BOLU ABANT IZZET BAYSAL UNIVERSITY
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

EFFICIENT SYNTHESIS OF THIAZOLO[3,2-C] PYRIMIDINONES VIA MULTICOMPONENT REACTIONS

MASTER OF SCIENCE

KÜBRA UYSAL

BOLU, MARCH 2019

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APPROVAL OF THE THESIS

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Director of Graduate School of Natural and Applied Sciences

To my brother,

DECLARATION

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

Kübra UYSAL

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ABSTRACT

EFFICIENT SYNTHESIS OF THIAZOLO[3,2-*C*]PYRIMIDINONES VIA MULTICOMPONENT REACTIONS
MSC THESIS
KÜBRA UYSAL
BOLU ABANT IZZET BAYSAL UNIVERSITY GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES
DEPARTMENT OF CHEMISTRY
(SUPERVISOR: ASSOC. PROF. DR. MUHAMMET YILDIRIM)

BOLU, MARCH 2019

Thiazolo[5,4-*d*]-, [4,5-*d*]-, and [3,2-*a*]-pyrimidines are known to have variety of biological properties which were well-documented in recent literature and they can be produced over variety of synthetic routes. As the last thiazolopyrimidine core structure, thiazolo[3,2-*c*]pyrimidines are quite unknown in the sense of their synthesis or biological properties in the literature. Novel synthetic examples of thiazolo[3,2-*c*]pyrimidines and their biological activity results were reported for the first time by our group in 2014, 2015 and 2018.

In order to advance the chemistry and biology of thiazolo[3,2-*c*]pyrimidines, synthesis of new potentially bioactive 3-oxothiazolo[3,2-*c*]pyridimine derivaties were aimed in the current dissertation work. To achieve the goal, first of all, the heterocyclic enamines as convenient precursors were prepared and characterized by IR and NMR analyses.

In the second and third parts of the work, 3-oxothiazolo[3,2-*c*]pyrimidines were efficiently synthesized via Mannich cyclizations of the heterocyclic enamines, ethyl 2-(4-oxothiazolidin-2-ylidene) acetate and ethyl 2-((*Z*)-5-benzylidene-4-oxothiazolidin-2-ylidene)acetate, with formaldehyde or acetaldehyde and primary amines under mild conditions.

After the characterization of all title compounds by IR, NMR and HRMS measurements, a preliminary antibacterial activity study for new 3-oxothiazolo[3,2-*c*]pyridimines were performed in the last part of the work. It was found that only one derivative exhibited bacteriostatic and moderate antibacterial activity against tested bacteria.

KEYWORDS:
3-oxothiazolo[3,2-*c*]pyrimidine, Enamine, Cyclization, Mannich, Antibacterial.

ÖZET

TİYAZOLO[3,2-*C*]PİRİMİDİNONLARIN ÇOK-BİLEŞENLİ REAKSİYONLAR YOLUYLA ETKİLİ SENTEZİ
YÜKSEK LİSANS TEZİ
KÜBRA UYSAL
BOLU ABANT İZZET BAYSAL ÜNİVERSİTESİ FEN BİLİMLERİ ENSTİTÜSÜ
KİMYA ANABİLİM DALI
(TEZ DANIŞMANI:DOÇ.DR.MUHAMMET YILDIRIM)

BOLU, MART - 2019

Tiyazolo[5,4-*d*]-, [4,5-*d*]- ve [3,2-*a*]-pirimidinlerin, güncel literatürde iyi detaylandırılmış şekilde sunulan çeşitli biyolojik aktivitelere sahip oldukları bilinmektedir ve çeşitli sentetik yöntemlerle de hazırlanabilmektedirler. Son tiyazolopirimidin ana yapısı olarak, tiyazolo[3,2-*c*]pirimidinler, literatürde sentezleri veya biyolojik özellikleri anlamında pek bilinmemektedirler. Tiyazolo[3,2-*c*]pirimidinlerin yeni sentetik örnekleri ve biyolojik aktivite sonuçları, ilk defa grubumuz tarafından 2014, 2015 ve 2018 yıllarında rapor edilmiştir.

Tiyazolo[3,2-*c*]pirimidinlerin kimya ve biyolojisini ilerletmek için, bu tez çalışmasında yeni potansiyel biyoaktif 3-oksotiyazolo[3,2-*c*]pirimidinlerin sentezi amaçlanmıştır. Bu hedefe ulaşmak için, öncelikle uygun başlangıç maddeleri olarak heterohalkalı enaminler hazırlanmış ve IR, NMR analizleriyle karaterize edilmiştir.

Çalışmanın ikinci ve üçüncü kısımlarında ise, 3-oksotiyazolo[3,2-*c*]pirimidinler, heterohalkalı enaminler, etil 2-(4-oksotiyazolidin-2-iliden)asetat ve etil 2-((Z)-5-benziliden-4-oksotiyazolidin-2-ilidene) asetat'ın formaldehit veya asetaldehit ve primer aminlerle Mannich halkalaşmaları yoluyla uygun koşullarda etkili şekilde sentezlenmiştir.

Elde edilen tüm ürünlerin, IR, NMR ve HRMS ölçümleriyle karakterizasyonu sonrası, yeni 3-oksotiyazolo[3,2-*c*]pirimidinler için bir ön antibakteriyel aktivite çalışması çalışmamızın son kısmında gerçekleştirilmiştir. Sadece bir türevin test edilen bakterilere karşı bakteriyostatik ve orta derecede antibakteriyel aktivite gösterdiği bulunmuştur.

ANAHTAR KELİMELER: 3-oksotiyazolo[3,2-*c*]pirimidin, Enamin, Halkalaşma, Mannich, Antibakteriyel.

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LIST OF ABBREVIATIONS AND SYMBOLS

Ac_2O	**:** Acetic anhydride
AcOH	**:** Acetic acid
AcONa	**:** Sodium acetate
(AD)	**:** Alzheimer's disease
A-DA	**:** Aza-Diels-Alder
Ag_2CO_3	**:** Silver (I) carbonate
aq.	**:** aqueous
Ar	**:** Aromatic
Ar-CHO	**:** Aromatic aldehyde
atm	**:** atmosphere
B-3CR	**:** Biginelli (three-component) reaction
CH_3	**:** Methyl
C_2H_5	**:** Ethyl
C_3H_5	**:** Allyl
C_3H_7	**:** Propyl
C_4H_9	**:** Butyl
C_6H_5	**:** Phenyl
C_6H_6	**:** Benzene
$CHBr_3$	**:** Bromoform
$CH_2C_6H_5$	**:** Benzyl
$CHCl_3$	**:** Chloroform
CH_2Cl_2	**:** Dichloromethane
CH_3CN	**:** Acetonitrile
C_6H_4I	**:** *p*-iodophenyl
Chloramine-T	**:** Tosylchloramide sodium salt
$(C_2H_5)_3N$	**:** Triethylamine
$(C_2H_5)_3O^+BF_4^-$	**:** Triethyloxonium tetrafluoroborate
CN	**:** Cyanide
conc'd	**:** concentrated
3-CR	**:** three-component reaction
$Cu(OAc)_2$	**:** Copper(II)acetate
DBU	**:** 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM : Dichloromethane

DEE : Diethyl ether

DHPMs : Dihydropyrimidinones

$(DHQD)_2PHAL$: Hydroquinidine-1,4-phthalazinediyl diether

DIEA : *N,N*-diisopropylethylamine

DMF : Dimethylformamide

DPPP : 1,3-Bis(diphenylphosphino)propane

EDG : Electron-donating group

Et_3N : Triethylamine

EtOAc : Ethyl acetate

EtOH : Ethanol

EtONa : Sodium ethoxide

EWG : Electron-withdrawing group

Fe_3O_4 : Iron (III) oxide

H : Hydrogen

Ha-3CR : Hantzsch dihydropyridine

HCl : Hydrochloric acid

$HCONH_2$: Formamide

HCOOH : Formic acid

H_2O : Water

H_2O_2 : Hydrogen peroxide

$H_3PW_{12}O_{40}$: Tungstophosphoric acid

hr. or h. : hour

hrs. : hours

H_2SO_4 : Sulfuric acid

IL-Fe_3O_4 NPs : Ionic liquid Fe_3O_4 nanoparticles

IR : Infrared

KCN : Potassium cyanide

K_2CO_3 : Potassium carbonate

$K_3[Fe(CN)_6]$: Potassium hexacyanoferrate (III)

KOH : Potassium hydroxide

LA : Lewis acid

***m*-CPBA** : *meta*-chloroperoxybenzoic acid

MCRs : Multicomponent reactions

Me : Methyl

MeCN/H_2O : Acetonitrile/hydrate

MeOH : Methanol

MgO : Magnesium oxide

min. : minute

mix. : mixture

Mn≡N : Manganese nitrido complex

MTSA : Melamine trisulfonic acid

MVE : Methyl vinyl ether

MW : Microwave

N_2 : Nitrogen

NaH : Sodium hydride

$NaHCO_3$: Sodium bircarbonate

$NaNO_2$: Sodium nitrite

$NaOBu^t$: Sodium tert-butoxide

NaOEt : Sodium ethoxide

NaOH : Sodium hydroxide

Na_2SO_4 : Sodium sulfate

***n*-BuOH** : *n*-Butanol

$NCCH_2CN$: Malononitrile

$NCCH_2CO_2Bu^t$: tert-butyl cyanoacetate

NH_2 : Amino

NH_3 : Ammonia

$NH_4CH_3CO_2$: Ammonium acetate

$(NH_4)_2CO_3$: Ammonium carbonate

$NH_2NH_2.H_2O$: Hydrazine hydrate

NH_2SO_3H : Sulfamic acid

NMP : *N*-methyl-2-pyrrolidone

NMR : Nuclear magnetic resonance

OCH_3 : Methoxy

OEt : Ethoxy

OH : Hydroxide

OsO_4 : Osmium tetroxide

P-3CR : Passerini (three-component) reaction

Pd : Palladium

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

$Pd(OAc)_2$: Palladium (II) acetate

$Pd(PPh_3)_2Cl_2$: Bis(triphenylphosphine)palladium (II) dichloride

Ph : Phenyl

Ph-N=C=S : Phenylisothiocyanate

$Ph_3P=O$: Triphenylphosphine oxide

PivOH : Pivalic acid

$POCl_3$: Phosphorus (V) oxychloride

P_2S_5 : Phosphorus pentasulfide

Py : Pyridine

PyHTs : Pyridinium tosylate

R : Functional group

R-N=C: : isocyanide

R-N=C=O : isocyanate

R-N=C=S : isothiocyanate

RT : Room temperature

sat'd : saturated

S-3CR : Strecker (three-component) reaction

SRR : Single reactant replacement

TBAI : Tetrabutylammonium iodide

TBATB : Tetrabutylammonium tribromide

t-BuOK : Potassium tert-butoxide

TEA : Triethylamine

temp. : Temperature

TFAA : Trifluoroacetic anhydride

THF : Tetrahydrofuran

$THF-H_2O$: Tetrahydrofuran-water

THQs : 1,2,3,4-tetrahydroquinolines

TMSCN : Trimethylsilyl cyanide

TPP : Triphenylphosphine

U-4CR : Ugi (four-component) reaction

UV : Ultraviolet

$ZrCl_4$: Zirconium tetrachloride

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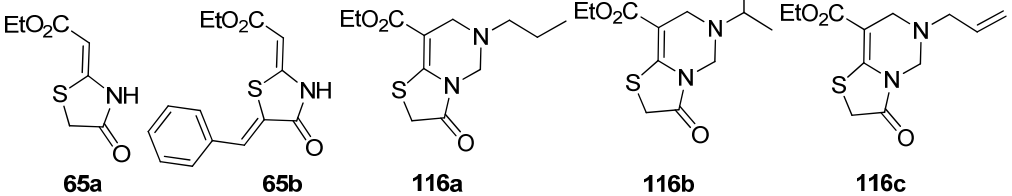
FORMULAE



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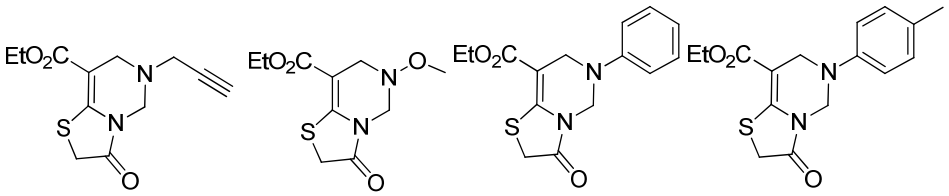

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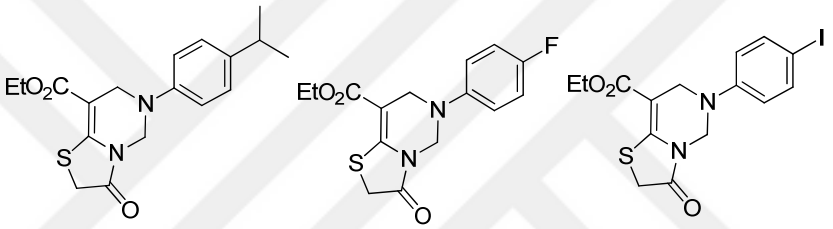

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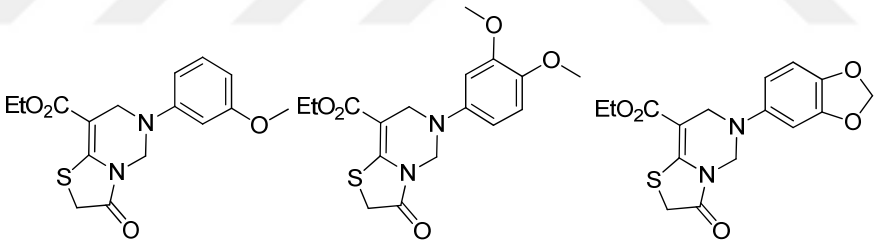

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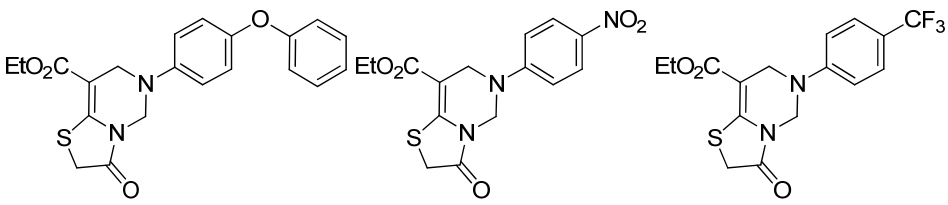

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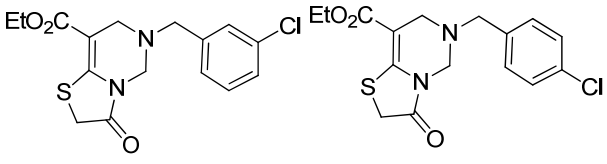

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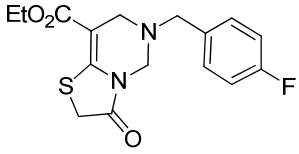

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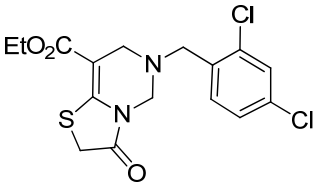

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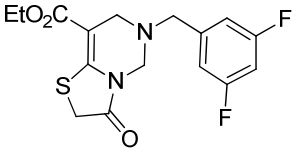

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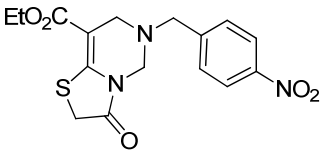

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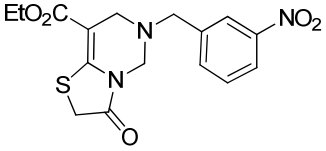

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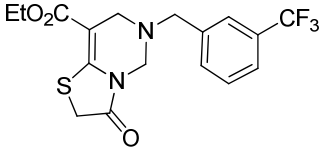

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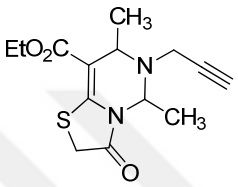

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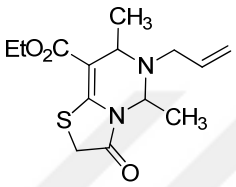

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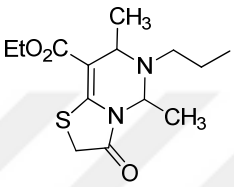

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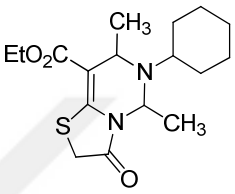

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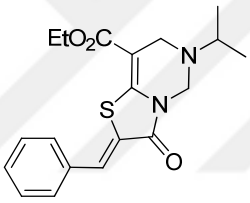

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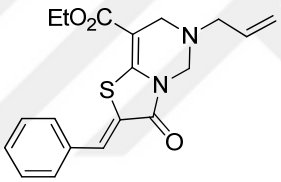

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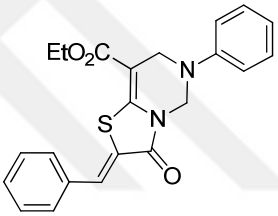

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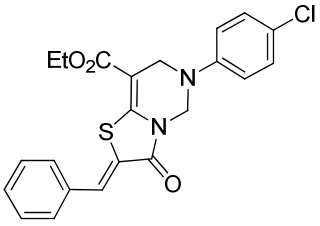

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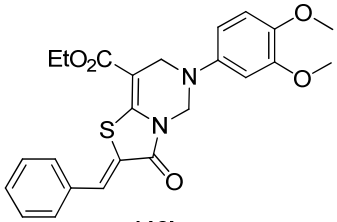

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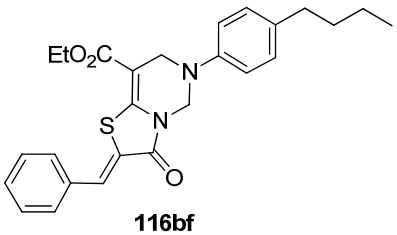

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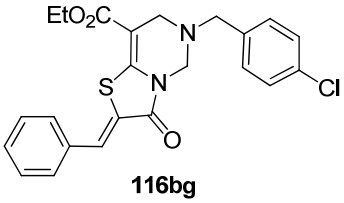

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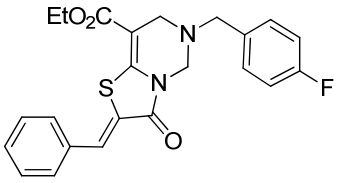

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1. INTRODUCTION

Introductory information has been given under four main subjects with individual titles of multicomponent reactions, heterocyclic enamines, thiazolopyrimidines, antibacterial activity for the current dissertation study.

1.1 MULTICOMPONENT REACTIONS (MCRs)

MCRs are reactions that form a new product to gather at least three reactants. The formed product in one-pot involves most of the atoms of substrates. The significance of MCRs contributing the medicinal and combinatorial chemistry is their efficiency for the synthesis of complex or natural products. MCRs are frequently used by synthetic chemists for the efficient production of various molecules from bifunctional starting materials which react intramolecular-fashion.

The advantages of MCRs are environmentally friendly, full-economic, highly diverse, fewer steps etc. They also provide the single-step synthesis of complex molecules. In addition, MCRs prevent the waste of time and expensive purification processes. (Torst, 1995; Noguez et al., 2011)

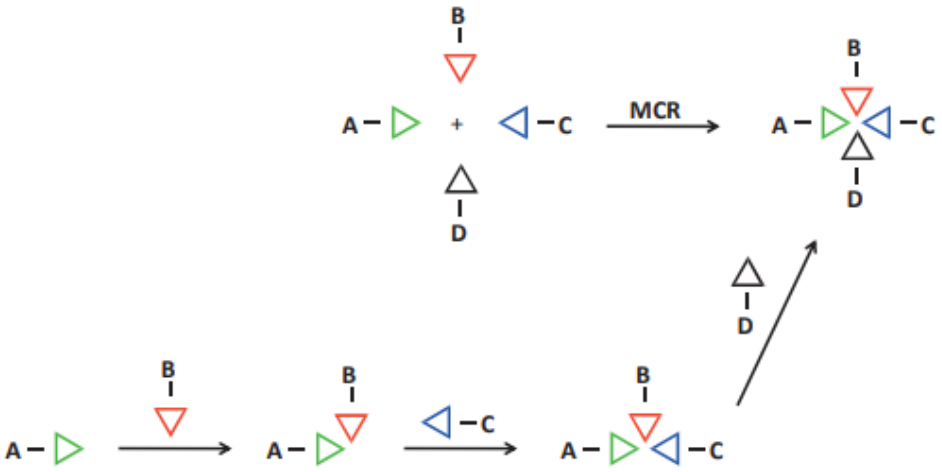


Figure 1.1. Classical multistep synthesis versus multicomponent reactions.

MCRs are convergent reactions that combine at least 3-,4-,5-,6- components and so on (Fig 1.2).

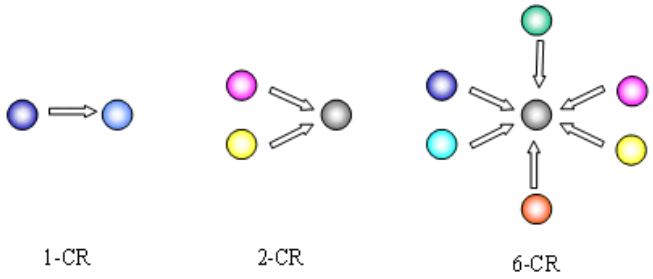
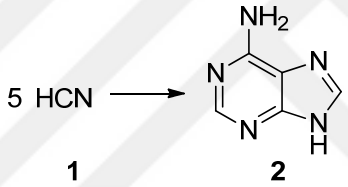


Figure 1.2. The formation of multiple bonds in a single step.

There are so many examples of MCRs in nature and they are used for 150 years. The simplest example is adenine **2** that comprises of 5 mol of isocyanic acid **1**. The efficient examples of MCRs are frequently encountered in the synthetic chemistry literature.



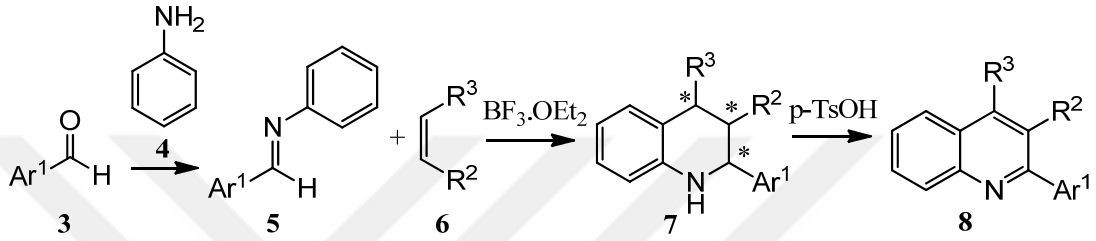
Scheme 1.1. The formation of adenine from isocyanic acid.

1.1.1 Multicomponent Reactions for the Preparation of Acyclic, Cyclic and Heterocyclic Compounds

An important example of two-component (three-center) reactions is the Povarov Reaction. However, 3-CR can be given as S-3CR, Ha-3CR, B-3CR, P-3CR, Gröbcke-Blackburn-Bienaymé, Kabachnik-Fields, Mannich, Petasis, Willgerodt-Kindler and Gewald reactions. U-4CR is a good example of four-component reactions. Six-component (seven-center) and seven-component reaction examples are Mannich-Ugi and Asinger-Ugi Reactions, respectively. (Ruijter et al., 2011; Muller, 2014)

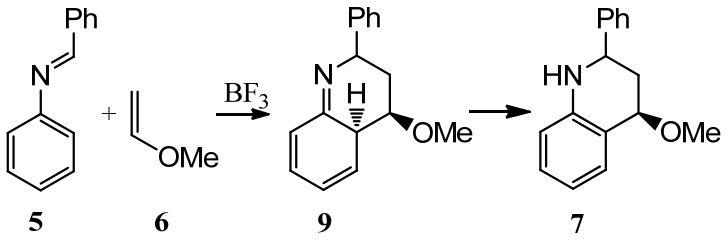
1.1.1.1 Povarov Reaction

In 1963, Povarov reported the original Povarov reaction which is constituted by an aromatic aldehyde **3**, aniline **4**, an arylaldimine **5** using ethyl vinyl ether or ethyl vinyl sulfide **6** as a catalyst to yield 2,4-disubstituted tetrahydroquinolines **7** which are oxidized to quinolones **8**. For instance, synthesis of 1,2,3,4-tetrahydroquinolines is composed of *N*-benzylideneaniline, vinyl alkyl ethers using boron trifluoride etherate as a LA catalyst. (Roy, 2014)



Scheme 1.2. Original protocol of LA-catalyzed one-pot Povarov reaction affording 1,2,3,4-tetrahydroquinolines.

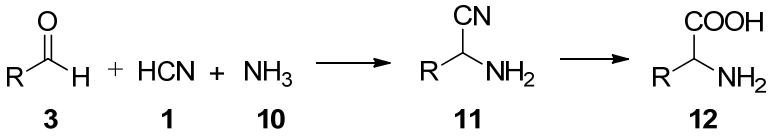
Povarov reactions are two cascade reactions that containing a) LA catalysed such as boron trifluoride, *N*-aryl amine as *N*-phenyl-*C*-phenyl imine **5**, ethylene as MVE **6** and b) 1,3-hydrogen migration to afford THQ product by DFT methods. The point is used for both electrophilic *N*-aryl imine derivative such as *N*-phenyl-*C*-phenyl imine and nucleophilic ethylene such as MVE which is carried out A-DA reaction in theoretical DFT study. (Ríos-Gutiérrez et al., 2015)



Scheme 1.3. LA-catalysed Povarov reaction of *N*-phenyl-*C*-phenyl imine with MVE.

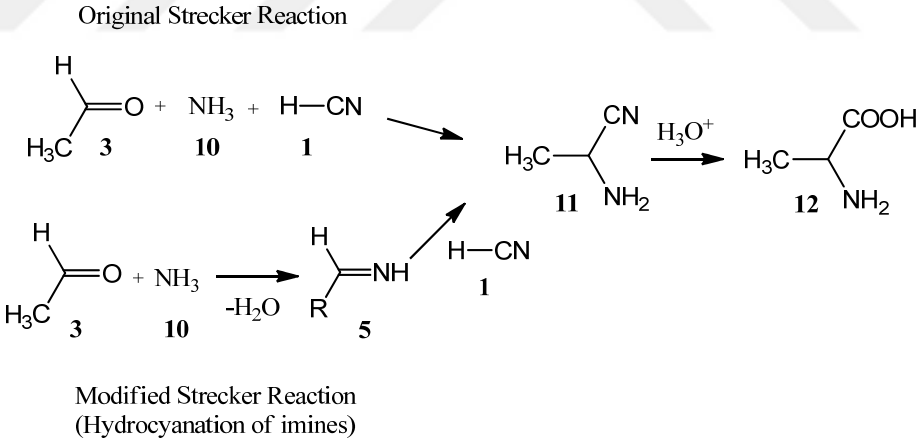
1.1.1.2 Strecker Synthesis

In 1850, Strecker discovered the S-3CR that includes a carbonyl compound (aldehyde or ketone), a potassium cyanide **1** and ammonium chloride to form an α-amino nitrile **11**, which is hydrolyzed to give an α-amino acid **12**. (Strecker, 1850)



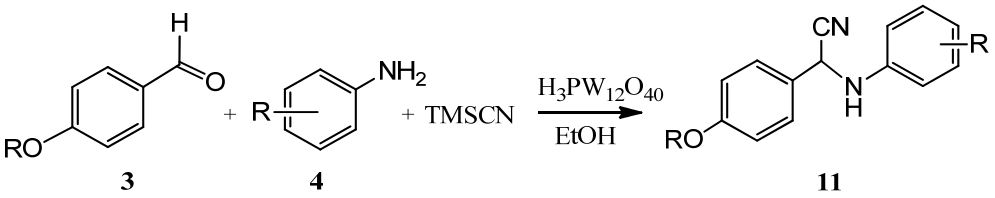
Scheme 1.4. Strecker synthesis of α-aminonitrile.

Original Strecker reaction is a three-component reaction which is an acetaldehyde **3**, an ammonia **10** and a hydrogen cyanide **1** yielding 2-aminopropane nitrile **11**. Then, Strecker intermediate is hydrolyzed to alanine **12**. The aim of this reaction is efficient synthesis of α-amino acids through α-aminonitriles. Modified Strecker reaction is a flat-out synthesis for hydrocyanation of imines. (Kouznetsov and Galvis, 2018)



Scheme 1.5. The classical Strecker reaction and its modified reaction, hydrocyanation of imines.

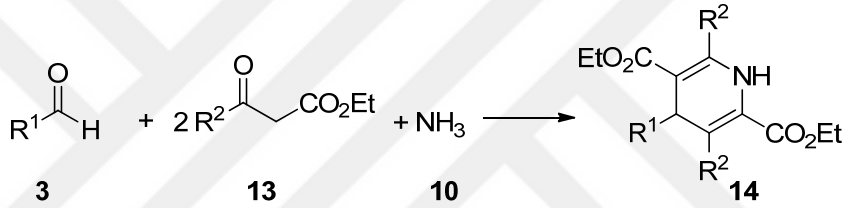
In another version, the formation of α-amino nitriles **11** in one-pot reaction is composed of an aldehyde **3**, amine **4** and excess TMSCN using tungstophosphoric acid (2 mol%) as a catalyst in EtOH at RT for 24 hours. (Khalafi-Nezhad et al., 2013)



Scheme 1.6. Strecker synthesis of benzoxazole/theophylline-based *α*-aminonitriles.

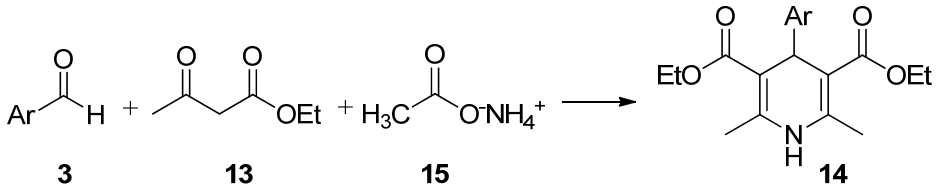
1.1.1.3 Hantzsch Dihydropyridine Synthesis

In 1882, Hantzsch, proposed the Ha-3CR that involves an aldehyde **3** such as formaldehyde, *β*-ketoesters or 1,3-dicarbonyl compounds **13** and an ammonia **10** to give 1,4-dihydropyridine derivatives **14**. (Hantzsch, 1882)



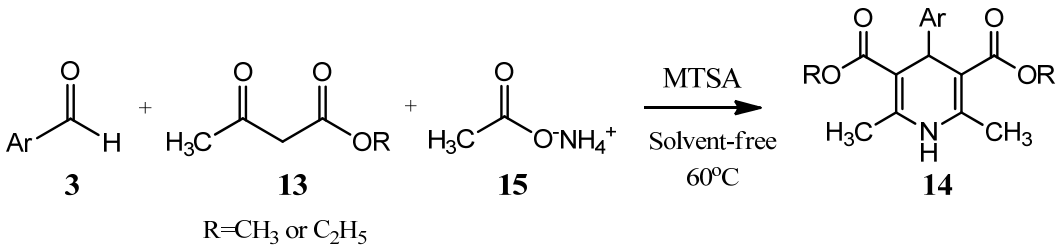
Scheme 1.7. Hantzsch dihydropyridine synthesis.

In a recent example, use of a nanocrystalline MgO as a reusable catalyst in the reaction of aromatic aldehydes **3** with ethyl acetoacetate **13** and ammonium acetate **15** afforded 1,4-dihydropyridines **14** in EtOH very efficiently. (Mirzaei and Davoodnia, 2012)



Scheme 1.8. Hantzsch 1,4-dihydropyridines catalyzed by MgO nanoparticles.

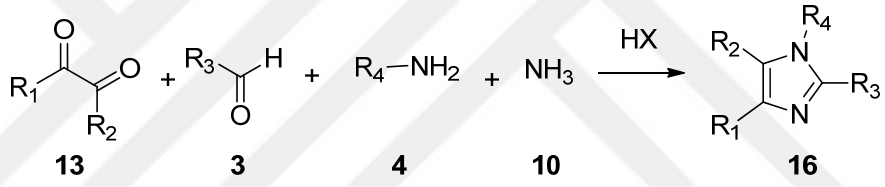
Also, 1,4-dihydropyridines **14** can be obtained with a reaction of aldehydes **3**, ethyl or methyl acetoacetate **13**, ammonium acetate **15** in the presence of MTSA (5 mol%) at 60°C under solvent-free conditions. (Mansoor et al., 2013)



Scheme 1.9. Solvent-free MTSA catalyzed Hantzsch 1,4-dihydropyridine synthesis.

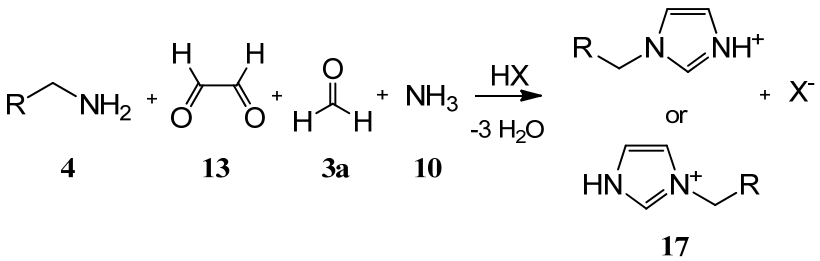
1.1.1.4 Radziszewski Imidazole Synthesis

This reaction is the MCR which is used for the synthesis of imidazole derivatives **16** which comprise of an *α*-dicarbonyl compound **13** such as glyoxal, an aldehyde **3**, ammonia **10** and an amine **4** providing *N*-substituted imidazoles. (Radziszewski, 1882)



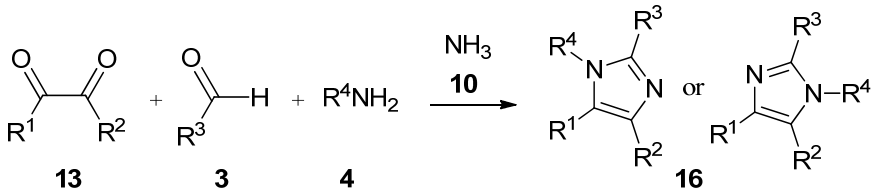
Scheme 1.10. Radziszewski imidazole synthesis.

The synthesis of imidazolium compounds by the modified Radziszewski reaction is carried out by the reaction of primary amines **4**, ammonia **10** and other components as mentioned above to give imidazolium salts **17** under mild conditions (Scheme 1.11). (Lindner, 2016)



Scheme 1.11. Radziswewski imidazole synthesis.

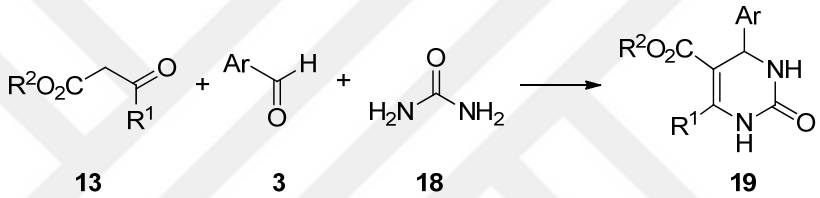
In Debus-Radziszewski MCR version, 1,2-dicarbonyl compounds **13** (e.g. glyoxal, 1,2-diketones or ketoaldehydes), aldehydes **3** and amines **4** in ammonia **10** are mixed to give 1,2,4,5-tetrasubstituted imidazoles **16**. (Wang et al., 2017)



Scheme 1.12. Debus-Radziszewski imidazole synthesis.

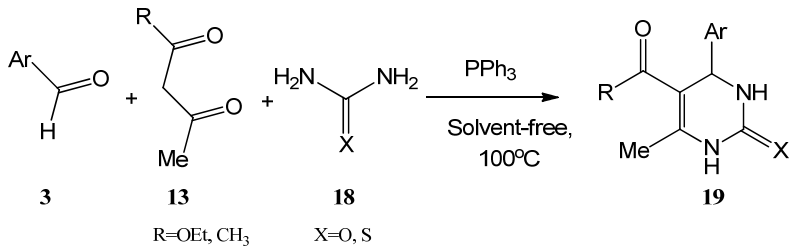
1.1.1.5 Biginelli Dihydropyridine Synthesis

The reaction described by Biginelli in 1892 is a MCR type which is incorporated by a *β*-ketoester **13**, an aromatic aldehyde **3** and an urea **18** to form dihydropyrimidinone derivatives **19** under acidic conditions. (Kappe, 2000)



Scheme 1.13. Biginelli dihydropyridine synthesis.

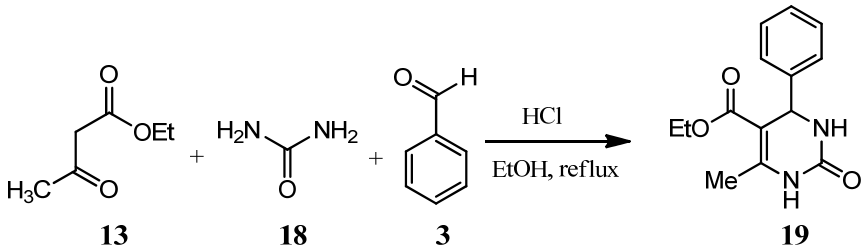
The synthesis of 3,4-dihydropyrimidin-2(1*H*)-one **19** is provided by the reaction of aromatic aldehyde **3**, ethyl acetoacetate **13**, urea or thiourea **18**, TPP as a Lewis base catalyst under neutral and solvent-free conditions at 100°C for 10 hours. The solvents such as acetonitrile, dioxane, EtOH, toluene can be used in the reaction, but best yields are obtained under solvent-free conditions. (Debache et al., 2008)



Scheme 1.14. Biginelli synthesis using TPP as a Lewis base catalyst.

3,4-dihydropyrimidin-2(1*H*)-ones **19** are also prepared by an acid-catalyzed reaction of active methylene compound such as ethyl acetoacetate **13**, urea **18**,

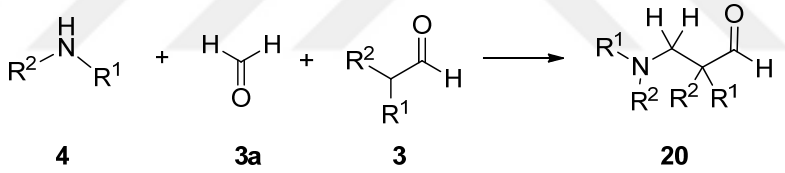
benzaldehyde **3** in EtOH under reflux. The catalysts can be Brønsted or Lewis acids, biocatalysts, heterogeneous catalysts and so forth. (Nagarajaiah et al., 2016)



Scheme 1.15. Acid-catalysed Biginelli reaction.

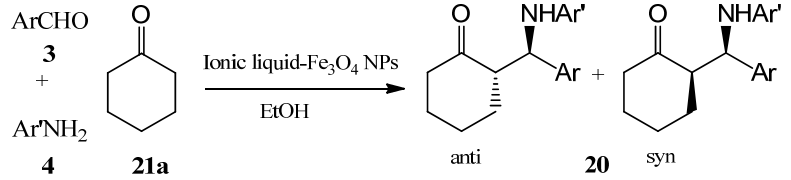
1.1.1.6 Mannich Reaction

In 1912, Mannich, explored the three-component reaction which consist of a primary or secondary amine **4**, a non-enolizable carbonyl compound and an enolizable carbonyl compound to convert a *β*-aminocarbonyl compound **20** (Mannich base) in the presence of acid or base catalyst. (Mannich and Krösche, 1912)



Scheme 1.16. A Typical Mannich reaction giving *β*-amino carbonyl compounds.

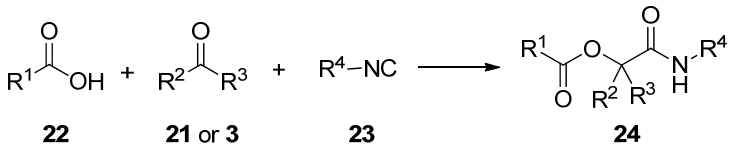
Very recently, synthesis of *β*-amino carbonyl compounds **20** is procured via a reaction of arylaldehydes or aromatic aldehydes **3**, arylamines or amines **4** and cyclohexanone **21** in the presence of IL-Fe_3O_4 NPs catalysis in EtOH under ultrasonic irradiation. (Ghomi and Zahedi, 2017)



Scheme 1.17. Mannich reaction catalyzed by IL–MNPs.

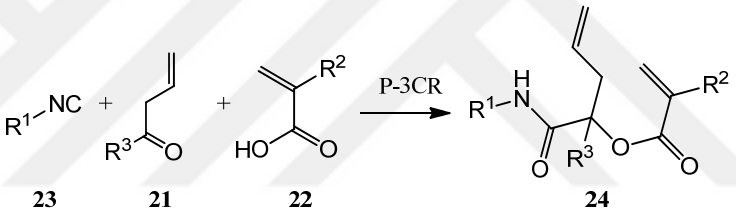
1.1.1.7 Passerini Reaction

This reaction stated by Passerini in 1921 is a P-3CR which includes a carboxylic acid **22**, a carbonyl compound (aldehyde **3** or ketone **21**) and an isocyanide **23** to prepare an *α*-acyloxycarboxamide **24**. (Passerini, 1923)



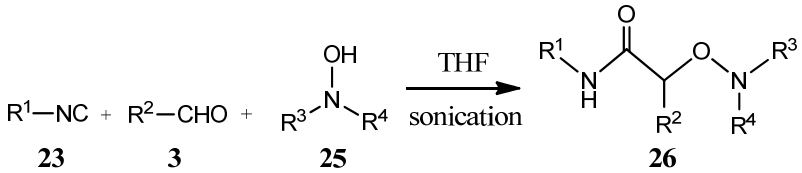
Scheme 1.18. A typical Passerini reaction giving *α*-acyloxycarboxamides.

For example, a mixture of isocyanide **23**, an allyl ketone **21** and carboxylic acids **22** afford an *α,β*-unsaturated lactone **24** in one-pot. (Schwäblein and Martens, 2011)



Scheme 1.19. Synthesis of *α,β*-unsaturated lactones via Passerini reaction.

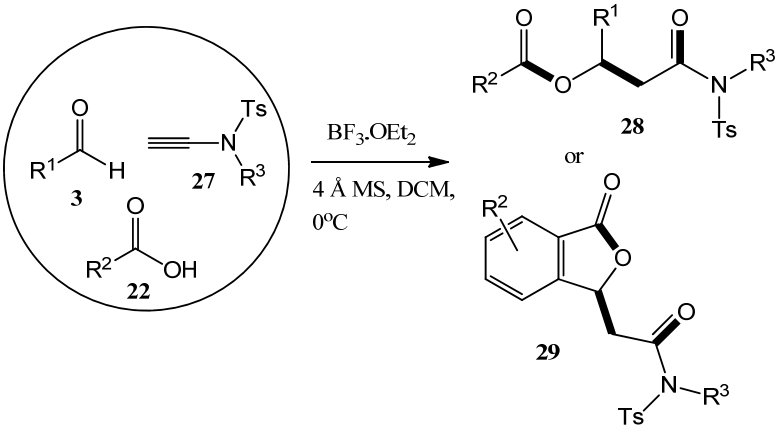
An efficient synthesis of *α*-aminoxy amides **26** can be done by the reaction of isocyanides **23**, acetaldehydes **3** and *N*-hydroxamic acids **25** in THF by sonication with the yield of 97%. However, aromatic aldehydes ended up with moderate yields. (Chandgude and Dömling, 2016)



Scheme 1.20. Synthesis of *α*-aminoxy-amides by ultrasonication.

Also, the synthesis of *β*-acyloxy amides **28** is comprised of carbonyls or aldehydes **3**, carboxylic acids **22** and ynamides **27** using boron trifluoride etherate (20 mol%) with 4Å MS in DCM under argon at 0°C for 1 hour. On the other hand,

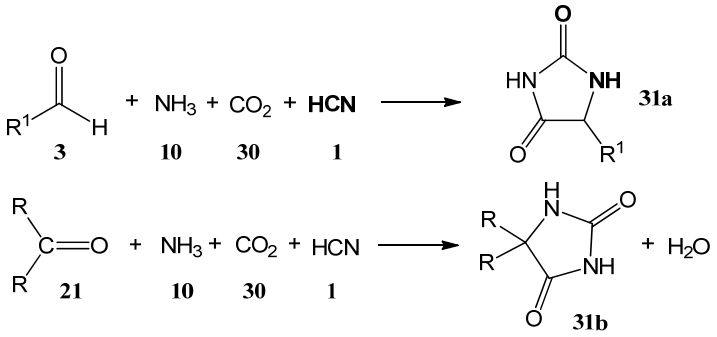
the synthesis of phthalides **29** is achieved by a mixture of 2-formylbenzoic acids **22** and ynamides **27**. (Shen et al., 2017)



Scheme 1.21. Passerini reaction by boron trifluoride-etherate catalyst.

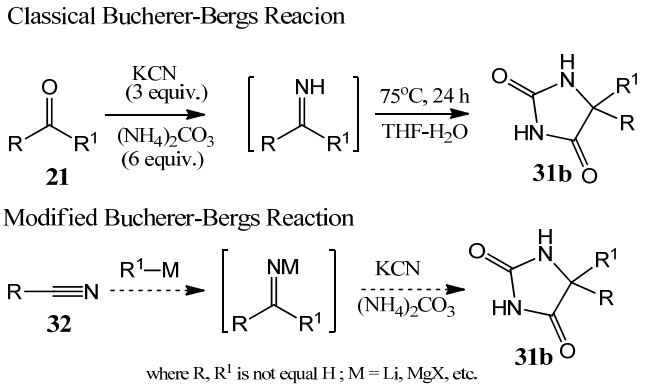
1.1.1.8 Bucherer-Bergs Hydantoin Synthesis

The reaction proposed by Bergs (1929) and Bucherer (1934) is a BB-4CR in which the formation of hydantoin **31** is provided by using carbonyl compounds (aldehyde **3** or ketone **21**), KCN, $(NH_4)_2CO_3$ and carbon dioxide **30**. (Bucherer and Barsch, 1934; Chubb et al., 1980)



Scheme 1.22. A Classical Bucherer-Bergs hydantoin synthesis.

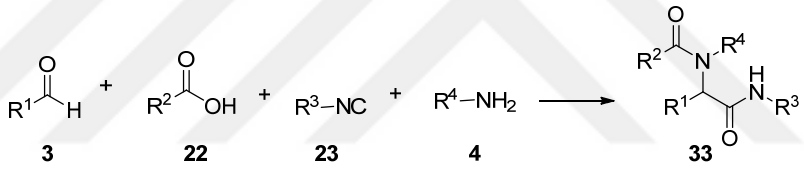
A modified BB-4CR is achieved by a reaction of nitrile **32** with organometallic reagents (e.g. RMgX or RLi) yielding 5,5‘-disubstituted hydantoin **31b** in moderate-good yields. After all, Grignard reagents are also used and organometallic reagent is added to nitrile using copper (I) iodide as catalyst through the metallated imine intermediate. (Montagne and Shipman, 2006)



Scheme 1.23. Classical and Modified Bucherer-Bergs reactions.

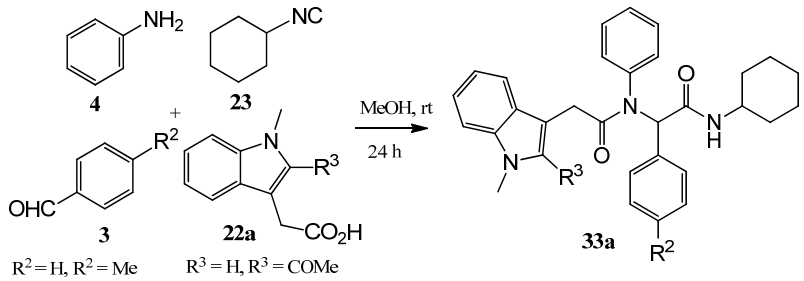
1.1.1.9 Ugi Reaction

In 1959, Ugi observed the four-component reaction (U-4CR) that is originated from a carbonyl compound (aldehyde **3** or ketone **21**), a carboxylic acid **22**, an isocyanide **23** and an amine **4**, affording α-aminoacyl amide derivatives **33**. (Ugi, 1959)



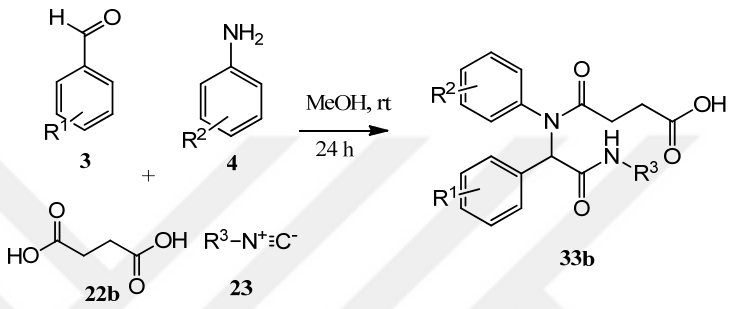
Scheme 1.24. Ugi reaction affording α-acylaminocarboxamides.

In an Ugi reaction, aniline **4**, benzaldehyde **3**, indoleacetic acid **22a** and cyclohexyl isocyanide **23** were combined in MeOH and then corresponding product **33a** obtained in good yields. After addition of corresponding indole carboxylic acids, the reaction mixture was stirred for 10 min, then cyclohexyl isocyanide is added and stirred at RT for 24 hours to give the desired products. (Neochoritis et al., 2016)



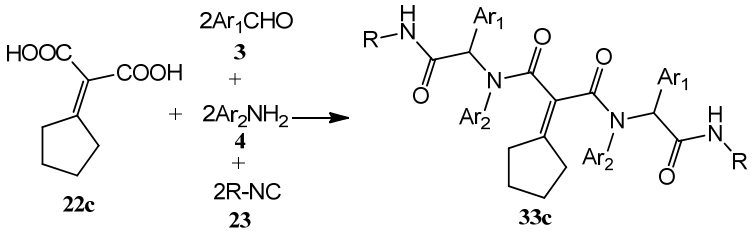
Scheme 1.25. U-4CR involving the indoleacetic moiety.

Aromatic aldehydes **3** bearing EDG and EWG, aromatic amines **4** involving the strongly EWG (e.g. nitroanilines), aniline derivatives bearing EDG and weakly EWG are useful for Ugi adducts. Finally, isocyanides **23** incorporating naphthyl isocyanide, cyclohexyl isocyanide and *tert*-butyl isocyanide are also used to gain bis-amides **33**. In such an Ugi reaction, aldehyde, amine in MeOH were mixed for 30 min. at room temperature and equal moles of succinic acid **22b** and isocyanide **23** are added to the reaction mixture and mixed for 24 h supplying the desired products **33b**. (Halimehjani and Sharifi, 2017)



Scheme 1.26. Ugi-4CR using succinic acid.

In a recent example of Ugi reaction, synthesis of symmetrical coumarine-3-carboxamide derivatives **33c** were provided by a reaction of 2-cyclopentylidene malonic acid **22c**, aromatic aldehydes **3**, aromatic amines **4** and isocyanides **23** in MeOH at RT. (Mokhtari et al., 2017)

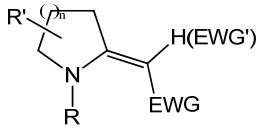


Scheme 1.27. Synthesis of tetraamides via U-4CR.

1.2 HETEROCYCLIC ENAMINES

An enamine system that contains N and the C=C bond on part of the ring is known as heterocyclic enamine **34** which acts as an ambident nucleophile because of the nitrogen lone pair electrons are delocalized into the double bond that increasing

enaminic reactivity. Also, the secondary amines are willing to attend in the nucleophilic reactions. The general structure of the heterocyclic enamines **34** is shown as below (Figure 1.3).



34

EWG, EWG' = CO_2R'', COR'', CN,

R = H, alkyl, aryl; R' = substituent(s)

Figure 1.3. The general structure of heterocyclic enamines.

The double bond isomerism is affected by agents affecting the stability of a double bond on the ring (e.g. *exo*- or *endo*-), the magnitude of ring and conjugation in the heterocyclic enamines. Exocyclic enamine contains the nitrogen on part of the ring with exocyclic C=C double bond. But, endocyclic enamine involves the nitrogen and C=C double bond on part of the cycle (Figure 1.4).

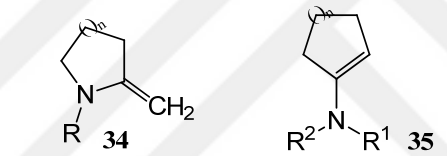
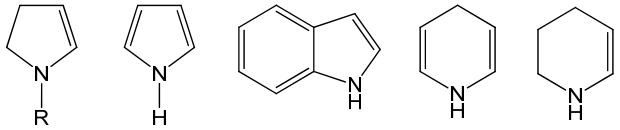


Figure 1.4. The structures of *exo*- and *endo*- cyclic enamines.

Other types of heterocyclic enamines can be given as pyrroline **36**, pyrrole **37**, indole **38**, 1,4-dihydropyridine **39** and tetrahydropyridine **40** (Scheme 1.28).

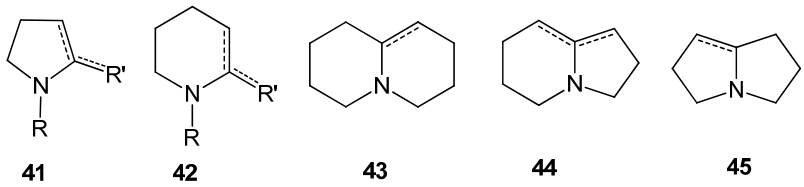


36 **37** **38** **39** **40**

Scheme 1.28. The examples of some heterocyclic enamines.

Furthermore, the heterocyclic enamines are versatile intermediates in the synthesis of several fused heterocycles, alkaloids and natural products (Scheme 1.29). (Cheng et al., 2014; Alvarez□Builla and Barluenga, 2012) Some heterocyclic compounds are substituted dehydroderivatives of pyrrolidine **41**, piperidine **42**, the derivatives of dehydro-1-azacycloalkanes which including the main scaffolds:

enamines of quinolizidine **43**, indolizidine **44**, pyrrolizidine **45** and their benzoderivatives as shown below. (Cook, 2017)

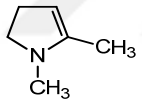
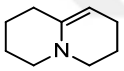
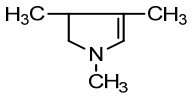
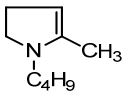
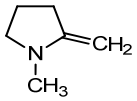
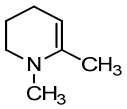
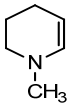
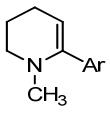
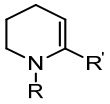
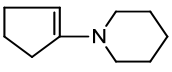
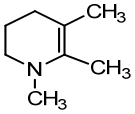
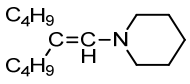


Scheme 1.29. The derivatives of some heterocyclic compounds.

1.2.1 Physical and Spectroscopic Properties of Heterocyclic Enamines

UV spectra of enamines give the enamine absorption band at 220-240 nm (ε_{max} = 5000-9000). (Patai, 1982) Besides, IR spectra of enamines give the enaminic double-bond stretching vibration in the range of 1600-1680 cm^{-1}. Conjugation with an aromatic ring decreases the stretching frequency (ν) under 1600 cm^{-1} (Table 1.1).

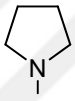
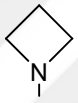
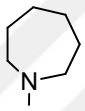
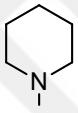
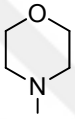
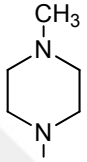
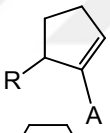
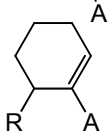
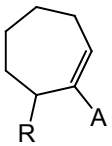
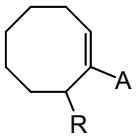
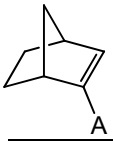
Table 1.1. IR C=C bond stretching frequencies of some enamines.

Compound	V_{max} Range (cm^{-1})	Compound	ν (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.	

In proton NMR of enamines, the hydrogens are defined with the degree of nitrogen electron pair double bond interaction. The *β*-proton of the enamine has larger shielding when increasing n-π electron interactions. For instance, the

pyrrolidine enamine signals have the largest n-π electron interactions, are shifted furthermost upfield in Table 1.2. However, morpholine and *N*-methylpyrazoline enamines have the lowest nitrogen-double bond overlap, *β*-vinyl proton signals are shifted furthermost downfield. Also, all these cyclic enamine *β*-vinyl signals are shifted upfield with respect to cyclic alkenes. For instance, cyclopentene and cyclohexene indicate olefinic proton signals at 5.60 and 5.59 ppm respectively. However, the representative enamines of them have *β*-vinyl proton signals at least 1 ppm upfield from those of the unsubstituted alkenes. The chemical shifts of cyclic enamines rely upon the ring magnitude of the cycloalkane. If the ring magnitude is increased from a five-membered ring to a 12-membered ring, the *β*-proton signal shifts downfield more, gaining the 7-membered ring thus shifts upfield again when the ring magnitude is larger (Table 1.2). (Cook, 2017)

Table 1.2. The *β*-vinyl ^{1}H-NMR chemical shifts of cyclic enamines.

				$(CH_3)_2N$			
	3.95	4.20	——	4.16	4.26	4.39	4.40
	4.20	4.04	4.25	4.41	4.58	4.61	4.56
	4.37	——	——	——	4.78		4.85
	4.08	——	——	——	4.48	4.50	4.53
	4.13	——	4.27	4.15	4.48	4.60	4.52

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

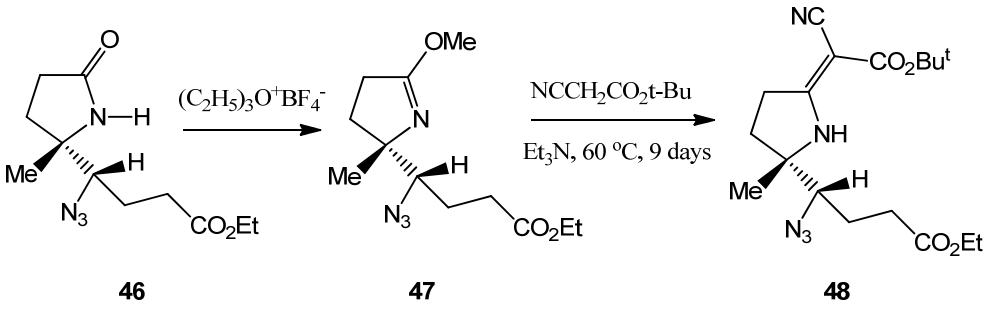
1.2.2 Preparation of Heterocyclic Enamines

The synthesis of heterocyclic enamines can be given in two categories. First one is *N*-heterocyclic compounds including lactam derivatives as starting materials. Second one is the construction of *N*-heterocyclic ring as a key step from non-heterocyclic materials.

1.2.2.1 Synthesis of Heterocyclic Enamines Starting from *N*-heterocyclic derivatives

Via The Eschenmoser Synthesis:

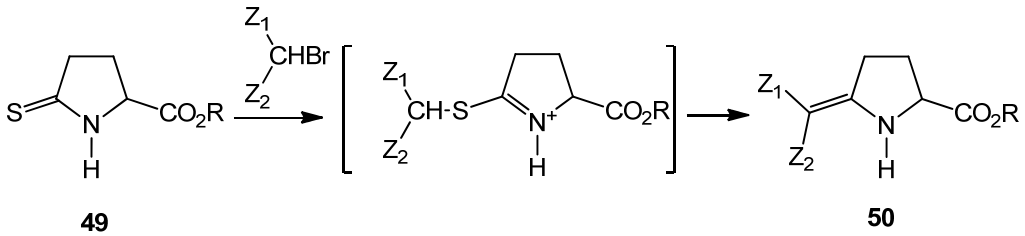
In 1964, the first synthesis of heterocyclic enamines are found by Eschenmoser et al. They reported a synthetic route to the corrin system that is a condensation reaction between active methylene compounds with lactim ethers **47**. The heterocyclic enamine **48** was formed by the reaction of γ-lactam derivative **46** with $(C_2H_5)_3O^+BF_4^-$, with $NCCH_2CO_2t$-Bu using Et_3N at 60°C in 86% yield. (Bertele et al., 1964)



46 **47** **48**

Scheme 1.30. The Eschenmoser synthesis of enamines.

Moreover, alkylidenepyrrolidines **50** can be obtained from the sulfide contraction of thiolactams **49** which is useful for the synthesis of *β*-enaminoesters. (Wang et al., 2013)

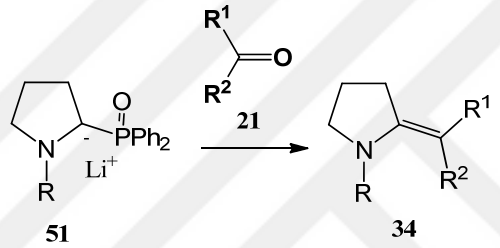


49 **50**

Scheme 1.31. The synthesis of *β*-enaminoesters via sulfide contraction.

From Lactam Acetals or Heterocyclic Iminium Salts:

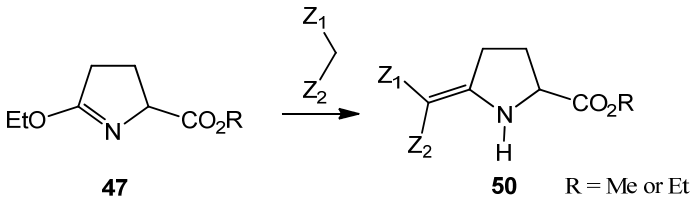
The lithiated adducts **51** are reacted with ketones **21** for overnight and after the work-up, heterocyclic enamines **34** are obtained in 81% yield. Functional groups are chosen in this way i.e. R = CH_3, R^1 = Ph, R^2 = H, respectively. (Bakker et al., 1984)



Scheme 1.32. The synthesis of heterocyclic enamines using lithiated adducts.

Via Condensations of Active Methylenes with Lactim Ethers:

The other method is a reaction of ethyliminoethers **47** with the active methylene reagents for the synthesis of *β*-enaminoesters **50**. (Fasseur et al., 1992)

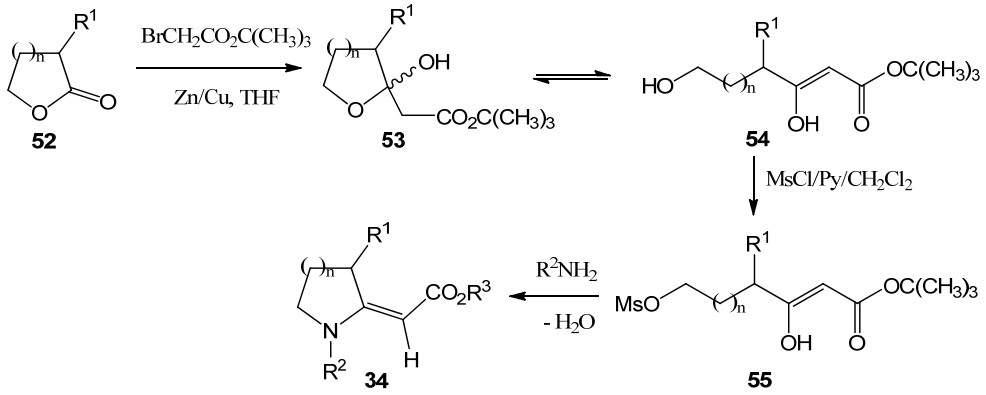


Scheme 1.33. Synthesis of *β*-enaminoesters using active methylene compounds.

From Direct Coupling Reaction of Lactams or Thiolactams with Organometallic Reagents:

Synthesis of heterocyclic enamines **34** was reported by a practical formal ring transformation reaction of lactones **52** over few steps. In last step, the

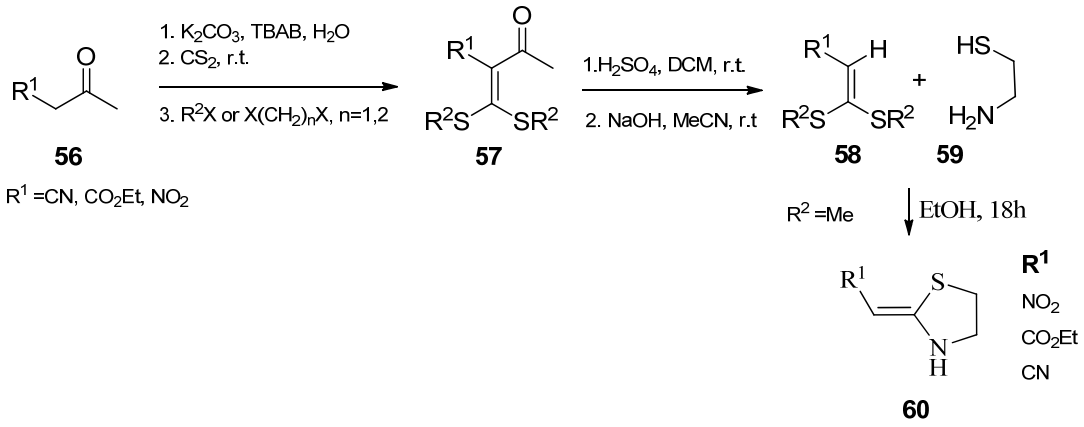
methylsulfonate intermediate **55** are reacted with aliphatic amines to yield *N*-alkyl heterocyclic enamines **34** at RT in DCM. (Wang et al., 2003)



Scheme 1.34. Preparation of heterocyclic enamines via the ring transformation of lactones.

1.2.2.2 Preparation of Heterocyclic Enamines from Non-heterocyclic Compounds

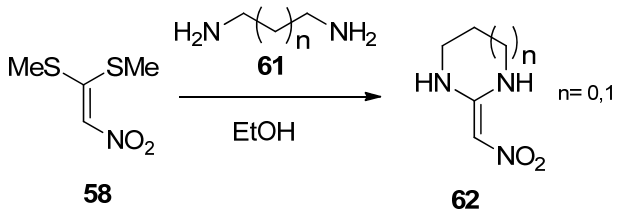
As an heterocyclic enamine, preparation of 2-(nitromethylene) thiazolidine **60** can be done by reacting 1,1-bis(methylmercapto)-2-nitroethylene **58** with cysteamine **59** in ethanol. (Rajappa and Advani, 1982) Besides, another efficient preparation of methylenethiazolidines bearing different EWG groups have been performed over ketene dithioacetals **57** in good yields (Scheme 1.35). (Yuan et al., 2010)



Scheme 1.35. Synthesis of 2-(nitromethylene) thiazolidine and other 2-substituted methylenethiazolidines.

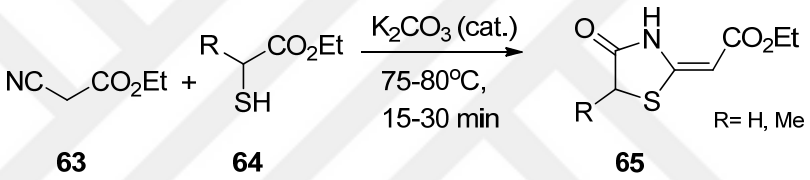
Using the similar method, (2-nitromethylene)-imidazolidines (or -hexahydropyrimidines) **62** were synthesized by cyclisation of 1,1-bis(methylthio)-2-

nitroethylene **58** with suitable diamines **61** in ethanol at reflux (Scheme 1.36). (Kalisiak et al., 2011)



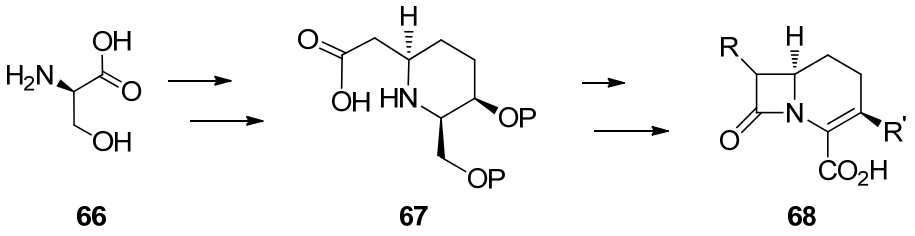
Scheme 1.36. Synthesis of (2-nitromethylene)-imidazolidines or hexahydro-pyrimidines.

Besides, methylene-4-oxothiazolidines **65** were prepared by the base-catalyzed reaction of ethyl cyanoacetate **63** and α-mercapto esters **64** under neat conditions via a simple way (Scheme 1.37). (Stojanović et al., 2011)



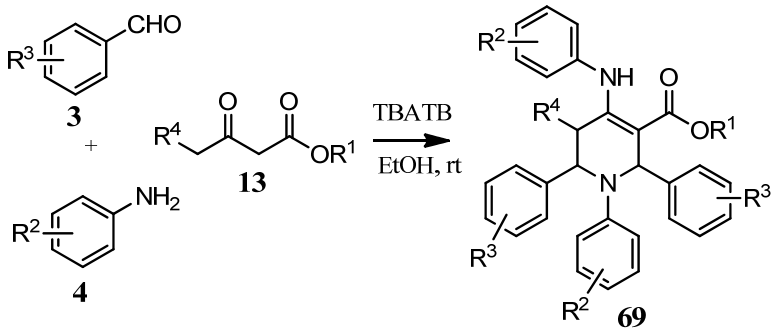
Scheme 1.37. Synthesis of methylene-4-oxothiazolidines.

In 1998, the synthesis of carbacephems **68** from *D*-serine **66** was discovered over reducing the double bond of enaminoesters **67** followed by cyclization (Sheme 1.38). (Folmer et al., 1998)



Scheme 1.38. Synthesis of carbacephems starting from *D*-serine.

Some piperidine-based enamines **69** were prepared by the reaction of 1,3-dicarbonyl compounds **13**, aromatic aldehydes **3**, amines **4** using TBATB in moderate yields. (Khan et al., 2010)

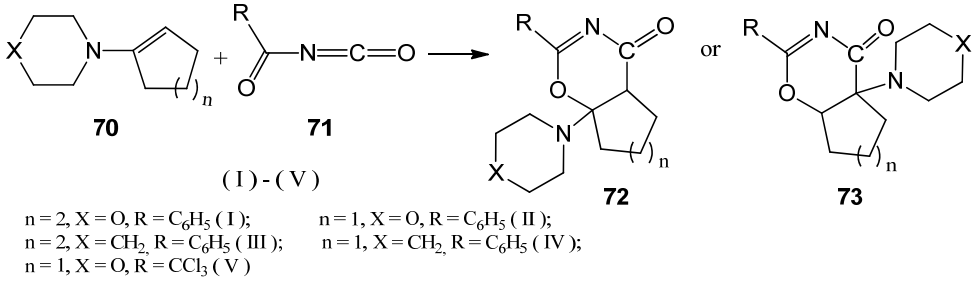


Scheme 1.39. Synthesis of piperidine-based enamines.

1.2.3 Reactions of Heterocyclic Enamines

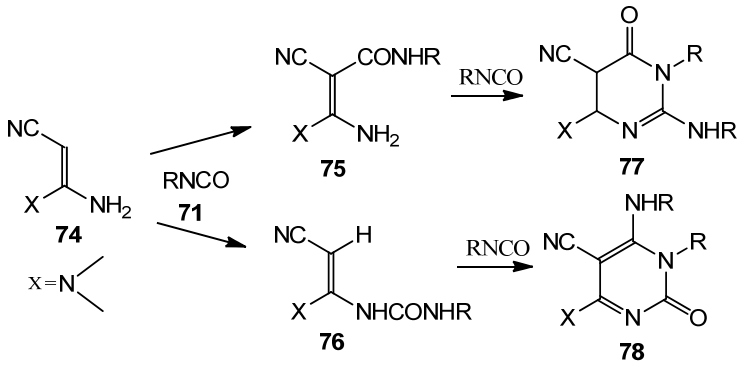
1.2.3.1 Reactions of Enamines with isocyanates

Benzoyl isocyanate **71** reacts with cyclic enamines **70** e.g. morpholinocyclohexene, morpholinocyclopentene, piperidinocyclohexene or piperidinocyclopentene to give 1,3-oxazin-4-one derivatives **72**, **73** via 1,4-cycloaddition reactions. Also, trichloroacetyl isocyanate reacts with the compounds except for the morpholinocyclopentene to afford 2-azetidinone derivatives via 1,2-cycloaddition reaction. (Arbuzov et al., 1972)



Scheme 1.40. The reaction of benzoyl and trichloroacetyl isocyanates with cyclic enamines.

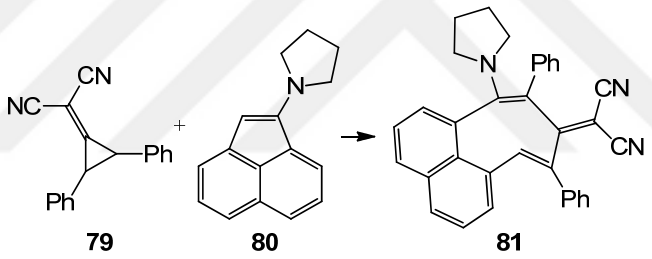
Heterocyclization reactions contain the reaction of enamines **74** with isocyanates **71** and isothiocyanates. For instance, the reaction of enaminonitriles **75**, **76** with benzyl isocyanate or phenyl isocyanate provides 4-pyrimidinone and 2-pyrimidinone derivatives **77**, **78** respectively. (Granik et al., 1998)



Scheme 1.41. The heterocyclization giving pyrimidinone derivatives.

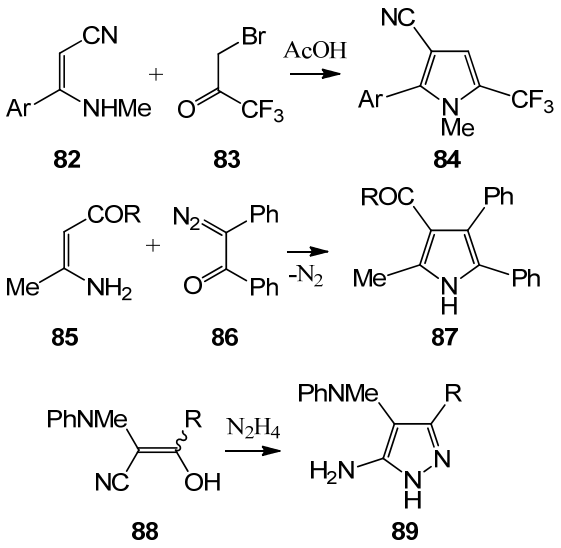
1.2.3.2 Reactions of Enamines with *α,β*-unsaturated Compounds

An unusual enamine, 1-(1-pyrrolidinyl) acenapthalene **80** reacts with the 2-(1,2-diphenyl-3-cyclopropenylidene)propanedinitrile **79** to afford the eight-membered cyclic compound **81** at RT in 92% yield. (Tsuge et al. 1982)



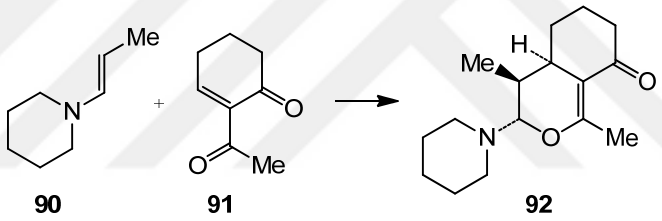
Scheme 1.42. The synthesis of eight-membered cyclic compound using enamines.

The synthesis of the N-methylpyrrole **84** is carried out by the reaction of secondary enamine **82** with 1-bromo-3,3,3-trifluoro-2-propanone **83** using acetic acid under reflux. Besides, the synthesis of 1*H*-pyrroles **87** are provided by the reaction of primary *β*-carbonylenamines **85** with diazodeoxybenzoin **86**. Also, the pyrazoles **89** are synthesized from the reaction of enamines **88** with hydrazine. (Boyd, 1994)



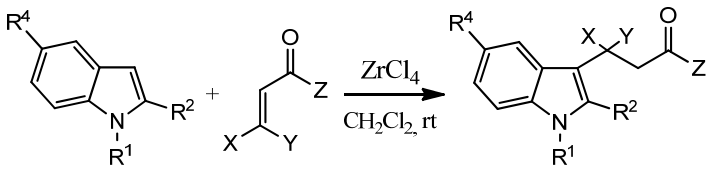
Scheme 1.43. The synthesis of pyrroles and pyrazoles from enamines.

The synthesis of dihydropyran **92** comprises of 2-acetylcyclohex-2-enone **91** with 1-piperidinopropene **90**. (Boyd, 1994)



Scheme 1.44. The synthesis of dihydropyran from enamines.

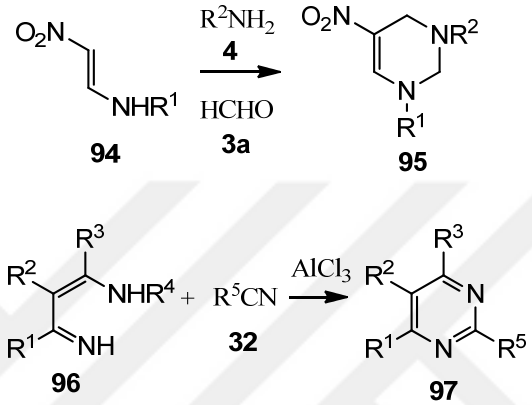
The synthesis of Michael adducts **93** is provided by the reaction of indole **38** with methyl vinyl ketone **21** in the presence of 2% mol of $ZrCl_4$ at RT in 92% yield. The point is that $ZrCl_4$ is a highly selective and efficient catalyst for the Michael addition of heterocyclic enamines with *α,β*-unsaturated olefins. (Kumar et al., 2006)



Scheme 1.45. Michael addition of het. enamines with *α,β*-unsaturated olefins.

