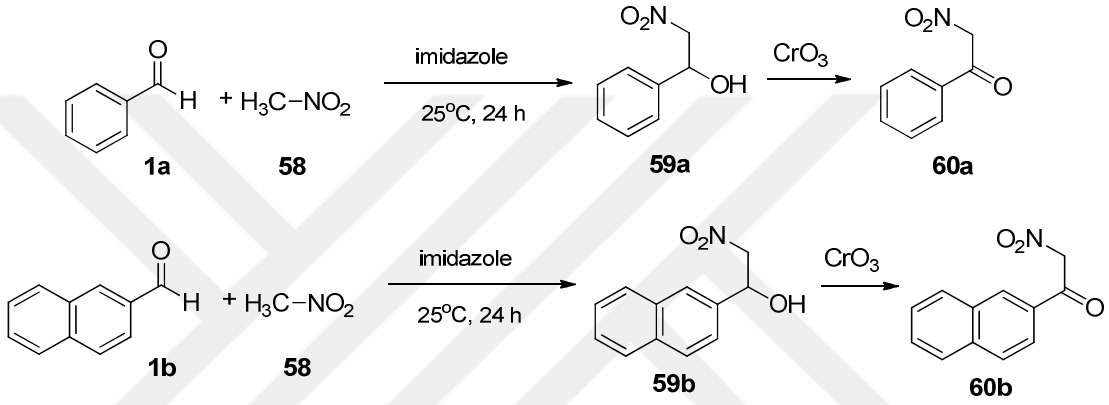
3. MATERIALS AND METHODS

All reagents and solvents were supplied from commercial sources in analytical grade (Merck, Sigma-Aldrich). A computer-controlled single-mode microwave reactor (CEM Discover Explorer SP) were used for microwave-assisted reactions. NMR spectra were recorded on a JEOL ECS400 Delta2 spectrometer (400 MHz for proton and 100 MHz for carbon) in $CDCl_3$ or DMSO-d_6 at room temperature. All chemical shifts (δ) were reported in parts per million (ppm) downfield from TMS; *J* values are given in Hz. The abbreviations used for NMR signals are: br s= broad singlet, s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, dd=doublet of doublets, dt=doublet of triplets, ddd=doublet of doublet of doublets. IR spectra were recorded on a SHIMADZU FTIR-8400S instrument using KBr pellets. High resolution mass measurements were run on a Waters Lct Premier XE oa-TOF Mass Spectrometer. Melting points were determined on a MELTEMP apparatus and they are uncorrected. TLC analyses were carried out to monitor the reaction progress using precoated plates with fluorescent indicator (Merck 5735). Column chromatographic separations were performed on silica gel (Merck, 230–400 mesh ASTM) and the eluents were mixtures of ethyl acetate (EA) and hexanes (H). Staining solutions of potassium permanganate and UV-254-366 were used for visualization of the TLC spots.

3.1 EXPERIMENTAL

3.1.1 PREPARATION OF STARTING MATERIALS (Harding et al.,1975)

3.1.1.1 General Procedures for Preparation of 2-nitro-1-(phenyl or naphthalen-2-yl)ethanones (60) (Aradi et al., 2017)

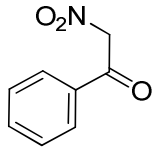


2-Nitro-1-arylethane-1-ols (59a,b): To a mixture of benzaldehyde (7.45 g, 70 mmol, 4.27 equiv.), nitromethane (12.8 g, 210 mmol; 12.8 equiv.), and imidazole (1.12 g, 16.4 mmol, 1 equiv.) in a reaction flask, distilled water (140 mL) was added. Then, reaction mixture was stirred at 25°C for 24 hour and reaction completion was controlled using TLC. Diethyl ether (40 mL) was added to the reaction mixture, the aqueous phase was extracted with diethyl ether (2×30 mL). The combined organics were washed with brine (1×30 mL), dried over anhydrous sodium sulfate, filtered, and evaporated. Yellow solid product was used in the next step (Jones oxidation) without purification.

2-Nitro-1-(phenyl or naphthalen-2-yl) ethanones (60a,b): 2-Nitro-1-arylethan-1-ol (59.2 mmol, 1 equiv.) was dissolved in acetone (97.5 mL), the mixture was cooled to 0°C, and then Jones reagent (CrO_3: 67.2 mmol, 1.13 equiv. and 6 mL conc. H_2SO_4 completed to 37.5 mL with distilled water) was added dropwise in 30 min until an orange color persist. After that the resulted mixture was stirred at 0–5°C for 22-24 hour. Isopropyl alcohol (50 mL) was added to the reaction mixture (100 mL) and deep green color was obtained. Mixture was extracted with diethyl ether (3 × 100

mL). The combined organics were washed with brine (1×50 mL), dried over anhydrous sodium sulfate, filtered, and evaporated. The crude residue was purified by column chromatography.

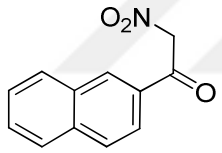
2-Nitro-1-phenylethanone (60a) (Aradi et al., 2017)



60a

Yellow solid. (8.6 g, 87%), m.p. 101-102°C;R_f (50% EtOAc/hexane) 0.70;IR (KBr) υ: 3020, 2962, 2928 (CH), 1693 (C=O), 1558 (NO_2), 1450, 1334(NO_2), 1230, 759 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.96–7.94 (2H, m), 7.77–7.73 (1H, m), 7.62–7.58 (2H, m), 6.55 (2H, s);^{13}C-NMR (100 MHz, DMSO-d_6) δ:188.4, 134.8, 133.4, 129.1, 128.4, 82.8.

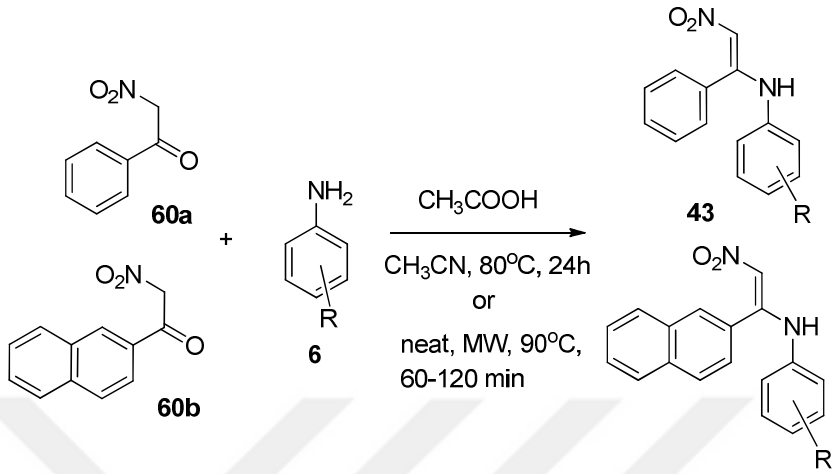
1-(Naphthalene-2-yl)-2-nitroethanone (60b) (Lian et al., 2015)



60b

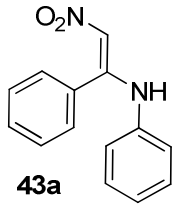
Light brown solid. (2.17 g, 85%), m.p. 130-132°C;R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ: 3059, 2966, 2837(CH), 1697 (C=O), 1629, 1558 (NO_2), 1356 (NO_2), 1309, 1192, 779 cm^{-1};^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.49 (1H, s), 7.95-7.74 (4H, m),7.55-7.40 (2H, m), 6.01 (2H,s);^{13}C-NMR (100 MHz, $CDCl_3$) δ:185.7, 136.3, 132.2, 130.7,130.5, 129.8, 129.7, 129.4, 128.0, 127.5, 123.0, 81.4. HRMS: MH^+, found: 216.0656. $C_{12}H_9NO_3$ requires 216.0661.

3.1.1.2 General Procedure for Preparation of (*Z*)-*N*-(2-nitro-1-arylvinyl)anilines (43) under conventional heating or MW irradiation



A mixture of 2-nitro-1-arylethan-1-one **60** (10.9 mmol, 1 equiv.), aniline **6** (15.3 mmol, 1.4 equiv.) and acetic acid (24 mmol, 2.2 equiv.) were refluxed in CH_3CN at 80°C under nitrogen atmosphere for 22-24 hour or heated with MW irradiation at 90°C for 60-120 min until TLC indicated the total consumption of corresponding ketone. After evaporation of all solvents, the crude residue was purified by column chromatographyusing mixtures of hexane-ethyl acetate (6:1/10:1) to afford nitroenamines (**43**) in pure state.

(*Z*)-*N*-(2-nitro-1-phenylvinyl)aniline (43a)

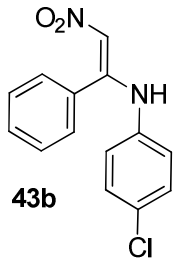


43a

With conventional heating for 22 hour and flash chromatography (15% EtOAc/hexane) afforded yellow powder. (1.38g, 55%), m.p. 121-122°C;R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ: 3138 (NH), 3055, 1606 (C-N), 1593, 1564 (C=C), 1481, 1363, 1192, 765 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 11.35 (NH, br s), 7.25 (1H, t, *J* 7.1 Hz), 7.18-7.08 (4H, m), 7.00 (2H, t, *J* 7.6 Hz), 6.91 (1H, t, *J* 7.4 Hz), 6.64 (2H, d, *J* 7.8 Hz), 6.59 (1H,s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.8, 137.6, 131.6, 130.9, 129.1, 129.0, 128.6, 126.0, 124.0, 114.2; (TOF-MS APCI⁻) *m/z*: 239

(100, $[M-H]^+$), 240 (20%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 239.0849. $C_{14}H_{11}N_2O_2$ requires 239.0815.

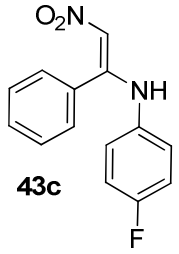
(*Z*)-4-chloro-*N*-(2-nitro-1-phenylvinyl)aniline (43b)



43b

With conventional heating for 22 hour and flash chromatography (10% EtOAc/hexane) afforded bright yellow solid. (1.60 g, 48%), m.p. 128-129°C; R_f (33% EtOAc/hexane) 0.60; IR (KBr) υ: 3248 (NH), 3113, 3066, 1599 (C-N), 1589, 1560 (C=C), 1491, 1363, 1290, 1197, 704 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ:11.38 (NH, br s), 7.49-7.40 (1H, m), 7.35 (1H, t, *J* 7.6 Hz),7.27 (2H, d, *J* 7.3 Hz),7.12 (1H, d, *J* 8.7 Hz),6.75 (2H, d, *J* 5.3 Hz), 6.72 (1H,s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.2, 136.2, 133.7, 131.5, 131.3, 131.2, 130.2, 129.3, 129.2, 128.6, 128.5, 125.1, 114.7; (TOF-MS APCI$^-$) *m/z*: 273 (100, $[M-H]^+$), 274 (20), 275 (40%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 273.0472. $C_{14}H_{10}ClN_2O_2$ requires 273.0425.

(*Z*)-4-fluoro-*N*-(2-nitro-1-phenylvinyl)aniline (43c)

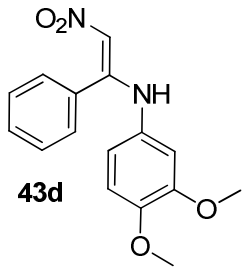


43c

With MW irradiation for 75 min and flash chromatography (10% EtOAc/hexane) afforded dark yellow solid. (1.10 g, 70%), m.p. 107-109°C; R_f (33% EtOAc/hexane) 0.70; IR (KBr) υ: 3149 (NH), 3072, 1606 (C-N), 1591, 1564 (C=C), 1508, 1475, 1357, 1278, 1192, 767, 705 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 11.42 (NH, br s), 8.11 (1H, d, *J* 9.2 Hz),7.47 (1H, t, *J* 7.7 Hz),7.41 (1H, d, *J* 7.2 Hz), 7.33 (2H, t, *J* 7.5 Hz),7.26 (2H, t, *J* 9.1 Hz), 6.86 (2H, t, *J* 8.5 Hz), 6.82-6.77(2H,m), 6.76 (1H,s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 161.7, 159.3, 155.9, 133.8, 131.3, 131.0, 130.2, 129.1,

128.7, 128.6,125.9, 125.8, 116.2, 116.0, 114.2; (TOF-MS APCI$^-$) *m/z*: 257 (100, [M-H]$^+$), 258 (20%); HRMS (TOF-MS APCI$^-$): [M-H]$^+$, found 257.0735. $C_{14}H_{10}FN_2O_2$ requires 257.0720.

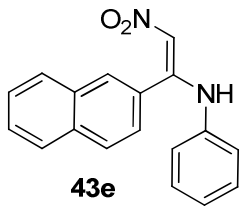
(*Z*)-3,4-dimethoxy-*N*-(2-nitro-1-phenylvinyl)aniline (43d)



43d

With MW irradiation for 120 min and flash chromatography (12.5-25% EtOAc/hexane) afforded orange solid. (1.22 g, 67%), m.p. 117-118°C; R_f (33% EtOAc/hexane) 0.30; IR (KBr) υ: 3130 (NH), 3018, 1593, 1562 (C=C), 1514, 1438, 1352, 1232, 1184, 767, 711 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 11.53 (NH, br s), 7.41 (1H, t, *J* 7.2 Hz),7.34 (2H, t, *J* 7.4 Hz),7.29 (2H, d, *J* 7.7 Hz), 6.75 (1H,s),6.65 (1H, d, *J* 8.6 Hz), 6.43 (1H, dd, *J* 8.6, 2.5 Hz), 6.26 (1H, d, *J* 2.4 Hz), 3.79 (3H, s), 3.55 (3H,s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.8, 148.9, 147.0, 131.8, 130.8, 130.5, 129.0, 128.6, 116.2, 113.6, 111.0, 108.1, 56.0, 55.8; (TOF-MS APCI$^-$) *m/z*: 299 (100, [M-H]$^+$), 300 (25%); HRMS (TOF-MS APCI$^-$): [M-H]$^+$, found 299.1027. $C_{16}H_{15}N_2O_4$ requires 299.1026.

(*Z*)-*N*-(1-(naphthalen-2-yl)-2-nitrovinyl)aniline (43e)

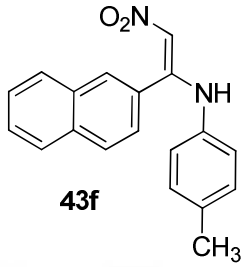


43e

With MW irradiation for 60 min and flash chromatography (10-15% EtOAc/hexane) afforded dark yellow solid. (0.410 g, 30%), m.p. 134-136°C; R_f (25% EtOAc/hexane) 0.50; IR (KBr) υ: 3130 (NH), 3053, 1602 (C-N), 1579, 1568 (C=C), 1489, 1363, 1195, 754 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 11.58 (NH, br s), 7.95 (1H,s), 7.85-7.80 (2H,m), 7.71 (1H, d, *J* 8.6 Hz), 7.61-7.50 (2H, m), 7.21 (1H, dd, *J* 8.6, 1.7 Hz), 7.13 (2H, t, *J* 7.7 Hz), 7.06 (1H, d, *J* 7.3 Hz), 6.89 (1H,s), 6.85 (2H, d, *J*

7.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.6, 137.6, 134.1, 132.8, 129.2, 129.1, 128.9, 128.7, 128.6, 128.1, 127.9,127.2, 126.0, 125.1, 125.0, 123.9, 114.6, 114.5;(TOF-MS ESI⁻)*m/z*: 289 (100, $[M-H]^+$), 290 (20%); HRMS (TOF-MS ESI⁻): $[M-H]^+$, found 289.1015. $C_{18}H_{13}N_2O_2$ requires 289.0971.

(*Z*)-4-methyl-*N*-(1-(naphthalen-2-yl)-2-nitrovinyl)aniline (43f)

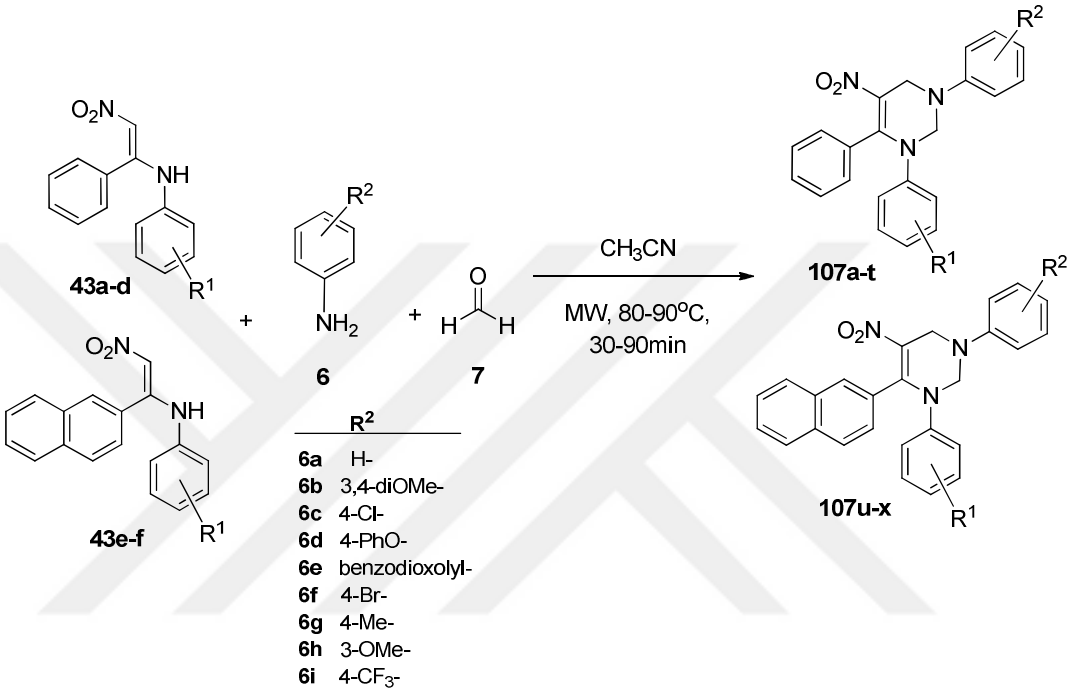


43f

With MW irradiation for 75 min and flash chromatography (10-12.5% EtOAc/hexane) afforded dark yellow solid. (0.300 g, 40%), m.p. 124-125°C; R_f (33% EtOAc/hexane) 0.70; IR (KBr) υ: 3128 (NH), 3051, 1589 (C-N), 1560 (C=C), 1473, 1356, 1186, 815 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 11.59 (NH, br s), 7.94 (1H,s), 7.82 (2H,dd, *J* 12.8, 8.9 Hz), 7.71 (1H, d, *J* 8.6 Hz), 7.59-7.50 (2H, m), 7.20 (1H, dd, *J* 8.5, 1.7 Hz), 6.92 (2H, t, *J* 8.3 Hz), 6.87 (1H,s), 6.73 (2H, d, *J* 8.3Hz), 3.21 (3H,s) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.9, 136.0, 135.0, 134.0, 132.8, 128.8, 128.7, 128.6, 128.0, 127.9, 127.2, 125.0, 123.8, 114.1, 20.8; (TOF-MS ESI⁻) *m/z*: 303 (75, $[M-H]^+$), 304 (100), 305 (25%); HRMS (TOF-MS ESI⁻): $[M-H]^+$, found 303.1169. $C_{19}H_{15}N_2O_2$ requires 303.1128.

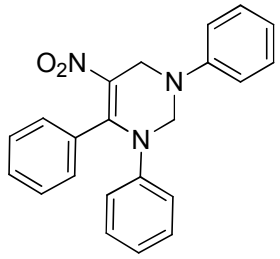
3.1.2 SYNTHESIS OF TARGET PRODUCTS

3.1.2.1 General Procedure for Preparation of 5-nitro-6-phenyl-1,3-diaryl-1,2,3,4-tetrahydropyrimidines and 5-nitro-6-naphthyl-1,3-diaryl-1,2,3,4-tetrahydropyrimidines (107)



(*Z*)-*N*-(2-nitro-1-arylvinyl)aniline **(43a-f)** (0.5 mmol, 1.0 equiv), aniline derivative **6a-i** (0.5 mmol, 1.0 equiv.)) and formaldehyde **7** (37 % v/v in H_2O, 1.0 mmol, 2.0 equiv.) were mixed with CH_3CN (2 mL) and the resulting mixture was prestirred for 15 seconds. Then, the mixture was heated with microwave irradiation for 30-90 min. The reaction progress was followed by TLC and upon completion, the reaction mixture was cooled to ambient temperature and the solvent was rotaevaporated. The resulting solid residue was purified by silica gel column chromatography using EtOAc-hexane mixtures specified, to afford the title compound (**107**) in good yields.

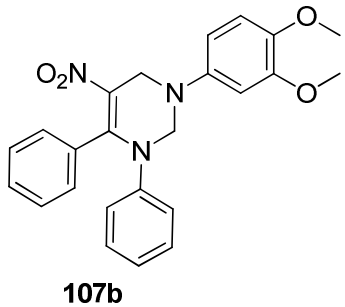
5-Nitro-1,3,6-triphenyl-1,2,3,4-tetrahydropyrimidine (107a)



107a

With MW heating for 40 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (140 mg, 78%), m.p. 153-155°C; R_f (25% EtOAc/hexane) 0.30; IR (KBr) υ: 3063, 2856 (CH), 1597, 1587, 1564, 1492, 1278, 1118, 935, 765, 694cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.28-7.20 (2H,m), 7.21-7.09 (5H,m), 7.03 (3H, ddd, *J* 14.8, 8.6, 4.4 Hz), 6.94 (3H, dd, *J* 9.1, 8.1 Hz), 6.65 (2H, dd, *J* 8.2, 1.3 Hz), 5.07 (2H, s), 4.72 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.7, 147.4, 143.6, 132.9, 129.7, 129.5, 129.3, 128.9, 128.6, 128.1, 127.0, 126.9, 126.1, 123.4, 122.1, 121.5, 118.2, 117.5, 70.6, 49.2; (TOF-MS APCI$^-$) *m/z*: 356 (80), 357 (100%, M^+); HRMS (TOF-MS APCI$^-$): M^+, found 357.1474. $C_{22}H_{19}N_3O_2$ requires 357.1477.

3-(3,4-Dimethoxyphenyl)-5-nitro-1,6-diphenyl-1,2,3,4-tetrahydropyrimidine (107b)

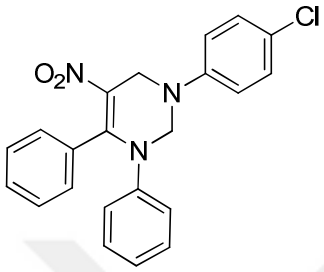


107b

With MW heating for 45 min and flash chromatography (20% EtOAc/hexane) afforded yellow solid. (65 mg, 32%), m.p. 137-139°C; R_f (50% EtOAc/hexane) 0.50;IR (KBr) υ:3059, 2926 (CH), 1593, 1577, 1554, 1491, 1294, 1138, 935, 765, 698 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ:7.36-7.29 (1H,m), 7.22-7.13 (3H,m), 7.10 (2H, dd, *J* 10.3, 5.0 Hz), 7.03 (2H, t, *J* 7.4 Hz), 6.97 (1H, d, *J* 7.2 Hz), 6.76 (1H, d, *J* 8.6 Hz), 6.62 (2H, d, *J* 8.9 Hz),6.54 (1H, dd, *J* 8.6, 2.7 Hz), 6.48 (1H, d, *J* 2.7 Hz),

5.02 (2H, s), 4.69 (2H, s), 3.82 (3H, s), 3.67 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ:155.5, 149.7, 144.6, 143.5, 141.7, 132.9, 129.5, 129.3, 128.8, 128.6, 128.0, 126.9, 126.8, 126.1, 123.1, 112.1, 109.9, 103.6, 71.6, 56.1, 55.7, 49.9; (TOF-MS APCI$^-$) *m/z*: 417 (100, M^+), 418 (50%); HRMS (TOF-MS APCI$^-$): M^+, found 417.1700. $C_{24}H_{23}N_3O_4$ requires 417.1688.

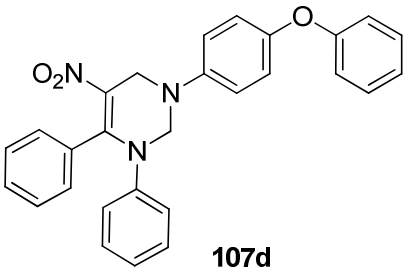
3-(4-Chlorophenyl)-5-nitro-1,6-diphenyl-1,2,3,4-tetrahydropyrimidine



(107c) **107c**

With MW heating for 45 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (64 mg, 33%), m.p. 132-134°C. R_f (50% EtOAc/hexane) 0.80; IR (KBr) υ: 3059, 2906 (CH), 1591, 1579, 1554, 1491, 1274, 1155, 819, 759, 696 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ:7.21-7.13 (5H,m), 7.13-7.07 (2H,m),7.05 (2H, d, *J* 7.9 Hz), 7.02 (1H, d, *J* 7.2 Hz),6.85 (2H, d, *J* 8.9 Hz), 6.66 (2H, d, *J* 7.8 Hz), 5.04 (2H, s), 4.68 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.4, 146.0, 143.4, 132.7, 129.7, 129.5, 129.2, 128.9, 128.8, 128.1, 127.5, 127.0, 126.7, 126.3, 126.2, 123.2, 119.3, 118.7, 70.5, 49.1; (TOF-MS APCI$^-$) *m/z*: 391 (100, M^+), 392 (50), 393 (40%); HRMS (TOF-MS APCI$^-$): M^+, found 391.1073. $C_{22}H_{18}ClN_3O_2$ requires 391.1087.

5-Nitro-3-(4-phenoxyphenyl)-1,6-diphenyl-1,2,3,4-tetrahydropyrimidine

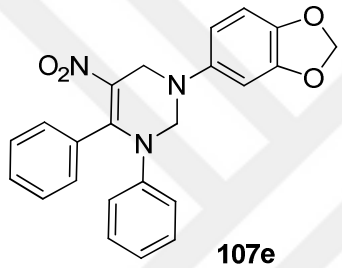


(107d) **107d**

With MW heating for 75 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (125 mg, 55%), m.p. 145-147°C. R_f (33% EtOAc/hexane)

0.45; IR (KBr) υ: 3057, 2868 (CH), 1585, 1558, 1546, 1491, 1286, 1120, 839, 765, 698 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33-7.26 (2H,m), 7.21-7.10 (5H,m), 7.05 (3H, t, *J* 8.4 Hz), 7.02-6.95 (3H, m), 6.95-6.88 (4H, m), 6.64 (2H, dd, *J* 8.2, 1.2 Hz), 5.03 (2H, s), 4.69 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 158.0, 155.6, 151.5, 143.7, 132.9, 130.2, 129.6, 129.3, 128.9, 128.6, 128.1, 127.9, 127.6, 127.0, 126.3, 126.1, 123.3, 122.5, 121.1, 120.4, 120.3, 119.5, 118.3, 117.5, 71.8, 49.5; (TOF-MS APCI⁻) *m/z*: 449 (100, M^+), 450 (40%); HRMS (TOF-MS APCI⁻): M^+, found 449.1730. $C_{28}H_{23}N_3O_3$ requires 449.1739.

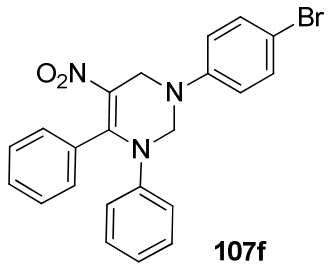
3-(Benzo[d][1,3]dioxol-5-yl)-5-nitro-1,6-diphenyl-1,2,3,4-tetrahydropyrimidine (107e)



107e

With MW heating for 85 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (43 mg, 21%), m.p. 161-162°C. R_f (33% EtOAc/hexane) 0.40; IR (KBr) υ: 3055, 2872 (CH), 1579, 1554, 1494, 1265, 1126, 1035, 933, 767, 698 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34 (1H,dt, *J* 16.0, 7.2 Hz), 7.20-7.09 (4H,m), 7.05 (2H, dd, *J* 14.5, 7.8 Hz), 6.98 (1H, t, *J* 7.5 Hz), 6.67 (3H, dd, *J* 16.5, 8.0 Hz), 6.54 (1H, d, *J* 2.2 Hz),6.46 (1H, dd, *J* 8.3, 2.1Hz),5.88 (2H,s), 4.95 (2H, s), 4.62 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 158.5, 155.6, 148.5, 143.4, 142.9, 132.9, 129.5, 129.3, 128.8, 128.6, 128.0, 127.8, 127.6, 127.0, 126.3, 126.1, 123.1, 119.9,111.7,111.2, 110.9, 110.4, 109.0,108.6, 107.7, 102.2, 101.3, 72.2, 49.9; (TOF-MS APCI⁻) *m/z*: 401 (100,M^+), 402 (40%); HRMS (TOF-MS APCI⁻): M^+, found 401.1362. $C_{23}H_{19}N_3O_4$ requires 401.1375.

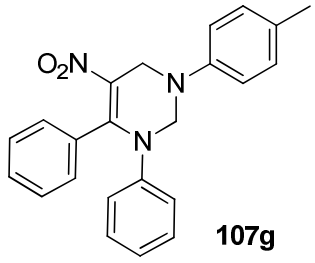
3-(4-Bromophenyl)-5-nitro-1,6-diphenyl-1,2,3,4-tetrahydropyrimidine (107f)



107f

With MW heating for 70 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (90 mg, 42%), m.p. 118-120°C. R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ: 3064, 2908 (CH), 1591, 1579, 1554, 1494, 1273, 1155, 1018, 817, 759, 696 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.31 (2H,d, *J* 8.9 Hz), 7.22-7.13 (3H,m), 7.13-6.98 (5H, m), 6.79 (2H, d, *J*8.9 Hz), 6.67 (2H, d, *J* 8.6 Hz), 5.03 (2H, s), 4.68 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.6, 146.5, 143.4, 132.7, 132.5, 132.1, 131.9, 129.4, 128.9, 128.8, 128.7, 128.1, 127.5, 126.9, 126.7, 126.3, 126.1, 123.2, 120.0, 119.5, 119.0, 114.0, 70.3, 49.0;(TOF-MS ESI$^-$) *m/z*:434 (100, $[M-H]^+$), 435 (30), 436 (100), 437(30%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 434.0515. $C_{22}H_{17}BrN_2O_3$ requires 434.0498.

5-Nitro-1,6-diphenyl-3-(p-tolyl)-1,2,3,4-tetrahydropyrimidine (107g)

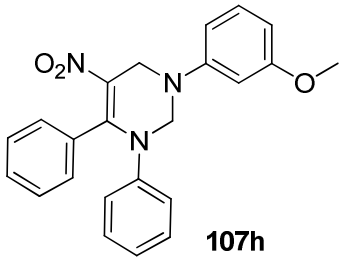


107g

With MW heating for 45 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (130 mg,70%), m.p. 133-135°C. R_f (33% EtOAc/hexane) 0.40; IR (KBr) υ: 3061, 2918 (CH), 1585, 1560, 1491, 1273, 1124, 1016, 763, 694 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.19-7.13 (3H,m), 7.13-7.08 (2H, m), 7.07-6.96 (5H, m), 6.87 (2H, d, *J* 8.5 Hz), 6.63 (2H, d, *J* 7.6 Hz), 5.03 (2H, s), 4.69 (2H, s), 2.26 (3H,s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.7, 145.1, 143.5, 133.0, 131.4, 130.3, 129.7, 129.4, 129.2, 129.0, 128.9, 128.6, 128.0, 127.1, 126.9, 126.8, 126.4, 126.2, 123.1, 118.4, 117.8, 71.2, 49.3, 20.6; (TOF-MS APCI$^-$) *m/z*: 370 (80, M^+), 371

(100), 372 (25%); HRMS (TOF-MS APCI$^-$): M^+, found 371.1591. $C_{23}H_{21}N_3O_2$ requires 371.1633.

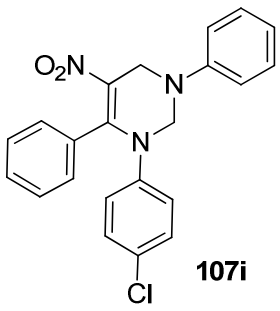
3-(3-Methoxyphenyl)-5-nitro-1,6-diphenyl-1,2,3,4-tetrahydropyrimidine



(107h) **107h**

With MW heating for 55 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (50 mg, 25%), m.p. 128-129°C.R_f (33% EtOAc/hexane) 0.35; IR (KBr) υ: 3061, 2924 (CH), 1597, 1585, 1552, 1492, 1294, 1197, 1018, 827, 759, 696 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.40-7.29 (1H, m), 7.21-7.10 (6H, m), 7.06 (2H, t, *J* 7.5 Hz), 7.00 (1H, t, *J* 7.3 Hz), 6.71 (2H, d, *J* 7.5 Hz), 6.52 (1H,dd, *J* 8.2, 2.2 Hz), 6.47 (1H,dd, *J* 8.2, 2.2 Hz), 6.44 (1H,d, *J* 2.2 Hz),5.05 (2H, s), 4.70 (2H, s), 3.67 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 160.7, 158.6, 155.6, 148.8, 143.6, 130.0, 129.5, 129.4, 128.9, 128.7, 128.6, 128.0, 127.0, 126.2, 123.7, 110.2, 110.8, 110.6, 103.9, 103.7, 70.2, 55.4, 49.2; (TOF-MS APCI$^-$) *m/z*: 387 (100,M^+), 388 (30%); HRMS (TOF-MS APCI$^-$): M^+, found 387.1597. $C_{23}H_{21}N_3O_3$ requires 387.1582.

1-(4-Chlorophenyl)-5-nitro-3,6-diphenyl-1,2,3,4-tetrahydropyrimidine

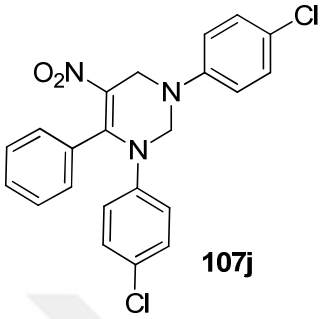


(107i) **107i**

With MW heating for 50 min and flash chromatography (15% EtOAc/hexane) afforded orange solid. (100mg, 50%), m.p. 127-129°C. R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ: 3057, 2922 (CH), 1600, 1579, 1546, 1491, 1265, 1087, 1010, 925, 763,694 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.27-7.15 (6H,m), 7.11 (2H, dd, *J* 6.9, 1.1 Hz), 6.99 (2H, d, *J* 8.5 Hz), 6.94 (2H, t, *J* 7.6 Hz), 6.56 (2H, d, *J* 8.6 Hz), 5.03

(2H, s), 4.69 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.0, 147.2, 142.3, 132.6, 132.0, 129.8, 129.5, 128.8, 128.3, 128.0, 127.4, 124.4, 122.3, 121.6, 118.2, 117.5, 71.1, 48.9; (TOF-MS APCI$^-$) *m/z*: 391 (100, M^+), 392 (40), 393 (35%); HRMS (TOF-MS APCI$^-$): M^+, found 391.1124. $C_{22}H_{18}ClN_3O_2$ requires 391.1087.

1,3-Bis(4-chlorophenyl)-5-nitro-6-phenyl-1,2,3,4-tetrahydropyrimidine

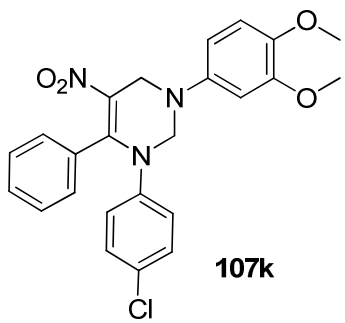


107j

(107j)

With MW heating for 30 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (95mg, 45%), m.p.163-165°C. R_f (33% EtOAc/hexane) 0.40; IR (KBr) υ: 3061, 2831 (CH), 1587, 1560, 1498, 1265, 1087, 1008, 827, 765, 698 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.10 (1H,d, *J* 8.2 Hz), 7.47 (1H,t, *J* 7.6 Hz), 7.28-7.15 (4H,m), 7.09 (2H, d, *J*8.0 Hz), 7.02 (2H, d, *J* 8.6 Hz), 6.84(2H, d, *J* 8.9 Hz), 6.58 (2H, d, *J* 8.6 Hz), 4.99 (2H, s), 4.66 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 154.9, 145.8, 142.2, 132.4, 132.2, 129.8, 129.6, 129.5, 129.2, 128.9, 128.8, 128.6, 128.3, 127.9, 124.1, 119.3, 118.7, 70.7, 49.0; (TOF-MS APCI$^-$) *m/z*: 425 (100,M^+),426 (50), 427 (75%); HRMS (TOF-MS APCI$^-$): M^+, found 425.0723. $C_{22}H_{17}Cl_2N_3O_2$ requires 425.0697.

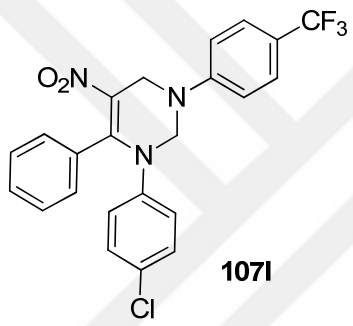
1-(4-Chlorophenyl)-3-(3,4-dimethoxyphenyl)-5-nitro-6-phenyl-1,2,3,4-tetrahydro pyrimidine (107k)



107k

With MW heating for 30 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (160 mg, 71%), m.p.118-120°C. R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ: 3064, 2926 (CH), 1585, 1560, 1491, 1259, 1089, 1012, 933, 761, 707 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.09 (2H,d, *J* 7.6 Hz), 7.46 (3H,t, *J* 7.7 Hz), 7.20 (2H,d, *J* 7.6 Hz), 7.09 (2H, dd, *J* 7.9, 1.4 Hz), 7.00-6.96 (2H,m), 6.75 (1H, d, *J* 8.3 Hz), 6.54 (2H, d, *J* 8.8 Hz), 4.97 (2H, s), 4.66 (2H, s), 3.82 (3H, s), 3.71 (3H, s); (TOF-MS APCI$^-$) *m/z*: 451 (100, M^+), 452 (35%); HRMS (TOF-MS APCI$^-$): M^+, found 451.1314. $C_{24}H_{22}ClN_3O_4$ requires 451.1298.

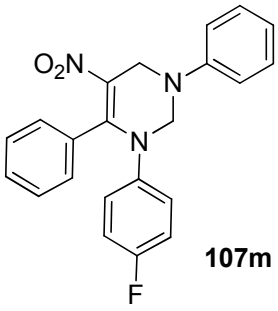
1-(4-Chlorophenyl)-5-nitro-6-phenyl-3-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine (107l)



107l

With MW heating for 45 min and flash chromatography (20% EtOAc/hexane) afforded yellow solid. (95 mg,70%), m.p. 197-199°C. R_f (33% EtOAc/hexane) 0.40; IR (KBr) υ: 3066, 2852 (CH), 1618, 1587, 1560, 1491, 1458, 1276, 1116, 1006, 829, 767, 698 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ:7.46 (2H,t, *J* 8.6 Hz), 7.23 (3H,dt, *J* 14.2, 5.2 Hz), 7.13 (2H, d, *J* 6.9 Hz), 7.06 (2H, d, *J* 8.6 Hz), 6.88 (2H, d, *J* 8.6 Hz), 6.67 (2H, d, *J* 8.7 Hz), 5.07 (2H, s), 4.72 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 154.9, 149.6, 142.1, 132.4, 132.2, 130.0, 129.4, 129.3, 128.6, 127.8, 126.8, 124.7, 116.0, 68.9, 48.6; (TOF-MS ESI$^+$) *m/z*: 458 (100, MH^+-2H), 460 (50%); HRMS (TOF-MS ESI$^+$): MH^+-2H, found 458.0902. $C_{23}H_{15}F_3N_3O_2$ requires 458.0877.

1-(4-Fluorophenyl)-5-nitro-3,6-diphenyl-1,2,3,4-tetrahydropyrimidine

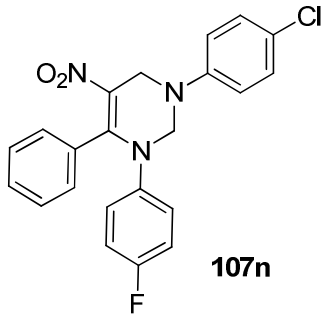


107m

(107m)

With MW heating for 45 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (150 mg, 80%), m.p.153-155°C. R_f (33% EtOAc/hexane) 0.45; IR (KBr) υ: 3061 (arom. CH), 2854 (CH), 1600, 1583, 1566, 1508, 1458, 1280, 1120, 1014, 931, 839, 765,698 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.25 (2H,t, *J* 7.7 Hz), 7.21-7.14 (3H,m), 7.09 (2H, dd, *J* 7.9, 1.6 Hz), 6.99-6.92 (3H, m), 6.71 (2H, t, *J* 8.5 Hz), 6.62-6.55 (2H, m),5.02 (2H, s), 4.70 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 161.8, 159.4, 155.5, 147.4, 139.7, 132.8, 129.6, 129.4, 129.1, 128.8, 128.7, 128.5, 123.7, 122.0, 118.0, 116.0, 115.8, 71.2, 48.9; (TOF-MS APCI$^-$) *m/z*: 375 (100, M^+), 376 (30%); HRMS (TOF-MS APCI$^-$): M^+, found 375.1388. $C_{22}H_{18}FN_3O_2$ requires 375.1383.

3-(4-Chlorophenyl)-1-(4-fluorophenyl)-5-nitro-6-phenyl-1,2,3,4-tetrahydro pyrimidine (107n)

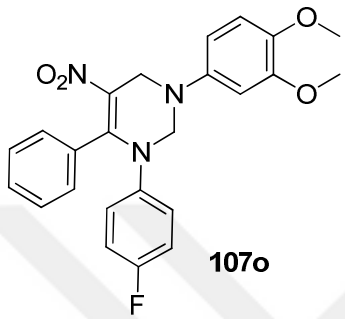


107n

With MW heating for 60 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (125 mg, 60%), m.p. 151-152°C. R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ:3057 (arom. CH), 2850 (CH), 1604, 1581, 1566, 1508, 1458, 1276, 1124, 1024, 929, 840, 765, 698 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.24-7.15 (5H,m), 7.08 (2H, dd, *J* 7.9, 1.4 Hz), 6.87 (2H, d, *J* 9.0 Hz), 6.74 (2H, t, *J* 8.5 Hz),6.62 (2H, dd, *J* 8.9, 4.7 Hz), 4.99 (2H, s), 4.66 (2H, s); ^{13}C-NMR (100 MHz,

$CDCl_3$) δ: 161.9, 159.4, 155.5, 146.0, 139.5, 132.6, 129.6, 129.5, 129.1, 128.7, 128.6, 128.5, 126.9, 123.4, 119.1, 116.2, 115.9, 70.9, 48.9; (TOF-MS APCI$^-$) *m/z*: 409 (100, M^+), 410 (80), 411 (40%); HRMS (TOF-MS APCI$^-$): M^+, found 409.0979. $C_{22}H_{17}ClFN_3O_2$ requires 409.0993.

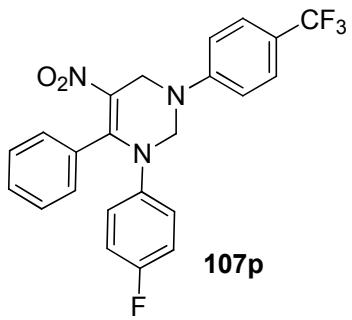
3-(3,4-Dimethoxyphenyl)-1-(4-fluorophenyl)-5-nitro-6-phenyl-1,2,3,4-tetrahydro pyrimidine (107o)



107o

With MW heating for 60 min and flash chromatography (15% EtOAc/hexane) afforded dark orange solid. (50 mg, 23%), m.p. 115-117°C. R_f (33% EtOAc/hexane) 0.25; IR (KBr) υ: 3068 (arom. CH), 2926 (CH), 1604, 1581, 1560, 1508, 1460, 1278, 1153, 1022, 931, 829, 767, 700 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.21-7.14 (3H,m), 7.07 (2H, dd, *J* 7.7, 1.7 Hz),6.76 (1H, d, *J* 8.4 Hz), 6.70 (2H, t, *J* 8.5 Hz), 6.60-6.51 (4H, m), 4.97 (2H, s), 4.66 (2H, s), 3.82 (3H, s), 3.72 (3H, s) ; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 161.7, 159.4, 155.5, 149.7, 144.8, 141.6, 139.7, 130.2, 129.5, 129.0, 128.7, 128.5, 123.4, 116.0, 115.8, 111.9, 110.1, 103.9, 72.2, 56.2, 56.0, 49.6; (TOF-MS APCI$^-$) *m/z*: 435 (100,M^+), 436 (40%); HRMS (TOF-MS APCI$^-$): M^+, found 435.1569. $C_{24}H_{22}FN_3O_4$ requires 435.1594.

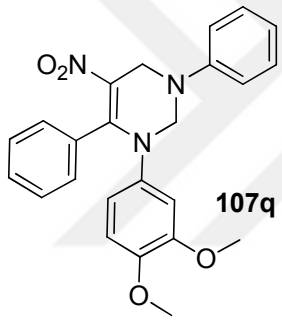
1-(4-Fluorophenyl)-5-nitro-6-phenyl-3-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine (107p)



107p

With MW heating for 45 min and flash chromatography (20% EtOAc/hexane) afforded yellowish-green solid. (185 mg, 83%), m.p. 160-162°C. R_f (33% EtOAc/hexane) 0.40; IR (KBr) υ: 3086 (arom. CH), 2850 (CH), 1616, 1572, 1508, 1467, 1282, 1116, 1074, 974, 835, 763, 700 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.47 (2H,d, *J* 8.8 Hz), 7.24-7.17 (3H,m), 7.11 (2H, dd, *J* 8.0, 1.4 Hz), 6.91 (2H, d, *J* 8.8 Hz), 6.78 (2H, t, *J* 8.4 Hz), 6.74-6.67 (2H, m), 5.07 (2H, s), 4.73 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 161.9, 159.5, 155.4, 149.7, 139.5, 129.8, 128.6, 128.5, 128.4, 126.9, 126.8, 124.1, 116.3, 116.2, 116.1, 69.3, 48.5; (TOF-MS ESI$^+$)*m/z*: 442 (100, MH^+-2H), 443 (25%); HRMS (TOF-MS ESI$^+$): MH^+-2H, found 442.1205. $C_{23}H_{15}F_4N_3O_2$ requires 442.1173.

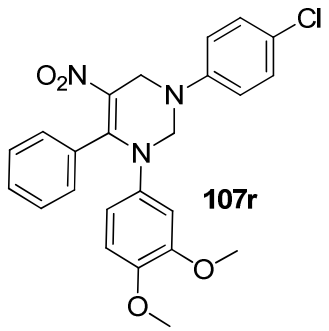
1-(3,4-Dimethoxyphenyl)-5-nitro-3,6-diphenyl-1,2,3,4-tetrahydropyrimidine (107q)



107q

With MW heating for 80 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (172 mg, 82%), m.p. 130-132°C.R_f (33% EtOAc/hexane) 0.25; IR (KBr) υ: 3093 (arom. CH), 2916, 2843 (CH), 1597, 1579, 1545, 1514, 1444, 1247, 1134, 1024, 920, 881, 771, 692cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.25 (2H, dd, *J* 9.3, 6.6 Hz), 7.20-7.13 (3H,m), 7.10 (2H,dd, *J* 7.7, 1.8 Hz),7.00 (2H,d, *J* 7.9 Hz), 6.94 (1H, t, *J* 7.3 Hz), 6.54 (1H, d, *J* 8.5 Hz),6.38 (1H, dd, *J* 8.5, 2.4 Hz),5.82 (1H, d, *J* 2.4 Hz), 5.04 (2H, s), 4.71 (2H, s), 3.73 (3H,s), 3.44 (3H,s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 156.0, 148.5, 147.6, 147.4, 136.6, 133.2, 129.5, 129.3, 128.9, 128.4, 122.6, 121.9, 118.9, 118.3, 110.8, 110.5, 71.5, 55.8, 55.7, 48.9; (TOF-MS ESI$^-$) *m/z*: 416 (100, $[M-H]^+$), 417 (25%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 416.1636. $C_{24}H_{22}N_3O_4$ requires 416.1604.

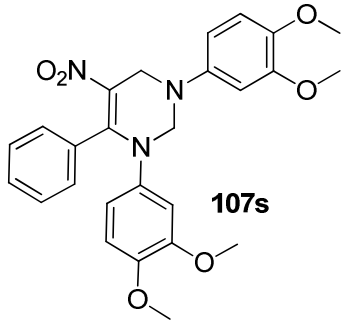
3-(4-Chlorophenyl)-1-(3,4-dimethoxyphenyl)-5-nitro-6-phenyl-1,2,3,4-tetrahydro pyrimidine (107r)



107r

With MW heating for 90 min and flash chromatography (15-25% EtOAc/hexane) afforded yellow solid. (95 mg, 42%), m.p.180-182°C. R_f (33% EtOAc/hexane) 0.25; IR (KBr) υ: 3091 (arom. CH), 2922 (CH), 1595, 1541, 1510, 1491, 1273, 1134, 1022, 918, 831, 765 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ:7.23-7.14 (5H,m), 7.09 (2H,dd, *J* 7.8, 1.6 Hz), 6.91 (2H, d, *J* 9.0 Hz), 6.55 (1H, d, *J* 8.5 Hz),6.38 (1H, dd, *J* 8.5, 2.5 Hz),5.84 (1H, d, *J* 2.4 Hz), 5.01 (2H, s), 4.67 (2H, s), 3.74 (3H,s), 3.48 (3H,s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.8, 148.6, 147.5, 146.3, 136.4, 132.9, 129.5, 128.9, 128.3, 126.9, 122.4, 119.5, 118.9, 110.6, 71.3, 55.9, 55.6, 49.0; (TOF-MS ESΙ) *m/z*: 450 (100, $[M-H]^+$), 451 (40), 452 (50%); HRMS (TOF-MS ESΙ): $[M-H]^+$, found 450.1254. $C_{24}H_{21}ClN_3O_4$ requires 450.1215.

1,3-Bis(3,4-dimethoxyphenyl)-5-nitro-6-phenyl-1,2,3,4-tetrahydropyrimidine (107s)

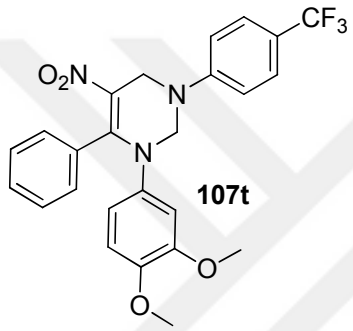


107s

With MW heating for 60 min and flash chromatography (20-33% EtOAc/hexane) afforded dark orange solid. (152 mg, 64%), m.p. 147-149°C. R_f (33% EtOAc/hexane) 0.30; IR (KBr) υ: 3080 (arom. CH), 2924 (CH), 1612, 1581, 1560, 1518, 1444, 1282, 1128, 1018, 920, 839, 767, 698cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$)

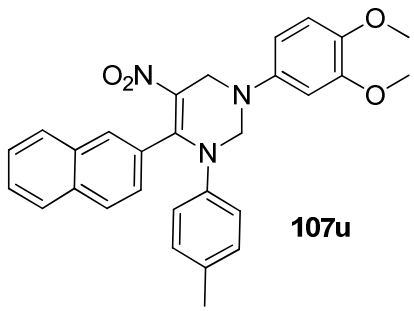
δ: 7.20-7.13 (3H,m), 7.09 (2H,dd, *J* 7.6, 1.9 Hz), 6.76 (1H, d, *J* 9.4 Hz), 6.60-6.55 (2H,m),6.52 (1H, d, *J* 8.6 Hz), 6.33 (1H, dd, *J* 8.5, 2.4 Hz), 5.86 (1H, d, *J* 2.4 Hz), 4.98 (2H, s), 4.67 (2H, s), 3.81 (3H,s), 3.73 (3H,s), 3.72 (3H,s), 3.46 (3H,s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.9, 149.7, 148.5, 147.4, 144.7, 141.9, 136.5, 133.2, 129.3, 128.9, 128.4, 122.3, 119.0, 111.8, 110.8, 110.5, 110.4, 104.2, 72.3, 56.2, 56.0, 55.9, 55.7, 49.8; (TOF-MS ESI$^+$) *m/z*: 476 (100, MH$^+$-2H), 477 (40%); HRMS (TOF-MS ESI$^+$): MH$^+$-2H, found 476.1831. $C_{26}H_{25}N_3O_6$ requires 476.1816.

1-(3,4-Dimethoxyphenyl)-5-nitro-6-phenyl-3-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine (107t)



With MW heating for 45 min and flash chromatography (20% EtOAc/hexane) afforded yellow solid. (140 mg, 96%), m.p. 152-154°C. R_f (33% EtOAc/hexane) 0.30; IR (KBr) υ: 3059 (arom. CH), 2918 (CH), 1616, 1595, 1543, 1514, 1464, 1284, 1116, 1024, 920, 844, 765, 698 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.47 (2H, d, *J*8.8 Hz), 7.23-7.15 (3H,m), 7.12 (2H,dd, *J* 8.0, 1.5 Hz), 6.95 (2H, d, *J* 8.7 Hz), 6.58 (1H, d, *J* 8.5 Hz), 6.43 (1H, dd, *J* 8.5, 2.5 Hz), 5.97 (1H, d, *J* 2.4 Hz),5.09 (2H, s), 4.74 (2H, s), 3.76 (3H,s), 3.49 (3H,s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.8, 150.0, 148.7, 147.6, 136.4, 132.8, 129.6, 129.0, 128.5, 126.8, 126.7, 122.9, 118.7, 116.6, 110.7, 110.5, 69.6, 55.9, 55.8, 48.6; (TOF-MS ESI$^-$) *m/z*: 484 (100, [M-H]$^+$), 485(30%); HRMS (TOF-MS ESI$^-$): [M-H]$^+$, found 484.1520. $C_{25}H_{21}F_3N_3O_4$ requires 484.1478.

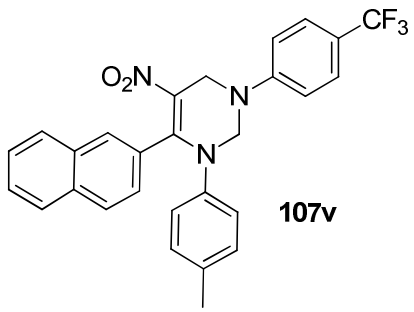
3-(3,4-Dimethoxyphenyl)-6-(naphthalen-2-yl)-5-nitro-1-(p-tolyl)-1,2,3,4-tetrahydropyrimidine (107u)



107u

With MW heating for 45 min and flash chromatography (15-33% EtOAc/hexane) afforded brick-red solid. (700 mg, 45%), m.p. 92-94°C. R_f (33% EtOAc/hexane) 0.20; IR (KBr) υ: 3057 (arom. CH), 2926 (CH), 1560, 1546, 1508, 1458, 1265, 1195, 1026, 815, 750 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.71 (1H,d, *J* 7.9 Hz), 7.65 (2H,d, *J* 8.3 Hz),7.58 (1H,s), 7.46-7.35 (2H,m), 7.22 (1H, dd, *J* 8.5, 1.6 Hz), 6.76 (3H, t, *J* 8.5 Hz), 6.57 (3H, dd, *J* 8.6, 2.6 Hz), 6.51 (1H, d, *J* 2.7 Hz),5.03 (2H, s), 4.71 (2H, s), 3.83 (3H, s), 3.69 (3H,s), 2.06 (3H,s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.9, 149.7, 141.8, 141.1, 136.3, 133.3, 132.8, 129.7,128.9, 128.1, 127.8, 127.0, 126.5, 126.3, 124.3, 123.4, 111.9, 109.9, 103.8, 71.9, 56.1, 55.8, 49.8, 20.8; (TOF-MS ESI$^+$) *m/z*: 480 (100, MH^+-2H), 481 (35%); HRMS (TOF-MS ESI$^+$): MH^+-2H, found 480.1945. $C_{29}H_{25}N_3O_4$ requires 480.1917.

