T.C.
BOLU ABANT İZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY

SYNTHESIS OF PYRIMIDINE-BASED HETEROCYCLIC COMPOUNDS VIA MULTICOMPONENT REACTIONS OF VARIOUS ENAMINES

MASTER OF SCIENCE, CHEMISTRY

ZAHİD İSLAM AYAN

THESIS SUPERVISOR
PROF. DR. MUHAMMET YILDIRIM

BOLU, DECEMBER 2024

ACCEPTANCE AND APPROVAL PAGE

The thesis title "**SYNTHESIS OF PYRIMIDINE-BASED HETEROCYCLIC COMPOUNDS VIA MULTICOMPONENT REACTIONS OF VARIOUS ENAMINES**" prepared by **Zahid İslam AYAN** has been accepted by our jury as a Master's Thesis in Chemistry Major with majority vote. 12/30/2024

Jury Members	**Signature**
Supervisor Prof. Dr. Muhammet YILDIRIM Bolu Abant İzzet Baysal University	.....
Member Assoc. Prof. Dr. Akın SAĞIRLI Bolu Abant İzzet Baysal University	.....
Member Asist. Prof. Dr. Bahadır BÜLBÜL Düzce University	.....

Institute of Graduate Studies Approval

Prof. Dr. İbrahim KÜRTÜL

Director of Institute of Graduate Studies

ETHICAL DECLARATION

In this thesis study, which I have prepared in accordance with Bolu Abant İzzet Baysal University, Institute of Graduate Studies' Thesis Writing Guide and Template;

- I have obtained the data, information and documents presented in the thesis within the framework of academic and ethical rules,
- I have presented all information, documents, evaluations, and results in accordance with the rules of scientific ethics and morality,
- I have cited and referenced all the works I have benefited from in the thesis study,
- I have not made any changes to the data used,
- I declare that the work I have presented in this thesis is original, and in any other case, I declare that I accept all loss of rights that may arise against me.

According to the similarity report obtained by applying the filters determined by the directorate of the institute in the Turnitin program related to the thesis, the similarity index of the thesis does not exceed 30%.

……..

ZAHİD İSLAM AYAN

ABSTRACT

SYNTHESIS OF PYRIMIDINE-BASED HETEROCYCLIC COMPOUNDS VIA MULTICOMPONENT REACTIONS OF VARIOUS ENAMINES
MSC THESİS
ZAHİD İSLAM AYAN
BOLU ABANT IZZET BAYSAL UNIVERSITY
INSTITUTE OF GRADUATE STUDIES
DEPARTMENT OF CHEMISTRY
(SUPERVISOR: PROF.DR. MUHAMMET YILDIRIM)

BOLU, 30 DECEMBER 2024
XI + 91

Pyrimidines play a vital role in biology, serving as fundamental building blocks of nucleic acids. They also hold significant pharmacological importance, as their derivatives exhibit a wide array of biological activities, including anticancer, anti-inflammatory, antitubercular, and antimicrobial effects. Specifically, dihydropyrimidines (DHPM) and 1,2,3,4-tetrahydropyrimidine (THPM) derivatives are utilized as calcium channel blocker and antihypertensive drug agents. Moreover, multicomponent reactions (MCRs) are extensively used in various studies for their efficiency in synthesizing diverse pyrimidine compounds.

The aim of the present dissertation was to combine the Mannich-based MCR method with innovative green synthesis techniques to efficiently produce new THPM derivatives (**62**) using enaminonitriles (**61**) and to evaluate their activities. So, polyethylene glycol (PEG) derivatives were selected as a safe and environmentally friendly alternative to organic solvents for the synthesis of new THPMs. To achieve this goal, first of all, new aryl substituted enaminonitriles as suitable precursors were prepared by a base-catalyzed reaction of aryl nitriles with acetonitrile and characterized by IR, NMR analyses. In the second part of the study, novel tetrahydropyrimidine carbonitriles were efficiently synthesized through Mannich cyclizations of enaminonitriles with formaldehyde and amine derivatives under heating in PEG-400 in hours. The structures of all the tetrahydropyrimidine products were confirmed by IR, NMR and HRMS analyses.

KEYWORDS: Tetrahydropyrimidine, Mannich, Green synthesis, Multicomponent reaction, enaminonitrile

ÖZET

ÇEŞİTLİ ENAMİNLERİN ÇOK BİLEŞENLİ REAKSİYONLARI YOLUYLA YENİ PİRİMİDİN TABANLI HETEROHALKALI BİLEŞİKLERİN SENTEZİ
YÜKSEK LİSANS TEZİ
ZAHİD İSLAM AYAN
BOLU ABANT IZZET BAYSAL ÜNİVERSİTESİ
LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ
KİMYA ANA BİLİM DALI
(TEZ DANIŞMANI: PROF. DR. MUHAMMET YILDIRIM)

BOLU, 30 ARALIK 2024
XI + 91

Pirimidinler, nükleik asitlerin temel yapı taşları olarak biyolojide hayati bir rol oynamaktadır. Ayrıca, türevleri antikanser, anti-enflamatuar, antitüberküloz ve antimikrobiyal etkiler de dahil olmak üzere çok çeşitli biyolojik aktiviteler sergilediğinden dolayı farmakolojik öneme sahiptirler. Özellikle, dihidropirimidin (DHPM) ve 1,2,3,4-tetrahidropirimidin (THPM) türevleri kalsiyum kanal bloker ve antihipertansif ilaç ajanları olarak kullanılmaktadır. Ayrıca, çok bileşenli reaksiyonlar (ÇBR'ler), çeşitli pirimidin bileşiklerinin sentezlenmesindeki etkinlikleri nedeniyle birçok çalışmalarda yaygın olarak kullanılmaktadır.

Bu tezin amacı, enaminonitriller (**61**) kullanarak yeni THPM türevlerini (**62**) verimli bir şekilde üretmek ve aktivitelerini değerlendirmek için Mannich tabanlı ÇBR yöntemini yenilikçi yeşil sentez teknikleriyle birleştirmektir. Bu nedenle, polietilen glikol (PEG) türevleri, yeni THPM'lerin sentezi için organik çözücülere kıyasla güvenli ve çevre dostu bir alternatif olarak seçilmiştir. Bu amaca ulaşmak için, ilk olarak, uygun başlangıç bileşikleri olarak yeni aril sübstitüe enaminonitriller, aril nitrillerin asetonitril ile baz katalizli reaksiyonu yoluyla hazırlandı ve IR, NMR analizleri ile karakterize edildi. Çalışmanın ikinci bölümünde, yeni tetrahidropirimidin karbonitriller, enaminonitrillerin formaldehit ve amin türevleri ile Mannich halkalaşmaları yoluyla PEG-400 içinde ısıtılarak saatler içinde verimli bir şekilde sentezlendi. Tüm tetrahidropirimidin ürünlerinin yapıları IR, NMR and HRMS yöntemleriyle doğrulanmıştır.

ANAHTAR KELİMELER: Tetrahidropirimidin, Mannich, Yeşil sentez, Çok-bileşenli reaksiyon, enaminonitril.

TABLE OF CONTENTS

Page

LIST OF FIGURES

Page

LIST OF TABLES

Page

LIST OF ABBREVIATIONS AND SYMBOLS

4-CR : Four component reaction
Ac : Acyl
Ar : Aryl
ATR : Attenuated Total Reflectance
BDSM : Bromine(dimethylsulfonium)bromide
bend. : Bending
Bn : Benzyl
C_6H_6 : Benzene
Cbz : Carbobenzyloxy
CC : Column Chromatography
CH_3CN : Acetonitrile
$CHCl_3$: Chloroform
DCM : Dichloromethane
DHPM : Dihydropyrimidine
DIPEAc : Diisopropylethylacetate
DMF : N,N-dimethylformamide
DNA : Deoxyribonucleic acid
Et : Ethyl
Et_3N : Triethyamine
EtO : Ethoxy
EtOAc : Ethyl acetate
EtOH : Ethanol
h : hour
HRMS : High-resolution mass spectrum
Hz : Hertz
IR : Infrared
J : coupling constant
KO*t*-Bu : Potassium tert-butoxide
MCR : Multicomponent Reaction
Me : Methyl
MeO : Methoxy
MHz : Megahertz
min : minute
MW : Microwave
NH_4OCOH : Ammoium acetate
NMR : Nuclear Magnetic Resonance
NPs : Nanoparticles

OAc **:** Acetate
^{o}C **:** Degree Celcius
OTf **:** Triflate
PEG-400 **:** poly(ethylene glycol) 400
Ph **:** Phenyl
Phen **:** Phenanthroline
ppm **:** parts per million
RNA **:** Ribonucleic acid
rpm **:** Rotation per minute
str. **:** Stretching
TEMPO **:** 2,2,6,6-Tetramethylpiperidyl-1-Oxyl
Tf_2O **:** Triflic anhydride
THPM **:** 1,2,3,4-tetrahydropyrimidine
TLC **:** Thin Layer Chromatography
TMS **:** tetramethylsilane
UV **:** Ultra-violet
wag. **:** Wagging
λ_{max} **:** Wavelength maximum

ACKNOWLEDGEMENT

The author expresses heartfelt gratitude to my supervisor, Prof. Dr. Muhammet YILDIRIM.

The author extends appreciation to Assoc. Prof. Dr. Erhan BUDAK for his valuable support.

Endless thanks are owed to the author's mother and father for their unwavering support and sacrifices.

Sincere thanks are extended to Havva ACAR and Hakan Emre ÖZÇAL, the author's friends, for their patience and unwavering moral support in completing this thesis.

Author would like to thank The Scientific and Technological Research Council of Türkiye (TÜBİTAK-KBAG) (Grant No: 124Z218) for their financial support for this study.

.

1. INTRODUCTION

1.1 History of Pyrimidines

Pyrimidine **1** is a nitrogen-containing heterocycle with a six membered aromatic ring containing two nitrogen atoms at 1,3-position. It is water-soluble solid and its melting point is quite low (22.5ºC). Pyrimidine is a weak base with a pKa value of 1.23 and can be isolated by $CHCl_3$ extraction from an aqueous solution (Fig.1.1) (Bredereckef et al., 1957). UV spectrum of pyrimidine gives two fine peaks at 243 and 298 nm (λ_{max}) in cyclohexane. It gives four proton signals at around 9.26-7.6 ppm in its ^{1}H-NMR spectrum and four carbon signals at 121.9-158.4 ppm in its ^{13}C-NMR (Riand et al., 1974). During the catabolism of pyrimidine, ammonia, carbondioxide and β-amino acids are produced (Pediaa, 2024).

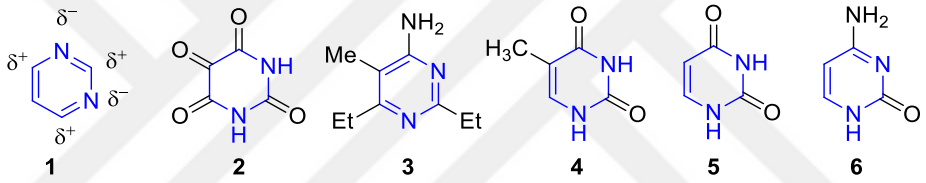


Figure 1.1. Pyrimidine, first pyrimidine compounds and DNA bases

Pyrimidine derivatives initially gained attention during the 19th century, when nucleotide bases were being separated and characterized. The first pyrimidine derivative, alloxan **2**, was isolated by oxidizing uric acid with nitric acid (Brugnatelli, 1818). A second pyrimidine derivative, 2,6-diethyl-5-methyl-4-pyrimidinamine **3**, was obtained by heating propionitrile with metallic potassium (Frankland and Kolbe, 1848). During the 20th century, pyrimidines were essential to biology, particularly as nucleic acid building blocks. When the structure of DNA was explained in 1953, the importance of pyrimidine bases - thymine **4**, uracil **5** and cytosine **6**, -in the storage and transfer of genetic information was empasized (Watson & Crick, 1953). By some genetic studies, it was seen that pyrimidine derivatives help processes like cellular signaling and energy metabolism by taking part in several metabolic pathways (Murray et al., 2003). The Biginelli reaction, which was first described in 1893, remains a basic method for producing pyrimidine derivatives with a variety of biological activities, such as antibacterial and

anticancer properties (Biginelli, 1893). More recent versions of this reaction by the use green solvents or ionic liquids, have significantly improved efficiency and sustainability of the reaction (Hegde et al., 2019; Myadaraboina et al., 2015). Nowadays, the development of environmentally friendly procedures that minimize waste and hazardous by products is a growing area of research interest (Jadhav et al., 2019). Furthermore, the development of THPM synthesis based on ionic liquids has highlighted sustainable methods in this area (Kakati et al., 2021).

1.2 Biological Importance of Pyrimidines

Pyrimidines are essential to life mainly because they are the building blocks of nucleotides, which are the monomeric units of nucleic acids. The pyrimidine bases uracil (U), thymine (T), and cytosine (C) are necessary for the transmission and storage of genetic information (Fig 1.1). Both cytosine and thymine are found in DNA, while uracil takes the role of thymine in RNA (Friedberg et al., 2006). In addition to their structural roles, pyrimidines are essential for cellular metabolism and energy transmission. For instance, RNA production and cellular signaling depend on uridine triphosphate (UTP) **7** and cytidine triphosphate (CTP) (Fig.1.2) (Murray et al., 2003). These nucleotides contribute to the creation of ATP, the main source of energy for cells, and are engaged in a number of metabolic processes. Pyrimidines are widely deployed in living organisms (e.g. vitamins, coenzymes, hormones, alkaloids) and are one of the most studied heterocyclic compounds by organic and medicinal chemists. Pyrimidines are present within the structure of some natural poducts like thiamine **9**, folic acid **10**, riboflavin **11** or their precursors which has functions in variety of biological processes (Fig.1.2) (Lagoja, 2005). Pyrimidines are also useful in a variety of therapeutic fields, demonstrating notable effectiveness in the treatment of many diseases, disorders and infections. Pharmacologically, pyrimidine derivatives exhibit many different biological activities, such as anticancer, antihepatitis, antiinflammatory, anti-HIV, antitubercular, antimicrobial, anitoxidant and antiviral (Fig.1.2) (Legraverend and Grierson, 2006; Chauhan and Kumar,2015; Nadar and Khan, 2022). In addition, critically important pyrimidine-based drugs such as Fluorouracil **12**, Etravirine **13**, Risperidone **14**, Pyrantel **15** are at the service of human health today (Fig.1.2) (Mahfoudh et al., 2017; Kajal et al., 2024).

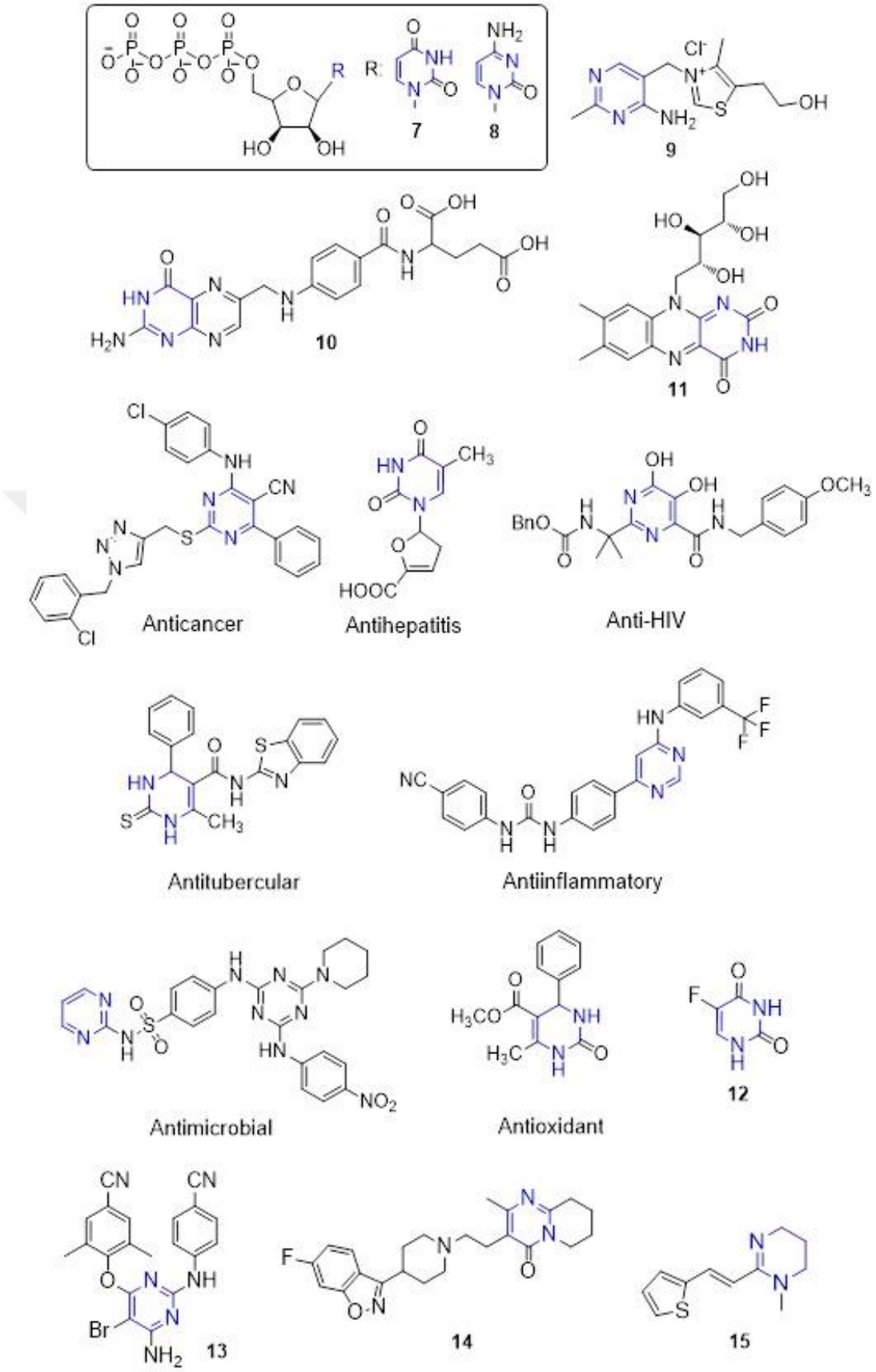


Figure 1.2. Biologically active natural and synthetic pyrimidine derivatives and therapeutic agents

Their broad range of therapeutic applications stems from the fact that these scaffolds serve as the structural foundation for nucleotides and various other compounds that regulate different physiological processes. They achieve this by interacting with multiple macromolecular targets, including cellular kinases, G proteins, and polymerases.

Among the pyrimidine structures, more specifically, dihydropyrimidine (DHPM) and 1,2,3,4-tetrahydropyrimidine (THPM) derivatives are reported as calcium channel blockers (Kshirsagar et al., 2013) and antihelmintic drugs like pyrantel **15** (Fig.1.2) (Nielsen, 2023). In addition, it is reported in the literature that compounds with these skeletal structures have antituberculosis, antibacterial, antifungal and cytotoxic effects (Kappe, 2000; Carosati et al., 2012). The structural groups affecting the antituberculosis properties of THPM and DHPM skeletons are the substituents on C-2, C-4, C-5 carbons and the lipophilic properties of the compounds. It was also found that these compounds showed similar or better effects than antituberculosis drugs such as isoniazid, rifampicin and moxifloxacin (Singh et al., 2011; Trivedi et al., 2010; Trivedi et al., 2008; Virsodia et al., 2008). In addition, it has been reported in the literature that many THPM and DHPM-derived compounds show effective antimicrobial properties against various bacteria (*S.aureus, E.coli, S.typhi, B.subtilis, P.aeruginosa, B.cereus, S.pyogenes, K.pneumonia*) and fungi (*C.albicans, A.Niger, A.flavus*) (Rani et al, 2014; Tale et al., 2011; Sedaghati et al., 2012; Basavaraja et al., 2012; Shah and Sen, 2012). Moreover, these derivatives are also reported to be promising anticancer compounds due to their cytotoxic effects (DNA fragmentation) against various anticancer cell lines (colon-HCT116, cervical, lung, CNS, breast-MCF-7) (Fig.1.3) (Rawat et al., 2022).

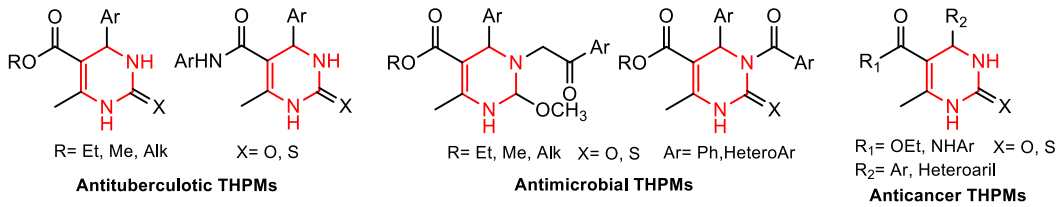


Figure 1.3. A variety of biologically active THPM derivatives

1.3 Synthesis of Pyrimidine and its Derivatives

Given their crucial significance in the creation of medicines, agrochemicals, and physiologically active molecules, the synthesis of pyrimidine derivatives is a fundamental aspect of medicinal chemistry. These nitrogen-containing heterocycles are present in many important compounds in biology, such as nucleotides, nucleic acids, and many medicinal substances. Because of varying chemical reactivity of pyrimidines, several synthetic approaches have been explored, resulting in the creation of novel derivatives in the past and today.

1.3.1. General Methods for Pyrimidine Synthesis

Soon after Biginelli, the indirect synthesis of unsubstituted pyrimidine was achieved by decarboxylation method first time (Gabriel and Colman, 1899). Some other indirect syntheses of pyrimidines have been made starting with different pyrimidine derivatives and reagents. For instance, 2-chloro- or 2,4-dichoro-pyrimidines **26** are hydrogenated by a base catalysis or 2,4,6-trichloropyrimidines **25** are dechlorinated by zinc-water catalyst or 2(1H)-pyrimidinethiones **27** are desulfurized with Raney-nickel or hydrogen peroxide or 2,4-dihydrazinopyrimidines **28** are decomposed oxidatively by $CuSO_4$ to give corresponding pyrimidines (Figure 1.4.) (Hunt et al., 1959; Gabriel, 1900; Boarland et al., 1952; Gabriel and Colman, 1899).

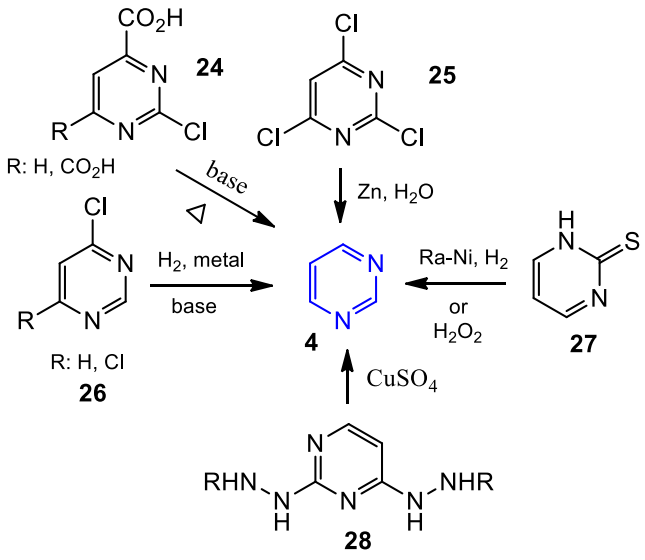


Figure 1.4. Synthesis of unsubstituted pyrimidines by indirect methods.

Moreover, primary synthesis of pyrimidine have been accomplished by the reaction of 1,1,3-triethoxy-3-methoxypropane **29** with formamide **30** or by the reaction of 3-aminoacrylaldehyde **31** with formamide **30** in the presence of piperidinium acetate (Figure 1.5.) (Bredereck et al., 1958; Breitmaier, 1971).

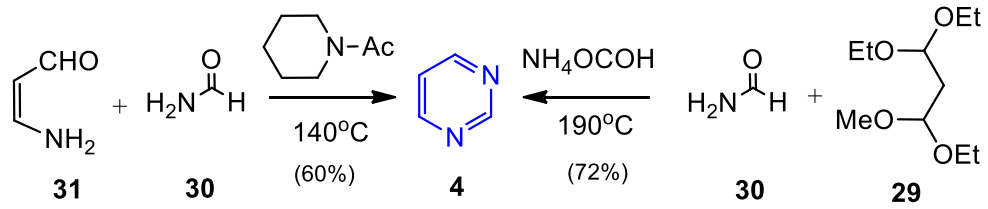


Figure 1.5. Primary synthesis of pyrimidines.

1.3.2. General Methods for Synthesis of Pyrimidine derivatives

First principal syntheses of pyrimidine derivatives were achieved by Adolf JohannVon Baeyer (1864) and by Grimaux (1879) by the condensation of malonic acid **16** and urea **17** with or without use of $POCl_3$ giving barbituric acid **18** (Von Baeyer,1864; Grimaux, 1879) (Figure 1.6.).

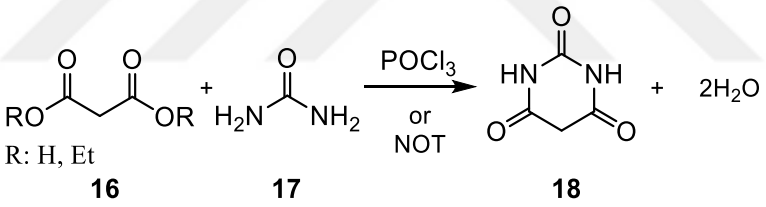


Figure 1.6. Synthesis of first pyrimidine derivatives, barbituric acid.

Later on, Pinner (1884) synthesized 2-substituted-6-hydroxy-4-methyl pyrimidine **21** from the reaction between an amidine derivative **19** and acetoacetic ester **20** (Figure 1.7.) (Pinner,1884).

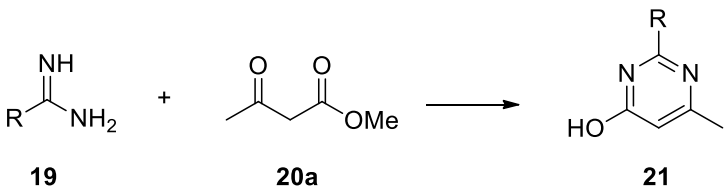


Figure 1.7. Pinner synthesis of hydroxypyrimidines

A conventional method for the synthesis of pyrimidines was establihed by Pietro Biginelli (1893) who created the 3,4-dihydropyrimidin-2(1H)-ones **23** via a condensation reaction of an aldehyde **22**, a β-dicarbonyl molecule **20**, and either urea **17** or thiourea (Figure 1.8.). A large variety of pyrimidine derivatives with important biological activity, such as antibacterial, antifungal, and anticancer have been synthesized due to the flexibility of Biginelli reaction (Biginelli, 1893). According to recent research, for example, the Biginelli reaction can produce compounds that have strong cytotoxic effects on a variety of cancer cell lines.

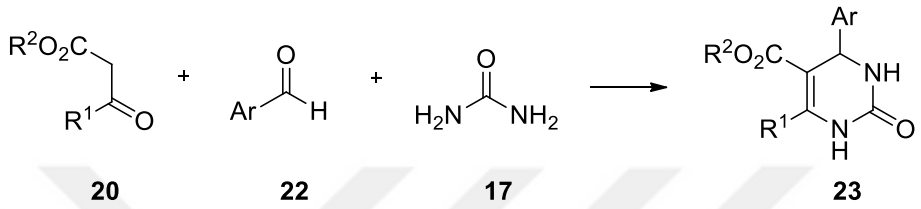


Figure 1.8. Biginelli synthesis of DHPMs

Some alkoxy-substituted 2-amino-5-cyanopyrimidines **26** have been obtained via cyclization reaction of 3-alkoxy-1,3-dicarbonitriles **24** and cyanamide **25** in the presence of sodium alkoxides (Figure 1.9.) (Perez and Soto, 1981).

Figure 1.9. Synthesis of 4-alkoxy substituted-cyanopyrimidines

Since its first synthesis, various pyrimidine derivative can be prepared by many different and innovative synthetic methods. Generally speaking, many pyrimidine compounds have been obtained from catalysed or uncatalysed cyclization reactions of different amidine compounds **19** with α,β-unsaturated esters **27** and ketones, saturated ketones **37**, alcohols, alkenes, 1,3-dicarbonyl compounds or condensation of compounds such as enamine **34**, enamide **29**, amide **35**, nitrile **30** and urea **17** with ketones (Figure 1.10.) (Zhichkin et al., 2002; Movassaghi and

Hill, 2006; Barthakur et al., 2007; Ahmad et al., 2009; Gayon et al., 2012; Chu et al., 2017; Romanov et al., 2020; Wu et al., 2023)

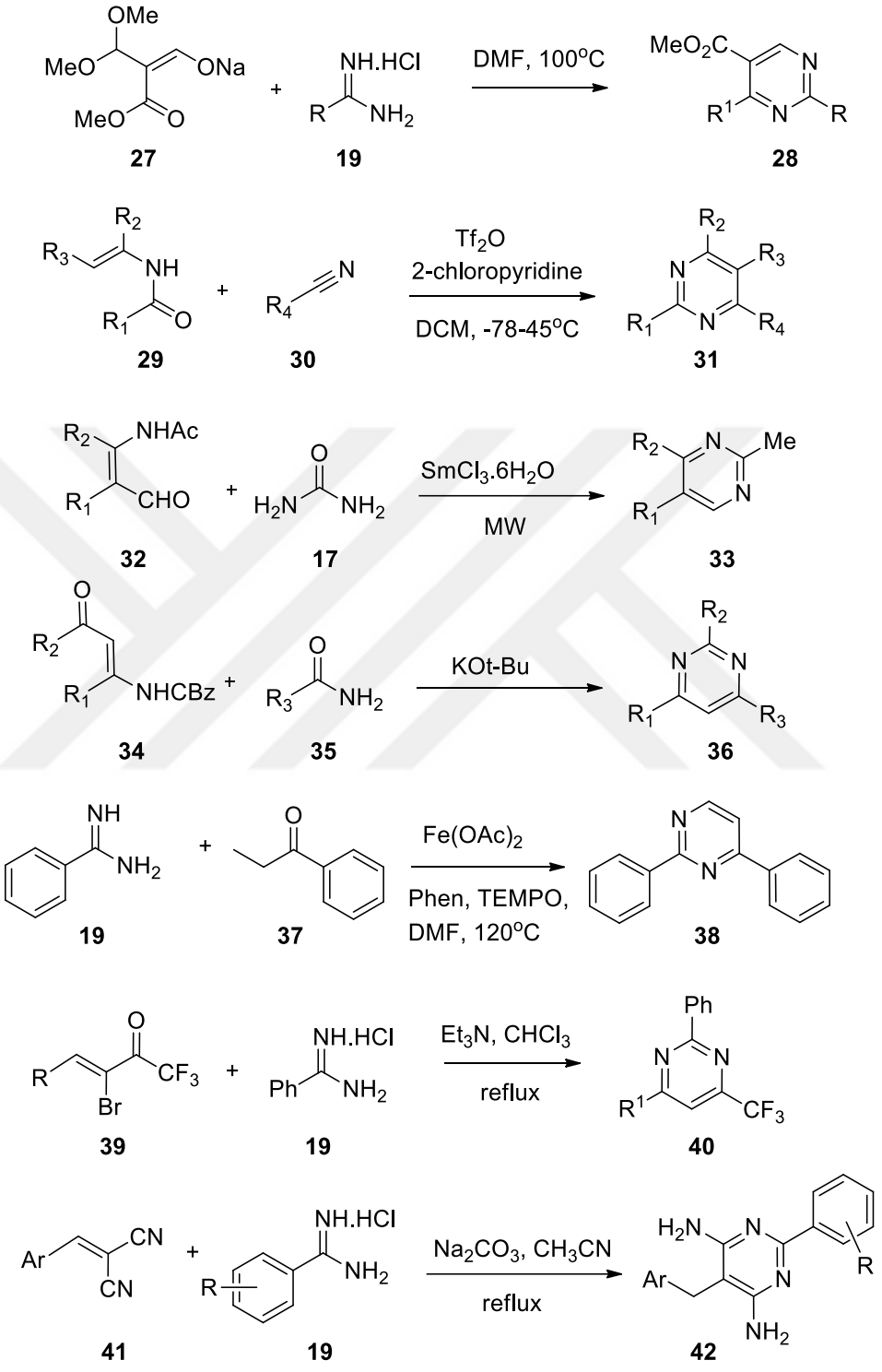


Figure 1.10. Synthesis of various pyrimidine derivatives

1.3.3. Multicomponent and Green Synthesis of Pyrimidines

Multicomponent reactions (MCRs) are important for organic chemistry because they enable the simultaneous assembly of numerous reactants into a single product. This method improves overall efficiency by streamlining the synthesis process and reducing the need for purification stages. MCRs drastically cut down on the time and resources needed for synthesis by enabling the creation of complex compounds in a single step. Moreover, MCRs have become an important pyrimidine synthesis technique within last two decades. In medicinal chemistry, the simultaneous introduction of many functional groups resulting in the identification of novel drug candidates will be very beneficial. One of the best known MCR for the synthesis of DHPM derivatives is the Biginelli synthesis (Biginelli, 1893). Although the Biginelli reaction is a simple and one-step MCR for the preparation of various pyrimidine compounds, low yield problems are frequently experienced in most synthesis reactions. For this reason, yields in pyrimidine synthesis can be increased by using various Lewis acid catalysts (ytterbium trfilate, Montmorillonite) in Biginelli type MCRs (Figure 1.11.) (Ma et al., 2000; Mitra et al., 2003).

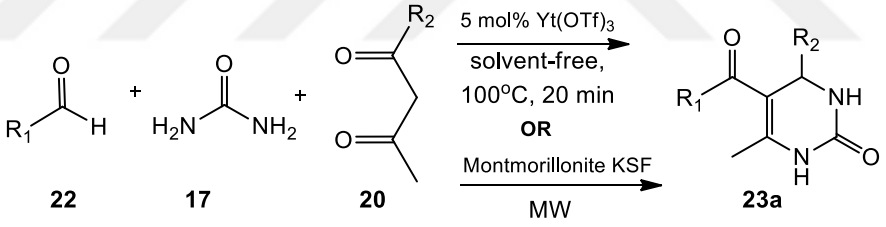


Figure 1.11. Synthesis of DHPMs by Lewis acid-catalysed Biginelli reactions

The synthesis of pyrimidine derivatives has placed an increasing focus on green chemistry concepts in recent years. By cutting waste, using non-toxic solvents, and implementing sustainable practices, the objective is to reduce the negative effects on the environment. The recent research studies on more environmentally friendly and economical methods for the synthesis of DHPM or THPM derivatives has been increasing rapidly. For this purpose, many new pyrimidine compounds have been synthesized over Biginelli method using various environmentally friendly catalysts (Amberlist-70, ionic solvent, polyphosphate esters) under solvent-free or microwave energy with concept of green chemistry (Figure 1.12.) (Chandak et al., 2009; Dong et al., 2007; Harikrishnan et al., 2013).

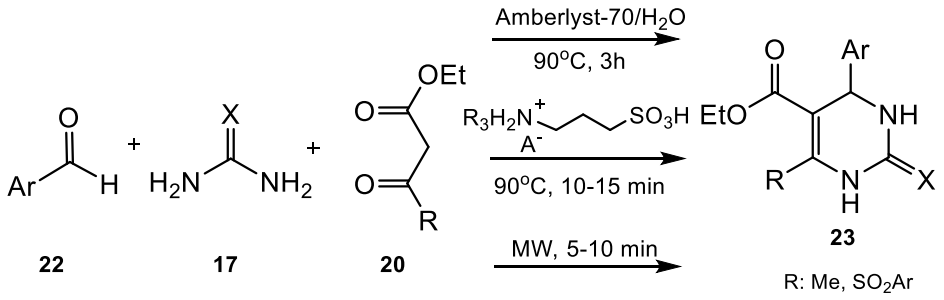


Figure 1.12. Synthesis of DHPMs by Green Biginelli reactions

The creative strategies demonstrated how green practices may successfully reduce the negative environmental effects of pharmaceutical manufacturing. This strategy not only fits with principals of green chemistry, but it also shows promise for creating safer and more powerful medications. At this point, recent studies on the synthesis of bioactive THPM or DHPM compounds via Biginelli reactions using green chemistry methods are frequently encountered in the literature. For example, 4-amino-6-arylpyrimidine-5-carbonitrile derivatives (**45**) presenting various antimicrobial activities have been prepared in good yields by MW heating in PEG-400 with a Biginelli-based MCR. (Hegde et al., 2019). In addition, some DHPM derivatives with anticancer, antibacterial and antifungal properties can be obtained from aryl aldehyde and aroylpurivate compounds in an environmentally friendly way using garlic with Biginelli reaction (El-Malah et al.). Besides, environmentally friendly synthesis of some DHPM compounds with antibacterial properties can also be achieved by Biginelli reactions with copper nanoparticles and diisopropyl ethyl ammonium acetate (DIPEAc), an ionic solvent (Sharma et al., 2023; Jadhav et al., 2019). THPM compounds showing antituberculosis activity with starting compounds similar to these synthetic methods can also be obtained with ammonium-based ionic solvents or by effective Biginelli reactions under MW conditions (Figure 1.13.) (Kakati et al., 2021; Mohan et al., 2012).

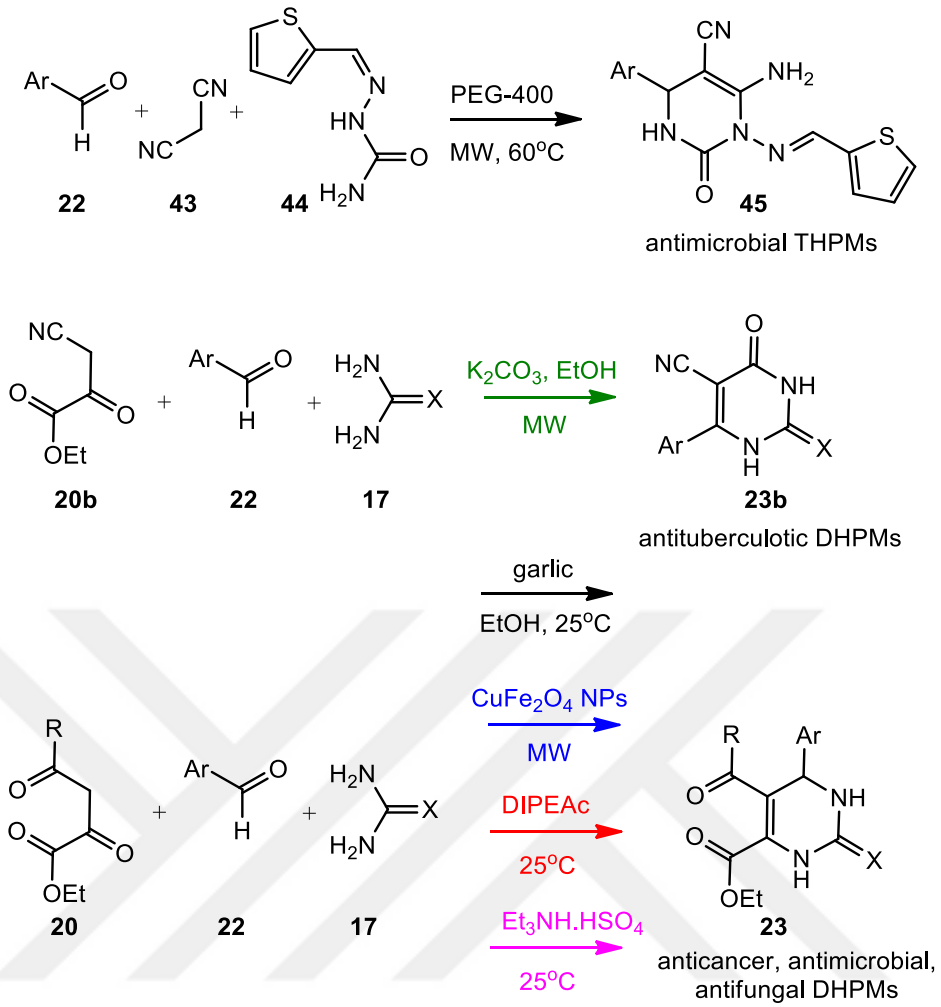


Figure 1.13. Some biologically active DHPMs or THPMs by Biginelli reaction under green conditions

Even the Biginelli reaction is an important MCR for synthesis of a variety of pyrimidine compounds, it has some limitations for the synthesis of new compounds with different pyrimidine skeletons. Apart from the Biginelli synthesis, various THPM or DHPM compounds have been obtained by other MCR approaches in recent studies, but these methods are very few in number. For instance, polysubstituted THPM derivatives can be successfully synthesized under mild conditions using diethylacetylene dicarboxylate **46** in PEG with a 4-CR or mechanochemically with gold (III) catalyst or solvent-free with BDSM (Kidwai et al., 2011; Vadivelu et al., 2018; Myadaraboina et al., 2016). Again, in a recent a high quality study, new THPM compounds were efficiently obtained by a 4-CR of diethylacetylene dicarboxylate **46** using captopril anchored on magnetic graphene nitride as a green catalyst (Figure 1.14.) (Rezai et al., 2023).