1.2.3.3 Reactions of Enamines with aromatic amines and nitriles

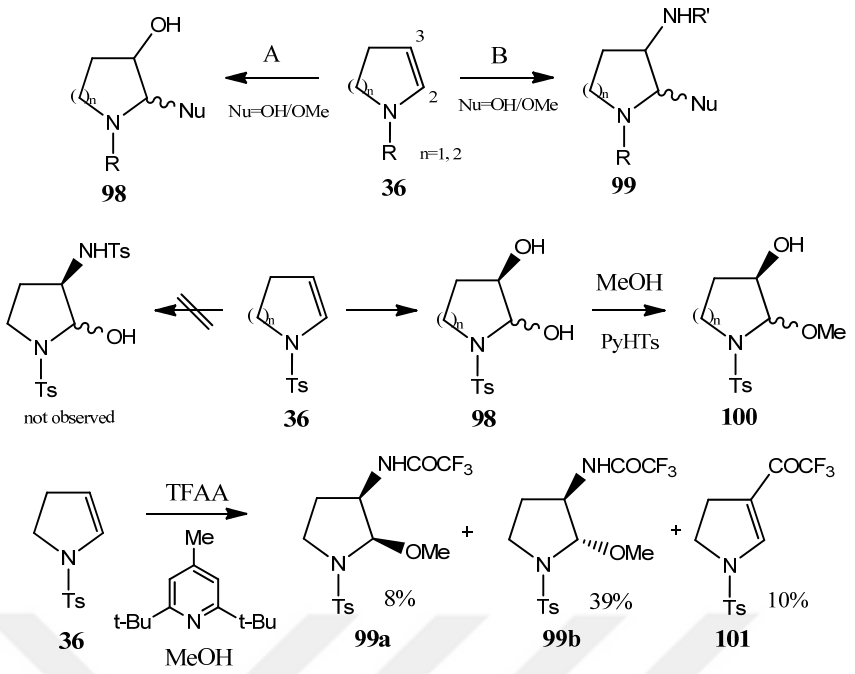
The synthesis of 1,2,3,4-tetrahydropyrimidines **95** is achieved by the reaction of *β*-nitroenamines **94** with primary aliphatic amines **4** and formaldehyde **3a**. (Khan et al, 2010) Moreover, the pyrimidines **97** are synthesized over the reaction of the azadienes **96** with aliphatic or aromatic nitriles **32** using aluminium chloride as a catalyst. (Boyd et al., 1994)



Scheme 1.46. The synthesis of pyrimidines vs the general synthesis of pyrimidines.

1.2.3.4 Reactions of Enamines with Oxygen and Nitrogen Nucleophiles

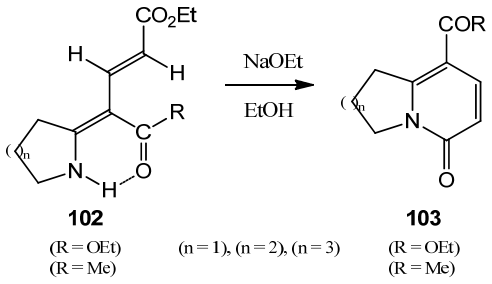
N-substituted heterocyclic enamines give epoxidation and hydroxylation reactions over path A and aminohydroxylation and aziridination reactions over path B. For example, epoxidation is carried out with *N*-toluenesulfonyl derivatives **36** under the Jacobsen's conditions including NMMO/*m*-CPBA oxidants and 3-hydroxy-2-methoxypyrrolidine **98** and piperidine derivatives **99** are obtained. Also, dihydroxylation is carried out to *N*-toluenesulfonyl derivatives **36** under the Sharpless conditions with Admix-*β*. The crude diols **98** are reacted with MeOH using PyHTs to obtain 2-methoxy adducts **100**. However, there is no observable amination, only 2,3-diols products are obtained, these are converted to the methoxy adducts. Lastly, *N*-toluenesulfonyl derivative **36** is added to Mn≡N complex (TFAA, 2,6-di(tert-butyl)-4-methylpyridine between -78ºC and RT to yield the *cis*- and *trans*-2-methoxy-3-*N*-(trifluoroacetyl) aminopyrrolidine **99a-b** and trifluoroacetylated enamine derivatives **101**. (Sunose et al., 1998)



Scheme 1.47. Epoxidation, dihydroxylation, aminohydroxylation, aziridination and aminohydroxylation of enamines.

1.2.3.5 Intramolecular Cyclisation Reactions of Enamines

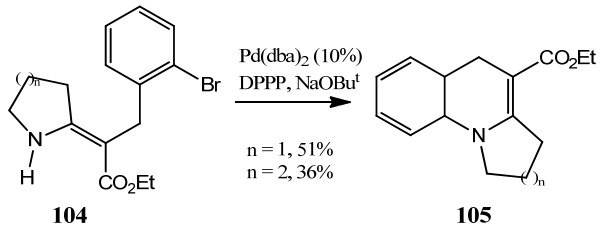
The synthesis of fused heterocycles is formed by intramolecular cyclisation of Michael adduct **102** with sodium ethoxide in ethanol yielding the 2-pyridinone-fused heterocyclic compounds **103**. (Wang et al., 1999)



Scheme 1.48. The synthesis of fused heterocycles.

A seven-membered heterocyclic enamine is reacted with *o*-bromobenzyl bromide to gain desired compound in CH_3CN under reflux conditions. When only the strong base is used as NaH, the *C*-benzylated products **104** are obtained in moderate yields. *C*-benzylated heterocyclic enamines **104** react through intramolecular cyclization with its bromobenzene moiety using Pd-catalyst yields the

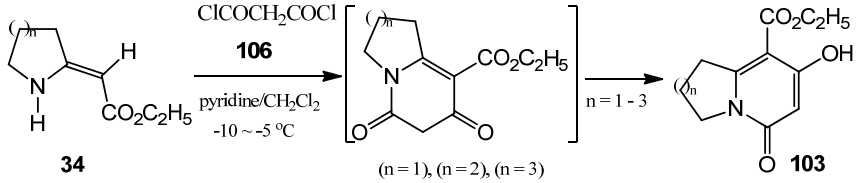
fused heterocyclic derivatives. At the same time, the coupling reaction was carried out between secondary enamine nitrogen and bromobenzene moiety using Pd catalyst at 110°C for 24 hours for preparation of fused 1,4-dihydroquinolines **105**. (Liu et al., 2003)



Scheme 1.49. The synthesis of fused 1,4-dihydroquinoline derivatives.

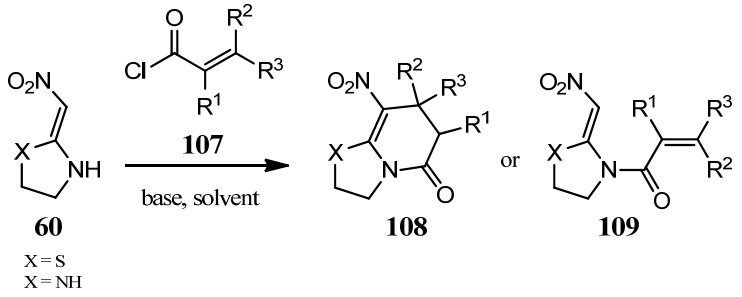
1.2.3.6 Reactions of Enamines with Carboxylic Acid Derivatives

Polyfunctionalized fused heterocycles can be prepared via the reaction of heterocyclic secondary enamines with dicarboxylic acid derivatives. For example, heterocyclic secondary enamines **34** are reacted with malonyl chloride **106** using pyridine to yield hydroxylated 2-pyridinone fused heterocyclic derivatives **103** under -5°C smoothly. (Cheng et al., 2001)



Scheme 1.50. The synthesis of 2-pyridinone fused heterocycles.

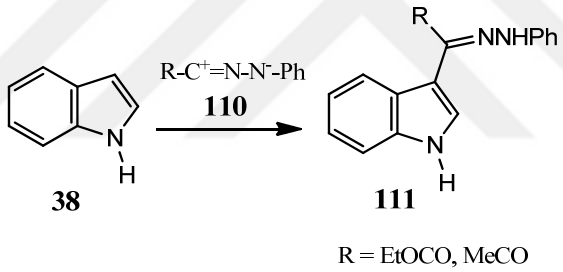
Also, thiazolo- and imidazolo-pyridinones can be synthesized via cyclocondensation reaction of *β*-nitroenamines such as (2-nitromethylene) thiazolidine or imidazolidine **60** with acryloyl or cinnamoyl chlorides **107** yielding the corresponding products **108**, **109** under mild basic conditions. (Yıldırım et al., 2014a)



Scheme 1.51. The synthesis of thiazolo(imidazolo) pyridinones from enamines.

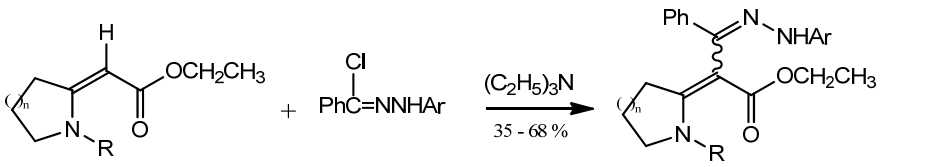
1.2.3.7 Reactions of Enamines with Nitrilimine Dipoles

The reaction of indole derivatives **38** as enamines with nitrilimines **110** have been investigated. Obviously, unsubstituted indole was reacted with *C*-acetyl- and *C*-ethoxycarbonyl nitrilimines to gain the desired 1,3-adducts **111** in low yields. (Shawali and Edrees, 2006)



Scheme 1.52. The synthesis of heterocyclic enamines with nitrilimines.

Also, the ester-substituted heterocyclic enamines **34** were reacted with nitrilimine dipoles **110** in the presence of Et_3N to afford *C*-adduct derivatives **112** via the nucleophilic reaction at RT. Also, *N*-methylated heterocyclic enamines were synthesized through the nucleophilic addition at RT in this way. (Miao et al., 2000)



34

n = 1 - 3

R= H
R = CH_3

110

Ar = Ph
Ar = 2,4-$(NO_2)_2C_6H_3$

112

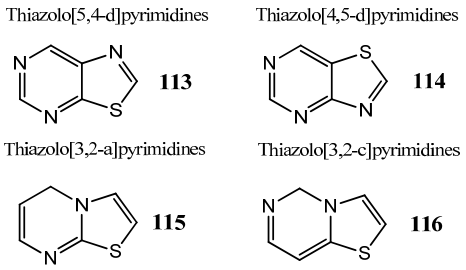
n = 1 - 3

R = H, Ar = Ph
R = H, Ar = 2,4-$(NO_2)_2C_6H_3$
R = CH_3, Ar = 2,4-$(NO_2)_2C_6H_3$

Scheme 1.53. Nucleophilic reaction of heterocyclic enamines with nitrilimines.

1.3 THIAZOLOPYRIMIDINES

Thiazolopyrimidines are originated from the two important cores that have a thiazole and pyrimidine in their structures. Thiazole is a heterocycle involving sulphur and nitrogen atoms at positions 1 and 3 of the five-membered ring. Pyrimidine is a heterocyclic compound including two nitrogen atoms at positions 1 and 3 of the six-membered ring. The varieties of thiazolopyrimidines are the thiazolo[5,4-*d*]pyrimidines **113**, thiazolo[4,5-*d*]pyrimidines **114**, thiazolo[3,2-*a*]pyrimidines **115** and thiazolo[3,2-*c*]pyrimidines **116**, are important for the pharmaceutical and medicinal chemistry. (Yıldırım et al., 2014b)

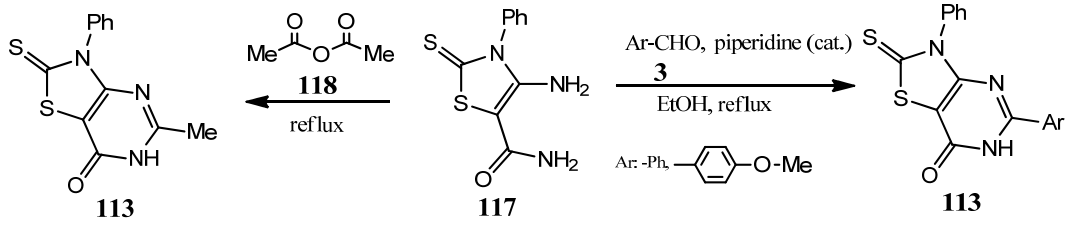


Scheme 1.54. The general structures of thiazolopyrimidines.

1.3.1 Synthesis of Thiazolopyrimidines

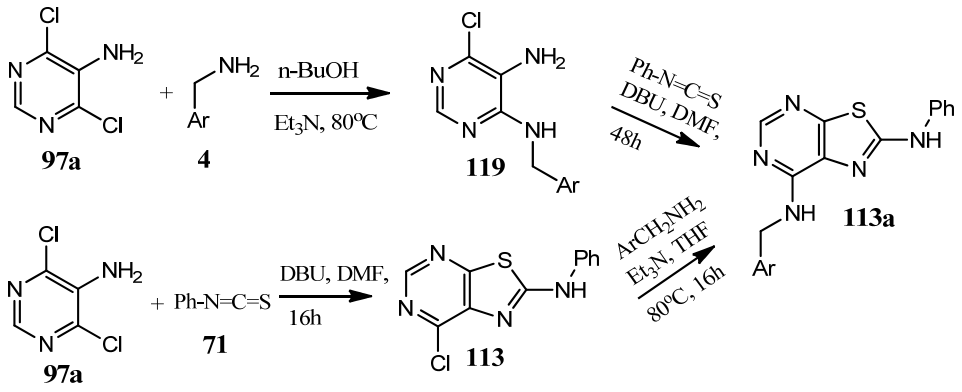
In a synthesis of thiazolo[5,4-*d*]pyrimidines **113**, a thiazolo-thione **117** reacts with aromatic aldehyde **3** or acetic anhydride **118** to gain heterocycles **113** by

intermolecular cyclizations. When aromatic aldehyde and acetic anhydride were used, the yields are obtained as 80% and 65%, respectively. (Kamal El-Dean, 1992)



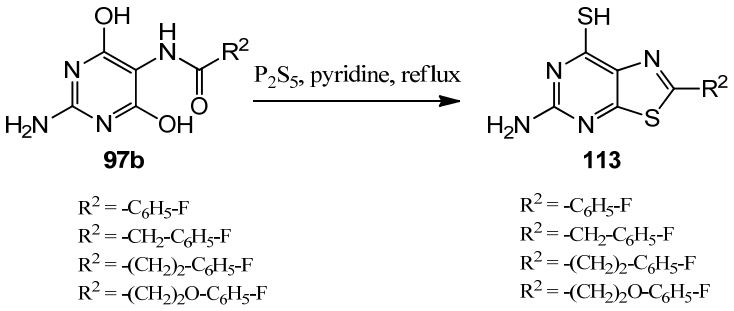
Scheme 1.55. Synthesis of some thiazolo[5,4-d]pyrimidines.

Besides, a diaryl substituted thiazolo[5,4-*d*]pyrimidine-2,7-diamine **113a** can be obtained over two ways. In first way, 4,6-dichloro-5-aminopyrimidine **97a** in *n*-BuOH is mixed with TEA, 3,4,5-trimethoxybenzylamine **4** and stirred for 16 h at 80°C to afford 6-chloro-N^4-(3,4,5-trimethoxybenzyl)pyrimidine-4,5-diamine **119**. After that, resulting product is added with DBU and phenylisothiocyanate **71** and stirred for 48 h at RT to attain benzothiazole structure **121**. In second way, 4,6-dichloro-5-aminopyrimidine **97a** is reacted with phenylisothiocyanate **71** to furnish thiazolo[5,4-*d*]pyrimidine structure **113**, then, it is reacted with 3,4,5-trimethoxybenzylamine yielding benzothiazole structure **113a** under basic conditions. (Liu et al., 2005)



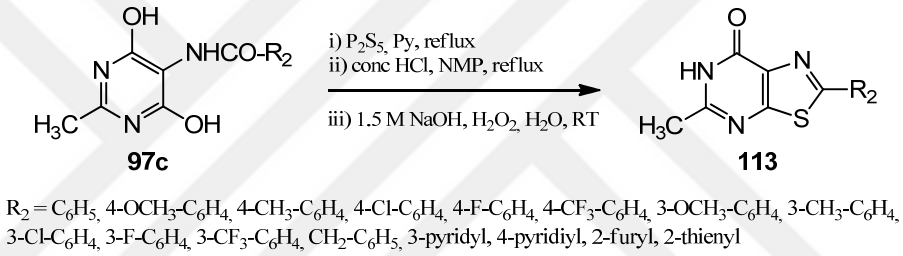
Scheme 1.56. Alternative routes for synthesis of diarylthiazolo[5,4-*d*] pyrimidine-2,7-diamine.

Moreover, 2,5,7-trisubstituted-thiazolo[5,4-*d*]pyrimidines **113** can be obtained by the reaction of 5-acylaminopyrimidine-4,6-diols **97b** with phosphorus pentasulfide in pyridine for 6 hours under reflux conditions. (Jang et al., 2010)



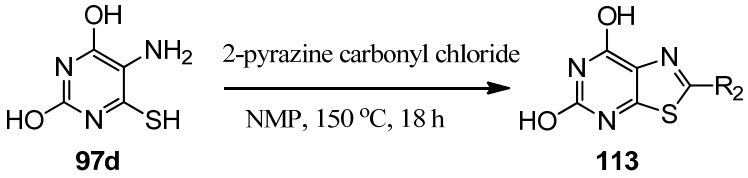
Scheme 1.57. The preparation of 2,5,7-substituted-thiazolo[5,4-*d*]pyrimidines.

The synthesis of 7-oxo-thiazolo[5,4-*d*]pyrimidines **113** contains the reaction of 4,6-dihydroxy-2-methyl-pyrimidine-5-amido derivatives **97c** with pyridine and P_2S_5 under reflux conditions. Then, mixture is reacted with conc'd HCl in *N*-methyl-2-pyrrolidone, hydrogen peroxide at RT and under reflux. (Varano et al., 2015)



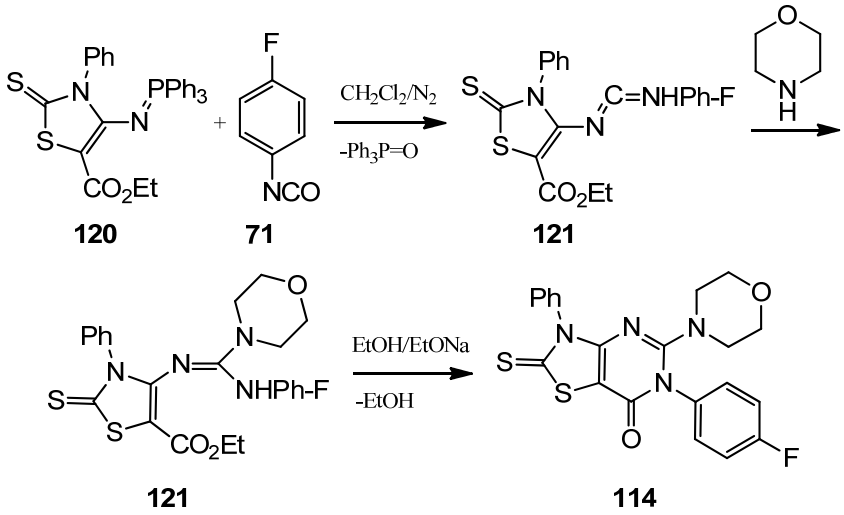
Scheme 1.58. The synthesis of thiazolo[5,4-*d*]pyrimidin-7-one derivatives.

A thiazolo[5,4-*d*]pyrimidin-5,7-diol **113** can be synthesized in good yields by the reaction of precursor **97d** in NMP with 2-pyrazine carbonyl chloride at 150°C under reflux for 18 h. (Varano et al., 2018a)



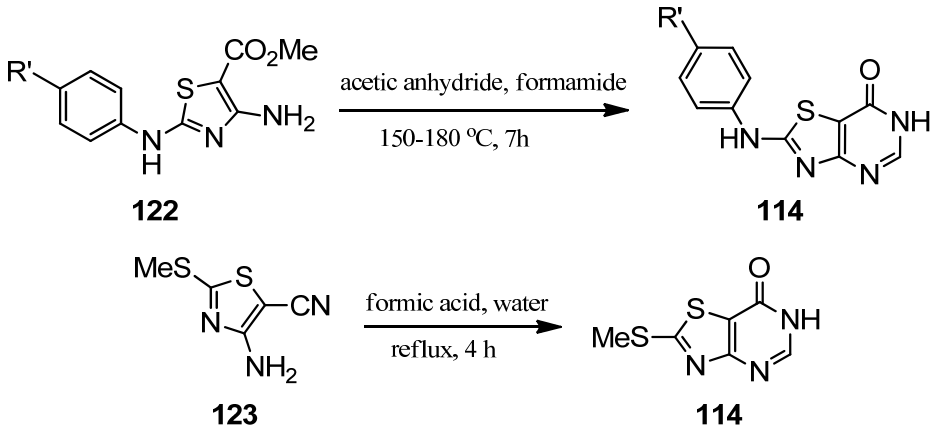
Scheme 1.59. Synthesis of 2-(pyrazin-2-yl)-thiazolo[5,4-*d*]pyrimidine-5,7-diol.

In the preparation of thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7-one **122**, firstly, 4-fluorophenyl isocyanate **71** was mixed with iminophosphorane of 4-amino-2,3-dihydro-3-phenyl-2-thioxothiazole-5-carboxylate **120** in CH_2Cl_2 and stirred at RT for 5-12 h. Then, morpholine was added into carbodiimide **121** with sodium ethoxide and stirred for 4 h to obtain the desired product **114**. (Fan et al., 2006)



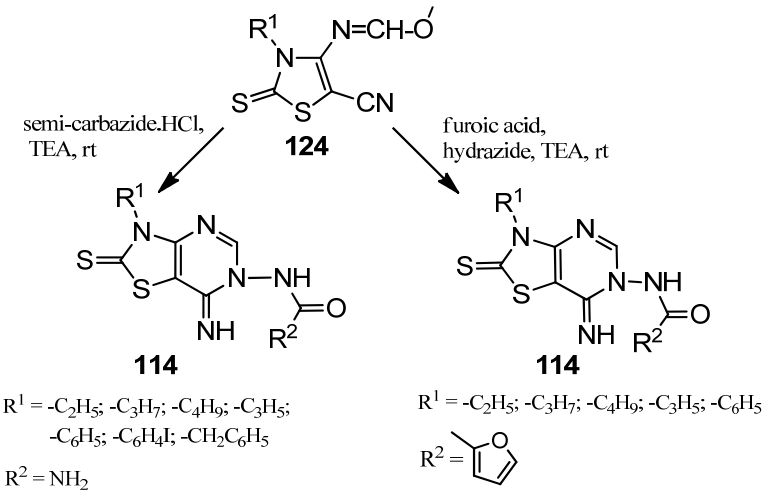
Scheme 1.60. Synthesis of 2-thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidin-7-one.

When 4-amino-2-phenylamino-thiazole-5-carboxylic acid methyl esters **122** are reacted with Ac_2O in formamide at 150-180°C for 7 h, the substituted 2-phenylamino-6*H*-thiazolo[4,5-*d*]pyrimidin-7-ones **114** were obtained. Also, 4-amino-2-methylsulfanyl-thiazole-5-carbonitrile **123** was treated with formic acid to gain 2-methylsulfanyl-6H-thiazolo[4,5-*d*]pyrimidin-7-one **114** under reflux for 4 h. (Lin et al., 2009)



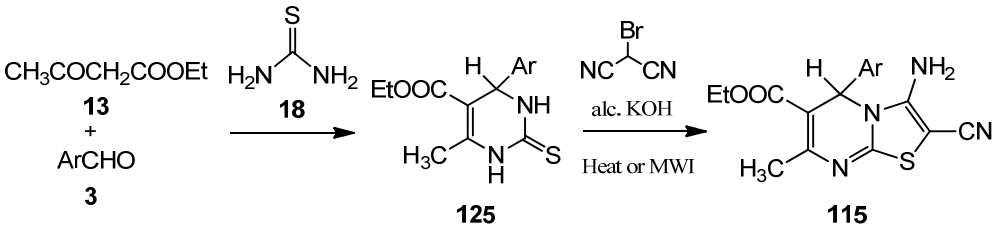
Scheme 1.61. The synthesis of some substituted thiazolo[4,5-*d*]pyrimidines.

The reaction of imino-ethers **124** with semi-carbazide hydrochloride or furoic acid hydrazide and TEA at RT for 12 hours provide the bicyclic thiazolopyrimidine urea or thiazolopyrimidine furonamide **114** derivatives, respectively. (Luthra et al., 2010)



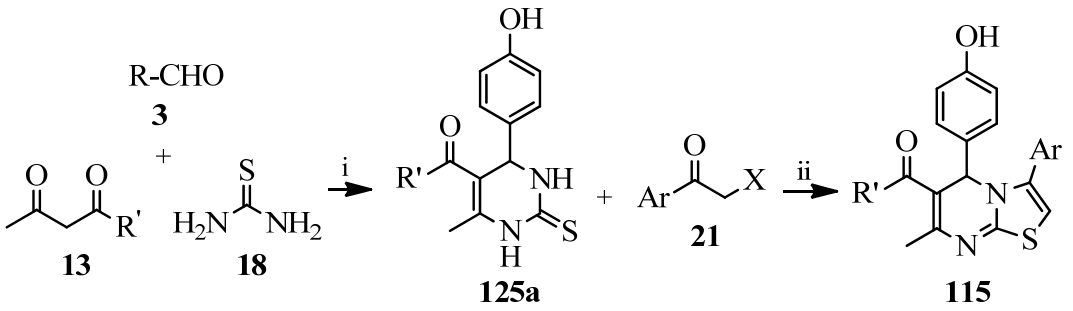
Scheme 1.62. The synthesis of thiazolo[4,5-*d*]pyrimidine urea or furonamide derivatives.

For the synthesis of ethyl 4-aryl-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxylates **125**, the condensation reaction of ethyl acetoacetate **13** was carried out with aromatic aldehydes **3** and thiourea **18** in EtOH involving HCl as a catalyst, then the product were reacted with bromomalononitrile in KOH-EtOH solution to furnish 5*H*-thiazolo[3,2-*a*]pyrimidine **115** by either stirring overnight at RT or heating in microwave at 140°C for 10 min. (Youssef and Amin, 2012)



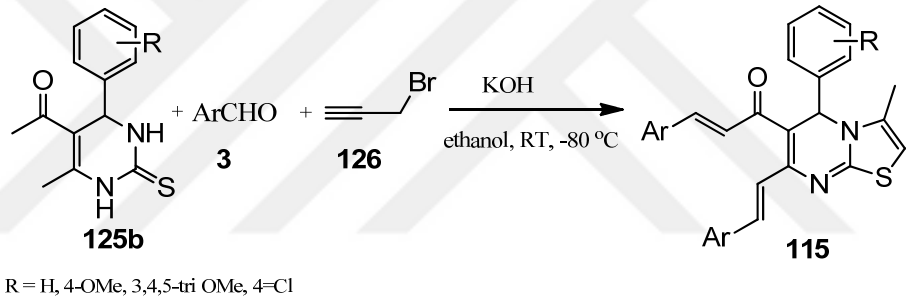
Scheme 1.63. Synthesis of ethyl 3-amino-5-aryl-2-cyano-7-methyl-5*H*-thiazolo[3,2-*a*]pyrimidine-6-carboxylates.

Besides, the mixture of substituted aldehyde **3**, ethyl acetoacetate or acetoacetone **13**, thiourea **18** in EtOH and conc'd HCl is stirred at 50°C for 10 h and then at 0°C overnight to get 6-methyl-3,4-dihydropyrimidine-2(1H)-thione **125a**. The obtained thione is refluxed with substituted phenacyl chloride and AcONa in AcOH for 8-24 h to afford 3-substituted 5*H*-thiazolo[3,2-*a*]pyrimidine derivatives **115** after recrystallization from EtOH. (Zhi et al. 2008)



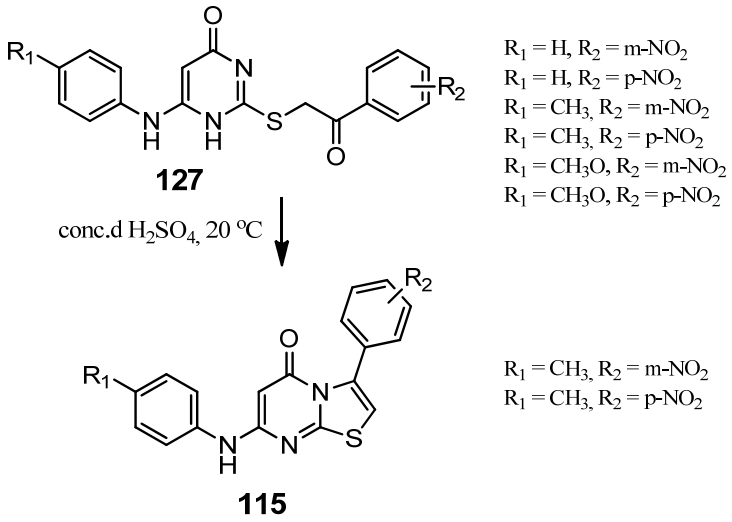
Scheme 1.64. Synthesis of 3-substituted 5*H*-thiazolo[3,2-*a*]pyrimidines.

In addition, the reaction of 5-acetyl-6-methyl-4-phenyl-dihydropyrimidine-2-thione **125b** with propargyl bromide **126** and benzaldehyde **3** using KOH or NaOEt in EtOH at 80ºC afforded corresponding styryl thiazolo[3,2-*a*]pyrimidines **115**. (Fatima et al., 2012)



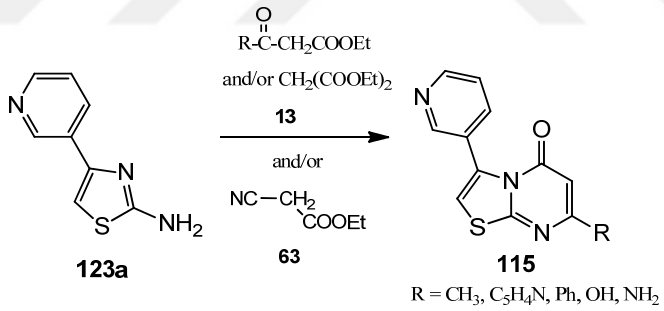
Scheme 1.65. Synthesis of 5-aryl-7-styryl-5*H*-thiazolo[3,2-*a*]pyrimidines.

However, preparation of (4-nitrophenyl)-7-(*p*-tolyamino)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **115** can be achieved by the reaction of *S*-alkylated derivatives **127** with conc. H_2SO_4 stirred at 20ºC for 72 h. (Cai et al., 2015)



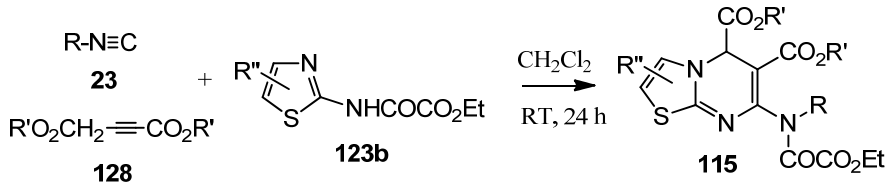
Scheme 1.66. Synthesis of (4-nitrophenyl)-7-(*p*-tolyamino)-5H-thiazolo[3,2-*a*] pyrimidin-5-ones.

3-(pyridine-3-yl)-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **115** can be prepared in 65-76% yields by the reaction of 4-(pyridine-3-yl)thiazol-2-amine **123a** with active methylene compounds, ketoesters (or diethylmalonate) **13**, ethyl cyanoacetate **63** in AcOH for 3-4 h under reflux. (El-Borai et al., 2017)



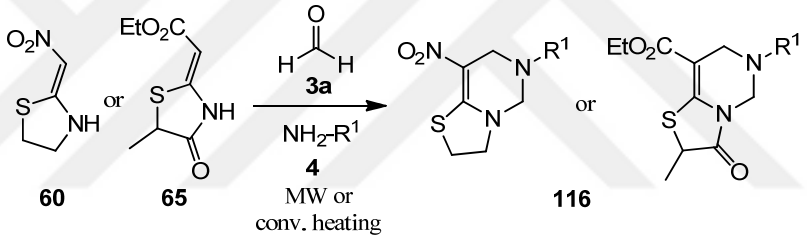
Scheme 1.67. Preparation of 7-substituted-3-(pyridine-3-yl)-5*H*-thiazolo[3,2-*a*] pyrimidin-5-ones.

A simple preparation of 5*H*-thiazolo[3,2-*a*]pyrimidines **115** consists of the reaction of isocyanides **23** with dialkyl acetylene-dicarboxylates **128** and ethyl 2-oxo-2-(1,3-thiazol-2-ylamino)acetates **123b** in CH_2Cl_2 at RT for 24 h in 83-90% yields. The synthesis of the corresponding compounds is provided via one-pot 3-CR. (Wu et al., 2018)



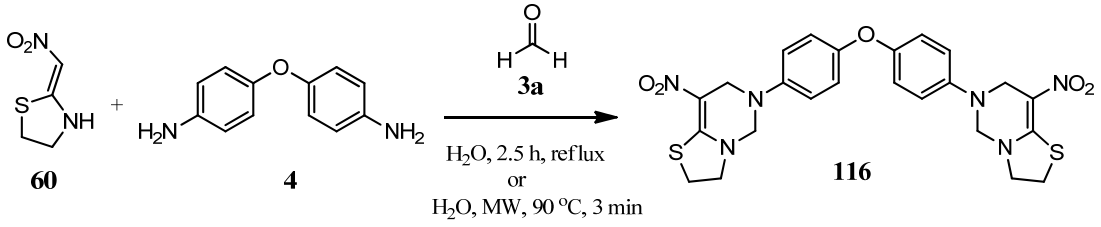
Scheme 1.68. The preparation of 5*H*-thiazolo[3,2-*a*]pyrimidines.

There are rare examples on the synthesis of thiazolo[3,2-*c*]pyrimidines **116** in the recent literature. An efficient preparation of nitrothiazolo[3,2-*c*]pyrimidines and oxothiazolo[3,2-*c*]pyrimidine carboxylates **116** were performed via three-component Mannich cyclisations of 2-(nitromethylene) thiazolidine **60** or (Z)-ethyl 2-(5-methyl-4-oxothiazolidin-2ylidene)acetate **65** with primary amines **4** and formaldehyde **3a** under reflux or MW conditions for 3-4 h or 3-4 min. This is a first example 3-CR of heterocyclic enamines affording thiazolo[3,2-*c*]pyrimidines. (Yıldırım et al., 2014b; Yıldırım and Çelikel, 2015)



Scheme 1.69. Synthesis of thiazolo[3,2-*c*]pyrimidines via Mannich cyclisations.

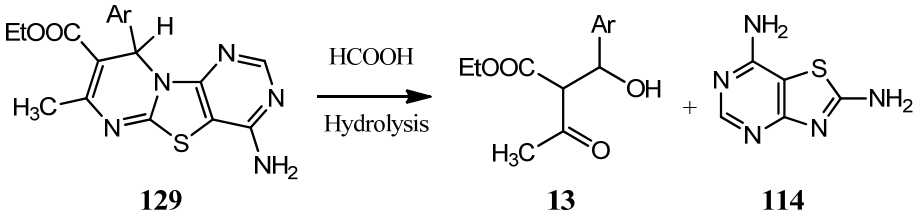
2-(nitromethylene) thiazolidine **60** is also mixed with 4,4'-oxydianiline **4** in 4 eq. of formaldehyde **3a** in water to furnish the required bicyclic product **116** under both conventional or MW heating conditions. (Yıldırım et al., 2014b)



Scheme 1.70. The synthesis of bicyclic thiazolo[3,2-*c*]pyrimidine derivative.

1.3.2 Reactions of Thiazolopyrimidines

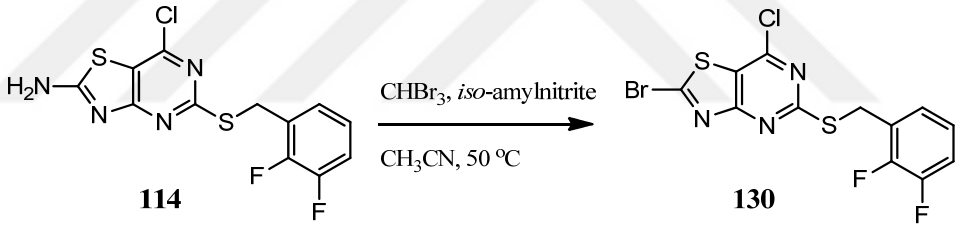
When thiazolo[3,2-*a*:4,5-*b*]dipyrimidine derivatives **129** are reacted with formic acid in dimethylformamide under reflux for 10 h, a 2,7-diaminothiazolo[4,5-*d*]pyrimidine **114** is obtained as a product. (Sherif et al., 1993)



129 **13** **114**

Scheme 1.71. The synthesis of 2,7-diaminothiazolo[4,5-*d*]pyrimidine.

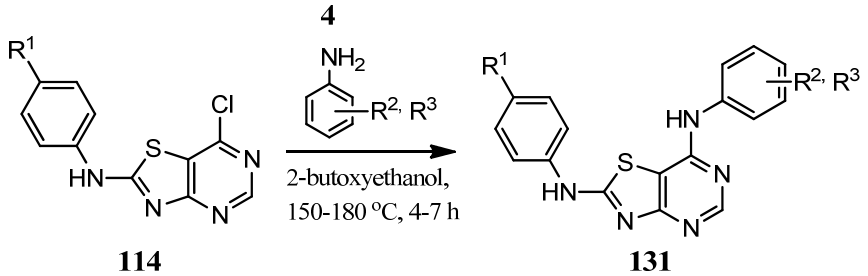
Besides, 2-aminothiazolo[4,5-*d*]pyrimidine **114** is reacted with *iso*-amyl nitrite in $CHBr_3$ using CH_3CN at 50ºC to furnish the corresponding 2-bromothiazolo[4,5-*d*]pyrimidine **130** in 82% yield. (Hunt et al., 2007)



114 **130**

Scheme 1.72. The synthesis of bromothiazolo[4,5-*d*]pyrimidines.

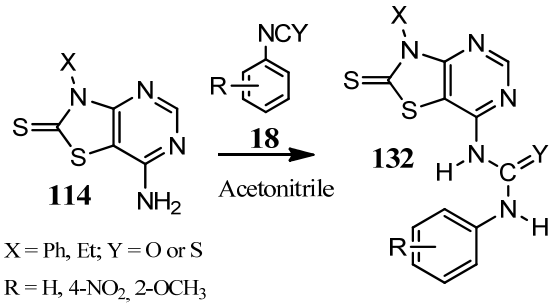
N^2,N^7-diphenyl-thiazolo[4,5-*d*]pyrimidine-2,7-diamines **131** can be synthesized by the reaction of (7-chloro-6,7-dihydrothiazolo[4,5-*d*]pyrimidin-2-yl)-phenylamines **114** with substituted phenylamines **4** in 20-65% yields. (Lin et al., 2009)



114 **131**

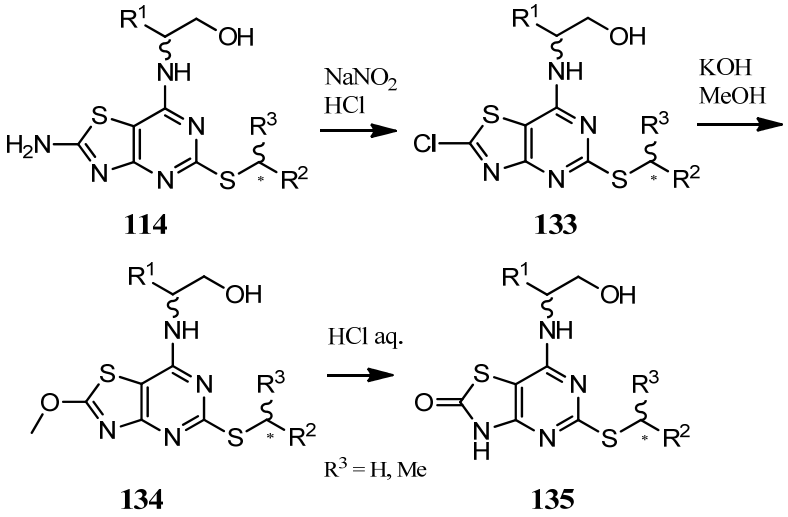
Scheme 1.73. The synthesis of substituted N^2,N^7-diphenyl-thiazolo[4,5-*d*] pyrimidine-2,7-diamines.

The urea and thiourea derivatives of 3-phenyl/ethyl-2-thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidines **132** are originated from the reaction of 7-amino-3-phenyl/ethylthiazolo[4,5-*d*]pyrimidine-2(3H)-thione **114** with isocyanate or isothiocyanate **18** in acetonitrile under reflux for 1-4 h. (Azam et al., 2009)



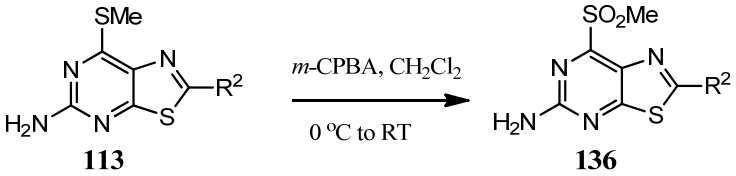
Scheme 1.74. The synthesis of urea and thiourea derivatives of 3-phenyl/ethyl-2-thioxo-2,3-dihydrothiazolo[4,5-*d*]pyrimidines.

2-amino-thiazolo[4,5-*d*]pyrimidines **114** can be first transformed into 2-chloro derivative **133** by Sandmeyer reaction. It is then converted into CH_3O derivative **134** using methanolic KOH and then, hydrolyzed with HCl to furnish [1,3]thiazolo[4,5-*d*]pyrimidin-2(3*H*)-ones **135**. (Karlström et al., 2013)



Scheme 1.75. The synthesis of [1,3]thiazolo[4,5-d]pyrimidin-2(3H)-ones.

7-thio-2-substituted-thiazolo[5,4-*d*]pyrimidines **113** can be oxidized with *m*-CPBA in CH_2Cl_2 at 0°C to afford the methylsulfonyl-2-substituted-thiazolo[5,4-*d*]pyrimidines **136**. (Jang et al., 2010)



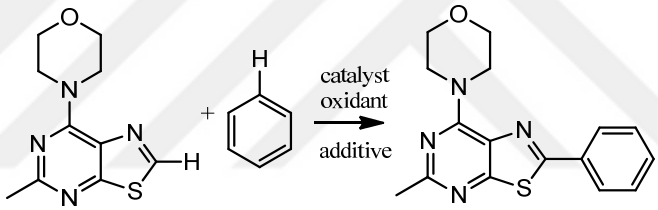
113 **136**

$R^2 = -C_6H_5\text{-}F$
$R^2 = -CH_2\text{-}C_6H_5\text{-}F$
$R^2 = -(CH_2)_2\text{-}C_6H_5\text{-}F$
$R^2 = -(CH_2)_2O\text{-}C_6H_5\text{-}F$

$R^2 = -C_6H_5\text{-}F$
$R^2 = -CH_2\text{-}C_6H_5\text{-}F$
$R^2 = -(CH_2)_2\text{-}C_6H_5\text{-}F$
$R^2 = -(CH_2)_2O\text{-}C_6H_5\text{-}F$, H
$R^2 = -C\text{-}C_6H_5\text{-}F$, CH_3

Scheme 1.76. The preparation of 5-amino-7-methylsulfonyl-2-substituted-thiazolo [5,4-*d*]pyrimidines.

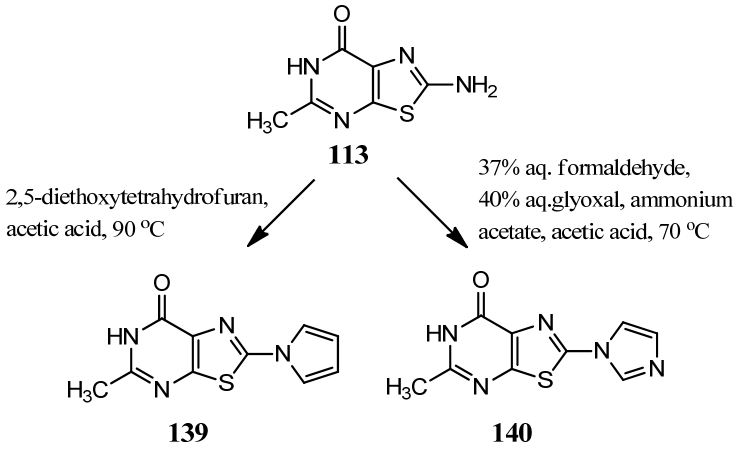
The coupling reaction of 4-(5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine **113** with benzene **137** furnished the 4-(5-methyl-2-phenyl-thiazolo[5,4-*d*]pyrimidin-7-yl)morpholine **138** using $Pd(OAc)_2$ in the presence of Ag_2CO_3 with PivOH and TBAI (20% mol) in benzene. (Yang et al., 2014)



113 **137** **138**

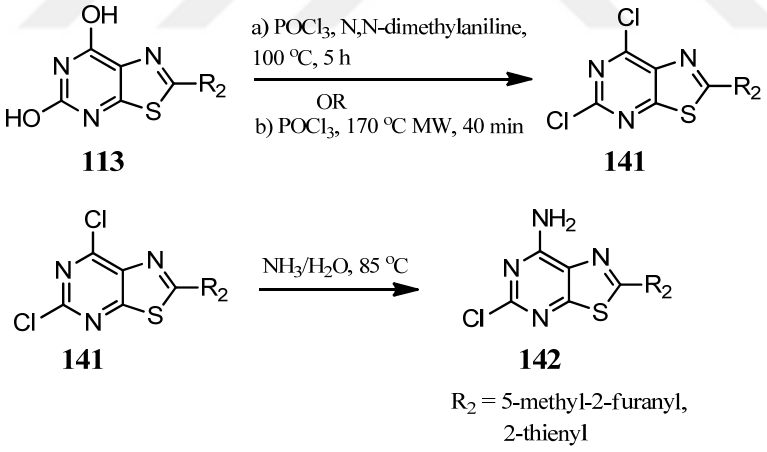
Scheme 1.77. The cross-coupling reaction of 4-(5-methylthiazolo[5,4-*d*] pyrimidin-7-yl)morpholine with benzene.

2-heteroaryl substituted thiazolo[5,4-*d*]pyrimidines **139**, **140** are synthesized by using 2-amino-5-methyl-7-oxo-thiazolo[5,4-*d*]pyrimidines **113** either with 2,5-diethoxy tetrahydrofuran in AcOH at 90ºC or with formaldehyde solution (37%), aqueous glyoxal (40%), $NH_4CH_3CO_2$ in AcOH at 70ºC. (Varano et al., 2015)



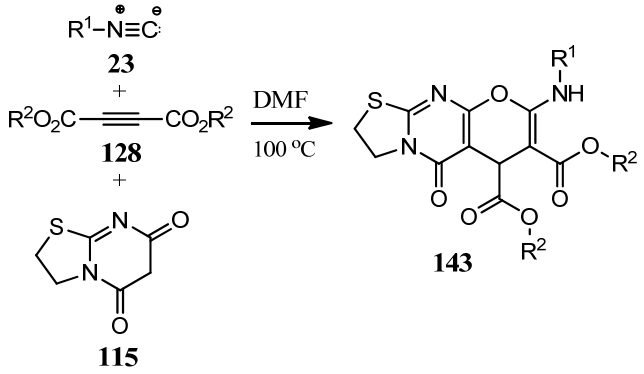
Scheme 1.78. The synthesis of 2-heteroaryl-thiazolo[5,4-*d*]pyrimidines.

The 5,7-diol derivatives of thiazolo[5,4-*d*]pyrimidines **113** are treated with $POCl_3$ and *N*,*N*-dimethylaniline at 100°C to afford 5,7-dichloro-2-(pyrazin-2-yl)-thiazolo[5,4-*d*]pyrimidines **141** [87]. The 5,7-dichlorothiazolo[5,4-*d*]pyrimidines **141** are further treated with 33% aqueous solution of NH_3 in EtOH at reflux for 6 hours to afford the 5-chloro-thiazolo[5,4-*d*]pyrimidin-7-amine derivatives **142**. (Varano et al., 2018b)



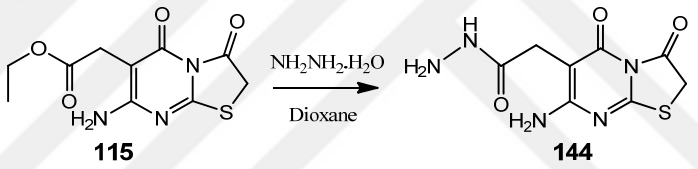
Scheme 1.79. Formation of 5,7-dichloro-2-(pyrazin-2-yl)-thiazolo[5,4-*d*] pyrimidines and 5-chloro-thiazolo[5,4-*d*]pyrimidin-7-amines.

A mixture of the acetylenic ester **128** and 2,3-dihydro-5H-[1,3]thiazolo[3,2-*a*] pyrimidine-5,7(6H)-dione **115** in DMF was added slowly into a solution of isocyanide **23** in DMF and the reaction mixture is heated at 100°C for 3 h to afford the pyranothiazolo[3,2-*a*]pyrimidines **143** in very good yields. (Zangouei et al., 2014)



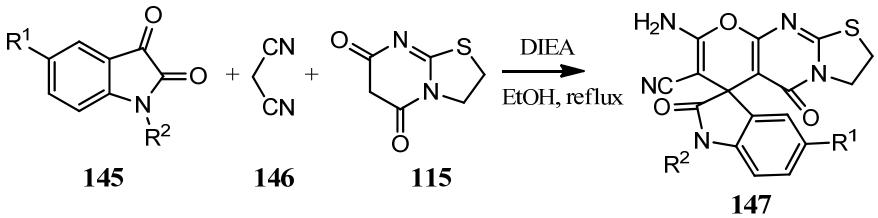
Scheme 1.80. The production of pyranothiazolo[3,2-*a*]pyrimidines through isocyanide-based 3-CR.

The pyrimidinyl acetate derivative of 5H-thiazolo[3,2-*a*]pyrimidines **115** is reacted with hydrazine hydrate in dioxane under reflux for 15 h and 2-(7-amino-3,5-dioxo-2,3-dihydro-5H-thiazolo[3,2-*a*]pyrimidin-6-yl)acetohydrazide **144** is provided in 83% yield. (Abu-Hashem et al., 2011)



Scheme 1.81. Synthesis of 2-(7-amino-3,5-dioxo-2,3-dihydro-5H-thiazolo[3,2-*a*]pyrimidin-6-yl)acetohydrazide.

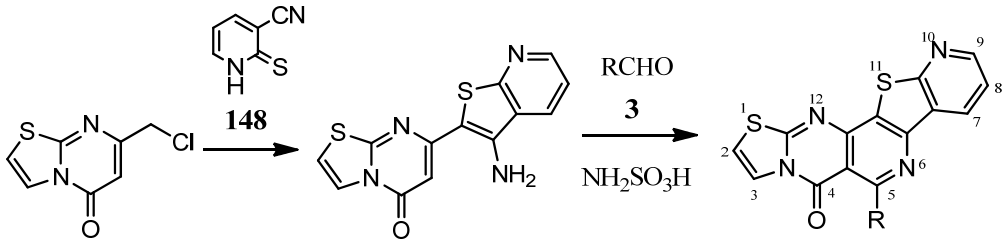
The spirooxindole derivatives **147** can be generated in good yields by the reaction of benzyl isatin **145** with malononitrile **146**, 2,3-dihydro-5H-[1,3]thiazolo[3,2-*a*]pyrimidine-5,7(6H)-dione **115** and DIEA in EtOH under reflux. (Esmaeili et al., 2015)



Scheme 1.82. The synthesis of spirooxindole derivatives.

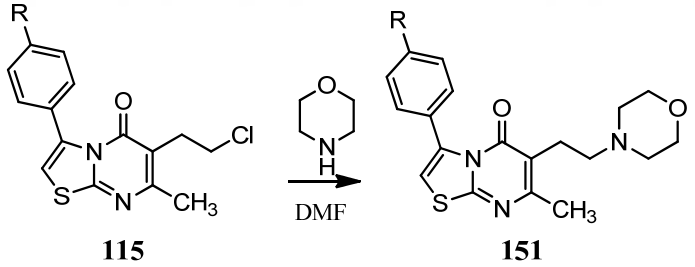
An efficient method for the synthesis of novel fused thiazolo[3,2-*a*] pyrimidinones:pyrido[3'',2'':4',5']thieno[3',2':2,3]pyrido[4,5:*d*][1,3]thiazolo[3,2-*a*]

pyrimidine-5-one derivatives **150** is obtained by the Pictet-Spengler reaction of 2-(3-aminothieno[2,3-*b*]pyridin-2yl)thiazolo[3,2-*a*]pyrimidin-4-one **149** with aromatic aldehydes **3** using NH_2SO_3H at 80ºC for 4 h and also the precursor **149** was generated from the reaction of 7-(chloromethyl)-5H-thiazolo[3,2-*a*]pyrimidin-5-one **115** with 3-cyanopyridine-2-thione **148**. (Wang et al., 2016)



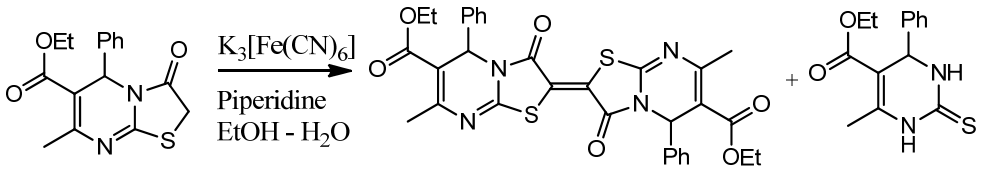
Scheme 1.83. The synthesis of novel-pyridothieno-fused thiazolo[3,2-*a*] pyrimidinones through Pictet-Spengler reaction.

6-(2-chloroethyl)-7-methyl-3-substituted-phenyl-5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **115** can be substituted with morpholine, sulfacetamide, sulfaguanidine at 90ºC in DMF using Et_3N for 18 h. (Ali et al., 2018)



Scheme 1.84. The synthesis of some morpholinoethyl-thiazolo[3,2-*a*] pyrimidines.

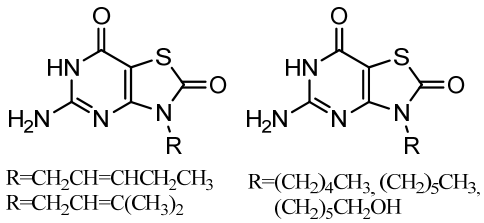
The thiazolo[3,2-*a*]pyrimidin-3(2H)-one **115** and $K_3[Fe(CN)_6]$ with piperidine are reacted to give a dimeric product **152** and 2-thioxo-1,2,3,4-tetrahydropyrimidine **125a** in EtOH-H_2O at 60ºC. (Lashmanova et al., 2018)



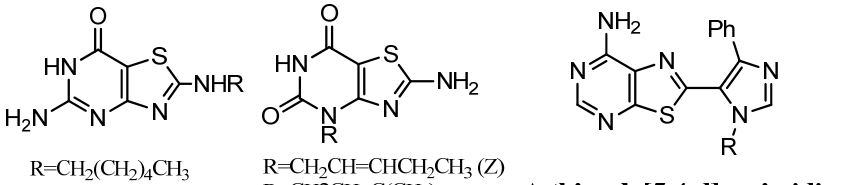
Scheme 1.85. The synthesis of dimeric thiazolo[3,2-*a*]pyrimidines.

1.3.3 Biological Importance of Thiazolopyrimidines

In general, thiazolopyrimidines are widely used as analgesic, antiparkinsonian, anticancer, pesticides, phosphatase inhibitor, acetylcholinesterase inhibitor, antimicrobial, anti-HIV, antibacterial, anti-inflammatory, antihypertensive, antioxidant, antitumor, anti-HSV, herbicidal agents. (Fatima et al., 2012; Youssef and Amin, 2012) Specifically, thiazolo[4,5-d]pyrimidines **114** have biological effects such as antibacterial, antiviral, anti-HIV, anticancer, analgesic, anti-inflammatory, antimicrobials, antifungal, COX inhibitors, immune-modulators, corticotropin-releasing factor receptor antagonist, chemokine receptor antagonists, adenosine receptor antagonists, anticancer. (Kuppast and Fahmy, 2016) Besides, thiazolo[3,2-c]pyrimidines **116** are very recently reported to exhibit some cyctotoxic effects against human breast and liver carcinoma cell lines. (Yildirim et al, 2018) Moreover, some 3-substituted-5H-thiazolo[3,2-a]pyrimidines **115** are used in the treatment of Alzheimer's disease (AD). (Zhi et al., 2008) And, some 7-*N*-piperazinylthiazolo[5,4-*d*]pyrimidine analogues are used as immunosuppressive agents. (Jang et al., 2010) Furthermore, the 5H-thiazolo[3,2-*a*]pyrimidin-5-ones are used as anti-inflammatory, antihypertensive, antifungal, antibiofilm, antibacterial, antiviral, antioxidant, antitumor, anti-HIV, calcium channel blocker, antitubercular, glutamate receptor antagonistic, 5-HT2a receptor antagonistic, group II metabotropic glutamate receptor antagonist activities. (Cai et al., 2015) Also, the 6-(2-morpholinoethyl)-thiazolo[3,2-*a*]pyrimidin-5-one is used as anticancer, enzymatic agents. (Luke at al., 2009; Ali et al., 2018; Lashmanova et al., 2018)



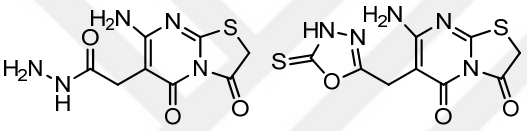
Antiviral and immune-potenting thiazolo[4,5-d]pyrimidines (114)



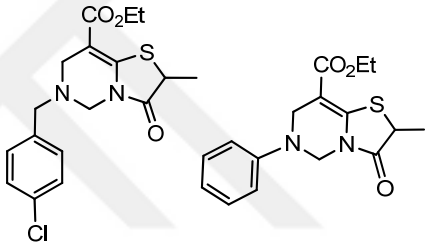
Anti-HCMV thiazolo[4,5-d]pyrimidines (114)

A thiazolo[5,4-d]pyrimidine Tie-2 kinase inhibitor (113)

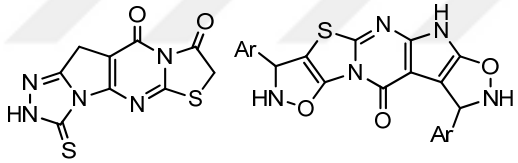
Figure 1.5. Some biologically active thiazolo[4,5-*d*]- and [5,4-*d*]-pyrimidines.



Antioxidant thiazolo[3,2-a]pyrimidines (115)



Cyctotoxic thiazolo[3,2-c]pyrimidines (116)



Antitumor thiazolo[3,2-a]pyrimidines (115)

Figure 1.6. Some biologically active thiazolo[3,2-*a*]- and [3,2-*c*]-pyrimidines.

1.4 ANTIBACTERIAL ACTIVITY

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

In this disc-diffusion test, a pathogenic microorganism is inoculated onto a Mueller-Hinton agar plate. Filter paper discs containing known amounts of antimicrobial agents or antibiotics are placed in middle of the agar plates which are then incubated at 37°C for 18-24 hours. The antimicrobial agents or antibiotics diffuse into the agar and cause an inhibition zone for the growth of the bacterial strain around the disc which corresponds to the susceptibility of the strains to the agents. At the end of the incubation period, a clear area depicting zone of inhibition around the disc is measured. The formed zones are compared to known values obtained with standard antibiotics. (Prescott et al., 1990) Standardized zones for each antibiotic disc have been established to determine whether the microorganism is sensitive (S), intermediately sensitive (IS), or resistant (R) to an antimicrobial agent or a particular antibiotic. This method is not applicable for filamentous fungi, anaerobes, or slowly-growing bacteria. (Atlas, 1988) A list of pathogenic bacteria frequently used in the antibacterial studies are given (Table 1.3). (Levinson and Jawetz, 2002)

Table 1.3. Pathogenic bacteria and their representative diseases, habitats and treatments.

	Pathogen	Representative Diseases	Drugs of Choice
Gram Positive	*Streptococcus pyogenes*	Tonsillopharyngeal cellulitis or abscess, Otitis media, Sinusitis, Necrotizing fasciitis, Streptococcal bacteremia, Meningitis or brain abscess.	Penicillin, ampicillin,cefazolin, cefuroxime, ceftriaxone, ofloxacin, vancomycin.
	Staphylococcus aureus	Boils and pimples (folliculitis), Pneumonia, Food poisoning (emesis or vomiting), Septicemia (invasion of the bloodstream), Osteomyelitis (invasion of bone), Toxic shock syndrome, Surgical wound infections, Scalded skin syndrome (analogous to scarlet fever).	Methicillin, oxacillin, penicillin, amoxicillin.
	Staphylococcus epidermidis	Wound infections, Cystitis (Urinary tract infection - catheterized patients), Septicemia, Endocarditis, Endopthalmitis, Catheter infections, Prosthetic implant infection.	Vancomycin, gentamicin or rifampin.
Gram Negative	*Escherichia coli*	Urinary tract infections, Sepsis/meningitis and Infectious diarrhea.	Ampicillin, ampicillin + sulbactam, cephalothin, cefuroxime, ceftriaxone, amikacin, ciprofloxacin, sulfamethoxazole.
	Pseudomonas aeruginosa	Septicemia, Urinary tract infections, Pneumonia, Chronic lung infections, Endocarditis, Dermatitis, and Osteochondritis.	Ticarcillin, piperacillin, ticarcillin-clavulanate, piperacillin-tazobactam.
	Salmonella typhimurium	Diarrhea, Abdominal cramps, Vomiting and Nausea. Pains in joints, irritation of the eyes, and painful urination (Reiter's syndrome), Chronic arthritis.	Cephalosporins, fluoroquinolones.
	Serratia marcescens	Conjunctivitis, keratitis, Endophthalmitis, and Tear duct infections.	Cephalosporins, fluoroquinolones, tetracycline, trimethoprim/sulfamethoxazole.
	Proteus vulgaris	Urinary tract infection, Bacteremia, Pneumonia and Focal lesions.	Carbenicillin.
	Enterobacter cloacea	Cloacae pneumonia, Acute necrotizing, Myocarditis.	Tetracycline or amoxicillin.
	Klebsiella pneumoniae	Pneumonia, Septicemia, Wound infection, Burn infection, Urinary tract infection (cystitis), Ankylosing spondylitis.	Gentamicin and cephalothin.

2. AIM AND SCOPE OF THE STUDY

Thiazolopyrimidines, specifically, the thiazolo[5,4-*d*]- or [4,5-*d*]- pyrimidines **113**, **114** which are the *S*-analogs of purine bases and thiazolo[3,2-*a*]pyrimidines **115** are pharmacologically interesting compounds due to their diverse biological activities. So, they have acquired a growing importance in the field of pharmaceutical and medicinal chemistry. Thiazolo[5,4-*d*]-, [4,5-*d*]-, [3,2-*a*]-pyrimidines **113**, **114**, **115** can be prepared via variety of synthetic methods and their chemical and biological properties are well-documented in recent literature. However, thiazolo[3,2-*c*]pyrimidines **116** are not known in terms of their preparations, chemical or biological properties in the literature. In 2014 and 2015, first examples of thiazolo[3,2-*c*]pyrimidines **116** by microwave irradiation and conventional heating were efficiently prepared and included in synthetic chemistry literature by our group. Also, the biological activity studies of thiazolo[3,2-*c*] pyrimidines **116** were performed for the first time in 2018 by our group.

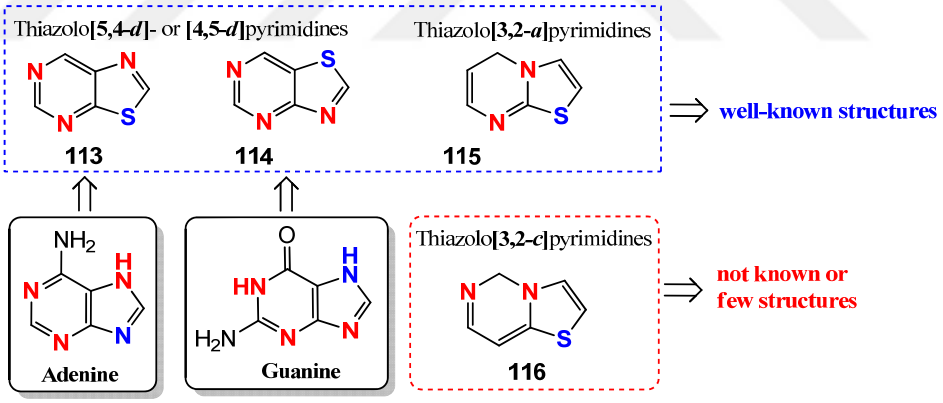


Figure 2.1. Main classes of thiazolopyrimidines.

With our ongoing interest on the chemistry of thiazolo[3,2-*c*]pyrimidines **116**, new series of potentially bioactive thiazolo[3,2-*c*]pyridimines **116** were aimed to prepare using multicomponent reactions of new heterocyclic enamines **65a**, **65b** with formaldehyde **3a** (or acetaldehye **3b**) and primary amines **4** in the present study. Secondly, biological activities of newly prepared thiazolo[3,2-*c*]pyridimines **116** such as antibacterial, antioxidant, cytotoxicity... etc. were planned to perform after purification and characterization of them.

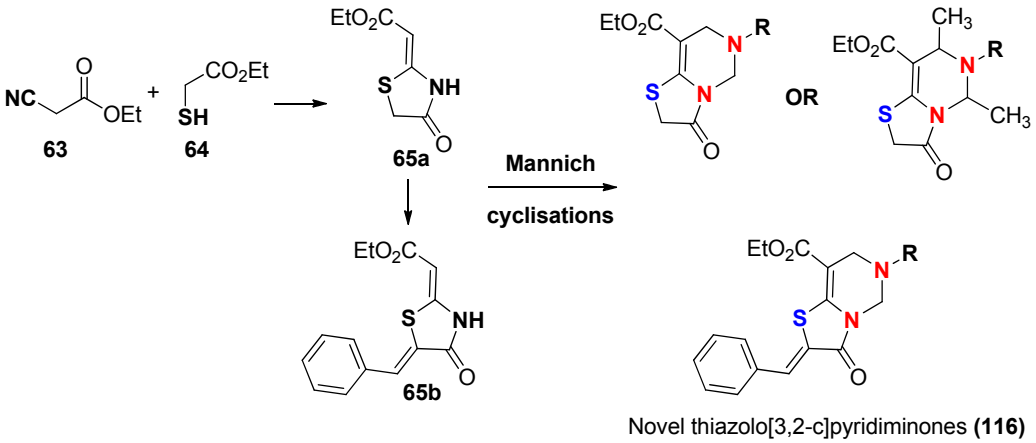


Figure 2.2. Synthetic route affording new thiazolo[3,2-*c*]pyrimidines **116**.

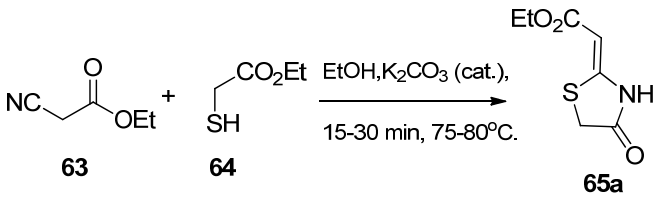
3. MATERIALS AND METHODS

All reagents and solvents were supplied from commercially available sources in analytical grade (Merck, Sigma-Aldrich) and used as received. ^{1}H- and ^{13}C- NMR spectra were recorded on JEOL ECS400 Delta2 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, hept = heptet, m = multiplet, dd=doublet of doublets. IR spectra were recorded on a SHIMADZU FTIR-8400S instrument (KBr pellet or NaCl discs). 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 was carried out for monitoring the reactions using precoated plates with fluorescent indicator (Merck 5735). Column chromatographic separations were performed on silica gel (Merck, 230–400 mesh ASTM) and the eluents were mixtures of ethyl acetate (EA) and hexanes (H). Staining solutions of potassium permanganate and UV-254-366 were used for visualization of the TLC spots.

3.1. EXPERIMENTAL

3.1.1. PREPARATION OF STARTING MATERIALS

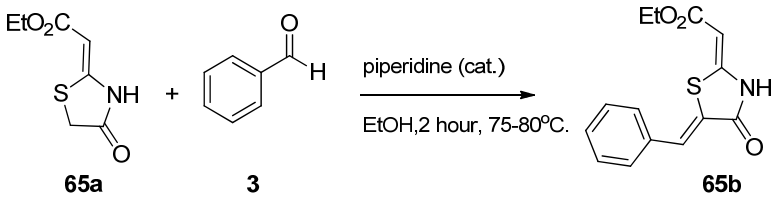
3.1.1.1. Preparation of (*Z*)-ethyl 2-(4-oxothiazolidin-2-ylidene)acetate (Stojanovic et al., 2011)



A mixture of ethyl cyanoacetate **63** (1 equiv), α-mercapto ethyl ester **64** (1.05 equiv), and K_2CO_3 (0.05 equiv) were mixed and heated with stirring at 75–80°C for 30 min and then cooled to room temperature. After addition of H_2O/EtOH (7:3) to the

reaction mixture, it was continued stirring for 1 hour at room temperature. After filtering and drying the precipitate, a white crystalline solid was obtained as **65a** in 87% yields.

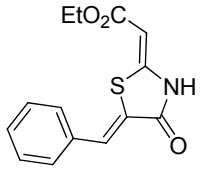
3.1.1.2. Preparation of (*Z*)-ethyl 2-((*Z*)-5-benzylidene-4-oxothiazolidin-2-ylidene)acetate (Yahya et al., 2015)



65a **3** **65b**

Benzaldehyde **3** (1.0 mmol) was added to a solution of **65a** (1.0 mmol) and piperidine (3 drops) in ethanol (20 mL). Then reaction mixture was heated under reflux for 2 hours, reaction completion was controlled by TLC, expected product **65b** crystallized out of solution as yellow precipitate. After cooling, the yellow solid product was filtered, washed with cold ethanol and dried.

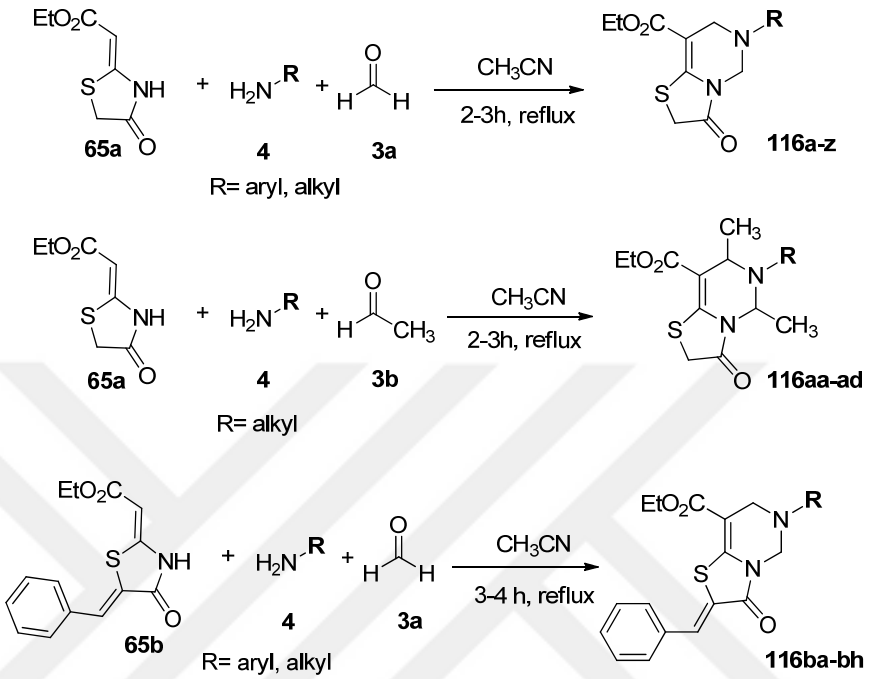
(*Z*)-ethyl 2-((*Z*)-5-benzylidene-4-oxothiazolidin-2-ylidene)acetate (65b)



Yellow powder. (0.900 g, 68%), m.p. 188-190°C; R_f (33% EtOAc/hexane) 0.70; IR (KBr) υ: 3063, 2978, 2862, 2746 (CH), 1689 (ester C=O), 1597 (amide C=O), 1450, 1280, 1234, 1157, 1095 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.68 (1H, s), 7.65-7.36 (5H, m), 5.94 (NH, br s), 5.26 (1H, s), 4.22-4.17 (2H, q, *J* 7.2 Hz), 1.29 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 167.3, 167.1, 150.6, 133.6, 130.9, 129.8, 120.1, 90.2, 60.6, 14.2; (TOF-MS APCI$^-$) *m/z*: 274 (100, $[M-H]^+$), 275 (20%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 274.0530. $C_{14}H_{12}NO_3S$ requires 274.0532.

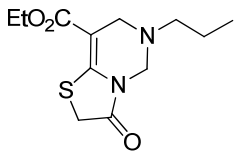
3.1.2. SYNTHESIS OF TARGET PRODUCTS

3.1.2.1. General Procedures for Preparation of Thiazolo[3,2-*c*] pyrimidinone carboxylates (116a-z, 116aa-ad, 116ba-bh)



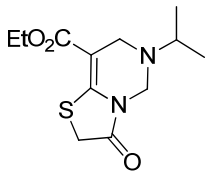
(Z)-ethyl 2-(4-oxothiazolidin-2-ylidene) acetate **65a** or (Z)-ethyl 2-((Z)-5-benzylidene-4-oxothiazolidin-2-ylidene) acetate **65b** (0.5 mmol, 1.0 equiv) and a primary amine **4** (0.5 mmol, 1.0 equiv.) were dissolved in CH_3CN (15 mL) and the resulting mixture was stirred for 5 min. Formaldehyde **3a** (37% v/v in H_2O, 1.0 mmol, 2.0 equiv.) or acetaldehyde **3b** (40% v/v in H_2O, 1.0 mmol, 2.0 equiv.) was added dropwise via a syringe and the resulting mixture was refluxed for 2-4 h under an argon atmosphere, respectively. The reaction progress was followed by TLC and upon completion, the reaction mixture was cooled to ambient temperature and the solvent was rotary evaporated. The resulting solid residue was purified by silica gel column chromatography using EtOAc-hexane mixtures specified, to afford the title compound (**116a-z, 116aa-ad, 116ba-bh**) in good yields.

Ethyl 3-oxo-6-propyl-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116a)



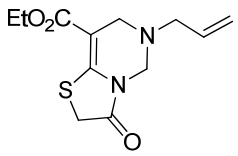
Flash chromatography (20% EtOAc/hexane) afforded yellow crystals. (68 mg, 50%), m.p. 120-122°C; R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ: 2960, 2929, 2872 (CH), 1712 (ester C=O), 1685 (amide C=O), 1583, 1452, 1259, 1222, 1111 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.50 (2H, s), 4.24-4.18 (2H, q, *J* 7.3 Hz), 3.66 (2H, s), 3.59 (2H, s), 2.43-2.39 (2H, m), 1.53-1.48 (2H, dd, *J* 14.8, 7.4 Hz), 1.28 (3H, t, *J* 7.1 Hz), 0.89 (3H, t, *J* 7.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.9, 166.5, 148.8, 98.4, 63.2, 60.3, 54.3, 49.2, 32.4, 21.0, 14.5, 11.6; (TOF-MS APCI$^-$) *m/z*: 269 (100, $[M-H]^+$), 270 (20), 271 (20%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 269.0973. $C_{12}H_{17}N_2O_3S$ requires 269.0965.

Ethyl 6-isopropyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116b)



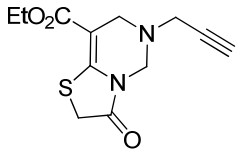
Flash chromatography (20% EtOAc/hexane) afforded purple solid. (111 mg, 82%), m.p. 68-70°C; R_f (33% EtOAc/hexane) 0.60; IR (KBr) υ: 2971, 2931, 2872 (CH), 1708 (ester C=O), 1683 (amide C=O), 1585, 1465, 1265, 1232, 1138, 1033 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.56 (2H, s), 4.24-4.19 (2H, q, *J* 7.6 Hz), 3.66 (2H, s), 3.64 (2H, s), 1.27 (3H, t, *J* 7.1 Hz), 1.10 (3H, s), 1.06 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.9, 166.5, 149.4, 99.4, 60.6, 60.5, 50.1, 46.5, 32.5, 20.6, 14.5; (TOF-MS APCI$^-$) *m/z*: 269 (100, $[M-H]^+$), 270 (15), 271 (15%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 269.0958. $C_{12}H_{17}N_2O_3S$ requires 269.0965.

Ethyl 6-allyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116c)



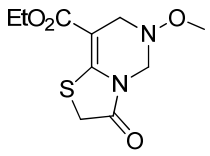
Flash chromatography (30% EtOAc/hexane) afforded brown oily solid. (95 mg, 71%). R_f (33% EtOAc/hexane) 0.70; IR (KBr) υ: 3240 (=CH), 2974 (CH), 1716 (ester C=O), 1658 (amide C=O), 1560, 1465, 1205, 1145, 1043 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.88-5.78 (1H, ddt, *J* 16.8, 10.3, 6.5 Hz), 5.20-5.14 (2H, m), 4.51 (2H, s), 4.24-4.18 (2H, q, *J* 7.1 Hz), 3.67 (2H, s), 3.60 (2H, s), 3.10 (2H, d, *J* 6.4 Hz), 1.28 (3H, t, *J* 8.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.4, 166.5, 148.7, 133.9, 119.2, 98.0, 62.4, 60.4, 55.5, 48.9, 32.3, 14.4; (TOF-MS APCI$^-$) *m/z*: 267 (100, $[M-H]^+$), 268 (15), 269 (15%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 267.0806. $C_{12}H_{15}N_2O_3S$ requires 267.0808.

