A CONVENIENT ONE-POT MULTI-COMPONENT PREPARATION OF NOVEL THIAZOLO[3,2-a] PYRIDINE SCAFFOLDS

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THESIS SUBMITTED TO THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES OF THE ABANT IZZET BAYSAL UNIVERSITY IN PARTIAL FULLFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN THE DEPARTMENT OF CHEMISTRY

JANUARY 2015

Approval of the Graduate School of Natural and Applied Science

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I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science.

Prof. Dr. Nedime DÜRÜST
Head of Chemistry Department

This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality as a thesis for the degree of Master of Science.

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ABSTRACT

A CONVENIENT ONE-POT MULTI-COMPONENT PREPARATION OF NOVEL THIAZOLO[3,2-a] PYRIDINE SCAFFOLDS

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In recent years, various heterocyclic compounds are being synthesized by using multi-component reactions and their biological activities are being examined. The aim of this project is to develop and optimize a multicomponent reaction of thiazoli(n)dines to form biologically interesting thiazolo[3,2-a]pyridines and to apply the method to the synthesis of different sorts of heterocycles to get a better understanding of the mechanism of this transformations. In the first part of this study, a series of 5-amino-7-aryl-8-nitrothiazolo[3,2-a]pyridines have been prepared using aromatic aldehydes, active methylene group containing nitriles (malononitrile, ethyl 2-cyanoacetate and 2-phenylsulfonylacetonitrile) and 2-nitromethylene thiazoline in presence of triethylamine in acetonitrile. In second part of this study, an efficient synthesis of 5-amino-7-aryl-3-oxo-8-(phenylsulfonyl)-

thiazolo[3,2-a]pyridine-6-carbonitrile derivatives was conducted utilizing multi-component reaction of aromatic aldehydes, malononitrile and 2-phenylsulfonylmethylene thiazolidin-4-one. Depending on the equivalance of the aromatic aldehyde, two different products were obtained. The structures of all multi-component reaction products have been characterized by means of spectroscopic methods IR, ^{1}H NMR, ^{13}C NMR, HRMS and physical characteristics (melting point and Rf values).

Key words: Multi-component reactions, Knoevenagel reaction, thiazoline, thiazolidin-4-one, thiazolopyridine

ÖZET

YENİ TİYAZOLO[3,2-a] PİRİDİN YAPILARININ ÇOK BİLEŞENLİ TEK BASAMAKLI REAKSİYONLAR YOLUYLA BASİTÇE SENTEZLENMESİ

Caner, Esra
Yüksek Lisans Tezi, Kimya Bölümü
Tez Danışmanı: Yard. Doç. Dr. Cevher ALTUĞ

Ocak 2015, 158 Sayfa

Son yıllarda, çeşitli hetero halkalı bileşikler çok bileşenli reaksiyonlar kullanılarak sentezlenmekte ve bu bileşiklerin biyolojik aktiviteleri incelenmektedir. Bu çalışmanın amacı tiyazoli(n)din in çok bileşenli reaksiyonlarını biyolojik açıdan ilginç tiyazolo[3,2-a]piridinleri oluşturmak ve reaksiyonları optimize ederek bu yöntemi farklı türlerde heterohalkalar sentezinde uygulayarak reaksiyonun oluşum mekanizmasının daha iyi anlaşılmasını sağlamaktır. Bu çalışmanın ilk kısmında, trietilamin varlığında aromatik aldehitler, nitril içeren aktif metilen grubu (malononitril, etil 2-siyanoasetat, 2-fenilsülfonilasetonitril) ve 2-nitrometilentiyazolidin bileşiklerini çoklu bileşen reaksiyonlarını kullanarak bir seri 5-amino-7-aril-8-nitrotiyazolo[3,2-a]piridin hazırlanmıştır. Bu çalışmanın ikinci kısmında ise, 5-

amino-7-aril-3-okzo-8-(fenilsülfonil) tiyazolo[3,2-a] piridin-6-karbonitril türevlerinin sentezi, aromatik aldehitler, malononitril ve 2-fenilsülfonilmetilentiyazolidin-4-on un çoklu bileşen reaksiyonları kullanılarak yüksek verimle gerçekleştirilmiştir. Başlangıçta kullanılan aromatik aldehitlerin katsayılarına göre iki farklı ürün elde edilmiştir. Çok bileşenli reaksiyon ürünlerinin yapı tayinleri spektroskopik olarak IR, ^{1}H NMR, ^{13}C NMR, HRMS ve fiziksel sabitler (erime noktası ve Rf değerleri) yardımıyla karakterize edilmiştir.

Anahtar kelimeler: Çok bileşenli reaksiyonlar, Knoevenagel reaksiyonu, tiyazolin, tiyazolin-4-on, tiyazolopiridin

To my big family

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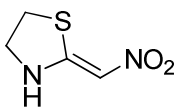
Finally, I would like to thank to my family, they were always supporting and encouraging me with their best wishes.

FORMULAE



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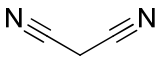

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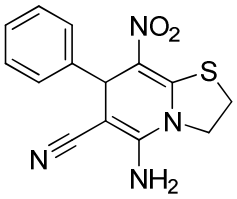

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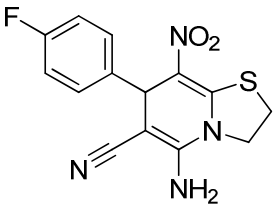

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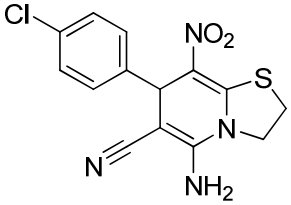

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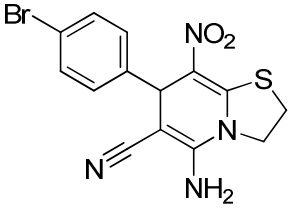

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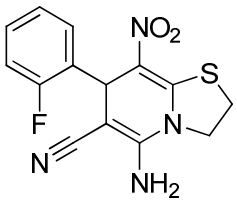

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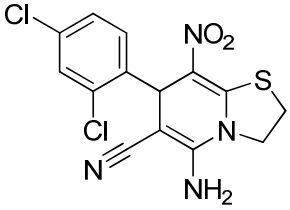

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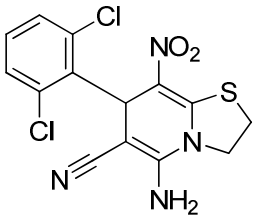

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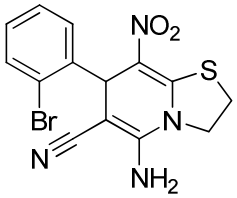

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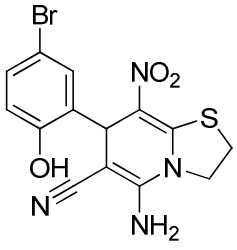

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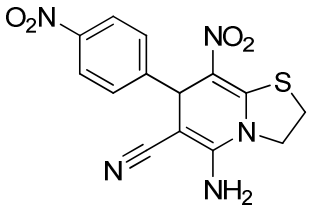

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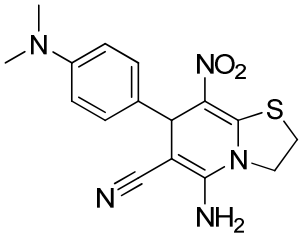

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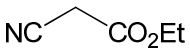

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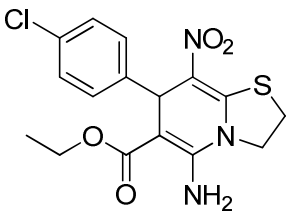

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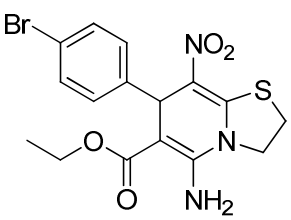

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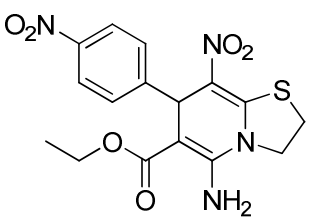

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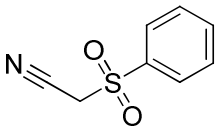

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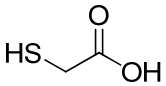

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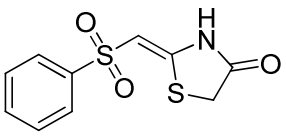

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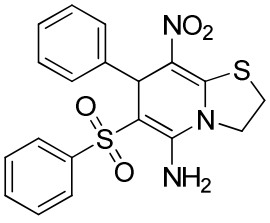

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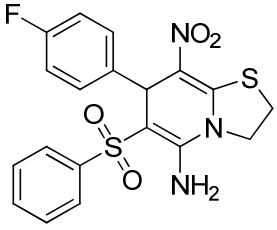

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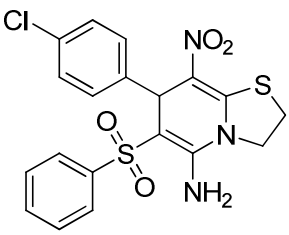

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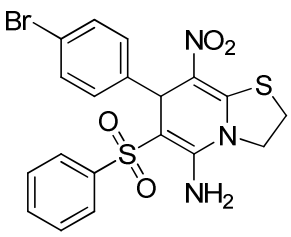

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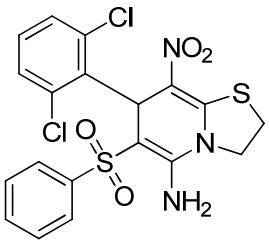

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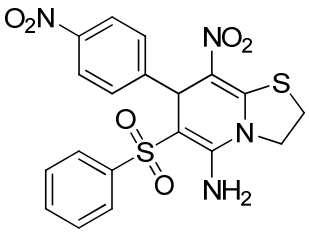

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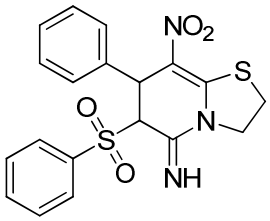

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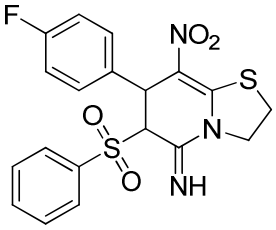

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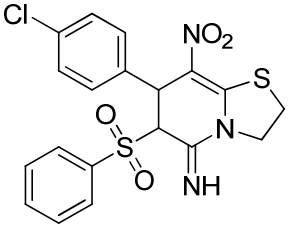

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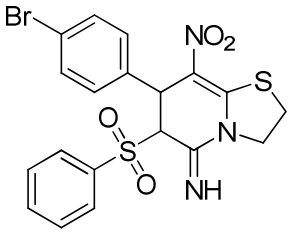

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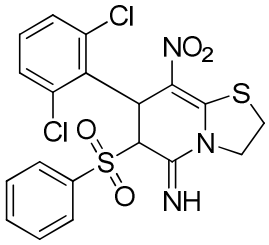

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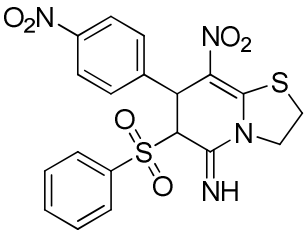

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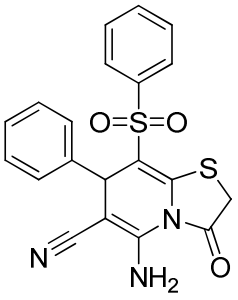

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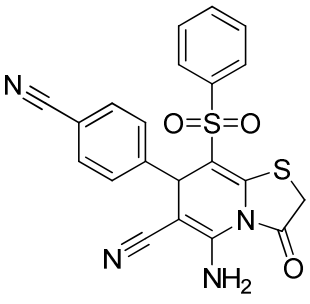

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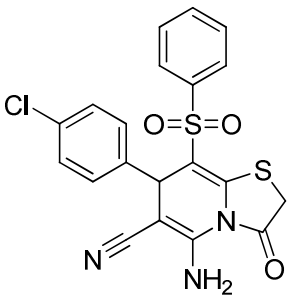

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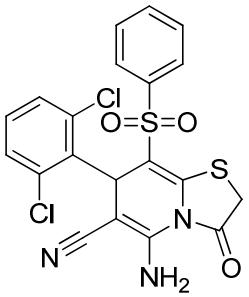

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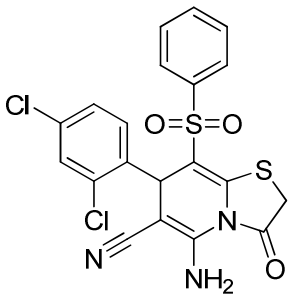

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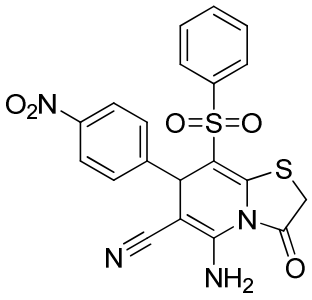

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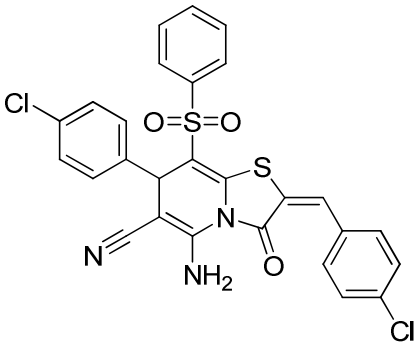

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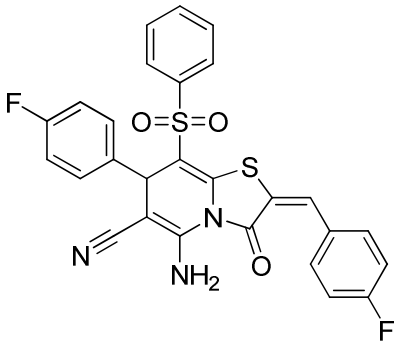

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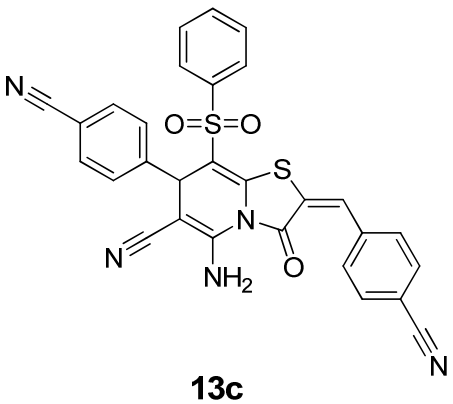

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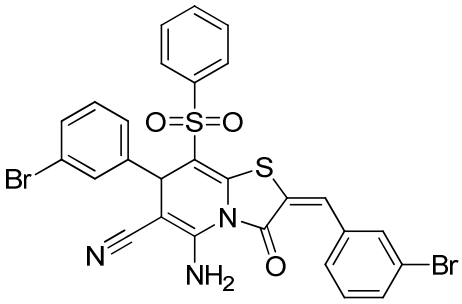

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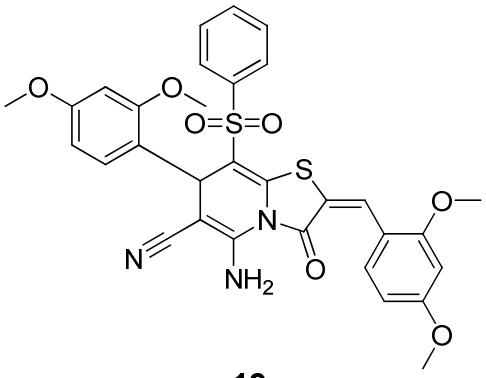

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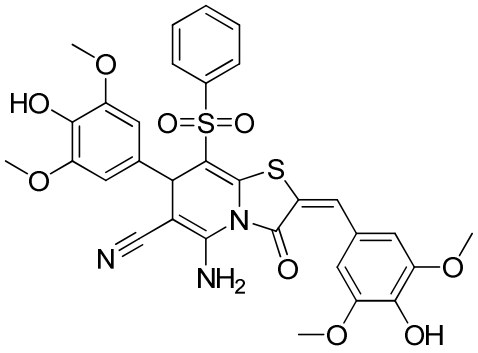

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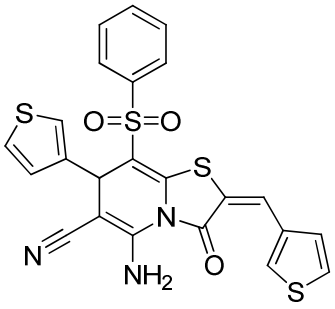

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ABBREVATIONS

Ac_2O	Acetic anhydride
CH_3COOH	Acetic acid
$CHCl_3$	Chloroform
CN	Nitrile
Comp.	Compound
Cys-OMe.HCl	L-cysteine methyl ester hydrochloride
d	Doublet (NMR)
dd	Doublet of doublet (NMR)
decomp.	Decompose
DEPT	Distortionless Enhencment by Polarization Transfer
d_6-DMSO	Deuterated dimethyl sulfoxide
DMAD	Dimethyl acetylenedicarboxylate
DMSO	Dimethyl sulfoxide
EtOH	Ethyl Alcohol
Et_3N	Triethylamine
eq.	Equivalent
FT-IR	Fourier Transform Infrared Spectroscopy
h	Hour
H-4CR	Hantzsch four component reaction

HCN	Hydrogen cyanide
HCl	Hydrochloric acid
HCT-116cells	Human COLORECTAL CARCINOMA cell line
HIV	Human Immunodeficiency Virus
Hz	Hertz
$IMCR_S$	Isocyanide Multi Component Reaction
J	Coupling constant (NMR)
KBr	Potassium bromide
MAO-B	Monoamide oxidase beta inhibitor
MH_Z	Megahertz
mg	Milligram
mmol	Millimolar
mL	Milliliter
m.p	Melting point
M^+	Molecular ion
$M\text{-}H^+$	Protonated molecular ion
m	Multiplet (NMR)
MCR	Multi-component reaction
MeCN	Acetonitrile
NMR	Nuclear magnetic resonance
NH_3	Ammonia
PMBA	p-chloromercuricbenzoicacid
P-3CR	Passerini three component reaction
R	Any group

Rf	Retardation factor
SAR	Structure Activity Relationship
s	Singlet
TLC	Thin layer chromatography
THF	Tetrahydrofuran
t	Triplet
Ugi-4CR	Ugi four component reaction
X	Any halogen atom
1,4-DPH	1,4-dihydropyridines
$\square_{max}$	Maximum frequency
δ	Chemical shift
Δ	Heat

CHAPTER I

1. INTRODUCTION

1.1. Definition of Multi-Component Reactions

Nowadays, the aim of the organic synhesis is to obtain a molecule from the reaction which has the easily available starting materials, high yield (total conversion), low cost (readly available reaction set up), low energy and environmentally friendly work-up steps.[1] For this reasons, one pot multi component reactions gain much importance.[2,3]

A multi-component reaction (MCR) is a domino reaction in which three or more easily accessible starting compounds are combined together in a single reaction vessel to produce a final product.[4] They are practically single-step conversions in which the reactions with an irreversible step. At this step the total equilibrium is shifted to the side of the products and increse the bond forming efficiency. Acording to the researches of Tietze,[3] highly efficient process means creating several bonds per reaction to generate molecular complexity.

Multi-component reactions are particularly effective at building functionalised drug-like structures.[5,6] Being one-pot reaction properties of

MCRs produce many advantages. Thanks to this features, very large library of different products can be built up within a short time and minimum effort by using small set of starting materials.[7] In the last decade, the importance of MCRs for drug discovery has been recognized and considerable. Inventing and developing new MCR processes are important pursuits in academic, industrial and pharmaceutical chemistry.[6,8,] Furthermore, the utility of the rigid well-defined structures of heterocycles was demonstrated in many detailed structure activity relationship(SAR)-studies.[9,10]

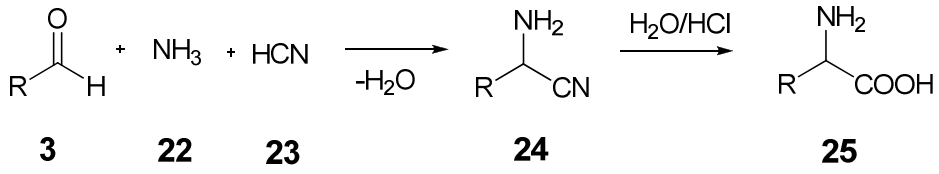
Multicomponent reactions (MCRs) have found increasing interest in assembling complex pharmacologically important structures in a small number of steps with the additional point of diversity in recent decades. Among these structures thiazolopyridine containing compounds have been studied due to their unique chemical and biological activities [11,12,13] such as antibacterial, antimicrobial, α-glucosidase inhibitor[14] and cholestrol controlling agent[15].

The chemistry of 2-alkylidenethiazolidin-4-one compounds has been extensively studied over the years. These compounds can be used for the synthesis of diverse functionalized molecules, depending on the substituent of the alkylidene part,[16] and scaffolds prepared using these compounds have shown to exhibit various biological properties.[17]

1.2. History of Multi-Component Reactions (MCRs)

Multicomponent Reactions (MCRs) are ordered pot reactions, in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly formed product.[18]MCRs are well known to be easy to perform, available starting materials, providing good yields, take less time[19] because of this properties they have been studied for over 150 years.

In 1850, Strecker reaction was develop by Adolph Strecker[20] that is known as the first MCR reaction. It is a three component reaction between aldehyde **(3)**, an amine (ammonia) **(22)** and hydrogen cyanide **(23)** to form an α-amino nitrile **(24)**. After researches, an α-amino nitrile is subsequently hydrolyzed to give the desired amino-acid **(25)**.

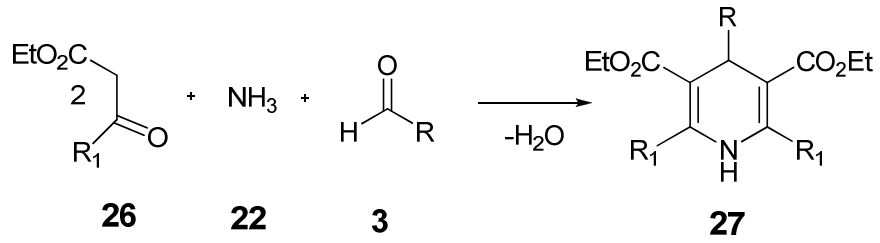


3 **22** **23** **24** **25**

Scheme 1.1. Amino-acid synthesis from The Stecker three component reaction.

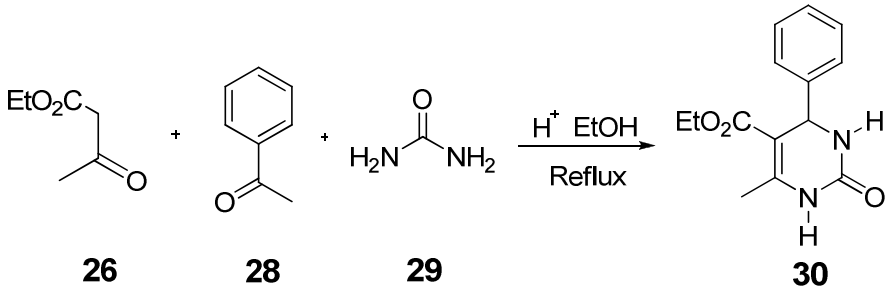
In 1882, 1,4-dihydropyridines which constitutes many important heterocycle system were first synthesized via MCRs by Arthur Rudolf Hantzsch.[21] This is a four component reaction and the product known as 1,4-DHP compound or a Hantzsch compound. He synthesized symmetrically

substituted dihydropyridines **(27)** from ammonia **(22)**, aldehyde **(3)** and two equivalents of β-ketoesters **(26)**.



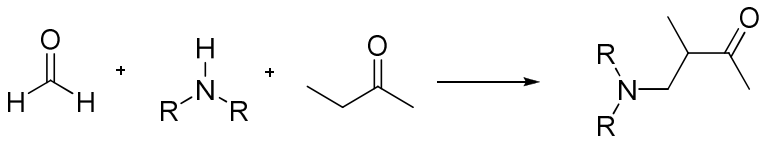
Scheme 1.2. 1,4-dihydropyridine synthesis from Hantzsch four component reaction.

In 1893, Italian chemist Pietro Biginelli described the acid-catalyzed cyclo-condensation reaction of ethyl β-ketoester **(26)**, benzaldehyde **(28)** and urea **(29)**. The reaction was realized at reflux temperature with three components dissolved in ethanol using a catalytic HCl. Dihydropyrimidinones **(30)**, the products of this novel one-pot Biginelli reaction, are widely used in the pharmaceutical industry[22] because pyrimidine derivatives have important biological properties as calcium channel blockers and antihypertensive agents.[23,24]



Scheme 1.3. Dihydropyrimidinone synthesis of one-pot Biginelli reaction.

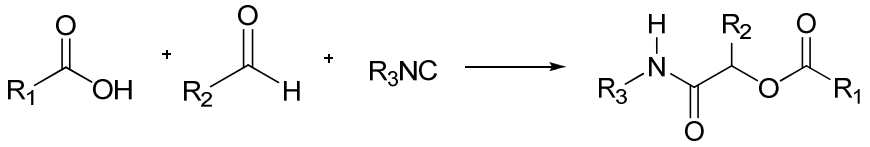
In 1912, the one-pot multi-component synthesis of β-aminocarbonyl compound was discovered by Carl Mannich[25] using formaldehyde **(31)** , secondary amine **(32)** and ketones **(33)**. The final product is a β-amino-carbonyl **(34)** compound also known as a Mannich base.



31 **32** **33** **34**

Scheme 1.4. β-amino-carbonyl synthesis that is also known as a Mannich base.

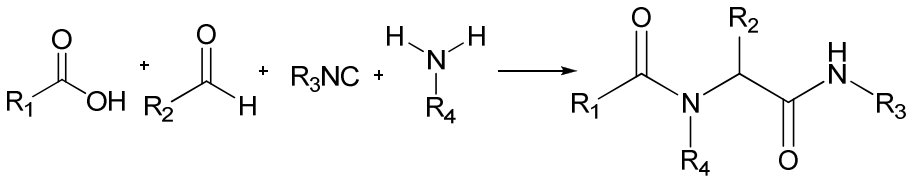
A large and important class of MCRs is based on the chemistry of isocyanide (IMCRs), one of the most important of these are the Passerini three-component reaction (P-3CR).[13] It was described for the first time in 1921,[26] involves an oxo-component (an aldehyde or a ketone) **(36)**, an isocyanide **(37)** and a nucleophile (typically a carboxylic acid) **(35)** to afford α-acyloxycarboxamides **(38)**. The high efficiency of the isocyanide based product currently plays a central role in synthetic organic chemistry. [6]



35 **36** **37** **38**

Scheme 1.5. α-acyloxycarboxamides synthesis by Passerini three-component reaction.

One of the most important multicomponent reactions was discovered in 1959 by Ugi[27] . The Ugi reaction is an isonitrile-based MCR that provides a rapid route for the preparation of α-acylamino amide derivatives by using aldehydes, primary amines, carboxylic acids and isocyanides. Ivan Carl Ugi was developped the Passerini reaction[28,29], described for the first time in 1921, involves an oxo-component (an aldehyde or a ketone) **(36)**, an isocyanide **(37)** and a nucleophile (typically a carboxylic acid) **(35)** to afford α-acyloxycarboxamides. To obtain final Ugi product, α-acylamino amides**(40)**, an amine **(39)** was added for fourth reactant because it is indeed the reaction of a Schiff base. The Ugi reaction can be coupled with a post condensation reaction to increase the number of possible pharmacologically important scaffolds.[30]



35 **36** **37** **39** **40**

Scheme 1.6. α-acylamino amide synthesis by using Ugi reaction.

Thanks to the discovery and development of Passerini and Ugi reactions, many new biological active natural products IMCRs were described. [31,32] Furthermore, they are widely applied in the construction of biologically relevant heterocycles such as oxazoles[33], oxazolines, thiazoles, thiazolines, pyrroles, imidazoles and imidazolines.[34] Therefore, the

isocyanides constitute a widely appreciated compound class in preparative and drug researches in medicinal chemistry.[6]

1.3. Some Important Drug-Like Structure Synthesized by MCRs

After fifty years, based on the Hantzsch synthesis, the Nifedipine (Adalat^{R}) which is used for the therapy of cardiovascular disease and calcium channel blocker was successfully prepared by the Bayer AG company.[33]

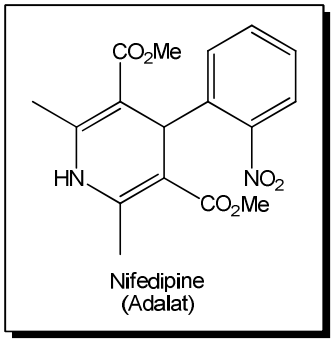
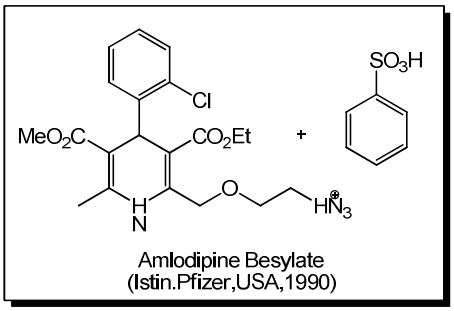
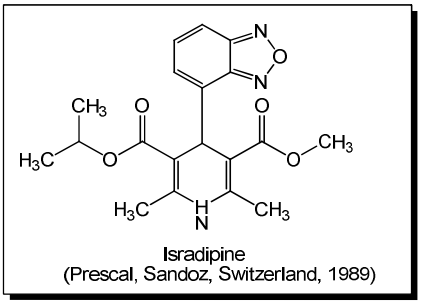


Figure 1.1. The one-step synthesis of Nifedipine, by Bayer AG company.

On the basis the biological activity of Nifedipine, some major pharmaceutical companies as Pfizer, Sandoz, Bayer are synthesised their original molecules like Nifedipine.





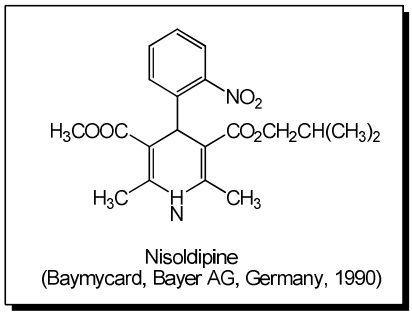


Figure 1.2. Some original molecules which they act like Nifedipine.

Scientists at the Merck company modified the original synthesis of the anti–HIV drug Crixivan(Indinavir) by incorporating a Ugi–4CR, thus making the synthesis shorter, easier and better yielding.[35]

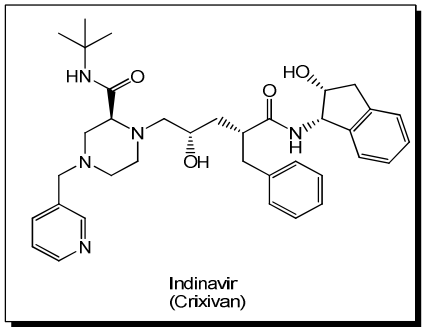


Figure 1.3. The anti-HIV drug Crixivan by incorporating a Ugi-4CR.

Lidocaine, the first amino-amide type local anesthetic and antiarrhythmic drug obtained from the three component reaction of formaldehyde, piperidine and 2,6-dimethylphenylisocyanide, was first synthesized under the name Xylocain® by Swedish chemist Nils Löfgren in 1943.[36]

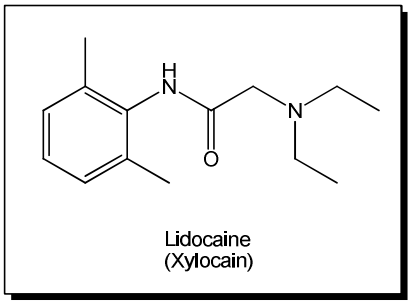


Figure 1.4. Lidocaine, the first amino-amide type local anesthetic and antiarrhythmic drug.

1.4. Thiazolo[3,2-a]pyridines

The thiazolopyridine ring system contains two fused heterocylic structure and there are six isomeric thiazolopyridine systems reported in the literature. Depending on the fusion of the thiazole moiety to the pyridine ring, thiazolopyridines can be classified into the following classes (see Figure 1.5.): Thiazolo[3,2-a]pyridine (**I**), thiazolo[3,4-a]pyridine (**II**), thiazolo[5,4-b]pyridine (**III**), thiazolo[5,4-c]pyridine (**IV**), thiazolo[4,5-c]pyridine (**V**), and thiazolo[4,5-b]pyridine (**VI**). [37]

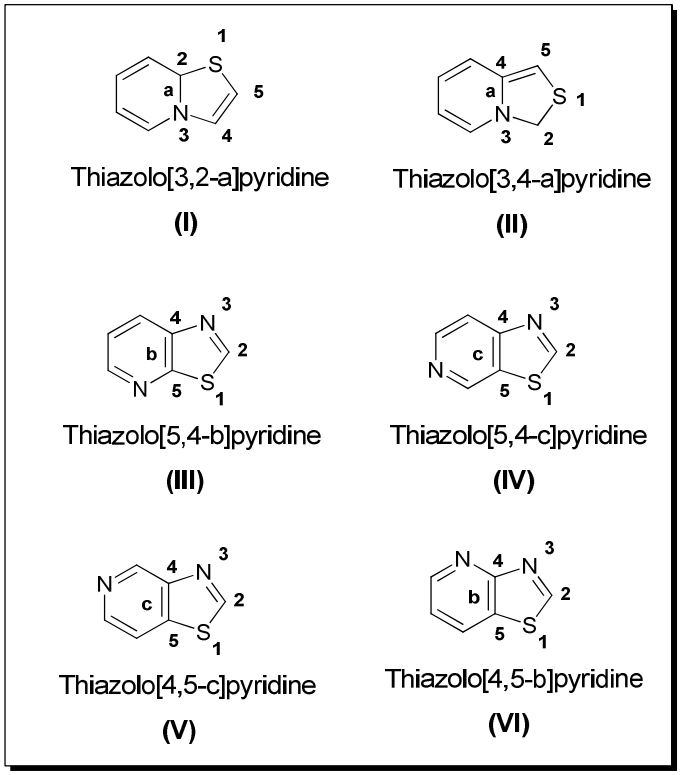


Figure 1.5. Thiazolopyridines can be classified into six isomeric pyridine rings.

The thiazolopyridines are found in a wide range of biologically active compounds. Especially, thiazolo[3,2-a]pyridine derivatives have potential anticancer activity and are used in chemotherapical treatment such as lung cancer, leukemia and melanoma.[38] Thiazolo[3,2-a]pyridine derivatives also have alpha glucosidase inhibitor (used as anti-diabetic drug)[39] , antimicrobial activity,[40] anti-imflammatory (are used in the treatment of a number of arthritic diseases)[41] and analgesic[42] properties. Some examles of thiazolopyridines with biological and pharmacological activities.

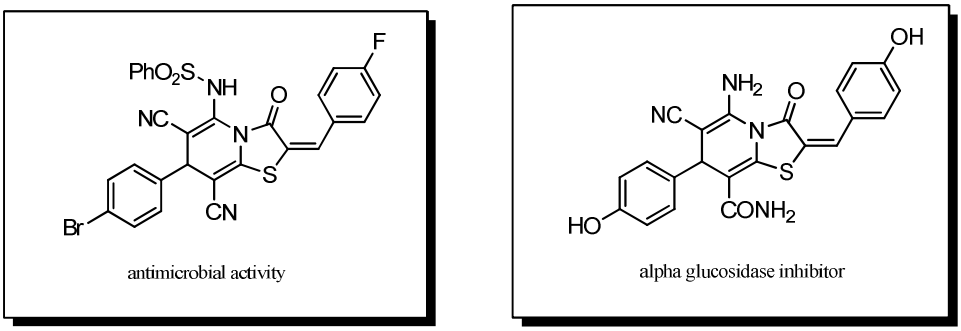
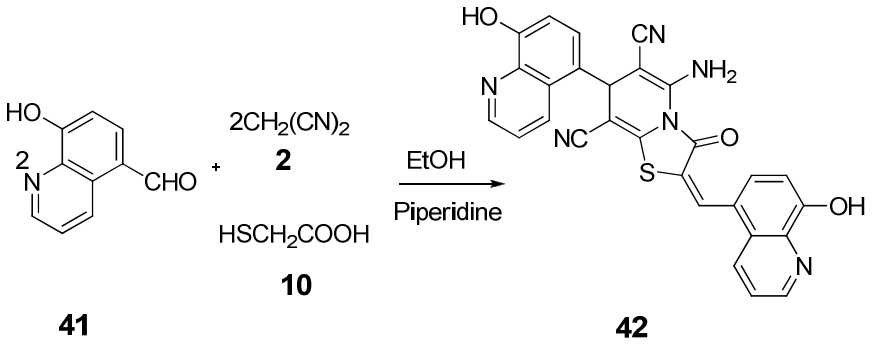


Figure 1.6. Some examles of thiazolopyridines with biyological and pharmacological activities.

In recent years, thiazolopyridines have been of interest due to their vital role in treatment of Parkinson's disease. Thiazolopyridines as monoamine oxidase B inhibitors (MAO-B) has been a therapeutic target of Parkinson's disease.[43] Due to their biological importance, thiazolopyridine derivatives have become targets for many organic and medicinal chemists.[44]

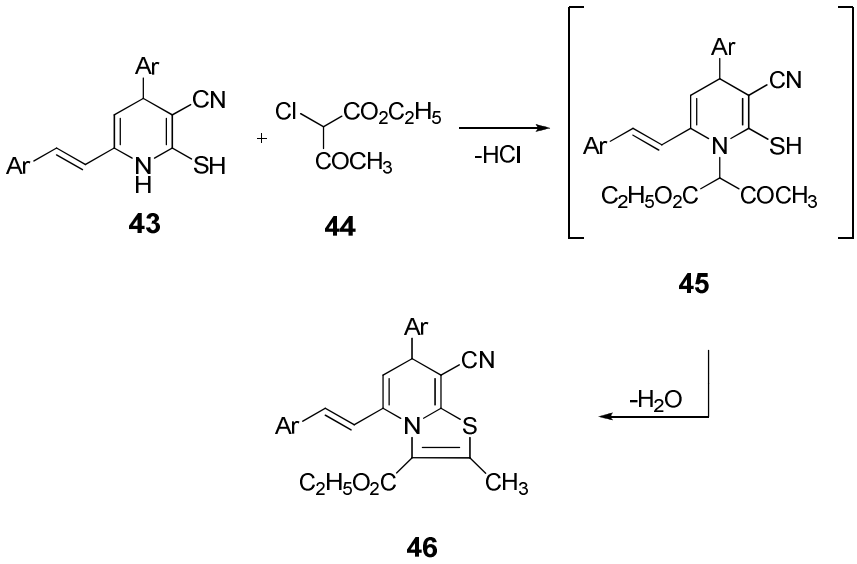
1.4.1. Synthetic Methods to Obtain Thiazolo[3,2-a]-pyridines

The synthesis of thiazolo[3,2-a]pyridines **(42)** was basically obtained from the reaction of the 2 equivalence of 8-hydroxyquinoline-5-carbaldehyde **(41)** with 2 equivalance of malononitrile **(2)** and thioglycolic acid **(10)** in ethanol with a catalytic amount of piperidine. Screening Antifungal tests for quinoline substitute some of these thiazolopyridine compounds showed active against four species of fungi.[45]



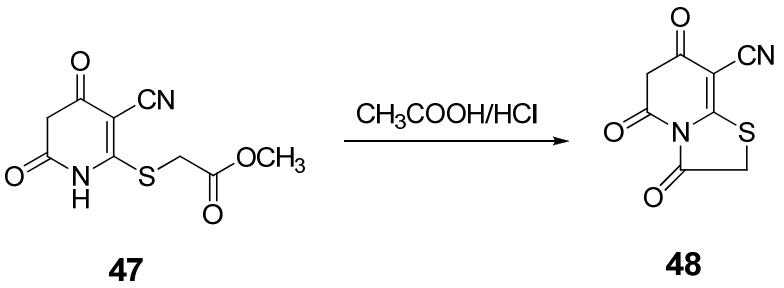
Scheme 1.7. Synthesis of thiazolopyridine derivatives by Marzoog S. Al-Thebeiti.

Dihydropyridines **(43)** can provides convenient access to thiazolo[3,2-a]-pyridine compounds, via initial dehydrochlorination with ethyl α-chloroacetoacetate **(44)** in glacial acetic acid to yield the condensation intermediate **(45)**, which then could be cyclized through enolization and loss of a water molecule under the applied reaction condition to furnish the final isolable **(46)**.[46]



Scheme 1.8. Synthesis of thiazolo[3,2-a]-pyridine compounds using Dihydropyridines.

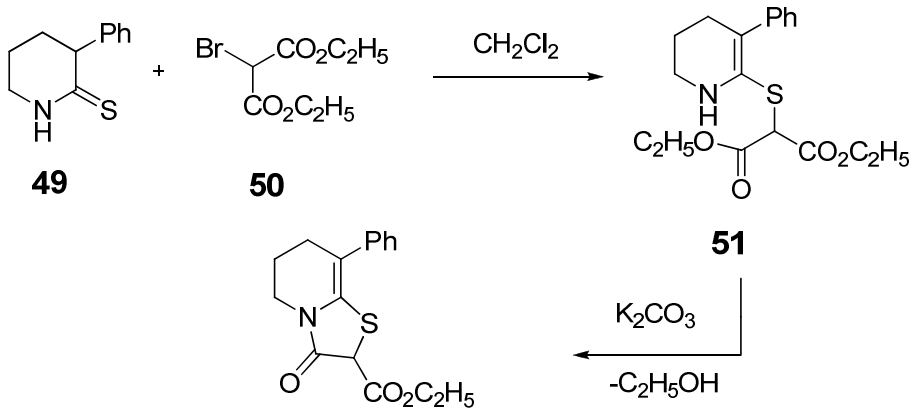
The same approach also utilized by reacting 5-cyano-2,4-dioxo-6-methoxycarbonyl methylthio-tetrahydropyridine **(47)** with acetic acid and hydrochloric acid to prepare thiazolo[3,2-a]pyridine derivatives with high yields. **(48)**.[47]



47 **48**

Scheme 1.9. Synthesis of thiazolo[3,2-a]pyridine derivatives with 5-cyano-2,4-dioxo-6-methoxycarbonyl methylthio-tetrahydropyridine.