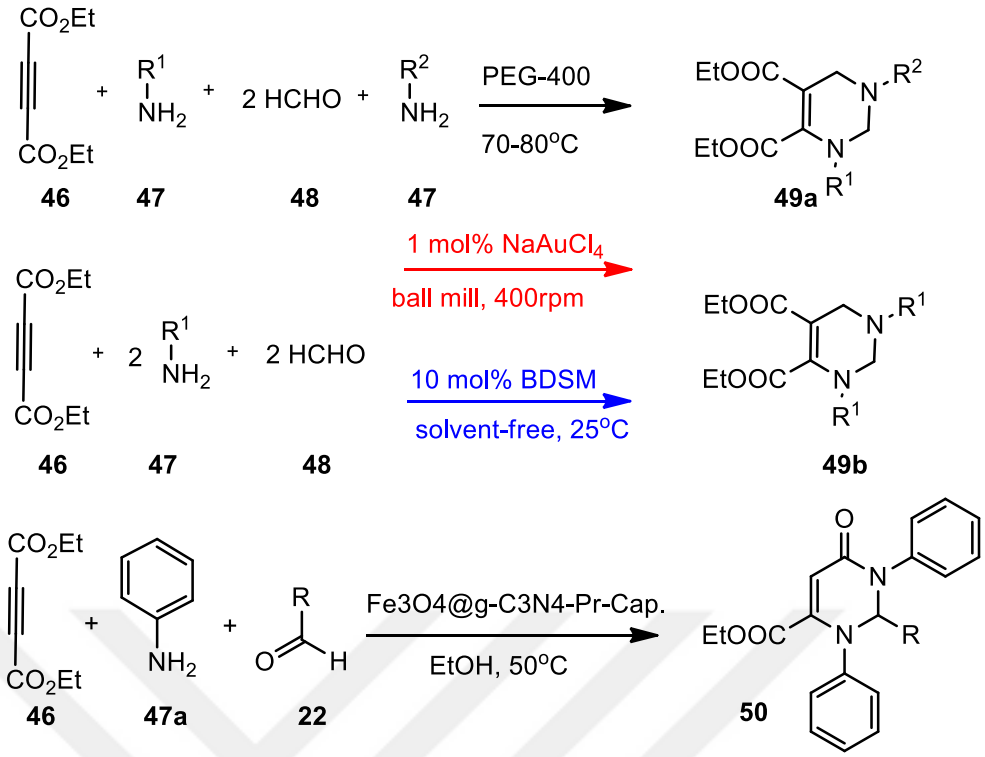


Figure 1.14. Synthesis of THPMs by different Green MCR approaches

We believed that the incorporation of new and green approaches into research will probably allow further progress in the synthesis of pyrimidine derivatives over time (Buth et al., 2019). Therefore, in our research studies over last decade, we have developed a Mannich reaction-based MCR for the synthesis of fused pyrimidine derivatives and a large number of new derivatives have been obtained by applying various and efficient green synthesis methods, both conventional and microwave assisted techniques. Cytotoxic, antioxidant and antibacterial activity studies of a wide variety of thiazolo[3,2-c]pyrimidines (**53-55**) or polysubstituted THPM compounds (**56**) have also been carried out and their biological properties have been revealed so far (Figure 1.15.) (Yıldırım et al., 2014; Yıldırım and Çelikel, 2015; Yildirim et al, 2018; Gülbenek et al., 2022; Uysal et al., 2024).

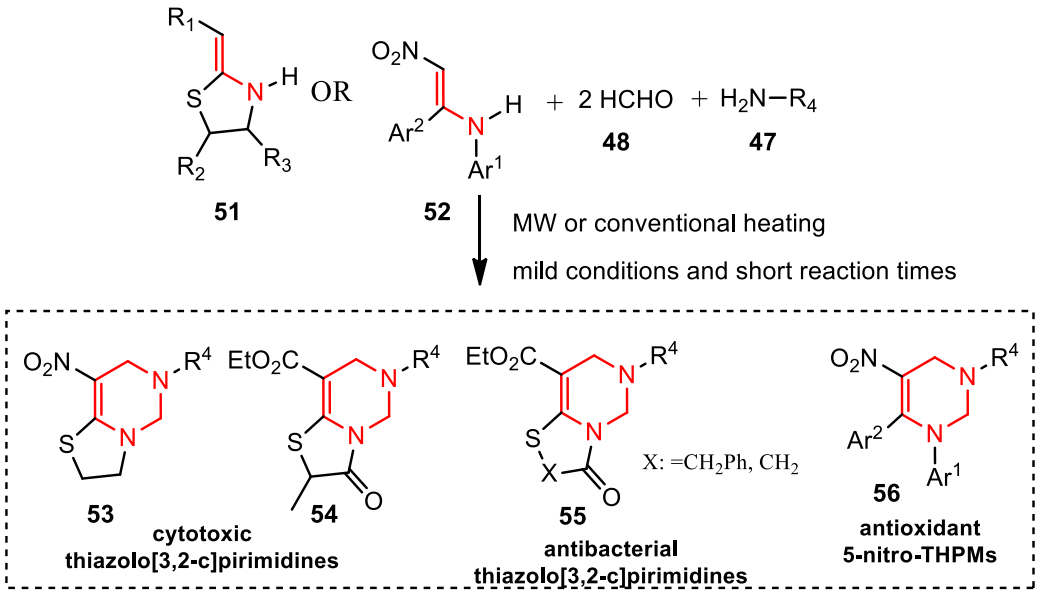


Figure 1.15. Synthesis of novel bioactive pyrimidines by our research group via Mannich-based MCR approaches

A few examples of Mannich-based MCRs are found in recent literature, however these studies have used very straightforward procedures other than green methods. For instance, 5-nitro-THPMs **56** were prepared by the Mannich reaction of different nitroenamines **52** with formaldehyde **48** and alkylamines **47** in EtOH and the product was further reduced to hexahydropyrimidines **57** with $NaBH_4$ (Fig. 1.16) (Sokolov et al. 1985). Also, synthesis of new 1,2,3,4-tetrahydropyrimidines (THPMs) **56** was achieved by the reaction of *β*-nitroenamines **52a** with aliphatic amines **47** and formaldehyde **48** (Figure 1.16) (Khan et al. 2010). In addition, some novel THPMs **60** as acetylcholine receptor (AchR) inhibitors were obtained via multicomponent Mannich cyclizations of enaminones **59** with primary amines **47** and formaldehyde **48** (Figure 1.16.) (Devi et al., 2011).

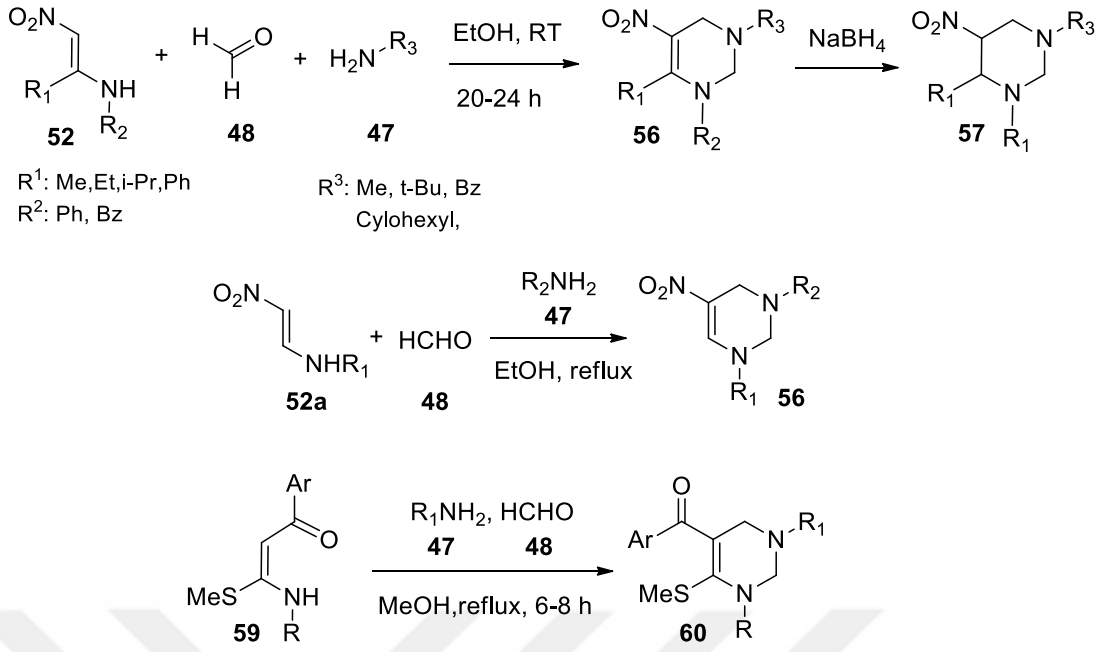


Figure 1.16. Synthesis of THPMs by Mannich MCRs

1.3.4. Aim of the current work

As highlighted in numerous literature examples, MCRs are widely employed in various recent studies due to their effectiveness in synthesizing a range of pyrimidine compounds. In the present thesis study, it was aimed to integrate Mannich-based MCR method with innovative green synthesis techniques to efficiently produce new THPM derivatives **62** using enamines **61** and to assess their activities. In this study, polyethylene glycol (PEG) derivatives were selected as a safe and environmentally friendly alternative to organic solvents for the synthesis of new THPMs. These compounds are cost-effective, thermally stable, non-toxic, and recyclable, and are commonly used in food and cosmetic products. (Jain et al., 2007; Chen et al., 2005; Kumar et al., 2007; Namboodiri and Varma, 2001). Moreover, the hydrophilicity and excellent water miscibility of PEG derivatives, along with their easy separation from organic compounds, offer additional advantages in purification processes. Leveraging these advantages, the study aimed to develop a clean, cost-effective, efficient, one-step, and environmentally friendly synthetic method for producing new THPM derivatives by combining the strengths of MCR and the use of PEG.

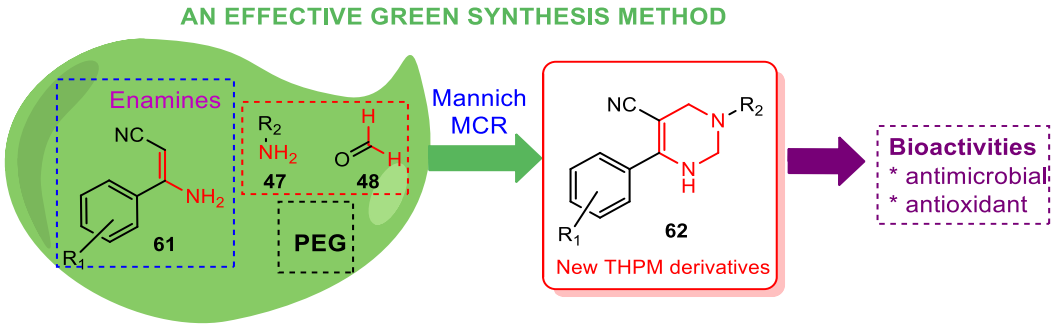


Figure 1.17. Synthesis of novel bioactive THPMs via a Green MCR method in the current study.

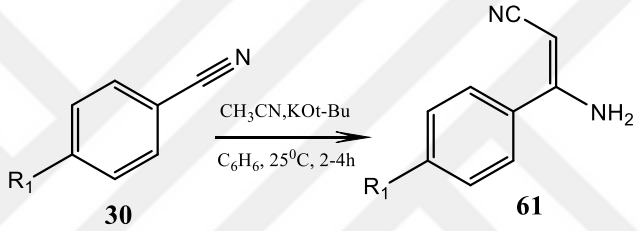
2. MATERIALS and METHOD

All chemicals (reagents, solvents) were supplied commercially in analytical grade (Merck, Sigma-Aldrich, TCI, BLDPharm). NMR spectra were obtained on a Bruker Ascend 400 spectrometer in $CDCl_3$ (internal standard: TMS) at ambient temp. IR spectra were recorded using a Thermo Nicolet iS20 FTIR spectrometer. High resolution mass results were obtained on a QTOF Mass Spectrometer (Waters Lct Premier XE).

2.1 Experimental

2.1.1 Preparation of Starting Compounds

General Procedure for Synthesis of 3-amino-3-aryl acrylonitriles (61) (Modified) (Yamaguchi et al., 1998)

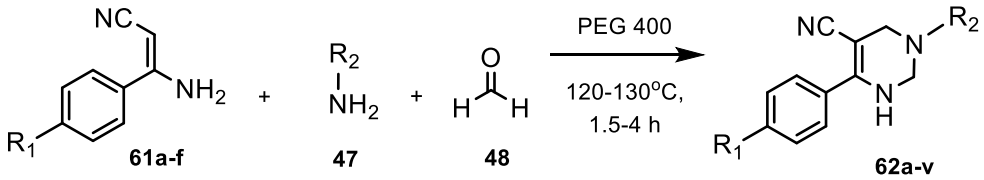


30 **61**

Potassium *t*-butoxide (30 mmoles) was added into a solution of p-substituted aryl nitrile **30** (10 mmoles) and acetonitrile (20 mmoles) in benzene (40 mL) at room temperature. After stirring at room temperature for 2-4 hours, the resulting suspension was mixed with aqueous sodium bicarbonate (50 mL) and extracted with diethyl ether (50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to afford enaminonitriles (**61**) as solid products in high yields.

2.1.2 Synthesis of Target Compounds

General Procedure for Synthesis of 3,6-(diaryl)-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (62)



R_1	
a	H
b	4-Me
c	4-Cl
d	4-F
e	4-SMe
f	4-CF_3

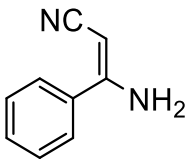
R^2	
47a	Ph
47b	4-Me-Ph
47c	4-SMe-Ph
47d	allyl
47e	4-Cl-Ph
47f	4-I-Ph

3-amino-3-aryl acrylonitriles **(61a-f)** (0.5 mmol, 1.0 equiv), amine derivative **47a-f** (0.65 mmol, 1.3 equiv.) and formaldehyde **48** (37 % v/v in H_2O, 1.3 mmol, 2.5 equiv.) were suspended in PEG-400 (5 mL) and the resulting mixture was prestirred for a few minutes. Then, the resulting mixture was heated at 120-130^oC for 1.5-4 h. The reaction progress was followed by TLC and upon completion, the reaction mixture was cooled to ambient temperature and extracted with Et_2O (3x20 mL). Collected ether layers were washed with brine and dried over sodium sulfate. Solvent was rotaevaporated and the resulting crude product was purified by silica gel column chromatography using EtOAc-hexane mixtures specified, to afford the title compounds (**62**) in good yields.

3. RESULTS

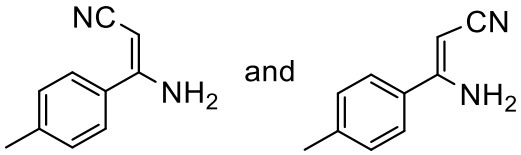
Following starting compounds (**61a-f**) and tetrahydropyrimidine products (**62a-v**) have been synthesized using the general procedures and their obtained physical and spectroscopic data sets were presented as below.

(*E*)-3-amino-3-phenylacrylonitrile (61a)



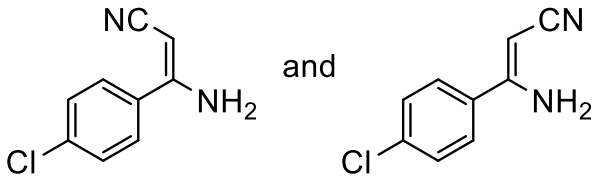
Applying the general procedure in section 2.1.1 and stirring at room temperature for 3.5 hour afforded pale yellow solid. (1.90 g, 90%), m.p. 91-93°C; R_f (25% EtOAc/hexane) 0.50; IR (ATR) υ: 3451-3352 (NH_2 str.), 3223 (NH_2 str.), 2994 (Alip CH str.), 2183 (C≡N str.), 1769, 1636 (NH_2 bend.), 1589 (C=C), 1559, 1494 (arom C=C), 1446, 1383, 1246 (C-N str.), 1056, 757 (NH wag.), 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.36 (m, 5H), 5.00 (br s, 2H, NH_2), 4.26 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (quart.C=C), 135.3, 130.9, 129.0, 126.0, 119.3 (C≡N), 63.6 (C=CH).

3-amino-3-(p-tolyl)acrylonitrile (61b) (Mixture of E-Z isomers-3:1)



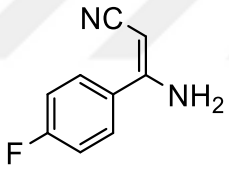
Applying the general procedure in section 2.1.1 and stirring at room temperature for 3 hour afforded white powder solid. (3.45 g, 85%), m.p. 95-97°C; R_f (25% EtOAc/hexane) 0.65; IR (ATR) υ: 3433-3344 (NH_2 str.), 3241 (NH_2 str.), 2989 (Alip CH str.), 2228 (C≡N str.), 2181 (C≡N str.), 1773, 1636 (NH_2 bend.), 1608, 1586 (C=C str.), 1556, 1510 (arom C=C), 1246 (C-N str.), 827, 816, 765 (NH wag.), 729, 604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ *7.56 (d, J = 8.1 Hz, 2H)*, 7.41 (d, *J* = 8.1 Hz, 2H), *7.29 (d, J = 7.9 Hz, 2H)*, 7.25 (d, *J* = 7.9 Hz, 2H), 4.98 (br s, 2H, NH_2), 4.24 (s, 1H), *2.44 (s, 3H)*, 2.43 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5 (quart.C=C), *143.7*, 141.3, *132.4*, 132.0, *129.8*, 129.6, *127.5*, 125.8, 119.7 (C≡N), *119.2 (C≡N)*, *109.3*, *65.1 (C=CH)*, 63.0 (C=CH), *21.8*, 21.3.

3-amino-3-(4-chlorophenyl)acrylonitrile (61c) (Mixture of E-Z isomers-2:1)



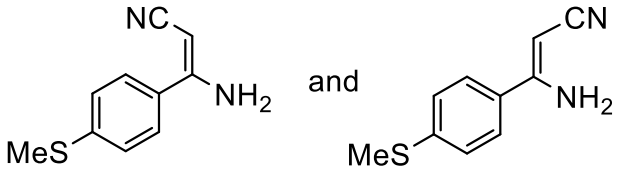
Applying the general procedure in section 2.1.1 and stirring at room temperature for 4 hour afforded white powder solid. (1.75 g, 89%), m.p. 108-110°C; R_f (25% EtOAc/hexane) 0.75; IR (ATR) υ: 3404-3340 (NH_2 str.), 3241 (NH_2 str.), 2925-2853 (Alip CH str.), 2182 (C≡N str.), 1773, 1642 (NH_2 bend.), 1584 (C=C), 1556, 1491 (arom. C=C), 1414, 1247 (C-N str.), 1086, 1012, 834, 749 (NH wag.), 683, 612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ *7.76 (d, J = 8.3 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 7.49 – 7.46 (m, 2H)*, 7.45 (d, *J* = 8.7 Hz, 2H), 7.43 – 7.38 (m, 2H), 4.94 (br s, 2H, NH_2), 4.23 (s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.3 (quart.C=C), 139.6, *138.3*, 137.0, *133.7*, 133.4, *131.6*, 129.7, 129.3, *128.9*, *128.8*, 127.4, 119.1(C≡N), *118.0 (C≡N)*, 110.7, 64.39 (C=CH).

(*E*)-3-amino-3-(4-fluorophenyl)acrylonitrile (61d)



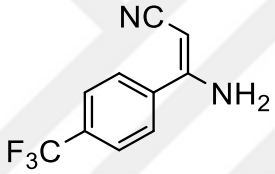
Applying the general procedure in section 2.1.1 and stirring at room temperature for 3 hour afforded white powder solid. (1.65 g, 82%), m.p. 98-100°C; R_f (25% EtOAc/hexane) 0.40; IR (ATR) υ: 3454-3347 (NH_2 str.), 3230 (NH_2 str.), 2992 (Alip CH str.), 2235 (C≡N str.), 2185 (C≡N str.), 1770, 1644 (NH_2 bend.), 1601 (C=C str.), 1505 (arom.C=C str.), 1236 (C-N str.), 1159, 838 (NH wag.), 684, 545 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.46 (m, 2H), 7.13 (t, *J* = 7.6 Hz, 2H), 4.99 (br s, 2H, NH_2), 4.21 (s, 1H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5 (quart.C=C), 163.0, 160.4, 131.4, 129.7, 128.1, 119.3 (C≡N), 116.2, 115.7, 63.9 (C=CH).

3-amino-3-(4-(methylthio)phenyl)acrylonitrile (61e) (Mixture of E-Z isomers-2:1)



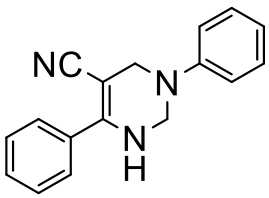
Applying the general procedure in section 2.1.1 and stirring at room temperature for 2 hour afforded white powder solid. (2.80 g, 87%), m.p. 108-110°C; R_f (25% EtOAc/hexane) 0.50; IR (ATR) υ: 3440-3323 (NH_2 str.), 3230 (NH_2 str.), 2989 (Alip CH str.), 2189 (C≡N), 1769, 1634 (NH_2 bend.), 1576 (C=C str.), 1484 (C=C str.), 1383, 1245 (C-N str.), 1086, 828, 749 (NH wag.), 686, 611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ *7.55 (d, J = 8.5 Hz, 2H),* 7.43 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 6.0 Hz, 2H), 4.95 (br s, 2H, NH_2), 4.25 (s, 1H), *2.53 (s, 3H),* 2.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9 (quart.C=C), *146.1*, 142.8, 132.1, 131.4, *128.8*, *128.0*, 126.2, 126.0, 125.5, 119.6 (C≡N), *119.0 (C≡N)*, 107.6, *65.4 (C=CH)*, 63.3 (C=CH), 15.1 (SCH_3), *14.7(SCH_3).*

(*E*)-3-amino-3-(4-(trifluoromethyl)phenyl)acrylonitrile (61f)



Applying the general procedure in section 2.1.1 and stirring at room temperature for 3.5 hour afforded white powder solid. (2.70 g, 87%), m.p. 123-125°C; R_f (25% EtOAc/hexane) 0.50; IR (ATR) υ: 3429-3337 (NH_2 str.), 3255 (NH_2 str.), 2921-2857 (Alip CH str.), 2185 (C≡N str.), 1759, 1641 (NH_2 bend.), 1571 (C=C str.), 1428, 1318, 1246 (C-N str.), 1131, 1064, 849, 763 (NH wag.), 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.67 (m, 2H), 7.65 (d, *J* = 8.1 Hz, 2H), 5.05 (br s, 1H, NH_2), 4.31 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0 (quart.C=C), 138.8, 133.3, 132.9, 132.6, 132.3, 128.2, 127.8, 126.6, 126.0, 125.6, 124.9, 122.2, 118.7 (C≡N), 65.4 (C=CH).

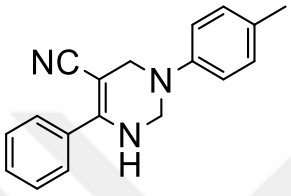
3,6-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62a)



Applying the general procedure in section 2.1.2 and heating at 120-130^oC for 2.5 hour and column chromatography (15% EtOAc/hexane) afforded light

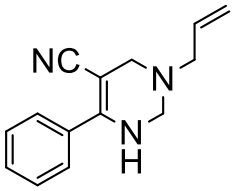
orange solid. (0.475 g, 57%), m.p. 108-110°C; R_f (25% EtOAc/hexane) 0.40; IR (ATR) υ: 3291 (NH), 3063 (arom CH), 2917-2857 (CH), 2183 (C≡N), 1595, 1506, 1493, 1360, 1293, 1193, 969, 921, 753, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 3H), 7.21 (dd, *J* = 16.7, 9.1 Hz, 2H), 6.99 (d, *J* = 7.9 Hz, 2H), 6.89 (t, *J* = 7.3 Hz, 1H), 4.73 (s, 1H, NH), 4.62 (d, *J* = 4.0 Hz, 2H), 4.09 (s, 2H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6 (quart.C=**C**-NH), 148.2 (quart.C), 134.4 (quart.C), 130.6, 129.4, 128.8, 127.8, 121.7, 121.1 (C≡N), 118.4, 75.4 (C=**C**-CH_2), 61.6 (N-**C**H_2-N), 48.8 (**C**H_2-N).

6-phenyl-3-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62b)



Applying the general procedure in section 2.1.2 and heating at 120-130°C for 3 hour and column chromatography (15% EtOAc/hexane) afforded light orange solid. (0.465 g, 58%), m.p. 137-139°C; R_f (25% EtOAc/hexane) 0.45; IR (ATR) υ: 3335 (NH), 3030 (arom CH), 2956-2856 (CH), 2175 (C≡N), 1595, 1567, 1503, 1475, 1360, 1291, 1188, 998, 809, 769, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 6.3 Hz, 2H), 7.42 (d, *J* = 7.4 Hz, 3H), 7.13 (d, *J* = 8.2 Hz, 2H), 7.00 (d, *J* = 8.3 Hz, 2H), 4.80 (s, 1H), 4.69 (s, 2H), 4.17 (s, 2H), 2.31 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 145.9, 134.5, 131.3, 130.6, 129.9, 128.7, 127.8, 121.2, 120.1, 118.7, 75.4, 62.0, 49.0, 20.5.

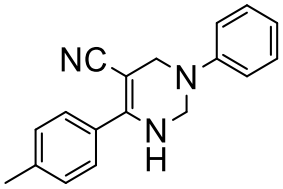
3-allyl-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62c)



Applying the general procedure in section 2.1.2 and heating at 120-130°C for 3 hour and column chromatography (25% EtOAc/hexane) afforded liht orange solid. (0.635 g, 85%), m.p. 93-95°C; R_f (50% EtOAc/hexane) 0.45; IR (ATR) υ: 3152 (NH), 3081 (arom CH), 2928-2857 (CH), 2179 (C≡N), 1595, 1523, 1444, 1278, 988, 922, 781, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 9.3 Hz, 2H), 7.45 (d, *J* = 7.0 Hz, 3H), 5.93 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.27 (t, *J* = 12.7 Hz, 2H), 4.71 (s, 1H), 4.16 (d, *J* = 3.7 Hz, 2H), 3.60 (s, 2H), 3.26 (d, *J* = 6.4 Hz, 2H).;

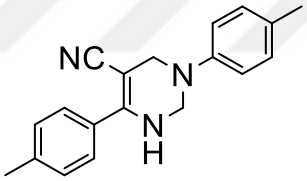
^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 134.6, 134.3, 130.5, 128.8, 127.7, 121.5, 118.9, 73.3, 61.5, 55.3, 50.5.

3-phenyl-6-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62d)



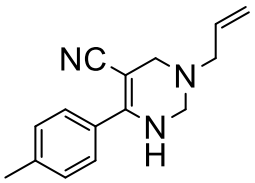
Applying the general procedure in section 2.1.2 and heating at 120-130ºC for 4 hour and column chromatography (15% EtOAc/hexane) afforded yellow solid. (0.405 g, 60%), m.p. 116-118°C; R_f (25% EtOAc/hexane) 0.60; IR (ATR) υ: 3362 (NH), 2999-2853 (CH), 2173 (C≡N), 1592, 1493, 1453, 1371, 1245, 1188, 921, 818, 748, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.1 Hz, 2H), 7.32 (dd, *J* = 15.5, 8.0 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 4.78 (s, 1H), 4.72 (s, 2H), 4.19 (s, 2H), 2.38 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 148.3, 140.9, 131.6, 129.4, 129.4, 127.7, 121.6, 121.3, 118.4, 75.0, 61.5, 48.8, 21.4.

3,6-di-p-tolyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62e)



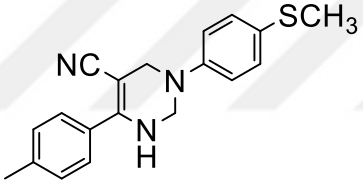
Applying the general procedure in section 2.1.2 and heating at 120-130ºC for 3 hour and column chromatography (15% EtOAc/hexane) afforded dark yellow solid. (0.567 g, 72%), m.p. 132-134°C; R_f (25% EtOAc/hexane) 0.65; IR (ATR) υ: 3319 (NH), 2989-2853 (CH), 2184 (C≡N), 1594, 1511, 1486, 1364, 1295, 1248, 1187, 1015, 813, 552 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 4.77 (s, 1H), 4.67 (d, *J* = 4.0 Hz, 2H), 4.15 (s, 2H), 2.38 (s, 3H), 2.31 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 146.0, 140.9, 131.6, 131.3, 129.9, 129.4, 127.7, 121.4, 118.6, 74.9, 61.9, 49.0, 21.4, 20.5.

3-allyl-6-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62f)



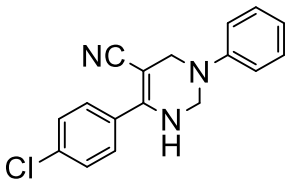
Applying the general procedure in section 2.1.2 and heating at 120-130ºC for 2.5 hour and column chromatography (25% EtOAc/hexane) afforded pale yellow solid. (0.512 g, 65%), m.p. 126-128°C; R_f (50% EtOAc/hexane) 0.50; IR (ATR) υ: 3343 (NH), 2917-2829 (CH), 2183 (C≡N), 1592, 1497, 1396, 1252, 1091, 1010, 942, 837, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 5.84 (td, *J* = 16.7, 6.5 Hz, 1H), 5.17 (t, *J* = 12.5 Hz, 2H), 4.60 (s, 1H), 4.06 (d, *J* = 3.5 Hz, 2H), 3.50 (s, 2H), 3.16 (d, *J* = 6.3 Hz, 2H), 2.31 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 140.8, 134.2, 131.7, 129.5, 127.6, 121.6, 119.0, 72.9, 61.5, 55.3, 50.5, 21.4.

3-(4-(methylthio)phenyl)-6-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62g)



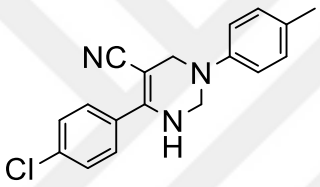
Applying the general procedure in section 2.1.2 and heating at 120-130ºC for 2.5 hour and column chromatography (15% EtOAc/hexane) afforded yellowish-green solid. (0.101 g, 75%), m.p. 140-142°C; R_f (25% EtOAc/hexane) 0.40; IR (ATR) υ: 3300 (NH), 2917-2857 (CH), 2180 (C≡N), 1602, 1525, 1495, 1392, 1316, 1256, 1182, 1081, 934, 820, 723, 660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 8.1 Hz, 2H), 7.24 (dd, *J* = 17.3, 8.3 Hz, 4H), 7.02 (d, *J* = 8.7 Hz, 2H), 4.80 (s, 1H), 4.69 (d, *J* = 4.1 Hz, 2H), 4.16 (s, 2H), 2.47 (s, H), 2.38 (s, H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 146.4, 141.0, 131.5, 130.2, 129.4, 129.2, 127.7, 121.2, 119.1, 74.8, 61.6, 48.9, 21.4, 17.2.

6-(4-chlorophenyl)-3-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62h)



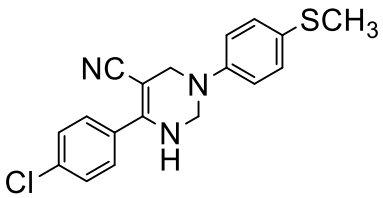
Applying the general procedure in section 2.1.2 and heating at 120-130ºC for 2.5 hour and column chromatography (15% EtOAc/hexane) afforded yellow solid. (0.635 g, 87%), m.p. 133-135°C; R_f (25% EtOAc/hexane) 0.65; IR (ATR) υ: 3362 (NH), 2953-2832 (CH), 2185 (C≡N), 1605, 1503, 1397, 1253, 1091, 1012, 941, 837, 754, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.5 Hz, 2H), 7.32 (dd, *J* = 16.8, 9.4 Hz, 2H), 7.08 (d, *J* = 7.8 Hz, 2H), 7.00 (t, *J* = 7.3 Hz, 1H), 4.81 (s, 1H), 4.73 (d, *J* = 4.2 Hz, 2H), 4.19 (s, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 148.1, 136.7, 132.7, 129.4, 129.2, 129.1, 121.8, 120.7, 118.3, 76.2, 61.6, 48.7.; (TOF-MS APCI$^+$) *m/z*: 294 (100, M-H$^+$), 295 (20%, M$^+$); HRMS (TOF-MS APCI$^+$): M$^+$, found 295.0862. $C_{17}H_{14}ClN_3$ requires 295.0876.

6-(4-chlorophenyl)-3-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62i)



Applying the general procedure in section 2.1.2 and heating at 120-130ºC for 3 hour and column chromatography (15% EtOAc/hexane) afforded pale yellow solid. (0.731 g, 90%), m.p. 145-147°C; R_f (25% EtOAc/hexane) 0.40; IR (ATR) υ: 3291 (NH), 2926-2846 (CH), 2179 (C≡N), 1600, 1513, 1492, 1098, 1013, 973, 932, 824, 724, 654 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.69 (s, 1H), 4.58 (d, *J* = 3.8 Hz, 2H), 4.05 (s, 2H), 2.21 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 145.8, 136.7, 132.8, 131.5, 129.9, 129.2, 129.0, 120.8, 118.6, 76.3, 62.0, 48.9, 20.5.

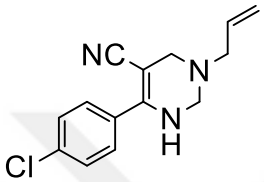
6-(4-chlorophenyl)-3-(4-(methylthio)phenyl)-1,2,3,4-tetrahydro pyrimidine-5-carbonitrile (62j)



Applying the general procedure in section 2.1.2 and heating at 120-130ºC for 1.5 hour and column chromatography (15% EtOAc/hexane) afforded yellowish-

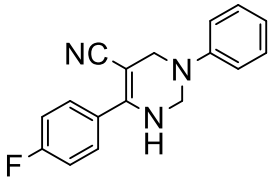
green solid. (0.135 g, 85%), m.p. 131-133°C; R_f (25% EtOAc/hexane) 0.30; IR (ATR) υ: 3342 (NH), 2917-2829 (CH), 2183 (C≡N), 1592, 1497, 1396, 1252, 1091, 1010, 942, 837, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.5 Hz, 2H), 7.29 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.77 (s, 1H), 4.59 (s, 2H), 4.06 (s, 2H), 2.37 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 146.1, 136.7, 132.7, 130.5, 130.0, 129.2, 129.2, 129.1, 129.0, 127.5, 125.4, 120.6, 120.6, 119.0, 117.9, 76.0, 61.6, 48.8, 17.2.

3-allyl-6-(4-chlorophenyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62k)



Applying the general procedure in section 2.1.2 and heating at 120-130°C for 2 hour and column chromatography (25% EtOAc/hexane) afforded off-white solid. (0.365 g, 80%), m.p. 102-104°C; R_f (50% EtOAc/hexane) 0.45; IR (ATR) υ: 3397 (NH), 3070 (arom CH), 2932-2843 (CH), 2172 (C≡N), 1587, 1465, 1368, 1291, 1091, 999, 926, 833, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 5.93 (dt, *J* = 23.3, 6.5 Hz, 1H), 5.35 – 5.20 (m, 2H), 4.70 (s, 1H), 4.16 (s, 2H), 3.58 (s, 2H), 3.25 (d, *J* = 6.3 Hz, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.5, 136.6, 134.0, 132.8, 129.1, 129.1, 121.0, 119.1, 74.2, 61.5, 55.3, 50.4.

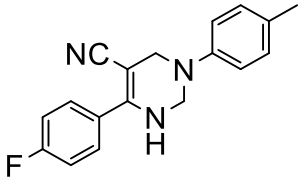
6-(4-fluorophenyl)-3-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62l)



Applying the general procedure in section 2.1.2 and heating at 120-130°C for 2.5 hour and column chromatography (15% EtOAc/hexane) afforded yellowish white solid. (0.620 g, 82%), m.p. 118-120°C; R_f (25% EtOAc/hexane) 0.30; IR (ATR) υ: 3305 (NH), 3067 (arom CH), 2917-2814 (CH), 2186 (C≡N), 1608, 1524, 1497, 1386, 1231, 1152, 1090, 939, 837, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.48 (m, 2H), 7.32 (dd, *J* = 17.3, 9.8 Hz, 2H), 7.09 (dd, *J* = 8.3, 3.3 Hz, 4H),

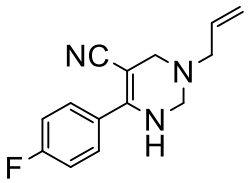
7.00 (t, *J* = 7.3 Hz, 1H), 4.76 (br s, 1H), 4.74 (s, 2H), 4.20 (s, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.26, 162.76, 154.6, 148.1, 130.5, 130.5, 130.0, 129.9, 129.4, 121.8, 120.8, 118.3, 116.0, 115.8, 76.0, 61.6, 48.7.

6-(4-fluorophenyl)-3-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62m)



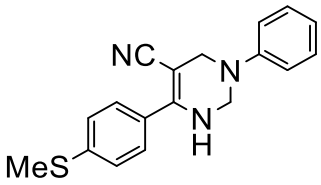
Applying the general procedure in section 2.1.2 and heating at 120-130^{o}C for 3 hour and column chromatography (15% EtOAc/hexane) afforded light orange solid. (0.570 g, 70%), m.p. 134-136°C; R_f (25% EtOAc/hexane) 0.35; IR (ATR) υ: 3333 (NH), 2921-2853 (CH), 2178 (C≡N), 1604, 1515, 1493, 1382, 1232, 1160, 944, 837, 801, 648 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.09 – 7.01 (m, 2H), 6.96 (d, *J* = 8.3 Hz, 2H), 4.77 (d, *J* = 26.5 Hz, 1H), 4.64 (s, 2H), 4.11 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 162.9, 154.6, 145.8, 131.4, 130.57, 130.54, 130.0, 129.9, 121.1, 118.6, 116.0, 115.8, 75.6, 61.9, 48.9, 20.5.

3-allyl-6-(4-fluorophenyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62n)



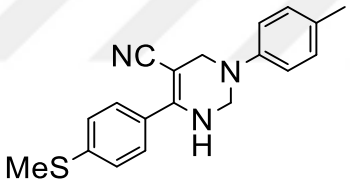
Applying the general procedure in section 2.1.2 and heating at 120-130^{o}C for 3 hour and column chromatography (25% EtOAc/hexane) afforded beige solid. (0.535 g, 81%), m.p. 98-100°C; R_f (50% EtOAc/hexane) 0.50; IR (ATR) υ: 3387 (NH), 3081 (arom CH), 2917-2853 (CH), 2175 (C≡N), 1600, 1508, 1466, 1277, 1222, 1154, 1097, 931, 837, 750 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 8.6, 5.3 Hz, 2H), 7.12 (t, *J* = 8.6 Hz, 2H), 5.90 (ddt, *J* = 16.7, 10.1, 6.5 Hz, 1H), 5.25 (dd, *J* = 22.9, 5.7 Hz, 2H), 4.58 (s, 1H), 4.13 (d, *J* = 3.8 Hz, 2H), 3.56 (s, 2H), 3.22 (d, *J* = 6.5 Hz, 2H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.8, 162.8, 153.7, 134.5, 130.73, 130.71, 129.9, 129.8, 121.4, 118.8, 116.0, 115.8, 73.9, 61.6, 55.3, 50.5.

6-(4-(methylthio)phenyl)-3-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62o)



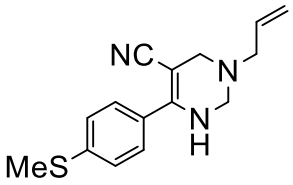
Applying the general procedure in section 2.1.2 and heating at 120-130ºC for 2.5 hour and column chromatography (15% EtOAc/hexane) afforded red-orange semi-solid. (0.440 g, 65%); R_f (25% EtOAc/hexane) 0.50; IR (ATR) υ: 3298(NH), 2921-2853 (CH), 2178 (C≡N), 1591, 1493, 1365, 1246, 1186, 1093, 1003, 821, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.5 Hz, 2H), 7.32 (dt, *J* = 14.3, 7.1 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 7.7 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 4.85 (s, 1H), 4.71 (s, 2H), 4.18 (s, 2H), 2.49 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 148.2, 142.3, 130.6, 129.4, 128.1, 125.8, 121.7, 121.2, 118.3, 75.2, 61.5, 48.8, 15.1.

