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

FACILE SYNTHESIS OF NEW OXOTHIAZOLO[3,2-*C*] PYRIMIDINE CARBONITRILES VIA MANNICH CYCLISATIONS

MASTER OF SCIENCE

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ACADEMIC SUPERVISOR
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APPROVAL OF THE THESIS

FACILE SYNTHESIS OF NEW OXOTHIAZOLO[3,2-*C*] PYRIMIDINE CARBONITRILES VIA MANNICH CYCLISATIONS submitted by **Çağrı ÖZBİL** and defended before the below named jury in partial fulfillment of the requirements for the degree of **Master of Science** in **Department of Chemistry, Institute of Graduate Studies of Bolu Abant Izzet Baysal University in 29.01.2021** by

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ÇAĞRI ÖZBİL

ABSTRACT

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MSC THESIS
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Thiazolopyrimidine scaffolds are known in the recent literature for their synthetic examples and their many important biological activities. But, one of the thiazolopyrimidine cores, thiazolo[3,2-*c*]pyrimidines, has very rare examples in the terms of synthesis and biological activity studies. In previous years, some syntheses with azole approach and cytotoxic activity studies on thiazolo[3,2-*c*]pyrimidines have been reported for the first time with the efforts of our research group.

In order to extend the scope of thiazolo[3,2-c]pyrimidine chemistry and increase the number of structural examples, a facile and efficient synthesis of novel 3-oxothiazolo[3,2-c]pyridimine carbonitriles (**102**) were planned in the present dissertation study. In this regard, firstly, a new heterocyclic enamine precursor (**64b**) was prepared and characterized by IR and NMR analyses. In the rest of the study, after performing some optimizations on a model reaction, novel examples of 3-oxothiazolo[3,2-*c*]pyrimidine carbonitriles (**102a-v**) were prepared in excellent yields via Mannich cyclizations of the heterocyclic enamine, 2-(4-oxothiazolidin-2-ylidene)-8-carbonitrile (**64b**) with formaldehyde **9** and primary amines (**8**) in minute reaction times under MW conditions. Then, the structures of target compounds (**102a-v**) were elucidated by fully characterizing by IR, NMR and HRMS data in the last part of the study.

KEYWORDS: Thiazolidinone Carbonitrile, Thiazolo[3,2-*C*]pyrimidinone, Heterocyclic Compound, Microwave, Heterocylic Enamine, Multicomponent.

ÖZET

YENİ OKSOTİYAZOLO[3,2-*C*]PİRİMİDİN KARBONİTRİLLERİN MANNICH HALKALAŞMALARI YOLUYLA KOLAY SENTEZİ
YÜKSEK LİSANS TEZİ
ÇAĞRI ÖZBİL
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ
LİSANSÜSTÜ EĞİTİM ENSTİTÜSÜ
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Tiyazolopirimidin heterohalkaları, sentetik örnekleri ve gösterdikleri birçok önemli biyolojik aktiviteleriyle güncel literatürde bilinmektedir. Fakat tiyazolopirimidin anayapılarından biri, tiyazolo[3,2-*c*]pirimidinler, sentetik ve biyolojik aktivite çalışmaları anlamında çok nadir örneklere sahiptir. Önceki yıllarda, tiyazolo[3,2-*c*]pirimidinler üzerine azol yaklaşımıyla bazı sentezler ve sitotoksik etki çalışmaları araştırma grubumuzun çabalarıyla ilk kez rapor edilmiştir.

Tiyazolo[3,2-c]pirimidin kimyasının kapsamını genişletmek ve yapısal örneklerin sayısını artırmak amacıyla, bu tez çalışmasında 3-oksotiyazolo[3,2-c]pirimidin karbonitrillerin (**102**) kolay ve etkili bir sentezi planlanmıştır. Bu bağlamda, öncelikle yeni bir heterohalkalı enamin başlangıç bileşiği (**64b**) hazırlanıp IR ve NMR analizleriyle karakterize edilmiştir. Çalışmanın kalan kısmında ise, bir model reaksiyon üzerinde optimizasyon çalışmalarının yapılması sonrası, 3-oksotiyazolo[3,2-*c*]pirimidin karbonitrillerin özgün örnekleri (**102a-v**), heterohalkalı enamin, 2-(4-oksotiyazolidin-2-iliden)-8-karbonitril (**64b**)'in formaldehit **9** ve birincil aminlerle (**8**) Mannich halkalaşmaları yoluyla dakikalık reaksiyon sürelerinde mikrodalga koşullarında çok iyi verimlerle hazırlanmıştır. Daha sonra, çalışmanın son kısmında hedef bileşiklerin yapıları (**102a-v**) IR, NMR ve HRMS verileri yoluyla tam karakterize edilerek aydınlatılmıştır.

ANAHTAR KELİMELER: Tiyazolidinon Carbonitrile, Tiyazolo[3,2-*C*]pirimidinon, Heterohalkalı Bileşik, Mikrodalga, Heterohalkalı Enamin, Çok Bileşenli.

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LIST OF ABBREVIATIONS AND SYMBOLS

3-CR : Three-component reaction

4-CR : Four-component reaction

8-CR : Eight-component reaction

Ac_2O : Acetic anhydride

acac : Acetylacetone

AcOH : Acetic acid

Alc. : Alcohol

ATR : Attenuated total reflectance

Br_2 : Bromine

BrCN : Cyanogen bromide

Bu : Butyl

BuLi : Butyl lithium

BuOH : butanol

cat. : Catalytic

CBz : Benzyloxycarbonyl

DBU : 1,8-Diazabicyclo(5.4.0)undec-7-ene

DCM : Dichloromethane

Diglyme : Bis(2-methoxyethyl) ether

DMF : *N*,*N*-dimethylformamide

DMSO : Dimethylsulfoxide

DPPP : 1,3-Bis(diphenylphosphino)propane

ED : Electron-donating

EDG : Electron-donating group

Et : Ethyl

Et_3N : Triethylamine

EtOH : Ethanol

EtONa : Sodium ethoxide

EWG : Electron-withdrawing group

FAp : Fluorapatite

h : Hour

HCA : Hierarchical Cluster Analysis

HOAc : Acetic acid

IR : Infrared

K-10 : Montmorillonite K-10

KH : Potassium hydride

KOH : Potassium hydroxide

LDA : Lithium diisopropylamide

MAOS : Microwave-assisted organic synthesis

Me : Methyl

MeCN : Acetonitrile

MeOH : Methanol

MW : Microwave

min : Minute

NaOAc : Sodium acetate

NaOEt : Sodium ethoxide

NaO*t*-Bu : Sodium *tert*-butoxide

NBS : N-bromosuccinimide

neat : No solvent or dry

NMP : N-methy pyrrolidone

NMR : Nuclear magnetic resonance

OAc : Acetate

^{o}C : Degree celcius

OEt : Ethoxy

OMs : Mesylate

Pd(dba)$_2$: Bis(dibenzylideneacetone)palladium(0)

Ph : Phenyl

PhMe : Toluene

Pr : Propyl

rt : Room temperature

t-Bu : tert-butyl

***t*-BuOK** : Potassium tertiary butoxide

THF : Tetrahydrofuran

TLC : Thin layer chromatography

TMS : Tetramethylsilane

UV : Ultraviolet

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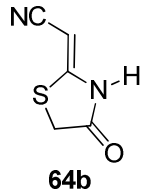
Finally, my deep and sincere gratitude to my family members for their continuous and unparalleled love, help and support through the process of research work and writing this thesis. This achievement would not have been possible without them, and I dedicate this work to them.

FORMULAE



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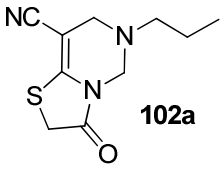

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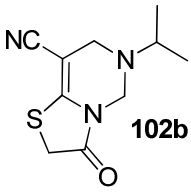

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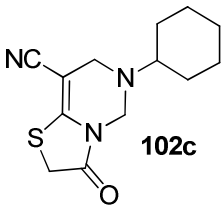

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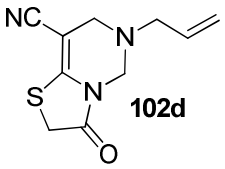

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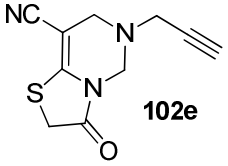

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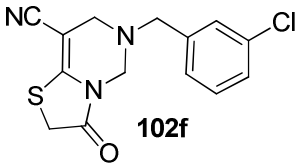

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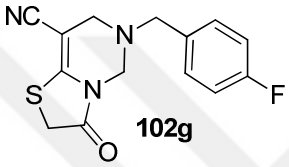

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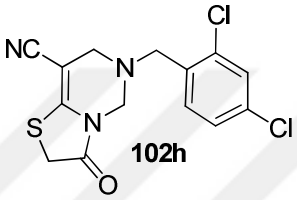

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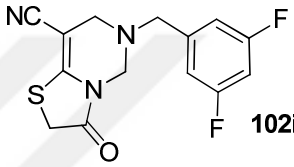

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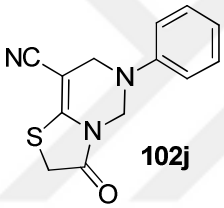

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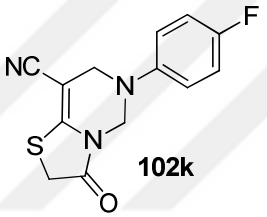

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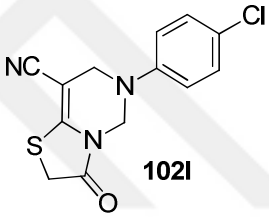

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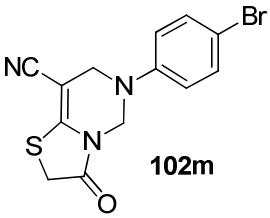

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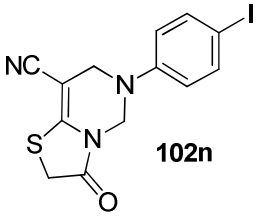

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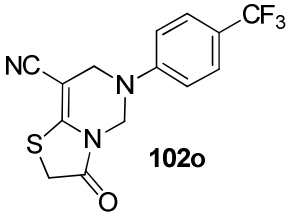

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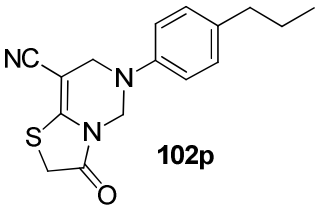

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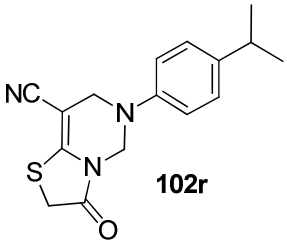

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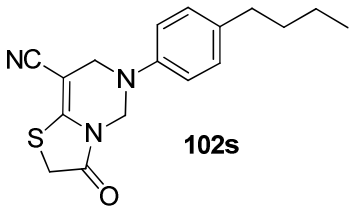

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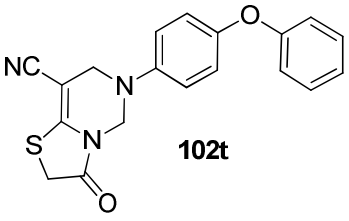

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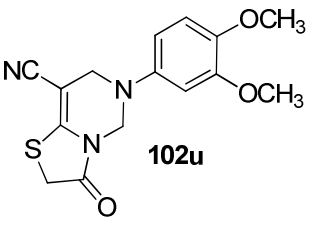

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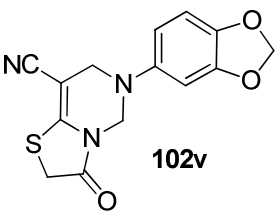


102v

1. INTRODUCTION

1.1. Multicomponent Reactions (MCRs)

Multicomponent reaction (MCR) is a synthetic methodology in which three or more reactants come together in a single reaction vessel to form a new product (Figure 1.1). Main characteristic of MCRs is that the final products contain almost all portions of substrates and generates almost no by-products (Ugi et al., 1994).

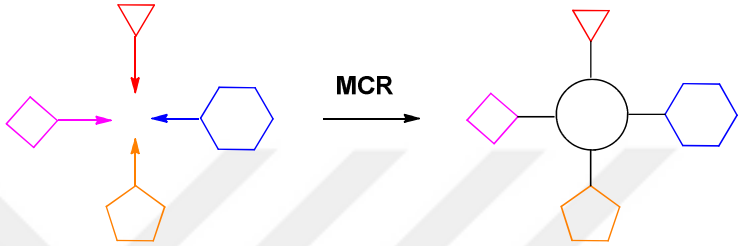


Figure 1.1 General design in MCRs.

Multicomponent reactions are important for the discovery of new drug molecules and they have some advantages such as environment-friendly, atom-economic, time- and labor-saving. MCR reactions have been accepted as useless in pharmaceutical industry, but today importance of its technology is mostly recognized in drug discovery researches by the industry and academia (Dömling et al., 2012). MCRs may range from classical 3-CR to complex 8-CR reactions. After increased interest in MCR reactions, variety of drug molecules were discovered such as nifedipine (oxytocin receptor antagonist) via Hantzsch 3-CR, epelsiban via Ugi 4-CR (Wyatt et al., 2005; Bortwick et al., 2005) (Figure 1.2).

There are very diverse examples of MCR reactions with different chemical entities for the construction of new biologically active heterocyclic compounds or natural products over different precursors and mechanisms.

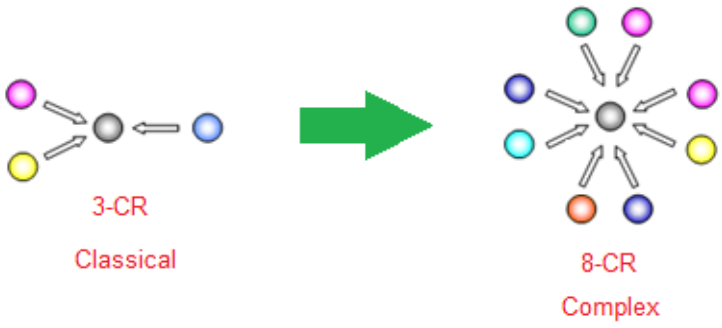
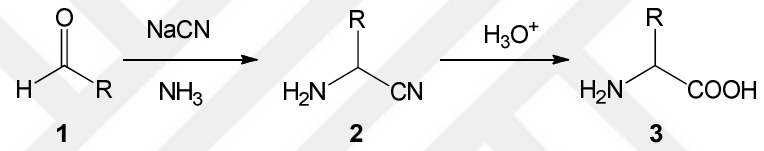


Figure 1.2 Types of MCRs from simple to complex.

Many types of MCRs such as Strecker, Hantzsch, Biginelli, Passerini, Gröbcke-Blackburn-Bienaymé, Kabachnik-Fields and Ugi reactions are used to get large chemical libraries of heterocyclic compounds in combinatorial and medicinal chemistry and also material science and catalysis chemistry (Burke and Schreiber, 2004; Nielsen and Schreiber,2008). A brief look at the history of these reactions, some simple examples of MCRs along with the scientists who discovered can be given as follows.

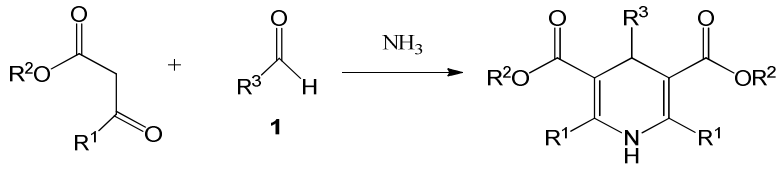
Firstly, a German chemist, A. Strecker reported the synthesis of α-amino acids **3** (Strecker, 1850). This reaction is known as the world's first multicomponent reaction which contains three components; sodium cyanide, aldehydes **1** and ammonia as substrates.



1 2 3

Picture 1.1 Synthesis of α-amino acids via Strecker reaction

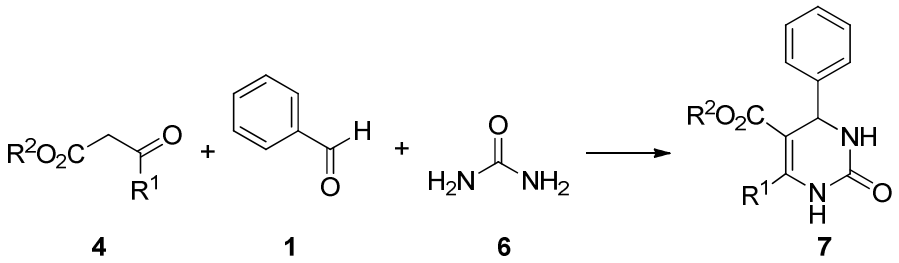
30 years later, A.R. Hantzsch have studied out a new 3-CR which allows the preparation of dihydropyridine derivatives **5** using aldehyde **1** with *α,β*-keto ester **4** in the presence of ammonia (Hantzsch, 1881). For example; nifedipine, a calcium channel blocker has been synthesized by applying this reaction.



4 1 5

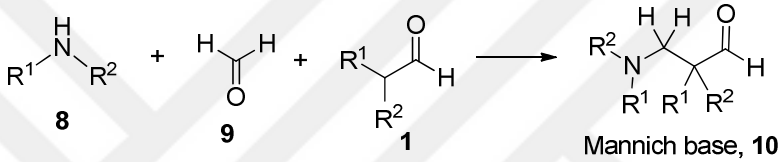
Picture 1.2 Synthesis of dihydropyrimidines via Hantzsch synthesis

After a short time, an Italian chemist, P.Biginelli has reported a three-component MCR using β-keto esters **4** such as ethyl acetoacetate, aromatic aldehydes **1** such as benzaldehyde, and ureas (or thioureas) **6** in the presence of acid catalyst (Brönsted or Lewis acids), affording dihydropyrimidinone derivatives **7** (Biginelli, 1891a-b).



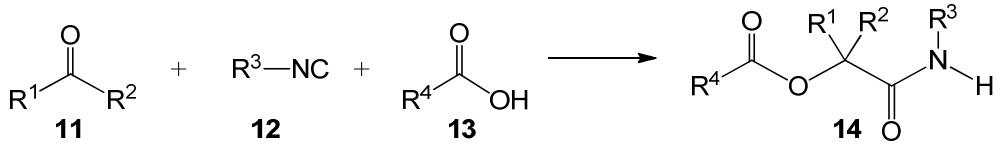
Picture 1.3 Synthesis of dihydropyrimidines via Biginelli Reaction

A German chemist, Carl Mannich, discovered a 3-CR which includes a primary or secondary amine **8**, formaldehyde **9** and an enolizable aldehyde **1** to form β-aminocarbonyl compounds (Mannich base) **10** in the presence of acid or base catalyst (Mannich and Krösche,1912).



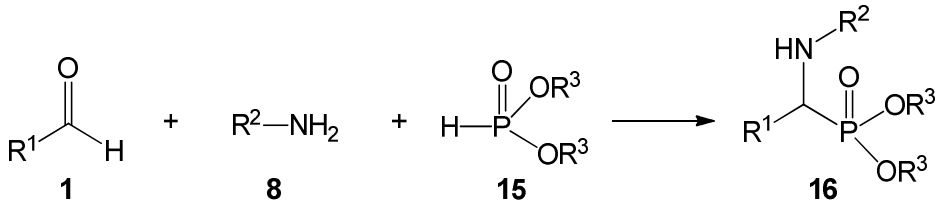
Picture 1.4 Synthesis of β-aminocarbonyl compounds via Mannich reaction

After a while, M. Passerini have reported a 3-CR containing a carbonyl compound **11**, an isocyanide **12** and a carboxylic acid **13** to form α-acyloxy carboxamides **14** (Passerini, 1921). The Passerini reaction has been also applied into pharmaceutical research.



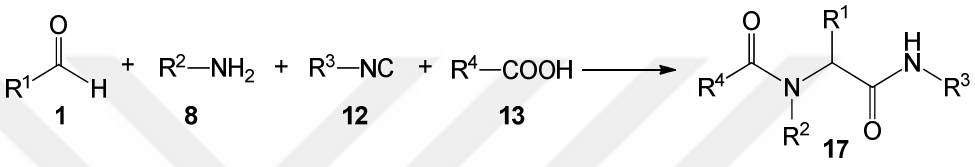
Picture 1.5 Synthesis of α-acyloxy carboxamides via Passerini Reaction

M.I.Kabachnik has discovered the efficient preparation of α-aminophosphonates **16** using aldehydes **1**, amines **8** and dialkyl phosphites **15** in the presence of an acid catalyst (Kabachnik and Medved, 1952). This reaction is very considerable in drug discovery studies to produce peptidomimetic compounds.



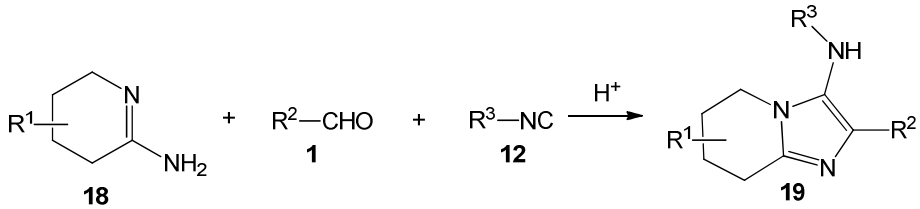
Picture 1.6 Synthesis of α-aminophosphonates via Kabachnik-Fields reaction

After a while, I. K. Ugi has reported a multicomponent reaction which includes four-components as a ketone or aldehyde **1**, an amine **8**, an isocyanide **12** and a carboxylic acid **13** to form a bis-amide **17** (Ugi, 1962). This reaction is much rapid while adding the isocyanide.



Picture 1.7 Synthesis of bis-amides via Ugi reaction

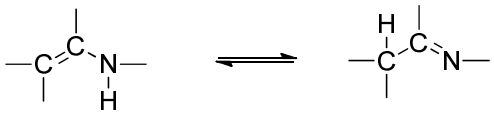
More recently, Gröbcke-Blackburn-Bienaymé reaction was developed as a new MCR type utilizing isonitriles **12**, aldehydes **1** and α-aminoazines **18** in the presence of an acid catalyst (Gröbke et al., 1998; Blackburn et al., 1998; Bienaymé et al., 1998a; Bienaymé et al, 1998b). The imidazo[1,2-*a*]pyridine products **19** of this kind reaction can be used for the synthesis of a variety of more complex scaffolds via postmodification reactions.



Picture 1.8 Synthesis of tetrahydropyridoimizadoles via Gröbcke-Blackburn-Bienaymé reaction

1.2. Enamines

"Enamine" term was first defined as structures which are similar to nitrogen analogs of enols (Wittig and Blumenthal, 1927). When there is a hydrogen atom as nitrogen substituents, the enamine **20** will be the tautomer of the imine **21** by replacing a hydrogen atom between nitrogen and β-doubly bonded carbon atom.



20 **21**

Picture 1.9 Enamine – imine tautomerization

Enamines are versatile intermediates and unsaturated compounds which form by the condensation of a ketones or aldehydes with a secondary amine. The double bond of the enamine may be a part of acyclic **22**, exocyclic **24**, endocyclic **23**, bicyclic and heterocyclic system **25** (Lue and Greenhill, 1997). The acyclic enamines contain acyclic C=C double bond in their structures. When the C=C double bond is inside a ring and substituent of nitrogen atom as exocyclic part is called as endocyclic enamine. When cyclic amine where nitrogen is a part of cycle with exocyclic C=C double bond is referred as exocyclic enamine. And the enamine which has nitrogen atom and the C=C double bond as part of a ring is known as heterocyclic enamine. Also the enamine containing bicyclic system and it is known as bicyclic enamine.

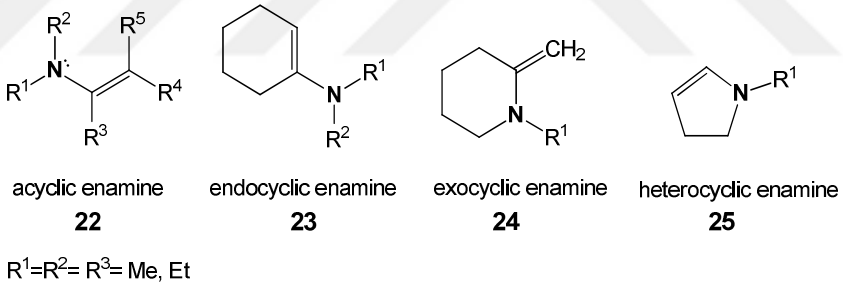


Figure 1.3 Common types of enamine structures

Especially, heterocyclic enamines (**25-30**) are sophisticated intermediates in the preparation of variety of heterocyclic systems such as alkaloids and natural products (Cheng et al., 2004; Alvarez‐Builla and 8Barluenga, 2012; Cook, 2017).

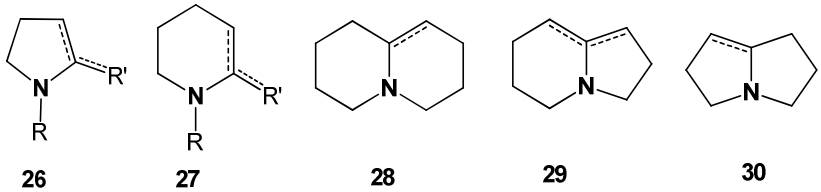


Figure 1.4 Some heterocyclic enamines and compounds.

Heterocyclic secondary enamines (**31**,**32**) are known with different names in respect to their attached EWG or EDG. For instance, they are named as exocyclic "*enamino esters"* if the group is ester; they are "*enaminonitriles"* if the group is cyano; and if the group is acyl or nitro, they are called "*enaminones"* or *"nitroenamines"*, respectively (Cheng et al, 2004).

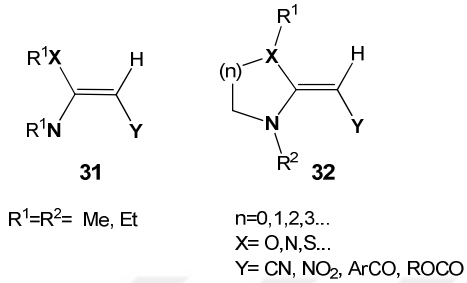
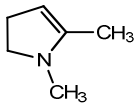
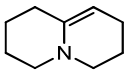
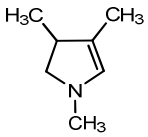
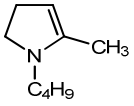
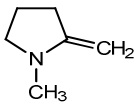
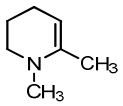
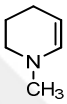
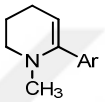
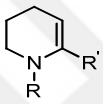
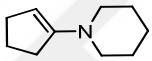
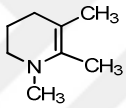
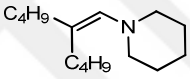


Figure 1.5 Examples of secondary heterocyclic enamines.

Under UV spectroscopy, heterocyclic enamines give an absorption in range of 220-240 nm. Besides, IR spectra of enamines give the enaminic double bond in range of 1620-1680 cm^{-1}. EWG-linked to β-carbon atom of the enamine structure will lower the IR frequency of enaminic double bond (Patai, 1982). More substituted enamines will give C=C double bond stretchings at higher frequencies with respect to the less substituted enamines (Table 1.1).

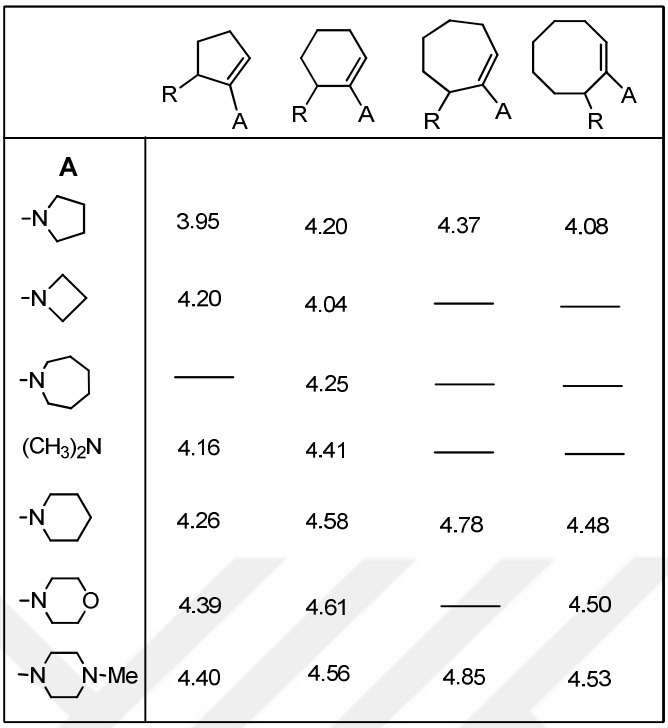
Table 1.1 Enaminic C=C bond stretching frequencies in IR.

Compound	v (C=C), cm^{-1}	Compound	v (C=C), cm^{-1}
	1632 - 1640		1652
	1648		1639
	1677		1650
	1642		1630
	1635 - 1650		1623
	1657		1656

R = aliphatic alkyl group (both cyclic and acyclic) . KBr disc.

The ^{1}H-NMR of heterocyclic enamines is a useful tool for determining the degree of nitrogen electron pair-double bond interaction. In general, enaminic =CH proton signal will appear between 4-6 ppm in their proton NMR spectra, however, olefinic proton signal in cyclic enamines will resonate at around 4-4.75 ppm. When amount of n-π electron interactions increase, the β-vinyl proton of the enamine will exhibit larger shielding. For example, the signals of pyrrolidine enamine have the greatest n-π electron interactions (3.95 ppm). β-vinyl protons are observed the furthest since morpholine, piperidine and *N*-methylpiperazine enamines demonstrate the smallest amount of nitrogen-double bond overlap (Table 1.2) (Ahmed et.al., 1980).

Table 1.2 C=CH proton chemical shifts of some endocyclic enamines

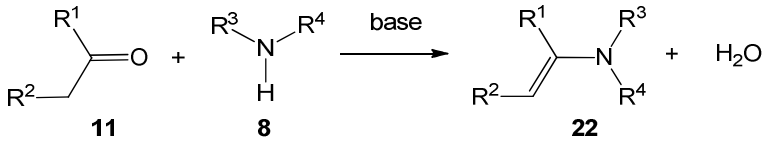


ppm (variance of about -0.05 or +0.05 for chemical shifts) ; A = amine; R = alkyl.

In ^{13}C-NMR of enamines derived from aldehydes, β-carbons usually resonate 105-132 ppm but β-carbon signals are generally observed 90-120 ppm in the enamines of the ketones (Stradi et.al., 1978; Ahmed et.al.,1977).

1.2.1. Preparation of Enamines

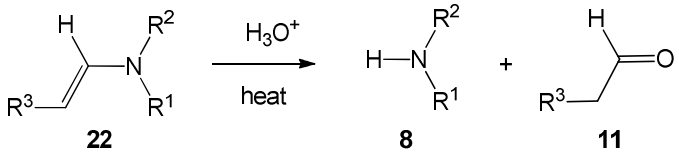
Enamines having push-pull type properties via attached ED amino group on one end of C=C bond and strongly EWG (NO_2, acyl, CN) on the other end of C=C bond represent a significant class of reactive intermediates in organic synthesis and many methods are known for their preparations. Most famous method is the Mannich-Davidsen procedure in which an enamine **22** is obtained by the condensation of secondary amines **8** with aldehydes **1** or ketones **11** using a base catalyst via elimination of water.



Picture 1.10 General reaction for the formation of an enamine.

Acyclic enamines are not readily stable upon treatment with acids and heat, they decompose into starting materials very easily. Among the enamines,

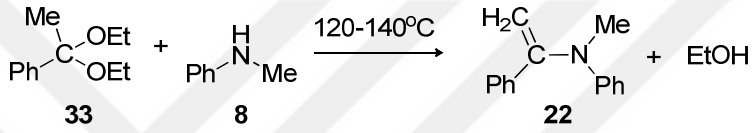
ketone enamines are the more stable than aldehyde derived enamines (Mannich and Davidsen, 1936).



22 8 11

Picture 1.11 Decomposition of the enamines.

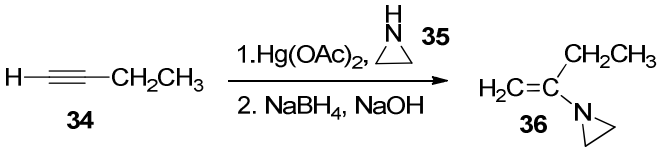
In Herr and Heyl method, enamines can be prepared by reacting a secondary amine with diethyl acetals at 120-140°C, followed by distillation of formed ethanol (Hoch, 1934).



33 8 22

Picture 1.12 Synthesis of enamines from acetals.

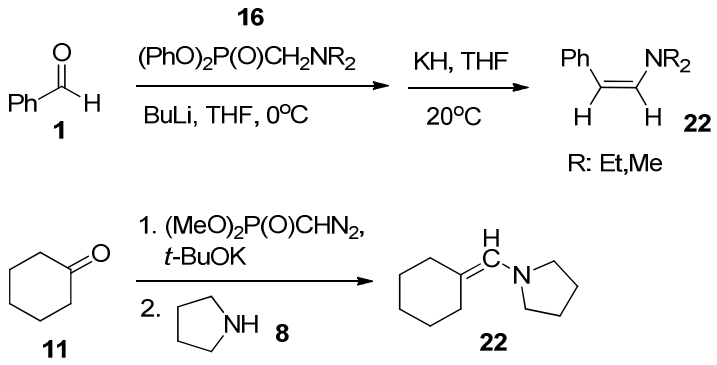
Aziridine bearing enamines **36** can be prepared from alkynes **34** by mercuric oxidation followed by base-catalysed sodium borohydride reduction (Hudrlik and Hudrlik, 1973).



34 36

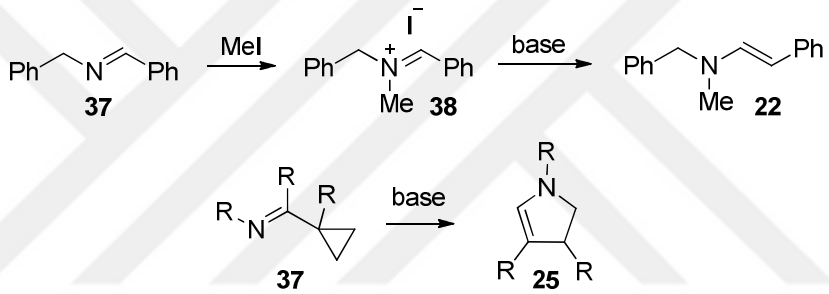
Picture 1.13 Synthesis of enamines aminomercuration-demercuration of alkynes.

Moreover, enamines of aldehydes and ketones **22** can be obtained via Horner-Wittig reaction utilizing aminomethylphosphonates **16** or iminoalkane phosphonic esters and aliphatic or aromatic aldehydes **1** and ketones **11** (Broekhof and van der Gen,1984; Gilbert and Weerasooriya,1983).



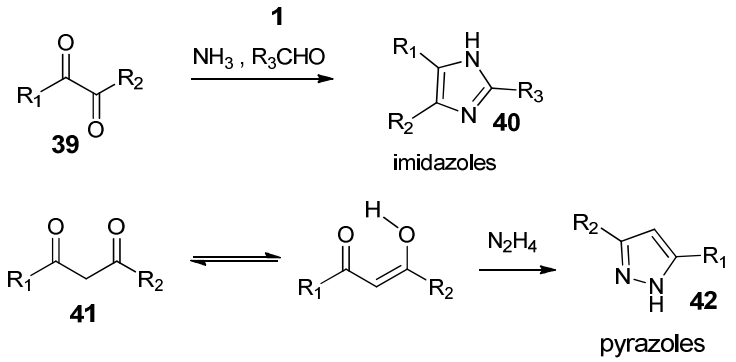
Picture 1.14 Enamines via Horner-Wittig reaction.

Some tertiary enamines **22** can also be prepared by direct *N*-alkylation of iminium salts **38** which subsequently give enamines by the bases. Besides, heterocyclic enamines **25** can be obtained over intramolecular alkylation of imines with cyclopropyl group **37** (Evans, 1951; Stevens, 1977).



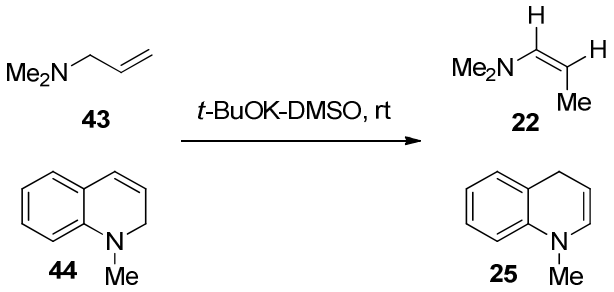
Picture 1.15 Preparation of tertiary and heterocyclic enamines from imines.

In similar fashion, condensation reactions of 1,2- and 1,3-dicarbonyl compounds (**39**,**41**) with primary amines and aldehydes **1** over imine formation afford variety of heterocyclic enamines such as imidazole **40** and pyrazole **42** derivatives (Knorr, 1883; Brackeen et. al., 1994)



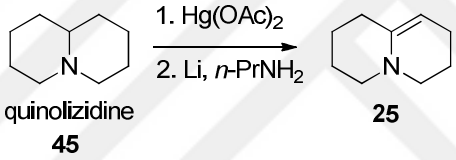
Picture 1.16 Dicarbonyl compounds for the synthesis of heterocyclic enamines.

When the aliphatic (**43**) and cyclic (**44**) allylamines treated with potassium tert-butoxide and dimethylsulfoxide mixture at room temperature, they isomerize into corresponding acyclic (**22**) or heterocyclic (**25**) enamines in very good yields (Coates and Johnson, 1971; Martinez and Joule,1978).



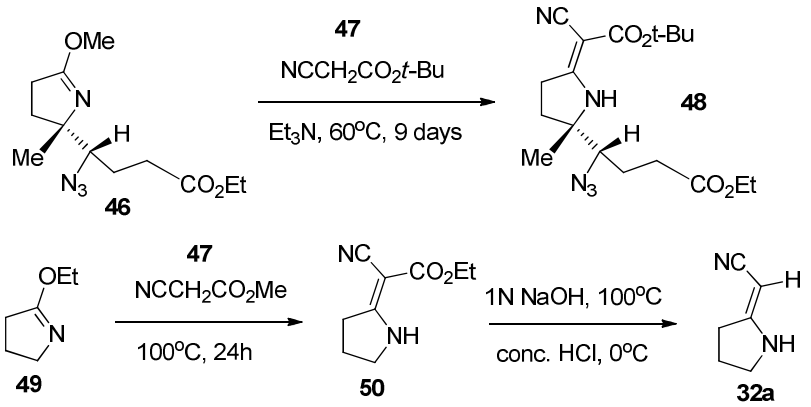
Picture 1.17 Enamines over isomerization of allyamines.

Heterocyclic enamines **25** can be prepared over oxidation of cyclic amines such quinolizidine **45** using mercury acetate and successive reduction of formed aromatic structure with Li and *n*-$PrNH_2$ with 60-66% yield (Leonard et.al., 1962).

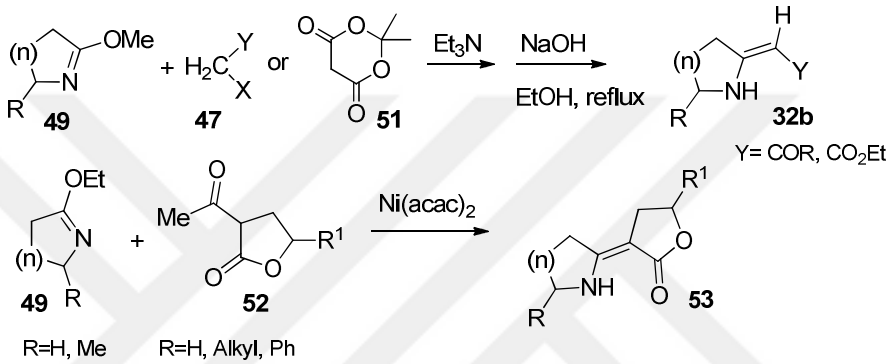


Picture 1.18 Preparation of heterocyclic enamines via mercuric oxidation.

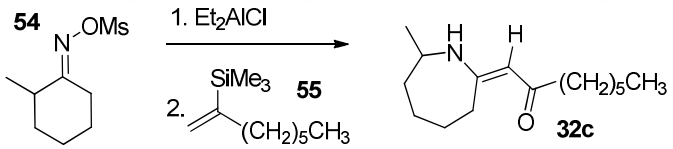
More specifically, heterocyclic secondary enamines such as exocyclic enaminoesters, enaminonitriles, enaminones and nitroenamines can directly be obtained starting from *N*-heterocyclic compounds. For instance, condensation of lactam ethers **46** with t-butyl cyanoacetate or methyl cyanoacetate **47** in the presence of bases will afford the corresponding heterocyclic enaminonitriles (Bertele et.al., 1964; Yamada et al., 1969). Similarly, when lactim ethers **49** condense with active methylene compounds (**47**,**52**) in the presence of triethylamine or $Ni(acac)_2$, different secondary heterocyclic enamines (**32**) will be produced efficiently (Celerier et.al.,1979; Fasseur et.al., 1992). In other interesting transformation, enoyl silyl ethers **55** couple with oxime sulfonates **54** in the presence of Et_2AlCl to afford larger ring heterocyclic enamines **32c** in high yields (Matsumura et.al., 1983).



Picture 1.19 Preparation of heterocyclic enaminonitriles from lactam ethers

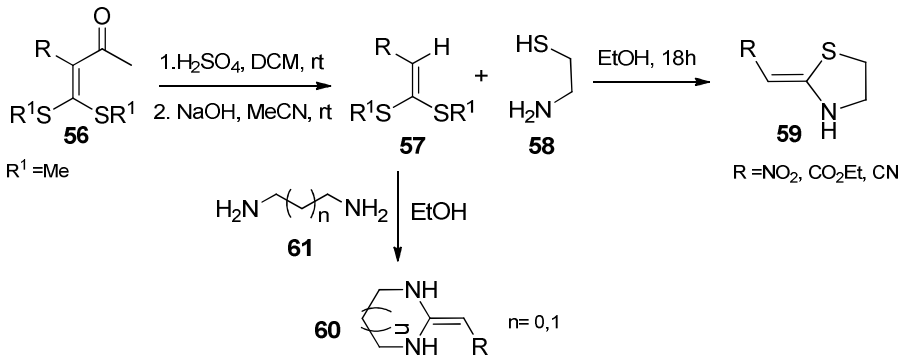


Picture 1.20 Preparation of heterocyclic enaminoesters from lactim ethers



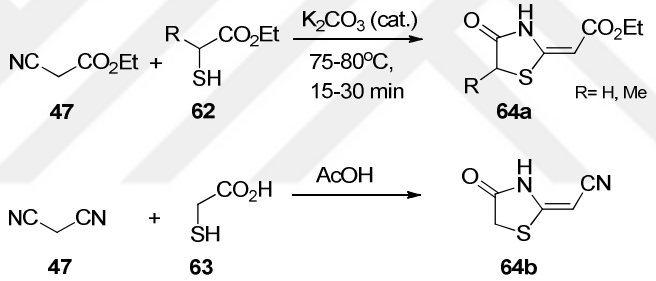
Picture 1.21 Synthesis of heterocyclic enamines with larger rings

EWG-bearing thiazolidine or imidazolidine based heterocyclic enamines (**59**,**60**) can be either prepared by the condensation of 1,1-bis(methylmercapto)-2-nitroethylene or ketene dithioacetals **57** with cysteamine or diamines (**58**) in ethanol under mild conditions (Rajappa and Advani, 1982; Yuan et al., 2010; Kalisiak et al., 2011).