The reaction of thiolactam (**49**) with diethyl bromomalonate (**50**) yielded thioimide (**51**), which on refluxing in the presence of potassium carbonate, afforded ethyl thiazolo[3,2-a]pyridine-2-carboxylate (**52**).[48]

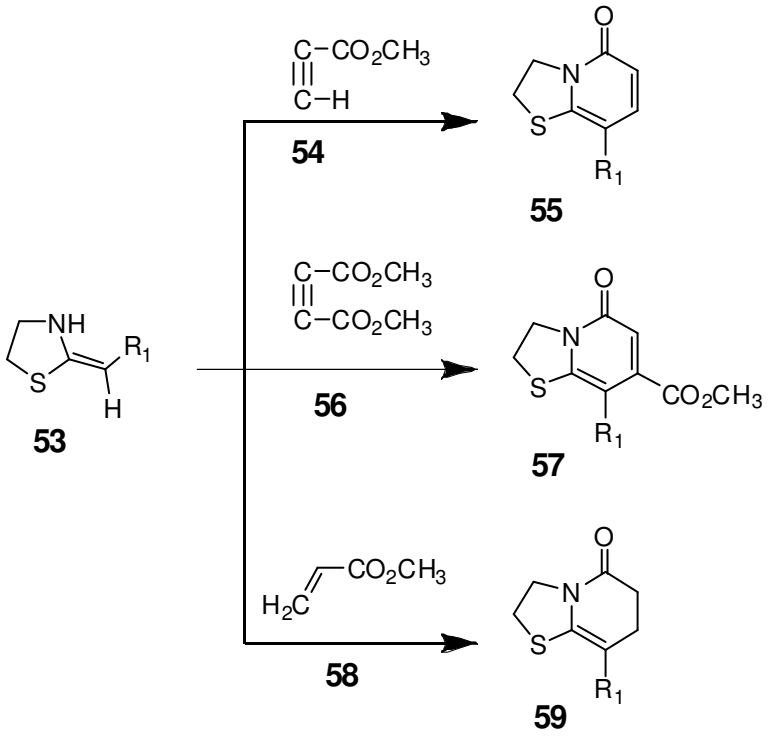


49 **50** **51**

52

Scheme 1.10. Synthesis of ethyl thiazolo[3,2-a]pyridine-2-carboxylate.

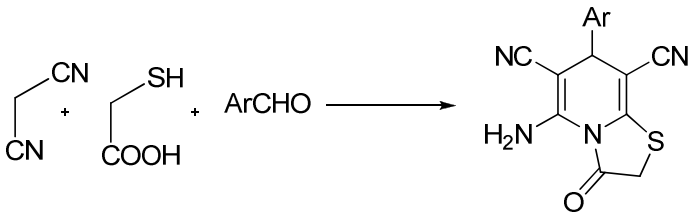
2-Methylenethiazoline (**53**) reacted readily with methyl propiolate **(54)** to produce thiazolo[3,2-a]pyridines **(55)** and 2-Methylenethiazoline (**53**) reacted with dimethyl acetylenedicarboxylate (**56**) to produce thiazolo[3,2-a]pyridines (**57**). Compounds (**53**) also reacted with methyl acrylate (**58**) in boiling ethanol to yield thiazolo[3,2-a]pyridines[49] (**59**).



Scheme 1.11. Synthesis of thiazolo[3,2-a]pyridine derivatives with 2-Methylenethiazoline.

Li et al. reported the green chemoselective synthesis of thiazolo[3,2-a]pyridine **(61)** derivatives with three-component reactions of malononitrile **(2)**, aromatic aldehydes **(60)** and 2-mercaptoacetic acid **(10)**. These compounds were subject to the experiments of antioxidant activity and

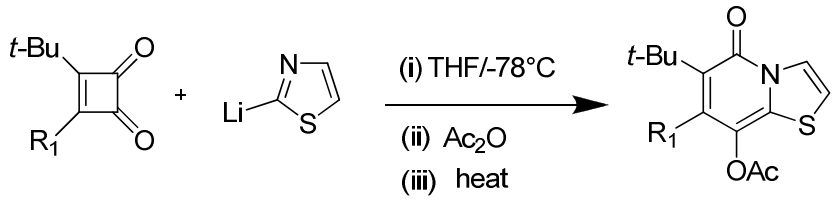
cytotoxicity to carcinoma HCT-116 cells and mice lymphocytes and showed promised anti-cancer properties.[50]



2 **10** **60** **61**

Scheme 1.12. Green chemoselective synthesis of thiazolo[3,2-a]pyridine derivatives and evaluation of their antioxidant activity and cytotoxicity.

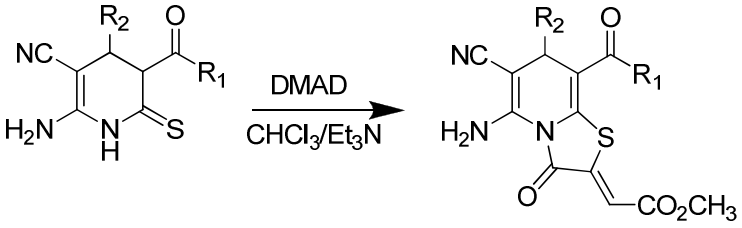
Moderate-to-high yields of *tert*-butyl substituted thiazolo[3,2-a]pyridines (**64**) were obtained by the addition of 2-lithiothiazole (**63**) to *tert*-butylcyclobutene-1,2-diones (**62**) followed by an acetic anhydride quench and the thermolysis of the crude reactions products[51]



62 **63** **64**

Scheme 1.13. Synthesis of tert-butyl substituted thiazolo[3,2-a]-pyridine compounds.

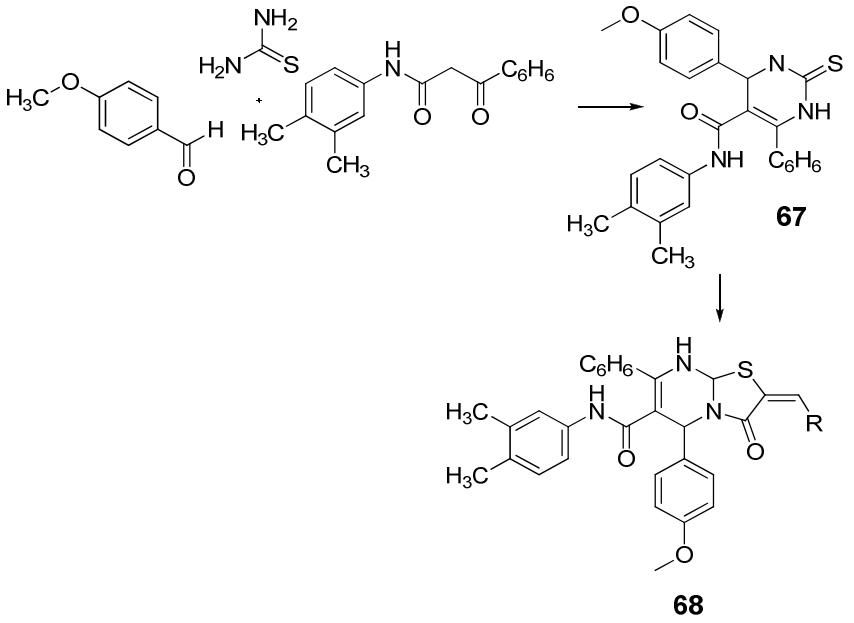
The reaction of pyridinethiones **(65)** with dimethyl acetylenedicarboxylate (DMAD) in chloroform in the presence of triethylamine affords thiazolo[3,2-a]pyridines **(66)**[52] in good yields.



65 **66**

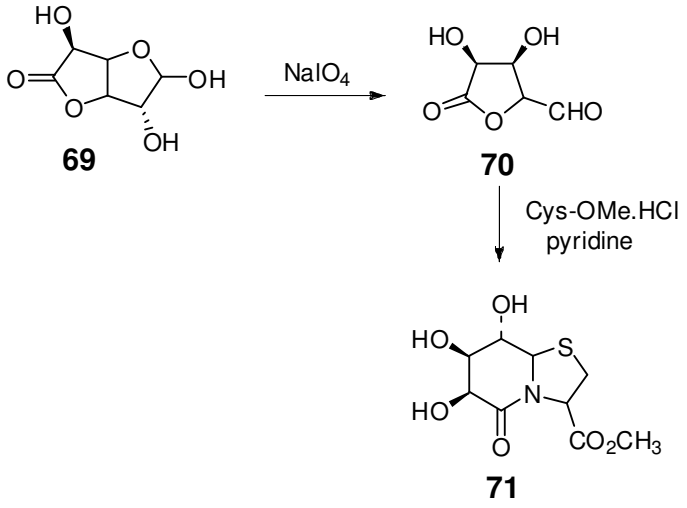
Scheme 1.14. Synthesis thiazolo[3,2-a]-pyridine compounds from the reaction of pyridinethiones.

Synthesis and biological evalution of thiazolo[3,2-a]pyrimidine derivatives **(68)** as a new type of potential antimicrobial agents were observed by Bapodra et al. The final products were synthesized under reflux condition by a simple one pot condensation reaction of 4-[(p-methoxyphenyl)-5-(3,4-dimethyl)-phenyl amino carbonyl]-6-phenyl-1,4-dihydro pyrimidin-2(1H)-thiones **(67)** and monochloro acetic acid, glacial acetic acid, acetic anhydride and different aromatic aldehydes in the presence of sodium acetate where, thiopyrimidine derivatives were prepared by three component.[53]



Scheme 1.15. The final products have potential antimicrobial agents.

Periodate cleavage[54] of D-glucurono-3,6-lactone (**69**) yielded D-arabinurono-2,5-lactone (**70**), which combined with L-cysteine methyl ester hydrochloride to give the methyl (3*R*, 6*S*, 7*R*, 8*S*, *8aS*)-6,7,8- trihydroxy-5-oxohexahydro-5 *H*-[1,3]-thiazolo[3,2-a]pyridine-3-carbox- ylate (**71**).



Scheme 1.16. Syntesis of thiazolo[3,2-a]pyridine-3-carbox- ylate derivatives.

CHAPTER II

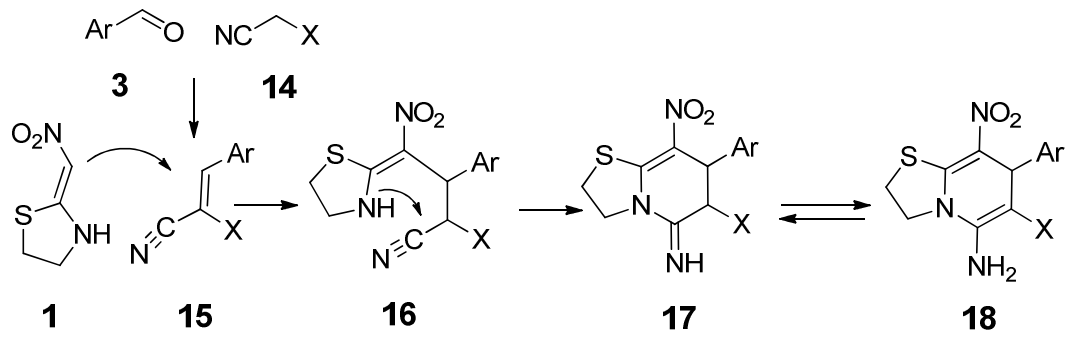
2. RESULTS and DISCUSSION

The synthetic applications of 2-phenylsulfonylmethylenethiazolidin-4-one and 2-nitromethylene thiazolidines are very uncommon in the literature comparing to those of 2-alkylidenethiazolidin-4-ones.[55] This has encouraged us to investigate these substances in multicomponent reactions, since phenylsulfonyl and nitro substituents increases biological activity in some heterocyclic compounds.[56]

Nitro containing compunds have been studied over the years. Interesting chemical behaviour of these compounds coming from their being uniqe starting materials for a diverse functionalized compounds.[57] Especially, heteroatom containing nitroalkenes are good electrophiles that reacts to give conjugate addition reactions with nucleophiles and radicals. In addition, they are also used in cycloaddition reactions as dienophiles.[58,59] Despite the proven synthetic utility of the 2-methylene substituted-thiazolidine compounds which contains both electrophilic and nucleophilic centers, reaction of 2-nitromethylene thiazolidine has been rarely investigated.[60] In the first part of this work, we studied a general MCRs of 2-nitromethylene thiazolidines with active methylene containing nitriles, since, to our best knowledge of literature there is no report of multicomponent reactions of 2-

nitromethylene thiazolidine with nitriles and aldehydes under mild condition through the Knoevenagel reaction, which is a plausible intermediate, and is afforded straightforwardly to 5-amino-7-aryl-8-nitrothiazolo[3,2-a]pyriminides. As active methylene components, malononitrile, ethylcyanoacetate and phenylsulfonylacetonitrile were used.

An easy one-pot process for the condensation of active methylenes of malononitrile/ethylcyanoacetate or phenylsulfonyl acetonitrile with aldehydes in the presence of catalytic amount of Et_3N results thiazolo[3,2-a]pyriminides *via* nucleophilic attack of an NH group on a cyano carbon then tautomerizaton gave the expected products **4a–k** and **6a–c** but when phenylsulfonylacetonitrile was used observed product was enamine – imine tautomers. (see table 2.3.) In all cases, complete consumption of the 2-nitromethylenethiazolidine reagents was observed. All compounds were characterized by spectroscopic and physical methods (IR, ^1H, ^{13}C, HRMS and Mp). Under milder conditions synthesis and work-up with synthesized molecules without chromatography techniques was easy and excellent yields were achieved.



Scheme 2.1. Knoevenagel condensation reaction.

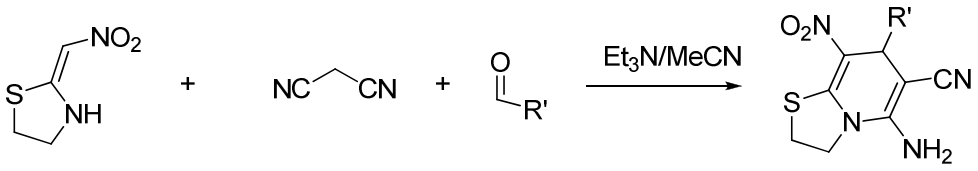
The reaction worked well with a variety of aldehydes including bearing an electron-releasing group in one case **4k**. Even, we have tried different reaction conditions; we couldn't observe MCR of ethylcyanoacetate/phenylsulfonylacetonitrile with electron releasing group bearing aldehydes. Although, using aliphatic aldehydes gave the desired products, which were investigated by ^{1}H NMR, we couldn't separate them to report. Aforementioned reactions were also investigated in water as a solvent and using mortar and pastel without using solvent in both cases we have observed desired products with excellent yields.

Multicomponent reaction of 2-nitromethylene thiazolidine with malonitrile and aromatic aldehydes were carried out in dry acetonitrile at room temperature and monitored by TLC. After 3 h, no starting 2-nitromethylene thiazolidine remained and the reaction went to completion without remaining any starting material. The reaction proceeds rapidly and affords the corresponding thiazolopyridines in high yields. The results shown in Table 2.1 clearly indicate the scope and generality of the reaction with respect to various aldehydes and nitriles. It was clear that amount of Et_3N was not essential to MCR of 2-nitromethylene thiazolidine with cyanomethylene reagents and aldehyde, even we have used different equivalance of base, we didn't use much more effect of it and the reactions were smoothly completed in excellent yield.

Complete cyclications evidence came from ^{1}H NMR analysis, which showed disappearance of the olefinic proton in precursors **1** and distinct

downfield shifts of the compounds **4a-4k**, NH_2 protons appeared at around 6.47-6.72 ppm. The carbon chemical shifts of CN appear at down field regions varying between 180-168 ppm while those of C-7 resonate at high field regions between 36-41 ppm.

Table 2.1. Substituents and yields of compound 4a-4k.



1 **2** **3** **4**

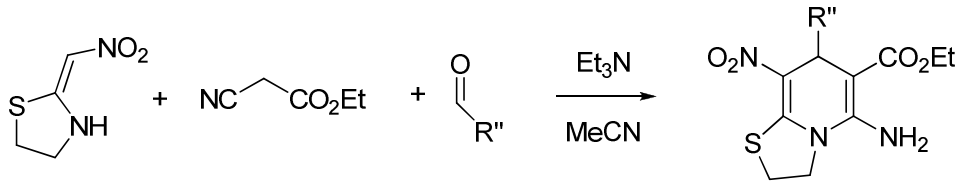
Comp.	R'	Time	Yield/%
4a	C_6H_5	3 h	95
4b	4-FC_6H_4	3 h	90
4c	4-ClC_6H_4	3 h	94
4d	4-BrC_6H_4	3 h	79
4e	2-FC_6H_4	3 h	93
4f	2,4-$DiClC_6H_3$	3 h	99
4g	2,6-$DiClC_6H_3$	3 h	97
4h	2-BrC_6H_4	3 h	97
4i	5-Br-2-OHC_6H_3	3 h	82
4j	4-$NO_2C_6H_4$	3 h	99
4k	4-$NMe_2C_6H_4$	3 h	90

Formation of compounds **6a-6c** can be easily deduced from TLC, disappearance of 2-nitromethylene thiazolidine spots on TLC plate gave us first clue about depicted structure of compounds **6a-6c** in all cases with high

yields. The C=O bond stretching vibration for compounds **6a-6c** is between 1665 - 1667 cm^{-1} and stretching vibration for C=C bond is between 1630 - 1632 cm^{-1}.

This reactions (Table 2.2) also prepared under solvent-free conditions with optaining approximately same yields. 2-Nitromethylenethiazolidine (0.5 mmol, 1 eq.), aromatic aldehyde (0.5 mmol, 1 eq.), ethyl 2-cyanoacetate (0.5 mmol, 1 eq.) and triethylamine (0.25 mmol, 0.5 eq.) were ground together for 10 minutes using a pestle and mortar at ambient temperature. The mixture was then dissolved in ethyl acetate (25 mL) and the solution washed with water (3 x 15 mL). The organic solution was then dried over magnesium sulfate and the solvent removed under reduced pressure. The crude product was recrystallised from hexane/ethyl acetate mixtures to give the pure products with data given below.

Table 2.2. Substituents and yields of compound 6a-6c.



1 **5** **3** **6**

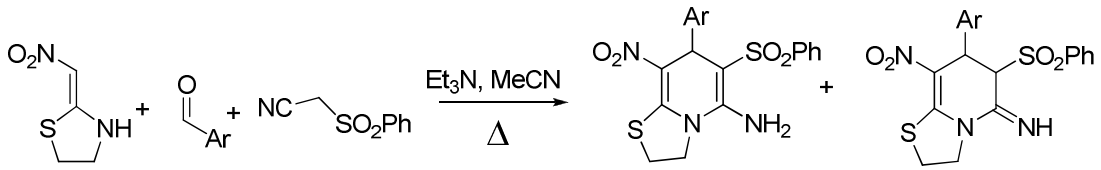
Comp.	R	Time	Yield/%[a]
6a	4-ClC_6H_4	1 h	78 (88)
6b	4-BrC_6H_4	1 h	73
6c	4-$NO_2C_6H_4$	1 h	70 (79)

[a] Yields in parentheses refer to reactions carried out under solvent-free conditions grinding with a pestle in a mortar.

In this reaction, the intermediate could cyclise onto either the nitrile or the ester; only the products **(6a-6c)** of cyclisation onto the nitrile were observed. Although these reactions were carried out for a shorter time compared to the previous experiments. The reactions with malononitrile were not closely monitored, and it is likely that they were also complete within 1 hr.

We wished to expand this repertoire of chemistry to the general preparation of thiazolopyridines and reacted 2-nitromethylenethiazolidine with variety of aldehydes and other electron – withdrawing group on the nitrile functionality. Phenylsulfonylmethyl substitue compounds **8a-f**, **9a-f** interestingly showed enamine – imine tautomers on the ^{1}H NMR spectrum. Inseparable mixtures of the enamine and imine tautomers were isolated by crystallization with the enamine tautomers generally being the major reaction product in most cases.

Table 2.3. Substituents and yields of compound (8,9)a-(8,9)f.



1 **3** **7** **8** **9**

Comp.	Ar	enamine-imine ratio(i)	Time	Yield/%
8a-9a	C_6H_5	1:1.35	1 h	77
8b-9b	4-FC_6H_4	1:0.8	1 h	80
8c-9c	4-ClC_6H_4	1:1.5	1 h	80
8d-9d	4-BrC_6H_4	1:0.7	1 h	63
8e-9e	2,6-$DiClC_6H_3$	1:0.2	1 h	83
8f-9f	4-$NO_2C_6H_4$	1:0.7	1 h	76

i:inseparable mixtures.

The identity of these compounds is fully supported by the spectroscopic data obtained. Compound **4g**, with two *ortho* substituents, showed hindered rotation of the aryl ring, with all fourteen carbon atoms giving distinct resonances in the ^{13}C NMR spectrum, as well as distinct ^{1}H peaks for the three hydrogen atoms on the aromatic ring.

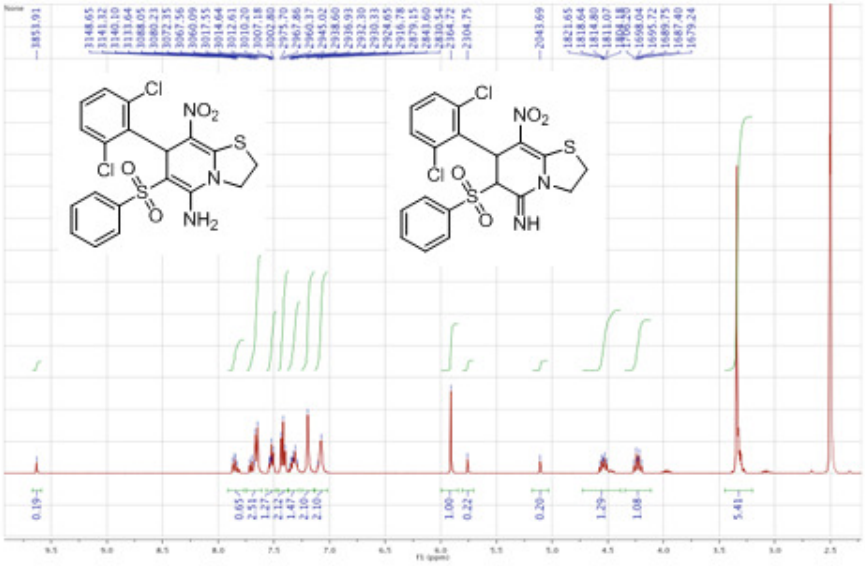


Figure 2.1. ^{1}H NMR spectrum of compound (8e-9e).

It is tempting to attribute the dramatically different ratio on compounds **8e**/**9e** to steric hindrance, although one might have then expected that the imine tautomer would permit the phenylsulfonyl group to position itself further from the 2,6-dichlorophenyl ring. It would appear that the imine tautomer is present in each case as a single diastereoisomer. In order to understand this process, calculations were carried out on compounds **8a**, **9a**, **8e** and **9e**.

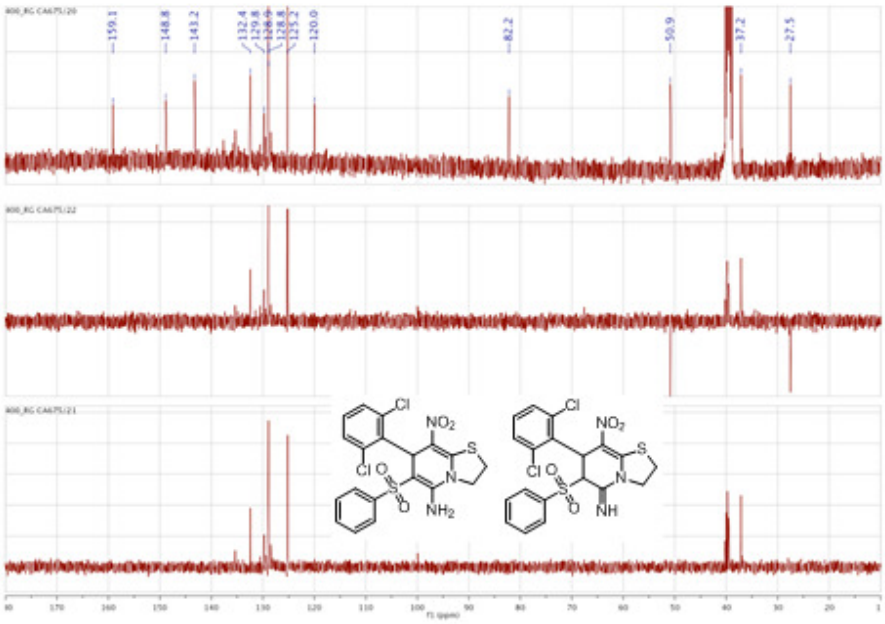


Figure 2.2. ^{13}C NMR spectrum of compound (8e-9e).

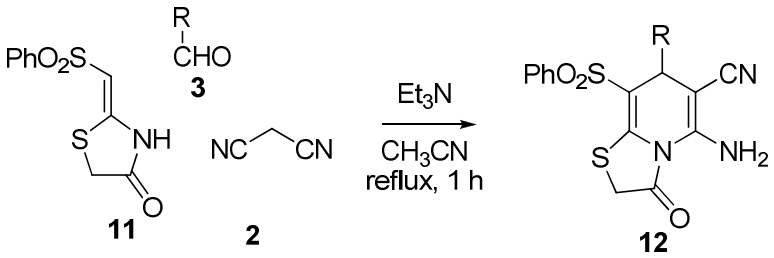
As an additional complication, these compounds are only fully soluble in DMSO. Running the ^{1}H NMR spectra in d_6-DMSO gave good results, although the peak due to adventitious water in the DMSO invariably obscured the CH_2S resonance. In the ^{13}C NMR spectrum, the methine resonance (C-7) in some instances overlapped with the deuterated solvent peak, although careful examination of the DEPT spectra allowed unambiguous assignment. The same products were formed, albeit in much lower yield and purity, with aliphatic aldehydes.

In the second part of this study, multicomponent reactions of 2-phenylsulfonylmethylene thiazolidin-4-one with malonitrile and aromatic aldehydes were performed in anhydrous acetonitrile at reflux temperature,

and monitored by thin layer chromatography (TLC). After 1 h, no 2-phenylsulfonylmethylene thiazolidin-4-one remained on TLC the plate, which is indicative of the completion of reaction. The reactions proceeded rapidly and afforded the corresponding thiazolopyridin-4-ones **12a-f** and benzylidene thiazolopyridin-4-ones **13a-g** in high yields. The results shown in Table 2.4. and Table 2.5. clearly indicated the scope and generality of the reaction with respect to aldehydes and malononitrile. The reactions worked efficiently with a variety of aldehydes including both electron-releasing and hetero-aromatic groups. Additionally, aforementioned reactions were also performed in water as a solvent and without use of solvent *via* solid state reaction. In both cases desired products were not obtained.

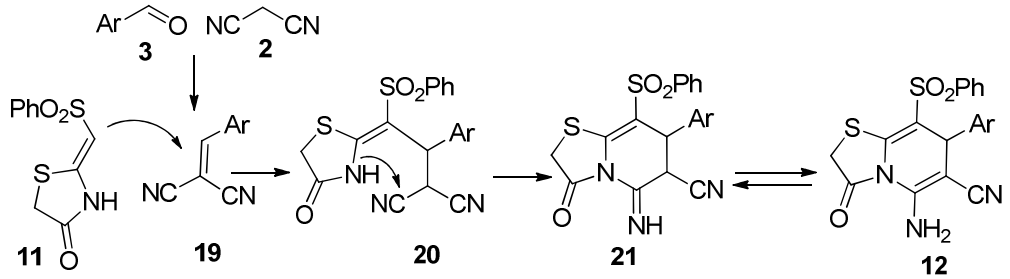
2-Phenylsulfonylmethylenethiazolidin-4-one was prepared according to a literature procedure, and identified by means of m.p., IR, ^{1}H and ^{13}C NMR. After reviewing related alkylidenethiazolidin-4-ones and alkylidenepyrrolidine ester and nitrile geometries in previous publications[61], we have decided to draw the double bond geometry of the starting compound **(11)** *Z* isomer rather than *E* isomer.

Table 2.4. Substituents and yields of compound 12a-12f.



Compound	R	Yield/%
12a	C_6H_5	73
12b	4-NCC_6H_4	84
12c	4-ClC_6H_4	74
12d	2,6-$DiClC_6H_3$	86
12e	2,4-$DiClC_6H_3$	68
12f	4-$O_2NC_6H_4$	71

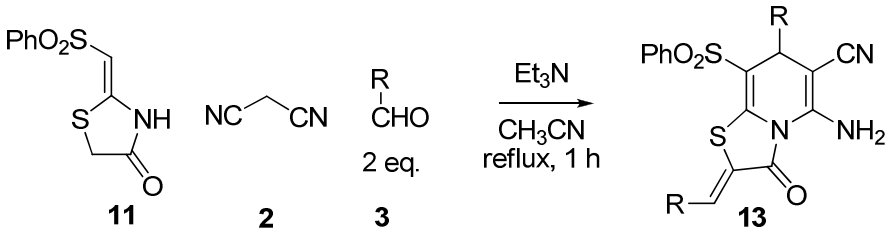
Reactions of 2-phenylsulfonylmethylenethiazolin-4-one **(11)** with malononitrile **(2)** and aldehydes **(3)** (Table 2.4. and Table 2.5.) proceed through the Knoevenagel condensation of the aldehyde with malononitrile and then, the addition of benzylidenemalononitrile **(19)** to enamine **(11)** followed by secondary amine attacks to one of nitrile on benzylidenemalononitrile **(19)** ends with ring cyclization. In our previous work, when 2-alkylidenethiazolin reacted with 2-phenylsulfonylacetonitrile and aldehyde; a mixture of enamine **(12)**, and imine **(21)** tautomers were obtained.[7] In the present work, we obtained compound **(12)** as a sole product.



Scheme 2.2. Possible reaction mechanism for the compounds 12.

When two equivalents of aldehyde were used, benzylidene substituted 5-amino-7-aryl-3-oxo-8-(phenylsulfonyl)-thiazolo[3,2-a]pyridine-6-carbonitriles were observed in moderate to high yields as shown in Table 2.5. It was also found that there was no direct effect of the stoichiometric amount of Et_3N as a base to the MCR yield of 2-phenylsulfonylmethylenethiazolidin-4-one with malononitrile and aldehyde.

Table 2.5. Substituents and yields of compound 13a-13g.



Compound	R	Yield/%
13a	4-ClC_6H_4	68
13b	4-FC_6H_4	80
13c	4-NCC_6H_4	62
13d	3-BrC_6H_4	73
13e	2,4-$DiMeOC_6H_3$	64
13f	4-HO-3,5-$DiMeOC_6H_2$	69
13g	3-Thienyl	81

In infrared spectra of compounds **12a-f** and **13a-g**, sulfone groups showed two strong bands due to asymmetric stretching at ca.1307 – 1329 cm^{-1} and symmetric stretching at ca.1144 – 1154 cm^{-1}. Bands at ca. 3312 – 3439 cm^{-1} are ascribed to NH_2 groups. Stretching vibrations of carbonyl groups appeared at *ca.* 1658 – 1743 cm^{-1} and distinct cyano peaks were observed at *ca.* 2189 – 2201 cm^{-1}. The ^{1}H and ^{13}C NMR spectra of compounds **12a–f** and **13a–g** were recorded in d_6-DMSO and the resulting spectra as well as HRMS confirmed the expected structures as follows. The signals due to the NH_2 protons appeared at *ca.* δ 7.08 – 7.55 ppm, but in some cases (compounds **12c**, **13g**, **13b**) NH_2 proton resonances overlapped with aromatic protons and they were not easily detectable. The chemical shifts of **12a–f** *CH*Ar protons showed remarkable differences (δ 5.02 – 5.92 ppm) compared with *CH*Ar protons **13a–f** (δ 4.49 – 4.70 ppm) due to the substitution of the benzylidene groups on the thiazoline fused to pyridine ring. Carbonyl carbons of compounds **13a-g** showed more deshielded peaks than that of the compounds **12a-f** due to electron-withdrawing effects of the benzylidene group next to carbonyl group in compounds **13a-g**. In mass spectra of compounds **13e** and **13f**, loss of M-Ar peaks 25 and 15 % were obtained, respectively.

CONCLUSION

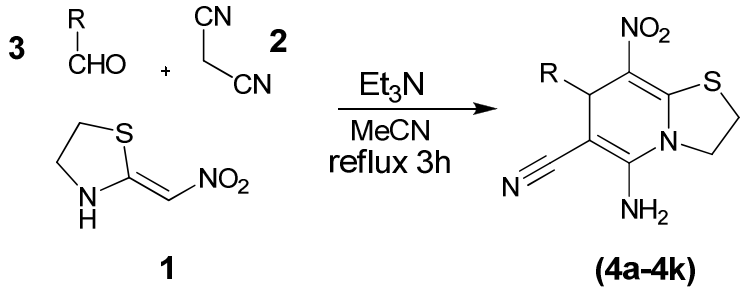
In conclusion, we have accomplished a very rapid and efficient synthesis of the thirty three new thiazolo[3,2-a]pyridines/4-ones through a very practical sequence, easily scalable, and identified these compounds by means of spectroscopic methods. This reaction was suitable for a wide range of active methylene containing nitriles, with the exception of the presence of phenylsulfonyl malononitrile substituent interestingly gave inseparable tautomer mixture. Besides this, electron-rich and electron-poor and sterically hindered aryl aldehydes proved to be reactive for this kind of transformation. A rational mechanism can be postulated, however it requires more evidence. One of the compounds prepared shows promising anticancer activity in a range of cell lines.

CHAPTER III

3. EXPERIMENTAL

Commercially available reagents and solvents were used without further purification. Infrared spectra were recorded on a SHIMADZU FTIR-8400S instrument (KBr disc). Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C at 25 °C. All chemical shifts are reported in ppm downfield from TMS. Coupling constants (*J*) are reported in Hz. Melting points were determined in open glass capillary with a MELTEMP apparatus and were uncorrected. TLC was done using pre-coated plates with fluorescent indicator (Merck 5735). Solutions of permanganate and PMBA were used for visualization of the TLC spots. 2-Nitromethylenethiazolidine[47] and 2-phenylsulfonylmethylenethiazolidin-4-one[62] was prepared according to literature procedure.

3.1. Synthesis of Thiazolo[3,2-a]pyridine derivatives with the reactions of 2-nitromethylenethiazolidine (1), malononitrile (2) and aldehydes (3).

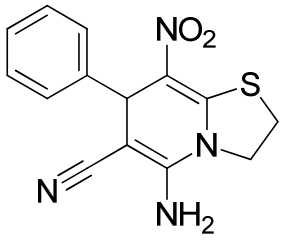


Scheme 3.1. Synthesis of Thiazolo[3,2-a]pyridine derivatives (4a-4k).

3.1.1. General Procedure for Synthesis of Thiazolo[3,2-a]pyridine derivatives (4a-4k).

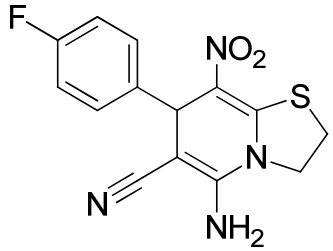
2-nitromethylenethiazolidine **(1)** (1.0 eq.,1.0 mmol, 146 mg), malononitrile **(2)** (1.0 eq., 1.0 mmol, 66 mg), and any aromatic aldehyde **(3)** (1.0 eq., 1.0 mmol) were mixed in acetonitrile (MeCN) (10mL) in round-bottomed flask and the reaction mixture was stirred and heated until all reactants dissolved. Then triethylamine (Et_3N) (0.5 eq, 0.5 mmol, 50 mg) was added slowly to the reaction mixture and it was heated under reflux for 3h. After cooling, the solvent was removed under reduced pressure and the residue recrystallised from hexane/ethyl acetate mixtures to give the pure products with data given below.

3.1.1.1. 5-Amino-8-nitro-7-phenyl-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (4a)



Obtained as an orange solid (285 mg, 95%), m.p. 198 – 199 °C (Found: M^+, 300.0685. $C_{14}H_{12}N_4O_2S$ requires M, 300.0681); ν_{max}. (KBr) 3345 (NH_2), 2184 (CN) and 1658 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 7.31 (2 H, app. t, *J* 7.3, aromatic CH), 7.22 (1 H, t, *J* 7.3, aromatic CH), 7.19 (2 H, d, *J* 7.0, aromatic CH), 6.57 (2 H, broad s, NH_2), 4.77 (1 H, s, C*H*Ph), 4.34 – 4.18 (2 H, m, CH_2N) and 3.41 – 3.30 (2 H, m obscured by water in DMSO, CH_2S); δ_C (100 MHz; d_6-DMSO) 157.9 (C), 149.6 (C), 144.5 (C), 128.9 (CH), 127.5 (CH), 127.4 (CH), 127.3 (C), 120.8 (C), 62.5 (C), 51.6 (CH_2), 41.4 (CH) and 28.3 (CH_2); *m/z* (TOF EI^+) 300 (M^+, 20%), 267 (60), 233 (100) and 223 (90).

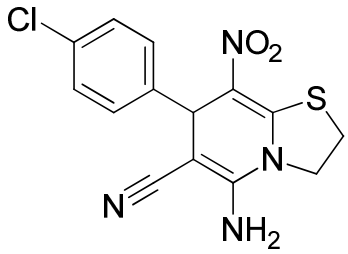
3.1.1.2. 5-Amino-7-(4-fluorophenyl)-8-nitro-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (4b)



Obtained as a yellow solid (287 mg, 90%), m.p. 232 – 233 °C (Found: $(M - H)^-$, 317.0511. $C_{14}H_{10}N_4O_2SF$ requires M, 317.0509); ν_{max}. (KBr) 3433 (NH_2), 2195 (CN) and 1659 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 7.28 – 7.22 (2 H, m, aromatic CH), 7.16 – 7.10 (2 H, m, aromatic CH), 6.60 (2 H, broad s, NH_2), 4.80 (1 H, s, C*H*Ar), 4.34 – 4.42 (2 H, m, CH_2N) and 3.44–

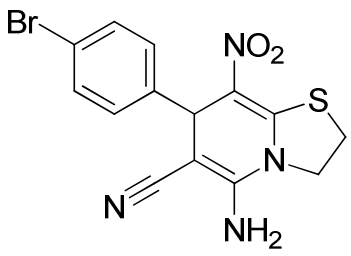
3.32 (2 H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; d_6-DMSO) 161.2 (d, $^1J_{C\text{-}F}$ 241.3, C-F), 157.6 (C), 149.2 (C), 140.3 (d, $^4J_{C\text{-}F}$ 3.0, C *para* to F), 129.0 (d, $^3J_{C\text{-}F}$ 8.2, CH *meta* to F), 121.8 (C), 120.3 (C), 115.2 (d, $^2J_{C\text{-}F}$ 21.2, CH *ortho* to F), 61.9 (C), 51.2 (CH2), 40.4 (CH) and 27.9 (CH_2); *m/z* (TOF ES^-) 317 (M – H, 100%).

3.1.1.3. 5-Amino-7-(4-chlorophenyl)-8-nitro-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (4c)



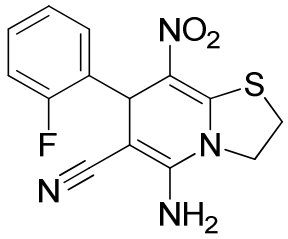
Obtained as an orange solid (315 mg, 94%), m.p. 213 – 215°C Found: $(M - 2H)^+$, 332.0137. $C_{14}H_9N_4O_2S^{35}Cl$ requires M, 332.0135); $\square_{max}$. (KBr) 3439 (NH_2), 2189 (CN) and 1649 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 7.37 (2 H, d, *J* 8.4, aromatic CH), 7.23 (2 H, d, *J* 8.4, aromatic CH), 6.62 (2 H, broad s, NH_2) ,4.80(1 H, s, C*H*Ar), 4.33 – 4.19 (2 H, m, CH_2N) and 3.40 – 3.10 (2 H,m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; d_6-DMSO) 158.2 (C), 149.6 (C), 143.5 (C), 132.0 (C), 129.4 (CH),128.9 (CH), 122.0 (C), 120.7 (C), 62.1 (C), 51.6 (CH_2), 41.0 (CH) and 28.3 (CH_2); *m/z* (TOF EI^+) 334 (M^+, 28%), 332 (M^+,86), 267 (60) and 84 (100).

3.1.1.4. 5-Amino-7-(4-bromophenyl)-8-nitro-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (4d)



Obtained as a yellow solid (299 mg, 79%), m.p. 240 °C (dec.) (Found: $(M - H)^+$, 376.9694. $C_{14}H_{10}N_4O_2S^{79}Br$ requires M, 376.9708); ν_{max}. (KBr) 3416 (NH_2), 2193 (CN) and 1640 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 7.50 (2 H, d, *J* 8.4, aromatic CH), 7.16 (2 H, d, *J* 8.4, aromatic CH), 6.62 (2 H, broad s, NH_2), 4.78 (1 H, s C*H*Ar), 4.33 – 4.17 (2 H, m, CH_2N), 3.40 – 3.30 (2 H, m,CH_2S); δ_C (100 MHz; d_6-DMSO) 157.8 (C), 149.2 (C), 143.5 (C),131.4 (CH), 129.3 (CH), 121.5 (C), 120.3 (C), 120.1 (C), 61.6 (C), 51.2 (CH_2), 40.7 (CH) and 27.9 (CH_2); *m/z* (TOF ES^-) 379 ($M - H^+$, 100%) and 377 (95).

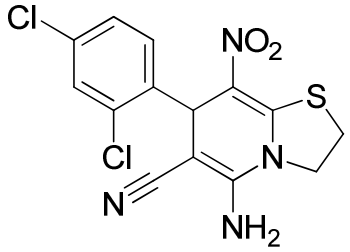
3.1.1.5. 5-Amino-7-(2-fluorophenyl)-8-nitro-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (4e)



Obtained as a yellow solid (297 mg, 93%), m.p. 230 °C (dec.) (Found: $(M - H)^-$, 317.0495. $C_{14}H_{10}N_4O_2SF$ requires M, 317.0509); ν_{max}. (KBr) 3431 (NH_2), 2187 (CN) and 1659 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 7.30 – 7.20 (2 H, m, aromatic CH), 7.17 – 7.11 (2 H, m, aromatic CH), 6.62 (2 H, broad s,NH_2), 5.10 (1 H, s, C*H*Ar), 4.27 (2 H, app. t, *J* 7.7, CH_2N) and 3.45 – 3.30 (2 H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; d_6-DMSO)

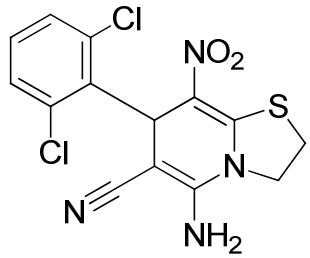
159.7 (d, $^{1}J_{C\text{-}F}$ 245.7, C-F), 158.1 (C), 149.4 (C), 130.7 (d, $^{2}J_{C\text{-}F}$ 13.1, C), 129.5 (d, $^{3}J_{C\text{-}F}$ 4.1, CH *meta* to F), 129.1 (d, $^{3}J_{C\text{-}F}$ 8.3, CH *meta* to F), 124.8 (d, $^{4}J_{C\text{-}F}$ 3.3, CH *para* to F), 120.8 (C), 120.2 (C), 115.5 (d, $^{2}J_{C\text{-}F}$ 21.2, CH *ortho* to F), 60.7 (C), 51.2 (CH_2), 35.2 (CH) and 27.9 (CH_2); *m/z* (TOF ES^-) 353 (M + ^{35}Cl, 45%) and 317 (M – H, 100).