6-(4-(methylthio)phenyl)-3-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62p)



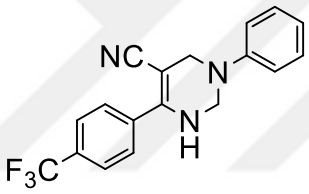
Applying the general procedure in section 2.1.2 and heating at 120-130ºC for 2 hour and column chromatography (15% EtOAc/hexane) afforded yellow solid. (0.517 g, 71%), m.p. 130-132°C; R_f (25% EtOAc/hexane) 0.65; IR (ATR) υ: 3294 (NH), 2996-2857 (CH), 2176 (C≡N), 1596, 1509, 1487, 1395, 1246, 1095, 935, 806, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 8.3 Hz, 2H), 7.15 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 4.66 (s, 1H), 4.57 (d, *J* = 4.0 Hz, 2H), 4.05 (s, 2H), 2.39 (s, 3H), 2.21 (s, 3H; ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 145.9, 142.2, 131.3, 130.7, 129.9, 128.1, 125.9, 121.2, 118.6, 75.4, 62.0, 49.0, 20.5, 15.1.

3-allyl-6-(4-(methylthio)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62r)



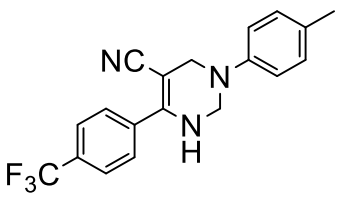
Applying the general procedure in section 2.1.2 and heating at 120-130°C for 3 hour and column chromatography (25% EtOAc/hexane) afforded orange-yellow solid. (0.700 g, 98%), m.p. 88-90°C; R_f (50% EtOAc/hexane) 0.40; IR (ATR) υ: 3315 (NH), 2992-2839 (CH), 2176 (C≡N), 1590, 1567, 1504, 1484, 1369, 1291, 1241, 1093, 923, 821, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 5.93 (td, *J* = 16.7, 8.3 Hz, 1H), 5.26 (t, *J* = 12.8 Hz, 2H), 4.68 (s, 1H), 4.15 (d, *J* = 3.8 Hz, 2H), 3.58 (s, 2H), 3.24 (d, *J* = 6.4 Hz, 2H), 2.52 (s, H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 142.1, 134.3, 130.8, 129.2, 128.0, 125.9, 121.5, 118.9, 73.4, 61.5, 55.3, 50.5, 15.2.

3-phenyl-6-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62s)



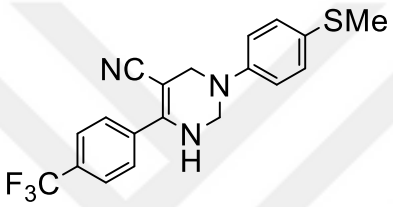
Applying the general procedure in section 2.1.2 and heating at 120-130°C for 3 hour and column chromatography (15% EtOAc/hexane) afforded orange-yellow solid. (0.455 g, 74%), m.p. 120-122°C; R_f (25% EtOAc/hexane) 0.40; IR (ATR) υ: 3372 (NH), 2932-2854 (CH), 2182 (C≡N), 1595, 1492, 1369, 1322, 1246, 1109, 1065, 845, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 4H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.06 (d, *J* = 7.9 Hz, 2H), 6.99 (t, *J* = 7.3 Hz, 1H), 4.83 (d, *J* = 22.5 Hz, 1H), 4.72 (s, 2H), 4.18 (s, 2H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2, 148.0, 137.7, 132.8, 132.5, 132.3, 132.1, 130.0, 129.5, 128.4, 126.8, 125.8, 124.7, 122.5, 121.9, 120.5, 119.9, 118.3, 76.8, 61.5, 48.7.

3-(p-tolyl)-6-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydro pyrimidine-5-carbonitrile (62t)



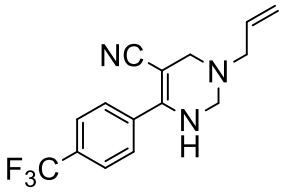
Applying the general procedure in section 2.1.2 and heating at 120-130ºC for 2.5 hour and column chromatography (15% EtOAc/hexane) afforded light brown crystal. (0.654 g, 91%), m.p. 134-136°C; R_f (25% EtOAc/hexane) 0.50; IR (ATR) υ: 3376 (NH), 2921-2857 (CH), 2182 (C≡N), 1599, 1512, 1484, 1369, 1322, 1242, 1111, 1066, 965, 814, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 4H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 4.73 (s, 1H), 4.62 (s, 2H), 4.08 (s, 2H), 2.22 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 145.7, 137.8, 132.9, 132.6, 132.3, 131.9, 131.6, 130.5, 130.0, 128.4, 125.8, 120.4, 120.0, 118.6, 77.2, 62.0, 48.9, 20.5.

3-(4-(methylthio)phenyl)-6-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62u) (Mixture of two isomers -2:1)



Applying the general procedure in section 2.1.2 and heating at 120-130ºC for 2.5 hour and column chromatography (15% EtOAc/hexane) afforded light brown crystal. (0.610 g, 80%), m.p. 120-122°C; R_f (25% EtOAc/hexane) 0.30; IR (ATR) υ: 3280 (NH), 2999-2829 (CH), 2192 (C≡N), 1613, 1495, 1395, 1319, 1247, 1109, 1065, 817, 749 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ *7.85 (d, J = 8.0 Hz, 2H)*, *7.65 (d, J = 8.7 Hz, 2H)*, 7.58 (s, 4H), *7.25 (d, J = 8.6 Hz, 2H)*, 7.17 (d, *J* = 8.8 Hz, 2H), *7.03 (d, J = 8.6 Hz, 2H)*, 6.93 (d, *J* = 8.8 Hz, 2H), 4.78 (s, 1H), 4.63 (s, 2H), 4.09 (s, 2H), *2.44 (s, 3H)*, 2.38 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ *167.8*, 160.7, 154.1, *150.6*, 146.0, *138.2*, 137.7, 133.0, 132.6, 132.3, 132.0, 130.7, 129.1, 128.8, 128.4, 127.5, 125.8, *125.5*, 120.5, *120.3*, 119.1, 118.0, *117.8*, *83.4*, 77.2, *65.1*, 61.6, 48.8, 17.1, *15.7*.

3-allyl-6-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (62v)



Applying the general procedure in section 2.1.2 and heating at 120-130ºC for 3 hour and column chromatography (15% EtOAc/hexane) afforded dark yellow

solid. (0.400 g, 76%), m.p. 116-118°C; R_f (25% EtOAc/hexane) 0.45; IR (ATR) υ: 3355 (NH), 2925-2850 (CH), 2173 (C≡N), 1592, 1473, 1323, 1245, 1123, 1069, 845, 727, 676 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 4H), 5.84 (td, *J* = 16.6, 6.5 Hz, 1H), 5.25 – 5.11 (m, 2H), 4.63 (s, 1H), 4.10 (d, *J* = 3.7 Hz, 2H), 3.52 (s, 2H), 3.18 (d, *J* = 6.4 Hz, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 137.9, 134.0, 132.6, 132.2, 128.3, 127.8, 125.9, 125.8, 125.8, 125.0, 122.3, 120.7, 119.2, 75.2, 61.6, 55.4, 50.4.

4. DISCUSSION

4.1 Synthesis and Characterization of Precursor Compounds

Enamines are important and very versatile precursors for the synthesis of different nitrogen-containing heterocyclic rings such as pyridines, pyrimidines, pyrroles, indoles etc. over several cyclization reactions and organic transformations (Kurihara & Mishima, 1977; Barluenga et al., 1979; Granik et al., 1998; Khan et al. 2010; Zhang et al., 2016; Chen et al., 2017; Gülbenek et al., 2022; Yildirim & Çelikel, 2015). In this dissertation, several 3-aryl-substituted acrylonitriles (**61a-f**) were synthesized as enamine precursors from various aryl nitriles (**30**) using a straightforward and efficient method reported in the literature (Figure 4.1.) (Yamaguchi et al., 1998).

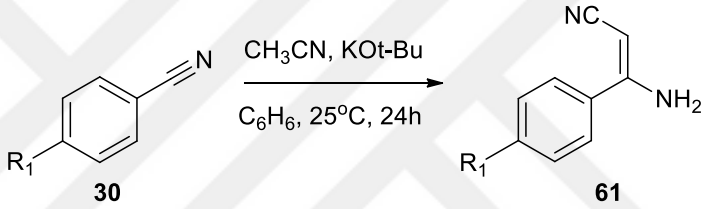


Figure 4.1. Preparation method for enamine precursors (**61a-f**)

The precursors, 3-amino-3-aryl acrylonitriles (**61a-f**) were preraped in excellent yields (82-90%) by the reaction of aryl nitriles **30** with acetonitrile in the presence of KOt-Bu in benzene at room temperature for 2-4 hour (entries 1-7, Table 4.1). It is seen that nitriles with EDGs (SMe, OH) on para-position of phenyl facilitated the formation of enamines (**61e**, **61g**) and their reactions completed faster in comparison to others. (entries 5,7, Table 4.1).

The structures of the enamine derivatives (**61a-f**) were determined using IR and NMR spectroscopy or by comparison with corresponding data from recent literature studies. Firstly, the structures of enamines **61a-f** were characterized by the peak of NH_2, C≡N and C=C IR vibrations at around 3451-3223, 2181-2235 and 1571-1601 cm^{-1}, respectively. Moreover, the structure of expected enamines **61a-f** were supported by broad NH_2 proton (4.94-5.05 ppm) and singlet C=CH proton peaks (4.21-4.31 ppm) in proton NMR spectra and by quarternary C=C and =CHCN

carbon peaks at 160.3-165.5, 63.0-65.4 ppm in carbon-13 NMR spectra, respectively (Table 4.2).

Table 4.1. Enamine precursors (**61**), reaction conditions and yields

Entry	Enamine	R	Time (h)	Yield (%)	Isomer
1	**61a**	H	3.5	90	single
2	**61b**	p-Me	3	85	E/Z
3	**61c**	p-Cl	4	89	E/Z
4	**61d**	p-F	3	82	single
5	**61e**	p-SMe	2	87	E/Z
6	**61f**	p-CF_3	3.5	87	single
7	**61g**	p-OH	2	90	single

Table 4.2. Indicative IR and NMR data for the enamine precursors **61a-f**

Enamine	IR (ν_{max}/cm^{-1})			^{1}H-NMR (δ,ppm)		^{13}C-NMR (δ,ppm)	
61	NH_2	C≡N	C=C	N**H₂**	C=C**H**	**C**=C	**=C**HCN
a	3451-3223	2183	1589	5.00	4.26	161.5	63.6
b	3433-3241	2181	1586	4.98	4.24	161.5	63.0
c	3404-3241	2182	1584	4.94	4.23	160.3	64.3
d	3454-3230	2235	1601	4.99	4.21	165.5	63.9
e	3440-3230	2189	1576	4.95	4.25	160.9	63.3
f	3429-3255	2185	1571	5.05	4.31	160.0	65.4

Representative IR, proton, and carbon-13 NMR spectra of enamine **61a** are provided below, highlighting the key IR absorptions and chemical shifts consistent with the expected structure (Figures 4.2-4.4). Proton NMR analysis revealed that some enamine precursors (**61b-c, 61e**) existed as E/Z isomeric mixtures in varying ratios, whereas the other enamines (**61a, 61d, 61g**) were mostly isolated as single isomer (see Results Section for details). The IR and NMR spectra of other enamines (**61b-f**) are given in figures A.4-A.18 in appendices section.

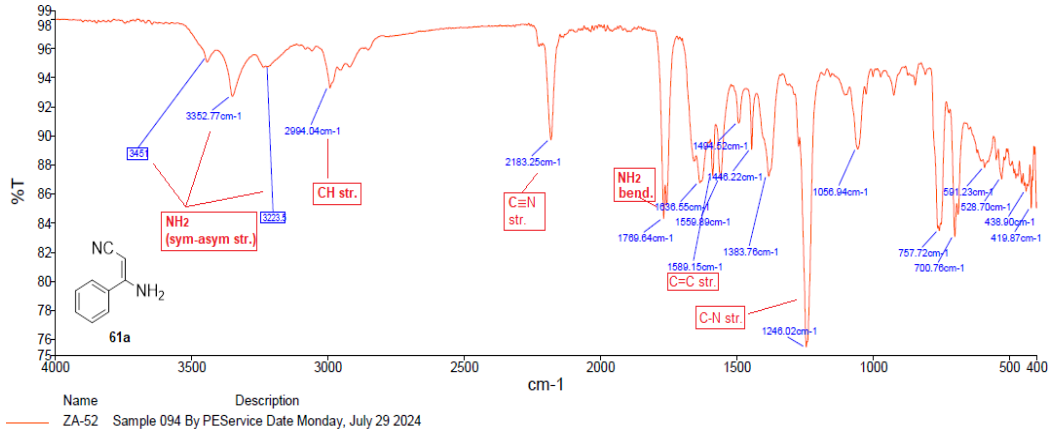


Figure 4.2. Main absorptions in IR spectrum of **61a**

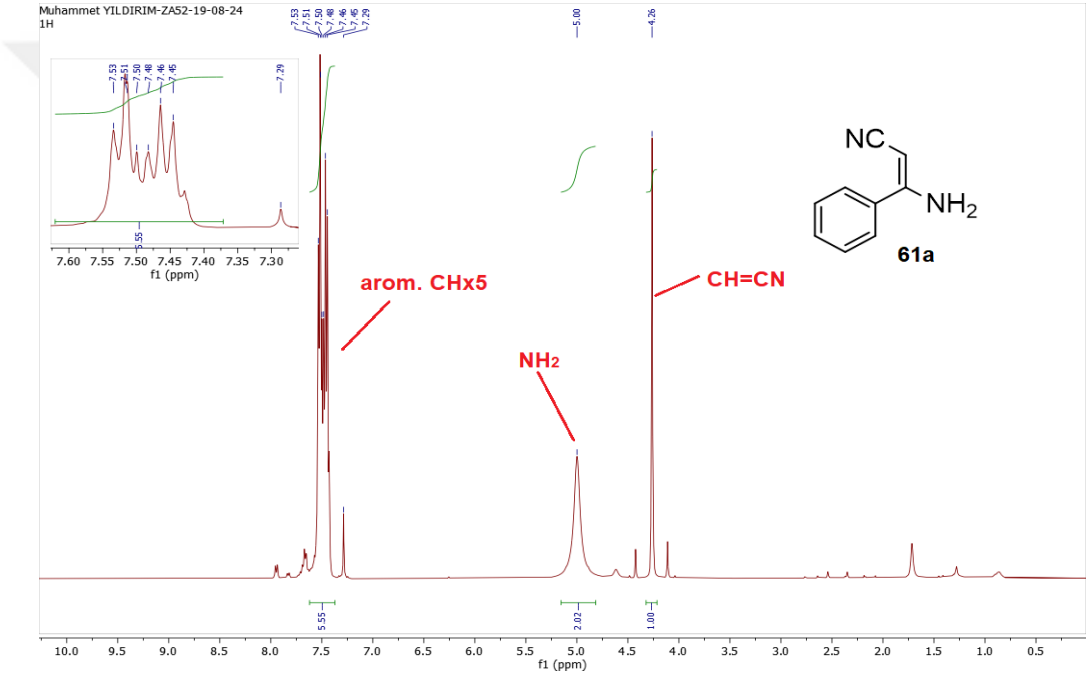


Figure 4.3. Proton NMR spectrum of **61a**

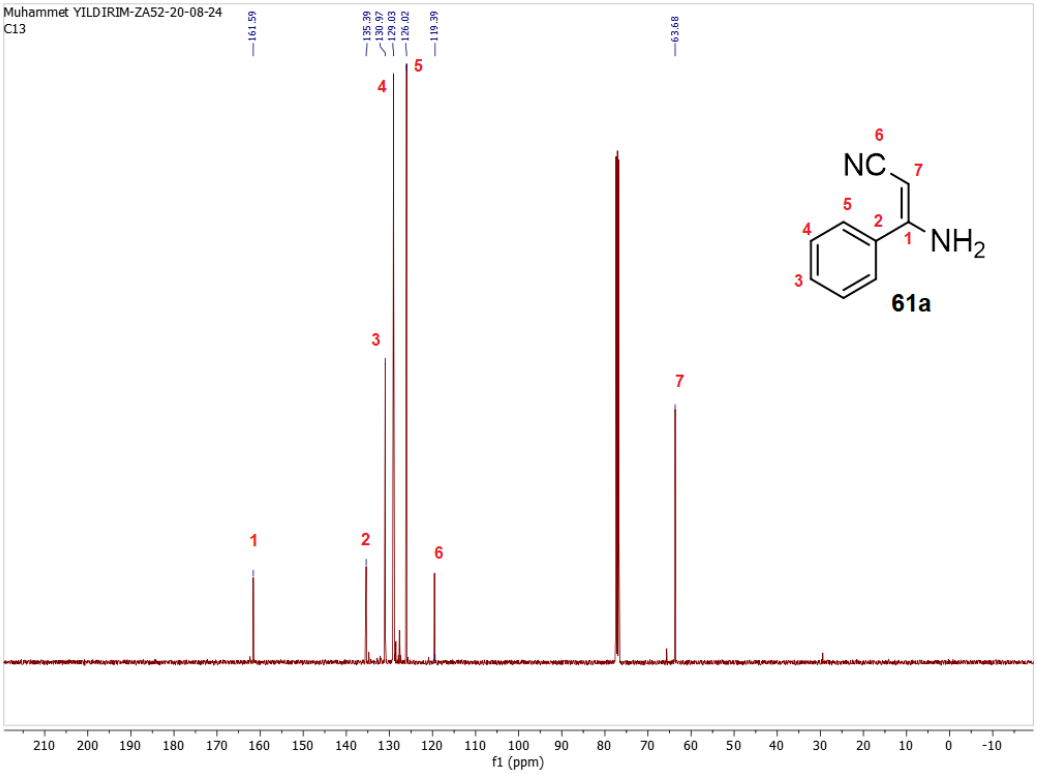
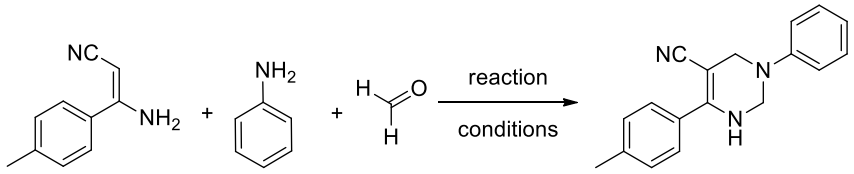


Figure 4.4. Carbon-13 NMR spectrum of **61a**

4.2 Synthesis and Characterization of 3,6-(diaryl)-1,2,3,4-tetrahydropyrimidine-5-carbonitriles (62)

Building on our ongoing interest in synthesizing novel pyrimidine-based compounds through enamine chemistry, this study planned eco-friendly three-component Mannich cyclizations of newly synthesized 3-amino-3-aryl acrylonitriles (**61**) with formaldehyde (**48**) and amine derivatives (**47**) to produce novel tetrahydropyrimidines (THPM) (**62**). Initially, a series of trial experiments were conducted to determine the optimal reaction conditions for the efficient synthesis of new THPMs (**62**). We conducted Mannich cyclization experiments under various conditions using 3-amino-3-phenyl acrylonitriles **61b**, formaldehyde **48**, and aniline **47a** as our model reaction (Table 4.3). In all trials, an excess amount of formaldehyde **48** was used relative to the enamine **61b** and aniline **47a** precursors. The progress or completion of each reaction was monitored by TLC.

Table 4.3. Reaction optimizations for the synthesis of compound **62d**



61b **47a** **48** **62d**

Entry	Reaction conditions	Cat.	Time	Temp.	Yield (%)[a]
1	Neat, **61b (**1eq**), 47a** (1eq)**, 48** (2.0 eq)	MW	1h	80ºC	decomp.
2	EtOH, **61b (**1eq**), 47a** (1eq)**, 48** (2.0 eq)	-	6h	reflux	NR
3	EtOH, **61b (**1eq**), 47a** (1eq)**, 48** (2.0 eq)	Et_3N	4h	80ºC	15
4	EtOH, **61b (**1eq**), 47a** (1eq)**, 48** (2.0 eq)	MW	1.5h	80ºC	26
5	CH_3CN, **61b (**1eq**), 47a**(1eq)**, 48** (2.0 eq)	-	5h	reflux	25
6	CH_3CN, **61b (**1eq**), 47a**(1eq)**, 48** (2.0 eq)	MW	1h	80ºC	28
7	PEG-600, **61b (**1eq**), 47a**(1.3eq)**, 48** (2.5 eq)	-	5h	100ºC	30
8	PEG-400, **61b (**1eq**), 47a**(1.3eq)**, 48** (2.5 eq)	-	5h	25ºC	NR
9	PEG-400, **61b (**1eq**), 47a**(1.3eq)**, 48** (2.5 eq)	-	5h	80ºC	20
10	PEG-400, **61b (**1eq**), 47a**(1.3eq)**, 48** (2.5 eq)	-	5h	100ºC[b]	35
11	PEG-400, **61b (**1eq**), 47a**(1.3eq)**, 48** (2.5 eq)	-	5h	120-130 ºC	**60**

[a] Yields after CC. [b] Not completed. NR= no reaction

The trial reaction was found to be inefficient under MW irradiation in neat conditions (entries 1, table 4.3). When ethanol, a protic solvent, was used in the reaction with or without Et_3N under reflux or MW heating, the product yields were low (0-26%) (entry 2-4, table 4.3). However, reactions conducted in acetonitrile, a polar aprotic solvent, under microwave irradiation or reflux resulted in low yields of product **62d** (entries 5,6, table 4.3). Subsequent model reactions were conducted in PEG derivatives as eco-friendly alternatives to traditional organic solvents. First trial reaction in PEG-600 at 100ºC afforded the product **62d** in low yield (30%) (entry 7, table 4.3). The reaction trials in PEG-400 at 25 or 80ºC gave either no product or low yields of the product (entry 8.9, table 4.3). Running the model reaction at 100°C resulted in a moderate increase in product yield (35%), however, the reaction did not go completion (entry 10, table 4.3). The final reaction trial in PEG-400 at 120–130°C yielded the desired product **62d** in higher amounts (60%) with complete consumption of enamine **61b** (entry 11, table 4.3).

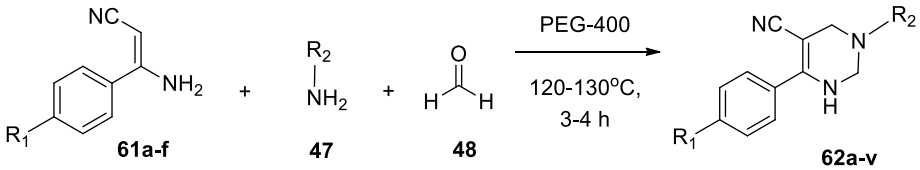
Once the optimal reaction conditions were established, 3-amino-3-aryl acrylonitriles (**61a-f**) were reacted with various amine derivatives (**47a-f**) in the presence of formaldehyde (**48**), affording new derivatives of 3,6-(diaryl)-1,2,3,4-

tetrahydropyrimidine-5-carbonitriles (**62a-v**) in moderate to high yields (57-98%) with a few exceptions (Table 4.4). Subsequently, all cyclization products (**62a–v**) were purified by flash column chromatography using 15–25% EtOAc/hexane mixtures as the eluent and were isolated with high purity.

Under optimized conditions in PEG-400, Mannich cyclizations of phenyl substituted enaminonitrile (**61a**) with two aniline derivatives and allylamine afforded the products **62a-c** in moderate-to-good yields (57-85%) within 2.5-3 hours (entries 1-3 table 4.4). The highest yield (85%) in this series of products (**62a-c**) was achieved in the cyclization reaction with allylamine within 3 hour (entry 3, table 4.4). Additionally, the cyclization reactions of *p*-tolyl substituted enaminonitrile (**61b**) with aniline derivatives (Ph, 4-Me-Ph, 4-SMe-Ph) and allylamine furnished the cyclization products (**62d-g**) in good yields (60-75%) within 2.5-4 hours (entries 4-7, table 4.4). In this series, the highest yields (72–75%) were obtained in the cyclizations with 4-methylaniline and 4-thiomethylaniline. It is clear that the ED groups (Me and SMe) on anilines positively affected the product formation (**62e,g**) in terms of reaction yields. Furthermore, the reactions of *p*-chlorophenyl substituted enaminonitrile (**61c**) with aniline derivatives (Ph, 4-Me-Ph, 4-SMe-Ph) and allylamine afforded the cyclization products (**62h-k**) in high yields (80-90%) within shorter reaction times (entries 8-11, table 4.4). However, the excellent yields (85-90%) were obtained in cyclization reactions of this enamine (**61c**) with 4-thiomethylaniline, aniline and 4-methylaniline, respectively (entries 8,9, table 4.4). The lowest yield in this series (80%) was observed in the reaction of enamine (**61c**) with allylamine (entry 11, Table 4.4); however, all reactions were very efficient under the optimized conditions. Another series of products (**62l-n**) were obtained by the reactions of *p*-fluorophenyl substituted enaminonitrile (**61d**) with aniline derivatives (Ph, 4-Me-Ph) and allylamine in 2.5-3 hour (entry 12-14, table 4.4). Moreover, Mannich cyclizations with an electron-rich enamine, *p*-thiomethylphenyl substituted enaminonitrile (**61e**) with aniline derivatives (Ph, 4-Me-Ph) provided the products (**62o,p**) in good yields (65-71%) within 2-2.5 hour. In contrast, the reaction of same enamine **61e** with allylamine afforded the product **62r** in 3 hour with nearly quantitative yields (98%) (entries 15-17, table 4.4). Last series of products (**62s-v**) were achieved by the reaction an electron-poor enamine, 4-trifluoromethylphenyl substituted enaminonitrile (**61f**) with aniline derivatives (Ph, 4-Me-Ph, SMe-Ph) and allylamine in good to excellent yields (74-91%). Best

yield (91%) in this series of products were found for the product **62t** in the reaction of enamine (**61f**) with p-methylaniline (entry 19, table 4.4).

Table 4.4. 3,6-disubstituted THPM carbonitriles **62a-v** and reaction yields



Entry	Product	R_1	R_2	48 (equiv.)	Time (h)	Yield (%)[a,b]
1	**62a**	Ph	Ph	2.5	2.5	57
2	**62b**	Ph	4-MePh	2.5	3	58
3	**62c**	Ph	Allyl	2.5	3	**85**
4	**62d**	4-MePh	Ph	2.5	4	60
5	**62e**	4-MePh	4-MePh	2.5	3	72
6	**62f**	4-MePh	Allyl	2.5	2.5	65
7	**62g**	4-MePh	4-SMePh	2.5	2.5	75
8	**62h**	4-ClPh	Ph	2.5	2.5	**87**
9	**62i**	4-ClPh	4-MePh	2.5	3	**90**
10	**62j**	4-ClPh	4-SMePh	2.5	1.5	**85**
11	**62k**	4-ClPh	Allyl	2.5	2	**80**
12	**62l**	4-FPh	Ph	2.5	2.5	**82**
13	**62m**	4-FPh	4-MePh	2.5	3	70
14	**62n**	4-FPh	Allyl	2.5	3	**81**
15	**62o**	4-SMePh	Ph	2.5	2.5	65
16	**62p**	4-SMePh	4-MePh	2.5	2	71
17	**62r**	4-SMePh	Allyl	2.5	3	**98**
18	**62s**	4-CF_3Ph	Ph	2.5	3	74
19	**62t**	4-CF_3Ph	4-MePh	2.5	2.5	**91**
20	**62u**	4-CF_3Ph	4-SMePh	2.5	2.5	**80**
21	**62v**	4-CF_3Ph	Allyl	2.5	3	76
22	**62w**	Ph	4-SMePh	4.0	3	-[d]
23	**62y**	4-MePh	4-IPh	2.5	16	-[d]
24	**62z**	4-MePh	4-ClPh	2.0	4	-[d]
25	**62ab**	4-ClPh	4-ClPh	2.0	6	-[c,d]
26	**62ac**	4-FPh	4-SMePh	4.0	3	-[d]
27	**62ad**	4-SMePh	4-SMePh	2.5	4	-
28	**62ae**	4-CF_3Ph	4-ClPh	2.5	3	-[d]
29	**62af**	4-HOPh	Ph	2.5	4	-

[a] 0.65 mmol (**47**), 1.3 mmol (**48**); [b] Total yields after CC; [c] Reaction in EtOH at 80°C.

[d] Decomposition during CC.

These findings indicated that Mannich cyclizations of 3-amino-3-aryl acrylonitriles (**61**) with formaldehyde (**48**) and amine derivatives (**47**) were highly efficient in PEG-400, yielding the desired THPM carbonitrile product (**62a-v**). Unfortunately, the Mannich cyclizations of some enaminonitriles (**61e**, **61g**) with

p-thiomethylaniline and aniline in PEG-400 did not give any expected product (entries 27,29, table 4.4). And, while Mannich cyclizations of various enaminonitriles (**61a-g**) with 4-thiomethylaniline, 4-iodoaniline, 4-chloroaniline, and aniline yielded products in PEG-400 and EtOH, the products were found to decompose during purification in silica gel column chromatography. (entries 22-26,28, table 4.4).

The structures of cyclization products (**62a-v**) were confirmed using IR, ^{1}H-NMR, ^{13}C-NMR and HRMS analyses. We can provide details on how the data was analyzed and which specific information was used for the characterization of the products. As an example, the structures of products **62a** was primarily determined by the disappearance of the $–NH_2$ stretching and bending vibrations (3451-3223 and 1636cm^{-1}) of precursor **61a**, along with changes in the intensities of the aliphatic CH stretching bands (2993-2854 cm^{-1}). Additionally, the appearance of single NH (3291 cm^{-1}) and strong C=C stretching (1595 cm^{-1}) peaks and increased intensity of aliphatic CH stretching peaks (2917-2857 cm^{-1}) in the IR spectra of products **62a** (Fig. 4.5) further confirmed its structure.

Additionally, the proton NMR spectrum of product **62a** showed two singlet peaks for the methylene protons at 4.62 (HN-CH_2-N) and 4.09 (N-CH_2-C=) ppm, as well as aromatic CH protons of the arylamino groups between 6.89 and 7.21 ppm, which supported the expected structure of 3,6-diphenyl tetrahydropyrimidine carbonitrile (Fig. 4.6). The carbon signals for the quaternary =C-N, =C-CN, CH_2, and C≡N groups at around 155.6, 75.4, 61.6, 48.8, and 121.1 ppm further confirmed the structure of the expected product (Fig. 4.7). Finally, the structure of product **62h** was confirmed by HRMS data (295.0862, M+) using the TOF-MS (APCI) technique (Fig. 4.8). The IR, NMR and HRMS spectra of other tetrahydropyrimidine products (**62b-v**) are given in figures A.19-A.82 in appendices section.

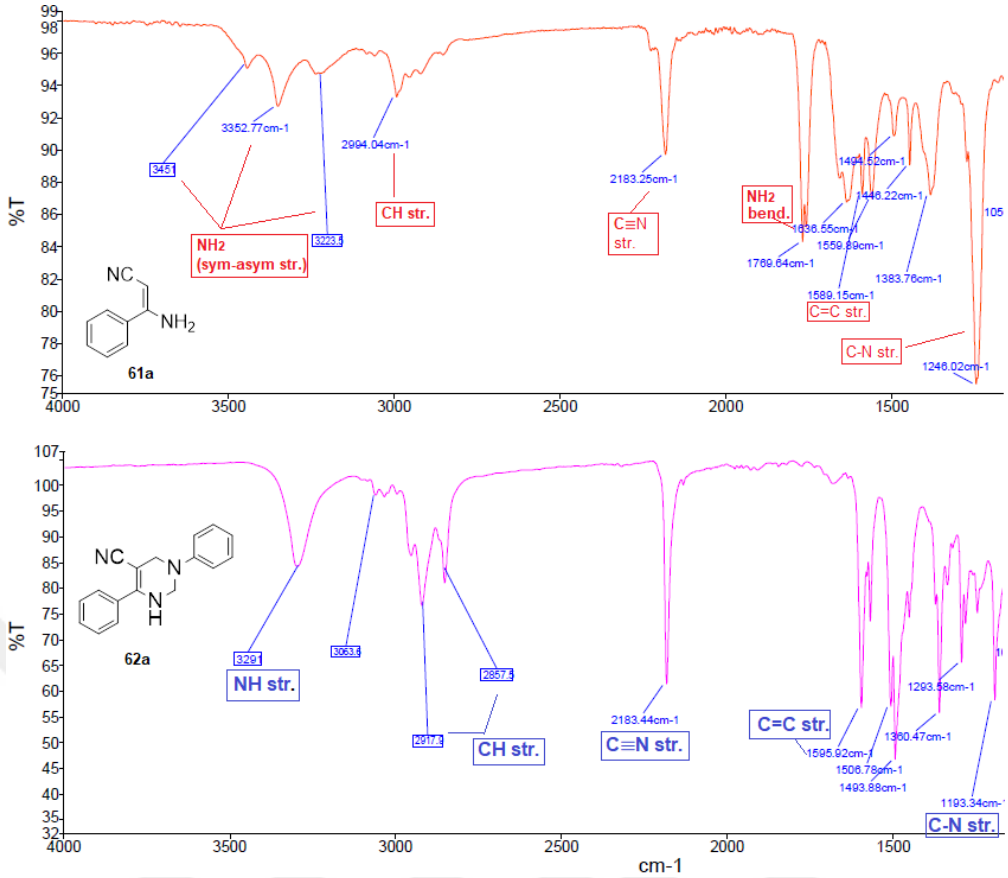


Figure 4.5. IR spectra of the precursor **61a** and product **62a**

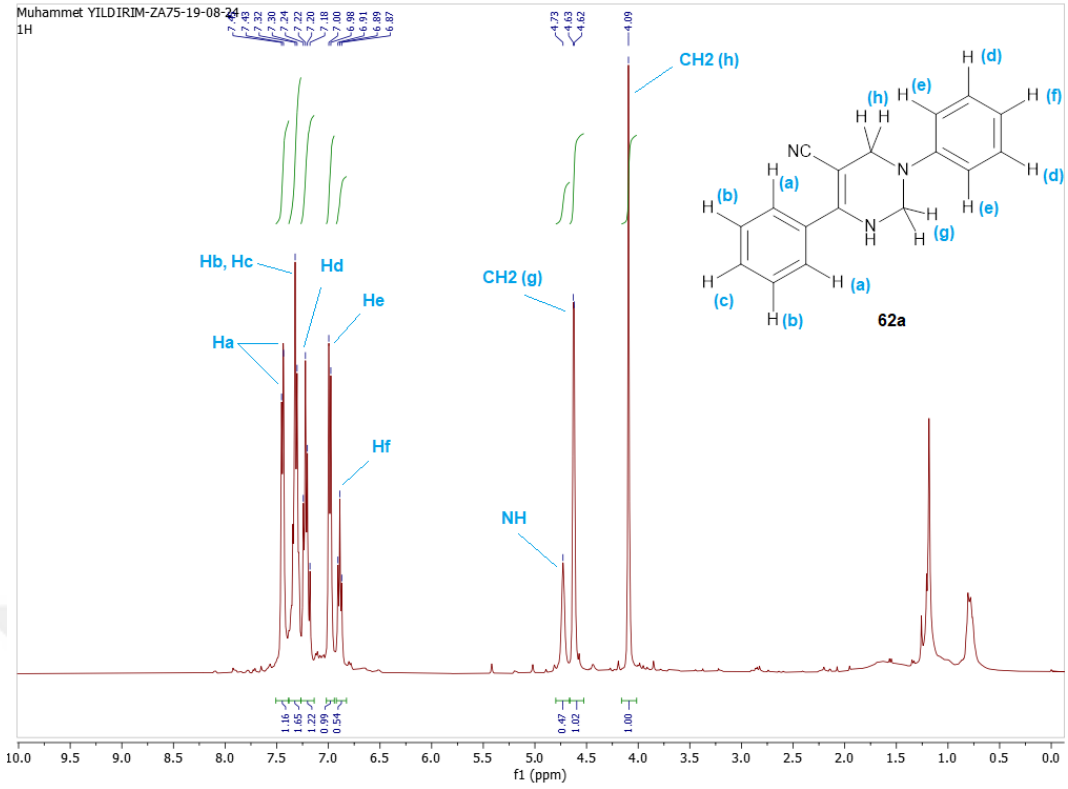


Figure 4.6. ^{1}H-NMR spectrum of the product **62a**

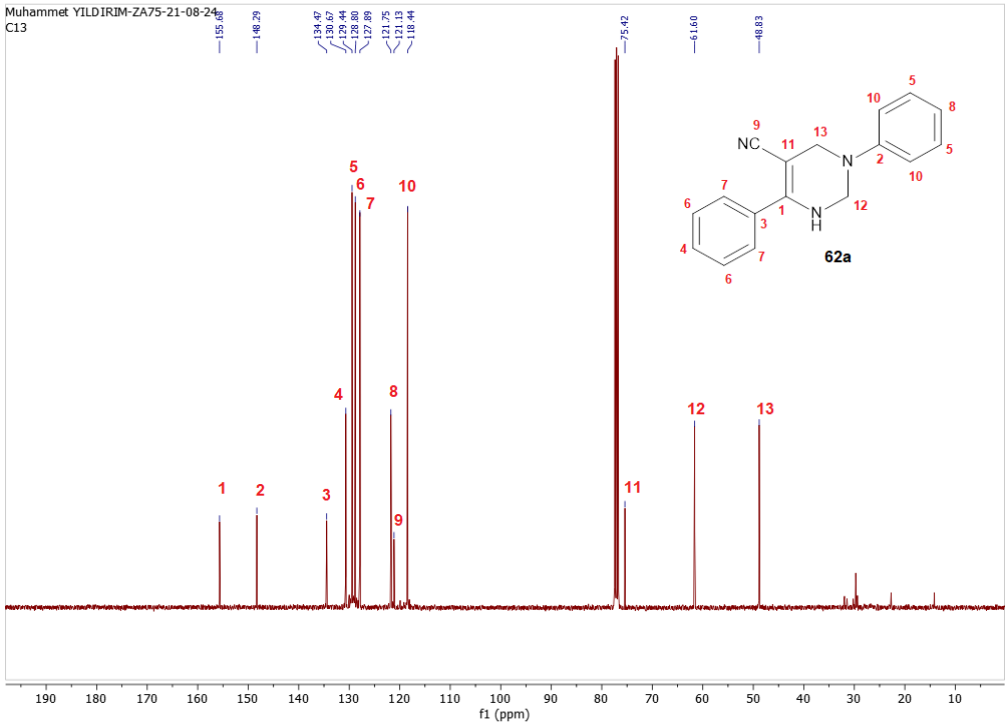


Figure 4.7. ^{13}C-NMR spectrum of the product **62a**

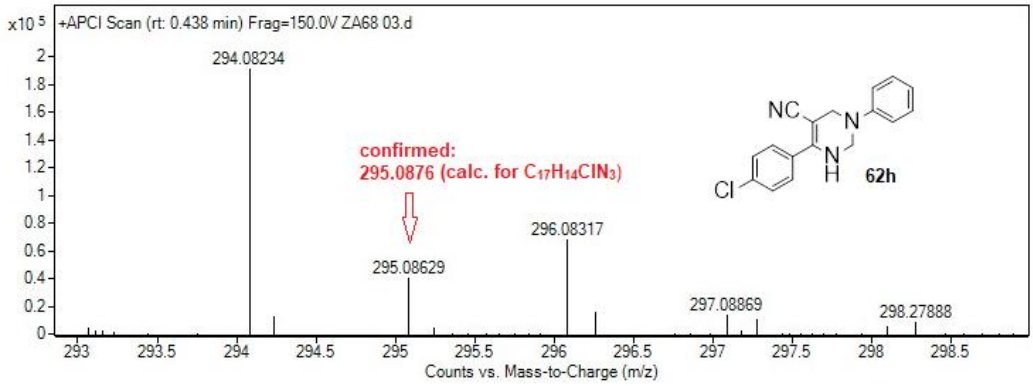


Figure 4.8. HRMS spectrum of the product **62h**

Using the same characterization methods and data, all of the tetrahydropyrimidine carbonitriles (**62a-v**) were characterized by their characteristic IR, 1H-NMR, 13C-NMR spectra, as demonstrated in the examples above. Key IR and NMR data for characterization of **62a-v** derivatives are given below (Tables 4.5).