Ethyl 3-oxo-6-(prop-2-yn-1-yl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116d)



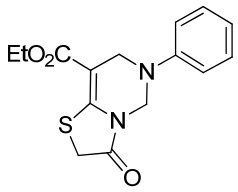
Flash chromatography (30% EtOAc/hexane) afforded orange semi-solid. (133 mg, 100%). R_f (33% EtOAc/hexane) 0.40; IR (KBr) υ: 3302 (≡CH), 3053, 2926, 2833 (CH), 1712 (ester C=O), 1681 (amide C=O), 1585, 1396, 1261, 1213, 1114, 1018 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.59 (2H, s), 4.25-4.20 (2H, q, *J* 7.4 Hz), 3.68 (2H, s), 3.42 (2H, s), 3.41 (2H, s), 2.23 (1H, t, *J* 2.5 Hz), 1.29 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.2, 166.4, 148.9, 97.9, 79.0, 72.9, 71.6, 62.0, 48.9, 42.1, 32.4, 14.5; (TOF-MS APCI$^-$) *m/z*: 265 (100, $[M-H]^+$), 266 (20), 267 (5%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 265.0662. $C_{12}H_{13}N_2O_3S$ requires 265.0641.

Ethyl 6-methoxy-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116e)



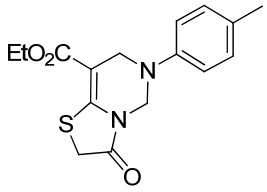
Flash chromatography (30% EtOAc/hexane) afforded creamy-white solid. (119 mg, 92%), m.p. 118-120°C. R_f (50% EtOAc/hexane) 0.60; IR (KBr) υ: 2980, 2931 (CH), 1714 (ester C=O), 1681 (amide C=O), 1589, 1464, 1288, 1240, 1128, 1041 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.25-5.14 (1H, d, *J* 12.1 Hz), 4.24-4.17 (2H, dd, *J* 14.4, 7.2 Hz), 4.10-4.0 (2H, d, *J* 16.7), 3.68 (3H, s, OCH_3), 3.54 (2H, s), 1.29 (3H, td, *J* 7.1, 0.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.8, 166.4, 148.7, 96.8, 62.9, 60.4, 60.0, 50.8, 32.6, 14.4; (TOF-MS APCI$^-$) *m/z*: 257 (100, $[M-H]^+$), 258 (20), 259 (15%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 257.0591. $C_{10}H_{13}N_2O_4S$ requires 257.0590.

Ethyl 3-oxo-6-phenyl-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116f)



Flash chromatography (20% EtOAc/hexane) afforded pale brown solid. (137 mg, 90%), m.p. 154–155°C. R_f (33% EtOAc/hexane) 0.70; IR (KBr) υ: 3061 (arom. CH), 2976, 2929 (CH), 1712 (ester C=O), 1681 (amide C=O), 1581, 1496, 1357, 1265, 1224, 1126, 1035 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.28-7.24 (2H, m), 6.96-6.93 (2H, m), 5.12 (2H, s), 4.28-4.23 (2H, q, *J* 7.1 Hz), 4.27 (2H, s), 3.85 (2H, s), 1.32 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.7, 165.8, 149.6, 147.0, 129.4, 121.6, 117.5, 90.0, 60.7, 60.5, 55.5, 48.1, 32.2, 14.3; (TOF-MS APCI$^-$) *m/z*: 303 (100, $[M-H]^+$), 304 (12), 305 (5%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 303.0806. $C_{15}H_{15}N_2O_3S$ requires 303.0797.

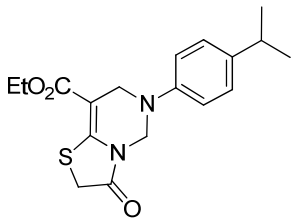
Ethyl 3-oxo-6-(p-tolyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116g)



HK18

Flash chromatography (20% EtOAc/hexane) afforded pale yellow crystals. (125 mg, 79%), m.p. 129-130°C. R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ: 2980, 2924 (CH), 1712 (ester C=O), 1683 (amide C=O), 1514, 1473, 1357, 1265, 1224, 1124, 1035 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.08-7.03 (2H, d, *J* 8.6 Hz), 6.85-6.81 (2H, d, *J* 8.5 Hz), 5.08 (2H, s), 4.27-4.22 (2H, q, *J* 7.2 Hz), 4.22 (2H, s), 3.63 (2H, s), 2.25 (3H, s), 1.31 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.1, 166.1, 149.7, 145.0, 131.4, 130.1, 117.7, 99.3, 61.2, 60.6, 48.4, 32.3, 20.6, 14.5; (TOF-MS APCI$^-$) *m/z*: 317 (100, $[M-H]^+$), 318 (20), 319 (15%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 317.0951. $C_{16}H_{17}N_2O_3S$ requires 317.0954.

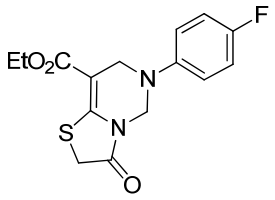
Ethyl 6-(4-isopropylphenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116h)



Flash chromatography (20% EtOAc/hexane) afforded brown solid. (130 mg, 75%), m.p. 104-106°C. R_f (33% EtOAc/hexane) 0.70; IR (KBr) υ: 2960, 2931 (CH), 1712 (ester C=O), 1683 (amide C=O), 1583, 1516, 1464, 1265, 1224, 1124, 1033 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.12-7.09 (2H, d, *J* 8.8 Hz), 6.87-6.84 (2H, d, *J* 8.7 Hz), 5.08 (2H, s), 4.27-4.22 (2H, q, *J* 7.7 Hz), 4.23 (2H, s), 3.64 (2H, s), 2.87-2.77 (1H, m), 1.31 (3H, t, *J* 7.1 Hz), 1.20-1.18 (6H, d, *J* 6.9 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.0, 166.1, 150.0, 145.4, 142.4, 127.4, 117.6, 99.3, 61.1, 60.6, 48.3,

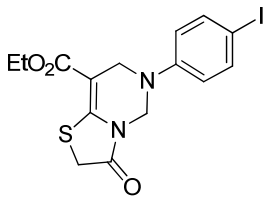
33.3, 32.2, 24.3, 14.5; (TOF-MS APCI$^-$) *m/z*: 345 (100, [M-H]$^+$), 346 (33%); HRMS (TOF-MS APCI$^-$): [M-H]$^+$, found 345.1286. $C_{18}H_{21}N_2O_3S$ requires 345.1267.

Ethyl 6-(4-fluorophenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116i)



Flash chromatography (20% EtOAc/hexane) afforded white crystals. (161 mg, 100%), m.p. 119-121°C. R_f (25% EtOAc/hexane) 0.70; IR (KBr) υ: 3076 (arom. CH), 2980, 2928 (CH), 1710 (ester C=O), 1685 (amide C=O), 1585, 1508, 1467, 1265, 1220, 1126, 1033, 827 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.96-6.84 (4H, m), 5.04 (2H, s), 4.27-4.21 (2H, dd, *J* 14.3, 7.1 Hz), 4.20 (2H, s), 3.65 (2H, s), 1.31 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.9, 166.0, 159.1, 156.9, 149.8, 143.8, 119.5, 119.4, 116.2, 116.0, 99.0, 61.6, 60.7, 48.7, 32.2, 14.6; (TOF-MS APCI$^-$) *m/z*: 321 (100, [M-H]$^+$), 322 (30), 323 (10%); HRMS (TOF-MS APCI$^-$): [M-H]$^+$, found 321.0736. $C_{15}H_{14}FN_2O_3S$ requires 321.0703.

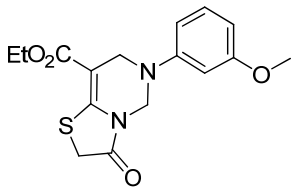
Ethyl 6-(4-iodophenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116j)



Flash chromatography (20% EtOAc/hexane) afforded yellow crystals. (148 mg, 69%), m.p. 163-165°C. R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ: 2978, 2926 (CH), 1710 (ester C=O), 1685 (amide C=O), 1585, 1491, 1357, 1263, 1222, 1124, 1033 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.53-7.51 (2H, d, *J* 8.9 Hz), 6.70-6.68 (2H, d, *J* 8.8 Hz), 5.07 (2H, s), 4.28-4.22 (2H, q, *J* 7.3 Hz), 4.22 (2H, s), 3.65 (2H, s), 1.31 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.0, 166.0, 149.7, 147.2, 138.4, 119.7, 99.0, 84.3, 60.8, 60.4, 48.2, 32.3, 14.5; (TOF-MS APCI$^-$) *m/z*: 428 (100, [M-

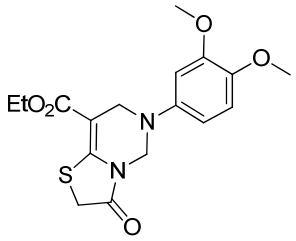
H]$^+$), 429 (20%); HRMS (TOF-MS APCI$^-$): [M-H]$^+$, found 428.9741. $C_{15}H_{14}IN_2O_3S$ requires 428.9764.

Ethyl 6-(3-methoxyphenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116k)



Flash chromatography (20% EtOAc/hexane) afforded transparent-white solid. (124 mg, 74%), m.p. 121-123°C. R_f (33% EtOAc/hexane) 0.70; IR (KBr) υ: 3082 (arom. CH), 2982, 2935 (CH), 1712 (ester C=O), 1681 (amide C=O), 1585, 1500, 1377, 1276, 1230, 1157, 1033, 945 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.18-7.00 (1H, m), 6.55-6.47 (2H, m), 6.32-6.22 (1H, m), 5.09 (2H, s), 4.27-4.22 (2H, q, *J* 7.2 Hz), 4.25 (2H, s), 3.75-3.74 (3H, d, *J* 5.7 Hz), 3.64 (2H, s), 1.31 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.0, 166.1, 160.7, 149.7, 148.8, 147.8, 130.3, 110.0, 107.9, 106.6, 104.2, 103.9, 101.1, 99.3, 60.7, 55.3, 48.2, 32.3, 14.5; (TOF-MS APCI$^-$) *m/z*: 333 (100, [M-H]$^+$), 334 (25%); HRMS (TOF-MS APCI$^-$): [M-H]$^+$, found 333.0904. $C_{16}H_{17}N_2O_4S$ requires 333.0903.

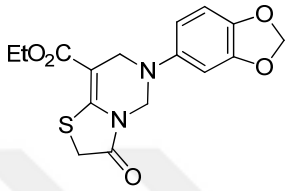
Ethyl 6-(3,4-dimethoxyphenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116l)



Flash chromatography (20% EtOAc/hexane) afforded dark yellow solid. (124 mg, 68%), m.p. 149-150°C. R_f (33% EtOAc/hexane) 0.60; IR (KBr) υ: 3066 (arom. CH), 2966, 2928 (CH), 1712 (ester C=O), 1670 (amide C=O), 1566, 1523, 1446, 1273, 1238, 1219, 1134, 1018, 767 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.74-6.71 (1H, d, *J* 8.7 Hz), 6.53-6.51 (1H, d, *J* 2.7 Hz), 6.42-6.40 (1H, dd, *J* 8.7, 2.8 Hz), 5.03 (2H, s),

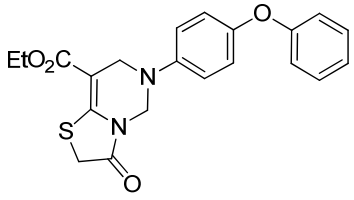
4.27-4.22 (2H, q, *J* 7.1 Hz), 4.19 (2H, s), 3.82 (3H, s), 3.80 (3H, s), 3.64 (2H, s), 1.30 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.1, 166.1, 149.6, 144.6, 141.6, 111.9, 109.3, 103.9, 99.3, 61.8, 60.6, 56.2, 55.9, 48.9, 32.3, 14.5; (TOF-MS APCI$^-$) *m/z*: 363 (100, $[M-H]^+$), 364 (30), 365 (10%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 363.1022. $C_{17}H_{19}N_2O_5S$ requires 363.1009.

Ethyl 6-(benzo[*d*][1,3]dioxol-5-yl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116m)



Flash chromatography (20% EtOAc/hexane) afforded dark brown solid. (139 mg, 80%), m.p. 145-146°C. R_f (33% EtOAc/hexane) 0.70; IR (KBr) υ: 3074 (arom. CH), 2980, 2926 (CH), 1712 (ester C=O), 1681 (amide C=O), 1589, 1502, 1489, 1269, 1222, 1143, 1037, 929, 798 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.68-6.64 (1H, d, *J* 8.4 Hz), 6.53-6.51 (1H, d, *J* 2.4 Hz), 6.35-6.32 (1H, dd, *J* 8.2, 2.7 Hz), 5.89 (2H, s), 4.99 (2H, s), 4.27-4.22 (2H, q, *J* 7.6 Hz), 4.15 (2H, s), 3.65 (2H, s), 1.31 (3H, t, *J* 7.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.1, 166.1, 149.7, 148.5, 143.0, 142.9, 110.7, 108.4, 101.1, 99.1, 62.0, 60.6, 49.1, 32.4, 14.6; (TOF-MS APCI$^-$) *m/z*: 347 (100, $[M-H]^+$), 348 (20), 349 (10%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 347.0696. $C_{16}H_{15}N_2O_5S$ requires 347.0696.

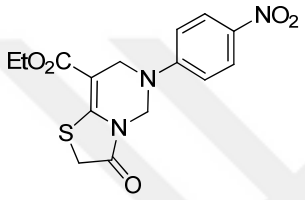
Ethyl 3-oxo-6-(4-phenoxyphenyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116n)



Flash chromatography (25% EtOAc/hexane) afforded brown solid. (120 mg, 60%), m.p. 137-138°C. R_f (33% EtOAc/hexane) 0.75; IR (KBr) υ: 3063 (arom. CH), 2982, 2924 (CH), 1708 (ester C=O), 1674 (amide C=O), 1577, 1508, 1473, 1273, 1246,

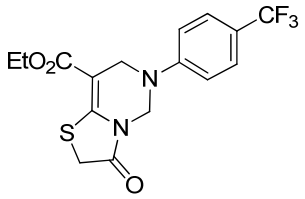
1130, 1014, 833, 756 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.31-7.24 (2H, t, *J* 7.5 Hz), 7.07-7.03 (1H, t, *J* 8.4 Hz), 6.98-6.85 (6H, m), 5.06 (2H, s), 4.28-4.22 (2H, q, *J* 7.2 Hz), 4.22 (2H, s), 3.66 (2H, s), 1.31 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.3, 166.2, 157.7, 151.7, 149.8, 143.5, 129.7, 122.9, 120.3, 119.2, 118.3, 99.3, 61.6, 60.5, 48.9, 32.2, 14.5; (TOF-MS APCI$^-$) *m/z*: 395 (100, $[M-H]^+$), 396 (30), 397 (10%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 395.1044. $C_{21}H_{19}N_2O_4S$ requires 395.1060.

Ethyl 6-(4-nitrophenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116o)



Flash chromatography (33% EtOAc/hexane) afforded yellow solid. (45 mg, 26%), m.p. 152-154°C. R_f (50% EtOAc/hexane) 0.70; IR (KBr) υ: 2983, 2924 (CH), 1716 (ester C=O), 1683 (amide C=O), 1591, 1500, 1329, 1269, 1224, 1112, 1035 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.10-8.18 (2H, d, *J* 9.2 Hz), 6.98-6.89 (2H, d, *J* 9.2 Hz), 5.19 (2H, s), 4.35 (2H, s), 4.29-4.20 (2H, q, *J* 7.1 Hz), 3.67 (2H, s), 1.31 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.7, 165.6, 152.2, 149.9, 141.4, 126.0, 115.7, 98.7, 60.9, 58.9, 47.8, 32.4, 14.5; (TOF-MS APCI$^-$) *m/z*: 348 (100, $[M-H]^+$), 349 (30%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 348.0668. $C_{15}H_{14}N_3O_5S$ requires 348.0648.

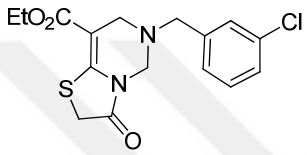
Ethyl 3-oxo-6-(4-(trifluoromethyl)phenyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116p)



Flash chromatography (25% EtOAc/hexane) afforded pale brown solid. (151 mg, 81%), m.p. 140-142°C. R_f (33% EtOAc/hexane) 0.70; IR (KBr) υ: 3070 (arom. CH),

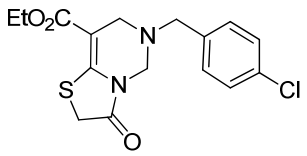
2932, 2931 (CH), 1716 (ester C=O), 1681 (amide C=O), 1566, 1330, 1269, 1226, 1111, 1030, 840 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.51-7.46 (2H, d, *J* 8.9 Hz), 7.00-6.94 (2H, d, *J* 8.9 Hz), 5.15 (2H, s), 4.31 (2H, s), 4.29-4.22 (2H, q, *J* 7.1 Hz), 3.66 (2H, s), 1.32 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 170.9, 165.8, 150.0, 149.8, 127.0, 116.8, 98.8, 60.8, 59.7, 48.0, 32.3, 14.6; (TOF-MS APCI$^-$) *m/z*: 371 (100, $[M-H]^+$), 372 (20), 373 (10%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 371.0673. $C_{16}H_{14}F_3N_2O_3S$ requires 371.0671.

Ethyl 6-(3-chlorobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116r)



Flash chromatography (20% EtOAc/hexane) afforded pale yellow semi-solid. (88 mg, 50%). R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ: 3063 (arom. CH), 2978, 2928 (CH), 1716 (ester C=O), 1685 (amide C=O), 1581, 1261, 1207, 1111, 1041cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.31 (1H, s), 7.26-7.21 (2H, m), 7.14-7.12 (1H, m), 4.53 (2H, s), 4.23-4.18 (2H, q, *J* 7.3 Hz), 3.70 (2H, s), 3.60 (2H, s), 3.59 (2H, s), 1.26 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.4, 166.5, 148.9, 139.2, 134.6, 129.7, 128.8, 127.7, 126.9, 97.9, 63.0, 60.5, 56.2, 49.1, 32.3, 14.4; (TOF-MS APCI$^-$) *m/z*: 351 (100, $[M-H]^+$), 352 (20%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 351.0566. $C_{16}H_{16}ClN_2O_3S$ requires 351.0564.

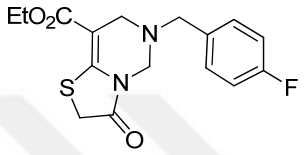
Ethyl 6-(4-chlorobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116s)



Flash chromatography (20% EtOAc/hexane) afforded creamy white solid. (167 mg, 95 %), m.p. 121-122°C. R_f (33% EtOAc/hexane) 0.45; IR (KBr) υ: 2978, 2928 (CH), 1712 (ester C=O), 1681 (amide C=O), 1583, 1491, 1257, 1205, 1111, 1043, 802 cm$^-$

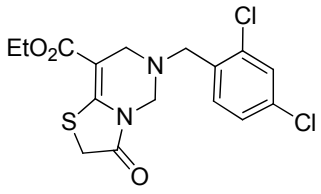
[1]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35-7.15 (2H, m), 4.51 (2H, s), 4.24-4.15 (2H, dd, *J* 15.2, 8.0 Hz), 3.69 (2H, s), 3.59 (4H, s), 1.26 (3H, t, *J* 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.6, 166.6, 148.8, 135.6, 133.6, 130.1, 128.6, 97.9, 63.2, 60.3, 55.9, 48.9, 32.3, 14.5; (TOF-MS APCI$^-$) *m/z*: 351 (100, $[M-H]^+$), 352 (25), 353 (40%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 351.0605. $C_{16}H_{16}ClN_2O_3S$ requires 351.0564.

Ethyl 6-(4-fluorobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116t)



Flash chromatography (25% EtOAc/hexane) afforded golden yellow solid. (158 mg, 94%), m.p. 88-90°C. R_f (33% EtOAc/hexane) 0.60; IR (KBr) υ: 2982, 2924 (CH), 1705 (ester C=O), 1685 (amide C=O), 1573, 1508, 1257, 1203, 1141, 1030 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.26-7.19 (2H, dd, *J* 8.7, 5.2 Hz), 7.03-6.96 (2H, t, *J* 8.6 Hz), 5.20-5.14 (2H, m), 4.51 (2H, s), 4.23-4.16 (2H, q, *J* 7.3 Hz), 3.69 (2H, s), 3.59 (2H, s), 3.58 (2H, s), 1.26 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.4, 166.5, 163.5, 161.0, 148.8, 132.8, 130.4, 115.5, 115.3, 98.0, 62.5, 60.4, 56.0, 49.0, 32.3, 14.4; (TOF-MS APCI$^-$) *m/z*: 335 (100, $[M-H]^+$), 336 (30), 337 (15%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 335.0877. $C_{16}H_{16}FN_2O_3S$ requires 335.0860.

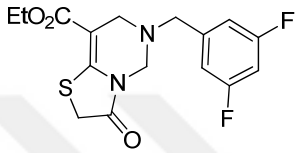
Ethyl 6-(2,4-dichlorobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116u)



Flash chromatography (25% EtOAc/hexane) afforded yellow solid. (154 mg, 80%), m.p. 114-116°C. R_f (33% EtOAc/hexane) 0.40; IR (KBr) υ: 2924, 2854 (CH), 1705 (ester C=O), 1678 (amide C=O), 1562, 1469, 1253, 1203, 1122, 1026 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39-7.35 (1H, d, *J* 1.9 Hz), 7.34-7.30 (1H, d, *J* 8.3 Hz), 7.24-

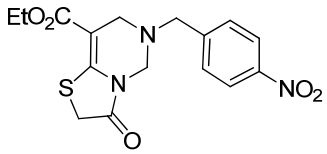
7.21 (1H, d, *J* 8.2, 1.8 Hz), 4.52 (2H, s), 4.25-4.17 (2H, q, *J* 7.2 Hz), 3.70 (2H, s), 3.68 (2H, s), 3.63 (2H, s), 1.27 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.4, 166.6, 149.0, 135.3, 134.2, 133.6, 131.5, 129.6, 127.2, 98.0, 63.0, 60.7, 53.4, 49.4, 32.5, 30.9, 14.5; (TOF-MS APCI$^-$) *m/z*: 385 (100, $[M-H]^+$), 386 (20), 387 (70%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 385.0166. $C_{16}H_{15}Cl_2N_2O_3S$ requires 385.0174.

Ethyl 6-(3,5-difluorobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116v)



Flash chromatography (20% EtOAc/hexane) afforded pale yellow solid. (140 mg, 79%), m.p. 103-105°C. R_f (33% EtOAc/hexane) 0.60; IR (KBr) υ: 3086 (arom. CH), 2982, 2931 (CH), 1716 (ester C=O), 1685 (amide C=O), 1581, 1462, 1261, 1114, 1030, 848 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 6.89-6.79 (2H, d, *J* 6.2 Hz), 6.75-6.66 (1H, tt, *J* 8.9, 2.3 Hz), 4.53 (2H, s), 4.23-4.16 (2H, q, *J* 7.2 Hz), 3.70 (2H, s), 3.61 (2H, s), 3.59 (2H, s), 1.25 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.5, 166.5, 164.3, 161.9, 148.9, 141.5, 111.6, 111.3, 103.2, 97.8, 63.5, 60.5, 56.0, 49.1, 32.4, 14.2; (TOF-MS APCI$^-$) *m/z*: 353 (100, $[M-H]^+$), 354 (20%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 353.0762. $C_{16}H_{15}F_2N_2O_3S$ requires 353.0766.

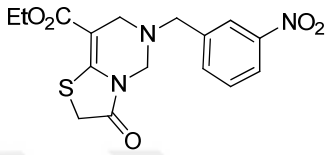
Ethyl 6-(4-nitrobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116x)



Flash chromatography (40% EtOAc/hexane) afforded cream-yellow solid. (91 mg, 50%), m.p. 175-176°C. R_f (33% EtOAc/hexane) 0.30; IR (KBr) υ: 2970, 2928 (CH), 1716 (ester C=O), 1651 (amide C=O), 1577, 1508, 1342, 1261, 1138, 1020 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.20-8.18 (2H, d, *J* 8.7 Hz), 7.50-7.48 (2H, d, *J* 8.6 Hz),

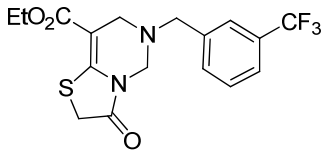
4.55 (2H, s), 4.23-4.17 (2H, q, *J* 7.1 Hz), 3.74 (2H, s), 3.72 (2H, s), 3.61 (2H, s), 1.25 (3H, t, *J* 8.0 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.5, 166.4, 149.1, 147.5, 144.9, 129.3, 123.8, 97.7, 63.2, 60.5, 56.1, 49.1, 32.4, 14.5; (TOF-MS APCI$^+$) *m/z*: 364 (100, MH^+), 365 (25%); HRMS (TOF-MS APCI$^+$): MH^+, found 364.0960. $C_{16}H_{18}N_3O_5S$ requires 364.0967.

Ethyl 6-(3-nitrobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116y)



Flash chromatography (40% EtOAc/hexane) afforded pale yellow semi-solid. (82 mg, 45%). R_f (33% EtOAc/hexane) 0.30; IR (KBr) υ: 3082 (arom. CH), 2924, 2854 (CH), 1716 (ester C=O), 1685 (amide C=O), 1577, 1523, 1350, 1257, 1107, 1026 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.21 (1H, s), 8.17-8.10 (1H, d, *J* 8.1 Hz), 7.64-7.58 (1H, d, *J* 7.6 Hz), 7.50 (1H, t, *J* 7.9 Hz), 4.55 (2H, s), 4.23-4.15 (2H, q, *J* 7.3 Hz), 3.73 (2H, s), 3.71 (2H, s), 3.61 (2H, s), 1.25 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.5, 166.4, 148.8, 148.4, 139.5, 134.6, 129.5, 123.5, 122.9, 97.5, 63.1, 60.5, 55.9, 48.9, 32.3, 14.4; (TOF-MS APCI$^+$) *m/z*: 364 (100, MH^+), 365 (20%); HRMS (TOF-MS APCI$^+$): MH^+, found 364.0976. $C_{16}H_{18}N_3O_5S$ requires 364.0967.

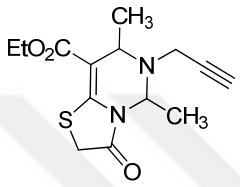
Ethyl 3-oxo-6-(3-(trifluoromethyl)benzyl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116z)



Flash chromatography (30% EtOAc/hexane) afforded orange-yellow solid. (129 mg, 67%), m.p. 72-74°C. R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ: 3055 (arom. CH), 2983, 2929 (CH), 1718 (ester C=O), 1685 (amide C=O), 1585, 1329, 1265, 1126, 1072, 1043 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.61-7.56 (1H, d, *J* 14.7 Hz), 7.55-

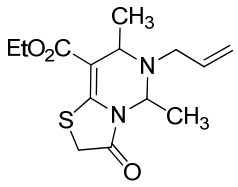
7.52 (1H, d, *J* 6.5 Hz), 7.49-7.41 (2H, m), 4.55 (2H, s), 4.23-4.16 (2H, q, *J* 7.4 Hz), 3.70 (2H, s), 3.68 (2H, s), 3.60 (2H, s), 1.25 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.5, 166.5, 148.8, 138.4, 132.1, 130.8, 129.1, 125.4, 124.5, 122.7, 97.8, 63.1, 60.5, 56.2, 48.7, 32.4, 14.4; (TOF-MS APCI$^-$) *m/z*: 385 (100, $[M-H]^+$), 386 (20), 387 (30%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 385.0845. $C_{17}H_{16}F_3N_2O_3S$ requires 385.0828.

Ethyl 5,7-dimethyl-3-oxo-6-(prop-2-yn-1-yl)-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116aa)



Flash chromatography (20% EtOAc/hexane) afforded orange-brown solid. (142 mg, 97%), m.p. 80-81°C. R_f (33% EtOAc/hexane) 0.40; IR (KBr) υ: 3269 (≡CH), 2983, 2935 (CH), 1708 (ester C=O), 1681 (amide C=O), 1575, 1371, 1234, 1132, 1053, 777 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.24-5.19 (1H, m), 4.34-4.14 (2H, m), 3.89-3.81 (1H, dd, *J* 14.3, 7.2 Hz), 3.66-3.62 (2H, d, *J* 2.2 Hz), 3.34-3.29 (2H, m), 2.24 (1H, t, *J* 2.4 Hz), 1.51-1.45 (6H, dd, *J* 6.9, 5.5 Hz), 1.30 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.4, 166.9, 147.2, 102.1, 79.7, 73.1, 68.6, 60.4, 53.8, 46.4, 32.3, 23.2, 21.1, 14.3; (TOF-MS APCI$^-$) *m/z*: 293 (100, $[M-H]^+$), 294 (20%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 293.0959. $C_{14}H_{17}N_2O_3S$ requires 293.0954.

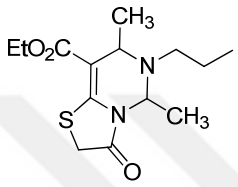
Ethyl 6-allyl-5,7-dimethyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116ab)



Flash chromatography (30% EtOAc/hexane) afforded orange oil. (70 mg, 47%). R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ: 3082 (=CH), 2980, 2935 (CH), 1708 (ester C=O), 1685 (amide C=O), 1577, 1265, 1232, 1138, 1053 cm^{-1}; ^{1}H-NMR (400 MHz,

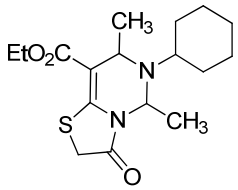
$CDCl_3$) δ: 5.86-5.74 (1H, m), 5.19-5.11 (2H, m), 5.06-4.99 (1H, dd, *J* 14.8, 6.8 Hz), 4.32-4.14 (2H, m), 3.76-3.70 (2H, dd, *J* 14.5, 6.6 Hz), 3.65 (2H, s), 3.10-3.02 (2H, m), 1.48-1.41 (6H, dd, *J* 9.5, 7.1 Hz), 1.29 (3H, t, *J* 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 171.4, 167.1, 147.2, 135.2, 118.3, 102.7, 69.1, 60.4, 60.1, 53.0, 32.3, 23.0, 20.9, 14.4; (TOF-MS APCI$^-$) *m/z*: 295 (100, $[M-H]^+$), 296 (30%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 295.1122. $C_{14}H_{19}N_2O_3S$ requires 295.1110.

Ethyl 5,7-dimethyl-3-oxo-6-propyl-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116ac)



Flash chromatography (30% EtOAc/hexane) afforded orange oil. (60 mg, 40 %). R_f (50% EtOAc/hexane) 0.50; IR (KBr) υ: 2964, 2933 (CH), 1707 (ester C=O), 1685 (amide C=O), 1577, 1462, 1371, 1265, 1236, 1168, 1095 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.76 (1H, d, *J* 3.6 Hz), 4.31-4.14 (4H, m), 3.75-3.64 (2H, m), 3.29-3.13 (1H, m), 3.02-2.93 (2H, m), 2.11 (1H, d, *J* 14.4 Hz), 2.04-1.76 (2H, m), 1.75-1.46 (2H, m), 1.37-1.18 (9H, m), 1.00-0.80 (3H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 173.1, 167.4, 142.5, 106.8, 75.0, 60.4, 35.4, 32.5, 29.7, 26.7, 21.0, 20.4, 14.4, 11.7; (TOF-MS APCI$^-$) *m/z*: 297 (100, $[M-H]^+$), 298 (20%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 297.1285. $C_{14}H_{21}N_2O_3S$ requires 297.1267.

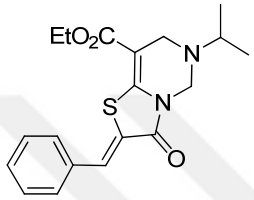
Ethyl 6-cyclohexyl-5,7-dimethyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116ad)



Flash chromatography (30% EtOAc/hexane) afforded brown solid. (90 mg, 53%), m.p. 110-111°C. R_f (50% EtOAc/hexane) 0.70; IR (KBr) υ: 2928, 2854 (CH), 1708 (ester C=O), 1685 (amide C=O), 1577, 1457, 1261, 1114, 1049 cm^{-1}; ^{1}H-NMR (400

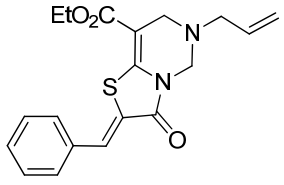
MHz, $CDCl_3$) δ: 5.35-5.25 (1H, m), 4.35-4.14 (2H, m), 3.75-3.57 (2H, m), 2.98-2.72 (1H, m), 2.57-2.35 (1H, m), 1.87-1.50 (9H, m), 1.37-1.26 (6H, m), 1.26-1.16 (5H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 172.4, 167.8, 149.6, 105.4, 77.3, 62.2, 60.4, 52.7, 36.8, 34.5, 32.9, 32.8, 26.0, 25.3, 25.0, 24.7, 22.1, 20.6, 14.5; (TOF-MS APCI$^-$) *m/z*: 337 (100, $[M-H]^+$), 338 (20), 339 (10%); HRMS (TOF-MS APCI$^-$): $[M-H]^+$, found 337.1604. $C_{17}H_{25}N_2O_3S$ requires 337.1580.

(Z)-ethyl 2-benzylidene-6-isopropyl-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116ba)



Flash chromatography (20% EtOAc/hexane) afforded yellow solid. (125 mg, 70 %), m.p. 112-114°C. R_f (33% EtOAc/hexane) 0.60; IR (KBr) υ: 2976, 2854 (CH), 1691 (ester C=O), 1595 (amide C=O), 1365, 1282, 1257, 1132, 1031, 759 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.64 (1H, s), 7.59-7.57 (2H, d, *J* 8.5 Hz), 7.45-7.41 (2H, t, *J* 7.6 Hz), 7.38-7.34 (1H, t, *J* 7.3 Hz), 4.75 (2H, s), 4.30-4.25 (2H, q, *J* 7.1 Hz), 3.77 (2H, s), 2.92-2.82 (1H, hept, *J* 6.4 Hz), 1.33 (3H, t, *J* 7.3 Hz), 1.14-1.12 (6H, t, *J* 6.4 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.2, 165.3, 144.7, 134.1, 130.6, 130.3, 129.7, 129.1, 123.3, 99.7, 60.7, 50.2, 46.8, 20.7, 14.5; (TOF-MS APCI$^-$) *m/z*: 358 (100, M^+), 359 (25%); HRMS (TOF-MS APCI$^-$): M^+, found 358.1364. $C_{19}H_{22}N_2O_3S$ requires 358.1351.

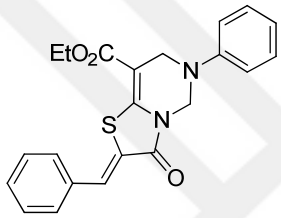
(Z)-ethyl 6-allyl-2-benzylidene-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116bb)



Flash chromatography (30% EtOAc/hexane) afforded yellow solid. (153 mg, 87 %), m.p. 102-104°C. R_f (33% EtOAc/hexane) 0.50; IR (KBr) υ: 3078 (=CH), 2926, 2852

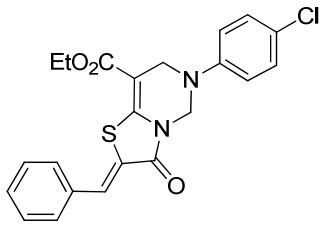
(CH), 1693 (ester C=O), 1597 (amide C=O), 1363, 1288, 1257, 1207, 1109, 1030, 758 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.65 (1H, s), 7.60-7.58 (2H, d, *J* 8.5 Hz), 7.46-7.42 (2H, t, *J* 7.5 Hz), 7.38-7.35 (1H, t, *J* 7.3 Hz), 5.91-5.81 (1H, ddt, *J* 16.8, 10.3, 6.5 Hz), 5.23-5.17 (2H, m), 4.69 (2H, s), 4.29-4.24 (2H, q, *J* 7.1 Hz), 3.73 (2H, s), 3.16-3.14 (2H, d, *J* 6.5 Hz), 1.32 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.3, 165.8, 144.2, 134.0, 130.8, 130.3, 129.7, 129.1, 123.0, 119.4, 98.4, 62.6, 60.7, 55.7, 49.3, 14.5; (TOF-MS APCI$^-$) *m/z*: 356 (100, M^+), 357 (35%); HRMS (TOF-MS APCI$^-$): M^+, found 356.1208. $C_{19}H_{20}N_2O_3S$ requires 356.1194.

(Z)-ethyl 2-benzylidene-3-oxo-6-phenyl-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*] pyrimidine-8-carboxylate (116bc)



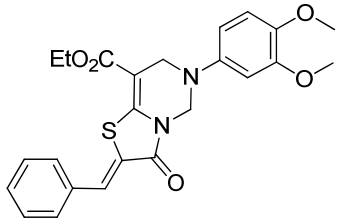
Flash chromatography (20% EtOAc/hexane) afforded yellow solid. (144 mg, 73%), m.p. 143-145°C. R_f (33% EtOAc/hexane) 0.70; IR (KBr) υ: 3059 (arom. CH), 2978, 2928 (CH), 1697 (ester C=O), 1683 (amide C=O), 1585, 1492, 1287, 1257, 1138, 1033, 750 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.66 (1H, s), 7.58-7.56 (2H, d, *J* 7.3 Hz), 7.45-7.41 (2H, t, *J* 7.5 Hz), 7.38-7.34 (1H, t, *J* 7.3 Hz), 7.29-7.25 (2H, m), 7.23-7.15 (1H, m), 7.02 -6.96 (3H, t, *J* 7.1 Hz), 6.97-6.92 (1H, t, *J* 7.4 Hz), 6.87-6.80 (1H, t, *J* 7.3 Hz), 5.29 (2H, s), 4.38 (2H, s), 4.34-4.27 (2H, q, *J* 7.1 Hz), 1.36 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 165.8, 165.4, 147.5, 145.0, 134.0, 131.2, 130.3, 129.8, 129.6, 129.1, 122.5, 117.8, 99.6, 68.6, 60.9, 48.8, 14.5; (TOF-MS APCI$^-$) *m/z*: 392 (100, M^+), 393 (25%); HRMS (TOF-MS APCI$^-$): M^+, found 392.1207. $C_{22}H_{20}N_2O_3S$ requires 392.1194.

(Z)-ethyl 2-benzylidene-6-(4-chlorophenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo [3,2-*c*]pyrimidine-8-carboxylate (116bd)



Flash chromatography (20% EtOAc/hexane) afforded yellow solid. (120 mg, 56%), m.p. 183-185°C. R_f (33% EtOAc/hexane) 0.60; IR (KBr) υ: 2985, 2924 (CH), 1681 (ester C=O), 1573 (amide C=O), 1496, 1280, 1257, 1134, 817, 763 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.66 (1H, s), 7.57-7.55 (2H, d, *J* 7.6 Hz), 7.45-7.42 (2H, t, *J* 7.5 Hz), 7.39-7.35 (1H, t, *J* 7.3 Hz), 7.22-7.20 (2H, d, *J* 9.1 Hz), 6.91-6.89 (2H, d, *J* 9.1 Hz), 5.24 (2H, s), 4.34 (2H, s), 4.33-4.27 (2H, q, *J* 7.2 Hz), 1.36 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 165.7, 165.4, 146.2, 145.1, 133.8, 131.5, 130.2, 129.8, 129.4, 129.0, 127.0, 122.5, 119.3, 118.9, 99.3, 61.0, 60.8, 48.8, 14.6; (TOF-MS APCI$^-$) *m/z*: 426 (100, M^+), 427 (25), 428 (35%); HRMS (TOF-MS APCI$^-$): M^+, found 426.0785. $C_{22}H_{19}ClN_2O_3S$ requires 426.0804.

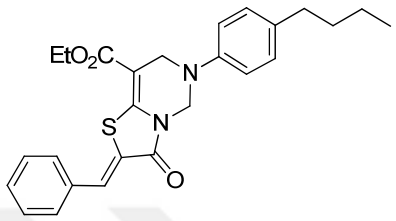
(Z)-ethyl 2-benzylidene-6-(3,4-dimethoxyphenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo[3,2-*c*]pyrimidine-8-carboxylate (116be)



Flash chromatography (15% EtOAc/hexane) afforded yellow solid. (90 mg, 40%), m.p. 156–158°C. R_f (50% EtOAc/hexane) 0.80; IR (KBr) υ: 2968, 2924 (CH), 1683 (ester C=O), 1593 (amide C=O), 1523, 1286, 1263, 1134, 1024, 758 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.65 (1H, s), 7.58-7.56 (2H, d, *J* 7.4 Hz), 7.45-7.41 (3H, t, *J* 7.4 Hz), 7.38-7.34 (1H, t, *J* 7.3 Hz), 6.74-6.72 (1H, d, *J* 8.7 Hz), 6.62-6.58 (1H, d, *J* 2.7 Hz), 6.47-6.44 (1H, dd, *J* 8.7, 2.7 Hz), 5.21 (2H, s), 4.33-4.27 (4H, m), 3.83 (3H, s), 3.80 (3H, s), 1.35 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 165.8, 165.2,

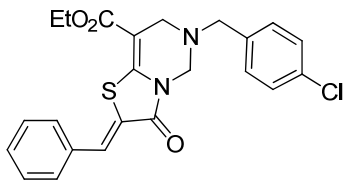
149.6, 144.9, 144.7, 141.8, 133.9, 131.1, 130.2, 129.8, 129.1, 122.7, 111.9, 109.5, 103.8, 99.7, 61.8, 60.9, 56.2, 55.9, 49.6, 14.6; (TOF-MS APCI$^-$) *m/z*: 452 (100, M^+), 453 (25%); HRMS (TOF-MS APCI$^-$): M^+, found 452.1425. $C_{24}H_{24}N_2O_5S$ requires 452.1405.

(Z)-ethyl 2-benzylidene-6-(4-butylphenyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo [3,2-*c*]pyrimidine-8-carboxylate (116bf)



Flash chromatography (20% EtOAc/hexane) afforded yellow semi-solid. (141 mg, 63%). R_f (33% EtOAc/hexane) 0.80; IR (KBr) υ: 3057 (arom. CH), 2955, 2928 (CH), 1689 (ester C=O), 1587 (amide C=O), 1514, 1396, 1261, 1128, 1031, 831, 761 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.65 (1H, s), 7.58-7.56 (2H, d, *J* 7.2 Hz), 7.45-7.41 (2H, t, *J* 7.4 Hz), 7.38-7.34 (1H, t, *J* 7.4 Hz), 7.08-7.06 (2H, d, *J* 8.6 Hz), 7.02-6.99 (1H, dd, *J* 8.5, 3.5 Hz), 6.90-6.88 (1H, d, *J* 8.6 Hz), 6.56-6.53 (1H, d, *J* 8.6 Hz), 5.25 (2H, s), 4.35 (2H, s), 4.33-4.28 (2H, q, *J* 7.1 Hz), 2.53-2.46 (2H, m), 1.59-1.48 (4H, m), 1.39-1.24 (5H, m), 0.92-0.86 (3H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 165.9, 165.4, 146.6, 145.3, 134.0, 131.0, 130.3, 129.7, 129.5, 129.1, 129.0, 123.0, 118.0, 117.9, 99.7, 69.6, 60.9, 48.9, 34.7, 33.7, 22.4, 14.5, 14.0; (TOF-MS APCI$^-$) *m/z*: 448 (100, M^+), 449 (40%); HRMS (TOF-MS APCI$^-$): M^+, found 448.1796. $C_{26}H_{28}N_2O_3S$ requires 448.1820.

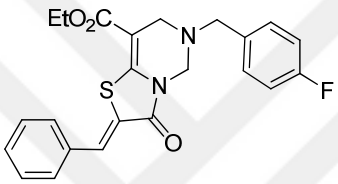
(Z)-ethyl 2-benzylidene-6-(4-chlorobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo [3,2-*c*]pyrimidine-8-carboxylate (116bg)



Flash chromatography (25% EtOAc/hexane) afforded pale brown semi-solid. (176 mg, 80%). R_f (33% EtOAc/hexane) 0.65; IR (KBr) υ: 2926, 2854 (CH), 1685 (ester

C=O), 1597 (amide C=O), 1491, 1396, 1286, 1263, 1126, 1014, 758 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.66 (1H, s), 7.61-7.59 (2H, d, *J* 7.7 Hz), 7.47-7.44 (2H, t, *J* 7.6 Hz), 7.40-7.36 (1H, t, *J* 7.3 Hz), 7.32-7.30 (2H, d, *J* 8.3 Hz), 7.25-7.23 (2H, d, *J* 8.0 Hz), 4.68 (2H, s), 4.29-4.23 (2H, q, *J* 7.1 Hz), 3.72 (2H, s), 3.64 (2H, s), 1.30 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.3, 165.9, 144.2, 135.6, 134.0, 133.6, 131.0, 130.3, 129.8, 129.1, 128.8, 122.9, 98.2, 62.8, 60.8, 56.1, 49.3, 14.5; (TOF-MS APCI$^-$) *m/z*: 440 (100, M^+), 441 (20), 442 (35%); HRMS (TOF-MS APCI$^-$): M^+, found 440.0926. $C_{23}H_{21}ClN_2O_3S$ requires 440.0961.

(Z)-ethyl 2-benzylidene-6-(4-fluorobenzyl)-3-oxo-3,5,6,7-tetrahydro-2*H*-thiazolo [3,2-*c*]pyrimidine-8-carboxylate (116bh)



Flash chromatography (20% EtOAc/hexane) afforded pale yellow solid. (117 mg, 55%), m.p. 126-127°C. R_f (33% EtOAc/hexane) 0.75; IR (KBr) υ: 3039 (arom. CH), 2978, 2904 (CH), 1697 (ester C=O), 1678 (amide C=O), 1593, 1508, 1286, 1259, 1220, 1120, 826, 758 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.67 (1H, s), 7.62-7.60 (1H, d, *J* 9.3 Hz), 7.48-7.44 (2H, t, *J* 8.3 Hz), 7.29-7.21 (3H, m), 7.05-7.00 (1H, t, *J* 8.9 Hz), 6.96-6.91 (2H, t, *J* 9.0 Hz), 4.68 (2H, s), 4.29-4.24 (2H, q, *J* 7.2 Hz), 3.73 (2H, s), 3.64 (2H, s), 1.30 (3H, t, *J* 7.1 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.3, 165.9, 163.6, 163.2, 161.2, 144.2, 134.0, 132.9, 131.0, 130.9, 130.4, 129.2, 129.0, 122.8, 115.1, 114.8, 98.3, 73.4, 62.6, 60.7, 56.2, 49.3, 14.5; (TOF-MS APCI$^-$) *m/z*: 424 (100, M^+), 425 (35%); HRMS (TOF-MS APCI$^-$): M^+, found 424.1253. $C_{23}H_{21}FN_2O_3S$ requires 424.1256.

3.1.3. ANTIBACTERIAL ACTIVITY ASSAY

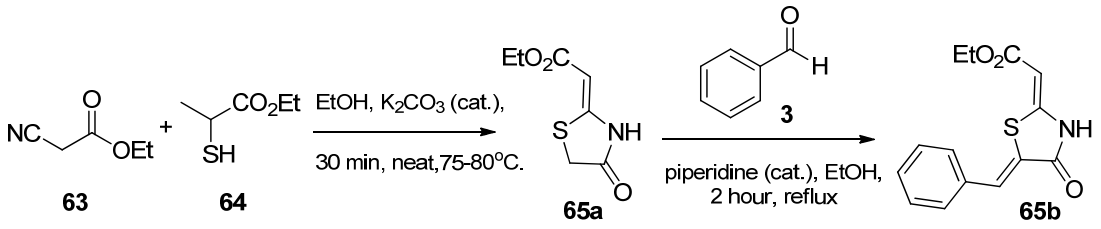
Disc diffusion (Kirby-Bauer) method was applied to evaluate anti-bacterial activity of the compounds **116**. Only two types of Gram (+) bacteria (*Staphylococcus aureus, Staphylococcus epidermidis*) were used and suspensions of stock

microorganisms was transferred to 2 ml of TSB in test tubes, and their absorbance values adjusted according to the standard microorganism. Then, the cultures were inoculated onto Mueller-Hinton agar containing petri dishes. 10 compounds **116** were dissolved separately in DMSO (1mg/10µL) and sterilized using 0.22-µm filter. 20µL of each prepared solution were added on the filter paper discs which was then placed on inoculated petri dishes. Two antibiotic discs (ampicillin and penicillin) were used for positive control. The inoculated petri dishes were kept in incubator at 37°C for 24 hours and then the the inhibition zone diameters were measured.

4. RESULTS AND DISCUSSION

4.1 SYNTHESIS AND CHARACTERIZATION OF STARTING MATERIALS

Heterocyclic enamines **65a-b** as starting compounds have been prepared by following literature methods over two steps (Stojanovic et al., 2011; Yahya et al., 2015) and their structures were characterized by means of IR, NMR and HRMS data or by comparing with relevant data in literature. First heterocyclic enamine, (*Z*)-ethyl 2-(4-oxothiazolidin-2-ylidene) acetate **65a** was prepared by following a reported literature protocol in good yield (Scheme 4.1). The structure of compound **65a** was characterized by IR ester C=O, amide –NH and C=O stretching vibrations at around 3252, 1716 and 1666 cm^{-1} which were consistent with the literature values (Stojanovic et al., 2011). In proton NMR of compound **65a**, NH and C=CH proton signals resonated around 9.60 and 5.62 ppm, respectively. Secondly, (*Z*)-ethyl 2-((*Z*)-5-benzylidene-4-oxothiazolidin-2-ylidene) acetate **65b** was prepared by reacting compound **65a** with benzaldehyde **3** using catalytic amount of piperidine in ethanol at reflux (Yahya et al., 2015). Structure of compound **65b** was elucidated by IR aromatic CH, ester and amide C=O stretching vibrations at around 3063, 1689 and 1597 cm^{-1}, respectively. In proton and carbon-13 NMR of compound **65b**, C=CH peaks at 7.68, 5.26 ppm, broad –NH peak at 5.94 ppm and aromatic carbon peaks around 133.7-120.1 ppm depicted the formation of arylidene heterocyclic enamine **65b**. The structure of compound **65b** was supported by its accurate mass data (274.0530) which was accordance with its expected accurate mass value (274.0532).



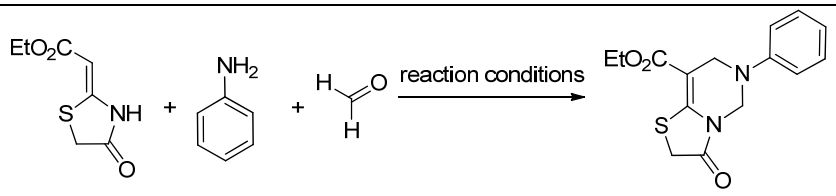
Scheme 4.1. Preparation of heterocyclic enamine precursors **65a-b**.

4.2 SYNTHESIS AND CHARACTERIZATION OF ETHYL 3-OXOTHIAZOLO[3,2-C]PYRIMIDINE-8-CARBOXYLATES (116)

First examples of 3-oxothiazolo[3,2-*c*]pyrimidines **116** were efficiently synthesized and reported by our group in 2015. (Yıldırım and Çelikel, 2015) Following this, the cytotoxic properties of 3-oxothiazolo[3,2-*c*]pyrimidines **116** were also reported for the first time by our group in 2018. (Yildirim et al., 2018) With our ongoing interest on the preparation of new potentially bioactive thiazolo[3,2-*c*]pyridimines **116**, three-component Mannich cyclizations of new heterocyclic enamines **65a**, **65b** with formaldehyde **3a** (or acetaldehye **3b**) and primary amines **4** were planned to perform in the present study.

Firstly, some trial experiments have been designed to find out the most suitable conditions for the synthesis of new 3-oxothiazolo[3,2-*c*]pyrimidines **116**. So, we tried the cyclisation under different conditions using the reaction of (*Z*)-ethyl 2-(4-oxothiazolidin-2-ylidene) acetate **65a**, formaldehyde **3a** and aniline **4f** as a model (Table 4.1). In all trial reactions, two equivalents of formaldehyde **3a** were used with respect to other precursors **65a** and **4f**.

Table 4.1. Optimization the reaction conditions for the synthesis of compound **116f**.



65a **4f** **3a** **116f**

Entry	Reaction conditions	Catalyst	Time	Yield (%)
1	EtOH, **65a** (1eq), **4f**(1eq), **3a**(2.0 eq) [a]	-	4h	45
2	EtOH, **65a** (1eq), **4f**(1eq), **3a**(2.0 eq) [a]	Et_3N	3h	52
3	Neat, **65a** (1eq), **4f**(1eq), **3a**(2.0 eq)[b]	-	1h	40
4	H_2O, **65a** (1eq), **4f**(1eq), **3a**(2.0 eq) [a]	-	3h	38
5	H_2O, **65a** (1eq), **4f**(1eq), **3a**(2.0 eq) [a]	MW	3-10min	28
6	CH_3CN,**65a** (1eq), **4f**(1eq), **3a**(2.0 eq)[a]	MW	3-10 min	-[c]
7	CH_3CN, **65a** (1eq), **4f**(1eq), **3a**(2.0 eq)[a]	Et_3N	3h	72
8	CH_3CN, **65a** (1eq), **4f**(1eq), **3a**(2.0 eq)[a]	-	**2h**	**90**

[a] Reaction performed at reflux temperature of the solvent. [b] The reaction carried out at 80°C. [c] No product was seen or isolated.

The reactions were not effective with or without using triethylamine in EtOH under reflux (entries 1-2, Table 4.1). Also, the solvent-free conditions did not cause

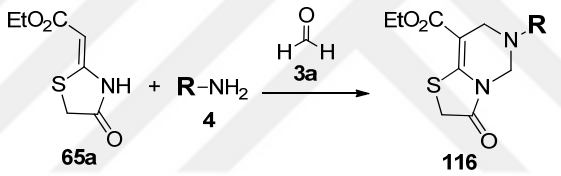
an increase in the reaction yields (40%) (entry 3, Table 4.1). When aqueous conditions have been applied under conventional or MW heating, the product yields were obtained low-to-medium (28-38%) (entries 4-5, Table 4.1). However, only decomposition reaction was observed within minutes when the reaction was carried out in CH_3CN under microwave irradiation (entry 6, Table 4.1). The model reactions carried out at reflux temperature of CH_3CN under conventional heating with or without using triethylamine provided the expected product **116f** in good yields (72-90%) (entries 7-8, Table 4.1).

After optimizing the reaction conditions, (*Z*)-ethyl 2-(4-oxothiazolidin-2-ylidene) acetate **65a** was reacted with a variety of alkyl or aryl amines **4** in the presence of formaldehyde **3a** to give the derivatives of cyclisation products **116**. Thus, a new series of 6-substituted-3-oxothiazolo[3,2-*c*]pyrimidines **116** were generally obtained in moderate to good yields (50-100%) with few exceptions (Table 4.2). Cyclization reactions with alkyl and methoxyl substituted amines afforded the products **116a-e** with moderate-to-good yields in 2-3 hours (entries 1-5, Table 4.2). Mannich cyclizations with aniline derivatives ended up with good to excellent yields (60-100%) in similar reaction times (entries 6-16, table 4.2). Besides, the reactions with benzylamine derivatives furnished the cyclization products **116r-z** with moderate to good yields (45-95%) for about 2-3 hours (entries 17-24, Table 4.2). Regarding the reaction yields, low-to-moderate yields (26-45%) were especially observed in cyclizations with nitro substituted arylamines **4o**, **4x-y** (entries 15, 22-23, Table 4.2) because strong EW-effect of nitro group decreased the nucleophilicity of amine groups, thus prevented the formation of imines or iminium ions giving the cyclization products **116**. However, the excellent yields were attined in cyclization reactions with propargylamine, 4-fluoroaniline, 4-chlorobenzylamine and 4-fluorobenzylamine (entries 4, 9, 18-19, Table 4.2).

After successful Mannich cyclizations to afford **116a-z** using formaldehyde and primary amines **4a-z**, we are motivated to try the cyclization reactions of (*Z*)-ethyl 2-(4-oxothiazolidin-2-ylidene) acetate **65a** with primary amines **4** using acetaldehyde **3b** under optimized reaction conditions (entries 1-8, Table 4.3). As expected, Mannich cyclisation products **116aa-ad** were obtained with alkyl amines in moderate to good yields in 2-3 hours (entries 1-4, Table 4.3). So, the products

116ab and **116ac** were isolated in good yields (70-97%) by the reaction of **65a** and acetaldehyde **3b** with allylamine and propargylamine, respectively (entries 2-3, Table 4.3). But, the reactions with saturated alkylamines (propylamine and cyclohexylamine) provided the cyclization products **116aa**, **116ad** in moderate yields (40-53%). However, no product formation was observed in the reactions with aniline or benzylamine derivatives even in longer reaction times (entries 5-8, Table 4.3). Arguably, the combination of low nucleophilicity of arylamines **4** with lower reactivity of acetaldehyde **3b** than formaldehyde **3a** did not tolerated well the formation of iminium intermediates to afford the expected cyclization products **116ae-ah**. All Mannich cyclization products **116a-z, 116aa-ad** were purified using flash column chromatography with ethyl acetate-hexane mixtures as eluent and obtained in high purity.

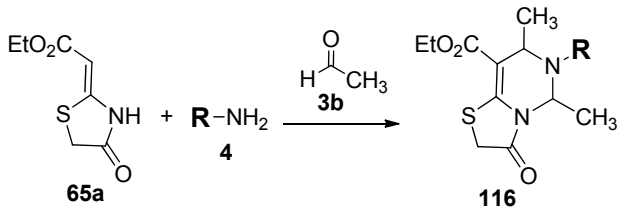
Table 4.1. Reaction conditions and yields of Mannich cyclization products **116a-z**.



Entry	Product	R	3a (equiv.)	Time (min) [a]	Yield (%)[b]
1	**116a**	propyl	2	120	50
2	**116b**	isopropyl	2	180	82
3	**116c**	allyl	2	105	71
4	**116d**	propargyl	2	120	**100**
5	**116e**	methoxyl	2	100	92
6	**116f**	phenyl	2	120	90
7	**116g**	p-tolyl	2	120	79
8	**116h**	4-isopropylphenyl	2	120	75
9	**116i**	4-fluorophenyl	2	120	**100**
10	**116j**	4-iodophenyl	2	110	69
11	**116k**	3-methoxyphenyl	2	120	74
12	**116l**	3,4-dimethoxyphenyl	2	120	68
13	**116m**	benzo[*d*][1,3]dioxol-5-yl	2	100	80
14	**116n**	4-phenoxyphenyl	2	120	60
15	**116o**	4-nitrophenyl	2	120	26
16	**116p**	4-(trifluoromethyl)phenyl	2	105	81
17	**116r**	3-chlorobenzyl	2	120	50
18	**116s**	4-chlorobenzyl	2	130	**95**
19	**116t**	4-fluorobenzyl	2	120	**94**
20	**116u**	2,4-dichlorobenzyl	2	120	80
21	**116v**	3,5-difluorobenzyl	2	120	79
22	**116x**	4-nitrobenzyl	2	120	50
23	**116y**	3-nitrobenzyl	2	120	45
24	**116z**	3-(trifluoromethyl)benzyl	2	135	67

[a] 0.5 mmol of each reactant (**65a**, **4**) in 15 mL of CH_3CN at reflux;[b] Total yields after purification.

Table 4.3. Reaction conditions and yields of Mannich cyclization products **116aa-ad**.



Entry	Product	R	3b (equiv.)	Time (min) [a]	Yield (%) [b]
1	**116aa**	propyl	2	120	40
2	**116ab**	allyl	2	180	**70**
3	**116ac**	propargyl	2	105	**97**
4	**116ad**	cyclohexyl	2	120	53
5	**116ae**	phenyl	2	180	-[c]
6	**116af**	p-tolyl	2	210	-[c]
7	**116ag**	4-chlorobenzyl	2	150	-[c]
8	**116ah**	4-(trifluoromethyl)benzyl	2	180	-[c]

[a] 0.5 mmol of each reactant (**65a**, **4**) in 15 mL of CH_3CN at reflux; [b] Total yields after purification; [c] No product obtained during the reaction

The structures of all products **116a-z**, **116aa-ad** were fully characterized by means of IR, ^{1}H-NMR, ^{13}C-NMR and HRMS measurements. For instance, the structures of **116f** and **116ab** were primarily determined by the disappearance of NH stretching peak of precursor **65a**, increasing intensities of aliphatic CH stretchings and slight shifts in C=O stretchings in their IR spectra (Figure 4.1**)**. Besides, in proton NMR spectra, singlet peaks of CH_2 protons at 5.12, 3.65 ppm for **116f** and quartets of CH protons next to nitrogens at 5.11, 3.72 ppm's and doublets of methyls next to nitrogens between 1.43-1.47 ppm for **116ab** also supported their expected structures (Figures 4.2, 4.3). The CH_2 and CH carbon signals at around 60.5, 48.0 and 69.0, 60.4 ppm's for **116f** and **116ab**, and CH_3 carbon signals at 23.0, 20.9 ppm's for **116ab** provided extra supporting data on the structure of expected products (Fig.4.4 and 4.5). Lastly, HRMS data of **116f** and **116ab** were determined accurately by TOF-MS technique as 303.0806 and 295.1122 as $[M-H]^+$ ions, respectively.

Analogously, all of the cyclization products **116a-z**, **116aa-ad** were characterized with their indicative IR, ^{1}H-NMR, ^{13}C-NMR and HRMS data following the same way (Table 4.4-4.5).

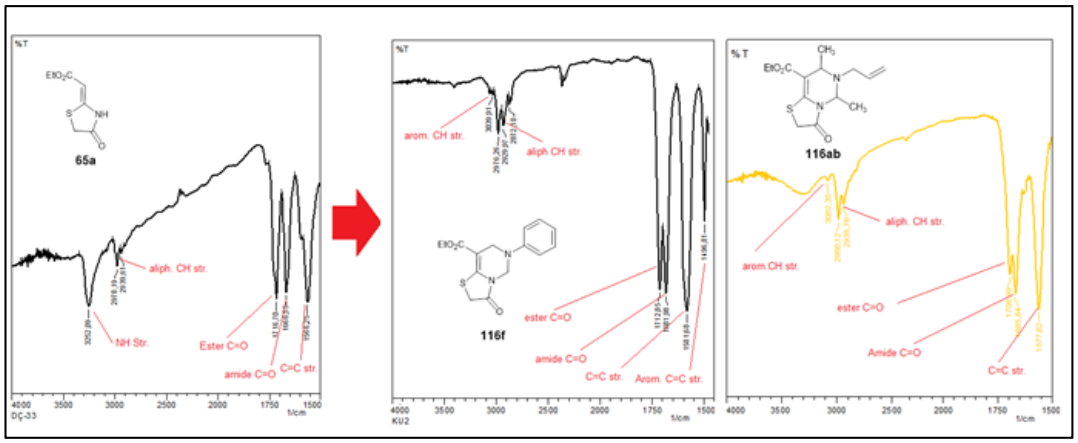


Figure 4.1. IR spectra of the precursor **65a** and products **116f**, **116ab**.

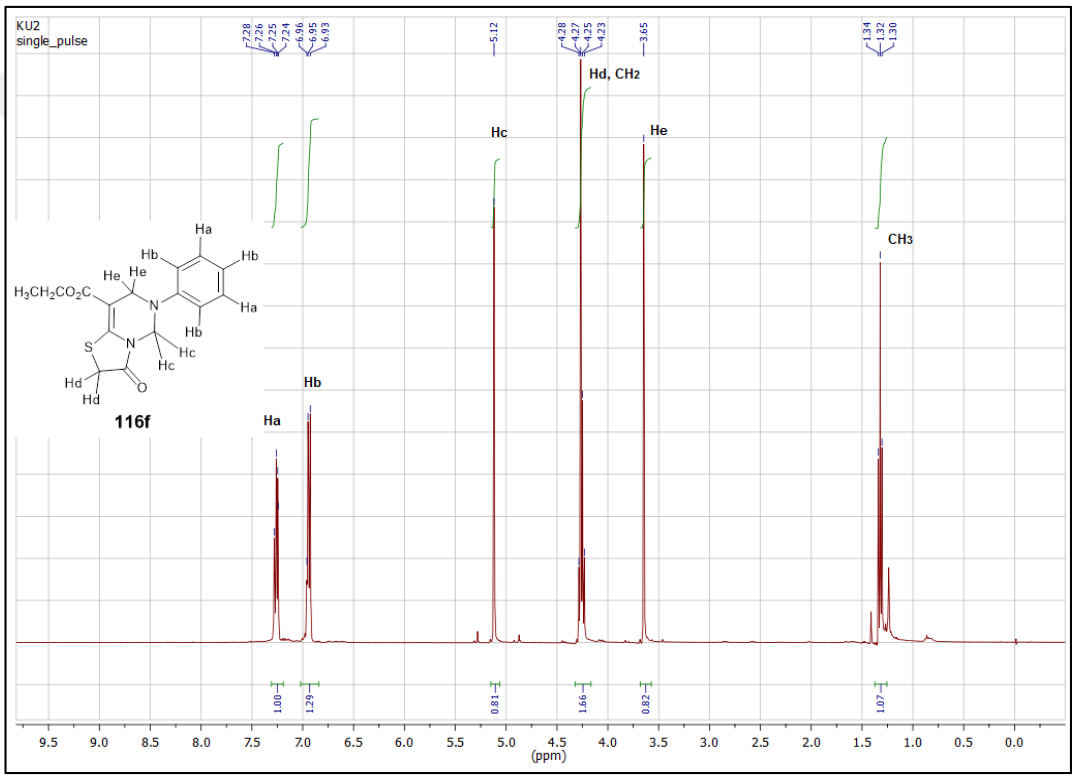


Figure 4.2. ^{1}H-NMR spectrum of the products **116f**.

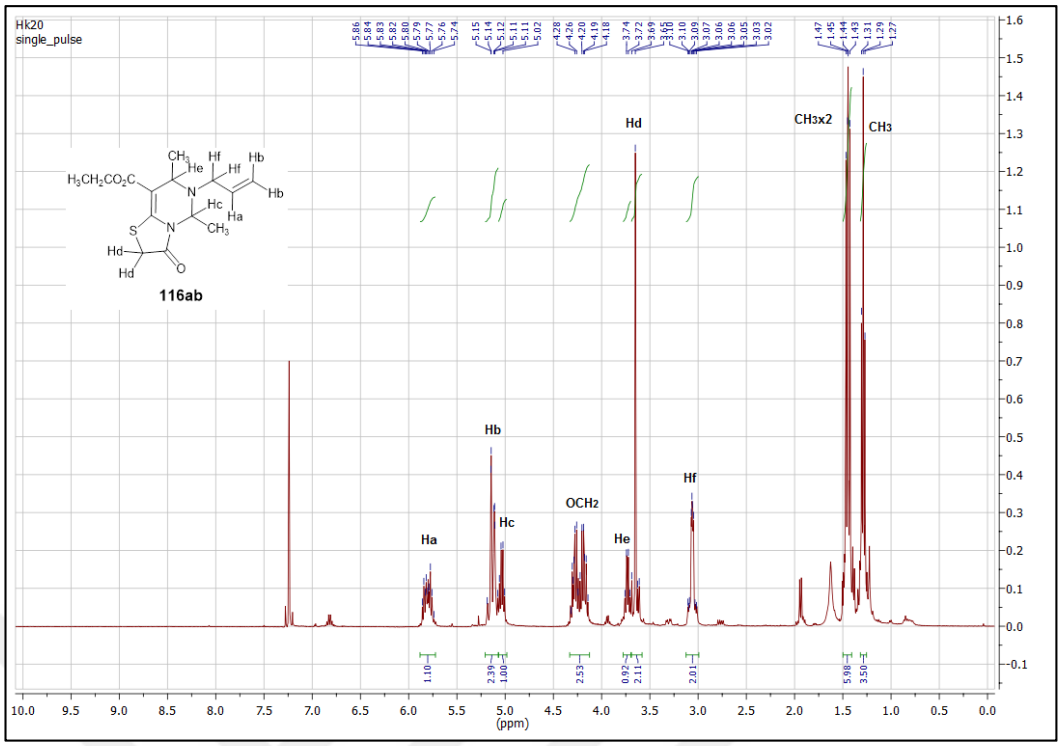


Figure 4.3. ^{1}H-NMR spectrum of the products **116ab**.

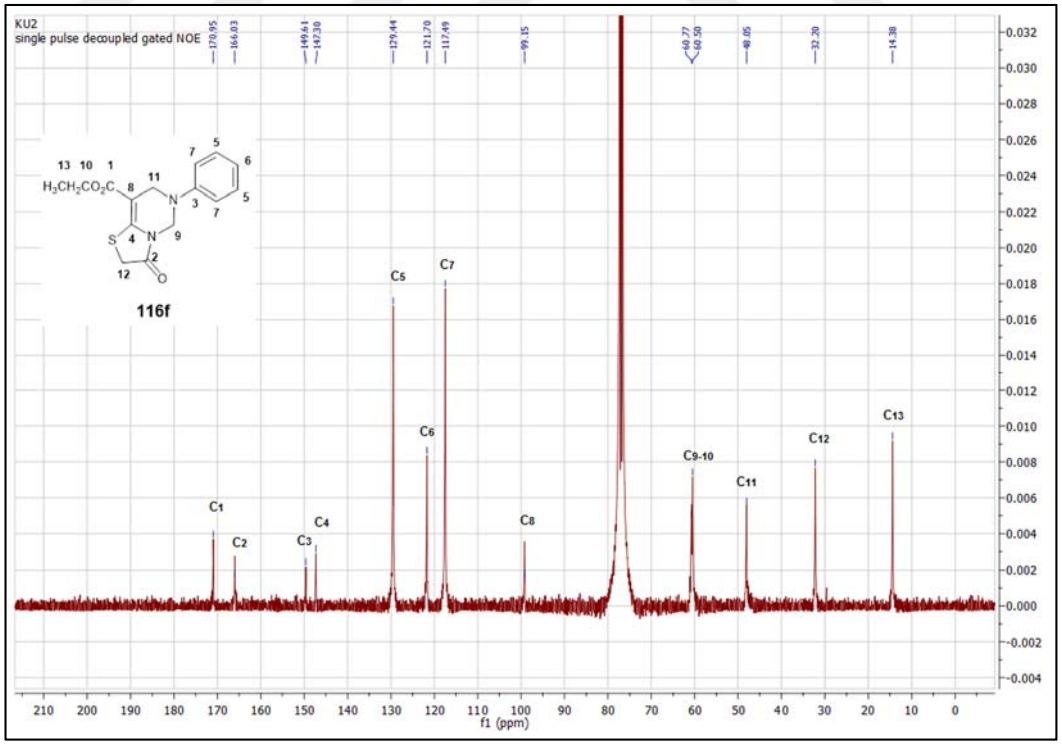


Figure 4.4. ^{13}C-NMR spectrum of the products **116f**.

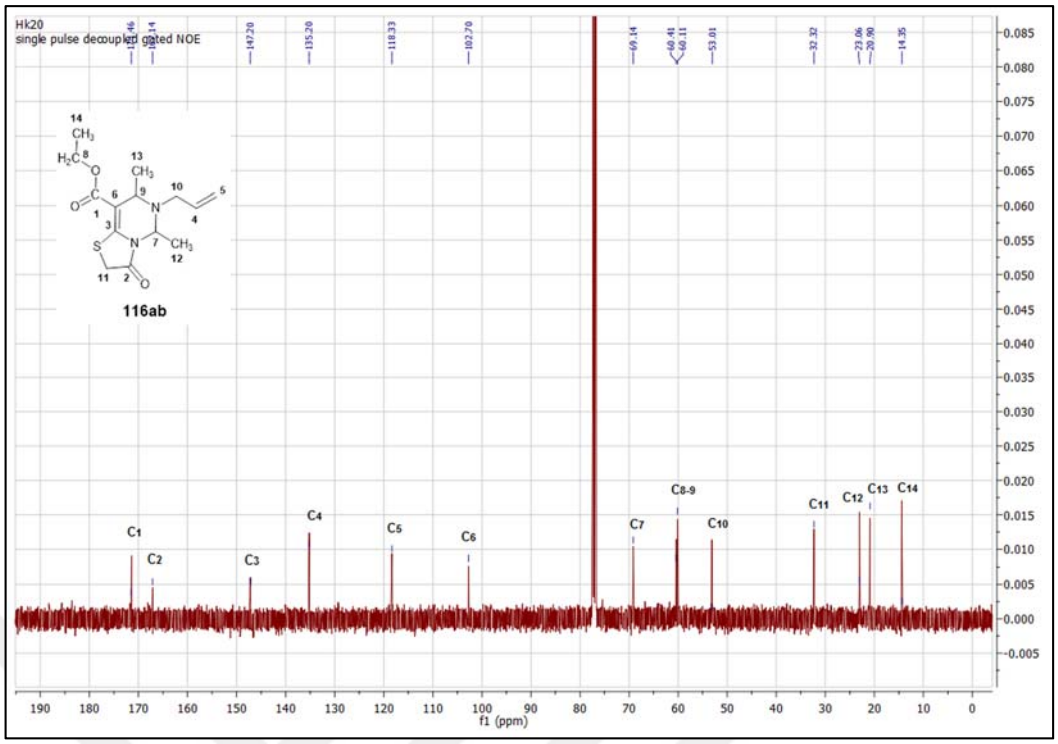


Figure 4.5. ^{13}C-NMR spectrum of the products **116ab**.

Table 4.2. Indicative IR and NMR data for the compounds **116a-z** and **116aa-ad**.

Comp.	IR (ν_{max}/cm^{-1})			^{1}H-NMR (δ,ppm)		^{13}C-NMR (δ,ppm)			
116	C=O ester	C=O amide	C=C	**CH$_2$**-N	N-C**H**-**CH$_3$**	**C**=O ester	**C**=O amide	**C**H$_2$-N	N-**C**H-**C**H$_3$
a	1712	1685	1583	4.50,3.66	-	171.9	166.5	63.2,49.2	-
b	1708	1683	1585	4.56,3.66	-	170.9	166.5	60.6,50.1	-
c	1716	1658	1560	4.51,3.67	-	171.4	166.5	62.4,48.9	-
d	1712	1681	1585	4.59,3.68	-	171.2	166.4	62.0,48.9	-
e	1714	1681	1589	4.10,3.54	-	171.8	166.4	62.9,50.8	-
f	1712	1681	1581	5.12,3.65	-	170.9	166.0	60.7,48.0	-
g	1712	1683	1514	5.08,3.63	-	171.1	166.1	61.2,48.4	-
h	1712	1683	1583	5.08,3.64	-	171.0	166.1	61.1,48.3	-
i	1710	1685	1585	5.04,3.65	-	170.9	166.0	61.6,48.7	-
j	1710	1685	1585	5.07,3.65	-	171.0	166.0	60.8,48.2	-
k	1712	1681	1585	5.09,3.64	-	171.0	166.1	60.7,48.2	-
l	1712	1670	1566	5.03,3.64	-	171.1	166.1	60.6,48.9	-
m	1712	1681	1589	4.99,3.65	-	171.1	166.1	62.0,49.1	-
n	1708	1674	1577	5.06,3.66	-	171.3	166.2	61.6,48.9	-
o	1716	1683	1591	5.19,3.67	-	170.7	165.2	60.9,47.8	-
p	1716	1681	1566	5.15,3.66	-	170.9	165.8	60.8,48.0	-
r	1716	1685	1581	4.53,3.70	-	171.4	166.5	63.0,49.1	-
s	1712	1681	1583	4.51,3.69	-	171.6	166.6	63.2,48.9	-
t	1705	1685	1573	4.51,3.69	-	171.4	166.5	62.5,49.0	-
u	1705	1678	1562	4.52,3.70	-	171.4	166.6	63.0,49.4	-
v	1716	1685	1581	4.53,3.70	-	171.5	166.5	63.5,49.1	-
x	1716	1651	1577	4.55,3.74	-	171.5	166.4	63.2,49.1	-
y	1716	1685	1577	4.55,3.73	-	171.5	166.4	63.1,48.9	-
z	1718	1685	1585	4.55,3.70	-	171.5	166.5	63.1,48.7	-
aa	1708	1681	1575	-	5.24,3.89 1.51-1.45	171.4	166.9	-	68.6,60.4 23.2,21.1

Table 4.3. (continued)

ab	1708	1685	1577	-	5.11,3.72 1.47-1.43	171.4	167.1	-	69.1,60.4 23.0,20.9
ac	1707	1685	1577	-	5.76, 3.28 1.34-1.19	173.1	167.4	-	75.0,60.4 21.0,20.4
ad	1708	1685	1577	-	5.35,2.98 1.37-1.26	172.4	167.8	-	62.2,60.4 22.1,20.6

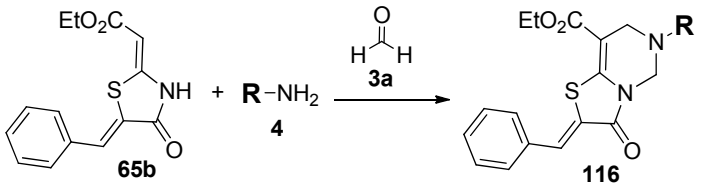
Table 4.5. HRMS (TOF-MS) data for the products **116a-z** and **116aa-ad**.