3.1.1.6. 5-Amino-7-(2,4-dichlorophenyl)-8-nitro-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (4f)



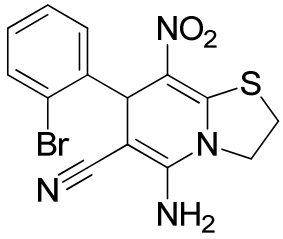
Obtained as a yellow solid (363 mg, 99%), m.p. 263 – 264 °C (Found: $(M - H)^-$, 366.9829. $C_{14}H_9N_4O_2{}^{35}Cl_2S$ requires M, 366.9823); ν_{max}. (KBr) 3396 (NH_2), 2191 (CN) and 1658 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 7.55 (1 H, d, *J* 1.6, aromatic CH), 7.37 (1 H, dd, *J* 8.3, 1.6, aromatic CH), 7.33 (1 H, d, *J* 8.3, aromatic CH), 6.65 (2 H, broad s, NH_2), 5.30 (1 H, s, C*H*Ar), 4.28 (2 H, app. t, *J* 7.6, CH_2N) and 3.4 – 3.3 (2 H, m, CH_2S); δ_C (100 MHz; d_6-DMSO) 158.6 (C), 149.5 (C), 140.3 (C), 132.8 (C), 132.2 (C), 131.3 (CH), 128.8 (CH), 127.9 (CH), 120.9 (C), 119.8 (C), 60.2 (C), 51.2 (CH_2), 38.1 (CH) and 27.9 (CH_2). *m/z* (TOF ES^-) 371 (M, 14), 369 (M, 70) and 367 (M, 100).

3.1.1.7. 5-Amino-7-(2,6-dichlorophenyl)-8-nitro-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (4g)



Obtained as an orange solid (356 mg, 97%), m.p. 279 – 281 ℃ (Found: $(M - H)^-$, 366.9810. $C_{14}H_9N_4O_2{}^{35}Cl_2S$ requires M, 366.9823); ν_{max}. (KBr) 3466 (NH_2), 2180 (CN) and 1643 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 7.46 (1 H, d, *J* 7.0, aromatic CH), 7.39 (1 H, d, *J* 7.4, aromatic CH) 7.27 (1 H, app. t, *J* 7.7, aromatic CH) 6.69 (2 H, broad s, NH_2), 5.87 (1 H, s, C*H*Ar), 4.42 – 4.37 (1 H, m, one of CH_2N) and 4.25 – 4.17 (1 H, m, one of CH_2N) (CH_2S peak obscured by broad water peak from DMSO); δ_C (100 MHz; d_6-DMSO) 160.2 (C), 150.8 (C), 136.2 (C), 136.0 (C), 134.8 (C), 130.9 (CH), 129.7 (CH), 129.0 (CH), 120.0 (C), 119.9 (C), 58.2 (C), 51.4 (CH_2), 38.1 (CH) and 28.1 (CH_2); *m/z* (TOF ES^-) 371 (M, 10%), 369 (M, 47), 367 (M, 63) and 221 (100).

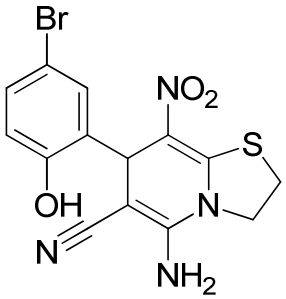
3.1.1.8. 5-Amino-7-(2-bromophenyl)-8-nitro-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (4h)



Obtained as a yellow solid (368 mg, 97%), m.p. 242 – 244 ℃ (Found: $(M - H)^+$, 376.9713. $C_{14}H_{10}N_4O_2S^{79}Br$ requires M, 376.9708); ν_{max}. (KBr) 3446 (NH_2), 2185 (CN) and 1649 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 7.55 (1 H, d, *J* 7.9, aromatic CH), 7.30 (1 H, app. t, *J* 7.4, aromatic CH), 7.27

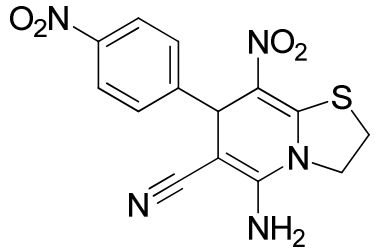
(1 H, dd, *J* 7.7, 1.5, aromatic CH), 7.16 (1 H, app. td, *J* 7.6, 1.5, aromatic CH), 6.60 (2 H, broad s, NH_2), 5.31 (1 H, s, C*H*Ar), 4.28 (2 H, app. t, *J* 7.7, CH_2N) and 3.45 – 3.20 (2 H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; d_6-DMSO) 158.3 (C), 149.4 (C), 142.8 (C), 132.7 (CH), 130.0 (CH), 128.9 (CH), 128.3 (CH), 122.3 (C) 121.5 (C), 119.8 (C), 60.9 (C), 51.1 (CH_2), 40.6 (CH) and 27.8 (CH_2); *m/z* (TOF ES^-) 379 ($M - H^+$, 100) and 377 (97).

3.1.1.9. 5-Amino-7-(5-bromo-2-hydroxyphenyl)-8-nitro-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (4i)



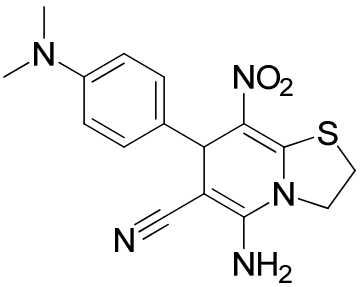
Obtained as a yellow solid (325 mg, 82%), m.p. 210 ℃ (dec.)(Found: $(M - H)^-$, 392.9674. $C_{14}H_{10}N_4O_3S^{79}Br$ requires M, 392.9657); □$_{max}$. (KBr) 3471 (NH_2), 2191 (CN) and 1649 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 9.86 (1 H, s, OH), 7.19 (1 H, dd, *J* 8.6, 2.5, aromatic CH), 7.11 (1 H, d, *J* 2.5, aromatic CH), 6.71 (1 H, d, *J* 8.6, aromatic CH), 6.48 (2 H, broad s, NH_2), 5.00 (1 H, s, C*H*Ar), 4.39 – 4.31 (1 H, app. td, *J* 10.7, 7.8, one of CH_2N)), 4.18 – 4.11 (1 H, app. td, *J* 10.7, 7.7, one of CH_2N) and 3.40 – 3.30 (2 H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; d_6-DMSO) 158.2 (C), 154.6 (C), 149.7 (C), 132.0 (C), 131.2 (CH), 130.5 (CH), 120.9 (C), 120.4 (C), 117.8 (CH), 109.9 (C), 60.7 (C), 51.1 (CH2), 36.6 (CH) and 27.8 (CH_2); *m/z* (TOF ES^-) 395 (M, 100), 393 (M, 100), 249 (81) and 247 (84).

3.1.1.10. 5-Amino-8-nitro-7-(4-nitrophenyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (4j)



Obtained as a yellow solid (342 mg, 99%), m.p. 214 °C (dec.) (Found: $(M - H)^-$, 344.0455. $C_{14}H_{10}N_5O_4S$ requires M, 344.0454); ν_{max}. (KBr) 3331 (NH_2), 2187 (CN) and 1661 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 8.19 (2 H, d, *J* 8.5, aromatic CH), 7.51 (2 H, d, *J* 8.5, aromatic CH), 6.72 (2 H, broad s, NH_2), 4.98 (1 H, s, C*H*Ar), 4.35 – 4.20 (2 H, m, CH_2N) and 3.50-3.33 (2 H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; d_6- DMSO) 158.4 (C), 151.4 (C), 149.4 (C), 146.6 (C), 128.4 (CH), 123.9 (CH) 121.0 (C), 120.1 (C), 60.8 (C), 51.3 (CH_2), 40.0 (CH), 28.0 (CH_2); *m/z* (TOF ES^-) 407 (M +CH_3CN + Na – H, 60%) and 344 (M – H, 100%).

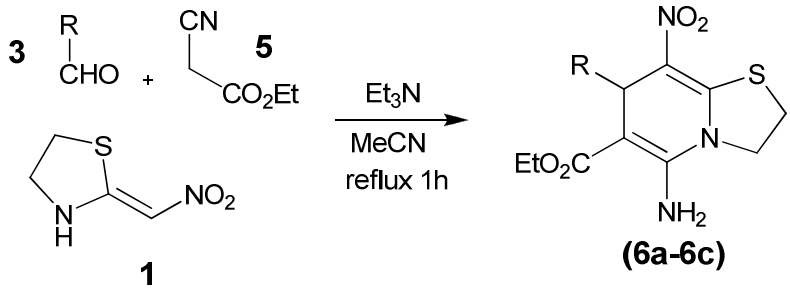
3.1.1.11. 5-Amino-7-(4-(dimethylamino)phenyl)-8-nitro-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (4k)



Obtained as a brick-red solid (308 mg, 90%), m.p. 226 °C (dec.) (Found: $(M - H)^-$, 342.1018. $C_{16}H_{16}N_5O_2S$ requires M, 342.1025); ν_{max}. (KBr) 3343 (NH_2), 2184 (CN) and 1649 (C=C) cm^{-1}; δ_H(400 MHz; d_6-DMSO) 6.98 (2 H, d, *J* 8.7, aromatic CH), 6.64 (2 H, d, *J* 8.7, aromatic CH) 6.48 (2 H, broad s, NH_2), 4.64 (1 H, s, C*H*Ar), 4.30 – 4.19 (2 H,

m, CH_2N) and 3.40 – 3.30 (2 H, m, obscured by water in DMSO, CH_2S); δ_C (100 MHz; d_6- DMSO) 157.0 (C), 149.8 (C), 149.1 (C), 131.9 (C), 127.9 (CH), 122.8 (C), 120.8 (C), 112.6 (CH), 63.1 (C), 51.3 (CH), 40.4 (2 x CH_3), 40.2 (CH) and 28.1 (CH_2); *m/z* (TOF ES^-) 342 (M – H, 100%).

3.2. Synthesis of Thiazolo[3,2-a]pyridine derivatives with the reactions of 2-nitromethylenethiazoline (1), ethyl 2-cyanoacetate (5) and aldehydes (3).



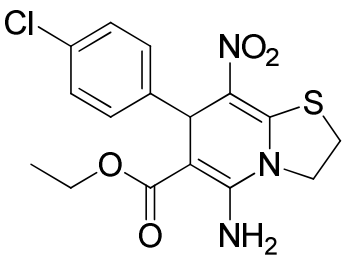
Scheme 3.2. Synthesis of Thiazolo[3,2-a]pyridine derivatives (6a-6c).

3.2.1. General Procedure for Synthesis of Thiazolo[3,2-a]pyridine derivatives (6a-6c)

2-nitromethylenethiazoline **(1)** (1.0 eq.,1.0 mmol, 146 mg), ethyl 2-cyanoacetate **(5)** (1.0 eq., 1.0 mmol, 113 mg), and any aromatic aldehyde **(3)** (1.0 eq., 1.0 mmol) were mixed in acetonitrile (MeCN) (10mL) in round-

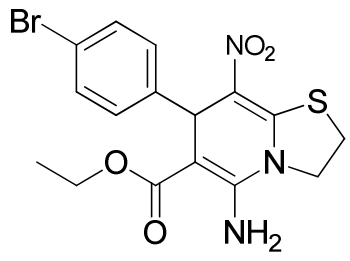
bottomed flask and the reaction mixture was stirred and heated until all reactants dissolved. Then triethylamine (Et_3N) (0.5 eq, 0.5 mmol, 50 mg) was added slowly to the reaction mixture and it was heated under reflux for 1h. After cooling, the solvent was removed under reduced pressure and the residue recrystallised from hexane/ethyl acetate mixtures to give the pure products.

3.2.1.1. Ethyl 5-amino-7-(4-chlorophenyl)-8-nitro-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carboxylate (6a)



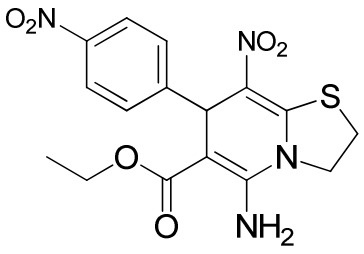
Obtained as an orange solid (295 mg, 78%), m.p. 214 – 216 °C (Found: $(M - H)^-$, 380.0486. $C_{16}H_{15}O_4N_3S^{35}Cl$ requires M, 380.0472); ν_{max}. (KBr) 3420 (NH_2), 1667 (CO) and 1632 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 7.27 (4 H, app. s, aromatic CH), 6.57 (2 H, broad s, NH_2), 5.36 (1 H, s, C*H*Ar), 4.41 – 4.32 (1 H, m, one of CH_2N), 4.17 – 4.08 (3 H, m, one of CH_2N and OCH_2), 3.43 – 3.35 (2 H, m, CH_2S) and 1.25 (3 H, t, *J* 8.5, CH_3); δ_C (100 MHz; $CDCl_3$) 169.0 (C), 154.9 (C), 149.9 (C), 143.1 (C), 132.4 (C), 129.7 (CH), 128.2 (CH), 125.7 (C), 84.0 (C), 60.1 (CH_2), 49.9 (CH_2), 39.1 (CH), 28.3 (CH_2) and 14.4 (CH_3); *m/z* (TOF ES^-) 382 (M – H, 40%) and 380 (M – H, 100).

3.2.1.2. Ethyl 5-amino-7-(4-bromophenyl)-8-nitro-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carboxylate (6b)



Obtained as an orange solid (310 mg, 73%), m.p. 213 – 214°C (Found: $(M - H)^-$, 423.9980. $C_{16}H_{15}N_3O_4S^{79}Br$ requires M, 423.9967); ν_{max}. (KBr) 3416 (NH_2), 1667 (CO) and 1632 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 7.34 (2 H, d, *J* 8.5, aromatic CH), 7.15 (2 H, d, *J* 8.5, aromatic CH), 6.50 (2 H, broad s, NH_2), 5.31 (1 H, s, C*H*Ar), 4.35 – 4.24 (1 H, m, one of CH_2N), 4.20 – 4.03 (3 H, m, one of CH_2N and OCH_2), 3.48 – 3.20 (2 H, m, CH_2S) and 1.19 (3 H, t, *J* 7.1, CH_3); δ_C (100 MHz; $CDCl_3$) 169.0 (C), 154.6 (C), 150.0 (C), 143.7 (C), 131.2 (CH), 130.0 (CH), 125.8 (C), 120.6 (C), 84.1 (C), 60.1 (CH_2), 49.9 (CH_2), 39.2 (CH), 28.3 (CH_2) and 14.4 (CH_3); *m/z* (TOF ES^-) 426 (M – H, 100%) and 424 (M – H, 97).

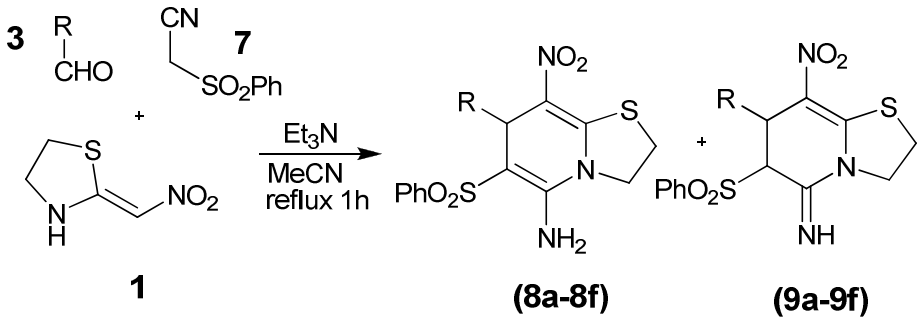
3.2.1.3. Ethyl 5-amino-8-nitro-7-(4-nitrophenyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carboxylate (6c)



Obtained as a yellow solid (275 mg, 70%), m.p. 145 °C (dec.) (Found: $(M - H)^-$, 391.0699. $C_{16}H_{15}O_6N_4S$ requires M, 391.0712); ν_{max}. (KBr) 3425 (NH_2), 1665 (CO) and 1630 (C=C) cm^{-1}; δ_H (400 MHz; d_6-DMSO) 8.10 (2 H, d, *J* 8.3,

aromatic CH), 7.40 (2 H, d, *J* 8.5, aromatic CH), 6.60 (2 H, broad s, NH_2), 5.40 (1 H, s, C*H*Ar), 4.41 – 4.29 (1 H, m, one of CH_2N), 4.16 – 4.02 (3 H, m, one of CH_2N and OCH_2), 3.55 – 3.29 (2 H, m, CH_2S) and 1.18 (3 H, t, *J* 7.1, CH_3); δ_C (100 MHz; $CDCl_3$) 168.7 (C), 155.3 (C), 151.9 (C), 150.2 (C), 146.9 (C), 129.3 (CH), 125.1 (C), 123.5 (CH), 83.3 (C), 60.2 (CH_2), 50.1 (CH_2), 39.9 (CH), 28.4 (CH_2) and 14.4 (CH_3); *m/z* (TOF ES^-) 393 (M – H, 100%).

3.3. Synthesis of Thiazolo[3,2-a]pyridine derivatives with the reactions of 2-nitromethylenethiazoline (1), phenylsulfonylacetonitrile (7) and aldehydes (3)

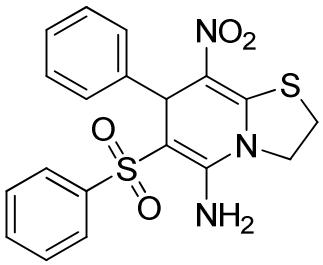


Scheme 3.3. Synthesis of Thiazolo[3,2-a]pyridine derivatives (8a-8f) and (9a-9f).

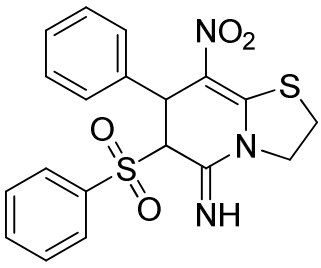
3.3.1. General Procedure for Synthesis of Thiazolo[3,2-a]pyridine derivatives (8a-8f) and (9a-9f)

2-nitromethylenethiazoline **(1)** (1.0 eq., 1.0 mmol, 146mg), phenylsulfonylacetonitrile **(7)** (1.0 eq., 1.0 mmol, 181 mg), and any aromatic aldehyde **(3)** (1.0 eq., 1.0 mmol) were mixed in acetonitrile (MeCN) (10mL) in round-bottomed flask and the reaction mixture was stirred and heated until all reactants dissolved. Then triethylamine (Et_3N) (0.5 eq., 0.5 mmol, 50 mg) was added slowly to the reaction mixture and it was heated under reflux for 1h. After cooling, the solvent was removed under reduced pressure and the residue recrystallized from hexane/ethyl acetate mixtures to give the pure products with data given below.

3.3.1.1. 8-Nitro-7-phenyl-6-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridin-5-amine (8a) and 8-nitro-7-phenyl-6-(phenylsulfonyl)-6,7-dihydro-2H-thiazolo[3,2-a]pyridin-5(3H)-imine (9a)



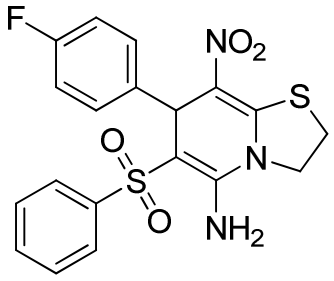
(8a)



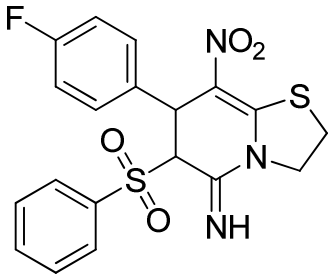
(9a)

Obtained as a pale yellow solid (320 mg, 77%, 1:1.35 mixture of **8a**: **9a** according to 1H NMR spectroscopic data), m.p. 227 – 230 °C (Found: $(M - H)^-$, 414.0569. $C_{19}H_{16}O_4N_3S_2$ requires M, 414.0582); $\nu_{max.}$ (KBr) 3298 (NH_2), 1636 (C=C), 1555, 1445, 1381, 1211 and 1138 cm^{-1}; δ_H (400 MHz; d_6-DMSO) 9.70 (1 H of **9a**, s, NH), 7.87 – 7.77 (3 H of **9a**, m, aromatic CH of SO_2Ph), 7.68 (2 H of **9a**, app. dd, *J* 8.3, 7.3, aromatic CH of SO_2*Ph*), 7.64 (2 H of **8a**, d, *J* 7.2, aromatic CH of SO_2*Ph*), 7.52 (1 H of **8a**, app. t, *J* 7.4, aromatic CH of SO_2*Ph*), 7.40 (2 H of **8a**, app. t, *J* 7.7, aromatic CH of SO_2*Ph*), 7.35 – 7.23 (3 H of **9a**, m, aromatic CH), 7.18 – 7.08 (5 H of **8a**, m, aromatic CH), 6.96 (2 H of **9a**, app. d, *J* 7.0, aromatic CH), 6.92 (2 H of **8a**, broad s, NH_2), 5.10 (1 H of **8a**, s, C*H*Ph), 4.92 (1 H of **9a**, s, C*H*Ph), 4.91 (1 H of **9a**, s, C*H*SO_2Ph), 4.41 (1 H of **9a**, ddd, *J* 11.8, 8.7, 3.3, one of CH_2N), 4.35 – 4.23 (2 H of **8a**, m, CH_2N), 4.13 (1 H of **9a**, app. td, *J* 11.4, 8.5, one of CH_2N), 3.37 (2 H of **8a**, app. t, *J* 7.6, CH_2S), 3.33 – 3.27 (1 H of **9a**, m, one of CH_2S) and 3.09 (1 H of **9a**, app. td, *J* 11.1, 8.8, one of CH_2S); δ_C (100 MHz; d_6-DMSO) 159.7 (C, **9a**), 157.1 (C, **8a**), 149.6 (C, **9a**), 147.7 (C, **8a**), 143.6 (C, **9a**), 143.5 (C, **8a**), 138.6 (C, **9a**), 135.7 (C, **9a**), 135.3 (CH, **9a**), 132.4 (CH, **8a**), 129.7 (CH, **8a**), 129.4 (CH, **9a**), 129.0 (CH, **8a**), 128.6 (CH, **9a**), 128.1 (CH, **8a**), 128.1 (CH, **9a**), 127.7 (CH, **9a**), 126.8 (CH, **8a**), 126.6 (CH, **9a**), 125.7 (CH, **8a**), 123.7 (C, **8a**), 119.6 (C, **9a**), 86.3 (C, **8a**), 69.9 (CH, **9a**), 51.5 (CH_2, **9a**), 51.0 (CH_2, **8a**), 40.2 (CH, **9a**), 39.9 (CH, **8a**), 28.2 (CH_2, **8a**) and 27.8 (CH_2, **9a**); *m/z* (TOF ES^-) 414 (M – H, 100%) and 340 (21).

3.3.1.2. 7-(4-Fluorophenyl)-8-nitro-6-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridin-5-amine (8b) and 7-(4-fluorophenyl)-8-nitro-6-(phenylsulfonyl)-6,7-dihydro-2H-thiazolo[3,2-a]pyridin-5(3H)-imine (9b)



(8b)

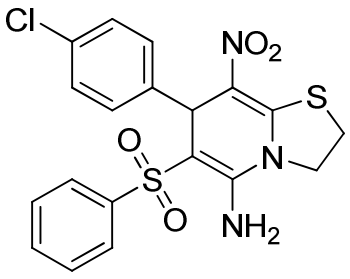


(9b)

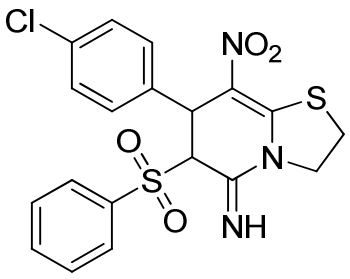
Obtained as a pale yellow solid (345 mg, 80%, 1.25:1 mixture of **8b**:**9b** according to 1H NMR spectroscopic data), m.p. 243 – 244 °C (Found: $(M - H)^-$, 432.0497. $C_{19}H_{16}O_4N_3S_2F$ requires M, 432.0488); ν_{max}. (KBr) 3293 (NH_2), 1638 (C=C), 1562, 1449, 1379, 1215 and 1138 cm^{-1}; δ_H (400 MHz; d_6-DMSO) 9.69 (1 H of **9b**, s, NH), 7.85 – 7.77 (3 H of **9b**, m, aromatic CH of SO_2*Ph*), 7.71 – 7.62 (2 H of **8b** and 2 H of **9b**, m, aromatic CH of SO_2*Ph*), 7.53 (1 H of **8b**, app. t, *J* 7.4, aromatic CH of SO_2*Ph*), 7.41 (2 H of **8b**, app. t, *J* 7.7, aromatic CH of SO_2*Ph*), 7.19 – 7.12 (4 H of **8b**, m, aromatic CH of *Ar*-F), 7.05 – 7.00 (2 H of **9b**, m, aromatic CH of *Ar*-F), 6.98 – 6.91 (2 H of **9b**, m, aromatic CH of *Ar*-F), 6.95 (2 H of **8b**, broad s, NH_2), 5.08 (1 H of **8b**, s, C*H*Ar), 4.92 (2 H of **9b**, app. s, C*H*Ar, C*H*SO_2Ph), 4.40 (1 H of **9b**, ddd, *J* 11.9, 7.0, 2.7, one of CH_2N), 4.34 – 4.24 (2 H of **8b**, m, CH_2N), 4.14 (1 H of **9b**, app. td, *J* 11.3, 8.5, one of CH_2N), 3.37 (2 H of **8b**, app. t, *J* 7.6, CH_2S), 3.35 – 3.27 (1 H of **9b**, m, one of CH_2S) and 3.08 (1 H of **9b**, app. td, *J* 11.1,

8.8, one of CH_2S); δ_C (100 MHz; d_6-DMSO) 161.6 (d, $^1J_{C\text{-}F}$ 244.3, C-F, **9b**), 161.0 (d, $^1J_{C\text{-}F}$ 242.8, C-F, **8b**), 157.1 (C, **8b**), 149.6 (C, **9b**), 147.7 (C, **8b**), 143.5 (C, **8b**), 139.8 (d, $^4J_{C\text{-}F}$ 3.2, C *para* to F, **9b**), 135.6 (C, **8b**), 135.3 (CH, **9b**), 134.7 (d, $^4J_{C\text{-}F}$ 3.0, C *para* to F, **9b**), 132.4 (CH, **9b**), 129. 7 (CH, **8b**), 129.7 (d, $^3J_{C\text{-}F}$ 7.6, CH *meta* to F, **9b**), 128.9 (CH, **8b**), 128.8 (d, $^3J_{C\text{-}F}$ 8.6, CH *meta* to F), 128.6 (C, **9b**), 125.7 (CH, **8b**), 123.4 (C, **8b**), 119.5 (C, **9b**), 116.1 (d, $^2J_{C\text{-}F}$ 21.7, CH *ortho* to F, **9b**), 114.7 (d, $^2J_{C\text{-}F}$ 21.3, CH *ortho* to F, **8b**), 86.1 (C, **8b**), 69.8 (CH, **9b**), 51.5 (CH2, **9b**), 51.0 (CH_2, **8b**), 40.0 (CH, **8b**), 39.87 (CH, **9b**), 28.2 (CH_2, **8b**) and 27.8 (CH_2, **9b**); *m/z* (TOF ES^-) 432 (M – H, 100%) and 180 (56).

3.3.1.3. 7-(4-Chlorophenyl)-8-nitro-6-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridin-5-amine (8c) and 7-(4-chlorophenyl)-8-nitro-6-(phenylsulfonyl)-6,7-dihydro-2H-thiazolo[3,2-a]pyridin-5(3H)-imine (9c)



(8c)

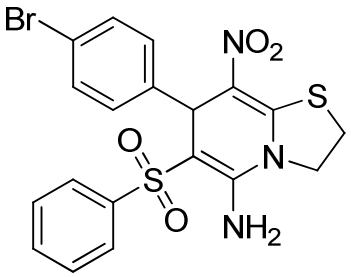


(9c)

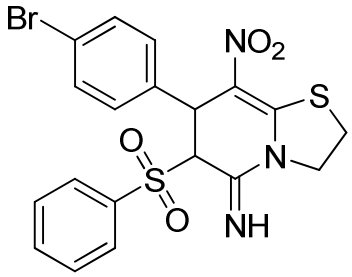
Obtained as a pale yellow solid (360 mg, 80%, 1:1.5 mixture of **8c**:**9c** according to 1H NMR spectroscopic data), m.p. 246 – 247 °C (Found: (M –

H)$^-$, 448.0183. $C_{19}H_{16}O_4N_3S_2$ ^{35}Cl requires M, 448.0193); $\square_{max}$. (KBr) 3293 (NH_2), 1638 (C=C), 1557, 1447, 1383, 1219 and 1138 cm^{-1}; δ_H (400 MHz; d_6-DMSO) 9.68 (1 H of **9c**, s, NH), 7.85 – 7.77 (3 H of **9c**, m, aromatic CH of SO_2Ph), 7.71 – 7.64 (2 H of **8c** and 2 H of **9c**, m, aromatic CH of SO_2Ph), 7.54 (1 H of **8c**, app. t, *J* 7.4, aromatic CH of SO_2Ph), 7.42 (2 H of **8c**, app. t, *J* 7.8, aromatic CH of SO_2Ph), 7.38 (2 H of **9c**, d, *J* 8.5, aromatic CH of Ar-Cl), 7.20 (2 H of **8c**, d, *J* 8.6, aromatic CH of Ar-Cl), 7.15 (2 H of **8c**, d, *J* 8.6, aromatic CH of Ar-Cl), 6.99 – 7.03 (2 H of **9c**, d, *J* 8.5, aromatic CH of Ar-Cl), 6.97 (2 H of **8c**, broad s, NH_2), 5.06 (1 H of **8c**, s, C*H*Ar), 4.93 (1 H of **9c**, s, C*H*Ar), 4.92 (1 H of **9c**, s, C*H*SO_2Ph), 4.39 (1 H of **9c**, ddd, *J* 11.9, 8.7, 3.3, one of CH_2N), 4.33 – 4.25 (2 H of **8c**, m, CH_2N), 4.13 (1 H of **9c**, app. td, *J* 11.4, 8.6, one of CH_2N), 3.37 (2 H of **8c**, app. t, *J* 7.6, CH_2S), 3.34 – 3.26 (1 H of **9c**, m, one of CH_2S) and 3.09 (1 H of **9c**, app. td, *J* 11.1, 8.8, CH_2S); δ_C (100 MHz; d_6-DMSO) 159.9 (C, **8c**), 157.3 (C, **9c**), 149.5 (C, **8c**), 147.7 (C, **9c**), 143.4 (C, **9c**), 142.6 (C, **9c**), 137.5 (C, **8c**), 135.6 (C, **8c**), 135.4 (CH, **8c**), 132.7 (C, **8c**), 132.4 (CH, **9c**), 131.4 (C, **9c**), 129.7 (CH,**8c**), 129.7 (CH, **9c**), 129.3 (CH, **8c**), 129.0 (CH, **9c**), 128.6 (CH, **8c**), 128.6 (CH, **8c**), 127.9 (CH, **9c**), 125.7 (CH, **9c**), 123.1 (C, **9c**), 119.2 (C, **8c**), 85.5 (C, **8c**), 69.6 (CH, **9c**), 51.5 (CH_2, **9c**), 51.0 (CH_2, **8c**), 39.2 (CH, **8c**), 39.0 (CH, **9c**), 28.2 (CH_2, **8c**) and 27.8 (CH_2, **9c**); *m/z* (TOF ES$^-$) 450 (M – H, 42%), 448 (M – H, 100), 341 (48), 339 (95) and 163 (55).

3.3.1.4. 7-(4-Bromophenyl)-8-nitro-6-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridin-5-amine (8d) and 7-(4-bromophenyl)-8-nitro-6-(phenylsulfonyl)-6,7-dihydro-2H-thiazolo[3,2-a]pyridin-5(3H)-imine (9d)



(8d)

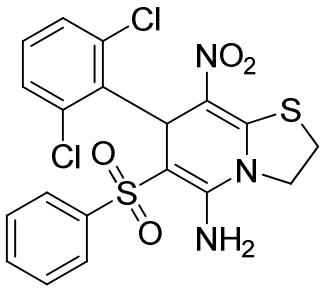


(9d)

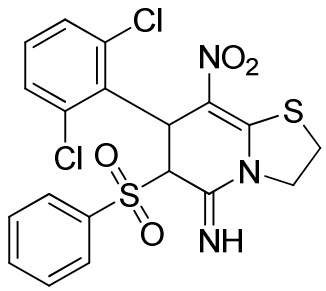
Obtained as a pale yellow solid (310 mg, 63%, 1.4:1 mixture of **8d**:**9d** according to 1H NMR spectroscopic data), m.p. 243 – 245 °C (Found: $(M - H)^-$, 491.9710. $C_{19}H_{16}O_4N_3S_2$ ^{79}Br requires M, 491.9687); ν_{max}. (KBr) 3293 (NH_2), 1638 (C=C), 1555, 1447, 1383, 1219 and 1138 cm^{-1}; δ_H (400 MHz; d_6-DMSO) 9.69 (1 H of **9d**, s, NH), 7.87 – 7.70 (2 H of **8d**, m, aromatic CH of SO_2*Ph*), 7.72 – 7.65 (5 H of **9d**, m, aromatic CH of SO_2*Ph*), 7.58 – 7.50 2 H of **9d** and 1 H of **8d**, m, aromatic CH), 7.43 (2 H of **8d**, app. t, *J* 7.7, aromatic CH of SO_2*Ph*), 7.34 (2 H of **8d**, app. d, *J* 8.4, aromatic CH of *Ar*-Br), 7.11 (2 H of **8d**, app. d, *J* 8.4, aromatic CH of *Ar*-Br), 6.99 (2 H of **8d**, broad s, NH_2), 6.96 (2 H of **9d**, app. d, *J* 8.5, aromatic CH from *Ar*-Br), 5.05 (1 H of **8d**, s, C*H*Ar), 4.94 (1 H of **9d**, s, C*H*Ar), 4.91 (1 H of **9d**, s, C*H*SO_2Ph), 4.39 (1 H of **9d**, ddd, *J* 11.2, 7.2, 2.9, one of CH_2N), 4.34 – 4.25 (2 H of **8d**, m, CH_2N), 4.13 (1 H of **9d**, app. td, *J* 11.5, 8.5, one of CH_2N), 3.38 (2 H of **8d**, app. t, *J* 7.7, CH_2S), 3.35 – 3.28 (1 H of **9d**, m, one of CH_2S) and 3.09 (1 H of **9d**,

app. td, *J* 11.1, 8.8, one of CH_2S); δ_C (100 MHz; d_6-DMSO) 160.0 (C, **9d**), 157.3 (C, **8d**), 149.5 (C, **9d**), 147.7 (C, **8d**), 143.4 (C, **8d**), 143.0 (C, **9d**), 137.9 (C, **9d**), 135.6 (CH, **9d**), 135.4 (C, **8d**), 132.4 (CH, **9d**), 132.2 (CH, **8d**), 130.9 (CH, **8d**), 130.1 (CH, **8d**), 129.7 (CH, **9d**), 129.0 (CH, **8d**), 128.9 (CH, **9d**), 128.6 (CH, **9d**), 125.7 (CH, **8d**), 123.1 (C, **8d**), 121.2 (C, **9d**), 119.9 (C, **8d**), 119.1 (C, **9d**), 85.7 (C, **8d**), 69.6 (CH, **9d**), 51.5 (CH_2, **9d**), 51.0 (CH_2, **8d**), 48.6 (CH, **8d**), 39.6 (CH, **9d**), 28.2 (CH_2, **8d**) and 27.8 (CH_2, **9d**); *m/z* (TOF ES^-) 494 ($M - H^+$, 48%), 492 (50), 339 (100), 325 (70), 311 (60) and 265 (75).

3.3.1.5. 8-Nitro-7-(2,6-dichlorophenyl)-6-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridin-5-amine (8e) and 7-(2,6-dichlorophenyl)-8-nitro-6-(phenylsulfonyl)-6,7-dihydro-2Hthiazolo[3,2-a]pyridin-5(3H)-imine (9e)



(8e)

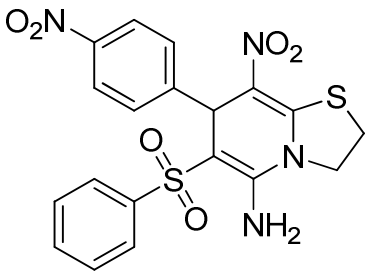


(9e)

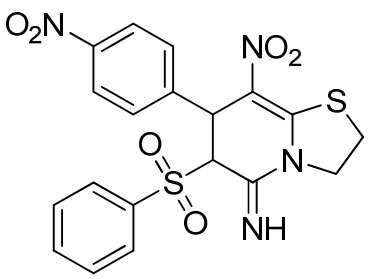
Obtained as an orange solid (0.5 mmol scale, 200 mg, 83%, 5:1 mixture of **8e**:**9e** according to 1H NMR spectroscopic data), m.p. 271 – 273 °C; (Found:

$(M - H)^+$, 481.9816; $C_{19}H_{14}O_4N_3S_2{}^{35}Cl_2$ requires M, 481.9803); $\square_{max}$. (KBr) 3443, 3339, 1639, 1444, 1296, 1246, 1230 and 1138 cm^{-1}; δ_H (400 MHz; d_6-DMSO) (data for **8e** only) 7.66 (2 H, app. d, *J* 7.5, aromatic CH of SO_2*Ph*), 7.52 (1 H, app. t, *J* 7.4, aromatic CH of SO_2*Ph*), 7.42 (2 H, app. t, *J* 7.7, aromatic CH of SO_2*Ph*), 7.36 – 7.27 (1 H, m, aromatic CH of *Ar*-Cl_2), 7.20 (2 H, broad s, NH_2), 7.12 – 7.05 (2 H, m, aromatic CH of *Ar*-Cl_2), 5.91 (1 H, s, C*H*Ar), 4.54 (1 H, app. td, *J* 11.6, 7.3, one of CH_2N), 4.23 (1 H, app. td, *J* 10.5, 8.2, one of CH_2N) and 3.37 – 3.27 (2 H, m, CH_2S); δ_C (100 MHz; d_6-DMSO) (data for **8e** only, quaternary carbon atoms of 2,6-dichlorophenyl not observed due to hindered rotation) 159.1 (C), 148.8 (C), 143.2 (C), 132.4 (CH), 129.8 (CH), 128.9 (CH), 128.8 (CH), 125.20 (CH), 120.0 (C), 82.2 (C), 50.9 (CH2), 37.2 (CH), 27.5 (CH_2); *m/z* (TOF ES^-) 486 (M – H, 23%), 484 (M – H, 64) and 482 (M – H^+, 100).

3.3.1.6. 8-Nitro-7-(4-nitrophenyl)-6-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridin-5-amine (8f) and 8-nitro-7-(4-nitrophenyl)-6-(phenylsulfonyl)-6,7-dihydro-2H-thiazolo[3,2-a]pyridin-5(3H)-imine (9f)



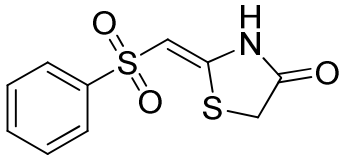
(8f)



(9f)

Obtained as light brown crystals (350 mg, 76%, 1.4:1 mixture of **8f**:**9f** according to 1H NMR spectroscopic data), m.p. 184 – 186 °C (Found: $(M - H)^-$, 459.0414. $C_{19}H_{16}N_4O_6S_2$ requires M, 459.0433); $\nu_{max.}$ (KBr) 3289 (NH_2), 1637 (C=C), 1559, 1443, 1383, 1219 and 1138 cm^{-1}; δ_H (400 MHz; d_6-DMSO) 9.69 (1 H of **9f**, s, NH), 8.18 (2 H of **9f**, d, *J* 8.7, aromatic CH of *Ar*-NO_2), 8.01 (2 H of **8f**, d, *J* 8.8, aromatic CH of *Ar*-NO_2), 7.86 – 7.80 (3 H of **9f**, m, aromatic CH of SO_2*Ph*), 7.73 – 7.67 (2 H of **8f** and 2 H of **9f**, m, aromatic CH of SO_2*Ph*), 7.54 (1 H of **8f**, app. t, *J* 7.4, aromatic CH of SO_2*Ph*), 7.47 – 7.40 (4 H of **8f**, m, aromatic CH of *Ar*-NO_2 and SO_2*Ph*), 7.33 (2 H of **9f**, app. d, *J* 8.7, aromatic CH of Ar-NO_2), 7.09 (2 H of **8f**, broad s, NH_2), 5.19 (1 H of **8f**, s, C*H*Ar), 5.09 (1 H of **9f**, s, C*H*Ar), 5.03 (1 H of **9f**, s, C*H*SO_2Ph), 4.41 (1 H of **9f**, ddd, *J* 12.0, 8.7, 3.4, one of CH_2N), 4.37 – 4.30 (2 H of **8f**, m, CH_2N), 4.17 (1 H of **9f**, app. td, *J* 11.4, 8.6, one of CH_2N), 3.40 (2 H of **8f**, app. t, *J* 7.7, CH_2S), 3.38 – 3.31 (1 H of **9f**, m, one of CH_2S) and 3.12 (1 H of **9f**, app. td, *J* 11.1, 8.9, one of CH_2S); δ_C (100 MHz; d_6-DMSO) 160.4 (C, **9f**), 157.9 (C, **8f**), 150.9 (C, **8f**), 149.4 (C, **9f**), 147.9 (C, **8f**), 147.2 (C, **9f**), 146.2 (C, **8f**), 145.7 (C, **9f**), 143.3 (C, **8f**), 135.5 (CH, **9f**), 132.5 (CH, **8f**), 129.8 (CH, **9f**), 129.2 (CH, **8f**), 129.0 (CH, **8f**), 128.6 (CH, **9f**), 128.3 (CH, **9f**), 125.7 (CH, **8f**), 124.4 (CH, **9f**), 123.2 (CH, **8f**), 122.4 (C, **8f**), 118.5 (C, **9f**), 85.1 (C, **8f**), 69.1 (CH, **9f**), 51.6 (CH_2, **9f**), 51.1 (CH_2, **8f**), 40.1 (CH, **8f**), 39.6 (CH, **9f**), 28.2 (CH_2, **8f**) and 27.9 (CH_2, **9f**); *m/z* (TOF ES^-) 459 (M – H, 100%) and 339 (60).

3.4. Synthesis of 2-Phenylsulfonylmethylenethiazolidin-4-one (11)



11

Phenylsulfonylacetonitrile **(7)** (1.0 eq., 3.624 g, 20 mmol) was dissolved in pyridine (10 mL) at room temperature. After that mercaptoacetic acid **(10)** (1.0 eq., 1.842 g, 20 mmol) was added to this mixture and reaction mixture was allowed to stir for overnight at 115℃. Reaction was monitored by TLC. After reaction completed, pyridine was removed by using evaporator and purified by flash column chromatography. (Ethyl acetate/n-Hexane: 1/3). Yellow crystalline product was obtained (3.2 g, 63% yield),

M.p. (120-122℃).

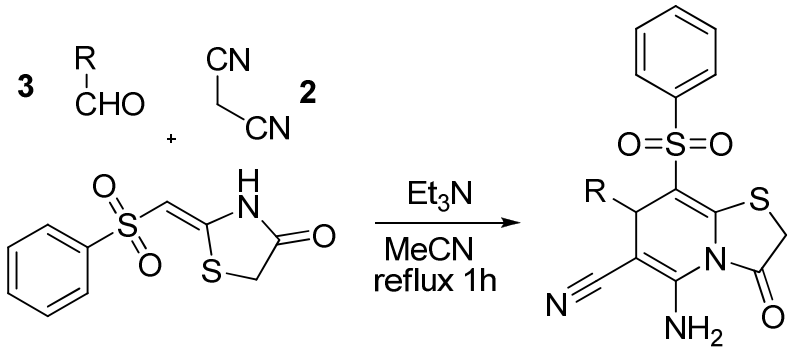
Rf : 0.42 (Ethyl acetate/n-Hexane: 1/1)

IR ν_{max} cm^{-1} (KBr): 3101 (NH_2), 1735 (CO), 1589 (C = C), 1301 (SO_2), 1138 (SO_2).