6-(Naphthalen-2-yl)-5-nitro-1-(p-tolyl)-3-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine (107v)

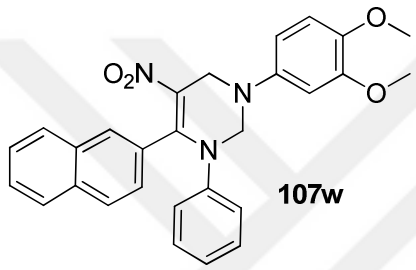


107v

With MW heating for 55 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (140 mg, 87%), m.p. 172-173°C. R_f (33% EtOAc/hexane) 0.60; IR (KBr) υ: 3055 (arom. CH), 2854 (CH), 1616, 1566, 1510, 1458, 1280, 1114,

1070, 815, 750 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.72 (1H,d, *J* 8.0 Hz), 7.69-7.63 (3H,m), 7.46 (3H,d, *J* 9.1 Hz),7.43-7.37 (1H,m), 7.25 (1H, dd, *J* 8.5, 1.5 Hz), 6.90 (2H, d, *J* 8.7 Hz), 6.83 (2H, d, *J* 8.4 Hz), 6.70 (2H, d, *J* 8.3 Hz), 5.12 (2H, s), 4.77 (2H, s), 2.11 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.8, 149.8, 136.6, 133.6, 130.1, 129.4, 128.5, 128.2, 127.8, 127.2, 126.8, 126.3, 126.2, 115.9, 69.0, 48.7, 20.9; (TOF-MS ESI$^+$) *m/z*: 490 (100,MH^+), 491(30%); HRMS (TOF-MS ESI$^+$): MH^+, found 490.1766. $C_{28}H_{23}F_3N_3O_2$ requires 490.1742.

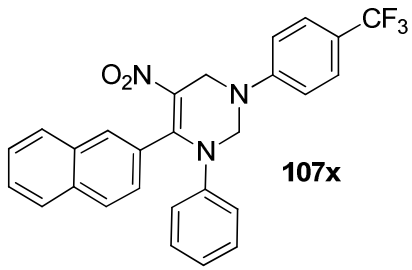
3-(3,4-Dimethoxyphenyl)-6-(naphthalen-2-yl)-5-nitro-1-phenyl-1,2,3,4-tetrahydropyrimidine (107w)



107w

With MW heating for 55 min and flash chromatography (15-20% EtOAc/hexane) afforded brick-red solid. (90 mg, 57%), m.p. 78-80°C. R_f (33% EtOAc/hexane) 0.25; IR (KBr) υ: 3057 (arom. CH), 2926 (CH), 1560, 1508, 1450, 1267, 1136, 1022, 819, 696 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ:7.70 (1H,d, *J* 7.6 Hz), 7.67-7.61 (2H,m), 7.58 (1H,s), 7.46-7.34 (2H, m), 7.24 (1H, dd, *J* 12.5, 10.3 Hz), 6.97 (2H, dd, *J* 13.6, 6.8 Hz), 6.88 (1H, d, *J* 6.4 Hz),6.76 (2H, dd, *J* 8.6,2.3 Hz),6.56 (1H, d, *J* 8.6 Hz),6.48 (1H, s), 5.06 (2H, s), 4.72 (2H, s), 3.82 (3H,s), 3.66 (3H,s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ:155.3, 149.6, 144.8, 143.9, 141.5, 132.6,129.2, 128.8, 128.4, 128.1, 127.8, 127.1, 126.7, 126.4, 126.3, 112.1, 109.7, 103.8, 71.6, 56.2, 55.7, 50.0; (TOF-MS ESI$^+$) *m/z*: 468 (100, MH^+), 469 (30%); HRMS (TOF-MS ESI$^+$): MH^+, found 468.1937. $C_{28}H_{26}N_3O_4$ requires 468.1923.

6-(Naphthalen-2-yl)-5-nitro-1-phenyl-3-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine (107x)



107x

With MW heating for 55 min and flash chromatography (15% EtOAc/hexane) afforded yellow solid. (141 mg, 86%), m.p. 133-134°C. R_f (33% EtOAc/hexane) 0.55; IR (KBr) υ: 3057 (arom. CH), 2854 (CH), 1616, 1560, 1452, 1265, 1114, 1070, 1016, 833, 746, 696 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.72 (1H,d, *J* 8.0 Hz), 7.66 (3H,dd, *J* 8.9, 3.5 Hz), 7.45 (3H,d, *J* 8.5 Hz), 7.43-7.37 (1H, m), 7.26 (1H, dd, *J* 8.1, 1.1 Hz), 7.04 (2H, t, *J* 7.7 Hz), 6.96 (1H, t, *J* 7.4 Hz),6.89 (2H, d, *J* 8.7 Hz),6.81 (2H, d, *J* 7.6 Hz),6.48 (1H, s), 5.15 (2H, s), 4.78 (2H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 155.6, 149.6, 143.6, 129.3, 128.5, 128.3, 127.8, 127.3, 126.8, 126.7, 126.5, 126.4, 126.2, 115.8, 69.0, 48.6; (TOF-MS ESI$^+$) *m/z*: 476 (100, MH^+), 477 (40%); HRMS (TOF-MS ESI$^+$): MH^+, found 476.1604. $C_{27}H_{21}F_3N_3O_2$ requires 476.1585.

3.1.3 ANTIOXIDANT ACTIVITY ASSAY

Antioxidant capacity of tetrahydropyrimidine products (**107a-x**) was determined using modified 2,2-diphenyl-1-picrylhydrazil (DPPH) radical photometric assay (Blois, 1958; Coruh et al., 2007). DPPH radical photometric method is based on spectrophotometrical monitoring the decay of DPPH.

For this purpose, DPPH radical was dissolved in MeOH to supply approx. 1.4 absorbance unit (0.13 mM DPPH solution) at 517 nm. Different concentrations of the products (**107**) and quercetin (antioxidant standard) were prepared in MeOH and mixed with DPPH solution to determine their antioxidant potential. Then, 0.1 mL of each compound **107**, quercetin or control (methanol) was added into 1.4 mL of DPPH solution and obtained samples were incubated in the dark at room temperature. After incubation, absorbance of each solution was measured against

blank (methanol) with Hitachi U-1900, UV-VIS Spectrophotometer 200V. The measurements for each solution was done at least four times. The DPPH• scavenging capacity of each product (**107**) was expressed as mM.

The following equation was used to calculate the capability of the tetrahdropyrimidine (**107**) samples to scavenge the DPPH· radical (Gülçin et al., 2003):

DPPH· Scavenging Effect (%) (% inhibition) = $[(A_0 - A_1/A_0) \times 100]$

A_0: the absorbance of the control reaction; A_1: the absorbance of each sample solution.

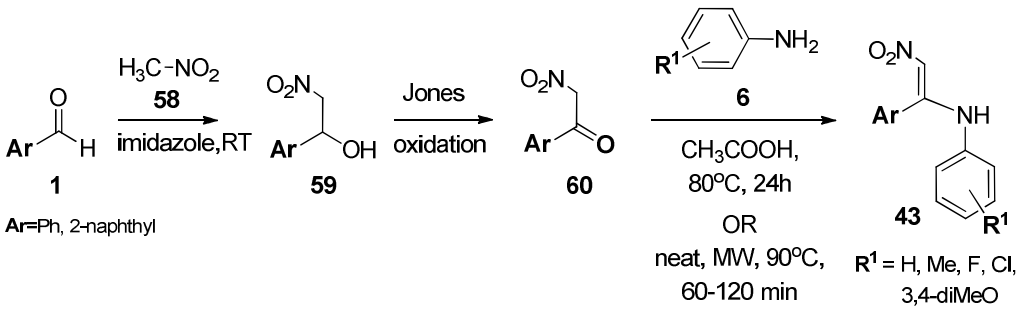
3.1.4 ANTIBACTERIAL ACTIVITY ASSAY

Disc diffusion (Kirby-Bauer) method was applied to evaluate anti-bacterial activity of the compounds (**107**). Only two types of Gram (+) bacteria (*Staphylococcus aureus, Staphylococcus epidermidis*) were used and suspensions of stock microorganisms was transferred to 2 ml of TSB in test tubes, and their absorbance values adjusted according to the standard microorganism. Then, the cultures were inoculated onto Mueller-Hinton agar containing petri dishes. 10 compounds (**107**) were dissolved separately in DMSO (1mg/10µL) and sterilized using 0.22-µm filter. 20µL of each prepared solution were added on the filter paper discs which was then placed on inoculated petri dishes. 2 antibiotic discs (ampicillin and penicillin) were used for positive control. The inoculated petri dishes were kept in incubator at 37°C for 24 hour and then the inhibition zone diameters were measured.

4. RESULTS AND DISCUSSION

4.1 SYNTHESIS AND CHARACTERIZATION OF STARTING MATERIALS

Since β-nitroenamines are important and suitable precursors in organic chemistry (Chakrabarti et al., 2005; Alizadeh et al., 2010; Wen et al., 2013), they are widely used for the synthesis of many fused heterocyclic compounds through different transformations (Michael additions, nucleophilic addition or substitution, and reductions etc.) (Alizadeh et al., 2010; Pilipecz et al., 2008; Yildirim et al., 2014a; Hammouda et al., 2005; Han et al., 2016; Tokumitsu and Hayashi, 1985; Pilipecz et al., 2012). Thus, in the current study, diaryl substituted β-nitroenamines (**43a-f**) as the precursors were prepared over three steps by applying synthetic methods (Scheme 4.1) reported in organic chemistry literature (Harding et al.,1975; Aradi et al., 2017; Lian et al., 2015) and the structures of nitroenamines and their precursors were elucidated by means of IR, NMR and HRMS data or by comparing with relevant data reported in recent literature.



Scheme 4. 1. Preparation of β-nitroenamine precursors (**43a-f**)

First of all, 2-nitro-1-arylethan-1-ols **59** were prepared in excellent yields by the reaction of benzaldehyde or 2-napthaldehyde (**1**) with excess nitromethane **58** using the catalytic amount of imidazole in water. And, isolated 2-nitro-1-arylethan-1-ols **59** were oxidized into 2-nitro-1-arylethanones **60** via Jones oxidation without further purification and obtained in good yields. The structures of 2-nitro-1-

arylethanones (**60**) were mainly determined by regarding the IR data of carbonyl (1693-1697 cm^{-1}), symmetrical and unsymmetrical nitro stretchings (1558, 1334 cm^{-1}) and NMR data of CH_2 proton signals (6.01, 6.55 ppm) as singlets and carbon signal of carbonyl groups (185-188 ppm). Lastly, the main precursors, (*Z*)-*N*-(2-nitro-1-arylvinyl)anilines (**43a-f**) were preraped in moderate to good yields (30-70%) by the reaction of 2-nitro-1-arylethanones **60** with aniline derivatives **6** using excess amount of acetic acid at 80°C for 24 hour or by microwave irradiation at 90°C for 1-2 hour (Table 4.1, entries 1-6). A few reactions to prepare the alkyl substituted nitroenamines (**43g-i**) have been tried but all the reactions failed to give the precursors in either Jones oxidation step or enamine formation step (Table 4.1, entries 7-11).

First of all, the structures of β-nitroenamines **43a-f** were elucidated by NH, C-N and C=C IR stretching vibration peaks at around 3128-3248, 1589-1606 and 1560-1568 cm^{-1}, respectively. Besides, the formation of expected β-nitroenamines **43a-f** were supported by relevant NH proton peaks (11.3-11.6 ppm, br s) and C=CH proton peaks (6.6-6.9 ppm, s) in proton NMR spectra and by quarternary C=C and =CH-NO_2 carbon peaks at 113-114, 155-156 ppm in carbon-13 NMR spectra, respectively. Lastly, the accurate masses of nitroenamines (**43**) were determined and they were in accordance with their expected accurate mass values (see experimental part).

Table 4.1. β-nitroenamine precursors (**43**), reaction conditions and yields

Entry	Nitroenamine	Ar	R^1	Method	Time	Yield (%)
1	**43a**	Ph	Ph	Conv.	22 h	55
2	**43b**	Ph	4-Cl-Ph	Conv.	22 h	48
3	**43c**	Ph	4-F-Ph	MW	1h 15min	70
4	**43d**	Ph	3,4-diMeO	MW	2 h	67
5	**43e**	2-Naphth.	Ph	MW	1 h	30
6	**43f**	2-Naphth.	4-Me-Ph	MW	1h 15min	40
7	**43g**	Cyclohexyl	Ph	Conv.	24 h	-[a]
8	**43h**	Me	Ph	Conv.	24 h	-[a]
9	**43i**	Et	Ph	Conv.	24 h	-[a]
10	**43j**	Ph	i-Pr	MW	2 h	-[a]
11	**43k**	Ph	4-CF_3	MW	2 h	-[a]

[a] No product obtained after the reaction.

Table 4.2. Indicative IR and NMR data for the nitroenamine precursors **43a-f**

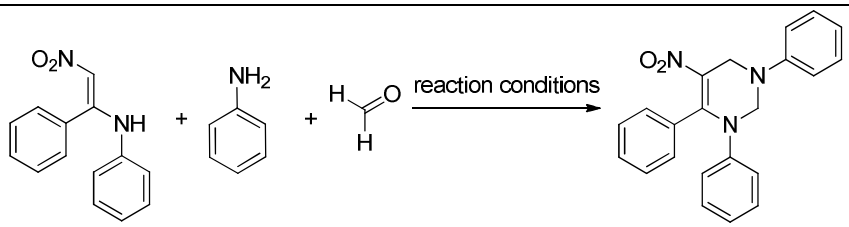
Comp.	**IR** (ν_{max}/cm^{-1})			**^{1}H-NMR** (δ,ppm)		**^{13}C-NMR** (δ,ppm)	
43	NH	C-N	C=C	N**H**	C=C**H**	**C**=C	**=C**HNO$_2$
a	3138	1606	1564	11.35	6.59	155.8	114.2
b	3248	1599	1560	11.38	6.72	155.2	114.7
c	3149	1606	1564	11.42	6.76	155.9	114.2
d	3130	1593	1562	11.53	6.75	155.8	113.6
e	3130	1602	1568	11.58	6.89	155.6	114.5
f	3128	1589	1560	11.59	6.87	155.9	114.1

4.2 SYNTHESIS AND CHARACTERIZATION OF 5-NITRO-6-PHENYL (OR NAPHTHYL)-1,3-DIARYL-1,2,3,4-TETRAHYDRO PYRIMIDINES (107)

As the examples of fused pyrimidine analogues, first thiazolo[3,2-*c*]pyrimidine compounds (**134**) and their cytotoxic properties were recently reported in synthetic and medicinal chemistry literature by our group in 2014, 2015 and 2018 (Yıldırım et al., 2014b; Yıldırım and Çelikel, 2015; Yıldırım et al., 2018). With our ongoing interest on the preparation of new pyridimine-based molecules using enamine chemistry, microwave-assisted three-component Mannich cyclizations of new disubstituted nitroenamines (**43**) with formaldehyde **7** and aniline derivatives **6** were planned to afford new polysubstituted tetrahydopyrimidines in the current study.

First of all, some trial experiments have been designed to determine the best reaction conditions for the synthesis of new tetrahydropyrimidines (**107**). So, we tried the proposed Mannich cyclisation under several conditions using the reaction of (*Z*)-*N*-(2-nitro-1-phenylvinyl)aniline **43a**, formaldehyde **7** and aniline **6a** as the model reaction (Table 4.3). In all trials, two equivalent excess of formaldehyde **7** were used with respect to the enamine **43a** and aniline **6** precursors and the reaction progress or completion were followed by TLC control in each reaction.

Table 4.3. Optimization the reaction conditions for the synthesis of compound 107a



43a **6a** **7** **107a**

Entry	Reaction conditions	Catalyst	Time	Yield (%)[c]
1	Neat, **43a** (1eq), **6a** (1eq), **7** (2.0 eq)[b]	-	18h	24
2	Neat, **43a** (1eq), **6a** (1eq), **7** (3.0 eq)[b]	MW	55min	28
3	EtOH, **43a** (1eq), **6a** (1eq), **7** (2.0 eq)[a]	-	18h	38
4	EtOH, **43a** (1eq), **6a** (1eq), **7** (2.0 eq)[a]	Et_3N	8h	32
5	EtOH, **43a** (1eq), **6a** (1eq), **7** (2.0 eq)[b]	MW	85min	52
6	CH_3CN, **43a** (1eq), **6a** (1eq), **7** (2.0 eq)[a]	-	18h	45
7	CH_3CN, **43a** (1eq), **6a** (1eq), **7** (2.0 eq)[a]	Et_3N	18h	40
8	CH_3CN, **43a** (1eq), **6a** (1eq), **7** (2.0 eq)[b]	MW	**40min**	**78**
9	H_2O, **43a** (1eq), **6a** (1eq), **7** (2.0 eq)[b]	MW	75min	36

[a]Reaction performed at reflux temperature.[b] The reaction carried out at 90°C.[c] Yields after CC.

The trial reactions were not very effective with or without using microwave irradiation in neat conditions (entries 1-2, table 4.3). When a polar protic solvent, ethanol, was used in the reaction with or without triethylamine under reflux, the product yields were obtained low-to-medium (32-38%) (entry 3-4, table 4.3). But, the use of triethylamine only provided shorter reaction times than in the reaction took place under neutral conditions. However, the reaction which was carried out in boiling ethanol under microwave irradiation afforded the expected product in moderate yields in 1 hour and 25 minutes (entry 5, table 4.3). Next, the model cyclization have been carried out in a polar aprotic solvent, CH_3CN, and the expected product (**107a**) were obtained in moderate yields (40-45%) after reflux overnight (entry 6-7, table 4.3). When the model reaction was carried out in CH_3CN without a base under microwave irradiaton the expected product **107a** afforded in good yields (78%) within 40 minutes (entry 8, table 4.3). Regarding the previous studies (Yıldırım et al., 2014a), last trial cyclization reaction was carried out in water, but this caused a significant decrease in product yields (entry 9, table 4.3).

After finding the optimum reaction conditions and solvent, (*Z*)-*N*-(2-nitro-1-arylvinyl)aniline derivatives (**43a-f**) were reacted with different aniline derivatives **6** in the presence of formaldehyde **7** to afford the derivatives of new polyaryl substituted tetrahydropyrimidines (**107**). Thus, a new series of 1,3,6-triaryl substituted-5-nitro-1,2,3,4-tetrahydropyrimidines (**107a-x**) were mostly obtained in moderate to good yields (50-100%) with a few exceptions under optimized reaction conditions using microwave heating (Table 4.4). Then, all the cyclization products (**107a-x**) were purified by flash column chromatography using 15-33% ethyl acetate/hexane mixtures as eluent and isolated in high purity.

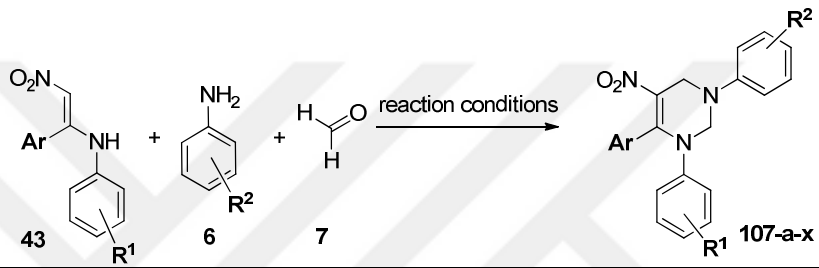
MW-assisted Mannich cyclizations with diphenyl substituted nitroenamine (**43a**) and aniline derivatives afforded the products **107a,d,f,g** in moderate-to-good yields in 40-75 minutes (entries 1,4,6,7, table 4.4) and the products **107b,c,e,h** in low-to-moderate yields in 45-85 minutes (entries 2,3,5,8, table 4.4). Among the series of products from diphenyl substituted nitroenamine (**43a**), the best yield (90%) was obtained in the cyclization reaction with 4-bromoaniline **6f** in 70 minutes (entry 6, table 4.4). Also, Mannich cyclizations with 4-methylaniline **6g**, aniline **6a** and 4-phenoxyaniline **6d** afforded the expected products (**107d,g,a**) in moderate-good yields (55-78%) in similar reaction times (entries 1,4,7, table 4.4). However, the lowest yields (25-33%) with diphenyl substituted nitroenamine (**43a**) were obtained in Mannich cyclizations of 3,4-dimethoxyaniline **6b**, 3-methoxyaniline **6h** and 4-chloroaniline **6c** in 45 minutes, respectively (entries 8,2,3, table 4.4). Besides, the cyclization reactions of *N*-(4-chlorophenyl) substituted nitroenamine (**43b**) with aniline derivatives (Ph, 4-Cl-Ph, 3,4-diMeO-Ph, 4-CF_3-Ph) furnished the cyclization products (**107i-l**) in moderate to good yields (45-71%) for 30-50 minutes (entries 9-12, table 4.4). Regarding the reaction yields of products in this series, the best yields (70-71%) were observed in cyclizations with 3,4-dimethoxyaniline **6b** and 4-trifluoromethylaniline **6i** (entries 11-12, table 4.4). It is clear that the strong EW or ED groups (CF_3 or 3,4-diMeO) in anilines have similar effects on the formation of expected products (**107k,l**) and the reaction yields. Furthermore, *N*-(4-fluorophenyl) substituted nitroenamine (**43c**) with aniline derivatives (Ph, 4-Cl-Ph, 3,4-diMeO-Ph, 4-CF_3-Ph) furnished the cyclization products (**107m-p**) in good yields (60-83%) with one exception (**107o**) (entries 13-16, table 4.4). However, the excellent yields (80-83%) were attained in cyclization reactions of this enamine (**43c**) with aniline **6a** and

4-(trifluoromethyl)aniline **6i** (entries 13,16, table 4.4). The cyclization reaction with 4-chloroaniline **6c** provided the expected product in moderate yields (60%) (entry 14, table 4.4) and the lowest yield (23%) was attained in the reaction of the enamine (**43c**) with 3,4-dimethoxyaniline **6b** (entry 15, table 4.4). This finding showed that the aniline bearing ED groups (3,4-diMeO) was inefficient in the formation of cyclization products under optimized reaction conditions. In addition, all the cyclization reactions in this series of products (**107m-p**) were completed within 45-60 minutes under MW heating. Successful Mannich cyclizations with enamines having weak and strong EW groups (**43b, 43c**) to afford the expected products (**107i-p**) with aniline derivatives **6** motivated us to try the same cyclizations using *N*-(3,4-dimethoxyphenyl) substituted nitroenamine (**43d**) as an electron rich enamine example. The cyclization reactions of this enamine (**43d**) with aniline derivatives **6** using formaldehyde **7** provided the products (**107q-t**) in moderate to excellent yields (42-96%) under optimized conditions within 45-90 minutes (entries 17-20, table 4.4). Best yield (96%) was attained in the cyclisation reaction with 4-(trifluoromethyl)aniline (**6i**) in 45 minutes (entry 20, table 4.4). Also, the products **107s** and **107q** were isolated in good yields (64-82%) by the reaction of nitroenamine (**43d**) with aniline **6a** and 3,4-dimethoxyaniline **6b** in 60-80 minutes, respectively (entries 2-3, table 4.3). But, the reaction with 4-chloroaniline **6c** provided the expected product (**107r**) in moderate yield (42 %). These findings on the cyclization reactions of *N*-(3,4-dimethoxyphenyl) substituted nitroenamine (**43d**) indicated that the aniline bearing strong EW group (-CF_3) was quite effective to afford the product in better yield when compared with aniline bearing weak EW group (-Cl).

Lastly, in order to find out the limitations of the Mannich cyclizations using different nitroenamines in the current study, we modified the phenyl group with 2-naphthyl group and produced two 2-naphthyl substituted enamines with *N*-phenyl or p-tolyl substitutions (**43e-f**) (entries 5,6, table 4.1). In Mannich cyclizations of 2-naphthyl substituted enamines (**43e-f**) using one electron-rich (3,4-dimethoxyaniline **6b**) and one electron-poor aniline (4-(trifluoromethyl)aniline **6i**), the products (**107u-x**) were generally obtained in moderate to good yields in 45-55 minutes under microwave heating (entries 21-24, table 4.4). In detail, cyclization reactions of 2-naphthyl substituted enamines (**43e-f**) with 4-(trifluoromethyl)aniline **6i** yielded the products (**107v, 107x**) in excellent yields in 55 minutes (entries 22,24, table 4.4),

however the cyclization reactions of enamines (**43e-f**) with 3,4-dimethoxyaniline **6b** afforded the expected products (**107u, 107w**) in moderate yields (45-57%) (entries 21,23, table 4.4). The results of the reactions with 2-naphthyl substituted enamines (**43e-f**) stated the electron-poor anilines (**6i**) caused a dramatical increase in reaction yields rather than electron-rich anilines (**6b**). Arguably, the combination of some less nucleophilic anilines (**6a, 6g, 6i**) with all nitroenamines (**43a-f**) tolerated well the formation and stabilization of iminium intermediates to afford the expected cyclization products (**107a,f,i,l,m,p,q,t,v,x**) in good yields.

Table 4.4. Polyaryl-substituted tetrahydropyrimidines **107a-x** and reaction yields



Entry	Product	Ar	R^1	R^2	7 (equiv.)	Time (min) [a]	Yield (%) [b]
1	**107a**	Ph	Ph	Ph	2	40	78
2	**107b**	Ph	Ph	3,4-diMeO-Ph	2	45	32
3	**107c**	Ph	Ph	4-Cl-Ph	2	45	33
4	**107d**	Ph	Ph	4-PhO-Ph	2	75	55
5	**107e**	Ph	Ph	Benzodioxol-Ph	2	85	42
6	**107f**	Ph	Ph	4-Br-Ph	2	70	**90**
7	**107g**	Ph	Ph	4-Me-Ph	2	45	70
8	**107h**	Ph	Ph	3-MeO-Ph	2	55	25
9	**107i**	Ph	4-Cl-Ph	Ph	2	50	50
10	**107j**	Ph	4-Cl-Ph	4-Cl-Ph	2	30	45
11	**107k**	Ph	4-Cl-Ph	3,4-diMeO-Ph	2	30	71
12	**107l**	Ph	4-Cl-Ph	4-CF_3-Ph	2	45	70
13	**107m**	Ph	4-F-Ph	Ph	2	45	**80**
14	**107n**	Ph	4-F-Ph	4-Cl-Ph	2	60	60
15	**107o**	Ph	4-F-Ph	3,4-diMeO-Ph	2	60	23
16	**107p**	Ph	4-F-Ph	4-CF_3-Ph	2	45	**83**
17	**107q**	Ph	3,4-diMeO-Ph	Ph	2	80	**82**
18	**107r**	Ph	3,4-diMeO-Ph	4-Cl-Ph	2	90	42
19	**107s**	Ph	3,4-diMeO-Ph	3,4-diMeO-Ph	2	60	64
20	**107t**	Ph	3,4-diMeO-Ph	4-CF_3-Ph	2	45	**96**
21	**107u**	2-naphthyl	4-Me-Ph	3,4-diMeO-Ph	2	45	45
22	**107v**	2-naphthyl	4-Me-Ph	4-CF_3-Ph	2	55	**87**
23	**107w**	2-naphthyl	Ph	3,4-diMeO-Ph	2	55	57
24	**107x**	2-naphthyl	Ph	4-CF_3-Ph	2	55	**86**

[a] 0.5 mmol of each reactant (**43**, **6**) in 5 mL of CH_3CN at 90°C under MW; [b] Total yields after CC.

The structures of cyclization products (**107a-t, 107u-x**) were fully determined by means of IR, ^{1}H-NMR, ^{13}C-NMR and HRMS measurements. We can give some details on how and which data was evaluated for the characterization of the products. Therefore, as an example data, the structures of products **107a** and **107x** were primarily determined by the disappearance of –NH stretchings and bendings (3130-3138 and 1602-1606 cm^{-1}) of precursors **43a** and **43e** and the changes in intensities of aromatic CH stretchings (3057-3063 cm^{-1}), the appearance of strong C-N stretching peaks (1265-1276 cm^{-1}) in the IR spectra of the products **107a** and **107x** (fig. 4.1).

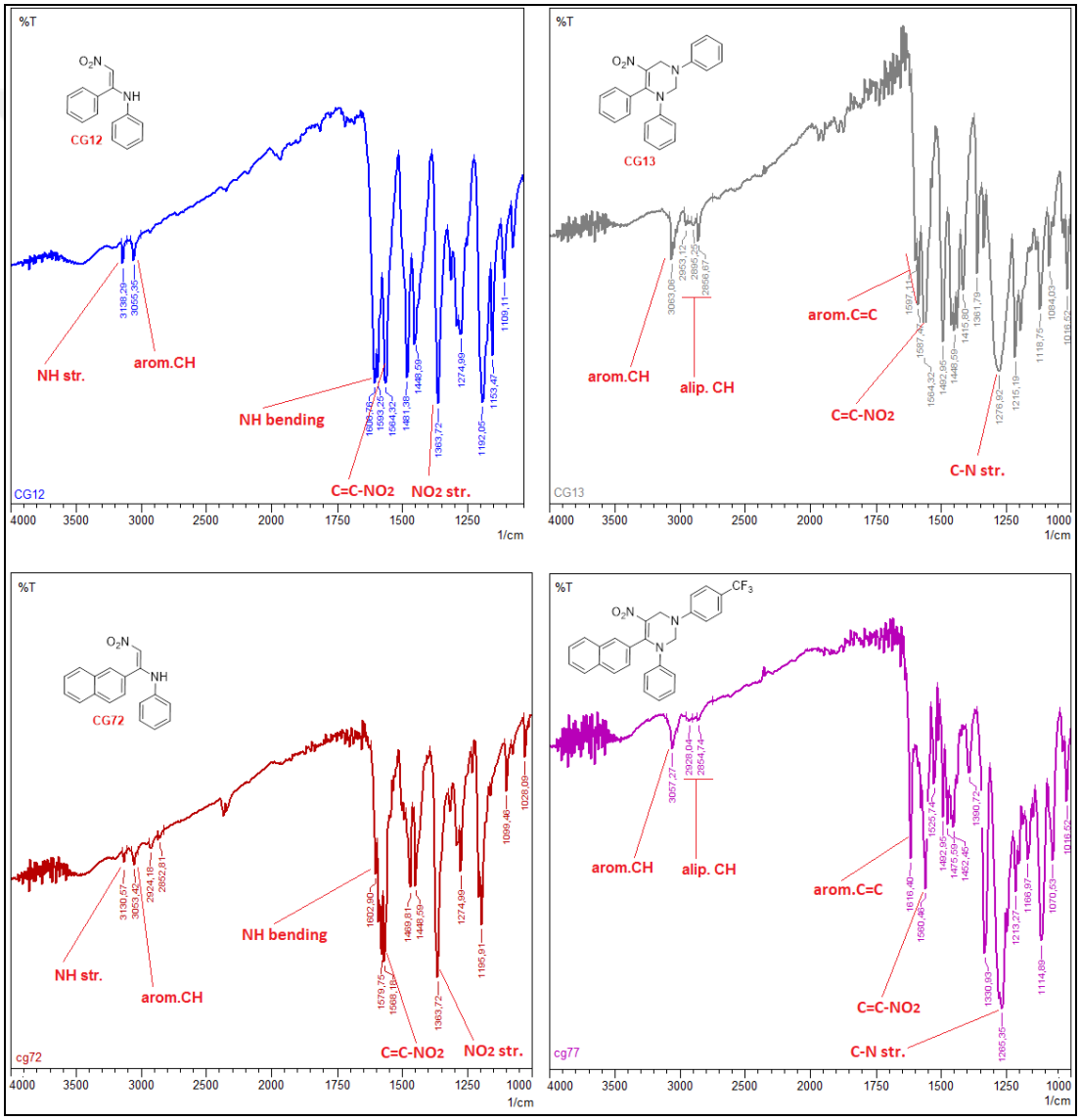


Figure 4.1. IR spectra of the precursors **43a, 43e** and products **107a, 107x**

Besides, in proton NMR spectra of the products of **107a** and **107x**, singlet peaks of methylenic protons at 5.15-5.07 (N-CH_2-N), 4.78-4.72 (N-CH_2-C=) ppm and aromatic CH protons of arylamino groups between 6.63-7.28 ppm also supported the structures expected polyaryl substituted tetrahyropyrimidines (figures 4.2 and 4.3). The CH_2 and quarternary =**C**-NO_2 carbon signals at around 70.6-69.0, 49.1-48.6 and 117.5-124.7 ppms for **107a** and **107x**, and quarternary =**C**-N carbon signals at around 143.6 ppm for **107a** and **107x** provided extra supporting data on the structure of expected products (figures 4.4 and 4.5). Also, ^{17}F-^{13}C coupling constants for trifluoromethylbezene in ^{13}C-NMR of the product **107x** were deteremined as $^{1}J(C\text{-}F)$ = 271 Hz (125.7-123.0 ppm); $^{2}J(C\text{-}F_{ortho})$ = 32.8 Hz (122.8-122.4 ppm); $^{3}J(C\text{-}F_{meta})$ = 3.7 Hz (126.89-126.78 ppm); $^{4}J(C\text{-}F_{para})$ = <1 (115.99 ppm) which were in accordance with the reported literature values (Reichenbacher & Popp, 2012; Schaefer et al., 1983; Ingeborg & Schuster, 1969) (fig. 4.5).

Lastly, the expected structures were also confirmed by HRMS data of the products **107a** (357.1474, M^+) and and **107x** (476.1604, $[M\text{-}H]^+$) accurately by using TOF-MS (ESI or APCI) technique (figures 4.6-4.7).

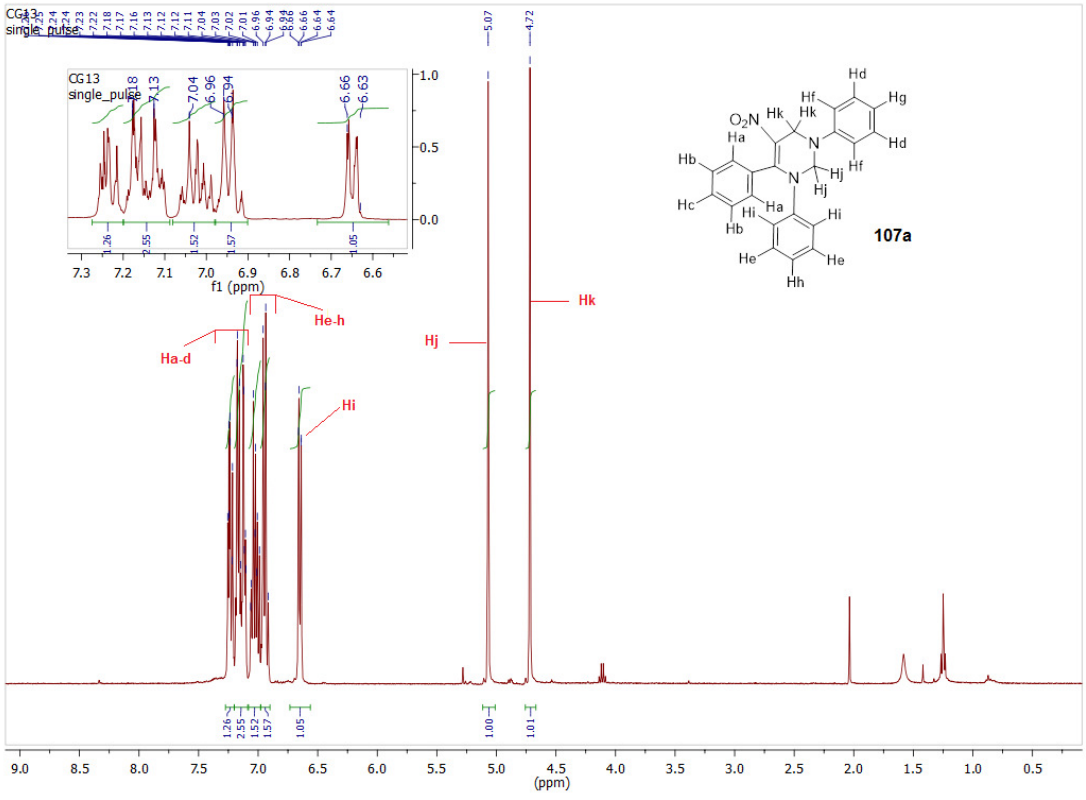


Figure 4.2. ^{1}H-NMR spectrum of the product **107a**

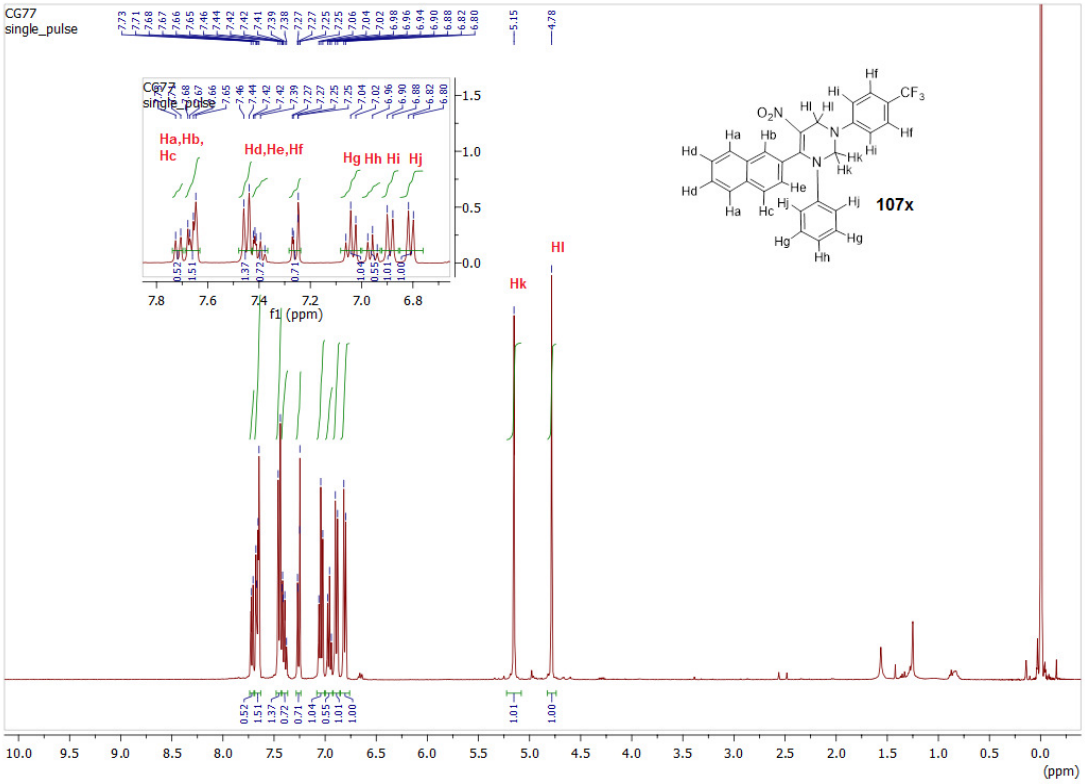


Figure 4.3. [1]H-NMR spectrum of the product **107x**

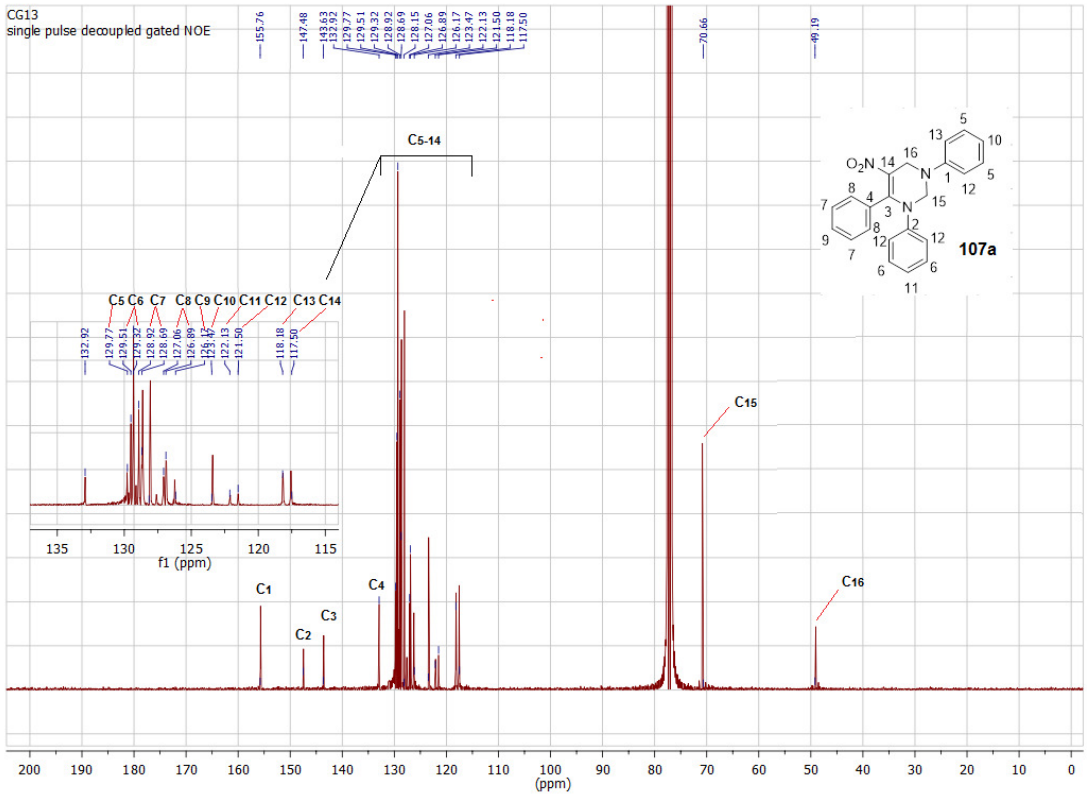


Figure 4.4. [13]C-NMR spectrum of the product **107a**

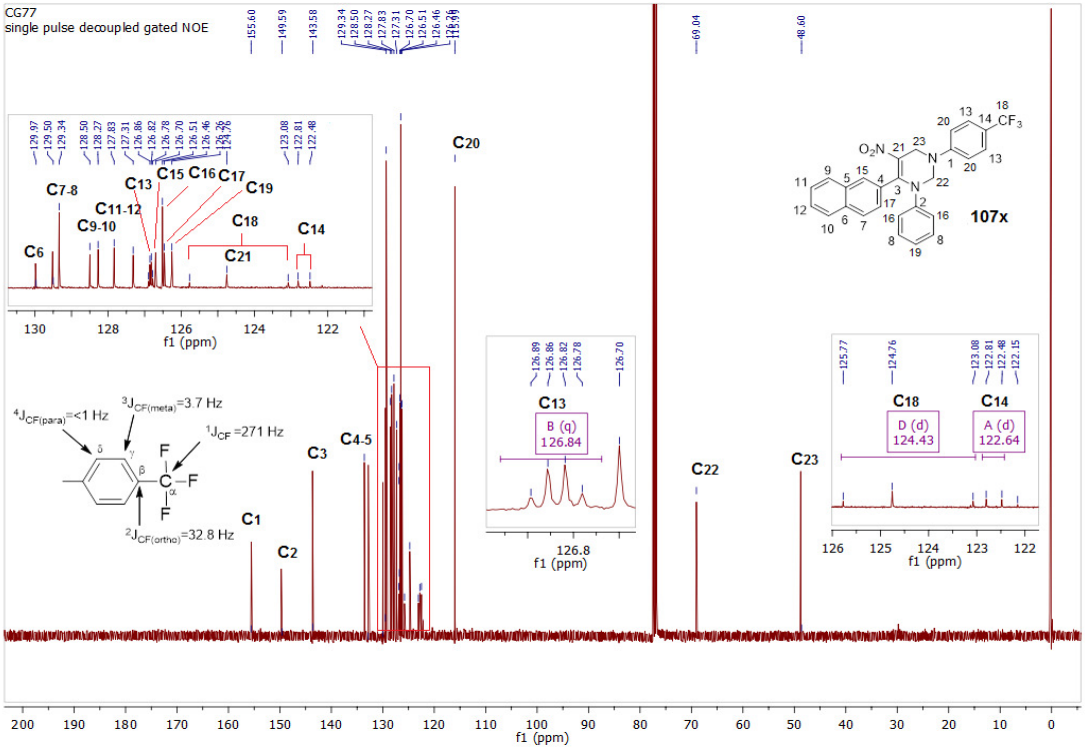


Figure 4.5. ^{13}C-NMR spectrum of the product **107x**

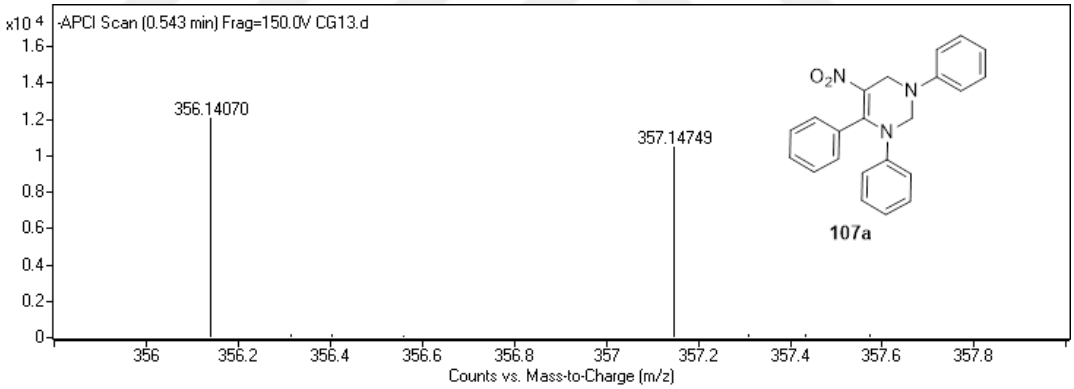


Figure 4.6. HRMS spectrum of the product **107a**

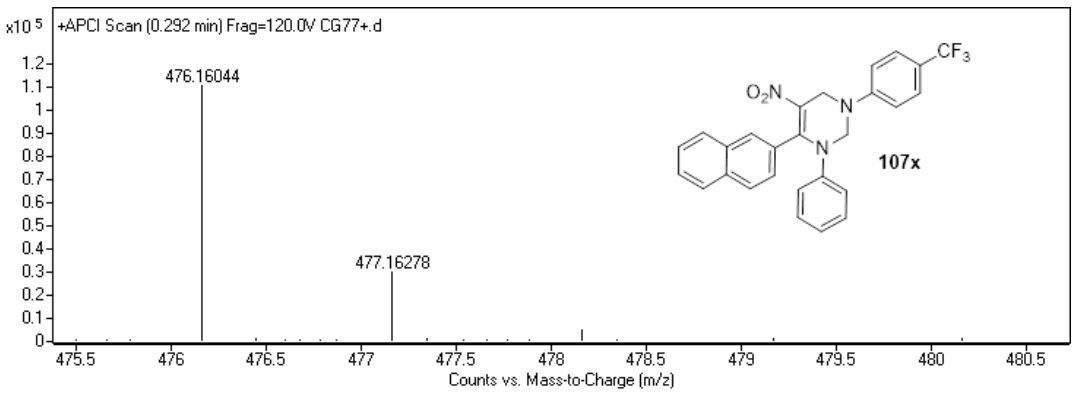


Figure 4.7. HRMS spectrum of the product **107x**

Table 4.5. Indicative IR and NMR data for the compounds **107a-t** and **107u-x**

Comp.	**IR** (ν_{max}/cm^{-1})			**^{1}H-NMR** (δ,ppm)		**^{13}C-NMR** (δ,ppm)		
107	CH (Ar.)	C=C-NO_2	C-N	NC**H_2**N	NC**H_2**C=	**C**H_2x2	=**C**-NO_2	=**C**-N
a	3063	1564	1276	5.07	4.72	70.6, 49.2	117.5	143.6
b	3059	1577	1294	5.02	4.69	71.6, 49.9	112.1	143.5
c	3059	1579	1274	5.04	4.68	70.5, 49.1	118.7	143.4
d	3057	1558	1286	5.03	4.69	71.8, 49.5	117.5	143.7
e	3055	1579	1265	4.95	4.62	72.2, 49.9	111.7	143.4
f	3064	1579	1273	5.03	4.68	70.3, 49.0	114.0	143.4
g	3061	1560	1273	5.03	4.69	71.2, 49.3	117.8	143.5
h	3061	1552	1294	5.05	4.70	70.2, 49.2	110.8	143.6
i	3057	1579	1265	5.03	4.69	71.1, 48.9	117.5	142.3
j	3061	1560	1265	4.99	4.66	70.7, 49.0	118.7	142.2
k	3064	1560	1259	4.97	4.66	na	na	na
l	3066	1560	1276	5.07	4.72	68.9, 48.6	116.0	142.1
m	3061	1566	1280	5.02	4.70	71.2, 48.9	115.8	139.7
n	3057	1566	1276	4.99	4.66	70.9, 48.9	115.9	139.5
o	3068	1560	1278	4.97	4.66	72.2, 49.6	115.8	139.7
p	3086	1572	1282	5.07	4.73	69.3, 48.5	116.1	139.5
q	3093	1579	1247	5.04	4.71	71.5, 48.9	118.3	147.4
r	3091	1595	1273	5.01	4.67	71.3, 49.0	118.9	146.3
s	3080	1581	1282	4.98	4.67	72.3, 49.8	119.0	147.4
t	3059	1595	1284	5.09	4.74	69.6, 48.6	118.7	147.6
u	3057	1560	1265	5.03	4.71	71.9, 49.8	111.9	141.1
v	3055	1566	1280	5.12	4.77	69.0, 48.7	115.9	136.6
w	3057	1560	1267	5.06	4.72	71.6, 50.0	112.1	143.9
x	3057	1560	1265	5.15	4.78	69.0, 48.6	115.8	143.6

na: data is not available for now

Following the same characterization methods and data, all of the tetrahydropyrimidine products **107a-t, 107u-x** were characterized using their indicative IR, ^{1}H-NMR, ^{13}C-NMR and HRMS data as presented in the examples (table 4.5 and table 4.6).

Unexpectedly, accurate mass results of some products (**107l, p, s, u, v**) bearing dimethoxy or trifluoromethyl groups on phenyl ring were found by the lose of two hydrogens from MH^+ ion in ESI^+ mode (table 4.6).

Table 4.6. HRMS (TOF-MS) data for the products **107a-t** and **107u-x**

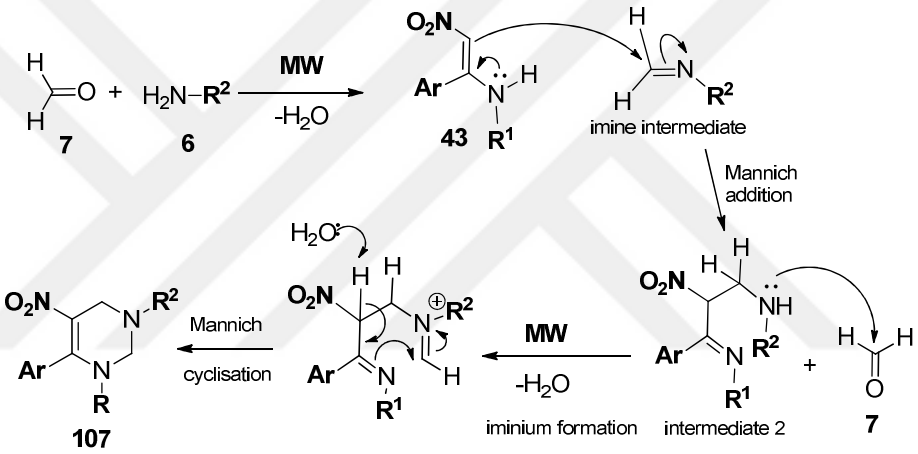
Comp.	HRMS			Comp.	HRMS		
107	**Found (m/z)**	**Calculated (m/z)**	**Ionization tech.**	**107**	**Found (m/z)**	**Calculated (m/z)**	**Ionization tech.**
a	357.1474	357.1477	$APCI^-$	**o**	435.1569	435.1594	$APCI^-$
b	417.1700	417.1688	$APCI^-$	**p***	442.1205	442.1173	ESI^+
c	391.1073	391.1087	$APCI^-$	**q**	416.1636	416.1604	ESI^-
d	449.1730	449.1739	$APCI^-$	**r**	450.1254	450.1215	ESI^-
e	401.1362	401.1375	$APCI^-$	**s***	476.1831	476.1816	ESI^+
f	434.0515	434.0498	ESI^-	**t**	484.1520	484.1478	ESI^-
g	371.1591	371.1633	$APCI^-$	**u***	480.1945	480.1917	ESI^+
h	387.1597	387.1582	$APCI^-$	**v***	490.1766	490.1742	ESI^+
i	391.1124	391.1087	$APCI^-$	**w**	468.1937	468.1923	ESI^+
j	425.0723	425.0697	$APCI^-$	**x**	476.1604	476.1585	ESI^+
k	451.1314	451.1298	$APCI^-$				
l*	458.0902	458.0877	ESI^+				
m	375.1388	375.1383	$APCI^-$				
n	409.0979	409.0993	$APCI^-$				

$APCI^-$: Accurate mass found as M^+ ; ESI^-: Accurate mass found as $[M-H]^+$; ESI^+: Accurate mass found as MH^+; * Accurate mass found as MH^+-2H

As a general comment, Mannich cyclizations with Cl, OMe, diOMe and benzodioxol substituted anilines (**6b,c,e,h)** were not very efficient with all β-nitroenamine precursors (**43a-f**) (table 4.4). However, the cyclizations with Br, Me,

phenoxy, CF_3 substituted anilines (**6d,f,g,i**) and unsubstituted aniline (**6a**) were highly efficient with all β-nitroenamines (tables 4.4). However, vast majority of the cyclization reactions were completed less than one hour using microwave heating under optimized conditions. Indeed, Mannich cyclization reactions with β-nitroenamines (**43a-f**) in the present work were not too efficient when compared with the Mannich cyclizations of heterocyclic secondary enamines (**60** or in our previous works (Yildirim et.al, 2014a; Yıldırım and Çelikel,2015).

A suitable mechanism can be offered over the formation of imine and iminium intermediates to afford the products **107** via Mannich addition-cyclization reactions below (Scheme 4.2).



Scheme 4.2. Mechanism for the formation of polysubstituted nitropyrimidines **(107)**

4.3 ANTIOXIDANT ACTIVITY STUDIES OF NITROTETRA-HYDROPYRIMIDINIES (107)

Natural or synthetic pyrimidine compounds are known to exhibit a wide range of biological effects, especially antioxidant activity which may support the anticarcinogenicity, anti-mutagenicity, and anti-aging activity (Cook & Samman, 1996; Liyana-Pathirana & Shahidi, 2006). Variety of synthetic examples of antioxidant pyrimidine-based molecules and their properties have been reported in recent literature (Lavanya et.al., 2018; El-Mekataby & Fadda, 2018; Akbas et,al., 2018; Vartale et. al., 2017; Koskova & Atanasov, 2017; Satisha et.al., 2016;

Venkatesh et.al., 2016; Salem & Omer, 2016; Pawde et.al, 2015; Kononevich et.al.,2014; Gouda et.al., 2014; Goudgaon & Reddy,2014)

The antioxidant (or antiradical) activities of the tetrahydropyrimidines (**107a-x**) have been determined using DPPH assay which is effective and very common method. During this assay, potentially antioxidant compound was tested to find out how much of DPPH in alcoholic solution would be reduced into non-radical form of DPPH during the reaction. And, the purple-colored DPPH solution with tested antioxidant compound (**107**) was left for 30 minutes in a dark place and its colour turned into yellow. So, the antioxidant potential of tetrahydropyrimidines (**107a-x**) was found by measuring the change in absorbances of the DPPH solution at 517 nm.