Comp.	HRMS			Comp.	HRMS		
116	**Found (m/z)**	**Calculated (m/z)**	**Ionization tech.**	**116**	**Found (m/z)**	**Calculated (m/z)**	**Ionization tech.**
a	269.0973	269.0965	APCI$^-$	**o**	348.0668	348.0648	APCI$^-$
b	269.0958	269.0965	APCI$^-$	**p**	371.0673	371.0671	APCI$^-$
c	267.0806	267.0808	APCI$^-$	**r**	351.0566	351.0564	APCI$^-$
d	265.0662	265.0641	APCI$^-$	**s**	351.0605	351.0564	APCI$^-$
e	257.0591	257.0590	APCI$^-$	**t**	335.0877	335.0860	APCI$^-$
f	303.0806	303.0797	APCI$^-$	**u**	385.0166	385.0174	APCI$^-$
g	317.0951	317.0954	APCI$^-$	**v**	353.0762	353.0766	APCI$^-$
h	345.1286	345.1267	APCI$^-$	**x**	364.0960	364.0967	APCI$^+$
i	321.0736	321.0703	APCI$^-$	**y**	364.0976	364.0967	APCI$^+$
j	428.9741	428.9764	APCI$^-$	**z**	385.0845	385.0828	APCI$^-$
k	333.0904	333.0903	APCI$^-$	**aa**	293.0959	293.0954	APCI$^-$
l	363.1022	363.1009	APCI$^-$	**ab**	295.1122	295.1110	APCI$^-$
m	347.0696	347.0696	APCI$^-$	**ac**	297.1285	297.1267	APCI$^-$
n	395.1044	395.1060	APCI$^-$	**ad**	337.1604	337.1580	APCI$^-$

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

In order to elaborate the scope and limitations of the cyclisation approach further, the reactions of (*Z*)-ethyl 2-((*Z*)-5-benzylidene-4-oxothiazolidin-2-ylidene) acetate **65b** with primary alkyl or arylamines **4** were carried out using formaldehyde **3a** under optimized reaction conditions (Table 4.6). In general, the highest yields were achieved by the reactions of **65b** with allylamine and 4-chlorobenzylamine affording the products **116bb** and **116bg** for about 4 hours (entries 2,7, Table 4.6), however, the lowest yield (40%) was obtained in the cyclization of **65b** with 3,4-dimethoxyaniline in 4 hours (entry 7, Table 4.6). Probably, the presence of two ED methoxy group on phenyl ring did not stabilize the formed iminium intermediate to give the cyclization product **116be** very rapidly. Other cyclization products were isolated in moderate to good yields by the reactions of **65b** with isopropylamine, aniline derivatives and 4-fluorobenyzlamine in 3-4 hours (entries 1,3-4,6,8, Table 4.6).

Table 4.6. Reaction conditions and yields of the cyclization products **116ba-bh**.



Entry	Product	R	3a (equiv.)	Time [a]	Yield (%) [b]
1	**116ba**	isopropyl	2	4h25min	70
2	**116bb**	allyl	2	4h25min	**87**
3	**116bc**	phenyl	2	4h20min	73
4	**116bd**	4-chlorophenyl	2	4h40min	56
5	**116be**	3,4-dimethoxyphenyl	2	4h40min	40
6	**116bf**	4-n-butylphenyl	2	4h30min	63
7	**116bg**	4-chlorobenzyl	2	4h25min	**80**
8	**116bh**	4-fluorobenzyl	2	3h20min	55

[a] 0.5 mmol of each reactant (**65b**, **4**) in 20 mL of CH_3CN at reflux; [b]Total yields after purification.

The structures of benzylidene-substituted 3-oxothiazolo[3,2-*c*]pyrimidines **116ba-bh** were elucidated by means of IR, ^{1}H-NMR, ^{13}C-NMR and HRMS measurements. As an example, the structure of **116ba** were first determined by the changes in the intensities of aliphatic CH stretchings and slight shifts in C=O and C=C stretchings in their IR spectra (Fig. 4.6**)**. In proton NMR spectrum of **116ba**, singlet peaks of CH_2 protons next to nitrogens at 4.75, 3.77 ppm and singlet of olefinic =CH proton at 7.64 ppm supported the expected structure (Figures 4.7). The CH_2 carbons attached to N atoms and –CO-**C**=C quarternary carbon signal at around 60.7, 46.8 and 99.7 ppm's provided extra supporting data on the structure of the product **116ba** (Fig.4.8). Finally, HRMS data of **116ba** was determined in high accuracy as 358.1364 (M^+ ion) by TOF-MS technique (Table 4.8). All other arylidene substituted-3-oxothiazolo[3,2-*c*]pyrimidine derivatives **116ba-bh** were characterized with their indicative IR, ^{1}H-NMR, ^{13}C-NMR and HRMS data following the same technique (Table 4.7-4.8).

As a general remark, Mannich cyclizations utilizing primary amines **4** and formaldehyde **3a** resulted with benzylidene substituted enamine **65b** in slightly lower yields than the cyclizations with unsubstituted enamine **65a** under similar conditions. However, the cyclizations of **65a** with primary amines **4** and formaldehyde **3a** gave

slightly better yields than the cyclizations of **65a** with primary amines **4** and acetaldehyde **3b** (Tables 4.2, 4.3, 4.6). However, all cyclization products were obtained in high purity after efficient chromatographic separations.

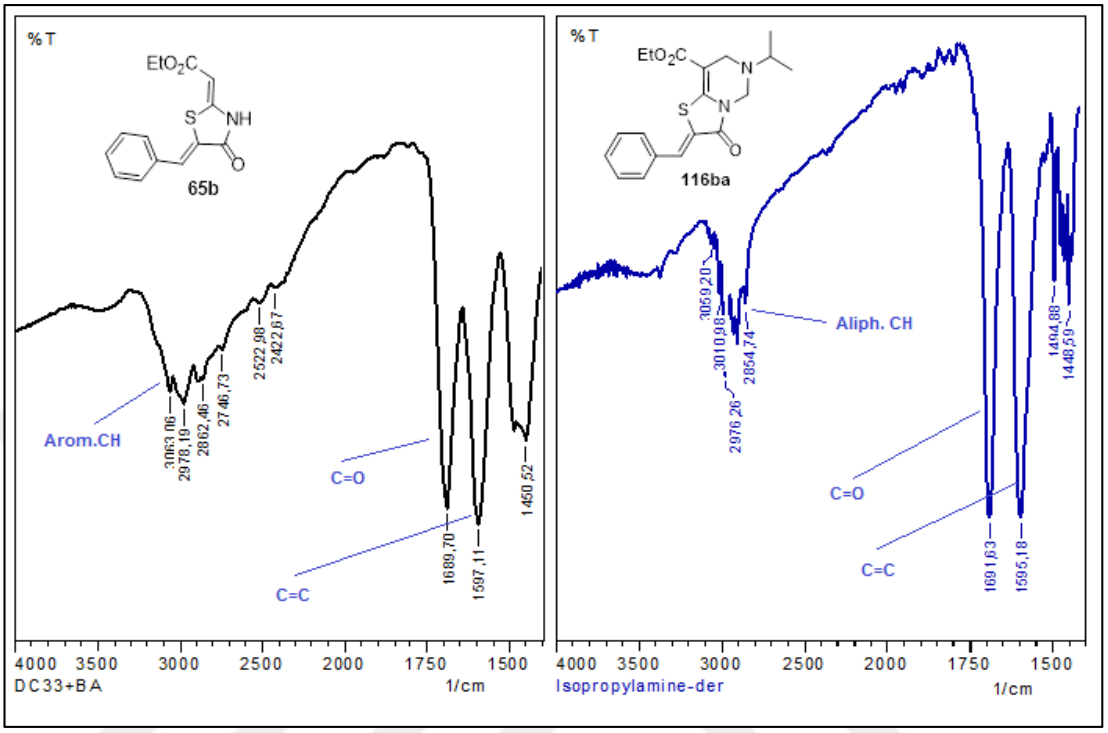


Figure 4.6. Changes in IR spectra of the precursor **65b** and product **116ba**.

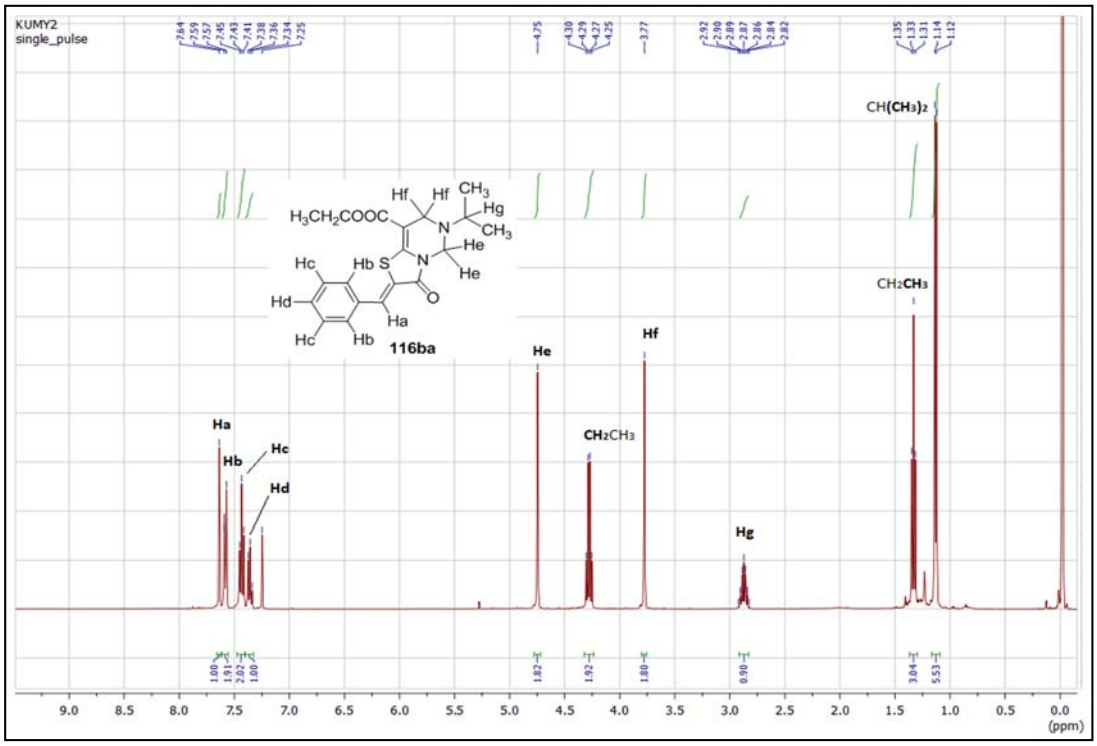


Figure 4.7. ^{1}H-NMR spectrum of the products **116ba**.

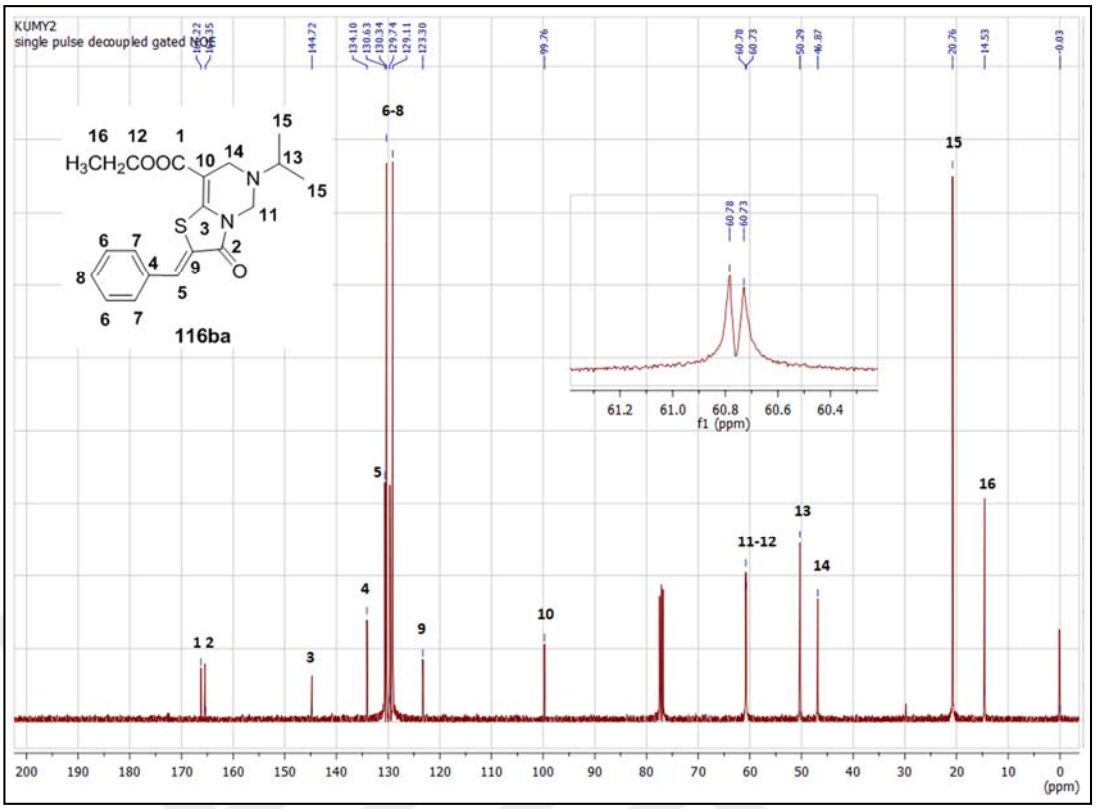


Figure 4.8. ^{13}C-NMR spectrum of the products **11ba**.

Table 4.7. Indicative IR and NMR peaks for cyclization products **116ba-bh**.

Comp.	**IR** (ν_{max}/cm^{-1})			**^{1}H-NMR** (δ,ppm)		**^{13}C-NMR** (δ,ppm)			
116	C=O ester	C=O amide	C=C	C**H$_2$**-N	C=C**H**	**C**=O ester	**C**=O amide	**C**H$_2$-N (C_{11},C_{14})	CO-**C**=C (C_{10})
ba	1691	1691	1595	4.75,3.77	7.64	166.2	165.3	60.7,46.8	99.7
bb	1708	1683	1585	4.56,3.66	-	170.9	166.5	60.6,50.1	-
bc	1716	1658	1560	4.51,3.67	-	171.4	166.5	62.4,48.9	-
bd	1712	1681	1585	4.59,3.68	-	171.2	166.4	62.0,48.9	-
be	1714	1681	1589	4.10,3.54	-	171.8	166.4	62.9,50.8	-
bf	1712	1681	1581	5.12,3.65	-	170.9	166.0	60.7,48.0	-
bg	1712	1683	1514	5.08,3.63	-	171.1	166.1	61.2,48.4	-
bh	1712	1683	1583	5.08,3.64	-	171.0	166.1	61.1,48.3	-

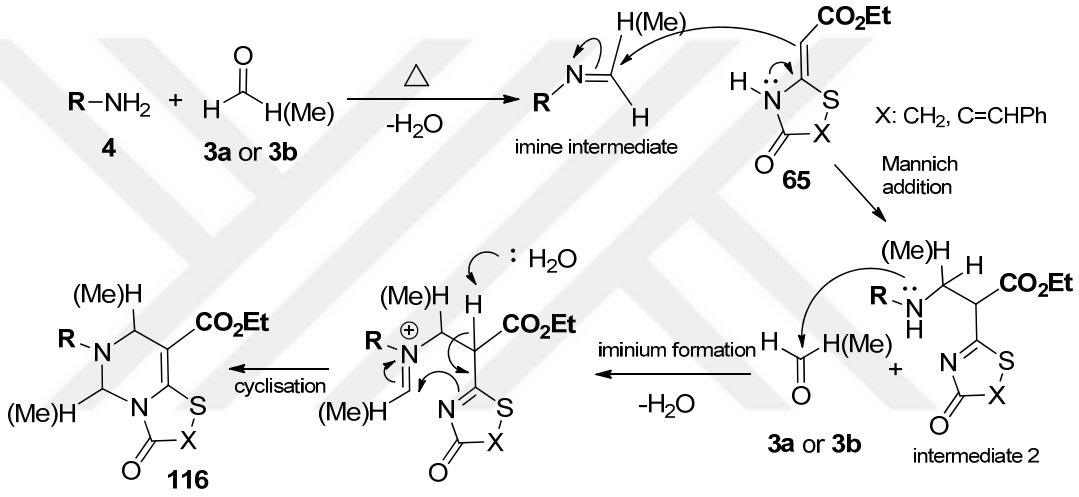
Table 4.8. HRMS (TOF-MS) data for the products **116ba-bh**.

Product	**HRMS**		
116	**Found[a] (m/z)**	**Calculated (m/z)**	**Ionization technique**
ba	358.1364	358.1351	APCI$^-$
bb	356.1208	356.1194	APCI$^-$
bc	392.1207	392.1194	APCI$^-$
bd	426.0785	426.0804	APCI$^-$
be	452.1425	452.1405	APCI$^-$
bf	448.1796	448.1820	APCI$^-$
bg	440.0926	440.0961	APCI$^-$
bh	424.1253	424.1256	APCI$^-$

[a]Accurate masses found as M^+ ions.

It can be concluded that the Mannich cyclization reactions of **65a** and **65b** with primary amines **4** and formaldehyde **3a** or acetaldehyde **3b** in the present work have occurred in similar efficiencies but a bit more rapid when compared with the Mannich cyclizations conducted with heterocyclic enamines **60** or **65** and primary amines **4** and formaldehyde **3a** in our previous studies. (Yıldırım et al., 2014b; Yıldırım and Çelikel, 2015; Çelikel, 2015)

A suitable mechanism over the formation of imine and iminium intermediates affording the products **116** via Mannich addition-cyclization reactions was described below (Scheme 4.2).



Scheme 4.2. Mechanism for the formation of 3-oxothiazolo[3,2-*c*] pyrimidines **116**.

4.3 PRELIMINARY ANTIBACTERIAL ACTIVITY STUDIES OF 3-OXOTHIAZOLO-[3,2-*C*]PYRIMIDINES (116)

Thiazolopyrimidine derivatives in particular, thiazolo[4,5-*d*]-,[5,4-*d*]-,[3,2-*a*]-pyrimidines are well described to show variety of biological activities in the literature. However, the cyctotoxic and antibacterial properties of thiazolo[3,2-*c*]pyrimidines **116** were first performed and reported in the studies by our group in 2015 and 2018 (Yıldırım and Çelikel, 2015; Çelikel, 2015; Yildirim et al., 2018) Since they are unique activity studies on thiazolo[3,2-*c*]pyrimidines and there is no other activity study on them, we are motivated to perform some preliminary antibacterial activity studies of newly synthesized 3-oxothiazolo[3,2-*c*]pyrimidines

116 in collaboration with in B.A.I.B.U, Department of Biology. The details and results of antibacterial activity tests were presented and explained below.

First of all, ten representative samples of **116 (g,i,l,m,p,s,t,v,be,bh)** derivatives were chosen randomly in order to be used in antibacterial activity test against two bacterial strains (*S.epidermidis*, *S.aureus*). Their solutions were prepared in DMSO according to the described procedure (experimental section 3.1.3-antibacterial activity assay). After incubation time for antibacterial activity test, the inhibition zone diameters (mm) of each compound **116** against bacteria were measured. According to the test results, only the compound **116i** exhibited bacteriostatic effect against *S.aureus* and moderate activity against *S.epidermidis* bacterial strains (Table 4.9, entry 2). No other inhibitory zones with the rest of tested compounds (**116g,l,m,p,s,t,v,be,bh**) was observed against used bacterial strains (Table 4.9, entry 1, 3-10).

Table 4.9. The inhibition effect by **116** derivatives against bacteria used and the zones of inhibition produced.

Entry	Compound	SA	SE
1	**116g**	0	0
2	**116i**	10-10 (bs)	11-11 (m)
3	**116l**	0	0
4	**116m**	0	0
5	**116p**	0	0
6	**116s**	0	0
7	**116t**	0	0
8	**116v**	0	0
9	**116be**	0	0
10	**116bh**	0	0
Control	Ampicillin	34-33	27-28
	Penicillin G	35-36	23-24

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

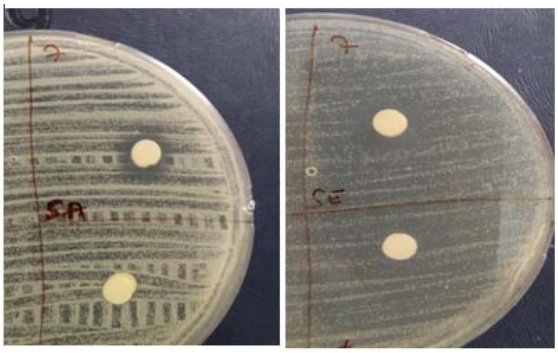


Figure 4.9. Inhibition zones of compound **116i** showing bacteriostatic and moderate effects against used bacteria.

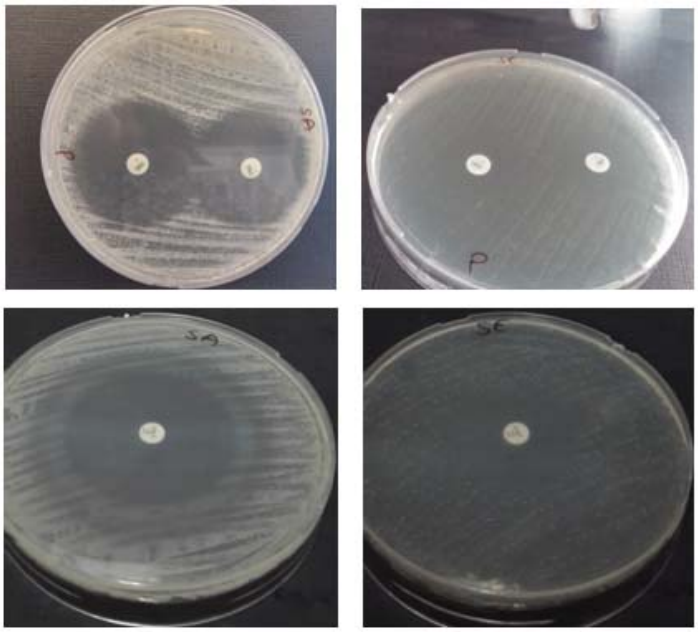


Figure 4.10. Inhibition zones of penicillin and ampicillin against used bacteria.

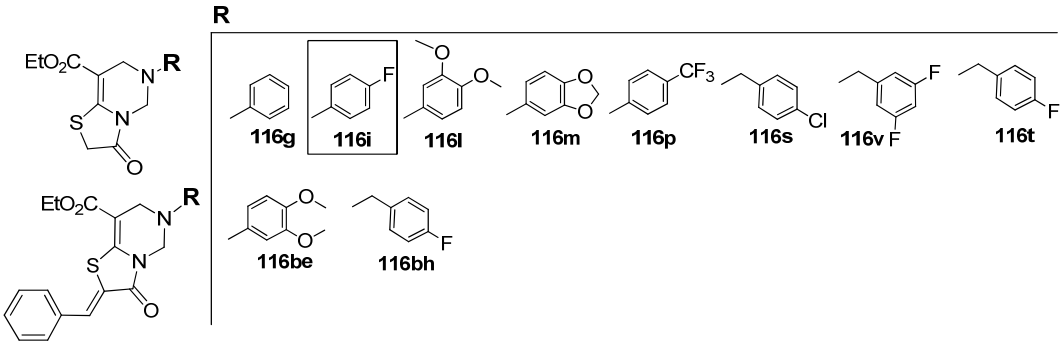


Figure 4.11. 3-oxothiazolo[3,2-*c*]pyrimidines used in antibacterial activity test.

According to the preliminary antibacterial activity test results, it was clear that 3-oxothiazolo[3,2-*c*]pyrimidines **116** exhibited some antibacterial effects against two bacterial strains, so, a wider range of antibacterial activity study will be performed against different pathogenic bacteria using the untested and tested derivatives of **116**.

5. CONCLUSIONS

Briefly, the outcomes procured in this dissertation study can be given below.

- ✓ In the first part, two heterocyclic secondary enamines **65a-b** were prepared as precursors using the literature methods and their structures were elucidated by means of IR, NMR, HRMS measurements.

- ✓ In the second part, we optimized and described an efficient synthetic protocol for the preparation of 28 novel 3-oxothiazolo[3,2-*c*]pyrimidine carboxylates **116a-z, 116ab-ad** bearing alkyl or aryl groups from various primary amines **4** and (*Z*)-ethyl 2-(4-oxothiazolidin-2-ylidene) acetate **65a** in the presence of formaldehyde **3a** or acetaldehyde **3b** under conventional reflux conditions. The structures of title compounds **116a-z, 116ab-ad** were fully characterized by means of IR, NMR (^{1}H, ^{13}C) and HRMS measurements. The novelty in this synthetic protocol was the first time use of acetaldehyde **3b** in double-Mannich cyclisation reactions affording 5,7-dimethyl substituted 3-oxothiazolo[3,2-*c*]pyrimidines **11ba-bd**, hence the applicability of the Mannich cyclizatios were tested and extended by the new derivatives of **116**.

- ✓ In the third part, we extended the scope of the present protocol by double-Mannich cyclization reactions of a new benzylidene substituted heterocyclic enamine **65b** with formaldehyde **3a** and primary amines **4** to furnish new 2-benzylidene substituted 3-oxothiazolo[3,2-*c*]pyrimidines **116ba-bh** under very mild conditions. Also, the structures of 8 novel compounds **116ba-bh** were elucidated based on the IR, NMR and HRMS measurements.

- ✓ Since various thiazolo[4,5-*d*]-, [5,4-*d*]-, [3,2-*a*]-pyrimidines exhibiting interesting biological effects are known in recent literature, our synthetic protocol would provide a new contribution to the relevant drug molecules containing thiazolo[3,2-*c*]pyrimidine cores. Therefore, ten derivatives of 3-oxothiazolo[3,2-*c*]pyrimidines (**116g,i,l,m,p,s,t,v,be,bh**) were chosen arbitrarily and screened for their antibacterial activities against two gram positive (+) bacterial strain. In antibacterial activity assay, only the product

116i exhibited bacteriostatic and moderate activity against tested bacteria, other tested compounds **116** showed no significant bacterial inhibition.

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APPENDICES

7. APPENDICES

IR, NMR, HRMS Spectra for the precursors and products

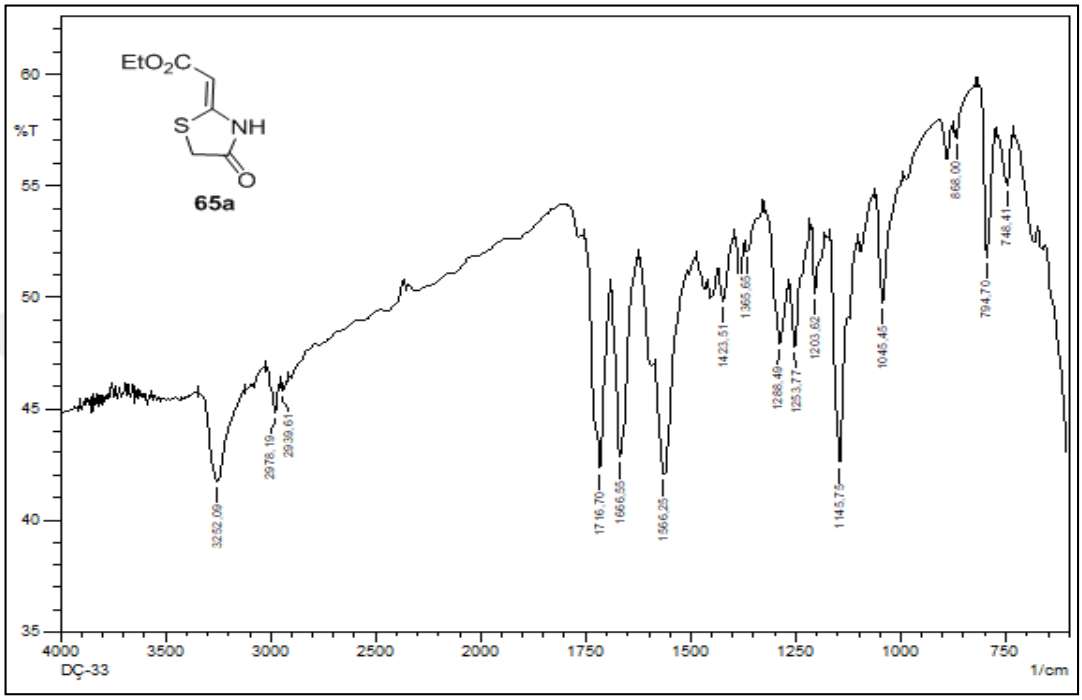

Figure 7.1. IR Spectrum of compound **65a**.

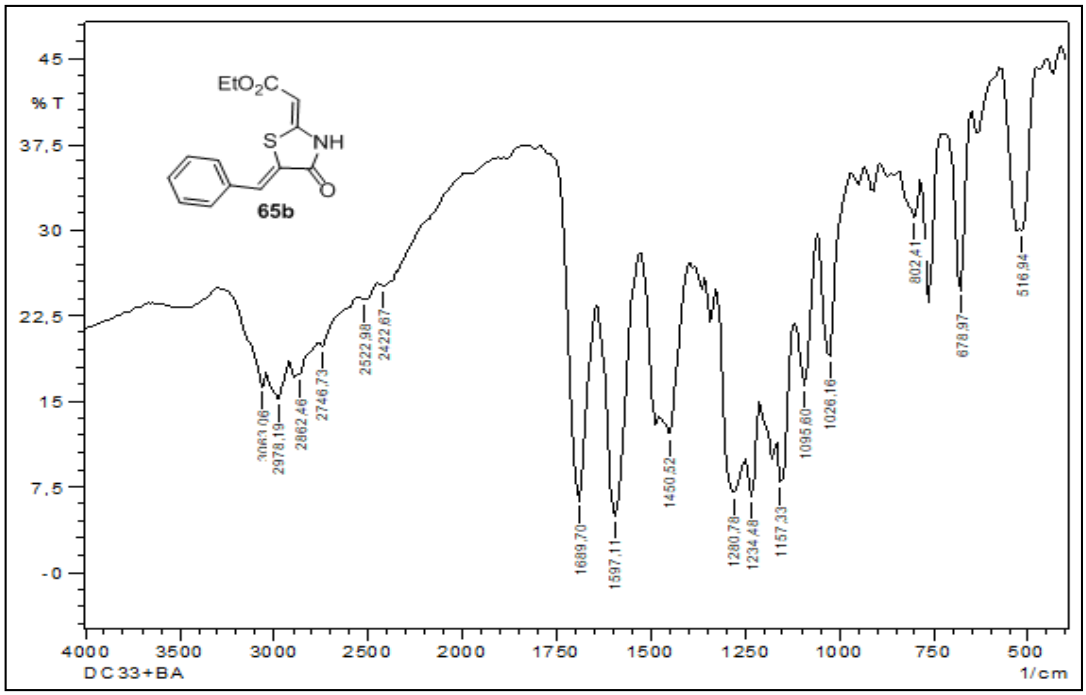

Figure 7.2. IR Spectrum of compound **65b**.

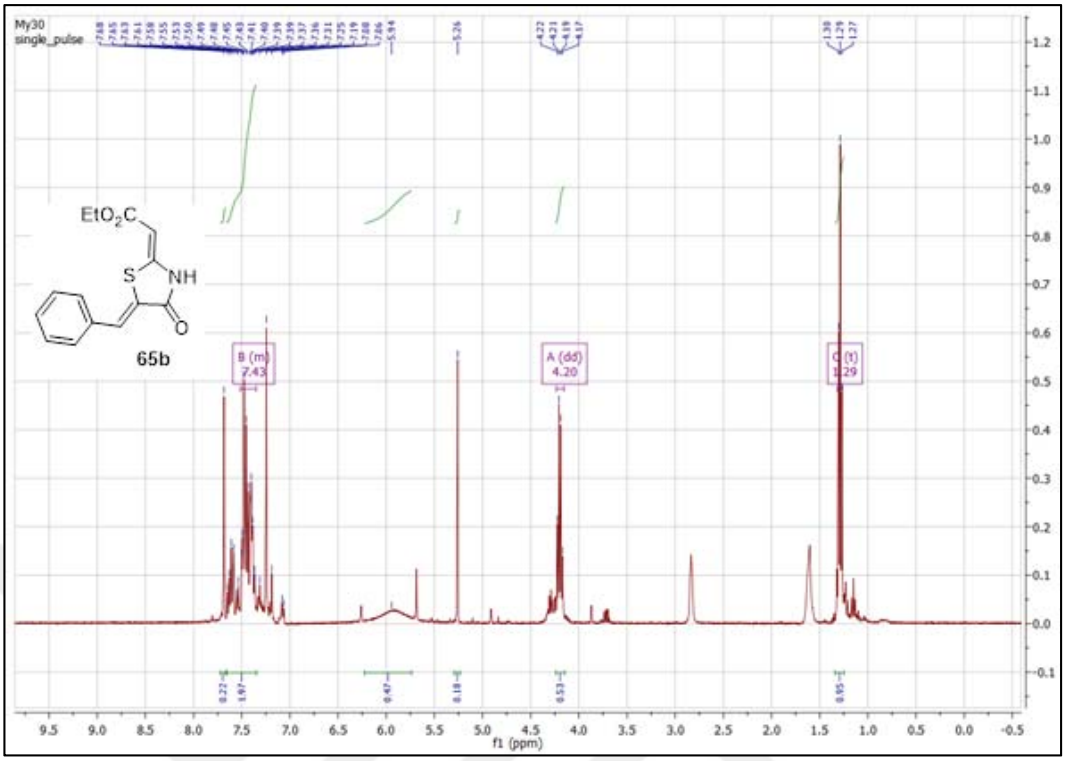

Figure 7.3. ^{1}H-NMR Spectrum of compound **65b**.

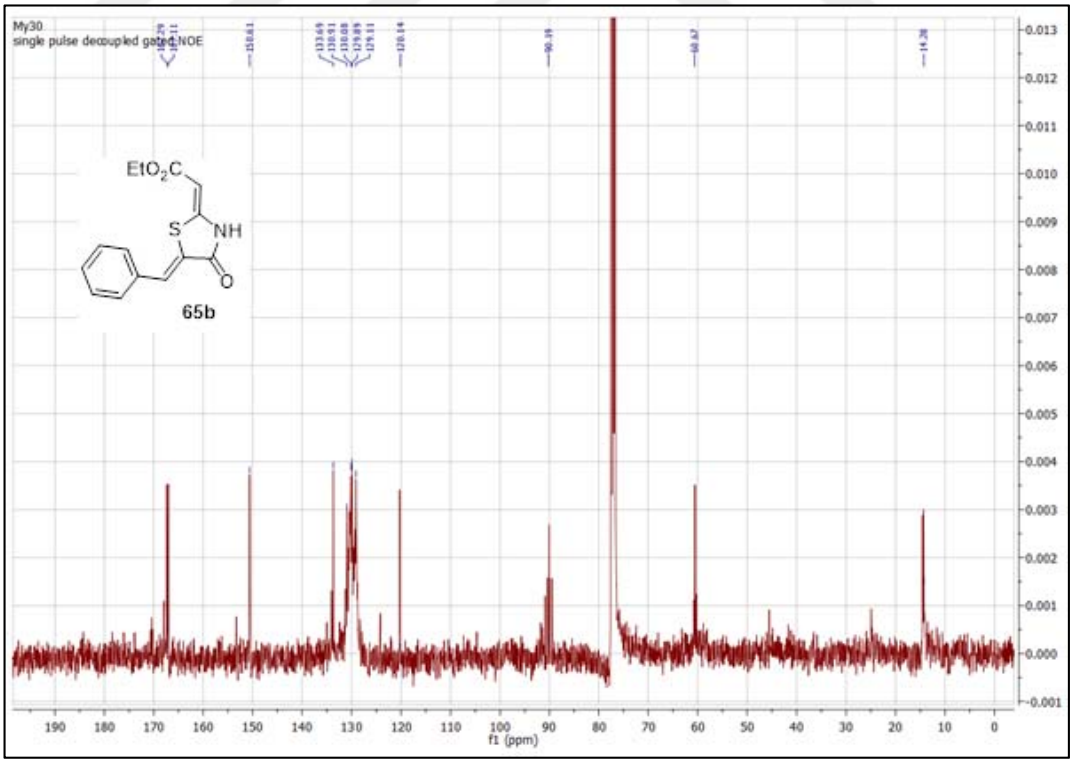

Figure 7.4. ^{13}C-NMR Spectrum of compound **65b**.

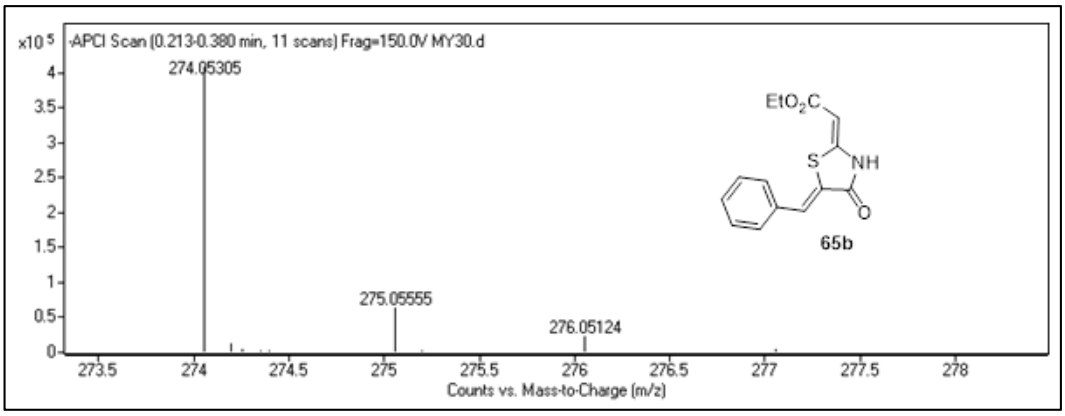

Figure 7.5. HRMS Spectrum of compound **65b**.

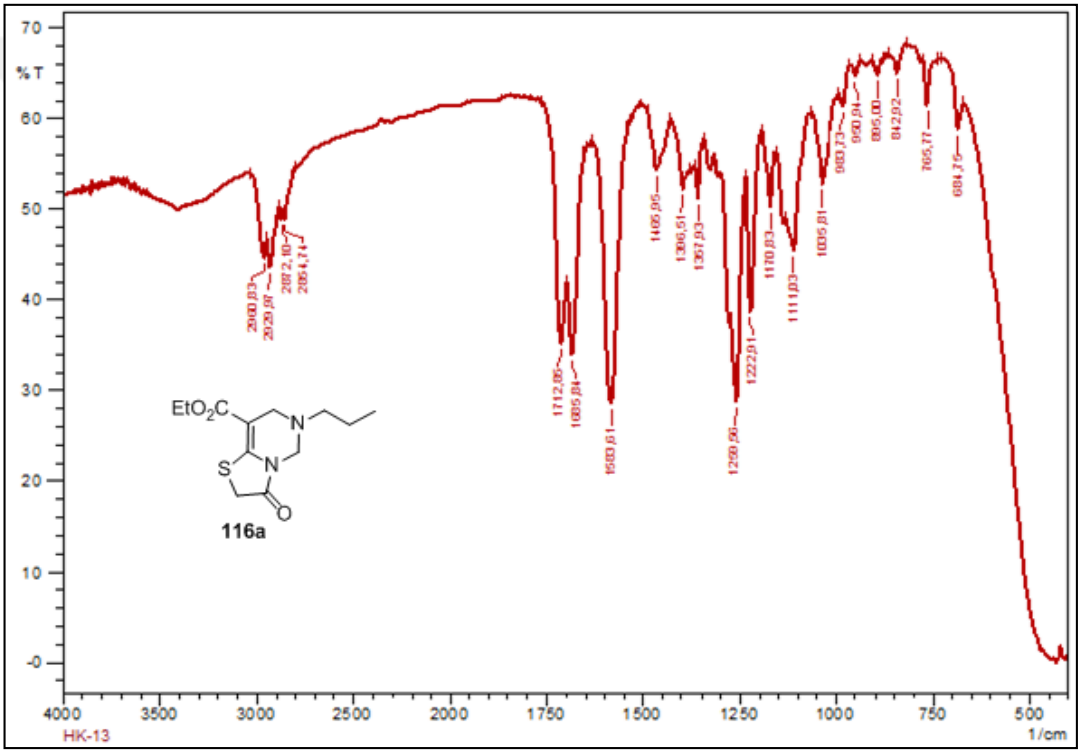

Figure 7.6. IR Spectrum of compound **116a**.

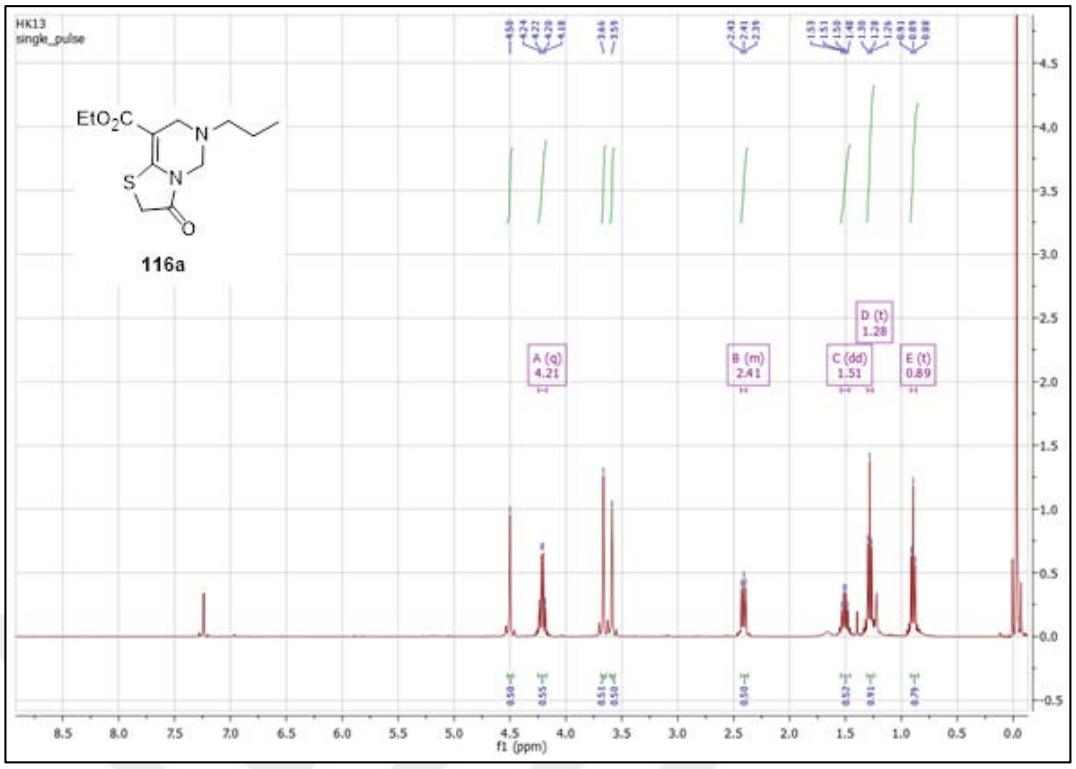

Figure 7.7. ^{1}H-NMR Spectrum of compound **116a**.

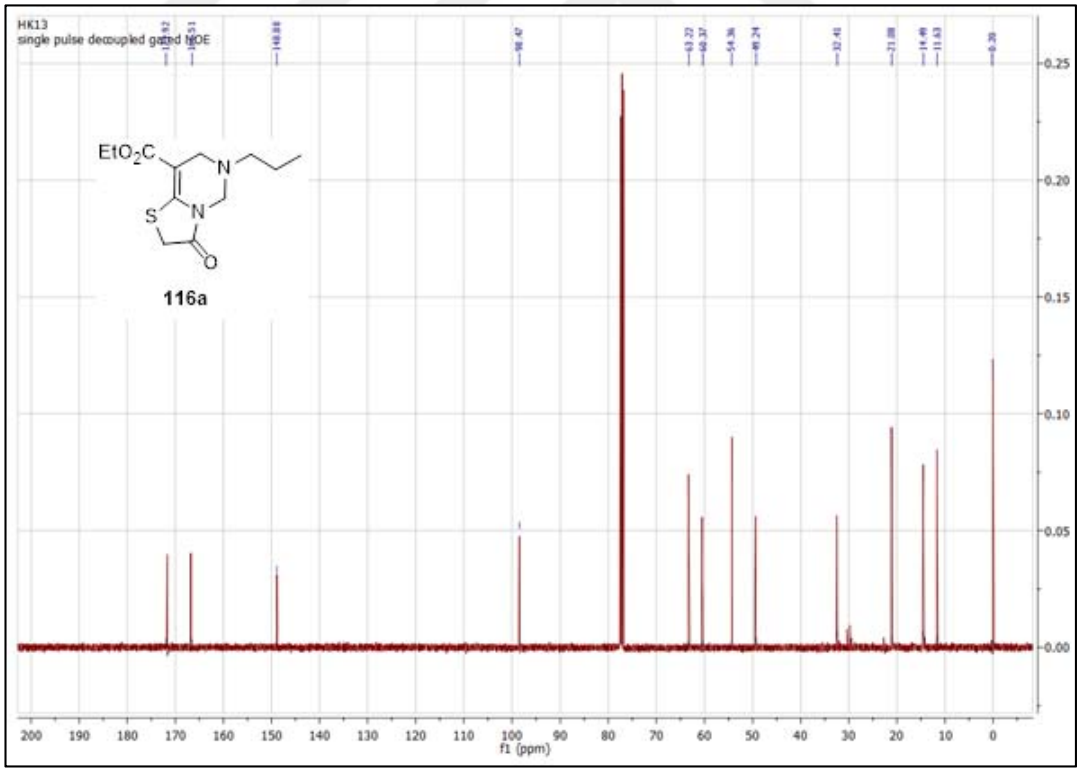

Figure 7.8. ^{13}C-NMR Spectrum of compound **116a**.

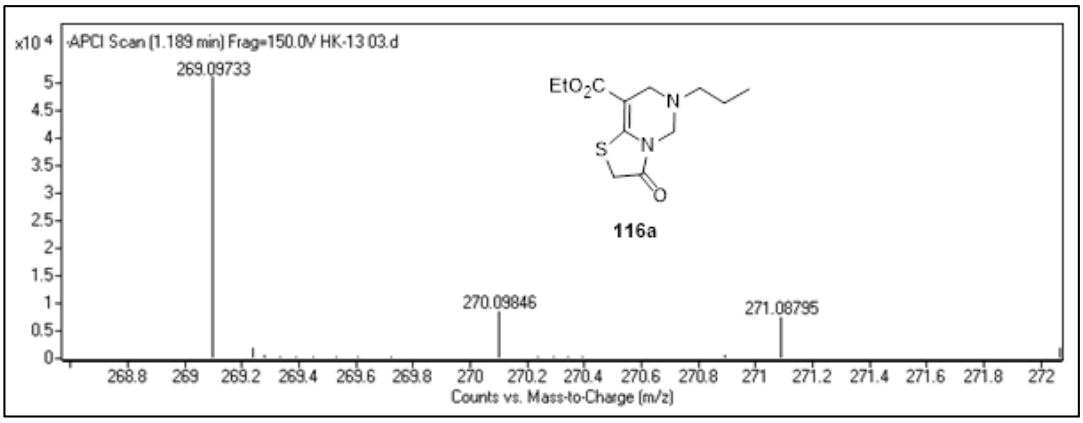

Figure 7.9. HRMS Spectrum of compound **116a**.

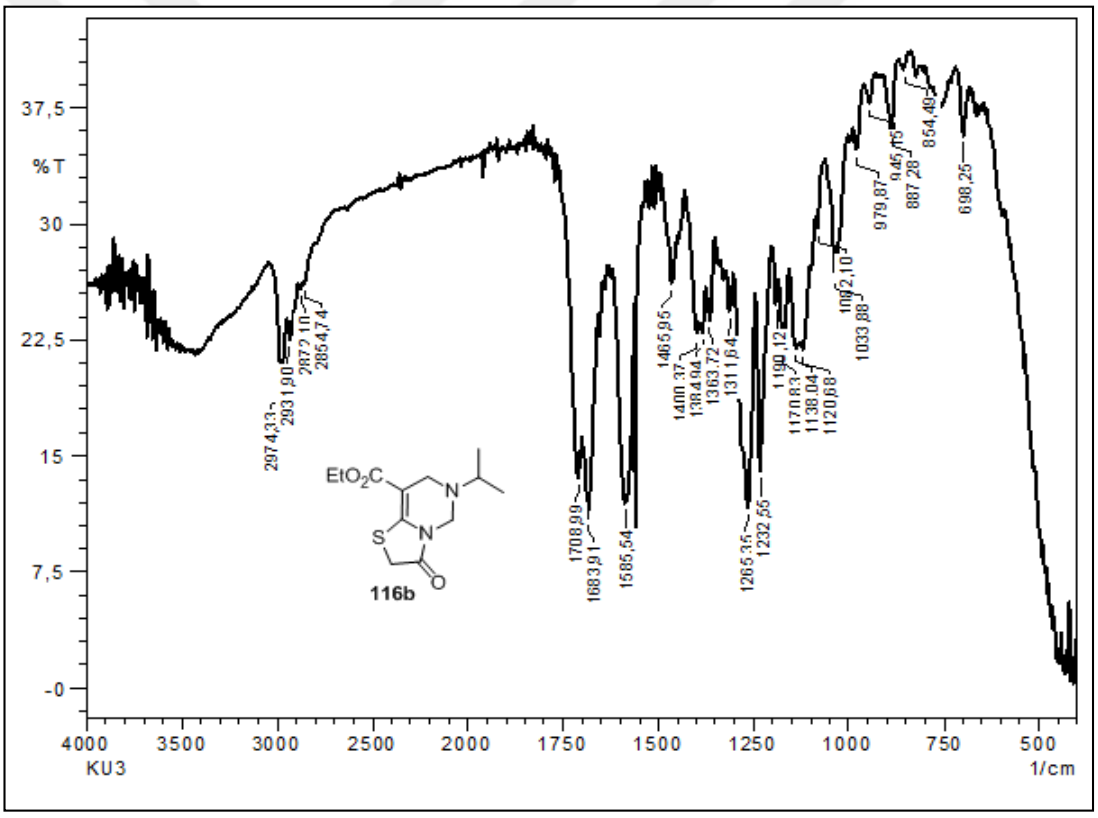

Figure 7.10. IR Spectrum of compound **116b**.

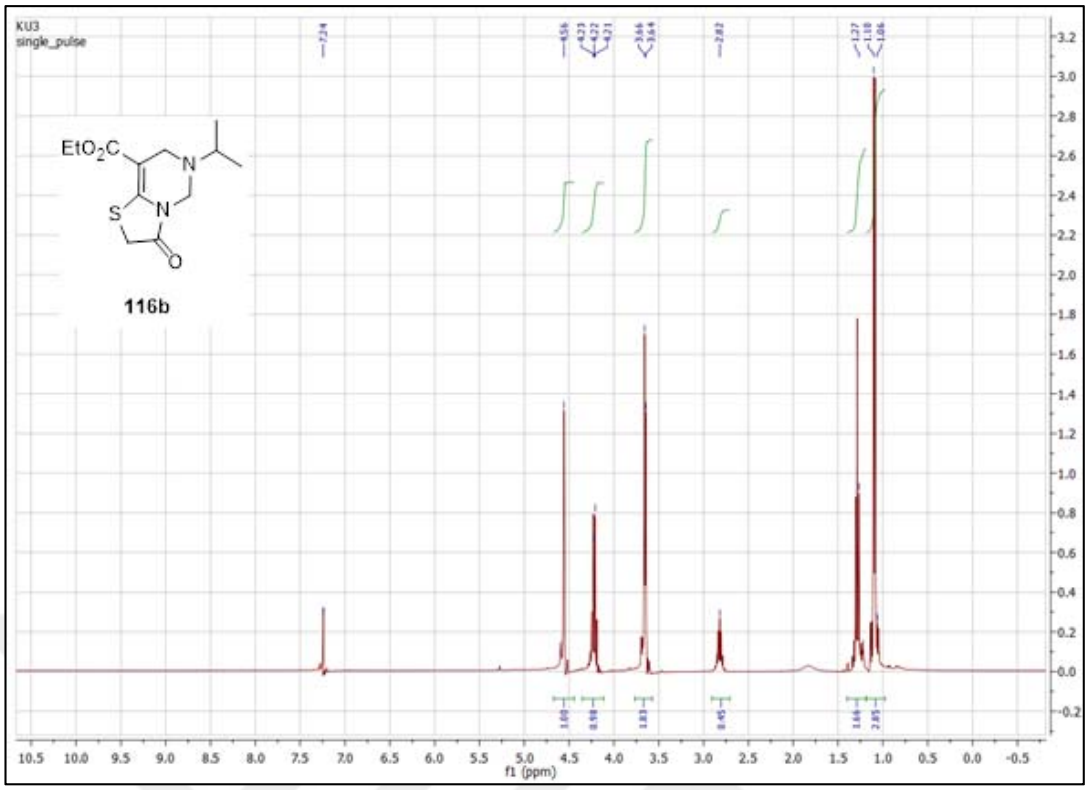

Figure 7.11. ^{1}H-NMR Spectrum of compound **116b**.

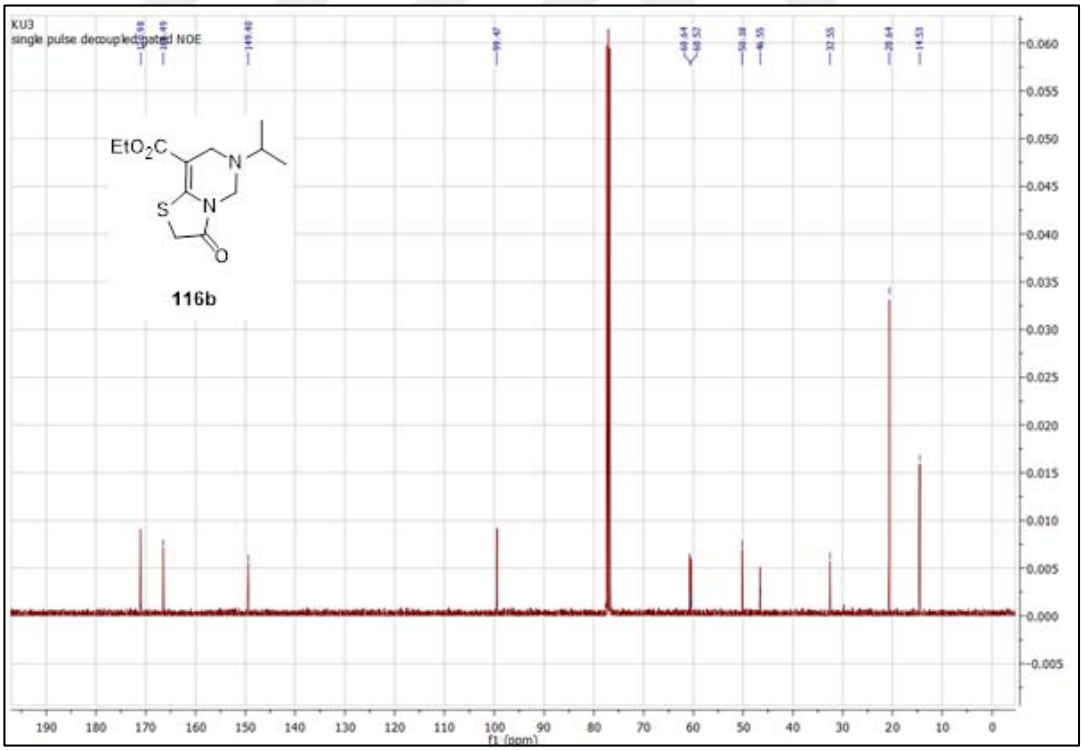

Figure 7.12. ^{13}C-NMR Spectrum of compound **116b**.

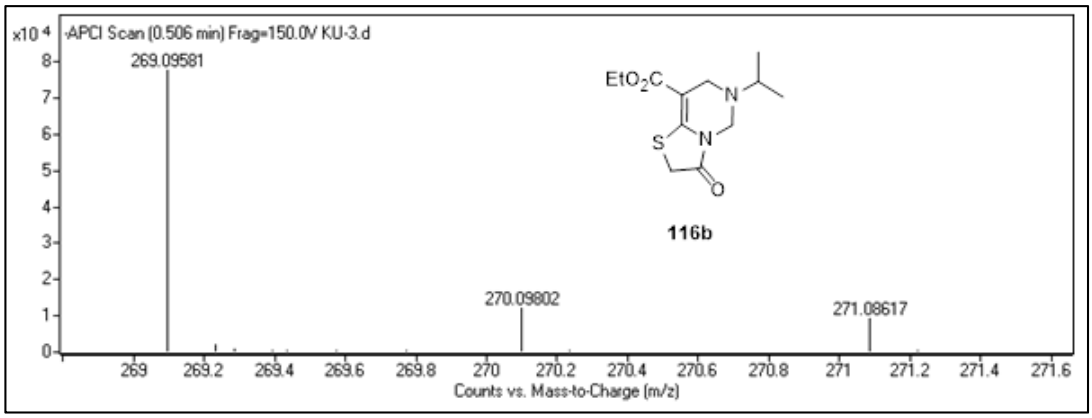

Figure 7.13. HRMS Spectrum of compound **116b**.

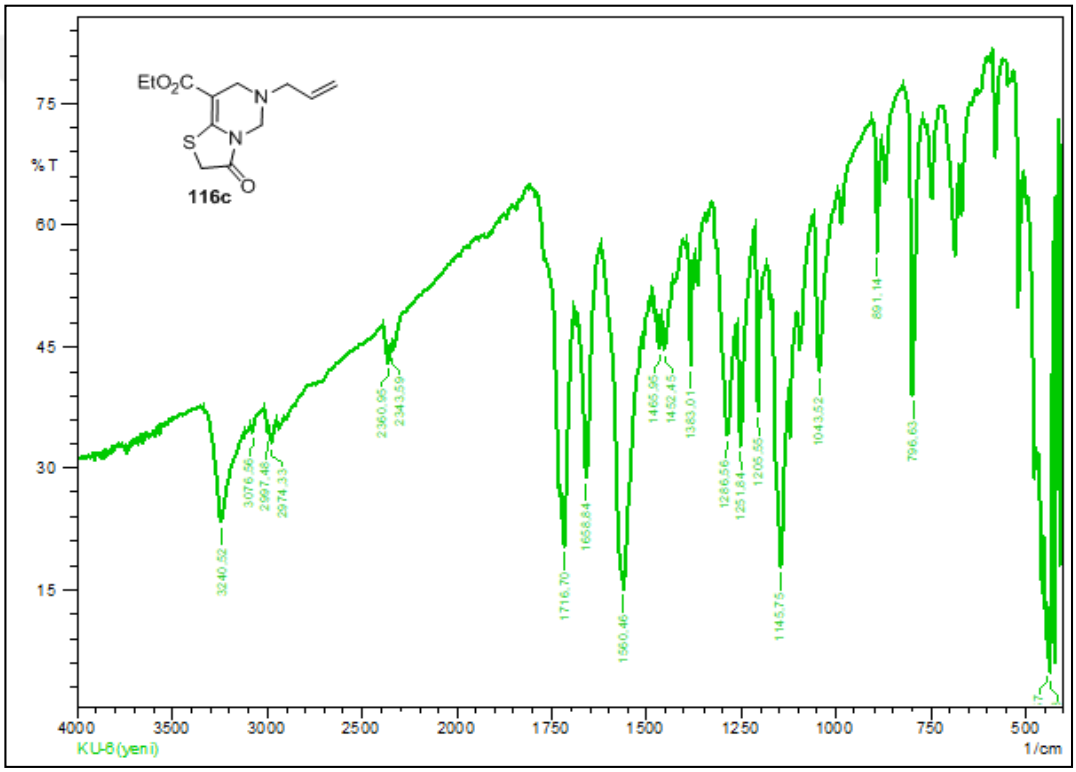

Figure 7.14. IR Spectrum of compound **116c**.

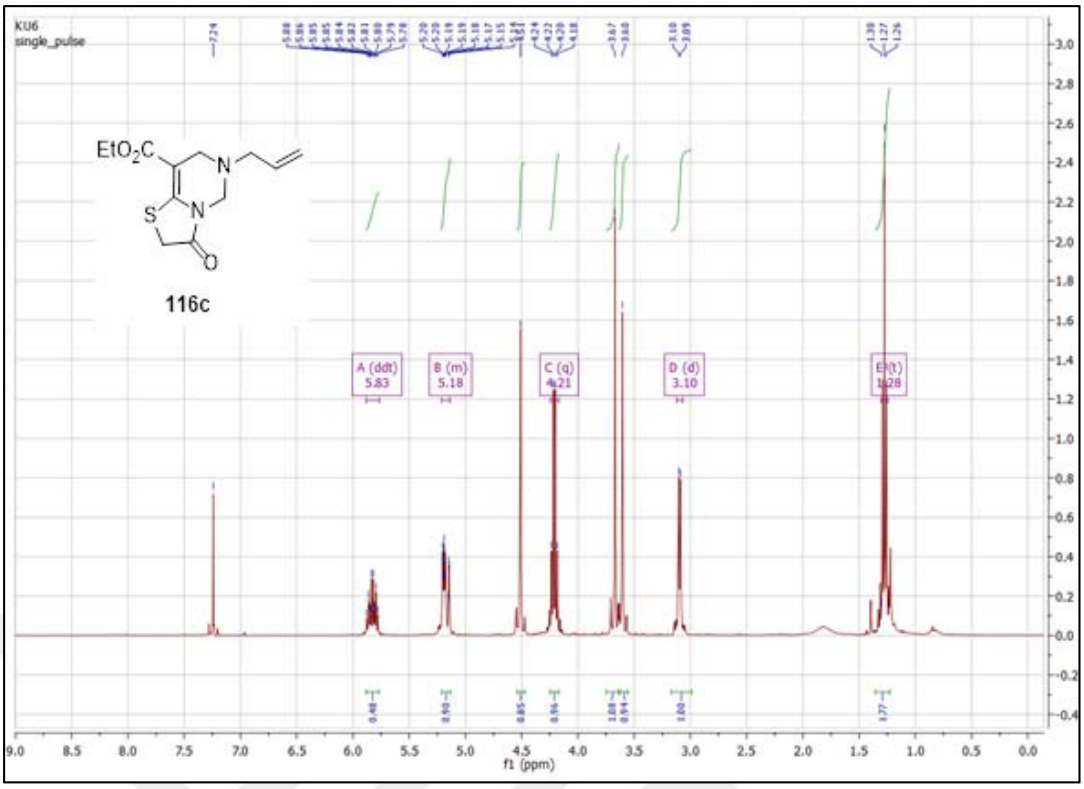

Figure 7.15. ^{1}H-NMR Spectrum of compound **116c**.

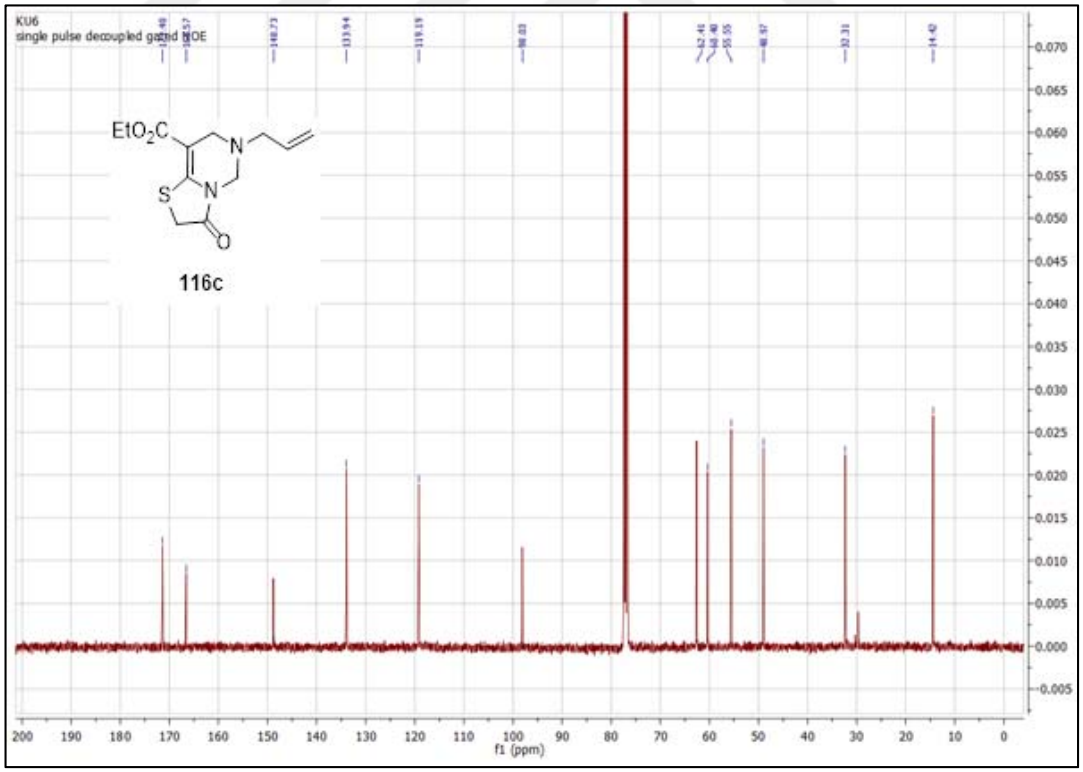

Figure 7.16. ^{13}C-NMR Spectrum of compound **116c**.

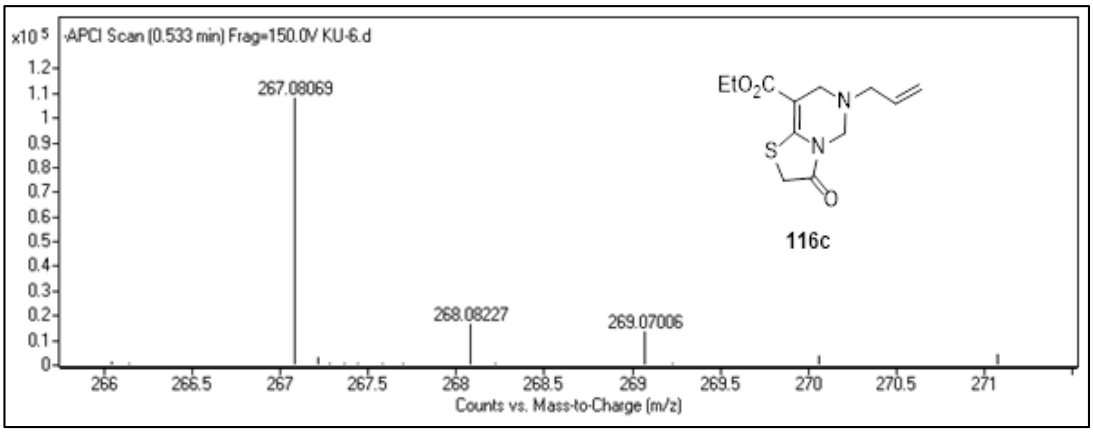

Figure 7.17. HRMS Spectrum of compound **116c**.

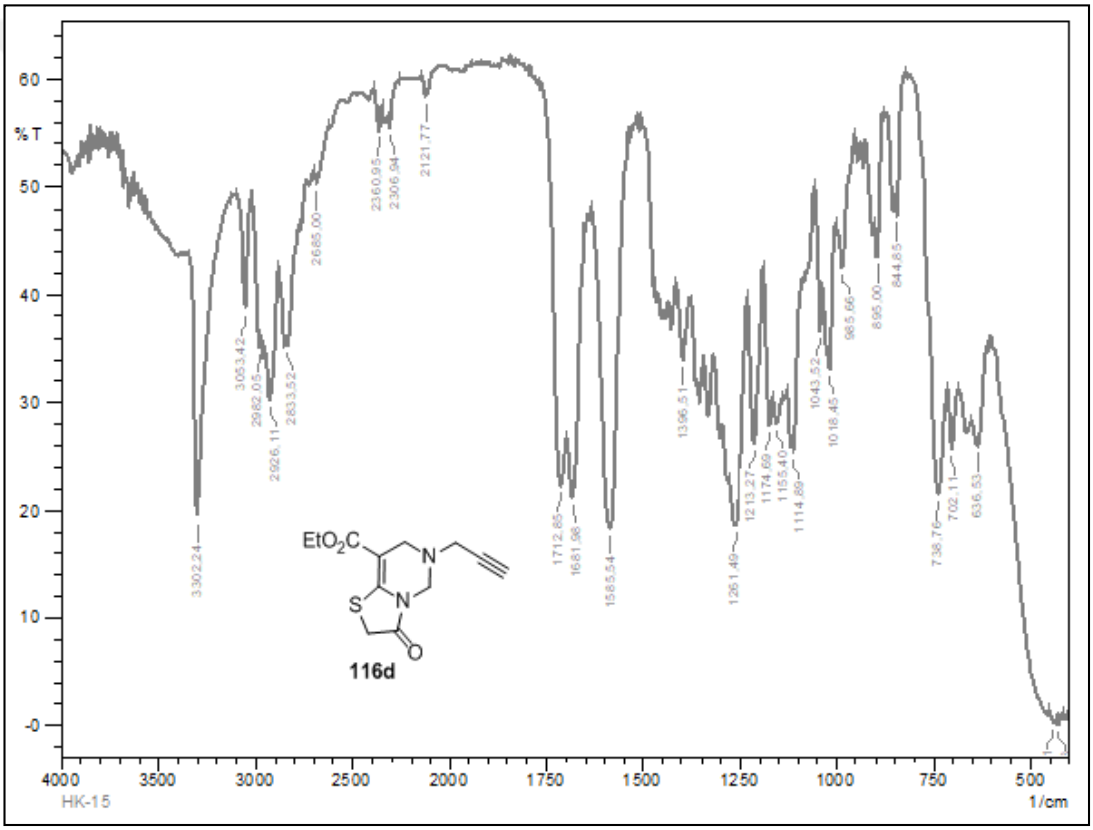

Figure 7.18. IR Spectrum of compound **116d**.

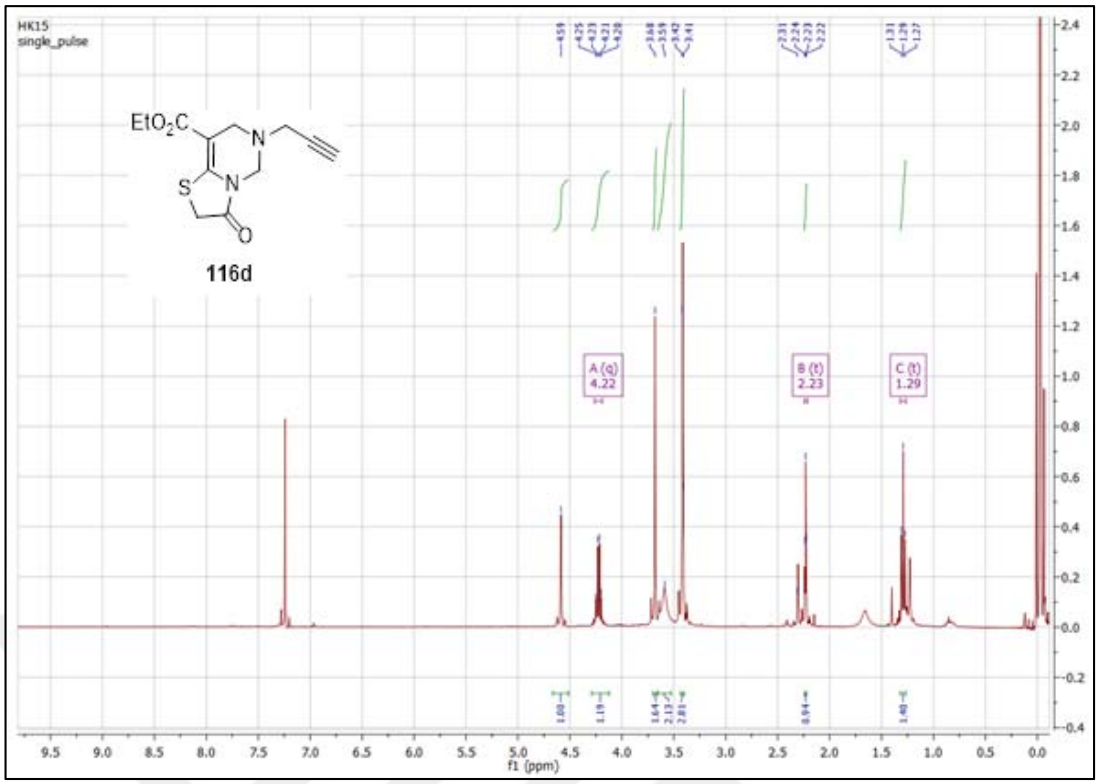

Figure 7.19. ^{1}H-NMR Spectrum of compound **116d**.

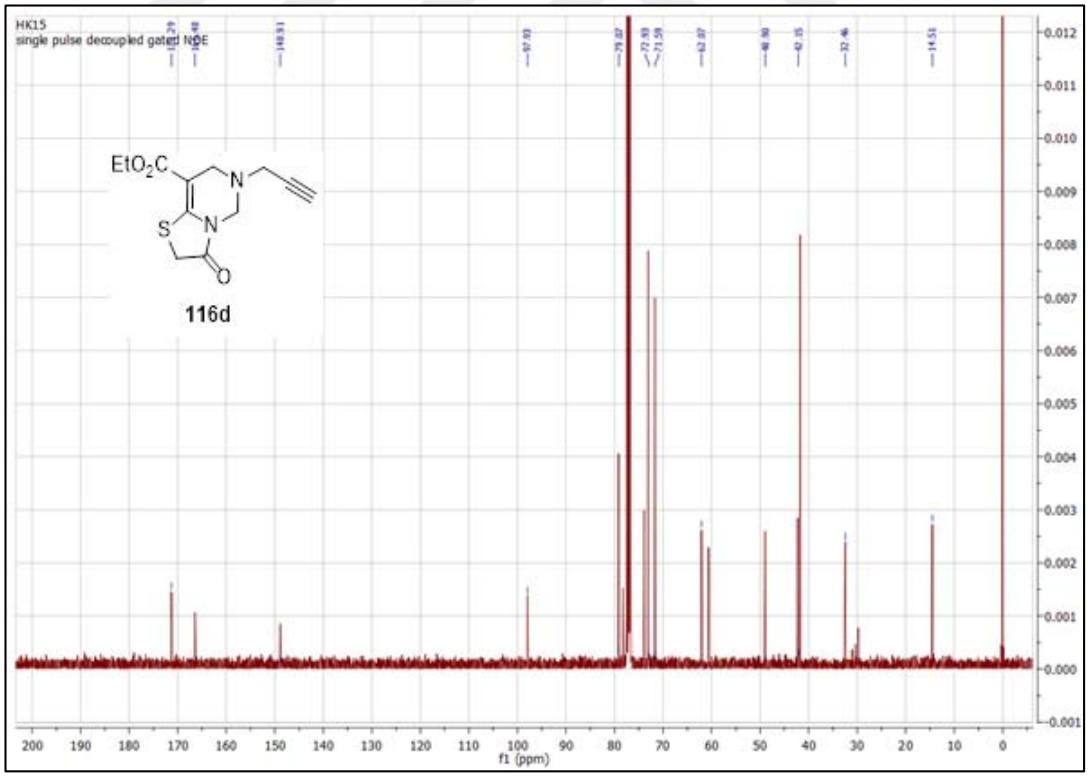

Figure 7.20. ^{13}C-NMR Spectrum of compound **116d**.

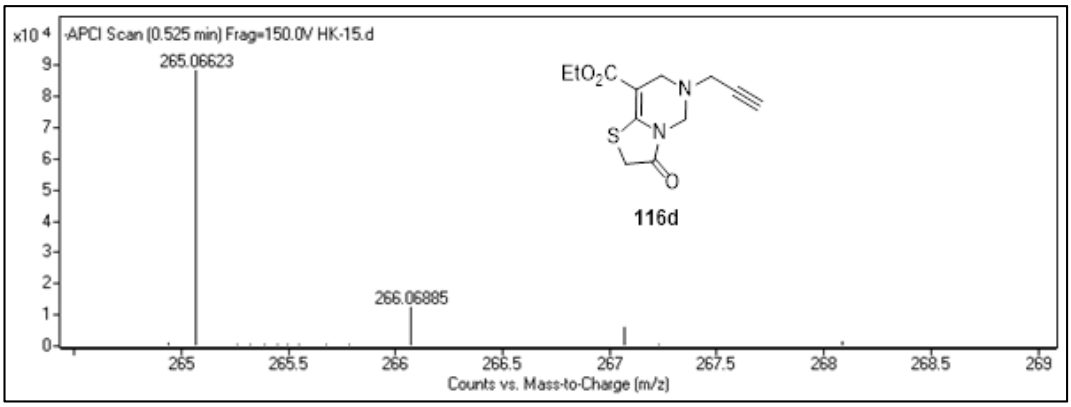

Figure 7.21. HRMS Spectrum of compound **116d**.