^{1}H NMR (400 MHz DMSO-d_6): 10.1 (br s, 1H, NH), 7.89 (d, 2H, J = 7.1 Hz, aromatic CH), 7.64 (t, 1H, J = 7.4 Hz, aromatic CH), 7.57 (t, 2H, J = 7.4, 7.1 Hz, aromatic CH), 5.36 (s, 1H, CH = C), 3.80 (s, 2H, CH_2S).

^{13}C NMR (100 MHz DMSO-d_6): 171.6, 152.2, 142.2, 133.3, 129.4, 126.6, 96.1, 77.3, 77.0, 76.8, 31.2.

3.5. Synthesis of Thiazolo[3,2-a]pyridine-4-one derivatives with the reactions of 2-Phenylsulfonylmethylenethiazolidin-4-one (11), malononitrile (2) and aldehydes (3).



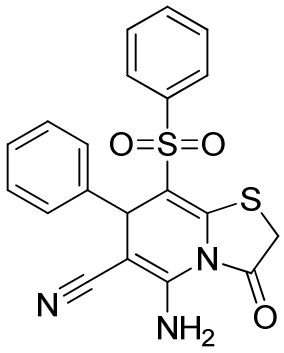
11 **(12a-12f)**

Scheme 3.4. Synthesis of Thiazolo[3,2-a]pyridine derivatives (12a-12f)

3.5.1. General Procedure for 5-Amino-3-oxo-7-aryl-8-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile derivatives (12a-12f)

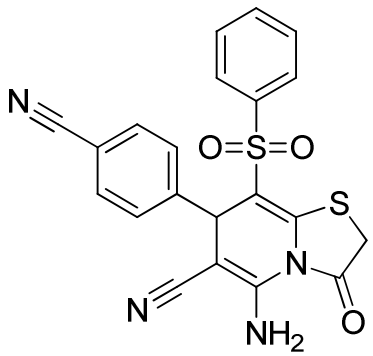
Aromatic aldehyde (1.0 mmol, 1.0 eq.), 2-phenylsulfonylmethylenethiazolidine (1.0 mmol, 1.0 eq., 255 mg) and malononitrile (1.0 mmol, 1.0 eq., 66 mg) were mixed in MeCN (10 mL) in a round-bottomed flask, and the reaction mixture was stirred and heated. Triethylamine (0.5 mmol, 0.5 eq., 50 mg) was added and the reaction mixture was heated under reflux for 1 h. After cooling, the solvent was removed under reduced pressure, and the residue recrystallised from n-hexane/ethyl acetate mixtures to give the pure products with data given below.

3.5.1.1. 5-Amino-3-oxo-7-phenyl-8-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (12a)



Obtained as yellow solid (300 mg, 73%), m.p. 229–230 °C. ν_{max}, cm^{-1} (KBr) 3416 (NH_2), 2189 (CN), 1701 (CO), 1647 (C = C), 1307 (SO_2), 1153 (SO_2). HRMS: requires for $C_{20}H_{15}N_3O_3S_2$ [M^+] 409.0555, found M^+, 409.0558. δ_H (400 MHz, DMSO-d_6) 7.79–7.70 (m, 3H, aromatic CH of SO_2Ph), 7.61 (t, J = 7.7 Hz, 2H, aromatic CH of SO_2Ph), 7.38 (t, J = 7.4 Hz, 2H, aromatic CH), 7.30 (t, J = 7.3 Hz, 2H, aromatic CH), 7.20 (d, J = 7.0 Hz, 1H, aromatic CH), 7.16 (s, 2H, NH_2), 5.16 (s, 2H, SCH_2), 5.02 (s, 1H, CHPh). δ_C (100 MHz; DMSO-d_6) 160.7, 154.2, 152.2, 144.5, 138.1, 134.7, 129.7, 129.2, 128.5, 127.9, 127.4, 120.1, 112.8, 58.4, 55.9, 38.6.

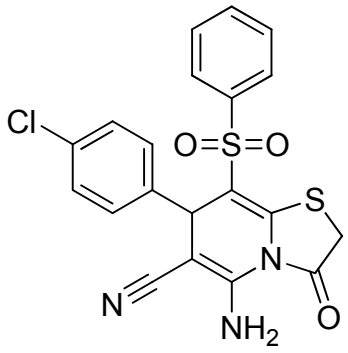
3.5.1.2. 5-amino-7-(4-cyanophenyl)-3-oxo-8-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (12b)



Obtained as brown solid (365 mg, 84%), mp. 197– 199 °C. ν_{max}, cm^{-1} (KBr) 3331 (NH_2), 2228 (CN of Ar), 2199 (CN), 1743 (CO), 1649 (C = C), 1327 (SO_2), 1144 (SO_2). HRMS: Found M^+ 435.0585 $C_{21}H_{15}N_4O_3S_2$ [M^+] requires 435.0586. δ_H (400 MHz, DMSO-d_6) 7.87 (d, J = 8.2 Hz, 2H, aromatic

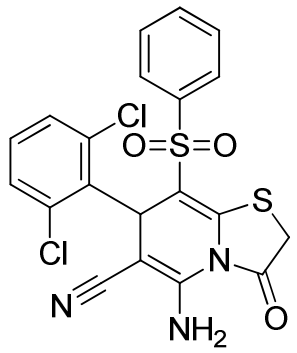
CH), 7.78−7.70 (m, 3H, aromatic CH of $PhSO_2$), 7.61 (app. t, J = 7.9 Hz, 2H, aromatic CH), 7.41 (d, J = 8.2 Hz, 1H, aromatic CH), 7.30 (2H, br s, NH_2), 5.18 (2H, app. s, CH_2S), 5.17 (1H, app. s, CHAr). δ_C (100 MHz; DMSO-d_6) 160.9, 154.8, 152.4, 149.7, 138.0, 134.8, 133.2, 129.7, 128.6, 128.5, 122.2, 118.8, 111.4, 110.8, 58.9, 54.9, 38.5.

3.5.1.3. 5-Amino-7-(4-chlorophenyl)-3-oxo-8-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (12c)



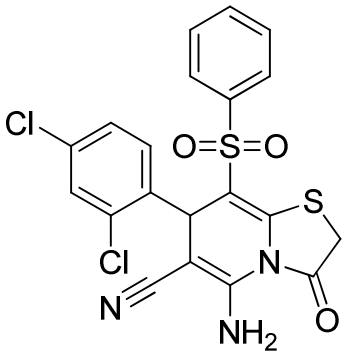
Obtained as pale yellow solid (330 mg, 74%), mp. 244–246 °C. ν_{max}, cm^{-1} (KBr) 3374 (NH_2), 2201 (CN), 1720 (CO), 1647 (C = C), 1329 (SO2), 1146 (SO_2). HRMS: Found M^+, 443.0163. $C_{20}H_{14}N_3O_3S_2{}^{35}Cl$ [M^+] requires 443.0165. δ_H (400 MHz, DMSO-d_6) 7.79–7.70 (3H, m, aromatic CH of SO_2Ph), 7.61 (2H, t, J = 7.8 Hz, aromatic CH of SO_2Ph), 7.45 (2H, d, J = 8.4 Hz, aromatic CH), 7.25–7.19 (4H, m, aromatic CH obscured with NH_2), 5.17 (2H, s, CH_2S), 5.06 (1H, s, CHAr). δ_C (100 MHz; DMSO-d_6) 160.3, 154.1, 151.9, 143.0, 137.8, 134.3, 132.1, 129.3, 129.0, 128.8, 128.1, 119.6, 111.9, 58.1, 55.3, 37.6.

3.5.1.4. 5-Amino-7-(2,6-dichlorophenyl)-3-oxo-8-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (12d)



Obtained as yellow solid (410 mg, 86%), mp. 277−278 °C. $\square_{max}$, cm^{-1} (KBr) 3422 (NH_2), 2189 (CN), 1728 (CO), 1647 (C = C), 1307 (SO_2), 1154 (SO_2). HRMS: Found M^+, 476.9758. $C_{20}H_{13}N_3O_3S_2{}^{35}Cl_2$ [M^+] requires 476.9775. δ_H (400 MHz, DMSO-d_6) 7.75−7.69 (3H, m, aromatic CH of SO_2Ph), 7.60 (2H, d, J = 7.7 Hz, aromatic CH of SO_2Ph), 7.57 (1H, dd, J = 8.0, 1.3 Hz, aromatic CH), 7.48 (1H, d, J = 6.9 Hz, aromatic CH), 7.40 (1H, t, J = 8.0 Hz, aromatic CH), 7.29 (2H, brs, NH_2), 5.92 (1H, s, CHAr), 5.20 (2H, q, J = 14.5 Hz, CH_2S). δ_C (100 MHz; DMSO-d_6) 161.6, 153.9, 153.6, 137.9, 135.7, 135.6, 134.7, 134.4, 131.5, 130.9, 129.6, 129.2, 128.6, 119.5, 108.7, 58.4, 52.4 and 35.3.

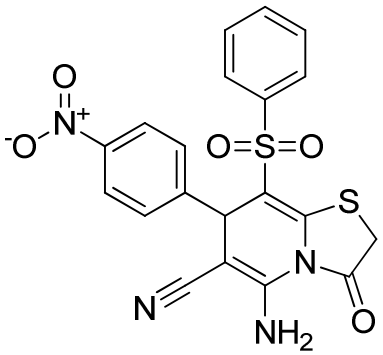
3.5.1.5. 5-amino-7-(2,4-dichlorophenyl)-3-oxo-8-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (12e)



Obtained as yellow solid (325 mg, 68%), mp. 251−252 °C. $\square_{max}$, cm^{-1} (KBr) 3439 (NH_2), 2189 (CN), 1722 (CO), 1657 (C = C), 1319 (SO_2), 1152 (SO_2). HRMS: Found M^+, 476.9764. $C_{20}H_{13}N_3O_3S_2{}^{35}Cl_2$ [M^+] requires 476.9775. δ_H (400 MHz, DMSO-d_6) 7.74−

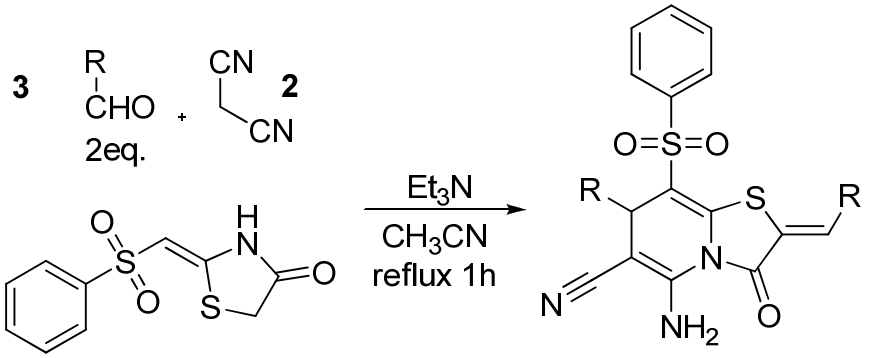
7.69 (3H, m, aromatic CH of SO_2Ph), 7.68 (1H, d, J = 2.0 Hz, aromatic CH), 7.59 (2H, t, J = 7.8 Hz, aromatic CH of SO_2Ph), 7.50 (1H, dd, J = 8.3, 2.0 Hz, aromatic CH), 7.37 (1H, s, aromatic CH), 7.34 (2H, br s, NH_2), 5.40 (1H, s, CHAr), 5.18 (2H, d, J = 2.6 Hz, CH_2S). δ_C (100 MHz; DMSO-d_6) 161.5, 154.4, 152.7, 139.4, 138.1, 134.6, 133.6, 133.1, 131.8, 129.9, 129.7, 128.7, 128.5, 119.8, 110.5, 58.3, 53.5 and 36.3.

3.5.1.6. 5-Amino-7-(4-nitrophenyl)-3-oxo-8-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (12f)



Obtained as pale yellow solid (322 mg, 71%), mp. 255–256 °C. ν_{max}, cm^{-1} (KBr) 3312 (NH_2), 2201 (CN), 1654 (CO), 1647 (C = C), 1327 (SO_2), 1144 (SO_2). HRMS: Found M^+, 454.0406. $C_{20}H_{14}N_4O_5S_2$ [M^+] requires 454.0406. δ_H (400 MHz, DMSO-d_6) 8.26 (2H, d, J = 7.9 Hz, aromatic CH), 7.77 – 7.70 (3H, m, aromatic CH of SO_2Ph), 7.62 (2H, t, J = 7.5 Hz, aromatic CH of SO_2Ph), 7.51 (2H, d, J = 7.9 Hz, aromatic CH), 7.33 (2H, br s, NH_2), 5.26 (1H, s, CHAr), 5.19 (2H, s, CH_2S). δ_C (100 MHz; DMSO-d_6) 160.9, 154.9, 152.5, 151.6, 147.3, 138.1, 134.7, 129.7, 129.0, 128.5, 124.6, 119.9, 111.3, 58.4, 54.9, 38.3.

3.6. Synthesis of Thiazolo[3,2-a]pyridine-4-one derivatives with the reactions of 2-Phenylsulfonylmethylenethiazolidin-4-one (11), malononitrile (2) and aldehydes (2 eq.) (3).



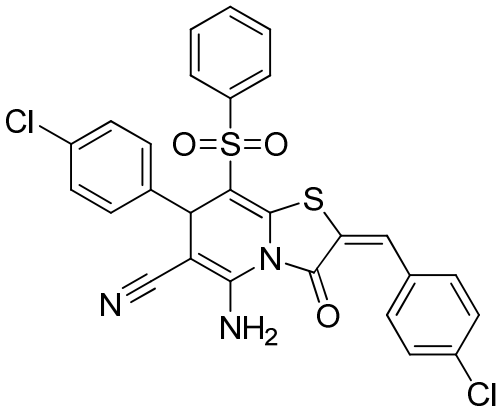
11 **(13a-13g)**

Scheme 3.5. Synthesis of Thiazolo[3,2-a]pyridine derivatives (13a-13g).

3.6.1. General Procedure for Synthesis of Thiazolo[3,2-a]pyridine derivatives (13a-13g)

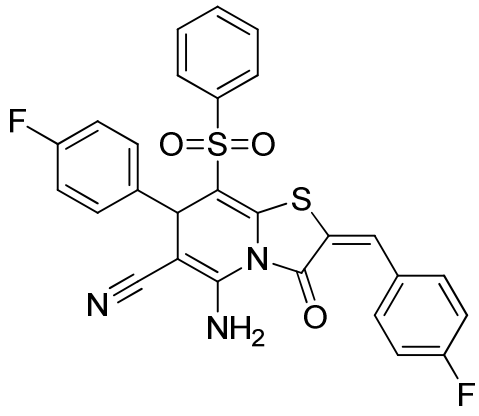
Aromatic aldehyde (2.0 mmol, 2.0 eq.), 2-phenylsulfonylmethylenethiazolidine (1.0 mmol, 1.0 eq., 255 mg) and malononitrile (1.0 mmol, 1.0 eq., 66 mg) were mixed in MeCN (10 mL) in a round-bottomed flask, and the reaction mixture was stirred and heated. Triethylamine (0.5 mmol, 0.5 eq., 50 mg) was added and the reaction mixture was heated under reflux for 1 h. After cooling, the solvent was removed under reduced pressure, and the residue recrystallized from n-hexane/ethyl acetate mixtures to give the pure products with data given below.

3.6.1.1. 5-Amino-2-(4-chlorobenzylidene)-7-(4-chlorophenyl)-3-oxo-8-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (13a)



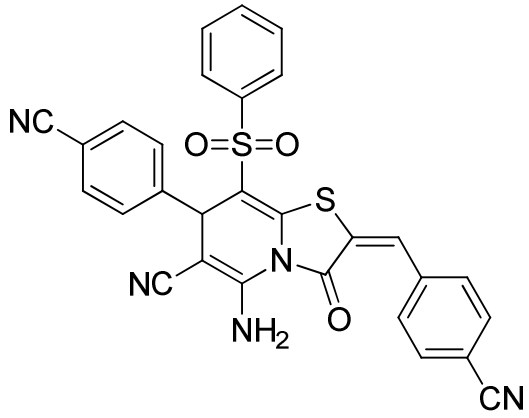
Obtained as yellow solid (384 mg, 68%), mp. 293–294 ℃. $\square_{max}$, cm^{-1} (KBr) 3373 (NH_2), 2199 (CN), 1721 (CO), 1653 (C = C), 1325 (SO_2), 1148 (SO_2). (Found: $(M\text{-}H)^+$, 566.0176. $C_{27}H_{18}N_3O_3S_2\ ^{35}Cl_2$ requires M, 566.0167). δ_H (400 MHz, DMSO-d_6) 7.79–7.75 (m, 3H, aromatic CH of SO_2Ph), 7.72 (d, J = 8.1 Hz, 2H, aromatic CH of SO_2Ph), 7.65–7.56 (m, 3H, CH = C and aromatic CH), 7.52 (br s, 2H, NH_2), 7.47–7.40 (m, 2H, aromatic CH), 7.28–7.21 (m, 2H, aromatic CH), 7.18–7.12 (m, 2H, aromatic CH), 4.54 (s, 1H, CHAr). δ_C (100 MHz; DMSO-d_6) 166.1, 148.2, 142.1, 141.5, 140.7, 135.5, 134.2, 132.6, 132.5, 132.3, 130.5, 130.3, 130.1, 129.6, 128.6, 127.3, 122.1, 119.0, 113.3, 65.9, 41.2. m/z (TOF ES^+) 566 ($M\text{–}H^+$, 100) and 331 (15).

3.6.1.2. 5-Amino-2-(4-fluorobenzylidene)-7-(4-fluorophenyl)-3-oxo-8-(phenyl sulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (13b)



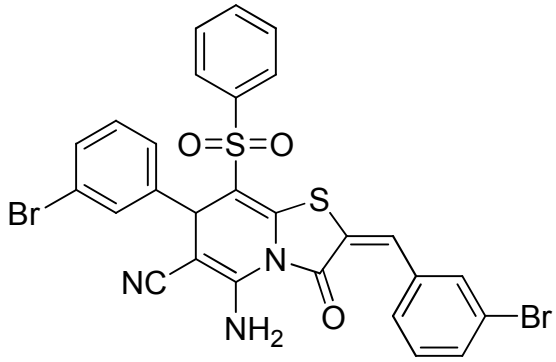
Obtained as pale yellow solid (425 mg, 80%), mp. 278–279 °C. $\square_{max}$, cm^{-1} (KBr) 3412 (NH_2), 2203 (CN), 1707 (CO), 1649 (C = C), 1327 (SO2), 1144 (SO_2). (Found: $(M-H)^+$, 534.0751. $C_{27}H_{18}N_3O_3S_2F_2$ requires M, 534.0758). δ_H (400 MHz, DMSO-d_6) 7.95–7.72 (m, 3H, aromatic CH of SO_2Ph and CH = C), 7.72–7.58 (m, 3H, aromatic CH of SO_2Ph), 7.58 – 7.51 (m, 4H, aromatic CH of ArF and NH_2), 7.49–7.42 (m, 2H, aromatic CH of ArF), 7.35–7.16 (m, 2H, aromatic CH of ArF), 7.01–6.80 (m, 2H), 4.57 (d, 1H). δ_C (100 MHz; DMSO-d_6) 166.2, 164.5, 163.0, 162.0, 160.6, 148.2, 142.1 140.9, 138.7, 134.2, 133.19, 130.6, 129.6, 127.3, 120.9, 119.1, 117.3, 115.6, 113.5, 66.2, 41.1. m/z (TOF ES^+) 534 ($M-H^+$, 100).

3.6.1.3. 5-Amino-2-(4-cyanobenzylidene)-7-(4-cyanophenyl)-3-oxo-8-(phenyl sulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (13c)



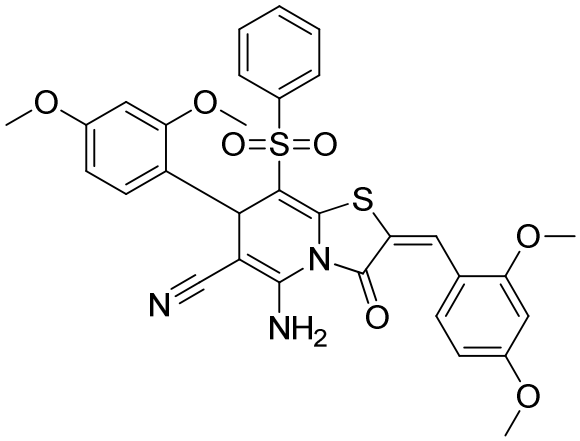
Obtained as yellow solid (339 mg, 62%), mp. 292–294 °C. $\square_{max}$, cm^{-1} (KBr) 3421 (NH_2), 2245 (CN), 2230 (CN), 2195 (CN of pyridine), 1701 (CO), 1643 (C = C), 1327 (SO2), 1146 (SO_2). (Found: $(M-H)^+$, 548.0850. $C_{29}H_{18}N_5O_3S_2$ requires M, 548.0851). δ_H (400 MHz, DMSO-d_6) 8.08 (d, J = 7.7 Hz, 2H, aromatic CH), 7.91 (d, J = 7.6 Hz, 2H, aromatic CH of SO_2Ph), 7.84 (s, 1H, CH = C), 7.68–7.62 (m, 3H, aromatic CH of SO_2Ph), 7.59 (d, J = 7.7 Hz, 2H, aromatic CH), 7.55 (brs, 2H, NH_2), 7.45 (app d, J = 5.5 Hz, 4H), 4.65 (s, 1H, CHAr). δ_C (100 MHz; DMSO-d_6) 165.9, 148.4, 147.8, 142.5, 140.4, 138.1, 134.5, 133.7, 132.7, 131.1, 129.7, 129.6, 129.4, 127.4, 125.1, 119.1, 118.9, 118.8, 113.0, 112.4, 110.6, 65.2, 41.6. m/z (TOF ES^+) 548 ($M - H^+$, 100) and 405 (20).

3.6.1.4. 5-Amino-2-(3-bromobenzylidene)-7-(3-bromophenyl)-3-oxo-8-(phenyl sulfonyl)-3,7-dihydro-2Hthiazolo[3,2-a]pyridine-6-carbonitrile (13d)



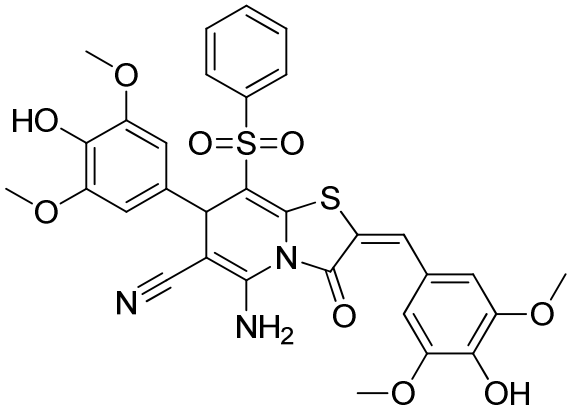
Obtained as yellow solid (480 mg, 73%), mp. 275–276 ℃. ν_{max}, cm^{-1} (KBr) 3404 (NH_2), 2201 (CN), 1697 (CO), 1653 (C = C), 1329 (SO_2), 1147 (SO_2). (Found: $(M-H)^+$, 653.9155. $C_{27}H_{18}N_3O_3S_2\ ^{79}Br_2$ requires M, 653.9156). δ_H (400 MHz, DMSO-d_6) 7.97 (s, 1H, aromatic CH), 7.77 (s, 1H, CH = C), 7.73 (d, J = 7.8 Hz, 2H, aromatic CH), 7.67–7.56 (m, 4H, aromatic CH of SO_2Ph and aromatic CH of ArBr), 7.53 (brs, 2H, NH_2), 7.47–7.40 (m, 2H, aromatic CH of SO_2Ph), 7.38 (s, 1H, aromatic CH), 7.30 (d, J = 7.7 Hz, 1H, aromatic CH), 7.24 (d, 1H, J = 7.7 Hz, aromatic CH), 7.12 (t, J = 7.7 Hz, 1H, aromatic CH), 4.57 (s, 1H, CHAr). δ_C (100 MHz; DMSO-d_6) 166.0, 148.2, 144.8, 142.3, 140.6, 136.2, 134.4, 133.8, 133.4, 132.1, 131.4, 130.9, 130.8, 129.8, 129.6, 128.5, 127.9, 127.2, 123.3, 123.1, 122.4, 119.1, 113.0, 65.8, 41.5. m/z (TOF ES^+) 655 ($M - H^+$, 100) and 653 (52).

3.6.1.5. 5-Amino-2-(2,4-dimethoxybenzylidene)-7-(2,4-dimethoxy phenyl)-3-oxo-8-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (13e)



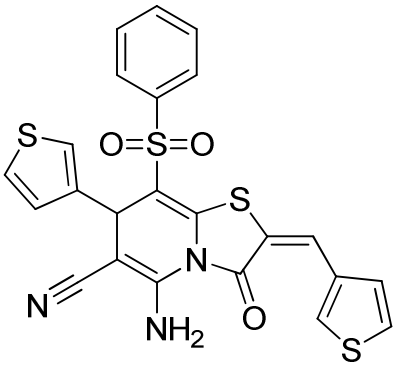
Obtained as yellow solid (395 mg, 64%), mp. 248–249 °C. $\square_{max}$, cm^{-1} (KBr) 3309 (NH_2), 2187 (CN), 1707 (CO), 1643 (C = C), 1325 (SO_2), 1144 (SO_2). (Found: (M–H)+, 618.1362. $C_{31}H_{28}N_3O_7S_2$ requires M, 618.1369). δ_H (400 MHz, DMSO-d_6) 7.93 (s, 1H, CH = C), 7.57–7.53 (m, 3H, aromatic CH of SO_2Ph), 7.47 (app. d, J = 7.6 Hz, 2H, aromatic CH of SO_2Ph), 7.37 (m, 1H, aromatic CH), 7.36 (br s, 2H, NH_2), 6.95 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.74 (d, J = 1.9 Hz, 1H), 6.32 (d, J = 7.2 Hz, 1H), 6.14 (s, 1H, aromatic CH), 4.63 (s, 1H, CHAr), 3.95 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 3.45 (s, 3H, OCH_3). δ_C (100 MHz; DMSO-d_6) 166.3, 163.8, 160.6, 160.3, 158.3, 153.8, 148.9, 141.9, 141.0, 133.8, 131.2, 131.0, 129.3, 126.9, 126.8, 121.2, 119.4, 116.7, 115.1, 112.6, 107.2, 105.5, 99.2, 98.9, 64.9, 56.5, 56.2, 55.9, 55.7. m/z (TOF ES^+) 618 (M–H^+, 100), 480 (M–Ar^+, 15) and 336 (35).

3.6.1.6. 5-Amino-2-(4-hydroxy-3,5-dimethoxybenzylidene)-7-(4-hydroxy-3,5-dimethoxy phenyl)-3-oxo-8-(phenylsulfonyl)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (13f)



Obtained as yellow solid (450 mg, 69%), mp. 220 °C decomp. $\square_{max}$, cm^{-1} (KBr) 3412 (NH_2), 2203 (CN), 1701 (CO), 1649 (C = C), 1327 (SO_2), 1144 (SO_2). (Found: $(M-H)^+$, 653.9155. $C_{27}H_{18}N_3O_3S_2{}^{79}Br_2$ requires M, 653.9156). δ_H (400 MHz, DMSO-d_6) 8.42 (s, 1H, OH), 8.24 (s, 1H, OH), 7.77 (app. d, J = 7.5 Hz, 2H, aromatic CH of SO_2Ph), 7.64−7.57 (m, 2H, CH = C and aromatic CH of SO_2Ph), 7.51−7.45 (m, 1H, aromatic CH of SO_2Ph), 7.37 (t, J = 7.1 Hz, 1H, aromatic CH of SO_2Ph), 7.08 (br s, 2H, NH_2), 6.48 (s, 1H, aromatic CH), 6.29 (s, 1H, aromatic CH), 5.16 (s, 1H, aromatic CH), 4.93 (s, 1H, aromatic CH), 4.49 (s, 1H, CHAr), 3.88 (s, 3H, CH_3O), 3.73 (s, 3H, CH_3O), 3.59 (s, 2H, CH_3O), 3.36 (s, 3H, obscured by water in DMSO, CH_3O). δ_C (100 MHz; DMSO-d_6) 160.8, 153.9, 151.9, 148.7, 148.6, 148.2, 141.2, 138.4, 135.8, 134.7, 133.8, 129.7, 129.2, 128.5, 127.2, 124.1, 120.3, 117.2, 113.6, 108.9, 106.8, 105.0, 66.6, 58.5, 56.6, 56.6, 56.5, 56.0, 42.1, 38.8. m/z (TOF ES^+) 650 ($M-H^+$, 100), 496 ($M-Ar^+$, 25).

3.6.1.7. 5-Amino-3-oxo-8-(phenylsulfonyl)-7-(thiophen-3-yl)-2-(thiophen-3-ylmethylene)-3,7-dihydro-2H-thiazolo[3,2-a]pyridine-6-carbonitrile (13g)



Obtained as pale yellow solid (410 mg, 81%), mp. 265– 266 °C. ν_{max}, cm^{-1} (KBr) 3408 (NH_2), 2205 (CN), 1701 (CO), 1647 (C = C), 1325 (SO_2), 1144 (SO_2). (Found: $(M-H)^+$, 510.0062. $C_{23}H_{16}N_3O_3S_4$ requires M, 510.0075). δ_H (400 MHz, DMSO-d_6) 8.16 (s, 1H, aromatic CH of thienyl), 7.90 – 7.76 (m, 2H, aromatic CH of thienyl), 7.68–7.56 (m, 3H, aromatic CH of SO_2Ph), 7.52 (s, 1H, CH = C), 7.50 – 7.36 (m, 4H, NH_2 and aromatic CH of SO_2Ph), 7.31 (s, 1H, aromatic CH of thienyl), 7.19 (s, 1H, aromatic CH of thienyl), 6.92–6.82 (m, 1H, aromatic CH of thienyl), 4.70 (s, 1H, CHAr). δ_C (100 MHz; DMSO-d_6) 166.2, 148.5, 143.1, 141.6, 140.8, 135.8, 134.1, 131.9, 129.5, 129.1, 128.6, 127.8, 127.4, 126.9, 125.8, 123.4, 119.7, 119.3, 113.3, 65.7, 36.8. m/z (TOF ES^+) 510 ($M-H^+$, 100), 336 (25) and 280 (45).

APPENDICES

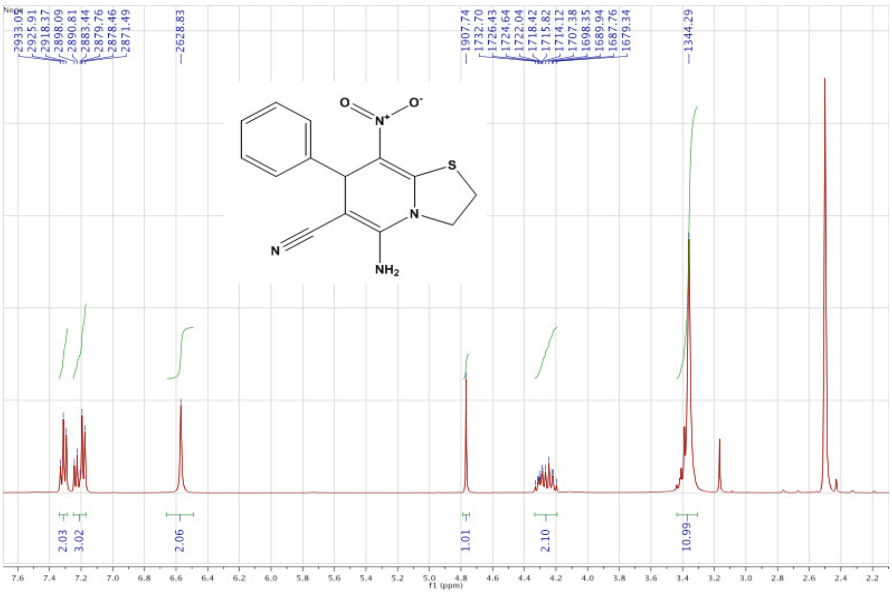


Figure 4.1. ^{1}H NMR spectrum of compound (4a).

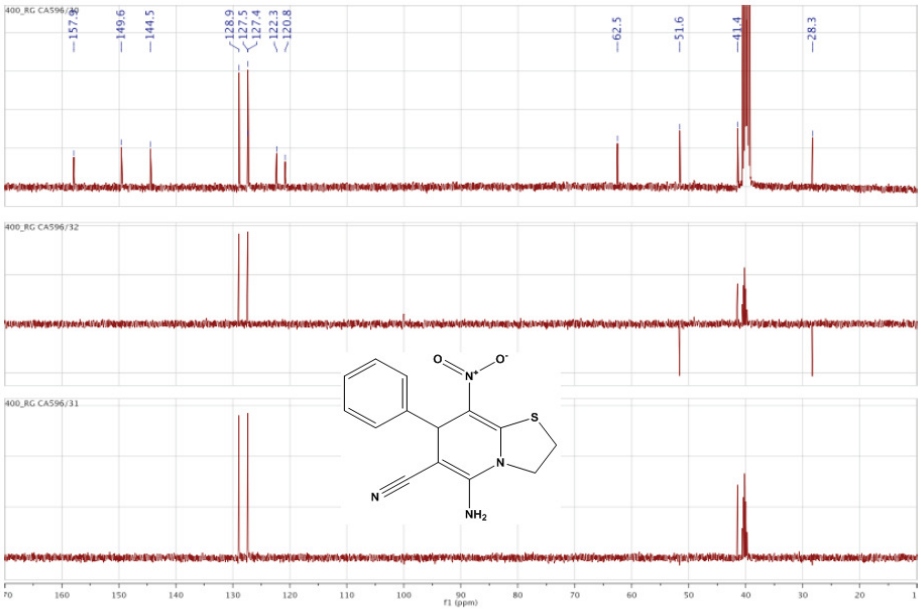


Figure 4.2. ^{13}C NMR spectrum of compound (4a).

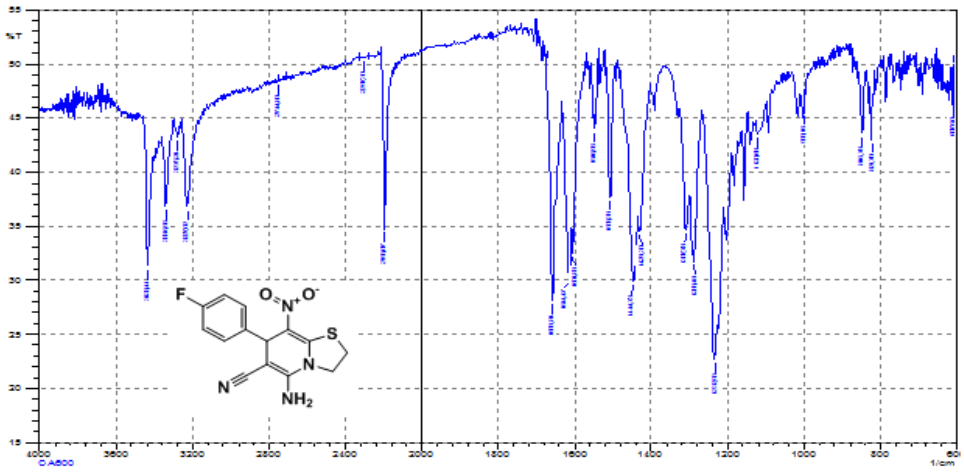


Figure 4.3. IR spectrum of compound (4b).

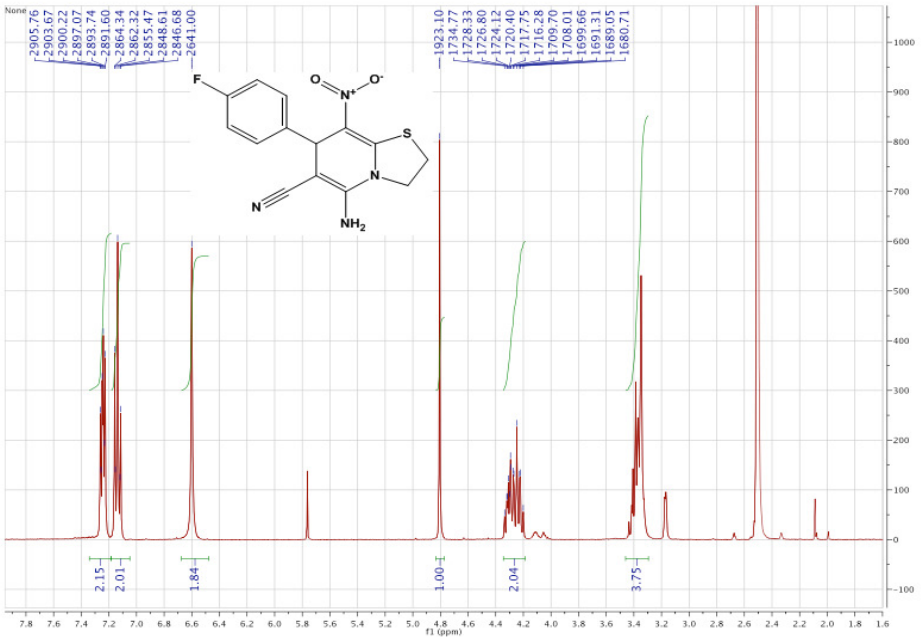


Figure 4.4. ^{1}H NMR spectrum of compound (4b).

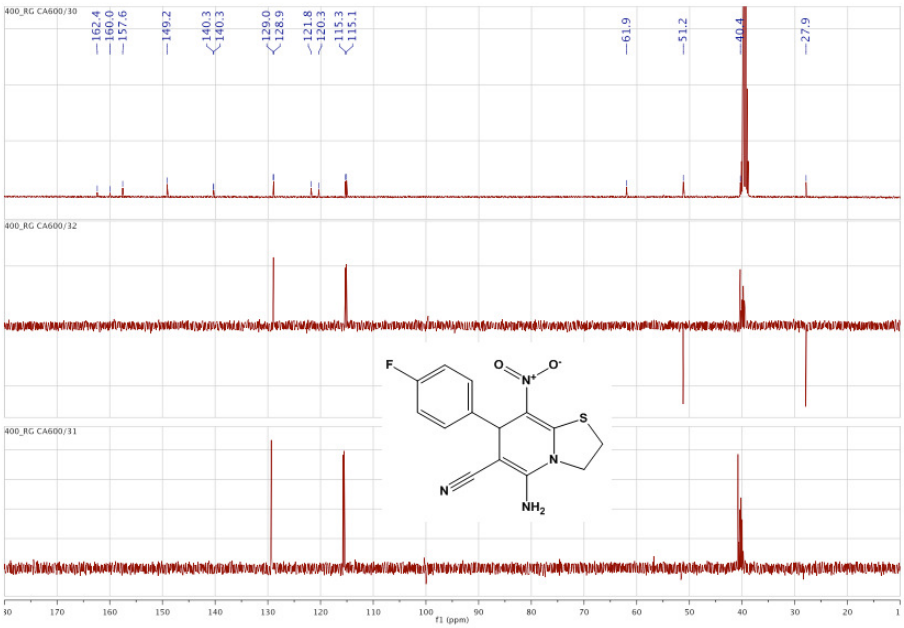


Figure 4.5. ^{13}C NMR spectrum of compound (4b).

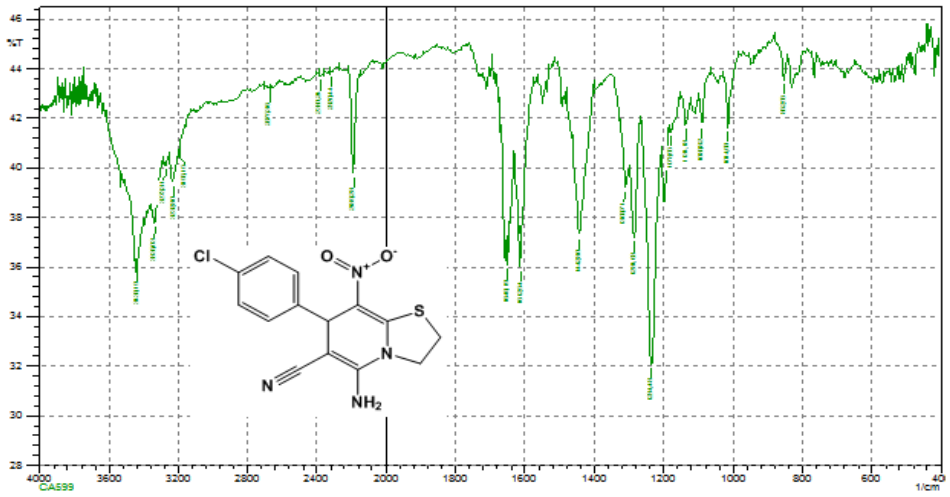


Figure 4.6. IR spectrum of compound (4c).

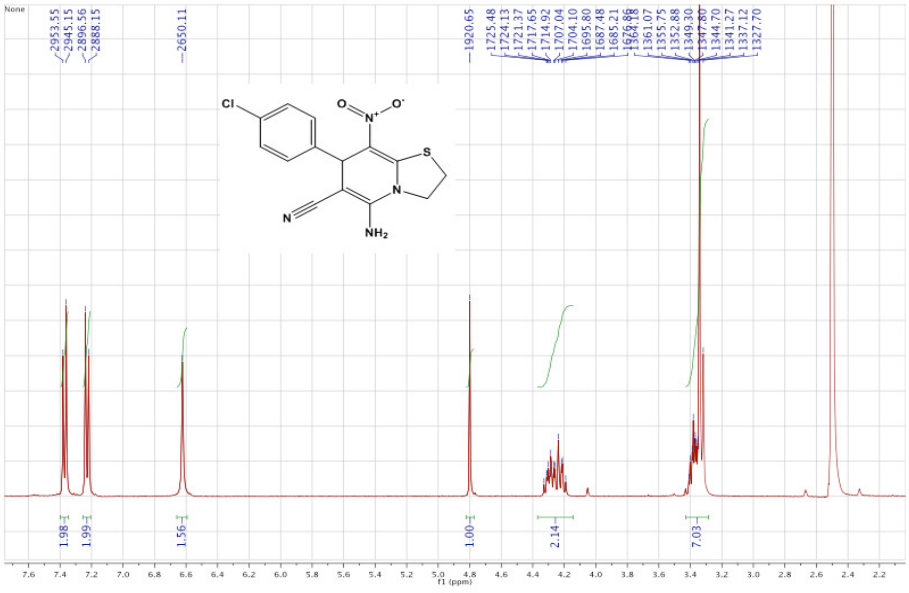


Figure 4.7. ^{1}H NMR spectrum of compound (4c).