Some noteworthy decreases as % inhibition was observed in DPPH concentration due to the scavenging activity of the tetrahydropyrimidines (**107**) (table 4.7). The percent inhibitions in most of the tested compounds showed a concentration-dependent trend except one or two molecules (Fig. 4. 9-4.11). The inhibition percentages of the compounds ranged from 40.6 % to 1.6% at 200 ppm level. The standard quercetin exhibited inhibition percentages of 96.2, 83.5, 53.7% at 200, 100, 50 ppm, respectively. The compounds **107s**, **107u**, **107i** showed highest inhibition percentages as 40.6, 37.1 and 30.5 % s at 200 ppm, respectively. Similarly, the compounds **107s**, **107u**, **107w, 107i** showed highest inhibition percentages as 28.3, 26.4, 24.4 and 21.6 % s at 100 ppm, respectively. However, the lowest % inhibitions (1.6-2.6%) were obtained with the compounds **107t**, **107p**, **107l** at 200 ppm level. Also, at 100 and 50 ppm levels, same compounds exhibited the lowest percentage inhibitions. However, most of the tested compounds (**107**) showed percentage inhibitions below 20% at all inhibition levels. The antioxidant standard, quercetin exhibited inhibition percentages from 53.7% to 96.2% between 50-200 ppm levels, whereas all the test compounds showed lower percentage inhibitions at all concentrations. Overally, two compounds (**107s** and **107u**) showed moderate and three of the compounds (**107i**, **107o** and **107w**) exhibited moderate-low antioxidant activities in comparison to the standard compound. Among all the tested compounds, compound **107s** and **107u** can be considered as promising antioxidant compounds but not very efficiently. According to antioxidant activity results, it is clear that 3,4-

dimethoxyphenyl substituted compounds show better antioxidant properties when compared wih other substitutions on the phenyl ring (Fig.4.8).

Table 4.7. % DPPH inhibitions for the products **107a-t** and **107u-x**

Treatments	% DPPH Inhibition		
	50	**100**	**200**
Quercetin	53.7	83.5	96.2
107a	5.0	5.3	8.2
107b	6.2	9.3	14.7
107c	2.7	4.4	6.7
107d	2.8	8.1	13.6
107e	4.3	8.6	12.6
107f	5.2	4.9	7.3
107g	3.4	5.8	9.1
107h	2.6	4.3	6.7
107i	**16.1**	**21.6**	**30.5**
107j	0.4	1.6	4.4
107k	3.8	9.8	16.9
107l	0.1	0.6	2.6
107m	1.1	4.8	10.5
107n	0.3	3.4	4.9
107o	**11.2**	**17.8**	**26.2**
107p	0.5	1.3	2.0
107q	3.9	6.3	10.7
107r	2.6	3.7	6.0
107s	**16.3**	**28.3**	**40.6**
107t	1.2	1.2	1.6
107u	**17.3**	**26.4**	**37.1**
107v	10.4	12.4	12.5
107w	**20.9**	**24.4**	**27.1**
107x	10.7	11.7	9.3

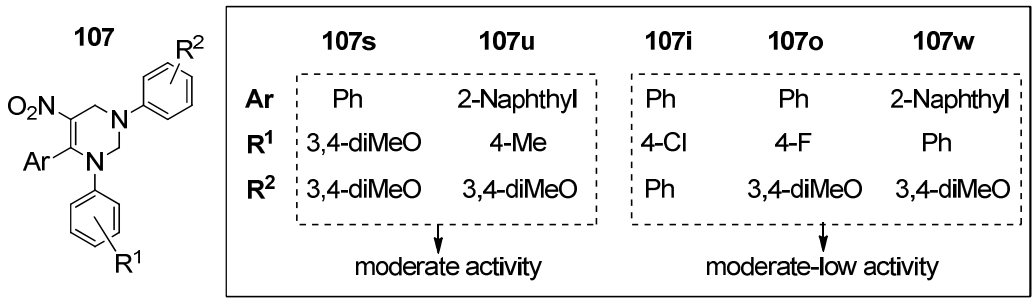


Figure 4.8. Nitrotetrahydropyrimidines exhibiting moderate antioxidant activities

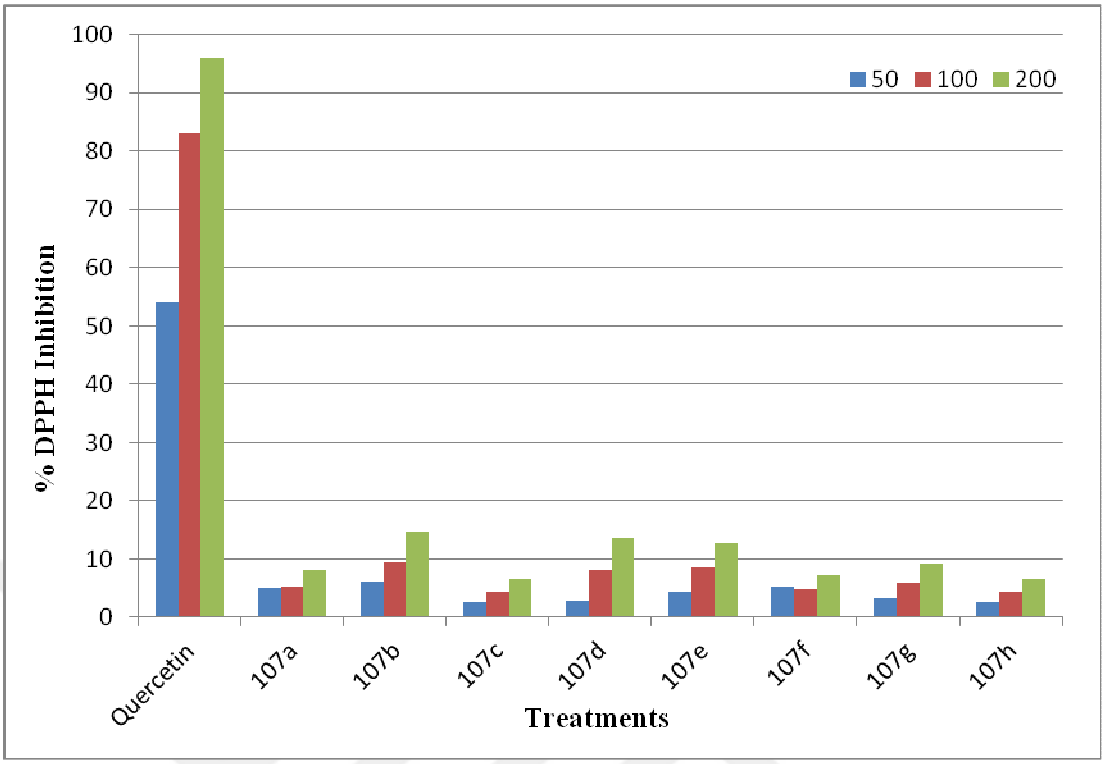


Figure 4.9. % DPPH Inhibitions for the products **107a-h**

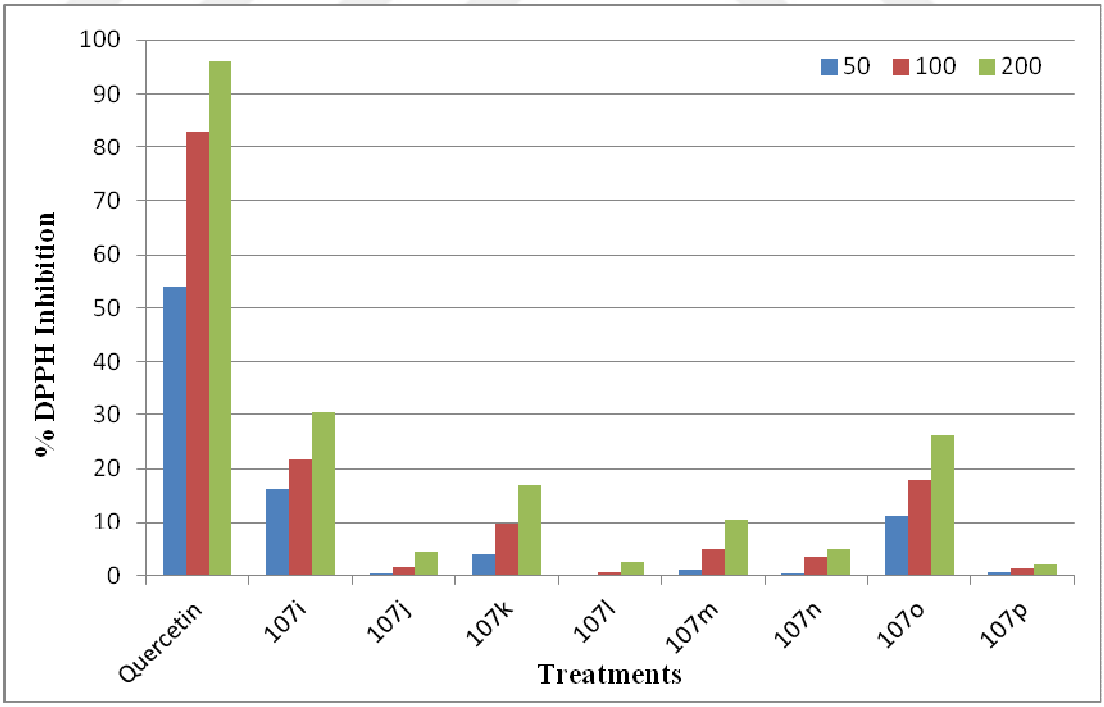


Figure 4.10. % DPPH Inhibitions for the products **107i-p**

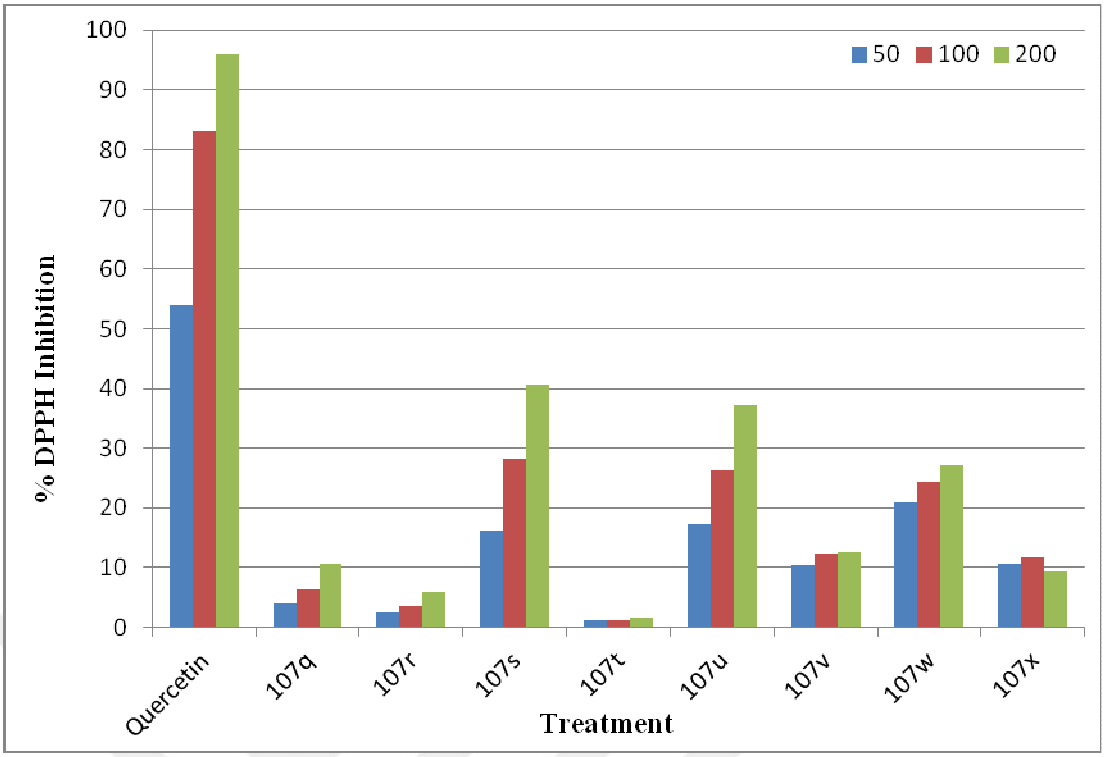


Figure 4.11. % DPPH Inhibitions for the products **107q-x**

4.4 PRELIMINARY ANTIBACTERIAL ACTIVITY STUDIES OF NITROPYRIMIDINES (107)

Pyrimidine compounds are well-established in the literature with the variety of biological activities such as antibacterial, antiviral, anti-inflammatory, anticancer, antioxidant etc. (see introduction). Since the pyrimidines exhibitied wide range of bioactivities, firstly, we were motivated to perform some preliminary antibacterial activity studies of new nitrotetrahydropyrimidines (**107**) in collaboration with in B.A.I.B.U, department of biology. The experimental details and results of antibacterial activity tests were presented and explained below.

Five representative samples of tetrahydropyrimidines (**107b,l,p,t,v)** and 3,4-dimethoxy substituted nitroamine (**43d**) were chosen randomly in order to evaluate their antibacterial potential against two bacterial strains (*S.epidermidis*, *S.aureus*). Their solutions of the six samples were prepared in DMSO according to the described procedure (experimental section 3.1.4). After incubation at 37°C for 24 hour for antibacterial effect, the inhibition zone diameters (mm) of each compound

(**107b,l,p,t,y** and **43d**) against bacteria were measured. According to the results of antibacterial assay, only the compound **107p** exhibited moderate activity against *S.epidermidis* bacterial strain (entry 3, table 4.8) (fig.4.12-14). No other inhibitory zones for tetrahydropyrimidines (**107b,l,t,y**) and nitroenamine **43d** was observed against used bacterial strains (table 4.8). This findings showed that both fluoro and trifluoromethyl substitution on phenyl rings of the product **107p** enhanced the antibacterial effect of tetrahydropyrimidines (**107**). So, a wide range of antibacterial activity study against different pathogenic bacteria will be performed using the untested and tested derivatives of **107.**

Table 4.8. The inhibition effect by **107** derivatives and **43d** against bacteria used and the zones of inhibition

Entry	Compound	SA	SE
1	**107b**	0	0
2	**107l**	0	0
3	**107p**	0	11-10 (m)
4	**107t**	0	0
5	**107v**	0	0
6	**43d**	0	0
Control	Ampicillin	34-33	27-28
	Penicillin G	35-36	23-24

SA: ***S.aureus***; ***SE***: ***S.epidermidis***; ***m: moderate effect.***

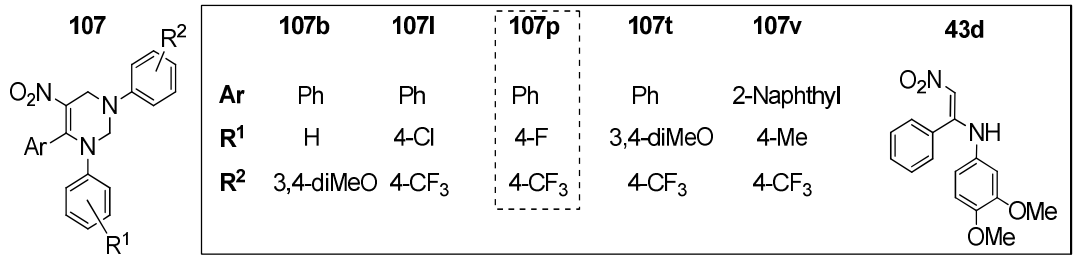


Figure 4.12. Nitrotetrahydropyrimidines and nitroenamine used in antibacterial activity test

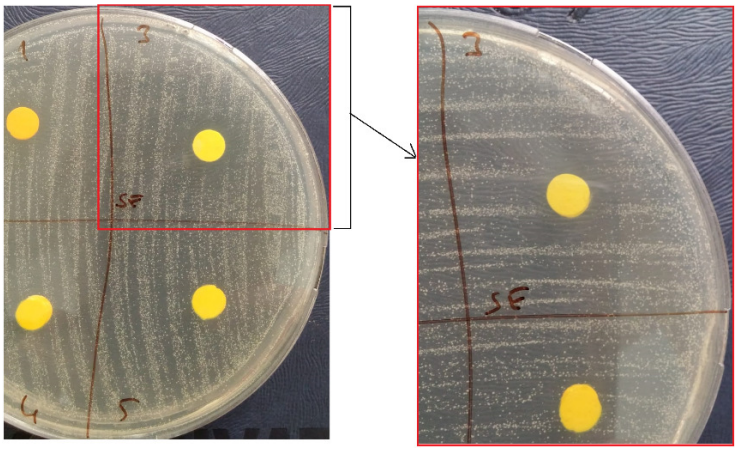


Figure 4.13. Inhibition zones of compound **107p** against SE

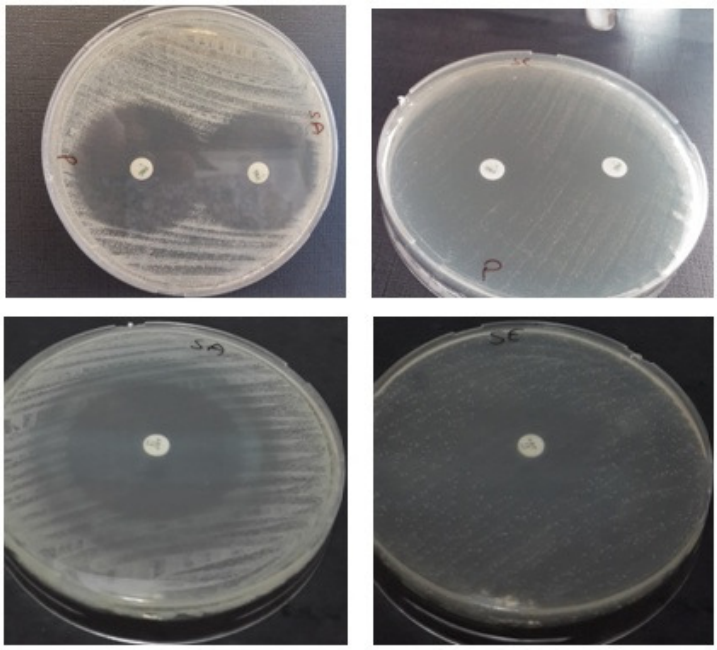


Figure 4.14. Inhibition zones of penicillin and ampicillin against SA and SE

5. CONCLUSIONS

Briefly, the outcomes obtained in the current dissertation study can be given as below.

- ✓ In the first part, as the precursors six aryl substituted β-nitroenamines (**43a-f)** were synthesized applying the literature methods and their structures were characterized by means of IR, NMR, HRMS measurements.

- ✓ In the second and main part of the work, we first optimized the conditions using a model reaction to give new polysubstituted nitropyrimidines (**107**) and described a MW-assisted very efficient protocol for the preparation of 24 novel nitrotetrahydropyrimidines (**107a-x**) bearing aryl groups from various aniline derivatives (**4**) and β-nitroenamines (**43a-f)** in the presence of formaldehyde (**3a**) under microwave heating conditions. The structures of title compounds (**116a-x**) were fully determined by means of IR, NMR (^{1}H,^{13}C) and HRMS measurements. The current synthetic protocol provides an easy and efficient access to nitropyrimidines (**107**) through the double-Mannich cyclisation reactions within 30-40 minutes under MW conditions, hence the applicability of the Mannich cyclizations were extended by the new derivatives of **107** using the enamine chemistry.

- ✓ Since a variety of pyrimidines are known to exhibit interesting biological properties in recent literature, our synthetic protocol would provide a new contribution to the relevant drug molecules containing 1,2,3,4-tetrahydropyrimidine core. Therefore, all nitropyrimidine products (**107a-x**) were screened for their antioxidant activities using DPPH radical scavenging activity assay in the third part of the work. According to the test results, two products (**107s** and **107u**) exhibited moderate percentage inhibitions (37-40%) and three of the products (**107i**, **107o** and **107w**) showed low-moderate inhibitions (26-30%) at 200 ppm concentration among all the tested compounds. Hovewer, the percentage inhibitions of these compounds

(**107s**,**107u**, **107i**, **107o**,**107w**) are low when compared with the percentage inhibition of standard compound, quercetin.

- ✓ Lastly, in the fourth part of the our work, five derivatives of nitropyrimidines (**107b,l,p,t,v**) and a β-nitroenamine **43d** were chosen arbitrarily and screened for their antibacterial activities against two gram positive (+) bacterial strain. As a result, only the product **107p** exhibited moderate antibacterial activity against *S.Epidermidis*, other tested nitropyrimidines (**107**) and nitroenamine **43d** showed no bacterial inhibition against the bacteria.

6. REFERENCES

Akbas E, Ekin S, Ergan E, Karakus Y. (2018). Synthesis, DFT calculations, spectroscopy and in vitro antioxidant activity studies on 4-hydroxyphenyl substituted thiopyrimidine derivatives. Journal of Molecular Structure. 1174:177-183.

Alizadeh A, Rezvanian A, Deng Y. (2010). Novel heterocyclic β-nitroenamines-based on a one-pot three-component reaction: a facile synthesis of fully substituted 1H-pyrrolo[1,2-a]-fused-1,3-diazaheterocycles.Tetrahedron. 66(52): 9933-9937.

Aradi K, Mészáros Á, Tóth, BL, Vincze Z. (2017). Copper-Catalyzed N-Arylation of Nitroenamines with Diaryliodonium Salts. The Journal of Organic Chemistry. 82(22): 11752-11764.

Aruoma OI. (1994). Nutrition and health aspects of free radicals and antioxidants. Food and Chemical Toxicology, 62:671–683.

Atlas RM (1988). Microbiology: Fundamentals and Applications. Macmillan Publishing Company, New York. 632-633.

Attri P, Bhatia R, Gaur J, Arora B, Gupta A, Kumar N, Choi EH (2017) "Triethylammonium acetate ionic liquid assisted one-pot synthesis of dihydropyrimidinones and evaluation of their antioxidant and antibacterial activities", Arabian Journal of Chemistry, 10(2):206-214.

Bagley MC, Lin Z, Pope SJ (2009) "Barium manganate in microwave-assisted oxidation reactions: synthesis of solvatochromic 2,4,6-triaryl pyrimidines", Tetrahedron Letters, 50(49):6818-6822.

Barluenga J, Aznar F, Liz R, Bayod M. (1983) "A Facile and Regioselective Synthesis of 1-Anilino-2-nitro-1-phenylethylenes(2-Nitro-1-phenyl enamines)" Synthesis, 2:159-160.

Barluenga J, Fernández MA, Aznar F, Valdés C (2002) "Novel method for the synthesis of enamines by palladium catalyzed amination of alkenyl bromides", Chemical Communications, 20:2362-2363.

Barluenga J, Tomas M, Fustero S, Gotor V (1979) "Reaction of Diimines with Carbonyl Compounds. Synthesis of Dihydropyrimidines", Synthesis, (5):346-348.

Barry AL, Thornsberry C. (1985). Susceptibility tests: Diffusion test procedures. In: Lennette EH, editor. Manual of Clinical Microbiology. Washington (DC): American Society for Microbiology, 978–987.

Bhat AR (2017) “Biological Activity of Pyrimidine Derivativies: A Review”, Organic & Medicinal Chemistry, 2(2): 555-581.

Biginelli P (1891) “Ueber aldehyduramide des acetessigäthers”, Berichte der Deutschen Chemischen Gesellschaft, 24(1):1317-1319.

Blois MS (1958). Antioxidant determinations by the use of a stable free radical. Nature, 181 (4617): 1199.

Bose AK, Manhas MS, Ghosh M, Shah M, Raju VS, Bari SS, Newaz SN, Banik BK, Chaudhary AG, Barakat KJ (1991) “Microwave-induced organic reaction enhancement chemistry. 2. Simplified techniques”, The Journal of Organic Chemistry, 56(25):6968-6970.

Boyd GV. (1994). Heterocyclic synthesis from enamines. Enamines, 1365-1439.

Brannock KC, Burpitt RD, Davis HE, Pridgen HS, Thweatt JG (1964) “Enamine Chemistry. VIII. Reactions with Miscellaneous Carbonyl and Active Hydrogen Compounds”, The Journal of Organic Chemistry, 29(9):2579-2582.

Brannock KC, Burpitt RD, Goodlett VW, Thweatt JG (1963) “Enamine Chemistry. II. Reactions with Acetylenedicarboxylates” The Journal of Organic Chemistry, 28(6):1464-1468.

Bucherer HT, Lieb, VA (1934) “Über die Bildung substituierter Hydantoine aus Aldehyden und Ketonen. Synthese von Hydantoinen” Journal für Praktische Chemie, 141(1-2): 5-43.

Bujok R, Cmoch P, Wróbel Z, Wojciechowski K (2017) “Transition-metal-free synthesis of 3-(1-pyrrolidinyl) quinolines and 3-(1-pyrrolidinyl) quinoline 1-oxides via a one-pot reaction of 3-(1-pyrrolidinyl) crotonates with nitrobenzenes”, Organic & Biomolecular Chemistry, 15(11):2397-2402.

Caddick S (1995) “Microwave assisted organic reactions”, Tetrahedron, 51 (38):10403-10432.

Carlson R, Nilsson A, Strömqvist M, (1983) “Optimum conditions for enamine synthesis by an improved titanium tetrachloride procedure”, Acta Chemica Scandinavica Series B, 37:7-13.

Chakrabarti S, Panda S, Misra NC, Ila H, Junjappa H. (2005) “Aza-Annulation of Polarized N,S- and N,N-Ketene Acetals with Itaconic Anhydride: Synthesis of Novel Functionalized 1,2,3,4-Tetrahydro-2-pyridones and Related Azabicycles”, Synlett, 9:1437-1441.

Chebanov VA, Saraev VE, Desenko SM, Chernenko VN, Knyazeva IV, Groth U, Glasnov TN, Kappe CO (2008) “Tuning of chemo-and regioselectivities in multicomponent condensations of 5-aminopyrazoles, dimedone, and aldehydes”, The Journal of Organic Chemistry, 73(13):5110-5118.

Chen G, Wang Z, Zhang X, Fan X (2017) “Synthesis of Functionalized Pyridines via Cu (II)-Catalyzed One-Pot Cascade Reactions of Inactivated Saturated Ketones with Electron-Deficient Enamines”, The Journal of Organic Chemistry, 82(20):11230-11237.

Chikhale R, Menghani S, Babu R, Bansode R, Bhargavi G, Karodia N, Rajasekharan MV, Paradkar A, Khedekar P (2015) “Development of selective DprE1 inhibitors: Design, synthesis, crystal structure and antitubercular activity of benzothiazolylpyrimidine-5-carboxamides”, European journal of medicinal chemistry, 96:30-46.

Cook, NC, Samman S. (1996). Flavonoids: chemistry, metabolism, cardioprotective effects and dietary sources. The Journal of Nutritional Biochemistry, 7(2):66-76.

Coruh N, Celep AS, Özgökçe F, İşcan M (2007). Antioxidant capacities of Gundelia tournefortii L. extracts and inhibition on glutathione-S-transferase activity. Food Chemistry, 100(3):1249-1253.

Dallinger D, Kappe CO (2007) “Microwave-assisted synthesis in water as solvent” Chemical Reviews, 107(6):2563-2591.

Darwish ES, Abdelrahman MA, Salaheldin AM (2011) “Enamines in Heterocyclic Synthesis: A Novel Simple and Efficient Route to Condensed Pyridazines”, Zeitschrift für Naturforschung B, 66(6):597-602.

De la Hoz A, Díaz A, Elguero J, Jiménez A, Moreno A, Ruiz A, Sánchez-Migallón A (2007) “Microwave-assisted synthesis of bipyrazolyls and pyrazolyl-substituted pyrimidines”, Tetrahedron, 63(3):748-753.

Desai NC, Makwana AH, Senta RD (2016) “Synthesis, characterization and antimicrobial activity of some novel 4-(4-(arylamino)-6-(piperidin-1-yl)-1, 3, 5-triazine-2-ylamino)-N-(pyrimidin-2-yl) benzenesulfonamides”, Journal of Saudi Chemical Society, 20(6):686-694.

Devi AS, Baruah RR, Laskar MA, Vishwakarma JN. (2011). AChR inhibiting properties of 1, 2, 3, 4-tetrahydropyrimidines: synthesis and in-silico studies. Chemical Sciences Journal.

Dömling A, Ugi I (2000) “Multicomponent reactions with isocyanides”, Angewandte Chemie International Edition, 39(18):3168-3210.

El-Mekabaty A, Fadda AA. (2018). Novel Pyrazolo[1,5-a]pyrimidines and pyrazolo [5,1-c][1,2,4]triazines incorporating indole moiety as a new class of antioxidant agents. Journal of Heterocyclic Chemistry, 55(10):2303-2308.

Erker G, Pfaff R, Kowalski D, Wuerthwein EU, Krueger C, Goddard R (1993) “Formation and structure of stable, isolable conjugated primary enamines”, The Journal of Organic Chemistry, 58(24):6771-6778.

Ferraro A, Bernardi L, Fochi M. (2016). Organocatalytic Enantioselective Transfer Hydrogenation of β-Amino Nitroolefins. Advanced Synthesis & Catalysis, 358(10):1561-1565.

Friary RJ, Gilligan JM, Szajewski RP, Falci KJ, Franck RW (1973) "Heterocyclic synthesis via the intramolecular acylation of enamines derived from amino acids", The Journal of Organic Chemistry, 38(20):3487-3491.

Gedye R, Smith F, Westaway K, Ali H, Baldisera L, Laberge L, Rousell J (1986) "The use of microwave ovens for rapid organic synthesis", Tetrahedron Letters, 27(3):279-282.

Giguere RJ, Bray TL, Duncan SM, Majetich G (1986) "Application of commercial microwave ovens to organic synthesis", Tetrahedron Letters, 27(41):4945-4948.

Gore RP, Rajput AP (2013) "A review on recent progress in multicomponent reactions of pyrimidine synthesis", Drug Invention Today, 5(2):148-152.

Gouda MA, Eldien HF, Girges MM, Berghot MA. (2014). Synthesis and antioxidant evaluation of some new sulphadimidine incorporating thiophene moiety. European Journal of Chemistry, 5(4):595-600.

Goudgaon NM, Reddy RY. (2014). Synthesis, Antimicrobial And Antioxidant Evaluation of 3-(2-(4-fluorobenzylthio)pyrimidin-4-yl-amino)-2-(3-substituted phenyl) thiazolidin-4-Ones. World Journal of Pharmacy and Pharmaceutical Sciences, 3(8):1094-1109.

Granik VG, Makarov VA, Parkanyi C. (1998). "Enamines as Synthons in the Synthesis of Heterocycles". Advances in Heterocyclic Chemistry (72): 283-359.

Grimaux E (1879) "Abstracts from American and Foreign Journals: Synthesis of Uric Derivatives of the Alloxan Series", Journal of the American Chemical Society, 1(7):275-276.

Groebke K, Weber L, Mehlin F (1998) "Synthesis of imidazo[1,2-a] annulated pyridines, pyrazines and pyrimidines by a novel three-component condensation", Synlett, 1998 (06):661-663.

Gülçin İ, Elias R, Gepdiremen A, Boyer L. (2006). "Antioxidant activity of lignans from fringe tree (Chionanthus virginicus L.)". European Food Research and Technology, 223:759–767.

Gülçin I, Oktay M, Kireçci E, Küfrevioğlu IÖ. (2003). "Screening of antioxidant and antimicrobial activities of anise (*Pimpinella anisum* L.) seed extracts". Food Chemistry, 83:371-382.

Guo DL, Zhang XJ, Wang RR, Zhou Y, Li Z, Xu JY, Chen KX, Zheng YT, Liu H (2012) "Structural modifications of 5,6-dihydroxypyrimidines with anti-HIV activity", Bioorganic & Medicinal Chemistry Letters, 22(23):7114-7118.

Häfelinger G, Mack HG (1994). "Enamines: General and theoretical aspects", ISBN: 0-471-93339-2 Wiley Online Library, Tübingen.

Hammouda M, Zeid ZA, Metwally MA. (2005). "New simple and one-pot synthetic routes to polyfunctionally substituted imidazo-[1, 2-a] pyridines, pyrido [1, 2-a]pyrimidines,pyrido-[1,2-a]-1,3-diazepines, and imidazo[1,2-a] pyrimidines". Chemistry of Heterocyclic Compounds, 41(12):1525-1528.

Han L, Feng Y, Luo M, Yuan Z, Shao X, Xu X, Li Z. (2016). "2,2,2-Trifluoroethanol activated one-pot Mannich-like reaction of β-nitroenamines, secondary amines, and aromatic aldehydes". Tetrahedron Letters, 57(25): 2727-2731.

Hantzsch A (1882) "Ueber die synthese pyridinartiger verbindungen aus acetessigäther und aldehydammoniak", Justus Liebigs Annalen der Chemie, 215(1):1-82.

Harding KE, May LM, Dick KF. (1975). "Selective Oxidation of Allylic Alcohols with Chromic Acid", The Journal of Organic Chemistry, 40(11):1664-1665.

Ingeborg I, Schuster M. (1969). "Substituent effects on the $^{13}C,^{19}F$ coupling constants of substituted benzotrifluorides, aryl trifluoromethyl ethers, and aryl trifluoromethyl sulfides", Journal of Magnetic Resonance, 17(1):104-111.

Kappe CO, Stadler A, Dallinger D (2012) "Microwaves in organic and medicinal chemistry", Second Edition, John Wiley & Sons, Weinheim.

Keche AP, Hatnapure GD, Tale RH, Rodge AH, Birajdar SS, Kamble VM (2012) "A novel pyrimidine derivatives with aryl urea, thiourea and sulfonamide moieties: synthesis, anti-inflammatory and antimicrobial evaluation", Bioorganic & Medicinal Chemistry Letters, 22(10):3445-3448.

Khan AT, Lal M, Khan MM. (2010). "Synthesis of highly functionalized piperidines by one-pot multicomponent reaction using tetrabutylammonium tribromide (TBATB)". Tetrahedron Letters, 51(33):4419-4424.

Koga Y, Sakamaki S, Hongu M, Kawanishi E, Sakamoto T, Yamamoto Y, Kimata H, Nakayama K, Kuriyama C, Matsushita Y, Ueta K, Tsukimoto MT, Nomura S (2013) "C-Glucosides with heteroaryl thiophene as novel sodium-dependent glucose cotransporter 2 inhibitors", Bioorganic & Medicinal Chemistry, 21(17):5561-5572.

Kononevich Y, Bobkova L, Smolski A, Demchenko A. (2014). "Synthesis and antioxidant activity of 7-thio derivatives of 6,7-Dihydro-1H-cyclopenta [d]pyrimidine-2,4 (3H, 5H)-dione". Scientia Pharmaceutica, 83(1):41-48.

Kostova I, Atanasov PY. (2017). “Antioxidant properties of pyrimidine and uracil derivatives”. Current Organic Chemistry, 21(20):2096-2108.

Kurihara H, Mishima H (1977) “A convenient synthesis of 2-aminopyridine-3-carbonitriies”, Journal of Heterocyclic Chemistry, 14(6):1077-1079.

Kuwabara J, Sawada Y, Yoshimatsu M. (2018). “Copper-Mediated Reactions of Nitriles with Nitromethanes: Aza-Henry Reactions and Nitrile Hydrations”. Organic Letters, 20(4):1130-1133.

Lacotte P, Buisson DA, Ambroise Y (2013) “Synthesis, evaluation and absolute configuration assignment of novel dihydropyrimidin-2-ones as picomolar sodium iodide symporter inhibitors”, European Journal of Medicinal Chemistry, 62:722-727.

Lagoja IM, (2005) “Pyrimidine as constituent of natural biologically active compounds”, Chemistry & Biodiversity, 2(1):1-50.

Lavanya M, Asharani IV, Thirumalai D. (2018). “One pot multi-component synthesis of functionalized spiropyridine and pyrido[2,3-d]pyrimidine scaffolds and their potent in-vitro anti-inflammatory and anti-oxidant investigations”. Chemical Biology & Drug Design.

Lian Z, Friis SD, Skrydstrup T. (2015). “Palladium-catalysed carbonylative α-arylation of nitromethane”. Chemical Communications. 51(17):3600-3603.

Liu Y, Wu G, Cui Y (2013) “Ag/CNT-catalyzed hydroamination of activated alkynes with aromatic amines”, Applied Organometallic Chemistry, 27(4):206-208.

Liyana-Pathirana CM, Shahidi F. (2006). “Antioxidant properties of commercial soft and hard winter wheats (Triticum aestivum L.) and their milling fractions”, Journal of the Science of Food and Agriculture, 86: 477-485.

Ma LY, Pang LP, Wang B, Zhang M, Hu B, Xue DQ, Shao KP, Zhang BL, Zhang E, Liu HM (2014) “Design and synthesis of novel 1, 2, 3-triazole-pyrimidine hybrids as potential anticancer agents”, European Journal of Medicinal Chemistry, 86:368-380.

Mannich C, Davidsen H (1936) “Über einfache Enamine mit tertiär gebundenem Stickstoff”, Berichte der Deutschen Chemischen Gesellschaft (A and B Series), 69(9):2106-2112.

Mannich C, Krösche W (1912) “Ueber ein kondensationsprodukt aus formaldehyd, ammoniak und antipyrin”, Archiv der Pharmazie, 250(1):647-667.

Moon JK, Shibamoto T. (2009). “Antioxidant assays for plant and food components”. Journal of Agricultural and Food Chemistry, 57(5):1655-1666.

Muravyova EA, Shishkina SV, Musatov VI, Knyazeva IV, Shishkin OV, Desenko SM, Chebanov VA (2009) "Chemoselectivity of multicomponent condensations of barbituric acids, 5-aminopyrazoles, and aldehydes", Synthesis, (08):1375-1385.

Ning Y, Zhao XF, Wu YB, Bi X (2017) "Radical Enamination of Vinyl Azides: Direct Synthesis of N-Unprotected Enamines", Organic Letters, 19(22):6240-6243.

Passerini M (1921) "Isonitriles. II. Compounds with aldehydes or with ketones and monobasic organic acids", Gazzetta Chimica Italiana, 51:181-189.

Pawde AV, Kawale DS, Vartale SP. (2015). "Synthesis and antioxidant, antimicrobial activity of 6-cyano-5-imino-2-methyl-7-(methylthio)-5H-thiazolo[3,2-a] pyrimidines", Der Pharma Chemica, 7:205-209.

Perez MA, Soto JL (1981) "Synthesis of 6-alkoxy-2-amino-5-cyanopyrimidines through sodium alkoxide-induced regiospecific cyclization of 1, 3-dicarbonitriles", Synthesis, 12(12):955-958.

Phukan M, Borah KJ, Borah R (2009) "Henry reaction in environmentally benign methods using imidazole as catalyst", Green Chemistry Letters and Reviews, 2(4):249-253.

Pilipecz MV, Varga TR, Mucsi Z, Scheiber P, Nemes P. (2008). "[3+3] Cyclization reactions of β-nitroenamines and β-enaminonitriles with α, β-unsaturated carboxylic acid chlorides". Tetrahedron, 64(23):5545-5550.

Pilipecz MV, Varga TR, Scheiber P, Mucsi Z, Fàvre-Mourgues A, Boros S, Nemes P. (2012). "Reductive transformations of unsaturated azabicyclic nitrolactams". Tetrahedron, 68(27):5547-5553.

Pinner A (1885) "Ueber die einwirkung von acetessigäther auf die amidine. pyrimidine", Berichte der Deutschen Chemischen Gesellschaft, 18(2):2845-2852.

Prescott LM, Harley JP, Klein DA. (1990). "Microbiology", Wm. C. Brown Publishers, Dubuque, IA, USA.

Radziszewski B (1882) "Ueber die Constitution des Lophins und verwandter Verbindungen", Berichte der Deutschen Chemischen Gesellschaft, 15(2):1493-1496.

Reichenbacher M., Popp J. (2012). "Challenges in Molecular Structure Determination", Science.

Salem MS, Omer Errayes A. (2016). "Synthesis and antioxidant properties of novel pyrimidine-containing heterocycles". Journal of Chemical Research, 40(5).

Sasada T, Kobayashi F, Sakai N, Konakahara T (2009) “An unprecedented approach to 4, 5-disubstituted pyrimidine derivatives by a ZnCl2-catalyzed three-component coupling reaction”, Organic Letters, 11(10):2161-2164.

Sathisha KR, Gopal S, Rangappa KS. (2016). “Biological activities of synthetic pyrimidine derivatives”. World Journal of Pharmaceutical Research, 5(2): 1467-1491.

Schaefer T, Marat K, Peeling J, Veregin RP. (1983). “Signs and mechanisms of 13C, 19F spin–spin coupling constants in benzotrifluoride and its derivatives”. Canadian Journal of Chemistry, 61(12):2779-2784.

Seko S, Komoto I. (1998). “A new synthesis of β-nitroenamines by amination of nitroolefins with methoxyamines”. Journal of the Chemical Society, Perkin Transactions 1, (18):2975-2976.

Shaikh, A. (2018). “Application of microwaves in sustainable organic synthesis”. In Green Chemistry, 647-671), Elsevier.

Shakya N, Vedi S, Liang C, Agrawal B, Tyrrell DL, Kumar R (2012) “A new class of pyrimidine nucleosides: inhibitors of hepatitis B and C viruses”, Bioorganic & Medicinal Chemistry Letters, 22(20):6475-6480.

Sharma V, Chitranshi N, Agarwal AK. (2014). “Significance and biological importance of pyrimidine in the microbial world”. International Journal of Medicinal Chemistry.

Shawali A, Edrees M (2006) “Reactions of nitrilimines with heterocyclic amines and enamines. Convenient methodology for synthesis and annulation of heterocycles”, Arkivoc, 9:292-365.

Singh K, Kaur H, Chibale K, Balzarini J (2013) “Synthesis of 4-aminoquinoline–pyrimidine hybrids as potent antimalarials and their mode of action studies”, European Journal of Medicinal Chemistry, 66:314-323.

Sokolov NA, Tishchenko IG, Raichonok TP, Buglakova LT. (1985). “Synthesis of 5-nitrotetrahydropyrimidines”, Vestsi Akademii Navuk BSSR, Seryya Khimichnykh Navuk, (2):70-4.

Stork G, Brizzolara A, Landesman H, Szmuszkovicz J, Terrell R (1963) “The enamine alkylation and acylation of carbonyl compounds”, Journal of the American Chemical Society, 85(2):207-222.

Strecker A (1850) “Ueber die künstliche Bildung der Milchsäure und einen neuen, dem Glycocoll homologen Körper”, Justus Liebigs Annalen der Chemie, 75(1):27-45.

Suryawanshi SN, Kumar S, Shivahare R, Pandey S, Tiwari A, Gupta S (2013) "Design, synthesis and biological evaluation of aryl pyrimidine derivatives as potential leishmanicidal agents", Bioorganic & Medicinal Chemistry Letters, 23(18): 5235-5238.

Tokumitsu T, Hayashi T. (1985). "Reaction of beta.-nitroenamines with electrophilic reagents. Synthesis of beta-substituted beta-nitroenamines and 2-imino-5-nitro-4-thiazolines". The Journal of Organic Chemistry, 50(9): 1547-1550.

Ugi I, Dömling A, Hörl W (1994) "Multicomponent reactions in organic chemistry", Endeavour, 18(3):115-122.

Ugi I, Werner B, Dömling A (2003) "The chemistry of isocyanides, their multicomponent reactions and their libraries", Molecules, 8(1):53-66.

Varma RS, Dahiya R (1998) "An expeditious and solvent-free synthesis of 2-amino-substituted isoflav-3-enes using microwave irradiation", The Journal of Organic Chemistry, 63(22):8038-8041.

Vartale SP, Sontakke SG, Ubale PN. (2017). "Synthesis of N-substituted pyrazolopyrimidopyrimidines and their antioxidant evaluation", Heterocyclic Letters, 7(4):1073-1077.

Venkatesh T, Bodke DY, Joy MN, Vinoda MB, Shiralgi Y, Dhananjaya LB. (2016). "Synthesis of some novel 5,7-disubstituted-2-phenyl-5H-[1,3,4]thiadiazolo[3,2-a] pyrimidine derivatives and evaluation of their biological cctivity". Letters in Organic Chemistry, 13(9):661-671.

Wen LR, Sun QC, Zhang HL, Li M. (2013). "A new rapid multicomponent domino heteroannulation of heterocyclic ketene aminals: solvent-free regioselective synthesis of functionalized benzo [g] imidazo [1, 2-a] quinolinediones". Organic & Biomolecular Chemistry, 11(5):781-786.

West JA (1963) "The chemistry of enamines", Journal of Chemical Education, 40(4):194-200.

Willis MC, Brace GN (2002) "Palladium catalysed enamine synthesis from vinyl triflates", Tetrahedron Letters, 43(50):9085-9088.

Xia S, Yin S, Tao S, Shi Y, Rong L, Wei X, Zong Z (2012) "An efficient and facile synthesis of novel substituted pyrimidine derivatives: 4-amino-5-carbonitrile-2-nitroaminopyrimidine", Research on Chemical Intermediates, 38(9):2435-2442.

Yıldırım AB, Mutlu E, Yıldırım M. (2018). "Cytotoxic effects of novel thiazolo[3,2-c]pyrimidines against MCF-7 and HEPG2/C3A carcinoma cell lines". Hacettepe Journal of Biology and Chemistry, 46(2): 237-246.

Yıldırım M, Celikel D, Dürüst Y, Knight DW, Kariuki BM. (2014b). "A rapid and efficient protocol for the synthesis of novel nitrothiazolo[3,2-c]pyrimidines via microwave-mediated Mannich cyclisation", Tetrahedron, 70(12):2122-2128.

Yıldırım M, Celikel D, Evis N, Knight DW, Kariuki BM. (2014a). "Base-promoted new C–C bond formation: an expedient route for the preparation of thiazolo- and imidazolo-pyridinones via Michael addition", Tetrahedron, 70(35):5674-5681.

Yıldırım M, Çelikel D. (2015). "A rapid access to novel and diverse 3-oxothiazolo[3,2-c]pyrimidine-8-carboxylates using multicomponent Mannich cyclisation reactions". Molecular Diversity, 19(1):1-13.

Yu W, Du Y, Zhao K (2009) "PIDA-mediated oxidative C−C bond formation: novel synthesis of indoles from N-aryl Enamines", Organic Letters, 11(11):2417-2420.

Zhang XY, Yang ZW, Chen Z, Wang J, Yang DL, Shen Z, Hu LL, Xie JW, Zhang J, Cui HL. (2016). "Tandem Copper-Catalyzed Propargylation/Alkyne Azacyclization/Isomerization Reaction under Microwave Irradiation: Synthesis of Fully Substituted Pyrroles". The Journal of Organic Chemistry, 81(5):1778-1785.

Zhuang Q, Han H, Wang S, Tu S, Rong L (2009) "Efficient and Facile Three-Component Reaction for the Synthesis of 2-Amine-4, 6-diarylpyrimidine Under Solvent-Free Conditions", Synthetic Communications, 39(3):516-522.