Picture 1.22 Synthesis of 2-substituted thiazolidine and imidazolidine type heterocyclic enamines.

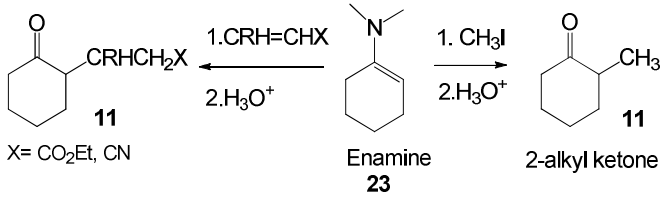
However, methylene-4-oxothiazolidine carboxylates **64a** and acetonitriles **64b** have been simply obtained by the base-catalyzed condensation of ethyl cyanoacetate **47** and α-mercapto esters **62** and by the acid-catalysed condensation of malonitrile and mercaptoacetic acid **63**, respectively (Stojanović et al., 2011; Sadek et.al., 1984)



Picture 1.23 Synthesis of methylene-4-oxothiazolidine carboxylates or acetonitriles.

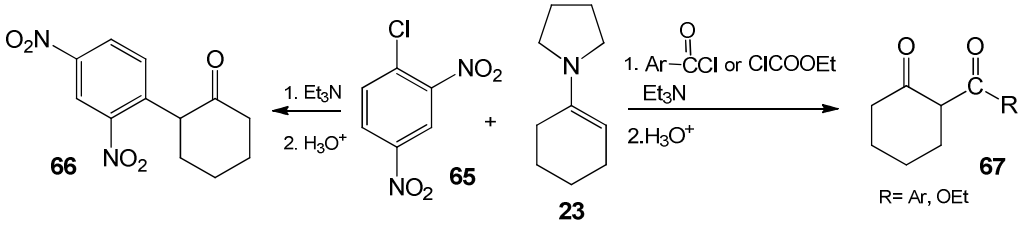
1.2.2. Reactions of Enamines

Alkylation of enamines took place over the resonance structure of enamine by an electrophilic attack on its β-carbon atom. In this way, enamines **23** react with halo alkanes and it is followed by acidic hydrolysis affording α-alkyl substituted ketones **11**. Likewise, when enamines are alkylated with unsaturated electrophiles such as α,β- unsaturated ketones, nitriles or esters, some monoalkylated ketone derivatives **11** will be obtained. (Stork et.al.,1954).



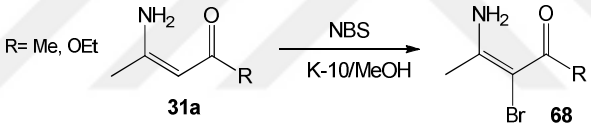
Picture 1.24 Examples for the alkylation of enamines.

Enamines **23** can be commonly acylated or arylated using acyl chlorides or chloroformates or chlorobenzenes **65** after acid hydrolysis to form β-keto carbonyl compounds **67** or α-aryl ketones **66** (Hünig et.al.,1957).



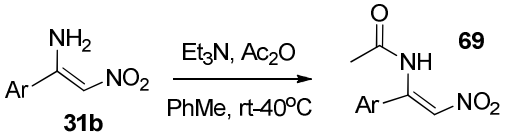
Picture 1.25 Acylation and arylation of enamines.

The conjugated double bond of enamines along with nitrogen atom in amine group easily undergo many kinds of reactions. For instance, bromination of enamines **31** can be achieved by different reagents such as Br_2/CCl_4, NBS/MeOH or BrCN. While bromination with Br_2 of BrCN affords the mixture of substituted products, NBS reagent can give monosubstituted enamines **68**, selectively (Jirkovsky,1974; Alberola et.al., 1986; Braibante et.al., 2001).



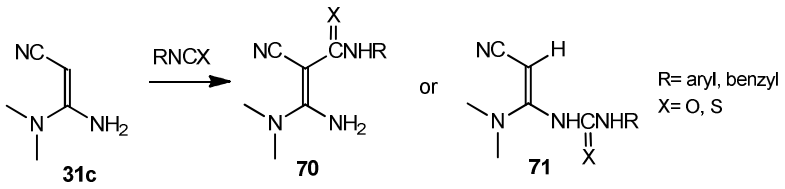
Picture 1.26 Selective α-bromination of enamines.

Aromatic nitroenamines **31b** are easily converted into acylated nitroenamines **69** in a mixture of acetic anhydride, triethylamine at 25-40^oC (Zhou et.al., 2013).



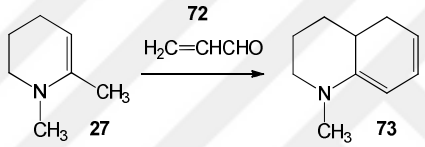
Picture 1.27 Preparation of *N*-acyl nitroenamines.

When enaminonitriles **31c** reacted with isocyanates or isothicyanates, corresponding *N*-acylated or *C*-acylated enamines (**70**,**71**) will be isolated in good yields (Granik et.al., 1998).



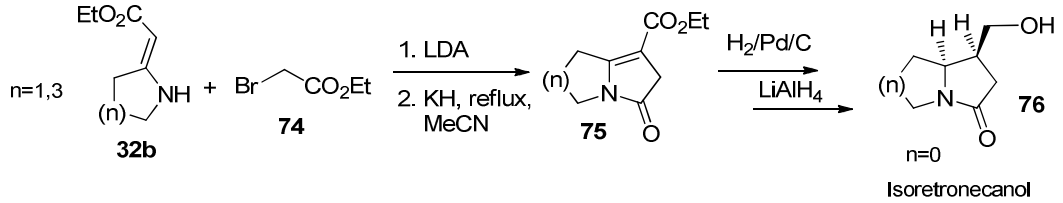
Picture 1.28 Reaction of isocyanates or isothiocyanates with enamines.

Besides the general reactions of acyclic enamines, many types of synthetic examples for the reactions of heterocyclic enamines **27** resulting the formation of various heterocyclic systems can be found in literature. For instance, the alkylation of heterocyclic enamines **27** with α,β-unsaturated electrophiles give rise the formation of bicyclic products such as 1-methylhexahydroquinoline **73** from the reaction of 1,2-dimethyldihydropyridine **27** with acrolein **72** (Červinka and Hub,1964).

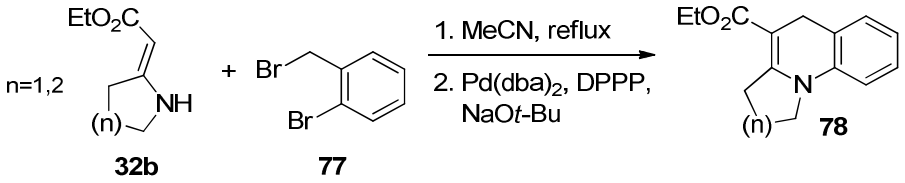


Picture 1.29 Formation of quinoline derivatives from heterocyclic enamines.

Cheng et.al. (1995) reported the reaction of seven-membered heterocyclic enamine **32b** with ethyl bromoacetate **74** and successive cyclisation to afford γ-lactam-fused heterocyclic products **75** very efficiently. Further hydrogenation and reduction of the bicyclic product will afford (+/-)-isoretronecanol (pyrrolizine alkaloid) **76** in moderate yields (Pinnick and Chang, 1978). When the same heterocyclic enamine **32b** reacted with *o*-bromobenzyl bromide **77** in acetonitrile at reflux and followed by Pd-catalysed cyclisation, pyrrolo-fused quinolines **78** were obtained in moderate yields (Liu et.al., 2003).



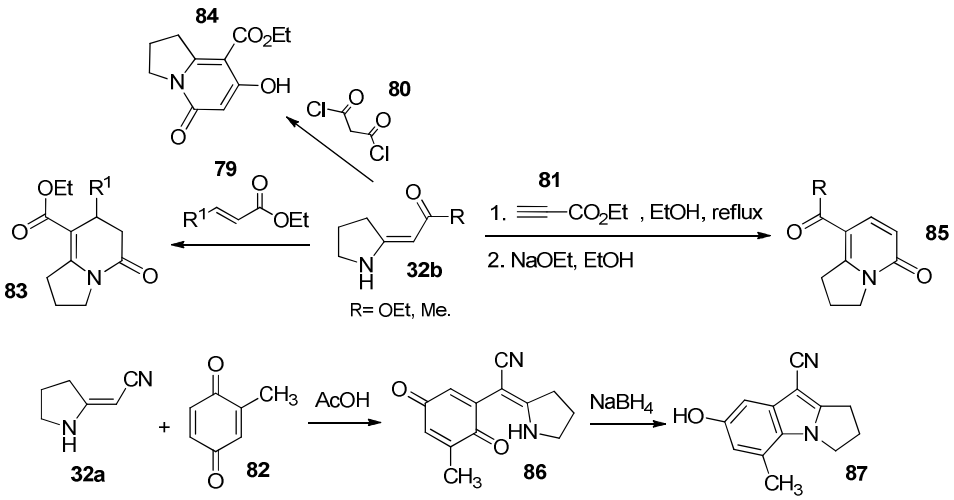
Picture 1.30 Formation of lactam-fused heterocyles from heterocyclic enamines.



Picture 1.31 Formation of pyrrolo-fused heterocyles from heterocyclic enamines.

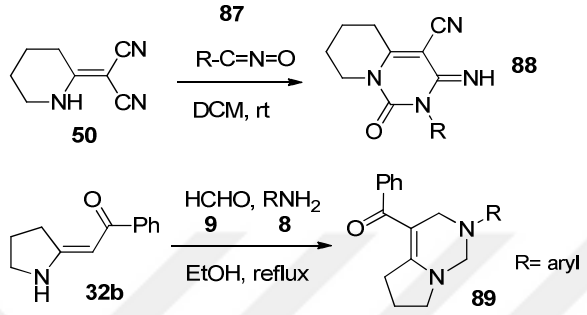
When the heterocyclic enamines **32a,b** reacted with α,β-unsaturated compounds such as methyl propiolate **81** or α,β-carboxylic ethyl ester **79**, variety of pyrrolopyridone derivatives (**83, 85**) are obtained in two steps with moderate to good yields (55-80%) (Nagasaka et.al., 1983; Bruneire et.al.,1985).

Also, some CN-substituted heterocyclic enamines (**32b**, **50**) reacts with methylquinone **82** to afford quinone substituted enamine product **86** in 70% yield and successively pyrrolo[1,2-*a*]indoles **87** in very low yields (Yamada and Matsui, 1970). Besides, when ethyl carboxylate-substituted enamine **32b** reacted with malonyl chloride **80**, this reaction afforded 2-hydroxypyrrolopyridinone products **84** rapidly (Cheng et.al., 2001).



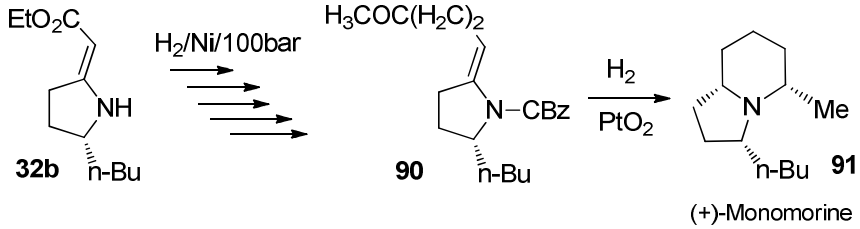
Picture 1.32 Formation of pyrrolopyridones and pyrrolo[1,2-*a*]indoles from heterocyclic enamines.

Moreover, 2-dicyanomethylidene piperidine type enamines **50** reacted with isocyanates **87** at very mild conditions to afford some piperidino[1,2-*c*]pyrimidinones **88** in very good yields (Ebeid et.al., 1995). When aroyl substituted enamines **32b** reacted with excess formaldehyde **9** and different amines **8**, this reaction gave rise the formation of pyrrolopyrimidines **89** over *N*-aminomethylation and iminium ion formation (Issartel et.al., 1996).



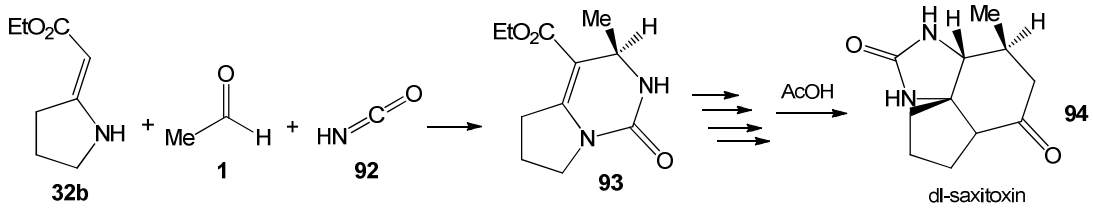
Picture 1.33 Preparation of pyrrolo- and piperidino-pyrimidines from heterocyclic enamines.

In addition to synthetic examples of heterocyclic enamines, some natural products can also be prepared from heterocyclic enamines. For example, some indolizine alkaloids **91** known as ant pheromones can be prepared starting from chiral heterocyclic enaminoesters **32b** over successive reductions, Wittig olefination and cyclisation reactions (Saliou et.al., 1991).



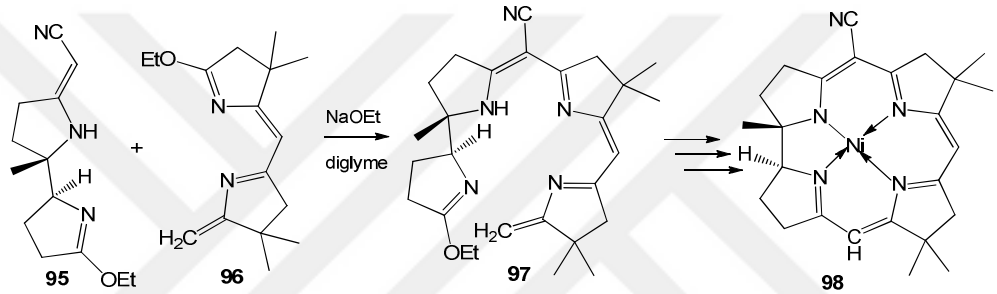
Picture 1.34 Preparation of indolizine alkaloids from heterocyclic enamines.

Besides, a neurotoxin known as Saxitoxin **94** is obtained efficiently over a multistep reaction sequence starting by the condensation reaction of heterocyclic enaminoester **32b** with acetaldehyde **1** and isocyanic acid **92** and ending by a cyclization in acetic acid (Taguchi et.al., 1977).



Picture 1.35 Preparation of saxitoxin from heterocyclic enaminoesters.

Also, cyano-substituted heterocyclic enamines **95** are good precursors for the preparation of the corrin systems. When this enamine condensed with a suitable lactim ether **96** using NaOEt in diglyme, a coupling product **97** is obtained and subsequent reactions of this product will afford the expected corrin structure **98** (Bertele et.al., 1964).



Picture 1.36 Preparation of corrin systems from heterocyclic enaminonitriles.

Due to richness in the chemistry of heterocyclic enamines as reactive intermediates, there can be found many other examples in synthetic chemistry literature, but the interest for the preparation of new heterocyclic compounds by utilizing different heterocyclic enamines are still in progress.

1.3. Thiazolopyrimidines

Thiazolopyrimidine structure consist of two heterocycles, a thiazole and a pyrimidine unit. Thiazole is five-membered heterocycle containing one sulfur and one nitrogen as heteroatom, but the pyrimidine is a six-membered heterocycle having two nitrogen atoms in 1,3-position of the ring. Fusion of two heterocycles over different positions form a new bicyclic core known as thiazolopyrimidine. The main structural isomers of thiazolopyrimidines are the thiazolo[5,4-*d*]pyrimidines **99**, thiazolo[4,5-*d*]pyrimidines **100**, thiazolo[3,2-*a*]pyrimidines **101** and thiazolo[3,2-*c*]pyrimidines **102**. They are all valuable heterocyclic cores for the pharmaceutical industry and medicinal chemistry. (Yıldırım et al., 2014)

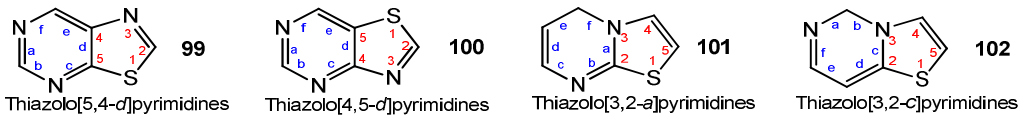


Figure 1.6 The general structures of thiazolopyrimidines.

1.3.1. Biological Importance of Thiazolopyrimidines

Drug molecules or natural products including thiazolopyrimidine rings play an important role in organisms due to their diverse biological activities. For instance, Ritanserin and setoperone are the antagonist of $5HT_2$ serotonine receptors bearing thiazolo[3,2-*a*]pyrimidine ring (Studzińska et al, 2016). Some other thiazolo[3,2-*a*] pyrimidine derivatives (**101**) are known to exhibit antibacterial, antiviral, analgesic, antiinflammatory activities (Pedersen and Nielsen, 1998; Pecorari et al.,1991; Ram et al.,1987; Amr et al., 2016). Moreover, some polyaryl substituted thiazolo[3,2-*a*] pyrimidines have been found highly active against human prostate adenocarcinoma (PC-3) cell lines (Yousif et al., 2017). Besides, pharmacological screening of a new series of thiazolopyrimidine derivatives showed that 2-chloro-6-ethoxypyridin-4-yl)-2-(phenylmethylene)-5-(2-thienyl)-2,3-dihydrothiazolo[3,2-*a*]pyrimidines exhibited very strong antiparkinsonian activity in comparison to the standard drug (Amr et al., 2008).

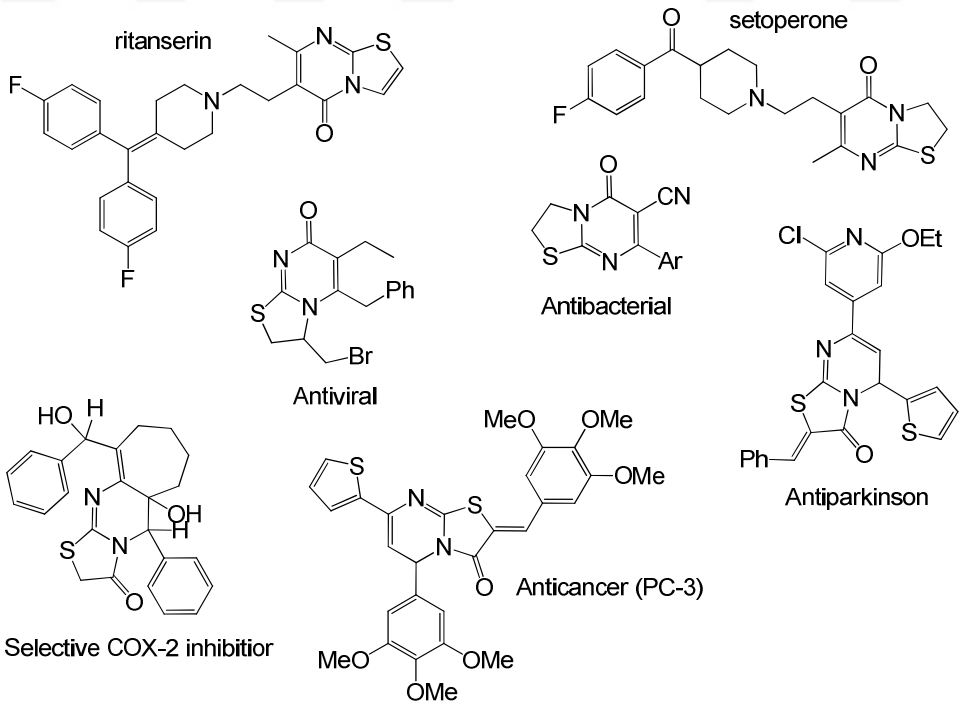


Figure 1.7 Thiazolo[3,2-*a*]pyrimidines (101) exhibiting biological activities

Another important structural isomers of thiazolopyridimines are thiazolo[4,5-*d*]pyrimidine derivatives (**100**) which are known as thia-analogues of the DNA purine bases, so they are of pharmacological interest in the area of medicinal chemistry. Some of them are recently found effective for the treatment of Parkinson's disease (Sugihara and Kawakita, 2008; Azam et al., 2009). Also, some benzofuran substituted 2-thioxothiazolo[4,5-*d*]pyrimidine derivatives exhibited significant antibacterial effects against gram (+) and gram (-) bacteria and showed weak cytotoxic effects against breast and lung carcinoma cell lines (Rida et al., 2006). On the other hand, some aniline substituted thiazolo[4,5-*d*]pyrimidines are reported as antitumor agents in the recent literature (Lin et al., 2009). In addition, Bekhit et al. (2003) reported that some pyrazoyl substituted thiazolo[4,5-*d*]pyrimidines showed stronger anti-inflammatory activities when compared with standard compound, indomethacin. Some new morpholino substituted thiazolo[4,5-*d*]pyrimidines are found to have strong antibacterial activities against *B. subtilis*, *P. Aeruginosa* and *E. coli* pathogens as much as standard antibiotics (Rahimizadeh et al., 2011). Moreover, a new series of fluorinated thiazolo[4,5-*d*]pyrimidine derivatives were studied against many different cancer cell lines and few compounds among them exhibited good anticancer activities (Fahmy et al., 2003). Also, thiazolo[4,5-*d*]pyrimidinethiones have already known to show some antipsychotic activities behaving as corticotrophin releasing factor antagonists (Beck et al., 1999).

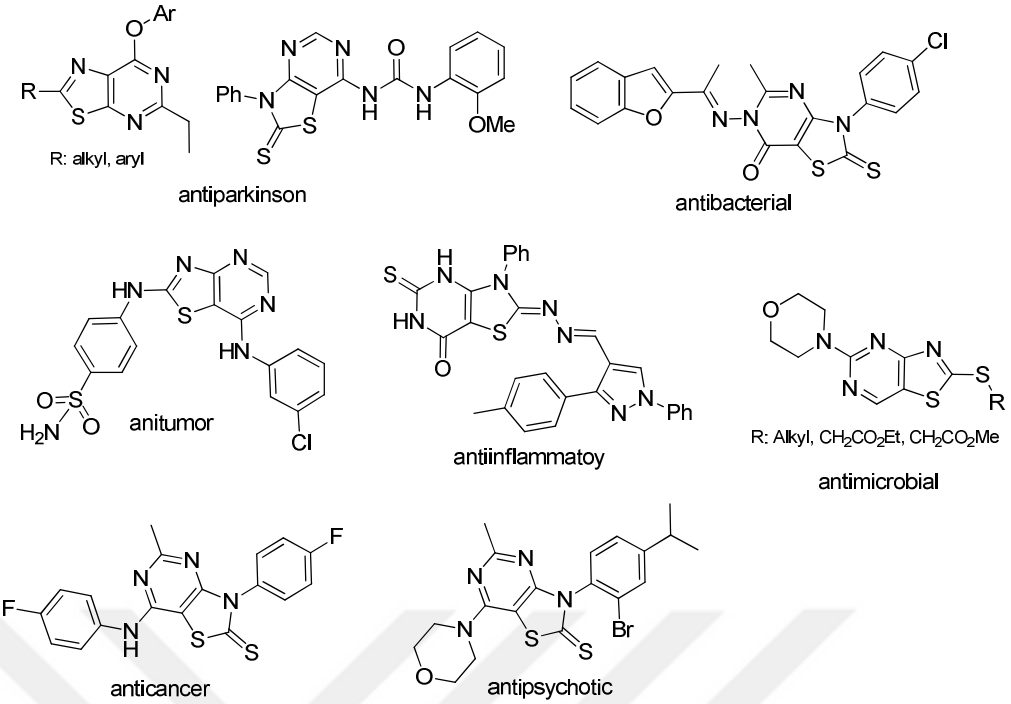
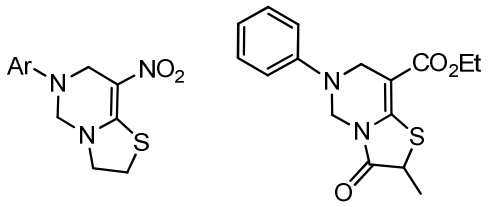


Figure 1.8 Thiazolo[4,5-*d*]pyrimidines (100) exhibiting biological activities

Third type of basic thiazolopyrimidine skeleton is the thiazolo[3,2-*c*] pyrimidine derivatives (**102**) which present very rare synthetic examples in the recent literature. The first and unique biological activity study performed by our research group (Yildirim et al., 2018) reports that thiazolo[3,2-*c*]pyrimidines or thiazolo[3,2-*c*]pyrimidinones exhibited some remarkable and strong cyctotoxic effects on human breast (MCF7) and liver carcinoma (HEPG2/C3A) cell lines (Yildirim et al, 2018). No other bioactivity study of thiazolo[3,2-*c*]pyrimidine derivatives are not present or reported to date, the recent literature on their bioactivities is very virgin and a lot of studies need to be done to identify their biological properties.



Cyctotoxic against (MCF7 and HEPG2) cancer cells

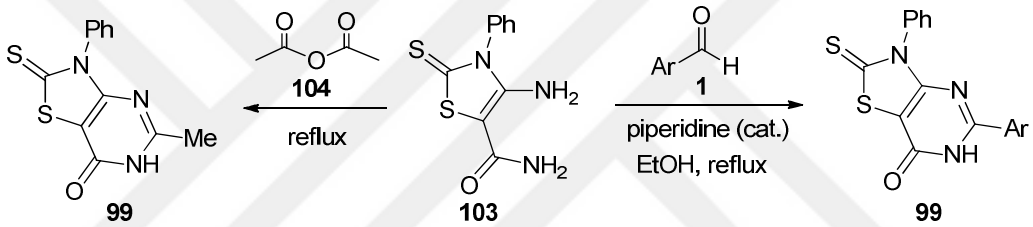
Figure 1.9 Thiazolo[3,2-*c*]pyrimidine derivatives (102) exhibiting biological activity

1.3.2. Synthesis of Thiazolopyrimidines

Since thiazolo[5,4-*d*] or [4,5-*d*]pyrimidines (**99**, **100**) are accepted as some thia-analogs of DNA bases such as adenine and guanine, various methods for their

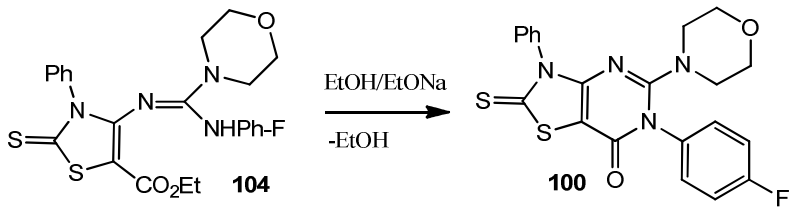
efficient preparations have developed in the literature for last three decades. Mainly, the synthesis of this important heterocyclic skeleton can be achieved either by conversion of substituents on thiazole ring into pyrimidine (**azole approach**) or by the annelation of thiazole on pyrimidine ring (**azine approach**) utilizing different synthetic pathways.

Some of the literature studies utilizing **azole approach** to afford thiazolo[5,4-*d*] or [4,5-*d*]pyrimidines are being presented below. For instance, in the preparation of thiazolo[5,4-*d*]pyrimidines, a thiazolo-thione **103** reacts with aromatic aldehydes **1** or acid anhydride **104** to furnish some thiazolo[5,4-*d*]pyrimidine-thiones **99** via intermolecular cyclization reactions. When aromatic aldehyde and acetic anhydride were used, the yields are obtained as 80% and 65%, respectively. (Kamal El-Dean, 1992)



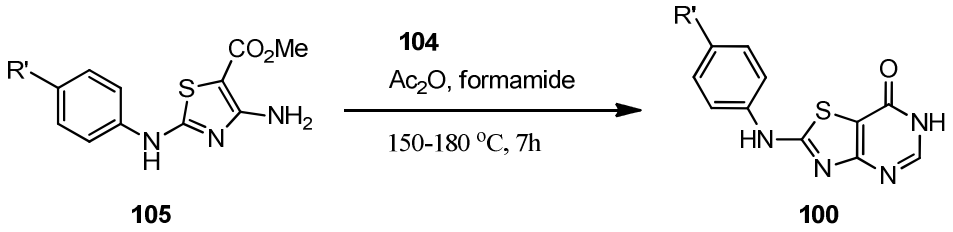
Picture 1.37 Synthesis of some thiazolo[5,4-*d*]pyrimidines.

Preparation of thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7-one **100** was achieved by intramolecular cyclization of morpholino-substituted carbodiimide of 2,3-dihydro-3-phenyl-2-thioxothiazole-5-carboxylate thione **103** with sodium ethoxide for 4 hour. (Fan et al., 2006)



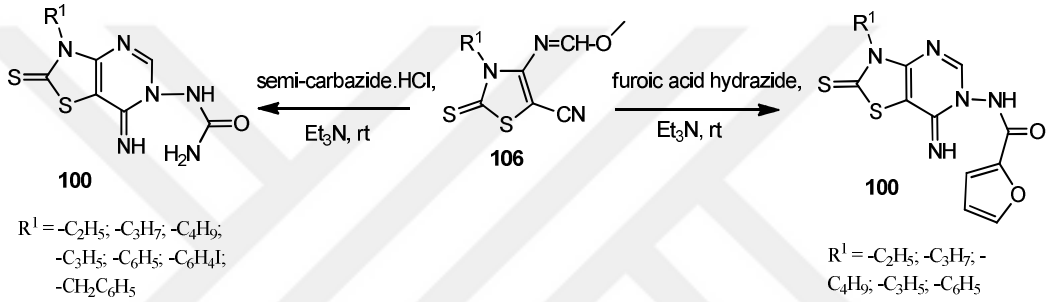
Picture 1.38 Synthesis of 2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7-one (2)thione.

Also, when 4-amino-2-phenylaminothiazole-5-carboxylic acid methyl esters **105** were reacted with Ac_2O in formamide at elevated temperatures for 7 hour, the 2-arylamino substituted 6*H*-thiazolo[4,5-*d*]pyrimidin-7-ones **100** were obtained successfully. (Lin et al., 2009)



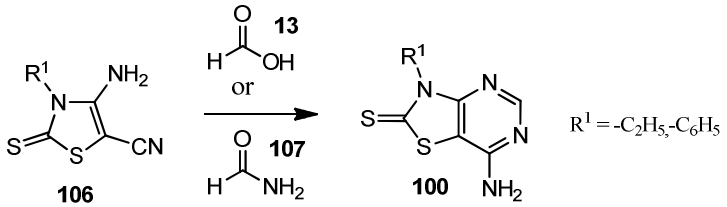
Picture 1.39 The synthesis of some *N*-arylaminothiazolo[4,5-*d*]pyrimidines.

Moreover, the cyclization reactions of methoxyimines of thiazole-thiones **106** with semicarbazide hydrochloride or furoic acid hydrazide gave thiazolo[4,5-*d*]pyrimidine urea or thiazolo[4,5-*d*]pyrimidine furonamide **100** in the presence of triethylamine at room temperature in 12 hour. (Luthra et al., 2010)



Picture 1.40 The preparation of thiazolo[4,5-*d*]pyrimidines from semicarbazide or hyrazides.

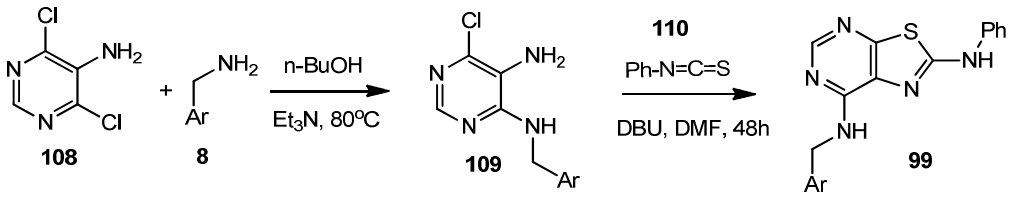
In another example, 4-amino-3-phenyl/ethyl-2-thioxo-2,3-dihydrothiazole-5-carbonitrile **106** was treated with formamide **107** or formic acid **13** by heating to produce 7-amino-3-phenyl/ethyl thiazolo[4,5-*d*]pyrimidine-thiones **100** in high yields (Azam et al.,2009).



Picture 1.41 The synthesis of thiazolo[4,5-*d*]pyrimidine using formamide or formic acid.

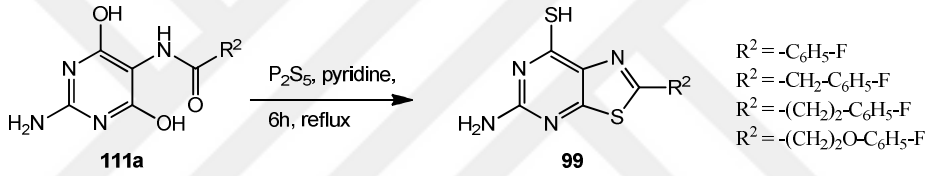
There are also studies utilizing **azine approach** for the preparation of thiazolo[5,4-*d*] or [4,5-*d*]pyrimidines in the recent literature and some of the examples are being presented below. A diaryl substituted thiazolo[5,4-*d*]pyrimidine-2,7-diamine **99** can be obtained the reaction of 4,6-dichloro-5-aminopyrimidine **108** with 3,4,5-trimethoxybenzylamine **8** and Et_3N at 80°C and

subsequent treatment of pyrimidine-4,5-diamine product **109** with DBU and phenylisothiocyanate **110** at rt. (Liu et al., 2005)



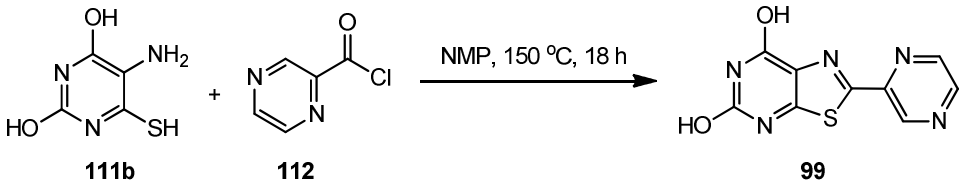
Picture 1.42 Synthesis of diarylthiazolo[5,4-*d*]pyrimidine-2,7-diamines from aminopyrimidines

In another study, some mercapto-substituted thiazolo[5,4-*d*]pyrimidine amines **99** were obtained via the reaction of 5-acylaminopyrimidine-4,6-diols **111a** with phosphorus pentasulfide in pyridine under reflux conditions. (Jang et al., 2010)



Picture 1.43 The synthesis of some substituted-thiazolo[5,4-*d*] pyrimidines.

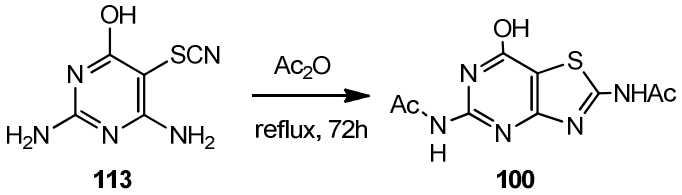
Besides, the reaction of 5-amino-6-mercaptopyrimidine-2,4-diol **111b** with 2-pyrazine carbonyl chloride **112** in NMP at 150°C is known to afford new thiazolo[5,4-*d*]pyrimidin-5,7-diol **99** in good yields. (Varano et al., 2018)



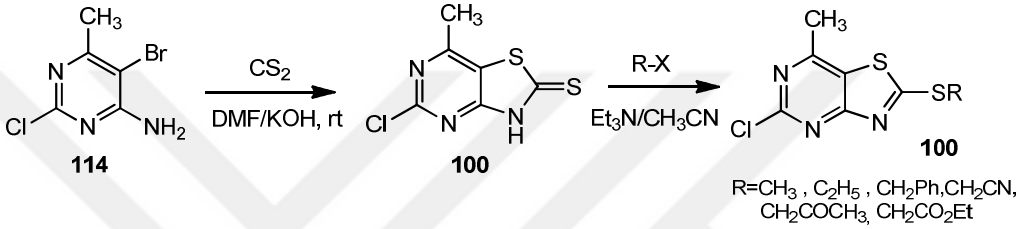
Picture 1.44 Synthesis of 2-pyrazinyl-thiazolo[5,4-*d*]pyrimidine-5,7-diol.

Moreover, the reaction of 2,4-diamino-6-hydroxythiocyanatopyrimidine **113** with acetic anhyride at reflux for 72 hour provides the formation of 2,5-diacetamido-7-hydroxythiazolo[4,5-*d*]pyrimidines **100** (Baker and Chatfield, 1969). Also, cyclization reaction of 4-amino-5-bromo-2-chloro-6-methyl-pyrimidine **114** with carbon disulfide in the presence of KOH afforded 5-chloro-7-methyl-2,3-dihydropyrimido[4,5-*d*][1,3]thiazol-2-thione **100** which was

subsequently refluxed with alkyl halides in the presence of Et_3N in CH_3CN to afford corresponding thiazolo[4,5-*d*]pyrimidine alkylmerceptans **100** in excellent yields (Rahimizadeh et al. 2011).

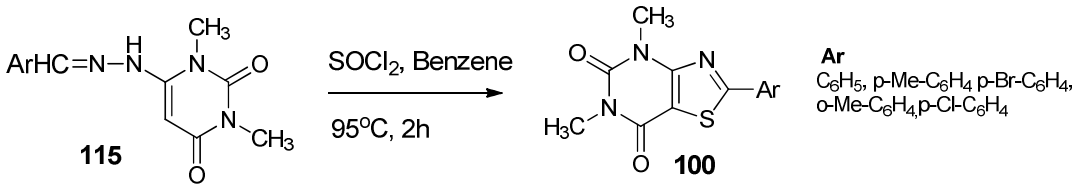


Picture 1.45 Synthesis of 2,5-diacetamidothiazolo[4,5-*d*]pyrimidines



Picture 1.46 Synthesis of mercapto-substituted thiazolo[4,5-*d*]pyrimidines

In addition, when 6-arylidenehydrazino-1,3-dimethyluracil derivatives **115** react with excess thionyl chloride in dry benzene at reflux, thiazolo[4,5-*d*]pyrimidines **100** are obtained with good yields at reflux in benzene via an intramolecular cyclization reaction (Ichiba and Senga, 1985).

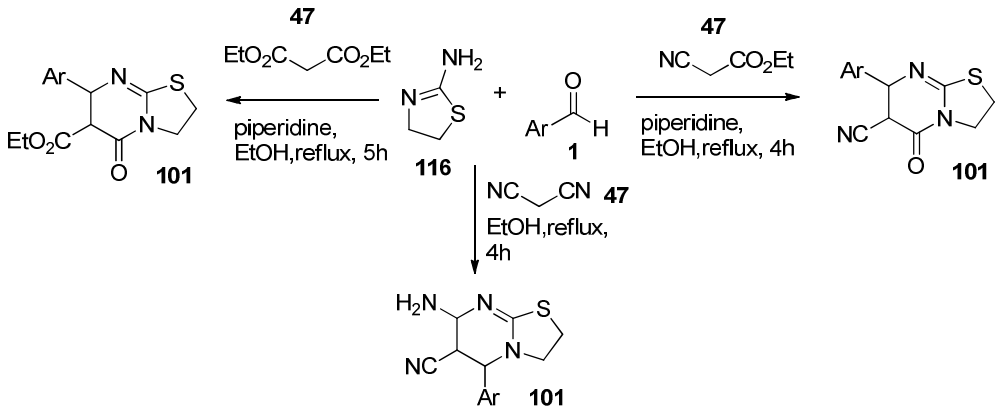


Picture 1.47 Example of thiazolo[4,5-*d*]pyrimidine-2,4-diones

Another important structural type, thiazolo[3,2-*a*]pyrimidines (**101**) are also known in the literature and they are rarely synthesized via **the azole approach** starting from very few precursors. Only a few examples from recent literature are given below.

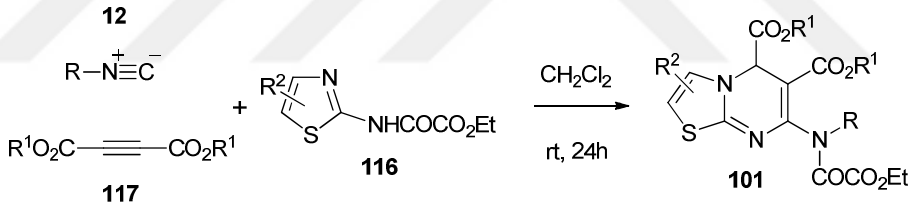
In a study conducted in past decades, a 3-CR reaction of 2-aminothiazoline **116** with an aromatic aldehyde **1** and activated methylene compounds (**47**) such as diethylmalonate, ethyl cyanoacetate and malononitrile at reflux in EtOH gave 5-oxothiazolo[3,2-*a*]pyrimidine-6-ethyl carboxylates, 5-oxothiazolo[3,2-

a]pyrimidine-6-carbonitriles and 5-aminothiazolo[3,2-*a*]pyrimidine-6-carbonitriles (**101**), respectively (Jeanneau-Nicolle et al., 1992).



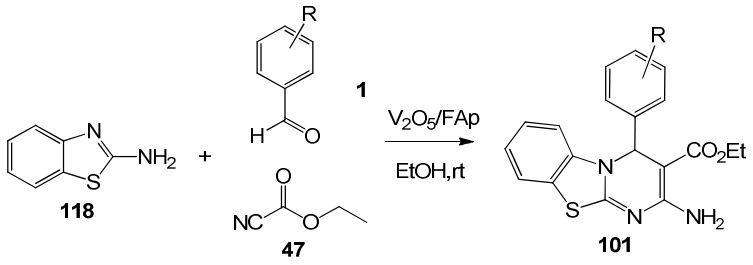
Picture 1.48 Synthesis of thiazolo[3,2-*a*]pyrimidine carboxylates and carbonitriles a 3-CR

In a recent study, the preparation of new 5*H*-thiazolo[3,2-*a*]pyrimidines **101** was accomplished over one-pot 3-CR reaction of ethyl 2-oxo-2-(1,3-thiazol-2-ylamino)acetates **116** with dialkyl acetylenedicarboxylates **117** and isocyanides **12** under very mild conditions with high yields (Adib et al., 2007).



Picture 1.49 Synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidines via a 3-CR

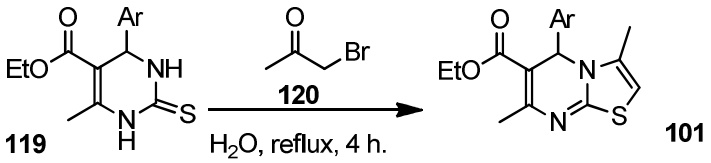
Also, in another very recent study of Kerru et al. (2020) some benzo[4,5]thiazolo[3,2-*a*]pyrimidines **101** were prepared via one-pot 3CR reactions of benzothiazole amine **118**, aldehydes **1** and ethyl cyanoacetate **47** by a V_2O_5/FAp catalyst at rt with high yields.



Picture 1.50 Synthesis of benzo[4,5]thiazolo[3,2-*a*]pyrimidines via a vanadium oxide/Fap catalyzed 3-CR.

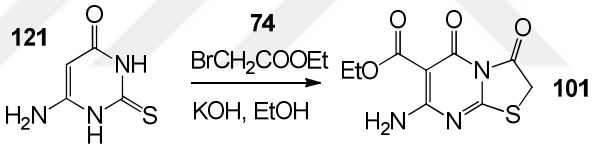
Majority of novel thiazolo[3,2-*a*]pyrimidines have been found to be prepared via **the azine approach** over different reactions in the literature. Some important and representative synthetic examples are given from literature below.