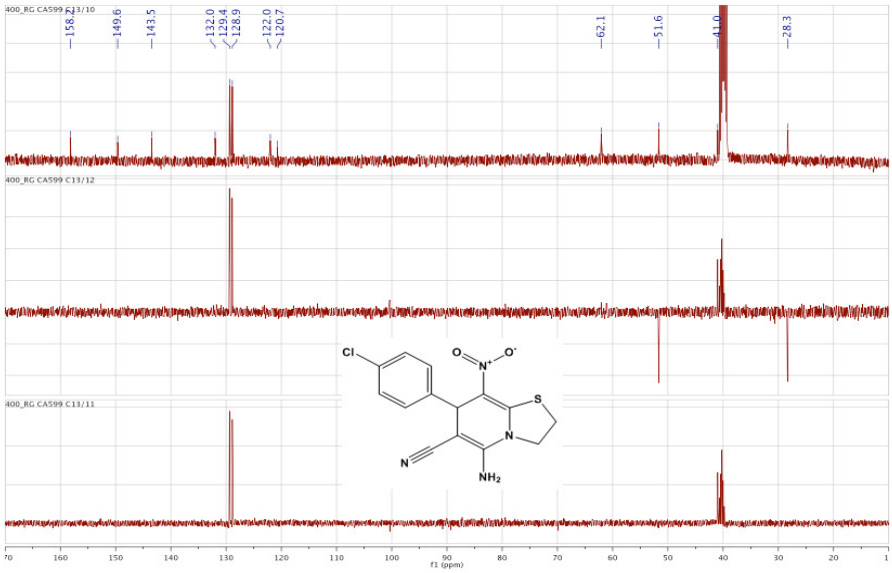


Figure 4.8. ^{13}C NMR spectrum of compound (4c).

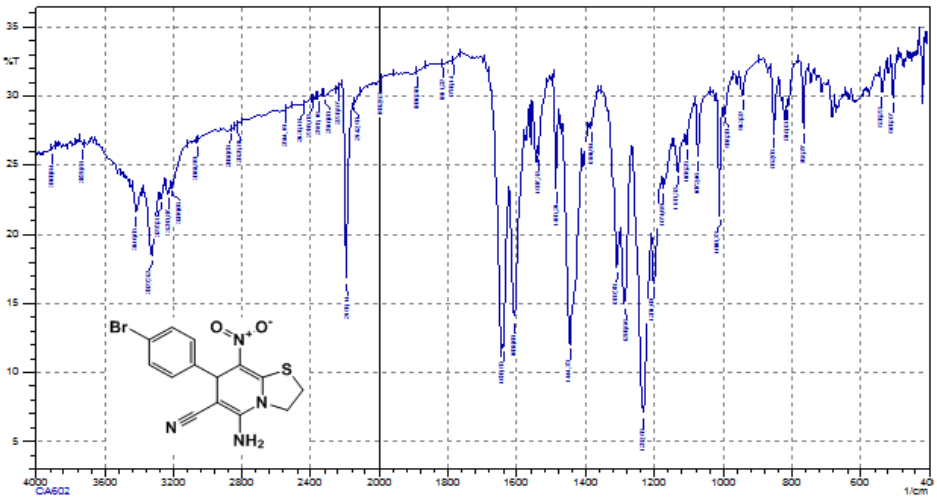


Figure 4.9. IR spectrum of compound (4d).

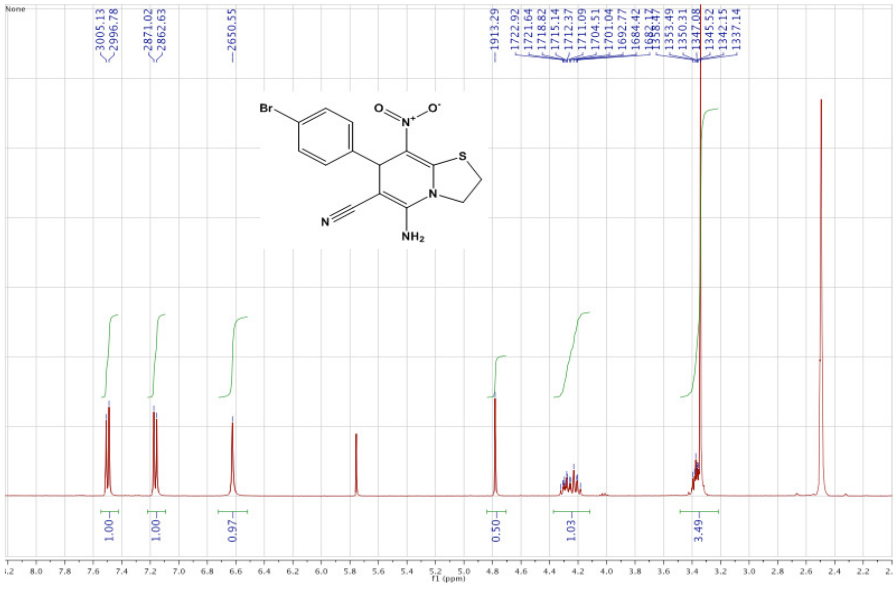


Figure 4.10. ^{1}H NMR spectrum of compound (4d).

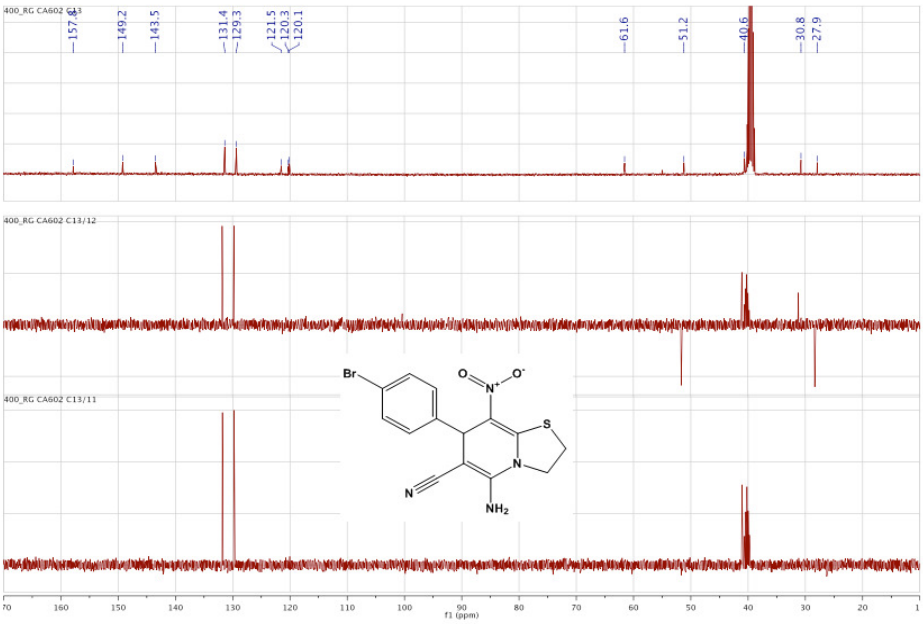


Figure 4.11. ^{13}C NMR spectrum of compound (4d).

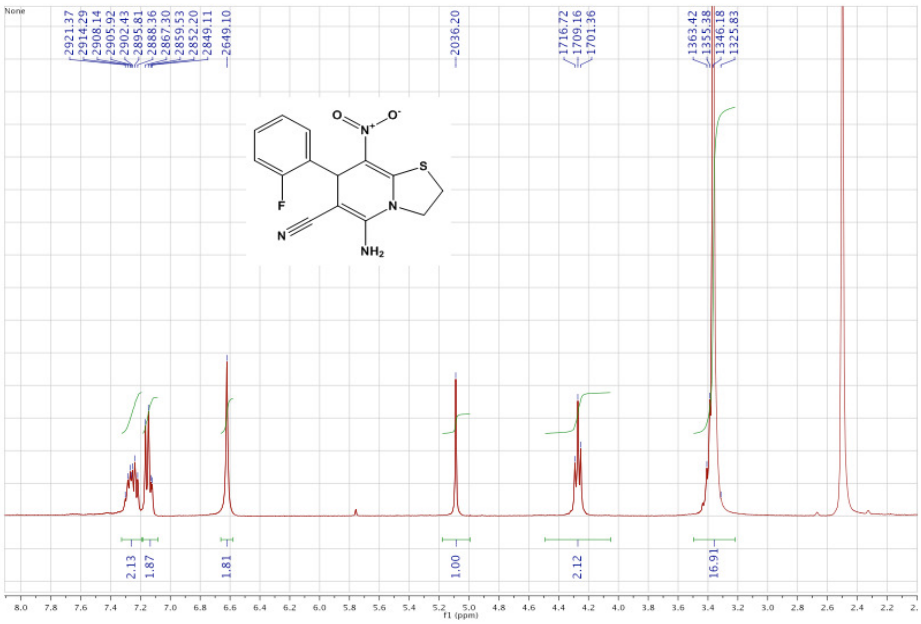


Figure 4.12. ^{1}H NMR spectrum of compound (4e).

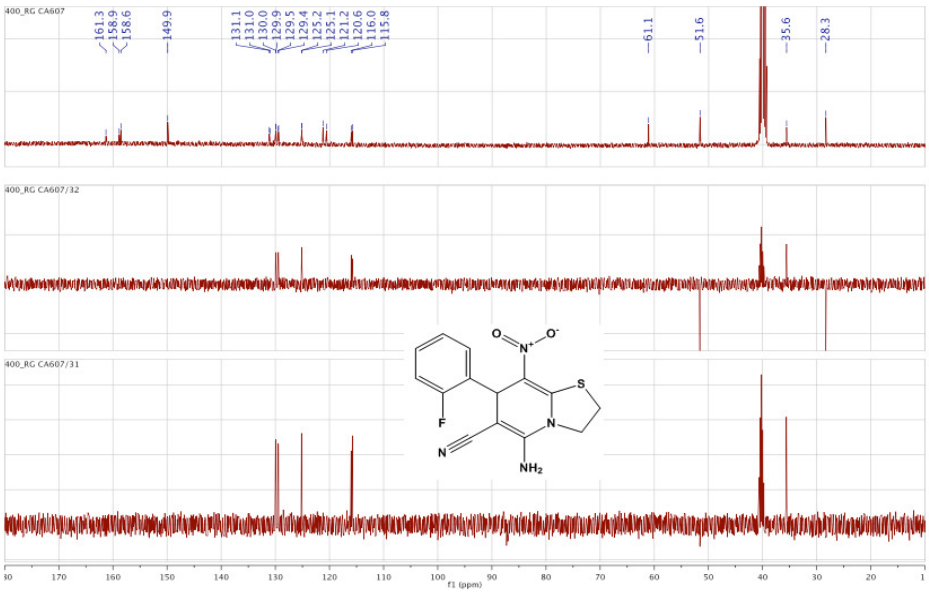


Figure 4.13. ^{13}C NMR spectrum of compound (4e).

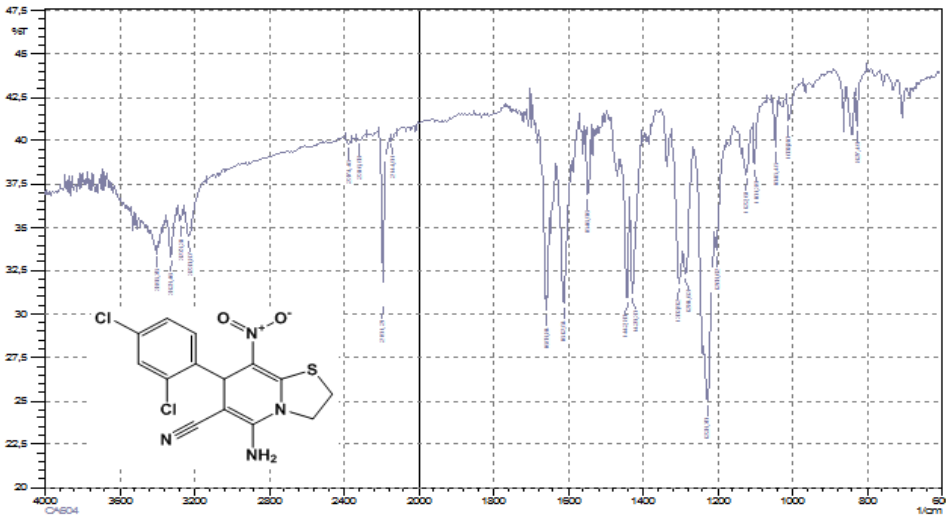


Figure 4.14. IR spectrum of compound (4f).

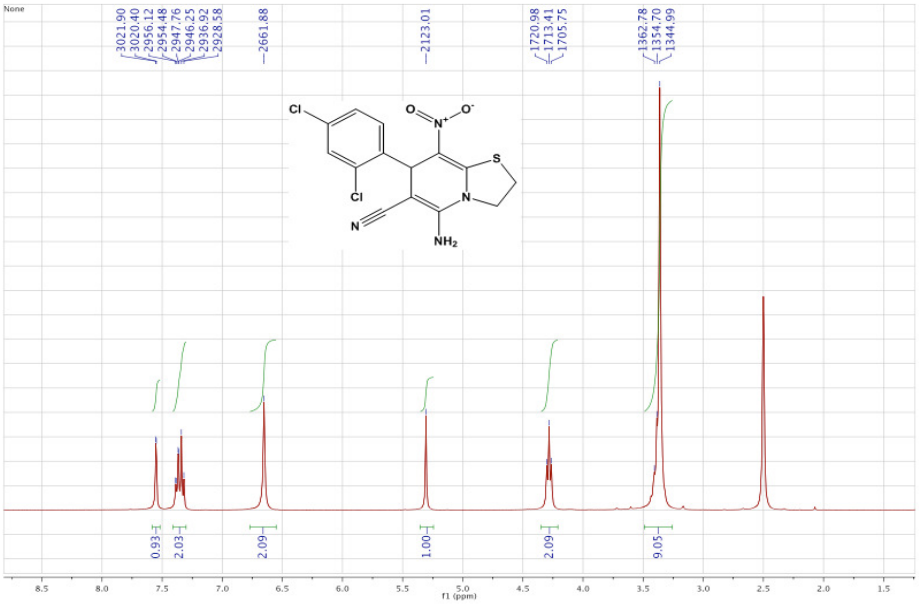


Figure 4.15. ^{1}H NMR spectrum of compound (4f).

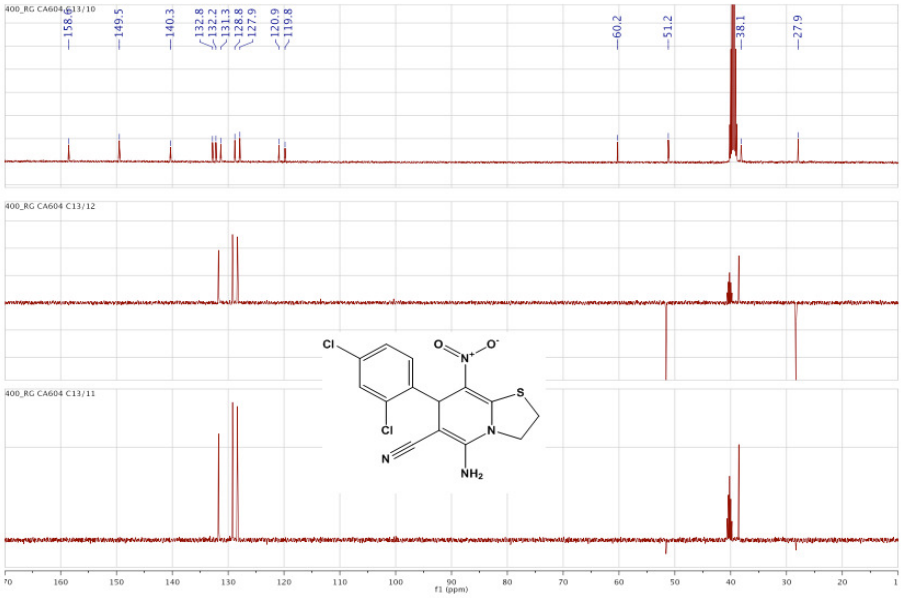


Figure 4.16. ^{13}C NMR spectrum of compound (4f).

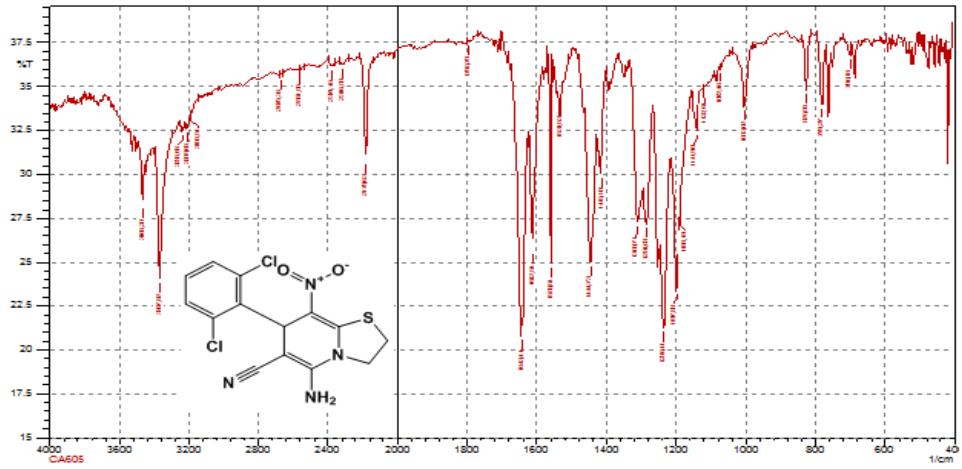


Figure 4.17. IR spectrum of compound (4g).

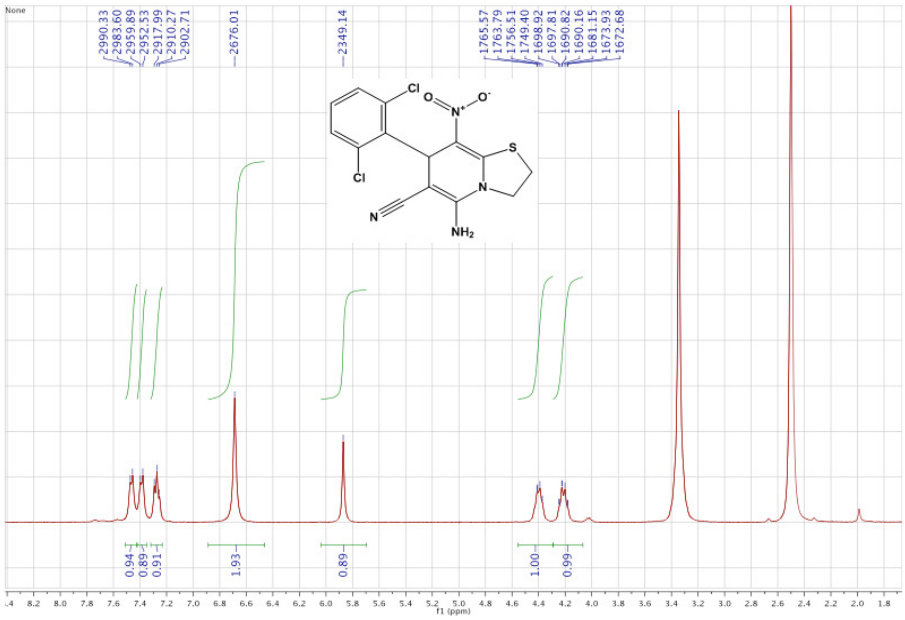


Figure 4.18. ^{1}H NMR spectrum of compound (4g).

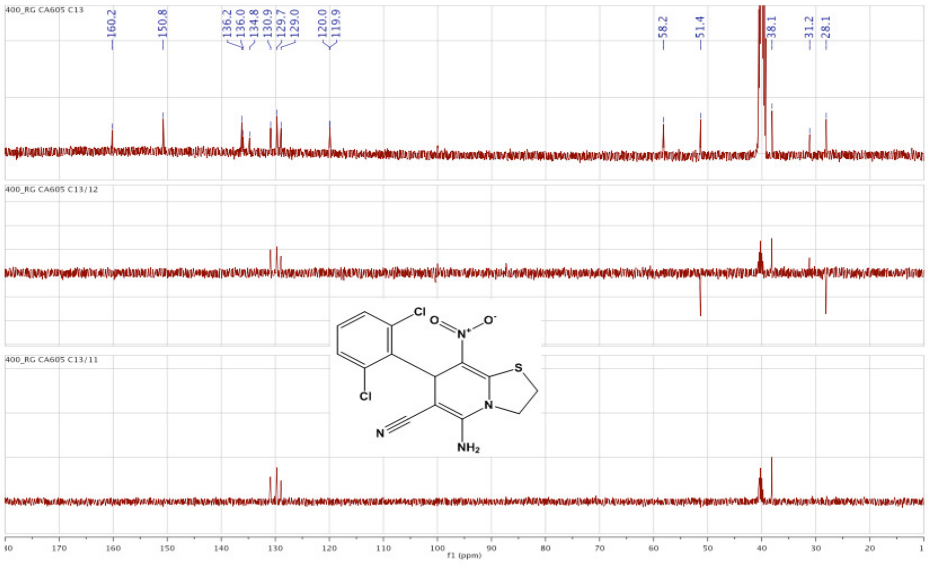


Figure 4.19. ^{13}C NMR spectrum of compound (4g).

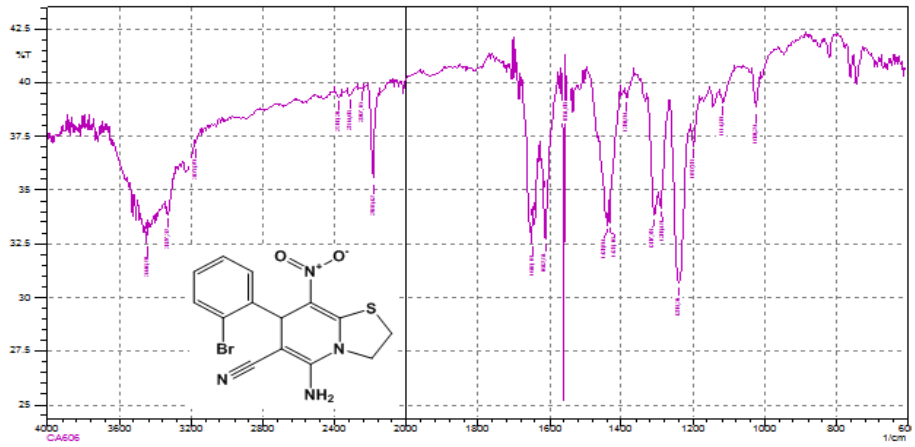


Figure 4.20. IR spectrum of compound (4h).

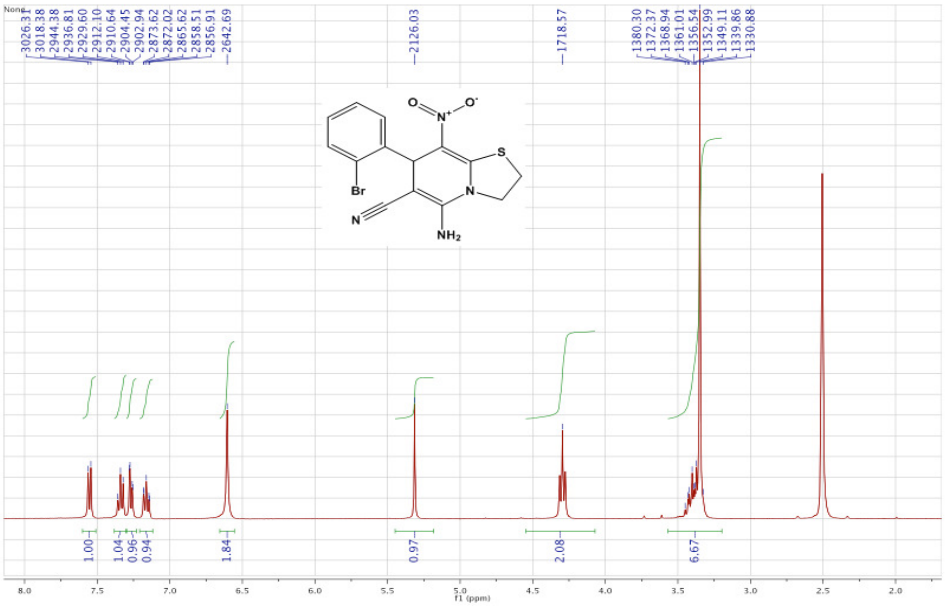


Figure 4.21. ^{1}H NMR spectrum of compound (4h).

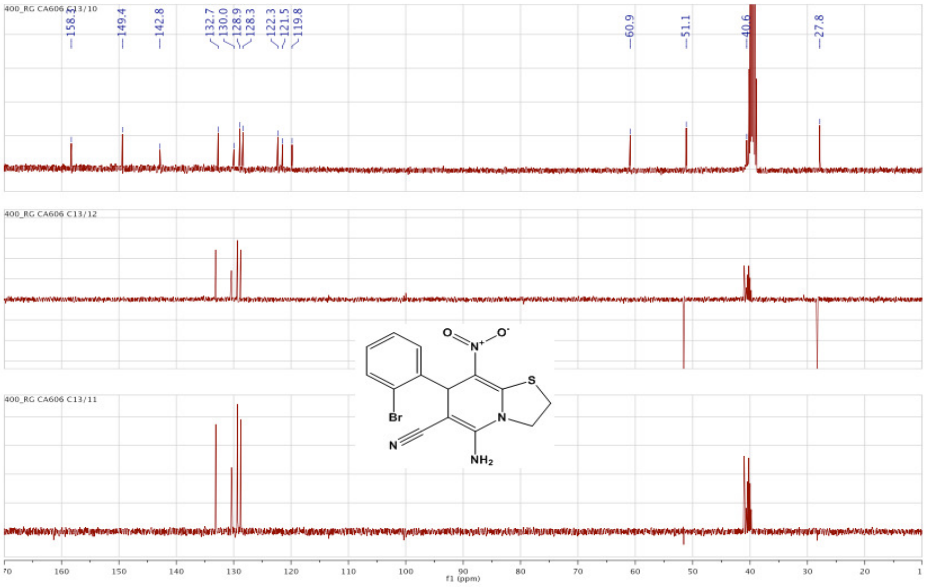


Figure 4.22. ^{13}C NMR spectrum of compound (4h).

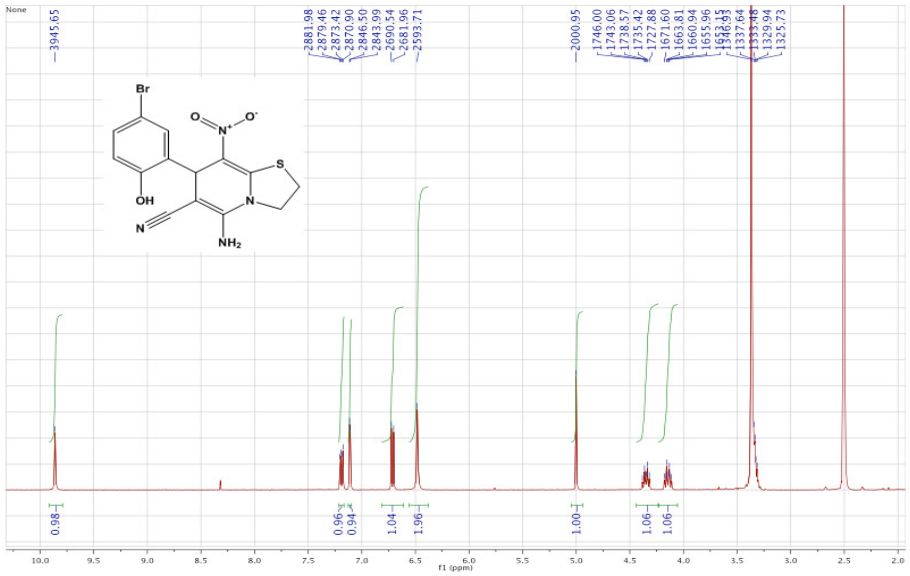


Figure 4.23. ^{1}H NMR spectrum of compound (4i).

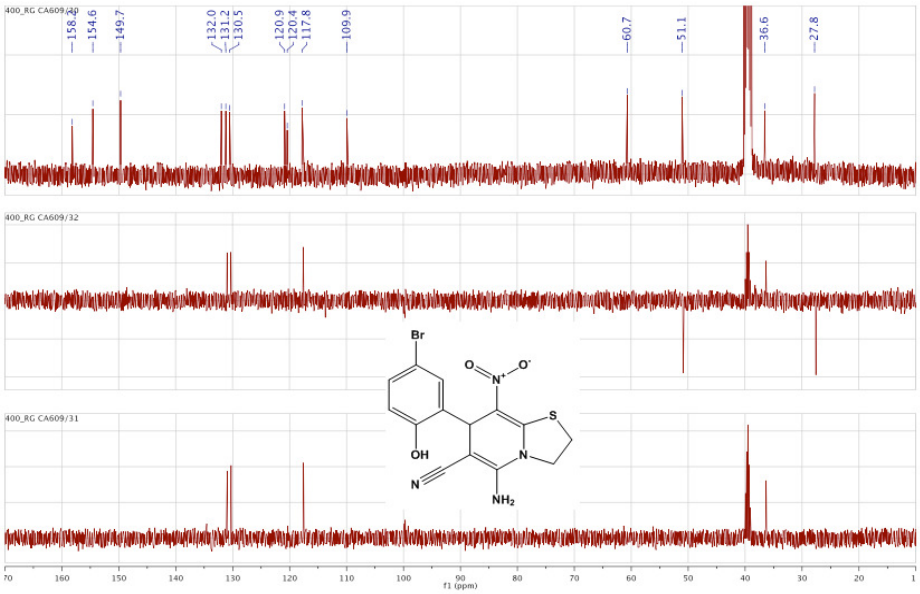


Figure 4.24. ^{13}C NMR spectrum of compound (4i).

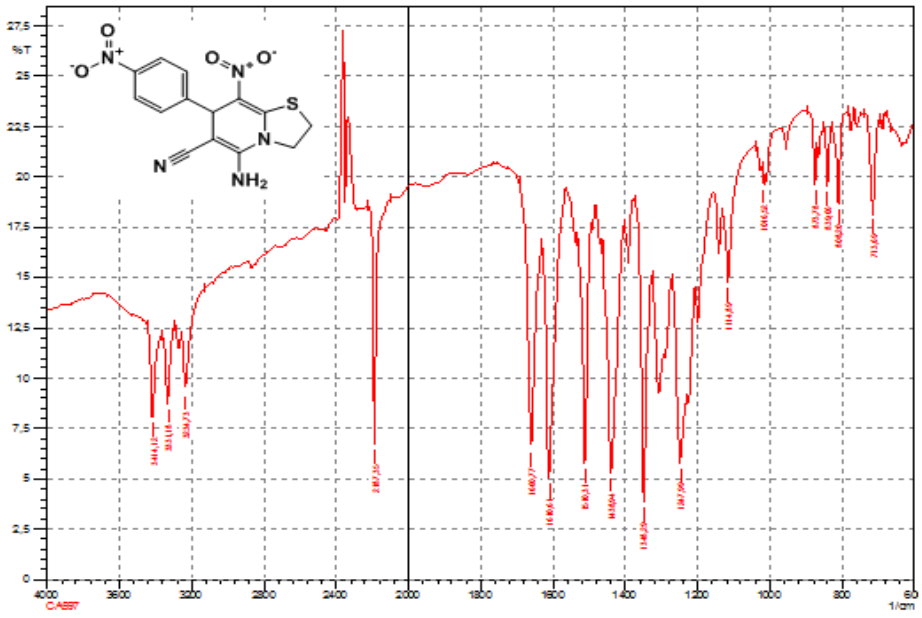


Figure 4.25. IR spectrum of compound (4j).

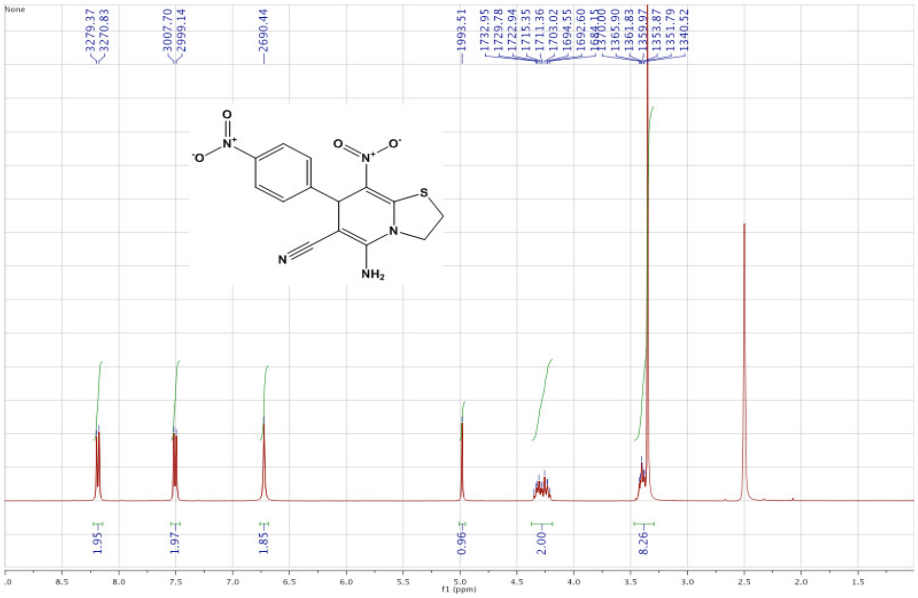


Figure 4.26. ^{1}H NMR spectrum of compound (4j).

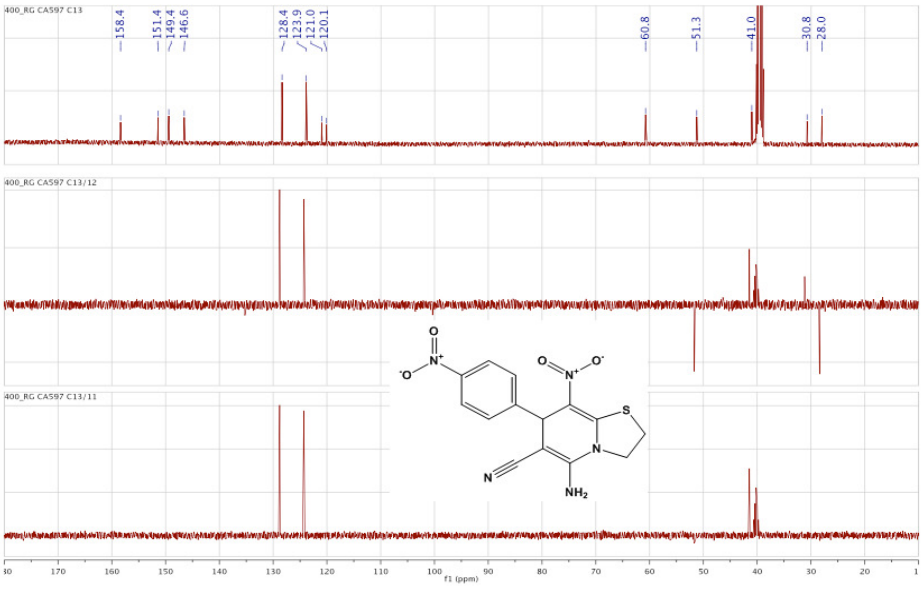


Figure 4.27. ^{13}C NMR spectrum of compound (4j).

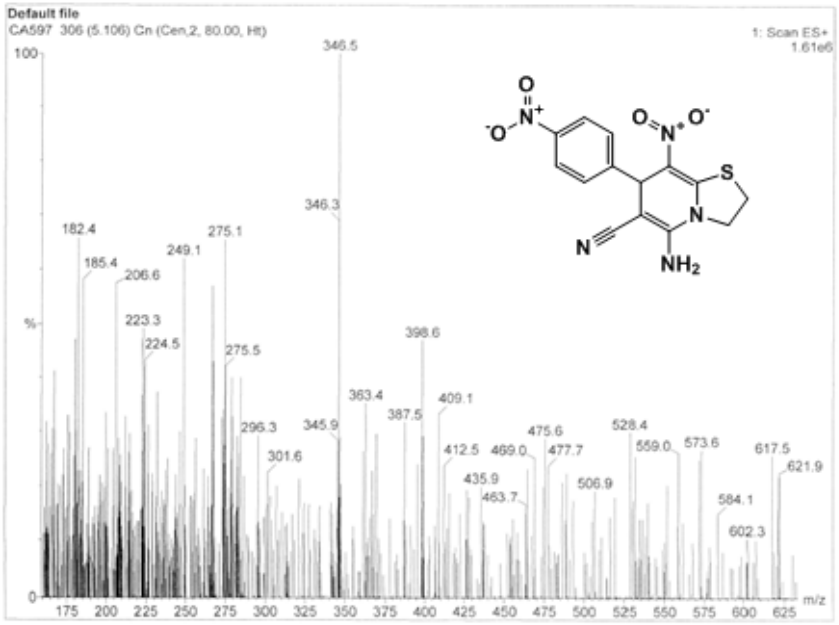


Figure 4.28. HRMS spectrum of compound (4j).

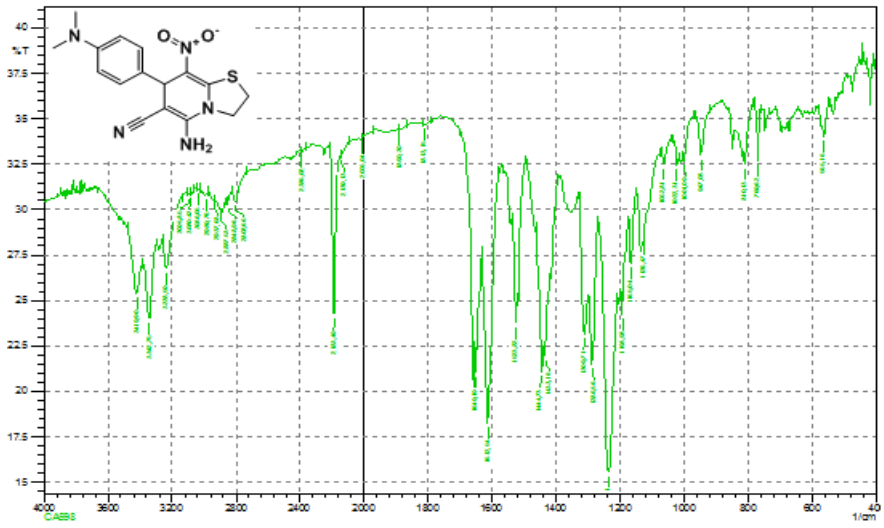


Figure 4.29. IR spectrum of compound (4k).

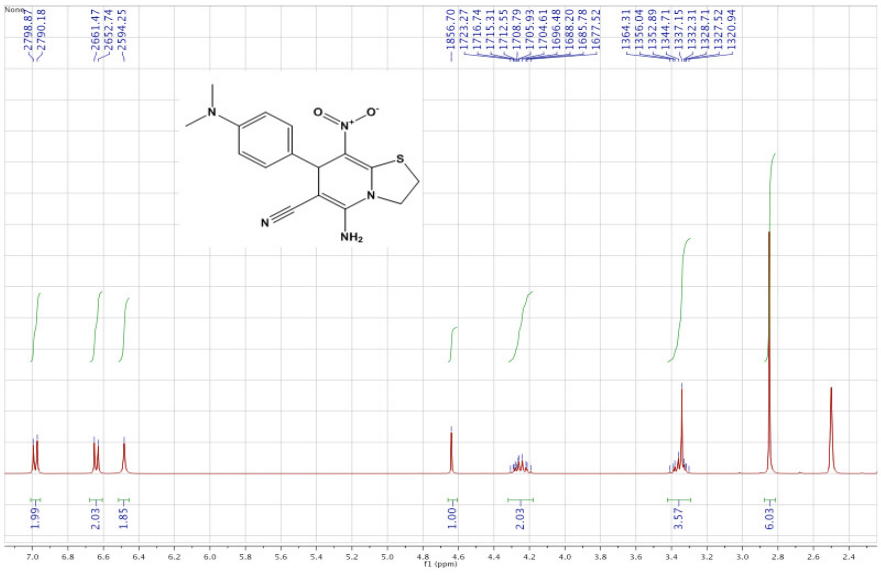


Figure 4.30. ^{1}H NMR spectrum of compound (4k).

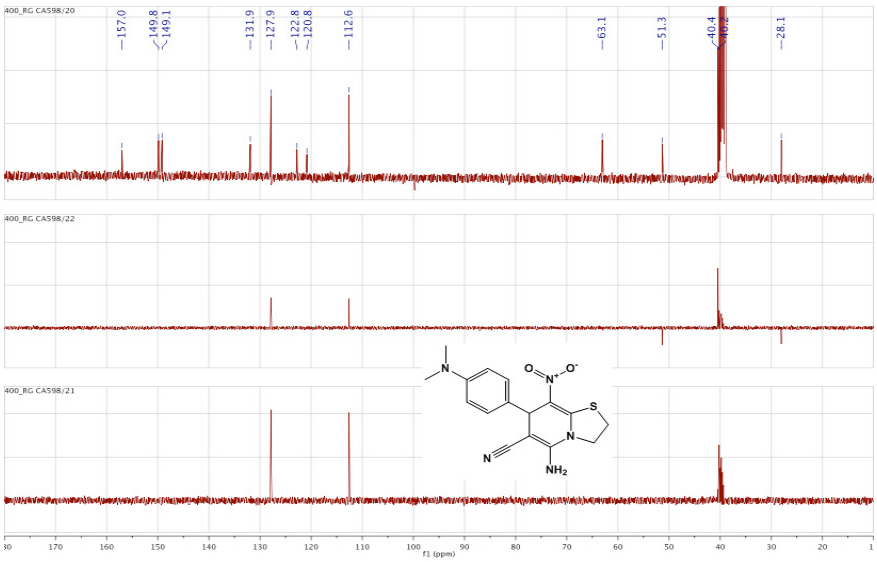


Figure 4.31. ^{13}C NMR spectrum of compound (4k).

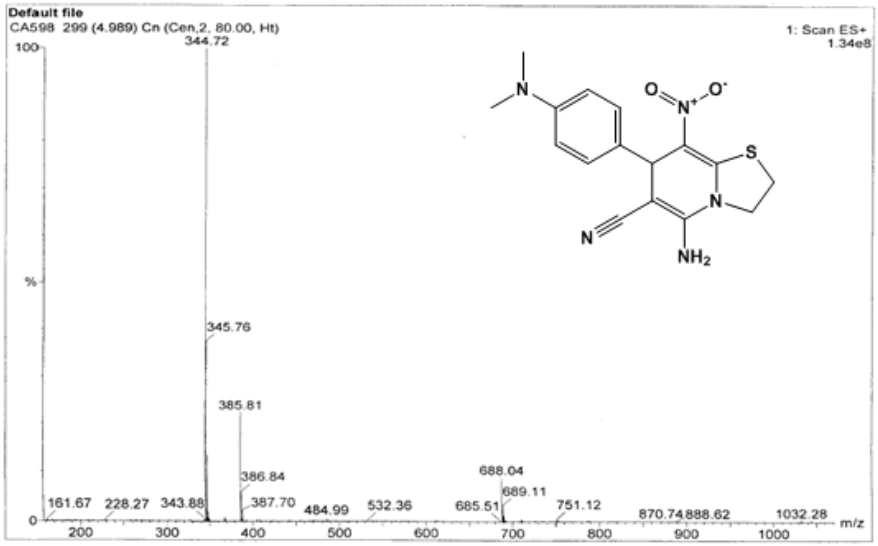


Figure 4.32. HRMS spectrum of compound (4k).