APPENDICES

7. APPENDICES

IR, NMR and HRMS Spectra for the precursors and products

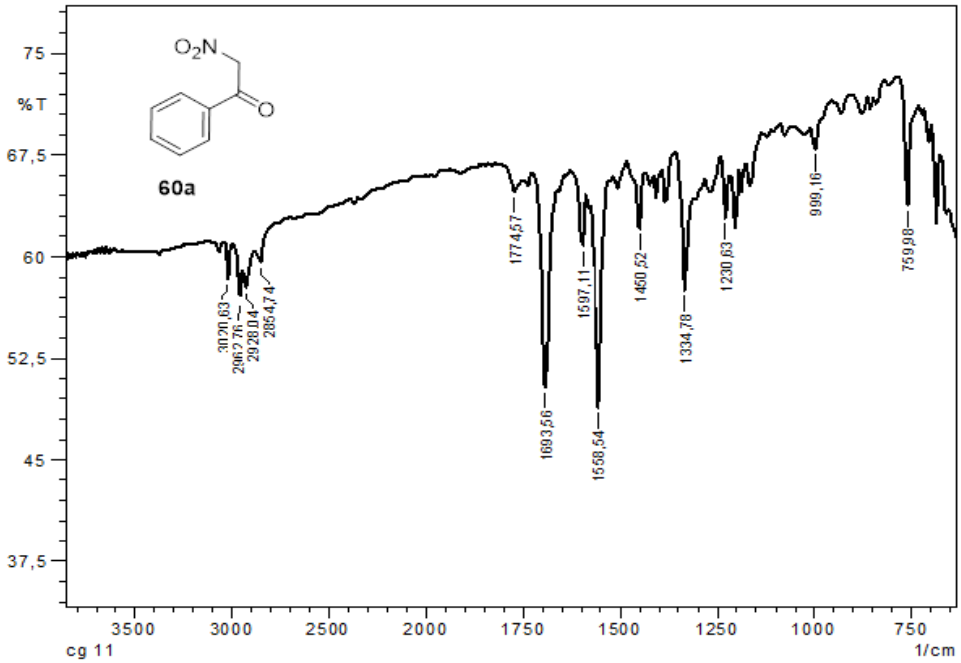


Figure 7.1. IR Spectrum of compound **60a**

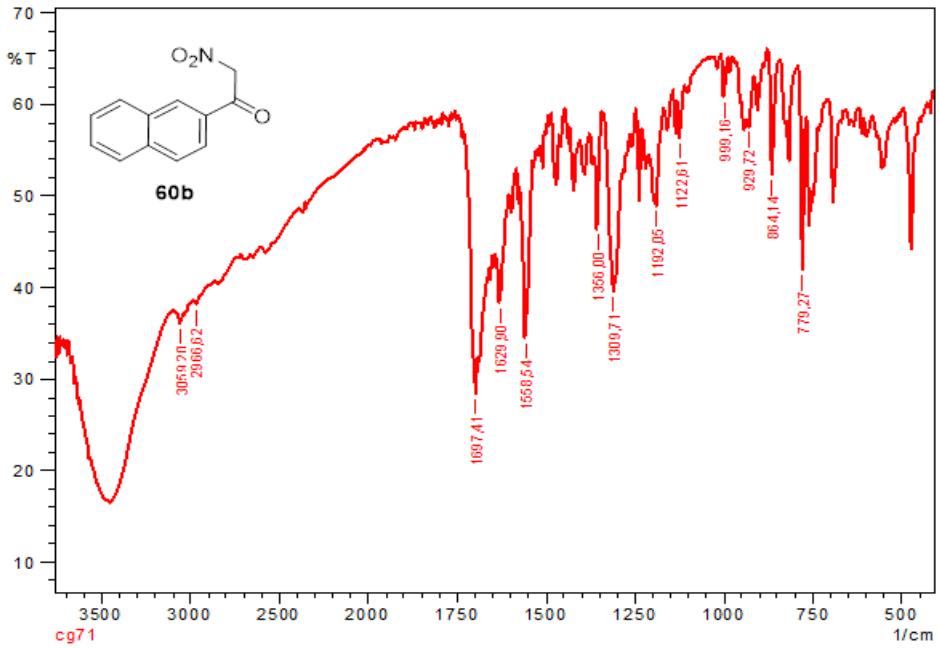


Figure 7.2. IR Spectrum of compound **60b**

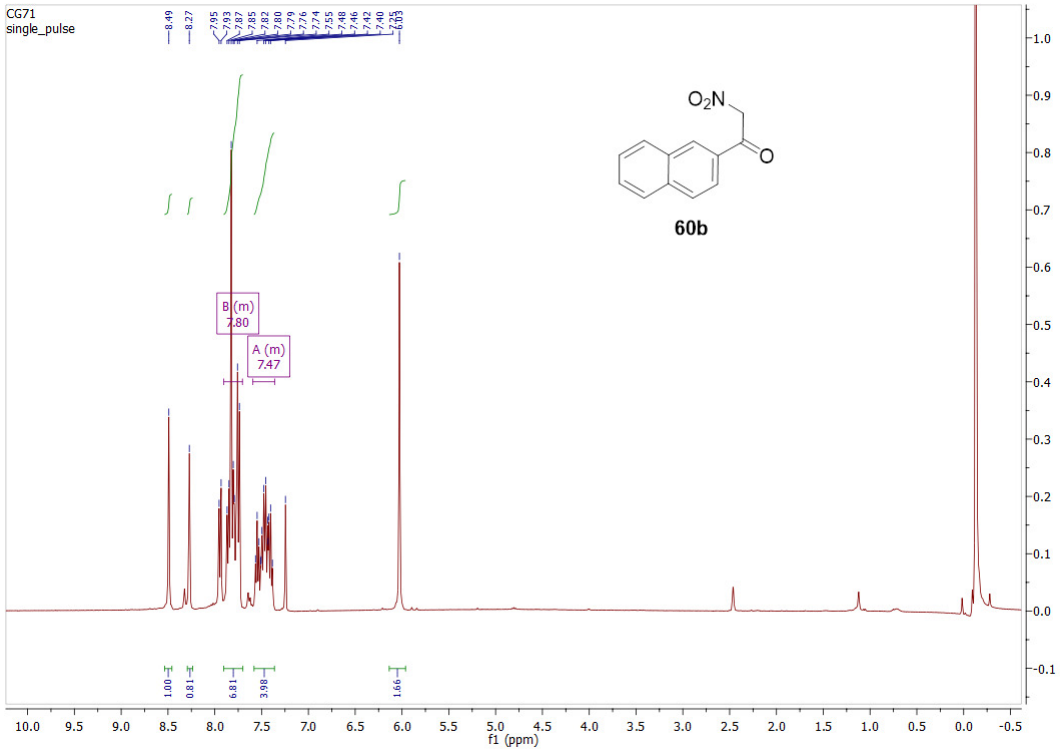


Figure 7.3. ^{1}H-NMR Spectrum of compound **60b**

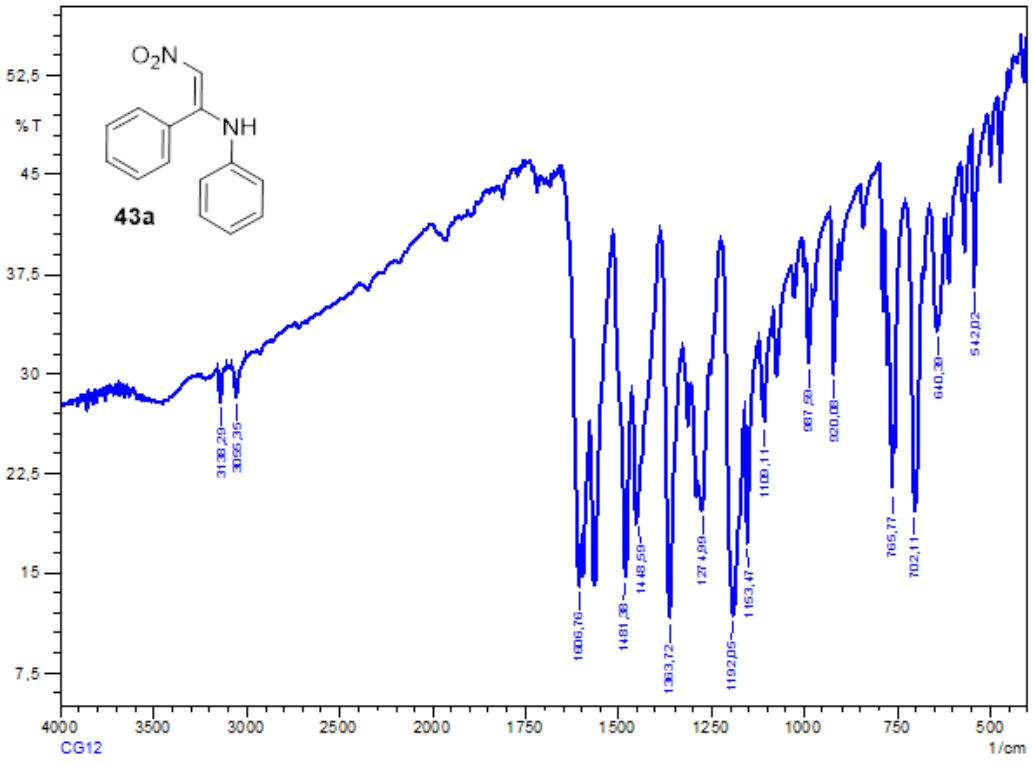


Figure 7.4. IR Spectrum of compound **43a**

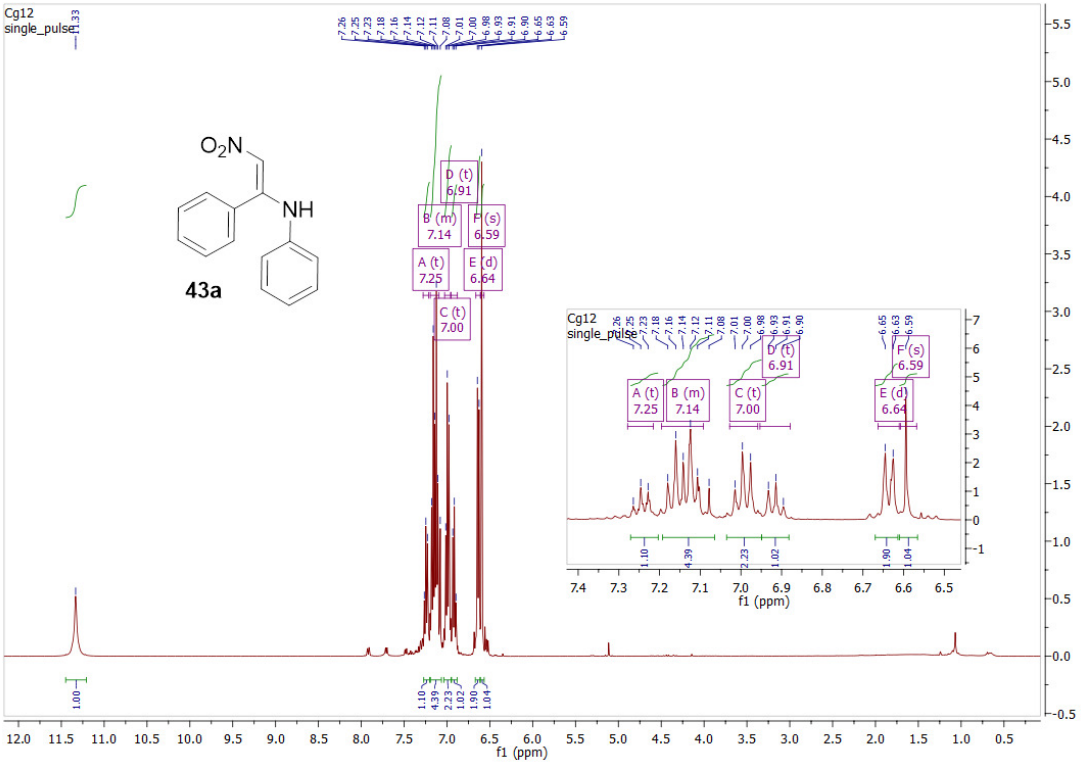


Figure 7.5. ^{1}H-NMR Spectrum of compound **43a**

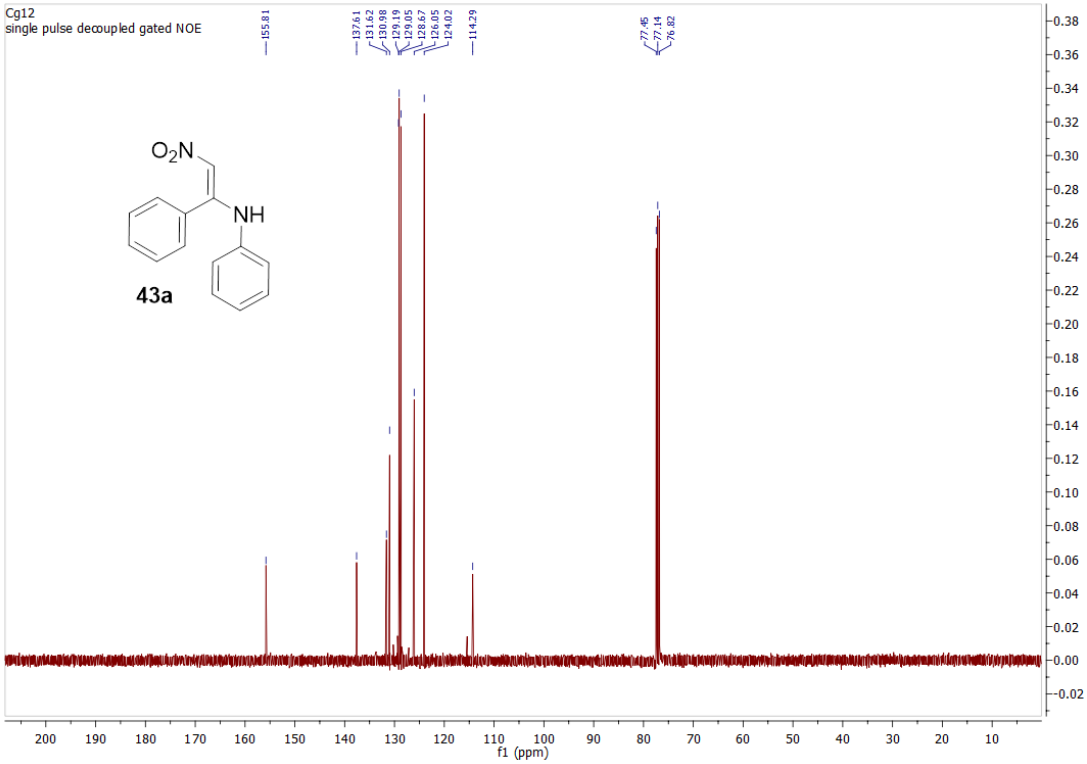


Figure 7.6. ^{13}C-NMR Spectrum of compound **43a**

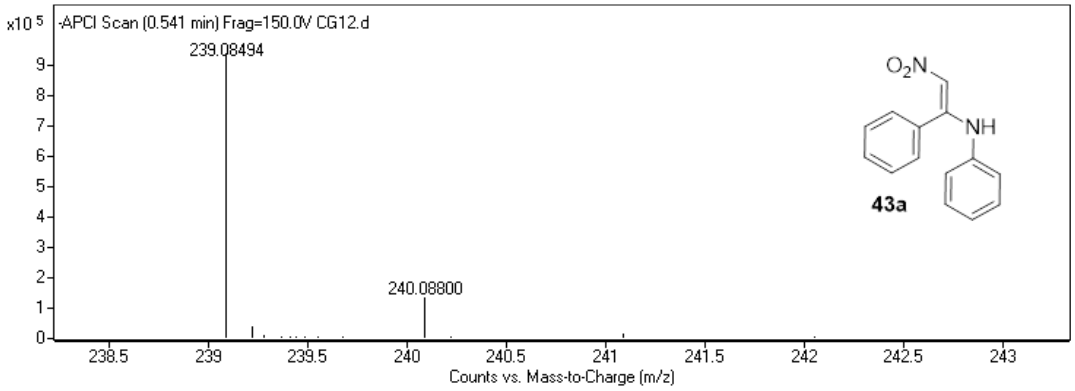


Figure 7.7. HRMS Spectrum of compound **43a**

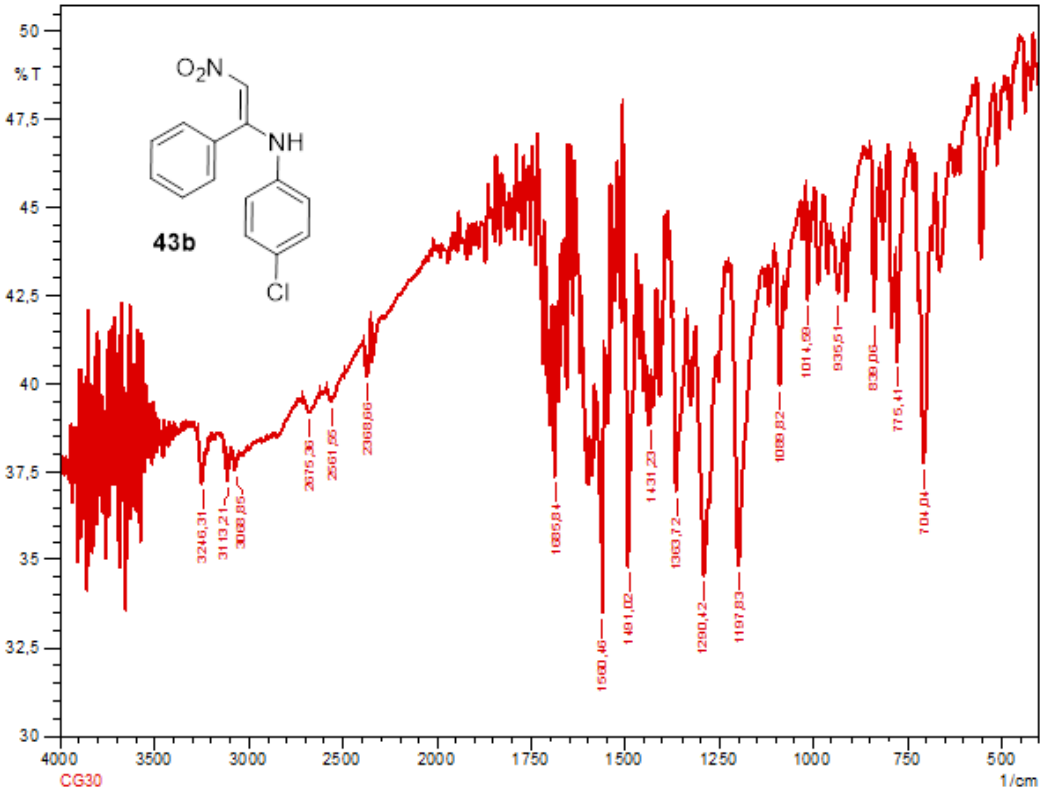


Figure 7.8. IR Spectrum of compound **43b**

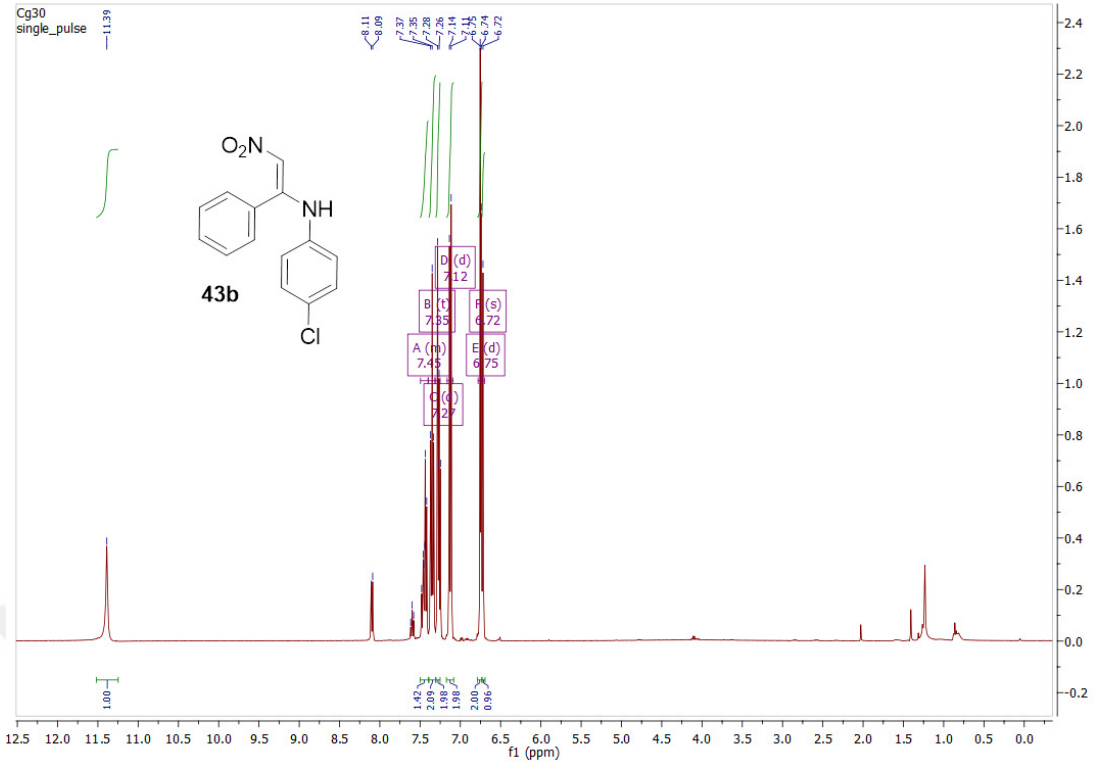


Figure 7.9. [1]H-NMR Spectrum of compound **43b**

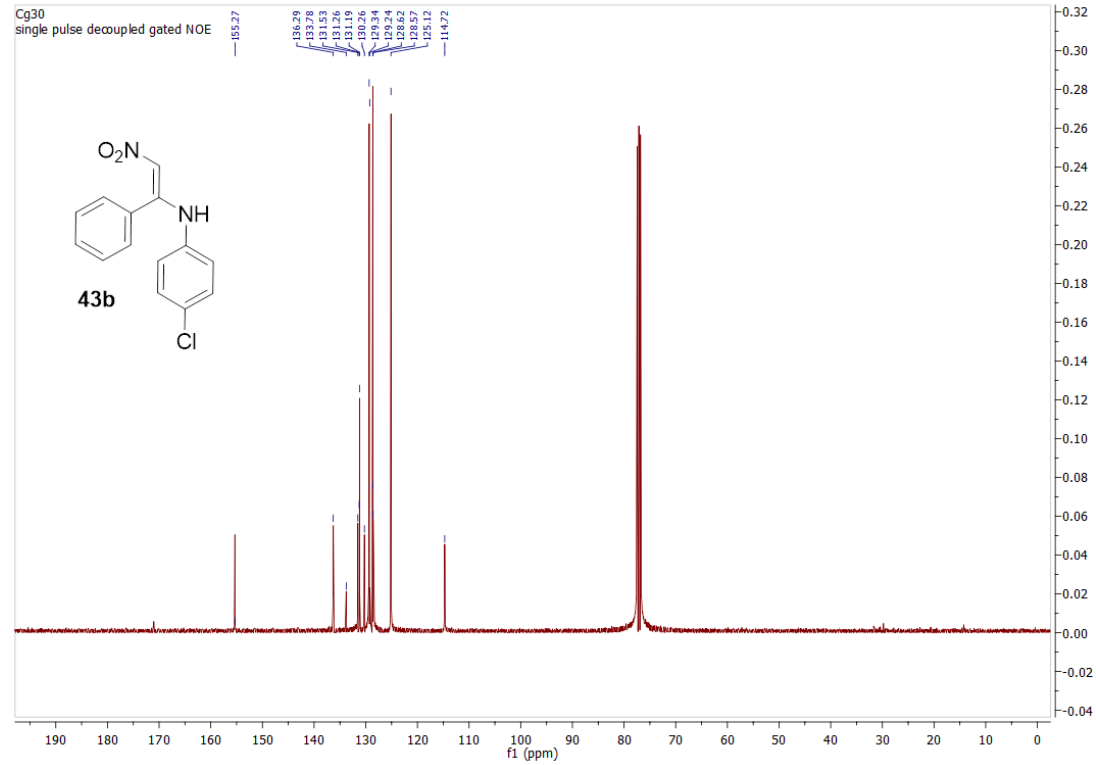


Figure 7.10. [13]C-NMR Spectrum of compound **43b**

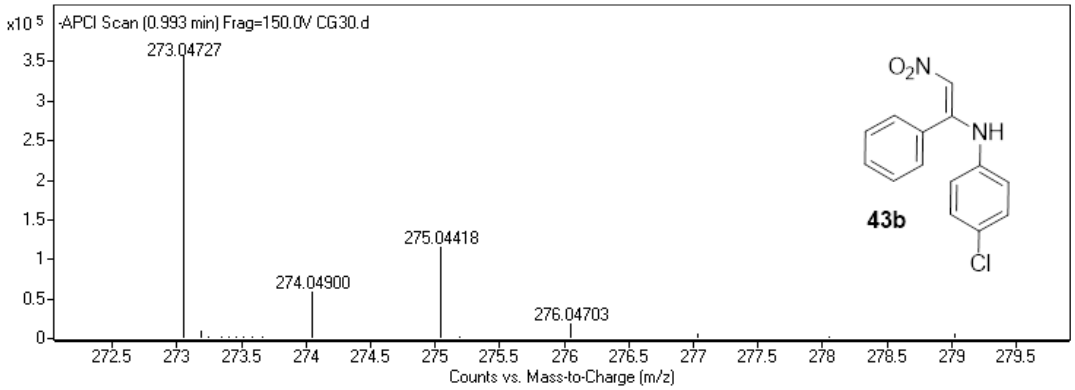


Figure 7.11. HRMS Spectrum of compound **43b**

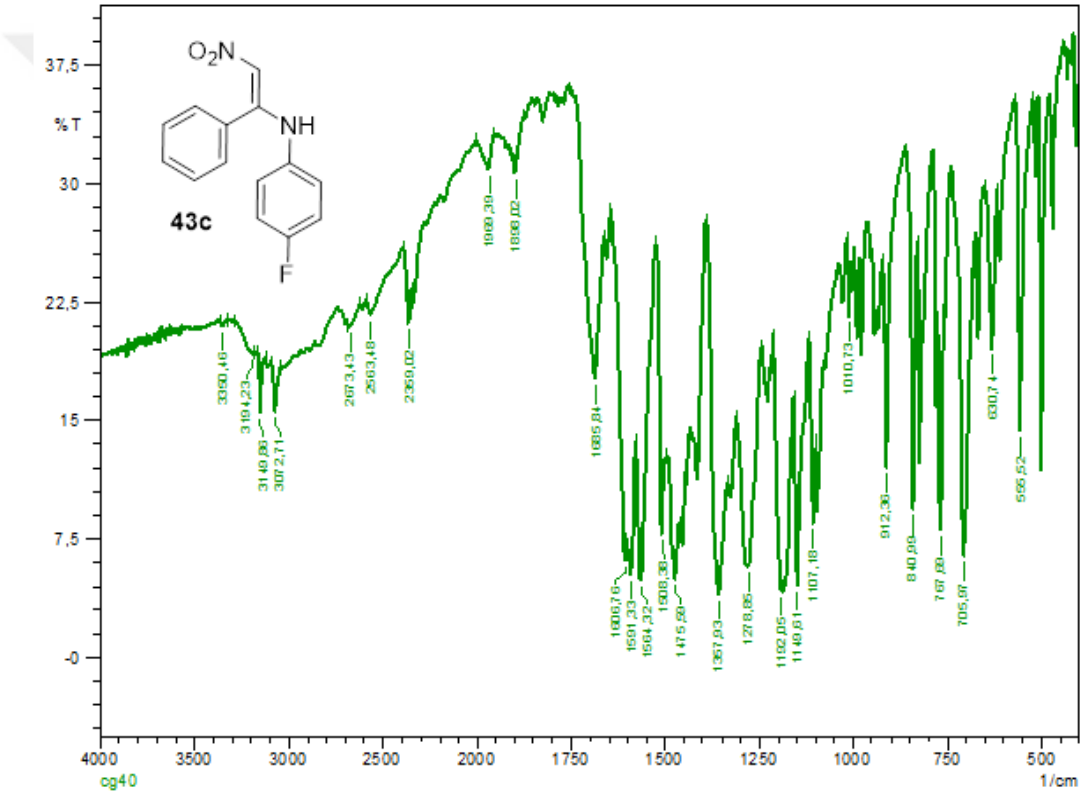


Figure 7.12. IR Spectrum of compound **43c**

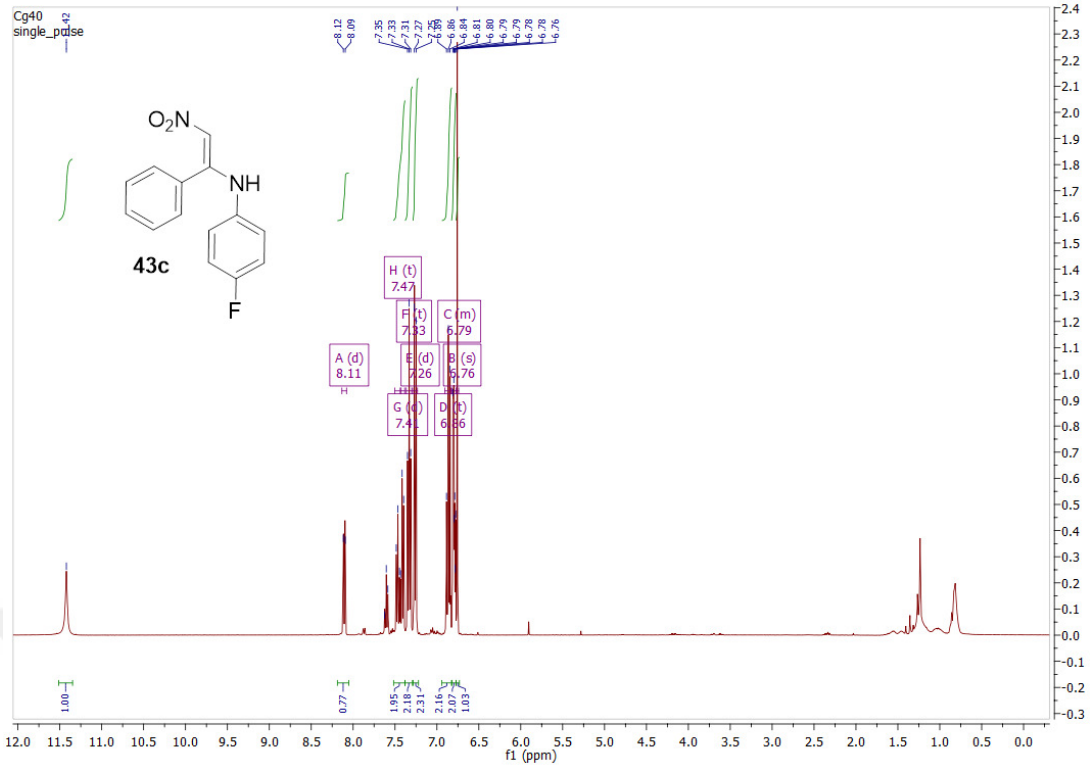


Figure 7.13. ^{1}H-NMR Spectrum of compound **43c**

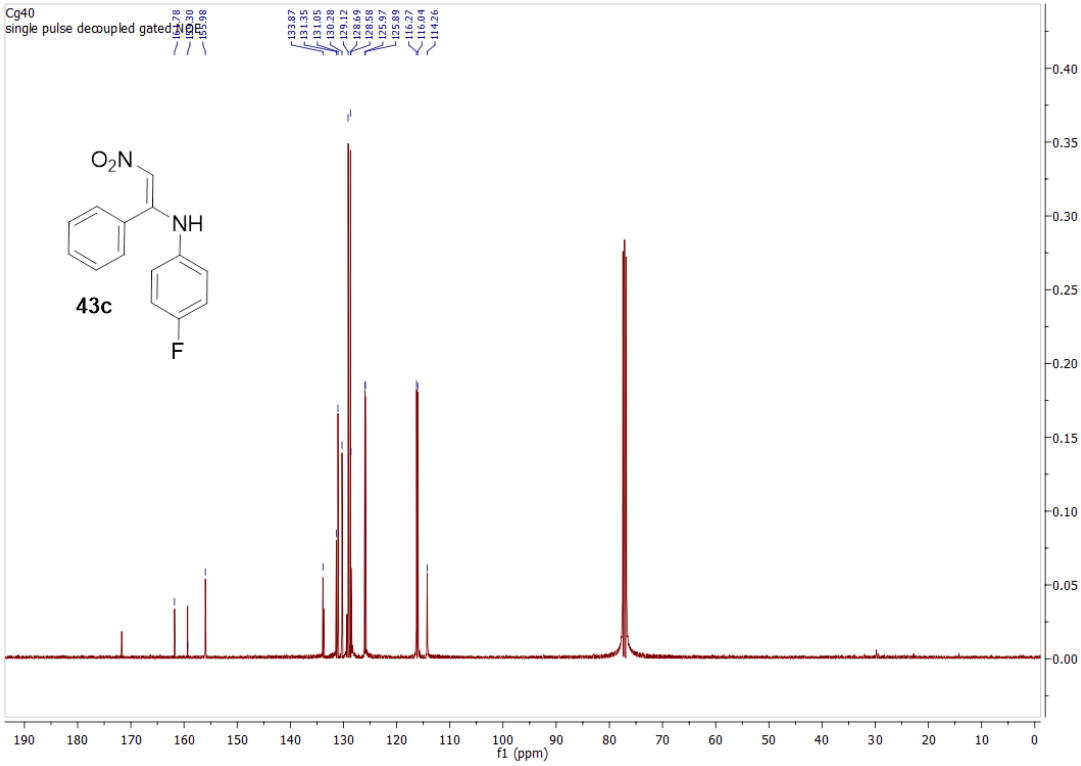


Figure 7.14. ^{13}C-NMR Spectrum of compound **43c**

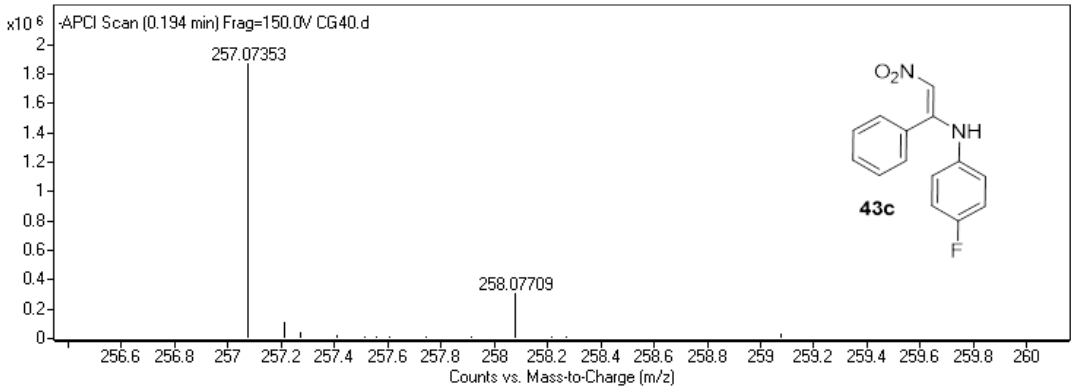


Figure 7.15. HRMS Spectrum of compound **43c**

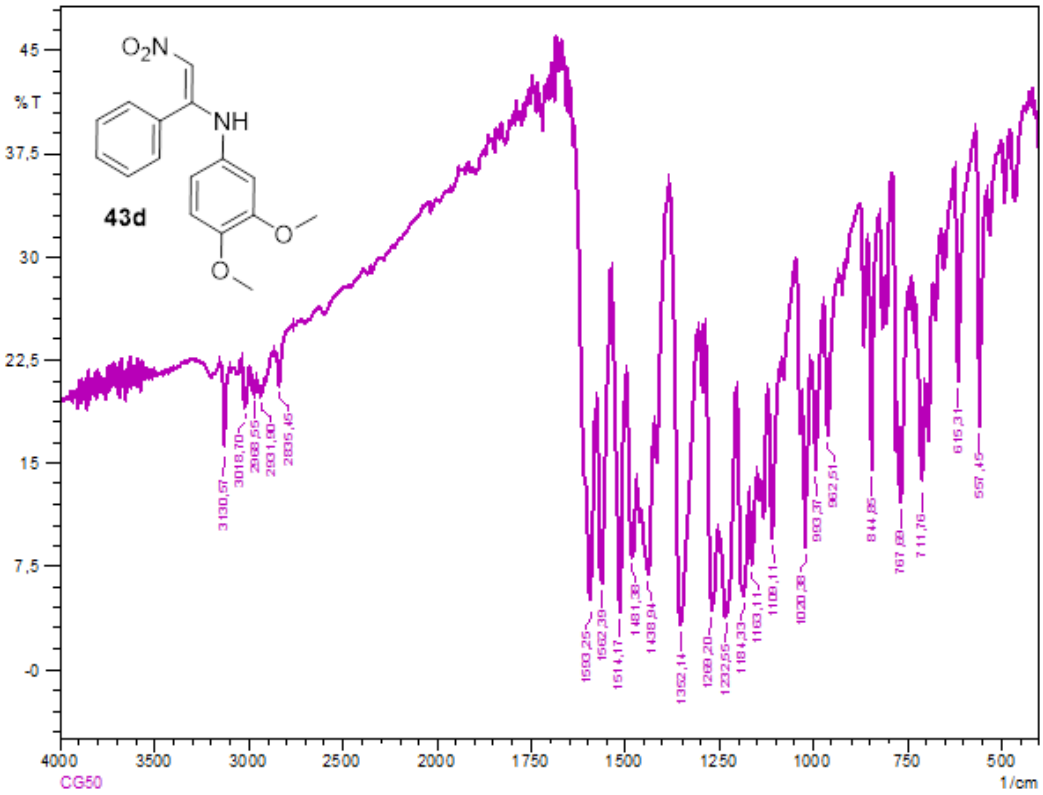


Figure 7.16. IR Spectrum of compound **43d**

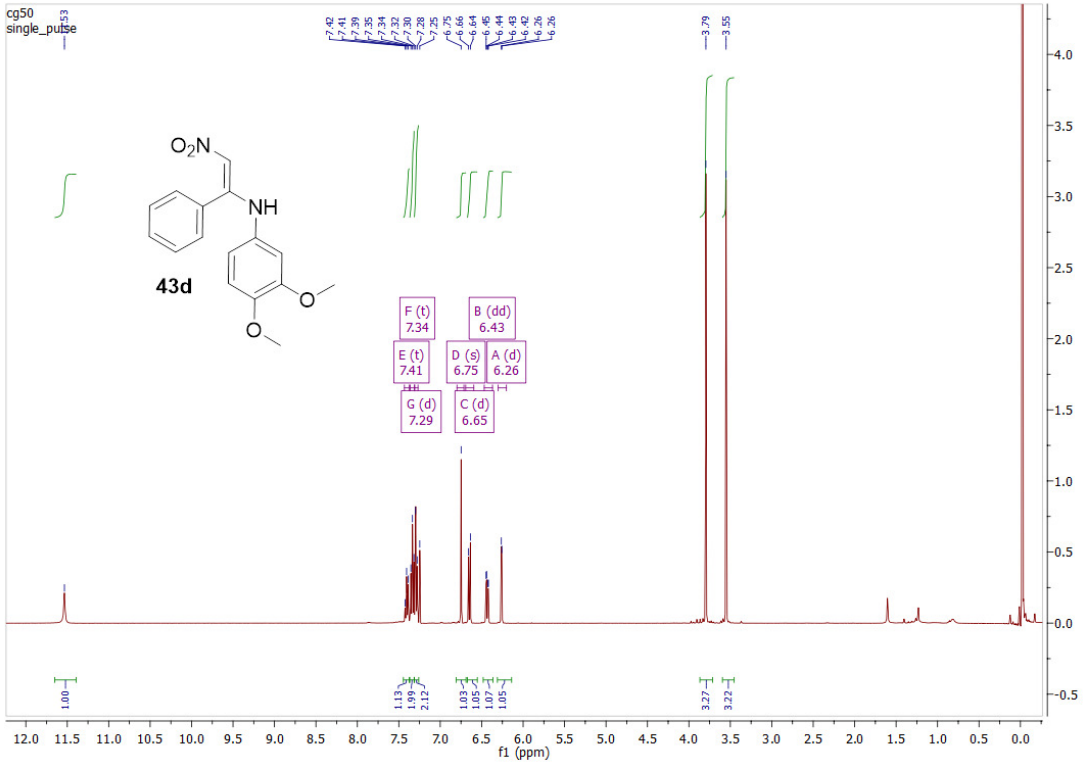


Figure 7.17. ^{1}H-NMR Spectrum of compound **43d**

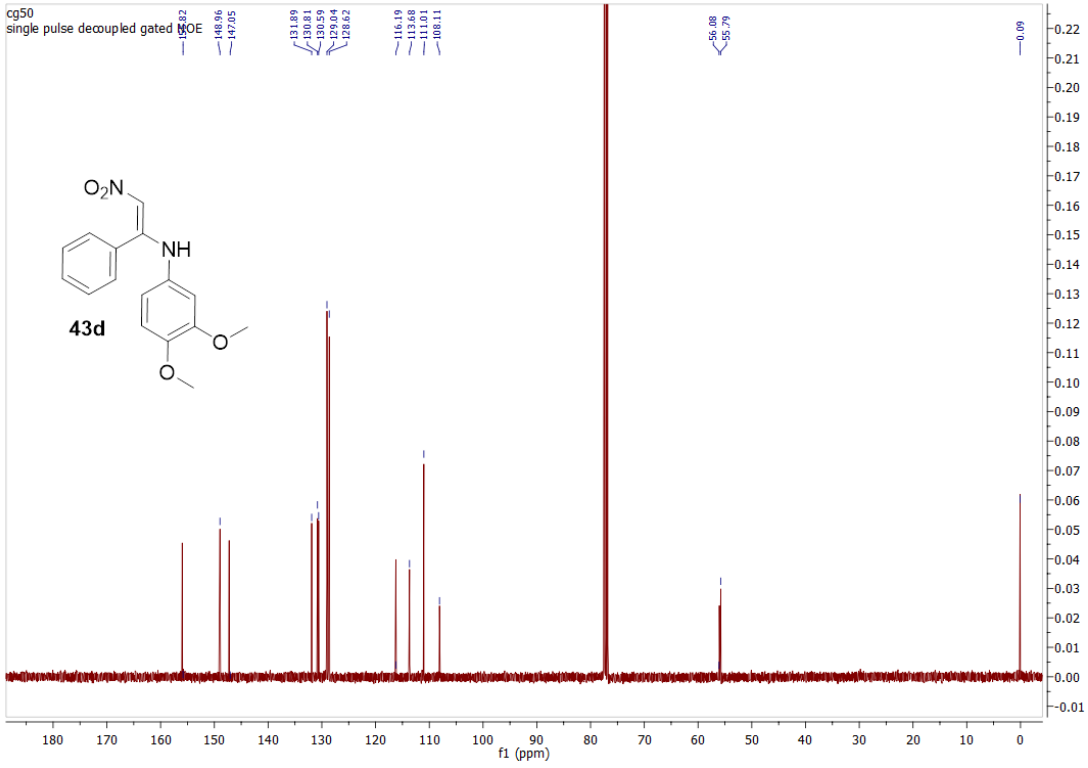


Figure 7.18. ^{13}C-NMR Spectrum of compound **43d**

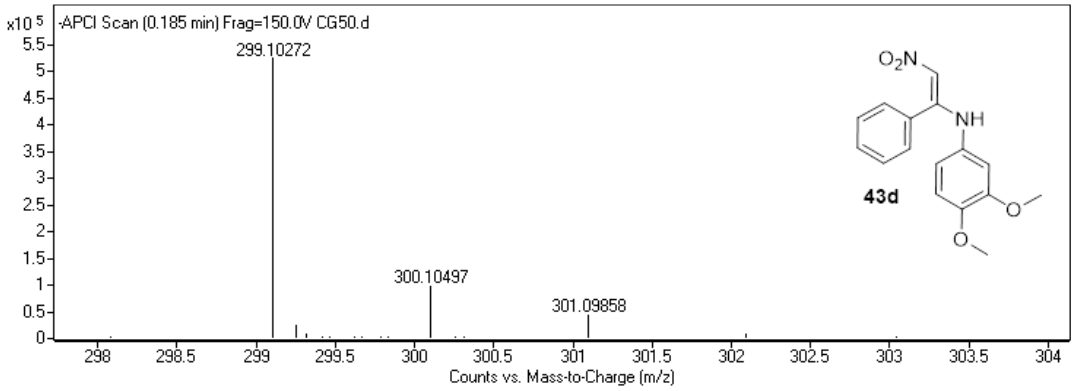


Figure 7.19. HRMS Spectrum of compound **43d**

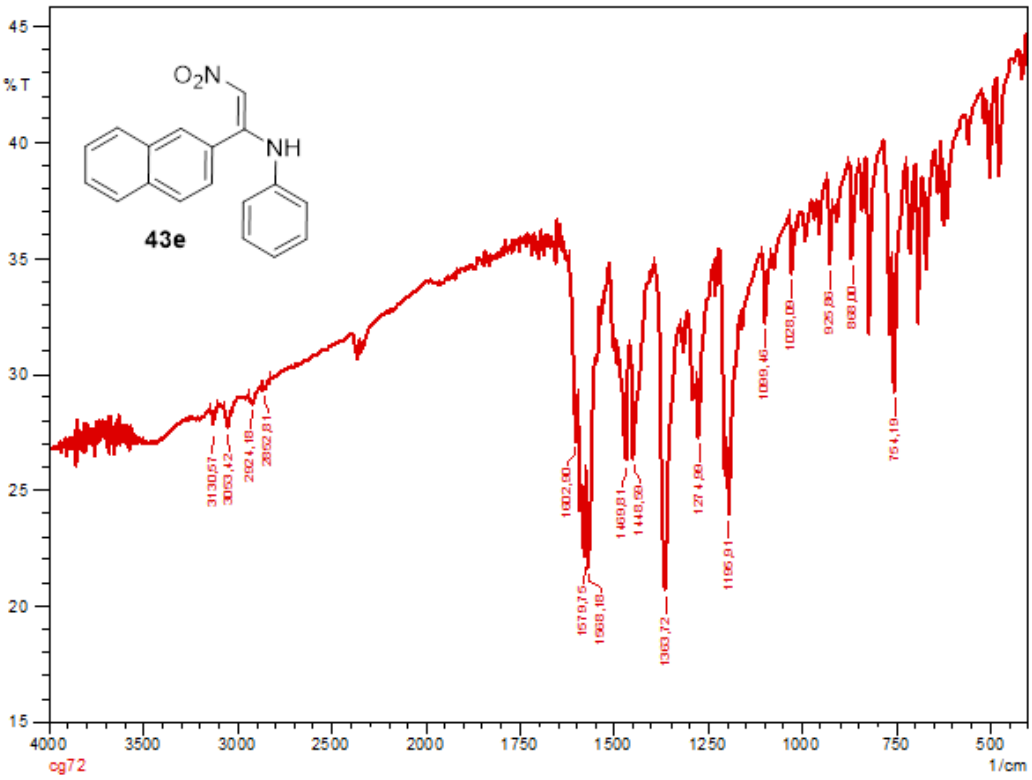


Figure 7.20. IR Spectrum of compound **43e**

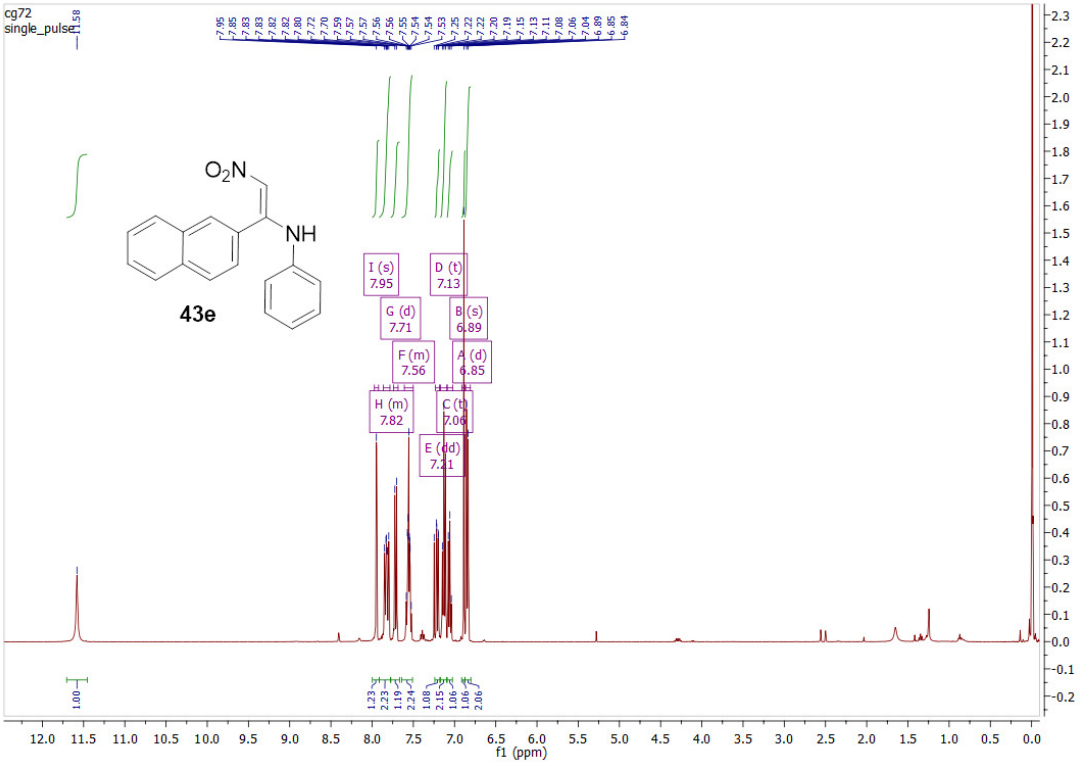


Figure 7.21. ^{1}H-NMR Spectrum of compound **43e**

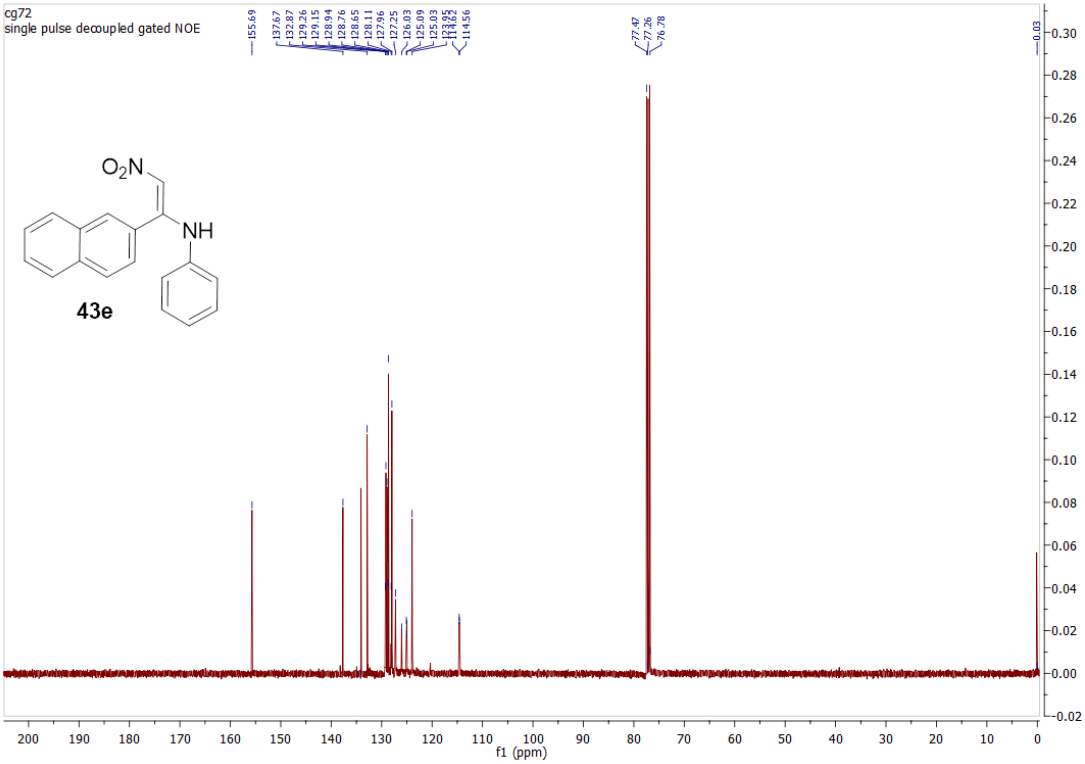


Figure 7.22. ^{13}C-NMR Spectrum of compound **43e**

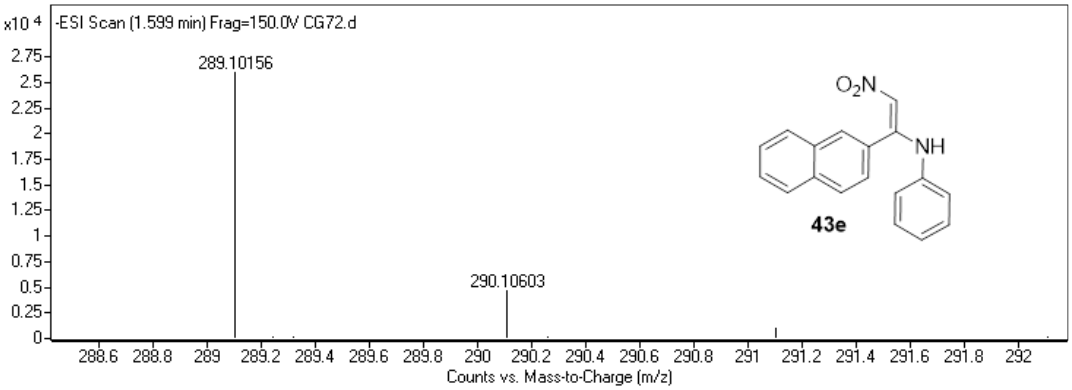


Figure 7.23. HRMS Spectrum of compound **43e**

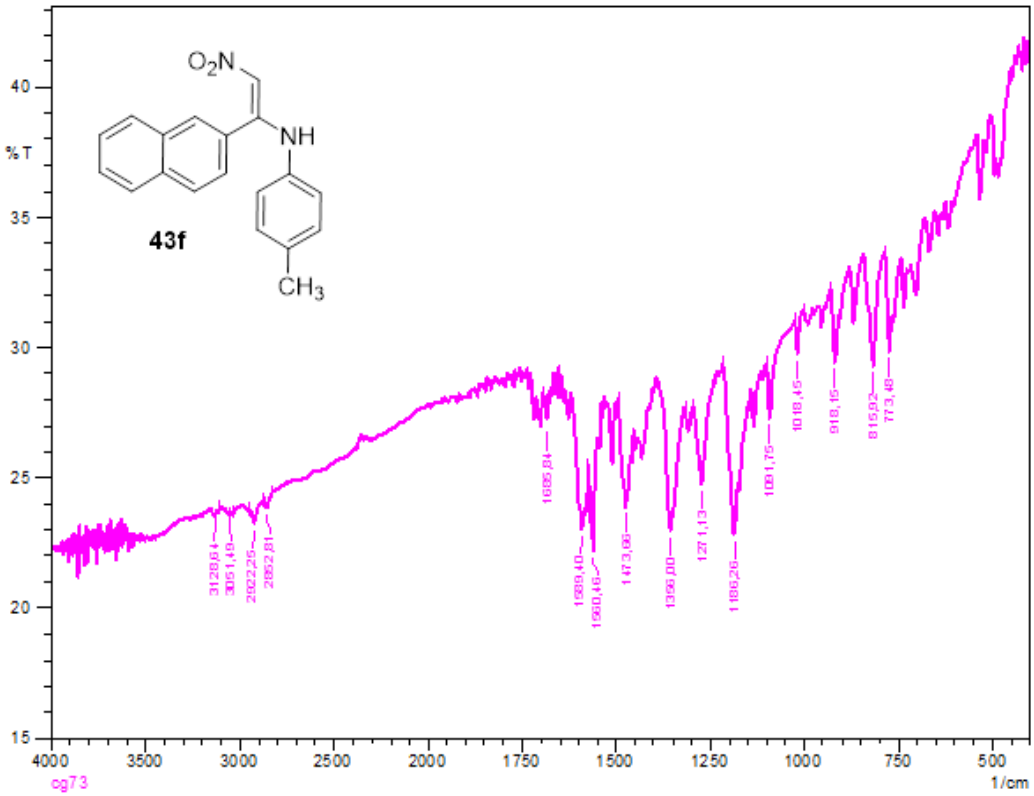


Figure 7.24. IR Spectrum of compound **43f**

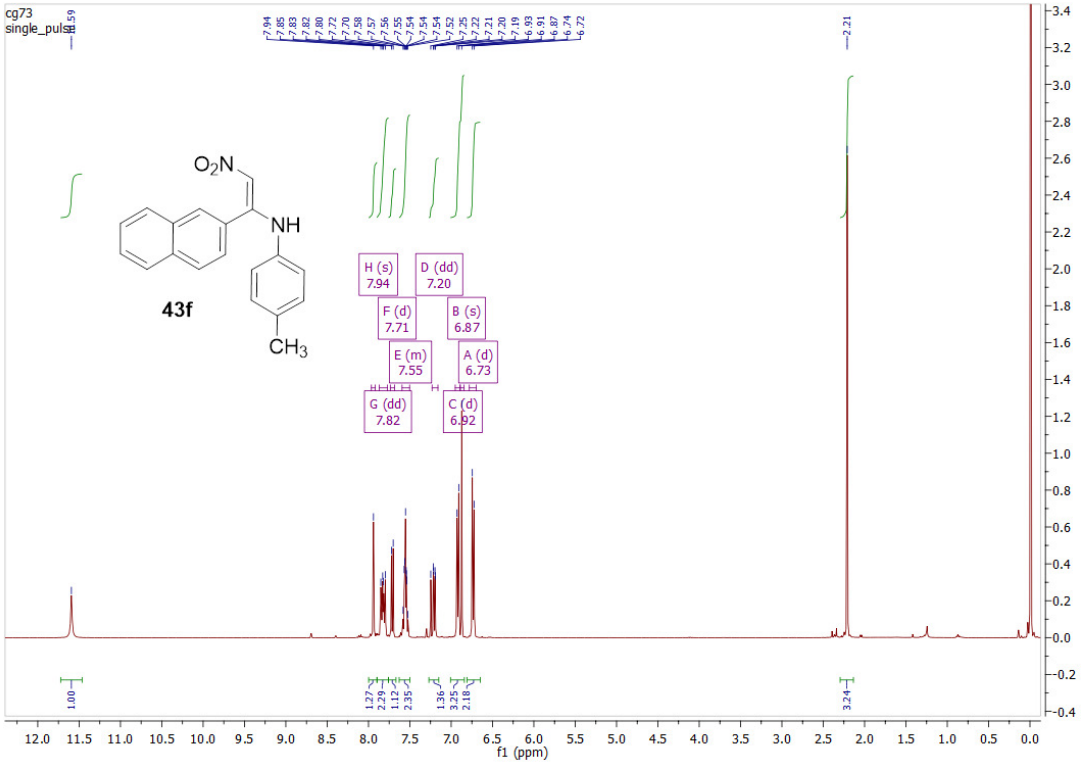


Figure 7.25. ^{1}H-NMR Spectrum of compound **43f**

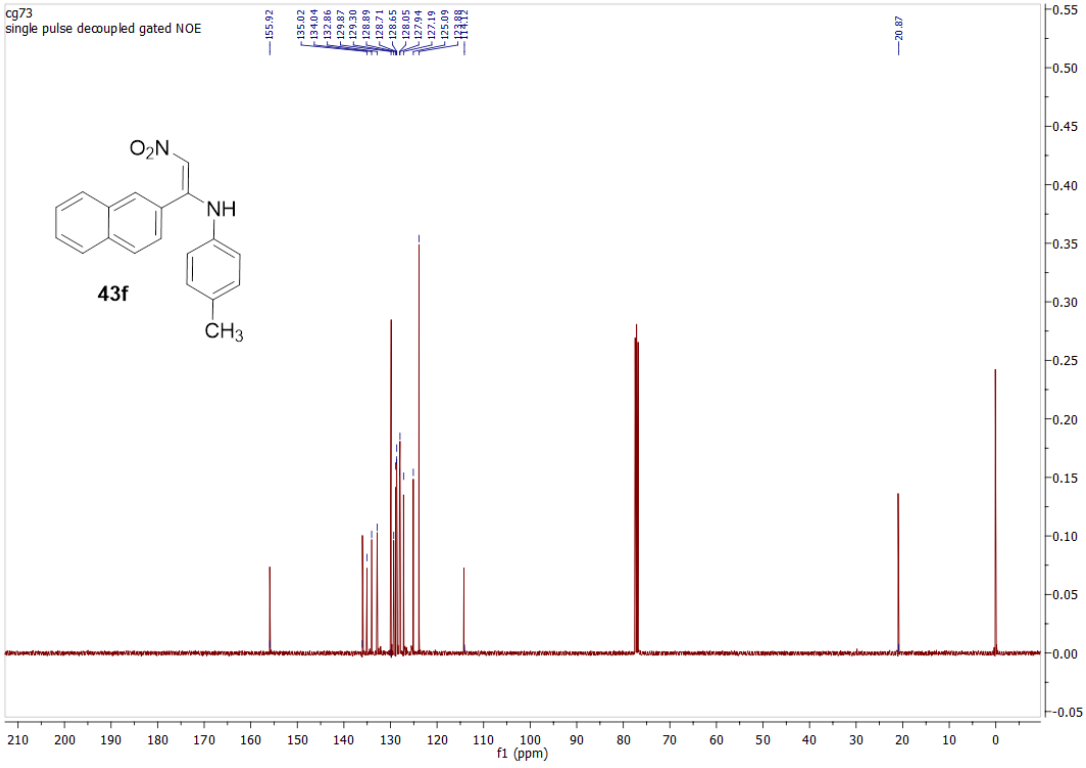