Recently, dihydropyrimidine-2-thione **119** was refluxed with α-bromoacetone **120** in water to afford 5*H*-thiazolo[3,2-*a*]pyrimidine carboxylates **101** in excellent yields (Wang et al. 2007).



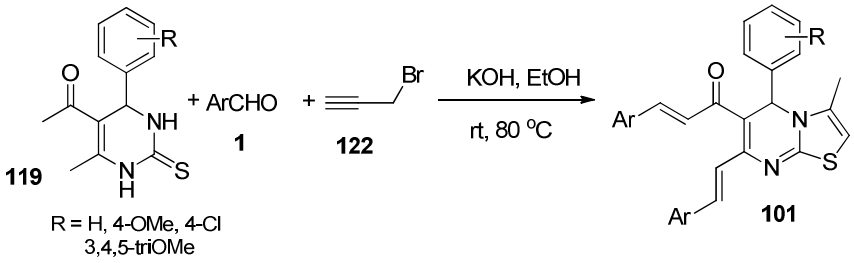
Picture 1.51 Synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidine carboxylates.

Similarly, the cyclocondensation reaction of 6-amino-2-thiouracil **121** with ethyl bromoacetate **74** under reflux in boiling potassium hydroxide easily afforded thiazolo[3,2-*a*]pyrimidines **101** exhibiting some antitumor activities (Abu-Hashem et al, 2011).



Picture 1.52 Reaction of thiazolo[3,2-*a*]pyrimidines by cyclocondensation.

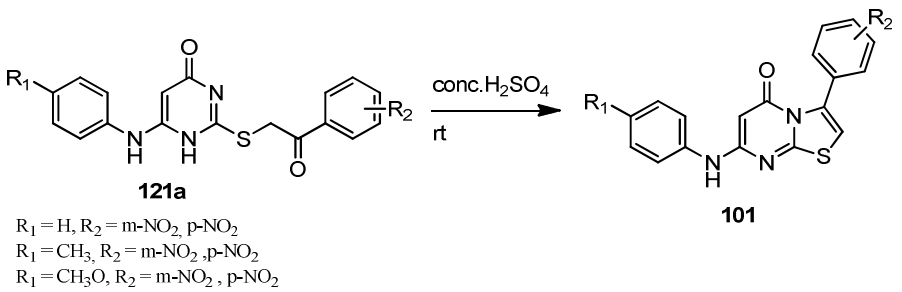
Also, in another recent study, the reaction of 6-aryldihydropyrimidine-2-thiones **119** with propargyl bromide **122** and benzaldehyde **1** in EtOH under basic conditions gave a variety of styryl-substituted thiazolo[3,2-*a*]pyrimidines **101** very efficiently (Fatima et al., 2012).



Picture 1.53 Synthesis of some styryl substituted thiazolo[3,2-*a*] pyrimidines.

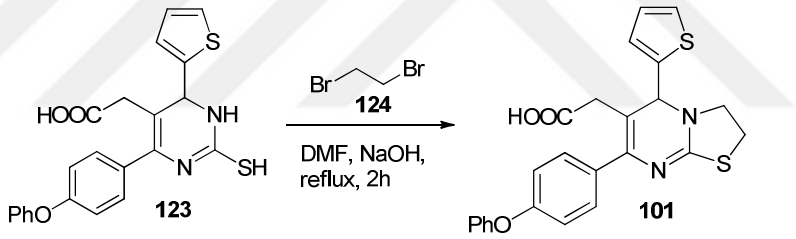
An even more recent study reports that acid-catalyzed intramolecular cyclization of *S*-alkylated-arylaminopyrimidinones **121a** furnished 4-nitrophenyl

substituted arylamino-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one derivatives **101** in high yields (Cai et al., 2015).



Picture 1.54 Synthesis of (4-nitrophenyl)-7-arylamino-thiazolo[3,2-*a*] pyrimidin-5-ones.

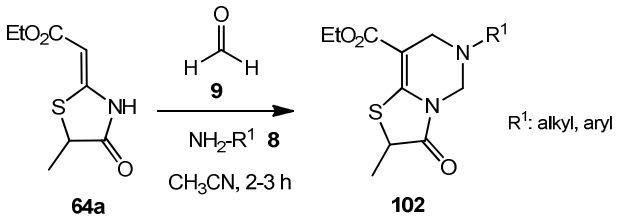
Very recently, Behalo (2018) reported the efficient synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl) acetic acid **101** by the reaction of 1,6-dihydropyrimidin-5-yl) acetic acid **123** with 1,2-dibromoethane **124** in DMF at reflux under basic conditions and the antimicrobial properties of 5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl) acetic acid.



Picture 1.55 Synthesis of 5*H*-thiazolo[3,2-*a*]pyrimidin-6-yl) acetic acid.

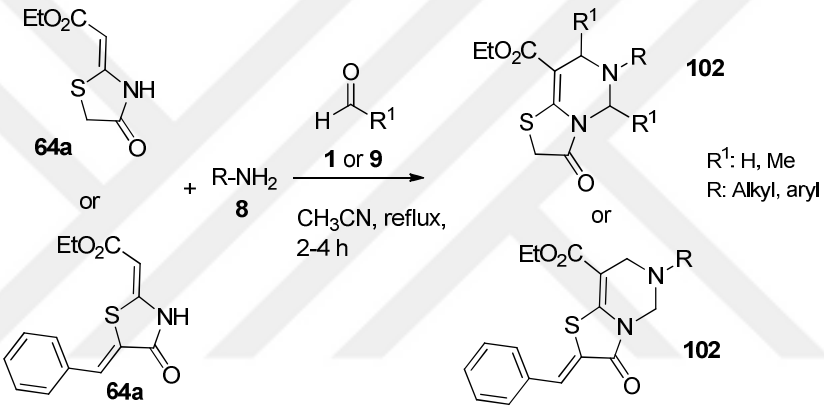
Third type of thiazolopyrimidines included in synthetic chemistry literature by the efforts of our group are the thiazolo[3,2-*c*]pyrimidines **102** which can only be prepared via **azole approach** over the reactions of some enamines. There are only 1-2 examples for their preparations in the recent literature.

Our research group reported the first conventional 3-CR Mannich cyclisations of a heterocyclic enamine, (Z)-ethyl 2-(5-methyl-4-oxothiazolidin-2ylidene) acetate **64a**, with primary amines **8** and formaldehyde **9** to afford oxothiazolo[3,2-*c*]pyrimidines **102** under reflux for 3-4 hour (Yıldırım and Çelikel, 2015)



Picture 1.56 Synthesis of thiazolo[3,2-*c*]pyrimidines via conventional Mannich cyclisations.

As a continuation of previous study, new thiazolo[3,2-*c*]pyridiminones **102** were obtained very efficiently over a 3-CR of novel heterocyclic enamines **64a** with formaldehyde **9** (or acetaldehye **1**) and primary amines **8** by refluxing in CH_3CN for 2-4 hour (Uysal, 2019).

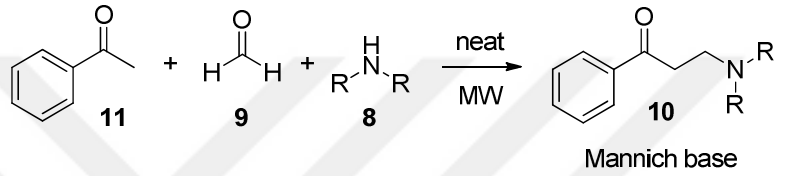


Picture 1.57 Preparation of new thiazolo[3,2-*c*]pyrimidinones.

1.4. Microwave-Assisted Organic Synthesis (MAOS)

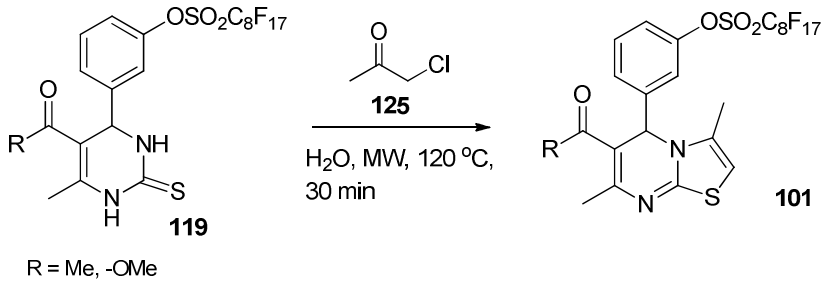
Originally, microwave energy was used to heat the foodstuffs by 1950s. But, microwave radiation has applied to chemical reactions in the mid 1980s (Kappe et al., 2012). Microwave-assisted synthesis made a revolution in organic chemistry and early studies began to be published showing that many types of organic reactions can be performed rapidly utilizing microwave heating (Gedye et al., 1986; Giguere et al., 1986). At first, development of the microwave technology was relatively slow due to some reasons such as its safety, reproducibility, temperature and pressure control. Some of the organic reactions with conventional instruments caused explosions till safer and more technological microwave instruments have been developed (Bose et al., 1991; Shaikh, 2017). Thousands of publications about the application of MW energy to speed up the organic transformations have been published in the last thirty years (Nain et al.,

2019). In the last 20 years, MAOS reactions have become more popular due to many advantages of them such as shorter reaction times, higher product yields and purities, fewer side reactions, uniform heating with lower energy and greater reproducibility (Dallinger and Kappe, 2007; Anastas and Eghbali, 2010; Lancaster, 2016). MAOS is important vehicle for the production of variety of organic structures via many organic transformations such as oxidation, reduction, Knoevenagel condensation, esterification, deacetylation and Mannich reactions (Nain et al., 2019). For instance, different Mannich bases **10** can be prepared efficiently by the aid of microwave energy.



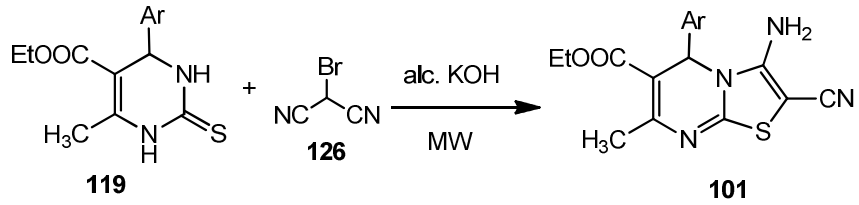
Picture 1.58 Example for microwave-assisted Mannich reaction.

In addition, recent examples for microwave-mediated preparation of thiazolo[3,2-*a*]pyrimidine derivatives **101** via **azine approach** are found in literature. For instance, Piqani and Zhang (2011) reported that the cyclocondensation reaction of perfluorooctanesulfonylaryl dihydropyrimidinethiones **119** with chloroacetone **125** afforded perfluorooctanesulfonylaryl-thiazolo[3,2-*a*]pyrimidines **101** in water under microwave heating for 30 min in good yields.



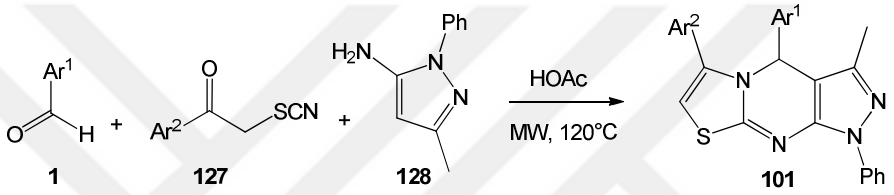
Picture 1.59 Synthesis of some perfluorooctanesulfonylaryl substituted thiazolo[3,2-*a*]pyrimidines.

In another study conducted with similar precursor, ethyl 4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, reacts with bromomalononitrile to give 5*H*-thiazolo[3,2-*a*]pyrimidines in ethanolic KOH solution under MW heating conditions (Youssef and Amin, 2012).



Picture 1.60 Synthesis of ethyl 3-amino-5-aryl-2-cyano-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates.

Besides, in another study with a **multicomponent approach**, some functionalized pyrazolo[3,4-*d*]-thiazolo[3,2-*a*]pyrimidines **101** are obtained in high yields via an acid-catalyzed 3-CR of α-thiocyanate ketones **127**, aryl aldehydes **1** with pyrazol-5-amines **128** under microwave conditions (Khobragade et al., 2010).

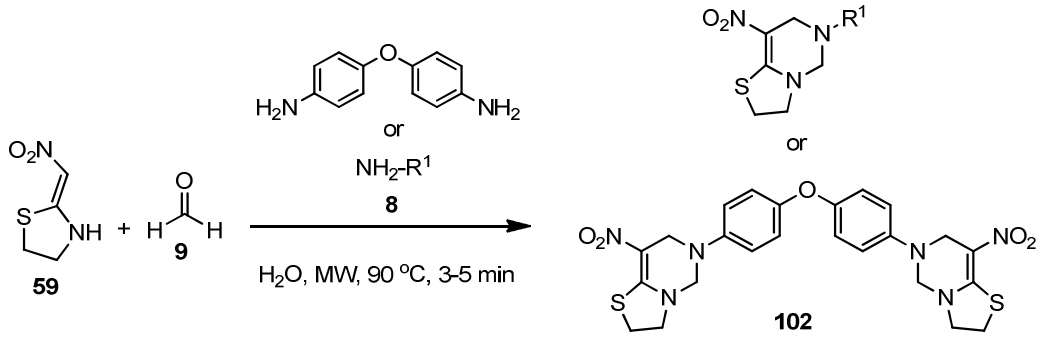


Ar^1: C_6H_5 , 4-BrC_6H_4 , 4-ClC_6H , 4-FC_6H_4 , 4-$CH_3C_6H_4$, 3,4,5-$OCH_3C_6H_2$, 4-OH-3-$OCH_3C_6H_3$, 2,4-ClC_6H_3 , 3-NO_2 , 4-NO_2

Ar^2: 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, C_6H_5

Picture 1.61 Synthesis of pyrazolo[3,4-*d*]-thiazolo[3,2-*a*]pyrimidines via an acid-catalyzed 3-CR.

However, there can be found only one example for microwave-assisted synthesis of thiazolo[3,2-*c*]pyrimidine derivatives via **azole approach** reported by our research group. In this study, an efficient preparation of nitrothiazolo[3,2-*c*]pyrimidines **102** were performed via a 3-component Mannich cyclisations of 2-(nitromethylene) thiazolidine **59** with formaldehyde **9** and primary amines (mono- or bis-amines) **8** under MW conditions within couple of minutes. (Yıldırım et al., 2014)



Picture 1.62 Synthesis of nitrothiazolo[3,2-*c*]pyrimidines via microwave-assisted Mannich cyclisations.

2. AIM AND SCOPE OF THE STUDY

Since we know that variety of thiazolopyrimidines (**99-102**) are pharmacologically interesting compounds and they exhibited diverse biological properties, they have been prepared via azine or azole approaches by applying many synthetic methods for last decades. However, thiazolo[3,2-*c*]pyrimidine derivatives **102** are not very well-known structures and there were almost no study on their preparations and biological properties until 2014 in the literature. Therefore, in last few years, examples of novel thiazolo[3,2-*c*]pyrimidines **102** have been added to heterocyclic chemistry literature with the studies (publications, dissertations) of our research group via **azole approach** applying microwave and conventional heating methods. Besides, first biological activity results of thiazolo[3,2-*c*]pyrimidines **102** were also reported in study of our group.

The successes in our studies on the chemistry of enamines affording thiazolo[3,2-*c*]pyrimidines **102** has prompted us to prepare some newer molecules with more in-depth follow-up studies. Therefore, efficient synthesis of some new thiazolo[3,2-*c*]pyridimine carbonitriles **102** were planned via microwave-assisted Mannich cyclisations of new heterocyclic enamine **64b** with formaldehyde **9** and various aliphatic or aromatic amines **8** in the current study.

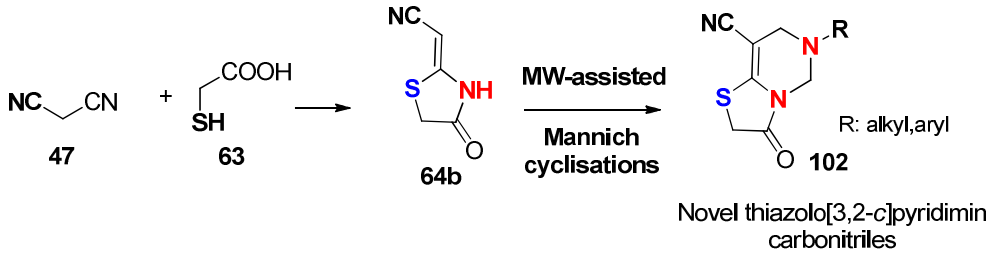


Figure 2.1 Synthetic route giving new thiazolo[3,2-*c*]pyrimidine carbonitriles 102.

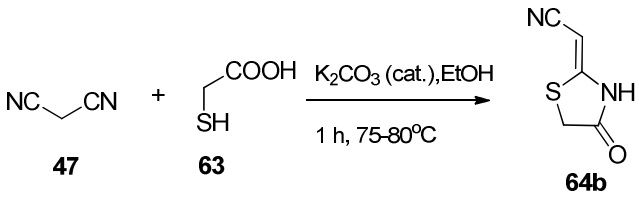
3. MATERIALS AND METHODS

All reagents and solvents were purchased from commercial sources in reagent and analytical grade (Merck, Sigma-Aldrich, TCI, Isolab) and used as received. A computer-assisted single-mode microwave reactor (CEM Discover Explorer SP) were used in microwave irradiation of the reactions. IR spectra were obtained on a PERKIN-ELMER Spectrum Two ATR equipped FTIR system. ^{1}H- and ^{13}C- NMR spectra measurements were performed on Bruker DPX 400 spectrometers (400 MHz for proton and 100 MHz for carbon) at ambient temperature. All chemical shifts (δ) were reported in parts per million (ppm) downfield from TMS; *J* values are given in Hz. The abbreviations used for NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, sx= sextet, hept = heptet, m = multiplet, dd=doublet of doublets. High resolution mass spectra were run on a Waters Lct Premier XE oa-TOF Mass Spectrometer. Melting points were determined on a MELTEMP apparatus and are uncorrected. TLC analysis was performed to monitor the reaction progress using precoated plates with fluorescent indicator (Merck 5735). Potassium permanganate staining solution and UV-lamp supplied with 254-366 nm were used to visualize the TLC spots.

3.1. Experimental

3.1.1. Preparation of Starting Material

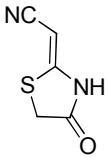
Preparation of (*Z*)-2-(4-oxothiazolidin-2-ylidene)acetonitrile with modified method of Stojanovic et al. (2011)



47 **63** **64b**

A mixture of malononitrile 47 (1 equiv), mercapto acetic acid 63 (1.05 equiv), and K_2CO_3 (0.05 equiv) was heated with stirring at 75–80°C for 1 hour and then cooled to room temperature. After addition of H_2O/EtOH (8:2) to the reaction mixture, it was continued stirring for 1 hour at room temperature. After stirring, a light brown crystalline precipitate was filtered and washed with mother liquor and then, collected as 64b in 95% yield.

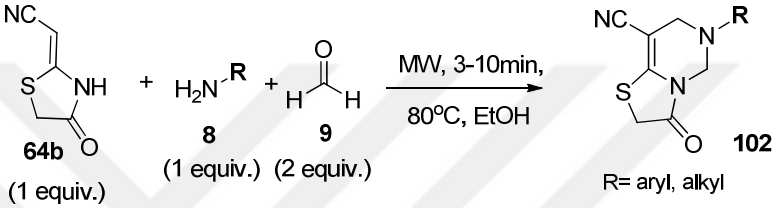
(*Z*)-2-(4-oxothiazolidin-2-ylidene)acetonitrile (64b)



Dark brown powder. (0.900 g, 95%), m.p. 184-186°C; R_f (50% EtOAc/hexane) 0.35; IR (ATR) υ: 3104 (NH), 3065 (=CH), 2987, 2853 (CH), 2207 (C≡N), 1713 (amide C=O), 1586 (C=C), 1237, 1196, 777cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.87 (1H, s), 3.98 (2H, s), 2.46 (NH, s).

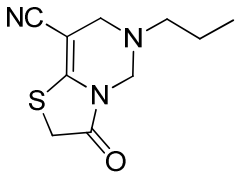
3.1.2. Synthesis of Target Products

General Procedure for Preparation of Thiazolo[3,2-*c*] pyrimidinone carbonitriles (102)



(Z)-2-(4-oxothiazolidin-2-ylidene) acetonitrile **64b** (0.5 mmol, 1.0 equiv) and aryl or alkyl primary amine **8** (0.5 mmol, 1.0 equiv.) were dissolved in EtOH (3-5 mL) and formaldehyde **9** (37% v/v in H_2O, 1.0 mmol, 2.0 equiv.) was added dropwise through a syringe and the resulting mixture was irradiated with microwave reactor for 2-3 min at 80°C. After 3 minutes, an aliquot from reaction mixture was analyzed by TLC and if the reaction is not complete, the reaction mixture was irradiated more for additional minutes until completion. Then, the reaction mixture was cooled to ambient temperature and the solvent was removed in rotary evaporator. The resulting solid residue was purified by recrystallization using hexane-EtOAc mixtures to afford the target product (**102**) in pure state.

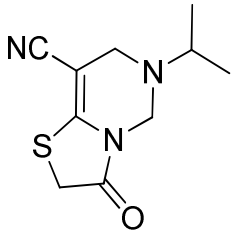
3-oxo-6-propyl-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102a)



Recrystallization (20% EtOAc/hexane) afforded dark orange powder. (92 mg, 83%), m.p. 74-76°C; R_f (50% EtOAc/hexane) 0.62; IR (ATR) υ: 2968, 2937 (aliph. CH), 2191(C≡N), 1702 (amide C=O), 1590 (C=C), 1356, 1271, 841, 658, 591 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.57 (s, 2H), 3.81 (s, 2H), 3.52 (s, 2H), 2.45 (t, *J* = 7.5 Hz, 2H), 1.52 (sx, *J* = 7.3 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C-

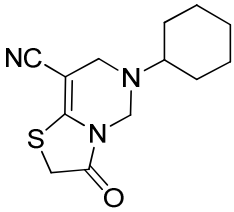
NMR (100 MHz, $CDCl_3$) δ: 170.1, 149.7, 117.0, 78.5, 63.2, 53.9, 49.9, 31.5, 20.9, 11.4.; (TOF-MS ESI$^-$) *m/z*: 222 (100, $[M-H]^+$), 223 (15), 224 (10%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 222.0684. $C_{10}H_{12}N_3OS$ requires 222.0701.

6-isopropyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102b)



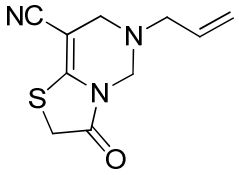
Recrystallization (20% EtOAc/hexane) afforded light brown solid. (100 mg, 90%), m.p. 108-110°C; R_f (50% EtOAc/hexane) 0.75; IR (ATR) υ: 2964, 2855 (aliph. CH), 2194(C≡N), 1694 (amide C=O), 1599 (C=C), 1460, 1363, 1235, 1169, 1117, 1016, 759, 657, 515 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.62 (s, 2H), 3.58 (s, 2H), 3.52 (s, 2H), 2.97 (s, 2H), 2.86 (hept, *J* = 6.3 Hz, 2H), 1.11 (d, *J* = 6.4 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.7, 162.5, 117.1, 69.8, 60.0, 55.8, 50.5, 47.3, 20.8; (TOF-MS ESI$^-$) *m/z*: 222 (100, $[M-H]^+$), 223 (20), 224 (10%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 222.0693. $C_{10}H_{12}N_3OS$ requires 222.0701.

6-cyclohexyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102c)



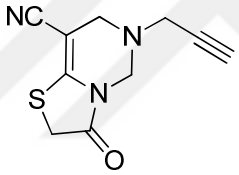
Recrystallization (20% EtOAc/hexane) afforded orange-brown solid. (125 mg, 95%), m.p. 135-137°C. R_f (50% EtOAc/hexane) 0.75; IR (ATR) υ: 2927, 2851 (aliph. CH), 2193(C≡N), 1703 (amide C=O), 1594 (C=C), 1445, 1322, 1268, 1184, 889, 691, 471 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.63 (s, 2H), 3.59 (s, 2H), 2.98 (d, *J* = 11.0 Hz, 1H), 2.87 (d, *J* = 11.0 Hz, 1H), 2.45 (s, 1H), 1.93-1.73 (m, 5H), 1.60 (d, *J* = 12.4 Hz, 1H), 1.64-1.51 (m, 5H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.4, 151.2, 117.2, 77.7, 59.8, 57.0, 47.2, 30.9, 30.1, 28.5, 25.8, 25.6, 25.1; (TOF-MS ESI$^-$) *m/z*: 262 (100, $[M-H]^+$), 263 (15%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 262.1013. $C_{13}H_{16}N_3OS$ requires 262.1014.

6-allyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102d)



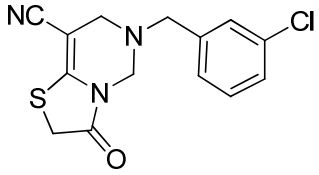
Recrystallization (20% EtOAc/hexane) afforded creamy-white solid. (105 mg, 95%). m.p. 106-108°C; R_f (50% EtOAc/hexane) 0.62; IR (ATR) υ: 3090 (=CH), 2921, 2847 (aliph. CH), 2197(C≡N), 1712 (amide C=O), 1596 (C=C), 1363, 1265, 1176, 932, 777, 690, 588 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.88 – 5.76 (m, 1H), 5.24 (dd, *J* = 13.6, 8.2 Hz, 2H), 4.59 (s, 2H), 3.82 (s, 2H), 3.55 (s, 2H), 3.14 (d, *J* = 6.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.9, 149.8, 132.9, 120.2, 116.7, 78.4, 62.4, 55., 49.2, 31.6; (TOF-MS ESI$^-$) *m/z*: 220 (100, $[M-H]^+$), 221 (15), 222 (10%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 220.0533. $C_{10}H_{10}N_3OS$ requires 220.0545.

3-oxo-6-(prop-2-yn-1-yl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102e)



Recrystallization (20% EtOAc/hexane) afforded orange solid. (96 mg, 87%), m.p. 124-126°C. R_f (50% EtOAc/hexane) 0.66; IR (ATR) υ: 3294 (≡CH), 2950, 2860 (aliph. CH), 2195 (C≡N), 1718 (amide C=O), 1587 (C=C), 1455, 1399, 1348, 1275, 1111, 836, 676, 516 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.66 (s, 1H), 3.83 (s, 2H), 3.63 (s, 2H), 3.43 (d, *J* = 2.4 Hz, 2H), 2.36 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.8, 149.9, 116.6, 78.0, 74.2, 73.0, 62.0, 49.2, 42.1, 31.7; (TOF-MS ESI$^-$) *m/z*: 218 (100, $[M-H]^+$), 219 (15%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 218.0381. $C_{10}H_8N_3OS$ requires 218.0388.

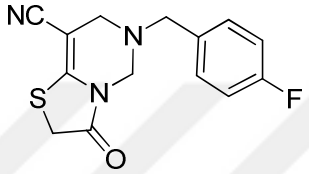
6-(3-chlorobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102f)



Recrystallization (10% EtOAc/hexane) afforded orange solid. (141 mg, 93%), m.p. 88-90°C. R_f (50% EtOAc/hexane) 0.66; IR (ATR) υ: 3050 (arom.

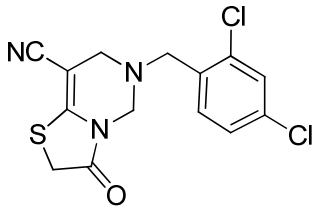
CH), 2940, 2816 (aliph. CH), 2200(C≡N), 1707 (amide C=O), 1598 (C=C), 1472, 1331, 1216, 1170, 88424, 778, 679 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34 (s, 1H), 7.31 – 7.23 (m, 1H), 7.20 (s, 1H), 7.16 (d, *J* = 5.0 Hz, 1H), 4.59 (s, 2H), 3.83 (s, 2H), 3.64 (s, 2H), 3.51 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: ^{13}C NMR (101 MHz, $cdcl_3$) δ 170.0, 149.9, 138.4, 134.2, 129.9, 128.8, 128.2, 126.8, 116.7, 78.0, 63.0, 56.1, 49.3, 31.5; (TOF-MS ESI$^-$) *m/z*: 304 (100, $[M-H]^+$), 305 (20), 306 (40%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 304.0314. $C_{14}H_{11}ClN_3OS$ requires 304.0311.

6-(4-fluorobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102g)



Recrystallization (10% EtOAc/hexane) afforded orange-brown solid. (125 mg, 86%), m.p. 153-155°C. R_f (50% EtOAc/hexane) 0.75; IR (ATR) υ: 3060 (arom. CH), 2980, 2820 (aliph. CH), 2192(C≡N), 1703 (amide C=O), 1595 (C=C), 1503, 1460, 1360, 1276, 1180, 820, 765, 681, 507 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.26 (dd, *J* = 8.4, 5.5 Hz, 2H), 7.04 (t, *J* = 8.6 Hz, 2H), 4.58 (s, 2H), 3.84 (s, 2H), 3.63 (s, 2H), 3.51 (s, 2H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.0, 163.6, 161.2, 149.8, 131.9, 130.5, 116.8, 115.8, 115.5, 78.0, 62.8, 55.8, 49.1, 31.5; (TOF-MS ESI$^-$) *m/z*: 288 (100, $[M-H]^+$), 289 (15), 290 (5%); HRMS (TOF-MS ESI$^-$):$[M-H]^+$, found 288.0597. $C_{14}H_{11}FN_3OS$ requires 288.0607.

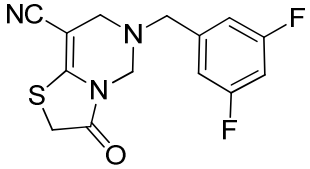
6-(2,4-dichlorobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102h)



Recrystallization (10% EtOAc/hexane) afforded orange-brown solid. (145 mg, 85%), m.p. 122-124°C. R_f (50% EtOAc/hexane) 0.77; IR (ATR) υ: 3080 (arom. CH), 2920, 2810 (aliph. CH), 2196 (C≡N), 1711 (amide C=O), 1602 (C=C), 1469, 1358, 1275, 1094, 828, 682, 512 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.43 – 7.41 (m, 1H), 7.37 (s, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 4.58 (s, 2H), 3.85 (s, 2H), 3.74 (s, 2H), 3.55 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.0, 150.0, 135.1, 134.5, 132.7, 131.5, 129.8, 129.6, 127.4, 116.8, 78.1, 62.9, 53.0, 49.7, 31.5;

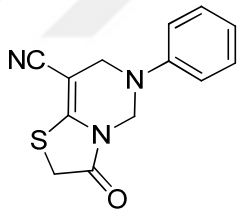
(TOF-MS ESI⁻) *m/z*: 337 (100, $[M-H]^+$), 338 (16), 339 (75%); HRMS (TOF-MS ESI⁻): $[M-H]^+$, found 337.9896. $C_{14}H_{10}Cl_2N_3OS$ requires 337.9922.

6-(3,5-difluorobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102i)



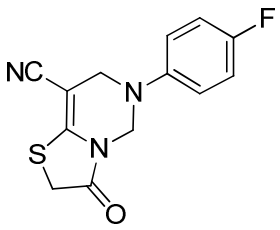
Recrystallization (10% EtOAc/hexane) afforded light-brown solid. (145 mg, 95%), m.p. 153-155°C. R_f (50% EtOAc/hexane) 0.75; IR (ATR) υ: 3080 (arom. CH), 2920, 2840 (aliph. CH), 2192(C≡N), 1709 (amide C=O), 1595 (C=C), 1447, 1355, 1280, 1115, 990, 857, 781, 671, 519 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.87 (d, *J* = 6.3 Hz, 2H), 6.76 (t, *J* = 8.8 Hz, 1H), 4.60 (s, 2H), 3.85 (s, 2H), 3.66 (s, 2H), 3.53 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.0, 164.1, 161.9, 149.8, 140.6, 116.5, 111.3, 111.0, 103.5, 78.0, 63.1, 55.7, 49.4, 31.5; (TOF-MS ESI⁻) *m/z*: 306 (100, $[M-H]^+$), 307 (15), 308 (5%); HRMS (TOF-MS ESI⁻): $[M-H]^+$, found 306.0510. $C_{14}H_{10}F_2NO_3S$ requires 306.0512.

3-oxo-6-phenyl-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102j)



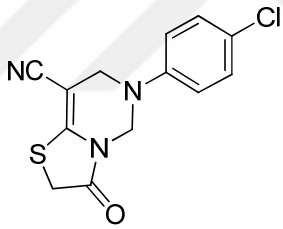
Recrystallization (10% EtOAc/hexane) afforded brown solid. (105 mg, 82%), m.p. 170-172°C. R_f (50% EtOAc/hexane) 0.66; IR (ATR) υ: 3050 (arom. CH), 2950, 2870 (aliph. CH), 2190(C≡N), 1715 (amide C=O), 1589 (C=C), 1485, 1356, 1285, 1181, 935, 746, 684, 519 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32 (t, *J* = 8.0 Hz, 2H), 7.03 (t, *J* = 6.9 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 2H), 5.15 (s, 2H), 4.17 (s, 2H), 3.79 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.4, 150.7, 146.5, 129.6, 122.7, 118.1, 116.2, 79.3, 61.3, 48.6, 31.6; (TOF-MS ESI⁻) *m/z*: 256 (100, $[M-H]^+$), 257 (20%); HRMS (TOF-MS ESI⁻): $[M-H]^+$, found 256.0543. $C_{13}H_{10}N_3OS$ requires 256.0544.

6-(4-fluorophenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102k)



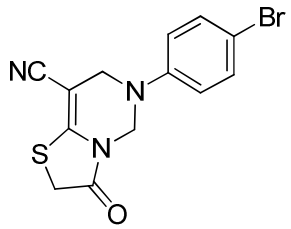
Recrystallization (10% EtOAc/hexane) afforded brown solid. (120 mg, 87%), m.p. 134-136°C. R_f (50% EtOAc/hexane) 0.75; IR (ATR) υ: 3090 (arom. CH), 2915 (aliph. CH), 2197 (C≡N), 1721 (amide C=O), 1597 (C=C), 1508, 1489, 1354, 1216, 1195, 1013, 829, 759, 653, 529 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.01 (t, *J* = 9.2 Hz, 2H), 6.91 (dd, *J* = 9.6, 3.8 Hz, 2H), 5.08 (s, 2H), 4.11 (s, 2H), 3.80 (s, 2H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.6, 159.7, 157.3, 150.7, 142.9, 119.8, 116.4, 116.2, 115.7, 115.5, 79.1, 61.9, 49.3, 31.6; (TOF-MS ESI$^-$) *m/z*: 274 (100, $[M-H]^+$), 275 (20), 276 (30%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 274.0475. $C_{13}H_9FN_3OS$ requires 274.0450.

6-(4-chlorophenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102l)



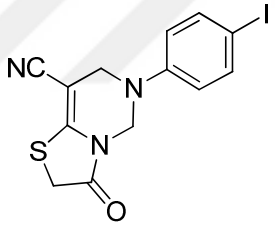
Recrystallization (10% EtOAc/hexane) afforded yellow-white solid. (132 mg, 91%), m.p. 164-166°C. R_f (50% EtOAc/hexane) 0.78; IR (ATR) υ: 3060 (arom. CH), 2960, 2880 (aliph. CH), 2200(C≡N), 1705 (amide C=O), 1595 (C=C), 1496, 1352, 1283, 1193, 823, 516 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.26 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.11 (s, 2H), 4.13 (s, 2H), 3.80 (s, 2H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.5, 150.8, 145.2, 129.7, 129.6, 127.9, 119.2, 116.2, 79.1, 61.2, 48.8, 31.6; (TOF-MS ESI$^-$) *m/z*: 290 (100, $[M-H]^+$), 291 (30), 292 (55%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 290.0145. $C_{13}H_9ClN_3OS$ requires 290.0154.

6-(4-bromophenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102m)



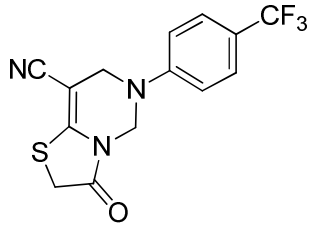
Recrystallization (10% EtOAc/hexane) afforded light yello solid. (152 mg, 90%), m.p. 162-164°C. R_f (50% EtOAc/hexane) 0.83; IR (ATR) υ: 3030 (arom. CH), 2980, 2831 (aliph. CH), 2188(C≡N), 1704 (amide C=O), 1591 (C=C), 1491, 1351, 1213, 1192, 821, 674, 503 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.41 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 5.11 (s, 2H), 4.13 (s, 2H), 3.80 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.5, 150.8, 145.6, 132.7, 132.6, 119.6, 116.1, 115.3, 79.1, 61.1, 48.8, 31.6; (TOF-MS ESI$^-$) *m/z*: 333 (95, $[M-H]^+$), 334 (20), 335 (100%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 333.9639. $C_{13}H_9BrN_3OS$ requires 333.9649.

6-(4-iodophenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102n)



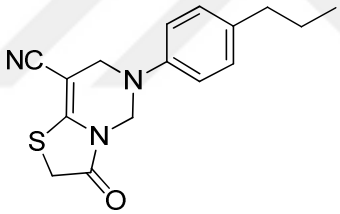
Recrystallization (10% EtOAc/hexane) afforded black-brown solid. (165 mg, 86%), m.p. 174-176°C. R_f (50% EtOAc/hexane) 0.68; IR (ATR) υ: 2980 (arom. CH), 2921 (aliph. CH), 2187 (C≡N), 1708 (amide C=O), 1588 (C=C), 1486, 1350, 1275, 1191, 807, 757, 500 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 8.9 Hz, 2H), 6.71 (d, *J* = 8.9 Hz, 2H), 5.10 (s, 2H), 4.13 (s, 2H), 3.79 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.5, 150.8, 146.3, 138.6, 138.5, 119.8, 116.2, 85.4, 79.1, 60.9, 48.6, 31.6; (TOF-MS ESI$^-$) *m/z*: 381 (100, $[M-H]^+$), 382 (20%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 381.9500. $C_{13}H_9IN_3OS$ requires 381.9511.

3-oxo-6-(4-(trifluoromethyl)phenyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carbonitrile (102o)



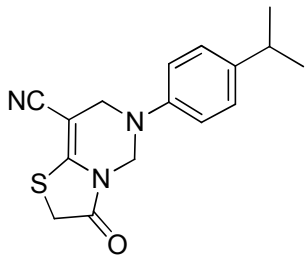
Recrystallization (25% EtOAc/hexane) afforded white solid. (150 mg, 92%), m.p. 172-174°C. R_f (50% EtOAc/hexane) 0.62; IR (ATR) υ: 3000 (arom. CH), 2950 (aliph. CH), 2190(C≡N), 1720 (amide C=O), 1588 (C=C), 1331, 1194, 1110, 829, 505 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 7.7 Hz, 2H), 5.19 (s, 2H), 4.23 (s, 2H), 3.82 (s, 2H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.7, 151.0, 149.2, 127.1, 127.0, 125.3, 124.5, 124.2, 122.6, 117.2, 116.0, 114.3, 79.0, 60.3, 48.5, 31.7; (TOF-MS ESI$^-$) *m/z*: 324 (100, $[M-H]^+$), 325 (20%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 324.0421. $C_{14}H_9F_3N_3OS$ requires 324.0418.

3-oxo-6-(4-propylphenyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102p)



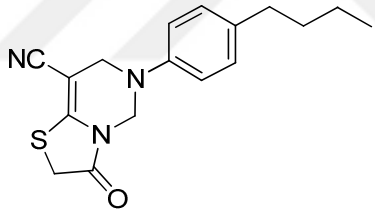
Recrystallization (20% EtOAc/hexane) afforded yellow-brown solid. (140 mg, 94%), m.p. 150-152°C. R_f (50% EtOAc/hexane) 0.75; IR (ATR) υ: 3040 (arom. CH), 2952, 2925, 2867 (aliph. CH), 2187(C≡N), 1715 (amide C=O), 1589 (C=C), 1513, 1347, 1187, 805, 662, 492 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.11 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.11 (s, 2H), 4.13 (s, 2H), 3.78 (s, 2H), 2.52 (t, *J* = 7.9 Hz, 2H), 1.61 (sx, *J* = 7.4 Hz, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.6, 150.7, 144.4, 137.2, 129.5, 118.0, 116.5, 79.5, 61.5, 49.0, 37.1, 31.6, 24.5, 13.8; (TOF-MS ESI$^-$) *m/z*: 299 (100, $[M]^+$); HRMS (TOF-MS ESI$^-$): $[M]^+$, found 299.0313. $C_{16}H_{17}N_3OS$ requires 299.1092.

6-(4-isopropylphenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102r)



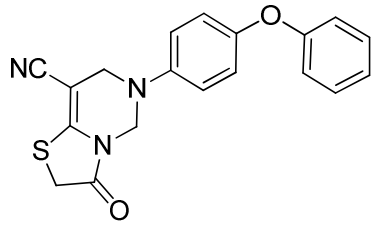
Recrystallization (20% EtOAc/hexane) afforded light-brown solid. (146 mg, 97%), m.p. 113-115°C. R_f (50% EtOAc/hexane) 0.68; IR (ATR) υ: 2959, 2850 (aliph. CH), 2190(C≡N), 1713 (amide C=O), 1587 (C=C), 1514,1352,1192, 1012, 817, 648, 487cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.16 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 5.12 (s, 2H), 4.13 (s, 2H), 3.78 (s, 2H), 2.86 (hept, *J* = 6.9 Hz, 1H), 1.22 (d, *J* = 7.0 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.7, 150.4, 144.5, 143.3, 127.9, 126.9, 118.1, 116.5, 79.6, 61.6, 48.9, 33.2, 31.6, 23.8; (TOF-MS ESI$^-$) *m/z*: 298 (100, $[M-H]^+$), 299 (20%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 298.1012. $C_{16}H_{16}N_3OS$ requires 298.1014.

6-(4-butylphenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102s)



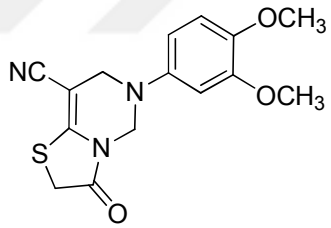
Recrystallization (20% EtOAc/hexane) afforded light brown solid. (156 mg, 100%), m.p. 115-117°C. R_f (50% EtOAc/hexane) 0.50; IR (ATR) υ: 3050 (arom. CH), 2960, 2921, 2851 (aliph. CH), 2187(C≡N), 1711 (amide C=O), 1589 (C=C), 1512, 1457, 1350, 1275, 1189, 807, 663, 514 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.10 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.10 (s, 2H), 4.12 (s, 2H), 3.78 (s, 2H), 2.54 (t, *J* = 7.8 Hz, 2H), 1.56 (p, *J* = 7.3 Hz, 2H), 1.33 (sx, *J* = 7.2 Hz, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.7, 150.8, 144.5, 137.5, 129.8, 129.4, 118.2, 117.9, 116.6, 79.6, 61.6, 49.1, 34.8, 33.7, 31.7, 22.4, 14.0; (TOF-MS APCI$^+$) *m/z*: 314 (100, $[M+H]^+$), 315 (25%); HRMS (TOF-MS APCI$^+$): $[M+H]^+$, found 314.1345. $C_{16}H_{16}ClN_2O_3S$ requires 314.1327.