Table 4.5. Key IR and NMR data for the compounds **62a-v**

Comp.	**IR** (ν_{max}/cm^{-1})			**^{1}H-NMR** (δ,ppm)		**^{13}C-NMR** (δ,ppm)		
62	**NH**	**CH** aliph.	**C=C**	2x**CH$_2$**	**NH**	**C**H$_2$x2	=**C**-CN	=**C**-N
a	3291	2917	1595	4.62,4.09	4.73	61.6, 48.8	75.4	155.6
b	3335	2956	1595	4.69,4.17	4.80	62.0, 49.0	75.4	155.6
c	3152	2928	1595	4.16,3.60	4.71	61.5, 50.5	73.3	154.7
d	3362	2999	1592	4.72,4.19	4.78	61.5, 48.8	75.0	155.6
e	3319	2989	1594	4.67,4.15	4.77	61.9, 49.0	74.9	155.6
f	3343	2917	1592	4.06,3.50	4.60	61.5, 50.5	72.9	154.7
g	3300	2917	1602	4.69,4.16	4.80	61.6, 48.9	74.8	155.6
h	3362	2953	1605	4.73,4.19	4.81	61.6, 48.7	76.2	154.4
i	3291	2926	1600	4.58,4.05	4.69	62.0, 48.9	76.3	154.4
j	3342	2917	1592	4.59,4.06	4.77	61.6, 48.8	76.0	154.4
k	3397	2932	1587	4.16,3.58	4.70	61.5, 50.5	74.2	153.5
l	3305	2917	1608	4.74,4.20	4.76	61.6, 48.7	76.0	154.6
m	3333	2921	1604	4.64,4.11	4.77	61.9, 48.9	75.6	154.6
n	3387	2917	1600	4.13,3.56	4.58	61.6, 50.5	73.9	153.7
o	3298	2921	1591	4.71,4.18	4.85	61.5, 48.8	75.2	155.1
p	3294	2996	1596	4.57,4.05	4.66	62.0, 49.0	75.4	155.0

r	3315	2992	1590	4.15,3.58	4.68	61.5, 50.5	73.4	154.1
s	3372	2932	1595	4.72,4.18	4.83	61.5, 48.7	76.1	154.2
t	3376	2921	1599	4.62,4.08	4.73	62.0, 48.9	77.2	154.1
u	3280	2999	1613	4.63,4.09	4.78	61.6, 48.8	77.2	154.1
v	3355	2925	1592	4.10,3.52	4.63	61.6, 50.4	75.2	153.2

Accurate mass results of the products (**62**) are not available for now except that of product **61h** and their TOF-MS analyses are in progress now.

In general, the Mannich cyclization products (**62**) were obtained as single isomers in pure form. However, one product, **62u**, was isolated as a mixture of two isomers in a 2:1 ratio, as indicated by the proton NMR data for **62u** (see Results Section). This outcome was likely due to the enamine precursor **61e**, which was previously obtained as a mixture of its E/Z isomers.

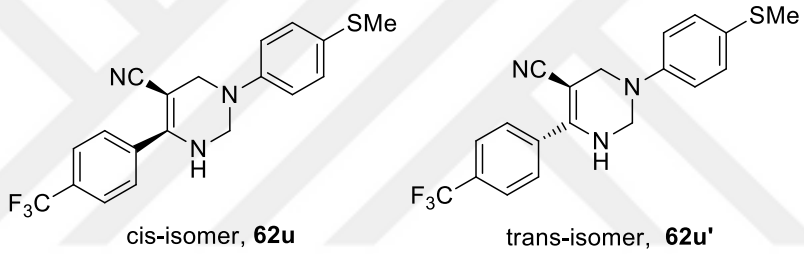


Figure 4.9. Two possible isomers of **62u**

A plausible mechanism involving the formation of imine and iminium intermediates can be proposed for the synthesis of products **62** through Mannich addition-cyclization reactions, as illustrated below. It is likely that the water molecules released during the imine and iminium formation steps are retained by the action of PEG, allowing the reaction to proceed more efficiently to produce the THPM product (Figure 4.10).

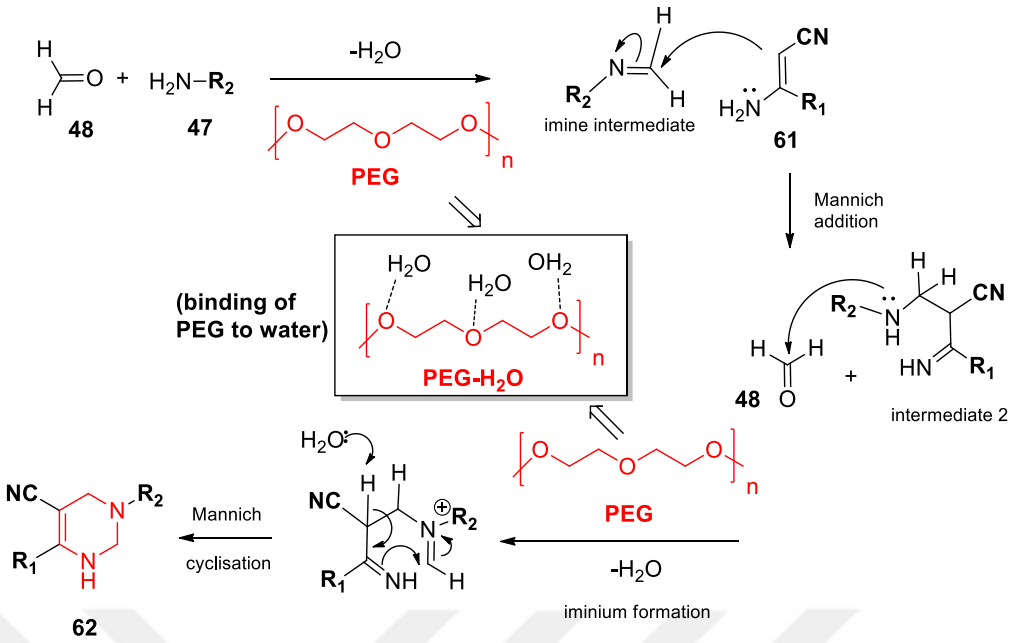


Figure 4.10. Mechanism for the formation of disubstituted tetrahydropyrimidines (**62**) in PEG medium

5. CONCLUSION

In summary, the key findings of the current dissertation study are outlined below.

In the first part of the study, six new aryl-substituted enaminonitrile precursors (**61a–f**) were synthesized using a modified literature method, and their structures were characterized successfully through IR and NMR analyses.

In the second and main part of the study, reaction conditions were first optimized using a model reaction to test the formation of new disubstituted tetrahydropyrimidine carbonitriles (**62**). An eco-friendly and highly efficient protocol was then developed for the synthesis of 21 novel tetrahydropyrimidine carbonitriles (**62a–v**) from reactions of various amine derivatives (**47**) and aryl-substituted enaminonitriles (**61a–f**) in the presence of formaldehyde (**48**) in PEG-400. The structures of target compounds (**62a-v**) were characterized by means of IR, NMR (^{1}H,^{13}C) and HRMS analyses. The current synthetic protocol offers a straightforward, eco-friendly, and efficient approach to synthesizing new tetrahydropyrimidines (**62**) via double-Mannich cyclization reactions within a few hours in a green environment. This approach broadens the applicability of Mannich cyclizations by introducing new pyrimidine derivatives through enamine chemistry.

As various pyrimidines are reported in recent literature to possess intriguing biological properties, two types of biological assays (antioxidant and antimicrobial) were designed to evaluate the activities of new tetrahydropyrimidine products (**62a–v**). However, the results are not yet available as the activity studies are still ongoing.

REFERENCES

Ahmad, O. K., Hill, M.D., Movassaghi, M. (2009). Synthesis of pyrimidine. *Journal of Organic Chemistry*, 74, 8460-8463.

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

Barthakur, M. G., Borthakur, M., Devi, P., Saikia, C. J., Saikia, A., Bora, U., Chetia A., Boruah, R. C. (2007). A novel and efficient lewis acid catalysed preparation of pyrimidines: Microwave-promoted reaction of urea and β-formyl enamides. *Synlett*, 2, 223-226.

Basavaraja, H.S., Sadyojatha, I., Shivakumar, B., padamashali, B., Vijay Kumar, M.M.J., Bharathi, D.R. (2012). Synthesis, QSAR and antimicrobial evaluation of some novel substituted tetrahydropyrimidine derivatives. *Int J Pharm Chem Sci*, 1, 319-325.

Biginelli, P. (1893). Ueber Aldehyduramide des Acetessigsäure. *Berichte der Deutschen Chemischen Gesellschaft*, 26(2), 447-449.

Boarland, M. P. V., McOmie, J. F. W., Timms, R. N. (1952). Pyrimidines. Part IV. Experiments on the synthesis of pyrimidine and 4: 6-dimethylpyrimidine. *Journal of the Chemical Society (Resumed)*, 4691-4695.

Bredereck, H., Gompper, R., Herlinger, H. (1958). Formamid-Reaktionen, XI. Darstellung, Eigenschaften und Umsetzungen des Pyrimidins. *Chemische Berichte*, *91*(12), 2832-2849.

Bredereckef, H., Gompper, R., Morlock, G. (1957). Formamid-Reaktionen, VIII. Eine Neue Pyrimidin-Synthese. *Chemische Berichte*, *90*(6), 942-952.

Breitmaier, E. (1971). Pyrimidine aus N,N-unsubstituierten β-Enaminocarbonylverbindungen und Formamid. *Angewandte Chemie*, *83*(8), 287-288.

Brugnatelli, G., Eiz, G. (1818). *Chim. Storia Natur*. *Pauia* [decade seconda], 1, 117.

Buth, G.S., Dražić, T., Rosić, M., Tomaš, Ž. (2019). Green Synthesis of Pyrimidine Derivatives. *Sustainable Chemistry Reviews*, 11(4), pp.274-281.

Carosati, E., Ioan, P., Micucci, M., Broccatelli, F., Cruciani, G., Zhorov, B.S., Chiarini, A., Budriesi, R. (2012). 1,4-Dihydropyridine scaffold in medicinal chemistry, the story so far and perspectives (Part 2): action in other targets and antitargets. *Curr Med Chem*, 19,25, 4306-4323.

Chandak, H.S., Lad, N.P., Upare, P.P. (2009). Recyclable Amberlyst-70 as a Catalyst for Biginelli Reaction: An Efficient one-pot Green Protocol for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones. *Catal. Lett.*, 131, 469-473.

Chauhan, M., Kumar, R. (2015). A comprehensive review on bioactive fused heterocycles as purine-utilizing enzymes inhibitors. *Medicinal Chemistry Research*, *24*, 2259-2282.

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.

Chen, J., Spear, S.K., Huddleston, J. G., Rogers, R. D. (2005). Polyethylene glycol and solutions of polyethylene glycol as green reaction media. *Green Chemistry*, 7,2, 64-82.

Chu, X. Q., Cao, W. B., Xu, X. P., Ji, S. J. (2017). Iron catalysis for modular pyrimidine synthesis through β-ammoniation/cyclization of saturated carbonyl compounds with amidines. *The Journal of Organic Chemistry*, 82, 2, 1145-1154.

Conde, C., Hahne, M. (1941). Pyrimidines by Condensation of a β-Keto Ester with Urea. *Journal of Organic Chemistry*, 6(3), 324-328.

Devi, A.S., Baruah, R.R., Laskar, M.A., Vishwakarma, J.N. (2011). AChR inhibiting properties of 1, 2, 3, 4-tetrahydropyrimidines: synthesis and in-silico studies. *Chemical Sciences Journal*.

Dong, F., Jun, L., Xinli, Z., Zhiwen, Y., Zuliang, L. (2007). One-pot Green Procedure for Biginelli Reaction Catalyzed by Novel Task-Specific Room-Temperature Ionic Liquids. *J. Mol. Catal. A Chem.*, 274, 208–211.

El-Malah, A., Mahmoud, Z., Hamed Salem, H., Abdou, A. M., Soliman, M. M., Hassan, R. A. (2021). Design, ecofriendly synthesis, anticancer and antimicrobial screening of innovative Biginelli dihydropyrimidines using β-aroylpyruvates as synthons. *Green Chemistry Letters and Reviews*, 14(2), 221-233.

Frankland, E., Kolbe, H. (1848). Ueber die zersetzungsproducte des cyanäthyls durch einwirkung von kalium. *Liebigs Ann. Chem.*, 65, 269.

Friedberg, E.C., Walker, G.C., Siede, W., Wood, R.D., Schultz, R.A., Ellenberger, T. (2006). *DNA Repair and Mutagenesis*, 2nd ed. Washington, D.C.: ASM Press.

Gabriel, S. (1900). Pyrimidin aus barbitursäure. *Berichte der deutschen chemischen Gesellschaft, 33*(3), 3666-3668.S.

Gabriel, S., Colman, J. (1899). Ueber das Pyrimidin. *Berichte der deutschen chemischen Gesellschaft, 32*(2), 1525-1538.

Gayon, E., Szymczyk, M., Gérard, H., Vrancken, E., Campagne, J. M. (2012). Stereoselective and catalytic access to β-enaminones: An entry to pyrimidines. *The Journal of Organic Chemistry*, 77(20), 9205-9220.

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.

Gülbenek, C. Yıldırım, M., Yıldırım, A. (2022). Microwave-mediated approach to highly substituted nitropyrimidines via double Mannich reactions and their biological properties. *Tetrahedron*, 120, 132904.

Harikrishnan, P.S., Rajesh, S.M., Perumal, S., Almansour, A.I. (2013). A Microwave-Mediated Catalyst- and Solvent-Free Regioselective Biginelli Reaction in the Synthesis of Highly Functionalized Novel Tetrahydropyrimidines. *Tetrahedron Lett.*, 54, 1076–1079.

Hegde, H., Ahn, C., Gaonkar, S.L. Shetty, N.S. (2019). A Facile Solvent and Catalyst-Free Synthesis of New Dihydro Pyrimidinones as Antimicrobial Agents. *Journal of Chemical Sciences*, 131(2), 120-128.

Hunt, R. R., McOmie, J. F. W., Sayer, E. R. (1959). Pyrimidines. Part X. Pyrimidine, 4: 6-dimethylpyrimidine, and their 1-oxides. *Journal of the Chemical Society (Resumed)*, 525-530.

Jadhav, C. K., Nipate, A. S., Chate, A. V., Songire, V. D., Patil, A. P., Gill, C. H. (2019). Efficient rapid access to Biginelli for the multicomponent synthesis of 1,2,3,4-tetrahydropyrimidines in room-temperature diisopropyl ethyl ammonium acetate. *ACS omega*, 4(27), 22313-22324.

Jain, S. L., Singhal, S., Sain, B. (2007). PEG-assisted solvent and catalyst free synthesis of 3, 4-dihydropyrimidinones under mild reaction conditions. *Green Chemistry*, 9(7), 740-741.

Kakati, P., Singh, P., Yadav, P., Awasthi, S. K. (2021). Aiding the versatility of simple ammonium ionic liquids by the synthesis of bioactive 1,2,3,4-tetrahydropyrimidine, 2-aminothiazole and quinazolinone derivatives. *New Journal of Chemistry*, 45(15), 6724-6738.

Kappe, C.O. (2000). Biologically active dihydropyrimidones of the Biginelli-type -a literature survey. *Eur J Med Chem*, 35, 1043-1052.

Karpov, A. S., Müller, T. J. (2003). Straightforward novel one-pot enaminone and pyrimidine syntheses by coupling-addition-cyclocondensation sequences. *Synthesis*, 2815-2826.

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

Kidwai, M., Mishra, N. K., Bhatnagar, D., Jahan, A. (2011). A green methodology for one-pot synthesis of polysubstituted-tetrahydropyrimidines using PEG. *Green Chemistry Letters and Reviews*, 4(2), 109-115.

Knoevenagel, E., (1898). Ueber eine directe Condensation des Malonaldehyds mit Ammoniak und primären Amiden. *Berichte der Deutschen Chemischen Gesellschaft*, 31(2).

Kshirsagar, S.S., Sundaram, P.S. (2013). Synthesis and Calcium Channel Blocking Activity of 1,2,3,4,-Tetrahydropyrimidine Derivatives Containing Carbamates and Carbamides. *International Journal of Chem Tech Research*, 5(6), 2899-2912.

Kumar, M. A., Babu, M. S., Srinivasulu, K., Kiran, Y. B., Reddy, C. S. (2007). Polyethylene glycol in water: A simple and environment friendly media for Strecker reaction. *Journal of Molecular Catalysis A: Chemical*, 265(1-2), 268-271.

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

Lagoja, I. M. (2005). The Pyrimidine Heterocycle as Constituent of Natural Active Compounds. *Chemistry & Biodiversity*, (2), 1-50.

Legraverend, M., Grierson, D. S. (2006). The purines: Potent and versatile small molecule inhibitors and modulators of key biological targets. *Bioorganic & medicinal chemistry*, *14*(12), 3987-4006.

Ma, L., Lei, Y., Liu, H., Zhang, Z., Hu, X. (2016). Recent Advances in Metal-Catalyzed Pyrimidine Synthesis. *Advanced Synthesis & Catalysis*, 358(17), pp.2701-2717.

Ma, Y., Qian, C., Wang, L., Yang, M. (2000). Lanthanide Triflate Catalyzed Biginelli Reaction. One-pot Synthesis of Dihydropyrimidinones Under Solvent-Free Conditions. *J. Org. Chem.*, 65, 3864–3868.

Mahfoudh, M., Abderrahim, R., Leclerc, E., Campagne, J. M. (2017). Recent approaches to the synthesis of pyrimidine derivatives. *European Journal of Organic Chemistry*, *2017*(20), 2856-2865.

Mitra, A.K., Banerjee, K. (2003). Clay Catalysed Synthesis of Dihydropyrimidinones Under Solvent-Free Conditions. *Synlett*, 1509–1511.

Mohan, S. B., Kumar, B. R., Dinda, S. C., Naik, D., Seenivasan, S. P., Kumar, V., Brahmkshatriya, P. S. (2012). Microwave-assisted synthesis, molecular docking and antitubercular activity of 1,2,3,4-tetrahydropyrimidine-5-carbonitrile derivatives. *Bioorganic & medicinal chemistry letters*, 22(24), 7539-7542.

Movassaghi, M., Hill, M. D. (2006). Single-step synthesis of pyrimidine derivatives. *Journal of the American Chemical Society*, 128(44), 14254-14255.

Murray, R.K., Granner, D.K., Mayes, P.A., Rodwell, V.W. (2003). *Harper's Illustrated Biochemistry*, 26th ed. New York: McGraw-Hill.

Myadaraboina, S., Alla, M., Parlapalli, A., Manda, S. (2016). Solvent-free one-pot synthesis of polysubstituted tetrahydropyrimidines and their antioxidant and antimicrobial properties. *Research on Chemical Intermediates*, 42, 923-937.

Nadar, S., Khan, T. (2022). Pyrimidine: An elite heterocyclic leitmotif in drug discovery-synthesis and biological activity. *Chemical Biology & Drug Design*, *100*(6), 818-842.

Namboodiri, V. V., Varma, R. S. (2001). Microwave-accelerated Suzuki cross-coupling reaction in polyethylene glycol (PEG). *Green Chemistry*, 3(3), 146-148.

Nielsen, M. K. (2023). Apparent treatment failure of praziquantel and pyrantel pamoate against anoplocephalid tapeworms. *International Journal for Parasitology: Drugs and Drug Resistance*, *22*, 96-101.

Perez, M.A., Soto, J.L. (1981). Synthesis of 6-alkoxy-2-amino-5-cyanopyrimidines through sodium alkoxide-induced regiospecific cyclization of 1, 3-dicarbonitriles. *Synthesis*, 12(12):955-958.

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

Rani, N.S., Reddy, G.V.S., Veera, K.N.J. (2014). Synthesis of new 4-aryl-3, 4-dihydropyrimidin-2(1H)- ones/ thiones/ imines and their antimicrobial evaluation. *J Chem Pharm Res*, 6 (2), 373-379.

Rezaei, F., Alinezhad, H., Maleki, B. (2023). Captopril supported on magnetic graphene nitride, a sustainable and green catalyst for one-pot multicomponent synthesis of 2-amino-4 H-chromene and 1,2,3,6-tetrahydropyrimidine. *Scientific Reports*, 13(1), 20562.

Riand, J., Chenon, M. T., Lumbroso-Bader, N. (1974). Etude par rmn du carbone-13 des effets de substituants dans le noyau de la pyrimidine. *Tetrahedron Letters*, *15*(36), 3123-3126.

Romanov, A. R., Rulev, A. Y., Popov, A. V., Kondrashov, E. V., Zinchenko, S. V. (2020). Reaction of Bromoenones with Amidines: A Simple Catalyst-Free Approach to Trifluoromethylated Pyrimidines. *Synthesis*, 52(10), 1512-1522.

Sedaghati, B., Fassihi, A., Arbabi, S., Ranjbar, M., Memarian, H.R., Saghaie, L., Omidi, A., Sardari, A., Jalali, M., Abedi, D. (2012). Synthesis and antimicrobial activity of novel derivatives of Biginelli pyrimidines. *Med Chem Res*, 21(12), 3973-3983.

Shah. D.H., Sen, D.J. (2012). Synthesis and antibacterial activity of some 4,5-disubstituted-6-Methyl-1,2,3,4-Tetrahydropyrimidin-2(1H)-one derivatives. *Int J Drug Develop Res*, 4, 330-335.

Sharma, K., Khatik, N., Khandelwal, A. R., Meena, R., Bhadauria, S., Singh, M., Sachdeva, H. (2023). Ecofriendly Synthesis of DHPMs using Copper-based Nano catalysts and Evaluation of Antibacterial Activity. *Croatica Chemica Acta*, 96(2), 1-11.

Singh, K., Singh, K., Wan, B., Franzblau, S., Chibale, K., Balzarini, J. (2011). Facile transformation of Biginelli pyrimidin-2(1H)-ones to pyrimidines. In vitro evaluation as inhibitors of Mycobacterium tuberculosis and modulators of cytostatic activity. *Eur J Med Chem*, 46, 2290-2294.

Sokolov, N.A., Tishchenko, I.G., Raichonok, T.P., Buglakova, L.T. (1985). Synthesis of 5-nitrotetrahydropyrimidines. Vestsi Akademii Navuk BSSR, *Seryya Khimichnykh Navuk*, (2), 70-4.

Trivedi, A., Dodiya, D., Surani, J., Jarsania, S., Mathukiya, H., Ravat, N., Shah, V. (2008). Facile onepot synthesis and antimycobacterial evaluation of pyrazolo[3,4-d]pyrimidines. *Arch Pharm Chem Life Sci*,341(7), 435-439.

Trivedi, A.R., Bhuva, V.R., Dholariya, B.H., Dodiya, D.K., Kataria, V.B., Shah, V.H. (2010). Novel dihydropyrimidines as a potential new class of antitubercular agents. *Bioorg Med Chem Lett*, 20(20), 6100-6102.

Uysal, K., Yıldırım, M., Karakuş, H., Yıldırım, A. (2024). A simple, facile and greener route to thiazolo[3,2-c]pyrimidinones in semi-aqueous medium and their antibacterial properties. *Synthetic Communications*, 1-13.

Vadivelu, M., Raheem, A. A., Sugirdha, S., Bhaskar, G., Karthikeyan, K., Praveen, C. (2018). Gold catalyzed synthesis of tetrahydropyrimidines and octahydroquinazolines under ball milling conditions and evaluation of anticonvulsant potency. *Arkivoc*, 3, 90-101.

Virsodia, V., Pissurlenkar, R.R., Manvar, D., Dholakia, C., Adlakha, P., Shah, A., Coutinho, E.C. (2008). Synthesis, screening for antitubercular activity and 3D-QSAR studies of substituted N-phenyl-6-methyl-2-oxo-4-phenyl-1,2,3,4- tetrahydro-pyrimidine-5-carboxamides. *Eur J Med Chem*, 43(10), 2103-2115.

Von Baeyer A. (1864). Untersuchungen über die Harnsauregruppe. *Annalen*,130, 129.

Watson, J.D., Crick, F.H.C. (1953). Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. *Nature*, 171(4356), 737-738.

Wu, C., Bian, X., Wang, L., Zhang, Y., Wang, C. (2023) Na2CO3-Mediated [3+3] annulation reaction of substituted benzamidines with 2-benzylidenemalononitriles: access to substituted pyrimidine-4, 6-diamines. *Synthesis*, 55(03), 457-464.

Yamaguchi, Y., Katsuyama, I., Funabiki, K., Matsui, M., Shibata, K. (1998). A new expedient route to 2,6-diaryl-3-cyano-4-(trifluoromethyl)pyridines. *Journal of heterocyclic chemistry*, *35*(4), 805-810.

Yıldırım, M., Celikel, D., Dürüst, Y., Knight, D.W., Kariuki, B.M. (2014). 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., 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.

Yildirim, A.B., Mutlu, E., Yildirim, 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.

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.

Zhichkin, P., Fairfax, D. J., Eisenbeis, S. A. (2002). A general procedure for the synthesis of 2-substituted pyrimidine-5-carboxylic esters. *Synthesis*, 06, 0720-0722.