Figure 7.26. ^{13}C-NMR Spectrum of compound **43f**

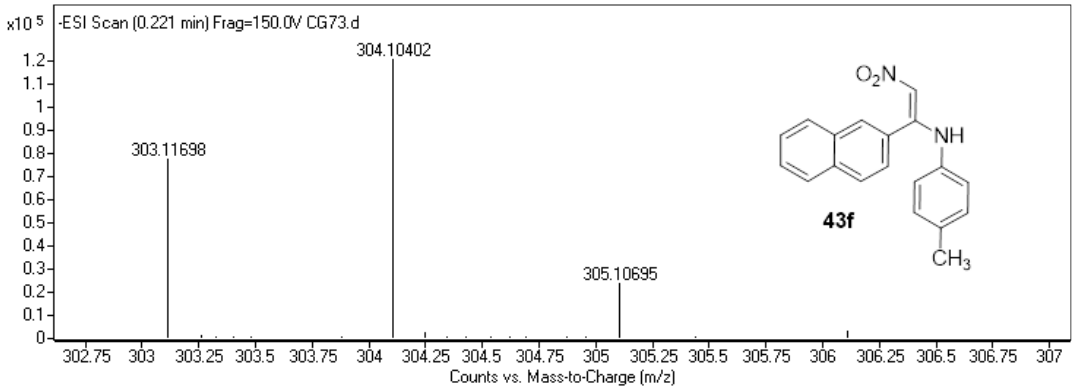


Figure 7.27. HRMS Spectrum of compound **43f**

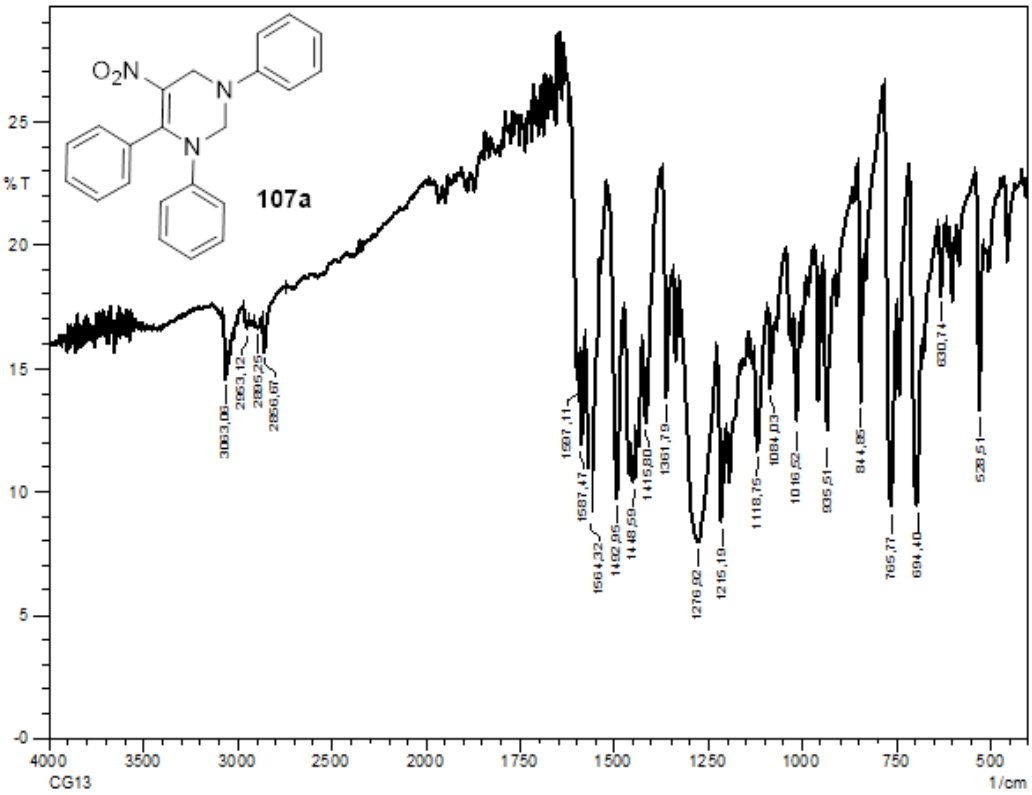


Figure 7.28. IR Spectrum of compound **107a**

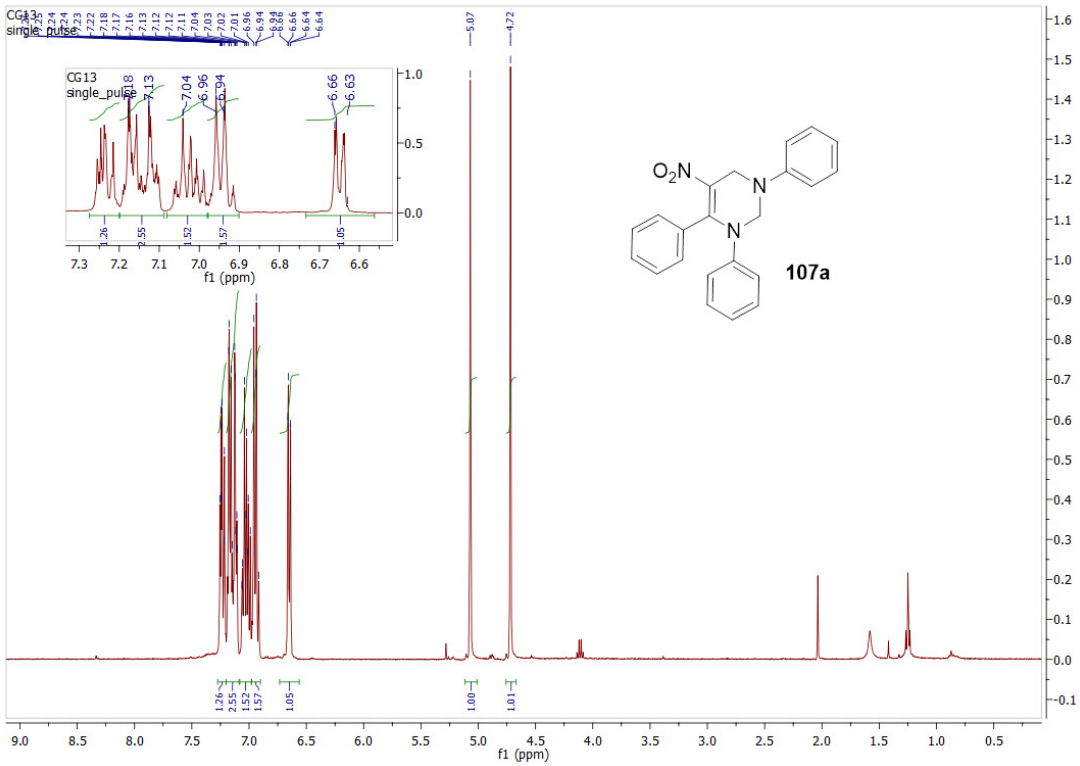


Figure 7.29. ^{1}H-NMR Spectrum of compound **107a**

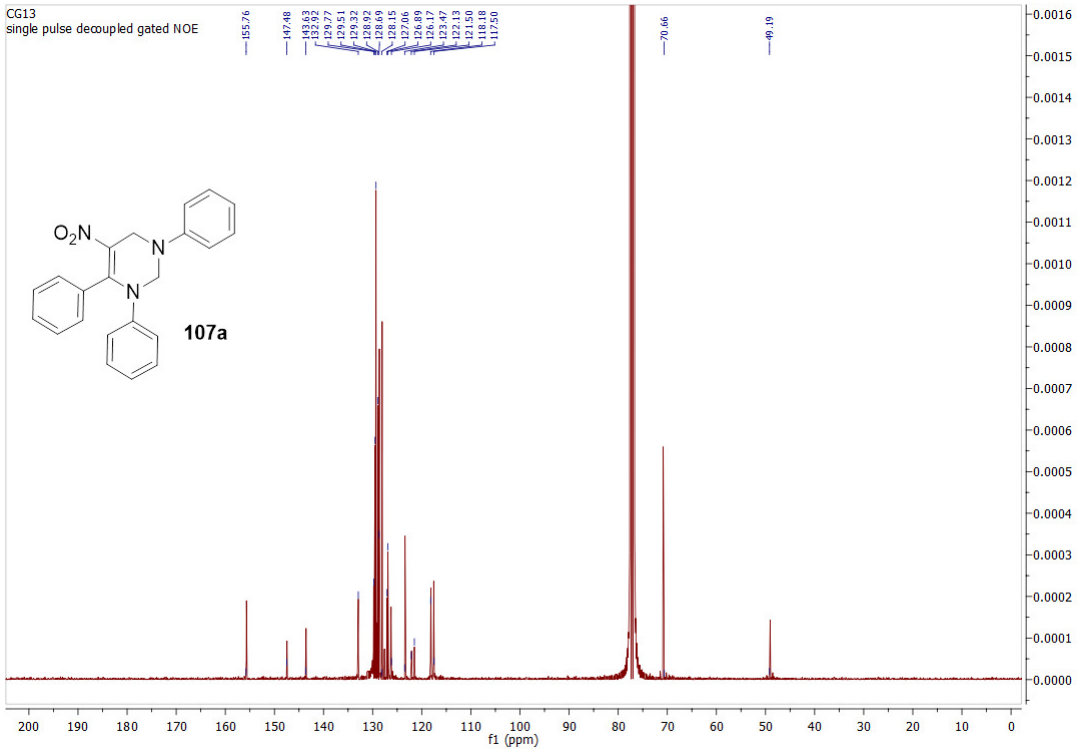


Figure 7.30. ^{13}C-NMR Spectrum of compound **107a**

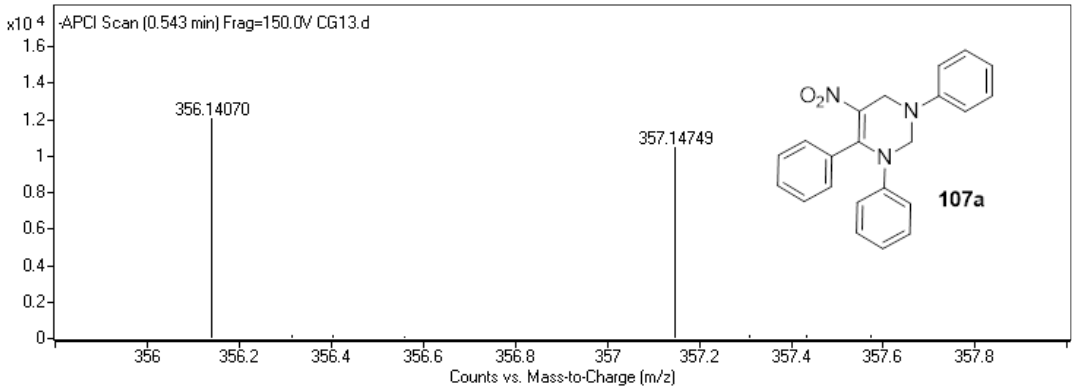


Figure 7.31. HRMS Spectrum of compound **107a**

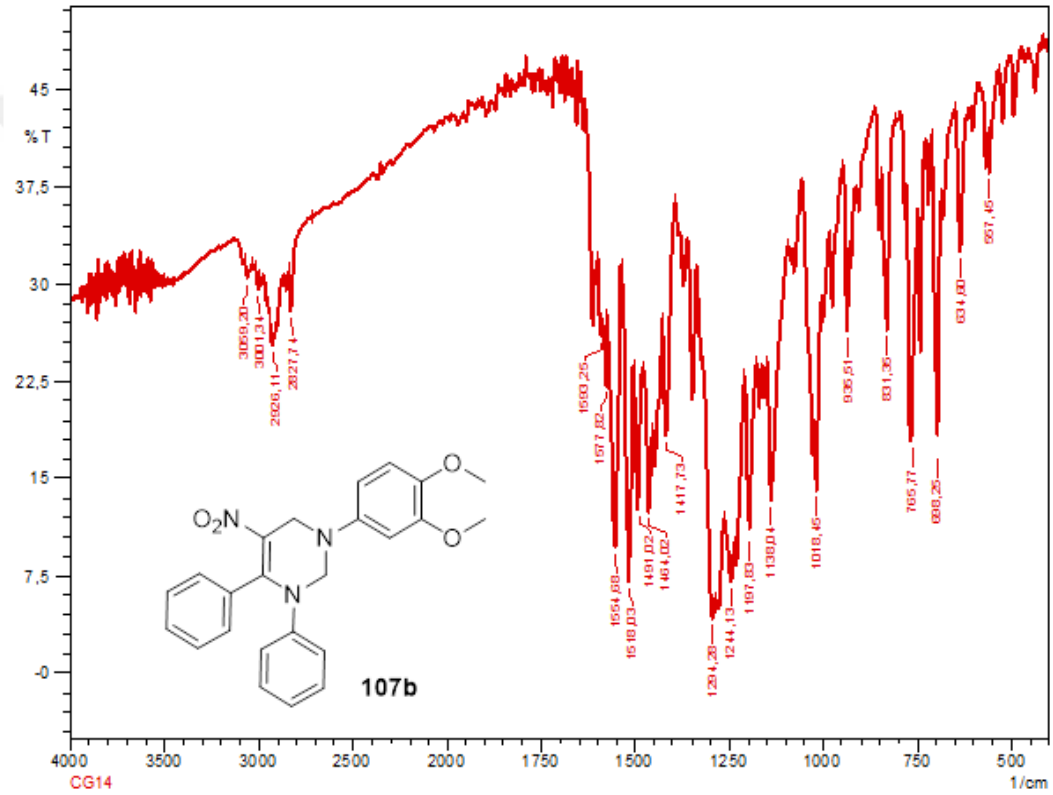


Figure 7.32. IR Spectrum of compound **107b**

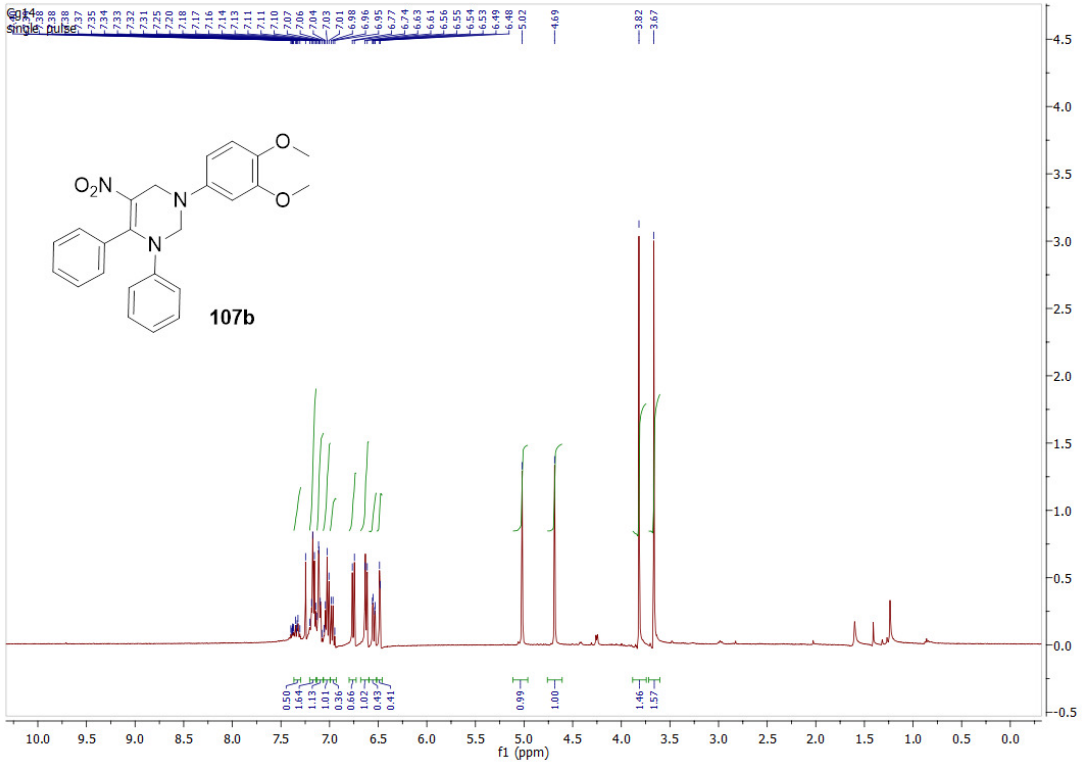


Figure 7.33. ^{1}H-NMR Spectrum of compound **107b**

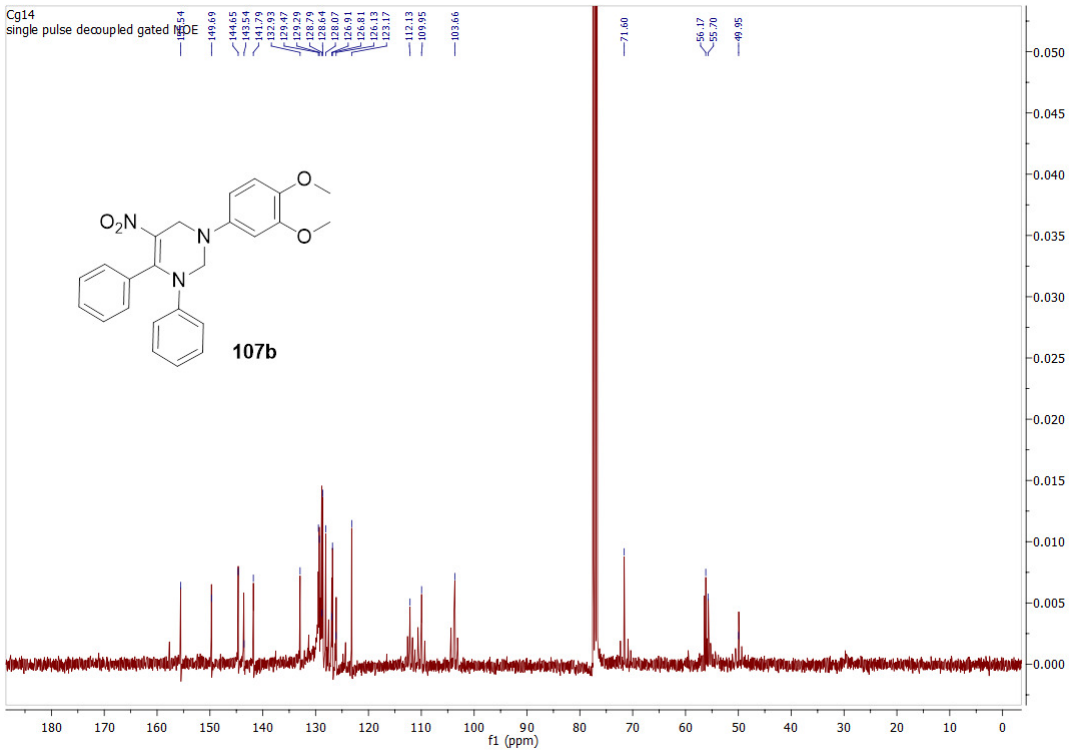


Figure 7.34. ^{13}C-NMR Spectrum of compound **107b**

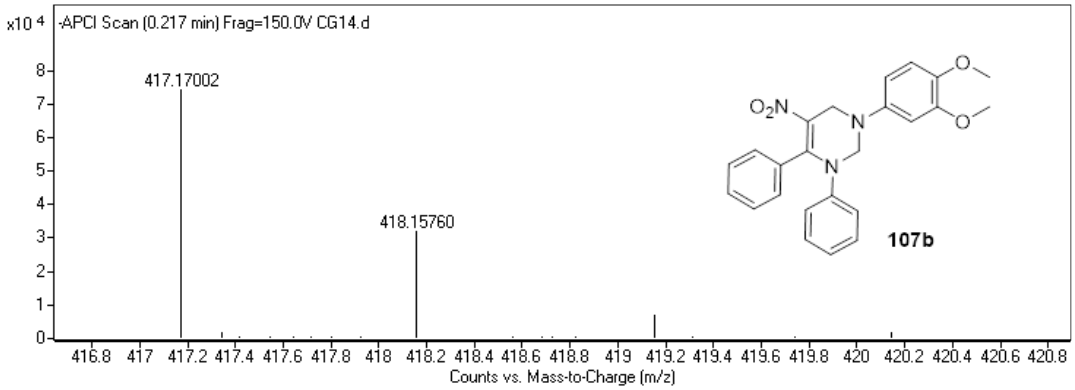


Figure 7.35. HRMS Spectrum of compound **107b**

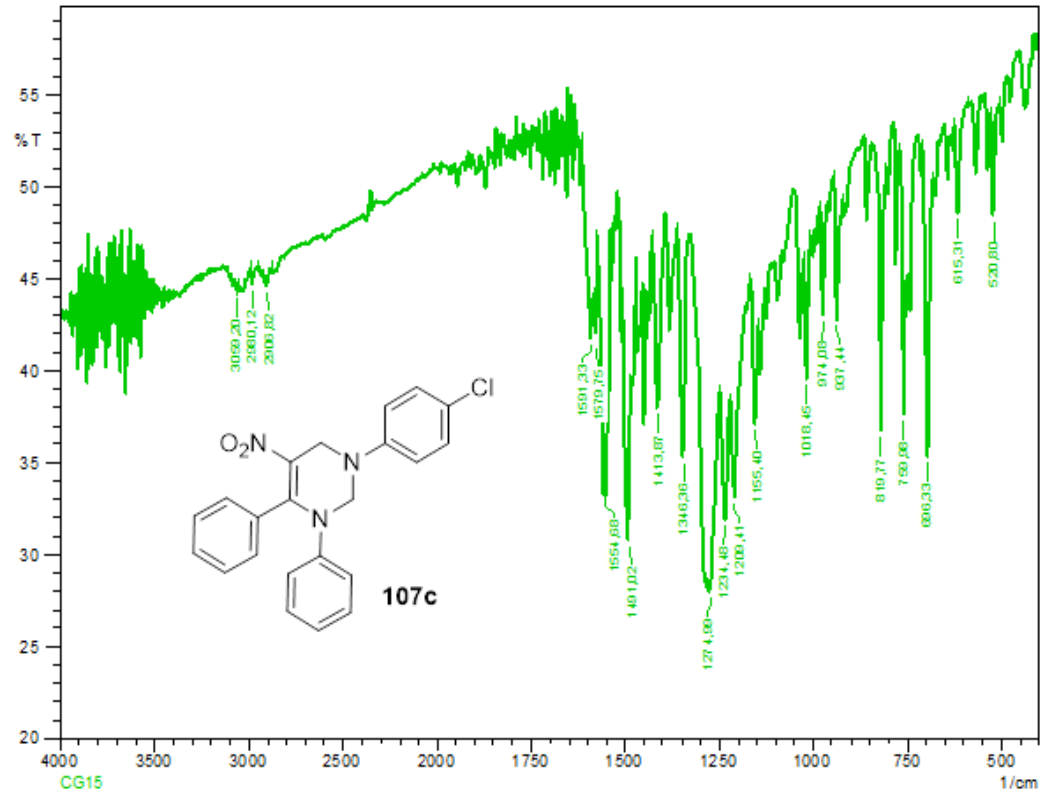


Figure 7.36. IR Spectrum of compound **107c**

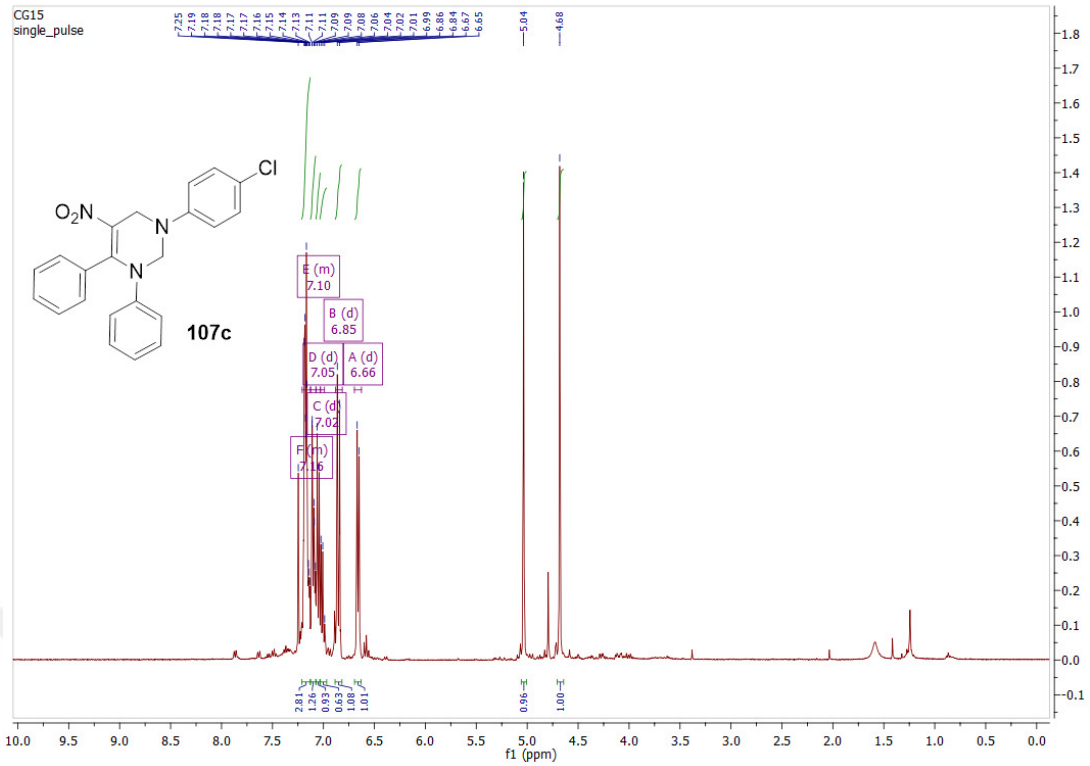


Figure 7.37. ^{1}H-NMR Spectrum of compound **107c**

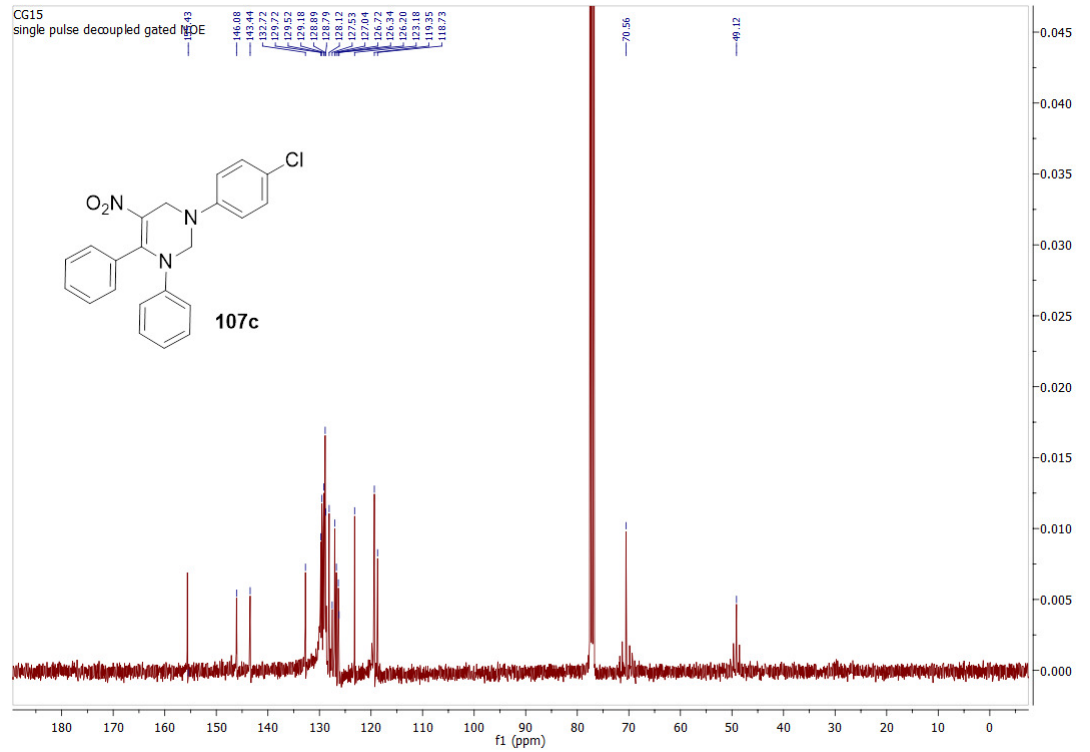


Figure 7.38. ^{13}C-NMR Spectrum of compound **107c**

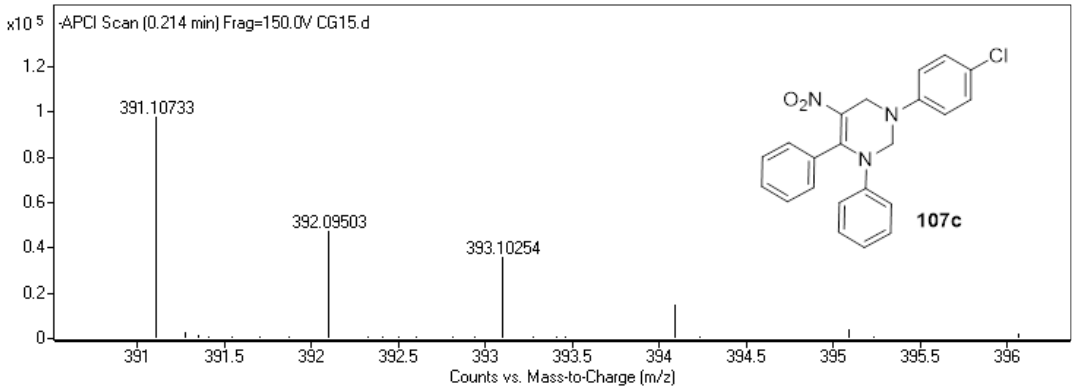


Figure 7.39. HRMS Spectrum of compound **107c**

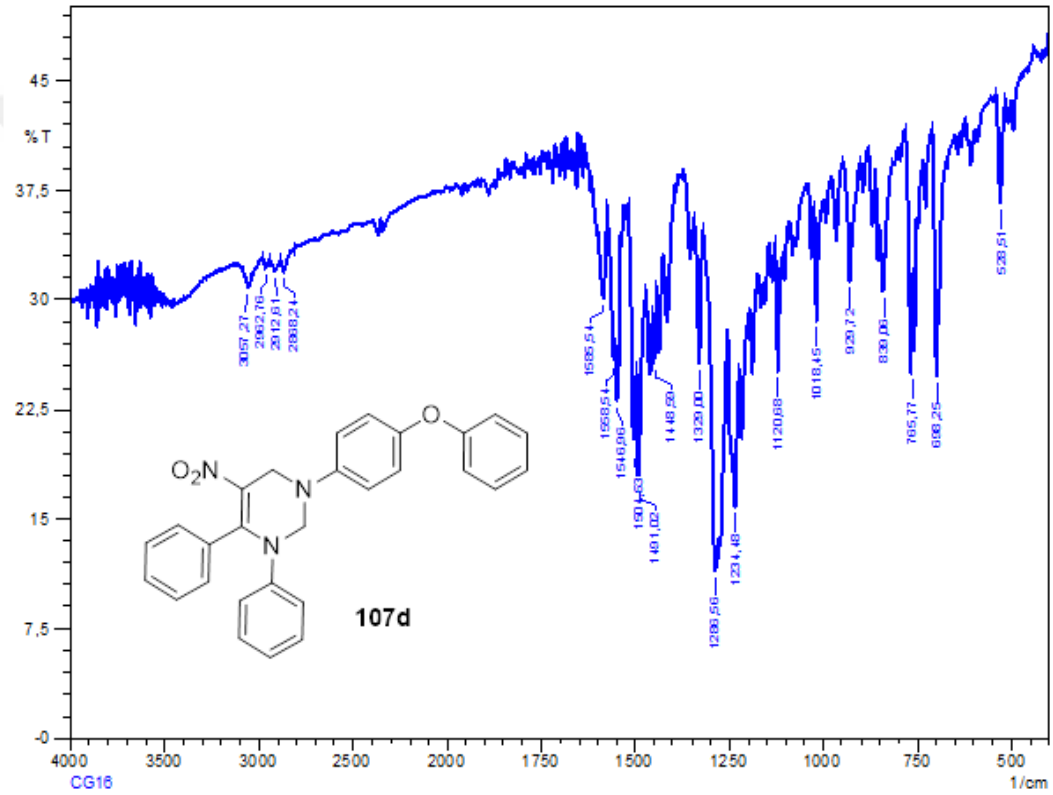


Figure 7.40. IR Spectrum of compound **107d**

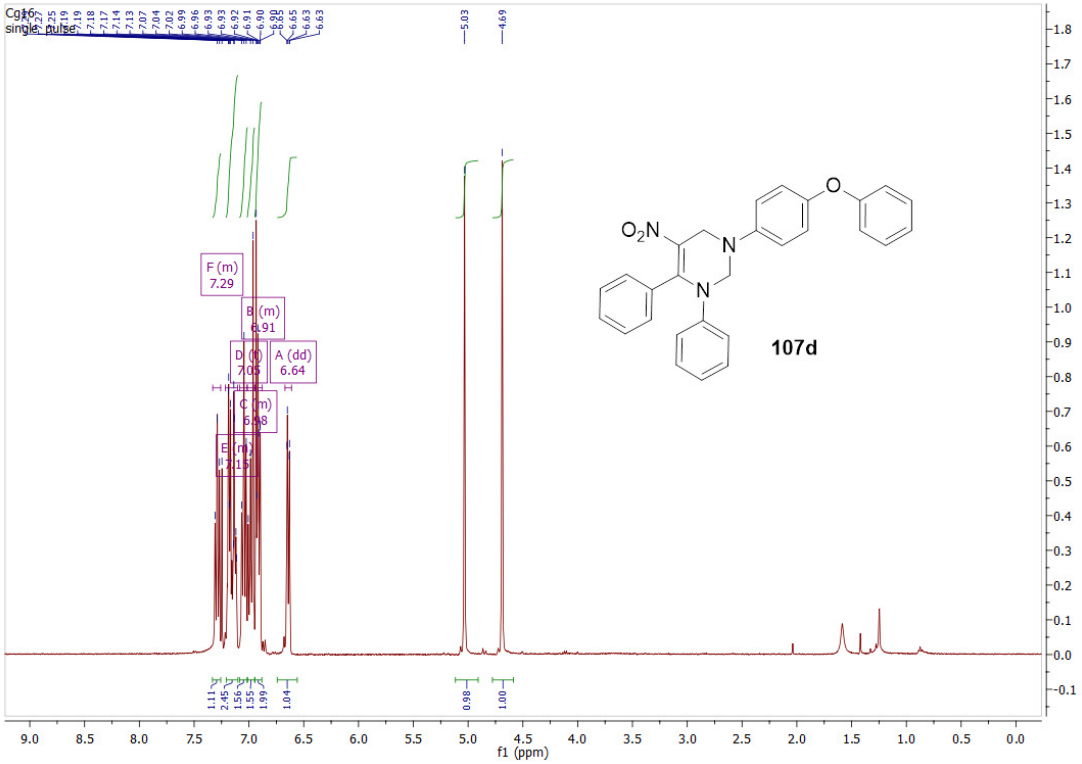


Figure 7.41. ^{1}H-NMR Spectrum of compound **107d**

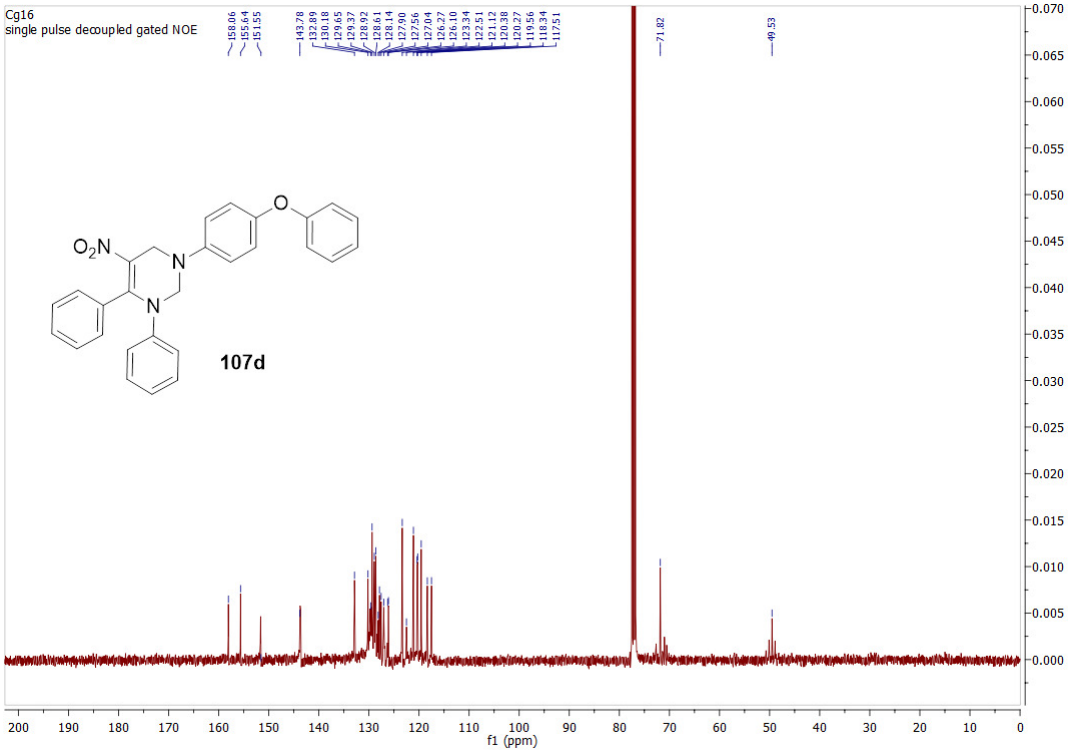


Figure 7.42. ^{13}C-NMR Spectrum of compound **107d**

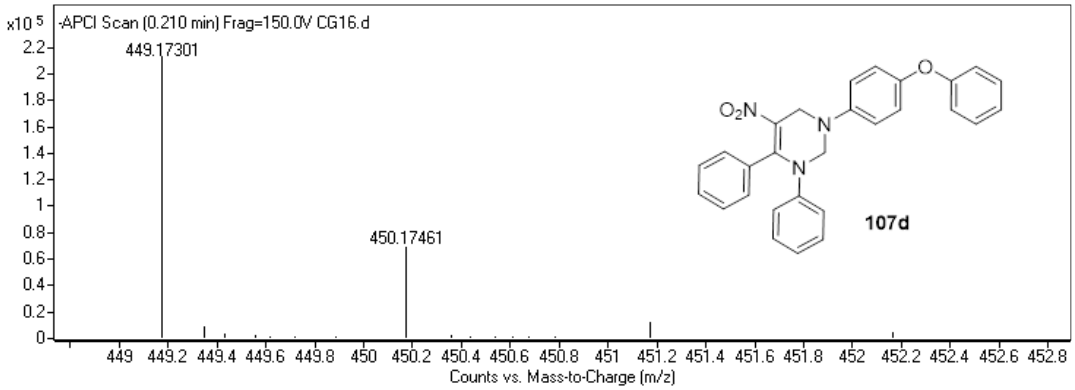


Figure 7.43. HRMS Spectrum of compound **107d**

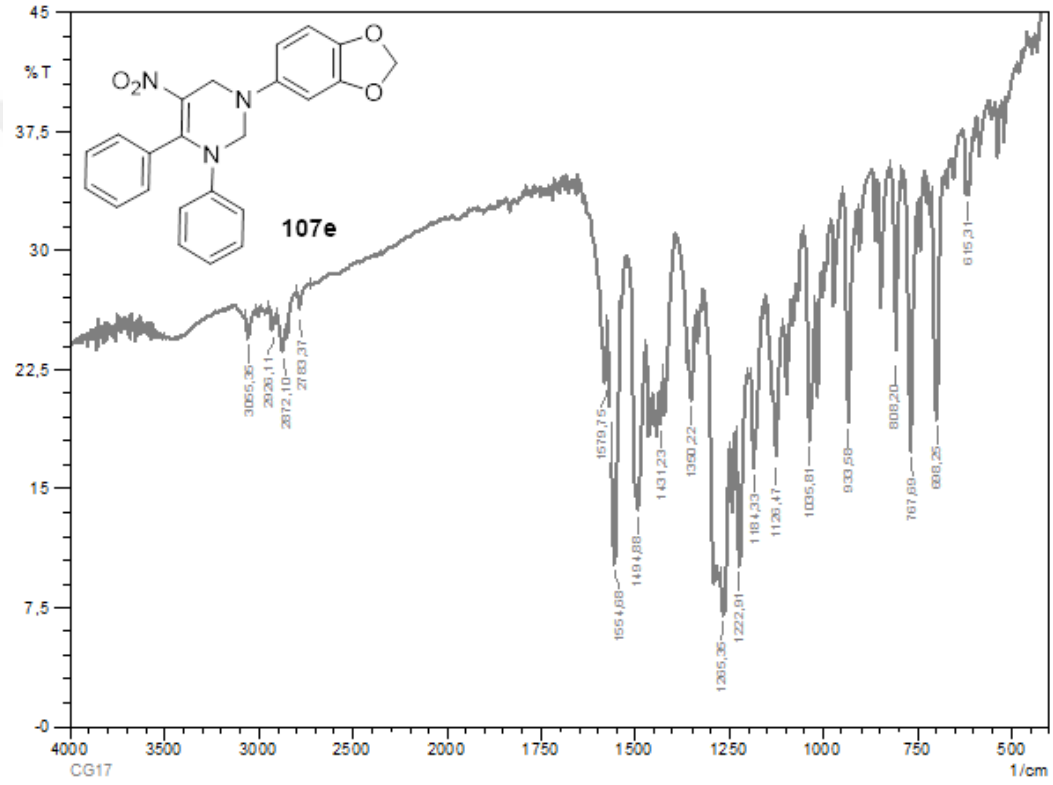


Figure 7.44. IR Spectrum of compound **107e**

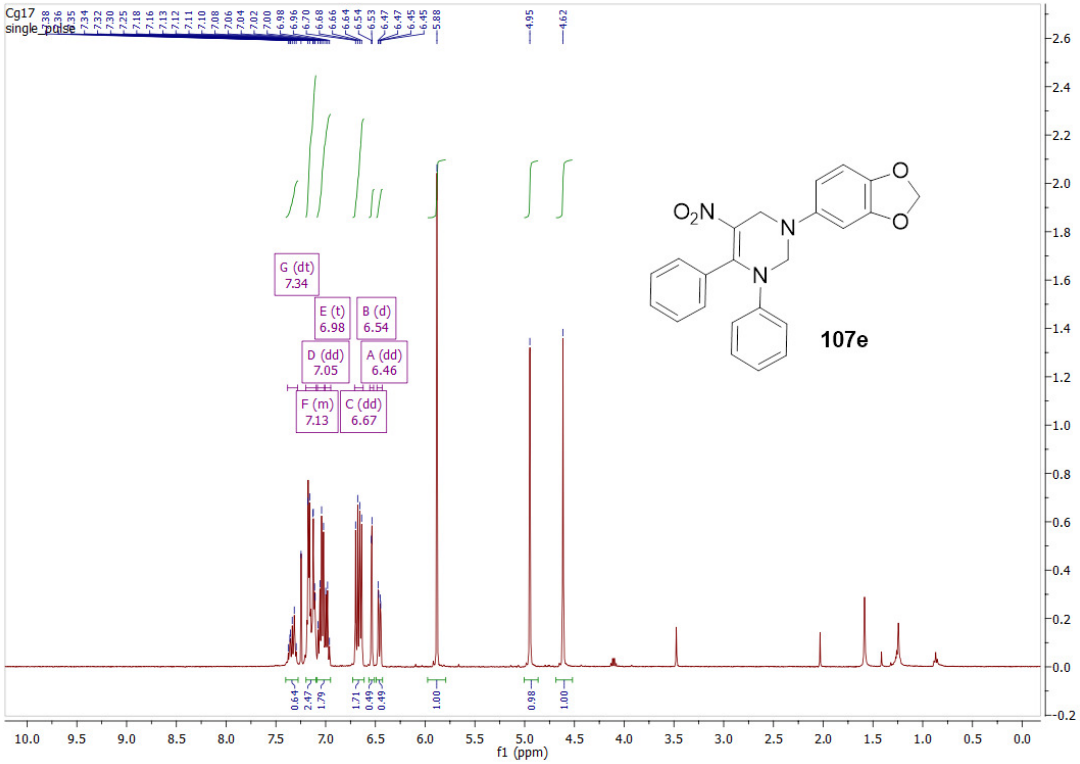


Figure 7.45. ^{1}H-NMR Spectrum of compound **107e**

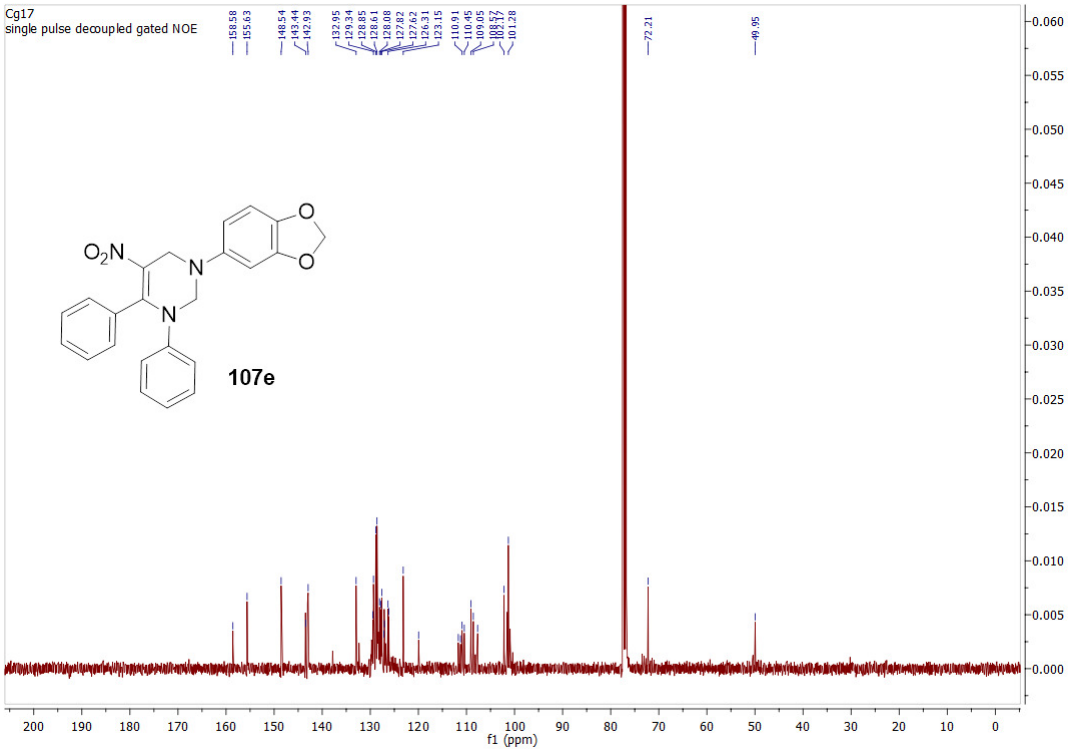


Figure 7.46. ^{13}C-NMR Spectrum of compound **107e**

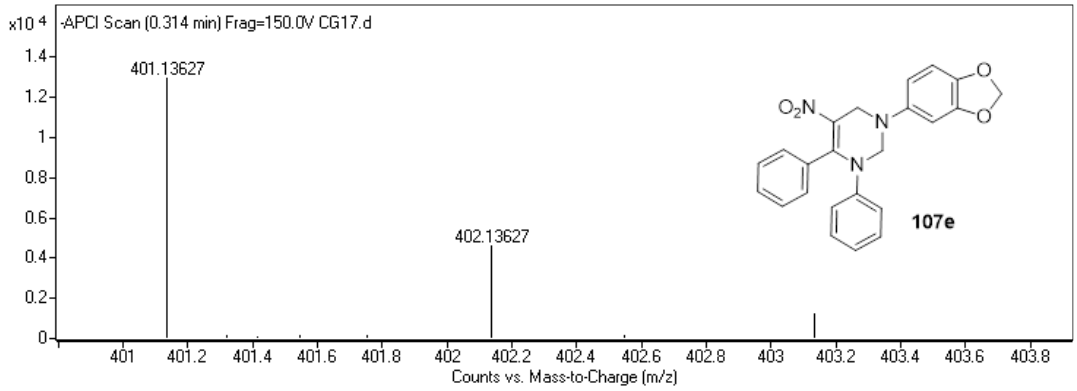


Figure 7.47. HRMS Spectrum of compound **107e**

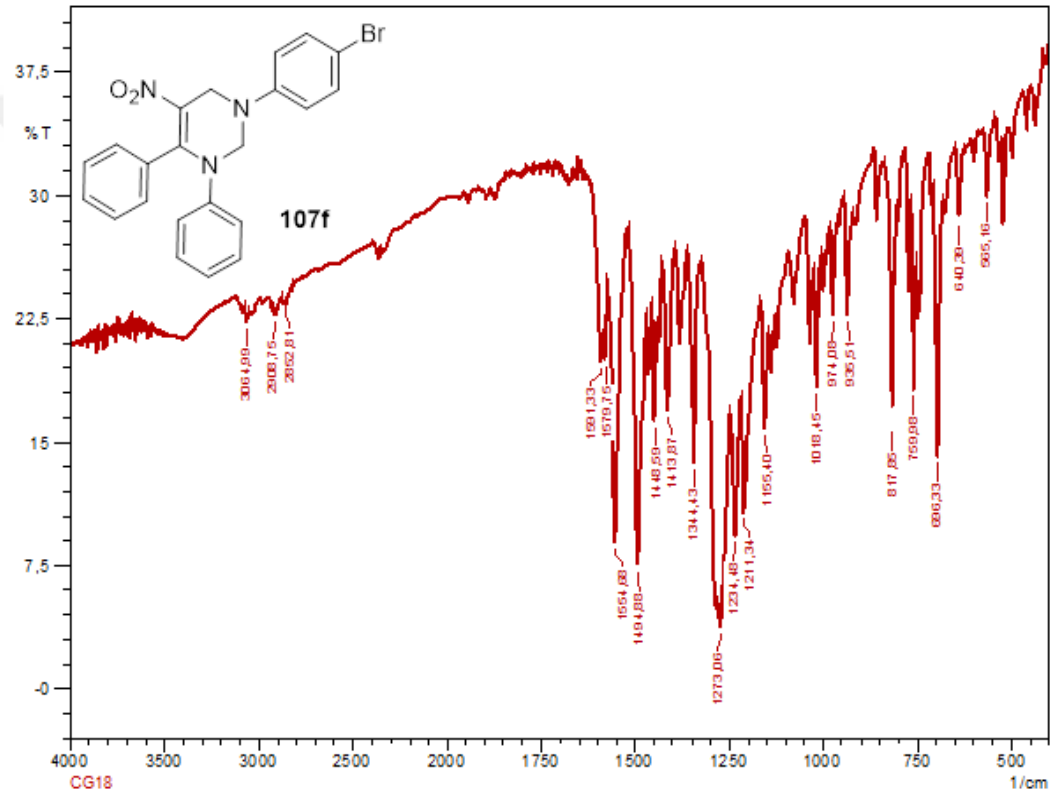


Figure 7.48. IR Spectrum of compound **107f**

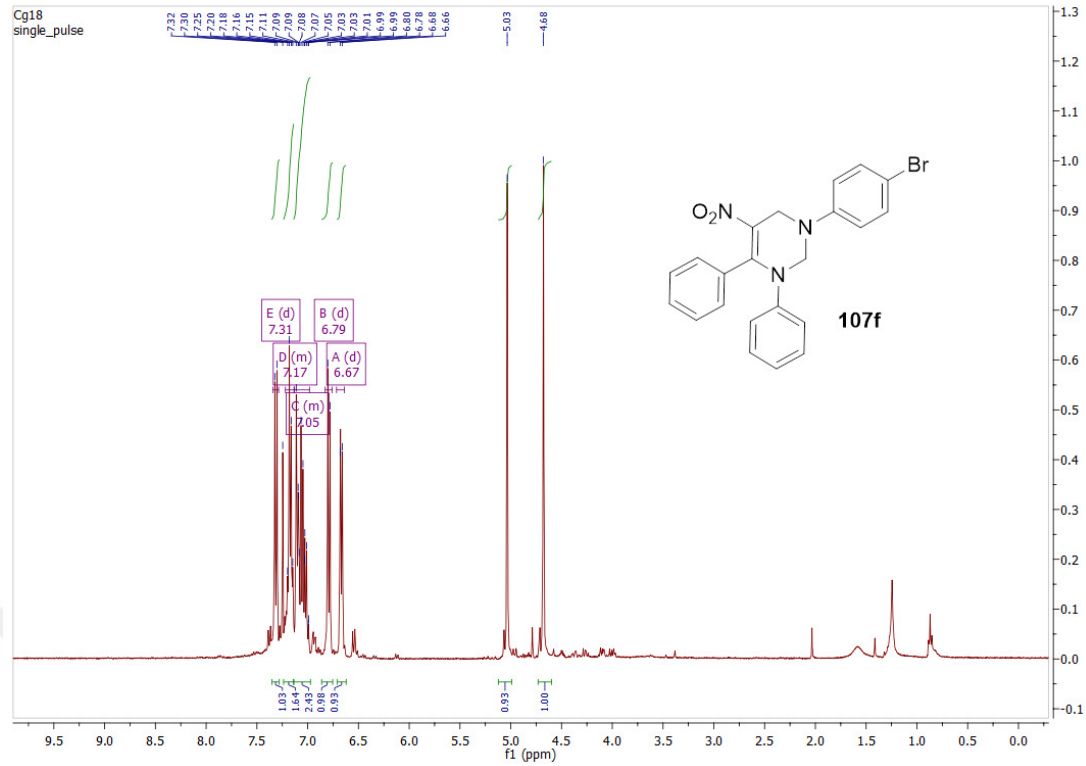


Figure 7.49. ^{1}H-NMR Spectrum of compound **107f**

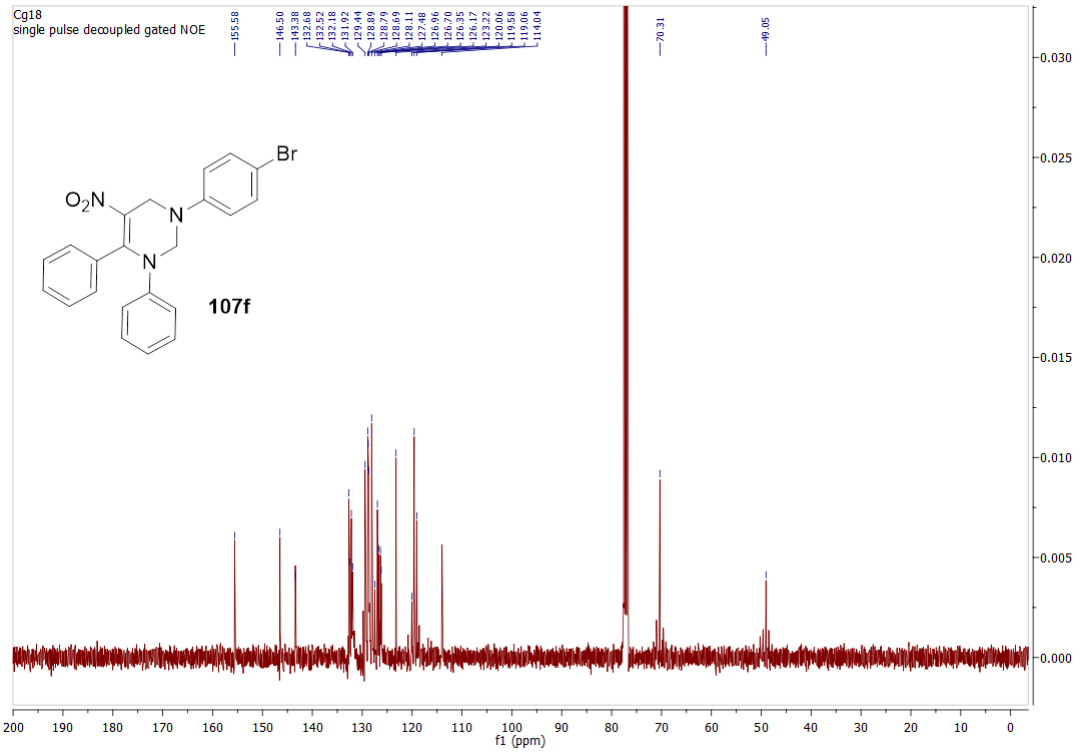


Figure 7.50. ^{13}C-NMR Spectrum of compound **107f**

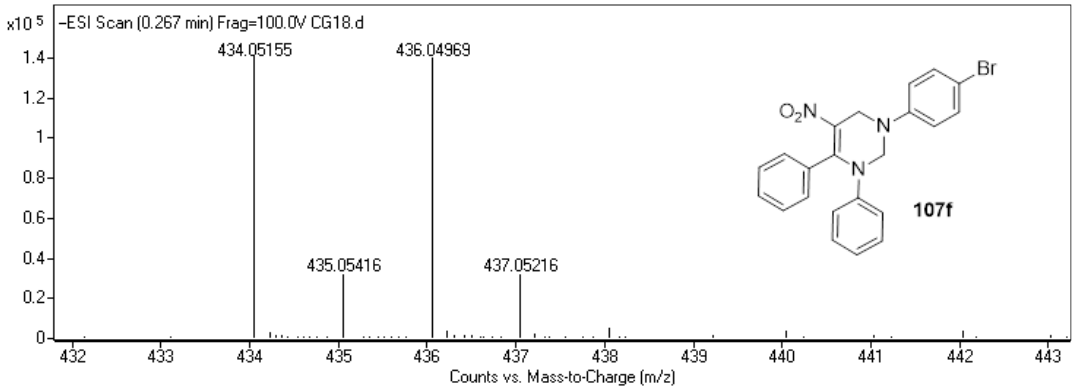


Figure 7.51. HRMS Spectrum of compound **107f**

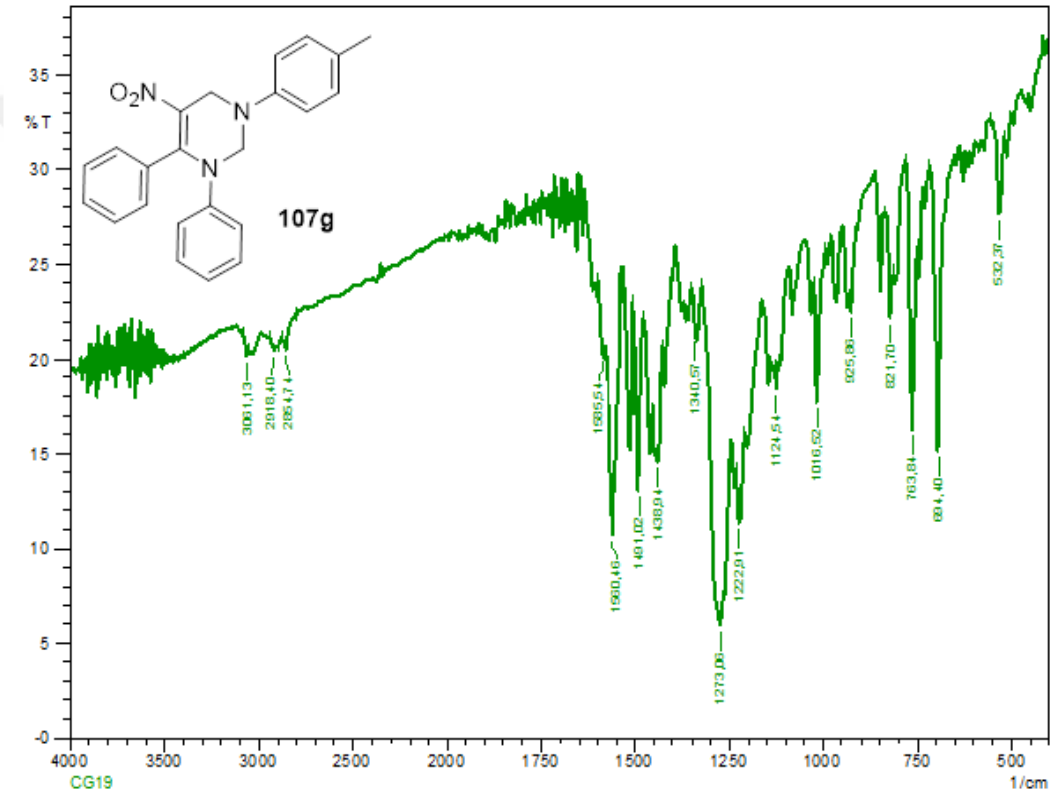