3-oxo-6-(4-phenoxyphenyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102t)



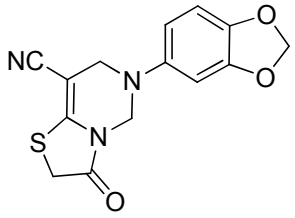
Recrystallization (25% EtOAc/hexane) afforded light brown solid. (145 mg, 83%), m.p. 170-172°C. R_f (50% EtOAc/hexane) 0.70; IR (ATR) υ: 3060 (arom. CH), 2921, 2851 (aliph. CH), 2187(C≡N), 1717 (amide C=O), 1584 (C=C), 1481, 1348, 1239, 1185, 824, 759, 663, 502 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.36 – 7.30 (m, 2H), 7.09 (t, *J* = 7.0 Hz, 1H), 6.97 (dd, *J* = 10.4, 5.1 Hz, 4H), 6.91 (d, *J* = 9.0 Hz, 2H), 5.10 (s, 2H), 4.12 (s, 2H), 3.81 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.6, 157.3, 152.6, 150.7, 142.4, 129.7, 129.7, 123.1, 120.2, 119.7, 118.4, 116.4, 79.4, 61.7, 49.4, 31.6; (TOF-MS ESI$^-$) *m/z*: 348 (100, $[M-H]^+$), 349 (20), 350 (10%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 348.0825. $C_{19}H_{14}N_3O_2S$ requires 348.0806.

6-(3,4-dimethoxyphenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carbonitrile (102u)



Recrystallization (20% EtOAc/hexane) afforded dark brown solid. (140 mg, 88%), m.p. 166-168°C. R_f (50% EtOAc/hexane) 0.50; IR (ATR) υ: 3010 (arom. CH), 2929, 2815 (aliph. CH), 2190(C≡N), 1709 (amide C=O), 1592 (C=C), 1509, 1459, 1351, 1226, 1012, 830, 772, 458 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.77 (d, *J* = 8.7 Hz, 1H), 6.55 (d, *J* = 2.7 Hz, 1H), 6.45 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.07 (s, 2H), 4.10 (s, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.79 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.6, 150.6, 149.7, 145.2, 140.7, 116.4, 111.8, 109.6, 103.8, 79.4, 62.1, 56.1, 56.0, 49.5, 31.7.; (TOF-MS ESI$^-$) *m/z*: 316 (100, $[M-H]^+$), 317 (20%); HRMS (TOF-MS ESI$^-$): $[M-H]^+$, found 316.0745. $C_{15}H_{14}N_3O_3S$ requires 316.0755.

6-(benzo[*d*][1,3]dioxol-5-yl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carbonitrile (102v)

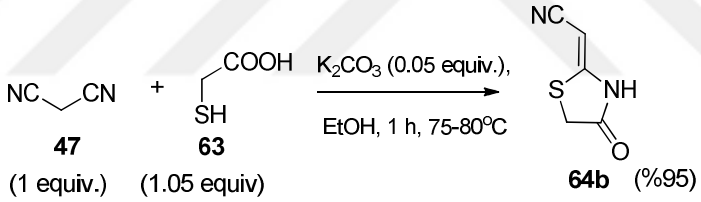


Recrystallization (15% EtOAc/hexane) afforded black-brown solid. (130 mg, 87%), m.p. 178-180°C. R_f (50% EtOAc/hexane) 0.56; IR (ATR) υ: 2990, 2900 (aliph. CH), 2188(C≡N), 1697 (amide C=O), 1584 (C=C), 1482, 1358, 1284, 1192, 1036, 933, 814, 671, 520 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.71 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.53 (t, *J* = 2.2 Hz, 1H), 6.36 (dt, *J* = 8.0, 2.2 Hz, 1H), 5.94 (d, *J* = 1.9 Hz, 2H), 5.03 (s, 2H), 4.06 (s, 2H), 3.80 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.6, 150.6, 148.3, 143.6, 141.9, 116.4, 111.0, 110.9, 108.4, 101.3, 79.3, 62.3, 49.7, 31.6; (TOF-MS ESI$^-$) *m/z*: 300 (100, MH^+), 301 (25%); HRMS (TOF-MS ESI$^-$): MH^+, found 300.0469 $C_{14}H_{10}N_3O_3S$ requires 300.0442.

4. RESULTS

4.1. Synthesis and Characterization of Precursors

Heterocyclic enamine **64b** as the precursor compound was prepared from the reaction of malononitrile **47** and mercaptoacetic acid **63** in the presence of catalytic amount of potassium carbonate by modifying the literature method (Stojanovic et al., 2011) and heterocyclic enamine, (Z)-2-(4-oxothiazolidin-2-ylidene) acetonitrile **64b**, was isolated as a brown solid in excellent yield (Picture 4.1). The structure of the precursor **64b** was characterized by analyzing data in its IR and ^{1}H-NMR spectra. In the IR spectrum of **64b**, the structure was confirmed by the amide NH, olefinic =CH, nitrile C≡N, amide C=O, and C=C stretching vibrations at around 3115, 3066, 2210, 1716 and 1589 cm^{-1}, respectively. These data is also consistent with the literature values (Sadek et.al., 1984). In proton NMR of **64b**, NH and C=CH proton signals appeared around 2.46 and 4.87 ppm, respectively. Also, methylenic proton signal resonated at 3.98 ppm clearly demonstrated the formation of heterocyclic enamine **64b**.

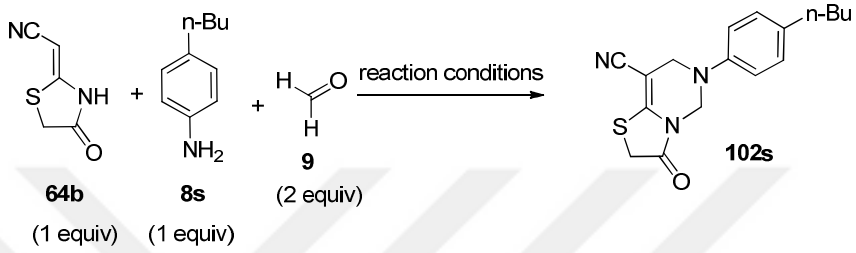


Picture 4.1 Synthesis of heterocyclic enamine precursor 64b.

4.2. Synthesis and Structural Characterization of Target Oxothiazolo[3,2-*c*]pyrimidine Carbonitriles (102)

In previous years, our group reported the synthesis and cytotoxic effects of various thiazolo[3,2-*c*]pyrimidine derivatives (**102**) starting from different heterocyclic enamine precursors via efficient protocols (Yildirim et al., 2014; Yıldırım and Çelikel, 2015; Yildirim et al., 2018; Uysal, 2019). Aformentioned successful and efficient studies on the preparation of thiazolo[3,2-*c*]pyridimine scaffolds (**102**) has prompted us to design new synthetic protocols. Therefore, a MW-assisted Mannich cyclization of a new heterocyclic enamine **64b** with formaldehyde **9** and primary amines **8** were performed for the synthesis of oxothiazolo[3,2-*c*]pyrimidine carbonitriles very efficiently in the current study.

At first, in order to determine the most convenient reaction conditions for the synthesis of new 3-oxothiazolo[3,2-*c*]pyrimidine carbonitriles **102** , some optimization reactions have been done with a model cyclization reaction (Picture 4.2). Thus, cyclization reactions of (Z)-2-(4-oxothiazolidin-2-ylidene) carbonitrile **64b** with formaldehyde **9** and 4-n-butylaniline **8s** were performed under different conditions and two equivalents of formaldehyde **9** and one equiv. of other precursors (**64b** and **8s**) were applied in each trial with model reaction (Table 4.1).



Picture 4.2 Model cyclization reaction between compounds 64b, 9 and 8s

Table 4.1 Optimization of the reaction conditions for the synthesis of compound 102.

Entry	Reaction condition	Catalyst	Temp. (°C)	Time	Yield (%)
1	Neat, **64b** (1eq), **8s** (1eq), **9** (2.0 eq)[a]	Et_3N	50°C	6 min	25
2	Neat, **64b** (1eq), **8s** (1eq), **9** (2.0 eq)[a]	-	80°C	5 min	45
3	H_2O, **64b** (1eq), **8s** (1eq), **9** (2.0 eq)[a]	-	100°C	6 min	30
4	CH_3CN, **64b** (1eq), **8s** (1eq), **9** (2.0 eq)[a]	-	50°C	6 min	55
5	CH_3CN, **64b** (1eq), **8s** (1eq), **9** (2.0 eq)[a]	-	80°C	5 min	60
6	CH_3CN, **64b** (1eq), **8s** (1eq), **9** (2.0 eq)[a]	Et_3N	80°C	6 min	55
7	EtOH, **64b** (1eq), **8s** (1eq), **9** (2.0 eq)[a]	Et_3N	80°C	5 min	75
8	EtOH, **64b** (1eq), **8s** (1eq), **9** (2.0 eq)[a]	-	80°C	6 min	**100**
9	EtOH, **64b** (1eq), **8s** (1eq), **9** (2.0 eq)[b]	-	80°C	3 hour	70

[a] Reactions performed under MW irradiation. [b] The reaction carried out at reflux under conventional heating.

When we evaluate the results of the optimization reactions, it is understood that trial reactions under solvent-free conditions or in water were not very efficient with or without base (entries 1-3, Table 4.1). Besides, when a nonprotic and polar solvent, CH_3CN was applied at varying temperatures with or without base, the product yields have increased to moderate levels (55-60%) (entries 4-6, Table 4.1). However, the model reactions carried out in ethanol with or without base provided much higher or quantitative yields (75-100%) at the same temperature (entries 7-8, Table 4.1). As a last trial, a model reaction has been carried out in ethanol under conventional heating for 3 hour, but the reaction took

place with lower product yield (75%) than those under microwave conditions (entries 9, Table 4.1).

After finding the suitable reaction conditions for the product formation, (Z)-2-(4-oxothiazolidin-2-ylidene) acetate **64b** was reacted with a various aliphatic or aromatic amines **8a-v** and formaldehyde **9** to produce a wide variety of thiazolo[3,2-*c*]pyrimidine products (**102**). Following the optimized reaction conditions, a series of novel 6-substituted-3-oxothiazolo[3,2-*c*]pyrimidines-8-carbonitriles (**102a-v**) were mostly synthesized with good to excellent yields (82-100%) (Table 4.2). MW-assisted MCRs of **64b** with formaldehyde **9** and alkyl amines furnished the products **102a-e** with good to excellent yields in 3-5 minutes (entries 1-5, Table 4.2). Similarly, the cyclizations with benzylamine derivatives were also completed with good to excellent yields (83-95%) in reaction times of 3-5 minutes (entries 6-9, table 4.2). Moreover, the reactions performed with arylamines afforded the target products **102j-v** with good to excellent yields (82-100%) within 3-10 minutes (entries 10-21, Table 4.2). When the cyclization reactions were categorized in terms of reaction yields, the most effective cyclization of heterocyclic amine, **64b** was observed with 4-n-butylaniline **8s** (100%) (entry 18, Table 4.2) and the least effective one was the cyclization between **64b** and aniline **8j** with a yield of 82%. Probably, ED alkyl groups on para position of anilines caused a small increase in the nucleophilicity of amino group which subsequently facilitated the formation of imines or iminium ions with formaldehyde **9** giving rise the formation of products **102** in higher yields. Even so, good to excellent yields were attained in the majority of Mannich cyclizations of **64b** with alkyl- or aryl-amines (Table 4.2) and this showed that ED or EW groups on the amines were not quite effective to cause large differences in the amount of product formation.

All the thiazolo[3,2-c]pyrimidine-8-carbonitrile products **102a-v** were purified by recrystallizing from different mixtures of ethyl acetate-hexane solvents and isolated in high purity.

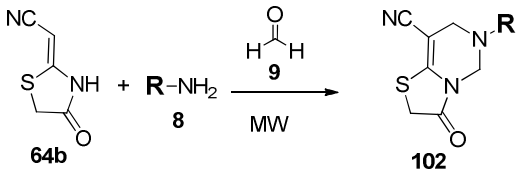


Table 4.2 Results of Mannich cyclizations affording the products 102a**-v**.

Entry	Product	R	9 (equiv.)	Time (min) [a]	Yield (%)[b]
1	**102a**	propyl	2	3	83
2	**102b**	isopropyl	2	5	90
3	**102c**	cyclohexyl	2	4	**95**
4	**102d**	allyl	2	3	**95**
5	**102e**	propargyl	2	3	**96**
6	**102f**	3-chlorobenzyl	2	3	93
7	**102g**	4-fluorobenzyl	2	3	86
8	**102h**	2,4-dichlorobenzyl	2	3	85
9	**102i**	3,5-difluorobenzyl	2	5	**95**
10	**102j**	phenyl	2	5	82
11	**102k**	4-fluorophenyl	2	3	87
12	**102l**	4-chlorophenyl	2	5	91
13	**102m**	4-bromophenyl	2	3	90
14	**102n**	4-iodophenyl	2	5	86
15	**102o**	4-(trifluoromethyl)phenyl	2	10	92
16	**102p**	4-n-propylphenyl	2	3	**94**
17	**102r**	4-isopropylphenyl	2	3	**97**
18	**102s**	4-n-butylphenyl	2	4	**100**
19	**102t**	4-phenoxyphenyl	2	3	83
20	**102u**	3,4-dimethoxyphenyl	2	6	88
21	**102v**	benzo[*d*][1,3]dioxol-5-yl	2	5	87

[a] 0.5 mmol of each reactant (**64b**, **8**) in 3 mL of EtOH at 80°C; [b] Total yields after recrystallization.

The structures of all target products **102a-v** were fully elucidated by means of IR, ^{1}H-NMR, ^{13}C-NMR and HRMS analyses. To illustrate with an example, the structure of target product **102j** were primarily identified by disappearing of –NH stretching vibration (3104 cm^{-1}) of the precursor **64b** in the IR spectrum of product **102j**. Also, slight shifts in C≡N (2190 cm^{-1}), amide C=O (1715 cm^{-1}) and C=C (1589 cm^{-1}) bond stretchings in the IR spectrum of product **102j** proved the product formation (Figure 4.1). Besides, in proton NMR spectrum of **102j**, singlet peaks of three methylenic protons resonating at 5.15, 4.17, 3.79 ppm support the structure of expected product (Fig. 4.2). In the 13C-NMR of product **102j**, three CH_2 carbon signals resonating at 61.3, 48.6 and 31.6 ppm provided extra supporting data on the structure of product (Fig. 4.3). Finally, HRMS result of **102j** found accurately as 256.0543 ($[M-H]^+$, ESI^- mode) by TOF-MS analysis was also confirmative data for the formation of cyclization product (Fig. 4.4).

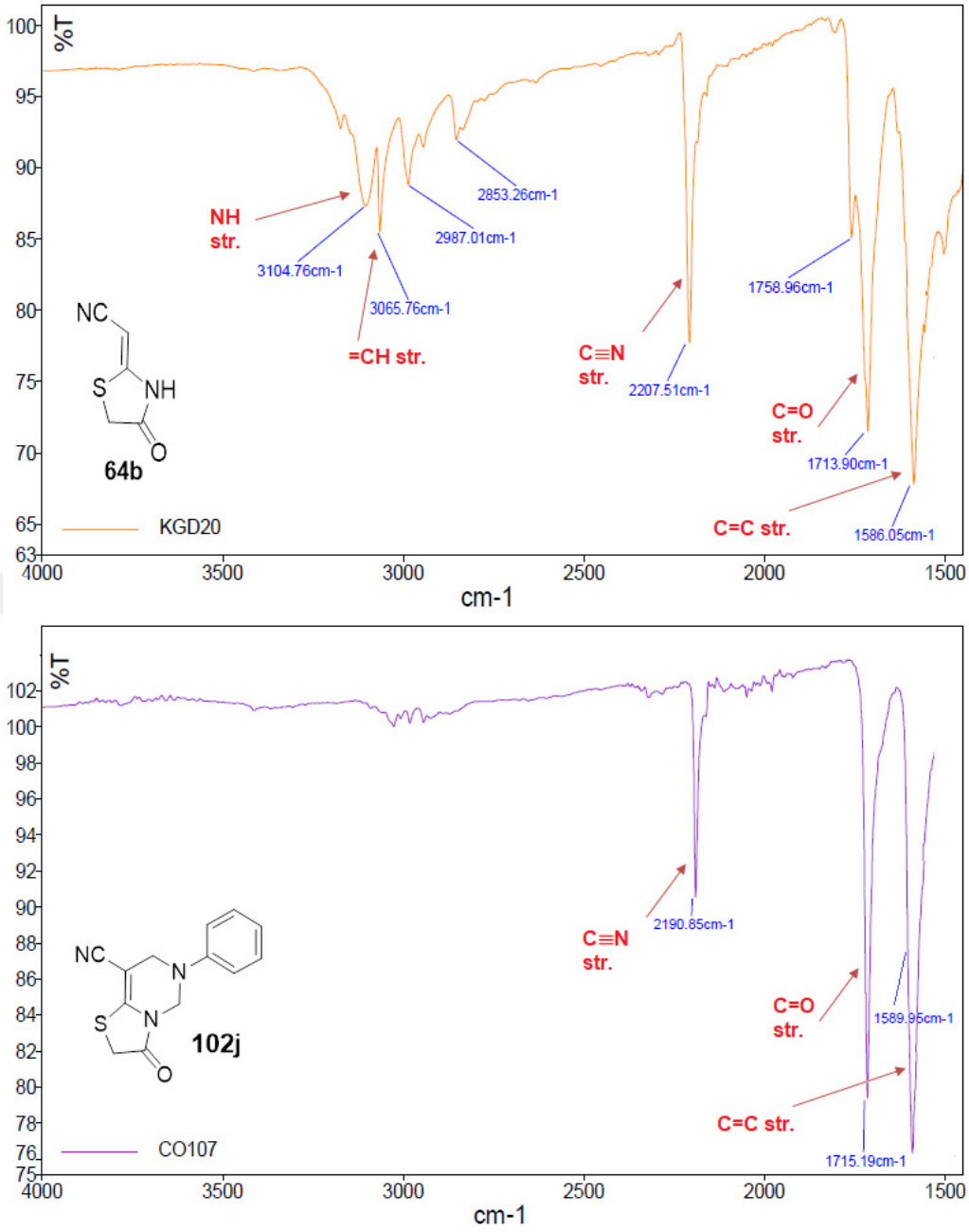


Figure 4.1 IR spectra of the precursor 64b and product 102j.

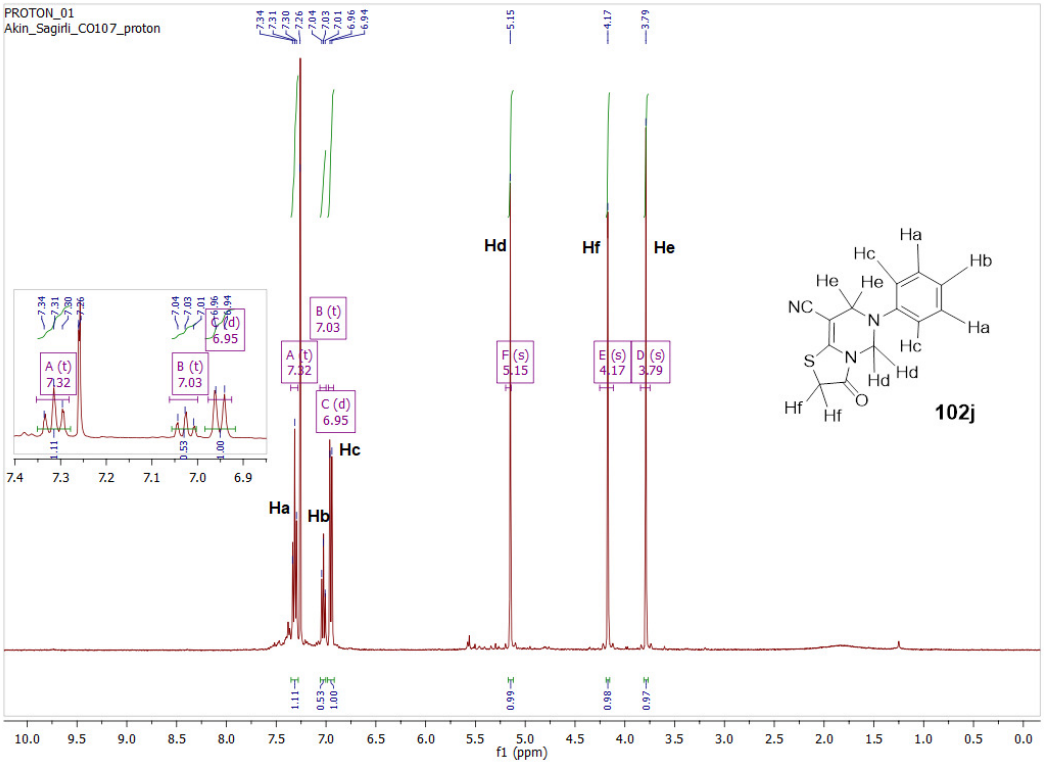


Figure 4.2 ^{1}H-NMR spectrum of the product 102j.

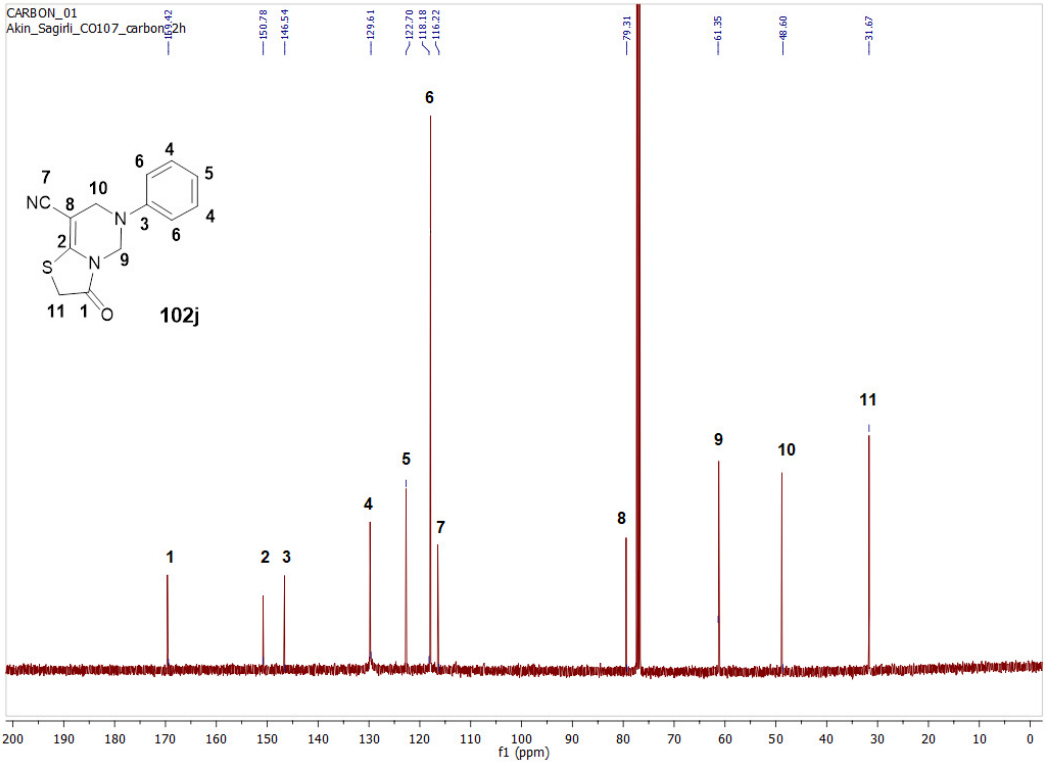


Figure 4.3 ^{13}C-NMR spectrum of the product 102j.

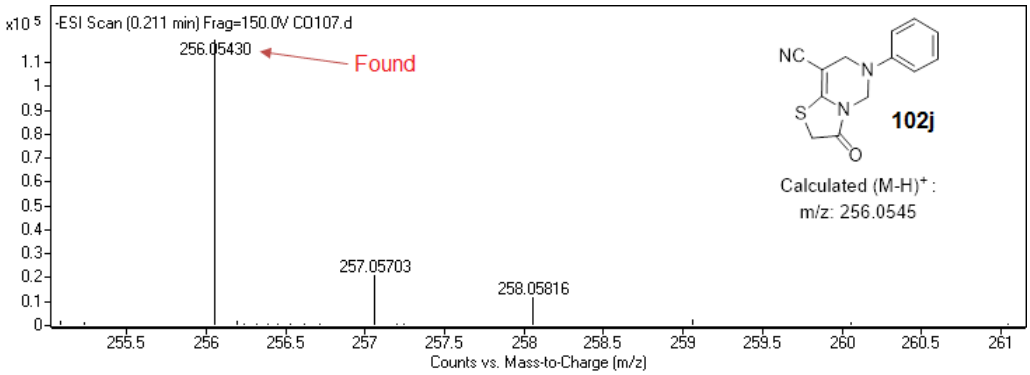


Figure 4.4 HRMS chromatogram of the product 102j

In similar fashion, the structures of all the cyclization products **102a-v** were characterized over their indicative data in IR, ^{1}H-NMR, ^{13}C-NMR spectra and accurate masses in HRMS chromatograms (table 4.3 and table 4.4).

In the current study, Mannich cyclization reactions of **64b** with primary amines **8a-v** and formaldehyde **9** have resulted mostly in high yields as in the microwave-assisted Mannich cyclizations conducted with heterocyclic enamine **59a**, primary amines **8** and formaldehyde **9** in our previous report. (Yıldırım et al., 2014)

Table 4.3 Indicative IR and NMR data for the compounds 102a-v

Prod.	**IR** (ν_{max}/cm^{-1})			**^{1}H-NMR** (δ,ppm)		**^{13}C-NMR** (δ,ppm)		
102	C≡N	C=O amide	C=C	N-C**H$_2$**-N	=C-C**H$_2$**-N	**C**=O amide	CN-**C**=C	**-**C**H$_2$**-N
a	2191	1702	1590	4.57	3.52	170.1	78.5	63.2,49.9
b	2194	1694	1599	4.62	2.97	169.7	69.8	60.0,47.3
c	2193	1703	1594	4.63	2.98	171.4	77.7	59.8,47.3
d	2197	1712	1596	4.59	3.55	169.9	78.0	62.4,49.2
e	2195	1718	1587	4.66	3.42	169.8	78.0	62.0,49.2
f	2200	1707	1598	4.51	3.59	170.0	78.1	63.0,49.3
g	2192	1703	1595	4.58	3.51	170.0	78.0	62.8,49.1
h	2196	1711	1602	4.58	3.55	170.1	78.1	62.9,49.7
i	2192	1709	1595	4.60	3.53	170.0	78.0	63.1,49.4
j	2190	1715	1589	5.15	3.79	169.4	79.3	61.3,48.6
k	2197	1721	1592	5.08	3.80	169.6	79.1	61.9,49.3
l	2200	1705	1595	5.11	3.80	169.5	79.1	61.2,48.8
m	2188	1704	1591	5.11	3.80	169.5	79.1	61.1,48.8
n	2187	1708	1588	5.10	3.79	169.5	79.1	60.9,48.6
o	2190	1720	1588	5.19	3.82	169.7	79.0	60.3,48.5
p	2187	1715	1589	5.11	3.78	169.6	79.5	61.5,49.0
r	2190	1713	1587	5.12	3.78	169.7	79.6	61.6,48.9
s	2187	1711	1589	5.10	3.78	169.7	79.6	61.6,49.1
t	2187	1717	1584	5.10	3.81	169.6	79.4	61.7,49.4
u	2190	1709	1592	5.07	3.79	169.6	79.4	62.1,49.5
v	2188	1697	1584	5.03	3.80	169.6	79.4	62.3,49.7

The formation of products (**102**) via Mannich cyclization reactions is understood to proceed over successive imine and iminium intermediates and this mechanism was also reported in detail in previous studies of our research group (Yıldırım et al., 2014; Yıldırım and Çelikel, 2015).

Table 4.4 HRMS (TOF-MS) data for the products 102a-v.

Comp.	HRMS			Comp.	HRMS		
102	**Found (m/z)**	**Calculated (m/z)**	**Ionization tech.**	**102**	**Found (m/z)**	**Calculated (m/z)**	**Ionization tech.**
a	222.0684	222.0701	ESI^-	**l**	290.0145	290.0154	ESI^-
b	222.0693	222.0701	ESI^-	**m**	333.9639	333.9649	ESI^-
c	262.1013	262.1014	ESI^{--}	**n**	381.9500	381.9511	ESI^-
d	220.0533	220.0545	ESI^-	**o**	324.0421	324.0418	ESI^-
e	218.0381	218.0388	ESI^-	**p**	299.0311	299.1092	ESI^-
f	304.0314	304.0311	ESI^-	**r**	298.1012	298.1014	ESI^-
g	288.0597	288.0607	ESI^-	**s**	314.1345	314.1327	$APCI^+$
h	337.9896	337.9922	ESI^-	**t**	348.0825	348.0806	ESI^-
i	306.0510	306.0512	ESI^{--}	**u**	316.0745	316.0755	ESI^-
j	256.0543	256.0545	ESI^-	**v**	300.0469	300.0442	ESI^-
k	274.0475	274.0450	ESI^-				

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

5. CONCLUSIONS AND RECOMMENDATIONS

The conclusions of this thesis study can be summarized as follows;

- ✓ In the first part of the study, heterocyclic secondary enamine **64b** were prepared from suitable precursors very efficiently following a modified literature method and its structure was characterized by means of IR and NMR analyses.
- ✓ In the next part of the study, after optimization of reaction conditions, an efficient synthetic protocol was established and 21 novel alkyl or aryl substituted 3-oxothiazolo[3,2-*c*]pyrimidine-8-carbonitriles **102a-v** were synthesized in a few minutes very efficiently over Mannich cyclisations of (Z)-2-(4-oxothiazolidin-2-ylidene) carbonitrile **64b** with various primary amines **8** and formaldehyde **9** under microwave conditions. The structures of all target compounds **102a-v** were completely characterized by means of IR, NMR (^{1}H, ^{13}C) and HRMS data. The novelty of the current study is the extention of the scope and applicability of efficient microwave-assisted Mannich cyclizations using a new heterocylic enamine **64b** via azole approach.
- ✓ Since there is still an ongoing interest for the preparation of novel thiazolopyrimidine derivatives exhibiting interesting biological effects, our synthetic study would make a new contribution to thiazolo[3,2-*c*]pyrimidine-based drug molecules.
- ✓ Preparation of novel thiazolo[3,2-*c*]pyrimidines via azine approach starting from interesting precursors is planned to be performed in near advance because no protocol for the synthesis of thiazolo[3,2-*c*]pyrimidines via azine approach has not been developed yet in the literature.

6. REFERENCES

Vancouver citation system was used in this thesis.

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7. APPENDICES

Appendix 1 IR, NMR, HRMS Spectra for the precursor and products

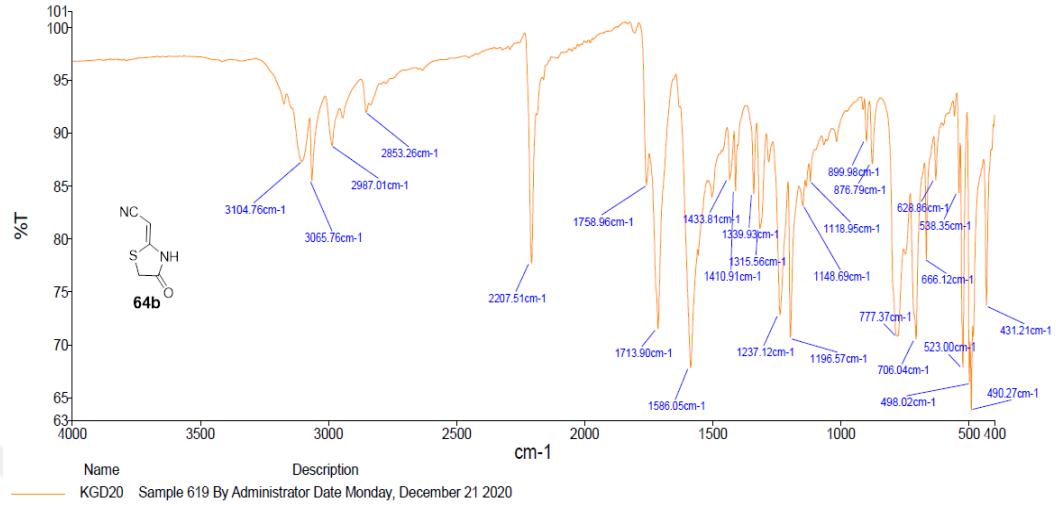

Figure 7.1 IR Spectrum of compound 64b.

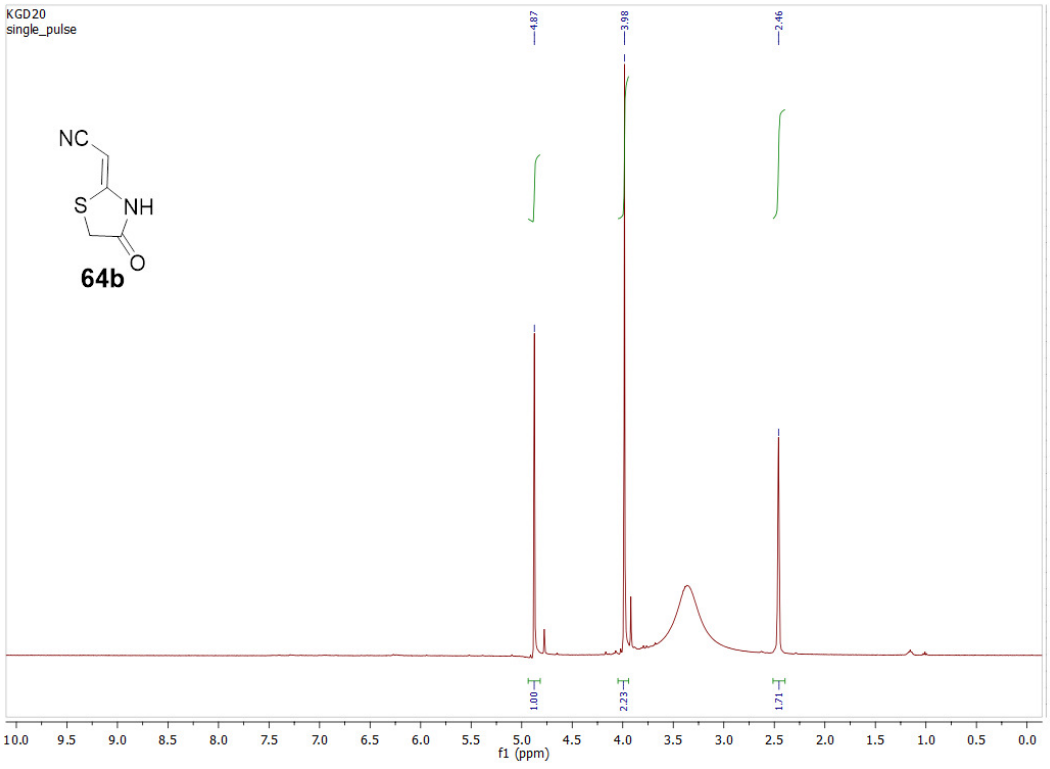

Figure 7.2 ^{1}H-NMR Spectrum of compound 64b.

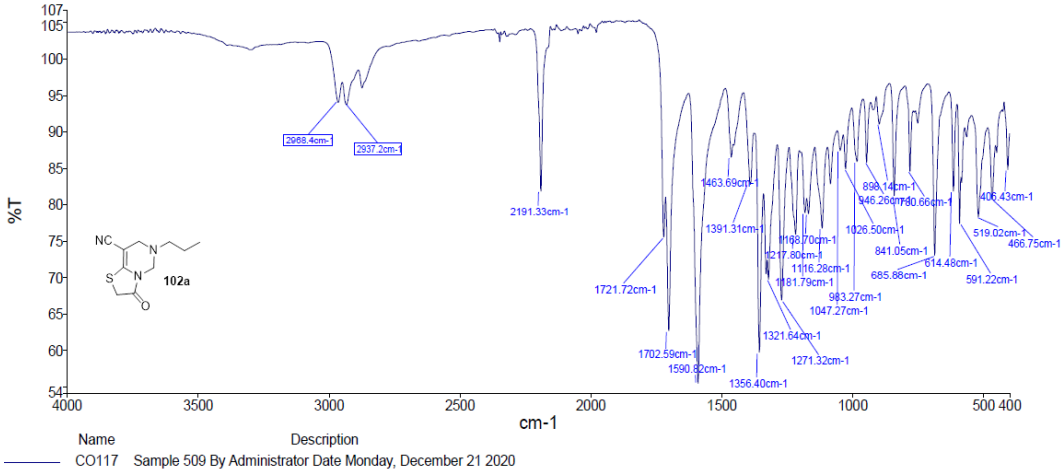

Figure 7.3 IR Spectrum of compound 102a.

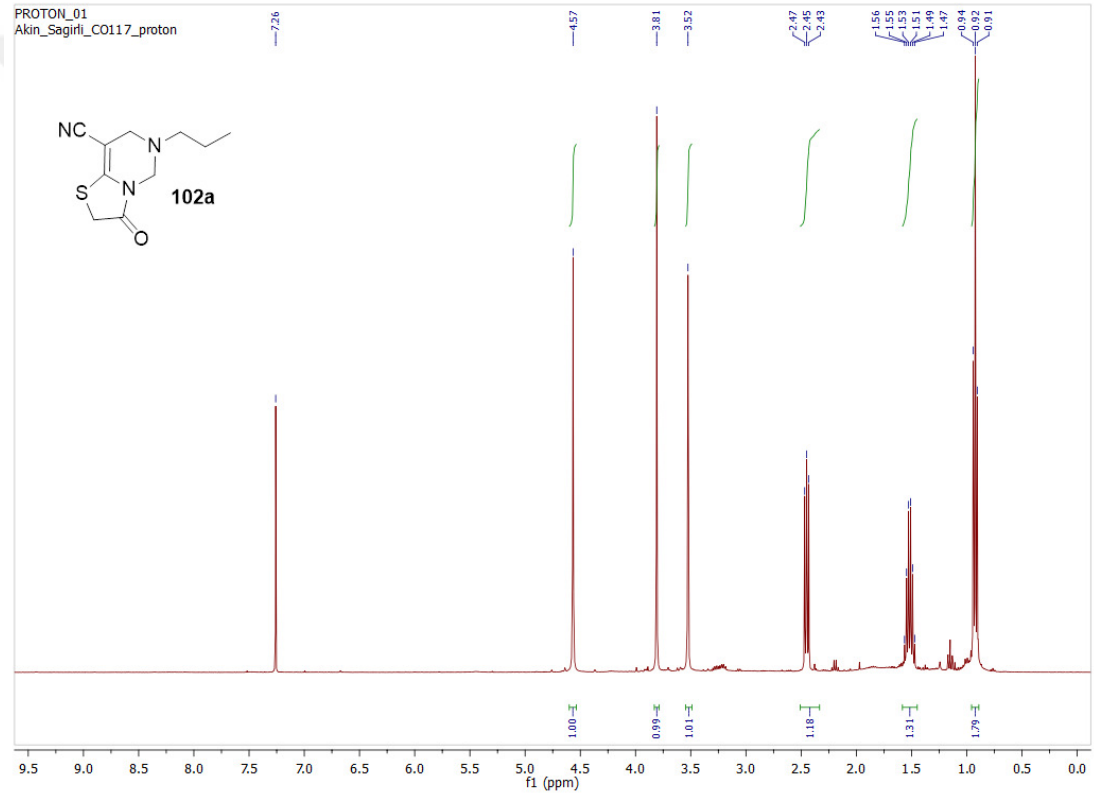

Figure 7.4 ^{1}H-NMR Spectrum of compound 102a.

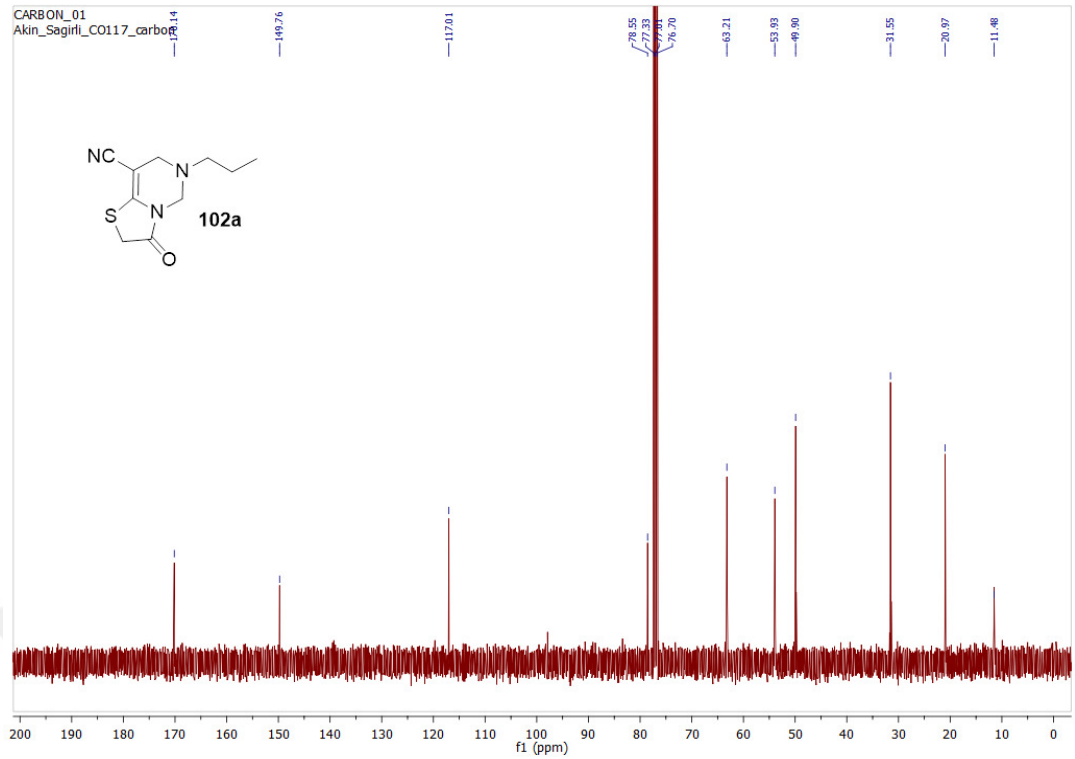

Figure 7.5 ^{13}C-NMR Spectrum of compound 102a.

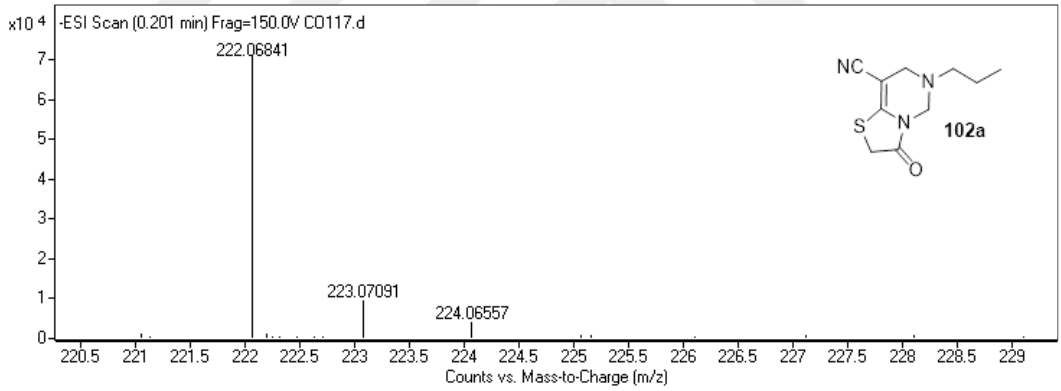

Figure 7.6 HRMS spectrum of compound 102a.