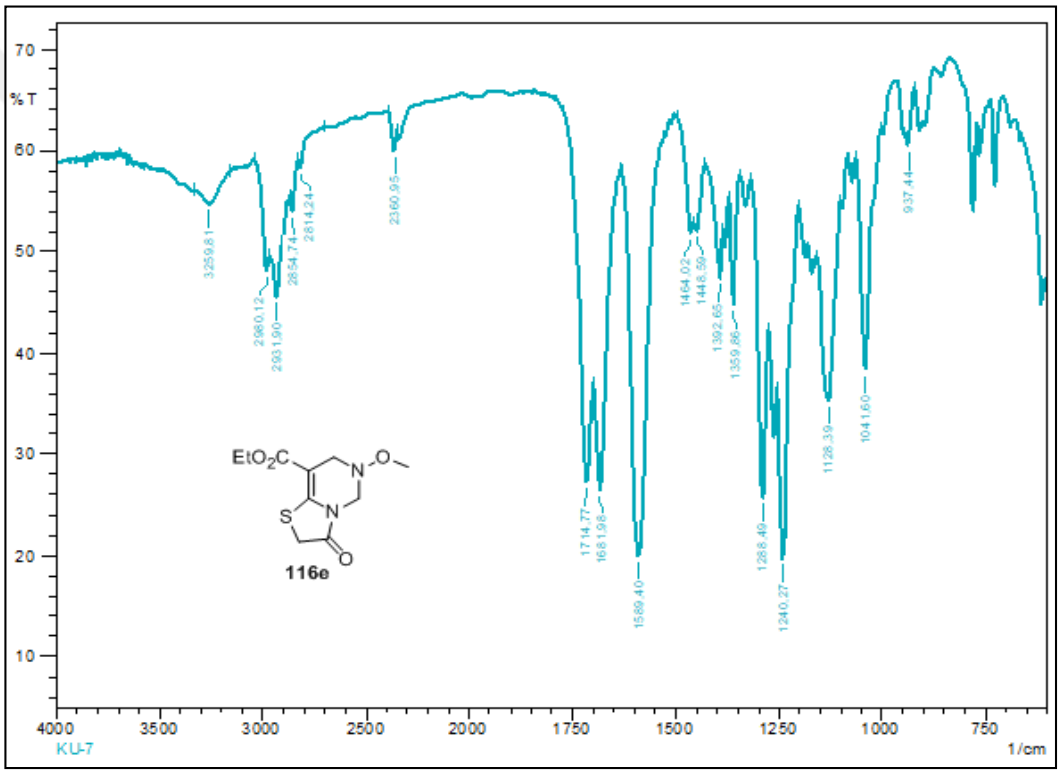

Figure 7.22. IR Spectrum of compound **116e**.

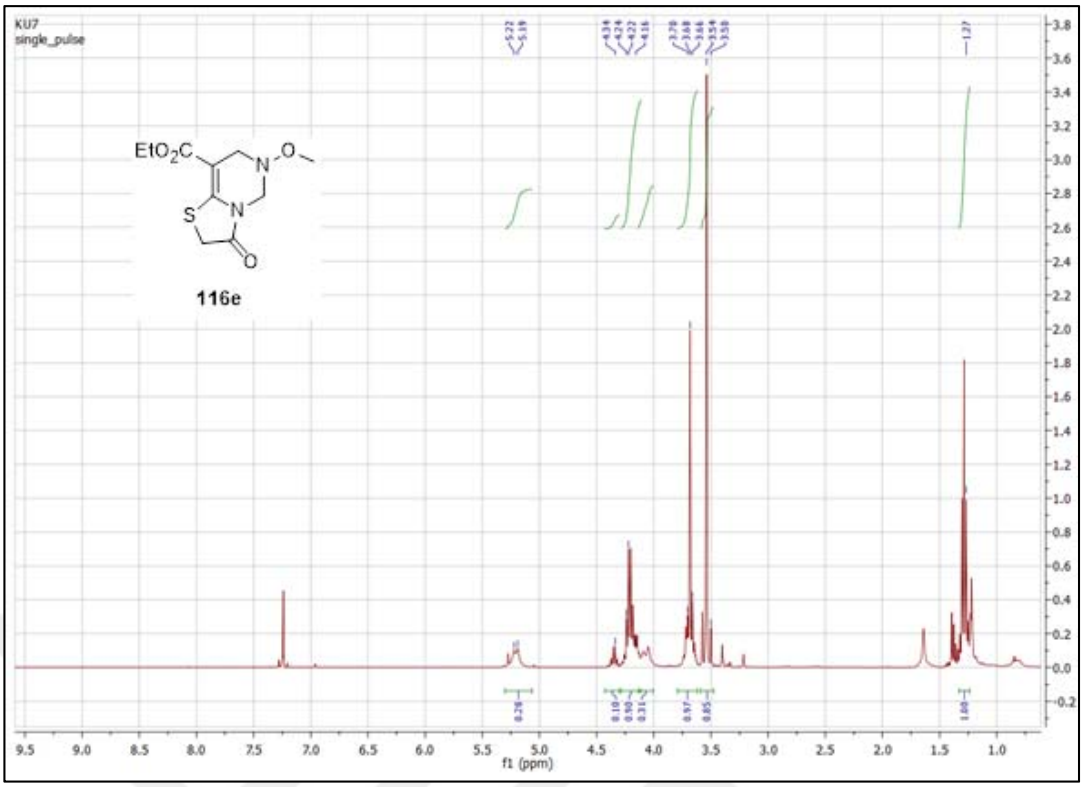

Figure 7.23. ^{1}H-NMR Spectrum of compound **116e**.

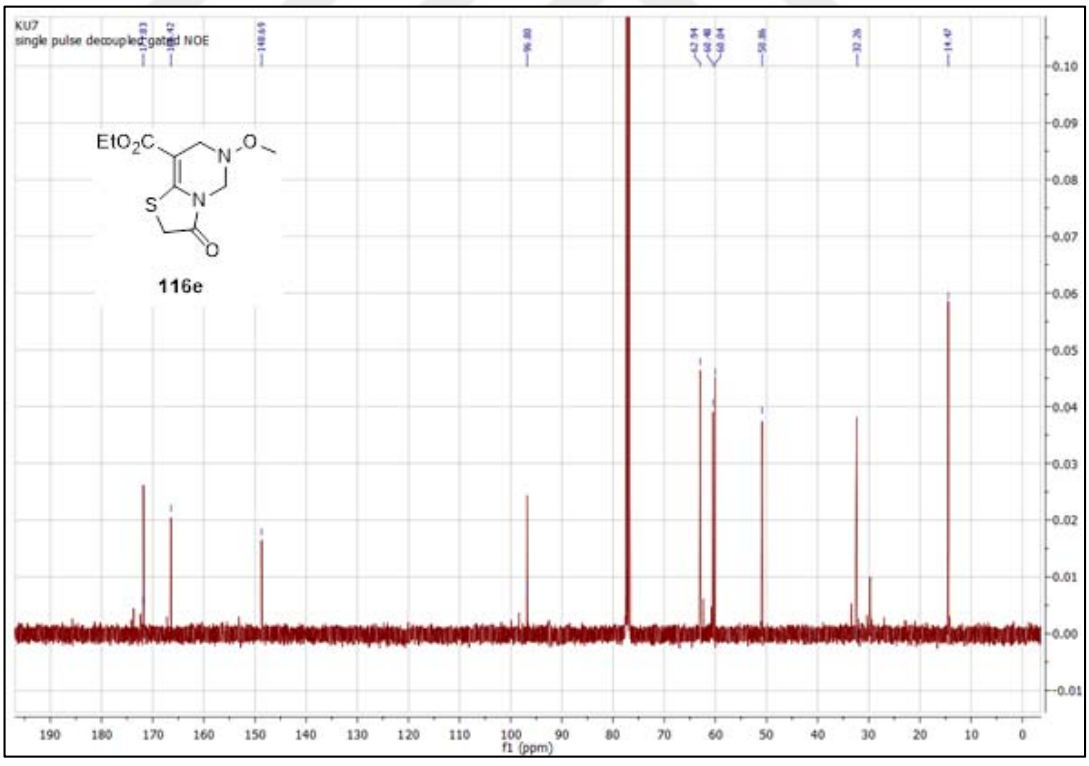

Figure 7.24. ^{13}C-NMR Spectrum of compound **116e**.

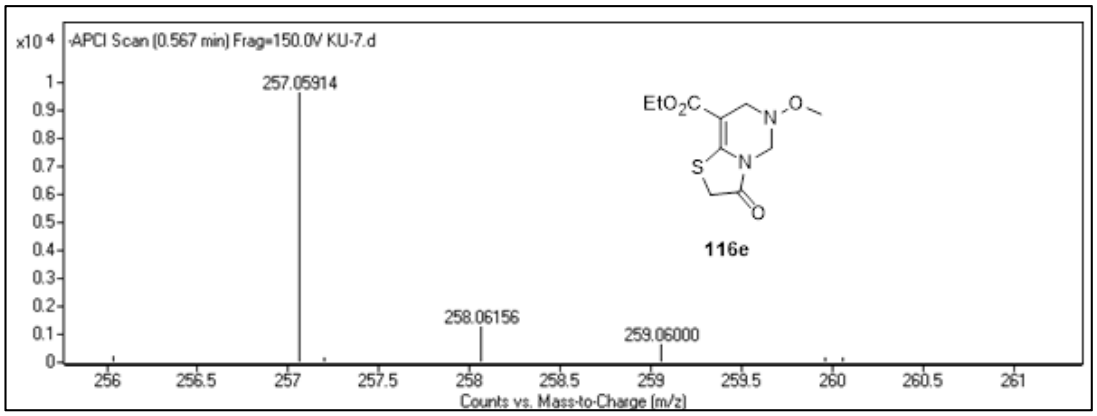

Figure 7.25. HRMS Spectrum of compound **116e**.

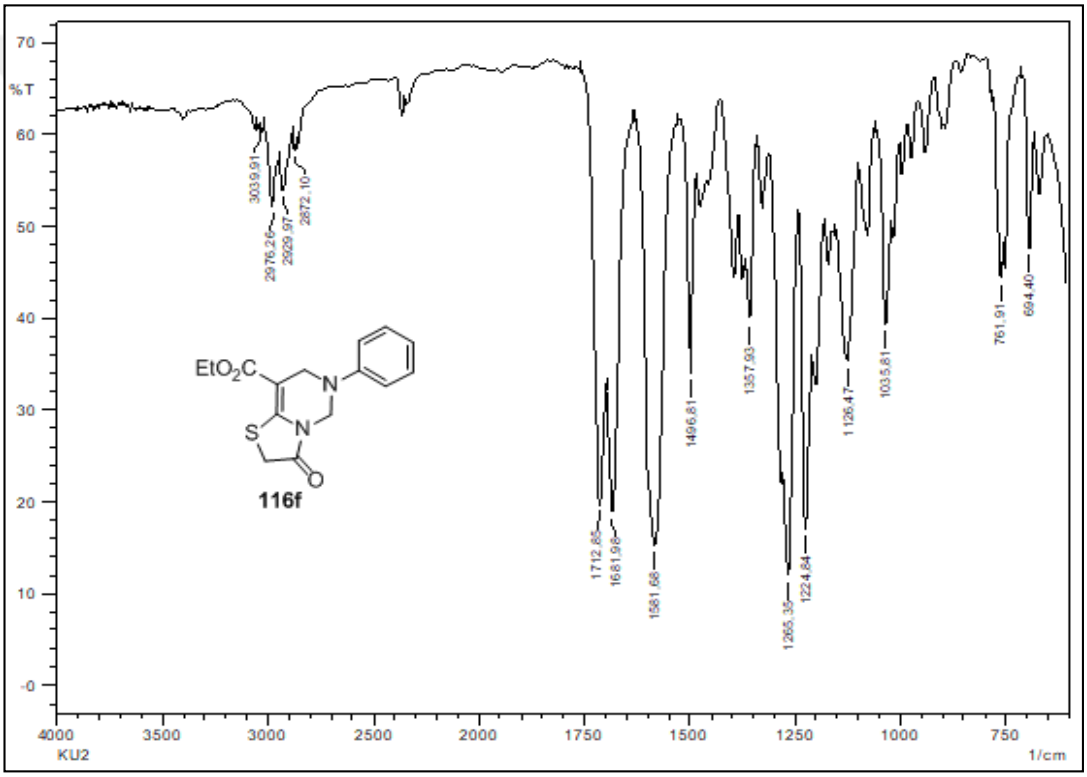

Figure 7.26. IR Spectrum of compound **116f**.

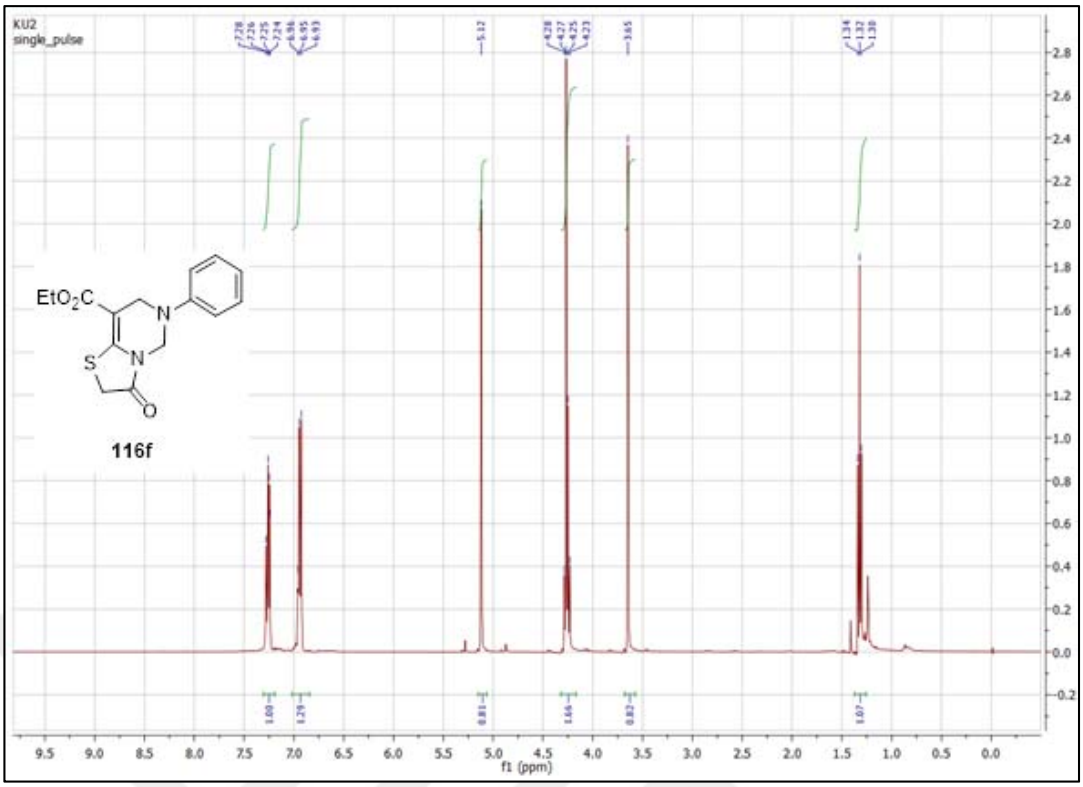

Figure 7.27. ^{1}H-NMR Spectrum of compound **116f**.

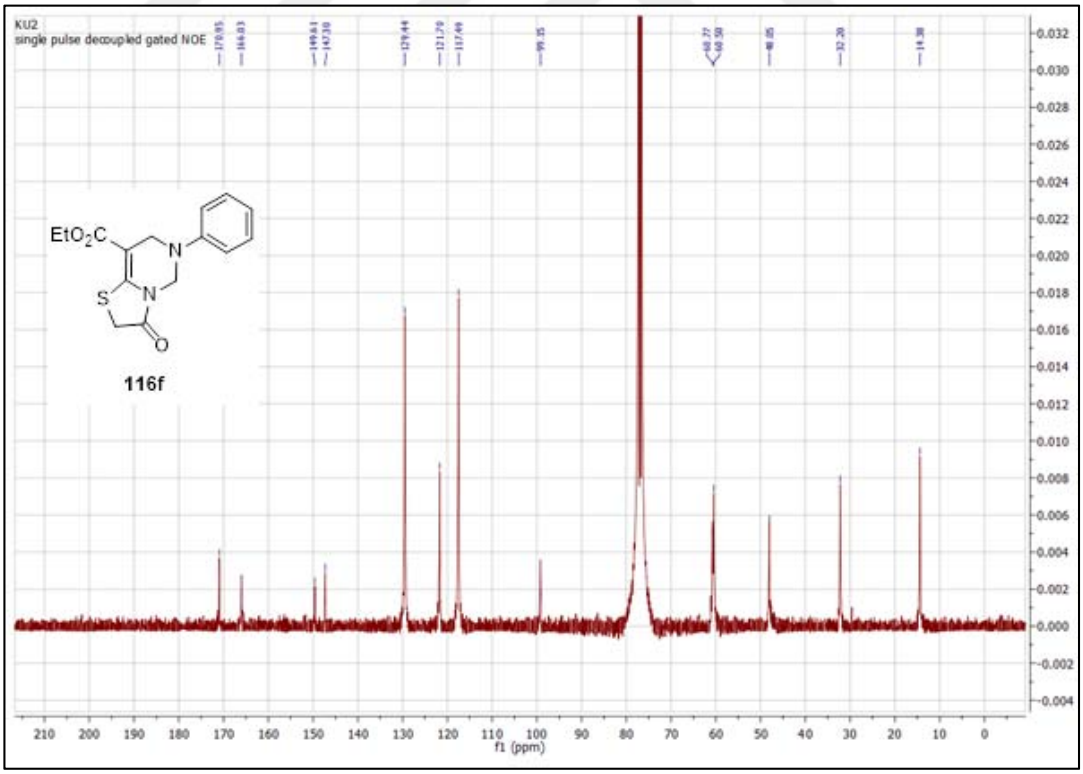

Figure 7.28. ^{13}C-NMR Spectrum of compound **116f**.

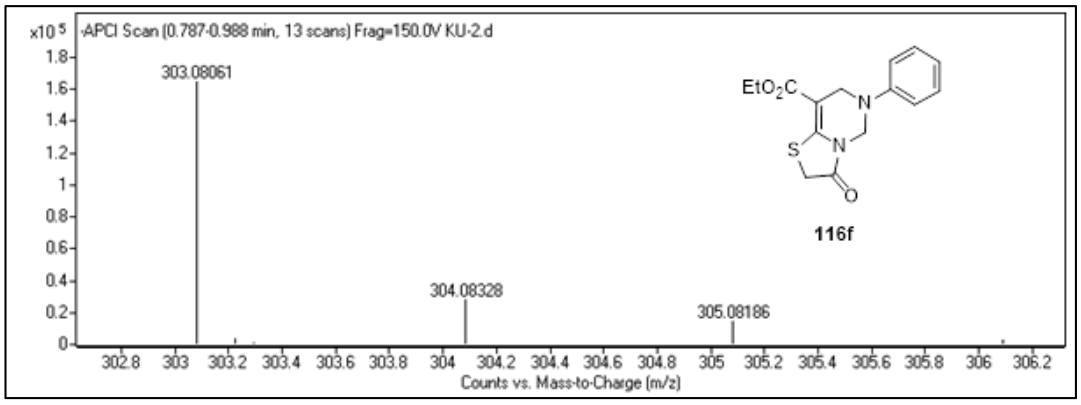

Figure 7.29. HRMS Spectrum of compound **116f**.

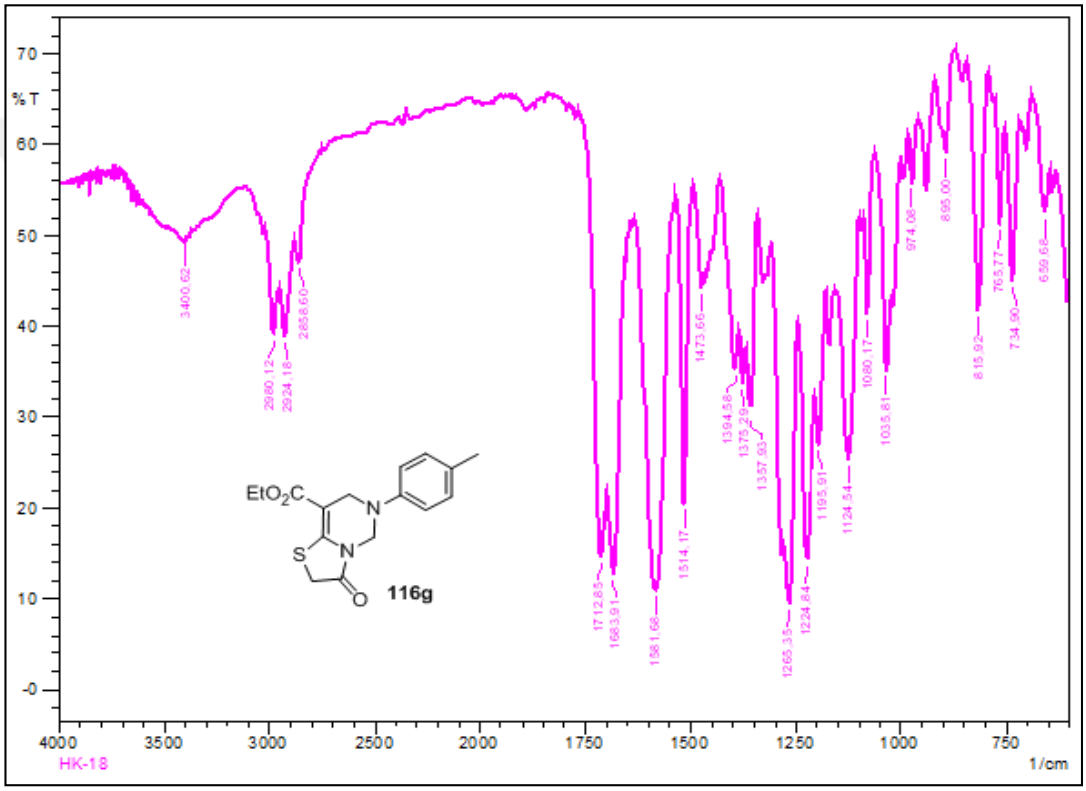

Figure 7.30. IR Spectrum of compound **116g**.

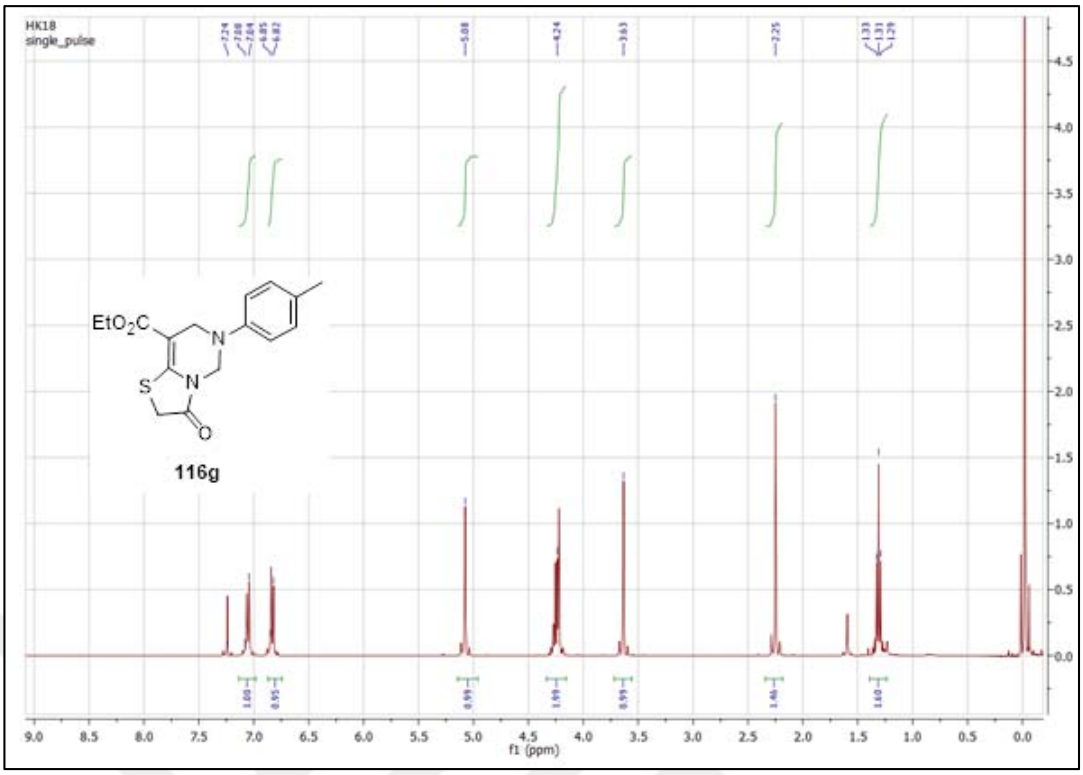

Figure 7.31. ^{1}H-NMR Spectrum of compound **116g**.

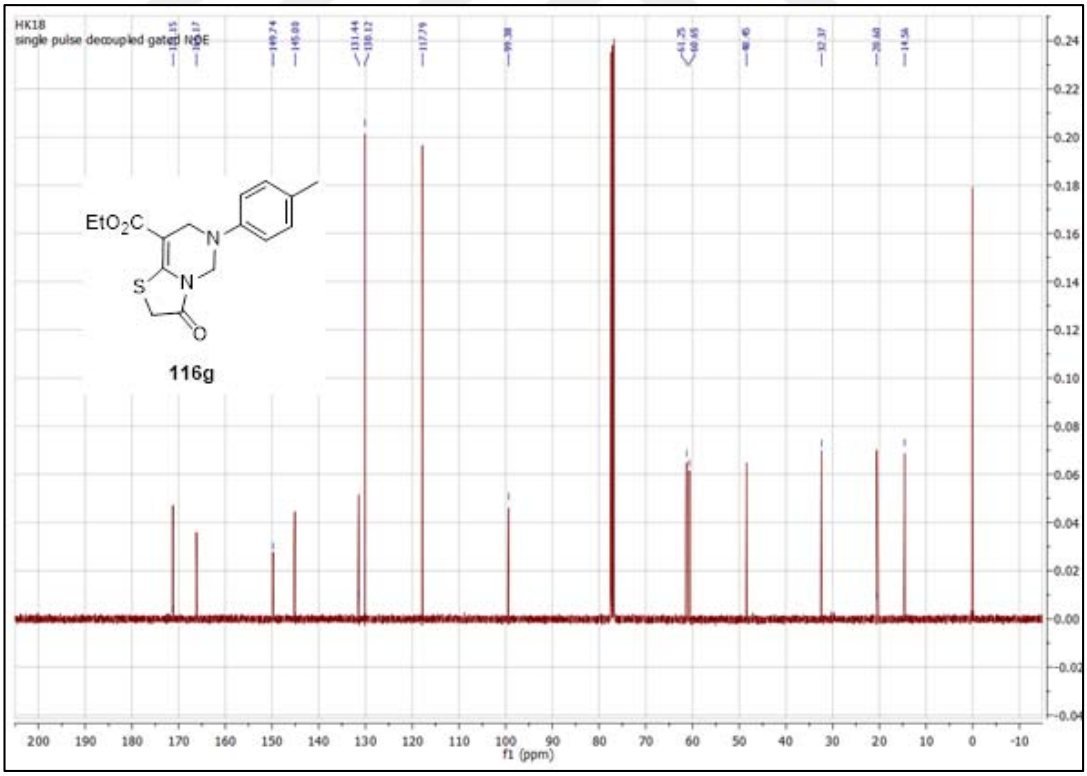

Figure 7.32. ^{13}C-NMR Spectrum of compound **116g**.

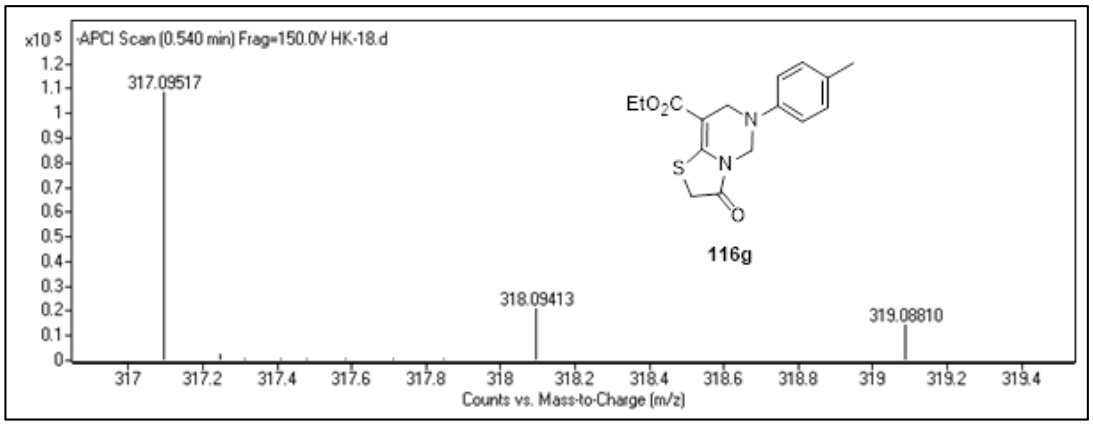

Figure 7.33. HRMS Spectrum of compound **116g**.

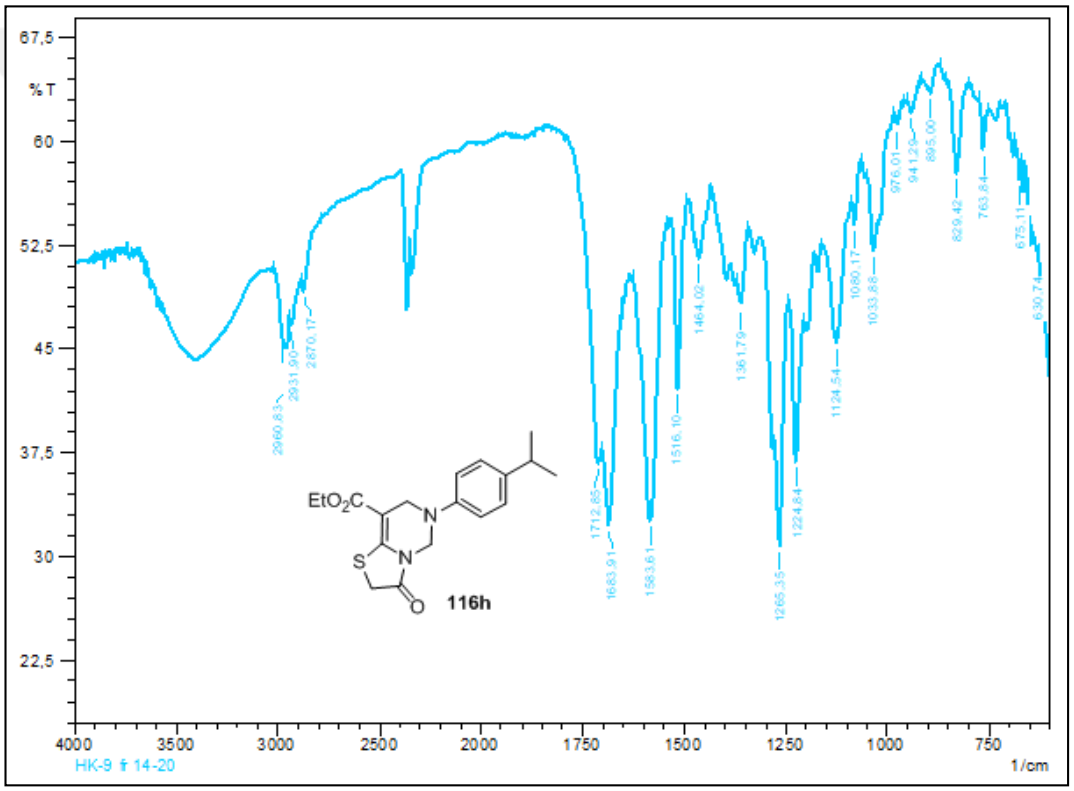

Figure 7.34. IR Spectrum of compound **116h**.

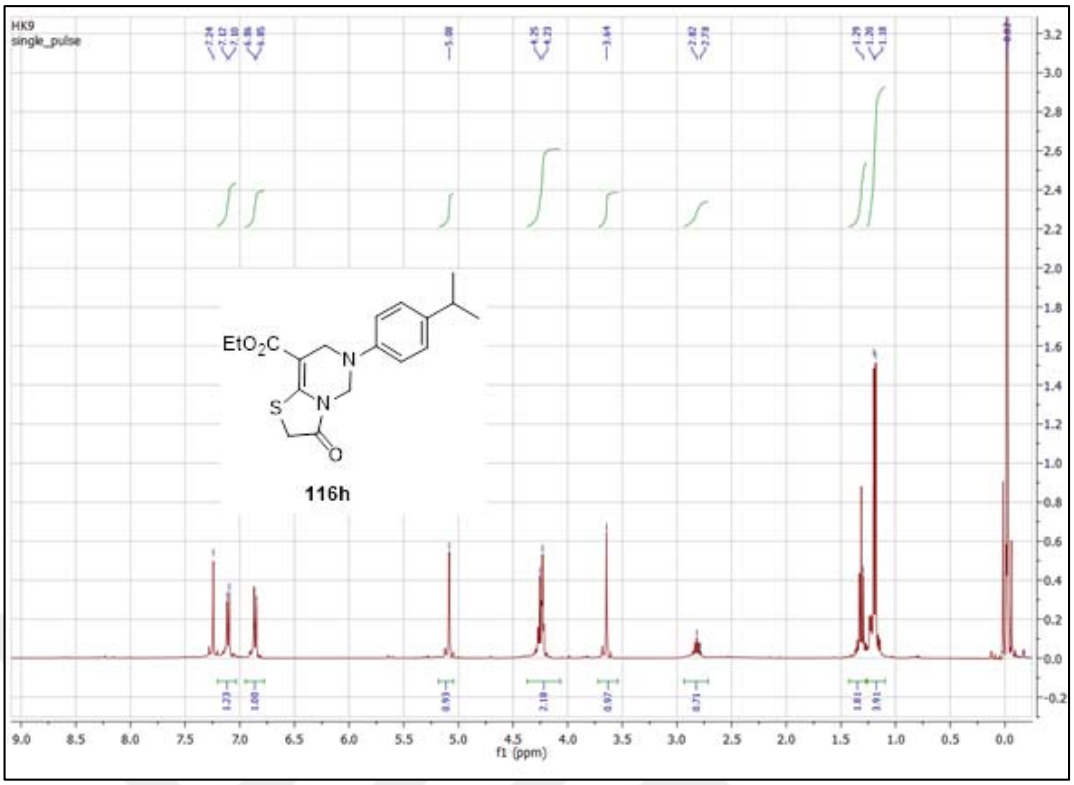

Figure 7.35. ^{1}H-NMR Spectrum of compound **116h**.

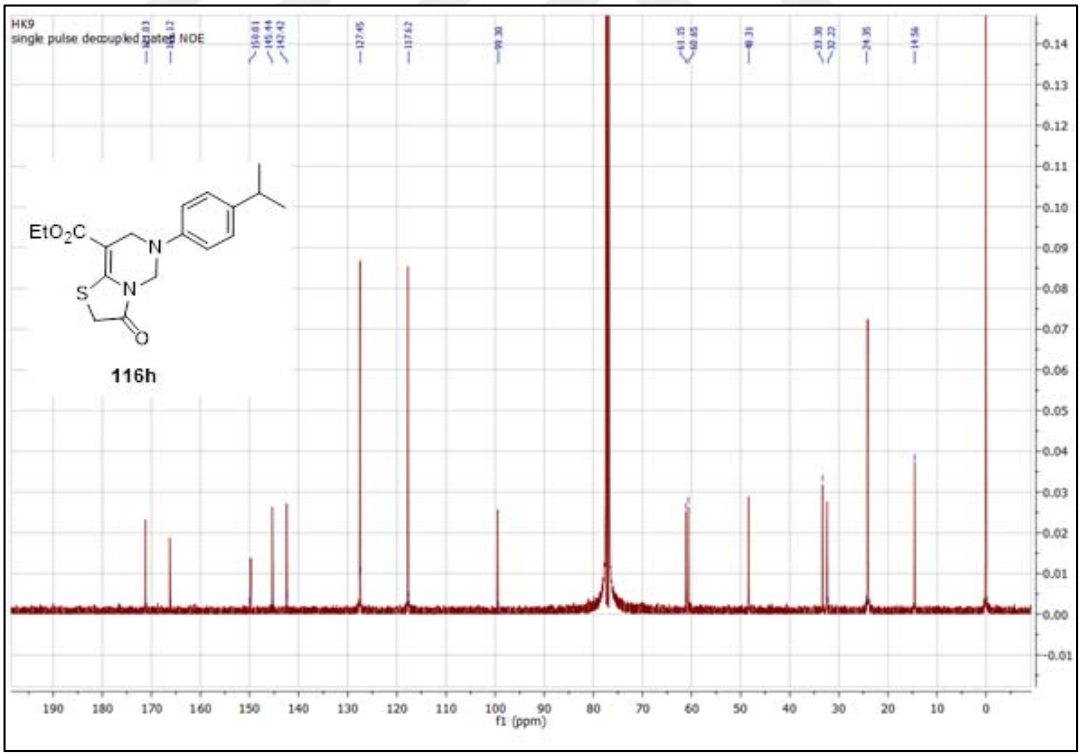

Figure 7.36. ^{13}C-NMR Spectrum of compound **116h**.

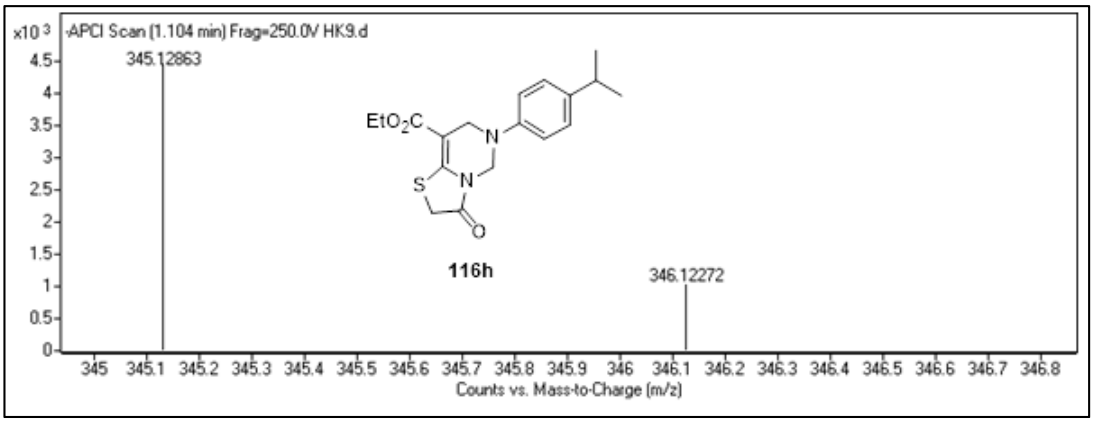

Figure 7.37. HRMS Spectrum of compound **116h**.

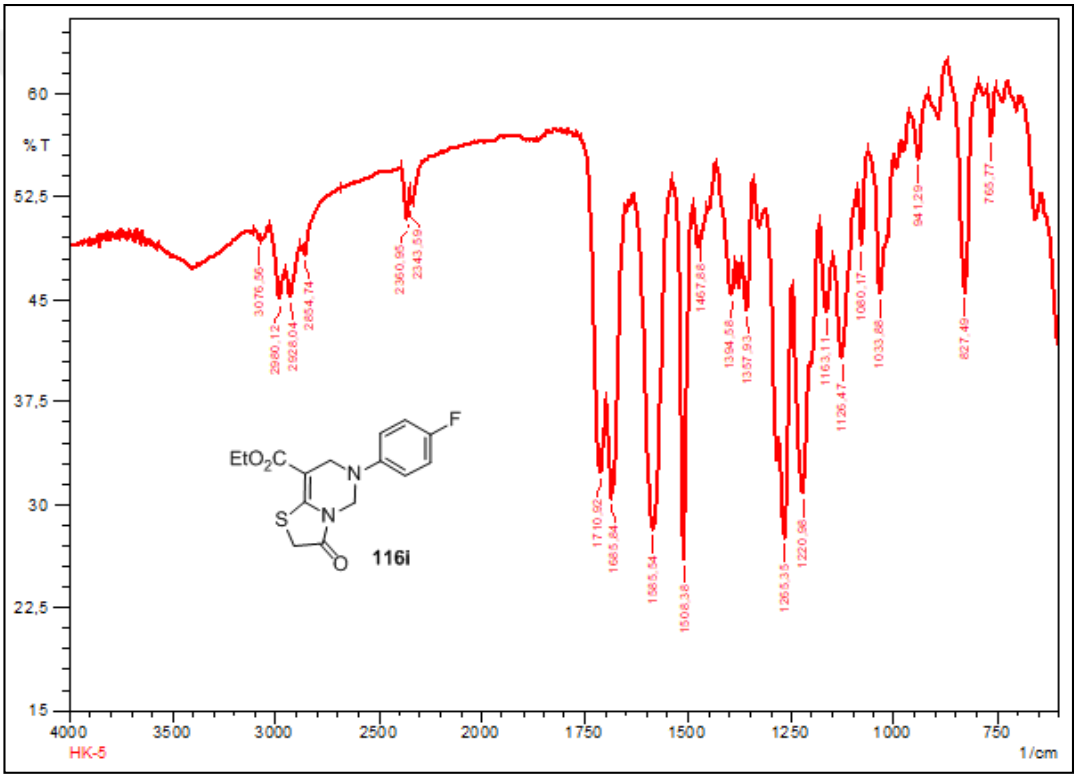

Figure 7.38. IR Spectrum of compound **116i**.

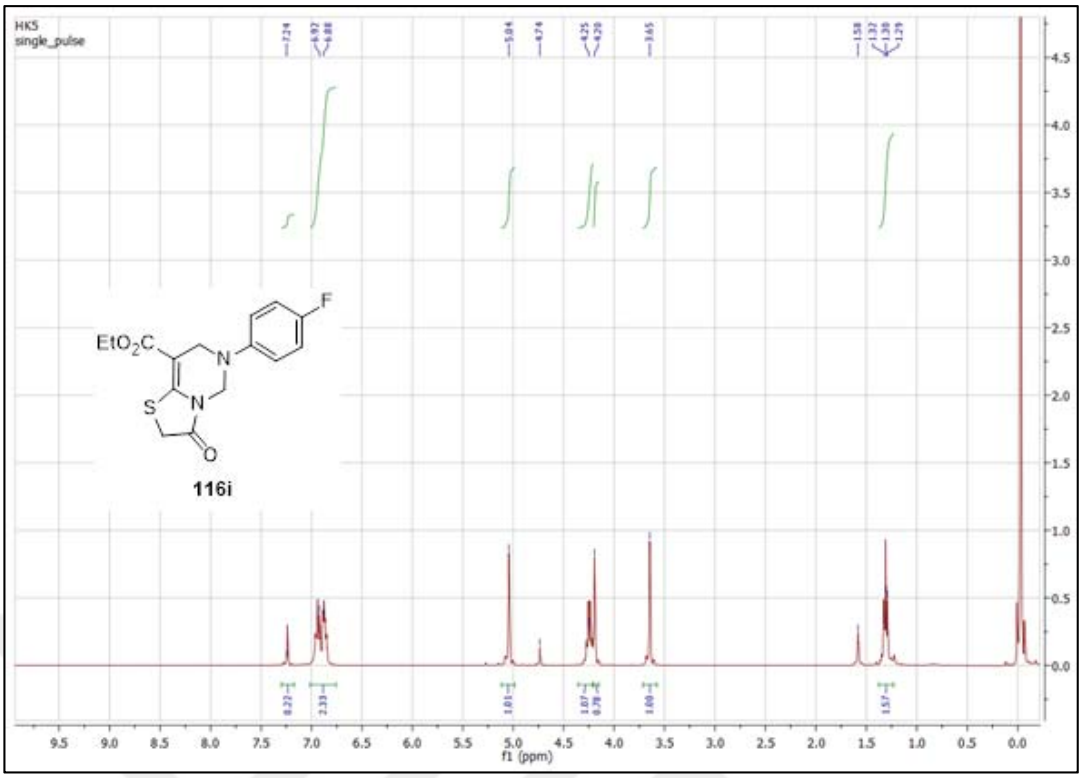

Figure 7.39. ^{1}H-NMR Spectrum of compound **116i**.

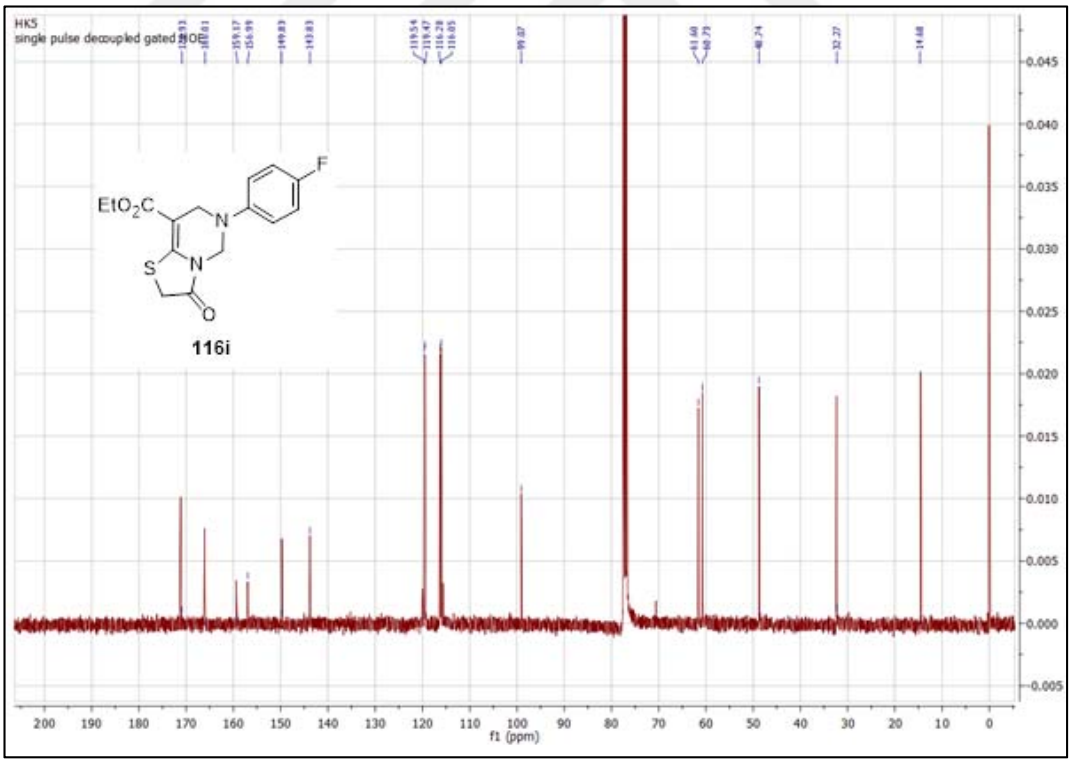

Figure 7.40. ^{13}C-NMR Spectrum of compound **116i**.

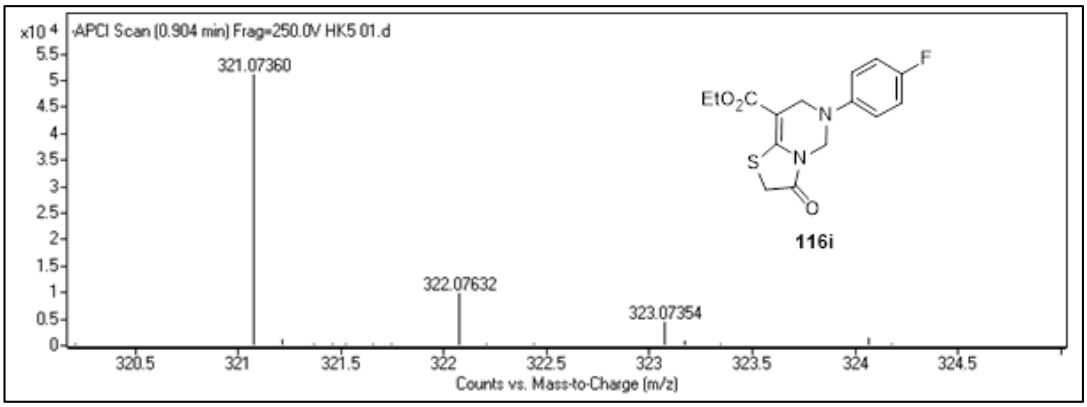

Figure 7.41. HRMS Spectrum of compound **116i**.

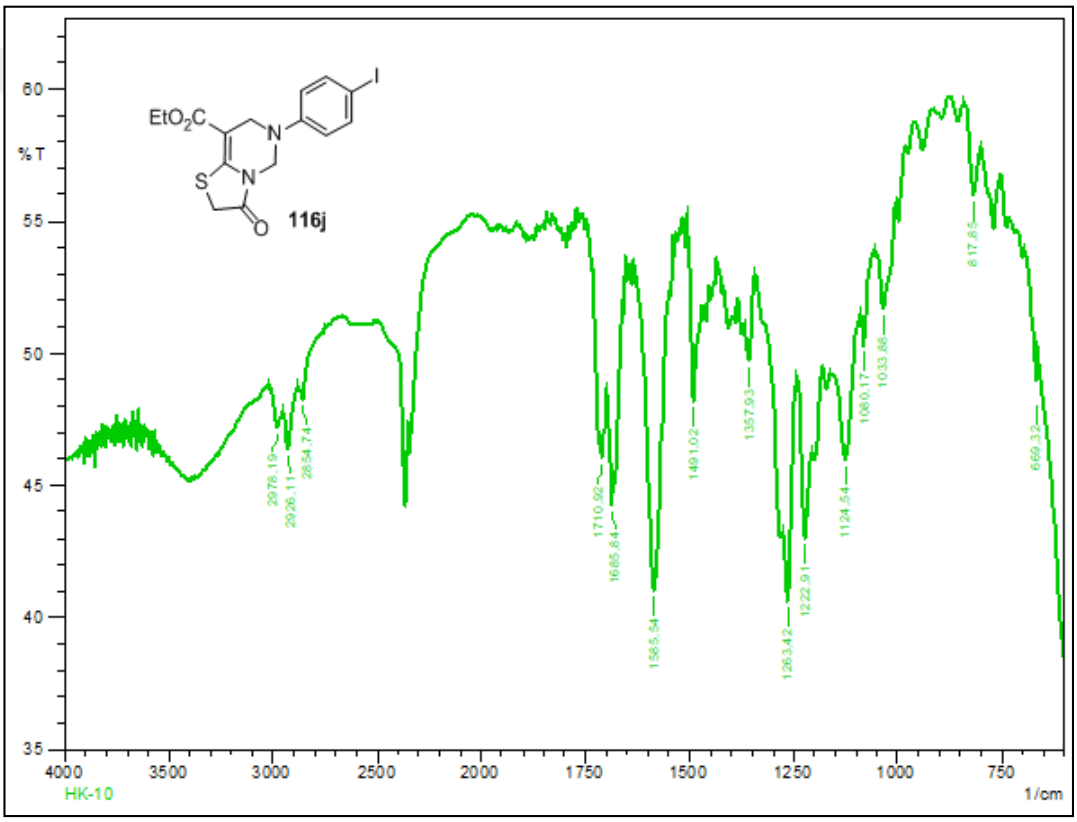

Figure 7.42. IR Spectrum of compound **116j**.

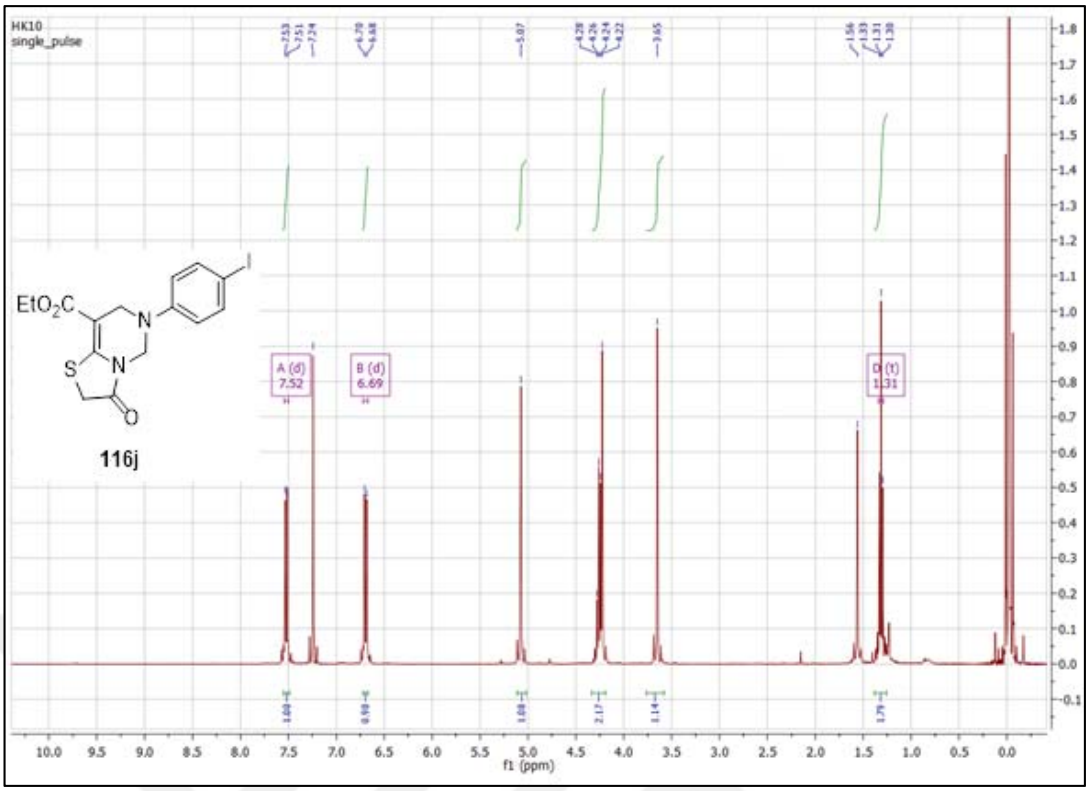

Figure 7.43. ^{1}H-NMR Spectrum of compound **116j**.

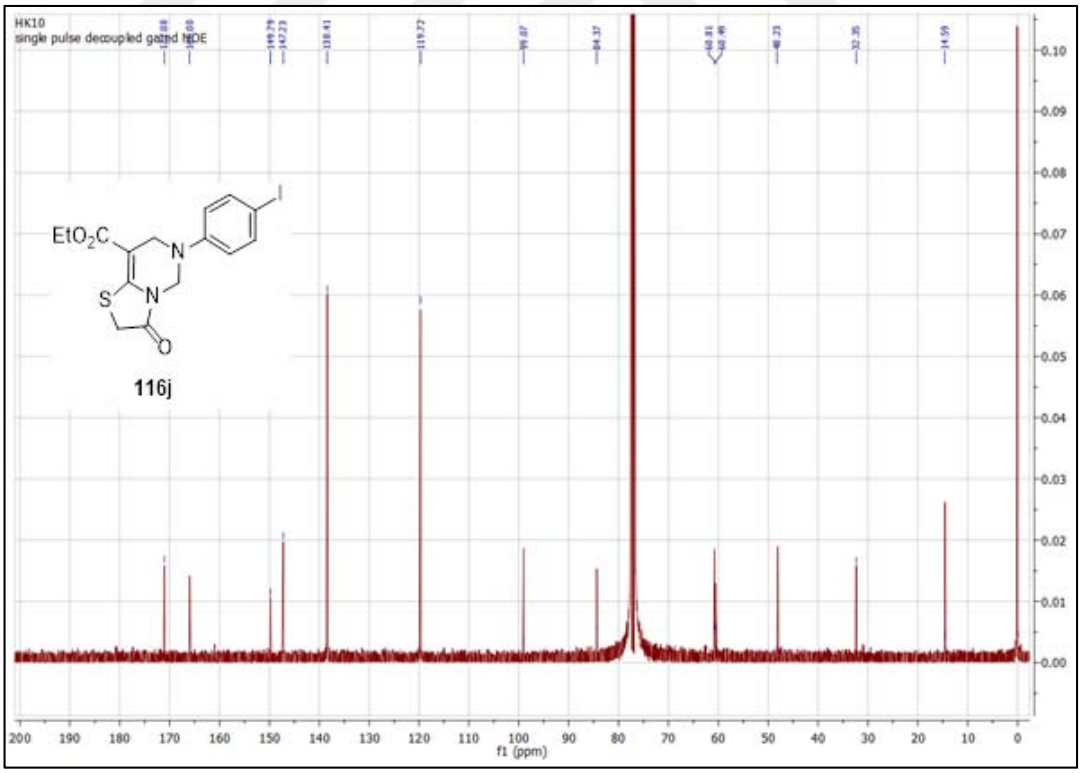

Figure 7.44. ^{13}C-NMR Spectrum of compound **116j**.

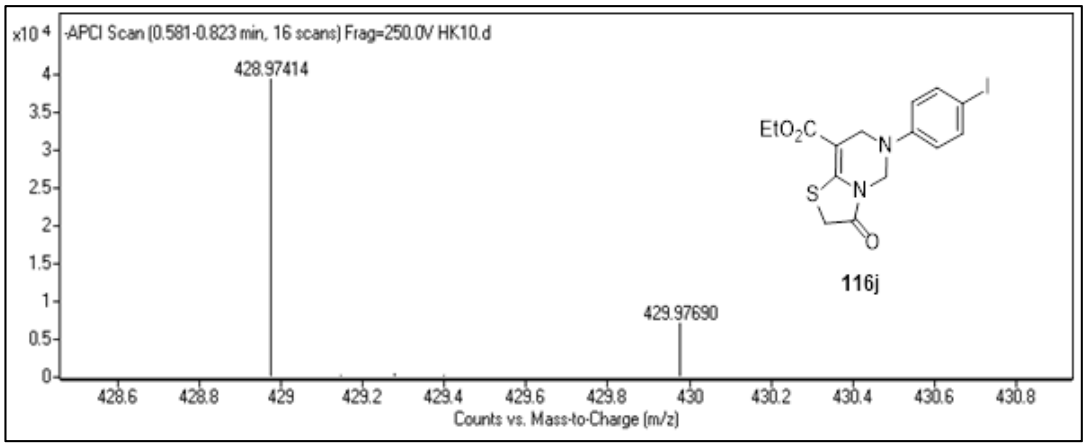

Figure 7.45. HRMS Spectrum of compound **116j**.

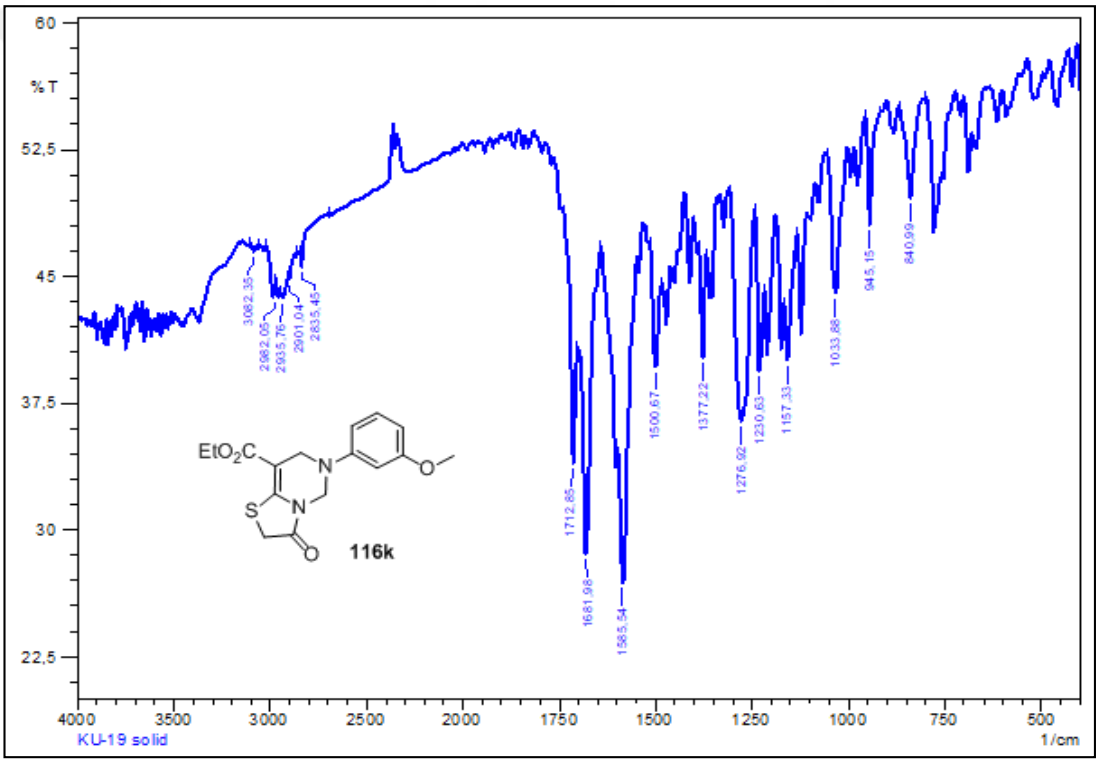

Figure 7.46. IR Spectrum of compound **116k**.

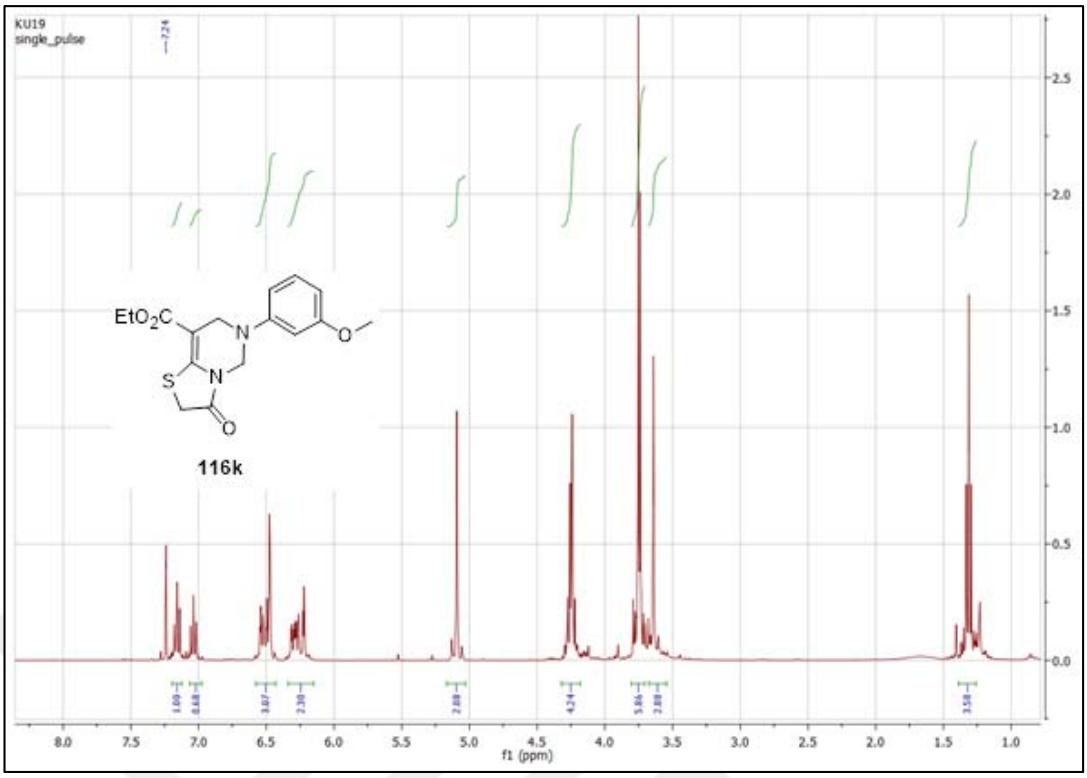

Figure 7.47. ^{1}H-NMR Spectrum of compound **116k**.

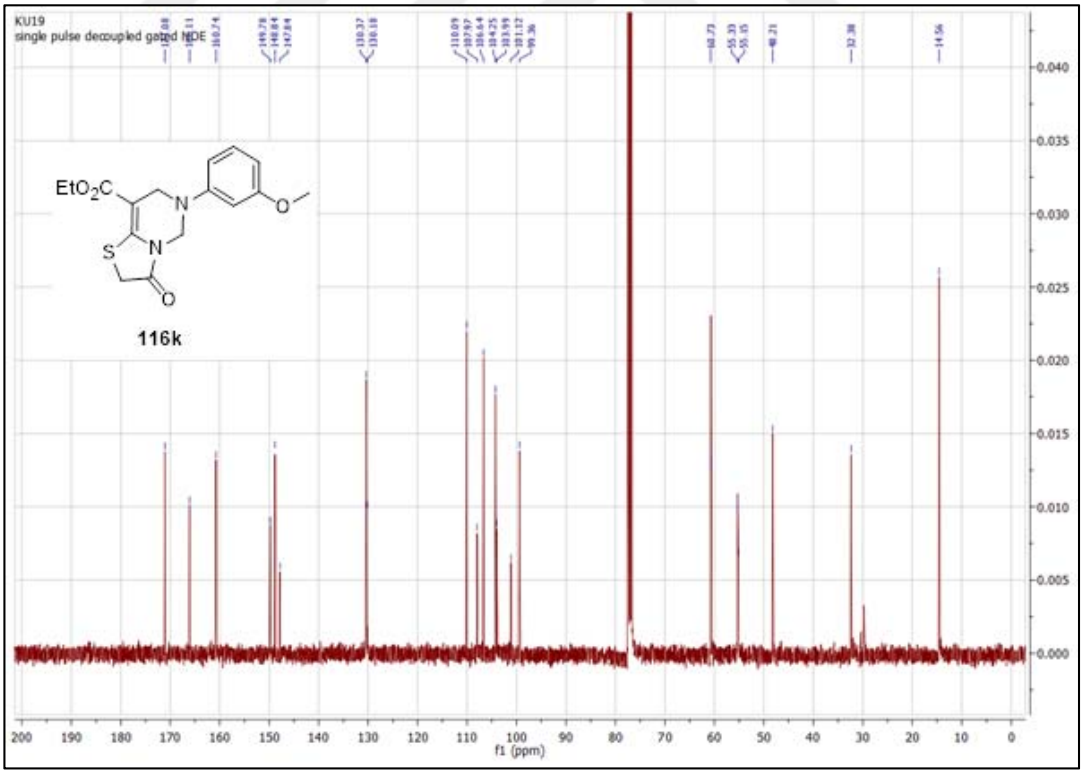

Figure 7.48. ^{13}C-NMR Spectrum of compound **116k**.

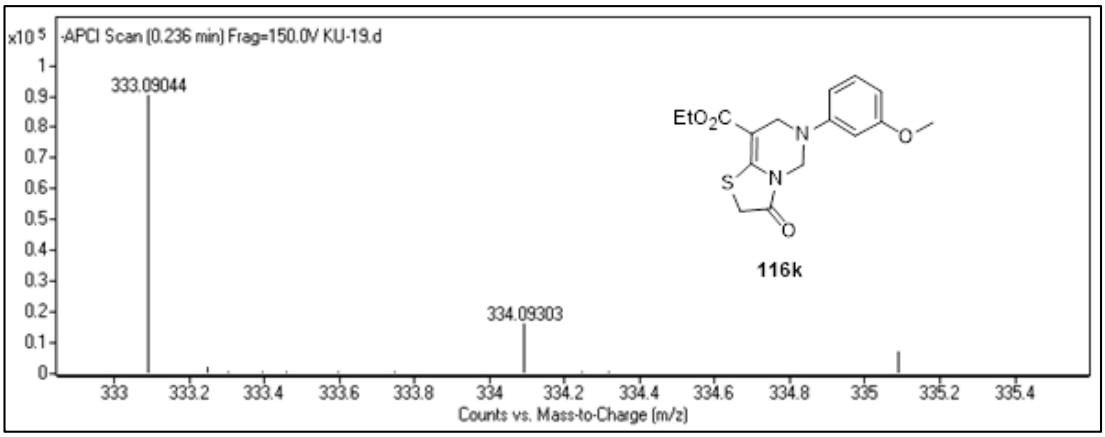

Figure 7.49. HRMS Spectrum of compound **116k**.

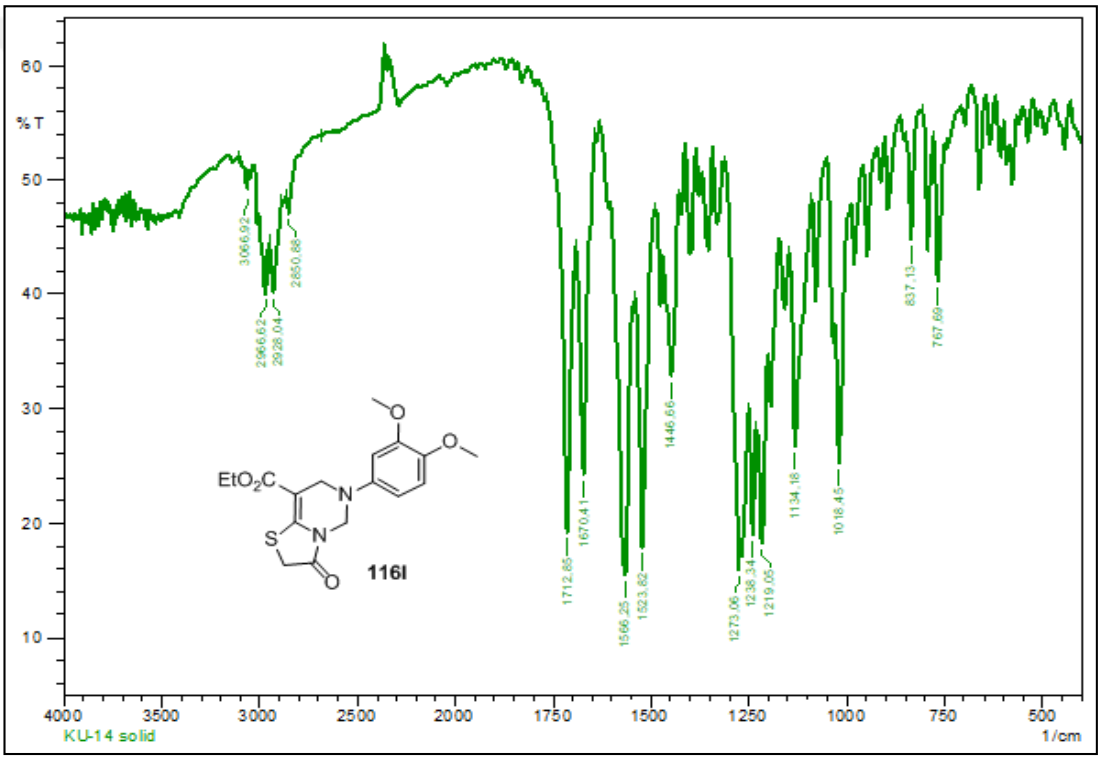

Figure 7.50. IR Spectrum of compound **116l**.

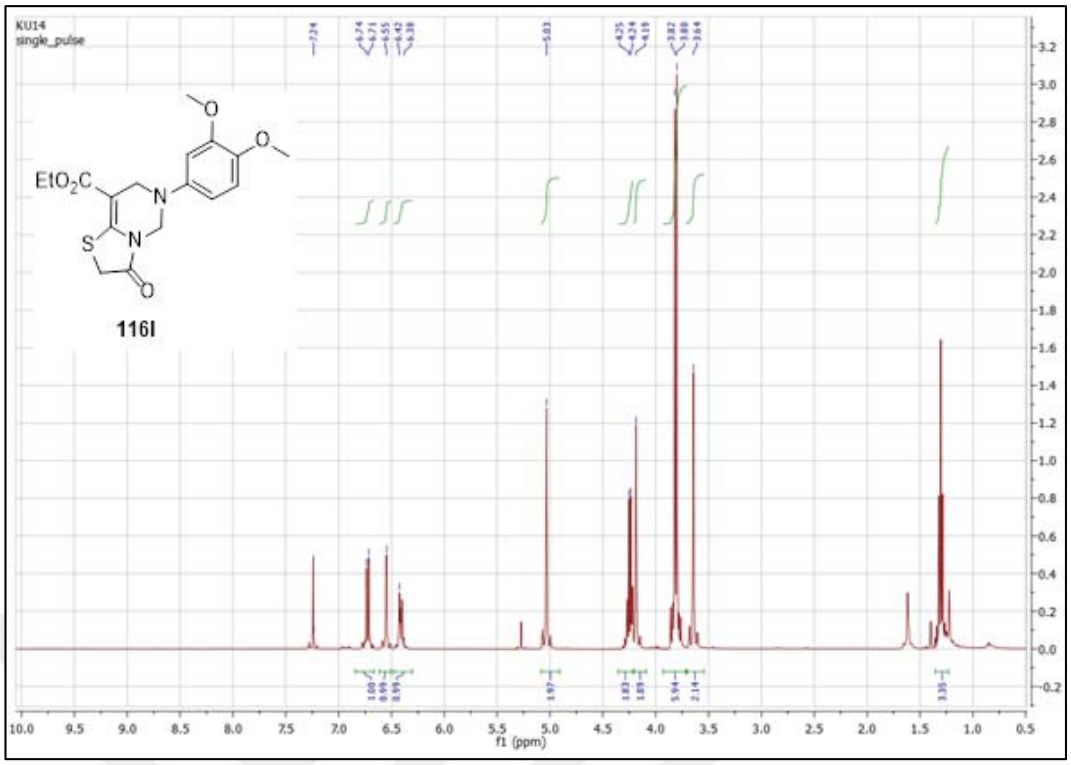

Figure 7.51. ^{1}H-NMR Spectrum of compound **116l**.

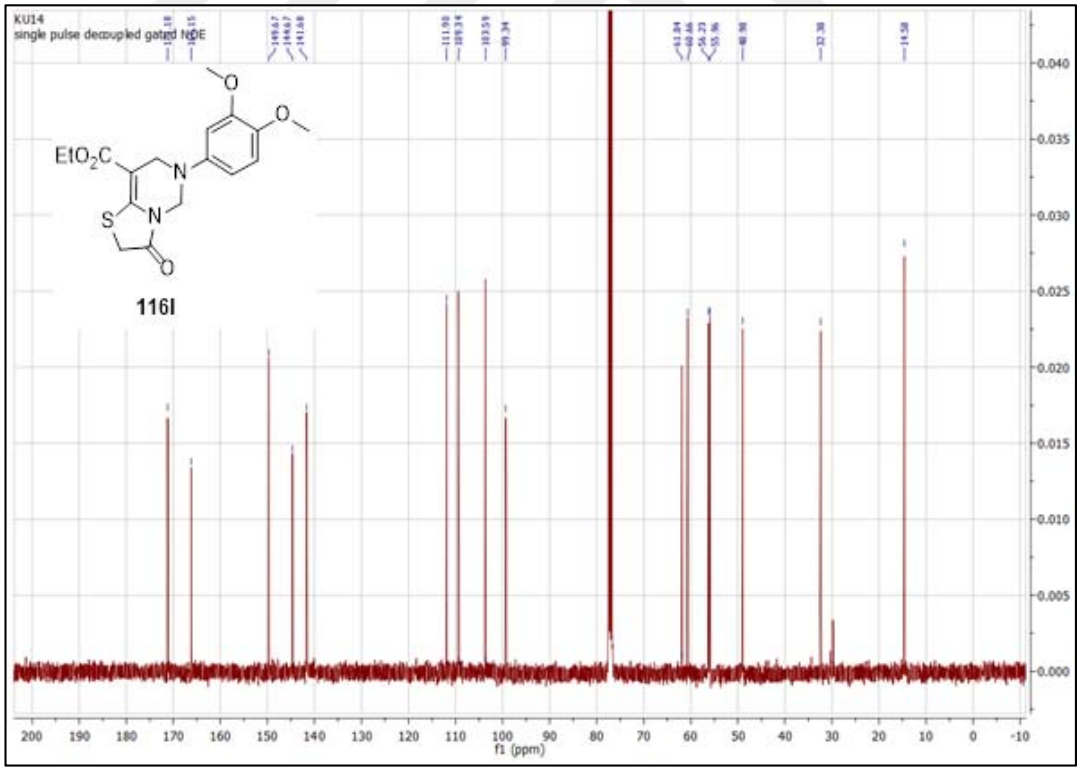

Figure 7.52. ^{13}C-NMR Spectrum of compound **116l**.

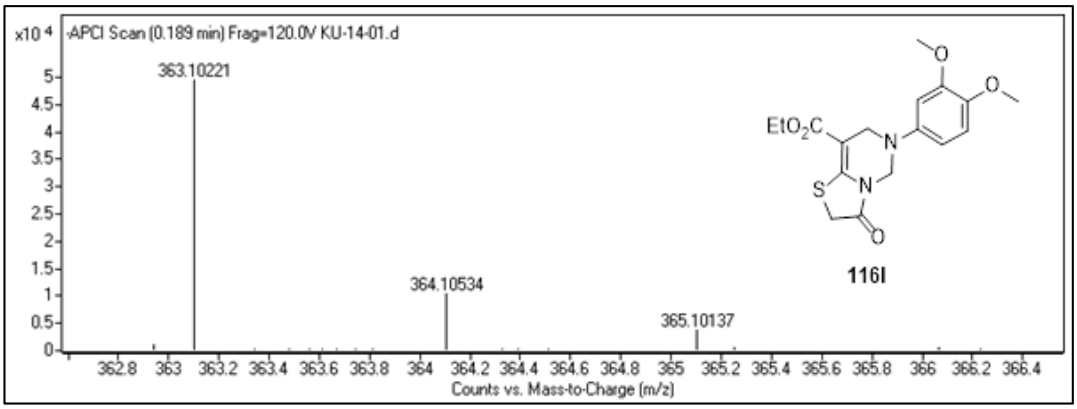

Figure 7.53. HRMS Spectrum of compound **116l**.