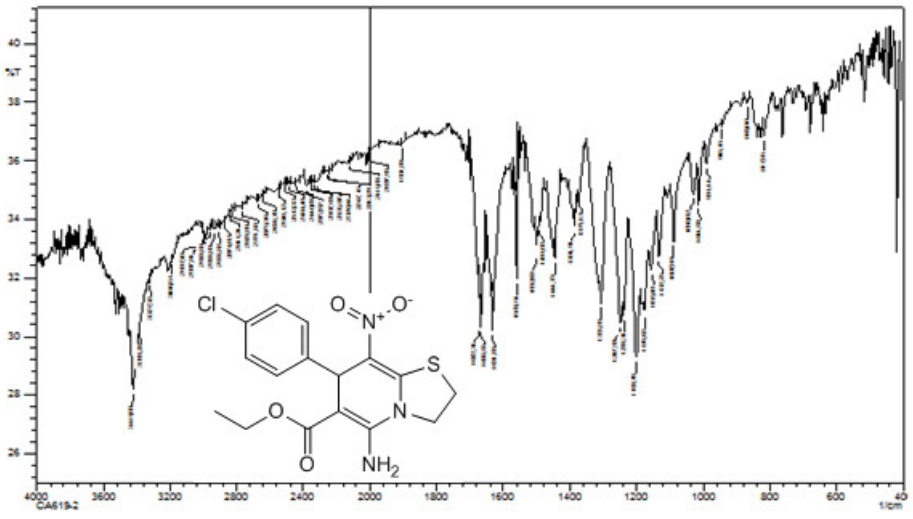


Figure 4.33. IR spectrum of compound (6a).

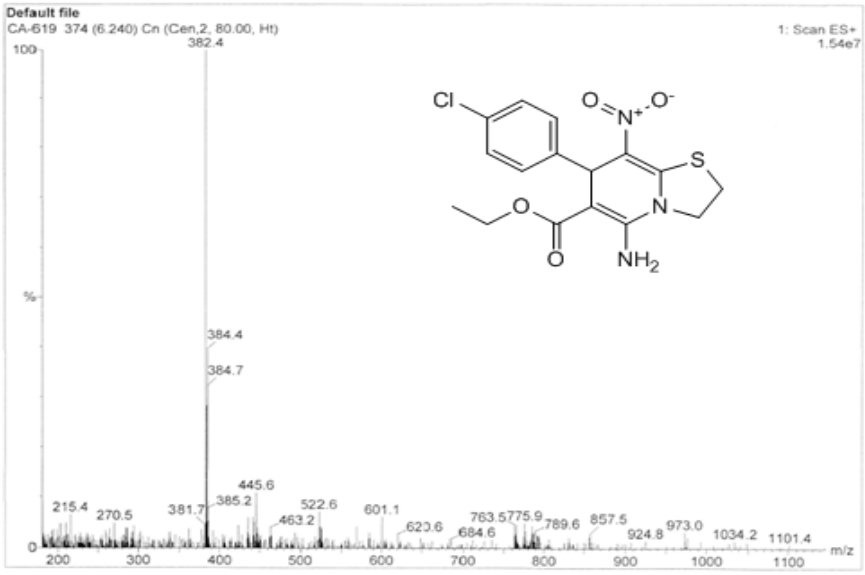


Figure 4.34. HRMS spectrum of compound (6a).

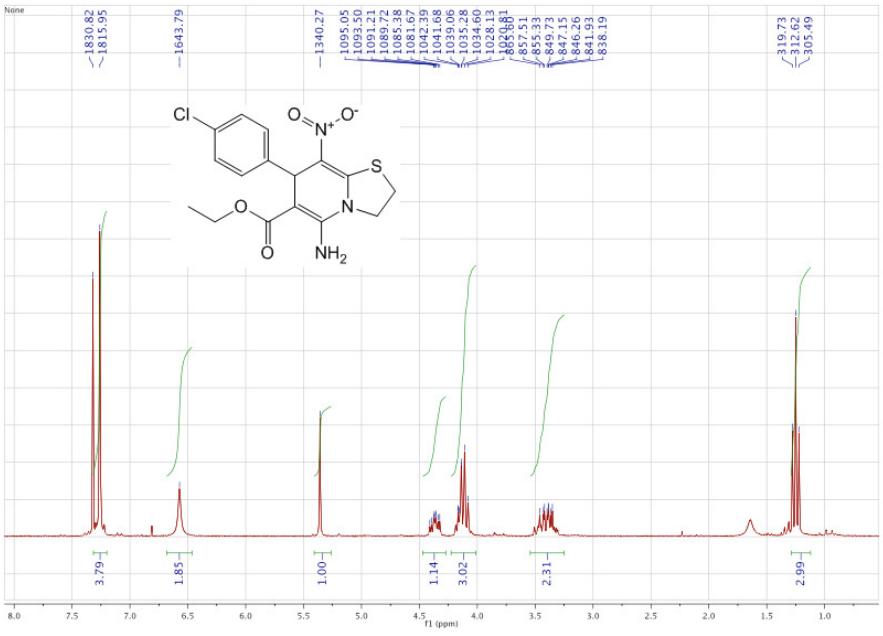


Figure 4.35. ^{1}H NMR spectrum of compound (6a).

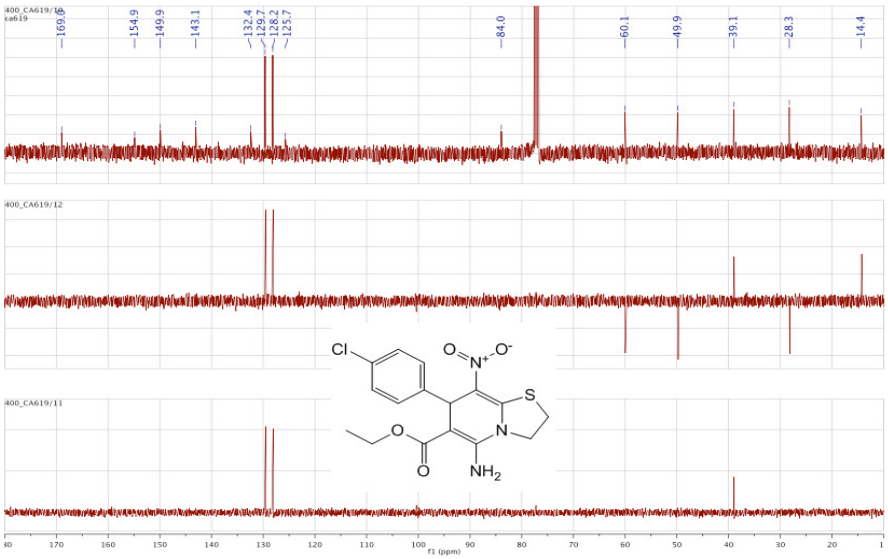


Figure 4.36. ^{13}C NMR spectrum of compound (6a).

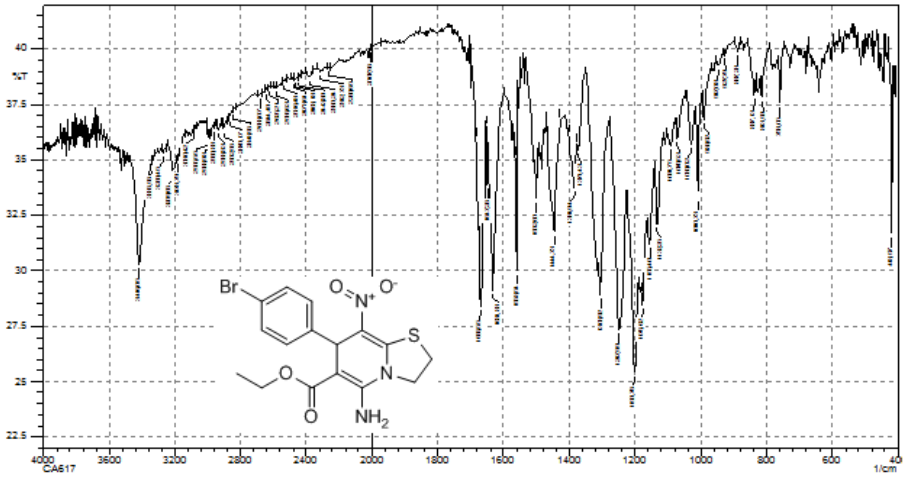


Figure 4.37. IR spectrum of compound (6b).

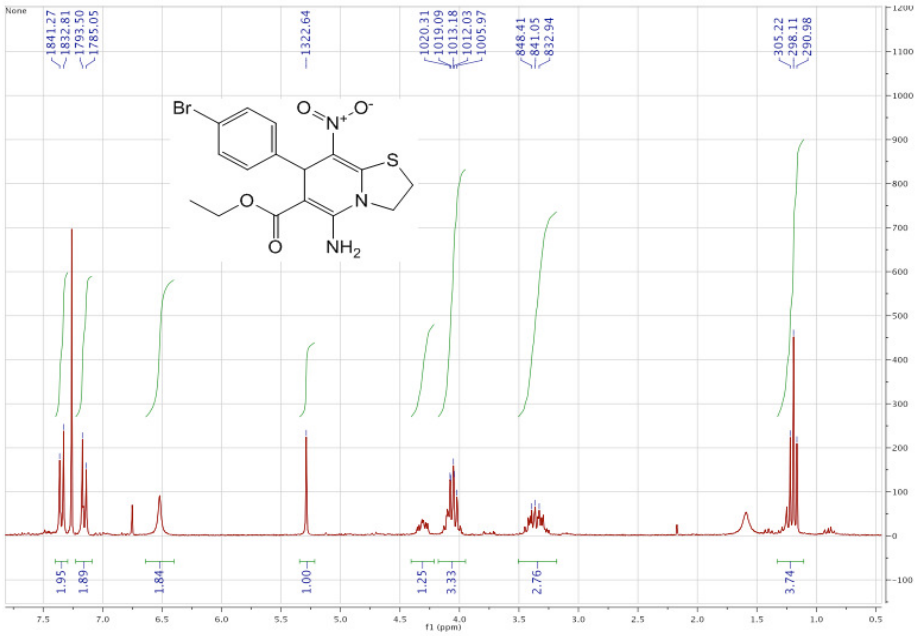


Figure 4.38. ^{1}H NMR spectrum of compound (6b).

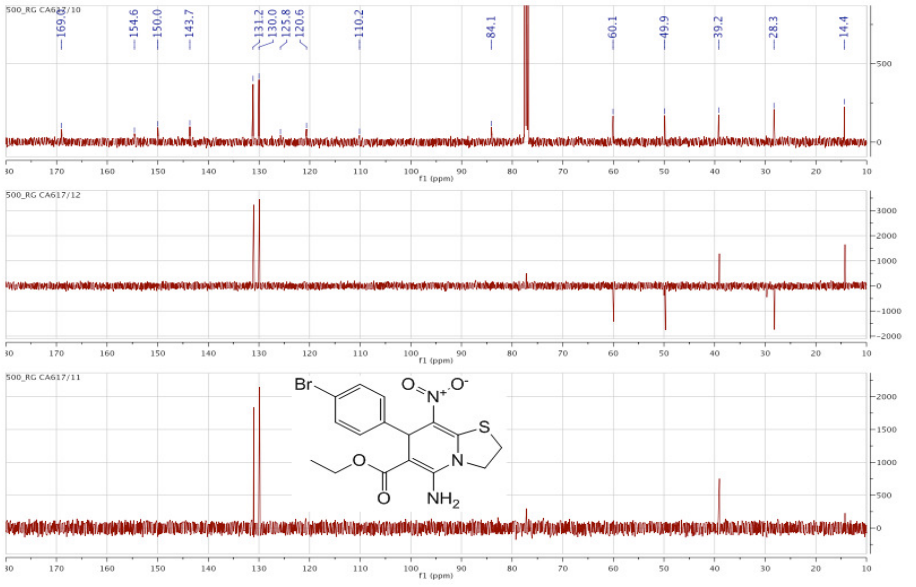


Figure 4.39. ^{13}C NMR spectrum of compound (6b).

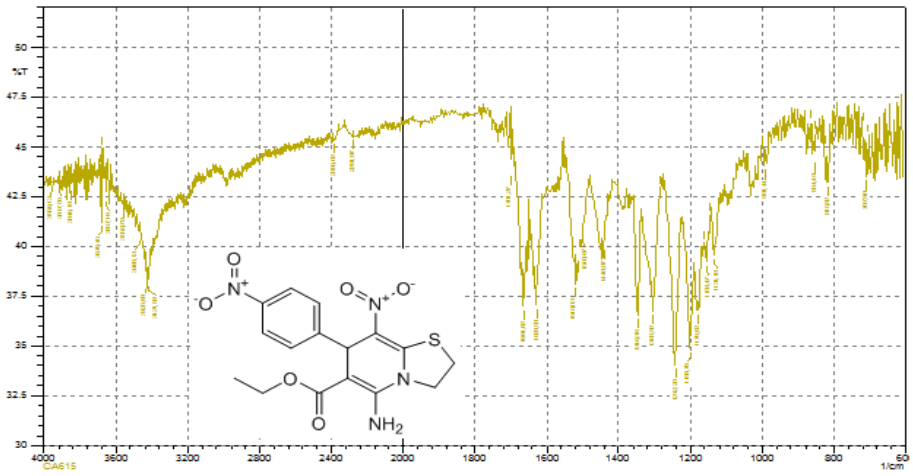


Figure 4.40. IR spectrum of compound (6c).

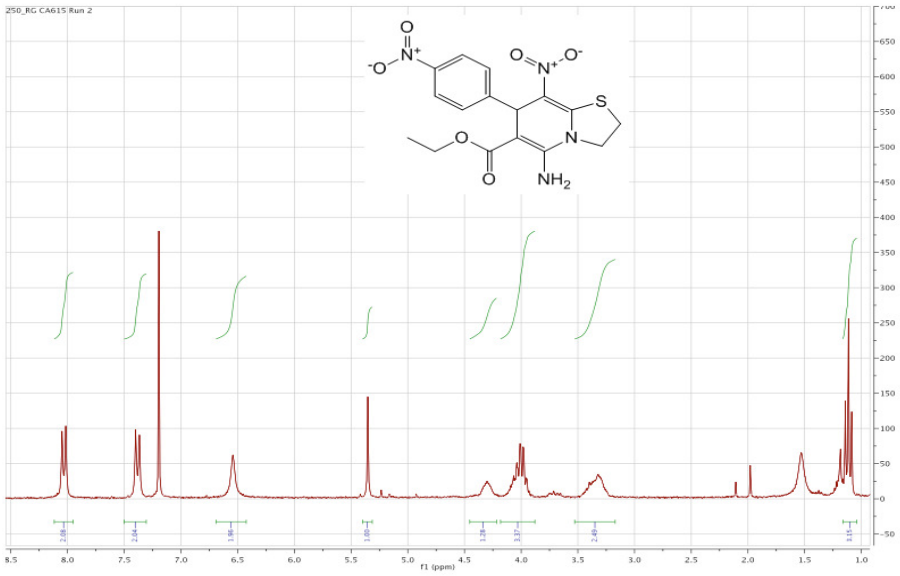


Figure 4.41. ^{1}H NMR spectrum of compound (6c).

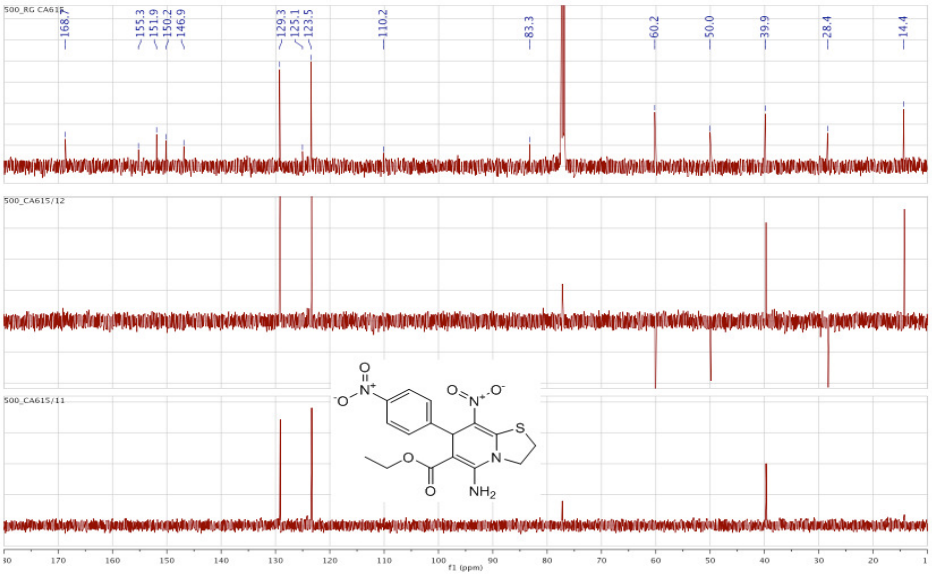


Figure 4.42. ^{13}C NMR spectrum of compound (6c).

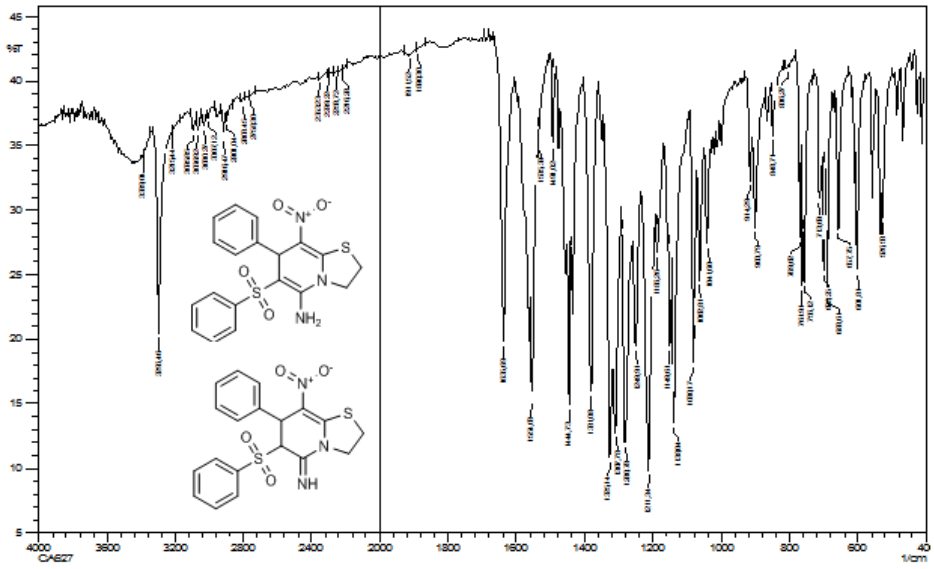


Figure 4.43. IR spectrum of compound (8a-9a).

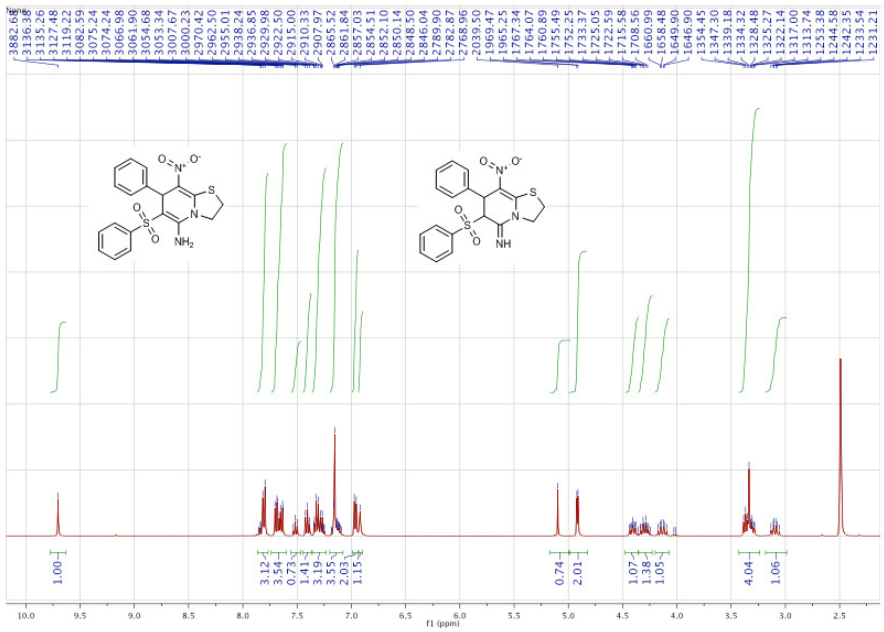


Figure 4.44. ^{1}H NMR spectrum of compound (8a-9a).

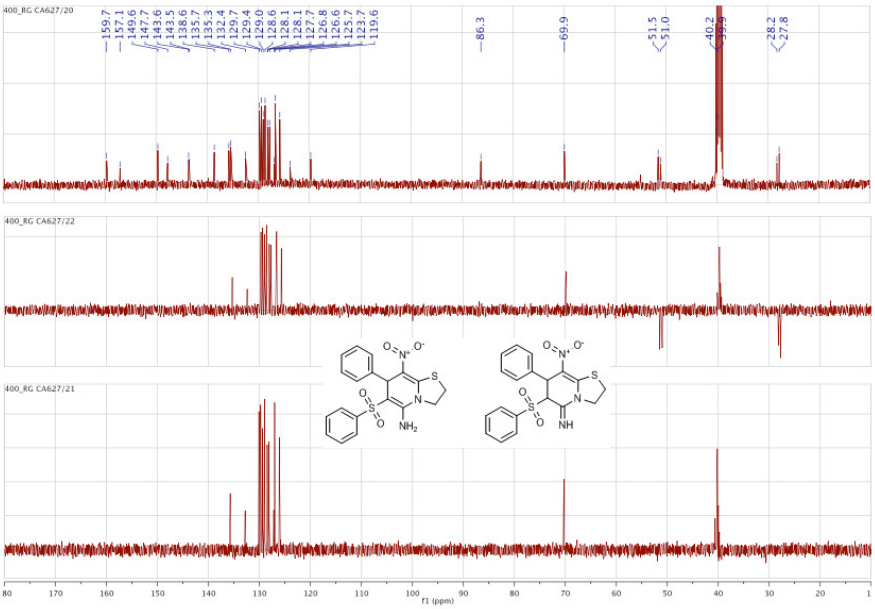


Figure 4.45. ^{13}C NMR spectrum of compound (8a-9a).

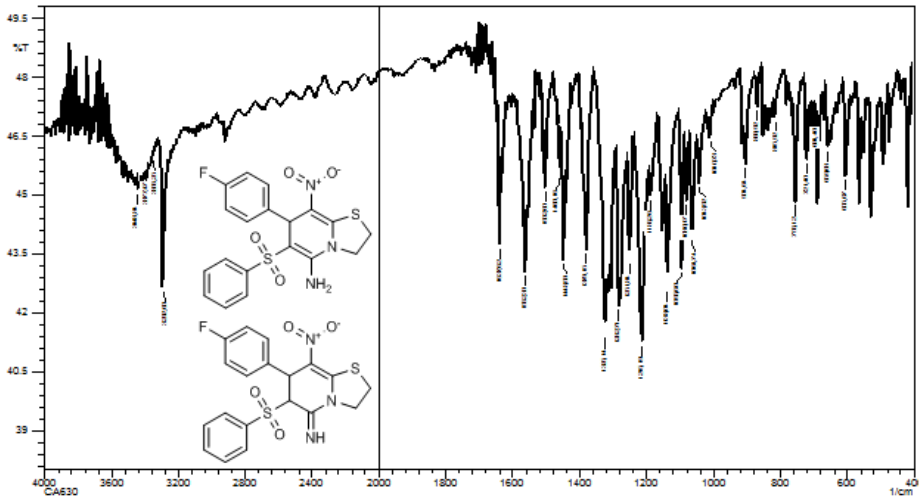


Figure 4.46. IR spectrum of compound (8b-9b).

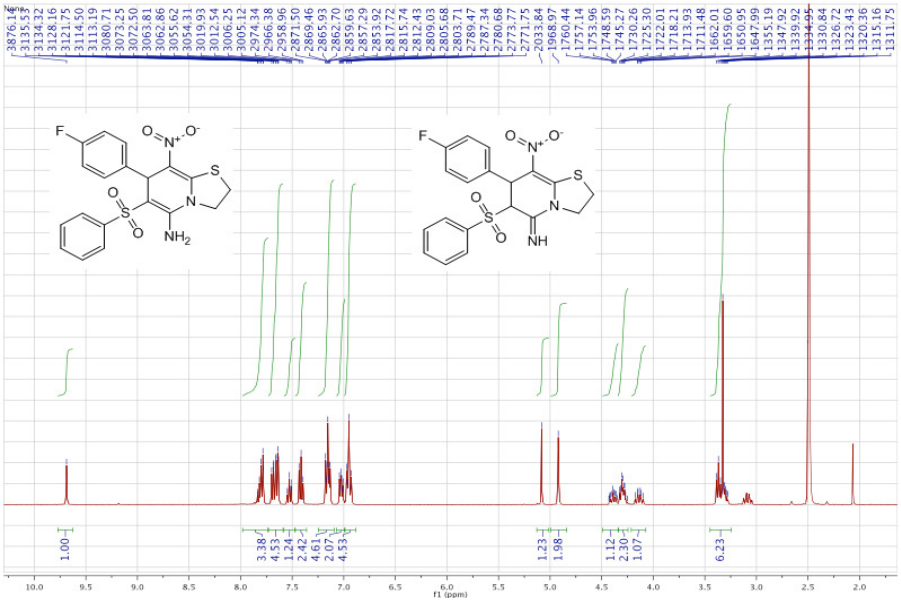


Figure 4.47. ^{1}H NMR spectrum of compound (8b-9b).

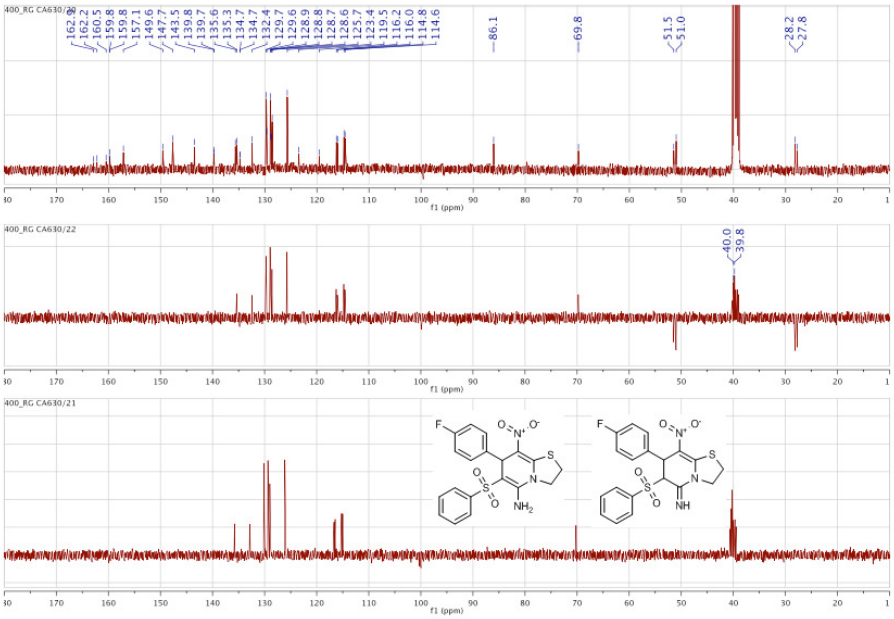


Figure 4.48. ^{13}C NMR spectrum of compound (8b-9b).

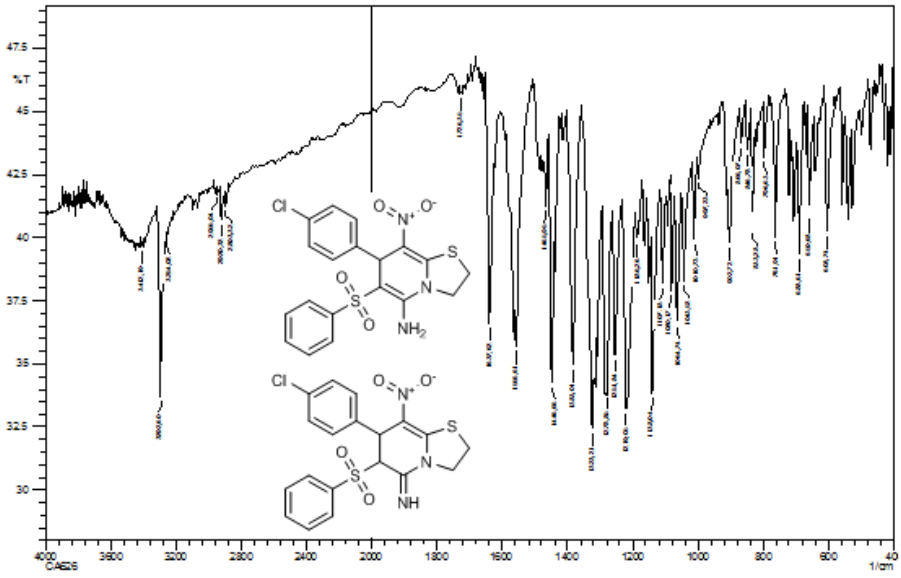


Figure 4.49. IR spectrum of compound (8c-9c).

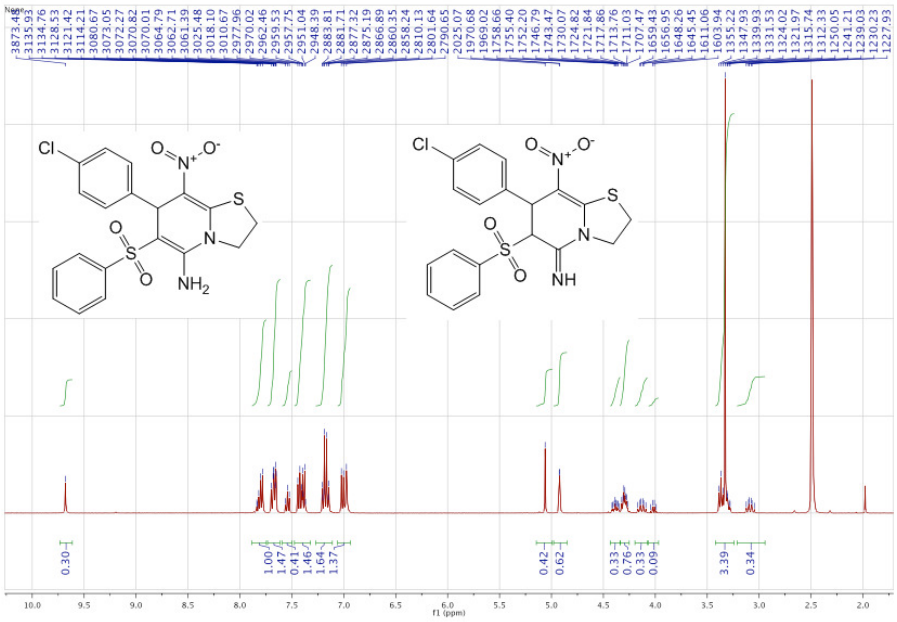


Figure 4.50. ^{1}H NMR spectrum of compound (8c-9c).

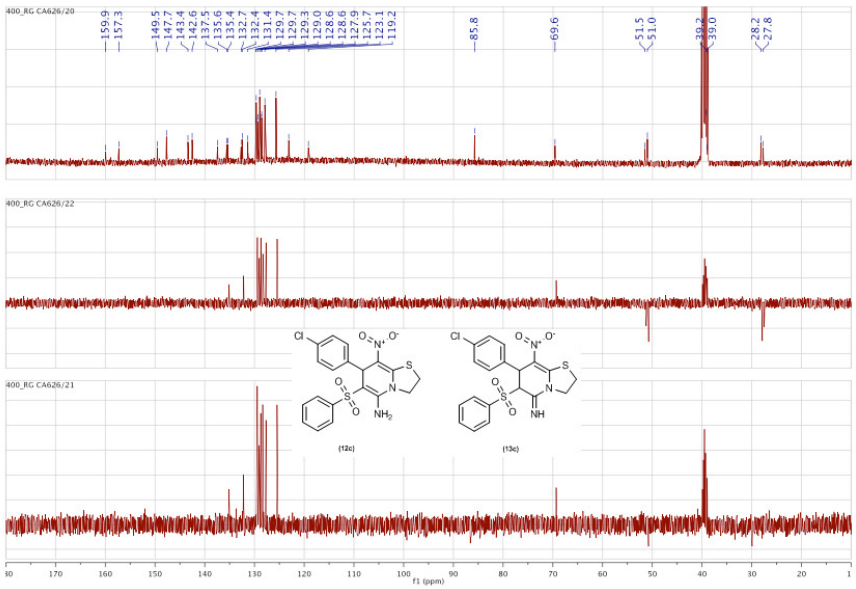


Figure 4.51. ^{13}C NMR spectrum of compound (8c-9c).

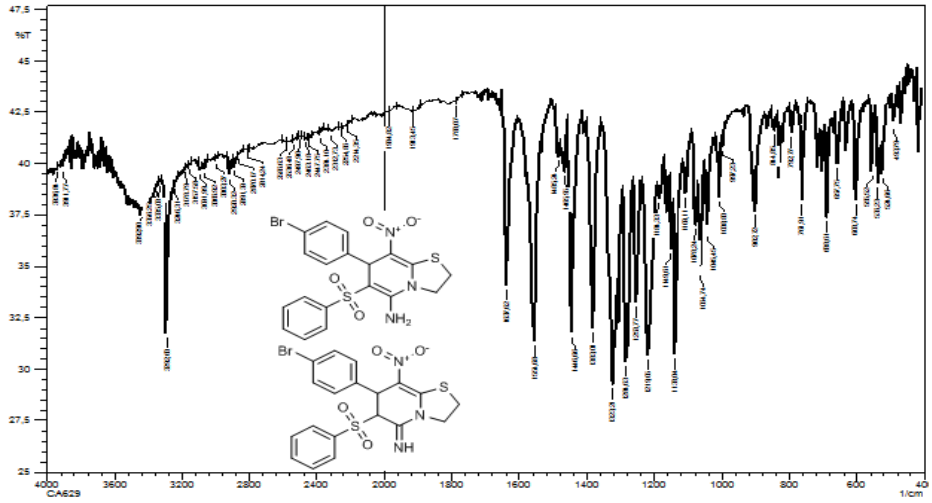


Figure 4.52. IR spectrum of compound (8d-9d).

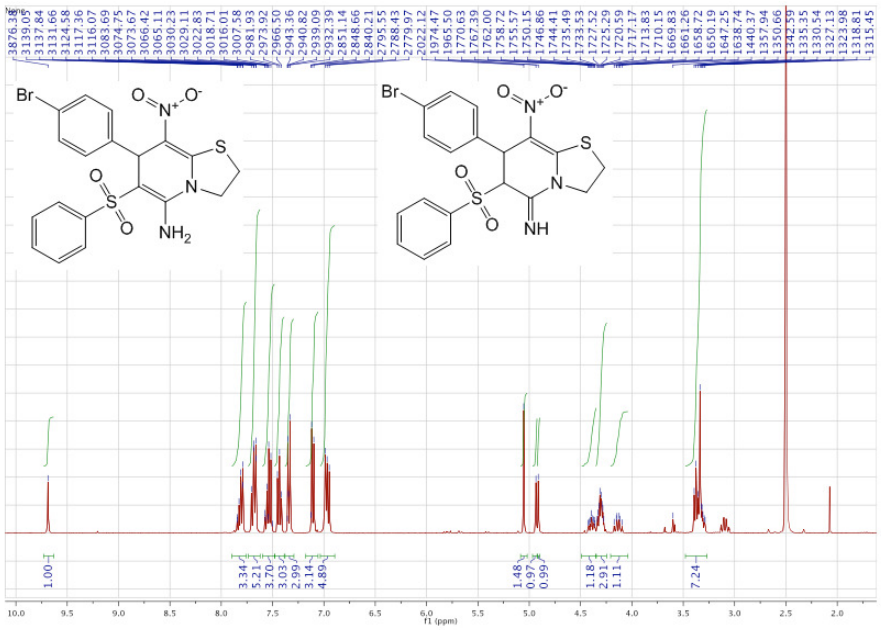


Figure 4.53. ^{1}H NMR spectrum of compound (8d-9d).

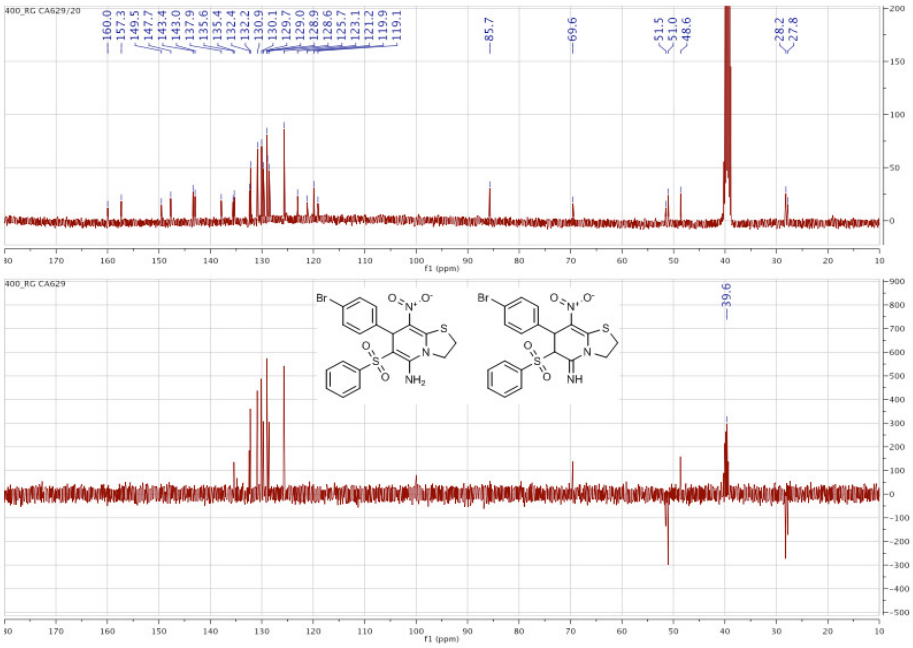


Figure 4.54. ^{13}C NMR spectrum of compound (8d-9d).

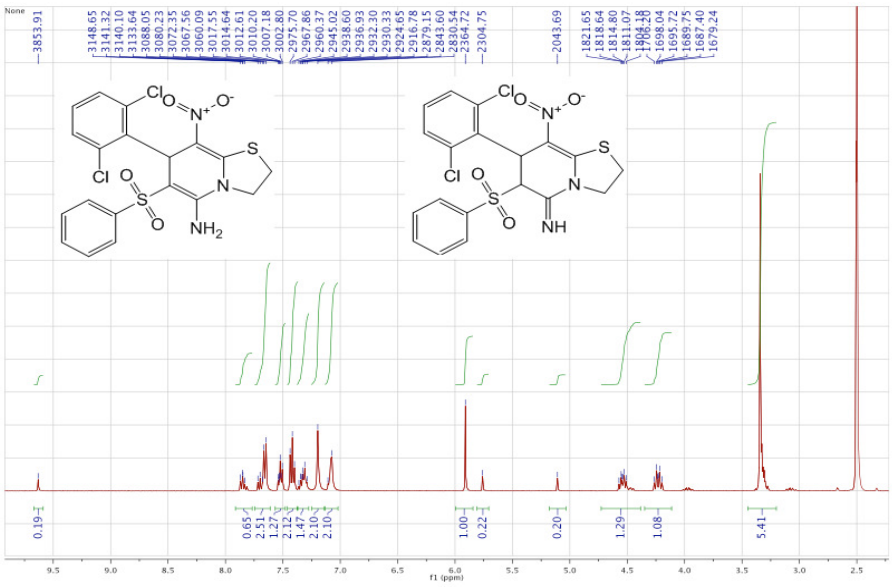


Figure 4.55. ^{1}H NMR spectrum of compound (8e-9e).

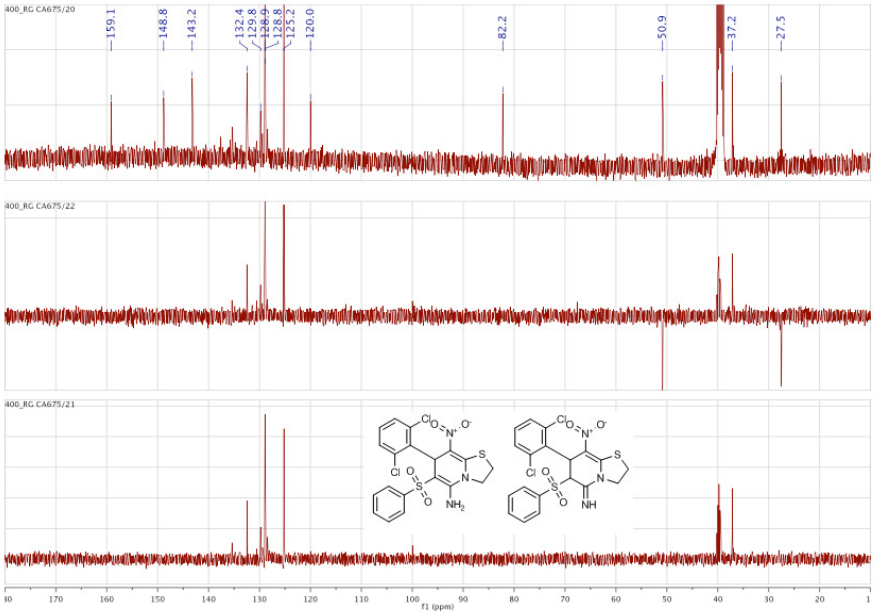


Figure 4.56. ^{13}C NMR spectrum of compound (8e-9e).

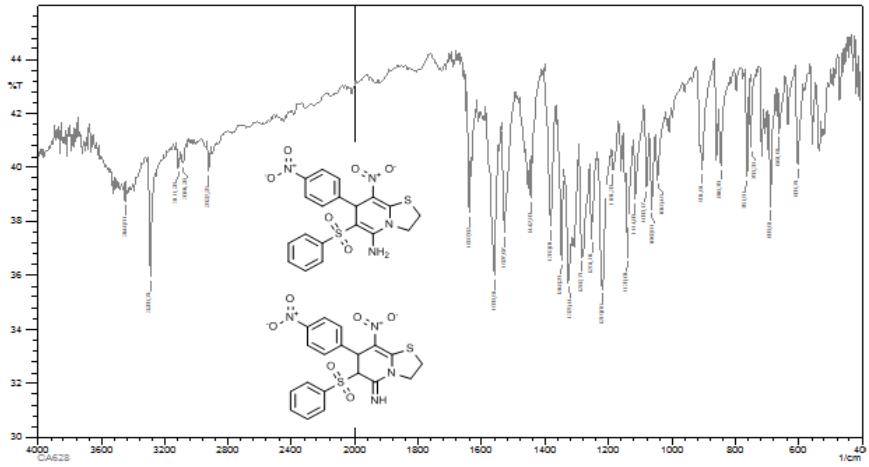


Figure 4.57. IR spectrum of compound (8f-9f).