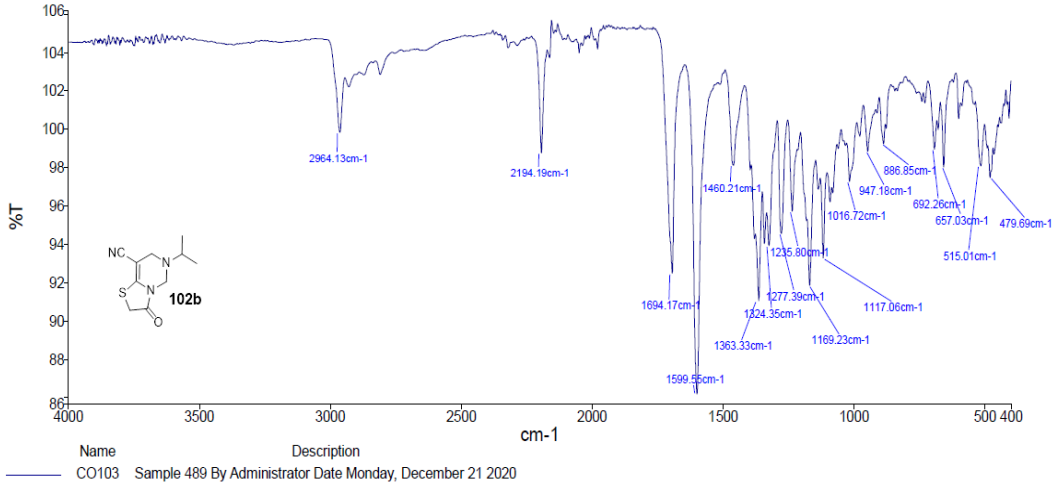

Figure 7.7 IR Spectrum of compound 102b.

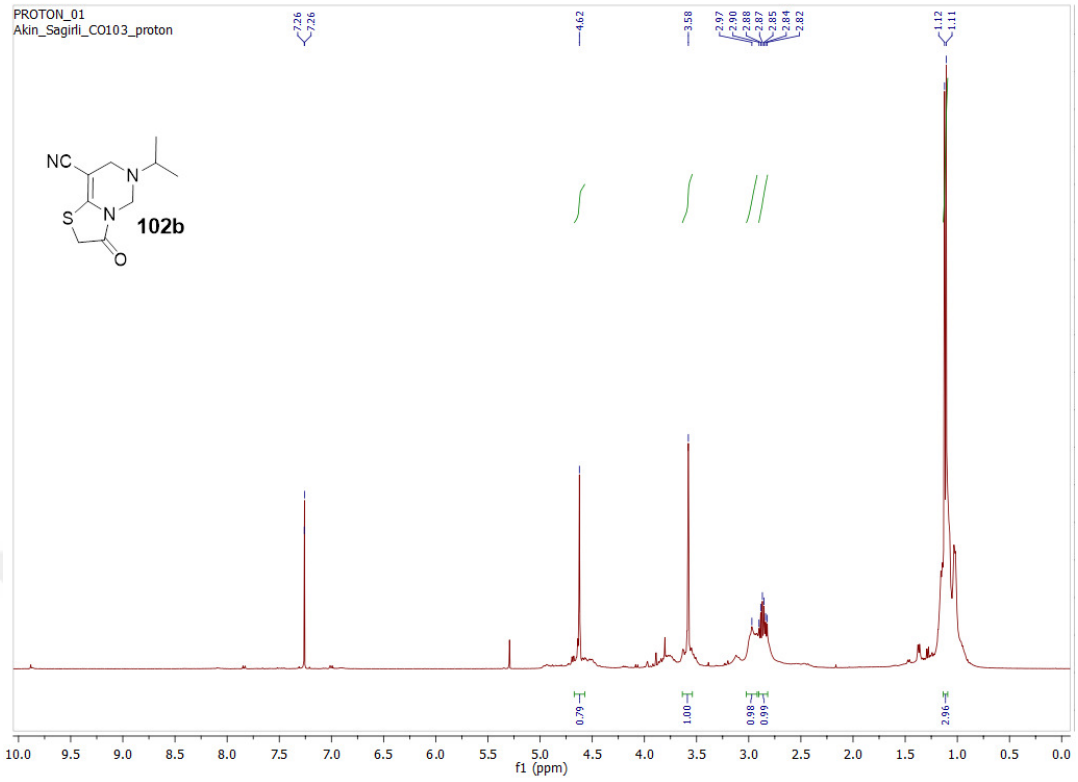

Figure 7.8 ^{1}H-NMR Spectrum of compound 102b.

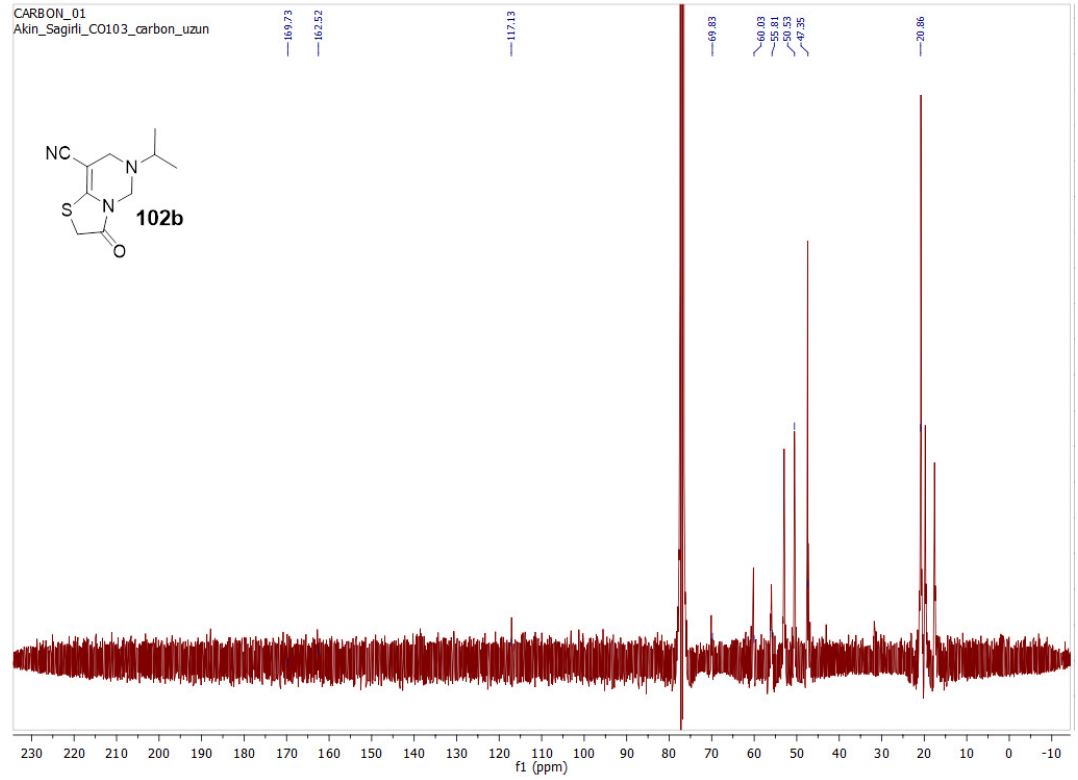

Figure 7.9 ^{13}C-NMR Spectrum of compound 102b.

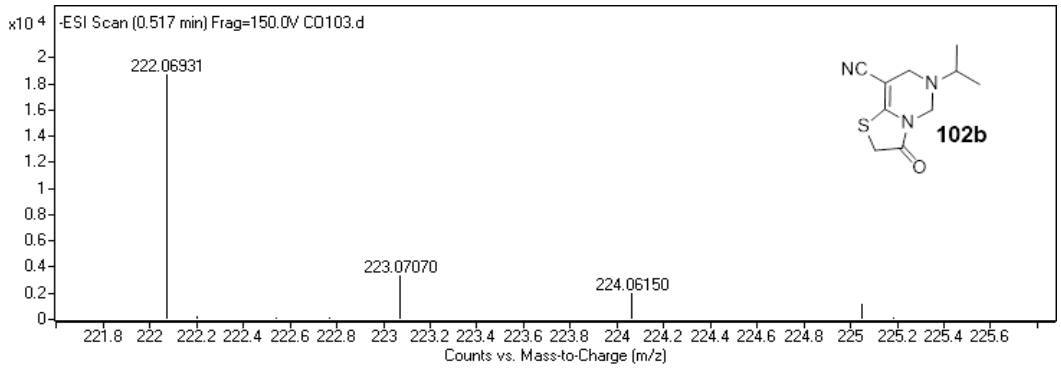

Figure 7.10 HRMS spectrum of compound 102b.

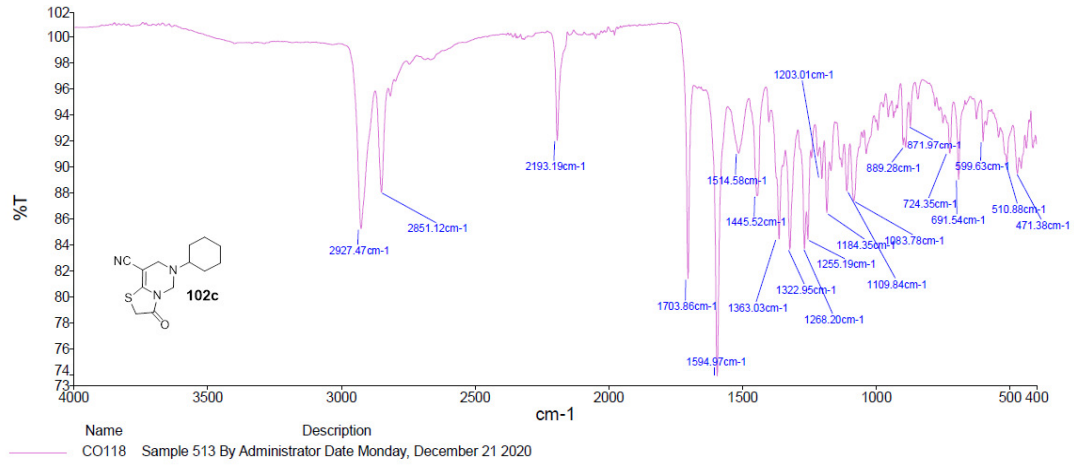

Figure 7.11 IR Spectrum of compound 102c.

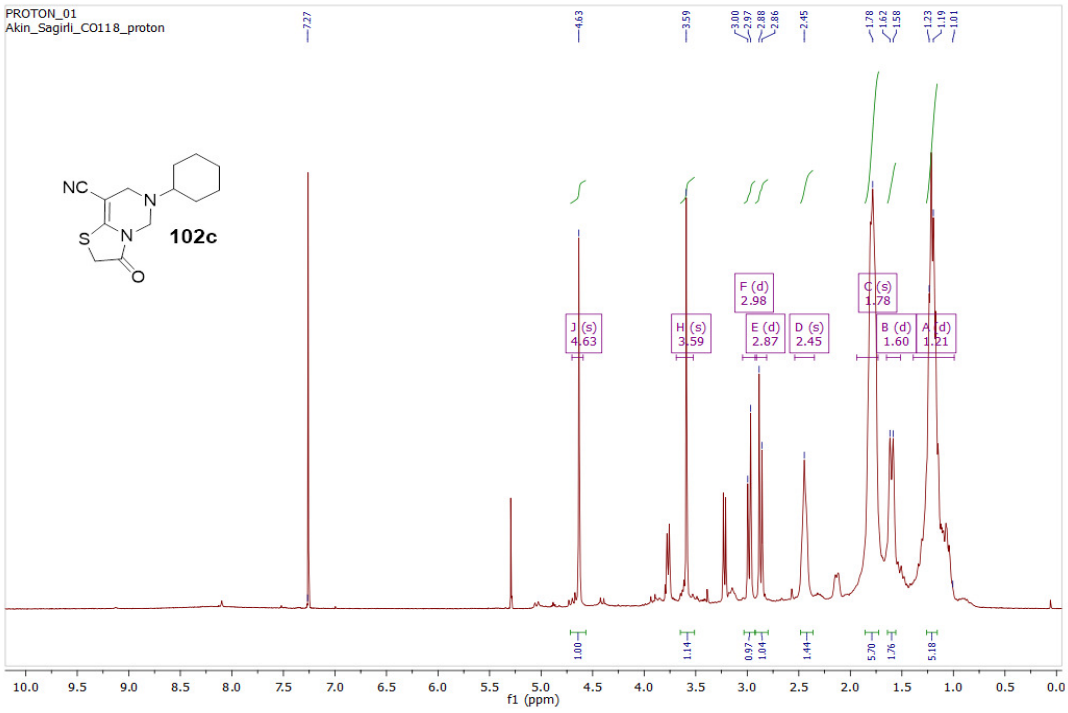

Figure 7.12 ^{1}H-NMR Spectrum of compound 102c.

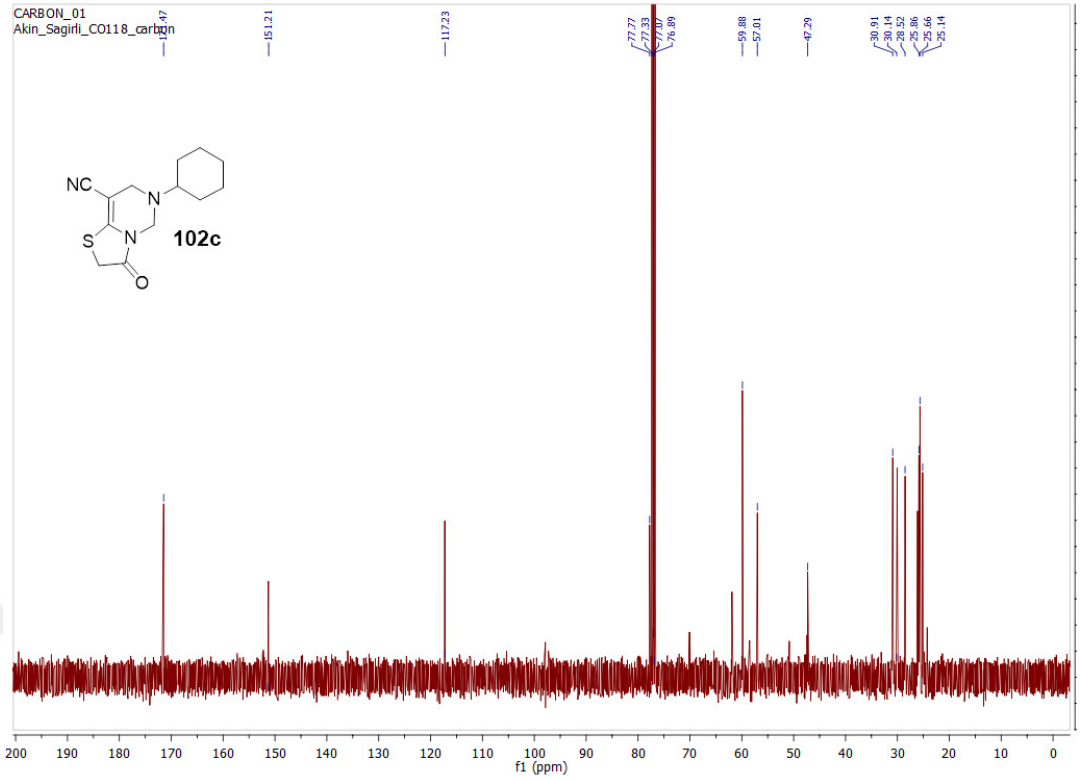

Figure 7.13 ^{13}C-NMR Spectrum of compound 102c.

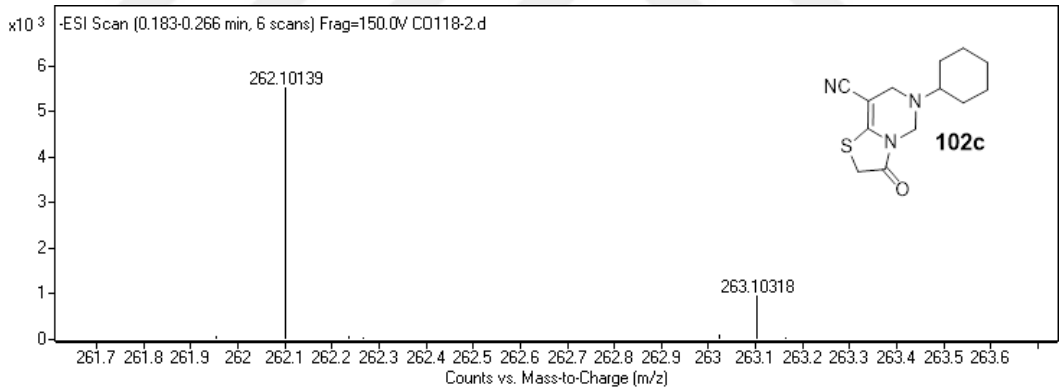

Figure 7.14 HRMS spectrum of compound 102c.

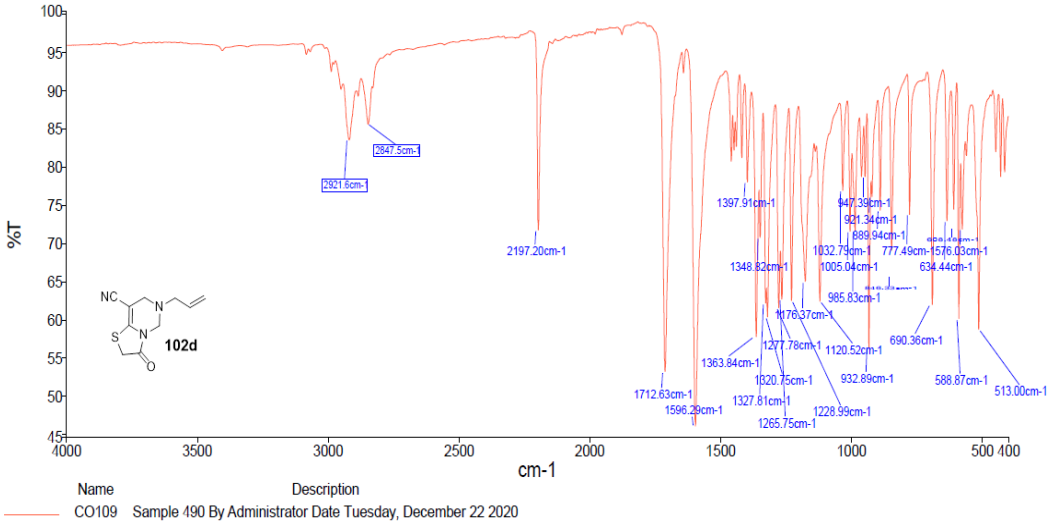

Figure 7.15 IR Spectrum of compound 102d.

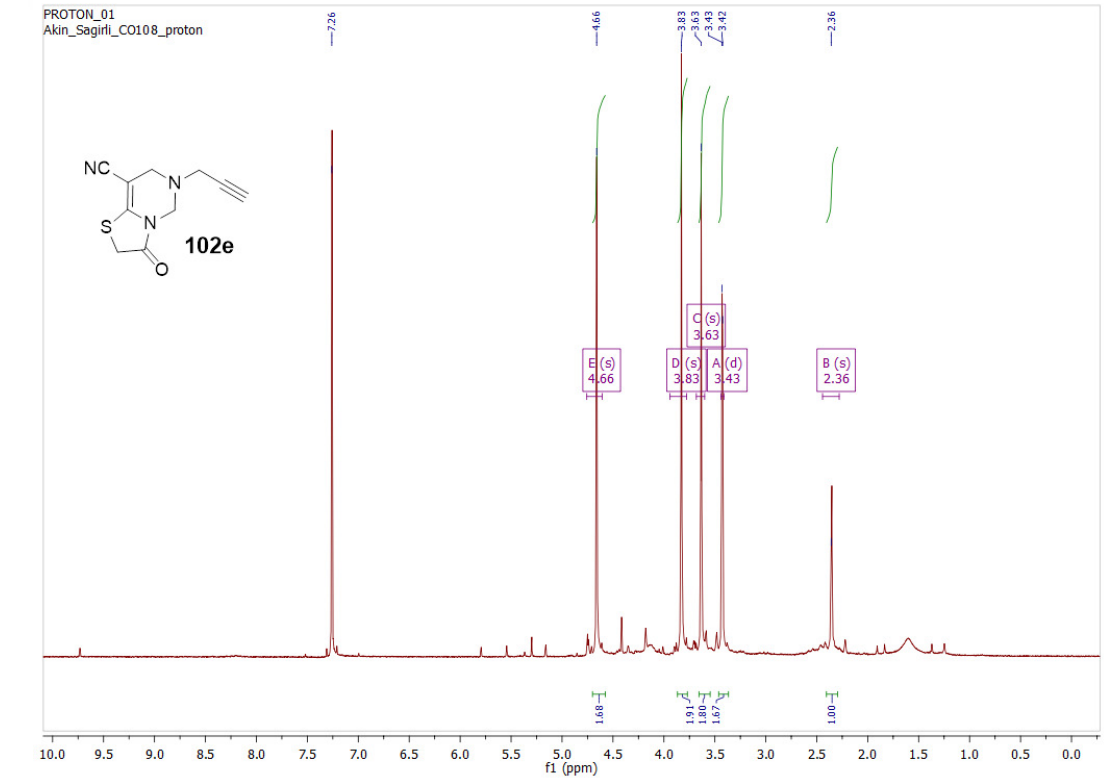

Figure 7.16 ^{1}H-NMR Spectrum of compound 102d.

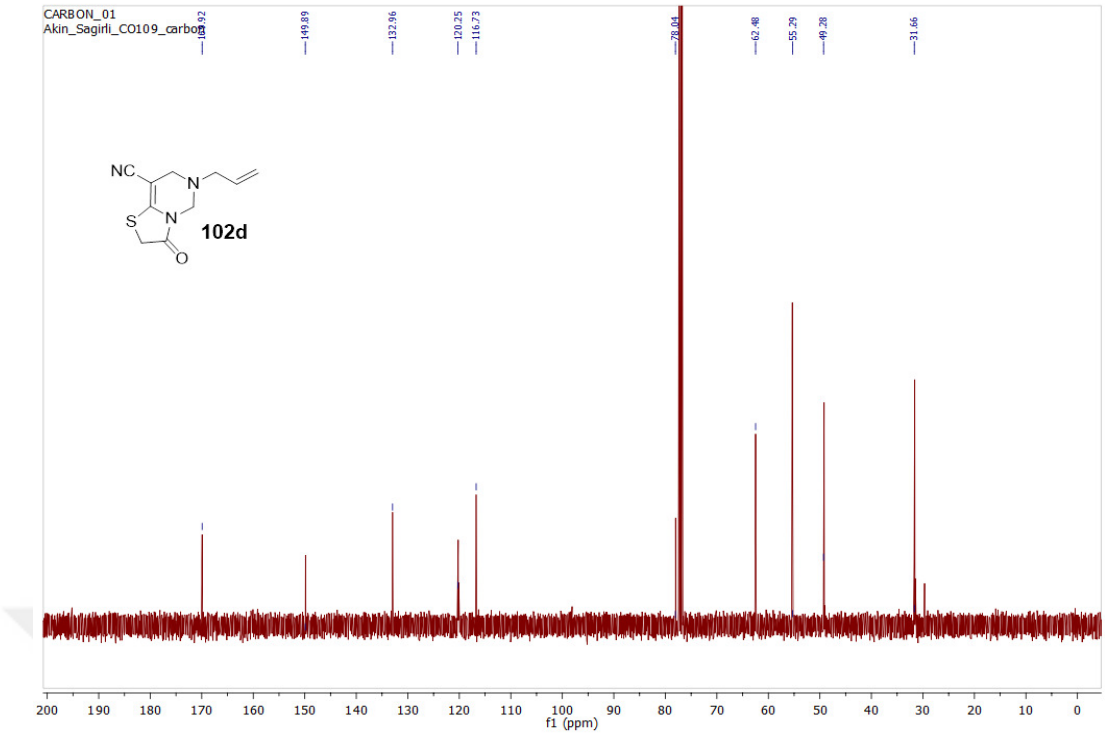

Figure 7.17 ^{13}C-NMR Spectrum of compound 102d.

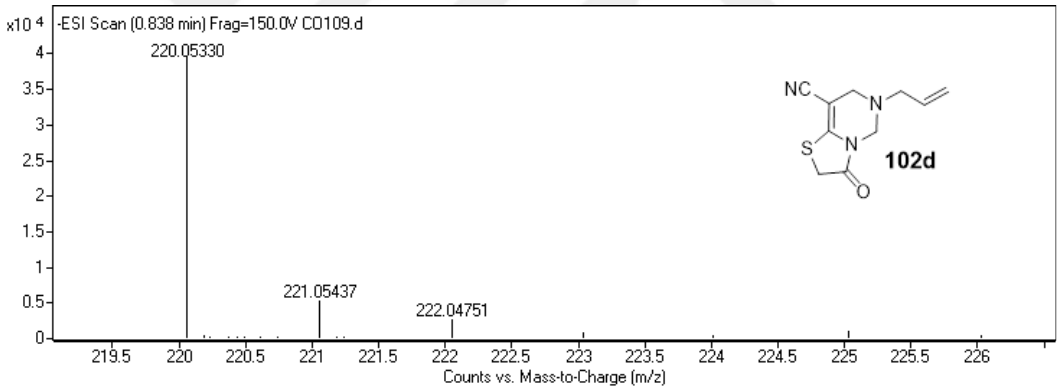

Figure 7.18 HRMS spectrum of compound 102d.

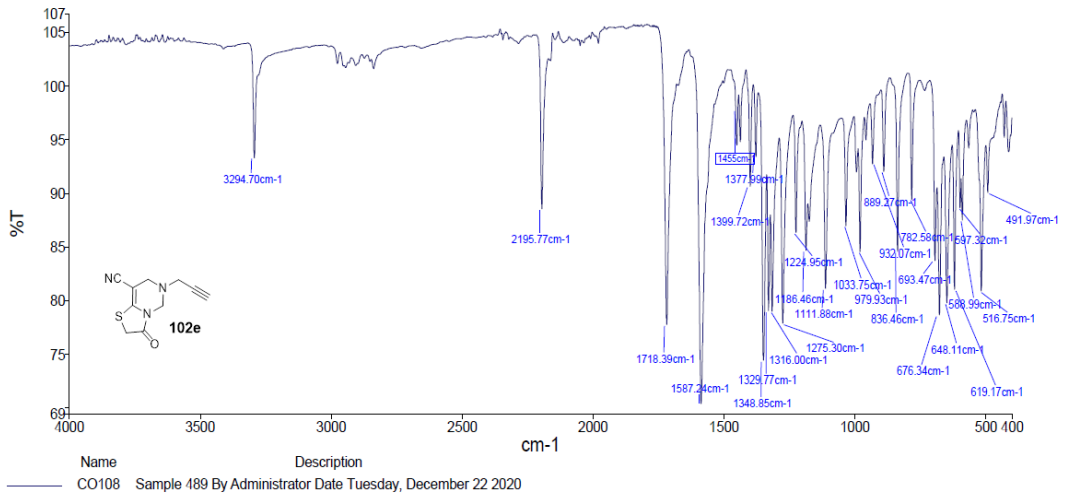

Figure 7.19 IR Spectrum of compound 102e.

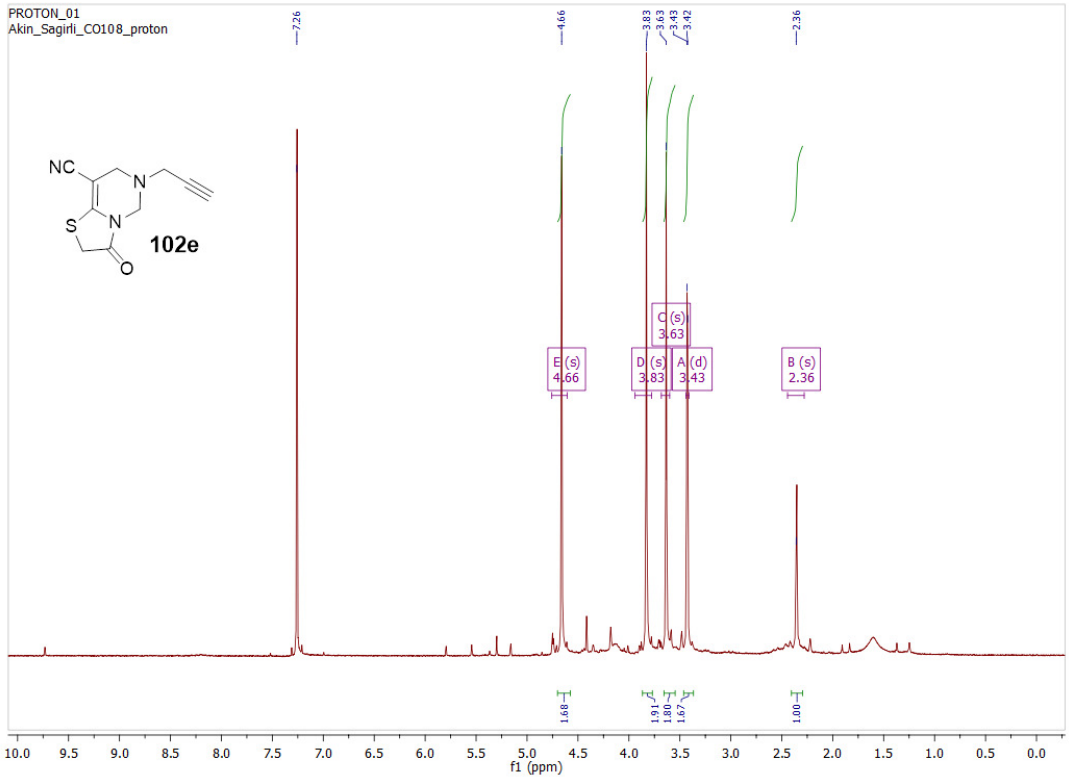

Figure 7.20 ^{1}H-NMR Spectrum of compound 102e.

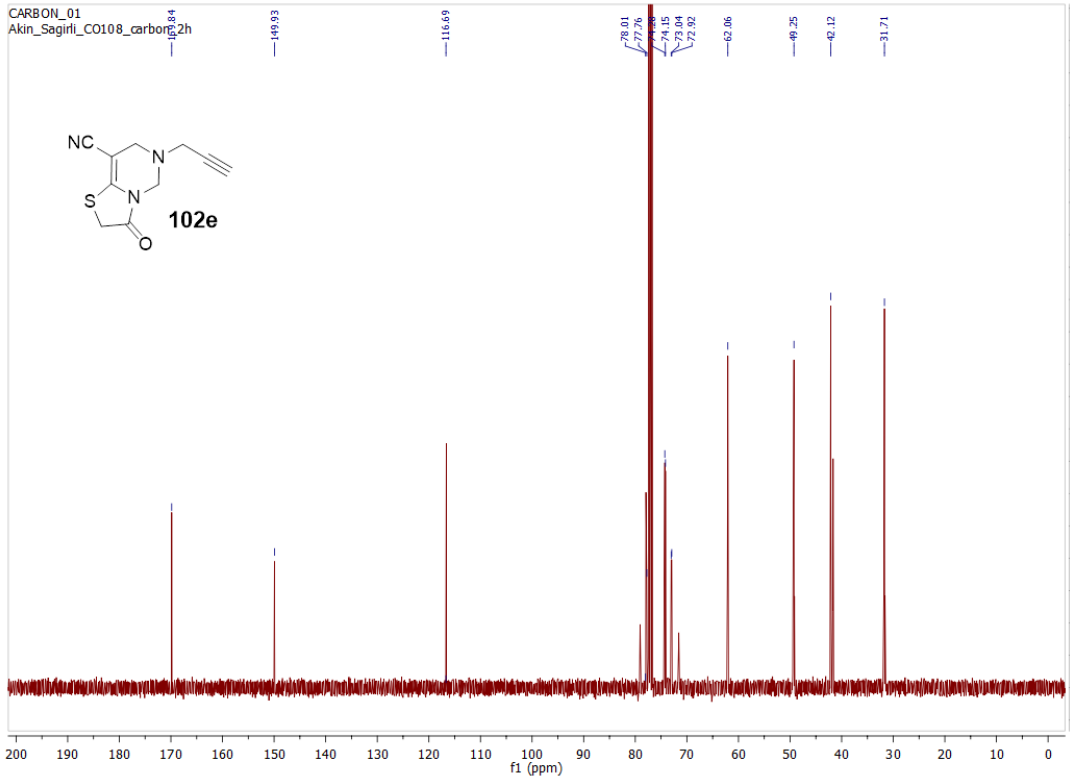

Figure 7.21 ^{13}C-NMR Spectrum of compound 102e.

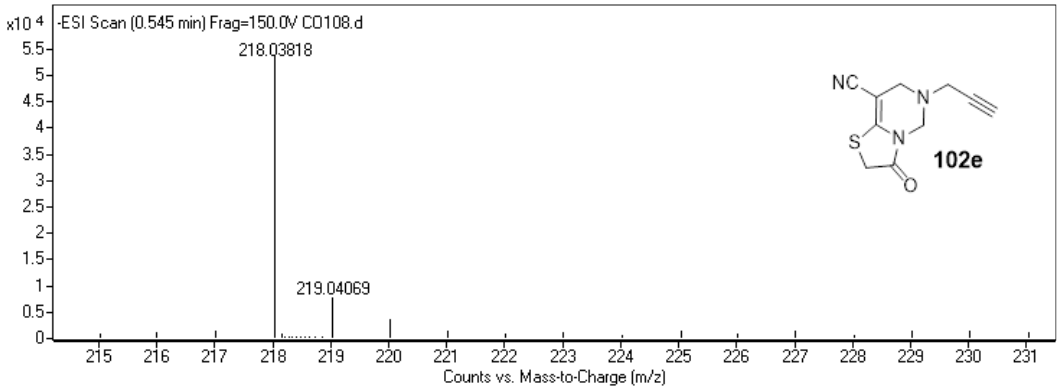

Figure 7.22 HRMS spectrum of compound 102e.

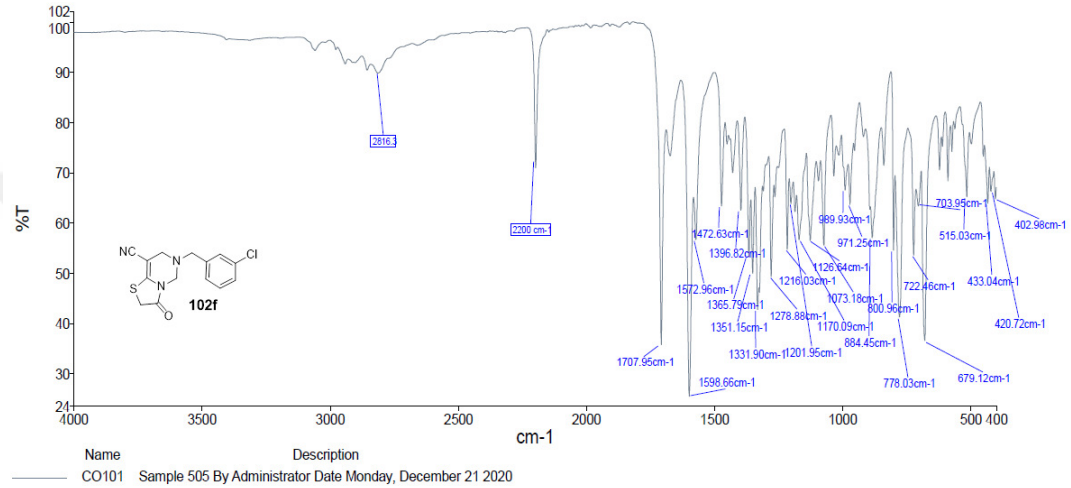

Figure 7.23 IR Spectrum of compound 102f.

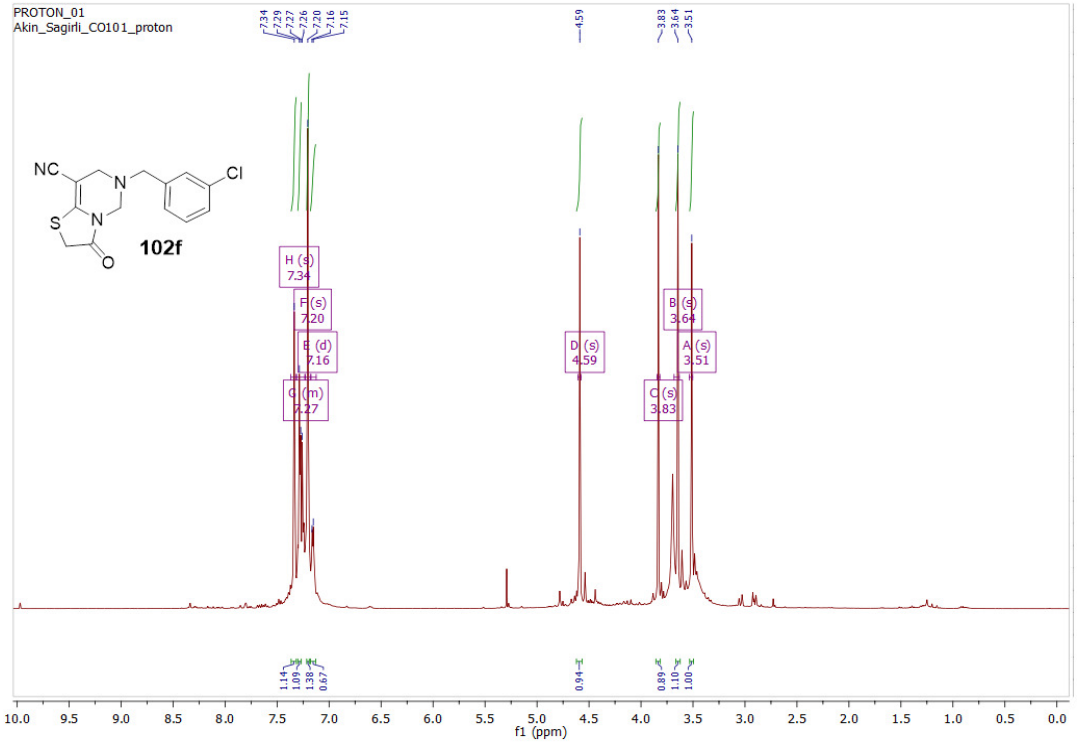

Figure 7.24 ^{1}H-NMR Spectrum of compound 102f.

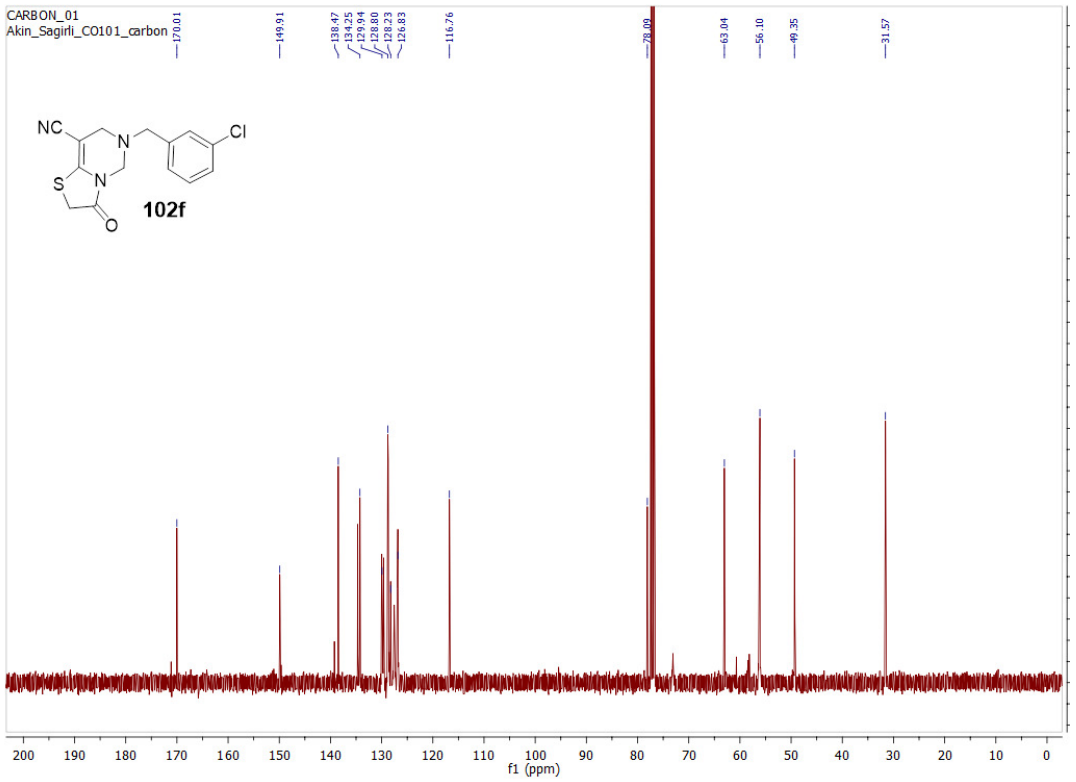

Figure 7.25 ^{13}C-NMR Spectrum of compound 102f.

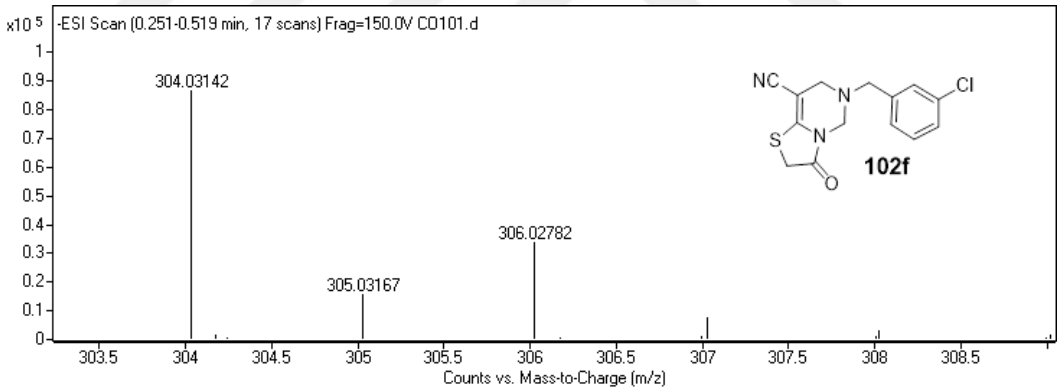

Figure 7.26 HRMS spectrum of compound 102f.

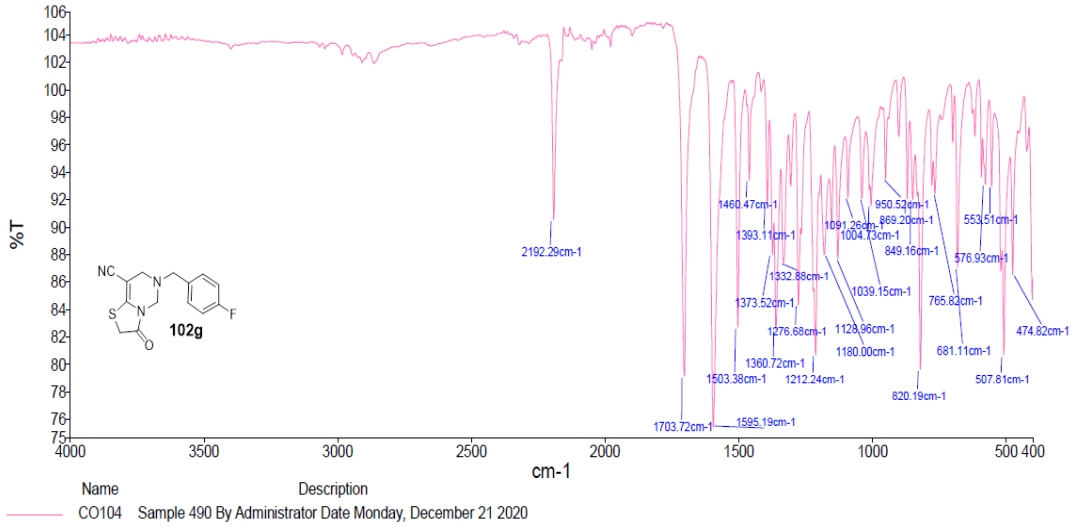

Figure 7.27 IR Spectrum of compound 102g.