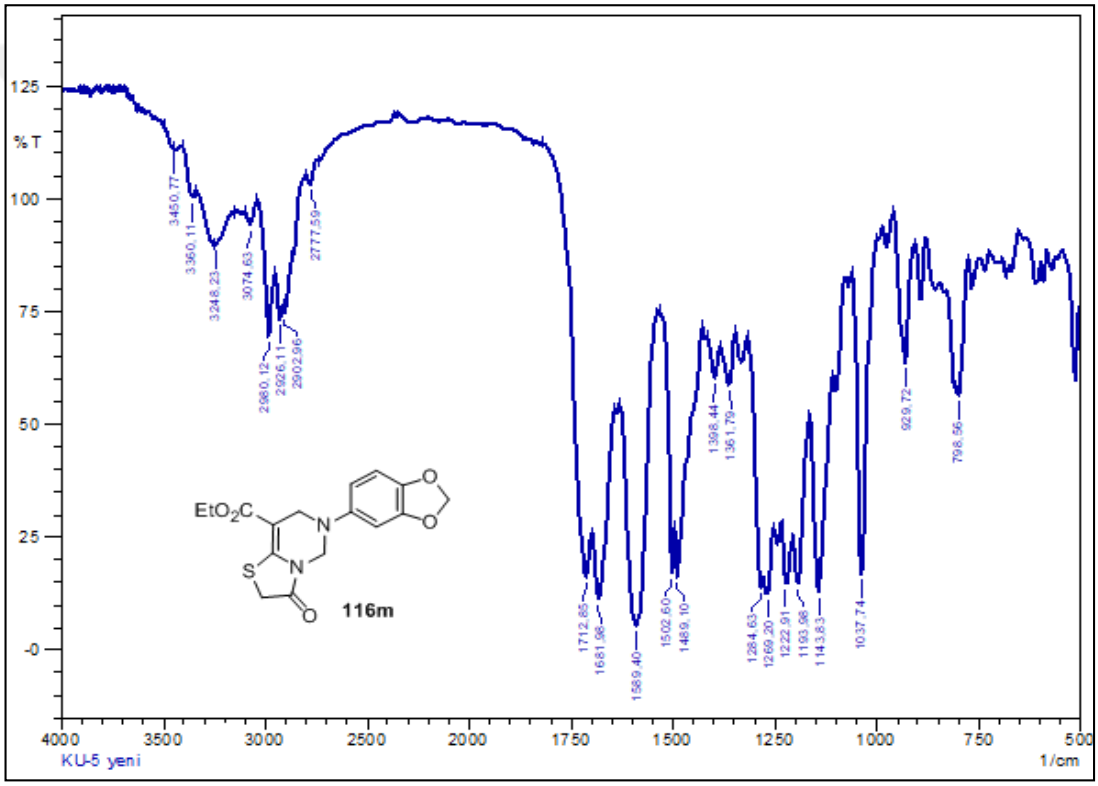

Figure 7.54. IR Spectrum of compound **116m**.

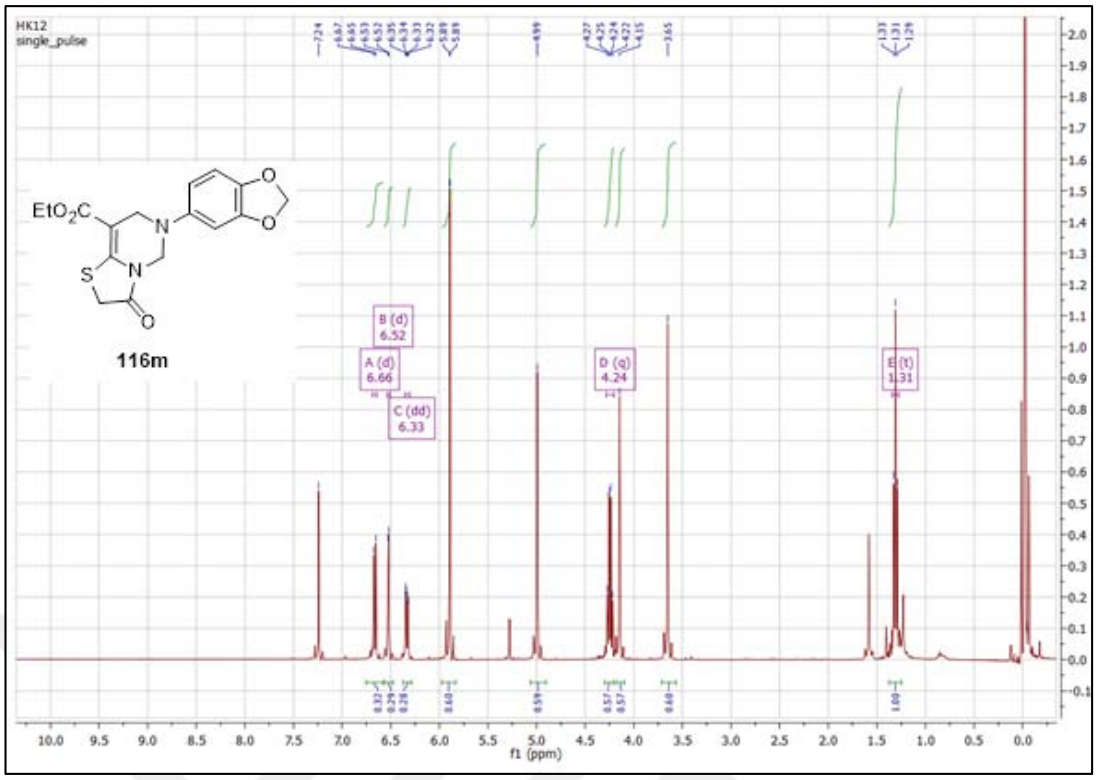

Figure 7.55. ^{1}H-NMR Spectrum of compound **116m**.

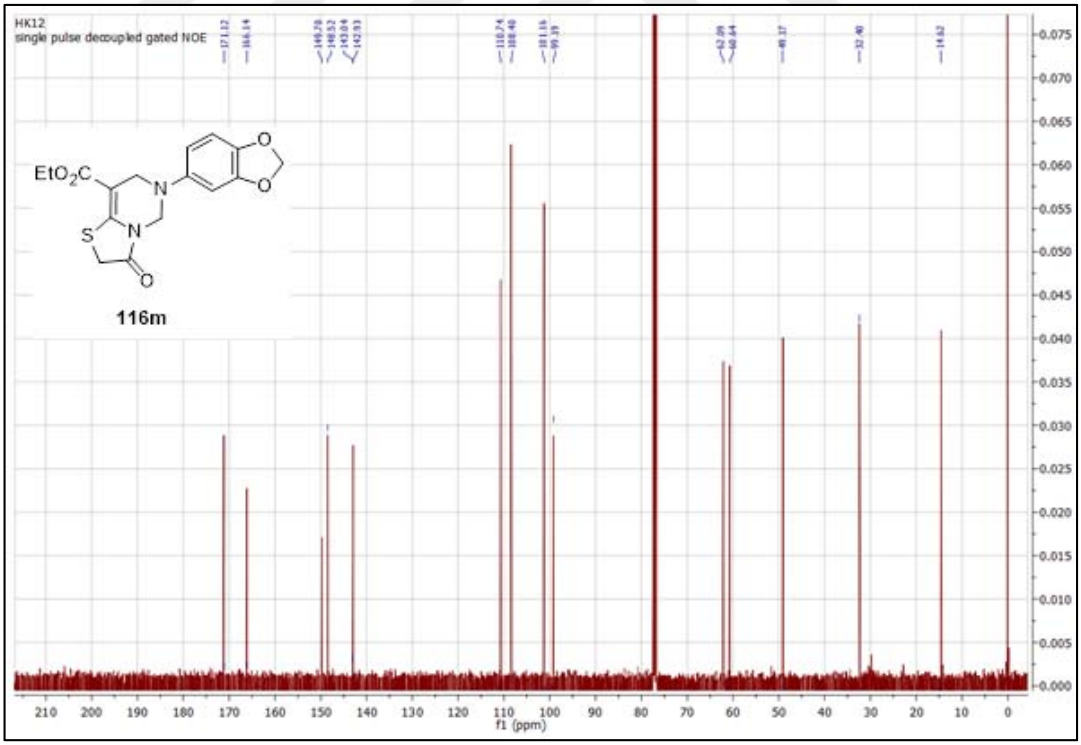

Figure 7.56. ^{13}C-NMR Spectrum of compound **116m**.

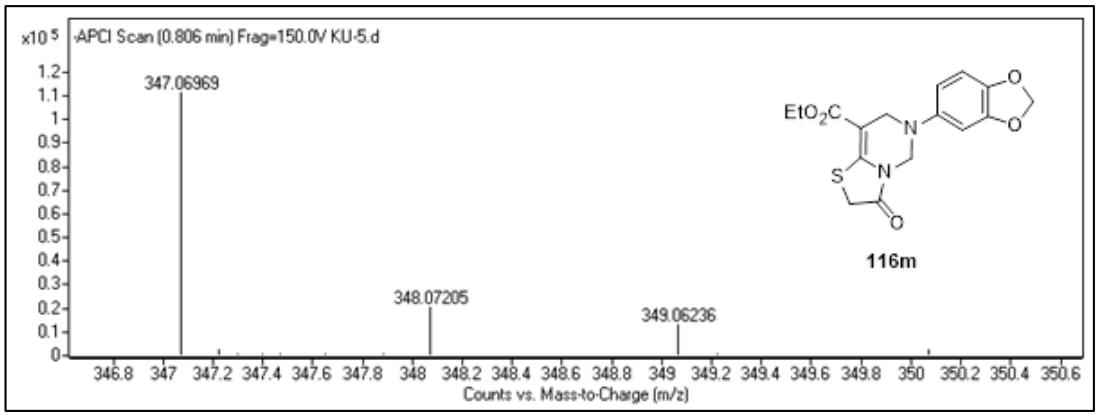

Figure 7.57. HRMS Spectrum of compound **116m**.

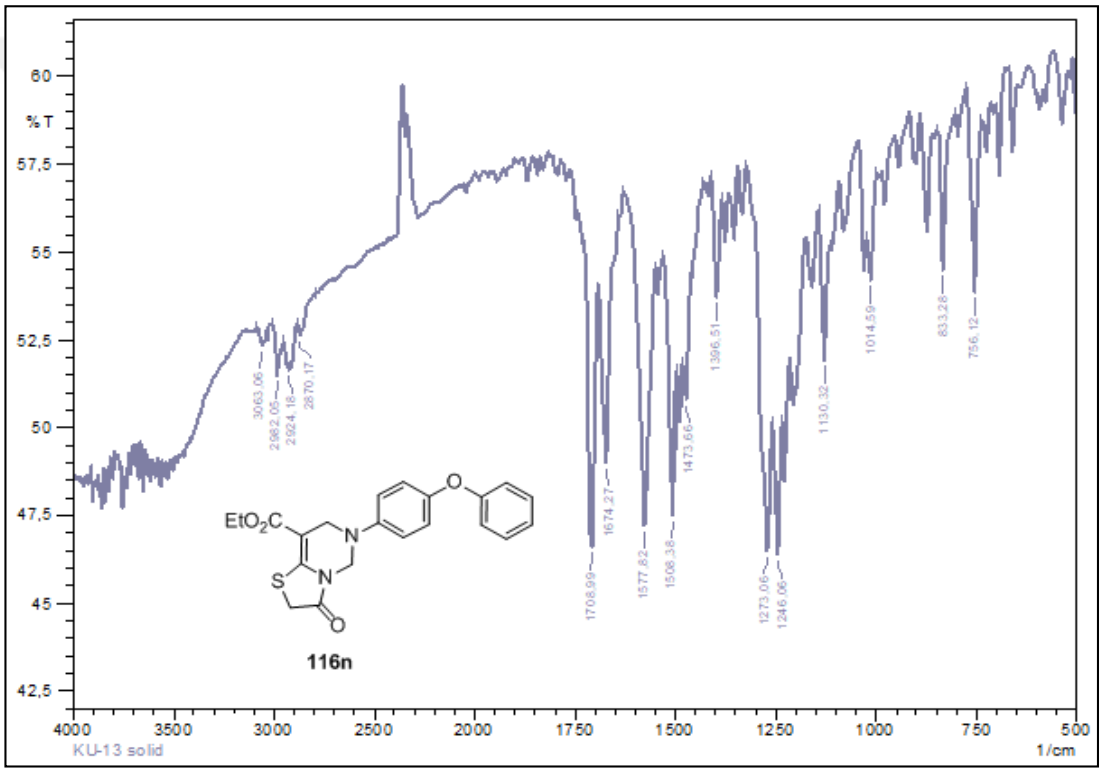

Figure 7.58. IR Spectrum of compound **116n**.

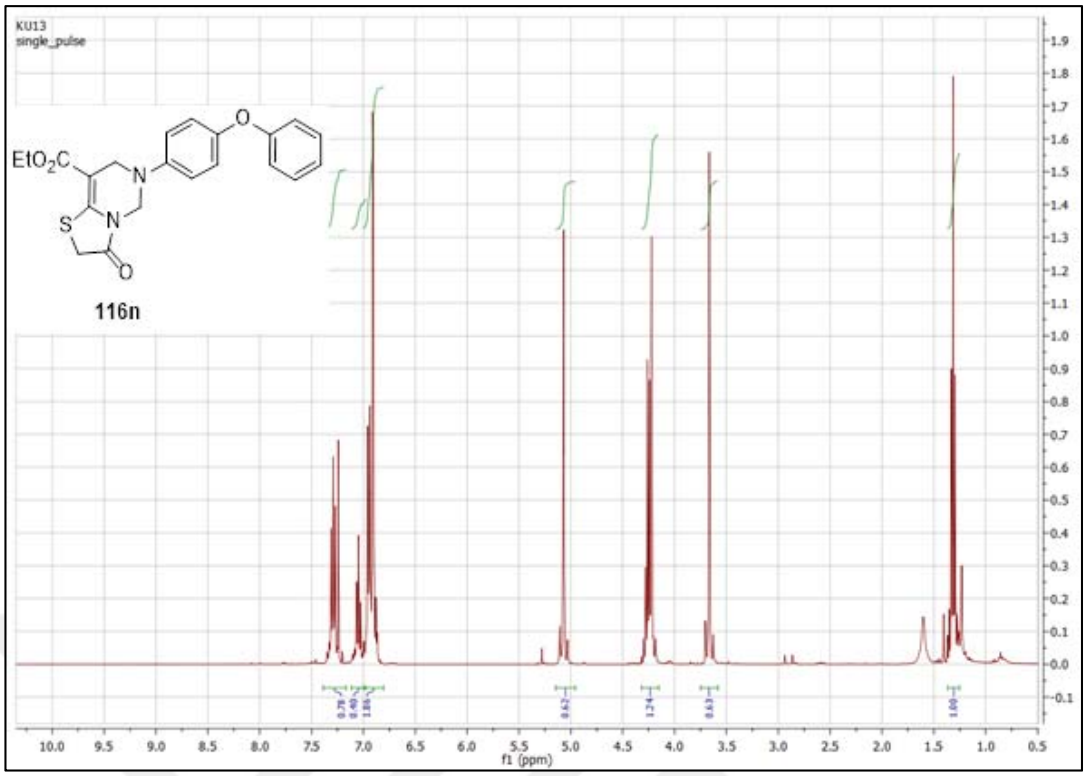

Figure 7.59. ^{1}H-NMR Spectrum of compound **116n**.

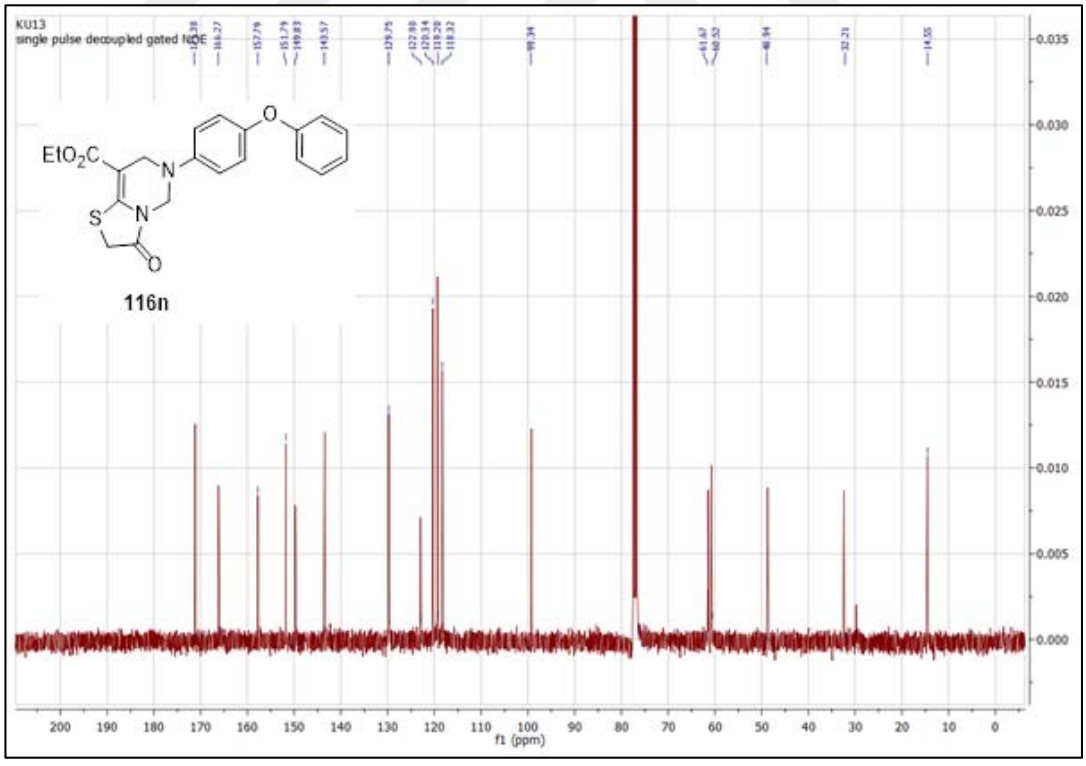

Figure 7.60. ^{13}C-NMR Spectrum of compound **116n**.

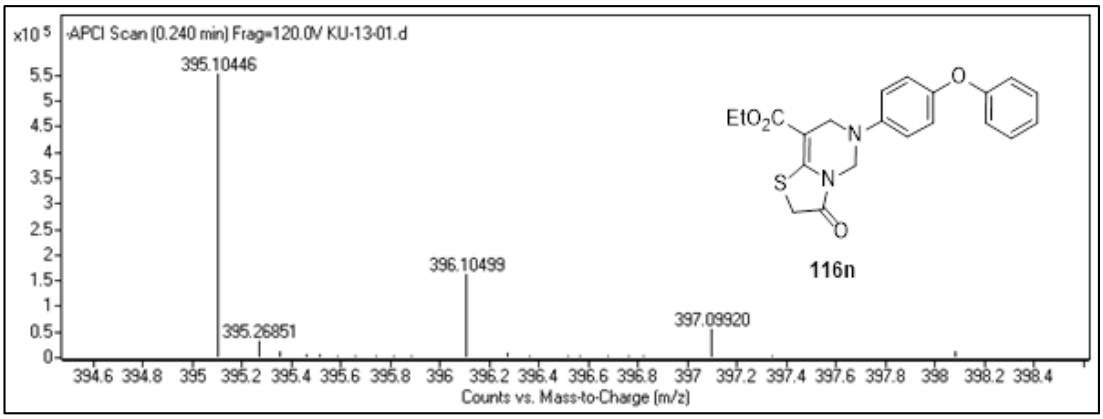

Figure 7.61. HRMS Spectrum of compound **116n**.

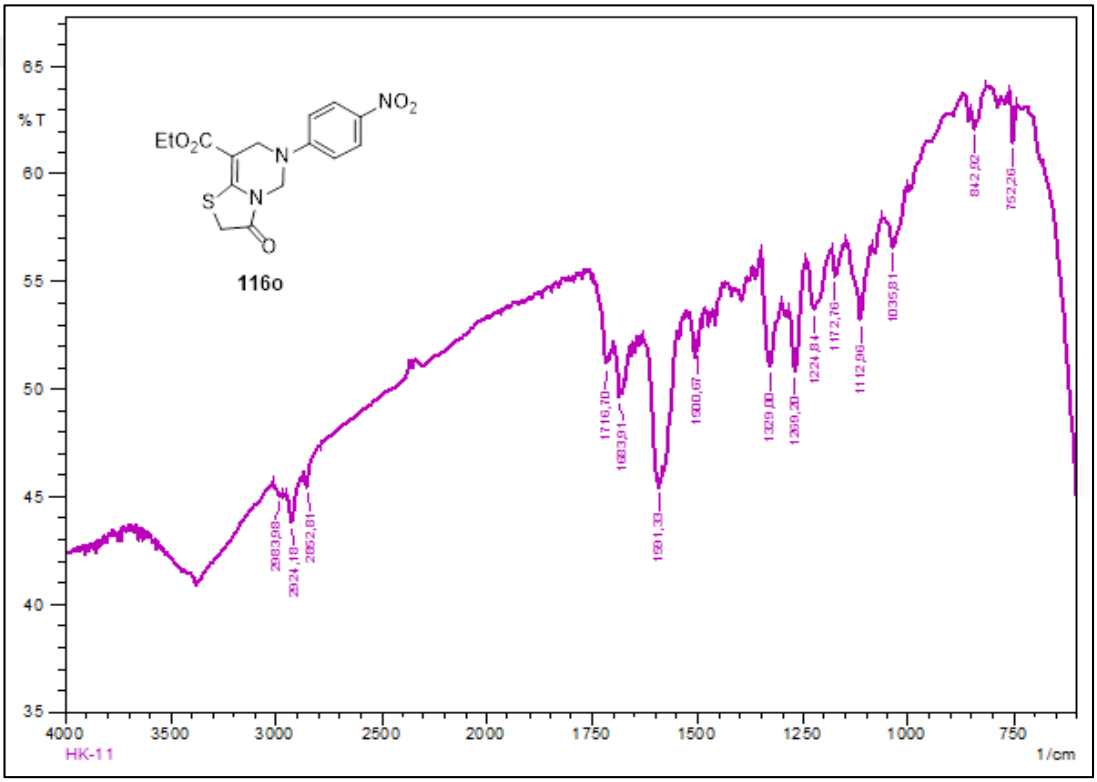

Figure 7.62. IR Spectrum of compound **116o**.

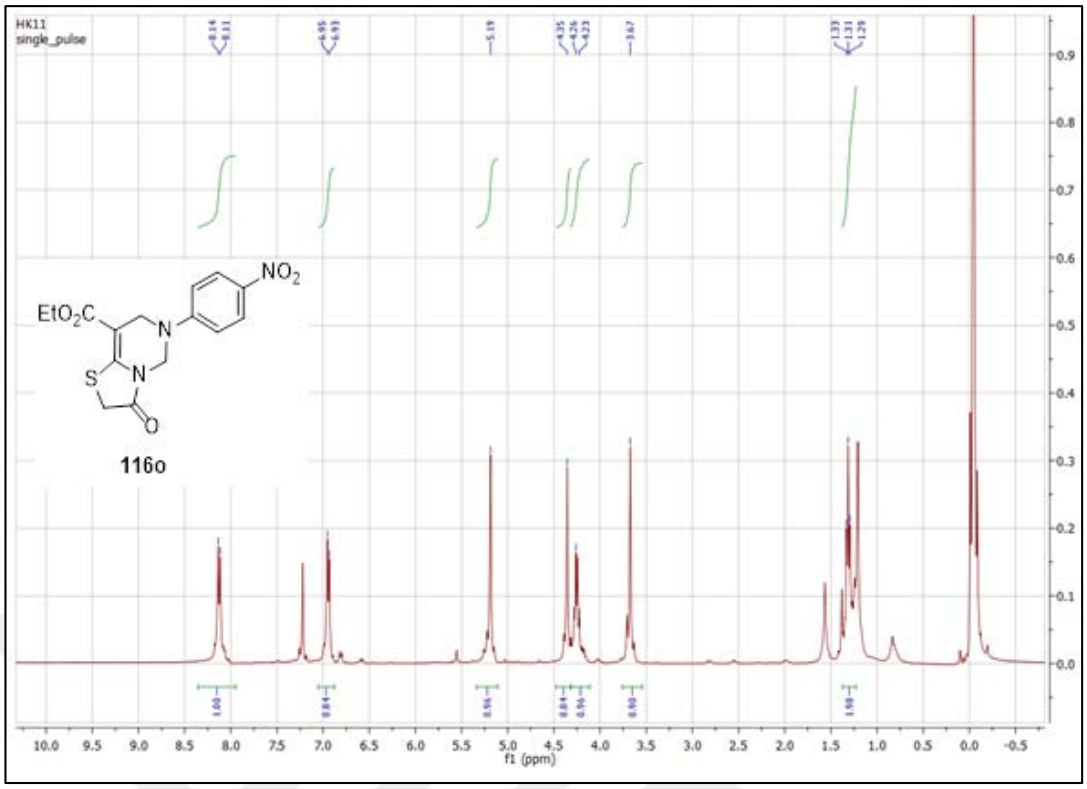

Figure 7.63. ^{1}H-NMR Spectrum of compound **116o**.

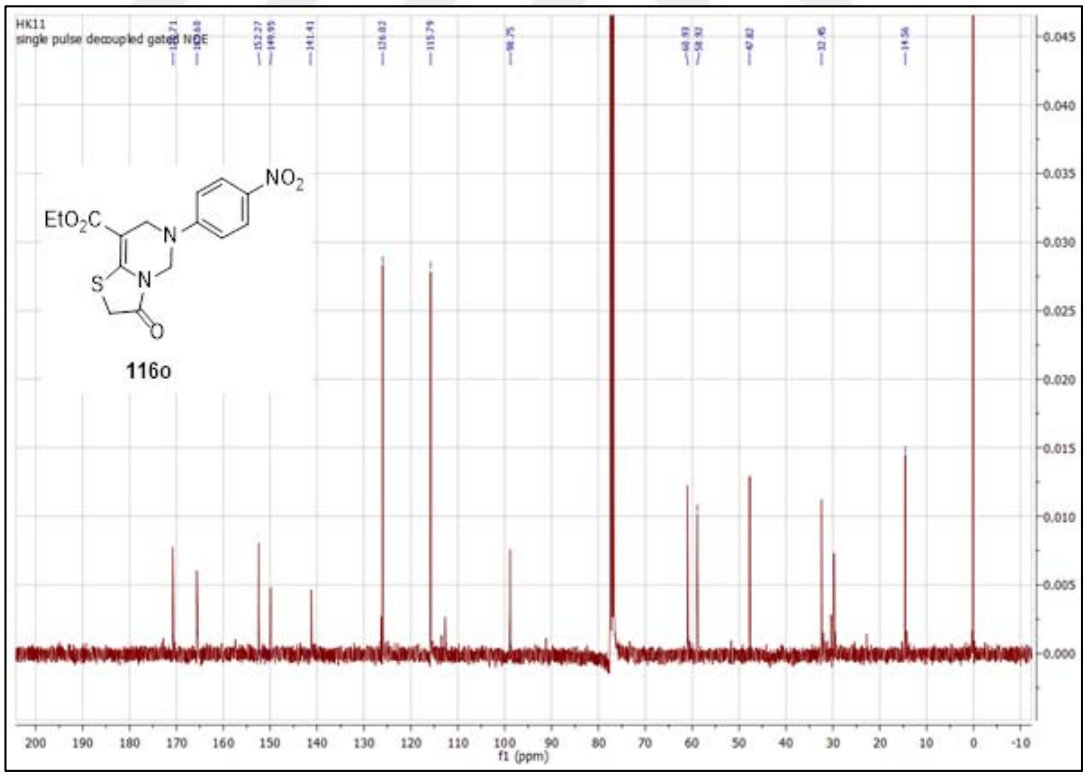

Figure 7.64. ^{13}C-NMR Spectrum of compound **116o**.

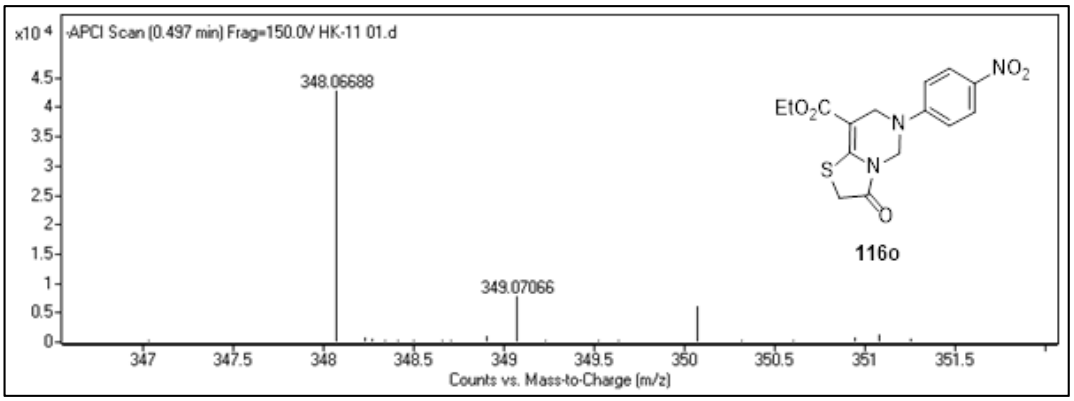

Figure 7.65. HRMS Spectrum of compound **116o**.

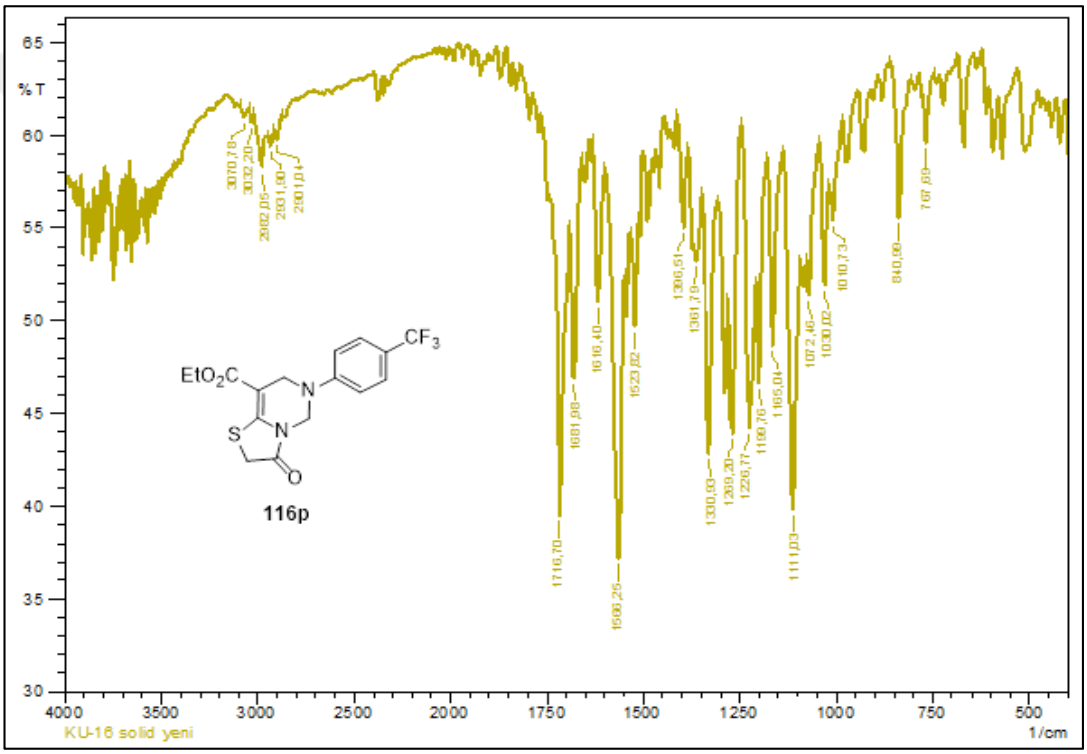

Figure 7.66. IR Spectrum of compound **116p**.

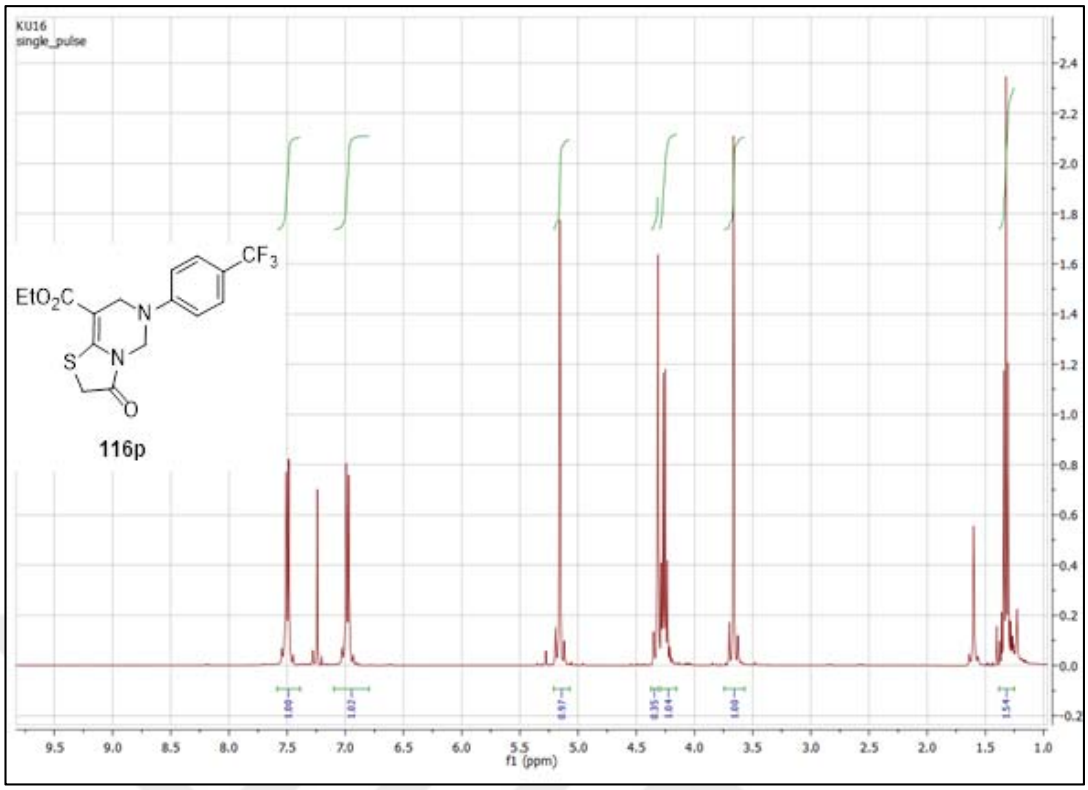

Figure 7.67. ^{1}H-NMR Spectrum of compound **116p**.

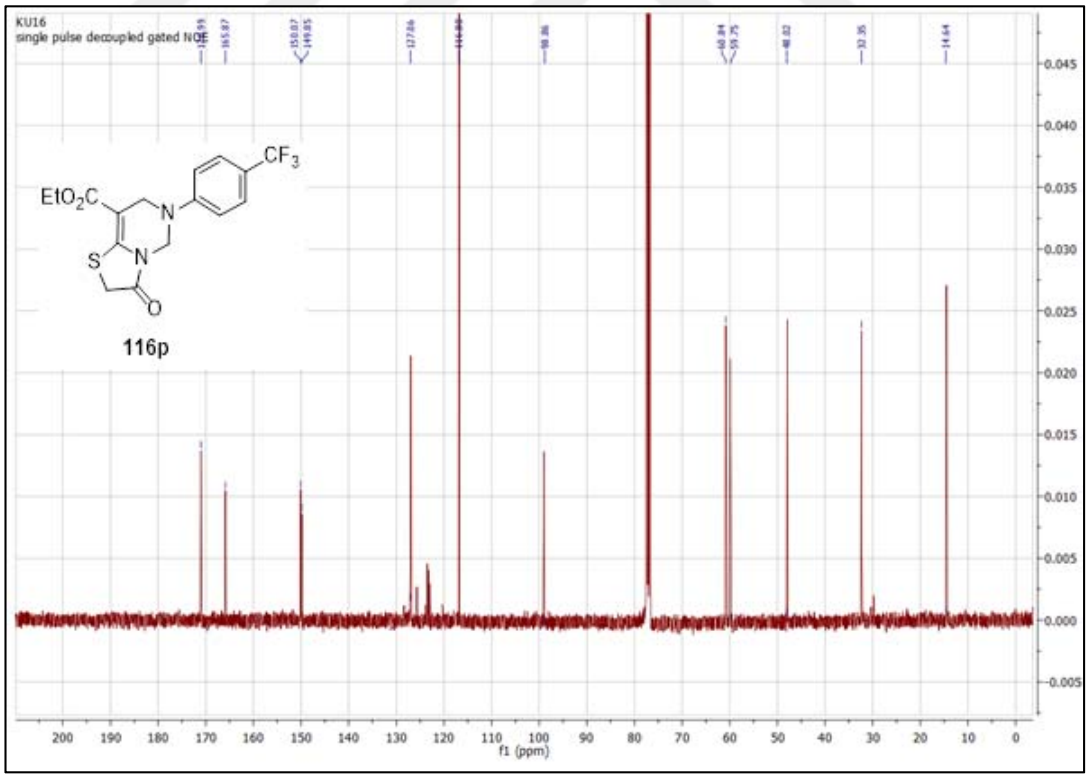

Figure 7.68. ^{13}C-NMR Spectrum of compound **116p**.

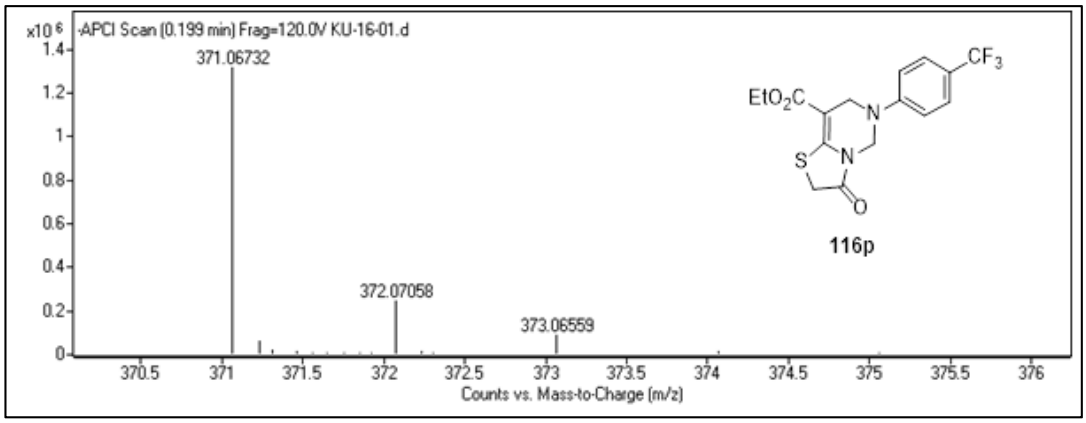

Figure 7.69. HRMS Spectrum of compound **116p**.

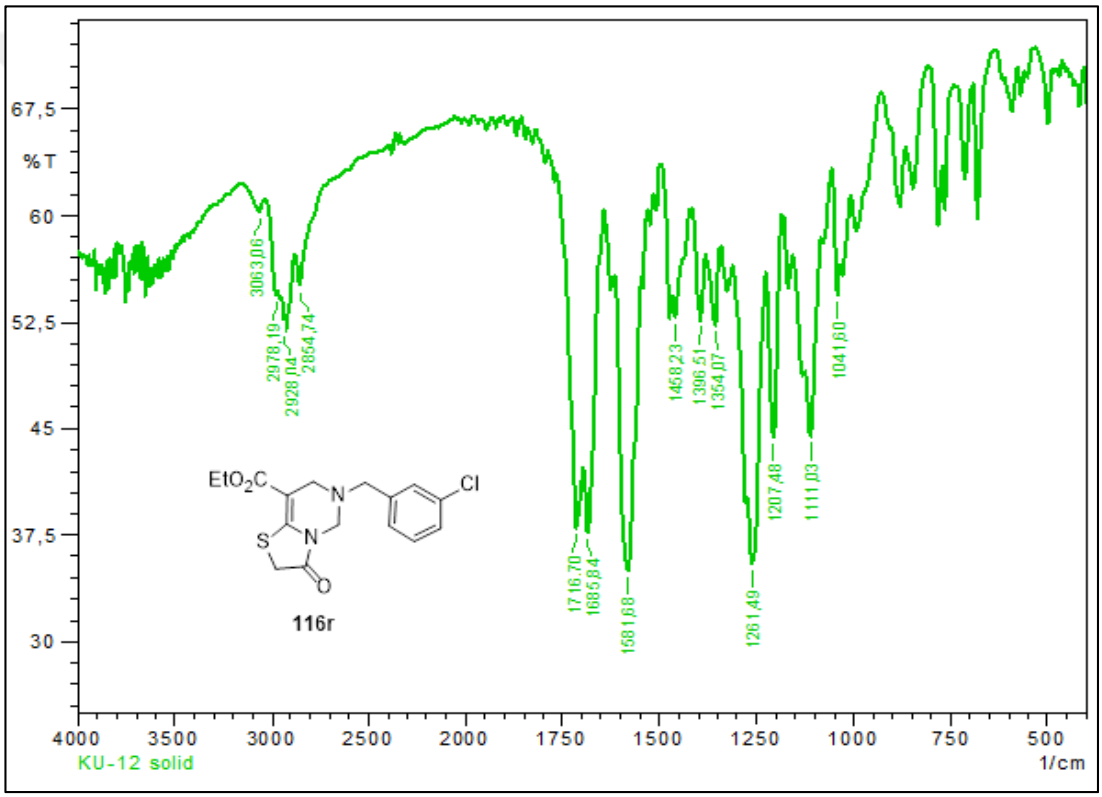

Figure 7.70. IR Spectrum of compound **116r**.

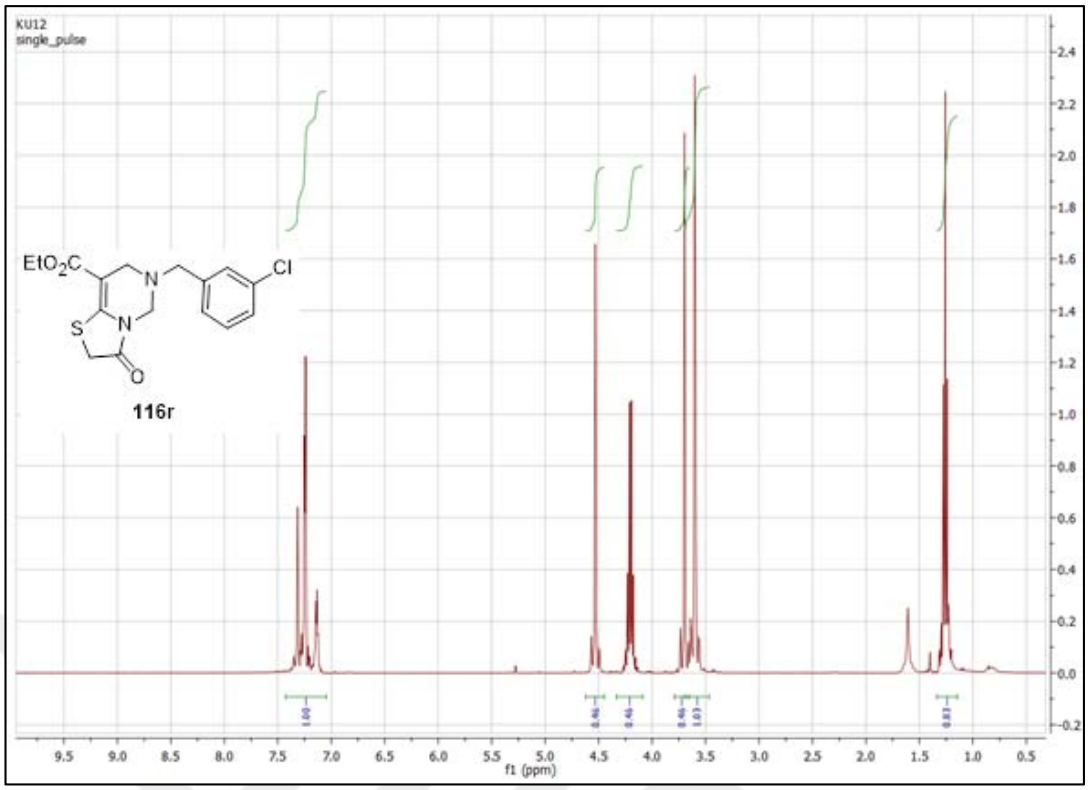

Figure 7.71. ^{1}H-NMR Spectrum of compound **116r**.

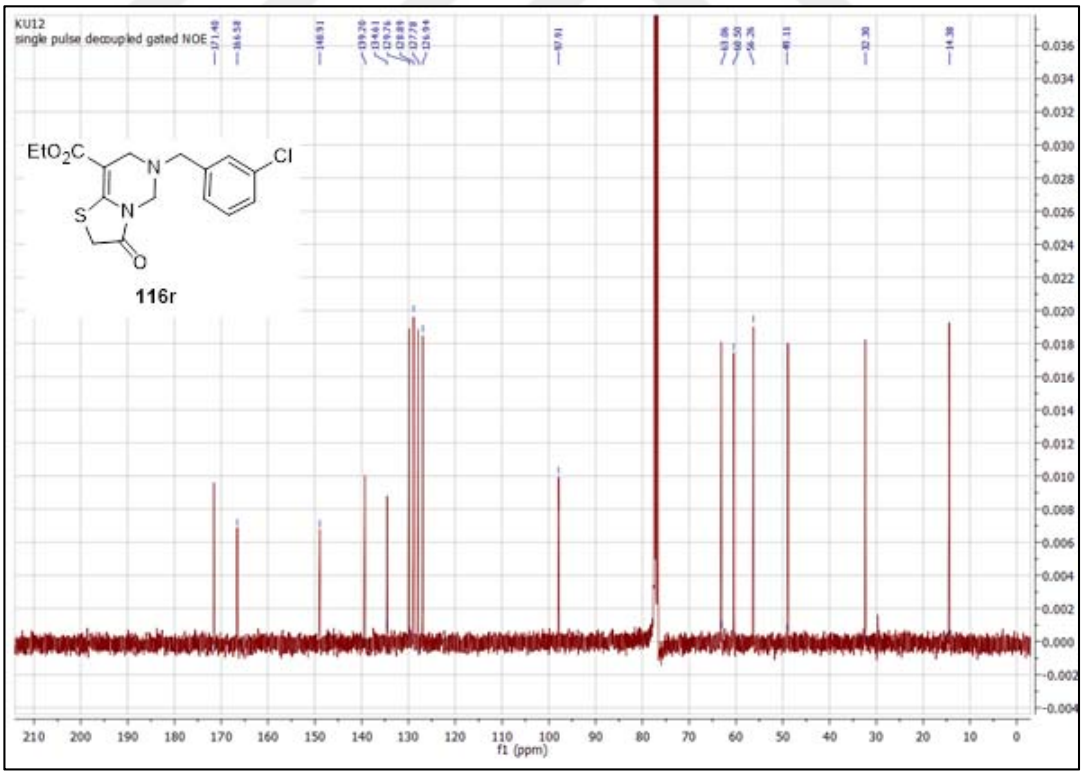

Figure 7.72. ^{13}C-NMR Spectrum of compound **116r**.

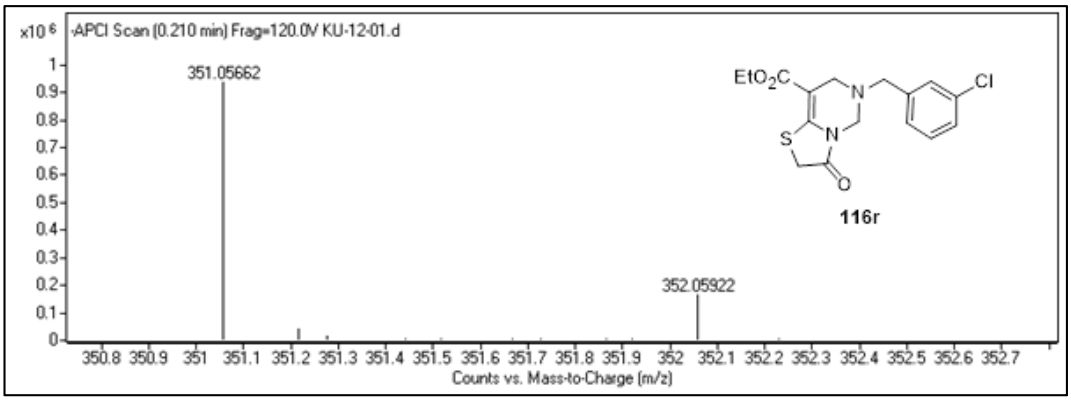

Figure 7.73. HRMS Spectrum of compound **116r**.

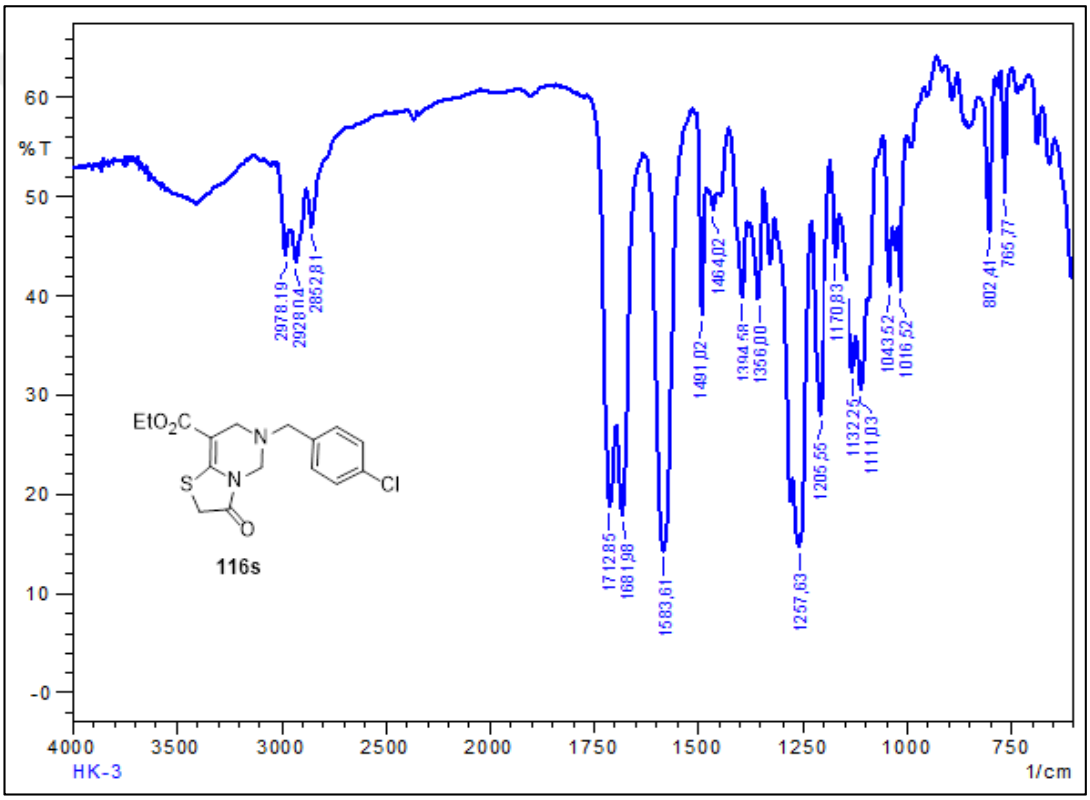

Figure 7.74. IR Spectrum of compound **116s**.

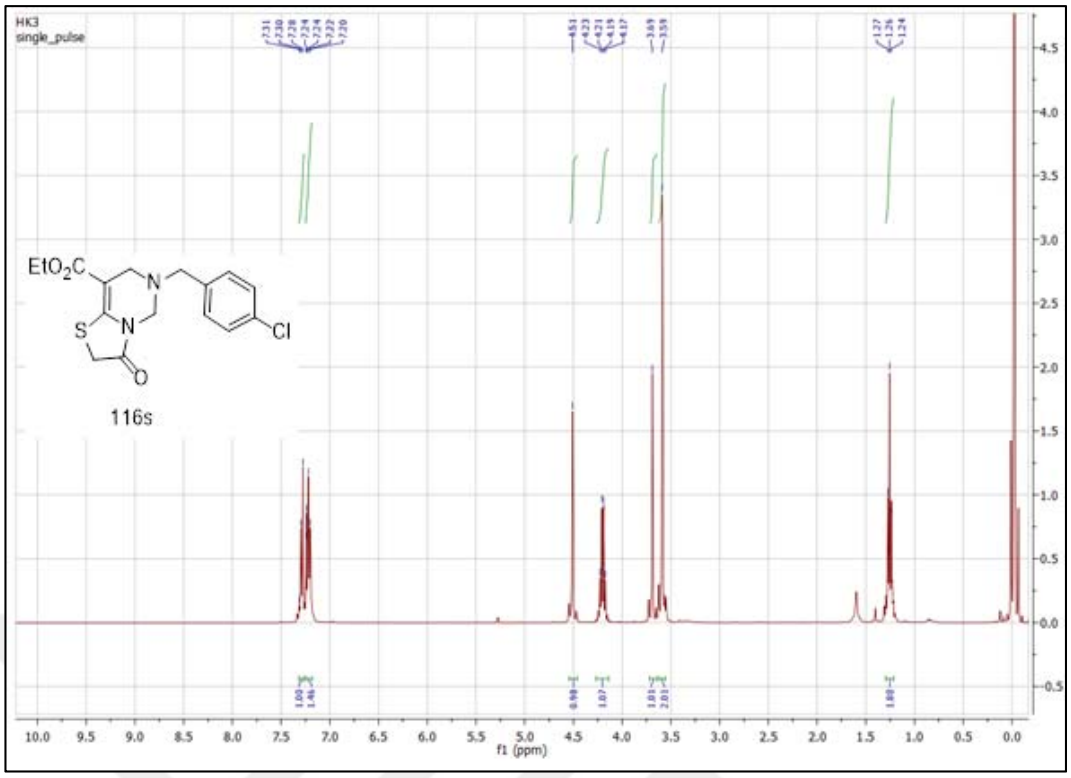

Figure 7.75. ^{1}H-NMR Spectrum of compound **116s**.

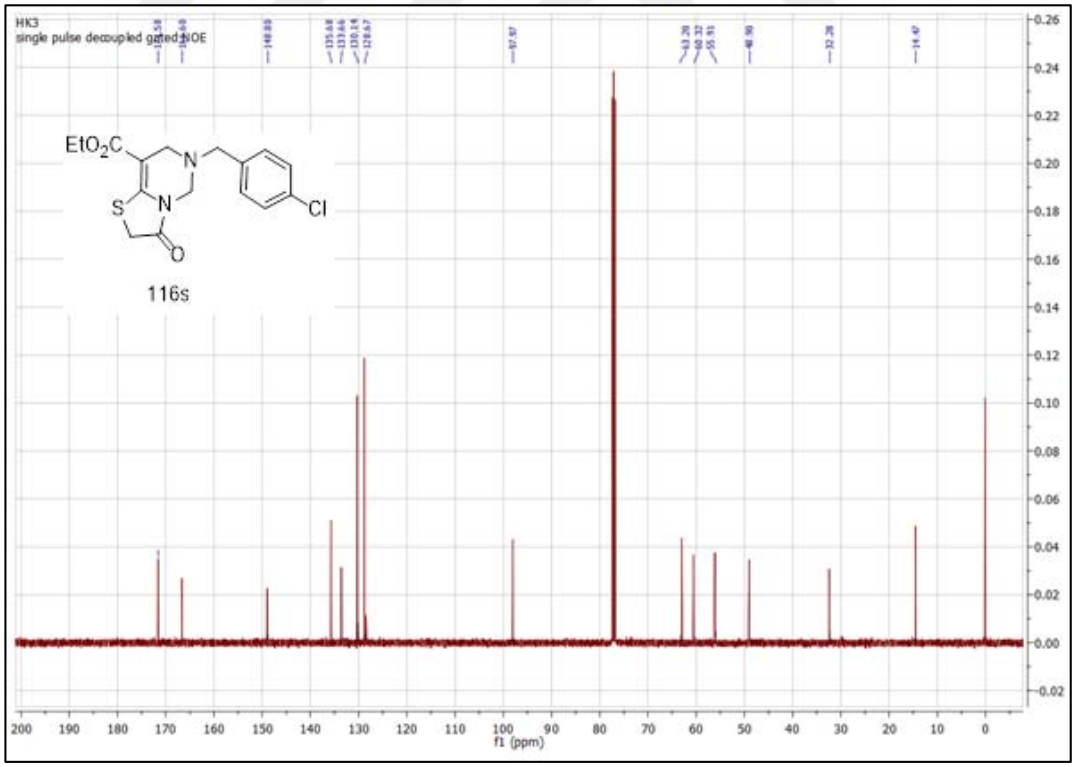

Figure 7.76. ^{13}C-NMR Spectrum of compound **116s**.

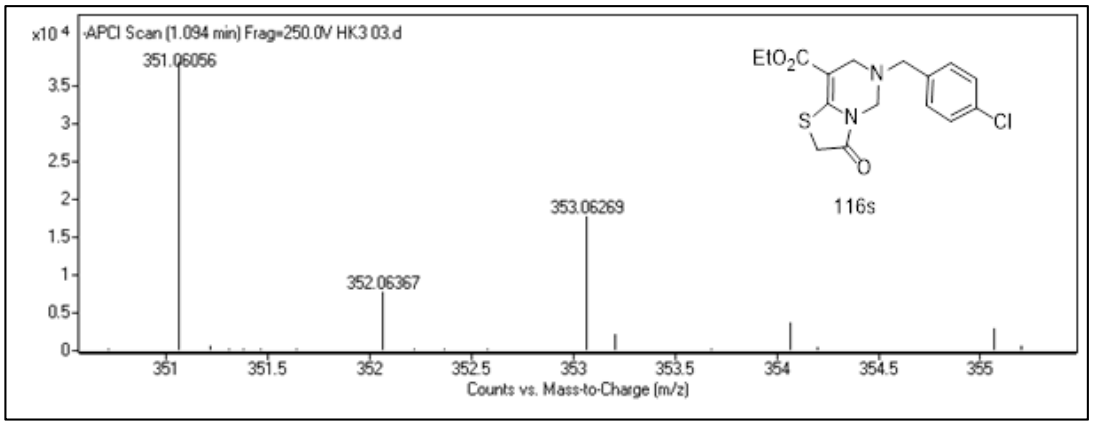

Figure 7.77. HRMS Spectrum of compound **116s**.

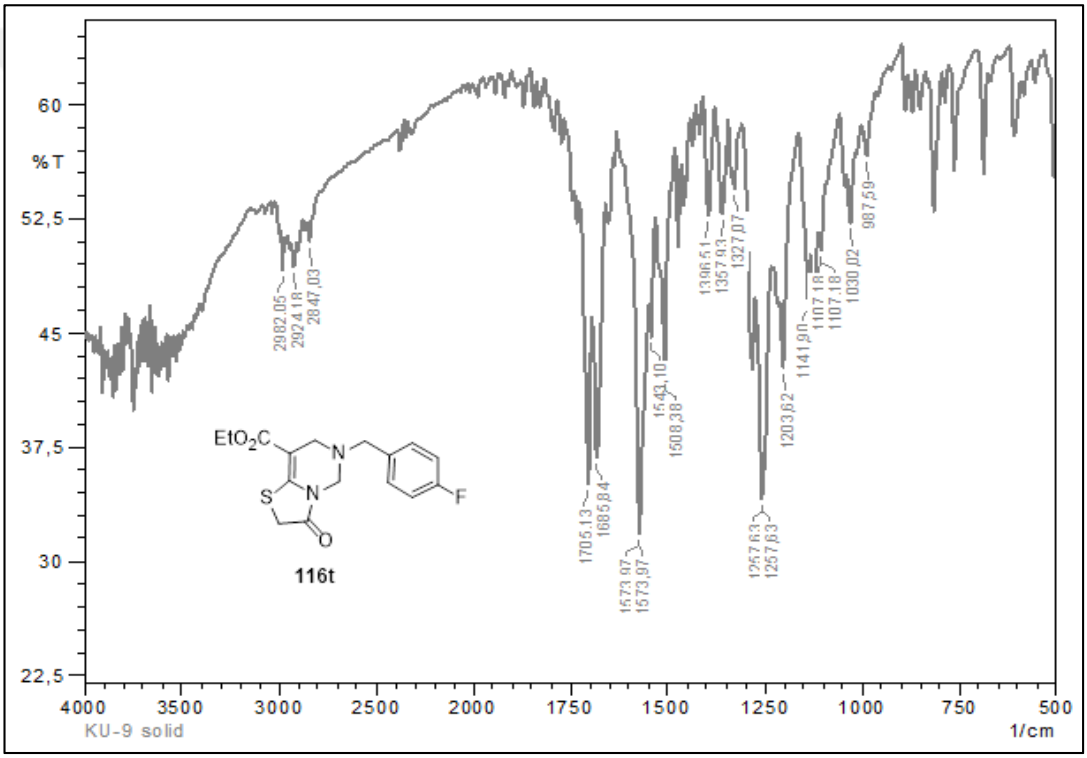

Figure 7.78. IR Spectrum of compound **116t**.

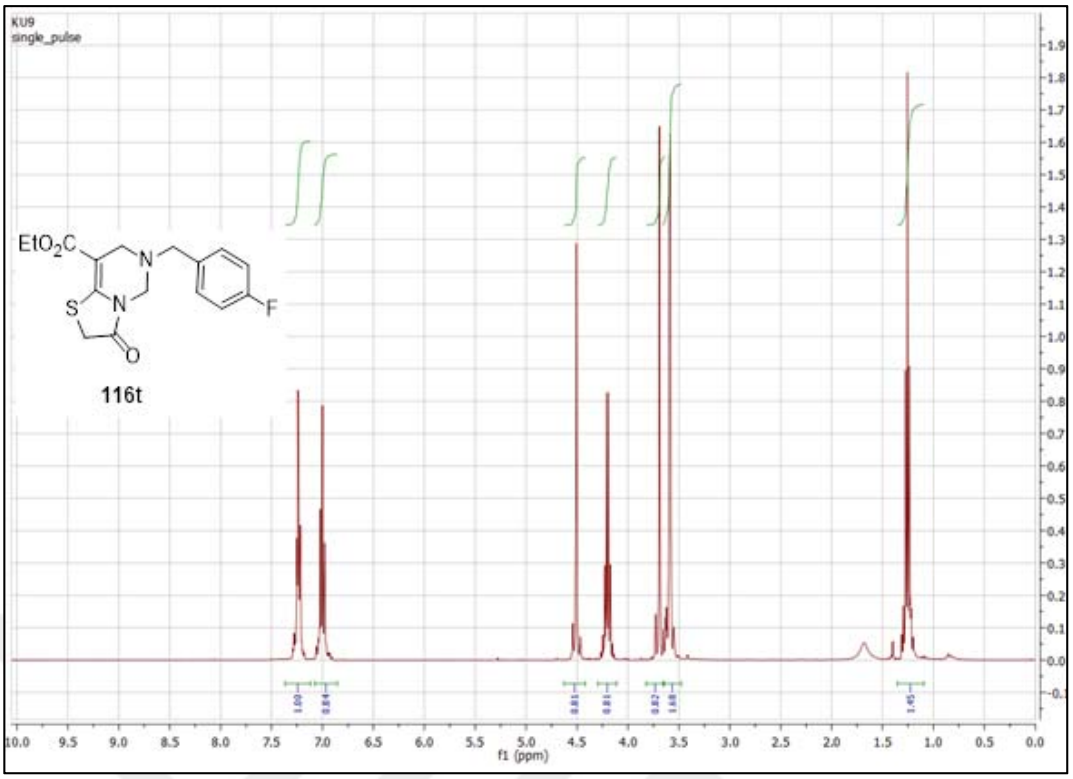

Figure 7.79. ^{1}H-NMR Spectrum of compound **116t**.

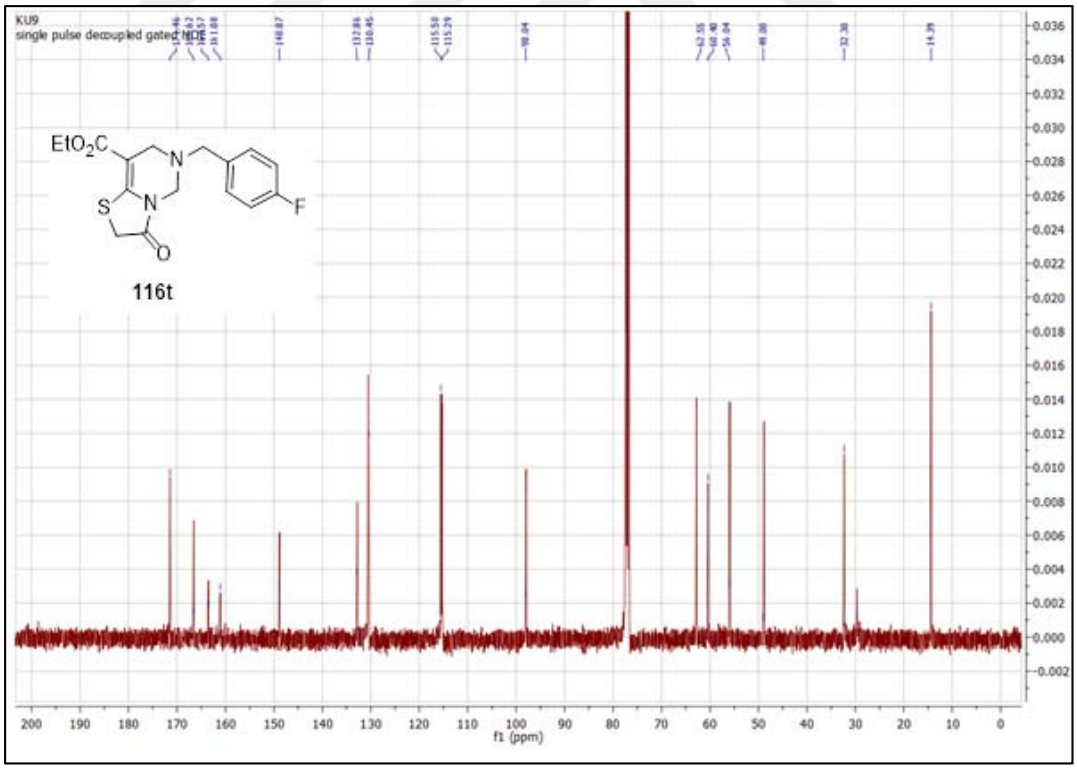

Figure 7.80. ^{13}C-NMR Spectrum of compound **116t**.

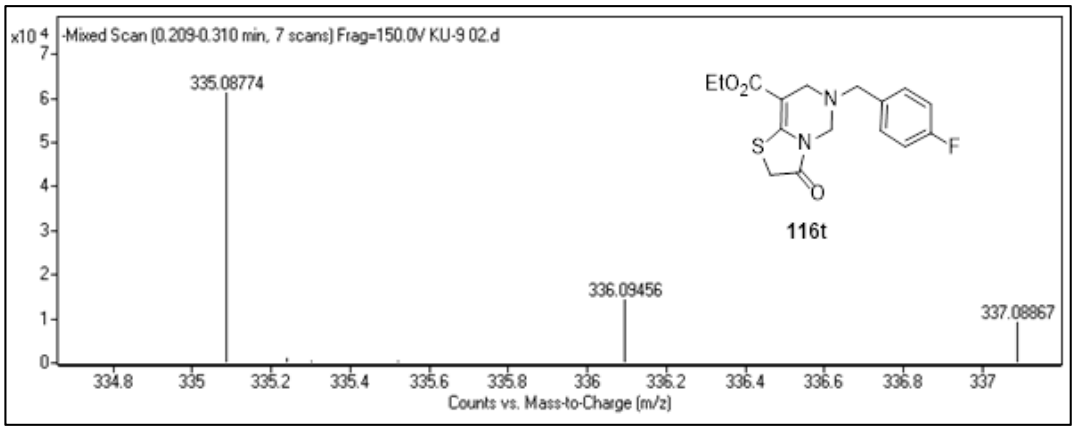

Figure 7.81. HRMS Spectrum of compound **116t**.

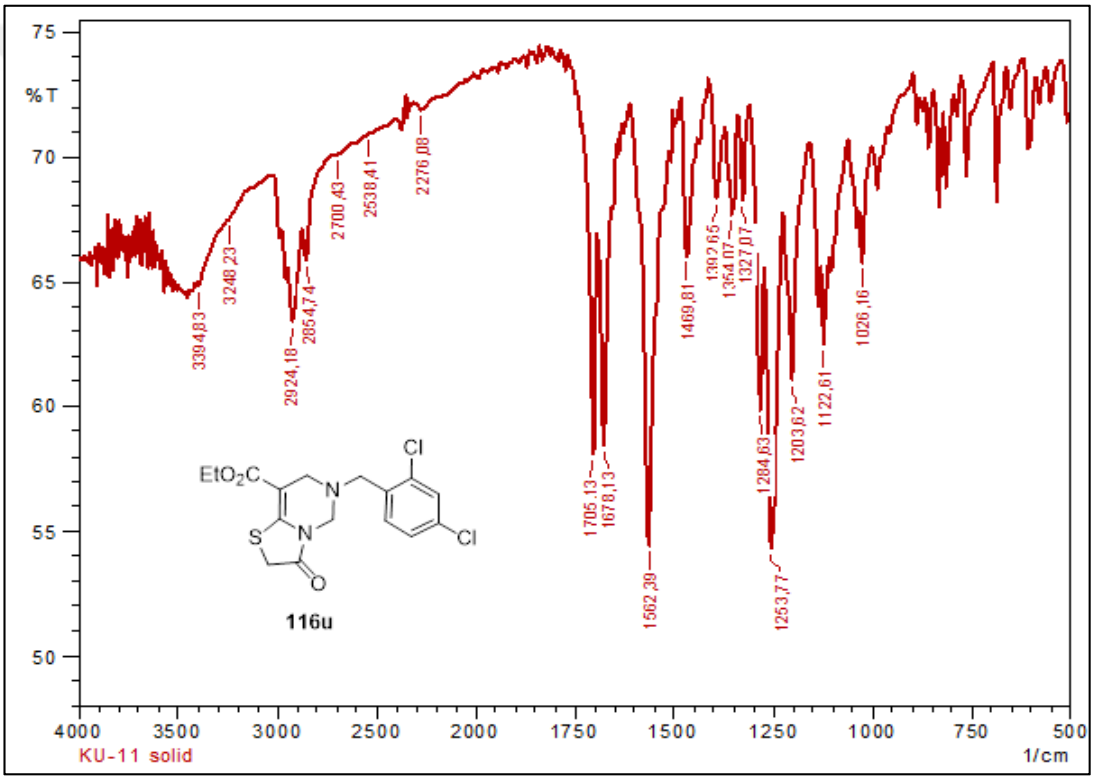

Figure 7.82. IR Spectrum of compound **116u**.

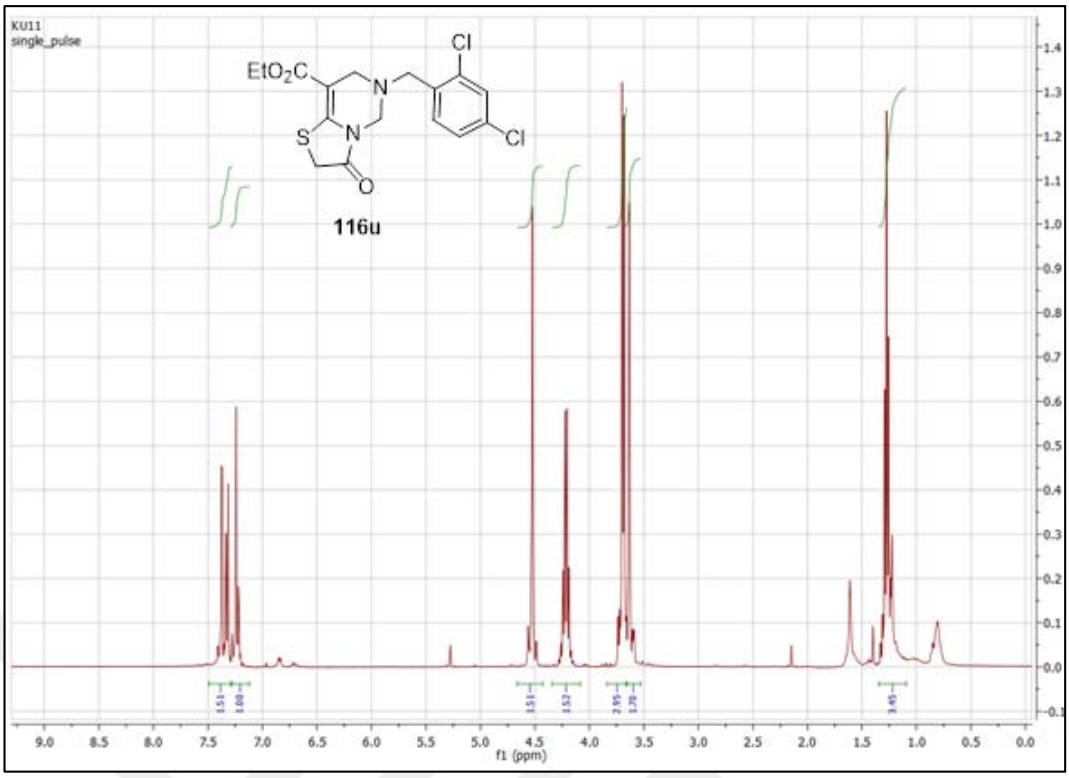

Figure 7.83. ^{1}H-NMR Spectrum of compound **116u**.

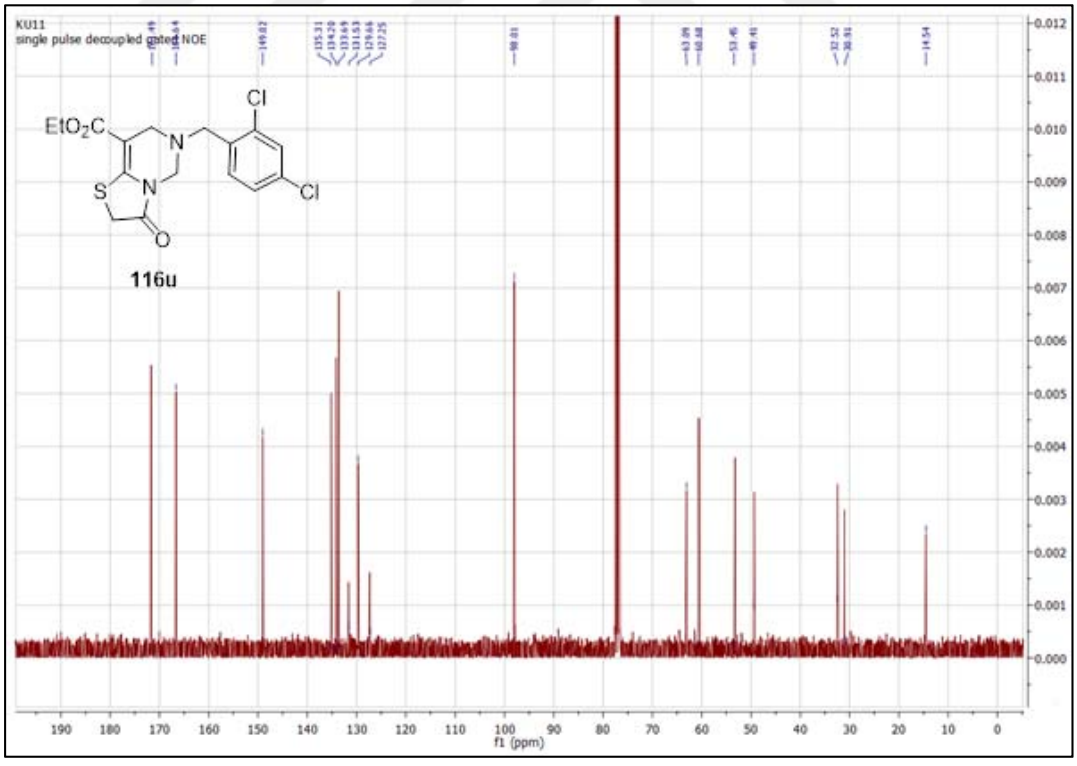

Figure 7.84. ^{13}C-NMR Spectrum of compound **116u**.

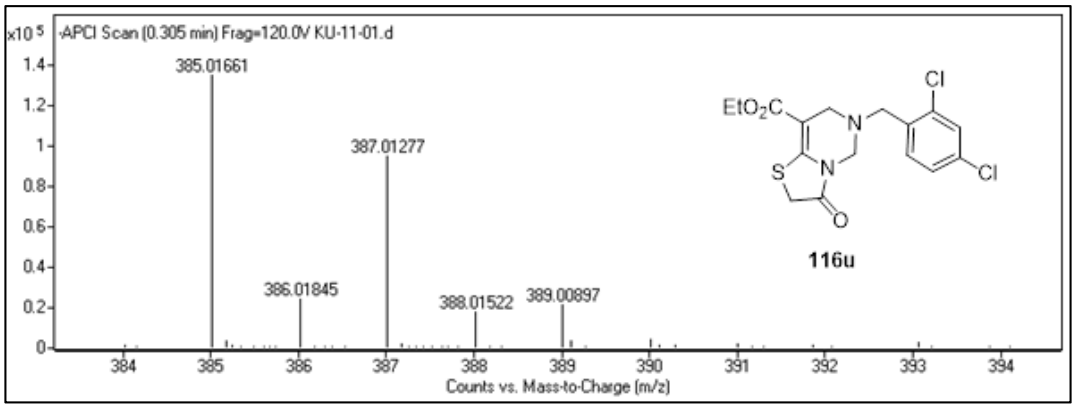

Figure 7.85. HRMS Spectrum of compound **116u**.