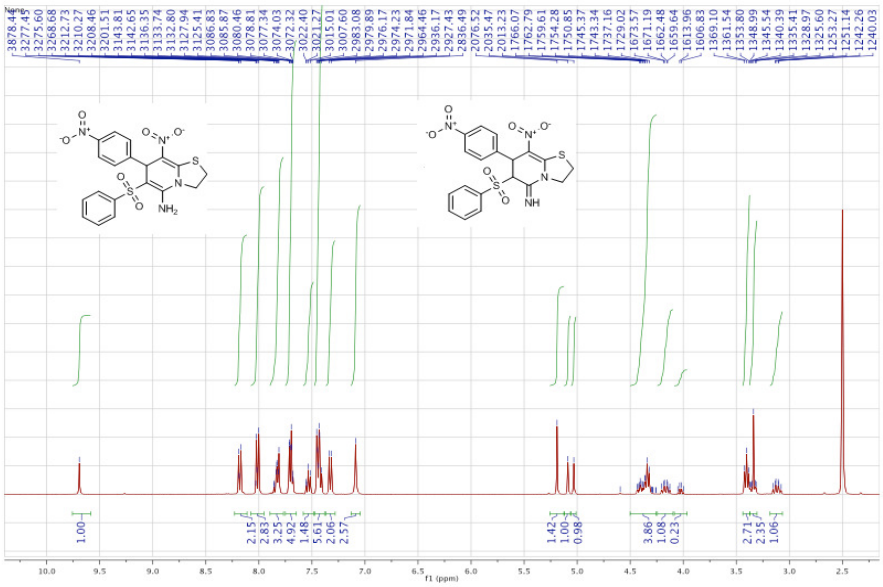


Figure 4.58. ^{1}H NMR spectrum of compound (8f-9f).

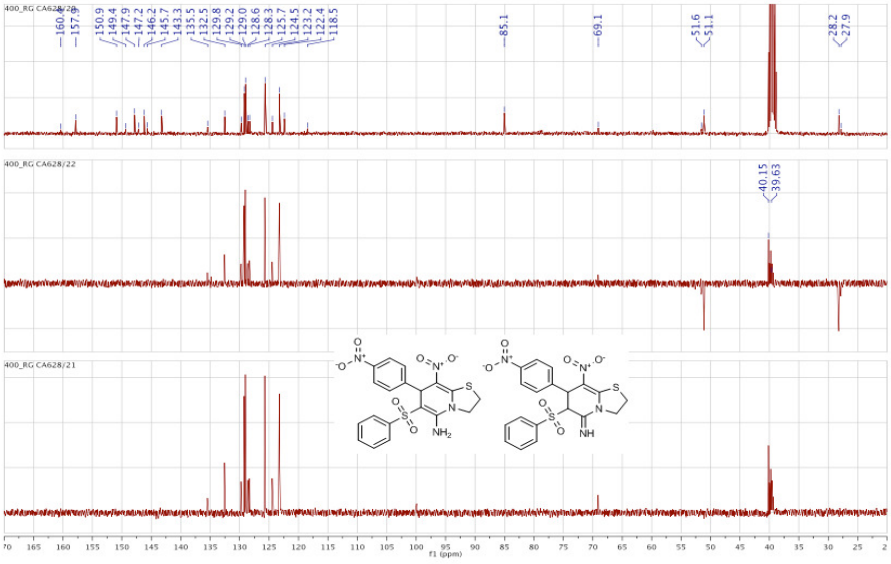


Figure 4.59. ^{13}C NMR spectrum of compound (8f-9f).

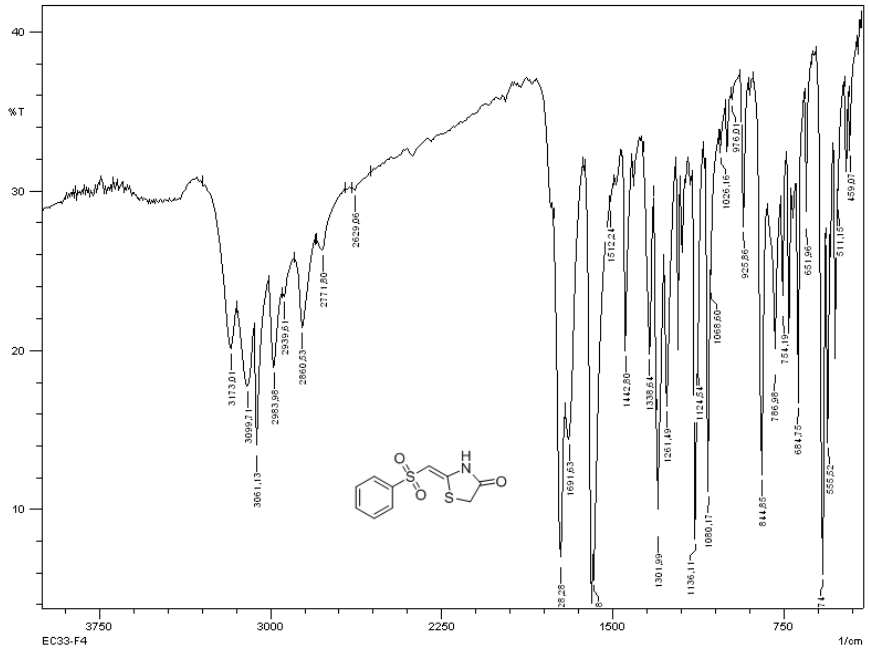


Figure 4.60. IR spectrum of compound (11).

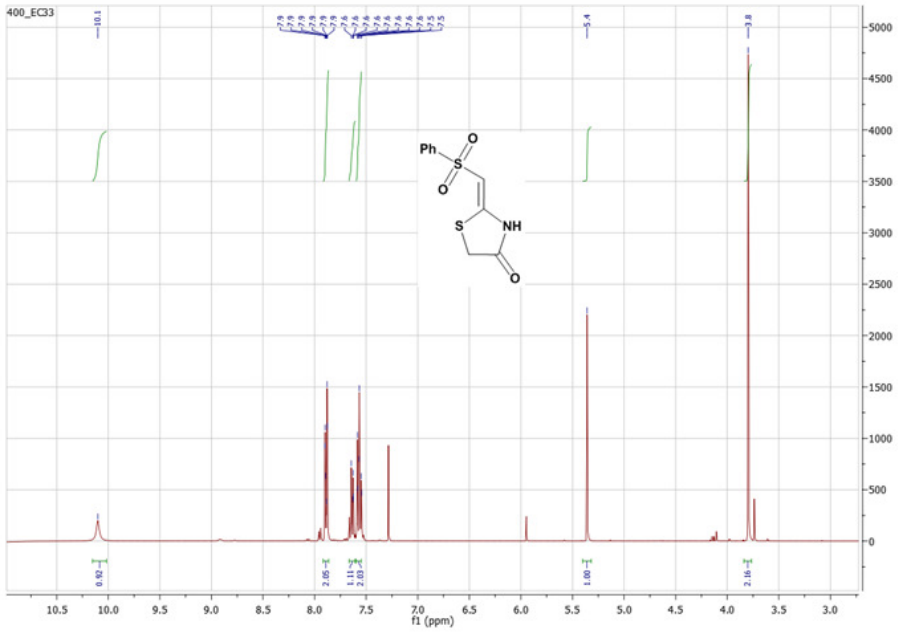


Figure 4.61. ^{1}H NMR spectrum of compound (11).

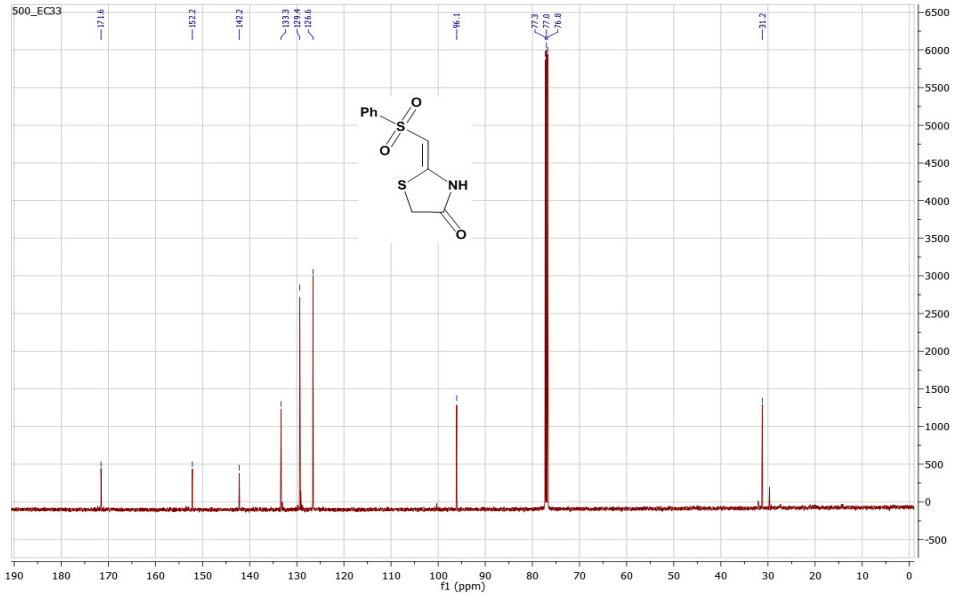


Figure 4.62. ^{13}C NMR spectrum of compound (11).

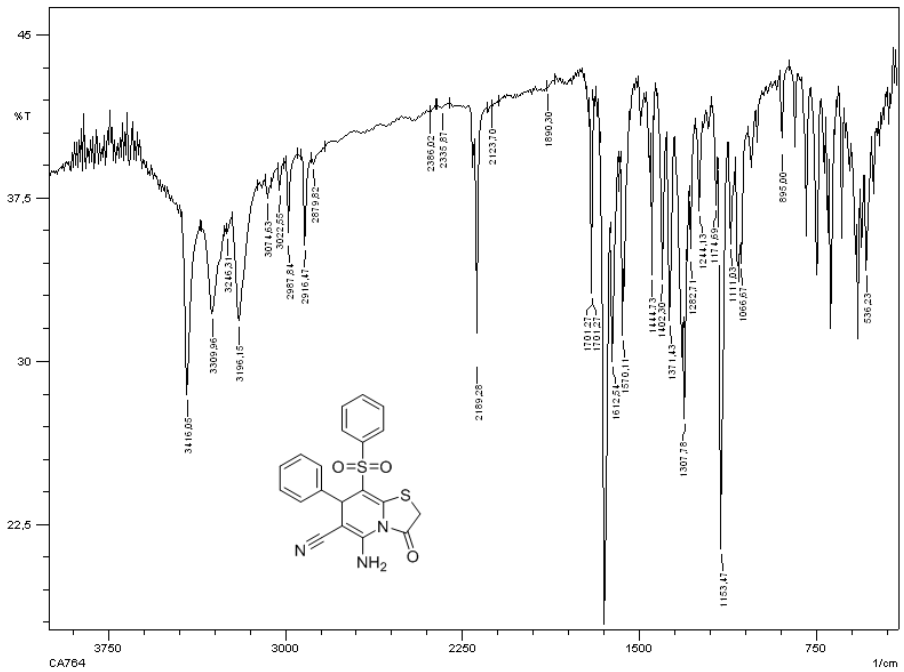


Figure 4.63. IR spectrum of compound (12a).

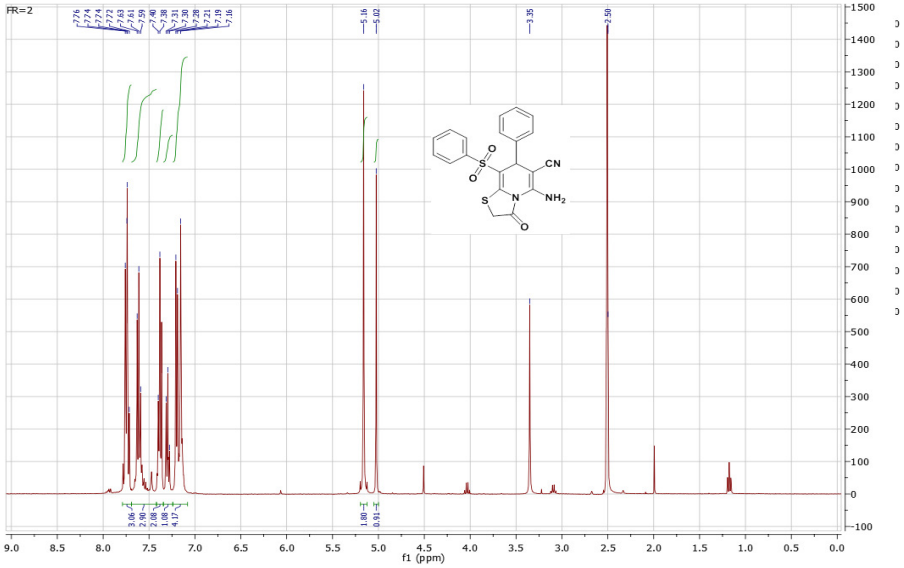


Figure 4.64. ^{1}H NMR spectrum of compound (12a).

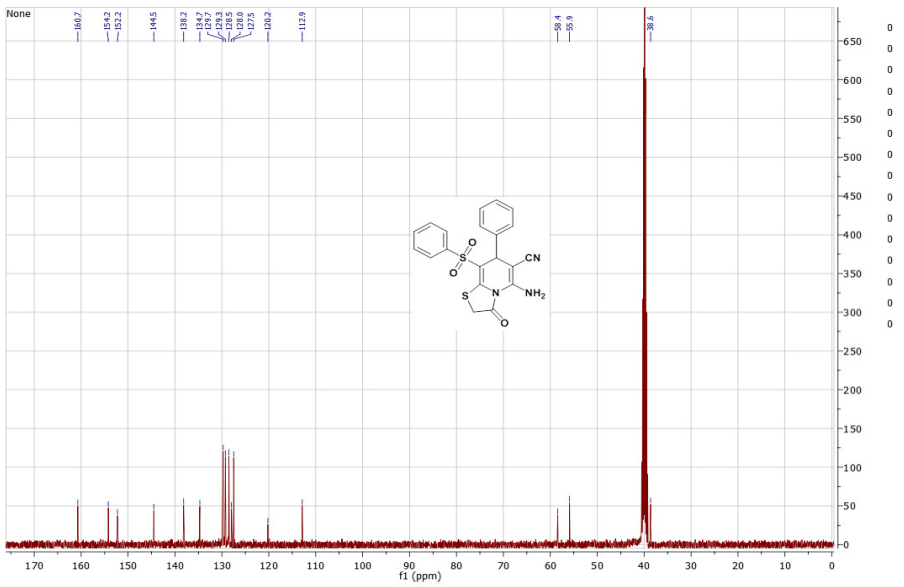


Figure 4.65. ^{13}C NMR spectrum of compound (12a).

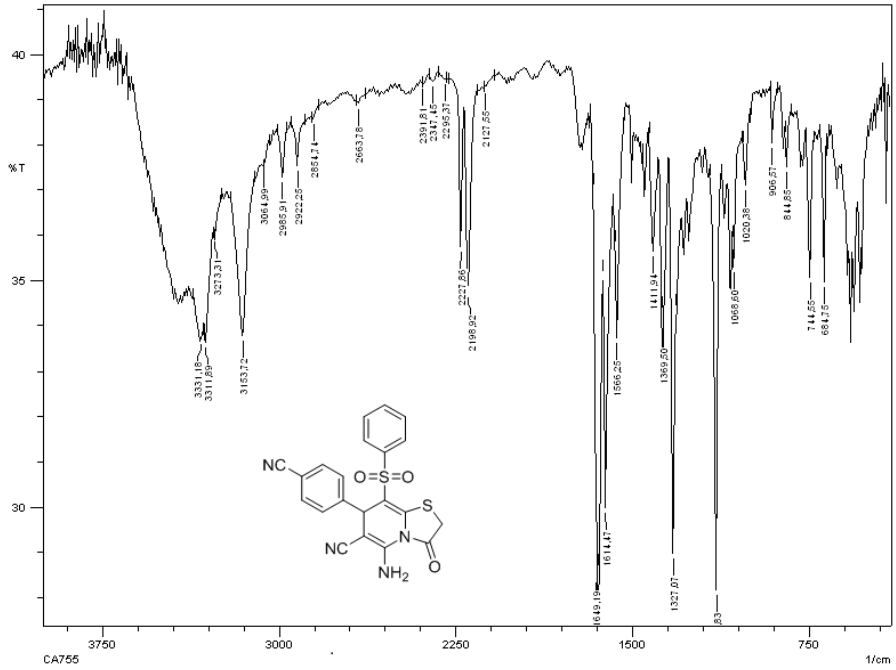


Figure 4.66. IR spectrum of compound (12b).

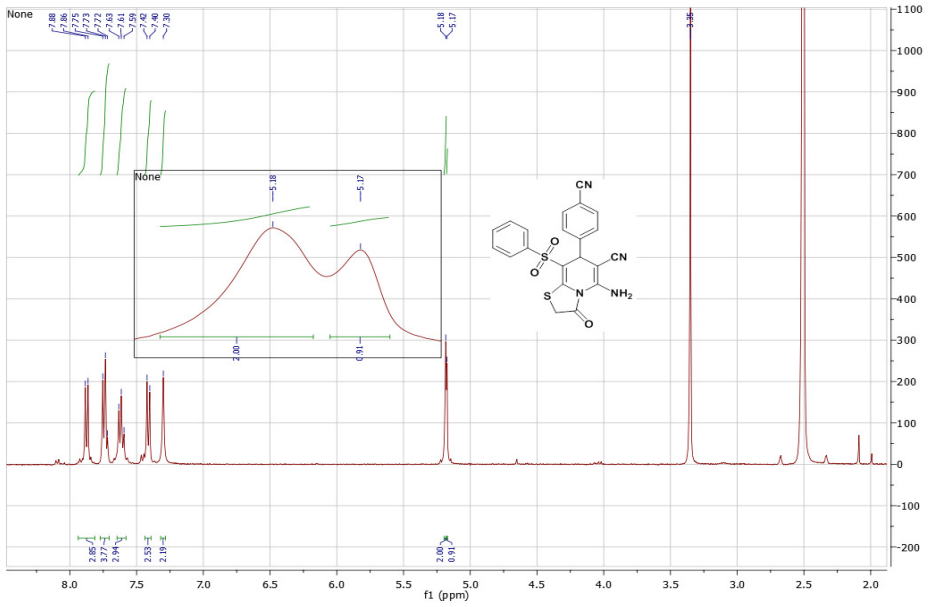


Figure 4.67. ^{1}H NMR spectrum of compound (12b).

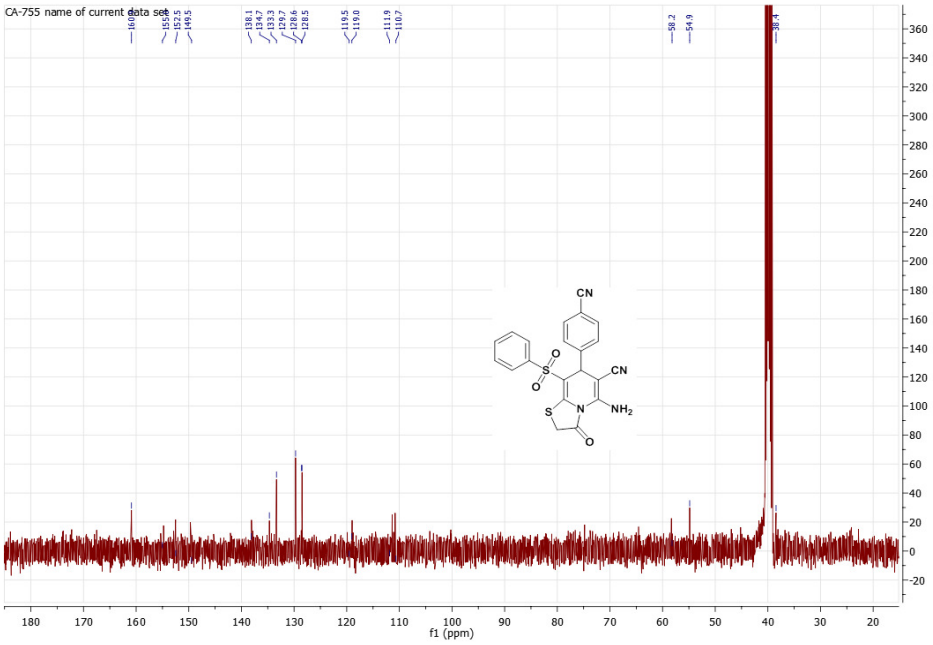


Figure 4.68. ^{13}C NMR spectrum of compound (12b).

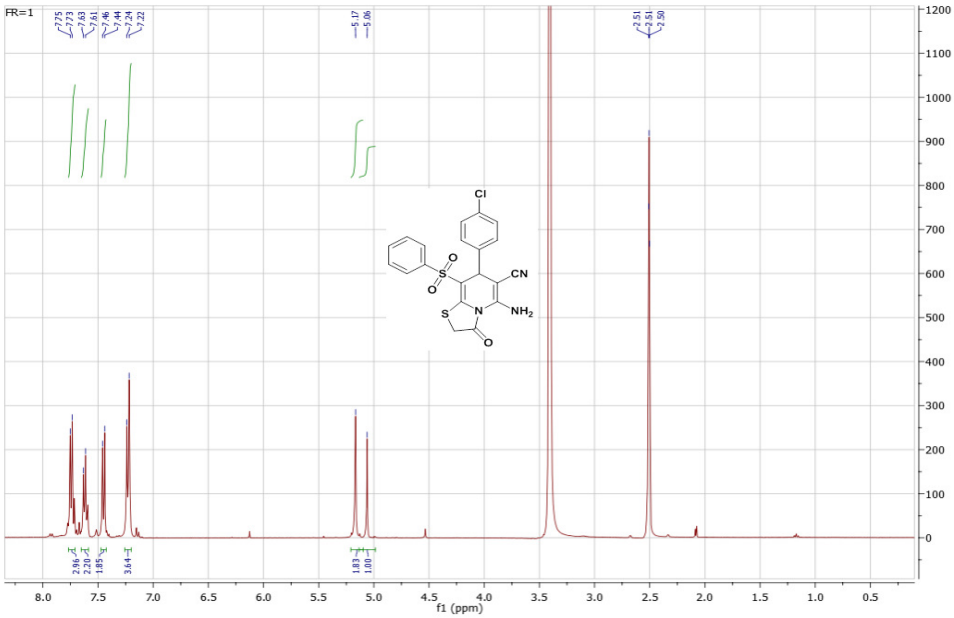


Figure 4.69. ^{1}H NMR spectrum of compound (12c).

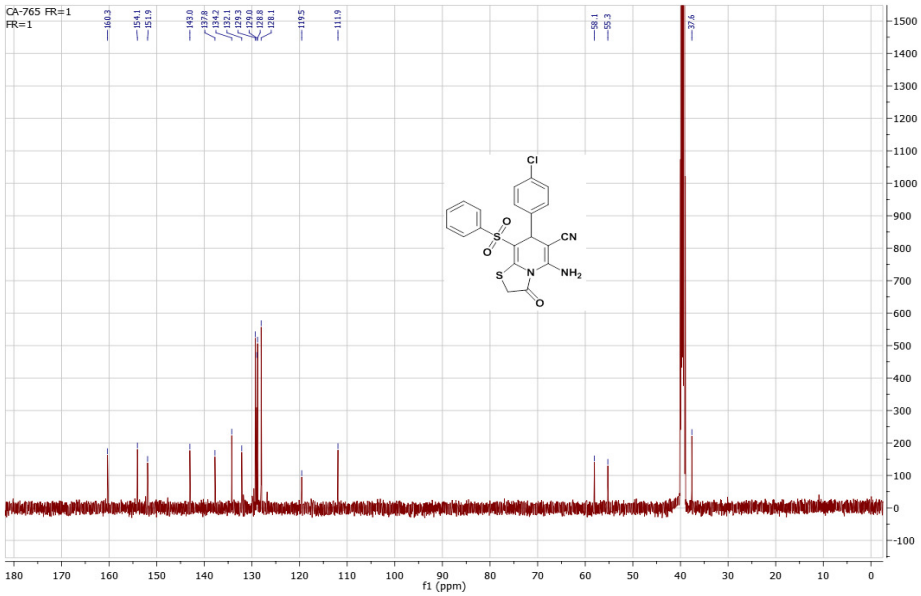


Figure 4.70. ^{13}C NMR spectrum of compound (12c).

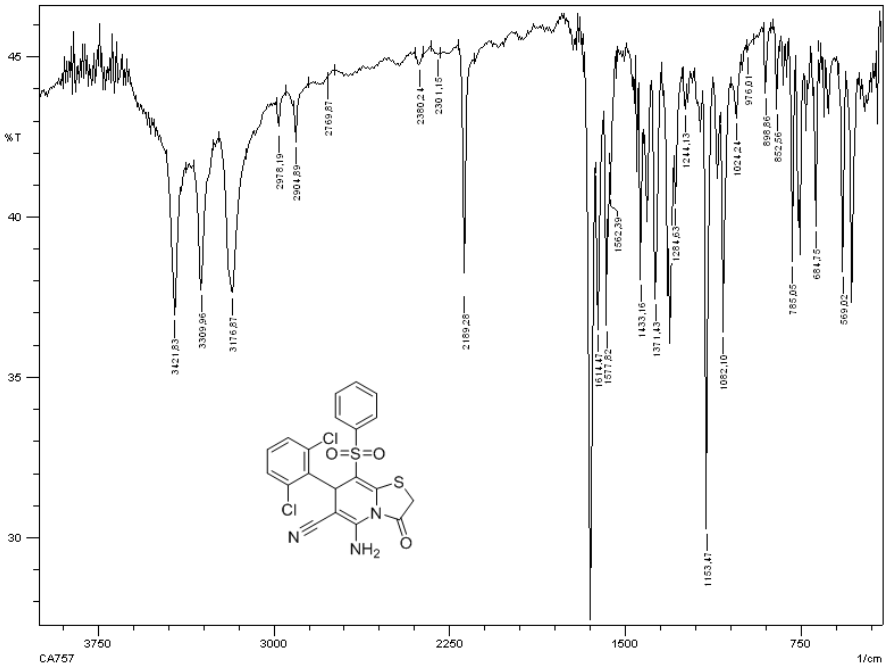


Figure 4.71. IR spectrum of compound (12d).

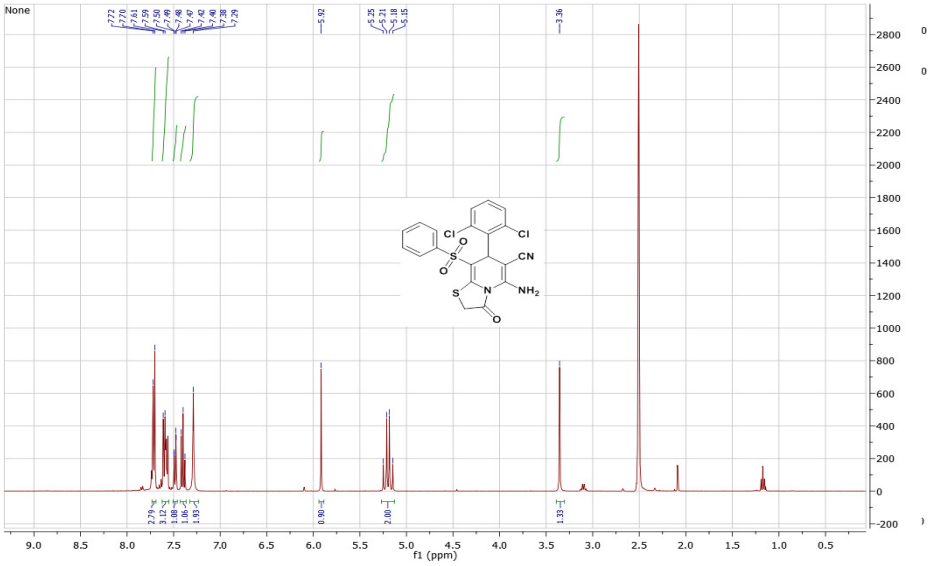


Figure 4.72. ^{1}H NMR spectrum of compound (12d).

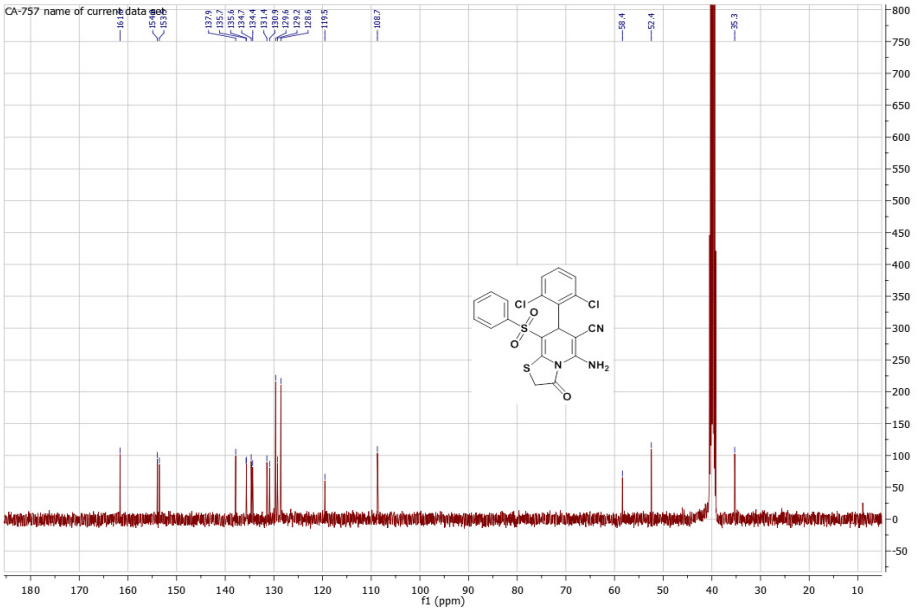


Figure 4.73. ^{13}C NMR spectrum of compound (12d).

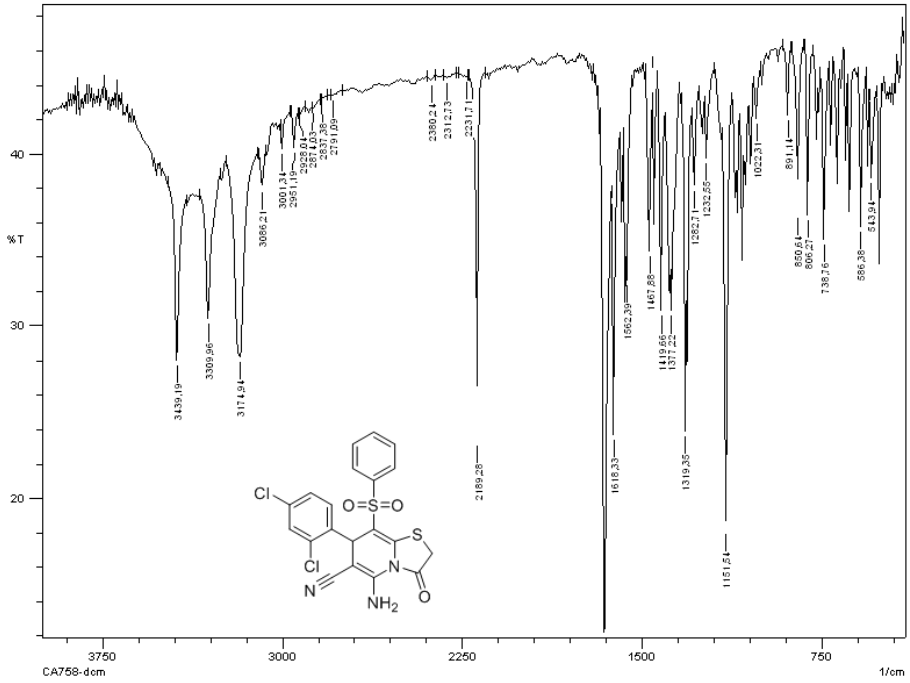


Figure 4.74. IR spectrum of compound (12e).

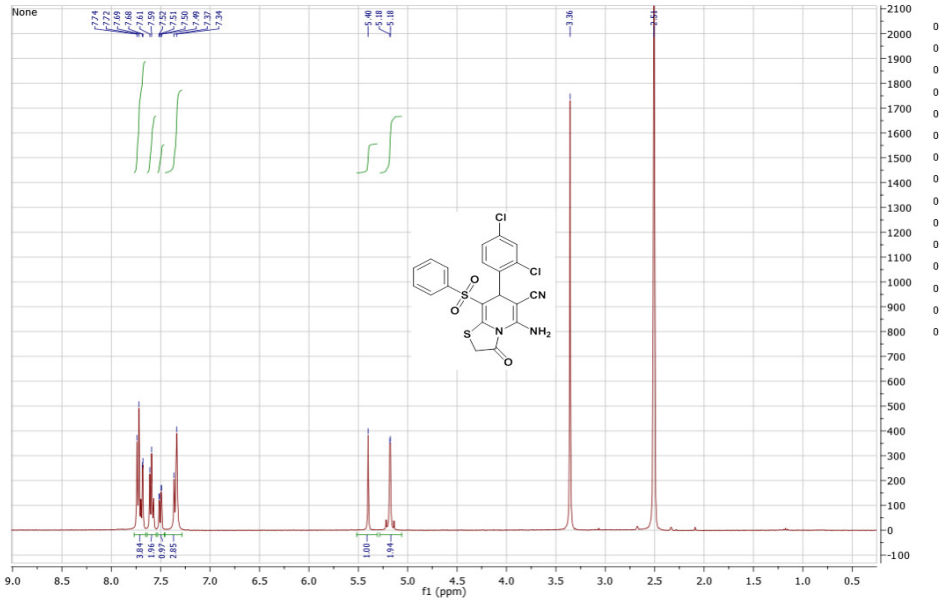


Figure 4.75. ^{1}H NMR spectrum of compound (12e).

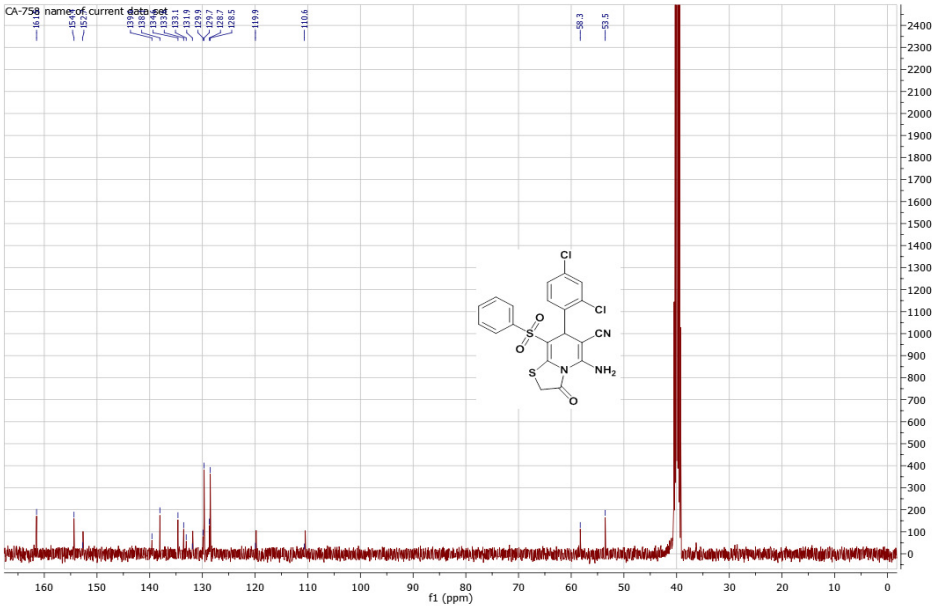


Figure 4.76. ^{13}C NMR spectrum of compound (12e).

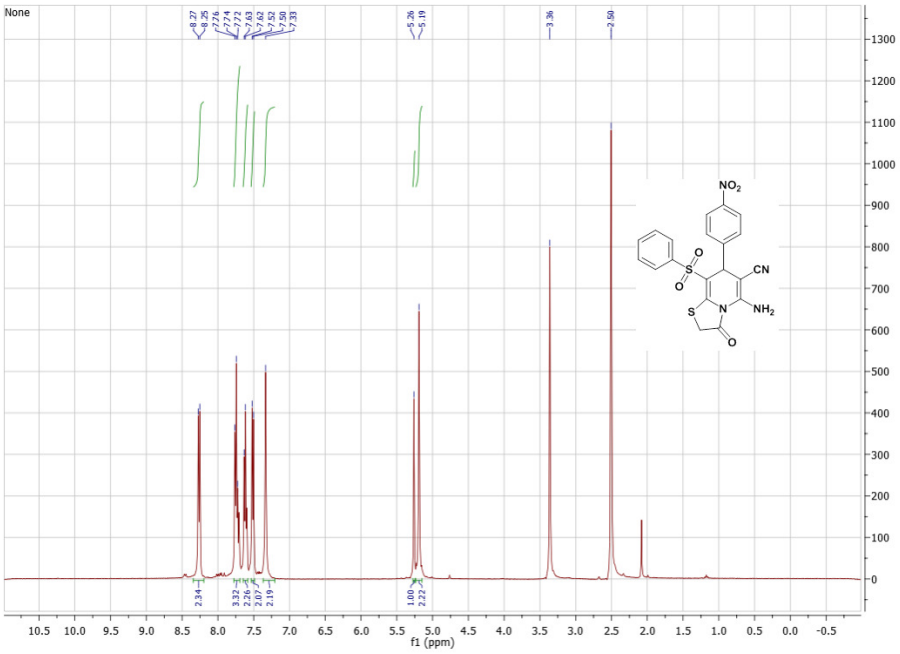


Figure 4.77. ^{1}H NMR spectrum of compound (12f).

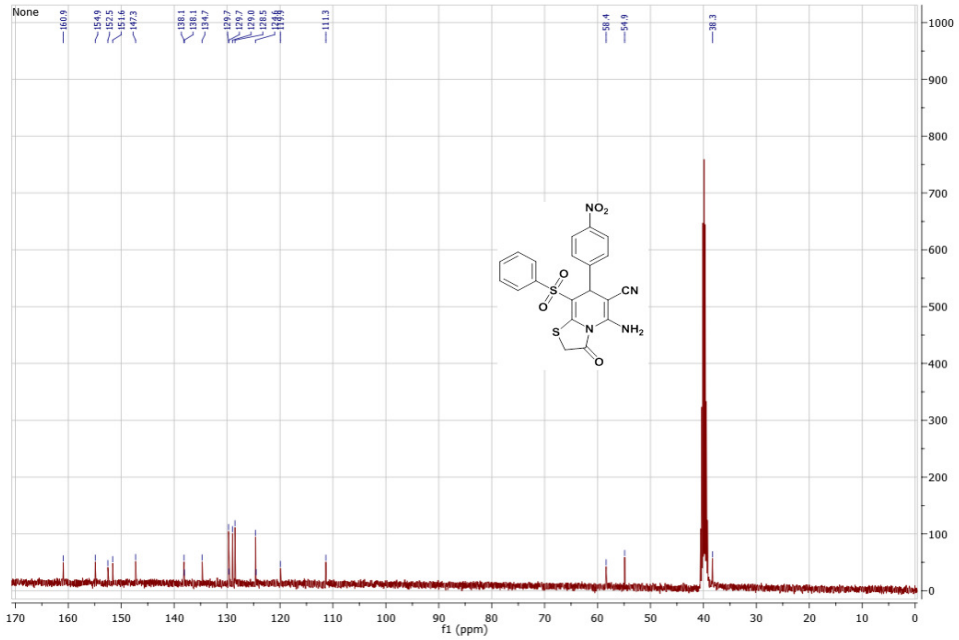


Figure 4.78. ^{13}C NMR spectrum of compound (12f).

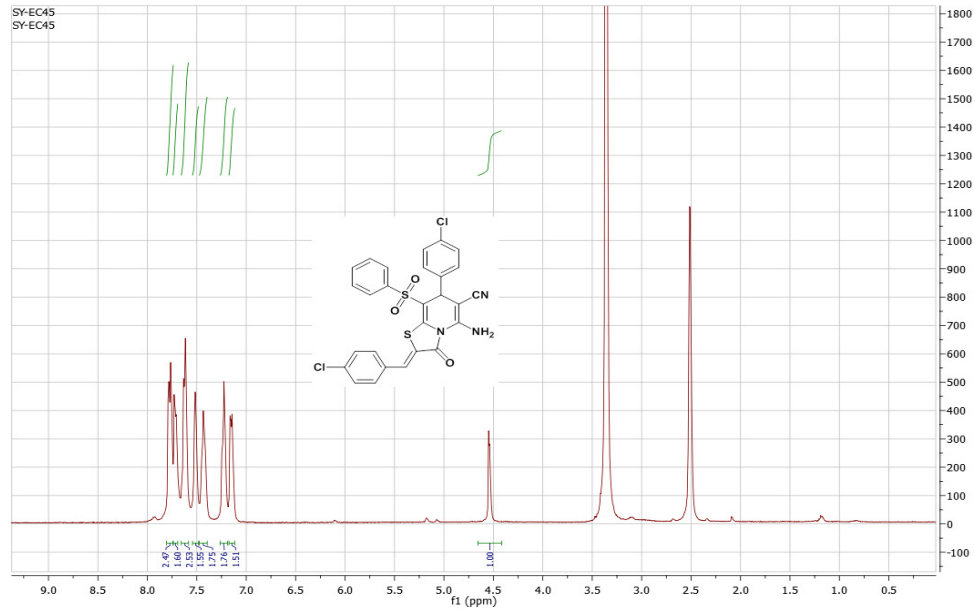


Figure 4.79. ^{1}H NMR spectrum of compound (13a).

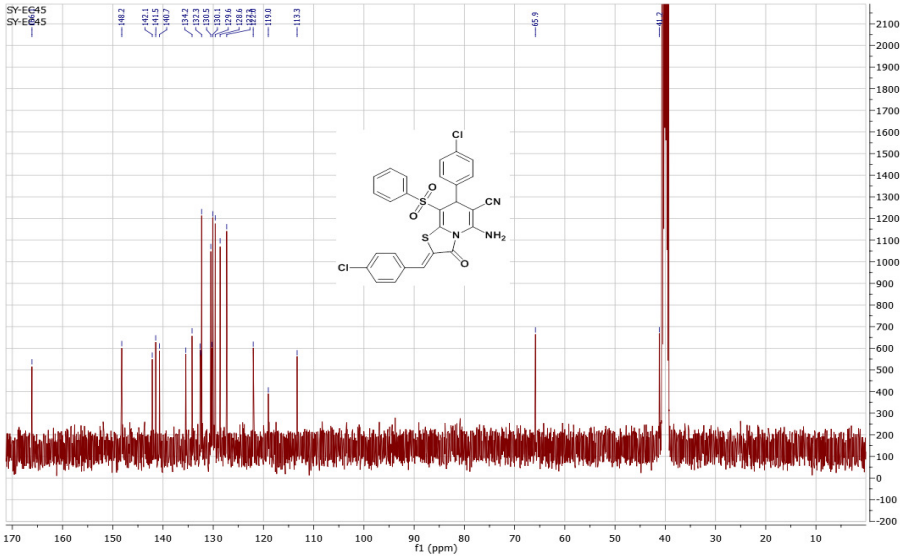


Figure 4.80. ^{13}C NMR spectrum of compound (13a).