APPENDICES

IR, NMR and HRMS Spectra for starting compounds and products

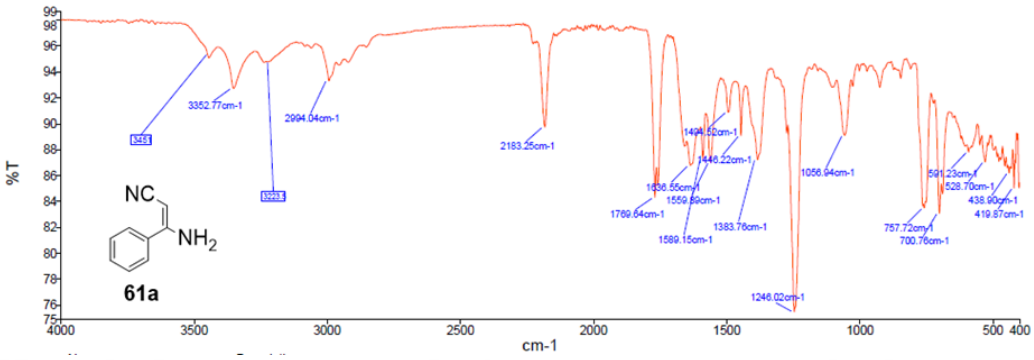


Figure A.1. IR Spectrum of compound **61a**

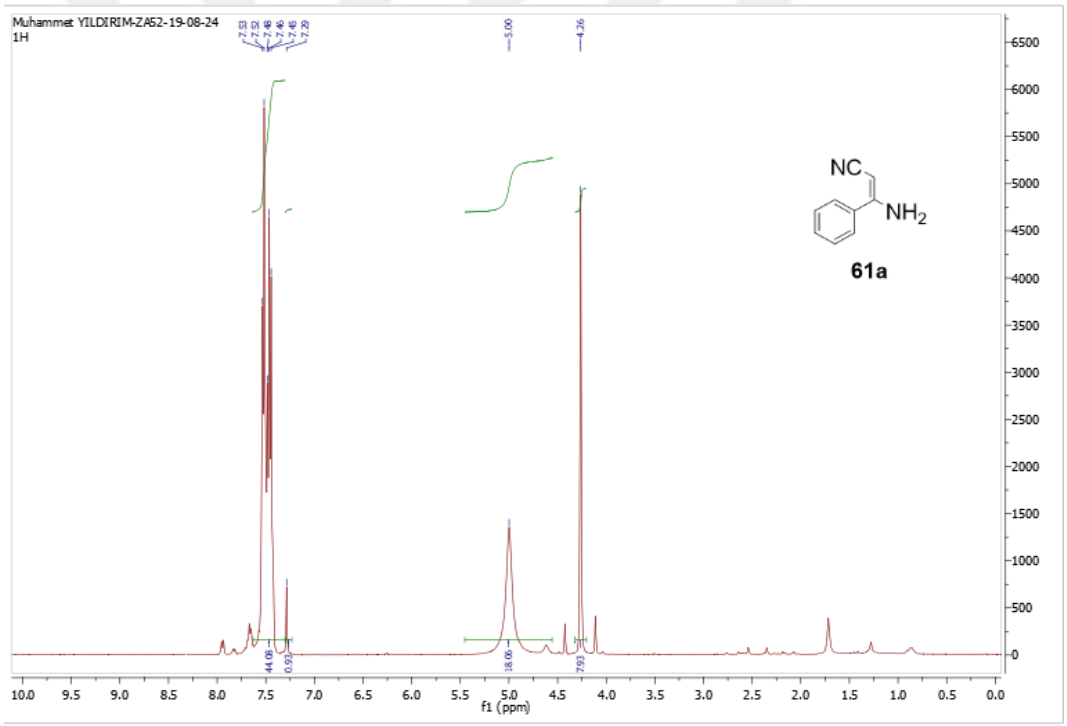


Figure A.2. 1H-NMR Spectrum of compound **61a**

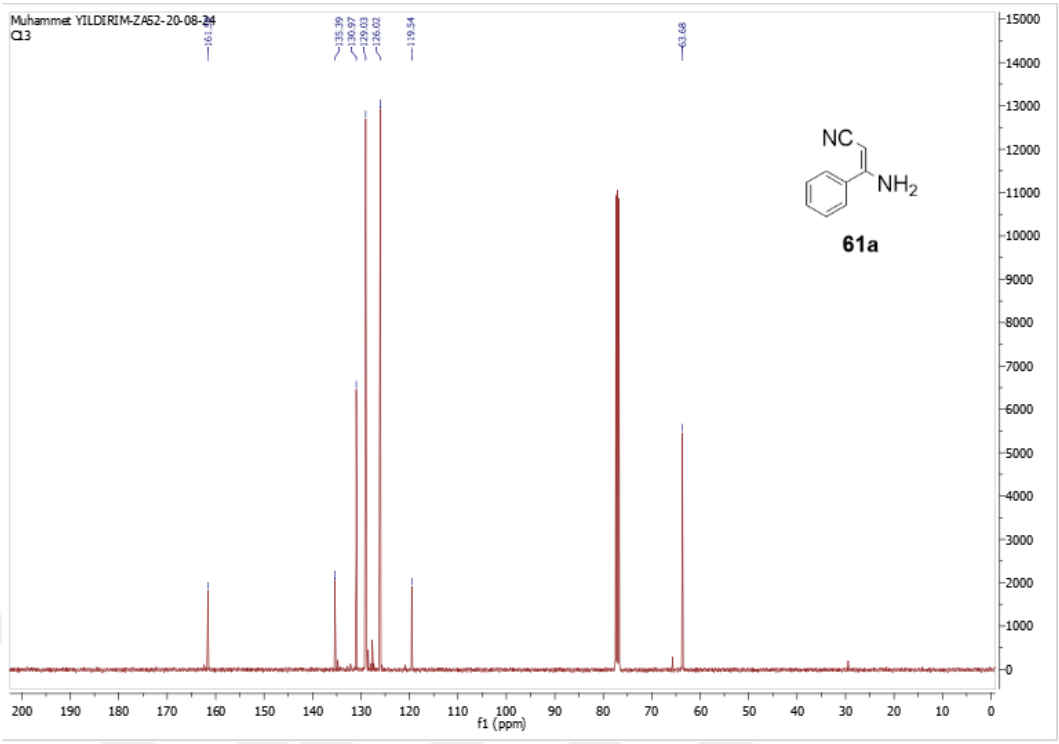


Figure A.3. ^{13}C-NMR Spectrum of compound **61a**

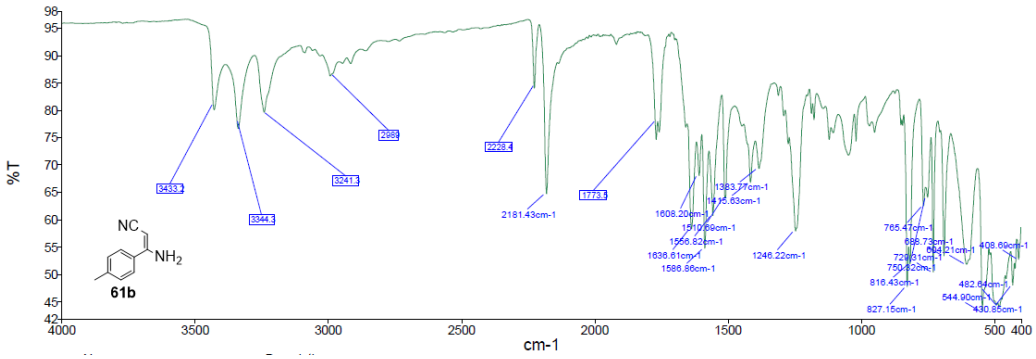


Figure A.4. IR Spectrum of compound **61b**

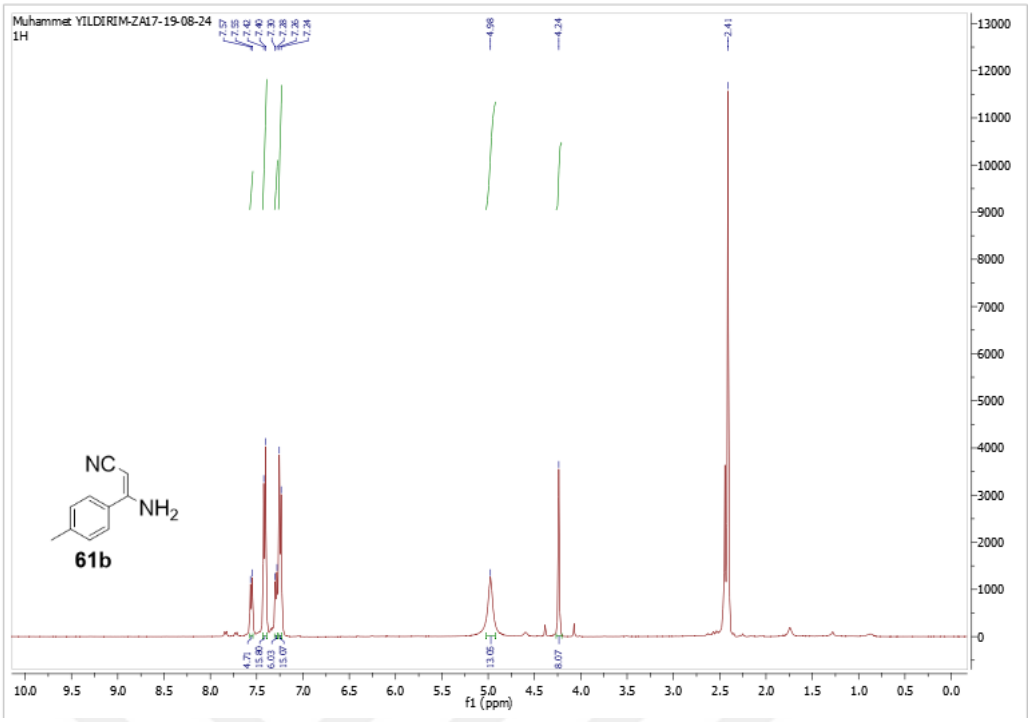


Figure A.5. 1H-NMR Spectrum of compound **61b**

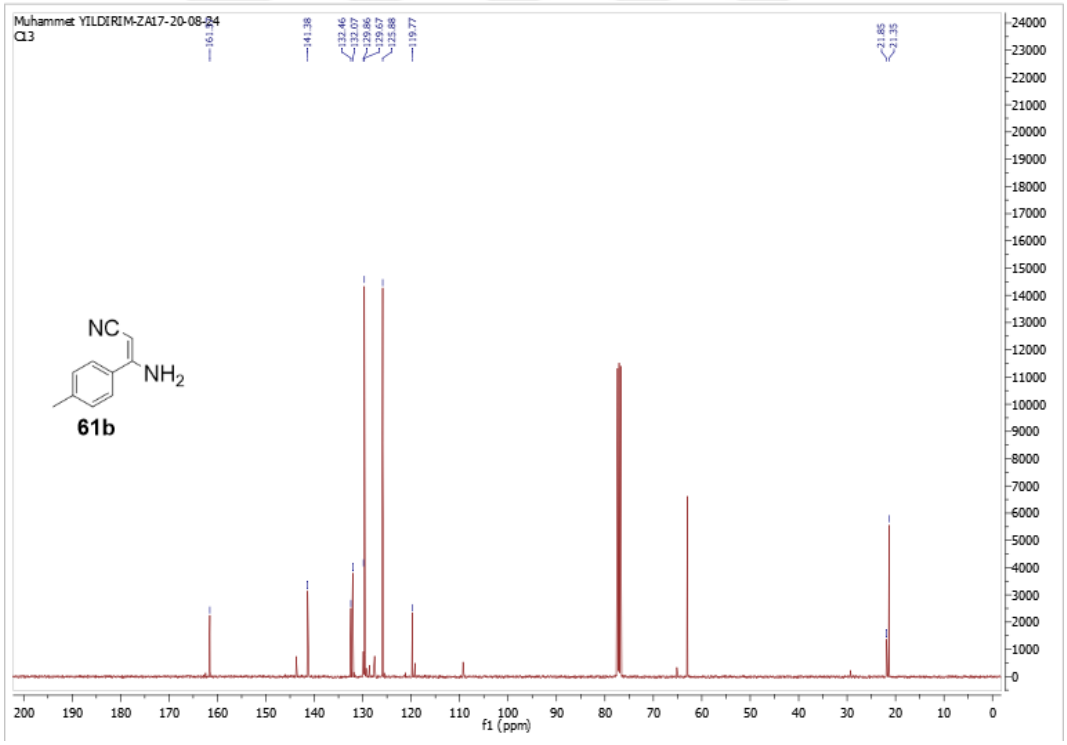


Figure A.6. ^{13}C-NMR Spectrum of compound **61b**

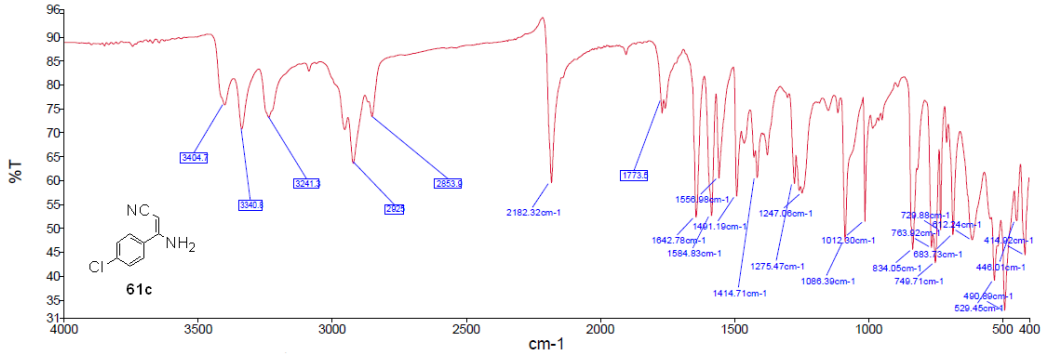


Figure A.7. IR Spectrum of compound **61c**

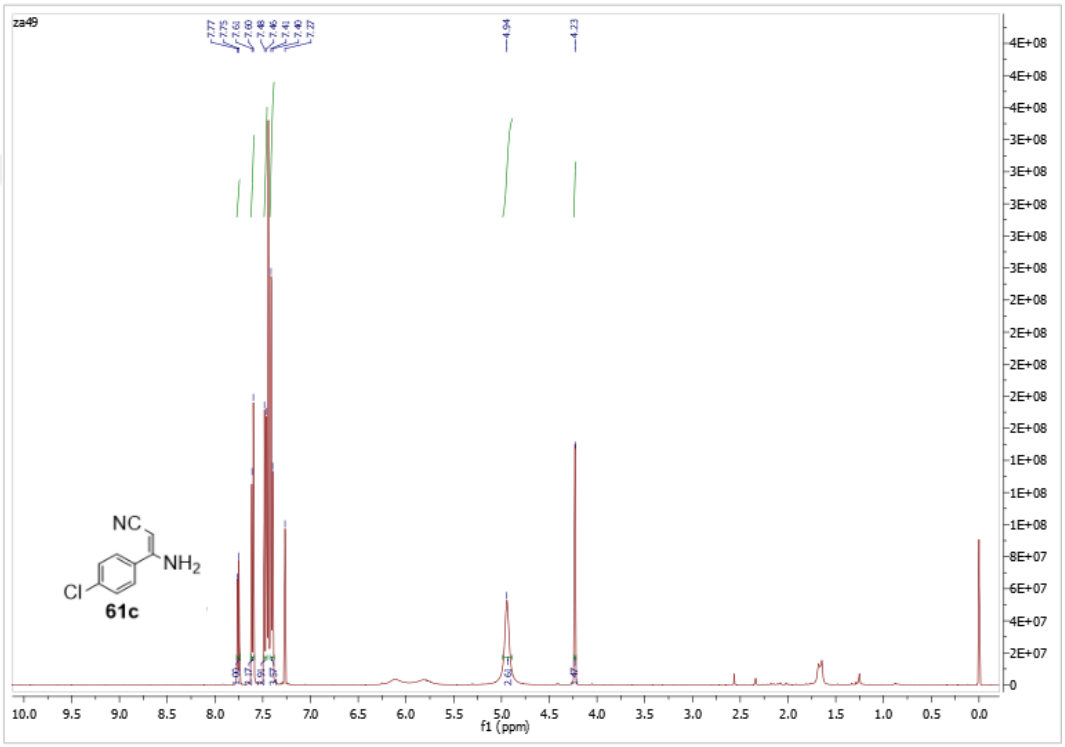


Figure A.8. 1H-NMR Spectrum of compound **61c**

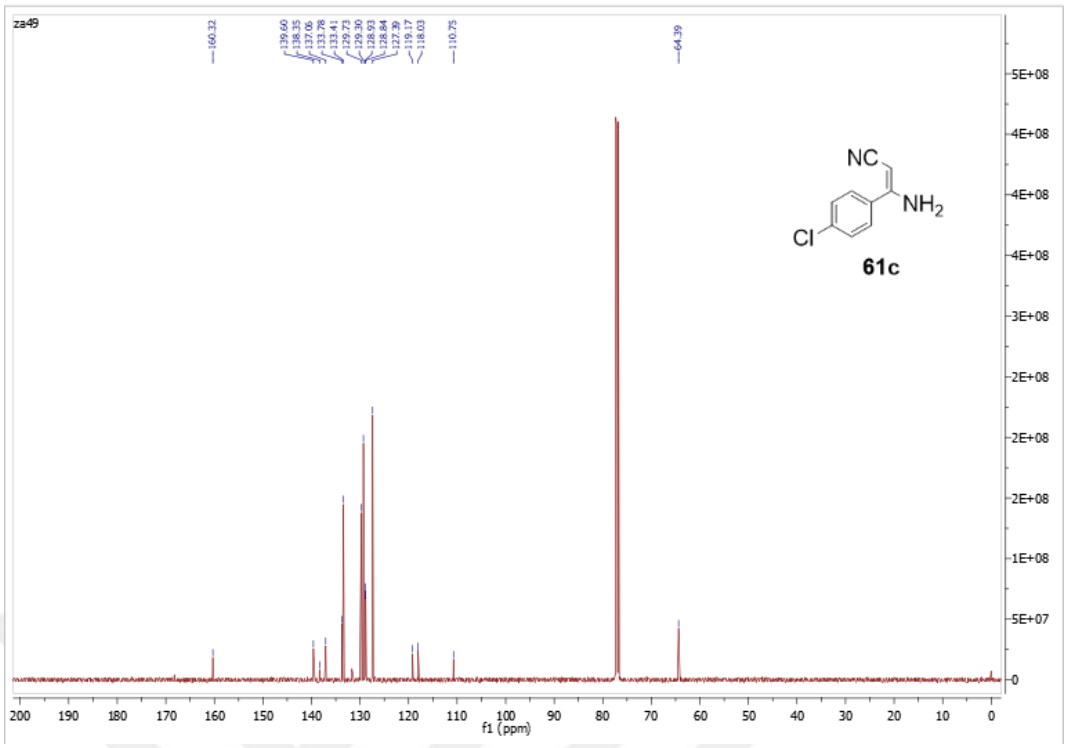


Figure A.9. ^{13}C-NMR Spectrum of compound **61c**

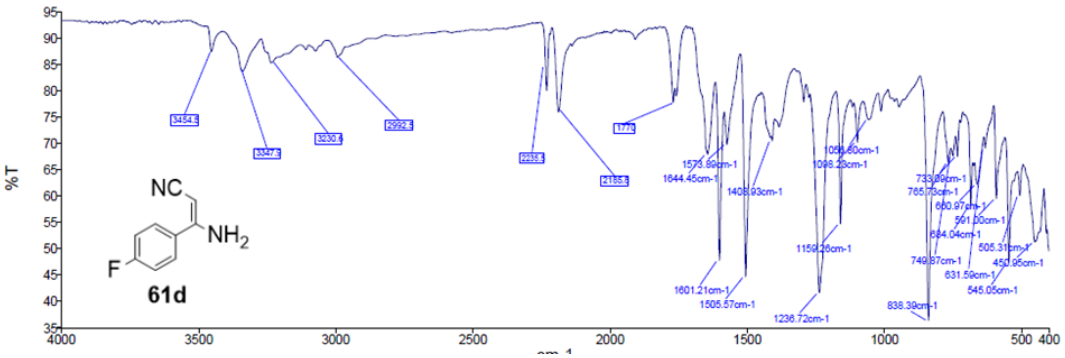


Figure A.10. IR Spectrum of compound **61d**

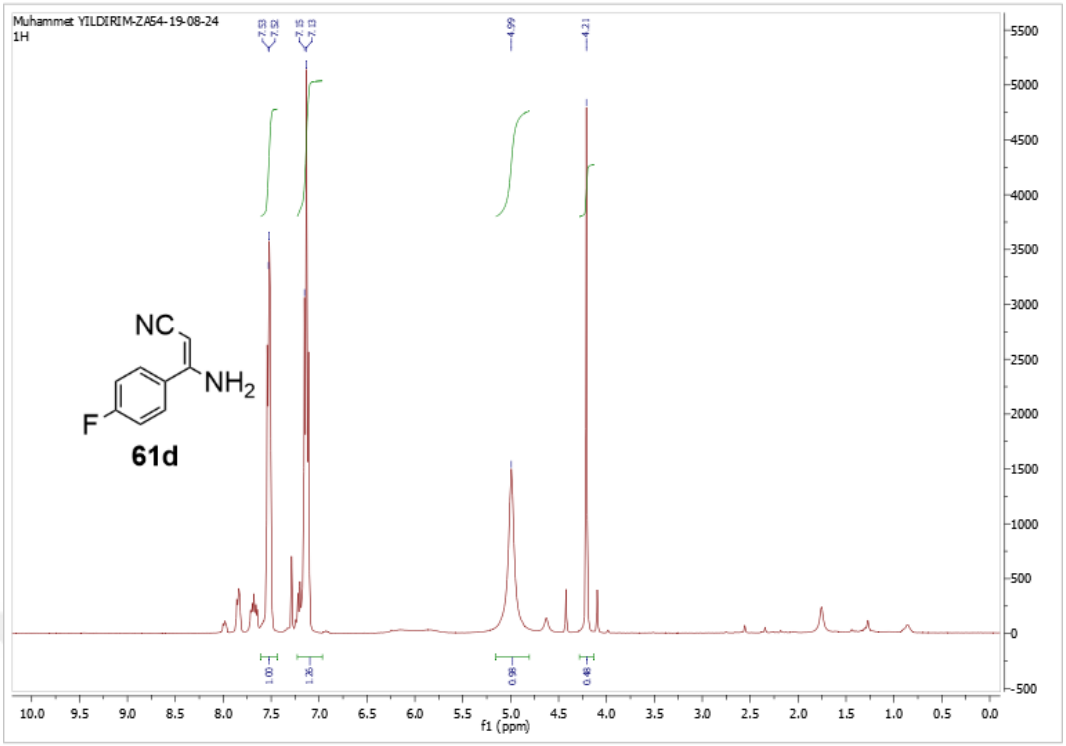


Figure A.11. 1H-NMR Spectrum of compound **61d**

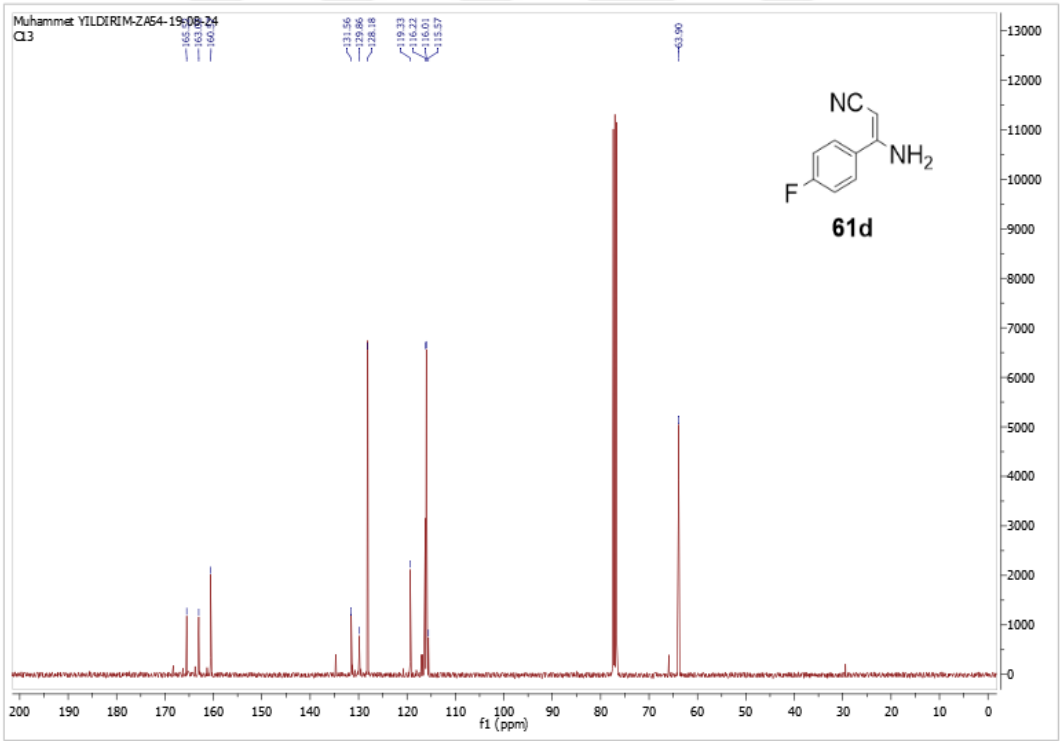


Figure A.12. ^{13}C-NMR Spectrum of compound **61d**

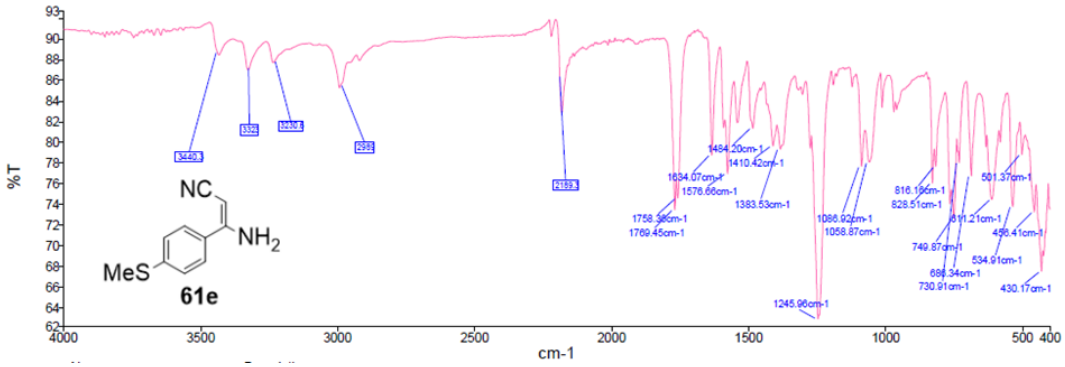


Figure A.13. IR Spectrum of compound **61e**

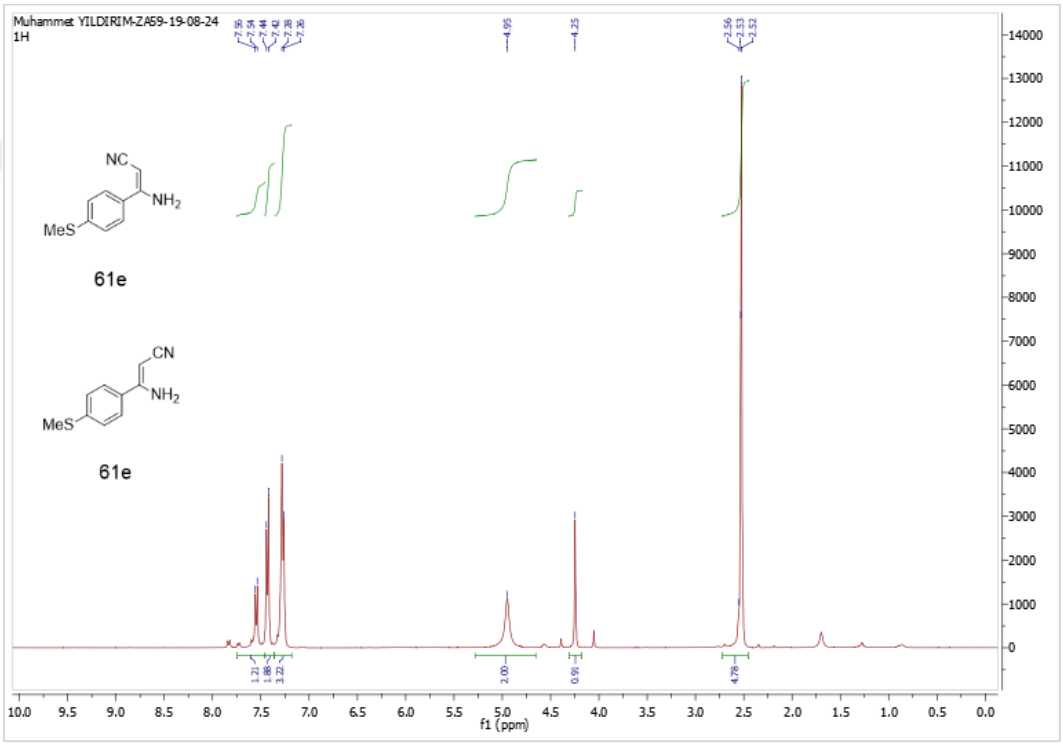


Figure A.14.1H-NMR Spectrum of compound **61e**

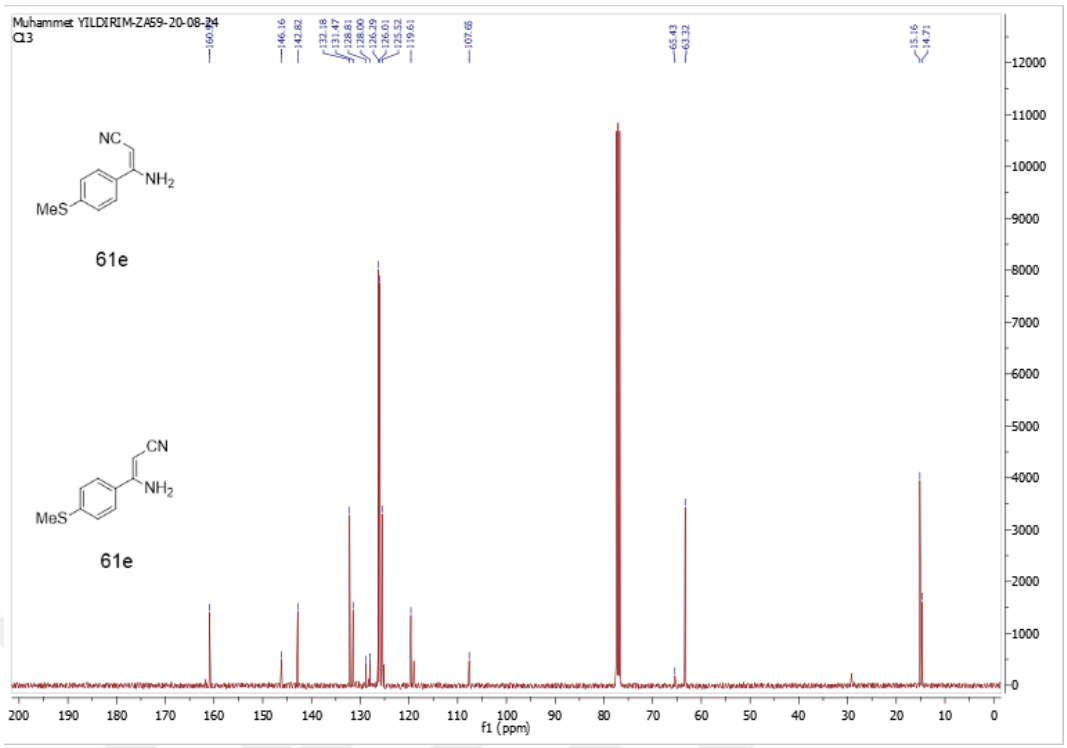


Figure A.15. ^{13}C-NMR Spectrum of compound **61e**

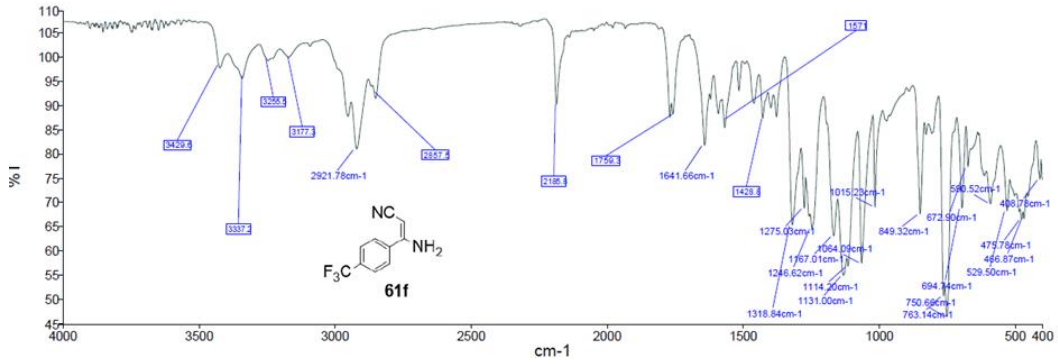


Figure A.16. IR Spectrum of compound **61f**

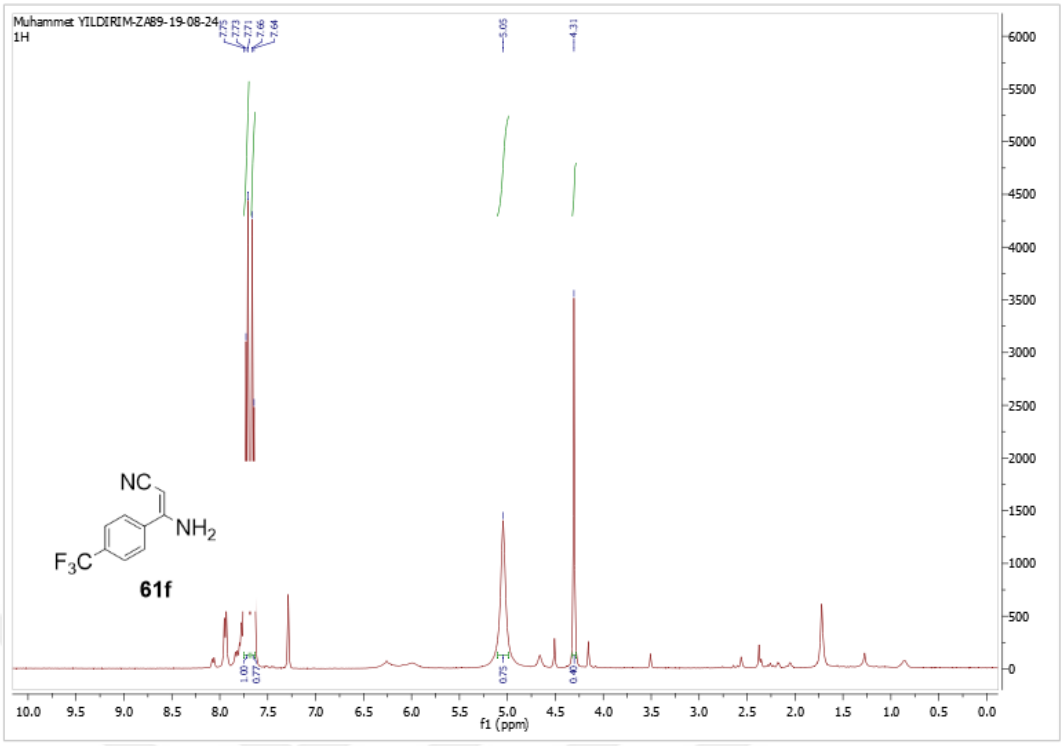


Figure A.17. 1H-NMR Spectrum of compound **61f**

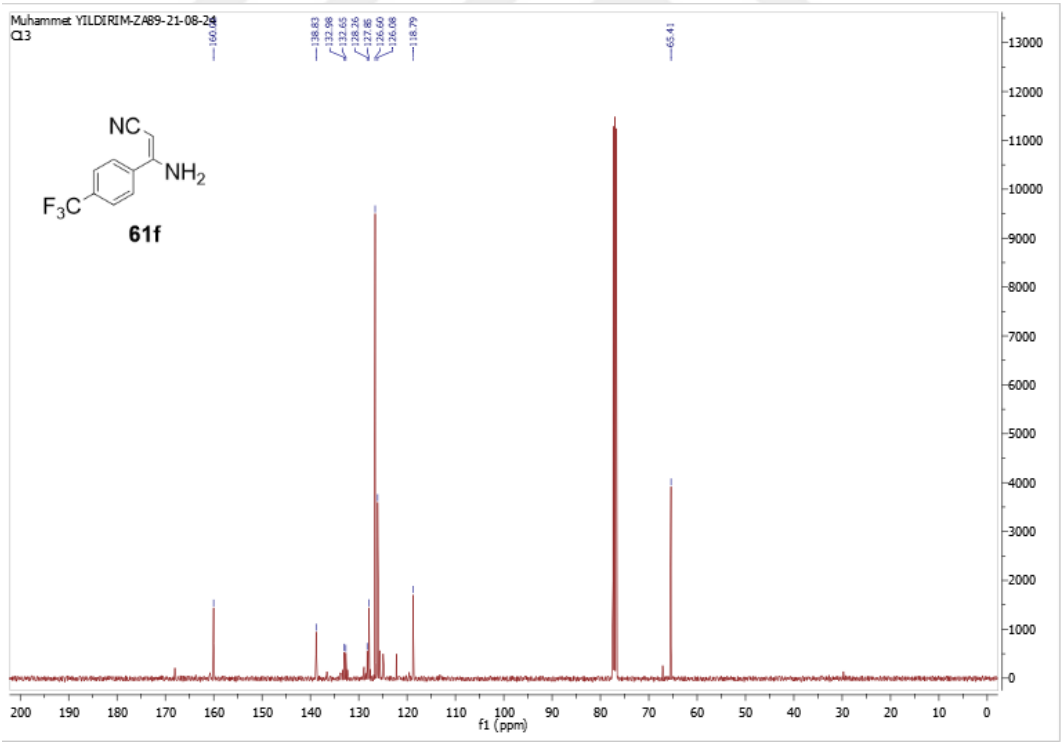


Figure A.18. ^{13}C-NMR Spectrum of compound **61f**

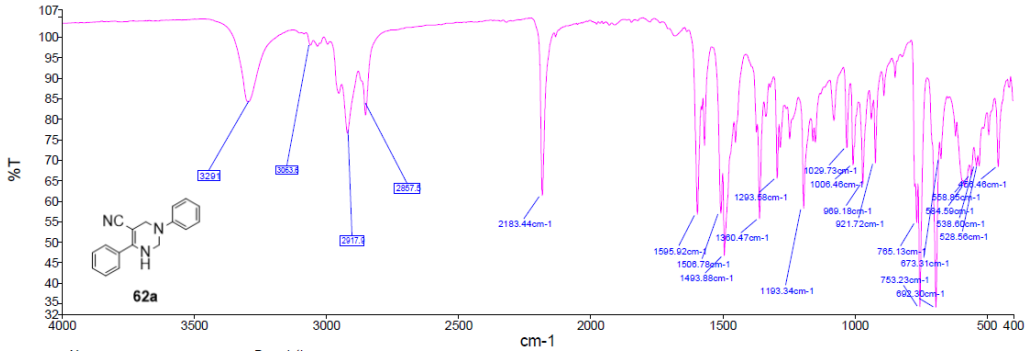


Figure A.19. IR Spectrum of compound **62a**

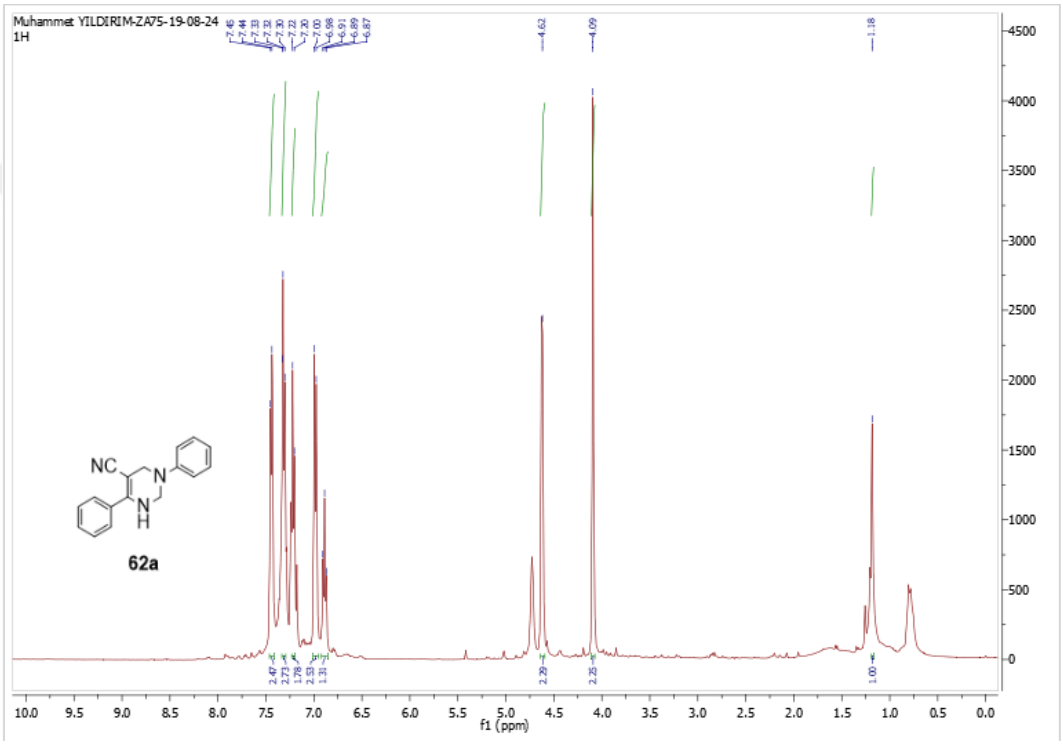


Figure A.20. 1H-NMR Spectrum of compound **62a**