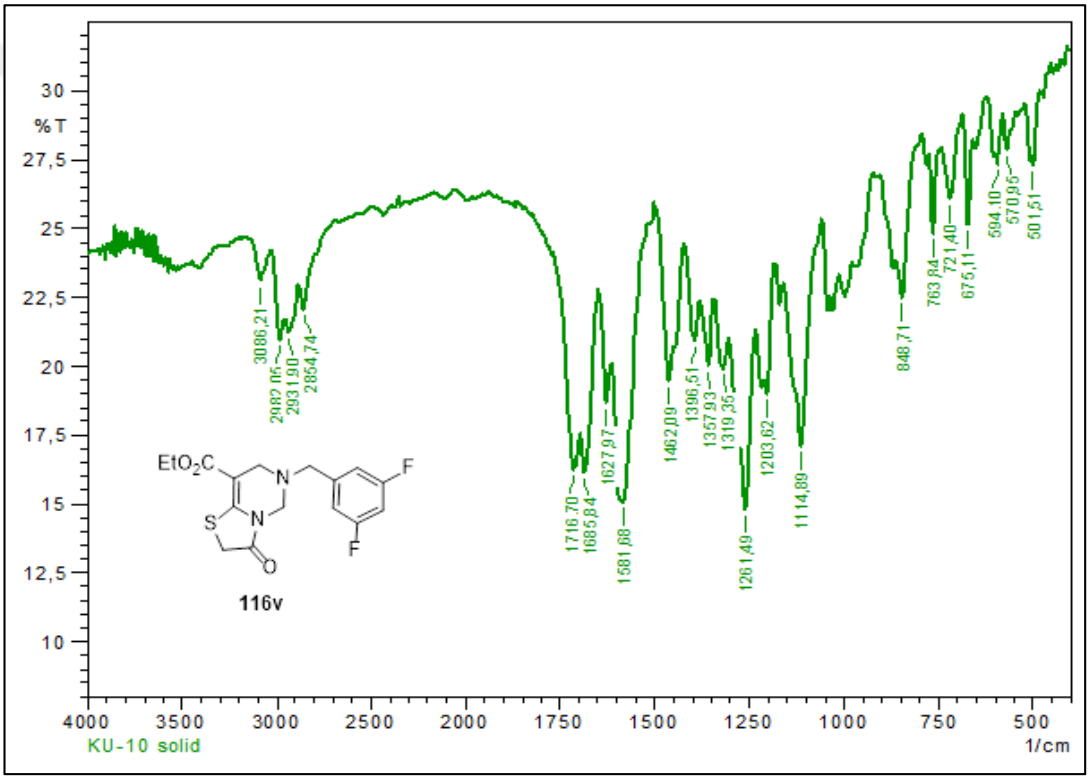

Figure 7.86. IR Spectrum of compound **116v**.

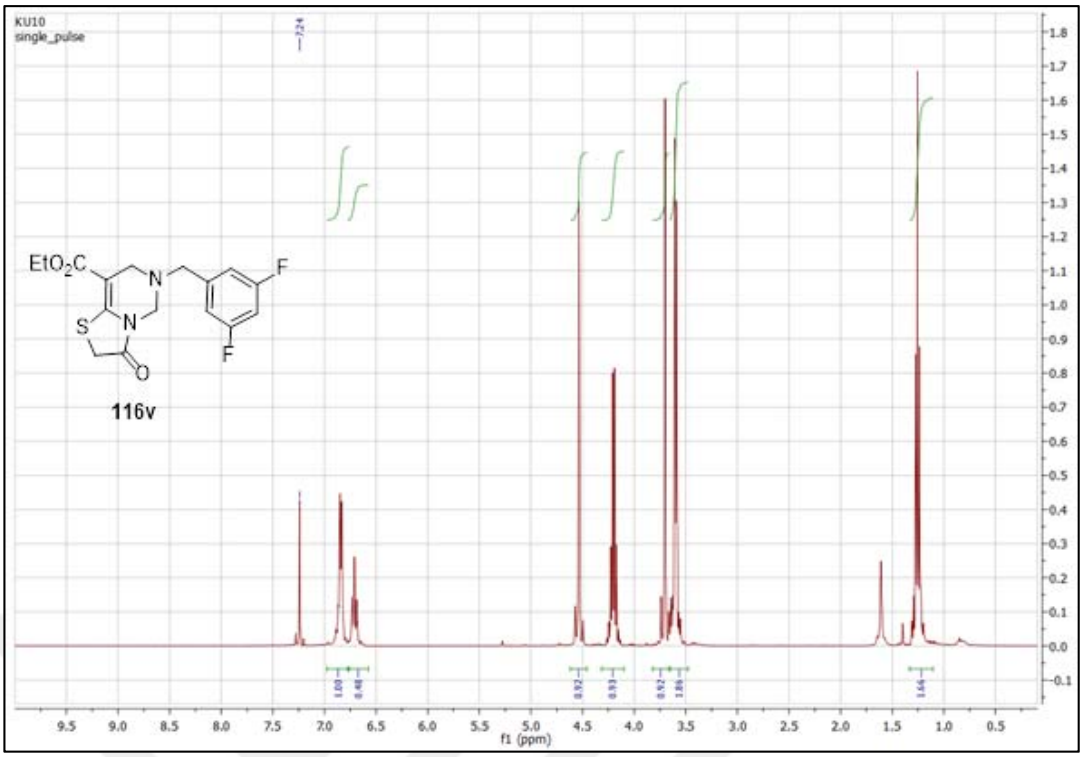

Figure 7.87. ^{1}H-NMR Spectrum of compound **116v**.

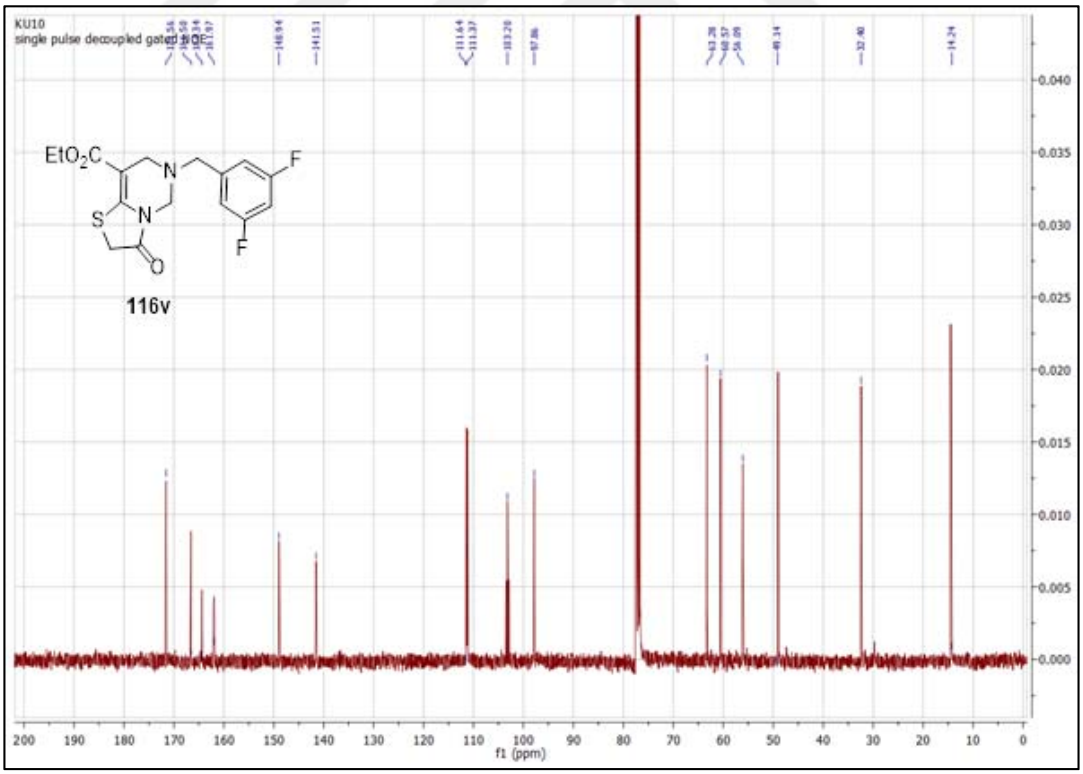

Figure 7.88. ^{13}C-NMR Spectrum of compound **116v**.

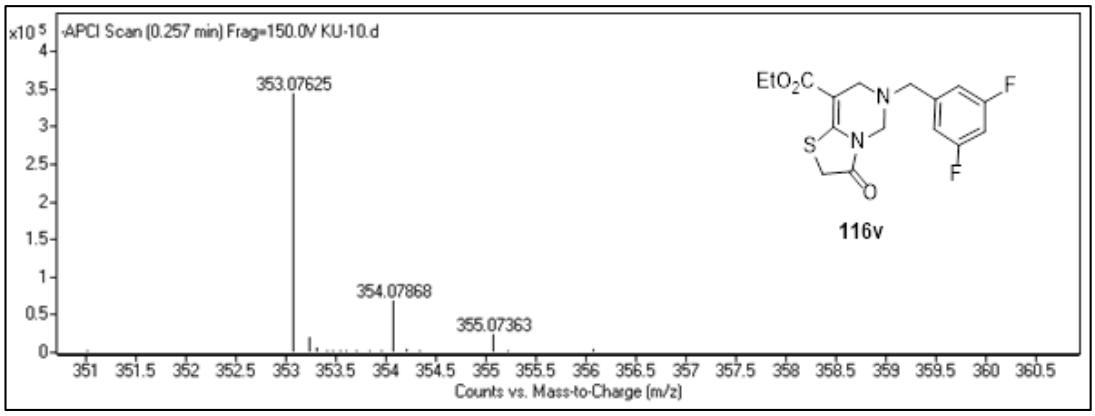

Figure 7.89. HRMS Spectrum of compound **116v**.

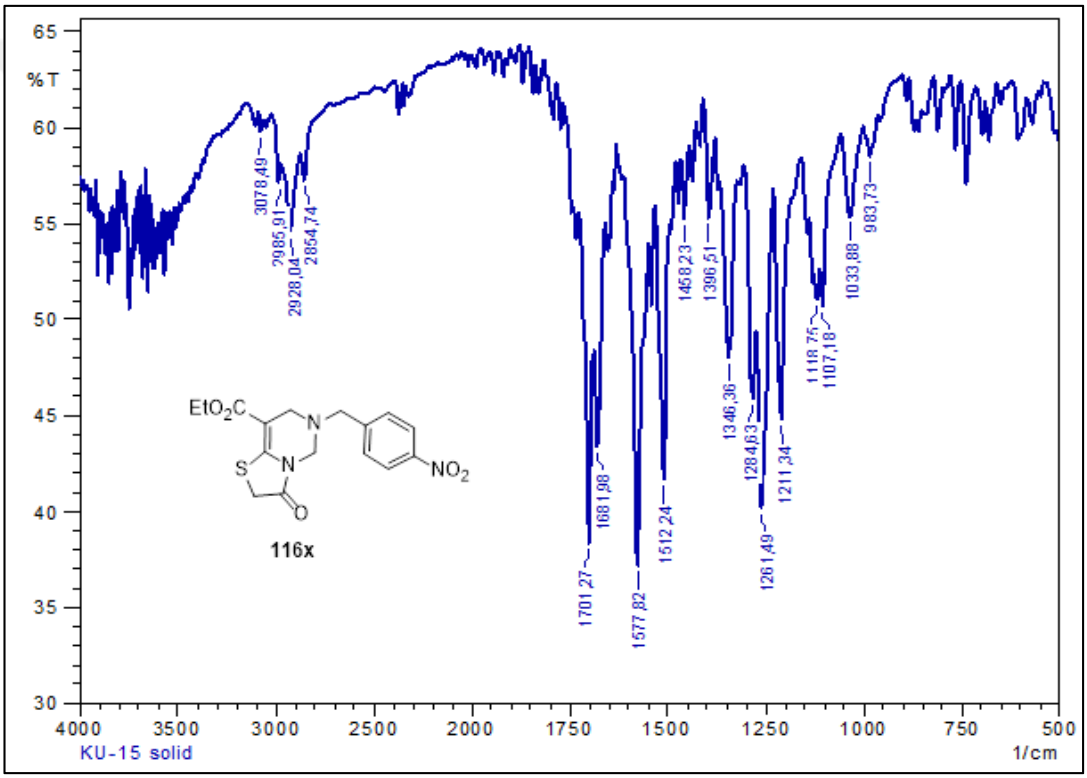

Figure 7.90. IR Spectrum of compound **116x**.

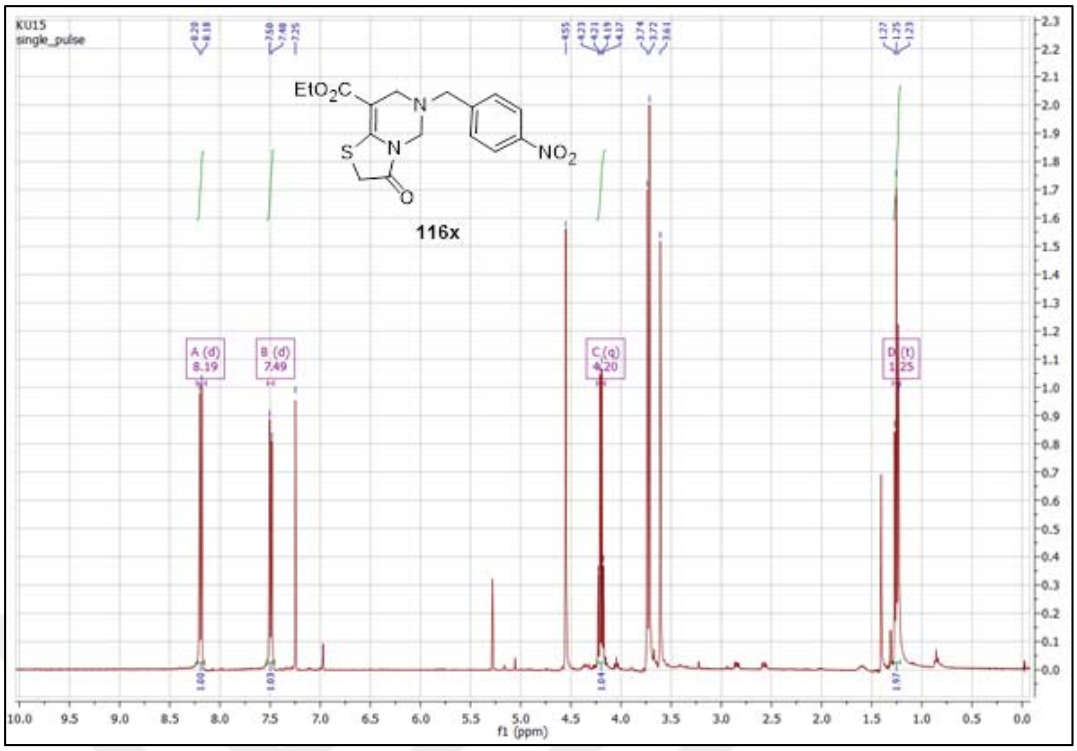

Figure 7.91. ^{1}H-NMR Spectrum of compound **116x**.

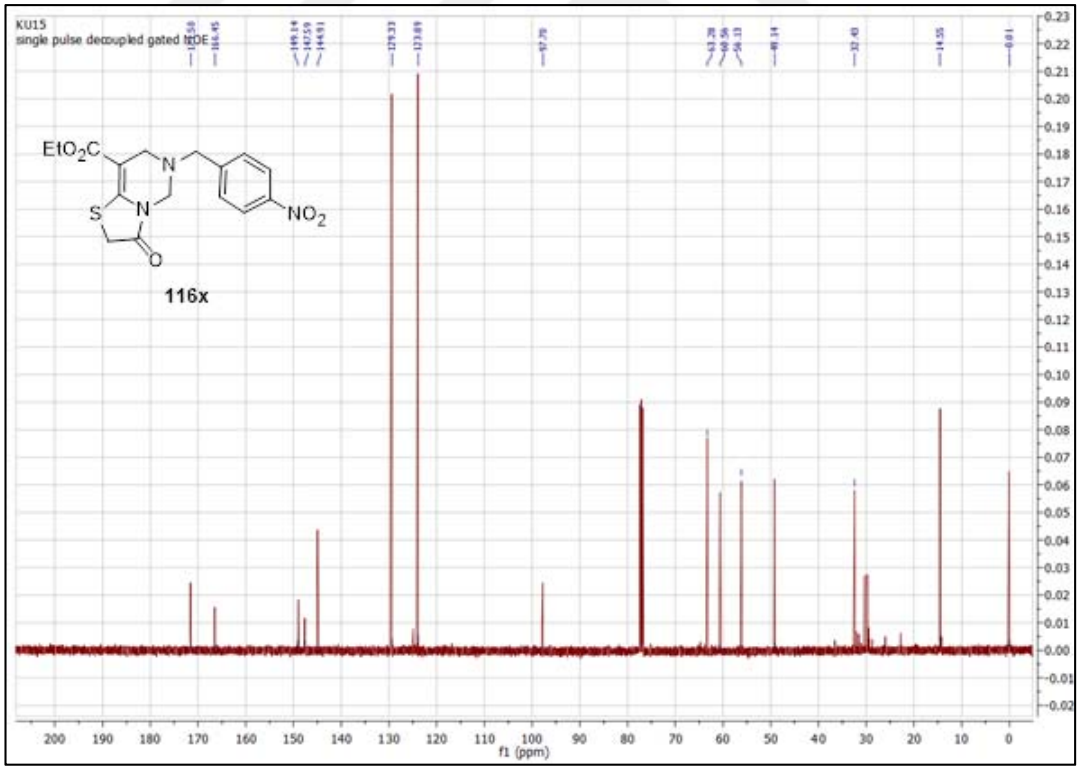

Figure 7.92. ^{13}C-NMR Spectrum of compound **116x**.

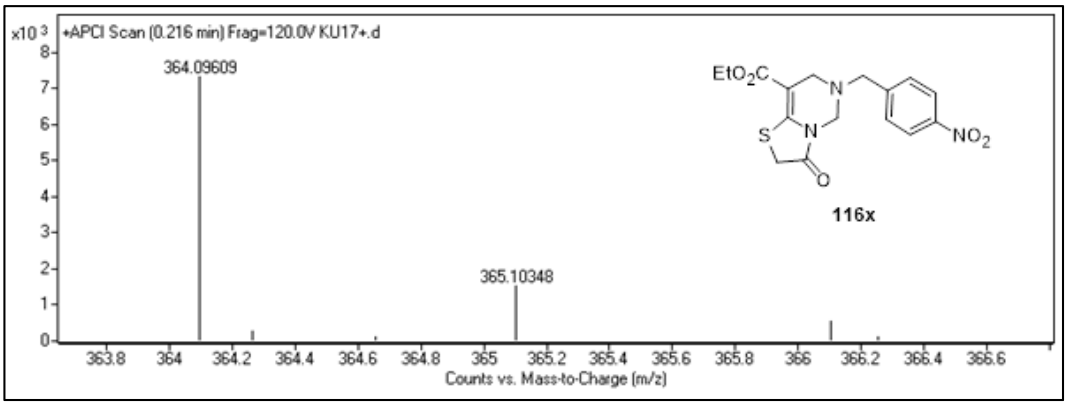

Figure 7.93. HRMS Spectrum of compound **116x**.

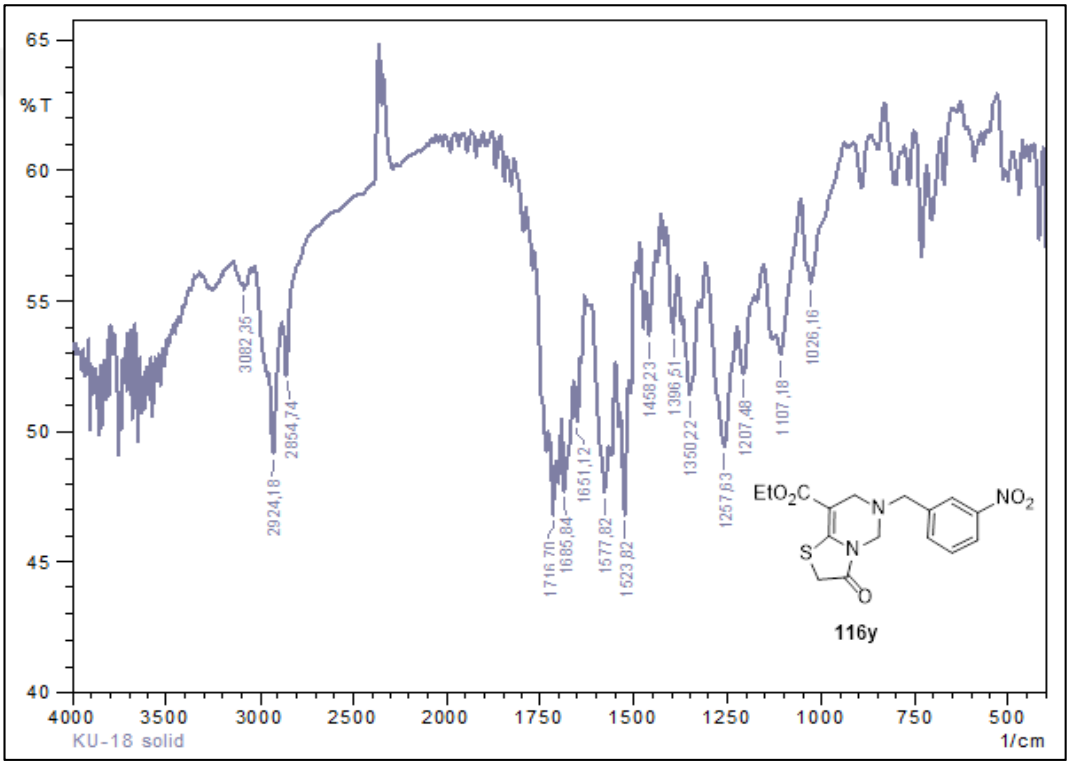

Figure 7.94. IR Spectrum of compound **116y**.

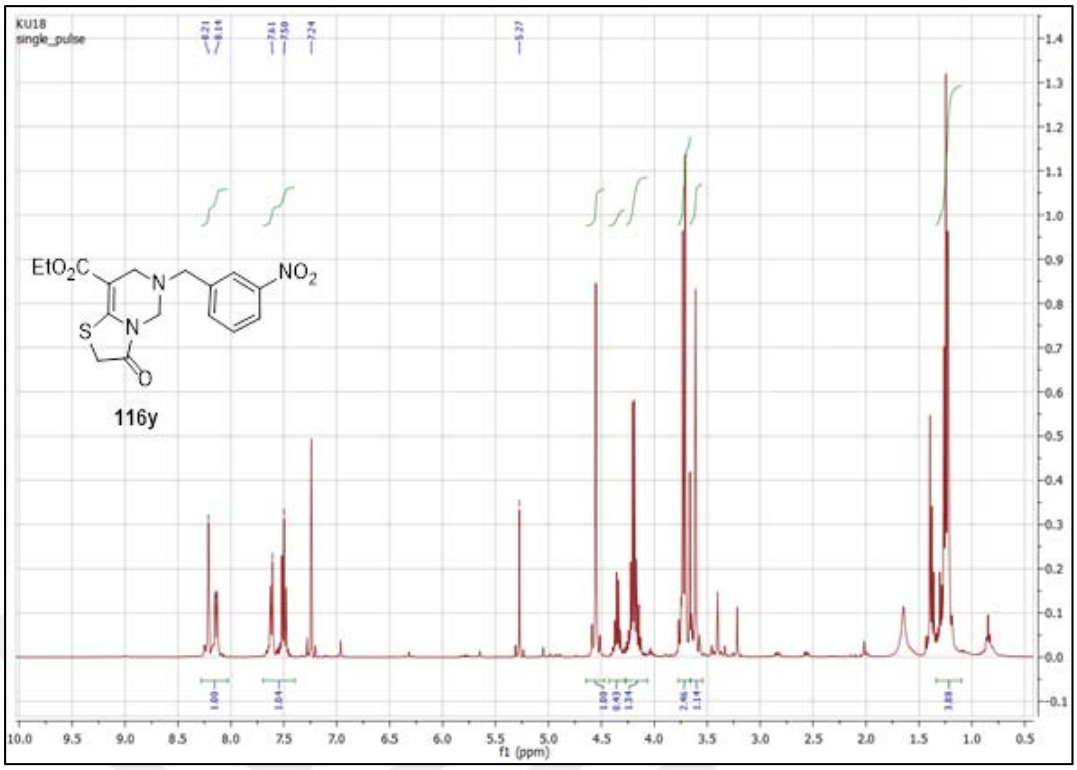

Figure 7.95. ^{1}H-NMR Spectrum of compound **116y**.

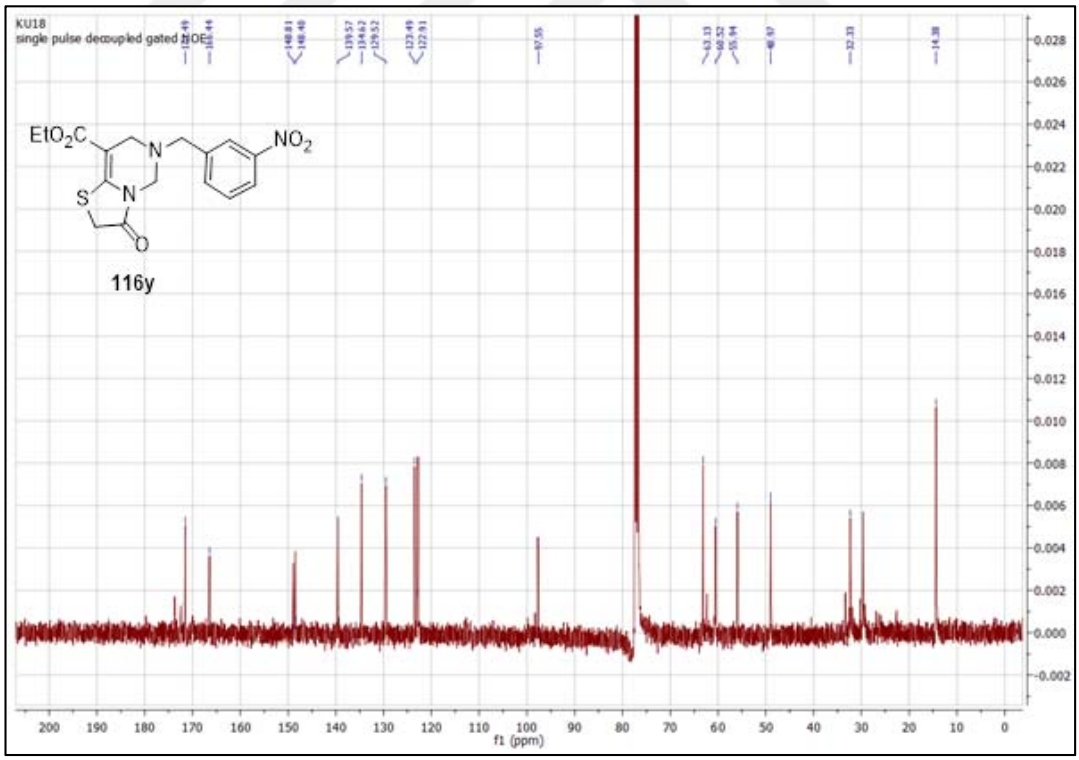

Figure 7.96. ^{13}C-NMR Spectrum of compound **116y**.

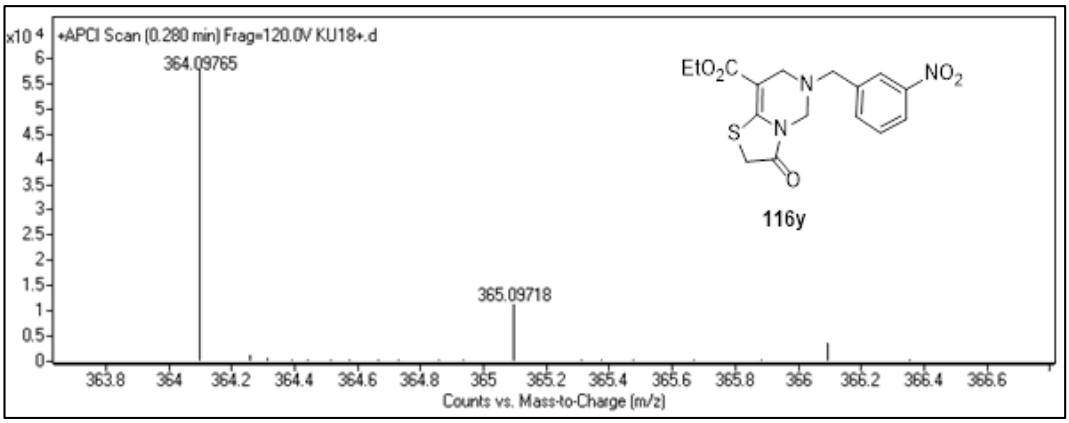

Figure 7.97. HRMS Spectrum of compound **116y**.

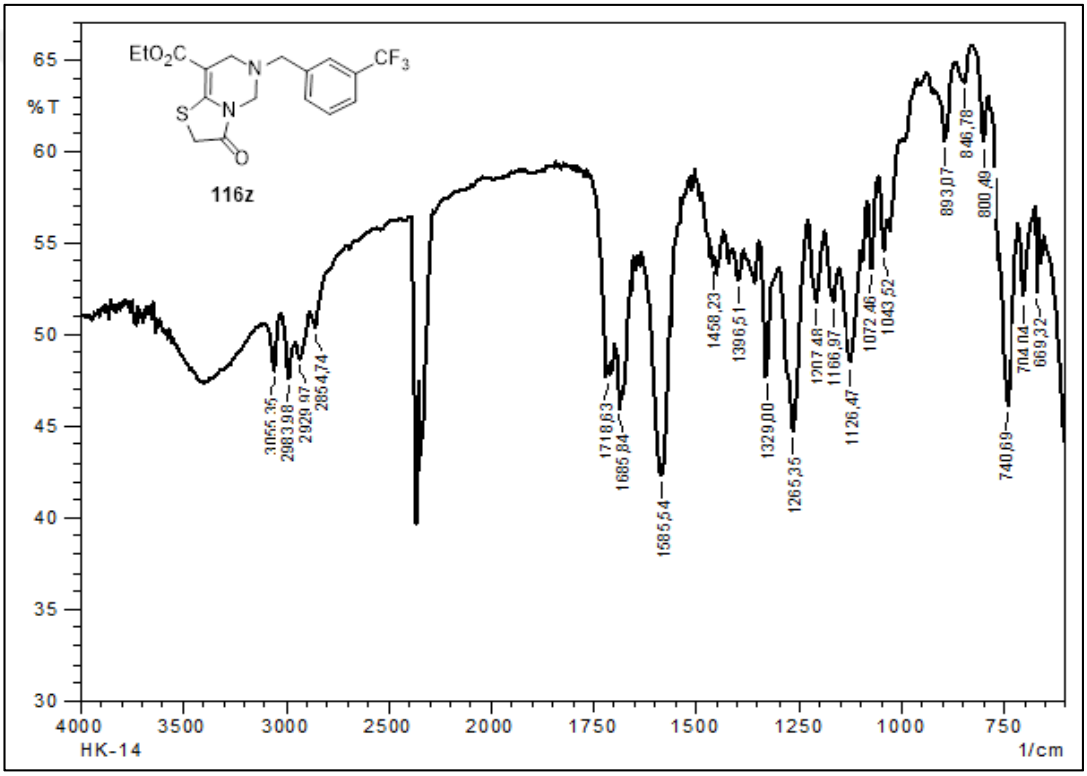

Figure 7.98. IR Spectrum of compound **116z**.

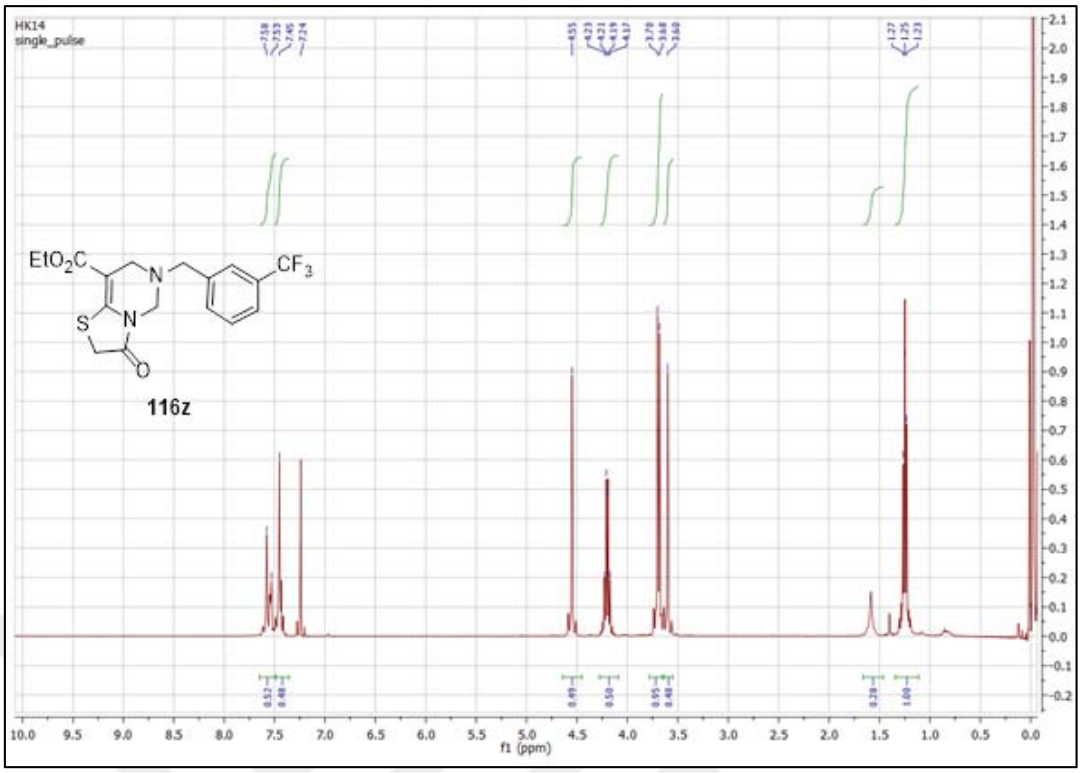

Figure 7.99. ^{1}H-NMR Spectrum of compound **116z**.

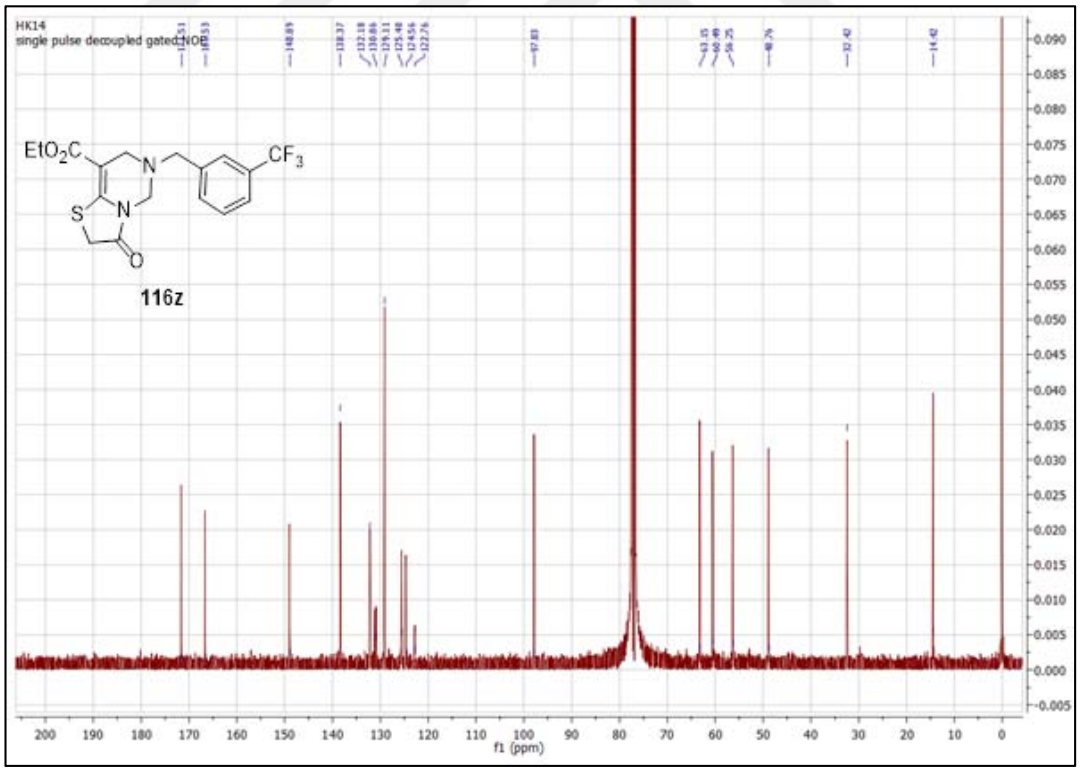

Figure 7.100. ^{13}C-NMR Spectrum of compound **116z**.

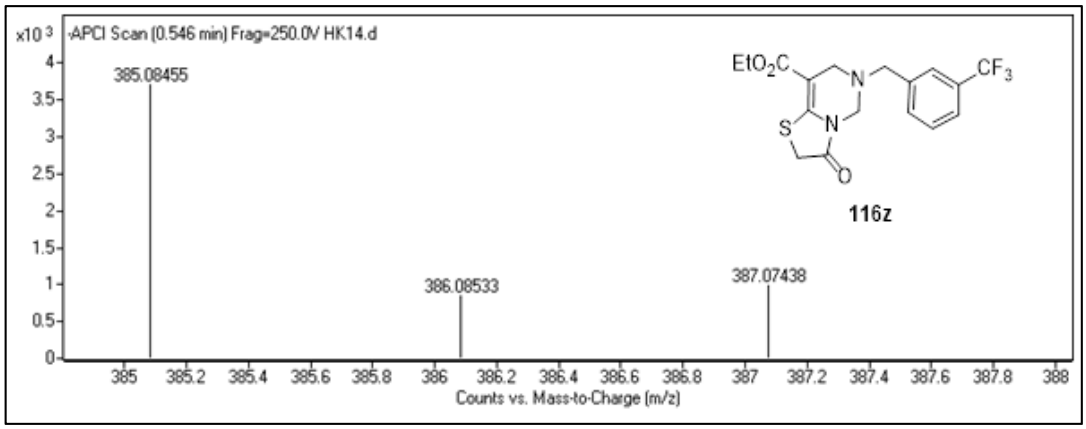

Figure 7.101. HRMS Spectrum of compound **116z**.

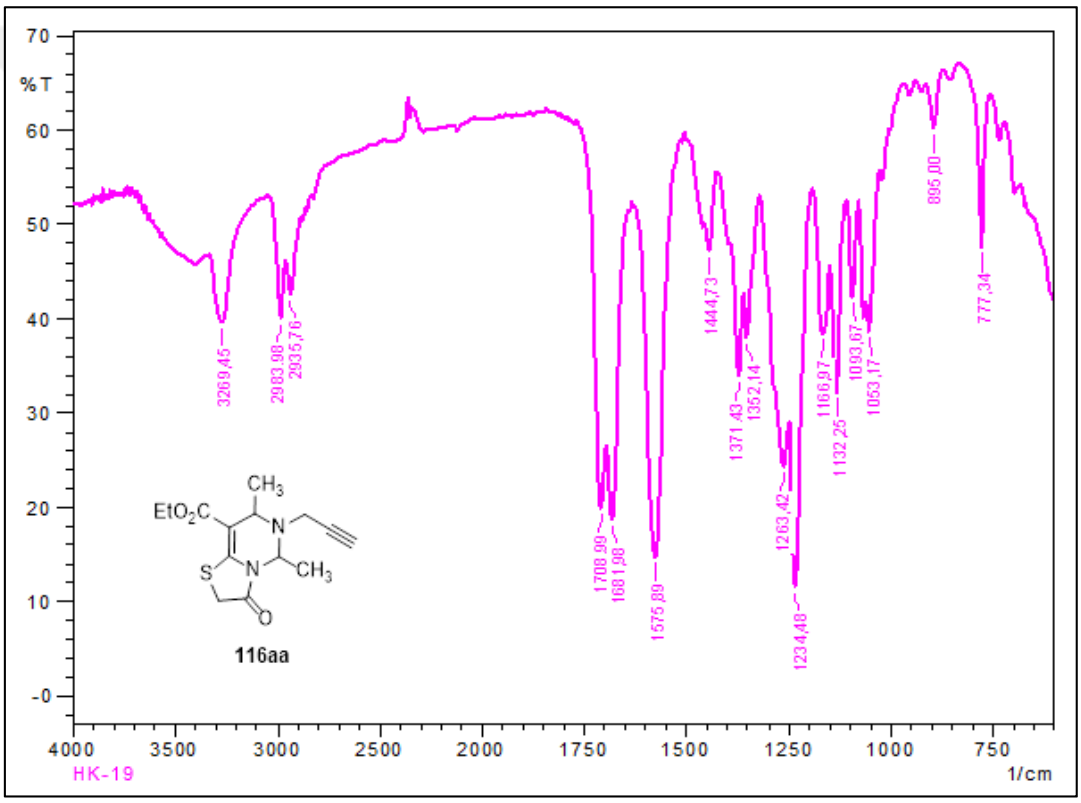

Figure 7.102. IR Spectrum of compound **116aa**.

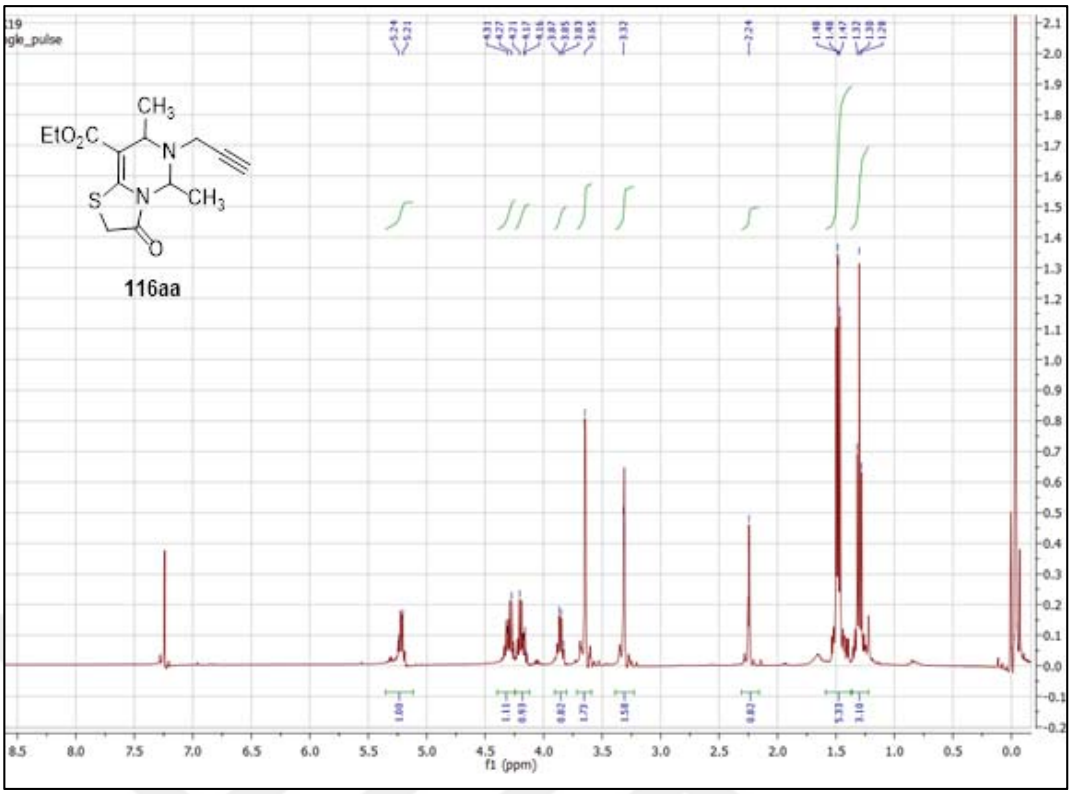

Figure 7.103. ^{1}H-NMR Spectrum of compound **116aa**.

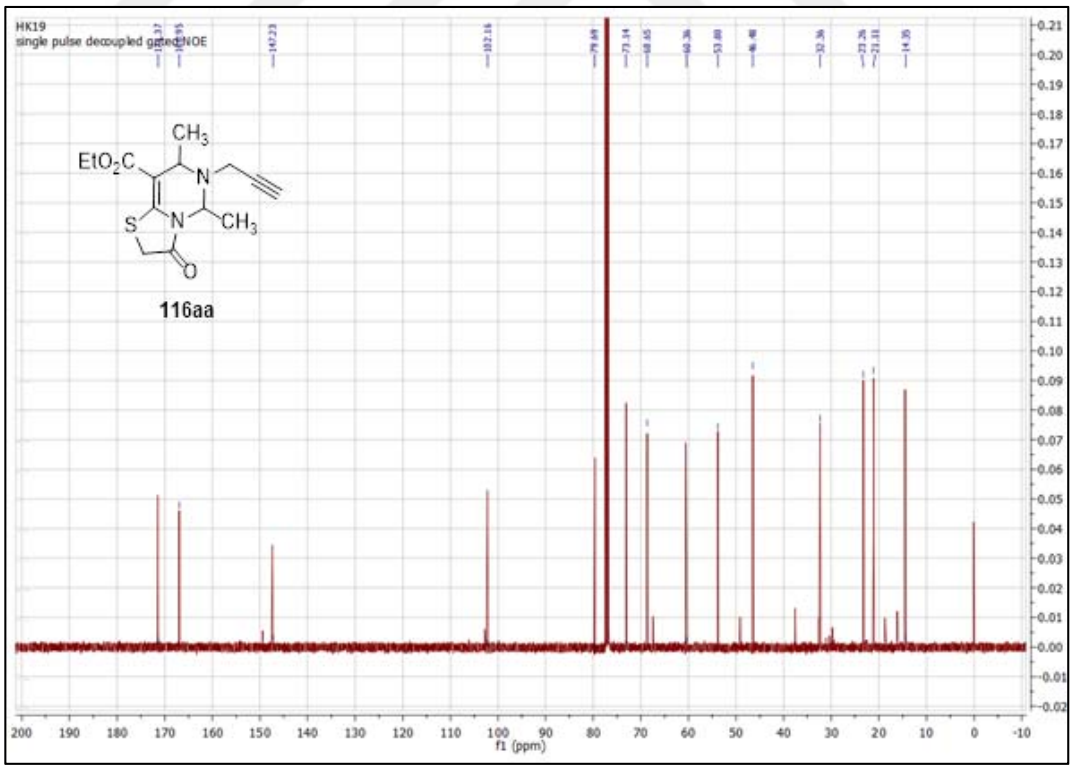

Figure 7.104. ^{13}C-NMR Spectrum of compound **116aa**.

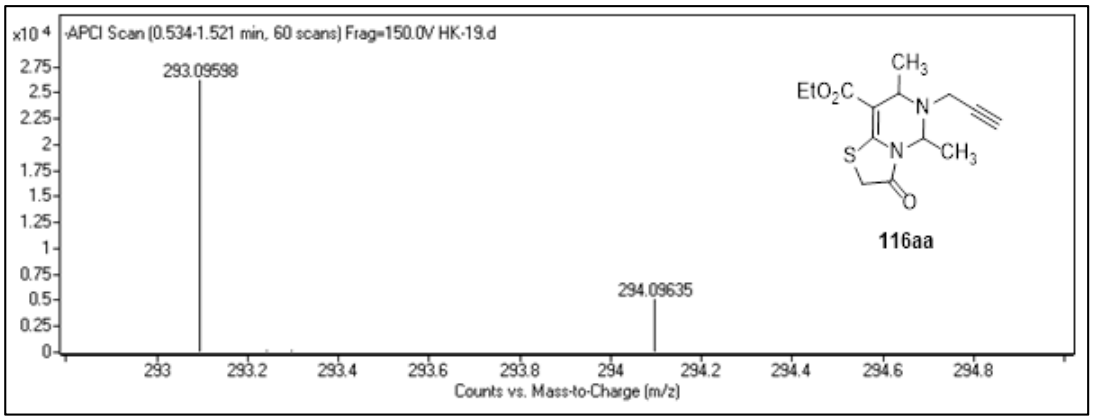

Figure 7.105. HRMS Spectrum of compound **116aa**.

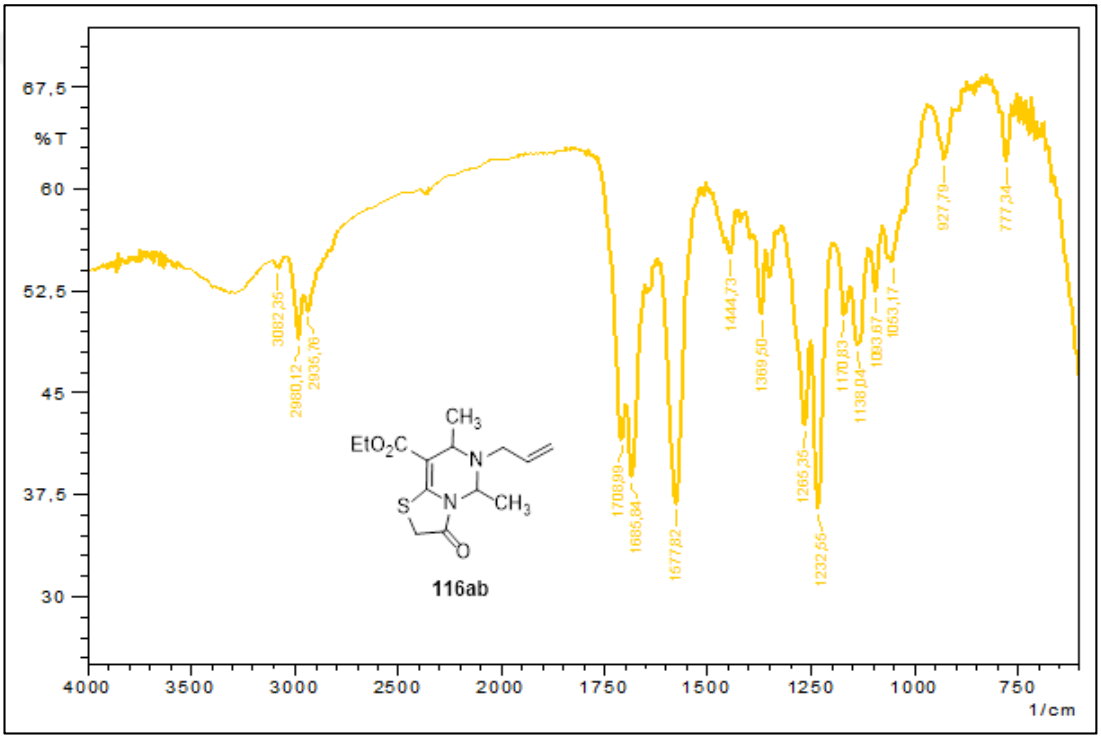

Figure 7.106. IR Spectrum of compound **116ab**.

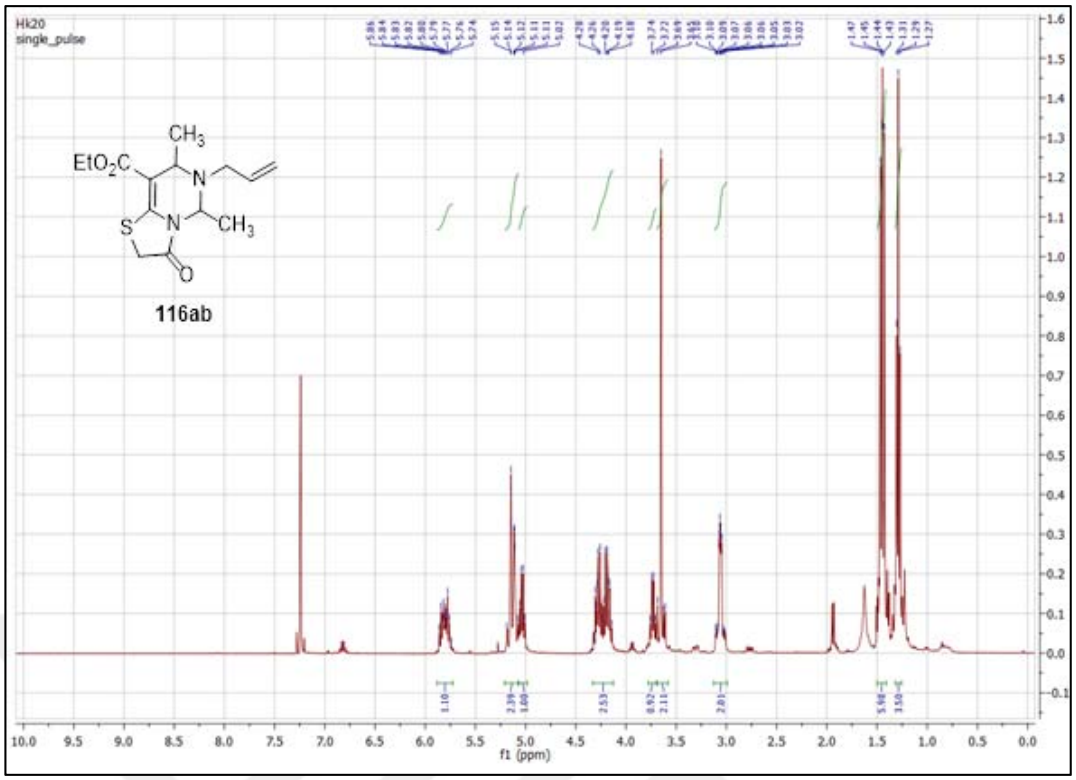

Figure 7.107. ^{1}H-NMR Spectrum of compound **116ab**.

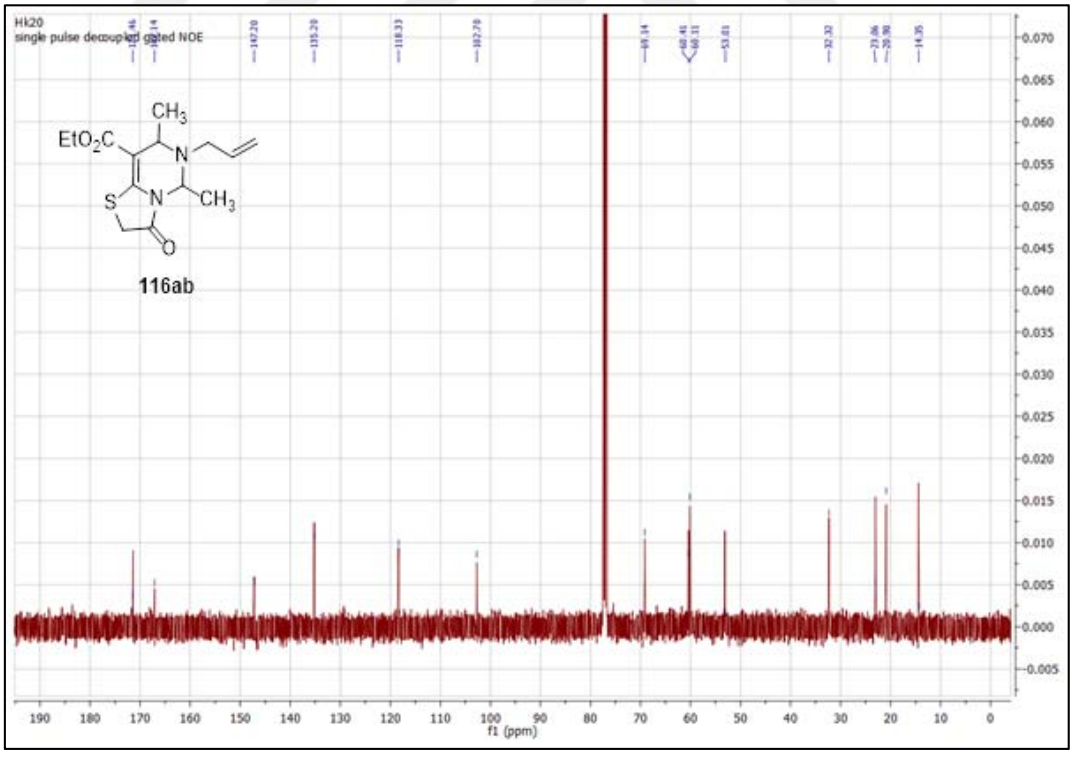

Figure 7.108. ^{13}C-NMR Spectrum of compound **116ab**.

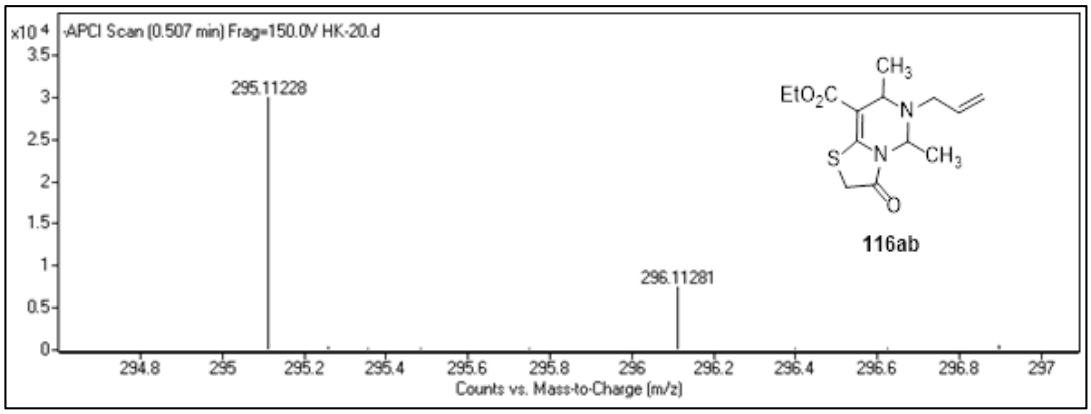

Figure 7.109. HRMS Spectrum of compound **116ab**.

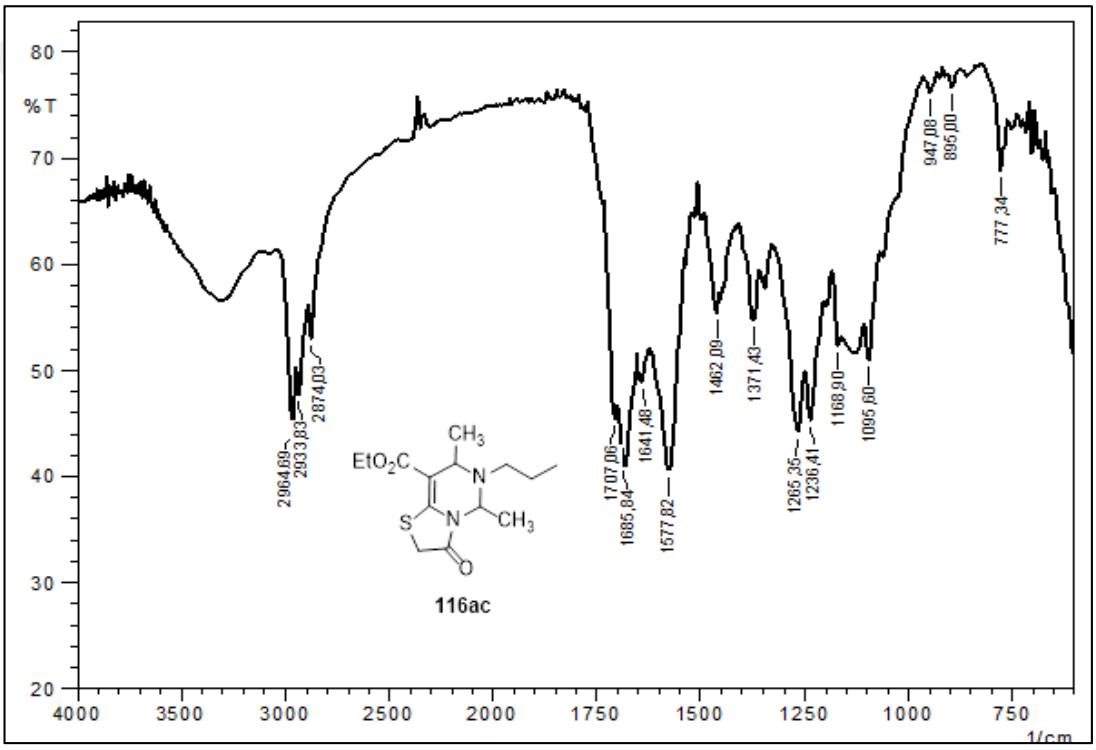

Figure 7.110. IR Spectrum of compound **116ac**.

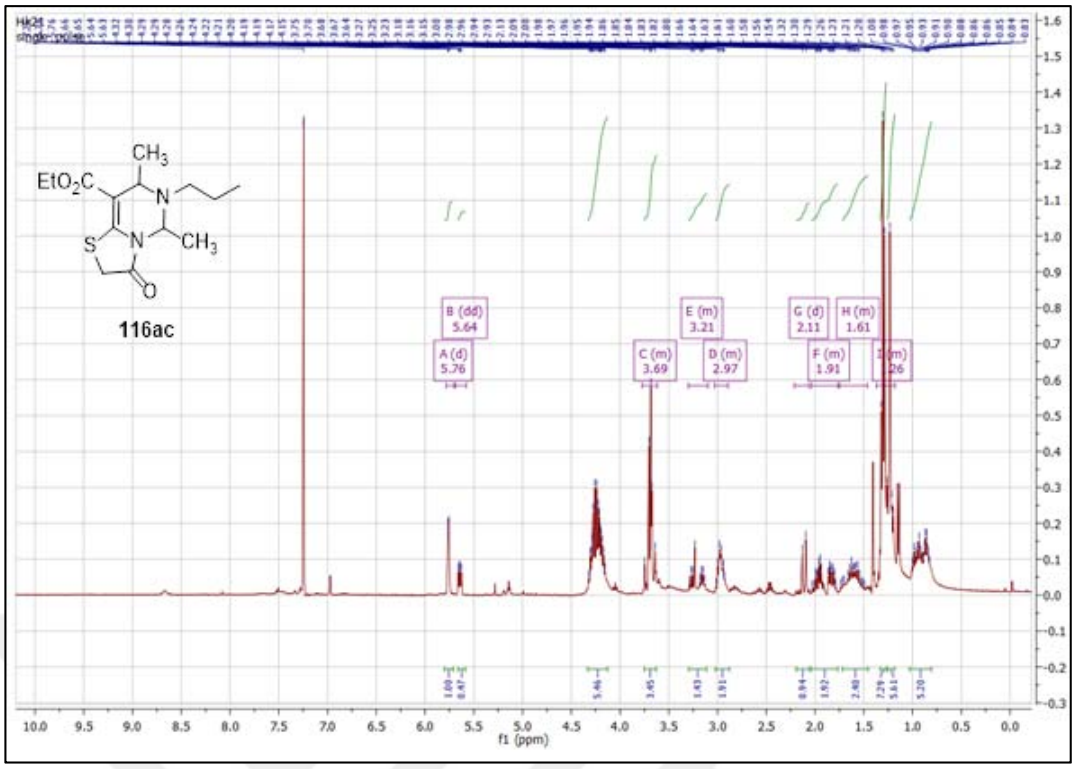

Figure 7.111. ^{1}H-NMR Spectrum of compound **116ac**.

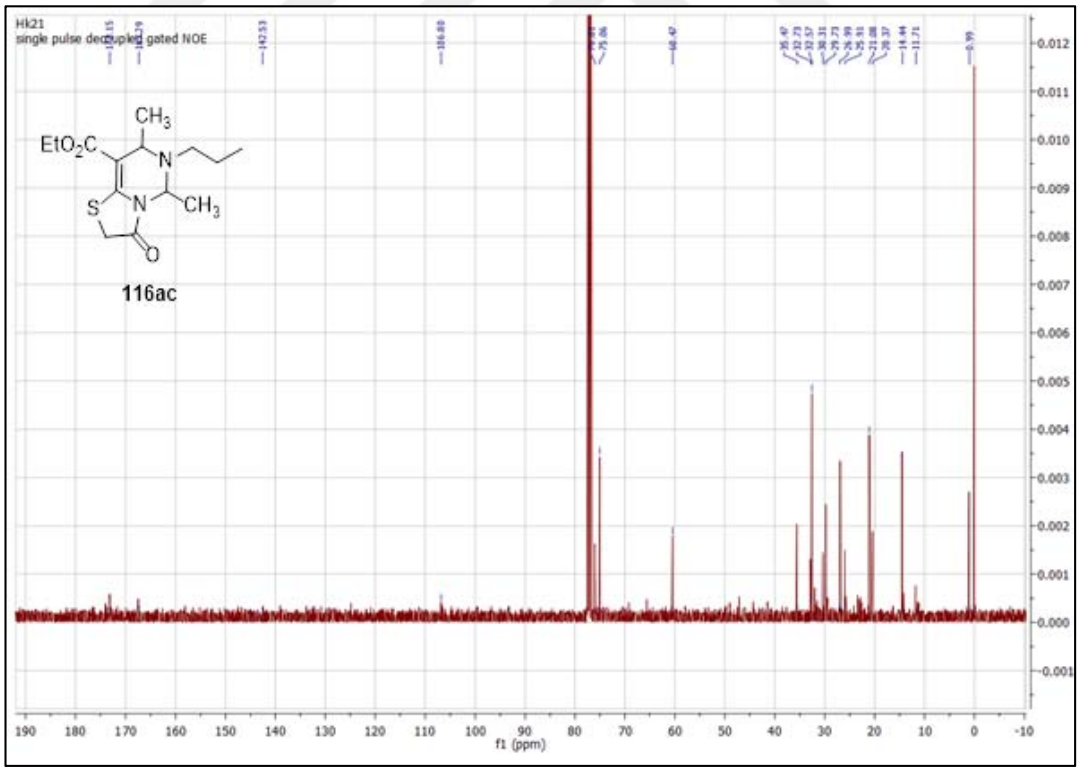

Figure 7.112. ^{13}C-NMR Spectrum of compound **116ac**.

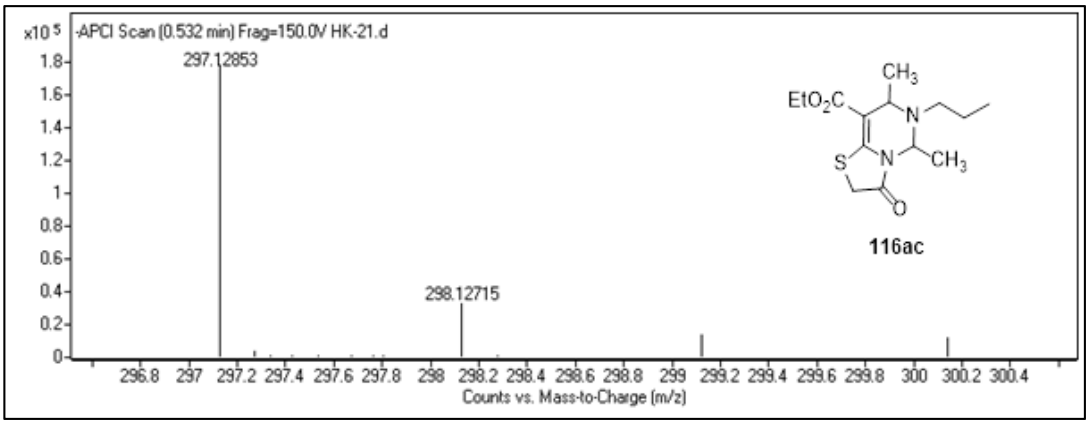

Figure 7.113. HRMS Spectrum of compound **116ac**.

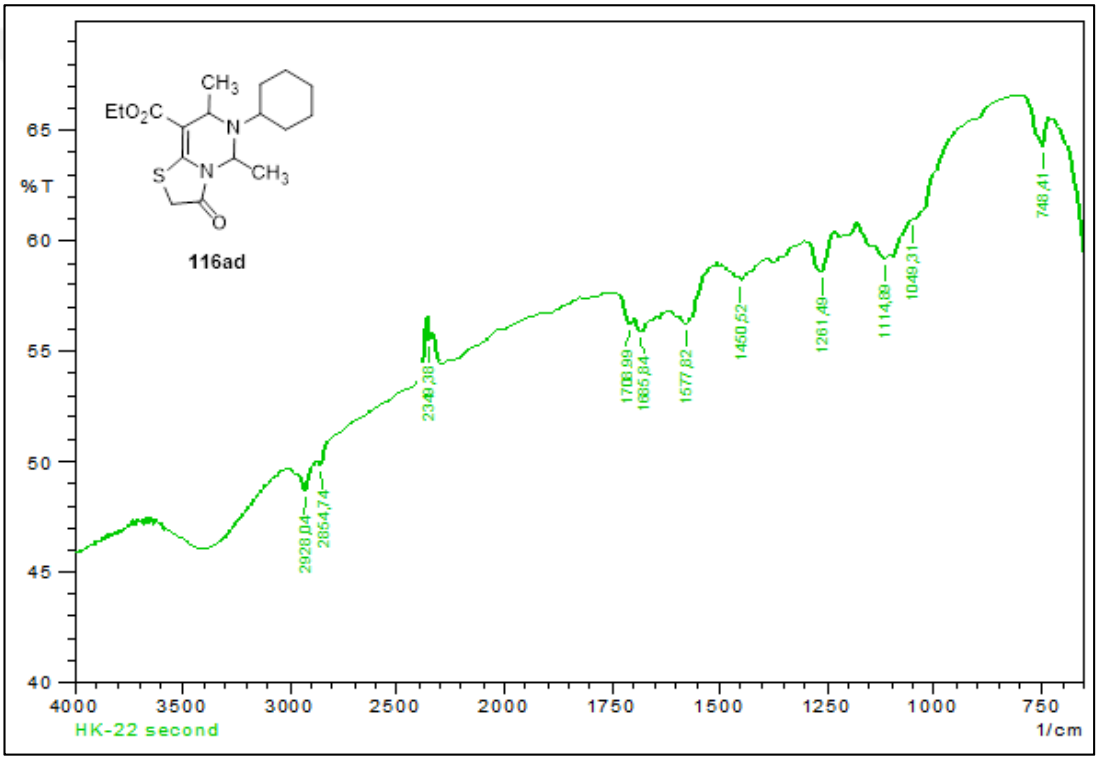

Figure 7.114. IR Spectrum of compound **116ad**.

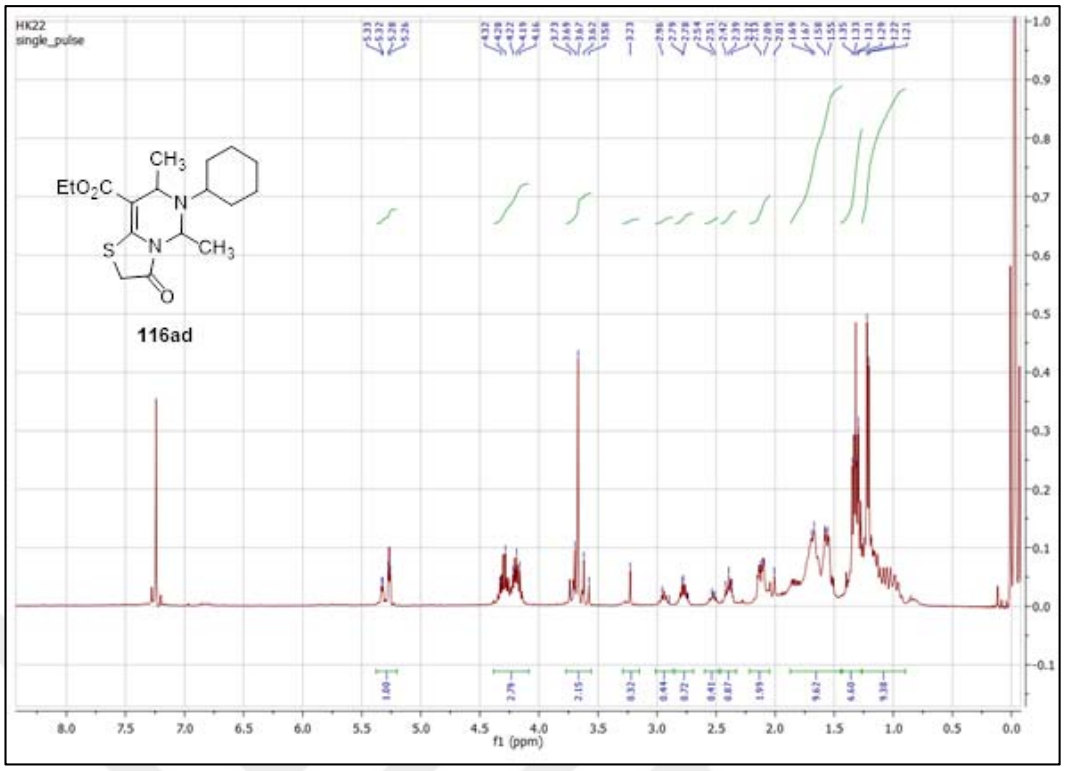

Figure 7.115. ^{1}H-NMR Spectrum of compound **116ad**.

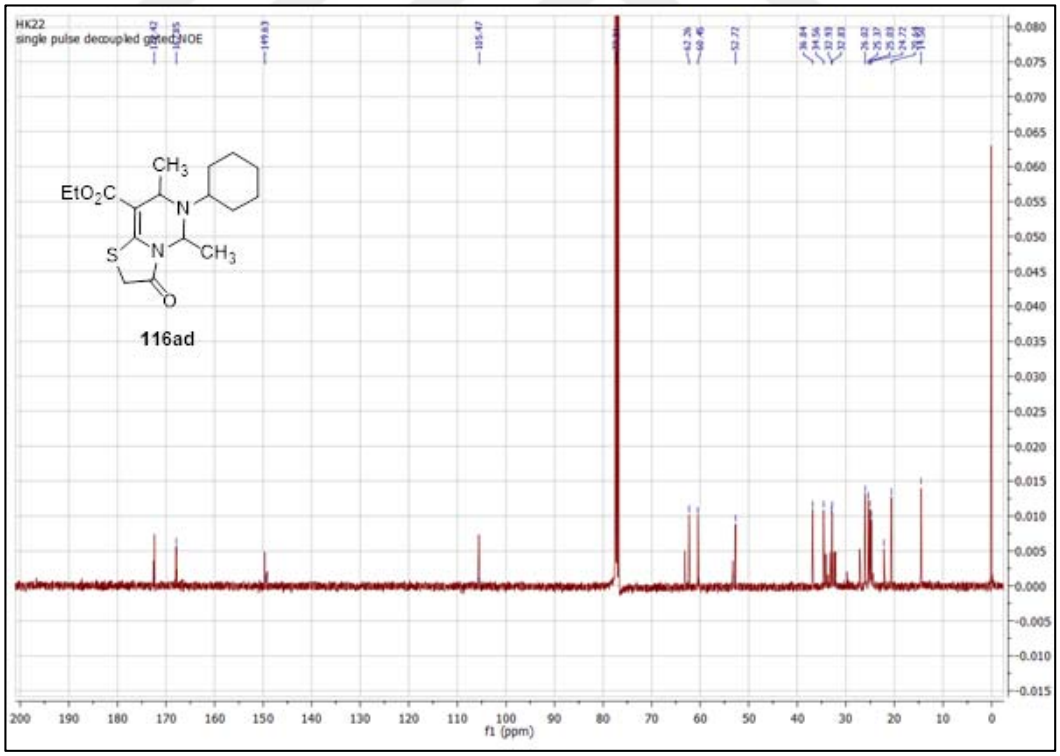

Figure 7.116. ^{13}C-NMR Spectrum of compound **116ad**.

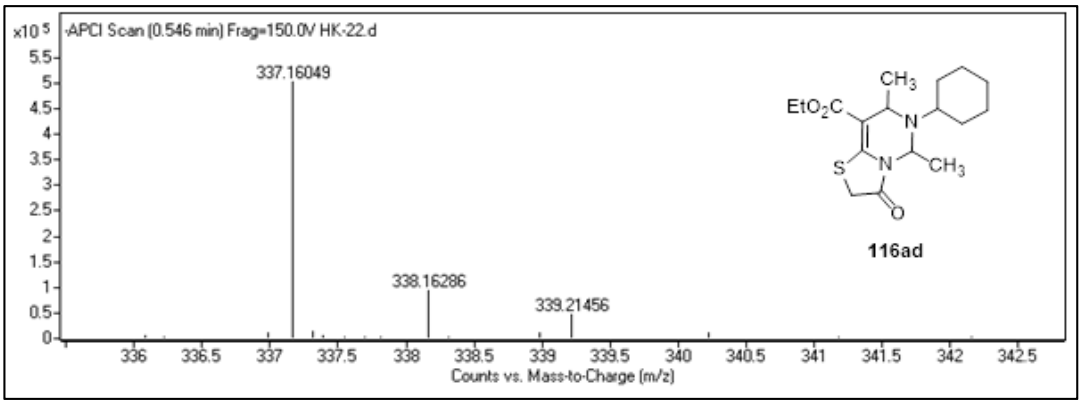

Figure 7.117. HRMS Spectrum of compound **116ad**.