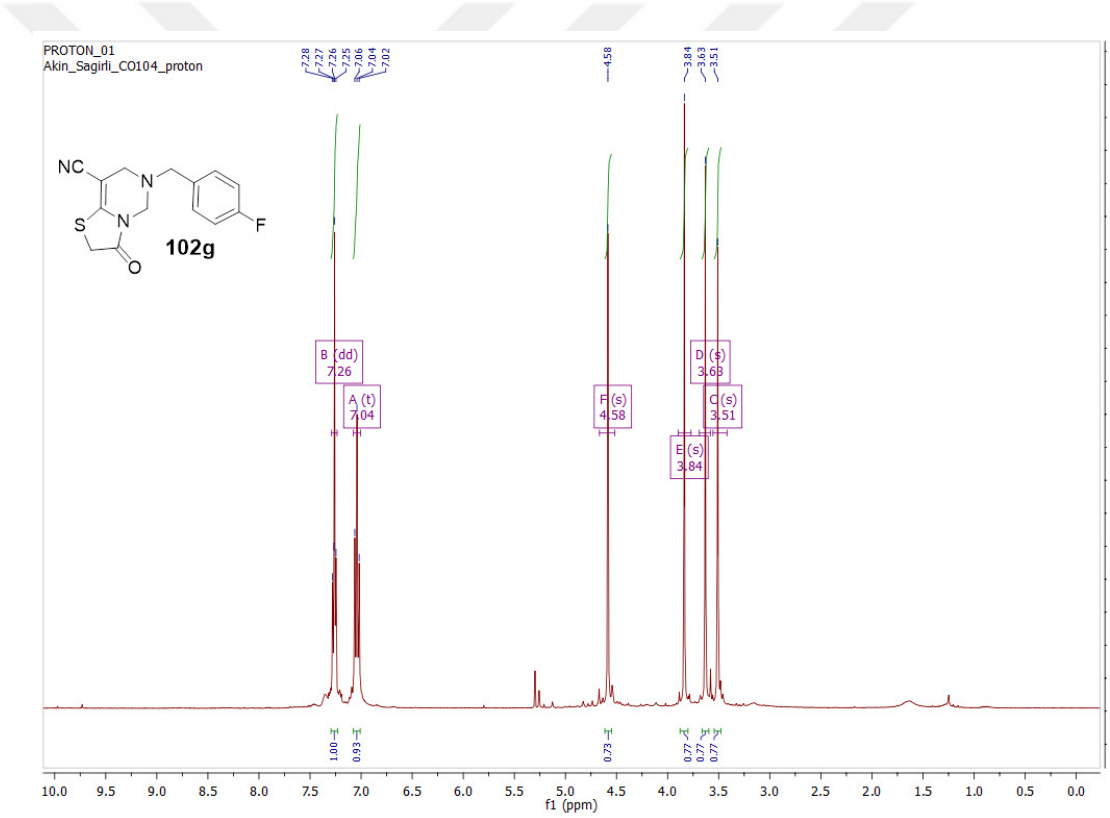

Figure 7.28 ^{1}H-NMR Spectrum of compound 102g.

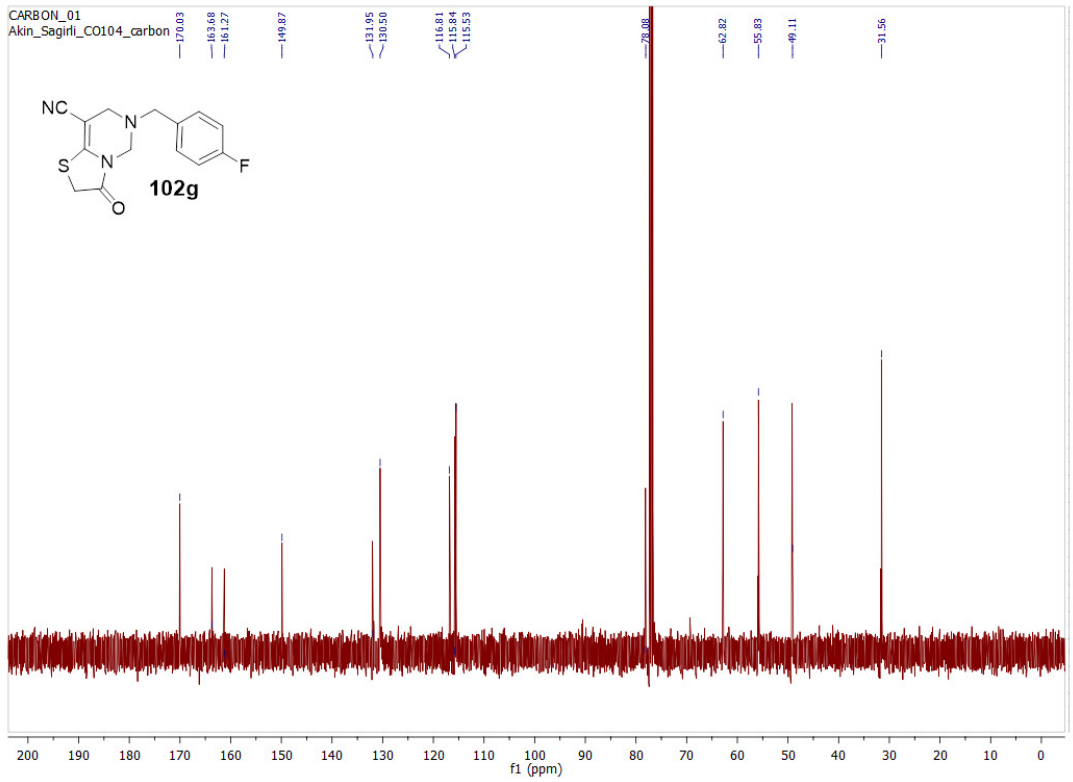

Figure 7.29 ^{13}C-NMR Spectrum of compound 102g.

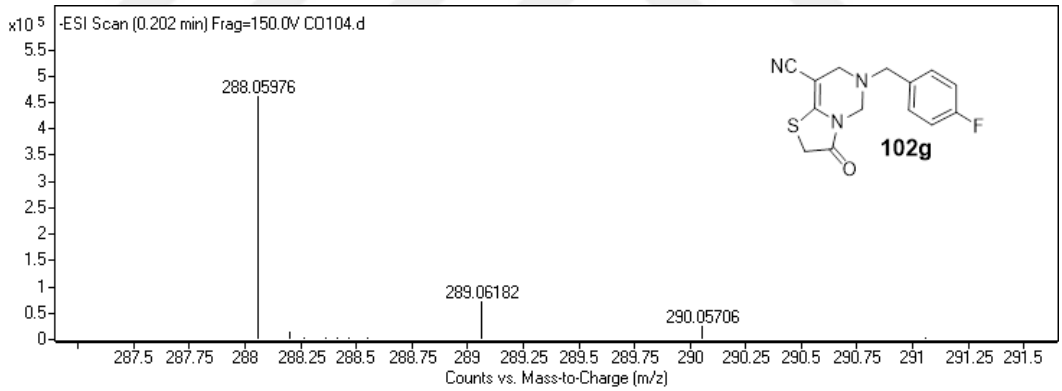

Figure 7.30 HRMS spectrum of compound 102g.

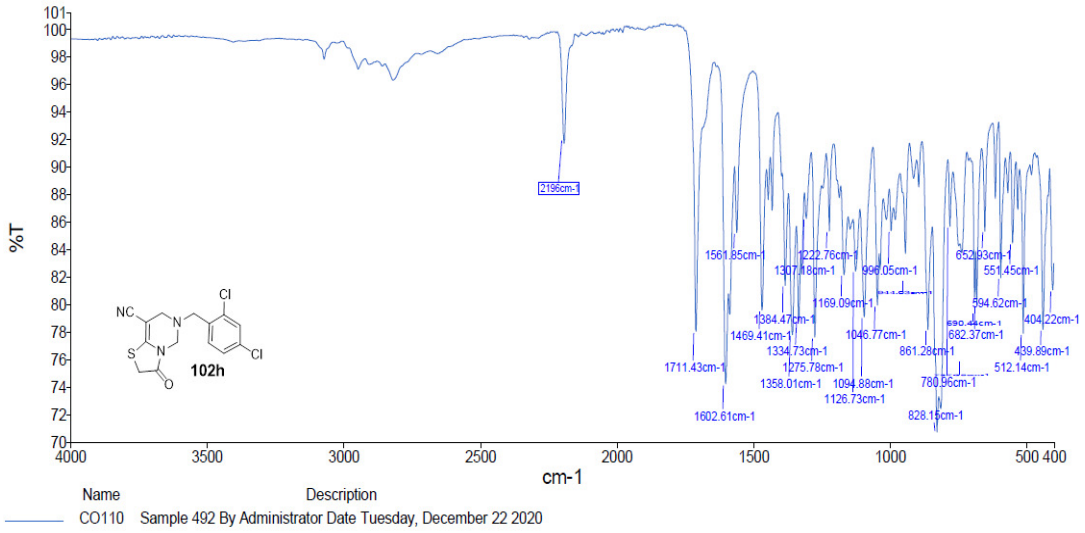

Figure 7.31 IR Spectrum of compound 102h.

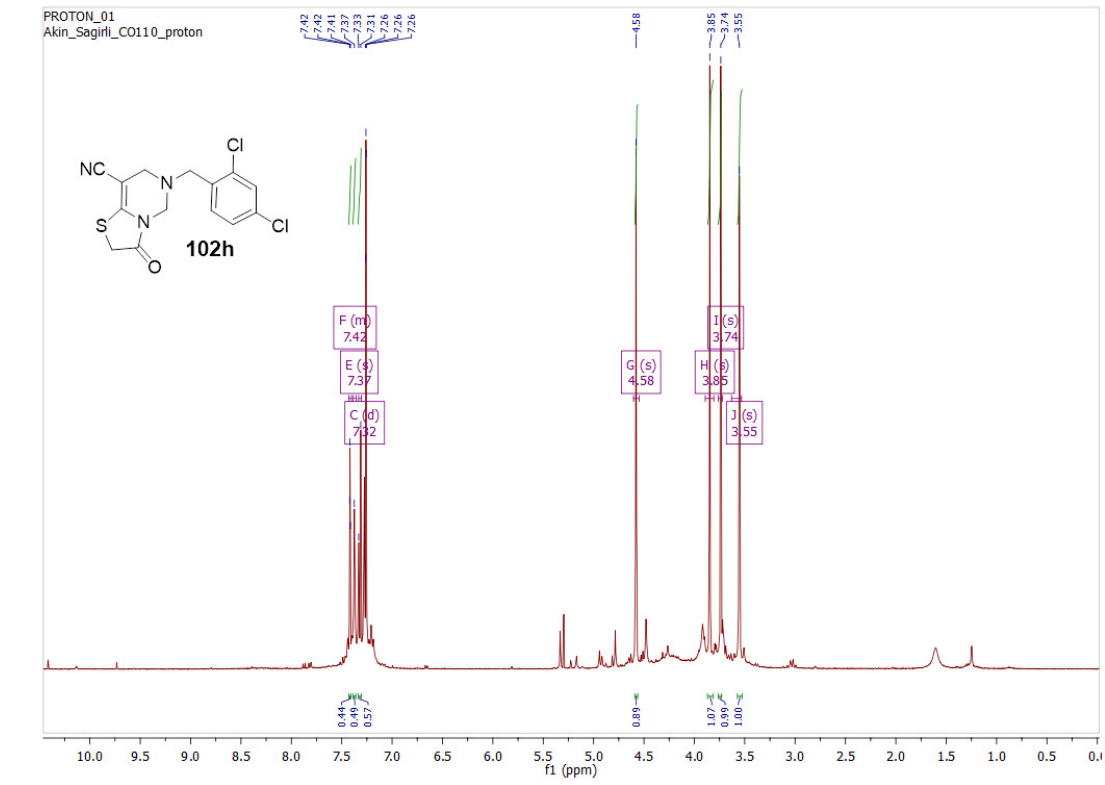

Figure 7.32 ^{1}H-NMR Spectrum of compound 102h.

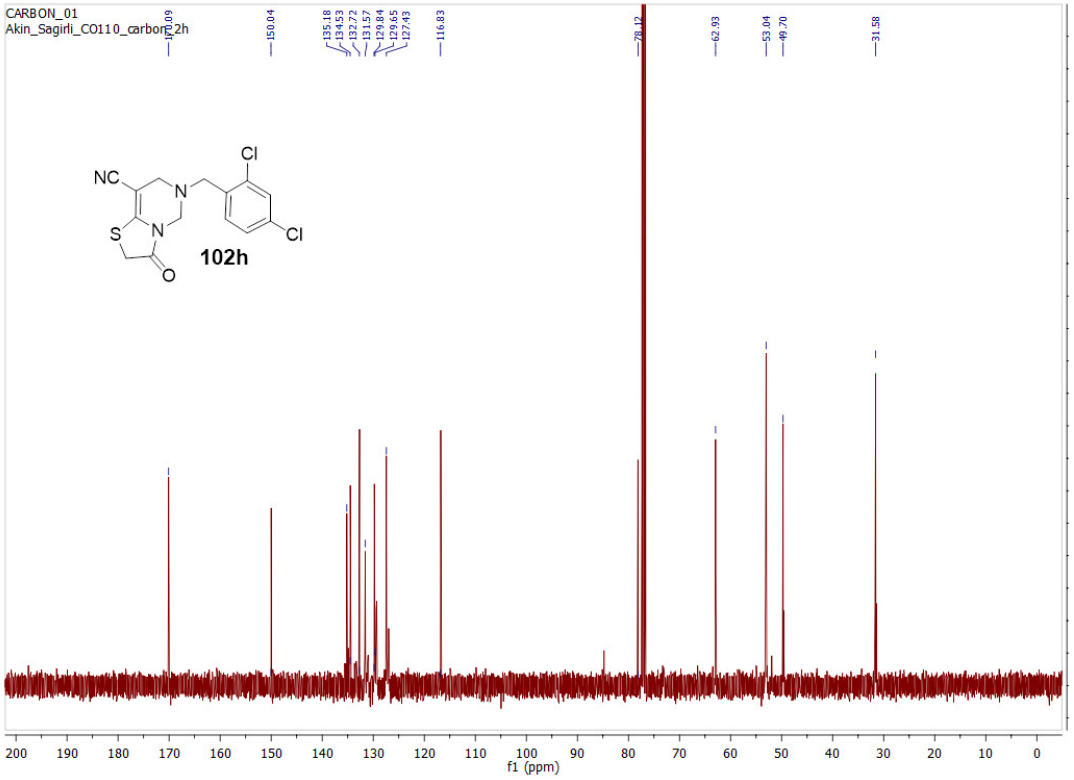

Figure 7.33 ^{13}C-NMR Spectrum of compound 102h.

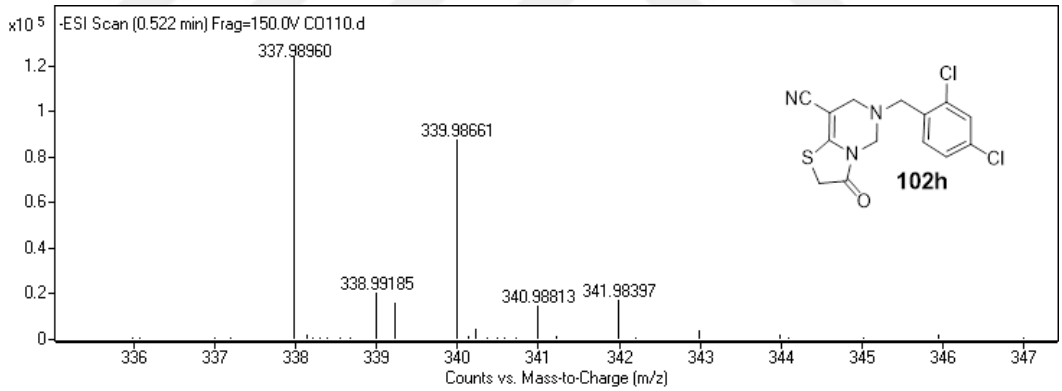

Figure 7.34 HRMS spectrum of compound 102h.

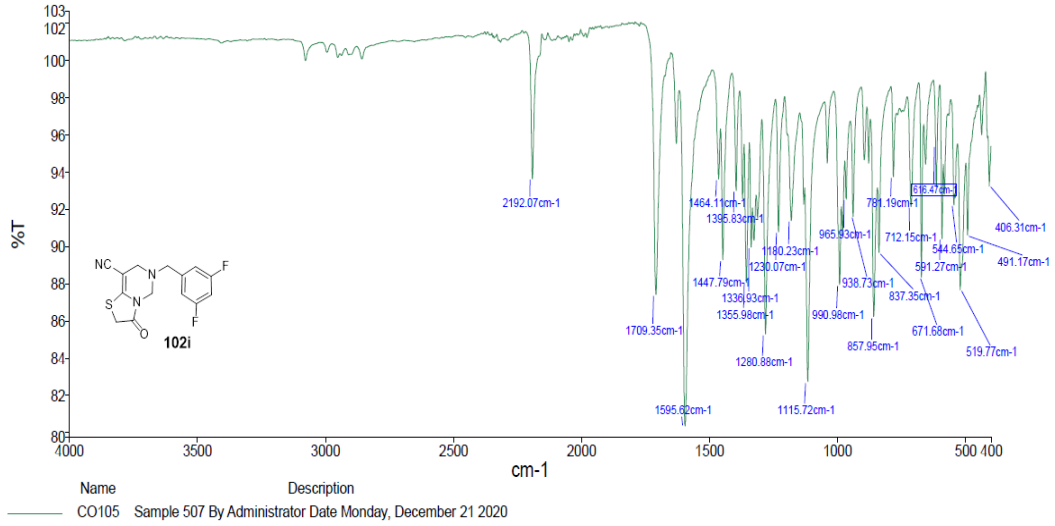

Figure 7.35 IR Spectrum of compound 102i.

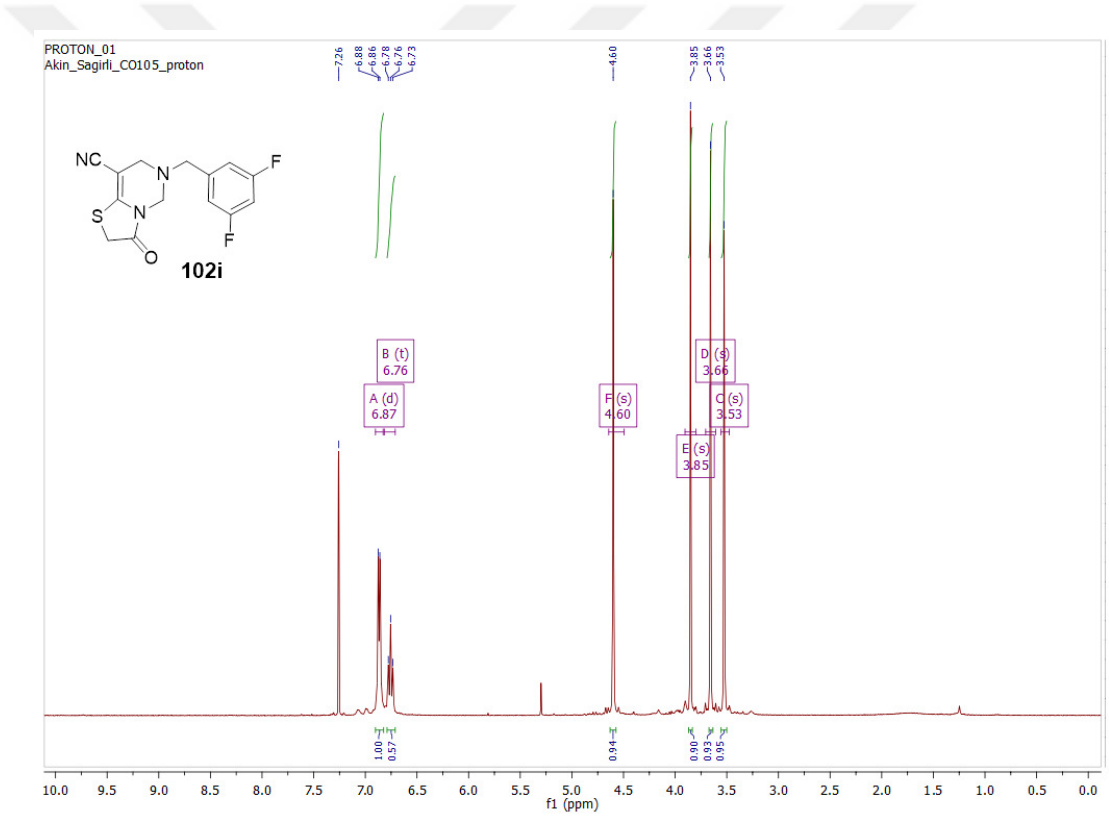

Figure 7.36 ^{1}H-NMR Spectrum of compound 102i.

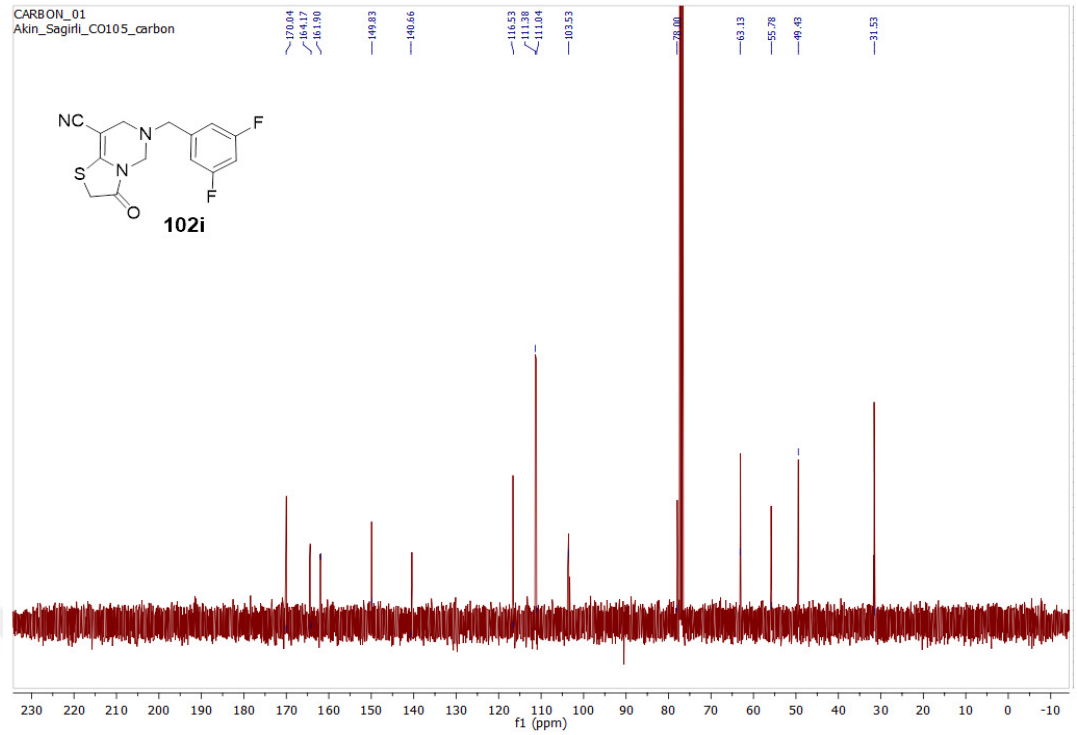

Figure 7.37 ^{13}C-NMR Spectrum of compound 102i.

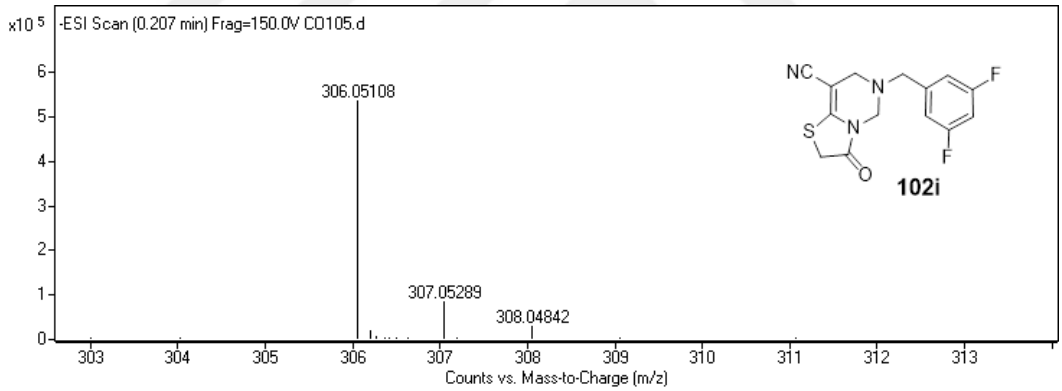

Figure 7.38 HRMS spectrum of compound 102i.

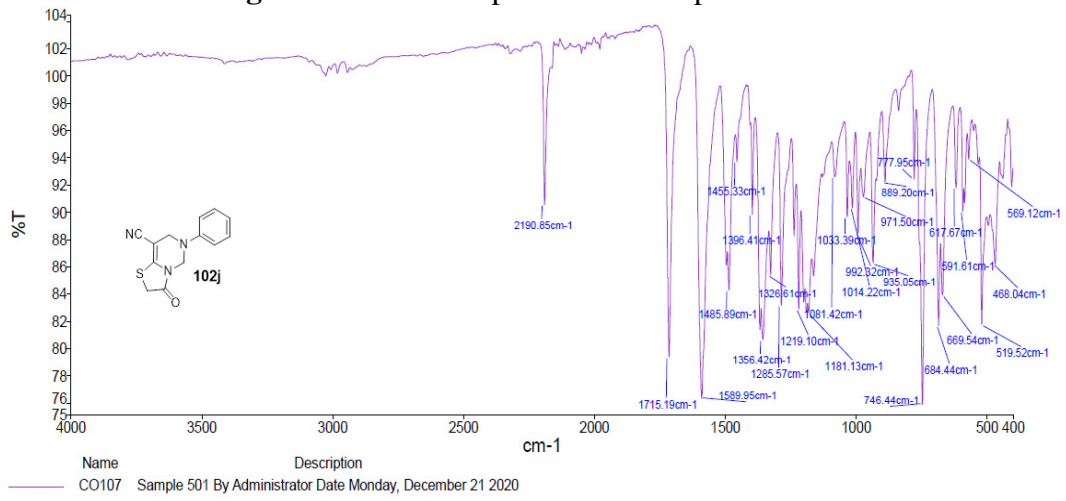

Figure 7.39 IR Spectrum of compound 102j.

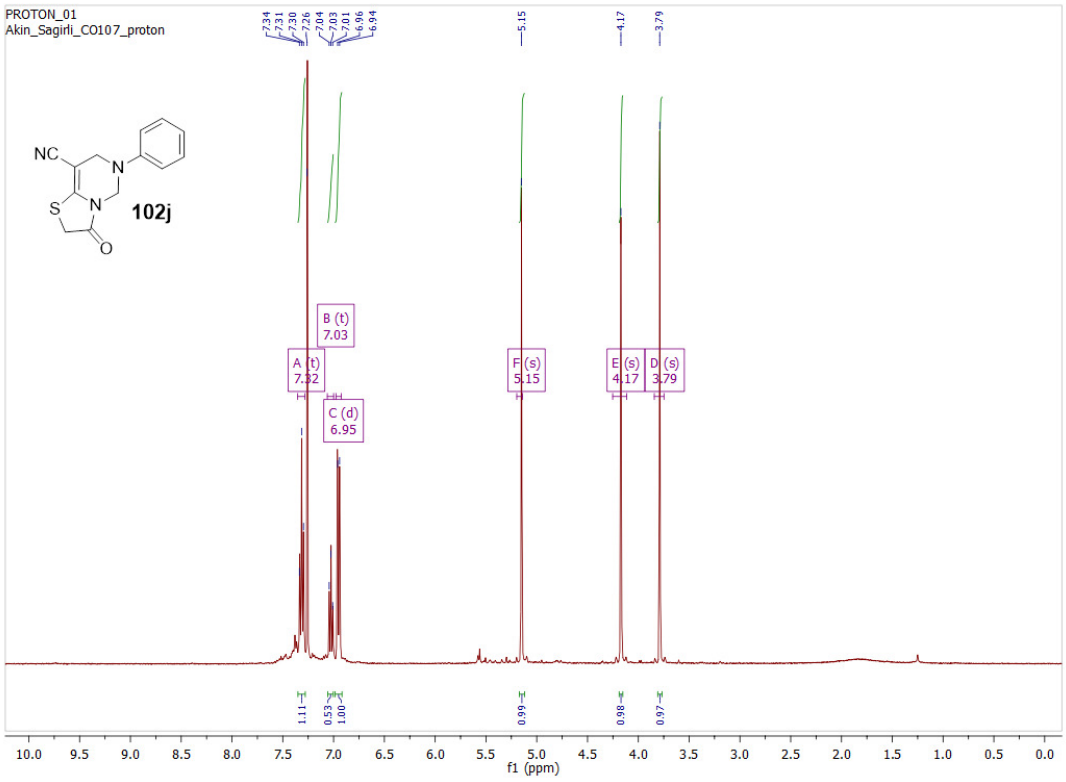

Figure 7.40 ^{1}H-NMR Spectrum of compound 102j.

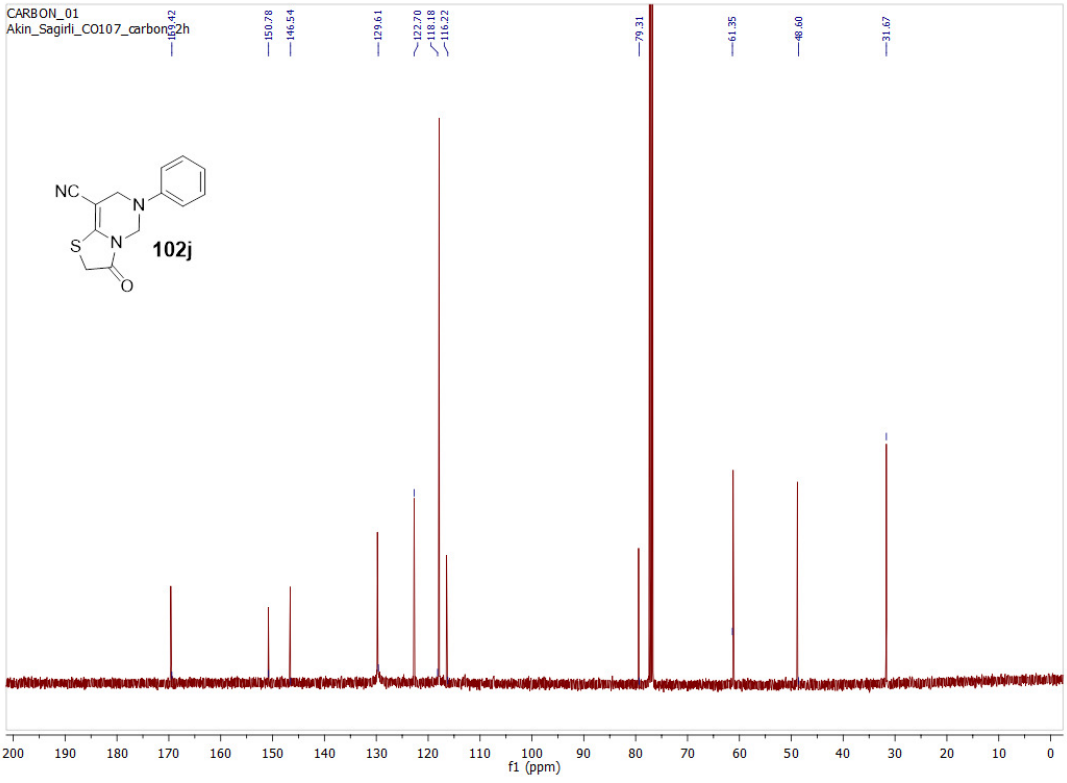

Figure 7.41 ^{13}C-NMR Spectrum of compound 102j.

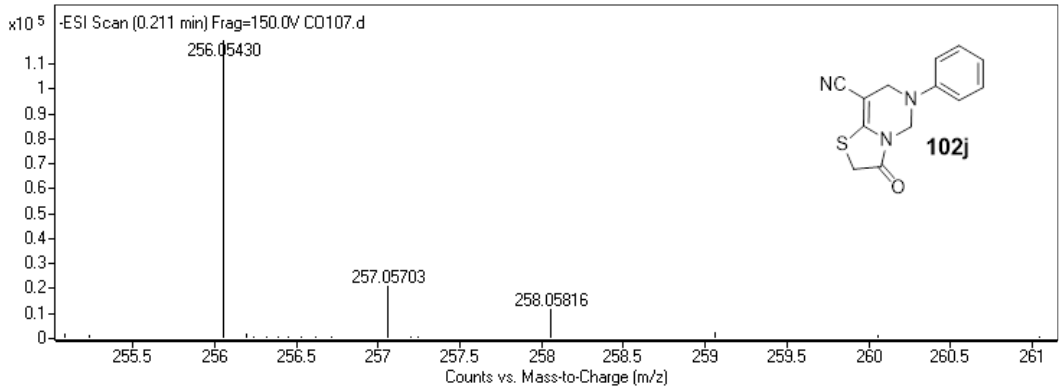

Figure 7.42 HRMS spectrum of compound 102j.

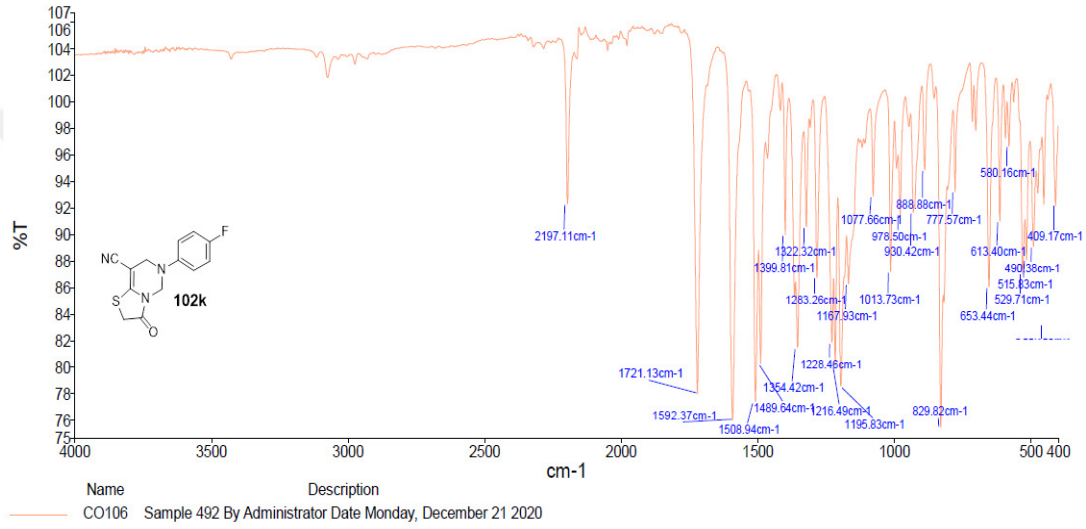

Figure 7.43 IR Spectrum of compound 102k.

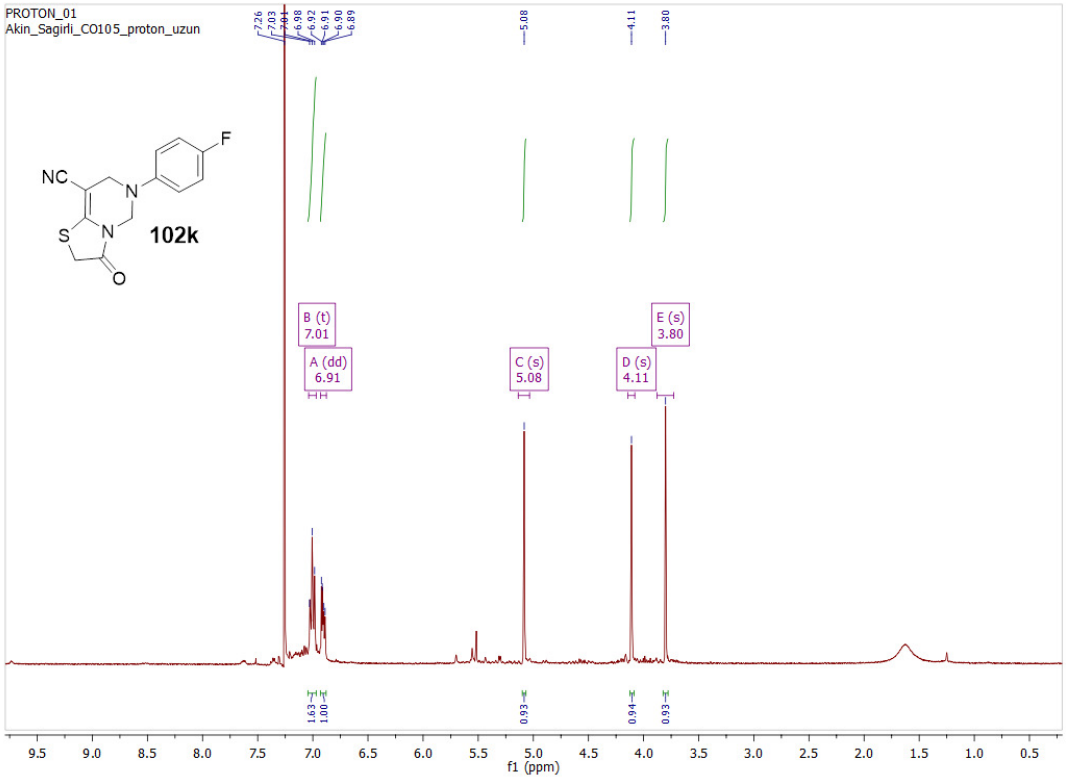

Figure 7.44 ^{1}H-NMR Spectrum of compound 102k.

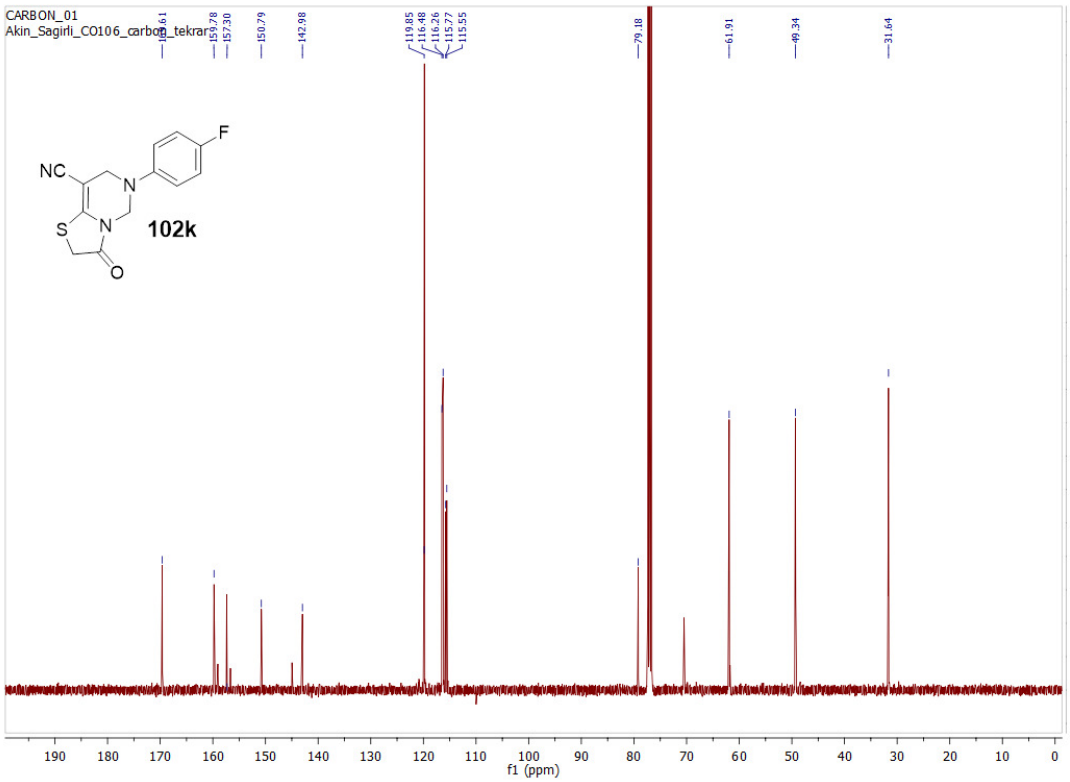

Figure 7.45 ^{13}C-NMR Spectrum of compound 102k.

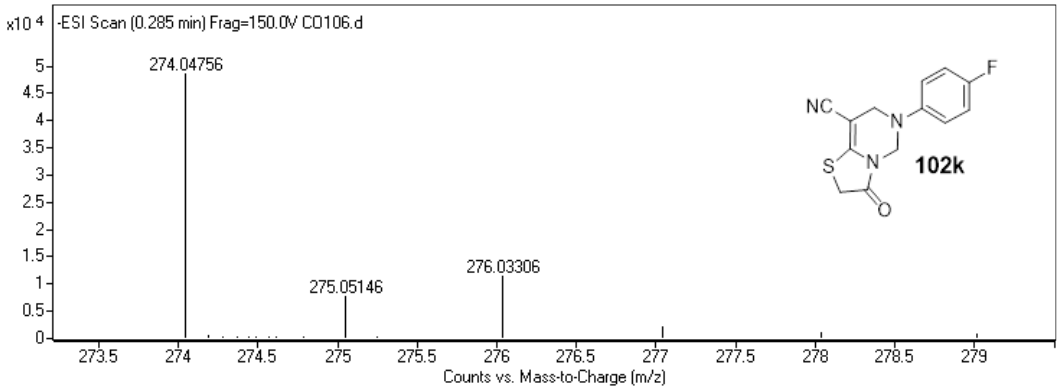

Figure 7.46 HRMS spectrum of compound 102k.