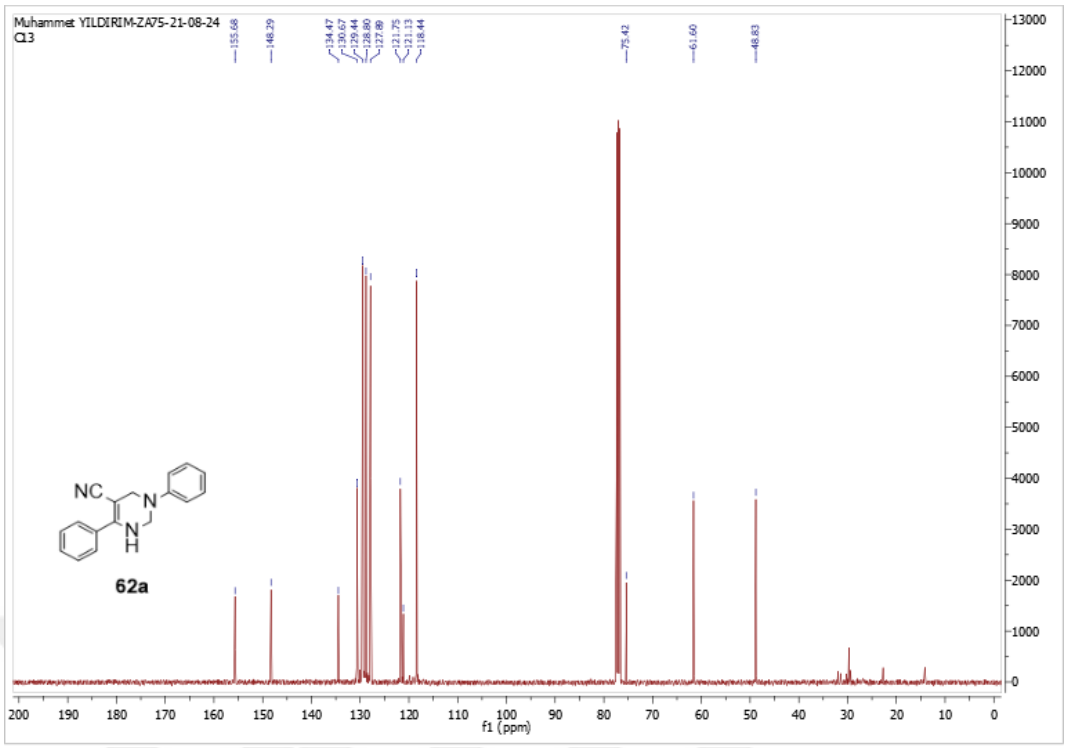


Figure A.21. ^{13}C-NMR Spectrum of compound **62a**

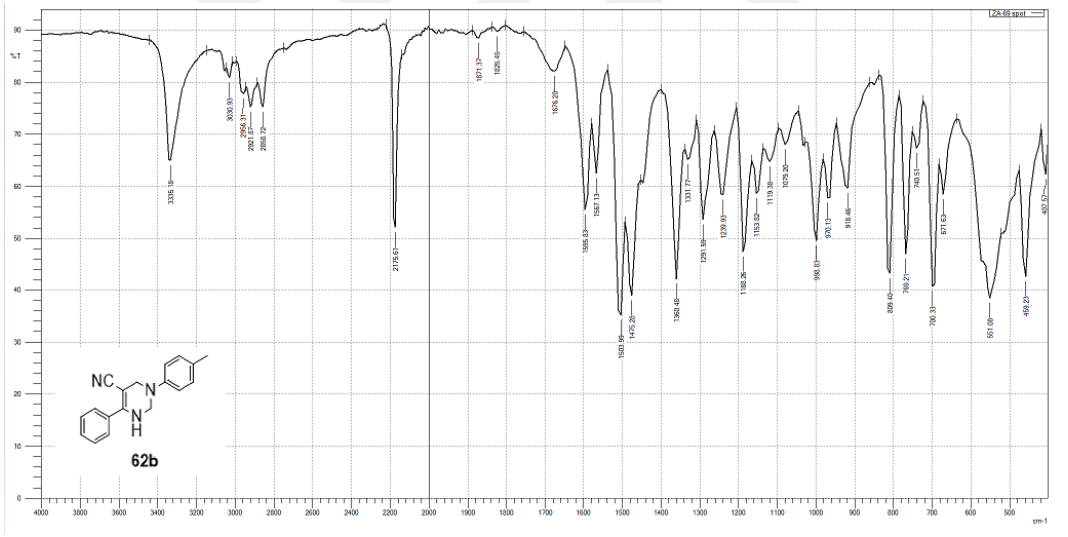


Figure A.22. IR Spectrum of compound **62b**

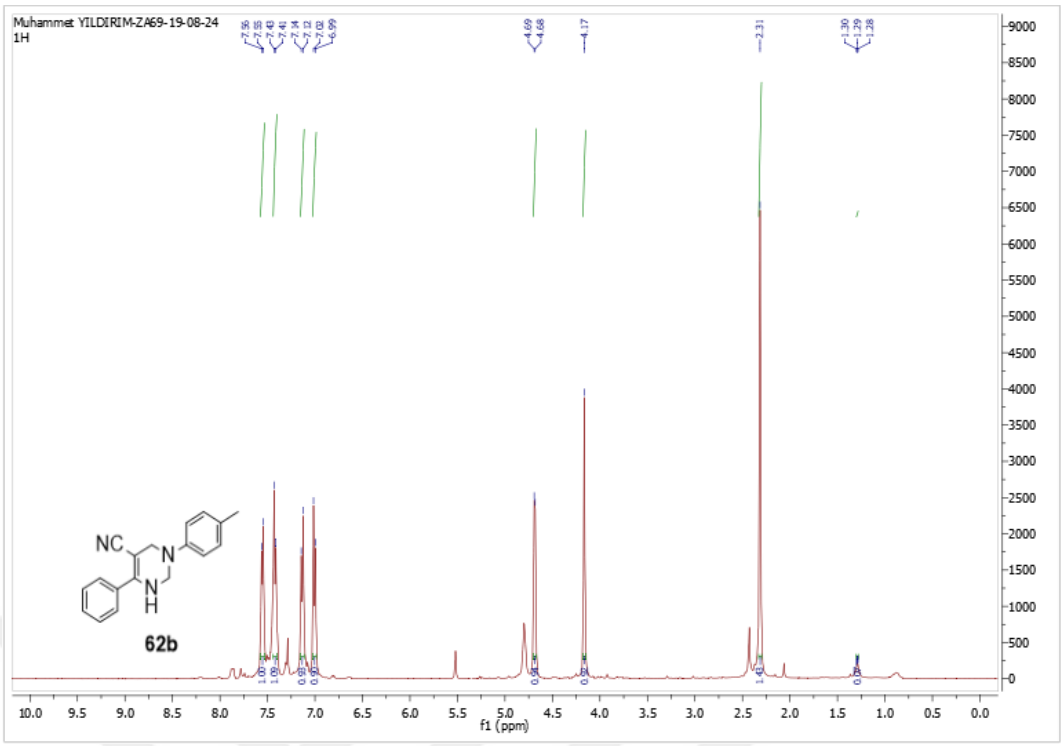


Figure A.23. 1H-NMR Spectrum of compound **62b**

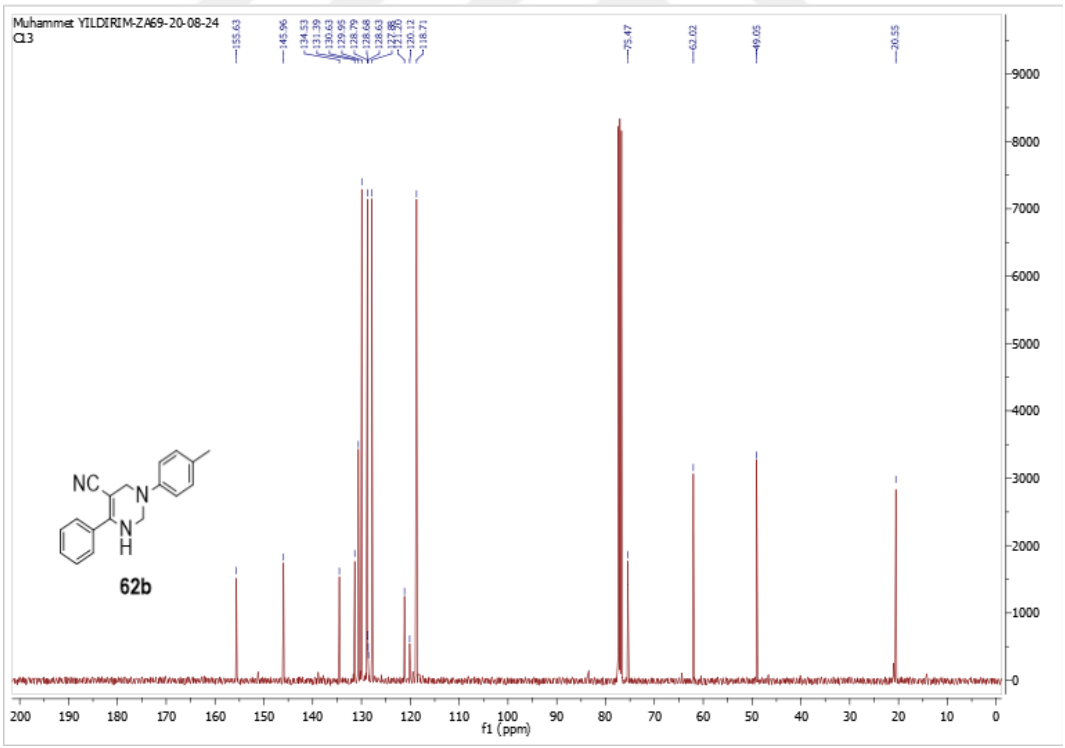


Figure A.24. ^{13}C-NMR Spectrum of compound **62b**

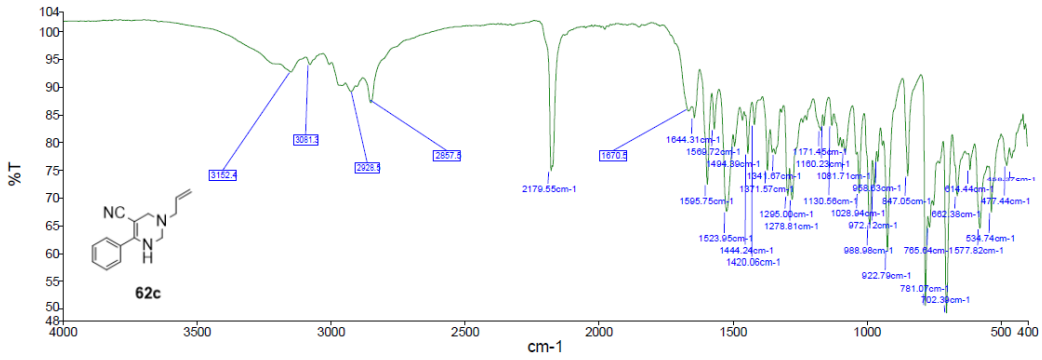


Figure A.25. IR Spectrum of compound **62c**

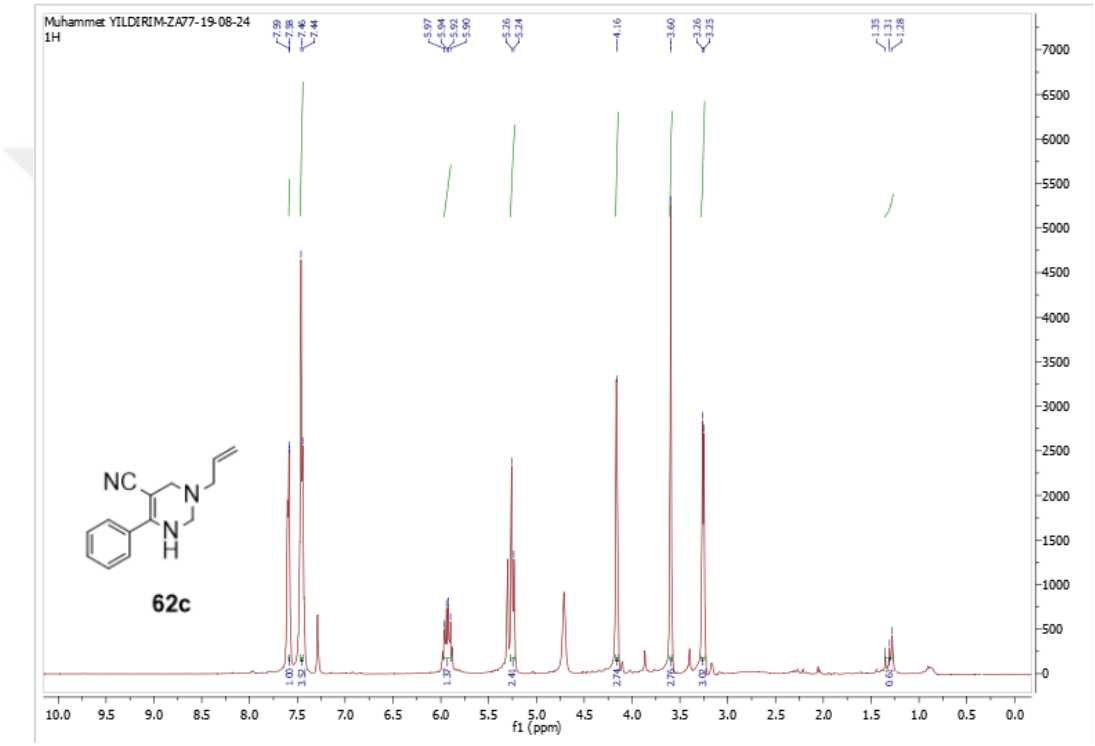


Figure A.26. 1H-NMR Spectrum of compound **62c**

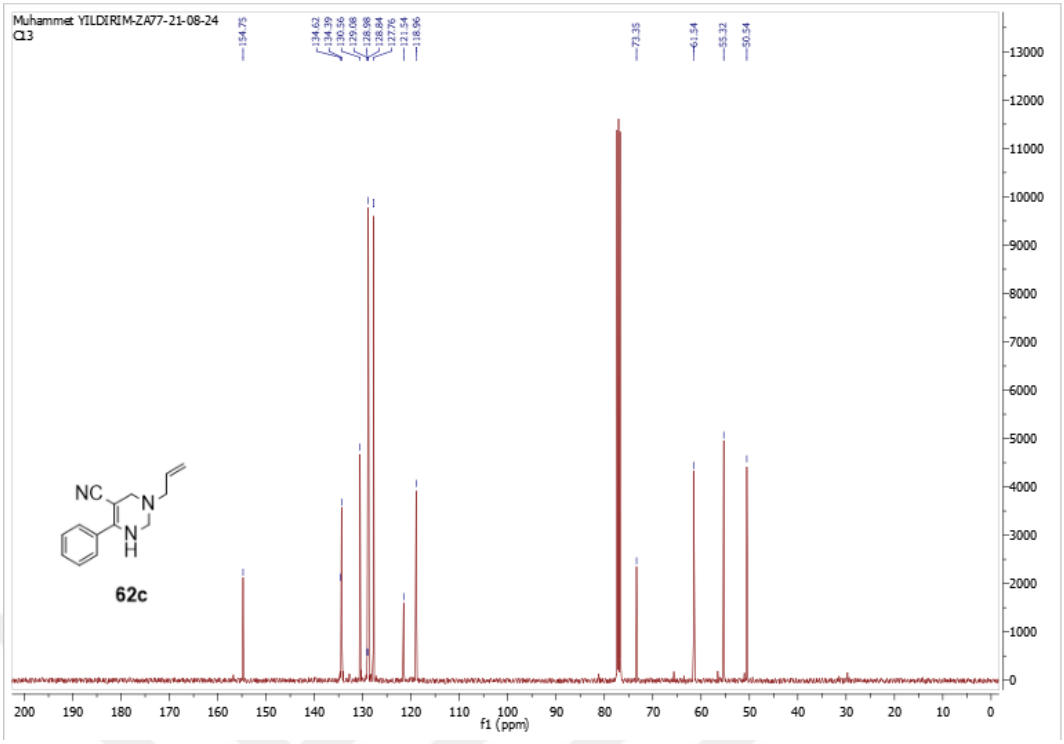


Figure A.27. ^{13}C-NMR Spectrum of compound **62c**

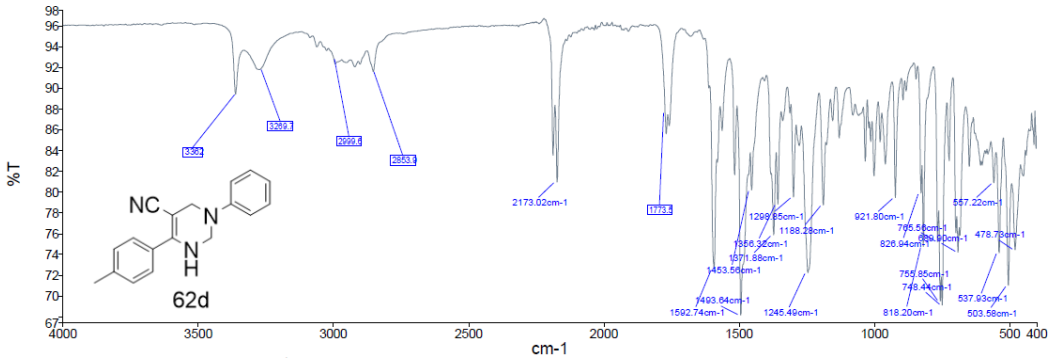


Figure A.28. IR Spectrum of compound **62d**

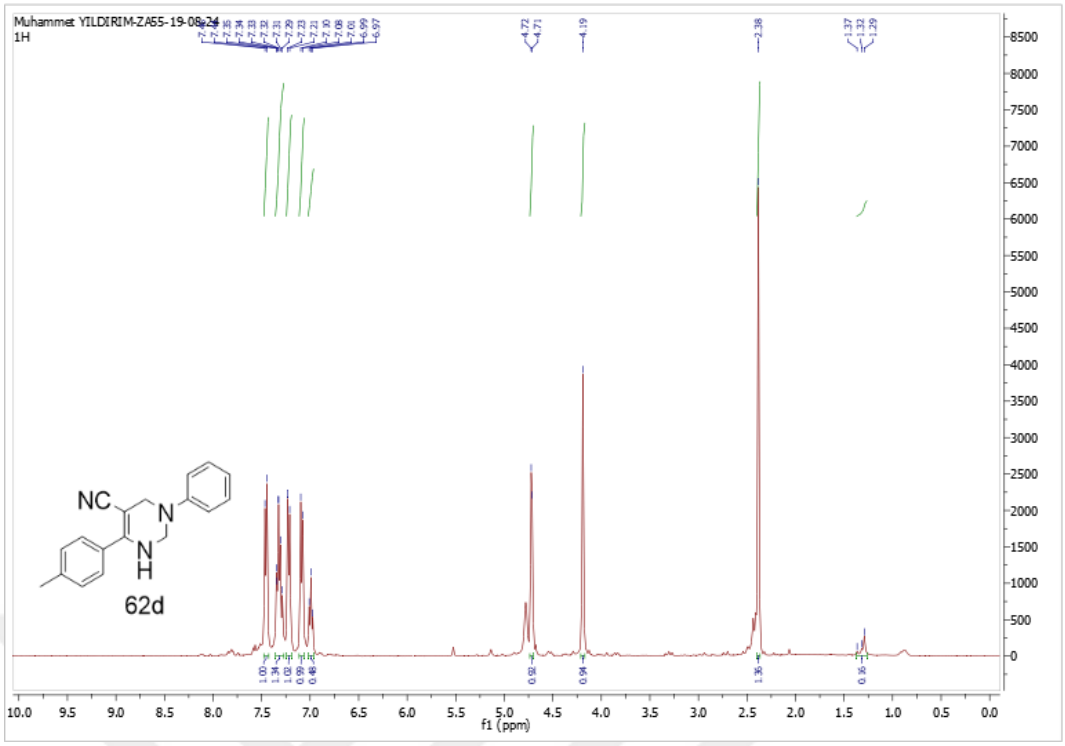


Figure A.29. 1H-NMR Spectrum of compound **62d**

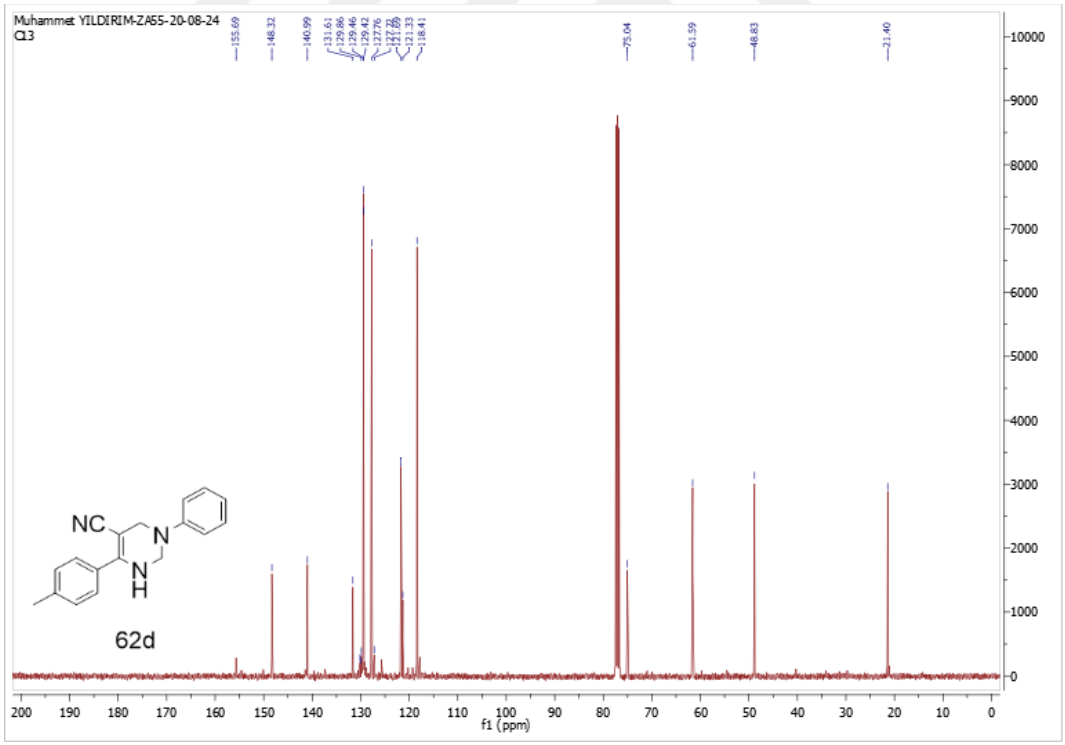


Figure A.30. ^{13}C-NMR Spectrum of compound **62d**

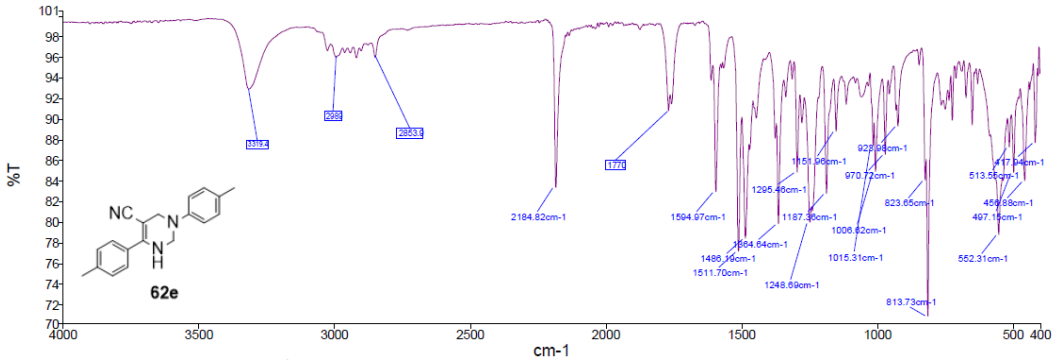


Figure A.31. IR Spectrum of compound **62e**

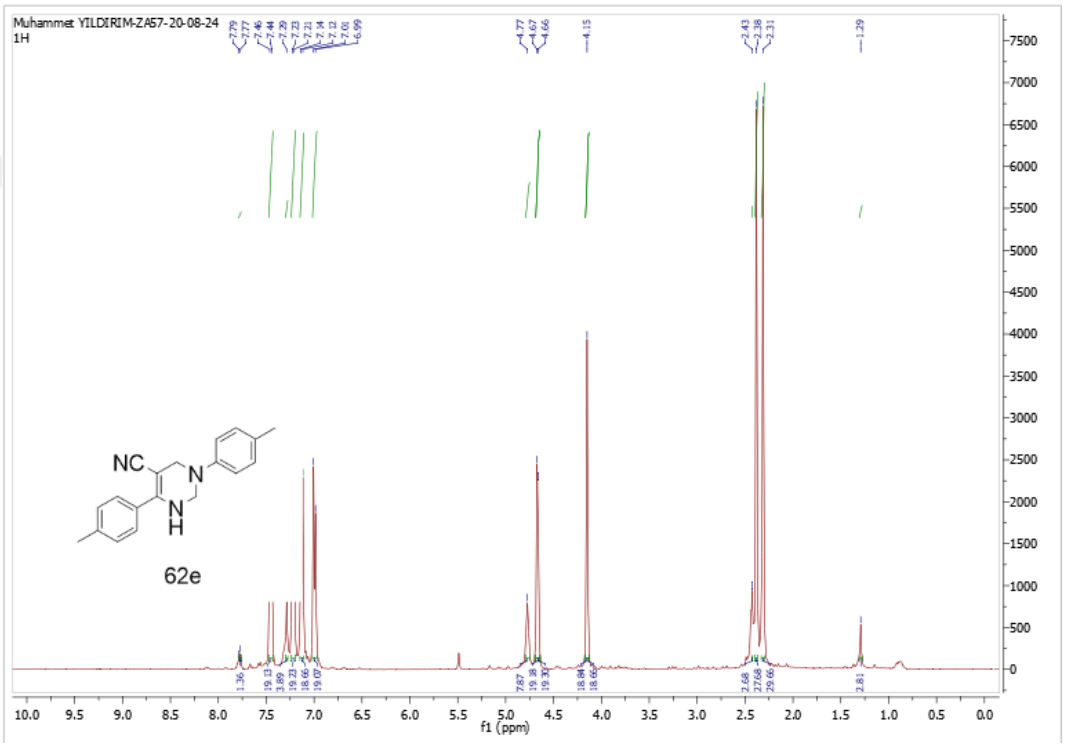


Figure A.32. 1H-NMR Spectrum of compound **62e**

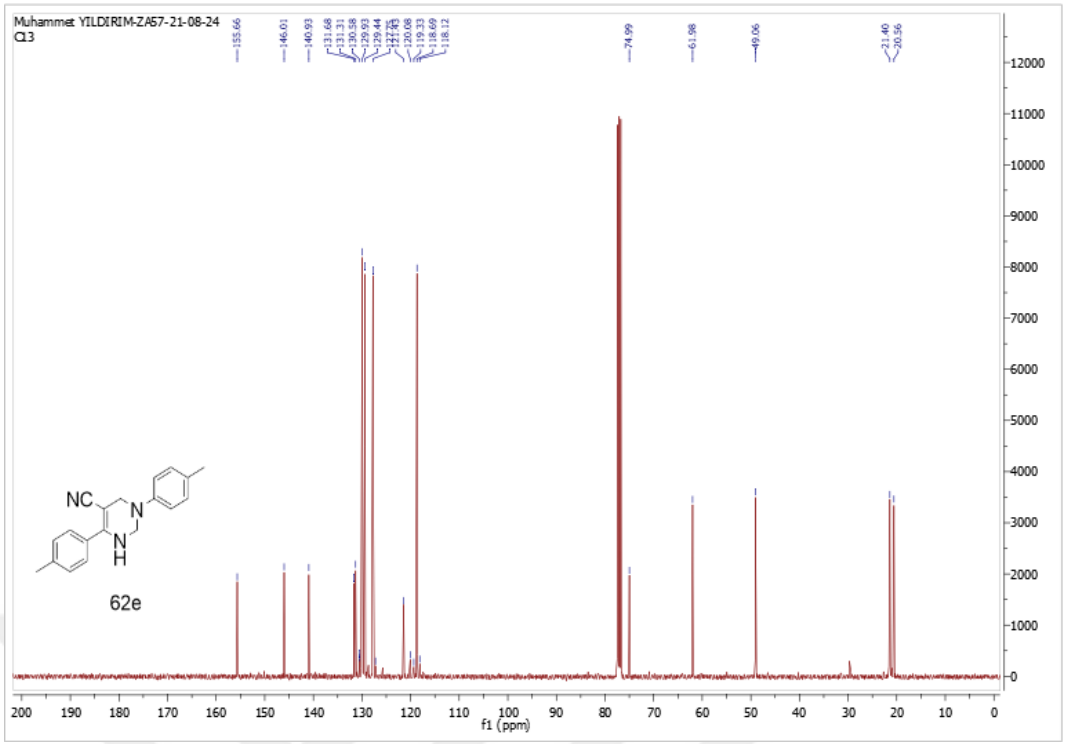


Figure A.33. ^{13}C-NMR Spectrum of compound **62e**

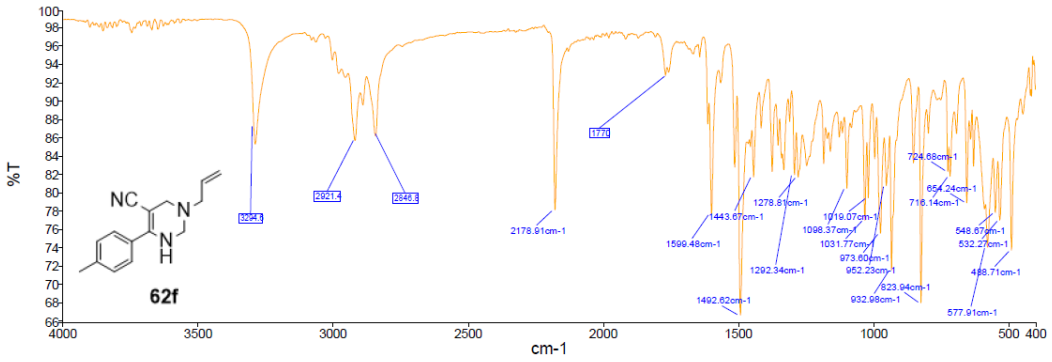


Figure A.34. IR Spectrum of compound **62f**

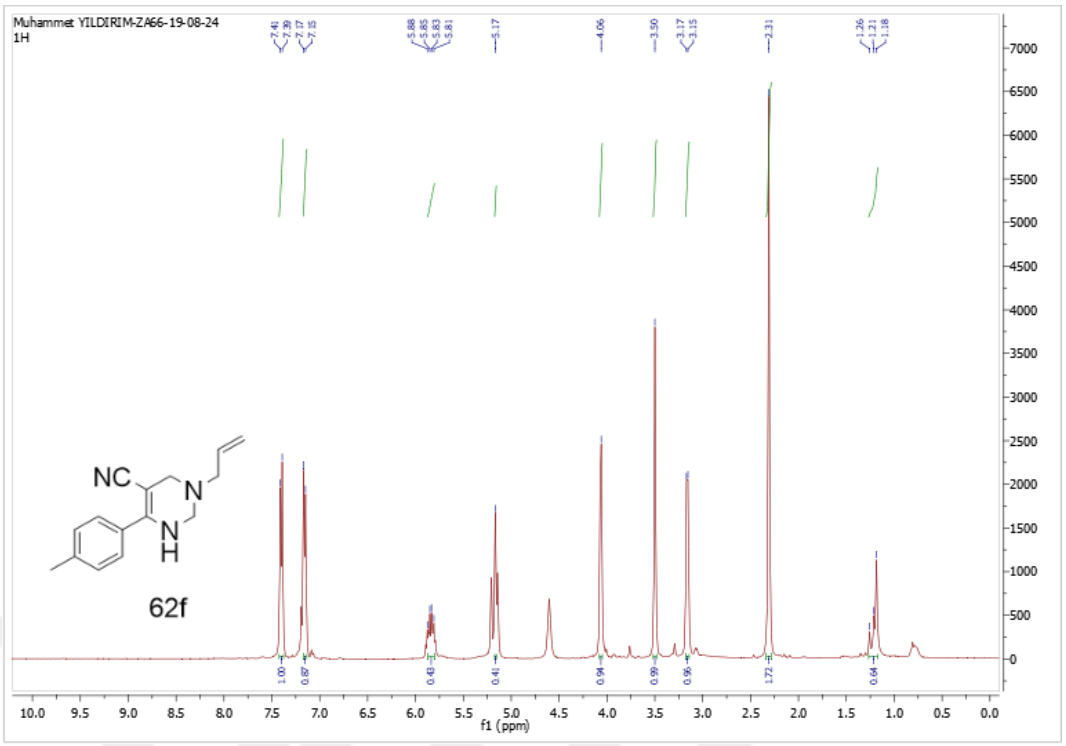


Figure A.35. 1H-NMR Spectrum of compound **62f**

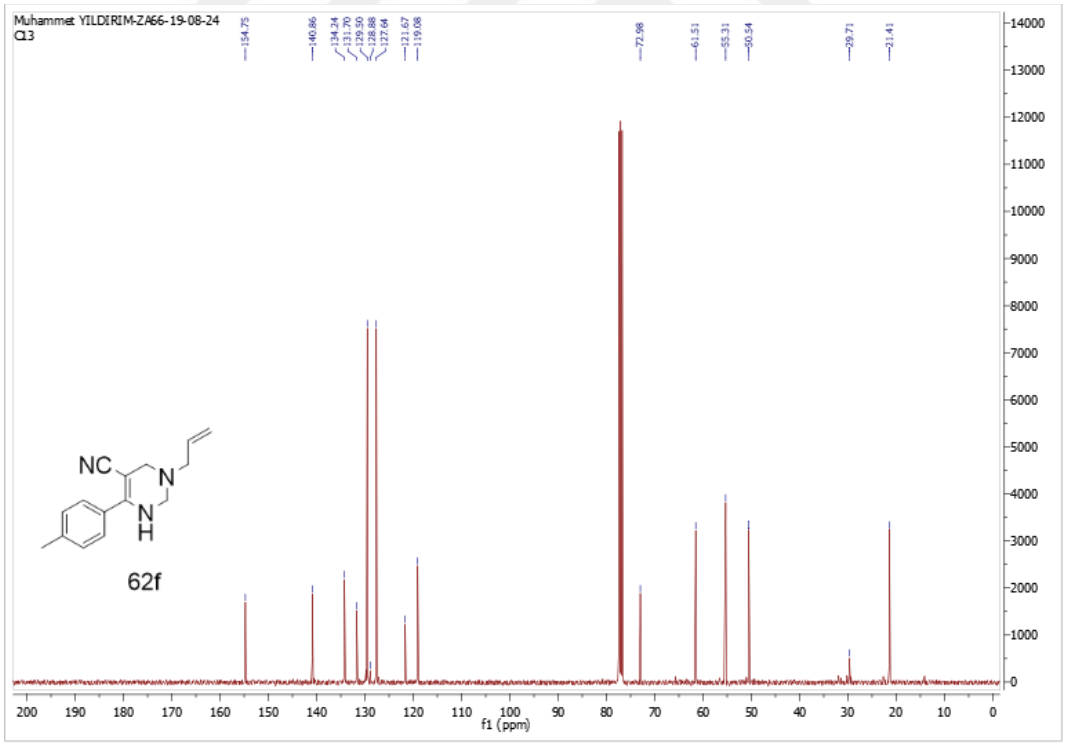


Figure A.36. ^{13}C-NMR Spectrum of compound **62f**

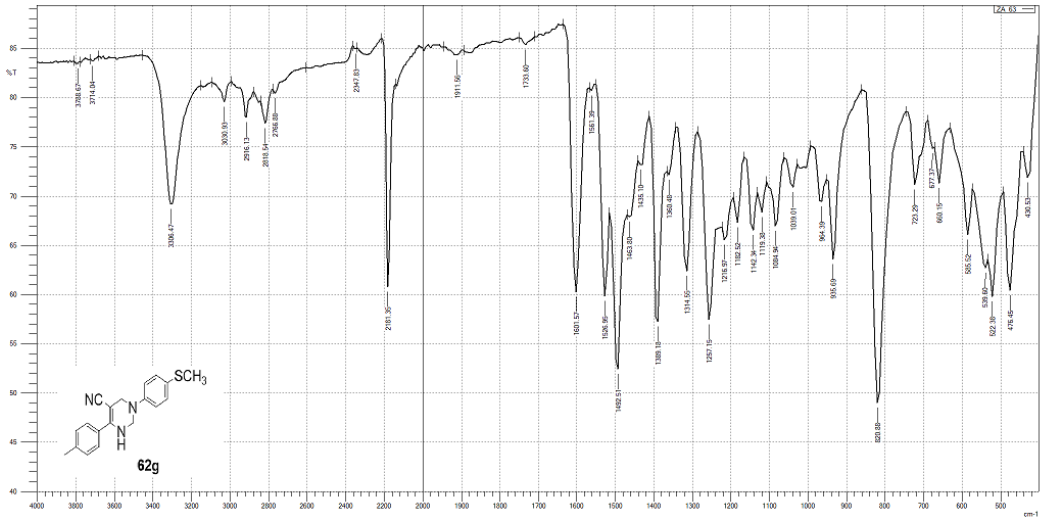


Figure A.37. IR Spectrum of compound **62g**

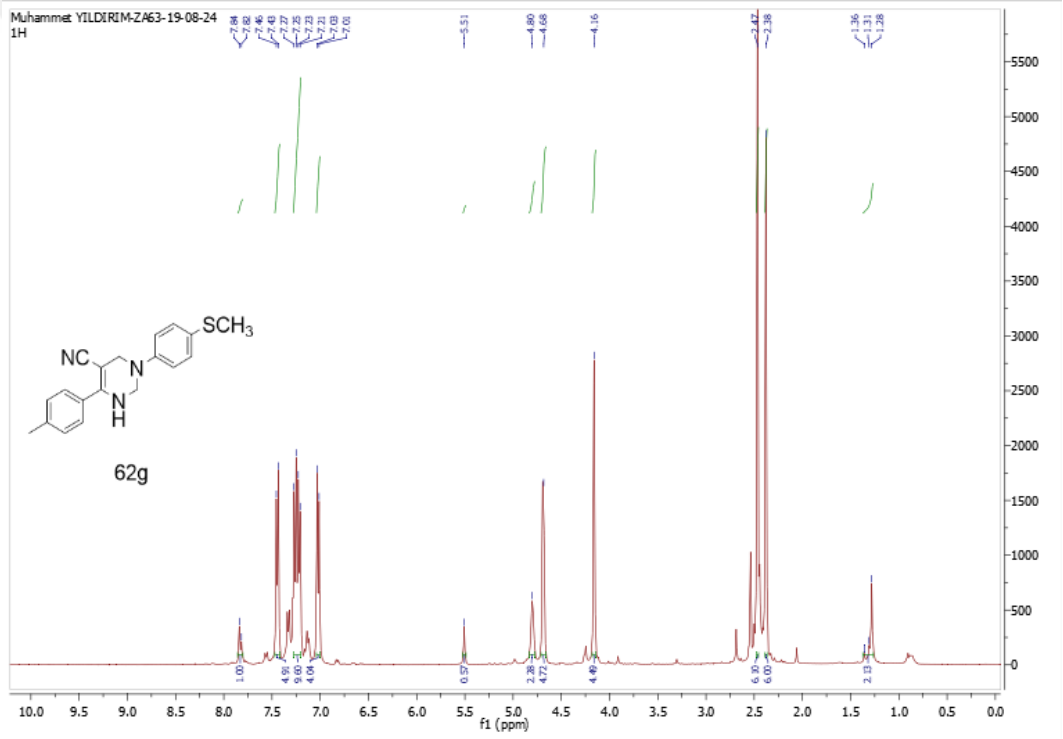


Figure A.38. 1H-NMR Spectrum of compound **62g**

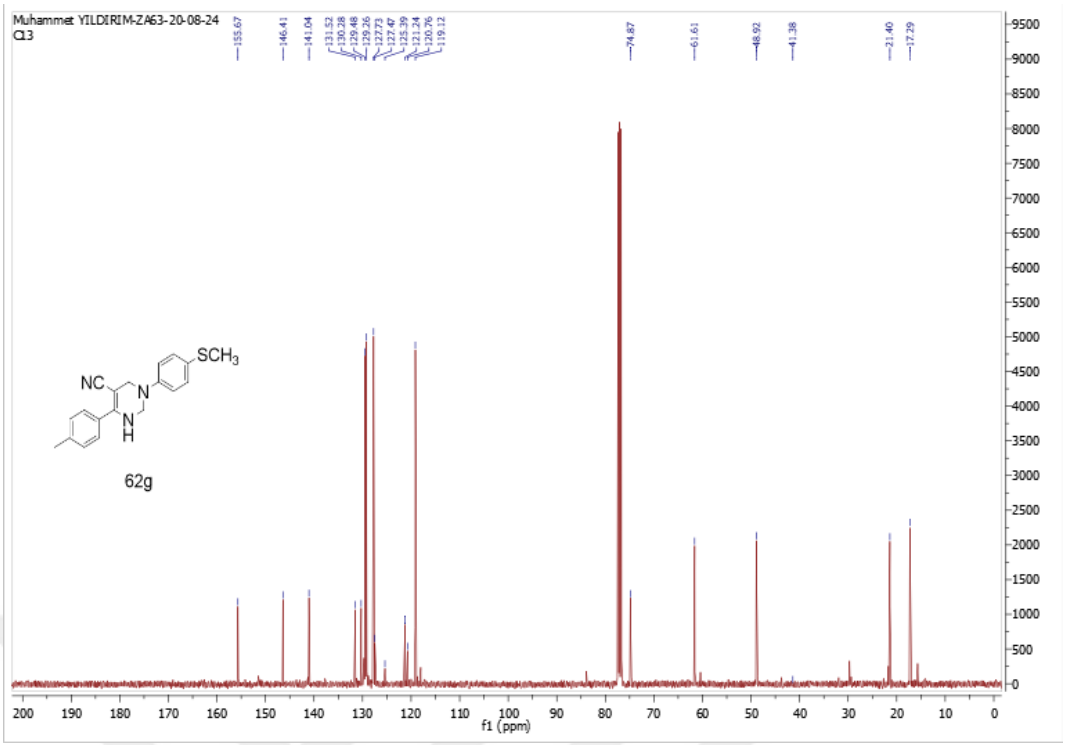


Figure A.39. ^{13}C-NMR Spectrum of compound **62g**

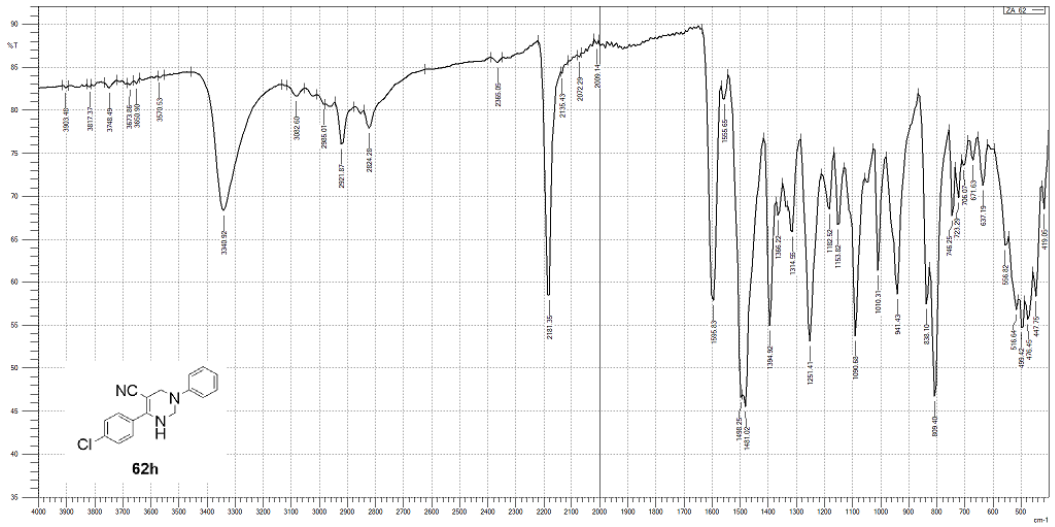


Figure A.40. IR Spectrum of compound **62h**

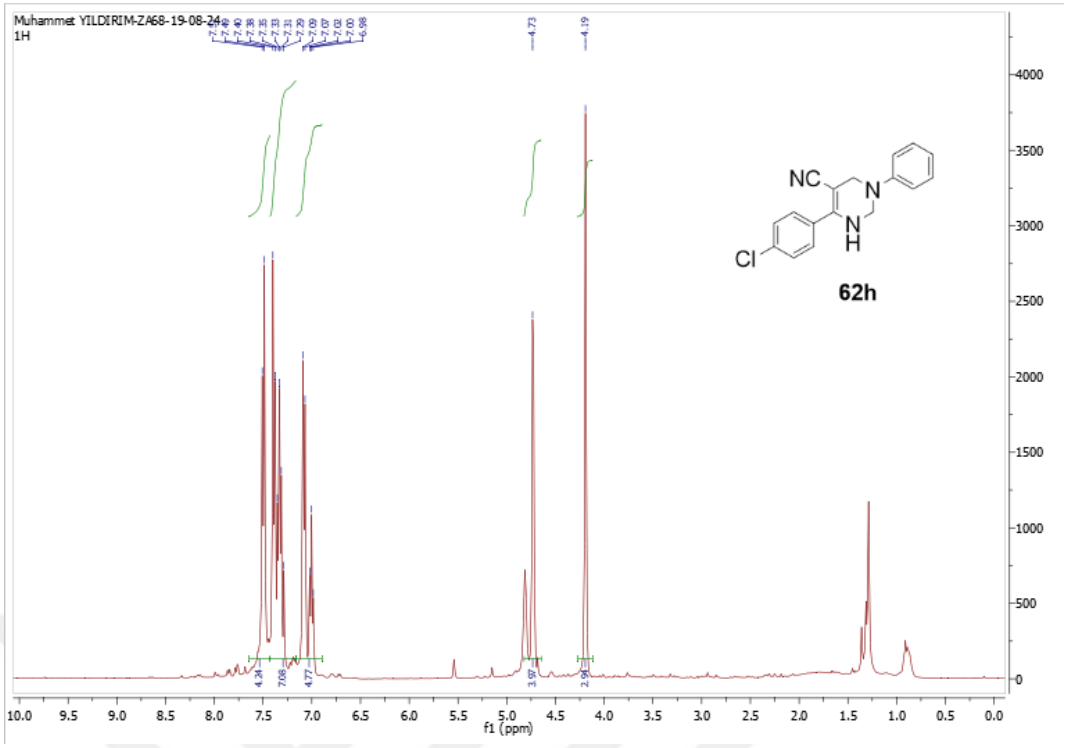