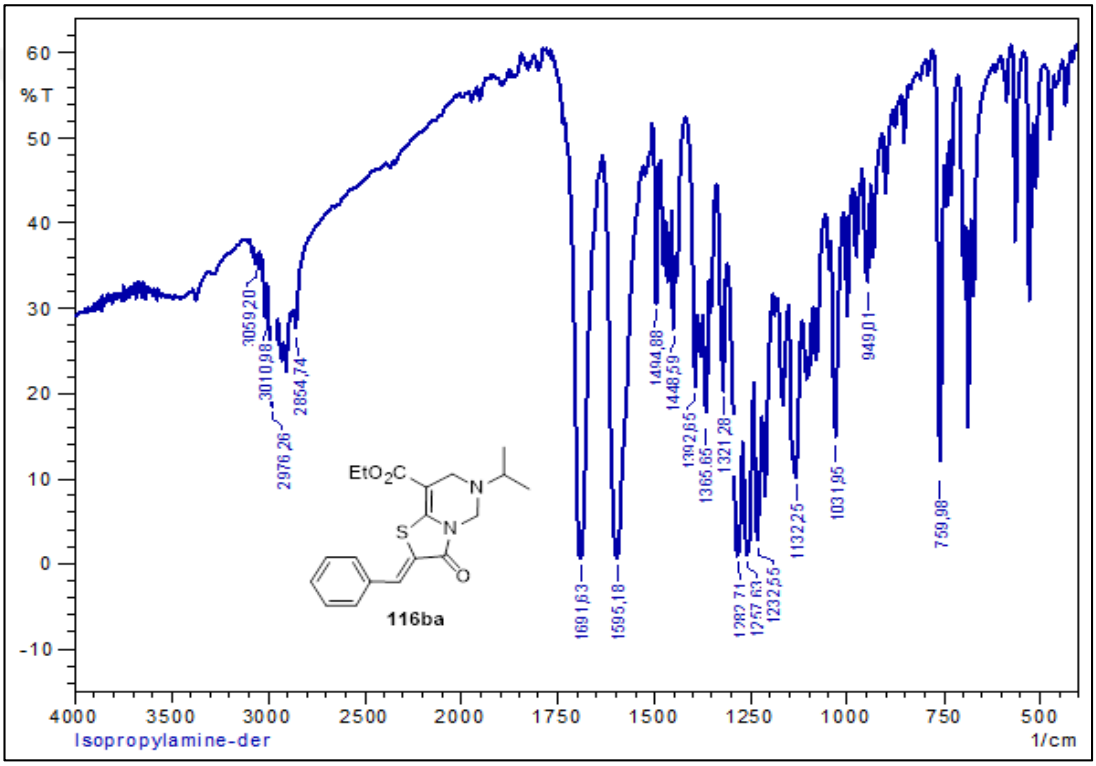

Figure 7.118. IR Spectrum of compound **116ba**.

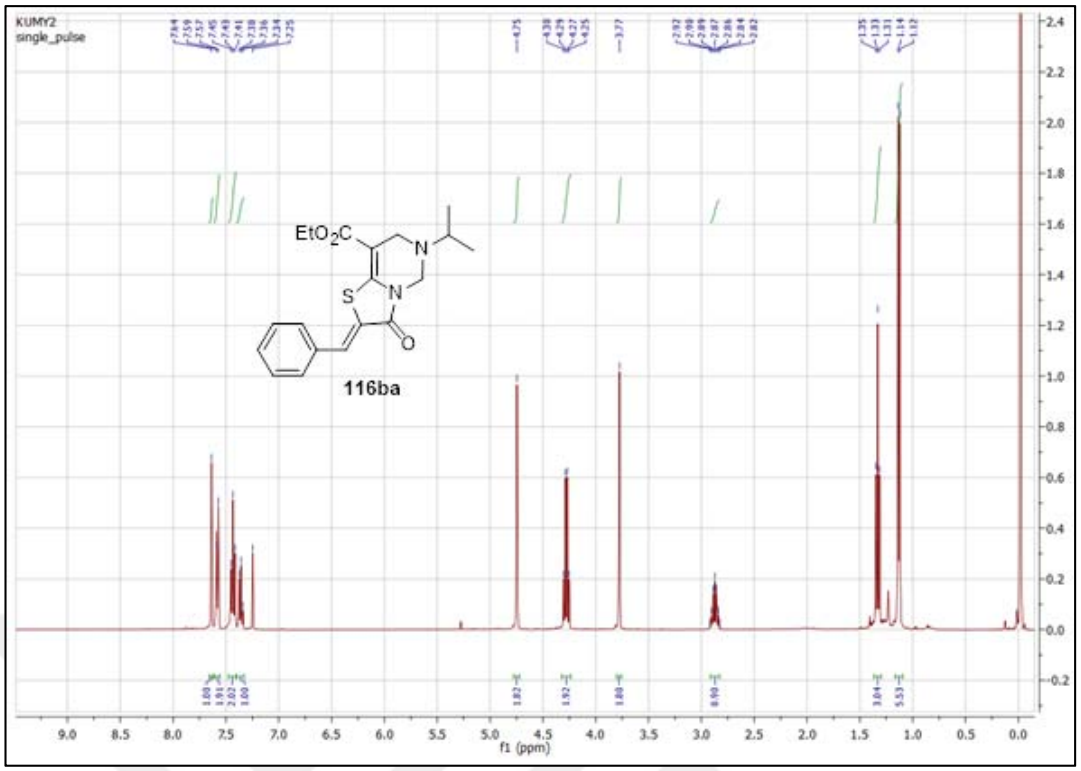

Figure 7.119. ^{1}H-NMR Spectrum of compound **116ba**.

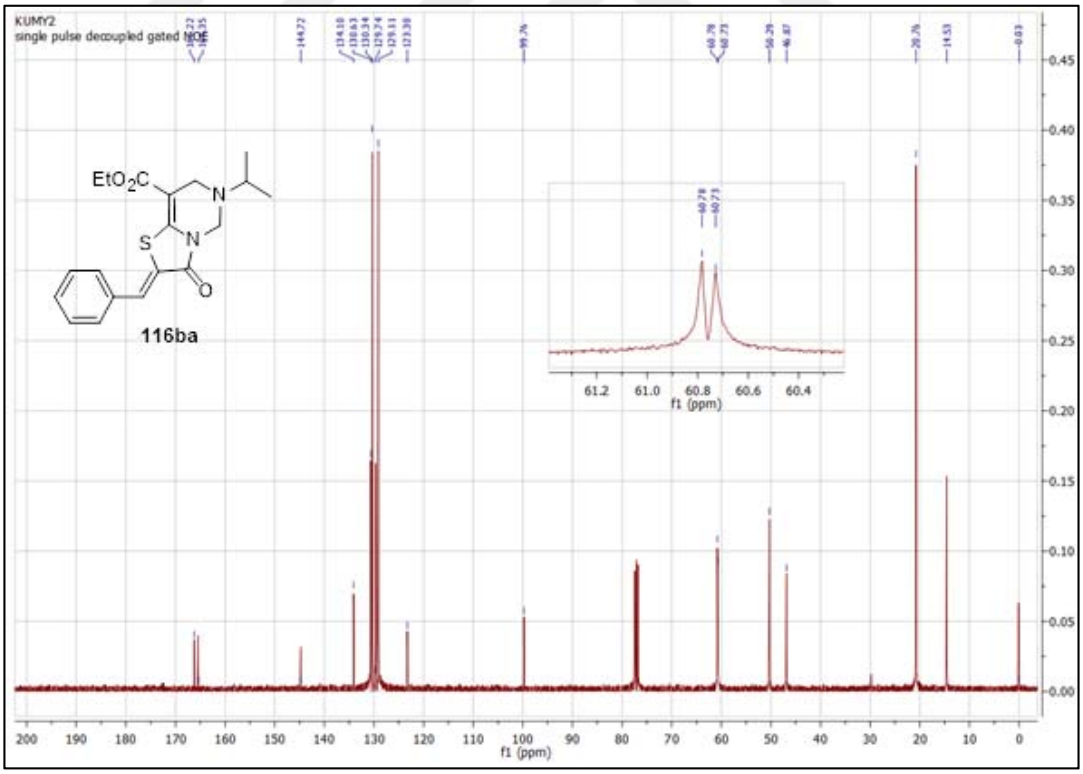

Figure 7.120. ^{13}C-NMR Spectrum of compound **116ba**.

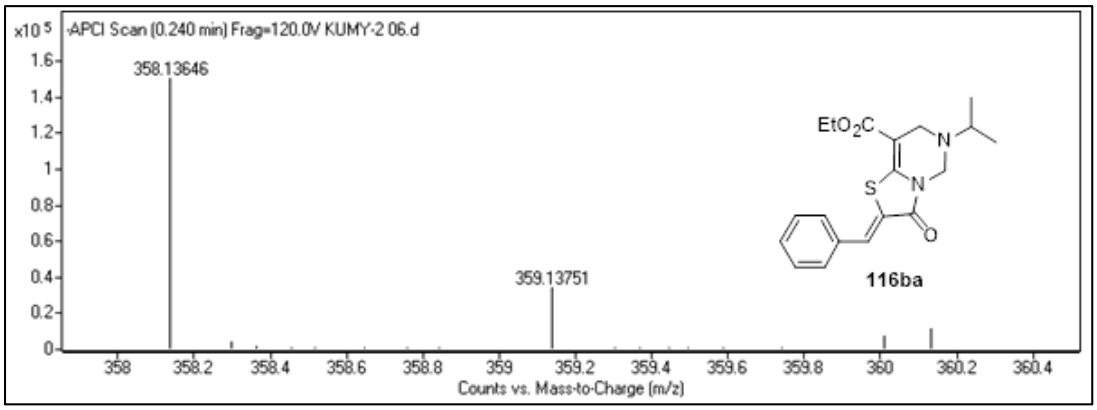

Figure 7.121. HRMS Spectrum of compound **116ba**.

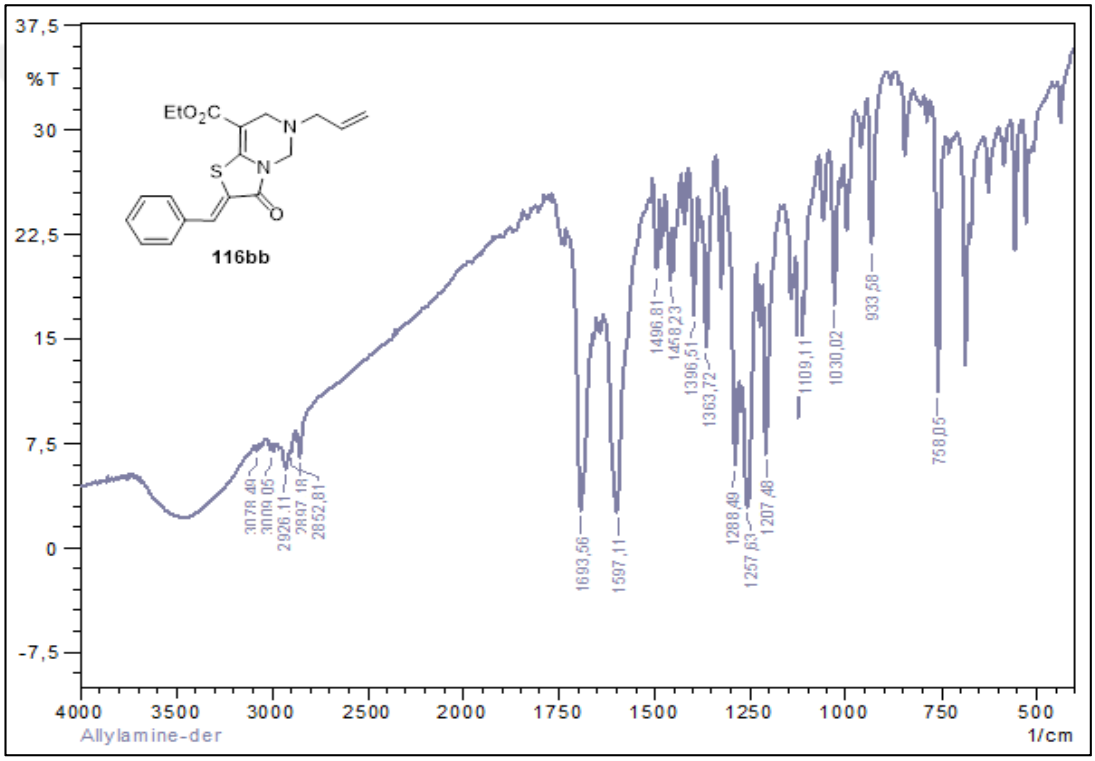

Figure 7.122. IR Spectrum of compound **116bb**.

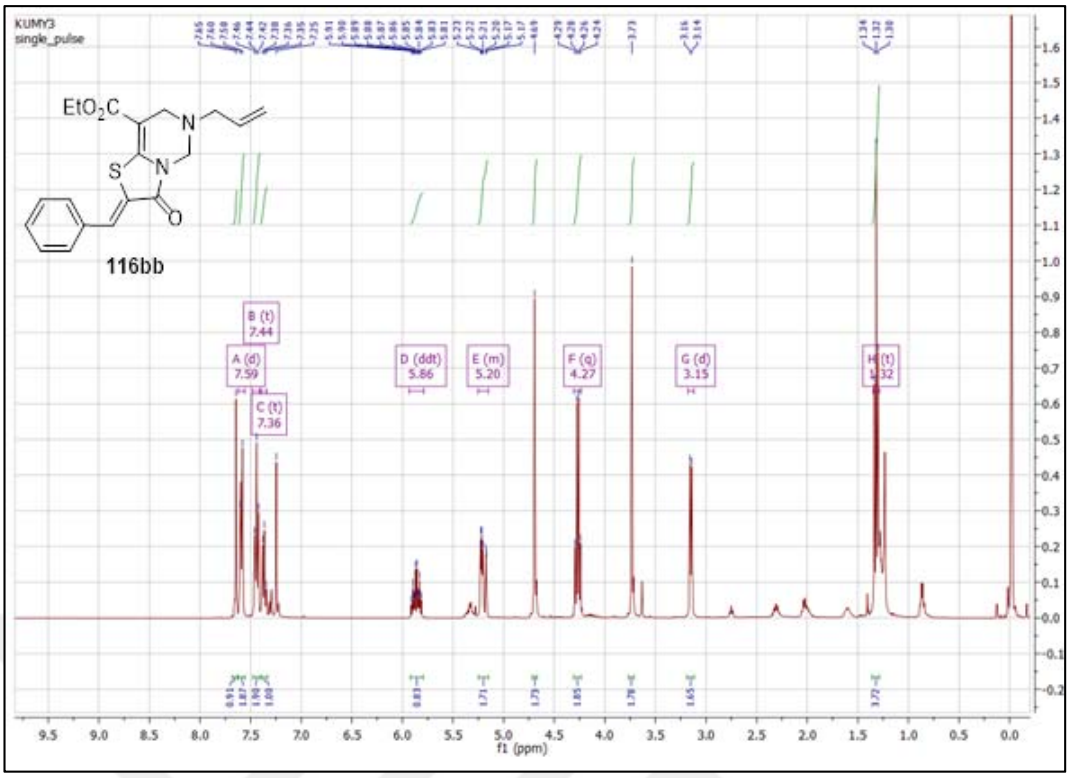

Figure 7.123. [1]H-NMR Spectrum of compound **116bb**.

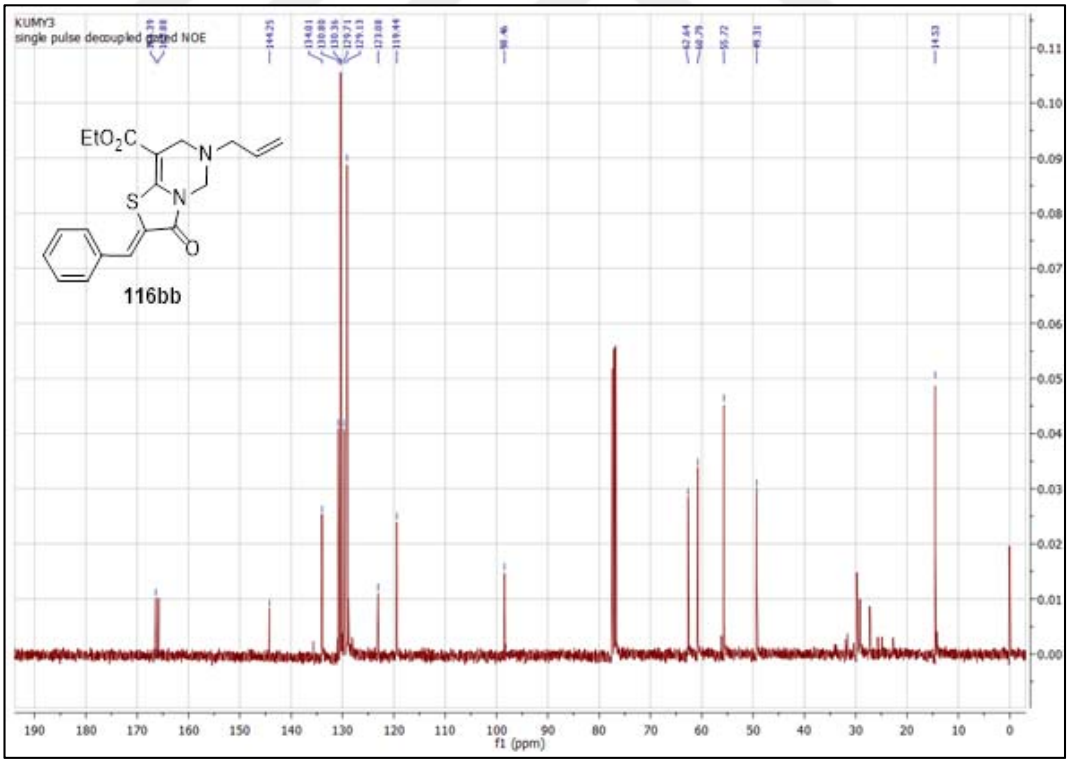

Figure 7.124. [13]C-NMR Spectrum of compound **116bb**.

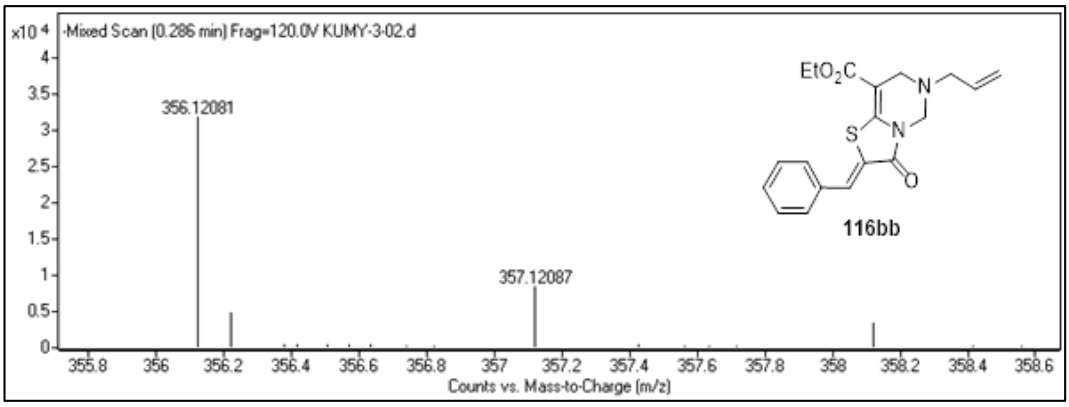

Figure 7.125. HRMS Spectrum of compound **116bb**.

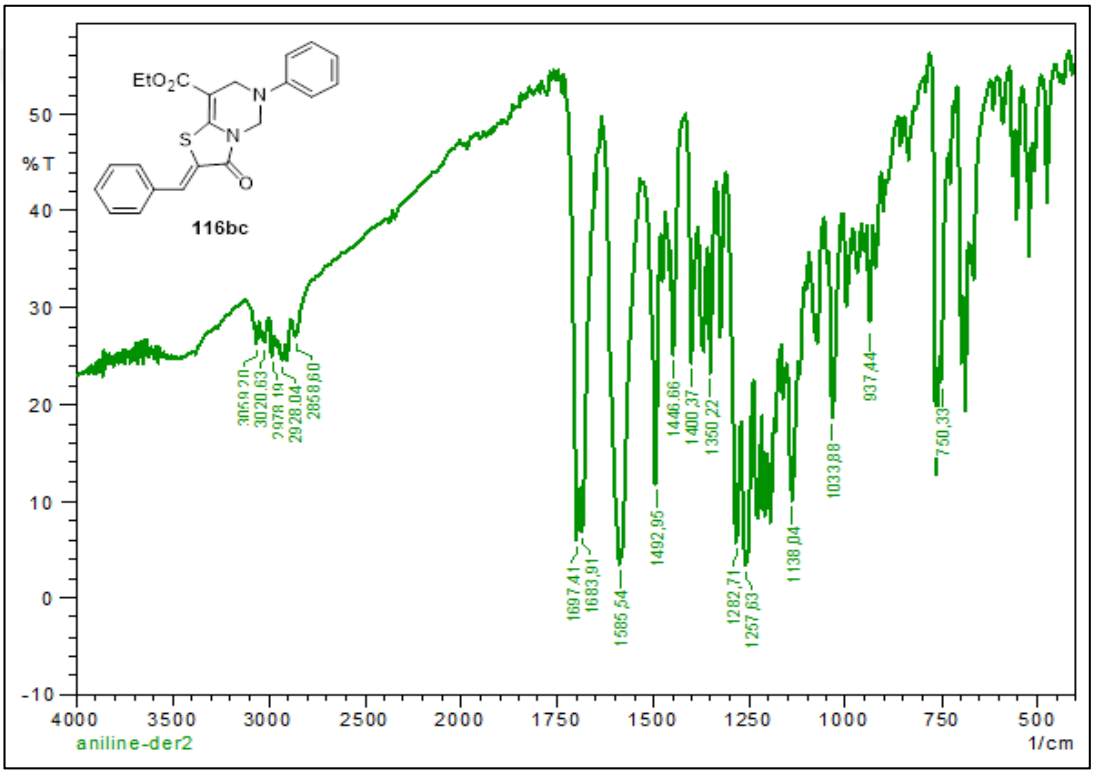

Figure 7.126. IR Spectrum of compound **116bc**.

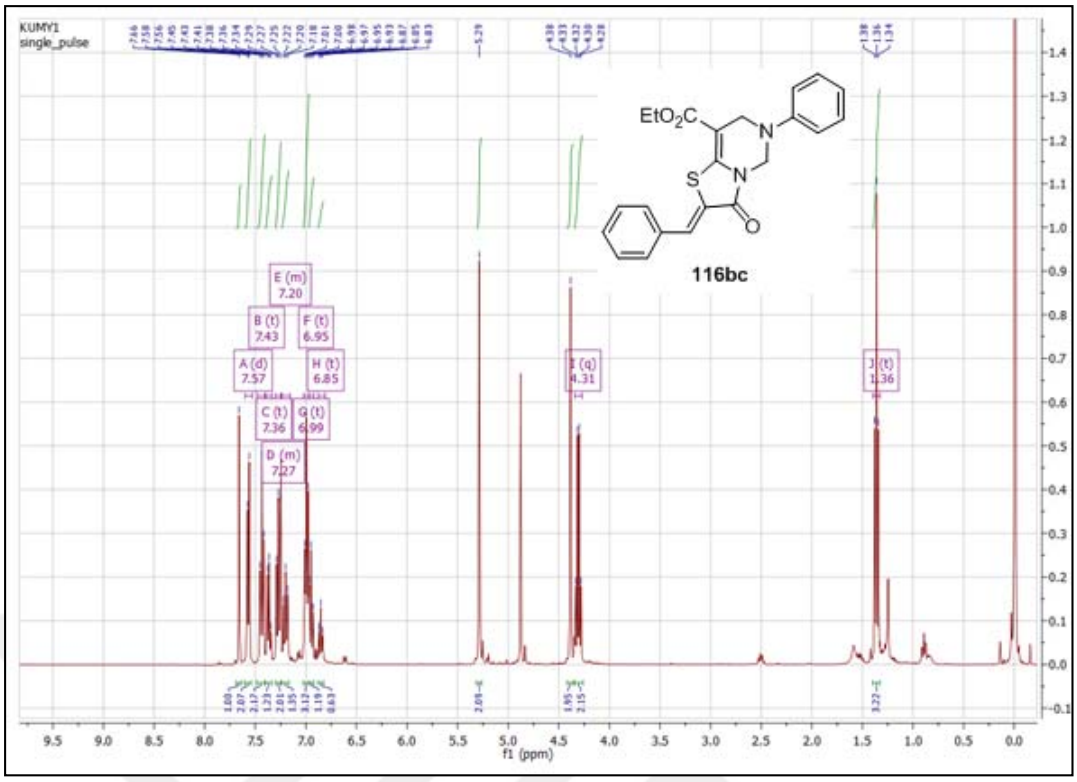

Figure 7.127. [1]H-NMR Spectrum of compound **116bc**.

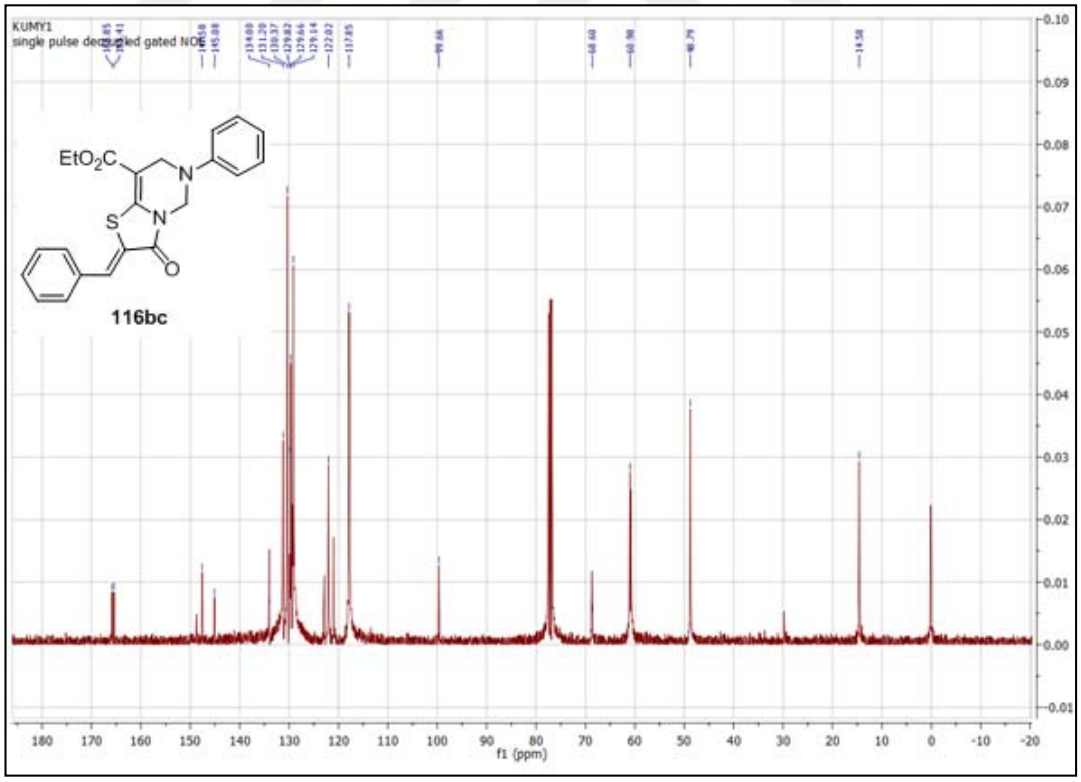

Figure 7.128. [13]C-NMR Spectrum of compound **116bc**.

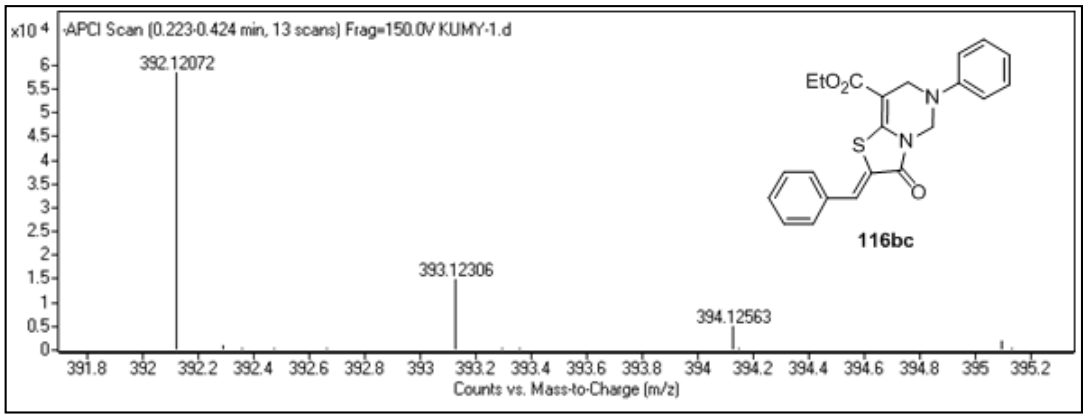

Figure 7.129. HRMS Spectrum of compound **116bc**.

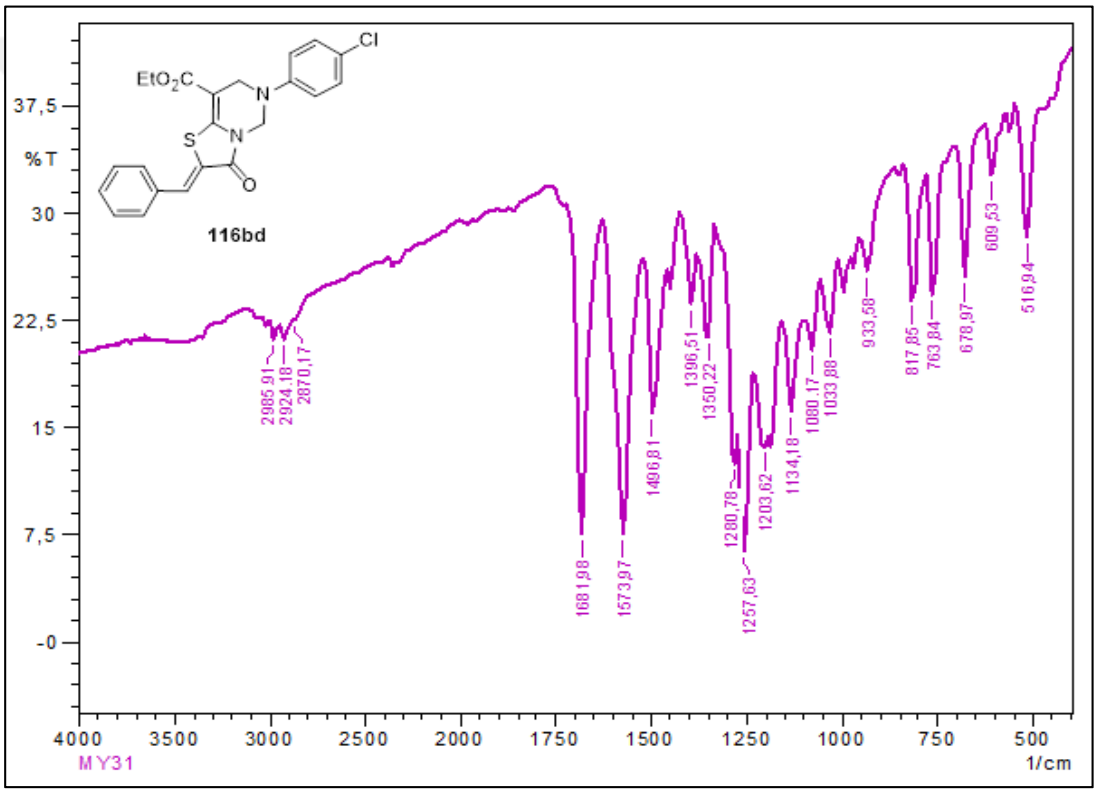

Figure 7.130. IR Spectrum of compound **116bd**.

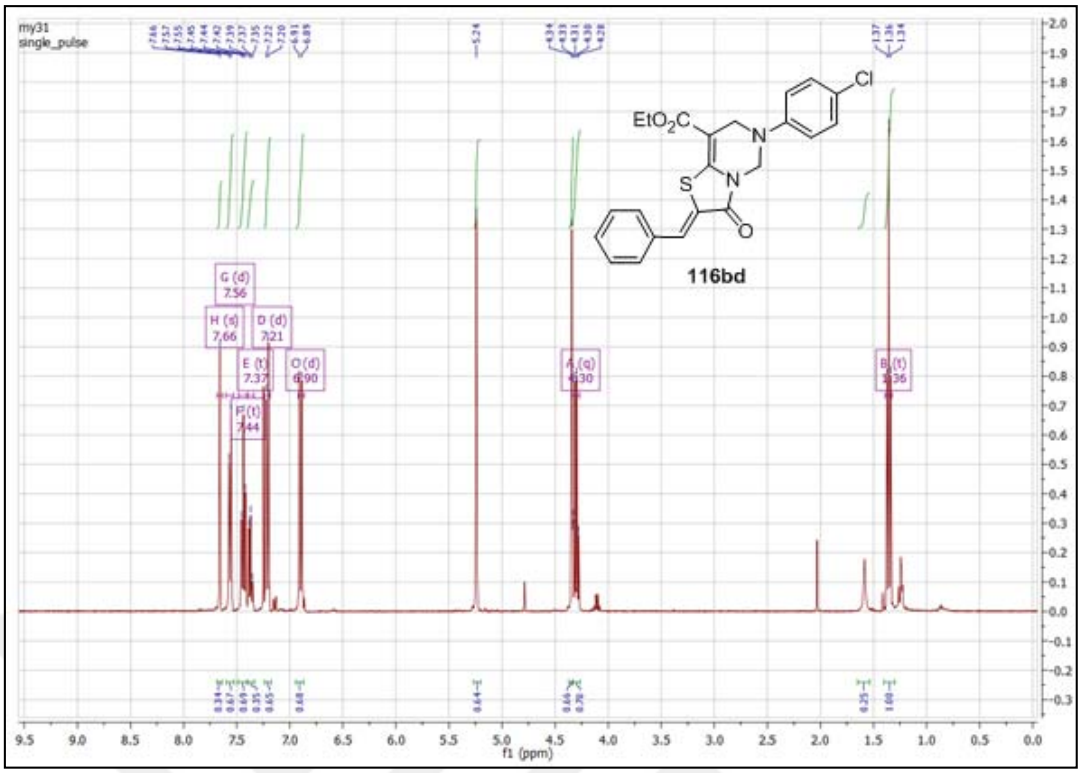

Figure 7.131. [1]H-NMR Spectrum of compound **116bd**.

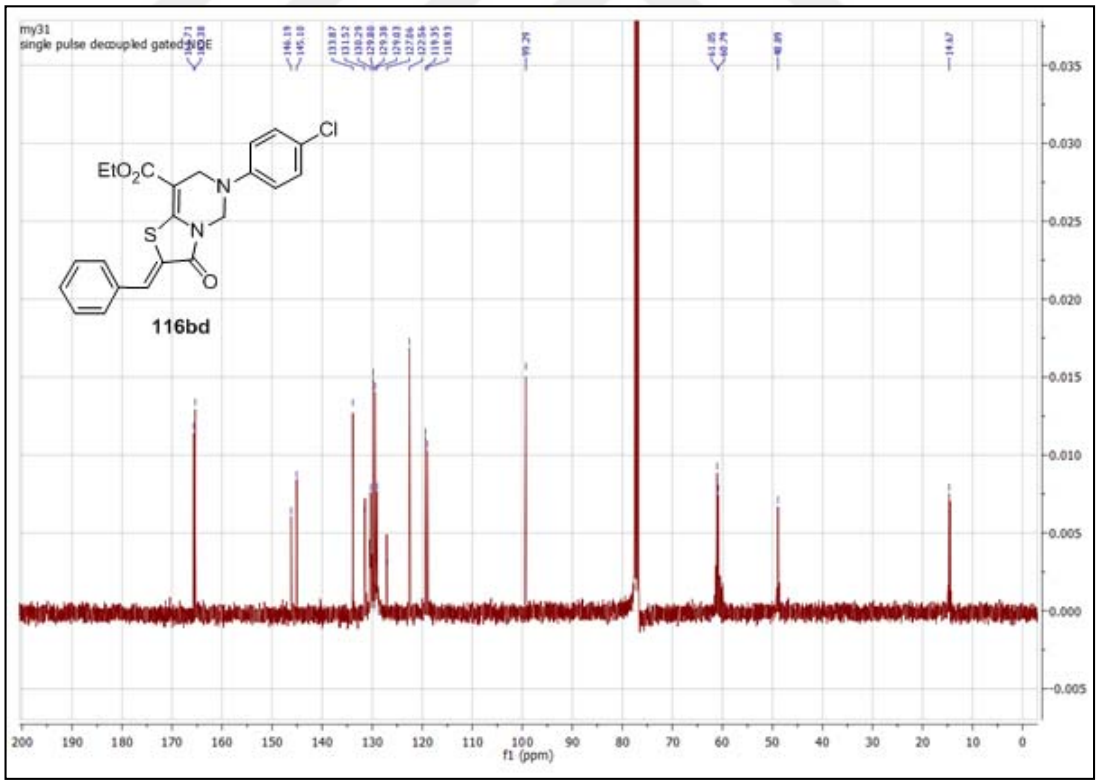

Figure 7.132. [13]C-NMR Spectrum of compound **116bd**.

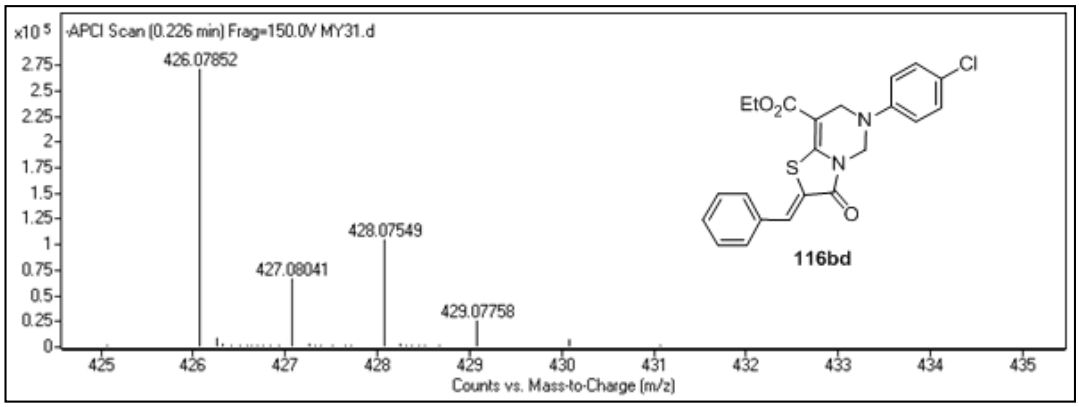

Figure 7.133. HRMS Spectrum of compound **116bd**.

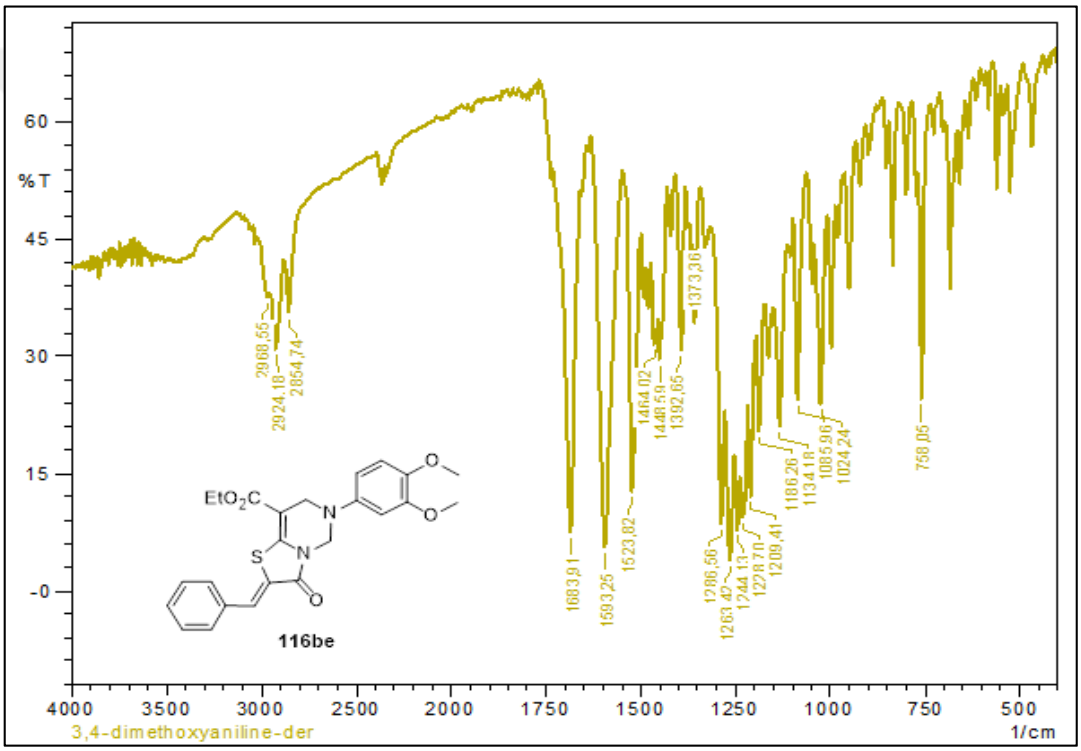

Figure 7.134. IR Spectrum of compound **116be**.

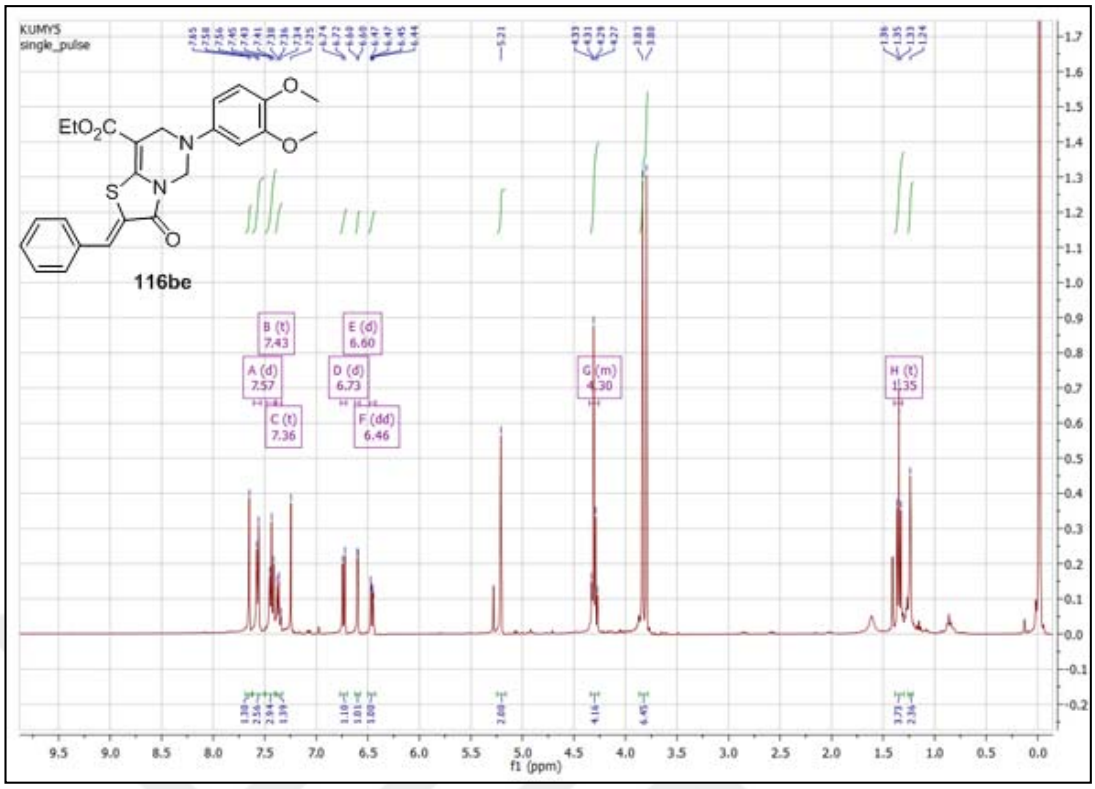

Figure 7.135. [1]H-NMR Spectrum of compound **116be**.

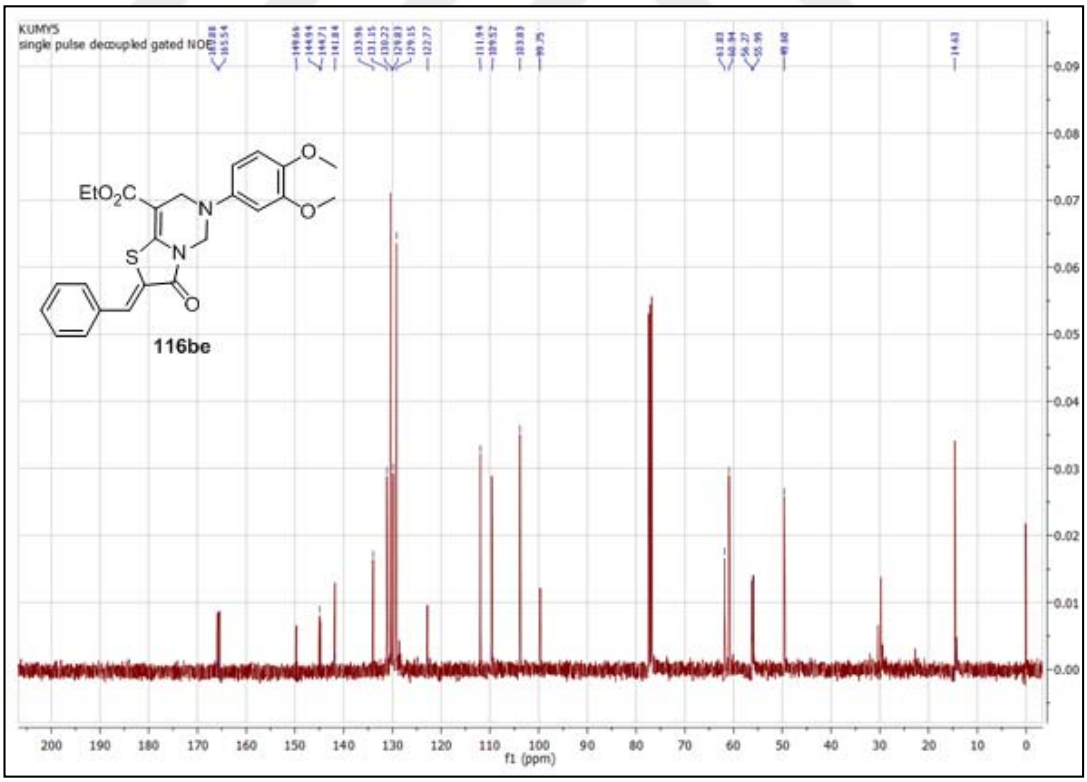

Figure 7.136. [13]C-NMR Spectrum of compound **116be**.

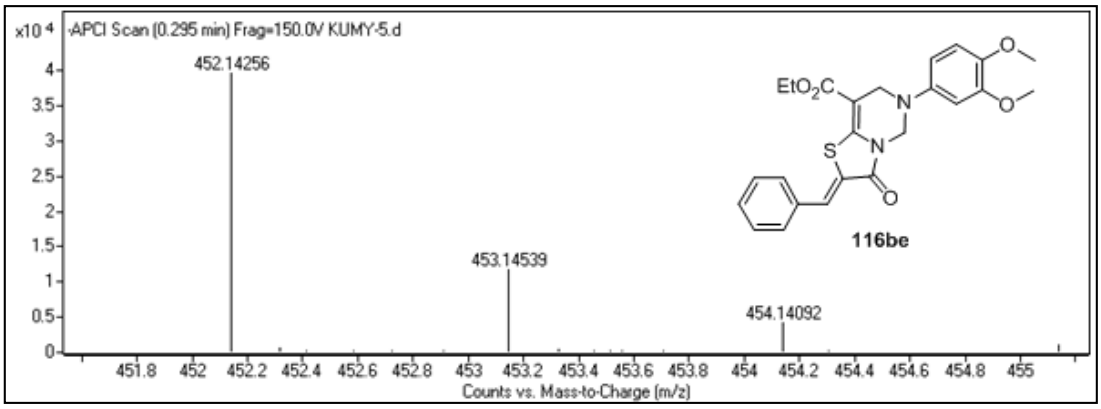

Figure 7.137. HRMS Spectrum of compound **116be**.

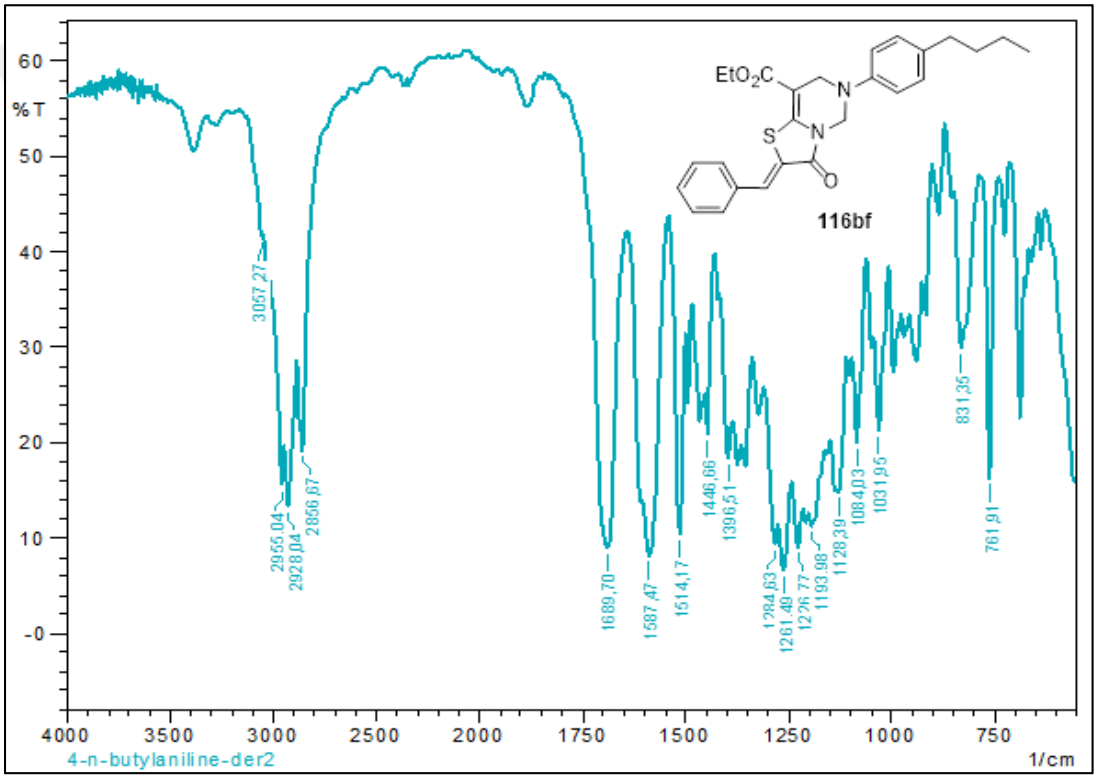

Figure 7.138. IR Spectrum of compound **116bf**.

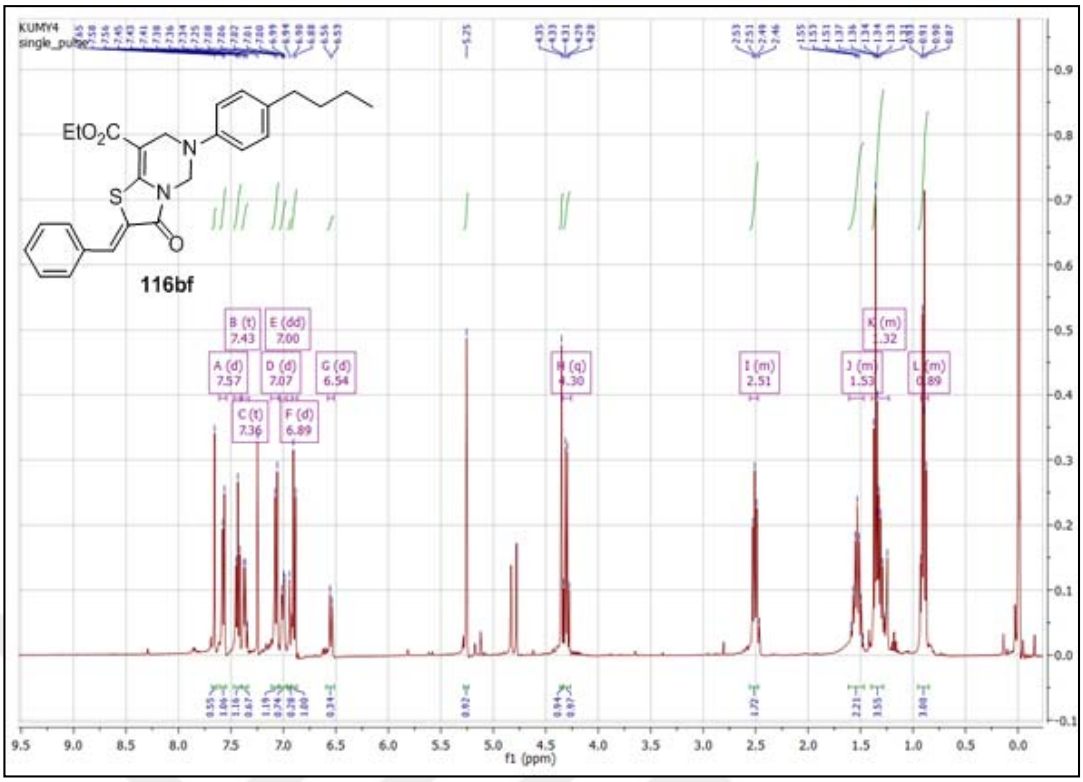

Figure 7.139. ^{1}H-NMR Spectrum of compound **116bf**.

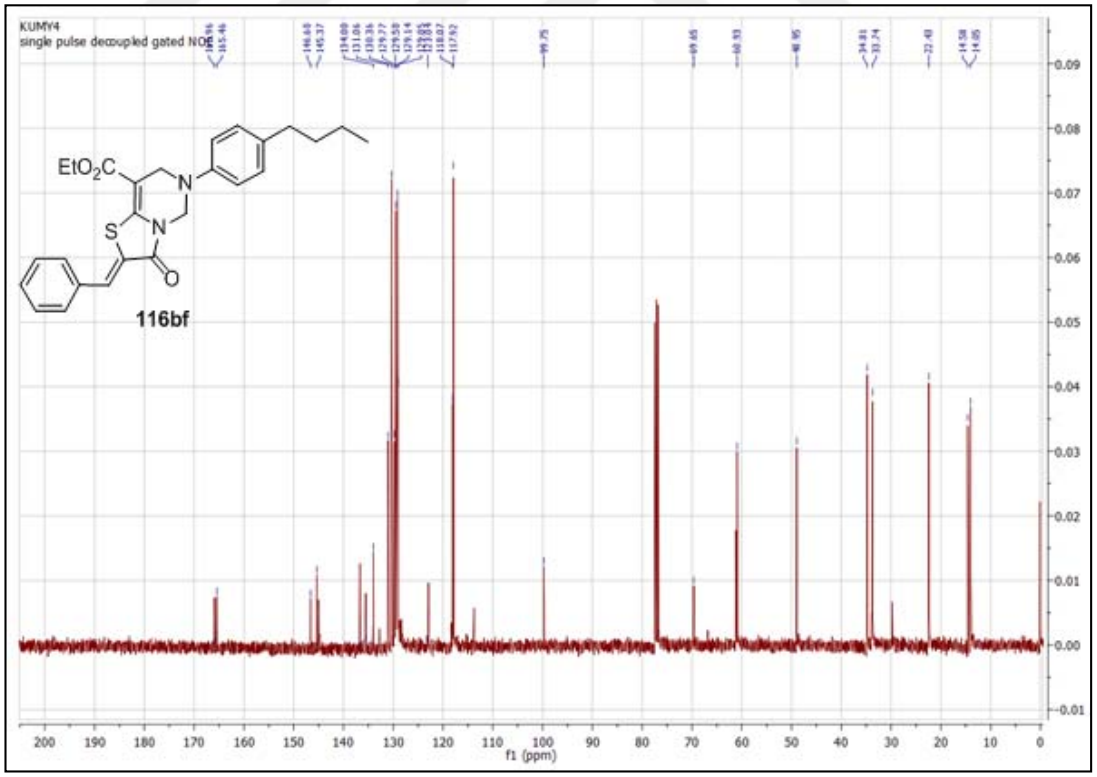

Figure 7.140. ^{13}C-NMR Spectrum of compound **116bf**.

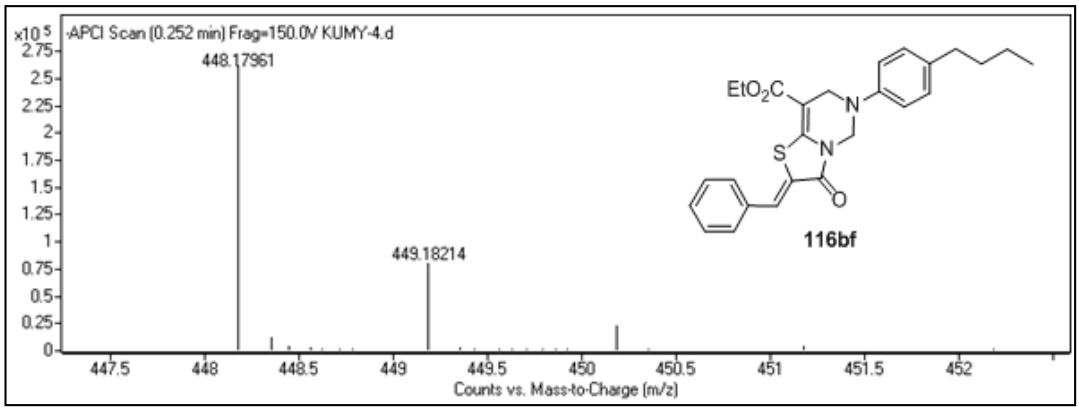

Figure 7.141. HRMS Spectrum of compound **116bf**.

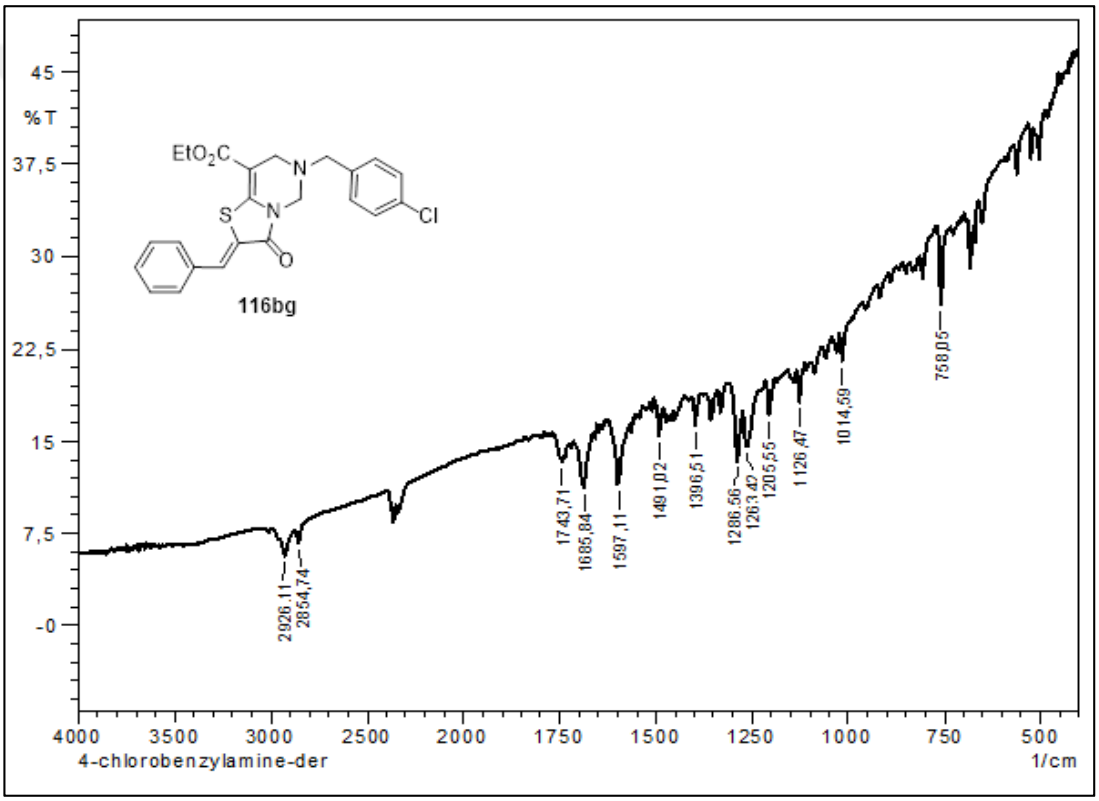

Figure 7.142. IR Spectrum of compound **116bg**.

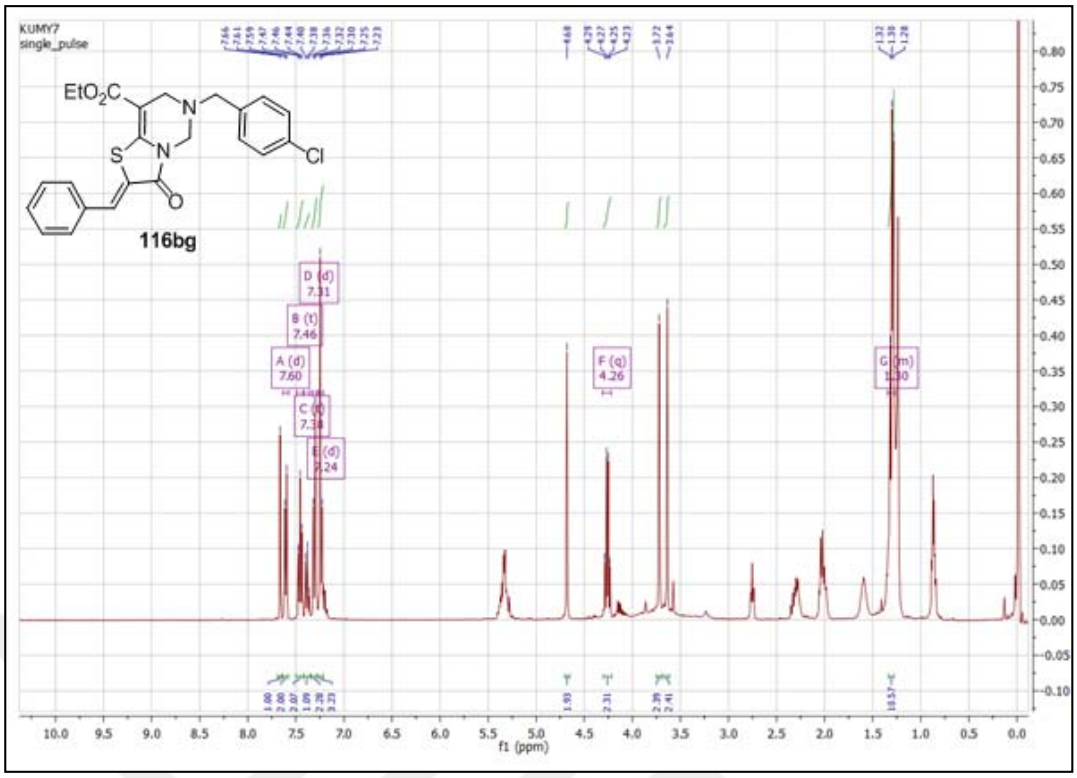

Figure 7.143. [1]H-NMR Spectrum of compound **116bg**.

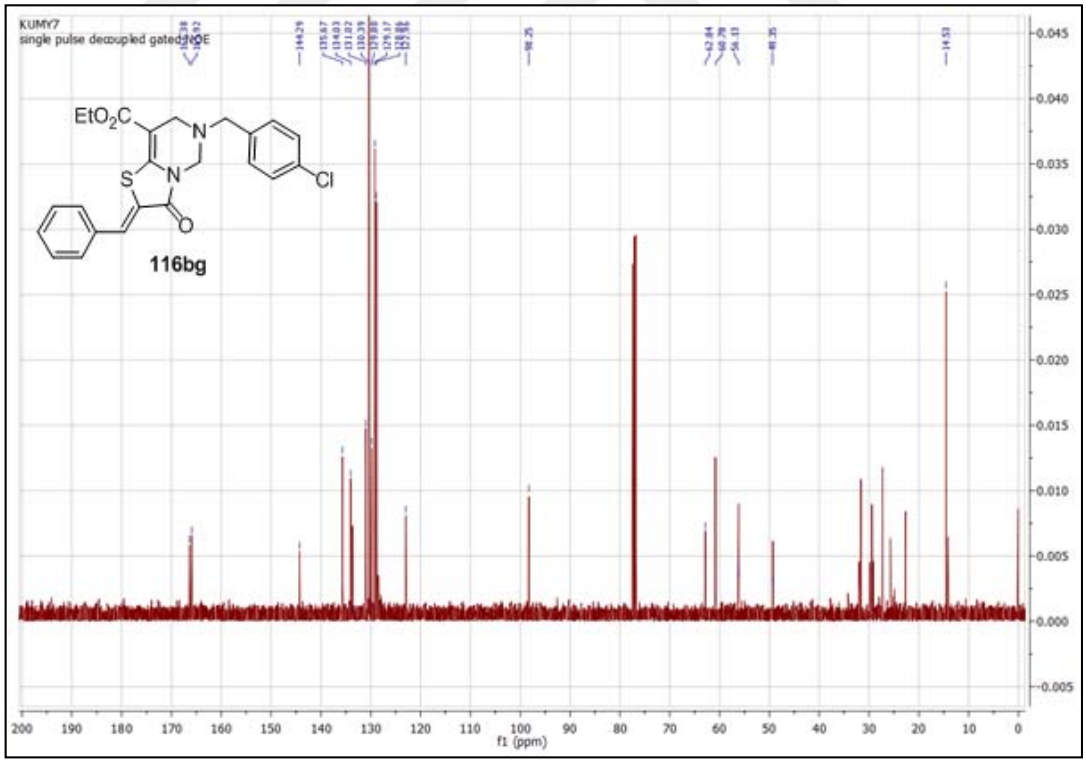

Figure 7.144. [13]C-NMR Spectrum of compound **116bg**.

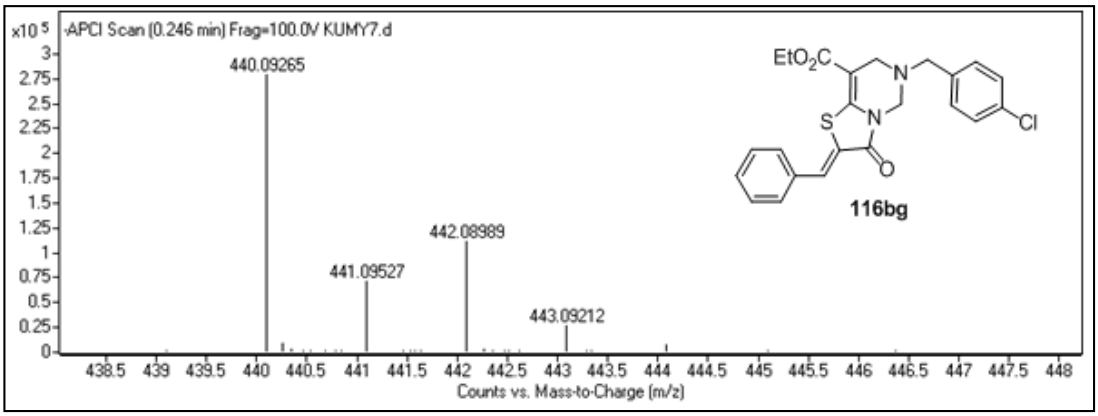

Figure 7.145. HRMS Spectrum of compound **116bg**.

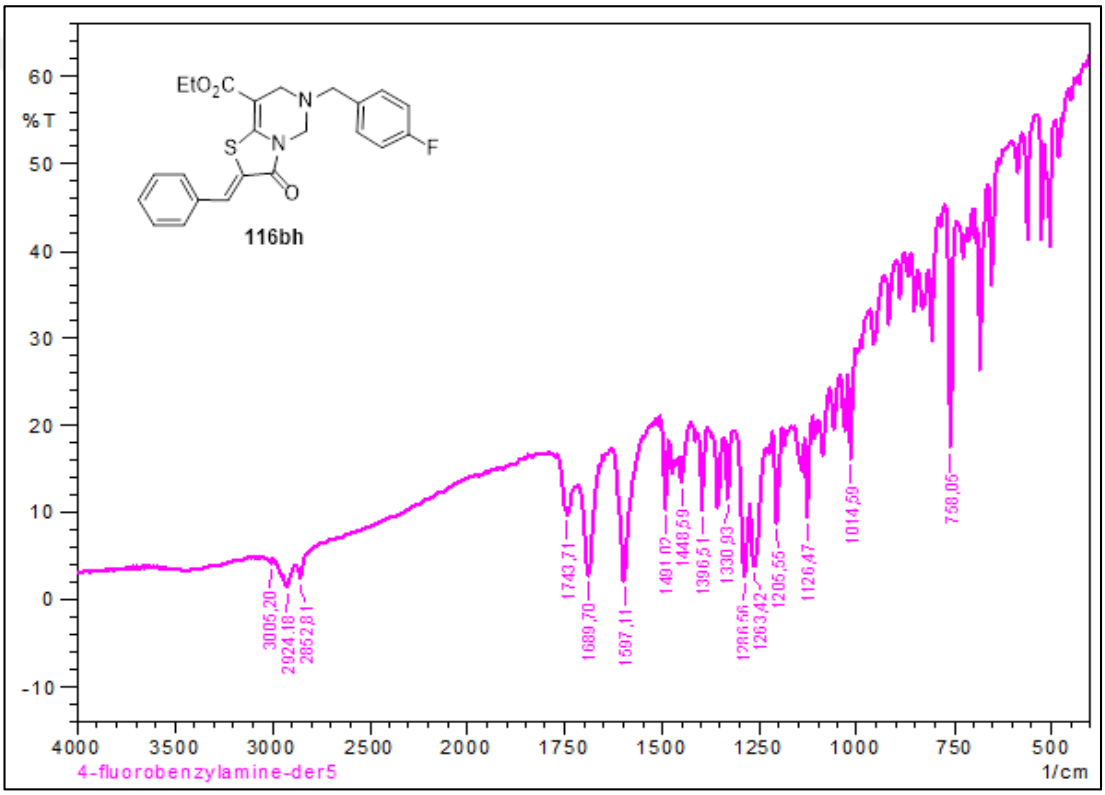

Figure 7.146. IR Spectrum of compound **116bh**.

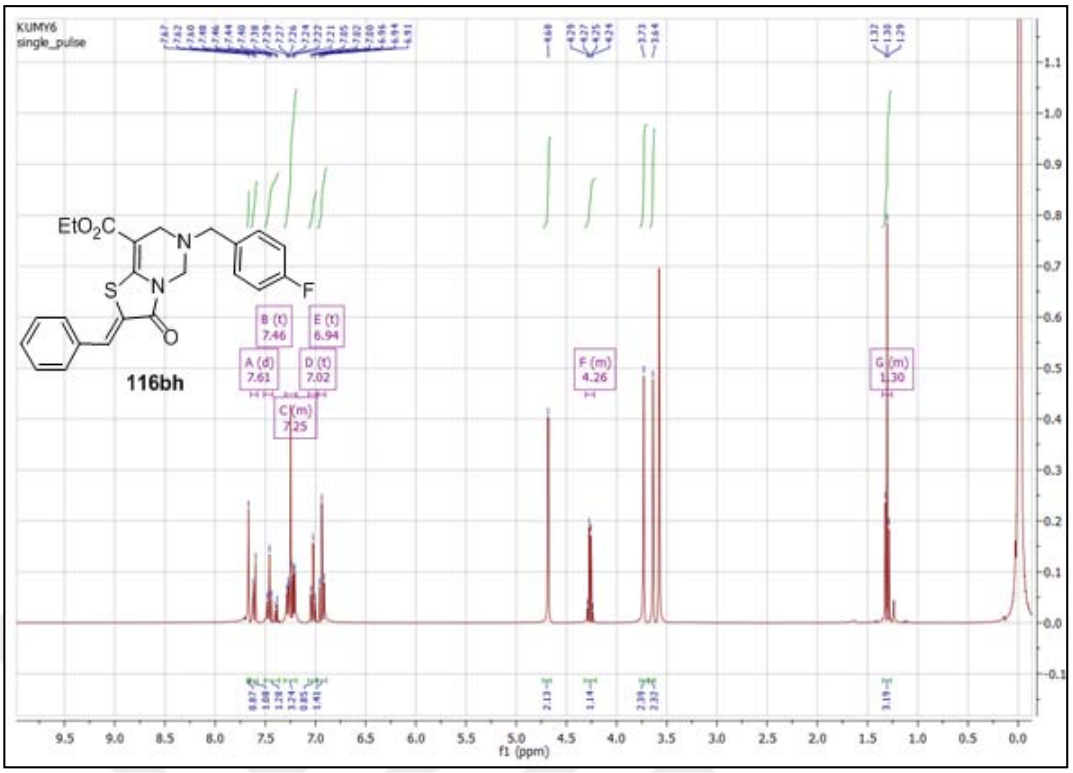

Figure 7.147. ^{1}H-NMR Spectrum of compound **116bh**.

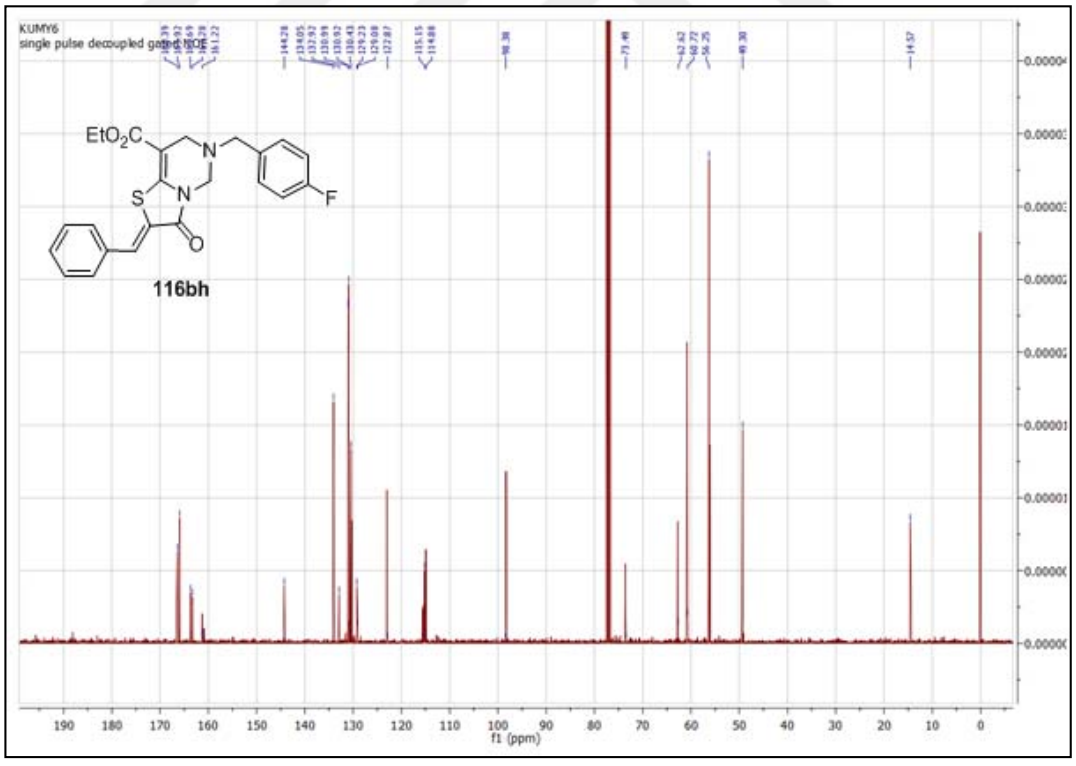

Figure 7.148. ^{13}C-NMR Spectrum of compound **116bh**.

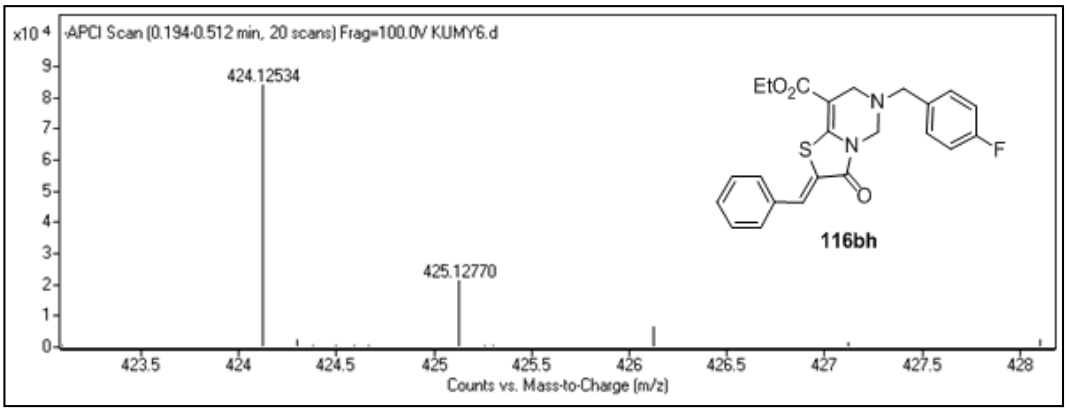

Figure 7.149. HRMS Spectrum of compound **116bh**.

8. CURRICULUM VITAE

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List of Presentations in International Conferences:

1- Kübra Uysal, Muhammet Yıldırım. *Simple Way to New Substituted Oxothiazolo[3,2-c]pyrimidines* (Poster Presentation), International Euroasian Conference on Biological and Chemical Sciences (EuroasianBiochem 2018), 26-27 April 2018, Ankara, TURKEY.