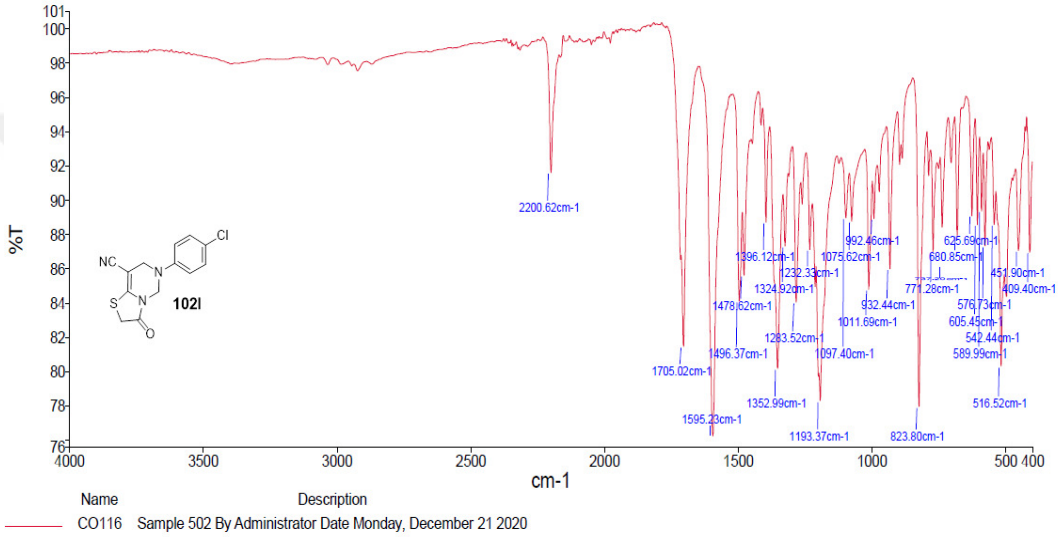

Figure 7.47 IR Spectrum of compound 102l.

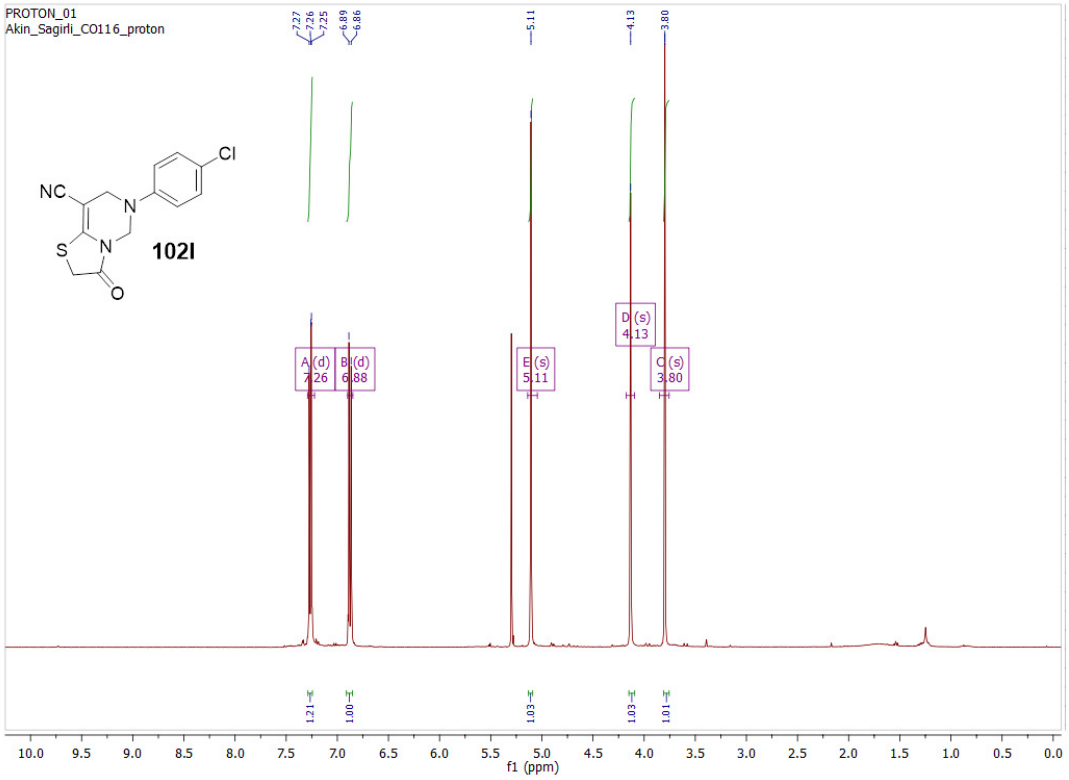

Figure 7.48 ^{1}H-NMR Spectrum of compound 102l.

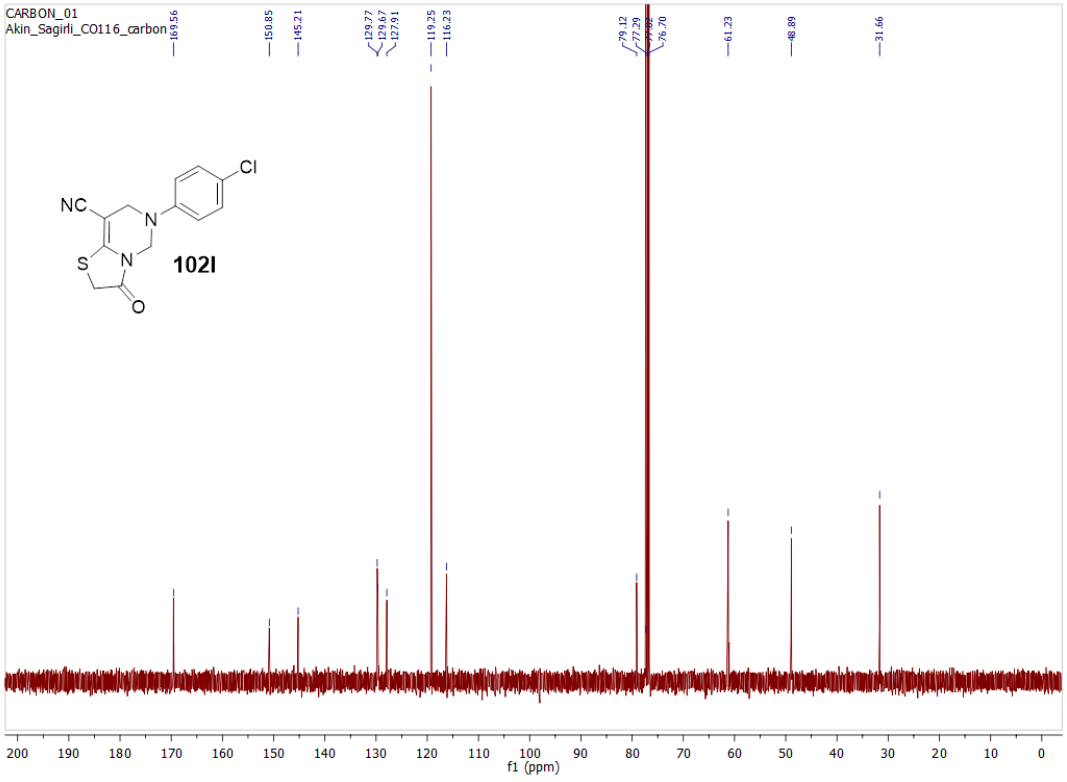

Figure 7.49 ^{13}C-NMR Spectrum of compound 102l.

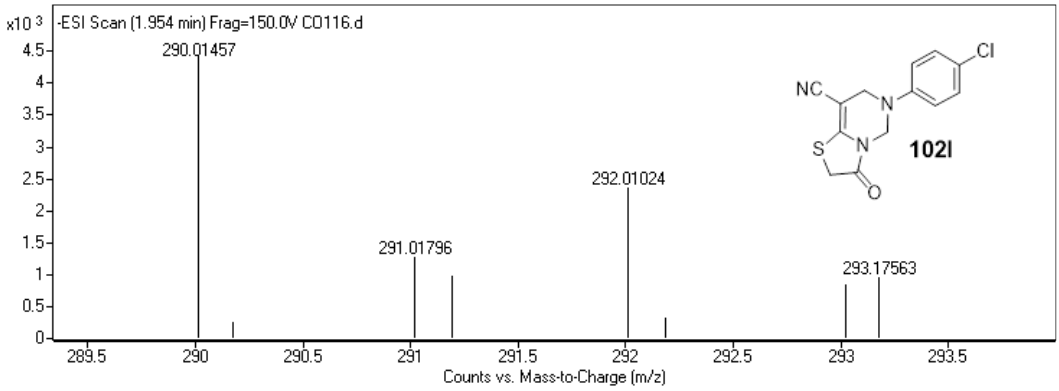

Figure 7.50 HRMS spectrum of compound 102l.

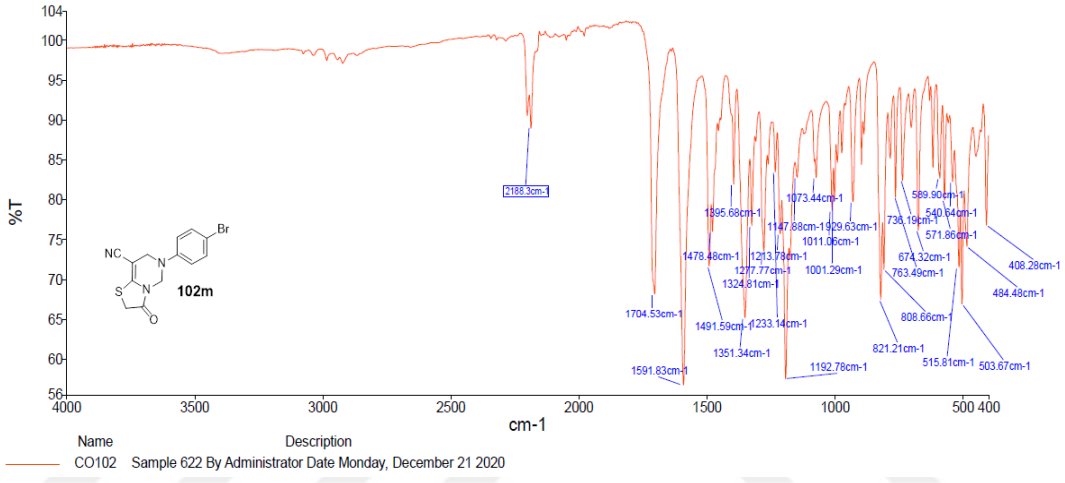

Figure 7.51 IR Spectrum of compound 102m.

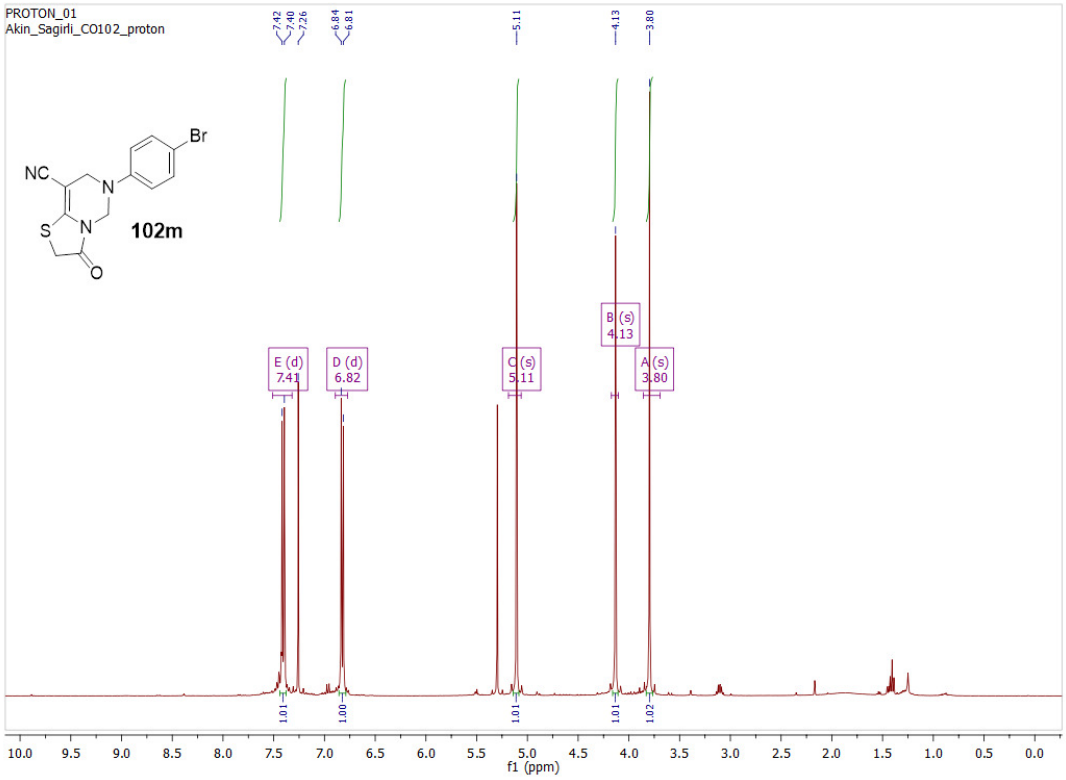

Figure 7.52 ^{1}H-NMR Spectrum of compound 102m.

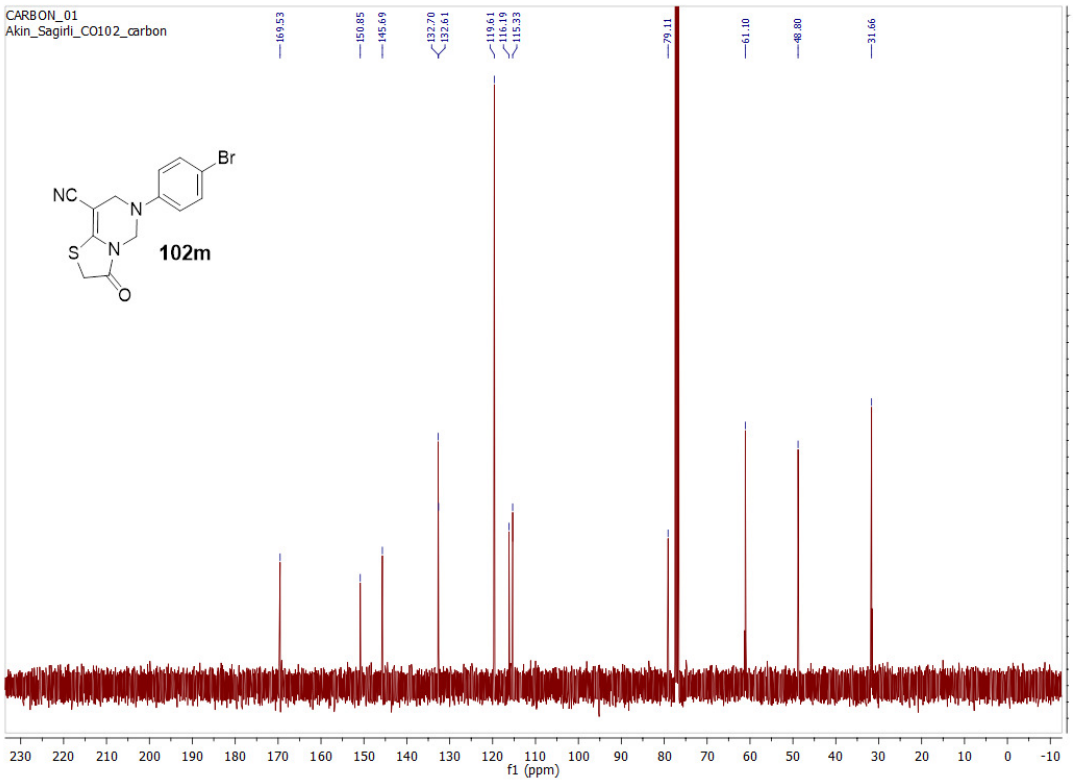

Figure 7.53 ^{13}C-NMR Spectrum of compound 102m.

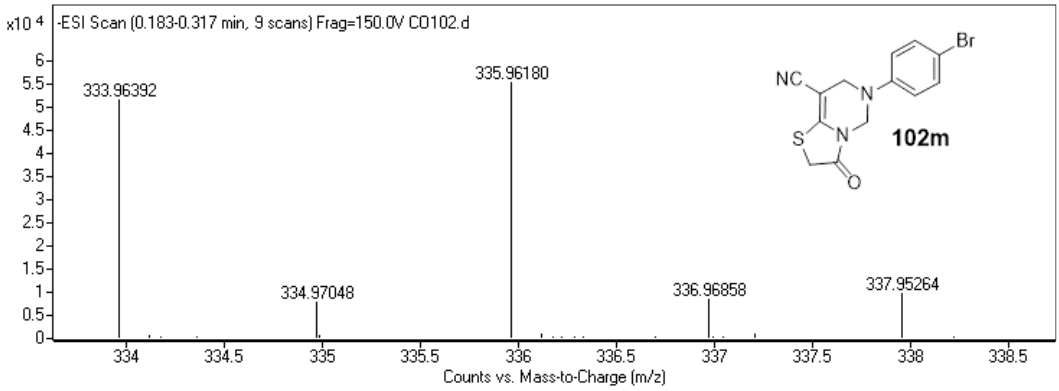

Figure 7.54 HRMS spectrum of compound 102m.

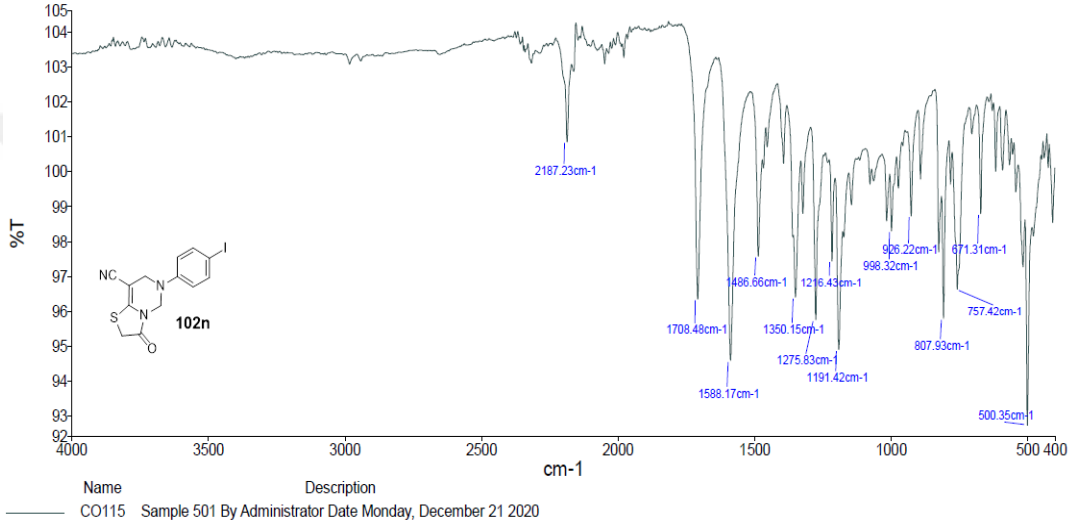

Figure 7.55 IR Spectrum of compound 102n.

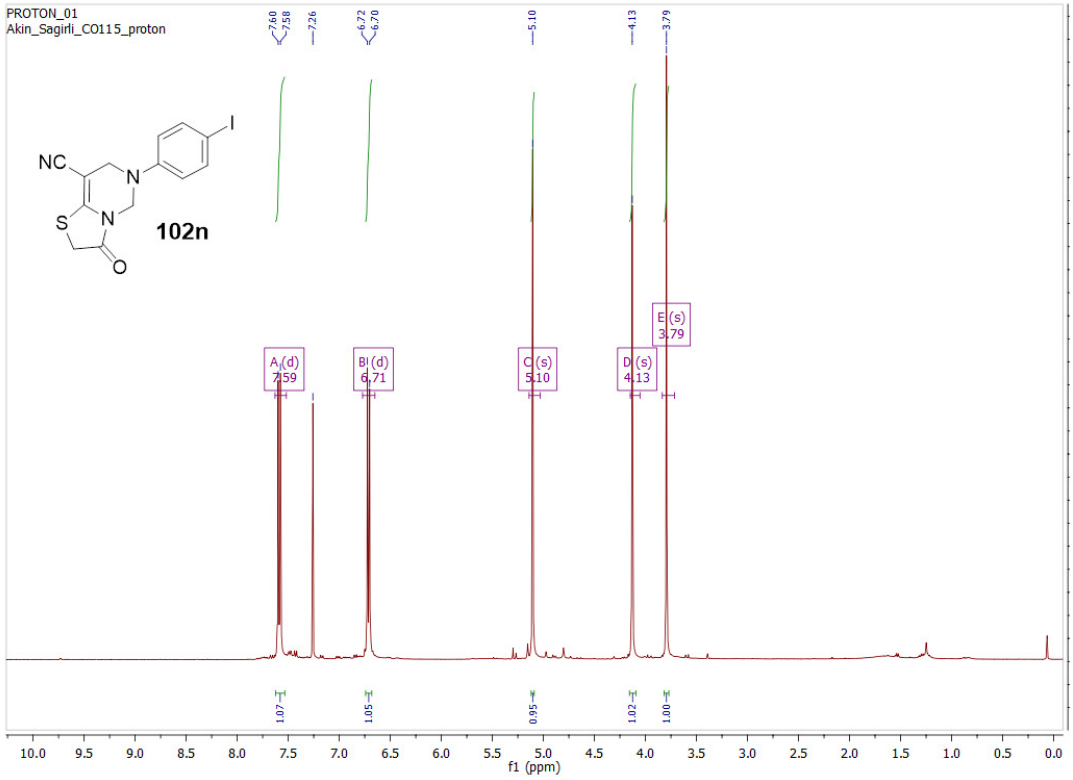

Figure 7.56 ^{1}H-NMR Spectrum of compound 102n.

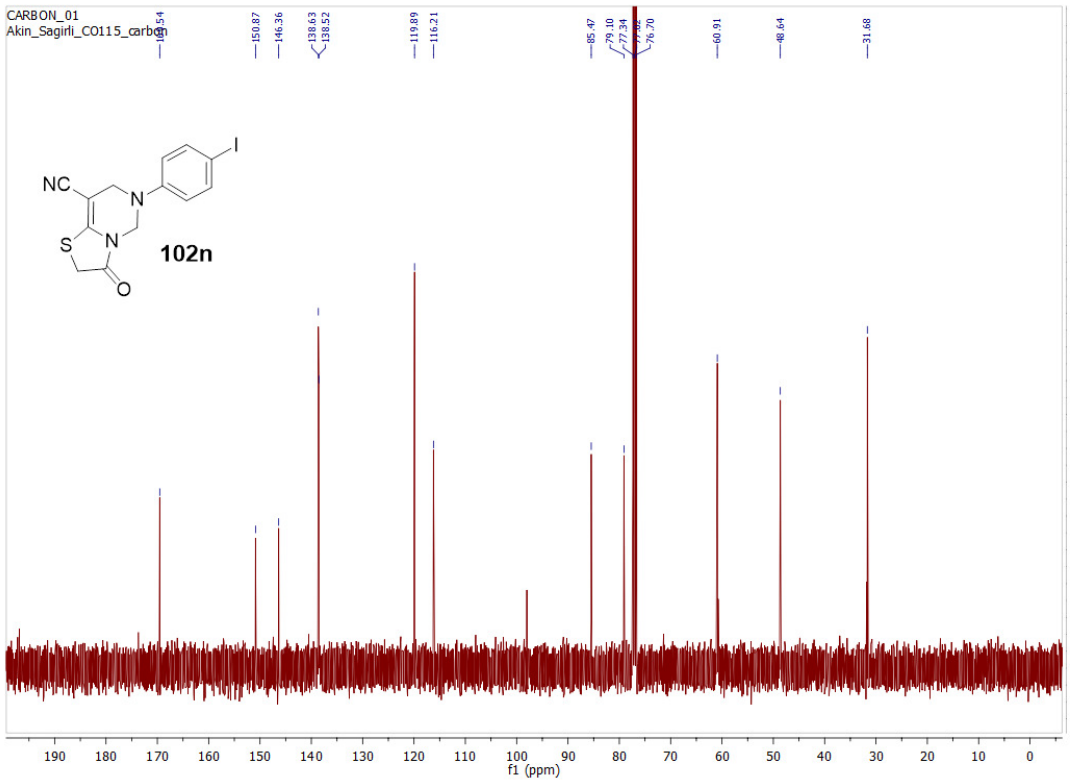

Figure 7.57 ^{13}C-NMR Spectrum of compound 102n.

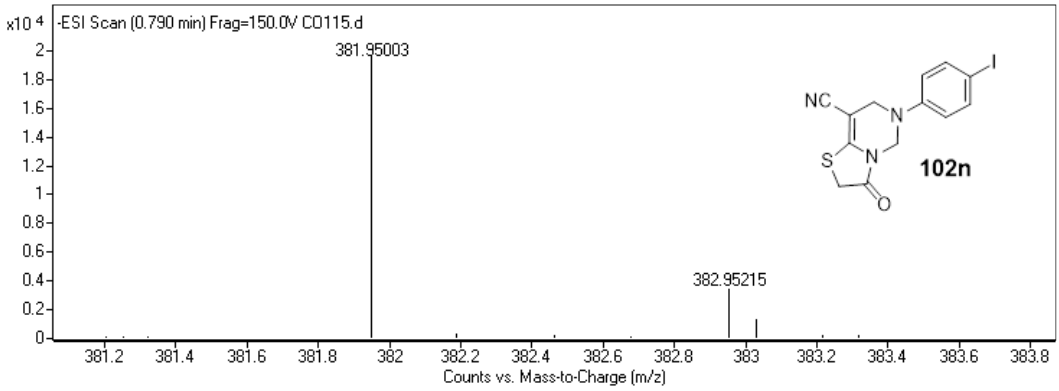

Figure 7.58 HRMS spectrum of compound 102n.

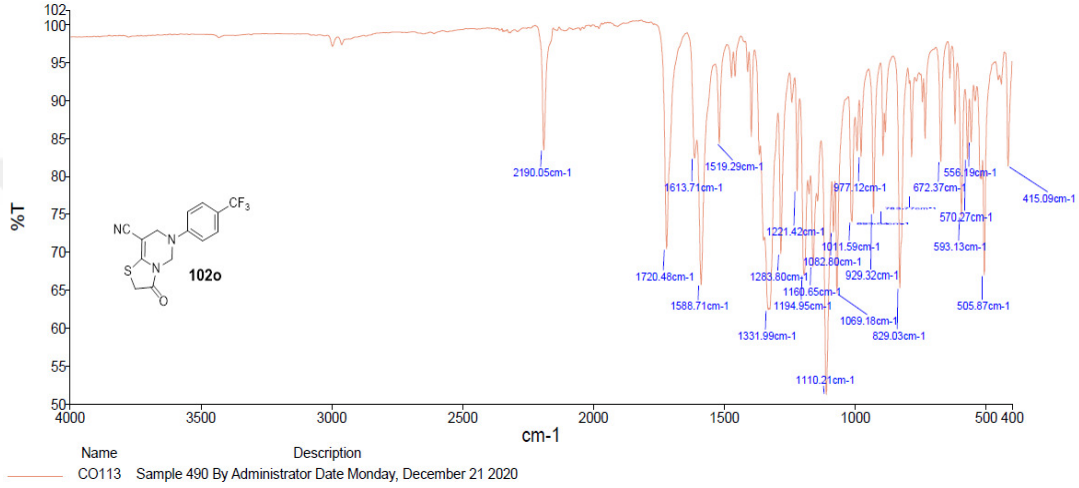

Figure 7.59 IR Spectrum of compound 102o.

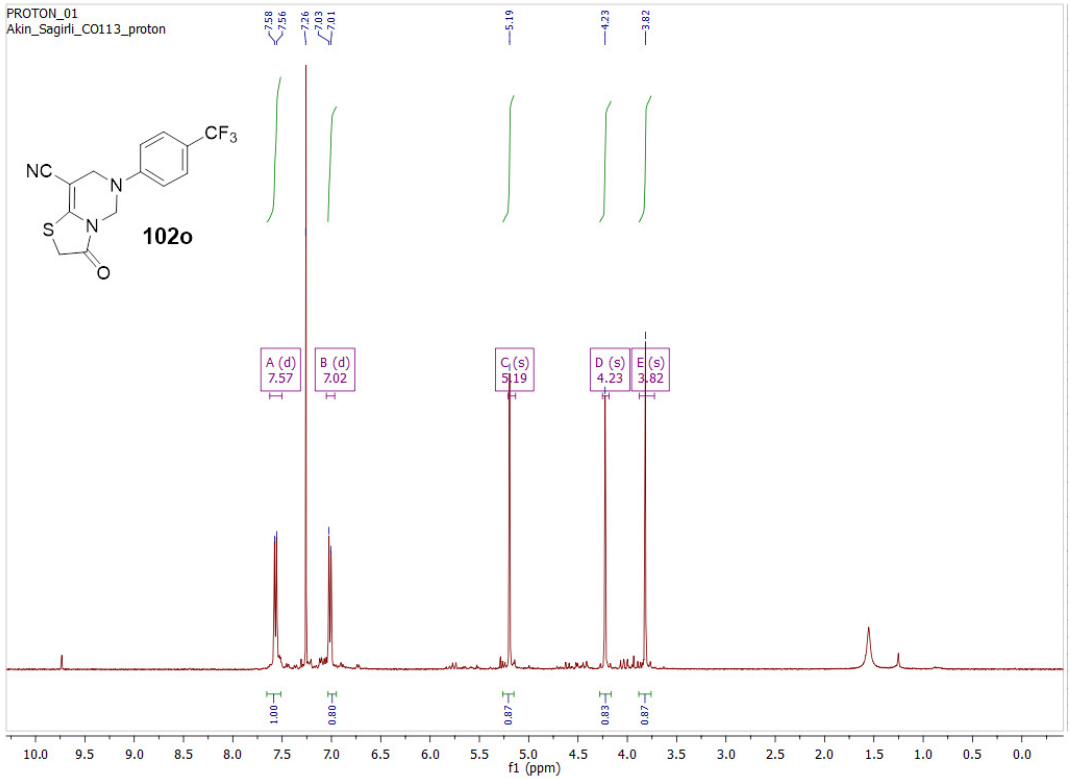

Figure 7.60 ^{1}H-NMR Spectrum of compound 102o.

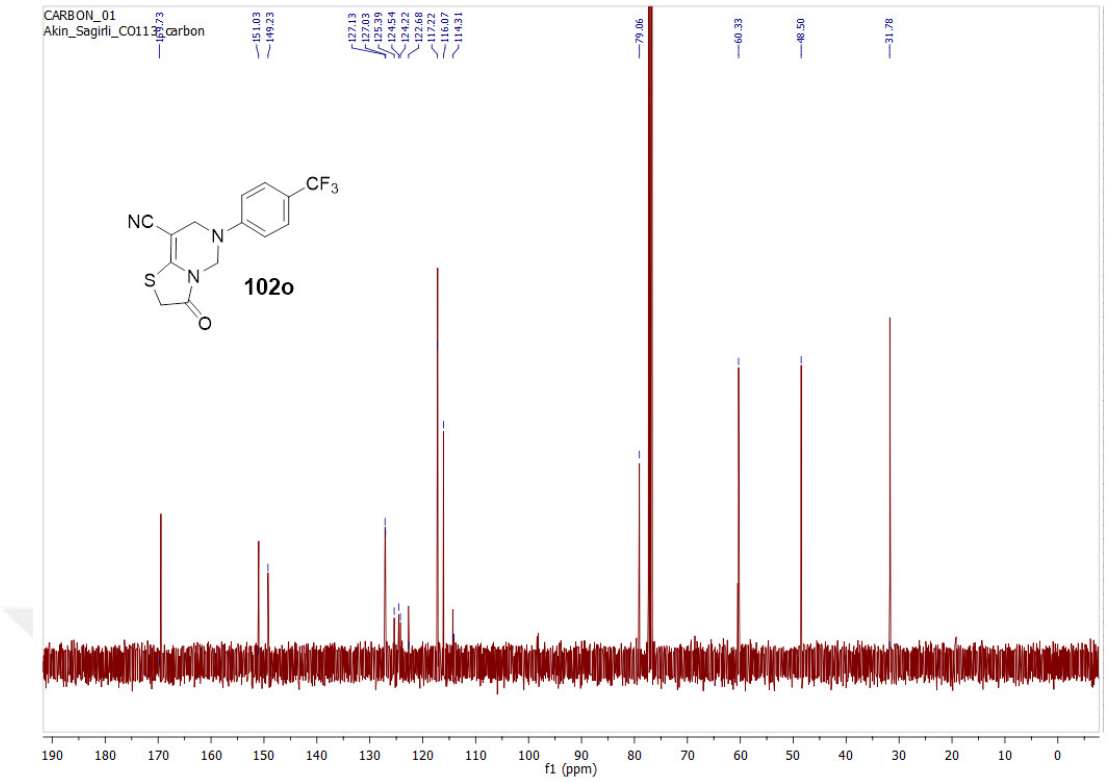

Figure 7.61 ^{13}C-NMR Spectrum of compound 102o.

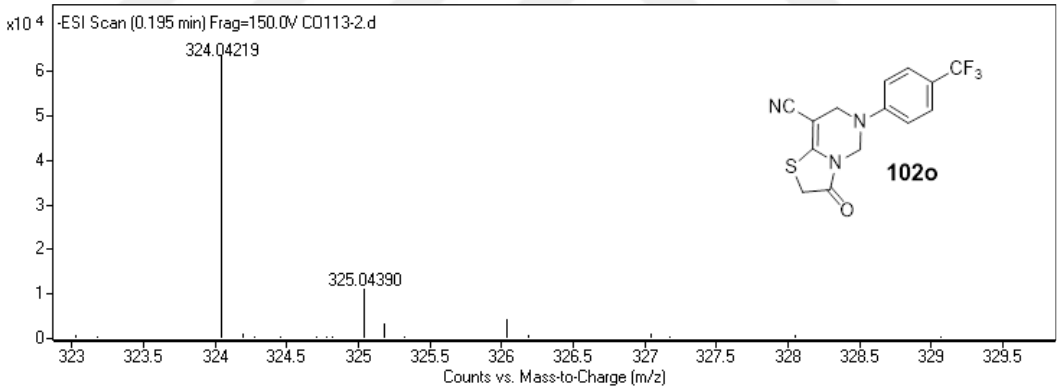

Figure 7.62 HRMS spectrum of compound 102o.

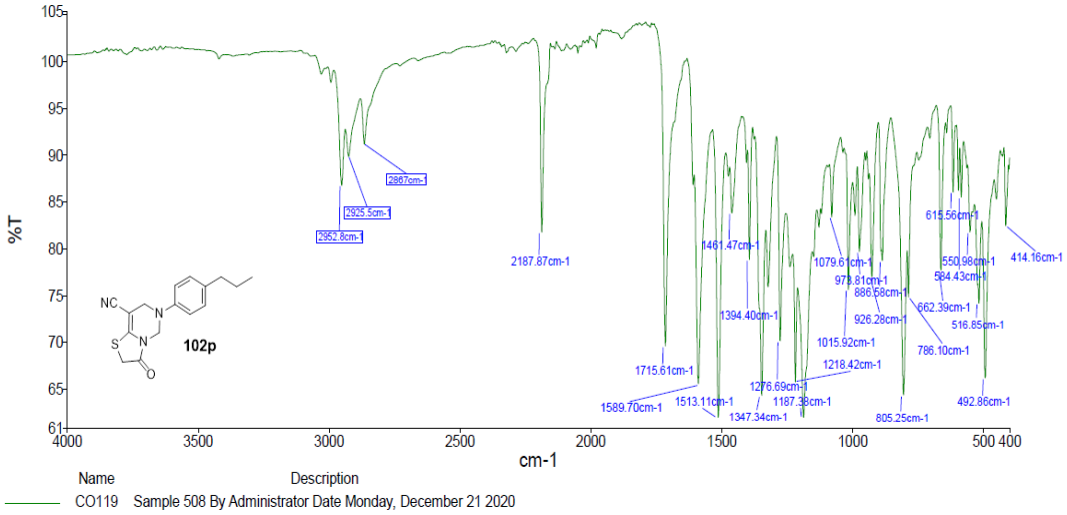

Figure 7.63 IR Spectrum of compound 102p.

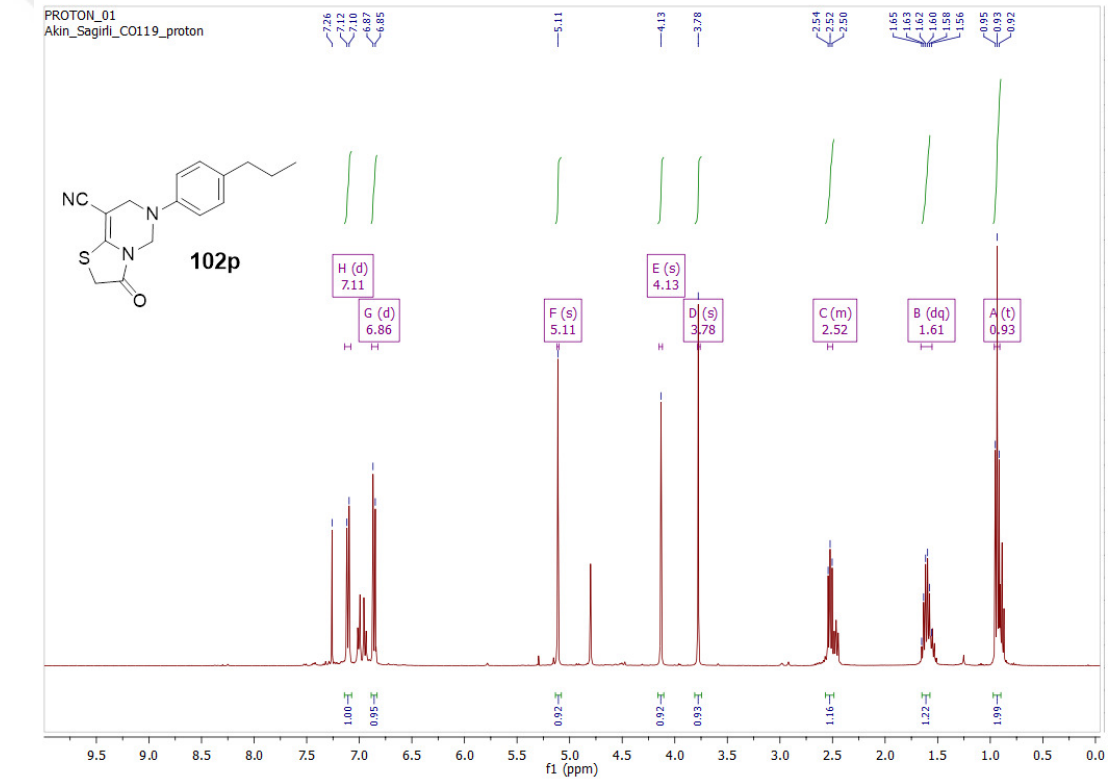

Figure 7.64 ^{1}H-NMR Spectrum of compound 102p.

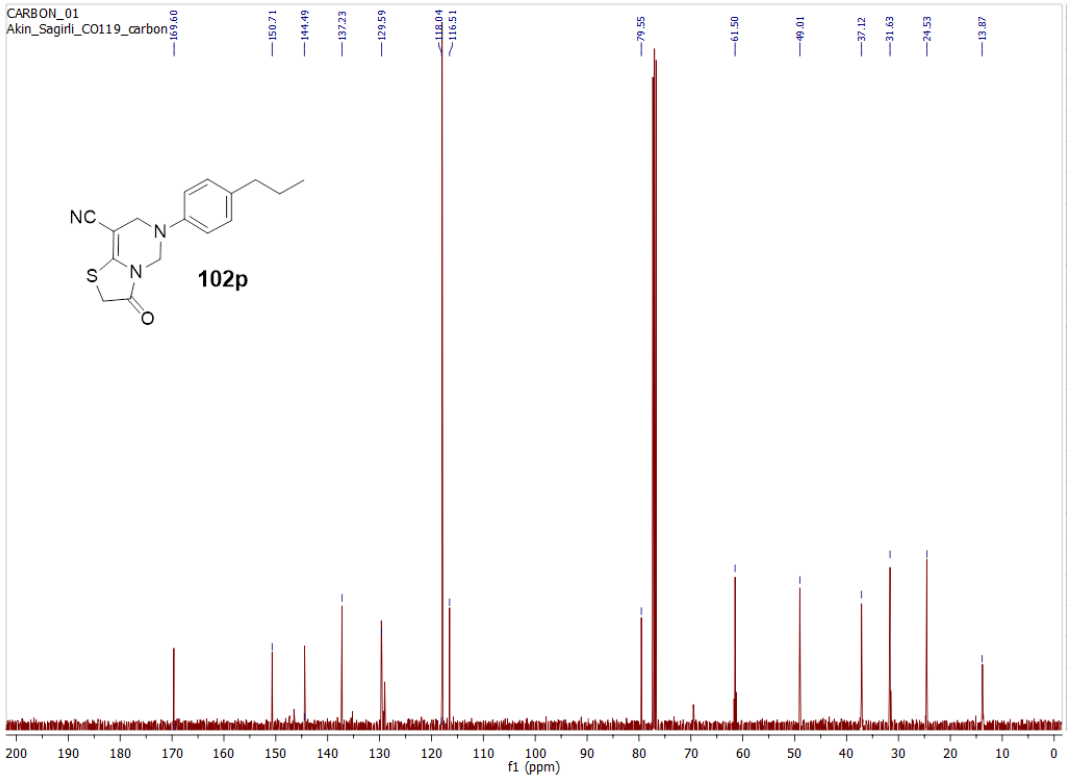

Figure 7.65 ^{13}C-NMR Spectrum of compound 102p.

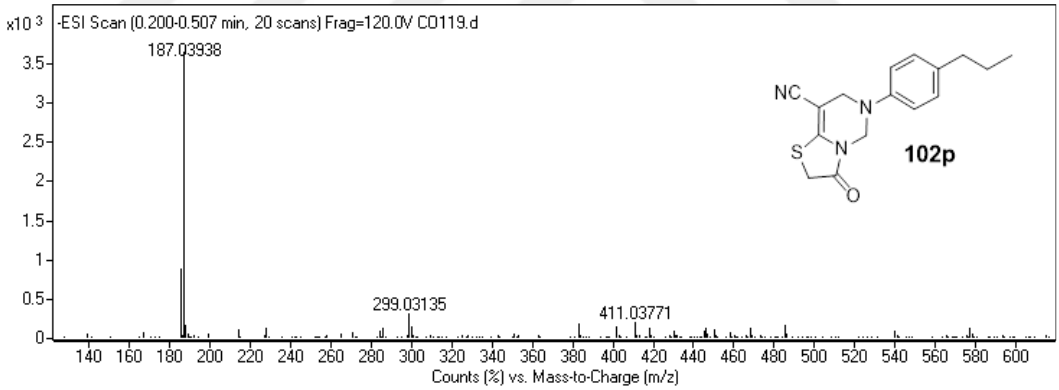

Figure 7.66 HRMS spectrum of compound 102p.

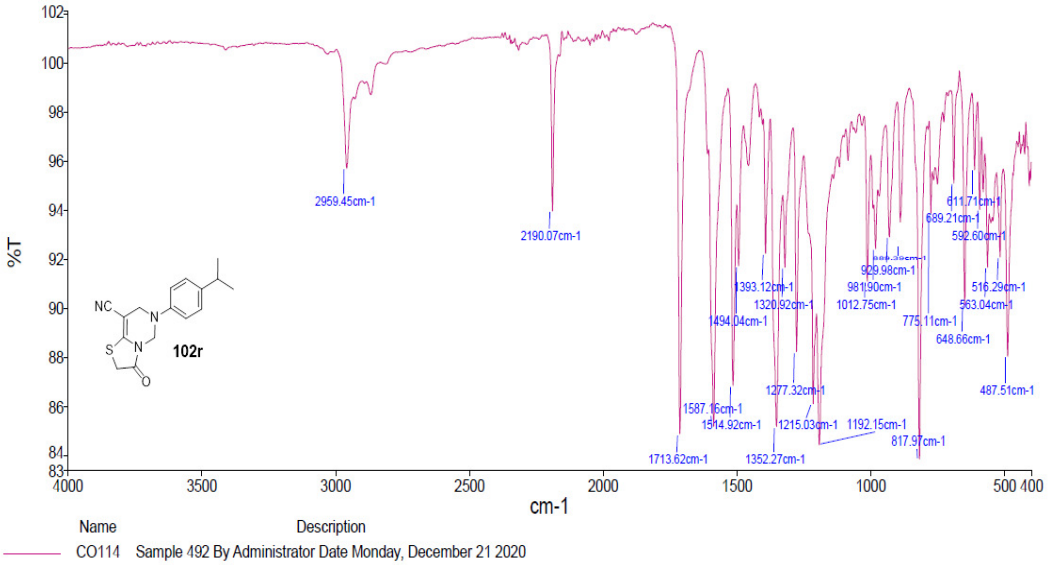

Figure 7.67 IR Spectrum of compound 102r.