Figure 7.52. IR Spectrum of compound **107g**

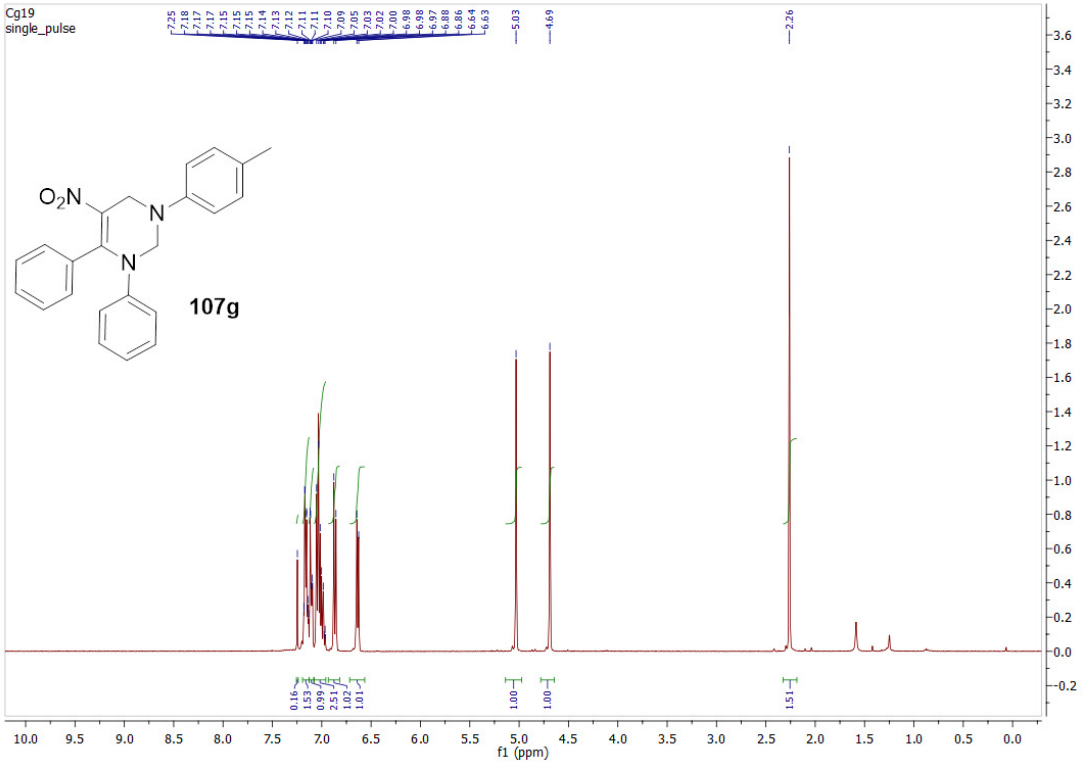


Figure 7.53. ^{1}H-NMR Spectrum of compound **107g**

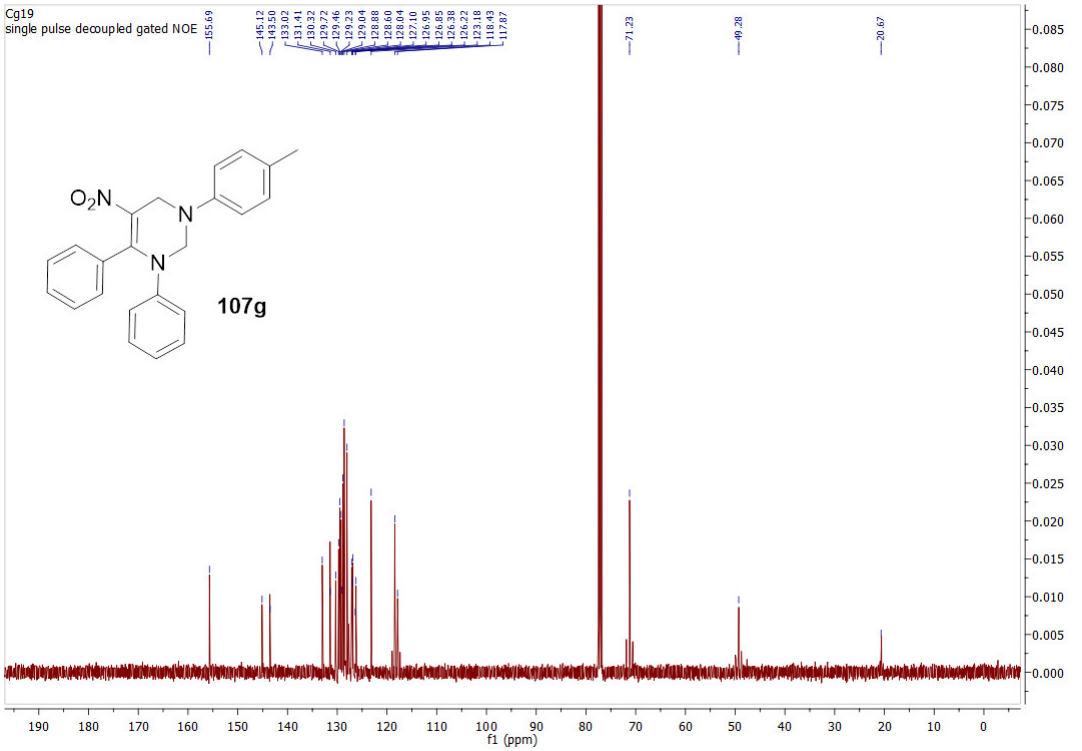


Figure 7.54. ^{13}C-NMR Spectrum of compound **107g**

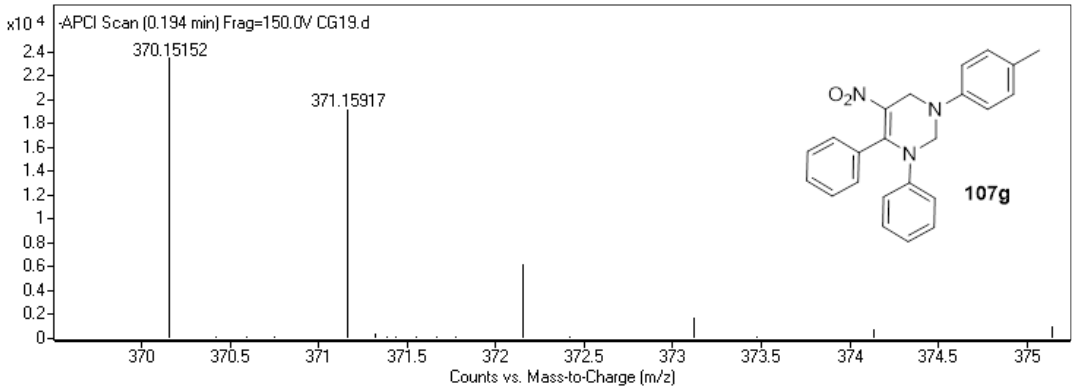


Figure 7.55. HRMS Spectrum of compound **107g**

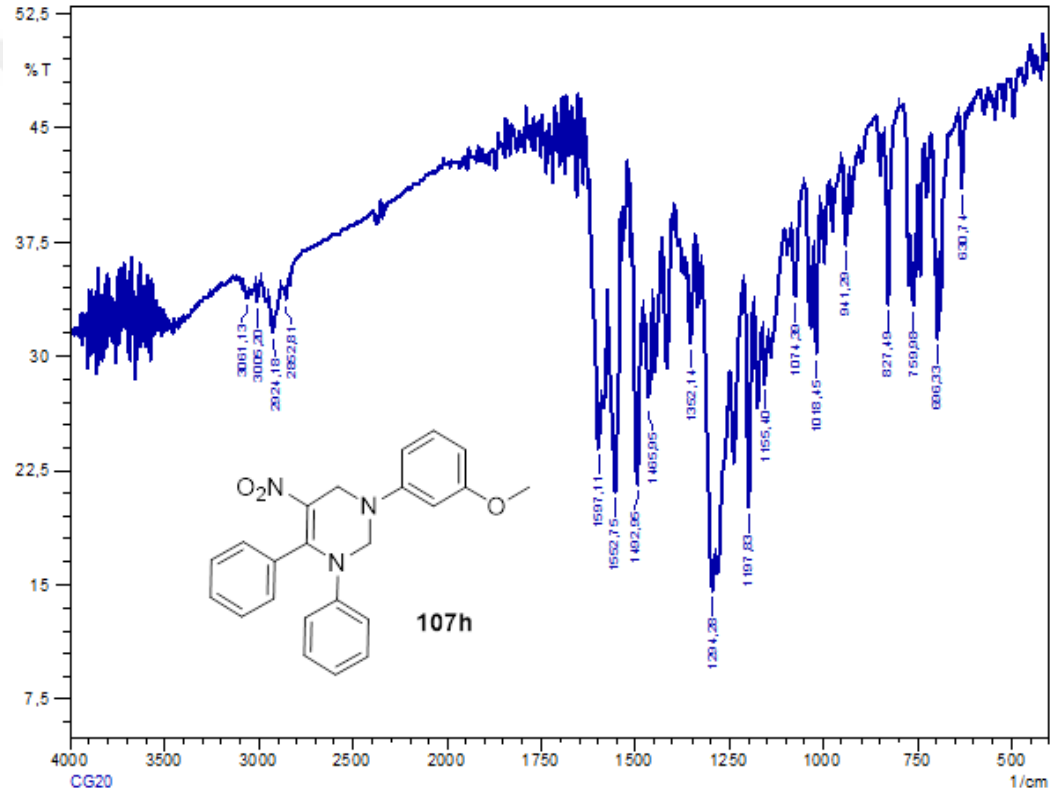


Figure 7.56. IR Spectrum of compound **107h**

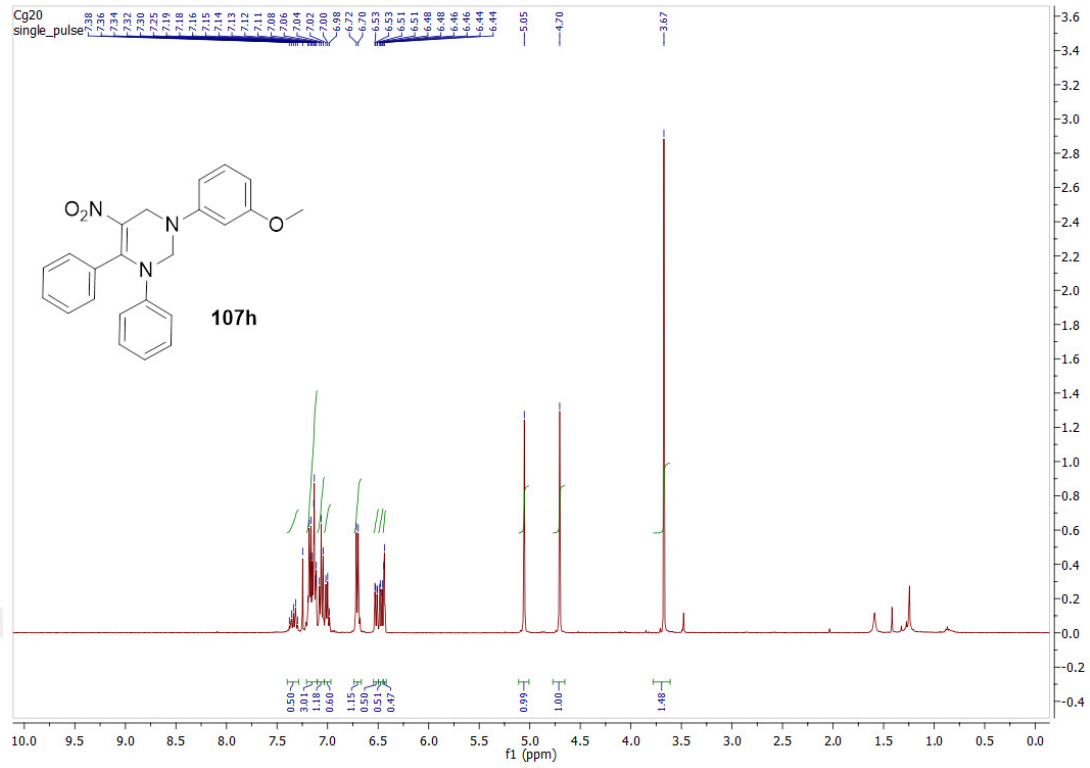


Figure 7.57. ^{1}H-NMR Spectrum of compound **107h**

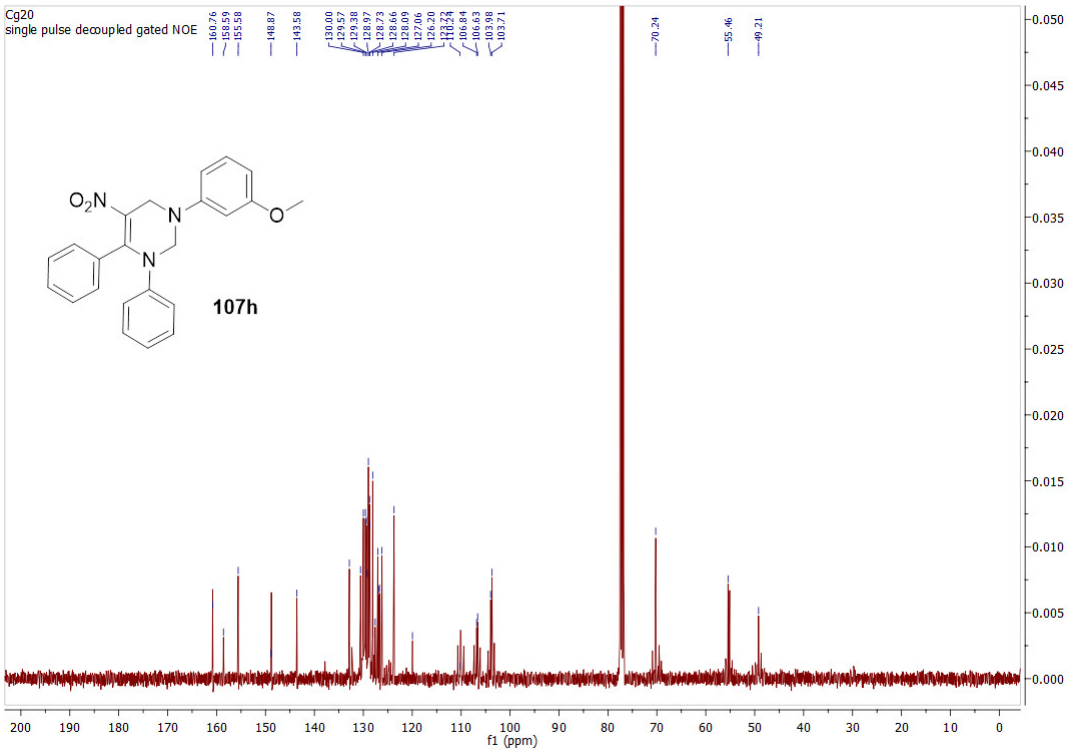


Figure 7.58. ^{13}C-NMR Spectrum of compound **107h**

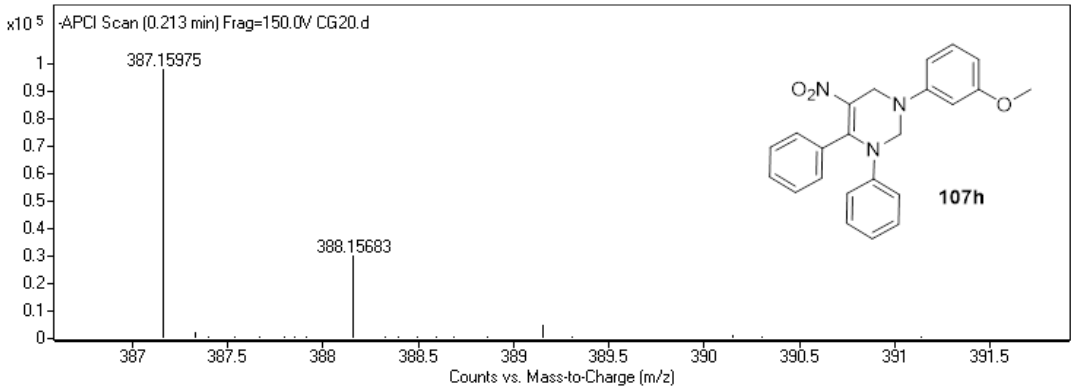


Figure 7.59. HRMS Spectrum of compound **107h**

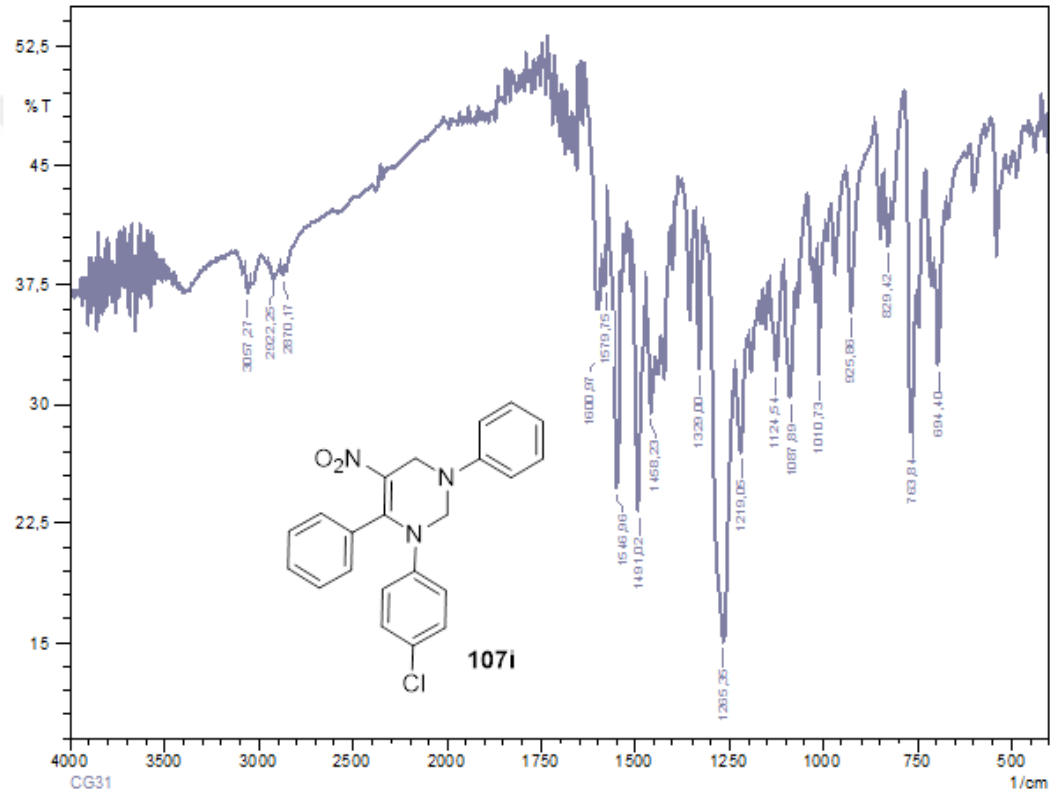


Figure 7.60. IR Spectrum of compound **107i**

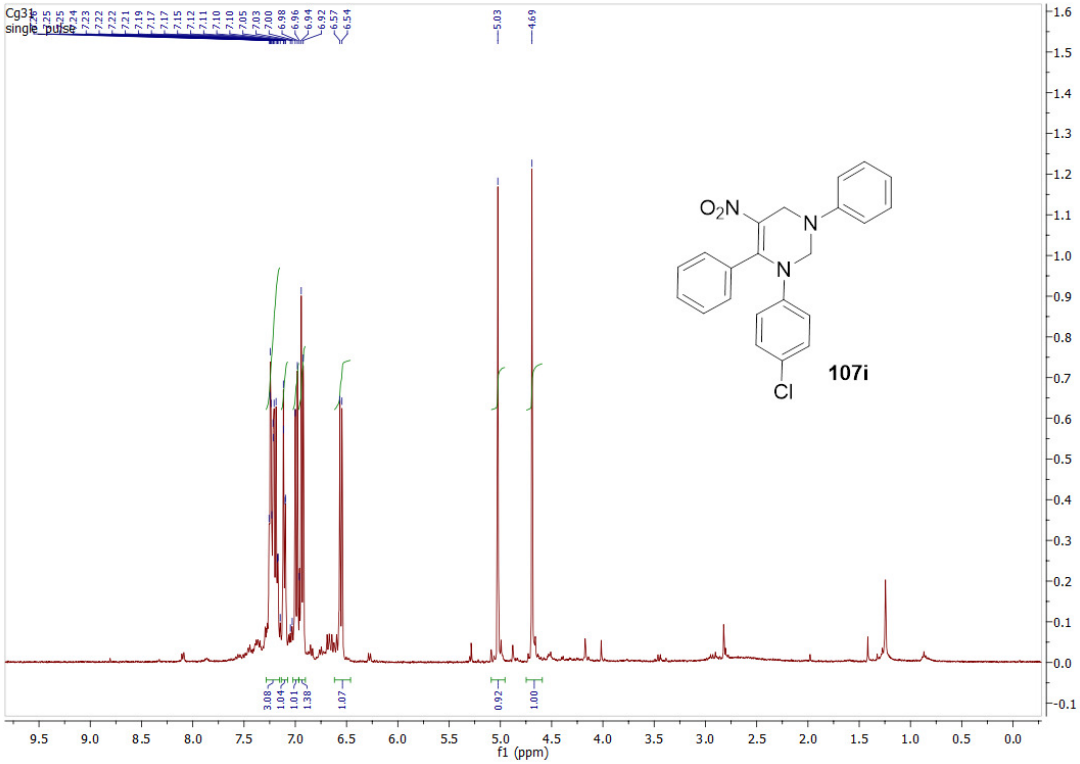


Figure 7.61. ^{1}H-NMR Spectrum of compound **107i**

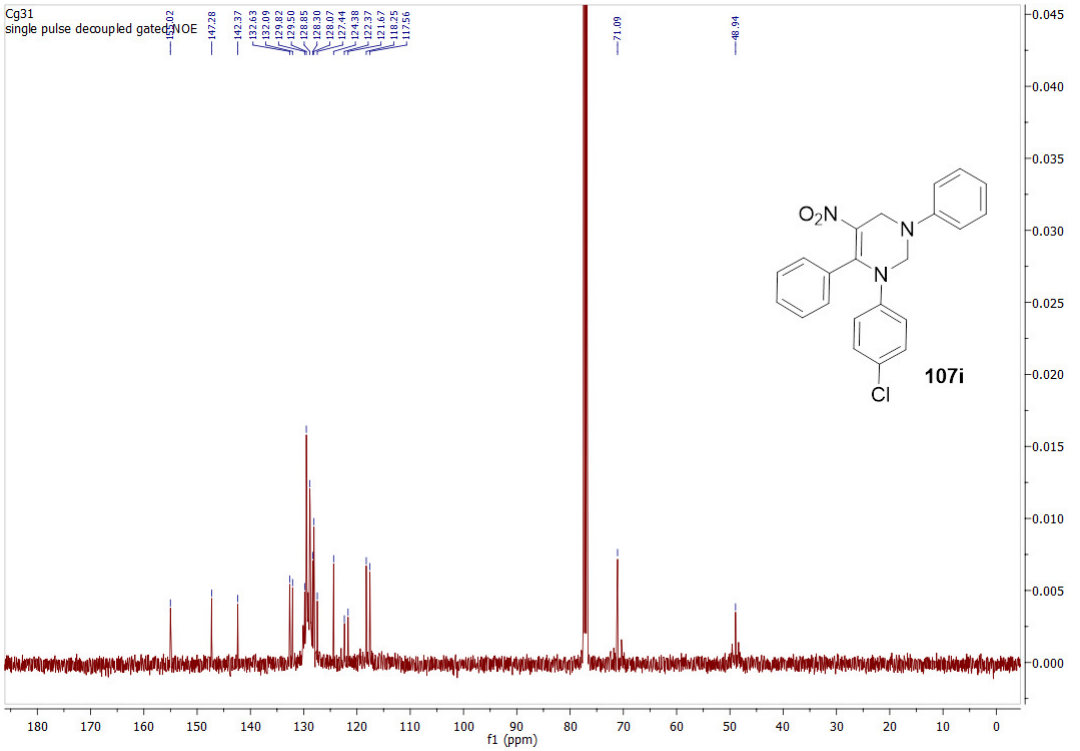


Figure 7.62. ^{13}C-NMR Spectrum of compound **107i**

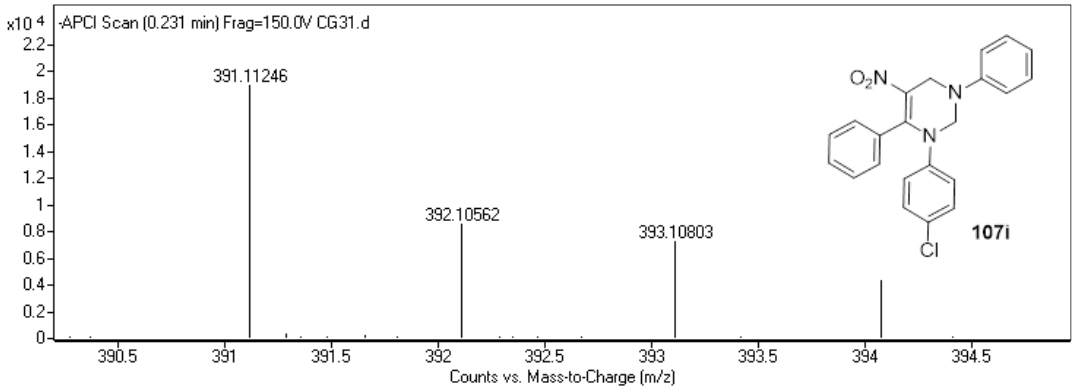


Figure 7.63. HRMS Spectrum of compound **107i**

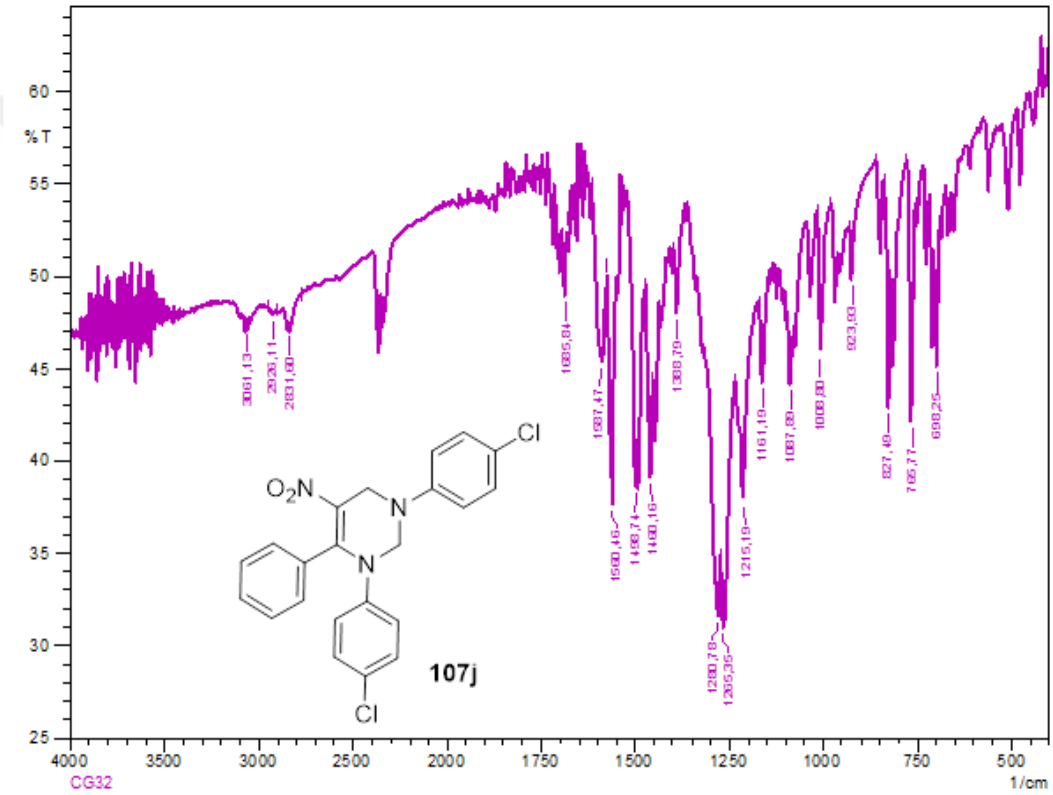


Figure 7.64. IR Spectrum of compound **107j**

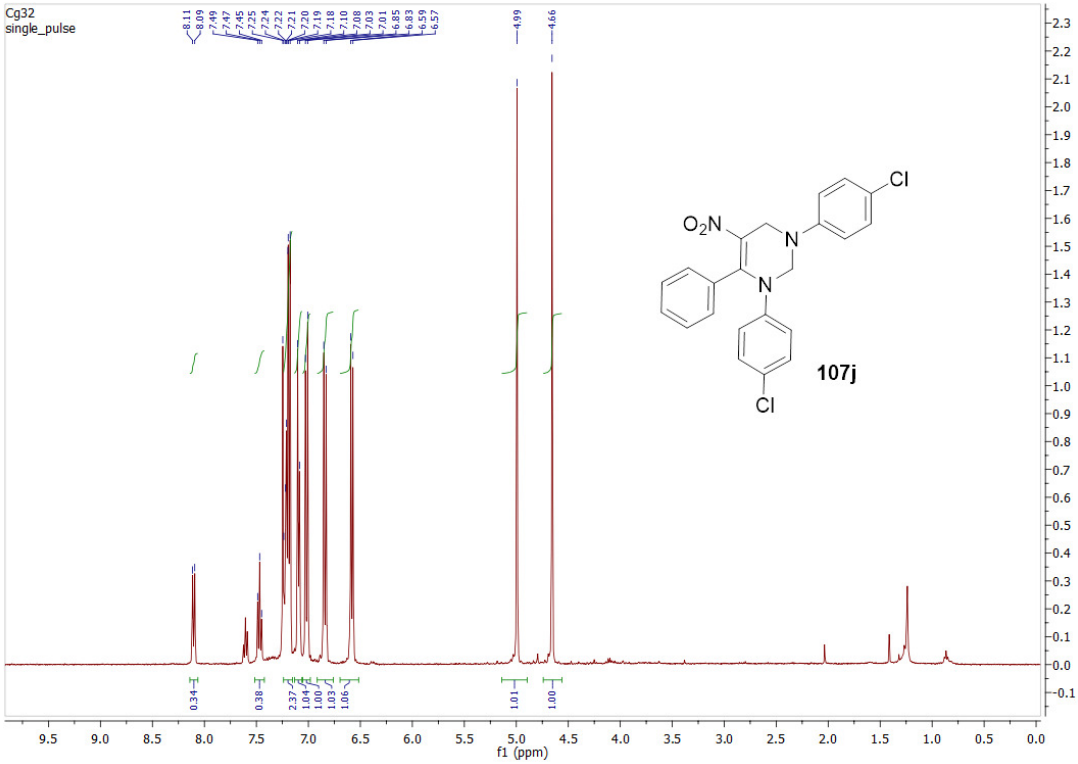


Figure 7.65. ^{1}H-NMR Spectrum of compound **107j**

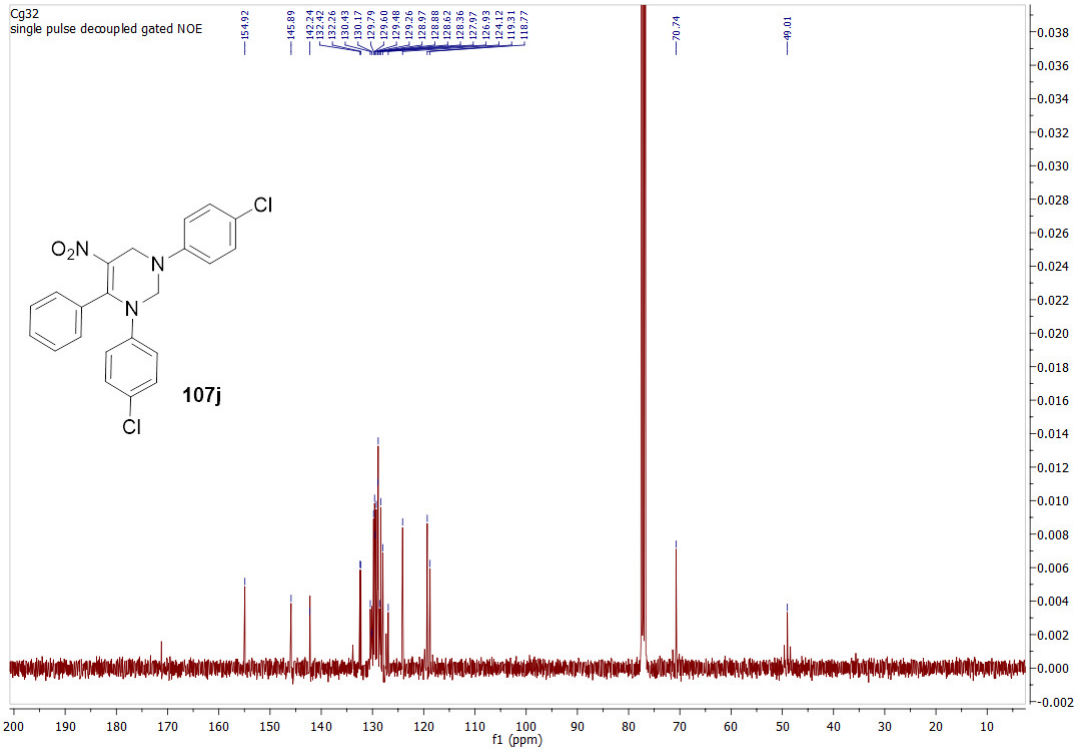


Figure 7.66. ^{13}C-NMR Spectrum of compound **107j**

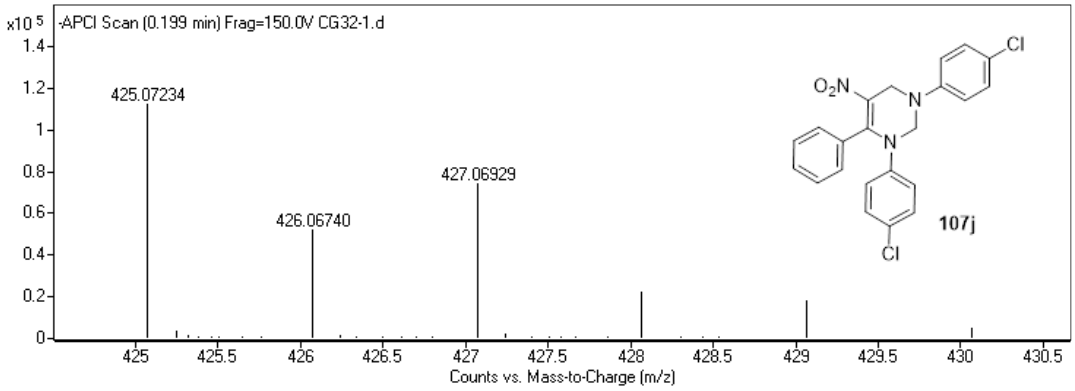


Figure 7.67. HRMS Spectrum of compound **107j**

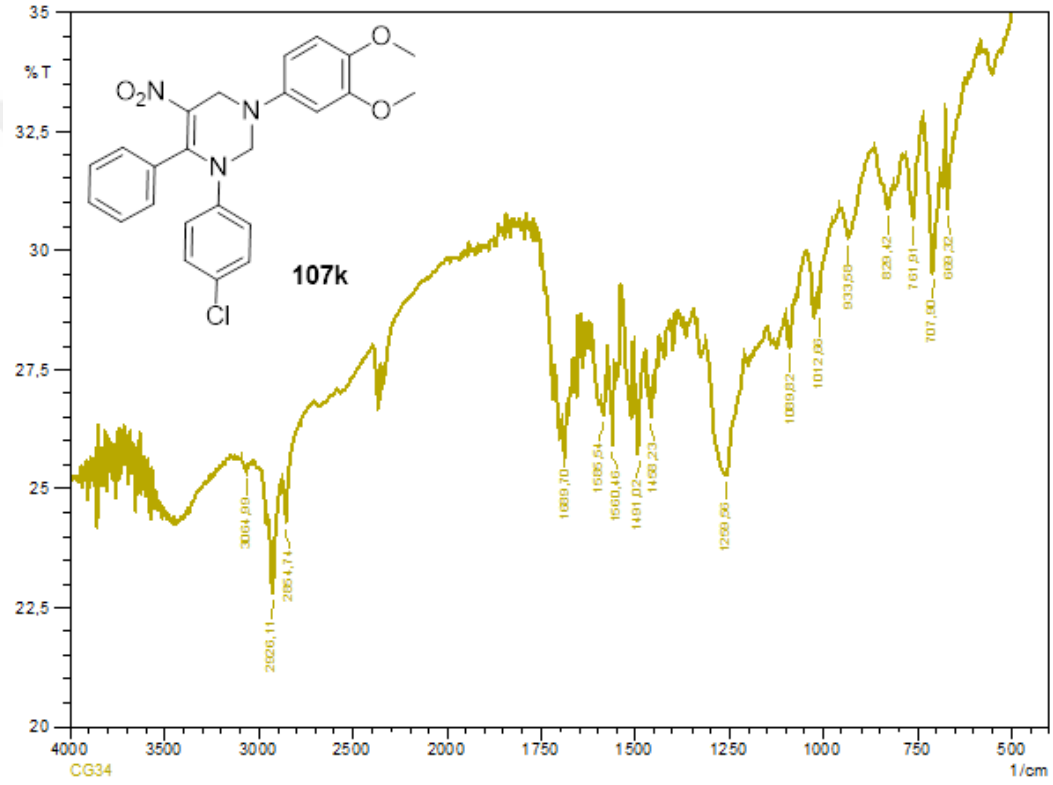


Figure 7.68. IR Spectrum of compound **107k**

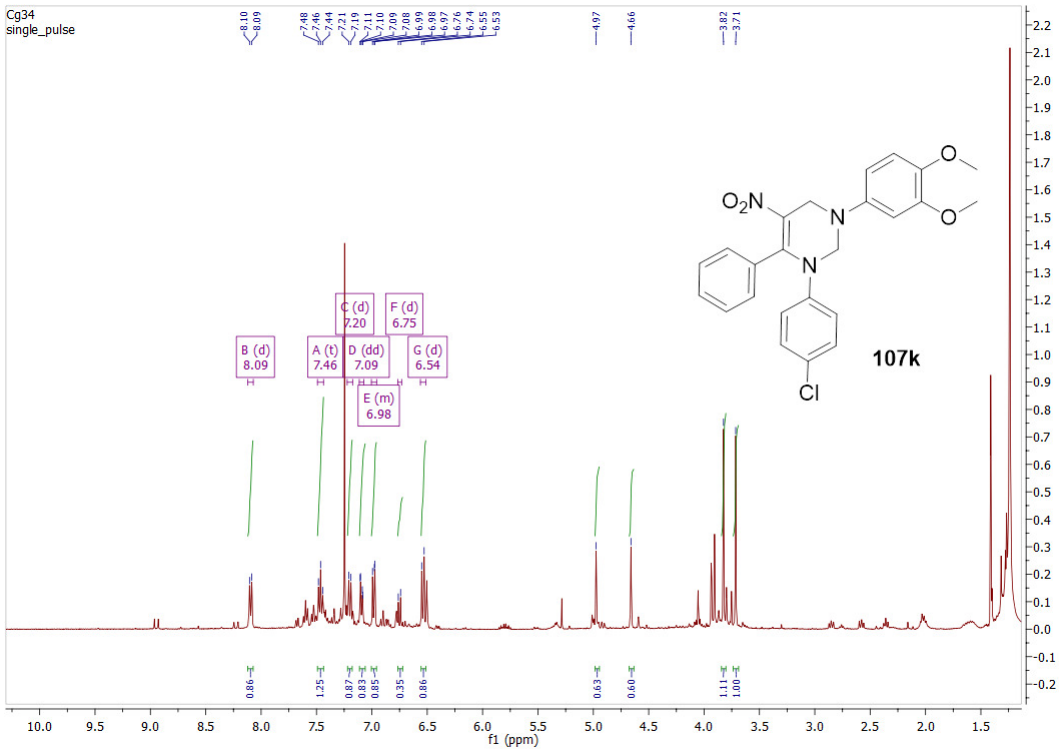


Figure 7.69. ^{1}H-NMR Spectrum of compound **107k**

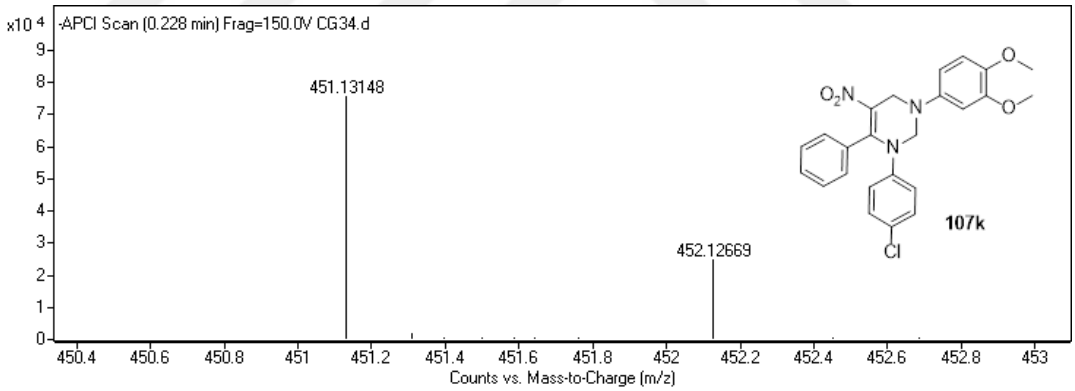


Figure 7.70. HRMS Spectrum of compound **107k**

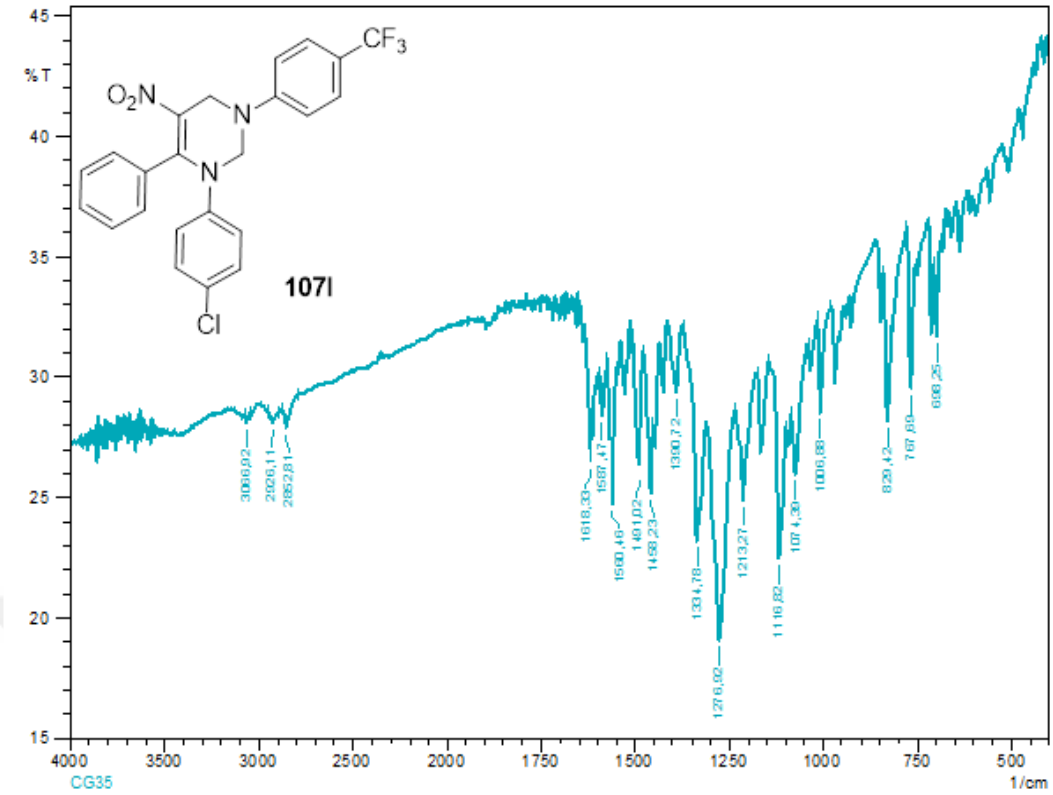


Figure 7.71. IR Spectrum of compound **107l**

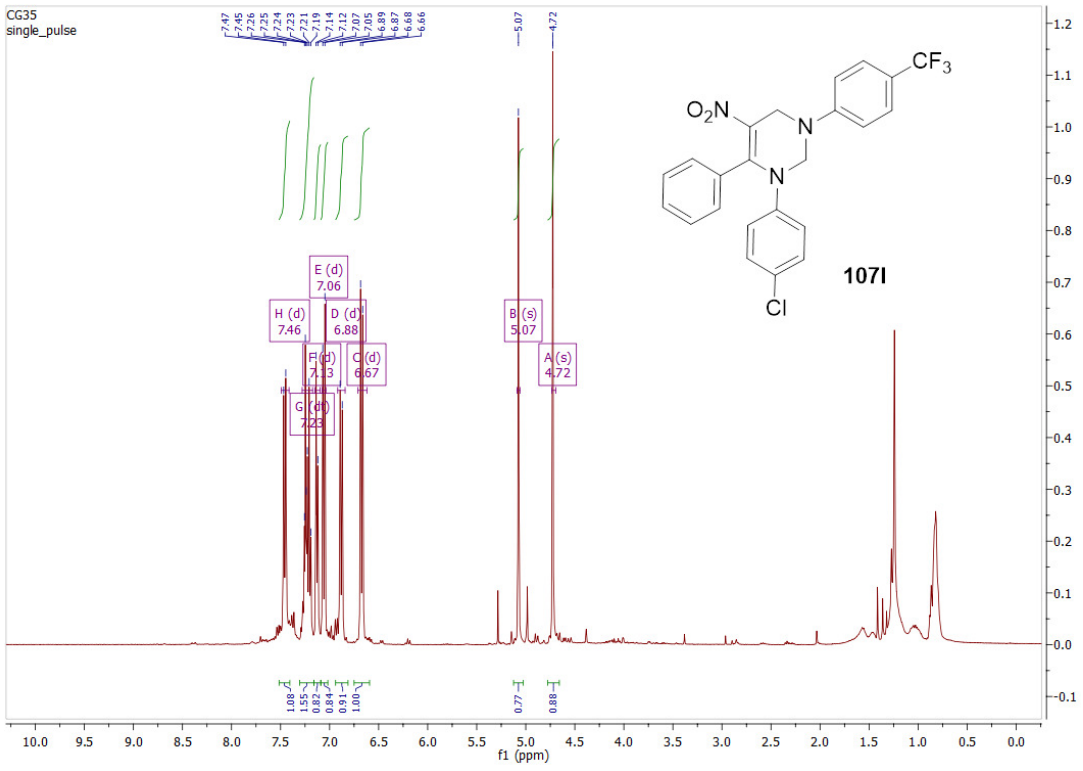


Figure 7.72. ^{1}H-NMR Spectrum of compound **107l**

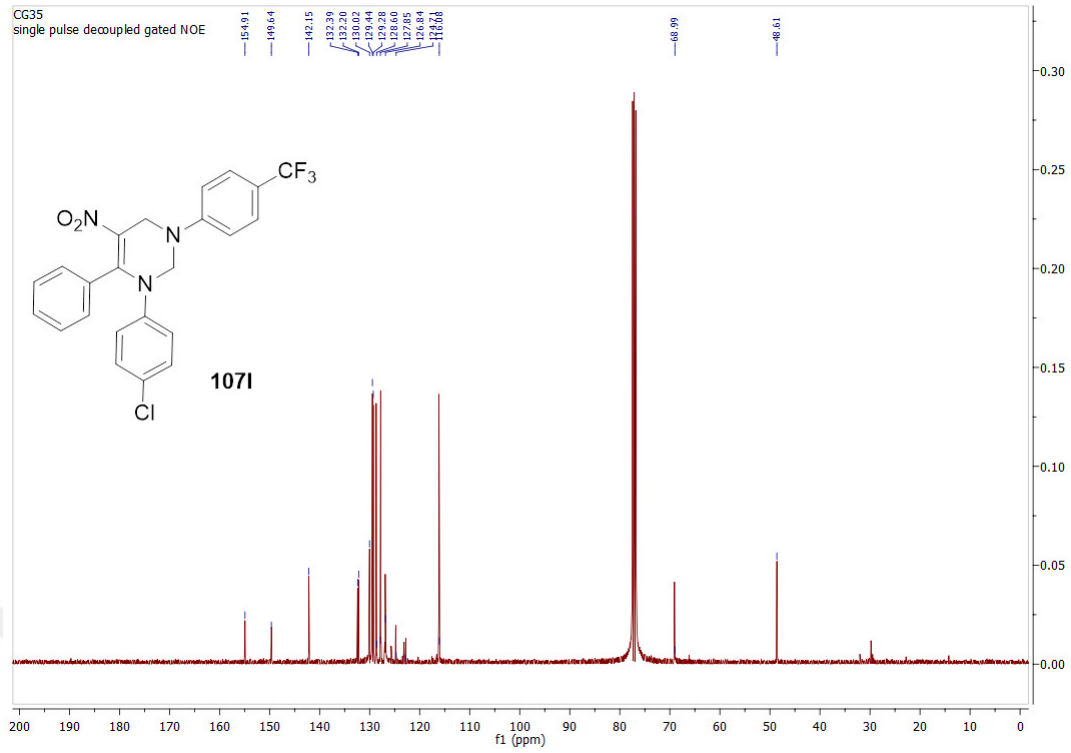


Figure 7.73. ^{13}C-NMR Spectrum of compound **107l**

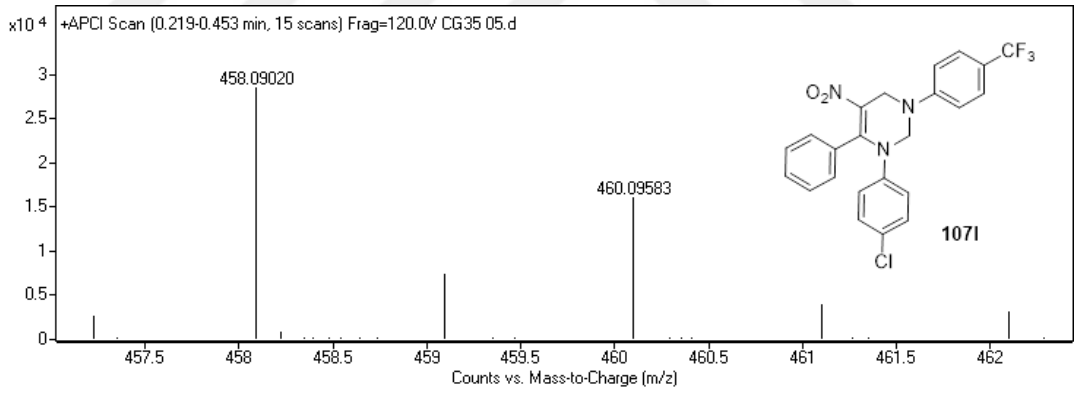


Figure 7.74. HRMS Spectrum of compound **107l**

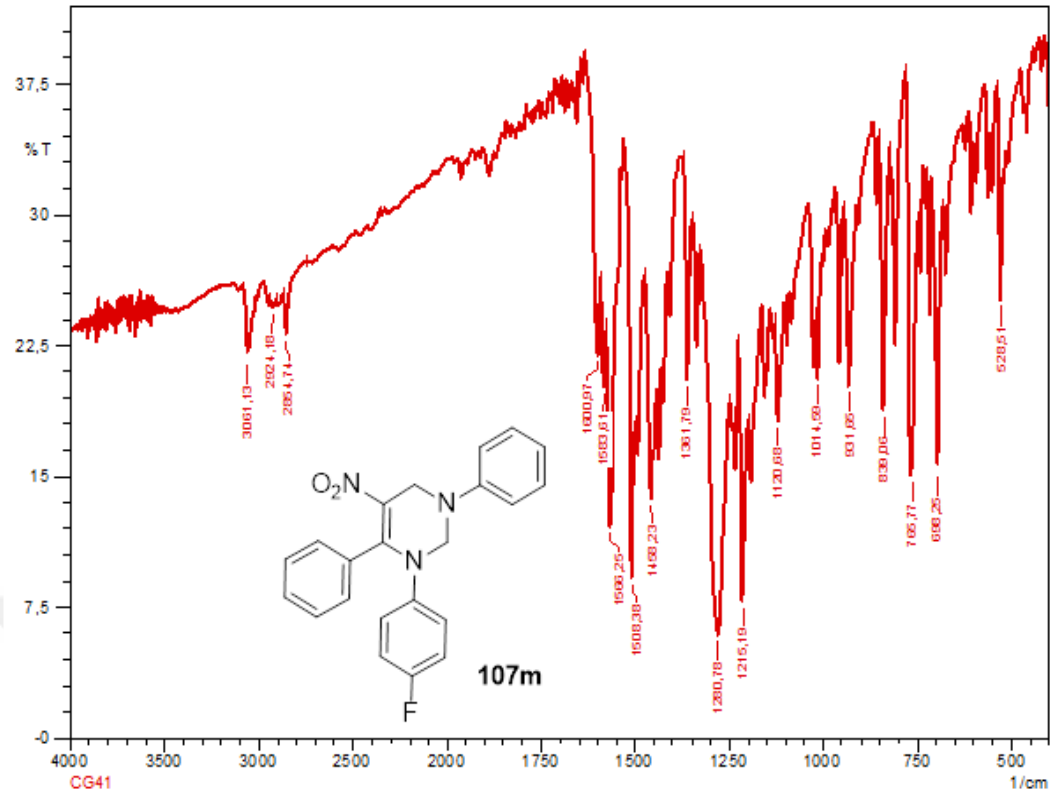


Figure 7.75. IR Spectrum of compound **107m**

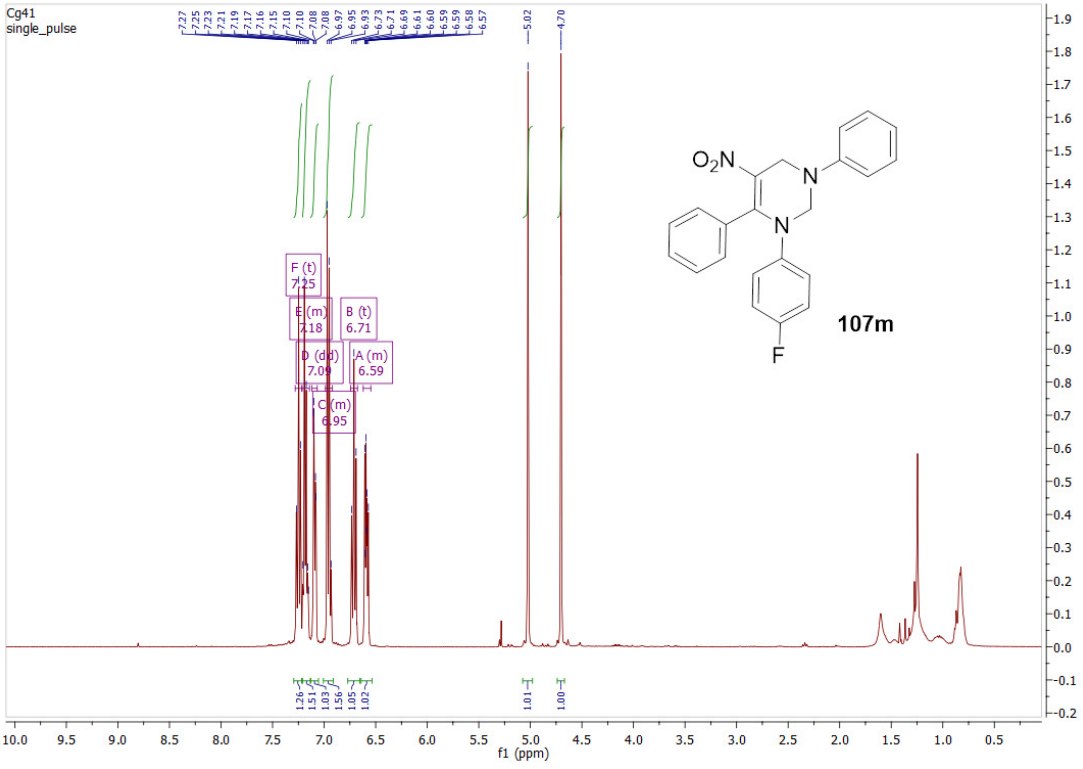


Figure 7.76. ^{1}H-NMR Spectrum of compound **107m**

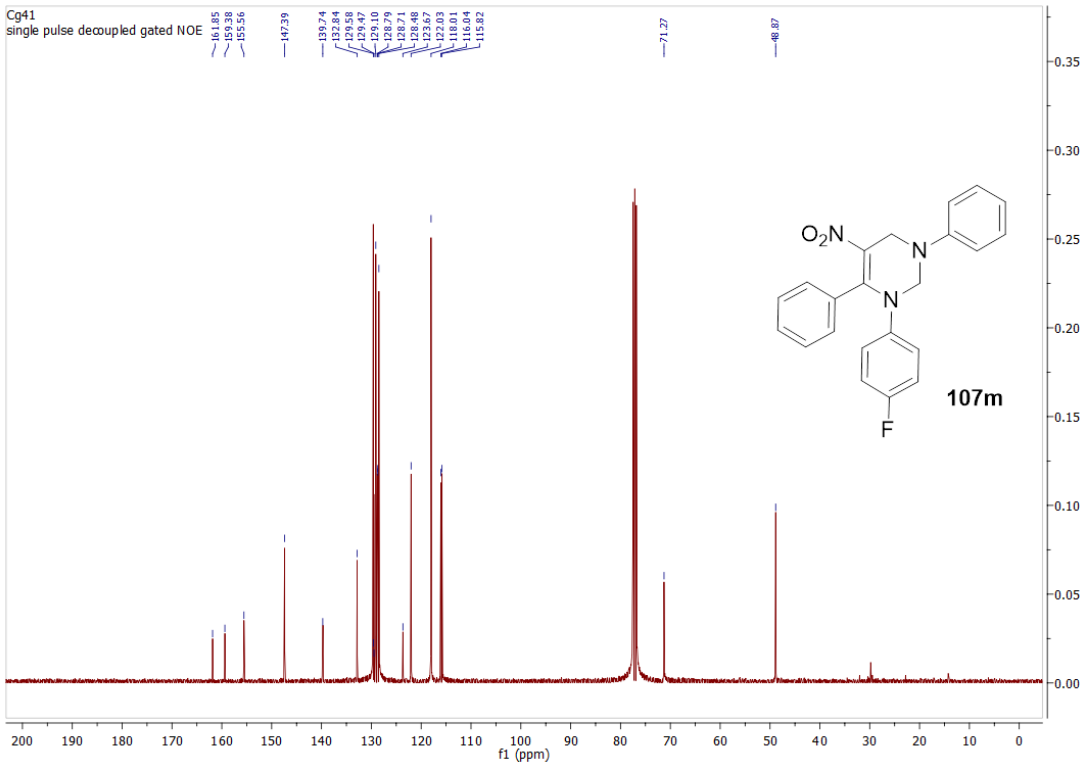


Figure 7.77. ^{13}C-NMR Spectrum of compound **107m**