Figure A.41. 1H-NMR Spectrum of compound **62h**

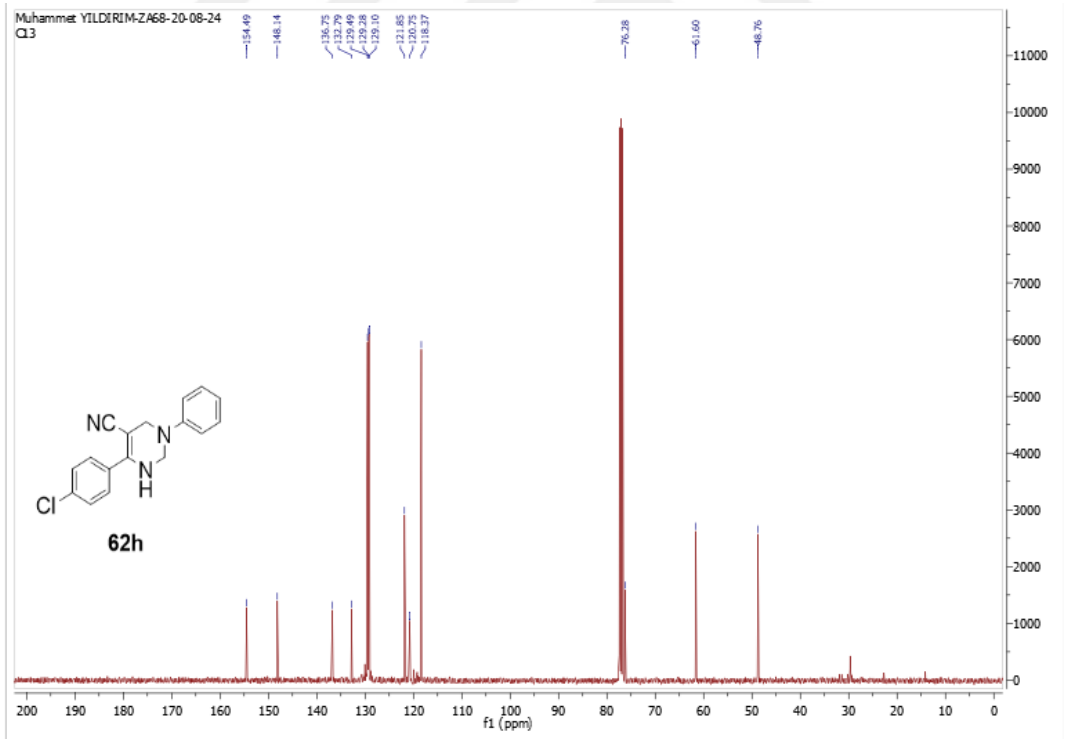


Figure A.42. ^{13}C-NMR Spectrum of compound **62h**

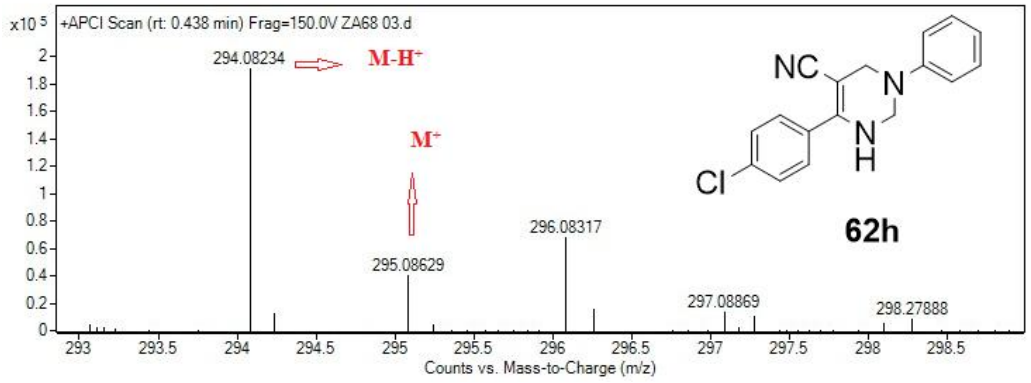


Figure A.43. HRMS Spectum of compound **62h**

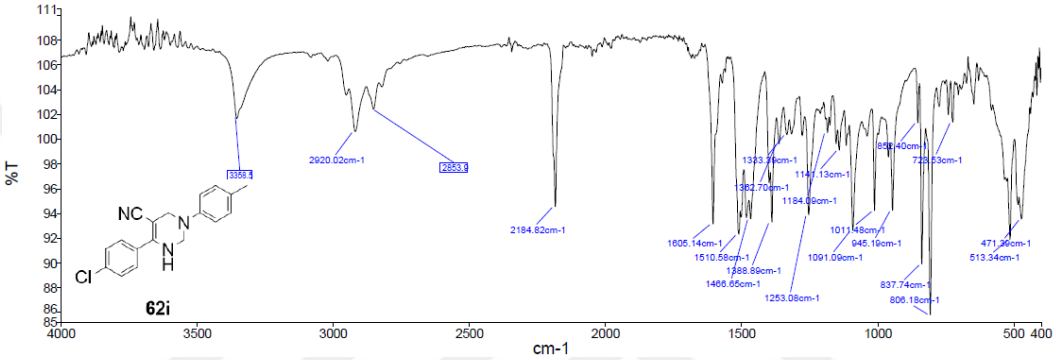


Figure A.44. IR Spectrum of compound **62i**

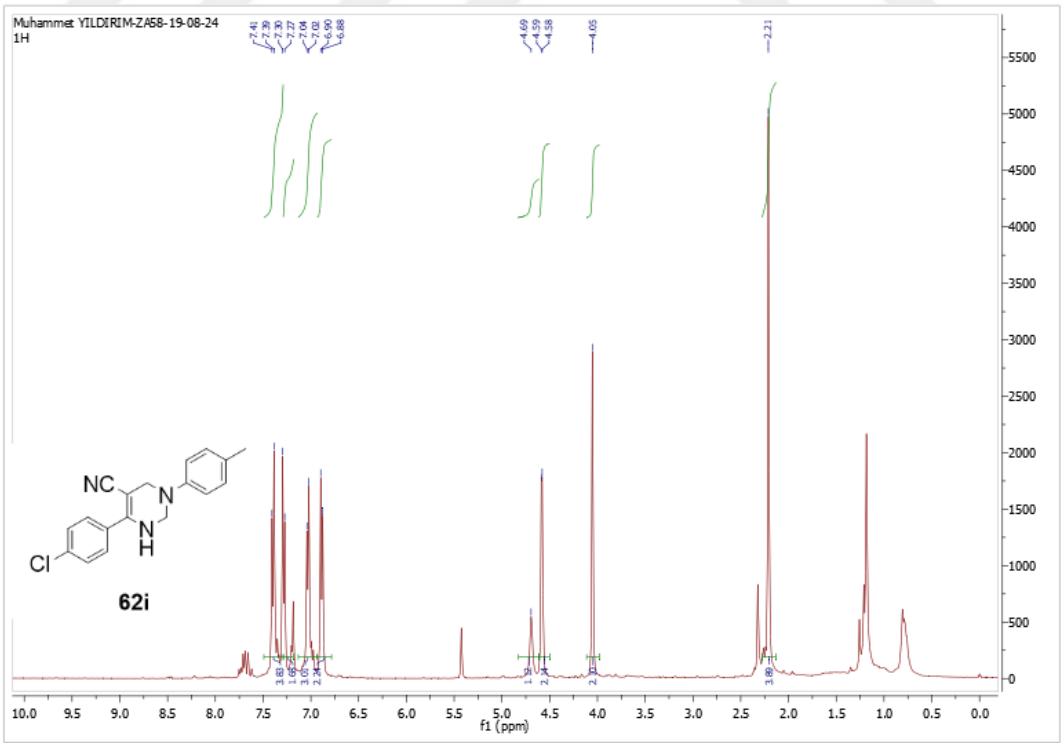


Figure A.45. 1H-NMR Spectrum of compound **62i**

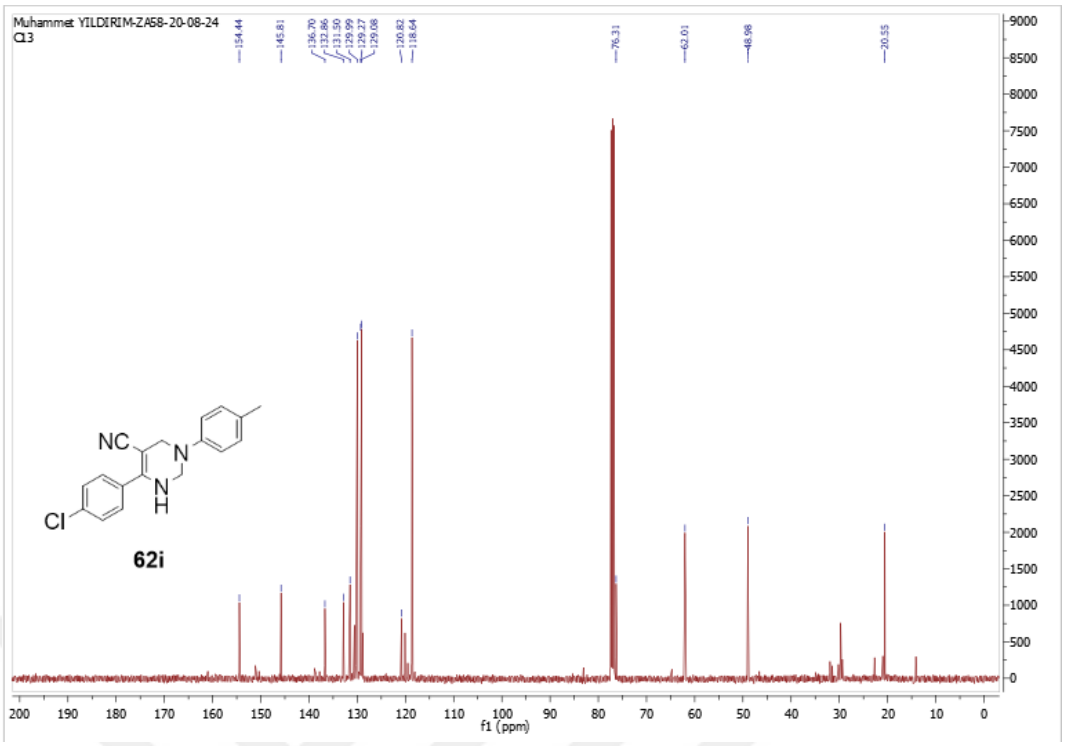


Figure A.46. ^{13}C-NMR Spectrum of compound **62i**

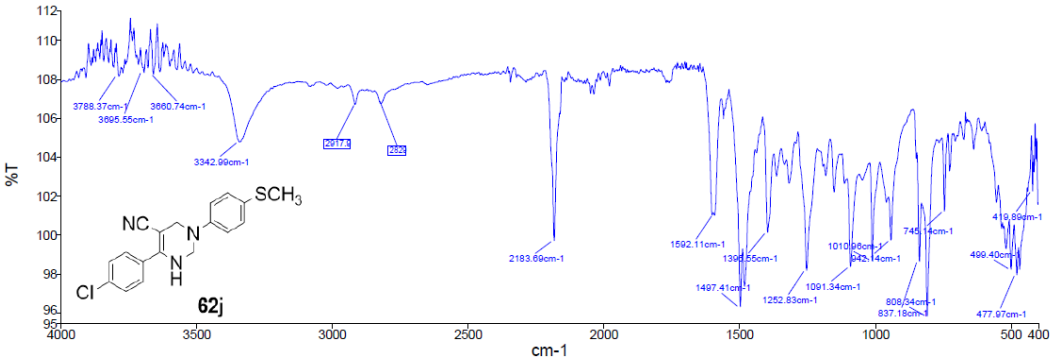


Figure A.47. IR Spectrum of compound **62j**

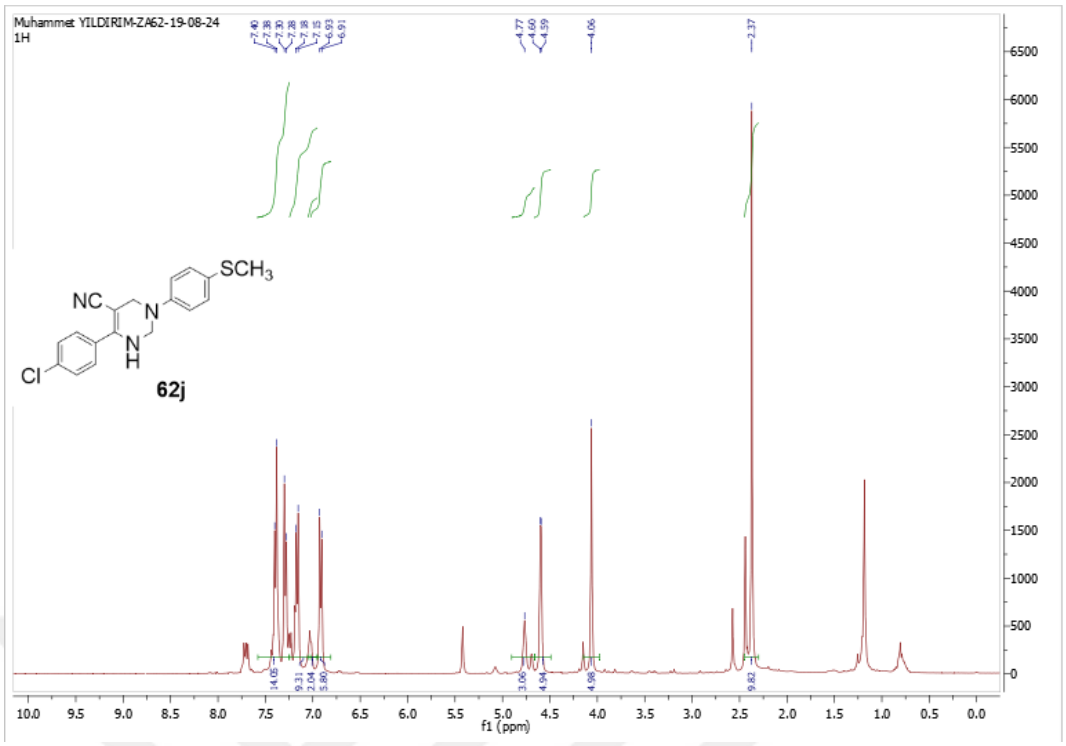


Figure A.48. 1H-NMR Spectrum of compound **62j**

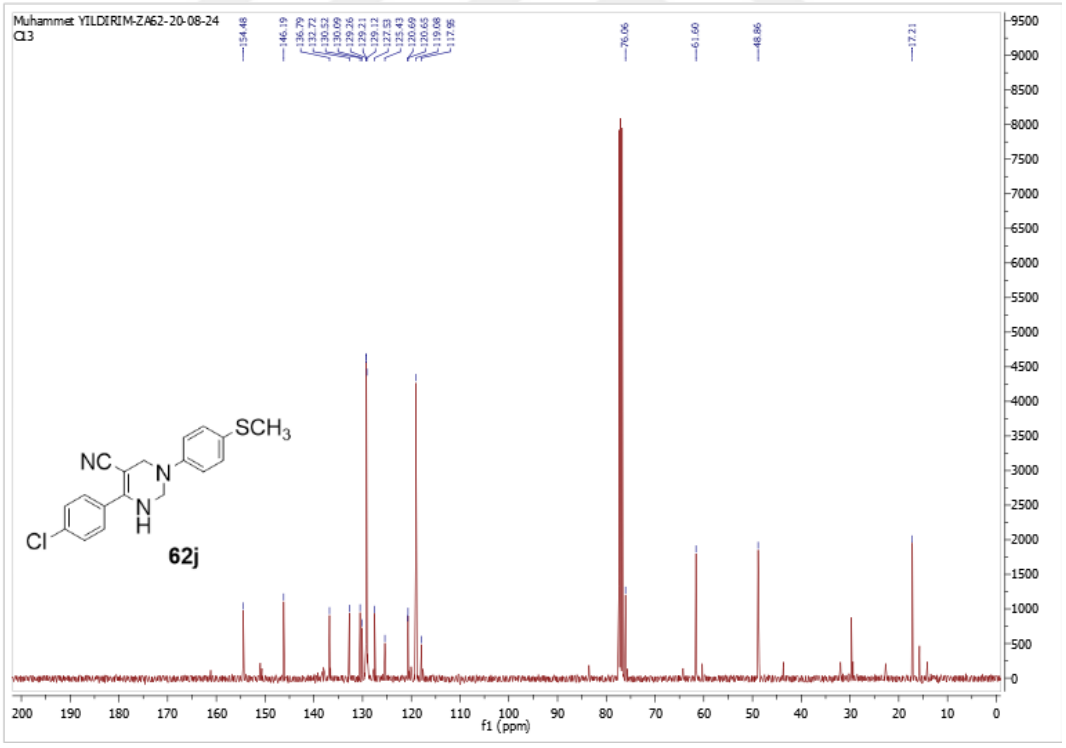


Figure A.49. ^{13}C-NMR Spectrum of compound **62j**

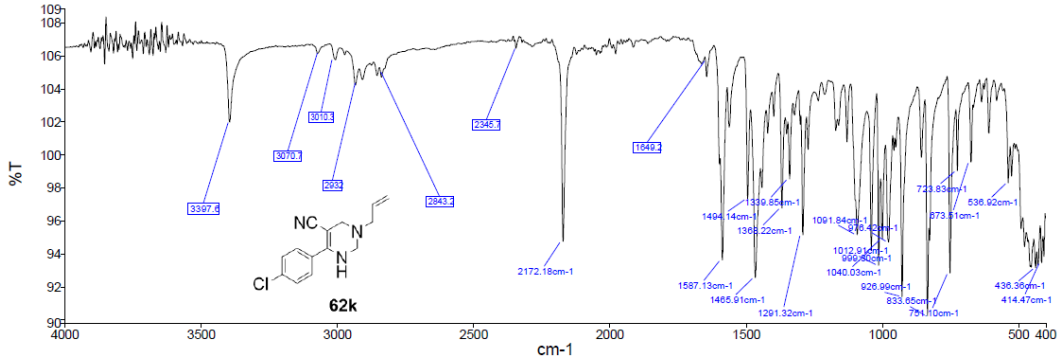


Figure A.50. IR Spectrum of compound **62k**

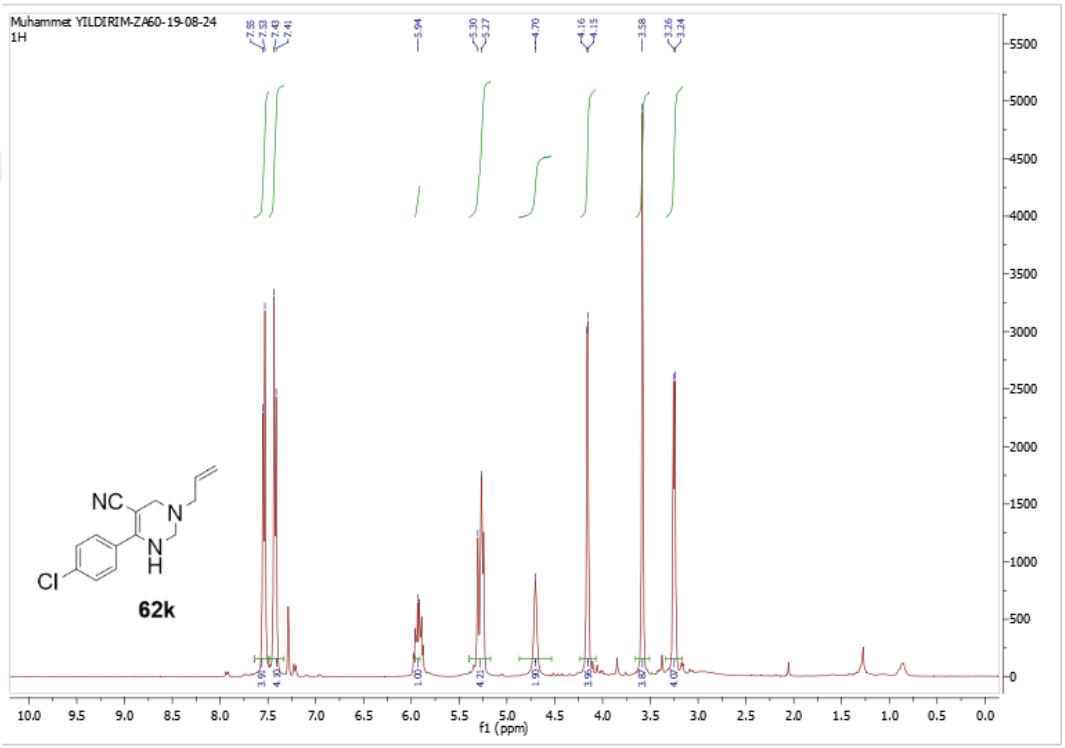


Figure A.51. 1H-NMR Spectrum of compound **62k**

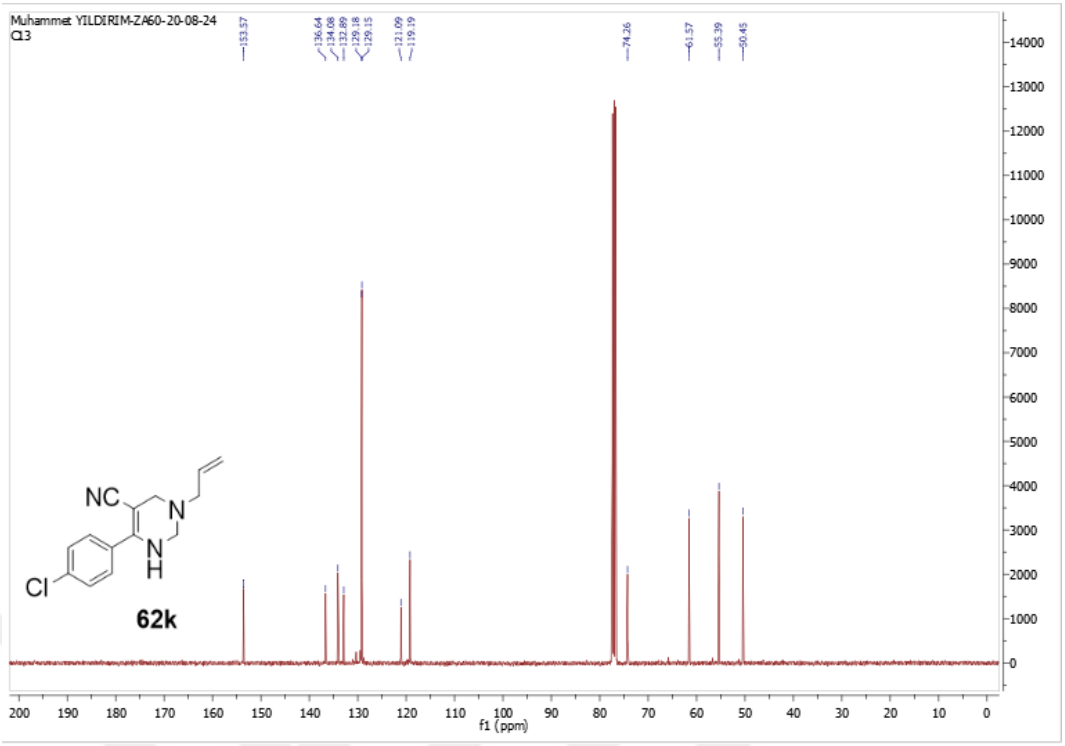


Figure A.52. ^{13}C-NMR Spectrum of compound **62k**

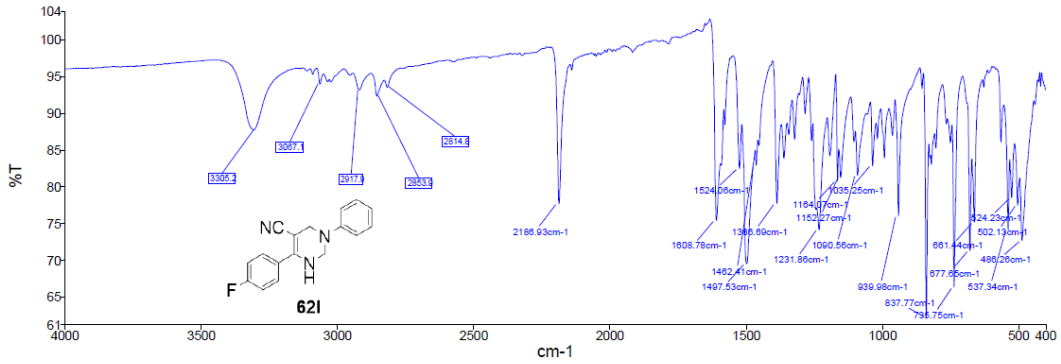


Figure A.53. IR Spectrum of compound **62l**

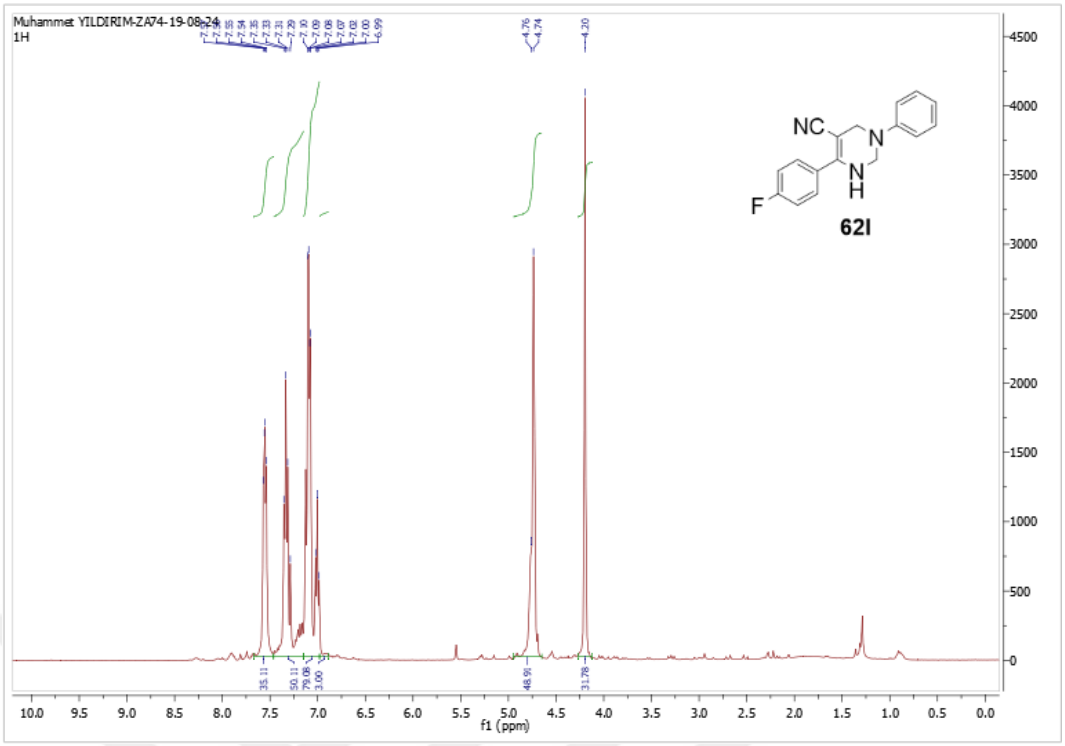


Figure A.54. 1H-NMR Spectrum of compound **62l**

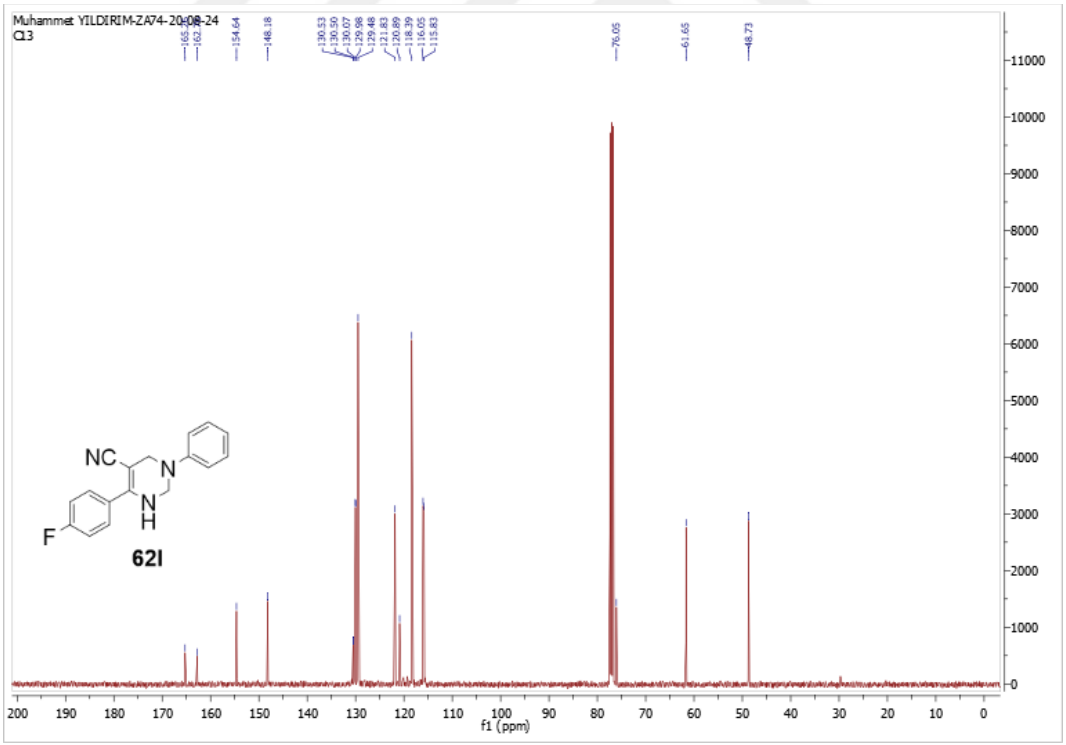


Figure A.55. ^{13}C-NMR Spectrum of compound **62l**

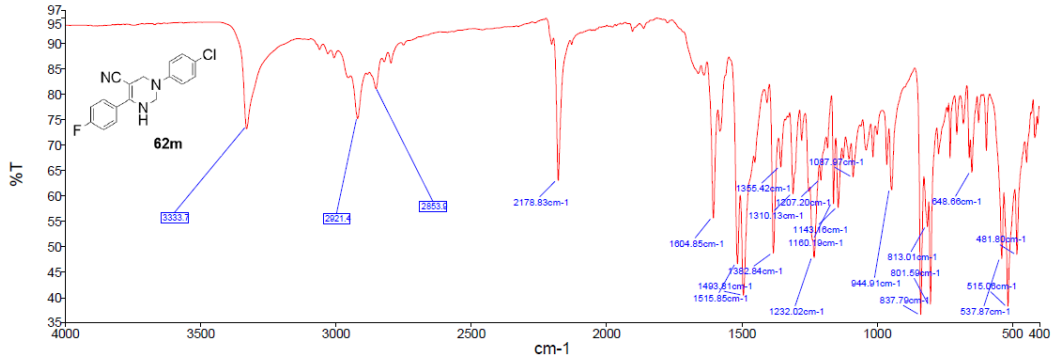


Figure A.56. IR Spectrum of compound **62m**

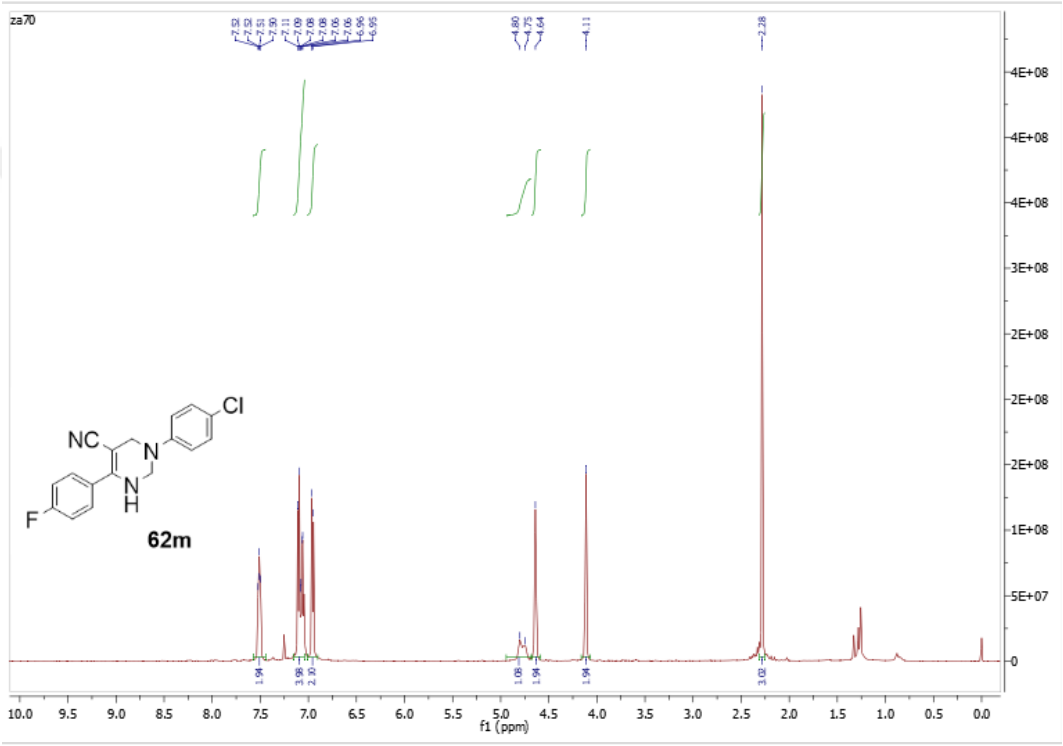


Figure A.57. 1H-NMR Spectrum of compound **62m**

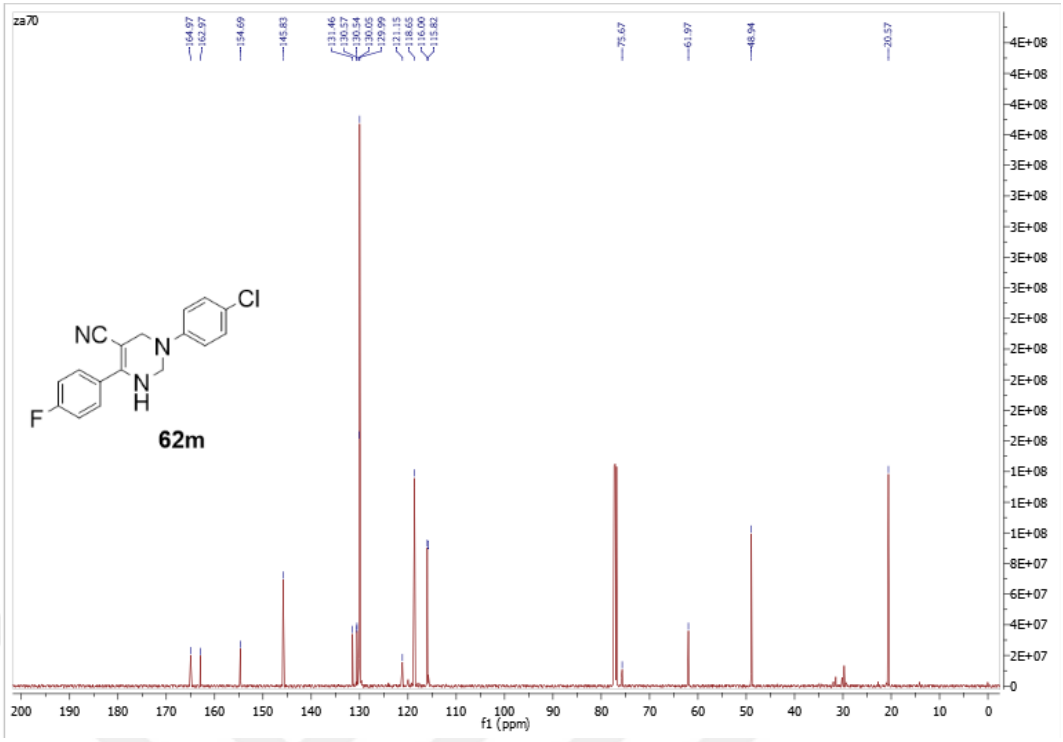


Figure A.58. ^{13}C-NMR Spectrum of compound **62m**

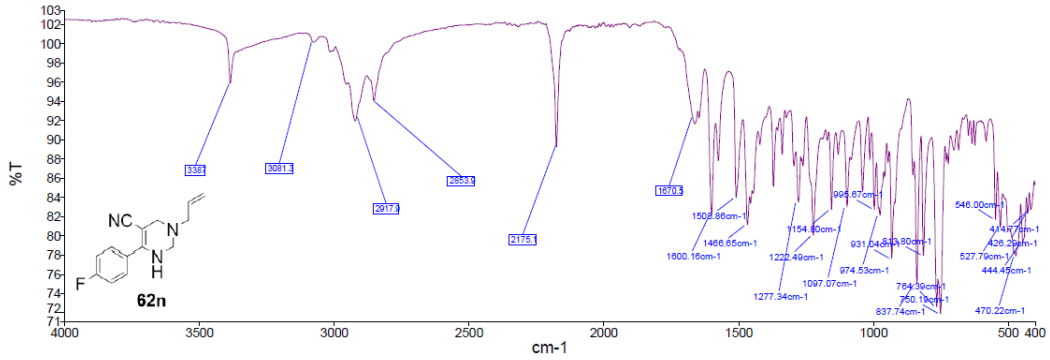


Figure A.59. IR Spectrum of compound **62n**

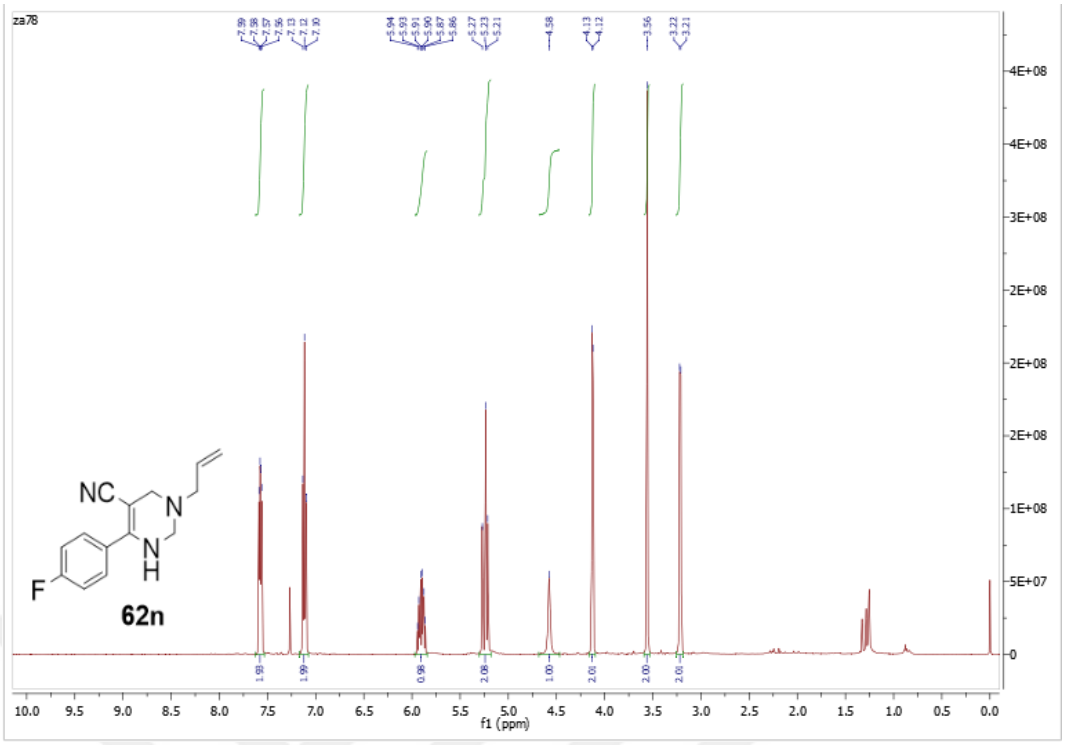


Figure A.60. 1H-NMR Spectrum of compound **62n**

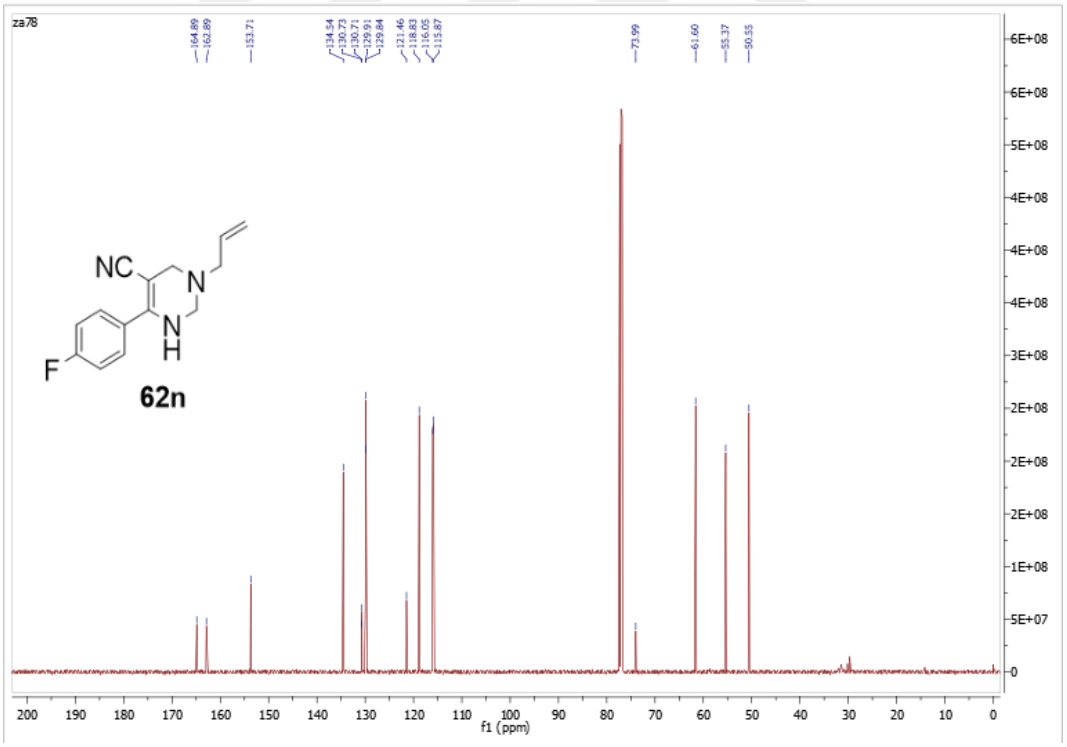


Figure A.61. ^{13}C-NMR Spectrum of compound **62n**

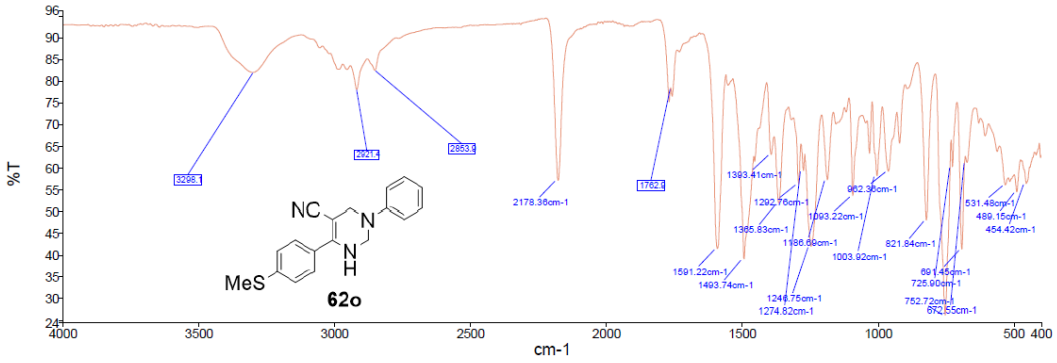