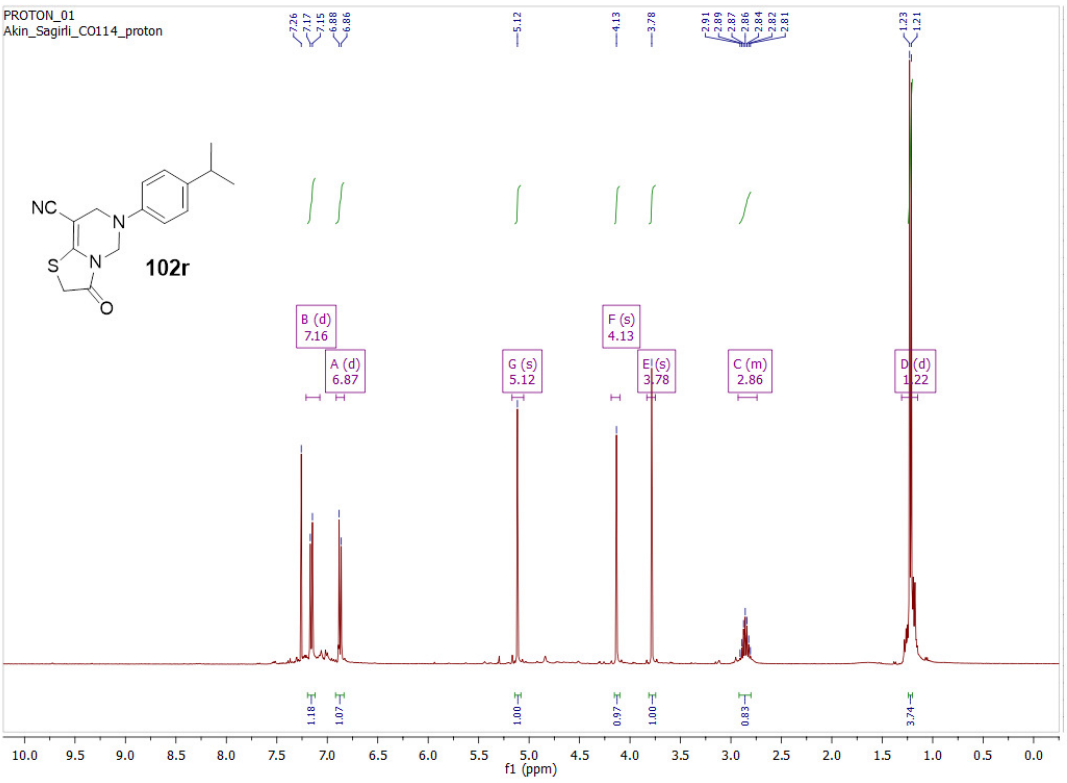

Figure 7.68 ^{1}H-NMR Spectrum of compound 102r.

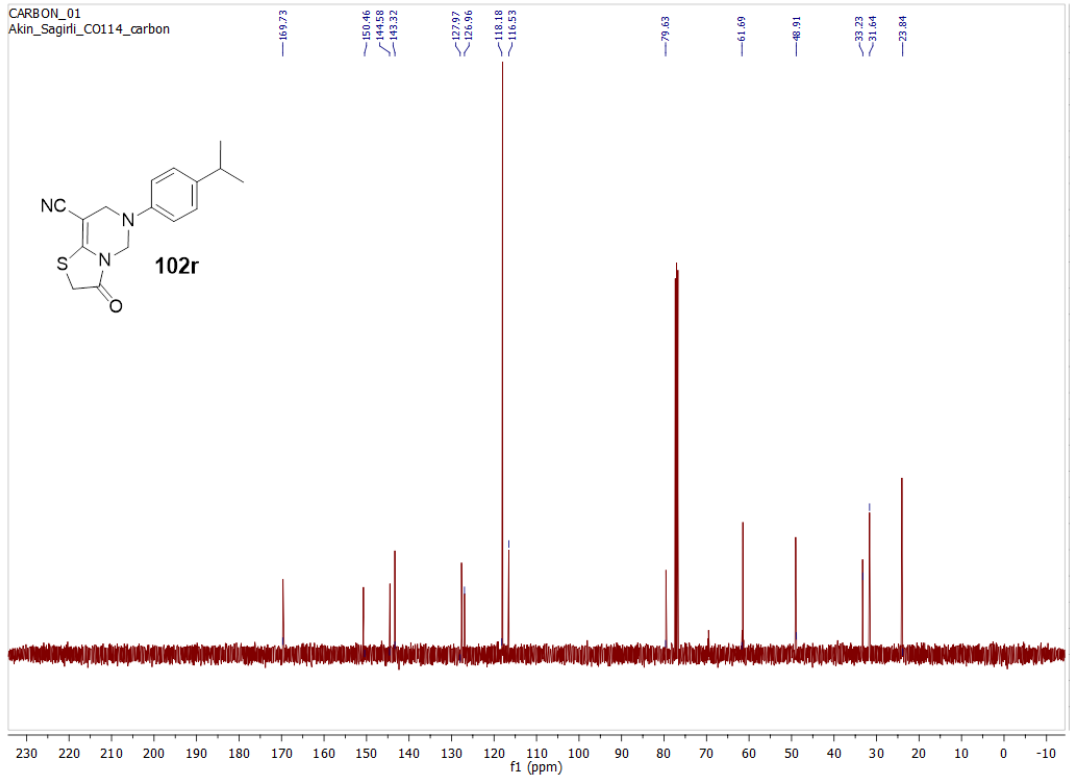

Figure 7.69 ^{13}C-NMR Spectrum of compound 102r.

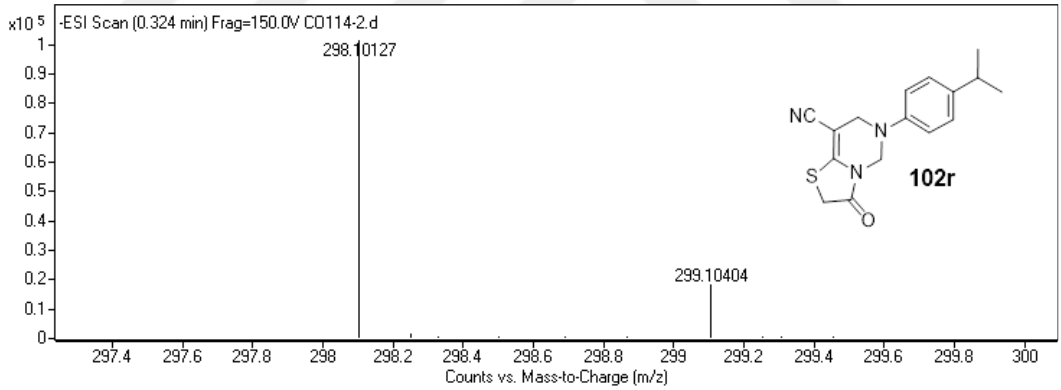

Figure 7.70 HRMS spectrum of compound 102r.

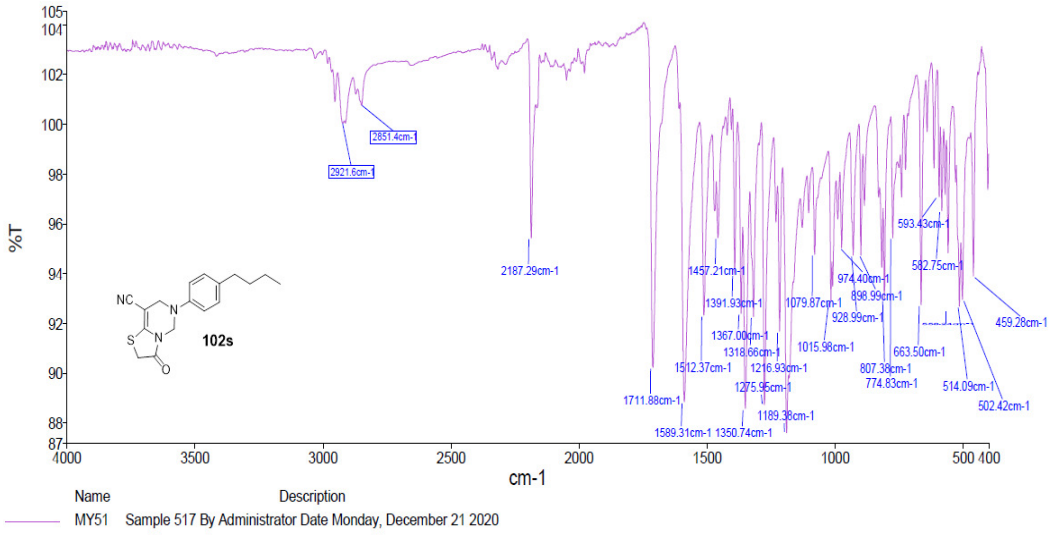

Figure 7.71 IR Spectrum of compound 102s.

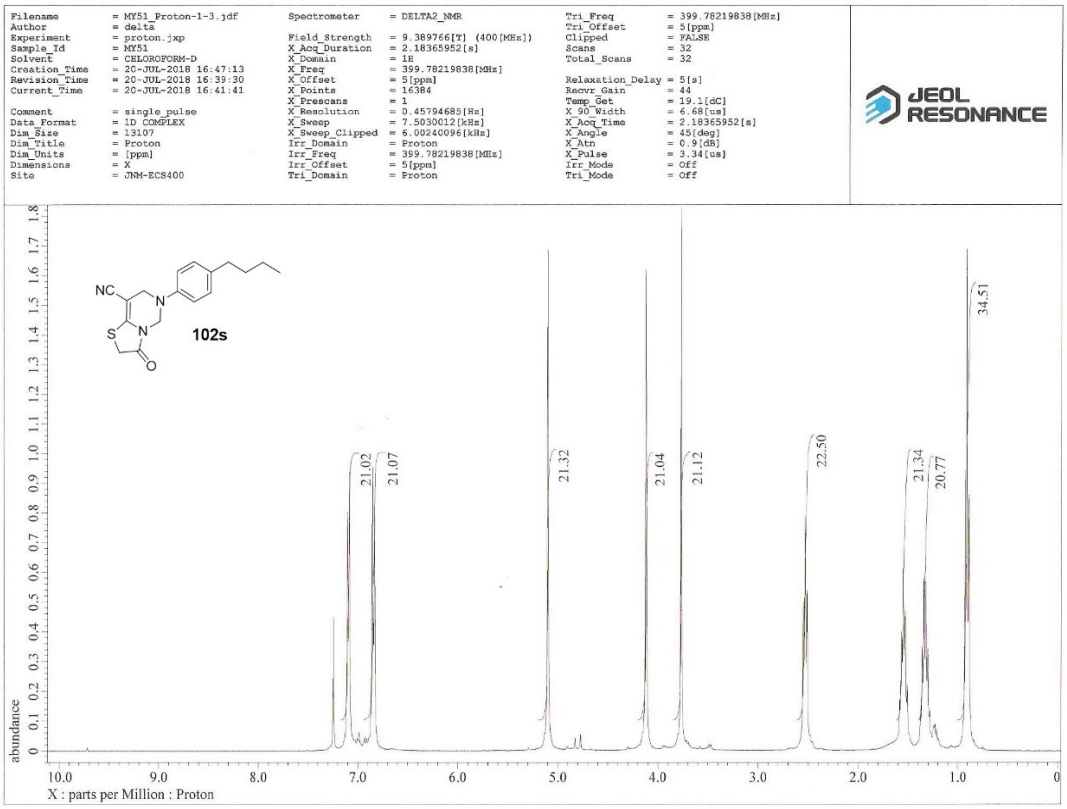

Figure 7.72 ^{1}H-NMR Spectrum of compound 102s.

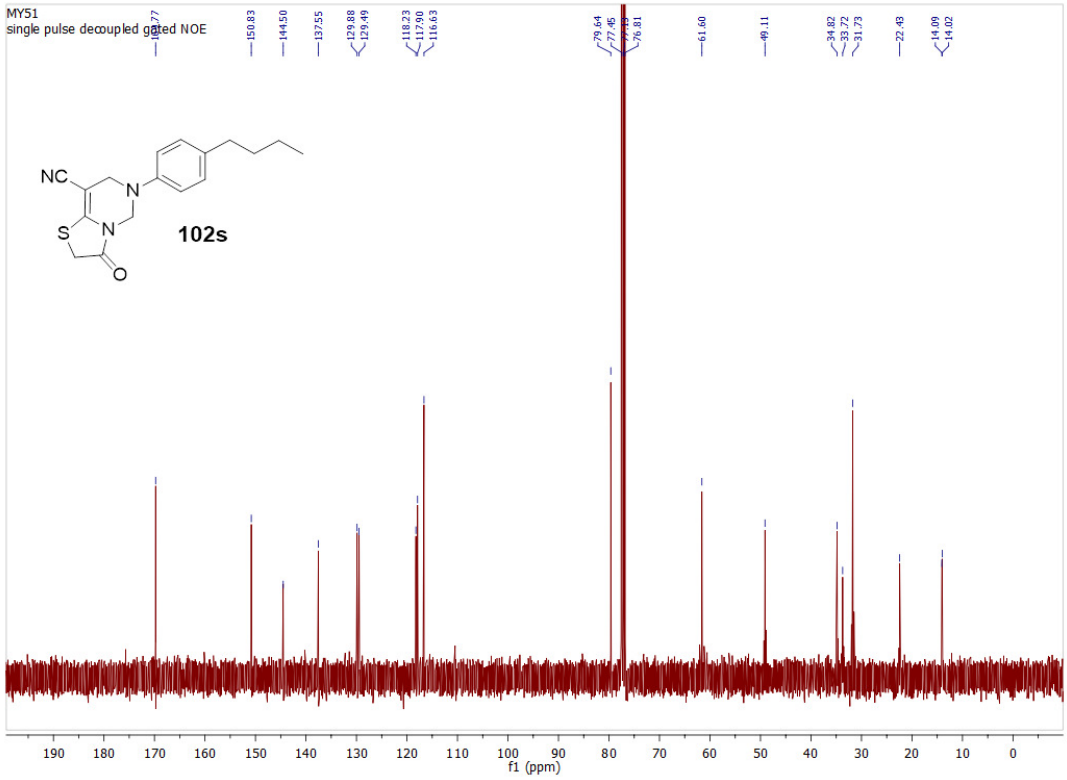

Figure 7.73 ^{13}C-NMR Spectrum of compound 102s.

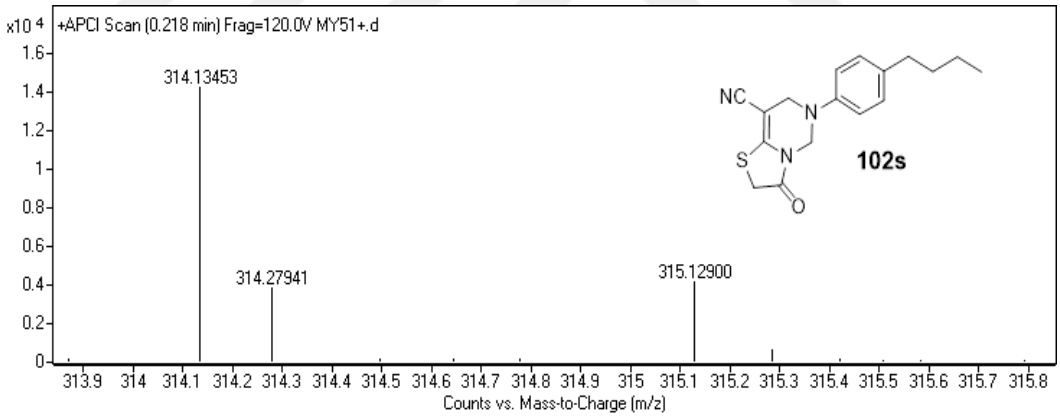

Figure 7.74 HRMS spectrum of compound 102s.

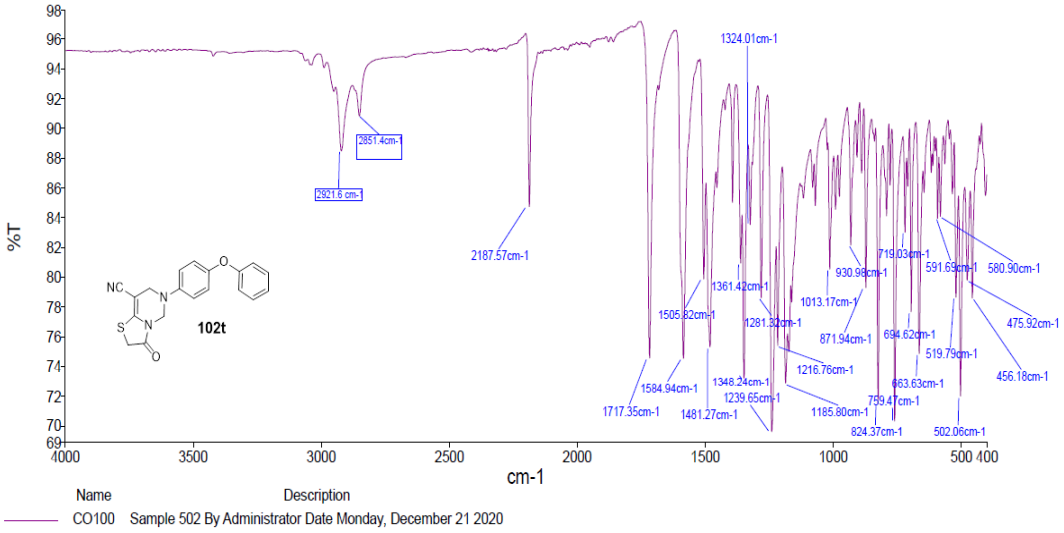

Figure 7.75 IR Spectrum of compound 102t.

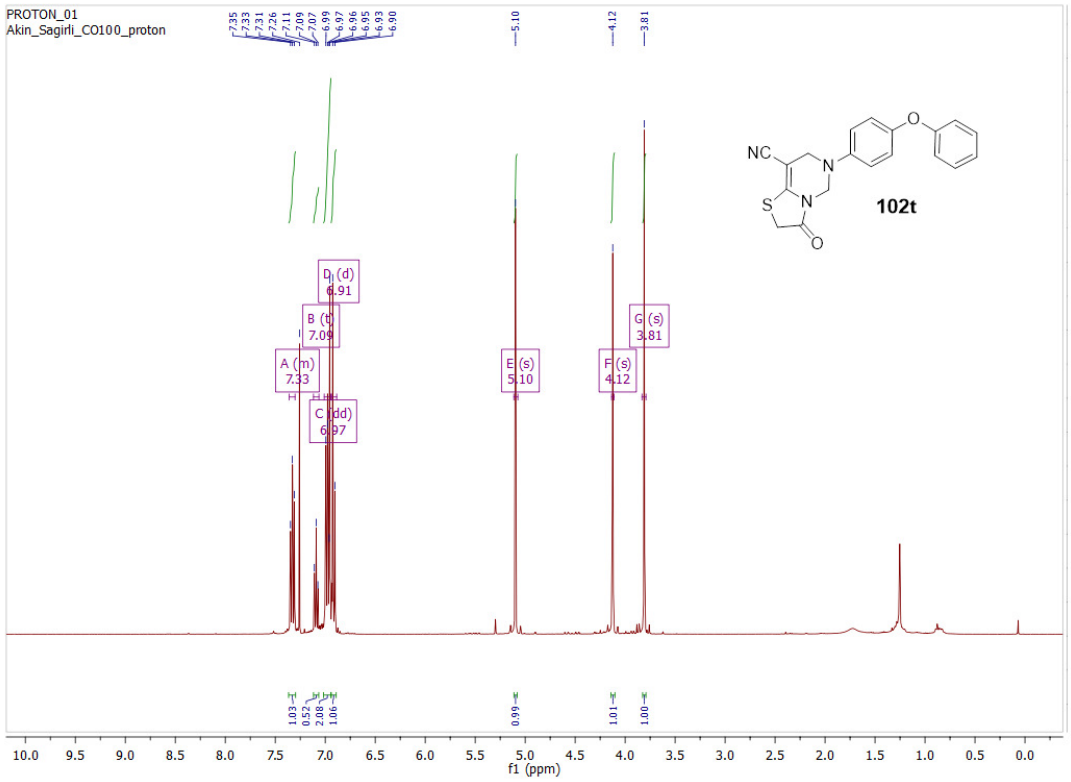

Figure 7.76 ^{1}H-NMR Spectrum of compound 102t.

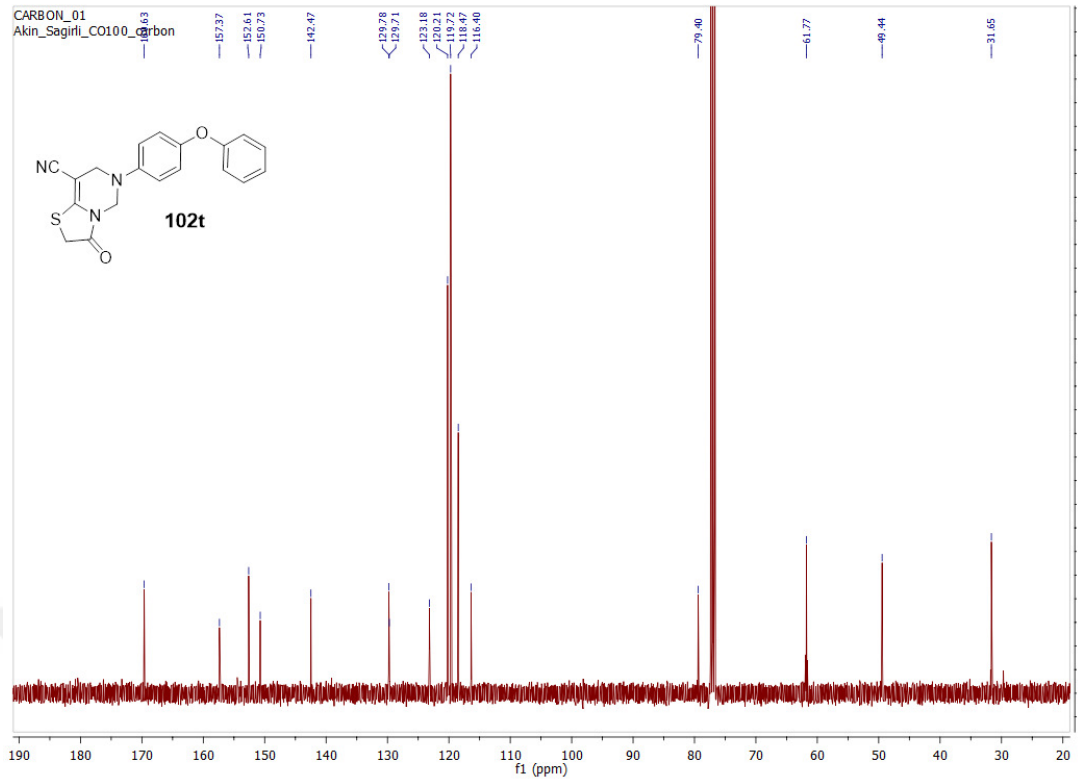

Figure 7.77 ^{13}C-NMR Spectrum of compound 102t.

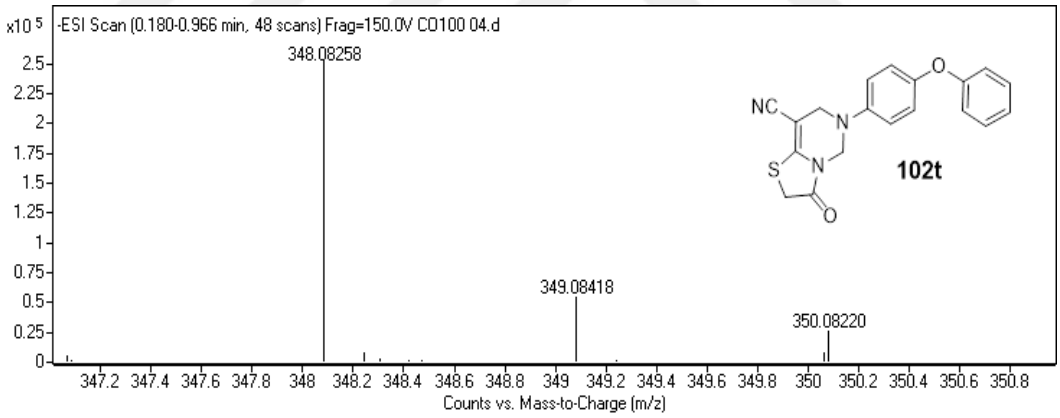

Figure 7.78 HRMS spectrum of compound 102t.

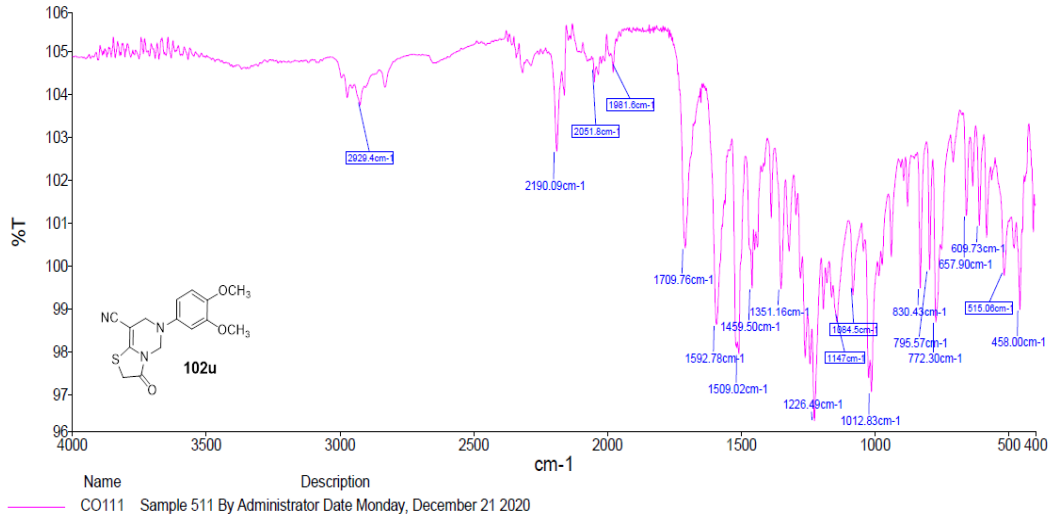

Figure 7.79 IR Spectrum of compound 102u.

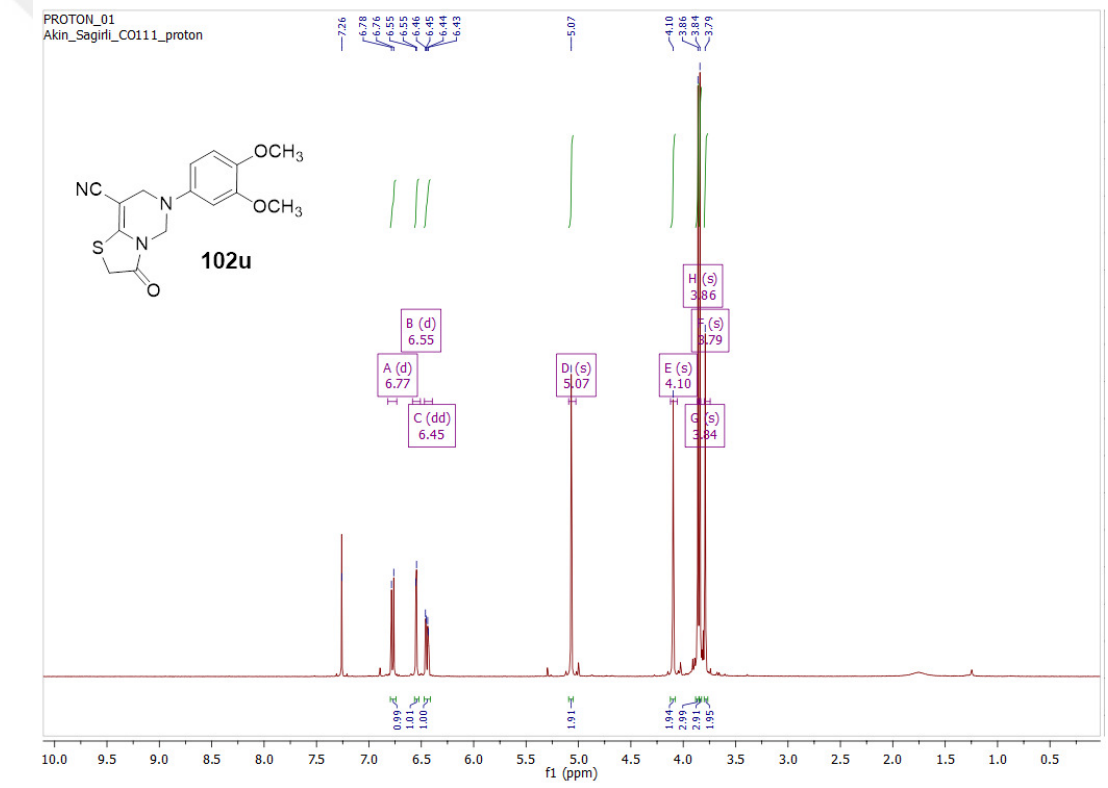

Figure 7.80 ^{1}H-NMR Spectrum of compound 102u.

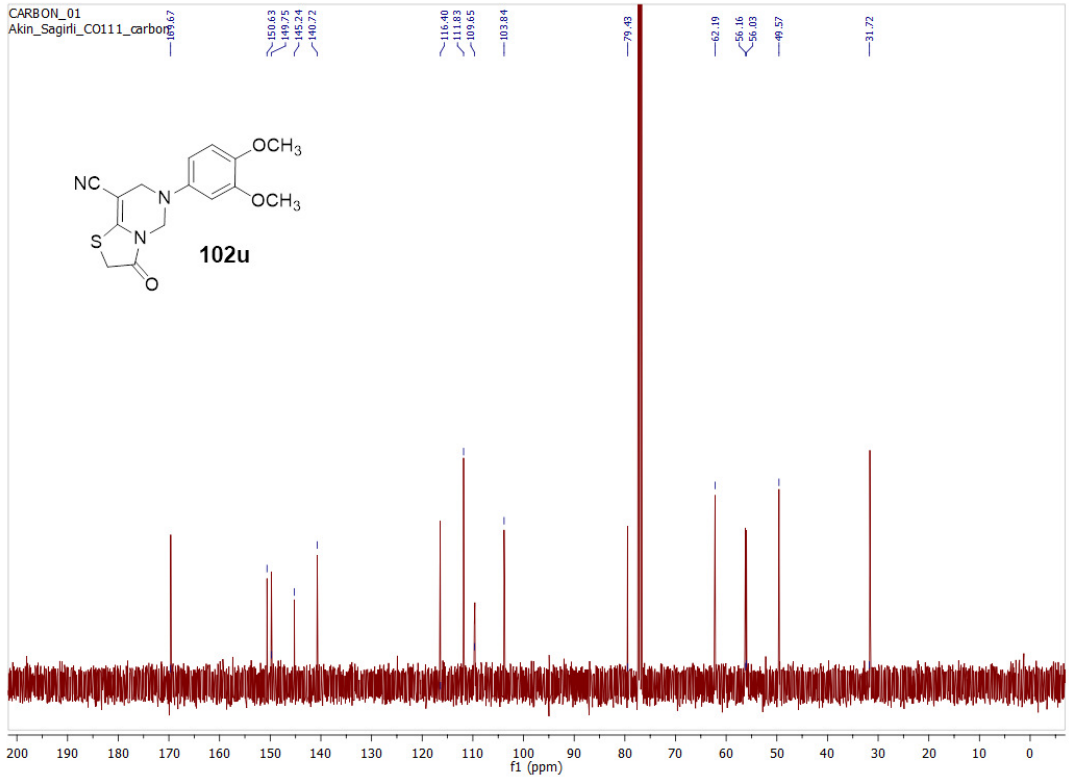

Figure 7.81 ^{13}C-NMR Spectrum of compound 102u.

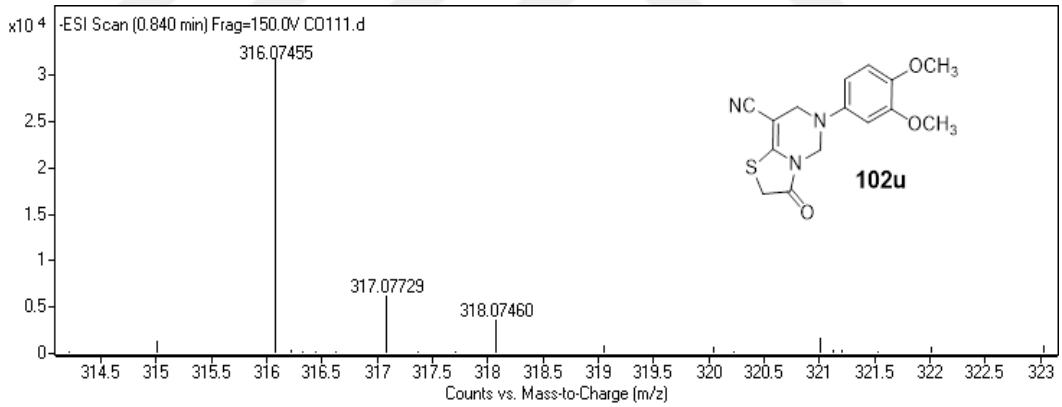

Figure 7.82 HRMS spectrum of compound 102u.

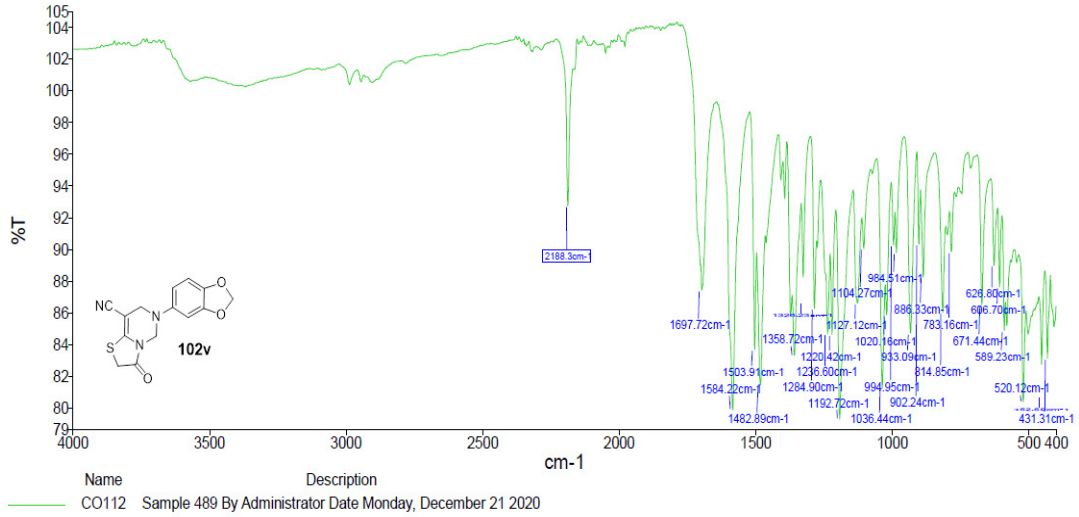

Figure 7.83 IR Spectrum of compound 102v.

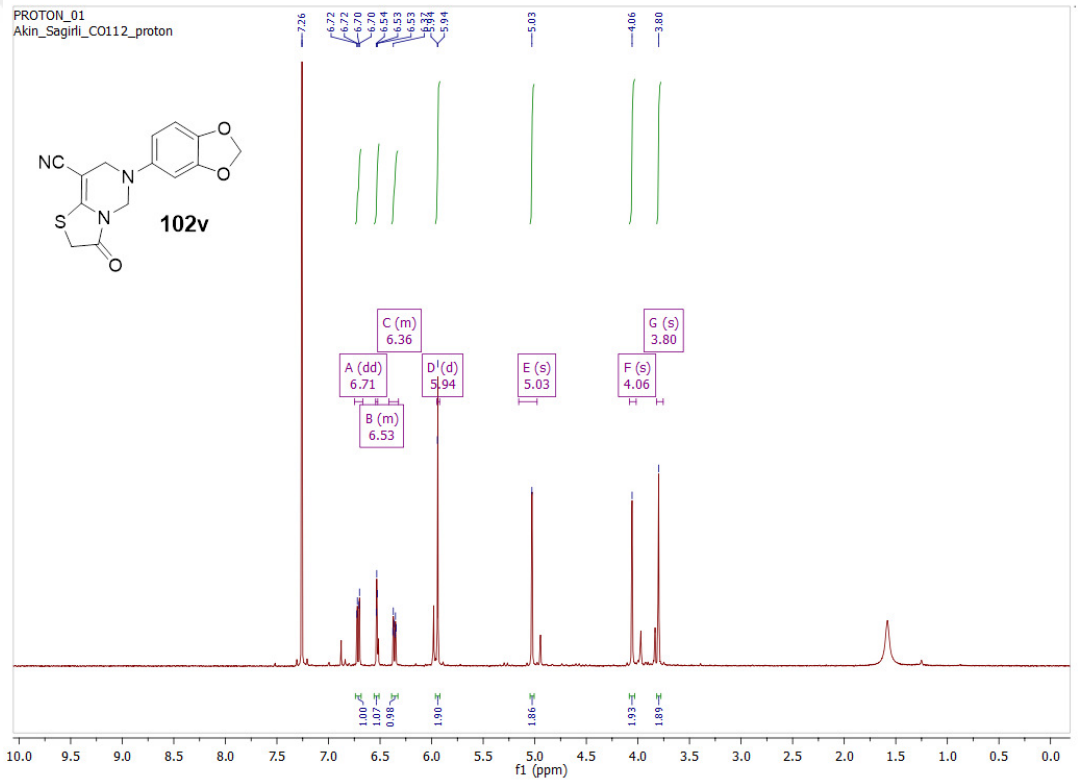

Figure 7.84 ^{1}H-NMR Spectrum of compound 102v.

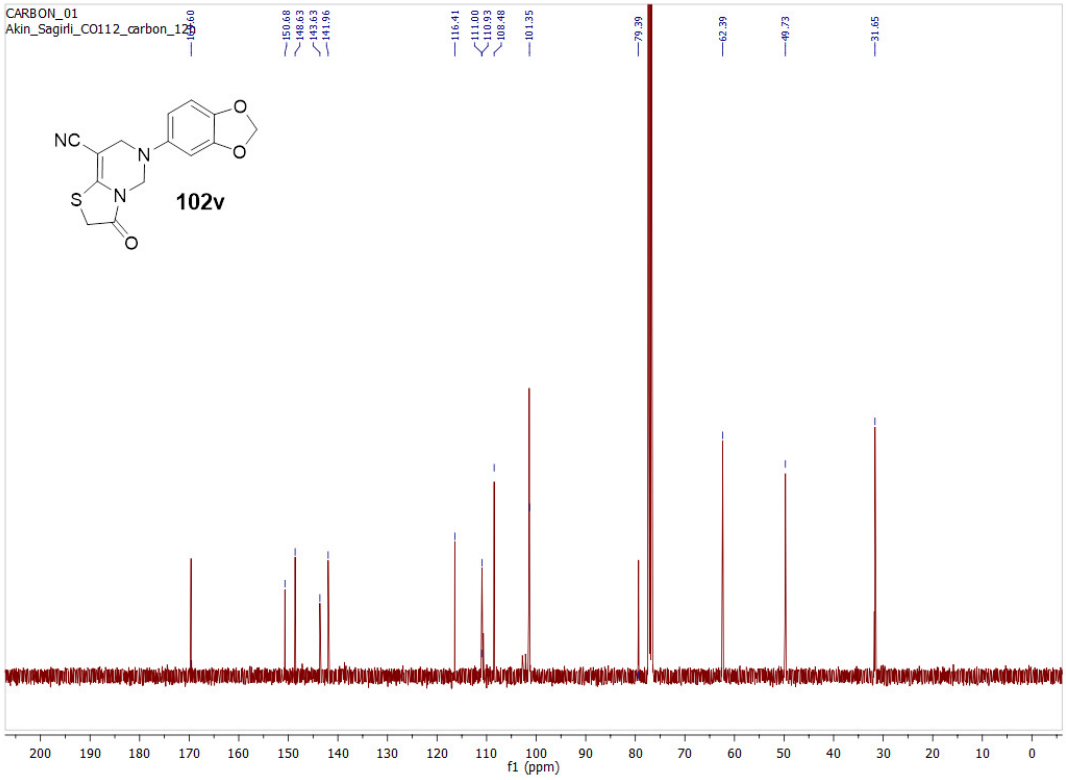

Figure 7.85 ^{13}C-NMR Spectrum of compound 102v.

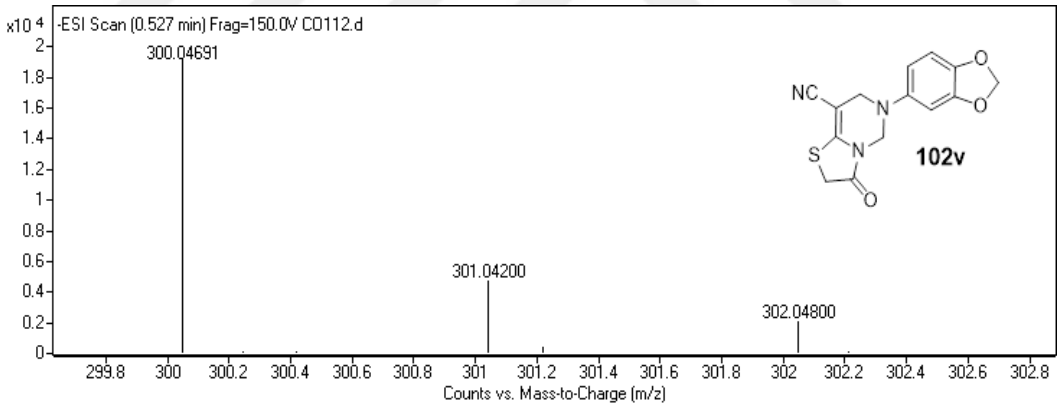

Figure 7.86 HRMS spectrum of compound 102v.

8. ORIGINALITY REPORT

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STUDENT & SUPERVISOR PLAGIARISM DECLARATION FORM

Department	CHEMISTRY		
Name and surname	ÇAĞRI ÖZBİL		
Student number	33112127044		
Postgraduate program	MSc with thesis ✓	PhD	
Academic year and semester of thesis examination	2020 / 2021	Autumn ✓	Spring
Thesis defence date	29/01/2021		
Number of pages	121		
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Thesis title (Eng)	FACILE SYNTHESIS OF NEW OXOTHIAZOLO[3,2-C]PYRIMIDINE CARBONITRILES VIA MANNICH CYCLISATIONS		

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