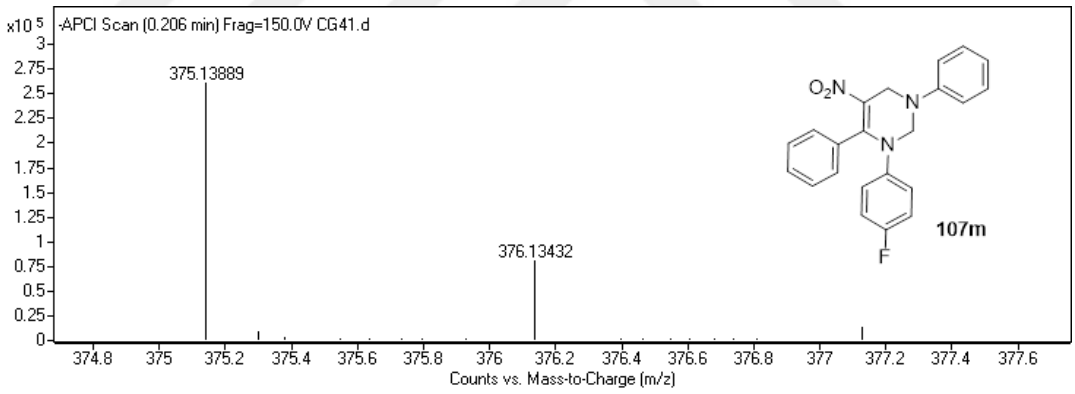


Figure 7.78. HRMS Spectrum of compound **107m**

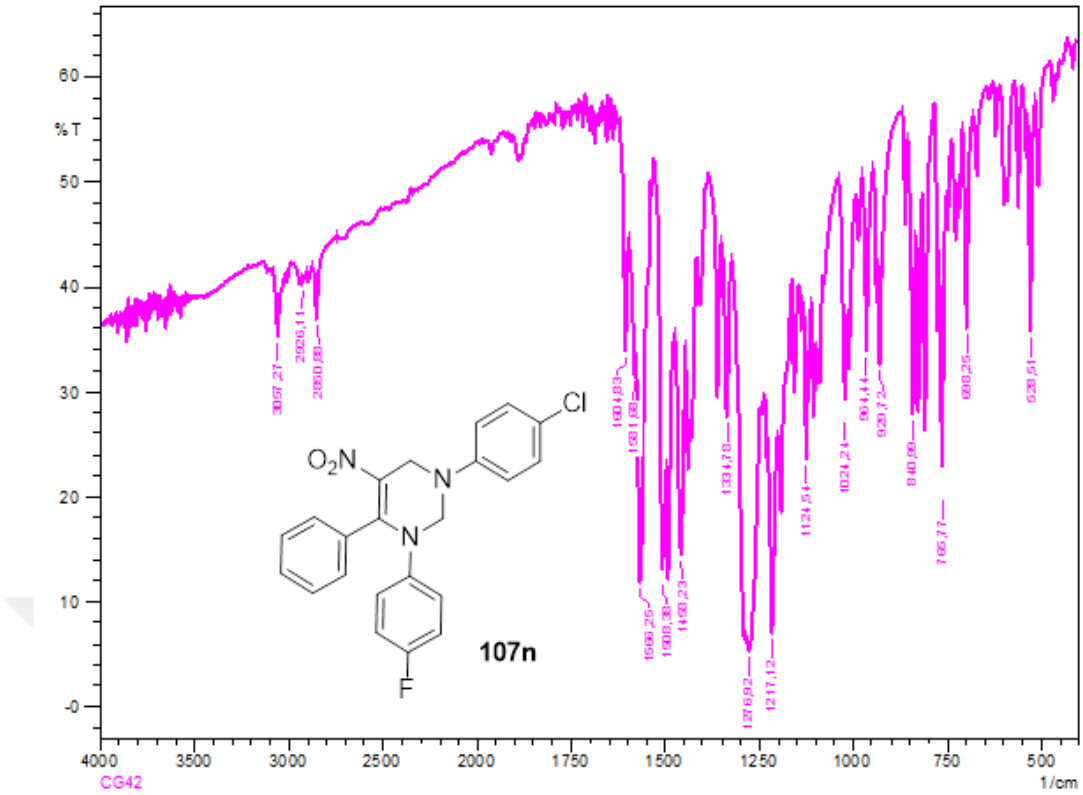


Figure 7.79. IR Spectrum of compound **107n**

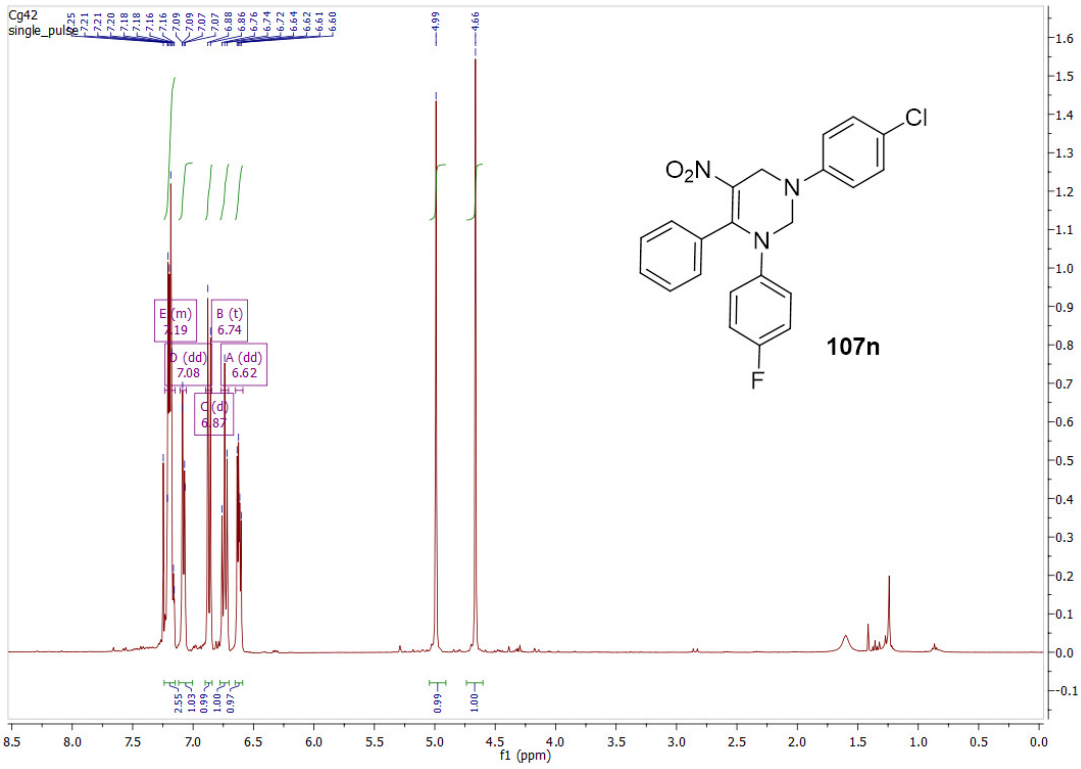


Figure 7.80. ^{1}H-NMR Spectrum of compound **107n**

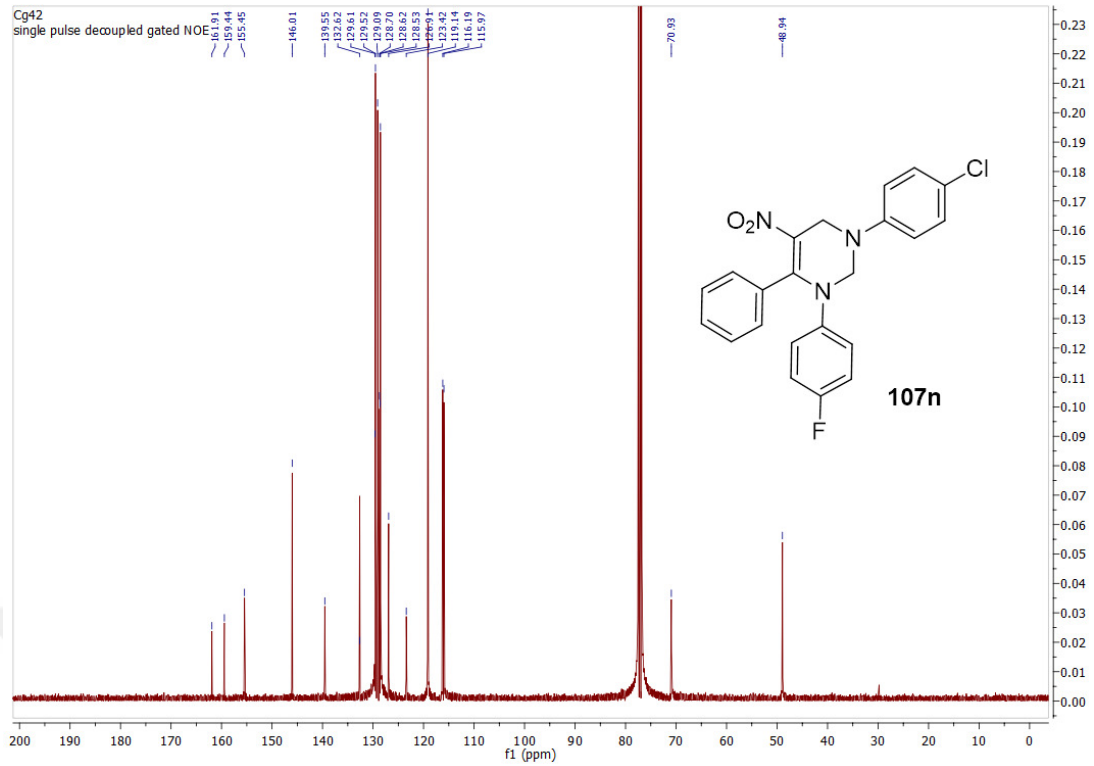


Figure 7.81. ^{13}C-NMR Spectrum of compound **107n**

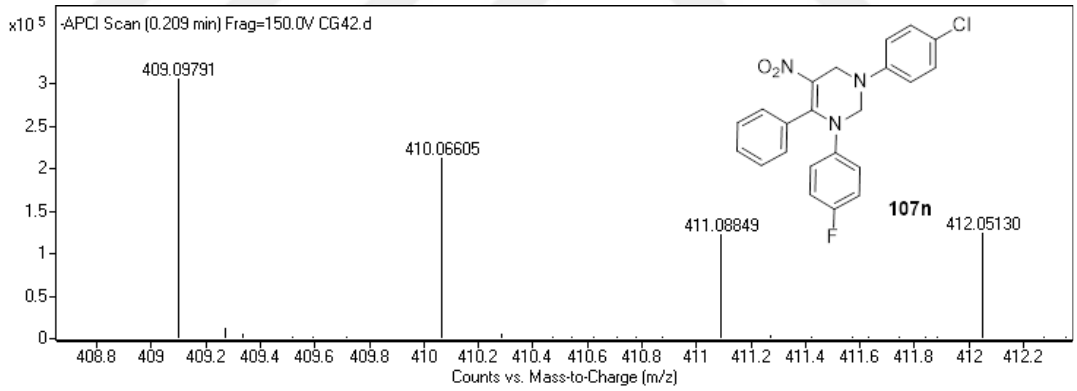


Figure 7.82. HRMS Spectrum of compound **107n**

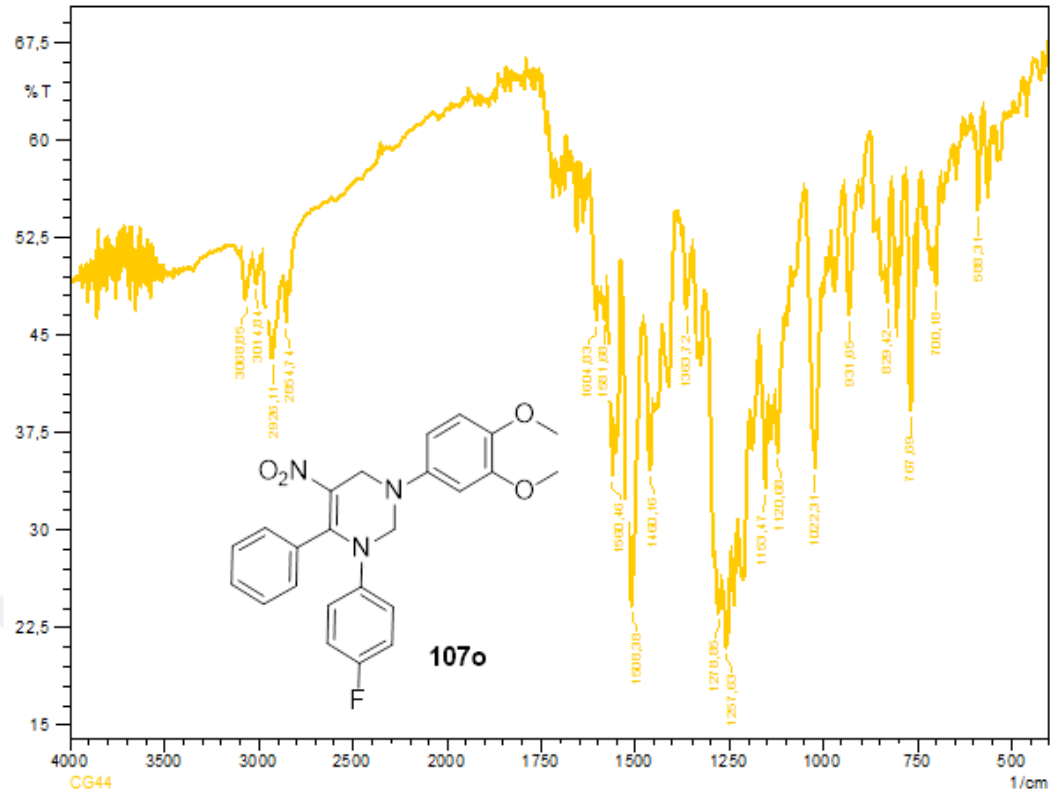


Figure 7.83. IR Spectrum of compound **107o**

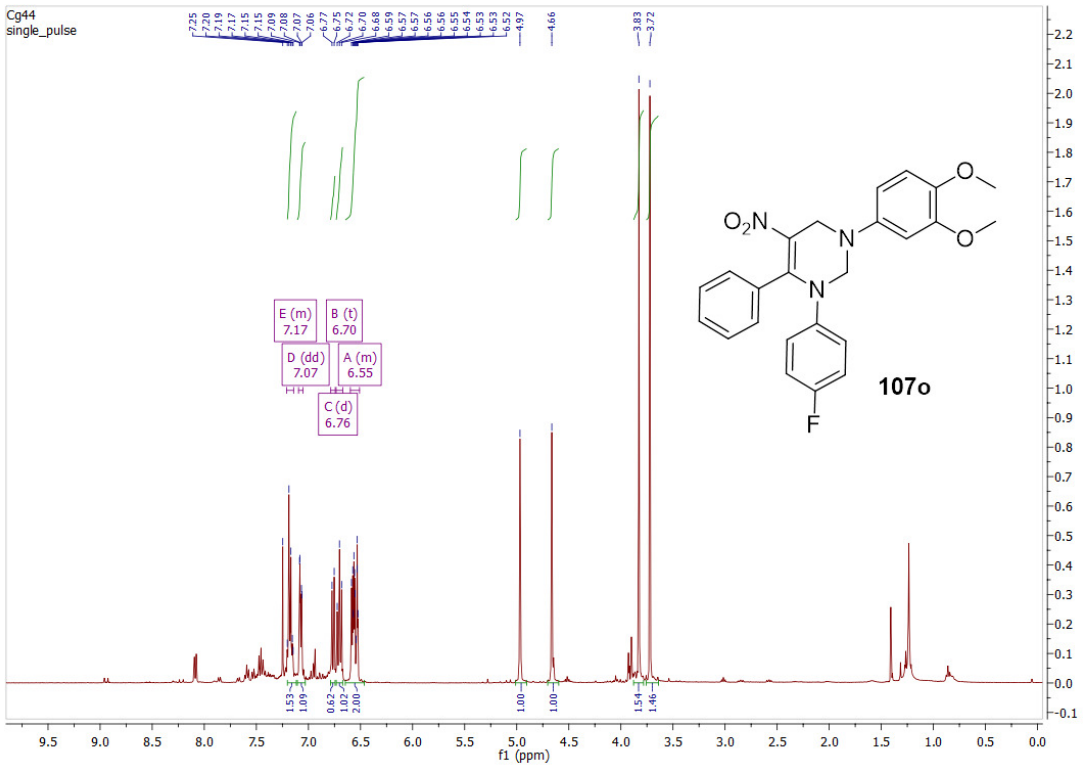


Figure 7.84. ^{1}H-NMR Spectrum of compound **107o**

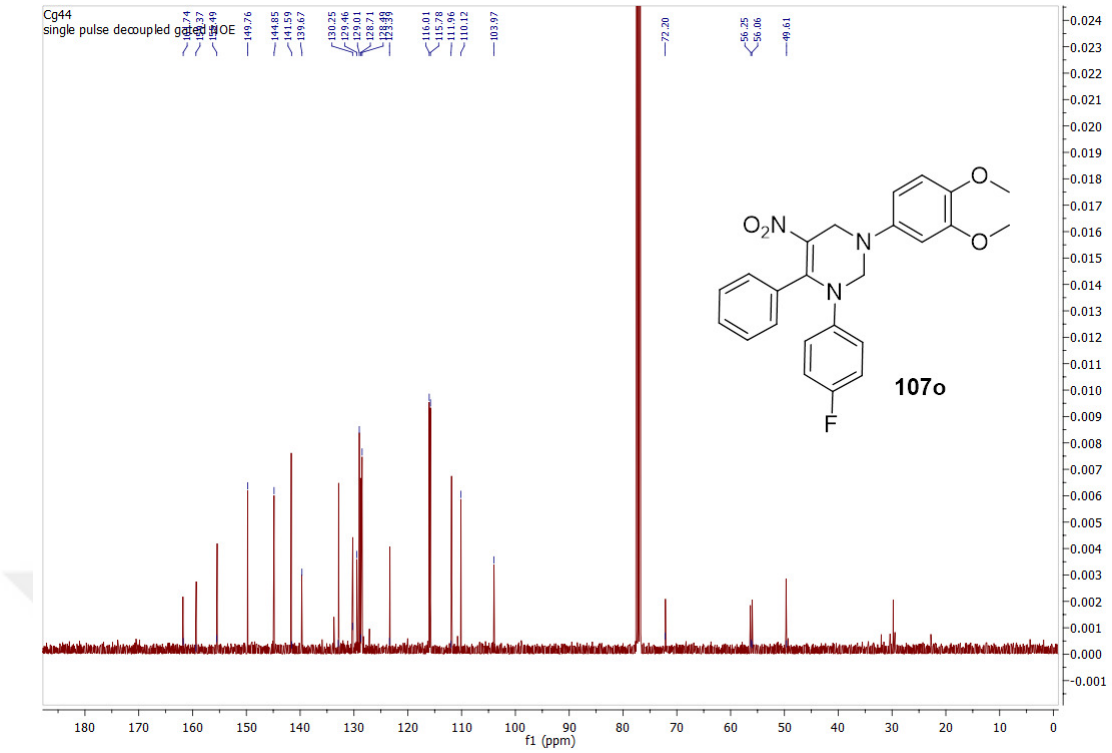


Figure 7.85. ^{13}C-NMR Spectrum of compound **107o**

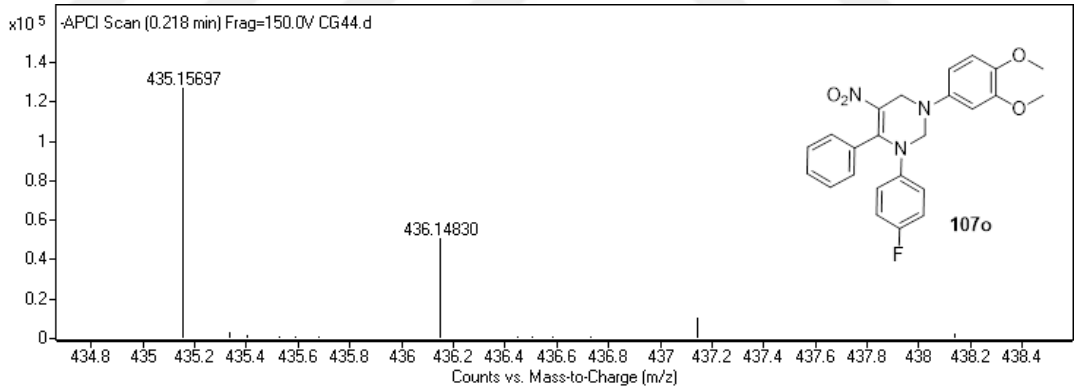


Figure 7.86. HRMS Spectrum of compound **107o**

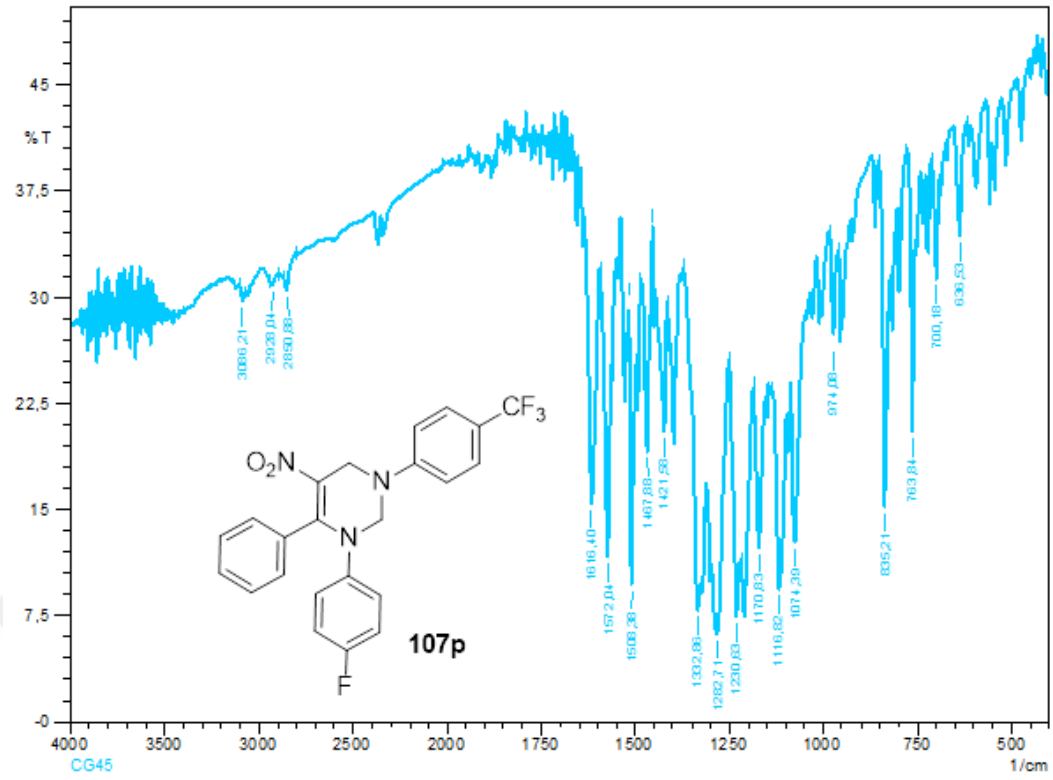


Figure 7.87. IR Spectrum of compound **107p**

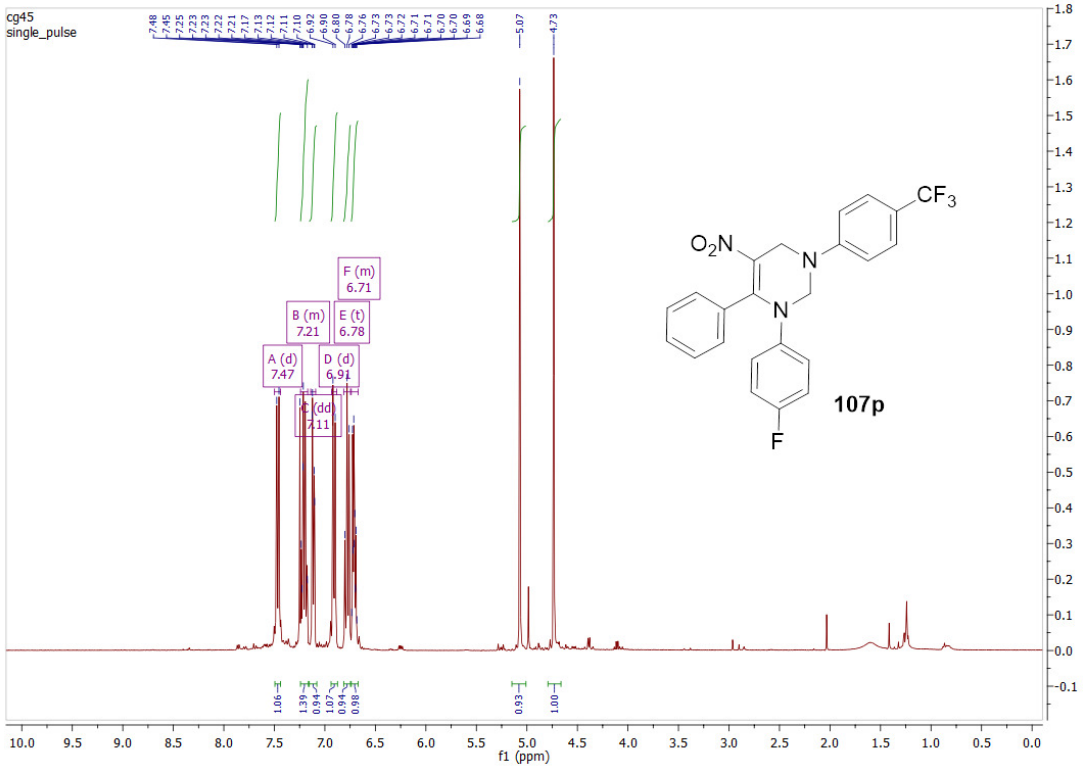


Figure 7.88. ^{1}H-NMR Spectrum of compound **107p**

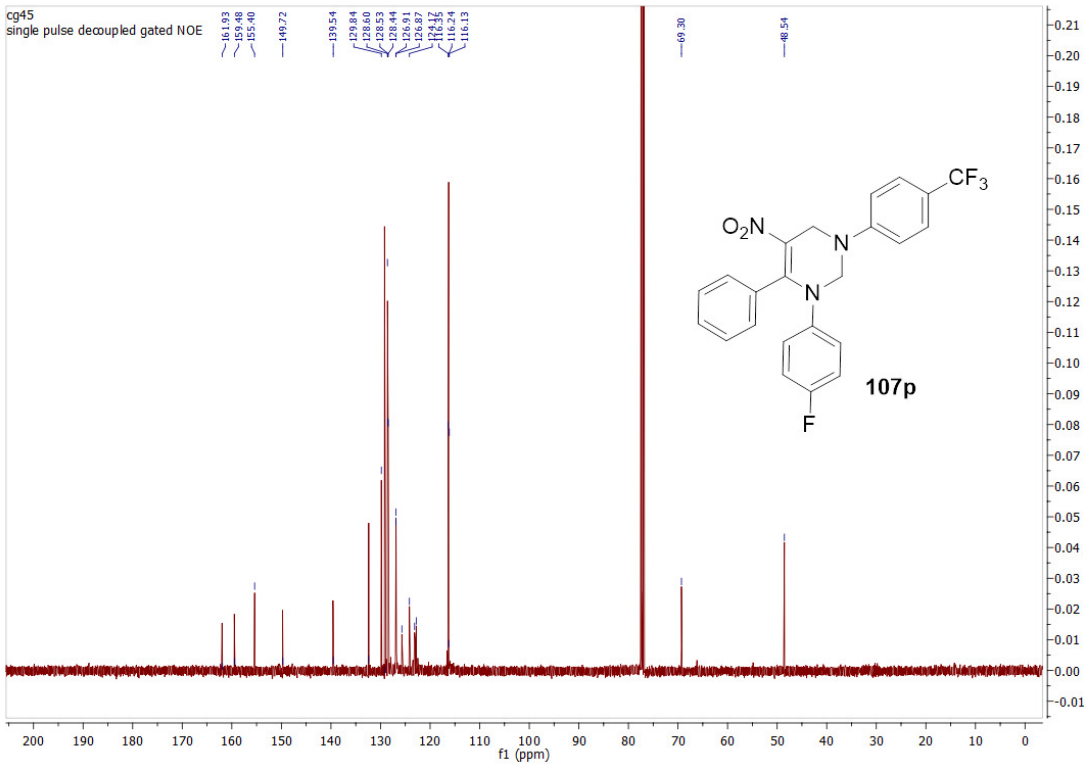


Figure 7.89. ^{13}C-NMR Spectrum of compound **107p**

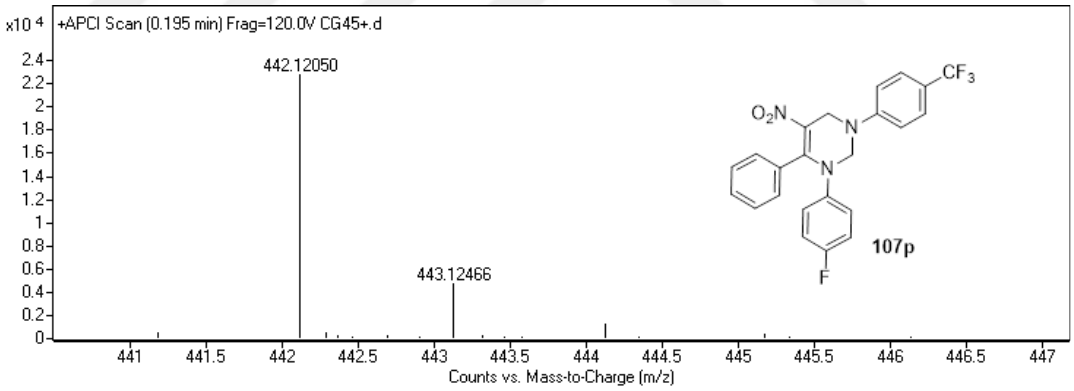


Figure 7.90. HRMS Spectrum of compound **107p**

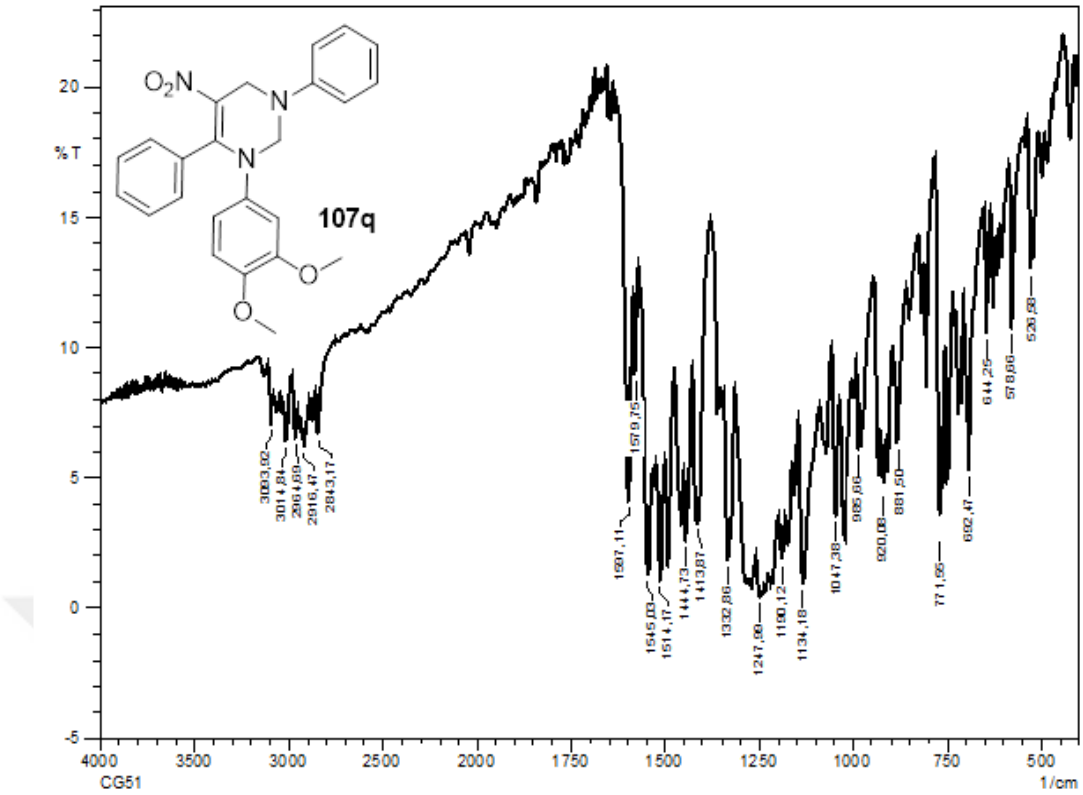


Figure 7.91. IR Spectrum of compound **107q**

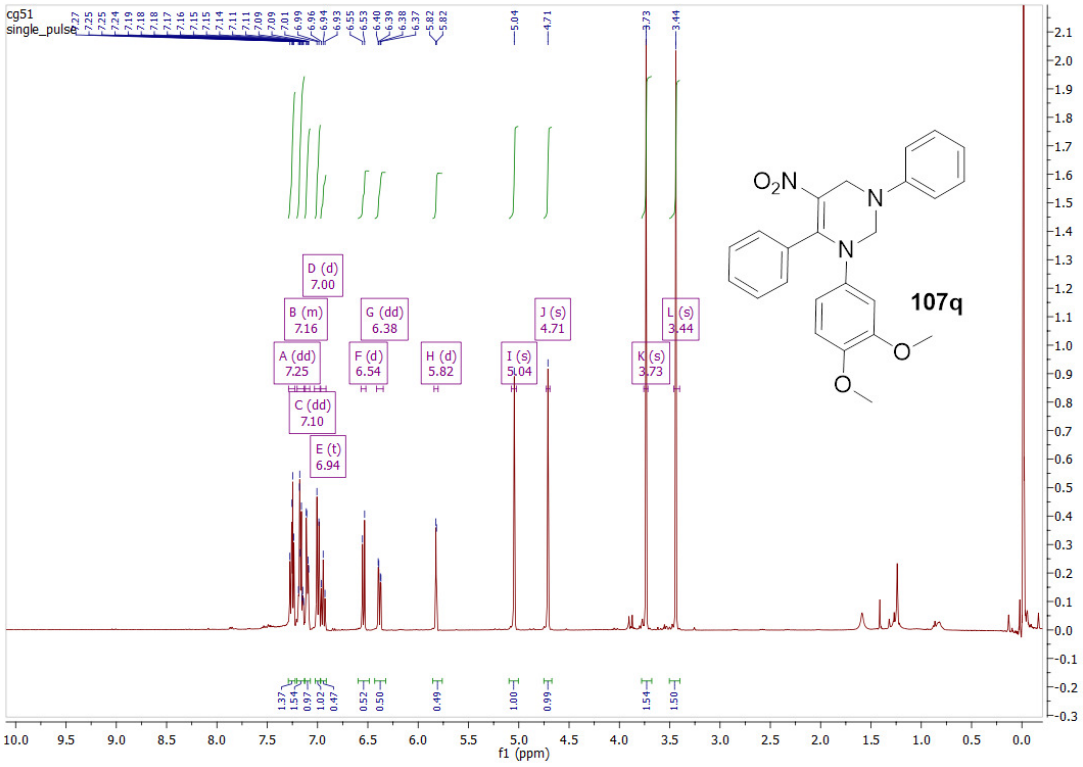


Figure 7.92. ^{1}H-NMR Spectrum of compound **107q**

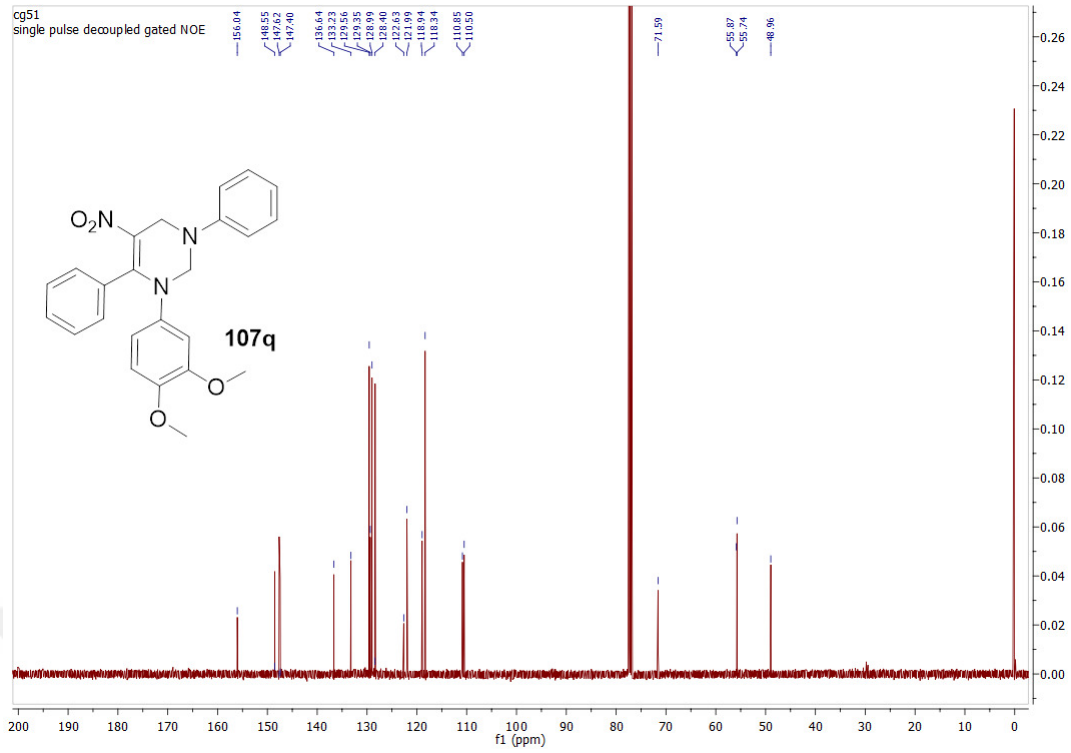


Figure 7.93. ^{13}C-NMR Spectrum of compound **107q**

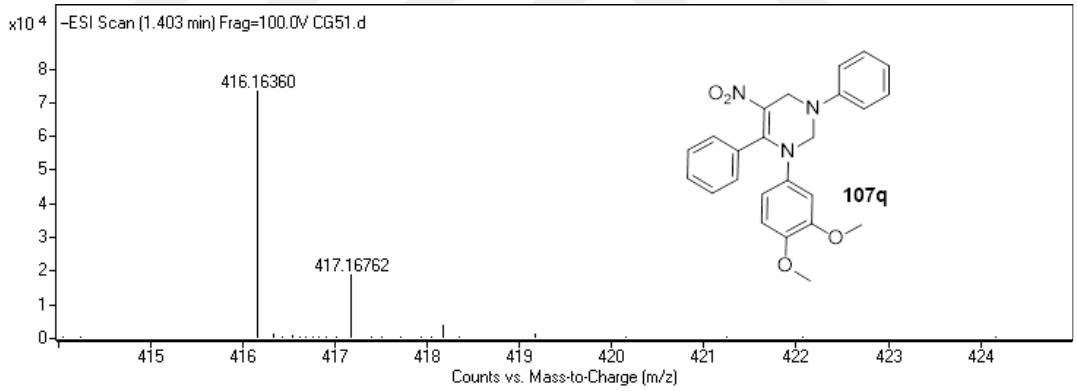


Figure 7.94. HRMS Spectrum of compound **107q**

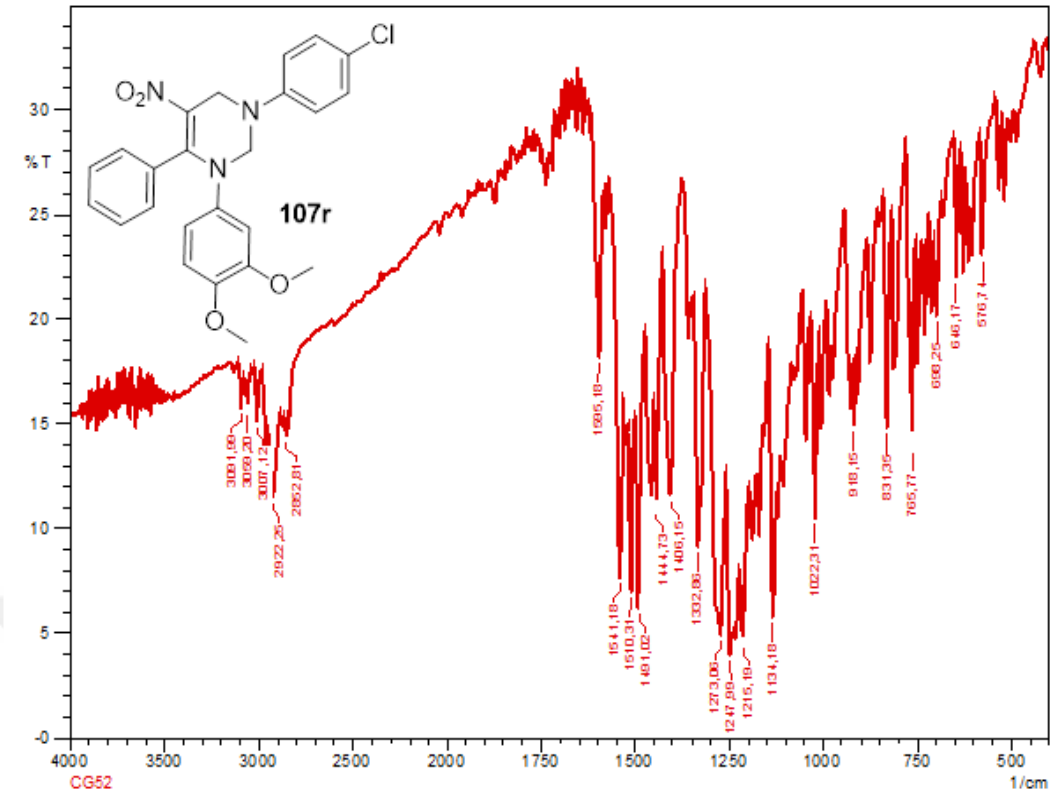


Figure 7.95. IR Spectrum of compound **107r**

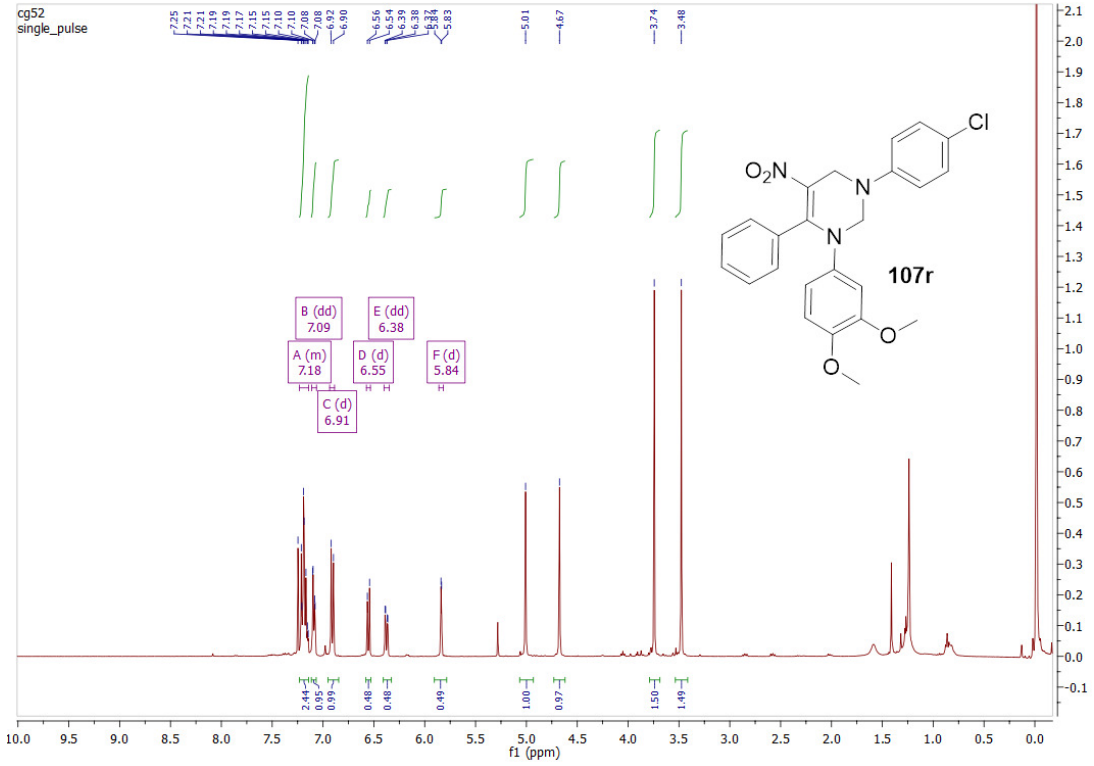


Figure 7.96. ^{1}H-NMR Spectrum of compound **107r**

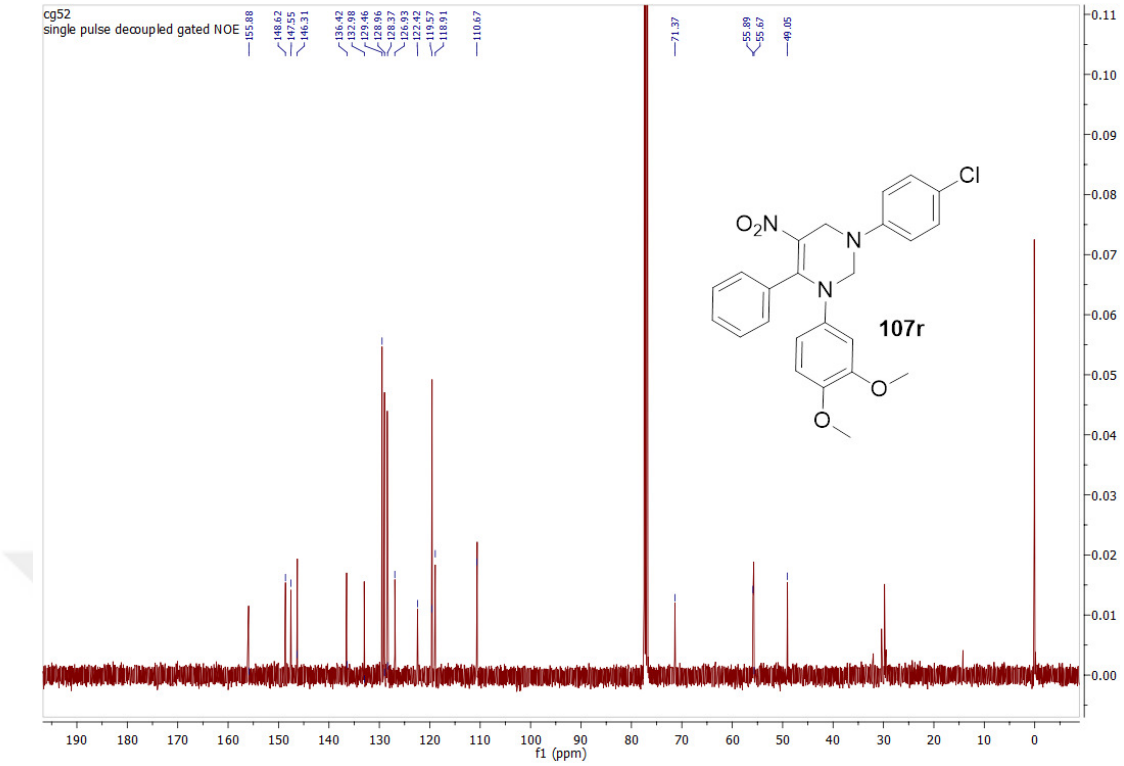


Figure 7.97. ^{13}C-NMR Spectrum of compound **107r**

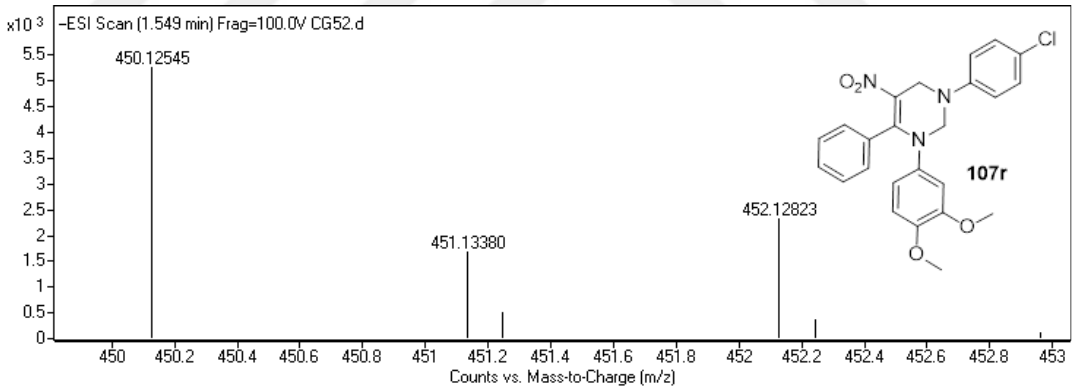


Figure 7.98. HRMS Spectrum of compound **107r**

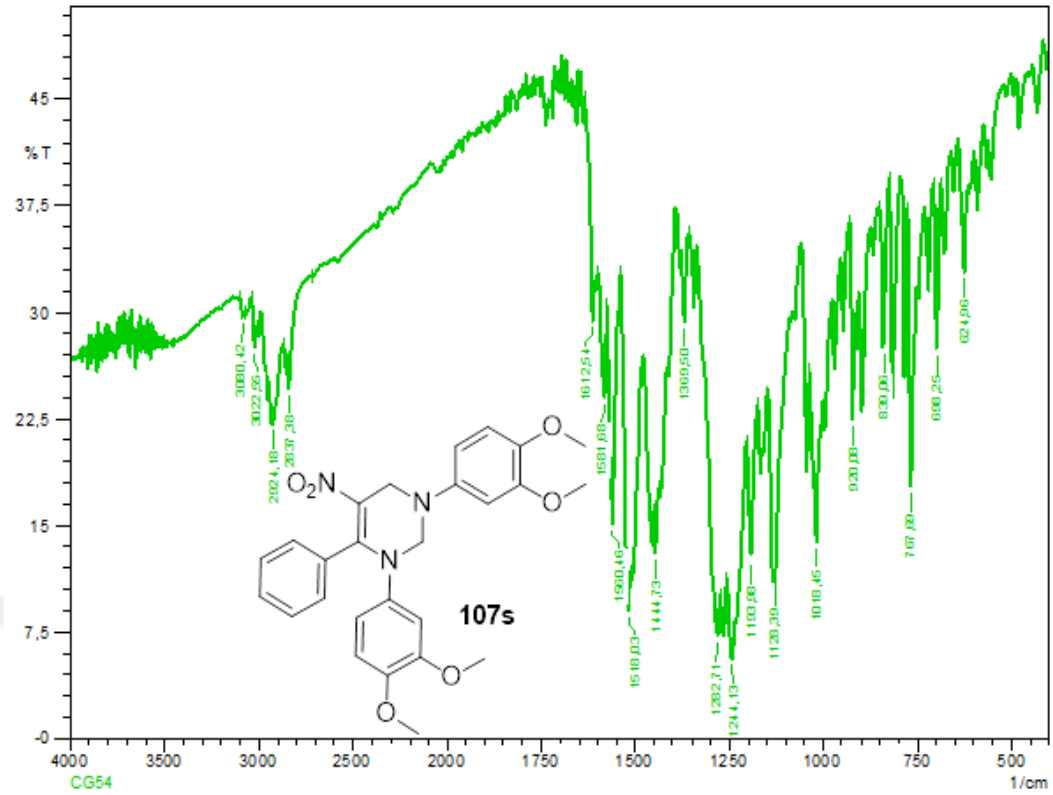


Figure 7.99. IR Spectrum of compound **107s**

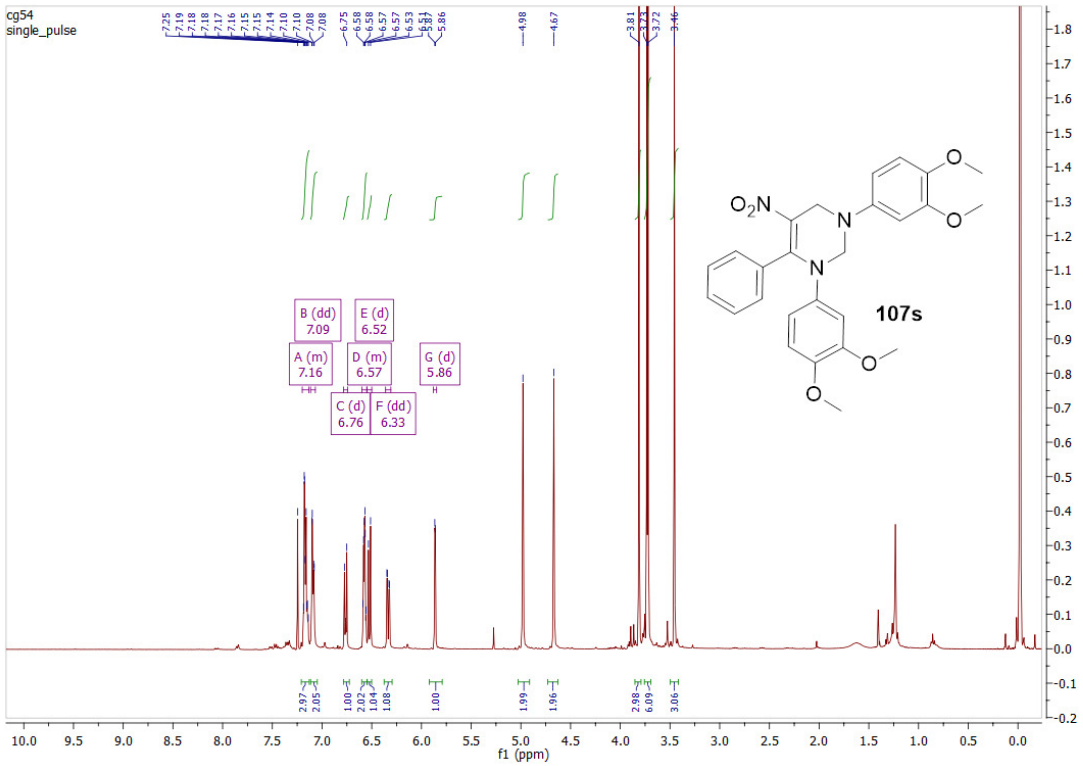


Figure 7.100. [1]H-NMR Spectrum of compound **107s**

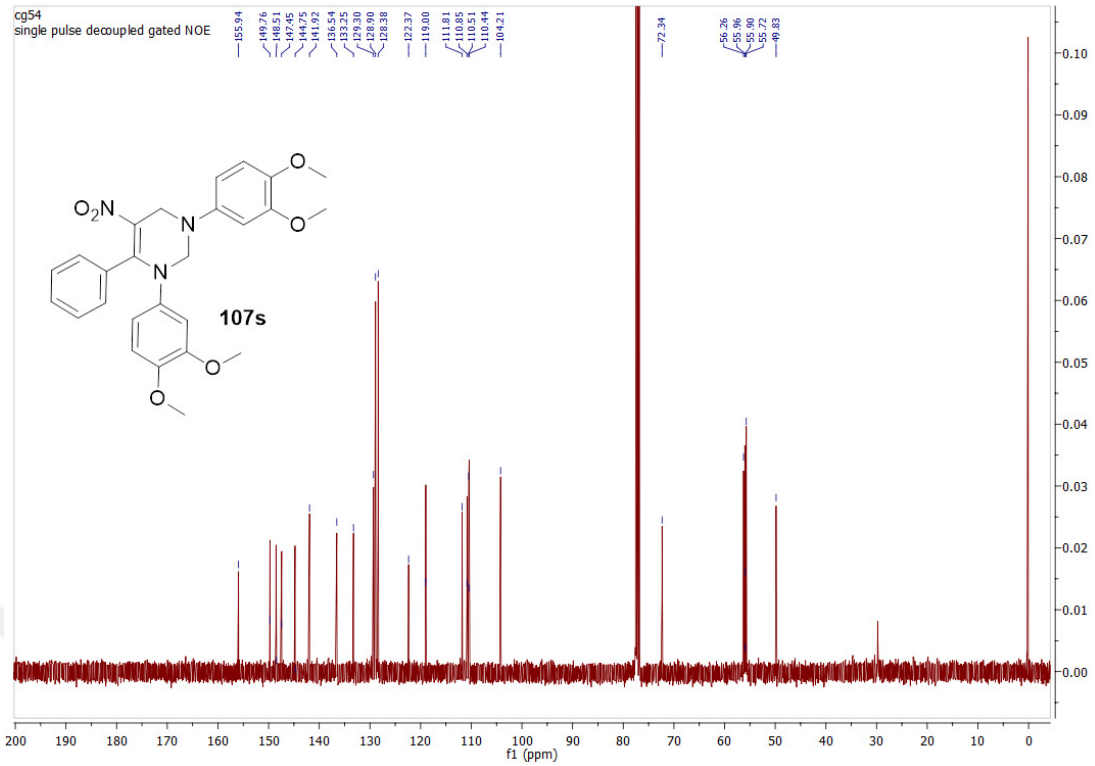


Figure 7.101. ^{13}C-NMR Spectrum of compound **107s**

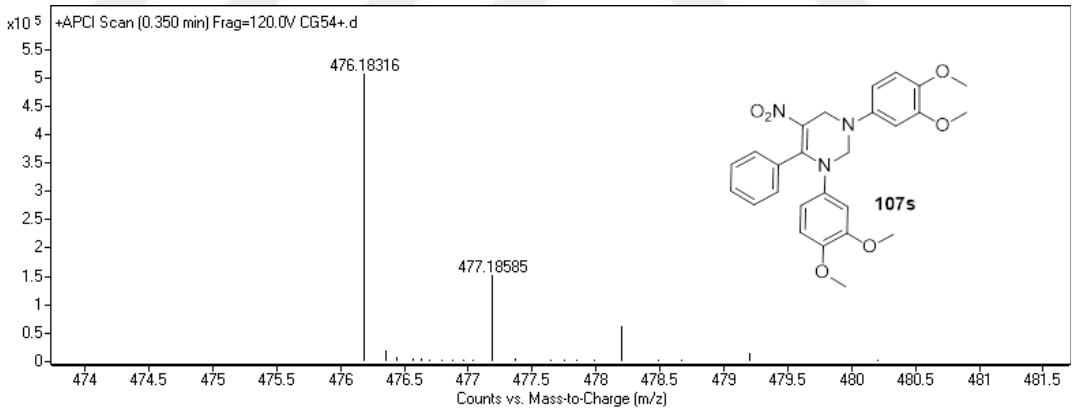


Figure 7.102. HRMS Spectrum of compound **107s**

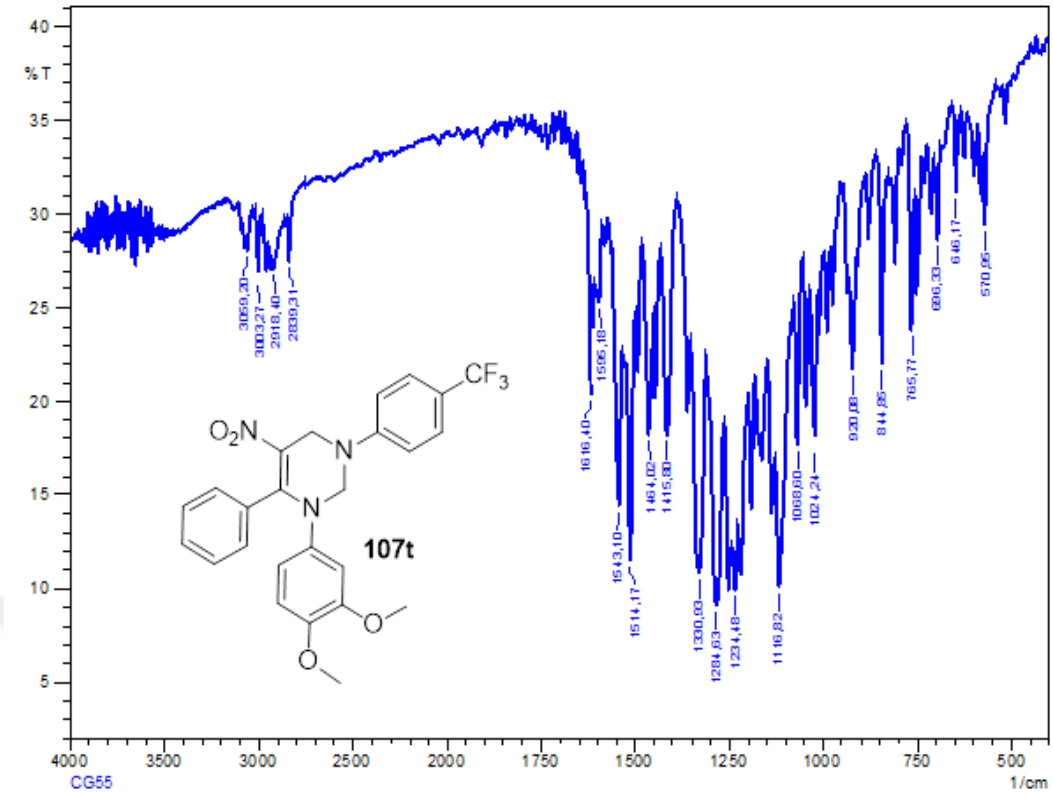


Figure 7.103. IR Spectrum of compound **107t**