Figure A.62. IR Spectrum of compound **62o**

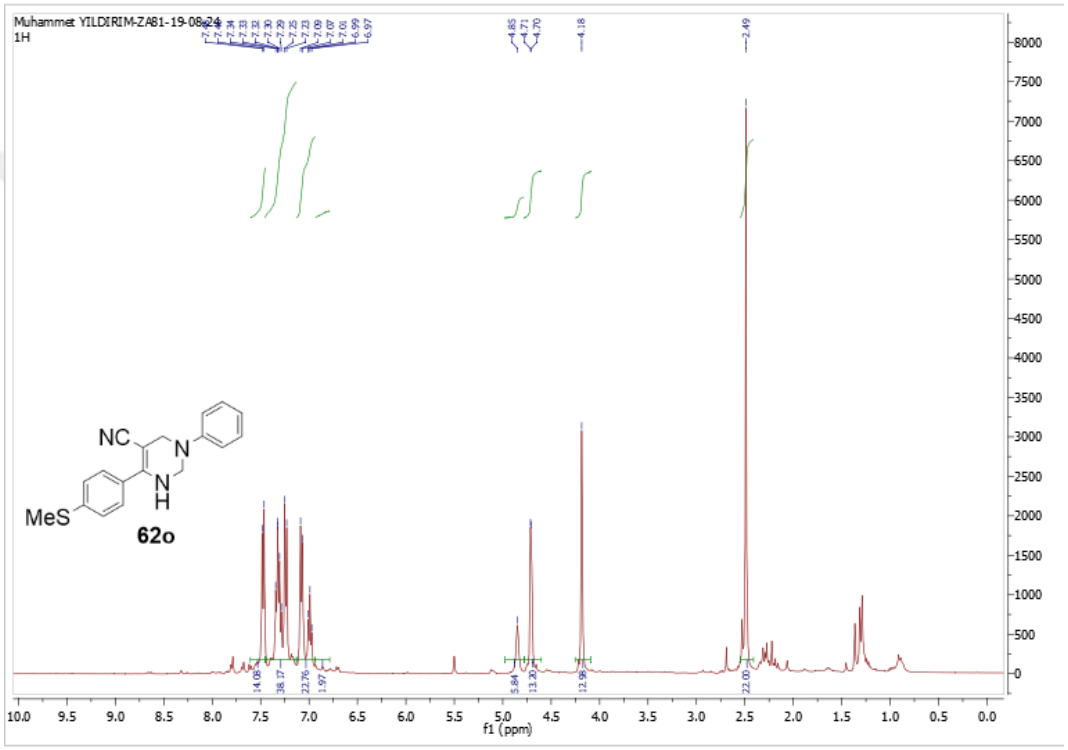


Figure A.63. 1H-NMR Spectrum of compound **62o**

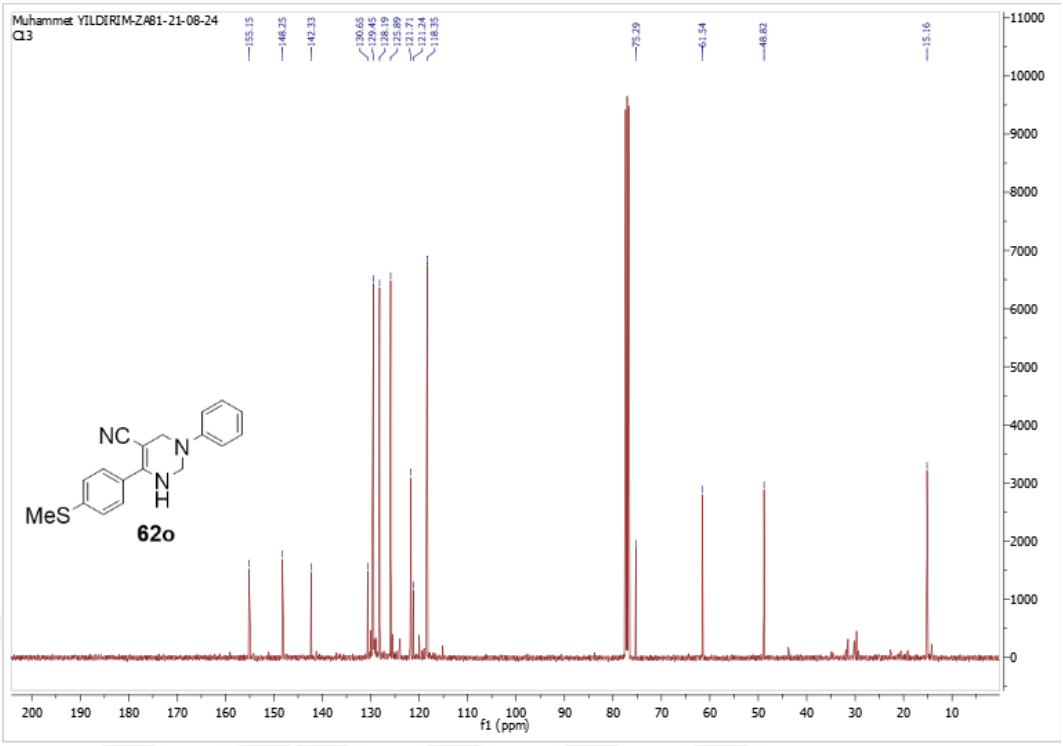


Figure A.64. ^{13}C-NMR Spectrum of compound **62o**

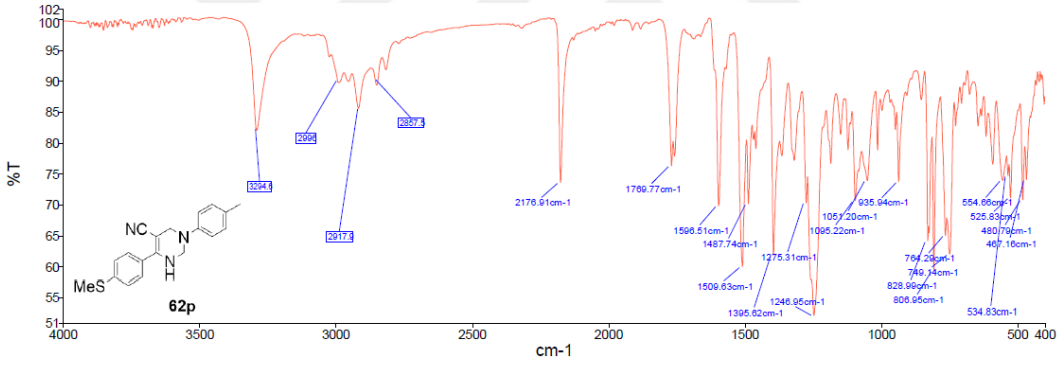


Figure A.65. IR Spectrum of compound **62p**

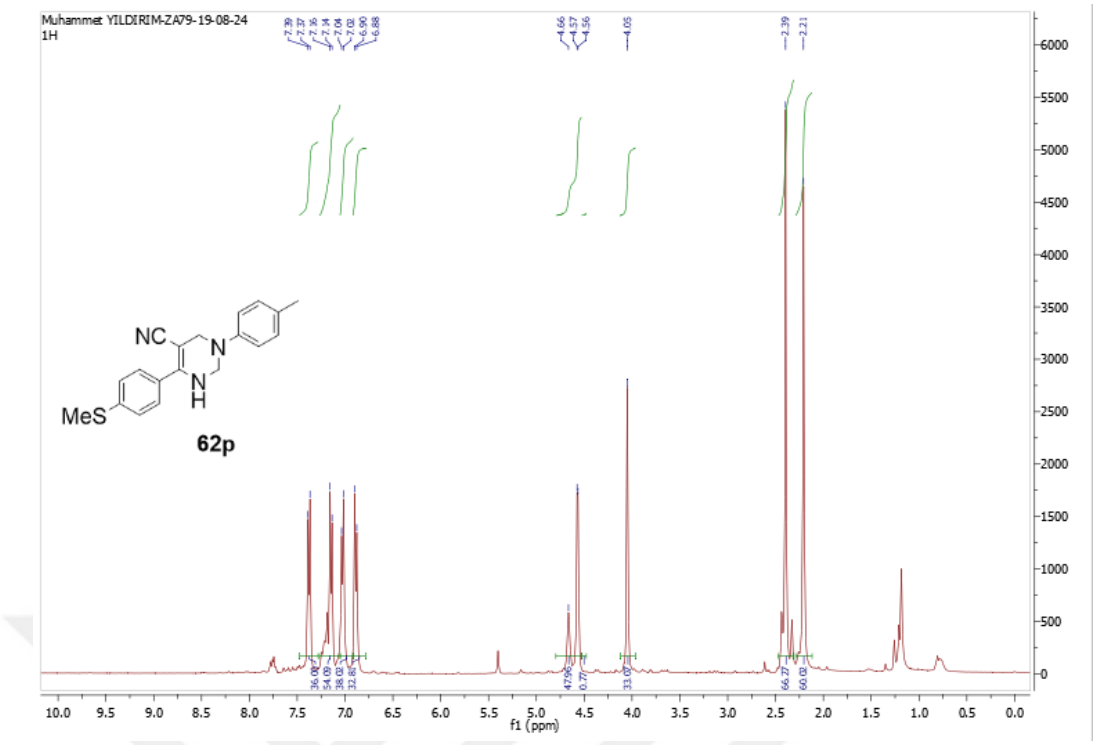


Figure A.66. 1H-NMR Spectrum of compound **62p**

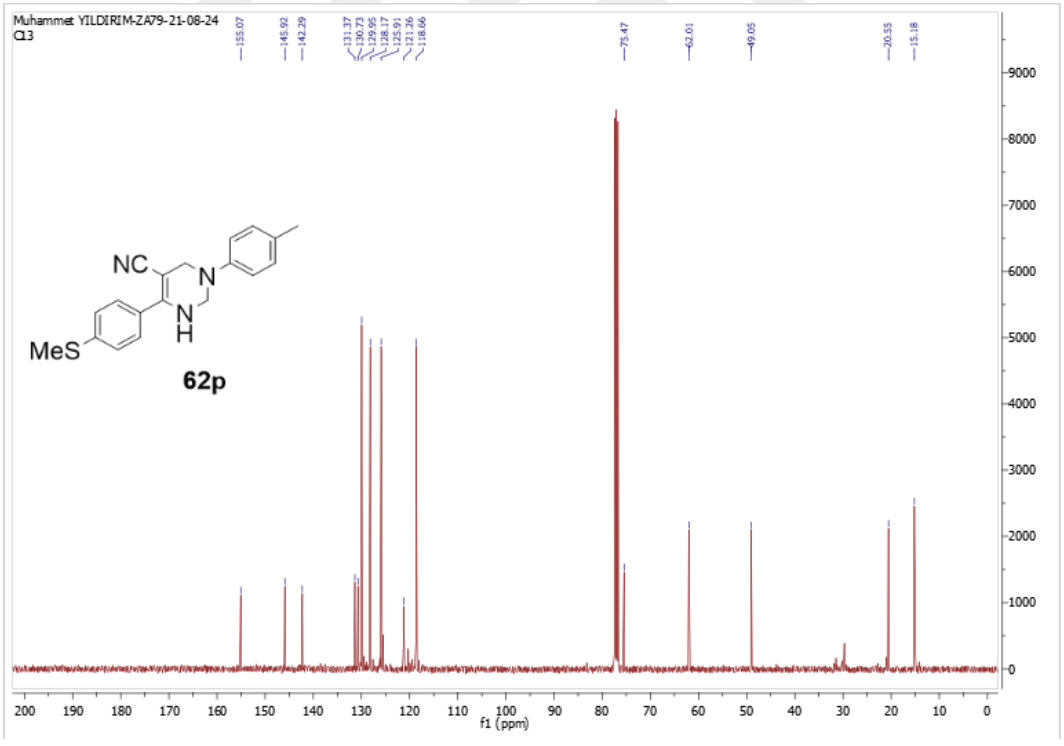


Figure A.67. ^{13}C-NMR Spectrum of compound **62p**

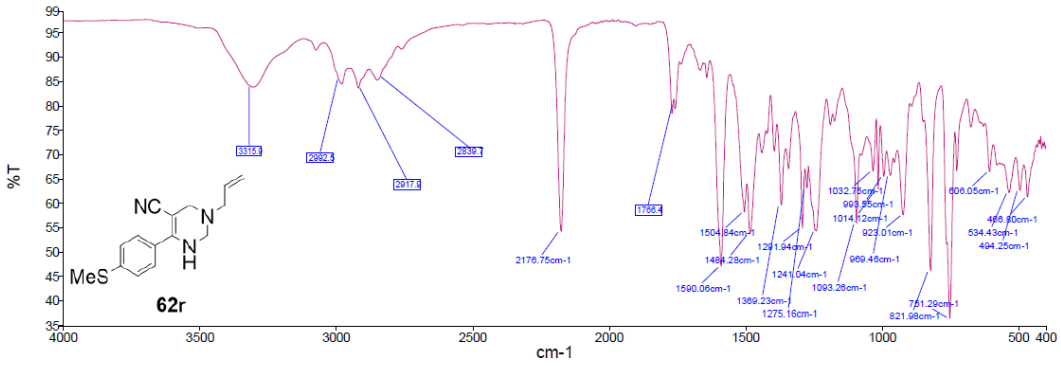


Figure A.68. IR Spectrum of compound **62r**

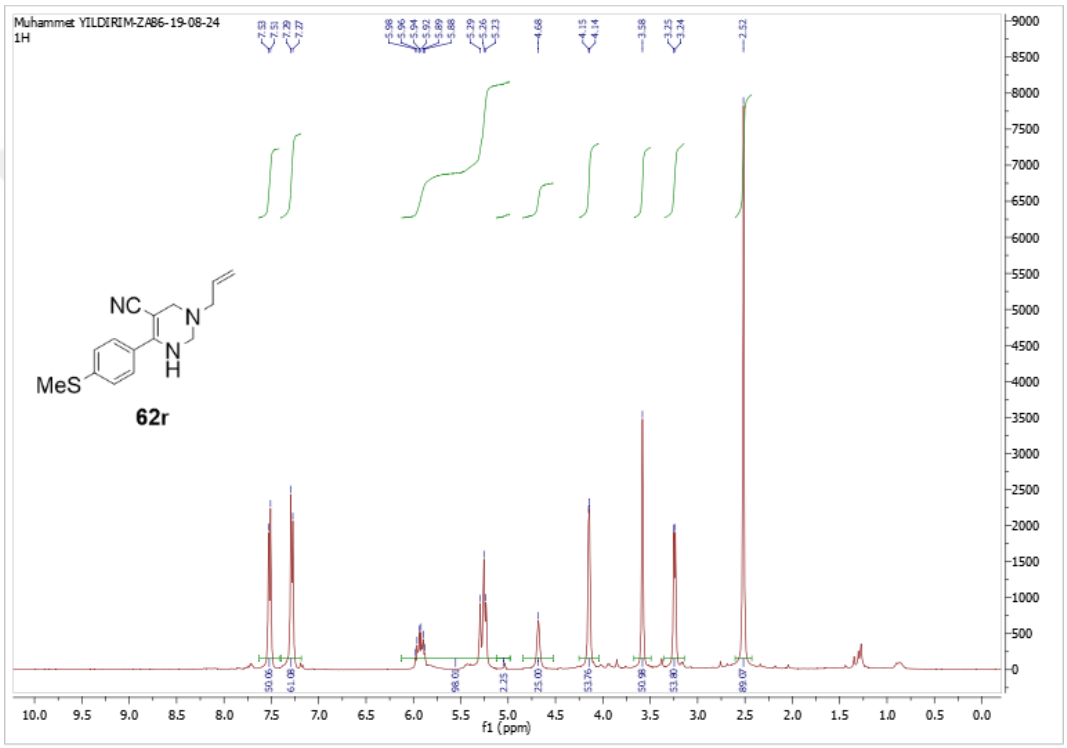


Figure A.69. 1H-NMR Spectrum of compound **62r**

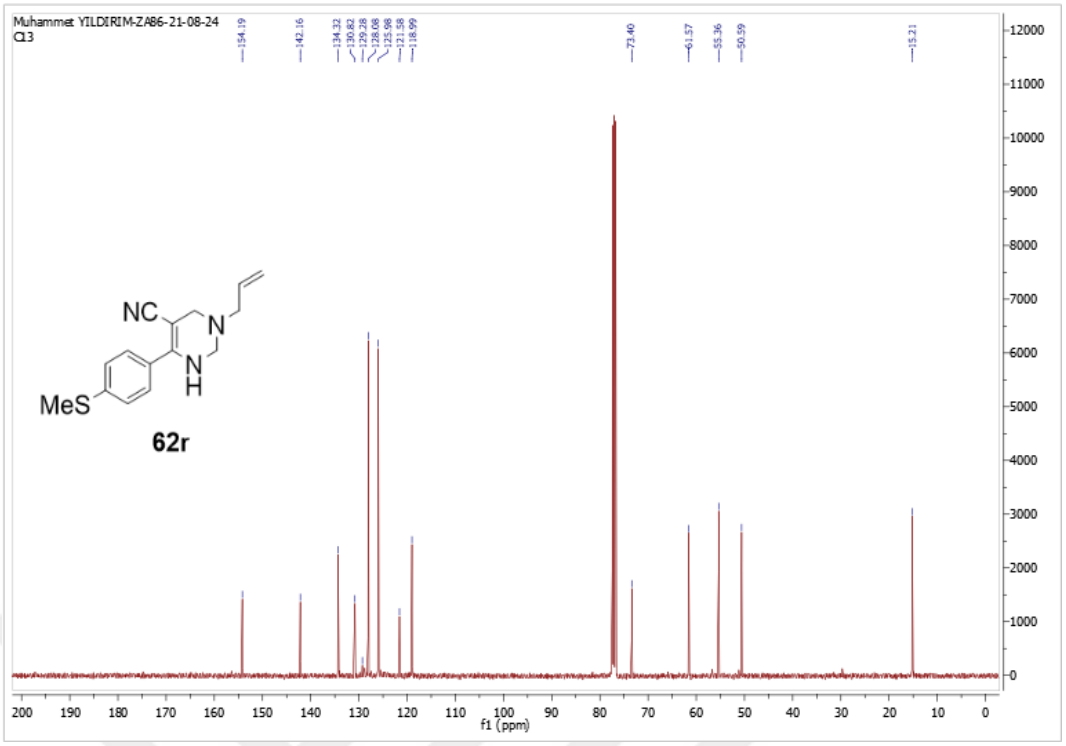


Figure A.70. ^{13}C-NMR Spectrum of compound **62r**

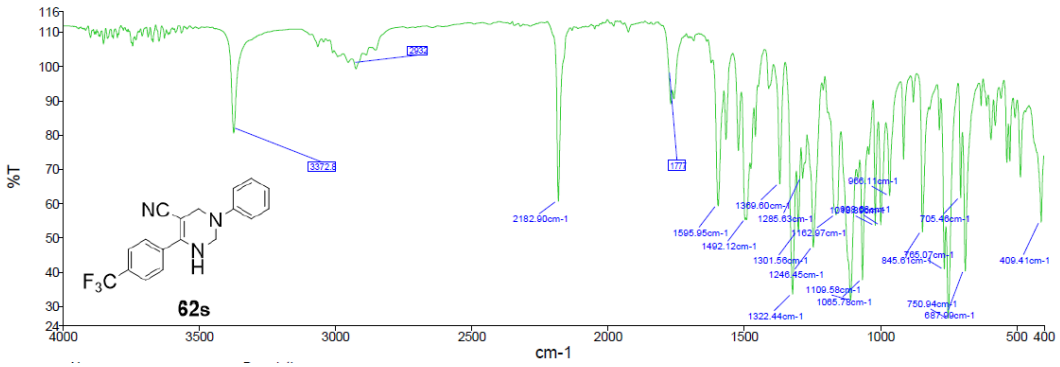


Figure A.71. IR Spectrum of compound **62s**

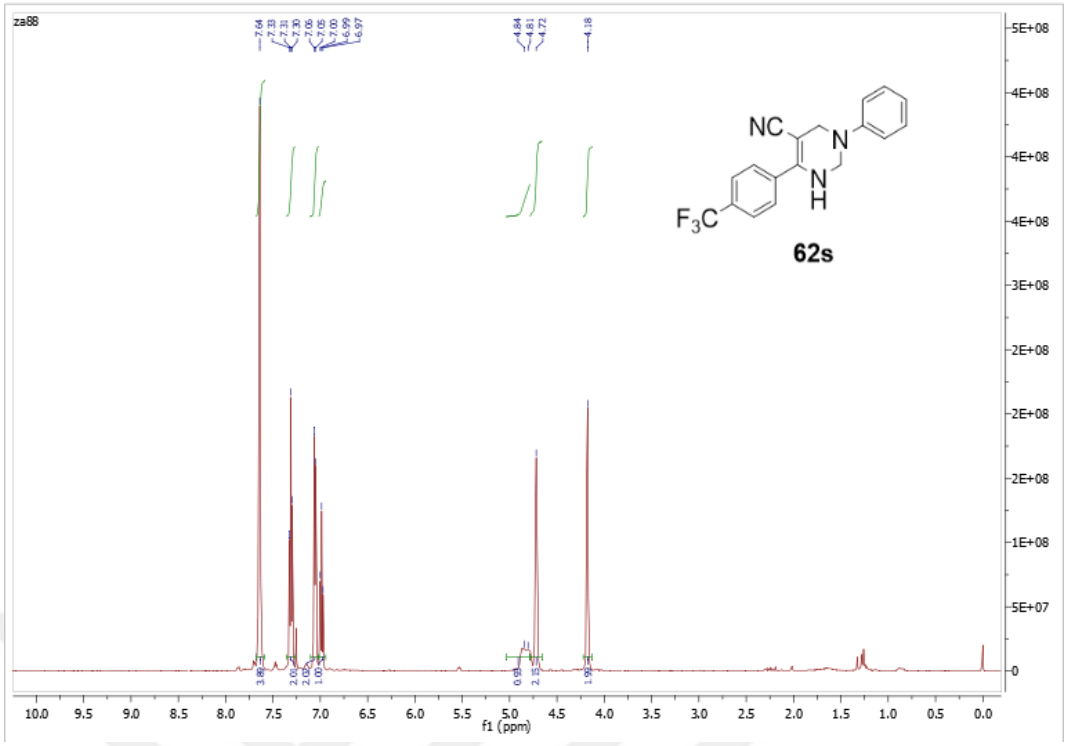


Figure A.72. 1H-NMR Spectrum of compound **62s**

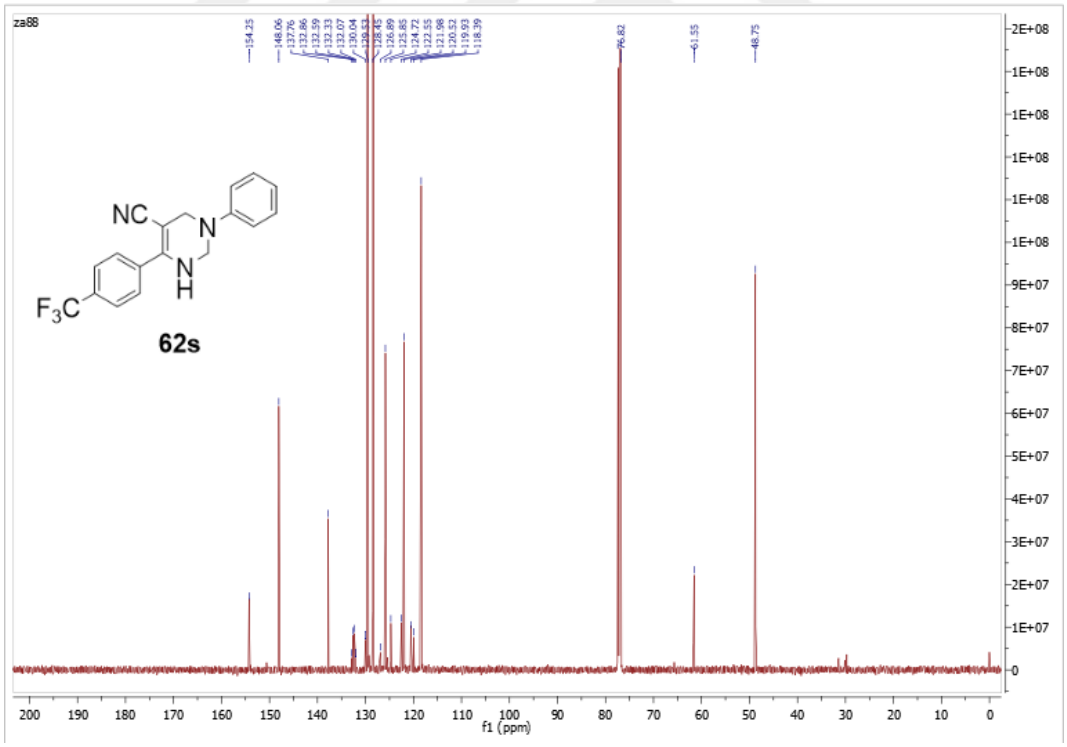


Figure A.73. ^{13}C-NMR Spectrum of compound **62s**

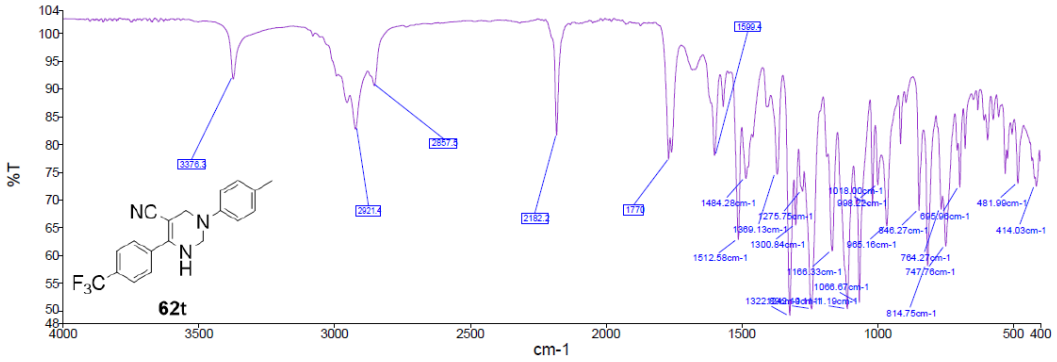


Figure A.74. IR Spectrum of compound **62t**

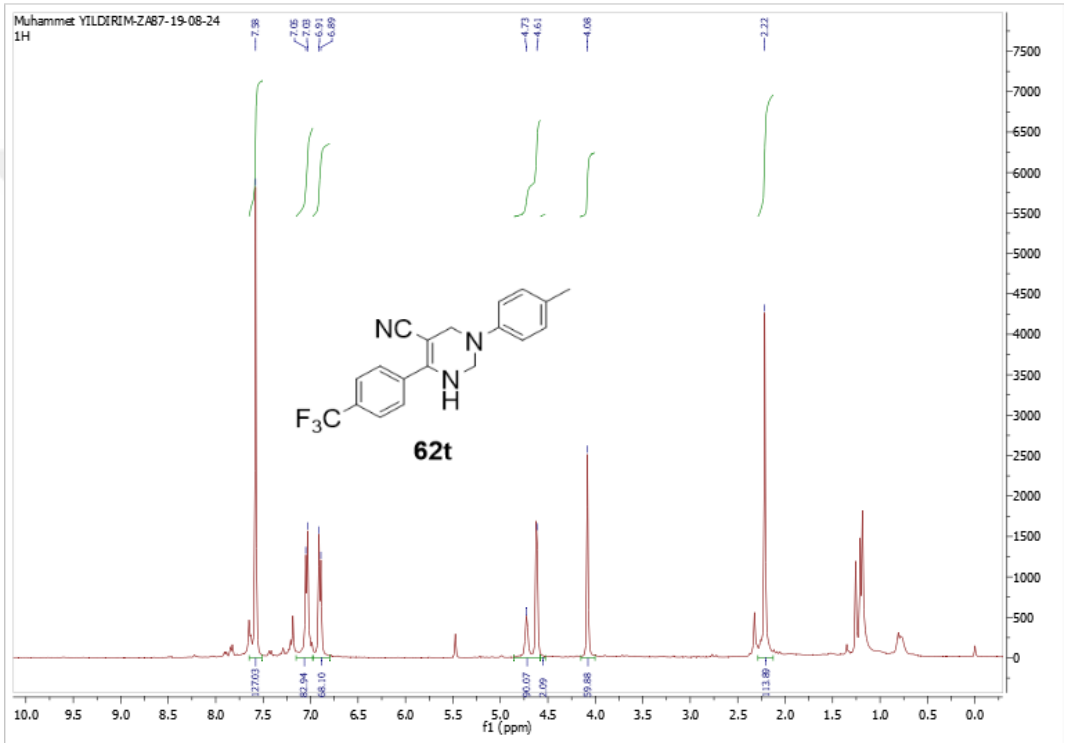


Figure A.75. 1H-NMR Spectrum of compound **62t**

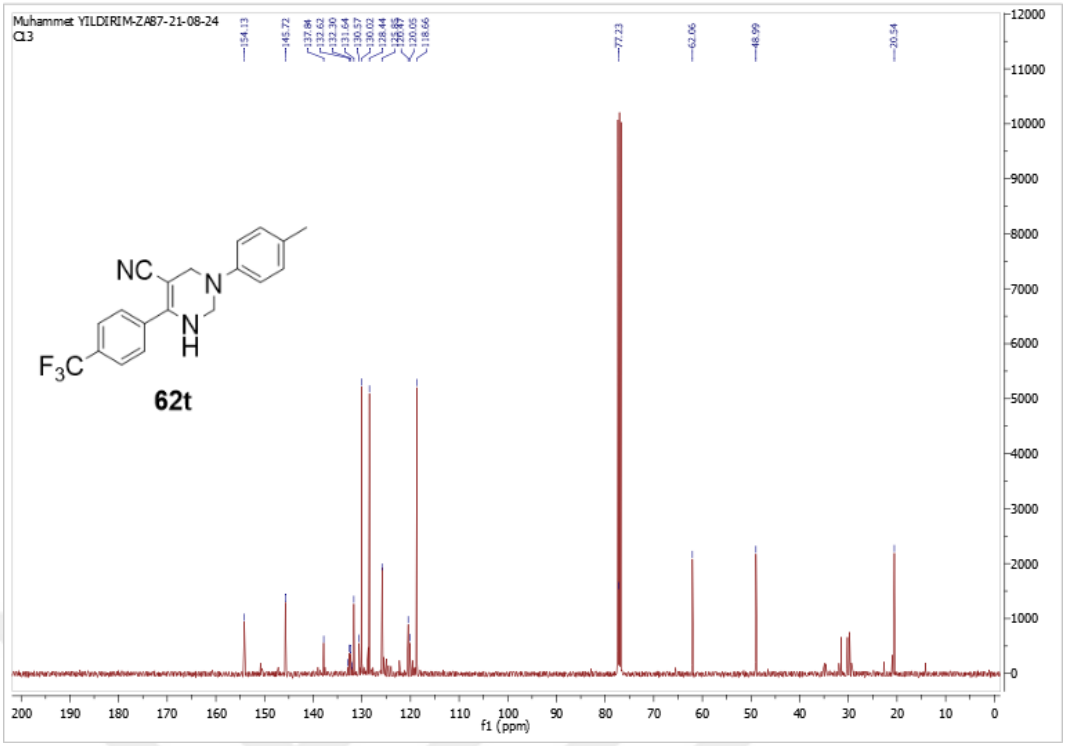


Figure A.76. ^{13}C-NMR Spectrum of compound **62t**

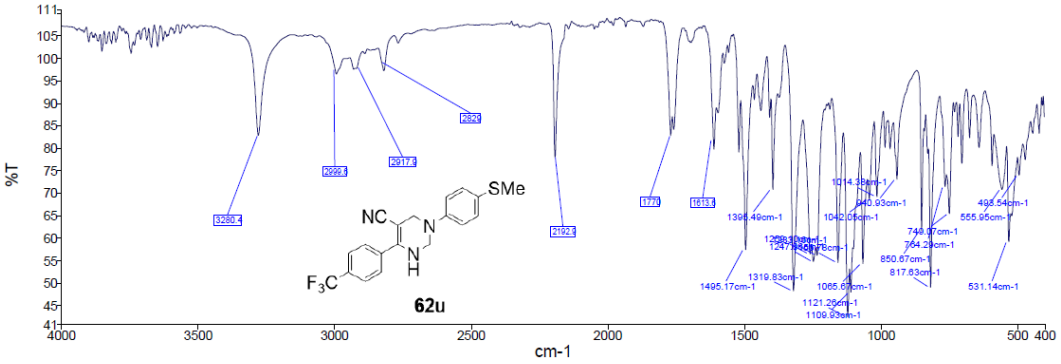


Figure A.77. IR Spectrum of compound **62u**

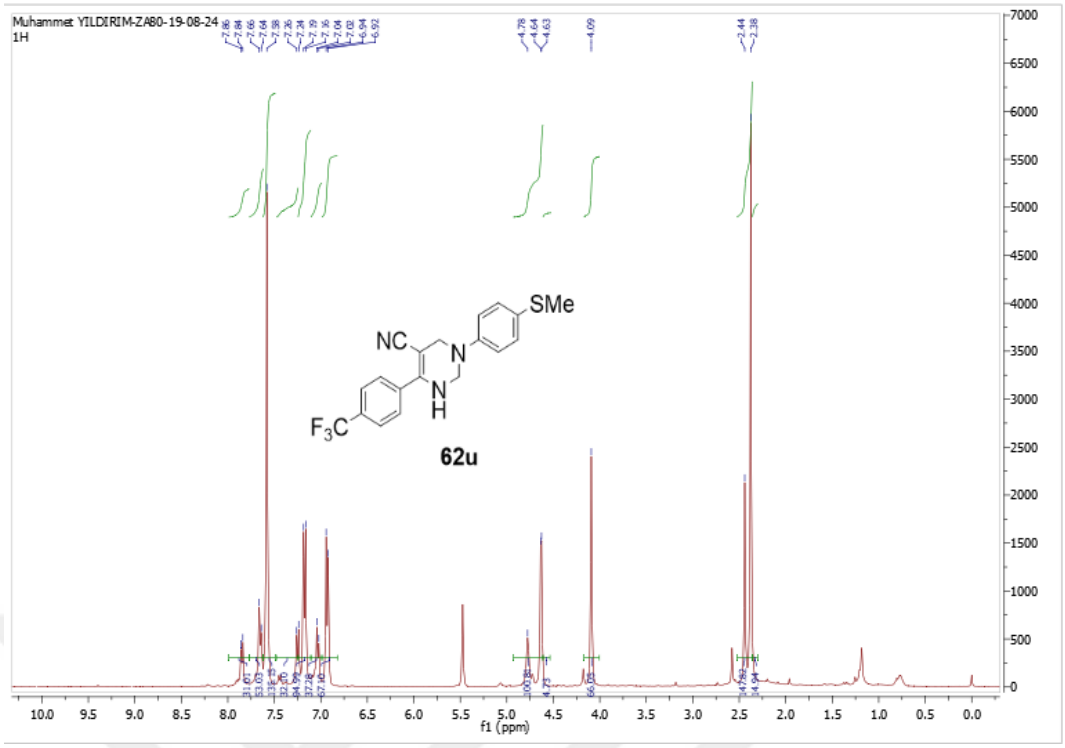


Figure A.78. 1H-NMR Spectrum of compound **62u**

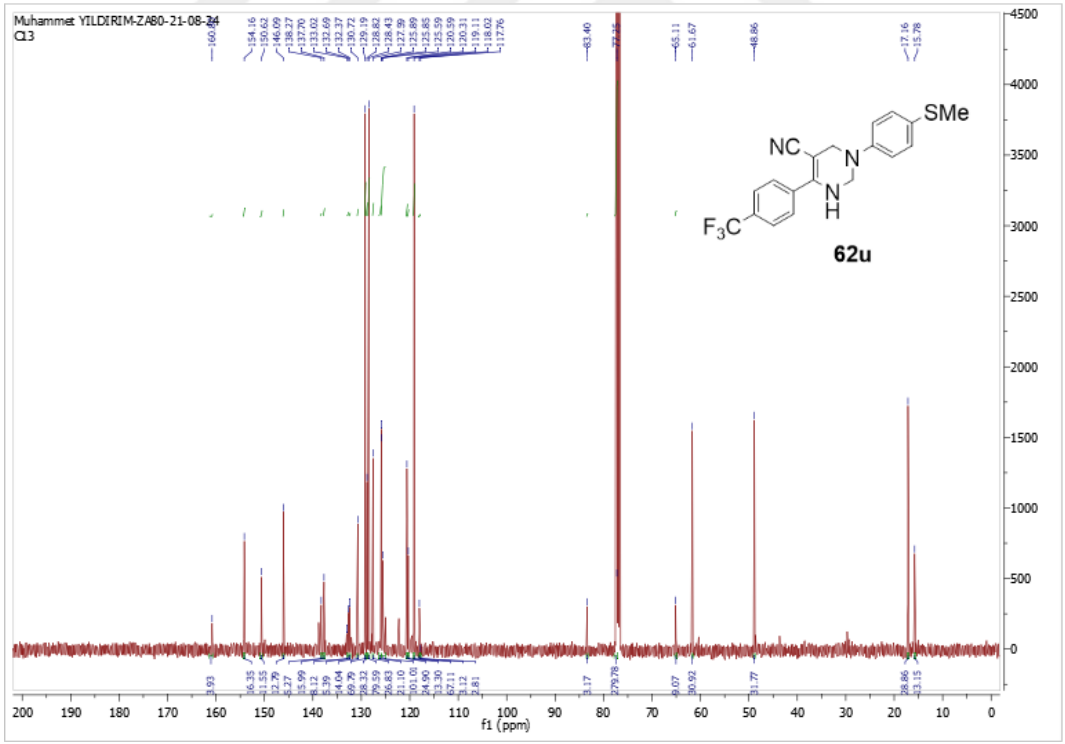


Figure A.79. ^{13}C-NMR Spectrum of compound **62u**

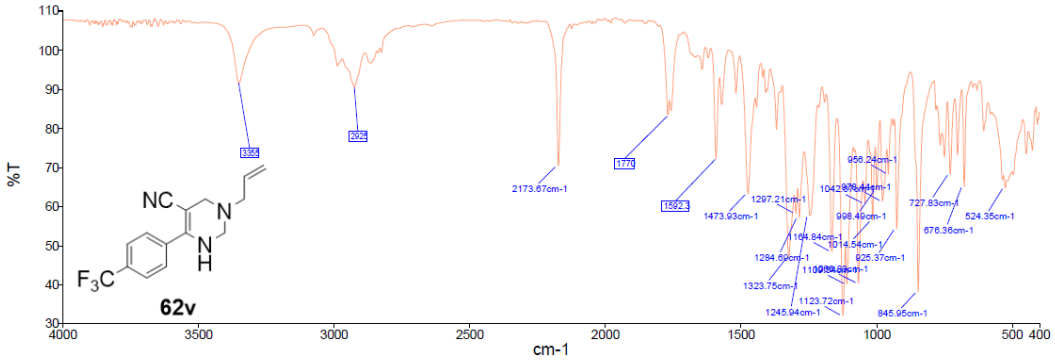


Figure A.80. IR Spectrum of compound **62v**

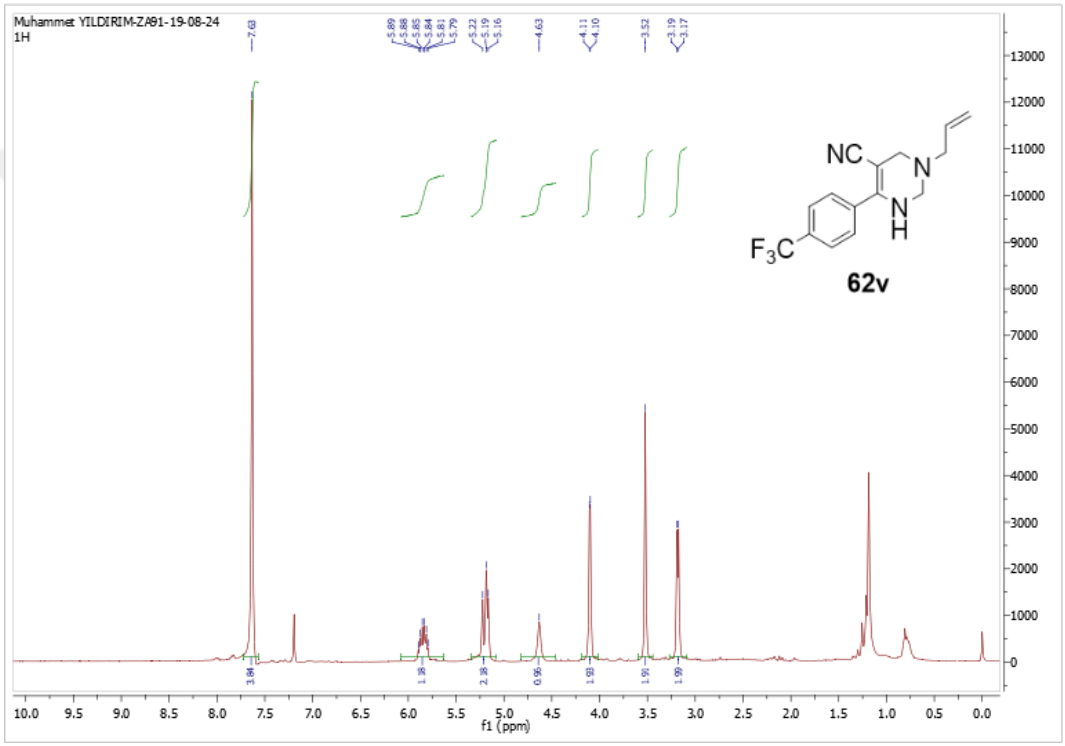


Figure A.81. 1H-NMR Spectrum of compound **62v**

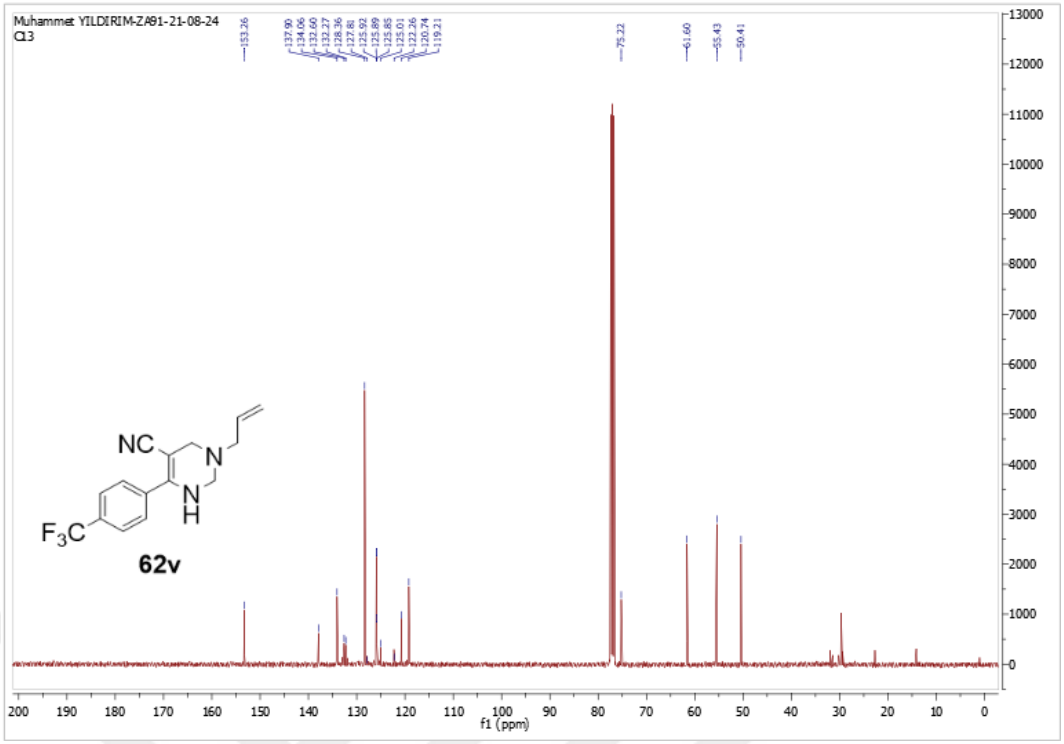


Figure A.82. ^{13}C-NMR Spectrum of compound **62v**