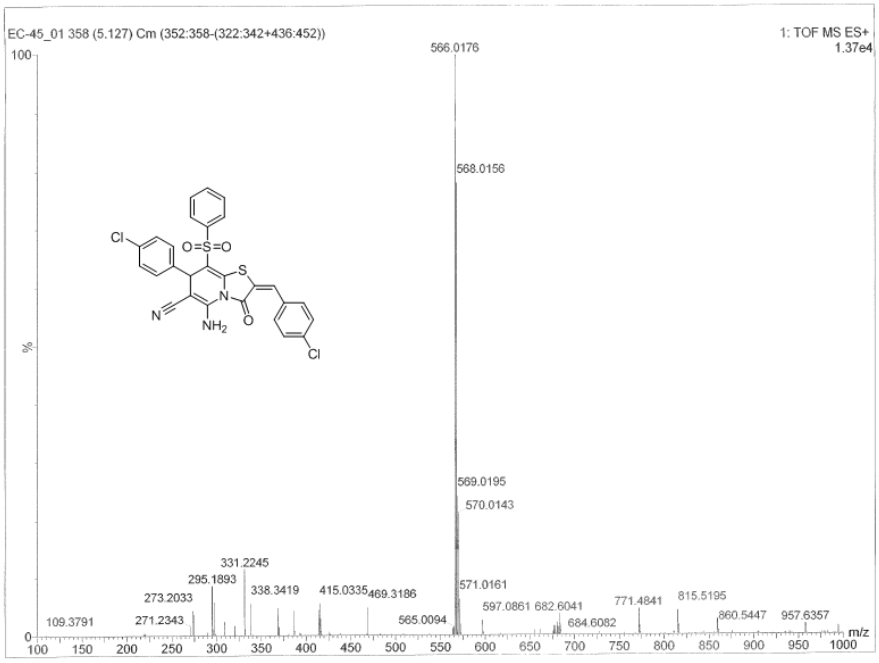


Figure 4.81. HRMS spectrum of compound (13a).

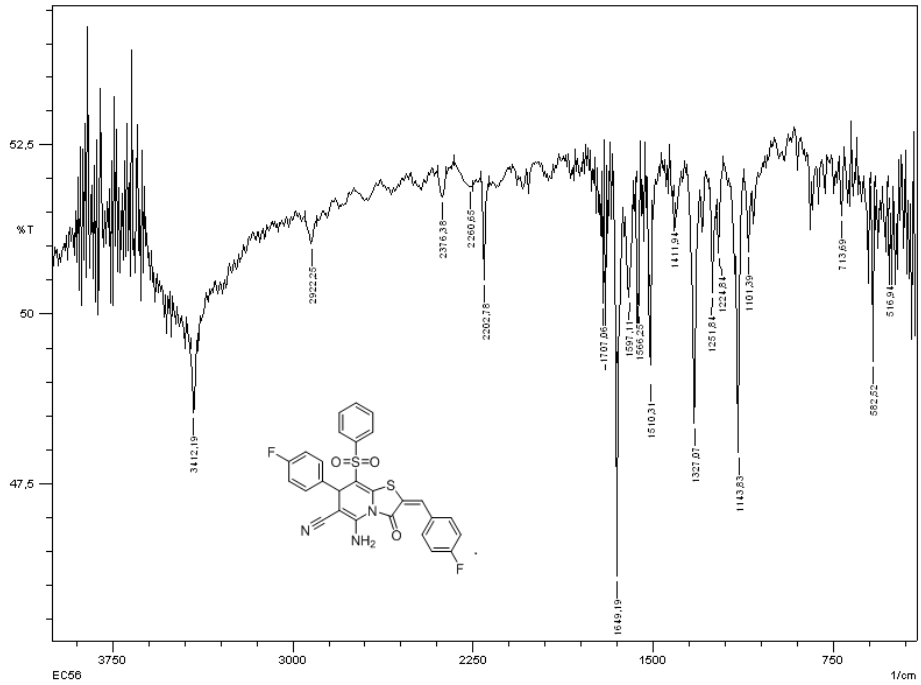


Figure 4.82. IR spectrum of compound (13b).

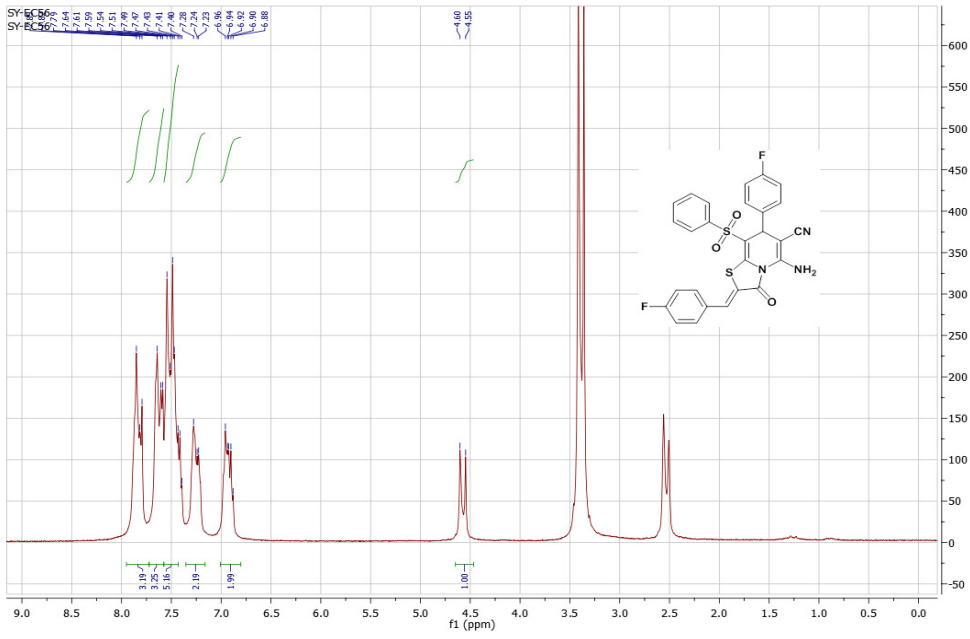


Figure 4.83. ^{1}H NMR spectrum of compound (13b).

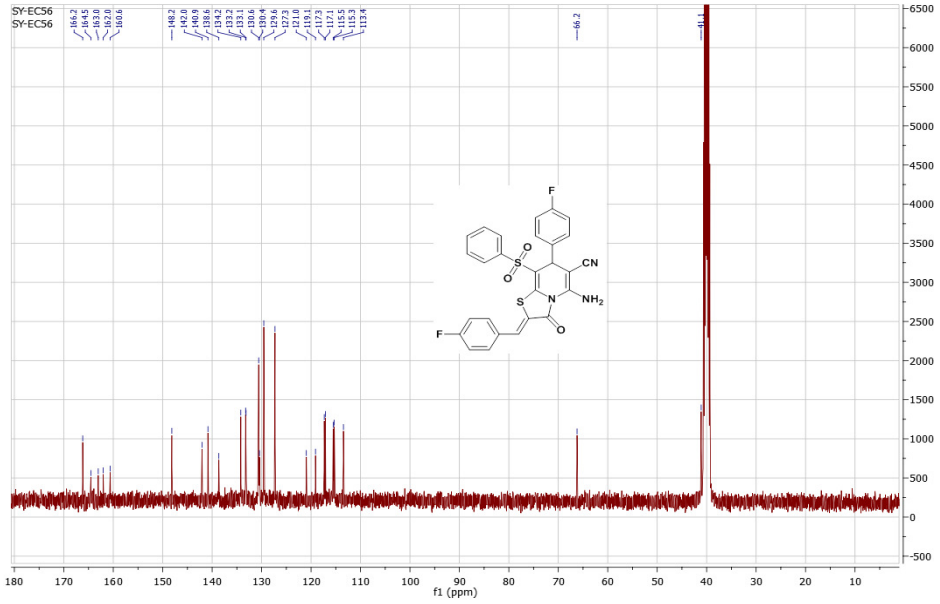


Figure 4.84. ^{13}C NMR spectrum of compound (13b).

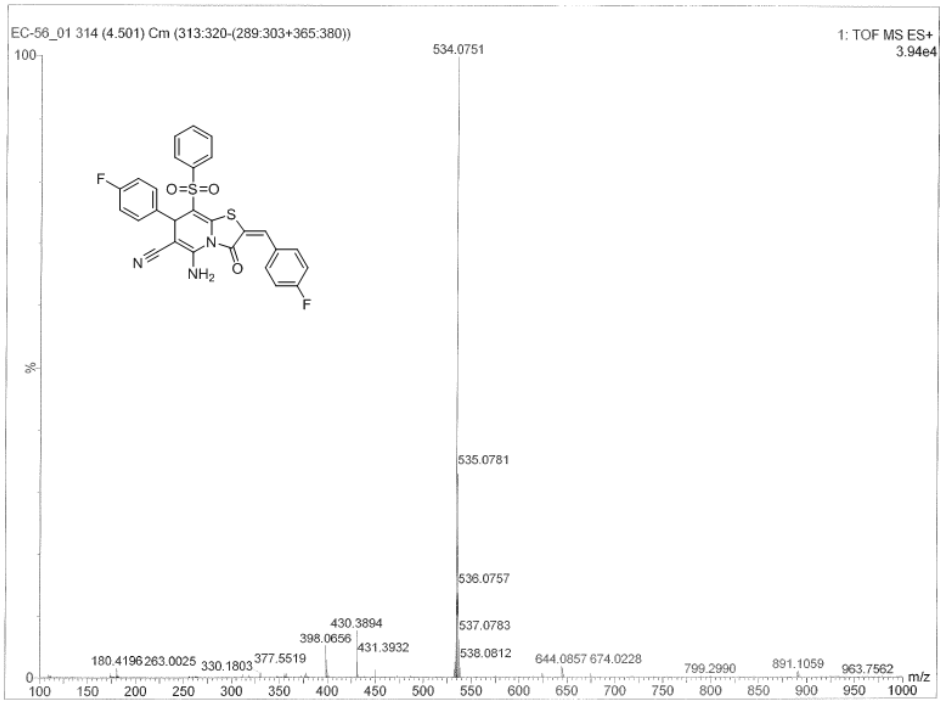


Figure 4.85. HRMS spectrum of compound (13b).

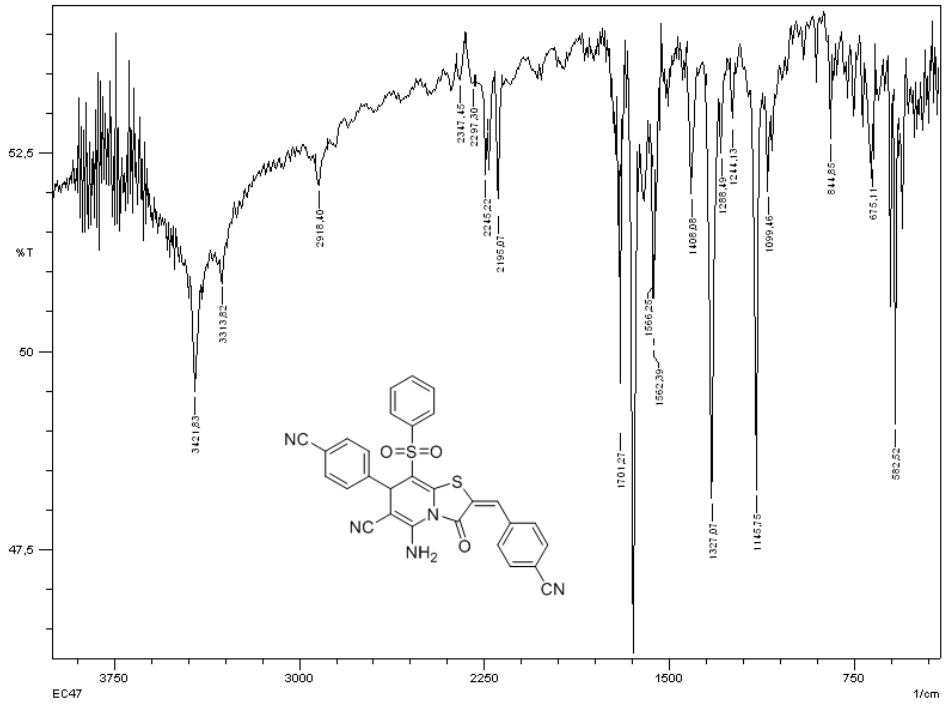


Figure 4.86. IR spectrum of compound (13c).

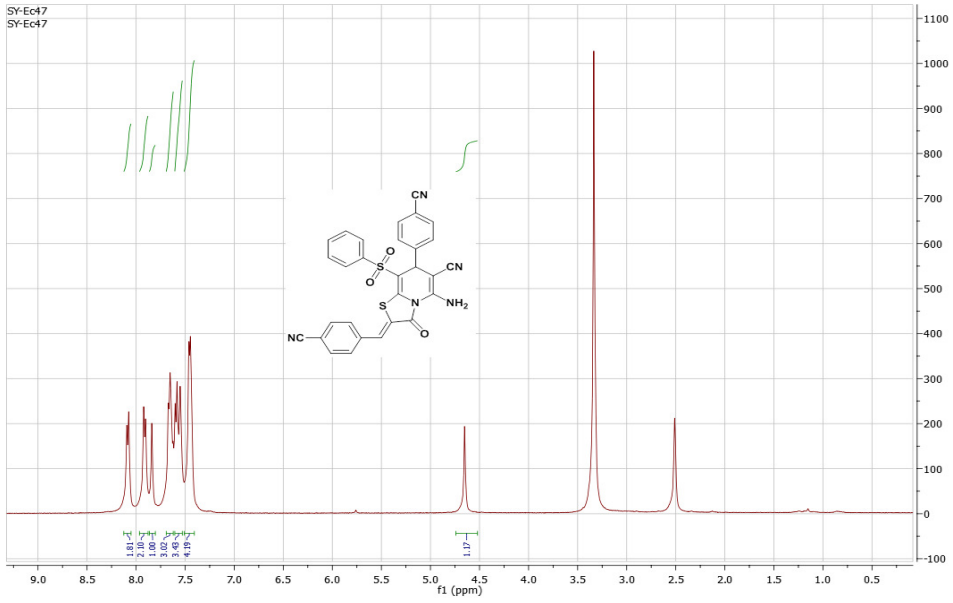


Figure 4.87. ^{1}H NMR spectrum of compound (13c).

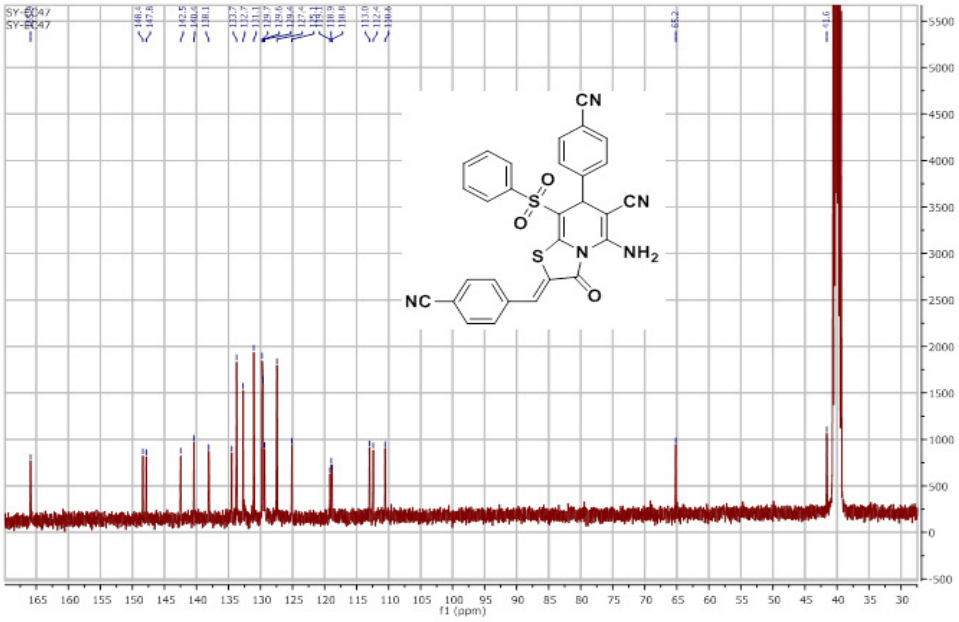


Figure 4.88. ^{13}C NMR spectrum of compound (13c).

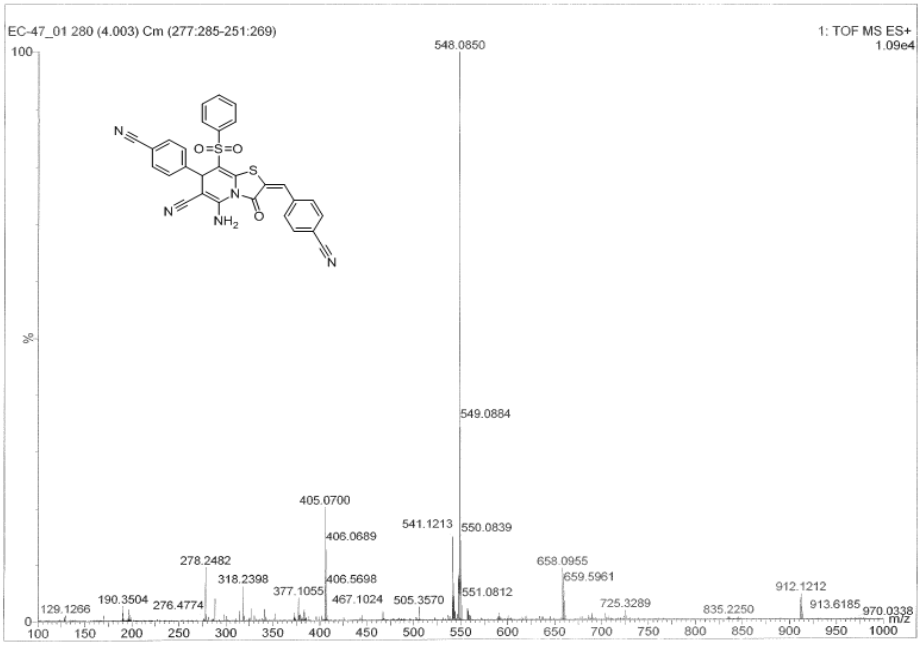


Figure 4.89. HRMS spectrum of compound (13c).

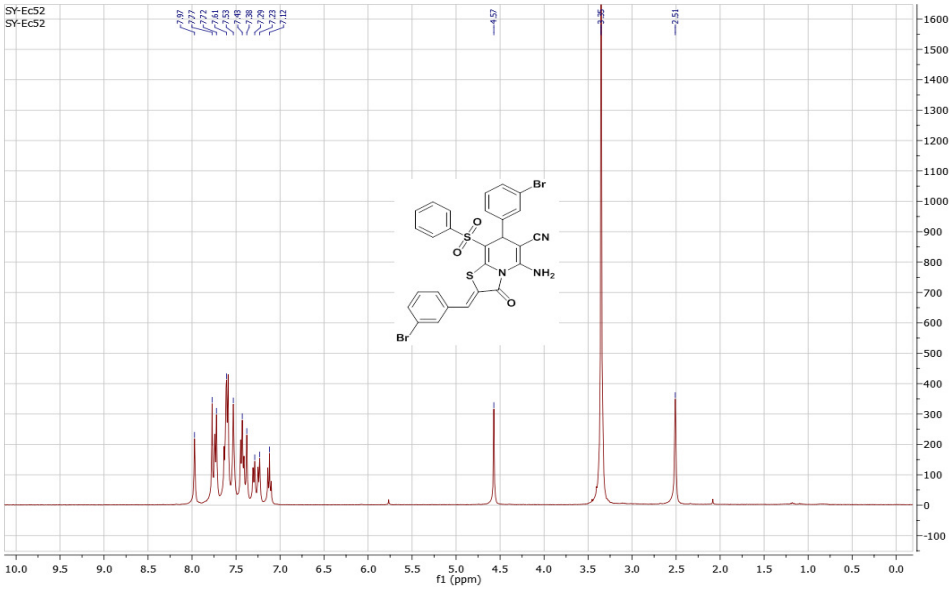


Figure 4.90. ^{1}H NMR spectrum of compound (13d).

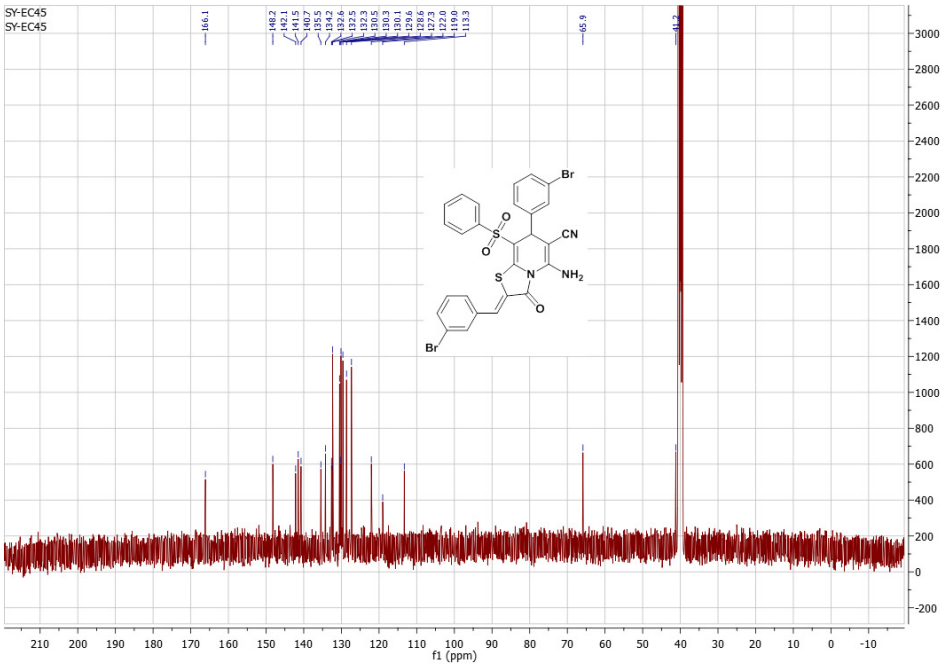


Figure 4.91. ^{13}C NMR spectrum of compound (13d).

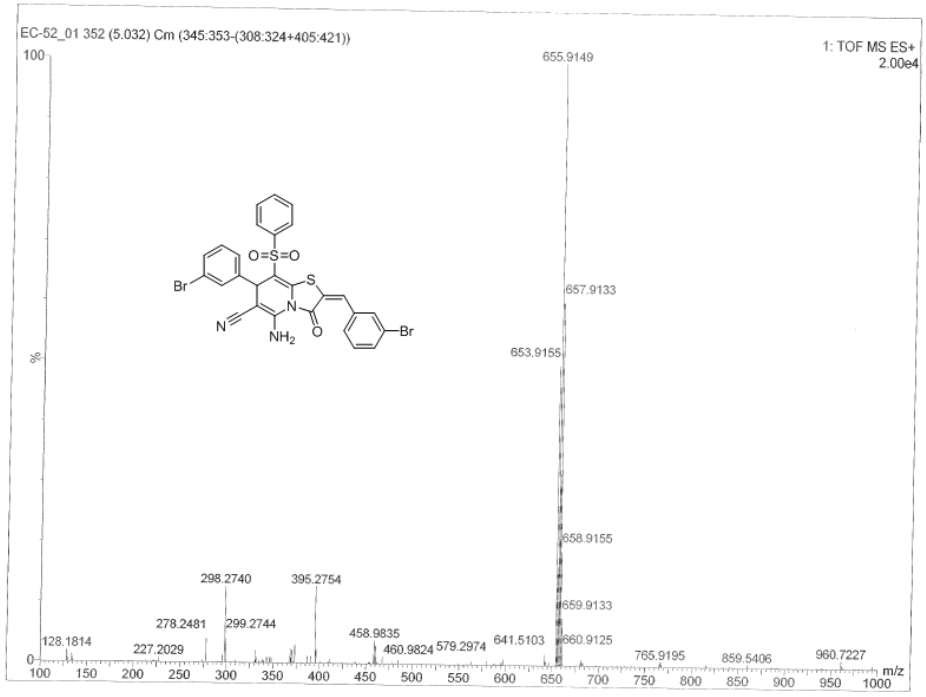


Figure 4.92. HRMS spectrum of compound (13d).

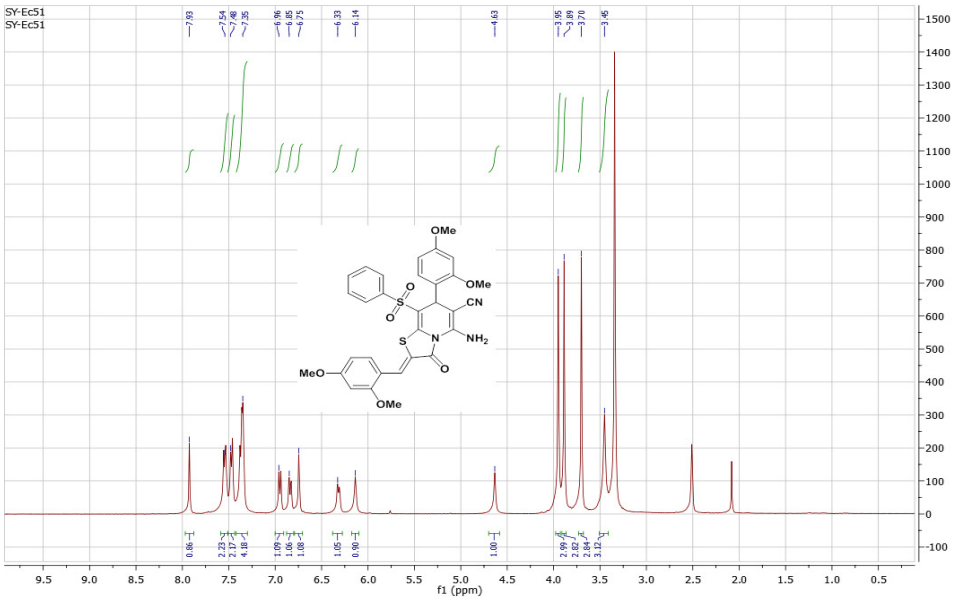


Figure 4.93. ^{1}H NMR spectrum of compound (13e).

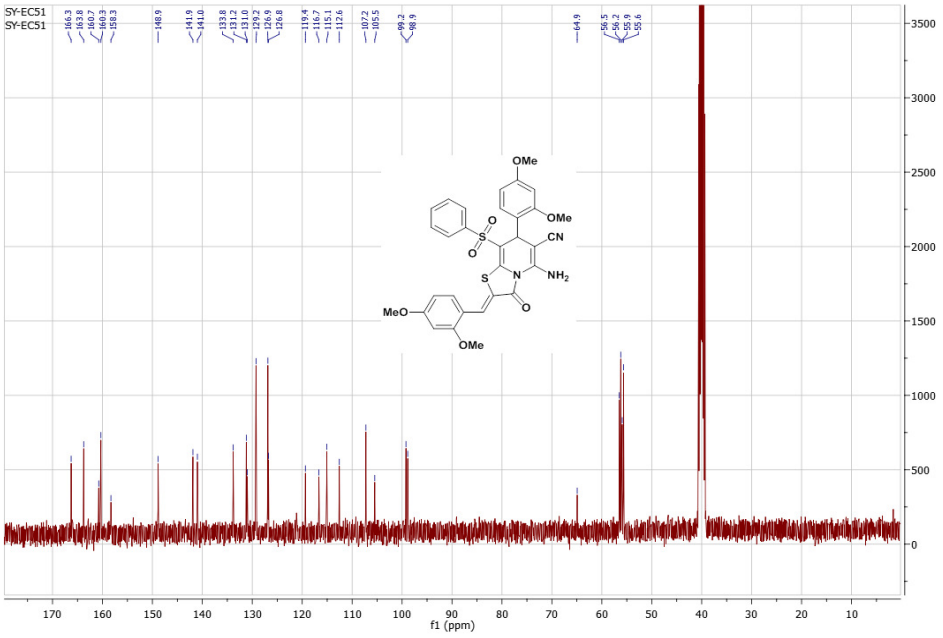


Figure 4.94. ^{13}C NMR spectrum of compound (13e).

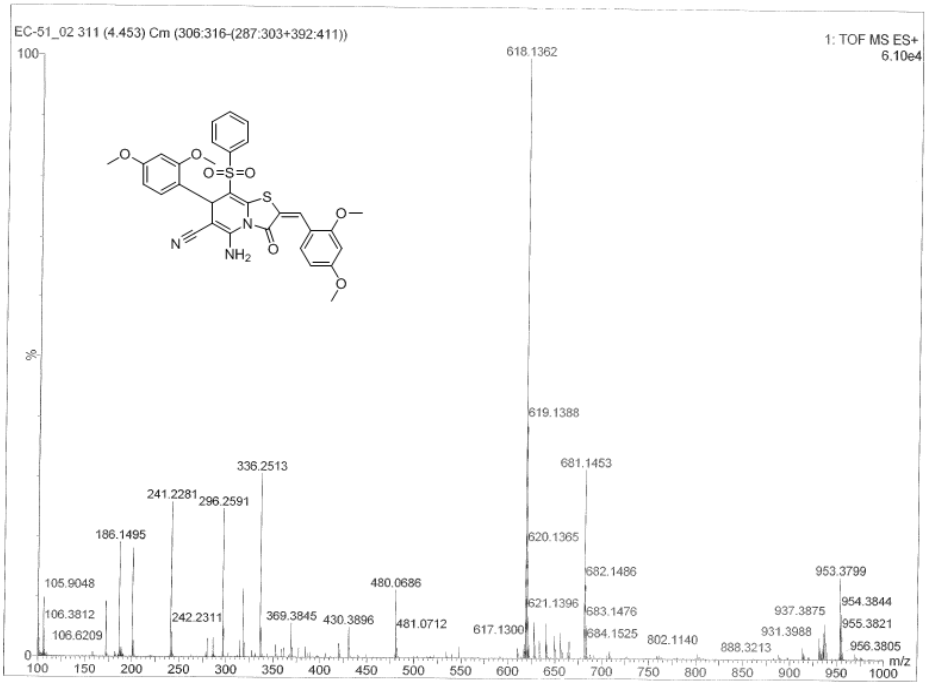


Figure 4.95. HRMS spectrum of compound (13e).

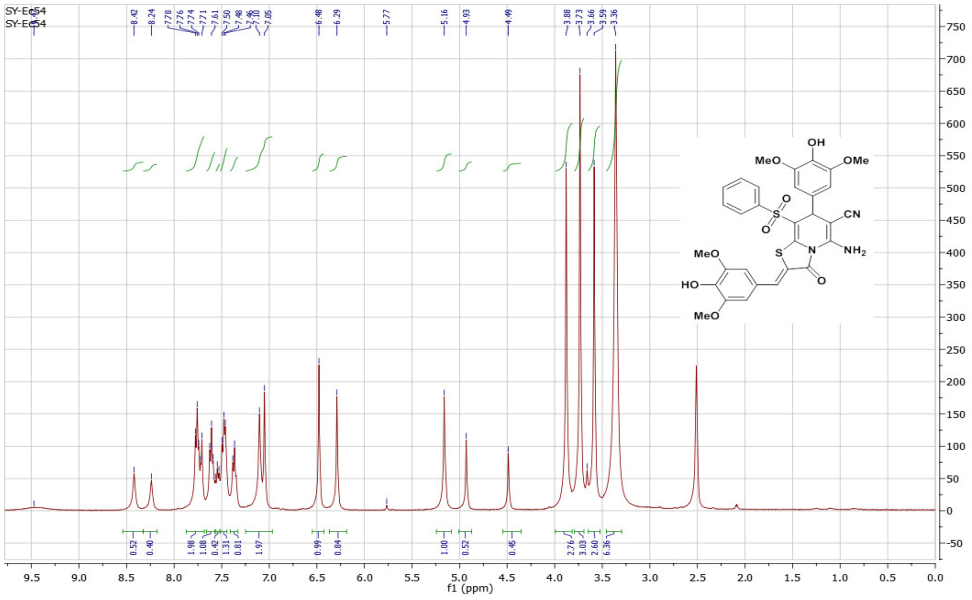


Figure 4.96. ^{1}H NMR spectrum of compound (13f).

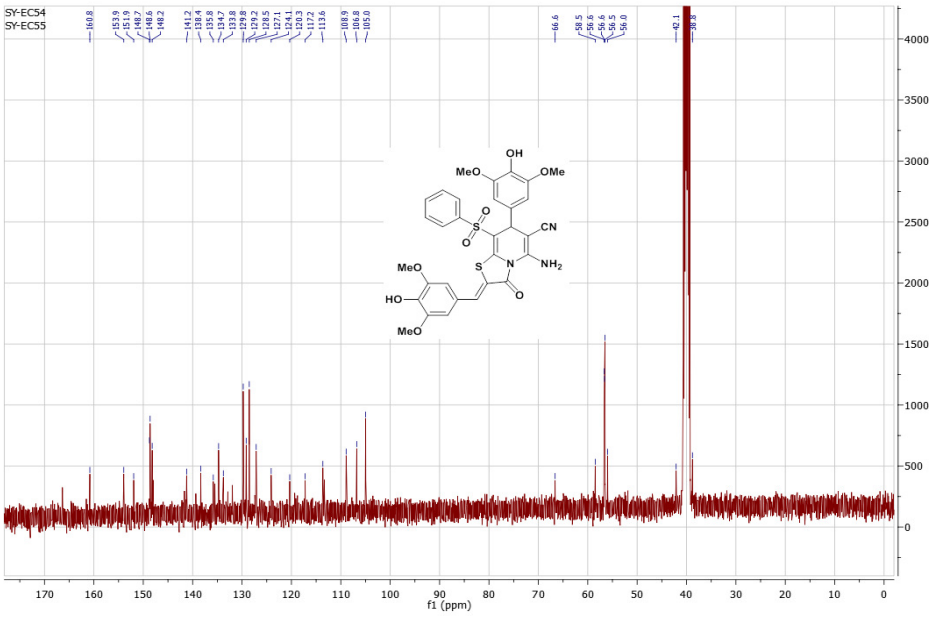


Figure 4.97. ^{13}C NMR spectrum of compound (13f).

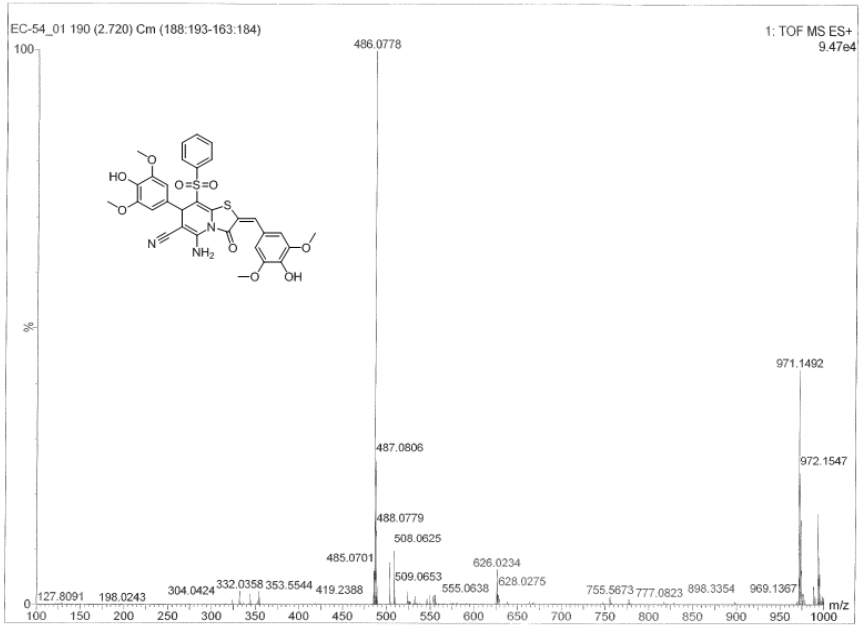


Figure 4.98. HRMS spectrum of compound (13f).

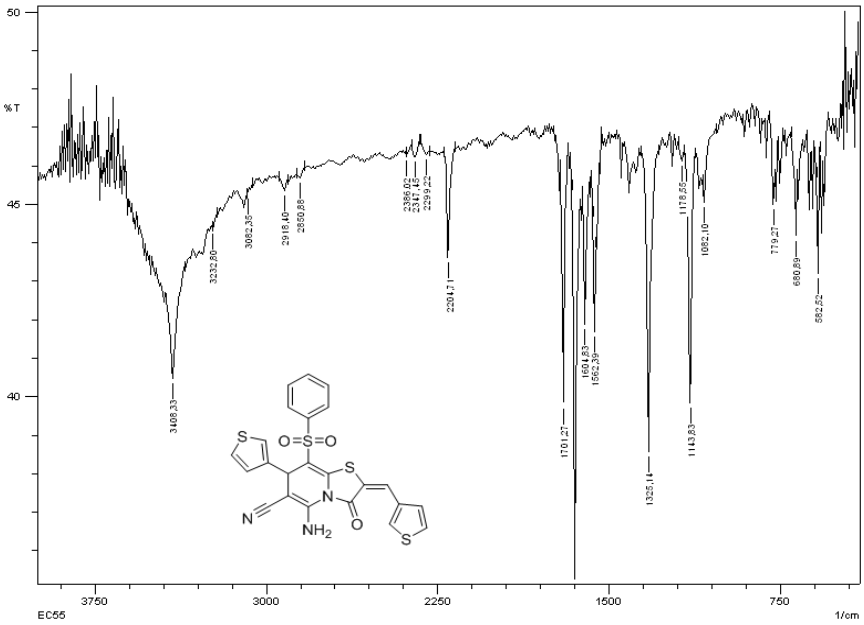


Figure 4.99. IR spectrum of compound (13g).

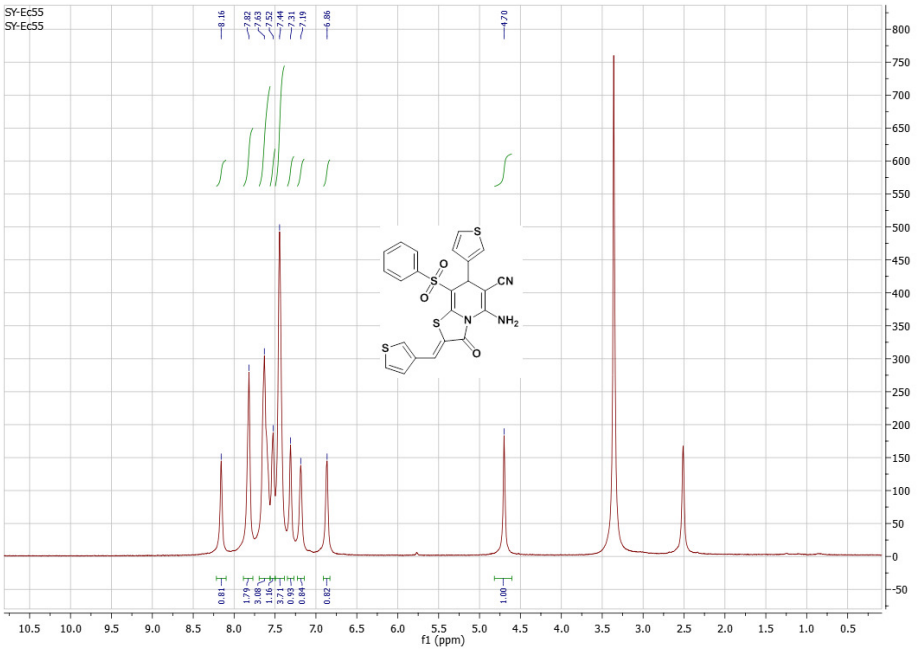


Figure 4.100. ^{1}H NMR spectrum of compound (13g).

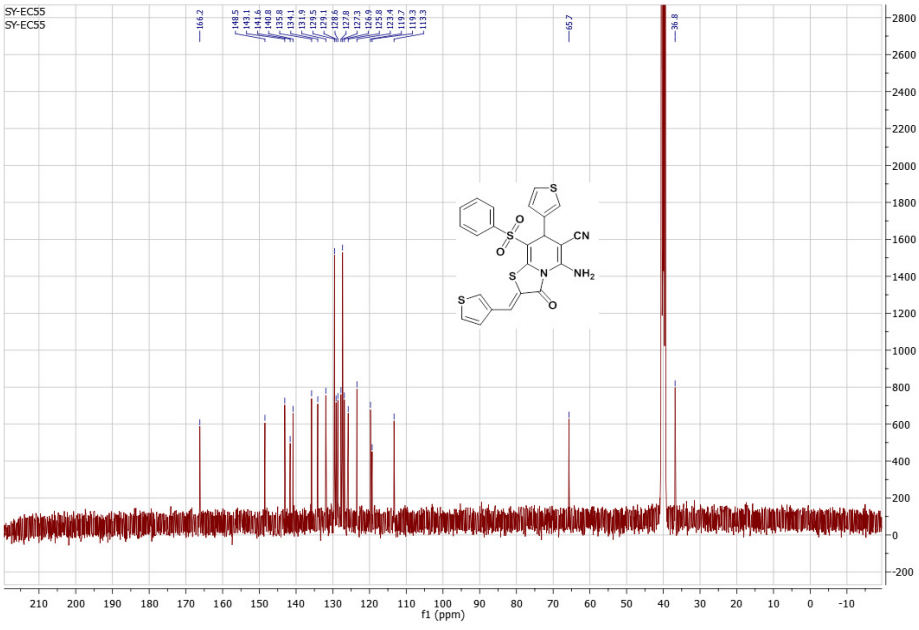


Figure 4.101. ^{13}C NMR spectrum of compound (13g).

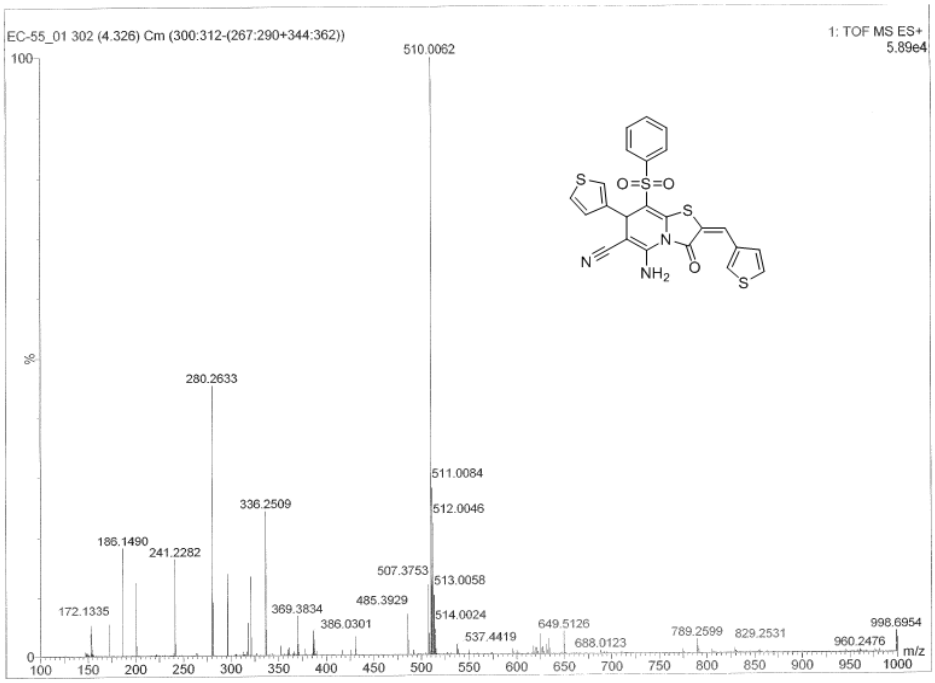


Figure 4.102. HRMS spectrum of compound (13g).

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