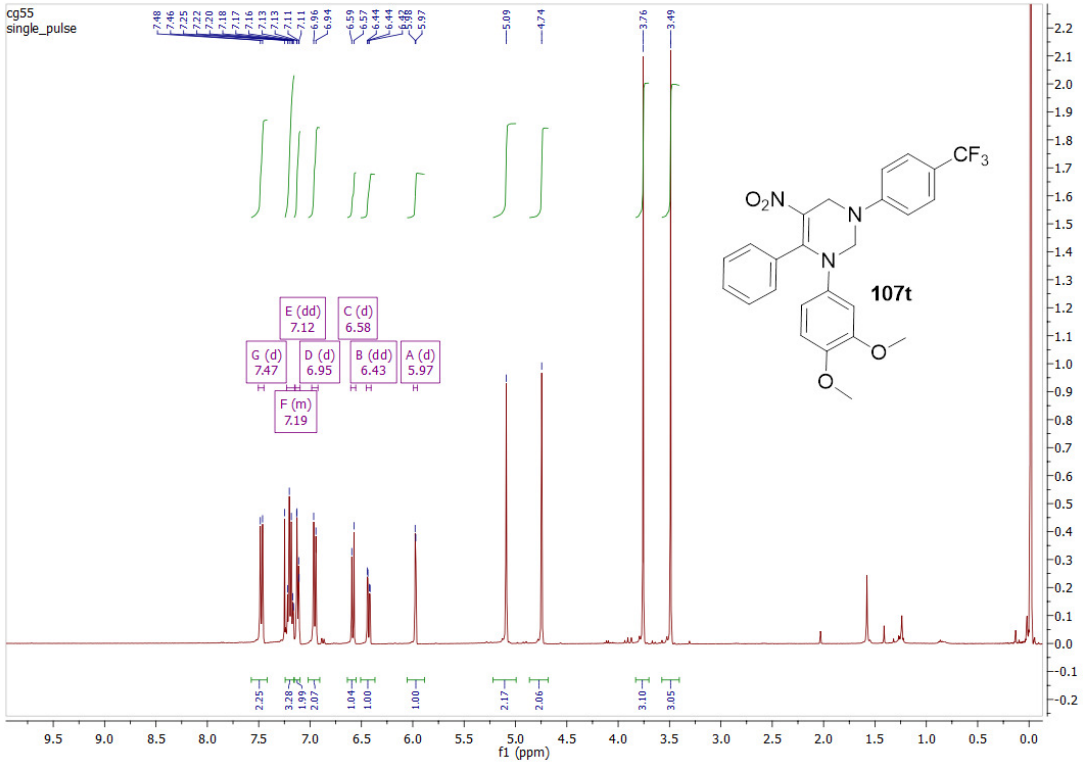


Figure 7.104. ^{1}H-NMR Spectrum of compound **107t**

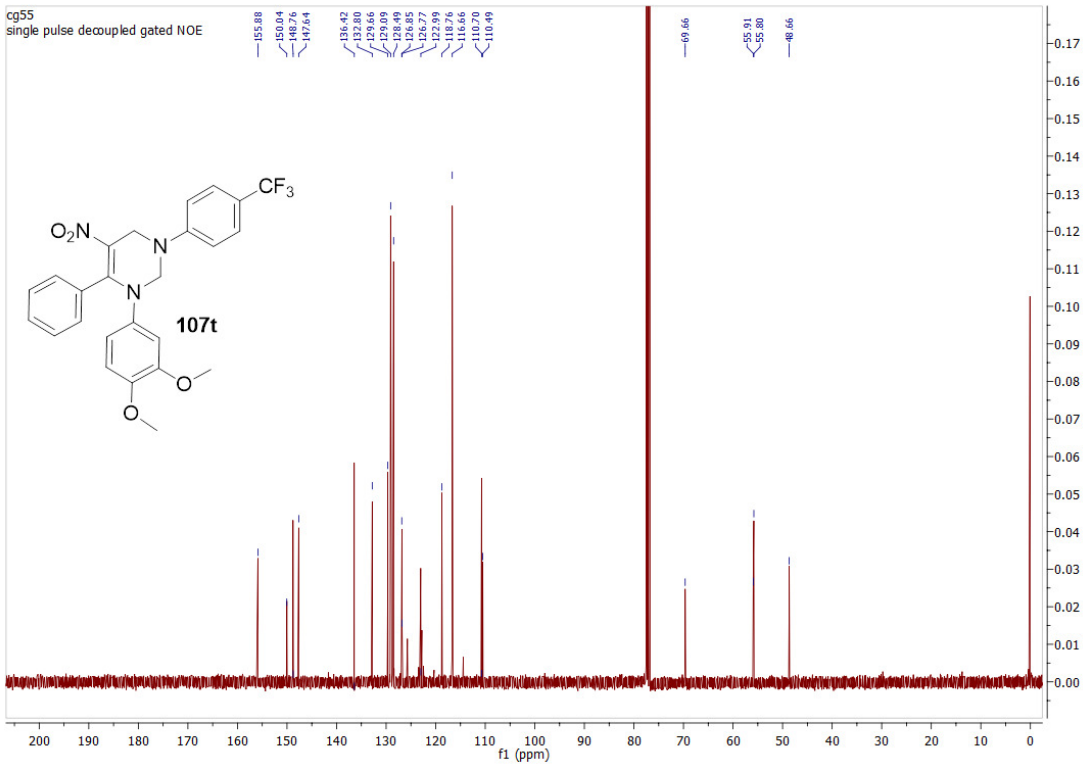


Figure 7.105. ^{13}C-NMR Spectrum of compound **107t**

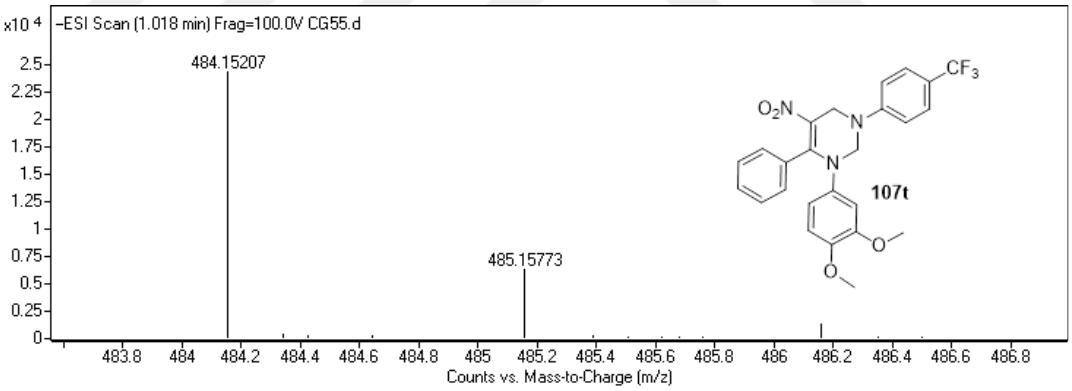


Figure 7.106. HRMS Spectrum of compound **107t**

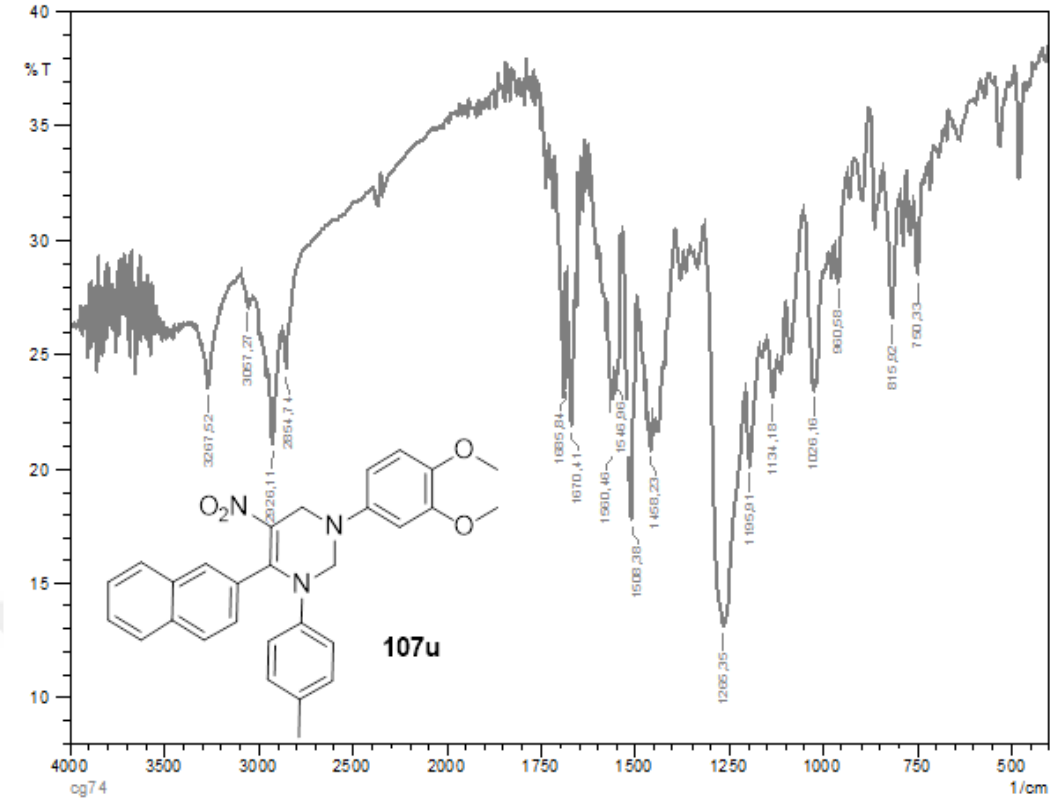


Figure 7.107. IR Spectrum of compound **107u**

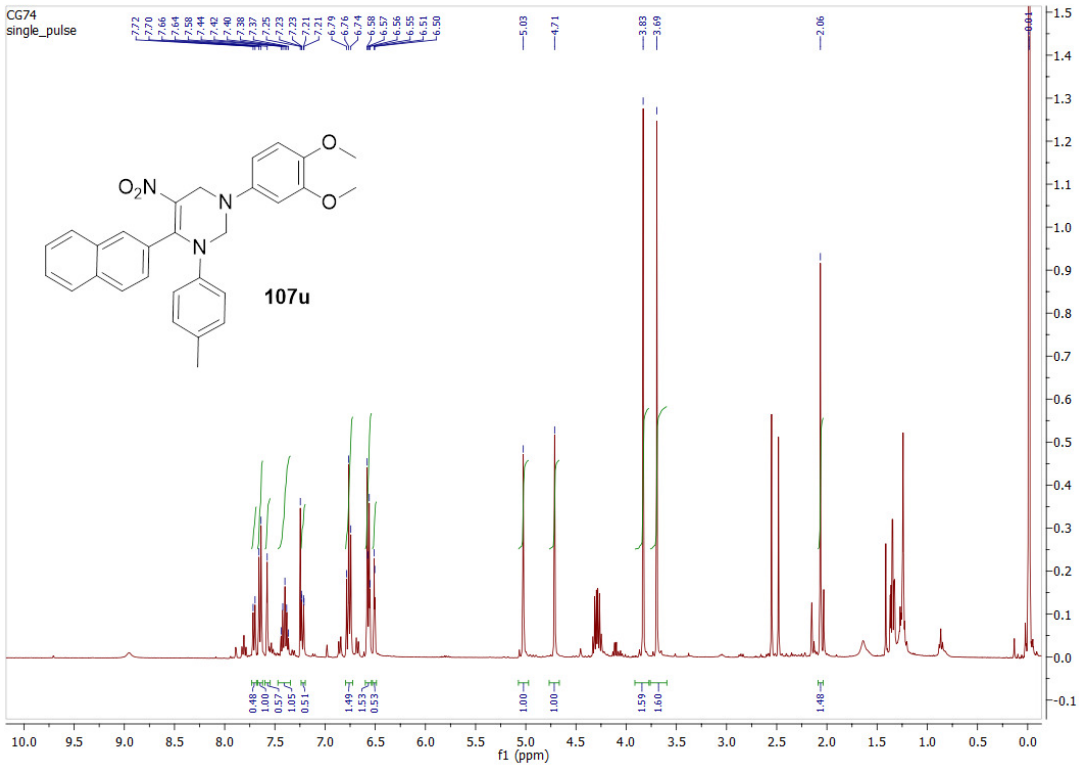


Figure 7.108. ^{1}H-NMR Spectrum of compound **107u**

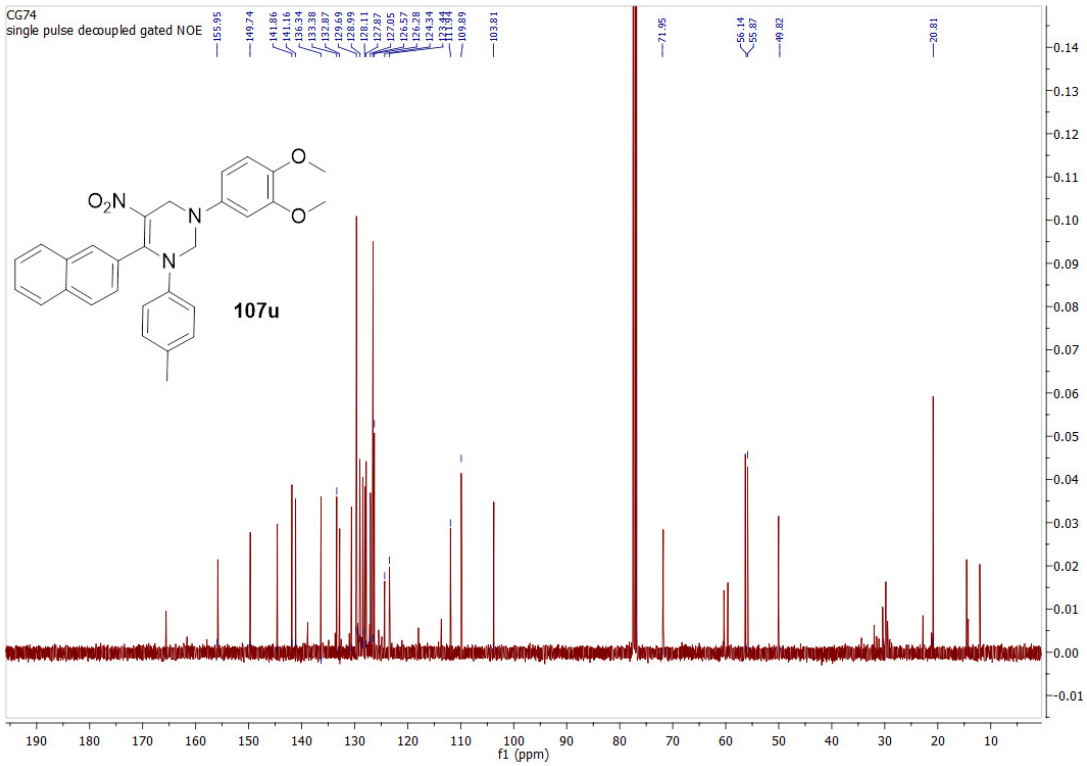


Figure 7.109. ^{13}C-NMR Spectrum of compound **107u**

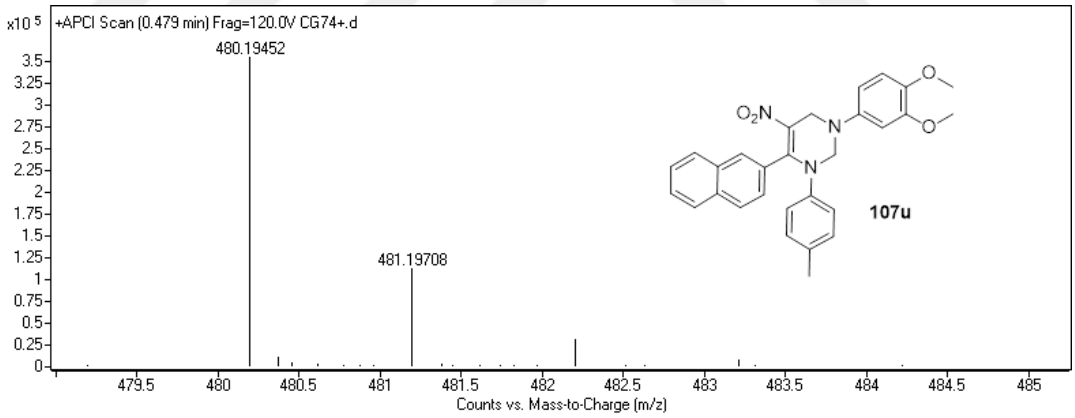


Figure 7.110. HRMS Spectrum of compound **107u**

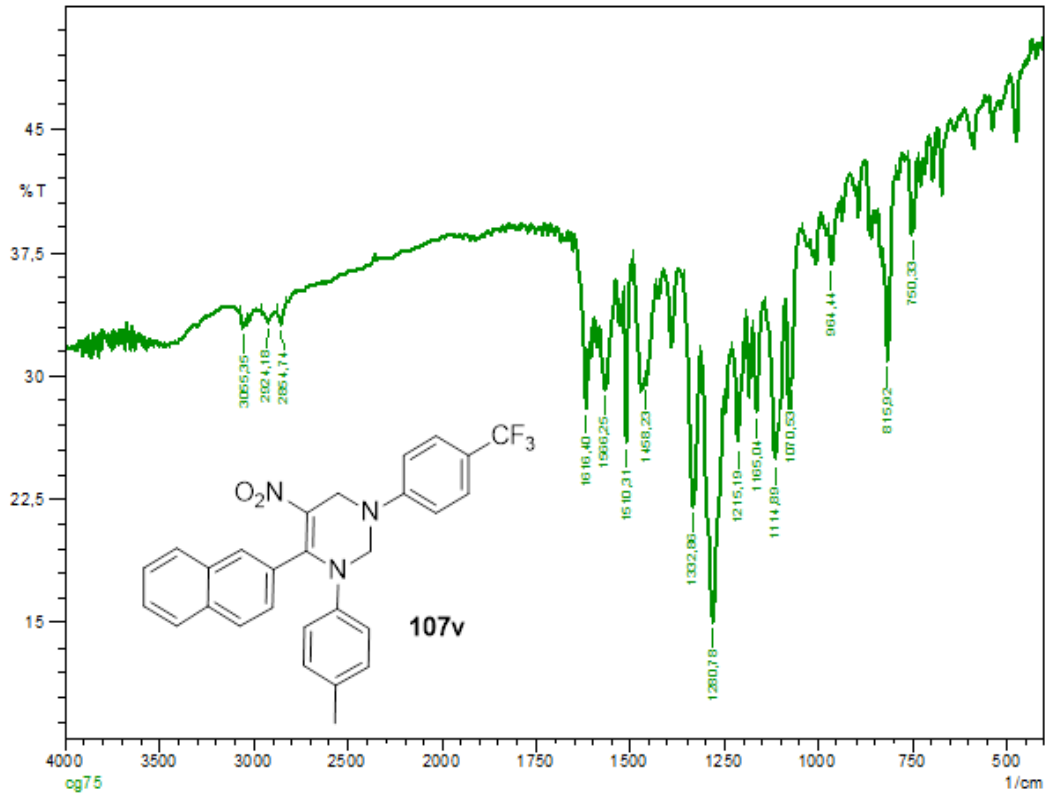


Figure 7.111. IR Spectrum of compound **107v**

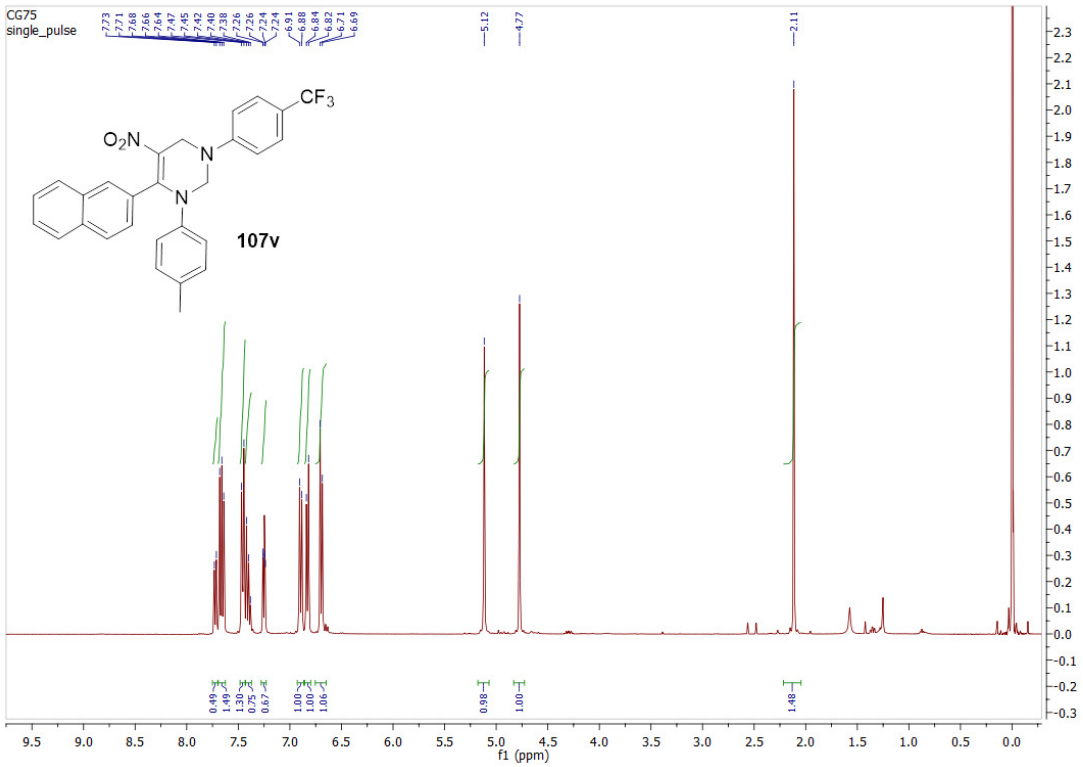


Figure 7.112. [1]H-NMR Spectrum of compound **107v**

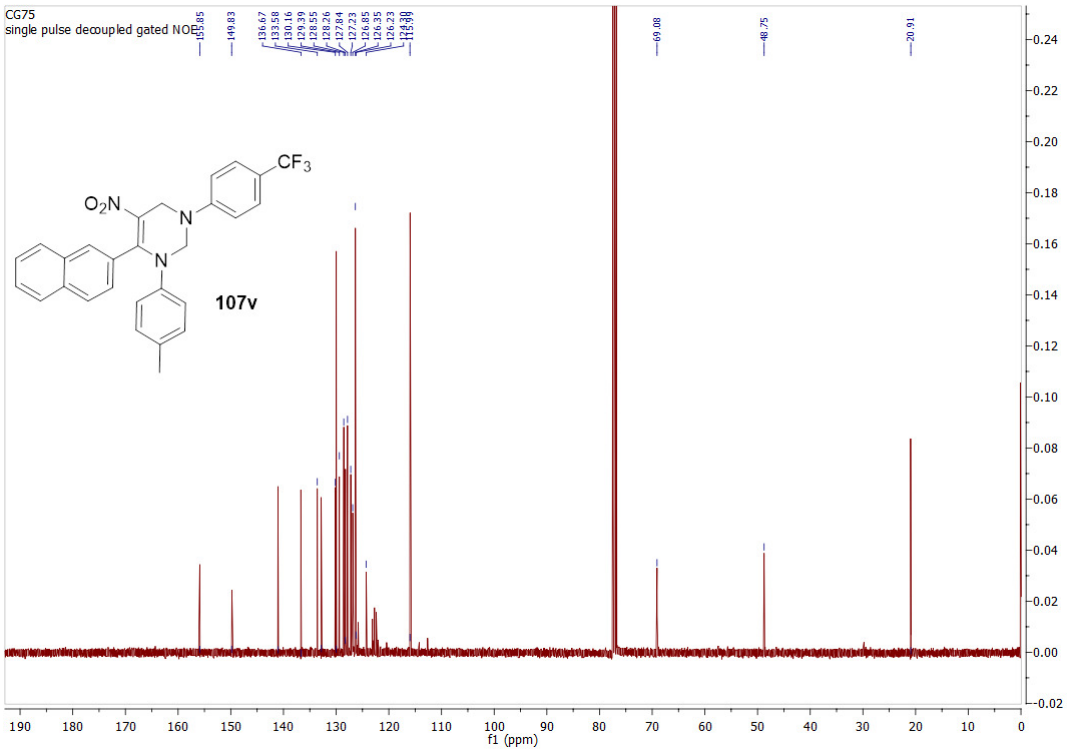


Figure 7.113. ^{13}C-NMR Spectrum of compound **107v**

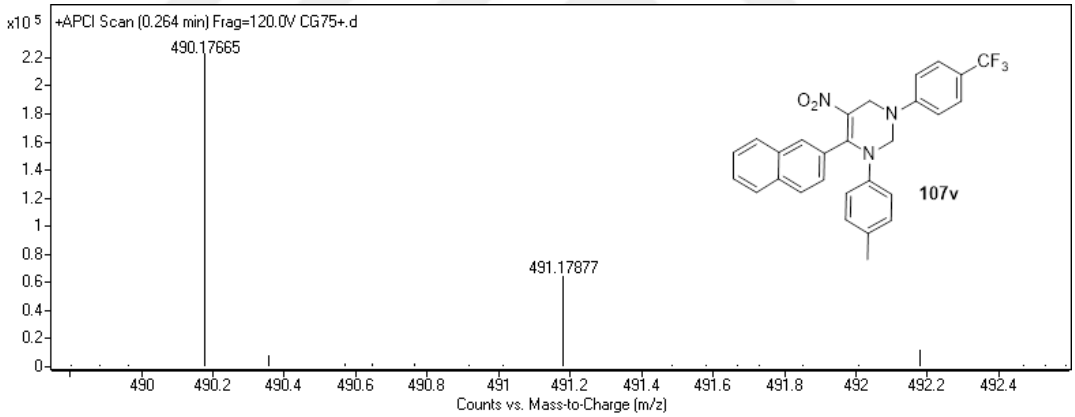


Figure 7.114. HRMS Spectrum of compound **107v**

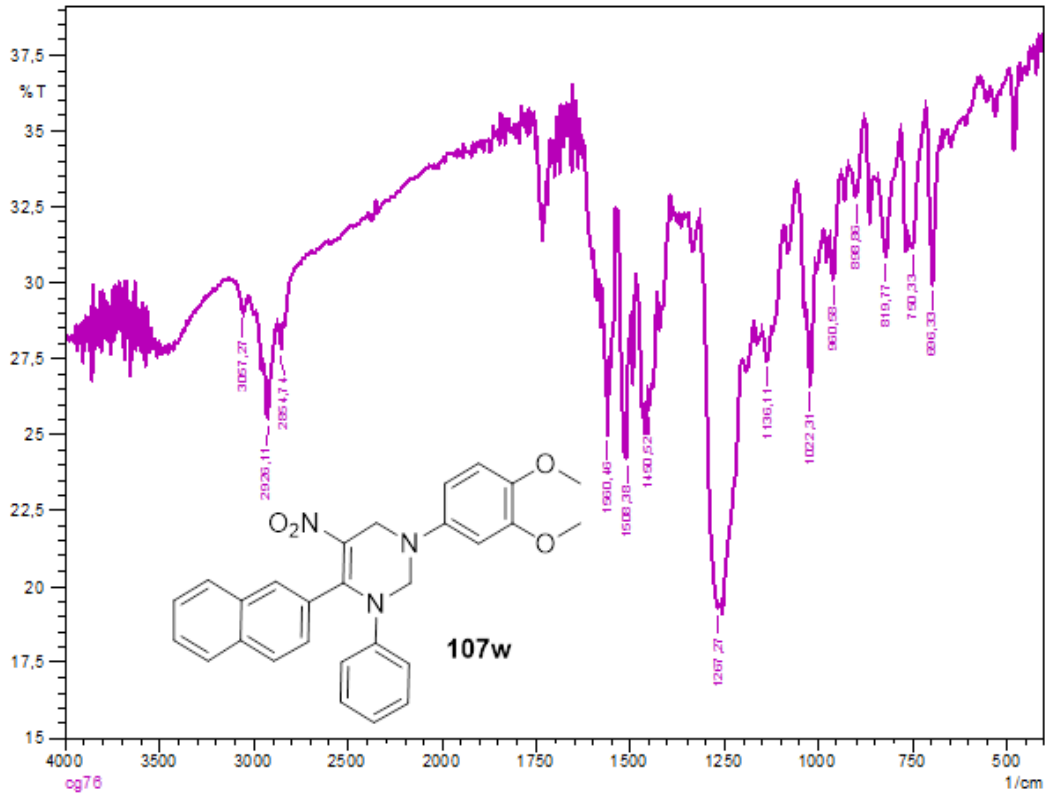


Figure 7.115. IR Spectrum of compound **107w**

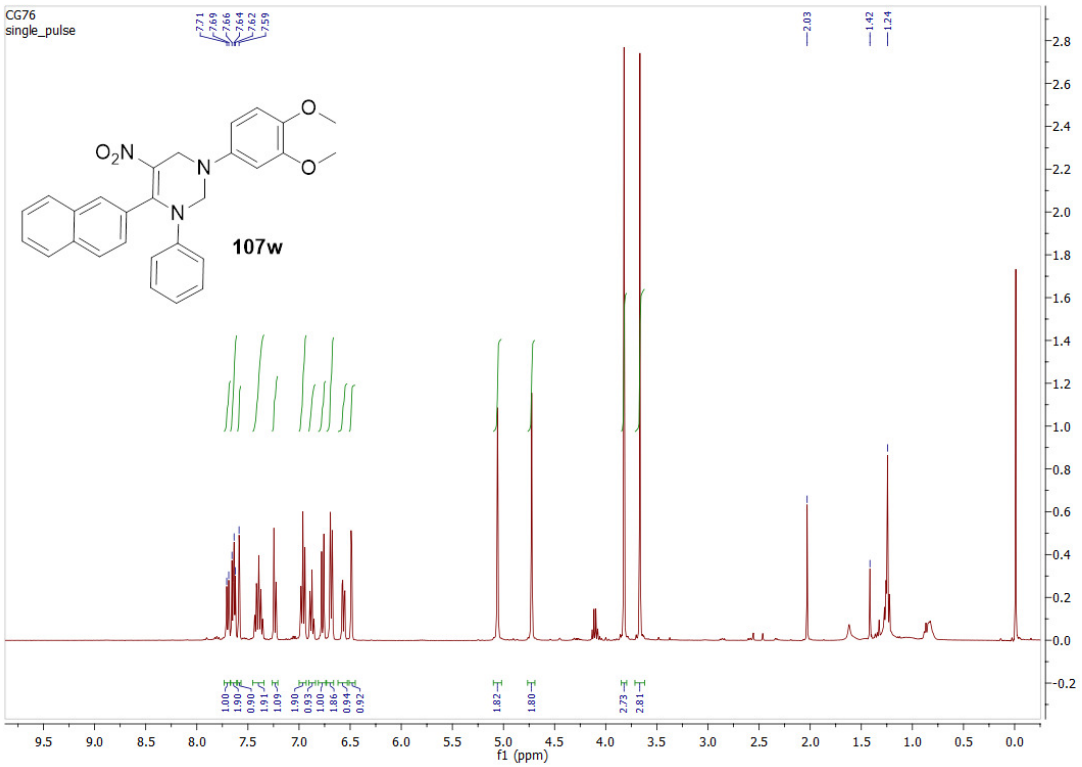


Figure 7.116. ^{1}H-NMR Spectrum of compound **107w**

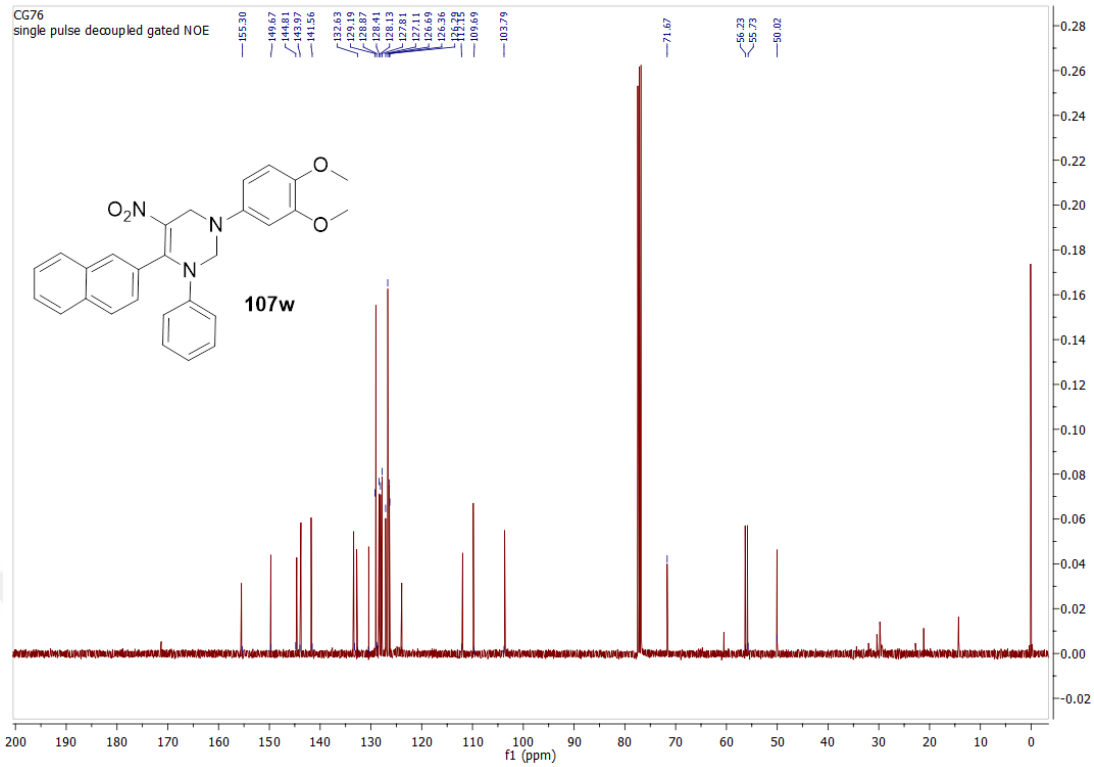


Figure 7.117. ^{13}C-NMR Spectrum of compound **107w**

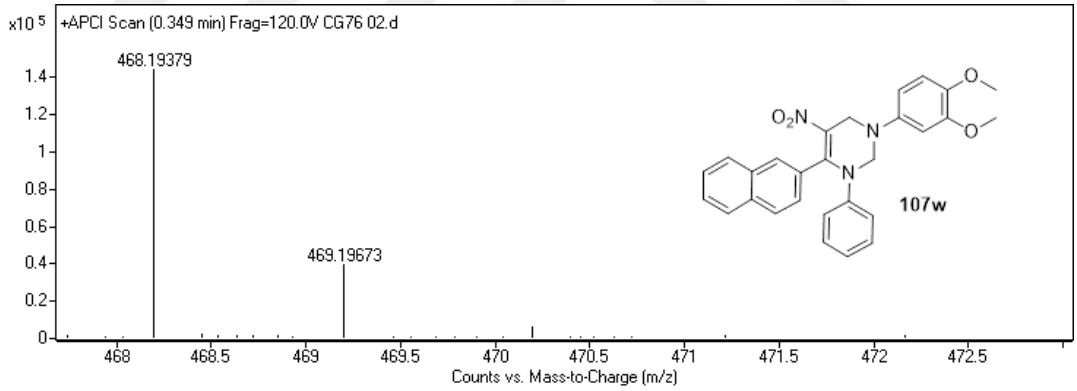


Figure 7.118. HRMS Spectrum of compound **107w**

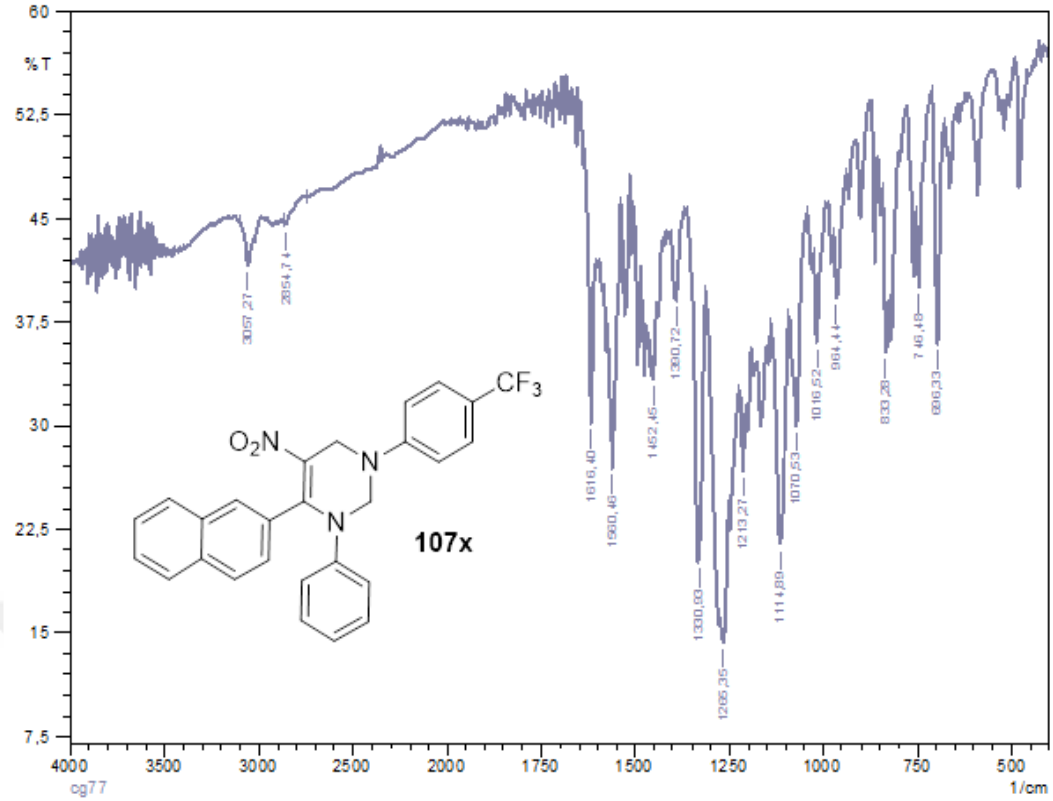


Figure 7.119. IR Spectrum of compound **107x**

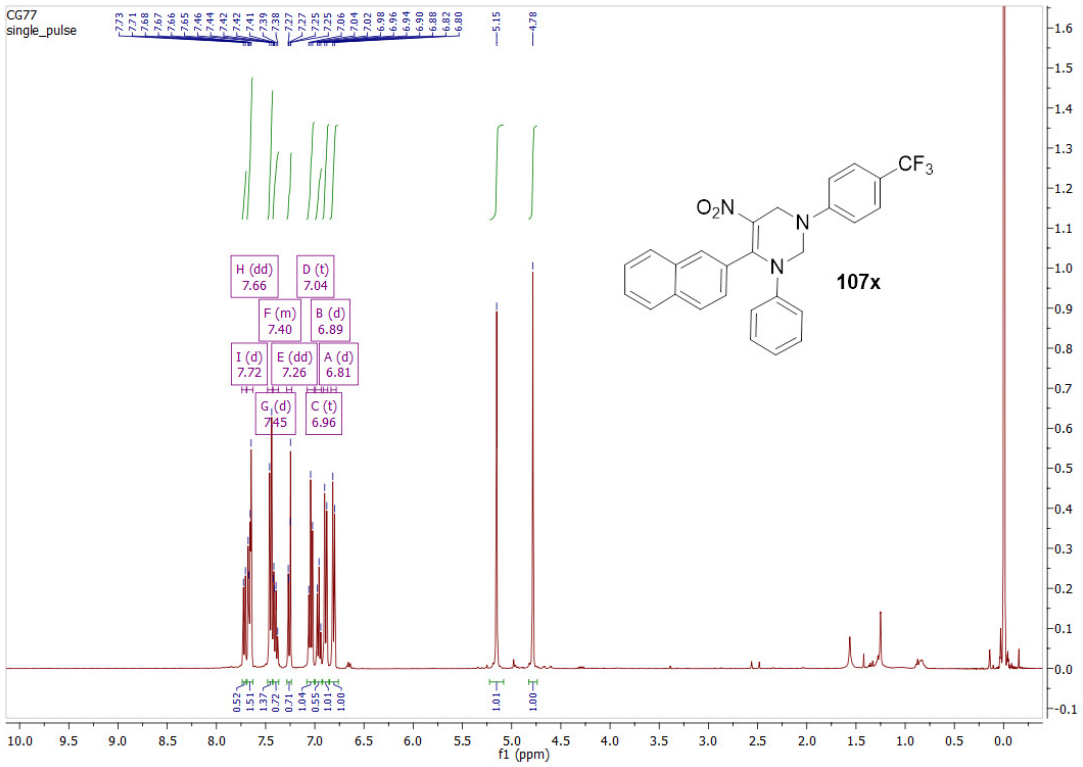


Figure 7.120. ^{1}H-NMR Spectrum of compound **107x**

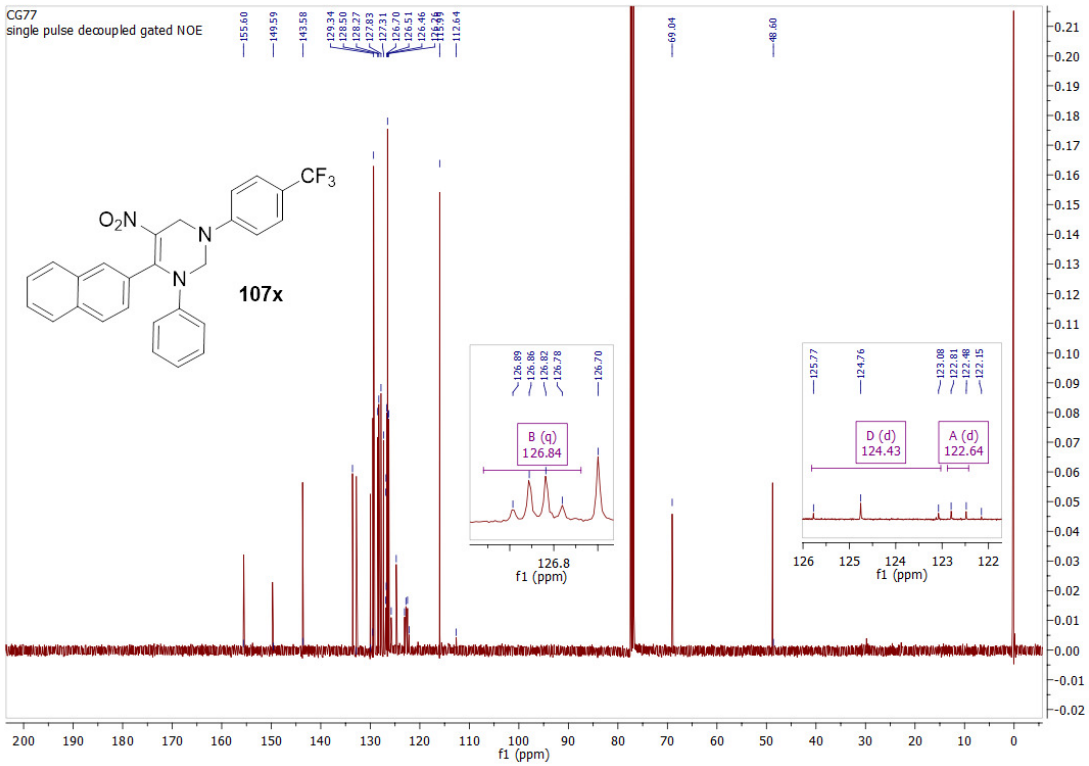


Figure 7.121. ^{13}C-NMR Spectrum of compound **107x**

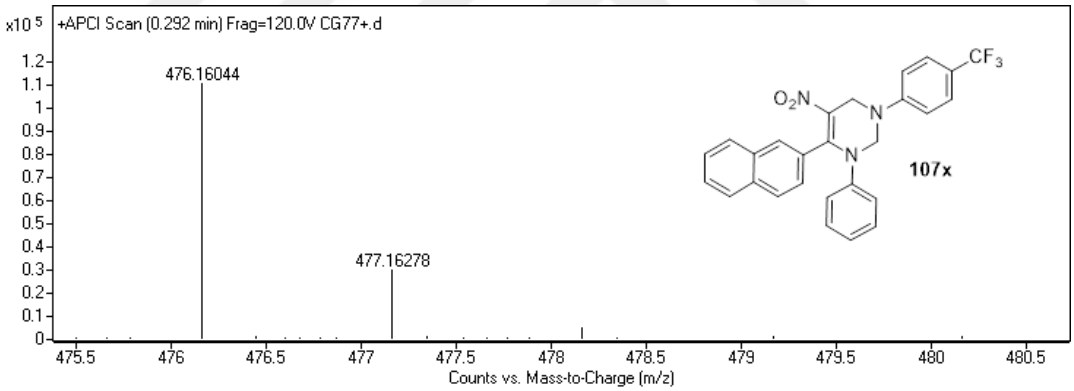


Figure 7.122. HRMS Spectrum of compound **107x**

8. CURRICULUM VITAE

Name SURNAME **:** Cansu GÜLBENEK

Place and Date of Birth **:** 13.11.1992

Universities **:** Abant Izzet Baysal University

Bachelor's Degree **:** 2,40

MSc Degree **:** 3,93

E-mail **:** cansu.gulbenek@gmail.com

Address **:** Vişnelik Mah. Atatürk Bulvarı Yasin Sitesi C Blok No:185/3 Odunpazarı/ESKİŞEHİR

List of Presentations in International Conferences:

1- Cansu Gülbenek, Muhammet Yıldırım. *Efficient Preparation of Novel Nitropyrimidines* (Poster Presentation), International Euroasian Conference on Biological and Chemical Sciences (EuroasianBiochem 2018), 26-27 April 2018, Ankara, TURKEY.